Main Group Metals
in Organic Synthesis

Edited by
Hisashi Yamamoto and Koichiro Oshima

Main Group Metals in Organic Synthesis. Edited by H. Yamamoto, K. Oshima

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Preface

Historically, main-group organometallics and metallorganics have played a major role in modern organic synthesis. The Grignard reagent has played quite a significant role in this field of chemistry for more than one hundred years. For most chemists, this type of magnesium compound is probably the first organometallic reagent that is encountered in their first organic-chemistry course. Although the use of Grignard reagents is truly impressive, the actual mechanistic details of reactions of these well-known organometallic compounds are still vague. Recent advances in various analytical technologies have allowed us to understand some of details of reactions that use the classical reagent. In light of the elucidation of various mechanisms, we now recognize the role of Grignard reagents in organic synthesis to be even greater than first anticipated.

Now that we are able to understand the chemical behavior of many main-group elements such as lithium, silicon, boron, and aluminum, the purpose of this book is to summarize these recent developments and show the promising future roles of complexes of these metals in modern organic synthesis. In fact, these reagents are both useful and much safer than most transition-metal compounds.

This volume focuses on areas of main-group organometallic and metallorganic reagents selected for their significant development during the last decade. Each author is very knowledgeable in their particular field of chemistry, and is able to provide a valuable perspective from a synthetic point of view. We are grateful to the distinguished chemists for their willingness to devote their time and effort to provide us with these valuable contributions.

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Chicago and Kyoto

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1
Lithium in Organic Synthesis

Katsuhiko Tomooka and Masato Ito

1.1
Introduction

Organolithium compounds are central to many aspects of synthetic organic chemistry and are primarily used as carbanions to construct carbon skeletons of a wide variety of organic compounds. Despite the strictly anhydrous conditions generally required for successful performance of reactions using organolithium compounds, their fundamental significance in synthetic organic chemistry remains unchanged. Tremendous efforts have therefore been devoted to the development of convenient methods for generation of tailor-made organolithium compounds and useful reactions using conventional organolithium compounds.

Because comprehensive literature [1–8] covering various aspects of organolithium chemistry has recently become available, the purpose of this chapter is to highlight "powerful synthetic tools" involving organolithium compounds. The definition of "organolithium" is here limited to those compounds in which there is a clear C–Li bond; compounds with enolate or ynolate structures or with heteroatom (Y)–Li bonds, etc., have been excluded.

This chapter is roughly divided into three sections. The nature of organolithium compounds, their structures, the configurational stability of their C–Li bond, and general guidelines regarding the handling organolithium compounds are briefly considered first (Section 1.2). The next section concerns the classification of useful methods for generation of organolithium compounds in which new C–Li bonds are created either by reduction, using lithium metal itself, or by the conversion of a C–Li bond into a less reactive C–Li bond (Section 1.3). The last section primarily describes potential methods for construction of the carbon framework, driven by conversion of a C–Li bond into a less reactive Y–Li bond (Section 1.4). All the examples dealt with in the last two sections have been selected on the basis of the distinct advantages of employing organolithium compounds compared with other organometallic reagents. We will not detail pioneering works underlying the establishment of selected examples, because we are concerned that excessive comprehensiveness might obscure their marked synthetic importance. There is no doubt, however, that modern synthetic technology has been developed on the basis of the considerable efforts of our forefathers, and readers are strongly recommended to

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refer to other books or reviews cited in this chapter for historical aspects and other issues regarding organolithium chemistry.

1.2 Nature of Organolithium Compounds

1.2.1 Overview

Because organolithium compounds are generally sensitive to oxygen and moisture, rigorous exclusion is required to prevent decomposition. They are, however, stable in anhydrous hydrocarbons under a nitrogen or, preferably, argon atmosphere at ambient temperature, and the solutions can be stored for longer at low-

Tab. 1.1 Commercially available organolithium compounds

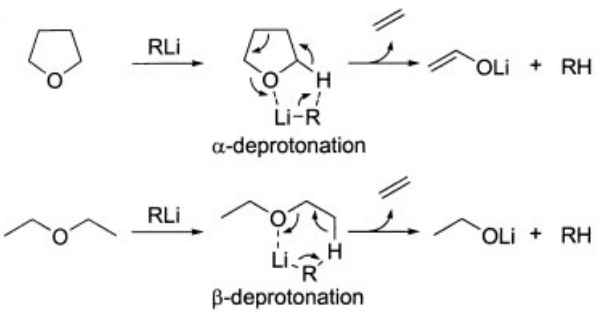
Organolithium compound	*Abbreviation*	*Solvent*	*Concn (M)*
Methyllithium	MeLi	Diethyl ether	1.0 [a)] 1.4 [c)]
Methyllithium-lithium bromide complex	MeLi–LiBr	Diethyl ether	1.5 [c)] 2.2 [b)]
Methyllithium-lithium iodide complex	MeLi–LiI	Diethyl ether	1.0 [c)]
n-Butyllithium	*n*-BuLi	Hexane	1.6 [a–c)] 2.5 [b, c)] 2.6 [a)] 3.0 [a)] 10.0 [c)]
		Cyclohexane	2.0 [c)]
		Pentane	2.0 [c)]
s-Butyllithium	*s*-BuLi	Cyclohexane	1.0 [a)] 1.3 [c)] 1.4 [b)]
t-Butyllithium	*t*-BuLi	Pentane	1.5 [a)] 1.7 [c)]
Phenyllithium	PhLi	Cyclohexane-diethyl ether	1.0 [a)] 1.8 [c)] 1.9 [b)]
		Dibutyl ether	2.0 [b)]
Lithium acetylide-ethylenediamine complex	$HC\equiv CLi–H_2NC_2H_4NH_2$	None (powder ca. 90% purity)	– [a–c]
		Toluene (suspension 25%, *w*/*w*)	– [b,c]

a) Kanto Kagaku. **b)** Wako Chemicals. **c)** Sigma-Aldrich.

er temperatures [1, 2]. Simple organolithium starting materials listed in Tab. 1.1 are commercially available as solutions in such solvents. Exceptionally, the lithium acetylide-ethylenediamine complex is available as a solid. Hydrocarbon solutions of *n*-, *s*-, and *t*-BuLi are the ultimate source of most organolithium compounds, and their availability has greatly contributed to the advancement of organolithium chemistry. In general, ethereal solvents such as diethyl ether or tetrahydrofuran are most frequently used either in the preparation of organolithium compounds or in their reactions, because they reduce the extent of aggregation of organolithium compounds and hence increase their reactivity (Section 1.2.2). To increase their reactivity further, *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA), 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidine (DMPU), or hexamethylphosphoramide (HMPA) are effective co-solvents, because of their high coordinating ability. It should be noted that organolithium compounds are thermally unstable in ethereal solvents; their half-lives [1, 9, 10] are summarized in Tab. 1.2. Thermal decomposition arises as a result of deprotonation of ethereal solvents by organo-

Tab. 1.2 Half-lives of organolithium compounds in common ethereal solvents

RLi	*Solvent*	*–70 °C*	*–40 °C*	*–20 °C*	*0 °C*	*+20 °C*	*+35 °C*
t-BuLi	DME	11 min					
	THF		5.6 h	42 min			
	ether			8 h	1.0 h		
s-BuLi	DME	2.0 h	2 min				
	THF			1.3 h			
	ether			20 h	2.3 h		
n-BuLi	DME			1.8 h	<5 min		
	THF				17 h	1.8 h	10 min
	ether					153 h	31 h
PhLi	ether						12 days
MeLi	ether					3 months	



Scheme 1.1

lithium compounds, because of their high basicity, leading to a variety of decomposition products with Li–O bonds, as illustrated in Scheme 1.1.

1.2.2 Structural Features

The electron-deficient lithium atom of an organolithium compound requires greater stabilization than can be provided by a single carbanionic ligand, and freezing measurements indicate that in hydrocarbon solution organolithium compounds are invariably aggregated as hexamers, tetramers, or dimers [11] (Tab. 1.3). The structures of these aggregates in solution can be deduced to some extent from the crystal structures of organolithium compounds [12] or by calculation [13]: the tetramers approximate to lithium atom tetrahedra unsymmetrically bridged by the organic ligands [4, 5]. The aggregation state of simple, unfunctionalized organolithium compounds depends primarily on steric hindrance. Primary organolithium compounds are hexamers in hydrocarbons, except when branching β to the lithium atom leads to tetramers. Secondary and tertiary organolithium compounds are tetramers whereas benzyllithium and very bulky alkyllithium compounds are dimers [1, 11].

Coordinating ligands such as ethers or amines, or even metal alkoxides can provide an alternative source of electron density for the electron-deficient lithium atoms. These ligands can stabilize the aggregates by coordinating to the lithium atoms at their vertices; this enables the organolithium compounds to shift to an entropically favored lower degree of aggregation. As shown in Tab. 1.3, the presence of ethereal solvents typically causes a shift down in the aggregation state, but only occasionally results in complete deaggregation to the monomer [1]. Methyllithium and butyllithium remain tetramers in diethyl ether, THF, or DME, with some dimers forming at low temperatures; *t*-BuLi becomes dimeric in diethyl

Tab. 1.3 Aggregation states of typical organolithium compounds

RLi	*In hydrocarbon solvent*	*In ethereal solvent*
MeLi	–	Tetramer
EtLi	Hexamer	Tetramer
n-BuLi	Hexamer	Tetramer
i-BuLi	Tetramer	–
BnLi	Dimer	Monomer
i-PrLi	Tetramer	Dimer
s-BuLi	–	Dimer
PhLi	–	Dimer
t-BuLi	Tetramer	Dimer

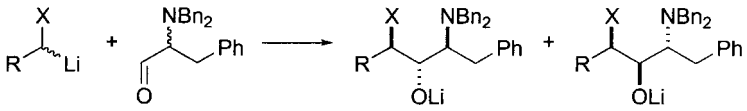
ether and monomeric in THF at low temperatures [14–17]. Coordinating solvents also greatly increase the reactivity of the organolithium compounds, and an ether or amine solvent is indispensable in almost all organolithium reactions.

1.2.3 Configurational Stability

In principle, the configurational stability at the metal-bearing stereogenic carbon in organometallic compounds decreases as the ionic character of the carbon–metal bond increases. Because organolithium compounds contain one of the most electropositive elements some charge separation occurs in their C–Li bonds. Coordinating solvents greatly enhance the extent of charge separation. Enantio-enriched organolithium compounds, if successfully generated, usually, therefore, undergo racemization, which can be explained by migration of the Li cation from one face of the anion to the other. For example, the half-lives for racemization of secondary, unfunctionalized organolithium compounds in diethyl ether are only seconds at –70 °C, even though those in non-polar solvents can be lengthened to hours at –40 °C and to minutes at 0 °C [18]. Accordingly, the design of stereoselective reactions with enantio-enriched organolithium compounds has long been unattractive to the synthetic organic community. The last decade, however, has witnessed a significant advance in this area, and a number of functionalized organolithium compounds with a configurationally stable C–Li bond have been found by taking advantage of the Hoffmann test [19], which provides a qualitative guide to the configurational stability of an organolithium compound.

The Hoffmann test, the essence of which is described briefly below, comprises of two experiments using a suitable chiral electrophile such as an aldehyde in either the racemic or enantiomerically pure form. The occurrence of sufficient kinetic resolution on reaction of a racemic organolithium compound (±)-**1** with a chiral electrophile **2** is established in the first experiment by using **2** in the racemic form. In a second experiment the organolithium compound (±)-**1** is added to the enantiomerically pure **2** and the ratios (a and a') of the diastereomeric products **3** and **4** resulting from the two experiments are compared. If they are identical ($a = a'$) at conversions of >50%, the organolithium compound **1** is configurationally labile on the time-scale set by the rate of its addition to **2**. If there is an analytically significant difference between the diastereomer ratios ($a \neq a'$), enantiomer equilibration of the organolithium compound is slower than its addition to the electrophile (Chart 1.1).

experiment I

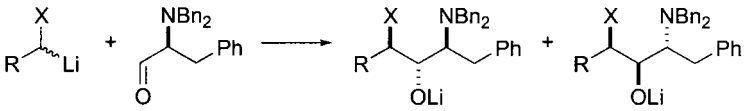


(±)-**1** (±)-**2** (±)-**3** (±)-**4**

diastereomer ratio *a* = (±)-**3**/(±)-**4**

If *a* = 1, test is insensitive.
If *a* ≠ 1, go to Experiment II.

experiment II



(±)-**1** **2** **3** **4**

diastereomer ratio *a'* = **3**/**4**

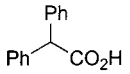
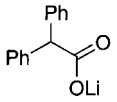
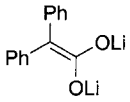
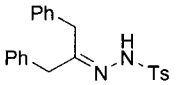
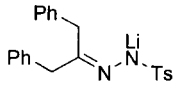
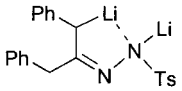
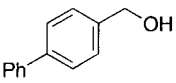
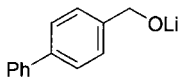
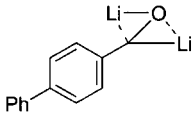
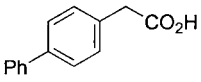
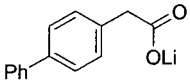
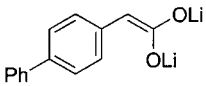
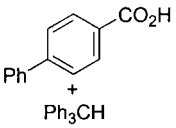
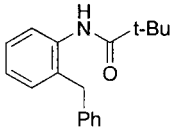
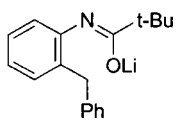
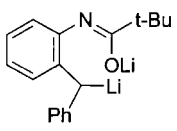
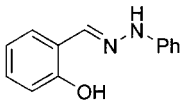
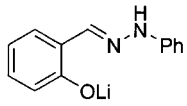
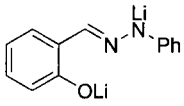
If *a'* = *a*, **1** is configurationally *unstable*.
If *a'* ≠ *a*, **1** is configurationally *stable*.

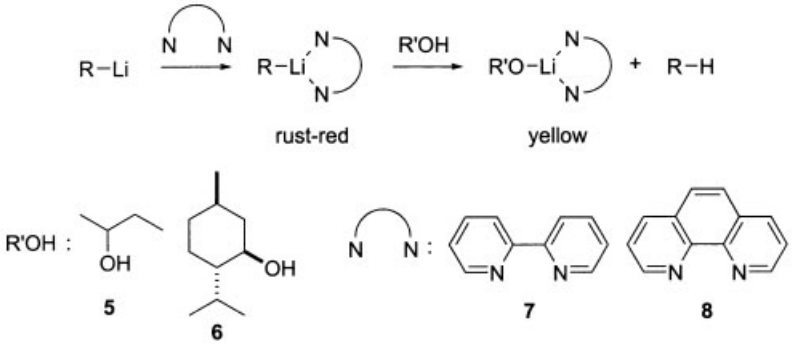
Chart 1.1 The Hoffmann test

1.2.4 Titration of Organolithium Compounds

One can easily and reliably check the identity, purity, and concentration of an organolithium compound in solution by several methods. One of the most standard methods is titration of the organolithium solution with alcohols such as 2-butanol (**5**) or (–)-menthol (**6**) in the presence of a small amount of 2,2′-bipyridine (**7**) or 1,10-phenanthroline (**8**) as a color indicator. This method is based on the color difference between the C–Li and O–Li compounds, with the ligands used as color indicators (Scheme 1.2). For example, addition of a spatula tip of **8** to a solution of an organolithium species in an ether or a hydrocarbon produces a characteristic rust-red charge-transfer (CT) complex. Titration with a standardized solution of **5** in xylene until complete decoloration enables determination of the concentration of the organolithium compound [20]. To minimize the experimental complexity a variety of indicators [21–25] bearing a functional group to coordinate to lithium and another to develop a color within the same molecule have been developed, as shown in Tab. 1.4. However, one should select appropriate color indicators depending on the structure of the organolithium compounds that correlate with the sharpness of color development.

Tab. 1.4 Color indicators in titration

Color indicator	*Color change*	*Suitable RLi*	*Reference*
	 colorless →  yellow	MeLi n-BuLi	[21]
	 colorless →  orange	MeLi n-BuLi t-BuLi PhLi	[22]
	 colorless →  orange red	MeLi n-BuLi s-BuLi t-BuLi	[23]
	 colorless →  bright yellow	n-BuLi s-BuLi t-BuLi	[23]
	colorless → deep red	n-BuLi s-BuLi t-BuLi	[23]
	 colorless →  yellow orange	MeLi n-BuLi s-BuLi t-BuLi PhLi	[24]
	 yellow →  red	MeLi n-BuLi t-BuLi	[25]

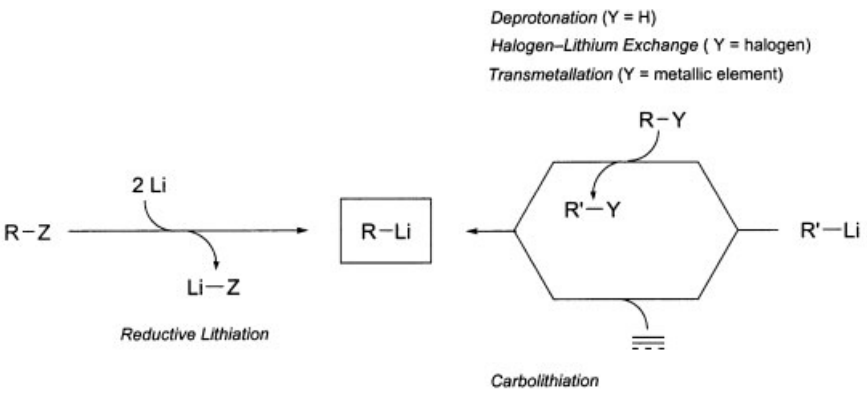


Scheme 1.2

1.3 Methods for the Preparation of Organolithium Compounds

1.3.1 Overview

A C–Li bond can be created by one of two principally different methods. One is the de novo creation of C–Li bonds in which the lithium metal undergoes reductive insertion to an organic compound with the leaving group Z; the other involves construction of new C–Li bonds by another organolithium reagent (Scheme 1.3). The former method, detailed in Section 1.3.2, is still the most straightforward and often also the most rational approach; it is therefore used in the industrial production of typical organolithium compounds. The latter method



Scheme 1.3

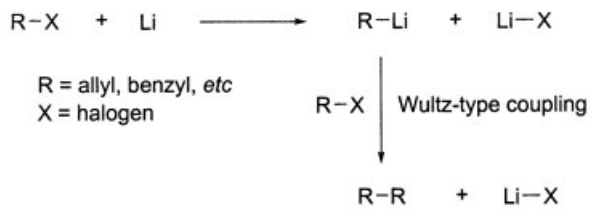
can be divided most simply into four distinct methods – deprotonation, halogen-lithium exchange, transmetallation with other organolithium compounds, and carbolithiation of the carbon–carbon unsaturated bond. The details of these methods are outlined in Section 1.3.3.

1.3.2
Reductive Lithiation using Lithium Metal

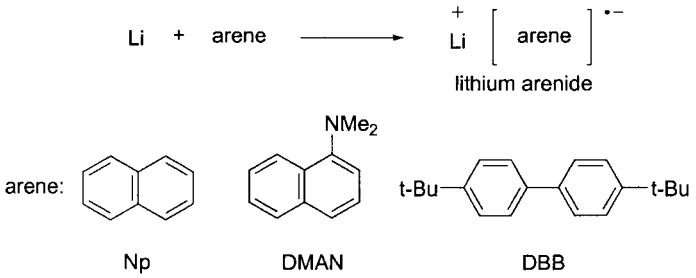
Simple, unfunctionalized organolithium compounds are usually prepared by reductive lithiation of alkyl halides with lithium metal at ambient temperature or above [26]. Reductive lithiation is fastest for alkyllithium compounds (the more substituted the better) and slowest for aryllithium compounds. The order of reactivity follows logically from the relative stabilities of the intermediate radicals, whose formation is the rate-determining step of the sequence.

$$R'R''R'''CLi > RCH_2Li > \text{vinyllithium} > \text{aryllithium}.$$

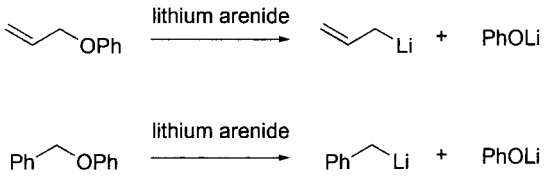
The use of lithium metal can pose problems, however, primarily because of the temperatures required. The newly formed organolithium compounds can attack unreacted starting materials or solvents. For example, the reductive lithiation of allyl and benzyl halides leads only to the formation of Wultz-type coupling products (Scheme 1.4). Also, secondary and tertiary alkyllithium compounds attack ethereal solvents even at temperatures around or below –25 °C (vide supra). One of the most promising solutions to these problems is the use of lithium arenide (Scheme 1.5). Arenes such as naphthalene (Np), (1-dimethylamino)naphthalene (DMAN) [27], and, in particular, 4,4′-bis(*t*-butyl)biphenyl (DBB) [28] can form soluble radical anions by accepting one electron from lithium metal; this facilitates the reductive lithiation. The homogeneity reduces the temperatures required for the critical electron-transfer process and minimizes the duration of contact between the organolithium compounds and their halogenated precursors. Recent studies have shown, that a catalytic amount of the arenes only is sufficient for the reductive lithiation [29]. These methods enable not only the efficient reductive lithiation of carbon–halogen bonds but also carbon–oxygen or carbon–sulfur bonds [26, 30]. The carbon–oxygen bond-cleavage reactions are particularly useful



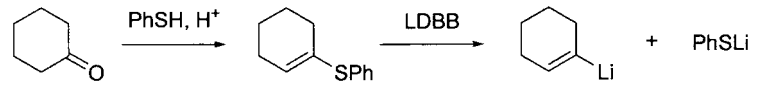
Scheme 1.4



Scheme 1.5



Scheme 1.6



Scheme 1.7

for preparation of allyl [31] or benzyl lithium compounds [32] from allyl or benzyl ethers (Scheme 1.6). Of a wider range of synthetic reactions involving carbon–sulfur bond cleavage, vinyllithium synthesis using Li with DBB (LDBB), shown in Scheme 1.7 [33], is attractive as a useful alternative to the Shapiro reaction (vide infra).

1.3.3 Preparation of Organolithium Compounds from Another Organolithium Compounds

1.3.3.1 Deprotonation

Because hydrogen is a poor nucleofugal leaving group, the reductive lithiation of C–H bonds with lithium metal plays only a very marginal role in the generation of organolithium compounds. In contrast, prototropic hydrogen transfer from organic compounds to organolithium compounds or lithium amides is the method of choice whenever applicable. In principle, a C–Li bond undergoes a permutational exchange with a C–H bond of lower basicity to generate a new organolithium with a more stable C–Li bond. In contrast, deprotonating lithiation of a C–H bond without sufficient acidity is often facilitated by introduction of hetero-

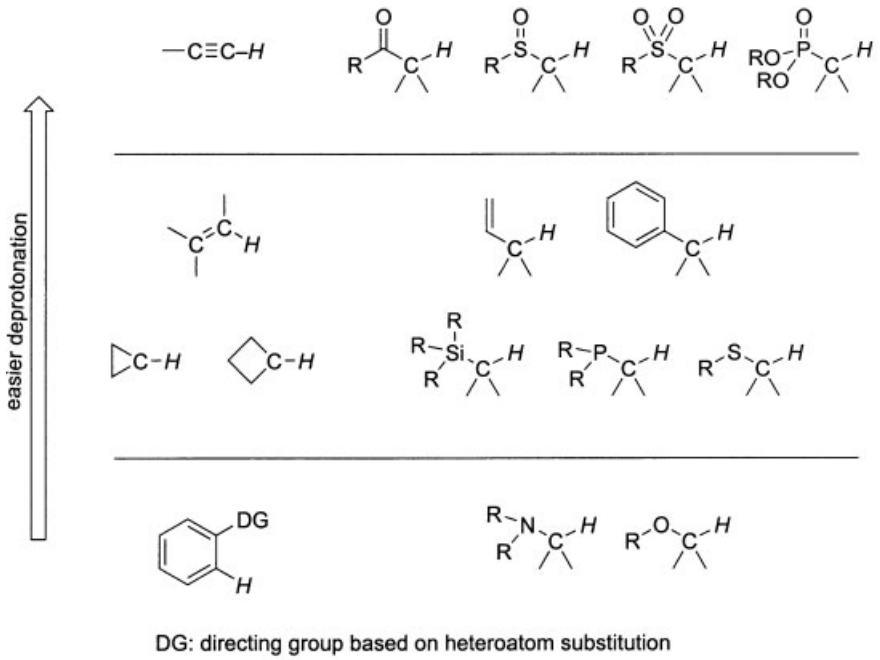
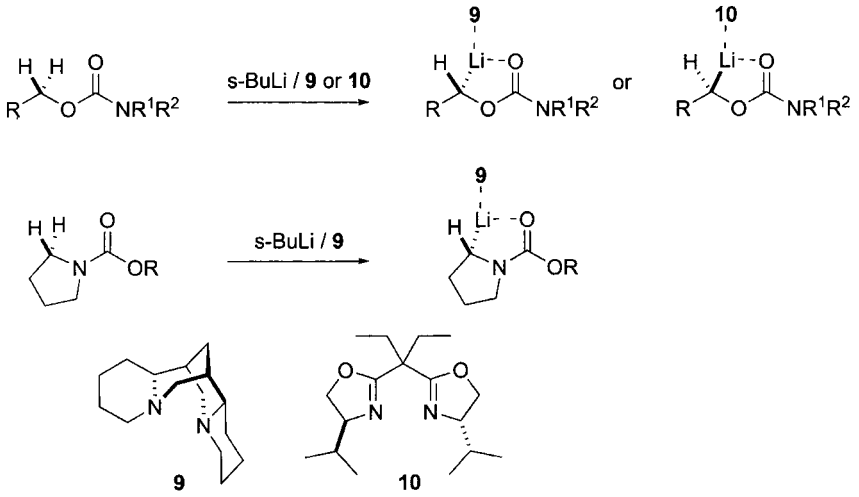


Chart 1.2 Reactivity in deprotonation



Scheme 1.8

atom functionality at a neighboring position, because the dynamic acidity of the C–H bond increases owing to intramolecular coordination of the electron-deficient lithium atom by the adjacent heteroatom. Readily available alkyllithium compounds such as *n*-, *s*-, and *t*-BuLi are sufficiently basic for deprotonating lithiation of a wide range of organic substrates. The feasibility of the deprotonation of such substrates decreases in the order illustrated in Chart 1.2.

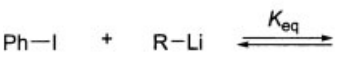
It should be noted that lithium amides, including lithium diisopropylamide (LDA) and lithium 2,2,6,6-tetramethylpiperidide (LTMP), are also used for the deprotonating lithiation, because of their high basicity, especially when selective deprotonation by organolithium compounds is hampered by their nucleophilicity. Alkyllithium compounds with an sp^3-hybridized C–Li bond are synthetically valuable because they can be prepared enantioselectively by use of organolithium compounds modified with (–)-sparteine **9** or (S,S)-bis(oxazoline) **10** as chiral deprotonating agents [34–39] (Scheme 1.8).

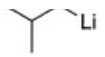
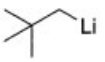
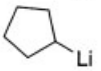
1.3.3.2 **Halogen–Lithium Exchange**

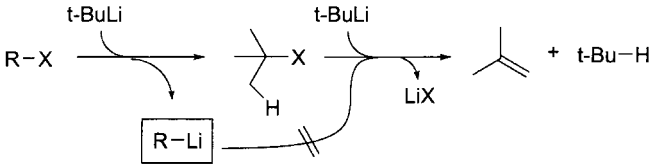
Halogen–lithium exchange is an equilibrium process favoring formation of the more stable, less basic, organolithium compounds. As shown in Tab. 1.5, the equilibrium constants for iodine–lithium exchange of PhI with different organolithium compounds (RLi) [40] can be correlated with the pK_a of RH.

Halogen–lithium exchange is useful for generation of organolithium compounds unless the organohalogen compounds formed in the exchange electrophilically quench the desired organolithium compounds. This problem is solved by use of two equivalents of *t*-BuLi; this has become a standard means of preparation

Tab. 1.5 Odine–lithium exchange and pK_a



RLi	K_{eq}	pK_a	RLi	K_{eq}	pK_a
	4×10^{-3}	36.5		4×10^{4}	42
PhLi	1	37		3×10^{5}	42
	10	39		10^{6}	43
	3×10^{3}	42		10^{7}	44
	7.5×10^{3}	42			



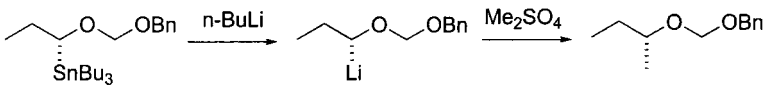
Scheme 1.9

of organolithium compounds by halogen–lithium exchange. An extra equivalent of *t*-BuLi not only makes the exchange irreversible but also protects the desired organolithium sacrificially. Thus the *t*-BuX formed in the exchange is quickly converted into harmless isobutane and isobutylene, as shown in Scheme 1.9 [41, 42].

The rate of halogen–lithium exchange decreases in the order RI > RBr > RCl >> RF, and the last two are not synthetically useful, because of their high tendency to undergo dehydrohalogenation. Halogen–lithium exchange of aryl or vinyl bromides and their iodo congeners, leading to organolithium compounds with an sp^2-hybridized C–Li bond, and that of alkyl iodides to an sp^3-hybridized C–Li bond are of great synthetic value. Owing to the mildness of this reaction even organolithium compounds with other polar functional groups can be generated. It should be noted that halogen–lithium exchange is accelerated by the presence of ethereal solvents, and the best solvent systems for use with alkyl halides are ether–pentane mixtures. Although TMEDA accelerates halogen–lithium exchange, it is not advisable to use because it also further accelerates deprotonation.

1.3.3.3 **Transmetallation**

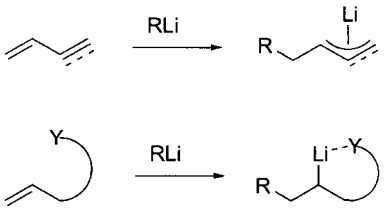
Several organometallic compounds, including B, Si, Sn, Pb, Sb, and Hg, are known to undergo transmetallation with organolithium compounds; a related exchange reaction can also be found in organochalcogenides and organophosphorus compounds. In this area the term "transmetallation" is, however, almost synonymous with tin–lithium exchange, because of its great synthetic potential. Organolithium compounds react rapidly and reversibly with organotin compounds, exchanging the alkyl group of the organolithium compound for one of their alkyl groups. The tin–lithium exchange proceeds via an ate complex and produces the most stable organolithium [43, 44]. Notably, transmetallation of chiral *α*-alkoxystannanes has been widely used to generate enantio-enriched *α*-alkoxyorganolithium compounds [45]; this reaction is quite likely to proceed with retention, as shown in Scheme 1.10.



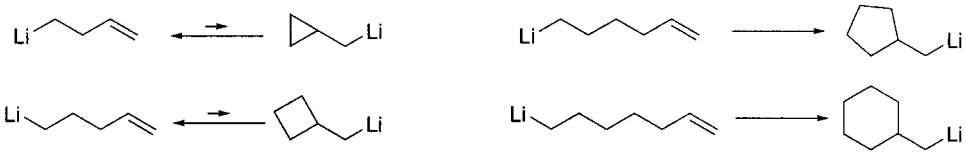
Scheme 1.10

1.3.3.4 Carbolithiation

The addition of an organolithium to an unactivated, non-polarized alkene can provide access to a new organolithium compound. This carbolithiation is a viable synthetic method, unless the product organolithium undergoes further carbolithiation leading to undesirable anionic polymerization. Carbolithiation is an equilibrium process favoring formation of the more stable, less basic organolithium compounds, and the rate of carbolithiation to an alkene essentially decreases in the order tertiary > secondary > primary organolithium. Intermolecular carbolithiations proceed smoothly with functionalized alkenes whose product organolithium compounds can be stabilized, either by conjugation or by coordination (Scheme 1.11). Unfortunately, however, their synthetic utility is limited, because of varying regioselectivity depending on the substrate structure. In contrast, several useful intramolecular carbolithiations of unfunctionalized alkenyllithium have been reported. Although organolithium compounds bearing a three- or four-membered ring at a position *α* to the C–Li bond undergo rapid ring-opening to give 3-butenyllithium or 4-pentenyllithium, for which anionic cyclization is difficult without careful design of the starting material, both five- and six-membered rings can be formed from 5-hexenyllithium and 6-heptenyllithium, respectively, and the corresponding cyclized organolithium compounds do not undergo a reverse ring-opening reaction (Scheme 1.12). The anionic cyclization of 5-hexenyllithium has been extensively studied and is now widely used as a synthetic method for the formation of five-membered carbocyclic rings [46, 47] (Tab. 1.6, Scheme 1.13). Finally, it should be noted that activation of the starting material by TMEDA, DABCO, or (–)-sparteine is sometimes advantageous, and chiral activators such as (–)-sparteine enable enantioselective carbolithiation [48, 49] (Scheme 1.14).

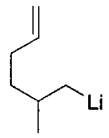
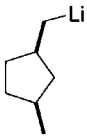
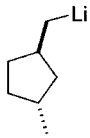
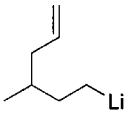
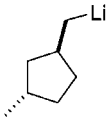
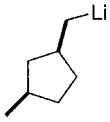
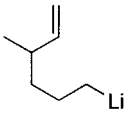
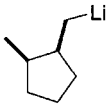
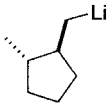


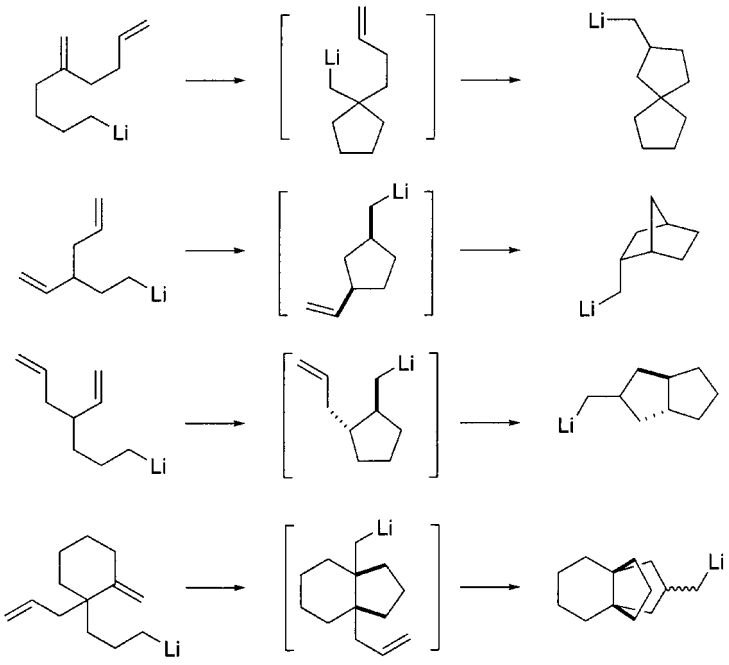
Scheme 1.11



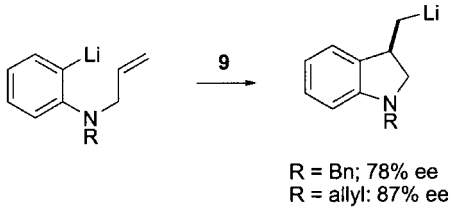
Scheme 1.12

Tab. 1.6 Stereoselectivity for carbolithiation of 5-hexenyllithium compounds

5-Hexenyllithium	*Cyclopentylmethyllithium*		*dr*
			1 : 10
			1 : 10
			1 : 12



Scheme 1.13

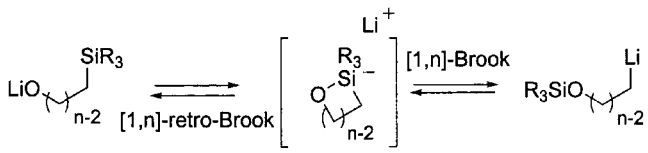


Scheme 1.14

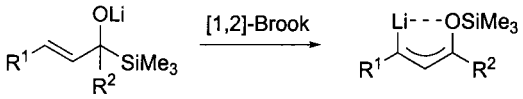
1.3.3.5 Miscellaneous

Siloxy-substituted Allyllithium Compounds via [1,2]-Brook Rearrangement

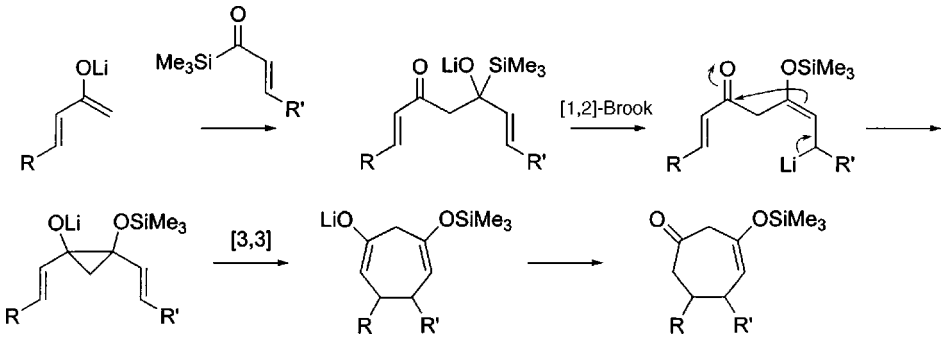
Organolithium compounds with siloxy groups at different positions can be prepared by [1,*n*]-Brook rearrangements ($n=2$–5) of lithium alkoxides bearing a C–Si bond (Scheme 1.15); these reactions are generally believed to proceed intramolecularly via pentacoordinate silicon-containing intermediates and to be driven by the favorable formation of the stronger Si–O bond compared with the Si–C bond. The equilibria resulting from the potential reverse process (retro-Brook rearrangements) limit their utility unless the product organolithium compound is also stabilized by introduction of second-row elements or conjugating groups. One of the most significant synthetic reactions is the preparation of siloxy-substituted allyllithium compounds via [1,2]-Brook rearrangements [50–55] (Scheme 1.16). Addition of a vinyllithium compound to an acylsilane and addition of a silyllithium compound to an enone both enable effective preparation of the requisite substrates, and thus the fabricated starting alkoxides undergo [1,2]-Brook rearrangement to afford the corresponding allyllithium compounds, which are synthetically valuable as homoenolate equivalents. An example of synthetic application of this procedure is shown in scheme 1.17 [55].



Scheme 1.15



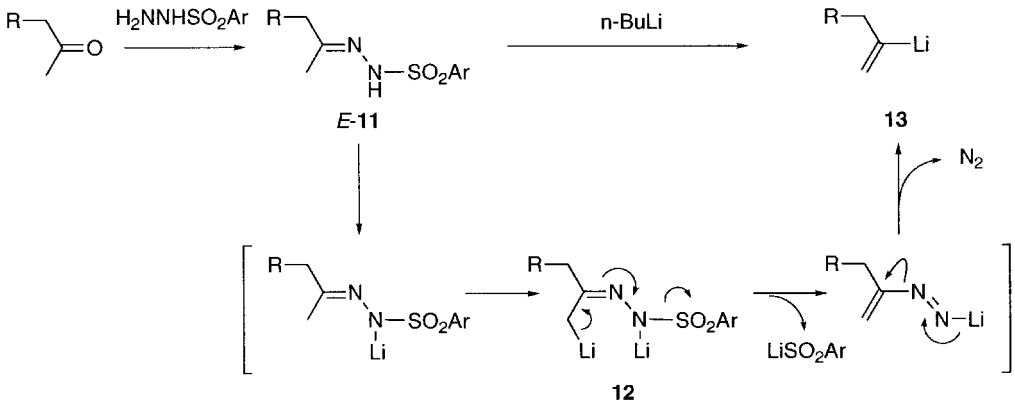
Scheme 1.16



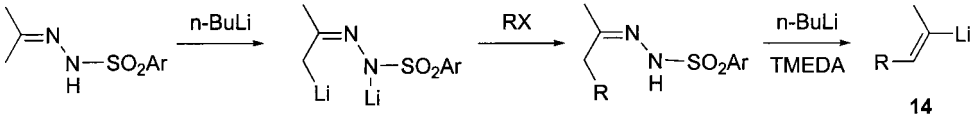
Scheme 1.17

Vinyllithium via the Shapiro Reaction

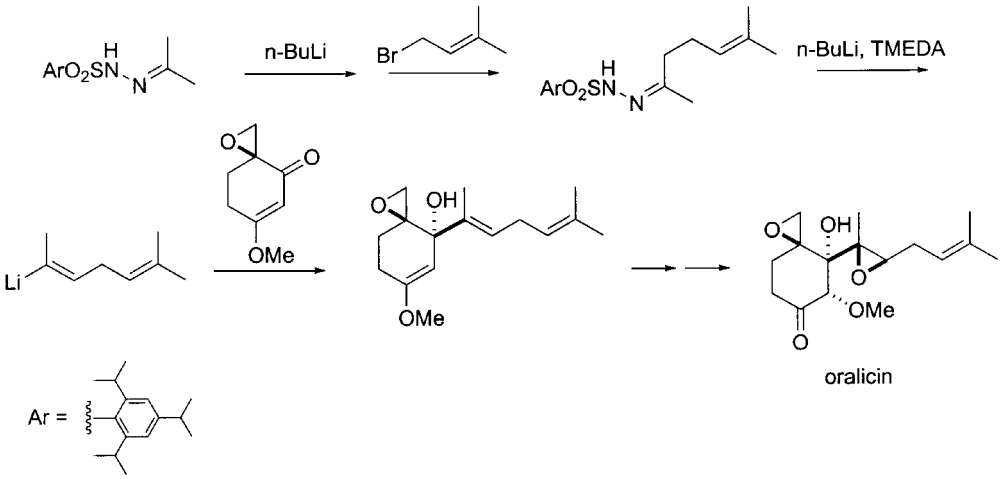
The reaction of arenesulfonylhydrazones (**11**) with alkyllithium compounds, known as the Shapiro reaction [56–58], is one of the most reliable ways of making vinyllithium reagents. Double-deprotonation of arenesulfonylhydrazone with two equivalents of BuLi leads to an azaenolate such as **12** which decomposes between 0 and 25 °C into vinyllithium compound **13** with extrusion of N_2 and lithium sulfinate (Scheme 1.18). Because **11** are readily accessible by condensation of ketones with arenesulfonylhydrazines, the Shapiro reaction enables efficient access to vinyllithium compounds from ketonic substrates. The second deprotonation usually occurs *syn* to the *N*-sulfonyl substituent, because of the kinetic activating effect of the lithiosulfonamide group. Therefore, two regioisomeric vinyllithium compounds **13** and **14** can be formed, depending on the stereochemistry of **11**, from unsymmetric ketones (Scheme 1.19). Condensation of an unsymmetrical ketone with arenesulfonylhydrazine usually yields an *E*-**11** whereas the *Z*-**11** can be prepared by deprotonation of a symmetric hydrazone then alkylation. Trisylhydrazone (**11**; Ar = 2,4,6-triisopropylphenyl) is the most suitable substrate among readily available arenesulfonylhydrazones, because it is resistant to ortholithiation by BuLi, which is typically formed if tosylhydrazone is used. Examples of synthetic application of this procedure are shown in Schemes 1.20 and 1.21 [59, 60]. It should be noted that related hydrazones based on 1-amino-2-phenylaziridine are useful alternatives to arenesulfonylhydrazones [61] and are sometimes superior for alkene synthesis, because they need only a catalytic amount of LDA [62] (Scheme 1.22).



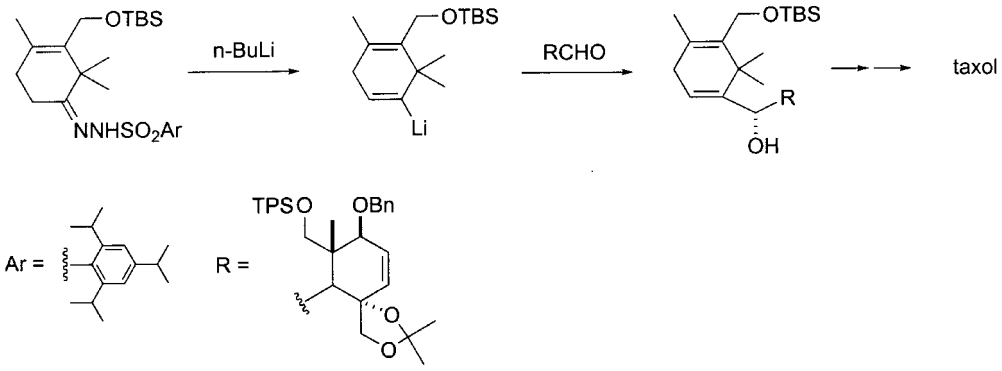
Scheme 1.18



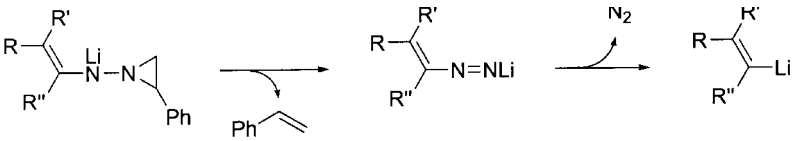
Scheme 1.19



Scheme 1.20



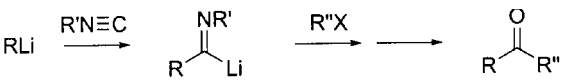
Scheme 1.21



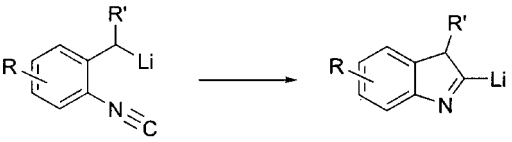
Scheme 1.22

Acyllithium and Iminoacyllithium using CO and Isonitriles

Carbon monoxide, and isonitriles bearing no α-hydrogen atoms, have been known to undergo insertion into C–Li bonds to produce acyllithium and iminoacyllithium compounds. While acyllithium compounds are too reactive as intermediates to be used in practical synthetic reactions unless the starting material is carefully designed, iminoacyllithium compounds can usually be used as an acyl anion equivalent for preparation of a variety of carbonyl compounds [63–65] (Scheme 1.23). They are also useful for preparation of nitrogen-containing compounds; one of the most elegant examples is the indole synthesis based on the intramolecular reaction of (*o*-lithiomethyl)phenylisonitriles [66, 67] (Scheme 1.24).



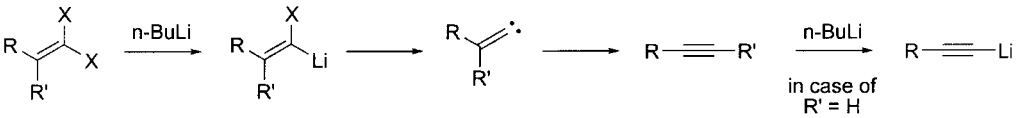
Scheme 1.23



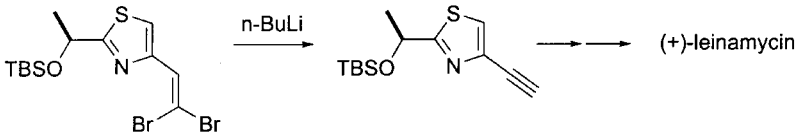
Scheme 1.24

Alkynyllithium Compounds from Aldehydes

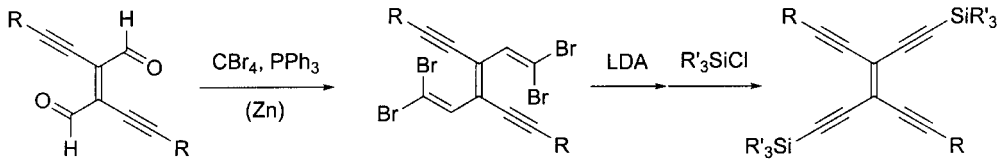
Vinyllithium compounds with a halogen in the α-position, which are readily accessible by halogen–lithium exchange of *gem*-dihaloalkenes with *n*- or *t*-BuLi, undergo a Fritsh-Buttenberg-Wiechell-type rearrangement to give alkynes when at least one of the two β-substituents is aryl, alkenyl, cyclopropyl, or H [68] (Scheme 1.25). The hydride shift in 1-bromo- and 1-chlorolithioalkenes occurs at temperatures above –70 °C, and alkynyllithium compounds can be obtained by subsequent deprotonation when excess BuLi is used in the initial halogen–lithium exchange. The combination of this reaction with the Corey-Fuchs method [69] for preparation of *gem*-dibromoalkenes from aldehydes with CBr_4–PPh_3 reagents is a particu-



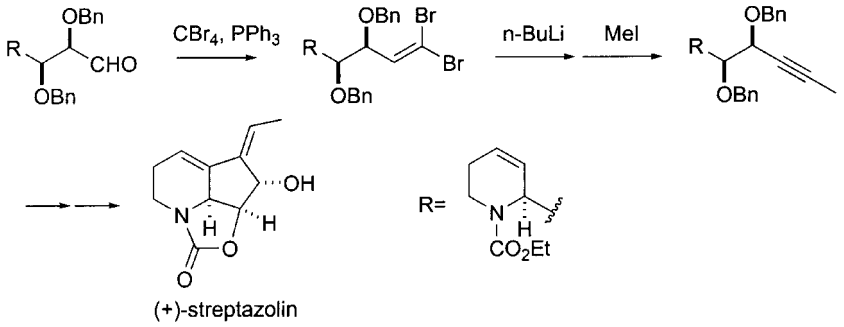
Scheme 1.25



Scheme 1.26



Scheme 1.27



Scheme 1.28

larly valuable route for converting aldehydes into alkynes in two steps. Examples of synthetic application of this procedure are shown in Schemes 1.26–1.28 [70–72].

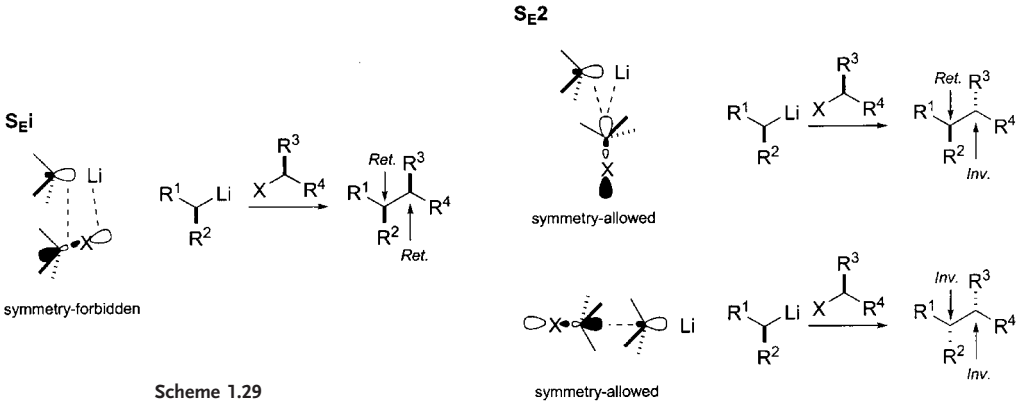
1.4 Methods for Construction of Carbon Frameworks by Use of Organolithium Compounds

1.4.1 Overview

As a natural consequence of the conversion of a C–Li bond into a less reactive Y–Li bond organolithium compounds become either carbanion synthetic equivalents toward electrophiles or reactive starting materials for subsequent skeletal rearrangement. Although numerous examples of
C–H, C–C, and C–heteroatom bond-forming reactions based on such reactivity are known, one can distinguish reactions in which organolithium compounds must be used from those that are possible with other organometallic reagents. Synthetically we will focus on methods characteristic of organolithium compounds and not mention those in which organolithium compounds are probably not the most suitable reagents. In this section, we first mention stereospecificity in the reaction of organolithium compounds with electrophiles, which serves as the basis of a strategy for stereoselective construction of a new carbon framework. In the illustrative examples that follow it will become clear that organolithium chemistry is now enjoying a wide range of application in stereoselective organic synthesis, taking advantage of effective methods for generating enantio-enriched organolithium compounds.

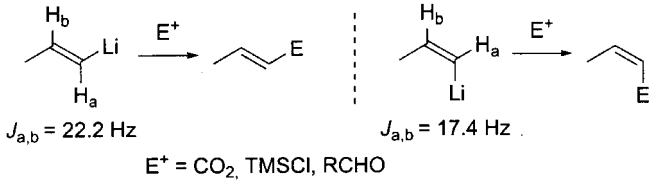
1.4.2 Stereospecificity

Possible pathways for electrophilic substitution of organolithium compounds are formally divided into two classes, depending upon whether cleavage of a C–Li bond and formation of a C–E bond occur sequentially or concurrently. The former pathway (S_E1 mechanism) can proceed via single-electron transfer, inevitably resulting in complete loss of stereospecificity. The latter affords two possibilities, referred to as S_Ei and S_E2, respectively [7, 8, 73] (Scheme 1.29). The S_Ei-type mechanism would proceed via a symmetry-forbidden transition state; it involves an interaction between the lithium cation and the leaving group X and hence requires retention of stereochemistry at the electrophilic center. In contrast, the symmetry-allowed S_E2-type mechanism, which operates most frequently, gives rise to inversion at the electrophilic center, because there is no interaction between Li and X in the transition state. In this mechanism, the stereochemistry at the nucleophilic center can be either retentive or invertive, although the former examples dominate.

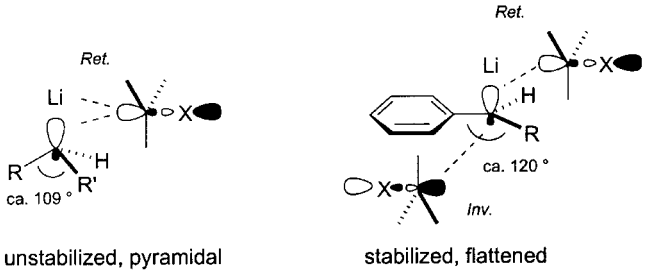


Scheme 1.29

Because stereospecificity does not become a matter of concern unless the organolithium itself is configurationally stable, only organolithium compounds with at least some configurational stability are dealt with herein. Before going into the detail of the stereochemistry at the nucleophilic center of the Li-bearing sp^3-hybridized carbon, that of the Li-bearing sp^2-hybridized carbon is worth noting. With use of two stereoisomeric alkenyllithium compounds whose geometry was confirmed by their NMR coupling constants the reaction of alkenyllithium compounds proceeds reliably with retention of stereochemistry [74] (Scheme 1.30). Likewise, the reaction of alkyllithium compounds generally proceeds in a highly retentive manner (S_E2-Ret.). The stereospecificity changes dramatically, however, when the alkyl moiety in the alkyllithium compounds has a π-system that can stabilize the adjacent C–Li bond. For such C–Li bonds, typically found in benzylic or allylic organolithium compounds (stabilized organolithium compounds), there is a greater possibility of attack by electrophiles on the rear lobe, because more pronounced p-character, owing to the stabilization, should increase the planarity of its nucleophilic center (Scheme 1.31). Accordingly, several enantio-enriched, stabilized organolithium compounds have been found to undergo inversion of configuration at their nucleophilic center on treatment with electrophiles (S_E2-Inv.). Unfortunately, however, mechanistic proposals accounting for each individual stereochemical outcome hinge on the structure of the nucleophiles and electrophiles, and some uncertainty remains in this area.

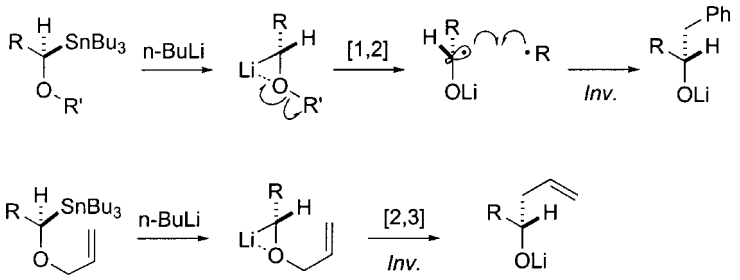


Scheme 1.30



Scheme 1.31

It should be noted that a high level of inversion of stereochemistry at the nucleophilic center (S_E2-Inv.) is usually observed in Wittig rearrangements, even though the starting organolithium compounds are non-stabilized (non-benzylic or allylic organolithium compounds) [75–80]. Wittig rearrangements, in which a lithium atom in lithiated allylic or benzylic ethers migrates from C to O, might, presumably, be facilitated by pre-coordination of ethereal oxygen to the electron-deficient Li atom, which enables the least motion of Li in the transition states (Scheme 1.32). Accordingly, migrating allylic or benzylic groups favor attack on the rear lobe of Li-bearing carbon.



Scheme 1.32

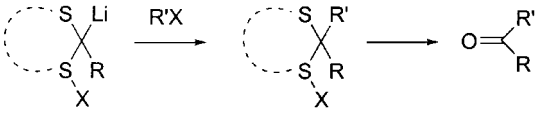
1.4.3 Synthetic Application

1.4.3.1 C–C Bond Formation: Conversion of C–Li to Halogen–Li

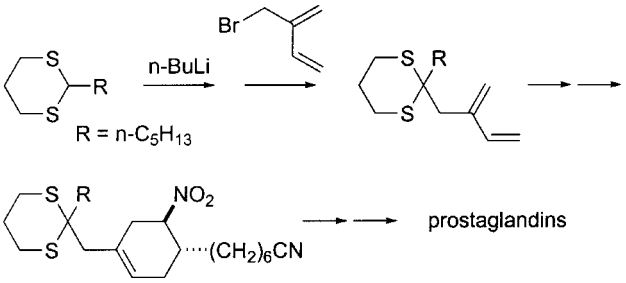
Organolithium compounds can react with a variety of halogen (X)-containing organic compounds to give C–C bond-formation products with the concomitant formation of LiX (Scheme 1.33).

Scheme 1.33

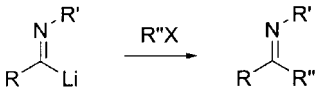
Akyl halides without acidic β-hydrogen electrophilically alkylate organolithium compounds, giving the corresponding C–C(sp^3) coupling products. MeI, allyl halides, and benzyl halides are typical alkylating agents which are sufficiently reactive to be used alone whereas others often require addition of highly coordinating solvents such as HMPA for successful C–C(sp^3) coupling. Because this type of reaction using acylanion equivalents is of great synthetic importance [81], several examples are shown here [63–65, 82] (Schemes 1.34–1.36).



Scheme 1.34

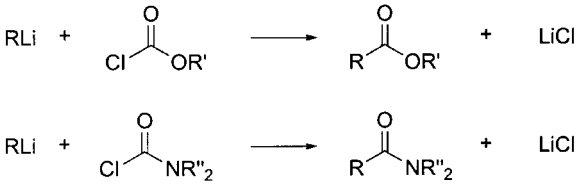


Scheme 1.35



Scheme 1.36

Esters or amides can be prepared by reaction of a wide variety of organolithium compounds with chloroformates or chlorocarbamates, which can be regarded as halogen (X)-containing electrophiles, leading to C–C(sp^2) coupling products (Scheme 1.37).



Scheme 1.37

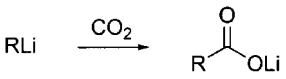
Acid halides or imidoyl halides are also basically good electrophiles for C–C(sp^2) coupling, but organolithium compounds are unsuitable nucleophiles for these reactions, because the product ketones or imines are not sufficiently inert to organolithium compounds and it is difficult to protect them from further nucleophilic attack. Alkenylhalides and alkynylhalides have little electrofugal activity at their halogen-containing carbon and their C–C(sp^2) or C–C(sp) coupling reactions using organolithium compounds are of no general importance.

1.4.3.2 C–C Bond Formation: Conversion of C–Li to O–Li

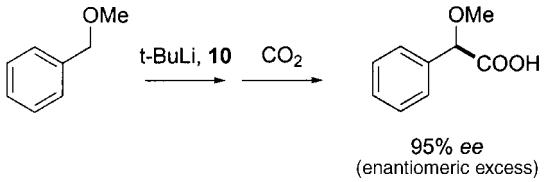
The reaction of organolithium compounds with oxygen-containing organic compounds in which the conversion of a C–Li bond to a less reactive O–Li bond provides a fundamental driving force and constitutes a major part of synthetic organic transformations. Several useful reactions in which an O–Li bond is finally formed can be classified as C–C(sp^2) or C–C(sp^3) coupling reactions, and are outlined in this order.

The C–C(sp^2) Coupling Reaction

On treatment with CO_2 organolithium compounds can be converted to the corresponding lithium carboxylates. The high efficiency and operational simplicity of this reaction make it a general route for carboxylic acid synthesis [83–86] (Scheme 1.38). For example, optically active carboxylic acids are accessible by deprotonation followed by the subsequent CO_2 treatment in the presence of **10** [85] (Scheme 1.39).



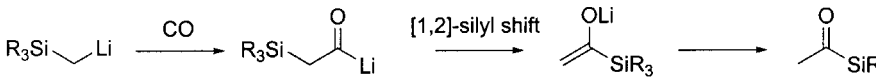
Scheme 1.38



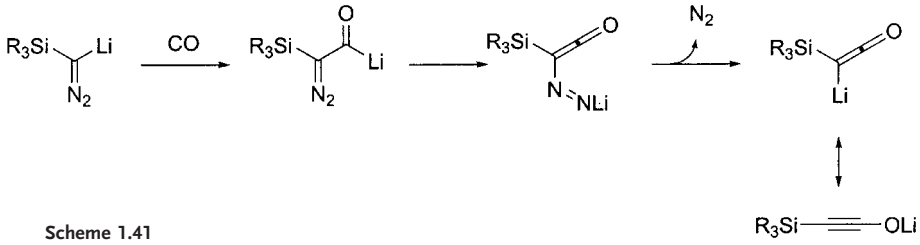
Scheme 1.39

The reaction of organolithium compounds with CO generates highly reactive acyllithium compounds which usually decompose into several compounds. The reaction becomes controllable, however, on introduction of a silyl group into these transient intermediates. *α*-Silylalkyllithium compounds react with CO, efficiently affording lithium enolates of acylsilanes [87] (Scheme 1.40). The potential of silyl groups for 1,2-anionic rearrangement is manifested after insertion of CO to con-

vert intermediary acyllithium compounds into the lithium enolates. As a result of this C–C(sp^2) coupling reaction a variety of acylsilanes or their silyl enolates can be obtained in high yield. Introduction of diazo group in addition to the silyl group at the Li-bearing carbon alters the reactivity of acyllithium compounds completely. Lithiated silyldiazomethanes react with CO to give the corresponding acyllithium compounds, which now undergo anionic Wolff-type rearrangement instead of 1,2-silicon shift, to give lithium silylynolates efficiently, as shown in Scheme 1.41 [88].

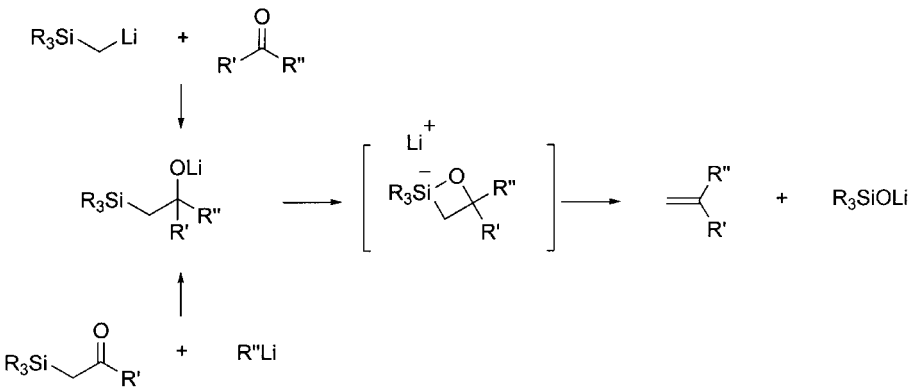


Scheme 1.40



Scheme 1.41

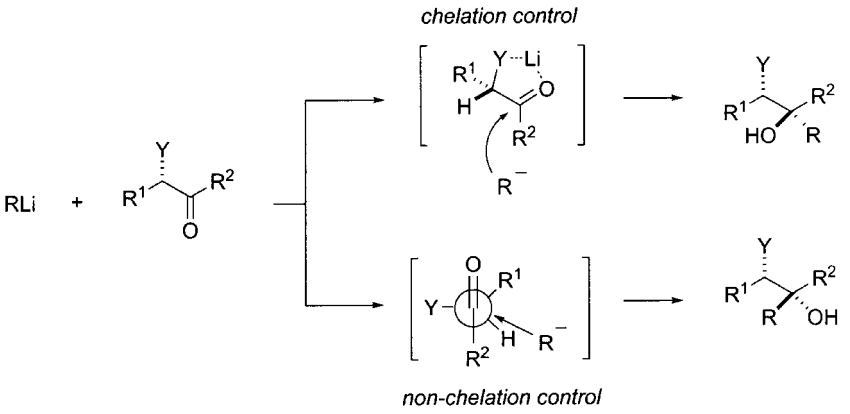
Another, final, example of C–C(sp^2) coupling is the so-called Peterson olefination [89, 90] (Scheme 1.42). Lithium *β*-silylethylalkoxides, accessible either by reaction of *α*-silylalkyllithium compounds with carbonyl compounds or of organolithium compounds with *α*-silylcarbonyl compounds, readily extrude lithium siloxides to leave C=C double-bond products. *α*-Silylalkyllithium compounds can therefore be regarded as alkylidenating agents for carbonyls.



Scheme 1.42

The C–C(sp^3) Coupling Reaction

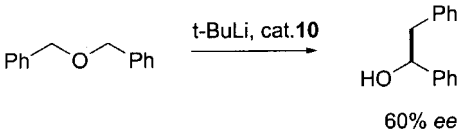
Organolithium compounds react with a wide variety of carbonyl compounds, including aldehydes, ketones, and esters, to give the C–C(sp^3) coupling products [91]. In their reactions with prochiral aldehydes and ketones stereocontrol of the newly formed lithium alkoxides of chiral secondary and tertiary alcohols is an important issue that should be addressed. In general, stereoselective generation of chiral organolithium compounds in an enantio-enriched form, or chiral modification of achiral organolithium compounds by the external chiral ligand do not lead to high stereocontrol. On the other hand, however, introduction of stereogenic center into the carbonyls at neighboring positions leads to some level of diastereofacial selectivity. The origin of such stereocontrol can be interpreted in terms of chelation or non-chelation control [92] (Scheme 1.43). Chelation control, in which the facial selectivity is effected by coordination of a lithium atom to the heteroatom substituent on the stereogenic center and to the carbonyl oxygen, does not exert such high stereoselectivity for organolithium compounds as it does for other organometallic reagents. In contrast, non-chelation control, in which steric hindrance offered by substituents on the stereogenic center determines facial selectivity, is important in the reaction with organolithium compounds and the diastereoselectivity is usually predictable by the Felkin-Anh model.



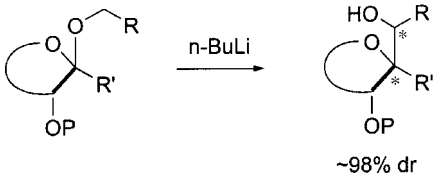
Scheme 1.43

Wittig rearrangements are an interesting class of C–C(sp^3) coupling reaction which are also driven by the favorable formation of an O–Li bond from a C–Li bond. Of particular synthetic importance are [1,2]- and [2,3]-Wittig rearrangements [93–96]. 1,2-Migration of an alkyl group from oxygen to carbon in α-alkoxyorganolithium compounds, furnishing alkoxides, are known as the [1,2]-Wittig rearrangement and it is now well-established that this reaction proceeds via formation of radical pairs and their recombination. [1,2]-Wittig rearrangements have therefore become synthetically useful when both migrating group and the organolithium substituent are radical-stabilizing. They also have some level of stereospecificity, as mentioned pre-

viously. The stereochemical course of the Li-bearing carbon is invertive and that of migrating alkyl group is retentive. It should be noted that the radical recombination step can be enantio-controlled by the external chiral ligand. For example, [1,2]-Wittig rearrangements with dibenzyl ethers proceed in the presence of a catalytic amount of **10** to provide the corresponding chiral alcohols in good enantiomeric excesses (ees) [97] (Scheme 1.44). Acetals, including glucosides, extend the potential of [1,2]-Wittig rearrangement, because the stability of radicals at the anomeric center is beneficial to the formation of synthetically useful *C*-glucosides [98–100] (Scheme 1.45).

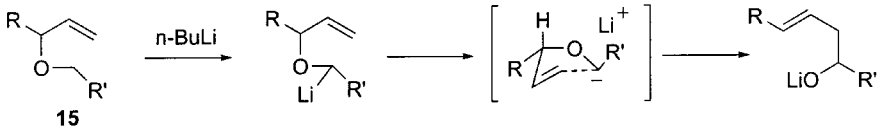


Scheme 1.44

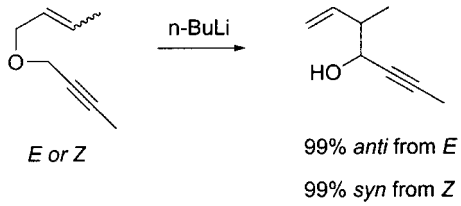


Scheme 1.45

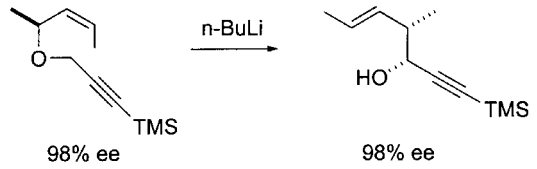
The mechanism of the vinylogous variant [2,3]-Wittig rearrangement in which *α*-allyloxyorganolithium compounds rearrange into lithium alkoxides of homoallyl alcohols differs substantially from that of [1,2]-Wittig rearrangement [101–105]. The [2,3]-Wittig rearrangement proceeds via a suprafacial six-electron pericyclic transition state which leads to its high stereochemical control on the allylic systems. In the [2,3]-Wittig rearrangement of secondary allyl ethers, e.g. **15**, *trans* homoallyl alcohols are generally obtained presumably because the R group favorably adopts a pseudoequatorial position in their envelope-like transition state (Scheme 1.46). On the other hand, the double bond geometry in crotyl ether systems can be translated into the *syn*/*anti*-relative stereochemistry in the products. The best stereospecificity was demonstrated in the reaction of crotyl propargyl ethers as illustrated in Scheme 1.47 [106, 107]. Furthermore, a high level of 1,3-chirality transfer is generally achieved in [2,3]-Wittig rearrangements of chiral non-racemic allyl ethers, owing to the suprafacial nature of this process (Scheme 1.48) [108]. In addition to the allylic stereocontrol, stereospecificity of the Li-bearing carbon in this process should be noted. As already mentioned, this reaction proceeds stereospecifically with inversion of stereochemistry at the Li-bearing carbon and stereoselective lithiation at the allyloxy-bearing carbon leads to enantioselective synthesis of *sec*-homoallyl alcohols. Lithiation using a chiral base or RLi-chiral coordinating agent is effective for this purpose [109–111] (Schemes 1.49, 1.50).



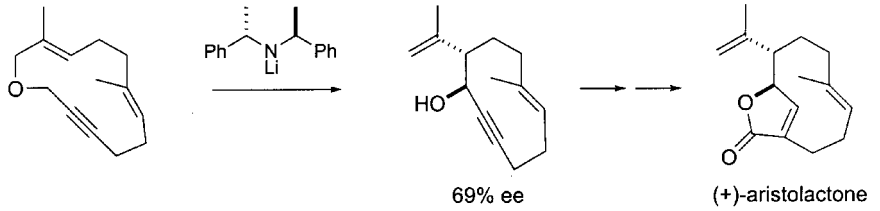
Scheme 1.46



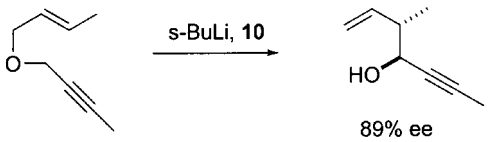
Scheme 1.47



Scheme 1.48



Scheme 1.49



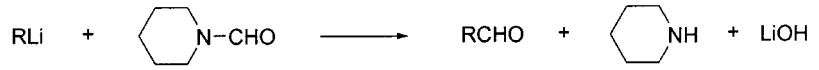
Scheme 1.50

1.4.3.3 C–C Bond Formation: Conversion of C–Li to N–Li

Similarly to Section 1.4.3.2, several useful C–C bond formation reactions, driven by the favorable formation of a nitrogen–lithium bond from a carbon–lithium bond, can be divided into the C–C(sp^2) coupling and C–C(sp^3) coupling reactions, and they are considered in this order.

C–C(sp^2) Coupling Reactions

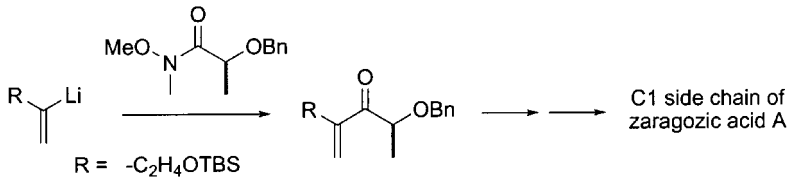
N-formyl dialkylamines can react as electrophilic formylating agents, because reaction of organolithium compounds with *N*-formyl dialkylamines selectively produces lithium alkoxides of *N,O*-hemiacetals which release aldehydes and dialkylamine on hydrolysis. Among various *N*-formyl dialkylamines, *N*-formylpiperidine is synthetically useful and a variety of organolithium compounds are convertible to the corresponding aldehydes [112] (Scheme 1.51).



Scheme 1.51

So-called Weinreb amides, higher analogs of *N*-formyl dialkylamines, are of particular importance. Weinreb amides, readily prepared by condensation of *N*-methoxymethylamine and carboxylic acids, undergo nucleophilic attack of organolithium compounds to generate intermediary *N,O*-acetals which produce the corresponding ketones on hydrolysis (Scheme 1.52). A methoxy substituent in the Weinreb amide is situated to stabilize the *N,O*-acetal structure by chelation and to prevent further nucleophilic attack on the carbonyl group [113, 114]. An example of synthetic application of this procedure is shown in Scheme 1.53 [100].

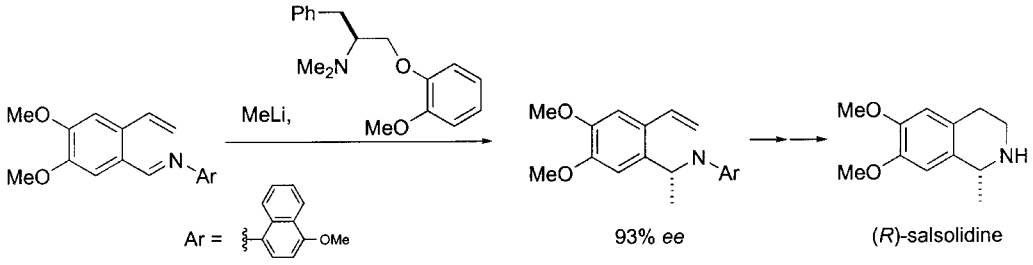
Scheme 1.52



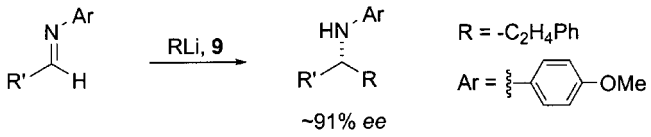
Scheme 1.53

C–C(sp^3) Coupling Reactions

Organolithium compounds undergo C–C(sp^3) coupling with aldimines and ketimines, providing lithium amides of *sec*- and *tert*-amines, respectively. In contrast with the oxa analog, enantioselective addition of organolithium compounds to prochiral imines has been developed and higher levels of stereocontrol have been achieved by chiral modification of organolithium compounds with external chiral ligands [115]. Examples of synthetic application of this procedure are shown in schemes 1.54 and 1.55 [116, 117].

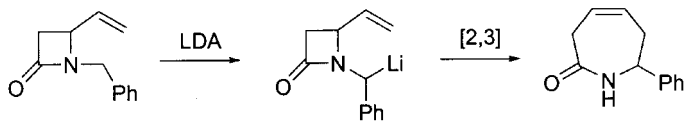


Scheme 1.54



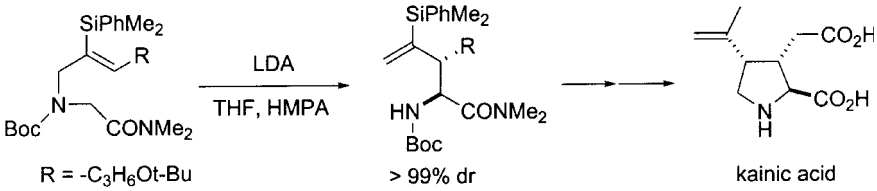
Scheme 1.55

Aza-Wittig rearrangements, regarded as nitrogen analogs of Wittig rearrangements, are also an important class of synthetically valuable C–C(sp^3) bond-forming reactions. Successful aza-Wittig rearrangements are designed to compensate for the relatively small energy gained by aza-Wittig rearrangement compared with that of the original Wittig rearrangement (R_2NLi compared with ROLi). The strain released in small ring systems has been used in this reaction. For example, [2,3]-type rearrangements with vinyl-substituted β-lactams and aziridines proceed smoothly to give the corresponding unsaturated ε-caprolactams [118] and piperidines [119], respectively (Schemes 1.56 and 1.57), and [1,2]-type rearrangements with phenyl-substituted β-lactams afford saturated γ-butyrolactams in high yields [118]. It was discovered quite recently that use of HMPA significantly facilitates the aza-[2,3]-Wittig rearrangement of acyclic allyl amines with no ring strain and leads to highly stereoselective synthesis of homoallylic amines [120, 121] (Scheme 1.58).



Scheme 1.56

Scheme 1.57



Scheme 1.58

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2
Rubidium and Cesium in Organic Synthesis

Seijiro Matsubara

2.1
Introduction

Rubidium and cesium metals are strong electron donors. They release one electron easily to form ionic salts, in which they become +1 ions. Their ionic radii are the largest among the metal ions except for Fr and Ra – the Pauling radius for Rb^+ is 1.48 Å and that for Cs^+ is 1.69 Å. Their electron negativity is smallest among the elements (for both Rb and Cs it is 0.9). This large ionic radius and small electron negativity are the keys to understanding their characteristic properties in reagents. The salts tends to form "naked anions".

Use of rubidium in organic reactions is less common than that of cesium. Cesium compounds are important reagents in fluorine chemistry and are also used as unique bases in organic reactions.

2.2
Organo-, Silyl-, Germyl-, and Stannylmetal

Because rubidium and cesium are the strongest electron donors of the group 1 metals, preparations of the corresponding organometallic compounds by direct reductions of organic halides with metals tend to proceed by Wurtz coupling. Treatment of toluene with cesium metal gives benzylcesium with evolution of hydrogen [1]. Alkylrubidium and -cesium are normally prepared by transmetalation from dialkylmercury. Deprotonation by trialkylsilylmethylcesium also gives a variety of organocesium compounds. These organometallic compounds have received little attention because of their high instability.

Structural studies of allylmetal derivatives have also been performed [2]. In allyl compounds in ethereal solvents, the cesium ion is well solvated and an allyl anion is formed. Crystals of cyclopentadienyl rubidium and cesium, which complexed with 18-crown-6, have been isolated and analyzed by X-ray diffraction [3].

Compounds containing Si–Rb or Si–Cs bonds can be prepared by a direct reduction of chlorotriphenylsilane with rubidium or cesium metal (Scheme 2.1).

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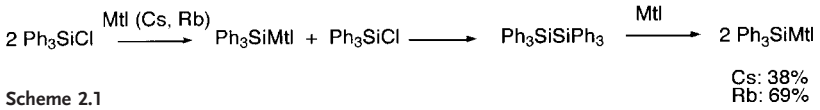
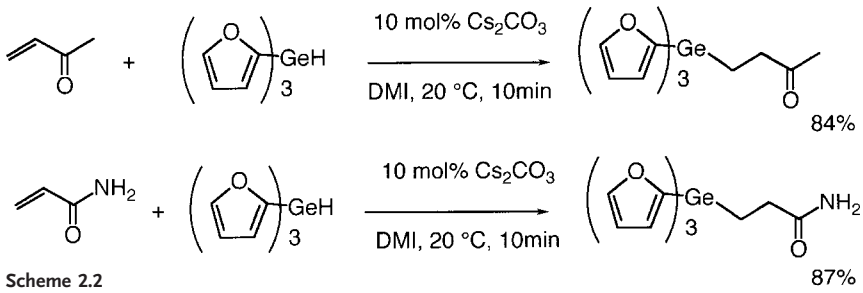
The reaction affords triphenylsilylrubidium and -cesium, via the disilane, in situ [4]. Trifurylgermane adds to *α,β*-unsaturated carbonyl compounds in the presence of catalytic amount of cesium carbonate (Scheme 2.2) [5]. The Ge–H bond in trifurylgermane releases a proton to form the Ge–Cs compound.

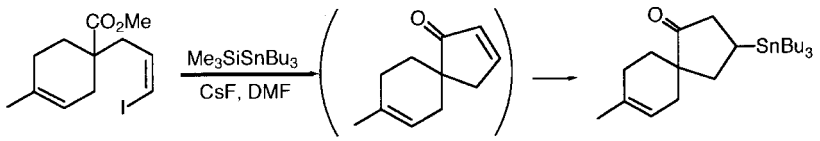


Scheme 2.1



Scheme 2.2

Alternatively, trialkylstannylcesium compounds can be prepared by fluoride ion-induced desilylation. Treatment of (trimethysilyl)tributylstannane with cesium fluoride affords a tributylstanyl anion. The anion reacts with a C–I bond to form a vinyl anion that promotes intramolecular cyclization [6]. The spiro ketone obtained is converted into a natural sesquiterpene acorone (Scheme 2.3).



Scheme 2.3

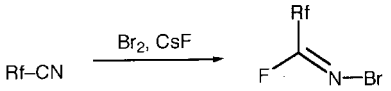
2.3 Fluoride Ion Source

Introduction of the fluorine atom into organic compounds has been important in organic syntheses. For this purpose the fluoride ion (F^-) has been regarded as the nucleophilic fluorination species to an organic molecule. It can, moreover, be used not only for nucleophilic introduction of a fluorine atom to organic compounds but also for desilylation. Although it might be assumed that a metal fluoride could be used as a source of fluoride ion, the strong affinity of the metal atom

for the fluoride ion often results in difficulty releasing the fluoride ion. The electron positive character and large ionic radius of cesium ion facilitate loss of the fluoride ion from the corresponding salt (CsF), especially in the presence of a coordinating solvent, and cesium fluoride has been widely used for this purpose.

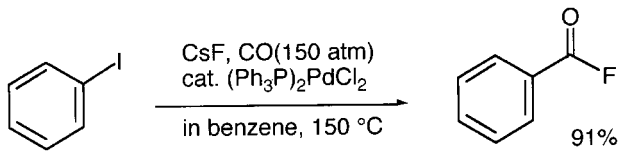
2.3.1
Nucleophilic Fluorination

Because of the low nucleophilicity of the fluoride ion, nucleophilic fluorination is not very easy. The reaction conditions and the reagent are, however, sufficiently mild to produce unstable compounds. Perfluoroalkylnitrile can be fluorinated with bromine and cesium fluoride (Scheme 2.4). The *N*-haloimines obtained are potentially unstable compounds [7].



Scheme 2.4

Although direct nucleophilic addition is limited because of the low nucleophilicity of the fluoride ion, a palladium-catalyzed reaction enables the weak nucleophile to participate the addition reaction. In the presence of cesium fluoride, palladium-catalyzed carbonylation of an aryl halide gives the acyl fluoride in good yield (Scheme 2.5) [8].



Scheme 2.5

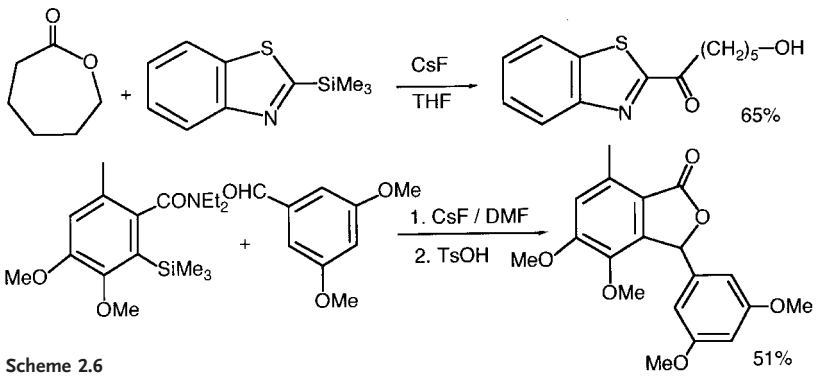
2.3.2
Desilylation Reactions

Desilylation with cesium fluoride has been the most common use of cesium compounds in organic synthesis. HI and tetraalkylammonium fluoride are also commonly used for desilylation but these reagents are difficult to use under anhydrous conditions. The cesium fluoride-induced reaction can be performed easily under anhydrous conditions, so desilylation produces carbanion-equivalent species which can be used for further C–C bond-forming reactions. The reaction seems to

form organocesium species, but care should be taken because the reactive species is sometimes a pentacoordinated silicate with a cesium ion. It should also be borne in mind that protiodesilylation is also an important transformation.

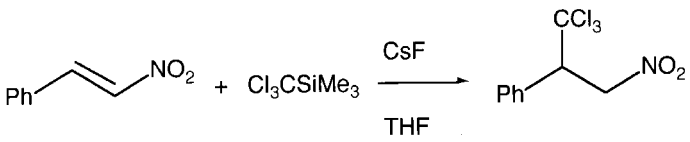
2.3.2.1 **Carbanion Equivalent Formation**

Carbanion equivalents with anion stabilizing groups are prepared by desilylation of the corresponding materials with cesium fluoride [9–15]. In Scheme 2.6 treatment of aryltrimethylsilanes with cesium fluoride affords carbanion equivalents which add to the carbonyl compounds. The reactive species are not simple organocesium compounds but react as nucleophilic carbanion equivalents.



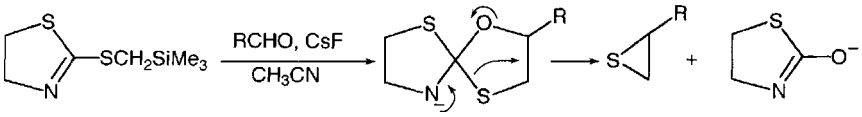
Scheme 2.6

Trichloromethyl(trimethyl)silane and cesium fluoride give the trichloromethyl nucleophile. This reacts with nitroalkenes by 1,4-addition (Scheme 2.7) [16]. Because the corresponding metal compounds, for example trichloromethyllithium or -magnesium, are too unstable to use even under mild conditions, this method is a convenient means of producing such anionic species.



Scheme 2.7

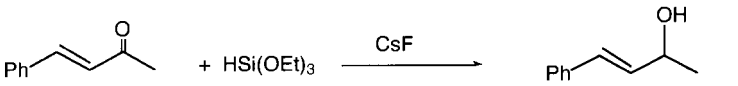
Scheme 2.8 shows a facile preparation of thiiranes. Desilylation with cesium fluoride induces formation of a sulfur-stabilized anion equivalent. This adds to the aldehyde and subsequent deoxygenation gives the thiirane [17].



Scheme 2.8

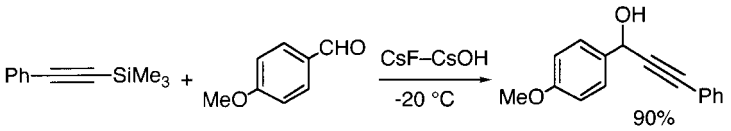
Desilylation with cesium fluoride also affords ylides, which can be used for the Wittig and Horner-Wadworth-Emmons reactions [18–20].

H–Si and C–Si bonds are activated by cesium fluoride to yield a hydride-equivalent species via a silicate intermediate. Enones are selectively reduced by 1,2-addition with cesium fluoride and triethoxysilane (Scheme 2.9) [21].



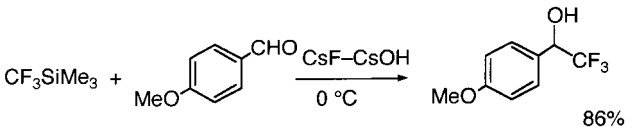
Scheme 2.9

The fused salt obtained from a mixture of CsF and CsOH undergoes desilylation much more effectively to give the corresponding anionic nucleophile [22]. In this process desilylation of the alkynyltrimethylsilane proceeds even at –20 °C and affords the acetylide equivalent (Scheme 2.10).



Scheme 2.10

Treatment of trifluoromethyl(trimethyl)silane with the fused salt gives the trifluoromethyl anion-equivalent species. This adds to the aldehyde in good yield to form the alcohol with a trifluoromethyl group (Scheme 2.11).



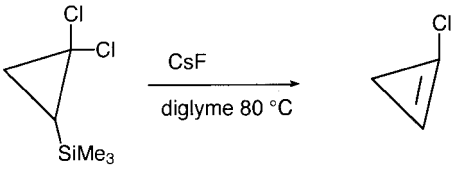
Scheme 2.11

Treatment of $Si(OEt)_4$ with cesium fluoride produces a base which is good mediator for 1,4-addition of amines and amides to enones (Scheme 2.12) [23].

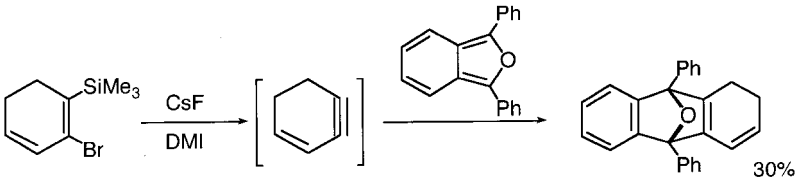
Scheme 2.12

2.3.2.2 **Desilylation-Elimination**

It is possible for organosilyl compounds with a leaving group at the β position to undergo E2-type reactions induced by cesium fluoride. In deprotonation-elimination, a strong base such as amide or alkoxide is required; the conjugated acid produced by deprotonation (e.g. amine or alcohol) may react with the elimination product. In the case of cesium fluoride-induced desilylation-elimination, the formed conjugated acid is silyl fluoride which is unreactive. The production of unstable products such as cyclopropene (Scheme 2.13), cyclohexene-3-yne (Scheme 2.14), or orthoquinodimethane has been reported [24–29].

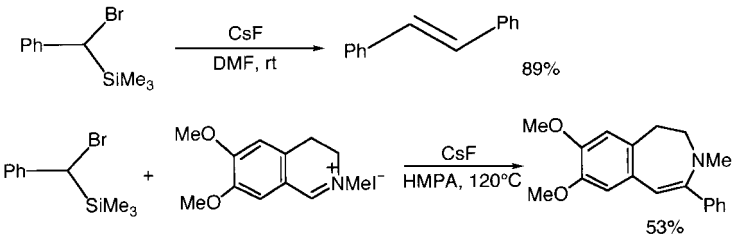


Scheme 2.13



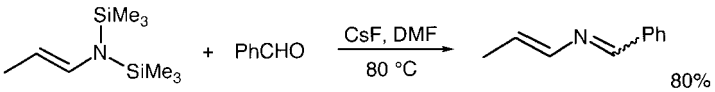
Scheme 2.14

α-Elimination as well as β-elimination has also been examined for production of carbene species [30]. The species obtained from α-trimethylsilylbenzyl bromide and cesium fluoride undergoes a self-coupling reaction and insertion into the C–N bond. These reactions can be explained by the formation of carbenoid species (Scheme 2.15).



Scheme 2.15

2-Aza-1,3-diene can be synthesized by treatment of an aldehyde with *N*,*N*-bis (trimethylsilyl)enamine in the presence of CsF. The reaction eliminates siloxane without forming water. This is an extremely useful means of producing such acid-sensitive compounds (Scheme 2.16) [31].

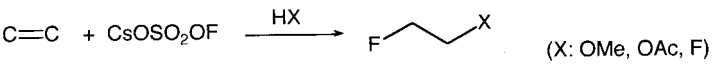


Scheme 2.16

2.4
Electrophilic Fluorination – Cesium Fluorosulfate

Electrophilic fluorination is regarded as a useful means of introducing a fluorine atom to an organic compound, but also suffers from the problem of finding a source of F^+. Fluorine gas seems to be the most convenient means of obtaining F^+, but is also a source of radicals. It is also difficult to handle in the laboratory, although it is common reagent in industry. Cesium fluoroxysulfate ($CsOSO_2OF$) fits for the purpose as a means of electrophilic fluorination and is reasonably stable for handling in the laboratory.

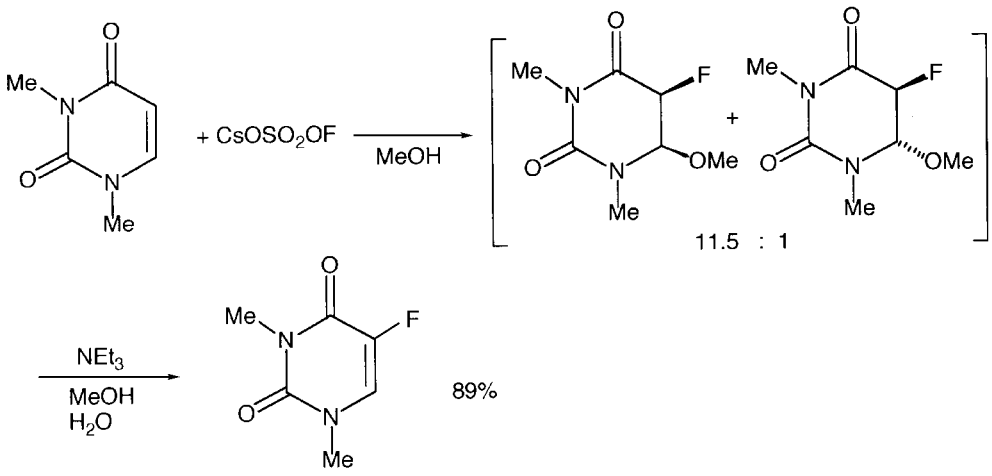
Alkenes can be converted into fluorinated products electrophilically with $CsOSO_2OF$, by incorporating solvents or external nucleophiles in the reaction (Scheme 2.17) [32].



Scheme 2.17

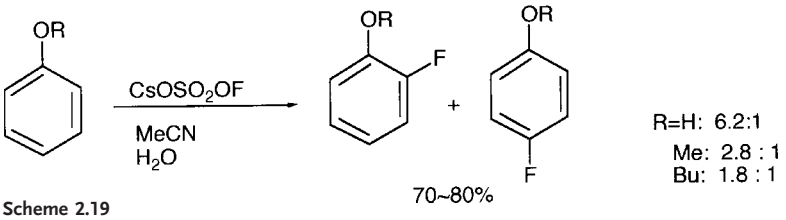
This reaction is mild enough to enable some functional groups to remain intact. It has, for example, been applied to the preparation of fluorinated uracil. Treatment of 1,3-dimethyluracil with $CsOSO_2OF$ in acetonitrile results in recovery of the starting material whereas in methanol a *cis* adduct is obtained diastereose-

lectively. Subsequent treatment with triethylamine affords 1,3-dimethyl-5-fluorouracil (Scheme 2.18) [33].



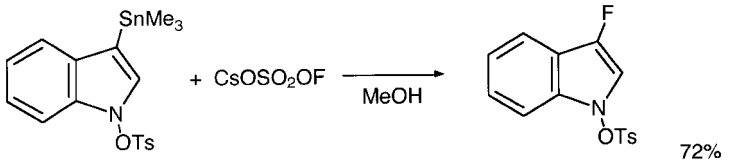
Scheme 2.18

Phenol is also fluorinated electrophilically with $CsOSO_2OF$ in acetonitrile. The fluorination occurs selectively at the *ortho* position (Scheme 2.19) [34].



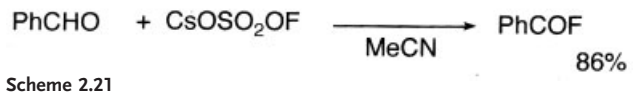
Scheme 2.19

Electrophilic fluorination of organotin compounds has also been examined. Organotin compounds can be oxidatively converted into the corresponding halides. In methanol trimethyltin-substituted alkenes are converted regiospecifically into the fluoroalkenes (Scheme 2.20) [35].



Scheme 2.20

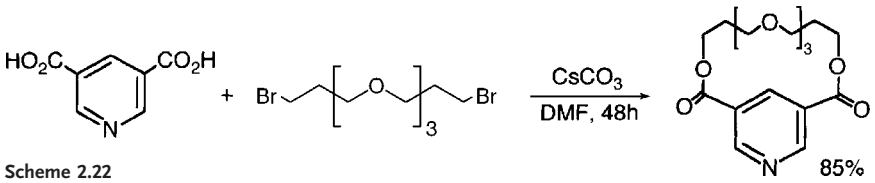
Aldehydes are converted into acid fluorides in good yields. The reaction pathway might be via a radical mechanism (Scheme 2.21) [36].



Scheme 2.21

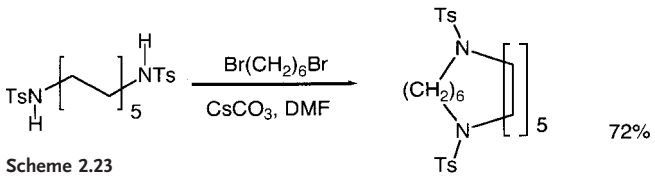
2.5 Cesium Salts as Bases

Cesium carbonate and fluoride are often used as bases. The cesium ion plays a characteristic role as a counter ion. The ionic radius of a cesium ion is ideal for the template effect for polyethers of particular ring size [37]. A typical example is the formation of a 20-membered polyether. The yield is excellent compared with the other large ring annulation method (Scheme 2.22).



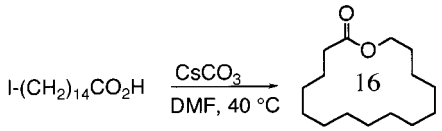
Scheme 2.22

The basicity of cesium carbonate is strong enough to deprotonate tosyl amides [38]. Although lithium, calcium, and rubidium carbonates have also been examined for use of the same reaction for cyclization of ditosyl amide, they do not work efficiently compared with cesium carbonate (Scheme 2.23). Cesium carbonate is also important base for the preparation of calix[4]arenes and carcerands [39].



Scheme 2.23

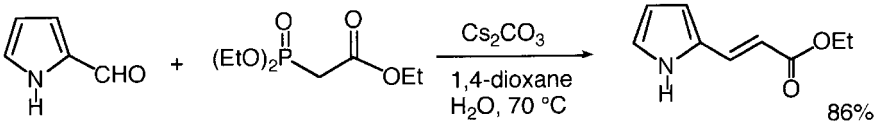
The superiority of the cesium ion has also been demonstrated for simple lactonization. Lactonization of 15-iodopentadecanoic acid has been examined with a variety of metal carbonates at a concentration of 0.1 M. Cesium carbonate gives outstanding results among the alkali metal compounds for formation of a lactone (Scheme 2.24) [40]. The "naked" carboxylate anion might be present when cesium carbonate is used.



Li_2CO_3	~0%
Na_2CO_3	54
K_2CO_3	67
Rb_2CO_3	68
Cs_2CO_3	80
Ag_2CO_3	53
Tl_2CO_3	64

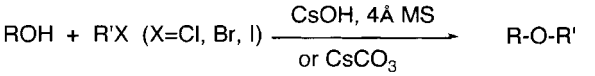
Scheme 2.24

Cesium carbonate has also been used as the base used to form the Horner–Wadsworth-Emmons reagent (Scheme 2.25) [41]. Even in the presence of an N–H bond in the substrate the reaction proceeds with deprotonation of the crucial carbon atom. The transformation gives an *α,β*-unsaturated ester with an amine substituent.

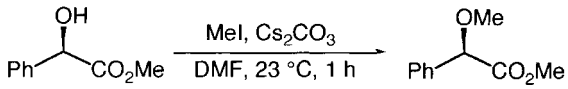


Scheme 2.25

Alkylation of alcohols with haloalkanes is promoted by cesium hydroxide [42]. This Williamson ether synthesis proceeds with efficiency that can be explained by dissociation of the cesium compound into ions. The alkoxide is highly nucleophilic. Treatment of a chiral mandelate with MeI and cesium carbonate is accompanied by partial racemization (Scheme 2.26).



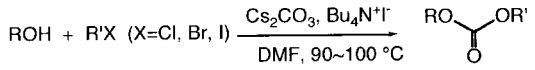
ROH: primary and secondary alcohol, R'X: primary halide



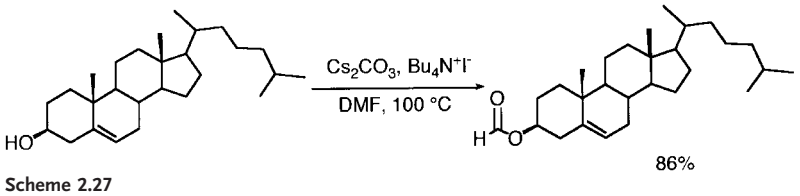
Scheme 2.26

90% (17% loss of optical purity)

Addition of tetrabutylammonium iodide and use of a higher reaction temperature changes the product of the above Williamson ether synthesis. In the reaction depicted by Scheme 2.27 the carbonates are obtained directly whereas reaction with a secondary halide resulted in the production of a formate (Scheme 2.28) [43]. Formation of the formate is explained by formation of the Vilsmeier-Haack salt from DMF.

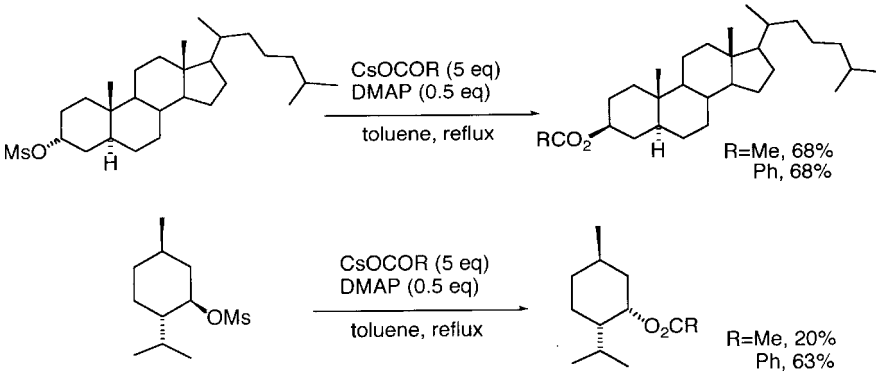


ROH: primary and secondary alcohol, R'X: primary halide



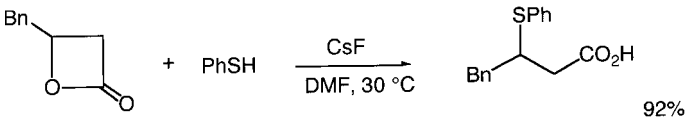
Scheme 2.27

Inversion of the configuration of an alcohol by cesium carboxylate has also been demonstrated. This Mitsunobu-type reaction is sometimes more convenient than the classical phosphine-based reaction. Although a small amount of the E2 elimination reaction also occurs, carboxylation of the mesylate of the alcohol proceeds perfectly with inversion of configuration (Scheme 2.28) [44].



Scheme 2.28

The ring-opening reaction of 3-substituted β-lactones is promoted by cesium fluoride (Scheme 2.29) [45], which works as a base to form the S–Cs compound. β-Lactones are converted into β-arylthiocarboxylic acids efficiently without elimination.

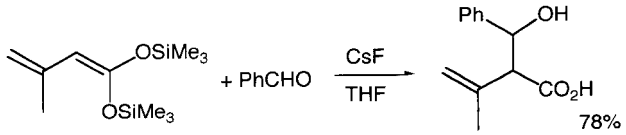


Scheme 2.29

2.6
Cesium Enolate

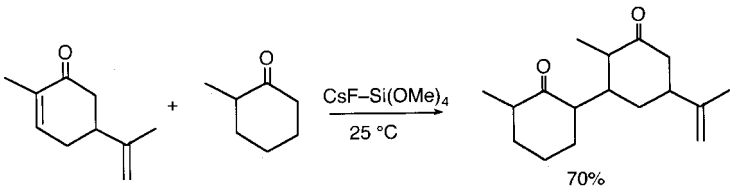
Metal enolates are expected to have individual selectivities depending on the character of metal atom. The structure of cesium enolate, and its reaction, have been well studied kinetically and theoretically by Streitwieser [46].

Desilylation of silyl enol ethers with cesium fluoride also gives the corresponding enolate equivalent. Under the action of cesium fluoride 1,1-disiloxydiene reacts with aldehydes at the β position (Scheme 2.30) [47].



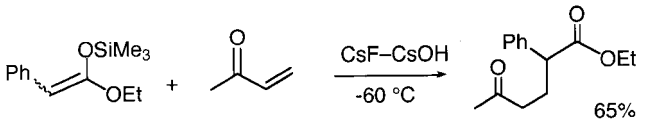
Scheme 2.30

$CsF–Si(OMe)_4$ has also been used for formation of enolates. Treatment of a mixture of ketone and enone with $Si(OMe)_4$–CsF gives a Michael reaction adduct (Scheme 2.31) [48]. Deprotonation of 2-methylcyclohexanone occurs kinetically to form the enolate which reacts with the enone by 1,4-addition.



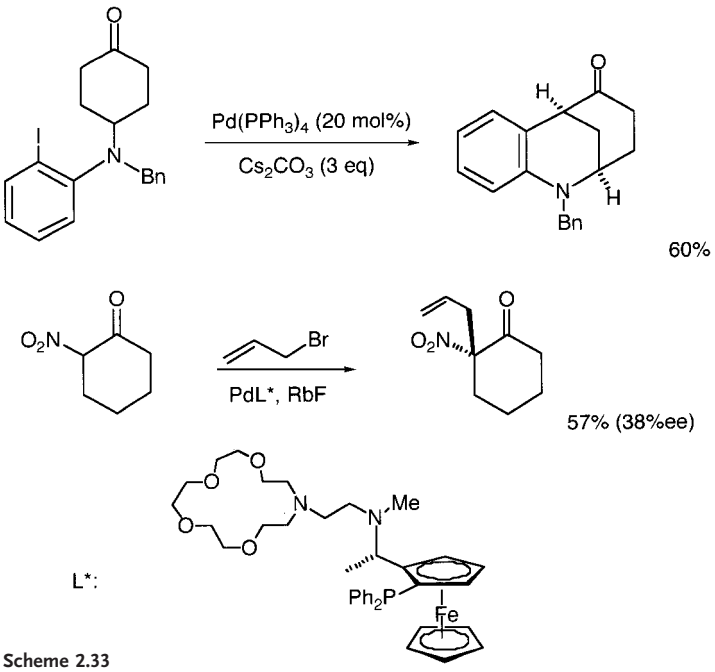
Scheme 2.31

The fused salt CsOH–CsF acts as a desilylating reagent on ketene silyl acetals to give the equivalent enolate. The reaction proceeds at –60 °C. The equivalent reaction with methyl vinyl ketone proceeds by 1,4-addition (Scheme 2.32) [22].



Scheme 2.32

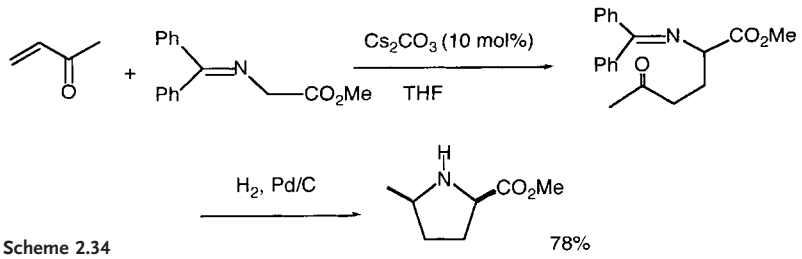
Palladium-catalyzed alkylation of enolate requires the presence of a base, and rubidium and cesium carbonates have been used for this purpose (Scheme 2.33) [48, 49]. After metal ion tuning, outstanding effects are often observed for these metal ions. The effect of the metal ion in these reactions is difficult to explain clearly.



Scheme 2.33

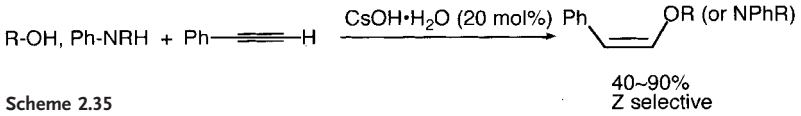
2.7 Catalytic Use

Use of a cesium salt as a catalytic base is very attractive method. Treatment of the Schiff base of glycine with an enone in the presence of 10 mol% cesium carbonate gives a 1,4 adduct. Hydrogenation gives proline derivative in 78% yield (Scheme 2.34) [50].



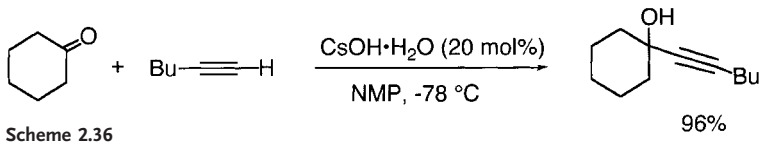
Scheme 2.34

Cesium hydroxide has unique properties as a catalytic base. Catalytic processes using cesium hydroxide have been well studied by Knochel. The method will be applied to industrial scale production. Alcohols and amines add to phenylacetylene in the presence of catalytic amounts of cesium hydroxide (Scheme 2.35) [51].

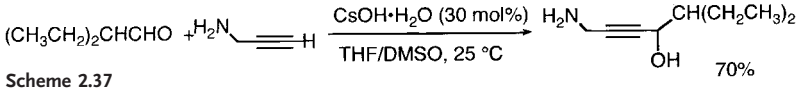


Scheme 2.35

Even formation of an acetylide which adds to ketones and aldehydes can be promoted by a catalytic amount of cesium hydroxide (Scheme 2.36). Propargylamine, which has an acidic proton, is deprotonated efficiently to form an acetylide. This adds to aldehydes in good yield without forming an imine (Scheme 2.37) [52].

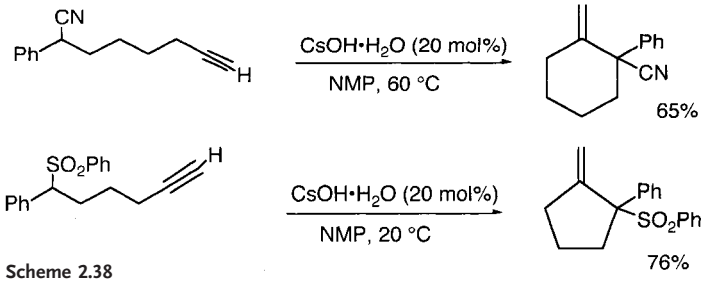


Scheme 2.36



Scheme 2.37

This catalytic system is also effective for formation of a stabilized carbanion which undergoes carbometalation to acetylene (Scheme 2.38) [53].



Scheme 2.38

2.8 Conclusion

Cesium and rubidium have important and unique positions in organic synthesis. To understand their role, their properties as metal ions should be kept in mind. They are large, highly electron-positive ions. The salts release the counter anion easily and always tend to form the "naked anion". This is important aspect of their use as catalysts. These metal compounds will not take the leading part very often but always appear in supporting roles in organic reactions.

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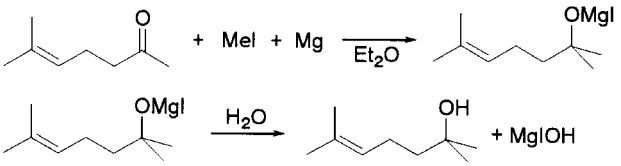
3
Magnesium in Organic Synthesis

Atsushi Inoue and Koichiro Oshima

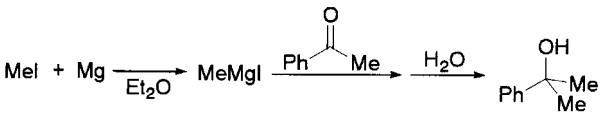
3.1
Introduction

The generation of organomagnesium compounds was first reported in 1859. After that several attempts were made to prepare dialkylmagnesium compounds and investigate their reactivity. In 1875, Wagner and Saytzeff reported that generation of the organozinc compound from an alkyl iodide and zinc in the presence of a carbonyl compound provided the desired carbinol. In 1898, Barbier improved the reaction by substituting the more reactive magnesium for zinc. He characterized the reaction as shown in Scheme 3.1.



Scheme 3.1

Victor Grignard, studying under the direction of Barbier, found that a compound of general formula RMgX was generated as an intermediate and that an ethereal solution of the organomagnesium reagent could be prepared by the reaction of the corresponding alkyl halide and magnesium in Et_2O. The resulting reagents in turn reacted with carbonyl compounds to afford the corresponding carbinols (Scheme 3.2). The first report on the new reagents appeared in 1900. Grignard received the Nobel Prize for his discovery in 1912, and organomagnesium halides are now called Grignard reagents in his honor.



Scheme 3.2

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After this sensational discovery, Grignard reagents soon became the most important tools of all organometallic compounds in the chemical laboratory. Numerous reports have been published on preparative methods, synthetic applications, chemical and physical properties, structures, the mechanism of formation, and reactions of the reagents. Many industrial applications of Grignard reagents have also been reported. Here we will describe the preparation of organomagnesium compounds and the synthetic application of those compounds. Recent development, specially halogen-magnesium exchange reactions and radical reactions with Grignard reagents are main topics of this chapter. Before those topics, several important reactions such as addition to carbonyl compounds, copper- or nickel-catalyzed coupling reactions, and deprotonation with magnesium amides will be discussed briefly.

3.2
Preparation of Organomagnesium Compounds

Grignard reagents have proved to be extremely powerful synthetic tools because of their easy accessibility and high reactivity; they enable the nucleophilic introduction of organic groups as carbanion equivalents and for that reason are in standard repertoires for both organic and organometallic synthesis.

3.2.1
Preparation from Alkyl Halides and Mg Metal [1]

By far the commonest method for preparing organomagnesium compounds remains the classical Grignard reaction of magnesium with organic halides, and most of those commercially available are solutions prepared in this way. Several manufacturers have facilities for preparing Grignard reagents on a "fine chemicals" scale, and a surprising number are offered for sale as laboratory chemicals.

A variety of methods for preparing organomagnesium compounds utilize elemental magnesium, and for many of these the purity and form of the metal is important or even critical. Magnesium turnings are often sold as "for Grignard reagents", and are convenient to use and often sufficiently reactive in many cases. Their reactivity is enhanced by the presence of surface dislocations resulting from their preparation.

Grignard introduced the entrainment procedure consisting in adding one equivalent of ethyl bromide to the ethereal solution of the refractory halide and dropping this mixture slowly on to sufficient magnesium to react with both halides. The auxiliary halide keeps the magnesium clean and active, possibly functioning by an exchange reaction. Ethylene dibromide is also used as entrainment reagent – it reacts with magnesium to form ethylene and magnesium bromide (Scheme 3.3). It cleanses and activates the magnesium for reaction with inert ha-

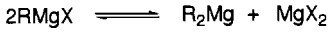
lide without introducing a second Grignard reagent. This procedure consistently gives yields higher than those obtained by entrainment with ethyl bromide.

Scheme 3.3

Diethyl ether is the most commonly used solvent for alkylmagnesium compounds, and almost all the classical studies involved Grignard reagents in diethyl ether. It continues to be a good general-purpose choice. Most alkylmagnesium compounds are soluble in it, and it is a convenient solvent for conventional work-up procedures, although its low boiling point is sometimes a disadvantage. For many reactions it is adequately dried by use of sodium wire, and its high vapor pressure at room temperature creates a "blanket" over the surface of the solution, which sometimes makes the provision of a nitrogen or argon atmosphere unnecessary. The hazardous properties of diethyl ether – its flammability, tendency to form peroxides, and toxicity – are well known, and appropriate safety precautions should be taken.

The general procedure for preparation of alkyl Grignard reagents is as follows. The required amount of magnesium turnings is placed in a flask, nitrogen is passed in, and both parts of the empty dropping funnel are flushed with the gas. When the air has been displaced, the flask is heated gently with a free flame under continued flow of nitrogen to ensure elimination of any moisture adhering to the surface of the glass or to the metal; use of nitrogen prevents surface oxidation of the warm metal. When the flask has cooled completely, the nitrogen flow is reduced to a barely perceptible rate and small quantities of halogen compound and ether are introduced through the funnel. The stirrer is started even though very little liquid is present, for the crushing of pieces of light magnesium is often effective in initiating reaction. If stirring alone is ineffective, one expedient is to insert a flattened stirring rod and crush a piece of metal with a twisting motion against the bottom of the flask. Another is to add a little methylmagnesium iodide or a small crystal of iodine; bromine is more effective as a starter than iodine.

The structure of a Grignard reagent, an important influence on reactions, is more elaborate than implied by the formula RMgX. In solution a Grignard reagent is a mixture (Schlenk equilibrium, Scheme 3.4) of RMgX, R_2Mg, and MgX_2, the composition varying with solvent and X. Mg is most commonly four-coordinate in solids but might have even higher coordination; all evidence indicates similar coordination in solution. The additional bonds to Mg result from some combination of association by bridging of the X atom (or R group) between two Mg atoms and coordination by donor molecules (usually solvent). Coordination by donor groups of substrates can play an important role in reactions.



Scheme 3.4

3.2.2 Preparation with Rieke Magnesium [2]

Numerous procedures have been used to activate the magnesium surface; often the procedures are empirical – it is not known whether they work merely by cleaning or etching the metal surface or whether the formation of an intermediate reactive magnesium compound is involved. Several procedures are well-known and widely used:

1. activation by halogens,
2. activation by alloying, and
3. activation by entrainment.

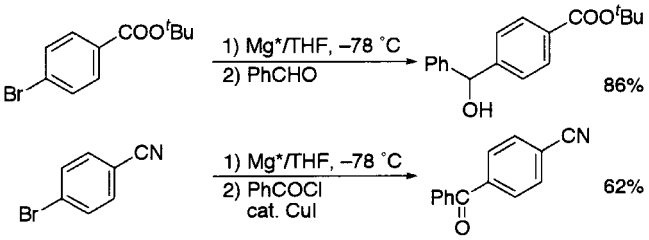
Examples of 1 and 3 have already been described above. Activation of magnesium by amalgamation or by alloying with copper or different transition metals has been reported, but these means of activation rarely offer advantages over other methods, and involve toxicity hazards and/or the risk of promoting side reactions. They are, therefore, not usually recommended, although the amalgamation method is occasionally useful.

Rieke has developed a procedure for preparing slurries of highly reactive magnesium (Rieke magnesium). He reduced magnesium halides to the metal by use of alkali metals, for example reaction of magnesium chloride with potassium in the presence of potassium iodide with THF as the medium. This procedure is, however, somewhat hazardous and a more recent procedure, in which the magnesium halide is reduced with lithium, with naphthalene as electron carrier, is safer and gives a slurry of activity comparable with that of the original Rieke magnesium.

Despite being 100 years old, the Grignard reagent still plays a central role in synthetic chemistry, although few functionalized Grignard reagents have been prepared because of low tolerance of functional groups. In 1998, several functionalized aromatic and vinylic Grignard reagents were prepared by iodine-magnesium exchange by using excess diisopropylmagnesium as metalating agent at a low temperature (–40 °C). The yields were excellent to moderate after reaction with allyl bromide or benzaldehyde as electrophiles. The thermodynamic nature of the equilibrium of exchange limits the range of substrates to arylic and vinylic halides, however, and transmetalation failed to afford functionalized Grignard reagents from brominated substrates. Chromium salts can form functionalized organochromium compounds, but the chromium salts needed a catalyst for the oxidative addition step and the functionalized organochromium compounds have so far reacted with aldehydes only [3].

In general the low functional group tolerance of Grignard reagents precludes the use of most groups in the same molecule. If, however, the oxidative addition reaction is conducted at low temperatures (–78 °C), the functionalized Grignard reagents are stable for a limited time. Functionalized Grignard reagents have been successfully prepared by direct oxidative addition to aryl bromide substrates containing a nitrile, ester, or chloride group, by use of highly active magnesium (Rieke magnesium) at low temperature (–78 °C). The oxidative addition was rapid

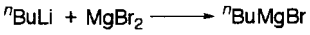
even at this temperature and was complete in 15 min. Reaction with the electrophiles (PhCHO, allyl iodide, and PhCOCl using 10% CuI) was conducted at low temperatures (–78, –40 °C) within ca 1 h, and the yields were good to moderate (Scheme 3.5). Rieke magnesium (Mg*) can be purchased from Rieke Metals, Inc. The preparative procedure is given in the literature [4].



Scheme 3.5

3.2.3 Transmetalation

The preparation of organomagnesium reagents by addition of one equivalent of a magnesium halide to a solution of an organoalkali metal compound is a commonly used procedure, giving products which certainly resemble conventional Grignard reagents in their reactions. The procedure is most commonly applied to organolithium compounds, although examples involving organosodium and organopotassium compounds have been described (Scheme 3.6). The use of magnesium bromide, magnesium chloride, and magnesium iodide has been described, but for practical purposes magnesium bromide is preferred, because it is readily prepared in the anhydrous form (often in situ).

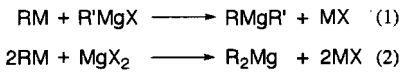


Scheme 3.6

The reaction of dialkylmercury compounds with magnesium is valuable for preparing dialkylmagnesium compounds, free from traces of halide, and either as solids or in a variety of solvents (Scheme 3.7). It has been used particularly to prepare samples for physicochemical studies. The reaction can be performed in the absence of solvent, in which case the product is extracted from the magnesium amalgam formed by use of a suitable solvent. In a solvent such as diethyl ether the reaction may be very slow, but proceeds in virtually quantitative yield.

Scheme 3.7

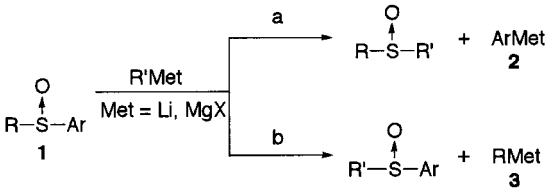
The reactions represented by Scheme 3.8 (Eqs. 1 and 2) have both been used to prepare symmetrical dialkylmagnesium compounds. Under suitable conditions good results can be obtained, although alternative routes are available for these compounds. For example, addition of dioxane to the Grignard reagent (RMgX) results in precipitation of magnesium halide and R_2Mg. The reaction of Eq. (1) can also be used to prepare unsymmetrical dialkylmagnesium compounds, for which few alternative methods are available.



Scheme 3.8

3.2.4
Sulfoxide-Magnesium Exchange (Ligand Exchange Reaction of Sulfoxides with Grignard Reagent)

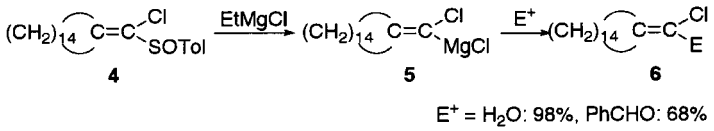
It is known that on treatment of alkyl aryl sulfoxide **1** with alkylmetal (alkyllithium or Grignard reagent) sulfur–aryl (path a) or sulfur–alkyl (path b) bond cleavage occurs to give arylmetal **2** or alkylmetal **3** (Scheme 3.9). This reaction is commonly called the ligand exchange reaction of sulfoxides. Although the predominant path of this reaction depends on the structure of the sulfoxide **1**, this dependence remains somewhat obscure at present.



Scheme 3.9

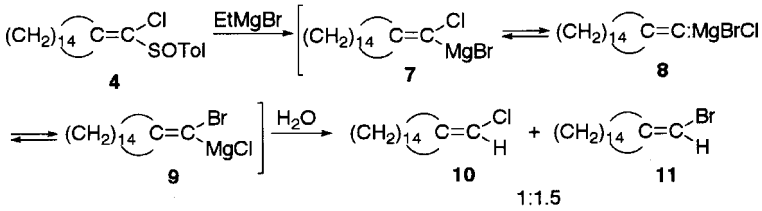
Recently, Satoh's group extensively studied application of the ligand exchange reaction of sulfoxides in the development of new synthetic methods. They found [5] that magnesium alkylidene carbenoids were generated from 1-halovinyl sulfoxides derived from ketones and aryl halomethyl sulfoxide by the ligand exchange reaction of sulfoxides with Grignard reagents. The magnesium alkylidene carbenoids generated were found to be stable at –78 °C for over 30 min. Although the carbenoids reacted with aldehydes to give the adducts in moderate yields, they were found to be relatively unreactive toward the usual electrophiles (Scheme 3.10).

The magnesium alkylidene carbenoid generated occurs in equilibrium between an *α*-halo alkenyl Grignard reagent and an alkylidene carbene-magnesium halide complex. 1-Chlorovinyl sulfoxide **4** reacted with EtMgBr to give a mixture of chloride **10** and bromide **11** (Scheme 3.11). This strange result implies that the struc-



Scheme 3.10

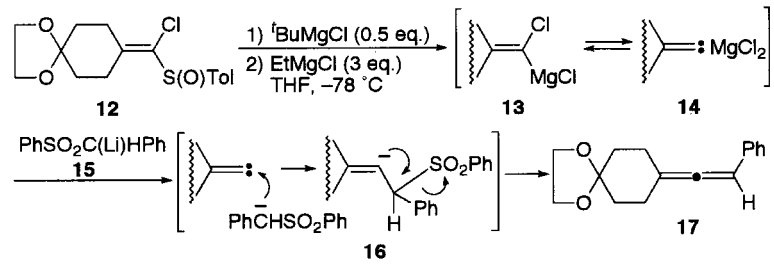
ture of the magnesium alkylidene carbenoid is not a simple vinylmagnesium compound such as **7** but is in equilibrium between the alkylidene carbene-magnesium complex **8** and **7**. This result is deduced from the presence of an equilibrium between **7** and **9** through the magnesium complex **8**.



Scheme 3.11

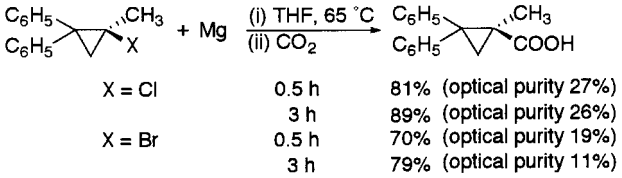
Further evidence for the alkylidene carbene-magnesium complex and the presence of the equilibrium was obtained experimentally. 1-Chlorovinyl sulfoxide **4** was added to a solution of EtMgCl in THF at –80 °C and after 3 min a solution of $MgBr_2$ etherate in ether was added to the reaction mixture. The reaction mixture was stirred for 15 min and quenched to give a mixture of **10** and **11** in a ratio of 1 : 2 in good yield. The result also suggested that there is an equilibrium between the complex of alkylidene carbene with magnesium chloride and magnesium bromide.

This sulfoxide-magnesium exchange reaction could be successfully applied to a new synthesis of allenes (Scheme 3.12) [6]. The procedure is a novel method for synthesis of allenes from three components, ketones, chloromethyl *p*-tolyl sulfoxide, and sulfones, in relatively short steps. A key step is an attack of the lithium *α*-sulfonyl carbanion on the electron-deficient carbene carbon. *β*-Elimination of the sulfoxyl group then occurs to give the allene.



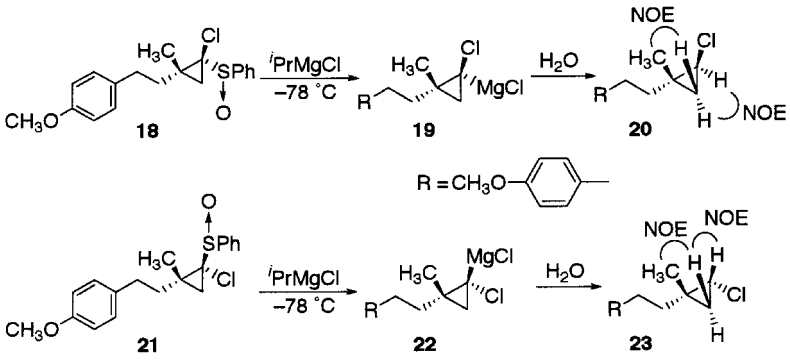
Scheme 3.12

Although molecules containing magnesium bound to an asymmetric carbon atom are not usually configurationally stable, there are some exceptions to this generalization, notably some cyclopropylmagnesium halides [7]; reaction of these magnesium proceeds with significant retention of configuration (Scheme 3.13) [8].



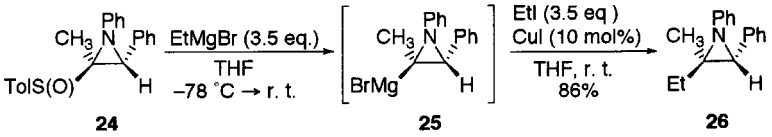
Scheme 3.13

Magnesium cyclopropylidenes were generated from 1-chlorocyclopropyl phenyl sulfoxides with Grignard reagents (EtMgCl or ^{i}PrMgCl) in THF at –78 °C in high yields by means of a sulfoxide-magnesium exchange reaction. The magnesium cyclopropylidenes generated were found to be stable at below –60 °C for at least 3 h. It was also found that pyramidal inversion of the magnesium carbenoid was quite slow at below –60 °C [9]. The cyclopropyl sulfoxide **18** was treated with 2.5 equivalents of EtMgCl at –78 °C for 5 min to give the desulfinylated product **20** in 82% yield without any trace of the starting sulfoxide **18**. Even ^{i}PrMgCl reacted quickly with **18** at –78 °C to give the desulfinylated product **20** in good yield. Quenching of these two reactions with CD_3OD gave the deuterated chlorocyclopropane with over 90% deuterium incorporation. These results showed that the intermediate of these reactions was the magnesium cyclopropylidene **19** (Scheme 3.14). Treatment of **21** with ^{i}PrMgCl under the same reaction conditions gave the desulfinylated product **23** in the same yield. The stereochemistry of **20** and **23** were determined by the examination of the NOESY spectra of both compounds.



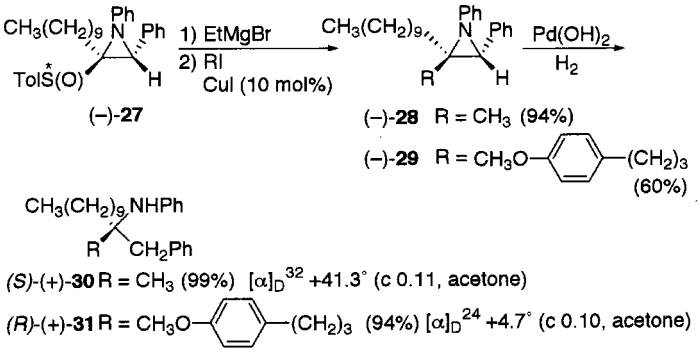
Scheme 3.14

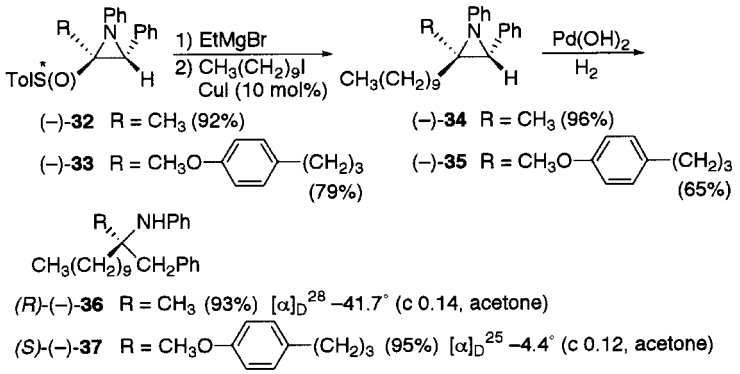
Satoh et al. also reported [10] the preparation and reaction of aziridinylmagnesium compounds. Treatment of sulfinylaziridines, which were synthesized from 1-chloroalkyl *p*-tolyl sulfoxides and imines, with ethylmagnesium bromide gave non-stabilized aziridinylmagnesiums by a sulfoxide-magnesium exchange reaction. Cross-coupling of the aziridinylmagnesiums with different alkyl halides was realized in high yields by use of Cu(I) iodide as catalyst, and the reaction was found to be stereospecific (Schemes 3.15 and 3.16). The coupling products were hydrogenated with $Pd(OH)_2$ in alcohol to give amines with a quaternary chiral center in quantitative yield. Synthesis of both enantiomers of the amines bearing a quaternary chiral center was realized starting from optically active (*R*)-chloromethyl *p*-tolyl sulfoxide; overall yields were good and asymmetric induction was perfect.



24 **25** **26**

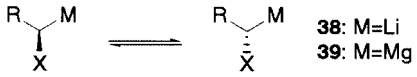
Scheme 3.15





Scheme 3.16

This sulfoxide-magnesium exchange reaction has been successfully applied to the generation of α-haloalkylmagnesium compound with high enantiomeric purity [11]. α-Heterosubstituted organolithium compounds **38** are chiral d^1 synthons. Of these, it is mainly the α-oxygenated and α-amino-substituted representatives which are used in stereoselective synthesis [12], because these compounds are configurationally stable at or above –78 °C for extended periods of time (Scheme 3.17).

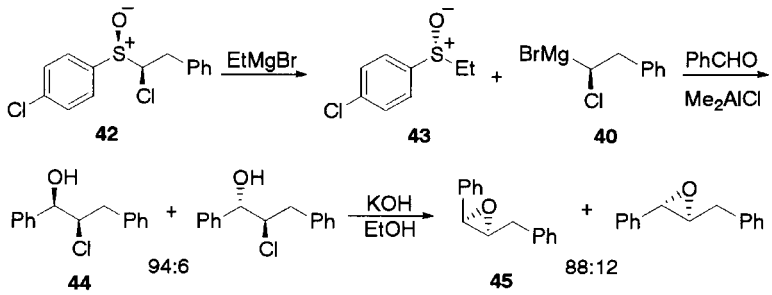


Scheme 3.17

In contrast with the former, the configurational stability of α-arylthio- or α-arylselenoalkyllithium compounds is so low that racemization or epimerization occurs during the time needed to generate these lithium compounds and to trap them with electrophiles. There are indications that the corresponding α-heterosubstituted Grignard reagents **39** would have a substantially higher configurational stability. Yet, before the study by Hoffmann there were no practical means of preparing species such as **39** in an enantiomerically pure form.

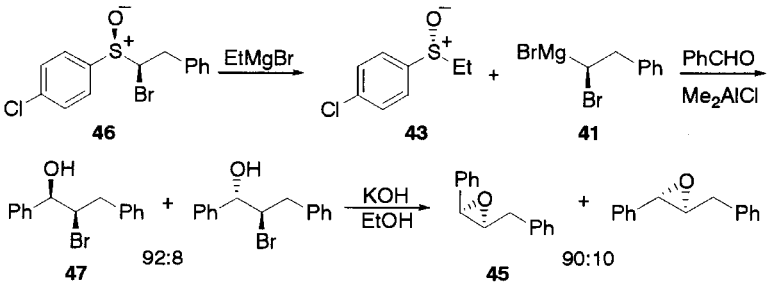
α-Chloro- and α-bromoalkyl Grignard reagents **40** and **41** with >97% ee (enantiomeric excess) were generated by a sulfoxide-magnesium exchange reaction from the enantiomerically and diastereomerically pure sulfoxides **42** and **46**. The resulting α-haloalkyl Grignard reagents are configurationally stable at –78 °C. Racemization begins at or above –60 °C, especially when the solution contains bromide ions. In the absence of halide ions, the configurational stability extends to –20 °C, when chemical decomposition commences.

Sulfoxide-magnesium exchange on the α-chloroalkyl sulfoxide **42** was performed with ethylmagnesium bromide followed by trapping with benzaldehyde-dimethylaluminum chloride, to furnish 99% of the sulfoxide **43** with 99% *ee*. Chlorohydrins **44** were obtained in 56% yield as a 94:6 diastereomer mixture. After conversion to the epoxide **45**, the latter had an *ee* of >98% (Scheme 3.18).



Scheme 3.18

The α-bromoalkyl Grignard reagent **41** was generated from the α-bromoalkyl sulfoxide **46** (Scheme 3.19): bromohydrins **47** were obtained as a 92:8 mixture of diastereomers. On closure to the epoxides the resulting **45** had an *ee* of merely 85%, even though the starting sulfoxide **46** had an *ee* of 99%, which was reflected in the enantiomeric purity of the coproduct, sulfoxide **43** (99% *ee*). Very recently, Hoffmann and Hölzer have reported the stereochemistry of the transmetalation of Grignard reagents to copper using the enantiomerically enriched Grignard reagent **40** [13].

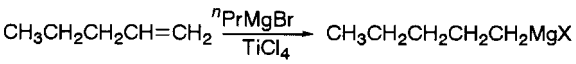


46 **43** **41** **47** **45**

Scheme 3.19

3.2.5 Hydromagnesation

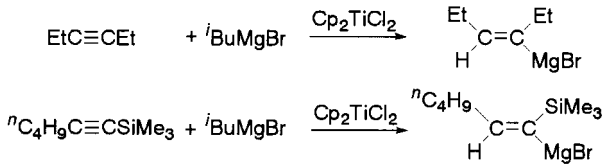
Thirty years ago it was reported that reactions of Grignard reagents with 1-alkenes, catalyzed by titanium tetrachloride, led to organomagnesium compounds, formally derived by addition of HMgX to the carbon-carbon double bond (Scheme 3.20) [14].



Scheme 3.20

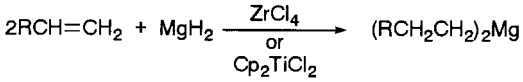
The reaction has since been extended to a variety of alkenes (including dienes and styrenes) and alkynes [15], and it has been established that the hydrogen atoms transferred are β-hydrogen atoms from the Grignard reagent.

Dicyclopentadienyltitanium dichloride is possibly superior to titanium tetrachloride as a catalyst. Nickel(II) compounds are also active, but with these catalysts concurrent addition of the organomagnesium compounds to carbon-carbon multiple bonds causes complications. Examples of hydromagnesation by Grignard reagents are shown in Scheme 3.21. As is apparent from these reactions, addition to alkynes proceeds in *syn* fashion. The regiochemistry is also usually predictable, one regioisomer is obtained mainly or exclusively.



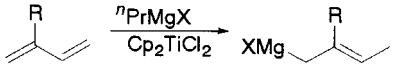
Scheme 3.21

More recently, a related reaction has been reported in which active forms of magnesium hydride, prepared in situ or pre-prepared, undergo addition to alkenes, catalyzed by titanium or zirconium(IV) halides, to give dialkylmagnesium compounds (Scheme 3.22) [16]. These reactions give high yields with 1-alkenes but are less satisfactory with alkynes or non-terminal alkenes.



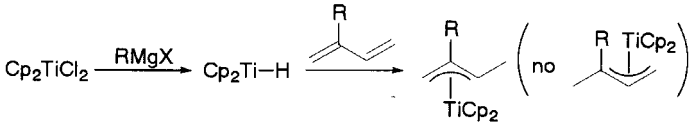
Scheme 3.22

Although the attempted $TiCl_4$-catalyzed olefin hydromagnesation did not work on conjugated dienes, switching the catalyst from $TiCl_4$ to Cp_2TiCl_2 dramatically increased the efficiency of the hydromagnesation. Thus, under these reaction conditions 2-alkyl-1,3-butadienes generally afforded allyl Grignard reagents in excellent yields. More surprisingly, a single regioisomer of the allyl Grignard reagent is exclusively formed, as shown in Scheme 3.23; this was verified by the subsequent reactions with electrophiles [17].



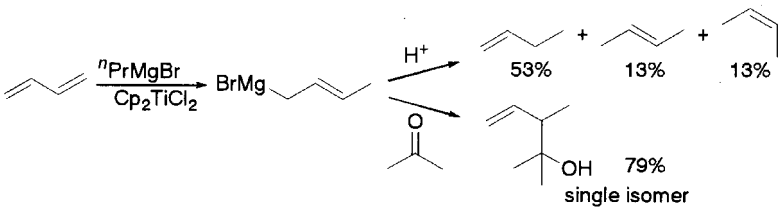
Scheme 3.23

The observed regioselectivity of hydromagnesation is identical with that of the hydrotitanation of the same substrates with a stoichiometric amount of Cp_2Ti-H. This fact strongly suggests that the regioselection of Scheme 2.23 originates in the hydrotitanation step (Scheme 3.24).



Scheme 3.24

Although the hydrolysis of the allyl Grignard reagents tends to yield a mixture of regio- and stereoisomeric olefins, reaction with carbon electrophiles such as carbonyl compounds and nitriles usually afforded a single regioisomer (Scheme 3.25).

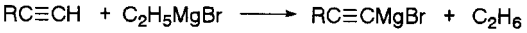


Scheme 3.25

3.2.6
Metalation (Deprotonation from Strong Carbon Acids)

The preparation of organomagnesium compounds by metalation was of value only for quite strong carbon acids ($pK_a \lesssim 25$), e.g. alkynes and cyclopentadienes, which are metalated by Grignard reagents. Dialkylmagnesium compounds are also reactive towards this type of substrate, the *n*-butyl-*s*-butylmagnesium reagent being particularly useful. Grignard reagents are also effective with some polyhalogenated compounds, but reactions such as the versatile *ortho* metalation of substituted aromatic compounds by organolithium compounds were poor with organomagnesium compounds. It has, however, since been reported that sterically hindered magnesium amides, analogous to lithium diisopropylamide (LDA) and lithium 2,2,6,6-tetramethylpiperidide (LTMP), are effective metalating reagents. They are probably less powerful than the lithium reagents, but have the advantage of being stable even in boiling THF [18]. *α*-Metalation of carbonyl compounds (enolization) and other *α*-metalations by organomagnesium compounds also occur, but their use has been overshadowed by the corresponding reactions of LDA and organolithium compounds; enolization by hindered magnesium amides such as BrMgTMP [19] promises to be useful, however. We will deal with recent developments in the use of magnesium amides in the next section.

Extensive studies have been made of the metalation of 1-alkynes by organomagnesium compounds. For preparative purposes, metalation by Grignard reagents (commonly ethylmagnesium bromide) in diethyl ether or THF is usually straightforward and convenient (Scheme 3.26).



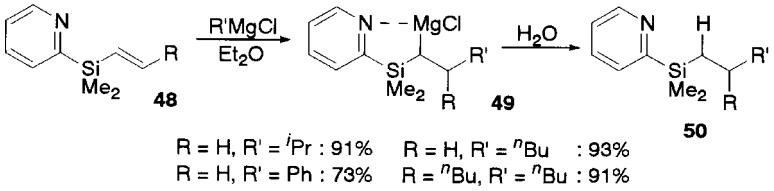
Scheme 3.26

3.2.7
Other Preparative Methods

The addition of organolithium reagents to vinylsilanes is one of the most powerful methods for the generation of synthetically useful α-silyl carbanions. Although Grignard reagents are viable alternatives for this addition reaction, serious limitations are associated with the carbomagnesation methodology:

- activating groups on silicon (e.g. chloro, alkoxy, and amino groups) are needed for the addition (no reaction with trialkyl(vinyl)silanes);
- substitutions at the silicon atom are often observed as unavoidable side reactions when these activating groups are used; and
- primary alkyl Grignard reagents cannot be used in the reaction.

These drawbacks profoundly reduce the synthetic usefulness of this otherwise attractive methodology. Highly efficient carbomagnesation of vinylsilanes utilizing the 2-pyridyldimethylsilyl group as a removable directing group has been reported [20]. Treatment of 2-pyridyldimethylvinylsilane **48** with ^{i}PrMgCl in ether at room temperature for 3 h gave the corresponding α-silyl organomagnesium compound, and **50** was isolated after aqueous work-up in 91% yield (Scheme 3.27). Not only secondary alkyl Grignard reagents but also primary alkylmagnesium reagents such as ^{n}BuMgCl add easily to the vinylsilane.

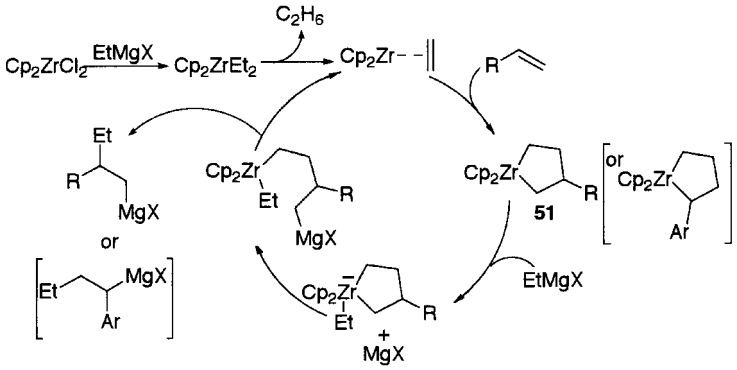


Scheme 3.27

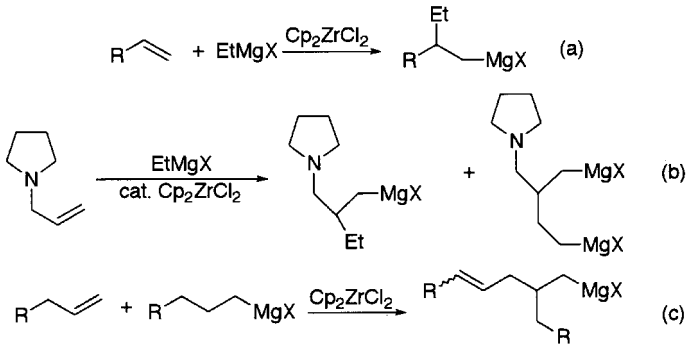
The reaction presumably involves a pre-equilibrium complex of **48** and R′MgX, and this makes the subsequent carbomagnesation step intramolecular in nature. The importance of this pre-equilibrium complex was further supported by the observation of dramatic solvent effects – weakly coordinating solvents such as Et_2O favor this reaction whereas strongly coordinating solvents such as THF suppress it. These results may be attributed to inhibition of the formation of the pre-equilibrium complex by the coordinating solvent.

Cp_2ZrCl_2 or related zirconocene derivatives are effective catalysts of the carbomagnesation of 1-alkenes and some bi- and tricyclic alkenes under mild reaction conditions (<25 °C). The reaction of aliphatic 1-alkenes with EtMgX is highly regioselective (Scheme 3.28), with internal double bonds being unreactive; 1-alkenes with functional groups (e.g. OR, OH, SR, NR_2, TMS) on the chain react similarly and allylic alcohols and ethers are active substrates. Addition to 1-alkenes with

aromatic substituents, e.g. styrene, mainly occurs with regioselectivity opposite to that of Scheme 3.28 to form a benzylic Grignard, and the disubstituted β-methylstyrene is also ethylmagnesated. $MgEt_2$ is more active than EtMgX (with activity varying in the order X = Cl > Br > I) in these zirconium-catalyzed reactions, although Grignard reagents do give good yields of the products in diethyl ether or THF. Hydrocarbon solvents are suitable if the stoichiometric complexes $R^1MgX \cdot NR^2_3$ are employed. Mechanistic studies have implicated alkene-zirconocene complexes (zirconacyclopropanes) and zirconacyclopentanes **51** as intermediates in these reactions, and one possible pathway for the catalytic reaction is illustrated in Scheme 3.28 [21]. Variations on Scheme 3.28 must occur, however; the formation of 1,4-di-Grignard reagents under some conditions can involve Zr–Mg transmetalation and cleavage of both Zr–C bonds of zirconacyclopentane **51** (Scheme 3.29 b); the formation of unsaturated Grignards in reactions of higher alkylmagnesium reagents (Scheme 3.29 c) must involve a β-hydrogen elimination step after head-to-tail coupling of alkene units to form the intermediate zirconacyclopentane [22]. A variety of alkenylmagnesium products has been noted in zirconium-catalyzed reactions of 1-octene and ^{n}PrMgBr.



Scheme 3.28



Scheme 3.29

Metal-halogen exchange between Grignard reagents and organic halides is an alternative useful method for the preparation of organomagnesium compounds (Scheme 3.30). We will discuss this method in detail in Section 3.4.

Scheme 3.30

3.3 Reaction of Organomagnesium Compounds

Almost 100 years have passed since Victor Grignard published his first paper on the preparation of ethereal solutions of compounds in which carbon is bonded to magnesium. Since then Grignard reagents have been an obvious choice for organic chemists in many preparations of complex molecules. The chemical literature on Grignard reagents and related organomagnesium compounds contains tens of thousands of references and the industrial production of Grignard reagents for captive use or for sale is estimated to exceed 50 000 tons annually. The scope and potential of the Grignard reaction continues to grow and new discoveries and improvements in method are regularly reported. Here, we will describe very briefly the fundamental reactions:

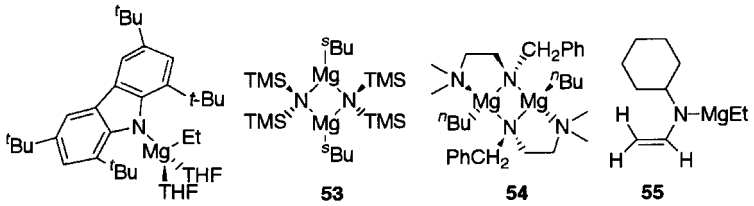
- preparation and reaction of organomagnesium amides;
- Cp_2TiCl_2- or Cp_2ZrCl_2-catalyzed reaction with Grignard reagents;
- substitution with Grignard reagents; and
- addition to carbon-carbon multiple bonds.

Recent topics related to halogen-magnesium exchange reactions and organomagnesium-mediated radical reactions will be discussed in subsequent sections.

3.3.1 Reaction with Organomagnesium Amides

3.3.1.1 Preparation of Magnesium Monoamides and Bisamides

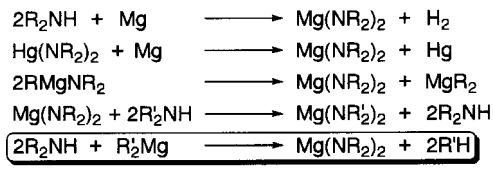
A simple synthetic route to compounds of the type $R^1Mg(NR^2R^3)$ is the reaction of equimolar amounts of MgR^1_2 and a secondary amine, HNR^2R^3. By this method sterically hindered 1,3,6,8-tetra-*t*-butylcarbazole and diethylmagnesium in THF afford **52** as the bistetrahydrofuran adduct, and hexamethyldisilazane ($HN(TMS)_2$) and ^{n}BuMg^{s}Bu in heptane form nonsolvated **53** [23]. Metalation of activated C–H groups by the amide bases $Mg(TMP)_2$ (TMPH = 2,2,6,6-tetramethylpiperidine) or $Mg(N^iPr_2)_2$ can also produce organomagnesium amides. Reactions of metal amide (MNR^2R^3 (M = Li or Na)) with the appropriate Grignard reagent have been used to produce **54** [24] and **55** [25] (Scheme 3.31).



52 53 54 55

Scheme 3.31

Several routes to Mg bisamides have been developed. These include the direct reaction between the metal and a protic amine, a variety of transmetalation strategies, disproportionation of alkylmagnesium amides, and transamination reactions (Scheme 3.32). On the other hand, the most straightforward and most routine synthesis involves the reaction of a dialkylmagnesium with two equivalents of amine. In some instances the amination reaction ceases after transfer of one amino function but gentle heating of the reaction mixture is usually sufficient to ensure complete conversion to the bisamide. Without doubt this route is now the method of choice, because ether-free Bu_2Mg (supplied as a 1:1 mixture of *n*- and *s*-butyl, with 5% *n*-octyl, in heptane) has become commercially available (Aldrich).



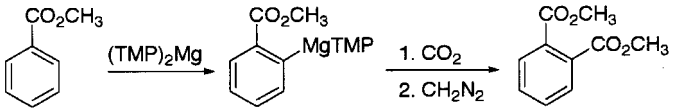
Scheme 3.32

3.3.1.2 **Reaction with Organomagnesium Amide [26]**

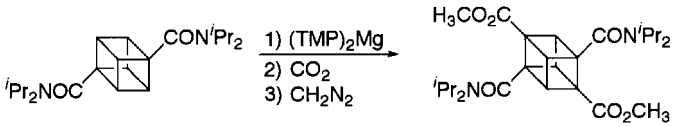
Removal of an acidic proton by a Mg bisamide is a versatile reaction akin to that of the widely used lithium amides, although differences between the reactivity (and thermal stability) of the bases often leads to different and complementary selectivity.

Eaton first developed the use of magnesium bis(2,2,6,6-tetramethylpiperidide), $(TMP)_2Mg$, as a selective proton abstractor [18]. Of particular note is the ease with which *ortho*-magnesation reactions can be accomplished in the presence of esters, which are normally more susceptible to nucleophilic attack if conventional Li-based reagents are used. For example, reaction of methyl benzoate for 45 min with excess $(TMP)_2Mg$ in THF at room temperature then quenching with carbon dioxide, acidification, and esterification gave dimethyl phthalate in 81% isolated yield (Scheme 3.33). Apparently, the intermediate organometallic, formulated as R′MgTMP, is not very reactive; an ester group can coexist with it for some time. Such $R'MgNR_2$ species are called "amide-Grignards". The amine substituent mod-

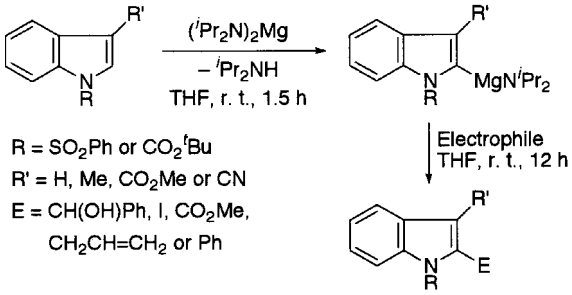
erates the Grignard reactivity of such compounds by reducing nucleophilicity and/or the tendency to complex with substrate. Electronic and/or steric reasons can be invoked. The mild reactivity of the Mg reagents also enables carbocubane systems to be selectively monometalated (adjacent to each amide unit) and subsequently carboxylated (Scheme 3.34). THF solutions of the base $(TMP)_2Mg$ were found to be stable on heating to reflux over several hours; this led to its application with relatively unreactive or low-solubility substrates. In a similar "high-temperature" metalation strategy, indoles can be deprotonated exclusively at the 2 position by $(^iPr_2N)_2Mg$. Subsequent quenching with a variety of electrophiles leads to 2-substituted indoles in good to excellent yields (Scheme 3.35).



Scheme 3.33



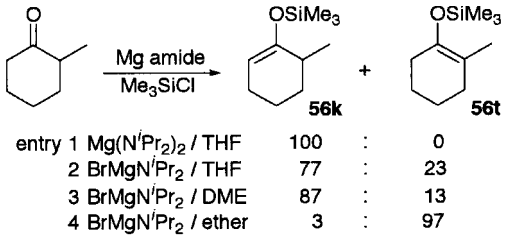
Scheme 3.34



Scheme 3.35

Mg bisamides can also be used as strong and selective bases in the formation of synthetically useful enolates. Less highly substituted silyl enol ethers are regiospecifically prepared in high yield, at approximately room temperature under kinetic conditions, from unsymmetrical cyclic ketones and magnesium bis(diisopropylamide)[$(DA)_2Mg$] in THF/heptane (Scheme 3.36) [27].

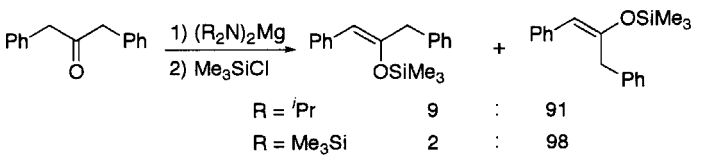
This high kinetic regioselectivity is markedly higher than these reported by Krafft and Holton when using DAMgBr/TMSCl/Et_3N/HMPA under kinetic conditions in THF (77:23) or in dimethoxyethane (DME) (87:13) and is even reversed



Scheme 3.36

in ether (3:97) [28]. One interesting aspect of these results is that this regiospecificity can be achieved at room temperature with $(DA)_2Mg$ in a relative short time.

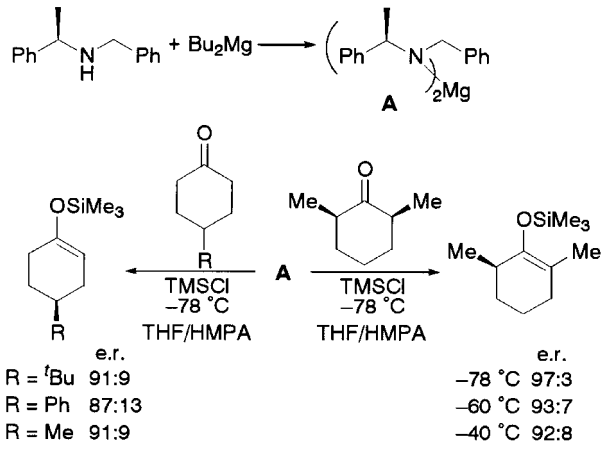
In addition, high *E*-enolization stereoselectivity is observed for benzylic ketones (Scheme 3.37) [26].



Scheme 3.37

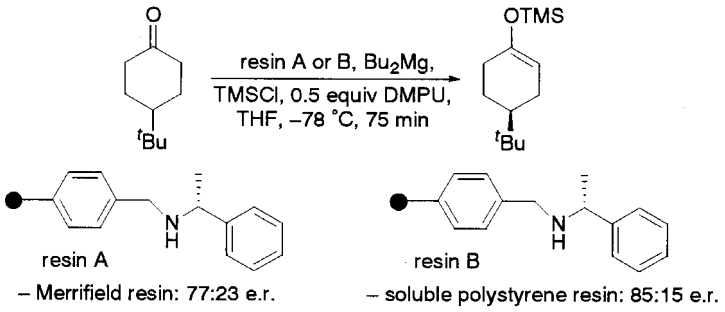
A series of novel, optically pure Mg-bisamides have been prepared and used to mediate enantioselective deprotonations of conformationally locked ketones. The most remarkable feature of these reactions is the level of asymmetric induction produced by using a structurally very simple amide base. For comparison, the enantioselective deprotonation of *tert*-butylcyclohexanone using the lithiated derivative of the same amine, (*R*)-*N*-benzyl-*α*-methylbenzylamine, gives a much-reduced enantiomeric ratio of 75.5:24.5. The Mg-based approach has the advantage over existing methods that the amine is commercially available (Aldrich) and is relatively inexpensive. In addition, the more practically acceptable additive *N,N′*-dimethyl-*N,N′*-propylene urea (DMPU) can be used to replace HMPA with comparable conversions (R = ^{t}Bu; 89%) and enantioselectivity (R = ^{t}Bu, 90:10 e.r.) (Scheme 3.38).

The deprotonation of *cis*-2,6-dimethylcyclohexanone results in an excellent e.r. of 97:3 using the Mg base, and is a dramatic improvement over the analogous lithium-mediated reaction using the same base, for which a very modest 64.5:35.5 e.r. was achieved using acetic anhydride as a trapping agent. The high selectivity of the Mg-based transformation is, furthermore, not unduly affected by significantly raising the reaction temperature (–78 to –40 °C) but the conversion achieved increases substantially (17% to >99%). The potential to perform these reactions at elevated temperatures is clearly exciting in terms of the more widespread use of the Mg reagents.



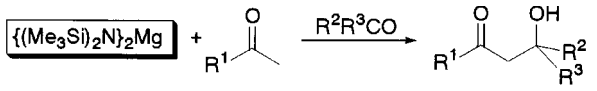
Scheme 3.38

Novel and readily accessible polymer-supported chiral magnesium amide reagents have been prepared and shown to be effective in the asymmetric deprotonation of a series of prochiral cyclohexanones, affording good to excellent conversion and enantiomeric ratio (up to 93:7); the Merrifield-based chiral amine species has been shown to be readily recyclable (Scheme 3.39) [29].



Scheme 3.39

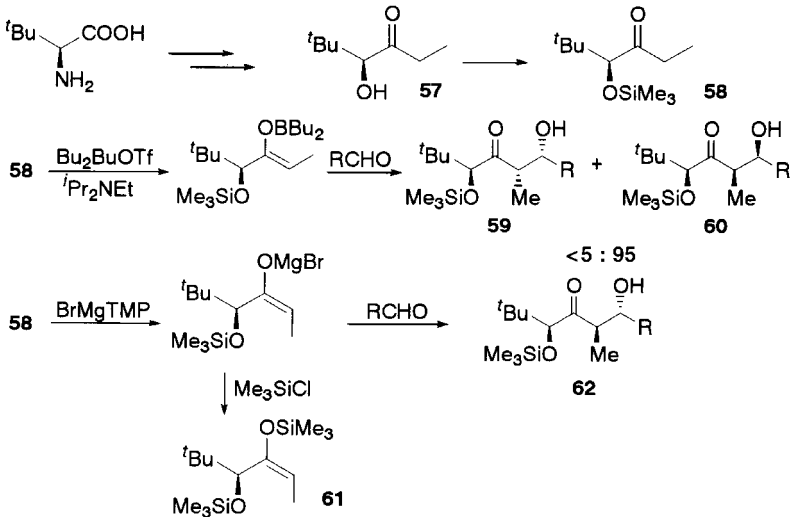
Mg enolates generated from Mg bisamides can be used in aldol addition reactions with alkyl, aryl, and cyclic ketones. As shown in Scheme 3.40, these reactions are significant in that the self-coupling of ketones in aldol reactions to give tertiary β-hydroxyketones are also possible. More specifically, these transformations are achieved principally by the use of relatively high reaction temperatures between 25 °C and 60 °C. Such conditions are a notable departure from the widely used lithium-mediated aldol additions, where increasing the reaction temperature results in retro-aldol processes and also elimination of LiOH to give enone products [30].



Scheme 3.40

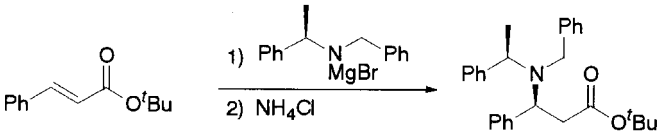
The thermal stability of the Mg aldolates is most probably a consequence of the strong chelation of the carbonyl function with the highly Lewis acidic metal within their dimeric structures. The molecular structure of the amide/aldolate derived from the self-coupled aldol reaction between pinacolone and $[(Me_3Si)_2N]_2Mg$ has been reported [26].

Heathcock et al. have reported [19] the preparation of each of the four possible stereoisomeric *α*-alkyl-*β*-hydroxy carboxylic acids from a single chiral aldol reagent. Procedures have been devised whereby all four possible stereoisomeric *α*-alkyl-*β*-hydroxy carboxylic acids can be derived from a single aldol reagent, hydroxy ketone **57**. Compound **57**, obtained in enantiomerically homogeneous form in 50% overall yield from *tert*-butylglycine, is used for aldol reactions in the form of its trimethylsilyl derivative **58**. Treatment of **58** with LDA or $Bu_2BOTf/^iPr_2NEt$ provides *Z* lithium enolate or *Z* boron enolate. The *Z* lithium and *Z* boron enolates of **58** react with a variety of aldehydes to give *erythro* aldols **59** and **60**, respectively. In contrast, deprotonation of **58** by bromomagnesium 2,2,6,6-tetramethylpiperidide (BrMgTMP) gives the *E* enolate, which can be trapped by trimethylsilyl chloride to furnish the *E* silyl enol ether **61**. The *E* bromomagnesium enolate of **58** reacts with aldehydes to give *threo* aldols of structure **62** (Scheme 3.41).



Scheme 3.41

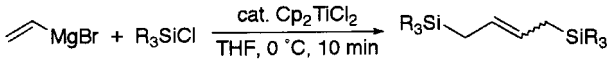
Optically active magnesium amide can add to *α,β*-unsaturated esters such as *tert*-butyl cinnamate to give *β*-amino esters with excellent diastereoselectivity (>95% d.e.) and in good yield (90%) (Scheme 3.42).



Scheme 3.42

3.3.2
Cp_2TiCl_2- or Cp_2ZrCl_2-catalyzed Reaction with Grignard Reagents

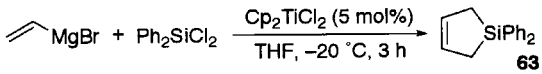
Titanocene dichloride catalyzes the reduction of alkyl, aryl, and vinyl bromides, aryl chlorides, alkoxy- and halosilanes; ketones, esters, and carboxylic acids with alkyl Grignard reagents. This Cp_2TiCl_2/RMgX system can also be used for the hydromagnesation of alkynes, dienes, and alkenes (Section 3.2.5). Kambe et al. have reported a new type of titanocene-catalyzed transformation with vinyl Grignard reagents and chlorosilanes to furnish 1,4-disilyl-2-butenes, as shown in Scheme 3.43 [31].



Scheme 3.43

Treatment of a mixture of chlorodimethylphenylsilane and a catalytic amount of titanocene dichloride with vinyl Grignard reagent at 0 °C afforded 1,4-bis(dimethylphenylsilyl)-2-butene in 94% yield with an *E*/*Z* ratio of 74:26. Only a trace amount of $CH_2=CHSiMe_2Ph$ (<1%) was found as a byproduct, probably via direct reaction of $CH_2=CHMgBr$ with $PhMe_2SiCl$.

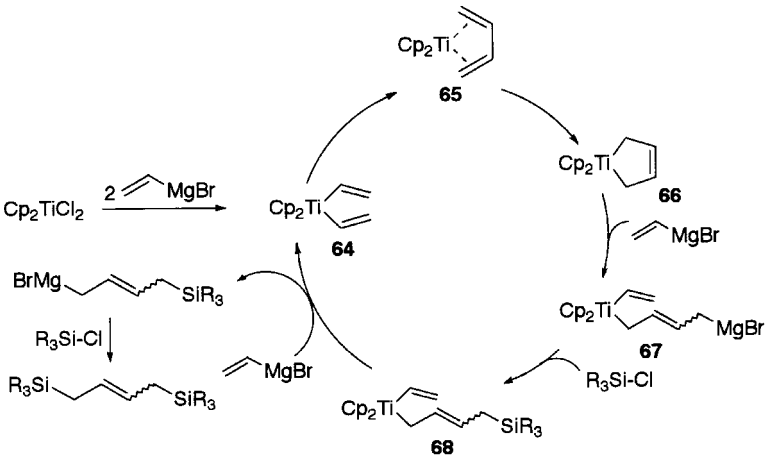
When dichlorodiphenylsilane (0.5 equiv.) was treated with vinyl Grignard reagent at –20 °C for 3 h, cyclization predominated to afford 1,1-diphenyl-1-silacyclo-3-pentene (**63**) in 73% yield (Scheme 3.44).



Scheme 3.44

A plausible reaction pathway is shown in Scheme 3.45. Titanocene dichloride reacts with 2 equiv. $CH_2=CHMgBr$ to generate divinyltitanocene complex **64**, which

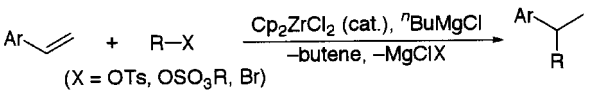
readily forms titanocene-butadiene complex **65** or its *s-trans* isomer via reductive coupling. Then **65** isomerized to titanacyclopentene **66**. The successive transmetalation of **66** with vinyl Grignard reagent affords allylmagnesium species **67**, which reacts with chlorosilane to give allylsilane **68** carrying a titanocene group on the other allylic position. Subsequent transmetalation of **68** with $CH_2=CHMgBr$ followed by trapping with a chlorosilane gives the corresponding product with regeneration of **64**.



Scheme 3.45

An alternative pathway from **66** to **68** might be assumed – reaction of **66** with R_3SiCl to give $Cp_2TiClCH_2CH=CHCH_2SiR_3$ followed by transmetalation with $CH_2=CHMgBr$ leading to **68**. This possibility might, however, be ruled out by the evidence that reaction of Cp_2TiCl_2 with 2 equiv. CH_2=CHMgBr in the presence of Me_3SiCl followed by protonolysis afforded no silylated products.

Zirconocene complexes catalyze the addition of organometallic reagents, such as organoaluminum, -zinc, and -magnesium compounds, to alkenes and alkynes. These reactions are synthetically useful for preparation of organometallic reagents with concomitant formation of carbon-carbon bonds, wherein anionic alkyl, allyl, or benzyl groups are introduced to a carbon atom of the unsaturated bonds. Zirconocene-catalyzed alkylation of aryl alkenes with alkyl tosylates, sulfates, and bromides has recently been reported [32]. This reaction proceeds under mild conditions using a catalytic amount of a zirconocene complex in the presence of a Grignard reagent to give saturated alkylation products in which an alkyl moiety is electrophilically introduced at the benzylic carbons regioselectively (Scheme 3.46).



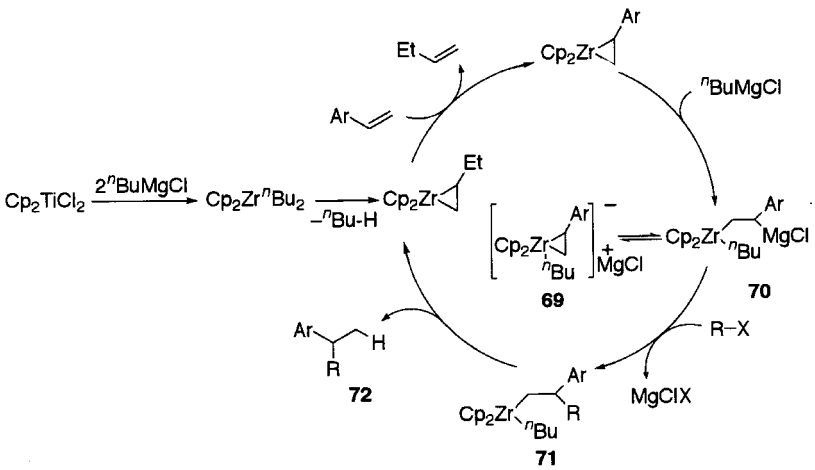
Scheme 3.46

For instance, addition of ^{n}BuMgCl to a mixture of styrene, octyl tosylate, and a catalytic amount of zirconocene dichloride in THF at 20 °C gave 2-phenyldecane in 62% yield. In this reaction octane was formed by the reduction of octyl tosylate as a byproduct in trace amounts (< 3% based on octyl tosylate) along with dodecane (< 1%) probably formed by direct reaction of octyl tosylate with ^{n}BuMgCl.

The reaction failed when ethyl triflate was used as the alkylating reagent, because of its rapid reaction with the Grignard reagent, whereas ethyl sulfate afforded 2-phenylbutane in 76% yield. Although 1-bromooctane gave 2-phenyldecane in 34% yield only under the same conditions, 2-phenyldecane was formed in 65% yield, based on 1-bromooctane, when excess styrene and ^{n}BuMgCl were used. Under the same conditions, Cp_2TiCl_2 and Cp_2HfCl_2 were ineffective.

Treatment of styrene with ethyl tosylate in the presence of $^{n}C_{14}H_{29}MgCl$ using a catalytic amount of "Cp_2Zr", prepared from Cp_2ZrCl_2 and 2 equiv. ^{n}BuMgCl via $Cp_2Zr^{n}Bu_2$, furnished nearly equal amounts of non-deuterated products 2-phenylbutane and 1-tetradecene on quenching the reaction with D_2O. This result suggests that the β-hydrogen of the tetradecyl group was removed and transferred into the terminal carbon of styrene leading to 2-phenylbutane.

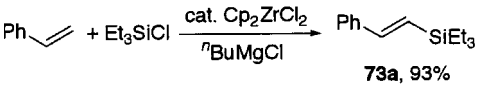
On the basis of this result and several other control experiments a plausible reaction pathway has been proposed (Scheme 3.47). It is possible that a zirconate complex **69** or a benzylmagnesium compound **70** serves as the key intermediate which reacts with an alkylating reagent at the benzylic carbon leading to the dialkyl zirconocene complex **71**. The successive hydrogen abstraction proceeds exclusively at the less hindered butyl group to afford the corresponding alkylated product **72** and a Cp_2Zr(butene) complex which acts as a "Cp_2Zr" to complete the catalytic cycle.



Scheme 3.47

Although chlorosilanes are the most readily available silylating reagents, their use in catalytic silylation has not yet been achieved, probably because of the difficulty of oxidative addition of the Si–Cl bonds to transition metal centers. The first example of the transition metal-catalyzed silylation of alkenes with chlorosilanes and silylsulfides, silylselenides, and silyltellurides has been reported [33]. This reaction proceeds under mild conditions with a catalytic amount of a zirconocene complex in the presence of a Grignard reagent to give alkenylsilanes and/or allylsilanes.

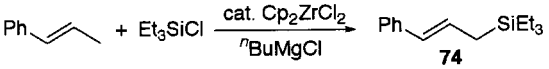
For example, styrene reacted with chlorotriethylsilane under reflux in THF in the presence of ^{n}BuMgCl and a catalytic amount of zirconocene dichloride to give the *E* isomer of alkenylsilane **73a** in 93% yield and with greater than 99% regio- and stereoselectivity (Scheme 3.48). In this reaction, only a trace amount of $Et_3Si^{n}Bu$ (<5%) was formed as byproduct, probably by direct reaction of Et_3SiCl with ^{n}BuMgCl.



Scheme 3.48

When Cp_2TiCl_2 was used instead of Cp_2ZrCl_2 **73a** was obtained in 21% yield only. The use of ^{s}BuMgCl and EtMgBr in place of ^{n}BuMgCl afforded **73a** in yields of 78 and 57%, respectively, but no reaction occurred with MeMgCl and ^{t}BuMgCl. When Me_3SiCl was used as the silylating reagent, (*E*)-2-phenyl-1-(trimethylsilyl) ethylene (**73b**) was obtained in only a moderate yield, with unchanged styrene, probably because of the low boiling point of Me_3SiCl. This problem was solved by employing Me_3SiSPh, which afforded **73b** in an excellent yield. The reaction also proceeded when $Me_3SiSePh$ and $Me_3SiTePh$ were used as the silylating reagents.

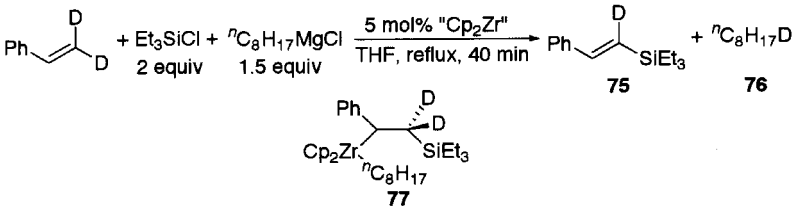
Interestingly, when *β*-methylstyrene was employed as an internal alkene, allylsilane **74** was obtained in 22% yield as the sole product rather than the corresponding alkenylsilane (Scheme 3.49). This result can be explained by assuming that in the reaction medium *β*-methylstyrene was isomerized to allylbenzene, which then underwent silylation to give **74**. Indeed, when allylbenzene was employed, **74** was obtained in 46% yield under the same conditions. A trimethylsilyl group could be introduced efficiently by use of either Me_3SiCl or Me_3SiSPh.



Scheme 3.49

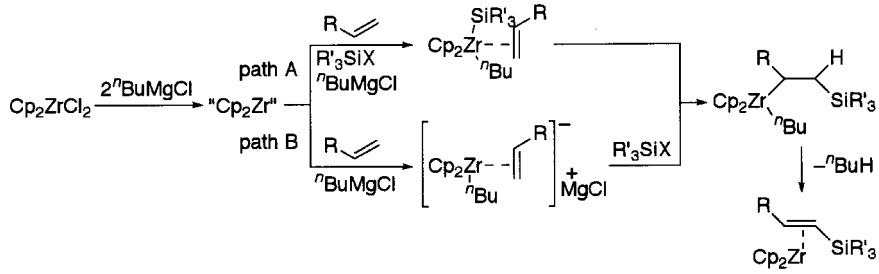
A labeling experiment was performed to prove the *β*-elimination mechanism. The reaction of $PhCH=CD_2$ with Et_3SiCl (2 equiv.) and $^{n}C_8H_{17}MgCl$ (1.5 equiv.) in the presence of "Cp_2Zr" (5 mol%), prepared in situ from [Cp_2ZrCl_2] and

^{n}BuMgCl (2 equiv.), was conducted under reflux for 40 min (Scheme 3.50). Addition of benzaldehyde to trap the remaining $^{n}C_8H_{17}MgCl$ then quenching with aqueous 0.1 M HCl gave nearly equal amounts of monodeuterated product **75** (deuterium content > 98%) and **76** (deuterium content > 95%). This result confirms that one of the deuterium atoms of $PhCH=CD_2$ was transferred to the terminal carbon atom of the octyl group by β-elimination from **77**.



Scheme 3.50

Plausible pathways have been proposed for this zirconocene-catalyzed silylation reaction (Scheme 3.51).



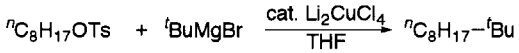
Scheme 3.51

3.3.3
Substitution at Carbon by Organomagnesium Compounds

In organic synthesis a good general method for creating carbon-carbon bonds by formal nucleophilic substitution would be invaluable. Unfortunately the apparently obvious methods, e.g. reactions of organometallic compounds with organic halides, are often far from satisfactory. Accordingly, many variations of both the nucleophilic component and the leaving group have been tried, and the mechanistic complexities of the reactions – they are rarely straightforward nucleophilic substitutions – have been extensively studied. The reaction ($R^1MgX^1 + R^2X^2 \rightarrow R^1R^2 + MgX^1X^2$) has significant limitations, even though organomagnesium compounds are somewhat less susceptible than organolithium compounds to side reactions involving metal-halogen exchange or deprotonation. The simple, uncata-

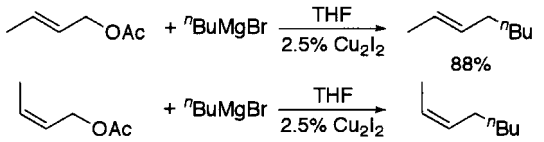
lyzed reaction indeed gives acceptable results for a fairly narrow range of organic halides only.

Reactions of saturated alkyl halides with saturated alkyl Grignard reagents are usually relatively slow and frequently produce little cross-coupling product. Reaction of Grignard reagents RMgBr with alkyl halides R′Hal, to give coupled products R–R′ can, however, be effected in good yield in THF solution in the presence of a catalytic amount of dilithium tetrachlorocuprate, Li_2CuCl_4, itself easily prepared from lithium chloride and copper(II) chloride. Primary halides react best, secondary and tertiary halides giving only poor yields of coupled products, but a wide variety of different Grignard reagents has been used. Even better results have been obtained with primary tosylates (Scheme 3.52). The catalytically active species in these reactions is believed to be an organocopper(I) complex produced by rapid metathesis between copper(I) and copper(II) halides and the Grignard reagents.

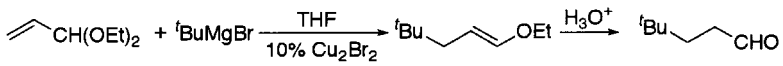


Scheme 3.52

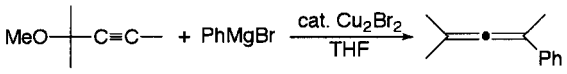
Primary allylic acetates also react readily with Grignard reagents in the presence of a catalytic amount of a copper(I) salt, with direct replacement of the acetate group (Scheme 3.53). Allylic ethers behave similarly, but here reaction might be accompanied by allylic rearrangement. This reaction has been extended to *α,β*-unsaturated acetals. In THF solution, in the presence of a catalytic amount of a copper(I) salt, they react with Grignard reagents with complete allylic rearrangement, to give the enol ether of an aldehyde. The reaction thus provides a useful route from an alkyl halide to an aldehyde containing three more carbon atoms (Scheme 3.54). Analogous substitution of propargyl esters or ethers leads to allenes (Scheme 3.55).



Scheme 3.53

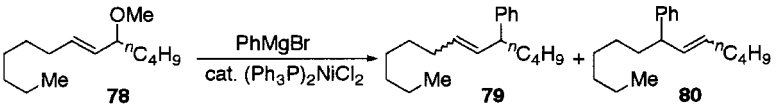


Scheme 3.54

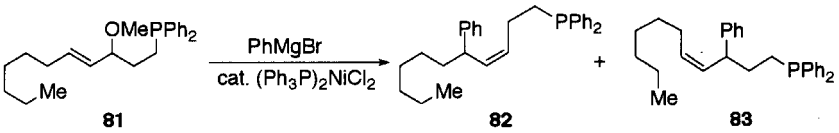


Scheme 3.55

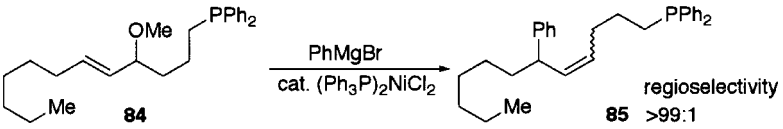
In 1995 Hoveyda et al. reported [34] that treatment of allylic ether **78** with PhMgBr in the presence of 5 mol% $(PPh_3)_2NiCl_2$ furnished equal amounts of **79** and **80** in only 10% total yield (Scheme 3.56). In contrast, when phosphine-containing allylic ether **81** is used, **82** is formed regioselectively (**82**/**83** = 8 : 1) within 3 h. Whereas ether **78** furnishes **79** and **80** in 10% yield, allylic substitution products from **81** (**82** and **83**) are obtained in 70–75% isolated yield (Scheme 3.57). When the tether length is increased by one methylene unit (**84** as substrate), C–C bond formation is more sluggish (24 h for **84** compared with 3 h for **81**), but somewhat unexpectedly, regioselectivity is enhanced to > 99 : 1 (Scheme 3.58). The influence of the resident Lewis basic phosphine is especially evident in reactions in which MeMgBr is used as the alkylating agent. With substrate **78**, < 2% product is detected after 18 h. In contrast, when **84** is treated with 5 equiv. MeMgBr and 5 mol% $(PPh_3)_2NiCl_2$ (THF, 22 °C), **86** is obtained in 74% isolated yield (Scheme 3.59). Moreover, C–C bond formation occurs with complete control of regiochemistry and the product alkene is exclusively *cis*.



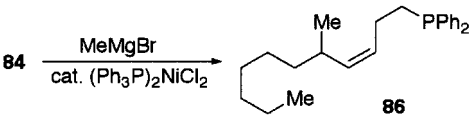
Scheme 3.56



Scheme 3.57

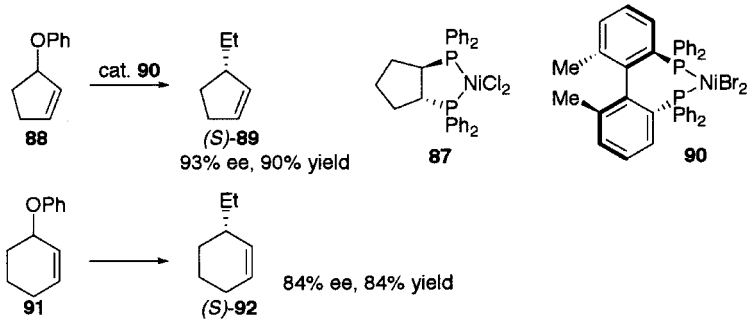


Scheme 3.58



Scheme 3.59

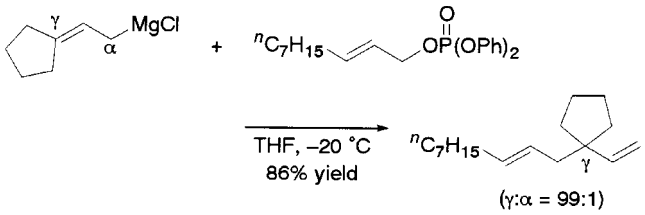
Consiglio and coworkers have shown that in the presence of an appropriate chiral Ni catalyst addition of EtMgBr to cyclic allylic phenyl ethers occurs with high enantioselection and excellent yield (>84%) [35]. Thus, in the presence of 2 mol% Ni(II) bromide or chloride complexes of (+)-(*R*,*R*)-cyclopentane-1,2-diyl-bis(diphenylphosphine) (**87**), reaction of cyclopentenyl ether **88** with EtMgBr results in the formation of 3-ethylcyclopentene (*S*)-**89** in 92% yield with 83% ee. Higher levels of enantiocontrol are observed when (*R*)-6,6′-dimethylbiphenyl-2,2′-diyl)bisdiphenylphosphine (diphemp, **90**) is used as the chiral ligand; (*S*)-**89** is obtained in 93% ee and 90% yield. Variation of catalyst structure revealed that the enantioselectivity is dependent on steric rather than electronic factors; in contrast, the nature of the leaving group, solvent, or halide of the Grignard reagent proved not to affect the outcome of catalytic alkylations. Catalytic allylic substitutions with cyclohexenyl substrate **91** follow similar overall trends but with generally lower levels of enantioselection (Scheme 3.60). Consiglio has suggested that this difference in enantiofacial selectivity might be attributable to the more rigid allyl moiety in the five-membered-ring starting material **88**. This catalytic enantioselective C–C bond-forming reaction is only appreciably enantioselective when EtMgBr is used (e.g. 12% ee with MeMgBr and 71% ee with ^{n}PrMgBr). Nonetheless this study is a critical first step towards the development of this class of catalytic asymmetric reactions and does enable ready access to a variety of optically enriched cyclic hydrocarbons.



Scheme 3.60

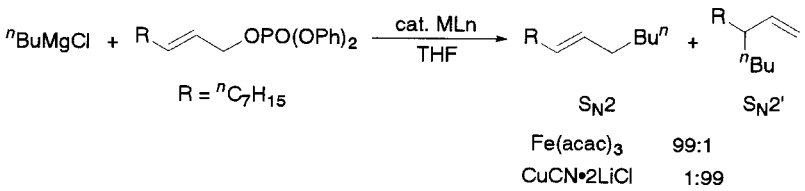
Yamamoto et al. have reported selective γ-coupling of an allylmagnesium reagent with diphenylphosphates [36]. Reaction of (*E*)-2-decenyl 1-diphenylphosphate with 1.1 equiv. 2-cyclopentylideneethylmagnesium chloride in THF at –20 °C gave the γ-alkylated product in 86% yield with a γ/α ratio of 99:1 (Eq. 1). Thus, the γ-carbon of the Grignard reagent attacked the primary carbon of the phosphate (Scheme 3.61).

They also reported transition metal-catalyzed regioselective substitution reactions of allylic diphenylphosphates with Grignard reagents – S_N2-selective coupling with Ni or Fe as catalyst and S_N2'-selective coupling reactions with a cataly-



Scheme 3.61

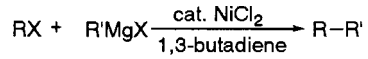
tic amount of CuCN · 2LiCl (Scheme 3.62) [37, 38]. The reaction was applied to the asymmetric γ-methylation of allylic Grignard reagents. Optically active methyl 1,1′-binaphthyl-2,2′-diylphosphate reacted with a variety of cinnamyl Grignard reagents to afford the corresponding γ-methylated products with up to 48% ee [39].



Scheme 3.62

Very recently, Kambe et al. have developed nickel-catalyzed cross-coupling reactions of Grignard reagents with alkyl halides and tosylates (Scheme 3.63) [40]. In 1972, Kumada's group and Corriu's group independently reported cross-coupling of Grignard reagents with aryl and alkenyl halides catalyzed by nickel(II) halides [41]. The catalytic cycle, which involves oxidative addition, transmetalation, and reductive elimination steps, has become a prototype of a more practical Pd-catalyzed cross-coupling reaction. These reactions proceed smoothly with a variety of organometallic reagents containing B, Mg, Li, Sn, Al, and Zn as the metal connecting to alkyl, alkenyl, aryl, alkynyl, allyl, and benzyl groups as the organic part. The coupling partner is, however, generally limited to aryl and alkenyl moieties. The use of alkyl halides, triflates, or tosylates usually gives unsatisfactory results, mainly because of the slow oxidative addition to transition metal catalysts and the facile β-elimination from the alkylmetal intermediates. Thus, the alkyl-alkyl cross-coupling reaction catalyzed by transition metal complexes has remained an interesting and challenging theme to be solved in this field. They have found that Ni catalyzes the cross-coupling reaction of alkyl chlorides, bromides, and tosylates with Grignard reagents in the presence of a 1,3-butadiene as additive.

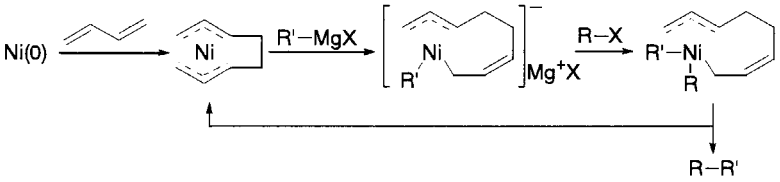
For example, reaction of *n*-decyl bromide with *n*-butylmagnesium chloride (1.3 equiv.) in the presence of isoprene (1.0 equiv.) and $NiCl_2$ (0.03 equiv.) at 25 °C for 3 h gave tetradecane in 92% yield with trace amounts of decane (<1%) and decenes (2%). In the absence of isoprene, tetradecane was obtained in only 2% yield



R = alkyl R' = alkyl, aryl
X = Cl, Br, OTs

Scheme 3.63

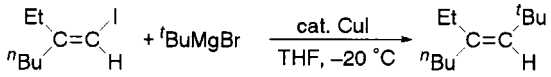
and significant amounts of decane and decenes were formed. The use of $Ni(acac)_2$ and $Ni(cod)_2$ also afforded tetradecane in high yields. Optimization of the reaction conditions using 1,3-butadiene revealed that use of only 1 mol% $NiCl_2$ and 10 mol% 1,3-butadiene, based on the halides, at 0 °C afforded coupling products quantitatively in the reaction of primary bromides with primary alkyl Grignard reagents. Interestingly, the bromo substituent on the aryl ring remained intact in this reaction system. This cross-coupling reaction also proceeds efficiently when alkyl tosylates are used. It should be noted that alkyl chlorides can also undergo this cross-coupling reaction, giving rise to the desired products in good yields. This is the first example of cross-coupling of inactivated alkyl chlorides. Aryl and secondary alkyl Grignard reagents also afforded the corresponding products in moderate to good yields, but no reaction occurred with $CH_2{=}CHMgBr$ and $PhC{\equiv}CMgCl$ under similar conditions, and most of the alkyl bromides were recovered. On the basis of results from several experiments performed to elucidate the reaction pathway, the following mechanism was assumed (Scheme 3.64).



Scheme 3.64

Not surprisingly, attempts at uncatalyzed cross-coupling between organomagnesium compounds and vinyl or aryl halides generally fail, and early studies of transition metal catalysis led to a variety of products, notably derived from homo-coupling (2RMgX → R–R), reduction, and elimination. Catalysts which lead to good yields of the desired products are now available, however, although small amounts of homo-coupling and reduction products are also commonly obtained and rearrangement of the organic group of the organomagnesium compound can also occur.

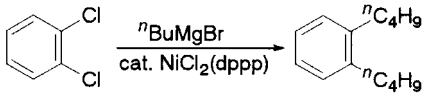
Alkenyl iodides are also readily alkylated by Grignard reagents under catalytic conditions to yield the corresponding alkenes with retention of the configuration of the double bonds (Scheme 3.65). Yields are usually higher than in the reaction with dialkylcuprates. Because alkenyl iodides themselves are readily obtained by a variety of procedures, the sequence provides a general route to di- or tri-substituted alkenes. The reactive intermediate is believed to be a homocuprate.



Scheme 3.65

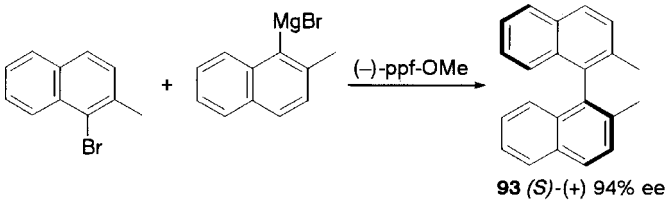
The most generally applicable catalysts are diphosphine complexes of nickel(II) halides, notably dichloro[1,3-bis(diphenylphosphino)propane]nickel(II), "$NiCl_2$(dppp)", and to a lesser extent analogous palladium(II) complexes. Many examples are listed in reviews [42–44].

For instance, treatment of a solution of 1,2-dichlorobenzene with ^{n}BuMgBr (2.0 equiv.) in the presence of catalytic amount of $NiCl_2$(dppp) afforded 1,2-dibutylbenzene in 83% yield (Scheme 3.66) [45].



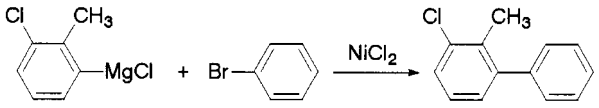
Scheme 3.66

The nature of the phosphine ligand can occasionally be critical, and some success has been achieved in inducing asymmetry by use of chiral ligands. A notable example is shown in Scheme 3.67 [46].



Scheme 3.67

In contrast, cross-coupling between arylmagnesium chlorides and aryl bromides is catalyzed by nickel(II) chloride, without any bidentate ligand (Scheme 3.68) [47].

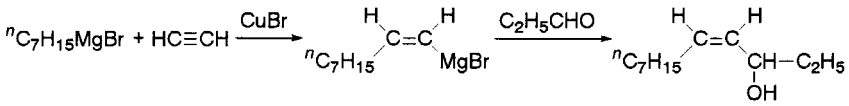


Scheme 3.68

3.3.4
Addition to Carbon-Carbon Multiple Bonds

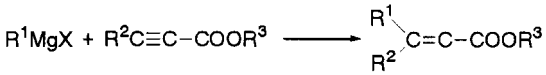
Cp_2TiCl_2-catalyzed hydromagnesation of alkynes, alkenes, and conjugated dienes has been described in Section 3.2, in which the method of preparation of organomagnesium compounds was discussed. Here, carbomagnesation of acetylenic bonds in the presence or absence of a copper catalyst will be discussed.

Acetylene is known to be metalated by Grignard reagents. In the presence of 5% copper(I) salt, however, 35–40% *syn* addition occurs (Scheme 3.69) [48].



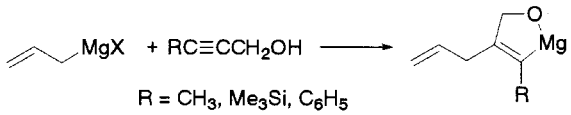
Scheme 3.69

Grignard reagents undergo conjugate addition reactions to some acetylenic acids, esters, and nitriles in the presence or absence of a copper catalyst (Scheme 3.70) [49].



Scheme 3.70

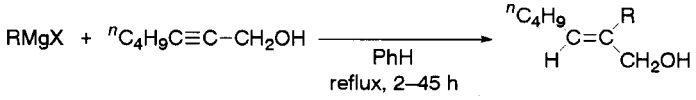
The enhanced reactivity of allylic Grignard reagents enables them to react with acetylenic alcohols by an anti-addition process (Scheme 3.71) [50].



Scheme 3.71

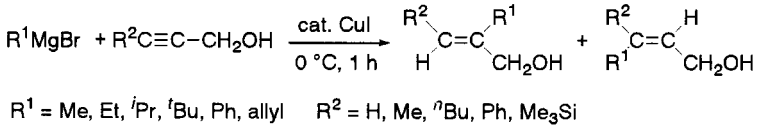
The reaction is clearly oxygen-assisted, because the yield drops to 7% for 6-hydroxy-2-hexyne, and 0% for 7-hydroxy-2-heptyne in which the heteroatom is too far removed for efficient assistance.

Grignard reagents other than those of the allylic type do not add as well to alkynols. Propargyl alcohols react with vinylmagnesium chloride in tetrahydrofuran (60%) and also with methyl, ethyl, *i*-propyl, and phenyl Grignard reagents in benzene (Scheme 3.72) [51].



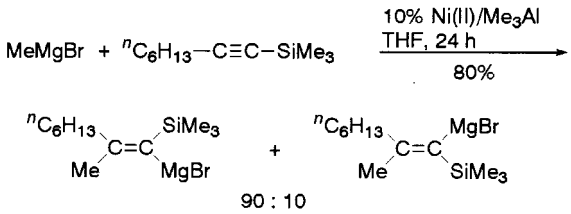
Scheme 3.72

In the presence of 10% copper(I) iodide, however, most Grignard reagents (except vinyl) can undergo addition under much milder conditions and, still, in an *anti* fashion (Scheme 3.73) [52].



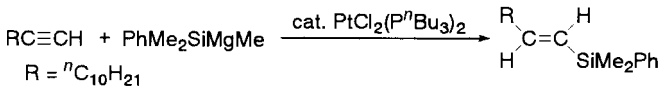
Scheme 3.73

Synthetically more useful is the reaction of silylated alkynes with methylmagnesium bromide catalyzed by 10 mol% of the 1:1 complex of nickel acetylacetonate and trimethylaluminum; in this reaction the regioselectivity is imposed by the bulky trimethylsilyl group (Scheme 3.74) [53].



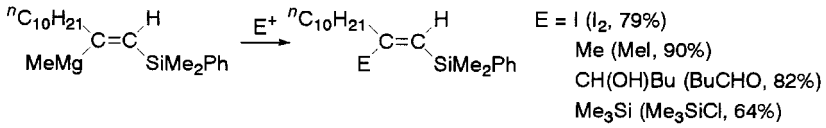
Scheme 3.74

Platinum- or copper-catalyzed silylmagnesation of acetylene with $PhMe_2SiMgMe$, derived from $PhMe_2SiLi$ and MeMgI, then aqueous quenching provided exclusively (*E*)-1-silyl-1-alkenes. For instance, treatment of 1-dodecyne with $PhMe_2SiMgMe$ in the presence of a catalytic amount of $PtCl_2(P^{n}Bu_3)_2$ gave (*E*)-1-(dimethylphenylsilyl)-1-dodecene in 90% yield (Scheme 3.75) [54].



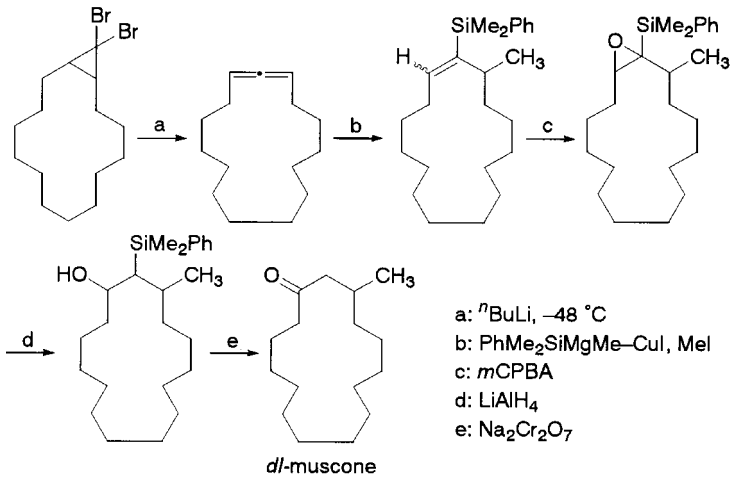
Scheme 3.75

This method provides not only simple silyl-substituted alkenes but also functionalized alkenylsilanes. Some electrophiles react with the alkenylmetal species without difficulty. For example, treatment of the intermediate derived from $PtCl_2(P^nBu_3)_2$-catalyzed silylmagnesation of 1-dodecyne with iodine, methyl iodide, and valeraldehyde gave the corresponding silylalkenes carrying the electrophilic partner in the *E* configuration (Scheme 3.76). All these electrophiles reacted at 25 °C within 1 h.



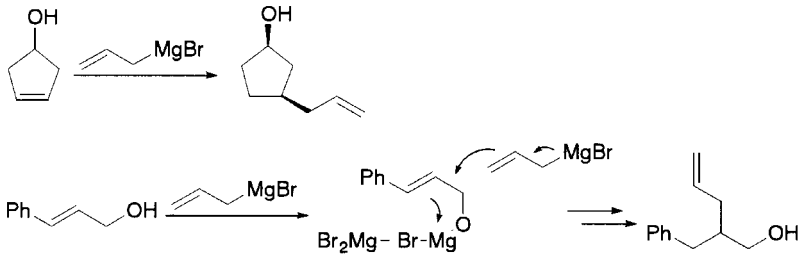
Scheme 3.76

Silylmagnesation of 1,2-cyclopentadecadiene then quenching with MeI gave 3-methyl-2-(dimethylphenylsilyl)-1-cyclopentadecene (77% yield). Epoxidation (97%) and oxirane ring-opening (47%) gave the hydroxysilane. Final oxidation of the hydroxysilane produced *dl*-muscone (96%, Scheme 3.77) [55].



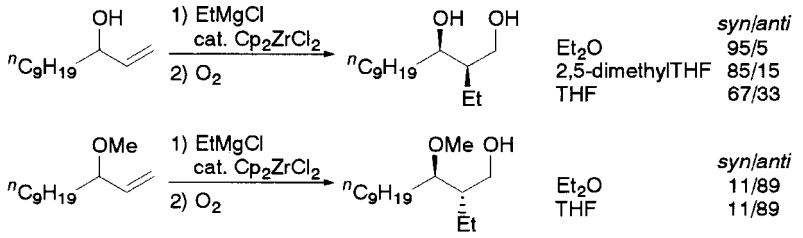
Scheme 3.77

Eisch and Husk reported the stereoselective addition of allylmagnesium halides to cyclic unsaturated alcohol (Scheme 3.78) [56]. The stereochemical outcome observed clearly implies involvement of the alcohol function as a directing unit. Felkin et al. subsequently reported that cinnamyl alcohol reacts with allylmagnesium bromide to afford the corresponding addition product in good yield [57].



Scheme 3.78

Hoveyda et al. have reported that allylic alcohols readily react in the presence of 5 mol% Cp_2ZrCl_2 to afford the corresponding diols diastereoselectively (Scheme 3.79) [58].



Scheme 3.79

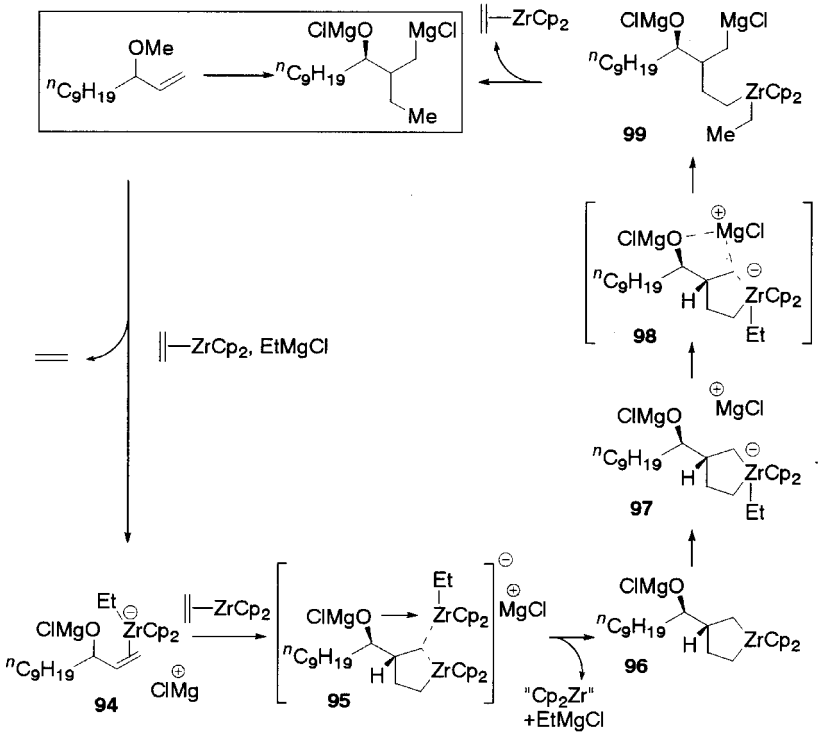
Allylic ethers also undergo catalytic ethylmagnesation with excellent selectivity and in good yield. There are, however, notable differences between the reactions of allylic ethers and alcohols:

- Zr-catalyzed reactions of allylic ethers afford the *anti* diastereomers predominantly (the *syn* isomers observed for alcohols); and
- as the size of the *α*-alkyl substituent increases, reaction selectivity is also increased, which is also in contrast with the reactions of allylic alcohols.

Another notable difference between the Zr-catalyzed ethylmagnesations of allylic ethers and alcohols is the effect of solvent Lewis basicity on reaction selectivity. Thus, as illustrated in Scheme 3.79, whereas reactions with allylic ethers are entirely insensitive to variations in solvent structure, those of allylic alcohols are strongly influenced. These observations led Hoveyda and coworkers to conclude that for allylic alcohols (allylic alkoxides after rapid deprotonation by the Grignard reagent) there is chelation between the Lewis basic heteroatom and a metal center (Zr or Mg); this association, which gives rise to transition state organization and high diastereocontrol, is altered in the presence of Lewis basic THF, with diminution in selectivity.

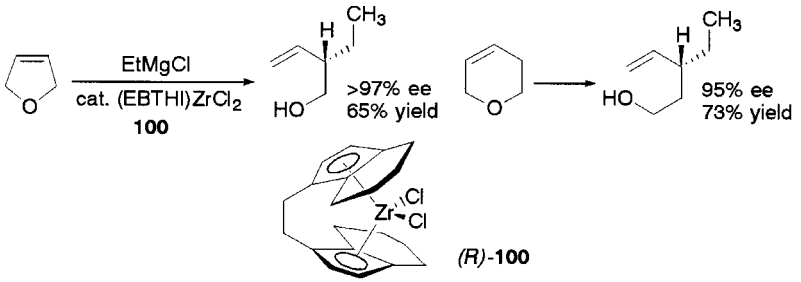
On the basis of extensive mechanistic studies they proposed [59] the mechanistic paradigm shown in Scheme 3.80. Some notable features of this proposed path-

way include the involvement of two zirconocene units (**94** → **95** → **96**), internal chelation between the resident metal alkoxide and the bound zirconocene (**95**), and heteroatom-directed cleavage of the intermediate zirconacyclopentane (**97** → **98** → **99**).



Scheme 3.80

Hoveyda and coworkers applied this new method to the enantioselective alkylation of alkenes. In the presence of 2.5–10 mol% non-racemic (EBTHI)$ZrCl_2$ (**100**) (or (EBTHI)Zr-binol) and EtMgCl as the alkylating agent, five-, six-, and seven-membered unsaturated heterocycles undergo facile asymmetric ethylmagnesation (EBTHI = ethylenebistetrahydroindenyl) (Scheme 3.81) [60]. The rate of the catalytic alkylation of the product terminal alkenes is sufficiently slower that unsaturated alcohols and amines can be isolated in high yield (the second alkylation is not generally diastereoselective). Zr-catalyzed asymmetric alkene alkylation thus affords non-racemic reaction products that bear alkene and a carbinol units, functional groups that are readily amenable to a wide range of subsequent derivatization procedures.



Scheme 3.81

3.3.5
Addition of Organomagnesium Compounds to Carbonyl Groups

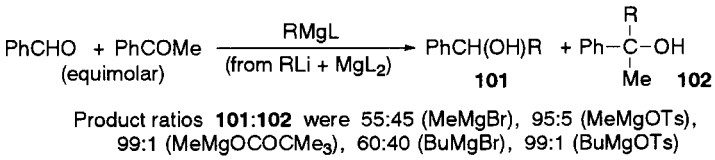
The addition of organomagnesium compounds to the carbonyl group of aldehydes and ketones has a long history, and remains one of the most important reactions for carbon-carbon bond formation. Although the overall reaction is simple, it is susceptible to a number of side reactions, and its mechanism might be far from straightforward. The mechanistic complexities are not merely academic, because an appreciation of these might be important in maximizing yields and minimizing side reactions.

Although many of these reactions proceed in nearly quantitative yield, a few result in poor yields. Poor yields are most likely to be encountered in the synthesis of tertiary alcohols with bulky alkyl groups in which side reactions compete more effectively. The two most important side reactions are enolization and reduction. Enolization can occur if the ketone has at least one hydrogen atom on either of the α-carbons and reduction can occur when the R of the Grignard reagent has hydrogen on its β-carbon.

Addition of an organomagnesium compound to an aldehyde is an excellent general method for preparing secondary alcohols, and the side reactions referred to above are a problem only in particularly unfavorable cases. Many examples have been described in Organic Synthesis. α,β-Unsaturated aldehydes normally undergo mainly, or exclusively, 1,2-addition (Scheme 3.82) [61].

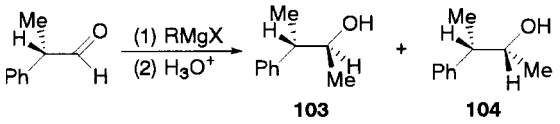
Scheme 3.82

Although the reactivity of aldehydes towards organomagnesium compounds is greater than that of ketones, selective reactions of conventional Grignard reagents with formyl groups in the presence of oxo groups are not usually viable. It has, however, been reported that ligand exchange between organolithium compounds and magnesium carboxylates and sulfonates gives reagents with much greater selectivity (Scheme 3.83) [62].



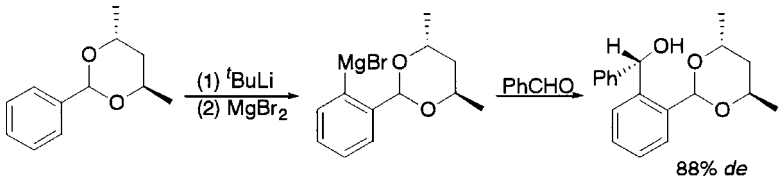
Scheme 3.83

Addition of an organomagnesium compound to an aldehyde gives rise to a new asymmetric carbon atom, and much effort has been devoted to maximizing the stereoselectivity of such additions. Three types of reaction have been studied: diastereoselective addition of organomagnesium compounds to α-chiral aldehydes, diastereoselective addition of chiral organomagnesium compounds to achiral aldehydes, and enantioselective additions of achiral organomagnesium compounds to achiral aldehydes in the presence of chiral ligands. Of these, the first is the most important. Cram attributed the diastereoselectivity observed in the addition of organomagnesium compounds to α-chiral aldehydes to steric approach control. A typical example was the reaction of Grignard reagents with 2-phenylpropanal depicted in Scheme 3.84 (only one enantiomer shown for convenience). For methylmagnesium bromide or iodide the ratio of Cram (**103**) to anti-Cram (**104**) products was approximately 2:1 to 7:3 [63], and for methylmagnesium chloride at –78 °C the ratio was approximately 87.5:12.5. For butylmagnesium chloride at –78 °C the ratio was approximately 90.6:9.4, falling to 83.9:16.1 at 22 °C. These ratios are somewhat lower than those obtained from use of methyllithium and butyllithium [64].



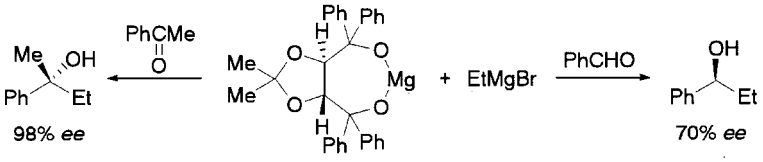
Scheme 3.84

The stereochemistry of reactions of aldehydes with chiral organomagnesium compounds has been less extensively studied, but good diastereoselectivity has been reported [65]. In Scheme 3.85 the organomagnesium reagent is more stereoselective than the organolithium compound from which it is prepared (or than a corresponding organotitanium reagent) [66].



Scheme 3.85

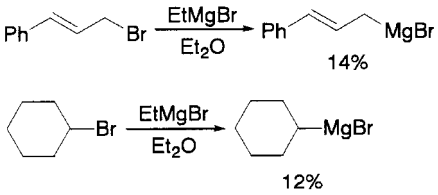
Asymmetric synthesis using reactions of achiral carbonyl compounds with achiral organomagnesium compounds in the presence of recoverable chiral solvating ligands would be very attractive. Unfortunately, only modest enantioselectivity has been achieved [67], although improvements are being made and, surprisingly, reactions with aldehydes are less promising than those with ketones (Scheme 3.86) [68].



Scheme 3.86

3.4
Halogen-Magnesium Exchange Reactions

Halogen-magnesium exchange is a very important means of preparation of organomagnesium reagents, in addition to the direct methods described in Section 3.2. Although exchange reactions between organomagnesium species and alkyl halides were observed in the early 1930s (Scheme 3.87) [69, 70], they were far from useful in organic synthesis. These reactions are generalized in Scheme 3.88. To shift the equilibrium to right, it is necessary for the resulting organomagnesium species to be much more stable than the Grignard reagent used for the reaction.



Scheme 3.87

Scheme 3.88

Although the mechanism of halogen-metal exchange reactions is not clear, three mechanisms are supposed – reaction via four-centered transition states, via radical intermediates, and via halogen ate complexes.

The order of reactivity of the halides as substrates is I > Br >> Cl >> F. Although iodides are most reactive, the use of bromides is favored because of their availability and stability. The chlorides are used rarely.

The effect of solvents on the exchange reactions has been studied [67]. The extent of exchange is proportional to the solvating power of the solvent and increases in the order diethyl ether < diethoxyethane < methoxyethoxyethane < diglym < tetrahydrofuran < dimethoxyethane.

In Section 3.4.1 practical examples of the halogen-magnesium exchange reactions are introduced. First, the preparation of perfluoroorganomagnesium compounds and polyhalogenated arylmagnesium compounds is described. Next, the exchange of polyhalomethanes and related compounds for the preparation of magnesium carbenoids is described, as is the formation of magnesium enolates via an exchange reaction. Last, other examples of the exchange reactions are summarized. ^{i}PrMgBr-mediated halogen-magnesium exchange for the preparation of polyfunctional organomagnesium reagents is described in Section 3.4.2 and in Section 3.4.3 halogen-magnesium exchange reactions via trialkylmagnesate reagents are described. The exchange of *gem*-dibromo compounds followed by alkylation via 1,2-migration of an alkyl group is discussed in Section 3.4.4.

3.4.1 Practical Examples of Halogen-Magnesium Exchange Reactions

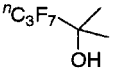
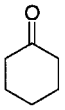
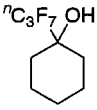
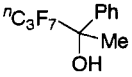
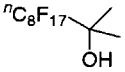
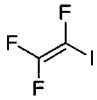
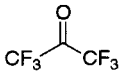
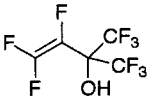
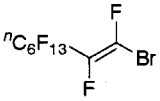
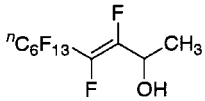
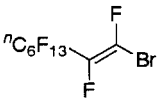
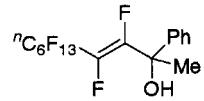
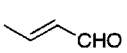
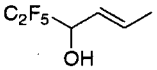
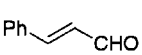
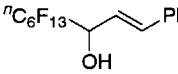
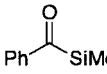
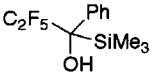
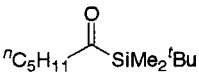
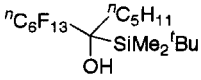
3.4.1.1 Perfluoro Organomagnesium Reagents [72–78]

The direct preparation of perfluoroalkylmagnesium reagents from a perfluoroalkyl halide and metallic magnesium does not give satisfactory results. McBee and coworkers were the first to employ a metal-halogen exchange reaction as a means of preparation of *n*-heptafluoropropylmagnesium bromide [72]. Since then examples of the preparation of perfluoro organomagnesium reagents have been reported. Representative examples are listed in Tab. 3.1.

Several points are worth making.

- Perfluoroalkyl and perfluoroalkenyl halides can be converted into the corresponding magnesium compounds with PhMgBr or EtMgBr in Et_2O or THF.
- The exchange reaction is usually conducted at low temperatures (below 0 °C), because of the thermal lability of the resulting magnesium species.
- Dimagnesium species can be prepared by treatment of 1,6-dibromoperfluorohexane with two equivalents of EtMgBr (entry 13).
- The resulting magnesium species are trapped by a variety of electrophiles such as aldehydes, ketones, chlorosilanes, and carbon dioxide.
- The reaction with *α*,*β*-unsaturated aldehydes provides 1,2-adducts exclusively (entries 9 and 10).
- Brook rearrangement does not occur for acylsilanes, in contrast with the reaction of lithium analogs, and the corresponding alcohols are obtained (entries 11 and 12).

Tab. 3.1 Preparation of perfluoro organomagnesium reagents

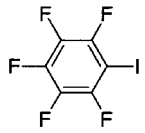
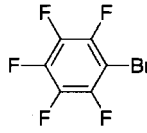
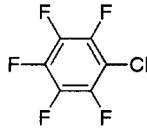
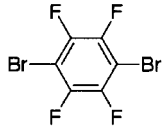
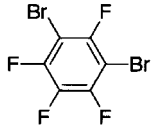
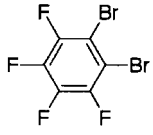
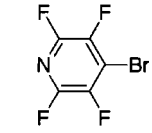
Entry	*Substrate*	*Reagent Solvent*	*Temp. Time*	*Electrophile*	*Product*	*Yield (%)*
1[69]	$^nC_3F_7I$	PhMgBr Et_2O	–78 °C 15 min			85
2[69]	$^nC_3F_7I$	PhMgBr Et_2O	–78 °C 15 min			90
3[69]	$^nC_3F_7I$	PhMgBr Et_2O	–78 °C 15 min			77
4[70]	$^nC_8F_{17}I$	PhMgBr Et_2O	–70 °C 15 min			90
5[70]	$^nC_8F_{17}I$	PhMgBr THF	–70 °C 15 min	Me_3SiCl	$^nC_8F_{17}SiMe_3$	77
6[71]		EtMgBr Et_2O	–70 °C 0.5 h			55
7[72]		PhMgBr Et_2O	0 °C 5 h	CH_3CHO		75
8[72]		EtMgBr Et_2O	0 °C 5 h			80
9[73]	C_2F_5I	PhMgBr Et_2O	–40 °C 5 min			60
10[73]	$^nC_6F_{13}I$	PhMgBr Et_2O	–40 °C 5 min			60
11[74]	C_2F_5I	EtMgBr Et_2O	–45 °C 0.5 h			83
12[74]	$^nC_6F_{13}I$	EtMgBr Et_2O	–45 °C 0.5 h			70
13[71]	$Br(CF_2)_6Br$	2EtMgBr Et_2O	–70 °C 15 min	CO_2	$HO_2C(CF_2)_6CO_2H$	81

3.4.1.2 **Polyhalogenated Arylmagnesium Reagents [79–83]**

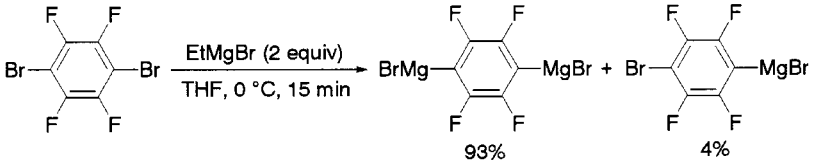
The exchange reactions of polyhalogenated arenes have been investigated by Tamborski's group. Bromopentafluorobenzene and its derivatives are converted into the corresponding magnesium compounds by the action of EtMgBr in THF, by bromine-magnesium exchange [82]. Representative examples are shown in Tab. 3.2. Not only iodo- and bromo- but also chloropentafluorobenzene can be con-

verted into pentafluorophenylmagnesium bromide in good yield. Reaction of 1,4-dibromo-2,3,5,6-tetrafluorobenzene with two equivalents of EtMgBr provided *p*-dimagnesium species (Scheme 3.89) [82].

Tab. 3.2 Preparation of polyfluorinated arylmagnesium reagents [a)]

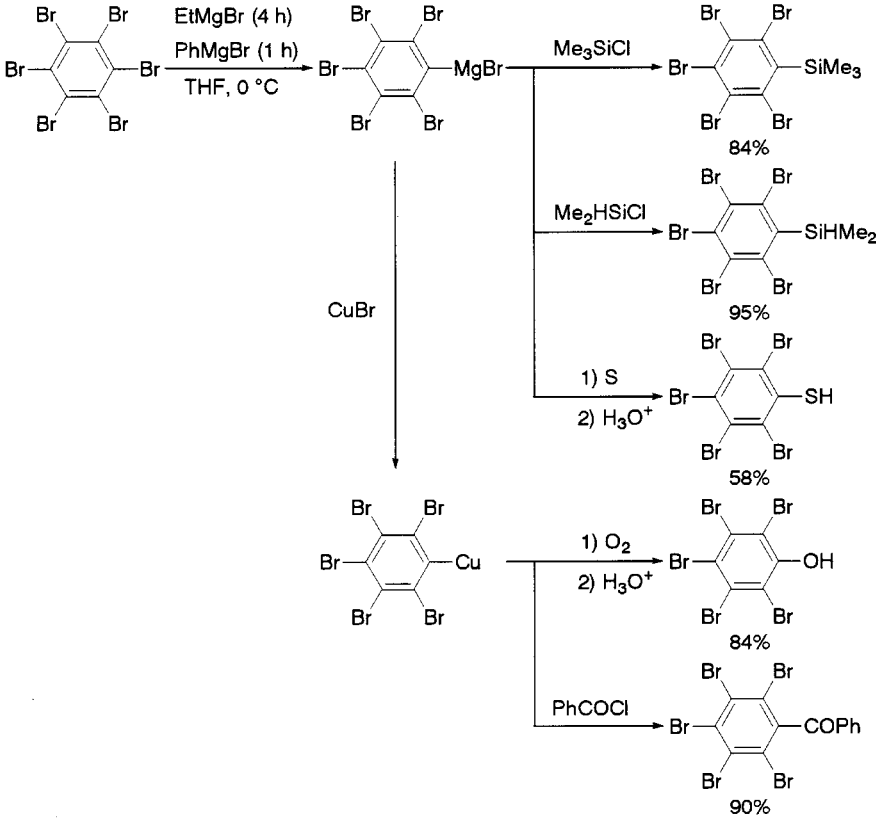
Entry	*Substrate*	*Temp.*	*Time*	*Yield (%)* [a)]
1		0 °C	1 min	100
2		0 °C	1 min	96
3		r. t.	1 h	85
4		0 °C	1 min	90
5		0 °C	15 min	95
6		0 °C	1 min	93
7		0 °C	6 min	96

a) EtMgBr is used for the exchange reaction. All reactions are performed in THF.
b) Yields of protonation products.



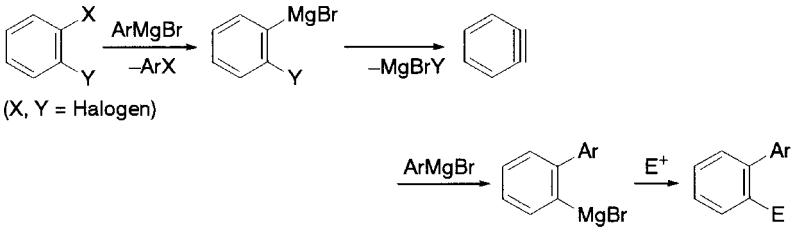
Scheme 3.89

The bromine-magnesium exchange of hexabromobenzene is also achieved by the reaction with EtMgBr or PhMgBr (Scheme 3.90) [83]. Subsequent reaction with electrophiles affords the corresponding coupling products in moderate to good yields. Transmetalation with CuBr followed by the addition of oxygen or benzoyl chloride provided pentabromophenol or pentabromophenyl phenyl ketone, respectively.



Scheme 3.90

o-Haloarylmagnesium species are known to decompose to form benzyne derivatives as intermediates; these readily react with the coexistent organometallic compounds (Scheme 3.91) [84–91]. Hart has reported the synthesis of terphenyls and alkenylbenzenes via a halogen-magnesium exchange and trapping of arynes. Examples are shown in Tab. 3.3.



Scheme 3.91

Biphenyls (entry 1) [84] or styrene derivatives (entries 2–4) [85], *p*-terphenyls (entry 5) [86], and *m*-terphenyls (entries 6–9) [87, 88] are synthesized from 2-bromo-1-iodobenzene, 2,5-dibromo-1,4-diiodobenzene, and 2,6-dibromo- or 2,6-dichloro-1-iodobenzene, respectively, in moderate to good yields.

3.4.1.3 **Exchange of Polyhalomethane Derivatives [92–99]**

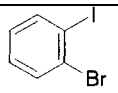
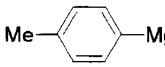
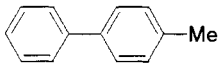
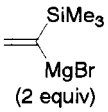
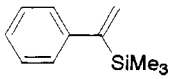
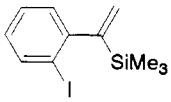
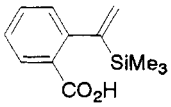
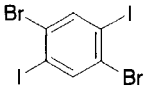
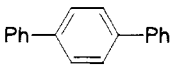
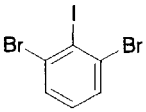
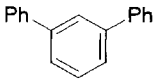
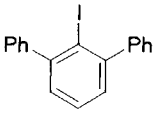
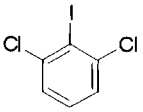
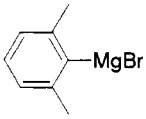
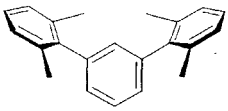
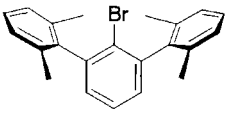
Magnesium carbenoids, which have magnesium and halogen on the same carbon atom, can be prepared by halogen-magnesium exchange with polyhalomethane derivatives. Although halogen atoms inductively stabilize the resulting anion, they are still quite unstable. Thus the reactions must be conducted at low temperatures, and occasionally with an electrophile present. Tab. 3.4 shows some examples. Halomethyl-, dihalomethyl-, and trihalomethylmagnesium species are generated and trapped with electrophiles. Silyl- or alkyl-substituted carbenoids can be also prepared (entries 4, 5, and 11).

Enantioselective halogen-magnesium exchange of 1,1-diiodoalkane has been reported by Hoffmann (Scheme 3.92) [95]. Treatment of diiodoalkane with the chiral isopropylmagnesium reagent induces iodine-magnesium exchange to generate the carbenoid species, which is configurationally stable under the conditions used. Addition of benzaldehyde and dimethylaluminum chloride affords the *cis* iodohydrin in 53% ee.

3.4.1.4 **Preparation of Magnesiated Nitrogen-Heterocycles [100–106]**

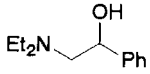
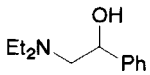
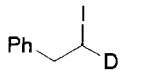
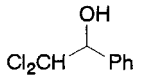
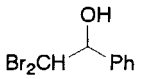
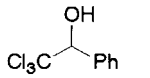
Direct access to pyridylmagnesium halides by use of metallic magnesium is difficult to achieve, and halogen-magnesium exchange is thus favored for the preparation of pyridylmagnesium reagents.

Tab. 3.3 Reaction via aryne intermediates [a)]

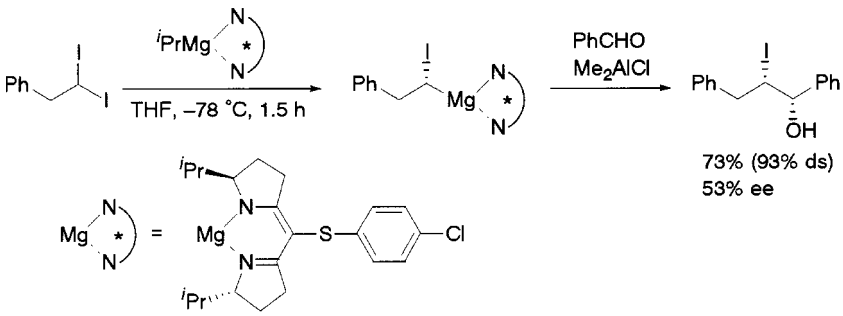
Entry	*Substrate*	*Reagent*	E^+	*Product*	*Yield (%)*
1		 (2 equiv)	H_2O		71
2		 (2 equiv)	H_2O		62
3			I_2		62
4			CO_2		55
5		PhMgBr (6 equiv)	H_2O		54
6		PhMgBr (3.5 equiv)	H_2O		77
7			I_2		88
8		 (3 equiv)	H_2O		70
9			Br_2		62

a) Reactions are performed at r.t. (entries 1, 5–7) or 40 °C (entries 2–4), or under reflux in THF (entries 8, 9).

Tab. 3.4 Preparation of magnesium carbenoids[a)]

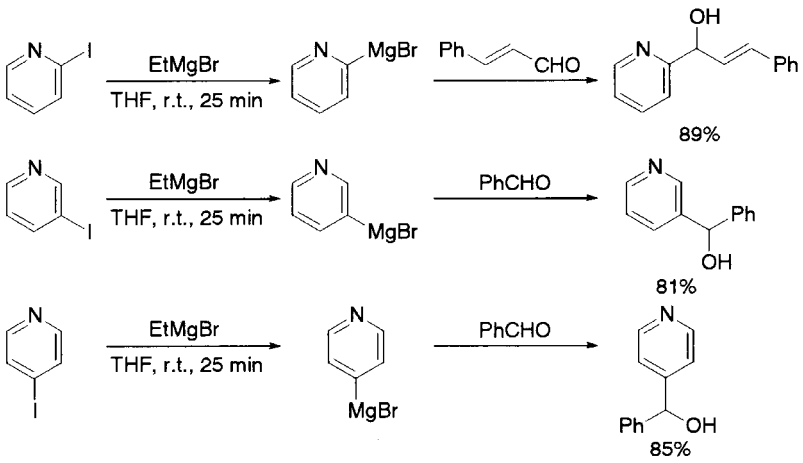
Entry	*Substrate*	*Temp.*	*Carbenoid*	E^+	*Product*	*Yield (%)*
1[88]	CH_2Br_2	–78 °C	$BrCH_2MgCl$	1) PhCHO 2) Et_2NH		50
2[88]	CH_2I_2	–78 °C	ICH_2MgCl	1) PhCHO 2) Et_2NH		45
3[89]	CH_2ICl	–78 °C	$ClCH_2MgCl$			good[b]
4[90]	^{n}BuCHICl	–70 °C	^{n}BuCHClMgCl			good[b]
5[91]	$PhCH_2CHI_2$	–78 °C	$PhCH_2CHIMgCl$	D_2O		98
6[88]	$CHCl_3$	–70 °C	$CHCl_2MgCl$	PhCHO		25
7[88]	$CHBr_3$	–78 °C	$CHBr_2MgCl$	PhCHO		71
8[92]				Me_3SiCl	$Br_2CHSiMe_3$	78
9[92]	$CHBr_2Cl$	–95 °C	$CHBrClMgCl$	Me_3SiCl	$BrClCHSiMe_3$	63
10[92]	CHI_3	–85 °C	CHI_2MgCl	Me_3SiCl	$I_2CHSiMe_3$	77
11[92]	Me_3SiCBr_3	–85 °C	Me_3SiCBr_2MgCl	Me_3SiCl	$(Me_3Si)_2CBr_2$	56
12[88]	CCl_4	–115 °C	CCl_3MgCl	PhCHO		74

a) ^{i}PrMgCl is used as reagent. Exchange reactions are conducted in THF except for entry 1 (THF–Et_2O).
b) Subsequent reaction with an electrophile was not reported.



Scheme 3.92

The exchange reactions of 2-, 3-, and 4-iodopyridine have been reported to proceed on treatment with EtMgBr in THF at room temperature [100]. Subsequent addition of aldehydes affords the corresponding alcohols (Scheme 3.93).



Scheme 3.93

Quéguiner has examined the exchange reactions of bromopyridines, which are cheaper than iodopyridines and often commercially available [101, 102]. The exchange reactions occur with ^{i}PrMgCl in THF at room temperature. Tab. 3.5 shows the results of exchange reactions and subsequent trapping by electrophiles.

The exchange reaction of 2-, 3-, and 4-bromopyridine with ^{i}PrMgCl proceeds smoothly to provide the corresponding magnesium species. The reaction of dibromopyridines affords mono-magnesium species, with complete regioselectivity for 2,3- and 2,5-dibromopyridine.

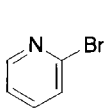
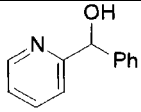
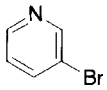
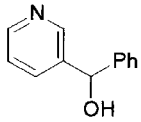
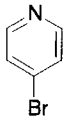
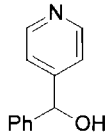
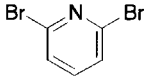
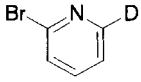
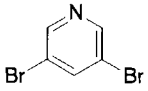
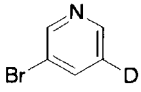
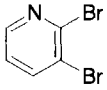
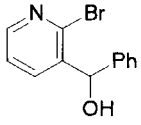
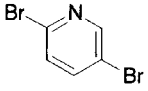
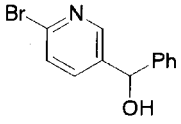
Examples of the preparation of other heterocyclic magnesium compounds are shown in Tab. 3.6. The preparation of Grignard reagents derived from bromofuran, bromothiophene, and bromoselenophene has been reported, but no synthetic application has been attempted [106].

3.4.1.5 Formation of Enolates by Halogen-Magnesium Exchange [107–113]

The halogen-magnesium exchange of α-halo carbonyl compounds has been reported to afford magnesium enolates which react with aldehydes to yield aldol products [107, 108]. The application of this reaction to the synthesis of penicillin derivatives has been reported (Scheme 3.94) [109–111].

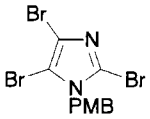
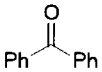
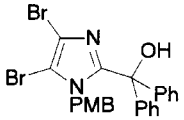
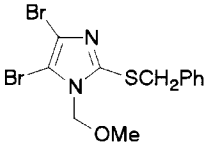
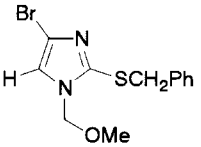
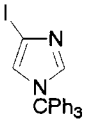
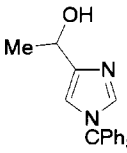
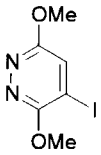
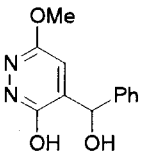
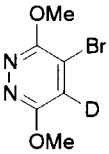
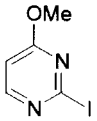
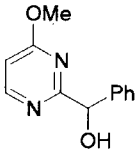
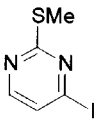
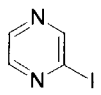
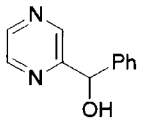
The exchange reactions of α-iodo ketones and α,α-dibromo ketones have been reported [112, 113]. Subsequent addition of aldehydes affords the corresponding β-hydroxy ketones in good yields. Representative examples are shown in Tab. 3.7.

Tab. 3.5 Preparation and reaction of pyridylmagnesium reagents [a)]

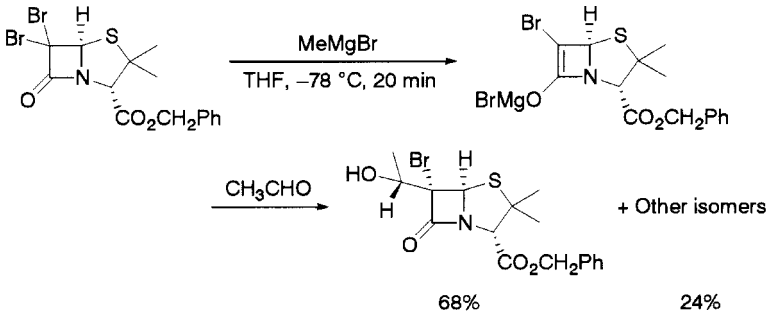
Entry	*Substrate*	*Time*	E^+	*Product*	*Yield (%)*
1		2 h	PhCHO		80
2		1 h	PhCHO		84
3		1 h	PhCHO		64
4		2 h	D_2O		95
5		1 h	D_2O		82
6		1 h	PhCHO		92
7		1 h	PhCHO		86

a) ^{i}PrMgCl is used for a reagent. Reactions are conducted in THF at room temperature.

Tab. 3.6 Preparation of heterocyclic Grignard reagents

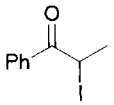
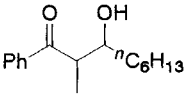
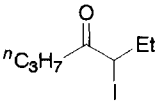
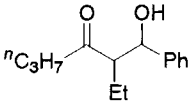
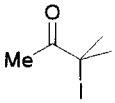
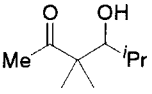
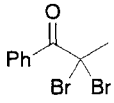
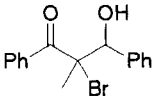
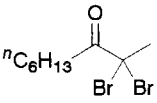
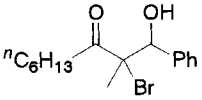
Entry	*Substrate*	*Reagent Solvent*	*Temp. Time*	*E^+*	*Product*	*Yield (%)*
1[99],a		EtMgBr Et_2O	reflux 4 h			83
2[99]		EtMgBr Et_2O	reflux 3 h	H_3O^+		81
3[100]		EtMgBr CH_2Cl_2	r. t. 0.5 h	CH_3CHO		83
4[101]		^{i}PrMgCl THF	r. t. 0.5 h	PhCHO		73
5[101]		^{i}PrMgCl THF	r. t. 0.5 h	EtOD		88
6[101]		^{i}PrMgCl THF	0 °C 1 h	PhCHO		69
7[101]		^{i}PrMgCl THF	0 °C 0.5 h	PhCHO		57
8[101]		^{n}BuMgCl THF	0 °C 0.5 h	PhCHO		59

a) PMB = *p*-methoxybenzyl.



Scheme 3.94

Tab. 3.7 Aldol reaction of enolates derived from α-halo carbonyl compounds[a)]

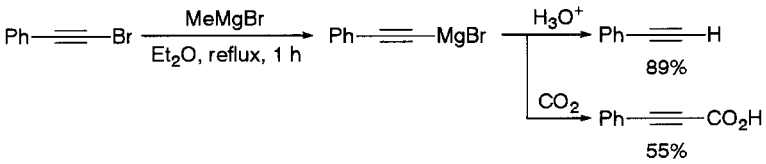
Entry	*Substrate*	*Reagent*	*Aldehyde*	*Product*	*Yield (%)*	*e/t*
1		PhMgBr	$^{n}C_6H_{13}CHO$		75	64/36
2		EtMgBr	PhCHO		81	39/61
3		EtMgBr	^{i}PrCHO		96	
4		PhMgBr	PhCHO		81	50/50
5		PhMgBr	PhCHO		87	50/50

a) All reactions are conducted in Et_2O at 0 °C.

3.4.1.6 Miscellaneous Reactions

Exchange Reaction of Alkynyl Halides [114]

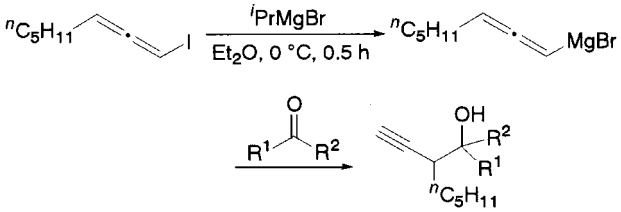
Reaction of phenylethynyl bromide and MeMgBr affords phenylethynylmagnesium bromide, as shown in Scheme 3.95.



Scheme 3.95

Exchange Reaction of Allenyl Iodides [115]

Iodine-magnesium exchange reaction of allenyl iodides occurs by the action of ^{i}PrMgBr in Et_2O. Subsequent reaction with aldehydes or ketones provides homopropargyl alcohols with high regioselectivity (Scheme 3.96).

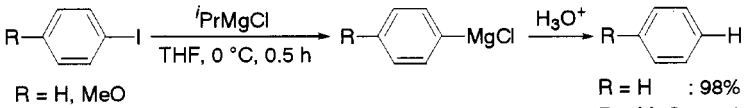


R^1 = Ph, R^2 = H 80% (e/t = 43/57)
R^1 = ^{t}Bu, R^2 = H 58% (e/t = <1/>99)
R^1 = $^{n}C_9H_{19}$, R^2 = Me 67% (e/t = 47/53)

Scheme 3.96

Exchange Reaction of Aryl Halides

Aryl iodides bearing no stabilizing group react with ^{i}PrMgCl in THF at room temperature to provide arylmagnesium species (Scheme 3.97) [116].



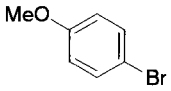
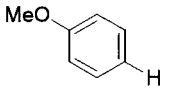
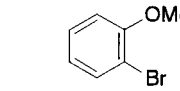
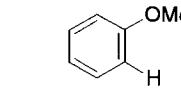
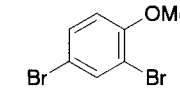
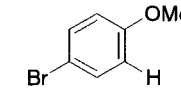
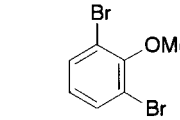
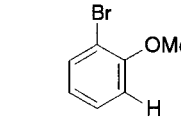
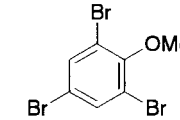
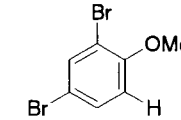
R = H, MeO

R = H : 98%
R = MeO : 95%

Scheme 3.97

In contrast, normal aryl bromides are much less reactive than aryl iodides. Some examples are shown in Tab. 3.8 [117].

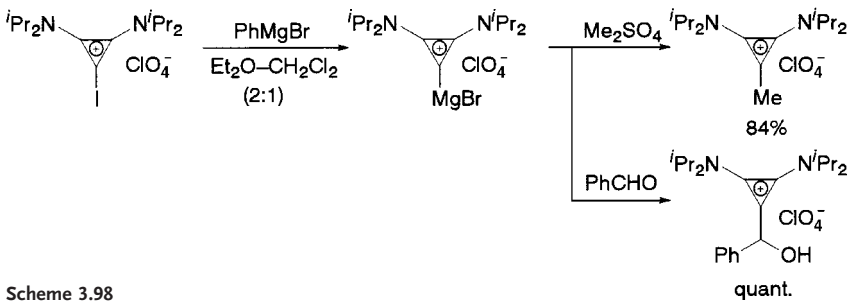
Tab. 3.8 Bromine-magnesium exchange of aryl bromides [a)]

Entry	*Substrate*	*equiv of ^{i}PrMgCl*	*Time (h)*	*Product* [b)]	*Yield (%)*
1		7.5	19		28
2		7.5	16		64
3		2.0	5		93
4		2.5	3		95
5		1.3	1		79

a) Reaction with ^{i}PrMgCl in THF at 40 °C. [b] Quenched with H_3O^+.

As is apparent from Tab. 3.8, an *ortho* methoxy group acts as a metal-directing group. Thus selective exchange occurs at the *ortho* position of a methoxy group. More than two bromines are necessary to complete the reaction.

The reaction of 1,2-bis(diisopropylamino)-3-iodocyclopropenium perchlorate with PhMgBr in Et_2O/CH_2Cl_2 (2:1) provides the magnesium derivative. Addition of electrophiles gives the coupling products in good yields (Scheme 3.98) [118].



Scheme 3.98

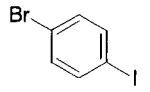
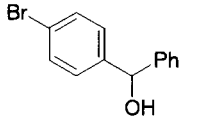
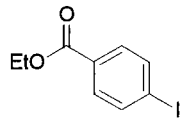
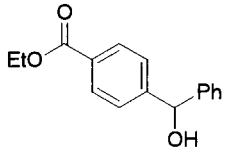
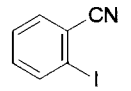
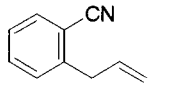
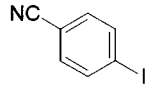
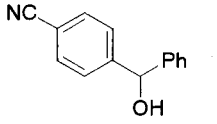
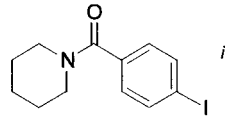
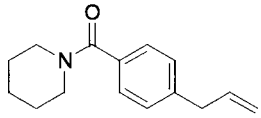
3.4.2 ^{i}PrMgBr-induced Halogen-Magnesium Exchange for the Preparation of Polyfunctional Organomagnesium Reagents

Organomagnesium compounds are highly reactive toward functional groups such as esters. Thus generation of polyfunctional organomagnesium reagents is achieved at low temperatures only. Knochel has reported the use of halogen-magnesium exchange for the preparation of polyfunctional organomagnesium reagents [119, 120]. Aryl, heteroaryl, and alkenyl halides bearing electron-withdrawing groups or metal-directing groups can be converted into the corresponding magnesium reagents by the action of ^{i}PrMgBr or $^{i}Pr_2Mg$ in THF at low temperatures.

3.4.2.1 Exchange Reaction of Aryl Halides

Iodine-magnesium exchange of aryl iodides bearing a functional group proceeds at low temperatures to provide the corresponding arylmagnesium compounds, which react with electrophiles [121]. Some examples are shown in Tab. 3.9.

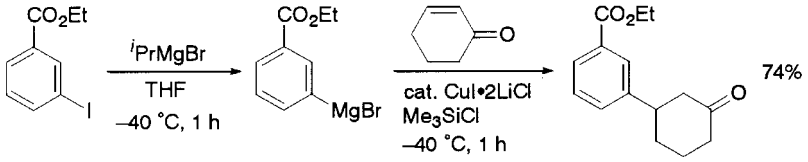
Tab. 3.9 Iodine-magnesium exchange of aryl iodides [a)]

Entry	*Substrate*	*Reagent*	*Temp. Time*	*E^+*	*Product*	*Yield (%)*
1		$^{i}Pr_2Mg$	–25 °C 0.5 h	PhCHO		93
2		^{i}PrMgBr	–40 °C 1 h	PhCHO		90
3		$^{i}Pr_2Mg$	–40 °C 0.5 h	CH_2=CHCH_2Br cat. CuCN•2LiCl		89
4		$^{i}Pr_2Mg$	–40 °C 1 h	PhCHO		94
5		$^{i}Pr_2Mg$	–25 °C 0.5 h	CH_2=CHCH_2Br cat. CuCN•2LiCl		81

a) All reactions are conducted in THF.

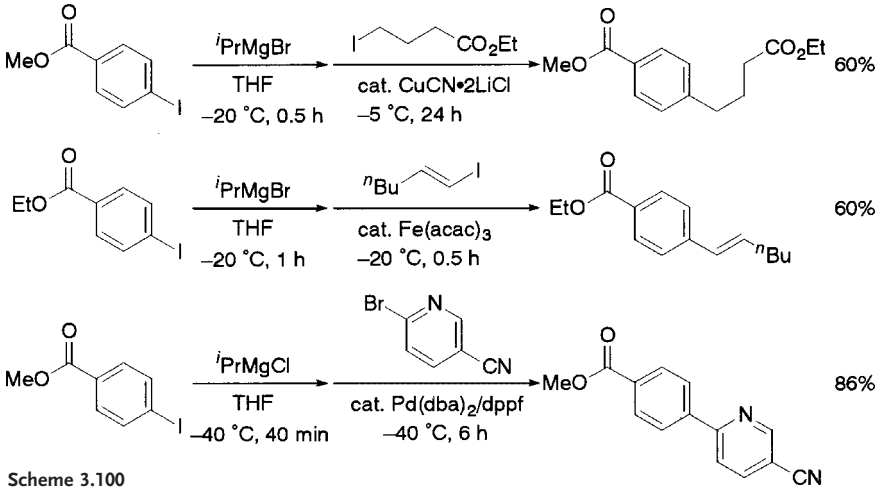
In these examples, functional groups such as ester, amide, nitrile, or halogen act as electron-withdrawing groups. The exchange reaction thus goes to completion under mild conditions.

The resulting magnesium species can be used in transition metal-catalyzed reactions. In the presence of a catalytic amount of a copper(I) salt and chlorotrimethylsilane, conjugate addition to a variety of enones occurs (Scheme 3.99) [122].



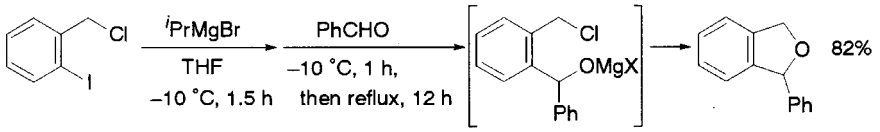
Scheme 3.99

Coupling reactions of polyfunctional organomagnesium reagents with alkyl [123], alkenyl [124], or pyridyl halides [125] are achieved by use of Cu, Fe, or Pd catalysis (Scheme 3.100).



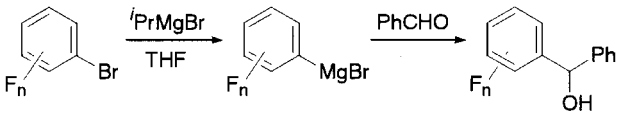
Scheme 3.100

A chloromethyl group can also be introduced into magnesium reagents, which react with aldehydes leading to the corresponding isobenzofurans (Scheme 3.101) [126].



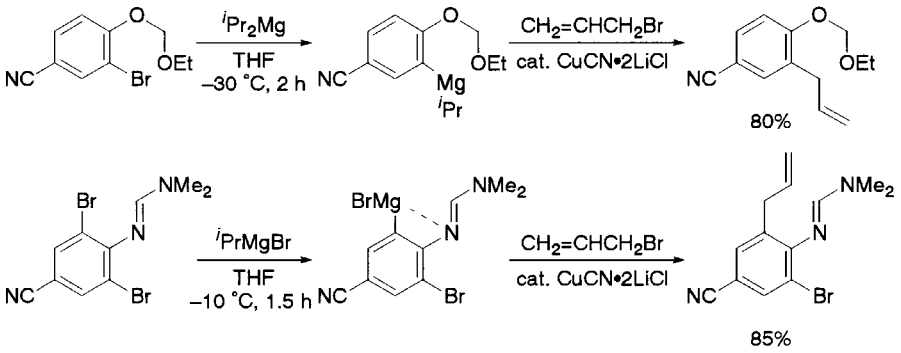
Scheme 3.101

Bromine-magnesium exchange of polyfunctionalized aryl bromides is achieved only occasionally. The effect of electron-withdrawing groups on the reactivity of aryl bromides has been studied (Scheme 3.102) [127]. To complete the exchange reaction at low temperatures strong activation with electron-withdrawing groups is needed. An metal-directing group at the *ortho* position is also effective (Scheme 3.103) [128].



3-fluoro	r. t., 3 h	50%
2,5-difluoro	r. t., 2 h	75%
2,4,5-trifluoro	–10 °C, 1 h	85%
2,3,4,5,6-pentafluoro	–78 °C, 0.5 h	88%

Scheme 3.102



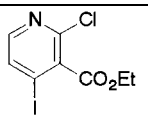
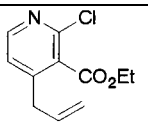
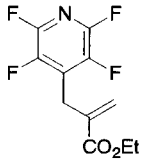
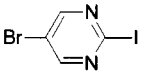
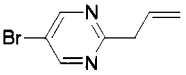
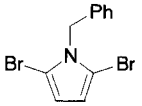
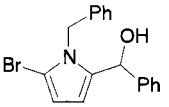
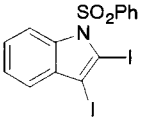
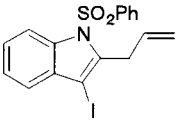
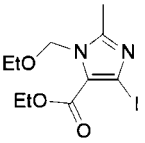
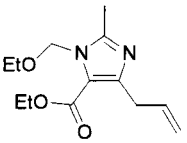
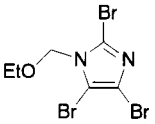
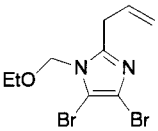
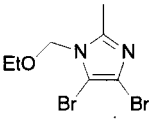
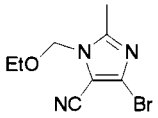
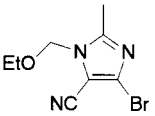
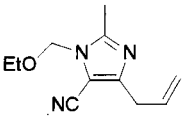
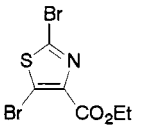
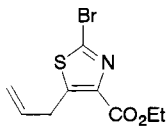
Scheme 3.103

3.4.2.2 Exchange Reaction of Heterocyclic Halides

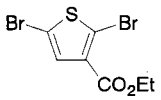
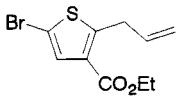
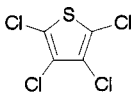
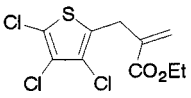
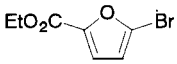
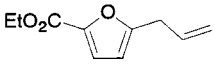
Polyfunctionalized heteroaromatic organomagnesium reagents are prepared from the corresponding halides by halogen-magnesium exchange with ^{i}PrMgBr or $^{i}Pr_2Mg$ in THF [129–131]. Examples are shown in Tab. 3.10. Magnesiated heterocycles, e.g. pyridines, pyrimidines, pyrroles, indoles, imidazoles, thiazoles, thiophenes, or furans, can be prepared and trapped with electrophiles. With dihalides or trihalides the exchange proceeds with complete regioselectivity.

Exchange of 5-iodouracils [132] or 4-iodoantipyrines [131] provided the corresponding magnesium compounds (Scheme 3.104).

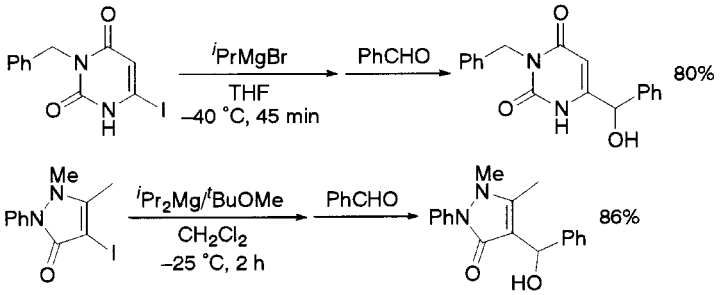
Tab. 3.10 Halogen-magnesium exchange of heteroaryl halides [a)]

Entry	*Substrate*	*Reagent Temp., Time*	E^+	*Product*	*Yield (%)*
1		^{i}PrMgBr –40 °C, 0.5 h	CH_2=CHCH_2Br cat. CuCN		82
2		^{i}PrMgBr –40 °C, 0.5 h	CH_2=C(CO_2Et)CH_2Br cat. CuCN		80
3		^{i}PrMgBr –80 °C, 10 min	CH_2=CHCH_2Br		81
4		^{i}PrMgBr –5 °C, 1 h	PhCHO		73
5		^{i}PrMgBr –30 °C, 2 h	CH_2=CHCH_2Br cat. CuCN		84
6		^{i}PrMgBr –40 °C, 1 h	CH_2=CHCH_2Br CuCN		91
7		^{i}PrMgBr –40 °C, 1 h	CH_2=CHCH_2Br CuCN		57
8		^{i}PrMgBr –40 °C, 1 h	$NCCO_2Et$		59
9		^{i}PrMgBr –40 °C, 7 h	CH_2=CHCH_2Br CuCN		68
10		^{i}PrMgBr –80 °C, 10 min	CH_2=CHCH_2Br CuCN		81

Tab. 3.10 (continued)

Entry	*Substrate*	*Reagent Temp., Time*	E^+	*Product*	*Yield (%)*
11		^{i}PrMgBr –30 °C, 2 h	CH_2=CHCH_2Br cat. CuCN		74
12		^{i}PrMgBr r. t., 2 h	CH_2=C(CO$_2$Et)CH_2Br cat. CuCN		96
13		^{i}PrMgBr –30 °C, 1 h	CH_2=CHCH_2Br cat. CuCN		80

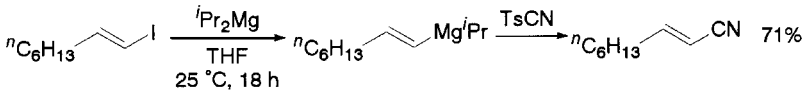
a) All reactions are performed in THF, except for entry 7 (Et_2O).



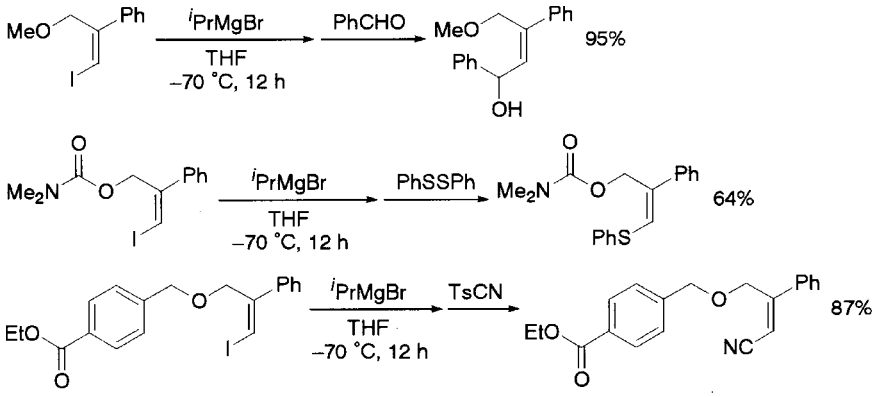
Scheme 3.104

3.4.2.3 Exchange Reaction of Alkenyl Halides

Iodine-magnesium exchange of a normal alkenyl iodide with ^{i}Pr$_2$Mg requires a reaction time of 18 h at 25 °C for complete conversion (Scheme 3.105) [133]. *β*-Iodostyrene derivatives bearing an oxygen-functionalized directing group can be converted into the corresponding alkenylmagnesium compounds at low temperatures (Scheme 3.106) [133].

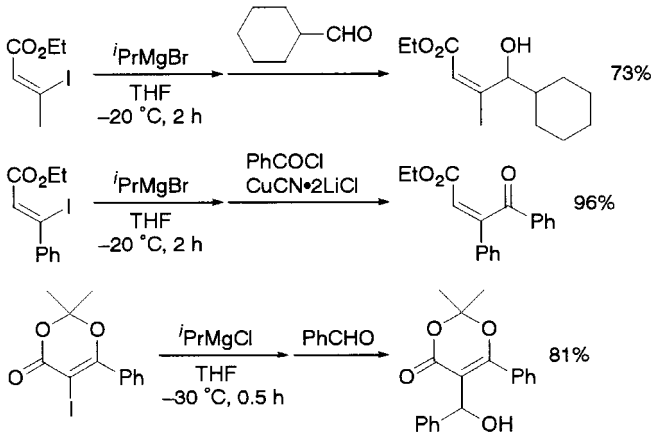


Scheme 3.105



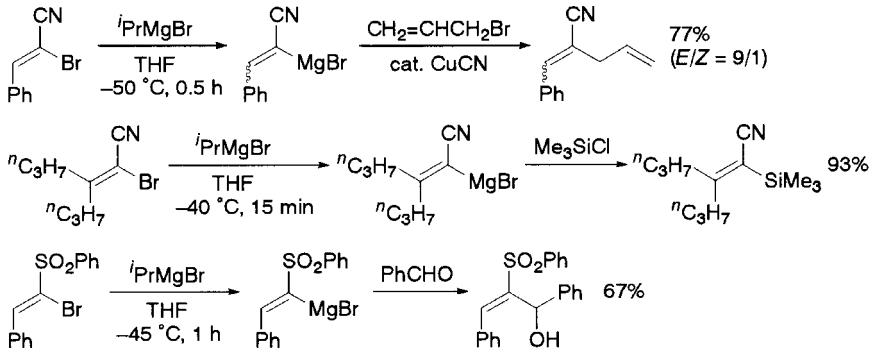
Scheme 3.106

As is apparent from Scheme 3.105, 2- or 3-iodo enoates undergo iodine-magnesium exchange under the action of ^{i}PrMgX in THF at low temperatures [134, 135].



Scheme 3.107

Bromine-magnesium exchange of alkenyl bromides proceeds only occasionally [136]. The presence of an electron-withdrawing group at the position *α* to the bromine facilitates the exchange reactions. Functionalized alkenyl bromides, e.g. bromonitriles and the bromosulfones are converted to the corresponding organomagnesium derivatives at low temperatures (Scheme 3.108).

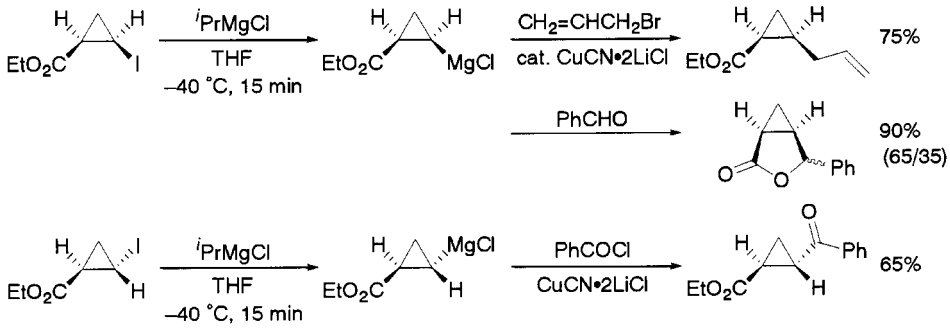


Scheme 3.108

3.4.2.4 Halogen-Magnesium Exchange of Other Halides

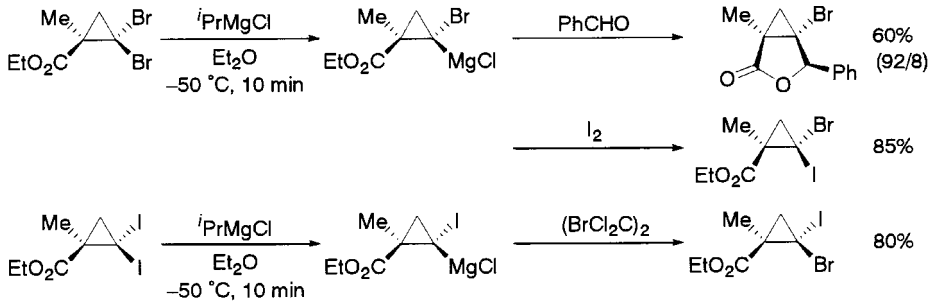
Functionalized Cyclopropylmagnesium Reagents

Iodine-magnesium exchange of 2-iodocyclopropanecarboxylates proceeds with ^{i}PrMgCl in THF at –40 °C for 15 min to afford the corresponding cyclopropylmagnesium species with retention of configuration [137]. Examples of the reaction are shown in Scheme 3.109.



Scheme 3.109

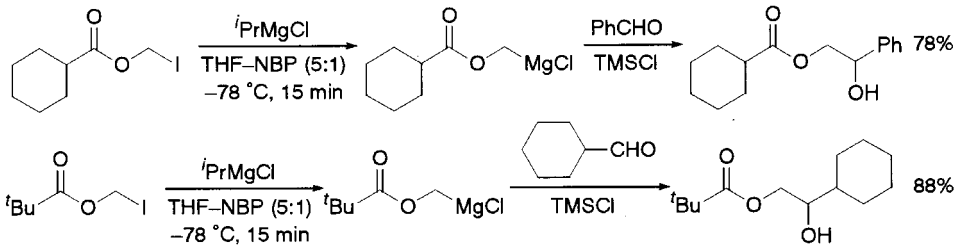
Selective exchange of *gem*-dihalocyclopropanecarboxylates is achieved in Et_2O [137]. The use of THF as a solvent reduces selectivity. Halogen-magnesium exchange occurs at the same side of an ester group, which acts effectively as a metal-directing group in a weakly coordinating solvent such as Et_2O. The resulting carbenoid species react with electrophiles with retention of configuration (Scheme 3.110).



Scheme 3.110

Functionalized Magnesium Carbenoids

The reaction of iodomethyl carboxylates with ^{i}PrMgCl in THF/*N*-butylpyrrolidinone (NBP) (5:1) at –78 °C affords the corresponding magnesium carbenoids, which react with a variety of electrophiles (Scheme 3.111) [138].



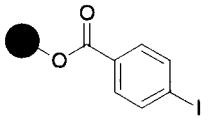
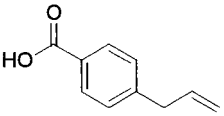
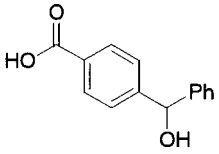
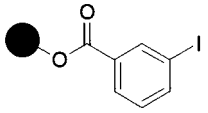
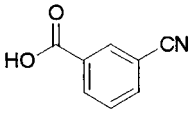
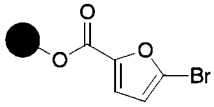
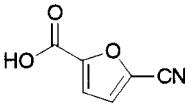
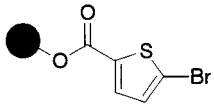
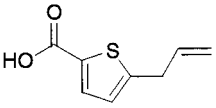
Scheme 3.111

3.4.2.5 Halogen-Magnesium Exchange of Resin-bound Halides

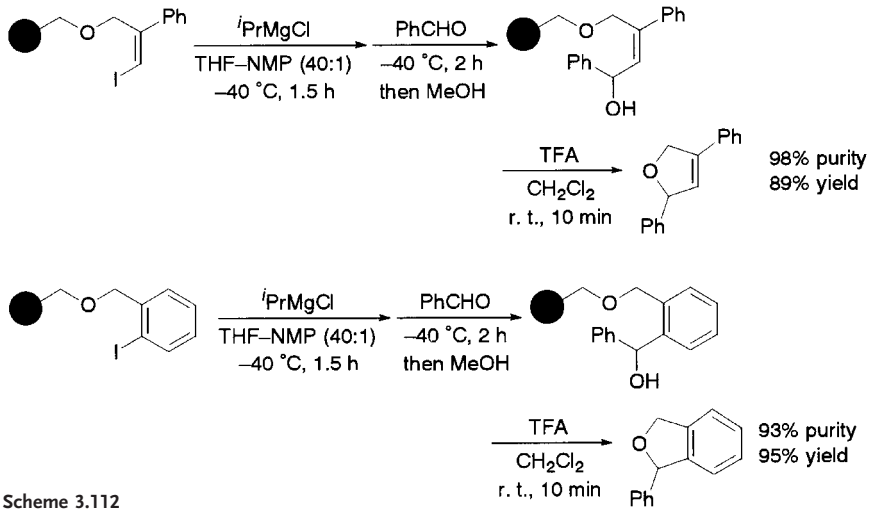
The halogen-magnesium exchange reaction with ^{i}PrMgBr can be used to generate an organomagnesium reagent on a polymer support; it therefore has applications in combinatorial chemistry. Aryl and heteroaryl halides attached to Wang resin by an ester function are converted into the magnesium derivatives, which are trapped with electrophiles. After cleavage from the resin with TFA the expected carboxylic acids are obtained in good to excellent purity (Tab. 3.11) [121].

Exchange reaction of (*Z*)-alkenyl and aryl iodides attached to Wang resin by an ether function then addition of aldehydes and subsequent cleavage with TFA provides 2,5-dihydrofurans and 1,3-dihydroisobenzofurans (Scheme 3.112) [139].

Tab. 3.11 Solid-phase synthesis via halogen-magnesium exchange[a)]

Entry	*Substrate*	E^+	*Product*	*Purity (%)*
1		CH_2=CHCH$_2$Br CuCN•2LiCl		98
2		PhCHO		95
3		TsCN		92
4		TsCN		94
5		CH_2=CHCH$_2$Br CuCN•2LiCl		99

a) Resin-bound aryl halides are treated with ^{i}PrMgBr (ca. 7 equiv.) in THF at –35 °C for 15–30 min. Addition of electrophiles then washing with DMF, MeOH, and CH_2Cl_2 (six cycles) and treatment with CF_3CO_2H (4 mL $CF_3CO_2H/CH_2Cl_2/H_2O$, 9:1:1) for 20 min provided the desired acids in >90% yields.



Scheme 3.112

3.4.3 Trialkylmagnesate-induced Halogen-Magnesium Exchange Reaction [140, 141]

As described in Section 3.4.2, polyfunctional organomagnesium reagents are prepared by halogen-magnesium exchange at low temperatures. However, substrates are often limited to rather electron-poor aryl or alkenyl halides, particularly the bromides. In this section, trialkylmagnesate (R_3MgLi)-induced halogen-magnesium exchange reactions are described. This reagent is highly effective for the preparation of polyfunctional aryl- and alkenylmagnesium compounds from the corresponding halides at low temperatures, because it is more reactive than Grignard reagents.

3.4.3.1 Iodine-Magnesium Exchange of Aryl Iodides

The iodine-magnesium exchange of aryl iodides with $^{n}Bu_3MgLi$, which is prepared by mixing ^{n}BuMgBr and ^{n}BuLi in a 1:2 ratio in THF at 0 °C, proceeds smoothly at 0 °C or –78 °C within 0.5 h, and the resulting arylmagnesium species are trapped by electrophiles. Examples are shown in Tab. 3.12.

Even electron-rich aryl iodides can be converted into the corresponding arylmagnesium compounds at –78 °C (entries 2–4). A half equivalent of the reagent is sufficient for complete exchange (entries 2 and 5). This procedure is applicable to the preparation of polyfunctional organomagnesium compounds. Iodobenzoates are converted into the magnesium species without a loss of the ester group (entries 5 and 6). The ester group of ethyl (2-iodophenoxy)acetate can survive under the reaction conditions, and 3-coumaranone is obtained by intramolecular attack of the resulting magnesium reagent (entry 7).

3.4.3.2 Bromine-Magnesium Exchange of Aryl Bromides

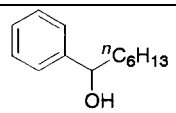
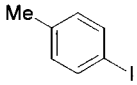
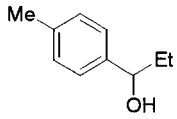
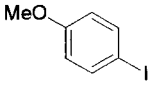
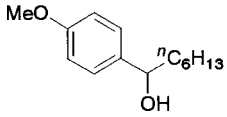
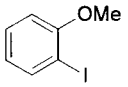
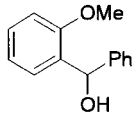
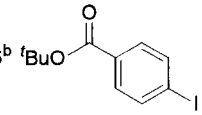
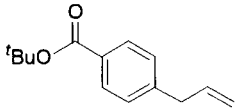
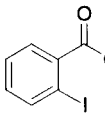
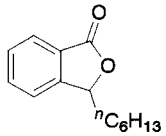
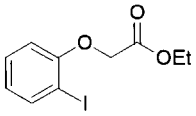
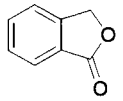
The bromine-magnesium exchange of aryl bromides proceeds on treatment with $^{n}Bu_3MgLi$ at 0 °C. Representative examples are shown in Tab. 3.13.

In contrast with aryl iodides, the exchange reaction of aryl bromides does not go to completion at –78 °C. Thus, the more powerful reagent $^{i}Pr^{n}Bu_2MgLi$, which is prepared by mixing ^{i}PrMgBr and ^{n}BuLi in a 1:2 ratio, is used for the preparation of polyfunctionalized arylmagnesium reagents from the corresponding bromides. Examples are shown in Tab. 3.14.

Functional groups such as ester, amide, or cyano groups are tolerated during the exchange procedure. The exchange reaction also proceeds smoothly at –40 °C with 0.5 equiv. $^{n}Bu_3MgLi$ (Scheme 3.113).

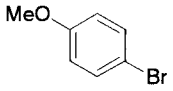
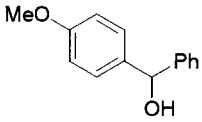
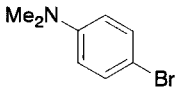
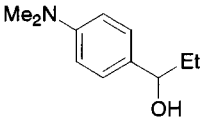
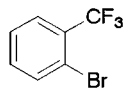
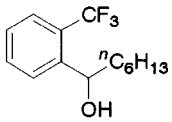
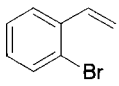
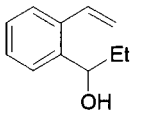
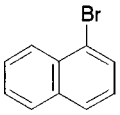
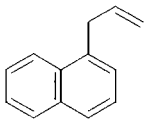
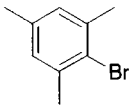
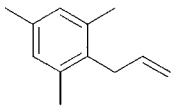
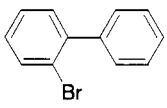
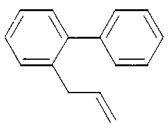
Treatment of the resulting functionalized arylmagnesium compounds with $TiCl_4$ affords the corresponding biaryls in good yields (Scheme 3.114).

Tab. 3.12 Iodine-magnesium exchange of aryl iodides with $^{n}Bu_3MgLi$ [a)]

Entry	*Substrate*	*Temp.*	E^+	*Product*	*Yield (%)*
1		0 °C	$^{n}C_6H_{13}CHO$		80
2		–78 °C	EtCHO		75
3		–78 °C	$^{n}C_6H_{13}CHO$		94
4		–78 °C	PhCHO		92
5[b]		–78 °C	CH_2=CHCH$_2$Br cat. CuCN•2LiCl		88
6[c]		–78 °C	$^{n}C_6H_{13}CHO$		72
7		–78 °C			85

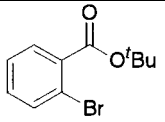
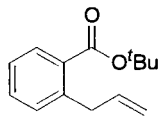
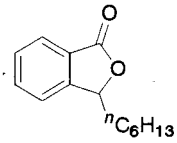
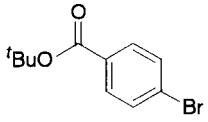
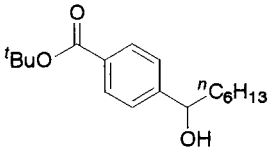
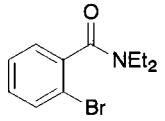
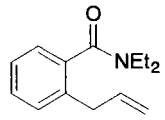
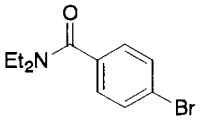
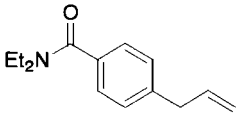
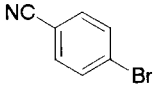
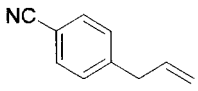
a) Substrates are treated with $^{n}Bu_3MgLi$ (1.2 equiv.) in THF for 0.5 h.
b) $^{n}Bu_3MgLi$ (0.5 equiv.) is used for exchange.
c) A solution of $^{n}Bu_3MgLi$ is added to a THF solution of the substrate and heptanal, and the mixture is stirred for 1.5 h.

Tab. 3.13 Bromine-magnesium exchange of aryl bromides [a)]

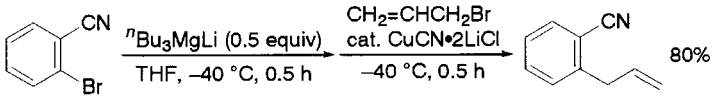
Entry	*Substrate*	E^+	*Product*	*Yield (%)*
1[b]		PhCHO		85
2		EtCHO		94
3		$^nC_6H_{13}CHO$		76
4[c]		EtCHO		62
5		CH_2=CHCH$_2$Br		97
6		CH_2=CHCH$_2$Br cat. CuCN•2LiCl		93
7		CH_2=CHCH$_2$Br cat. CuCN•2LiCl		100

a) $^nBu_3MgLi$ (1.2 equiv.) is used as reagent. All reactions were performed in THF at 0 °C for 0.5 h.
b) $^nBu_3MgLi$ (0.5 equiv.) is used.
c) $^nBuMe_2MgLi$ (1.0 equiv.) is used.

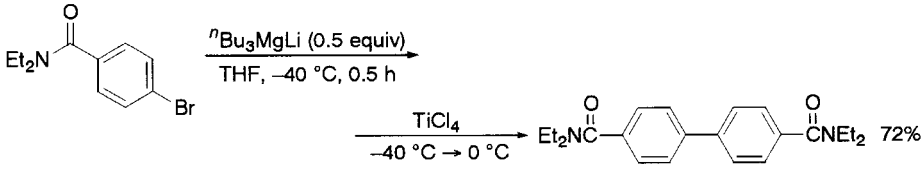
Tab. 3.14 Bromine-magnesium exchange of aryl bromides bearing reactive functional groups [a)]

Entry	*Substrate*	E^+	*Product*	*Yield (%)*
1		CH_2=CHCH_2Br cat. CuCN•2LiCl		99
2		$^nC_6H_{13}CHO$		61
3		$^nC_6H_{13}CHO$		71
4		CH_2=CHCH_2Br cat. CuCN•2LiCl		80
5		CH_2=CHCH_2Br cat. CuCN•2LiCl		79
6		CH_2=CHCH_2Br cat. CuCN•2LiCl		87

a) $^iPr^nBu_2MgLi$ (1.2 equiv.) is used as reagent. All reactions are performed in THF at –78 °C for 1 h.



Scheme 3.113

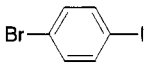
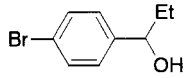
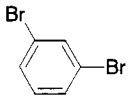
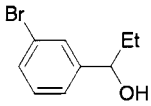
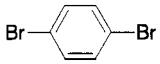
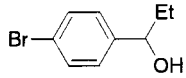
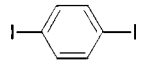
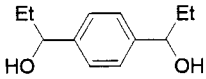
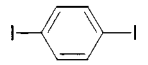
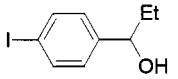
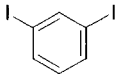
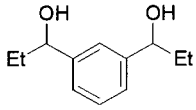
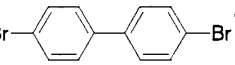
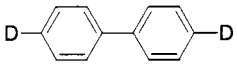


Scheme 3.114

3.4.3.3 Halogen-Magnesium Exchange of Dihaloarenes

The selective halogen-magnesium exchange of dihaloarenes has been examined (Tab. 3.15).

Tab. 3.15 Halogen-magnesium exchange of dihaloarenes [a]

Entry	*Substrate*	*Conditions*	E^+	*Product*	*Yield (%)*
1		$^{i}Pr^{n}Bu_2MgLi$ (1.0) –78 °C, 0.5 h	EtCHO		65
2		$^{i}Pr^{n}Bu_2MgLi$ (1.0) 0 °C, 0.5 h	EtCHO		78
3		$^{n}Bu_3MgLi$ (1.0) 0 °C, 0.5 h	EtCHO		85
4		$^{n}Bu_3MgLi$ (1.0) –78 °C, 0.5 h	EtCHO		80
5		$^{n}BuMe_2MgLi$ (1.0) –78 °C, 0.5 h	EtCHO		64
6		$^{n}Bu_3MgLi$ 2.0) –78 °C, 0.5 h	EtCHO		48
7		$^{n}BuMe_2MgLi$ (1.0) –78 °C, 0.5 h	D_2O		100

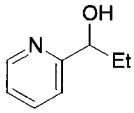
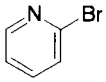
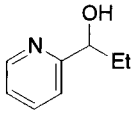
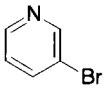
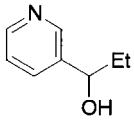
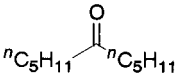
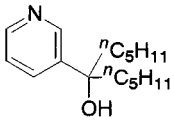
a) All reactions were conducted in THF.

With *p*-bromoiodobenzene the iodine-magnesium exchange occurs (entry 1). Only one of the two bromides of *m*- or *p*-dibromobenzene is exchanged (entries 2 and 3). *p*-Diiodobenzene, on the other hand, is converted into dimagnesated benzene on treatment with 1.0 equiv. $^{n}Bu_3MgLi$ (entry 4) whereas dimetalation of *m*-diiodobenzene requires 2.0 equiv. of the reagent to furnish *m*-dimagnesiobenzene (entry 6). The reagent $^{n}BuMe_2MgLi$ is employed to induce selective mono-metalation of *p*-diiodobenzene (entry 5). Dimagnesated biphenyl is formed by the double exchange reaction of 4,4′-dibromobiphenyl (entry 7).

3.4.3.4 Halogen-Magnesium Exchange of Halopyridines

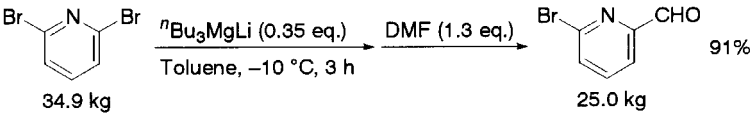
The halogen-magnesium exchange of halopyridines has been achieved by use of $^{n}BuMe_2MgLi$, which is prepared by mixing $^{n}BuMgBr$ and MeLi in a 1:2 ratio. Use of $^{n}Bu_3MgLi$ reduces the yields. Examples are shown in Tab. 3.16.

Tab. 3.16 Halogen-magnesium exchange of halopyridines [a)]

Entry	*Substrate*	*E^+*	*Product*	*Yield (%)*
1		EtCHO		58
2		EtCHO		67
3		EtCHO		73
4				49

a) $^{n}BuMe_2MgLi$ was used as reagent. All reactions are conducted in THF at 0 °C for 0.5 h

The exchange of 2,6-dibromopyridine is performed on a kilogram-scale (Scheme 3.115) [142–144].



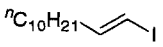
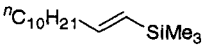
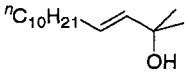
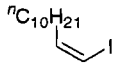
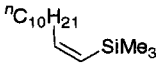
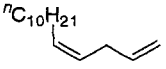
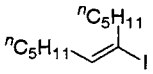
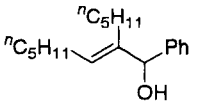
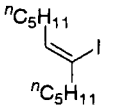
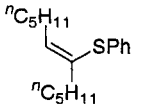
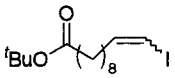
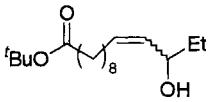
Scheme 3.115

3.4.3.5 Halogen-Magnesium Exchange of Alkenyl Halides

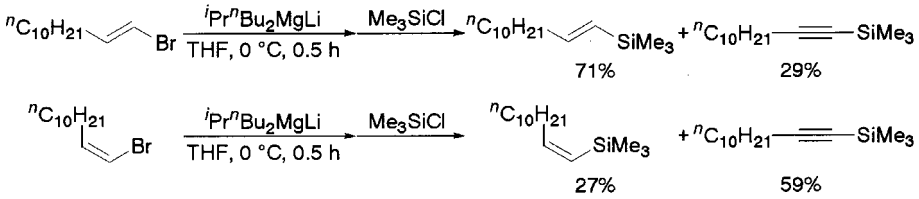
The iodine-magnesium exchange of alkenyl iodides proceeds at 0 °C or –78 °C with complete retention of configuration of the double bond (Tab. 3.17). The presence of an ester functionality is compatible with the formation of the alkenylmagnesium reagent at –78 °C (entry 7).

In contrast, the bromine-magnesium exchange of alkenyl bromides does not give satisfactory results (Scheme 3.116). Because the exchange is slow, dehydrobromination and deprotonation affording magnesium acetylides compete with the exchange reaction.

Tab. 3.17 Iodine-magnesium exchange of alkenyl iodides[a]

Entry	Substrate	E^+	Product	Yield
1		Me_3SiCl		95[b]
2		CH_3COCH_3		75
3		Me_3SiCl		83[b]
4		CH_2=$CHCH_2Br$ cat. CuCN•2LiCl		70
5		PhCHO		87
6		PhSSPh		77
7		EtCHO		80[b]
	E/Z = 11/89		*E/Z* = 11/89	

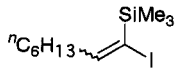
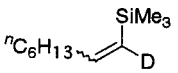
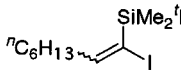
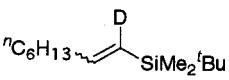
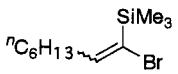
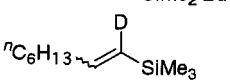
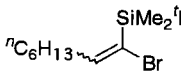
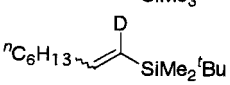
a) $^iPr^nBu_2MgLi$ is used. Reactions are conducted in THF at 0 °C for 1 h.
b) The exchange reaction is performed at –78 °C.



Scheme 3.116

The exchange of 1-silyl-substituted alkenyl halides proceeds in good yields with isomerization of the double bond (Tab. 3.18). The bulky silyl groups prefer *trans* orientation of the alkyl group.

Tab. 3.18 Halogen-magnesium exchange of 1-silylalkenyl iodides [a)]

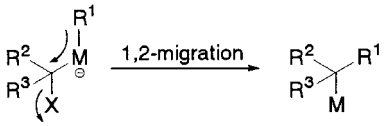
Entry	Substrate (E/Z)		Product (E/Z)		Yield (%)
1		(85/15)		(32/68)	98
2		(84/16)		(96/4)	89
3		(100/0)		(93/7)	90
4		(84/16)		(93/7)	86

a) $^{i}Pr^{n}Bu_2MgLi$ was used as reagent. The reactions were performed in THF at 0 °C for 1 h and quenched with D_2O.

3.4.4

Bromine-Magnesium Exchange of *gem*-Dibromo Compounds and Subsequent Migration of an Alkyl Group [145–149]

The bromine-magnesium exchange of *gem*-dibromo compounds provides the ate-type carbenoid species, which undergo 1,2-migration of the alkyl group on magnesium to the adjacent carbon to form new organomagnesium reagents (Scheme 3.117).



Scheme 3.117

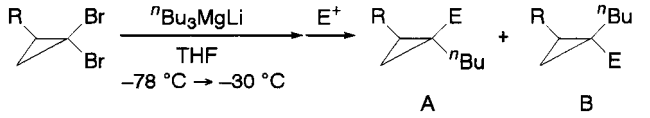
In this section, the reactions of *gem*-dibromocyclopropanes and dibromomethylsilanes with trialkylmagnesate reagents are described. Preparation of a chiral secondary Grignard reagent by alkylation of the chiral magnesium carbenoid species is also discussed.

3.4.4.1 Reaction of *gem*-Dibromocyclopropanes [145]

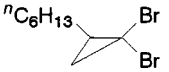
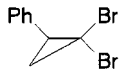
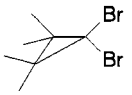
The reaction of *gem*-dibromocyclopropanes with $^{n}Bu_3MgLi$ provides the butylated cyclopropylmagnesium species, which react with a variety of electrophiles (Tab. 3.19 and 3.20).

The mechanism of this reaction is suggested in Scheme 3.118. The bromine-magnesium exchange occurs mainly at the less hindered bromine atom to afford the ate-type carbenoid species. Next, the butyl group on magnesium migrates to the adjacent carbon atom with concomitant elimination of the bromide ion with inversion of configuration on the cyclopropane carbon.

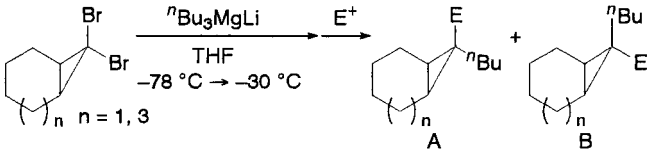
Tab. 3.19 Reaction of *gem*-dibromocyclopropanes with $^{n}Bu_3MgLi$



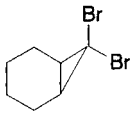
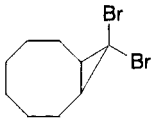
A B

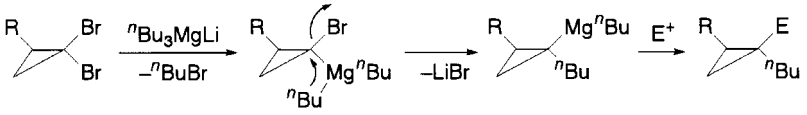
Entry	Substrate	E^+	Yield (%)	A/B
1		I_2	80	62/38
2		CH_2=$CHCH_2Br$	65	51/49
3		MeI	74	45/55
4		PhCHO	78	44/56
5		CH_2=$CHCH_2Br$ cat. CuCN•2LiCl	65	51/49
6		CH_2=$CHCH_2Br$ cat. CuCN•2LiCl	73	

Tab. 3.20 Reaction of bicyclic *gem*-dibromocyclopropanes with $^{n}Bu_3MgLi$



A B

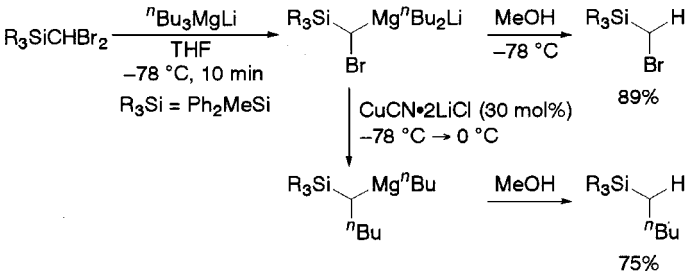
Entry	Substrate	E^+	Yield (%)	A/B
1		I_2	91	61/39
2		CH_2=$CHCH_2Br$ cat. CuCN•2LiCl	89	73/27
3		PhCOCl CuCN•2LiCl	88	88/12
4		I_2	86	64/36



Scheme 3.118

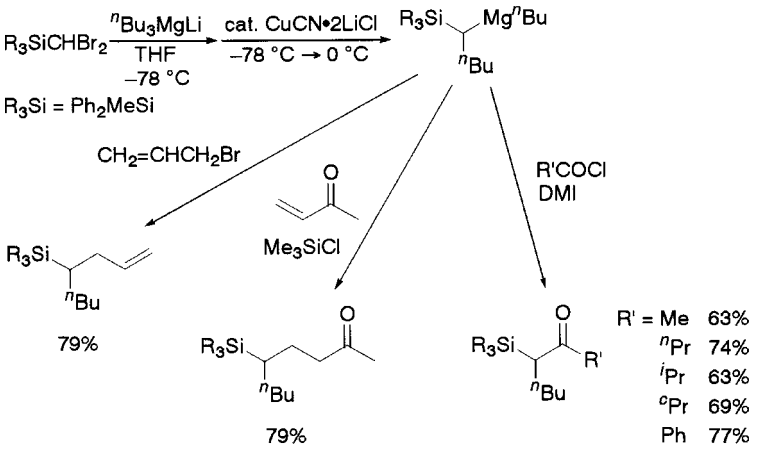
3.4.4.2 **Copper(I)-catalyzed Reaction of Dibromomethylsilanes [145, 146]**

Treatment of (dibromomethyl)methyldiphenylsilane with $^{n}Bu_3MgLi$ at –78 °C induces clean bromine-magnesium exchange to provide bromomethylsilane. Addition of CuCN · 2LiCl (30 mol%) and warming to 0 °C induces migration of the butyl group to afford the α-silyl-substituted magnesium species (Scheme 3.119).



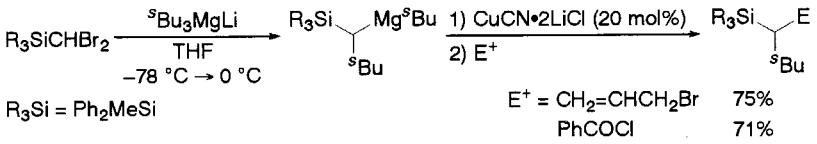
Scheme 3.119

The intermediate α-silylalkylmagnesium species can couple with allyl bromide, acyl chlorides, or α,β-unsaturated ketones under the action of the copper catalyst (Scheme 3.120).



Scheme 3.120

Introduction of a *sec*-butyl group does not require the addition of a copper salt (Scheme 3.121).

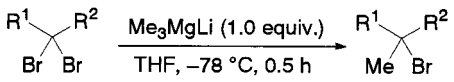


Scheme 3.121

3.4.4.3 Reaction of Dibromomethylsilanes with Me_3MgLi [145, 147]

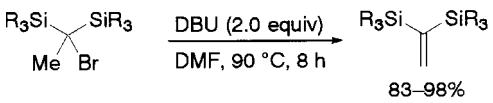
The reactivity of Me_3MgLi is different from that of $^nBu_3MgLi$. The reaction of dibromomethylsilanes or dibromodisilylmethanes with Me_3MgLi affords the monomethylation product in good yields (Tab. 3.21).

Tab. 3.21 Reaction of *gem*-dibromo compounds with Me_3MgLi



Entry	R^1	R^2	*Yield (%)*
1	Ph_2MeSi	H	98
2	Ph_2MeSi	Me	89
3	Ph_2MeSi	Me_3Si	93
4	Ph_2MeSi	Ph_2MeSi	90
5	Me_3Si	Me_3Si	89
6	Ph_2MeSi	Et_3Ge	93

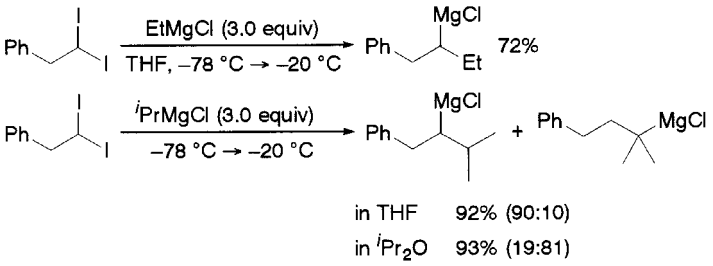
The resulting monomethylated products are converted into the corresponding 1,1-disilylethenes by dehydrobromination (Scheme 3.122).



Scheme 3.122

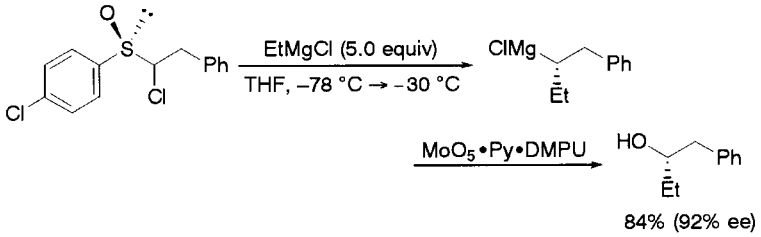
3.4.4.4 Alkylation of Carbenoids with Grignard Reagents [148, 149]

Reaction of diiodoalkanes with excess Grignard reagent induces iodine-magnesium exchange and subsequent alkylation to provide the secondary Grignard reagent. The use of ^iPrMgCl induces a novel rearrangement to afford the tertiary Grignard reagent (Scheme 3.123) [148].



Scheme 3.123

This alkylation process has been used to synthesize a chiral secondary Grignard reagent [149]. Treatment of the diastereomerically pure *α*-chloroalkyl sulfoxide with excess EtMgCl induces sulfoxide-magnesium exchange and alkylation to provide secondary Grignard reagent of 93% ee. Oxidation of the resulting chiral Grignard reagent affords the corresponding alcohols of 92% ee (Scheme 3.124, see also Section 3.2.4).

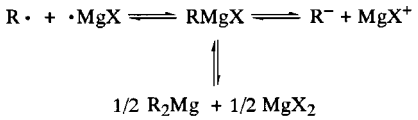


Scheme 3.124

3.5
Radical Reactions Mediated by Grignard Reagents

Since the Grignard reagent was discovered in 1900 it has been widely used for the construction of organic molecules. It is the most basic and indispensable tool for organic chemists [150, 151]. There have been reports of radical reactions using Grignard reagents in the presence or absence of transition metal catalysts [152]. Synthetic applications of this type of reaction have, however, been quite limited so far.

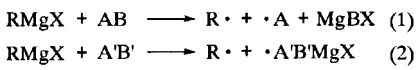
Although most of the so-called "normal" Grignard reagent reactions seem to be essentially ionic in nature, some reactions, especially among those commonly regarded as "abnormal", are most readily explicable upon the basis of the hypothesis that the R–MgX bond undergoes homolytic scission. Such reactions might result in the liberation of free radicals in the reaction system, but the occurrence of *free* radicals is by no means an essential feature of a radical reaction. It is therefore unnecessary, in general, to assume an equilibrium such as that shown in Scheme 3.125.



Scheme 3.125

It is probable that in some "forced" reactions dissociation of the Grignard reagent in the sense (R–MgX → R• + •MgX) occurs, but in general no equilibrium is achieved in such reactions, because of the reactivity of the radicals R• toward each other or toward other components of the reaction system.

It seems highly probable, however, that, in general, the homolytic dissociation of the R–MgX bond in Grignard reactions is an induced phenomenon requiring the participation of a co-reactant. Such induced homolytic dissociations might liberate *free* radicals by processes like those represented in Eqs (1) and (2) in Scheme 3.126 [153].

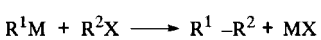


Scheme 3.126

First (Section 3.5.1), cross-coupling of alkyl halides with Grignard reagents will be discussed, then conversion of vicinal methoxyiodoalkanes into (*E*)-alkenes with Grignard reagent (Section 3.5.2), radical cyclization of *β*-iodo allylic acetals with ethylmagnesium bromide (Section 3.5.3), EtMgBr-iodoalkane-mediated coupling of arylmagnesium compounds with tetrahydrofuran (Section 3.5.4), and reductive cross-coupling of *α*,*β*-unsaturated carbonyl compounds with aldehydes mediated by Mg metal (Section 3.5.5) will be described.

3.5.1
Cross-coupling of Alkyl Halides with Grignard Reagents

The cross-coupling reaction is arbitrarily defined as a process of single carbon-carbon bond formation between two unlike carbon groups by reaction of an organometallic species with an organic halide or a related electrophilic derivative (Scheme 3.127).

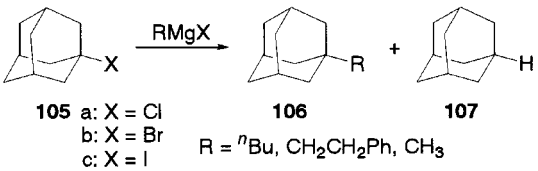


Scheme 3.127

This reaction is one of the most straightforward methods of carbon-carbon bond formation. It might even be said that if one could achieve any type of cross

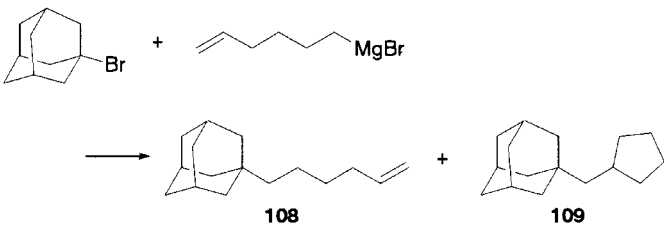
coupling at will most of the problems of organic skeletal construction would be solved. Despite its inherent simplicity, however, its synthetic utility had been quite limited until recently.

The scope and mechanism of this reaction have been reviewed concisely by Negishi [154]. In general, an S_N2 mechanism (two-electron-transfer process) plays a significant role, and, thus, a primary group for R^1 is essentially favored. On the other hand, a radical recombination mechanism (single-electron-transfer process) is occasionally involved. We can choose the reaction of a *tert*-alkyl halide with a Grignard reagent as an example. In dichloromethane, 1-haloadamantane **105** underwent a cross-coupling reaction with Grignard reagents to give bridgehead-substituted products **106** in moderate yields. Usually **107** was formed in 15–25% yield in addition to the coupling product **106**. Representative results are shown in Scheme 3.128. In this instance the same kind of halogen in both **105** and a Grignard reagent was favored; if not, functional exchange (i.e., **105a** to **105c**) occurred first. The reaction of **105a**, **105b**, and **105c** with the corresponding butylmagnesium chloride, bromide, and iodide gave bridgehead-butylated adamantane **106a** (R = ^{n}Bu) in 55–60% isolated yield [155].

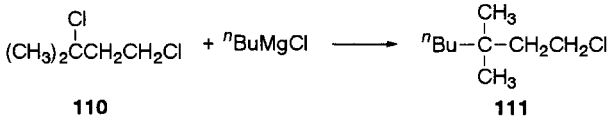


Scheme 3.128

The reaction with 5-hexenylmagnesium bromide as radical probe afforded uncyclized/cyclized coupling products (**108**/**109**) in a 6:4 ratio (Scheme 3.129). These facts suggested the significant participation of the single-electron-transfer process in these reactions. This method could be extended to *tert*-butylation with some Grignard reagents. Interestingly, 1,3-dichloro-3-methylbutane (**110**) coupled with butylmagnesium chloride selectively at the tertiary position to give 1-chloro-3,3-dimethylheptane (**111**) in 70% yield (Scheme 3.130).



Scheme 3.129



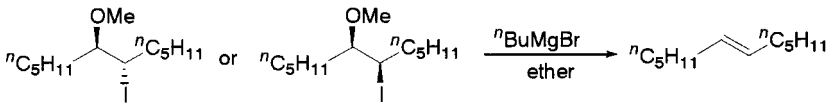
110 **111**

Scheme 3.130

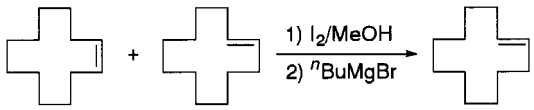
3.5.2

Conversion of Vicinal Methoxyiodoalkanes into (*E*)-Alkenes with Grignard Reagent

A radical intermediate is assumed in the 1,2-elimination reaction of vicinal methoxyiodoalkanes with butylmagnesium bromide providing (*E*)-alkenes with high stereoselectivities irrespective of the stereochemistry of the starting alkoxyiodoalkane [156]. For example, treatment of *erythro*-6-iodo-7-methoxydodecane or *threo*-6-iodo-7-methoxydodecane with ^{n}BuMgBr in ether at 25 °C gave the same (*E*)-6-dodecene, exclusively, in 92% or 96% yield, respectively (Scheme 3.131). Single-electron transfer from Grignard reagent into iodoalkanes followed by departure of iodide would produce the carbon radical. A second single-electron transfer would provide a carbanion that collapses to an alkene with elimination of the methoxide ion. A mixture of (*E*)- and (*Z*)-alkenes could be converted into (*E*)-pure alkene by sequential treatment with I_2/MeOH and butylmagnesium bromide. For example, *trans*-cyclododecene (>99 : <1) was obtained in 80% overall yield from commercially available *cis*- and *trans*-cyclododecene (34 : 66) (Scheme 3.132).



Scheme 3.131



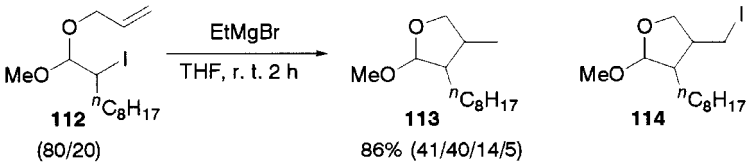
Scheme 3.132

3.5.3

Radical Cyclization of β-Iodo Allylic Acetals with EtMgBr [157]

Radical cyclization by means of tin hydride has been extensively explored during the past two decades. Currently, however, it is desirable to avoid the use of tin compounds, because of their neurotoxicity and the difficulty of completely eliminating them from the reaction products. In contrast, organomagnesium reagents have few toxicity problems and are readily prepared or commercially available. For these reasons this facile radical cyclization reaction using Grignard reagents has significant advantages over tin-mediated radical cyclization reactions.

Addition of ethylmagnesium bromide to a THF solution of iodo acetal **112** provided cyclized product **113** as a mixture of stereoisomers in good yield (Scheme 3.133).



Scheme 3.133

This stereoselectivity is identical with that of $^nBu_3SnH$–Et_3B-mediated radical cyclization of **112**. The reaction proceeded very cleanly without any byproducts. There were no traces of vinyl ethers, which could be derived from elimination of iodine and an alkoxy group of **112**, in the reaction mixture. The use of ^{n}BuMgBr instead of EtMgBr also afforded **113** in a similar yield. The reaction with ^{i}PrMgBr was sluggish, however, and took 4 h to reach completion. On this occasion a trace amount of iodide **114** was observed in the reaction mixture. When methylmagnesium iodide was used as a Grignard reagent no reaction occurred and the starting material **112** was recovered quantitatively. Cyclization of a variety of substrates, mediated by ethylmagnesium bromide, are summarized in Tab. 3.22.

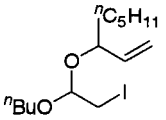
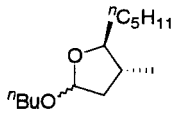
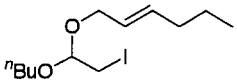
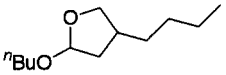
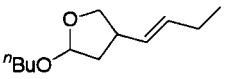
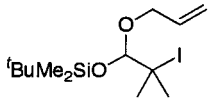
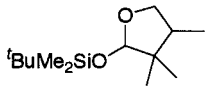
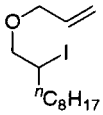
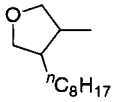
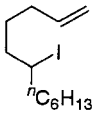
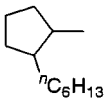
Interestingly, it was found that the use of DME as a reaction solvent instead of THF led to a dramatic change to the course of the reaction and the cyclic magnesium compound **116** was formed in good yield. Tetrahydrofuranylmethylmagnesium **116** could be coupled with a variety of electrophiles. For example, in the presence of a catalytic amount of CuCN · 2LiCl **116** reacted with allyl bromide to give allylated product **117** in good yield (Scheme 3.134).

The reaction mechanism in Scheme 3.135 is proposed. First, EtMgBr or Et_2Mg induces atom transfer radical cyclization of **118** to provide iodide **119**. The Grignard reagent would then reduce iodide **119** to **120** in THF. A molecule of THF might act as a hydride source in this reduction. In DME, the iodide **119** would be converted into magnesium species **121** via a iodine-magnesium exchange reaction.

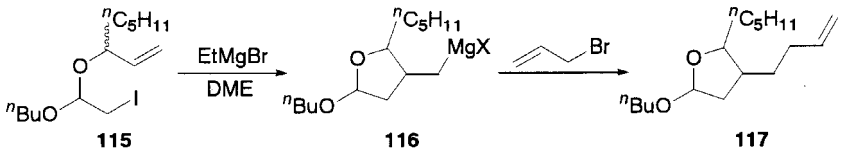
3.5.4
EtMgBr-iodoalkane-mediated Coupling of Arylmagnesium Compounds with Tetrahydrofuran via a Radical Process

Extremely facile coupling of arylmagnesium compounds and THF by means of an iodoalkane-EtMgBr system provides 2-aryltetrahydrofurans [158]. Treatment of a solution of 4-methoxyphenylmagnesium bromide (**122**) and EtI (4.0 equiv.) with EtMgBr (2.0 equiv.) in THF at 25 °C for 5 h afforded 2-(4-methoxyphenyl)tetrahydrofuran (**123**) in 43% yield. Use of a more sterically hindered iodoalkane,

Tab. 3.22 EtMgBr-mediated radical cyclization reactions [a)]

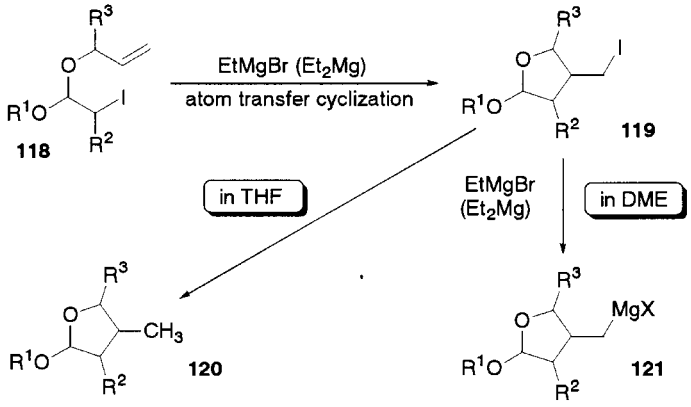
Entry	*Substrate*	*Product*	*Yield*
1	 (50/50)		85% (50/50)
2			54% (50/50)
			12% (50/50)
3			90% (35/65)
4			81% (cis/trans = 70/30)
5			83% (cis/trans = 73/27)

a) In each experiment, substrate (1.0 mmol), EtMgBr (2.0 mL, 1.0 M THF solution, 2.0 mmol), and THF (5 mL) were employed. The mixture was stirred for 2–3 h at room temperature under an argon atmosphere.



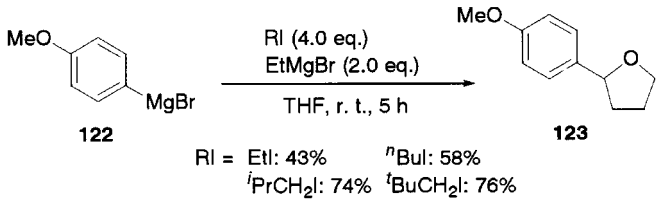
115 **116** **117**

Scheme 3.134



Scheme 3.135

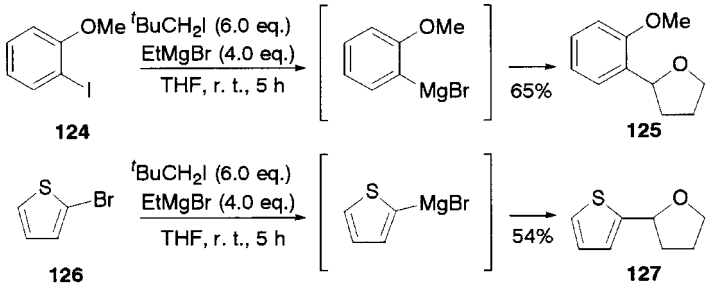
which could hardly react with EtMgBr via an S_N2 or E2 process, e.g. $^{i}PrCH_2I$ or $^{t}BuCH_2I$ in place of EtI improved the yield of **123** to 74% or 76%, respectively (Scheme 3.136). The reaction proceeded very cleanly to give only **123** and anisole without contamination by any byproducts.



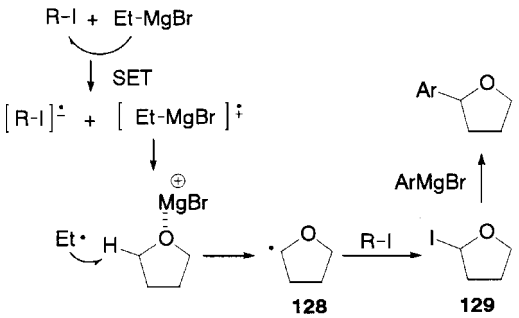
Scheme 3.136

It is well known that arylmagnesium compounds are readily prepared by halogen-magnesium exchange. Thus, it is expected that aryl halides could be converted into arylated tetrahydrofurans in one pot. This was indeed so, and treatment of 2-iodoanisole (**124**) or 2-bromothiophene (**126**) with $^{t}BuCH_2I$ and EtMgBr in THF provided **125** or **127** in 65% or 54% yields, respectively (Scheme 3.137).

Although the reaction mechanism has not yet been clarified, a possible mechanism might be that envisaged in Scheme 3.138. Single-electron transfer from EtMgBr to the iodoalkane would provide an ethyl radical which could abstract a hydrogen from the C2 carbon of THF. The resulting 2-tetrahydrofuryl radical **128** would attack the iodoalkane to give 2-iodotetrahydrofuran **129** which would be converted into an arylated product by the action of the arylmagnesium compound. Because $^{i}PrCH_2I$ or $^{t}BuCH_2I$ would not be wasted by an anionic S_N2 or E2 process, the radical process could proceed effectively in the reaction using these iodides.



Scheme 3.137

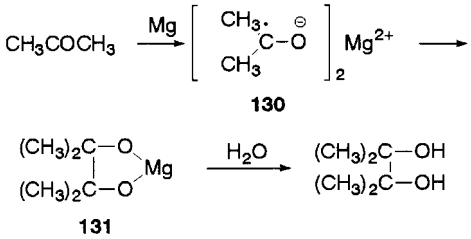


Scheme 3.138

3.5.5

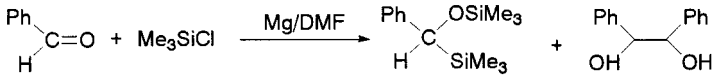
Mg-promoted Reductive Cross-coupling of α,β-unsaturated Carbonyl Compounds with Aldehydes or Acyl Chlorides

The reaction of ketones with magnesium metal in the absence of protonic solvents leads to the production of ion pairs **130** from the metal cation and the anion radicals which combine to form the salts of pinacols **131** (Scheme 3.139).



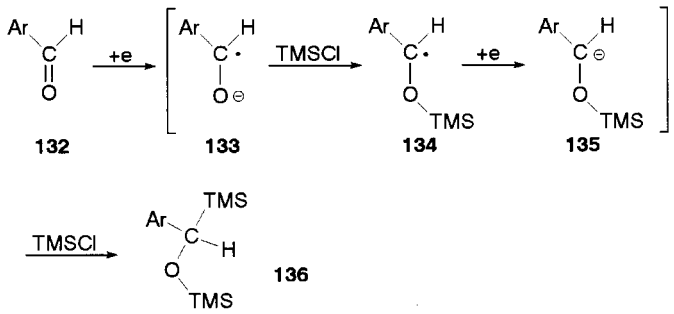
Scheme 3.139

Nishiguchi et al. have recently developed several reductive cross-coupling reaction mediated by magnesium metal [159]. Mg-promoted cross-coupling of aromatic carbonyl compounds with trimethylsilyl chloride (TMSCl) in DMF at room temperature brought about reductive carbon-silicon bond formation to give the corresponding α-trimethylsilylalkyl trimethylsilyl ethers, selectively, in good yields. For instance, treatment of benzaldehyde with Mg turnings in DMF in the presence of TMSCl at room temperature afforded α-trimethylsilyl-α-trimethylsiloxytoluene in 82% yield with a small amount of the homo-coupling byproduct, 1,2-diphenyl-1,2-ethanediol (Scheme 3.140).



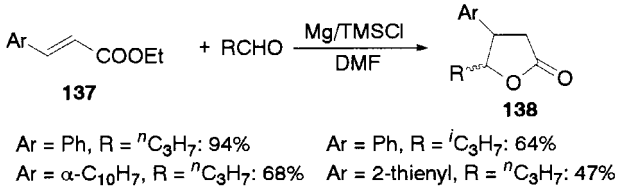
Scheme 3.140

Although the detailed role of TMSCl in this reaction remains ambiguous, the reaction mechanism might be that depicted in Scheme 3.141. The reaction might be initiated by one-electron transfer from Mg metal, activated by TMSCl, to aldehydes **132** to give the corresponding anion radicals **133**. The anion radicals **133** then undergo the first electrophilic attack of TMSCl, generating the radical species **134**, followed by the fast second electron transfer. Subsequently, the formed anionic cross-coupling intermediates **135** are transformed to the products, α-trimethylsilylalkyl trimethylsilyl ethers **136**, by a second electrophilic attack of TMSCl.



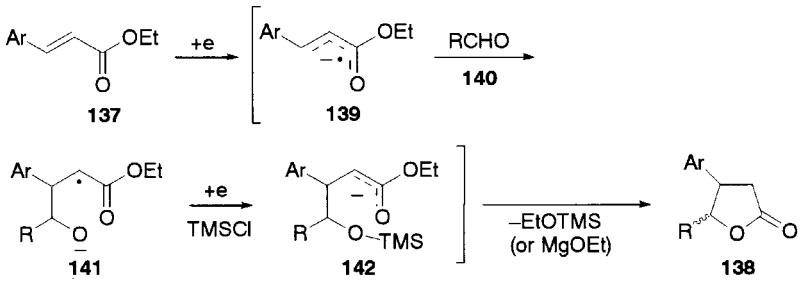
Scheme 3.141

The method has been applied to the reductive cross-coupling of ethyl β-arylacrylates with aldehydes in the presence of TMSCl [160]. Addition of Mg metal to a solution of ethyl β-arylacrylate, aldehyde, and TMSCl in DMF provided the corresponding γ-lactones as a *cis*/*trans* stereoisomeric mixture in good to excellent yields (Scheme 3.142).



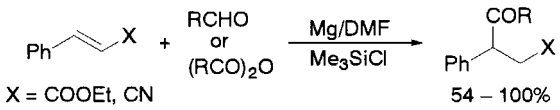
Scheme 3.142

The reaction might be initiated by one-electron transfer from magnesium metal, activated by TMSCl, to *β*-arylacrylates **137** to give the corresponding anion radicals **139** (Scheme 3.143), which might be then subject to electrophilic attack by aldehydes **140**, activated by TMSCl, generating anionic radical species **141**, followed by the fast second electron transfer. Subsequently, the formed anionic cross-coupling intermediates **142** (possibly coordinated with Mg^{2+} ion or stabilized by TMSCl) can be transformed to the product, *γ*-lactones **138**, by intramolecular cyclization.



Scheme 3.143

Treatment of an aromatic *α,β*-unsaturated carbonyl compound, e.g. ethyl cinnamate, with Mg turnings in the presence of acid anhydrides and TMSCl or acyl chlorides in DMF brought about facile and efficient cross-coupling to give C-acylation products which are useful 1,4-dicarbonyl compounds, in good to excellent yields, in a regio- and stereoselective manner (Scheme 3.144). The reaction also might be initiated by electron transfer from magnesium to the substrates [161].

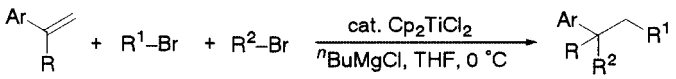


Scheme 3.144

3.6
Radical Reaction Mediated by Grignard Reagents in the Presence of Transition Metal Catalyst

3.6.1
Titanocene-catalyzed Double Alkylation or Double Silylation of Styrenes with Alkyl Halides or Chlorosilanes

Transition metal catalysts are powerful tools for 1,2-addition reactions to carbon-carbon double bonds, and enable versatile and useful transformations of alkenes by introducing a variety of functionalities at the olefinic carbons. Kambe et al. have developed an unprecedented metal-catalyzed double alkylation of alkenes with alkyl halides (Scheme 3.145) [162]. This reaction proceeds, via use of Cp_2TiCl_2 in the presence of ^{n}BuMgCl, to give rise to *vic*-dialkylated products regioselectively in high yield under mild conditions. For instance, addition of ^{n}BuMgCl to a solution of styrene, 1-bromopentane, and *t*-butyl bromide in the presence of a catalytic amount of titanocene dichloride provided 2,2-dimethyl-4-phenylnonane in 88% isolated yield. Representative results are shown in Tab. 3.23. The combined use of secondary and primary bromides or tertiary and secondary bromides afforded the corresponding dialkylated products in good yields with high regioselectivity. Interestingly, when 1,4-dibromobutane was used as the alkylating reagent, cyclohexylbenzene was obtained in 46% yield.

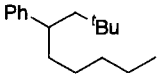
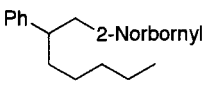
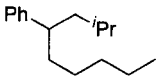
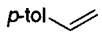
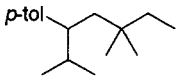
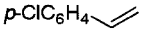
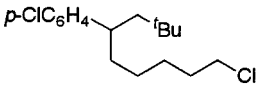
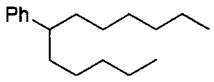
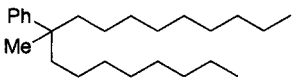


Scheme 3.145

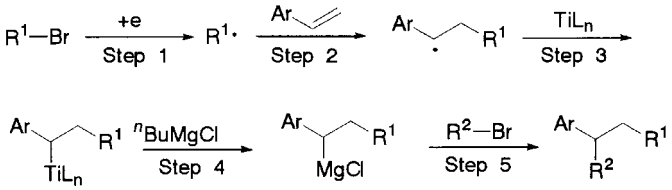
A plausible reaction pathway is shown in Scheme 3.146. Alkyl radicals, formed by electron transfer to alkyl bromides from a reduced titanocene complex (step 1), add to the terminal carbon of styrene yielding benzyl radical intermediates (step 2). Recombination of the benzyl radicals with a titanocene complex gives rise to benzyl-Ti intermediates (step 3) which then undergo transmetalation with ^{n}BuMgCl to afford benzylmagnesium chlorides (step 4). The dialkylated products are formed by reaction of benzylmagnesium chlorides with the alkyl halides (step 5).

The reaction with cyclopropylmethyl bromide confirms the proposed pathway. As might be expected, cyclopropylmethyl and 3-butenyl units were introduced regioselectively giving rise to **143** as the sole dialkylation product in 50% yield (Scheme 3.147). This result, with the evidence that ring opening of cyclopropylmethyl radical to the 3-butenyl radical is a rapid process which is much faster than the addition of primary radicals to styrene strongly supports the proposal that the first alkylation step is a radical process but that the second step is not.

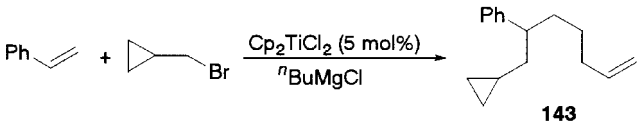
Tab. 3.23 Titanocene-catalyzed double alkylation of olefins with alkyl bromides

Entry	*Olefin*	*R^1–Br, R^2–Br*	*Product*	*Yield (%)* [a]
1		^{t}Bu—Br ^{n}C$_5$H$_{11}$—Br		94 (88)
2		2-Norbornyl—Br ^{n}C$_5$H$_{11}$—Br		91 (79)
3		^{i}Pr—Br ^{n}C$_5$H$_{11}$—Br		63 (54)
4		^{t}Amyl—Br ^{i}Pr—Br		65 (52)
5		^{t}Bu—Br Cl(CH$_2$)$_5$—Br		76 (71)
6		^{n}C$_5$H$_{11}$—Br		76 (72)
7		^{n}Oct—Br		76 (72)

a) NMR yield. Isolated yield is in parentheses.



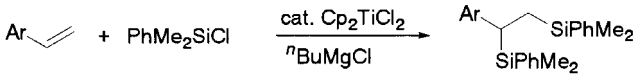
Scheme 3.146



143

Scheme 3.147

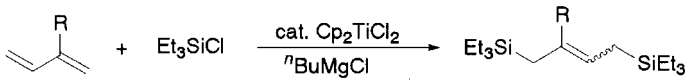
The use of chlorosilanes instead of alkyl halides afforded 1,2-disilylated products under similar conditions [163]. *p*-Chlorostyrene afforded **144a** in only 29% yield with a substantial amount of Me_2PhSi^nBu upon treatment with ^{n}BuMgCl in the presence of titanocene dichloride catalyst. This result suggests that silylation of *p*-chlorostyrene is slow and competes with the direct reaction of $Me_2PhSiCl$ with ^{n}BuMgCl. In practice this problem was overcome by using a large amount of the catalyst and by adopting a dropwise addition procedure (Scheme 3.148).



144a Ar = *p*-ClC_6H_4 72%
144b Ar = Ph 64%

Scheme 3.148

Double silylation of 1,3-butadienes with chlorosilanes was found to proceed by the same procedure. Treatment of a mixture of isoprene, chlorotriethylsilane, and titanocene dichloride with ^{n}BuMgCl provided 2-methyl-1,4-bis(triethylsilyl)-2-butene in 91% yield ($E/Z = 91/9$) (Scheme 3.149).

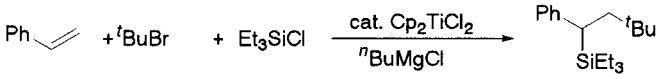


R = H 68% (E/Z = 60/40)
R = Me 91% (E/Z = 91/9)

Scheme 3.149

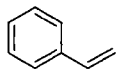
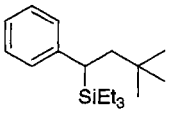
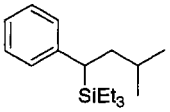
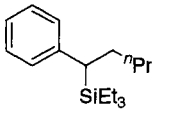
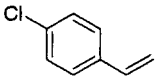
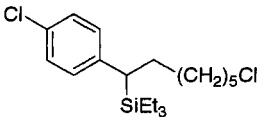
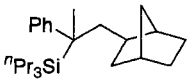
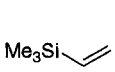
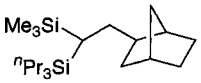
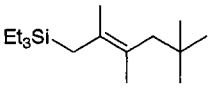
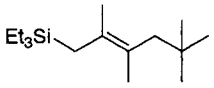
The method was successfully applied to the regioselective carbosilylation of alkenes and dienes [164]. To a THF solution of styrene, chlorotriethylsilane (1.1 equiv.), a catalytic amount of titanocene dichloride (0.05 equiv.), and ^{n}BuMgCl (2.2 equiv.) was added *tert*-butyl bromide (1.1 equiv.) at 0 °C for 10 min under nitrogen, and the solution was stirred for 1 h. NMR analysis of the crude mixture indicated the formation of addition product **145** in 96% yield (Scheme 3.150). This reaction is highly regioselective and yields a single regioisomer with *tert*-butyl group at the terminal carbon and a triethylsilyl group at the benzylic carbon (Tab. 3.24, entry 1). The reaction proceeds efficiently when secondary bromides are used. Primary alkyl bromides can also be employed as the alkylating reagents, but the reaction is somewhat less efficient, affording moderate yields of products (entries 3, 4).

A plausible pathway for this reaction for dienes is outlined in Scheme 3.151. Titanocene dichloride (**146**) reacts with ^{n}BuMgCl to generate the dibutyltitanate(III) complex **148** via Cp_2TiCl and butyltitanocene (**147**). One-electron transfer from **148** to alkyl halides leads to cleavage of the C–X bond to give the corresponding alkyl radical and dibutyltitanocene (**149**), which readily forms Cp_2Ti (**150**) by *β*-hy-



Scheme 3.150 **145**

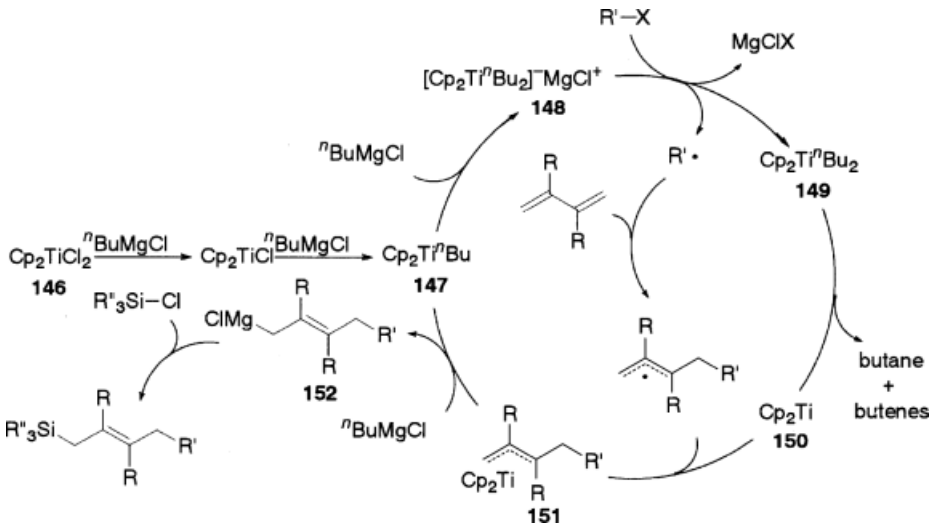
Tab. 3.24 Titanocene-catalyzed carbosilylation using alkyl halides and chlorosilanes

Entry	*Alkene or Diene*	*R–X*	*R'_3Si–Cl*	*Product*	*Yield (%)* [a]
1		^{t}Bu–Br	Et_3Si–Cl		96 (95)
2		^{i}Pr–Br	Et_3Si–Cl		85 (84)
3		^{n}Pr–Br	Et_3Si–Cl		51 (41)
4		$Cl(CH_2)_5$–Br	Et_3Si–Cl		48 (40)
5		2-Norbornyl–Br	$^n Pr_3Si$–Cl		85 (74)
6		2-Norbornyl–Br	$^n Pr_3Si$–Cl		66 (35)
7		^{t}Bu–Br	Et_3Si–Cl		83 (78) *E/Z* = 96/4
8		^{t}Bu–Cl	Et_3Si–Cl		76 (64) *E/Z* = 98/2

a) NMR yield. Isolated yield is in parentheses.

drogen elimination. Addition of the thus-formed alkyl radical to a diene at the terminal carbon affords allyl radical species, which recombines with **150** to give the corresponding allyl titanium complex **151**. Subsequent transmetalation of **151**

with ^{n}BuMgCl gives the corresponding allyl Grignard reagent **152**, with regeneration of **147**. Then **152** reacts with a chlorosilane to give carbosilylation product.



Scheme 3.151

3.6.2

Reaction of Grignard Reagents with Organic Halides in the Presence of Cobaltous Chloride

Kharasch and Fields [165] discovered that reaction of a Grignard reagent with an organic halide in the presence of a catalytic quantity of cobaltous chloride gave a coupling product derived from two molecules of the Grignard reagent. They postulated the following free radical chain reaction in which cobalt sub-chloride is the chain carrier (Scheme 3.152).

$$RMgX + CoCl_2 \longrightarrow RCoCl + MgXCl$$

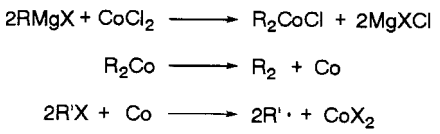
$$2RCoCl \longrightarrow R_2 + 2CoCl$$

$$R'X + CoCl\cdot \longrightarrow CoClX + R'\cdot$$

(R, R' = alkyl or aryl groups, X = Cl, Br, or I)

Scheme 3.152

The following alternative mechanism involving metallic cobalt as the chain carrier was subsequently suggested by Wilds and McCormack [166], who believed the continuously regenerated metal would be in a favorable state of subdivision and activity (Scheme 3.153).



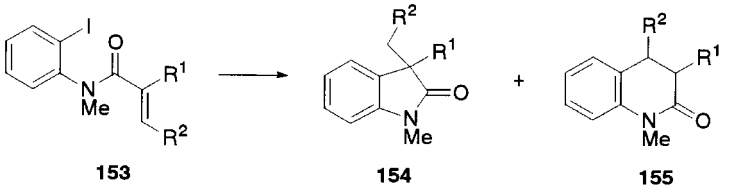
Scheme 3.153

Although it is very difficult to clarify the precise reaction mechanism, the reaction between a Grignard reagent and an organic halide in the presence of cobalt chloride results in the production of free radicals. The effect of varying the reactants has been studied for the cobalt-catalyzed reaction of Grignard reagents with organic halides in the presence of monosubstituted benzene derivatives [167].

3.6.3
Cobalt-catalyzed Aryl Radical Cyclizations with Grignard Reagent

Although tributyltin hydride-mediated radical cyclizations have proved to be particularly useful in synthesis, the toxicity of the tin hydride reagent has stimulated the search for alternative methods of performing such reactions. In the alkyl radical field several alternatives have been developed, involving a variety of methods. The greater instability of the aryl radical precludes the application of many of these methods to aromatic systems, however. The use of cobalt(I) complexes generated in situ has been explored but suffers from the drawback that such complexes are very unstable and considerable practical expertise is required for their successful use [168]. When considering this problem, A. J. Clark et al. [169] paid attention to the early work of Kharasch [165] on the use of Grignard reagents to which various transition metal salts had been added. This work was followed up by Hey [167] who performed quantitative studies involving intermolecular trapping of aryl radicals generated from aryl halides by the cobalt(II) chloride-Grignard reagent combination. This work shed considerable light on the reaction pathway and clearly implicated the involvement of aryl radicals.

Reaction of *N*-methyl-*N*-acryloyl-2-haloanilines with anhydrous cobalt(II) chloride and a Grignard reagent has been reported to lead to the formation of indol-2(3*H*)-ones by a reductive aryl radical cyclization. Methylmagnesium iodide was added to a solution of a catalytic amount of $CoCl_2$ in THF and the solution was heated under reflux for several minutes to give a black solution. Addition of the aryl iodide **153a** provided the oxindole **154a**. When the aryl iodide was **153c**, dihydroquinolone **155c** was obtained with **154c** (Scheme 3.154).



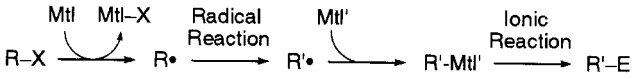
153a	$R^1 = R^2 = H$	71%	0%
153b	$R^1 = H$, $R^2 = Me$	67.5%	0%
153c	$R^1 = Me$, $R^2 = H$	52%	17%

Scheme 3.154

3.6.4

Cobalt-catalyzed Phenylative Radical Cyclization with Phenyl Grignard Reagent

Cobalt-catalyzed tandem radical cyclization and cross-coupling reactions have been reported. Radical reaction with organometallic reagents is a fascinating and developing area in synthetic radical chemistry. The most attractive feature of this strategy is the generation of a new carbon-metal bond by the capture of a carbon-centered radical, derived from a radical transformation, with a metallic reagent. Sequential ionic reaction offers multibond-forming events, i.e. a heterogenerative process [170] (Scheme 3.155).



Scheme 3.155

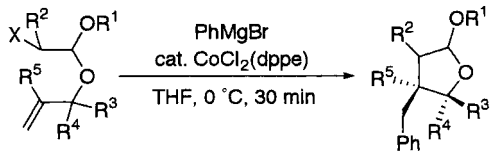
Cobalt-catalyzed coupling of halo acetal with a phenyl Grignard reagent proceeded smoothly, and involved radical cyclization before coupling. A variety of substrates were examined; the results obtained are shown in Tab. 3.25 and Scheme 3.156 [171].

Halo acetals bearing a terminal alkene moiety underwent phenylative cyclization to give the corresponding benzyl-substituted tetrahydrofuran derivative in good to

156a: R = H, X = I, Y = 4-Me-C_6H_4N **157a**: 81% (Ar = Ph)
156b: R = $^nC_5H_{11}$, X = Br, Y = O **157b**: 59% (Ar = Ph)
156c: R = H, X = I, Y = CH_2 **157c**: 59% (Ar = 4-MeO-C_6H_4)

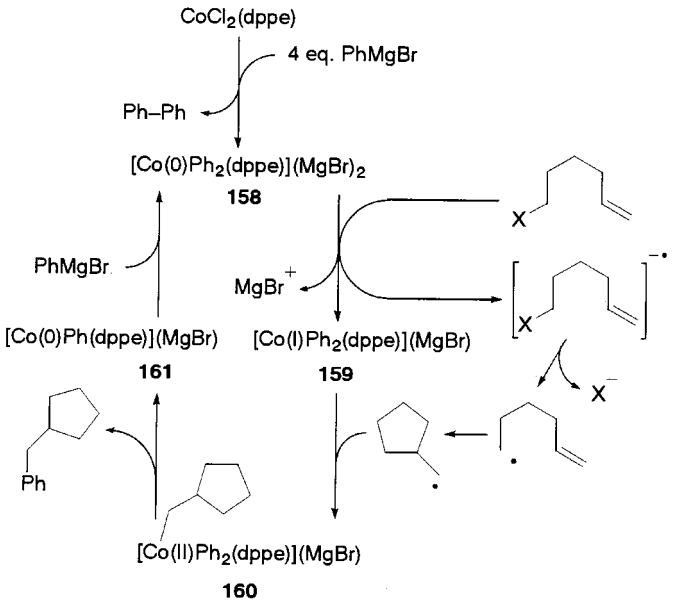
Scheme 3.156

Tab. 3.25 Cobalt-catalyzed phenylative radical cyclization [a)]



Entry	*X*	R^1	R^2	R^3	R^4	R^5	*Yield* [b)]
1	Br	$^nC_4H_9$	H	H	$^nC_5H_{11}$	H	80% (55/45)
2	I	$^nC_4H_9$	H	H	$^nC_5H_{11}$	H	78% (55/45)
3	Cl	$^nC_4H_9$	H	H	$^nC_5H_{11}$	H	N. R.
4	Br	$(CH_2)_3$		H	$^nC_5H_{11}$	H	71% (51/49)
5	Br	$(CH_2)_3$		Me	Me	H	84% (62/38)
6	I	$(CH_2)_3$		Me	Me	H	84% (60/40)
7	Br	$(CH_2)_3$		H	H	Me	51% (single)
8	I	$(CH_2)_3$		H	H	H	22% (91/9)

a) Substrate (0.5 mmol), $CoCl_2$ (dppe) (0.05 mmol), PhMgBr (1.1 mmol), and THF (1 mL) were employed.
a) Isolated yield. Diastereomer ratios are in parentheses.



Scheme 3.157

excellent yield (Tab. 3.25). It is worth noting that the stereochemistry of the products was quite similar to that in the previous reports of radical reaction. This observation is highly suggestive of the same transition state of the cyclization step in this reac-

tion as in the free radical reaction. Allylic alcohols, the substrates, were not detected in the reaction mixture. Thus, β-alkoxy elimination, which could be facilitated by halogen-metal exchange, did not occur. Therefore, a mechanism involving halogen-cobalt exchange followed by intramolecular carbocobaltation is improbable.

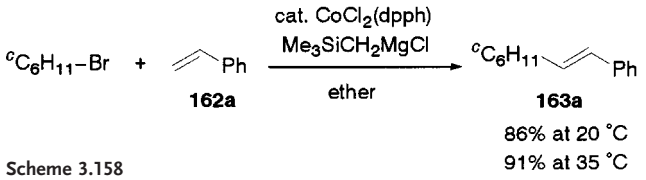
The reaction mechanism assumed is that reaction of $CoCl_2$(dppe) with 4 equiv. PhMgBr gives [Co(0)Ph_2(dppe)](MgBr)$_2$ (**158**) with concomitant production of 1 equiv. biphenyl. The zero-valent-ate complex undergoes single-electron transfer to a substrate to yield an anion radical of the substrate and cobalt(I) complex **159**. The immediate loss of bromide from the anion radical affords the 5-hexenyl radical intermediate, which is transformed into a cyclopentylmethyl radical. The cobalt species **159** then recombines with the carbon-centered radical to form divalent cobalt species **160**. Subsequent reductive elimination provides the product and the Co(0) complex **161**, which is reconverted into **158** by the action of the remaining PhMgBr (Scheme 3.157).

3.6.5
Cobalt-catalyzed Heck-type Reaction of Alkyl Halides with Styrenes

Because the Heck reaction is a powerful tool in organic synthesis its scope and limitations have been well investigated. The main limitation is that one cannot use alkyl halides with hydrogen at the position β to the halide atom, because such substrates suffer from the β-hydride elimination problem. Although there are some examples of the palladium-catalyzed Heck reaction of alkyl halides, the reactions employ only bridgehead halides such as 1-adamantyl bromide [172]. A nickel-catalyzed reaction of alkyl bromides with styrenes has also been reported. Few alkyl bromides were examined, however, and the yields were moderate. A similar catalytic transformation with a cobaloxime is known, although photolysis was required for the successful reaction. Very recently, Kambe et al. have reported titanocene-catalyzed alkylation of styrenes, using butylmagnesium bromide as base [173]. This procedure enables use of a variety of alkyl bromides and some alkyl chlorides as precursors, although yields are still not satisfactory. Functional group compatibility of this titanocene-based method remained uninvestigated.

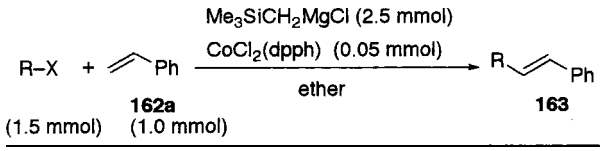
A method complementary to the palladium-catalyzed reaction has been reported. A cobalt-phosphine complex catalyzes a Heck-type reaction of alkyl halides with styrenes in the presence of Me_3SiCH_2MgCl [174]. Trimethylsilylmethylmagnesium chloride was added to a mixture of styrene and bromocyclohexane in ether in the presence of a catalytic amount of $CoCl_2$(dpph) at 0 °C. Heating the reaction mixture under reflux (35 °C) provided **163a** in 91% yield (Scheme 3.158).

Not only secondary alkyl bromides but also the primary and tertiary compounds participated in the alkylation reaction (Tab. 3.26). Reaction of lauryl bromide with styrene at 20 °C yielded β-laurylstyrene in 76% yield. *tert*-Butyl bromide was less reactive and required heating to achieve a satisfactory result. Use of lauryl iodide resulted in a low yield of **163c** (entry 7). It is particularly noteworthy that alkyl



Scheme 3.158

Tab. 3.26 Cobalt-catalyzed alkylation of styrene



Entry	*R–X*	*Time/h*	*Temp./°C*	*Product*	*Yield/%*
1	$^{n}C_6H_{13}CH(Br)CH_3$	8	20	**163b**	73
2	$^{n}C_{12}H_{25}Br$	8	20	**163c**	76
3	$^{n}C_{12}H_{25}Br$	3	35	**163c**	71
4	Ad–Br[a]	8	20	**163d**	87
5	$^{t}C_4H_9Br$	8	20	**163e**	11
6	$^{t}C_4H_9Br$	3	35	**163e**	67
7	$^{n}C_{12}H_{25}I$	3	35	**163c**	57
8	$^{n}C_{12}H_{25}Cl$	3	35	**163c**	74
9	Ad–Cl[a]	3	35	**163d**	90
10	$^{c}C_6H_{11}Cl$	3	35	**163a**	84
11	CH_3I	3	35	**163f**	55[b]

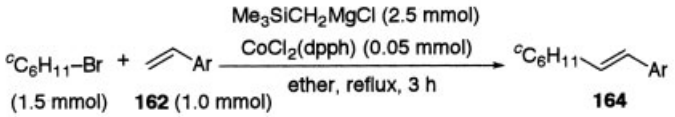
a) Ad = 1-adamantyl.
b) *p*-Chlorostyrene was used instead of styrene.

chlorides, which are usually less reactive in transition metal-catalyzed reactions, proved to be good alkyl sources in this reaction (entries 8–10). For instance, treatment of a mixture of lauryl chloride and styrene with Me_3SiCH_2MgCl in ether under reflux furnished **163c** in 74% yield under $CoCl_2$(dpph) catalysis. The reaction with iodomethane afforded *β*-methylstyrene **163f** in moderate yield (entry 11).

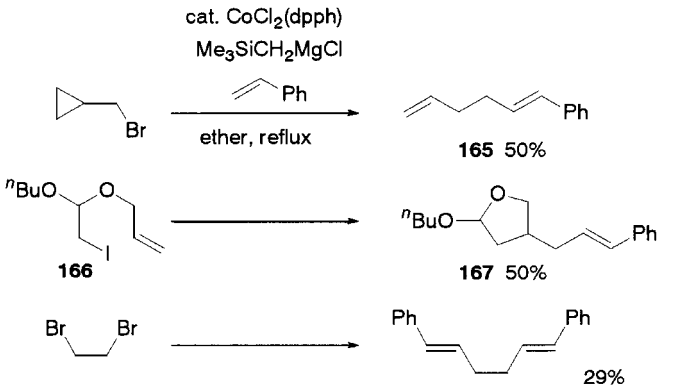
The reaction tolerates a variety of functionalities (Tab. 3.27). Methoxy- and chlorostyrenes were alkylated efficiently under standard, heated, conditions. Disappointingly, the presence of a carbamoyl group at the *para* position reduced the yield of the product. In contrast, the *meta* isomer **162h** underwent efficient alkylation. A *tert*-butoxycarbonyl group survived under the reaction conditions. The reaction with cyclopropylmethyl bromide provided a ring-opening product, *β*-(3-butenyl)styrene (**165**), in 50% yield (Scheme 3.159). In addition, tetrahydrofuran derivative **167** was obtained when iodo acetal **166** was employed. Ring opening of a cyclopropylmethyl radical and ring closure of a 5-hexenyl radical are well-known processes. Generation of an alkyl radical from an alkyl halide is consequently sug-

gested. It is notable that bisstyrylation of 1,2-dibromoethane proceeded albeit the yield was low. A mechanism via carbometalation of styrene is unlikely, because a 2-bromoethylmetal reagent undergoes rapid β-bromine elimination.

Tab. 3.27 Cobalt-catalyzed alkylation of styrene derivatives



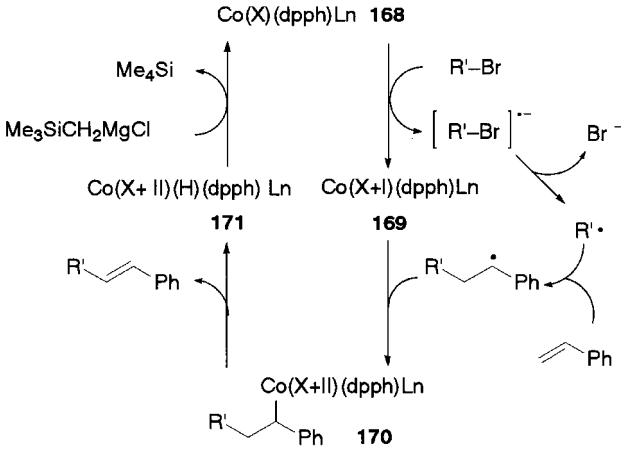
Entry	*162*	*Ar*	*164*	*Yield/%*
1	**162b**	C_6H_4-*p*-Me	**164b**	87
2	**162c**	C_6H_4-*p*-Cl	**164c**	85
3	**162d**	C_6H_4-*m*-Cl	**164d**	82
4	**162e**	C_6H_4-*o*-Cl	**164e**	85
5	**162f**	C_6H_4-*p*-OMe	**164f**	82
6	**162g**	C_6H_4-*p*-$CON(CH_2Ph)_2$	**164g**	29
7	**162h**	C_6H_4-*m*-$CON(CH_2Ph)_2$	**164h**	95
8	**162i**	C_6H_4-*m*-$COO^tC_4H_9$	**164i**	66



Scheme 3.159

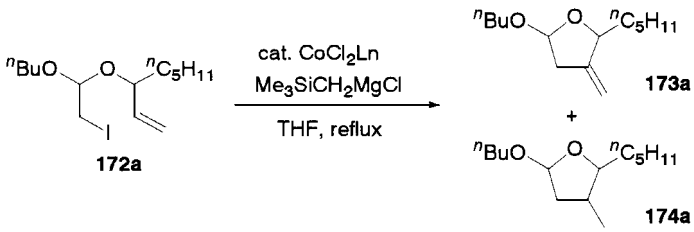
On the basis of these observations the draft mechanism shown in Scheme 3.160 has been proposed for the catalytic reaction, by analogy with the previous reaction. The reaction of $CoCl_2$(dpph) with Me_3SiCH_2MgCl gives complex **168**, which is electron-rich, because of coordination of the Grignard reagent. Complex **168** effects single-electron transfer to an alkyl halide to yield an anion radical of the halide and cobalt complex **169**. Immediate loss of halide from the anion radical affords an alkyl radical intermediate, which adds to styrene to yield a benzyl radical. Cobalt species **169** would then recombine with the carbon-centered radical to form cobalt species **170**. Finally, β-hydride elimination provides

the product and complex **171**, which affords **168** as a result of the action of remaining Me_3SiCH_2MgCl.



Scheme 3.160

Cobalt-catalyzed cyclization of 6-halo-1-hexenes into methylene cyclopentanes has also been reported [175]. Iodo acetal **172a** was selected as model substrate. Trimethylsilylmethylmagnesium chloride (1.0 M THF solution, 1.5 mmol) was added to a mixture of cobalt(II) chloride (0.05 mmol) and 1,4-bis(diphenylphosphino)butane (0.06 mmol) in THF. The resulting mixture was stirred for 5 min and iodo acetal **172a** (0.50 mmol) was then added to the mixture at 0 °C. The whole mixture was heated under reflux for 5 min. Aqueous work-up then silica gel column purification afforded the desired product **173a** in 84% yield in addition to its saturated analog **174a** (Scheme 3.161).



Ln	DPPM	DPPE	DPPP	DPPB	DPPPEN	DPPH	DPPF
173a/%	58	8	68	84	78	69	81
174a/%	28	74	20	9	8	8	11

Scheme 3.161

The choice of the ligand was important. Use of DPPM, DPPE, DPPP, DPPPEN, DPPH, and DPPF furnished **173a** in 58, 8, 68, 78, 69, and 81% yields, respectively. Surprisingly, **174a** was obtained in 74% yield when DPPE was employed. No deuterium incorporation into **174a** was observed when the reactions were quenched with DCl/D_2O. The formation of **174a** would thus involve a radical cyclization path, and the corresponding oxacyclopentylmethyl radical would abstract hydrogen from THF. A radical intermediate similar to that suggested in the former report [174] was assumed for formation of **173a**. Use of a trialkylsilylmethyl Grignard reagent was essential for successful reaction. For example, Me_3CCH_2MgBr was far inferior to Me_3SiCH_2MgCl, which afforded **173a** and **174a** in 18% and 60% yields, respectively. Other alkyl Grignard reagents such as ^{n}BuMgBr also yielded **174a** as a major product.

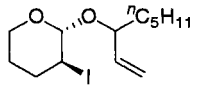
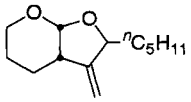
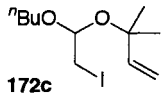
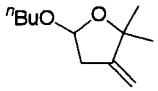
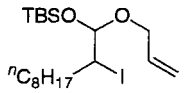
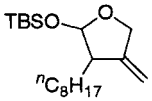
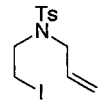
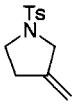
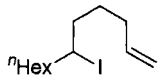
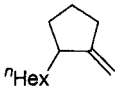
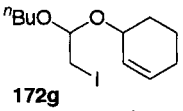
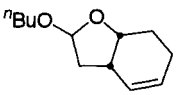
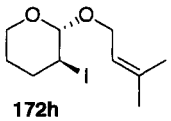
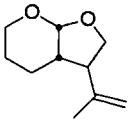
These conditions were slightly different from the conditions used for the intermolecular reaction [174]. The reaction at ambient temperature was slow and yielded a slightly complicated crude mixture compared with reaction in THF under reflux. Reaction in ether under reflux resulted in a lower yield of **173a**. The bromo analog of **172a** was less suitable than **172a**, leading to a lower yield of **173a** (59%, with contamination by 20% **174a**).

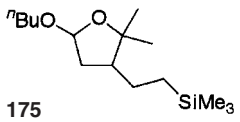
Examples of cobalt-catalyzed intramolecular Heck-type reaction are summarized in Tab. 3.28. Substrates with terminal alkene moieties **172b–f** underwent cyclization to provide the corresponding products in good yields. For example, reaction of **172d** proceeded smoothly to give **173d** in 94% yield. Such substrates bearing nonsubstituted allyloxy groups were not suitable for the cobalt-catalyzed tandem cyclization/phenylation reaction. Interestingly, whereas the standard heated conditions provided the expected product **173c** in 79% yield, the Me_3SiCH_2 group was introduced to give **175** in 20% yield upon treatment of **172c** at 25 °C. The reaction was effective for construction not only of oxacycles but also aza- and carbocycles **173e** and **173f**. For each of **173b–f** the level of the saturated analog was less than 9%. Exposure of **172g** to Me_3SiCH_2MgCl in the presence of $CoCl_2$(dppb) afforded bicyclic product **173g** with a disubstituted olefin. Cyclization on to a trisubstituted alkene resulted in a moderate yield of the expected Heck-type product. Use of DPPP instead of DPPB slightly increased the yield of **173h** to 66%. Considerable amounts of isopropyl-substituted product were obtained in both reactions (DPPB 13%, DPPP 14%).

3.6.6
Radical Cyclization of *β*-Halo Allylic Acetal with a Grignard Reagent in the Presence of Manganese(II) Chloride or Iron(II) Chloride

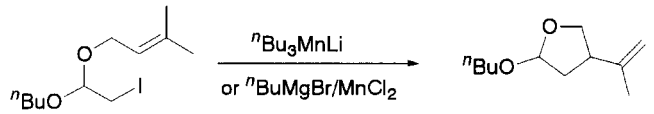
Treatment of unsaturated 2-iodoethanal acetal **176a** with $^n Bu_3MnLi$, generated from $MnCl_2$ and three molar equivalents of ^{n}BuLi, in THF gave the cyclized product **177** in 82% yield. Further investigation proved that the reaction proceeded with ^{n}BuMgBr in the presence of a catalytic amount of $MnCl_2$. For instance, treatment of **176a** (1.0 mmol) with ^{n}BuMgBr (2.0 mmol) in the presence of $MnCl_2$ (0.1 mmol) at 0 °C afforded **177** in 80% yield (Scheme 3.162).

Tab. 3.28 Cobalt-catalyzed intramolecular Heck-type conversion

Entry	Substrate	Product	Yield
1	 **172b** d. r. = 1/1		**173b:** 74% d. r. = 67/33
2	 **172c**		**173c:** 79%
3	 **172d** d. r. = 1/1		**173d:** 94% d. r. = 62/38
4	 **172e**		**173e:** 91%
5	 **172f**		**173f:** 82%
6	 **172g** d. r. = 1/1		**173g:** 82% d. r. = 50/50
7	 **172h**		**173h:** 58% (DPPB) 66% (DPPP) d. r. = 63/37



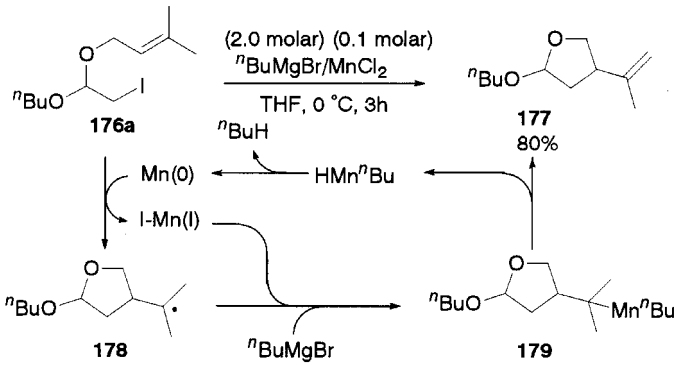
175



176a **177**

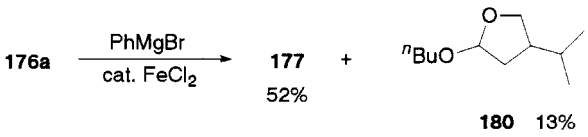
Scheme 3.162

The mechanism of the catalytic reaction might be that reaction between **176a** and tributylmanganate, derived from ^{n}BuMgBr and $MnCl_2$, provides **177** and ^{n}BuMnH which decomposes to Mn(0). Single-electron transfer from this zero-valent manganese to **176a** then affords an alkyl radical and a manganese(I) species. Radical cyclization of the alkyl radical into **178** followed by recombination with manganese(I) could give **179** (Scheme 3.163) [176].



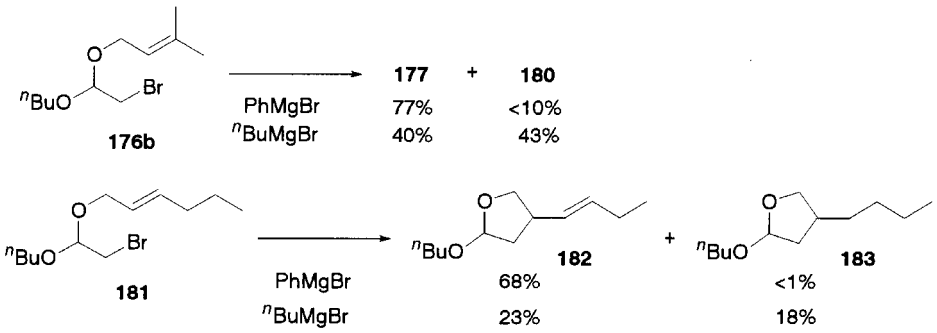
Scheme 3.163

A similar cyclization reaction proceeded on treatment of 2-haloethanal allyl acetal and allyl 2-halophenyl ether with Grignard reagents in the presence of an Fe(II) salt catalyst [177]. Addition of phenylmagnesium bromide to a solution of 2-iodoethanal prenyl acetal **176a** in the presence of a catalytic amount of $Fe(II)Cl_2$ gave the isopropenyl-substituted tetrahydrofuran derivative **177** in 52% yield with an isopropyl-substituted product **180** (13%) (Scheme 3.164).



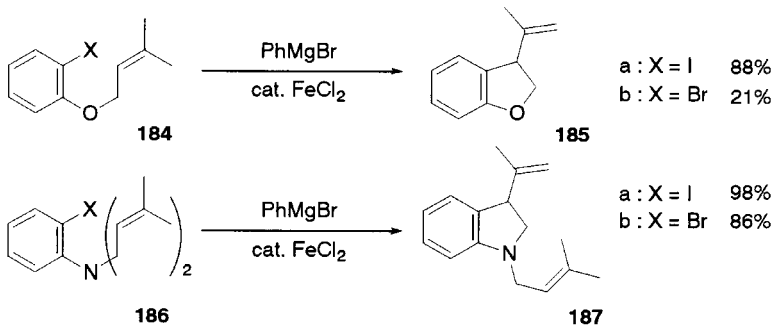
Scheme 3.164

The distribution of the products (**177** and **180**) depended heavily on the nature of the Grignard reagent employed. Use of PhMgBr resulted in less of saturated product **180** than use of ^{n}BuMgBr. This tendency was more clearly seen when 2-bromoethanal allyl acetals were used as substrates. For instance, whereas treatment of 2-bromoethanol acetal **176b** or **181** with PhMgBr gave alkenyl-substituted tetrahydrofuran derivatives **177** or **182** almost exclusively, reaction with ^{n}BuMgBr provided a mixture of **177** and **180** or **182** and **183** (Scheme 3.165). Thus, the combined use of 2-bromoethanal acetals with phenylmagnesium bromide is recommended for the selective formation of alkenyl-substituted tetrahydrofuran derivatives **177** or **182**.



Scheme 3.165

Treatment of 2-iodophenyl prenyl ether **184a** with PhMgBr in the presence of a catalytic amount of $FeCl_2$ provided benzofuran derivative **185** as a single product in 88% yield (Scheme 3.166). Saturated benzofuran derivative, 3-isopropyl-2,3-dihydrobenzofuran could not be detected in the reaction mixture. *N,N*-Diprenyl-2-iodoaniline **186a** gave *N*-prenyl-3-isopropenyl-2,3-dihydroindole **187** in 98% yield. Whereas reaction of bromide **186b** gave **187** in 86% yield under the same reaction conditions, use of 2-bromophenyl derivative **184b** in place of an iodo compound afforded **185** in only 21% yield in addition to the recovered starting material **184b** (25%).



Scheme 3.166

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4
Calcium in Organic Synthesis

Jih Ru Hwu and Ke-Yung King

4.1
Introduction

One of the most popular reactions in organic chemistry is dissolving metal reductions [1–3]. Two systems are frequently used – sodium dissolved in ammonia with alcohol and lithium dissolved in alkylamines [4]. Although calcium is seldom used, it has been successfully applied to the reduction of a variety of compounds and functional groups [5], including aromatic hydrocarbons, carbon–carbon double and triple bonds, benzyl ethers, allyl ethers, epoxides, esters, aliphatic nitriles, dithianes, als well as thiophenyl and sulfonyl groups.

The reducing strength of dissolved metals follows the trend Li > K > Rb > Na > Ca. The weaker reducing strength of calcium enables the use of mild conditions thus results in better selectivity for reactions with some organic functional groups during the reduction process. This chapter focuses on discussion of recent developments in the reduction of organic compounds by calcium in amines.

4.2
Reductive Cleavage of Various C–O Bonds

4.2.1
O-Debenzylation

The benzyl group is frequently used for protection of alcohols. The resulting benzyl ethers are stable to most acidic, basic, and oxidative conditions [6]. The system containing calcium metal in liquid ammonia is a practical means to achieve chemoselective removal of the benzyl group from benzyl ether substrates containing other functionalities. For example, in the study of Aplyronine A, a potent antitumor substance of marine origin, Yamada et al. [7] removed two benzyl protecting groups in **1** with calcium in liquid ammonia to give diol **2** in 98% yield (Scheme 4.1). The triethylsilyl protecting groups in **2** remain intact. Ley et al. [8] used calcium metal in ammonia under reflux in the last step of a total synthesis of the protein phosphatase inhibitor okadaic acid (**4**). Reductive removal of the

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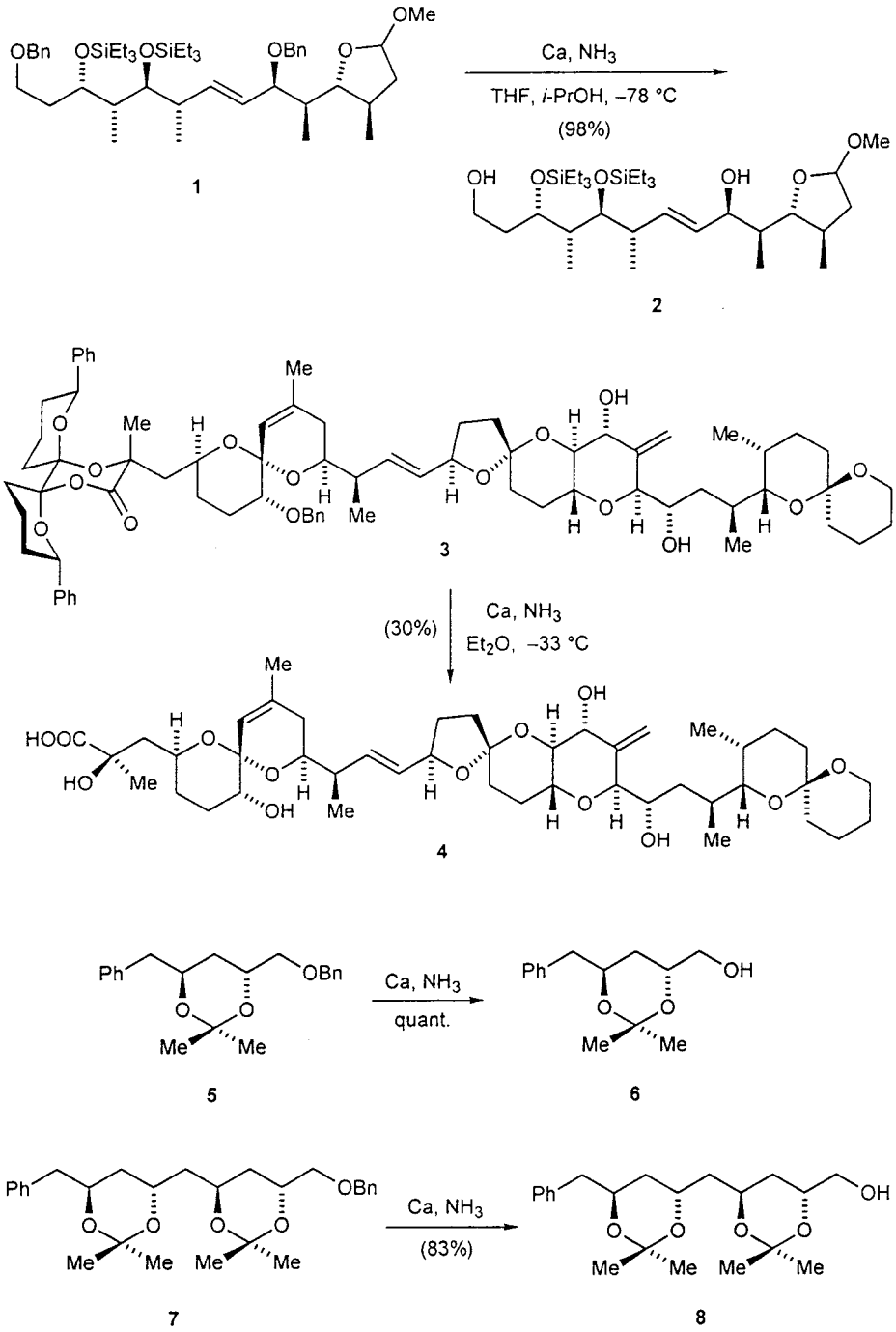
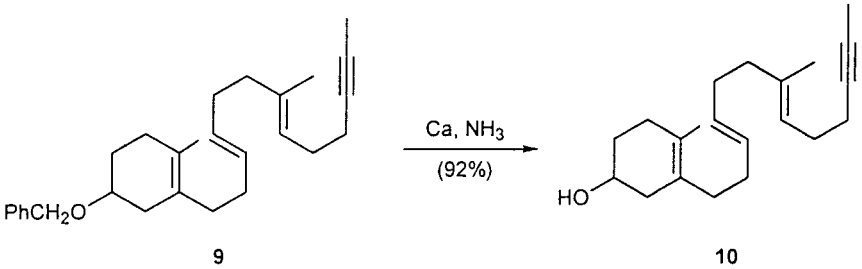


Scheme 4.1 Selective removal of benzyl groups from benzyl ethers containing other functionalities with Ca in ammonia

benzyl group and dephenyldispiroketal in **3** gives 30% yield of **4** without optimization; the allylic acetal moiety, however, survives.

Enders and Hundertmark [9] recently reported that debenzylation of **5** with calcium in liquid ammonia gives the corresponding alcohol **6** in quantitative yield [10]. Similar debenzylation of **7** produces **8** in 83% yield. The use of calcium, in contrast with the more reactive lithium, circumvents reduction of the existing phenyl ring. They also found that the calcium method is far more reliable than palladium-catalyzed hydrogenolysis, which is very sensitive to catalyst poisoning by traces of sulfur and tin by-product.

In a total synthesis of sterols, van Tamelen et al. [11] developed a new method for selective removal of a benzyl group in an alkyne bearing a non-terminal C–C triple bond. Treatment of polyenyne benzyl ether **9** with 4.4 equiv. calcium in liquid ammonia gives the corresponding alcohol **10** in 92% yield (Scheme 4.2). The –C≡C– functionality remains intact. In 1986, results from a systematic study revealed that successful, selective debenzylation of substrates containing a variety of functional groups could be achieved with 2.2 equiv. calcium (Tab. 4.1) [12]. These groups include benzene, furan, and cyclopropyl rings; allylic, furfuryl, cyclopropyalkoxyl, and *tert*-butyldimethlysilyl ethers; and the C≡C triple bond.



9 **10**

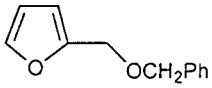
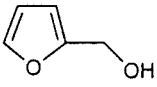
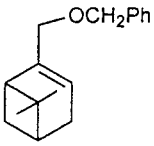
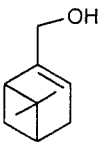
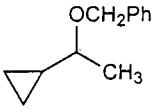
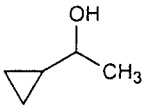
Scheme 4.2 Selective removal of a benzyl group from a benzyl ether containing a non-terminal C≡C triple bond with Ca in ammonia

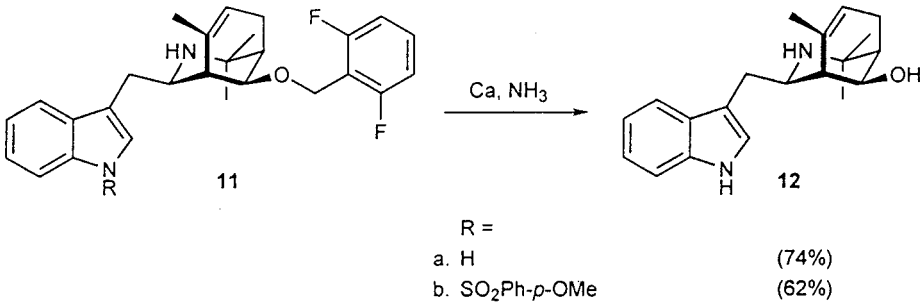
In the synthesis of *Aristotelia*-type alkaloids, Burkard and Borschberg [13] found that the best method for elimination of the 2,6-difluorobenzyl group of the indole derivative **11a** was a procedure involving calcium in ammonia. This led to the desired indolyl alcohol **12** in 74% yield (Scheme 4.3). Use of excess dissolved calcium also enabled simultaneous removal of both the (4-methoxyphenyl)sulfonyl and the 2,6-difluorobenzyl protecting groups from **11b** to give **12** in 62% yield [14].

4.2.2
Cleavage of the (O=C)–OAc Single Bond

In the development of a non-oxidative method for ketone transposition, Marshall and Roebke [15] reductively removed the *α*-acetoxy group from the ketone **13**, to give **14**, by use of calcium in ammonia (Scheme 4.4). This synthetic strategy was

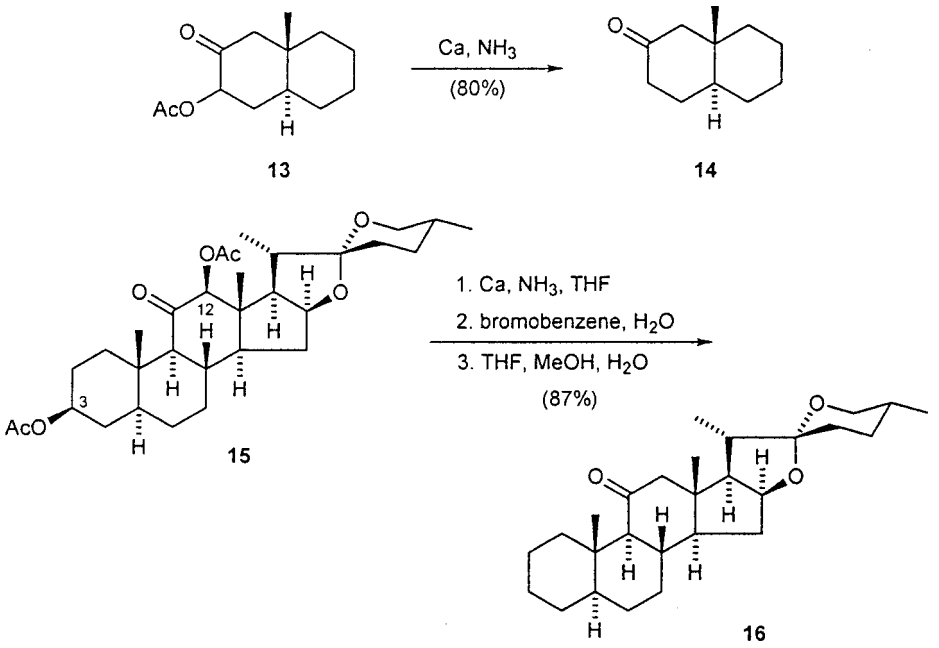
Tab. 4.1 Selective reduction of benzyl ethers containing a variety of functional groups with 2.2 equiv. calcium metal in liquid ammonia

Entry	*Substrate*	*Products*	*Yield (%)*
1	$PhCH_2CH_2CH_2OCH_2Ph$	$PhCH_2CH_2CH_2OH$	100
2			69
3			90
4			96
5	*t*-$BuMe_2SiOCH_2CH_2OCH_2Ph$	*t*-$BuMe_2SiOCH_2CH_2OH$	93
6	$CH_3C{\equiv}CCH_2CH_2OCH_2Ph$	$CH_3C{\equiv}CCH_2CH_2OH$	90



Scheme 4.3 Removal of the 2,6-difluorobenzyl group with Ca in ammonia

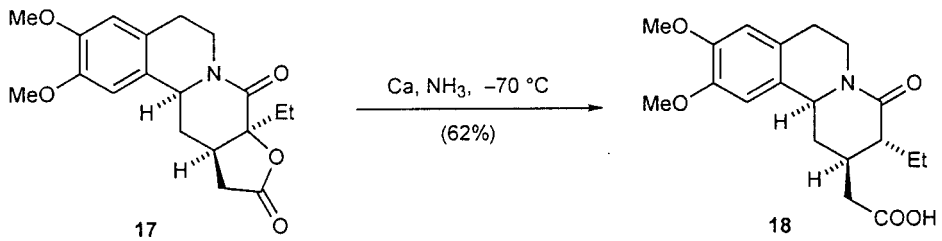
later applied by Pfizer's team [16] in the synthesis of a 11-ketotigogenin cellobioside (pamaqueside), a potent cholesterol absorption inhibitor in the hamster. Under the calcium reductive conditions, both of the C-3 and the C-12 acetoxy groups are removed from **15** to give ketone **16** in 87% yield.



Scheme 4.4 Reduction of α-acetoxyketones with Ca in ammonia

4.2.3
Cleavage of the $R_2N(O{=}C)C{-}O(C{=}O)R$ Single Bond

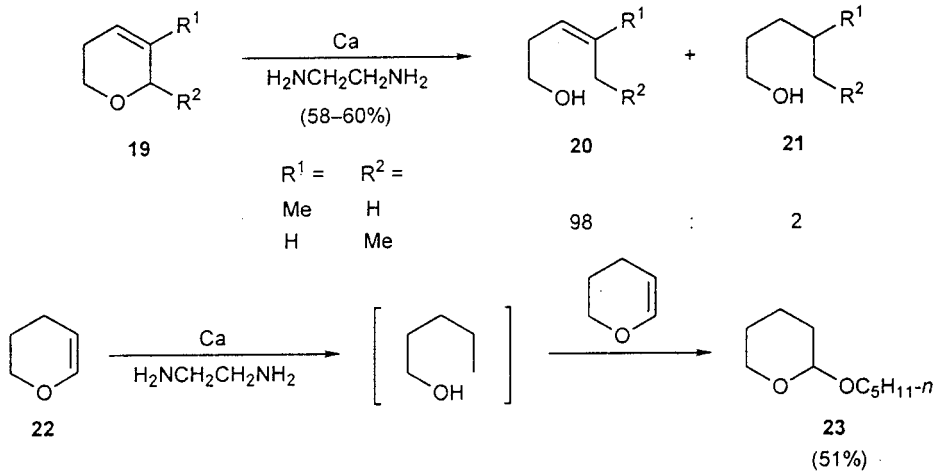
In the reductive cleavage of γ-lactone **17**, Naito et al. [17] reported that use of calcium in liquid ammonia at –70 °C enables the production of the desired carboxylic acid **18** as the sole product in 62% yield (Scheme 4.5). Other procedures including use of aluminum amalgam, chromium(II) chloride, and zinc in acetic acid led to complete recovery of the starting γ-lactone **17**.



Scheme 4.5 Reduction of γ-lactone **17** to the corresponding carboxylic acid **18** with Ca in ammonia

4.2.4
Cleavage of the C–O Bond in Dihydropyrans

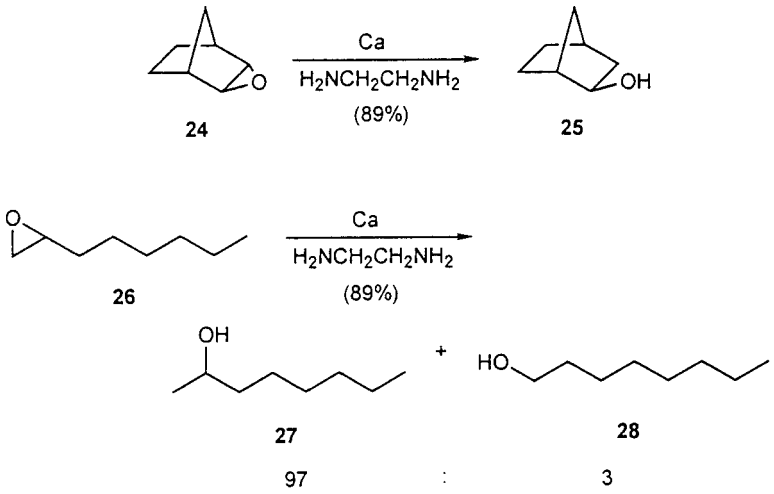
Zhou et al. [18] reported the use of calcium in ethylenediamine for reductive cleavage of dihydropyrans (Scheme 4.6). In 5,6-dihydro-2*H*-pyrans **19**, the allylic C–O bond is cleaved selectively to give a mixture of alkenyl alcohol **20** and saturated alcohol **21** in a 98 : 2 ratio with an overall yield of 58–60%. Application of the same reducing agent to 3,4-dihydro-2*H*-pyran (**22**), however, led to tetrahydropyranyl pentyl ether **23** in 51% yield. This involves reduction followed by an addition process.



Scheme 4.6 Reduction of 5,6-dihydro- and 3,4-dihydro-2*H*-pyrans with Ca in ethylenediamine

4.2.5
Conversion of Epoxides to Alcohols

Calcium in ethylenediamine can efficiently reduce epoxides to alcohols in excellent yields. Benkeser et al. [19] reported that reduction of *exo*-2,3-epoxynorbornane (**24**) by calcium gives *exo*-2-epoxynorbornanol (**25**) in 89% yield (Scheme 4.7). This epoxide is rather difficult to reduce with $LiAlH_4$; its use leads to the production of 7-norbornanol as the by-product in 16% yield by rearrangement. For asymmetric epoxides such as **26**, production of the corresponding secondary alcohol **27** overwhelms that of the primary alcohol **28** (Scheme 4.7).

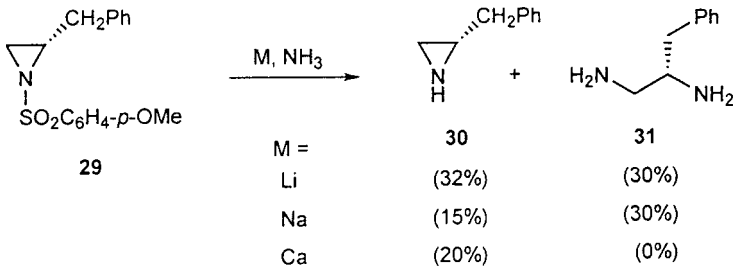


Scheme 4.7 Reduction of epoxides with Ca in ethylenediamine

4.3
Reductive Cleavages of Various C–S Bonds

4.3.1
Desulfonylation

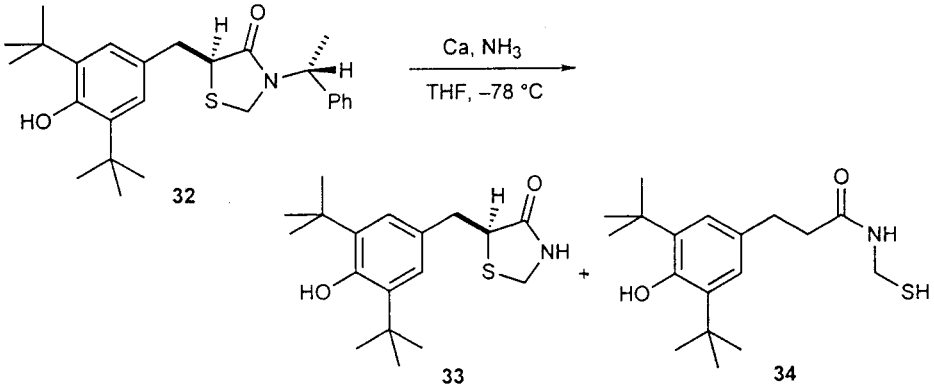
Alonso and Andersson [20] explored the desulfonylation of aziridine **29**, in which the amino group is protected by a *p*-MeO-$C_6H_4SO_2$ moiety. They found that a mixture of benzylaziridine **30** and 1,2-diamine **31** is generated by use of Li and Na in ammonia (Scheme 4.8). Diamine **31** is produced by nucleophilic ring opening with sodium amide along with an *N*-desulfonylation process. Because the reduction potential is lower for Ca than Li and Na, the use of calcium as the reducing agent led to the desulfonylated aziridine **30** (20% yield) exclusively. In other examples, calcium could not be used to remove a toluenesulfonyl group from a nitrogen atom [21].



Scheme 4.8 *N*-Desulfonylation of aziridine **29** with Li, Na, and Ca

4.3.2
Cleavage of a (R_2NCO)C–S Bond

The cleavage of a C–S bond α to an amido group can be accomplished by use of calcium in ammonia. In an attempt to remove the (α-methyl)benzyl group from protected thiazolidinone **32** to give **33** by use of calcium, Hansen et al. [22] obtained a high level of thiol **34** (Scheme 4.9). Use of the dissolved metal under these conditions causes cleavage of both the C–S bond and the N–C bond in **32**.

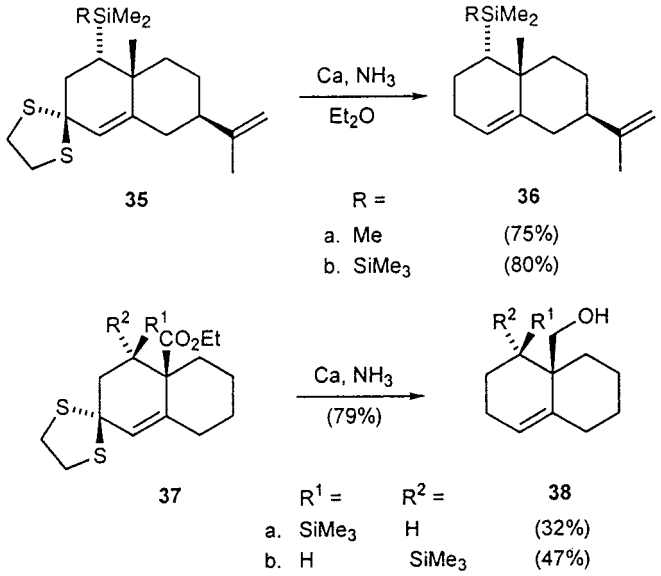


Scheme 4.9 Cleavage of a C–S bond α to an amido group with Ca in ammonia

4.3.3
Removal of Dithiolanes from an Allylic Position

Total synthesis has been achieved for (–)-solavetivone [23], which inhibits germination, germ tube, and mycelial growth. One of the key steps in the synthesis involves removal of the 1,3-dithiolane moiety from an allylic position in the silicon-containing intermediate **35**. Use of calcium in liquid ammonia with ether as the cosolvent enables the conversion of **35a** to **36a** in 75% yield (Scheme 4.10). Its analog, **35b**, contains an Me_3SiMe_2Si– group, in which the Si–Si bond is relative weak. Nevertheless, this disilyl group remains intact upon exposure of **35b** to calcium in ammonia during the conversion of the thioacetal moiety to a methylene unit in **36b** [24]. The 80% yield of **36b** obtained by isolation indicates the mild nature of calcium in the reduction process. In contrast, reduction of **35b** with sodium in liquid ammonia produces **36b** in 7% yield only.

The same reductive conditions have also been applied to thioacetal substrates containing an ester functionality, which is reduced to a hydroxyl group in situ [25]. Treatment of a diastereomeric mixture of thioacetal esters **37** with excess calcium in liquid ammonia under reflux produces, after separation, alcohol **38a** in 32% yield and alcohol **38b** in 47% yield.



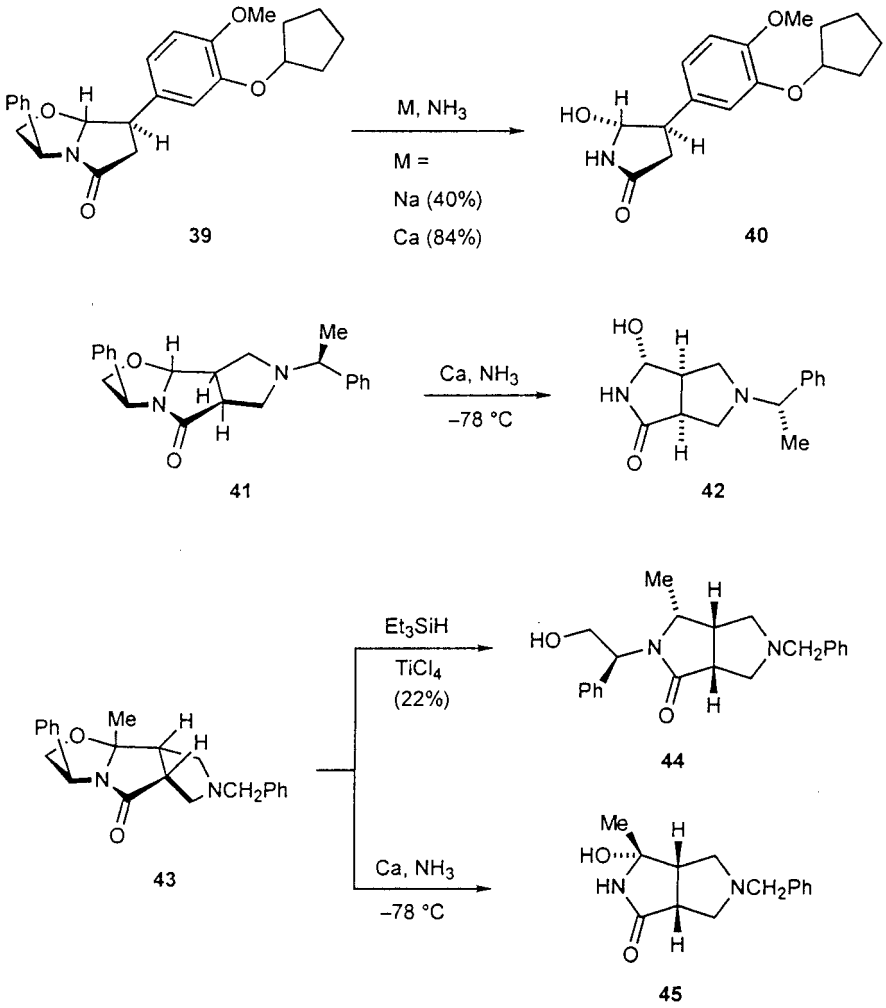
Scheme 4.10 Reductive removal of dithiolane moieties from silicon-containing compounds with calcium reagents

4.4
Reductive Cleavage of Various C–N Bonds

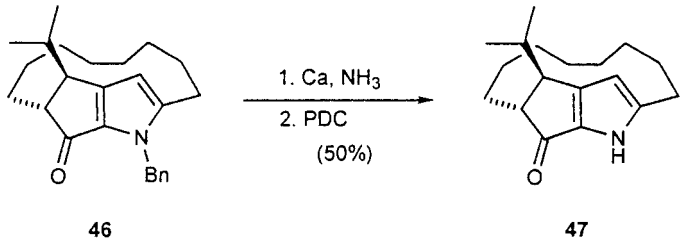
4.4.1
Cleavage of a PhC–N Bond

In the synthesis of the antidepressant (–)-Rolipram, Meyers et al. [26] tried to convert bicyclic lactam **39** to hydroxylactam **40** by use of dissolved metals. The increased yield of **40** on going from Li → K → Na parallels the reduction potential of the metals Li (3.0), K (2.9), and Na (2.7). The reduction potential of calcium is known to be even lower. When **39** is treated with calcium metal (10 equiv.) in liquid ammonia, the desired **40** is produced in 84% yield (Scheme 4.11). The same type of reduction is applicable to the conversion of **41** to **42** [27]. Furthermore, treatment of tricyclic lactam **43** with Et_3SiH and $TiCl_4$ gives poor isolated yield (22%) of the polar diamino alcohol **44**. In contrast, calcium–ammonia reduction of **43** produces *N*-unsubstituted hydroxylactam **45** in an excellent yield.

N-Debenzylation with calcium is also used in the synthesis of roseophilin. Reaction of **46** with calcium in liquid ammonia then reoxidation of the adjacent carbonyl group leads to the desired macrotricyclic core of intermediate **47** (Scheme 4.12) [28], which is finally converted to roseophilin.



Scheme 4.11 Removal of benzyl-type blocks from γ-lactams by various reducing agents



46 47

Scheme 4.12 *N*-Debenzylation of keto pyrrole **46** by Ca in ammonia

4.4.2
Reduction of Nitriles

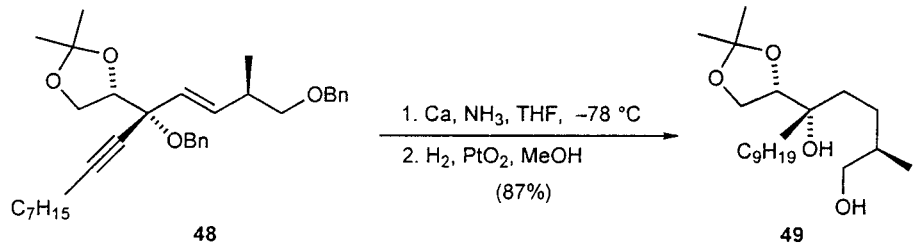
Reduction of tertiary nitriles with lithium in ethylamine or sodium in ammonia often affords reductive decyanation products exclusively. Primary and secondary nitriles give both the expected amine and decyanation products [29, 30]. Doumaux [31] found that calcium in ammonia reduces primary, secondary, and tertiary nitriles to produce modest, synthetically useful amounts of the expected amines. Little decyanation occurs on the basis of the results obtained by use of dodecylcyanide as the substrate.

4.5
Reduction of C=C and C≡C Bonds

4.5.1
Reduction of Alkynes

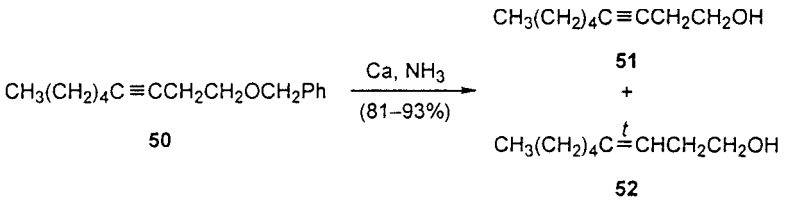
In 1945, Campbell and McDermott [32] found that the reduction of dialkylacetylenes by calcium hexamine [$Ca(NH_3)_6$] in diethyl ether yielded the corresponding *trans* alkenes. In 1984, Benkeser and Belmonte [33] reported results from detailed studies of the reduction of internal and terminal alkynes by calcium in a mixture of methylamine and ethylenediamine (1:1 *v*/*v*). For example, reduction of 4-octyne gives a mixture of isomeric *trans* octenes in 75% overall yield; it includes *trans*-2-, 3-, and 4-octenes in the ratio 1:9:88. Treatment of 1-heptyne, a terminal alkyne, with a fivefold excess of calcium produces 70% of a mixture containing 87% *n*-heptane, 7% *trans*-2-heptene, and 3% 1-heptene.

With a more complicated substrate **48**, Suzuki et al. [34] removed the benzyl protecting group by use of calcium in ammonia, in which part of the diol product underwent partial saturation of the triple bond (Scheme 4.13). Hydrogenation of this mixture gave the fully saturated diol **49** in 87% yield. A thorough study was performed on selective reduction of benzyloxy alkyne **50** to give a mixture of hydroxy alkyne **51** and hydroxy *trans*-alkene **52** in 81–93% overall yields (Scheme 4.14) [12]. The study involved the use of different quantities of calcium and lithium in liquid ammonia.



48 49

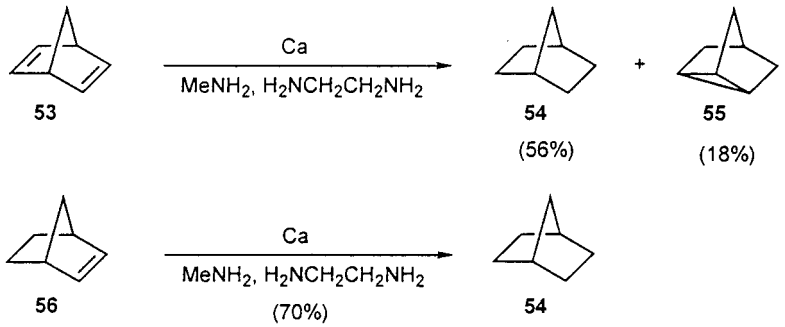
Scheme 4.13 *O*-Debenzylation and partial saturation of the triple bond in **48** by Ca



Scheme 4.14 Partial reduction of a triple bond occurring simultaneously with debenzylation

4.5.2
Reduction of Strained C=C Bonds

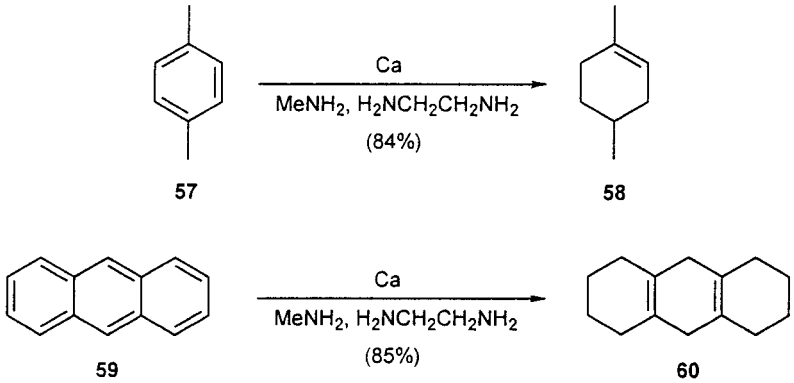
Carbon–carbon double bonds are often stable to dissolved metals. Considerable amounts of norbornane (**54**) are obtained when either norbornadiene (**53**) or norbornene (**56**) is reduced by calcium in methylamine–ethylenediamine (Scheme 4.15) [35]. The C–C double bonds in both substrates are highly strained, which enables the reduction to proceed smoothly. In the reduction of diene **53**, a tricyclic compound **55** is produced as a by-product in 18% yield.



Scheme 4.15 Saturation of strained alkenes with calcium in methylamine–ethylenediamine

4.5.3
Reduction of Aryl Rings

Aromatic hydrocarbons can be reduced to cycloalkenes by calcium dissolved in a mixture of methylamine and ethylenediamine. For example, calcium reduction of *p*-xylene (**57**) and anthracene (**59**) gives 1,4-dimethyl-1-cyclohexene (**58**) or decahydroanthracene (**60**) in 84% and 85% yield, respectively (Scheme 4.16). Calcium–amine combinations are different from lithium–amine systems in that they have little or no propensity to reduce internal double bonds despite the large excess of calcium employed. A grayish white precipitate, seemingly calcium alkyl amide,



Scheme 4.16 Reduction of aromatic hydrocarbons with Ca in amines

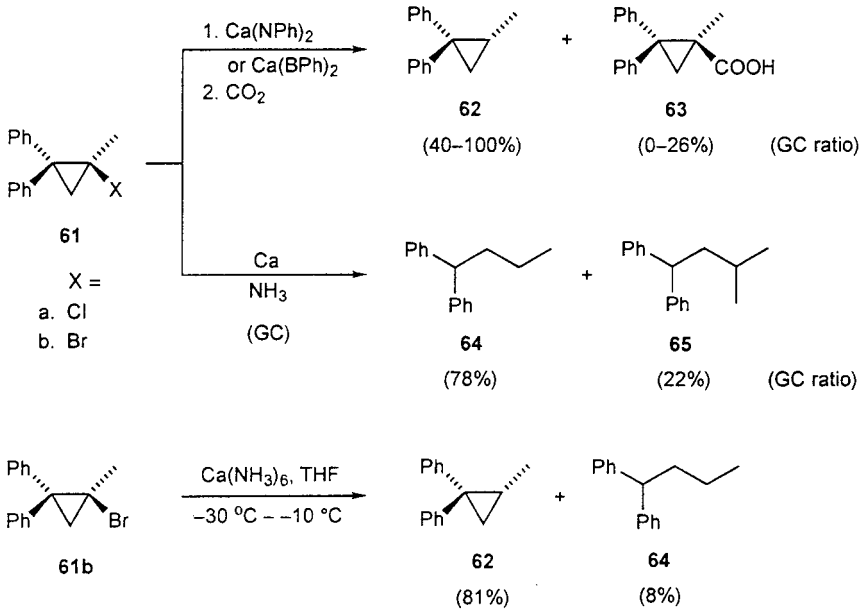
often forms during the course of such reductions and remains until hydrolysis. The reduction rate can be greatly enhanced by addition of small amounts of HMPA [36].

When *tert*-butyl alcohol is used with the calcium–amine system, aromatic compounds can be reduced to products identical with those obtained by Birch reduction of the same substrates [37]. Advantages of the calcium–amine–alcohol procedure are, first, that calcium is much safer to handle than sodium and lithium and is therefore more amenable to large-scale reductions, and, second, the amine solvents are relatively high-boiling and are, therefore, much easier to manipulate than liquid ammonia.

Pétrier and Suslick [38] have recently developed an ultrasound method for enhancing the reactivity of calcium in the reduction of aromatic hydrocarbons. Under the action of ultrasound the reductions proceed more quickly (×10) and require less metal than reactions conducted with an efficient mechanical stirrer. In addition, selective reduction of aromatic hydrocarbons could be accomplished by addition of specific alcohols under the action of ultrasound at ambient temperature.

4.6
Calcium Reagents in Different Forms in the Reduction of Organic Halides

Optically active 1-halo-1-methyl-2,2-diphenylcyclopropanes **61** are used as probes to investigate the mechanisms of calcium reduction [39]. Treatment of **61** with calcium biphenyl ($Ca(BPh)_2$) or calcium naphthalene ($Ca(NPh)_2$) then addition of CO_2 gives a mixture of cyclopropane derivative **62** and the corresponding carboxylic acid **63** (Scheme 4.17). Walborsky and Hamdouchi have provided evidence showing that these reactions occur by single electron transfer to yield free radicals



Scheme 4.17 Reduction of cyclopropyl halides with calcium reagents in different forms

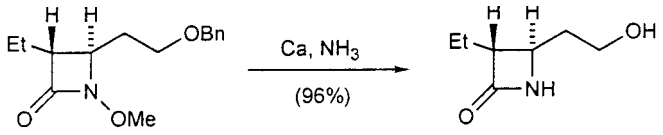
as intermediates. They suggest that the structures of these complexes should be viewed as calcium–aromatic anion radicals rather than organocalcium reagents.

On the other hand, reduction of cyclopropyl halides **61** with dissolved calcium in liquid ammonia at low concentration and at the boiling point of ammonia gives two ring-opened products **64** (78%) and **65** (22%). This reaction is believed to involve a solvated electron–calcium cation pair [40–43].

Metallic bronze $Ca(NH_3)_6$ can, furthermore, be prepared from calcium–ammonia solution by evaporation of the ammonia. A bronze solid is obtained, which in THF at –30 °C behaves as a solid surface in its reaction with alkyl halides (Scheme 4.17) [39]. Its application in the reduction of **61 b** produces a mixture of cyclopropane derivative **62** (81%) and straight-chain diphenylbutane **64** (8%). The process involves the formation of a tight anion radical–cation radical as an intermediate. Carbon–halogen bond cleavage occurs on the surface of the metallic cluster.

4.7
Reductive Cleavage of an N–O Bond

During the development of carbapenem (+)-PS-5 as an antibiotic agent, Naito et al. [44] found that the N–O bond of β-lactam **66** can be cleaved by calcium in liquid ammonia (Scheme 4.18). In situ, the benzyl group is also removed and the



66 67

Scheme 4.18 Cleavage of the N–O and O–CH_2Ph bonds in β-lactam **66** with calcium in ammonia

desired product **67** is obtained in 96% yield. Use of the conventional method involving sodium metal meets with failure.

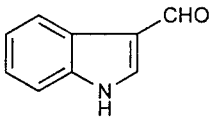
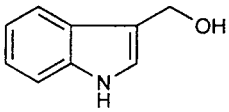
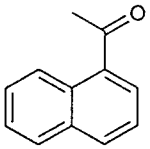
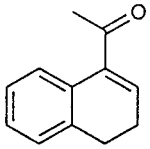
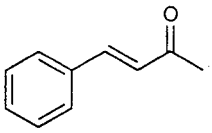
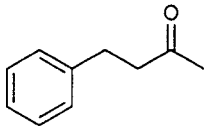
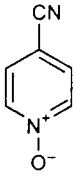
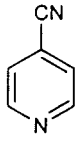
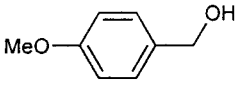
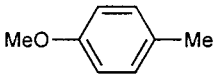
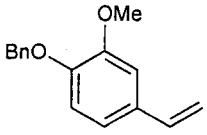
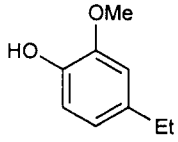
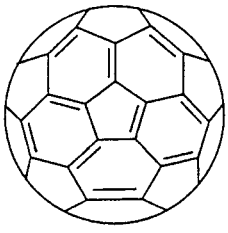
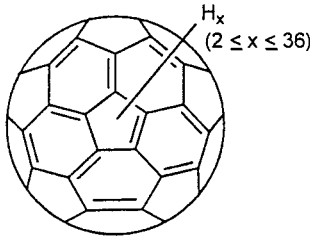
4.8 Reduction of Various Types of Functional Group

In addition to being more selective, dissolved calcium metal functions in a similar way to lithium and sodium metals towards organic functional groups [45]. Tab. 4.2 lists reductions giving the same products by the three dissolved metals. Among these, calcium affords the highest yields for some substrates (entries 1–3). The compounds in Tab. 4.2 include an aldehyde, indole [46], aryl ketone, enone, naphthalene [47], pyridine *N*-oxide [48], benzyl alcohol, styrene, and buckminsterfullerene.

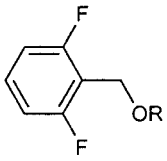
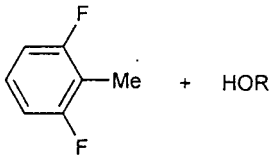
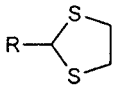
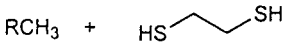
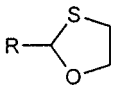
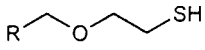
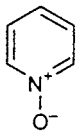
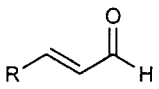
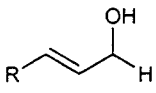
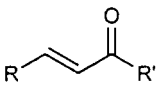
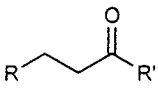
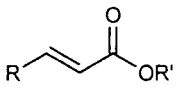
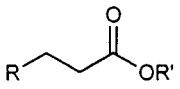
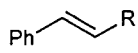
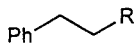
4.9 Chemoselectivity and Limitation

Tab. 4.3 contains many functional groups in approximate order of decreasing ease of reduction by dissolved calcium metal [45]. The order is on the basis of the valuable information reported by leading groups in the field of metal reductions. Reduction proceeds more easily for the functional groups in the first level than the second level; the second level is easier than the third level. Good chemoselectivity can be expected for reduction of the functional groups in Level 1 in the presence of those in Level 3. For bifunctional compounds containing two functional groups in Levels 1 and 2 or in Levels 2 and 3, reductions often lead to a mixture.

Tab. 4.2 Reduction of organic compounds containing a variety of functional groups with metal in liquid ammonia at –33 °C

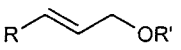
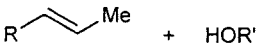
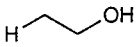
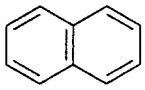
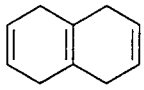
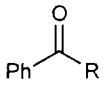
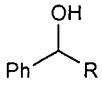
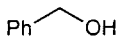
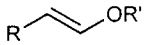
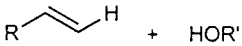
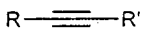
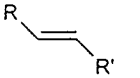
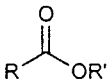
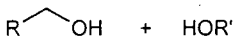
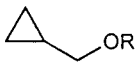
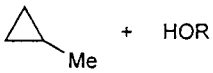
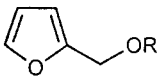
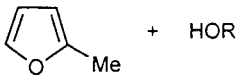
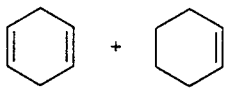
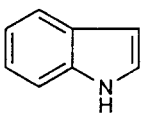
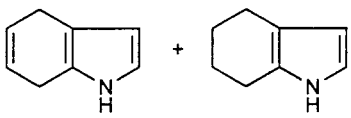
Substrate	*Ca (equiv) yield (%)*	*Li (equiv) yield (%)*	*Na (equiv) yield (%)*	*Product*
	2.0 80	4.0 32	4.0 40	
	2.0 90	4.0 75	4.0 70	
	2.0 90	4.0 72	4.0 67	
	1.2 95	2.4 96	2.4 91	
	2.2 95	4.4 96	4.4 83	
	2.0 95	4.0 93	4.0 92	
	2.0 ~8	4.0 ~8	4.0 ~8	

Tab. 4.3 Relative reactivity of functional group toward reduction by use of calcium metal in liquid ammonia

Level	*Functional group*	*Product*	*Basis*
1			ref 13
	$PhCH_2OR$	$PhCH_3$ + HOR	ref 12
	PhSR	PhSH + HR	ref 12
	$PhSO_2R$	PhH	ref 12
			ref 24
			ref 24
			ref 45
			ref 45
			ref 45
			ref 45
			ref 45

(to be continued)

Tab. 4.3 (cont.)

Level	Functional group	Product	Basis
2			ref 18
			ref 19
			ref 37
			ref 45
		$PhCH_3$	ref 45
3			ref 45
			ref 12
			ref 25
			ref 12
			ref 12
			ref 12
			ref 46
	$R_3Si—SiR'_3$	R_3SiH + $HSiR'_3$	ref 24
	$R_3Si—OR'$	R_3SiOH + HR'	ref 12

4.10 Conclusions

Recent advances in reductions with calcium dissolved in different amine solvents demonstrate value of calcium in organic synthesis. Use of calcium provides a better chance of chemoselectivity than use of lithium and sodium. The reaction conditions are also milder for calcium than for lithium and sodium. It is expected that, in the coming decade, organic chemists will continue to find that use of calcium in a variety of reaction media has advantages in the synthesis of complicated compounds of significance.

4.11 Acknowledgment

We thank the National Science Council of Republic of China and Academia Sinica for support during the preparation of this manuscript.

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5
Barium in Organic Synthesis

Akira Yanagisawa

5.1
Introduction

Although barium compounds are not as popular as magnesium or calcium compounds and have found little application in organic synthesis, with the appearance of allylic barium reagents as selective allylating agents the heavier alkaline-earth metal compounds have attracted attention of organic chemists [1]. This chapter focuses on use of barium compounds in carbon–carbon bond-forming reactions.

Homo- and cross-coupling reactions of allylic halides and reactions of conjugated dienes with dichloroalkanes using reactive barium are reviewed in Section 5.2. The next section covers methods of generating allylic barium reagents and reactions of these carbanions with a variety of electrophiles. The last section describes examples of other carbon–carbon bond forming reactions promoted by barium compounds.

5.2
Reactive Barium-promoted Carbon–Carbon Bond-forming Reactions

Reactive barium (Ba*) is generally prepared from barium iodide and lithium biphenylide according to Rieke's procedure for reactive alkaline-earth metals (Mg and Ca) [2–4], and used immediately for the succeeding reactions (Scheme 5.1) [1]. The reactive barium is known to be a favorable promoter of homo- and cross-coupling reactions of allylic halides [5, 6]. These coupling reactions are among the most basic carbon–carbon bond-forming methods for preparation of 1,5-diene compounds in organic synthesis. Highly α,α'-selective and stereocontrolled homocoupling of allylic bromides or chlorides has been achieved by use of reactive barium. After early studies by Corey and Hamanaka [7] on the use of nickel carbonyl as a low-valent metal in the homocoupling of allylic halides, many groups have made significant contributions to the continuous improvement of this methodology and numerous low-valent metals have been examined [8, 9]. Among reactive

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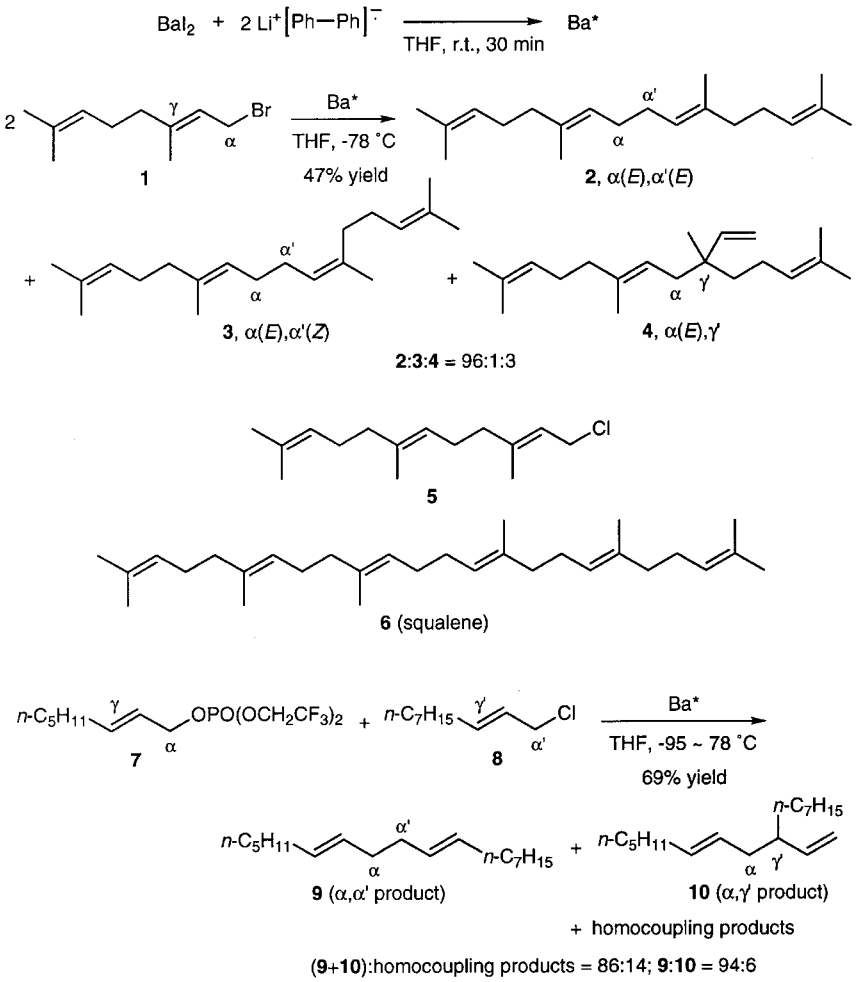
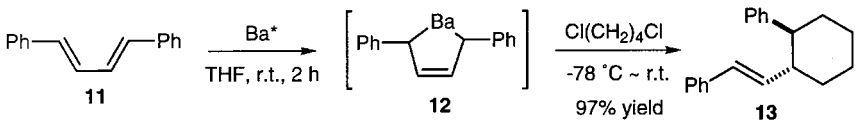
alkali and alkaline-earth metals, reactive barium has unique α,α' selectivity in the homocoupling reaction. For example, when geranyl bromide (**1**) is treated with 0.7 equiv. reactive barium at low temperature, a 97:3 mixture of α,α' homocoupling products (**2**+**3**) and α,γ' homocoupling product (**4**) are formed in 47% combined yield as shown in Scheme 5.1 [5, 6]. Suppression of the configurational isomerization (*E* to *Z*) of the in-situ generated allylic barium compound during the coupling reaction is noteworthy. By use of this procedure a variety of γ-mono- and disubstituted allyl halides can be converted to the corresponding homocoupling products with more than 90% α,α' selectivity, with the exception of (*Z*)-2-alkenyl halides. In general, allylic chlorides give higher yields than the corresponding allylic bromides. (*E*, *E*)-Farnesyl chloride (**5**) is regio- and stereoselectively trans-



Scheme 5.1

formed into squalene (**6**). Regioselective cross-coupling of allylic alcohol derivatives and allylic chlorides is also promoted by reactive barium, with bis(2,2,2-trifluoroethyl) phosphate as a leaving group [10]. Reaction of a 1:1 mixture of (*E*)-2-octenyl 1-bis(2,2,2-trifluoroethyl)phosphate (**7**) and (*E*)-2-decenyl chloride (**8**) with an equimolar amount of reactive barium results in the formation of a mixture of α,α' cross-coupling product **9** and α,γ' cross-coupling product **10** with 86% selectivity and an $\alpha,\alpha'/\alpha,\gamma'$ ratio of 94:6 (Scheme 5.1).

Rieke metals (Mg and Ca) are known to react with 1,3-dienes to generate metal–diene complexes which can react with a variety of electrophiles including alkyl halides, carboxylic esters, epoxides, and imines [2, 3]. Reactive barium has also been shown to react smoothly with (*E,E*)-1,4-diphenyl-1,3-butadiene (**11**) and on treatment with 1,*n*-dichloroalkanes the in situ generated barium-diene complex **12** produces carbocycles [11]. Occasionally the barium complex **12** is more reactive in the alkylation reaction than the corresponding magnesium metallocycle. A typical example affording the cyclohexane derivative **13** is shown in Scheme 5.2. This cyclization occurs with high regio- and stereoselectivity.



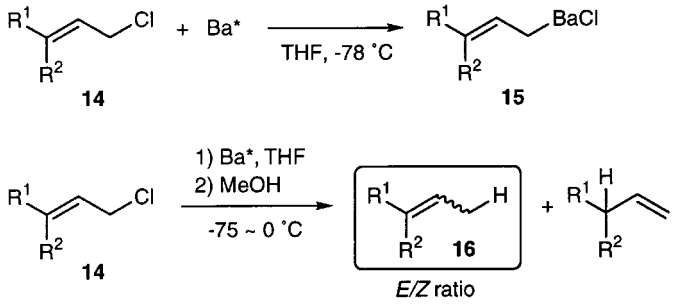
Scheme 5.2

5.3
Preparation of Allylic Barium Reagents and Reactions of these Carbanions with Electrophiles

Allylic barium reagents are known as allylic organometallics which can allylate electrophiles such as aldehydes or ketones with high α-regioselectivity [1]. Allylic barium reagents are generally prepared by a direct insertion method or a transmetalation method. Most of the barium reagents are generated by the former method using the aforementioned activated barium (Ba*) and allylic chlorides.

When the activated barium is exposed to allylic chloride **14** at –78 °C, a slightly exothermic reaction occurs immediately to give a solution or suspension of allylic barium reagent **15** that can be used directly for the subsequent reaction (Scheme 5.3) [1, 12, 13]. Allylic bromides or iodides are not suitable substrates for generating allylic barium reagents because of the homocoupling reaction of these allylic halides. By use of this direct insertion method stereochemically pure allylic barium reagents can be generated directly from allylic chlorides. When a γ-monosubstituted allylic chloride **14** (R^1 = H or R^2 = H) is converted into the corresponding barium reagent **15** at different temperatures followed by quenching with MeOH, analysis of the *E*/*Z* ratios of the resulting alkene **16** reveals that stereoretention is almost complete below –75 °C (Scheme 5.3) [1, 12]. With the γ-disubstituted allylic barium reagent **15** the double-bond geometry is retained even at –50 °C. The

transmetalation method is used in the preparation of siloxyallylbarium reagents [14]. The corresponding siloxyallyllithiums can be effectively transmetalated into the barium reagents by treatment with anhydrous barium iodide.

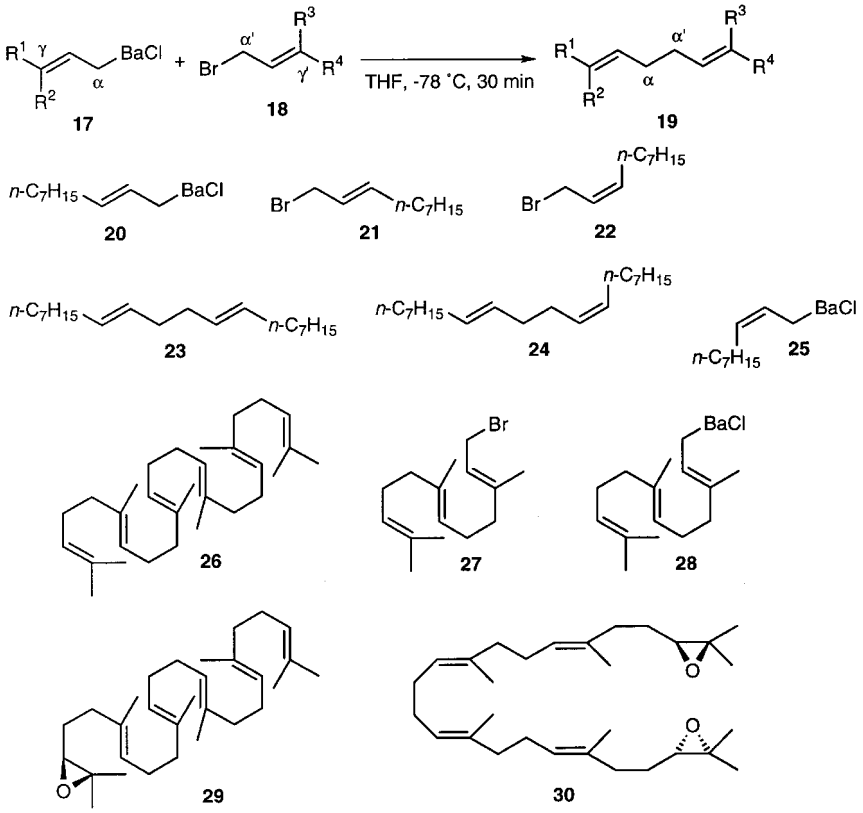


Scheme 5.3

Allylic barium reagents prepared in this way can realize highly *α*-selective reactions with different electrophiles, e.g. cross-coupling reactions with allylic halides or allylic phosphates, additions to carbonyl compounds or imines, and ring opening of epoxides. A selective Michael addition reaction with an *α,β*-unsaturated cycloalkanone can also be performed by use of an allylic barium reagent.

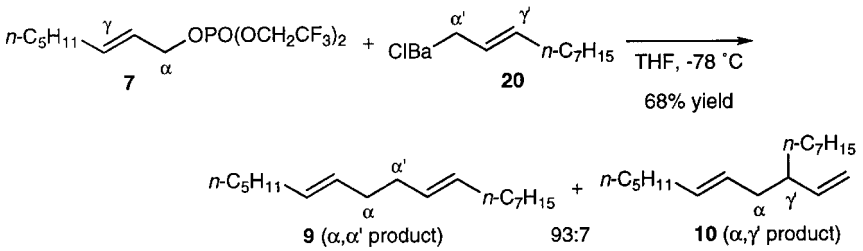
Cross-coupling reaction of allylic halides with allylic metal compounds is a useful means of construction of unsymmetrical 1,5-dienes. Although numerous allylic organometallics have been developed [8, 9], there have been few excellent regioselective and stereospecific methods. Among these an allylic barium reagent **17** has unusually high *α*-regioselectivity in the cross-coupling reaction with allylic bromide **18**. In addition, the double-bond geometry of the barium reagent is retained throughout the reaction at –78 °C. Thus, *α,α′* cross-coupling products **19** can be prepared regio- and stereoselectively by this method (Scheme 5.4) [5, 6]. To obtain superior *α,α′* selectivity and yields in the reaction it is more convenient to employ allylic bromides as electrophiles. For instance, the reaction of (*E*)-2-decenylbarium reagent **20** with (*E*)-2-decenyl bromide (**21**) and (*Z*)-2-decenyl bromide (**22**) gives (8*E*,12*E*)-8,12-eicosadiene (**23**) and its (*E,Z*) isomer **24**, respectively, in high yields. Use of (*Z*)-2-decenylbarium reagent **25**, however, results in a lower yield and *α,α′* selectivity in the coupling with (*E*)-2-decenyl bromide (**21**). These cross-coupling reactions using allylic barium reagents furnishing exceptionally high *α,α′* selectivity and stereospecificity are widely applicable in organic synthesis. Actually, all-*E* squalene (**26**) has been synthesized regio- and stereoselectively by coupling of farnesyl bromide (**27**) with (*E,E*)-farnesylbarium reagent **28** [15]. Selective syntheses of (3*S*)-2,3-oxidosqualene (**29**) [16] and glabrescol-related compound **30** [17] have been also accomplished by taking advantage of this coupling process.

Allylic phosphate is also a useful electrophile in reactions with allylic barium reagents as is allylic bromide for the *α,α′* regioselective cross-coupling reaction. Among a variety of phosphate leaving groups bis(2,2,2-trifluoroethyl)phosphate has remarkable *α,α′* regioselectivity in the reaction [10]. For example, when (*E*)-2-



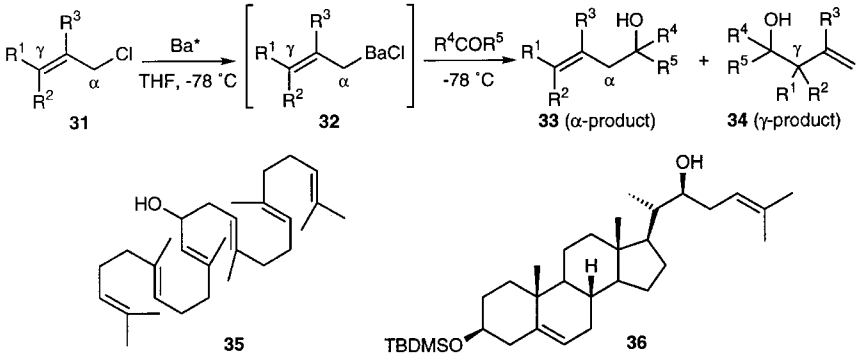
Scheme 5.4

octenyl 1-bis(2,2,2-trifluoroethyl)phosphate (**7**) is treated with (*E*)-2-decenylbarium chloride (**20**) at –78 °C, a 93 : 7 mixture of the cross-coupling products **9** and **10** is obtained in 68% combined yield (Scheme 5.5). Geometrical isomerization (*E* to *Z*) of the allylic barium reagent **20** is kept at a minimum during the coupling reaction and the (*E*) isomer of the *α,α′* coupling product **9** is formed as the major isomer. The *α,γ′* coupling reaction, in contrast, occurs selectively when the allylic phosphate **7** is treated with the corresponding allylic magnesium reagent [10].



Scheme 5.5

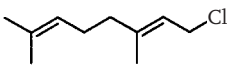
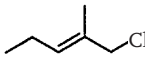
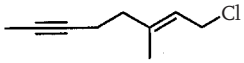
The main concern in the utilization of an allylic metal reagent for the synthesis of homoallylic alcohols is the regio- and stereocontrol of the reaction [18, 19]. γ-Monosubstituted allylmetals usually react with carbonyl compounds at the γ carbon with the exception of sterically hindered ketones [8, 20]. In contrast, the α-regioselective synthesis of homoallylic alcohols remains a challenge in organic synthesis [21, 22]. Allylic barium reagents are extraordinary allylic organometallics which have high α-selectivity and stereospecificity in reactions with carbonyl compounds (Scheme 5.6) [12, 23]. The α/γ-selectivity in the addition of allylic metals to carbonyl compounds depends on the identity of the metal. It is known that allylic magnesium or calcium compounds furnish predominantly γ-substituted products whereas allylation with a lithium or potassium reagent proceeds less selectively. An allylic cerium compound is also moderately α-selective [22]. Table 1 shows the generality of the α-selectivity obtained in the reaction of a variety of aldehydes or ketones with allylic barium reagents **32** generated from the corresponding allylic chlorides **31** in THF at –78 °C. In addition to γ-monosubstituted allylbarium reagents, γ,γ- and β,γ-disubstituted allylbarium reagents also afford significant α-selectivity. In each reaction the double bond geometry of the allylic chloride **31** is almost perfectly retained. Although (*Z*)-γ-monosubstituted allylbarium affords comparatively low α-selectivity in the reaction with hexanal (entry 2), its addition to a bulky ketone produces the α product **33** almost exclusively (entry 3). The presence of an alkyl substituent at the β position or a triple bond in allylic barium reagent does not affect the course of the reaction (entries 5 and 6). 12-Hydroxysqualene (**35**) [12] and oxysterol precursor **36** [24] have been also effectively synthesized by this α-allylation method.



Scheme 5.6

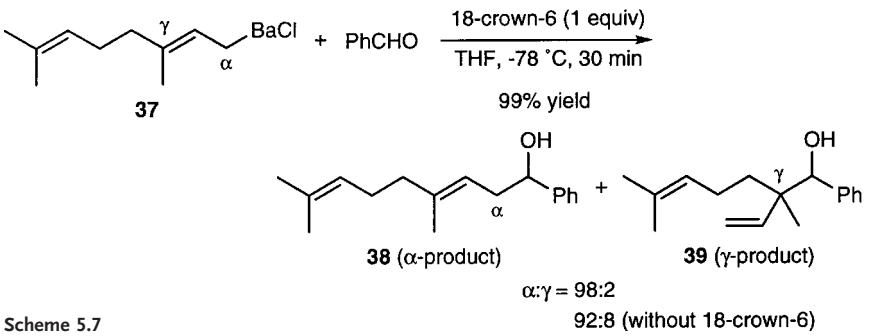
The α-selectivity can be improved to some extent by using a crown ether as an additive for the reaction of allylic barium reagents with aldehydes (Scheme 5.7) [25]. For example, addition of an equimolar amount of 18-crown-6 to geranylbarium reagent **37** in THF at –78 °C followed by treatment with benzaldehyde results in the formation of a 98:2 mixture of α product **38** and γ product **39** in a nearly quantitative combined yield, whereas reaction without the crown ether results in

Tab. 5.1 α-Selective allylation reaction of aldehydes or ketones with allylic barium reagents

Entry	*Allylic chloride 31*	*R^4COR^5*	*Combined yield (%) [a]*	*$\alpha:\gamma$ [b]*	*$E:Z$ [b,c]*
1	(*E*)-*n*-$C_7H_{15}CH{=}CHCH_2Cl$	*n*-$C_5H_{11}CHO$	82	98:2	97:3
2	(*Z*)-*n*-$C_7H_{15}CH{=}CHCH_2Cl$	*n*-$C_5H_{11}CHO$	75	86:14	2:98
3	(*Z*)-*n*-$C_7H_{15}CH{=}CHCH_2Cl$	*t*-BuCO(*t*-Bu)	99	>99:1	<1:99
4		PhCHO	90	92:8	98:2
5		*n*-$C_5H_{11}CHO$	64	94:6	>99:1
6		PhCHO	98	91:9	>99:1

a) Isolated yield of a mixture of chromatographed α-product **33** and γ-product **34**.
b) Determined by GC analysis.
c) The value corresponds to the α-product **33**.

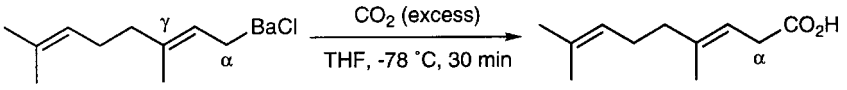
an α/γ ratio of 92:8. Use of more than 1 equiv. 18-crown-6 is ineffective in raising the α/γ ratio. Complexation of the allylic barium reagent with the crown ether is assumed to be the reason for the higher α-regioselectivity.



Scheme 5.7

β,γ-Unsaturated carboxylic acids and their derivatives are useful synthons of natural products. Although numerous methods are available for the synthesis of β,γ-unsaturated acids, there is a problem with E/Z stereoselectivity [26]. One direct way to the acids is reaction of allylmetal compounds with carbon dioxide. With substituted allylic metals carboxylation usually occurs at the more substituted allylic terminus (γ-carboxylation) [8]. In contrast, an allylic barium reagent undergoes α-selective carboxylation without isomerization of the double bond [12, 13, 27]. For example, exposure of geranylbarium chloride (**37**) to carbon dioxide almost specifically forms the α-carboxylated product, **40**, whereas the γ product is

obtained from the corresponding magnesium reagent [8, 27]. In general, allylic barium reagents prepared from γ-mono- and γ-disubstituted allyl chlorides afford high α-selectivity and the double-bond geometry is almost completely retained throughout the reaction. Even if an alkyl substituent is present at the β position of an allylic barium reagent the regioselectivity is not affected.

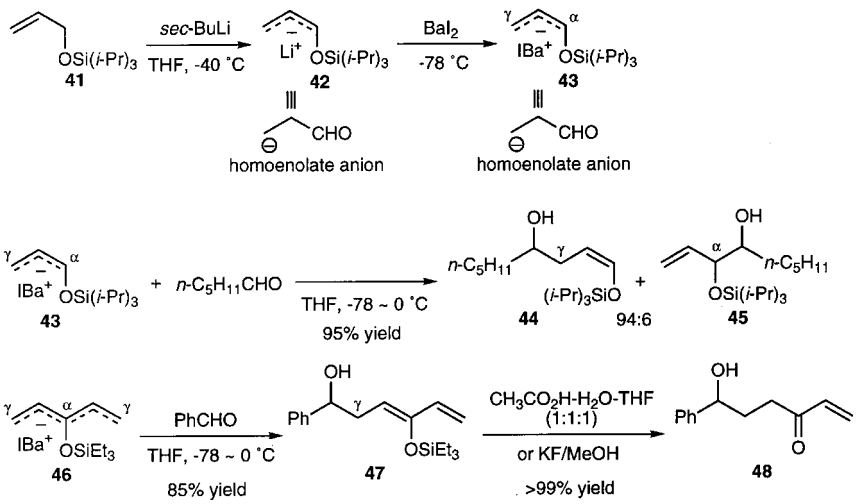


37 87% yield **40**

α:γ > 99:1; *E*:*Z* = 98:2

Scheme 5.8

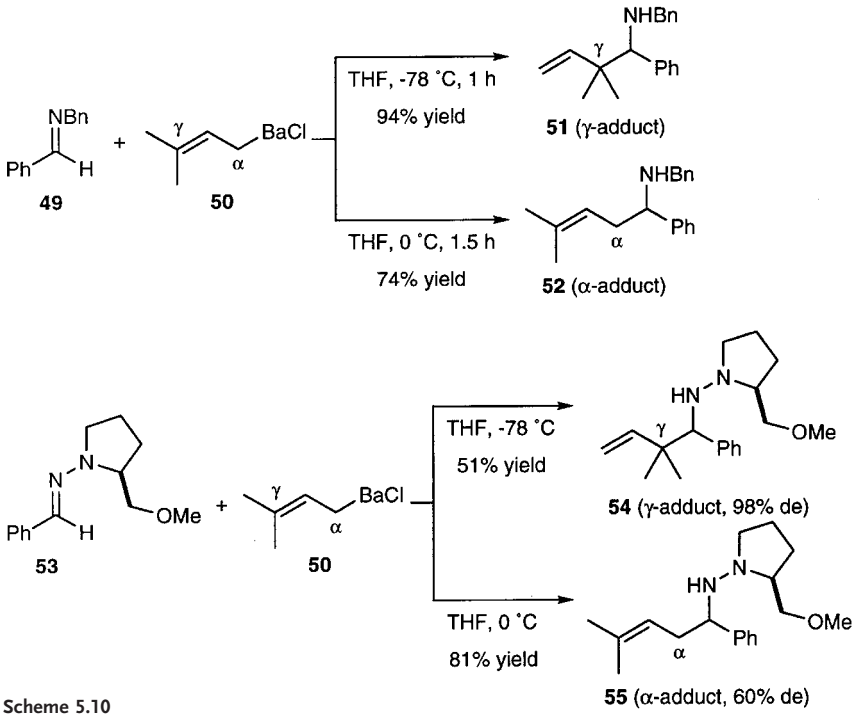
Allylic barium reagents can also be generated from the corresponding allylic lithiums and anhydrous barium iodide (BaI_2) by transmetalation. α- or γ-Heteroatom-substituted allylic metals are homoenolate anion equivalents which are often used in organic synthesis. Siloxyallylbarium reagents, prepared from BaI_2 and siloxyallyllithium, react at the less substituted allylic terminus (the γ position in this instance) with electrophiles, although typical siloxyallylmetal reagents react at the more substituted allylic terminus (α position) [1, 14]. For example, deprotonation of allyl triisopropylsilyl ether (**41**) with *sec*-BuLi then treatment of the resulting triisopropylsiloxyallyllithium (**42**) with BaI_2 gives the corresponding siloxyallylbarium iodide **43** which can react with hexanal to furnish a 94 : 6 mixture of the γ adduct **44** and the α adduct **45**, in 95% combined yield (Scheme 5.9). The γ product has *Z*-stereoconfiguration. Allylation with the corresponding lithium reagent, in contrast, results in moderate α selectivity (**44** : **45** = 37 : 63). Condensation of 3-(triethylsiloxy)pentadienylbarium iodide (**46**), an α-substituted siloxyallylbarium re-



Scheme 5.9

agent, with benzaldehyde also occurs at the γ carbon to afford the siloxydienol **47**, with *Z* stereochemistry, in 85% yield without contamination of any regioisomer (Scheme 5.9) [14]. The triethylsilyl group of **47** can be removed by two methods leading to the vinyl ketone **48**.

Addition of allylic organometallics to imines is a beneficial means of synthesizing homoallylic amines, which can be further converted to a variety of biologically important molecules, e.g. β-lactams [8, 28, 29]. An α adduct (linear product) and/or γ adduct (branched product) are formed when γ-substituted allylmetal compounds are employed in the reaction. In general, γ-substituted allylic lithium, magnesium, and zinc reagents are not usefully regioselective in their reactions with aldimines; allylic barium reagents can, however, give the α and γ adducts selectively if the reaction temperature is controlled [30]. If *N*-benzyl benzaldimine **49** is treated with prenylbarium chloride (**50**) in THF at –78 °C, the γ adduct **51** is obtained in 94% yield. In contrast, the α adduct **52** is almost specifically formed by reaction at 0 °C (Scheme 5.10). The utility of allylic barium reagents for regioselective addition to imines has been further proved by asymmetric allylation of the SAMP-derived chiral hydrazone **53** (SAMP = (*S*)-(–)-1-amino-2-methoxymethylpyrrolidine). The reaction of **53** with prenylbarium reagent **50** at –78 °C furnishes the γ-allylated hydrazine **54** with 98% de, whereas α isomer **55** is obtained as the major product in 60% de when the reaction is performed at 0 °C (Scheme 5.10) [30]. This regiochemical result is assumed to arise from the reversibility of the ad-



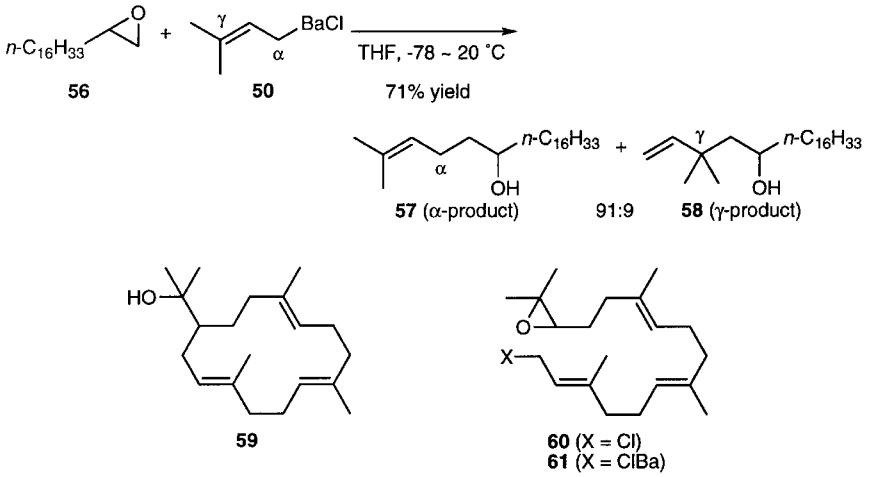
Scheme 5.10

dition of an allylic barium reagent to an aldimine, in which the γ adduct is initially formed and slowly isomerizes to the more thermodynamically stable α adduct at higher temperature.

Olefinic alcohols and related compounds are versatile synthetic intermediates of natural products. Ring opening of epoxides with allylic metal compounds is one straightforward route to 4-alken-1-ols. To obtain the alcohols selectively numerous cross-coupling processes have been developed taking advantage of allylic organometallics; however, there is trouble with α/γ regioselectivity of the allylating agents and/or E/Z stereoselectivity of the products [8, 31]. The value of allylic barium reagents for nucleophilic addition has been further verified by the reaction with epoxides and significant α selectivity has been seen in the cross-coupling reaction [6, 32]. For instance, a 91:9 mixture of α-coupling product **57** and γ-coupling product **58** is formed in 71% combined yield when epoxide **56** is treated with prenylbarium reagent **50** (Scheme 5.11). Characteristic features of the ring opening reaction of a variety of epoxides with allylic barium reagents are:

- both γ-mono- and γ-disubstituted allylbarium reagents have high α selectivities and their double bond geometry is retained to some extent even if the reaction temperature is elevated to 20 °C;
- the substitution occurs at the less-substituted carbon of the epoxides; and
- the coupling reaction proceeds with inversion.

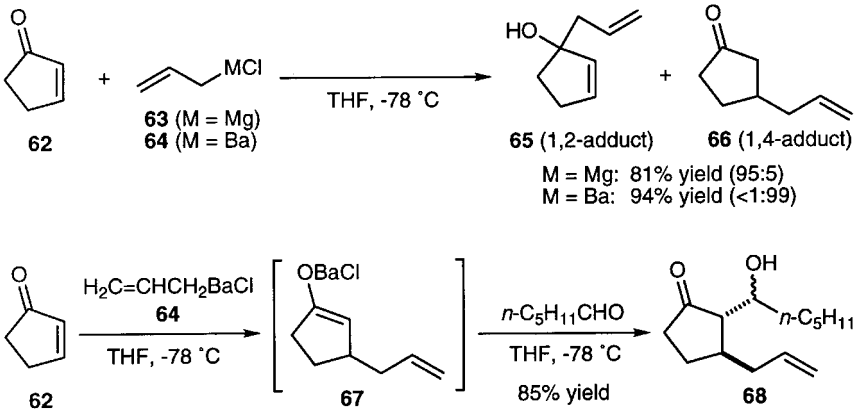
This α-regioselective cross-coupling reaction has been used in the synthesis of cembrol A (**59**) from the epoxy chloride **60**, and cyclization of epoxy allylic barium compound **61** occurs regioselectively (Scheme 5.11) [15].



Scheme 5.11

Michael addition of an allylic carbanion to an α,β-unsaturated carbonyl compound is a favorable route to a carbonyl compound with a 2-alkenyl group at the β position. For this purpose, two allylating methods are frequently employed –

allylic silanes with $TiCl_4$ and allylic copper reagents. Although the usefulness of these reagents is unambiguous, with the former method it is difficult to achieve sequential functionalization at the α position and the latter method does not always provide desirable results. Replacement of the metal of an allylic metal reagent with barium also enables 1,4-addition [12]. When 2-cyclopentenone (**62**) is treated with allylmagnesium reagent **63** in THF at –78 °C, 1,2-adduct **65** is formed selectively, whereas allylbarium reagent **64** affords exclusive 1,4-selectivity (Scheme 5.12). As a result, simply by changing magnesium for barium the reaction course is converted from 1,2-addition into 1,4-addition. The in situ generated barium enolate has adequate nucleophilicity toward electrophiles and thus, one-pot sequential double alkylation of α,β-unsaturated ketones is attainable (Scheme 5.12). Aldol condensation of the enolate **67**, generated by reaction of 2-cyclopentenone (**62**) with allylbarium reagent **64**, is accomplished by treating it with 2 equiv. hexanal to afford α,β-dialkylated cyclopentanone **68** in 85% yield [12]. The *trans*/*cis* and *threo*/*erythro* ratios of **68** are >99/1 and 83/17, respectively. Direct alkylation and acylation of the enolate **67** also proceed with equal efficiency.

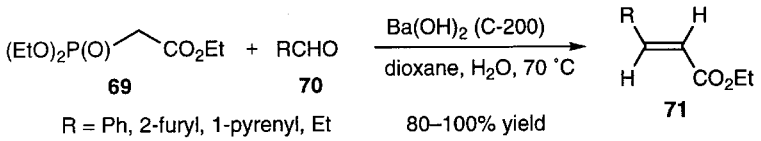


Scheme 5.12

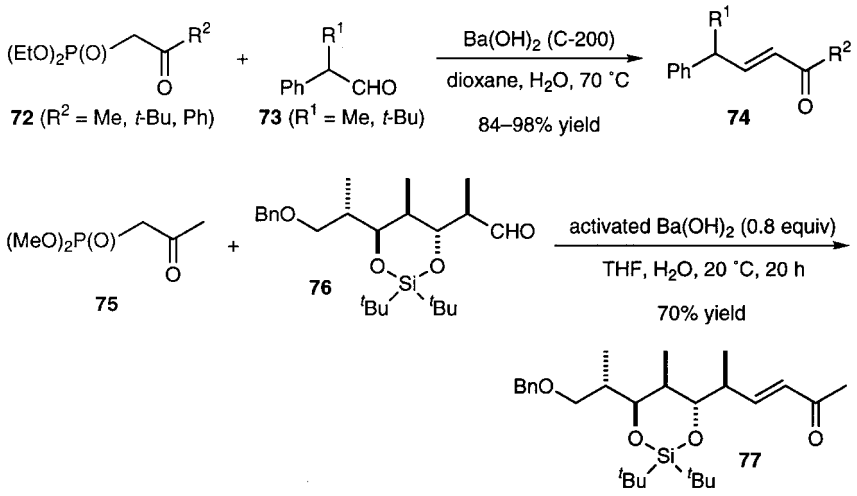
5.4
Other Carbon–Carbon Bond-forming Reactions Promoted by Barium Compounds

Barium hydroxide [33, 34] is a strong base which has been employed not only in organic synthesis but also for other purposes. The commercially available octahydrate, $Ba(OH)_2 \cdot 8H_2O$ is often used after transformation to the anhydrous form at 200–500 °C. Dehydrated $Ba(OH)_2$ activated at 200 °C is denoted C-200. It is known to be a heterogeneous basic catalyst in the Horner-Wadsworth-Emmons (HWE) reaction of triethyl phosphonoacetate (**69**) with aldehydes **70** to give the 3-substituted ethyl acrylates **71** (Scheme 5.13) [35]. The HWE reaction proceeds at 70 °C in 1,4-dioxane with a small amount of water. The yields of products **71** are usually better than those provided by typical basic catalysts such as NaOH or

K_2CO_3. No side reactions like the Cannizzaro or Knoevenagel reactions are observed on treatment with C-200. In the reaction with benzaldehyde and furfural the products **71** (R = Ph and 2-furyl) are formed nearly quantitatively. Bulky aromatic aldehydes such as pyrene-1-carboxaldehyde and aliphatic aldehydes are also suitable substrates for this process. (*E*)-acyclic *α,β*-unsaturated ketones **74** can be prepared by use of a similar HWE reaction of 2-oxoalkanephosphonates **72** with aliphatic aldehydes **73** under the influence of barium hydroxide C-200 (Scheme 5.14) [36]. The HWE procedure employing activated $Ba(OH)_2$ is applicable to the structurally complex, base-sensitive aldehydes which are susceptible to elimination and/or epimerization under the traditional basic conditions of the HWE reaction using NaH. For instance, when phosphonate **75** and aldehyde **76** are exposed to 0.8 equiv. activated $Ba(OH)_2$ in aqueous THF at 20 °C, (*E*)-enone **77** is obtained in 70% yield (Scheme 5.14) [37].



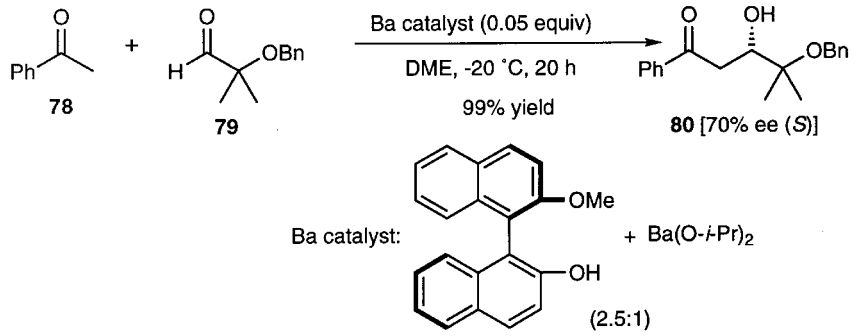
Scheme 5.13



Scheme 5.14

A catalytic asymmetric aldol reaction is a favorable route to optically active *β*-hydroxy carbonyl compounds [38]. Although a variety of methods have been developed, most are the chiral Lewis acid-catalyzed Mukaiyama aldol reactions using silyl enol ethers or ketene silyl acetals. Organic chemists have recently devoted much attention to direct catalytic asymmetric aldol reactions, starting from

unmodified ketones and aldehydes, because of their synthetic utility and atom economy [39, 40]. An asymmetric barium complex, prepared from a 2.5 : 1 mixture of (*R*)-2-hydroxy-2′-methoxy-1,1′-binaphthyl and Ba(*O*-*i*-Pr)$_2$ in DMF, has been found to be an effective catalyst for the aldol reaction. For example, the condensation of acetophenone (**78**) with the aldehyde **79** in the presence of 5 mol% barium catalyst in DME at –20 °C results in the formation of the (*S*)-enriched aldol adduct **80** in 99% yield with 70% ee (Scheme 5.15) [41].



Scheme 5.15

5.5 Summary and Conclusions

Described herein are examples of organic transformations using barium compounds. Reactive barium has enabled *α,α′*-selective homo- and cross-coupling reactions of allylic halides and/or allylic phosphates with high *E*/*Z*-stereoselectivity. This barium compound is also effective in reactions of 1,3-dienes with 1,*n*-dichloroalkanes. Allylic barium reagents, mostly generated from the reactive barium and allylic chlorides, have been often used in organic synthesis and a variety of selective carbon–carbon bond-forming reactions, including cross-coupling reactions with allylic halides, additions to aldehydes and imines, and ring opening reaction of epoxides, have been developed. Michael addition with *α,β*-unsaturated cycloalkanones can also be achieved by use of allylic barium reagent. The activated barium hydroxide-promoted Horner-Wadsworth-Emmons reaction has furnished significant *E*-stereoselectivity and has proven to be an excellent synthetic method for *α,β*-unsaturated ketones and esters. The barium complex, prepared from a 1,1′-bi-2-naphthol derivative, is remarkable as a chiral catalyst for a direct catalytic asymmetric aldol reaction. These examples clearly indicate that barium compounds are quite effective in forming carbon–carbon bonds with regio- and stereoselectivity.

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6
Aluminum in Organic Synthesis

Susumu Saito

6.1
Introduction

Among Lewis acids, aluminum has been the most extensively investigated (Fig. 6.1). This implies that aluminum species are among the most versatile metal reagents in organic synthesis. This chapter provides comprehensive and more profound understanding of the *recent* development of aluminum reagents and their application not only in simple bimolecular reactions but also in multi-molecular reactions including polymerization. This chapter excludes as much as possible the use of classical aluminum reagents (AlX_3, $RAlX_2$, R_2AlX, etc., where R = organic group, X = halogen or small heteroatom-containing group) unless particularly noteworthy features are involved. The reader can refer to earlier reviews or mono-

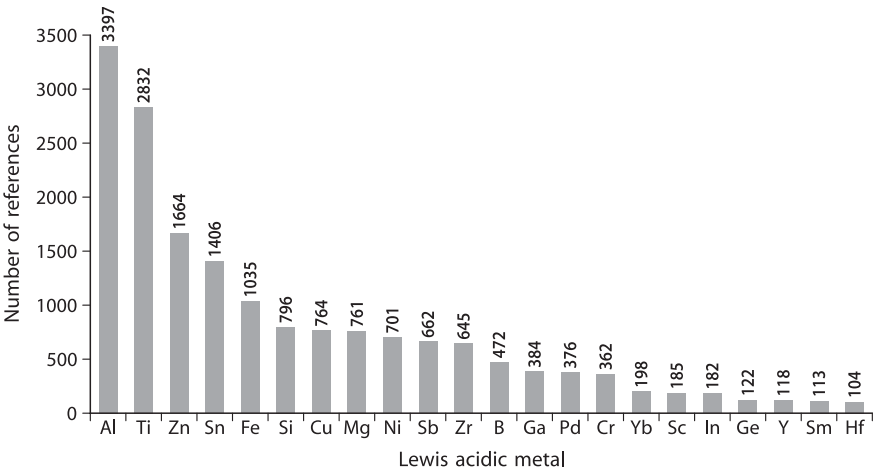

Fig. 6.1 The Lewis acids investigated. The data were obtained by means of SciFinder Scholar 2001 by use of crossover phrase search: "Lewis acid" and each metal

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graphs for more classical [1–4] and modern [5–7] applications of aluminum reagents and asymmetric transformations [8, 9] in organic synthesis.

6.1.1 Natural Abundance and General Properties

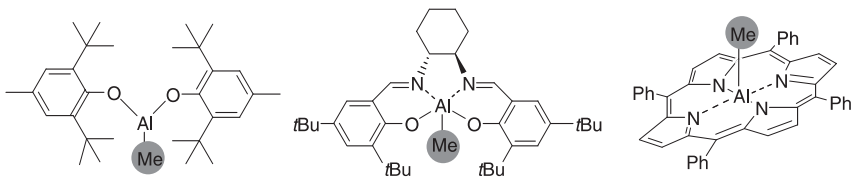
Aluminum is one of the most plentiful metal elements in our planet. The list of the most abundant elements by weight in the Earth's layers is headed by oxygen (48.9%), followed by silicon (26.3%), aluminum (7.7%), iron (4.7%), and calcium (3.4%). Organoaluminum compounds are the cheapest organometallic compounds.

Aluminum(III) reagents have high oxygenophilicity. Trialkylaluminum compounds, especially trimethylaluminum, ignite spontaneously in air at ambient temperature. All aluminum alkyls react violently with water. Thus special care must be taken with their handling; this is explicitly indicated in other reviews [7]. Increasing the molecular weight by increasing the number of carbons in trialkylaluminum compounds or by substituting halogens for the alkyl groups generally reduces pyrophoric reactivity. Replacing alkyl groups by alkoxy or other heteroatom-containing groups reduces the mobile nature of the remaining alkyl groups. For example, Me_3Al works as an effective methylating (anionic) agent whereas methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide) (abbreviated MAD) does not under similar conditions (Fig. 6.2). The (salen)Al-Me complex is a shelf-stable compound. The tetraphenylporphyrin (TPP)-based aluminum reagent (TPP)Al-OMe frequently has higher reactivity in initiating polymerization than (TPP)Al-Me, as will be demonstrated in later chapters.

6.1.2 Interaction of Aluminum(III) with Different Functional Groups

6.1.2.1 Coordination and Covalent Bonds in Aluminum(III)

Neutral aluminum(III) species interact with a variety of functional groups. The strong Lewis acidity of aluminum(III) species enables formation of a 1:1 complex by either covalent or coordination bonding – the former bond is constructed by more reactive anionic species R–M, RO–M or RNH–M (M = metal), and the latter

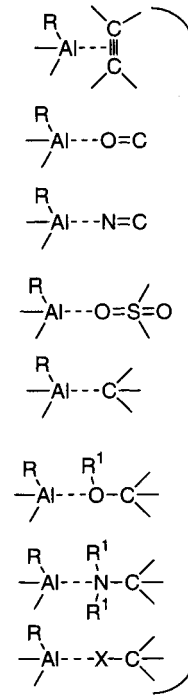
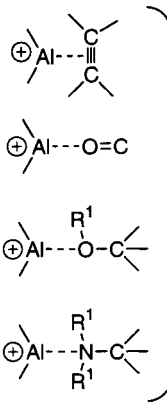


MAD (salen)Al-Me (TPP)AlMe

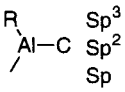
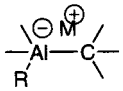
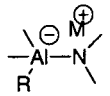
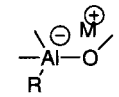
Fig. 6.2 The structures of MAD, (salen)Al–Me, and (TPP)AlMe

by more neutral Lewis bases, including carbonyl compounds, ethers, and nitrogen-containing molecules. Whichever bond is preferred, tetracoordination and even higher coordination e.g. penta- and hexacoordination make an aluminum atom rather anionic ("ate" complex). Classification of the order of reactivity corroborating ligand mobility in such anionic aluminum species has been a major area of research for the last three decades. In fact, known classical variants expressing a range of interactions are summarized in Tab. 6.1. The covalent bonds have discrete mobility and their order of reactivity has been roughly estimated as $H^- > \text{alkynyl} > \text{vinyl} > \text{alkyl}$. Heteroatom-containing anions RO^-, RS^-, RSe^-, RTe^-, R_3Si^-, and R_3Sn^- are sufficiently mobile to create the corresponding carbon–heteroatom bonds via, for example, Tischenko reaction or conjugate addition reaction. Interpretation of the instability and the mobile nature of anionic ligands of aluminum(III) was well reviewed in an earlier monograph [7]. This chapter is concerned with more specialized and current topics on neutral and cationic aluminum species whose interaction features are worth mentioning.

Tab. 6.1 Important coordination and covalent bonds in aluminum-Lewis base complexes

Bond type	*Neutral aluminum species*	*Reaction type employed*	*Cationic aluminum species*	*Reaction type employed*
Coordination Bonds		• Activation of the corresponding Functional Group by Coordination Bond • Movement of Covalently-attached R Group (R = H, C, O, N, X, etc.) (X = F, Cl, Br, I)		Catalyst

Tab. 6.1 (cont.)

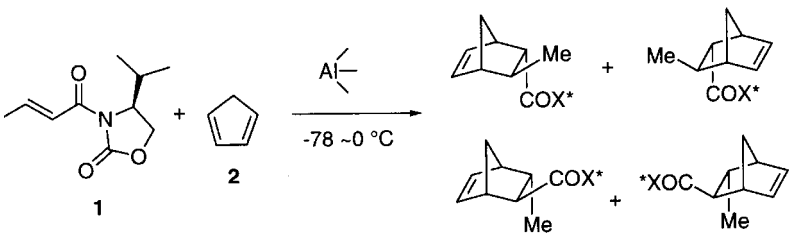
Bond type	*Neutral aluminum species*	*Reaction type employed*	*Anionic aluminum species*
Covalent Bonds		•Hydride Transfer (Reduction, Hydroalumination)	
		•C–C bond Formation (Addition of C=O, Carboalumination) •Hydride Transfer (β-Hydride Elimination) •Radical Reaction (Homolytic Cleavage)	
		•C-N Bond Formation •Deprotonation	
		•Oxidation (Oppenauer Oxidation) •Hydride Transfer (β-Hydride Elimination: Meerwein-Ponndorf-Verley Reduction) • C-O Bond Formation (Tischenko Reaction)	
		C-S Bond Formation (Michael addition, Tischenko reaction)	
		C-Se Bond Formation	
		C-Te Bond Formation	
		C-Si Bond formation (Silylalumination)	
		• Alkylhalide reduction • C-Sn bond formation	
		Work as Strong Lewis Acids Movement of Al-C group Source of Aluminum Cation	

6.1.2.2 **Cationic Aluminum(III): Structural and Reaction Features**

Cationic aluminum species are known to be involved in two main processes – when the electron-richness of aluminum stabilizing a cationic center is enhanced by higher coordination or when a vacant aluminum orbital is superimposed on expanded arrays of orbitals provided by the ligand to enable electron delocalization. Obviously those species have higher Lewis acidity, as would be expected.

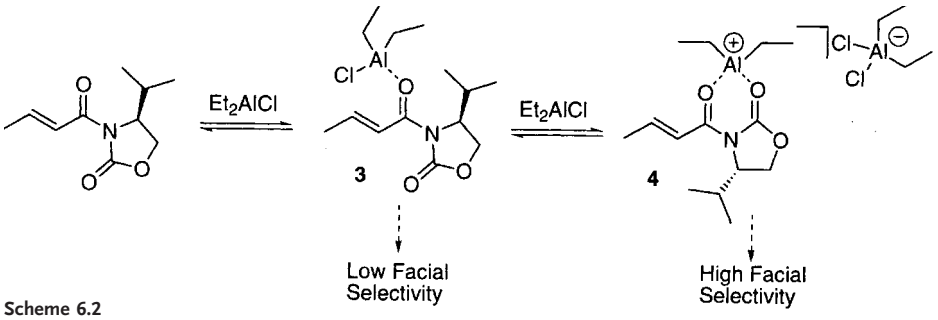
In bimolecular reactions the importance of cationic aluminum species has attracted worldwide attention since excess R_2AlCl (R = Me, Et) was found to behave differently from less than 1 equiv. R_2AlCl in the Diels-Alder reaction between **1**

and **2** (Scheme 6.1) [10]. The diastereoselectivity was dependent upon the stoichiometry of the aluminum Lewis acid. The equilibrium $2[Et_2AlCl]$ $[Et_2Al]^+ + [Et_2AlCl_2]^-$ was suggested by Evans and coworkers to rationalize the high reactivity and selectivity.



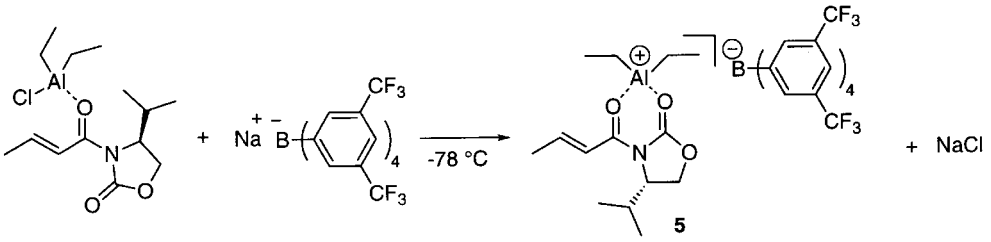
Scheme 6.1

Later Castellino and coworkers focused on a search for the solution structures of the Et_2AlCl–**1** complex and supported Evans's hypothesis [11]. The initially formed species (1 equiv. Et_2AlCl) was assumed to be **3**. The species when 2 equiv. Et_2AlCl are present was assumed to be **4**. Complex **4** was responsible for high diastereocontrol whereas complex **3** led to poor selectivity, as was observed in the Diels-Alder reaction. Because ordinary aluminum(III) favors tetracoordination, which fulfills the electron-octet, the chelation structure **4** should be possible when the cationic species was generated (Scheme 6.2).



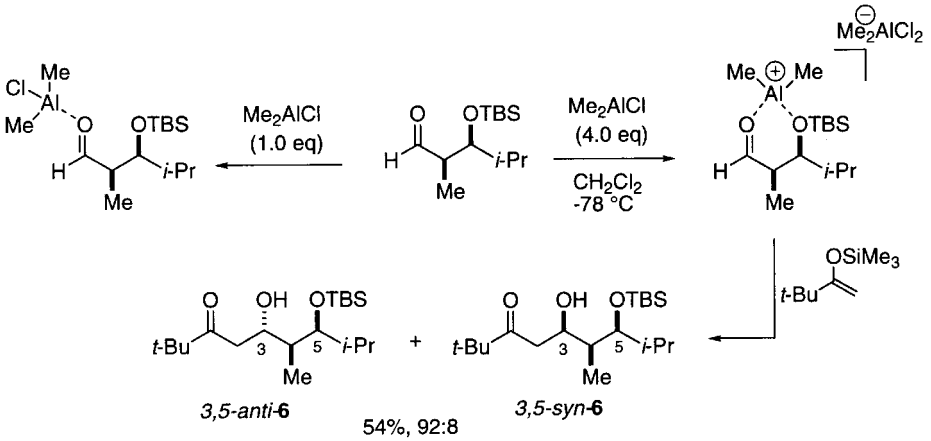
Scheme 6.2

Further confirmation of the formation of the aluminum chelate was obtained by generating this intermediate through a separate pathway. Addition of Et_2AlCl (1 equiv.) to the oxazolidinone **1** at –78 °C followed by addition of sodium tetrakis(bis(3,5-ditrifluoromethyl)phenyl) borate produced **5** (Scheme 6.3). Use of **5** in the Diels-Alder reaction with cyclopentadiene, however, resulted in an *endo*/*exo* ratio and *endo* facial selectivity not as high as those reported by Evans for the use of 1.4 equiv. Et_2AlCl, despite the higher reactivity which caused loss of selectivity.



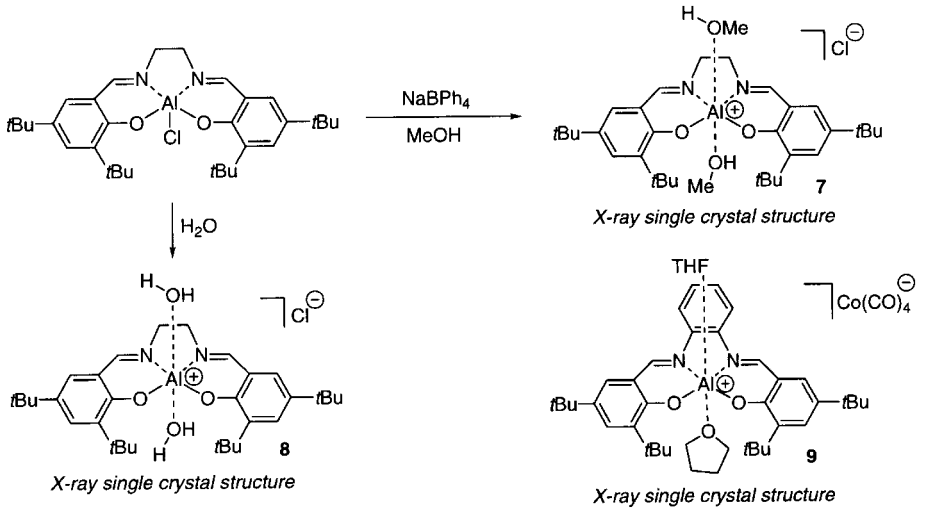
Scheme 6.3

A similar aluminum cation was also available in the Mukaiyama-aldol reaction. It is worth noting that the *t*-butyldimethylsilyloxy (TBSO) group, which otherwise is unable to make chelation complex with neutral bidentate Lewis acids, is under chelation control with excess Me_2AlCl or $MeAlCl_2$ [12]. Aldehyde and ketone carbonyls are capable of participating in the chelation-controlled aldol reaction to give *anti*-**6** with high diastereoselectivity (Scheme 6.4).

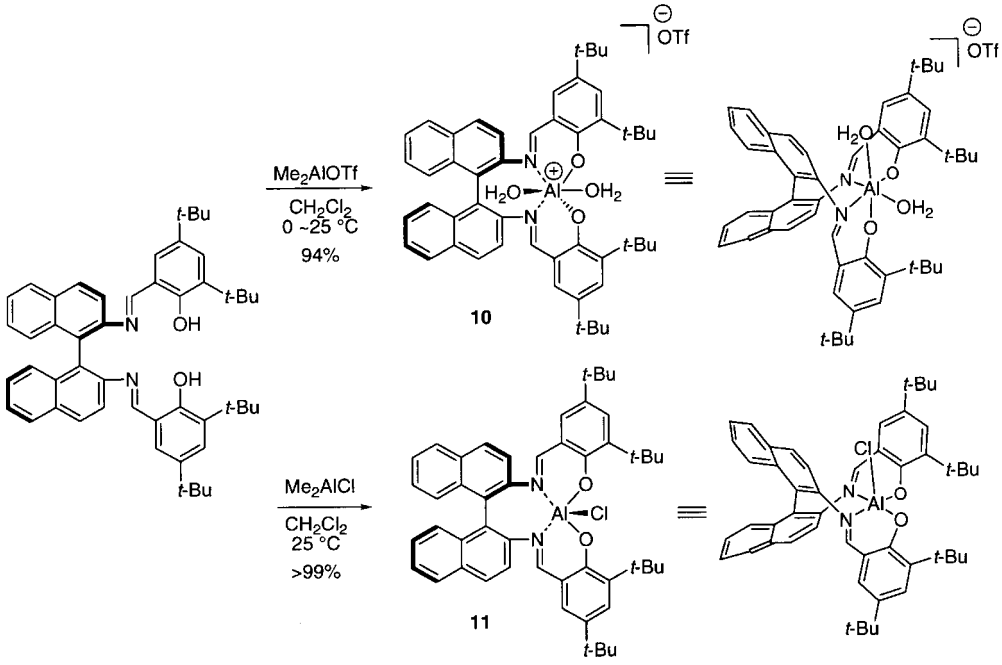


Scheme 6.4

Because those classical aluminum cations might be discovered rather accidentally, the next issue was to design a tailor-made relative. Several well-designed aluminum cations were synthesized and structurally characterized by X-ray single-crystal analysis (Schemes 6.5–6.7). Subtle changes in ligand structure had large effects on the octahedral geometry of aluminum. Although (salen)Al cations **7**–**10** contain two identical molecules which occupy two vacant orbital to complete the sp^3d^2 hybridization orbital, a distinct type of occupation is perceptible. Two H_2O molecules are in a *cis* relationship in **10** [13], whereas two THF [14], MeOH [15] or H_2O [15] molecules are in two apical positions corresponding to a *trans* relationship in **7**–**9** (Scheme 6.5). Of particular note is that structure **10** has one of

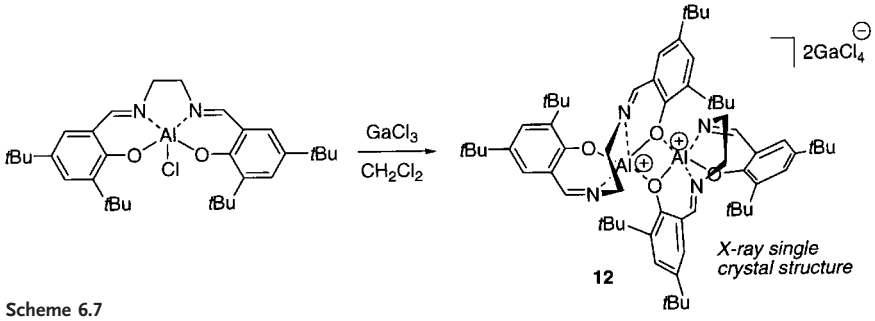


Scheme 6.5



Scheme 6.6

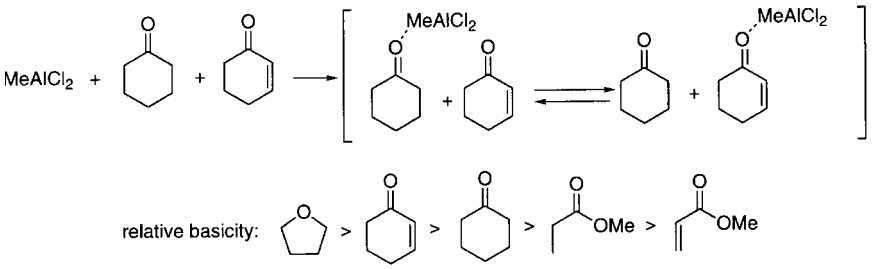
the phenoxy oxygen atoms in the apical direction whereas related neutral though rather anionic species **11** enable the two phenoxy oxygen atoms to take equatorial positions (Scheme 6.6). Later studies isolated solvent-free, five-coordinate aluminum cations **12** (Scheme 6.7) [16]. These species were especially useful in both bimolecular and polymerization reactions, which will be discussed in more detail in forthcoming sections.



Scheme 6.7

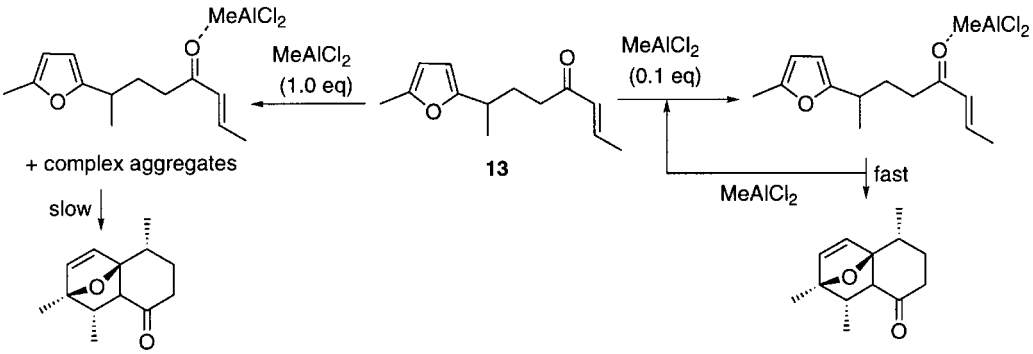
6.1.2.3 **Neutral Aluminum(III): Coordination Aptitude and Molecular Recognition**

Among the aforementioned interactions involving aluminum(III), coordination bonding with neutral aluminum species also plays a significant role in forming Lewis acid–base complexes. The importance of molecular recognition has been emphasized even in classical aluminum(III) Lewis acid–base complexes. Keay and coworkers clarified the coordination ability of $MeAlCl_2$ toward several Lewis bases [17]. Low-temperature NMR measurement gave the relative basicity order as: THF > cyclohexenone > cyclohexanone > methyl propionate > methyl acrylate (Scheme 6.8). It should be noted that conjugated esters are less basic than nonconjugated esters, but that olefin conjugated ketones and aldehydes are more basic than the non-conjugated systems. When 2-methylfuran was mixed with $MeAlCl_2$ in a 1 : 1 ratio, polymerization of the furan predominated.



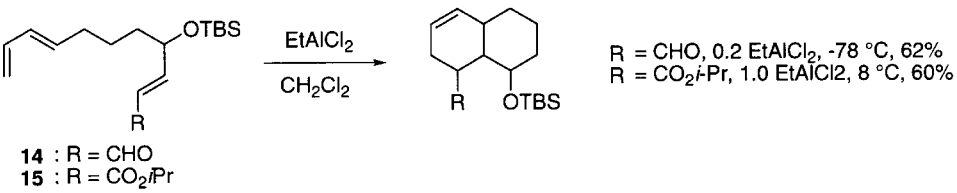
Scheme 6.8

Further experiments have shown that $MeAlCl_2$ in catalytic amounts promotes the intramolecular Diels-Alder reaction of furans because the most basic site in the system is the reactive site in **13** so that the cycloadduct does not inhibit the catalysis (Scheme 6.9). In contrast, increasing the number of equivalents of $MeAlCl_2$ reduces the conversion because $MeAlCl_2$–**13** interaction is the more stable of the complexed forms; this might be partly because of the diverse aggregates preferred by $MeAlCl_2$.



Scheme 6.9

With the understanding gained by fundamental studies, another divergent experimental observation was rationalized (Scheme 6.10). Intramolecular Diels-Alder reaction of **14** proceeded catalytically because an unsaturated aldehyde is more basic than a saturated aldehyde. In contrast, **15** required 1 equiv. $MeAlCl_2$ due to product inhibition, because of the high basicity of the saturated ester compared with the unsaturated ester.



Scheme 6.10

Classical aluminum reagents ($AlCl_3$, Me_2AlCl, $MeAlCl_2$, etc.) activate a wide variety of functional groups of substrates on complexation, and the reactions usually proceed efficiently but are rather unpredictable. The relatively simple design of the ligands of classical aluminum reagents leads to monomeric Lewis acids in organic solvent and consequently to high Lewis-acidity and reactivity.

Furthermore, on coordination with designed ligand(s), well-designed Lewis acids have new selectivity. By this means several bulky aluminum reagents were prepared from sterically hindered phenols. Most aluminum reagents exist in solution as dimeric, trimeric, or higher oligomeric structures [18] whereas MAD [19] and aluminum tris(2,6-diphenylphenoxide) (ATPH) [20] are monomeric in organic solvent (Fig. 6.3). The Lewis acidity of these reagents decreases on coordination of more electron-donating aryl oxides, but this can be compensated by loosening of the aggregation. Compared with classical Lewis acids the steric effect of aluminum reagents also plays an important role in selective organic synthesis.

We thus first evaluated the molecular recognition ability of ATPH using competitive binding experiments at low temperatures (–78 to –40 °C) (Fig. 6.4) [21]. Two different carbonyl compounds were mixed with ATPH in a 1:1:1 ratio to determine the relative steric and electronic properties of each carbonyl compound (Fig. 6.5). The results are summarized in Fig. 6.4, where the K_{sample}/K_{PhCHO} ratio denotes the relative binding constant of each substrate, where the binding constant of PhCHO (**24**) is defined as unity, and the shift change ($\Delta\delta = \delta_{bound} - \delta_{free}$)

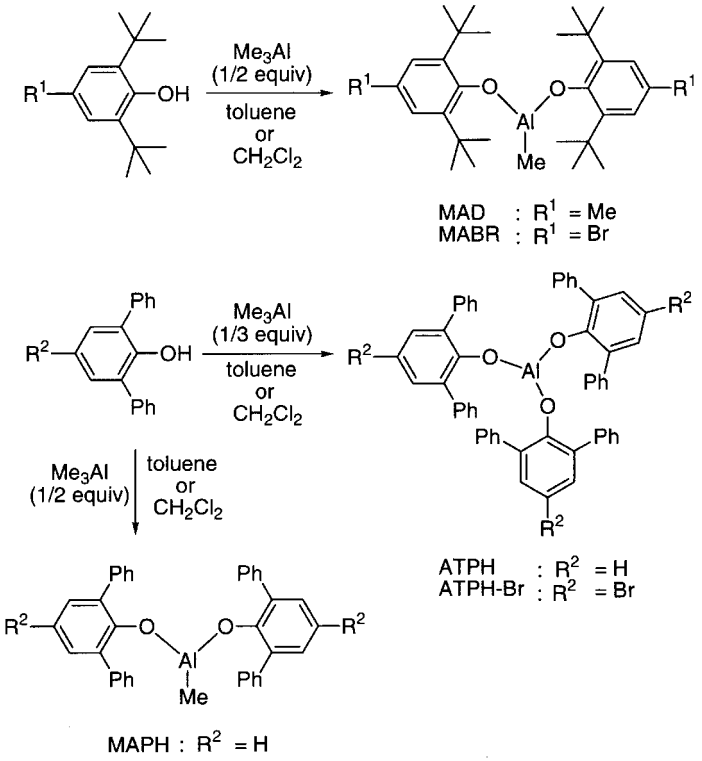


Fig. 6.3 Well-designed aluminum reagents

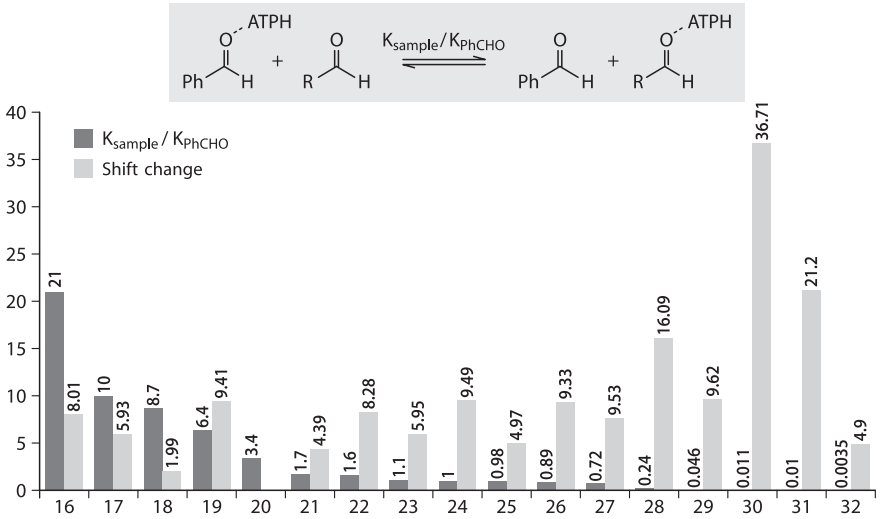


Fig. 6.4 Molecular recognition ability of ATPH measured by use of competitive binding experiments at low temperatures

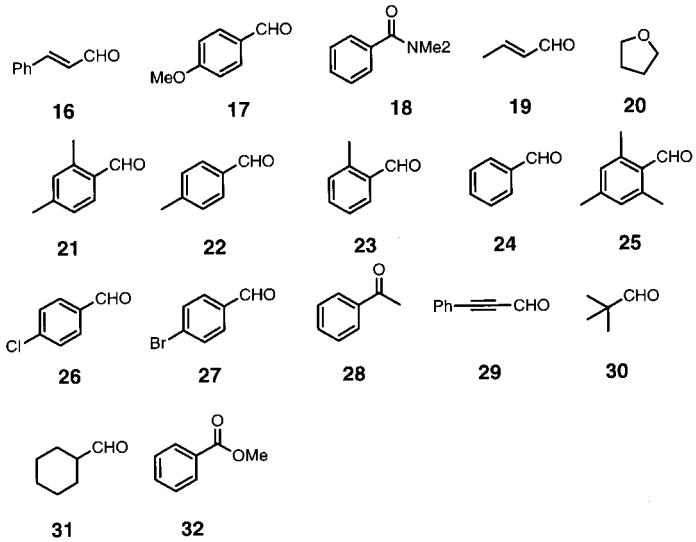


Fig. 6.5 Structures of the carbonyl compounds used to measure the molecular recognition ability of ATPH

is measured by ^{13}C NMR and is equal to the changes in chemical shifts of the carbonyl carbon from free (δ_{free}) to bound (δ_{bound}) substrates.

Several characteristic features are apparent.

- The preference for binding of the aromatic series reduces in the order aldehyde > ketone > ester.
- The substitution pattern of the methyl groups on the aromatic rings have a substantial effect on binding. Electronic and steric effects of these methyl groups must both be considered to evaluate the relative basicity of each substrate. In general, the greater the amount of methyl substitution, the stronger the binding; this is readily understandable from electronic considerations. *para* substituents promote binding more than *ortho* substituents and two *ortho* methyl groups reduced binding, presumably because steric constraints override electronic contributions.
- The *para*-chloro group resulted in stronger binding than the bromo group, suggesting that the resonance effect overrides the inductive effect.
- Unsaturated aldehydes are better suited for binding than saturated aldehydes.

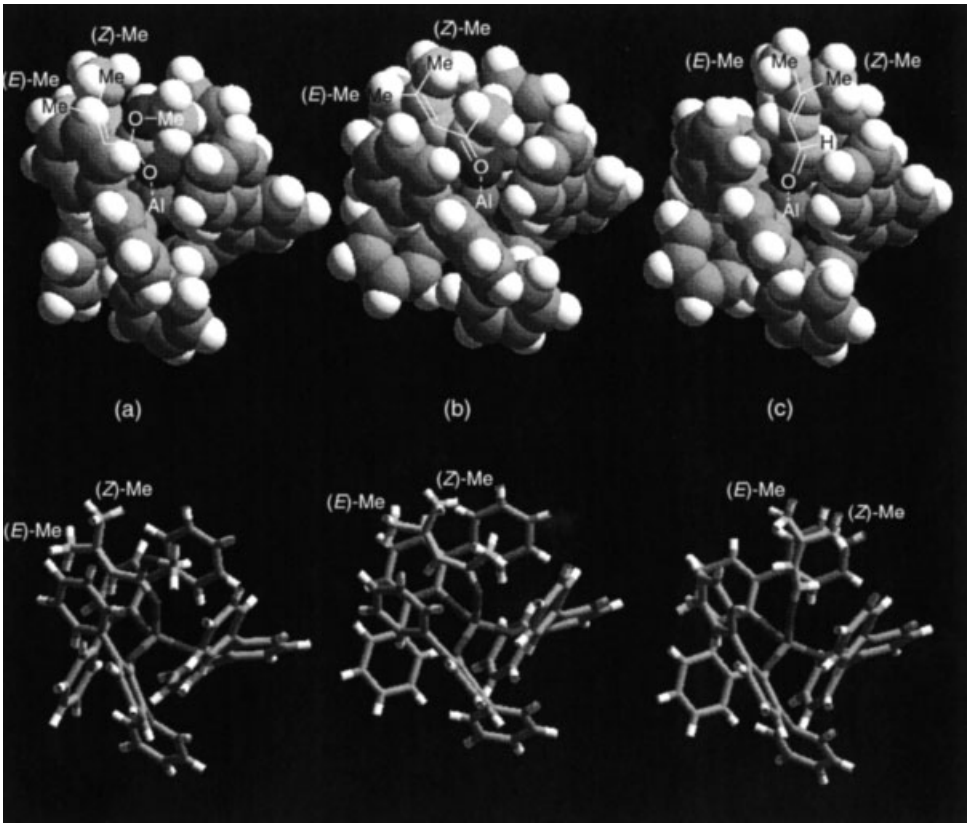


Fig. 6.6 The X-ray crystal structures (CPK (upper) and cylinder (lower) models) of the complexes (a) ATPH–**33**, (b) ATPH–**34**, and (c) ATPH–**35**

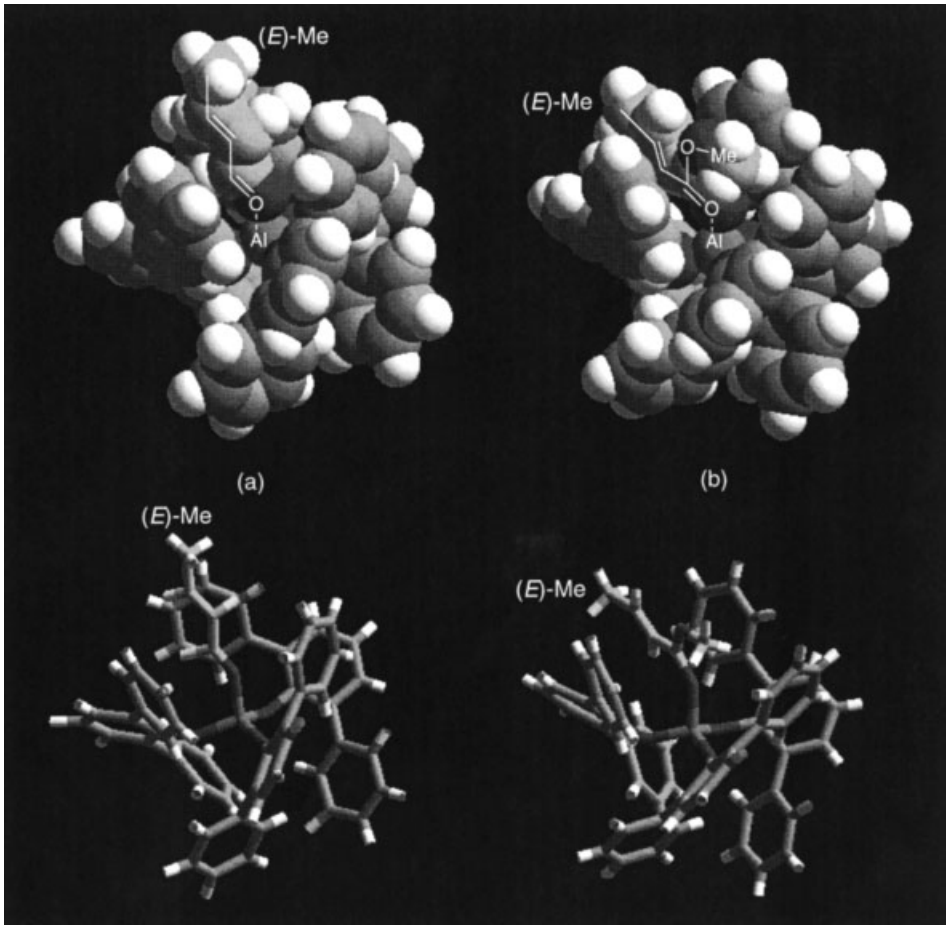
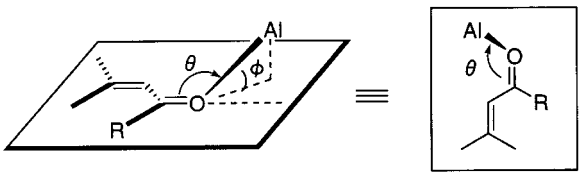


Fig. 6.7 The X-ray crystal structures (CPK (upper) and cylinder (lower) models) of the complexes (a) ATPH–**36** and (b) ATPH–**37**

X-ray single crystal structures also enable understanding of the recognition behavior of ATPH at the molecular level. [22] The ATPH complexes of **33**–**37** are shown in Figs 6.6 and 6.7. Particularly notable structural features of these ATPH–carbonyl complexes are the Al–O–C angles and Al–O distances (Tab. 6.2), which confirm that the size and shape of the cavity change flexibly, depending on the substrate.

The values of the angles θ and φ [23, 24] shed light on the mode of coordination of carbonyls, and several results obtained from X-ray crystal structures of ATPH–carbonyl complexes are worthy of comment. Except when coordination of the metal deviates slightly from the π nodal plane (i.e. mode **A** with $\varphi < 5\ ^{\circ}$), the φ values show that the carbonyl is instead coordinated with the metal in mode **B** (Fig. 6.9). The θ values

Tab. 6.2 Selected physical data for ATPH–carbonyl complexes



Property	*ATPH-33 (R=OMe)*	*ATPH-34 (R=Me)*	*ATPH-35 (R=H)*	*ATPH-36 (R=OMe)*	*ATPH-37 (R=H)*
C=O, Å	1.249(5)	1.262(3)	1.128(6)	1.30(1)	1.152(5)
Al-O (sp^2), Å	1.833(3)	1.823(2)	1.810(3)	1.803	1.829(2)
θ, °	136.2(3)	148.1(2)	193.9(4)	143.1(3)	214.1(3)
ϕ, °	4.2	13.5	16.9	19.9	6.1
Other	132.5(3)	130.7(2)	137.3(3)	133.0(1)	136.7(2)
Al-O-C	152.4(4)	150.0(2)	142.3(3)	142.7(4)	145.0(2)
Angles	159.2(3)	151.8(2)	145.0(3)	148.9(4)	150.8(2)

vary widely of the different carbonyl substrates, i.e. the coordination seems inherent to each substrate. Apparently the selective coordination, well characterized by both θ and φ values, of carbonyls to bulky ATPH is quite flexible, and steric effects predominate. There are, however, some general rules expected from a series of these distinctive θ values. ATPH–carbonyl complexes stay within these rules. All five ATPH complexes adopt an *s-trans* conformation (Fig. 6.9) relative to the (O=C)–(C=C) single bond axis [25] even though the coordination of each carbonyl substrate (shown in light blue) is obviously different. Whereas aldehydes **35** and **37** (Al–O=C angles (θ) = 193.9(4)° and 214.1(3)°) favor *anti* complexation ($\theta > 180°$), esters **33** and **36** and ketone **34** (θ = 136.2(3)°, 143.2(3)°, and 148.2(2)°) show *syn* complexation ($\theta < 180°$) (Tab. 6.2 and Fig. 6.9) [23]. Thus, aldehydes **35** and **37** prefer the *anti*, *s-trans* conformation whereas methyl esters **33** and **36**, and ketone **34** prefer the *syn*, *s-trans* conformation on complexation with ATPH. These results are in accord with the coordination bias of conjugated carbonyl compounds with relatively small Lewis acids [23–25]. Given the preferential conformation, each *Z* and *E* γ-methyl group of these three substrates is affected by a distinct steric environment. The (*Z*)-γ-methyl of **33** and the (*E*)-γ-methyl of **35** occupy sterically less hindered space, i.e. somewhat outside the cavity of ATPH (Figs 6.6–6.8). At first sight, it is rather difficult to discriminate between the different steric effects on the two γ-methyl groups of the ketone complex. It should also be pointed out that the methyl group of the methoxy group of esters **33** and **36** adopts the *trans* (or *Z*) conformation relative to the carbonyl [26], being arranged around the C–O single-bond axis (Fig. 6.9). This is consistent with the general highly preferential *trans* orientation of the methyl and ethyl groups of the alkoxy groups of free esters [26]. The MAD aptitude in molecular recognition of heteroatom-containing molecules has been investigated qualitatively in more depth [27].

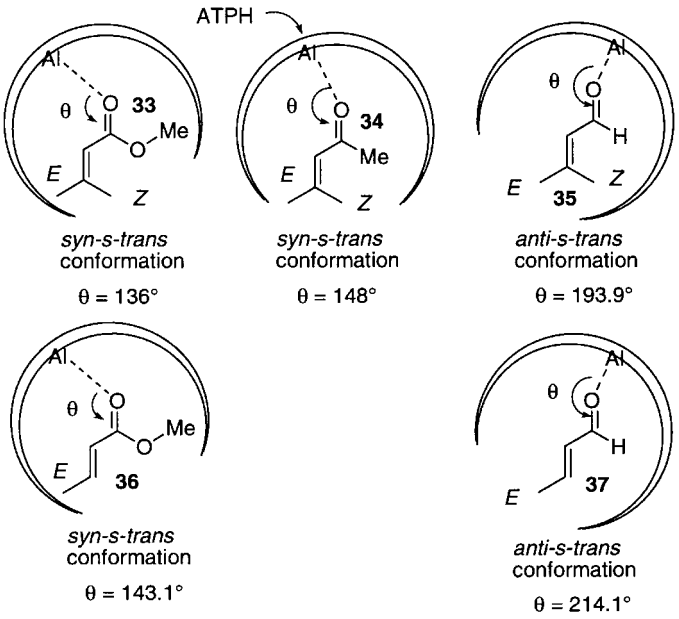


Fig. 6.8 Coordination of various carbonyl compounds with ATPH

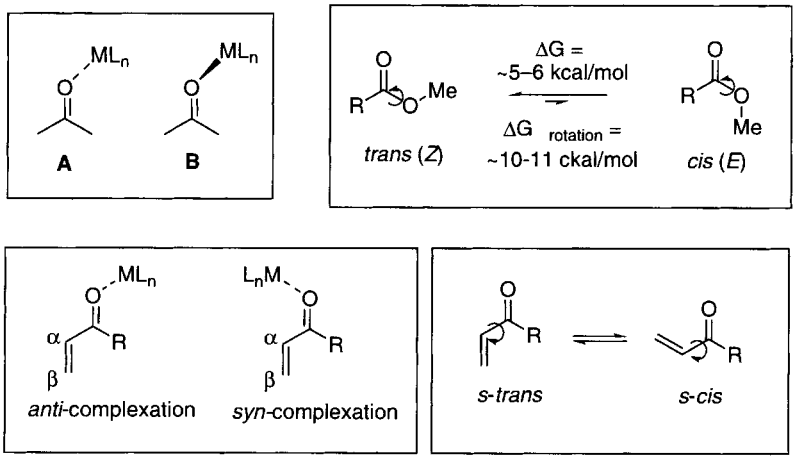
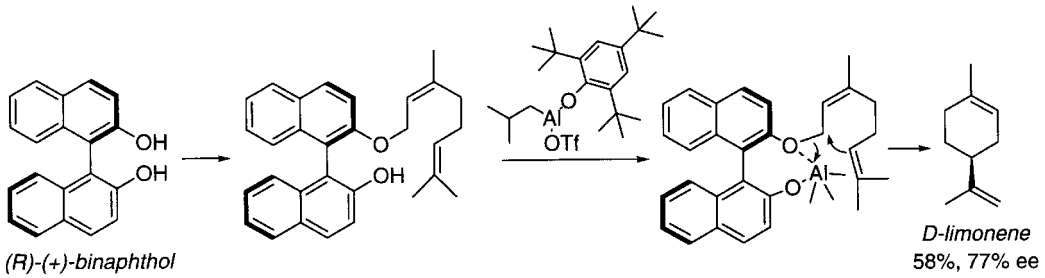


Fig. 6.9 Important carbonyl conformations in molecular recognition

6.1.2.4 **Other Novel Interactions Involving Neutral Aluminum(III)**

As has been done with other metals, fine-tuning of the electronic properties of aluminum(III) has been a central target, with the goal of exploiting, e.g., a co-catalyst candidate for olefin polymerization. In any event, the idea is very simple – at-

tachment of strongly electron-withdrawing groups to aluminum(III) by which Lewis acidity could be strengthened. Yamamoto and coworkers during the asymmetric synthesis of D-limonene (Scheme 6.11) [28] first introduced this concept of ligand improvement in aluminum chemistry in 1983. A range of related achiral reagents appeared thereafter (Fig. 6.10).



Scheme 6.11

This class of aluminum species had unprecedented interactions with a variety of functional groups. Interesting neutral aluminum–arene interactions were observed when $Al(C_6F_5)_3$ was mixed with toluene or benzene [29]. Arenes are coordinated in a η^1 fashion, and the conformations of the two molecules are very similar. The toluene molecule in **38** is attached in the *para* position (Scheme 6.12). The experimentally determined bond angle of 96.1° for **38** is closer to those for structure **39**, which involves idealized sp^2 hybridization. The interactions between arenes and $Al(C_6F_5)_3$ are sufficiently strong that complex **38** persists in solution. Competitive binding experiments revealed the sequence of donor strength THF > benzene > Et_2O toward $Al(C_6F_5)_3$.

Marks and coworkers are particularly interested in catalysts that can be isolated and then characterized by X-ray crystallography, to enable study of the molecular basis of the polymerization catalysis [30]. During their research they found an

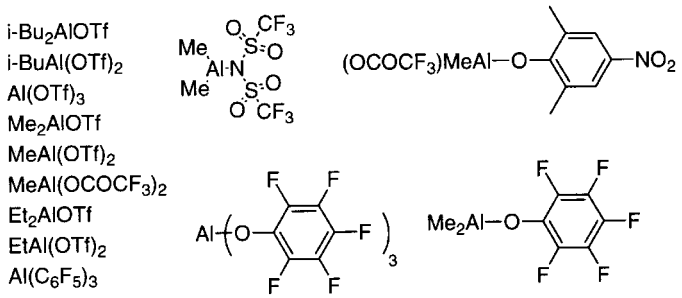
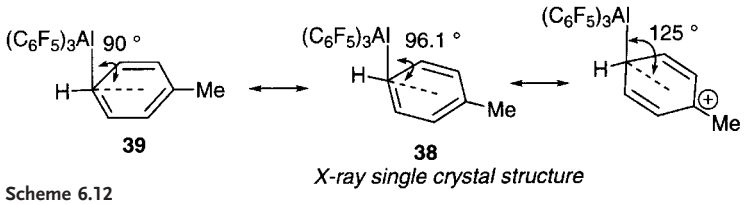
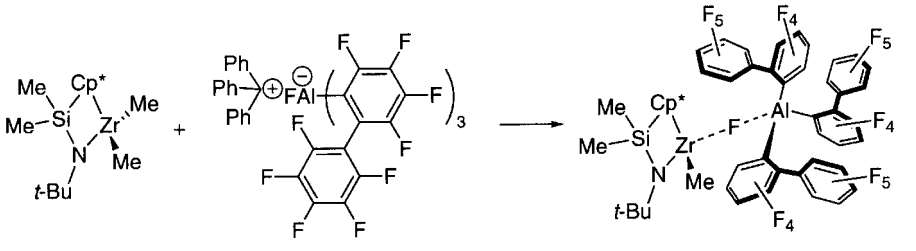


Fig. 6.10 Aluminum Lewis acids bearing electron-withdrawing groups



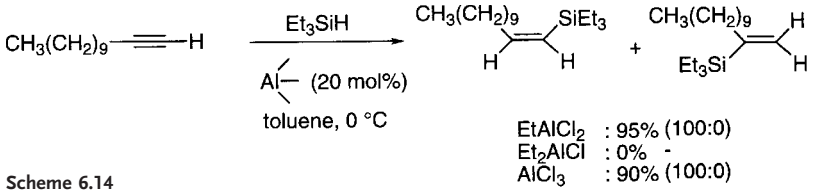
Scheme 6.12

$Al(C_{12}F_9)$–fluorine interaction consistent with an aluminum anion–zirconium cation pair (Scheme 6.13). Polymerization using this anion–cation pair will be discussed briefly in Section 6.2.5.



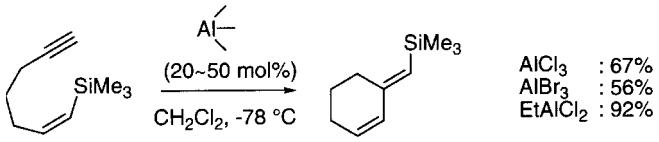
Scheme 6.13

Aluminum–alkyne interactions were invoked when hydrosilylation of alkynes proceeded in the presence of catalytic amounts of $AlCl_3$ or $EtAlCl_2$ [31]. Although most hydrometalations of alkynes occur in a *cis* configuration, *trans*-selective hydrosilylation was consistently observed (Scheme 6.14).



Scheme 6.14

This system was further extended to intermolecular carbosilylation [32]. The vinylsilylation reaction also proceeded in a *trans* configuration, most effectively in the presence of catalytic amounts of $EtAlCl_2$ (Scheme 6.15).



Scheme 6.15

6.1.2.5 Ligand Effect on Aluminum(III) Geometry and Interactions

Aluminum is usually a trivalent metal adopting trigonal geometry with sp^2 hybridization relative to the aluminum center which makes a geometrical change to tetrahedral (sp^3 hybridization) on complexation with an external base. The geometry of aluminum can, however, be changed significantly by the ligand structure attached to it, which is consistent with other than sp^2–sp^3 exchange (Fig. 6.11). The X-ray crystal structures of a variety of aluminum(III) species shed light on this possibility. As demonstrated in Section 6.1.2.2, although (salen)-Al-X complexes adopt square bipyramidal (sp^3d) geometry relative to aluminum, their potential reactivity is preserved, affording typical Lewis acid-promoted reactions. This fact and the single crystal structure are indicative of an available vacant orbital in either an equatorial or an apical direction which facilitates sp^3d^2 hybridization.

It is interesting to note that the Lewis acidic nature of aluminum varies substantially with subtle changes in aluminum geometry (Fig. 6.12). Nelson and coworkers recently pointed out that ligands **40** and **41** have entirely different effects not only on the structural geometry but also on the carbonyl activation capacity of aluminum [33]. This was proved unambiguously by the reactions they promoted and their single-crystal structures. Whereas distorted metal coordination geometry and Lewis acidity expressed by **42** was validated, geometry optimization of complex **43** indicated that the expanded chelate size of the propylene triamine-derived ligand conferred sufficient conformational mobility to enable the Al(III) ion to adopt a low-energy, tetrahedral (sp^3) coordination geometry. The authors concluded that the sp^3d Al ion hybridization in **42** and **44** furnishes a low-lying metal-centered LUMO, thus ideally disposing the Al(III) center to accommodate a fifth ligand and complete the trigonal bipyramidal coordination geometry achieved in the Lewis acid–base complex. Conversely, the electron-rich highly coordinated complex **43**, lacking any ligand-imposed coordinative distortion, has minimal Lewis acidic character.

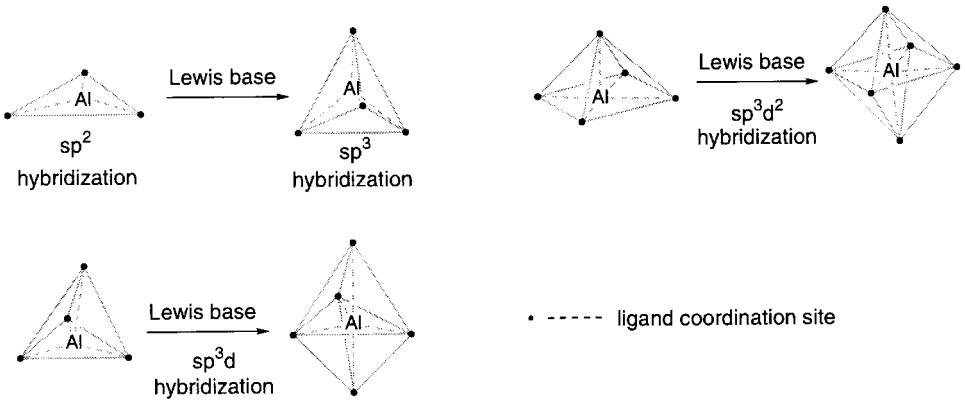


Fig. 6.11 Possible hybridizations and geometries of aluminum

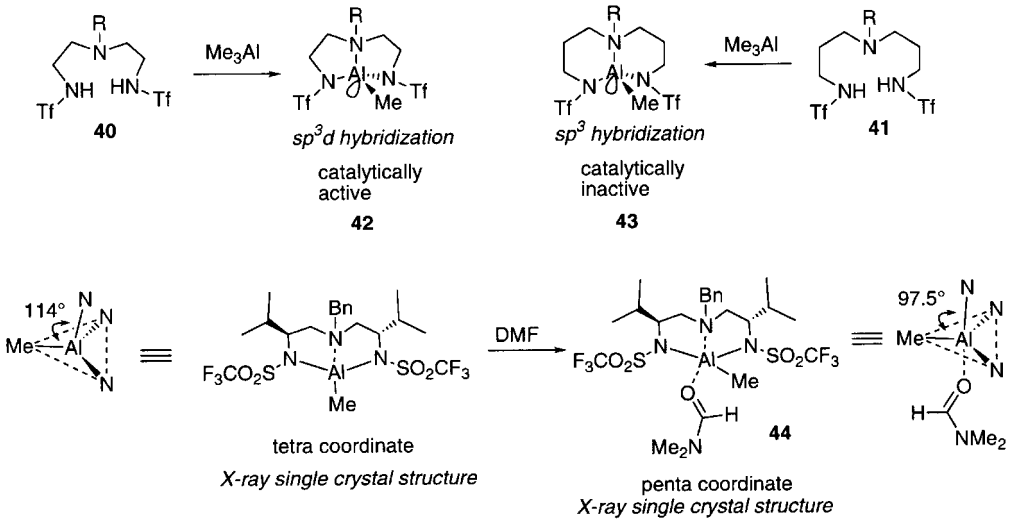
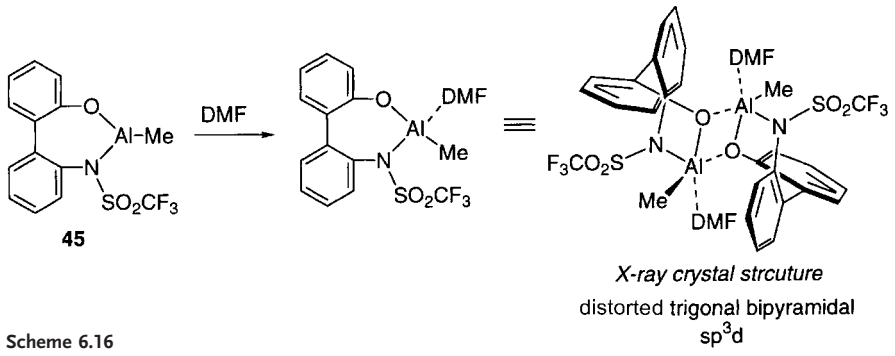


Fig. 6.12 Ligand-dependent subtle change in the geometry of aluminum

Penta-coordinate trigonal bipyramidal sp^3d hybridization was also observed for the other neutral aluminum species [34]. It is well known that by lowering the LUMO of the metal to which an electron-withdrawing group is attached results in preference of silicon and tin for higher coordination – penta- and hexacoordination – thus enabling the participation of d-orbitals [35]. Similar behavior be observed for the aluminum complex **45**, in which the LUMO of aluminum is reduced in energy by the triflylamide group, which has strongly electron-withdrawing properties (Scheme 6.16). Besides these electronic considerations, the effect of the ligand structure on aluminum geometry could not be ruled out, as suggested by Nelson.



Scheme 6.16

6.2
Modern Aluminum Reagents in Selective Organic Synthesis

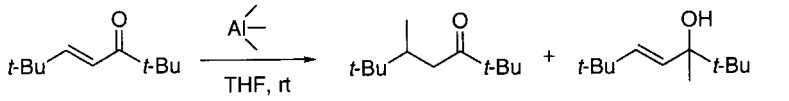
6.2.1
Carbon–Carbon Bond Formation

6.2.1.1 Generation and Reaction of Aluminum Enolates (Al–O–C=C Bond Formation and Reaction)

Enolates are undoubtedly the most versatile intermediates for C–C, C–N, C–O bond-forming reactions [36]. Continuous progress has been made not only in fundamental operations involving these anionic species but also during the synthesis of complex natural products. Compared with metal enolates with counter cations of, e.g., B, Si, Li, Na, K, Mg, Ti, Sn, Cu, etc., aluminum enolates have found fewer applications, probably because no particular advantages over the other metals have been perceptible. There are, however, still intriguing aspects of novel reactivity and selectivity in the formation and reaction of aluminum enolates. Specifically, very recent development have highlighted pre-formation of Lewis acid–carbonyl complexes by use of bulky aluminum compounds as precursors of aluminum enolates; the behavior of these complexes is unprecedented.

By Michael Addition to *α,β*-unsaturated Carbonyl Compounds

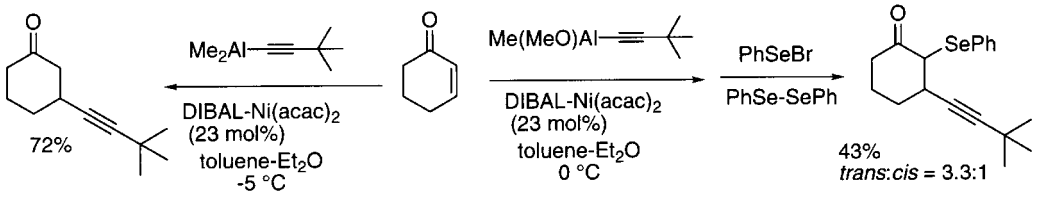
This section briefly describes earlier applications of organoaluminum reagents in conjugate additions, giving aluminum enolates. Aluminum-alkyls are transferable to the *β* position of *α,β*-unsaturated carbonyl compounds even in the absence of catalytic amounts of transition metals (Scheme 6.17) [37]. Such systematic studies were performed by screening the methylaluminum species of general formula of Me_nAlX_{3-n} (X = Cl, Br, I; n = 0–3) and by determining the ratio of 1,2- and 1,4-adducts. Although changing the methyl substituents to heavy halogens enhanced the extent of conjugate addition, yields decreased significantly. The low yield of the 1,4-adduct is indicative of contaminated reactions and thus this method is not valid for clean formation of its enolate precursor.



Me_3Al : 75%, 0:100
Me_2AlCl : 71%, 6:94
Me_2AlCl : 58%, 20:80
Me_2AlI : 42%, 98:2
$MeAlI_2$: 32%, 100:0

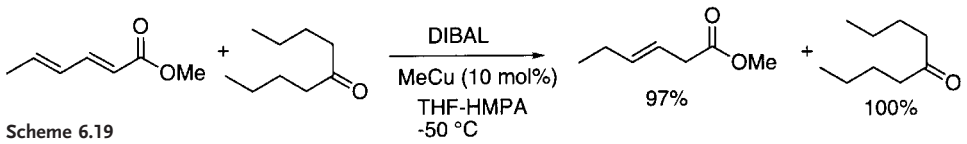
Scheme 6.17

Catalytic effect of transition metals on the smooth conjugate addition reaction was next tested [38]. Alkynylation at the β position was followed by capture of the aluminum enolate in the presence of $Ni(acac)_2$ (Scheme 6.18). Yields of 1,4-adducts were moderate, however, indicating the methods were still unsatisfactory for enolate generation.



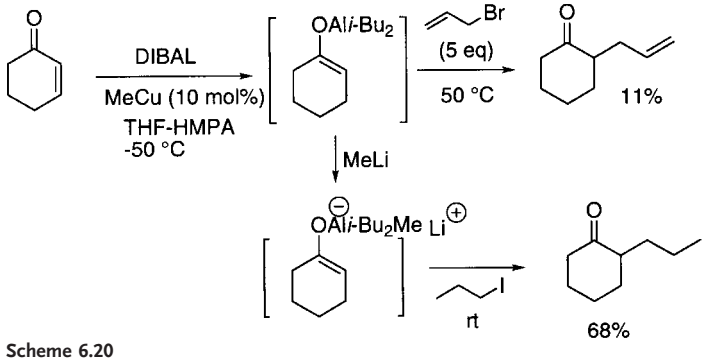
Scheme 6.18

DIBAL was used for the conjugate reduction to produce aluminum enolates in the presence of MeCu catalyst [39]. Unlike strong bases that readily deprotonate the α-hydrogen of carbonyl compounds, this method tolerates a ketone carbonyl and its α hydrogen, and was thus chemoselective as well as quantitatively reducing the α,β-unsaturated ester (Scheme 6.19).



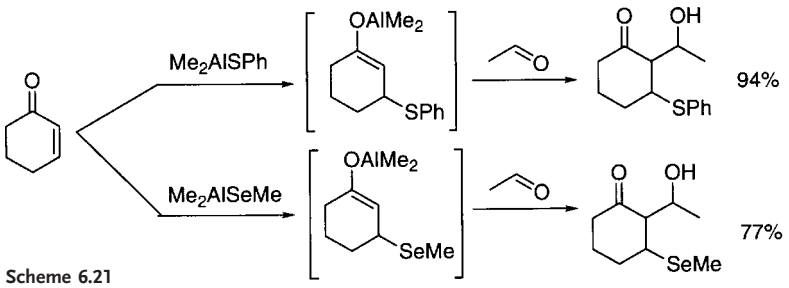
Scheme 6.19

The electrophilic capture of the aluminum enolates formed by primary alkyl halides, even by allylation, was, however, sluggish. Instead, formation of an "ate" complex of an aluminum enolates significantly improved the yields of the corresponding α-alkylation products (Scheme 6.20) [40].



Scheme 6.20

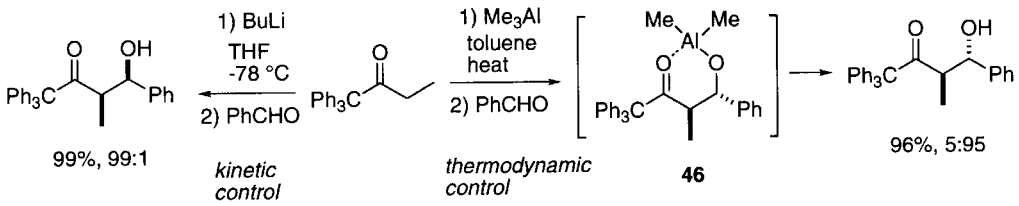
Unlike aluminum species that needed an externally added catalyst in the conjugate addition of aluminum alkyls or hydride, the transfer of heteroatom-containing groups including alkylthiolates and alkylselenoates was found even more viable [41]. These aluminum species bearing hetero-atoms do not require the aid of a transition metal catalyst. The reaction was nearly quantitative and enabled versatile transformation involving aldol reaction of the corresponding enolate intermediates (Scheme 6.21).



Scheme 6.21

By Deprotonation with Trialkylaluminum

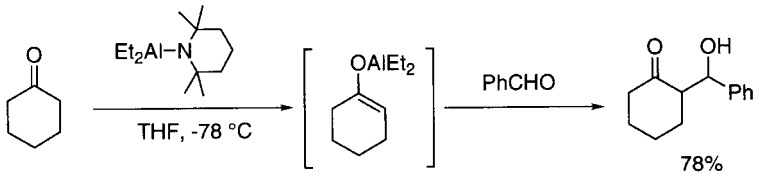
An early reference teaches us that even trimethylaluminum can cause deprotonation of a specialized ketone to generate the aluminum enolate under rather drastic conditions (toluene, reflux) [42]. As expected, the reaction proceeded under thermodynamic control, in which aldol and retro-aldol reactions occurred reversibly, to give a high level of *anti* diastereoselectivity, with concomitant removal of chelation complex **46** from the solvent (Scheme 6.22).



Scheme 6.22

By Deprotonation with Aluminum Amides

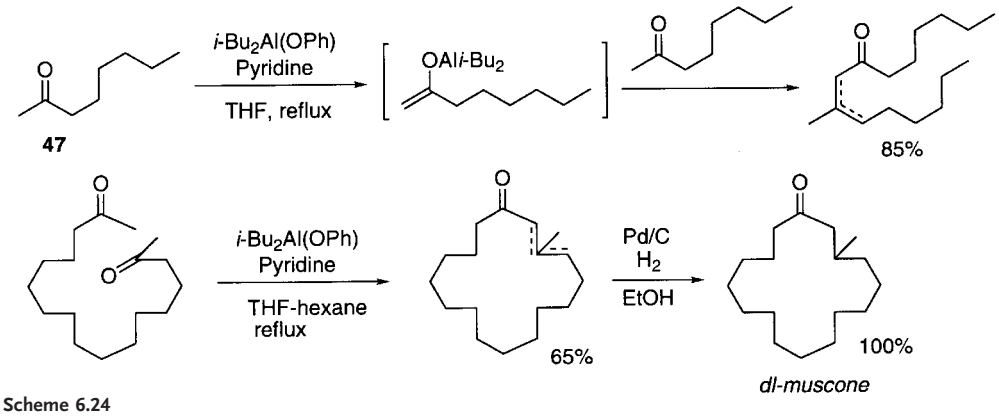
Nozaki and coworkers reported that diethylaluminum 2,2,6,6-tetramethylpiperidine (DATMP) is capable of producing diethylaluminum enolates by deprotonation of ketones or esters at –23 °C in THF (Scheme 6.23) [43]. Unlike the instability of the corresponding lithium enolate, the aldol reaction of the aluminum enolate of *t*-butyl acetate prevails over the alkoxy elimination that produces the ketene species, even at –23 °C.



Scheme 6.23

By Deprotonation with Aluminum Phenoxides

Whereas a lower temperature is essential to mediate deprotonation with DATMP, diisobutyl aluminum phenoxide requires quite a high temperature (THF, reflux) to generate the aluminum enolates, with the aid of a slight excess of pyridine (Scheme 6.24) [44]. Self-aldol condensation of ketone **47** proceeded with acceptable yield under these conditions. An efficient synthesis of *dl*-muscone was achieved by way of an intramolecular aldol reaction by use of these reagents.

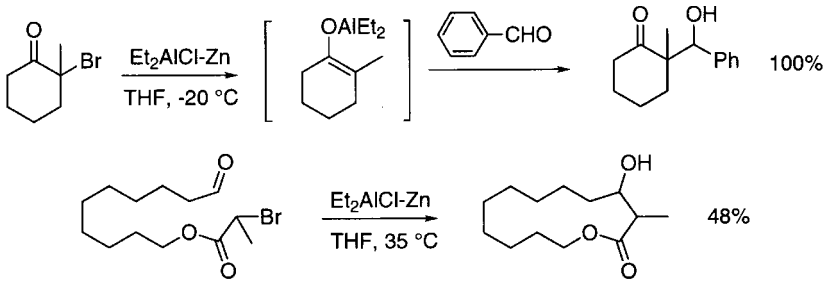


Scheme 6.24

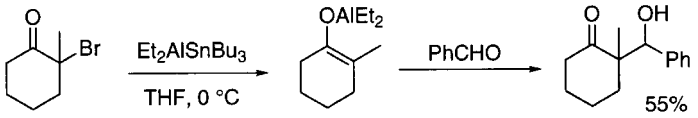
By Reduction of α-Bromo Carbonyl Compounds

Zinc(0) is capable of reducing alkyl halides. The interplay of the reductive action of zinc and the ability of aluminum Lewis acids to activate the carbonyl group enabled effective generation of aluminum enolates from α-bromo carbonyl compounds (Scheme 6.25) [45]. This method is convenient for aldol cyclization reaction, producing macrolactones in moderate to high yields. Note that the possibility of a zinc enolate, rather than the aluminum enolate, promoting the actual reactions could not be excluded.

Another approach, originally discovered by Nozaki and coworkers, is available for the generation of aluminum enolates from α-halo ketones (Scheme 6.26) [46]. This method involves reduction of a bromo group with $Bu_3SnAlEt_2$; subsequent reaction with aldehydes or ketones under mild conditions gave aldol adducts in acceptable yields. The aldol step is accelerated by participation of catalytic amounts of $Pd(PPh_3)_4$.



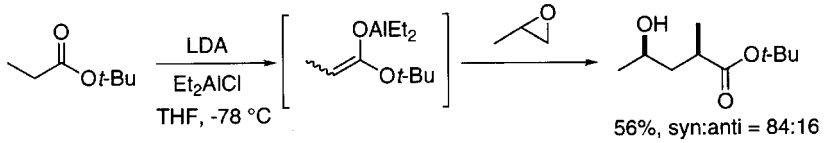
Scheme 6.25



Scheme 6.26

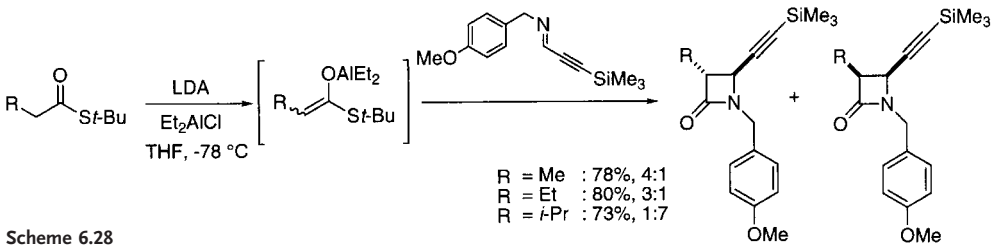
By Transmetalation of Lithium Enolates

Lithium enolates are stronger bases than aluminum enolates [47]. One advantage of using aluminum enolates is that base-labile functional groups are tolerated. Another advantage is the higher Lewis acidic nature of aluminum. Thus whereas lithium enolates require relatively harsh conditions to react with epoxides, the aluminum enolate, generated by treatment of the lithium enolate with Et_2AlCl, reacts more readily with epoxides, affording ring-opening reactions (Scheme 6.27) [48].



Scheme 6.27

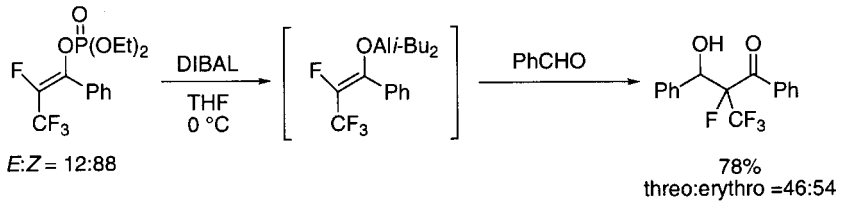
The lithium enolates of thioesters are also amenable to this transformation, involving transmetalation, to Et_2AlCl, producing the corresponding aluminum enolates which undergo Mannich-type reaction with aldimine **48**; subsequent intramolecular cyclization gave β-lactams in fairly good yields (Scheme 6.28) [49].



Scheme 6.28

Other types of enolate formation and reactions

The F-alkyl ketone enolates were readily prepared by dephosphorylation of the corresponding 1-substituted F-1-alkenyl phosphates with DIBAL at 0 °C for a few minutes (Scheme 6.29) [50]. The resulting diisobutylaluminum enolate undergoes aldol reaction with benzaldehyde to give the β-hydroxycarbonyl compound in a reasonable yield.



Scheme 6.29

By carbonyl recognition by complexation with specialized aluminum reagents

Examination of electronic and thermodynamic factors in the aforementioned conventional enolate formation revealed that steric factors were of fundamental importance in the reaction. One alternative is to complex a carbonyl compound with a bulky Lewis acid (Fig. 6.13). Bulky aluminum reagents usually form relatively stable 1:1 complexes irreversibly with carbonyl compounds. We first hypothesized that even in the presence of a strong base (LDA or LTMP), a steric environment applied in the aluminum-carbonyl complex would kinetically adjust site-selective deprotonation of carbonyl compounds which offer multiple sites for enolization and kinetically stabilize the resulting bulky enolates by retarding the rate of proton transfer or other undesirable side reactions. These fundamental considerations found particular application in the formation and reaction of novel aluminum enolates.

An unsymmetrical dialkyl ketone can form two regioisomeric enolates upon deprotonation under either kinetic or thermodynamic control. Ideal conditions for the kinetic control of less-substituted enolate formation are those using lithium diisopropylamide (LDA), in which deprotonation is irreversible. At equilibrium, on the other hand, the more substituted enolate is the dominant species with moderate selectivity. A hitherto unknown method, the kinetically controlled generation of the more substituted enolate, was realized by combined use of ATPH and LDA (Scheme 6.30) [51].

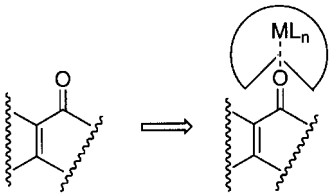
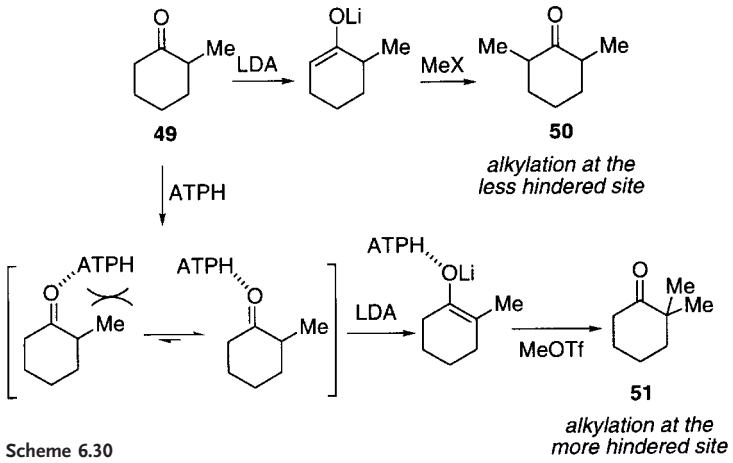
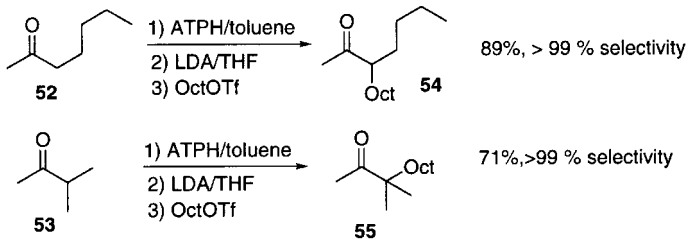


Fig. 6.13 The use of the bulky Lewis acid–carbonyl complex in place of a carbonyl compound itself



Scheme 6.30

Precomplexation of ATPH with 2-methylcyclohexanone (**49**) at –78 °C in toluene was followed by treatment with LDA in tetrahydrofuran (THF) and the mixture was stirred for 1 h. Subsequent treatment with methyl trifluoromethanesulfonate (MeOTf) furnished 2,2-dimethylcyclohexanone (**51**) and 2,6-dimethylcyclohexanone (**50**) in an isolated yield of 53% in a ratio of 32 : 1. Similarly, highly regiocontrolled alkylation of unsymmetrical **52** and **53** with octyl triflate (OctOTf) was achieved to give **54** and **55**, respectively (>99 : 1) (Scheme 6.31). Replacing ATPH with MAD resulted in lack of regioselectivity (**50** : **51** = ~1 : 1).



Scheme 6.31

Generation of the kinetically deprotonated more substituted enolate can be explained in terms of the effect of ATPH on the inherent coordination preference of unsymmetrical ketones. Most probably the bulky aluminum reagent ATPH prefers coordination with one of the lone pairs *anti* to the more hindered *α* carbon of the unsymmetrical ketones (*anti*-complexation) (Fig. 6.14). The X-ray single crystal structure of the ATPH-enolate is suggestive of preformation of the *anti*-complex, because the structure of the enolate strongly resembles that of the ATPH-**49** complex adopting *anti*-complexation, rather than that adopting *syn*-complexation. The aluminum reagent surrounds the less hindered site of the carbonyl group, thus obstructing the trajectory of the nucleophilic attack of LDA.

Surprisingly, in the presence of THF and TBSOTf, regioselective siloxybutylation occurred smoothly to give mono-alkylation product in high yield (Scheme 6.32) [52]. Interestingly, when 3-methylcyclohexanone was used, the 6 position of the ketone was the site of dominant deprotonation and subsequent alkylation.

In contrast, MAD was proved to be effective for in situ double siloxybutylation (Scheme 6.33). Although excess LDA and TBSOTf coexist during the first alkyla-

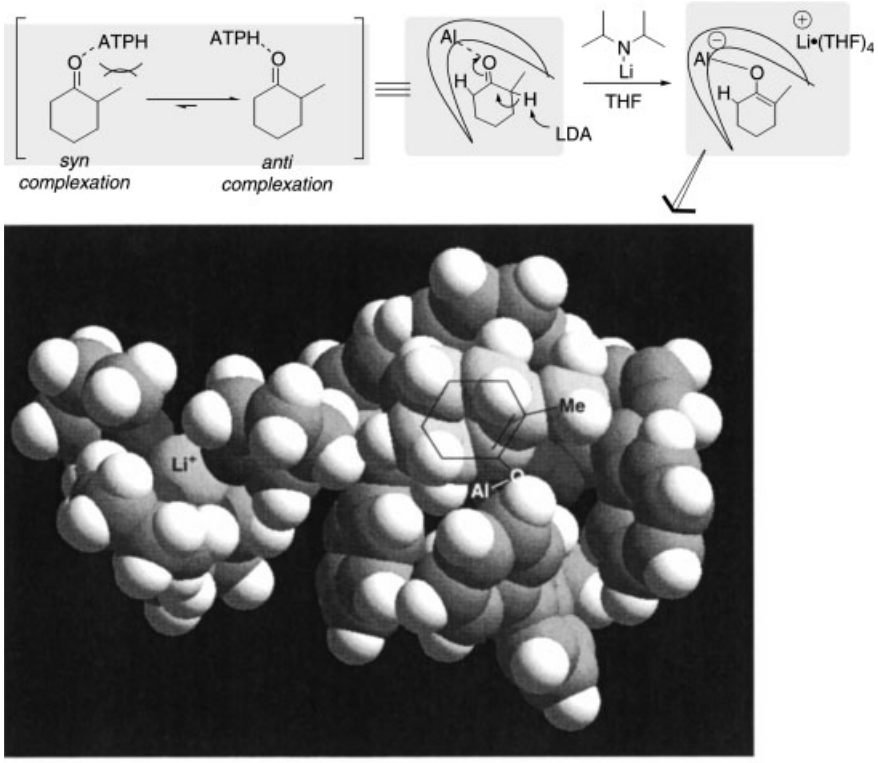
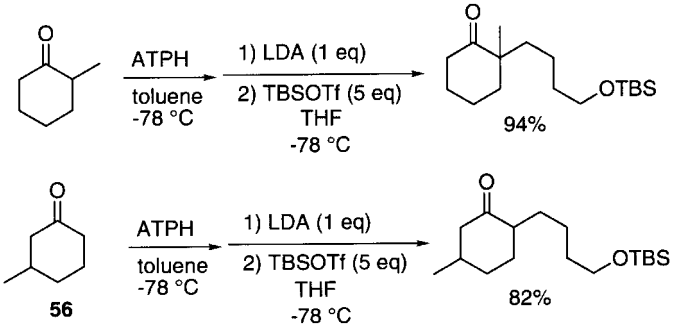
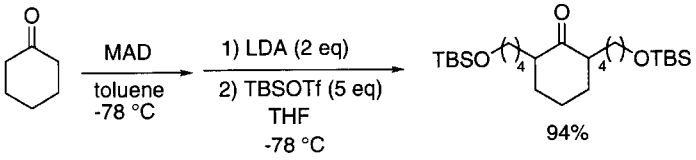


Fig. 6.14 X-ray crystal structure of a higher substituted enolate generated from the ATPH-2-methylcyclohexanone complex



Scheme 6.32



Scheme 6.33

tion, LDA maintains its potential and subsequent second alkylation proceeded very cleanly [52].

ATPH has been shown to form a cavity which can encapsulate a variety of molecules (Figs 6.6 and 6.7). When both Nu^- and E^+ are complexed with ATPH the steric effect of the cavity can obviate direct coupling between the former two which coexist in a reaction vessel, where a third component eventually intervenes (Fig. 6.15); otherwise these two components (Nu^- and E^+) would couple with each other solely by taking advantage of their electronic interactions. The general principle of this sequence is represented in Fig. 6.15.

On the basis of this working model, a novel strategy for the three-component coupling of ketone, cyclic ether, and epoxide was realized using ATPH and LDA (Scheme 6.34) [53].

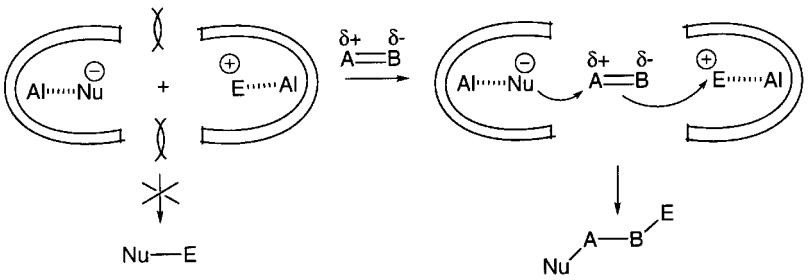
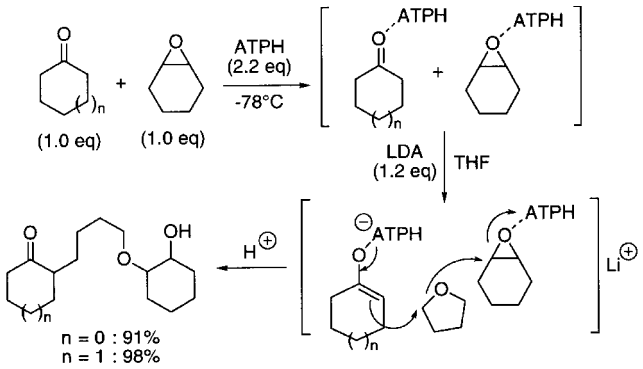


Fig. 6.15 Reaction between bulky ATPH complexes, allowing intervention of the third reactive component



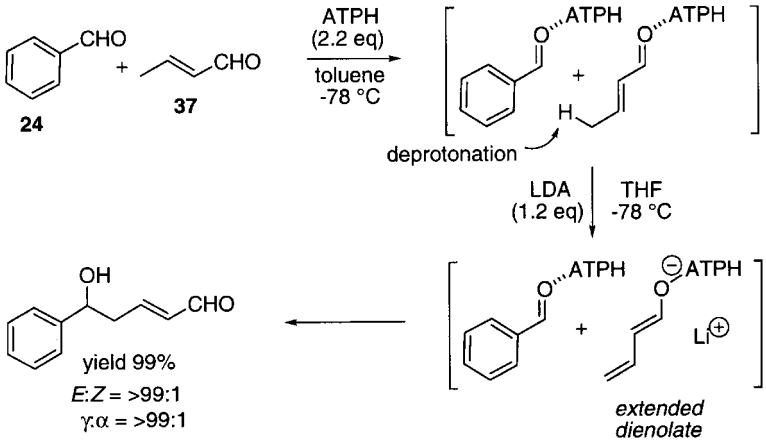
Scheme 6.34

Other efforts have been focused on a conceptually new, directed aldol condensation [54]. Mixed aldol condensations between two different carbonyl compounds with several possible sites for enolization are extremely difficult and there is a variety of undesired pathways involving proton transfer and over-alkylation. The aldol reaction of an *α,β*-unsaturated carbonyl compound with an aldehyde was investigated in the presence of ATPH. The reaction first involves the demand for control of reactivity and selectivity of the *α,β*-unsaturated carbonyl compound, which upon deprotonation leads to the corresponding extended dienolate of ATPH. A second carbonyl compound aldehyde which serves as an electrophile is activated electronically (but sterically deactivated) by complexation with ATPH. This activation would enable rapid in-situ capture of the extended dienolate. ATPH was the reagent of choice, because it could effectively make a strong coordination bond upon encapsulating a number of *α,β*-unsaturated carbonyl compounds.

Precomplexation of PhCHO (**24**) and crotonaldehyde (**37**) with ATPH was followed by treatment with LDA to give the *γ*-aldol adduct in 99% yield (Scheme 6.35). The reaction includes operational simplicity and consistently gave an extremely high level of *E* and *γ* selectivity [55, 56].

The substrate generality is remarkable and thus synthetically very useful (Fig. 6.16). *α,β*-Unsaturated aldehydes, ketones and esters all give comparable results. Highly elongated unsaturation is also compatible with this reaction sequence. Electrophilic components include aromatic and aliphatic, and even *α,β*-unsaturated aldehydes, and *α,β*-unsaturated ketones react at the *β*-position.

The behavior of *β,β*-disubstituted-*α,β*-unsaturated carbonyl compounds in a similar reaction sequence using ATPH and LDA (or LTMP) was even more interesting (Fig. 6.17). Entirely opposite selectivity was observed, depending on the carbonyl functionality employed. The predominant alkylation site was the (*Z*)–*γ* position of methyl 3-methyl-2-butenoate, whereas senecialdehyde gave the (*E*)–*γ*-addition product exclusively. This could be ascribed to specific complexation of ATPH with a different carbonyl compound by molecular recognition: several sets of X-ray crys-



Scheme 6.35

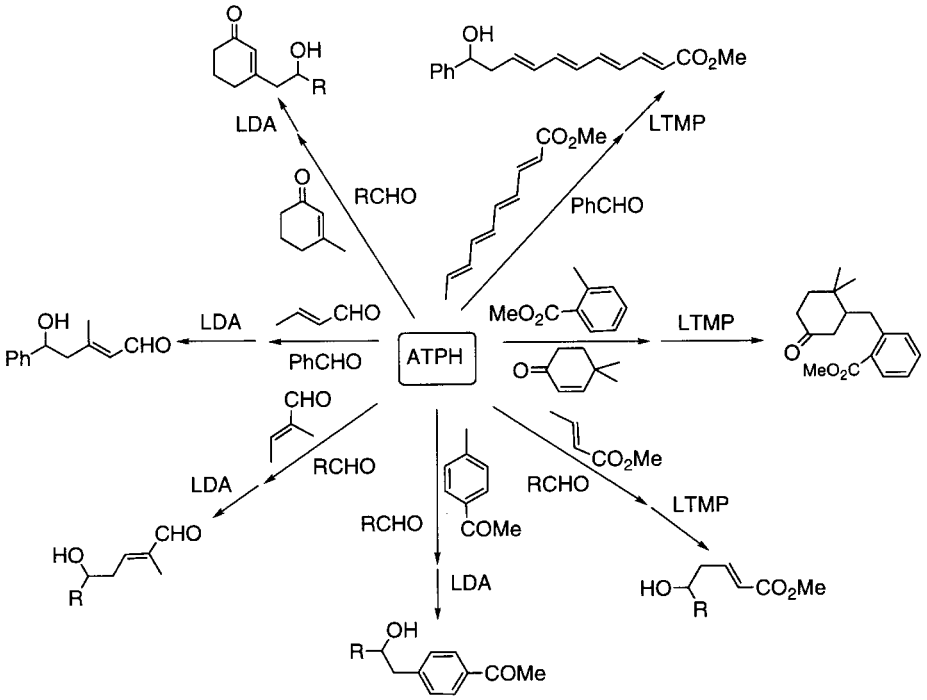


Fig. 6.16 Directed aldol condensation using ATPH

tal analyses (Figs 6.6–6.8) and NOE measurements [57] strongly suggested that ATPH-carbonyl complexes resemble the corresponding extended dienolates (Fig. 6.17).

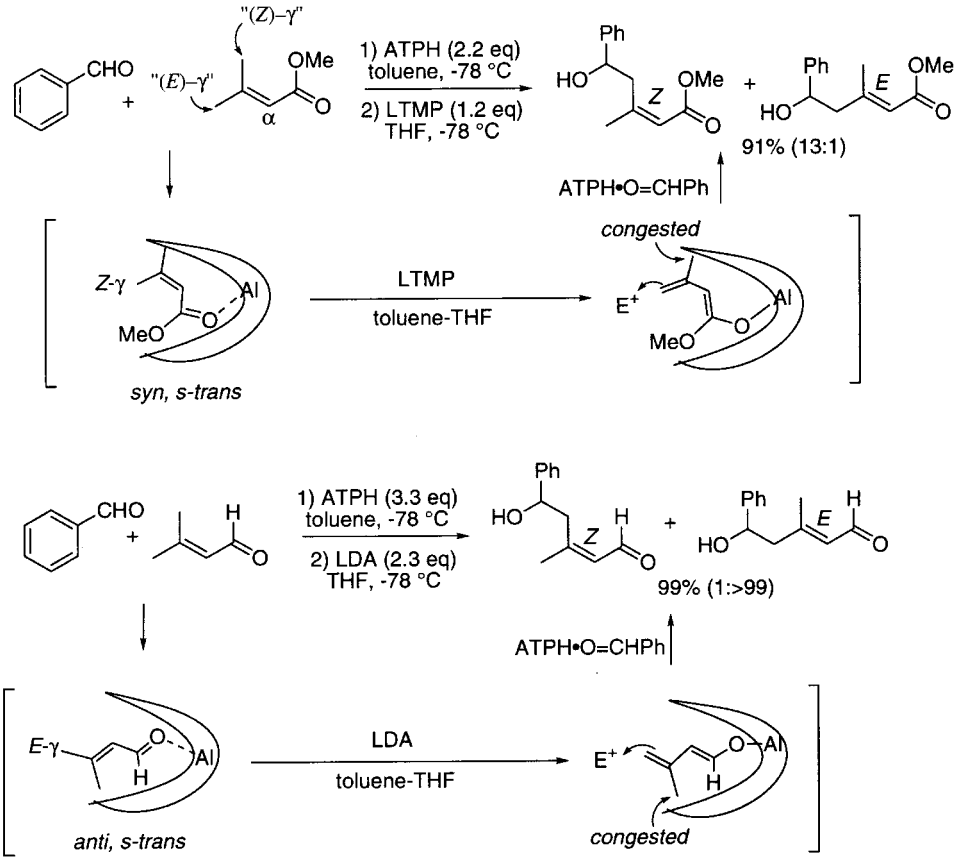
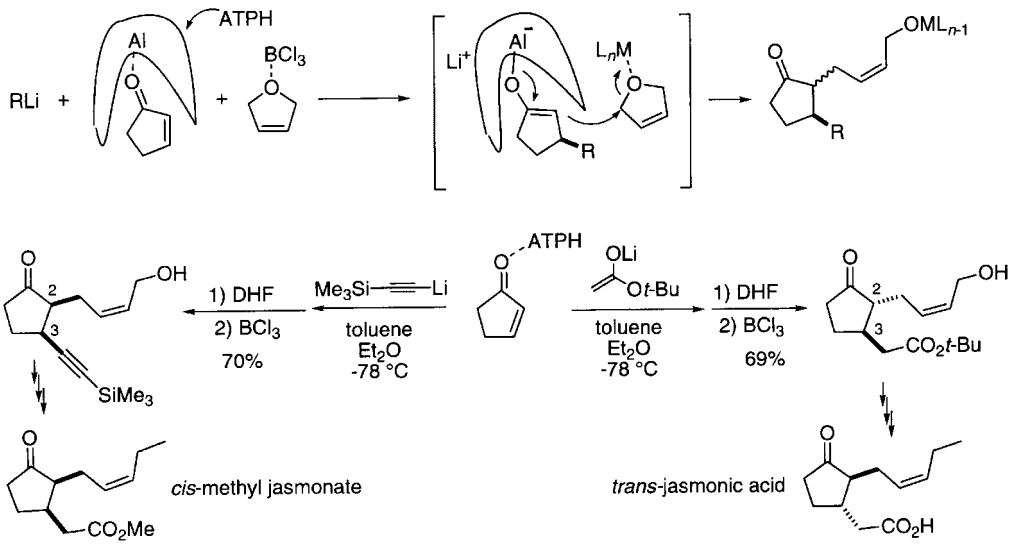


Fig. 6.17 Conformations of ATPH-carbonyl and ATPH-dienolate complexes and their reactivities and selectivities

One-pot three-component coupling is an important procedure in organic synthesis and provides a powerful and rapid means of construction of the prostaglandin and jasmonate families. We recently developed a novel strategy for three-component coupling involving the combined use of organolithium reagent (RLi), aluminum tris(2,6-diphenylphenoxide) (ATPH)–cyclopentenone complex, and 2,5-dihydrofuran (DHF)–BCl_3 complex (Scheme 6.36). The astonishing reversal of diastereoselectivity (2,3-*trans*/*cis*) is worth mentioning – whereas alkynyllithiums are predominant in the 2,3-*cis* relationship, 2,3-*trans* selectivity was obtained exclusively with lithium enolates. This approach leads efficiently to both *trans*- and *cis*-jasmonate derivatives [58].



Scheme 6.36

6.2.1.2 Aluminum–Carbonyl Complexation, Activation, and Nucleophilic Reaction

Pericyclic Reaction and Asymmetric Reaction

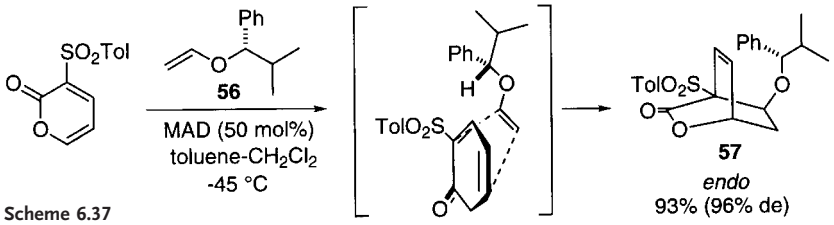
Pericyclic addition reactions are attractive C–C, C–N, and C–O bond-formation reactions for many reasons. They involve:

- easy stereocontrol, because of the nature of pericyclic reactions;
- ready construction of complex carbon frameworks, because of the powerful and rapid skeletal compacting nature of this method; and
- the viability of Lewis acid–base complexation in reducing the LUMO of substrates even in reverse-electron-demand reactions.

Synthetically more readily availability of aluminum chemistry in pericyclic reaction was made possible, in particular, by Yamamoto and coworkers, who showed that the steric bulk of aluminum reagents is synthetically strategic, facilitating unprecedented selectivity and reactivity.

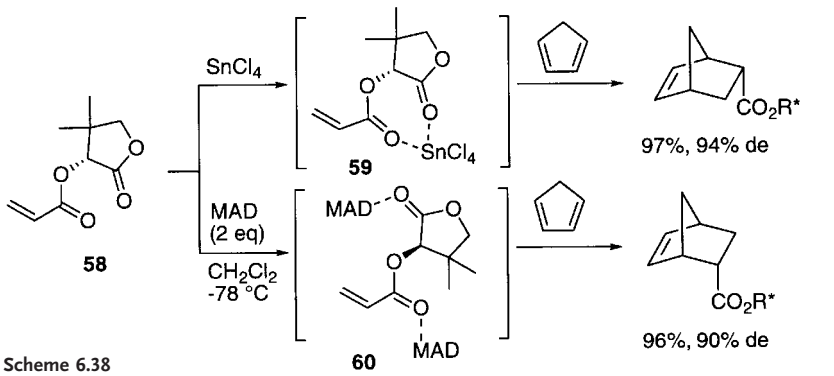
[4+2] Cycloaddition Yamamoto's "MAD" Lewis acid promoted very mild and highly stereocontrolled [4+2] cycloaddition between the pyrone sulfone and enantiomerically pure vinyl ether **56**; by use of 50 mol% MAD, cycloadducts were isolated on a 1.5-g scale in 93% yield as a 98:2 ratio of *endo* diastereomers with **57** being a major isomer (Scheme 6.37) [59].

Stereocontrol using MAD in the [4+2] cycloaddition of the acrylate of D-pantolactone and cyclopentadiene revealed intriguing behavior which is worth mentioning (Scheme 6.38) [60]. Cycloaddition in the presence of 2 equiv. MAD gave diastereo-



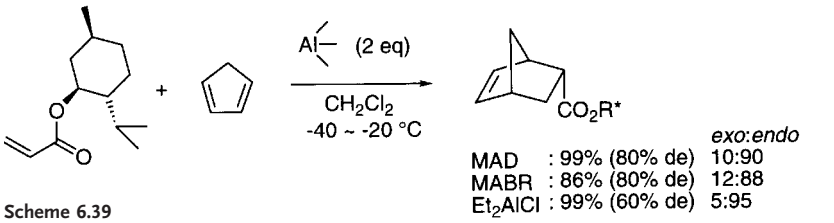
Scheme 6.37

selectivity opposite to that obtained by use of $SnCl_4$. The 1:2 complex of **58** and MAD might adopt a conformation consistent with structure **60**, because of steric constraints. It is reasonable to suggest a highly preferred conformation **59** by the chelation complex of $SnCl_4$. The reversal of the diastereocontrol was best accounted for by exposure of each π-face to approach of the diene in the opposite direction.



Scheme 6.38

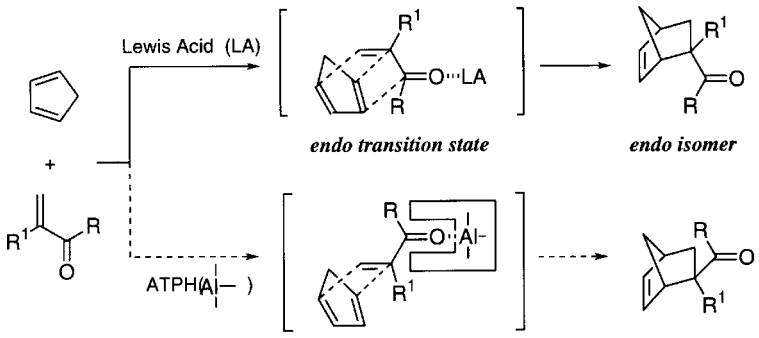
The use of MAD in [4+2] cycloaddition of cyclopentadiene with chiral acrylate resulted not only in greater diastereoselectivity but also greater *exo*-selectivity, although to a small degree, than other ordinary Lewis acids (Scheme 6.39) [61].



Scheme 6.39

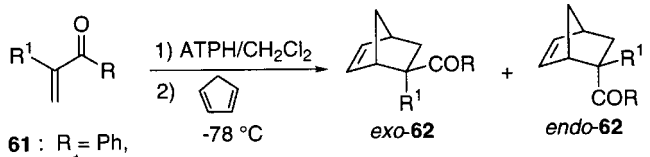
The *exo*-selectivity was more apparent when using ATPH although a characteristic stereochemical feature of the Diels-Alder reaction is *endo*-selectivity. The origin of the *endo*-preference in Diels-Alder reactions can be ascribed to "secondary orbi-

tal interactions". If the carbonyl functions of dienophilic *α,β*-unsaturated carbonyl substrates are effectively shielded by complexation with ATPH, secondary interaction is decreased, thereby disfavoring the hitherto preferred *endo* transition state (Scheme 6.40).



Scheme 6.40

As expected, precomplexation of *α,β*-unsaturated ketone **61** with ATPH in CH_2Cl_2 at –78 °C, then cyclization with cyclopentadiene, resulted in stereochemical reversal to furnish *exo*-**62** as major product (Scheme 6.41) [62]. Similarly, the Diels-Alder reaction with other dienophiles complexed with ATPH proceeded with *exo*-selectivity.



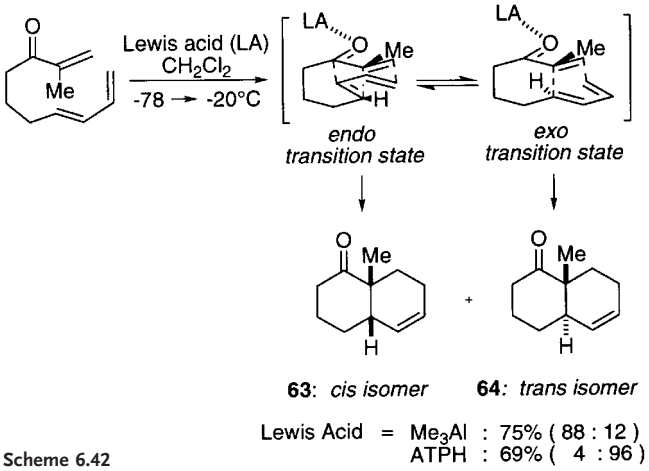
61 → **62** ; 81 % (73 : 27)

R = Ph, R^1 = Me : 81 % (96 : 4)
R = R^1 = Me : 87 % (87 : 13)

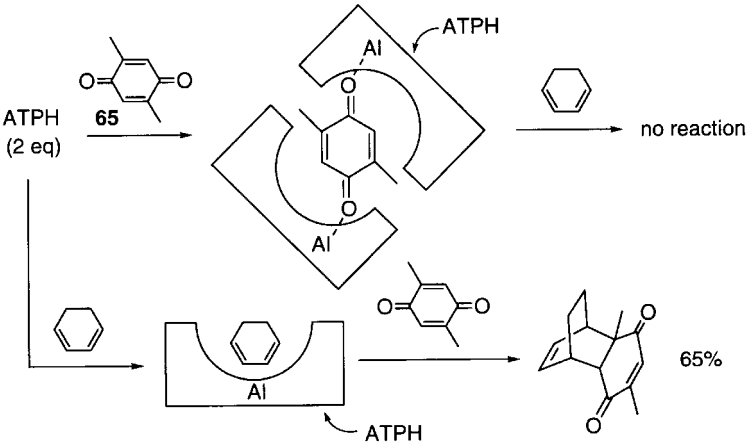
Scheme 6.41

This concept was extended intramolecularly to give the *trans*-fused stereoisomer **64**, whereas an ordinary aluminum reagent gave the *cis* isomer **63** *via* an *endo* transition state (Scheme 6.42).

A 1:2 mixture of a quinone and ATPH self-assembled to make a 1:2 complex, because they form a molecular capsule in which the quinone was encapsulated within two ATPH molecules [63]. This "dienophile" complex did not undergo [4+2] cycloaddition with cyclohexadiene (Scheme 6.43). In contrast, when a 1:2 mixture of the cyclohexadiene and ATPH was treated with the quinone, the cycloadduct was obtained. It was concluded that pre-inclusion of the diene by interaction with the aromatic concave of ATPH facilitated the ensuing cycloaddition.



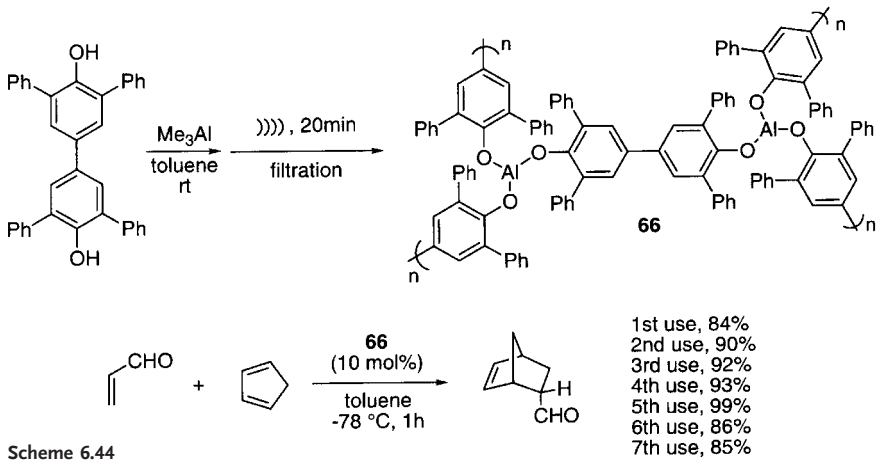
Scheme 6.42



Scheme 6.43

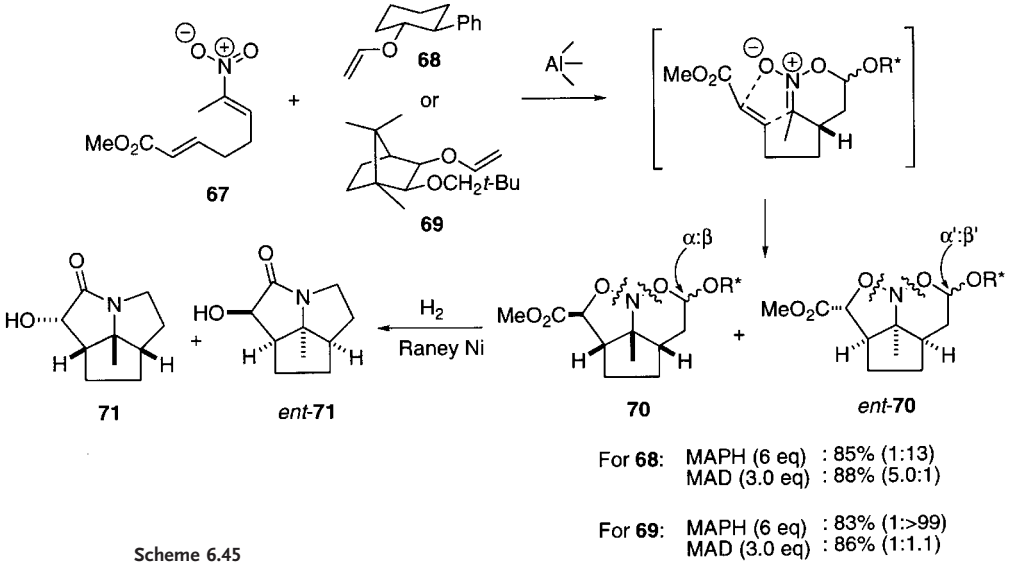
Polymeric, solid ATPH was adapted for [4+2] cycloaddition [64]. The polymer catalyst **66** was prepared by treatment of Me_3Al with the appropriate biphenol, followed by exposure to ultrasonic irradiation, and could be recovered quantitatively by simple filtration and reused (Scheme 6.44). The activity of the recovered **66** did not decrease even after seven uses. It is worthy of note that the [4+2] addition competes with the Tischenko reaction, which is a major path when solid alumina catalysts are used.

Novel stereoselectivity in tandem inter[4+2]/intra[3+2] nitroalkene cycloaddition was achieved by use of bulky aluminum reagents (Scheme 6.45). When MAD was employed as the Lewis acid the cycloaddition between nitroalkene **67** and vinyl ether **68** yielded an inseparable mixture of nitroso acetal diastereomixtures in 88%



Scheme 6.44

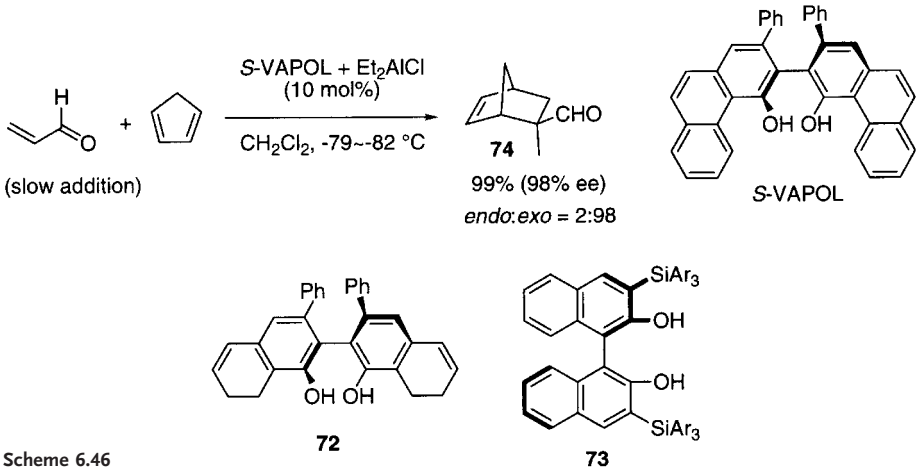
yield [65]. Because the stereoselectivity was high in the [3+2] cycloaddition, three diastereomers were present in the ratio 3.5:1.5:1.0 (α:β:β'). An interesting observation was made when MAPH was used as the Lewis acid promoter. Under optimized reaction conditions, tandem reaction proceeded at –78 °C to yield a mixture of nitroso acetal diastereomers **70** in 86% yield. Surprisingly, a β-anomer predominated (α:β:β' = 1:2:38.7). The corresponding lactam *ent*-**71** was found to be enriched in the opposite enantiomeric series, 79% ee (*R*), to that observed with MAD (72% ee (*S*)).



Scheme 6.45

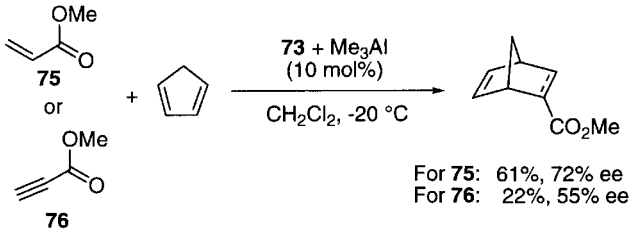
Further screening of the chiral moiety of vinyl ethers indicated that cycloaddition with **69** gave an excellent level of diastereo- and enantioselectivity in the presence of MAPH. One reasonable explanation for the observed reversal of the sense of asymmetric induction is that a corresponding reversal in the *exo*/*endo* preference of the [4+2] cycloaddition had occurred. Thus MAPH favored an *exo*-transition state, which was also preferred by ATPH.

Catalytic Asymmetric [4+2] Cycloaddition Compared with the metals Ti, Sn, and B, the development of chiral aluminum catalysts that enable asymmetric [4+2] cycloaddition reaction between simple dienes and *α,β*-unsaturated aldehydes is not an easy task if a Lewis acid and a dienophile make a highly reactive combination. A new vaulted chiral ligand *S*-VAPOL was introduced by Wulff and coworkers to achieve improved performance over the linear biaryls **72** and **73** (Scheme 6.46) [66]. In fact, the asymmetric [4+2] cycloaddition of cyclopentadiene and methacrolein proceeded effectively with catalyst, generated by treatment of *S*-VAPOL with Et_2AlCl, to give cycloadduct **74** quantitatively with 91–99% ee. This reaction is best performed with slow addition of dienophile, giving the highest ee of 98%. This implies "autoinduction", among the important subjects in a discussion of the effects of the hyper-coordination aptitude of aluminum (vide post). Catalysts derived from **72** and **73** proved ineffective (up to 41% ee), probably because of the insufficient depth of their chiral pockets.



Scheme 6.46

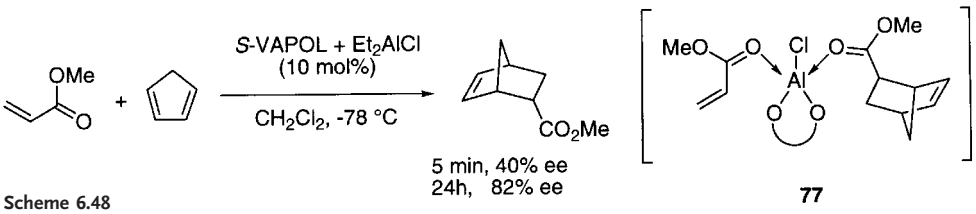
In contrast with the ineffectiveness of the aluminum catalyst derived from **73** in the aforementioned reaction, the [4+2] cycloaddition of *α,β*-unsaturated esters (i.e. **75**) resulted in greater enhancement of asymmetric induction (Scheme 6.47) [67]. The reaction was best performed in toluene (or CH_2Cl_2) at –40 to –20 °C to give cycloadducts in 70–77% ee, which varied depending on subtle changes in reaction



Scheme 6.47

conditions. The first example of asymmetric [4+2] cycloaddition of alkynyl ester **76** seemed to give a moderate ee of 55%.

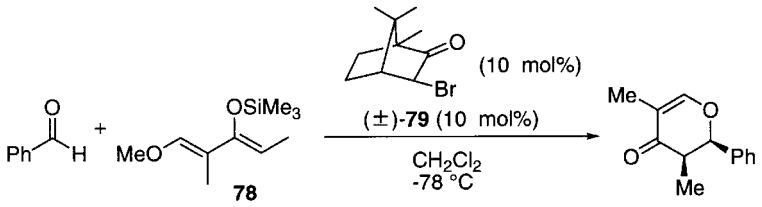
In a similar [4+2] reaction of *a,β*-unsaturated esters, the aluminum catalyst complexed with the ligand *S*-VAPOL resulted in "autoinduction", because of cooperative interaction of the product with the catalyst to generate a more selective catalytic species (Scheme 6.48) [68]. The ee% gradually increased as the reaction time lengthened. In the proposed intermediate, penta-coordinated aluminum complex **77**, the cycloadduct is recognized as a complementary ligand, leading to substantial asymmetric induction. The acrylate is activated effectively within this hybridized complex which adopts pentacoordination [87].



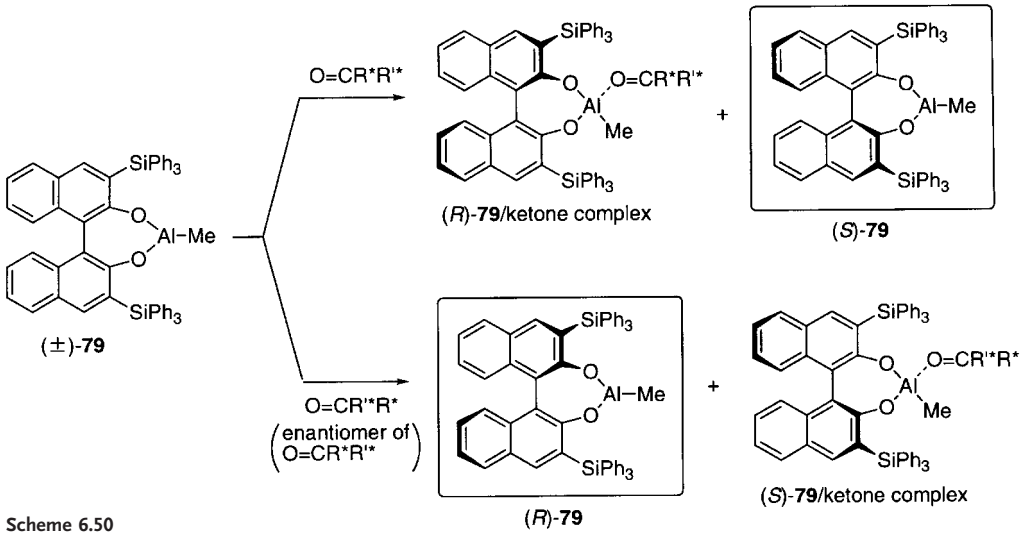
Scheme 6.48

It is reasonable to expect that some chiral ketones might discriminate between racemic organoaluminum reagents by diastereoselective complexation – leading to preferential formation of one of the two diastereomers by chiral molecular recognition [69]. Indeed, the Lewis acidic enantiomer **79** that remained intact in situ promoted the asymmetric hetero-Diels–Alder reaction of aldehydes with substituted Danishefsky-type diene **78**, with high enantioselectivity (Scheme 6.49). The so called concept of "chiral poisoning" of one of two active enantiomers triggers the selective and relative activation of another enantiomer (Scheme 6.50). Similar approaches involving this strategic "chiral poisoning", first validated by Yamamoto and Maruoka, for asymmetric synthesis have subsequently been reported [70].

Development of enantioselective polymer catalysts is important in the efficient production of optically pure compounds. The main advantage of a polymer catalyst is the ease of recovery and reuse of the expensive catalyst. The use of polymer catalysts might also enable the reactions to be performed in flow reactors or flow membrane reactors for continuous production. Asymmetric hetero-Diels-Alder re-

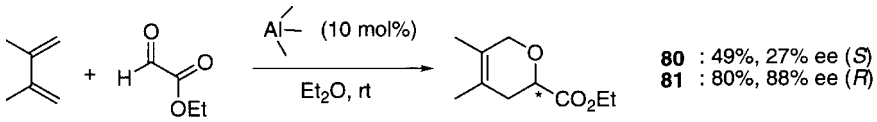


Scheme 6.49



Scheme 6.50

action catalyzed by chiral polybinaphthyl-based Lewis acid complexes was investigated by Pu and coworkers [71]. The insoluble chiral polymer catalyst was generated in toluene by treatment of Me_3Al and polymer **81**. Changing the solvent to Et_2O results in significant improvement of yield and chemoselectivity. A high ee of 89% of the cycloadduct is obtained even at r.t (Fig. 6.18, Scheme 6.51). In contrast, results for the polymeric **80**-AlCl catalyst, generated by treatment of polymer **80** with Et_2AlCl, showed that exchange of the methyl substituent with chlorine reduces both the yield and ee of the cycloadduct dramatically.



Scheme 6.51

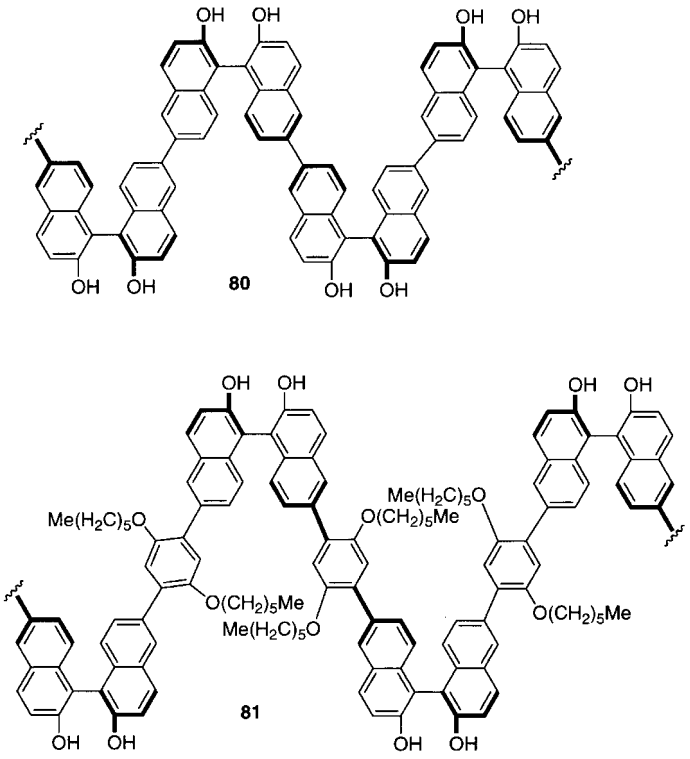
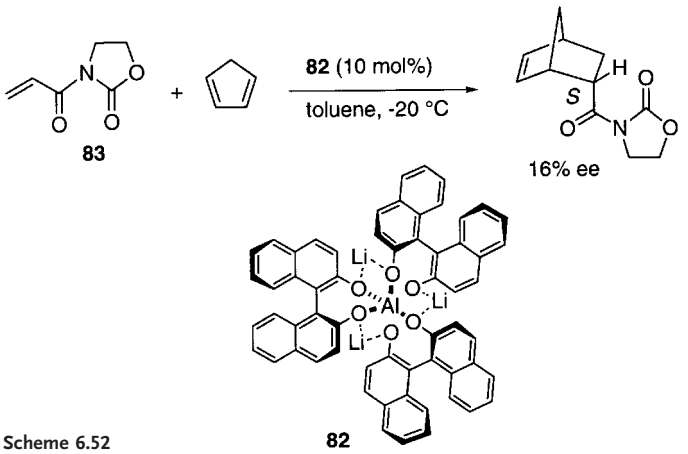


Fig. 6.18 Binaphthol-based polymer ligands

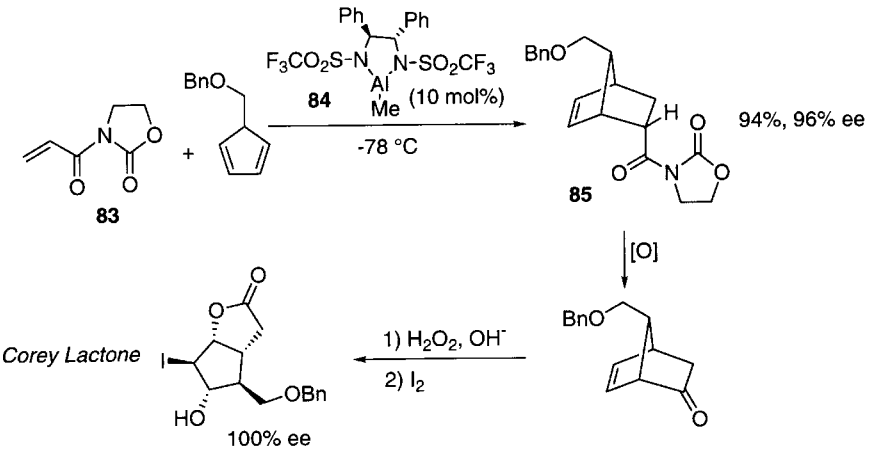
Such structural modification of a chiral binaphthol had a beneficial effect on enantioselectivity. In contrast, other emphasis was placed on structural modification of the aluminum geometry, rather than the binaphthol ligand itself. The reactivity and selectivity of the hexacoordinated aluminum complex **82** with three binaphthols on one aluminum atom was evaluated in the [4+2] cycloaddition of cyclopentadiene and dienophile **83** (Scheme 6.52) [72]. Catalyst **82** has a saturated coordination number with regard to the aluminum atom, which thus no longer has vacant orbitals for further complexation with other incoming Lewis bases. Although the ee of the adduct was very low (16%), this result strongly suggests the greater probability that lithium ions in **82** serve as Lewis acids in non-polar solvents.

The cycloaddition of functionalized cyclopentadiene and dienophile **83** was better performed by use of an entirely different, non-phenoxide-type aluminum complex (Scheme 6.53). Thus a chiral catalyst endowed with the more electron-withdrawing bis(sulfonamide) ligand was explored by Corey and coworkers [73]. The reaction of the *trans*-crotyl derivative **83** and cyclopentadiene with 20 mol% **84** as catalyst at –78 °C for 16 h provided adduct **85** in 88% yield and 94% ee. The ad-



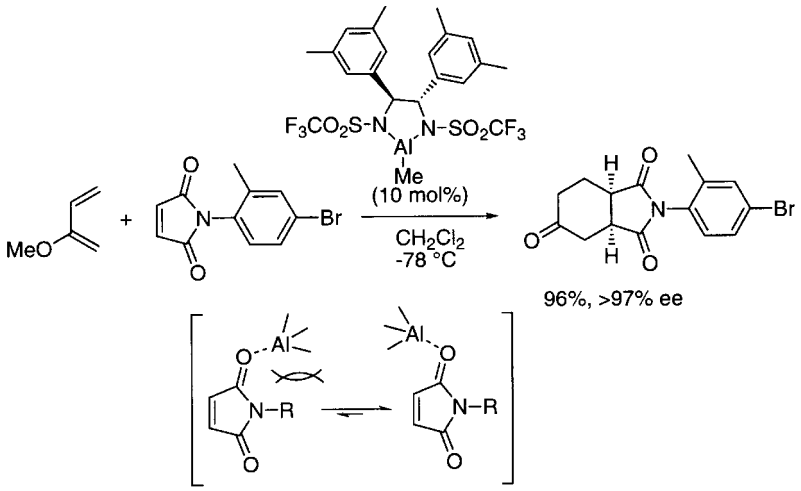
Scheme 6.52

duct was converted in short steps to the Corey lactone, which is a critical and versatile synthetic intermediate for prostaglandin synthesis.



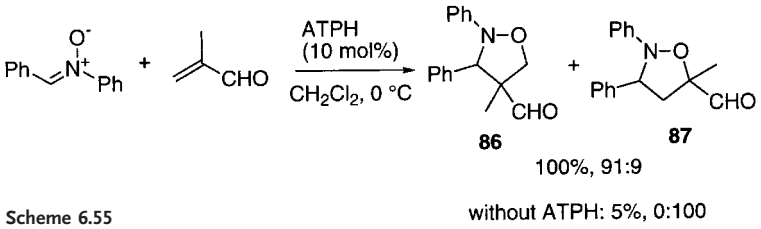
Scheme 6.53

Changing the dienophile from a simple diene to a maleimide was also successful (Scheme 6.54) [74]. For high asymmetric induction it was found that 3,5-dimethyl substituents on the phenyl group of the catalyst and an *ortho* substituent on the phenyl group of the maleimide are required. This intriguing observation can be accounted for by preferential coordination, for steric reasons, of the chiral catalyst, thus altering one of the lone pairs of carbonyl oxygen.



Scheme 6.54

[3+2] Cycloaddition The [2+3] cycloaddition of *N*-benzylidene *N*-oxide with *α,β*-unsaturated carbonyl compounds has been promoted by catalytic amounts of ATPH (Scheme 6.55) [75]. ATPH was effective both in rate enhancement and in improving the regioselectivity. Cycloaddition of *N*-benzylidene *N*-oxide and acrolein with 10 mol% ATPH proceeded at 0 °C to give cycloadducts **86** and **87** quantitatively in a ratio of >99 : 1. Methacrolein, crotonaldehyde, and 3-buten-2-one undergo cycloaddition with similar effectiveness, but methyl acylate is not reactive when ATPH is used.



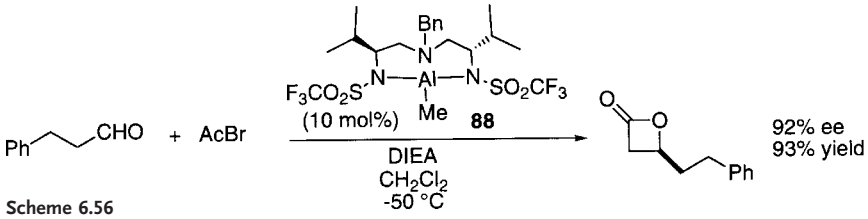
Scheme 6.55

[2+2] Cycloaddition

C=O + C=C Addition

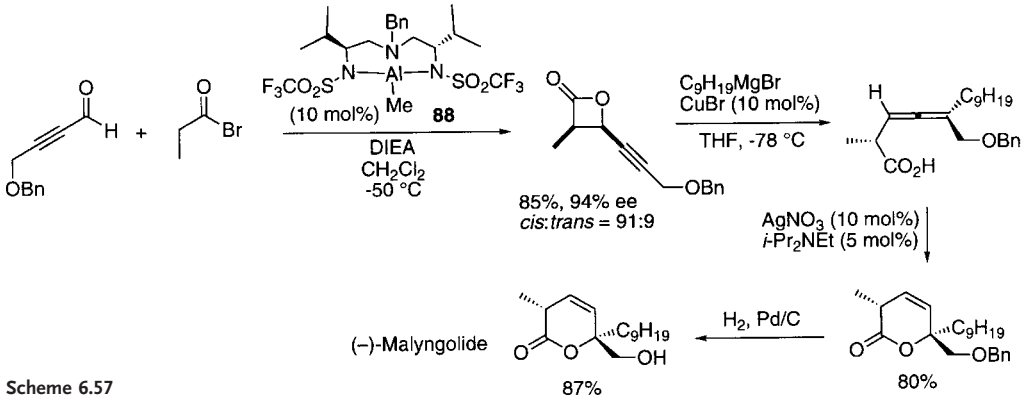
Ketene and aldehydes undergo [2+2] cycloaddition in the presence of aluminum catalysts (Scheme 6.56). The reaction involves either isolable or in situ-generated unstable ketenes and is regarded as a variant of the aldol reaction. During the development of the Al(III)-catalyzed ketene–aldehyde reaction, the optically active Al(III)-triamine complex **88** was found to catalyze the cyclocondensation of acetyl bromide (AcBr) and benzyloxyacetaldehyde, with di(isopropyl)ethylamine (DIEA)

as base, to afford the optically active β-lactone in 92% ee [76]. Catalyst **88** rendered a variety of structurally diverse, enolizable and alkynyl aldehydes as effective electrophiles for the catalyzed asymmetric aldehyde–ketene cycloaddition reaction. In addition, a variety of functional groups including benzyloxy TBDPS-oxy, and TBDMS-oxy substituents were tolerated.



Scheme 6.56

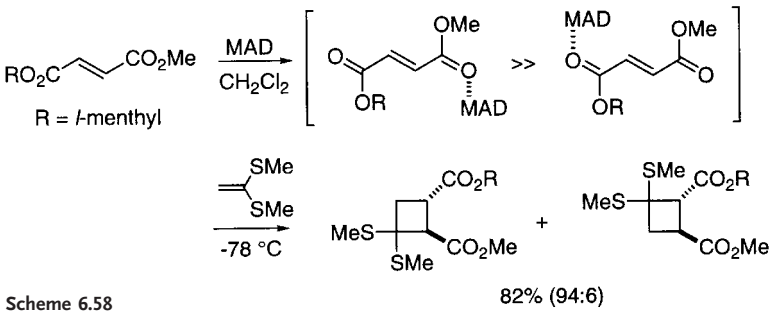
The cycloadducts of alkynyl aldehydes were readily converted to the optically active allenyl compounds on exposure to Grignard reagents with catalytic amounts of CuBr or CuCN.2LiBr [77]. This copper-catalyzed addition of Grignard reagents to β-lactone electrophiles uniformly proceeded in high yield and with consistent chirality transfer from the β-lactones to the derived β-allenic acids. The utility of this reaction technology for asymmetric synthesis has been demonstrated by a concise and efficient synthesis of the naturally occurring antibiotic (–)-malyngolide (Scheme 6.57).



Scheme 6.57

C=C + C=C Addition

MAD has been used to catalyze the [2+2] cycloaddition reaction between fumarates and electron-rich olefins (Scheme 6.58) [78]. Unsymmetrical fumarates were discriminated by MAD, in which the coordination of carbonyl oxygen of the methyl ester was favored, to give high regioselectivity. Regioselective [4+2] cycloaddition was also achieved by use of this procedure for discriminating molecules [79].

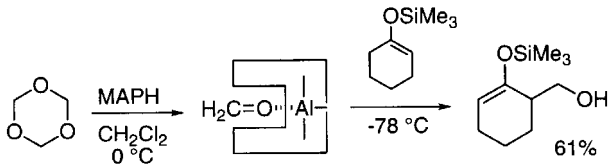


Scheme 6.58

Ene Reaction and Asymmetric Reaction

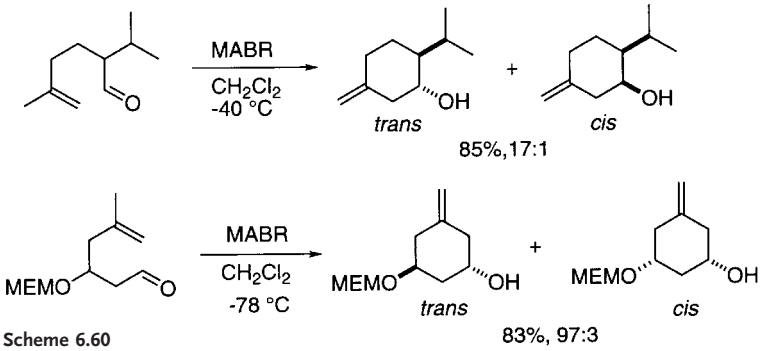
Ene reactions occur between alkenes with allyl hydrogen (an "ene") and compounds containing an electron-deficient double bond (an "enophile") to form a σ-bond with migration of the ene double bond and a 1,5-hydrogen shift [80]. The beneficial effects of classical aluminum Lewis acids on the ene reaction have been thoroughly investigated by several groups. Despite their enormous efforts, intermolecular ene reactions usually suffered from side reactions and low selectivity [81]. Intramolecularly the reaction has found wider application, for example in cyclizations affording a 12-membered ring [82].

In contrast, well-designed aluminum phenoxides controlled the reactivity and selectivity of both "ene" and "enophile", providing clean reactions and high product yields. For example, reactive aldehydes including formaldehyde and α-chloroaldehydes can be generated by treatment of readily available trioxane and α-chloroaldehyde trimers, respectively, by complexation with MAPH (Scheme 6.59) [83]. When the aldehydes sterically stabilized but rather electronically destabilized by MAPH were subjected to "ene" substrates, smooth and clean reaction proceeded to give homoallyl alcohols in high yields, and frequently with better selectivity with regard to the migrated ene position.



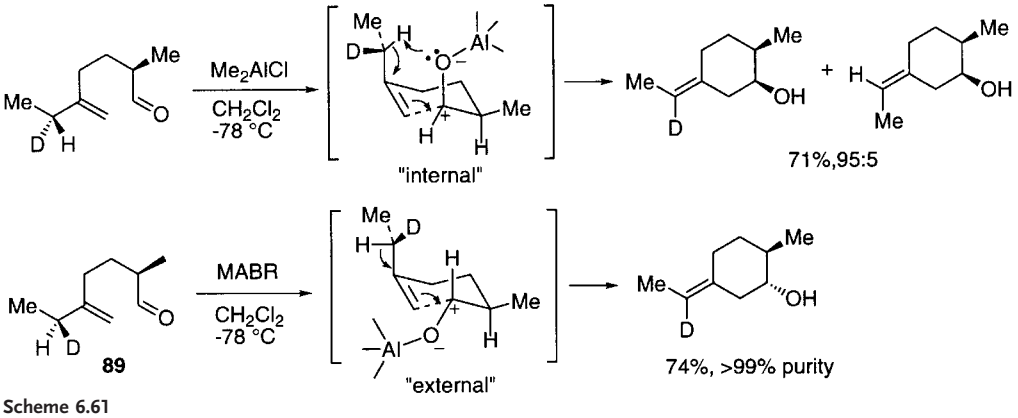
Scheme 6.59

Stereoselective intramolecular ene reactions of α-substituted-δ,ε-unsaturated aldehydes have been achieved by use of MABR (Scheme 6.60) [84]. The reaction has unprecedented *trans* selectivity, in contrast with the *cis* selectivity frequently observed in the type II ene reaction with other ordinary Lewis acids. Not only 1,2-diastereocontrol but also 1,3-diastereocontrol [85] was similarly facilitated.



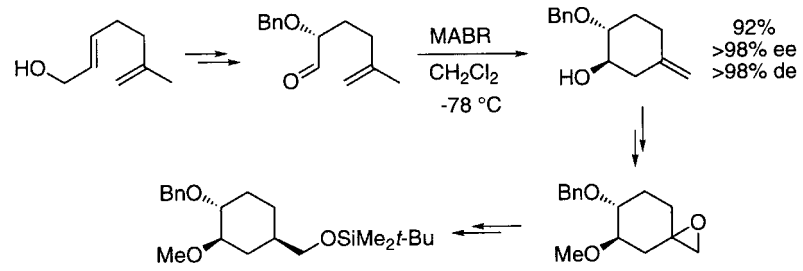
Scheme 6.60

Marshall later pointed out that the MABR-promoted cyclization of **89** must be preceded by an external proton transfer, whereas the classical aluminum reagent Me_2AlCl favors the ene cyclization pathway involving internal proton transfer (Scheme 6.61) [86].

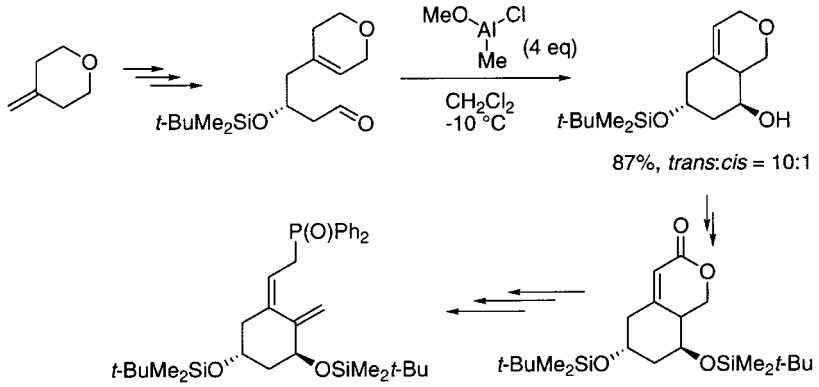


Scheme 6.61

The cyclohexyl fragment of FK-506 (Scheme 6.62) [85] and 1α,25-dihydroxy-Vitamin D_3 Ring A synthon (Scheme 6.63) [87] were readily accessible by *trans*- and *cis*-selective cyclization, respectively.

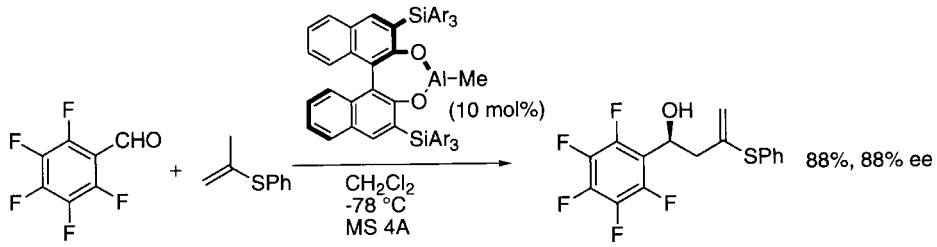


Scheme 6.62



Scheme 6.63

Asymmetric ene Reaction In 1988 Yamamoto and coworkers provided the first indication that asymmetry in ene-reactions could be induced by catalytic amounts of chiral Lewis acids in the presence of 4-Å molecular sieves (Scheme 6.64) [88]. They described the first example of asymmetric ene-reaction between prochiral, halogenated aldehydes and alkenes catalyzed by chiral binaphthol-derived aluminum complexes. The hindered 3,3-silyl substituents in the chiral catalyst are essential to achieve good enantioselectivity and high yield. In fact, the use of a catalyst derived from Me_3Al and 3,3′-biphenylbinaphthol led to the racemic product in a low yield.



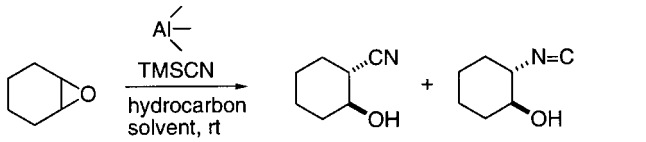
Scheme 6.64

Other asymmetric ene-reactions were also tested, but the ee was usually moderate [8].

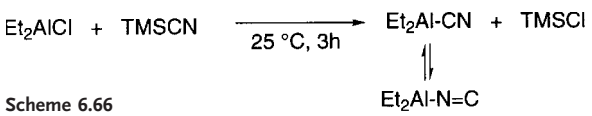
Hydrocyanation and Asymmetric Reaction

Catalytic hydrocyanation and closely related systems have found widespread application because of both their synthetic usefulness and the ready production of cyanohydrins, versatile synthetic intermediates in the synthesis of a variety of functional groups. Hydrocyanation with aluminum compounds also resulted in several

examples of interesting behavior worth mentioning. Epoxides are hydrocyanated in the presence of catalytic amounts of Et_2AlCl (Scheme 6.66) [89]. The reaction is believed to involve preformation of aluminum cyanide, which is effected more readily at higher temperatures (i.e. r.t.), with a concomitant exchange equilibrium with the corresponding isocyanate (Scheme 6.65).

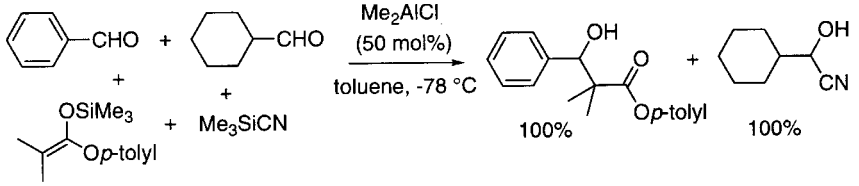


Scheme 6.65



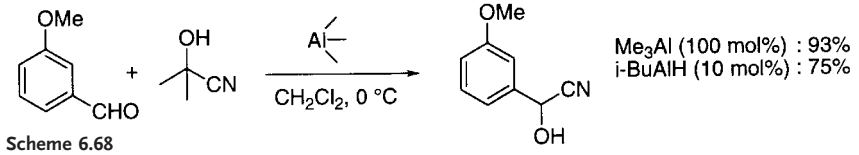
Scheme 6.66

In contrast, a similar reaction with aldehydes at lower temperatures (–78 °C) might not involve such a preformation of the aluminum cyanide [90]. The reaction had a strong preference for aromatic aldehydes over aliphatic aldehydes in the presence of Me_2AlCl (Scheme 6.67).



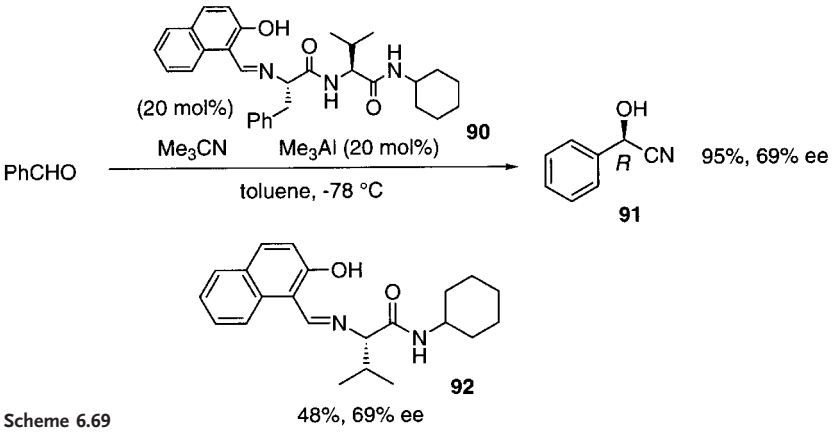
Scheme 6.67

Meerwein-Ponndorf-Verley-type hydrocyanation was explored in the presence of catalytic amounts of DIBAL (Scheme 6.68) [91]. The retro-hydrocyanation reaction proceeded from acetone-cyanation products, with concomitant cyanation of aldehyde under equilibrium conditions.



Scheme 6.68

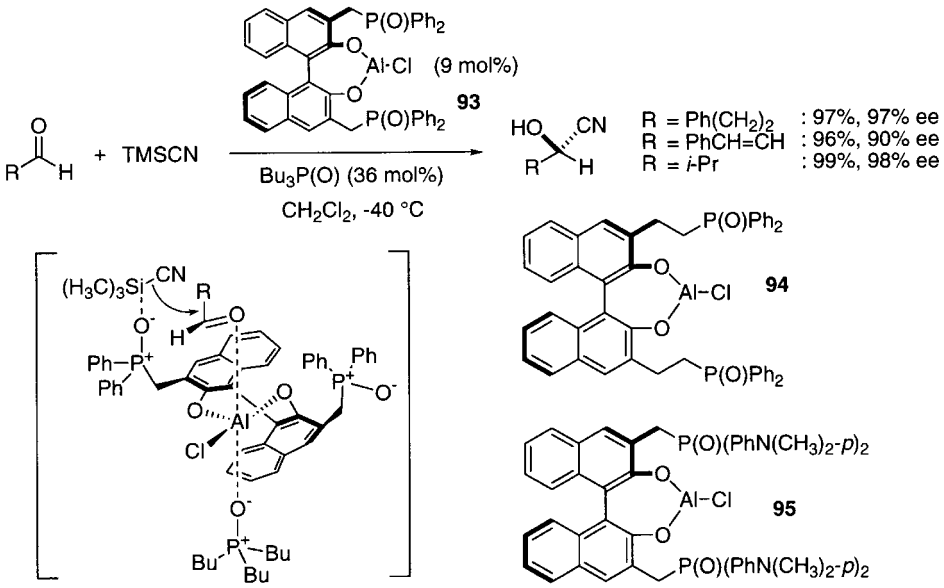
Asymmetric Hydrocyanation Several different catalysts have been investigated, including enzymes, polymeric reagents, organometallic species, and artificial peptides. Among these, peptide-derived metal and non-metal catalysts are the most attractive, because of the commercial availability of a variety of *α*-amino acids suitable for creation of molecular libraries. With this in view, Mori and coworkers synthesized a range of peptide-derived chiral Schiff bases which worked as effective ligands on aluminum for the predictable creation of an effective chiral environment (Scheme 6.69) [92]. The aluminum complexes of peptides are not good catalysts for asymmetric addition of HCN but are rather good for addition of Me_3SiCN. Hydrocyanation with Me_3Al-**90** or -**92** (20 mol%) proceeded at –78 °C to give **91** in 95% yield with 69% ee.



Scheme 6.69

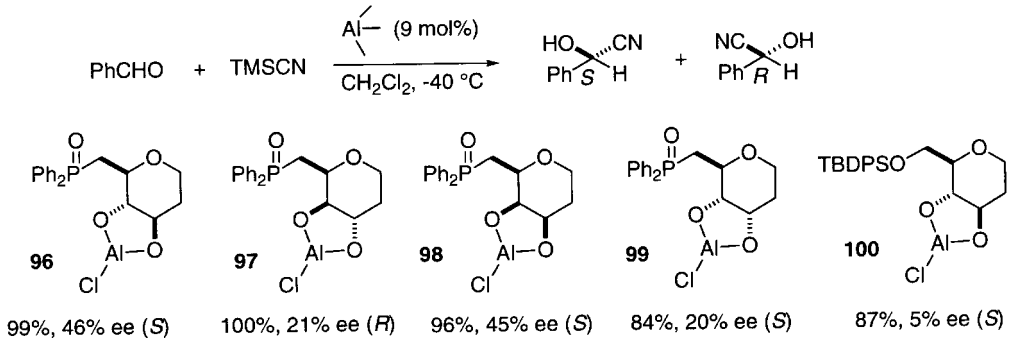
Non-peptide-based chiral ligands were recently exploited by Shibasaki and coworkers [93]. The first were derived from chiral 1,1′-binaphth-2,2′-ol with two phosphine oxides at 3- and 3′-positions. Aluminum complex **93** enabled dual activation of the functionalities of both aldehyde carbonyls and cyanating agents. In all respects catalyst **93** exceeded catalyst Me_3Al-**90** and -**92** in catalytic efficiency, enantioselectivity, and substrate generality. Addition of Bu_3PO had a beneficial effect on ee which could be ascribed to coordination to aluminum which makes the aluminum complex five-coordinate and in a preferential conformation to induce high ee (Scheme 6.70). In the absence of Bu_3PO, the ee decreased significantly. In contrast, an analogous catalyst **94** promoted reaction very slowly whereas catalyst **95** resulted in a 1.2-fold higher rate of reaction. Molecular modeling revealed that with **93** the internal coordination of P=O to aluminum seemed quite stable and without strain; this might have considerably reduced the activity of aluminum.

The second generation catalysts utilizing the "dual" activating system made an effective ligand from chiral pools other than *α*-amino acids [94]. The dual functions of **96–100** compared very well with those of **93** with the exception that the chiral ligand was derived from a carbohydrate and thus the catalyst had alkoxide,



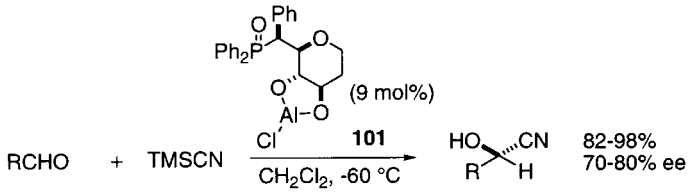
Scheme 6.70

rather than phenoxide, links (Scheme 6.71). Another advantage in making use of carbohydrate ligands is the easy access to any subtle change in ligand structure. Five different carbohydrates have been examined to identify the positive and negative effects of a chiral environment, composed of three stereogenic centers and steric bulk, on enantioselectivity. With this information available, new aluminum catalyst **101** had a superb effect on ee (Scheme 6.72).

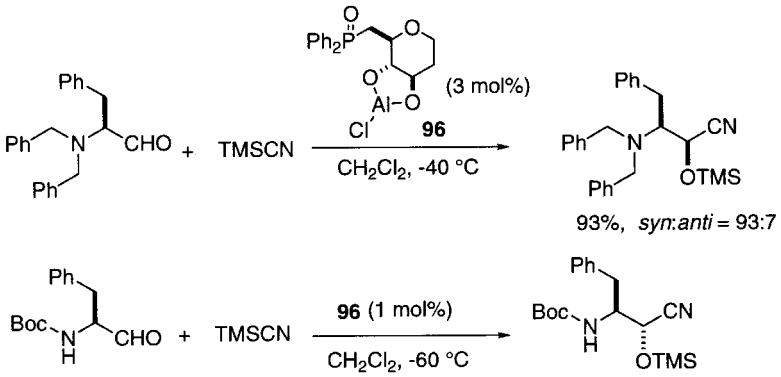


Scheme 6.71

Double stereo-differentiation was also tested using catalyst **96** and chiral *α*-amino aldehydes (Scheme 6.73) [95]. Both *anti* and *syn* isomers for the synthesis of HIV protease and bestatin were obtained, depending on the type of protecting



Scheme 6.72

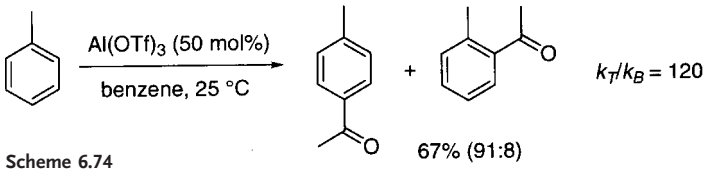


Scheme 6.73

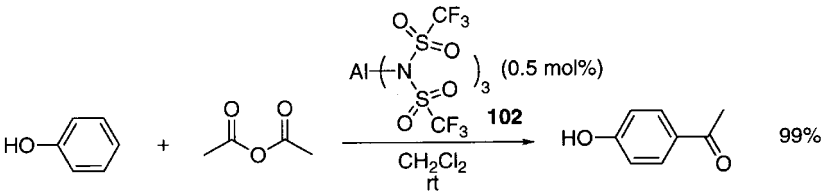
group on the nitrogen. A chelation effect of aluminum adopting five-coordinate geometry was invoked to account for these differences in selectivity.

Friedel-Crafts Reaction

In older applications of aluminum species in the Friedel-Crafts reaction AlX_3 (X = Cl, Br, I) have been used as catalysts [6]. Effects of covalently-attached strongly electron-withdrawing groups on the reactivity of aluminum(III) were investigated. The tris(triflate) catalyst $Al(OTf)_3$ was originally devised by Olah and coworkers (Scheme 6.74) [96]. As expected, tris(trifryl)imide catalyst **102** had more pronounced catalytic efficiency, because of its greater Lewis acidity (Scheme 6.75) [97].

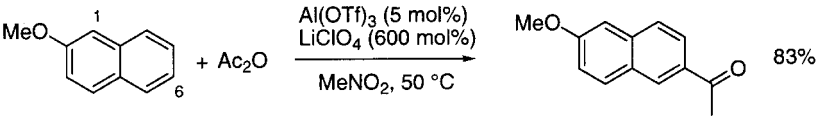


Scheme 6.74



Scheme 6.75

The salt effects of alkali metal salts on reactivity and selectivity in acylation reactions were systematically studied by Kobayashi and coworkers [98]. In the presence of excess $LiClO_4$ the Friedel-Crafts reaction proceeded most effectively with a catalytic amount of $Al(OTf)_3$ to give acylation regioselectively at the 6 position of the naphthalene ring (Scheme 6.76).



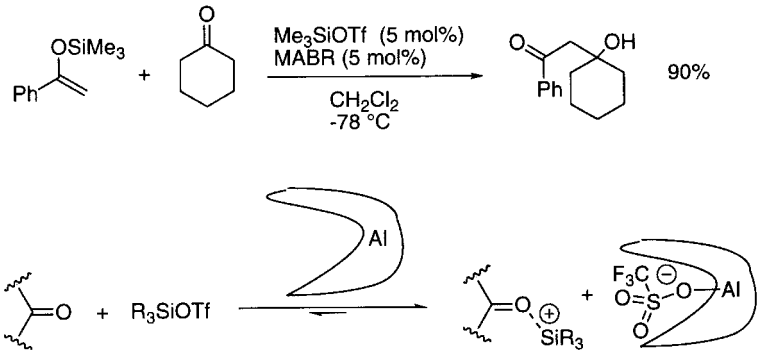
Scheme 6.76

The asymmetric Friedel-Crafts reaction was also studied, but the ee was usually low [8].

Aldol Reaction and Asymmetric Reaction

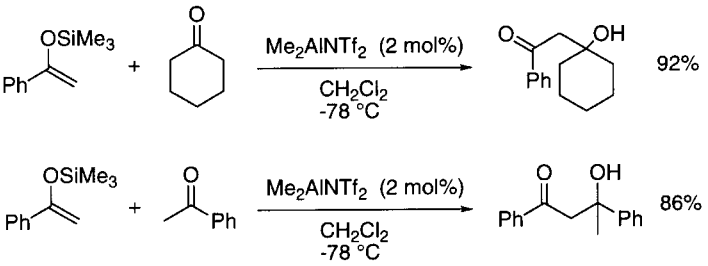
The Mukaiyama aldol reaction that utilizes silyl vinyl ethers is promoted by a Lewis acid [99]. Among the most important aspects chemists must always consider is, however, whether the reaction is promoted by the Lewis acid or an in situ-generated silyl cationic species. The involvement of silyl cations makes the reaction go out of control, usually leading to low selectivity. Although the silyl cations are believed to be the strongest Lewis acids, occasionally the reactivity of aluminum Lewis acids exceeds that of silyl cations and this rectifies otherwise disabled organic transformations. This section mainly focuses on such intriguing aspects of aluminum reagents.

The "nakedness" of silyl cations mainly relied on the use of donor solvents and π-electron donors, whereas the reactivity of silyl cations was increased by creating more naked species by use of bulky aluminum reagents (Scheme 6.77) [100]. Silyl triflates are strong Lewis acids and involved in exchange equilibria corresponding to complexation–decomplexation with carbonyls, in which the exchange rate is very rapid and is mostly shifted to the decomplexation side. This new approach facilitated the shifting of equilibria to the complexation side. Thus, tight complexation of a silyl cation with a carbonyl in a 1:1 ratio was spectroscopically observable, leading to a clean system with highly active silyl cations that enabled the ketone aldol reaction.

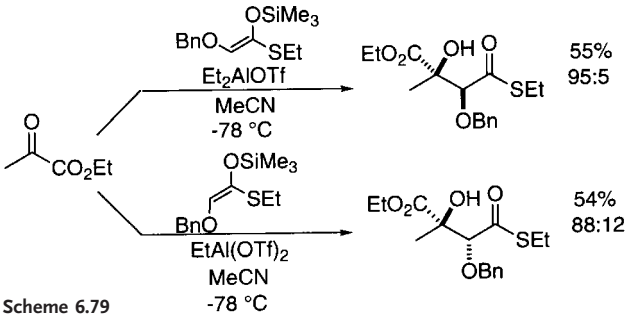


Scheme 6.77

The aldol reaction of ketones proceeded similarly with catalysts R_2AlNTf_2 (Scheme 6.78) or $R_nAl(OTf)_{3-n}$ ($n=1$, 2) (Scheme 6.79), which is otherwise difficult to achieve with a single use of an ordinary Lewis acid [101, 102].



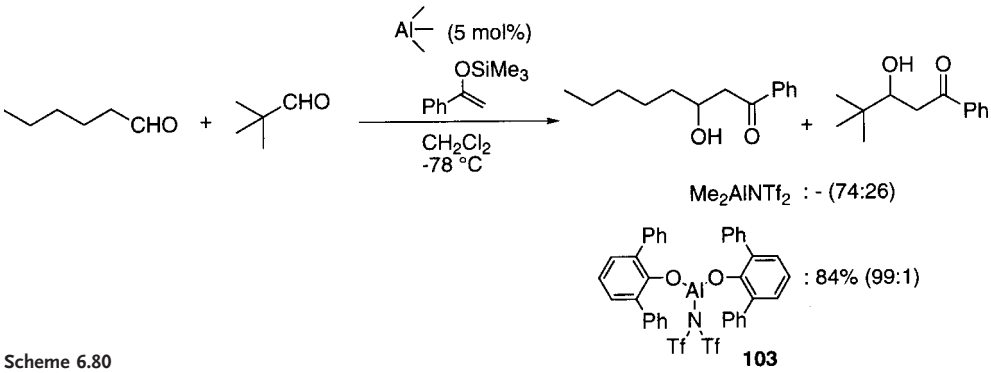
Scheme 6.78



Scheme 6.79

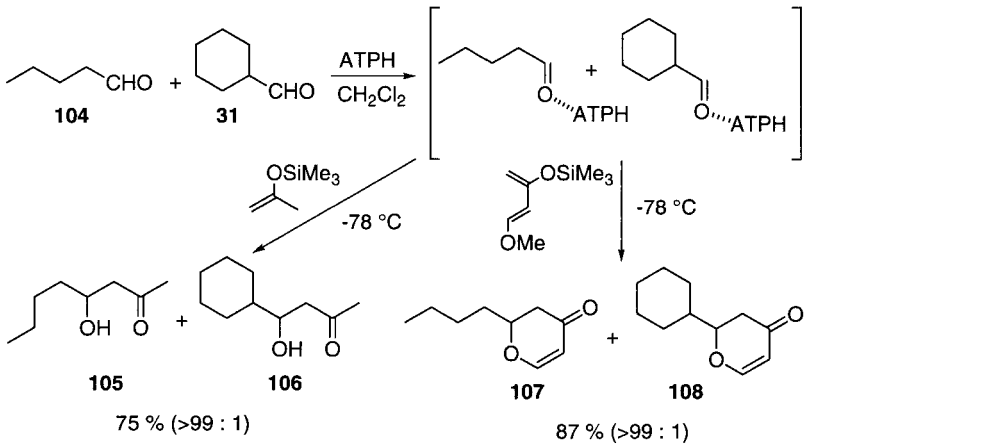
Apart from the remarkable ability of R_2AlNTf_2 to catalyze the ketone aldol reaction with unprecedented efficiency and versatility, more subtle aspects of this aluminum-derived species were observed, enabling design of a suitable catalyst that would recognize and activate a less-shielded carbonyl functionality which would

then undergo a chemoselective aldol reaction (Scheme 6.80) [103]. Sterically more crowded **103** turned out to be an effective and efficient catalyst for this purpose.



Scheme 6.80

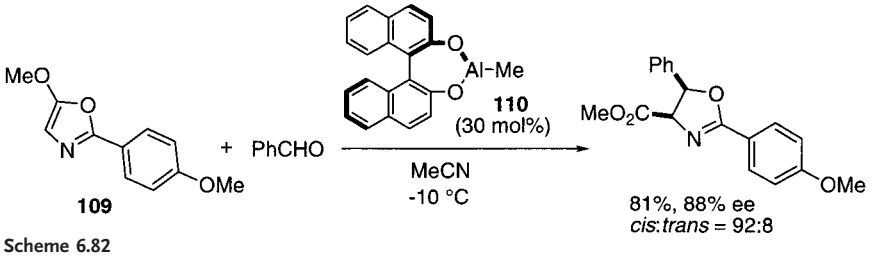
A molecular recognition approach was used to enable a similar chemoselective aldol reaction [104]. ATPH can discriminate between structurally similar aldehydes, thereby facilitating the selective functionalization of the less hindered aldehyde carbonyl (Scheme 6.81). Treatment of an equimolar mixture of valeraldehyde (**104**) and cyclohexane-carboxaldehyde (**31**) with 1.1 equiv. ATPH in CH_2Cl_2 at –78 °C, followed by addition of Danishefsky's diene at this temperature gave hetero-Diels-Alder adducts **107** and **108** in a ratio of >99:1. It should be noted that the complexed aldehyde could only react with the diene. The reaction resulted in relatively low chemoselectivity when other typical Lewis acids were used (**107**/**106** ratios: $(Pr^iO)_2TiCl_2$=6.2:1; Me_3Al=5:1; MAD=3.7:1; $TiCl_4$=2:1; $BF_3 \cdot OEt_2$=1.3:1; MAPH=1:3.4). This emphasizes that the cavity of ATPH plays



Scheme 6.81

an important role in differentiating between the reactivities of the two different aldehydes. In a similar manner the aldol reaction of a mixture of **104** and **31** was effected equally well with ATPH to furnish 4-hydroxy-2-octanone **105** without **106**.

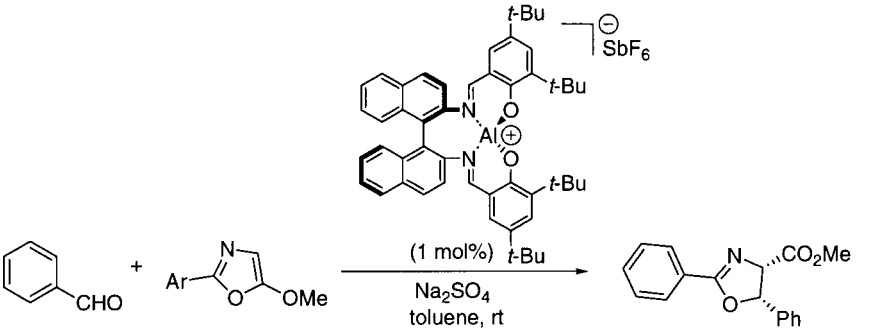
Asymmetric Aldol Reaction Although several examples showed that reaction rates with aluminum reagents exceed those with silyl cations, direct reflection on this basis to the corresponding asymmetric reaction remains challenging [8]. Apart from the Mukaiyama aldol reaction, an alternative reaction candidate was oxazole **109** in the asymmetric aldol reaction, giving *β*-hydroxy-*α*-amino acids (Scheme 6.82). Suga and coworkers showed in their original papers that the reaction of **109** with a series of aromatic aldehydes was best performed using 30 mol% catalyst **110** at –10 °C to r.t.; this gave an ee ranging from 74% to 90% [105]. Moderate to high diastereoselectivities and yields were obtained.



Scheme 6.82

Evans and coworkers recently expanded the scope of this reaction by using chiral aluminum-(salen) cations which were either penta- or hexacoordinated (Scheme 6.83) [13]. The results are intriguing in several ways.

- The aluminum catalyst loading was reduced to no less than 1 mol%.
- The enantioselectivity and product yield were consistently as high as 99% and the diastereoselectivity (*cis*:*trans*) was also as high as 99% de.



Scheme 6.83

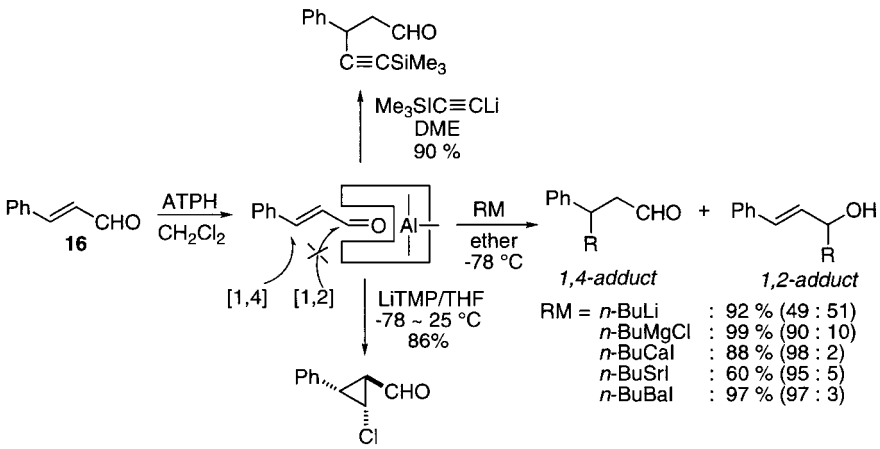
- This system expanded the substrate scope with respect to aromatic aldehyde components.
- The X-ray single crystal structures of two discrete aluminum-(salen) catalysts were established as mentioned in Section 6.1.

The effectiveness of the dihydrate aluminum complex suggested that strict reaction conditions including use of extremely dry solvents are not required, although 3-Å molecular sieves or other popular dehydrating agents should be used.

Conjugate Addition and Asymmetric Reactions

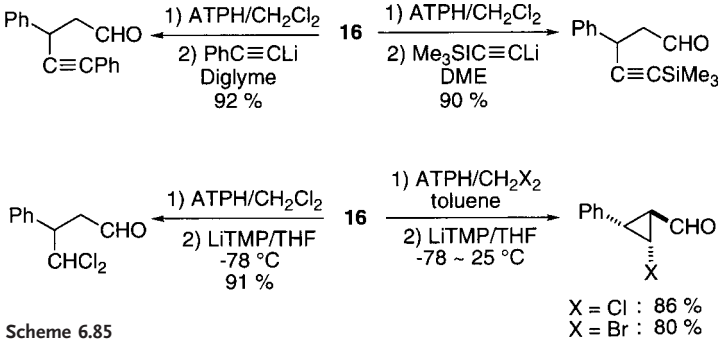
As described in Section 6.2.1.1, earlier application of conjugate addition involved transferable aluminum hydrides and alkyls. This section is devoted to asymmetric conjugate addition using a chiral aluminum catalyst and newer aspects that enable substrate generality with respect to both Michael acceptor and donor components, by use of well-designed aluminum reagents.

Organocuprates are the most widely used reagents for Michael addition to *α,β*-unsaturated ketones, and for one of the most powerful and important carbon–carbon bond-forming reactions. In contrast, ATPH can be used as a carbonyl protector on complexation, which facilitates 1,4-addition even to *α,β*-unsaturated aldehydes for which 1,4-addition is virtually unexplored (Scheme 6.84) [106]. Complexation of cinnamaldehyde (**16**) with 1.1 equiv. ATPH in CH_2Cl_2 at –78 °C, followed by subsequent addition of 1.5 equiv. *n*-butylmagnesium bromide (*n*-BuMgBr), gave the 1,4-addition product preferentially. Alkylation of **16** with MAD and *n*-BuMgBr gave unsatisfactory results (95%; 1,4/1,2-adduct ratio = 7 : 93). The combination of MAPH with the same butylating agent gave an equal mixture of 1,4- and 1,2-adducts (98%; ratio = 49 : 51). Replacing organomagnesium reagents with organocalcium, strontium, and barium enhanced 1,4-selectivity. Allylcerium reagents were found to be particularly applicable to 1,4-addition [107].



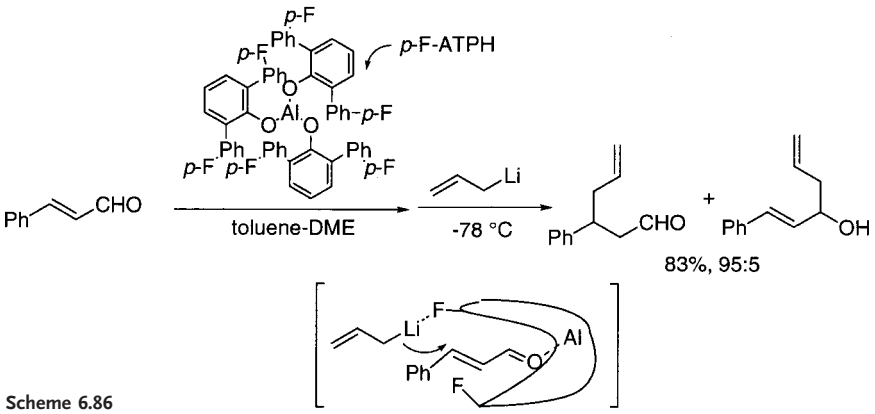
Scheme 6.84 Conjugate addition to the cinnamaldehyde complex

One advantage of this method over organocopper-mediated conjugate addition is the availability of lithium alkynides and thermally unstable lithium carbenoids as Michael donors (Scheme 6.85). With alkynides, raising the reaction temperature after the Michael addition afforded cyclopropanation to give a single diastereomer.



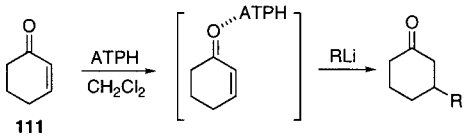
Scheme 6.85

Despite the usefulness of this reaction, several alkyllithiums failed to react in a 1,4-manner. For example, MeLi and allyllithiums are prone to 1,2-addition. Ooi and Maruoka addressed some of these problems by using ATPH analogs bearing fluorine directing groups [108]. The *p*-F-ATPH–allyllithium system was superior to the ATPH–allyllithium system in terms of 1,4-selectivity (Scheme 6.86). This selectivity enhancement was ascribed to the directing nature of the fluorine atoms, which enables chelation of allyllithium reagents, approximating to the *β*-carbons.



Scheme 6.86

Application of this system to *α,β*-unsaturated ketones resulted in even more general and pronounced 1,4-selectivity (>99 : 1) [109]. In this reaction a variety of alkyllithiums can be used as Michael donors, and this ATPH/RLi system enables

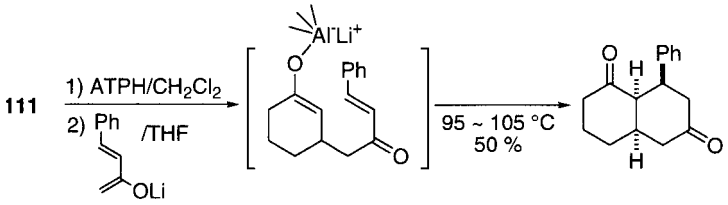


RLi = MeLi (83 %), PhLi (86 %), PhC≡CLi (99%), Cl_3CLi (60 %), CF_3CF_2Li (75 %)

Scheme 6.87

the introduction of perfluoroalkyl or perfluoroaryl substituents at the β positions of carbonyl functions (Scheme 6.87) [110].

Several ketone lithium enolates and dianions of β-dicarbonyl substrates similarly undergo highly selective 1,4-addition to a variety of α-enones. Thus, tandem inter- and intramolecular Michael addition using the enolates of α,β-unsaturated ketones as Michael donors was achieved successfully (Scheme 6.88) [111]; treatment of **111**-ATPH complex in toluene with a THF solution of the benzalacetone lithium enolate at –78 °C, then heating under reflux for 13 h gave the stereochemically homogeneous annulation product in 50% yield almost exclusively.

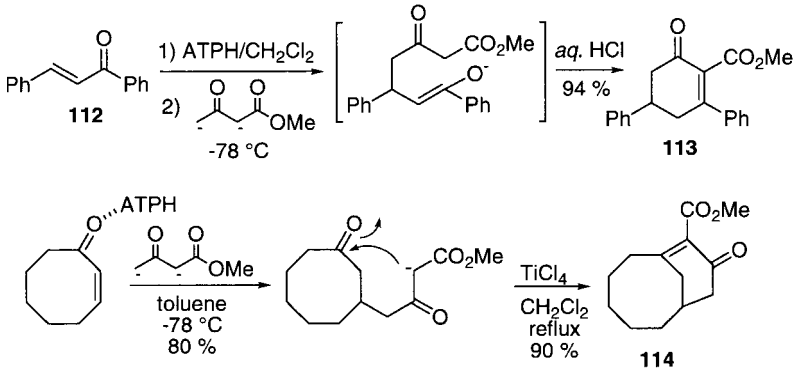


Scheme 6.88

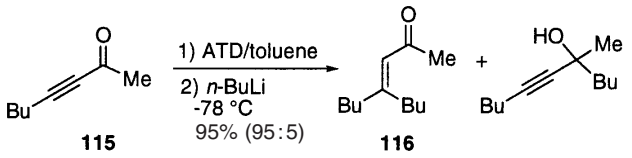
Michael addition of the dianions derived from β-dicarbonyl compounds facilitated yet another annulation – Michael addition of a dianion then intramolecular aldol condensation (Scheme 6.89) [112]. Complexation of ATPH with *trans*-chalcone (**112**) in CH_2Cl_2 at –78 °C, followed by treatment with the dianion of methyl acetoacetate gave, after quenching with aqueous HCl, bicyclic product **113** in a nearly quantitative yield. This system can be used for elaboration of the bicyclo [3,5,1]undecane ring system in **114**, as can be found in the backbones of terpenoids and the taxol family.

Exceedingly bulky aluminum reagent aluminum tris(2,6-di-*tert*-butyl-4-methylphenoxide) (ATD) [113] was superior to ATPH or MAD as a carbonyl protector in ynones [114]. Initial complexation of 3-octyn-2-one (**115**) in toluene with ATD and subsequent addition of a hexane solution of *n*-BuLi at –78 °C generated 1,4-adduct **116** in 92% yield with a small amount of the 1,2-adduct (Scheme 6.90).

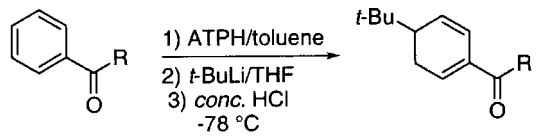
Selective 1,6-addition of alkyllithiums to aromatic carbonyl substrates such as benzaldehyde or acetophenone was achieved with ATPH to give cyclohexadienyl compounds **24** and **28**, respectively (Scheme 6.91) [115]. It is obvious from the



Scheme 6.89



Scheme 6.90

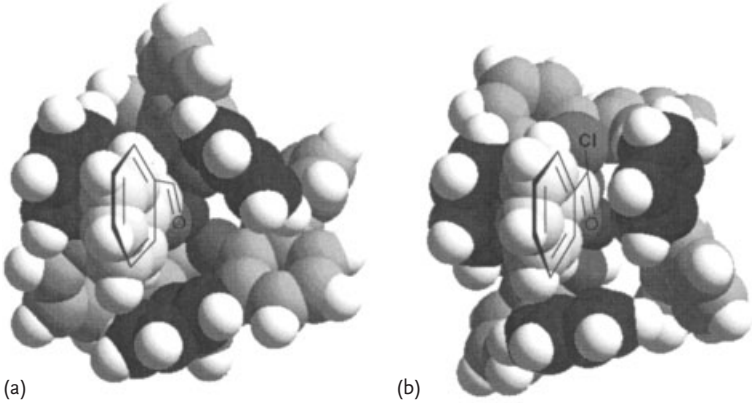


24 : R = H : 81 %
28 : = Me : 93 %

Scheme 6.91

molecular structure of the benzaldehyde–ATPH complex (Fig. 6.19) that the *para* position of benzaldehyde is deshielded by the three arene rings; this effectively blocks the *ortho* position and the carbonyl carbon from nucleophilic attack.

Unfortunately, however, conjugate addition to the ATPH–PhCHO complex did not proceed effectively with smaller nucleophiles, including MeLi and lithium acetates. In contrast, the ATPH–PhCOCl complex undergoes conjugate addition with MeLi to give 1,6- and 1,4-adducts in a ratio of 2.6:1 in 99% yield (Scheme 6.92) [116]. Further studies indicated that ATPH–PhCOCl was superior to ATPH–PhCHO in terms of substrate generality with regard to nucleophiles that add in a 1,6-manner (Scheme 6.93). Insight regarding the change in product distribution for the two types of complex was derived from X-ray single crystal structures (Fig. 6.19) and competitive binding experiments. The X-ray crystal structure of ATPH-PhCHO shows one face of the extended π-system to be relatively exposed, at least in the region distal to the carbonyl group. In contrast, for ATPH-PhCOCl it was revealed that two of the phenyl rings of ATPH and flat PhCOCl



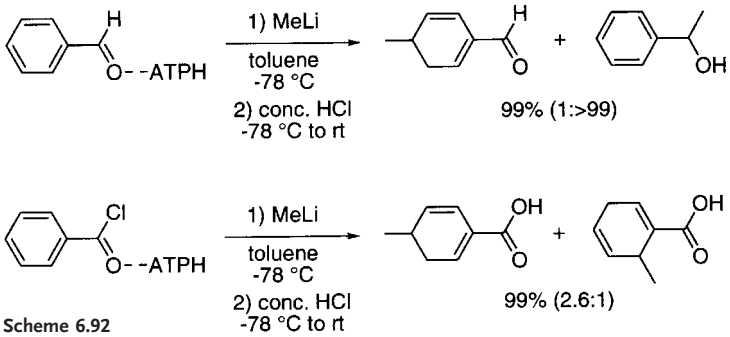
(a) (b)

Fig. 6.19 X-ray crystal structures (space-filling model) of the complexes ATPH-PhCHO (a) and ATPH-PhCOCl (b)

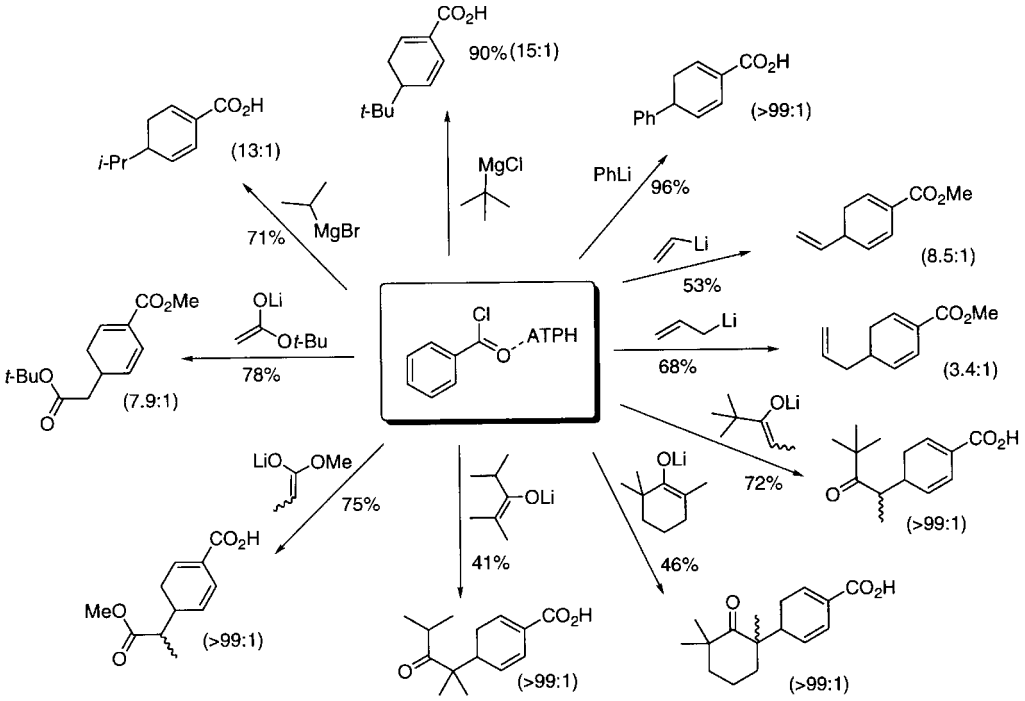
form a sandwich structure rendering the C=O highly congested. π-Stacking between two π-donors (ATPH phenyls) and one π-acceptor (complexed PhCOCl) involving the C=O carbon might act as a "molecular tweezer" to stabilize the ATPH–PhCOCl complex. A ^{13}C NMR (CD_2Cl_2, –78 °C to r.t.) competition experiment using a 1:1:1 mixture of ATPH, PhCHO, and PhCOCl showed that PhCOCl contributes to complex stabilization >14 kJ mol^{-1} (at 298 K) less than does PhCHO. It should be emphasized that the relative destabilization, i.e. the higher reactivity of ATPH–PhCOCl compared with ATPH–PhCHO, might be compensated for to some extent by the formation of the "molecular tweezer".

Efficient conjugate reduction of several *α,β*-unsaturated carbonyl substrates was similarly realized by the combined use of ATPH and diisobutylaluminum hydride-*n*-butyllithium "ate" complex (DIBAL-*n*-BuLi) as a reducing agent (Scheme 6.94) [117]. Diisobutylaluminum hydride-*tert*-butyllithium (DIBAL-*t*-BuLi) was more effective for the 1,4-reduction of *α,β*-unsaturated aldehydes.

Although MAD was proven to be inferior to ATPH for a range of conjugate additions [118], we can still find several outstanding examples that demonstrate the

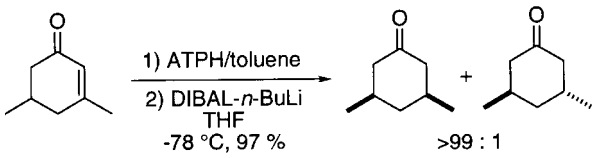


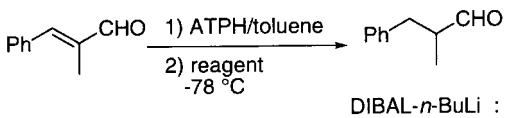
Scheme 6.92



The values in parentheses are the ratios of 1,6- and 1,4-adducts

Scheme 6.93



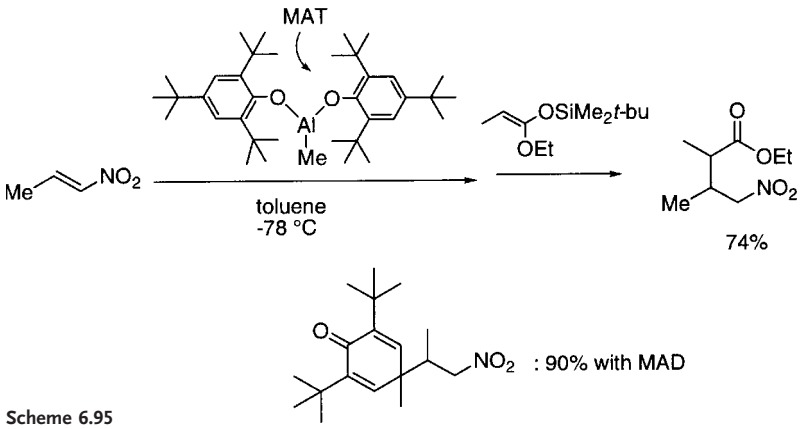


DIBAL-*n*-BuLi : 80 %
DIBAL-*t*-BuLi : 94 %

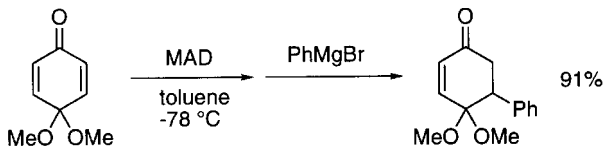
Scheme 6.94

effectiveness of MAD and its derivatives. Good to excellent results were obtained by use of MAT in the alkylation of ketene silyl acetals with nitroolefins (Scheme 6.95). The successful use of nitroethylene in this reaction is a significant extension of the utility of this relatively unused "$^{+}CH_2CH_2NH_2$" synthon [119].

Complexation of quinone monoketals and quinol ethers with MAD, followed by addition of organolithium or Grignard reagents gives products from 1,4-addition (Scheme 6.96) [120]. The success of these 1,4-additions is in marked contrast to re-



Scheme 6.95



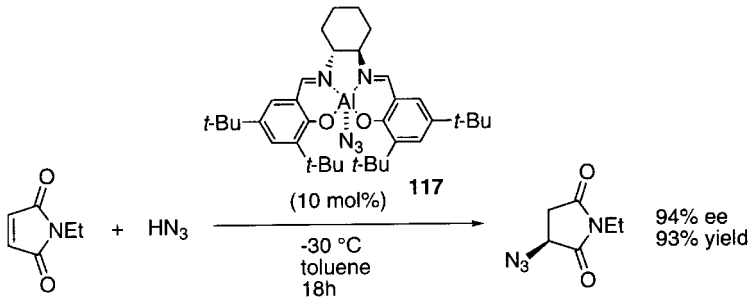
Scheme 6.96

ported MAD-mediated additions of alkyllithium reagents to cyclohexenone, which afford 1,2-addition products.

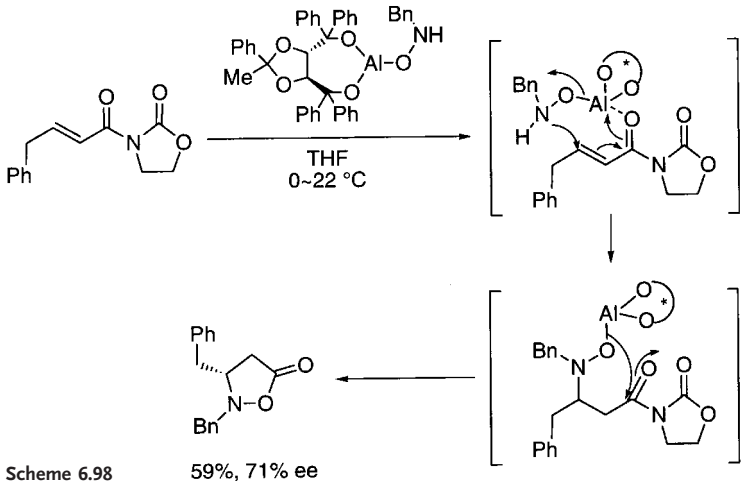
Asymmetric Conjugate Addition Interest in synthetic routes to β-amino acids can be traced to the presence of these building blocks in a variety of biologically interesting natural products. Excellent reactivity and enantioselectivity were observed in the conjugate addition of HN_3 to *N*-alkylmaleimides, in the presence of **117**, to give β-azide maleinimides (Scheme 6.97) [121]. Although the activity of aluminum complex **117** after prolonged storage was irreproducible, it could be generated conveniently in situ in two ways, either by treatment of the salen ligand with diethylaluminum azide or by using the shelf-stable (salen)Al(III)-Me complex as precatalyst.

An alternative approach to 1,4-addition affording β-amino acid derivatives, by use of Lewis acid-hydroxyamine hybrid reagents (LHHR), was also investigated [122]. LHHR were ten times more reactive than benzylhydroxyamine itself. This reagent-controlled asymmetric 1,4-addition using aluminum–hydroxyamine complexes resulted in moderate enantioselectivity (43–71% ee) (Scheme 6.98).

Shibasaki and coworkers reported the first example of a catalytic asymmetric 1,4-addition of a Horner-Wadsworth-Emmons reagent to enones (Scheme 6.99) [123]. The reaction used heterobimetallic catalyst **118** and proceeded in the presence of bases NaO*t*-Bu or BuLi to give high yields with extremely high ee. Without these bases no reaction was observed. Thus the actual structure having high catalytic ac-



Scheme 6.97

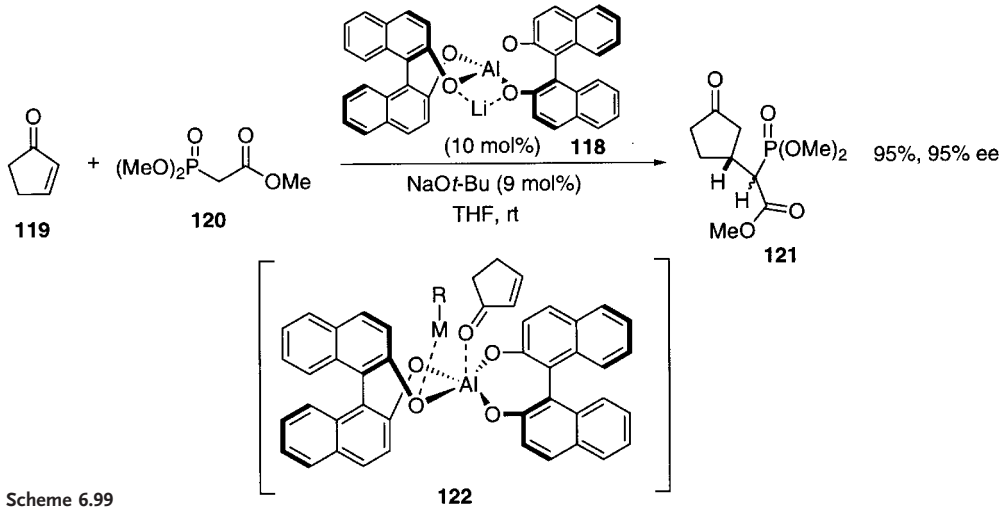


Scheme 6.98

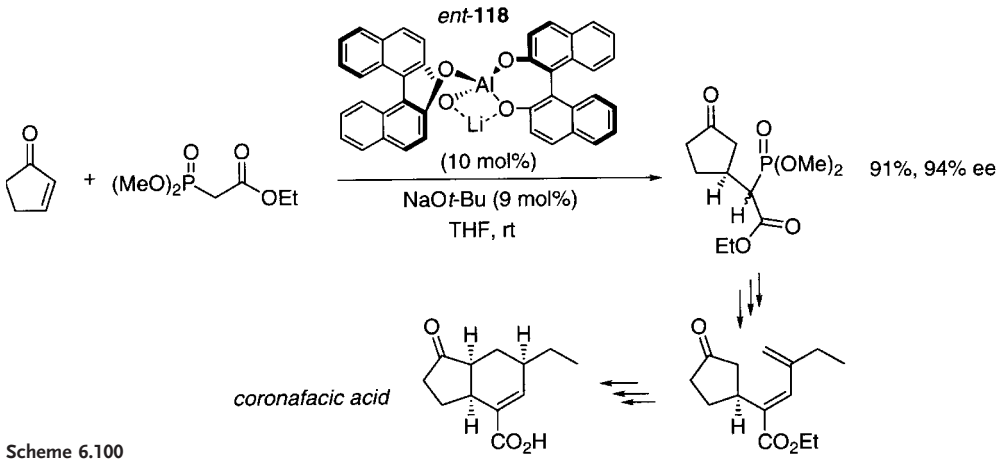
tivity was an attractive issue to address. Treatment of AlLibis(binaphthoxide)complex (ALB) **118** with organolithium reagents MeLi or BuLi resulted in a hexacoordinate compound consistent with the structure of **82**. The reaction of **119** with **120** was sluggish, however, and needed more drastic conditions, giving **121** in 28% yield with 57% ee. Another pentacoordinate structure (**118**-dimer) was also obtained from screening conditions for growing crystals and this seemed to enable for smooth reaction with high ee. The transition structure of **122** was proposed on the basis of these experiments and crystal structure analyses.

This astonishing behavior of ALB was also very useful for the efficient synthesis of the natural products coronafacic acid (Scheme 6.100) [123], tubifolidine (Scheme 6.101) [124], and 11-deoxy-$PGF_{1\alpha}$ (Scheme 6.102) [125].

Feringa and coworkers extended Shibasaki's "heterobimetallic"-based procedure by using ALB for the asymmetric conjugate addition of α-nitroesters to α,β-unsaturated ketones (Scheme 6.103) [126]. The main stereochemical issue was the configuration of the Michael adduct with the donor components, rather than the ac-



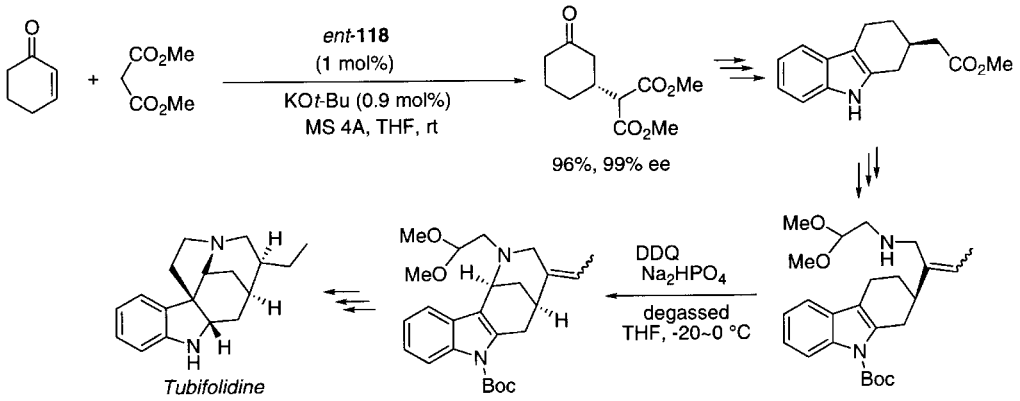
Scheme 6.99



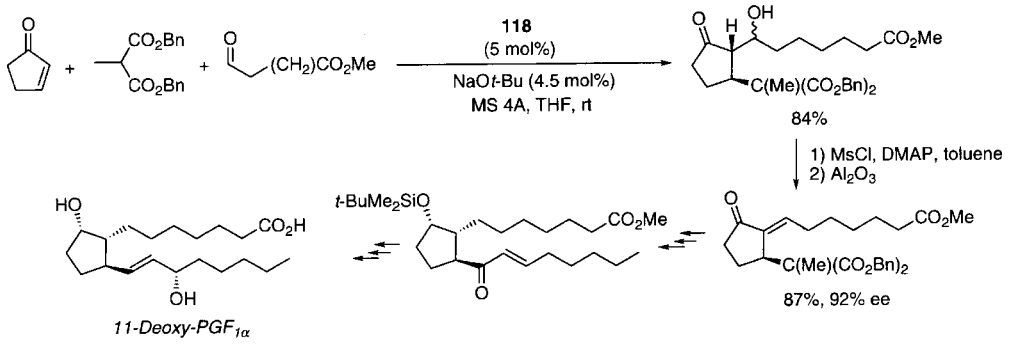
Scheme 6.100

ceptors. The enantioselectivity of the conjugate addition proved to be extremely temperature-dependent – for adduct **123** ee was 7% when the reaction was performed at r.t. whereas 72% ee of the opposite enantiomer of **123** was obtained when the 1,4-addition was performed at –23 °C. High dependence of ee on the solvent used was also observed; THF proved to be the best.

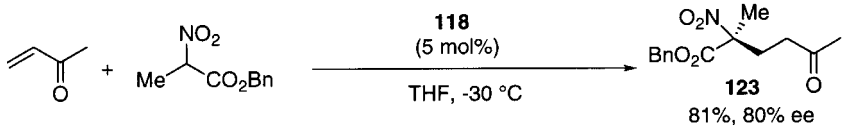
A C_2-symmetric chiral amino diol **124** has been used for conjugate addition of malonic esters and thiophenols to α,β-unsaturated compounds [127]. The heterobimetallic catalyst, generated by treatment of 2 equiv. **124** with $LiAlH_4$, was more reactive Shibasaki's ALB catalyst and led to high ee with malonic esters, whereas with thiophenols it gave low ee (32–45%).



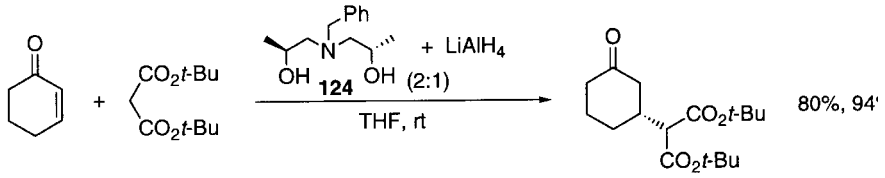
Scheme 6.101



Scheme 6.102



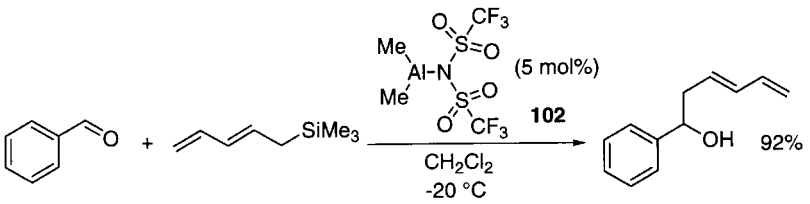
Scheme 6.103



Scheme 6.104

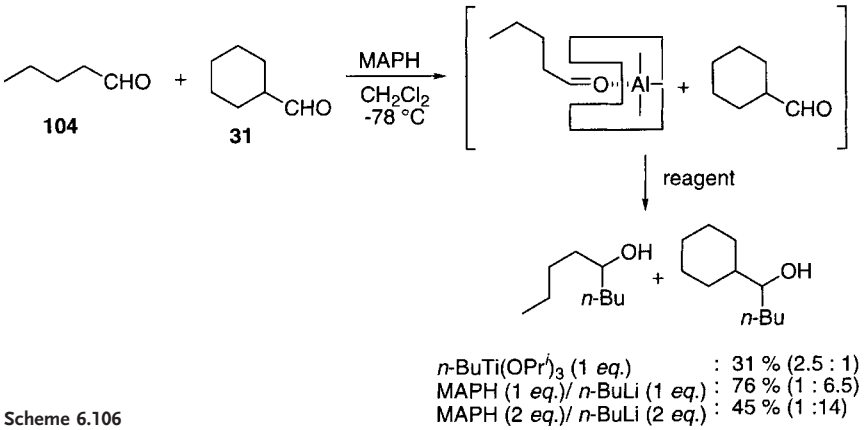
Carbonyl Addition using Other Nucleophiles

Carbonyl allylation is generally better promoted by allylstannanes than allylsilanes in the presence of a Lewis acid. Metal triflates are frequently employed as Lewis acids to promote allylation with allylstannanes though they are still limited in scope from economically and toxicologically. The use of a small amount of catalyst Me_2AlNTf_2 (5 mol%) enabled effective carbonyl allylation with a variety of allylsilanes (Scheme 6.105) [103]. With pentadienylsilanes the less hindered end of the carbon chain should form carbon–carbon bonds more favorably. The reaction is general in substrate scope in respect of both aldehyde and allylsilane components. Intramolecular allylation using allylsilanes and classical aluminum reagents are well summarized in a review by Fleming [128].



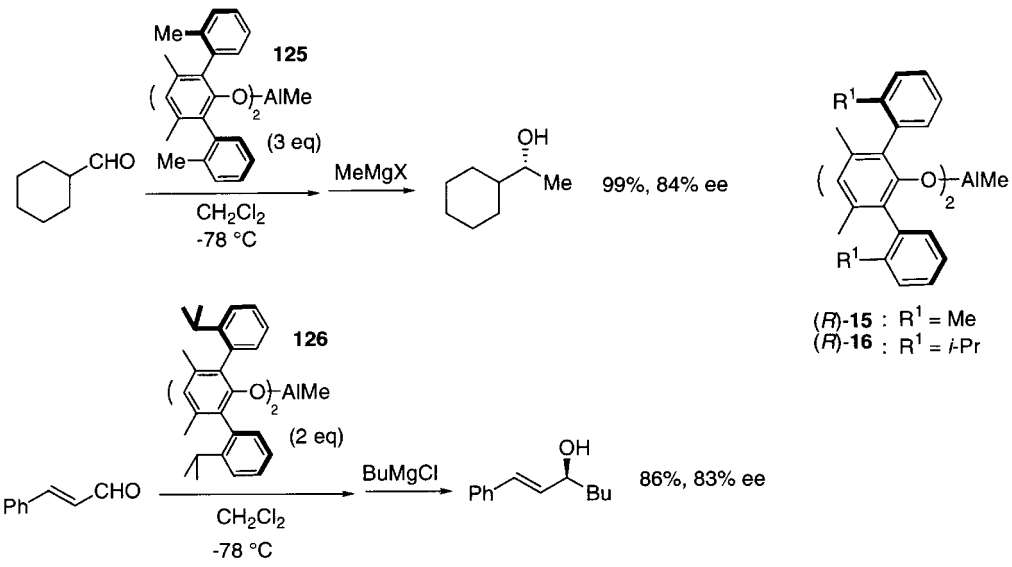
Scheme 6.105

Obviously, the coordinated aldehyde is electronically activated but sterically deactivated with bulky aluminum reagents. The selective functionalization of more sterically hindered aldehydes was accomplished by the combined use of MAPH and alkyllithiums (RLi, where R = *n*-Bu or Ph) [129]. In this system, MAPH acted as a carbonyl protector of a less hindered aldehyde such as **104**, and therefore the carboanions reacted preferentially with more hindered carbonyl groups (Scheme 6.106). It should be noted that alkyllithium reagents could react with aldehydes in the absence of the aluminum reagent.



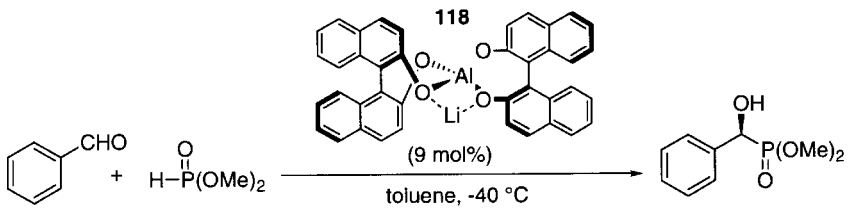
Scheme 6.106

Carbonyl addition by Grignard reagents is among the most fundamental operations for the construction of C–C bonds. An asymmetric version of this process was realized by use of the novel chiral aluminum bisphenoxide reagents **125** and **126** (Scheme 6.107) [130]. Because Grignard reagents alone sufficient capability to react with carbonyl carbons, strong complexation of the carbonyl groups with a chiral Lewis acid is the first indispensable requirement for inducing high ee. Decomplexed carbonyls induce no ee. Thus aluminum Lewis acids are the reagents of choice, because of their high oxygenophilicity, which also enables slow exchange between complexation and decomplexation. The high ee obtained is also indicative of negligible ligand exchange between aluminum and magnesium.



Scheme 6.107

Shibasaki's procedure found particular application in asymmetric carbonyl addition by use of dialkylphosphites (Scheme 6.108) [131]. Although the ee observed were rather moderate to good (55–90% ee), the α-hydroxy phosphonate structures



Scheme 6.108

thus obtained would be useful for the synthesis of renin, ESPS synthetase, and HIV protease inhibitors.

Reaction with C1 Unit: CO_2 and CO

Chemical fixation and subsequent reaction of volatile small molecules including CO_2, CO, and epoxides at an aluminum(III) center are especially useful, and take advantage of the high oxygenophilicity of aluminum. Tetraphenylporphyrin-Al ((TPP)Al) [132] and (salen)Al complexes [14] have special merit in this context. Unlike trialkylaluminum, an alkylaluminum porphyrin (e.g. (TPP)Al-Et) does not react with CO_2 under ambient conditions. In contrast, on irradiation with visible light in the presence of 1-methylimidazole (MeIm), an apically coordinating base, CO_2 was inserted into the Al-Et bond to form the corresponding aluminum carboxylate species (Fig. 6.20) [133]. On the basis of these findings Inoue and Aida further reported that the (TPP)Al-OMe complex produces a five-membered cyclic carbonate from carbon dioxide and epoxides as a result of the catalytic reaction only when MeIm coexists in the reaction system coordinates with the metal center of metalloporphyrin [134]. In the presence of MeIm no irradiation was needed [135] for (TPP)Al-OMe and the reaction proceeded under the standard pressure of

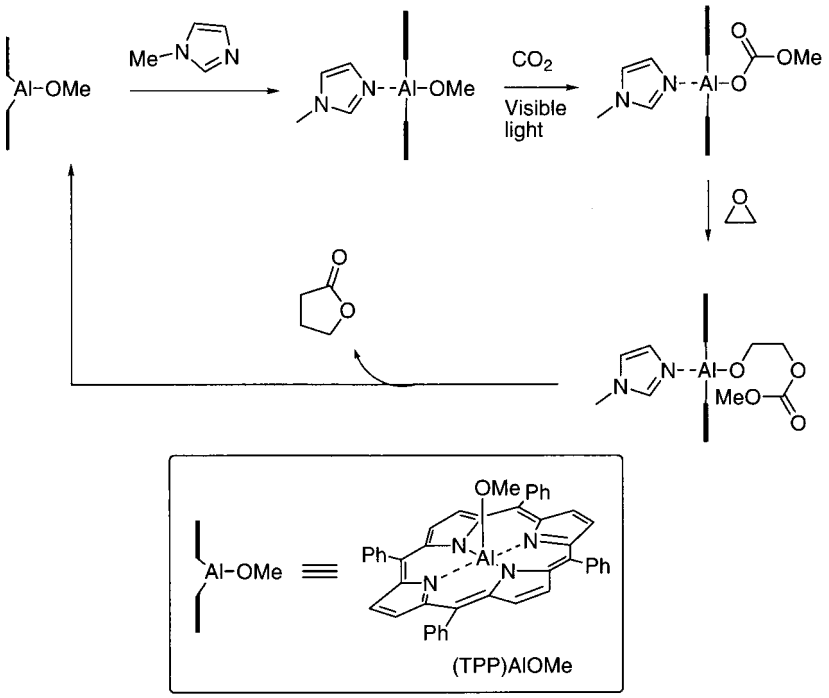


Fig. 6.20 Imidazole and light-induced reaction between CO_2 and epoxide

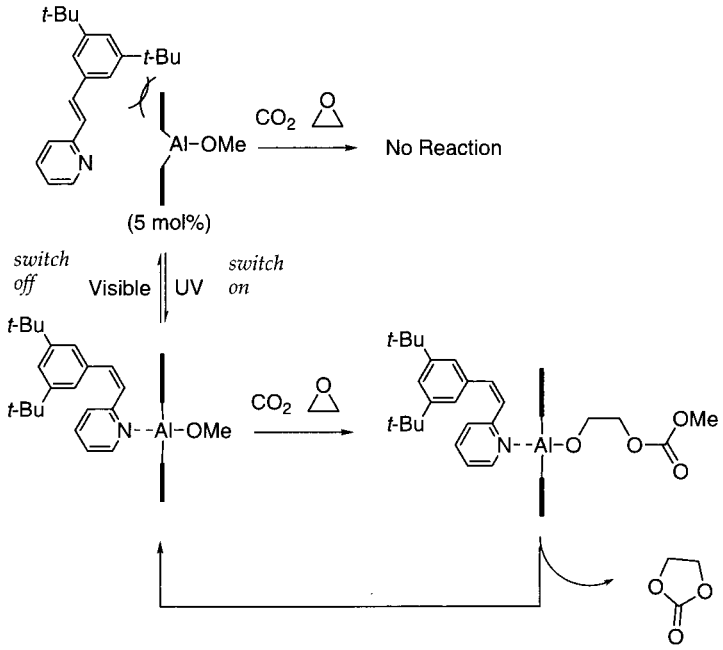
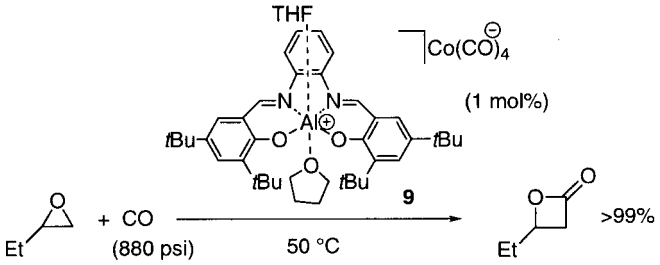


Fig. 6.21 Light-driven switching of the coordination and subsequent reaction

CO_2. It is worth noting that in the absence of MeIm polymerization of the epoxide occurred without the formation of the cyclic carbonate.

Photocontrol of chemical and physical functions could be used in this system (Fig. 6.21). Stilbazole, a compound related to natural photoresponsive molecules, was used as the photoresponsive switch [136]. Because stilbazole undergoes isomerization from the *trans* form to the *cis* form on UV irradiation, and the reverse in visible light, via complexation of the pyridine group to the metal center of metalloporphyrins, the (TPP)Al-OMe–stilbazole system on irradiation with UV light serves as an on-switch to speed up the reaction whereas in visible light the system worked as an off-switch to reduce the rate of the once accelerated reaction.

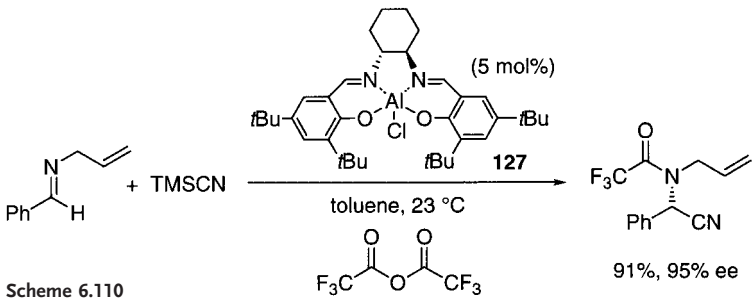
Discrete cationic aluminum complexes of $Co(CO)_4^-$ have unprecedented activity and selectivity for epoxide carbonylation (Scheme 6.109) [14]. Complex **9** carbonylated propylene oxide with 95% conversion in 1 h under a high pressure of CO. Because (+*R*)-*β*-butyrolactone is of particular interest for polymerization and other asymmetric transformations, (*R*)-propylene oxide was treated with CO and catalyst **9**. Propylene oxide was converted to (*R*)-*β*-butyrolactone with >98% retention of configuration.



Scheme 6.109

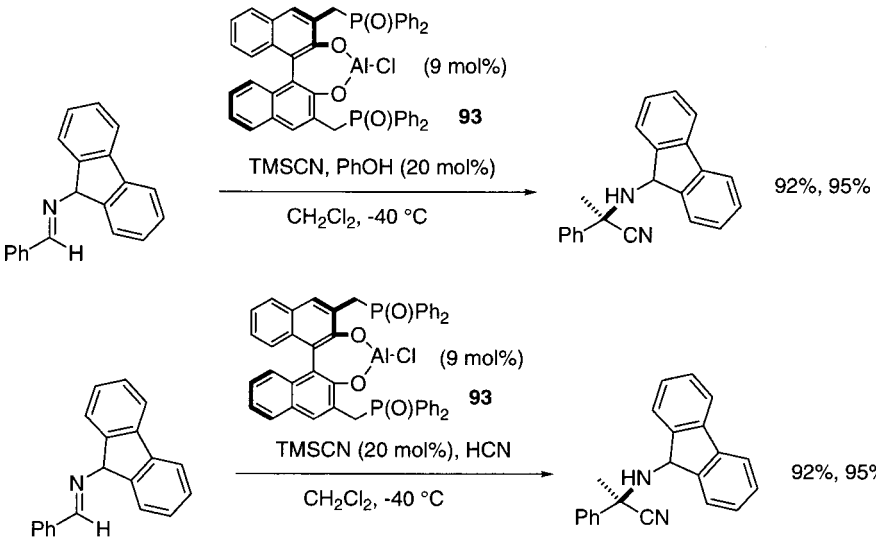
6.2.1.3 Strecker Reaction (Addition of CN^- to C=N Bonds)

The principal synthetic utility of the asymmetric Strecker reaction is that optically active α-amino acids are readily obtainable. Two outstanding examples of the asymmetric Strecker reaction with well-designed aluminum catalysts were recently reported. The first example involves those in which the chiral salen–Al-Cl catalyst **127** adopting penta- and/or hexacoordination with square-bipyramidal geometry was used for activation of aldimines (Scheme 6.110) [137]. Interestingly, no reaction occurred under strictly anhydrous conditions in the reaction catalyzed by **127**, suggesting that the reacting species is HCN rather than Me_3SiCN. It should be pointed out that the catalyst survives even in the presence of small amounts of H_2O, in complete contrast with typical trivalent neutral aluminum reagents which readily decompose on exposure to H_2O. The reaction proceeded at –70 °C with 5 mol% of the catalyst in toluene usually giving ee ranging from 80–95%.



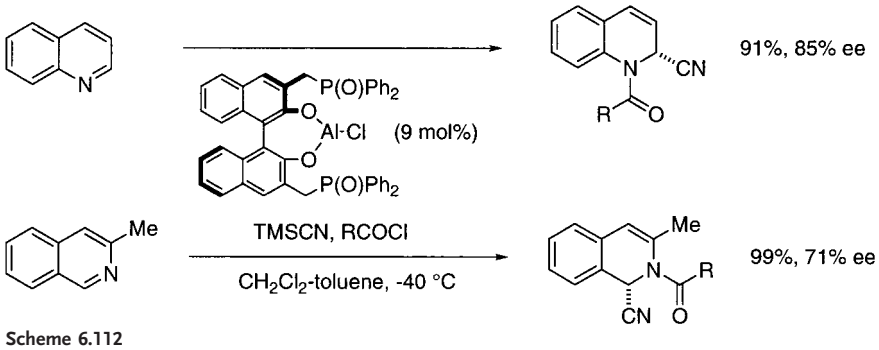
Scheme 6.110

A later example involves the use of a novel aluminum catalyst which is thought to adopt pentacoordinate geometry in the requisite transition structure (Scheme 6.111) [138]. Whatever the detail, one function of the phosphite group seems to be direction of Me_3SiCN addition – when the Me_3Si group was tethered to the P=O group the reaction occurred with preferential attack from one enantioface of the imine double bond. Two discrete, though quite similar, procedures led to comparable enantioselectivity, implying that the cyanating species actually involved are identical.



Scheme 6.111

This catalyst was also applicable in the Strecker reaction of ketimines including quinoline and isoquinoline (Scheme 6.112) [139]. Acid chlorides were combined for use in making iminium cations to enhance the reactivity of this class of poorly electrophilic substrate. Thus the reaction involves dual activation of the acyl quinolium or isoquinolinium ion and Me_3SiCN by the Lewis acid (Al) and the Lewis base (oxygen atom of phosphor oxide) of **93**, respectively. The reaction proceeded with moderate to high enantioselectivity.



Scheme 6.112

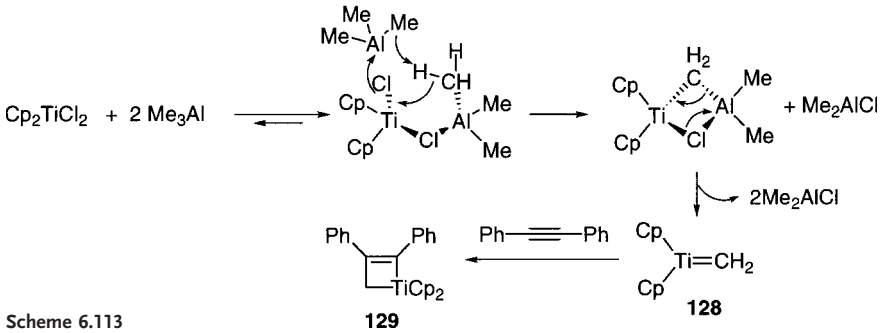
6.2.1.4 **Carboalumination (Addition of Al–C Bonds to C=C and CC≡Bonds)**

Substantial progress in the field of carboalumination chemistry was recently made as a result of the great efforts of Negishi and coworkers. Several reviews by them

[140] and others [141] have highlighted comprehensive aspects, highly detailed experimental results, and mechanistic analysis of this subject.

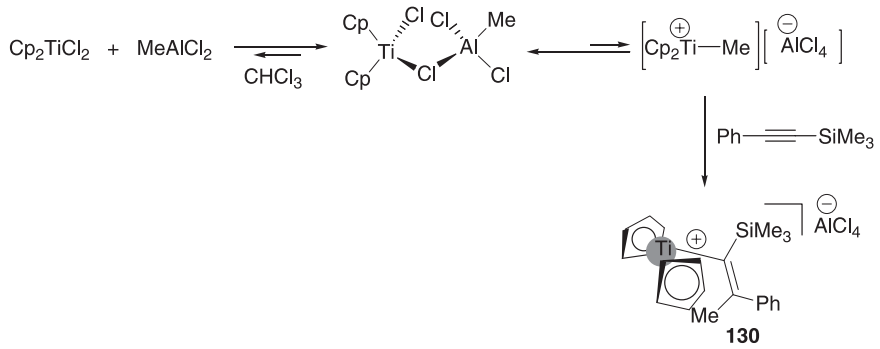
Carboalumination of Alkynes

Compared with the hydroalumination of alkynes carboalumination is rather inert to those substrates. A variety of transition metals that promote carboalumination have been screened in earlier investigations. In a concurrent but independent study, Cp_2TiCl_2–$2Me_3Al$, the so-called Tebbe reagent [142], was reported; the structure of this is consistent with **128** (Scheme 6.113), suggesting involvement of C–H activation as elucidated by Grubbs [143]. Despite its usefulness, this system using Cp_2TiCl_2 required a stoichiometric amount of Ti, produced diverse results which were difficult to control, and was limited in scope. Under some reaction conditions the structure **129** was isolated [145]. Thus alkylaluminum species are unlikely to be directly involved in the carbometalation of alkynes.



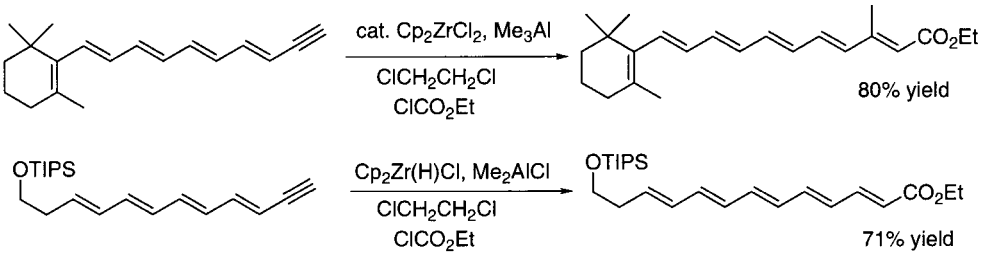
Scheme 6.113

Although the detailed structure of the reaction product between Tebbe reagent and alkynes for a time remained elusive, a related structure was established in later X-ray analysis studies [144] (Scheme 6.114).



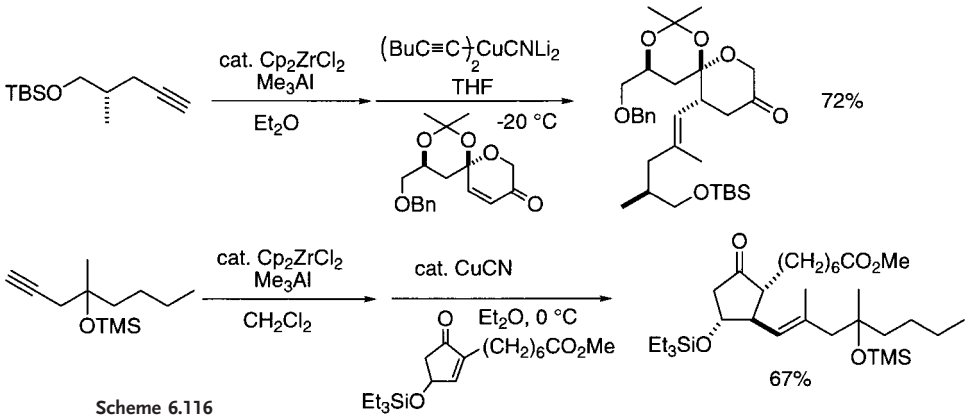
Scheme 6.114

Because of its synthetic scope and catalytic efficiency, Cp_2ZrCl_2 is a superb reagent [146], and initial attempts were made to achieve methylalumination, in which the methyl group has no β protons amenable to β-elimination or hydroalumination. Several useful procedures enabling synthesis of complex carbon frameworks have recently been highlighted [147, 148]. Me_3Al and Me_2AlCl were frequently used as methylating agents.



Scheme 6.115

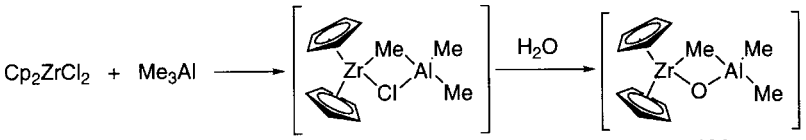
Because methylcarbonation of alkynes takes precedence over alkenes, the reaction tolerates an elongated conjugated chain and is very clean and regioselective (Scheme 6.115) [149]. A variety of oxygenated functional groups are also tolerated. A vinylaluminum species generated by carbometalation was transferable to other metals such as copper (Scheme 6.116) [147, 148], enabling conjugate addition of an alkenyl chain to α,β-unsaturated carbonyl compounds.



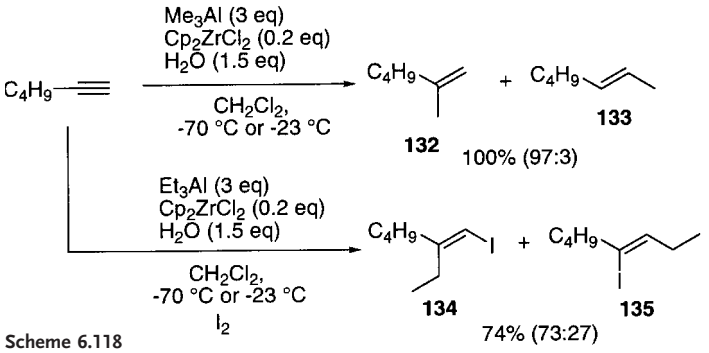
Scheme 6.116

Addition of water to the carboalumination reaction mixture led to a considerable increase in the reaction rate (Scheme 6.118) [150] and even at –70 °C methylalumination of 1-hexyne was essentially complete in 10 min in the presence of 1.5 equiv. H_2O. Zirconocene dichloride is necessary as a co-catalyst, and the rate-

determining effects are not a result of the formation of methylalumoxane (AlMeO)$_n$, MAO), a well known and highly active co-catalyst for the polymerization of α-olefins. It was proposed that a thermodynamically labile, but catalytically highly active oxo-bridged dimer **131** was formed in mixtures of alkylalane, Cp_2ZrCl_2, and water at temperatures below 0 °C. The effect of H_2O on ethylalumination was also investigated and, as expected, the turnover number was greatly increased – after 30 min at –23 °C, trapping of the alkenylalane with I_2 provided vinyl iodides **134** and **135** (ratio 73 : 27) in 74% yield.

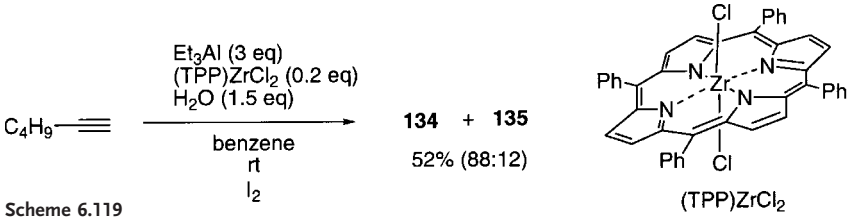


Scheme 6.117 **131**



Scheme 6.118

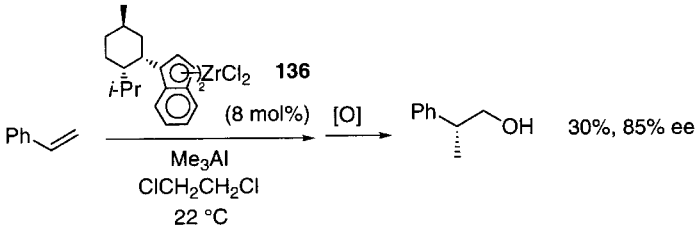
A more efficient procedure was reported by Inoue and coworkers (Scheme 6.119) [151]. With Zr complexes of tetraphenylporphyrin (TPP) [(TPP)$ZrCl_2$] the turnover number with Et_3Al was slightly improved and led to the ethylalumination products **132** and **133** (ratio 88 : 12) in 52% yield after reaction for 24 h in benzene.



Scheme 6.119

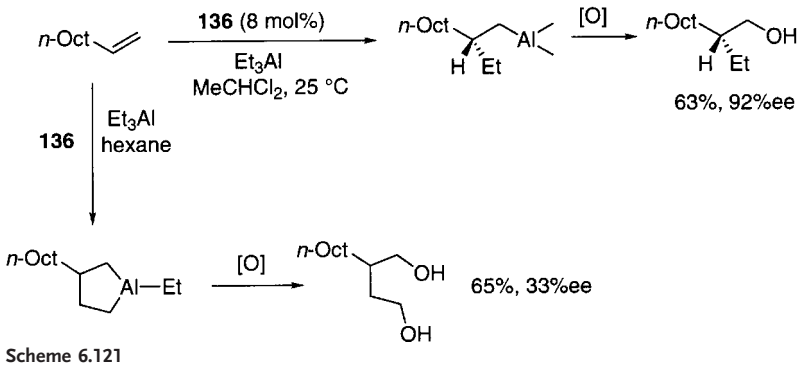
Carboalumination of Alkenes

Asymmetric methylalumination of alkenes bears fruit because chiral zirconium **136** was discovered to be an effective catalyst (Scheme 6.120) [152]. In initial attempts, the reaction proceeded in high yield but with moderate to high ee (65–85%). More promising results were obtained by re-examining conditions that involved a proper choice of solvent CH_3CHCl_2.



Scheme 6.120

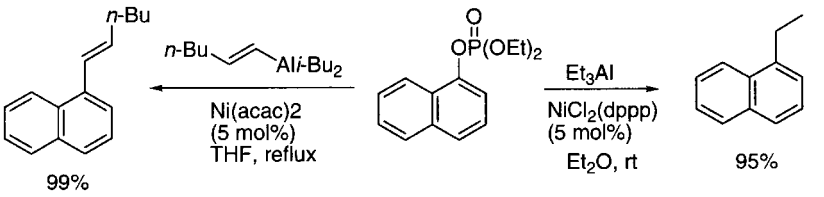
Thus ethylalumination was the next issue to be addressed and catalyst **136**, in conjunction with an appropriate solvent, was similarly effective (Scheme 6.121) [153]. Fortunately, the reaction proceeded almost without any side reactions that would be expected from detailed mechanistic analyses deduced from many carbometalation experiments using Cp_2ZrCl_2 [140, 154]. In general, very slow reaction and greatly inferior regioselectivity are often observed in carboaluminations with higher alkylaluminums such as Et_3Al. The greater steric bulk of **136** might obviate some preferred transition structures that led to undesired hydroalumination and other side reactions. The ethylalumination reaction is general in substrate scope with regard to *α*-olefins, usually giving no less than 90% ee, and was best performed in CH_3CHCl_2 or CH_2Cl_2, rather than $(CH_2Cl)_2$ or hexane. Other higher alkylaluminations, e.g. *n*-propylation and *n*-octylation, were also compatible with this reaction procedure and gave ee up to 91%.



Scheme 6.121

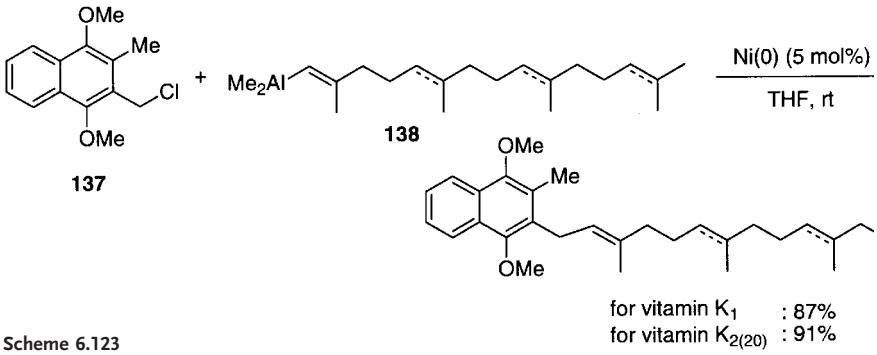
6.2.1.5 Coupling Reactions using Transition Metals (Addition of Al–C Bonds to Other Metals and Reductive Elimination)

Ni-catalyzed cross-coupling of arylphosphonates occurs effectively not only with Grignard reagents but also with aluminum alkyls (Scheme 6.122) [155]. The effect of the diphenylphosphinopropane (dppp) ligand on Ni is noticeable because alkyl nickel species are otherwise prone to β-hydride elimination before reductive elimination. This bisphosphine-specific tendency of preferred reductive elimination that affords coupling products had also been claimed in an earlier report [156] of work in which alkyl Grignard reagents were used. The reaction proceeded with neutral aluminum species, i.e. no ate complexes and no inorganic bases were required. This implies that transmetalation of Al–R to Ni–Cl proceeded readily without even a basic ligand interacting with aluminum. In contrast, alkenylaluminum undergoes the corresponding coupling even with $Ni(acac)_2$ as a catalyst.



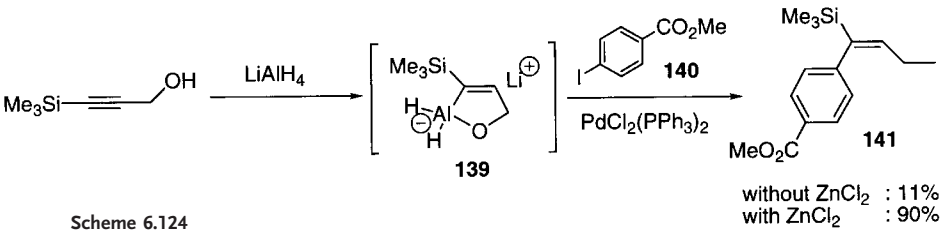
Scheme 6.122

Although, occasionally, benzylic halides readily undergo coupling with vinylalanes in the absence of transition metal catalysts [174], exploitation of more general methods was re-investigated. Treatment of benzyl halide **137** with the C_{19} vinylalane **138** and 5 mol% Ni(0) afforded coupling in high isolated yield (87%), within minutes at room temperature (Scheme 6.123) [157]. Even smaller amounts of catalyst, as low as 0.5 mol%, are equally effective. Use of Pd(0) instead, however, resulted in almost no reaction. This approach was also extended to the protected hydroquinone precursors of CoQ_3 and CoQ_5. Likewise, precursors to vitamins K_1 and $K_{2(20)}$ were prepared efficiently.



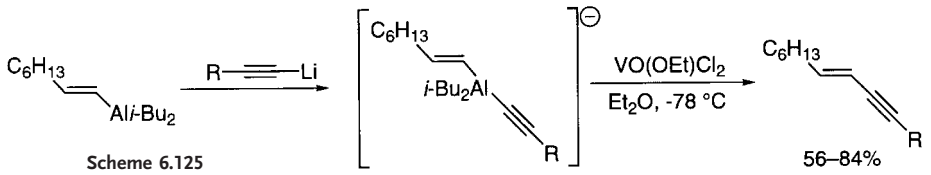
Scheme 6.123

Pd was preferred to Ni as a catalyst under some reaction conditions. When the resulting vinylaluminate **139** was subjected to reaction with methyl-4-iodobenzene **140** in the presence of $PdCl_2(PPh_3)_2$, only a low yield of **141** was obtained, whereas addition of $ZnCl_2$ increased the yield dramatically. The optimum amount of $ZnCl_2$ was found to be 60 mol%, giving **141** in 90% yield (Scheme 6.124) [158].



Scheme 6.124

Ate complexes of alkynylaluminum species undergo alkynyl coupling in the presence of more than stoichiometric amounts of oxovanadium reagents [159]. The reaction is intriguing in several ways. When aluminum has alkynyl, alkenyl, and alkyl groups attached the first two of these groups favorably undergo reductive elimination on vanadium, affording cross-coupling (Scheme 6.125). Neither alkynyl–alkynyl coupling nor alkenyl–alkenyl coupling was observed. This group-selective coupling depends on oxovanadium species and reaction conditions. $VO(O\textit{i}\text{-}Pr)_2Cl$ is preferable to $VO(OEt)Cl_2$ and lower temperatures ($<0\,^{\circ}C$) are required. Although neutral tri(organo)aluminum compounds are considered to be less reactive than the ate complexes, the former species are also capable of cross-coupling under some conditions. At higher temperatures aryldiethylaluminums undergo ethyl–aryl coupling in the presence of $VO(OEt)Cl_2$.



Scheme 6.125

6.2.2 Reduction

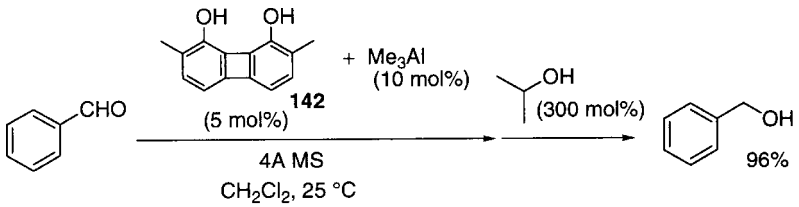
The ate complex of aluminum hydride $LiAlH_4$ [160], neutral aluminum hydrides of general formula X_nAlH_{3-n} (X = halogen and/or organic group, $n = 0$–3) [161], and their alkoxy variants [162] including chiral hydride reagents [163] have unquestionably been the most convenient reagents for the reduction of a variety of polar functional groups. Old and modern reviews and monographs cover numer-

ous applications of these hydride reagents [160–163]; readers will gain information and understanding in depth from these. This chapter excludes most of these issues and instead covers more recent applications of other types of aluminum reagent in reduction.

6.2.2.1 Carbonyl Reduction (H^- Addition to a C=O Bond)

Because the instability of Al–H bonds at higher temperatures results in an explosion hazard [164], there has been much eagerness to exploit a new class of reducing agents as substitutes for aluminum hydrides. Meerwein-Ponndorf-Verley (MPV) reduction with aluminum alkoxides is an attractive candidate not only in this context but also because of its environmentally benign nature, easy handling, commercial availability, and low cost. In the original investigation $Al(O\textit{i}\text{-}Pr)_3$ was put to use [165] although the reduction proceeded very sluggishly even with excess of the reagent.

The bidentate aluminum catalyst reported by Ooi and Maruoka completely changed this situation [166]. Treatment of benzaldehyde with 1 equiv. catalyst Me_3Al-**142** in CH_2Cl_2 at r.t. produced benzyl alcohol instantaneously and almost quantitatively (Scheme 6.126). The reaction was performed with a catalytic amount (5 mol%) of Me_3Al-**142** and 1–3 equiv. *i*-PrOH [167].



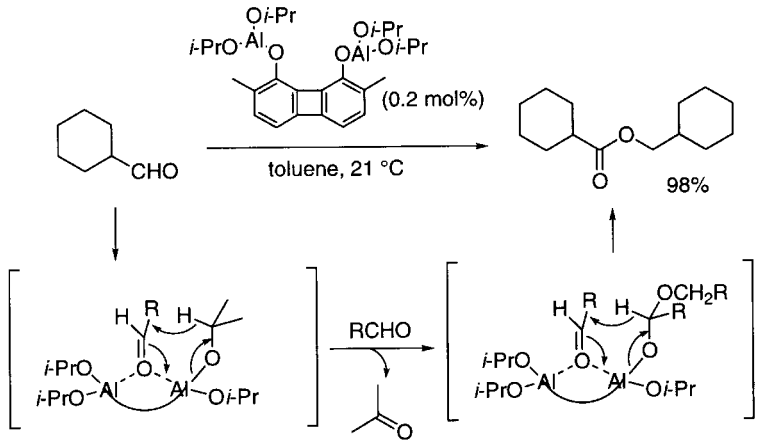
Scheme 6.126

The Tischenko reaction involves single or double hydride transfer and is readily promoted by the bidentate aluminum reagent (Scheme 6.127) [168]; the product in which two aldehydes were assembled was isolated quantitatively.

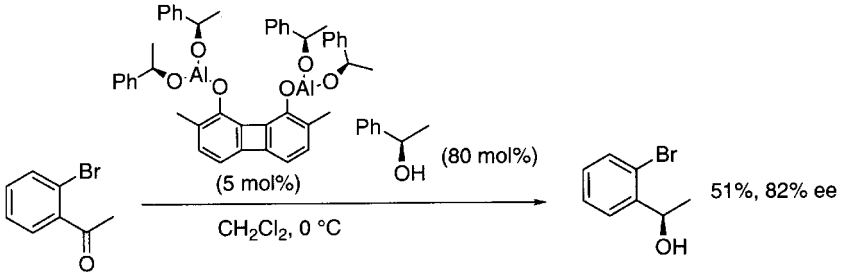
Asymmetric reduction of ketones by means of this MPV reduction was also tested (Scheme 6.128). The reduction proceeded with substoichiometric amounts of optically pure *α*-phenethylalcohol to give the product secondary alcohol in a moderate yield with fairly high ee of 82% [167].

An asymmetric MPV reduction that uses *i*-PrOH, Me_3Al, and a chiral binaphthol has also been reported [169]. (*R*)-BINOL and Me_3Al were mixed in a 1 : 1 ratio in toluene and the resulting white precipitate was treated with a prochiral ketone (tenfold excess) and *i*-PrOH (40-fold excess) (Scheme 6.129). This simple method was found to effect the catalytic reduction of 2-chloroacetophenone at r.t. to give the alcohol in 80% ee and 99% yield.

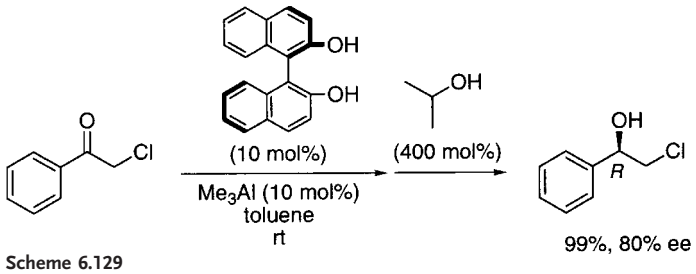
An intriguing example of a well-designed aluminum catalyst **143** that powerfully promotes MPV reduction was first reported by the same group [34]. The catalyst com-



Scheme 6.127



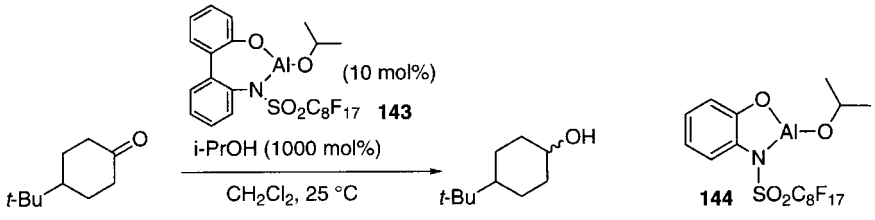
Scheme 6.128



Scheme 6.129

posite is completely different in several ways from those reported previously for MPV reduction. With the goal of high catalytic efficiency aluminum needs a bidentate ligand composed of sulfonamide and phenoxy backbone; the activity of catalyst **144** was poor, however. It was assumed that the structure and geometry of aluminum species, in addition to fine-tuning of electronic and steric properties of aluminum, are critical for high activity. The X-ray single-crystal determination of the DMF-**45**

complex shed light on this possibility. Unlike the usual tetracoordination of neutral aluminum, the structure of **45** is consistent with a binuclear composite, each aluminum center being pentacoordinate. Although other possibilities cannot be ruled out, this unusual hybridization of aluminum(III) might have some effect on the catalytic activity, as was also suggested by Nelson [33]. This procedure is amenable to large-scale experiments and is characterized by operational simplicity – simple mixing of 10 mol% each of Al(O*i*-Pr)$_3$ and the phenol in CH_2Cl_2 at r.t., then treatment with *i*-PrOH (10 equiv.) and 4-*t*-butylcyclohexanone for several hours gave the alcohol in 99% yield (Scheme 6.130).



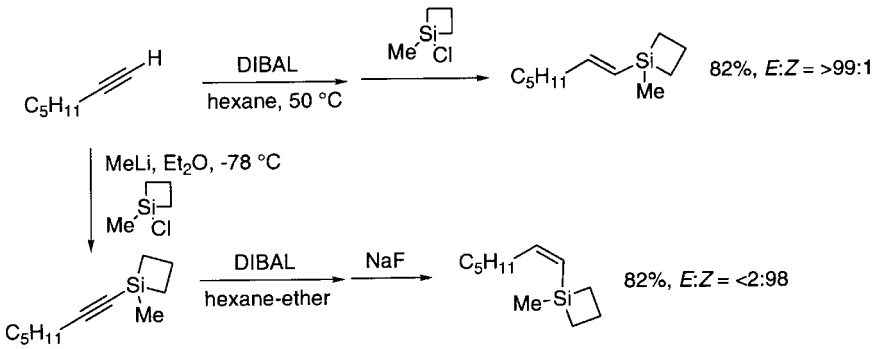
Scheme 6.130

6.2.2.2 Hydroalumination (H^- Addition to C=C or CC≡Bonds)

Hydroalumination is rather old chemistry about which many papers have been written. Readers can refer to specialized reviews on this subject [2, 170]. This chapter focuses on the recent application of hydroalumination in selective organic synthesis.

Hydroalumination of Alkynes

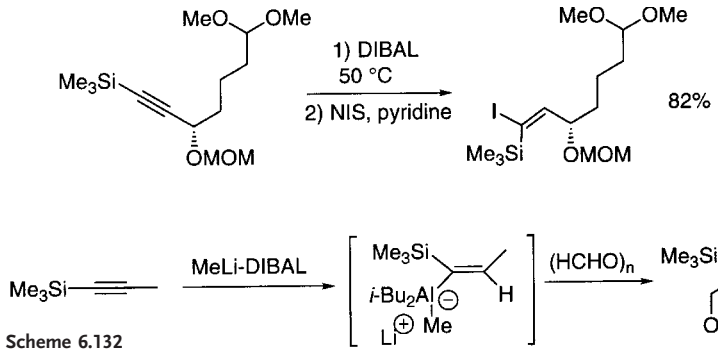
Hydroalumination of alkynes has been well investigated and has provided a very convenient way of synthesizing vinylaluminum species stereoselectively (Scheme 6.131). A general reaction sequence can be used to prepare either *E* or *Z* alkenes. The pro-



Scheme 6.131

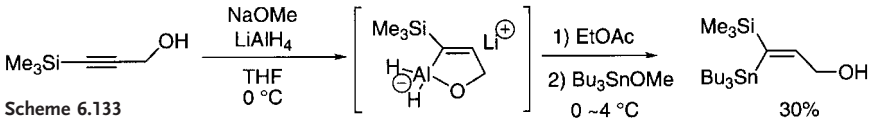
cedures involve hydroalumination of terminal alkynes then electrophilic functionalization of vinylaluminum species, to give the *E* product, or functionalization of the terminal carbon of alkynes then hydroalumination, to give the *Z* product. A recent representative example is the stereoselective synthesis of (*E*)- or (*Z*)-vinylsilane [171].

In general, terminal alkynes, the terminal sp carbon of which is ended by a silicon cap, enables attachment of aluminum at the *α*-carbon of the silicon cap (Scheme 6.132) [172]. It does not seem important whether neutral or ate complexes of aluminum hydrides are used [158].

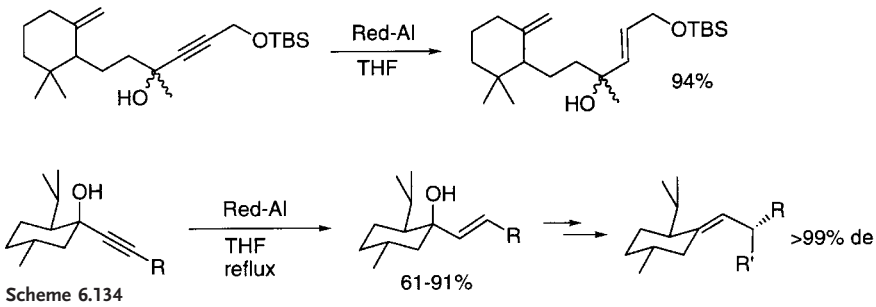


Scheme 6.132

Propargyl alcohols are useful alkynes that produce the corresponding *E*-alkenes exclusively. The hydroxy group is a useful directing group that enables aluminum to be attached at the distal end of sp-carbons (Schemes 6.133 and 6.134) [158, 173].

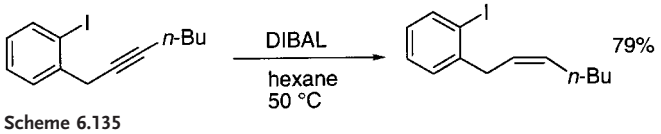


Scheme 6.133



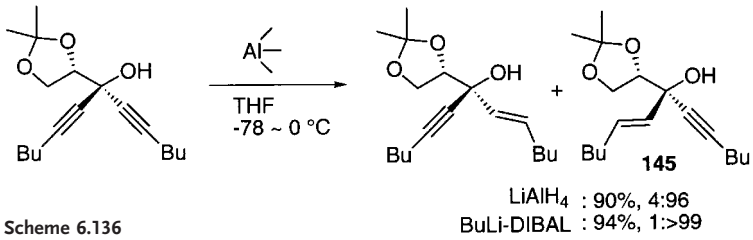
Scheme 6.134

In contrast, as has already been well reported, ordinary alkynes gave *Z* alkenes [174]. The aryl iodide remained intact under these conditions (Scheme 6.135).



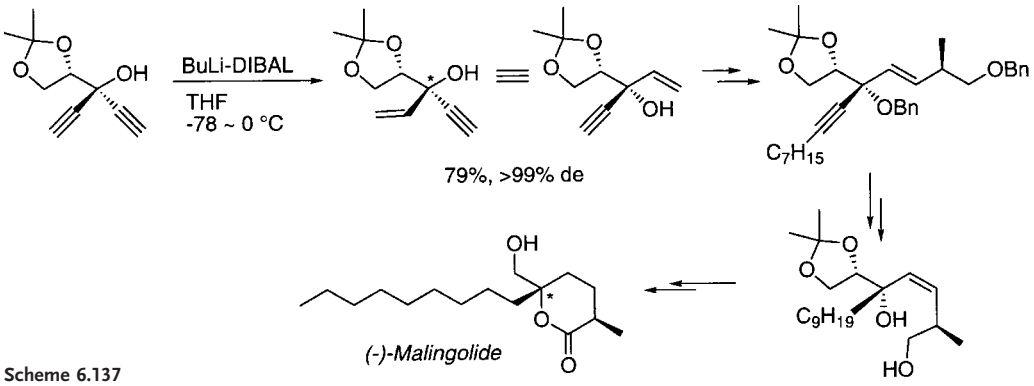
Scheme 6.135

Group-selective hydroalumination in which aluminum hydrides discriminate between diastereotopic alkynes provides access to a class of stereo-defined *tertiary* alcohols with potential utility in natural product synthesis [175]. Among the hydride reagents tested, BuLi–DIBAL or *t*-BuLi–DIBAL enabled superior discrimination to give sp^3-sp^2-sp-attached alcohol **145** with extremely high diastereoselectivity (>99% de) (Scheme 6.136).



Scheme 6.136

This perfect level of group selectivity was successfully applied in the total synthesis of (–)-malyngolide (Scheme 6.137) [176].

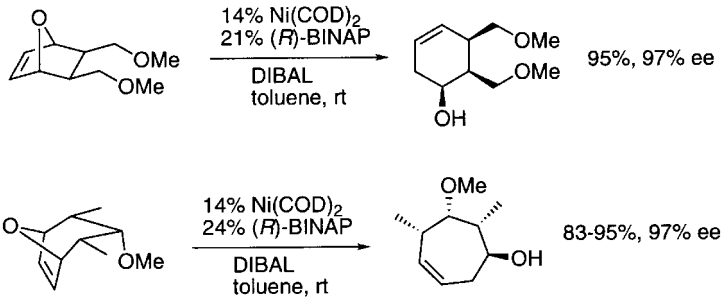


Scheme 6.137

Hydroalumination of Alkenes

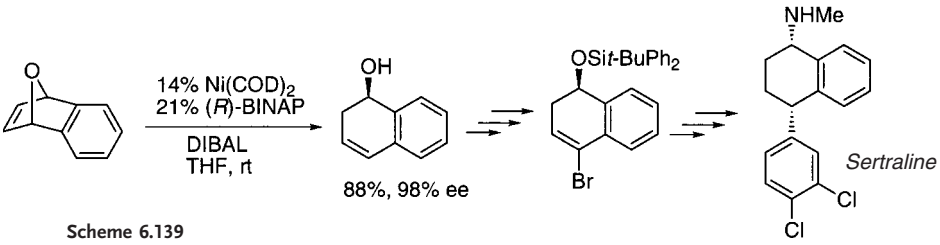
Compared with alkynes, alkenes are rather inert to hydroalumination. Most required an external catalyst that aided hydride transfer from aluminum to alkenes [169]. A variety of transition metal catalysts was extensively studied for this; among these the Group IV metals Ti and Zr were found generally applicable.

In contrast, Lautens and coworkers recently focused on asymmetric hydroalumination using Ni–BINAP as catalyst [177]. The reaction involves ring-opening desymmetrization of several 1,4-dihydrofuran derivatives that produce important chiral building blocks for natural product synthesis; high ee is usually obtained (Scheme 6.138) [178].



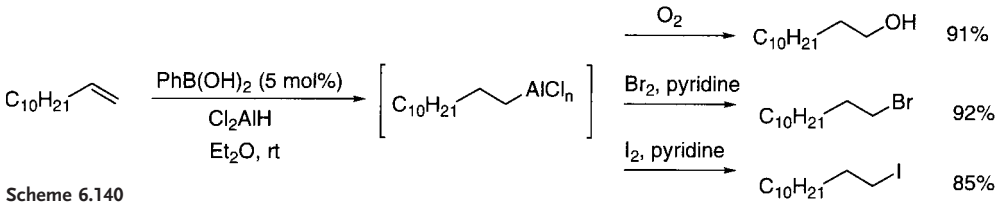
Scheme 6.138

Sertraline is readily accessible by this hydroalumination-based desymmetrization [179] (Scheme 6.139).



Scheme 6.139

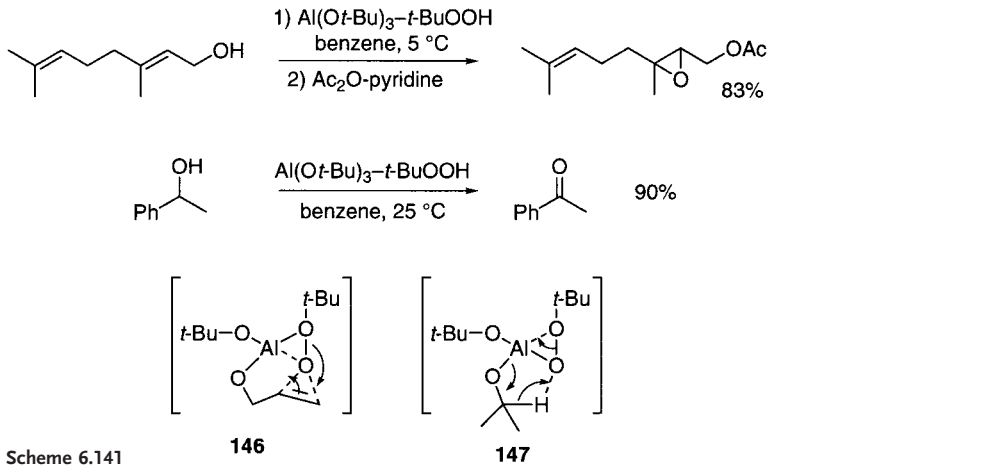
Other than transition metals, organoboron compounds also catalyzed hydroalumination (Scheme 6.140). Regio- and chemoselectivity was extremely good [180].



Scheme 6.140

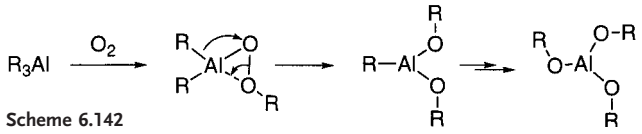
6.2.3
Oxidation

By analogy with other organometallic alkoxide reagents, e.g. Ti, V, and Mo, aluminum alkoxides are susceptible to peroxygenation by peroxide reagents. The peroxidation of aluminum and further oxidation of organic molecules is very useful in organic syntheses. The following examples employ mild conditions and catalytic amounts of $Al(Ot\text{-}Bu)_3$ and *t*-BuOOH and have found particular application in the epoxidation of allylic alcohols and the oxidation of secondary alcohols (Scheme 6.141) [181]. Whatever the mechanistic detail, the reaction is likely to proceed via five-membered transition states **146** and **147**. Regeneration of $Al(Ot\text{-}Bu)_3$ makes this system catalytic and of practical importance.



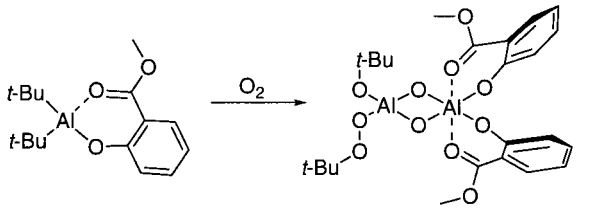
Scheme 6.141

Similarly, organoaluminum compounds in which the aluminum center is tetracoordinated by way of a peroxo three-membered heterocycle subsequently undergo migration of alkyls, giving aluminum alkoxides (Scheme 6.142) [182]. The reaction is very similar to the boron-alkyl migration via a peroxoboron complex, which produces a variety of alcohols very efficiently. Likewise, mild oxidation of aluminum alkyls by controlled introduction of dry air has found substantial application in industrial production of the corresponding alcohols.



Scheme 6.142

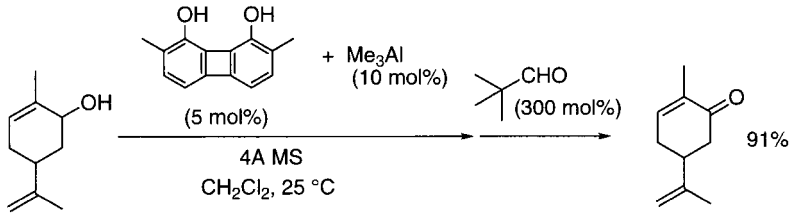
Lewinski and coworkers recently used this reaction sequence and achieved full characterization of the aluminum–peroxide complex by X-ray single-crystal analysis (Scheme 6.143) [183]. The structure is consistent with a mixture of tetra- and hexacoordination and with solution spectroscopic data. Unlike the usual instability of alkylperoxide complexes of aluminum, this peroxo complex is relatively stable, partly because of the hexacoordination also because of the steric bulk of the *t*-Bu groups attached to oxygen atoms.



Scheme 6.143

X-ray single crystal structure

Peroxide intermediates are not the only species that enable oxidation of secondary alcohols. Oppenauer oxidation of secondary alcohols is of practical value, because only catalytic amounts of aluminum species are required and without aid from transition metals, which are usually more toxic. A new type of Oppenauer oxidation was recently discovered by Ooi and Maruoka [167]. This method includes the use of bidentate aluminum catalyst which is also effective for MPV reduction (Scheme 6.144). The Oppenauer oxidation is the reverse of MPV reduction; when pivalaldehyde is used as hydride-capturing agent, however, the reaction is virtually irreversible, giving the ketone in high yield.

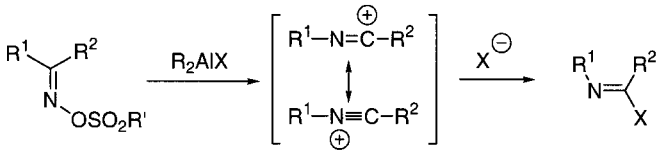


Scheme 6.144

6.2.4 Rearrangement and Fragmentation

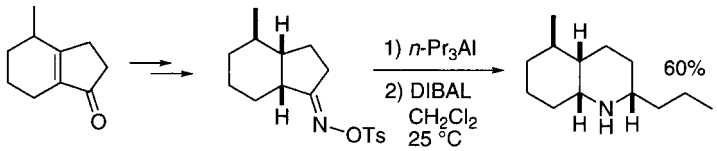
6.2.4.1 Beckmann Rearrangement

The Beckmann rearrangement was originally the skeletal rearrangement of ketoximes in the presence of certain acids under aqueous conditions to give amides or lactams. This reaction was re-examined using oxime sulfonates under aprotic conditions in the presence of organoaluminum reagents [184]. Abstraction of the sulfonyl group by the aluminum reagent was followed by capture of the intermediate iminocarbocation or alkylidyneammonium ion with the nucleophilic group (X; R_2AlX, where X = R, SR′, SeR′) on the aluminum (Scheme 6.145). Thus the aluminum reagent acts not only as a Lewis acid but also as a base.



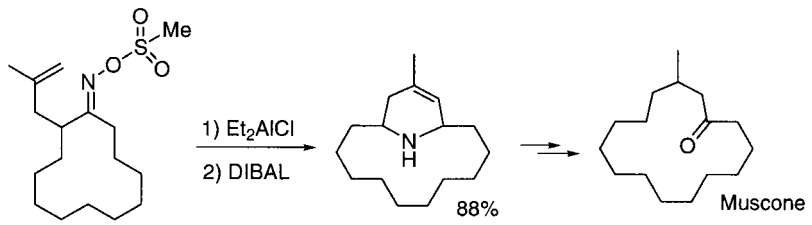
Scheme 6.145

These methods open a new synthetic pathway to alkaloids, including the pumiliotoxin C (Scheme 6.146) [185].



Scheme 6.146

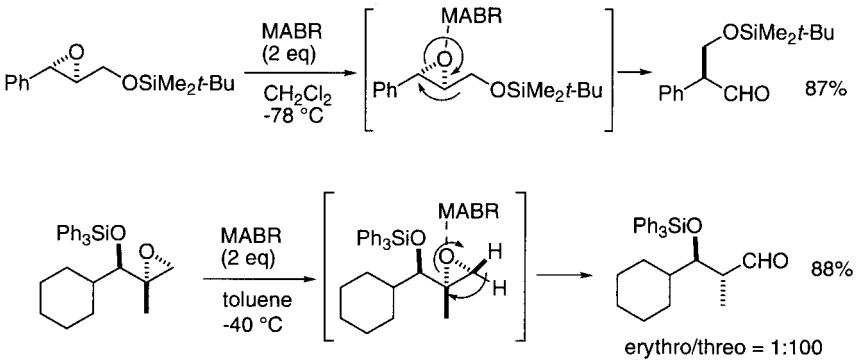
The intermediate iminocarbocation or alkylidyneammonium ion generated by an organoaluminum compound can be trapped intramolecularly by means of olefinic groups [186]. This interesting rearrangement–cyclization sequence was extended to an efficient synthesis of muscone or muscopyridine (Scheme 6.147) [187].



Scheme 6.147

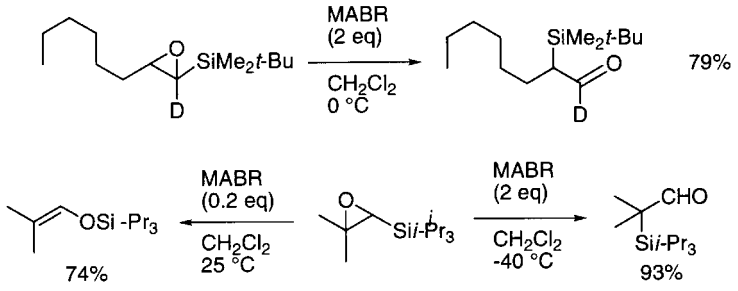
6.2.4.2 **Epoxide Rearrangement**

Two different rearrangement types of *β*-siloxy epoxide gave distinct *β*-siloxy aldehydes when MABR was used as key reagent, depending on the substrate employed (Scheme 6.148) [188, 189]. Because optically pure *α*-siloxyepoxides are readily accessible by use of the Katsuki-Sharpless asymmetric epoxidation, this rearrangement procedure is a very useful means of obtaining optically pure *β*-siloxyaldehydes which are often key building blocks in natural product syntheses.



Scheme 6.148

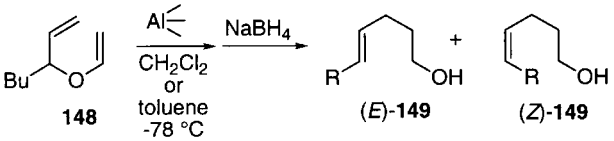
Further investigations showed that *α*-silylepoxides undergo a similar rearrangement despite interesting behavior that relies on the quantity of MABR (Scheme 6.149) [190]. Silyl anionic species undergo migration preferably over hydride and this could account for the silyl group being a better stabilizer of *β*-cations. The stoichiometry in MABR has an effect on the final product distribution – with 1 equiv. MABR the *α*-silylaldehyde derived by silyl migration was produced whereas with 20 mol% the silyl enol ether was obtained.



Scheme 6.149

6.2.4.3 **Claisen Rearrangement**

Although the Claisen rearrangement was readily promoted, even by *i*-Bu_3Al, when large allyl vinyl ethers were used [191], more useful methods characterized by substrate generality, including use of smaller substrates, had remained challenging. Claisen rearrangement is believed to proceed via a six-membered transition state. The preferential conformation of the reactant in the transition state might be because of the shape and size of the cavity of bulky aluminum reagents. This hypothesis was verified by treatment of 1-butyl-2-propenyl vinyl ether (**148**) with ATPH at –78 °C (Scheme 6.150). Isomeric rearrangement products (*E*)- and (*Z*)-**149** were obtained in 66% yield in the ratio 50 : 1 [192]. In contrast, MAPH-mediated rearrangement of **148** resulted in slightly lower stereoselectivity ((*E*)-**149** : (*Z*)-**149** = 32 : 1). The *E*-selectivity was further enhanced to >200 : 1 by use of the more Lewis acidic ATPH-Br, which accelerated reaction rates and rendered the rearrangement catalytic [193]. MABR was entirely ineffective for the catalytic rearrangement. ATPH and MAPH had a similar preference for *E*-selectivity. It is worth remarking that reversal of the stereochemistry of olefin geometry was observed when MABR was used to give *Z*-products [194].



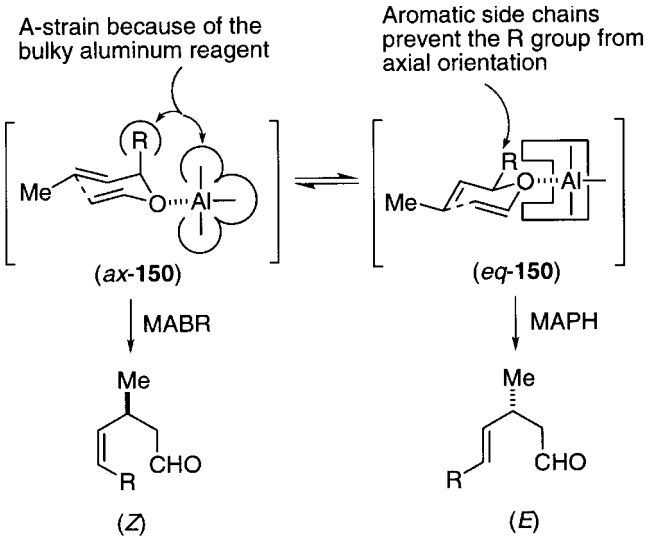
Scheme 6.150

Those reversals can be explained in terms of two possible chair-like transition-state structures *ax*-**150** and *eq*-**150**, respectively, which were proposed on the basis of the absolute configuration of the double bonds and the allylic carbons of the aldehydes produced (Scheme 6.151) [195].

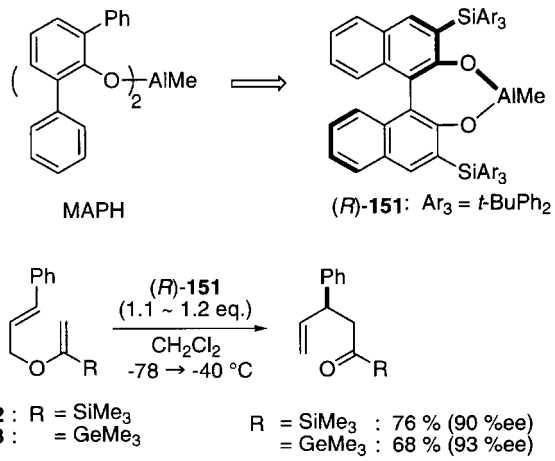
Asymmetric Claisen Rearrangement

Optically pure aluminum reagent (*R*)-**151** was synthesized from 1 equiv. each of (*R*)-(+)-3,3′-bis(triarylsilyl)-1,1′-bi-2-naphthol and Me_3Al [196], on the basis of the structure of MAPH [197]. Chiral (*R*)-**151** is an excellent promoter of the asymmetric Claisen rearrangement of allyl vinyl ethers **152** or **153** which have bulky substituents such as trialkylsilyl- or trialkylgermanium groups, but is totally ineffective for sterically less hindered substrates (Scheme 6.152).

An optically active catalyst, aluminum tris((*R*)-1-*α*-naphthyl-3-phenyl-2-naphthoxide) ((*R*)-ATBN), was synthesized on the basis of the structure of ATPH and used in the asymmetric Claisen rearrangement of (*E*)-**154**–**157** to give the corresponding aldehydes, with moderate enantioselectivity (>60% ee) (Scheme 6.153). In con-

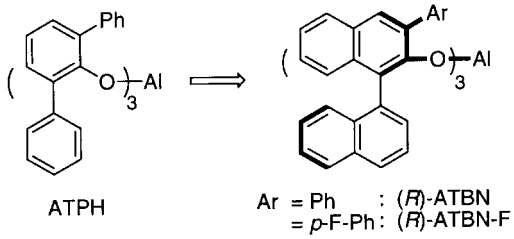


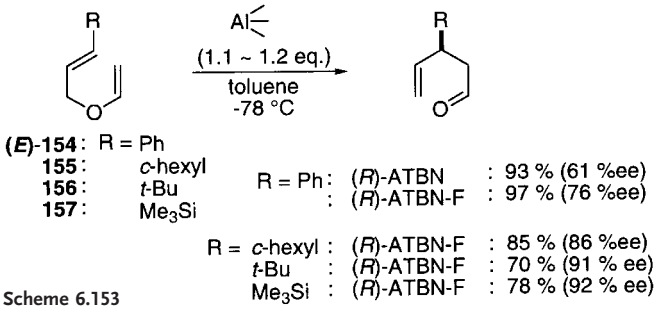
Scheme 6.151



Scheme 6.152

trast, the more elaborate (*R*)-ATBN analog, aluminum tris((*R*)-1-*α*-naphthyl-3-*p*-fluorophenyl-2-naphthoxide) ((*R*)-ATBN-F) generated products with up to 92% ee [192]. Taking into account the decomposition of (*E*)-**154**, which took precedence over rearrangement with (*R*)-**151**, optimum design of Lewis acid catalysts was proven to be important for stereoselective and asymmetric Claisen rearrangement.

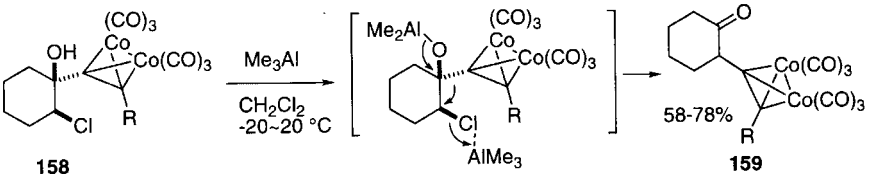




Scheme 6.153

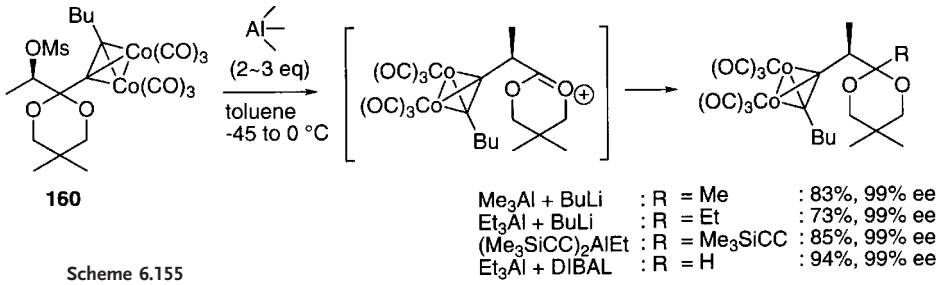
Meerwein Pinacol Rearrangement

It is well documented that an alkyne-Co complex strongly stabilizes a cationic charge at its α position. By analogy, neighboring group participation of alkyne-Co complexes toward the β-cation, followed by their rearrangement, the so-called Meerwein pinacol rearrangement, was also investigated (Scheme 6.154). When Me_3Al was used the reaction of **158** proceeded smoothly at lower temperatures, giving ketone **159**, owing to rearrangement, in high yield [198]. The migratory tendency of Co-complexes proved to be far larger than had been expected and, in fact, exceeded that of alkyl or even aryl groups.



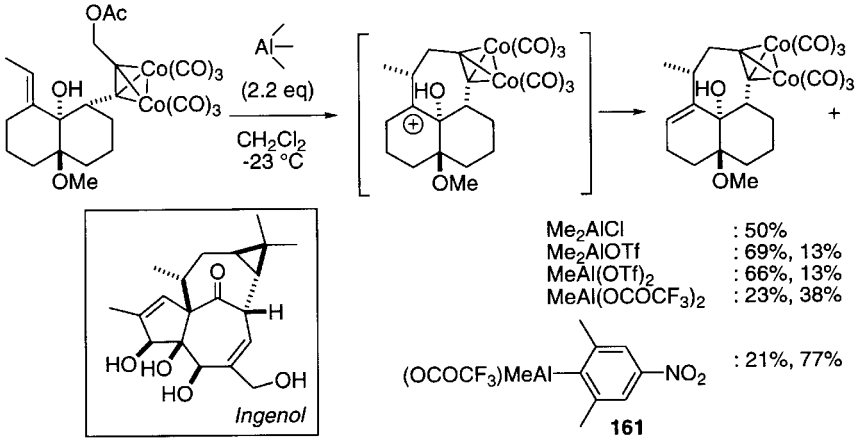
Scheme 6.154

Further studies indicated that aluminum alkyls are capable of capturing an oxonium intermediate generated from the corresponding acetal (Scheme 6.155) [199]. The substrate **160**, in which a hydroxy group was substituted by acetal, was amenable to this type of rearrangement and subsequent alkylation by alkylaluminum species. Again the dual function of organoaluminum as a Lewis acid and a base were demonstrated.



Scheme 6.155

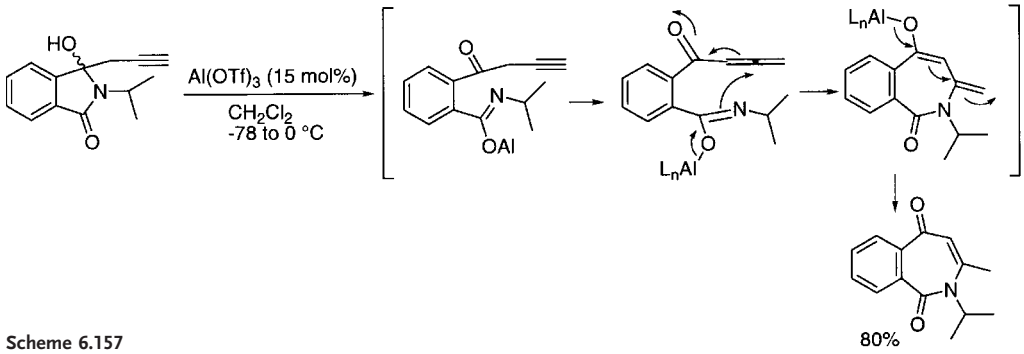
During ingenol synthesis, fragmentation involving the Meerwein pinacol rearrangement followed the intramolecular ene reaction which had generated a β-cation (Scheme 6.156) [200]. β-Elimination competed significantly with the desired rearrangement. Several aluminum Lewis acids were screened, and **161** was eventually found to be a superb reagent, use of which promoted rearrangement on preference to β-elimination. Its steric bulk and high Lewis acidity, and the effect of a counter anion which stabilized the carbocation were thought to account for this interesting behavior.



Scheme 6.156

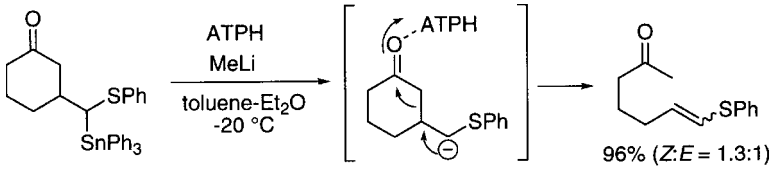
6.2.4.5 **Other Rearrangements and Fragmentation**

The reaction of succinimide derivatives with catalytic amounts of $Al(OTf)_3$ proceeded via several stepwise reactions, resulting in ring-enlargement (Scheme 6.157) [201]. Both bond-breaking and bond-making were assumed to be readily promoted by the strong Lewis acidity of $Al(OTf)_3$. These involve intramolecular rearrangement of the C–N bond consistent with attack at the central carbon atom of the allenyl intermediate.



Scheme 6.157

Enone fragmentation was achieved by conjugate addition of α-stannylalkyllithiums to an enone, then treatment of the resulting γ-stannylalkanone with ATPH and MeLi (Scheme 6.158) [202]. The push–pull relay arranged by interplay of ATPH complexation and the γ-carbanion enabled smooth fragmentation of the C_α–C_β bonds, resulting in clean formation of the corresponding acyclic alkanones. Irrespective of the acyclic enone used this reaction sequence proceeded with similar effectiveness.



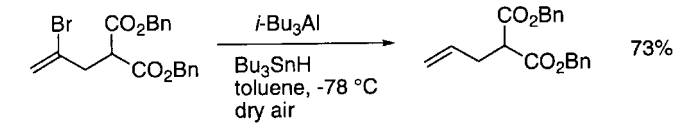
Scheme 6.158

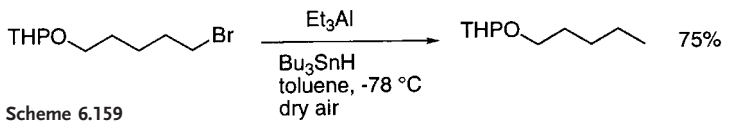
6.2.5
Radical Initiation and Reactions

Alkyl aluminum compounds are known to be radical initiators. Kabalka and coworkers reported the first unequivocal example of a free-radical process in which the classical organoaluminum reagent Pr_3Al was used in the presence of O_2 or under UV irradiation [203]. In modern studies, modified alkylaluminum reagents enabled more practical improvement in the control of diastereo- and enantioselectivity in radical initiation and reactions.

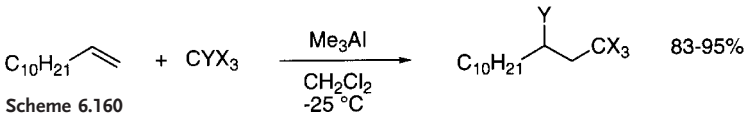
Similar to the Et_3B–Bu_3SnH combination reported by Oshima and coworkers [204], classical aluminum alkyls (Et_3Al and i-Bu_3Al) and Bu_3SnH have found particular application in the reduction of alkyl halides (Scheme 6.159) [206].

Although there is still controversy over whether free radical species are involved, their relevance is also apparent from the usefulness of the cyclopropanation reaction using polyhalomethane and Me_3Al (Scheme 6.160) [205].



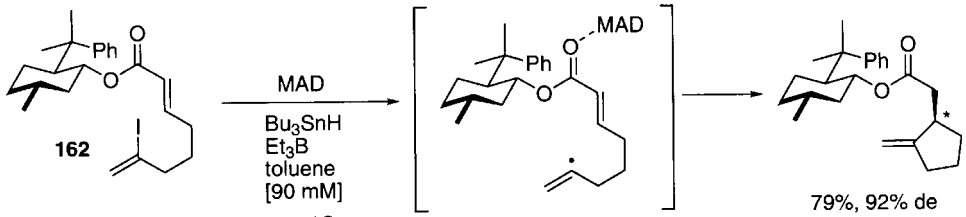


Scheme 6.159



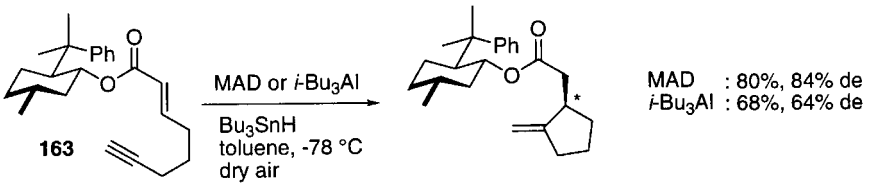
Scheme 6.160

Radical addition to *α,β*-unsaturated carbonyl compounds is a challenging issue, because stereocontrol in radical reactions is rather difficult compared with the corresponding addition of carbanion species. Nishida and coworkers succeeded in this operation involving intramolecular radical cyclization by proper choice of chiral auxiliary and aluminum reagent (Scheme 6.161) [206]. The radical cyclization of **162** was initiated under conditions reported by Oshima and Utimoto (**162**, 90 mM; *n*-Bu_3SnH (1.5 equiv.), Et_3B (1.1 equiv.), and 0 °C in toluene under Ar–Ar seems to contain small amounts of O_2) [207] in the presence of MAD. The reaction is likely to proceed via an *s-trans* conformation of the unsaturated ester, which is tightened by complexation with bulky MAD; the highest diastereoselectivity obtained was 92%. Classical aluminum reagents Me_3Al, Et_3Al, Me_2AlCl, Et_2AlCl, and *i*-Bu_3Al resulted in lower selectivity.



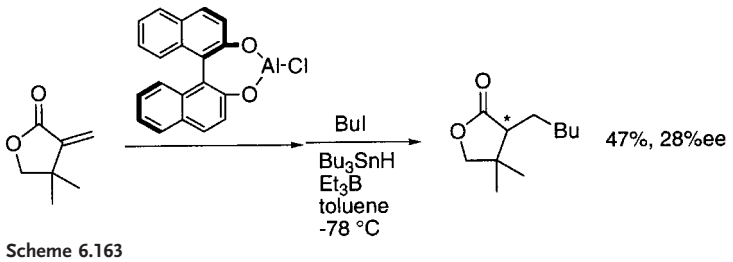
Scheme 6.161

The function of MAD is not only to reduce the LUMO of the *β*-carbon and to fix the conformation of the *α,β*-unsaturated ester, but also to initiate radical reaction [208]. This was demonstrated when a similar reaction was performed without Et_3B (Scheme 6.162). Reaction of **163** occurred with equal effectiveness, although with a slight decline in diastereoselectivity.



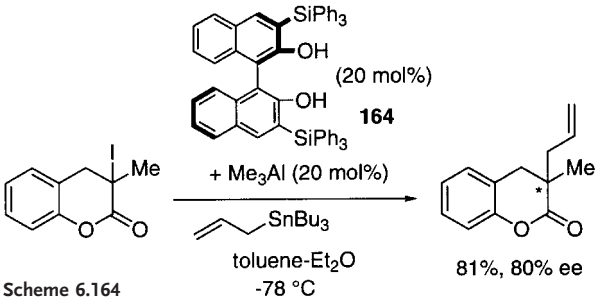
Scheme 6.162

Asymmetric intermolecular radical Michael addition was investigated with a chiral aluminum reagent. As would be expected from the general difficulties encountered in the control of intermolecular radical addition, ee was low (Scheme 6.163) [209].



Scheme 6.163

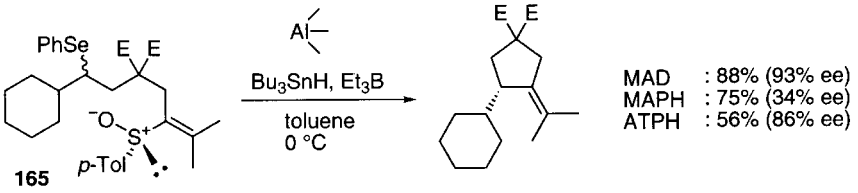
Thus asymmetric induction was rather difficult when the β-position of the carbonyl compounds was involved in the asymmetric construction of a stereogenic center. This might be because of the small steric effect of a chiral fragment that is relatively far from the β position. In contrast, a greater effect should be expected on the α-position of carbonyl groups. In fact, the quaternary carbon center was created with high ee when sterically more congested aluminum Me_3Al-**164** was used to enable tight complexation with the carbonyl group [210]. It is worthy of note that the reaction proceeded a much faster on complexation with Me_3Al-**164**, and this rendered the aluminum reagent catalytic (Scheme 6.164). Another strik-



Scheme 6.164

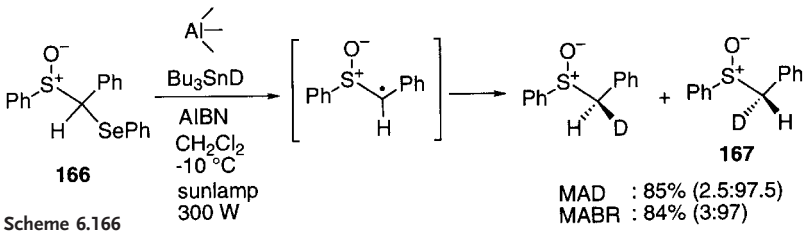
ing feature was the participation of Et_2O in the enhancement of ee – without Et_2O, ee decreased significantly despite a comparable reaction rate. The pentacoordinated aluminum was believed to account for this hitherto unknown behavior.

Such chiral aluminum reagents with steric bulk play significant role in enhancing ee and reaction rates. This positive effect was also illustrated by more complicated systems in which a negative effect of steric bulk was also observed [211]. When **165** was subjected to the radical cyclization a greater increase in ee was obtained with MAD than with MAPH or reagents of smaller size (Scheme 6.165). In contrast, ATPH bulkier than MAD gave ee lower than that obtained by use of MAPH.



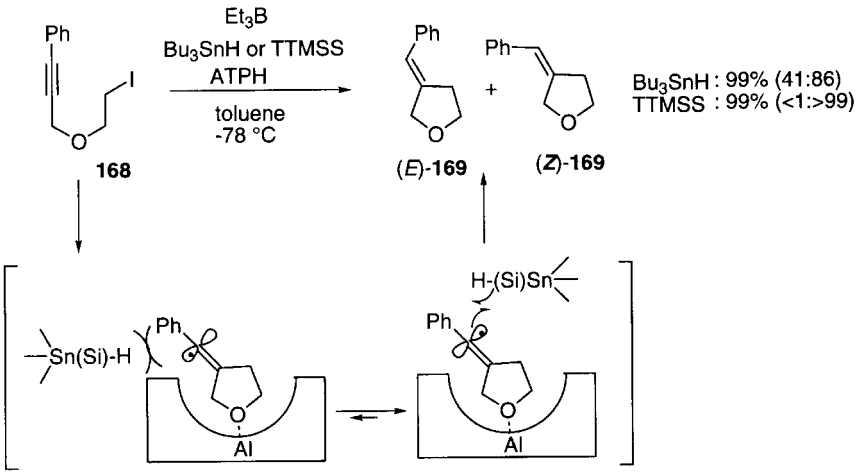
Scheme 6.165

Effects of solvents and Lewis acids were evaluated during monitoring of the deuteration of sulfinylated benzyl radicals (Scheme 6.166) [212]. Again the steric bulk of MAD and MABR proved stereochemically strategic. Excellent selectivity (>94% de) was obtained for **166** with preferential formation of **167**.



Scheme 6.166

A new procedure in which the rate of radical cyclization was accelerated was demonstrated by Ooi and Maruoka [213]. They used the cavity of ATPH that would be expected to hold substrates in a favorable conformation for the cyclization (Scheme 6.167). In fact, the radical cyclization of iodide **168** proceeded even at –78 °C, for 1 h, to afford (*Z*)-**169** in 99% yield. The selectivity in the olefinic geometry of the cyclized products was significantly enhanced by proper choice of radical propagation reagent. TTMSS afforded absolute *Z*-selectivity whereas $E:Z = 14:86$ was obtained with Bu_3SnH. It seemed that steric constraint played an important role when a second radical eventually generated by the cyclization was trapped by bulky hydride reagents.



Scheme 6.167

6.2.6
Polymerization

Several papers have dealt with the discovery and development of novel aluminum catalysts useful in polymerization and reviews are available describing early applications of classical aluminum species with the general structural formula R_nAlX_{3-n} (R = organic group, X = halogen, alkoxy group; n = 0–3) [214]. This section is devoted to very recent applications of aluminum compounds in polymerization. Obviously polymerization involves several fundamental bimolecular reaction sequences; these include novel reactivity and structural features of aluminum species which are worth mentioning and which are rarely encountered in the simple bimolecular reactions described in the previous sections.

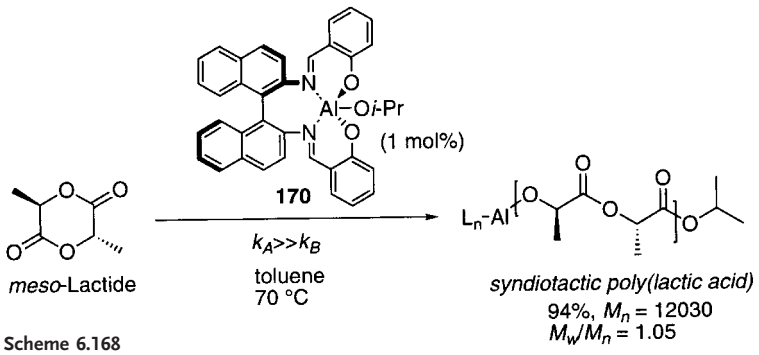
The physical and mechanical properties of a polymeric material are critically dependent on many factors, one of which is stereochemistry. Polymers with stereo centers in the repeating unit can form two structures with maximum order, isotactic and syndiotactic. Sequential stereo centers of isotactic polymers are of the same stereochemistry whereas those of syndiotactic polymers are of opposite configurations. Because of this stereoselectivity, easy structural modification of catalysts is of practical importance in the rapid discovery of suitable catalysts. In fact, selectivity in the propagation of lactones depends strongly on the structure of the active species. It is apparent from the large store of data obtained for ATPH- and MAD-promoted bimolecular reactions that if reactivities are similar greater steric hindrance increases selectivity. Thus, exploitation of selective aluminum species while retaining high reactivity is one of the ultimate goals in this important field of chemistry.

6.2.6.1 Anionic Polymerization

Ring-opening polymerization of cyclic ethers and lactones has been a major area of research in Lewis acid-promoted reactions. In particular, aluminum compounds have been investigated in depth not only because of their high oxophilicity and ability to initiate polymerization but also because of their commercial availability and low cost.

Polymerization of Lactones

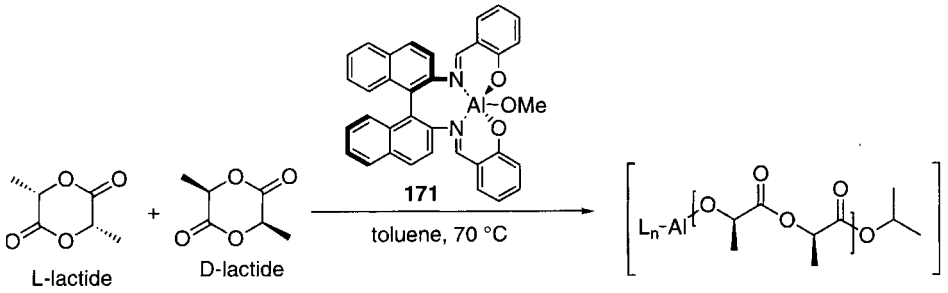
A new method for constructing syndiotactic polymers, which consists in stereoselective ring-opening polymerization (ROP) of a cyclic monomer containing two stereo centers, has been extensively studied by Coates and coworkers [215]. They used salen-Al species **170** derived from chiral binaphthol and this catalyst promoted stereoselective ring-opening polymerization of *meso*-lactide, the cyclic dimer of lactic acid, to give poly(lactide) (PLA) (Scheme 6.168). Conversion of 94% was reached in 40 h, and an M_n of 12 030 (theoretical $M_n = 13\,540$) and a molecular weight distribution (M_w/M_n) of 1.05 were obtained with high syndiotacticity (96%). This narrow polydispersity and the linear correlation between M_n and percentage conversion are indicative of the living nature of the polymerization and the single type of reaction site.



Scheme 6.168

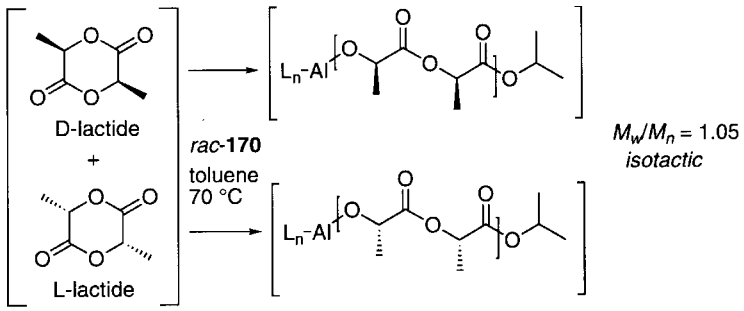
Chiral catalyst **171** was used to effect kinetic resolution of the racemic lactide in the polymerization of the racemic lactide [216]. At low conversion high enantiomeric enrichment in the polymer was observed (Scheme 6.169). The stereochemistry of the catalyst overrides the tendency for syndiotactic placements that are typically favored by chain-end control. At higher conversions, the ee in the polymer decreases.

This observation is of particular value when racemic polymers have physical properties superior to those of the enantiopure polymers. In fact, L-PLA and D-PLA form a stereocomplex that has a T_m fifty degrees higher than for the homochiral polymers. Polymerization of racemic lactide with racemic **170** yields nearly mono-disperse chains ($M_w/M_n = 1.05$) consistent again with "living" polymeriza-



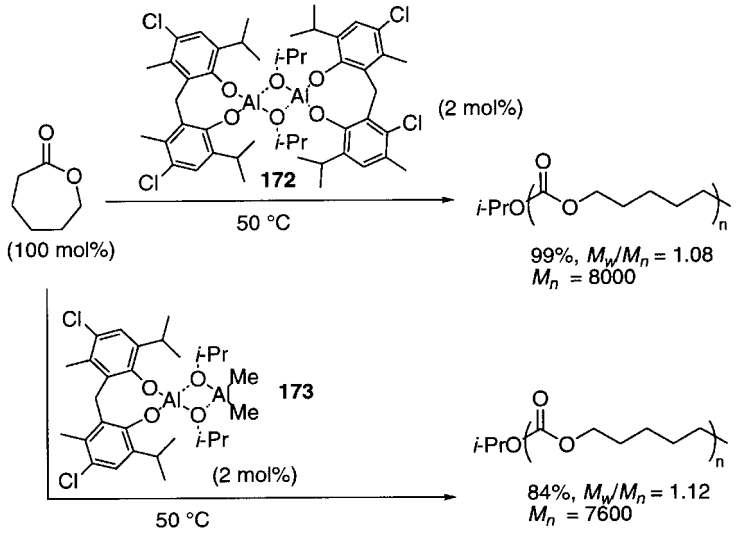
Scheme 6.169

tion and the absence of transesterification (Scheme 6.170) [217]. It is worthy of note that the (*R,R*)-lactide reacts more quickly with (–)-**170** whereas the (*S,S*)-lactide reacts with (+)-**170** more readily. This leads to an equal mixture of isotactic homochiral polymers, each of the opposite stereochemistry. This obviates the requirement that separate pools of enantiopure lactide monomers must be polymerized independently to obtain enantiopure polymers. Thus, this parallel ROP of D- and L-lactide, followed by subsequent combination of the resulting chiral poly(lactide) chains, is no longer needed.



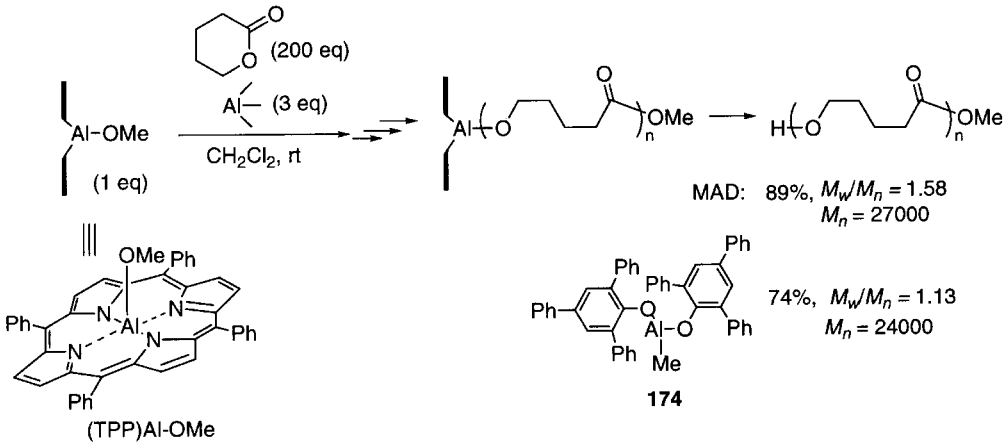
Scheme 6.170

The catalytic activity of **172** and **173** toward ROP of ε-caprolactone (ε-CL) and δ-valerlactone (δ-VL) have been reported [218]. Experimental results showed that this aluminum alkoxide catalyzed the polymerization of ε-CL in both "living" and "immortal" fashions, yielding PCL with a very narrow MWD in a wide range of monomer-to-initiator ratios (Scheme 6.171). In the presence of 2-propanol as the chain-transfer agent, exchange between the growing alkoxide species and the alcohol leads to chain transfer, because the resulting aluminum alkoxide can reinitiate polymerization. This exchange reaction takes place reversibly and much more rapidly than the reaction with the epoxide monomer. This "immortal" polymerization enabled as much as a 32-fold amount of *i*-PrOH to be added and gave narrow MWD ranging from 1.11 to 1.17.



Scheme 6.171

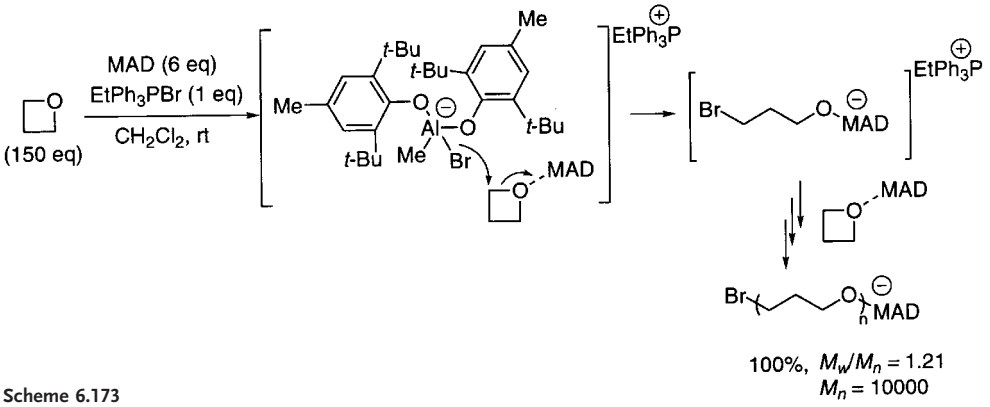
((5,10,15,20)-Tetraphenylporphinato)aluminum alkoxide ((TPP)AlOR) brought about the "living" polymerization of δ-VL, whereas no polymerization occurred when (TPP)AlCl was used [219]. In contrast, addition of (TPP)AlCl to the polymerization initiated with (TPP)AlOR resulted in remarkable acceleration without loss of the "living" nature (Scheme 6.172). MAD had a powerful accelerating effect on this polymerization of δ-VL, although resulting in a broad MWD (1.58) at the later stage of polymerization [220]. In contrast, use of MAPH analog **174** resulted in high activity and narrow MWD.



Scheme 6.172

Polymerization of Ethers

Oxetane undergoes ring-opening polymerization under the action of MAD in conjunction with onium salts, including quaternary ammonium and phosphonium halides, giving a narrow MWD polyether (Scheme 6.173) [221]. Use of Me_3Al in place of MAD resulted in no polymerization. The aluminum ate complex seemed to be an initiator, which underwent a trigger reaction involving halide transfer to the aluminum–oxetane complex.



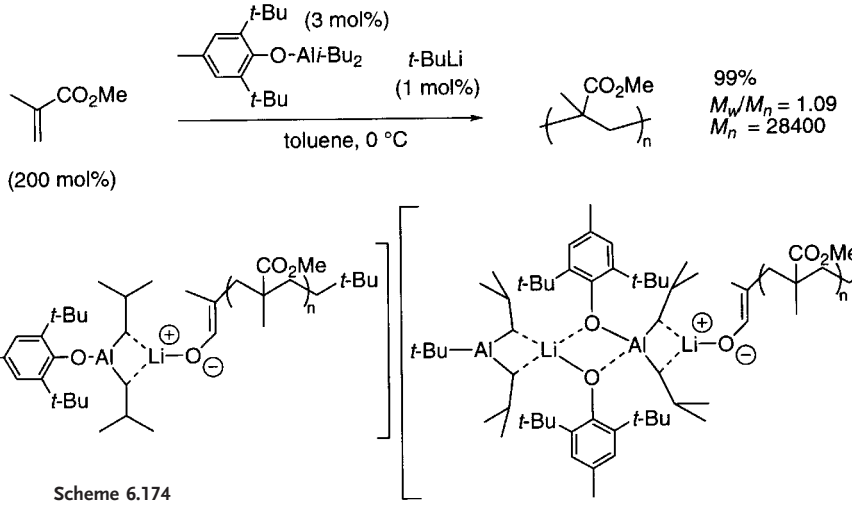
Scheme 6.173

Polymerization of Methacrylates

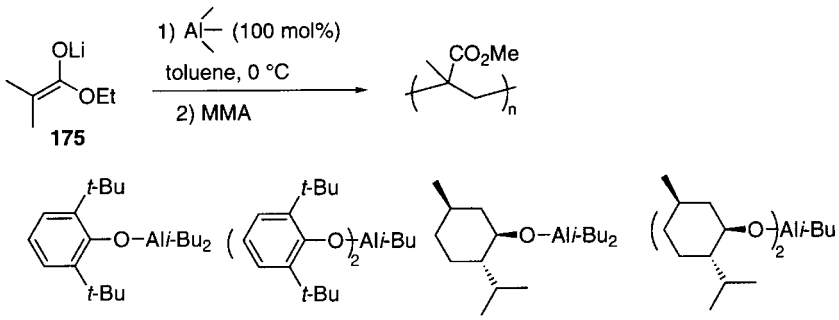
Anionic polymerization of methacrylates involves enolate intermediates of diverse molecular weight. These distinctive enolates are readily formed via a number of consecutive conjugate addition steps. As discussed in Section 6.1, control of reactivity and selectivity of enolates should directly reflect the stereoselective synthesis of poly(methyl methacrylate)s (PMMA). Thus it is advisable to compare the nature of aluminum enolates involved in bimolecular and polymolecular reactions.

The simple lithium tetraorganoaluminates including $LiAlEt_4$ are known to polymerize methyl methacrylate monomers [222]. This is, however, only possible at the very low temperature of –78 °C. In contrast, preformation of the *i*-Bu_2Al(BHT)–*t*-BuLi complex, then treatment of methyl methacrylate at 0 °C afforded PMMA with a molecular weight of 28 400 (Scheme 6.174) [223]. NMR analysis revealed that the alkyl group bonded to the end of the polymer chain is the *t*-Bu moiety derived from *t*-BuLi and not alkyl groups from aluminum. The contribution of two enolate intermediates, monomeric and dimeric aluminum species, was invoked to account for the structure of the initiation species.

The steric and electronic effects of oxygen-substituted ligands attached to aluminum on the tacticity of the polymers were particularly apparent for use of lithium enolate initiator **175** in the presence of organoaluminum catalysts at near-ambient temperature in toluene (Scheme 6.175) [224]. It was demonstrated that the nature of the species $R_nAl(OR)_{3-n}$ determines the mode of interaction with the lithium enolates and the monomer, which in turn controls the final tacticity of the PMMA.



Scheme 6.174

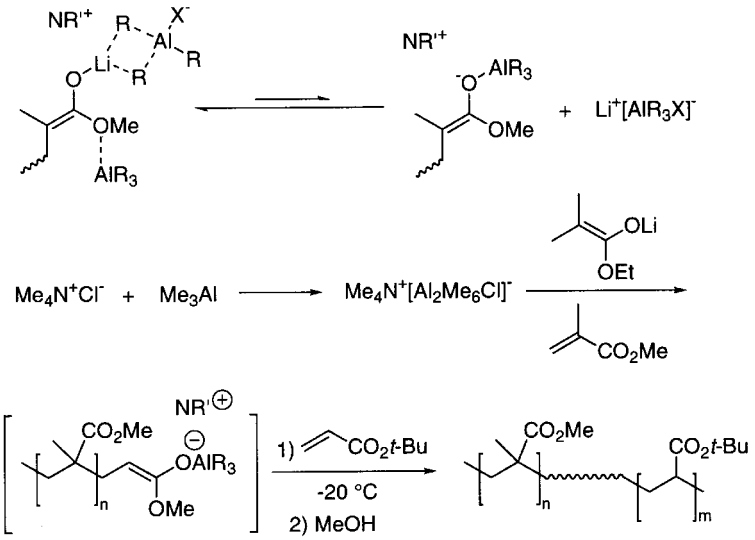


yield, M_w/M_n	83%, 1.15	100%, 1.11	100%, 1.08	100%, 4.24	85%, 4.04
mm:mr:rr	6:34:60	4:31:65	2:22:76	65:22:13	74:19:7

Scheme 6.175

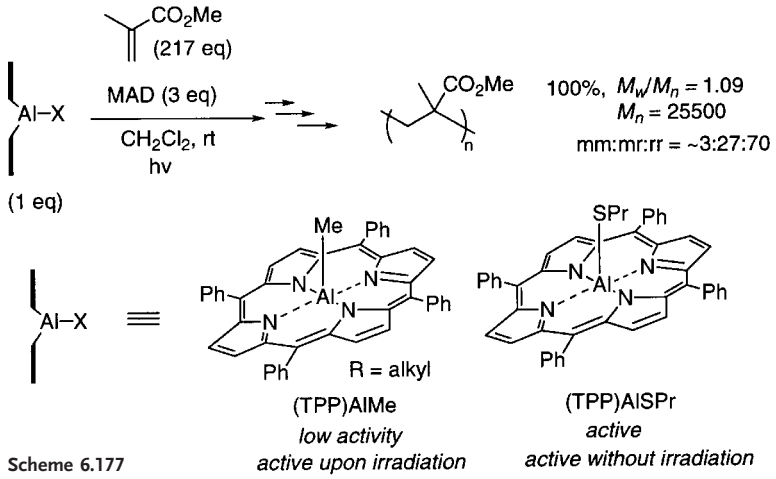
Living anionic polymerization can also be used to produce well-controlled block copolymers. For PMMA, the best procedures need temperatures below 0 °C and are therefore unlikely to be commercially attractive. They are, furthermore, largely unsuccessful for the controlled polymerization of acrylates, which are far too reactive. The use of tetraalkyl ammonium ate complexes, in conjunction with an appropriate aluminum catalyst, solved this problem [225]. The function of the ammonium counterion is to promote dissociation of the complex ion to form the reactive ate complex of the aluminum enolate of the ester (Scheme 6.176). Thus, polymerization was initiated by the lithium enolate of isobutylate in the presence of the ate complex of $Me_3Al–R_3NCl$. A controlled block copolymer (PMMA–block–

PtBMA) with a narrow molecular weight range can be formed by sequential acrylate monomer addition. In general, the controlled polymerization of butyl acrylates requires a low temperature (–78 °C), but high molecular weight (120 000 g mol^{-1}) and low MWD (< 1.2) can now be achieved even at higher temperatures.



Scheme 6.176

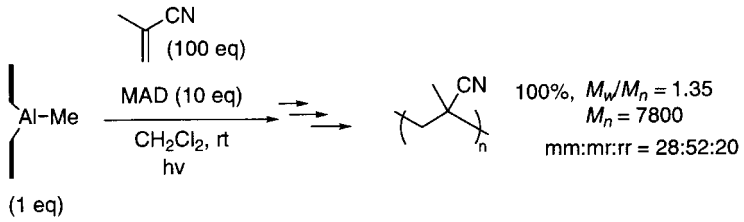
The first steps of alkylation of MMA, which initiates polymerization, were also triggered by the (TPP)AlMe complex on irradiation with visible light (> 420 nm) (Scheme 6.177) [226]. The initial reaction occurs only on irradiation and not in the dark. In contrast, no irradiation was needed during initiation by (TPP)AlSPr, because of the easier transfer of the PrS^{-} group from the aluminum of TPP [227]. The reaction intermediates are highly likely to be aluminum enolates, and propagation steps involving these species proceeded even in the dark. The polymerization was so called high-speed living polymerization, because it reached completion within 3 s at r.t. with the indispensable aid of MAD; a longer reaction time was needed with ATPH [228]. The M_w/M_n value (~1.09) is as good as for monodisperse chains (Scheme 6.177). In contrast with the significant ligand effect on tacticity, moderate syndiotacticity (mm : mr : rr = ca. ~3 : 27 : 70) was consistently observed despite several structural and electronic variations of the MAD and ATPH derivatives. This implies that (TPP)Al cations make a considerable contribution to monomer activation and the propagation steps [229].



Scheme 6.177

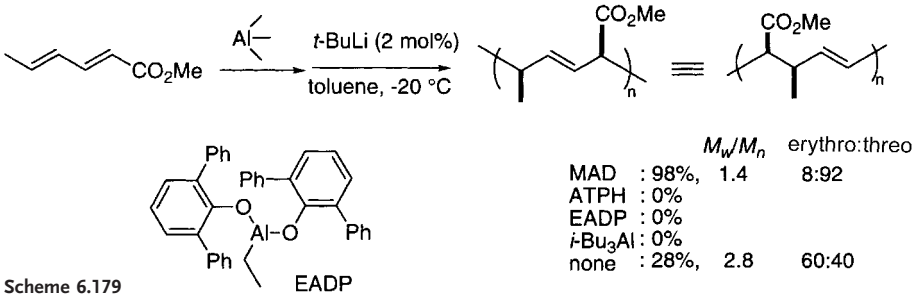
Other Type of Polymerization Involving Aluminum Enolate Intermediates

The MAD-(TPP)AlX system was extended to the polymerization of methacrylonitrile (Scheme 6.178). The high-speed living nature of this procedure was preserved to give atactic (mm : mr : rr = 28 : 52 : 20) polymers [230].



Scheme 6.178

threo-Selective polymerization of (*E*,*E*)-methylsorbate was realized by using *t*-BuLi as initiator in the presence of the bulky aluminum reagent MAD (Scheme 6.179) [231]. In contrast with the effectiveness of MAD, ATPH, which is more bulky than MAD, had scant reactivity. Other aluminum reagents examined were similarly ineffective. Control of MWD is rather difficult; it is not easy to obtain values below ~1.4. MAD has less steric influence on the δ position of methyl sorbate that forms the C–C bonds, whereas polymerization of MMA involves the β carbon under significant steric control.

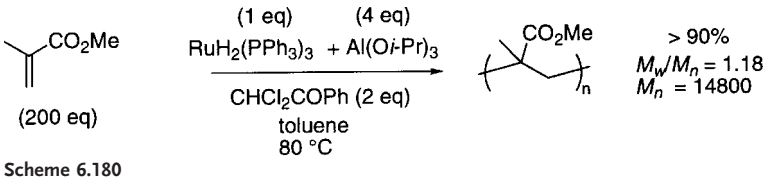


Scheme 6.179

6.2.6.2 **Radical Polymerization**

Although are no examples of stereocontrol aided by bulky or well-designed aluminum reagents in radical polymerization, the remarkable effects of aluminum species are still worthy of comment.

A ruthenium hydride complex, $RuH_2(PPh_3)_4$, has been employed for polymerization of methyl methacrylate (MMA) in conjunction with a chloride-type initiator, $CHCl_2COPh$, and $Al(O\textit{i}\text{-}Pr)_3$ in toluene at 80 °C (Scheme 6.180) [232]. Although $RuH_2(PPh_3)_4$ is active even in the absence of $Al(O\textit{i}\text{-}Pr)_3$, this aluminum additive has a substantial accelerating effect on the reaction rate. The polymers obtained had narrow MWD ($M_w/M_n = \sim 1.1$).



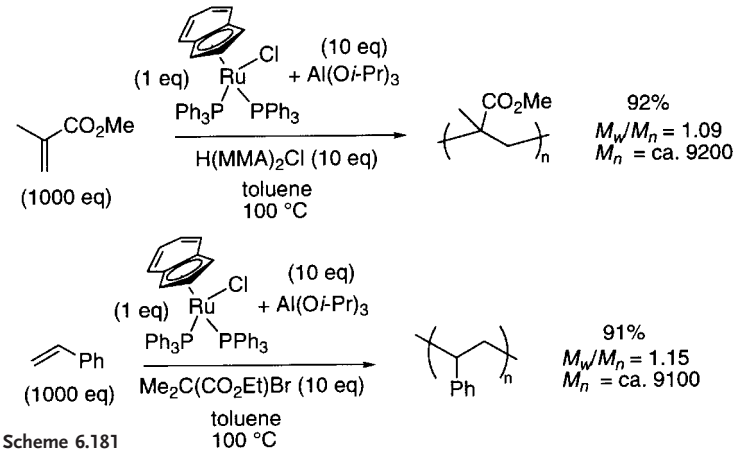
Scheme 6.180

A half-ruthenocene complex, Ru(indenyl)$Cl(PPh_3)_2$ was similarly used for polymerization of MMA in conjunction with an MMA-dimer-type initiator, $H(MMA)_2Cl$ (Scheme 6.181) [233]. Addition of $Al(O\textit{i}\text{-}Pr)_3$ accelerated the polymerization rate to afford similar living polymers ($M_w/M_n = \sim 1.1$). The behavior of the Ru–Ind complex was similar in the polymerization of styrene. Polystyrene with narrow MWD ($M_w/M_n = \sim 1.1$) was obtained by use of a suitable radical initiator – $Me_2C(CO_2Et)Br$.

6.2.6.3 **Cationic Polymerization**

Use as Co-catalysts

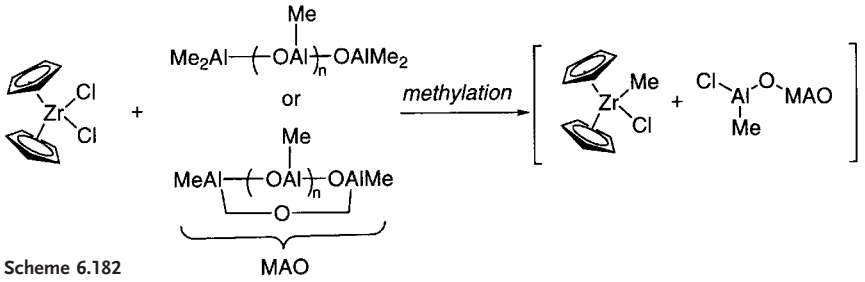
The search for an efficient catalyst for cationic polymerization has attracted much attention since 1953 when the Ziegler-Natta catalyst was found to readily promote olefin polymerization [234]. The general formula of Ziegler-Natta catalysts in-



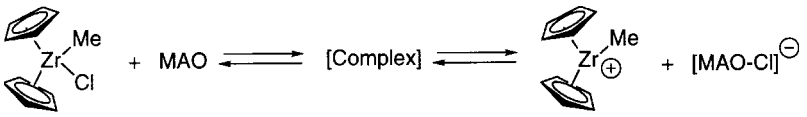
Scheme 6.181

cludes a transition metal species and organometallic compounds of Group 1, 2, or 3. In their advanced system ($TiCl_4$–Me_3Al), aluminum is assumed to be a co-catalyst which activates Ti(IV) creating real catalytic sites that enable π-coordination of olefins or alkynes and polymer chain growth. The serendipity of this reaction procedure still remains as a milestone and was applied well in the development of modern variants of polymerization co-catalysts [235]. Although the Ziegler-Natta catalyst ($TiCl_4$–Me_3Al) is capable of polymerization of ethylene, propylene and other higher α-olefins did not polymerize [236]. In contrast, the catalyst $TiCl_3$–Me_3Al afforded polymerization of propylene.

The second milestone in this field was the discovery that methylaluminoxane (MAO) was a co-catalyst in the zirconocene(IV) dichloride-mediated polymerization of α-olefins (Scheme 6.182) [237]. MAO works in the same way as Me_3Al in Ziegler–Natta catalysis, but more effectively. Its activity was maximum when mixed with 0.2 and 0.5 mol water mol^{-1} aluminum alkyl [238]. The function of MAO could be summarized as methylation and subsequent abstraction of the chloro (or the methyl) from the zirconocene (Schemes 6.182 and 6.183). This sequence generates active Zr cationic species and at this stage MAO also serves as a pivotal backbone of counter anions. The active sites also enable temporary ligation of Zr–C σ bonds, consistent with the living end of growing polymers. The actual reaction involves alkylation of Cp_2ZrCl_2 then abstraction of Cl from the metal center; the vacant orbital (or cationic site) thus formed enables coordination of unsaturated C–C bonds, which undergo a subsequent insertion reaction with Zr–C σ-bonds. The coordination–insertion sequence is repeated regularly, resulting in sequential chain growth and affording polymers until the reaction is terminated by, for example, a chain-transfer mechanism (β-elimination, β-hydride transfer, etc.). Because a huge amount of MAO (100–300 equiv.) is required per equivalent of Zr, much effort has been devoted to identifying the actually reactive site (or species) – a "hot spot" hidden within MAO. This is challenging because the structure of MAO is very complicated, lies in dynamic equilibria, and hence remains unsolved.

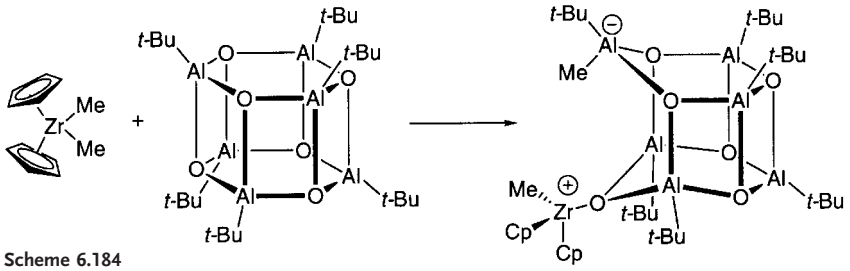


Scheme 6.182



Scheme 6.183

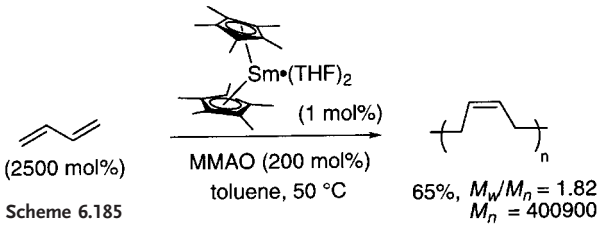
Barron and coworkers recently focused on the structure of oligomers of tetra-*t*-butyldialuminoxane and *t*-butylaluminoxane and the situation for MAO might be best viewed in this light (Scheme 6.184) [239]. The interaction of a Zr catalyst with these aluminoxanes has been characterized by X-ray single crystal structure analysis of the corresponding Al–O–Zr complex, for which catalytic activity in promoting ethylene polymerization was one-fifth that of the Cp_2ZrCl_2–MAO system.



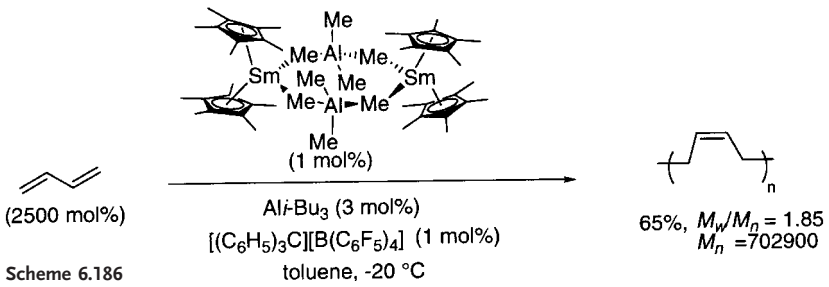
Scheme 6.184

Lanthanide metallocene complexes $Cp_2Sm(THF)_2$ or $[Cp_2Sm(\mu\text{-}H)]_2$ alone do not have catalytic activity when applied to polymerization of butadiene. In contrast, when smarocene complex $Cp_2Sm(THF)_2$ was treated with methylaluminoxane containing isobutylaluminoxane (MMAO) or $Al(i\text{-}Bu)_3/[Ph_3C][B(C_6F_5)_4]$ it had extremely high activity in the polymerization (Scheme 6.185) [240] and yielded polybutadiene with high 1,4-*cis* microstructures (up to 98.8%), of high molecular weight ($M_n = 105 \sim 106$), and with a narrow MWD ($M_w/M_n < 2$).

Further studies revealed $[Cp_2Sm(\mu\text{-}Me)_2AlMe_2]_2$ with co-catalyst $Al(i\text{-}Bu)_3/[Ph_3C][B(C_6F_5)_4]$ to be an excellent "living" system for the stereospecific 1,4-*cis*-polymerization of butadiene (Scheme 6.186).

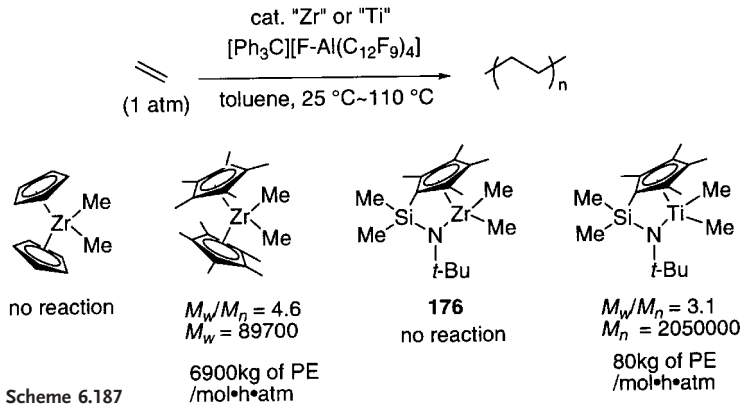


Scheme 6.185



Scheme 6.186

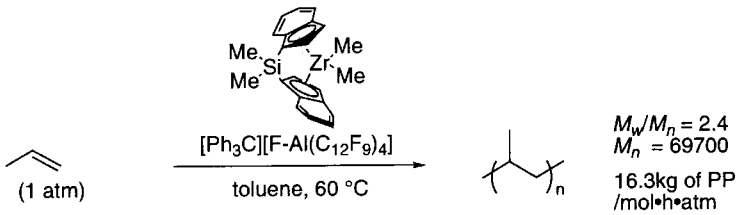
Among the aforementioned abstractors MAO- or MMAO-promoted reactions are complicated, and intractable species are produced. Despite the elusiveness of MAO and MMAO, the reaction of metallocene dialkyls with electrophiles which either generate or contain very weakly coordinating anions has proved a particularly successful strategy for the generation of highly active, MAO-free polymerization catalysts. Marks reported isolable and X-ray crystallographically characterizable catalysts for study of the molecular basis of this type of polymerization catalysis [30].



Scheme 6.187

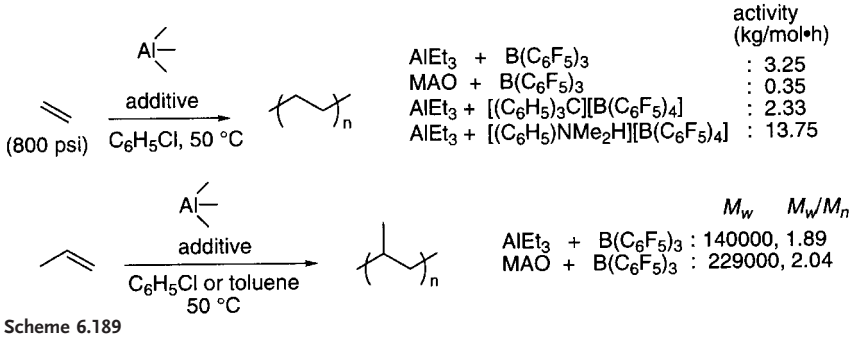
Whereas $Cp_2ZrMe^+[F\text{-}Al(C_{12}F_9)_4]^-$ and **176** have negligible activity in the polymerization of ethylene at 25 °C and 1.0 atm monomer pressure, increasing the

bulk of the ancillary ligand effects dramatic increases in polymerization activity (Scheme 6.187). CGCMMe$^+$ polymerization characteristics are markedly temperature-dependent, with CGCTiMe$^+$[F-Al($C_{12}F_9$)$_4$]$^-$-mediated polymerization at 60 and 110 °C affording ultrahigh molecular weight polyethylene. Under some reaction conditions (60 °C, 20 μmol catalyst) the strongly ion-paired catalyst **177** produces highly isotactic polypropylene ([*mmmm*] = 98%) (Scheme 6.188).



Scheme 6.188

The aluminum-based polymerization of higher alkenes, e.g. propylene, had barely been reported when Sen and coworkers discovered $AlEt_3$–$B(C_6F_5)_3$ and related systems (Scheme 6.189). With these catalysts high molecular weight, linear homo- and co-polymers of ethylene and propylene were prepared [241]. When $AlEt_3$ and $B(C_6F_5)_3$ were mixed near-quantitative exchange of organic groups occurred between aluminum and boron to form triethylboron and $Al(C_6F_5)_3$. None of the combinations triethylboron and $B(C_6F_5)_3$ (1 : 1) or triethylboron and triethylaluminum (1 : 1), or $Al(C_6F_5)_3$ alone, catalyzed the polymerization of ethylene. Clearly, the $AlEt_3$ and $B(C_6F_5)_3$ combination is critical for formation of a hitherto unknown active species which facilitates polymerization; this awaits further research. Other combinations, e.g. MAO–$B(C_6F_5)_3$ or $AlMe_3$–$B(C_6F_5)_3$, were also capable of polymerizing ethylene and even propylene. Either boron co-catalyst $[Ph_3C][B(C_6F_5)_4]$ or $[PhNMe_2][B(C_6F_5)_4]$ worked as an effective substitute for $B(C_6F_5)_3$.

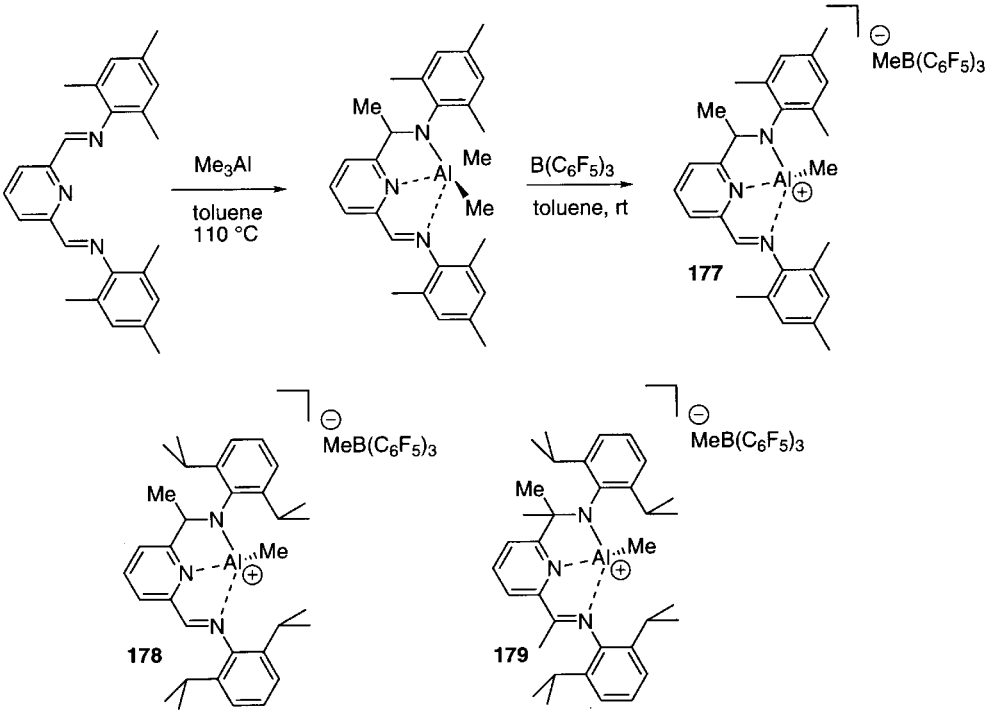


Scheme 6.189

Cationic Aluminum Catalysts

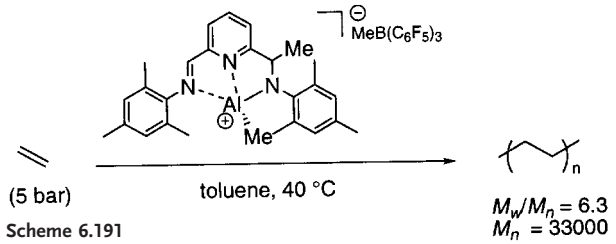
As already mentioned, neutral aluminum has strong Lewis acidity and high oxophilicity. It has long been a concern of chemists whether cationic aluminum species would have unprecedented reactivity and even more Lewis acidity. Several aluminum cations were isolated and characterized by X-ray single-crystal analysis, as described in Section 6.1.2.2; most were, however, hexacoordinated aluminum that catalyzed bimolecular reactions. They were also useful in the polymerization of α-olefins, the subject of this section.

Cationic complexes **178–180** are readily prepared from Me_3Al and $B(C_6F_5)_3$ (Scheme 6.190), and are active in the polymerization of ethylene, affording solid polyethylene – their activities are 60 and 120 g mol^{-1} h^{-1} bar^{-1} [242]. The polymer products obtained from each catalyst are low molecular weight, with M_w ranging from 13 000 to 33 000 (Scheme 6.191). It is noteworthy that a change in the ligand backbone from a single methyl group in **179** to three methyl groups in **180** has the effect of reducing the molecular weight by almost half.



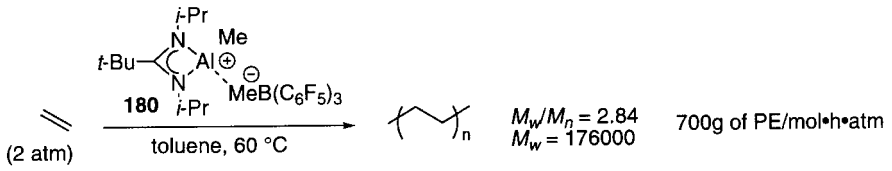
Scheme 6.190

A toluene solution of **181** polymerizes ethylene (2 atm) to solid polyethylene at 60 °C (Scheme 6.192). More active catalysts are generated by activation of **182** with 1 equiv. $[Ph_3C][B(C_6F_5)_4]$ in toluene (Scheme 6.193) [243]. It was proposed that

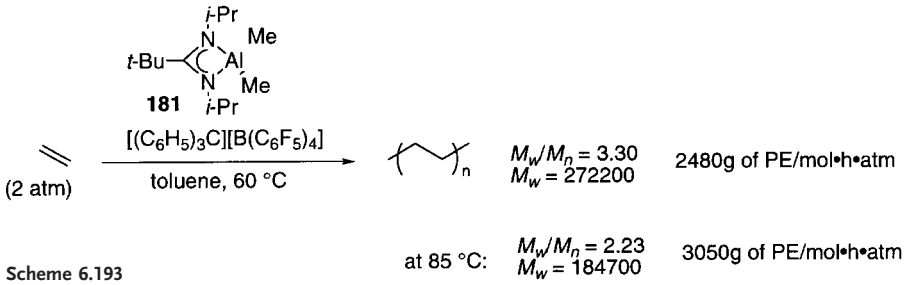


Scheme 6.191

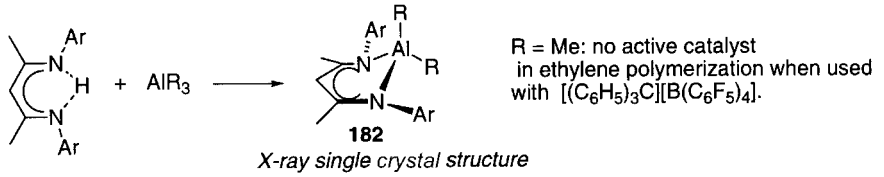
three-coordinate $[RC(NR')_2]AlR^+$ cations are the active species in these polymerizations, although aluminum cations **183** and **184** have no catalytic activity in ethylene polymerizations (Schemes 6.194 and 6.195) [244].



Scheme 6.192

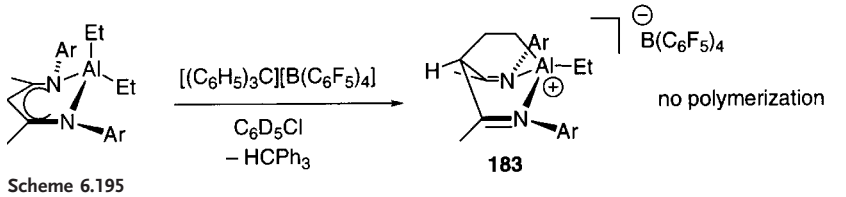


Scheme 6.193



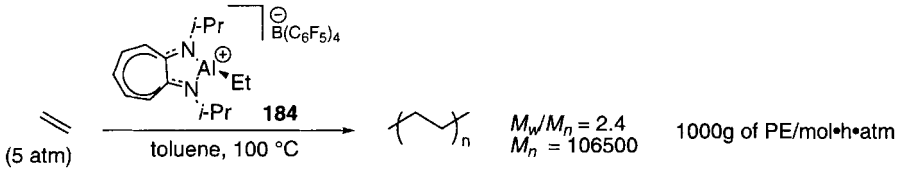
Scheme 6.194

Base-free compound **185** has activity in the polymerization of ethylene (Scheme 6.196) whereas dinuclear cations **186** have only trace activity. Dinuclear hydride cation **186** polymerized MMA to, predominantly, syndiotactic PMAA (Scheme 6.197) [245]. In contrast, neutral hydride **187**, dinuclear methyl cation

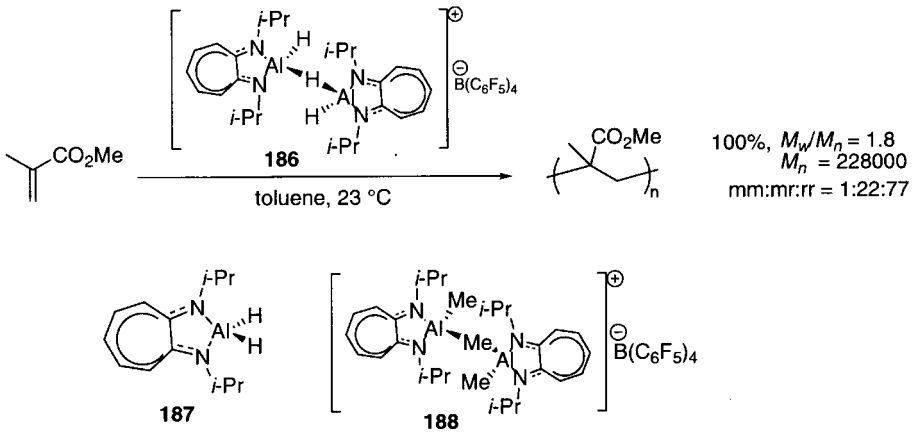


Scheme 6.195

188, and base-free cation **185** do not polymerize MMA under similar conditions. It is clear that the reactivity of cationic Al species is strongly influenced by their structures – nuclearity and identity of Al–R.

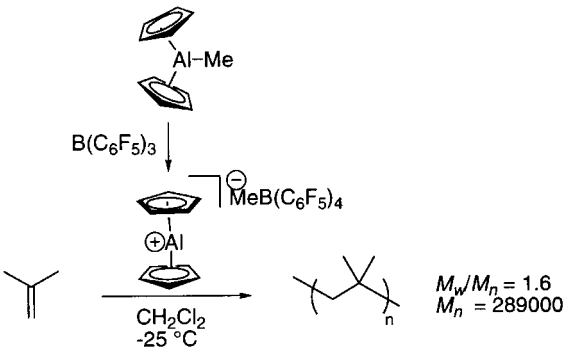


Scheme 6.196



Scheme 6.197

For carbocationic initiation metal–carbon σ-bonds are not required. Thus, the hitherto unknown aluminocenium cation **189**, readily synthesized from Cp_2AlMe and $B(C_6F_5)_3$, was evaluated for its potential ability to initiate polymerization of isobutene [246]. Poly(isobutene) was obtained within a few minutes at –25 °C to give a high molecular weight polymer (M_w = 289 000) with an MWD of 1.6 (Scheme 6.198). This high-speed polymerization occurred similarly even at –78 °C within a few minutes to give a polymer of considerably higher molecular weight (M_w = 1 800 000) despite a large MWD (M_w/M_n = 3.0).



Scheme 6.198

Taking into account the mechanism of aluminum cation-mediated polymerization of olefins, the balance between olefin insertion and β-hydride transfer to the monomer, both of which occur on aluminum cation centers, should be discussed. An interesting theoretical study predicted that none of the proposed active cationic species should give a high-molecular-mass polymer [247]. The authors concluded that olefin polymerization at a single aluminum center is rather unlikely.

6.3 Conclusions

Compared with classical Lewis acids, the "designer Lewis acid", originally named by Yamamoto, in principle corresponds to the aluminum catalysts that promote a variety of selective organic reactions effectively and efficiently by appropriate choice of ligand. Synthetically this strategic concept has found widespread application. As exemplified by ATPH, a trivalent aluminum species (sp^2) that subsequently assumes tetracoordination (sp^3) by complexation with a Lewis base, has served as an effective reagent for selective transformations. Attachment of the electron-withdrawing groups –OTf and $–NTf_2$ is expanding the scope of hitherto unachievable organic transformations. In contrast, two other large advances have appeared very recently. One involves aluminum species with higher coordination, including penta- (sp^3d) and hexa- (sp^3d^2) coordination; the other is consistent with aluminum cations. Studies so far on these subjects suggest that the structures of the ligands accommodate special electronic properties, and the shape and geometry of the aluminum; this results in relatively stable aluminum species even when the aluminum(III) is highly electron-deficient. Higher-coordinated reagents gave us new terms of reference with which to interpret the stability and reactivity of aluminum(III). The phrase "organoaluminums are labile to water and air" no longer makes a general sense in this respect. Aluminum(III) species endowed with such stability facilitate the preparation of long-lived catalysts and render or-

ganic reactions catalytically more efficient. The search for these new aspects has just started and remains a significant challenge in selective organic synthesis including stereo-controlled polymerization.

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7
Gallium in Organic Synthesis

Masahiko Yamaguchi

Gallium compounds have become very important in the electronics industry, and some gallium complexes have been examined for use as anticancer agents or diagnostic agents [1]. In this regard, considerable advances have been made since the nineteen-eighties in the synthesis and structural analysis of the organometallic compounds of gallium; this has revealed they tend to aggregate to form dimers, trimers, or higher polymers [2–4]. In contrast, organogallium compounds have been considered less attractive in organic synthesis, because their nucleophilicity and Lewis acidity are generally less than for the corresponding organoaluminum compounds and compounds of other group 13 elements, and they are more expensive. Recent studies have, however, revealed that gallium compounds can have novel properties in organic synthesis, whereas aluminum compounds cannot. Summarized in this review are their use as Lewis acids, organometallic alkylating reagents, radical reagents, and low valence reagents. Although the toxicity of many organogallium compounds is not known, for $Ga(NO_3)_3$ intravenous LD_{50} for mice is 55 mg kg^{-1} [5, 6].

7.1
Use as Lewis Acids

Gallium trichloride has been used in Friedel-Crafts alkylation and acylation reactions as a Lewis acid [7, 8]. Although its Lewis acidity is lower than that of aluminum trichloride, its greater solubility in organic solvents makes it useful for kinetic studies. Gallium trichloride is soluble even in hexane. Recent studies by Yamaguchi have, however, revealed novel aspects of gallium compounds in electrophilic aromatic substitution reactions. It has been shown by spectroscopic studies that gallium trichloride interacts with π-acids such as silylethyne [9–11] or silylallene [12]. The gallium complexes are sufficiently electrophilic to react with aromatic hydrocarbons even at –78 °C, giving organogallium arenium intermediates (Scheme 7.1) [9–11]. Although aluminum trichloride is also known to interact with alkynes, gallium complexes are more reactive in these reactions. Addition of bases such as butyllithium or THF results in deprotonation, generating a vinylgallium intermediate and, finally, protodegallation produces the β-silylethenylated

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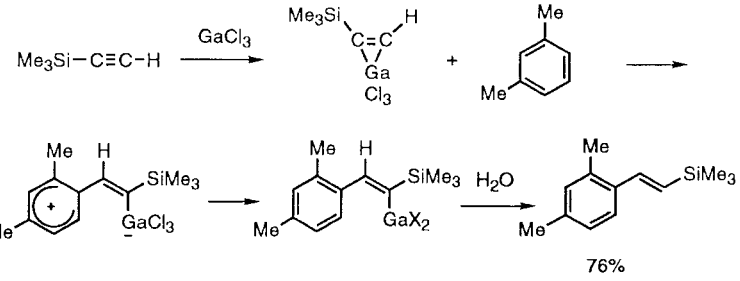
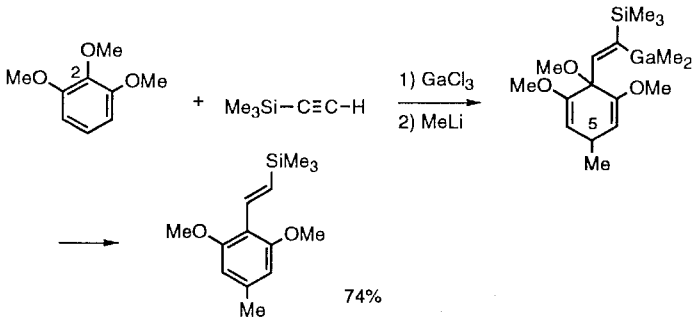
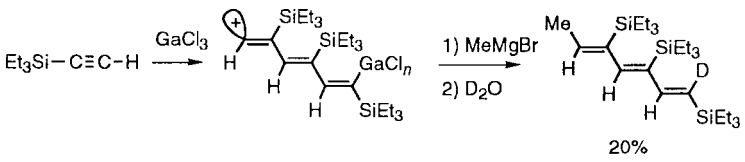
arenes. *ipso*-Substitution of 1,2,3-trimethoxybenzene occurs at the 2 position, and treatment of the arenium cation thus formed with methylmagnesium halide gives 2,5-dihydrobenzene methylated at the 5 position (Scheme 7.2). Aqueous work-up induces protodegallation and elimination of methanol, giving 1,4-dialkylated benzene derivatives. In the absence of aromatic hydrocarbons the silylethyne–gallium trichloride complex spontaneously trimerizes to a conjugated trienyl cation which, on treatment with organolithium or magnesium compounds, gives alkylated trienes (Scheme 7.3) [13]. In the presence of gallium trichloride, cationic species such as arenium cations or vinyl cations seem to survive long enough to be attacked by organometallic reagents. Although a stoichiometric amount of gallium trichloride is required in these reactions, Murai found that a catalytic amount of the reagent (10 mol%) promotes intramolecular reaction of acetylene and arene via in situ protonation of the allylgallium intermediate [14].



Scheme 7.1

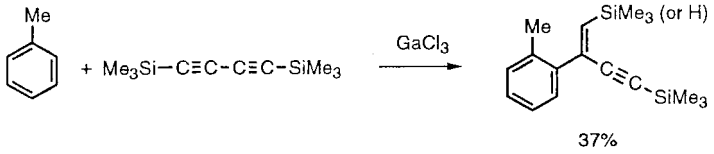


Scheme 7.2



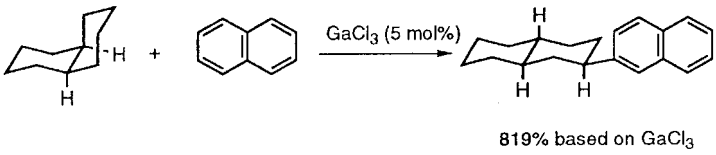
Scheme 7.3

Unusual orientation has been observed by Yamaguchi in electrophilic aromatic substitution using gallium trichloride. The reaction of toluene and bis-silylated 1,3-butadiyne gives an *o*-substituted product exclusively (Scheme 7.4), and even isopropylbenzene reacts at the *o*-position predominantly [15]. The tendency of the reaction to occur at the vicinity of the alkyl substituent is, however, restricted to the diyne-based electrophile; for other related electrophiles derived from silylethyne, silylallene, or bissilylated 1,3,5,7-octatetrayne normal *o*/*p* orientation is observed.



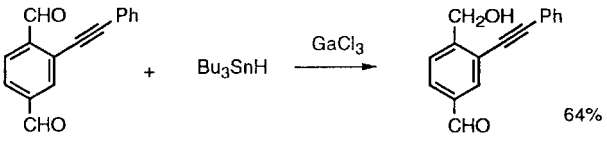
Scheme 7.4

Gallium trichloride activates even cycloalkane C–H bonds, which can be used for catalytic aromatic alkylation (Scheme 7.5) [16]. The reaction of *cis*-perhydronaphthalene and naphthalene in the presence of a catalytic amount of gallium trichloride (5 mol%) gives 2-naphthylated *trans*-perhydronaphthalene. Carbon–carbon bond formation occurs predominantly at the 2 position of naphthalene and the 3 position of perhydronaphthalene. It is worth noting that *cis*-perhydronaphthalene reacts much more effectively than the *trans*-isomer. These observations indicate that the equatorial tertiary proton of the cycloalkane, rather than the axial proton, is activated selectively, and the carbocation resulting after the migration reacts with naphthalene. This is an interesting example of selective CH activation of alkanes.



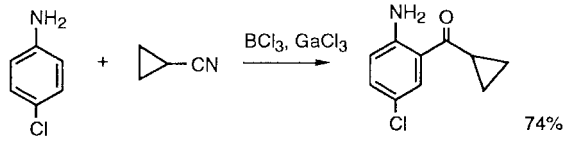
Scheme 7.5

Such interaction of gallium trichloride with an alkyne π-acid was used by Yamamoto in the regioselective reduction of aldehyde groups located in the vicinity of an ethynyl group (Scheme 7.6) [17].

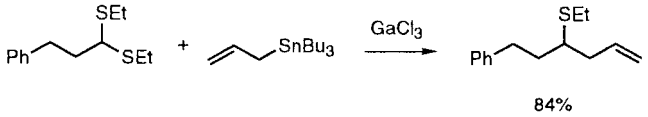


Scheme 7.6

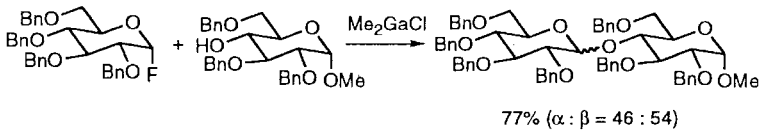
The Lewis acid interaction of gallium(III) compounds with heteroatoms is also important in organic synthesis. Gallium trichloride can be used for catalytic aromatic acylation reactions as indicated by Mukaiyama [18]; aliphatic and aromatic acid anhydrides react with anisole derivatives in the presence of 10 mol% gallium trichloride and 10–20 mol% silver perchlorate, giving *p*-acylated products. Olah developed gallium tris(trifluoromethanesulfonate) for the Friedel-Crafts alkylation [19] and later Kobayashi found the reagent to be effective for the selective acylation of 2-methoxynaphthalene at the 6 position [20]. Kobayashi also used gallium tris(nonafluorobutanesulfonate) for the catalytic acylation reaction [21]. Houpis observed that the boron trichloride-promoted *o*-acylation of anilines with nitriles is accelerated by gallium trichloride; this is ascribed to abstraction of chlorine from the organoboron intermediate with concomitant formation of a stable $GaCl_4$ anion (Scheme 7.7) [22, 23]. It was found that gallium trichloride is more effective than aluminum trichloride in this transformation. As shown by Saigo, the soft nature of gallium can be utilized effectively in the activation of dithioacetals – in the presence of gallium trichloride and water thioacetals are hydrolyzed to aldehydes or ketones [24]; allylstannanes react with thioacetals to give allylated products (Scheme 7.8) [25]. Kobayashi showed that chlorodimethylgallium serves as a promoter for glycosidation using glucosyl fluorides (Scheme 7.9) [26].



Scheme 7.7



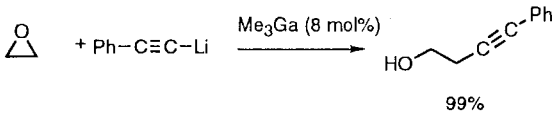
Scheme 7.8



Scheme 7.9

Utimoto found that the presence of a catalytic amount (8 mol%) of trimethylgallium promotes the alkynylation of oxiranes with lithium acetylides (Scheme 7.10) [27, 28]. The Lewis acid interaction of the oxirane oxygen with trimethylgallium is believed to be involved. Maruoka later observed that an additional adjacent oxygen

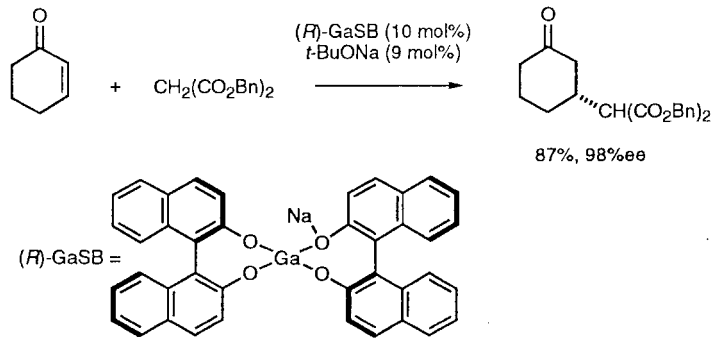
functionality dramatically accelerates the ring-opening reaction even with 1 mol% trimethylgallium; it is explained that the pentacoordinated gallium species is involved [29].



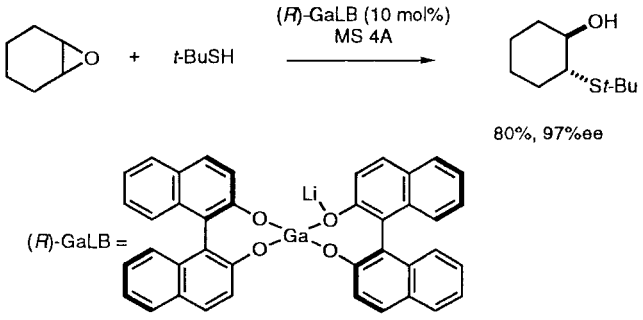
Scheme 7.10

7.2 Use as Bases

Organogallium compounds serve as bases – chiral phenoxygalliums, in particular, have been employed in asymmetric catalysis by Shibasaki. Gallium sodium bis(binaphthoxide) (GaSB) prepared from gallium trichloride, sodium *t*-butoxide (4 equiv.) and 2,2′-binaphthol (2 equiv.) is an excellent catalyst for the asymmetric Michael addition of malonate to 2-cyclopentenone and 2-cyclohexenone (Scheme 7.11) [30, 31]. Use of 10 mol% catalyst gives the adducts in high yields and high enantiomeric excesses up to 98%. The reaction can be accelerated by the presence of an additional equivalent of sodium *t*-butoxide, which is probably involved in rapid complex formation between sodium malonate and GaSB. Gallium lithium bis(binaphthoxide) (GaLB) catalyst, prepared from gallium trichloride and lithiated binaphthol, can be used in the asymmetric ring opening of *meso*-epoxides with *t*-butyl mercaptan [32]. The reaction, which is accelerated by the presence of 4-Å molecular sieves (MS), is conducted with 10 mol% of the complex, giving the thioalcohol in 97% ee from cyclohexene oxide (Scheme 7.12). The asymmetric ring opening of the same epoxide with *p*-methoxyphenol is catalyzed by 20 mol% of the GaLB catalyst to give the alkoxycyclohexanol in 93% ee [33].

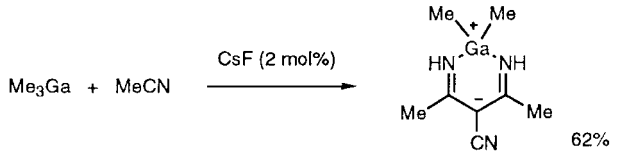


Scheme 7.11



Scheme 7.12

Neumüller observed that in the presence of a catalytic amount (2 mol%) of cesium fluoride reaction of trimethylgallium with excess acetonitrile gives oligomeric compounds (Scheme 7.13) [34]. Because trimethylgallium itself is inert, it is believed that an ate complex, Me_3GaF^-, which is more basic than trimethylgallium, deprotonates acetonitrile to give the condensation product.



Scheme 7.13

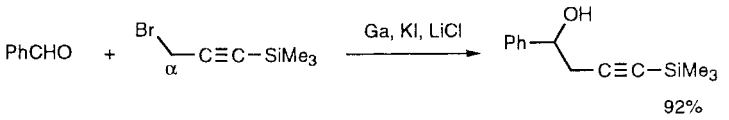
7.3
Use as Organometallic Alkylating Reagents

Organolithium and magnesium reagents, the most common main element reagents used in organic synthesis, are employed in transformations such as carbonyl addition, organohalogen substitution, conjugate addition, or cross coupling. Because these reagents are often too reactive for selective synthesis, derivatives of other metals are used, including B, Al, In, Si, Sn, An, or Cd. Organogallium compounds have also become important in this regard, and several characteristic reactions have been discovered.

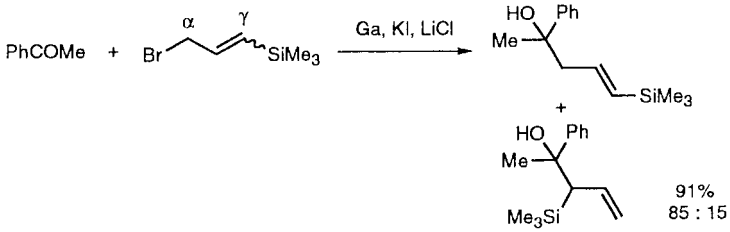
7.3.1
Carbonyl Addition Reaction

Huang reported that organogallium reagents can be generated by treating allyl or propargyl halides with gallium metal in the presence of activators such as potassium iodide and lithium chloride [35, 36], and that Barbier synthesis with alde-

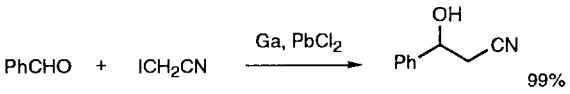
hydes or ketones gives unsaturated alcohols. Carbon–carbon bond formation by use of propargylgallium generally occurs at the α position (Scheme 7.14). Selectivity depends on substituents on the allylgalliums: Methyl derivatives react at the γ position and silyl derivatives at the α position (Scheme 7.15). Takai showed that such allylgallium formation can be catalyzed by indium metal [37]. Oshima and Wang found that carbonyl addition by use of allylgalliums occurs even in aqueous solvents [38, 39]. The former authors prepared the organometallic reagent from gallium trichloride and allylmagnesium bromide, the latter from gallium metal. Huang generated gallium enolates from metallic gallium and trichloroacetate or iodoacetonitrile in the presence of a catalytic amount of lead dichloride, and added it to aldehydes (Scheme 7.16) [40]. Gallium triiodide prepared in-situ from gallium metal and iodine promotes aldol addition of α-bromo ketone to aldehydes or imines (Scheme 7.17) [41]. The diastereoselectivity of the addition in the presence of methylgallium diiodide, prepared from gallium metal, iodine, and methyllithium, can be controlled by changing the solvent either to DMF or THF. Treatment of 1-alkynes with gallium triiodide and tributylamine converts them to alkynylgallium compounds, which can be added to aldehydes (Scheme 7.18) [42]. Gallium trichloride and aluminum triiodide did not perform this transformation effectively. Ate complexes derived from triorganogallium compounds and alkyllithium compounds transfer an alkyl group to acid chlorides, giving ketones (Scheme 7.19). The ease of alkyl transfer decreases in the order: $PhCH_2 > Ph > PhC\equiv C > Bu$, Me > cyclopentyl [43].



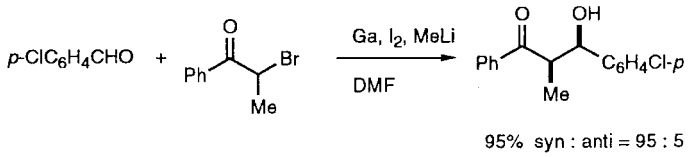
Scheme 7.14



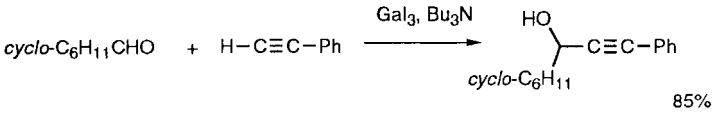
Scheme 7.15



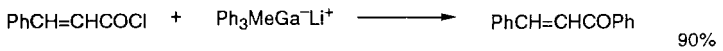
Scheme 7.16



Scheme 7.17

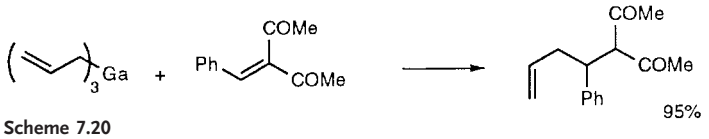


Scheme 7.18

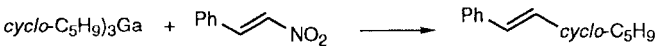


Scheme 7.19

Araki found that triallylgallium and trimethylgallium add to olefins activated by two electron-withdrawing groups (Scheme 7.20) [44]. The reactions of *β*-nitrostyrenes with trialkylgalliums were examined by Huang; they were found to give substituted products at the nitro group (Scheme 7.21) [45]. A single electron transfer mechanism was proposed on the basis of ESR studies.

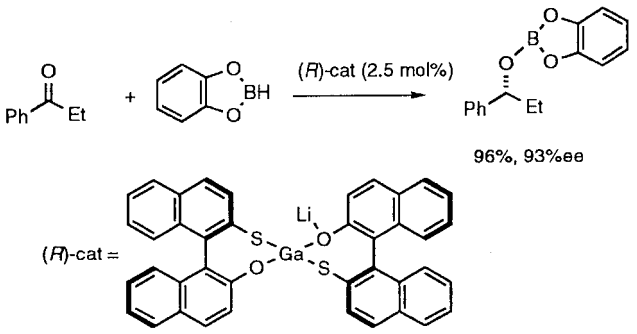


Scheme 7.20



Scheme 7.21

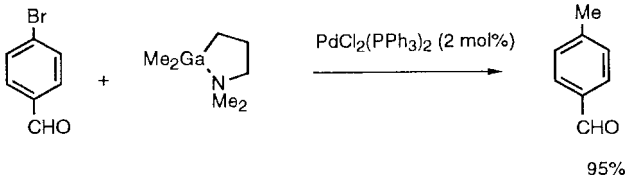
Woodward developed an asymmetric carbonyl reduction using catecolborane in the presence of a catalytic amount of a gallium thiobinaphthol (2.5 mol%) and obtained the optically active secondary alcohol from propiophenone in 93% ee (Scheme 7.22) [46, 47].



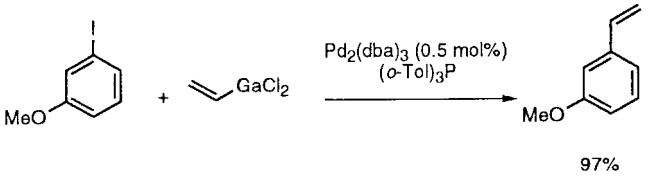
Scheme 7.22

7.3.2
Cross-coupling Reactions

Organogallium compounds can be used as alkylating reagents in cross-coupling reactions with aromatic or alkenyl halides. Blum examined intramolecular tetra- or pentacoordinated methylgallium derivatives for the palladium-catalyzed methylation of aromatic halides (Scheme 7.23) [48–50]. Although the reactivity of the gallium compounds is generally less than that of the aluminum compounds, unlike the aluminum complex the gallium complex tolerates functional groups such as carbonyl, cyano, nitro, and benzylic halides. The reaction rate with $Me_2N(CH_2)_2OGaMe_2$ is more than those with $MeO(CH_2)_2OGaMe_2$, *t*-$Bu_2P(CH_2)_3GaMe_2$, and $Me_2N(CH_2)_3GaMe_2$. Oshima conducted aromatic vinylation reactions with vinylgallium dichloride generated from vinylmagnesium halide and gallium trichloride. Aromatic iodides react in the presence of a palladium complex and tris(*o*-tolyl)phosphine (Scheme 7.24) [51].



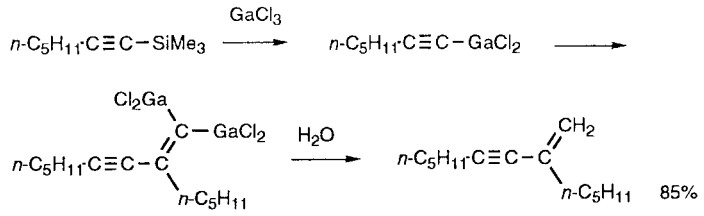
Scheme 7.23



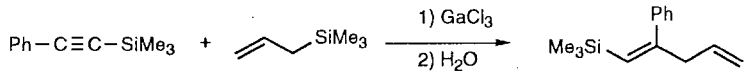
Scheme 7.24

7.3.3
Carbometalation Reactions

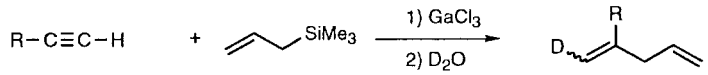
Carbometalation (carbogallation) with a carbon–carbon triple bond is a characteristic reaction of organogallium compounds and proceeds more effectively than with organoaluminum compounds. Carbogallation to carbon–carbon triple bonds was reported for the first time by Yamaguchi in the dimerization of alkynylgallium [52]. Treatment of silylated 1-alkynes with gallium trichloride gives enynes (Scheme 7.25). The alkynyldichlorogallium generated by the transmetalation is unstable in hydrocarbon solvents and spontaneously dimerizes to give a bisgallated enyne compound which on protodegallation is converted to the enynes. This is an unusual dimerization reaction of a main element metal acetylide. Aluminum trichloride is much less effective for this transformation. Such coupling also occurs with lithium acetylides in the presence of gallium trichloride. Allylgalliums add to 1-alkyne or silylated alkynes, giving 1,3-dienes after protodegallation (Schemes 7.26 and 7.27) [53]. Whereas 1-silylated alkynes undergo *cis*-addition, the stereochemistry of the reactions of 1-alkynes depends on the alkyl substituents. Smaller alkyl derivatives give comparable amounts of (*E*) and (*Z*) isomers on deuteration whereas *cis*-addition predominates with the cyclohexylacetylene. Takai observed acceleration of allylgallation of 1-alkynes in the presence of diisopropylethylamine; this was attributed to the in-situ formation of alkynylgallium [54].



Scheme 7.25



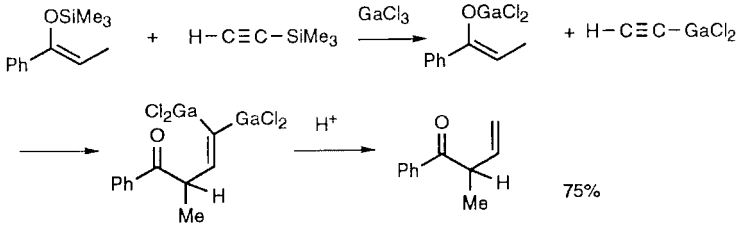
Scheme 7.26



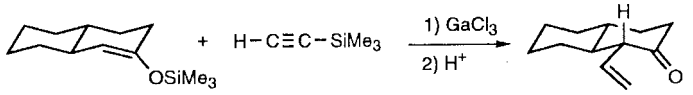
R = *n*-C_9H_{19} 74%, E:Z = 1:1
R = *cyclo*-C_6H_{11} 56%, E:Z = 9:1

Scheme 7.27

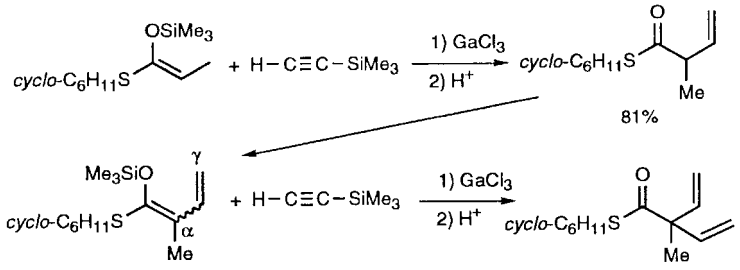
Gallium enolate and ethynylgallium, generated, respectively, from silyl enol ether and silylethyne by treatment with gallium trichloride, undergo carbogallation, giving α-ethenylated ketones after work-up with aqueous acid (Scheme 7.28) [55]. This reaction, which is complete within 5 min at room temperature, is a novel and convenient means of direct ethenylation of enolate. The reaction can be applied to the synthesis of ethenyl ketones with acidic α-protons, and isomerization to the thermodynamically stable conjugated enone is not usually observed. Equatorial preferences are observed in the ethenylation of cyclohexanone enolates; for example, ethenylation of a silyl enol ether derived from *trans*-3-decalone gave the equatorial isomer predominantly (Scheme 7.29) [56]. This contrasts with the stereochemistry of enolate alkylation, which occurs at the axial site of the enolate plane. Silyl dienolates, synthesized by α-ethenylation of thioesters then silylation, are ethenylated by this method at the α-position and not the γ-position (Scheme 7.30) [57]. The overall synthesis provides α,α-diethenylated carbonyl compounds, which are not readily accessible by conventional methods. The ethenylation also occurs with silylated 1,3-dicarbonyl compounds [58], and an ethenylmalonate with an acidic α-proton was obtained by this method (Scheme 7.31). The ethenylmalonate turns out to be relatively insensitive to acid, whereas it rapidly isomerizes to the conjugated compound in the presence of triethylamine.



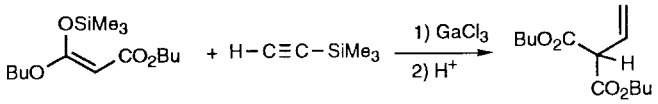
Scheme 7.28



Scheme 7.29

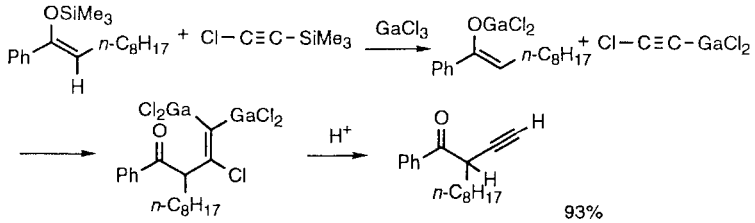


Scheme 7.30

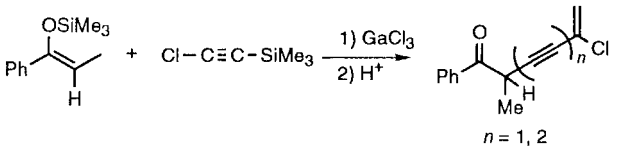


Scheme 7.31

When trimethylsilylated chloroethyne is used instead of the silylated ethyne, the silyl enol ether is ethynylated at the *α* position via carbogallation and *β*-elimination (Scheme 7.32) [59]. The *β*-elimination occurs during work-up. The ethynylated ketone with an acidic *α*-proton is obtained by careful isolation; it is less stable toward conjugation than the *α*-ethenyl ketones. Under conditions when *β*-elimination occurs during the reaction, sequential carbon–carbon bond formation occurs, giving *α*-ethynylated ketones and *α*-endiynylated ketones (Scheme 7.33) [60]. Although *α*-alkylation of carbonyl compounds via metal enolates is extensively used in organic synthesis, *α*-ethenylation and *α*-ethynylation, which connect sp^2 and sp carbon, respectively, to the carbonyl *α*-position, are much less investigated. Organogallium chemistry is found to be effective in these transformations.



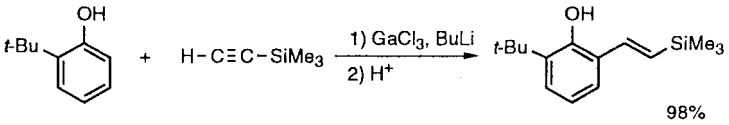
Scheme 7.32



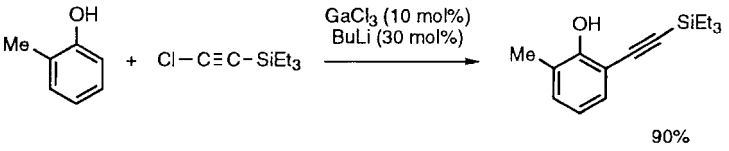
Scheme 7.33

Gallium phenoxide generated from gallium trichloride and butyllithium reacts with silylethyne to give *o*-(*β*-silylethenyl)phenols; this again involves carbogallation (Scheme 7.34) [61]. Studies on organogallium and organotin compounds revealed that both undergo a similar carbometalation reaction. Gallium and tin are elements that sit diagonally in the periodic table, and this interesting example shows that organometallic reagents of such elements have similar reactivity, reminiscent of organolithium and organomagnesium compounds in carbonyl addition reactions. The carbometalation reaction of phenoxygallium with chloroethyne gives *o*-ethynylated phenols (Scheme 7.35) [62]. Because gallium trichloride is regenerated

by the β-elimination, a catalytic amount of gallium trichloride (10 mol%) effectively promotes the ethynylation reaction.



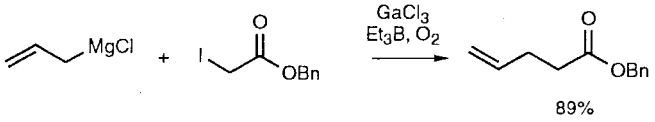
Scheme 7.34



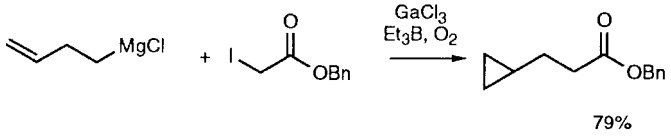
Scheme 7.35

7.4
Use as Radical Reagents

One interesting property of organogallium compounds is their tendency to undergo radical reactions, as indicated by Oshima. Allylgallium dichloride generated in situ from allylmagnesium halide and gallium trichloride promotes allylation of α-haloesters in the presence of triethylborane and oxygen (Scheme 7.36) [63]. Because allylgallium itself does not induce such reactions, a radical intermediate is formed by the boron reagent. The reaction proceeds more effectively in aqueous media than in organic solvents. The homoallylgallium reagent undergoes concomitant cyclization, giving cyclopropane derivatives, a typical cyclization reaction of the 3-butenyl radical (Scheme 7.37) [64]. Dichlorogallium hydride generated from gallium trichloride and $NaAlH(OCH_2CH_2OMe)_2$ (Red-Al) promotes radical cyclization of dienes [65].



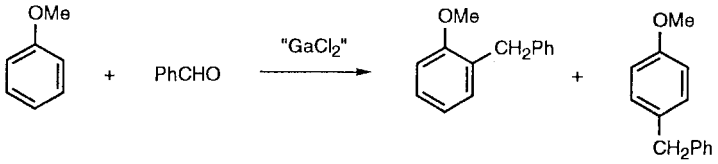
Scheme 7.36



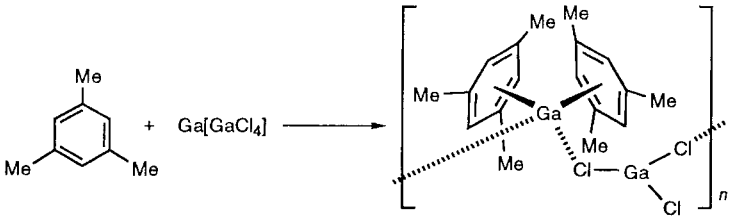
Scheme 7.37

7.5
Use as Low Valence Reagents

Unlike organoaluminum compounds, stable gallium(I) compounds are known. Formal gallium(II) dichloride "Ga_2Cl_4" has the dual reactivity of a mixed salt, $Ga[GaCl_4]$, or a gallium–gallium bonded compound, $Cl_2Ga–GaCl_2$. Saigo indicated that the reaction of "Ga_2Cl_4" with benzaldehyde in the presence of anisole gives *o*- or *p*-benzylated arenes by the reductive Friedel–Crafts alkylation (Scheme 7.38) [66, 67]. Acetals can also be used for this transformation. As extensively studied by Schmidbauer, the reactions of aromatic hydrocarbons with "Ga_2Cl_4" give π-complexes of gallium(I) (Scheme 7.39) [68].

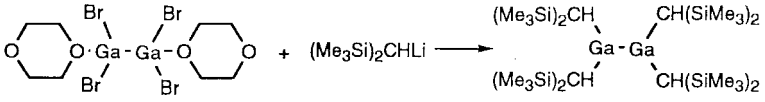


Scheme 7.38 77% (56 : 44)



Scheme 7.39 86%

The dioxane complex of "Ga_2Br_4" has been shown to be a compound with a gallium–gallium bond, and Uhl alkylated this with a bulky organolithium reagent to give a tetraalkylated gallium compound, the structure of which was determined by X-ray analysis (Scheme 7.40) [69]. Use of low valence organogallium compounds with gallium(I)–arene bonds or gallium–gallium bonds [4] in organic synthesis might become an interesting subject.



Scheme 7.40 63%

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8
Indium in Organic Synthesis

Shuki Araki and Tsunehisa Hirashita

8.1
Introduction

Indium is one of the Group 13 elements, of which boron and aluminum have widely been used in organic synthesis. In contrast, gallium and indium received little attention until a decade ago. Although the first organoindium compound was prepared as early as 1928 [1], and a very few applications of organoindium reagents in organic synthesis have been reported [2], their extensive use had to wait until the late 1980s. In 1988 it was revealed that allylic indium reagents are readily prepared in organic solvents by reaction of allylic halides and indium powder, and that these compounds are useful for the allylation of carbonyl compounds [3]. Since then applications of allylindium reagents and related organoindium reagents to organic transformations have been widely studied. In 1991 indium-

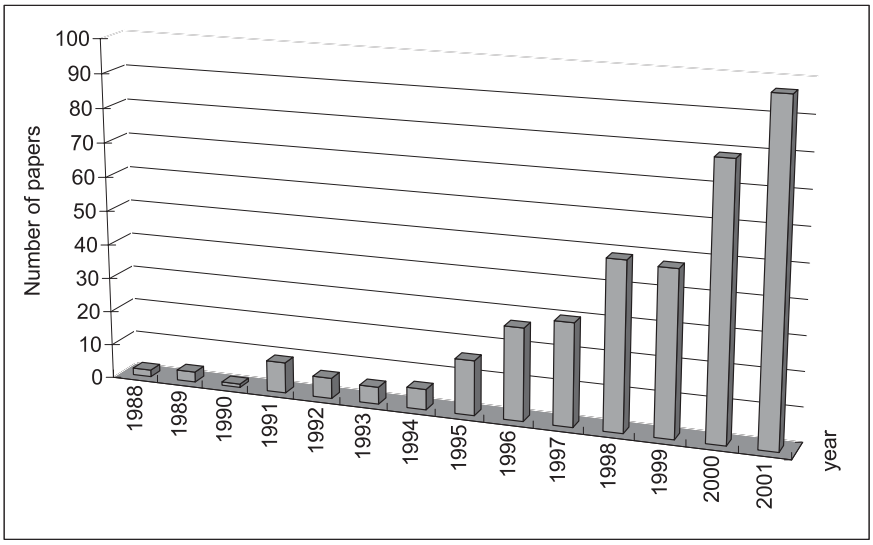

Fig. 8.1 Number of papers on inidium-mediated organic reactions

Main Group Metals in Organic Synthesis. Edited by H. Yamamoto, K. Oshima

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mediated Barbier-type allylations in water were reported [4]. Since the publication of this paper reactions in aqueous media mediated and catalyzed by indium have been receiving increasing interest for economic and environmental reasons. The number of papers devoted to indium-assisted organic reactions is illustrated in Fig. 8.1, which clearly shows that interest in the synthetic utility of organoindium reagents has increased over the last decade.

Indium metal is stable in air, and the toxicity observed for many metals is little known for indium. Because the first ionization potential of indium (5.8 eV) is as low as that of Li or Na, it is easy for indium to act as an effective single electron transfer (SET) agent. A feature of organoindium reagents is their ease of preparation – organoindium reagents can be prepared simply by mixing appropriate organic halides with indium. For example, allylindium sesquihalides are obtained without a formation of Wurtz-coupling by-products. Tolerance of water characterizes organoindium reagents in organic synthesis; their reactions can be performed under aqueous conditions without protection of hydroxyl and other protic groups on the reactants, a property which makes the reagents unique and important in respect of environmentally benign chemistry. Indium(III) salts such as indium trichloride and indium triflate have also been used as catalysts in both aqueous media and organic solvents. Organoindium reagents have a strong tendency to coordinate to heteroatoms, particularly oxygen functionalities such as hydroxyl or carboxyl groups in the substrates. This extraordinarily strong oxophilicity sometimes makes the indium-mediated reactions highly regio-, stereo-, and chemoselective. Because several reviews have been published on organoindium chemistry in organic synthesis [5], this chapter deals mainly with recent advances in indium-mediated organic synthesis published after these reviews.

8.2 Allylation and Propargylation

In the past decade much effort in organoindium chemistry has been devoted to study of carbonyl allylation and allylindation of carbon–carbon multiple bonds with allylic indium reagents. Apart from the conventional transmetalation of allyllithium or allyl Grignard reagents with indium(III) halides, a method widely used for preparation of allylindium(III) compounds is the oxidative addition of metallic indium or indium(I) iodide to allylic substrates [3, 6]. Transmetalation of allylstannane with indium(III) chloride also gives allylindium(III) [7]. Allylindium(I) was recently prepared by transmetalation of allylmercury with metallic indium in water; this compound is regarded as an intermediate in the allylation of carbonyl compounds in aqueous media [8]. A new method of preparation of allylic indium(III) reagents – reductive transmetalation of a π-allylpalladium(II) complex with indium(I) salts has been reported; this enables the use of a wide variety of allylic compounds and solvents [9].

8.2.1 Allylation and Propargylation of Carbonyl Compounds

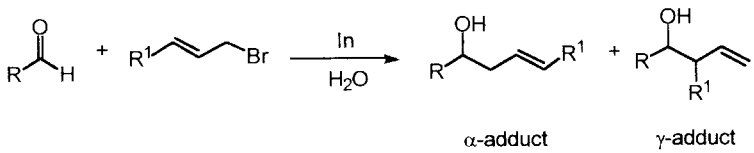
Allylation and propargylation of carbonyl compounds have been surveyed [5]. This section focuses on regio- and stereochemical aspects of the carbonyl allylation reactions in organic and aqueous media. Allylation of carbonyl compounds also proceeds under solvent-free conditions [10] or in liquid carbon dioxide [11]. Allylation with a catalytic amount of indium (0.01–0.1 equiv.) in combination with manganese and chlorotrimethylsilane has been reported [12]. Allylindium reagents have successfully been applied to syntheses of several natural products [13].

8.2.1.1 Regioselectivity

γ-Substituted allylindium reagents react in organic and aqueous media with carbonyl compounds regioselectively at the γ-position to afford the corresponding branched homoallylic alcohols, if no sterically bulky carbonyl or allyl substituent is involved. The reaction proceeds via a six-membered transition state [14]. Loh and co-workers recently reported that indium-mediated reactions of crotyl or cinnamyl bromide with aldehydes in the presence of 10 M water exclusively give the α-adduct irrespective of the bulkiness of aldehydes (Tab. 8.1) [15]. On the basis of NMR study it has been proved that the initially formed γ-homoallylic alcohol is converted to the thermodynamic α-homoallylic alcohol.

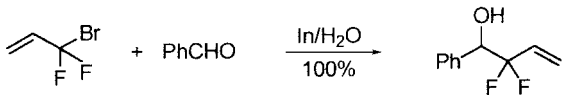
Fluorinated organoindium reagents undergo regio- and stereoselective reactions. Allylindium reagents containing a CF_2 unit react with aldehydes at the CF_2 terminus to give the corresponding 1-substituted 2,2-difluorobut-3-en-1-ols (Scheme 8.1)

Tab. 8.1 Allylation of aldehydes with γ-substituted allylindium reagents



R	*R*[1]	*Yield*	*α*:*γ*	*E*/*Z*
Ph	Me	60%	99:1	55/45
c-C_6H_{11}	Me	85%	99:1	70/30
n-C_5H_{11}	Me	75%	98:2	65/35
$PhCH_2CH_2$	Me	67%	97:3	55/45
Ph	Ph	72%	98:2	*E*
c-C_6H_{11}	Ph	71%	99:1	90/10
$PhCH_2CH_2$	Ph	50%	99:1	95/5

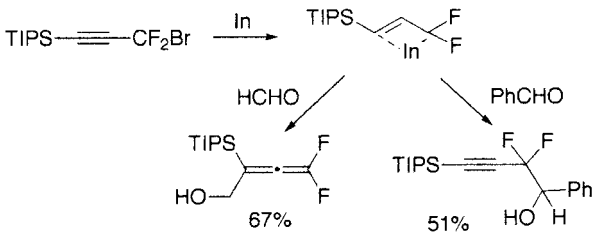
[16]. Aldehydes react with 1-substituted 3-bromo-3,3-difluoropropynes in the presence of $InCl_3$ and Sn. The reaction occurs exclusively at the CF_2 terminus to afford the corresponding *gem*-difluorohomopropargyl alcohols (Scheme 8.2).



Scheme 8.1

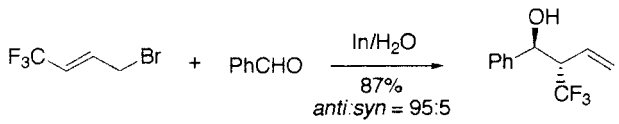
Scheme 8.2

Stable *gem*-difluoroallenylindium(I) is prepared from bromodifluoromethyl silyl acetylene, which couples with aldehydes to give homopropargylic *gem*-difluoro alcohols; with aqueous formaldehyde allenyl alcohols are obtained (Scheme 8.3) [17].



Scheme 8.3

Indium-mediated reaction of 4-bromo-1,1,1-trifluoro-2-butene with aldehydes in water proceeds stereoselectively to afford the β-trifluoromethylated homoallylic alcohols selectively (Scheme 8.4) [18].

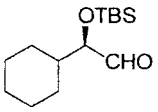
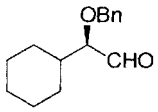
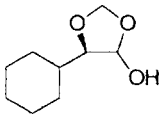
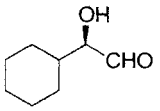
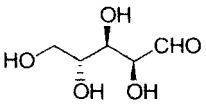
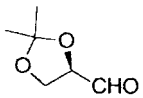
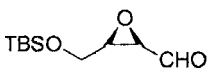


Scheme 8.4

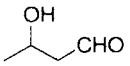
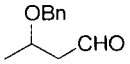
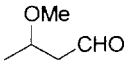
8.2.1.2 **Diastereoselectivity**

Paquette and co-workers have extensively surveyed the effect of proximal groups on diastereoselectivity in the addition of allylindium to a carbonyl group. When α- and β-hydroxy aldehydes are subjected to the allylation, excellent diastereocontrol

Tab. 8.2 Indium-mediated allylation of α-oxygenated aldehydes

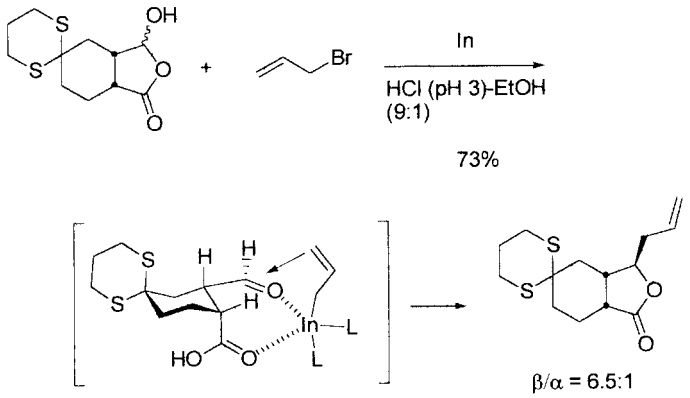
Aldehyde	*Solvent*	*Time (h)*	*syn : anti*	*Yield (%)*
	H_2O	3.5	1:3.9	90
	H_2O-THF (1:1)	2.5	1:4.2	87
	THF	36-50	1:4.0	92
	H_2O	3	1:1.2	92
	H_2O-THF (1:1)	2.5	1:2.2	93
	THF	40-47	1:3.9	87
	H_2O	24-30	2.3:1	90-95
	H_2O-THF (1:1)	20-26	2.3:1	90-93
	THF	No reaction		
	H_2O	5	9.8:1	85-90
	H_2O	24-30	10.2:1	90
	H_2O-THF (1:1)	18-30	8.2:1	87
	H_2O-EtOH (1:1)	12	9.1:1	85
	H_2O	3.5	1:3.2	83
	H_2O-THF (1:1)	3.5	1:3.9	80
	THF	21-25	1:5.9	86
	H_2O	2.5-3.5	1:2	78
	H_2O-THF (1:1)	3.5	1:2	82
	THF	20-25	1:5.2	89

Tab. 8.3 Indium-mediated allylation of β-oxygenated aldehydes

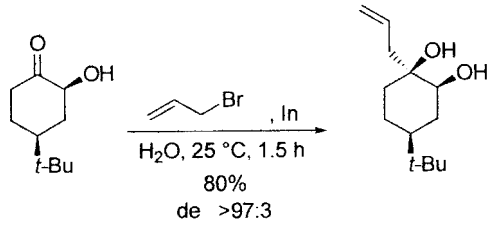
Aldehyde	*Solvent*	*Time (h)*	*syn:anti*	*Yield (%)*
	H_2O	2	1:8.5	77
	H_2O-THF (1:1)	2	1:8.2	74
	THF	No reaction		
	H_2O	2.5	1:1	80
	H_2O-THF (1:1)	2.7	1:1	84
	THF	10	1:1	72
	H_2O	2.7	1:4	78
	H_2O-THF (1:1)	3	1:4	78
	THF	8.5	1:3.3	69

is achieved and *syn*-1,2-diol and *anti*-1,3-diol products are formed at accelerated rates. Protection of the free hydroxyl group results in the alternative formation of 1,2-*anti* products (Tab. 8.2 and 8.3) [19].

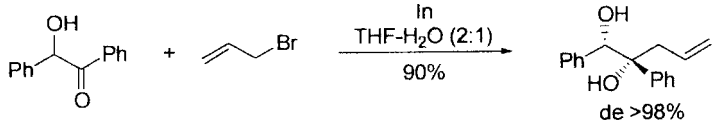
α-Amino [20], α-acylamino [21], and β-carboxyl groups on aldehydes [22] can also affect diastereoselectivity. The high diastereoselectivity observed in the last reaction can be rationalized by the chelated transition state with the carboxylic acid group (Scheme 8.5). The α-hydroxy- [23] and α-methoxy ketone derivatives [24] exert a similar outcome (Scheme 8.6). 2-Hydroxyketones and 2-ketoaldehydes undergo indium-mediated diastereoselective mono- and bis-allylation reactions to give respective 1-allyl- and 1,2-bis(allyl)-1,2-diols (Schemes 8.7 and 8.8) [25]. Indium-mediated allyla-



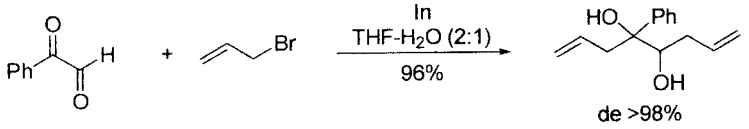
Scheme 8.5 Allylation of γ-hydroxy lactone



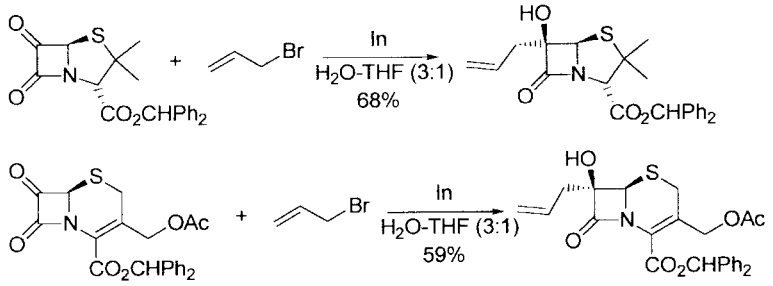
Scheme 8.6



Scheme 8.7



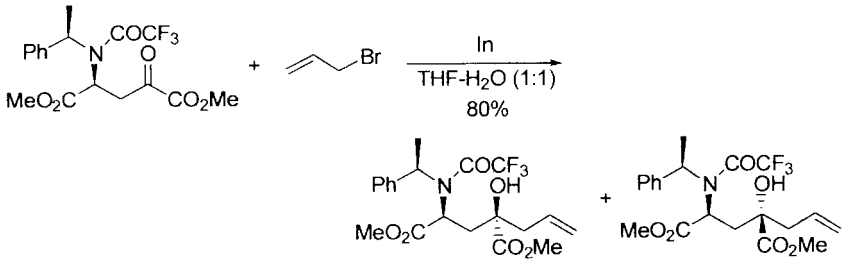
Scheme 8.8



Scheme 8.9

tion of *α*-keto-*β*-lactams such as 6-oxopenicillanate and 7-oxocephalospranate proceeds diastereoselectively to afford *α*-allyl-*β*-lactams in aqueous media (Scheme 8.9) [26].

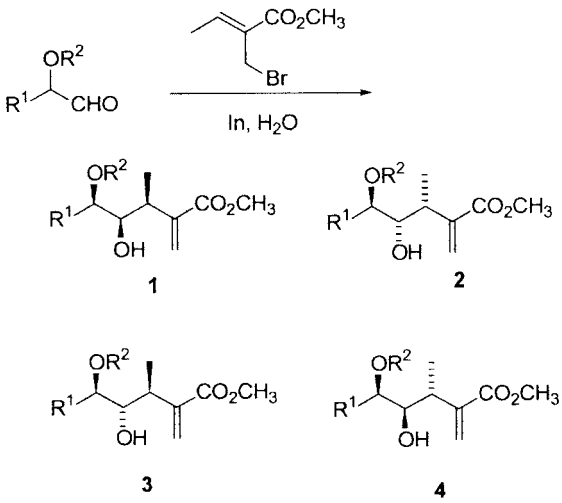
Stereoselective synthesis of 1,3-amino alcohols is realized by the allylation of *α*-keto ester possessing an amino substituent at the *β*-position (Scheme 8.10) [27].



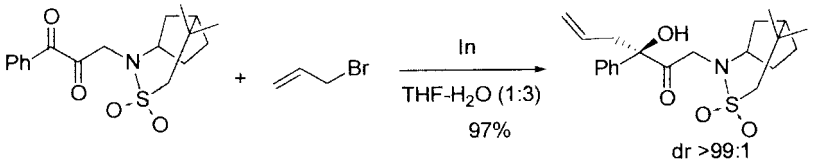
Scheme 8.10

Indium-promoted addition of methyl (*Z*)-2-(bromomethyl)-2-butenoate to α-protected hydroxy aldehydes in water results in the formation of diastereomer **2** selectively via a Felkin-Anh transition state (Tab. 8.4) [28]. Diastereoselective allylation of α-ketoimides derived from Oppolzer's sultam proceeds in aqueous THF (Scheme 8.11) [29].

Tab. 8.4 Indium-mediated allylation of α-protected hydroxy aldehydes



R^1	R^2	1:2:3:4	Yield (%)
CH_3	TBS	3:97:0:0	75
Ph	TBS	5:95:0:0	92
c-C_6H_{11}	TBS	13:87:0:0	72
c-C_6H_{11}	Bn	7:88:5:0	79
CH_3	Bn	28:52:16:4	81

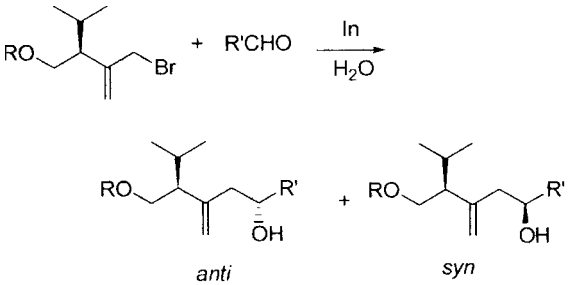


Scheme 8.11

Oxygen-bearing Allylindium Reagents

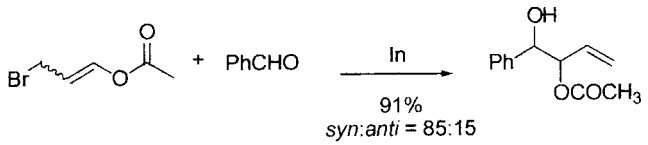
Stereoselective 1,4-asymmeric stereoinduction under aqueous conditions is realized by use of oxygen-substituted allylic indium reagents (Tab. 8.5) [30]. *O*-Silylated allylindium shows moderate *anti* selectivity, via the Felkin-Anh transition state, whereas hydroxy-bearing allylindium exhibits *syn* selectivity by dual coordination of indium intramolecularly to the hydroxy group and intermolecularly to the aldehyde.

Tab. 8.5 Reaction with oxygen-substituted allylic indium reagents

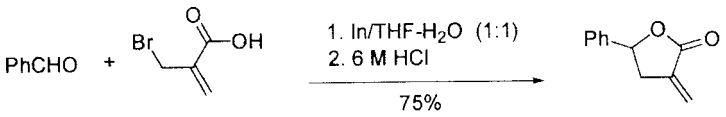


R	*R'*	*Yield (%)*	*anti:syn*
TBS	*i*-Pr	72	76:24
TBS	Ph	83	75:25
TBS	*c*-C_6H_{11}	71	75:25
H	*i*-Pr	95	11:89
H	Ph	79	13:87
H	*c*-C_6H_{11}	91	14:86

γ-Oxygenated allylindium reacts with aldehydes at the oxygenated carbon to give *vic*-diol derivatives in which the *syn*/*anti* selectivity depends on the nature of the aldehydes (Scheme 8.12) [31]. The indium-mediated reaction of 2-(bromomethyl) acrylic acid with carbonyl compounds gives the corresponding α-methylene-γ-lactones after acidic work-up (Scheme 8.13) [32].

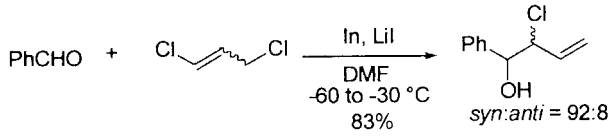


Scheme 8.12

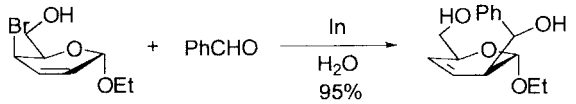


Scheme 8.13

3,3- or 1,3-Dichloropropene react with indium in the presence of LiI to generate a γ-chloroallylindium reagent, which couples with aldehydes giving the corresponding chlorohydrins (Scheme 8.14) [33]. 2-*C*-Branched sugars and *C*-disaccharides are prepared by indium-mediated reaction with 4-bromo-2-enpyranoside (Scheme 8.15) [34].



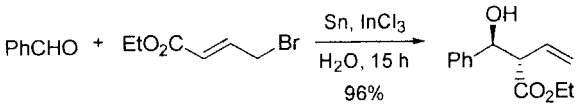
Scheme 8.14



Scheme 8.15

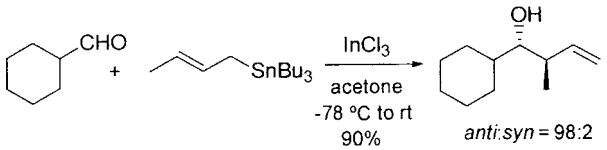
Allylindium Reagents Prepared by Transmetalation

The allylation of aldehydes with allylic bromide in water, in the presence of stoichiometric amounts of $InCl_3$ and Sn, proceeds cleanly to give the corresponding *anti* γ-adducts predominantly (Scheme 8.16) [7b]. It has been postulated that transmetalation from allylic stannane to allyllic indium via an S_E2' process occurs during this reaction; the high *anti* selectivity can be explained in terms of a six-membered ring transition state.

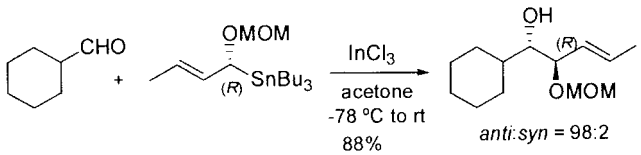


Scheme 8.16

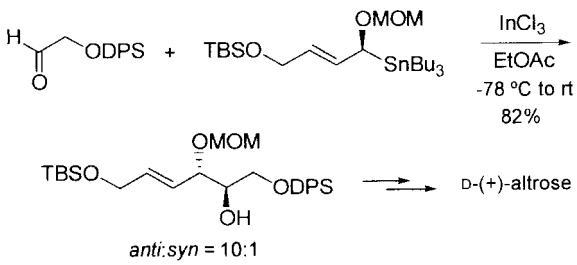
In a variety of donor solvents such as acetone and acetonitrile, $InCl_3$ undergoes transmetalation with crotylstannane, and the resulting allylic indium species affords *anti* adducts with aldehydes (Scheme 8.17) [7a]. Indium trichloride-mediated addition of the (*R*)-*α*-(methoxymethoxy) allylic stannane (>95% ee) to cyclohexanecarboxaldehyde affords the *anti* adduct predominantly (*anti*:*syn* = 98:2) and stereoselectively (>95% ee) (Scheme 8.18). Production of a transient allylic reagent via a stereospecific *anti* S_E2' transmetalation is postulated. This *α*-(methoxymethoxy) allylic stannane reacts without allylic inversion, whereas reaction of the crotylstannane in Scheme 8.18 proceeds with net allylic inversion. *δ*-Oxygenated allylic stannanes also undergo transmetalation with $InCl_3$. In situ addition to *α*-ODPS acetaldehyde leads mainly to the *anti* adduct, which is a potential precursor to D-(+)-altrose (Scheme 8.19) [35]. Transmetalation of allenylstannane with $InCl_3$ and subsequent addition to a chiral aldehyde leads to the *anti,syn* and *anti,anti* adducts (Scheme 8.20) [36]. Indium trichloride mediates the intramolecular cyclization of the prochiral allylstannyl diketone to afford the desymmetrized *cis–cis* cyclohexanol predominantly. The use of $TiCl_4$ in place of $InCl_3$ gives the *cis–trans* diastereomer (Scheme 8.21) [37].



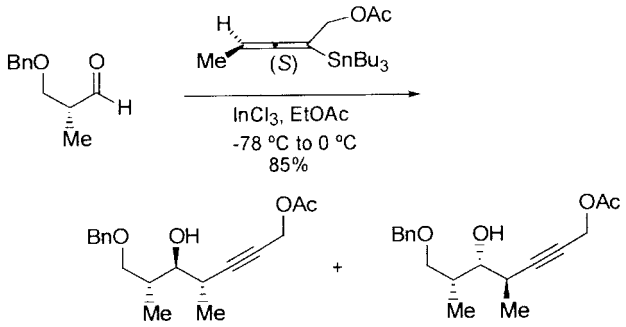
Scheme 8.17



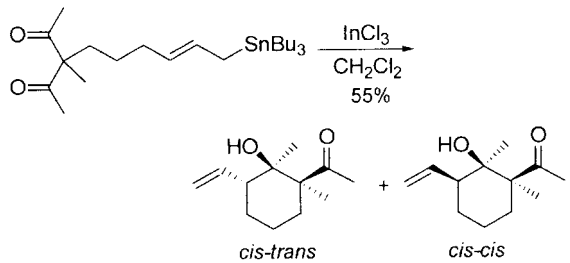
Scheme 8.18



Scheme 8.19



Scheme 8.20 71:29

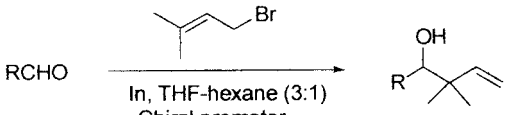


Scheme 8.21 3:97

8.2.1.3 **Enantioselectivity**

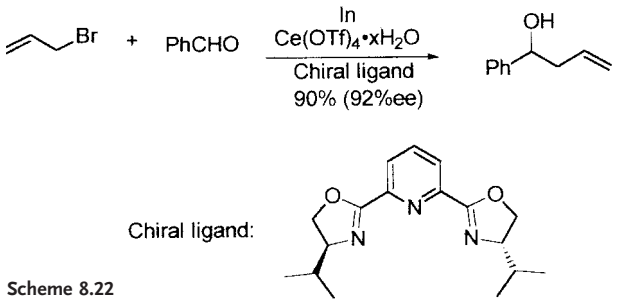
The indium-mediated enantioselective allylation of aldehydes is realized in the presence of external chiral ligands (+)-cinchonine and (–)-cinchonidine (Tab. 8.6) [38]. By

Tab. 8.6 Enantioselective indium-mediated allylation of aldehydes



R	***Chiral promoter***	
	(+)-cinchonine ***Yield, ee***	***(–)-cinchonidine*** ***Yield, ee***
Ph	98% 76 (*S*)	99% 90 (*R*)
3-$MeOC_6H_4$	96% 62 (*S*)	95% 77 (*R*)
4-$MeOC_6H_4$	98% 29 (*S*)	97% 78 (*R*)
1-naphthyl	91% 41 (*S*)	83% 64 (*R*)
2-naphthyl	86% 29 (*S*)	95% 81 (*R*)
(*E*)-PhCH=CH	88% 72 (*S*)	98% 56 (*R*)
n-octyl	87% 27 (*R*)	89% 41 (*S*)

using (*S*,*S*)-2,6-bis(4-isopropyl-2-oxazolin-2-yl)pyridine as the chiral source, high enantioselectivity (up to 92% ee) is obtained in an aqueous medium (Scheme 8.22) [39].

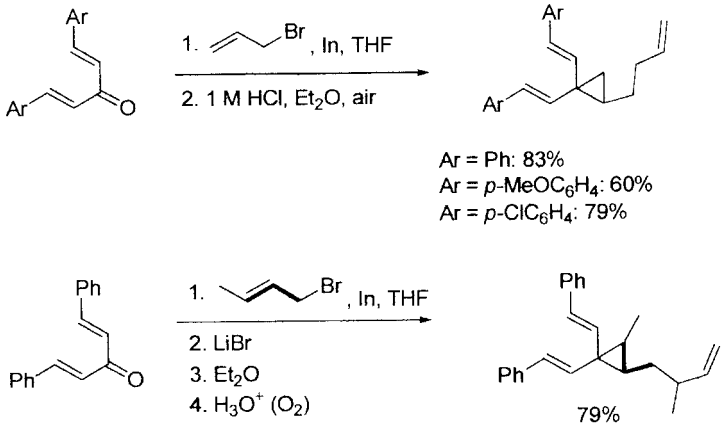


Scheme 8.22

8.2.1.4 **Other Allylation Reactions**

Cyclopropane Synthesis

Lloyd-Jones and co-workers discovered the direct synthesis of homoallyl-substituted vinylcyclopropanes from *α,β*-unsaturated ketones and allylindium reagents. In this transformation, the indium-mediated deoxygenation process delivers two allyl units to *α,β*-unsaturated ketones (Scheme 8.23) [40].

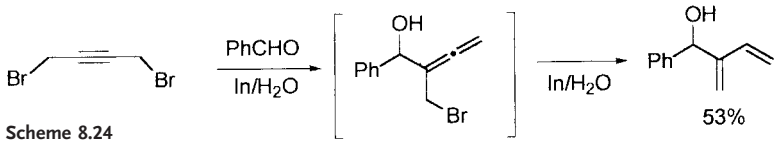


Scheme 8.23

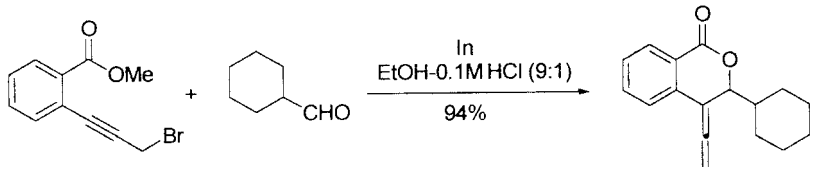
Miscellaneous

Indium-mediated coupling of prop-2-ynyl bromides with aldehydes in aqueous media occurs regioselectively to give either homoprop-2-ynyl alcohols or allenylic alcohols depending on the *γ*-substituent of the prop-2-ynyl bromide [41 a, b]. Indium-promoted reaction of 1,4-dibromo-2-butyne with carbonyl compounds gave 1,3-butadien-2-ylmethanols via the allenic intermediates (Scheme 8.24) [41 c]. Allene

aryl δ-lactones are conveniently synthesized by reaction of (*o*-methoxycarbonylaryl)propargyl bromide with aldehydes mediated by indium in aqueous ethanol (Scheme 8.25) [42].

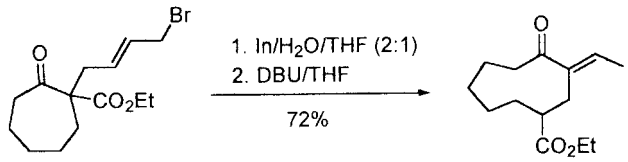


Scheme 8.24

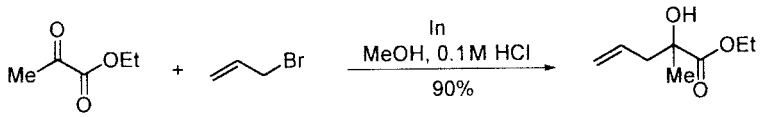


Scheme 8.25

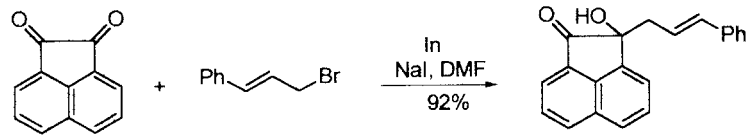
A two-atom carbocycle enlargement is accomplished by Barbier-type reaction in water (Scheme 8.26) [43]. The coupling reaction of α-keto esters with allyl, propargyl, and allenyl halides using indium metal in aqueous solvents afforded α-hydroxy-γ,δ-unsaturated esters (Scheme 8.27) [44]. Indium-mediated allylation of 1,2-diones affords α-hydroxy keto compounds. In some cinnamylation reactions the corresponding α-coupling products are obtained (Scheme 8.28) [45].



Scheme 8.26

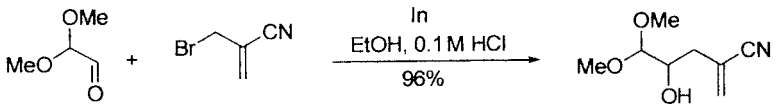


Scheme 8.27

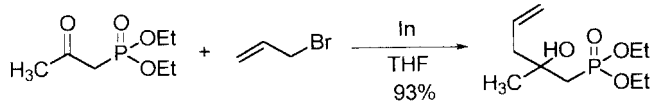


Scheme 8.28

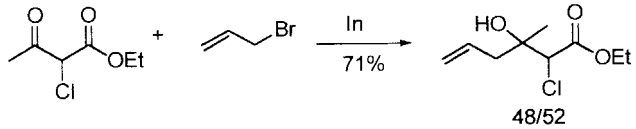
Indium-mediated Barbier-type reaction of glyoxal monoacetal with bromomethyl acrylonitrile or bromomethyl acrylate gives a masked α-hydroxyaldehyde (Scheme 8.29) [46]. β-Keto phosphonates give the corresponding β-hydroxy phosphonates in good yields by indium-mediated allylation (Scheme 8.30) [47]. Indium-mediated allylation of α-chlorocarbonyl compounds with allyl bromides in aqueous media gives the corresponding homoallylic chlorohydrins, which can be transformed to allylepoxides (Scheme 8.31) [48].



Scheme 8.29

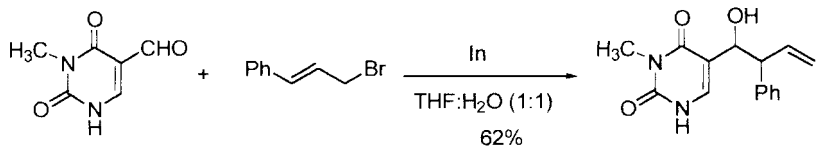


Scheme 8.30

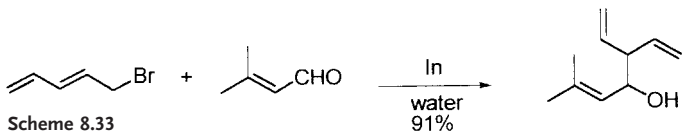


Scheme 8.31

The indium-mediated reaction of cinnamyl bromide with 5-formyluracil derivatives gives the corresponding homoallylic alcohols. The presence of C-4 carbonyl is essential for high diastereoselectivity owing to complexation with indium (Scheme 8.32) [49]. Pentadienylindium, a vinylog of allylindium, reacts with carbonyl compounds selectively at the γ position to give 1,4-pentadiene derivatives (Scheme 8.33) [50].



Scheme 8.32

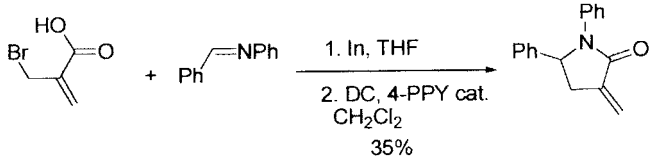


Scheme 8.33

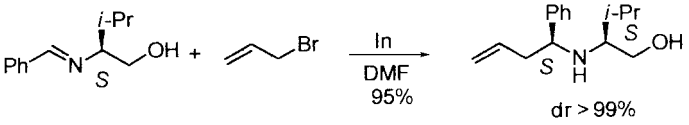
8.2.2
Allylation and Propargylation of Compounds other than Carbonyl

8.2.2.1 Imines and Enamines

The allylation of imines with allylindium reagents in organic solvents is known to give the corresponding homoallylic amines [51]. *α*-Methylene-*γ*-butyrolactams are prepared by indium-mediated reaction of 2-(bromomethyl)acrylic acid with aldimines (Scheme 8.34) [52]. Diastereoselective Barbier-type allylation of chiral imines bearing a hydroxyl group on the chiral auxiliary is achieved in DMF (Scheme 8.35) [53]. The chelation between the nitrogen and the hydroxyl group of the imine with indium is crucial for high stereoselectivity. The palladium-catalyzed indium-mediated allylation of imines also works well with InI prepared in situ from In and I_2 [53c].

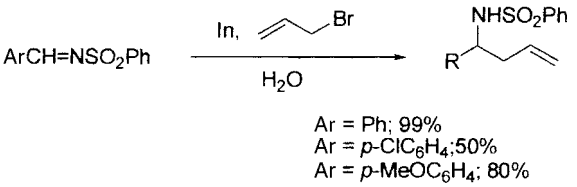


Scheme 8.34



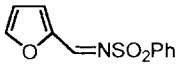
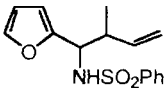
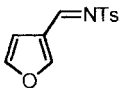
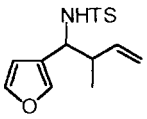
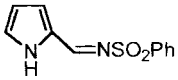
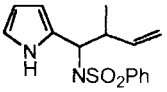
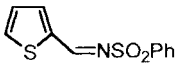
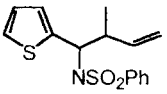
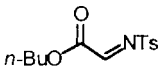
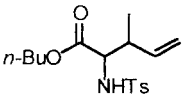
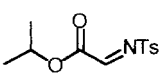
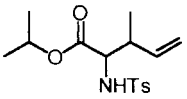
Scheme 8.35

Examples of imine allylation in aqueous media are rather limited compared with the carbonyl version. This is ascribed to the lower electrophilicity of the C=N function and its ease of hydrolysis to carbonyl compounds. To overcome undesired side reactions, sulfonimines are used in place of simple imines for the allylation under aqueous conditions (Scheme 8.36) [54]. Crotylation of *α*-sulfoimino esters gives the *syn* adducts as high as 19:1 in H_2O/THF (1:1) (Tab. 8.7) [54c].

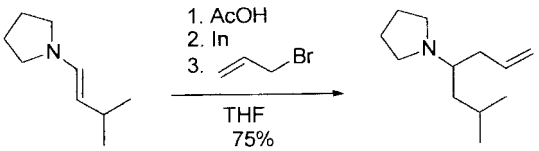


Scheme 8.36

Tab. 8.7 Aqueous allylindation reaction of sulfonimines bearing α-chelating groups

Sulfonimine	*Product*	*Solvent THF:H_2O*	*Yield (%)*	*syn:anti*
		0:100 50:50 10:1	90 94 99	76:24 93:7 93:7
		0:100 50:50	85 91	59:41 86:14
		0:100 50:50	72 80	68:32 94:6
		0:100 50:50	83 92	57:43 85:15
		50:50 100:0	45 56	93:7 87:13
		50:50	40	95:5

Indium-mediated reaction of enamines with allyl bromides gives homoallylamines. Addition of one equivalent of acetic acid accelerates the reaction. An analogous reaction of methyl bromoacetate instead of allylic bromides also proceeds. The iminium salts formed by protonation of the enamines are considered to be the intermediates (Scheme 8.37) [55].

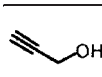
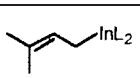
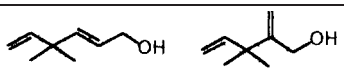
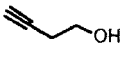
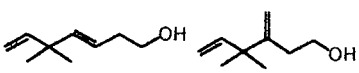
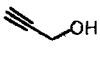
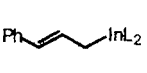
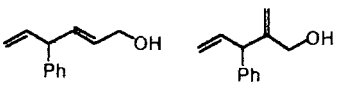
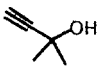
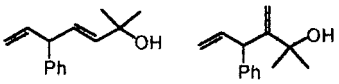
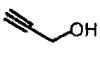
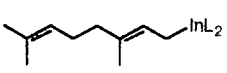
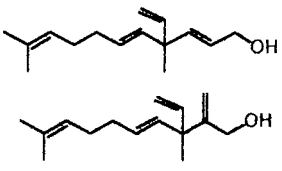
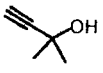
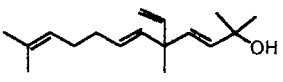


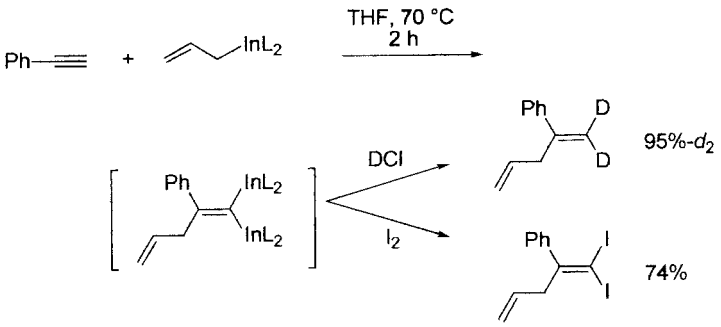
Scheme 8.37

8.2.2.2 Alkenes and Alkynes

The reaction of allylindium reagents with terminal alkynes proceeds in DMF giving 1,4-dienes; the proximal hydroxyl group is essential for clean allylation (Tab. 8.8) [56].

Tab. 8.8 Allylindation of alkynols

Alkynol	*Allylindium*	*Product*	*Yield (%)*
			91 (65:35)
	"		85 (73:27)
			56 (14:86)
	"		68 (90:10)
			59 (75:25)
	"		75

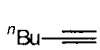
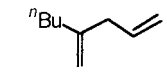
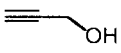
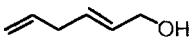
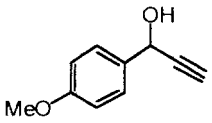
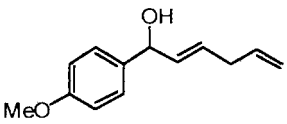
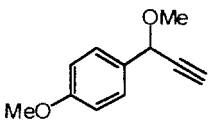
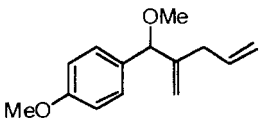
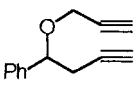
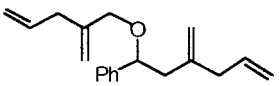


Scheme 8.38

On changing the solvent to THF, allylindation of unfunctionalized alkynes proceeds smoothly [57]. When this reaction is quenched with I_2 or D_2O, the diiodinated product or the d_2-containing allylated product is obtained, showing that the allylindation of terminal alkynes in THF proceeds through the double-indation intermediate (Scheme 8.38).

The regioselectivity of the allylation depends on the presence of an adjacent free hydroxyl group; the predominant formation of linear 1,4-dienes (*anti*-Markovnikov products) is achieved from propargylic alcohols whereas simple terminal alkynes with a protected hydroxyl group give the corresponding branched 1,4-dienes (Markovnikov products) (Tab. 8.9) [57 c].

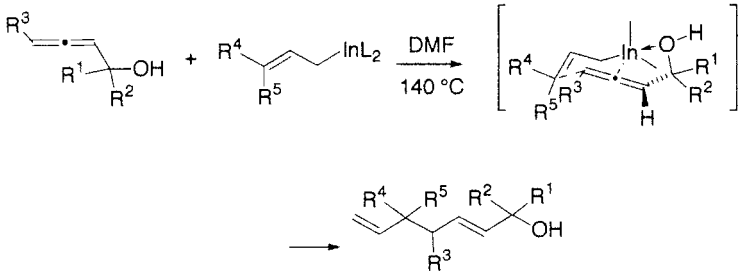
Tab. 8.9 Allylindation of alkynes

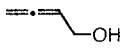
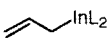
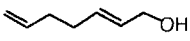
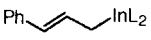
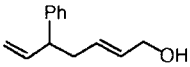
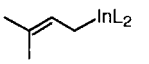
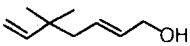
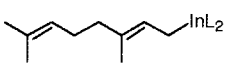
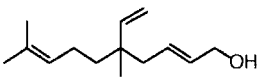
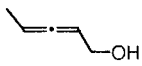
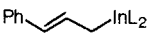
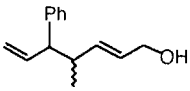
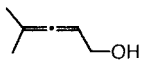
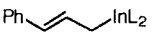
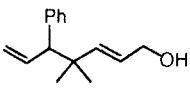
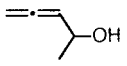
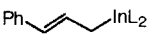
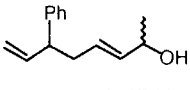
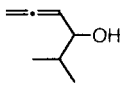
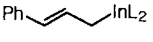
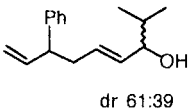
Alkyne	*Product*	*Yield (%)*
		86
		80
		83
		90
		86

Allylindation of allenols proceeds regio- and stereoselectively to afford 1,5-dienes via a hydroxy-chelated bicyclic transition state (Tab. 8.10) [58].

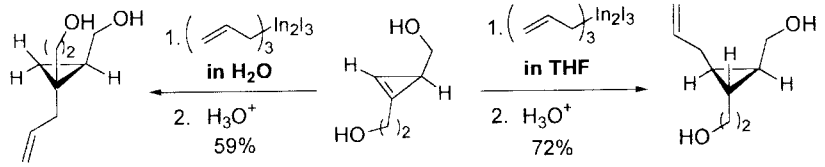
Allylindation of electron-deficient olefins [59] and norbornenols [60] also proceeds to give the allylated products. Hydroxy-bearing cyclopropenes undergo clean allylindation both in organic and aqueous media [61]. The regio- and stereoselectivity are determined both by the location of the hydroxyl group in the molecules and the reaction solvents. Occasionally regio- and stereoselectivity are totally the

Tab. 8.10 Allylindation of allenols



Allenol	*Allylindium*	*Product*	*Yield (%)*
			100
			97
			79
			89
		 dr 72:28	99
		 dr 61:39	54
		 dr 67:33	44
		 dr 61:39	63

opposite in water and in organic solvents (Scheme 8.39). Stable cyclopropylindium intermediates are isolated and characterized by crystallography.

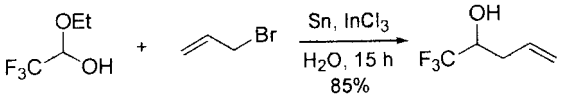


Scheme 8.39

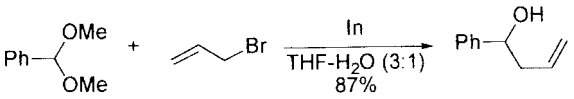
8.2.2.3 Other Compounds

Reaction with Acetals and Epoxides

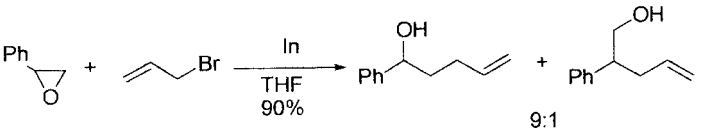
The reactions of allylindium reagents with trifluoroacetaldehyde hydrate or hemiacetal in water (Scheme 8.40) [62], or with aldehyde dimethyl acetals in aqueous THF [63], give the corresponding homoallylic alcohols (Scheme 8.41). Allylindium reacts with terminal epoxides to afford the corresponding bishomoallyl alcohols (Scheme 8.42) [64].



Scheme 8.40



Scheme 8.41

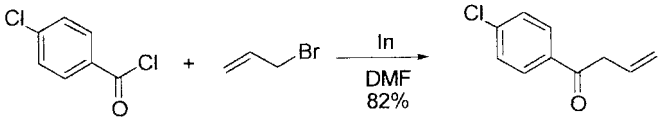


Scheme 8.42

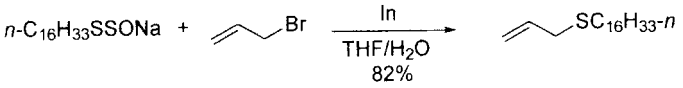
Reaction with Acid Chlorides and Related Compounds

β,γ-Unsaturated ketones are prepared from acid chlorides, allyl bromide, and indium in DMF (Scheme 8.43) [65]. Allylic bromides react with sodium alkyl thiosulfates in the presence of indium in aqueous THF to give allyl sulfides (Scheme 8.44) [66]. Indium-mediated coupling of allyl bromide with aromatic sulfonyl chloride gives the corresponding sulfones in aqueous media (Scheme 8.45)

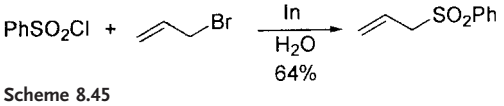
[67]. Indium-mediated coupling of allylic bromides with acylimidazoles or -pyrazoles in aqueous media gives the corresponding ketones (Scheme 8.46) [68]. Indium-mediated allylation of acyl cyanides with allyl halides in aqueous media affords a variety of β,γ-unsaturated ketones (Scheme 8.47) [69]. Indium is effective in 2-pyridyl esters with allyl bromides or with iodide in pure water (Scheme 8.48) [70].



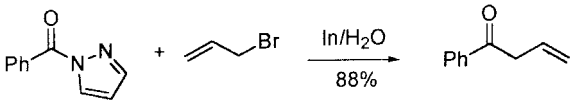
Scheme 8.43



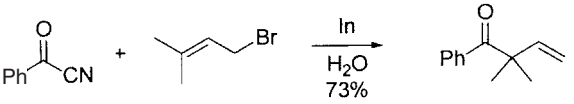
Scheme 8.44



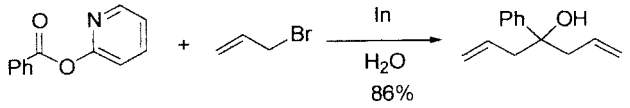
Scheme 8.45



Scheme 8.46



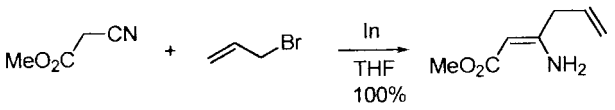
Scheme 8.47



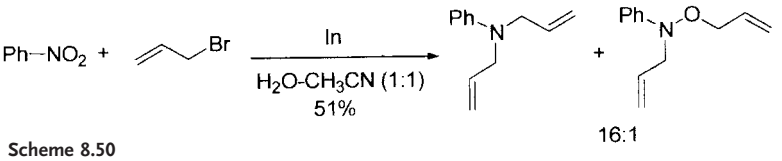
Scheme 8.48

Others

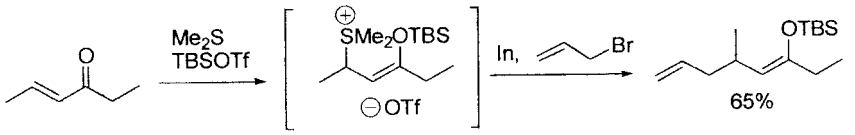
The reaction of allylindium reagents with methyl cyanoacetates affords the corresponding allylation-enamination products (Scheme 8.49) [71]. Indium-mediated allylation of a nitro group is achieved in aqueous media to give *N,N*-diallylamine and *N,O*-diallylhydroxylamine (Scheme 8.50) [72]. In situ-generated sulfonium salts derived from *α,β*-enones undergo nucleophilic substitution with allylindium reagents to give the corresponding Michael addition products (Scheme 8.51) [73]. 1-Acyl-1,2-dihydropyridines are prepared by indium-mediated allylation of 1-acylpyridinium salts (Scheme 8.52) [74]. The direct allylation of aromatic compounds with allylic chlorides is achieved in the presence of a catalytic amount of indium metal. Indium is considered to act as a Lewis acid (Scheme 8.53) [75]. Allyl and propargyl bromides react with diorganodiselenides in aqueous media to give allyl and propargylselenides (Scheme 8.54) [76].



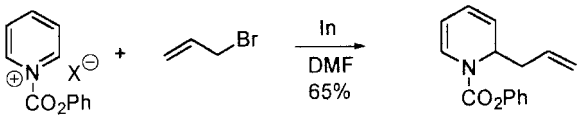
Scheme 8.49



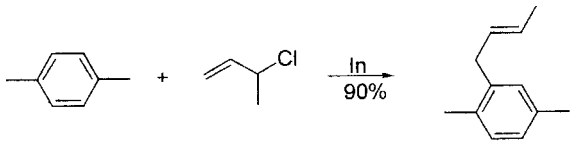
Scheme 8.50



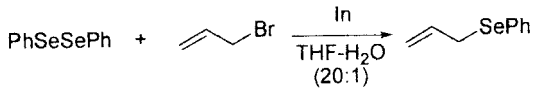
Scheme 8.51



Scheme 8.52

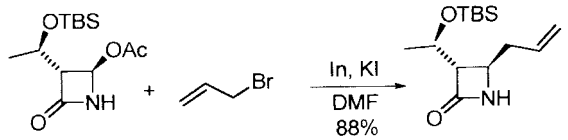


Scheme 8.53

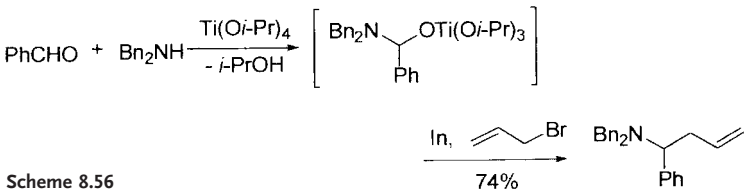


Scheme 8.54

Indium-mediated allylation of 4-acetoxy-2-azetidinones affords 4-allyl-substituted azetidinones with retention of stereochemistry (Scheme 8.55) [77]. An aminoalkoxy titanium complex is readily allylated with allylindium reagents to give homoallylic amines (Scheme 8.56) [78]. In the presence of TMSCl, allylindium adds to cyclohexenone to give the Michael adduct in 63% yield [79].



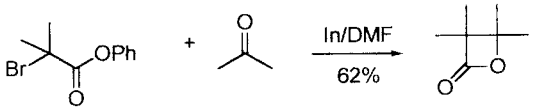
Scheme 8.55



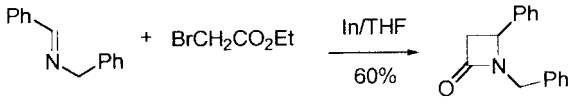
Scheme 8.56

8.3
Reformatsky and Other Reactions

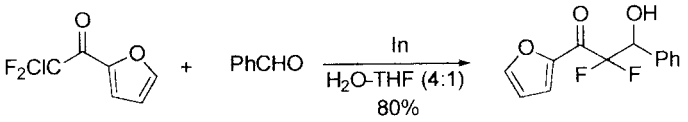
Indium enolates, prepared conveniently by transmetalation of lithium enolates with $InCl_3$, react with aldehydes to give the corresponding β-hydroxy esters [80]. Ultrasound irradiation promotes the Reformatsky reaction of aldehydes and ethyl bromoacetate with indium [81]. Indium-mediated Reformatsky reaction of phenyl α-bromoalkanoates with ketones or aldehydes gives di-, tri-, and tetrasubstituted β-lactones (Scheme 8.57) [82]. Indium-mediated reaction of imines with ethyl bromoacetate gives 3-unsubstituted β-lactams (Scheme 8.58) [83]. An indium-Reformatsky reagent prepared from 2-(chlorodifluoroacetyl)furan couples with aldehydes (Scheme 8.59) [84].



Scheme 8.57

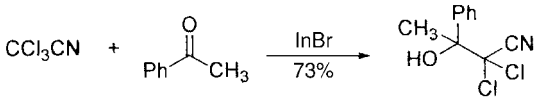


Scheme 8.58

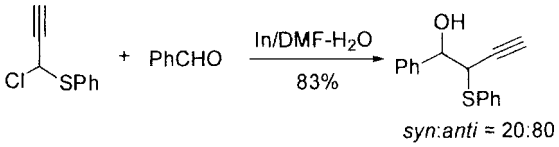


Scheme 8.59

Carbonyl compounds are efficiently transformed into 2,2-dichloro-3-hydroxynitriles by the action of trichloroacetonitrile and indium(I) bromide (Scheme 8.60) [85 a]. Bromocyanomethylation of carbonyl compounds is also achieved by reaction of dibromoacetonitrile and indium(I) bromide [85 b]. Indium-mediated reaction of *α*-chloropropargyl phenyl sulfide and aldehydes gives *β*-hydroxysulfides regio- and stereoselectively in aqueous media (Scheme 8.61) [86].

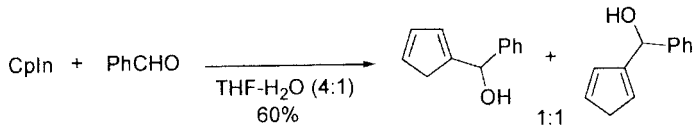


Scheme 8.60



Scheme 8.61

The reaction of cyclopentadienylindium(I) with aldehydes gives isomeric mixtures in aqueous media (Scheme 8.62) [87].

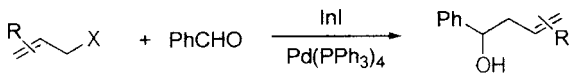


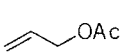
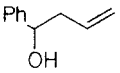
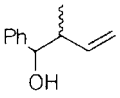
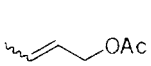
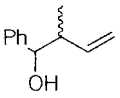
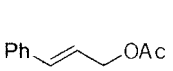
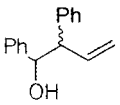
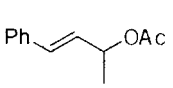
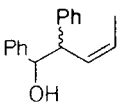
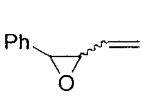
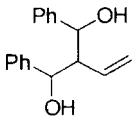
Scheme 8.62

8.4
Reactions in Combination with Transition Metal Catalysts

The use of organoindium reagents in combination with transition metal catalysts, which greatly expands the scope of indium chemistry in organic synthesis, has recently received much attention. A new preparation of allylic and allenic indium reagents by use of Pd catalysts has been reported. Allyl acetate and InI react with benzaldehyde in the presence of a catalytic amount of $Pd(PPh_3)_4$ to give the corresponding homoallylic alcohol in high yield (Tab. 8.11) [9]. The reaction proceeds via a π-allylpalladium(II) complex then reductive transmetalation with InI to give an allylindium compound. The reaction can be performed in a variety of solvents including THF, 1,3-dimethyl-2-imidazolidinone (DMI), and dichloromethane. Protic solvents such as water, methanol, and ethanol can also be used. A variety of allylic substrates, e.g. allyl chloride, vinyloxirane, and acrolein acetal, can be em-

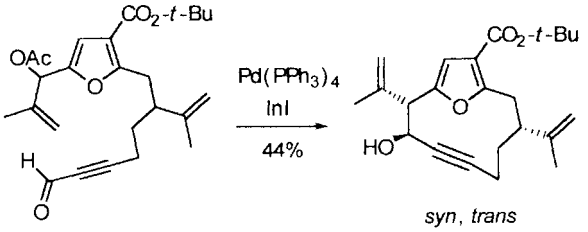
Tab. 8.11 Indium-mediated palladium-catalyzed allylation of benzaldehyde with allylic compounds



Allylic compound	*Product*	*Yield (syn:anti)*
		91%
		92% (58:42)
 (*E*:*Z* = 96:14)		98% (32:68)
		100% (14:86)
		79% (11:89)
 (*cis*:*trans* = 31:69)		80% (85:15)[a]

a Diastereomeric ratio.

ployed. Intramolecular cyclization of the acetate to the macrocyclic alcohol is achieved highly stereoselectively (Scheme 8.63) [88].

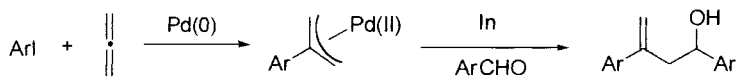


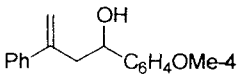
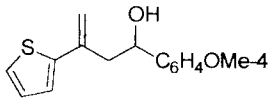
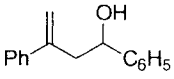
Scheme 8.63

This indium-mediated palladium-catalyzed Barbier-type allylation of aldehydes is expanded to cascade reactions with allenes, which give three-component coupling products (Tab. 8.12 and 8.13) [89].

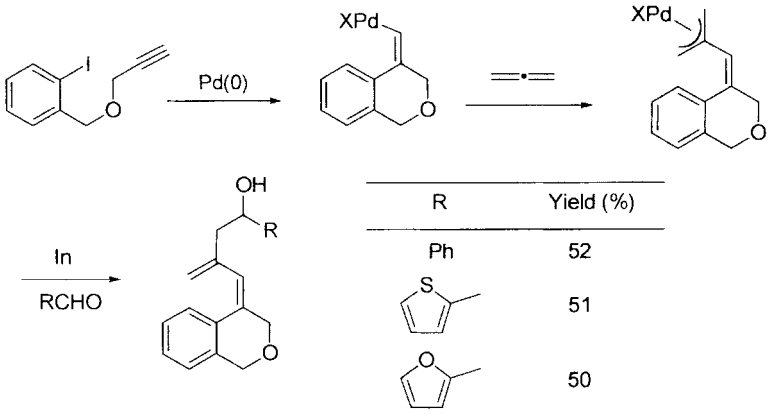
The InI-Pd(0)-promoted allylation of aldehydes with *N*-activated vinylaziridines or allylic acetates proceeds with regio- and stereoselectivity, irrespective of the chirality of the allylic carbon bearing the vinyl group, to provide *syn,syn*-2-vinyl-1,3-amino alcohols with three contiguous chiral centers (Scheme 8.64) [90]. In a similar manner, 2-ethynyl-1,3-amino alcohols are synthesized from 2-ethynylaziridines (Scheme 8.65) [91].

Tab. 8.12 Indium-mediated palladium-catalyzed cascade reaction with allene

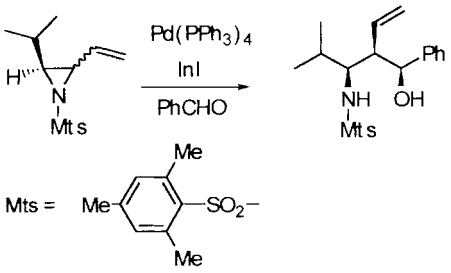


ArI	*RCHO*	*Product and Yield (%)*	
PhI	4-MeOC$_6$H$_4$CHO		64
	4-MeOC$_6$H$_4$CHO		66
PhI	PhCHO		43

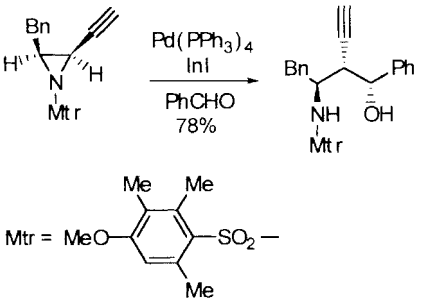
Tab. 8.13 Indium-mediated palladium-catalyzed reaction of alkynylarene, allene, and aldehydes



R	Yield (%)
Ph	52
	51
	50



Scheme 8.64

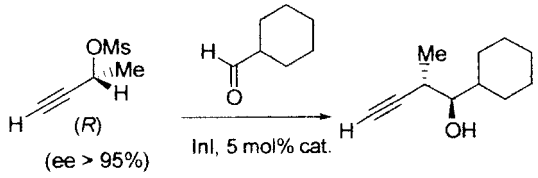


Scheme 8.65

Transmetalation of an allenylpalladium intermediate with InI proceeds stereoselectively. (*R*)-Propargyl mesylate (>95% ee) reacts with cyclohexanecarboxaldehyde in the presence of InI and 5 mol% palladium catalyst to give, via an allenylindium intermediate, the adduct stereoselectively with high enantiomeric excess (Tab. 8.14)

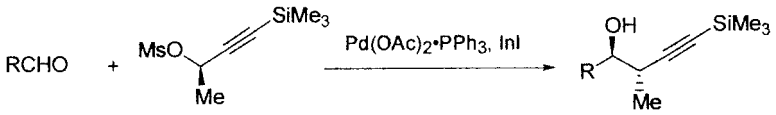
[92]. The addition is most efficient in 3:1 THF–HMPA and 1:1 THF–DMPU. *Anti*:*syn* ratios are excellent with α-branched aldehydes but only modest with unbranched and conjugated aldehydes. The reaction of a matched combination of the mesylate with chiral α-oxygenated aldehydes proceeds with high stereoselectivity giving the *anti,anti* adducts, whereas a mismatched combination affords a mixture of diastereoisomers (Scheme 8.66) [93]. The mesylate of a chiral alcohol undergoes high enantio-, regio-, and diastereoselective addition to a variety of aldehydes, leading to the homopropargylic alcohol adducts (Tab. 8.15) [94].

Tab. 8.14 Reaction of chiral propargyl mesylate with cyclohexanecarboxaldehyde

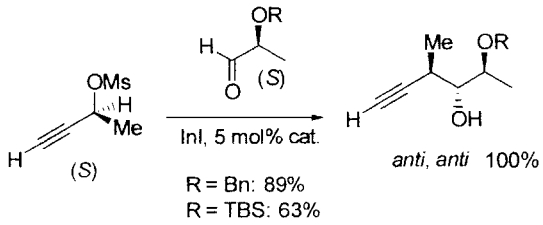


catalyst	*Solvent*	*Yield (%)*	*anti:syn*	*ee (%)*
none	THF-HMPA (3:1)	66	96:4	0
$Pd(dppf)Cl_2$	THF-HMPA (3:1)	76	95:5	95
$Pd(dppf)Cl_2$	THF-DMPU (3:1)	63	87:13	90
$Pd(dppf)Cl_2$	THF-DMPU (1:1)	80	91:9	87
$Pd(dppf)Cl_2$	THF-HMPA (20:1)	66	93:7	91
$Pd(OAc)_2 \cdot PPh_3$	THF-HMPA (3:1)	75	95:5	91

Tab. 8.15 Reaction of chiral propargyl mesylate with aldehydes

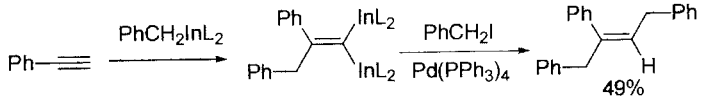


R	*Yield (%)*	*anti:syn*	*er*
c-C_6H_{11}	75	>99:1	99:1
i-Pr	89	98:2	99:1
$Ph(CH_2)_2$	69	>99:1	>99:1
C_6H_{13}	80	98:2	99:1
(*E*)-BuCH=CH	73	99:1	99:1

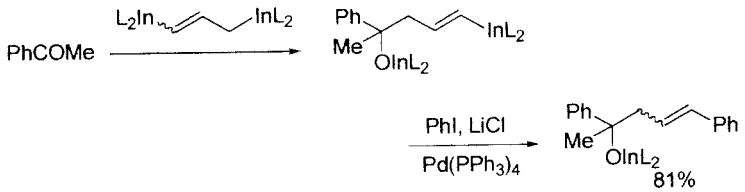


Scheme 8.66

The vinylindium compounds obtained by the addition of allylindium to alkynes react with organic halides in the presence of a palladium-catalyst to give three-component coupling products (Scheme 8.67) [57b]. 3,3-Dibromopropene or 3-bromo-1-iodopropene reacts with indium to give diindiopropene [95]. This novel diindium compound readily reacts with carbonyl compounds to afford the vinylindium reagent which, with the aid of a palladium catalyst, couples further with electrophiles to give linear homoallylic alcohols (Scheme 8.68).

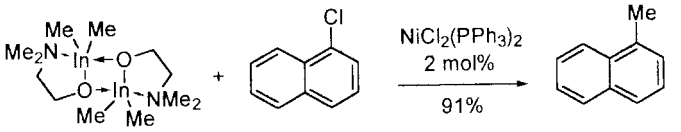


Scheme 8.67



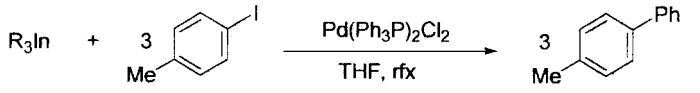
Scheme 8.68

Intramolecularly stabilized alkylindium compounds react with chloroarenes in the presence of $NiCl_2(PPh_3)_2$ to give the corresponding alkylated arenes in high yields (Scheme 8.69) [96]. Palladium-catalyzed cross-coupling of triorganoindiums with vinyl and aryl triflates or iodides proceeds in excellent yield with high chemoselectivity (Tab. 8.16) [97, 98]. All three of the organic groups attached to indium are transformed. With acid chlorides the corresponding ketones are obtained in high yields (Tab. 8.17). A nickel catalyst is equally effective for the transfer of the three organic groups attached to indium (Scheme 8.70). A similar coupling can be performed in aqueous media with diorganoindium compounds under palladium catalysis [99].



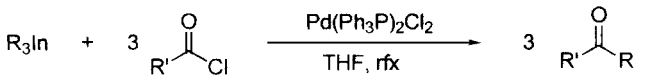
Scheme 8.69

Tab. 8.16 Palladium-catalyzed alkylation of 4-iodotoluene with triorganoindium

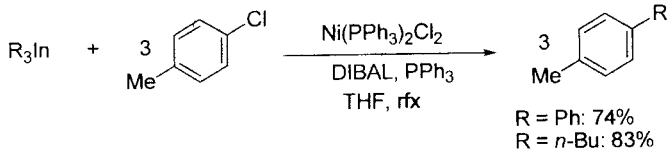


R	*Yield (%)*
Ph	96
CH_2=CH	89
PhC≡C	90
TMSC≡C	93
n-Bu	82
Me	85
c-C_3H_5	92

Tab. 8.17 Palladium-catalyzed reaction of triorganoindium with acid chlorides

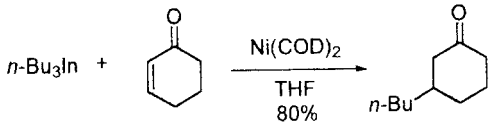


R	*R'*	*Yield (%)*
Ph	Ph	89
PhC≡C	Ph	94
Me	Ph	97
Ph	Me_2C=CH	87
PhC≡C	Me_2C=CH	90
TMSC≡C	Me_2C=CH	90

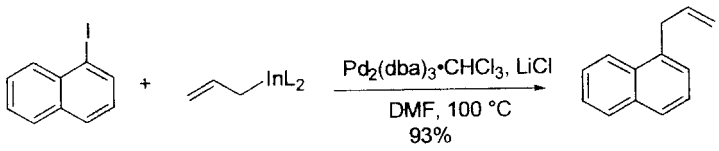


Scheme 8.70

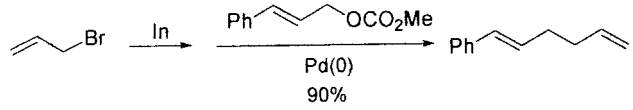
The 1,4-conjugate addition of triorganoindium to enones is promoted by a catalytic amount of $Ni(COD)_2$ (Scheme 8.71) [100]. Allylindium reagents can be used in Pd-catalyzed cross-coupling reaction with aryl halides (Scheme 8.72). The Pd-catalyzed allylic substitution of allyl carbonate produces 1,5-dienes (Scheme 8.73) [101]. The indium-mediated palladium-catalyzed Ullmann-type reductive coupling of aryl halides proceeds in aqueous media under air (Scheme 8.74) [102].



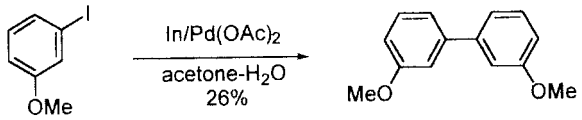
Scheme 8.71



Scheme 8.72



Scheme 8.73



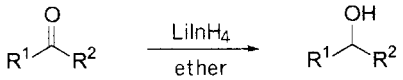
Scheme 8.74

8.5 Reduction

8.5.1 Reduction of Carbonyl Groups

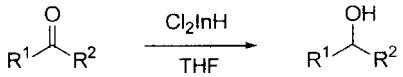
Lithium indium hydride ($LiInH_4$), prepared in situ by mixing LiH and $InCl_3$ in ether, readily reduces aldehydes. Reduction of ketones is less effective, giving lower yields of alcohols. Carbon–carbon double bonds are not reduced (Tab. 8.18) [103]. Acid chlorides are converted to esters with this reagent. Esters, in turn, are

Tab. 8.18 Reduction of carbonyl compounds with $LiInH_4$



R^1	R^2	Yield [%]
4-ClC_6H_4	H	93
(*E*)-PhCH=CH	H	92
n-C_7H_{15}	H	89
Ph	Me	64

Tab. 8.19 Reduction with dichloroindium hydride

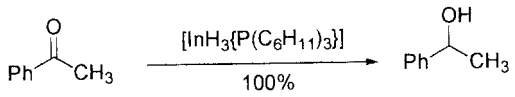


R^1	R^2	Yield [%]
Ph	H	93
n-C_5H_{11}	H	78
t-Bu	H	84
(*E*)-PhCH=CH	H	99
4-$NO_2C_6H_4$	H	75
4-CNC_6H_4	H	76
4-$MeOCOC_6H_4$	H	96
Ph	Me	23
(*E*)-PhCH=CH	Ph	93[a]
Ph	CH(OMe)Ph	82 (>99% de)

a 1,4-Reduciton product.

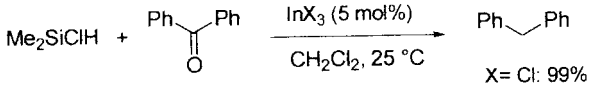
little affected. The reducing ability of $LiInH_4$ is increased by introduction of phenyl groups; $LiPhInH_3$ and $LiPh_2InH_2$ readily reduce aldehydes, ketones, acid chlorides, and even esters to the corresponding alcohols.

Dichloroindium hydride (Cl_2InH), generated by reaction of $InCl_3$ with tributyltin hydride, has also been successfully used for the reduction of carbonyl compounds and for the debromination of alkyl bromides [104]. This reductant has features such as the chemoselective reduction of functionalized benzaldehydes, chelation-controlled reduction of benzoin methyl ether, and 1,4-reduction of chalcone (Tab. 8.19). The stable carbene and tertiary phosphine adducts of indium trihydride, $[InH_3\{CN(Mes)C_2H_2N(Mes)\}]$ and $[InH_3\{P(C_6H_{11})_3\}]$ reduce ketones to alcohols (Scheme 8.75) [105].

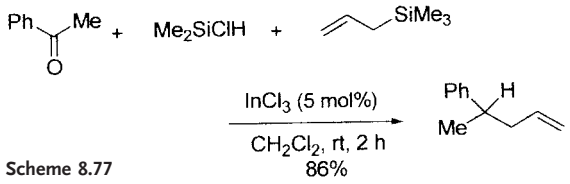


Scheme 8.75

A combination of chlorodimethylsilane and a catalytic amount (5 mol%) of $InCl_3$ is effective for deoxygenation of aryl ketones and *sec*-benzylic alcohols to the corresponding hydrocarbons (Scheme 8.76) [106]. This system is selective for carbonyl groups; functionalities such as halogen, ester, ether, and nitro groups tolerate the reduction conditions. A combination of chlorodimethylsilane and allyltrimethylsilane effectively promotes the deoxygenative allylation of aromatic ketones in the presence of a catalytic amount of $InCl_3$ to give the terminal alkenes (Scheme 8.77) [107]. The choice of solvent is definitely significant in this deoxygenative allylation; the reaction of acetophenone proceeds only in dichloromethane or 1,2-dichloroethane. Aldehydes and aliphatic ketones give complicated mixtures.



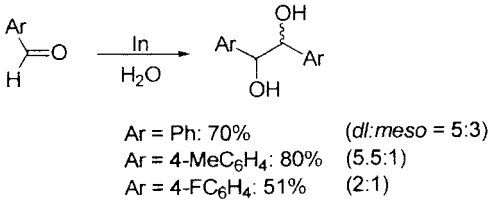
Scheme 8.76



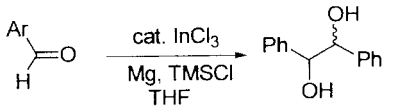
Scheme 8.77

8.5.2
Reductive Coupling

Indium-mediated pinacol coupling of aromatic aldehydes in neutral aqueous media under the action of sonication gives the corresponding diols in moderate to good yields (Scheme 8.78) [108a]. Pinacols are also obtained by use of $InCl_3$, TMSCl and Mg or Al (Scheme 8.79) [106b, c]. $InCl_3$-Zn-mediated deoxygenative coupling of carbonyl compounds gives (*E*)-alkenes (Tab. 8.20) [109].



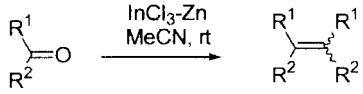
Scheme 8.78



Ar = Ph: 67% (*dl:meso*= 68:32)
Ar = 4-ClC_6H_4: 59% (50:50)
Ar = 4-MeC_6H_4: 69% (56:44)
Ar = 4-$MeOC_6H_4$: 43% (85:15)

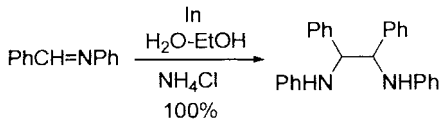
Scheme 8.79

Tab. 8.20 $InCl_3$-Zn-mediated reductive coupling of carbonyl compounds

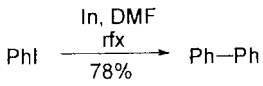


R^1	R^2	t [h]	Yield [%]	E/Z
Ph	H	8	93	98:2
4-ClC_6H_4	H	9	90	86:14
4-MeC_6H_4	H	7	88	90:10
4-$MeOC_6H_4$	H	8	80	75:25
4-$NO_2C_6H_4$	H	9	70	70:30
Ph	Me	9	60	80:20
n-pentyl	H	9	72	70:30

Aldimines are reductively coupled by indium in aqueous ethanol [110], or by $InCl_3$, TMCSl, and Al in THF [108c], to vicinal diamines in good yields (Scheme 8.80). Reductive homocoupling of alkyl and aryl iodides with indium metal in DMF produces bialkyls and biaryls in good yields (Scheme 8.81) [111].



Scheme 8.80

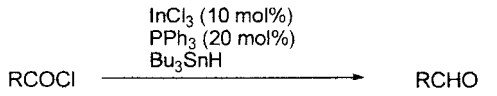


Scheme 8.81

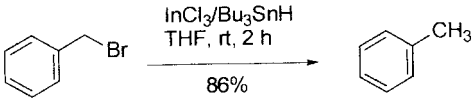
8.5.3 Dehalogenation

Dichloroindium hydride is inert in the reduction of acid chlorides. On addition of 20 mol% triphenylphosphine, however, high-yield reduction to aldehydes can be realized (Tab. 8.21) [112]. Over-reduction to alcohols is negligible. This reduction works even with a catalytic amount (10 mol%) of $InCl_3$. Neither electron-withdrawing nor -donating substituents on aromatic acid chlorides disturb the facile formation of aldehydes. Cyano and nitro substituents tolerate the reduction conditions. Primary aliphatic acid chlorides also give good yields even when terminal olefin and chlorine substituents are present. Bulky aliphatic acid chlorides give low yields accompanied with over-reduction to alcohols. Dichloroindium hydride acts as a radical initiator in the reduction of halides with tributyltin hydride (Scheme 8.82) [113]. Debromination of aryl-substituted *vic*-dibromides with indium metal in MeOH or Cp_2TiCl_2/In in THF leads exclusively to *trans* alkenes (Scheme 8.83) [114]. A wide range of structurally varied aryl-substituted *gem*-dibromides undergoes reduction by indium metal to give the corresponding (*E*)-vinyl bromides predominantly in high yields (Tab. 8.22) [115]. The $NaBH_4$–cat.$InCl_3$ system is found to be a convenient radical reagent and is proposed as an alternative to the tributyltin hydride system (Scheme 8.84) [116].

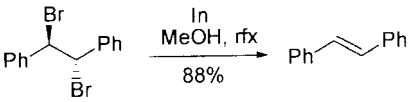
Tab. 8.21 Reduction of acid chlorides



R	*Solvent*	*T [°C]*	*Yield [%]*
Ph	toluene	–30	97
4-MeC_6H_4	toluene	–30	93
4-ClC_6H_4	toluene	–30	80
n-C_6H_{13}	toluene	–30	93
$Cl(CH_2)_5$	THF	–30	83
CH_2=$CH(CH_2)_8$	THF	–30	92
n-$C_4H_9(C_2H_5)CH$	THF	rt	42
c-C_6H_{11}	THF	rt	62
t-Bu	THF	rt	39

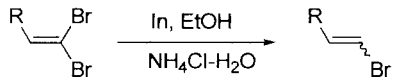


Scheme 8.82

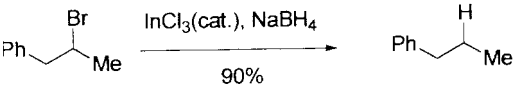


Scheme 8.83

Tab. 8.22 Reduction of 1,1-dibromoalkenes



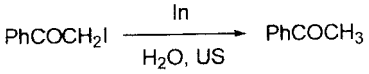
R	*t [h]*	*Yield [%]*	*E/Z*
Ph	16	95	95:5
1-naphthyl	16	80	90:10
4-ClC_6H_4	15	92	82:18
4-$MeOC_6H_4$	17	88	75:25
4-MeC_6H_4	16	90	76:24
3-MeC_6H_4	16	91	70:30
4-TBDMSOC_6H_4	17	92	82:18
2-allylOC_6H_4	16	85	80:20
3,4-$(MeO)_2C_6H_3$	17	93	76:24
3-MeO-4-BzOC_6H_3	16	90	75:25
PhCH=CH	18	80	60:40
	15	70	50:50
	15	85	55:45



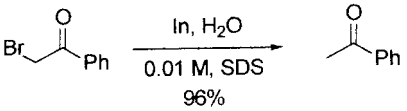
Scheme 8.84

Under the action of sonication indium metal in water reduces *α*-halocarbonyl compounds and benzyl iodides to the corresponding dehalogenated products in excellent yields, although simple alkyl and aryl iodides remain inert under these conditions (Scheme 8.85) [117a]. Similar dehalogenation in micellar systems in the presence of a catalytic amount of sodium dodecyl sulfate in water affords the corresponding parent carbonyl compounds in excellent yields (Scheme 8.86) [117b]. The allylic iodide or acetate is reduced by indium into the corresponding 3-methylcephems and 3-

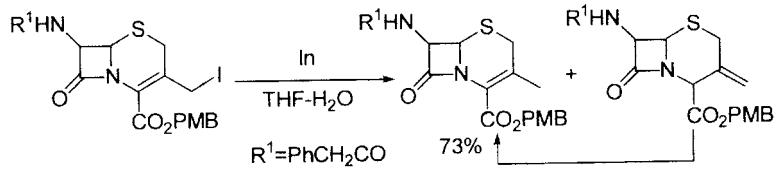
methylenecephams in an aqueous system (Scheme 8.87) [118]. The latter are converted quantitatively into the former under basic conditions.



Scheme 8.85



Scheme 8.86

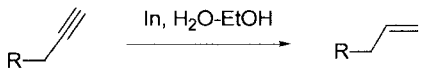


Scheme 8.87

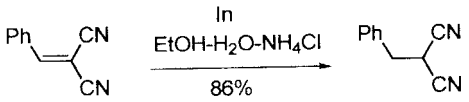
8.5.4
Reduction of Functional Groups

Indium metal reduces the terminal triple bond of aryl propargyl ethers, amines, and esters in aqueous ethanol to produce the corresponding alkenyl compounds (Tab. 8.23) [119]. Indium metal in aqueous ethanolic ammonium chloride reduces the carbon–carbon double bond of activated conjugated alkenes such as *α,α*-dicyano olefins, *β*-arylenones, and enone esters (Scheme 8.88) [120].

Tab. 8.23 Reduction of terminal alkynes

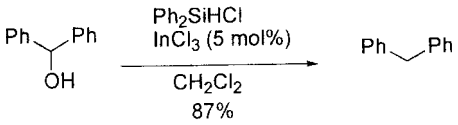


R	*t [h]*	*Yield [%]*
PhO	40	90
$PhCH_2O$	50	45
PhNH	40	90
c-$C_6H_{11}NH$	40	20
PhCOO	40	95
c-$C_6H_{11}COO$	50	42

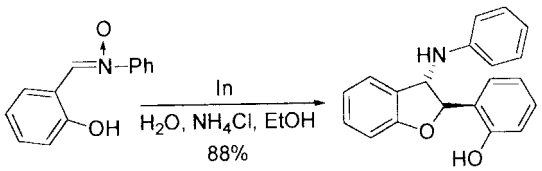


Scheme 8.88

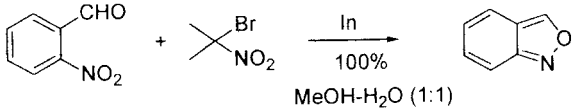
The reduction of alcohols using chlorodiphenylsilane as a hydride source proceeds in the presence of a catalytic amount of $InCl_3$ (Scheme 8.89) [121]. In the presence of indium, nitrones undergo deoxygenative reductive coupling and subsequent cyclization to give 3-arylamino-2,3-dihydrobenzofuran derivatives under aqueous conditions at ambient temperature (Scheme 8.90) [122]. 2-Nitro-substituted acylbenzenes or iminobenzenes are cyclized to 2,1-benzisoxazoles with 2-bromo-2-nitropropane and indium in aqueous methanol. The reaction is considered to involve the 2-nitropropan-2-yl radical, which is generated by reduction of 2-bromo-2-nitropropane with indium (Scheme 8.91) [123].



Scheme 8.89

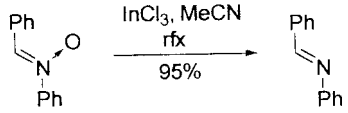


Scheme 8.90

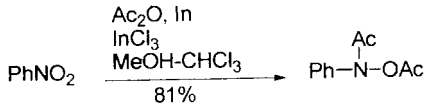


Scheme 8.91

The deoxygenation of *N*-oxides such as *N*-arylnitrones, azoxybenzenes, and *N*-heteroarene *N*-oxides, proceeds smoothly with indium trichloride in MeCN (Scheme 8.92) [124]. Nitroarenes are transformed to *N*,*O*-diacetylated *N*-arylhydroxylamines with indium metal, Ac_2O, MeOH, and a catalytic amount of $InCl_3$ (Scheme 8.93) [125].

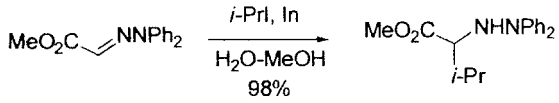


Scheme 8.92

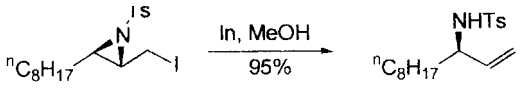


Scheme 8.93

Intermolecular alkyl radical addition to imine derivatives proceeds in aqueous media when indium is used as an SET radical initiator. The one-pot reaction based on radical addition to glyoxylic hydrazone provides an *α*-amino acid (Scheme 8.94) [126]. A similar indium-mediated radical addition to an electron-deficient C–C bond gives the corresponding adduct. Chiral allylic amines are synthesized in high yields by treatment of 2-iodomethyl *N*-tosyl aziridines with indium in MeOH under reflux (Scheme 8.95) [127].

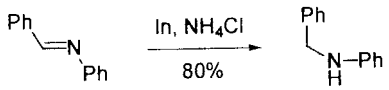


Scheme 8.94

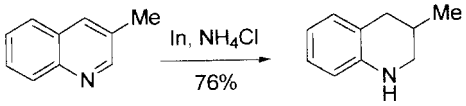


Scheme 8.95

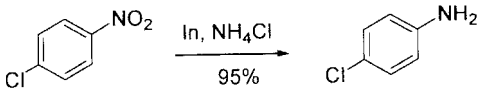
Indium metal is used for the reduction of imines (Scheme 8.96), iminium salts, quinolines (Scheme 8.97), conjugate alkenes, nitro compounds (Scheme 8.98), and azides in aqueous ethanolic ammonium chloride [128a–g]. Oximes (Tab. 8.24) [128a, h] and azides are also reduced to the corresponding amines with indium in acidic THF (Tab. 8.25) [128i].



Scheme 8.96

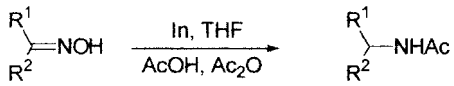


Scheme 8.97



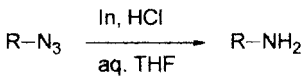
Scheme 8.98

Tab. 8.24 Reduction of oximes



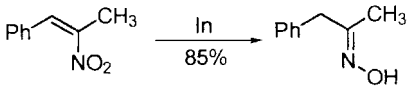
R¹	*R²*	*Yield [%]*
CO_2Me	CO_2Me	65
CO*i*-Pr	CO_2Me	85
COPh	COMe	69
Me	CO_2Et	98
Me	COPh	96
H	COPh	100

Tab. 8.25 Reduction of azides

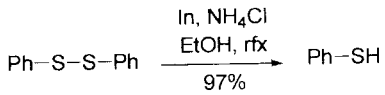


R	*t [h]*	*Yield [%]*
$PhCH_2$	2	85
(*E*)-PhCH=CH	3	92
Ph_3C	8	90
Ph_2CH	8.5	96
$PhCH_2OCOCH_2$	3	85
4-$^{n}BuC_6H_4$	3	95
dodecyl	2	92

β-Nitrostyrenes are selectively reduced to the corresponding oximes by indium metal in aqueous methanol (Scheme 8.99) [129]. The reduction of disulfides by use of In/NH_4Cl gives thiols (Scheme 8.100) [130].



Scheme 8.99



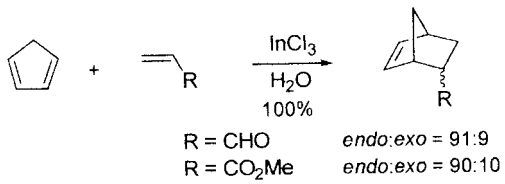
Scheme 8.100

8.6 Indium Salts as Lewis Acids

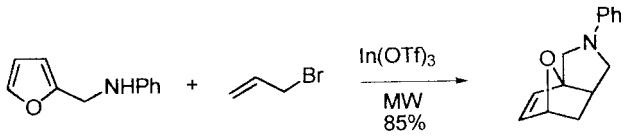
Indium(III) chloride and indium(III) triflate have been introduced to organic syntheses as versatile Lewis acids. They are stable in water, and catalyze a variety of organic reactions, e.g. the Diels-Alder reaction, the aldol reaction, Michael addition, the Friedel-Crafts reaction, and other organic transformations.

8.6.1 The Diels-Alder Reaction

It was first reported in 1996 that indium trichloride catalyzes the Diels-Alder reaction in water [131]. The reaction of acrolein with cyclopentadiene in the presence of 20 mol% $InCl_3$ proceeds stereoselectively (*endo*:*exo*=91:9) (Scheme 8.101). Without catalyst the reaction only goes to 60% completion (*endo*:*exo*=74:26). The $InCl_3$-catalyzed Diels-Alder reaction works with either cyclic or non-cyclic dienes. $InCl_3$ can be recovered for reuse after the reaction is completed. Indium triflate is also an effective catalyst for intramolecular Diels-Alder reactions of furans under microwave irradiation (Scheme 8.102) [132].

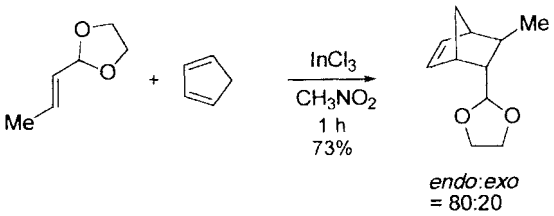


Scheme 8.101



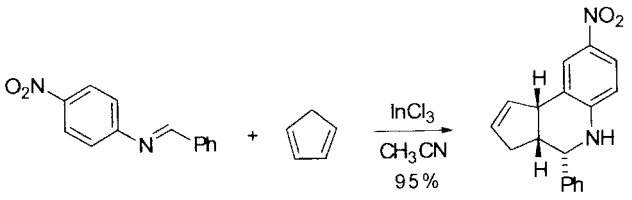
Scheme 8.102

Indium chloride is also an excellent catalyst for ionic Diels-Alder reactions. Acyclic and cyclic olefinic acetals undergo reactions with isoprene and cyclopentadiene in the presence of 20 mol% $InCl_3$ to form the corresponding cyclic adducts in good yield with good selectivity (Scheme 8.103) [133]. With cyclopentadiene, the *endo*/*exo* ratio is fairly good and comparable with that for the $LiClO_4$- and Nafion-H-based reactions. With other Lewis acids, e.g. $Yb(OTf)_3$ or $Sc(OTf)_3$, no cycloadduct is formed.

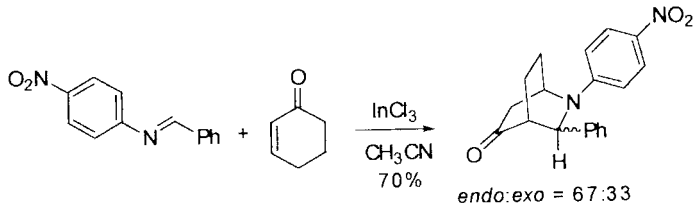


Scheme 8.103

Indium trichloride and indium triflate are good catalysts also for the imino Diels-Alder reactions. With 20 mol% $InCl_3$, *N*-benzylideneaniline reacts with cyclopentadiene to give the corresponding tetrahydroquinoline derivative (Scheme 8.104) [134]. Similar $InCl_3$-catalyzed imino Diels-Alder reactions proceed with 3,4-dihydro-2*H*-pyrane, indene [135], and cyclic enamides [136]. In contrast, cyclohexen-2-one gives no phenanthridinone, but azabicyclo [2.2.2]octanone is isolated (Scheme 8.105) [137]. The reaction seems to proceed through the formation of dienolate ion by strong coordination of $InCl_3$ with the enone.

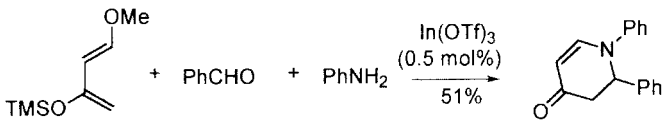


Scheme 8.104

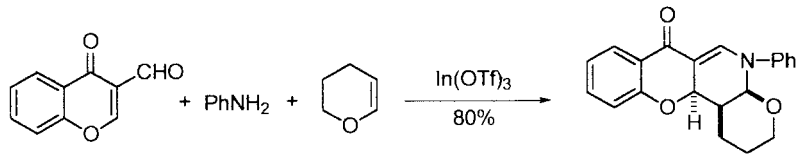


Scheme 8.105

At a loading as low as 0.5 mol%, indium triflate catalyzes the three-component coupling reaction between aldehydes, amines, and Danishefsky's diene to afford tetrahydropyridine derivatives (Scheme 8.106) [138]. In the presence of indium triflate, 3,4-dihydro-2*H*-pyran reacts with *in situ*-generated chromone Schiff's bases to give the *endo* cycloadducts (Scheme 8.107) [139].



Scheme 8.106



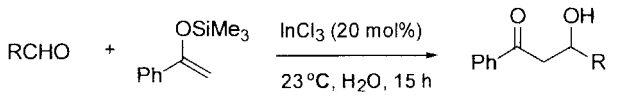
Scheme 8.107

8.6.2
Aldol and Mannich Reactions

In combination with *t*-butyldimethylsilyl chloride, $InCl_3$ catalyzes the aldol reaction between aldehydes and *t*-butyldimethylsilyl enol ethers in anhydrous organic solvents [140]. It has recently been found that the $InCl_3$-catalyzed Mukaiyama aldol reaction proceeds in water (Tab. 8.26) [141]. The reaction proceeds cleanly under almost neutral conditions to give *β*-hydroxy ketones. The aqueous phase with $InCl_3$ can be reused. Water-soluble aldehydes such as glyoxylic acid and a commercial formaldehyde solution can be used directly for these reactions.

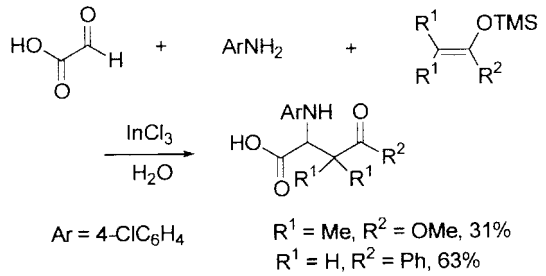
In contrast with these results it has been claimed that hydrolysis of silyl enol ethers is superior to the desired aldol reactions with aldehydes in water [142]. The reactions have been found to proceed to some extent in the presence of $InCl_3$ under neat (solvent free) conditions [142, 143]. With the surfactant sodium dodecyl-

Tab. 8.26 $InCl_3$-catalyzed reaction of silyl enol ether with aldehydes

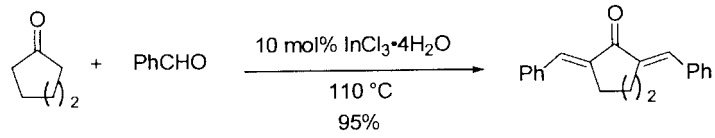


RCHO	*Yield (%)*
PhCHO	88
HCHO	91
$HO_2CCHO \cdot H_2O$	91
2-PyCHO	96
4-PyCHO	96

sulfate (SDS, 35 mM, 0.2 equiv.) and 0.2 equiv. $InCl_3$, benzaldehyde reacts with 1-phenyl-1-trimethylsilyloxypropene in micellar systems to give the corresponding aldol adduct in 75% yield [142]. Indium chloride catalyzes the aldol reaction between D-glucose-derived silyl enol ether and formaldehyde in water to give the corresponding adduct diastereoselectively ($R/S = 96:4$) [144]. One-pot Mannich-type reactions between aldehydes, amines and silyl enol ethers are also catalyzed by $InCl_3$ in water to give β-amino ketones and esters. With glyoxylic acid as the aldehyde component, α-amino acids can be obtained (Scheme 8.108) [145]. $InCl_3$ can be used in the addition of silyl enolates to aromatic aldimines [146]. The greater selectivity for aldimines than for aldehydes is demonstrated in the $InCl_3$-catalyzed coupling with propiophenone silyl enol ether [147]. The $InCl_3 \cdot 4H_2O$-catalyzed condensation of cycloalkanones with aromatic aldehydes proceeds in a sealed tube to afford α,α'-dibenzylidenecycloalkanones (Scheme 8.109) [148].



Scheme 8.108

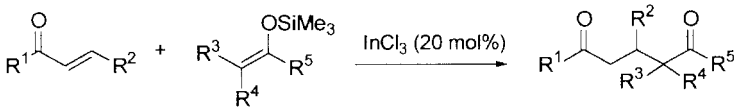


Scheme 8.109

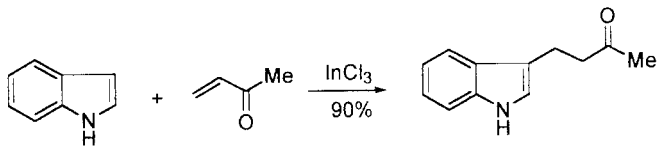
8.6.3
Michael Addition

The conjugate addition of primary and secondary amines to *α,β*-ethylenic compounds, such as acrylates, crotonates, and acrylonitrile, is promoted by $InCl_3$ in water under mild conditions [149]. When the reaction of acrylonitrile with diisopropylamine is conducted in the presence of $InCl_3$ (20 mol%), the Michael product is obtained in 82% yield. The catalyst can be reused. Under neat conditions, $InCl_3$ is also an effective catalyst for Michael addition of silyl enol ethers and ketene silyl enol acetals to *α,β*-unsaturated ketones, affording the corresponding adducts (Tab. 8.27) [150]. Allyltrimethylsilane also reacts with *α,β*-unsaturated ketones to give the 1,4-adducts in the presence of $InCl_3$ and TMSCl [151]. Indole and 2-methylindole undergo conjugate addition with electron-deficient olefins in the presence of a catalytic amount of $InCl_3$ to afford the corresponding Michael adducts (Scheme 8.110) [152].

Tab. 8.27 Michael addition of silyl enol ethers and ketene silyl enol acetals



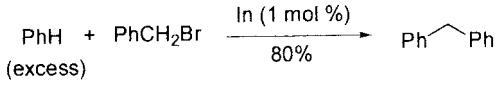
R^1	R^2	R^3	R^4	R^5	*Yield (%)*
$(CH_2)_3$		H	H	Ph	67
$(CH_2)_3$		Me	Me	OMe	82
$(CH_2)_3$		Me	H	Ph	86 (*syn*:*anti* = 65:35)
$(CH_2)_3$		H	$(CH_2)_3$		90 (de 65:35)
$(CH_2)_2$		H	H	Ph	60
H	H	H	H	Ph	68



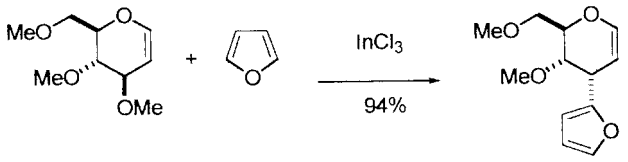
Scheme 8.110

8.6.4
Friedel-Crafts Reaction

The treatment of aromatic compounds with benzyl halides in the presence of a catalytic amount of indium (1 mol%) gives the corresponding diaryl compounds (Scheme 8.111) [153]. Glycals react smoothly with furan in the presence of a catalytic amount of $InCl_3$ to afford C-3-substituted glycals (Scheme 8.112) [154].



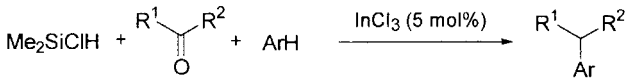
Scheme 8.111



Scheme 8.112

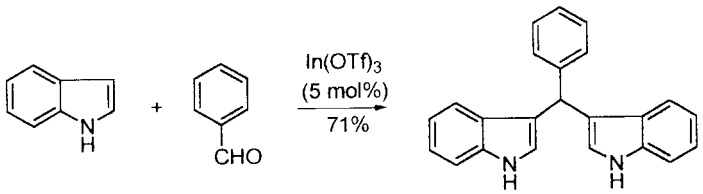
A catalytic amount of $InCl_3$ promotes the reductive Friedel-Crafts alkylation of aromatic compounds with aldehydes or ketones using chlorodimethylsilane as a hydride source (Tab. 8.28) [155]. Typical Friedel-Crafts catalysts, e.g. $AlCl_3$, $ZnCl_2$, and CF_3SO_3H, have less effect. Both aromatic and aliphatic ketones can be used to give the corresponding alkylbenzenes, whereas aliphatic aldehydes such as hexanal result in the quantitative formation of the dialkyl ether. Functional groups such as halogen, ester, and ether on the ketones are tolerated under the reductive conditions.

Tab. 8.28 Reductive Friedel-Crafts alkylation of aromatics with carbonyl compounds



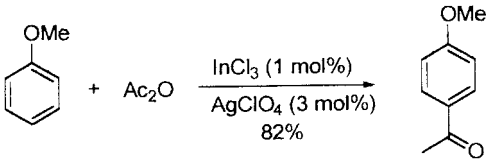
R^1	R^2	ArH	Yield (%) (o:m:p)
Ph	H	PhH	79
Ph	Me	PhMe	99 (15:4:81)
4-ClC_6H_4	Me	PhMe	91 (16:3:81)
4-CNC_6H_4	Me	PhMe	97 (32:10:58)
4-$NO_2C_6H_4$	Me	PhMe	87 (29:10:61)
Ph	Me	PhMe	99 (15:4:81)

Indium chloride and indium triflate are efficient catalysts for the synthesis of bis-indolylmethane and indolylquinoline derivatives. Indium triflate needs lower catalytic loading (Scheme 8.113) [156].

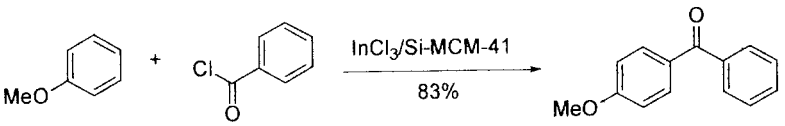


Scheme 8.113

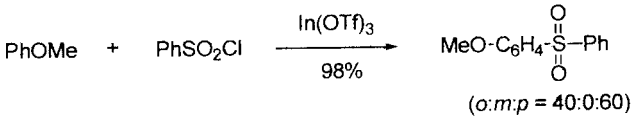
Catalytic acylation of electron-rich aromatics is achieved with a combination of $InCl_3$ and silver perchlorate (Scheme 8.114) [157]. Acetic anhydride, acetyl chloride and isopropenyl acetate serve as satisfactory acyl donors. By using an $InCl_3$-impregnated Si-MCM-41 catalyst at low concentration, acylation of aromatic compounds (benzene, toluene, *p*-xylene, mesitylene, anisole, naphthalene, methylnaphthalene, and methoxynaphthalene) by acyl chlorides (benzoyl chloride, phenylacetyl chloride, propionyl chloride, or butyryl chloride) can be accomplished rapidly (3 h) at 80 °C in high yield, even in the presence of moisture in the aromatic substrate or solvent (dichloroethane) (Scheme 8.115) [158]. $In(OTf)_3$ is an efficient catalyst in the sulfonylation of both activated and deactivated aromatic compounds (Scheme 8.116) [159].



Scheme 8.114



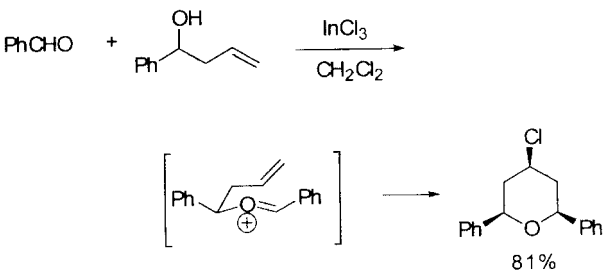
Scheme 8.115



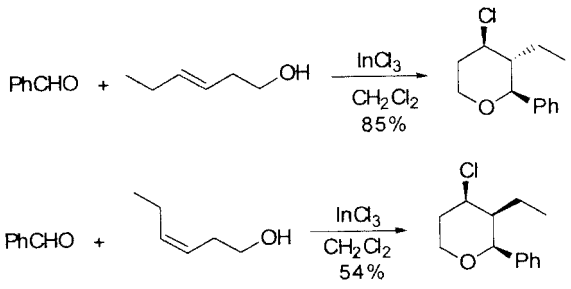
Scheme 8.116

8.6.5
Heterocycle Synthesis

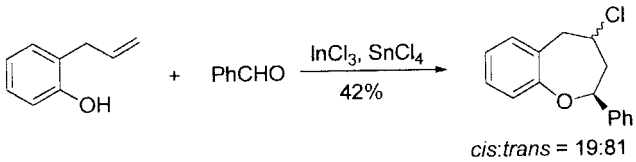
The Prins-type reaction of aldehydes with homoallyl alcohols mediated by $InCl_3$ gives 4-chlorotetrahydropyrans with high stereoselectivity [160]. When a mixture of benzaldehyde and 1-phenyl-3-buten-1-ol is stirred with $InCl_3$ at room temperature, 4-chloro-2,6-diphenyltetrahydropyran is formed (Scheme 8.117). The two phenyl groups and the chlorine are equatorial. Other aromatic and aliphatic aldehydes are similarly converted into 4-chlorotetrahydropyran derivatives with high stereoselectivity. The cross-cyclization of aldehydes with *trans*-homoallylic alcohols generates (*up–down–up*) 2,3,4-trisubstituted tetrahydropyrans, whereas *cis*-homoallylic alcohols give (*up–up–up*) 2,3,4-trisubstituted products (Scheme 8.118). In contrast, the reaction of both *cis*- and *trans*-homoallyl mercaptans with aldehydes provides the same major diastereomers (*up–down–up*) [161]. A similar stereochemical correlation is observed for the $InCl_3$-catalyzed cross-cyclization of epoxides and homoallyl alcohols [162]. The $InCl_3$-mediated, tin(IV)-catalyzed Prins-type coupling of allylphenols with carbonyl compounds gives oxepanes as a mixture of diastereomers (Scheme 8.119) [163]. The reaction of γ-(trimethylsilyl)allyltributylstannane with aliphatic aldehydes leads to the formation of 2,6-dialkyl-3,4-dihydropyrans with *cis* diastereoselectivity (Scheme 8.120) [164]. Aromatic aldehydes did not lead to the cyclization products.



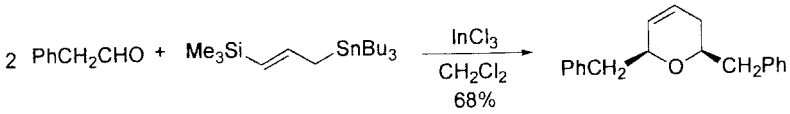
Scheme 8.117



Scheme 8.118



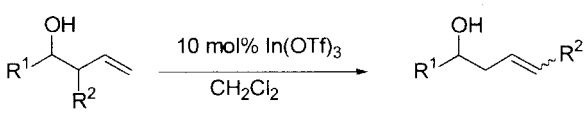
Scheme 8.119



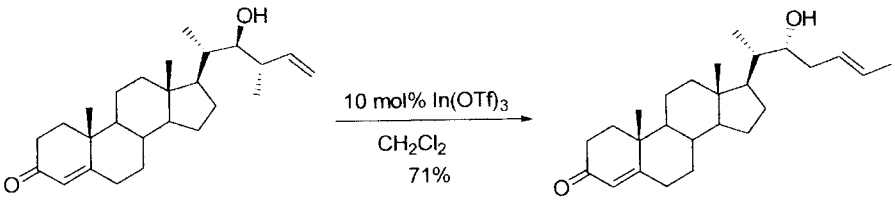
Scheme 8.120

Branched homoallylic alcohols are converted to the thermodynamically preferred linear regioisomers in the presence of 10 mol% $In(OTf)_3$ (Tab. 8.29). When this conversion is applied to an optically pure branched homoallylic sterol the stereochemically inverted isomer is formed (Scheme 8.121). It is suggested that both undergo retro-cleavage to generate the parent aldehyde in situ and a 2-oxonia [3,3]-sigmatropic rearrangement is involved (Scheme 8.122) [165].

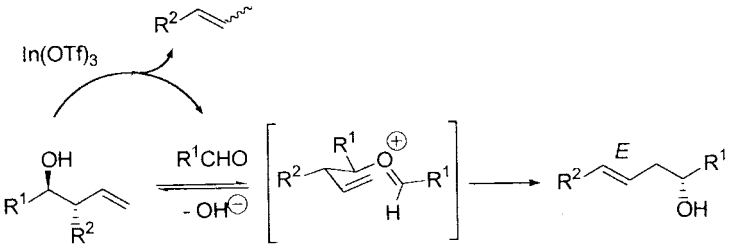
Tab. 8.29 Rearrangement of branched homoallylic alcohols to the linear isomers



R^1	R^2	*anti/syn*	*T* [°C]	*Yield (%) [E/Z]*
c-C_6H_{11}	Me	80/20	25	78 (68/32)
c-C_6H_{11}	Ph	98/2	25	81 (*E*)
c-C_6H_{11}	CO_2Et	85/15	40	69 (85/15)
Ph	CO_2Et	86/14	40	19 (*E*)
$PhCH_2CH_2$	Me	50/50	25	72 (55/45)
$PhCH_2CH_2$	Ph	70/30	25	36 (>99/1)
$PhCH_2CH_2$	CO_2Et	80/20	40	74 (84/16)
$PhCH_2CH_2$	CO_2Et	>99/1	40	78 (*E*)
$CH_3(CH_2)_4$	Me	55/45	25	53 (65/35)
$CH_3(CH_2)_4$	Ph	90/10	25	76 (97/3)
$CH_3(CH_2)_4$	CO_2Et	70/30	40	73 (80/20)

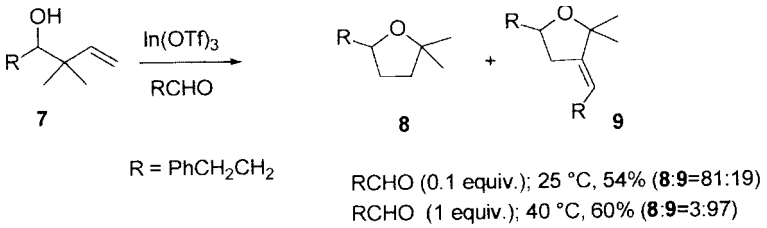


Scheme 8.121



Scheme 8.122 2-Oxonia [3,3]-sigmatropic rearrangement

2-Substituted 5,5-dimethyltetrahydrofuran **8** is obtained by reaction of homoallylic alcohol **7** with a catalytic amount of $In(OTf)_3$ (0.1 equiv.) and aldehyde (0.1 equiv.) (Scheme 8.123). When the reaction is conducted with an equimolar amount of aldehyde and catalytic $In(OTf)_3$ (0.1 equiv.), compound **9** is formed selectively. A tandem 2-oxonia [3,3]-sigmatropic rearrangement/cyclization mechanism is postulated [166].

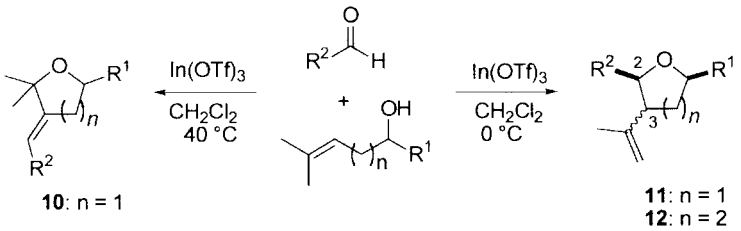


Scheme 8.123

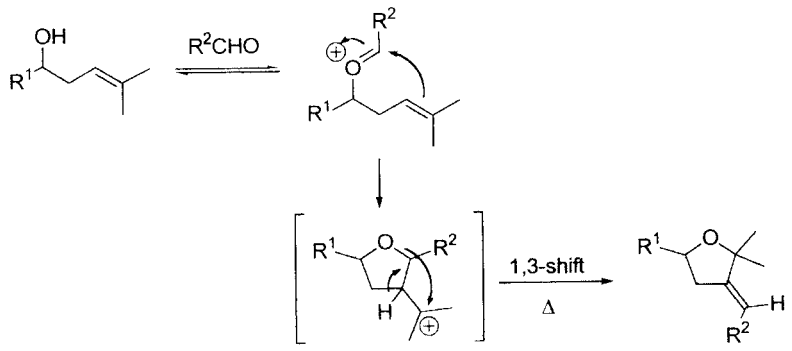
The $In(OTf)_3$-catalyzed (3,5) oxonium-ene type cyclization affords various multisubstituted tetrahydrofurans and tetrahydropyrans (Tab. 8.30). For tetrahydrofuran syntheses the reaction is temperature-dependent – increasing the reaction temperature converts the kinetic product **11** to the thermodynamic isomer **10** via a 1,3-shift (Scheme 8.124) [167].

The $InCl_3$-catalyzed reaction of ethyl diazoacetate with aldimines under mild conditions gives aziridine carboxylates. In the presence of 2 mol% $InCl_3$, *N*-benzylidene

Tab. 8.30 $In(OTf)_3$-catalyzed (3,5) oxonium-ene type cyclization

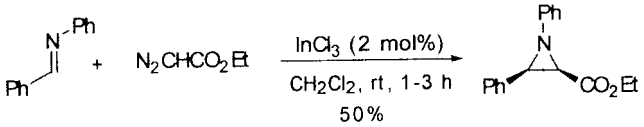


n		R^1	R^2	*T* [°C]	*Yield (%)*	*2,3-trans:cis*
1	**a**	*c*-C_6H_{11}	$PhCH_2CH_2$	40	65 (**10a**)	–
1	**a**	*c*-C_6H_{11}	$PhCH_2CH_2$	0	95 (**11a**)	65:35
1	**b**	*c*-C_6H_{11}	$CH_3(CH_2)_7$	40	81 (**10b**)	–
1	**b**	*c*-C_6H_{11}	$CH_3(CH_2)_7$	0	69 (**11b**)	62:38
1	**c**	*c*-C_6H_{11}	Ph	40	97 (**10c**)	–
1	**c**	*c*-C_6H_{11}	Ph	0	72 (**11c**)	80:20
1	**d**	*c*-C_6H_{11}	*c*-C_6H_{11}	40	75 (**10d**)	–
1	**d**	*c*-C_6H_{11}	*c*-C_6H_{11}	0	77 (**11d**)	87:13
2	**a**	Me	$PhCH_2CH_2$	40	39 (**12a**)	–
2	**a**	Me	$PhCH_2CH_2$	0	88 (**12a**)	95:5
2	**b**	Me	$CH_3(CH_2)_7$	0	87 (**12b**)	97:3
2	**c**	Me	Ph	0	77 (**12c**)	92:8
2	**e**	Me	PhCH=CH	0	89 (**12e**)	90:10
2	**f**	Me	*p*-CNC_6H_4	0	86 (**12f**)	93:7
2	**g**	Me	2-furyl	0	63 (**12g**)	99:1
2	**h**	Me	*o*-OHC_6H_4	0	56 (**12h**)	99:1

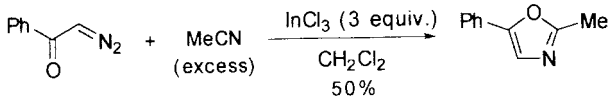


Scheme 8.124 Formation of the thermodynamic isomer via a 1,3-shift

aniline affords the corresponding *cis*-aziridine in 50% yield (Scheme 8.125) [168]. $InCl_3$ is effective in the cyclization of α-diazoketones with nitriles to produce 2,5-disubstituted oxazoles (Scheme 8.126). In this reaction, excess (2–3 equiv.) $InCl_3$ is necessary for complete consumption of the α-diazoketone and suppression of α-chloroketone formation [169].

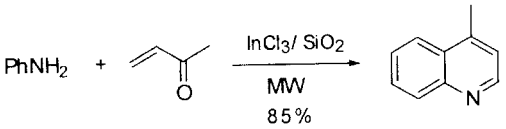


Scheme 8.125

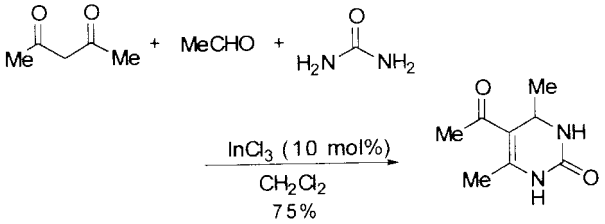


Scheme 8.126

A microwave-assisted one-pot synthesis of quinolines is realized with $InCl_3$. Amines and alkyl vinyl ketones react on the surface of $InCl_3$-impregnated silica gel, without solvent, affording 4-alkylquinolines in high yields (Scheme 8.127) [170]. The coupling of a β-dicarbonyl compound, an aldehyde, and urea in THF under reflux in the presence of $InCl_3$ (10 mol%) gives the corresponding dihydropyrimidinones (Scheme 8.128) [171]. A variety of substituted aromatic, aliphatic, and heterocyclic aldehydes have been subjected to this condensation. β-Keto aldehydes do not give the corresponding dihydropyrimidinones.

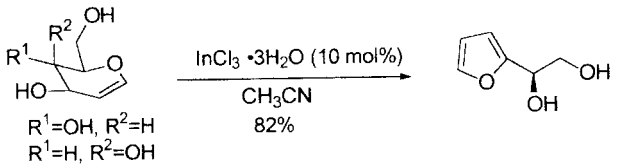


Scheme 8.127

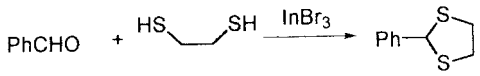


Scheme 8.128

When D-glucal is treated with 10 mol% $InCl_3 \cdot 3H_2O$ in acetonitrile the chiral furan diol is obtained. D-Galactal also undergoes transformation to the same product (Scheme 8.129) [172]. Indium tribromide and trichloride efficiently catalyze the chemoselective thioacetalization of carbonyl compounds (Scheme 8.130) [173].



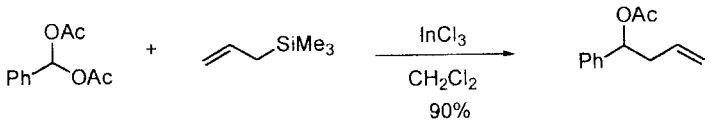
Scheme 8.129



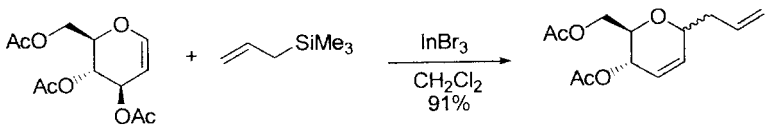
Scheme 8.130

8.6.6
Miscellaneous Reactions

Indium(III) chloride catalyzes the allylation of *gem*-diacetates with allyltrimethylsilane to afford the corresponding homoallylic acetates (Scheme 8.131) [174]. Glycals react with silyl nucleophiles, e.g. allyltrimethylsilane, cyanotrimethylsilane, and azidotrimethylsilane, in the presence of a catalytic amount of $InBr_3$ to give the corresponding 2,3-unsaturated allyl-, cyano-, and azidoglycosides, respectively (Scheme 8.132) [175].

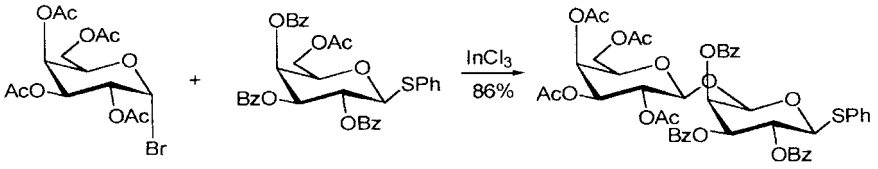


Scheme 8.131



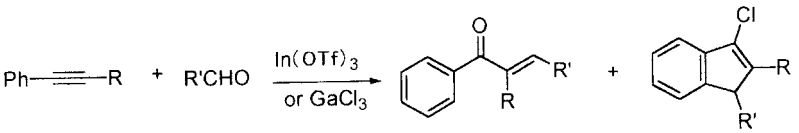
Scheme 8.132

A variety of glycosides and disaccharides are synthesized by coupling of glycosyl bromides with alcohols and sugars in the presence of indium chloride as a promoter (Scheme 8.133) [176].



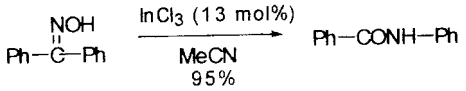
Scheme 8.133

A catalytic amount (5 mol%) of $InCl_3$ alters the ratio of 1,2- to 1,4-addition of Grignard reagents to α,β-unsaturated carbonyl compounds [177]. In the presence of indium triflate or gallium chloride coupling of internal alkynes and aldehydes proceeds (Scheme 8.134) [178].

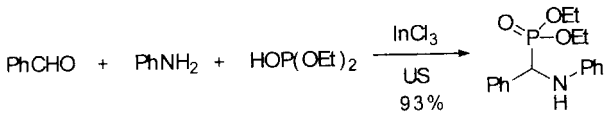


Scheme 8.134

$InCl_3$ can be used as an efficient reagent for the conversion of aldoximes to nitriles and ketoximes to amides. Benzaldoxime gives benzonitrile, and benzophenone oxime is converted to the Beckmann rearrangement product, benzanilide, in 95% yield (Scheme 8.135) [179]. Sonication of a mixture of a carbonyl compound, an amine, and diethyl phosphite in the presence of a catalytic amount of $InCl_3$ produces α-aminophosphonate (Scheme 8.136) [180].



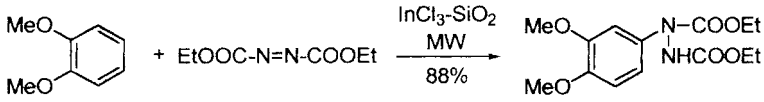
Scheme 8.135



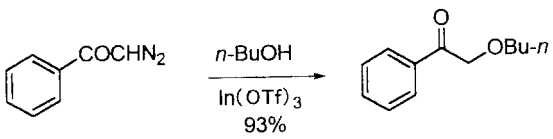
Scheme 8.136

Under the action of microwave irradiation electron-rich arenes undergo electrophilic amination with diethyl azocarboxylate on the surface of indium trichloride-impregnated silica gel to afford *para*-substituted aryl hydrazides (Scheme 8.137) [181]. In the presence of indium triflate, O–H insertion reactions of α-diazo ketones with aliphatic/aromatic alcohols or benzenethiol afford α-alkoxy ketones

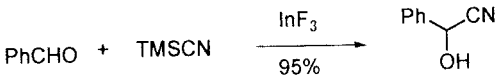
(Scheme 8.138) [182]. Indium trifluoride promotes the addition of TMSCN to carbonyl compounds in water to give the respective cyanohydrins [183 a]. $InCl_3$ and $InBr_3$ also promote the addition of cyanide to carbonyls and imines in organic solvents (Scheme 8.139) [183 b, c].



Scheme 8.137

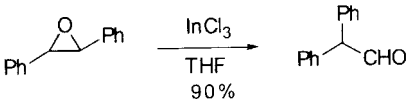


Scheme 8.138

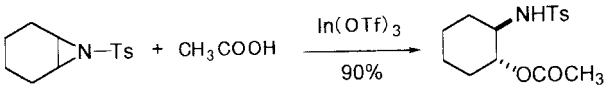


Scheme 8.139

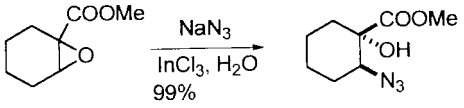
Indium trichloride induces rearrangement of aryl-substituted epoxides to the respective aryl-substituted acetaldehydes via an exclusive hydride shift. As phenyl group migration occurs more readily than hydride migration, stilbene oxide is converted to diphenylacetaldehyde (Scheme 8.140) [184]. *N*-Tosyl aziridines react smoothly with carboxylic acids in the presence of a catalytic amount of indium triflate to afford the corresponding *β*-aminoacetates and benzoates (Scheme 8.141) [185]. Indium trichloride and indium bromide catalyze regio- and diastereoselective azidolysis, bromolysis, and iodolysis of *α,β*-epoxycarboxylates in water (Scheme 8.142) [186].



Scheme 8.140

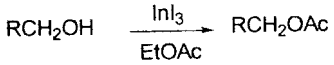


Scheme 8.141

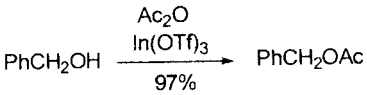


Scheme 8.142

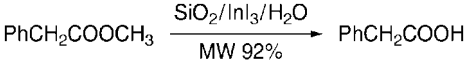
Indium triiodide catalyzes transesterification processes, e.g. the acylation of alcohols or amines and the conversion of THP ethers to acetates (Scheme 8.143) [187]. Indium triflate is also an efficient catalyst for the acylation of alcohols and amines (Scheme 8.144) [188]. Carboxylates are hydrolyzed to the corresponding carboxylic acids in high yield by microwave-assisted reaction on the surface of moistened silica gel in the presence of indium triiodide (Scheme 8.145) [189].



Scheme 8.143



Scheme 8.144



Scheme 8.145

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9
Thallium in Organic Synthesis

Sakae Uemura

Thallium (Tl), one of Group 13 elements, is quite a useful element in organic synthesis and, especially, the strong oxidizing strength of Tl(III) has been used for many oxidative organic transformations where the formation of C–Tl bonds and their facile bond cleavage are generally involved. Among other characteristic features are the strongly electrophilic nature of the Tl(III) species, quite high regioselectivity in aromatic substitution reactions, because of the bulkiness of $Tl(III)Z_2^+$ species and the strong affinity of Tl for the oxygen atom of the substituents, the highly efficient one-electron accepting nature of Tl(III), the unique reactivity of organothallium(I) salts, usually very high product yield, etc. One serious drawback to the use of Tl salts in organic synthesis is, on the other hand, their toxicity (e.g. TlOAc, LD_{50} orally in female rats 32 mg kg^{-1}; Tl_2SO_4, LD_{50} orally in rats 25 mg kg^{-1}) [1], despite the remarks of Markó et al. [2] that Tl is not a cumulative poison, in contrast with mercury (Hg) and lead (Pb). Very careful attention must therefore be paid to its treatment and handling, and also to waste disposal [3]. Hopefully, the catalytic use of Tl salts will be favored, although this has not yet been well developed.

Several excellent review articles appeared in the early 1970s [3a, 4] and in the 1980s [5] in which all the fundamental and characteristic reactions using Tl salts were included. A recent review by Ferraz et al. [6] thoroughly summarized results from use of Tl(III) in organic synthesis from 1989 to 1998.

This short article deals mainly with typical synthetically useful and important organic transformations using Tl(III) and Tl(I) salts, e.g. commercial $Tl(OAc)_3$, $Tl(OCOCF_3)_3$, $Tl(NO_3)_3 \cdot 3H_2O$ (abbreviated as TTA, TTFA, and TTN, respectively), TlOEt and TlOH and some Tl(III) species generated in situ. Because the examples cited here were selected arbitrarily, readers should consult the reviews mentioned above for more detailed and thorough chemistry.

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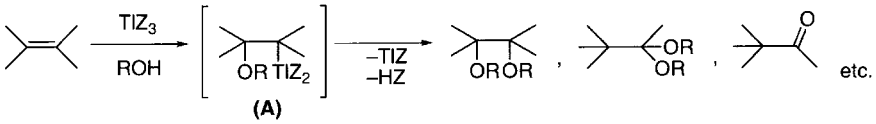
9.1
Tl(III) Salts in Organic Synthesis

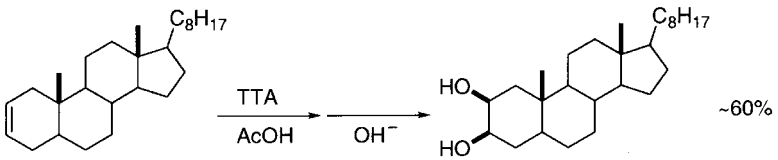
9.1.1
Alkene Oxidations

The basic reaction is the oxythallation of alkenes in a variety of solvents, e.g. methanol, acetic acid, aqueous tetrahydrofuran and aqueous acetonitrile to afford the so-called oxythallation adducts or β-oxyalkylthallium compounds (**A**) which readily give the oxidation products by oxidative cleavage of the C–Tl bond (Scheme 9.1). Here, a Tl(III) species works as an electrophile and the species is reduced to a Tl(I) compound. The products are diols, their esters or ethers, ketones, aldehydes or their acetals, etc., depending on the substitution pattern on alkenes. The oxidation is quite often accomplished by alkyl or aryl group transfer, ring contraction, and ring enlargement, reflecting a carbocationic nature of the carbon after the C–Tl bond fission.

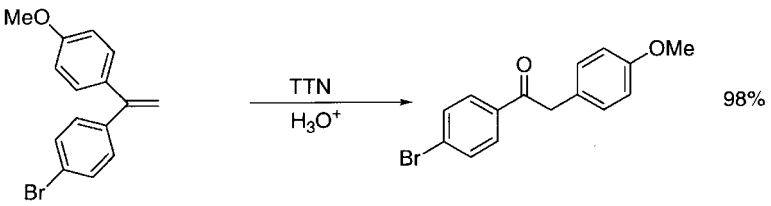


Scheme 9.1

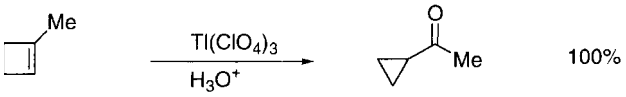
Typical synthetically useful reactions are shown in Schemes 9.2 [7], 9.3 [8], 9.4 [9], 9.5 [10], 9.6 [11], 9.7 [12], 9.8 [13], and 9.9 [14]. Organothallium(III) compounds (**A**) have sometimes been isolated and *ipso* substitution of the Tl moiety by halogens and pseudohalogens has been known to afford α,β-difunctionalized alkanes regioselectively (Schemes 9.10 [15] and 9.11 [16]). Aminothallation is also a useful method for production of nitrogen-containing compounds (Scheme 9.12 [17]).



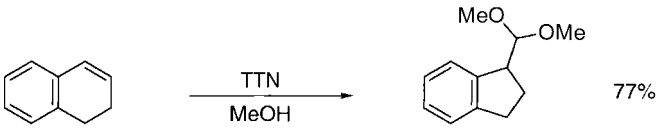
Scheme 9.2



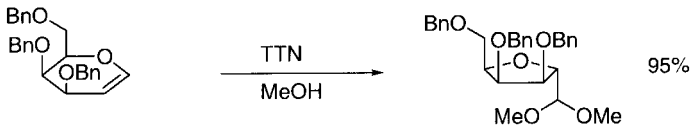
Scheme 9.3



Scheme 9.4

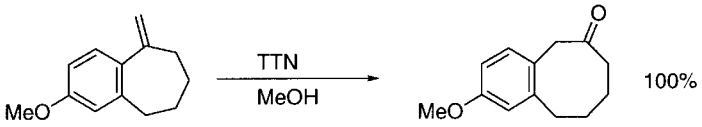


Scheme 9.5

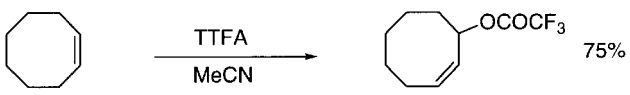


Scheme 9.6

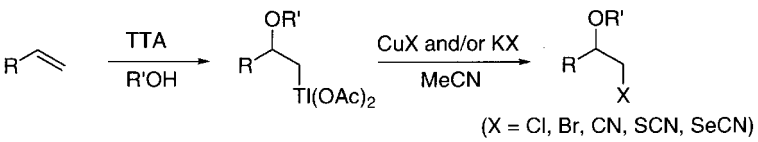
Scheme 9.7



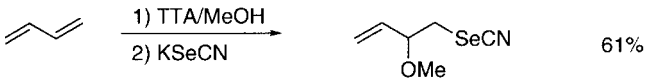
Scheme 9.8



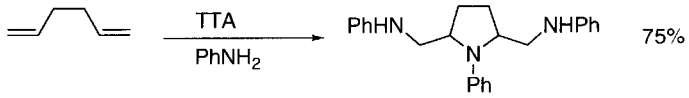
Scheme 9.9



Scheme 9.10

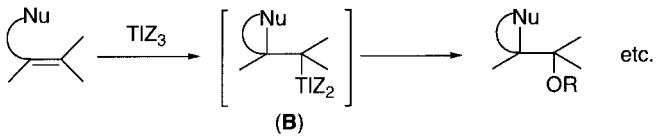


Scheme 9.11

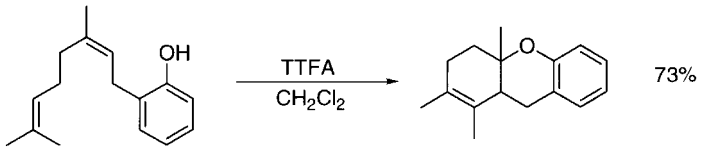


Scheme 9.12

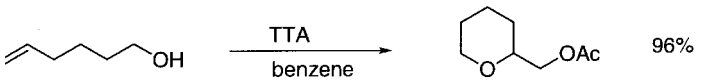
When the reaction is applied to alkenes bearing a nucleophile in a suitable position, oxythallation occurs intramolecularly to furnish cyclic products via the corresponding oxythallated adducts (**B**) (Scheme 9.13). Several useful examples are chosen from many reported reactions (Schemes 9.14 [18], 9.15 [19], 9.16 [20] and 9.17 [21]).



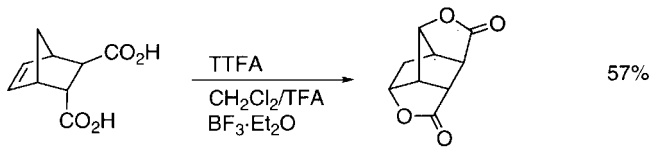
Scheme 9.13



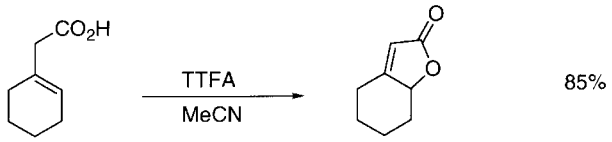
Scheme 9.14



Scheme 9.15

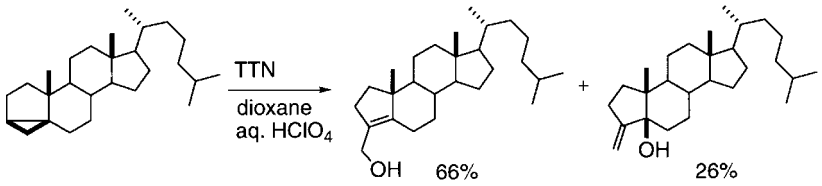


Scheme 9.16

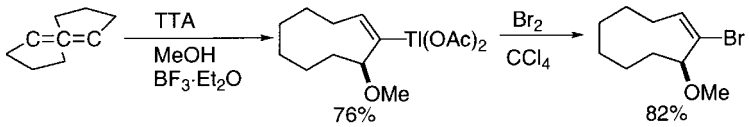


Scheme 9.17

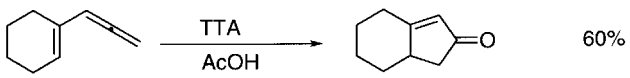
Although the examples are less compared than for alkenes, cyclopropanes and allenes are also oxidized by Tl(III) salts via oxythallation (Schemes 9.18 [22], 9.19 [23], and 9.20 [24]). Alkynes react with TTN to give a variety of oxidation products such as diketones and carboxylic acids via oxythallation, the products depending on the substitution pattern on the alkynes (Schemes 9.21–9.23 [25]).



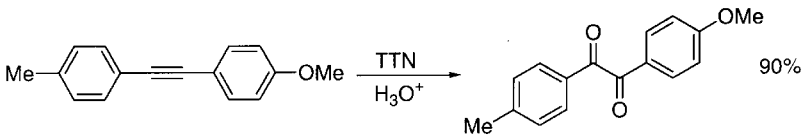
Scheme 9.18



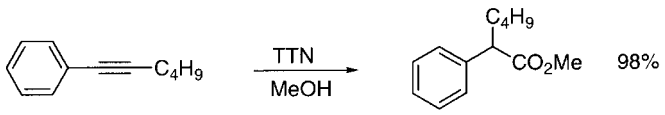
Scheme 9.19



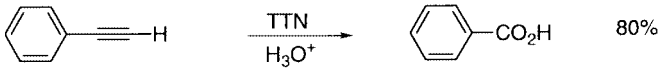
Scheme 9.20



Scheme 9.21



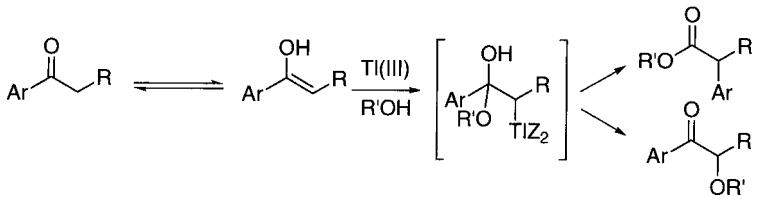
Scheme 9.22



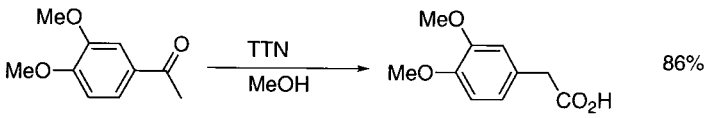
Scheme 9.23

9.1.2 Ketone Oxidations

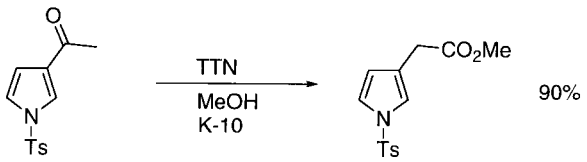
Oxidation of easily enolizable ketones such as alkyl aryl ketones affords either *α*-oxylated ketones or carboxylic acid derivatives via oxythallation of the enol forms, the products depending on the kind of Tl(III) salts and/or solvents employed (Scheme 9.24). Use of TTN usually induces aryl group migration leading to the formation of carboxylic acids or their esters [26], making this oxidative transformation useful for organic synthesis (Schemes 9.25 [27], 9.26 [28], 9.27 [29] and 9.28 [30]). Use of TTA, thallium tosylate [$Tl(OTs)_3$], thallium triflate [$Tl(OTf)_3$], and thallium mesylate [$Tl(OMs)_3$], on the other hand, produces *α*-oxylated ketones which sometimes further react to give useful compounds (Schemes 9.29 [31], 9.30 [32], 9.31 [33], 9.32 [34] and 9.33 [35]).



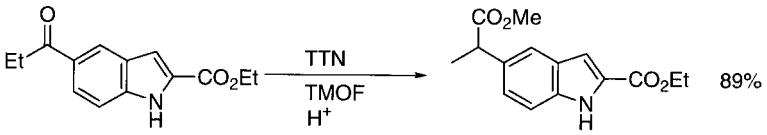
Scheme 9.24



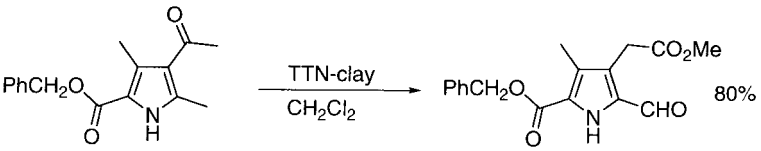
Scheme 9.25



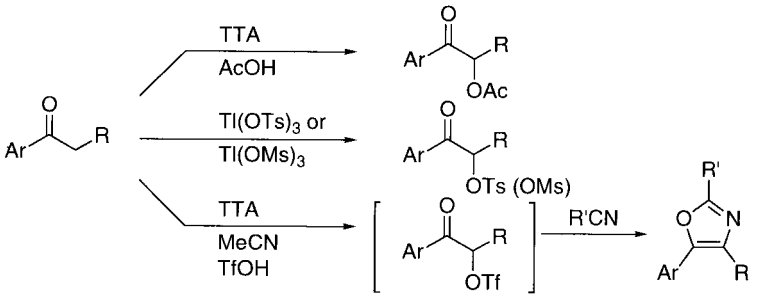
Scheme 9.26



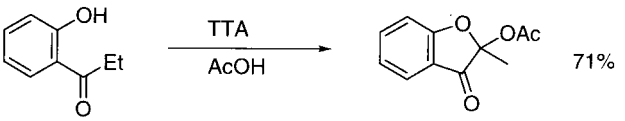
Scheme 9.27



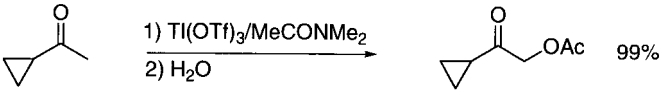
Scheme 9.28



Scheme 9.29–9.31

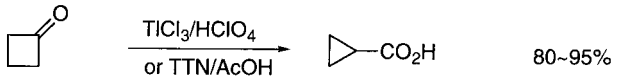


Scheme 9.32

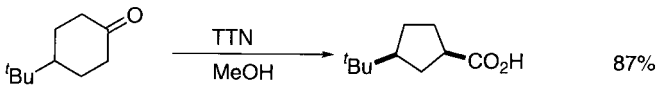


Scheme 9.33

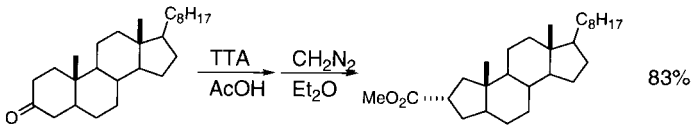
With cyclic ketones ring contraction usually occurs to give the corresponding carboxylic acids (Schemes 9.34 [36], 9.35 [37], and 9.36 [38]), but the treatment of flavanones affords either ring-contracted carboxylic acids or flavone derivatives, the products being very dependent on the type of Tl(III) salts employed, as exemplified in Schemes 9.37 [39], 9.38 [40], 9.39 [41] and 9.40 [42].



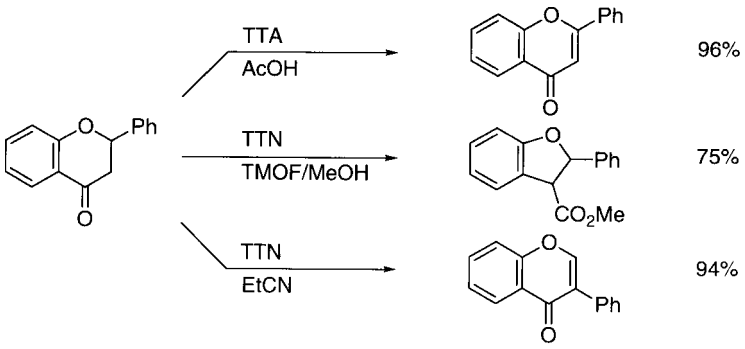
Scheme 9.34



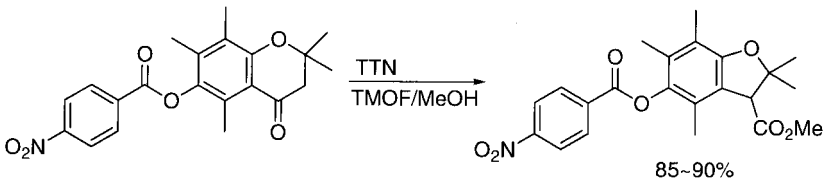
Scheme 9.35



Scheme 9.36

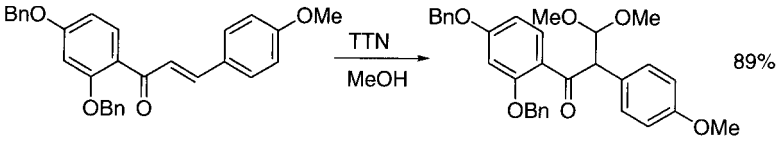


Scheme 9.37–9.39

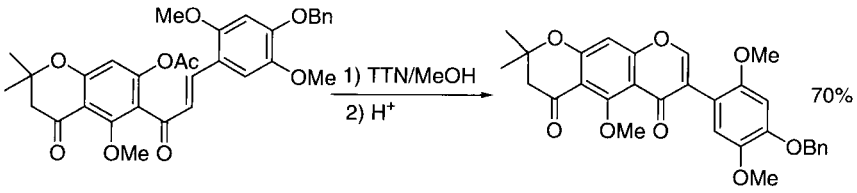


Scheme 9.40

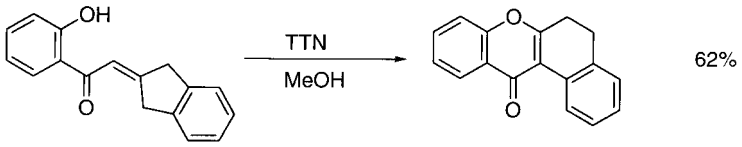
Oxidation of chalcones with Tl(III) salts gives the aryl group rearranged ketals via oxythallation to carbon–carbon double bonds (Scheme 9.41 [43]). When chalcones bear a hydroxyl or an acetoxy group at the *ortho* position, this reaction becomes synthetically useful because the ketals produced normally afford isoflavone derivatives by acid treatment, as exemplified in Schemes 9.42 [44], 9.43 [45], and 9.44 [46].



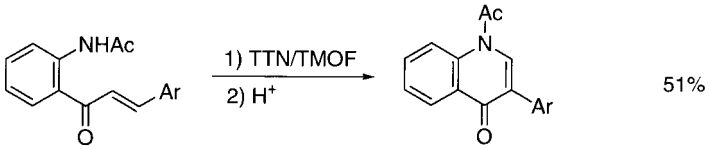
Scheme 9.41



Scheme 9.42



Scheme 9.43

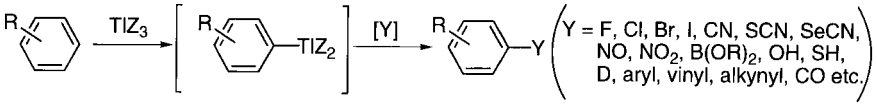


Scheme 9.44

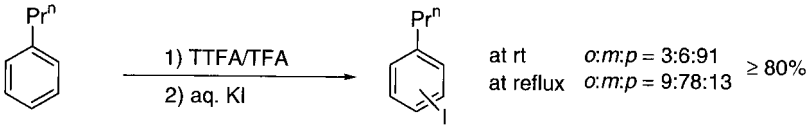
9.1.3
Aromatic Thallation

A highly regioselective aromatic thallation followed by *ipso*-substitution of the Tl(III) moiety by a variety of groups such as halogens, pseudohalogens, NO_x, $B(OR)_2$, OH, SH, D, aryl, vinyl, alkynyl, CO, etc., is a synthetically useful and important reaction for producing various aromatic derivatives, TTFA being the most commonly used salt (Scheme 9.45 [3a, 4, 5]). It is not necessary to isolate the arylthallium(III) compounds, which are subjected in situ to the subsequent reactions. The orientation of thallation is controlled by the reaction temperature and time, and oxygen-containing substituents such as alkoxy, hydroxy, and oxycarbonyl, which can chelate with the approaching Tl(III) species, as exemplified by aryl iodide formation by, especially, facile iodide replacement of thallium moiety

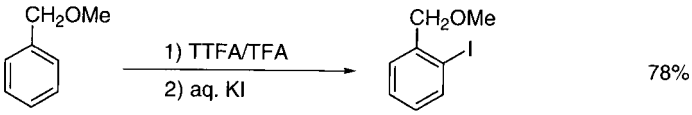
(Schemes 9.46 and 9.47 [47]). Pd(II) salt-catalyzed carbon–carbon bond-forming reactions using CO or alkenes makes this methodology quite useful in organic synthesis (Schemes 9.48 [48], 9.49 [49], 9.50 [50] and 9.51 [51]).



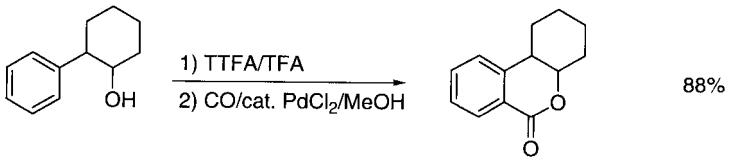
Scheme 9.45



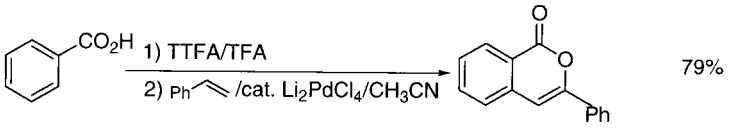
Scheme 9.46



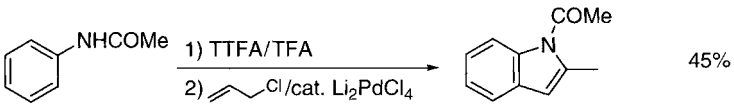
Scheme 9.47



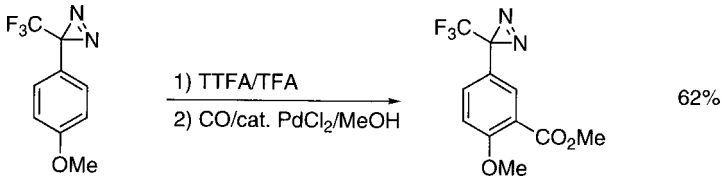
Scheme 9.48



Scheme 9.49



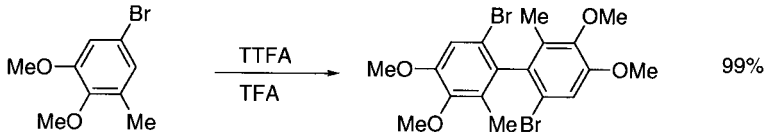
Scheme 9.50



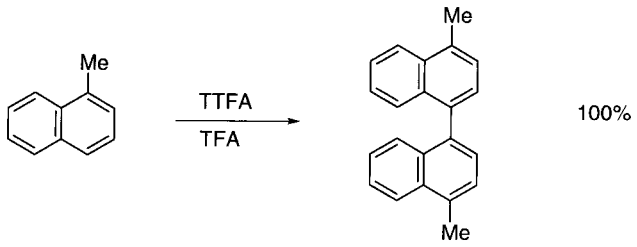
Scheme 9.51

9.1.4
Aryl Couplings via One-electron Transfer

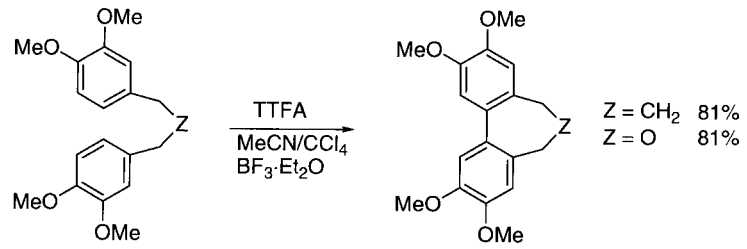
Reaction of electron-rich aromatic compounds with TTFA leads to intermolecular oxidative coupling to form the corresponding biaryls without aromatic thallation. The reaction proceeds through one-electron transfer from aromatic compounds to Tl(III) to give an aromatic radical cation which leads to biaryls (Schemes 9.52 and 9.53 [52]). Intramolecular aryl coupling also occurs (Schemes 9.54 [53] and 9.55 [54]) and, further, when the carboxylic acid moiety is present, intramolecular as well as intermolecular lactonization occurs (Schemes 9.56 [55] and 9.57 [56]).



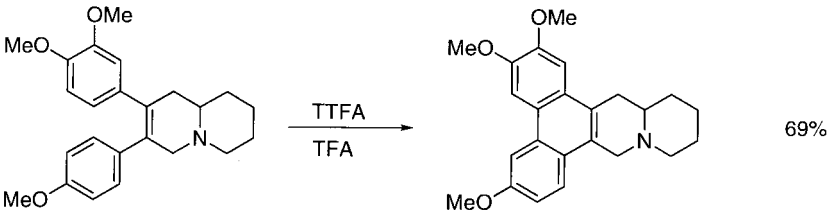
Scheme 9.52



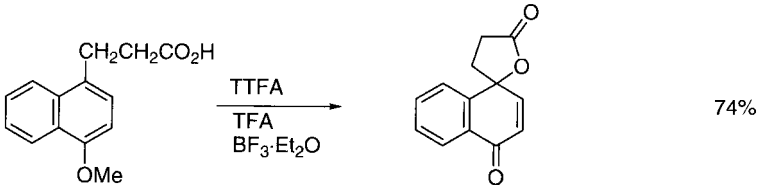
Scheme 9.53



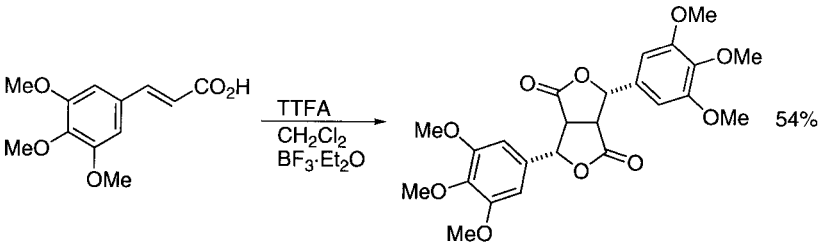
Scheme 9.54



Scheme 9.55



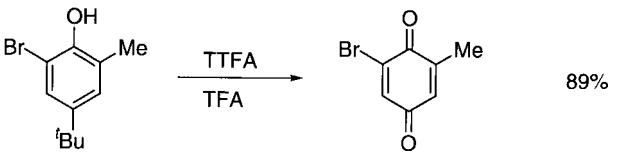
Scheme 9.56



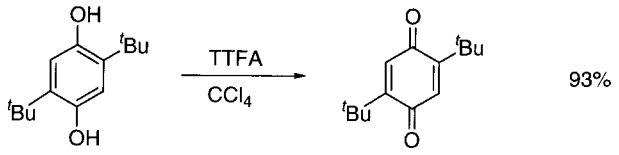
Scheme 9.57

9.1.5
Phenol Oxidations

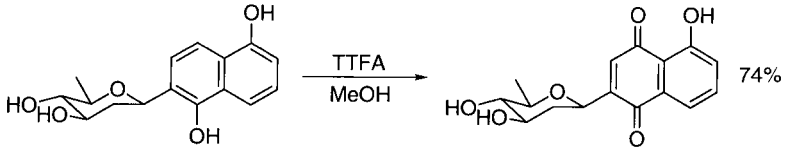
Phenols are oxidized to the corresponding quinones or their derivatives. If an aromatic nucleus is present at a suitable position as a nucleophile, intramolecular oxidative phenol coupling occurs. Typical examples are shown in Schemes 9.58 [57], 9.59 [57], 9.60 [58], 9.61 [59], 9.62 [60] and 9.63 [61].



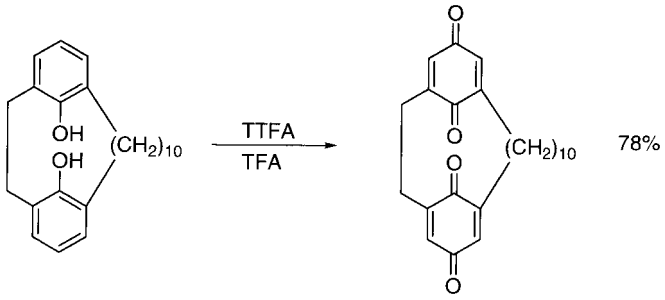
Scheme 9.58



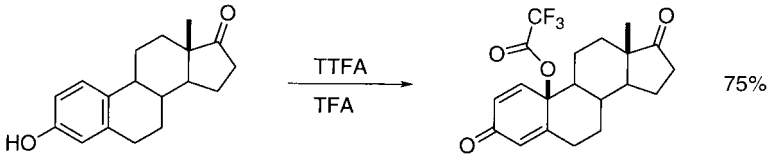
Scheme 9.59



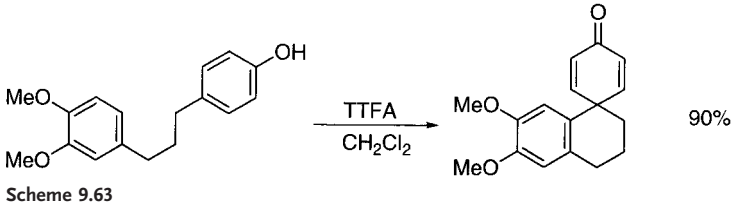
Scheme 9.60



Scheme 9.61



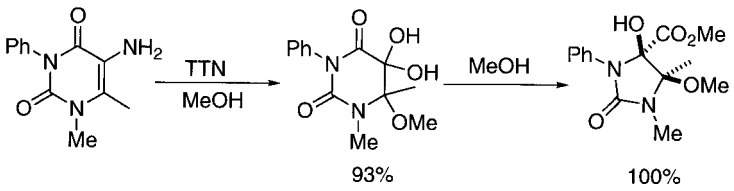
Scheme 9.62



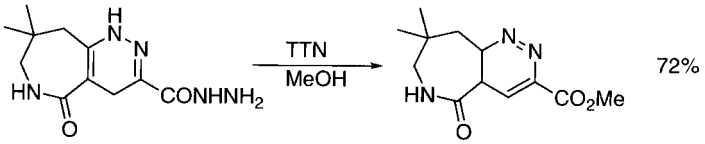
Scheme 9.63

9.1.6
Miscellaneous Reactions and Catalytic Reactions

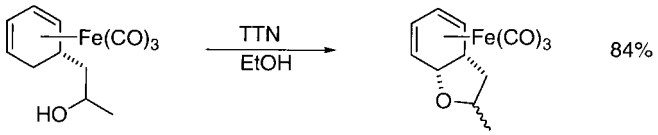
Several miscellaneous but interesting reactions chosen from many examples are shown in Schemes 9.64 [62], 9.65 [63], 9.66 [64], 9.67 [65], 9.68 [66], and 9.69 [67]. Triorganothallium compounds react cleanly with acid chlorides and alkyl chlorides to give the corresponding products (Scheme 9.70 [68]). Tetraorganothallium ate complexes react with enones to afford either 1,2 or 1,4 addition compounds depending on the structure of enones (Scheme 9.71 [69]). These reactions can be performed with thallium as catalyst, as shown in Schemes 9.72 and 9.73 [70]. Unfortunately, catalytic organic reactions using Tl(III) salts or organothallium(III) compounds are still quite limited, as exemplified in Schemes 9.74 [71], 9.75 [72], 9.76 [73], and 9.77 [74]. Aromatic bromination is promoted by the presence of a large amount of TTA, and the reaction is also catalyzed by TTA though the regioselectivity becomes lower. In the transesterification shown in Scheme 9.75 a variety of organic and inorganic Tl(III) and Tl(I) salts including TTA, TTFA, aryl thallium(III) compounds, and $TlNO_3$ work specifically as effective catalysts. A variety of thallium salts including $TlCl_3 \cdot 4H_2O$ [75] and low-surface-area zirconia supported Tl_2O_3 [76] work as catalysts for Friedel-Crafts-type aromatic benzylation and acylation.



Scheme 9.64



Scheme 9.65



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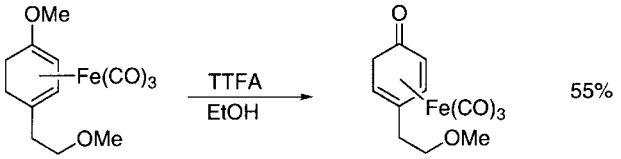
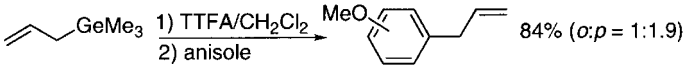
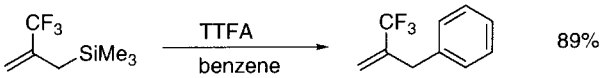


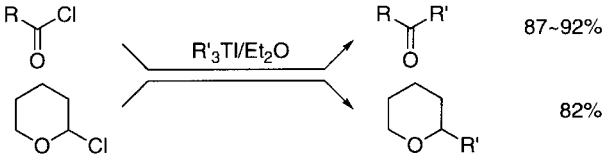
Scheme 9.67



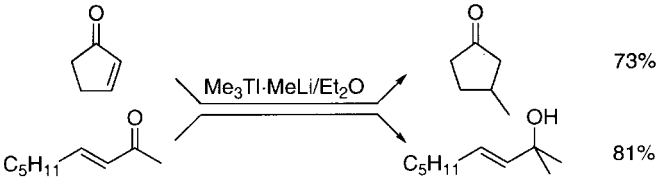
Scheme 9.68



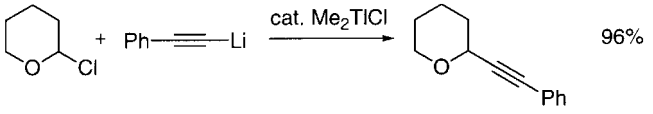
Scheme 9.69



Scheme 9.70

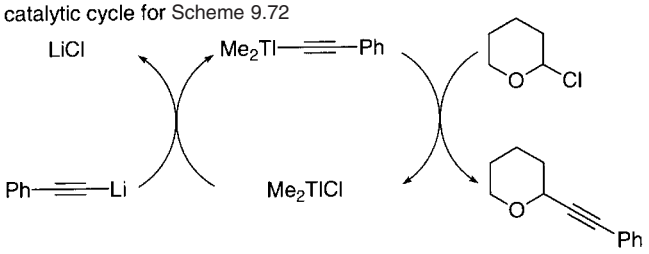


Scheme 9.71

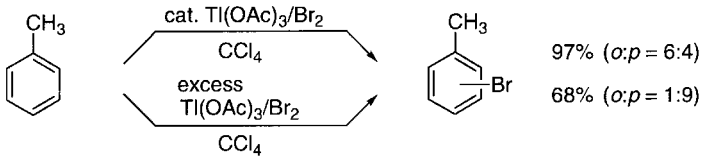


Scheme 9.72

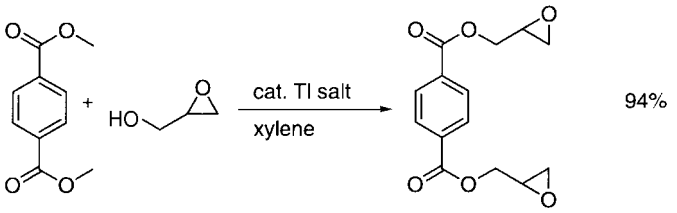
catalytic cycle for Scheme 9.72



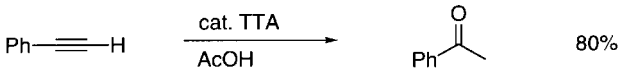
Scheme 9.73



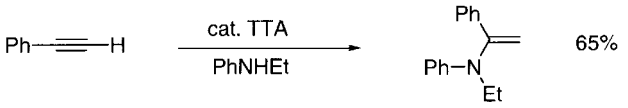
Scheme 9.74



Scheme 9.75



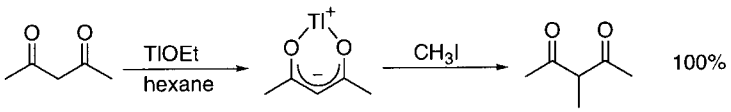
Scheme 9.76



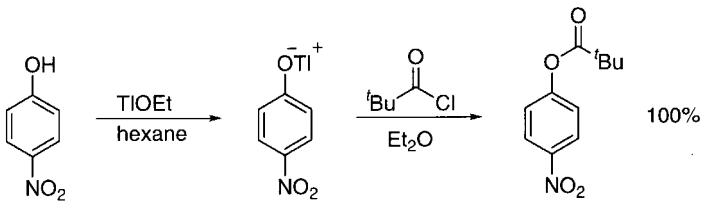
Scheme 9.77

9.2
Tl(I) Salts in Organic Synthesis

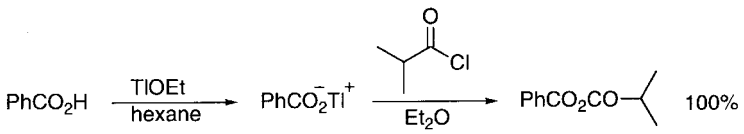
Compared with the versatile utility of Tl(III) salts in organic synthesis, the use of Tl(I) salts for this purpose is still limited. The most useful reagents are thallium(I) ethoxide and thallium(I) hydroxide. The former reacts with β-diketones, phenols, carboxylic acids, and pyridones, etc., to give the corresponding Tl(I) salts which can subsequently be used for a variety of organic transformations, as shown in Schemes 9.78 [77], 9.79 [78], 9.80 [78], 9.81 [79] and 9.82 [80].



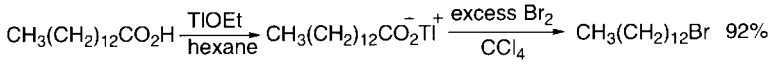
Scheme 9.78



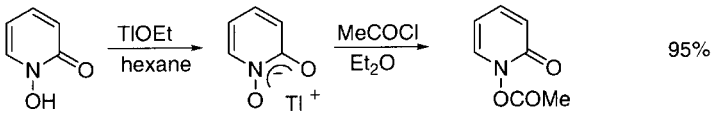
Scheme 9.79



Scheme 9.80



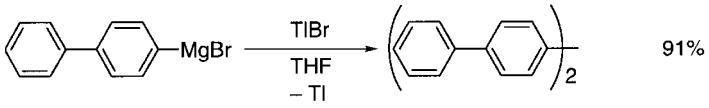
Scheme 9.81



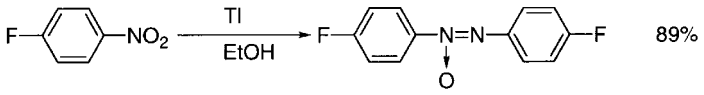
Scheme 9.82

Tl(I) also works as an oxidant in the pinacol cleavage and in the coupling of Grignard reagents (Schemes 9.83 [81] and 9.84 [82]); Tl(0) can be used for the reduction of nitroaromatic compounds (Scheme 9.85 [83]).

Scheme 9.83

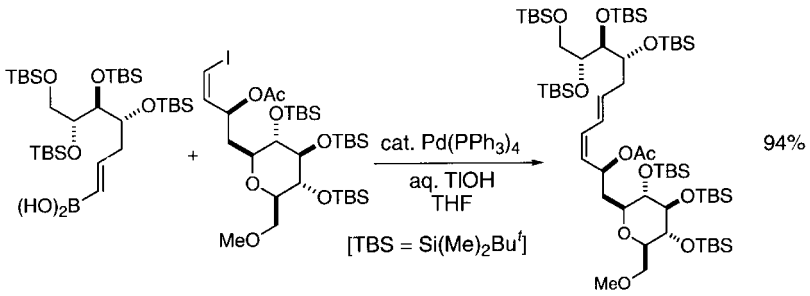


Scheme 9.84

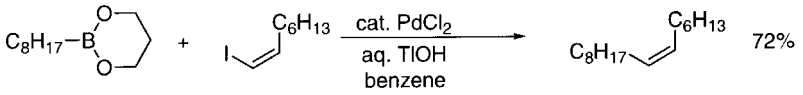


Scheme 9.85

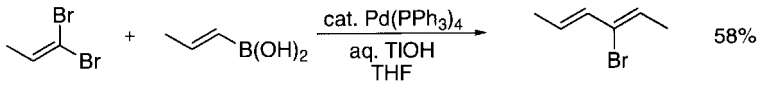
Either thallium(I) hydroxide or thallium(I) ethoxide as a base substantially promotes the coupling of aryl and vinyl halides with organic boronic acids (Suzuki coupling) (Schemes 9.86 [84], 9.87 [85], 9.88 [86], 9.89 [87], 9.90 [88], 9.91 [89], and 9.92 [90]). Both reagents are air- and moisture-sensitive, TlOEt being significantly more stable than TlOH, and should be handled under an inert atmosphere. Unfortunately, these reactions are not catalytic in thallium and excess thallium salt (2–3 equiv.) relative to the halide is necessary.



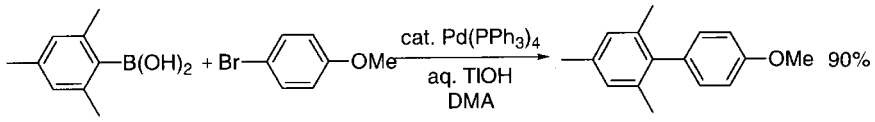
Scheme 9.86



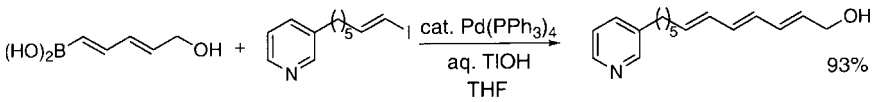
Scheme 9.87



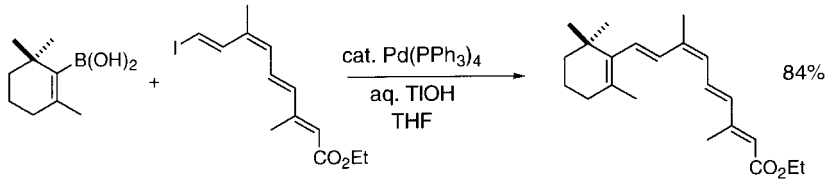
Scheme 9.88



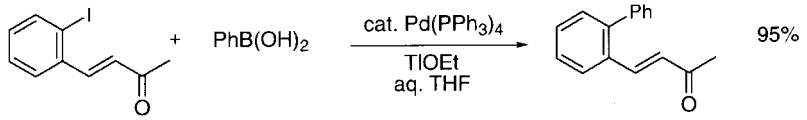
Scheme 9.89



Scheme 9.90



Scheme 9.91



Scheme 9.92

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10
Silicon in Organic Synthesis

Katsukiyo Miura and Akira Hosomi

10.1
Introduction

Organosilicon reagents are widely used for modern organic synthesis because of their unique and moderate reactivity, which enables highly efficient and selective organic reactions, their ready availability, and their relatively low toxicity [1–10]. In particular, their use for carbon–carbon bond formation has been extensively studied in the past three decades. As a result, several synthetically valuable named reactions using organosilicon reagents (e.g. the Mukaiyama aldol reaction with silyl enolates [11, 12], the Hosomi-Sakurai reaction with allylsilanes [13, 14], and the Hiyama coupling with alkenyl-, alkynyl-, and arylsilanes [15]) have been developed. These reagents act as stable synthetic equivalents of the corresponding carbanions and efficiently react with a variety of carbon electrophiles, with the aid of a catalyst such as a Lewis acid or a transition metal complex. The recent explosive growth of asymmetric synthesis using homochiral Lewis acids has further enhanced the synthetic utility of silicon-based nucleophiles [16, 17]. Several reviews and books on organosilicon chemistry with emphasis on organic synthesis have been published. This review deals mainly with the development, in the last decade, of selective carbon–carbon bond-forming processes using organosilicon reagents.

10.2
Silyl Enolates

In 1973, Mukaiyama and co-workers reported that in the presence of $TiCl_4$ ketone trimethylsilyl enolates react smoothly with aldehydes to give aldol products [18]. Since the discovery of the so-called Mukaiyama aldol reaction, the use of silyl enolates as enolate equivalents has received much attention from synthetic organic chemists. Nowadays, silyl enolates are well recognized as very valuable reagents for highly efficient and selective carbon–carbon bond-formation and functionalization introducing a carbonyl group.

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10.2.1 Aldol Reactions

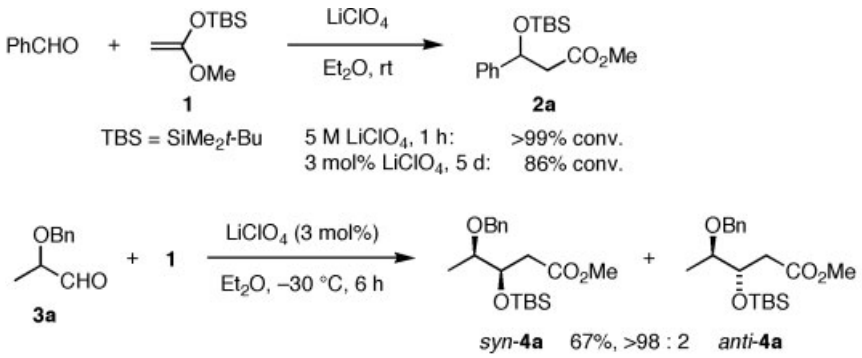
The original methods for directed aldol and aldol-type reactions of aldehydes and acetals with silyl enolates required a stoichiometric amount of a Lewis acid such as $TiCl_4$, $BF_3 \cdot OEt_2$, or $SnCl_4$ [18]. Later studies have introduced many Lewis acids which accelerate these processes with a catalytic quantity (vide infra). In addition, it has been found that fluoride ion sources also work as effective catalysts of the aldol reaction [19]. In the last decade, much attention has been paid for the development of diastereo- and enantioselective aldol reactions [20, 21], aqueous aldol reactions using water-stable Lewis acids [22], and novel types of silyl enolate with unique reactivity.

10.2.1.1 Achiral Lewis Acid-promoted Reactions in Anhydrous Solvent

In the nineteen-eighties many researchers developed a variety of Lewis acid catalysts of the Mukaiyama aldol reaction. In particular, $TrClO_4$ [23] and TMSOTf [24] effectively promote reaction of silyl enolates with aldehydes or acetals. These studies suggested that introduction of a soft Lewis base such as the ClO_4 or OTf anion into the Lewis acidic center should lead to effective catalysts. Based on this concept, further studies have been continued to develop novel Lewis acid catalysts with higher catalytic activity or higher chemo- and stereoselectivity.

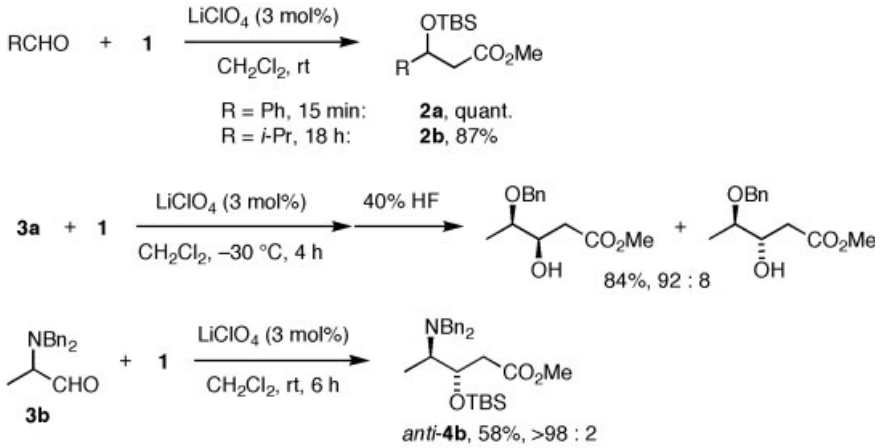
Lithium Lewis Acids

Reetz et al. have reported that the lithium ion can promote the aldol reaction of several aldehydes with ketene silyl acetals (KSA, ester silyl enolates) (Scheme 10.1) [25]. In a 5.0 M ethereal solution of $LiClO_4$, the reaction of benzaldehyde with KSA **1** is complete in 1 h to give silylated aldol **2a** quantitatively. The use of a catalytic amount (3 mol%) of $LiClO_4$ results in a marked decrease in the reaction rate. In contrast, the reaction of *α*-alkoxyaldehyde **3a** proceeds smoothly even with a catalytic amount of $LiClO_4$, affording *syn* adduct **4a** with high diastereoselectivity. The observed high reactivity and diastereoselectivity is attributable to chelation of **3a** to $LiClO_4$.



Scheme 10.1

$LiClO_4$ has higher catalytic activity in CH_2Cl_2, a non-coordinating solvent, although $LiClO_4$ does not dissolve in CH_2Cl_2 (Scheme 10.2) [26]. Addition of 3 mol% $LiClO_4$ to a solution of **1** and benzaldehyde in CH_2Cl_2 leads to complete conversion into **2a** within 15 min at room temperature. Under similar conditions, the reaction of isobutyraldehyde requires 18 h for complete conversion; the desired adduct, **2b**, is, however, obtained in a good yield. It is notable that the catalyst is readily recyclable. Similar to the reaction in Et_2O, the aldol reaction of **3a** in CH_2Cl_2 also proceeds with chelation control. On the other hand, the reaction of *α*-(dibenzylamino)aldehyde **3b** gives *anti* adduct **4b** as a single diastereomer, corresponding to non-chelation control.

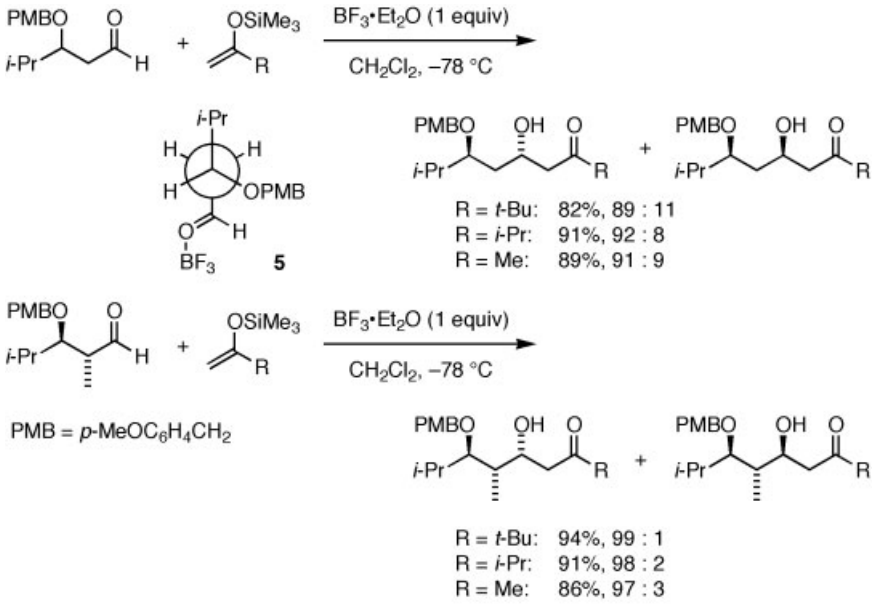


Scheme 10.2

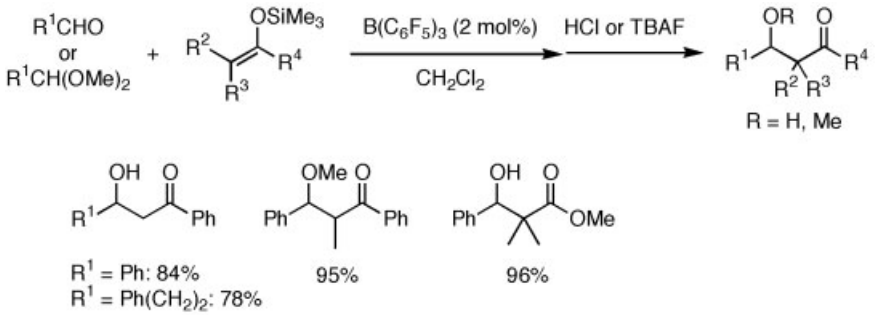
Boron Lewis Acids

The utility of $BF_3 \cdot OEt_2$, a monodentate Lewis acid, for acyclic stereocontrol in the Mukaiyama aldol reaction has been demonstrated by Evans et al. (Scheme 10.3) [27, 28]. The $BF_3 \cdot OEt_2$-mediated reaction of silyl enol ethers (SEE, ketone silyl enolates) with *α*-unsubstituted, *β*-alkoxy aldehydes affords good 1,3-*anti* induction in the absence of internal aldehyde chelation. The 1,3-asymmetric induction can be reasonably explained by consideration of energetically favorable conformation **5** minimizing internal electrostatic and steric repulsion between the aldehyde carbonyl moiety and the *β*-substituents. In the reaction with *anti*-substituted *α*-methyl-*β*-alkoxy aldehydes, the additional stereocontrol (Felkin control) imparted by the *α*-substituent achieves uniformly high levels of 1,3-*anti*-diastereofacial selectivity.

Unlike $BF_3 \cdot OEt_2$, a catalytic quantity of tris(pentafluorophenyl)borane ($B(C_6F_5)_3$) effectively accelerates the aldol reactions of aldehydes and acetals with KSA and SEE (Scheme 10.4) [29]. Diarylborinic acids such as bis(pentafluorophenyl)borinic acid and bis(3,4,5-trifluorophenyl)borinic acid are also effective catalysts of aldol reactions [30].



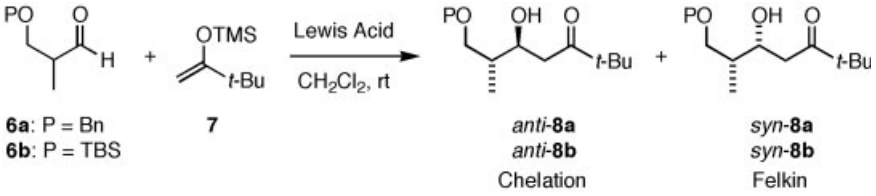
Scheme 10.3

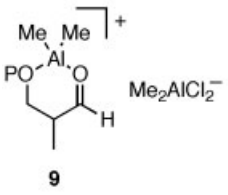


Scheme 10.4

Aluminum Lewis Acids

The catalytic ability of Me_2AlCl for the Mukaiyama aldol reaction was first reported by Yamamoto et al. [31]. Recently, Evans et al. have demonstrated that the use of more than two equivalents of Me_2AlCl or $MeAlCl_2$ enables high levels of chelation control in the carbonyl addition of SEE to *β*-alkoxy- and *β*-siloxyaldehydes (Scheme 10.5) [32]. In the reactions of *α*-chiral aldehydes **6a** and **6b** with SEE **7**, $BF_3 \cdot OEt_2$ promotes Felkin-controlled addition to afford *syn*-**8** selectively. The $TiCl_4$-promoted addition to **6a** exhibits the highest level of chelation control followed by Me_2AlCl. The unique chelating ability becomes apparent when aldol additions to the TBS-protected aldehyde **6b** are performed. Whereas $TiCl_4$ and $SnCl_4$ show good Felkin control, both of the aluminum halide-based Lewis acids



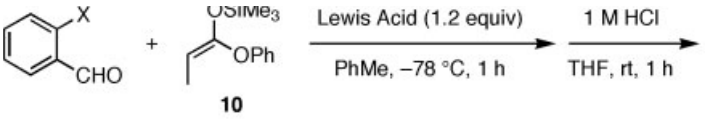


	P = Bn		P = TBS	
Lewis Acid	Yield (%)	*anti* : *syn*	Yield (%)	*anti* : *syn*
BF_3•OEt_2	76	26 : 74	55	9 : 91
$SnCl_4$	87	50 : 50	41	7 : 93
$TiCl_4$	74	97 : 3	55	7 : 93
Me_2AlCl	45	90 : 10	62	97 : 3
$MeAlCl_2$	70	78 : 22	55	77 : 23

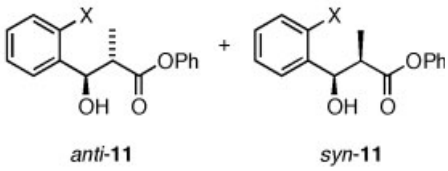
Scheme 10.5

retain the capacity for chelation even with the OTBS moiety. It has been proposed that Me_2AlCl chelates the substrates **6** through the cationic complex **9**.

Aluminum has exceedingly high affinity toward fluorine, as is evident from the bond strengths in several metal–fluorine diatomic molecules: Al–F, 663.6 ± 6.3; Li–F, 577 ± 21; Ti–F, 569 ± 34; Si–F, 552.7 ± 2.1; Sn–F, 466.5 ± 13; and Mg–F, 461.9 ± 5.0 kJ mol^{-1} [33]. This characteristic feature can be used for chelation-controlled aldol reaction of fluorinated aldehydes with KSA. Thus, in the presence of a stoichiometric amount of Me_3Al, 2-fluorobenzaldehyde reacts smoothly with KSA **10** to give aldol **11** with high *anti* selectivity. Other Lewis acids and non-fluorinated aldehydes lead to less stereoselectivity (Scheme 10.6) [34].

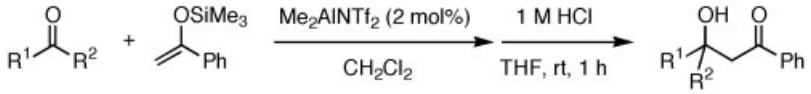


X	Lewis Acid	Yield (%)	*anti* : *syn*
F	BF_3•OEt_2	70	1 : 1.8
F	$TiCl_4$	74	2.9 : 1
F	TMSOTf	85	1 : 1.5
F	Me_3Al	96	16 : 1
OMe	Me_3Al	89	5.3 : 1
H	Me_3Al	88	5.3 : 1



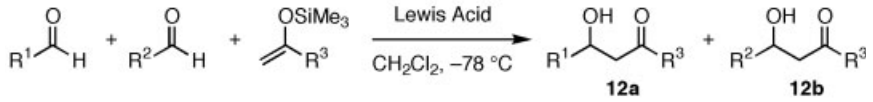
Scheme 10.6

Dimethylaluminum bis(trifluoromethanesulfonyl)amide (Me_2AlNTf_2), developed by Yamamoto et al., is a highly active Lewis acid catalyst of the Mukaiyama aldol reaction (Scheme 10.7) [35]. A catalytic amount of Me_2AlNTf_2 effectively induces addition to ketones as well as aldehydes.

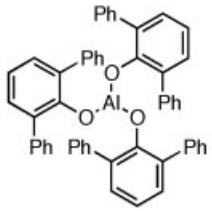


Scheme 10.7

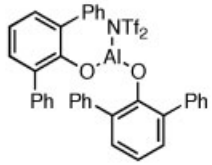
Aluminum tris(2,6-diphenylphenoxide) (ATPH), an aluminum-based Lewis acid with bulky substituents, is valuable as an extremely selective activator of less hindered aldehyde carbonyls (Scheme 10.8) [36]. In competitive aldol reactions of two different aldehydes, more than one equivalent of ATPH achieves highly chemoselective functionalization of less hindered aldehydes. Unfortunately, catalytic use of ATPH reduces the chemical yield and chemoselectivity. In contrast, a catalytic quantity of aluminum bis(trifluoromethanesulfonyl)amide **13** can promote the chemoselective aldol reaction.



Lewis Acid	R^1	R^2	R^3	Yield (%)	**12a** : **12b**
ATPH (1-2 equiv)	Bu	*c*-Hex	Me	75	>99 : 1
	Bu	*t*-BuCH$_2$	Me	63	91 : 1
	Bu	Ph	Me	61	15 : 1
13 (2 mol%)	*n*-C$_5$H$_{11}$	*t*-Bu	Ph	84	99 : 1
	c-Hex	*t*-Bu	Ph	84	99 : 1



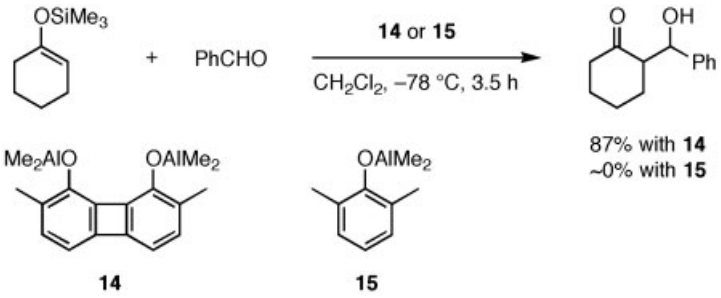
ATPH



13

Scheme 10.8

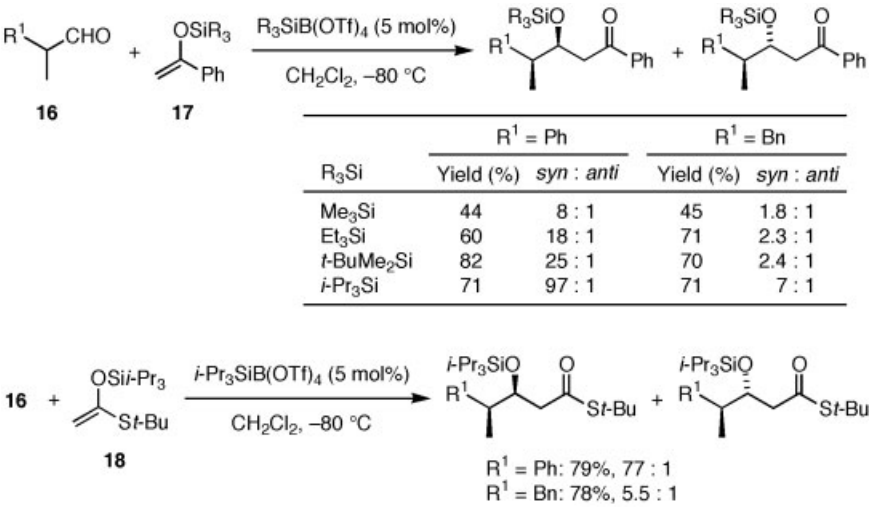
Maruoka et al. have developed the aluminum-based bidentate Lewis acid **14** for double electrophilic activation of carbonyl compounds (Scheme 10.9) [37]. The aldol addition of cyclohexanone TMS enolate to benzaldehyde is effected by the bidentate **14**, whereas its monodentate counterpart **15** shows no evidence of reaction under similar conditions. In competitive reactions of aldehydes and acetals, **14** effects aldehyde-selective addition [38].



Scheme 10.9

Silicon Lewis Acids

Several silicon-based Lewis acids have been developed and used for the Mukaiyama aldol reaction since the utility of TMSOTf as a Lewis acid catalyst was described by Noyori and his colleagues [24]. Davis et al. found that $R_3SiB(OTf)_4$, supersilylating agents prepared from R_3SiOTf and $B(OTf)_3$, are valuable for high levels of 1,2-asymmetric induction (Scheme 10.10) [39, 40]. In the reaction of α-chiral aldehydes **16** with SEE **17**, introduction of a sterically demanding silyl group into both the catalyst and **17** achieves high *syn* selectivity by Felkin control. Ketene silyl thioacetal **18** can also be used for the highly stereoselective aldol reaction. $R_3SiB(OTf)_3Cl$, prepared from R_3SiCl and $B(OTf)_3$, have a similar catalytic activity [41].

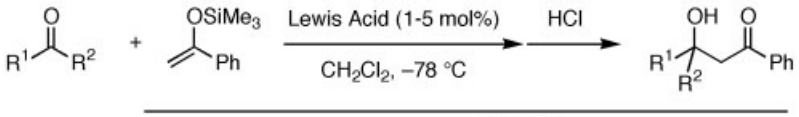


	R^1 = Ph		R^1 = Bn	
R_3Si	Yield (%)	*syn* : *anti*	Yield (%)	*syn* : *anti*
Me_3Si	44	8 : 1	45	1.8 : 1
Et_3Si	60	18 : 1	71	2.3 : 1
t-$BuMe_2Si$	82	25 : 1	70	2.4 : 1
i-Pr_3Si	71	97 : 1	71	7 : 1

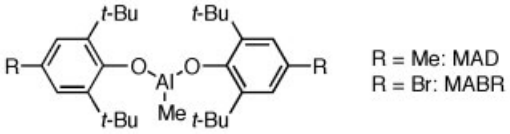
Scheme 10.10

Yamamoto et al. have reported that the exceptionally bulky Lewis acids MAD and MABR effectively enhance the catalytic activity of TMSOTf (Scheme 10.11) [42]. Although TMSOTf is a poor catalytic activator of ketones, an equimolar mixture

of TMSOTf and MAD or MABR effectively catalyzes the addition of SEE to ketones. The same method is applicable to the activation of TMSOMs and $TMSOSO_2F$.



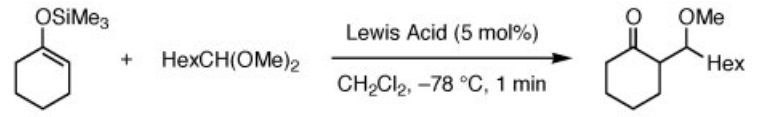
	Yield (%)		
R^1, R^2	Me_3SiOTf	Me_3SiOTf-MAD	Me_3SiOTf-MABR
$Ph(CH_2)_2$, H	20	61	83
t-Bu, H	2	-	74
$-(CH_2)_5-$	30	86	90
Ph, Me	3	60	72
i-Pr, Me	1	77	91



Scheme 10.11

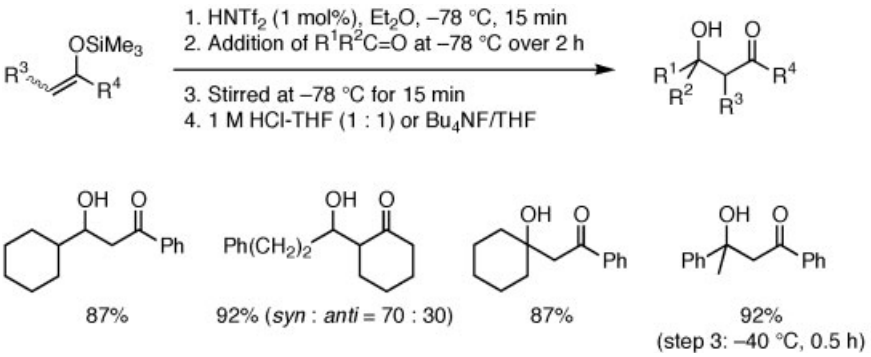
In ^{29}Si NMR of $TMSN(SO_2F)_2$, the silicon signal appears downfield compared with that of TMSOTf (Scheme 10.12). As expected from this, $TMSN(SO_2F)_2$ is a more active catalyst than TMSOTf for the aldol-type reaction of acetals [43]. $TMSNTf_2$ is thermally more stable than $TMSN(SO_2F)_2$, and the ^{29}Si chemical shift of $TMSNTf_2$ suggests that it should be a stronger Lewis acid than TMSOTf and $TMSN(SO_2F)_2$ [44]. Yamamoto et al. have recently demonstrated the efficiency of $TMSNTf_2$ as a strong Lewis acid catalyst of the Mukaiyama aldol reaction (Scheme 10.13) [45]. The key to the successful reaction is slow addition of carbonyl compounds to a solution of $TMSNTf_2$ and SEE and the use of Et_2O as solvent. $TMSNTf_2$ is generated in situ by reaction of SEE with commercially available triflylimide ($HNTf_2$). It is noteworthy that the $TMSNTf_2$-catalyzed reaction with ketones gives the desired aldols in high yields.

	Me_3SiOTf	$Me_3SiN(SO_2F)_2$	$Me_3SiN(SO_2CF_3)_2$
^{29}Si Chemical Shift (ppm):	43.5	44.9	55.9



73% with $Me_3SiN(SO_2F)_2$
27% with Me_3SiOTf

Scheme 10.12

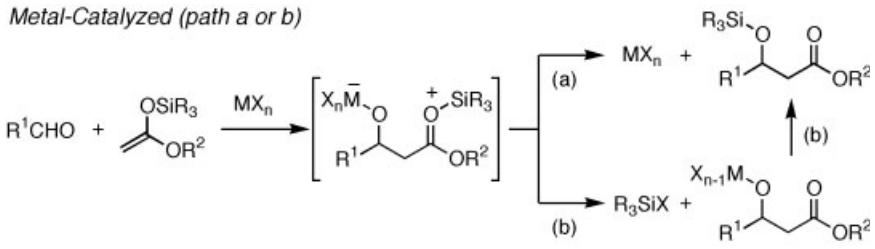


Scheme 10.13

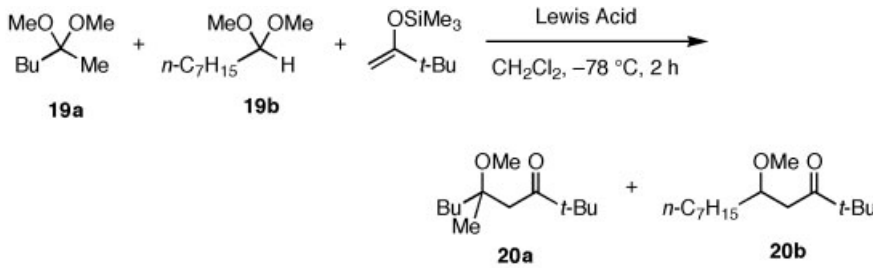
Mukaiyama aldol reactions using a catalytic amount of a Lewis acidic metal salt afford silylated aldols (silyl ethers) as major products, but not free aldols (alcohols). Three mechanistic pathways which account for the formation of the silylated aldols are illustrated in Scheme 10.14. In a metal-catalyzed process the Lewis acidic metal catalyst is regenerated on silylation of the metal aldolate by intramolecular or intermolecular silicon transfer (paths a and b, respectively). If aldolate silylation is slow, a silicon-catalyzed process (path c) might effectively compete with the metal-catalyzed process. Carreira and Bosnich have concluded that some metal triflates serve as precursors of silyl triflates, which promote the aldol reaction as the actual catalysts, as shown in path c [46, 47]. Three similar pathways are possible in the triarylcarbenium ion-catalyzed reaction. According to Denmark et al. triarylcarbenium ions are the actual catalysts (path b) [48], whereas Bosnich has insisted that hydrolysis of the salts by a trace amount of water generates the silicon-based Lewis acids working as the actual catalysts (path c) [47]. Otera et al. have reported that 10-methylacridinium perchlorate is an efficient catalyst of the aldol reaction of ketene triethylsilyl acetals [49]. In this reaction, the perchlorate reacts smoothly with the acetals to produce the actual catalyst, triethylsilyl perchlorate.

Tin Lewis Acids

The use of Sn(II) and Sn(IV) salts as Lewis acid catalysts of silicon-directed aldol reactions was reported by Mukaiyama et al. before 1990 [50]. Otera and Nozaki et al. subsequently disclosed that organotin(IV) compounds such as $Bu_2Sn(OTf)_2$ [51] and $Bu_3Sn(ClO_4)$ [52] have enough Lewis acidity as the catalyst. $Bu_2Sn(OTf)_2$ works as a highly chemoselective activator of ketone acetals in the coexistence of aldehyde acetals (Scheme 10.15) [51]. Thus, the $Bu_2Sn(OTf)_2$-catalyzed reaction of a mixture of acetals **19a** and **19b** with pinacolone TMS enolate (**19a**:**19b**:enolate = 1:1:1) gave only adduct **20a**. No such distinct discrimination is observed with other Lewis acids.



Scheme 10.14

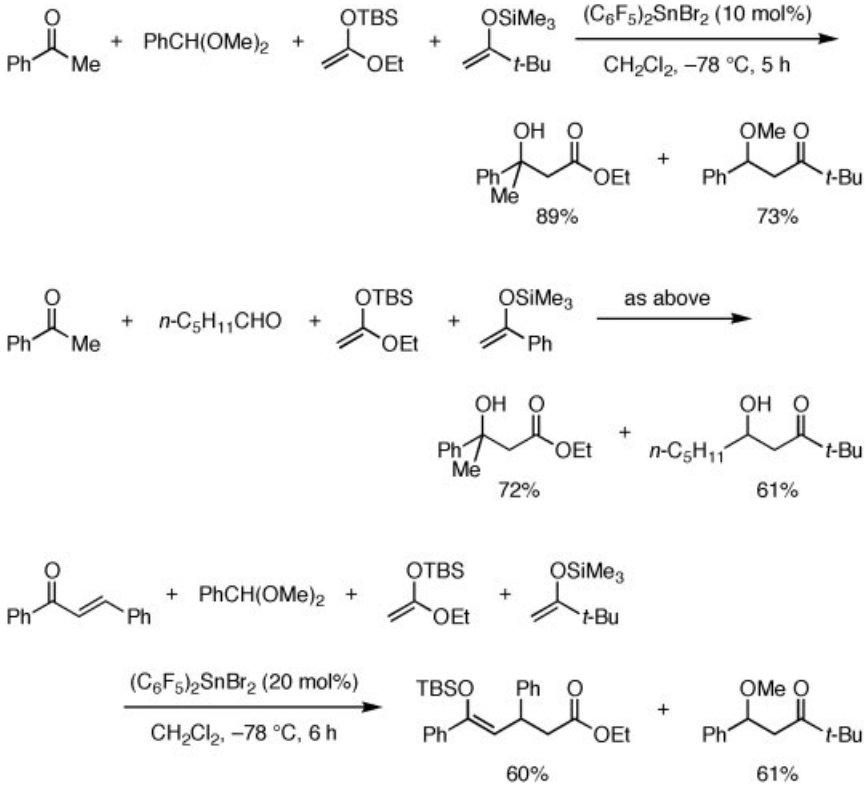


Lewis Acid (equiv), Yield / % (**20a** : **20b**):
$Bu_2Sn(OTf)_2$ (0.05), 80 (100 : 0); $TiCl_4$ (1), 36 (78 : 22); $SnCl_4$ (1), 100 (72 : 28); $AlCl_3$ (1), 51 (58 : 42); Me_3SiOTf (0.1), 59 (85 : 15); $TrClO_4$ (0.1), 55 (89 : 11)

Scheme 10.15

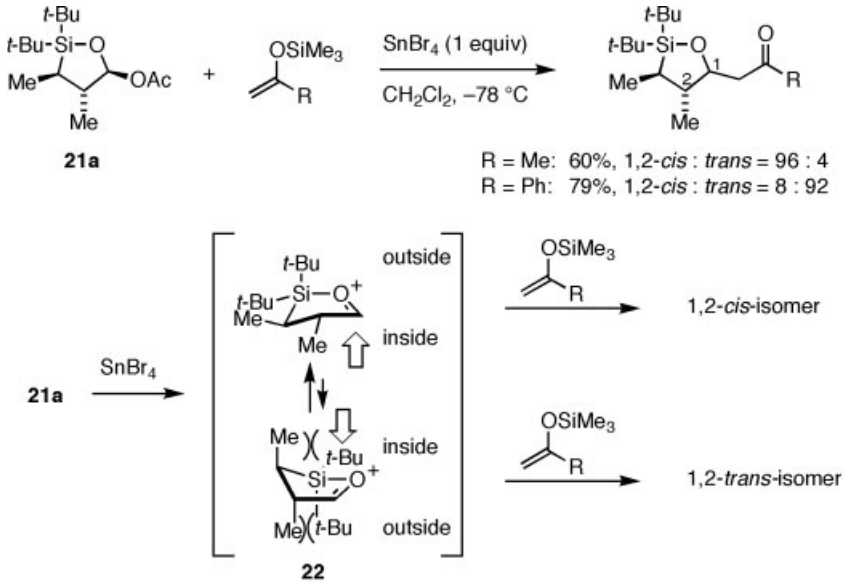
$Bu_2Sn(OTf)_2$, $Bu_3Sn(ClO_4)$, and $Bu_2Sn(ClO_4)_2$ promote chemoselective addition of KSA to aldehydes over the corresponding acetals [52]. The organotin perchlorate-promoted reaction of SEE to aldehydes is quite slow compared with that of KSA. On the other hand, in the $(C_6F_5)_2SnBr_2$-catalyzed system, ketones and α-enones were much more reactive to KSA than aliphatic aldehydes, and SEE react smoothly with aldehydes and acetals [53]. Otera et al. have utilized the unique behavior of $(C_6F_5)_2SnBr_2$ for parallel recognition, a new concept for compacting synthetic processes in which different transformations are performed simultaneously on separate reaction sites (Scheme 10.16) [54]. For instance, ketones/α-enones and aldehydes/acetals can react with KSA and SEE, respectively, in parallel with high chemoselectivity.

Woerpel et al. have recently reported the $SnBr_4$-promoted diastereoselective aldol-type reaction of oxasilacyclopentane acetals such as **21a** with SEE (Scheme



Scheme 10.16

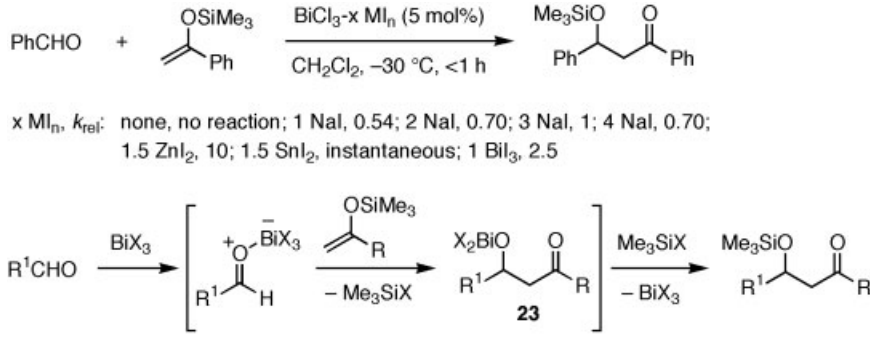
10.17) [55]. The sense of diastereoselectivity strongly depends on the size of the SEE; reaction with acetone silyl enolate gives the 1,2-*cis* product predominantly whereas the use of acetophenone silyl enolate results in high *trans* selectivity. The diastereoselectivity can be understood by application of the inside attack model for five-membered ring oxocarbenium ion **22**. This stereoelectronic model requires attack of the nucleophile from the face of the cation that provides the products in their lower energy staggered conformations. Acetone silyl enolate adds to the inside of the lower energy ground-state conformer of **22** (the upper conformer in Scheme 10.17). In contrast, acetophenone silyl enolate, a sterically demanding SEE, adds to the inside of the lower conformer to avoid steric repulsion by the C-2 substituent of **22**, regardless of the ground-state conformer population.



Scheme 10.17

Bismuth Lewis Acids

The use of $BiCl_3$ as a Lewis acid catalyst of the Mukaiyama aldol reaction was introduced by Wada et al. [56]. The catalytic activity of $BiCl_3$ is not so high; however, Dubac et al. found that addition of metal iodides such as NaI, ZnI_2, and SnI_2 is very effective in the $BiCl_3$-catalyzed reaction (Scheme 10.18) [57]. Treatment of $BiCl_3$ with these iodides forms BiI_3, but BiI_3 alone and the BiI_3–metal chloride system do not have high activity. In contrast, a mixture of BiI_3 and $BiCl_3$ is very effective. BiI_3 generated in situ from $BiCl_3$ would promote silylation of the intermediary bismuth aldolates **23** with TMSX to facilitate the catalytic cycle.



Scheme 10.18

Transition Metal Lewis Acids

Transition metal compounds also have been used as Lewis acid catalysts of the Mukaiyama aldol reaction. In particular, as shown in later sections, transition metal-catalyzed systems have been extensively studied for aqueous and asymmetric aldol reactions. Recent reports on the use of achiral transition metal Lewis acids in anhydrous solvent are described herein.

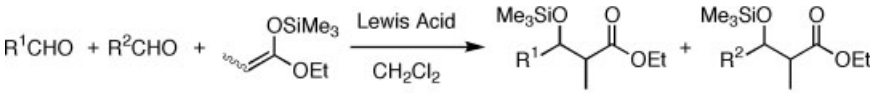
Cationic complexes such as [CpFe(DPPE)(acetone)](PF_6) [58], [Ru(salen)(NO)(H_2O)](SbF_6) [59], [Cp_2Zr(O*t*-Bu) · THF](BPh_4) [60], [W($HC(py)_3$)($NO)_2$(CO)]($SbF_6)_2$ [61], and an oxovanadium(IV) complex [62] are effective catalysts. Matsuda et al. recently reported that a cationic Ir complex generated in situ from [Ir(COD)($PPh_3)_2$]OTf and H_2 catalyzes aldol and aldol-type reactions of aldehydes and acetals with silyl enolates in CH_2Cl_2 [63].

Bosnich et al. have found that 0.5 mol% $Cp_2Ti(OTf)_2$ or $Cp_2Zr(OTf)_2$ effects an efficient aldol reaction of aldehydes and ketones in CH_3NO_2 at 25 °C [64]. It has been proposed that $Cp_2Ti(OTf)_2$ acts only as a precursor of the actual catalyst TMSOTf. In contrast, the $Cp_2Zr(OTf)_2$-catalyzed reaction of sterically unhindered or aromatic aldehydes would proceed via a Zr-catalyzed rather than a Si-catalyzed mechanism (Scheme 10.14) [65].

Although the catalytic activity of some lanthanide compounds was reported in the 1980's [66], Mikami and Nakai have disclosed that Eu(dppm)$_3$ is quite valuable for chemoselective aldol reaction with KSA (Scheme 10.19) [67]. Eu(dppm)$_3$ differentiates between steric differences in aldehydes to a much higher extent than is observed with a stoichiometric use of $TiCl_4$, even at a lower temperature. In addition, Eu(dppm)$_3$ recognizes the delicate difference in electronic effects involved in benzaldehydes. Interestingly, *p*-nitrobenzaldehyde is less reactive than benzaldehyde in the Eu-catalyzed process. More significantly, Eu(dppm)$_3$ has a remarkable preference for *o*-methoxybenzaldehyde over benzaldehyde. These results suggest that the relative reactivity of aldehydes in the Eu-catalyzed process is determined almost solely by the strength of coordination of aldehydes to Eu(dppm)$_3$, not by the electrophilicity of the aldehydes themselves.

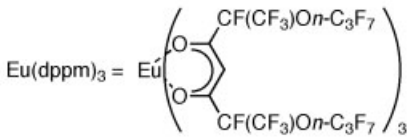
The Eu-catalyzed aldol reactions of chiral *α*-siloxy and *α*-alkoxy aldehydes with KSA show high levels of diastereocontrol, the sense depending on the nature of the *α*-substituent (Scheme 10.20) [68]. The stereoselectivity with the *α*-siloxy aldehyde can be explained by an antiperiplanar transition state merged with Felkin control, whereas reaction of the *α*-alkoxy aldehyde would proceed mainly via a synclinal transition state involving chelation of the substrate and coordination of the acetal alkoxy group of KSA.

Kobayashi et al. have reported that Sc(OTf)$_3$ works as an effective and reusable Lewis acid catalyst of the aldol and aldol-type reactions of aldehydes and acetals with silyl enolates in CH_2Cl_2 [69]. The activities of Sc(OTf)$_3$ and other rare earth triflates (Y(OTf)$_3$ and Yb(OTf)$_3$) were evaluated in the reaction of cyclohexanone TMS enolate with benzaldehyde (Scheme 10.21). The results clearly indicate that Sc(OTf)$_3$ is more active than Y(OTf)$_3$ and Yb(OTf)$_3$.

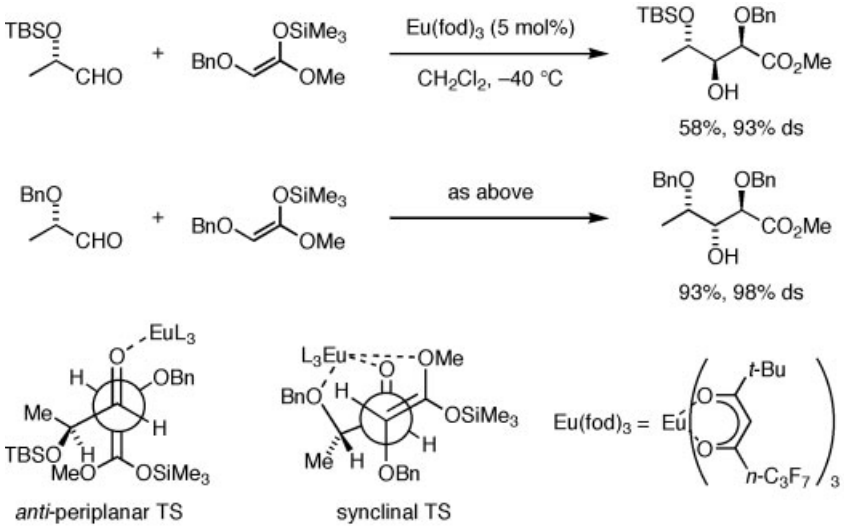


24a **24b**

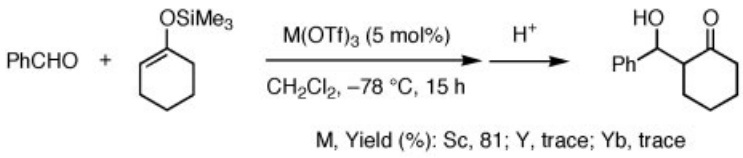
R^1	R^2	Lewis Acid (mol%)	Temp. / °C	Yield / %	**24a** : **24b**
Et	*t*-Bu	Eu(dppm)$_3$ (2.5)	0	61	99 : <1
		$TiCl_4$ (100)	−78	88	77 : 23
p-$O_2NC_6H_4$	Ph	Eu(dppm)$_3$ (2.5)	−70	66	1 : >99
o-$MeOC_6H_4$	Ph	Eu(dppm)$_3$ (2.5)	−78	78	95 : 5
		$TiCl_4$ (100)	−78	82	68 : 32



Scheme 10.19



Scheme 10.20



M, Yield (%): Sc, 81; Y, trace; Yb, trace

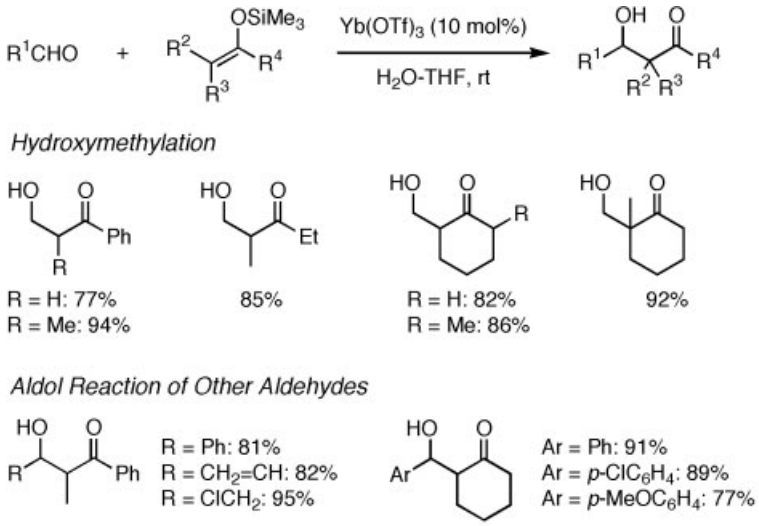
Scheme 10.21

10.2.1.2 Aqueous Aldol Reaction with Water-stable Lewis Acids

The importance of aqueous reactions is now generally recognized, and development of carbon–carbon bond-forming reactions that can be conducted in aqueous media is now one of the most challenging topics in organic synthesis [22]. As for the Mukaiyama aldol reaction, strictly anhydrous conditions are needed when conventional Lewis acids such as $TiCl_4$, $SnCl_4$, $BF_3 \cdot OEt_2$, etc. are used. In 1991 Kobayashi et al. reported that $Yb(OTf)_3$ works as a water-stable Lewis acid to catalyze hydroxymethylation of SEE with a commercial aqueous solution of formaldehyde [70a]. Since this pioneering effort Mukaiyama aldol reactions in aqueous solvent or pure water have been extensively studied to develop environmentally more benign synthetic methods. Thus, many metal salts have been found to be usable as water-stable Lewis acids.

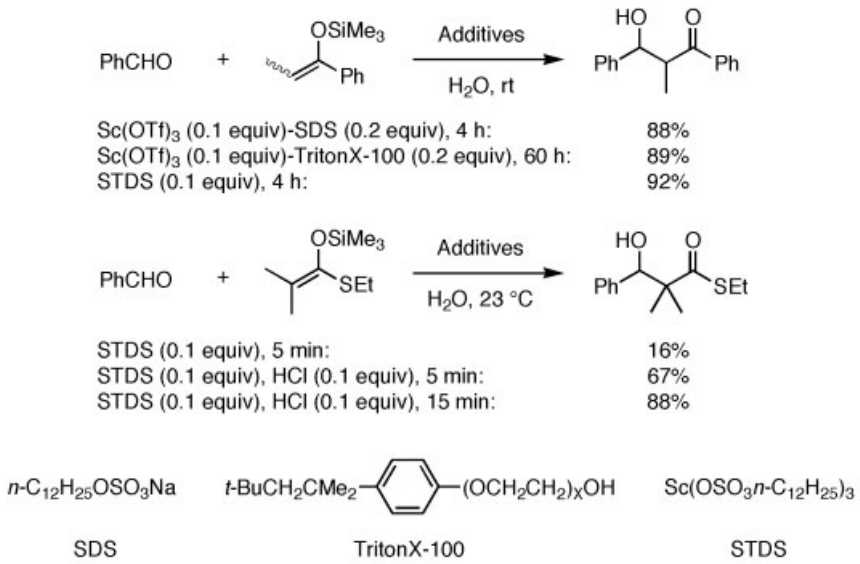
Rare Earth Metal Lewis Acids

Kobayashi et al. discovered that $Yb(OTf)_3$ and other lanthanide triflates ($Ln(OTf)_3$, Ln = La, Pr, Nd, Sm, Eu, Gd, Dy, Ho, and Er) are excellent catalysts of hydroxymethylation of propiophenone TMS enolate with aqueous formaldehyde solution at room temperature (Scheme 10.22) [70, 71]. The $Yb(OTf)_3$-catalyzed hydroxymethylation of a variety of SEE, including sterically hindered compounds, proceeds regiospecifically in high yield. In addition, almost 100% of $Yb(OTf)_3$ is quite easily recovered from the aqueous layer and can be reused. $Yb(OTf)_3$ also has high catalytic activity in the aqueous aldol reaction of other aldehydes. Interestingly, the catalytic activity is rather low in the absence of water. In aqueous media water would coordinate to ytterbium to form active ytterbium cations.



Scheme 10.22

$Sc(OTf)_3$ is an effective catalyst of the Mukaiyama aldol reaction in both aqueous and non-aqueous media (vide supra). Kobayashi et al. have reported that aqueous aldehydes as well as conventional aliphatic and aromatic aldehydes are directly and efficiently converted into aldols by the scandium catalyst [69]. In the presence of a surfactant, for example sodium dodecylsulfate (SDS) or Triton X-100, the $Sc(OTf)_3$-catalyzed aldol reactions of SEE, KSA, and ketene silyl thioacetals can be performed successfully in water without using any organic solvent (Scheme 10.23) [72]. They also designed and prepared a new type of Lewis acid catalyst, scandium trisdodecylsulfate (STDS), for use instead of both $Sc(OTf)_3$ and SDS [73]. The Lewis acid–surfactant combined catalyst (LASC) forms stable dispersion systems with organic substrates in water and accelerates the aldol reactions much more effectively in water than in organic solvents. Addition of a Brønsted acid such as HCl to the STDS-catalyzed system dramatically increases the reaction rate [74].



Scheme 10.23

Other Lewis Acids

Kobayashi et al. have demonstrated that some metal salts (e.g. Fe(II), Cu(II), Zn(II), Cd(II), and Pb(II) perchlorates) other than rare earth metal salts are also water-stable Lewis acids and work as catalysts of the aqueous aldol reaction of SEE [75]. Metal salts with good catalytic activity have pK_h values (K_h = hydrolysis constant) from 4.3 to 10.08 and WERC (water exchange rate constant) greater than 3.2×10^6 M^{-1} s^{-1}. If $pK_h < 4.3$, metal cations are readily hydrolyzed to give oxonium ions, which promote hydrolysis of SEE. Metal cations with $pK_h > 10.08$ do not have sufficient Lewis acidity to promote the aldol reaction. When the WERC

values are less than 3.2×10^6 M^{-1} s^{-1} aldehydes hardly coordinate to metal cations, because of slow water exchange.

$Cu(OTf)_2$ is a stable Lewis acid in aqueous media and can be used for activation of aldehydes [76]. The $Cu(OTf)_2$-catalyzed reaction of aromatic aldehydes with acetophenone TMS enolate gives the corresponding adducts in good to high yields. The same reaction of aliphatic aldehydes results in moderate yields.

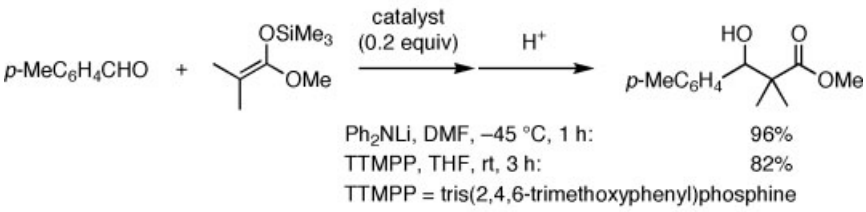
Loh et al. reported that $InCl_3$ worked as an effective catalyst of aldol reactions of SEE in water [77]. Later, Kobayashi et al. reported different results [78] – hydrolysis of SEE is faster than the desired reaction in the $InCl_3$-catalyzed aqueous system; the $InCl_3$-catalyzed reaction proceeds to some extent under solvent-free conditions; $InCl_3$ is an effective catalyst in micellar systems.

10.2.1.3 Aldol Reactions via Activation of Silyl Enolates

Fluoride ion-catalyzed aldol reactions of silyl enolates are valuable for stereoselective carbon–carbon bond formation [19]. In this system fluoride ion works as an activator of silyl enolates to produce reactive metal-free enolates, which add to aldehydes as the actual nucleophiles. Similar aldol reactions via activation of silyl enolates by nucleophilic reagents and solvents have been reported in recent years. In addition, activation of silyl enolates by transmetalation has attracted much attention because of its possible application to diastereo- and enantioselective transformation.

Activation by Nucleophilic Reagents and Solvents

KSA react with aldehydes smoothly in the presence of a catalytic amount of a phosphine [79] or a lithium amide (Scheme 10.24) [80]. In addition, uncatalyzed aldol reactions of KSA proceed efficiently in polar aprotic solvents such as DMSO, DMF, DME [81], and MeCN [82]. Lubineau et al. reported an uncatalyzed aldol reaction of SEE in H_2O in 1986 [83]. Recently, Loh et al. have found a similar reaction of KSA although KSA are much more sensitive to hydrolysis than SEE [84].



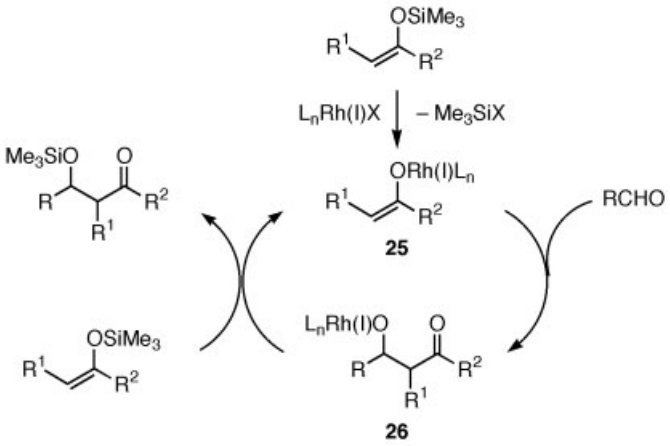
Scheme 10.24

Activation by Transmetalation

TMS enolates are well known to react with some metal compounds to afford the corresponding metal enolates or *α*-metallo ketones [85]. For instance, the reaction of TMS enolates with MeLi provides a convenient method for preparation of salt-

free lithium enolates [86]. Catalytic aldol reactions via transmetalation of silyl enolates are, however, currently rather limited.

Bergman and Heathcock have demonstrated that the Rh(I)-catalyzed aldol reaction, originally reported by Matsuda et al. [87], proceeds via Rh(I) enolates **25** and aldolates **26** (Scheme 10.25) [88]. This type of transition metal-catalyzed aldol reaction has been used for asymmetric synthesis using readily accessible chiral phosphines (vide infra).

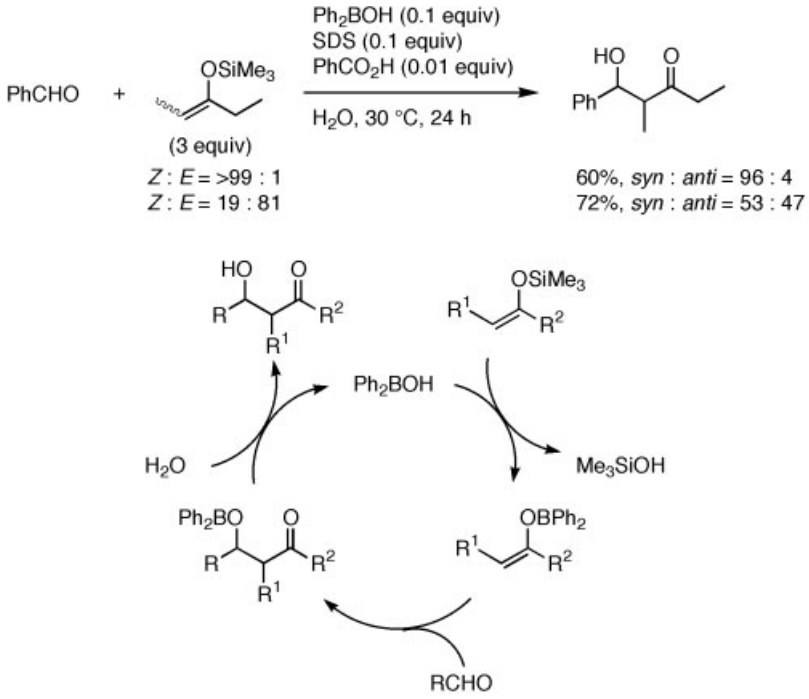


Scheme 10.25

Kobayashi et al. recently found that a combination of diphenylborinic acid (Ph_2BOH) and benzoic acid effectively catalyzes the aldol reaction of SEE in a micellar system using SDS as a surfactant (Scheme 10.26) [89]. Stereoselectivity depends on the geometry of SEE, and the use of *Z*-isomers effects high *syn* selectivity. These stereochemical outcomes are consistent with those observed in the traditional boron enolate-mediated aldol reactions. The rate of disappearance of a SEE is independent of the reactivity of aldehydes and dependent only on the amount of SEE. On the basis of these facts they proposed a mechanism involving a boron enolate intermediate. Benzoic acid may accelerate the Si–B exchange step, which is thought to be rate-determining.

10.2.1.4 **New Types of Silyl Enolate**

TMS enolates and other unstrained triorganosilyl enolates have been widely used for silicon-directed aldol reactions since the discovery of the Mukaiyama aldol reaction. In the last decade, however, several researchers have developed new types of silyl enolate with unique reactivity to achieve high reaction efficiency, high chemo- and stereoselectivity, mild reaction conditions, etc.



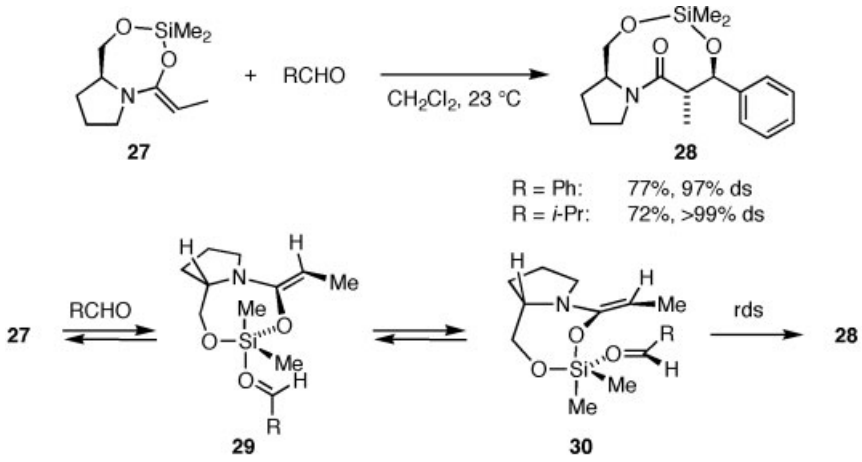
Scheme 10.26

Cyclic Silyl Enolates of Amides

Myers et al. found that silyl enolates derived from amides undergo a facile non-catalyzed aldol addition to aldehydes at or below ambient temperature [90]. In particular, the use of cyclic silyl enolate **27**, derived from (*S*)-prolinol propionamide, realizes high levels of diastereoface-selection and simple diastereoselection (*anti* selectivity) (Scheme 10.27). It has been proposed that this non-catalyzed highly stereoselective reaction proceeds via attack of an aldehyde on **27** to produce a trigonal bipyramidal intermediate **29** in which the aldehyde is apically bound; **29** then turns to another isomer **30** by pseudorotation and **30** is then converted into **28** through a six-membered boat-like transition state (rate-determining step).

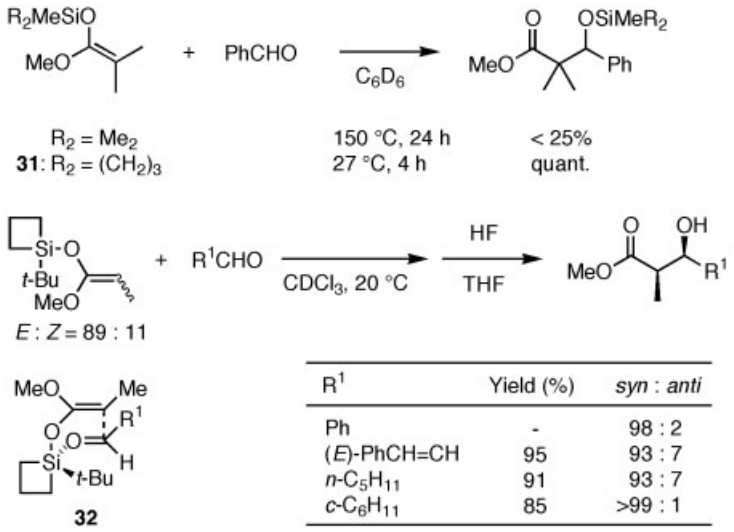
Enoxysilacyclobutanes

Myers et al. have also found that introduction of a silicon-containing small ring such as silacyclobutane in place of the Me_2Si group markedly increases the reactivity of **27** [91]. They and Denmark et al. also disclosed that a similar rate-accelerating effect is observed in the aldol reactions of SEE and KSA (Scheme 10.28) [91–93]. For instance, when the TMS enolate derived from methyl isobutyrate is heated with benzaldehyde in benzene (0.2 M, 150 °C, 24 h), the aldol adduct is obtained in less than 25% yield. In marked contrast, enoxysilacyclobutane **31** reacts completely and



Scheme 10.27

cleanly with benzaldehyde within 4 h at 27 °C to afford the corresponding aldol adduct quantitatively [91]. The high reactivity can be rationalized by the increased Lewis acidity of the silicon atom, which is a consequence of the release of strain caused by Lewis base coordination. Another synthetically valuable feature of enoxysilacyclobutanes is that high *syn* selectivity is observed for KSA of *E* configuration. On the basis of results from computational modeling, the origin of the stereochemical outcome has been explained by boat-like transition state **32** [93].

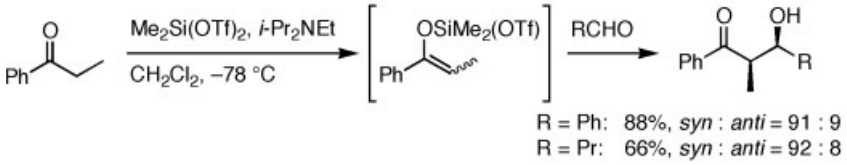


R^1	Yield (%)	*syn* : *anti*
Ph	-	98 : 2
(*E*)-PhCH=CH	95	93 : 7
n-C_5H_{11}	91	93 : 7
c-C_6H_{11}	85	>99 : 1

Scheme 10.28

Dimethyltrifloxysilyl Enolates

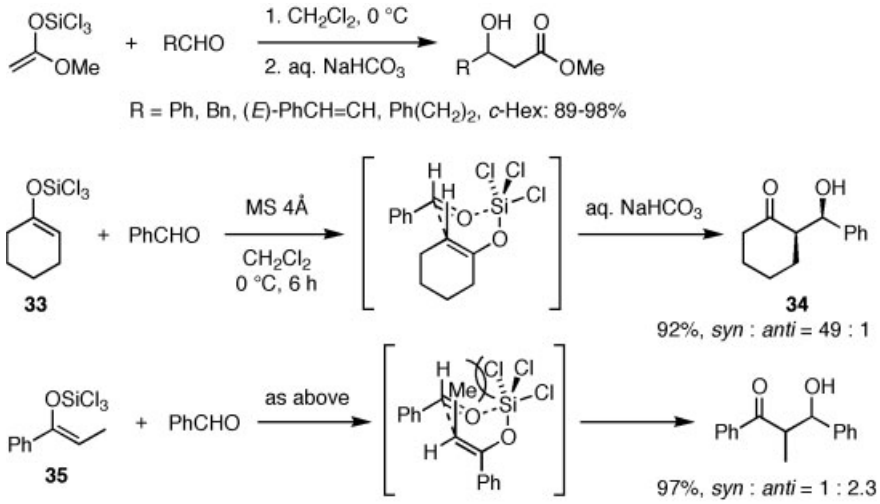
Kobayashi et al. have found that dimethyltrifloxysilyl enolates, prepared in situ from ketones and dimethylsilyl ditriflate in the presence of a tertiary amine, react smoothly with electrophiles such as aldehydes and acetals without catalyst at –78 °C to afford the corresponding aldol adducts in high yields [94]. The use of ethyl ketones as the substrates achieves high levels of *syn* selectivity (Scheme 10.29).



Scheme 10.29

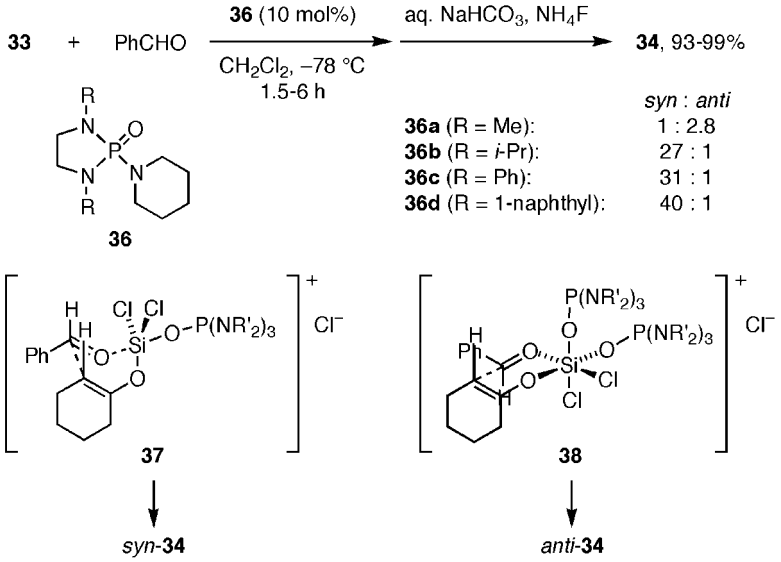
Trichlorosilyl Enolates

Denmark et al. have reported that trichlorosilyl enolates also undergo non-catalyzed aldol reaction with aldehydes (Scheme 10.30) [95]. The sense of diastereoselectivity depends on the geometry of the enolates – (*E*)-enolate **33** adds to aldehydes with high *syn* selectivity, whereas low *anti* selectivity is observed for (*Z*)-enolate **35** [96]. The stereochemical outcomes can be rationalized by boat-like transition structures arranged by the Lewis acidity of the silicon atom, in which the configuration around silicon is trigonal bipyramidal with aldehyde binding in the apical position. In the transition structure from **35** there are severe steric interactions caused by the enolic *Z* substituent, which is attributable to the low *anti* selectivity.



Scheme 10.30

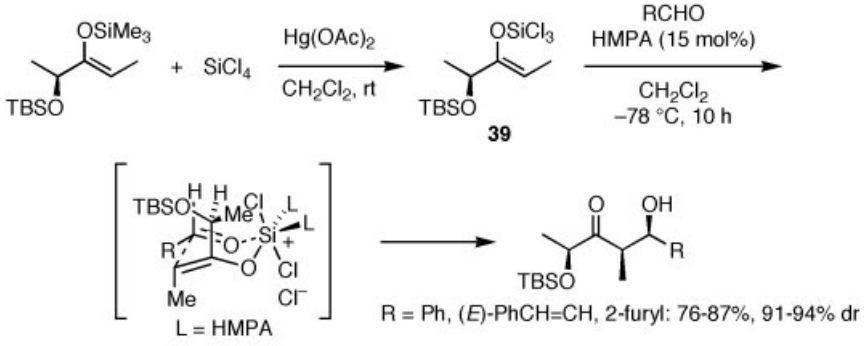
Interestingly, a catalytic amount of a phosphoramide not only effectively accelerates the aldol reaction of trichlorosilyl enolates but also strongly affects the diastereoselectivity [96]. To evaluate the effects of catalyst structure, phosphoramides **36** were employed as catalysts of the aldol reaction of **33** with benzaldehyde (Scheme 10.31) [97]. The results show that increasing the bulk of the *N*-substituent has a dramatic effect on the diastereoselectivity. In addition, the *syn* selectivity with **36c** decreases with increased loading of the catalyst. The rate acceleration and these stereochemical outcomes suggest two plausible transition structures **37** and **38**, leading to *syn* and *anti* adducts, respectively. The former has a pentacoordinate cationic silicon center with one phosphoramide ligand in the trigonal bipyramidal structure, and the latter has a hexacoordinate cationic silicon center with two phosphoramide ligands in the octahedral structure. The origin of the rate acceleration stems from the ionization of the enolate by the phosphoramides. Sterically demanding phosphoramides bind to the enolate in a 1:1 fashion and the resulting pentacoordinate cationic siliconate **37** favors a boat-like arrangement. Sterically less demanding phosphoramides can bind in a 2:1 fashion, and the resulting hexacoordinate cationic siliconate **38** favors a chair-like arrangement. Increased loading of **36c** promotes the reaction path via **38** to diminish the *syn* selectivity. These divergent mechanistic and stereochemical pathways have been ascertained by kinetic studies and linear/non-linear effects observed in the asymmetric aldol reactions using chiral phosphoramides (Section 10.2.2.4) [98].



Scheme 10.31

The HMPA-catalyzed reaction of homochiral (*Z*)-enolate **39** generated from the corresponding TMS enolate provides *syn,syn* adducts with high diastereoselectivity (Scheme 10.32) [99]. The observed stereoselectivity is explainable by a chair-like

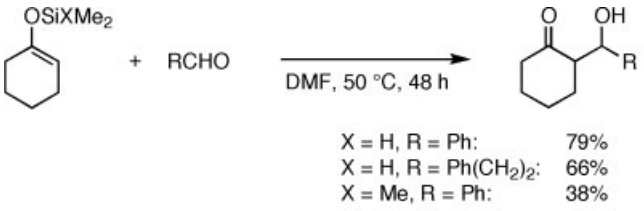
cationic transition structure like **38**. As shown in the later section, the base-catalyzed system using trichlorosilyl enolates is successfully used for catalytic asymmetric aldol reactions.



Scheme 10.32

Dimethylsilyl Enolates

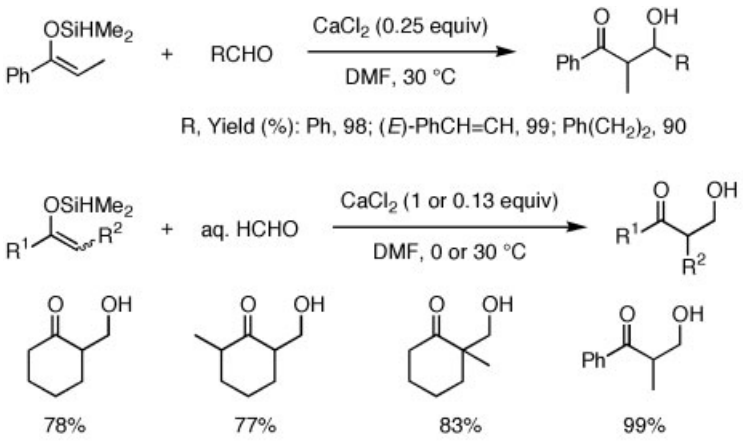
We have found that dimethylsilyl (DMS) enolates derived from ketones react with aldehydes without promoter in DMF at 50 °C, affording aldol adducts in moderate to good yields (Scheme 10.33) [100]. The corresponding TMS enolates are not so reactive to aldehydes under the same conditions. The high reactivity of DMS enolates could originate from the relatively less crowded silicon center, which would facilitate the coordination of DMF to silicon to enhance the nucleophilicity of the enolates.



Scheme 10.33

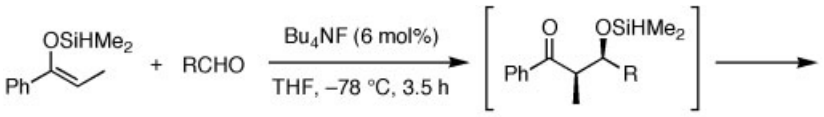
We recently disclosed that salts of alkali and alkaline earth metals effectively promote the aldol reaction of DMS enolates (Scheme 10.34) [101]. For example, the $CaCl_2$-catalyzed reaction of propiophenone DMS enolate with aldehydes proceeds smoothly in DMF at 30 °C with high reaction efficiency. In the metal salt-catalyzed aldol reaction the counter anion of the metal salt plays a crucial role in rate acceleration. The activity of metal salt increases with increasing intrinsic nucleophilicity of the counter anion: $TfO^- < I^- \leq Br^- < Cl^-$. This result indicates that metal salts work as Lewis bases to activate DMS enolates. To our surprise, the

$CaCl_2$-catalyzed aldol reaction of DMS enolates proceeds efficiently even in the presence of water. Thus, the catalytic system can be utilized for hydroxymethylation using a commercial aqueous solution of formaldehyde.

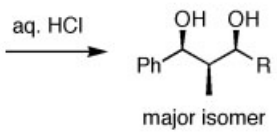


Scheme 10.34

In the presence of a fluoride ion source, DMS enolates work as bifunctional silicon reagents to enable the tandem aldol-reduction reaction of aldehydes (Scheme 10.35) [102]. The TBAF-catalyzed reaction of DMS enolates with aldehydes produces *syn,syn*-1,3-diols with moderate to high diastereoselectivity.



R	Yield (%)	dr
Ph	91	97 : 3
p-MeC_6H_4	87	96 : 4
p-$MeOC_6H_4$	74	94 : 6
2-furyl	73	91 : 9
$Ph(CH_2)_2$	43	82 : 18

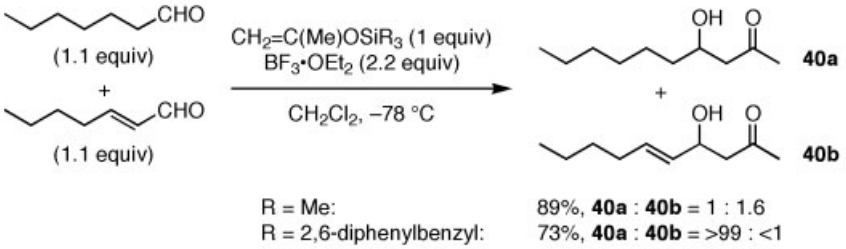


Scheme 10.35

Tris(2,6-diphenylbenzyl)silyl Enolates

The chemoselective aldol reaction of α-enals with KSA has been achieved under the influence of organotin Lewis acids in competition with saturated aldehydes [52c]. Maruoka et al. have, on the other hand, recently reported a highly chemoselective aldol reaction of saturated aldehydes over α-enals with tris(2,6-diphenylben-

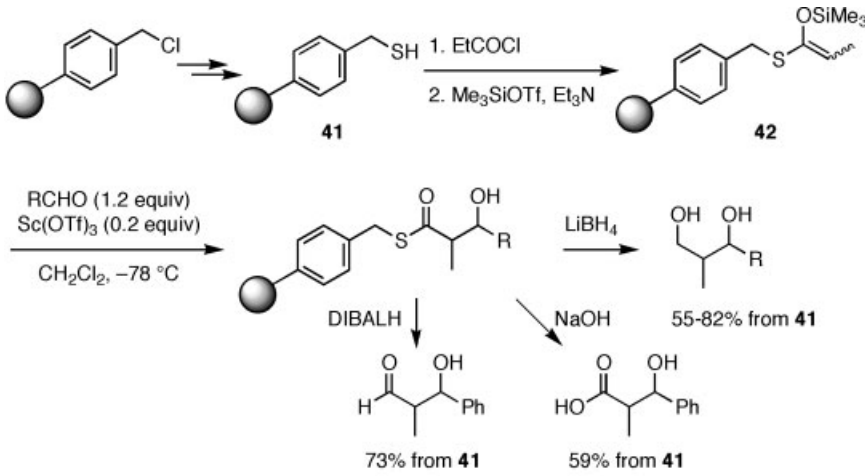
zyl)silyl (TDS) enolates (Scheme 10.36) [103]. The BF_3-promoted reaction of an equimolar mixture of heptanal and (*E*)-2-heptenal with acetone TMS enolate forms a 1:1.6 mixture of both aldol adducts, whereas acetone TDS enolate adds to only heptanal under the same reaction conditions.



Scheme 10.36

Polymer-supported Silyl Enolates

Kobayashi et al. reported the first synthesis of polymer-supported silyl enolates (thioketene silyl acetals) and their reactions with aldehydes for the preparation of 1,3-diol, *β*-hydroxy carboxylic acid, and *β*-hydroxy aldehyde libraries (Scheme 10.37) [104]. In the presence of 20 mol% $Sc(OTf)_3$, polymer-supported silyl enolate **42** derived from chloromethyl copoly(styrene–1% divinylbenzene) resin via **41** reacts smoothly with a variety of aldehydes. The resulting adducts can be easily purified by acid treatment and subsequent washing with water and organic solvents. The purified adducts are converted into 1,3-diols with $LiBH_4$, *β*-hydroxy carboxylic acids with NaOH, and *β*-hydroxy aldehydes with DIBALH. This strategy has been used for efficient synthesis of diverse monosaccharide derivatives [105].



Scheme 10.37

10.2.2 Asymmetric Aldol Reactions

Since the middle of the 1980's remarkable progress has been achieved in the development of asymmetric aldol reactions of silyl enolates. In the beginning of this evolution, chiral auxiliary-controlled reactions were extensively studied for this challenging subject [106]. As new efficient catalysts and catalytic systems for the aldol reactions were developed, much attention focused on catalytic enantiocontrol using chiral Lewis acids and transition metal complexes. Thus, a number of chiral catalysts realizing high levels of enantioselectivity have been reported in the last decade.

10.2.2.1 Use of a Chiral Auxiliary

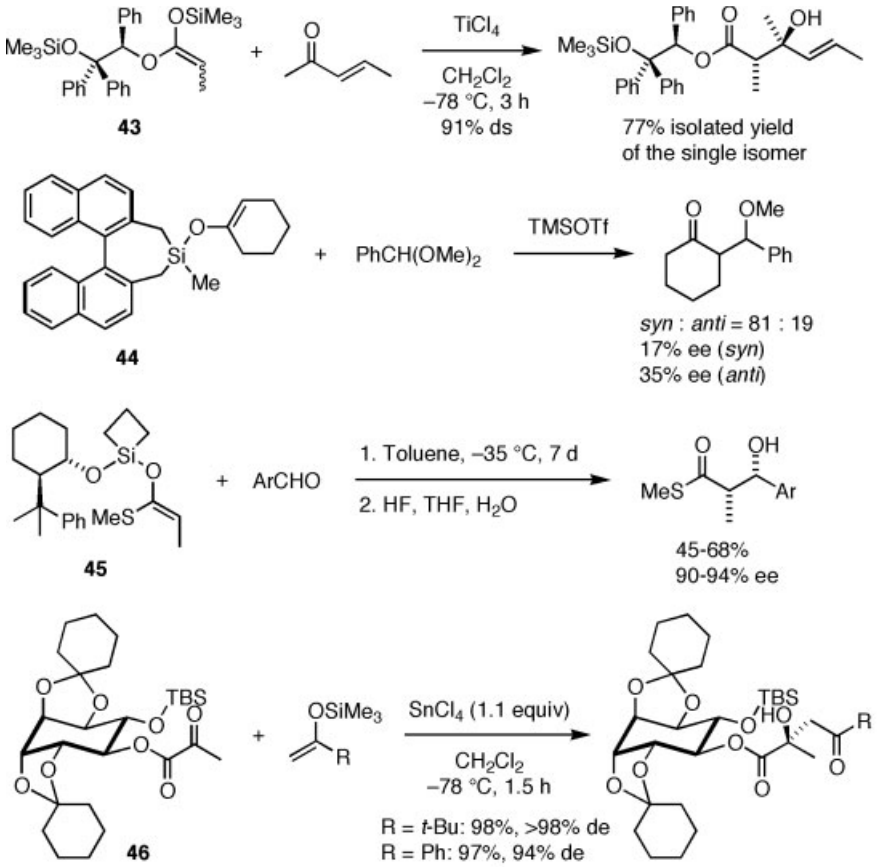
In the middle of the 1980's some silyl enolates derived from homochiral esters were reported to enable highly enantioselective synthesis of aldols [106]. Later, Oppolzer et al. disclosed the utility of camphor sultam as a chiral auxiliary for asymmetric aldol reactions [107]. Braun et al. have recently achieved high levels of asymmetric induction in the aldol reaction of ketones with homochiral silyl enolate **43** (Scheme 10.38) [108].

Introduction of a chiral auxiliary into the silyl group of silyl enolates has been attempted [109–111]. The enantioselectivity of the reaction with binaphthyl-based silyl enolate **44** is, however, rather low [109]. Denmark et al. have reported that enoxysilacyclobutane **45**, bearing a chiral auxiliary, adds to aldehydes without any catalyst to give the corresponding adducts with high diastereo- and diastereofaceselectivity [111].

Chiral auxiliary-bound substrates have also been used for the asymmetric process. The aldol reaction of chiral pyruvates such as **46** is a reliable method for highly enantioselective synthesis of functionalized tertiary alcohols (Scheme 10.38) [112]. The Lewis acid-catalyzed aldol-type reactions of chiral acetals with silyl enolates are valuable for the asymmetric synthesis of β-alkoxy carbonyl compounds [113, 114].

10.2.2.2 Use of Chiral Lewis Acids and Transition Metal Complexes

In 1986, Reetz et al. reported that chiral Lewis acids (B, Al, and Ti) promoted the aldol reaction of KSA with low to good enantioselectivity [115]. The following year they also introduced asymmetric aldol reaction under catalysis by a chiral rhodium complex [116]. Since these pioneering works asymmetric aldol reactions of silyl enolates using chiral Lewis acids and transition metal complexes have been recognized as one of the most important subjects in modern organic synthesis and intensively studied by many synthetic organic chemists.

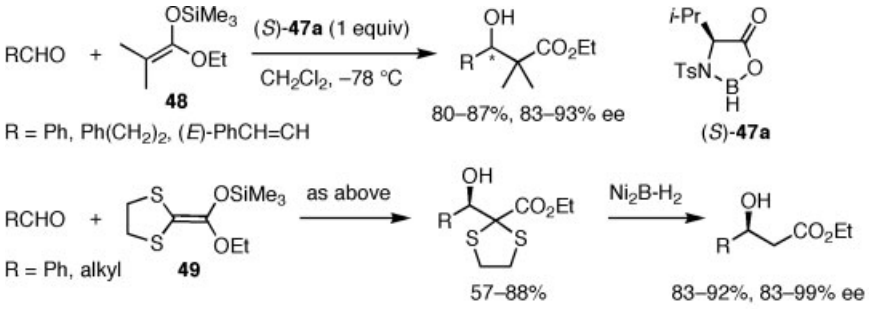


Scheme 10.38

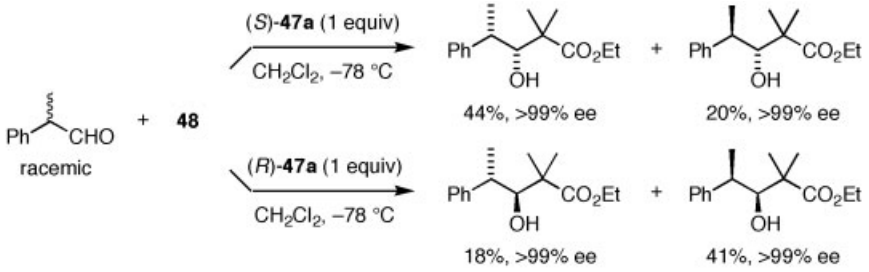
Chiral Boron and Aluminum Lewis Acids

Kiyooka et al. have reported that stoichiometric use of chiral oxazaborolidines (e.g. (*S*)-**47**), derived from sulfonamides of α-amino acids and borane, is highly effective in enantioselective aldol reactions of ketene TMS acetals such as **48** and **49** (Scheme 10.39) [117]. The use of TMS enolate **49** achieves highly enantioselective synthesis of dithiolane aldols, which can be readily converted into acetate aldols without epimerization. The chiral borane **47**-promoted aldol reaction proceeds with high levels of reagent-control (Scheme 10.40) [118] – the absolute configuration of a newly formed stereogenic center depends on that of the promoter used and not that of the substrate.

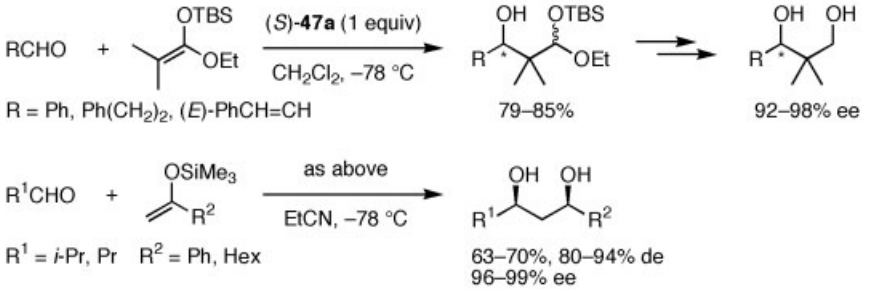
Interestingly, reaction of ketene TBS acetals under the same conditions forms β-hydroxy acetals by a tandem aldol-reduction process (Scheme 10.41) [117a]. A similar tandem reaction using ketone TMS enolates provides a highly enantioselective route to 1,3-diols [119].



Scheme 10.39



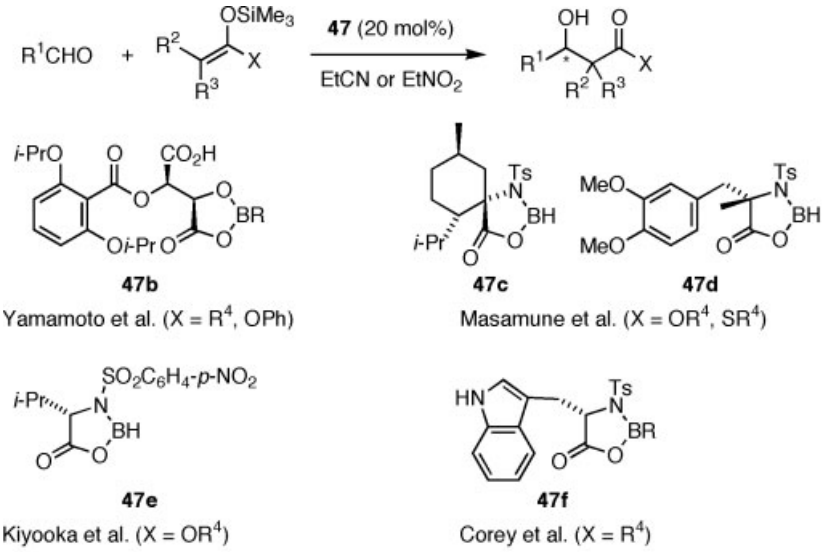
Scheme 10.40



Scheme 10.41

In 1991 Kiyooka et al. described the chiral borane-promoted aldol reaction, then Yamamoto [120], Masamune [121], Kiyooka [122], and Corey [123] all independently reported chiral borane-catalyzed systems for highly enantioselective aldol reactions of silyl enolates (Scheme 10.42).

Yamamoto et al. found that chiral borane **47b** (R = H), derived from monoacyloxytartaric acid and diborane, works as an excellent catalyst of enantioselective aldol reactions (from 80 to >95% ee) of aldehydes with SEE [120]. The **47b** (R = H)-catalyzed reaction has high *syn* selectivity (60 to >90% de) irrespective of the geometry of the



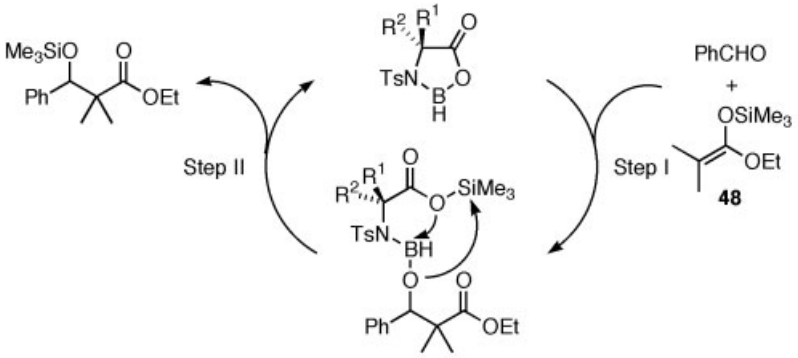
Scheme 10.42

enolates. This observation can be well explained by an acyclic antiperiplanar transition state model. Introduction of a 3,5-$(CF_3)_2C_6H_3$ group as R improves the catalytic activity without reducing the enantioselectivity. When R = *o*-$PhOC_6H_4$, higher diastereo- and enantioselectivity can be achieved without reducing the chemical yield. The catalyst system using **47b** (R = H) is applicable to highly enantioselective addition of KSA derived from phenyl esters.

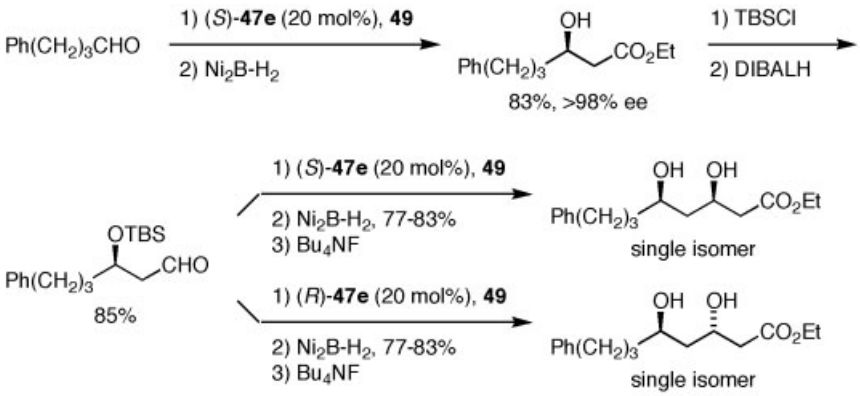
Masamune et al. examined the catalytic activity of several boron Lewis acids derived from $BH_3 \cdot THF$ and the *p*-toluenesulfonamides of simple *α*-amino acids towards the aldol reaction of benzaldehyde with TMS enolate **48** [121]. As a result, the borane catalysts derived from *α*,*α*-disubstituted glycine *p*-toluenesulfonamides were found to have high activity. The disubstitution would accelerate the second step (Step II) of the catalytic cycle (Scheme 10.43). On the basis of this observation, they developed chiral borane catalysts **47c** and **47d**, which enable highly enantioselective aldol reactions of KSA and thioketene silyl acetals (84–99% ee with **48**).

Kiyooka et al. succeeded in developing a catalytic version of the chiral borane-promoted aldol reaction of KSA by modification of the promoter (the use of **47e**) and the use of $EtNO_2$ as solvent (Schemes 10.39 and 10.42) [122]. The solvent effect realizing an efficient catalytic cycle would arise from acceleration of Step II (Scheme 10.43) by nucleophilic assistance of the polar solvent. The **47e**-catalyzed reaction of KSA **49** in $EtNO_2$ can be used for enantioselective synthesis of both isomers of 1,3-diols (Scheme 10.44).

Corey et al. disclosed that tryptophan-derived oxazaborolidine **47f** (R = Bu) is an effective asymmetric catalyst of the aldol reaction of terminal silyl enolates derived from acetophenone and 2-hexanone in $EtNO_2$ (86–93% ee) (Scheme 10.42) [123]. The level of enantioselectivity is lower when CH_2Cl_2 is used as solvent or when



Scheme 10.43

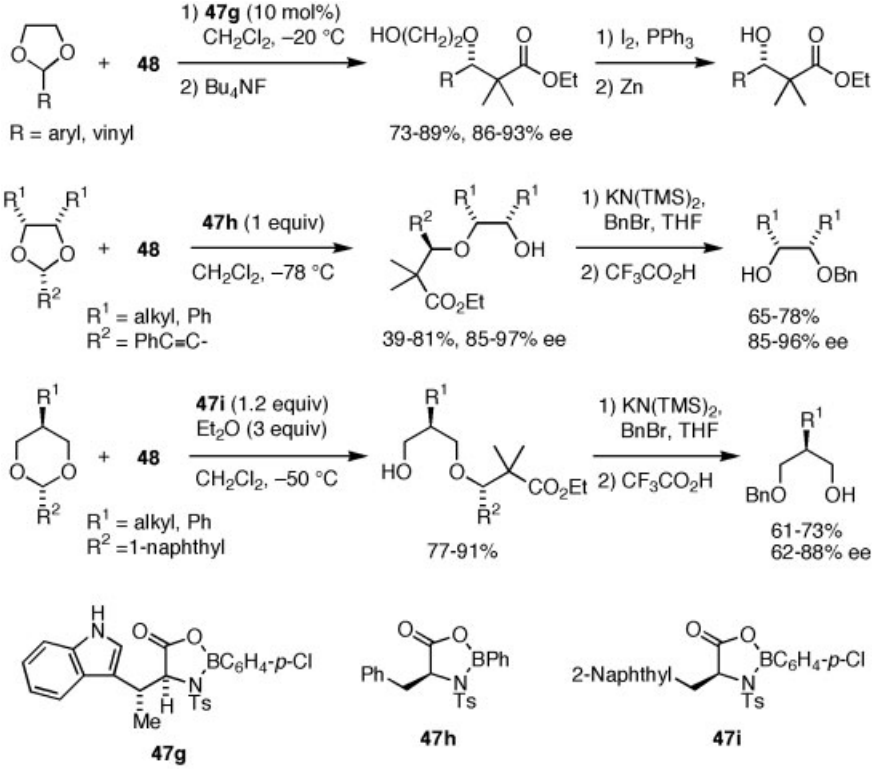


Scheme 10.44

47 f (R = Me) is used as catalyst. Quite recently Yamamoto et al. reported that introduction of a 3,5-$(CF_3)_2C_6H_3$ group as R makes **47 f** much more active, and 10 mol% or less of the modified catalyst can achieve high chemical and optical yields [124].

Chiral borane catalyst **47 g**, prepared from *N*-tosyl-(*αS*,*βR*)-*β*-methyltryptophan and (*p*-chlorophenyl)dibromoborane, is fairly effective in asymmetric aldol-type reaction of 1,3-dioxolanes bearing an aryl or vinyl group at the 2-position (Scheme 10.45) [125]. The ring-cleavage products can be converted into free aldols without epimerization by iodination and subsequent reduction. The chiral borane-promoted reaction with **48** is very valuable for asymmetric desymmetrization of symmetric 1,3-dioxolanes and 1,3-dioxanes leading to mono protected 1,2- and 1,3-diols, respectively [126].

In sharp contrast to the utility of chiral boron Lewis acids, chiral aluminum Lewis acids have been little used for asymmetric aldol reactions of silyl enolates since the first example reported by Reetz et al. [115]. Fujisawa et al. have reported that an equimolar amount of a chiral Lewis acid prepared from Et_2AlCl and a bornane-2,3-diol promotes the aldol reaction of **48** in moderate yields with good enantioselectivity [127].

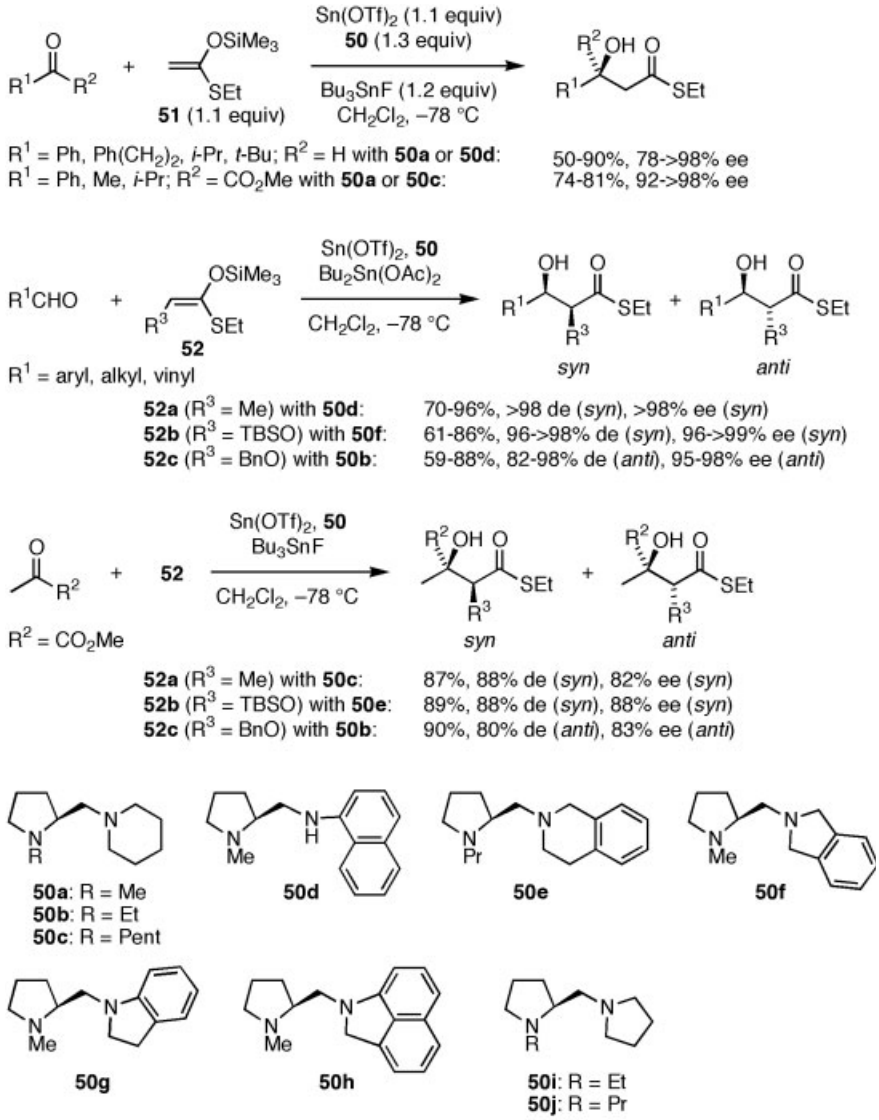


Scheme 10.45

Chiral Tin and Lead Lewis Acids

In 1989, Kobayashi and Mukaiyama reported a tin-based chiral promoter system, $Sn(OTf)_2$–chiral diamine **50**–Bu_3SnF (stoichiometric use), for highly enantioselective aldol reaction of ethanethioate silyl enolate **51** with aldehydes and ketones (Scheme 10.46) [128]. In the reactions of (*Z*)-silyl enolates **52** (R^3 = Me, BnO, TBSO) with aldehydes, a similar promoter system using $Bu_2Sn(OAc)_2$ instead of Bu_3SnF realizes good yields and extremely high diastereo- and enantioselectivity [129–131]. This method has been used for the synthesis of the C26–C33 segment of rapamycin [132]. Bu_3SnF or $Bu_2Sn(OAc)_2$ would serve as an additional ligand bound to the Lewis acidic Sn(II) center.

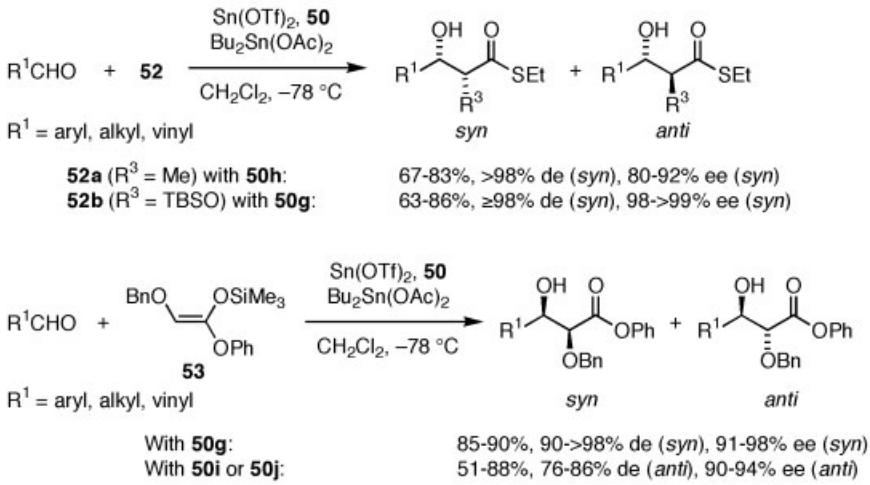
Unlike the case of R^3 = Me and TBSO, the BnO-substituted silyl enolate **52c** has *anti* selectivity. The stereochemical outcome with **52c** can be rationalized by a synclinal transition structure assisted by coordination of the BnO group to the tin(II) nucleus. In contrast, when R^3 = Me and TBSO, the reaction would proceed via an antiperiplanar transition structure [131]. Interestingly, *E*-isomers of **52** are rather less reactive than **52** although the origin of the low reactivity is not clear [133]. α-Keto esters such as pyruvates undergo the tin-promoted aldol reaction with **52** to give the corresponding aldol adducts with good diastereo- and enantioselectivity [134].



Scheme 10.46

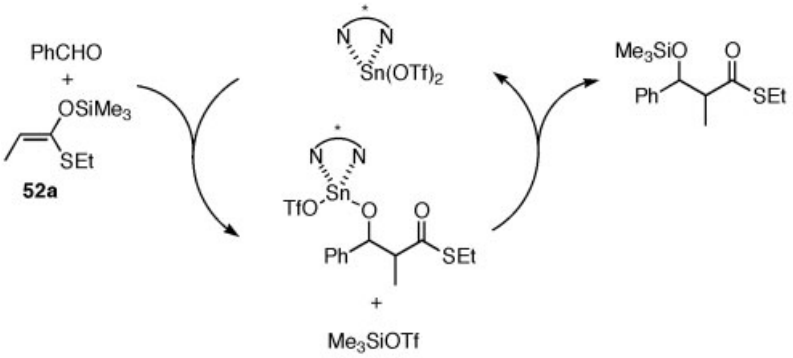
The $Sn(OTf)_2$-based chiral promoter system enables highly selective synthesis of both enantiomers of the aldol adducts by using similar types of chiral diamines derived from L-proline (Scheme 10.47). Diamines **50d** and **50h** are highly effective chiral sources for the synthesis of (2*S*,3*R*) and (2*R*,3*S*) adducts, respectively, from **52a** [135]. In the aldol reaction of **52b**, diamines **50f** and **50g** realize the selective synthesis of both enantiomers of the *syn* adducts [136]. The sense of diastereoselectivity can also be controlled by choice of the diamine ligands. The use of **50g**

leads to *syn*-selective addition of BnO-substituted KSA **53**, whereas the same reaction with **50i** or **50j** has *anti* selectivity [137]. In addition, these reactions proceed with high enantioselectivity.

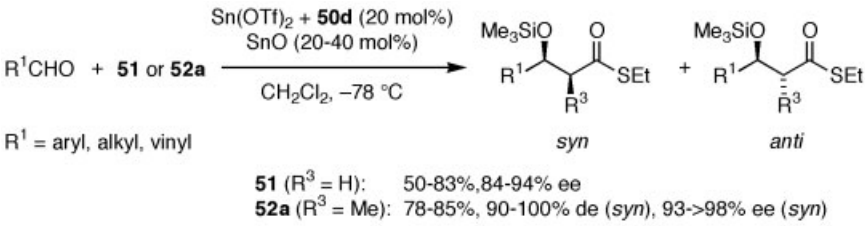


Scheme 10.47

According to the above asymmetric processes, optically active aldols can be readily prepared from both achiral aldehydes and silyl enolates; stoichiometric use of the chiral source is not, however, favorable for practical use. In the course of mechanistic investigation it was found that the chiral tin(II) complex-promoted reaction of **52a** with benzaldehyde gave a mixture of the corresponding aldol and its TMS ether when less than half an equivalent of $Bu_2Sn(OAc)_2$ was used [138]. In addition, the ee and de of the TMS ether were lower than those of the free aldol. The formation of the TMS ether indicates the possibility that metal exchange from tin to silicon on the intermediate aldolate occurs with regeneration of the chiral promoter, as shown in Scheme 10.48. The lower stereoselectivity of the TMS ether is attributable to achiral TMSOTf-promoted reaction. The key to a successful catalytic asymmetric aldol reaction is probably to keep TMSOTf at low concentration. On the basis of this consideration, slow addition of substrates to the chiral promoter was found to be effective in improving stereoselectivity. The use of propionitrile as solvent with a slow addition procedure achieved high stereoselectivity [139]. The solvent effect would originate from acceleration of the metal-exchange step consuming TMSOTf. Furthermore, it turned out that tin(II) oxide reduced the catalytic activity of TMSOTf to bring about higher diastereo- and enantioselectivity [140]. Under the optimized conditions, the aldol reaction of silyl enolates **51** and **52a** with aromatic and aliphatic aldehydes usually proceeds in greater than 90% ee and 90% de (Scheme 10.49) [140b]. This catalytic asymmetric aldol reaction has been used in the total synthesis of several natural products such as L-fucose [140a], sphingofungins [141], febrifugine, isofebrifugine [142], and khafrefungin [143].



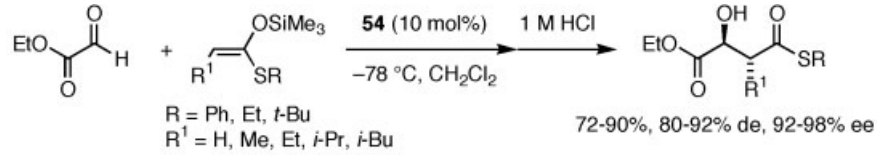
Scheme 10.48

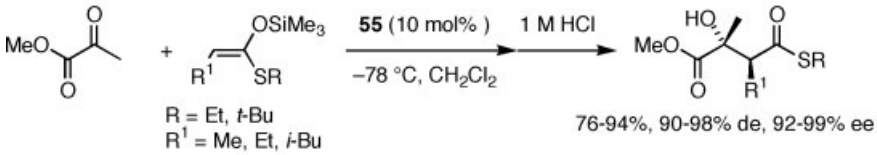


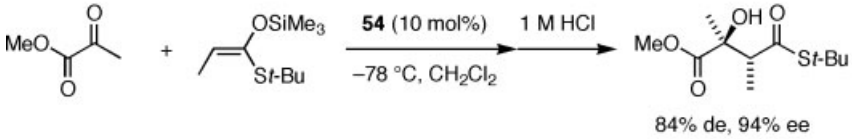
Scheme 10.49

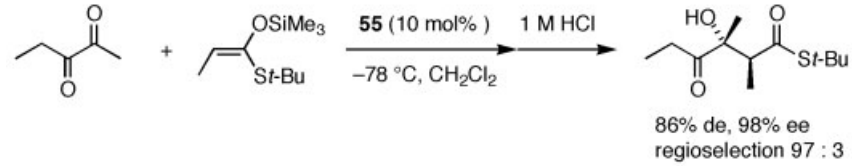
Evans et al. have demonstrated that the Sn(II) complexes **54** and **55** with bidentate bis(oxazoline) (box) and tridentate pyridylbis(oxazoline) (pybox) ligands are efficient *anti*-aldol catalysts of the enantioselective addition of (*Z*)-thioester silyl enolates to 1,2-dicarbonyl compounds such as ethyl glyoxylate and methyl pyruvate (Scheme 10.50) [144]. The **54**-catalyzed aldol reaction of ethyl glyoxylate shows high diastereo- and enantioselectivity and good to high yields, irrespective of substituent variation in the silyl enolate. A similar catalyst system has been applied to the total synthesis of phorboxazole B [145]. Although chiral Lewis acid **55** is ineffective in the aldol reaction of ethyl glyoxylate, it effects high stereoselectivity in the reaction of methyl pyruvate. Interestingly, in the latter reaction, the sense of enantioselectivity with **55** is different from that with **54**. The **55**-catalyzed system enables highly regioselective addition to the MeCO moiety of 2,3-pentanedione.

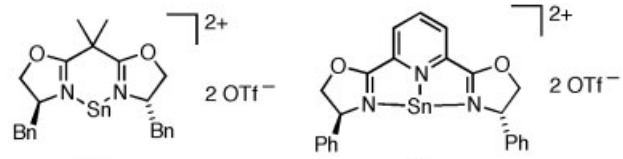
Kobayashi et al. recently developed the $Pb(OTf)_2$-crown ether **56** complex as an efficient chiral catalyst of asymmetric aldol reactions in aqueous media (Scheme 10.51) [146]. This catalyst system achieves good to high yields and high levels of diastereo- (*syn*-selective) and enantioselectivity in the aldol reaction of a variety of aldehydes with propiophenone TMS enolate. The hole size of **56** is essential because **57** and **58** show no chiral induction. The unique structure of the $Pb(OTf)_2$–**56** complex as a chiral catalyst has been revealed by X-ray diffraction.





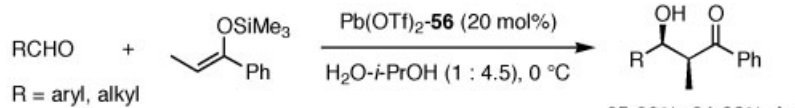


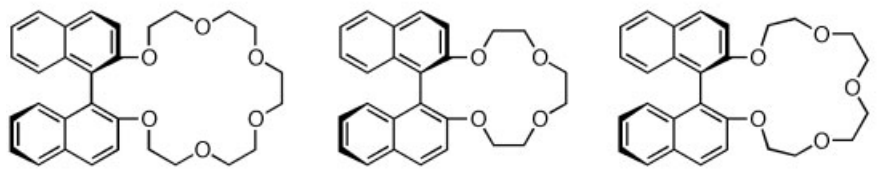




54 55

Scheme 10.50





56 57 58

Scheme 10.51

Chiral Titanium and Zirconium Complexes

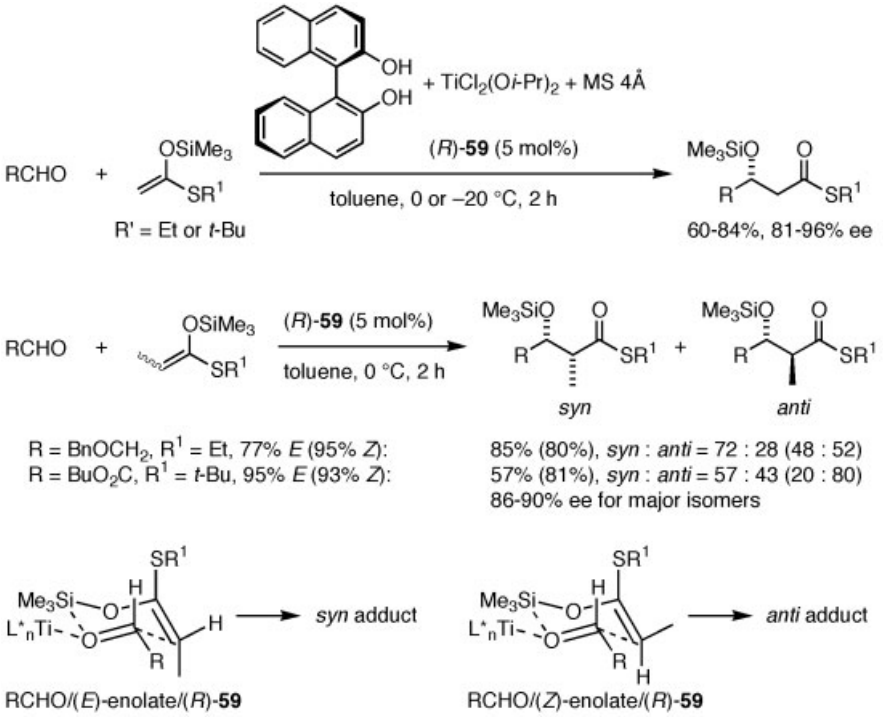
Reetz et al. reported that a chiral Ti complex prepared from $TiCl_4$ and the dilithium salt of (*S*)-BINOL promoted the aldol reaction of 3-methylbutanal with KSA **48** with only poor enantioselectivity (60%, 8% ee) [115 b]. After this pioneering work, the titanium-based catalyst system has been intensively improved to attain an efficient catalytic cycle and high stereoselectivity [147–155].

Mukaiyama et al. have shown that a BINOL-derived oxotitanium catalyzes the asymmetric aldol reaction of aldehydes with thioester silyl enolates [147]. In the presence of the chiral complex (20 mol%), the TBS enolate of *S*-*t*-butyl thioacetate reacts smoothly with aromatic and *α*,*β*-unsaturated aldehydes in toluene to give silylated aldols in high yields with moderate to good enantioselectivity (91–98%, 36–85% ee). The use of the TBS enolate of *S*-ethyl thioacetate results in lower enantioselectivity.

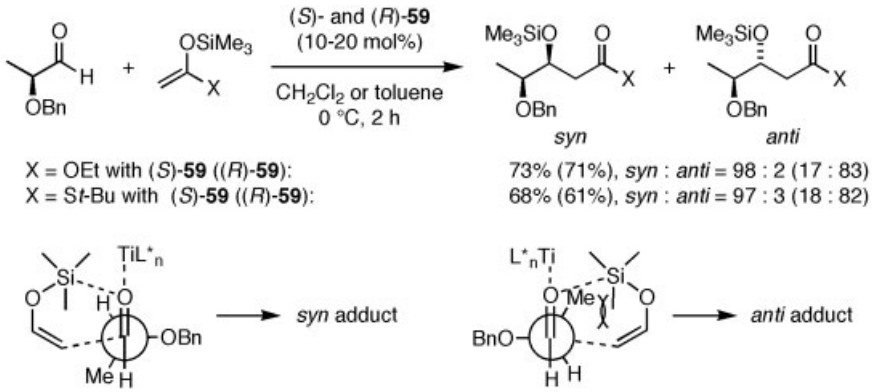
Significant improvement of the titanium-based system has been achieved by three research groups – those of Mikami, Keck, and Carreira. Mikami et al. disclosed that chiral BINOL-Ti complex **59**, prepared in situ from enantiomerically pure BINOL and $TiCl_2(O\textit{i}\text{-}Pr)_2$ in the presence of 4-Å molecular sieves (MS), is quite an efficient catalyst of the aldol reaction of thioester TMS enolates (Scheme 10.52) [148]. With only 5 mol% **59** structurally flexible *β*-siloxy thioesters are obtained in high enantiomeric purity. The enantioselectivity is enhanced in toluene, a non-polar solvent, rather than polar solvents such as CH_2Cl_2, EtCN, and $EtNO_2$. In consistence with the result reported by Mukaiyama et al., higher enantioselectivity is observed with *S*-*t*-butyl thioacetate silyl enolate than with the *S*-ethyl counterpart. The **59**-catalyzed reaction with thiopropanoate TMS enolates proceeds stereospecifically, that is, the (*E*)- and (*Z*)-enolates have *syn* and *anti* selectivity, respectively. These stereochemical outcomes agree well with a silatropic ene mechanism via a chair transition structure. The synchronous formation of C–C and Si–O bonds is supported by the fact that no crossover is observed in the reaction of an aldehyde with two kinds of silyl enolate bearing different silyl and alkylthio groups.

Catalyst-controlled stereoselectivity is observed for the **59**-catalyzed aldol reaction of (*S*)-2-benzyloxypropanal: the sense of diastereoselectivity depends on the absolute configuration of the catalyst (Scheme 10.53) [149]. The level of stereoselectivity with (*R*)-**59** is, however, lower than that with (*S*)-**59**. Thus, a slight influence of substrate control is observed. The stereochemical outcome can be rationalized in terms of steric repulsion between the methyl and TMS groups in the cyclic transition structure leading to *anti* adducts.

Similarly, Keck et al. have demonstrated the utility of chiral BINOL-Ti complex **60**, prepared by heating enantiomerically pure BINOL, $Ti(O\textit{i}\text{-}Pr)_4$, (BINOL–Ti 1:1) and 4-Å MS in CH_2Cl_2 under reflux for 1 h [150]. In the **60**-catalyzed aldol reaction of benzaldehyde with *S*-*t*-butyl thioacetate TMS enolate, a high isolated yield and the optimum enantiomeric excess (90%, 97% ee) are obtained when the reaction is performed with 20 mol% **60** in Et_2O at –20 °C. Under these conditions the aldol reactions of aromatic and aliphatic aldehydes proceed in good to high yields with high enantioselectivity (70–90%, 89 to >98% ee).



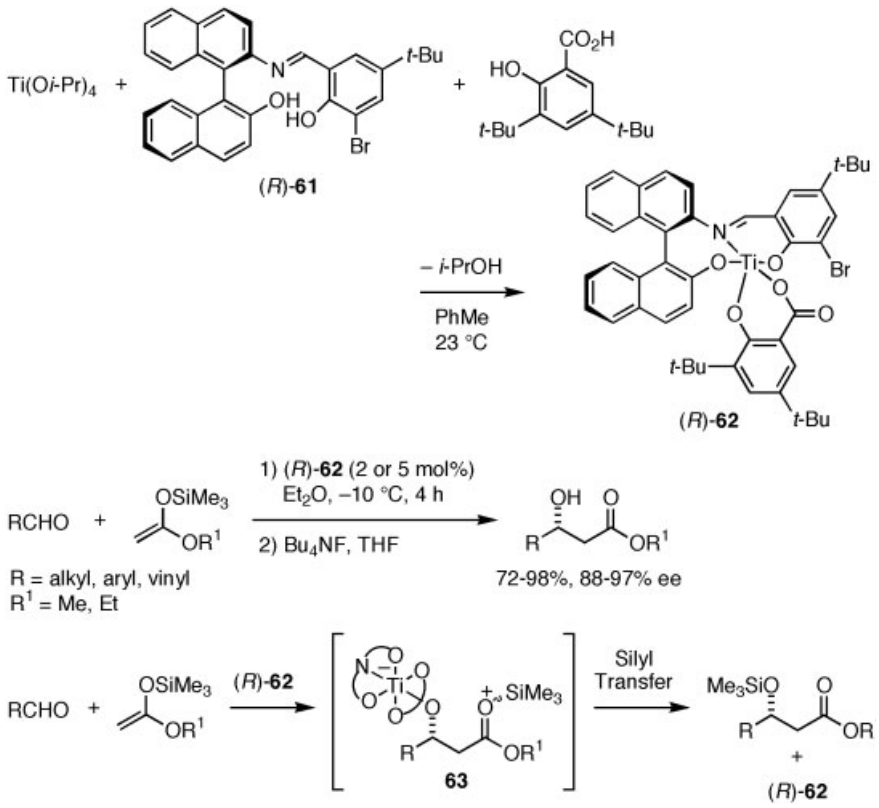
Scheme 10.52



Scheme 10.53

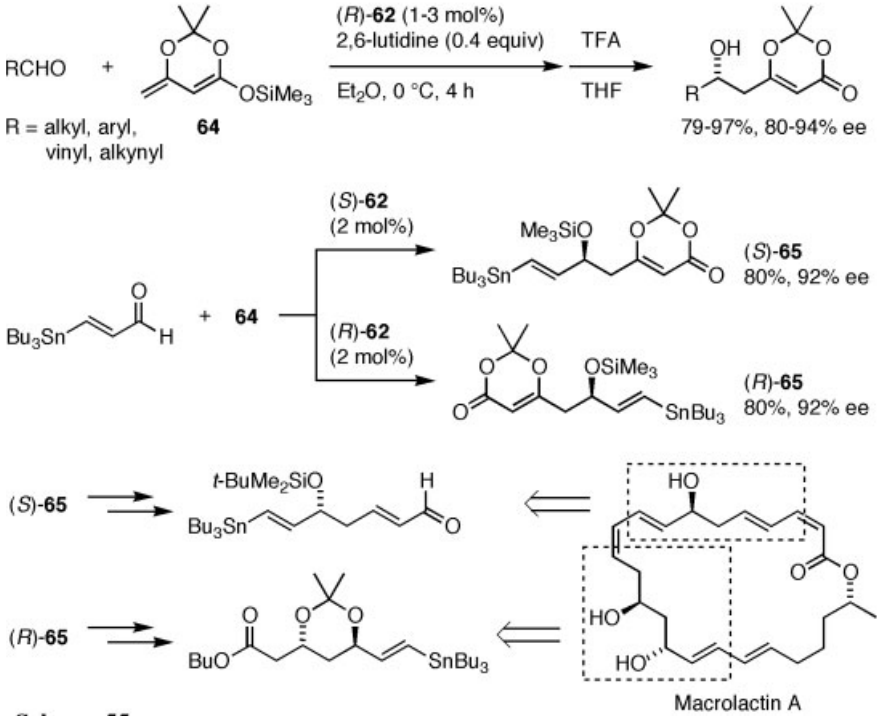
Carreira et al. have developed chiral Schiff base-Ti complex **62** as an asymmetric catalyst of aldol reactions of acetate silyl enolates (Scheme 10.54) [151]. The Ti complex **62** is prepared by treatment of chiral Schiff base **61** with Ti(O*i*-Pr)$_4$ and 3,5-di-*t*-butylsalicylic acid in toluene at 23 °C, followed by solvent removal in vacuo. The aldol reactions of TMS enolates derived from methyl and ethyl acetates are effectively cat-

alyzed by 2–5 mol% **62** to afford silylated aldols. Desilylation of the products with Bu_4NF furnishes *β*-hydroxy esters in good to high total yields from aldehydes, with excellent enantioselectivity. The addition of 3,5-di-*t*-butylsalicylic acid as a counterion has a remarkable effect on the yield, enantioselectivity, and catalytic efficiency. The salicylate chelate would facilitate intramolecular silyl transfer of the zwitterionic intermediate **63** to form the silylated aldol and regenerate the catalyst. The silyl transfer is likely to proceed via the metal-bound silylated salicylate as proposed in the chiral acyloxyborane-catalyzed Mukaiyama aldol reaction (Scheme 10.43).



Scheme 10.54

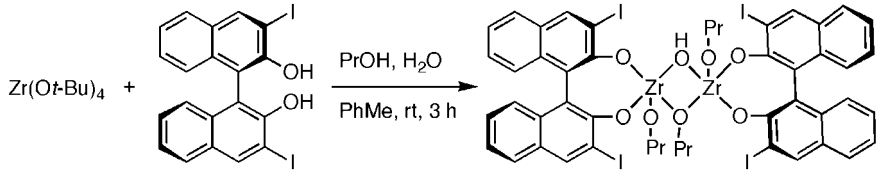
The catalytic system using **62** is applicable to highly enantioselective preparation of acetoacetate aldol adducts (Scheme 10.55) [152]. The use of 1–3 mol% **62** and 0.4 equiv. 2,6-lutidine promotes the aldol reaction of a variety of aldehydes with silyl dienolate **64** in good to high optical yields. The dienolate addition provides a convergent and enantioselective route to 1,3-polyols by appending a protected acetoacetate in a single step. The **62**-catalyzed aldol reactions of methyl acetate TMS enolate and dienolate **64** have been used in the total syntheses of Roflamycoin [153] and Macrolactin A [154], respectively. In the latter both enantiomers

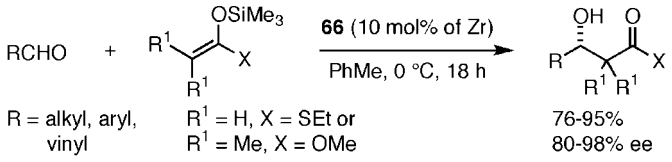


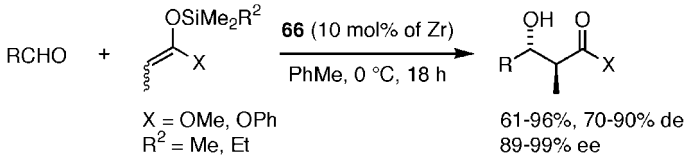
Scheme 10.55

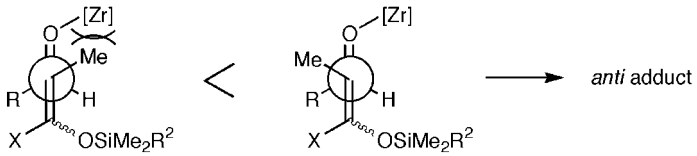
of acetoacetate aldol adduct **65** prepared by the (*R*)- and (*S*)-**62**-catalyzed additions serve as synthetic intermediates of two different components.

Kobayashi et al. recently performed catalytic asymmetric Mukaiyama aldol reactions with ester and thioester TMS enolates using a novel chiral zirconium catalyst (**66**), prepared from $Zr(Ot\text{-}Bu)_4$, (*R*)-3,3′-diiodo-1,1′-binaphthalene-2,2′-diol ((*R*)-3,3′-I_2BINOL), 1-propanol, and a small amount of water (Scheme 10.56) [156]. The reactions of aromatic, *α,β*-unsaturated, and aliphatic aldehydes proceed in high yields with high enantioselectivity under mild conditions (0 °C) although *α*- and *β*-branched aldehydes are not reactive in this catalyst system. Propanoate silyl enolates added to aldehydes with high *anti* selectivity irrespective of the geometry of the enolates. Both 1-propanol and water are essential for obtaining high yields and stereoselectivity. 1-Propanol would serve to not only form **66** but also accelerate the regeneration of **66** from a zirconium metal aldolate intermediate in the catalytic cycle, while water would be required only for the catalyst formation. Judging from NMR analysis and positive non-linear correlation between catalyst and product ee, **66** is assumed to have a dimeric structure bearing two kinds of propoxide moiety. This *anti*-diastereoselectivity can be interpreted in terms of steric repulsion between the *α* methyl group of propanoate silyl enolates and the chiral catalyst bound to the carbonyl oxygen in acyclic transition state models (Scheme 10.56).









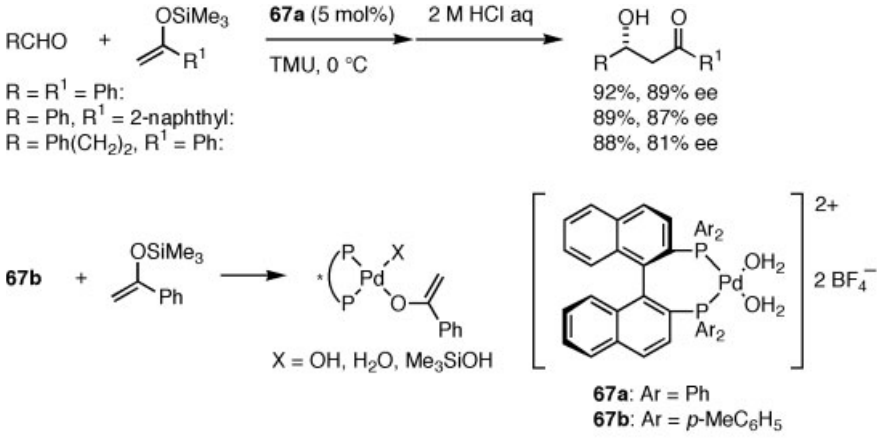
Scheme 10.56

Chiral Palladium and Platinum Complexes

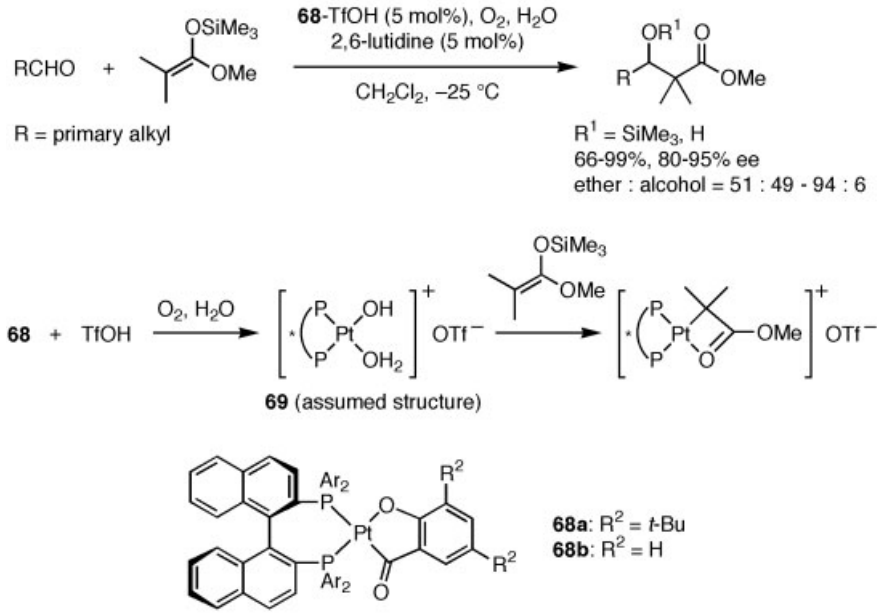
In contrast with the above Lewis acid-catalyzed asymmetric aldol reactions, chiral Pd and Pt cationic complexes have been found to catalyze the asymmetric process by a transmetalation mechanism involving a metal enolate intermediate (Section 10.2.1.3).

Sodeoka et al. have developed novel chiral diaqua Pd(II)-BINAP and -Tol-BINAP complexes **67** as efficient asymmetric catalysts of the aldol reaction of SEE (Scheme 10.57) [157]. These complexes are readily prepared from $PdCl_2$(BINAP) and $PdCl_2$(Tol-BINAP) by treatment of 2 equiv. $AgBF_4$ in wet acetone, and are quite stable to air and moisture. The results of ^{1}H NMR experiments indicate that reaction of **67b** with acetophenone TMS enolate forms an O-bound Pd enolate.

Fujimura, on the other hand, reported that chiral Pt complexes **69** prepared from the chelating acyl Pt(II) complexes **68** and TfOH in the presence of air and water are effective in the asymmetric aldol reaction of methyl isobutyrate TMS enolate with primary aliphatic aldehydes (Scheme 10.58) [158]. In this reaction, 2,6-lutidine is used as proton scavenger, to avoid the effects of residual acid, and a free aldol and its TMS ether are obtained with the same enantioselectivity. IR and



Scheme 10.57



Scheme 10.58

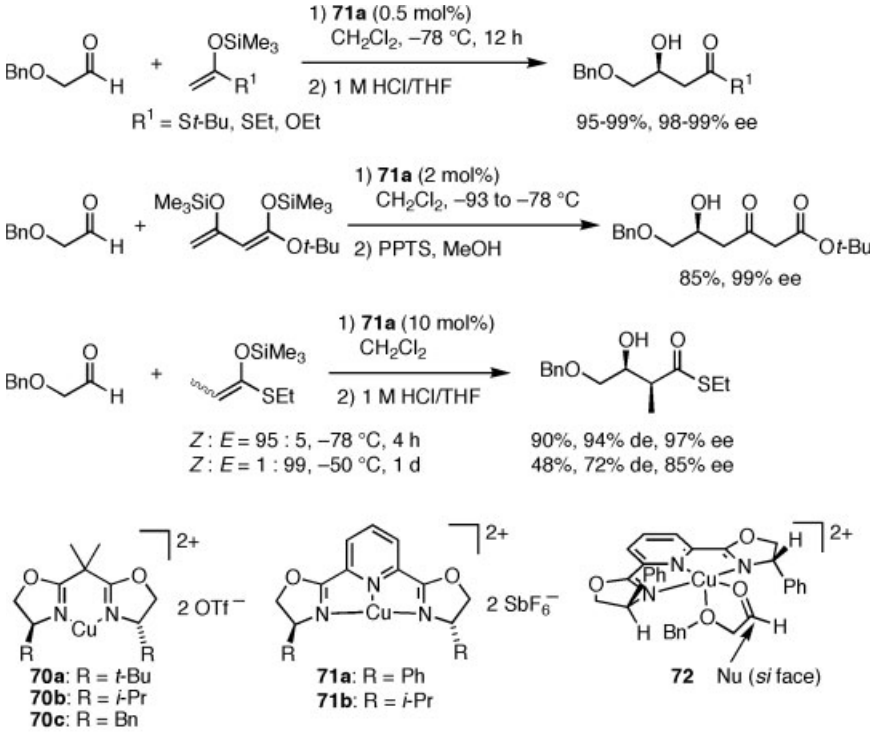
^{31}P NMR analyses are indicative of the intermediacy of a C-bound Pt enolate in the catalytic cycle.

Chiral Copper, Zinc, and Silver Complexes

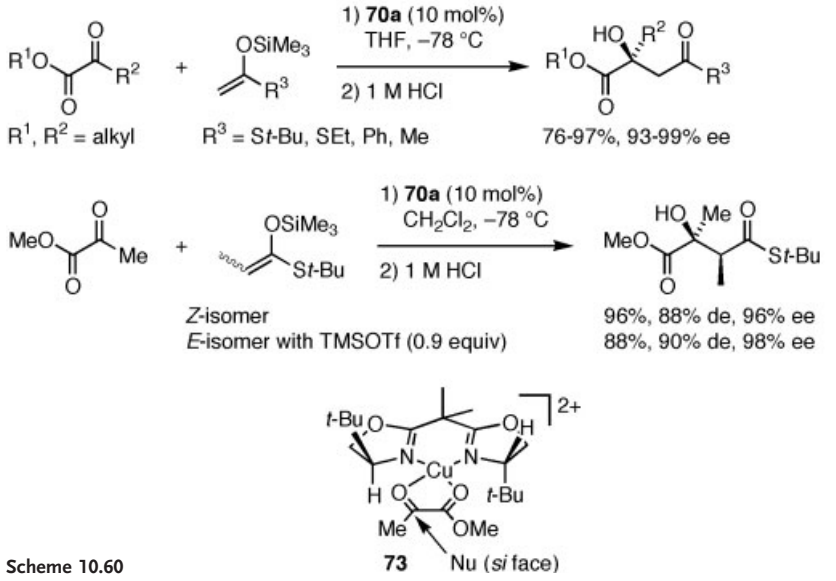
Evans et al. have demonstrated that bidentate box- and tridentate pybox-Cu(II) complexes, **70** and **71**, bearing a weakly coordinating counter anion such as OTf^- or SbF_6^-, are highly efficient catalysts of the aldol reaction of (benzyloxy)acetaldehyde with a range of ester and thioester silyl enolates [159]. In particular, the pybox complex **71a** has high catalytic activity and results in exceptional levels of asymmetric induction, as shown in Scheme 10.59. The **71a**-catalyzed reaction with 1,3-bis (trimethylsiloxy)-1-*t*-butoxy-1,3-butadiene, providing the acetoacetate aldol adduct in excellent yield and enantioselectivity, has been used for the total synthesis of phorboxazole B [160]. The addition of thiopropanoate silyl enolates proceeds with high *syn* selectivity, irrespective of enolate geometry, although (*E*)-enolates are much less reactive. X-ray structural analysis of the substrate–**71a** complex **72** reveals that the copper geometry is square pyramidal, with the carbonyl oxygen coordinated to the more acidic equatorial site in the ligand plane and the ether oxygen occupying an apical site. It is evident from this structure that the sense of enantioselectivity, that is, the *si* face-selective attack to the aldehyde carbonyl, arises from the shielding of the *re* face by the phenyl substituent on the ligand.

The box and pybox Cu(II) catalysts are effective also in the enantioselective aldol reaction of *α*-keto esters (Scheme 10.60) [161]. In the reactions of *α*-keto esters with terminal silyl enolates derived from thioacetates and methyl ketones, excellent optical yields and good to high chemical yields can be achieved by using 10 mol% **70a** in THF. Interestingly, TMSOTf generally accelerates the reactions without degrading enantioselectivity, although TMSOTf is frequently a liability in the execution of enantioselective aldol reactions catalyzed by metal triflate–ligand complexes, because this reagent is also an effective catalyst. The silylating agent would promote the rate-limiting intermolecular silyl-transfer step in the catalytic cycle. With *α*-substituted thioester silyl enolates, high *syn* diastereoselectivity is observed, irrespective of enolate geometry. The (*E*)-enolate of *S*-*t*-butyl thiopropanoate has low reactivity; use of TMSOTf, however, effects high yield and ee. The enantioselectivity of the **70a**-catalyzed pyruvate aldol reaction (*si* face attack) can be rationalized by the computational structure (PM3) of the **70a**-pyruvate complex **73** with distorted square-planar copper geometry.

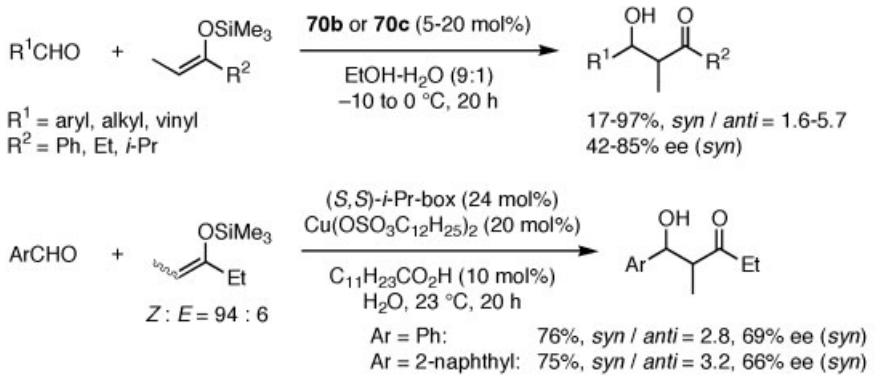
The box-$Cu(OTf)_2$ complexes **70b** and **70c** effectively catalyze enantioselective aldol reaction of SEE in aqueous solvent (Scheme 10.61) [162]. The aldol reaction in EtOH–H_2O (9:1) produces *syn* adducts preferentially with moderate to good enantioselectivity. Without water, much lower yields and stereoselectivity are observed. Water serves not only to generate a dissociated cationic box-Cu(II) complex as the active catalyst but also to suppress TMSOTf-catalyzed undesired achiral side reaction. The use of $Cu(O_3SOC_{12}H_{25})_2$, a Cu(II)-based LASC, in combination with the box ligand of **70b** ((*S*,*S*)-*i*-Pr-box) and a carboxylic acid (Section 10.2.1.2) enables asymmetric aldol reactions in pure water, although reaction efficiency and stereoselectivity are not satisfactory [163].



Scheme 10.59

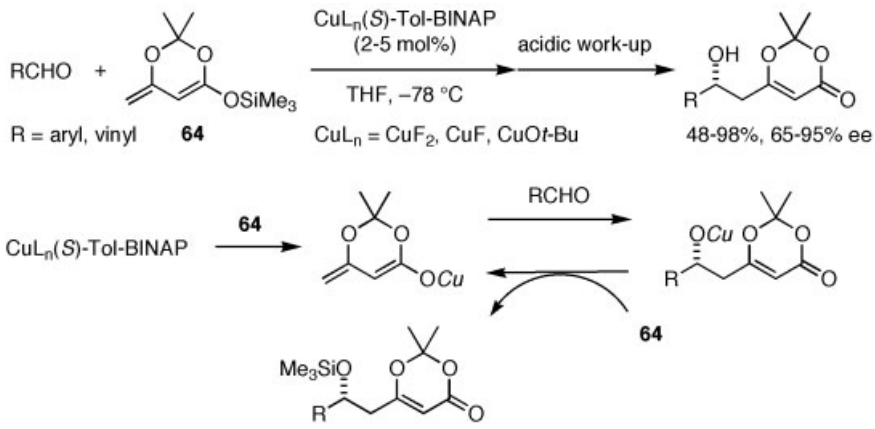


Scheme 10.60



Scheme 10.61

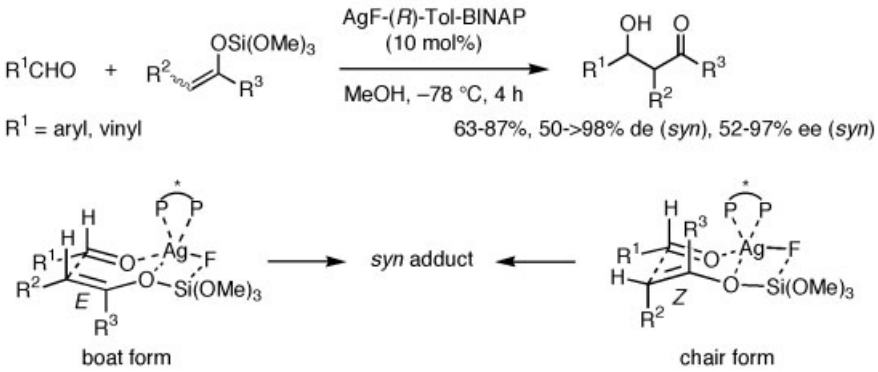
The Tol-BINAP complexes of CuF_2, CuF, and CuO*t*-Bu also work as efficient chiral catalysts of the aldol reactions of aromatic and *α,β*-unsaturated aldehydes with dienolate **64** (Scheme 10.62) [164]. IR spectroscopy has revealed that the stoichiometric reaction of **64** with Cu(O*t*-Bu)(*S*)-Tol-BINAP forms a Cu(I) enolate, and that subsequent reaction with an aldehyde gives a copper aldolate. The copper enolate is also obtained by stepwise treatment of **64** with $Bu_4NPh_3SiF_2$ and $Cu(ClO_4)$(*S*)-Tol-BINAP. These results, with the known reduction of Cu(II) to Cu(I) by SEE, indicate that the Cu-catalyzed aldol reactions proceed through a transmetalation mechanism involving a chiral Cu(I) enolate.



Scheme 10.62

Silver(I)–chiral diphosphine complexes also are available for asymmetric aldol reactions in polar solvent. In the reaction of ketone TMS enolates in DMF, $AgPF_6$-(*S*)-BINAP cationic chiral complex has high catalytic activity and good enantioselectivity

(up to 80% ee) [165]. The AgF-(*R*)-Tol-BINAP complex, on the other hand, is a fairly effective asymmetric catalyst of *syn*-selective addition of ketone trimethoxysilyl enolates to aromatic and *α,β*-unsaturated aldehydes in MeOH (Scheme 10.63) [166]. The fluoride ion of the catalyst and the trimethoxysilyl group of the enolate play crucial roles in promoting high yields and stereoselectivity. NMR analysis of a mixture of the catalyst and a trimethoxysilyl enolate suggests no formation of a silver enolate species, but the presence of a significant interaction between the two compounds. It has been proposed that the Ag-catalyzed reaction proceeds via a cyclic transition states (boat form from (*E*)-enolates and chair form from (*Z*)-enolates) directed by the Lewis acidity of Ag(I) ion and the high affinity of fluoride ion for silicon.



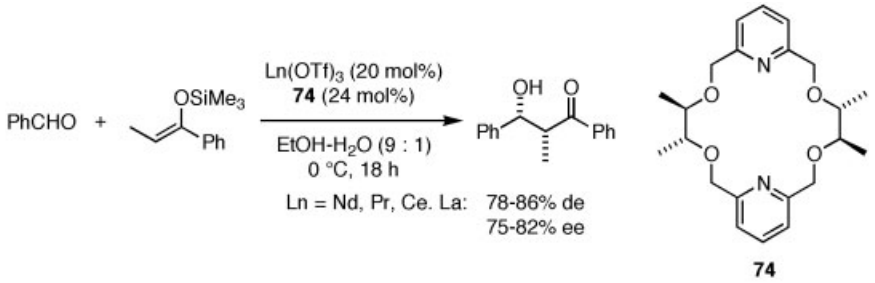
Scheme 10.63

Chiral Lanthanide Metal Complexes

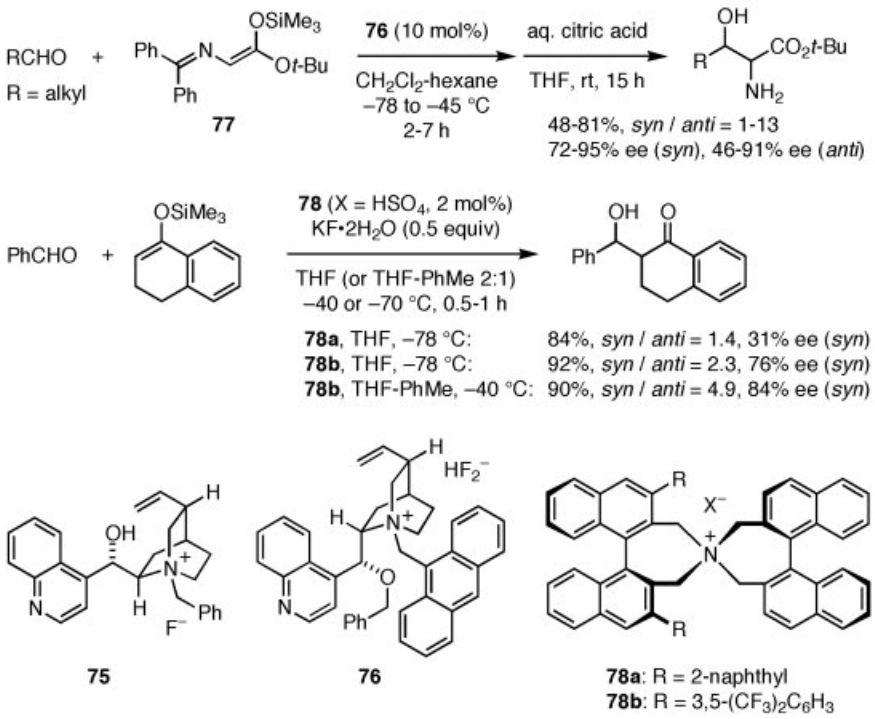
Kobayashi et al. recently reported that a combination of a lanthanide triflate and chiral crown ether **74** can be used as a chiral Lewis acid catalyst of asymmetric aldol reactions in aqueous media (Scheme 10.64) [167]. When $Ce(OTf)_3$ and **74** are used, the reaction of benzaldehyde with propiophenone TMS enolate in EtOH–H_2O (9:1) at 0 °C gives the corresponding aldol adduct with good *syn* selectivity and enantioselectivity. Systematic evaluation of $Ln(OTf)_3$ and other rare earth metal triflates in this reaction has revealed that the ionic diameter significantly affects diastereo- and enantioselectivity. The larger cations such as La, Ce, Pr, and Nd bring about high stereoselectivity. Although the chiral ligand **74** binds strongly to these lanthanide ions, the **74**–$Ln(OTf)_3$ complexes have enough Lewis acidity to catalyze the aldol reaction. Thus, retention of Lewis acidity is the key to realizing asymmetric induction.

10.2.2.3 Use of Chiral Fluoride Ion Sources

The fluoride ion-catalyzed aldol reaction can be utilized for asymmetric synthesis by using chiral quaternary ammonium fluorides (Scheme 10.65). Shioiri et al. reported the first example of the asymmetric process, in which *N*-benzylcinchonium fluoride (**75**) was used for reaction with SEE (up to 72% ee) [168]. Corey et al.



Scheme 10.64

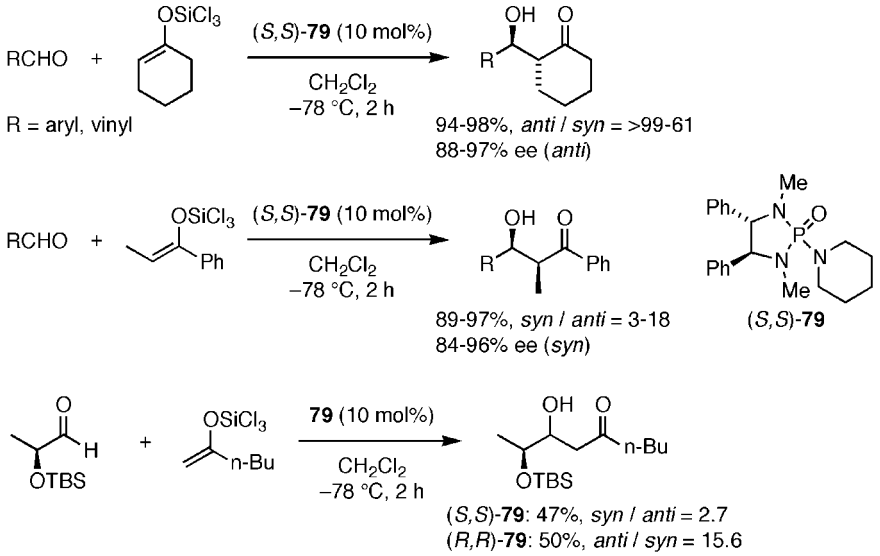


Scheme 10.65

have shown that the cinchonidine-derived bifluoride salt **76** works as an efficient asymmetric catalyst of the aldol reaction of the TMS enolate **77** leading to optically active *β*-hydroxy-*α*-amino esters [169]. Maruoka et al. recently demonstrated that C_2-symmetric chiral quaternary ammonium fluoride **78b** (X = F), generated in situ from the corresponding hydrogensulfate **78b** ($X = HSO_4$) and $KF \cdot H_2O$, catalyzes the aldol reaction of tetralone TMS enolate with good to high diastereo- and enantioselectivity [170]. Interestingly, changing the substituent R in **78** has a profound effect on selectivity as well as reaction efficiency.

10.2.2.4 Use of Trichlorosilyl Enolates and Chiral Lewis Bases

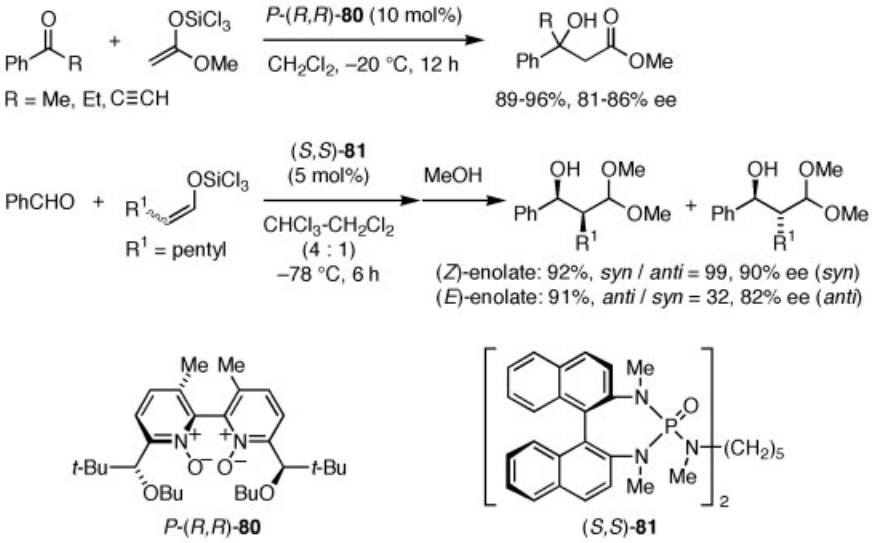
As described in Section 10.2.1.4, the aldol reaction of trichlorosilyl enolates is effectively catalyzed by a Lewis base. The base-catalyzed process has been applied to asymmetric synthesis of aldols by using a chiral Lewis base [171]. The chiral phosphoramide **79** is an efficient catalyst realizing high diastereo- and enantioselectivity in the reaction of ketone trichlorosilyl enolates (Scheme 10.66) [96]. In the presence of **79** the (*E*)- and (*Z*)-enolates of ketones have *anti* and *syn* selectivity, respectively. This stereochemical response to the enolate geometry can be rationalized by chair transition structures like **38** (Scheme 10.31). The **79**-catalyzed asymmetric process shows a positive non-linear effect supporting the hypothesis of a transition structure with two molecules of **79** [97]. When either enol or aldehyde partner has a stereogenic center, high diastereoselectivity is observed with one enantiomer of **79** (matched case), while the other enantiomer provides low diastereoselectivity (mismatched case) [99, 172, 173].



Scheme 10.66

Although addition of the trichlorosilyl enolate of methyl acetate to aldehydes is accelerated by a Lewis base catalyst, poor enantioselectivity is observed for the asymmetric version using **79**, because of competition by the uncatalyzed achiral process (Scheme 10.30 in Section 10.2.1.4) [95]. Denmark et al. recently demonstrated that reactive silyl enolates are valuable for asymmetric addition to ketones (Scheme 10.67) [174]. The use of bis-*N*-oxide **80** as catalyst achieves high enantioselectivity in the reaction with aromatic ketones.

Aldehyde trichlorosilyl enolates as well as ketone trichlorosilyl enolates are useful for catalytic, diastereoselective, and enantioselective cross-aldol reactions (Scheme



Scheme 10.67

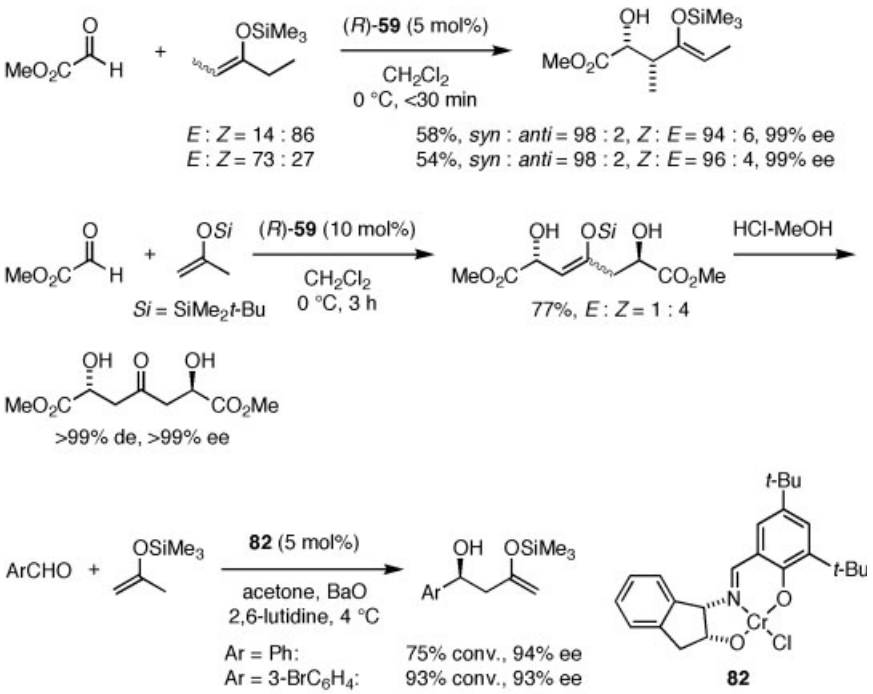
10.67) [175]. The dimeric 1,1′-binaphthyl-2,2′-diamine-derived phosphoramide **81** effectively catalyzes the asymmetric process, occasionally with high stereoselectivity. The adducts, β-hydroxyaldehydes, can be isolated as the stable dimethyl acetals by treatment of the reaction mixture with MeOH.

10.2.3
Carbonyl–Ene Reactions

As described in the sections above, it is well established that reactions of Lewis acid-activated aldehydes and ketones with silyl enolates afford β-hydroxy or β-siloxy carbonyl compounds (Mukaiyama aldol reactions). Occasionally, however, ene-type adducts, that is γ-siloxy homoallyl alcohols, are the main products. The first example of the carbonyl–ene reaction of silyl enolates was reported by Snider et al. in 1983 [176]. They found that the formaldehyde–Me_3Al complex reacted smoothly with ketone TMS enolates to give γ-trimethylsiloxy homoallyl alcohols in good yield. Yamamoto et al. reported a similar reaction of formaldehyde complexed with methylaluminum bis(2,6-diphenylphenoxide) [177]. After these early reports, Kuwajima et al. have demonstrated that the aluminum Lewis acid-promoted system is valuable for the ene reactions of several aldehydes [178] and formaldimine [179] with silyl enolates bearing a bulky silyl group. A stepwise mechanism including nucleophilic addition via an acyclic transition structure has been proposed for the Lewis acid-promoted ene reactions.

A catalytic asymmetric version of the ene reaction of silyl enolates was first reported by Mikami et al. (Scheme 10.68) [180]. They disclosed that the Ti-BINOL

complex (*R*)-**59** catalyzes the ene reaction of glyoxylate esters with high *syn* and *Z* selectivity and excellent enantioselectivity, irrespective of enolate geometry. Interestingly, acetone TBS enolate undergoes the double ene reaction with two molecules of methyl glyoxylate to give the 2:1 adduct in more than 99% de and ee [181]. The Ti complex-catalyzed ene reaction is proposed to proceed through a concerted mechanism including a cyclic chair transition state. Jacobsen et al. recently reported that the tridentate Schiff base–Cr(III) complex **82** is a quite efficient catalyst of the asymmetric ene reaction of acetone TMS enolate with aromatic aldehydes (Scheme 10.68) [182].



Scheme 10.68

10.2.4
Mannich-type Reactions

The original Mannich reaction is the acid-catalyzed aminomethylation of enolizable ketones with non-enolizable aldehydes and ammonia, primary amines, or secondary amines, which involves nucleophilic addition of ketone enols to iminium salts generated in situ from the aldehydes and the nitrogen compounds [183]. This three-component coupling reaction provides a powerful tool for carbon–carbon bond formation and introduction of nitrogen functionality. The classical Mannich reaction has some drawbacks in reaction efficiency, regioselectivity, and appli-

cability, however. To improve the original method, reactions of preformed iminium salts, imines, and aminoacetals with metal enolates, so-called "Mannich-type" reactions, have been studied extensively.

The use of silyl enolates for Mannich-type reactions was first reported by Danishefsky and Ojima in the late nineteen-seventies. Danishefsky et al. found that silyl enolates added smoothly to *N,N*-dimethyl(methylene)iminium iodide, without promoter, to give *β*-dimethylamino ketones after hydrolysis of the initially formed aminomethylated silyl enolates [184]. Ojima et al., on the other hand, introduced the $TiCl_4$-promoted reaction of imines with silyl enolates forming synthetically more valuable secondary Mannich bases [185]. Since this pioneering study much attention has been focused on Lewis acid-promoted Mannich-type reactions of imines and aminoacetals. Current topics in this field are concerned with environmentally more benign methods using water as solvent, rapid and efficient synthesis by three-component coupling of aldehydes, amines, and silyl enolates, and diastereo- and enantioselective reactions using Lewis acid catalysts.

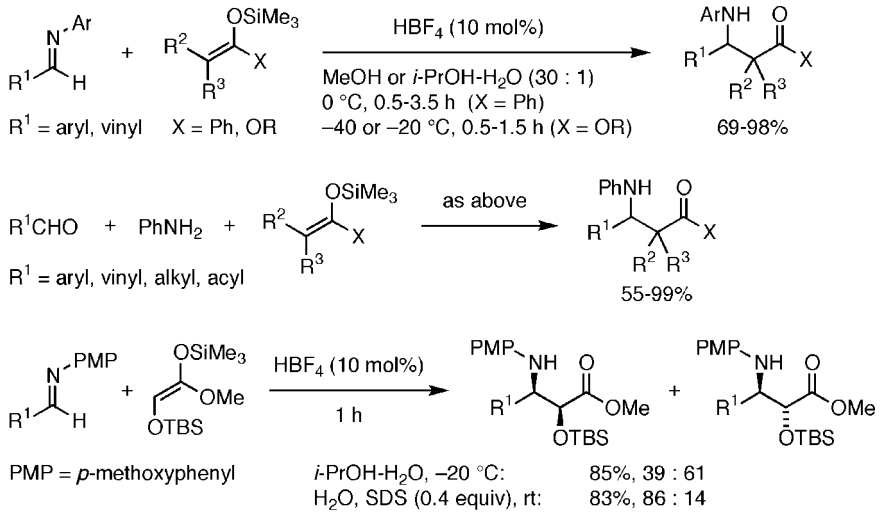
10.2.4.1 Achiral Brønsted and Lewis Acid-promoted Reactions

Studies in the nineteen-eighties revealed that some Mannich-type reactions of imines with silyl enolates can be controlled with high diastereoselectivity, and that use of a chiral auxiliary enables highly enantioselective synthesis of *β*-aminocarbonyl compounds [186]. Some Lewis acids, for example TMSOTf and zinc halides, were also found to be effective in catalytic quantities [187–190] although the original method requires a stoichiometric amount of $TiCl_4$ [185]. In the last decade, further progress has been made by development of new acid catalysts.

Brønsted Acids

Unlike Mukaiyama aldol reactions, Mannich-type reactions with silyl enolates can be effectively catalyzed by a Brønsted acid as well as by a Lewis acid. Akiyama et al. have reported that HBF_4 works as an efficient catalyst of the addition of silyl enolates to *N*-arylimines in aqueous MeOH or *i*-PrOH (Scheme 10.69) [191]. HBF_4 enables the three-component coupling of aldehydes, aniline, and silyl enolates, in which not only aromatic aldehydes but also enolizable aliphatic aldehydes are converted into *β*-amino carbonyl compounds in good to high yield. With a surfactant such as sodium dodecylsulfate (SDS), the HBF_4-catalyzed Mannich-type reaction proceeds efficiently in pure water [192]. An increased amount of HBF_4 also promotes the aqueous reactions effectively even without any surfactant [193]. The observed diastereoselectivity is strongly affected by the solvent system employed [194]. This solvent effect has been used for the stereo-divergent synthesis of *β*-amino-*α*-siloxy esters.

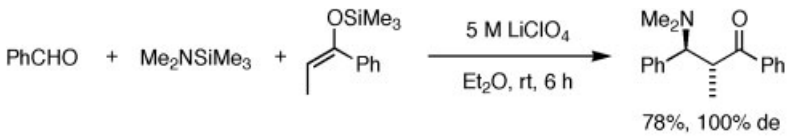
Kobayashi et al. have reported that the three-component Mannich-type reaction of aldehydes, *o*-anisidine, and silyl enolates can be successfully performed by using dodecylbenzenesulfonic acid (10 mol%) as a Brønsted acid-surfactant-combined catalyst (23 °C, 2 h, 63–90% yield) [195].



Scheme 10.69

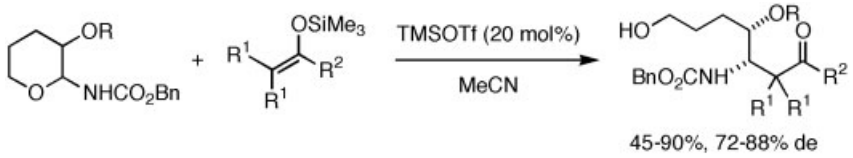
Main-group Element Lewis Acids

An ethereal solution of $LiClO_4$ promotes the three-component coupling of aldehydes, silyl amines, and ketone silyl enolates to give *β*-aminoketones in good yields with high *anti* selectivity (Scheme 10.70) [196]. $B(C_6F_5)_3$ [29b, 197] and trityl salts [198] as well as TMSOTf catalyze the addition of KSA to imines. The catalytic activity of $B(C_6F_5)_3$ is much greater than that of trityl salts and TMSOTf. $InCl_3$ is valuable for the three-component Mannich-type reaction of non-enolizable aldehydes, aryl amines, and silyl enolates in pure water [199].



Scheme 10.70

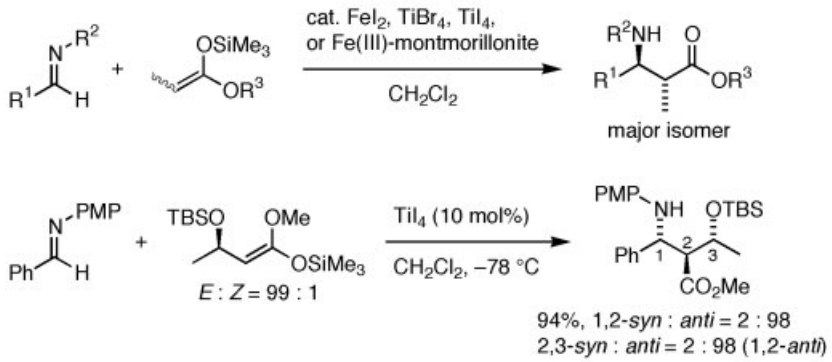
Kobayashi et al. have reported that the TMSOTf-catalyzed ring-opening of benzyl (3-oxytetrahydropyran-2-yl)carbamates with silyl enolates proceeds with high 1,2-*syn* diastereoselectivity (Scheme 10.71) [200]. It has been proposed that the reaction mechanism involves the transient formation of an acyclic iminium ion species as the reactive intermediate. The stereoselective Mannich-type reaction is applicable to the synthesis of piperidine alkaloids.



Scheme 10.71

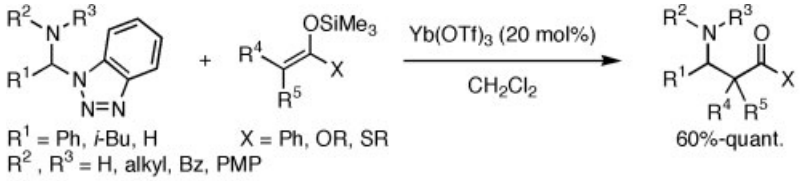
Transition Metal Lewis Acids

Mukaiyama et al. have disclosed that several transition metal salts ($TiCl_4$, FeI_2, ZnI_2, CdI_2, and HgI_2) catalyze the addition of the TMS enolate of methyl propanoate to *N*-benzylideneaniline (Scheme 10.72) [198]. FeI_2, in particular, has high catalytic activity, and the FeI_2-catalyzed system enables *anti*-selective Mannich-type reaction of a variety of imines with propanoate TMS enolates. Titanium halides ($TiBr_4$, TiI_4) [201] and, Fe(III)-exchanged montmorillonite [202] as well as FeI_2 are valuable for the *anti*-selective reaction. The TiI_4-catalyzed reaction with a homochiral silyl enolate proceeds with high diastereoface selectivity.



Scheme 10.72

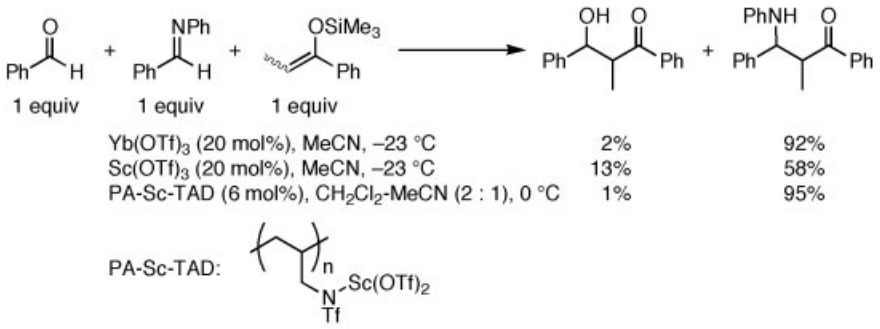
Kobayashi et al. have demonstrated that metal triflates such as $Zr(OTf)_4$, $Hf(OTf)_4$ [203], $Sc(OTf)_3$, and $Yb(OTf)_3$ [204] are efficient catalysts of the addition of silyl enolates to imines in anhydrous CH_2Cl_2 or CH_3CN. With these catalysts the three-component coupling of aldehydes, amines, and silyl enolates can be efficiently achieved in the presence of a dehydrating agent such as $MgSO_4$ or 4-Å MS [205]. The $Sc(OTf)_3$- and $Yb(OTf)_3$-catalyzed systems are applicable to the Mannich-type reactions of *O,N*- and *N,N*-acetals [206]. Thus, the $Yb(OTf)_3$-catalyzed reaction of *N*-(*α*-aminoalkyl)benzotriazoles with silyl enolates proceeds with the loss of benzotriazole to give *β*-amino carbonyl compounds in good to high yield (Scheme 10.73).



Scheme 10.73

The three-component Mannich-type reaction can be successfully performed in water by using $Sc(OTf)_3$, $Yb(OTf)_3$, or $Cu(OTf)_2$ as catalyst and SDS as surfactant [207]. Lewis acid-surfactant-combined catalysts (LASC) such as scandium trisdodecylsulfate ($Sc(O_3SOC_{12}H_{25})_3$) and copper bisdodecylsulfate ($Cu(O_3SOC_{12}H_{25})_2$) also promote the aqueous reaction [73 b]. The $Sc(OTf)_3$- and $Yb(OTf)_3$-catalyzed reactions of imines with silyl enolates proceed smoothly in supercritical CO_2 ($scCO_2$) containing poly(ethylene glycol) (PEG) or its derivatives [208]. PEG in $scCO_2$ would work as surfactant to accelerate the reactions by forming emulsions.

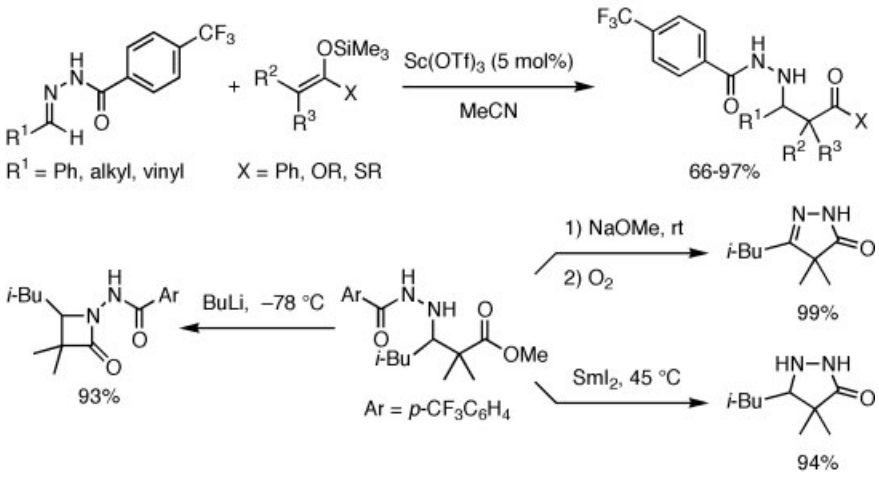
It is well recognized that aldimines are less reactive than aldehydes toward nucleophilic addition. In the presence of a catalytic amount of $Yb(OTf)_3$, however, silyl enolates react with aldimines exclusively to afford *β*-aminocarbonyl compounds in high yield, even when aldehydes are present (Scheme 10.74) [209]. Selective formation of aldimine-$Yb(OTf)_3$ complexes rather than aldehyde-$Yb(OTf)_3$ complexes is attributable to the inverted reactivity. Polyallylscandium trifylamide ditriflate (PA-Sc-TAD), a polymer-supported Sc catalyst, also has high aldimine-selectivity.



Scheme 10.74

Hydrazones are much more stable than imines and are often isolated as stable crystals which can be stored at room temperature. A drawback of using hydrazones as electrophiles is their low reactivity. Kobayashi et al. have found that benzoylhydrazones serve as stable surrogates of unstable imines in $Sc(OTf)_3$-catalyzed Mannich-type reactions (Scheme 10.75) [210]. Benzoylhydrazones derived from aldehydes including functionalized or unstable ones react smoothly with silyl eno-

lates in the presence of a catalytic amount of $Sc(OTf)_3$ to afford β-*N*-benzoylhydrazinocarbonyl compounds, which are readily converted to β-lactams, pyrazolones, and pyrazolidinones.



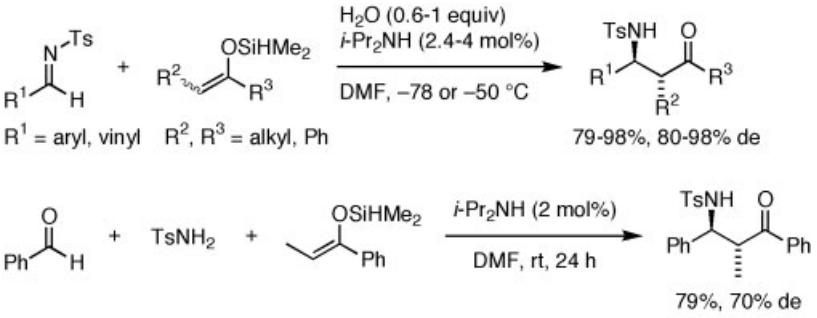
Scheme 10.75

The Sc(III)-catalyzed system has been applied to combinatorial synthesis of nitrogen compounds using polymer-supported reagents and catalysts [211–213]. $Sc(OTf)_3$-catalyzed reactions of polymer-supported benzoylhydrazones and α-iminoesters with silyl enolates are useful for the synthesis of pyrazolone and α-amino acid libraries, respectively [211]. Parallel synthesis of a γ-amino alcohol library can be achieved by the Mannich-type reaction of polymer-supported thioester silyl enolates followed by reductive cleavage with $LiBH_4$ [212]. PA-Sc-TAD (Scheme 10.74) and $Sc(OTf)_3$ microencapsulated with polystyrene (MC $Sc(OTf)_3$) are efficient and readily re-usable catalysts of three-component Mannich-type reactions of aldehydes, amines, and silyl enolates [213]. These reactions, using a polymer-supported Sc catalyst, provide convenient routes, of high quality and with good yields, to many structurally distinct β-aminocarbonyl compounds. Interestingly, in the competing reaction of benzaldehyde and *N*-benzylideneaniline with propiophenone TMS enolate, PA-Sc-TAD has higher aldimine selectivity than $Sc(OTf)_3$ (Scheme 10.74). This fact can be explained by the stability of the aldimine–polymer-supported catalyst complex.

10.2.4.2 **Base-catalyzed Reactions**

We recently reported that the Mannich-type reaction of *N*-sulfonylimines with ketone dimethylsilyl (DMS) enolates proceeds smoothly in the presence of water and a catalytic amount of a base such as diisopropylamine (Scheme 10.76) [214]. The novel base-catalyzed reaction has high *anti* diastereoselectivity irrespective of enolate geometry. In this reaction DMS enolates would be activated by the coop-

erative action of water and the base catalyst. We have also found that *i*-Pr_2NH catalyzes the three-component coupling of aromatic aldehydes, sulfonamides, and DMS enolates to give *β*-aminocarbonyl compounds. The mechanism of the three-component reaction is condensation of the aldehyde and sulfonamide to form an *N*-sulfonylimine and water, and subsequent addition of DMS enolate to the *N*-sulfonylimine, promoted by the in-situ-generated water and *i*-Pr_2NH.



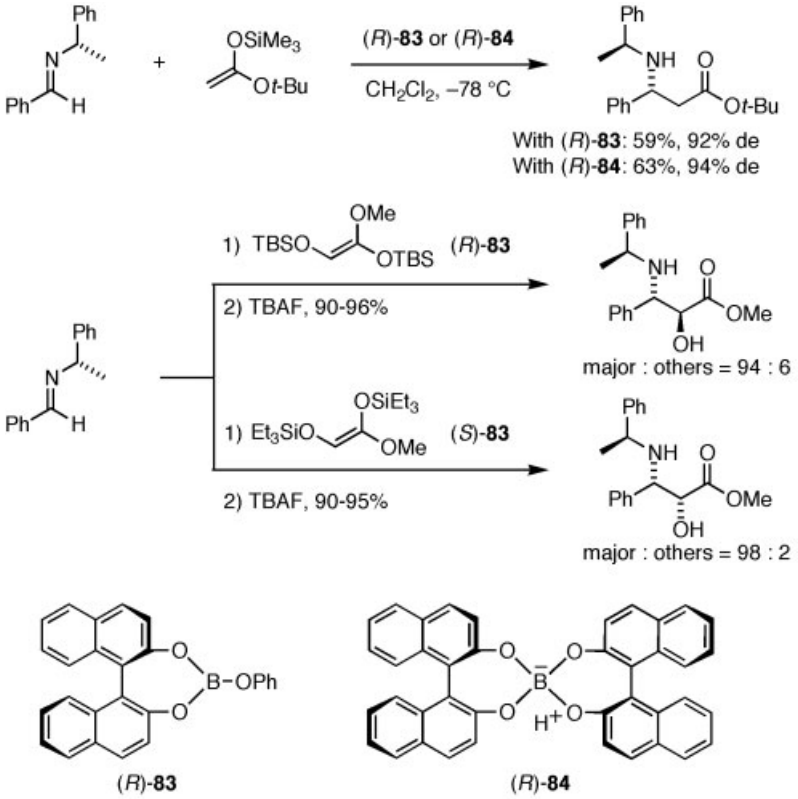
Scheme 10.76

10.2.4.3 **Asymmetric Mannich-type Reactions**

The development of enantioselective Mannich-type reactions is an important subject in synthetic organic chemistry, because these reactions provide optically active nitrogen-containing compounds which are very valuable in syntheses of biologically active products and their derivatives. Until recently, this subject had been solved by use of chiral auxiliaries [215]. In recent years, catalytic asymmetric Mannich-type reactions using chiral Lewis acids have been studied extensively [216]. This section deals with chiral Lewis acid-promoted reactions.

Stoichiometric Use of Chiral Lewis Acids

Yamamoto et al. have disclosed that an equimolar amount of the chiral borane Lewis acid **83** is valuable for highly stereoselective Mannich-type reaction of imines bearing a chiral auxiliary by double stereodifferentiation (Scheme 10.77) [217]. The **83**-promoted reaction of *N*-(1-phenylethyl)imines with KSA achieves more than 90% de with a matched pair of reagents. The relative configuration between newly formed stereogenic centers in the reaction with *α*-substituted KSA can be controlled by the enolate geometry. The synthetic utility of this route to enantiomerically pure *β*-aminoesters has been demonstrated by syntheses of key intermediates leading to biologically active compounds [218]. The Brønsted acid-assisted chiral Lewis acid (BLA) **84** also is effective in double stereodifferentiation using chiral imines [219]; **84** also promotes the Mannich-type reaction of achiral imines such as *N*-benzhydrylimines, with high enantioselectivity.

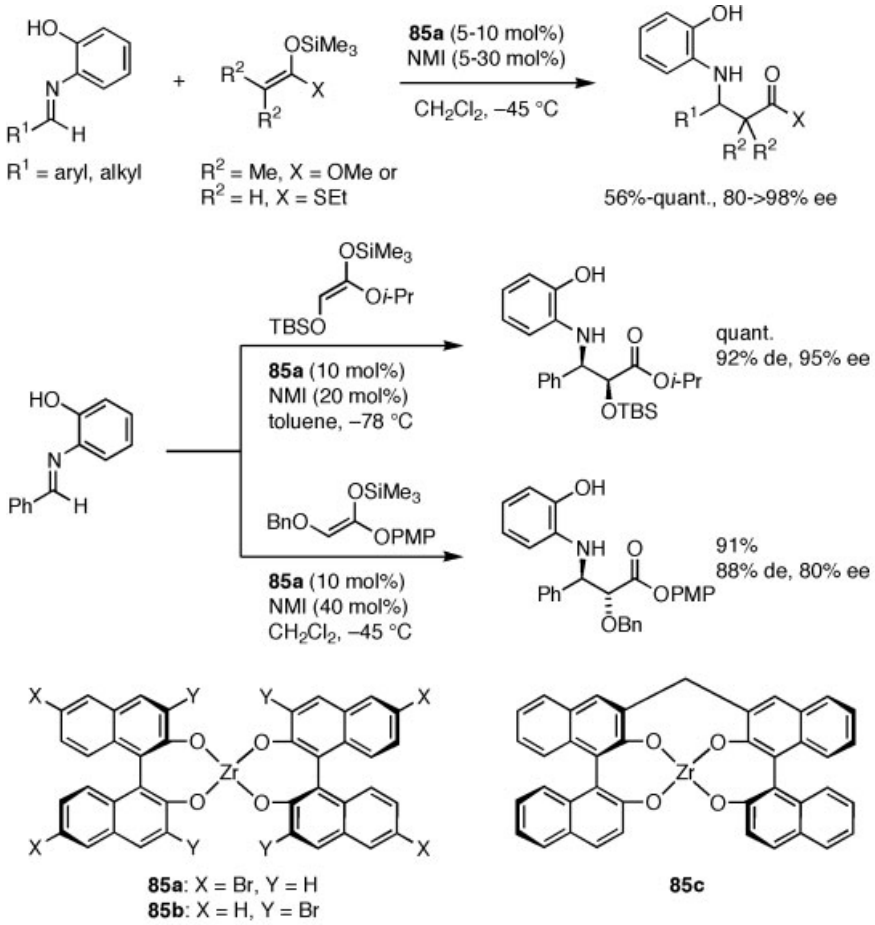


Scheme 10.77

Catalytic Asymmetric Reactions

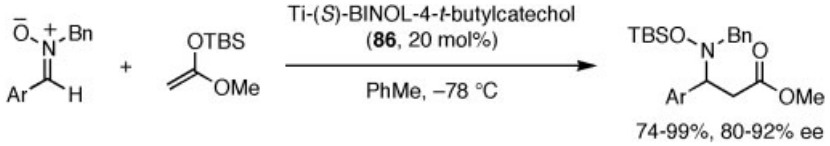
The first truly catalytic enantioselective Mannich-type reaction of aldimines with silyl enolates was reported by Kobayashi et al. in 1997 [220]. They reported that the combined use of chiral zirconium complex **85 a**, prepared from $Zr(Ot\text{-}Bu)_4$ and (*R*)-6,6-dibromo-BINOL, and *N*-methylimidazole (NMI) realizes highly enantioselective addition of silyl enolates to *N*-(2-hydroxyphenyl)aldimines (Scheme 10.78). The 2-hydroxyphenyl group, which would serve for the formation of a rigid imine-**85 a** complex by bidentate chelation, can be readily removed by methylation of the hydroxy group and subsequent oxidation with $Ce(NH_4)_2(NO_3)_6$. The **85 a**-catalyzed system has been successfully used for enantioselective synthesis of both *syn*- and *anti*-*β*-amino alcohols by proper choice of *α*-oxy silyl enolates, as shown in Scheme 10.78 [221]. The **85 a**-catalyzed enantioselective three-component coupling of an *α*-alkoxy aldehyde, 2-amino-*m*-cresol, and a thioester silyl enolate has been used for synthesis of a novel inhibitor of ceramide trafficking, (1*R*,3*R*)-HPA-12 [222]. The chiral zirconium complex **85 c**, bearing a methylene-tethered bis(BINOL) ligand, also works as an efficient asymmetric catalyst of the reaction of *N*-(2-hydroxyphenyl)aldimines

[223]. The use of **85 b** as catalyst is effective in highly enantioselective Mannich-type reaction of benzoylhydrazones [224].



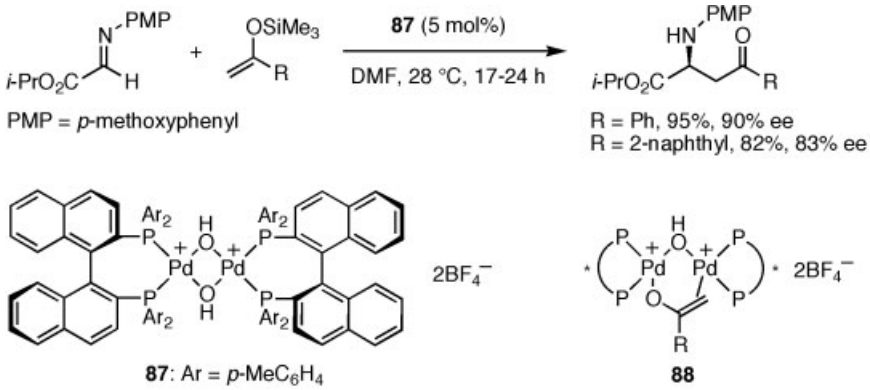
Scheme 10.78

Murahashi et al. have shown that the chiral titanium catalyst **86**, prepared from Ti(O*i*-Pr)$_4$, (*S*)-BINOL, and 4-*t*-butylcatechol, effects high optical yields in the addition of KSA to aromatic nitrones (Scheme 10.79) [225]. The catechol ligand plays a crucial role in achieving the high enantioselectivity. The adducts, *N*-siloxy-*β*-amino esters, are readily converted into the corresponding *β*-amino esters by reduction of the nitrogen–oxygen bond with Zn/H_2SO_4. In this asymmetric reaction a positive non-linear relationship is observed between the enantiomeric purity of **86** and the adduct, indicating that a binaphtholato-bridged dimeric complex seems to be involved as the active species.



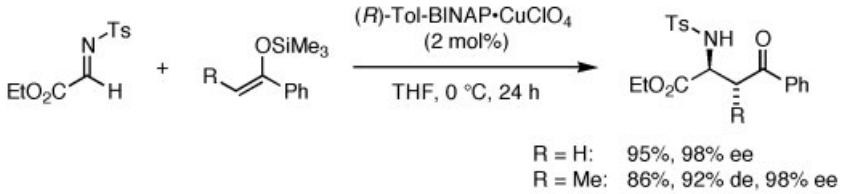
Scheme 10.79

Sodeoka et al. have found that binuclear μ-hydroxo palladium complex **87** is an efficient catalyst of the asymmetric Mannich-type reaction of α-*N*-arylimino esters with SEE (Scheme 10.80) [226]. Mechanistic studies using ^{1}H NMR and electrospray ionization mass spectrometry suggest that a unique binuclear palladium-sandwiched enolate **88** is involved in the palladium-catalyzed reaction.



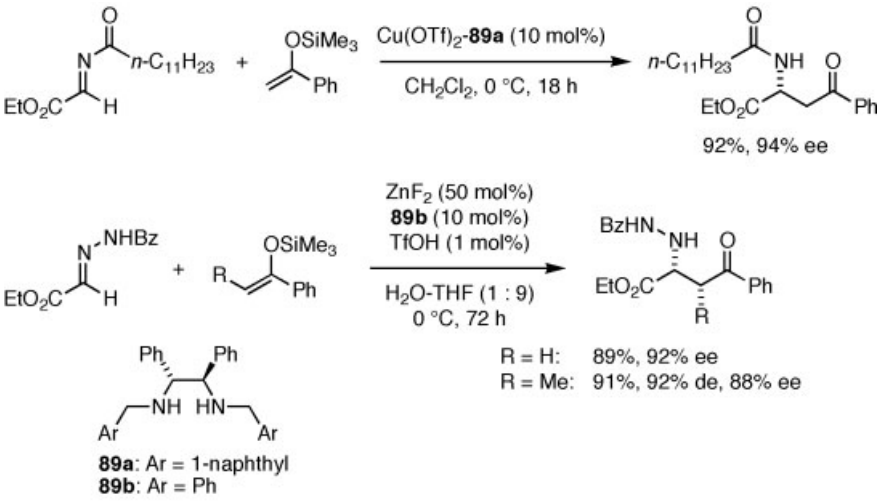
Scheme 10.80

Lectka et al. have reported that Tol-BINAP-coordinated $CuClO_4$ catalyzes the addition of SEE to α-*N*-tosylimino esters with high enantioselectivity (Scheme 10.81) [227]. The use of α-substituted SEE gives *anti* adducts with high diastereoselectivity. The Tol–BINAP complex is superior to the corresponding BINAP complex in diastereo- and enantioselectivity. It has been proposed that this asymmetric Mannich-type reaction proceeds by a Lewis acid-catalyzed mechanism, not a transmetalation mechanism as reported by Sodeoka et al.



Scheme 10.81

Quite recently, chiral diamine ligands have been used by Kobayashi et al. for highly enantioselective Mannich-type reactions [228, 229]. The chiral complex prepared from chiral diamine **89a** and $Cu(OTf)_2$ effects highly enantioselective addition of silyl enolates to *α*-*N*-acylimino esters (Scheme 10.82) [228]. The first example of catalytic asymmetric Mannich-type reaction in aqueous media has been achieved by the combined use of ZnF_2, diamine **89b**, and TfOH in the reaction of *α*-hydrazono esters [229].



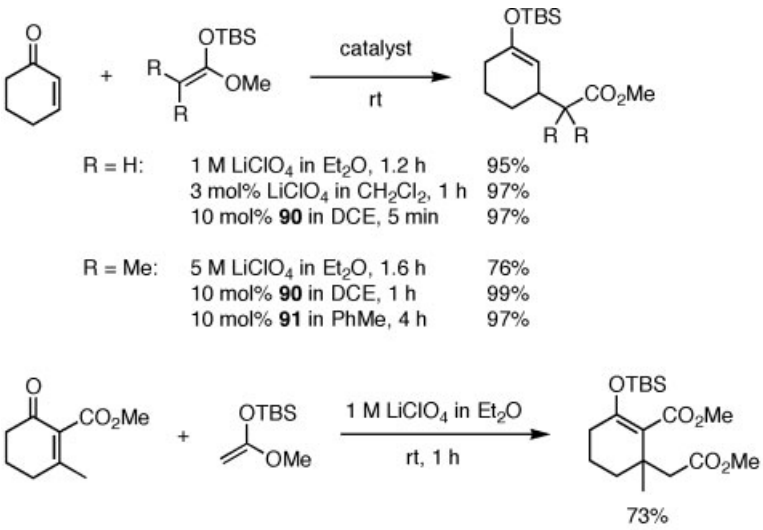
Scheme 10.82

10.2.5
Mukaiyama-Michael Reactions

Similar to the Mukaiyama aldol reaction, conjugate addition of silyl enolates to *α*,*β*-unsaturated carbonyl compounds, denoted the Mukaiyama-Michael reaction, is a highly important carbon–carbon bond-forming process in modern organic synthesis [230, 231]. This reaction variant is an attractive alternative to the conventional metal enolate process, because of the mild reaction conditions and frequently superior regiocontrol (1,2- versus 1,4-addition). The original procedure requires a stoichiometric amount of a Lewis acid such as $TiCl_4$ [230]. After the early studies, however, in the nineteen-eighties Mukaiyama et al. and other research groups developed a variety of efficient reaction systems using a catalytic amount of a Lewis acid [50, 232] or a fluoride ion source [233]. These reaction systems were applied to highly diastereoselective conjugate addition of silyl enolates. In the last decade there has been continuous interest in the development of new catalysts and reaction systems to realize high reaction efficiency and high diastereo- and enantioselectivity.

10.2.5.1 **Achiral Lewis Acid-promoted Reactions**

Grieco et al. have reported that an ethereal solution of $LiClO_4$ effectively promotes conjugate addition of KSA to *α,β*-unsaturated ketones at ambient temperature (Scheme 10.83) [234]. Sterically hindered KSA and enones can be used successfully. Reetz et al., on the other hand, have disclosed that $LiClO_4$ suspended in CH_2Cl_2 works as an efficient catalyst of the conjugate addition [26]. The heterogeneous catalyst is readily recyclable. $LiCo(B_9C_2H_{11})_2$ (**90**) [235] and $LiAl[OCPh(CF_3)_2]_4$ (**91**) [236] are effective catalytic systems. The former lithium salt has high catalytic activity in 1,2-dichloroethane (DCE). The latter lithium salt can catalyze the Michael addition of KSA effectively in toluene, a less hazardous solvent.

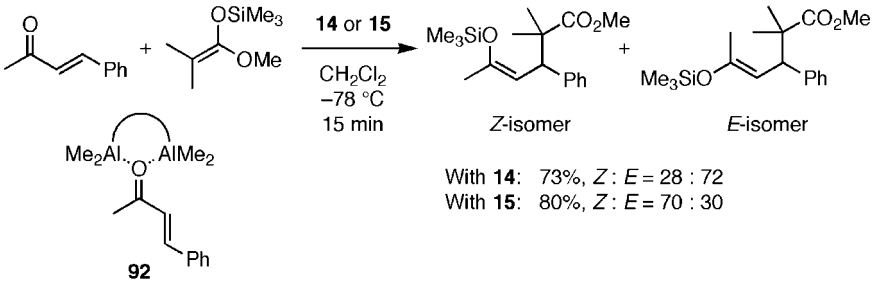


Scheme 10.83

$B(C_6F_5)_3$, an air-stable, water-tolerant Lewis acid catalyst, is applicable to conjugate additions of SEE and KSA to *α,β*-unsaturated ketones as well as aldol and Mannich-type reactions of silyl enolates [29].

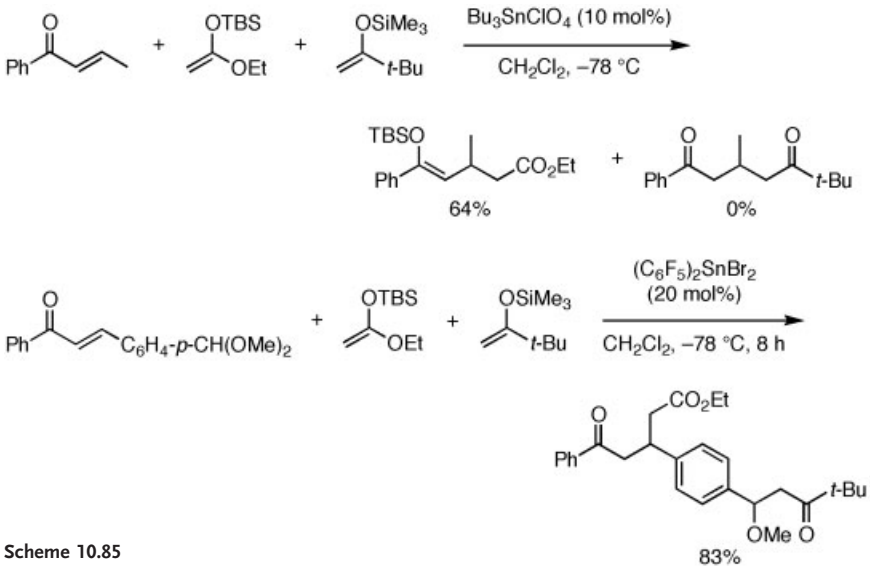
Use of aluminum-based bidentate Lewis acid **14** results in unique stereoselectivity in the Michael addition of KSA (Scheme 10.84) [37]. The **14**-promoted reaction of the KSA derived from methyl isobutyrate with 4-phenyl-3-buten-2-one gives the corresponding *E* adduct selectively, in contrast with the **15**-promoted reaction, which is *Z*-selective. The origin of the inverse selectivity is probably that **14** forces the enone to take the *s-trans* formation **92** by double coordination of the carbonyl oxygen.

Tin-based Lewis acids such as $Bu_2Sn(OTf)_2$ [237], Bu_3SnClO_4 [52c], and $(C_6F_5)_2SnBr_2$ [53, 54a] are efficient catalysts of the Mukaiyama-Michael addition. The last two catalysts are particularly valuable for chemoselective addition of silyl enolates. In the presence of 10 mol% Bu_3SnClO_4, the competitive Michael addi-



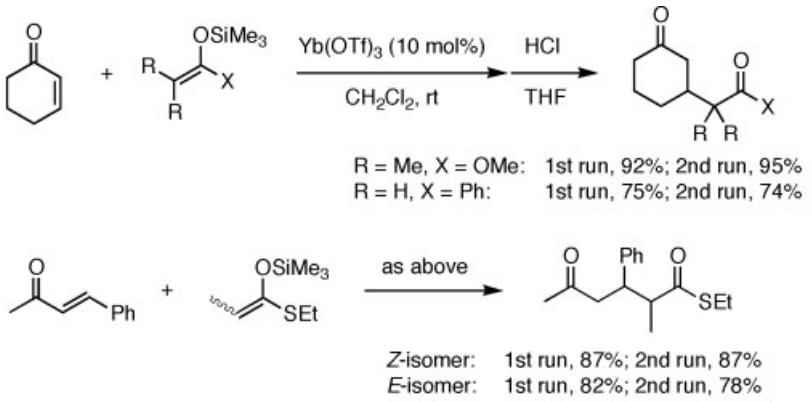
Scheme 10.84

tion of a KSA and a SEE affords the KSA adduct exclusively (Scheme 10.85). Parallel recognition using $(C_6F_5)_2SnBr_2$ realizes highly selective three-component coupling of an enone bearing an acetal moiety, a KSA, and an SEE.



Scheme 10.85

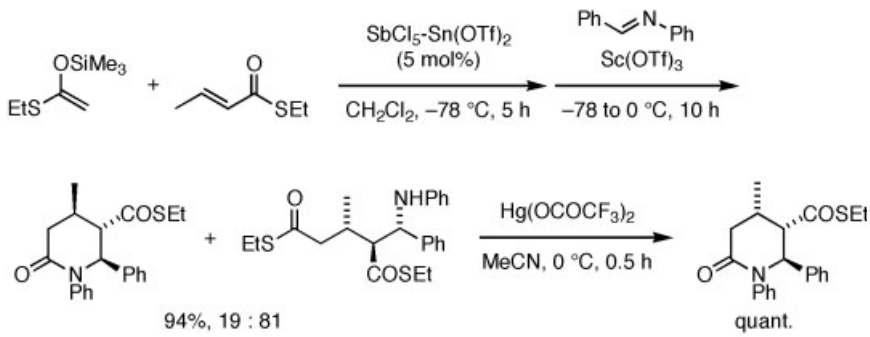
Lanthanide triflates and $Sc(OTf)_3$ effectively catalyze conjugate addition of SEE, KSA, and ketene silyl thioacetals under mild conditions (0 °C to room temperature, 1–10 mol% catalyst) (Scheme 10.86) [69, 238]. After an aqueous work-up these Lewis acids can be recovered almost quantitatively from the aqueous layer and can be re-used without reduction of their catalytic activity. $Eu(fod)_3$ also is effective in not only aldol reactions but also Michael addition of KSA [239]. The $Eu(fod)_3$-catalyzed addition of KSA is highly chemoselective for enones in the presence of ketones.



Scheme 10.86

The $BiCl_3$-ZnI_2 catalyst system also is effective in conjugate addition of SEE at room temperature [57]. [Ir(COD)$(PPh_3)_2$]OTf activated by the hydrogen molecule works as the catalyst under slightly severe conditions (50–70 °C, more than 10 h) [240].

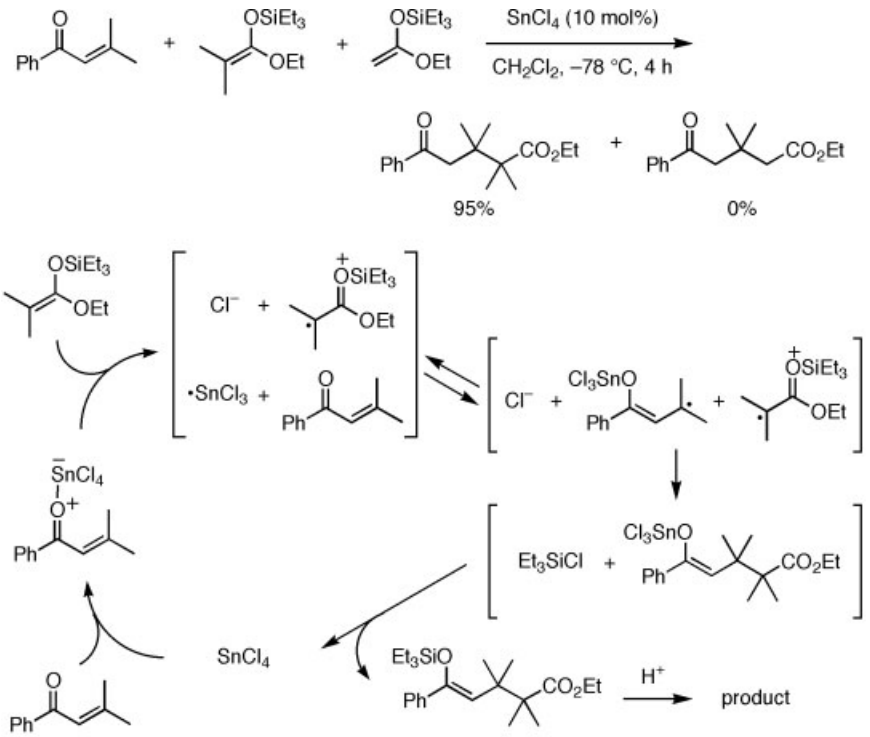
Three-component coupling reaction of α-enones, silyl enolates, and aldehydes by successive Mukaiyama-Michael and aldol reactions is a powerful method for stereoselective construction of highly functionalized molecules valuable as synthetic intermediates of natural compounds [231c]. Kobayashi et al. recently reported the synthesis of γ-acyl-δ-lactams from ketene silyl thioacetals, α,β-unsaturated thioesters, and imines via successive $SbCl_5$-$Sn(OTf)_2$-catalyzed Mukaiyama-Michael and $Sc(OTf)_3$-catalyzed Mannich-type reactions (Scheme 10.87) [241].



Scheme 10.87

Otera et al. have found that KSA bearing more substituents at the reaction site add to β-substituted α-enones much faster than less substituted KSA when the KSA have a relatively small trialkylsilyl or alkoxy group (Scheme 10.88) [242]. On the basis of the experimental results and semi-empirical PM3 MO calculations they have proposed that the Mukaiyama-Michael reaction of KSA is initiated by

electron transfer from KSA to Lewis acids [242c]. The electron-transfer mechanism for the $SnCl_4$-catalyzed reaction is shown in Scheme 10.88.



Scheme 10.88

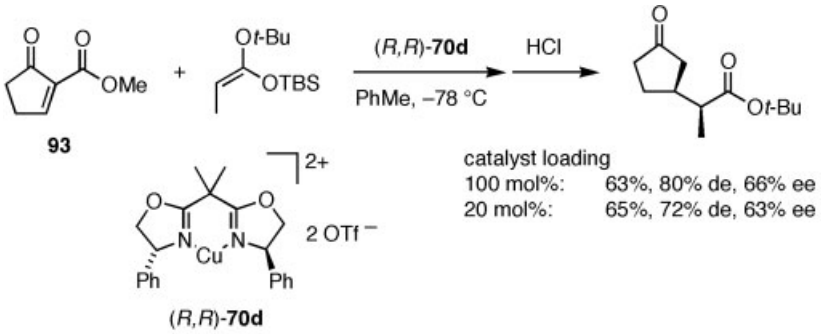
10.2.5.2 **Solvent-promoted Reactions**

When $MeNO_2$ [233a] and DMSO [81] are used as solvents, Michael addition of KSA proceeds smoothly at room temperature without additional catalyst. Coordination of the solvent molecule to the silicon atom would enhance the nucleophilicity of KSA to effect the uncatalyzed reaction.

10.2.5.3 **Asymmetric Michael Reactions**

In 1988, Mukaiyama et al. reported the $Sn(OTf)_2$–**50d**-catalyzed asymmetric Michael reaction of a trimethylsilyl enethiolate, CH_2=C(SMe)$SSiMe_3$ (up to 70% ee) [243]. It was proposed that the catalytic reaction proceeded via an Sn(II) enethiolate. They also demonstrated that a BINOL-derived oxotitanium catalyzes the Michael addition of ketene silyl thioacetals to α-enone with high enantioselectivity (up to 90% ee) [244]. After this pioneering work other research groups developed new reaction systems for enantioselective Mukaiyama-Michael reactions.

Bernardi and Scolastico have reported the use of chiral Ti complexes, prepared in situ from $TiCl_2(Oi\text{-}Pr)_2$ and $\alpha,\alpha,\alpha',\alpha'$-(4*R*, 5*R*)-tetraaryl-1,3-dioxolane-4,5-dimethanol (TADDOLs), for Michael addition of KSA to α-enone **93** [245]. The reaction is only modestly enantioselective (up to 47% ee), however, even with stoichiometric use of the titanium complex. Chiral Cu(II)-box complex (*R,R*)-**70d** has also been used for the same reaction (Scheme 10.89) [246]. The catalyst system is more enantioselective, and a catalytic quantity of **70d** can be used.

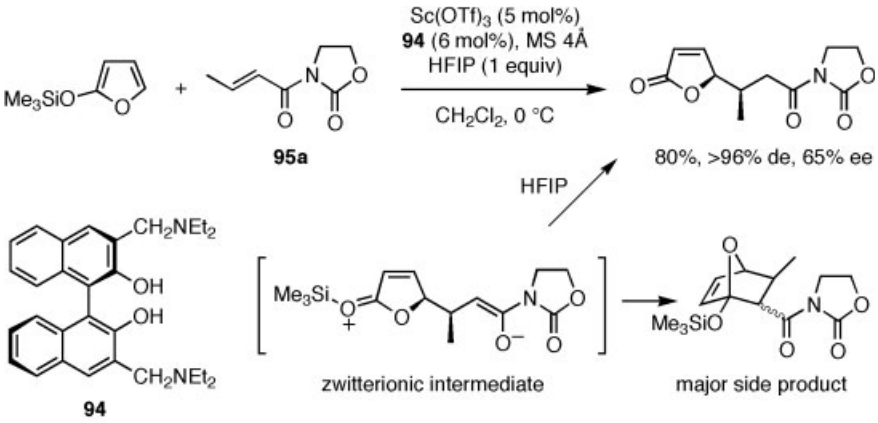


Scheme 10.89

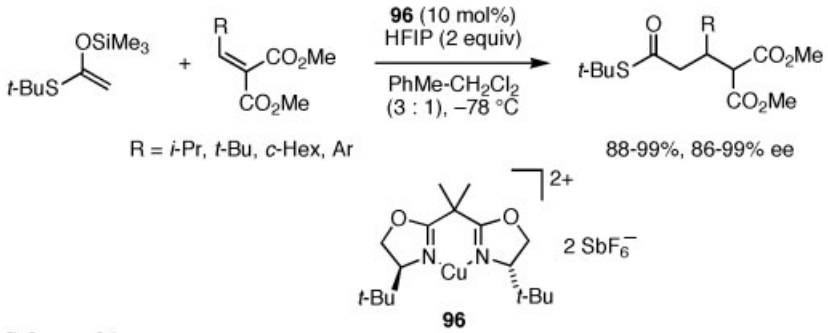
Katsuki et al. have shown that the chiral Sc catalyst prepared from $Sc(OTf)_3$ and the BINOL derivative **94** catalyzes the conjugate addition of 2-(trimethylsiloxy) furan to 3-[(*E*)-2-butenoyl]-1,3-oxazolidin-2-one (**95a**) with high *anti* diastereoselectivity and good enantioselectivity (Scheme 10.90) [247]. The use of hexafluoro-2-propanol ($(CF_3)_2CHOH$, HFIP) is effective in improving the chemical yield of the Michael adduct. It has been proposed that HFIP suppresses the formation of the major side product by quenching the zwitterionic intermediate. In the same reaction chiral Cu(II) complex **70a** can achieve high enantioselectivity but with slightly lower *anti* selectivity (89%, 79% de, 95% ee).

The utility of Cu(II)-box complex **96** for asymmetric Mukaiyama-Michael reaction has been intensively studied by Evans et al. (Scheme 10.91) [248]. In the presence of HFIP the **96**-catalyzed reaction of *S*-*t*-butyl thioacetate TMS enolate with alkylidene malonates provides the Michael adducts in high chemical and optical yield. HFIP plays a crucial role in inducing catalyst turnover. Slow addition of the silyl enolate to a solution of **96**, alkylidene malonates, and HFIP is important in achieving high yields, because the enolate is susceptible to protonolysis with HFIP in the presence of **96**. The glutarate ester products are readily decarboxylated to provide chiral 1,5-dicarbonyl synthons. Quite recently, Sibi et al. reported enantioselective synthesis of β-amino acid derivatives by Cu(II)-box-catalyzed conjugate addition of silyl enolates to aminomethylenemalonates [249].

The catalytic system using **96** is also valuable for highly enantioselective addition to 3-[(*E*)-2-alkenoyl]-1,3-oxazolidin-2-ones **95** (Scheme 10.92) [250]. Addition to **95** proceeds stereospecifically, depending on the geometry of the enolate. On the



Scheme 10.90



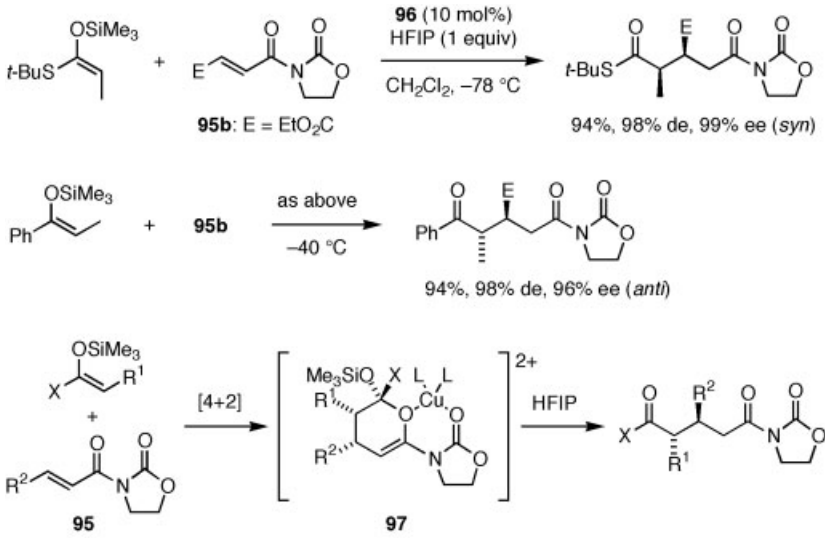
Scheme 10.91

basis of the stereochemical outcome and monitoring by in-situ IR spectroscopy the reaction mechanism proposed involves formation of dihydropyrans **97** by a hetero Diels-Alder reaction and the subsequent protonolysis by HFIP.

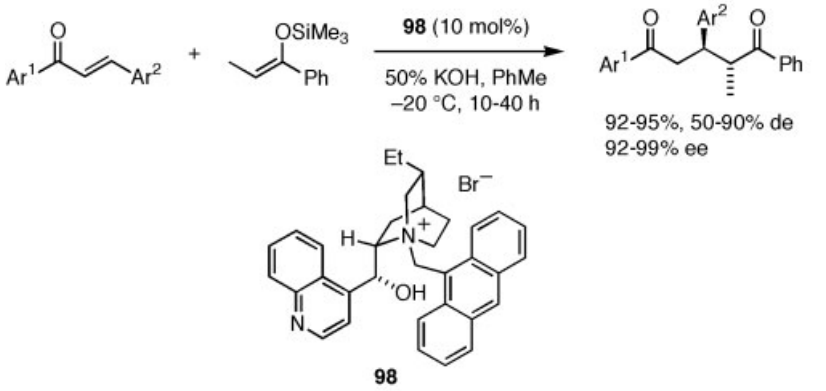
Base-catalyzed conjugate addition of silyl enolates also has been extended to the asymmetric version. Corey et al. have disclosed that chiral quaternary ammonium salt **98** is an effective catalyst of diastereo- and enantioselective Michael addition of SEE to chalcones under toluene/50% aqueous KOH biphasic conditions (Scheme 10.93) [251].

10.2.6
Alkylation and Allylation of Silyl Enolates

Alkylation of silyl enolates with primary and secondary alkyl electrophiles can be performed by generation of active enolates with MeLi [86] and fluoride ion sources [19c, 252]. These S_N2 type reactions are not suitable for alkylation with tertiary alkyl



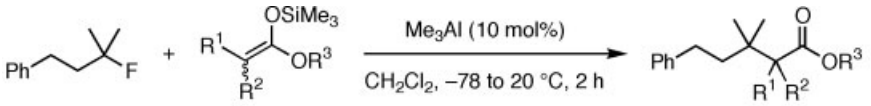
Scheme 10.92



Scheme 10.93

electrophiles, because base-promoted elimination is likely. In contrast, the Lewis acid-promoted reactions, which involve initial activation of the electrophiles, like S_N1 reactions, are quite valuable for introduction of tertiary alkyl groups [253, 254].

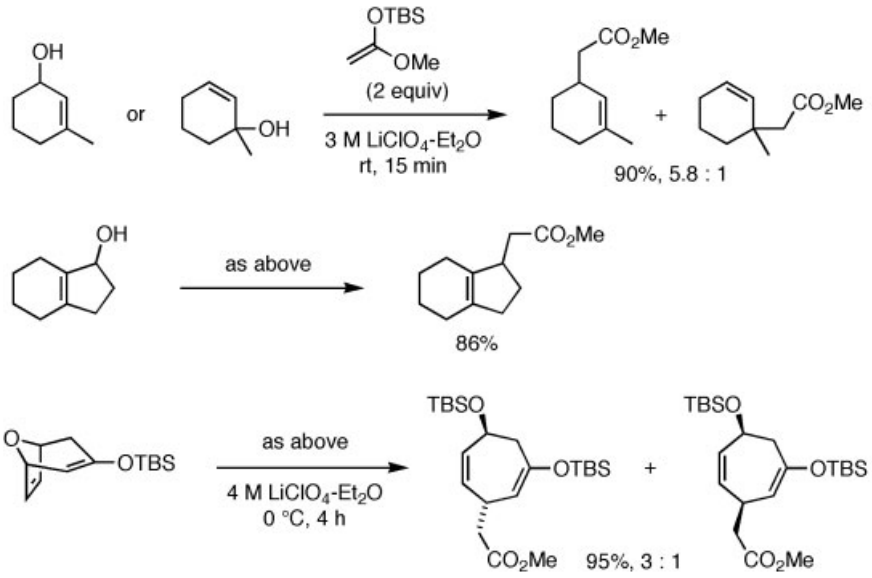
Alkyl fluorides are relatively stable and have been rarely used as alkylation agents in alkylation chemistry compared with other alkyl halides. Maruoka et al., however, found that Me_3Al efficiently catalyzes the alkylation of KSA with tertiary alkyl fluorides (Scheme 10.94) [255]. Under the same conditions alkylation with the corresponding chloride does not proceed. The strong activation of tertiary alkyl fluorides by Me_3Al originates from the exceedingly high affinity of aluminum for the fluorine atom (Section 10.2.1.1).



$R^1 = R^2 = R^3 = Me$: 63%
$R^1 = H, R^2 = R^3 = Me$: 74%
$R^1 = R^2 = H, R^3 = Ph$: 63%

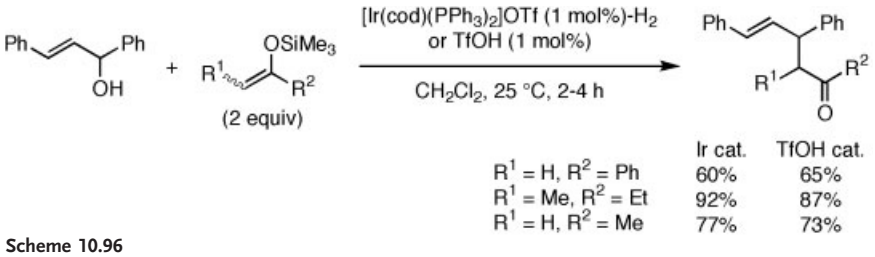
Scheme 10.94

A concentrated solution of $LiClO_4$ in Et_2O effectively induces allylation of silyl enolates with allyl alcohols [256] and acetates [257]. The reactions of 3-methyl-2-cyclohexen-1-ol and its regioisomeric alcohol with methyl acetate TBS enolate give similar results in terms of yield and regioselectivity, which is indicative of an allylic carbocation intermediate (Scheme 10.95). Ring-opening of 8-oxabicyclo[3.2.1]octa-2,6-dienes at the bridgehead has recently been achieved by means of the $LiClO_4$-promoted reaction [258]. This method provides a convenient route to highly functionalized 1,4-cycloheptadienes that can be further manipulated for use in natural-product synthesis.



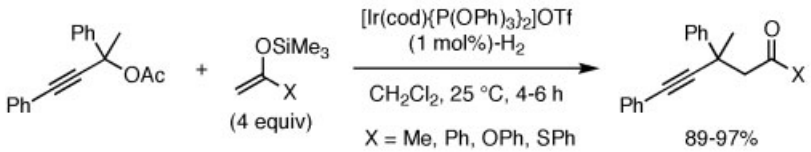
Scheme 10.95

Matsuda et al. have reported that $[Ir(cod)(PPh_3)_2]OTf$ activated by H_2 is an effective catalyst of allylation of SEE with allyl alcohols (Scheme 10.96) [259]. TfOH also has comparable catalytic activity in the allylation. This implies that the Ir complex might work as a source of TfOH.



Scheme 10.96

Although the Nicholas reaction is a reliable method for propargylation of silyl enolates, it requires a stoichiometric amount of alkyne–$Co_2(CO)_6$ complexes [260]. Recently, Matsuda et al. successfully used the Ir-catalyzed system for highly regioselective propargylation of silyl enolates with propargyl acetates (Scheme 10.97) [261].

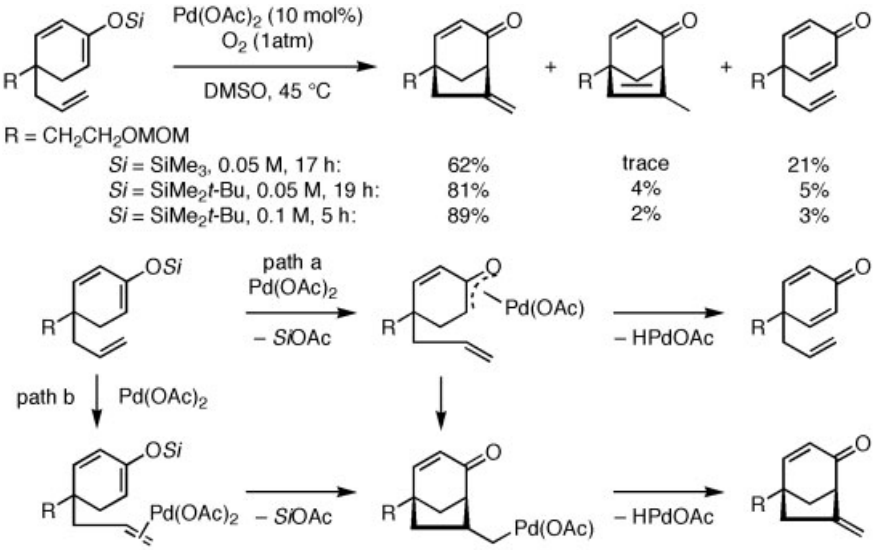


Scheme 10.97

10.2.7
Vinylation and Arylation of Silyl Enolates

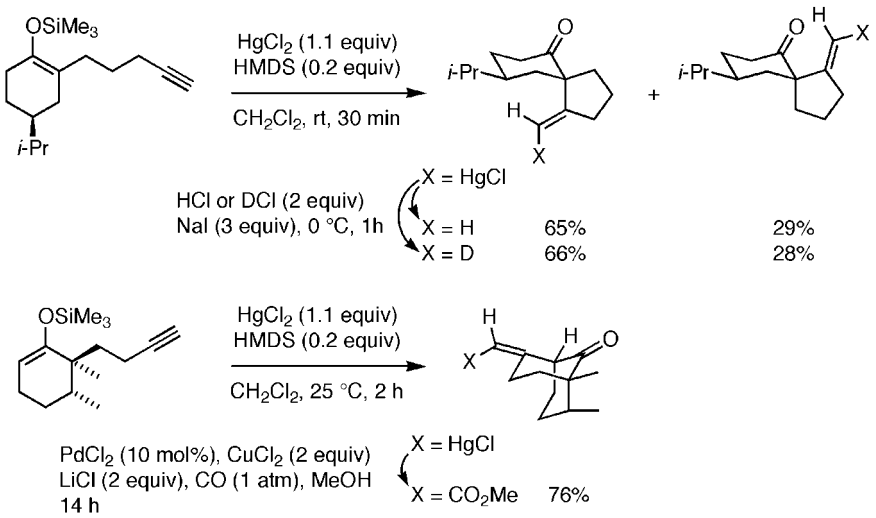
In 1979 Ito and Saegusa discovered that SEE bearing an ω-vinyl group provide β,γ-unsaturated cyclic ketones in the presence of a stoichiometric amount of Pd(II) salts [262]. This cyclization is quite useful for the synthesis of biologically active natural compounds. Toyota and Ihara recently developed the catalytic version of the cycloalkenylation using molecular oxygen as reoxidant and applied it to the construction of bicyclo[3.2.1]octane frameworks in natural product synthesis (Scheme 10.98) [263, 264]. When a small silyl group, for example TMS, is employed the proposed reaction mechanism involves a palladium enolate intermediate (path a), whereas cyclization of the TBS enolates would proceed by nucleophilic addition of the enolate terminus to the remote Pd-coordinated alkene (path b).

Metal-mediated additions of silyl enolates to alkynes also are valuable for intra- and intermolecular vinylation of ketones. The Hg(II)-induced cyclization of alkynyl-branched SEE provides regio- and stereochemically homogeneous exocyclic vinyl mercurial products that can be converted into a variety of functionalized alkenes [265–267]. Two plausible mechanisms for the intramolecular carbomercuration have been proposed, as in the above Pd(II)-mediated cycloalkenylation–nucleophilic enolate addition to the Hg(II)-activated alkyne and concerted addition of an α-keto mercurial species generated by Si-Hg transmetalation. Forsyth et al. have determined that carbomercuration occurs in an *anti* fashion by the former



Scheme 10.98

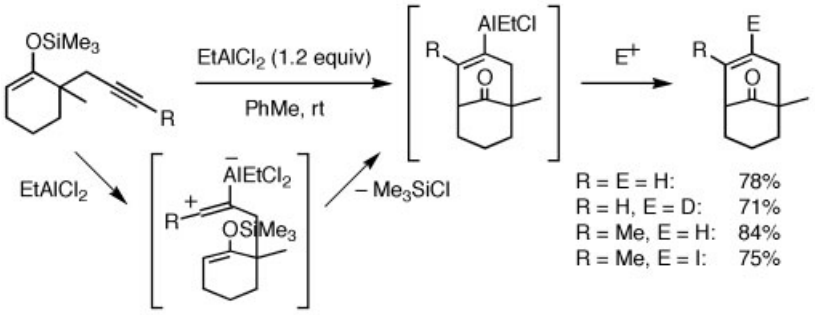
mechanism (Scheme 10.99) [266], which stands in marked contrast to the latter *syn* addition mechanism proposed by Drouin and Conia [265].



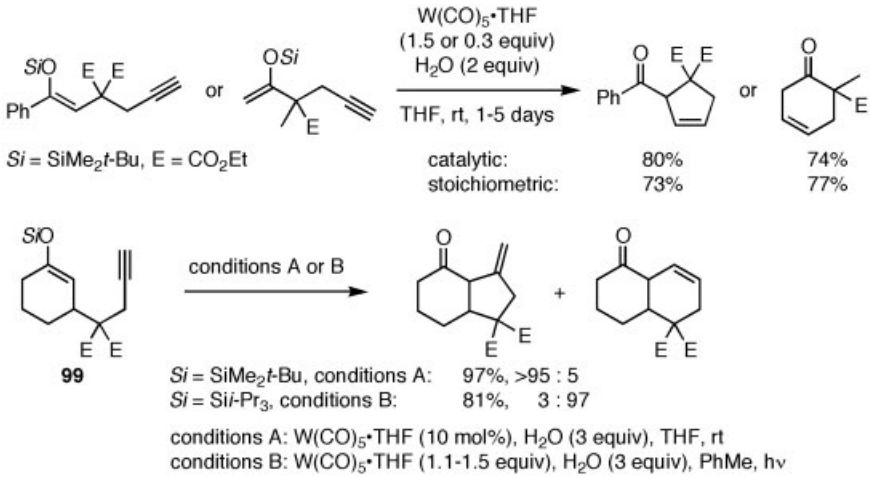
Scheme 10.99

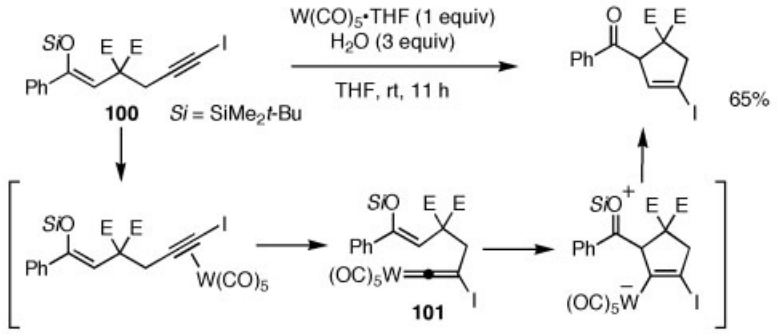
Yamamoto et al. have reported that the $EtAlCl_2$-promoted intramolecular addition of SEE to both terminal and internal unactivated alkynes proceeds in an *endo* fashion to give 3-cyclohexen-1-ones in good yields (Scheme 10.100) [268]. Quench-

ing the reaction mixtures with D_2O and I_2 introduces D and I at the 4-position. This, and the *endo*-selective cyclization, suggest the mechanism via nucleophilic addition of the enolate to a zwitterionic intermediate generated from the alkyne moiety and $EtAlCl_2$.



Scheme 10.100

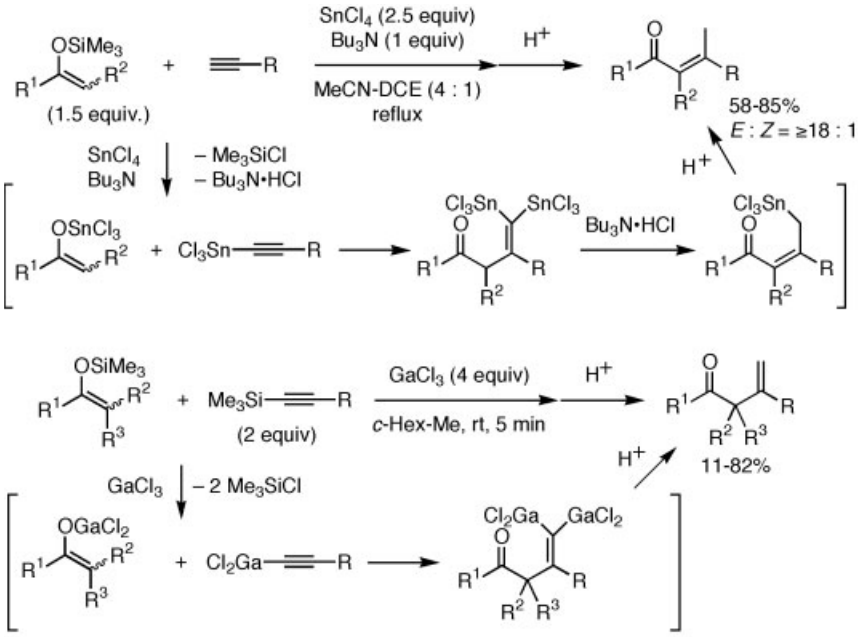




Scheme 10.101

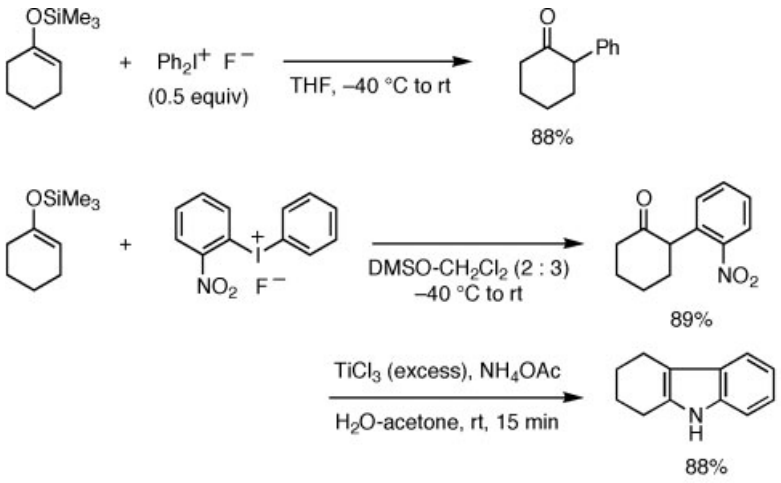
Iwasawa et al. have demonstrated that the *endo*-selective cycloalkenylation of ω-acetylenic SEE is successfully achieved by stoichiometric or catalytic use of $W(CO)_5 \cdot THF$ (Scheme 10.101) [269]. In the reaction of SEE **99** the mode of cyclization (*endo* or *exo*) can be controlled by appropriate choice of the silyl group, the amount of $W(CO)_5$, and the solvent. The $W(CO)_5$-promoted cyclization would proceed by nucleophilic addition of the enolate to a $W(CO)_5$-coordinated alkyne and/or a vinylidene $W(CO)_5$-complex. Quite recently, the cyclization of ω-iodoacetylenic SEE such as **100** has been found to afford the iodine-migrated products in good yields [270]. This observation indicates the presence of the vinylidene complex intermediate **101**.

Intermolecular additions of silyl enolates to alkynes were introduced by Yamaguchi et al. (Scheme 10.102) [271]. In the presence of $SnCl_4$ and Bu_3N reaction of SEE with terminal alkynes gives α,β-unsaturated ketones with high *E* selectivity. The proposed mechanism involves the carbometalation of an alkynylstannane with an α-stannylketone, protonation of the resultant *gem*-bisstannylated intermediate, and double bond shift to an allylmetal species. In contrast, the $GaCl_3$-mediated addition of SEE to trimethylsilylethyne forms β,γ-unsaturated ketones, vinylation products, without isomerization to α,β-unsaturated ketones [272]. A similar mechanism via a *gem*-bismetalated intermediate formed by carbometalation has been postulated for the $GaCl_3$-mediated vinylation.



Scheme 10.102

The Pd-catalyzed arylation of SEE with aryl bromides was introduced by Kuwajima and co-workers in 1982 [273]. Koser et al. have developed a novel arylation of SEE using diaryliodonium fluoride (Scheme 10.103) [274]. This method of arylation has been used for the regiocontrolled synthesis of carbocycle-fused indoles [275].



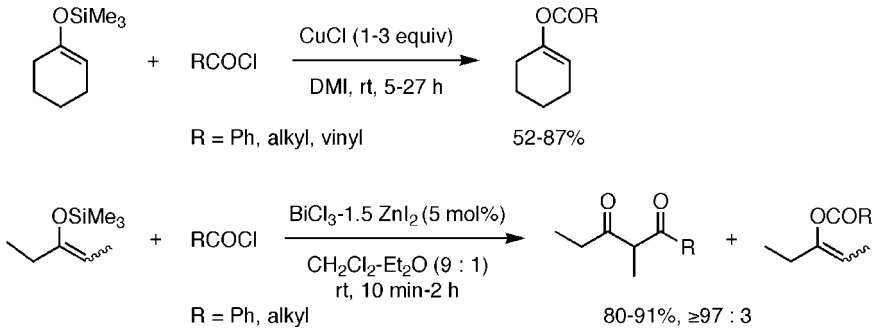
Scheme 10.103

10.2.8
Acylation of Silyl Enolates

The reaction of silyl enolates with acyl cation equivalents leads to the *C*-acylated products and/or the *O*-acylated products [276]. Acylation of SEE with some reactive acylating agents proceeds without a promoter. Catalytic acylation of SEE using $HgCl_2$ [277] and TASF [278] is useful for *O*-acylation, whereas *C*-acylation leading to 1,3-diketones can be realized by use of a stoichiometric amount of $ZnCl_2$ and $SbCl_3$ [279]. Recent studies have revealed the utility of CuCl [280] and $BiCl_3$ [281] for these transformations (Scheme 10.104). We have reported that the CuCl-promoted acylation of SEE with acyl chloride proceeds smoothly to give the *O*-acylation products in good yields [280]. Le Roux and Dubac, on the other hand, have found that the combined use of $BiCl_3$ and a metal iodide such as ZnI_2 or NaI is valuable for the catalytic *C*-acylation of SEE [281].

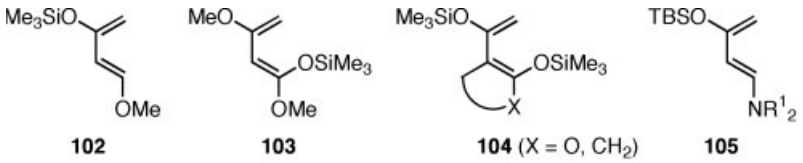
10.2.9
Diels-Alder Reactions of Siloxy-substituted 1,3-Diene

The Diels-Alder (DA) reaction is probably the most powerful means of stereocontrolled synthesis of complex molecules. In a single step it produces six-membered carbocycles and heterocycles with up to four stereocenters. Since it was reported



Scheme 10.104

by Diels and Alder, the synthetic potential of the DA reaction has been greatly expanded by modification of the diene and dienophile counterparts. The initial observation that introduction of lone-pair-containing heteroatoms into the diene structure leads to an increase in the rate and regioselectivity of the cycloadditions induced the use of siloxydienes as reactive and functionalized dienes readily accessible from *α,β*-unsaturated carbonyl compounds [282]. The development of siloxydienes **102** (Danishefsky's diene) [283, 284] and **103** (Brassard's diene) [285] significantly enhanced the utility of the DA reaction, because these dienes are highly reactive with a range of dienophiles, including heterodienophiles, and their cycloadditions provide versatile synthetic intermediates leading to enones and to aromatic and heterocyclic compounds (Scheme 10.105) [286, 287]. Recent studies on new types of siloxy-substituted 1,3-diene have revealed the reactivity and synthetic utility of inner-outer-ring 1,3-bissiloxy-1,3-dienes **104** and 1-amino-3-siloxy-1,3-dienes **105**.



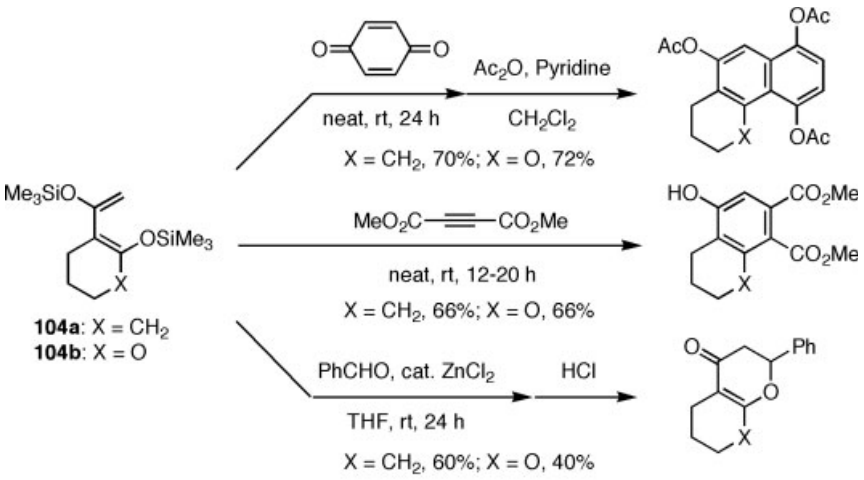
102 **103** **104** (X = O, CH_2) **105**

Scheme 10.105

The use of Lewis acids also has made a great contribution towards expanding the synthetic potential of the DA reaction. In the last decade several Lewis acids have been applied to cycloadditions of siloxydienes to dienophiles, particularly to heterodienophiles, for high reaction efficiency and high levels of regio- and stereocontrol. The progress of catalytic enantioselective hetero-Diels-Alder (HDA) reactions of siloxydienes using chiral Lewis acids is currently an attractive topic in asymmetric organic synthesis [288].

10.2.9.1 **New Types of Siloxy-substituted 1,3-Diene**

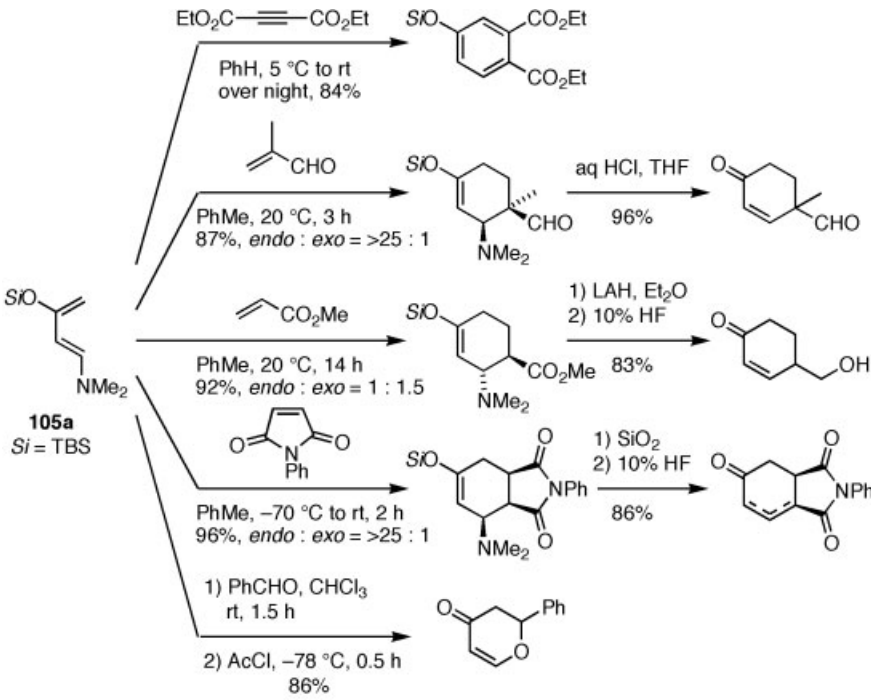
Inner-outer-ring dienes **104** are particularly useful for the synthesis of polycyclic structures, because they enable the incorporation of additional rings into the six-membered ring formed by the DA reaction (Scheme 10.106) [289]. Highly electron-deficient alkenes and alkynes react smoothly with **104** at room temperature. Benzaldehyde and *N*-benzylideneaniline can also be used as dienophiles in the presence of a catalytic amount of $ZnCl_2$. Overall, the Diels-Alder reactivity of **104** is comparable with that of **102**.



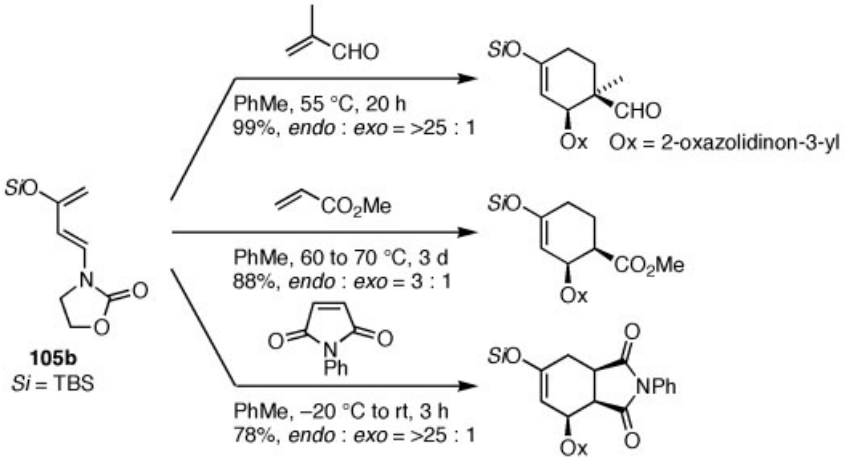
Scheme 10.106

Rawal et al. have reported that under mild reaction conditions 1-amino-3-siloxy-1,3-butadiene **105a** adds smoothly to a variety of dienophiles, for example electron-deficient alkynes and alkenes [290], aldehydes, aldimines [291], and ketones [292], with complete regiocontrol and, occasionally, high *endo* selectivity (Scheme 10.107). These cycloadducts, except for alkyne adducts susceptible to aromatization, can be easily converted into conjugated enones by deaminosilylation. A competitive reaction of **105a** and **102** with methacrolein shows that **105a** is over 25 times more reactive than **102**.

Oxazolidinone-substituted siloxydiene **105b** also is applicable in DA reactions with electron-deficient alkenes under slightly vigorous conditions (Scheme 10.108) [293]. The reduced reactivity of **105b** is a natural consequence of having an electron-withdrawing group on the nitrogen. Interestingly, **105b** has been found to be somewhat more reactive than **102**.



Scheme 10.107

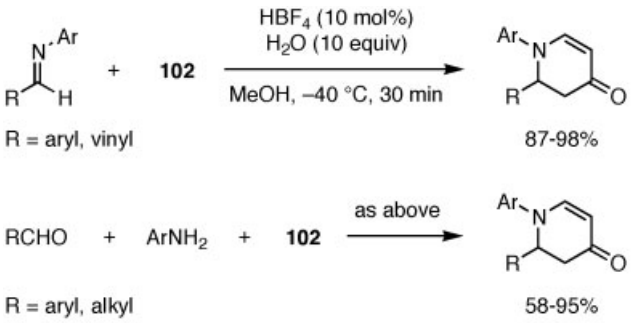


Scheme 10.108

10.2.9.2 Achiral Brønsted and Lewis Acid-promoted Reactions

In the nineteen-eighties stoichiometric amounts of conventional Lewis acids such as $TiCl_4$, $AlCl_3$, $SnCl_4$, $BF_3 \cdot OEt_2$, $MgBr_2$ and $ZnCl_2$ were frequently used for HDA reactions of siloxy-substituted dienes with heterodienophiles [286, 287]. Danishefsky et al., however, found that a lanthanide shift reagent such as $Eu(fod)_3$ can promote the cycloaddition catalytically [294]. Several Brønsted and Lewis acids have recently been shown to have high catalytic activity in the DA reaction of siloxy-substituted dienes in non-aqueous or aqueous media, and elaboration of Lewis acids has achieved unique chemo- and regioselectivity.

Akiyama et al. have reported that the cycloaddition of **102** to imines is effectively accelerated by 10 mol% of a Brønsted acid such as HBF_4 in aqueous media, affording dihydro-4-pyridones in good to high yield (Scheme 10.109) [295]. This catalytic system is applicable to three-component synthesis of dihydro-4-pyridones from aldehydes, anilines, and **102**. The three-component coupling can be achieved efficiently in water without any organic solvent by using SDS as surfactant.

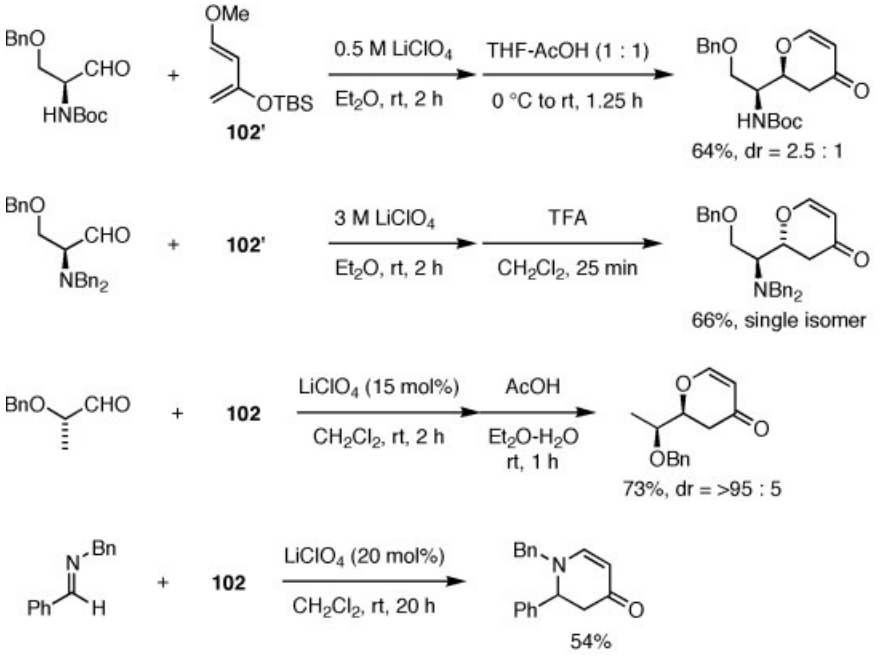


Scheme 10.109

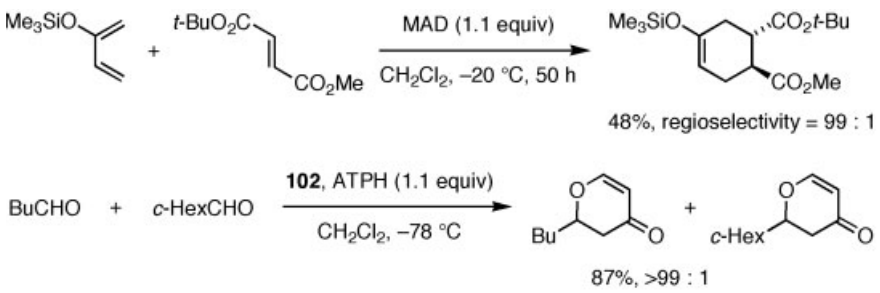
Grieco et al. have demonstrated that an ethereal solution of $LiClO_4$ is useful for the diastereoselective HDA reaction of Danishefsky's diene **102′** with *α*-amino aldehydes by chelation and non-chelation control (Scheme 10.110) [296]. According to a report by Reetz et al., a catalytic amount of $LiClO_4$ suspended in CH_2Cl_2 efficiently promotes similar reactions with aldehydes and imines [297].

MAD, an exceptionally bulky Lewis acid developed by Yamamoto et al. (Scheme 10.11), enables highly regioselective DA reaction of 2-trimethylsiloxy-1,3-butadiene with *t*-butyl methyl fumarate by selective activation of the less bulky ester group (Scheme 10.111) [298]. The discriminating ability of ATPH (Scheme 10.8) for less hindered aldehydes is applicable to the chemoselective HDA reaction of pentanal in the presence of cyclohexanecarbaldehyde [36].

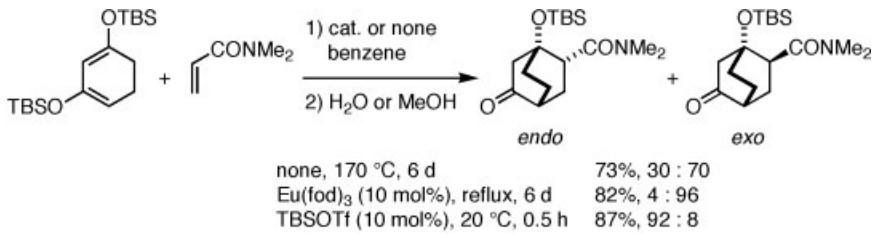
Silicon-based Lewis acids are also used to activate dienophiles [299–303]. TBSOTf effectively catalyzes the *endo*-selective cycloaddition of a 1,3-bissiloxy-1,3-diene with an acrylamide, whereas non-catalyzed thermal reaction or $Eu(fod)_3$-catalyzed reaction is *exo*-selective (Scheme 10.112) [299]. In the cycloaddition to methyl acrylate the catalytic activity of $TMSNTf_2$ is much higher than that of TMSOTf [301]. Silyl triflates are useful for the HDA reaction with imines catalytically or stoichiometrically [302, 303].



Scheme 10.110

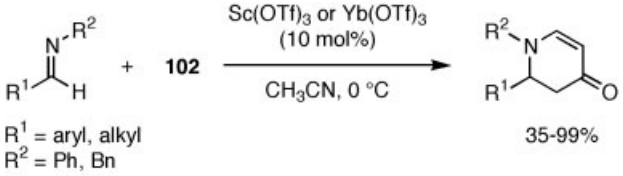


Scheme 10.111



Scheme 10.112

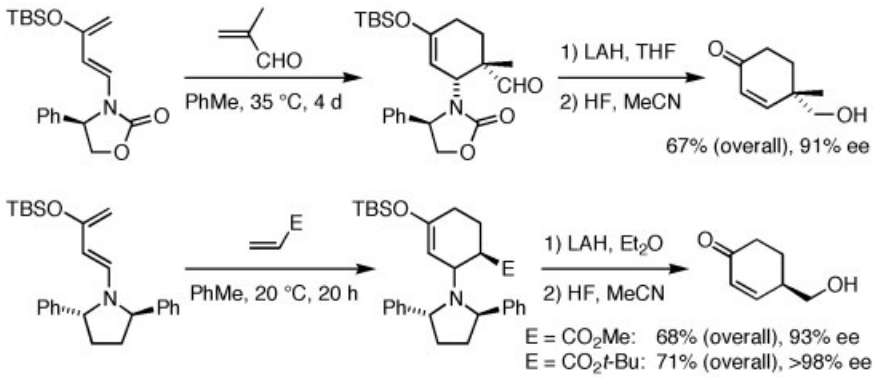
$Sc(OTf)_3$ and $Yb(OTf)_3$ are quite valuable catalysts of the aza-DA reaction of **102** [204] (Scheme 10.113). With these catalysts, three-component coupling of aldehydes, anilines, and **102** proceeds smoothly [304]. $Sc(OSO_2C_8F_{17})_3$ enables an efficient aza-DA reaction in supercritical CO_2 [305]. Cationic lanthanide complexes, $[(C_5Me_5)_2Ce][BPh_4]$ and the corresponding Sm and La complexes, have high catalytic activity in the HDA reaction of **102** with aromatic aldehydes [306].



Scheme 10.113

10.2.9.3 **Asymmetric Reactions using Chiral Auxiliaries**

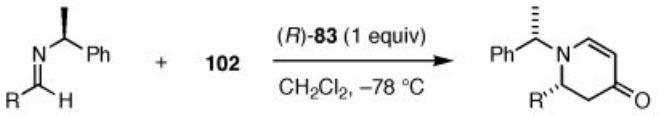
In the nineteen-eighties Danishefsky [307] and Stoodley [308] reported asymmetric DA reactions of 3-siloxy-1,3-butadienes bearing a chiral alkoxy group at the 1-position. Recently, Rawal et al. described similar reactions using an oxazolidinone or 2,5-diphenylpyrrolidine as a chiral auxiliary and their applications to the asymmetric synthesis of 2-cyclohexen-1-ones (Scheme 10.114) [309].



Scheme 10.114

Asymmetric aza-DA reactions using chiral imines derived from α-amino esters and carbohydrates were extensively studied by Waldmann [310] and Kunz [311], respectively, at the end of the nineteen-eighties. After these significant works Yamamoto et al. reported the utility of homochiral *N*-(1-phenylethyl)imines in asymmetric cycloaddition [219, 312]. In the presence of a stoichiometric amount of chiral boron mediators **83** and **84**, the cycloaddition of Danishefsky's diene **102** to these imines realizes almost complete diastereocontrol in the matched cases (Scheme 10.115), although

the reaction with achiral *N*-benzylimines proceeds with good enantioselectivity (74–85% ee) [313].



R = aryl, alkyl

31-63%, 90-98% de

Scheme 10.115

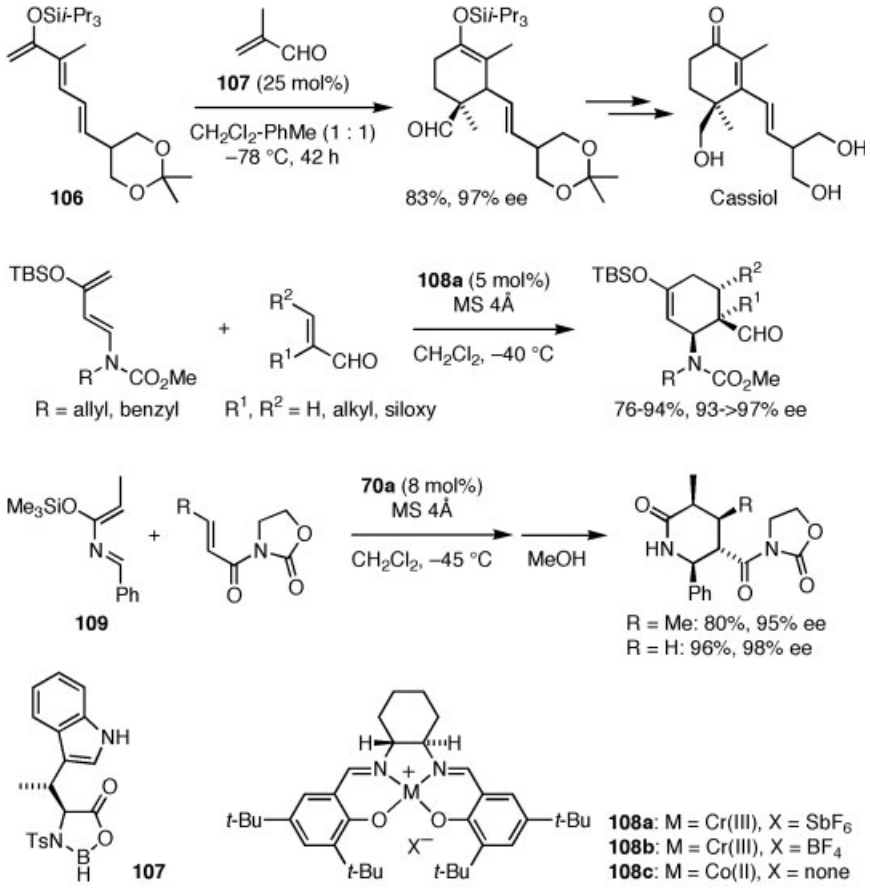
10.2.9.4 **Catalytic Asymmetric Reactions with Alkenes**

In the last decade a variety of catalytic asymmetric DA reactions with alkenes has been developed; most, however, involve the use of a cyclic diene, particularly cyclopentadiene. There are a few examples of catalytic asymmetric reactions of siloxydienes with alkenes. Corey et al. have reported enantioselective cycloaddition of siloxydiene **106** to methacrolein as the key step of the asymmetric synthesis of cassiol (Scheme 10.116) [314]. Recently, Rawal et al. have demonstrated that Cr(III)-salen complex **108a** catalyzes the cycloaddition of 1-amino-3-siloxy-1,3-dienes to *α,β*-unsaturated aldehydes with high enantioselectivity [315]. The highly functionalized cyclohexene products have been used for alkaloid synthesis. Ghosez et al. have introduced asymmetric DA reaction of siloxy-substituted azadienes **109** under catalysis by Cu(II)-box complex **70a** [316].

10.2.9.5 **Catalytic Asymmetric Reactions with Heterodienophiles**

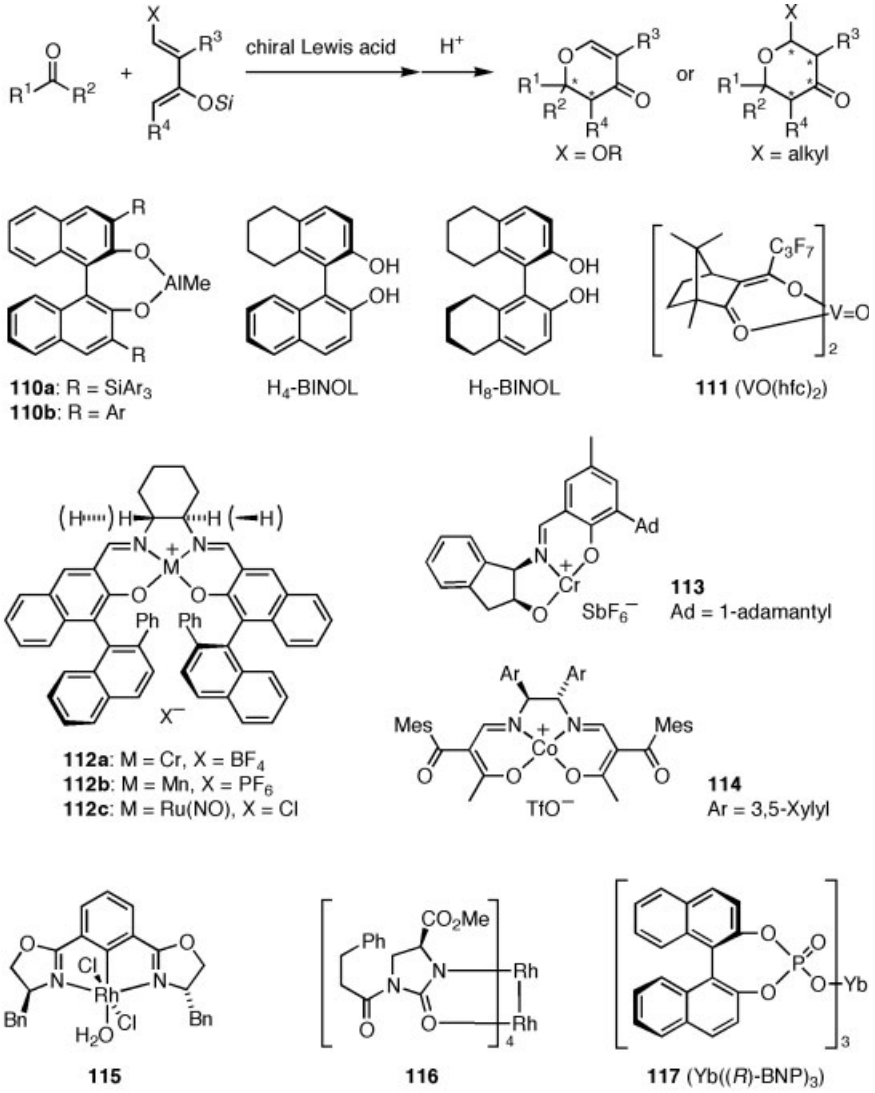
The catalytic asymmetric HDA reaction of siloxydienes is of considerable interest, because of its efficient access to six-membered and partly saturated heterocycles, compounds in extensive use as starting materials for total synthesis of many natural products and other highly functionalized heterocycles [288]. Since the first report by Danishefsky et al. [317], the asymmetric carbonyl-DA reaction has been achieved by using various chiral Lewis acids prepared from metal compounds and homochiral ligands (Scheme 10.117) – acyloxyboranes (**47b**, **47f**) [318], Al(III)-3,3′-disubstituted BINOL (**110**) [319], Ti(IV)-BINOL or H_n-BINOL (n=4, 8) [320], Zr(IV)-3,3′-diiodo-BINOL [321], VO(hfc)$_2$ (**111**) [322], Cr(III)-salen (**108b**, **112a**) or Schiff base (**113**) [323], Mn (IV)-salen (**112b**) [323c, d], Co(II)-salen (**108c**) or ketoiminato (**114**) [324], Cu(II)-box (**70a** etc.) or *N*-monoalkylidene diamine [325], Zn(II)-box [325e], Ru(II)-bisphosphine or salen (**112c**) [326], Rh(III)-phebox (**115**) or carboxamidate (**116**) [327], Eu(hfc)$_3$ [317], and Yb(III)-bistrifylamide, BNP (**117**), or box [328].

In contrast to the intensive studies on the carbonyl-DA reaction, the catalytic asymmetric version of the aza-DA reaction with imino dienophiles is largely unexplored, although Kobayashi [329] and Whiting [330] have recently reported some successful examples of this process (Scheme 10.118).



Scheme 10.116

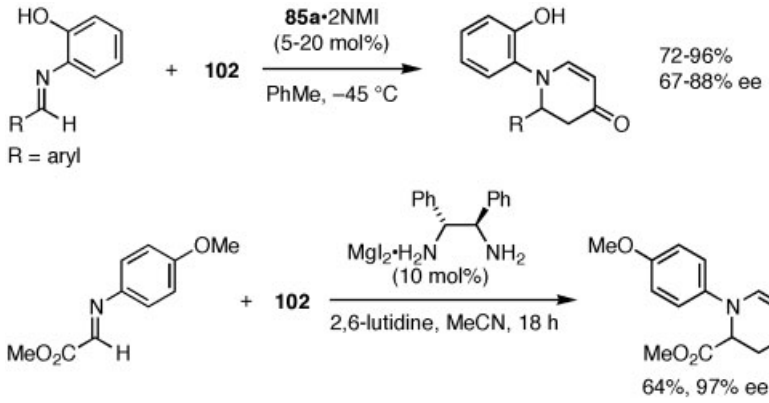
In the Lewis acid-catalyzed reaction of a Danishefsky diene (**102** or **102′**) with a carbonyl dienophile, two different reaction paths, the Mukaiyama aldol path and the concerted DA path, are available for formation of the cyclic product, depending on the Lewis acid used (Scheme 10.119) [331]. Strictly speaking, the former path is not that of DA reaction, but the stepwise reaction also is generally classified as an HDA reaction. The B(III)- and Ti(IV)-catalyzed HDA reactions probably proceed through the Mukaiyama aldol path [318, 320]. The concerted path has been positively identified in reactions catalyzed by Lewis acids based on Al(III) [319], Cr(III) [323], Co(III) [324], Zn(II) [331], Rh(II) [327], and Eu(III) [294, 317].



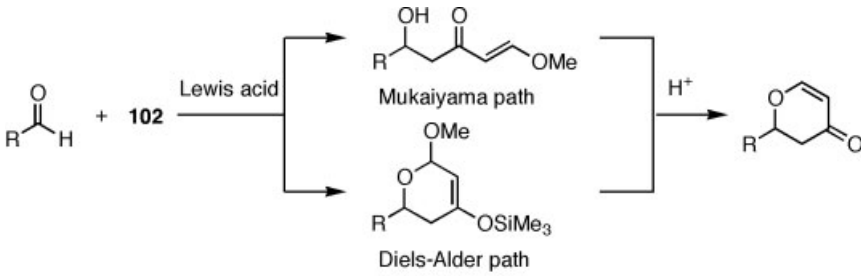
Scheme 10.117

10.3
Allylsilanes, Allenylsilanes, and Propargylsilanes

Since the discovery of the Hosomi-Sakurai allylation reaction [332] much attention has been devoted to syntheses and synthetic applications of allylsilanes and the related organosilanes (allenyl- and propargylsilanes), which have several advantages over other β,γ-unsaturated organometallic compounds [13, 14]. These silicon reagents are thermally stable and relatively inert to water and oxygen; they are, therefore, iso-



Scheme 10.118



Scheme 10.119

lable and storable without special precautions. The stability also enables synthesis of highly functionalized reagents. The Lewis acid-promoted reactions with carbon electrophiles occur at the position γ to the silicon atom in a regiospecific manner. In addition, high chemo- and stereoselectivity can be achieved by the proper choice of the promoter and reaction conditions. The great utility of allylsilanes in fine organic synthesis has been fully proved by extensive studies in the last few decades.

10.3.1
Allylation, Propargylation, and Allenylation of Carbon Electrophiles

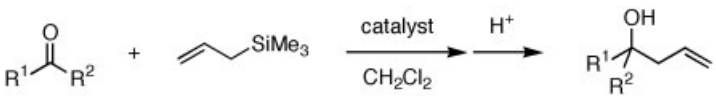
In 1976 we reported that aldehydes and ketones are efficiently allylated with allyltrimethylsilane in the presence of a substoichiometric amount of $TiCl_4$ [332]. Subsequently, Bu_4NF, a fluoride ion source, was found to be an effective catalyst of this allylation reaction [333]. After these initial reports of the Hosomi-Sakurai reaction, several allylsilanes, including highly functionalized compounds, were used for regio- and stereoselective allylation of a variety of carbon electrophiles [6, 13, 14, 334]. In the nineteen-eighties, some Lewis acids (TMSOTf [335], TMSI [336]

etc.) were found to promote the allylation of acetals catalytically, and the reactivity and synthetic utility of allenyl- and propargylsilanes was also reported [4, 6, 334]. Recent studies on the Hosomi-Sakurai and related reactions have mainly focused on the development of an efficient catalytic system for carbonyl allylation, new types of allylation reaction with allylsilanes other than allyltrimethylsilanes, and asymmetric allylation using homochiral catalysts and allylsilanes.

10.3.1.1 Lewis Acid-promoted Reactions of Aldehydes, Ketones, and Acetals

The Hosomi-Sakurai reaction of aldehydes, ketones, and acetals requires a (sub)stoichiometric amount of conventional Lewis acids such as $TiCl_4$, $SnCl_4$, and $BF_3 \cdot OEt_2$. The catalytic allylation of acetals with allyltrimethylsilanes is successfully achieved by means of a variety of acid catalysts – TMSOTf [335], TMSI [336], Ph_3CClO_4 [337], Ph_2BOTf [337], acidic montmorillonites [338], $TMSN(SO_2F)_2$ [43], $TMSNTf_2$ [339], $TMSOSO_2F$ [340], $Cp_2Ti(OTf)_2$ [341], $BiBr_3$ [342], and $Bi(OTf)_3$ [343]. In contrast, TMSOTf, TMSI, Ph_3CClO_4, and $Bi(OTf)_3$ have no catalytic activity toward carbonyl allylation under the same conditions although montmorillonites (K10, Almont), Ph_2BOTf, $Cp_2Ti(OTf)_2$, and $BiBr_3$ are good catalysts of carbonyl allylation.

Davis et al. have reported that $TMSB(OTf)_4$ [344] and $R_3SiB(OTf)_3Cl$ [41] are highly active catalysts of the allylation of aldehydes with allyltrimethylsilane (Scheme 10.120). Yamamoto et al. have demonstrated the utility of $TMSNTf_2$ [45], Me_2AlNTf_2 [35], and PS-$C_6F_4CHTf_2$ [345] for catalytic allylation. In particular, $TMSNTf_2$, prepared in situ from allyltrimethylsilane and $HNTf_2$, has exceedingly high activity and realizes highly efficient allylation of ketones as well as aldehydes. Trehan et al. have shown that $HN(SO_2F)_2$ also catalyzes the carbonyl allylation smoothly [346]. $HN(SO_2F)_2$ is, however, relatively unstable and not commercially available, unlike $HNTf_2$. Quite recently, Yadav et al. have found that TMSI, prepared in situ from allyltrimethylsilane and I_2, has high catalytic activity in MeCN, in sharp contrast with the previous observation in CH_2Cl_2 [347]. Although the $Sc(OTf)_3$-catalyzed allylation of aldehydes in $MeNO_2$ has been reported by Aggarwal [348], the catalytic activity does not seem as high as that of the above mentioned catalysts.

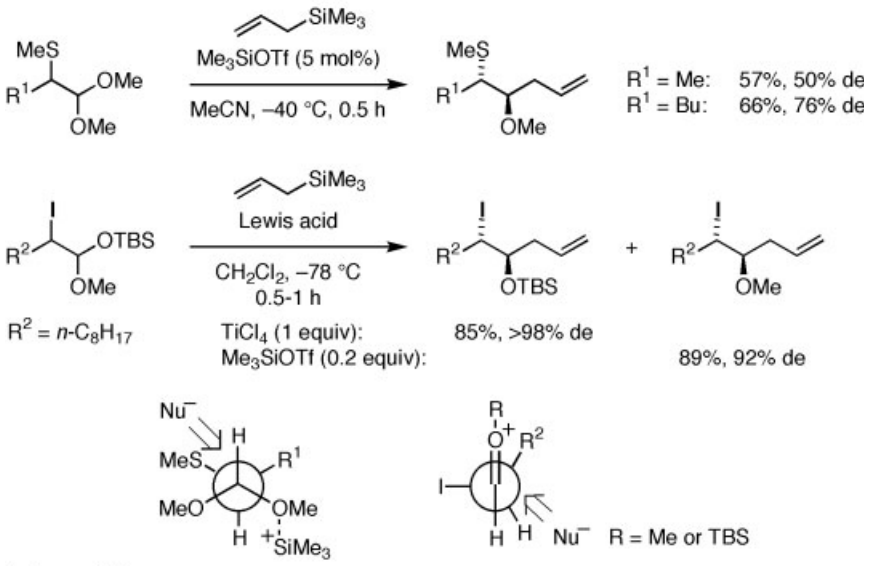


catalyst (/ mol%)	R^1	R^2	yield / %
$Me_3SiB(OTf)_4$ (1)	Ph	H	80
	c-Hex	H	84
Me_3SiNTf_2 (0.5)	Ph	H	89
	c-Hex	H	92
	Hex	Me	89
Me_2AlNTf_2 (5)	Ph	H	93
$HN(SO_2F)_2$ (5)	Ph	H	94
	c-Hex	H	86

Scheme 10.120

Stereocontrolled carbon–carbon bond formation is a central subject in modern organic synthesis. In this context, the stereochemical aspects of the Lewis acid-promoted Hosomi-Sakurai reaction and related reactions have been intensively investigated by using chiral aldehydes and acetals or γ-substituted allyl- and allenylsilanes. Studies in the nineteen-eighties provided important information about diastereofacial selectivity [14]. The allylation of 2-phenylpropanal [349] and its acetal [350] proceeds with moderate Cram-selectivity. Chiral aldehydes bearing an α or β alkoxy group result in high levels of chelation control in the reaction using a Lewis acid with two coordination sites (e.g. $SnCl_4$) [349, 351], whereas β-alkoxy-substituted acetals do not undergo chelation-controlled allylation [350].

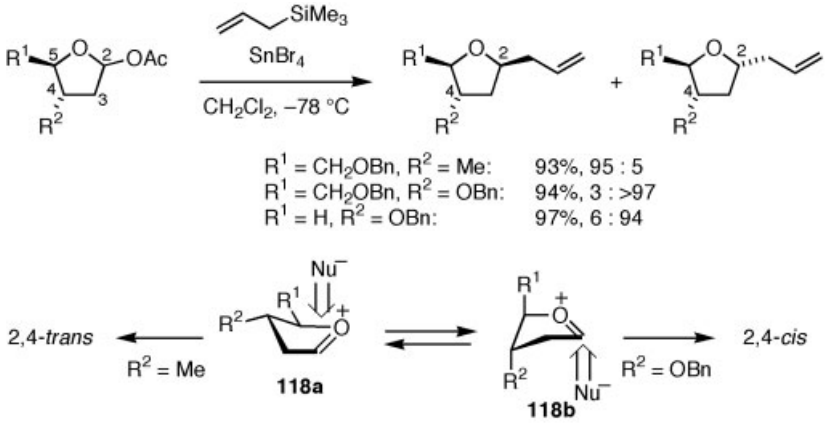
Saigo and coworkers have found that the allylation of α-alkylthio acetals provides *anti* adducts predominantly (Scheme 10.121) [352]. Oshima et al. also have reported *anti*-selective allylation of α-iodo mixed acetals [353]. These stereochemical outcomes were explained differently by selective activation of the methoxy group antiperiplanar to the alkylthio group followed by an S_N2 reaction, or by the Felkin-Anh model of the oxocarbenium ion. Interestingly, in the allylation of the mixed acetals the $TiCl_4$-promoted reaction gives iodohydrin silyl ethers whereas use of a catalytic amount of TMSOTf leads to iodohydrin methyl ethers.



Scheme 10.121

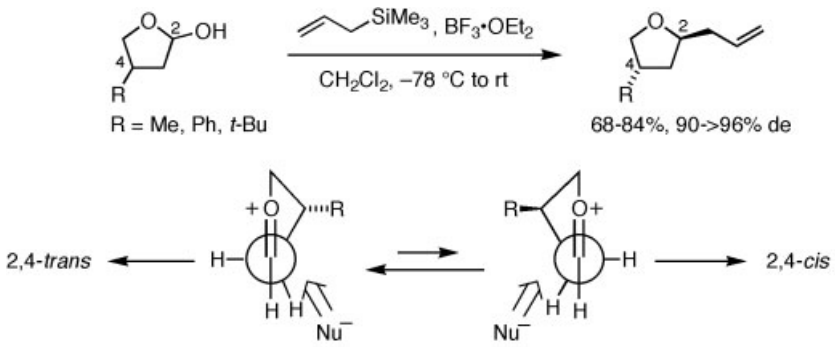
Woerpel et al. have reported the stereoselective allylation of 5- and 6-membered oxocarbenium ions derived from 2-acetoxytetrahydrofuran (2-acetoxy-THF) [354] and 2-acetoxytetrahydropyran (2-acetoxy-THP) [355] derivatives. The $SnBr_4$-promoted allylation of 4-alkyl-2-acetoxy-THF derivatives with allyltrimethylsilane results in high 2,4-*trans* selectivity (Scheme 10.122) [354]. This result can be rational-

ized in terms of stereoelectronically favored inside attack to the stable conformer **118a** of the oxocarbenium ion intermediate. In contrast, the same reaction of 4-alkoxy-2-acetoxy-THF derivatives proceeds with completely inverted diastereoselectivity. The origin of the 2,4-*cis* selectivity is probably that the conformer **118b**, bearing the 4-alkoxy group at the pseudoaxial position, is more stable than **118a** (R^2 = OBn) because of the electrostatic effect between the alkoxy oxygen and the positively charged carbon, and allyltrimethylsilane reacts with **118b** selectively by inside attack. Similar stereochemical divergence is observed in the allylation of 4- or 5-substituted 2-acetoxy-THP derivatives [355].



Scheme 10.122

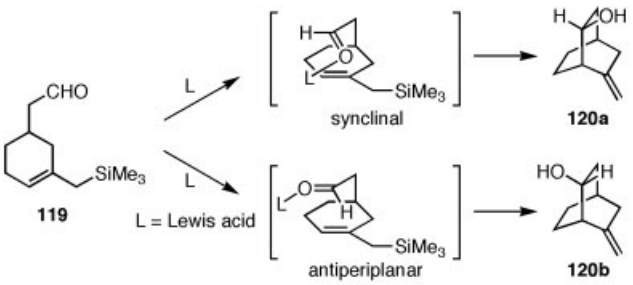
Reißig et al. have also studied the allylation and allenylation of 5-membered oxocarbenium ions generated from γ-lactols (Scheme 10.123) [356]. The $BF_3 \cdot OEt_2$-promoted reaction of 4-alkyl-substituted γ-lactols has high 2,4-*trans*-selectivity as in the above example with 4-alkyl-2-acetoxy-THF derivatives. Reißig et al. gave a similar explanation for the origin of the *trans* selectivity on the basis of the conforma-



Scheme 10.123

tional stability of the oxocarbenium ion intermediate, although they used a Felkin-Anh model to explain the direction of nucleophilic attack.

In general, the Lewis acid-promoted allylation and propargylation of aldehydes with γ-substituted allylsilanes [357] and allenylsilanes [358] are *syn*-selective. Information about the preferred orientation of the reactive double bonds in the transition structure is essential for rationalizing the stereochemistry. Denmark et al. examined the Lewis acid-promoted cyclization of the formyl-substituted allylsilane **119** to clarify the transition structure (Scheme 10.124) [359]. It was found that the allylation occurs from the synclinal and antiperiplanar arrangements, and the former is somewhat important. Thus, synclinal and antiperiplanar transition state models have been frequently used to explain the origin of the simple diastereoselection [14, 334].

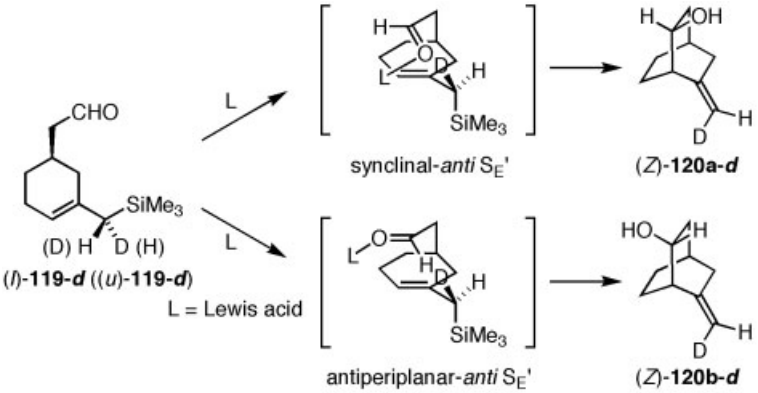


L (**120a** : **120b**): BF_3•OEt_2 (80 : 20), $FeCl_3$ (70 : 30), Et_2AlCl (66 : 34), $SnCl_4$ (49 : 51)
Scheme 10.124

Hayashi and Kumada demonstrated the *anti*-$S_{E'}$ process of aldehyde allylation by using optically active α,γ-disubstituted allylsilanes [357a]. Similarly, the propargylation with allenylsilanes was proved to proceed via an *anti*-$S_{E'}$ mechanism [360]. Denmark et al. have used a modified model system (**119-*d***) to establish both the position of the silyl group relative to the incoming aldehyde (*syn*- or *anti*-$S_{E'}$) and the arrangement of the carbon–carbon and carbon–oxygen double bonds (synclinal or antiperiplanar) in the transition structure of the aldehyde allylation (Scheme 10.125) [361]. Treatment of (*l*)-**119-*d*** with a Lewis acid promoter ($BF_3 \cdot OEt_2$, $SnCl_4$, and $SiCl_4$) gave (*Z*)-**120 a-*d*** and (*Z*)-**120 b-*d***, whereas (*u*)-**119-*d*** led to (*E*)-**120 a-*d*** and (*E*)-**120 b-*d***. These results support the synclinal- and antiperiplanar-$S_{E'}$ transition structures previously proposed.

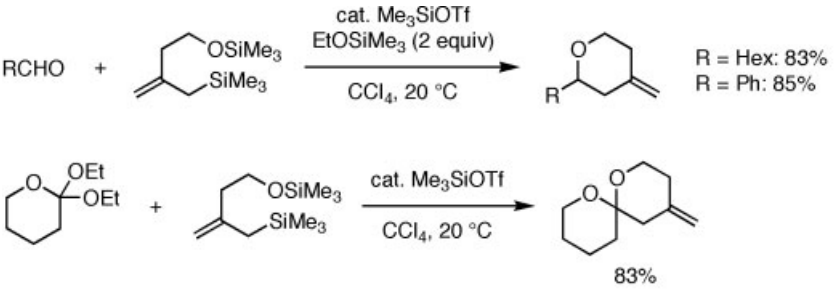
The allylation of acetals with γ-substituted allylsilanes is occasionally highly *syn*-selective [362]. Panek et al. have succeeded in highly diastereo- and enantioselective synthesis of homoallyl ethers by allylation using homochiral α,γ-disubstituted allylsilanes [334] (Section 10.3.1.3).

Tandem acetalization–allylation reaction using allylsilanes is quite useful for direct conversion of aldehydes and ketones into homoallyl ethers [363]. Markó et al. have applied this reaction to the construction of 4-methylene-THP derivatives using β-(2-trimethylsiloxyethyl)allylsilane (Scheme 10.126) [364]. The use of another silyl ether such as $EtOSiMe_3$ is effective in suppressing the isomerization of



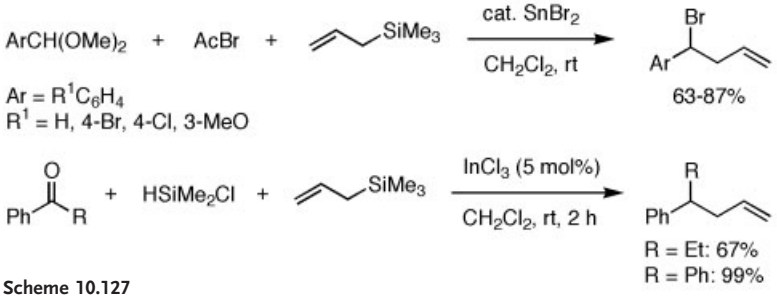
Scheme 10.125

the carbon–carbon double bond of the product [364b]. The TMSOTf-catalyzed reaction of acetals with the functionalized allylsilane also provides the corresponding THP derivatives in good yields even without another silyl ether. The annulation of ortholactones is valuable for the synthesis of spiroacetals.



Scheme 10.126

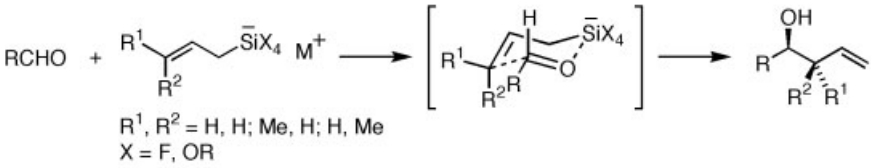
In the presence of excess acetyl halide and a tin(II) catalyst aromatic acetals react with allyltrimethylsilane to give α-allylbenzyl halides in good yield by double substitution of the acetal alkoxy groups (Scheme 10.127) [365]. The indium-catalyzed tandem reaction using a hydrosilane-allylsilane system enables deoxygenative allylation of aromatic ketones [366].



Scheme 10.127

10.3.1.2 New Types of Allylation Reaction of Carbonyl Compounds

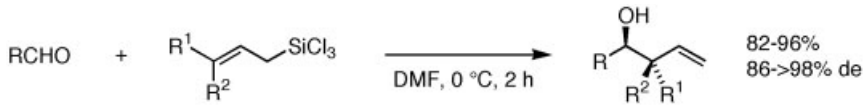
Pentacoordinate silicates can be readily prepared, particularly when the silicon bears electron-negative atoms and groups [367]. The synthetic use of pentacoordinate allylsilicates bearing fluoride and/or alkoxy ligands was intensively studied by a few research groups, including our group, in the late nineteen-eighties [368–370]. These studies revealed the unique reactivity of allylsilicates, which does not appear in tetracoordinate allylsilanes bearing carbon ligands. The pentacoordinate allylsilicates spontaneously react with aldehydes at the γ-position to give homoallyl alcohols (Scheme 10.128). In addition, the allylation proceeds stereospecifically – high *anti*- and *syn* selectivity are observed for (*E*)- and (*Z*)-crotylsilicates, respectively. This stereochemical outcome can be interpreted in terms of a chair-like six-membered cyclic transition state with a hexacoordinate silicon node. Enhanced nucleophilicity of the allyl ligand by higher coordination and strong Lewis acidity of the pentacoordinate silicon imparted by the electron-negative ligands are responsible for the synthetically valuable reactivity.



Scheme 10.128

Significant progress in the synthetic use of pentacoordinate allylsilicates has been made by Kobayashi et al. They have found that allyltrichlorosilanes have reactivity similar to that of pentacoordinate allylsilicates when DMF is used as solvent (Scheme 10.129) [371]. Allylation of aldehydes with allyltrichlorosilanes proceeds without any promoter and has the same sense of regio- and stereospecificity. On the basis of NMR study it has been proposed that the key intermediate of this reaction is a pentacoordinate silicate bearing one DMF molecule as the additional ligand. This allylation method is synthetically more valuable than previous methods using isolable or in-situ generated pentacoordinate allylsilicates, because the allylating agents can be readily prepared in an isomerically pure form by reaction of allyl chlorides or 1,3-dienes with $HSiCl_3$. In addition, allylation with allyltrichlorosilanes is applicable to the one-pot synthesis of homoallyl alcohols from allyl chlorides or 1,3-dienes. In an extended study on the synthetic use of DMF-activated trichlorosilanes, Kobayashi et al. have also found that propargyl- and allenyltrichlorosilanes work as efficient allenylating and propargylating agents, respectively, in the reaction of aldehydes [372].

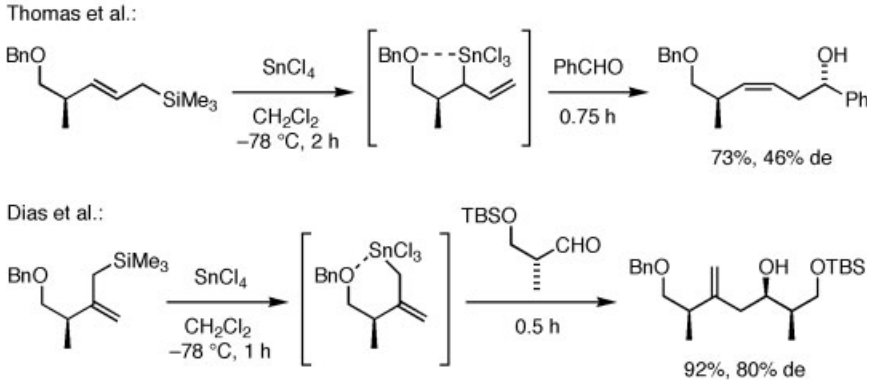
Judging from the function of DMF in this allylation, it is conceivable that a catalytic amount of a Lewis base can effectively promote the reaction of allyltrichlorosilanes. In this context, Denmark et al. have disclosed that HMPA is an efficient catalyst of the allylation, and asymmetric allylation of aldehydes is achieved by use of homochiral phosphoramides (vide infra) [373].



R = Ph, Ph(CH$_2$)$_2$, (*E*)-PhCH=CH
R^1, R^2 = H, H; Me, H (*E* : *Z* = 97 : 3); H, Me (*E* : *Z* = <1 : 99)

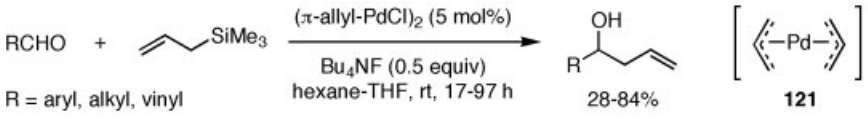
Scheme 10.129

In the Lewis acid-promoted allylation with allylsilanes, the promoter is usually regarded as activating electrophiles. Thomas [374] and Dias [375] have, however, described $SnCl_4$-promoted allylation reactions proceeding via a transmetalation mechanism (Scheme 10.130). In the latter equation of Scheme 10.130, the formation of the allylstannane species has been observed by NMR spectroscopy [375 b].



Scheme 10.130

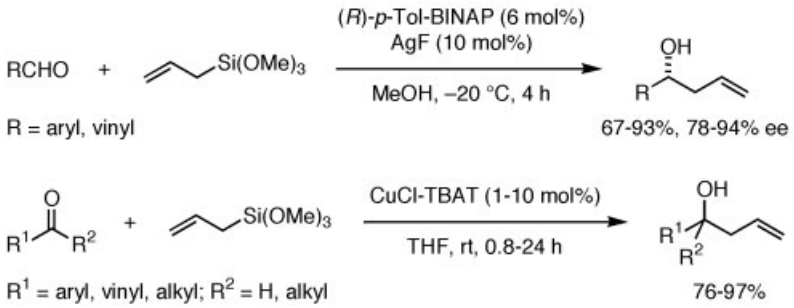
It is known that allylation of aldehydes with allyltrimethylsilane occurs in the presence of a catalytic amount of TBAF under reflux in THF [333]. In contrast, a Pd-TBAF co-catalyst system effectively promotes the allylation even at room temperature (Scheme 10.131) [376]. A plausible reaction mechanism for this allylation involves the formation of bis-π-allylpalladium complex **121**, which can be observed in a stoichiometric reaction of π-allylpalladium chloride dimer, allyltrimethylsilane, and TBAF.



R = aryl, alkyl, vinyl

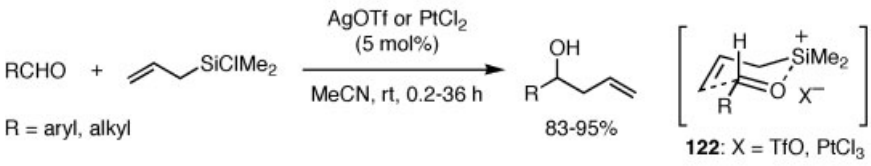
Scheme 10.131

Under catalysis by (*p*-Tol-)BINAP · AgF, allyltrimethoxysilanes are efficient allylating agents for catalytic asymmetric allylation of aldehydes (Scheme 10.132) [377]. Similarly, CuF generated in situ from CuCl and $Bu_4N[Ph_3SiF_2]$ (TBAT) is an effective catalyst of allylation with allyltrimethoxysilanes [378]. In the Ag-catalyzed system allylation of benzaldehyde with crotyltrimethoxysilane proceeds at the γ-position with high *anti* selectivity, irrespective of alkene geometry. The same reaction using CuCl-TBAT is also completely γ-selective; the *syn* adduct is, however, mainly formed from both (*E*)- and (*Z*)-crotylsilanes. It has been proposed that the Ag-catalyzed allylation proceeds via a transmetalation step; the mechanism of the Cu-catalyzed process seems rather complicated.



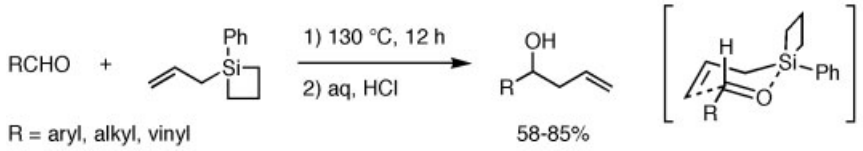
Scheme 10.132

Allylchlorodimethylsilanes are valuable for allylation of aldehydes and acetals in the presence of a catalytic amount of halophilic transition metal salts such as AgOTf and $PtCl_2$ (Scheme 10.133) [379]. In these catalytic systems (*E*)- and (*Z*)-crotylchlorodimethylsilanes react with aldehydes at the γ-position to give *anti*- and *syn*-allylation products, respectively, with high diastereoselectivity. These results mean that the allylation proceeds via a chair-like six-membered cyclic transition state **122**. With AgOTf, instantaneous precipitation of AgCl is observed, indicating the formation of allyldimethylsilyl triflate as the actual allylating agent. This reactive species reacts with aldehydes via **122** (X = TfO), and it must be efficiently regenerated in situ to maintain a catalytic cycle, in which AgOTf acts merely as initiator rather than catalyst. In contrast, $PtCl_2$ would work as the actual catalyst for halophilic activation of the allylating agent, which enables the allylation via **122** ($X = PtCl_3$).



Scheme 10.133

Allylation of aldehydes with allylsilacyclobutanes occurs at 130–160 °C without catalyst (Scheme 10.134) [380]. In contrast, allyldimethylphenylsilane is insensitive to benzaldehyde under the same conditions. Similar to allylation with allylsiliconates, the thermal allylation proceeds stereospecifically. The stereospecificity is indicative of a six-membered cyclic transition state, which would be assisted by the relatively strong Lewis acidity of the strained silyl group.



Scheme 10.134

Strained allylsilacycles prepared by the reaction of allylchlorosilanes with 1,2-diols, β-aminoalcohols, and 1,2-diamines enable uncatalyzed allylation of aldehydes at room temperature [381]. Such allylsilanes have been used for asymmetric allylation by introducing a homochiral substituent on to silicon (Section 10.3.1.3).

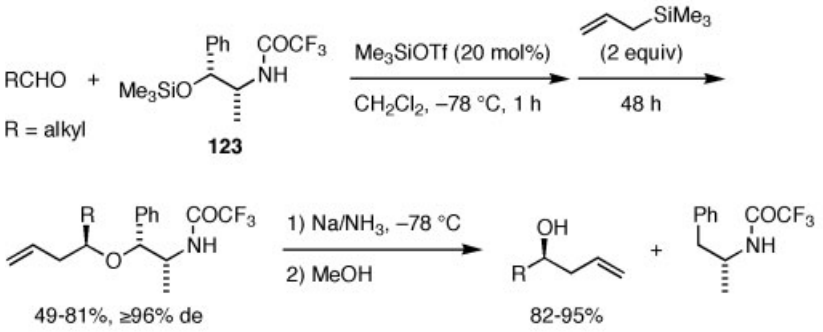
10.3.1.3 Asymmetric Reactions of Aldehydes, Ketones, and Acetals

To achieve asymmetric allylation with allylsilanes, the control of absolute configuration by use of chiral auxiliaries was extensively studied in the nineteen-eighties. Recently, much effort has been directed toward the use of optically active α-chiral allylsilanes and catalytic asymmetric allylation using chiral Lewis acids and bases.

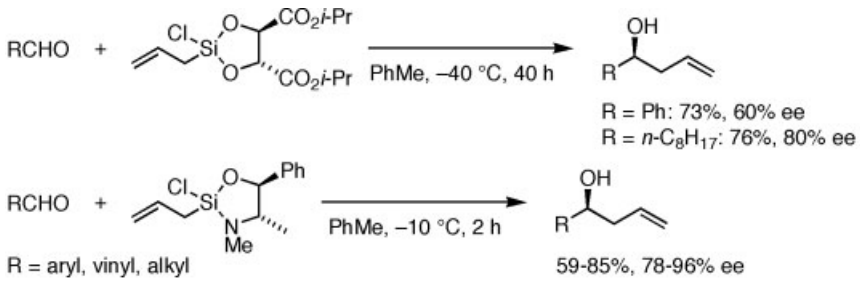
Homochiral Substrates and Reagents

The use of C_2-symmetric 1,2- and 1,3-diols as chiral auxiliaries is a reliable method for asymmetric allylation of acetals [382]. Acyclic acetals derived from homochiral 1-phenylethanol undergo the Hosomi-Sakurai allylation with high diastereoselectivity [383]. Tietze et al. have, on the other hand, reported that the TMSOTf-catalyzed successive acetalization–allylation reaction of aliphatic aldehydes with homochiral silyl ethers **123** and allyltrimethylsilane gives the corresponding homoallyl ethers with complete diastereocontrol; these ethers can be readily converted into enantiomerically pure homoallyl alcohols without epimerization (Scheme 10.135) [384]. This method is applicable to asymmetric allylation of methyl ketones [385].

Allylsilanes bearing a chiral ligand on the silicon atom can be used for asymmetric allylation of aldehydes [386]. Initial studies of this approach gave somewhat disappointing results for enantioselectivity; recent studies have, however, disclosed that the use of homochiral 1,2-diols [381 a–c], β-aminoalcohols, and 1,2-diamines [381 d] as the ligand leads to high enantioselectivity (Scheme 10.136).



Scheme 10.135

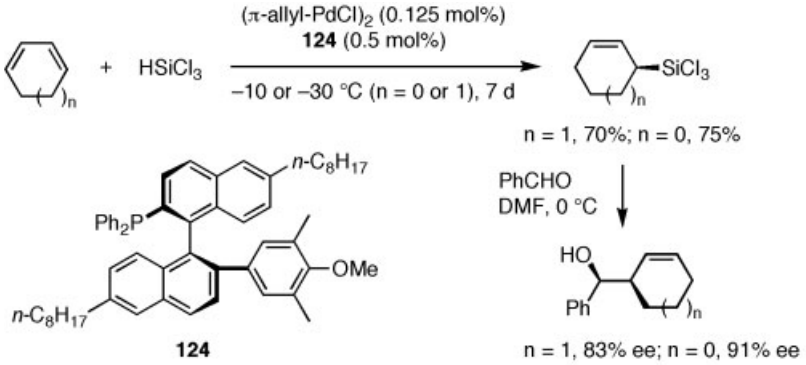


Scheme 10.136

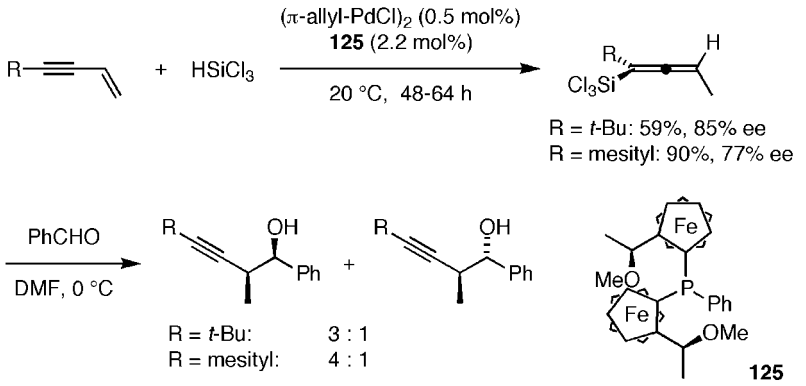
In the last decade there have been remarkable advances in the syntheses and applications of optically active α-chiral allylsilanes. Asymmetric hydrosilylation of 1,3-dienes provides convenient access to these allylsilanes [387]. Hayashi et al. have demonstrated that axially chiral monophosphines (MOP) are efficient chiral ligands in the Pd-catalyzed asymmetric hydrosilylation [388]. In particular, the MOP ligand **124** can realize high catalytic activity and enantioselectivity in the reaction of cyclic 1,3-dienes with $HSiCl_3$ (Scheme 10.137) [388 a, b]. The allyltrichlorosilanes obtained are quite valuable for highly diastereo- and enantioselective allylation of aldehydes by Kobayashi's procedure [371].

Optically active allenyltrichlorosilanes can be prepared by the Pd-catalyzed asymmetric hydrosilylation of 1,3-enynes with $HSiCl_3$ (Scheme 10.138) [389]. In this reaction use of bisPPFOMe (**125**) as the chiral ligand achieves high enantioselectivity. The allenylsilanes smoothly react with PhCHO in DMF to give optically active homopropargyl alcohols, and the axial chirality of allenylsilanes is completely transferred to the central chirality of the products by a *syn*-$S_{E'}$ process.

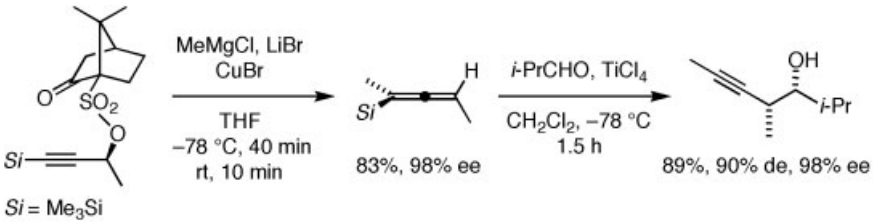
Fleming et al. have achieved the preparation of enantiomerically pure allyltrimethylsilanes via highly diastereoselective conjugate addition of Me_2CuLi to (*E*)-β-TMS-acrylamide derived from homochiral camphor sultam as the key step [390]. They have also succeeded in highly enantioselective synthesis of allenyltrimethylsilanes by *anti*-S_N2' reaction of homochiral γ-TMS-substituted propargyl sulfonates



Scheme 10.137



Scheme 10.138

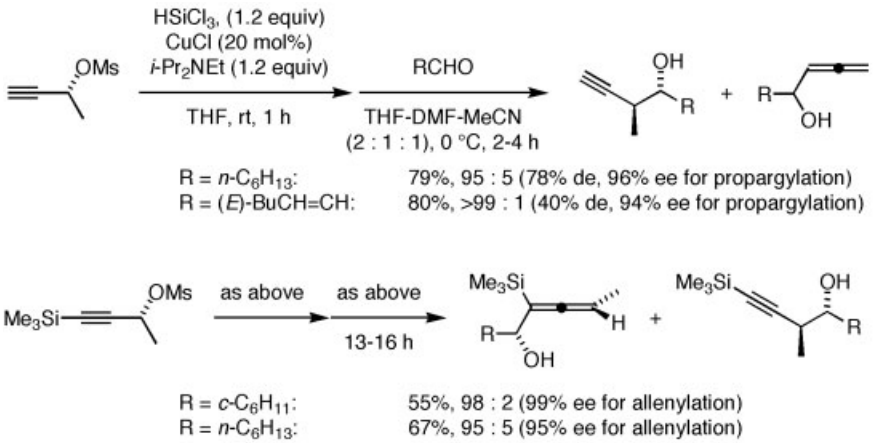


Scheme 10.139

with MeMgCl–LiBr–CuBr [360] (Scheme 10.139). The reaction of these optically active silicon reagents with electrophiles proceeds via an *anti*-$S_{E'}$ process.

Nucleophilic substitution (S_N2 or S_N2') of homochiral propargyl sulfonates with silicon–copper reagents (Cl_3SiCu or $(PhMe_2Si)_2CuLi$) is valuable for the synthesis of optically active propargyl and allenylsilanes [391, 392]. Treatment of a non-racem-

ic γ-unsubstituted propargyl sulfonate with $HSiCl_3$ and CuCl, followed by reaction with aldehydes in DMF gives homopropargyl alcohols with moderate to good *anti* selectivity and high enantioselectivity (Scheme 10.140) [391]. This observation is indicative of the formation of an optically active allenyltrichlorosilane in the initial step. In contrast, the use of a non-racemic γ-TMS-substituted propargyl sulfonate leads to highly diastereo- and enantioselective allenylation. Thus, the γ-substitution assists in the formation of the corresponding propargyltrichlorosilane.



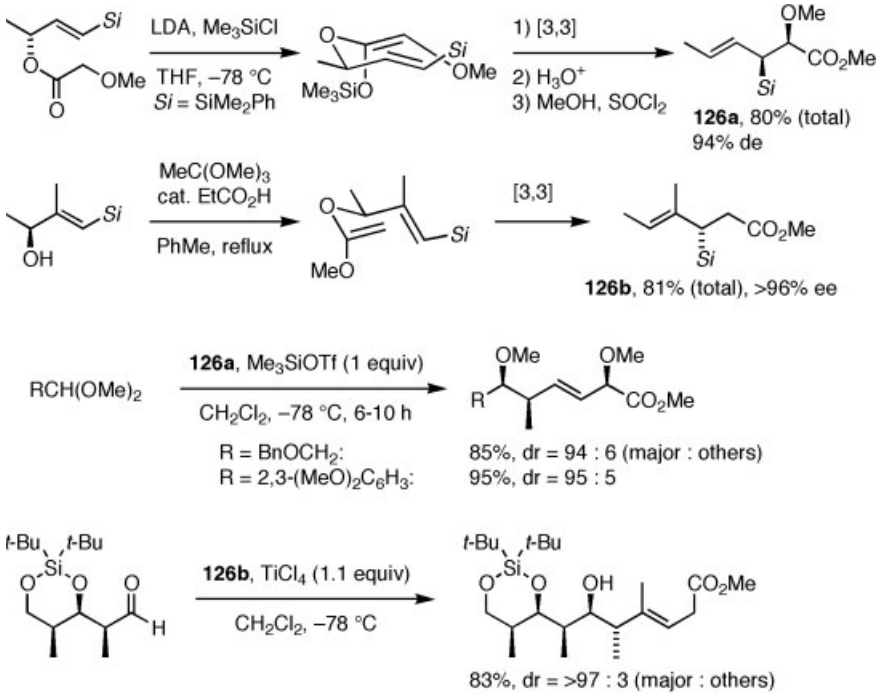
Scheme 10.140

Panek et al. introduced the synthesis of optically active crotylsilanes by Claisen rearrangement of allyl vinyl ethers derived from homochiral γ-silylated allyl alcohols (Scheme 10.141) [393]. These allylsilanes have been used for highly diastereo- and enantioselective allylation of aldehydes and acetals [334], which enables efficient syntheses of complex natural products [394].

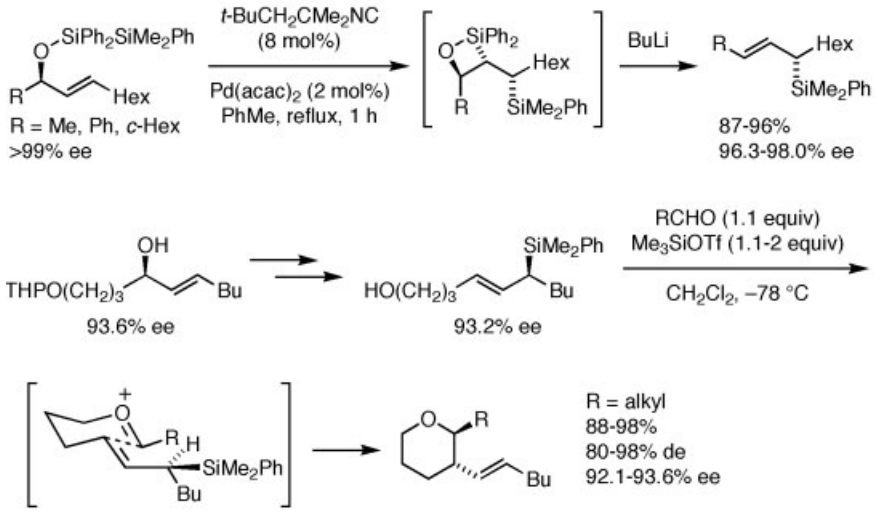
Suginome and Ito have developed a reliable method for the synthesis of highly enantioenriched allyl- and allenylsilanes. The synthetic process involves 1,3-chirality transfer from homochiral allyl and propargyl alcohols through Pd-catalyzed intramolecular bis-silylation and subsequent Peterson-type elimination (Scheme 10.142) [395]. This method provides an efficient route to enantioenriched allylsilanes bearing a hydroxyalkyl group, which are very valuable as synthetic intermediates for diastereo- and enantioselective synthesis of heterocycles and carbocycles [396]. Polymer-supported highly enantioenriched allylsilanes have been prepared from enantioenriched allyl alcohols and a polymer-supported disilanyl chloride [397].

Lewis Acid- and Transition Metal-catalyzed Reactions

Yamamoto et al. described the first example of catalytic asymmetric allylation of aldehydes with allylsilanes using chiral boron Lewis acid **47b** (R = H, 3,5-$(CF_3)_2C_6H_3$) [398]. The allylation of aliphatic and aromatic aldehydes with β-substi-



Scheme 10.141

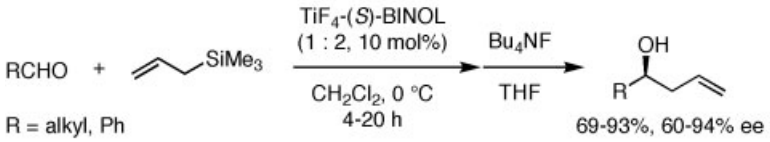


Scheme 10.142

tuted allylsilanes is highly enantioselective (up to 96% ee) whereas use of unsubstituted allyltrimethylsilane leads to lower chemical and optical yields.

The BINOL-Ti complex **59** can achieve good enantioselectivity in the crotylation of methyl glyoxylate although the catalytic activity and diastereoselectivity are not so high (48%, 66% de (*syn*), 80% ee) [399].

The fluorotitanium complex prepared from TiF_4 and homochiral BINOL (1 : 1) in MeCN is an efficient catalyst of asymmetric allylation with allyltrimethylsilane (Scheme 10.143) [400]. In particular, sterically demanding aldehydes undergo the allylation with high enantioselectivity. Judging from the disappointing results with the corresponding $TiBr_4$ and $Ti(Oi\text{-}Pr)_xCl_{4-x}$ complexes, the fluorine ligand plays a crucial role in the acceleration and stereocontrol of the allylation; this probably originates from the strong affinity of fluorine for titanium.

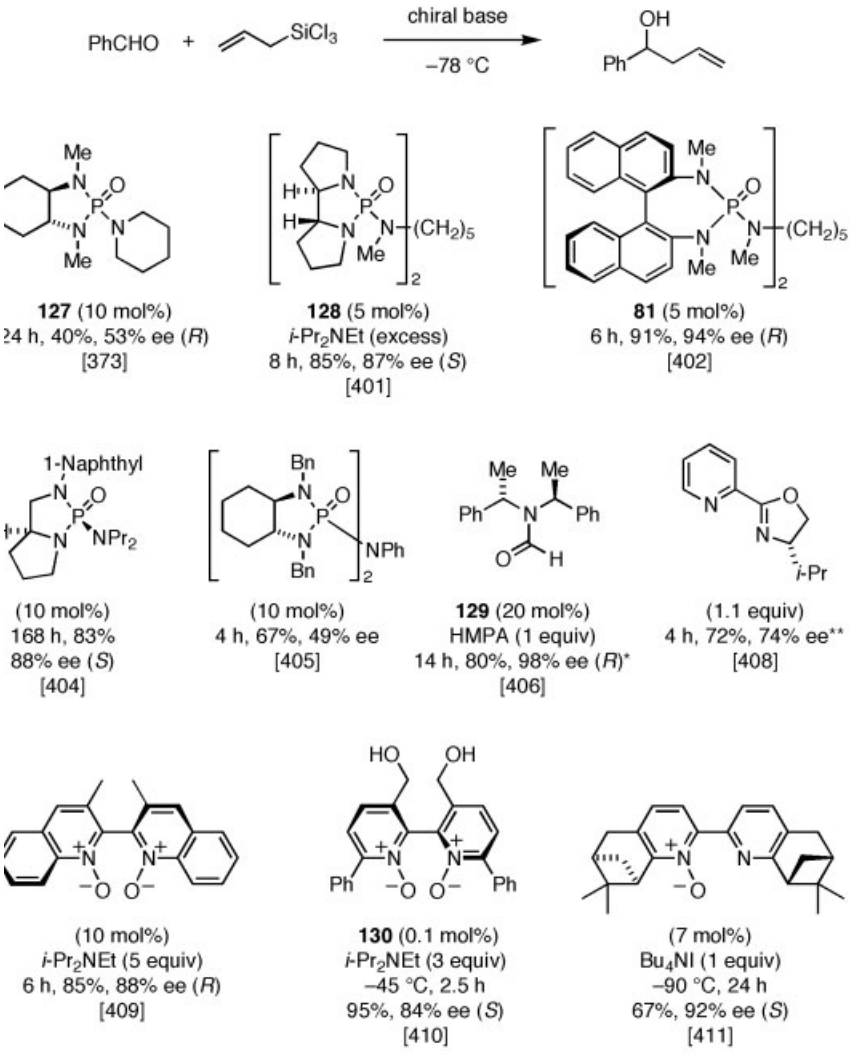


Scheme 10.143

As shown in Scheme 10.132 (Section 10.3.1.2), Yamamoto et al. have recently reported highly enantioselective allylation of aromatic and *α,β*-unsaturated aldehydes with allyltrimethoxysilane using (*R*)-(*p*-Tol-)BINAP · AgF as catalyst [377]. Shibasaki et al., on the other hand, have succeeded in asymmetric allylation of acetophenone with allyltrimethoxysilane by use of a *p*-Tol–BINAP · CuCl–TBAT co-catalyst system (up to 61% ee) [378].

Lewis Base-catalyzed Reactions

Since its discovery by Kobayashi et al. [371], the base-promoted carbonyl allylation with allyltrichlorosilanes has been extended to the catalytic asymmetric version, using a chiral Lewis base, by several research groups. In the first example, introduced by Denmark et al., chiral phosphoramides such as **127** were used as the basic catalysts (Scheme 10.144) [373]. Later they developed efficient bisphosphoramide catalysts **128** [401] and **81** [402] to achieve highly enantioselective allylation of aromatic and *α,β*-unsaturated aldehydes. These Lewis bases activate the allylsilanes as bidentate ligands, and coordination to the Lewis acidic silicon would enable the formation of a cationic octahedral silicon center, for example **38**, in the transition state (Scheme 10.31) [403]. With **128**, the addition of *γ*-substituted allyltrichlorosilanes proceeds stereospecifically (i.e. *anti* adducts from (*E*)-allylsilanes and *syn* adducts from the *Z* isomers) with high enantioselectivity. As shown in Scheme 10.144, other Lewis bases have been used for the asymmetric allylation [404–411]. Among these bases, the formamide **129** is fairly effective in asymmetric allylation of aliphatic aldehydes [406]. Bipyridine *N,N′*-dioxide **130** has high catalytic activity in the allylation of aromatic aldehydes [410].



127 (10 mol%)
24 h, 40%, 53% ee (*R*)
[373]

128 (5 mol%)
i-Pr_2NEt (excess)
8 h, 85%, 87% ee (*S*)
[401]

81 (5 mol%)
6 h, 91%, 94% ee (*R*)
[402]

(10 mol%)
168 h, 83%
88% ee (*S*)
[404]

(10 mol%)
4 h, 67%, 49% ee
[405]

129 (20 mol%)
HMPA (1 equiv)
14 h, 80%, 98% ee (*R*)*
[406]

(1.1 equiv)
4 h, 72%, 74% ee**
[408]

(10 mol%)
i-Pr_2NEt (5 equiv)
6 h, 85%, 88% ee (*R*)
[409]

130 (0.1 mol%)
i-Pr_2NEt (3 equiv)
–45 °C, 2.5 h
95%, 84% ee (*S*)
[410]

(7 mol%)
Bu_4NI (1 equiv)
–90 °C, 24 h
67%, 92% ee (*S*)
[411]

*With *c*-HexCHO. **With (*E*)-MeCH=CHCH$_2$SiCl$_3$. The ee is shown for the *anti* adduct.

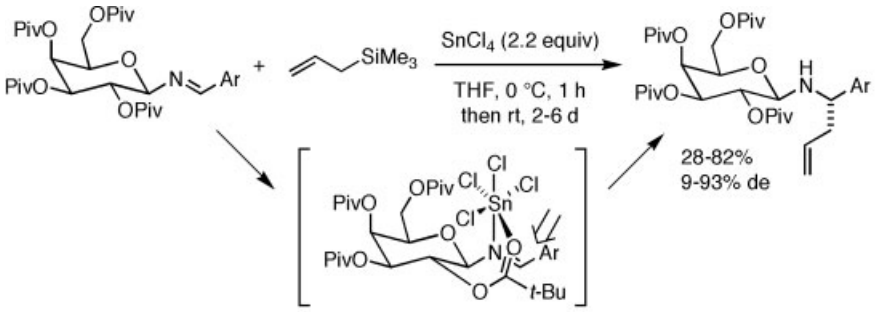
Scheme 10.144

10.3.1.4 **Allylation of Carbon–Nitrogen Double Bonds**

The Hosomi-Sakurai reaction of in situ-generated iminium salts were extensively studied in the nineteen-eighties, and its synthetic utility for the stereoselective synthesis of amines is well recognized [183c, 412]. The allylation of imines with allylsilanes has, on the other hand, been largely unexplored, because of the low reactivity of the C–N double bond. In the last decade, however, some interesting pa-

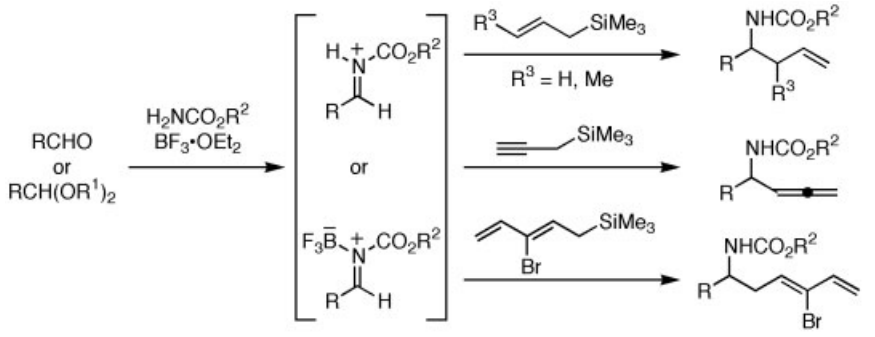
pers on imine allylation have been published. This section describes recent progress in the Hosomi-Sakurai reactions of imines and the related compounds.

Allylation of imines with allyltrimethylsilane usually requires a stoichiometric amount of a strong Lewis acid such as $SnCl_4$, $TiCl_4$, or BF_3 [413–419]. Laschat et al. have reported that $SnCl_4$ promotes the allylation of imines derived from aromatic aldehydes and galactopyranosylamine with low to high diastereoselectivity (Scheme 10.145) [413]. The preferred formation of the *S*-configured diastereomers can be rationalized by conformational fixation of the imines by $SnCl_4$, which prohibits attack of the allylsilane from the *Re* side, that is, the front side of the imine.



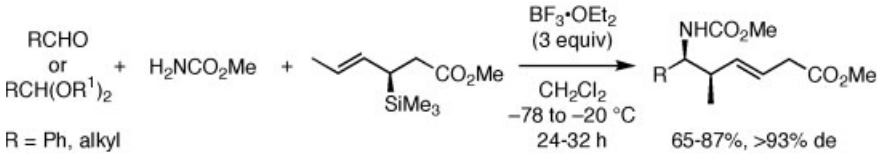
Scheme 10.145

In the presence of BF_3, *N*-acylimines generated in situ from aldehydes or acetals and carbamates smoothly react with allylsilanes, propargylsilanes, and 2,4-pentadienylsilanes to give homoallyl [415], allenylmethyl [416], and 3,5-hexadienyl amines [417], respectively (Scheme 10.146). The three-component coupling reaction with crotyltrimethylsilane proceeds with moderate *syn* selectivity as in the crotylation of aldehydes [418].



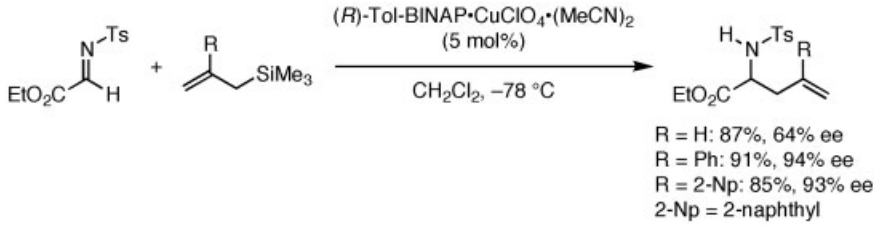
Scheme 10.146

The BF_3-promoted reaction of aldehydes or acetals, methyl carbamate, and homochiral crotylsilanes is valuable for highly diastereo- and enantioselective synthesis of homoallylamines (Scheme 10.147) [419]. Interestingly, reaction using aromatic aldehydes or their acetals at low temperature forms stereo-controlled functionalized pyrrolidines predominantly by a formal [3+2] cycloaddition (Section 10.3.3.1).



Scheme 10.147

Highly activated imines such as *α*-*N*-tosylimino esters can be catalytically allylated with a Lewis acid. Jørgensen [420] and Lectka [227b] have reported the Lewis acid-catalyzed enantioselective allylation of an *α*-imino ester with allylsilanes (Scheme 10.148). Tol–BINAP–Cu(I) complex is effective in this asymmetric process as well as the Mannich-type reaction with silyl enolates. Aromatic substituents on the allyl group dramatically improve the enantioselectivity.

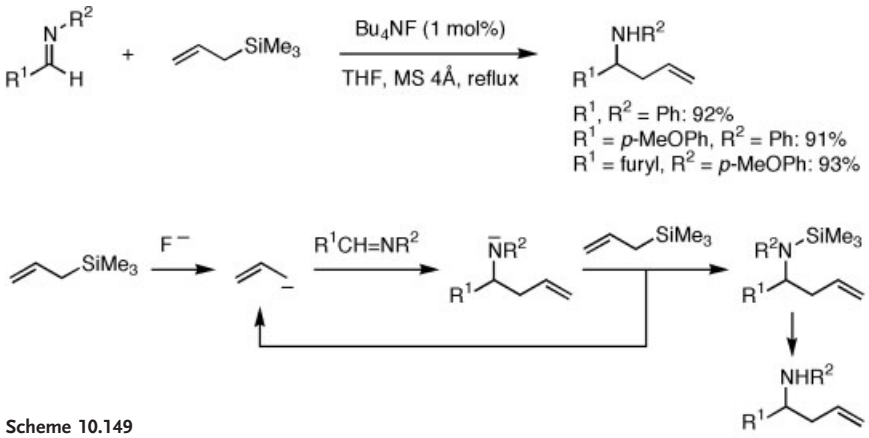


Scheme 10.148

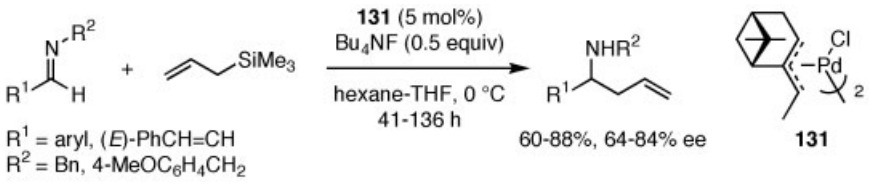
TBAF is an effective catalyst for the allylation of aromatic imines with allylsilanes (Scheme 10.149) [421]. In the presence of 4-Å MS and 1 mol% TBAF, allyltrimethylsilane smoothly reacts with aromatic imines in THF under reflux to give the corresponding homoallylamines. The mechanism of allylation of imines can be reasonably interpreted in terms of a fluoride-triggered autocatalytic cycle.

Yamamoto et al., on the other hand, reported that a *π*-allylpalladium–TBAF cocatalyst system enables allylation of aromatic imines with allyltrimethylsilane at room temperature [376]. As described in Scheme 10.131, this allylation would proceed via a transmetalation mechanism involving the bis-*π*-allylpalladium intermediate **121**. The use of chiral *π*-allylpalladium complex **131** enables asymmetric synthesis of homoallyl amines with good enantioselectivity (Scheme 10.150).

Dual activation of allylsilanes and imines by fluoride ion and a Lewis acid also has been used for allylation of imines at room temperature [422]. In the presence of tetrabutylammonium triphenyldifluorosilicate (TBAT, $Bu_4N[Ph_3SiF_2]$), a soluble,

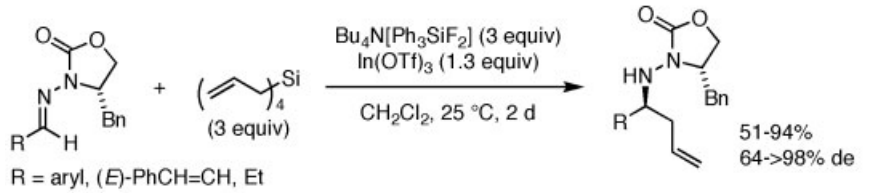


Scheme 10.149



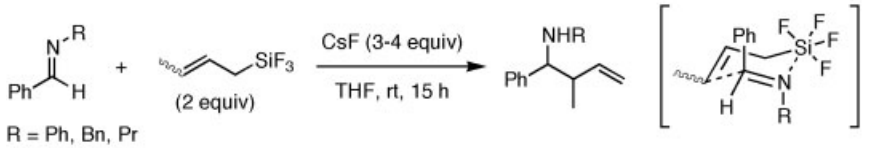
Scheme 10.150

air-stable, non-hygroscopic fluoride ion source, tetraallylsilane adds to the complexes prepared from chiral *N*-acylhydrazones and $In(OTf)_3$ to provide homoallylamines in good to high yields with high diastereoselectivity (Scheme 10.151). Without TBAT or $In(OTf)_3$, the allylation is rather slow.



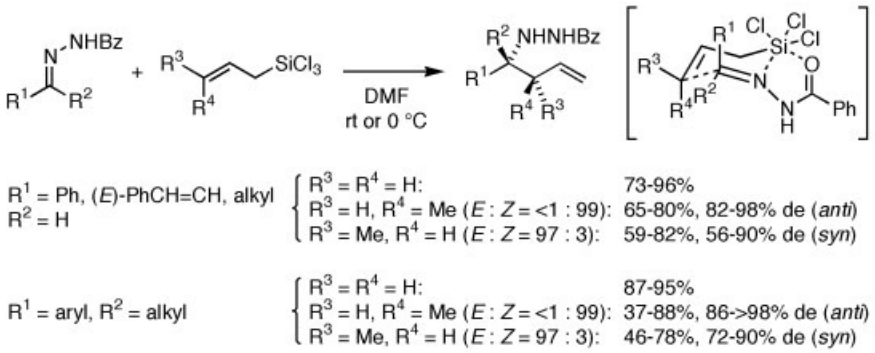
Scheme 10.151

Pentacoordinate allylsilicates can be used for allylation of imines as well as carbonyl compounds [423]. Allylation with pentacoordinate crotylsilicates generated from crotyltrifluorosilanes and CsF gives the corresponding homoallylamines efficiently in a regiospecific manner, in the same way as aldehyde allylation (Scheme 10.152). The diastereoselectivity is not high, but it is mostly predictable on the basis of a six-membered cyclic transition structure.



Scheme 10.152

The allylation strategy using allyltrichlorosilane developed by Kobayashi et al. [371] is applicable to the allylation of benzoylhydrazones (Scheme 10.153) [424]. Allyltrichlorosilanes react spontaneously with benzoylhydrazones derived from aldehydes and ketones in DMF to afford the corresponding homoallylic benzoylhydrazines in good to high yields. The allylation proceeds at 0 °C to room temperature under mild conditions. Crotylation with (*E*)- and (*Z*)-crotyltrichlorosilanes proceeds with high *syn* and *anti* diastereoselectivity, respectively, even when ketone hydrazones are used as the substrates. These reactions are most likely to involve a cyclic chair-like transition state in which the R^1 group takes an axial position. In the allylation of *α*-heteroatom-substituted chiral benzoylhydrazones, high *anti* diastereoselectivity is observed. The allylation products can be readily converted to homoallylamines in high yields without epimerization.



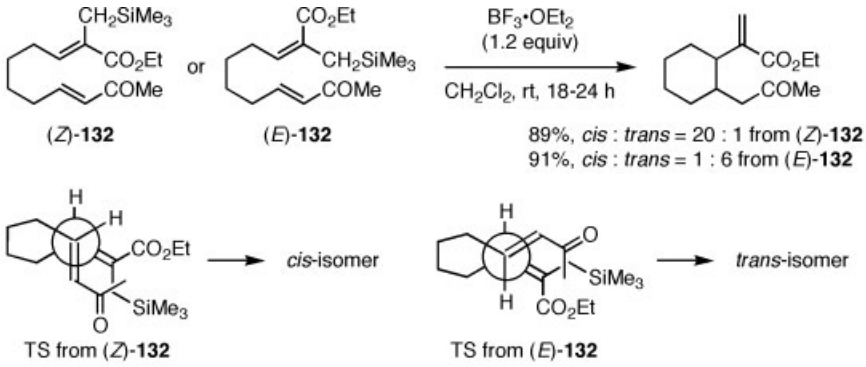
Scheme 10.153

10.3.1.5 Conjugate Addition to *α,β*-Unsaturated Carbonyl Compounds

The Hosomi-Sakurai reaction is a powerful method for conjugate allylation of *α,β*-unsaturated ketones [425]. In the presence of $TiCl_4$ the allylation occurs smoothly at the *γ*-position of allylsilanes and the *β*-position of *α,β*-unsaturated ketones. This highly regioselective process has been widely used for introduction of functionalized carbon chains and construction of carbocycles in natural product synthesis [6, 426]. When TBAF is used as catalyst, both conjugate addition and 1,2-addition occur competitively [333]. The fluoride ion-catalyzed procedure is, however, effec-

tive in the conjugate allylation of *α,β*-unsaturated esters, amides, and nitriles, which cannot be achieved by the $TiCl_4$-promoted procedure [427]. Occasionally intramolecular conjugate allylation of *α,β*-unsaturated ketones is also catalyzed efficiently by TBAF [428]. In the last decade, diastereo- and enantio-controlled conjugate allylations catalyzed by Lewis acids have attracted much attention.

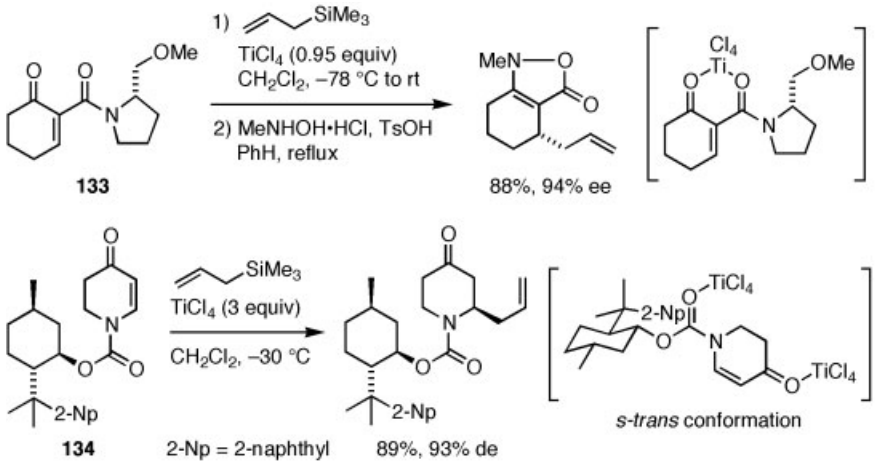
Kuroda et al. have found that the diastereoselectivity of the Lewis acid-promoted cyclization of **132** is highly dependent on the geometry of the allylsilane moiety (Scheme 10.154) [429]. The stereochemical outcomes can be rationalized by chair transition structures involving a secondary orbital interaction without severe steric repulsion.



Scheme 10.154

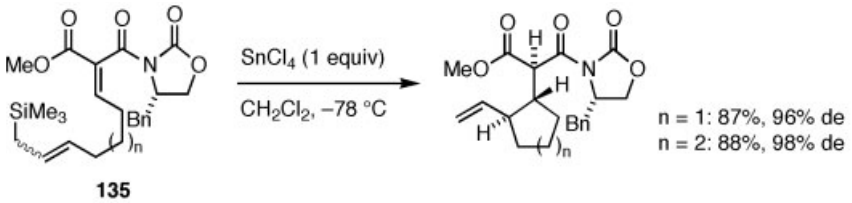
Homochiral *α,β*-unsaturated ketones **133** [430] and **134** [431] undergo $TiCl_4$-promoted conjugate allylation with high diastereoselectivity (Scheme 10.155). In the former allylation a six-membered ring chelate complex has been proposed as the reactive intermediate. The fine stereocontrol observed in the latter reaction might originate from a *π*-stacking interaction between the naphthyl ring and the $TiCl_4$-complexed enone portion, which makes the *s-trans* conformation (with regard to the amide C–N bond) thermodynamically more favorable to block the *si* face attack of the allylsilane.

Although *α,β*-unsaturated *N*-acyloxazolidinones are good acceptors for conjugate allylation with allyltrimethylsilane, the diastereoselectivity for substrates derived from chiral oxazolidinones is not so high [432]. Intramolecular allylation of alkylidene 1,3-dicarbonyl compounds **135** bearing a chiral oxazolidinone moiety is highly diastereoselective when $SnCl_4$ is used as promoter (Scheme 10.156) [433].



133 **134** 2-Np = 2-naphthyl 89%, 93% de

Scheme 10.155



135

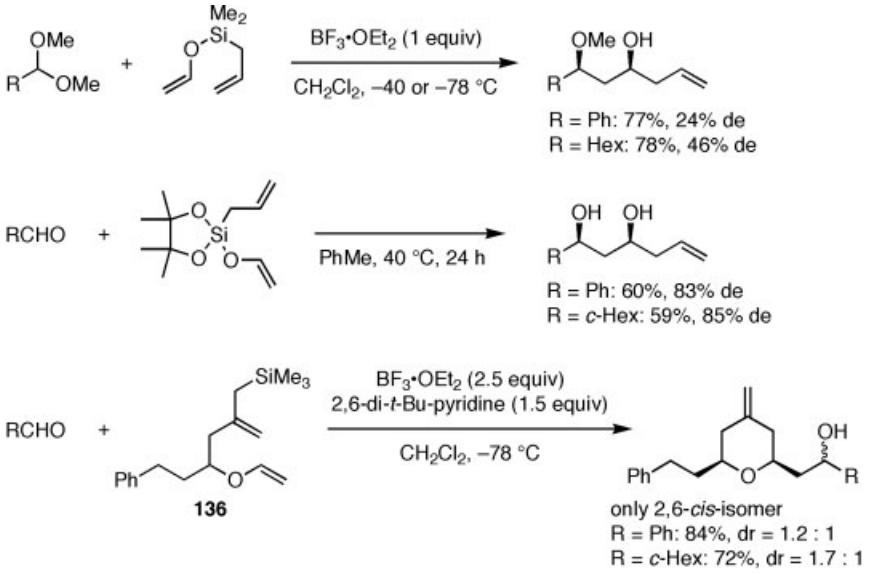
Scheme 10.156

10.3.1.6 Tandem Reactions Including Two or More Carbon–Carbon Bond-forming Processes

Tandem reactions, in which two or more bond-forming processes result from a single step, are useful for rapid synthesis of complex molecules [434]. Allylsilanes and the related silicon compounds have been extensively used for tandem reactions, because of their moderate and controllable reactivity [6]. As described in Sections 10.3.1.1 and 10.3.1.4, these reagents are valuable for tandem acetalization–allylation and amination–alkylation of aldehydes. Allylsilanes bearing another reactive carbon center on the allylic moiety can be used for the construction of carbocycles by successive carbon–carbon bond formation with other reactants [435]. Cationic polyene cyclization terminated by allylsilanes and propargylsilanes provides an efficient route to polycyclic compounds [436]. Much attention has recently been paid to the tandem reaction with multifunctional allylsilanes bearing other reactive group(s) on the silicon atom. This section deals with recent progress in the study of tandem reactions including both allylation with allylsilanes and other carbon–carbon bond-forming processes.

Berrisford et al. have reported the Lewis acid-promoted tandem aldol–allylation reaction of acetals with allyldimethylsilyl enolates (Scheme 10.157) [437]. Leighton et al. have reported that introduction of the pinacolate ligand into difunctional sili-

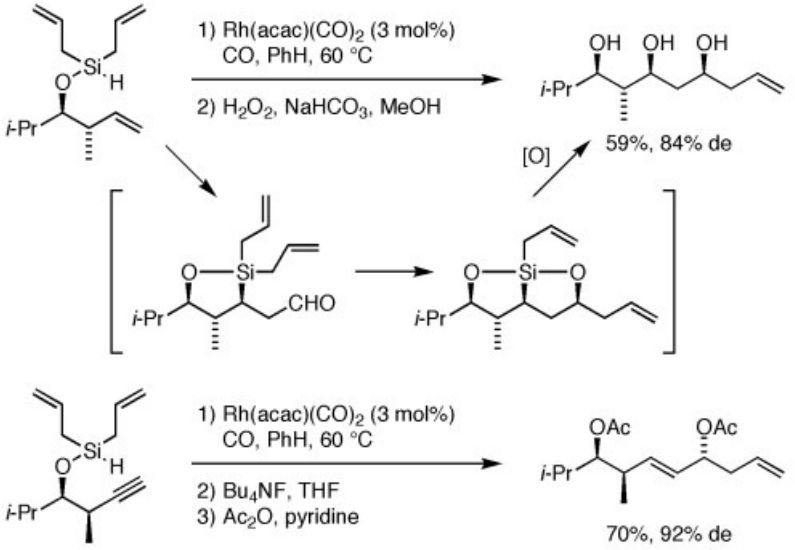
con reagents realizes a similar tandem reaction of aldehydes without a catalyst [438]. The uncatalyzed reaction is valuable for stereoselective synthesis of 1,3-diols. The tandem aldol–allylation reaction using allylsilane **136** is useful for the stereoselective construction of *cis*-2,6-dialkyl-4-methylene-THP derivatives [439].



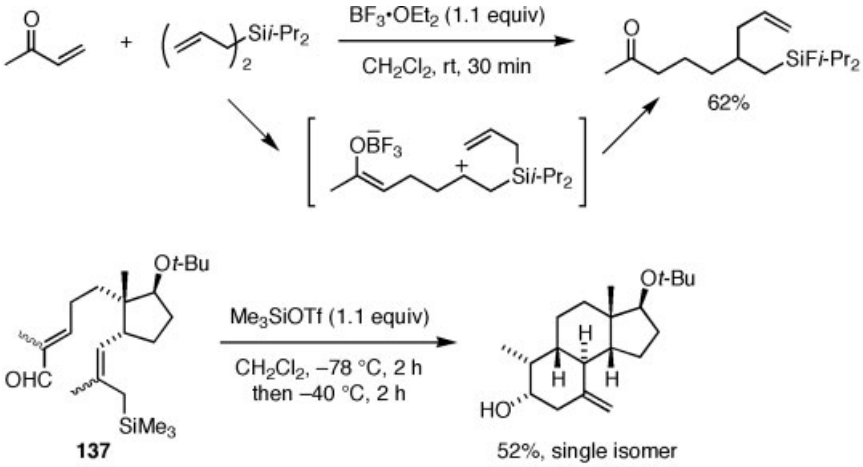
Scheme 10.157

Leighton et al. have developed tandem intramolecular silylformylation–allylation using diallylhydrosilyl ethers derived from homoallyl alcohols (Scheme 10.158) [440]. This reaction is a convenient means of stereoselective synthesis of 1,3,5-triols convertible to more oxygen-functionalized compounds [441]. The second allylation step of the tandem process occurs without any promoter. The intramolecular allylation would be facilitated by the formation of a strained silacycle intermediate, the silicon center of which has enough Lewis acidity to activate the formyl group. The tandem reaction using substrates derived from homopropargyl alcohols achieves the stereoselective synthesis of 1,5-diols by remote 1,5-asymmetric induction (Scheme 10.158) [442].

The $BF_3 \cdot OEt_2$-promoted reaction of α-enones with diallylsilanes forms conjugate adducts bearing a 2-silylmethyl-4-pentenyl group at the β-position (Scheme 10.159) [443]. The tandem allylation would proceed via intramolecular allylation of the β-silylcarbenium ion intermediate generated by the initial conjugate addition of diallylsilanes. Allylsilane **137**, bearing an α-enal moiety, can be transformed into a tricyclic product with high diastereoselectivity by the TMSOTf-promoted tandem conjugate allylation–carbonyl ene reaction [444].

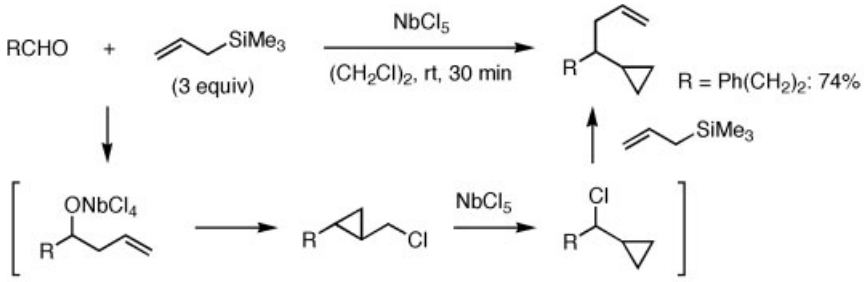


Scheme 10.158



Scheme 10.159

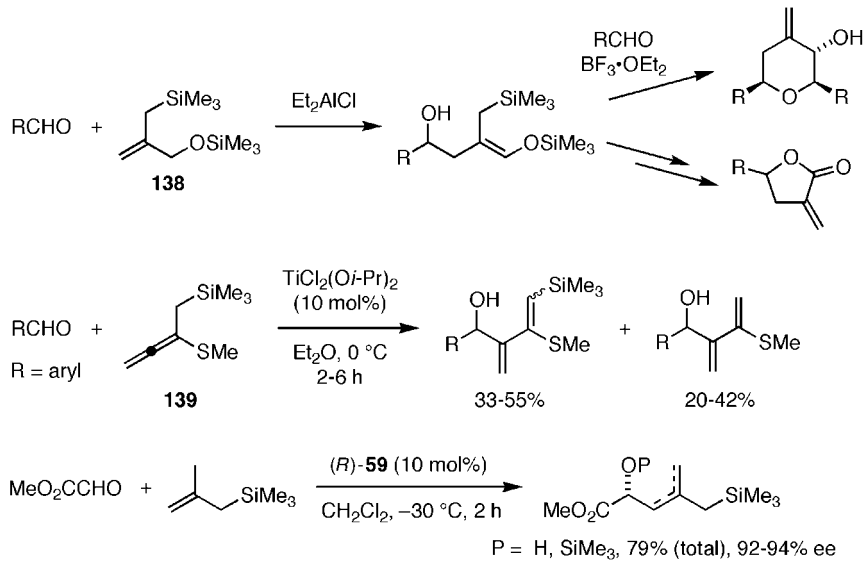
In the presence of $NbCl_5$, allyltrimethylsilane reacts with aldehydes in 2:1 stoichiometry with concomitant formation of a cyclopropane ring (Scheme 10.160) [445]. It has been proposed that this reaction proceeds via cationic isomerization of a cyclopropylmethyl chloride intermediate.



Scheme 10.160

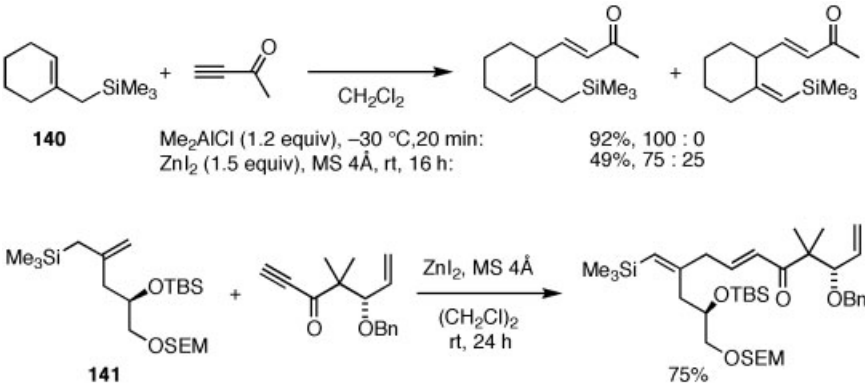
10.3.2
Ene Reactions of Allylsilanes

Allylsilanes substituted at the *β*-position sometimes undergo Lewis acid-promoted ene reactions with carbon electrophiles such as aldehydes and *α,β*-unsaturated carbonyl compounds to give allylsilane and vinylsilane products. The Et_2AlCl-promoted reaction of *β*-siloxymethyl-substituted allylsilane **138** with aldehydes forms more functionalized allylsilanes, which are useful for syntheses of *exo*-methylene-THP derivatives and *γ*-butyrolactones (Scheme 10.161) [446]. The use of $TiCl_4$ leads to the formation of the normal allylation products. We have reported the ene-type reaction of allenylmethylsilane **139** with aldehydes [447]. Highly enantioselective carbonyl–ene reaction of methallylsilanes using the BINOL-Ti complex (*R*)-**59** has been achieved by Mikami et al. [399b].



Scheme 10.161

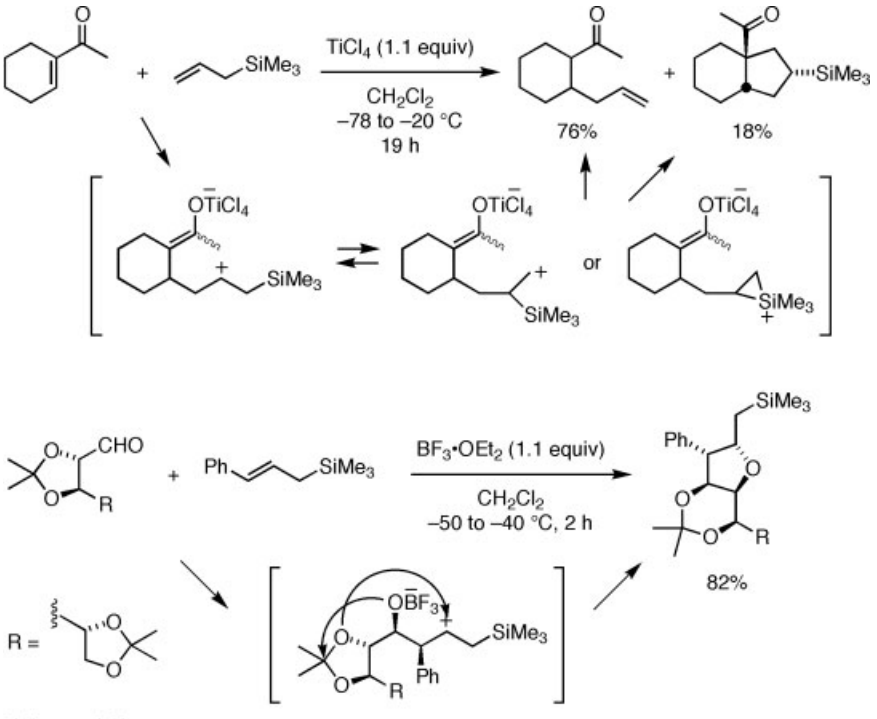
In the presence of Me_2AlCl, isocyclic allylsilane **140** reacts with 3-butyn-2-one to give an α-enone bearing an allylsilane moiety in high yield (Scheme 10.162) [448]. The ZnI_2-promoted reaction provides an α-enone bearing a vinylsilane moiety as a minor product. In contrast, under similar reaction conditions reaction of allylsilane **141** with an α-ynone forms a vinylsilane product with high regioselectivity [449].



Scheme 10.162

10.3.3
Lewis Acid-promoted Cycloadditions

In the nineteen-eighties, Danheiser [4, 450] and Miginiac [451] reported Lewis acid-promoted [3+2] cycloadditions of allenylsilanes and propargylsilanes, which provide efficient routes to unsaturated five-membered carbocycles and heterocycles. The reaction mechanism for these silicon-directed cycloadditions would involve formation of an unsaturated β-silylcarbenium ion intermediate (R_3Si–CR^1=C^+R^2 or R^1CH=C^+–$CHR^2(SiR_3)$), 1,2-silyl migration, and intramolecular addition to the cationic center. A similar cycloaddition of allyltrimethylsilane to α-enones was introduced by Knölker et al. in 1990 [452, 453] (Scheme 10.163). They pointed out that the cyclic silylated by-products in the Lewis acid-promoted reaction of allyltrimethylsilane with α-enones are not cyclobutanes ([2+2] adducts) but cyclopentanes ([3+2] adducts) although other researchers had incorrectly assigned the by-products to cyclobutanes [454]. In the same year, Sugimura reported that the $BF_3 \cdot OEt_2$-promoted reaction of α-oxyaldehydes with allylsilanes gives 2-silylmethyl-THF derivatives in good yields [455] (Scheme 10.163). It was proposed that this cycloaddition also proceeded via intramolecular nucleophilic addition to a β-silylcarbenium ion. These studies by Knölker and Sugimura thus revealed the utility of saturated β-silylcarbenium ions arising from allylsilanes for intramolecular bond formation, and thus initiated recent progress in Lewis acid-promoted cycloadditions using allylsilanes [334, 456].



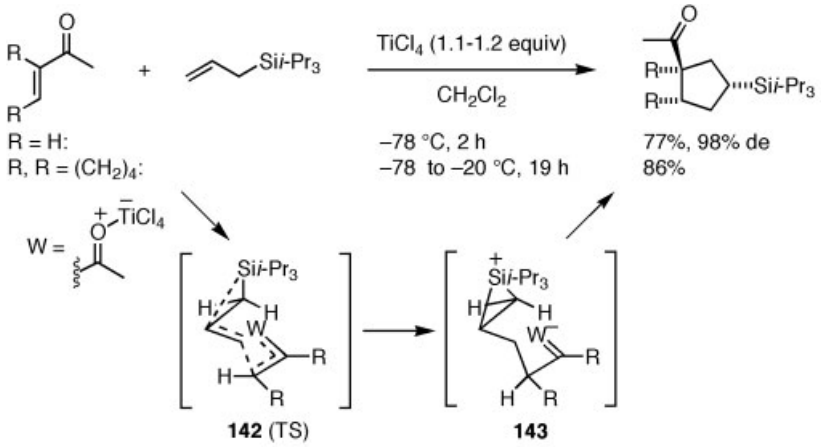
Scheme 10.163

10.3.3.1 **Cycloadditions with 1,2-Silyl Migration**

The 1,2-silyl migrative [3+2] cycloadditions of allylsilanes are applicable to a variety of electron-deficient multiple bonds. High diastereoselectivity is usually observed. These silicon-directed reactions are, therefore, valuable for stereocontrolled syntheses of highly functionalized five-membered carbocycles and heterocycles.

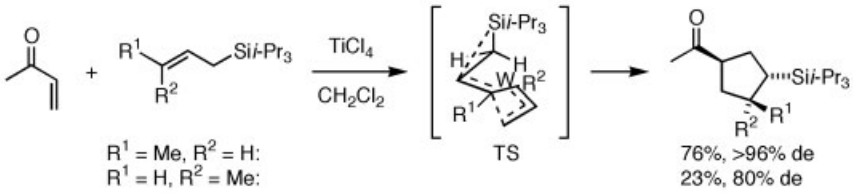
Cycloadditions to Electron-deficient Alkenes and Alkynes

As unambiguously proved by Knölker et al. [452], the Lewis acid-promoted reaction of some α-enones with allyltrimethylsilanes forms trimethylsilylcyclopentanes as well as conjugated allylation products [457]. Danheiser [458] and Knölker [459] have revealed that allylsilanes bearing a bulky silyl group such as *i*-Pr_3Si (TIPS) can achieve highly efficient and stereoselective [3+2] cycloaddition to a variety of α-enones (Scheme 10.164). The stereochemical outcomes can be rationalized in terms of synclinal transition structure **142** in which the carbonyl group assumes *endo* orientation toward the allyl group [458]. The bulky silyl group decelerates the path leading to allylation products, probably by suppressing nucleophilic attack on the silicon center of the β-silylcarbenium ion intermediate **143**.



Scheme 10.164

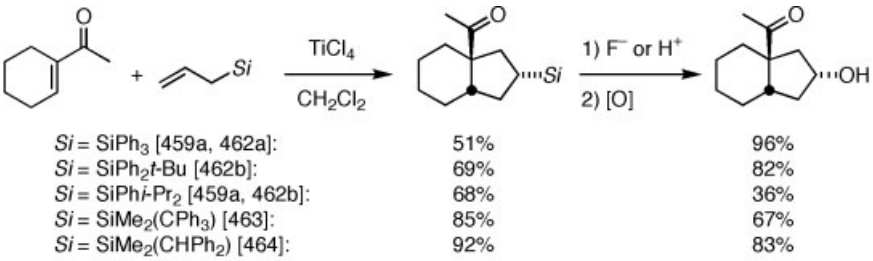
The cycloaddition of (*E*)- and (*Z*)-crotyltriisopropylsilanes to methyl vinyl ketone proceeds stereospecifically (Scheme 10.165): *r*-1-acetyl-*c*-3-methyl-*t*-4-silylcyclopentane is obtained from the *E* isomer, and the *r*-1,*t*-3,*t*-4 isomer is the major product in the reaction of the *X* isomer. These observations also can be interpreted in terms of a transition structure similar to **142** [460].



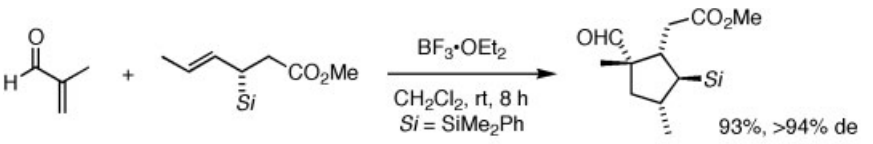
Scheme 10.165

It is well recognized that some silyl groups serve as efficient latent hydroxy groups [461]. In the [3+2] cycloaddition of an allylsilane the silyl group remains in the cyclic product. From the viewpoint of synthetic utility, therefore, the silyl group should not only be effective in promoting the cycloaddition but also readily convertible to a hydroxy group by oxidative cleavage of the silicon–carbon bond. Allyltriisopropylsilane is an efficient reagent for [3+2] cycloaddition to enones; it is, however, quite difficult to convert the silyl group into a hydroxy group. To solve this problem new allylsilanes bearing a bulky and easily oxidizable silyl group have been developed (Scheme 10.166) [462–465].

The reaction of homochiral crotylsilanes with α-enones and α-enals is very valuable for the asymmetric synthesis of multi-substituted cyclopentanes (Scheme 10.167) [466].



Scheme 10.166

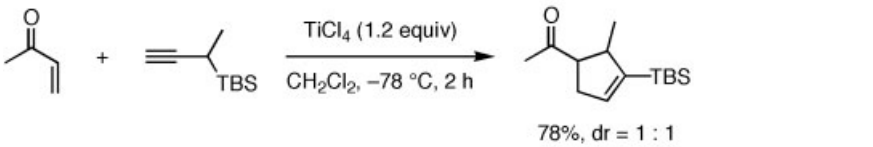


Scheme 10.167

The activated carbon–carbon double bonds of *p*-quinones and *p*-quinoneimines are suitable for the [3+2] cycloaddition [467]. Interestingly, the reaction of naphthoquinone at –78 °C provides a mixture of [2+2] and [3+2] adducts, although the former product is not observed at 0 °C (vide infra).

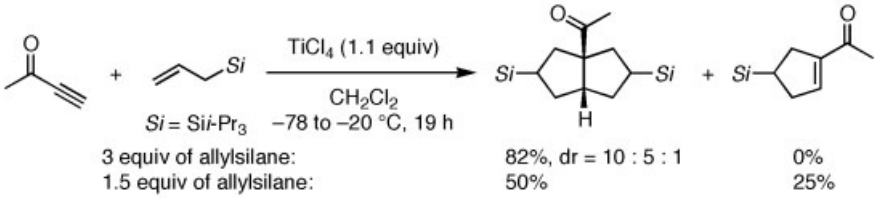
The intramolecular version of the [3+2] addition is a powerful method for stereocontrolled construction of a bicyclic system [426].

In the presence of $TiCl_4$, *α*-substituted propargylsilanes bearing a bulky silyl group also add to *α*-enones to give cyclopentenes in good yields (Scheme 10.168) [458]. The [3+2] cycloaddition does not occur when *α*-unsubstituted propargylsilanes are used. The *α*-substituent would facilitate the requisite 1,2-silyl migration by stabilizing the rearranged *β*-silylcarbenium ion intermediate.



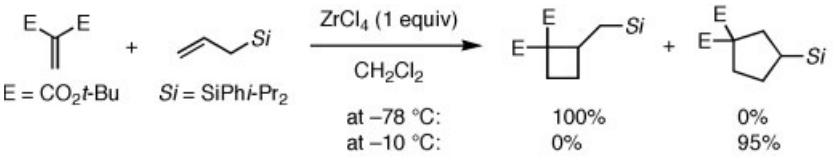
Scheme 10.168

3-Butyn-2-one undergoes tandem [3+2] cycloadditions of allyltriisopropylsilane to give a bicyclo[3.3.0]octane as a mixture of three possible diastereomers in a good yield (Scheme 10.169) [468]. The use of a reduced amount of the allylsilane forms a silylated cyclopentene as a minor product. This indicates that the 1 : 1 cycloadduct is the precursor of the bicyclic product. In contrast, the ZnI_2 or Me_2AlCl-promoted reaction of 3-butyn-2-one with an isocyclic allyltrimethylsilane affords a [2+2] adduct without [3+2] adducts [448a, 469] (vide infra).



Scheme 10.169

The Lewis acid-promoted reactions of acrylates and propiolates with allylsilanes usually afford [2+2] adducts as described in the next section [470–473]. The corresponding [3+2] adducts are obtained as minor products although there are a few exceptions. The ratio of the two kinds of cycloadduct depends on the reaction temperature [470] – the proportion of [3+2] adducts increases with increasing temperature. The product ratio from cycloaddition to alkylidenemalonates and their derivatives is markedly temperature-dependent (Scheme 10.170) [474, 475]. Cyclobutanes are major products at low temperature, and [3+2] cycloaddition proceeds predominantly at higher temperature. In addition, the [2+2] cycloadducts are smoothly isomerized to the [3+2] adducts in the presence of a Lewis acid. This behavior clearly shows that [3+2] cycloaddition is thermodynamically favored.



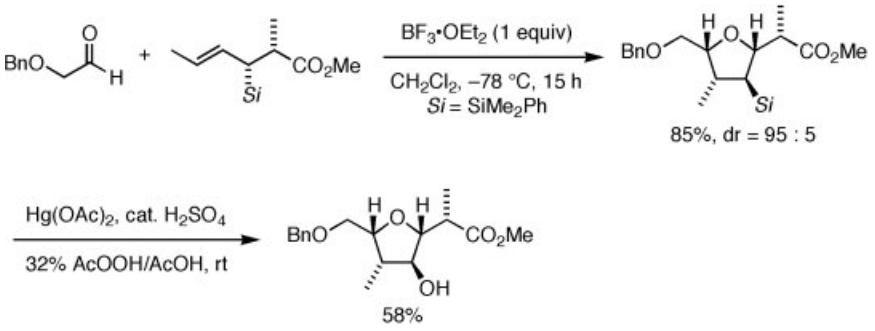
Scheme 10.170

Cycloadditions to Aldehydes, Ketones, Aldimines, and Isocyanates

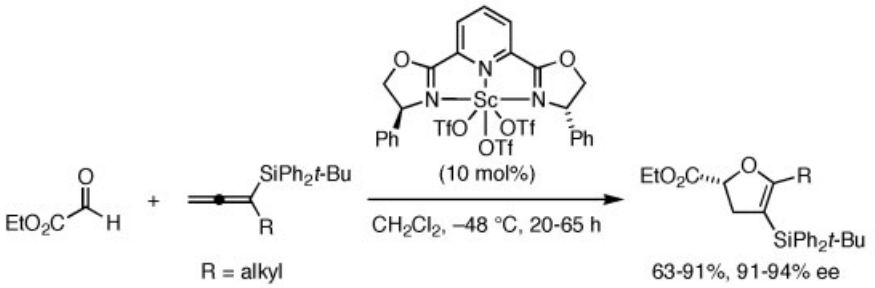
The Lewis acid-promoted reaction of aldehydes with α-substituted allylsilanes affords 3-silyltetrahydrofurans, in good to high yields, with homoallyl alcohols [476–479]. The use of homochiral α-substituted allyl- and crotyldimethylphenylsilanes realizes highly diastereo- and enantioselective syntheses of tri- and tetrasubstituted THF derivatives, which can be converted into 3-hydroxy-THF derivatives by oxidative cleavage of the carbon–silicon bond (Scheme 10.171) [476–478].

The [3+2] cycloaddition of aldehydes with α-substituted allenylsilanes is a powerful means of access to dihydrofurans [450b]. Quite recently Evans et al. reported the first example of the catalytic asymmetric version using a chiral scandium triflate complex (Scheme 10.172) [480].

Reactive ketones such as α-keto esters also undergo [3+2] cycloaddition with allylsilanes to give multi-substituted THF derivatives with high diastereoselectivity (Scheme 10.173) [481]. Interestingly, the reaction of allyl-*t*-butyldiphenylsilane at –78 °C forms a 2-silylmethyloxetane as the major product with 3-silyltetrahydrofur-

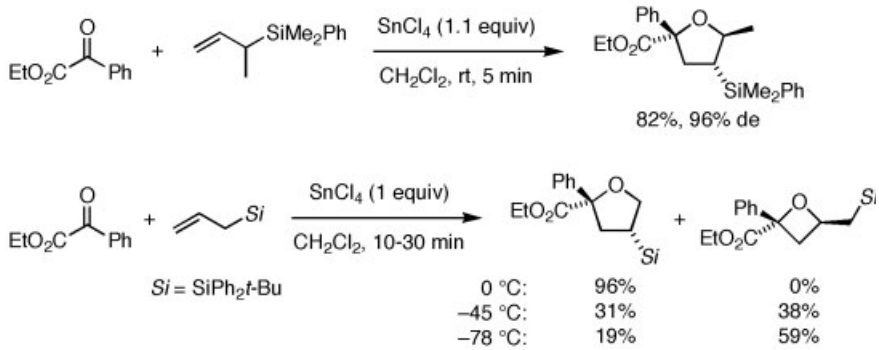


Scheme 10.171



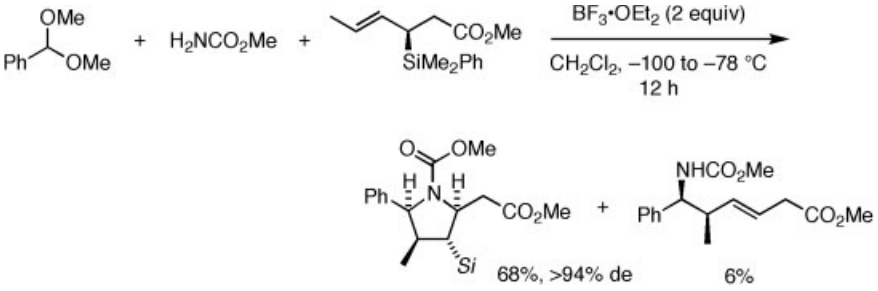
Scheme 10.172

an, although no [2+2] cycloadduct is observed at 0 °C [482]. Intramolecular [3+2] cycloaddition to ketones is a convenient means of construction of polycyclic systems containing a THF ring [483].



Scheme 10.173

The [3+2] cycloaddition of allylsilanes is applicable to imines and iminium salts [419, 484, 485]. Highly substituted pyrrolidines can be synthesized with high diastereo and enantio control by reaction of homochiral crotylsilanes with carbon–nitrogen double bond generated in situ from acetals and methyl carbamate (Scheme 10.174) [419]. The cycloaddition to *N*-tosylaldimines of aromatic aldehydes proceeds with excellent 2,4-*cis* selectivity whereas the stereoselectivity with aliphatic aldimines is rather low [484]. With *N*-tosylaldimines, the formation of [2+2] adducts is not observed (vide infra).



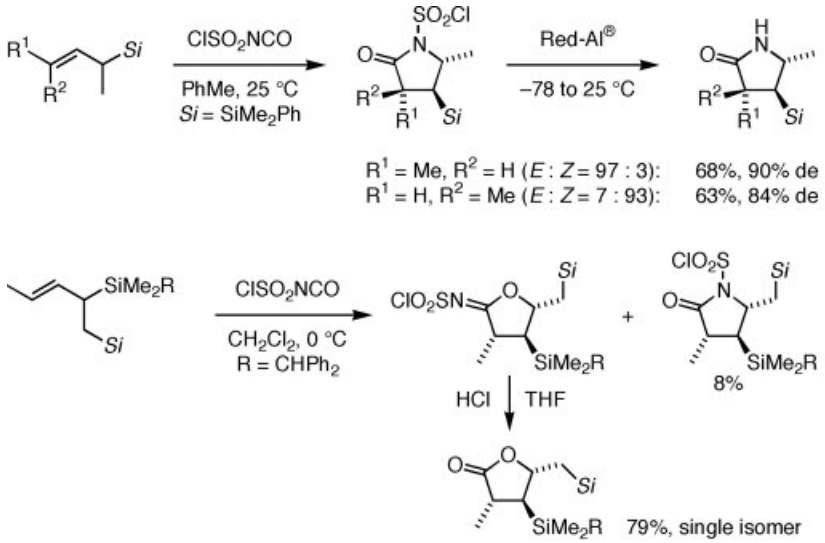
Scheme 10.174

N-Chlorosulfonyl isocyanate reacts spontaneously with *α*-substituted allylsilanes at room temperature to give *N*-chlorosulfonyl-2-pyrrolidinones with high diastereoselectivity (Scheme 10.175) [486, 487]. The unstable products can be reduced to stable *N*-unsubstituted 2-pyrrolidinones with Red-Al. The cycloaddition of (*E*)- and (*Z*)-crotylsilanes proceeds stereospecifically. In contrast with results obtained with *α*-substituted allylsilanes, *α*-unsubstituted allylsilanes favor the [2+2] pathway. Use of allylsilanes bearing a bulky group at the *α*-position effects predominant formation of *N*-chlorosulfonyl iminolactones, formed by cycloaddition across the carbon–oxygen double bond [488]. The iminolactones can be efficiently converted into the corresponding lactones by hydrolysis with 1 M HCl in THF. These [3+2] cycloadditions across the carbon–oxygen and carbon–nitrogen bonds of *N*-chlorosulfonyl isocyanate have been used for the synthesis of natural products [488, 489].

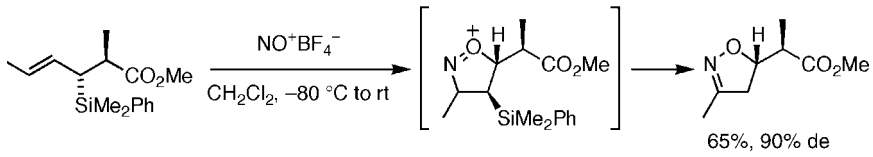
Nitrosium tetrafluoroborate ($NOBF_4$) also undergoes [3+2] cycloaddition to *α*-substituted allylsilanes without use of a promoter (Scheme 10.176) [490]. The Δ^2-isoxazoline products would be formed by deprotonation and the subsequent protodesilylation of the initial [3+2] adducts, Δ^1-isoxazolines. Δ^2-Isoxazolines serve as precursors of *β*-hydroxy ketones and *γ*-amino alcohols.

Other 1,2-Silyl Migrative Cycloadditions

In the presence of a catalytic or substoichiometric amount of $AlCl_3$ and excess TMSCl, unactivated conjugated dienes react with allyltrimethylsilane to afford *trans*-1-trimethylsilyl-3-vinylcyclopentanes without the *cis* isomers (Scheme 10.177) [491]. The mechanism proposed for the [3+2] cycloaddition involves addition of a

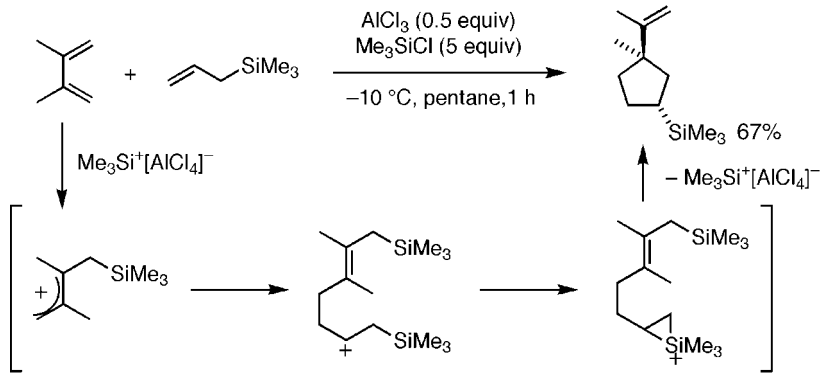


Scheme 10.175



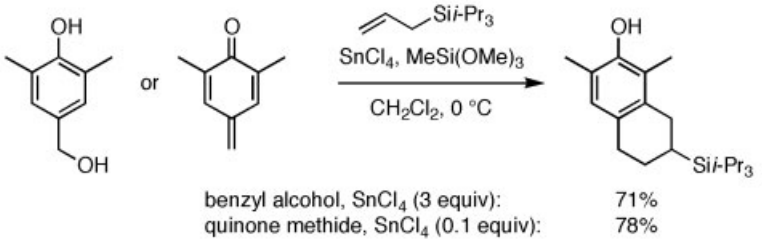
Scheme 10.176

trimethylsilyl cation or its equivalent to a diene, electrophilic attack of the resulting allyl cation to allyltrimethylsilane, and 1,2-silyl migrative cyclization of the resulting β-silylcarbenium ion intermediate.



Scheme 10.177

Allylsilanes serve as three-carbon dipole equivalents for the synthesis of tetrahydronaphthalenes by formal [3+3] cycloaddition to benzyl cations generated from benzyl alcohols and quinone methides by the action of $SnCl_4$ (Scheme 10.178) [492]. With secondary and tertiary benzyl cations a competing [3+2] pathway leads to the formation of dihydro(1*H*)indenes.

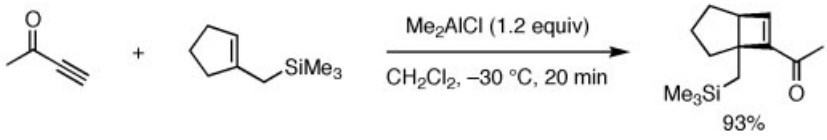


Scheme 10.178

10.3.3.2 [2+2] Cycloadditions

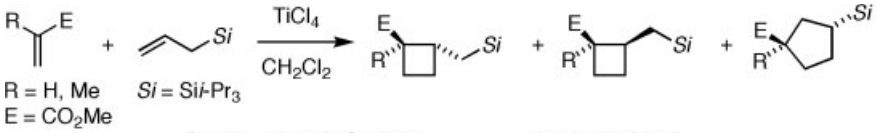
Several uncatalyzed [2+2] cycloadditions of allylsilanes to highly activated carbon–carbon and carbon–heteroatom bonds were reported before and during 1990 [493]. The first example of Lewis acid-promoted [2+2] cycloaddition of allyltrimethylsilane was introduced by Snider et al. in 1979 [494]. They reported that the $AlCl_3$-promoted reaction of methyl propiolate with allyltrimethylsilane forms a cyclobutene. In the last decade similar cycloadditions to a variety of electron-deficient unsaturated bonds have been developed for efficient syntheses of cyclobutanes, cyclobutenes, oxetanes, and azetidines, as described below.

The Me_2AlCl-promoted reaction of naphthoquinone with allyltrimethylsilane at –78 °C gives [2+2] and [3+2] adducts in 34% and 23% yield, respectively [467a]. When the reaction is warmed to 0 °C, the latter adduct is formed in a quantitative yield. Under similar reaction conditions 3-butyn-2-one reacts with an isocyclic allyltrimethylsilane to afford the corresponding [2+2] adduct only in high yield (Scheme 10.179) [448a]. The ZnI_2-catalyzed reaction of 3-butyn-2-one with allyltriisopropylsilane also favors the [2+2] pathway [471]. This is in sharp contrast with $TiCl_4$-catalyzed reaction of the same compounds, which furnishes [3+2] adducts, as shown in Scheme 10.169 [468].



Scheme 10.179

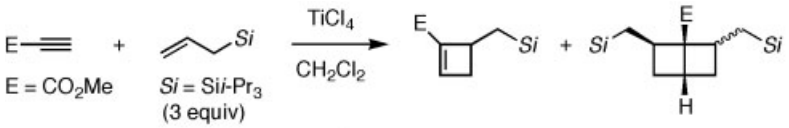
α,β-Unsaturated esters and their derivatives are efficient substrates for Lewis acid-catalyzed [2+2] addition of allylsilanes. $TiCl_4$-catalyzed reaction of acrylates and maleates with allylsilanes bearing a bulky silyl group furnishes a diastereomeric mixture of [2+2] adducts as the major product, with a small amount of the [3+2] adduct (Scheme 10.180) [470]. In reaction with methyl methacrylate at higher temperature (40 °C), however, [3+2] cycloaddition is the main path. With alkylidenemalonates and their derivatives selective synthesis of both [2+2] and [2+3] adducts can be achieved by a proper choice of reaction temperature as shown in Scheme 10.170 [474, 475].



R = H, –40 to 0 °C, 19 h:	100%, 42 : 53 : 5
R = H, 40 °C, 3 h:	97%, 19 : 70 : 11
R = Me, –78 to –20 °C, 19 h:	40%, 81 : 9 : 10
R = Me, –78 to 40 °C, 19 h:	57%, 28 : 5 : 67

Scheme 10.180

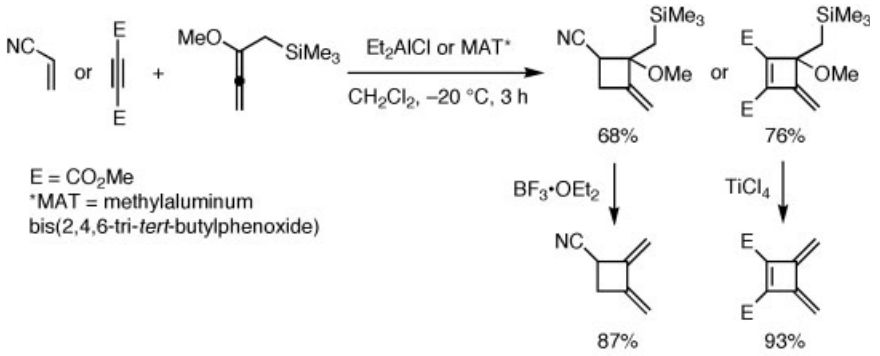
The Lewis acid-promoted reaction of methyl propiolate with allylsilanes usually proceeds with selective formation of cyclobutenes [470–472]. Use of excess allyltriisopropylsilane at high temperature induces double [2+2] cycloaddition, forming a bicyclo[2.2.0]hexane (Scheme 10.181) [470]. The [2+2] cycloadditions of (*E*)- and (*Z*)-crotylsilanes occur stereospecifically [495]. As an exceptional example, it has been reported that a cyclic allylsilane causes [3+2] cycloaddition to methyl propiolate in preference to the [2+2] cycloaddition [472].



–78 to –20 °C, 19 h:	98%	-
25 to 40 °C, 19 h:	34%	64%

Scheme 10.181

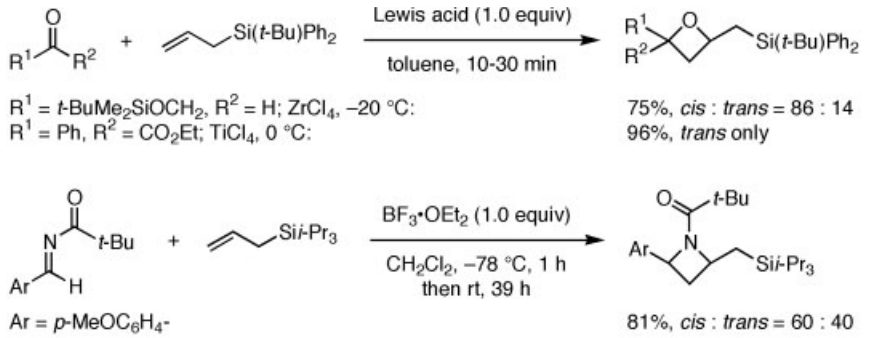
We have reported that an allenylmethylsilane adds smoothly to electron-deficient alkenes and alkynes to give [2+2] adducts (Scheme 10.182) [496]. The products are easily convertible to di-*exo*-methylenecyclobutanes and -cyclobutenes valuable for further ring-construction by the DA reaction.



Scheme 10.182

The Lewis acid-promoted intramolecular addition of a propargylsilane to a doubly activated alkene constructs a fused cyclobutene unit [497]. The propargylsilane serves as a 1,2-dipole equivalent.

The [2+2] cycloaddition of allylsilanes is applicable to the synthesis of substituted oxetanes from aldehydes and ketoesters [482, 498]. With aldehydes a $ZrCl_4$-mediated system using toluene as solvent is effective in the formation of oxetanes, whereas ketoesters are efficiently converted into oxetanes in a $TiCl_4$-mediated system (Scheme 10.183). *N*-Acylaldimines also undergo a similar [2+2] cycloaddition to afford azetidines [414]. The reactivity of *N*-acylaldimines to allyltriisopropylsilane is completely different from that of *N*-tosylaldimines, which are transformed into [3+2] cycloadducts by the $BF_3 \cdot OEt_2$-promoted reaction [484].

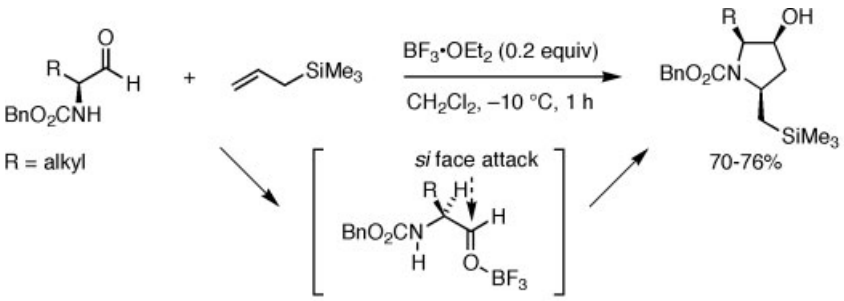


Scheme 10.183

10.3.3.3 **Other Cycloadditions without 1,2-Silyl Migration**

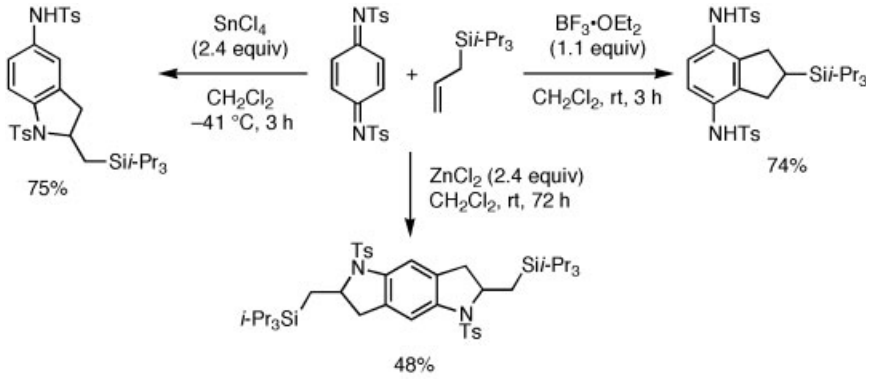
The $BF_3 \cdot OEt_2$-promoted reaction of α-oxyaldehydes with allylsilanes provides a highly stereoselective route to substituted THF derivatives (Scheme 10.163) [455]. This cycloaddition has been successfully used for the total synthesis of (–)-*trans*-kumausyne [499]. A similar reaction using α-aminoaldehydes is valuable for highly

stereoselective synthesis of 2,3,5-trisubstituted pyrrolidines with all-*cis* configurations (Scheme 10.184) [500]. Use of a catalytic amount of $BF_3 \cdot OEt_2$ is effective in the formation of the cycloadducts. The stereochemical outcome, i.e. chelation-controlled stereochemistry, might result from the inherent conformational arrangement of the aldehyde–BF_3 complex.



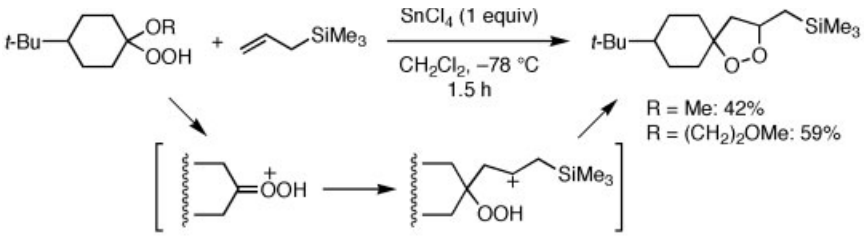
Scheme 10.184

p-Quinoneimines also undergo a similar cycloaddition in which an allylsilane works as a 1,2-dipole equivalent (Scheme 10.185) [467 b]. The $SnCl_4$-promoted reaction of *p*-quinone di-*N*-tosylimine with allyltriisopropylsilane at –41 °C leads to the selective formation of a dihydroindole derivative. The use of $ZnCl_2$ at room temperature induces double cycloaddition to construct two *N*-containing cyclic units. Interestingly, when the reaction is promoted by $BF_3 \cdot OEt_2$ the allylsilane works as a 1,3-dipole equivalent to afford an indan derivative, as in the reaction of naphthoquinone [466 a].



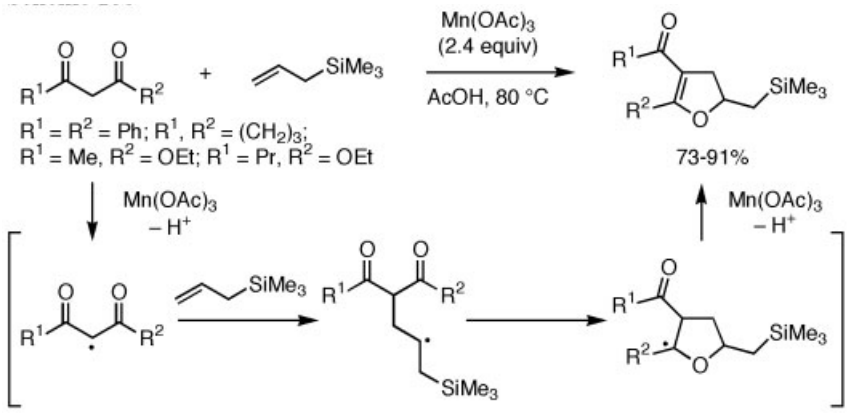
Scheme 10.185

Alkoxyhydroperoxides, readily prepared by ozonolysis of alkenes in the presence of an alcohol, can be transformed into 1,2-dioxolanes by Lewis acid-promoted reaction with allyltrimethylsilane (Scheme 10.186) [501]. This cycloaddition would proceed via a hydroperoxycarbenium ion and a β-silylcarbenium ion bearing a hydroperoxy group.



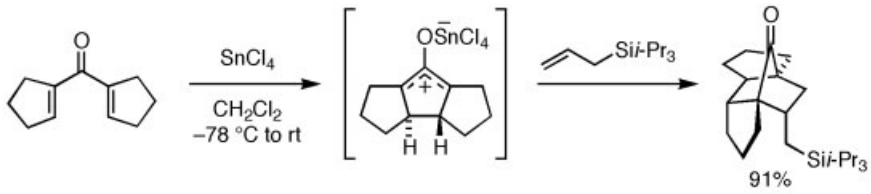
Scheme 10.186

In the presence of $Mn(OAc)_3 \cdot 2H_2O$ in AcOH, allyltrimethylsilane reacts with 1,3-diketones and β-ketoesters to give trisubstituted dihydrofurans in good to high yield (Scheme 10.187) [502]. $Mn(OAc)_3$ serves as an oxidizing agent to generate an electrophilic carbon radical intermediate from the substrate. It is probable that annulation of the carbon radical with the allylsilane followed by oxidation with another equivalent of Mn(III) forms the silicon-containing cyclic products.



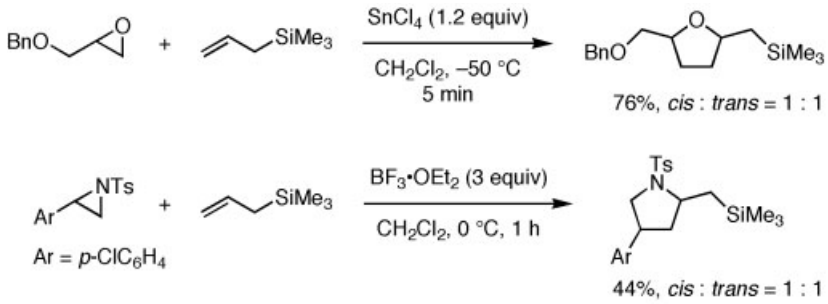
Scheme 10.187

Allylsilanes are good acceptors of 1,3-dipolar compounds such as nitrones [503] and oxyallyl cations [504]. West et al. have used allylsilanes to trap oxyallyl cations generated during the Nazarov cyclization of 1,4-dien-3-ones (Scheme 10.188). The tandem bicyclization provides bicyclo[2.2.1]heptanes with high diastereoselectivity.



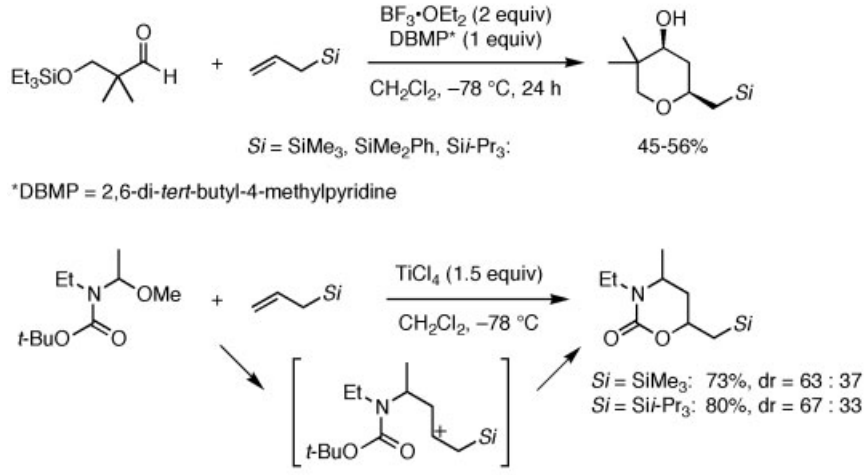
Scheme 10.188

The 1,3-dipole species arising from electronically activated cyclopropanes and a Lewis acid can be trapped by allylsilanes [505, 506]. Epoxides [507] and aziridines [508] also serve as 1,3-dipole precursors to react with allylsilanes inter- or intramolecularly, affording 2-silylmethyl-THF derivatives and pyrrolidines, respectively (Scheme 10.189).



Scheme 10.189

The cycloaddition using allylsilanes as 1,2-dipole equivalents is applicable to the construction of six-membered rings. *β*-Oxyaldehydes as well as *α*-oxyaldehydes undergo Lewis acid-promoted cycloaddition with allylsilanes to provide substituted THP derivatives in moderate yields (Scheme 10.190) [509]. When *N*-*t*-butoxycarbonyl-*O,N*-acetals are used as the substrates, silylated oxazinones are obtained as major products [510]. In this reaction the *t*-butoxycarbonyl group adds to a *β*-silylcarbenium ion intermediate for ring-closure.

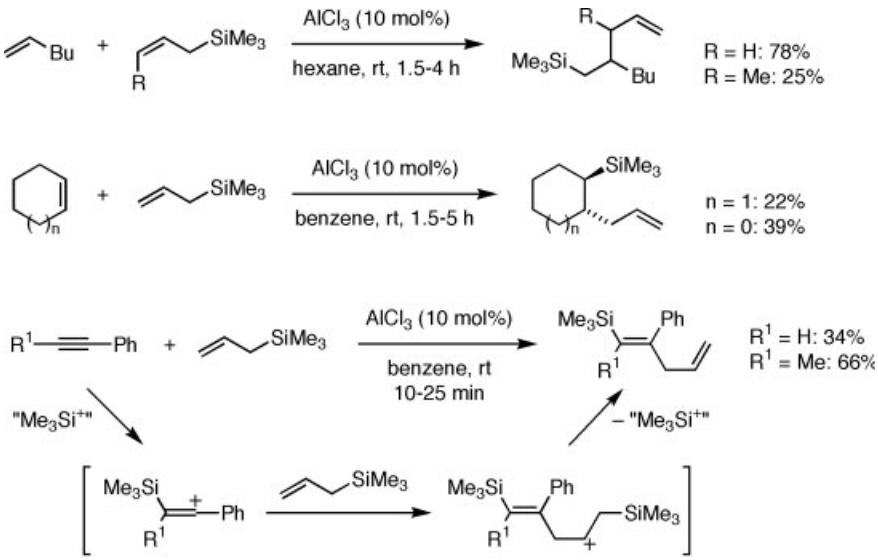


Scheme 10.190

10.3.4

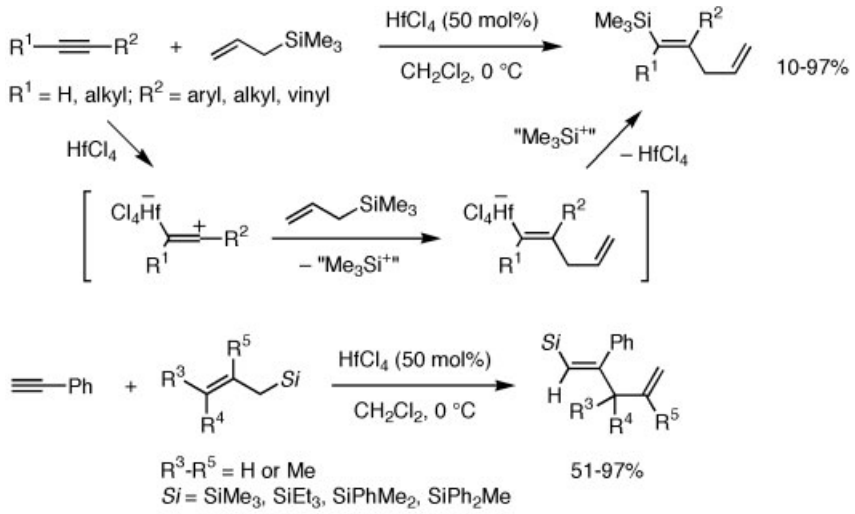
Lewis Acid-catalyzed Carbosilylation of Unactivated Alkynes and Alkenes

The Lewis acid-catalyzed allylsilylation of alkynes and alkenes with allylsilanes was introduced by Jung [511] and Yamamoto [512]. Jung and co-workers found that $AlCl_3$ catalyzes the allylsilylation of simple alkenes and phenyl-substituted alkynes with allylsilanes (Scheme 10.191) [513]. The allylation occurs regiospecifically at the γ-position of the allylsilanes. When cycloalkenes are used as substrates, *trans* adducts are obtained exclusively. Jung et al. initially reported [513a] that the allylsilylation of alkynes proceeded in a *cis*-addition mode; they later noted, however, that the stereochemical assignment of the allylsilylation products was incorrect and the products were not *cis* but *trans* adducts [511]. It has been proposed that the mechanism of the $AlCl_3$-catalyzed allylsilylation involves addition of a silyl cation or its equivalent to the carbon–carbon multiple bond and subsequent allylation of the resulting β-silylcarbenium ion [511].



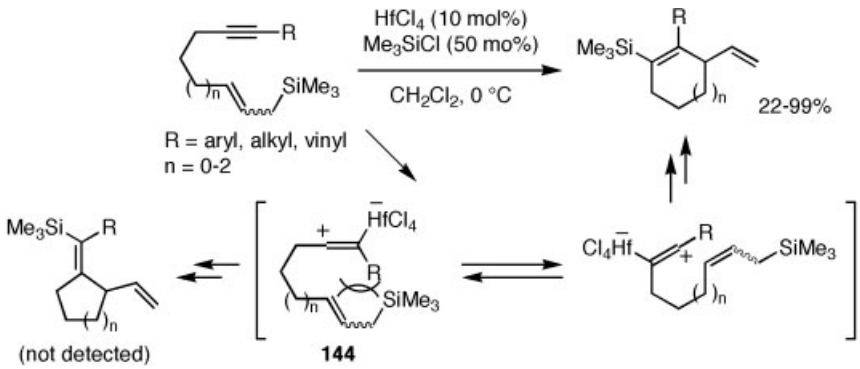
Scheme 10.191

Yamamoto et al. have systematically studied the Lewis acid-catalyzed carbosilylation of alkynes with allylsilanes and related compounds [512]. They have disclosed that the $EtAlCl_2$ (cat.)–Me_3SiCl (excess) catalyst system or a sub-stoichiometric amount of $HfCl_4$ effectively induces the *trans*-allylsilylation of the alkynes (Scheme 10.192) [514]. The $HfCl_4$-promoted method, in particular, is quite useful for stereo- and regioselective allylsilylation of a variety of allylsilanes under mild conditions. In sharp contrast to the mechanism proposed by Jung et al., Yamamoto et al. have proposed that $EtAlCl_2$ or $HfCl_4$ adds to an alkyne, the activated alkyne is allylated by an allylsilane, and the resulting vinylmetal becomes an allylsilylation product by transmetalation.



Scheme 10.192

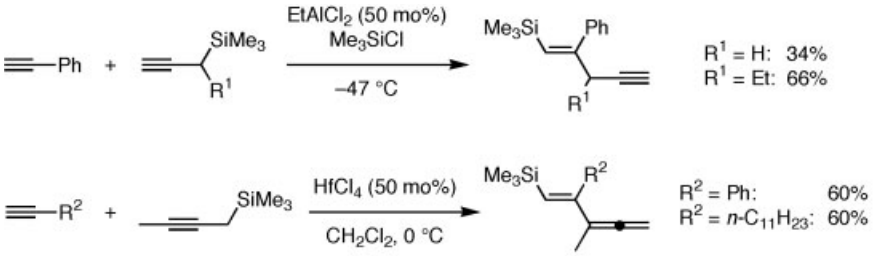
Intramolecular allylsilylation of alkynes is a convenient route to cyclic vinylsilanes. The $HfCl_4$–Me_3SiCl catalyst system effectively induces *endo* cyclization of alkynylated allylsilanes to 1-silyl-3-vinylcycloalkenes (Scheme 10.193) [515]. The *endo* selectivity is probably because the *exo* cyclization pathway via zwitterionic intermediate **144** is inhibited by a severe steric repulsion between the substituent R and the allylsilane moiety.



Scheme 10.193

The $EtAlCl_2$–Me_3SiCl catalyst system enables efficient *trans* carbosilylation of alkynes with propargylsilanes (Scheme 10.194) [516]. The use of γ-unsubstituted propargylsilanes leads to the formation of β-propargylated vinylsilanes, and the expected β-allenylated vinylsilanes are not obtained. In contrast, carbosilylation with

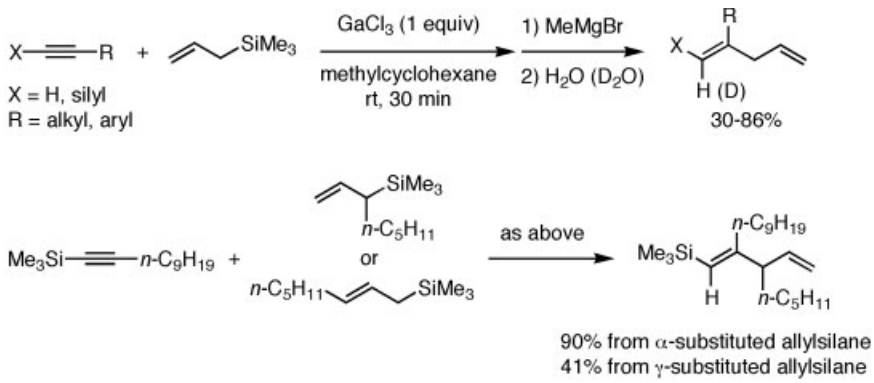
γ-substituted propargylsilanes provides the expected β-allenylated vinylsilanes. In the former reaction γ-unsubstituted propargylsilanes are isomerized to allenylsilanes under the conditions used. This isomerization is responsible for the formation of β-propargylated vinylsilanes.



Scheme 10.194

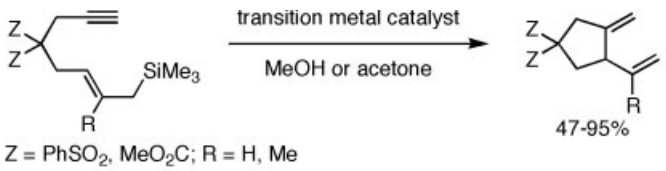
10.3.5
Metal-promoted Allylation of Alkynes and Dienes

In the presence of $GaCl_3$ allylsilanes smoothly add to simple terminal alkynes and silylated alkynes to give allylation products in moderate to good yield (Scheme 10.195) [517]. Allylation of 1-silyl-1-alkynes proceeds in a *syn*-addition mode. Quenching the reaction mixture with deuterium oxide forms deuterated products; this is indicative of the presence of vinylgallium species. Reaction of an alkyne with two regioisomeric allylsilanes furnishes the same allylation product. These observations are consistent with a stepwise mechanism including the formation of an allylgallium species and subsequent metallo–ene reaction with an alkyne.



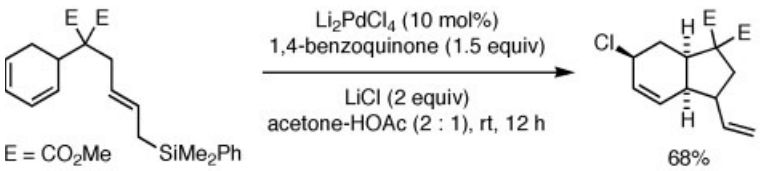
Scheme 10.195

Intramolecular allylation of alkynes with allylsilanes is catalyzed by a variety of electrophilic transition metal halides and complexes (e.g. Pt(II), Pd(II), Ru(II), Au(III), and Ag(I)) (Scheme 10.196) [518]. Unlike the $EtAlCl_2$- or $HfCl_4$-catalyzed reaction, alkynylated allylsilanes are cyclized in an *exo* mode by these catalysts. The proposed reaction mechanism involves nucleophilic addition of an allylsilane to a metal-coordinated alkyne.



Scheme 10.196

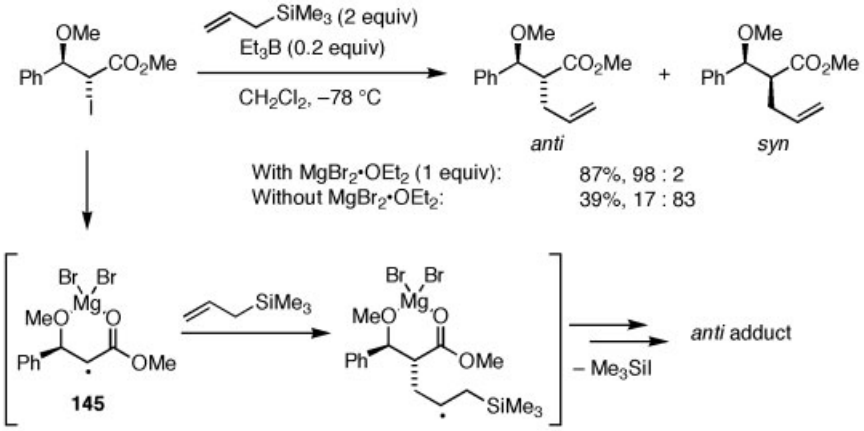
In a Pd(II)-catalyzed system using a reoxidant, allylsilanes add to 1,3-dienes intramolecularly (Scheme 10.197) [519]. The Pd(II)-catalyzed allylation achieves overall 1,4-oxidation of the dienes with high diastereoselectivity; *anti* addition of the allylsilane to a Pd(II)-coordinated diene is probably responsible for the stereochemical outcome.



Scheme 10.197

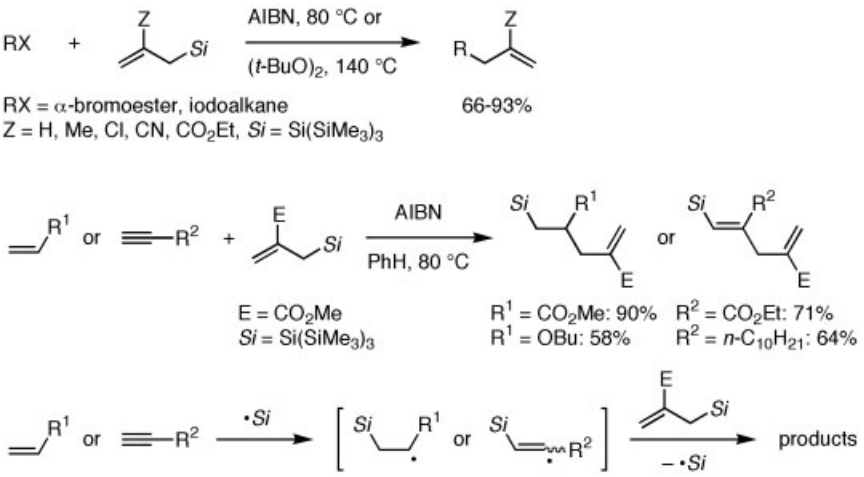
10.3.6
Homolytic Allylation

Allyltrimethylsilane is valuable for radical-initiated allylation of reactive alkyl halides and selenides [520–522]. It has been proposed that this type of allylation proceeds by atom- or group-transfer radical addition (Kharasch reaction) of the substrates to the allylsilane and subsequent elimination of silyl halides and selenides. Guindon et al. have reported highly diastereoselective allylation of *α*-halo- and *α*-selenoesters with allyltrimethylsilane in the presence of both $MgBr_2 \cdot OEt_2$ (Lewis acid) and Et_3B (radical initiator) (Scheme 10.198) [521]. Addition of the Lewis acid is effective in improving both yield and diastereoselectivity of the allylation product. Coordination of the Lewis acid to the radical intermediate **145** would enhance the reactivity to allyltrimethylsilane and serve for conformational fixation of **145**, leading to high diastereoselectivity. The use of a chiral Lewis acid enables highly enantioselective allylation of *α*-bromoamides via a similar radical process [522].



Scheme 10.198

Chatgilialoglu and Curran have found that allyltris(trimethylsilyl)silanes react with a variety of alkyl halides to provide allylation products via an S_H2' process mediated by the tris(trimethylsilyl)silyl (TTMSS) radical (Scheme 10.199) [523]. In this system the allylsilanes work as radical-allylating agents and TTMSS radical sources. We have used the reactivity of allyltris(trimethylsilyl)silanes for allylsilylation of alkenes and alkynes via a radical chain mechanism (Scheme 10.199) [524].



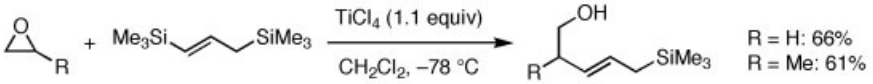
Scheme 10.199

10.4
Vinylsilanes, Arylsilanes, and Alkynylsilanes

Vinyl-, aryl-, and alkynylsilanes work as the corresponding carbanion equivalents in carbon–carbon bond-forming reactions. Electrophilic substitution of these silicon reagents with heteroatom-stabilized carbenium ions generated by the action of a Lewis acid provide powerful methods for coupling between sp^2 or sp carbon and sp^3 carbon [4, 10]. The carbon electrophiles add to the sp^2 or sp carbon adjacent to silicon to form relatively stable β-silylcarbenium ions. Subsequent elimination of the silyl group affords substitution products. Pd-catalyzed cross-coupling reaction of these silicon reagents with organic halides and pseudohalides (Hiyama coupling) is also synthetically valuable for carbon–carbon bond formation [15]. It is well established that the cross-coupling proceeds via a catalytic cycle consisting of oxidative addition, transmetalation, and reductive elimination. In the last decade much attention has been devoted to the development of new types of Lewis acid- and transition metal-catalyzed reactions.

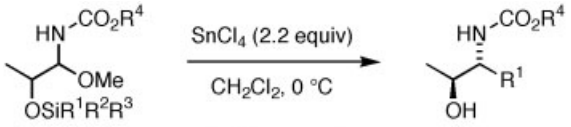
10.4.1
Lewis Acid-promoted Electrophilic Substitution

Intramolecular vinylation of Lewis acid-activated carbon electrophiles with vinylsilanes is very valuable for construction of carbocycles and oxygen- or nitrogen-containing heterocycles [4]. In contrast, there are few reports of intermolecular vinylation [525]. Schaumann et al. recently reported $TiCl_4$-promoted vinylation of epoxides with 1,3-bis(trimethylsilyl)-1-propene (Scheme 10.200) [526].



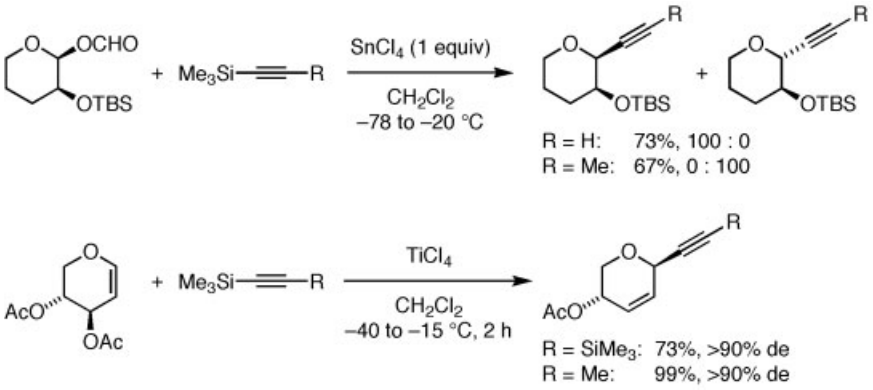
Scheme 10.200

Aldehydes, acetals, aminoacetals, and hemiaminals bearing a phenylsilyl or vinylsilyl group undergo intramolecular phenylation or vinylation on treatment with a Lewis acid [527–530]. The reaction of α-vinylsiloxy- and α-phenylsiloxy-substituted aminoacetals is suitable for highly diastereoselective synthesis of β-aminoalcohols (Scheme 10.201) [529].



Scheme 10.201

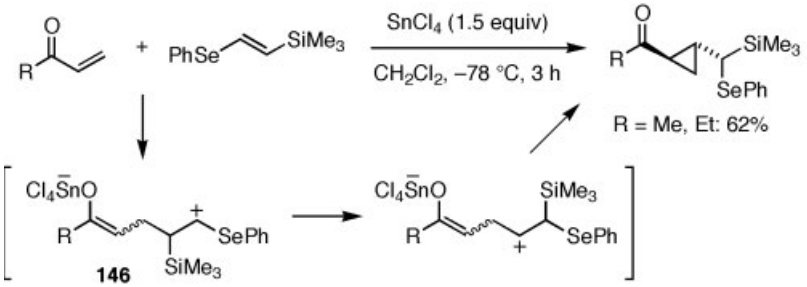
The Lewis acid-promoted alkynylation of acetals with alkynylsilanes is frequently used for the synthesis of propargyl ethers [531]. Recent studies have disclosed that the alkynylation of 2-oxy-THP derivatives and 4-oxy-3,4-dihydro-2*H*-pyrans proceeds with high diastereoselectivity (Scheme 10.202) [532, 533].



Scheme 10.202

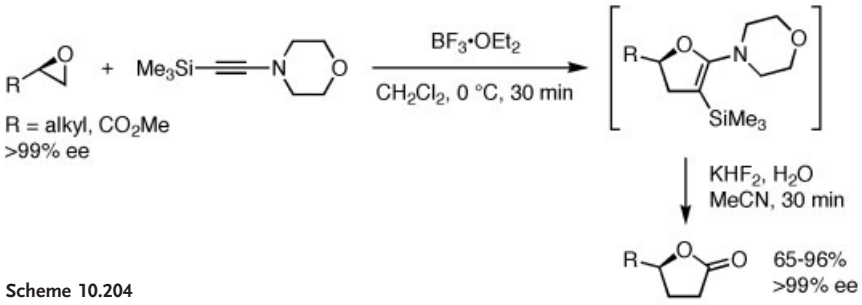
10.4.2
Lewis Acid-promoted Reactions Forming Silylated Products

The Lewis acid-promoted reactions of 1-seleno-2-silylethene with *α*-enones and 2-phosphonoacrylates give cyclopropane products (Scheme 10.203) [534]. The [2+1] cycloaddition would proceed via 1,2-silyl migration of *α*-seleno-*β*-silylcarbenium ion intermediate **146** and subsequent ring-closure. Interestingly, dimethyl 1,1-dicyanoethene-2,2-dicarboxylate, a highly electron-deficient alkene, undergoes [2+2] cycloaddition under similar conditions [535].



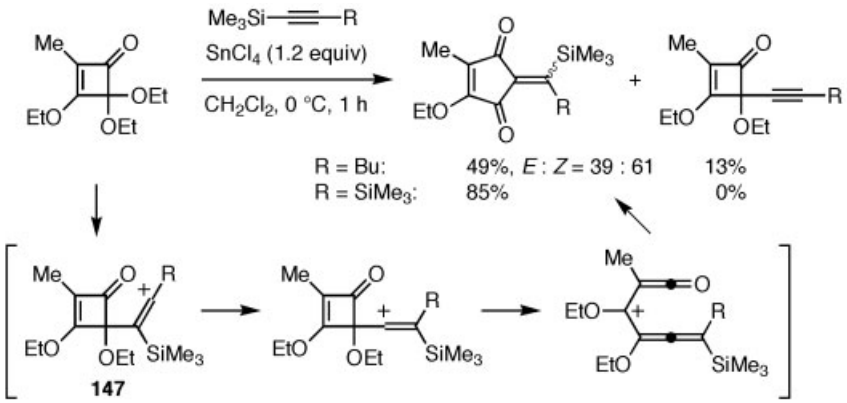
Scheme 10.203

1-Morpholino-2-trimethylsilylethyne is valuable for direct synthesis of *γ*-butanolides from epoxides (Scheme 10.204) [536]. In the presence of $BF_3 \cdot OEt_2$ the alkynylsilane reacts with homochiral epoxides to afford [3+2] cycloadducts, which can be readily converted into *γ*-butanolides, by hydrolysis, without racemization.



Scheme 10.204

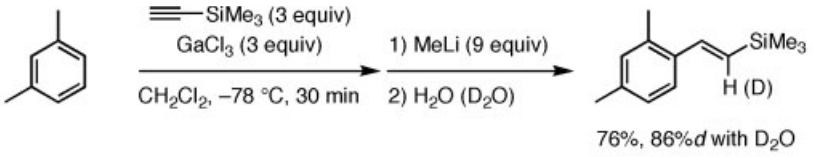
When a CH_2Cl_2 solution of a cyclobutenedione monoacetal and an alkynylsilane is treated with a Lewis acid, 1,2-silyl-migrative ring-expansion is favored over simple alkynylation (Scheme 10.205) [537]. A plausible reaction mechanism is Lewis acid-promoted addition of the alkynylsilane to the acetal, 1,2-silyl migration of the resulting β-silylcarbenium ion **147**, ring-opening of the rearranged cationic intermediate, and dealkylative ring-closure of the pentadienyl cation formed.



Scheme 10.205

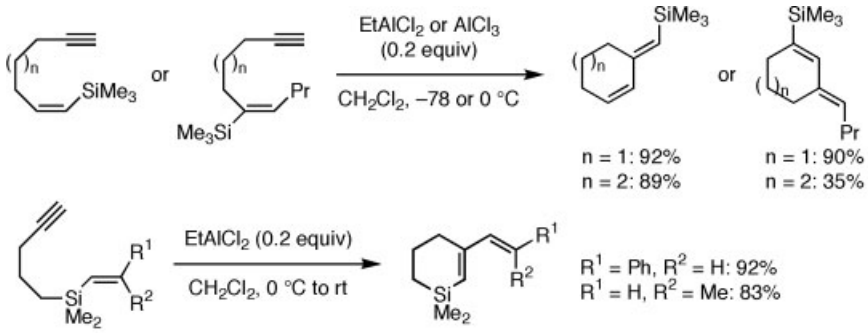
The $GaCl_3$-promoted reaction of alkynylsilanes with arenes, then treatment with MeLi followed by hydrolysis, yields β-arylvinylsilanes (Scheme 10.206) [538]. When D_2O is added in the hydrolysis step, the α-carbon of the vinylsilane product is deuterated. This indicates the presence of vinylgallium species in the reaction mixture. The arylation mechanism probably involves the Friedel-Crafts-type reaction of $GaCl_3$-coordinated alkynylsilanes at the β-position.

In the presence of a Lewis acid vinyl- and arylsilanes as well as allylsilanes add to internal alkynes to afford *trans*-carbosilylation products (Scheme 10.207) [539]. Vinyl- and arylsilanes bearing a 4- or 5-alkynyl group at the β- (or *ortho*-) position undergo *exo* cyclization whereas α-alkynyl-substituted vinylsilanes lead to cycloalkenylsilanes



Scheme 10.206

by *endo* cyclization. When the alkynyl group is located on the silicon of vinyl- and arylsilanes, silacycloalkenes with a vinyl or aryl group are obtained. Although intermolecular vinylsilylation of alkynes has also been reported, it is rather limited in applicability [540].



Scheme 10.207

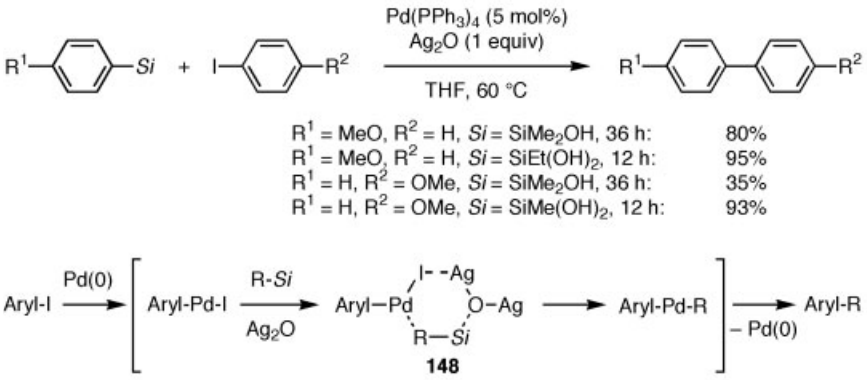
10.4.3
Transition Metal-catalyzed Carbon–Carbon Bond Formation

Pd-catalyzed cross-coupling between fluoride-activated organosilicon reagents and organic halides or pseudohalides (Hiyama coupling) is one of the most important reactions in silicon-mediated organic synthesis [15]. In recent years development of organosilicon reagents and additives has been studied to realize a more practical and reliable method for the silicon-based coupling. Recent interest has also been focused on the utility of Rh complexes and Cu salts for carbon–carbon bond formation using organosilicon reagents.

10.4.3.1 Palladium-catalyzed Reactions

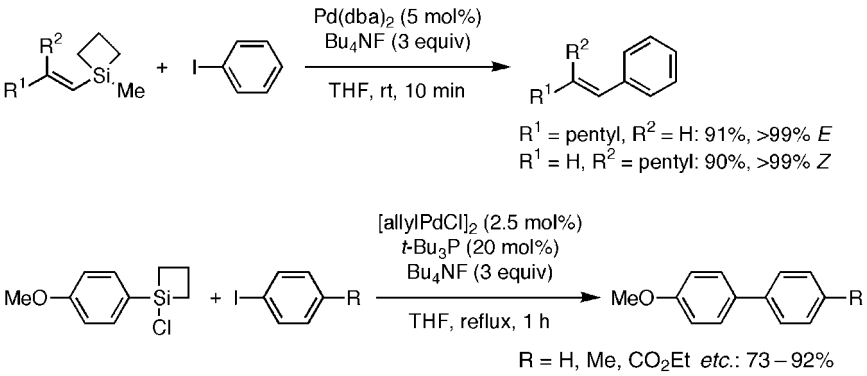
Pioneering work by Hiyama and Ito established that aryl- and vinylsilanes bearing one or more fluorine atoms or alkoxy groups on the silicon work as effective donors in the Pd-catalyzed coupling [15, 541]. Hiyama and Mori recently reported that in the presence of Ag_2O aryl- and vinylsilanols are reactive in Pd-catalyzed coupling with aryl iodides (Scheme 10.208) [542]. Arylsilanediols are more reactive than the corresponding silanols. Judging from the inertness of aryl bromides and

triflates and the lower efficiency of AgOTf and $AgBF_4$, Ag_2O might play two roles in accelerating the Si–Pd transmetalation – iodine-abstraction from an arylpalladium iodide intermediate and nucleophilic activation of the silicon reagent via a transition state such as **148**.



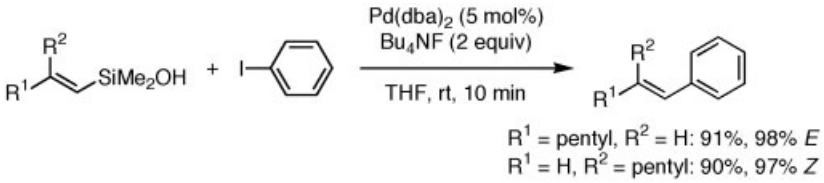
Scheme 10.208

Denmark et al. have found that in the presence of excess TBAF the Pd-catalyzed coupling of vinylsilacyclobutanes with aryl iodides and vinyl halides proceeds efficiently and highly stereospecifically at room temperature (Scheme 10.209) [543]. Although aryl(methyl)silacyclobutanes are insensitive to aryl and vinyl halides under a variety of conditions, aryl(chloro)silacyclobutanes have enough reactivity for coupling with aryl iodides [544]. In this biaryl coupling the use of *t*-Bu_3P serves to suppress the formation of homo-coupling products.



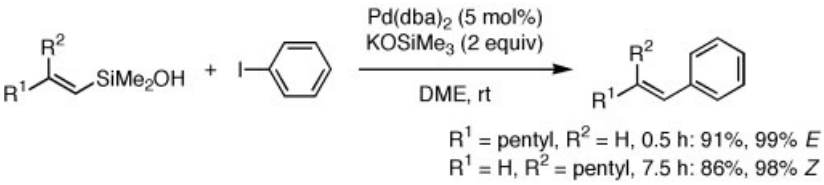
Scheme 10.209

Mechanistic investigation of the reaction of vinylsilacyclobutanes has suggested the presence of a silanol–fluoride adduct as the actual vinyl donor [545]. Similar species can be generated from vinylsilanols and bis(vinyl)disiloxanes by the action of TBAF. Consistently with the reactivity of vinylsilacyclobutanes, these silicon reagents work as effective vinyl donors (Scheme 10.210) [546–548]. Vinylhydrosilanes [547] and vinyl(2-pyridyl)silanes [549] also can be successfully used for the Pd-catalyzed coupling, because they are readily converted into vinylsilanols by fluoride ion-catalyzed hydrolysis.



Scheme 10.210

The Pd-catalyzed coupling of vinylsilanols with aryl iodides can also be achieved efficiently by using a base instead of a fluoride ion source (Scheme 10.211) [550]. The formation of an arylpalladium siloxide bearing a pentacoordinated silicon center might accelerate the transmetalation step.

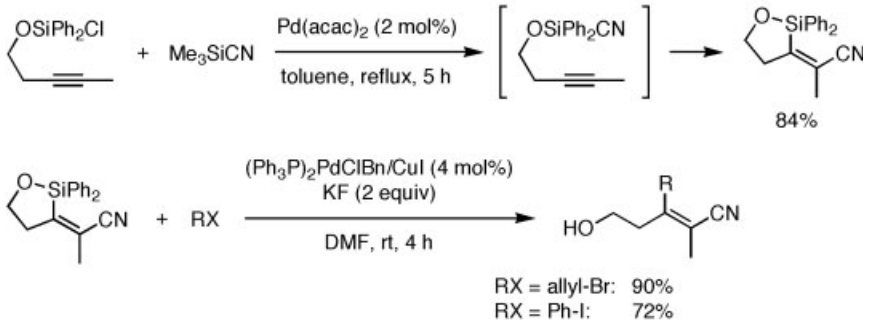


Scheme 10.211

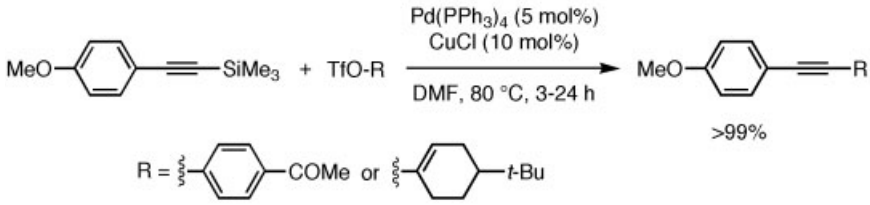
Ito et al. have reported that a sequence of intramolecular hydrosilylation or cyanosilylation and the Pd-catalyzed coupling reaction is useful for regio- and stereodefined synthesis of tri- or tetrasubstituted homoallyl alcohols from homopropargyl alcohols (Scheme 10.212) [551, 552]. More recently Denmark et al. have used ring-closing metathesis for the alkene synthesis via vinylsilanes [553].

Alkynyltrimethylsilanes act as effective alkynyl donors in the presence of a fluoride ion source [15]. Recent studies on the Sonogashira-type reaction of alkynylsilanes have revealed that the use of a Cu(I) [554] or Ag(I) [555] salt leads to highly efficient coupling with vinyl and aryl triflates (Scheme 10.213).

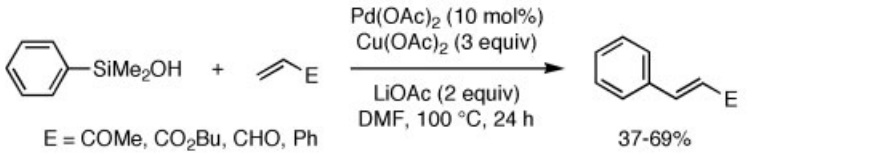
Hiyama and Mori introduced the Mizoroki-Heck-type reaction of aryl- and vinylsilanols in a Pd-catalyzed system using $Cu(OAc)_2$ as reoxidant (Scheme 10.214) [556]. This halogen-free reaction is suitable for arylation and vinylation of electron-deficient alkenes and styrene.



Scheme 10.212



Scheme 10.213

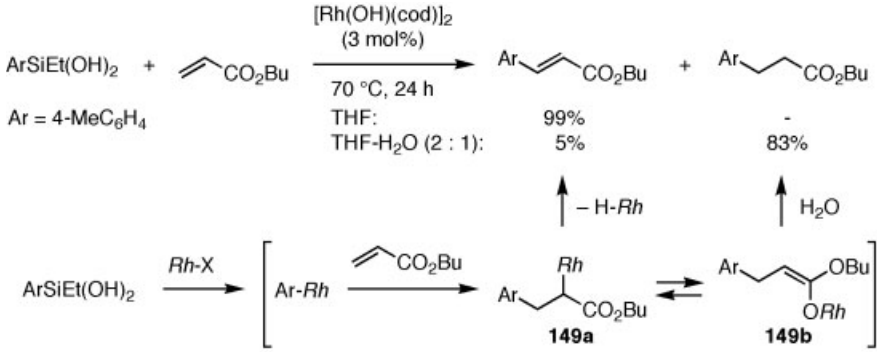


Scheme 10.214

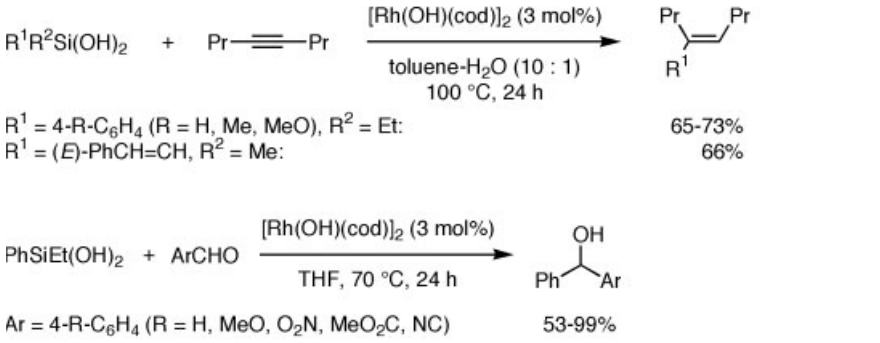
10.4.3.2 **Rhodium-catalyzed Reactions**

Mori et al. have reported that the Rh-catalyzed reaction of arylsilanols with acrylates in THF affords 3-arylacrylates in good yields (Scheme 10.215) [557]. This Mizoroki-Heck-type reaction would proceed by conjugate addition of an arylrhodium intermediate and subsequent β-hydride elimination from the resulting rhodium enolate **149a**. Interestingly, when the reaction is run in aqueous THF conjugate addition products are obtained exclusively. This change of the reaction pathway is attributable to hydrolysis of the rhodium enolate intermediate **149b**. Similar Rh-catalyzed conjugate additions of arylsilicones [558], arylchlorosilanes [559], and aryltrialkoxysilanes [560] have been reported by Mori and others.

The Rh-catalyzed reaction of aryl- and vinylsilanediols with internal alkynes in aqueous solvent gives hydroarylation and hydrovinylation products, respectively (Scheme 10.216) [561]. It has been proposed that this reaction occurs via carborhodation of an aryl- or vinylrhodium intermediate to an alkyne then protonation with the silanediol. Arylation and vinylation of aromatic aldehydes with organosilicon reagents can also be achieved in Rh-catalyzed systems (Scheme 10.216) [560, 562].



Scheme 10.215

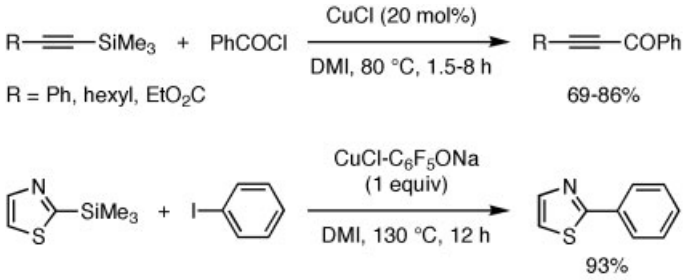


Scheme 10.216

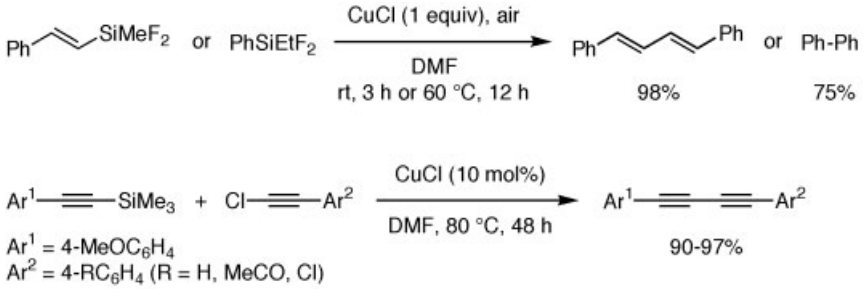
10.4.3.3 **Copper-promoted Reactions**

We have found that alkynylsilanes are smoothly converted into alkynylcopper compounds by treatment with CuCl in 1,3-dimethyl-2-imidazolidinone (DMI); the copper reagents can be isolated in good yields [563]. This study was the first example of preparation and isolation of organocopper compounds by use of organosilicon reagents. The Si–Cu transmetalation is applicable to the synthesis of alkynyl ketones by Cu-catalyzed alkynylation of acid chlorides (Scheme 10.217). We have also shown that a Cu-mediated system is effective in the cross-coupling reaction between arylsilanes or heteroarylsilanes and aryl halides [564].

Hiyama and Mori have reported that homo-coupling reactions of vinyl-, aryl-, and alkynylsilanes are effectively promoted by an equimolar amount of CuCl and air (Scheme 10.218) [565]. The reaction mechanism probably involves formation of organocopper species by Si–Cu transmetalation and subsequent oxidative dimerization by air. The strong tendency of CuCl to activate alkynylsilanes has been used for coupling reactions with 1-chloroalkynes (Scheme 10.218) [566].



Scheme 10.217

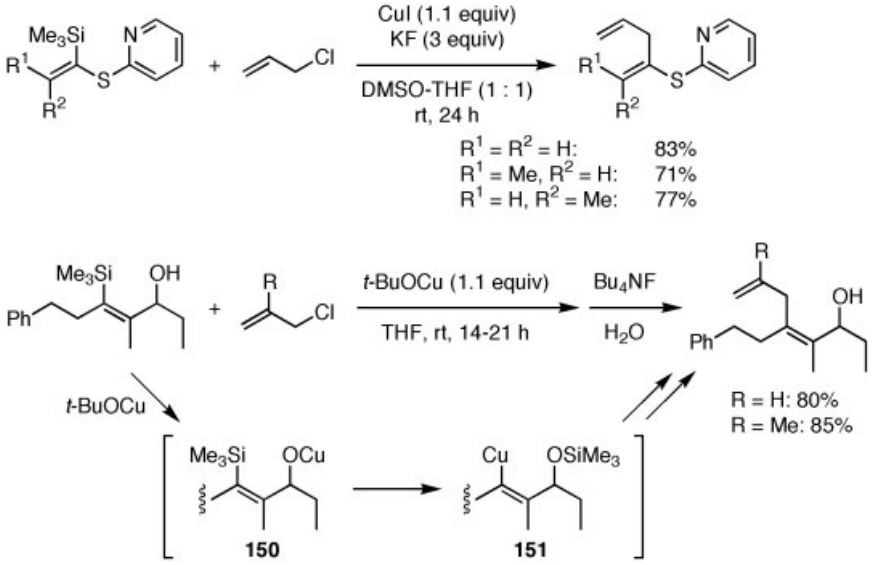


Scheme 10.218

Takeda et al. have shown that vinyl- and allylsilanes bearing a 2-pyridylthio group at the α-position smoothly undergo Cu-mediated allylation with allyl chloride (Scheme 10.219) [567]. The use of the substrates bearing a 4-pyridylthio group gives no allylated products. This indicates that intramolecular coordination of nitrogen to silicon facilitates the Cu-mediated allylation. The same authors have reported the preparation of vinylcopper reagents **151** by intramolecular Si–Cu transmetalation of copper alkoxides **150**, and their application to carbon–carbon bond formation [568, 569].

10.5
α-Heteroatom-substituted Organosilanes

Organosilanes bearing an electronegative heteroatom(s) at the α-carbon are susceptible to nucleophilic activation leading to silicon–carbon bond-cleavage, because of the electronic effect of the heteroatom. α-Heteroatom-substituted organosilanes are therefore quite valuable as protected carbon nucleophiles. The silicon–carbon bond is also readily activated by a transition metal complex. The reactivity is successfully utilized for catalytic carbon–carbon bond formation.

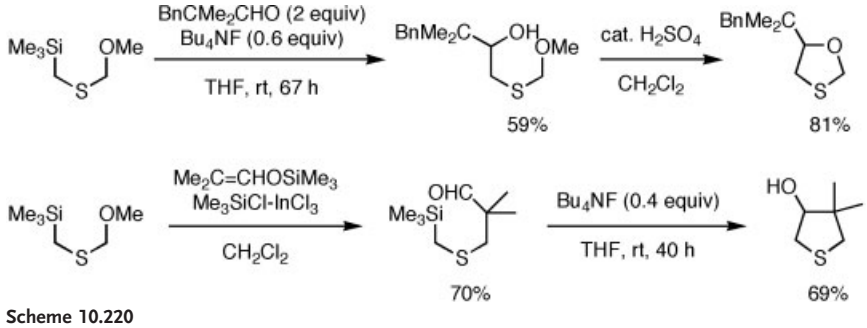


Scheme 10.219

10.5.1
Nucleophile-promoted Addition of α-Halo- and α-Thioalkylsilane

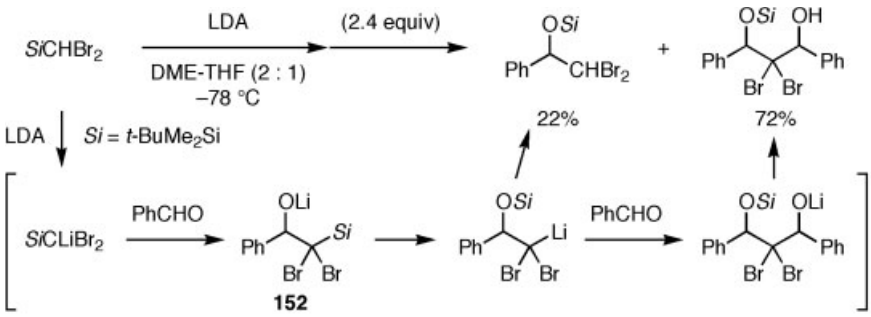
In the presence of fluoride ion trimethyl(trifluoromethyl)silane works as an effective trifluoromethyl anion equivalent [570]. According to a recent report a catalytic amount of *N*-benzylcinchonium fluoride, a chiral source of fluoride ion, enables asymmetric trifluoromethylation of aldehydes (up to 51% ee) [571].

Thiomethylsilanes also add to carbonyl compounds with the aid of fluoride ion [572]. The fluoride ion-catalyzed addition of alkoxymethylthiomethylsilanes to aldehydes followed by acid-catalyzed cyclization affords 1,3-oxathiolanes (Scheme 10.220) [573]. The Lewis acid-promoted aldol-type reaction of thiomethylsilanes with silyl enolates and subsequent fluoride ion-catalyzed cyclization leads, on the other hand, to tetrahydrothiophenes. In these reactions the thiomethylsilanes serve as thiocarbonyl ylide equivalents.



Scheme 10.220

The successive reaction of (dibromomethyl)silanes with LDA (lithium diisopropylamide) and two equivalents of benzaldehyde gives 1,3-diol monosilyl ethers in good yield (Scheme 10.221) [574]. This tandem reaction would proceed via anionic 1,3-silyl migration of *β*-lithioxyalkylsilane intermediate **152** and addition of the resulting lithium carbenoid to benzaldehyde. Thus, internal activation of the silicon–carbon bond by the lithium alkoxide promotes nucleophilic addition of *α*-haloalkylsilanes. Similar tandem reactions of 2-trimethylsilyl-1,3-dithiane with aldehydes [575] and epoxides [576] have been reported.



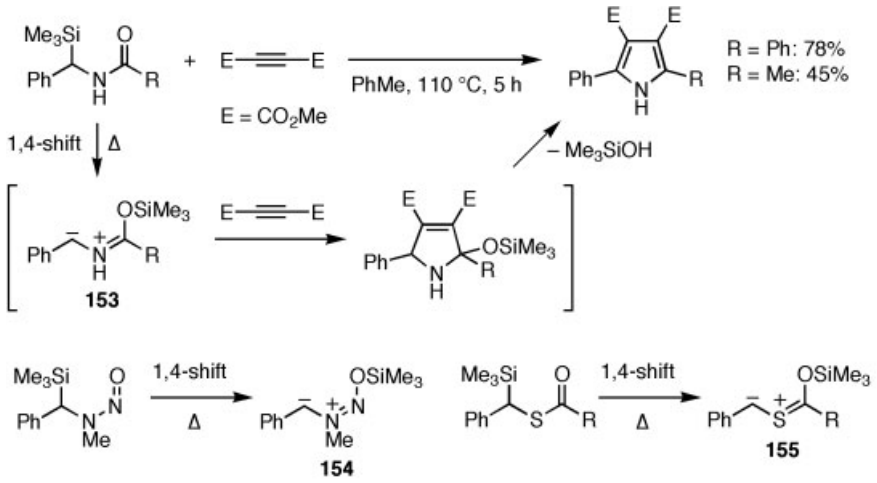
Scheme 10.221

10.5.2
[3+2] Cycloadditions of Silyl-protected 1,3-Dipoles

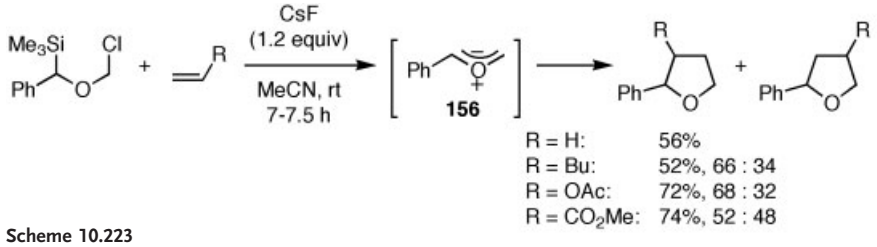
Some amino- and thiomethylsilanes are known to serve as equivalents of azomethine and thiocarbonyl ylides [577]. Recent examples of the use of organosilanes as protected 1,3-dipoles have been reported by Komatsu and by us.

Komatsu et al. have developed unique methods for the generation of 1,3-dipoles from organosilanes (Scheme 10.222). Under thermal conditions, *N*-(*α*-silylbenzyl) imines and -amides are converted, via 1,2- or 1,4-silatropic shift of the silyl group, into azomethine ylides (**153** from the amide) which react with dipolarophiles [578]. Similar thermal 1,4-silyl migrations of *α*-silylnitrosamines and *S*-*α*-silylbenzyl thioesters provide convenient routes to azomethine imines **154** [579] and thiocarbonyl ylides **155** [580], respectively.

In the course of our study on the preparation and [3+2] cycloadditions of silyl-protected 1,3-dipoles [581] we succeeded in generating carbonyl ylides **156** by CsF-promoted 1,3-elimination of chloromethyl *α*-trimethylsilylbenzyl ethers (Scheme 10.223) [582]. The carbonyl ylides react smoothly with a variety of alkenes, alkynes, allenes, and heterodipolarophiles to give five-membered cyclic ethers in good to high yields.



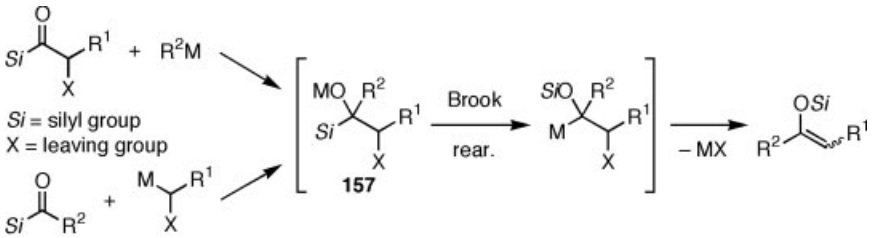
Scheme 10.222



Scheme 10.223

10.5.3
Carbon–Carbon Bond Formation with Acylsilanes

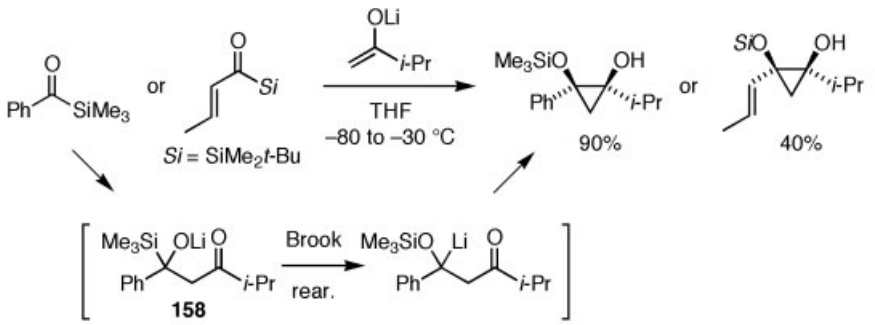
Acylsilanes as well as aldehydes undergo nucleophilic addition of alkylmetals to give alcohols [583]. The directing effect of the silyl group often brings about high stereo- [584] and regioselectivity [585] which cannot, however, be realized with aldehydes. Because the α-silylated alcohols obtained from acylsilanes are readily converted into desilylated alcohols by fluoride ion-induced hydrolysis with stereochemical retention, acylsilanes have been used as aldehyde equivalents for highly stereo- and regioselective synthesis of alcohols. Acylsilanes are synthetically valuable also as precursors of silyl enolates [586]. In the reaction of acylsilanes with alkylmetals, the use of acylsilanes or alkylmetals bearing a leaving group at the α-position affords silyl enolates via the Brook rearrangement of the α-silylalkoxide intermediate **157** followed by elimination of the leaving group (Scheme 10.224). Recent topics in the synthetic use of acylsilanes are tandem carbon–carbon bond formation via the Brook rearrangement, transition metal-catalyzed acylation, and radical addition accompanied by a Brook-type rearrangement. This section describes these new aspects of acylsilane chemistry.



Scheme 10.224

10.5.3.1 **Tandem Carbon–Carbon Bond Formation via Brook Rearrangement**

Takeda et al. have reported that the reactions of benzoyl- and crotonylsilanes with lithium enolates of methyl ketones produce 1,2-cyclopropanediol monosilyl ethers via the Brook rearrangement of the initial 1,2-adduct **158** and the subsequent internal nucleophilic addition (Scheme 10.225) [587]. No formation of the corresponding cyclopropanes with alkanoylsilanes implies that the Brook rearrangement is accelerated by the phenyl or vinyl group.

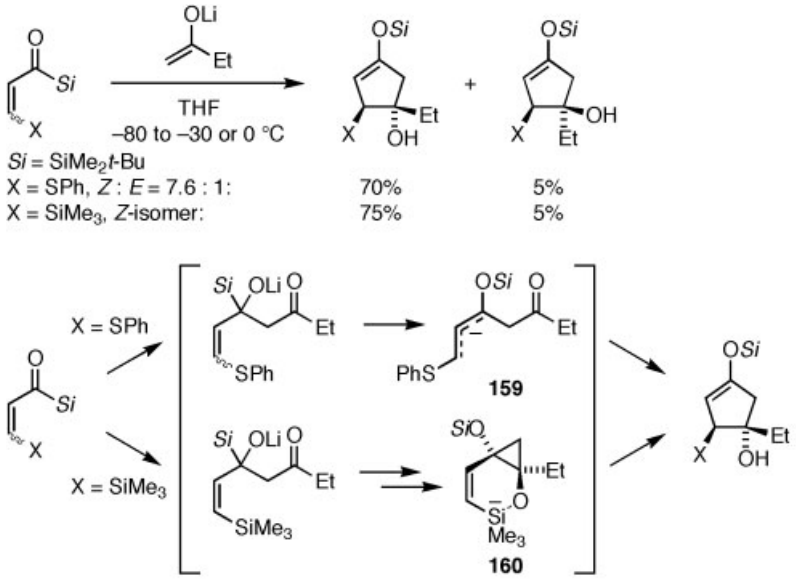


Scheme 10.225

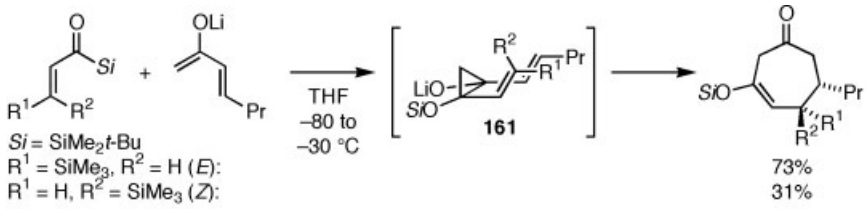
The use of *β*-thio- and *β*-silylacryloylsilanes switches the reaction mode from [2+1] to [3+2] annulation to form cyclopentanone silyl enolates (Scheme 10.226) [588]. The annulation with *β*-thioacryloylsilanes might proceed via the delocalized allylic carbanion **159** whereas a reaction pathway through 1,3-sigmatropic rearrangement of the vinylcyclopropane intermediate **160** has been proposed for *β*-silylacryloylsilanes [589].

The reactions of (*E*)- and (*Z*)-*β*-silylacryloylsilanes with lithium enolates of *α*,*β*-unsaturated methyl ketones afford *cis*-5,6- and *trans*-5,6-disubstituted 3-cycloheptenones, respectively (Scheme 10.227) [590, 591]. The observed stereospecificity in the [3+4] annulation can be rationalized by a reaction mechanism via an anionic oxy-Cope rearrangement of the 1,2-divinylcyclopropane intermediate **161** generated by [2+1] annulation between the substrates.

Acylsilanes bearing an acrylate Michael acceptor are smoothly cyclized by treatment with PhLi or $LiP(O)(OMe)_2$ (Scheme 10.228) [592]. The tandem Brook rearrangement–intramolecular Michael reaction is useful for the construction of four- to



Scheme 10.226



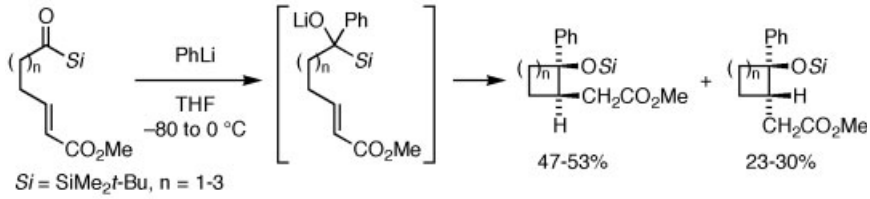
Scheme 10.227

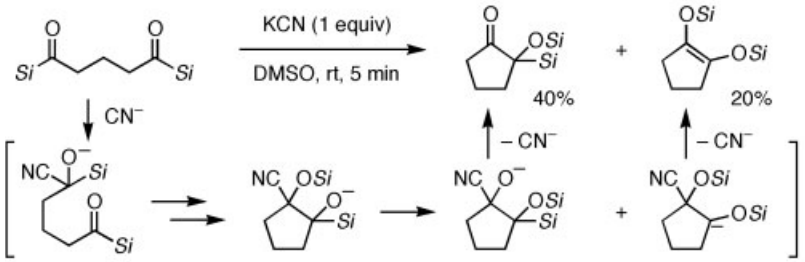
six-membered carbocycles. The cyanide-promoted reaction of a 1,5-bis(acylsilane) results in the formation of two cyclic products via a multistep sequence combining inter- and intramolecular nucleophilic additions, two silyl migrations, and β-elimination (Scheme 10.228) [593].

Kuwajima et al. developed an efficient route to (*Z*)-γ-siloxyallylmagnesium bromides utilizing the Brook rearrangement of α-silylalkoxides derived from acylsilanes and vinylmagnesium bromide [594]. Corey et al. recently applied this method to the generation of (*Z*)-γ-siloxyallyllithiums to achieve rapid syntheses of natural products [595].

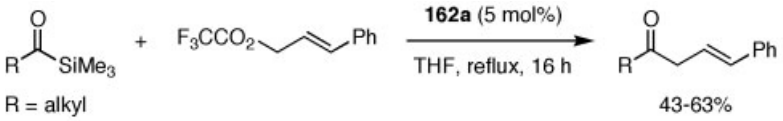
10.5.3.2 **Transition Metal-catalyzed Acylation**

In the presence of a catalytic amount of palladium complex **162a**, acylation of allyl trifluoroacetates with acylsilanes proceeds selectively to afford β,γ-unsaturated ketones in moderate yields (Scheme 10.229) [596]. Allyl acetates are unreactive to





Scheme 10.228

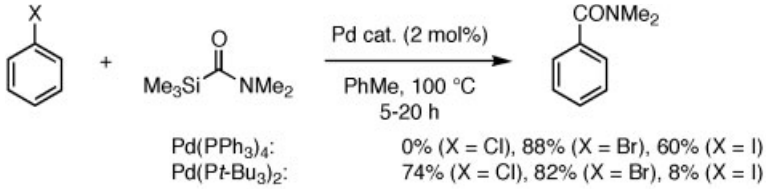


162a: Pd(η^3-PhCH=CHCH$_2$)(CF$_3$CO$_2$)
162b: Pd(η^3-PhCH=CHCH$_2$)(MeCO$_2$)

Scheme 10.229

acylsilanes under the same conditions, possibly because of the low reactivity of the π-allylpalladium intermediate **162b** bearing an acetate ligand.

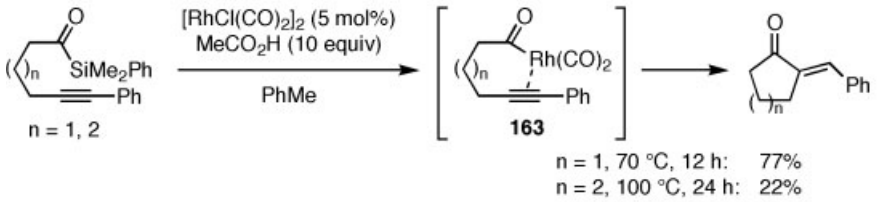
Direct carbamoylation of aryl halides with a carbamoylsilane can be performed under the action of catalysis by a Pd(0) complex (Scheme 10.230) [597]. The use of $Pd(PPh_3)_4$ is suitable for the conversion of unhindered aryl bromides and iodides into the corresponding amides. The carbamoylation of aryl chlorides and hindered aryl bromides, less reactive substrates, is effectively catalyzed by $Pd(Pt\text{-}Bu_3)_2$.



Scheme 10.230

Acylsilanes are available for intramolecular acylation of alkynes under catalysis by an Rh(I) complex (Scheme 10.231) [598]. In the presence of $[RhCl(CO)_2]_2$ and

acetic acid, 5- and 6-alkynoylsilanes are cyclized to α-alkylidenecycloalkanones probably via the alkynoylrhodium intermediate **163**.



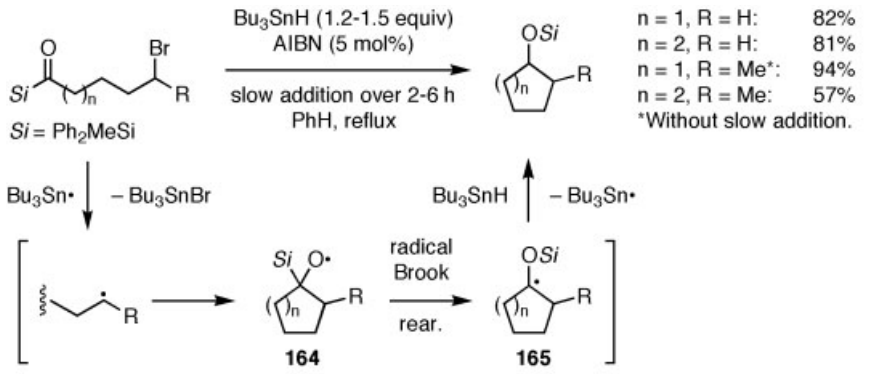
Scheme 10.231

10.5.3.3 Radical Addition Followed by Brook-type Rearrangement

Tsai et al. have disclosed that AIBN-initiated reactions of 5- and 6-bromoalkanoylsilanes with Bu_3SnH give cyclopentanol and cyclohexanol silyl ethers, respectively, in moderate to high yields (Scheme 10.232) [599]. This radical cyclization might proceed via the following radical chain mechanism:

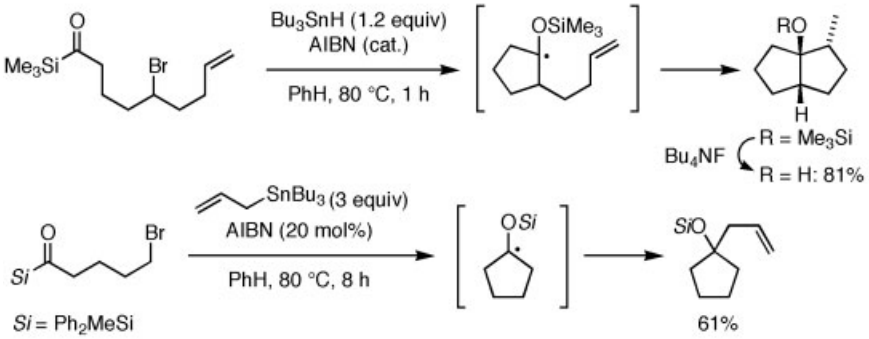
1. generation of $Bu_3Sn•$ by the action of AIBN which abstracts bromine from a substrate;
2. addition of the resulting carbon radical to the internal acylsilane moiety at the carbonyl carbon;
3. irreversible Brook-type rearrangement (radical Brook rearrangement) of the α-silylalkoxy radical **164**, and
4. abstraction of hydrogen from Bu_3SnH by the rearranged α-siloxyalkyl radical **165**, regenerating $Bu_3Sn•$.

Intramolecular competition experiments using a radical clock have revealed that the 5- and 6-*exo* cyclizations of primary alkyl radicals bearing an acylsilane moiety are slightly faster than those of the 5- and 6-alkenyl radicals [600]. The rate of cyclization depends on the substituents on silicon – the presence of a phenyl group on silicon increases the rate, probably because of its electron-withdrawing nature.



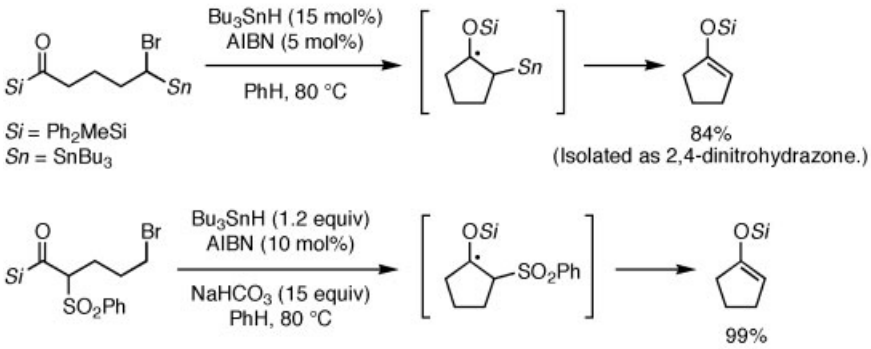
Scheme 10.232

The α-siloxyalkyl radical intermediate can be used for carbon–carbon bond formation by intra- and intermolecular trapping (Scheme 10.233). In the Bu_3SnH-mediated system, a bromoalkenoylsilane is efficiently converted into a bicyclic compound by tandem radical cyclization [601]. When allyltributylstannane is used instead of Bu_3SnH, the α-siloxyalkyl radical generated from a 5-bromoalkanoylsilane undergoes homolytic allylation to provide a homoallyl silyl ether [602].



Scheme 10.233

Radical cyclization using acylsilanes is applicable to the synthesis of cyclic silyl enolates by β-elimination of the α-siloxyalkyl radical intermediate (Scheme 10.234) [603]. 5-Bromo-5-stannyl- and 5-bromo-2-sulfonyl-alkanoylsilanes are cyclized to cyclopentanone silyl enolates with elimination of the stannyl and sulfonyl groups.



Scheme 10.234

10.5.4
Carbon–Carbon Bond Formation with Cyanosilanes

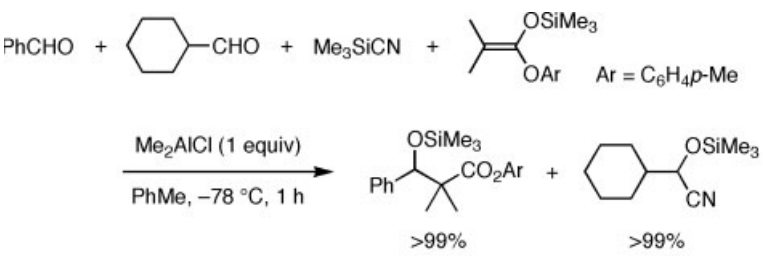
Cyanotrimethylsilane (TMSCN) is one of the most versatile silicon reagents in organic synthesis [604]. This cyanide ion equivalent is soluble in a variety of organic solvents and reacts with a wide range of carbon electrophiles to give functional-

ized nitriles or isonitriles. The most important and synthetically valuable reactions using TMSCN are cyanosilylations of carbon–oxygen and carbon–nitrogen double bonds, because the products, cyanohydrin TMS ethers and α-amino nitriles, serve as synthetic intermediates in the preparation of a variety of natural products [604, 605]. Although HCN also adds to these unsaturated bonds to afford cyanohydrins and α-amino nitriles, use of TMSCN instead of HCN provides an efficient and safer route to these compounds. Cyanosilylation with TMSCN is accelerated by acid and base catalysts. In recent years a variety of organic and inorganic compounds have been found to work as effective catalysts, and much attention has been devoted for the development of chiral catalysts for asymmetric cyanosilylation of aldehydes, ketones, and imines.

10.5.4.1 Cyanosilylation using Achiral Catalysts

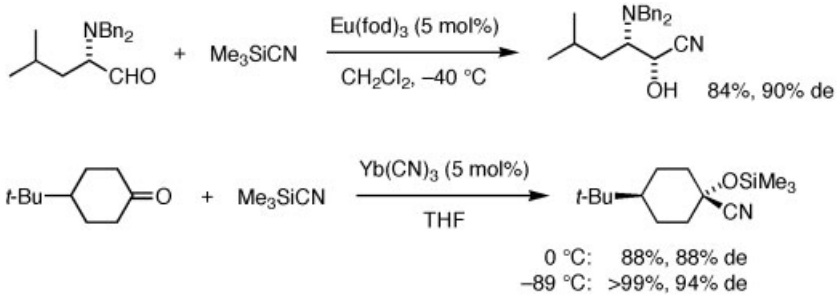
Since the pioneering work of Evans et al. [606] cyanosilylation of aldehydes and ketones and synthetic use of cyanohydrin silyl ethers have been extensively studied by many synthetic organic chemists [604]. The development of efficient catalysts and catalytic systems for the cyanosilylation is the main objective in these studies. In the nineteen-seventies and eighties some Lewis acids (ZnI_2, $AlCl_3$, $TiCl_4$, TMSOTf, etc.) and nucleophilic reagents (KCN/18-crown-6, Bu_4NCN, etc.) were reported to work as effective catalysts [604]. Studies after 1990 have revealed that the cyanosilylation is catalyzed by the following inorganic and organic compounds: $LiClO_4$ [26], $LiBF_4$ [607], LiOR [608], Me_2AlCl [609], $TMSNTf_2$ [610], Bu_3SnCN [611], R_2SnCl_2 [612], $BiBr_3$ [342], $L_2M(OTf)_2$ (M = Ti and Zr) [613], $[HC(Py)_3W(NO)_2(CO)](SbF_6)_2$ [61], $Cu(OTf)_2$ [614], $La_3(Ot\text{-}Bu)_9$ [615], $Eu(fod)_3$ [616], $Yb(OTf)_3$ [617], $Yb(CN)_3$ [618], amines and phosphines [619], tetracyanoethylene [620], and solid bases and acids [621].

Me_2AlCl has unique character in the discrimination of reaction pathways in Lewis acid-promoted reactions of aldehydes with organosilicon reagents (Scheme 10.235) [609]. The Me_2AlCl-promoted reaction of benzaldehyde and cyclohexanecarbaldehyde with a ketene silyl acetal and TMSCN affords the corresponding aldol adduct of benzaldehyde and the cyanohydrin TMS ether of cyclohexanecarbaldehyde, exclusively.



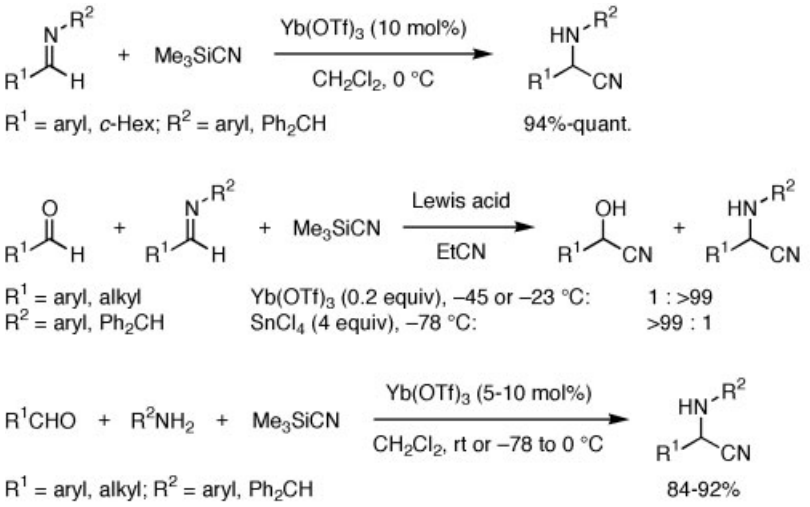
Scheme 10.235

The use of $Eu(fod)_3$ and $Yb(CN)_3$ is quite effective in highly diastereoselective cyanosilylation (Scheme 10.236). Under the action of catalysis by $Eu(fod)_3$, TMSCN adds smoothly to α-alkoxy- and α-aminoaldehydes to give chelation (*syn*) products predominantly [616]. In the $Yb(CN)_3$-catalyzed cyanosilylation of 4-*t*-butylcyclohexanone, axial attack of the cyano group prevails over equatorial attack [617]. Catalysis by $Yb(CN)_3$ can also be successfully applied to easily enolizable ketones.



Scheme 10.236

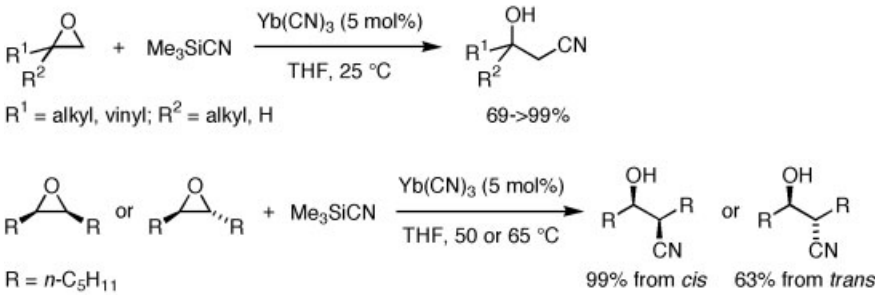
Cyanosilylation of imines (Strecker-type reaction) is efficiently promoted by conventional Lewis acids such as ZnX_2, $AlCl_3$, and $TiCl_4$ [604]. Kobayashi et al. recently disclosed that $Yb(OTf)_3$ has high catalytic activity in this cyanosilylation (Scheme 10.237) [622]. In the competitive reaction of aldehydes and the corresponding imines with TMSCN, $Yb(OTf)_3$ activates imines to give only α-aminoni-



Scheme 10.237

triles [209 b]. The behavior of $Yb(OTf)_3$ is in marked contrast with that of $SnCl_4$, which promotes the cyanosilylation of aldehydes exclusively. The strong affinity of $Yb(OTf)_3$ for imines in addition to its stability to water and amines enables efficient cyanosilylation of imines generated in situ from aldehydes and amines (Scheme 10.237). This type of three-component coupling can also be achieved by using $LiClO_4$ in Et_2O [623].

The Lewis acid-catalyzed reaction of epoxides with TMSCN leads to the formation of β-siloxy-nitriles or -isonitriles [604]. The reaction pathway depends mainly on the Lewis acid used. The $Yb(CN)_3$-catalyzed reaction of epoxides proceeds stereospecifically to give β-siloxynitriles in good yields (Scheme 10.238) [624 a]. The catalytic system is applicable to the synthesis of β-aminonitriles from aziridines [624 b]. A Ti(O*i*-Pr)$_4$–Schiff base complex also is useful in the ring-opening reaction of epoxides leading to β-siloxynitriles [625].

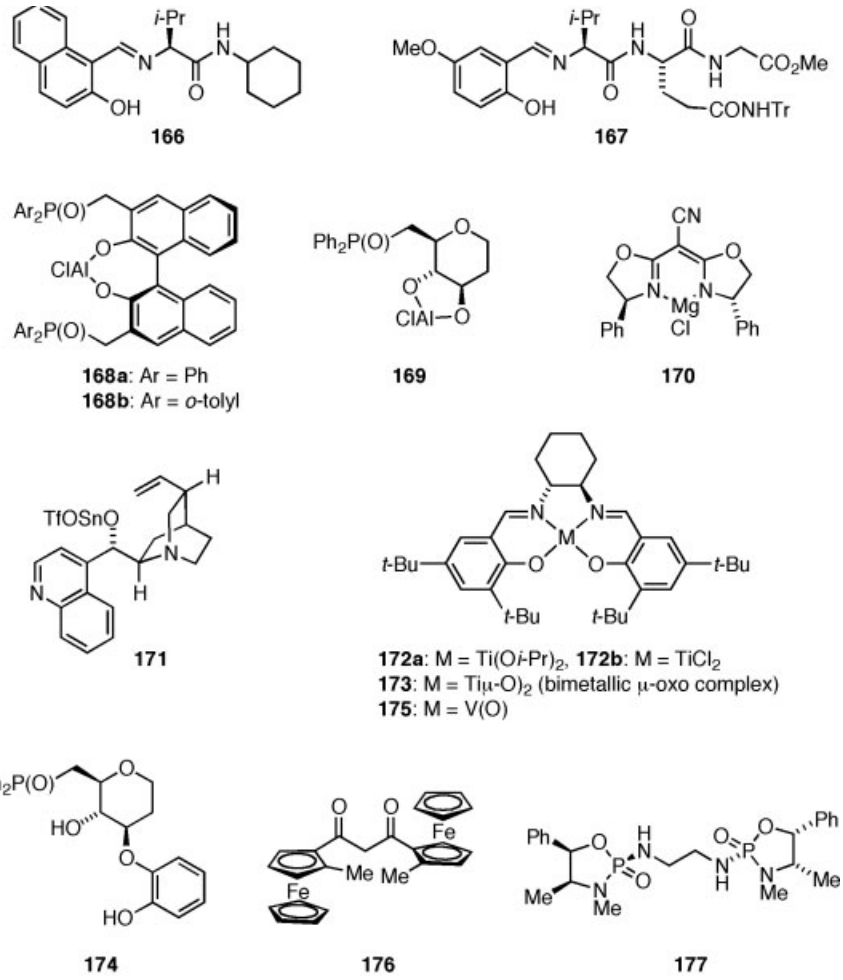


Scheme 10.238

10.5.4.2 **Asymmetric Cyanosilylation of Aldehydes and Ketones**

The Lewis acid-catalyzed cyanation of acetals bearing a chiral auxiliary with TMSCN provides an asymmetric route to cyanohydrin ethers [113, 626]. In the last decade, however, much effort has been directed to catalytic asymmetric cyanosilylation of aldehydes and ketones using a chiral Lewis acid or base [627]. The first example of this approach was reported by Reetz et al. in 1986 [115]. They showed that a catalytic amount (10–20 mol%) of a chiral B, Al, or Ti Lewis acid effects enantioselective cyanosilylation of 3-methylbutanal (up to 82% ee). In the next year, Narasaka et al. found that stoichiometric use of a titanium complex prepared from a chiral 1,4-diol and $(i\text{-PrO})_2TiCl_2$ brings about high optical yields with aromatic and aliphatic aldehydes [628]. After these studies many chiral catalysts were developed for asymmetric cyanosilylation of aldehydes and ketones (Scheme 10.239): $AlCl_3$-pybox [629], $AlMe_3$-peptide Schiff base **166** [630], Al(O*i*-Pr)$_3$-peptide Schiff base **167** [631], Al-BINOL complex **168 a** [632], Al-diolate complex **169** [633], Mg-box complex **170** [634], Sn(II)-cinchonine **171** [635], $BiCl_3$-diethyl tartrate [636], Ti(O*i*-Pr)$_4$-diisopropyl tartrate [637], Ti(O*i*-Pr)$_4$-Schiff base [638], Ti-salen complexes **172** [639, 640], bis-Ti-salen complex **173** [641], Ti(O*i*-Pr)$_4$-BINOL [642], Ti(O*i*-Pr)$_4$-polymer-supported BINOL [643], Ti(O*i*-Pr)$_4$-β-amino alcohol [644], Ti(O*i*-Pr)$_4$-diol **174** [645], Ti(O*i*-Pr)$_4$-triol [646], V(IV)-salen complex **175**

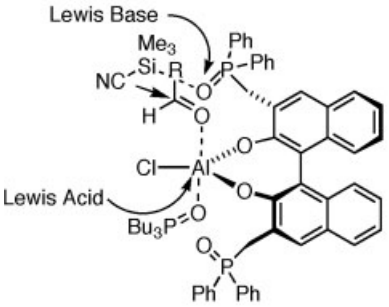
[647], Mo(VI) diimide complex [648], $Y_5(O)(O\textit{i}\text{-Pr})_{13}$-1,3-diketone **176** [649], $SmCl_3$-bisphosphoramidate **177** [650], and $Ln(O\textit{i}\text{-Pr})_3$-diol **174** [651].



Scheme 10.239

Inoue et al. reported that a complex prepared from $AlMe_3$ and peptide Schiff base **166** is available for asymmetric cyanosilylation of aldehydes (Scheme 10.239) [630]. The enantioselectivity observed is not as high, even with a stoichiometric amount of the complex (up to 71% ee). A more recent study by Snapper and Hoveyda has, however, revealed that a similar catalyst system using $Al(O\textit{i}\text{-Pr})_3$ and peptide Schiff base **167** is quite effective in catalytic asymmetric cyanosilylation of both aromatic and aliphatic ketones (66–>98%, 80–95% ee with 10–20 mol% of the catalyst) [631].

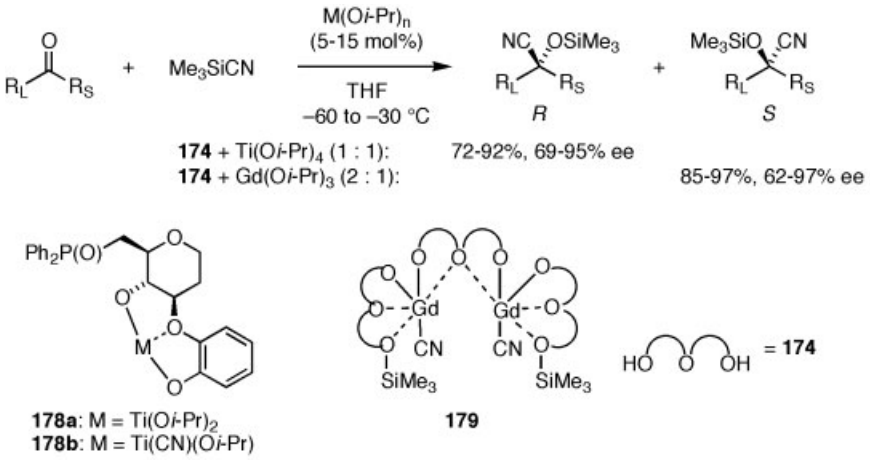
Al-BINOL complex **168a**, developed by Shibasaki et al., is one of the most efficient catalysts for asymmetric cyanosilylation of aldehydes (Scheme 10.239) [632]. In the presence of **168a** (9 mol%) and a phosphine oxide ($Bu_3P(O)$ and $Ph_2P(O)Me$ for aromatic and aliphatic aldehydes, respectively, 36 mol%), slow addition of TMSCN achieves excellent enantioselectivity with a wide range of aldehydes (86–100%, 83–98% ee). The Al complex has been proposed to work as a bifunctional catalyst for dual activation of the two reactants – the Lewis acidic Al center enhances the electrophilicity of aldehydes and the Lewis basic phosphine oxide induces cyanide addition by nucleophilic activation (Scheme 10.240). This catalytic asymmetric cyanosilylation has been used for the total synthesis of epothilones [652].



Scheme 10.240

The Lewis acid–Lewis base bifunctional catalyst **178a**, prepared from $Ti(Oi\text{-}Pr)_4$ and diol **174** (1:1), realizes highly enantioselective cyanosilylation of a variety of ketones to (*R*)-cyanohydrin TMS ethers (Scheme 10.241) [645]. The proposed mechanism involves Ti monocyanide complex **178b** as the active catalyst; this induces reaction of aldehydes with TMSCN by dual activation. Interestingly, the catalyst prepared from $Gd(Oi\text{-}Pr)_3$ and **174** (1:2) serves for exclusive formation of (*S*)-cyanohydrin TMS ethers [651]. The catalytic activity of the Gd complex is much higher than that of **178a**. The results of ^1H NMR and ESI–MS analyses indicate that Gd cyanide complex **179** is the active catalyst. It has been proposed that the two Gd cyanide moieties of **179** play different roles – one activates an aldehyde as a Lewis acid and the other reacts with the aldehyde as a cyanide nucleophile.

Belokon' and North have investigated the utility of Ti-salen complexes **172** and **173** as chiral catalysts (Scheme 10.239) [639–641]. With only 0.1 mol% **172b** cyanosilylation of benzaldehyde and other aromatic aldehydes bearing an electron-donating group proceeds with good optical yields (62–86% ee) at room temperature; reaction of aliphatic and electron-deficient aromatic aldehydes results in lower selectivity, however [640b]. Similar enantioselectivity is observed for the alkoxy complex **172a** [639]. In the **172**-catalyzed reactions a trace amount of water plays a critical role in achieving high conversion and optical yield. With **172b** addition of Et_3N to the reaction mixture to remove HCl also has a positive effect. On the ba-



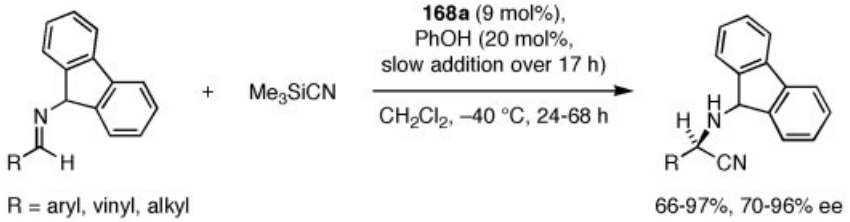
Scheme 10.241

sis of these facts Belokon' and North have found that bimetallic μ-oxo complex **173**, generated from **172**, acts as the actual catalyst for these asymmetric cyanosilylations. Use of isolated **173** under anhydrous conditions affords an enantiomeric excess similar to or better than that obtained with **172b** under non-anhydrous conditions [640b]. In addition, **173** is useful for asymmetric cyanosilylation of acetophenones (up to 72% ee) [641a].

10.5.4.3 Asymmetric Hydrocyanation of Imines

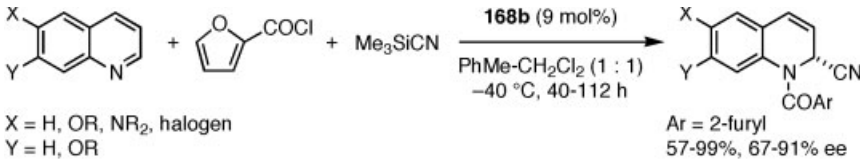
Since the pioneering work by Ojima et al. [653] the Strecker-type reaction of imines bearing a chiral auxiliary with TMSCN has frequently been used for asymmetric synthesis of α-aminonitriles [654]. In recent years catalytic asymmetric hydrocyanation of imines with TMSCN has been intensively studied to establish a more efficient route to optically active α-aminonitriles [655].

Shibasaki et al. have reported that on slow addition of PhOH the Al complex **168a** smoothly catalyzes asymmetric addition of TMSCN to a variety of *N*-fluorenylimines with high chemical and optical yields (Scheme 10.242) [656]. Addition of PhOH effectively increases the reaction rate and does not affect the enantioselectivity. When HCN is used instead of TMSCN-PhOH, both the reaction rate and the ee value decrease markedly. This observation denies the possibility that HCN arising from TMSCN and PhOH works as the reactive nucleophile. This asymmetric process as well as the **168a**-catalyzed cyanosilylation of aldehydes might proceed by dual activation of TMSCN and imines. The role of PhOH in the catalytic system is probably to facilitate the regeneration of **168a**, from an intermediate Al-amide complex, by protonolysis. Polymer-supported **168a** also has been used for the enantioselective cyanation [657]. The solid catalyst is easily reusable although the enantioselectivity is slightly lower than that of free **168a**.



Scheme 10.242

Asymmetric acylcyanation of quinolines (Reissert-type reaction) with 2-furoyl chloride and TMSCN is successfully performed by using the chiral catalyst **168** (Scheme 10.243) [658]. In this reaction the sterically more demanding complex **168b** exceeds **168a** in enantioselectivity.



Scheme 10.243

Homochiral 3,3′-dimethyl-2,2′-bisquinoline *N*,*N*′-dioxide serves as a Lewis base catalyst for asymmetric hydrocyanation of aromatic *N*-(diphenylmethyl)imines, although the enantioselectivity is still modest (37–77% ee) [659].

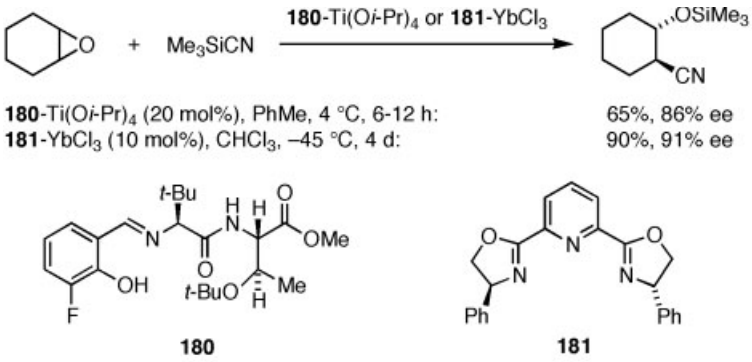
Jacobsen et al. have reported that peptide Schiff bases and an Al–salen complex are valuable for asymmetric hydrocyanation of imines with TBSCN [660] and TMSCN [661], respectively. It is, however, most likely that HCN arising from these cyanosilanes and adventitious water is the reactive nucleophile. Hoveyda et al. also have used TMSCN as a source of HCN in the hydrocyanation of imines catalyzed by a Ti-peptide Schiff base complex [662].

Asymmetric hydrocyanation of ketimines with TMSCN, a more challenging subject, has been reported by Vallée et al. They investigated the utility of chiral Ti-BINOL complexes for hydrocyanation of the *N*-benzylketimine derived from acetophenone [663]. The best result (80% conversion, 56% ee) was obtained by catalytic use of Ti(O*i*-Pr)$_2$(BINOL) (10 mol%) in the presence of TMEDA (20 mol%). More recently they have found that Sc(BINOL)$_2$Li works as an efficient chiral catalyst for the same hydrocyanation (10 mol% of the catalyst: >95% conversion, 88% ee) [664].

10.5.4.4 Asymmetric Desymmetrization of *meso* Epoxides

The Ti- and Yb-catalyzed ring-opening reactions of epoxides with TMSCN (Section 10.5.4.1) have been applied to asymmetric desymmetrization of *meso* epoxides by use of a chiral ligand (Scheme 10.244). A Ti complex prepared from Ti(O*i*-Pr)$_4$

and peptide Schiff base **180**, developed by combinatorial strategy, enables the desymmetrization with good enantioselectivity [665]. The use of **181**-$YbCl_3$ leads to higher ee at lower temperature although the reaction is rather slow [666]. In the Yb-catalyzed reaction a non-linear relationship is obtained between ligand and product ee, and results from kinetic study are indicative of second-order dependence on the catalyst. On the basis of these observations it has been proposed that the cyanation reaction proceeds via a bimetallic mechanism in which one Yb complex serves as a Lewis acid to activate an epoxide and another complex reacts with the epoxide as a cyanide donor.

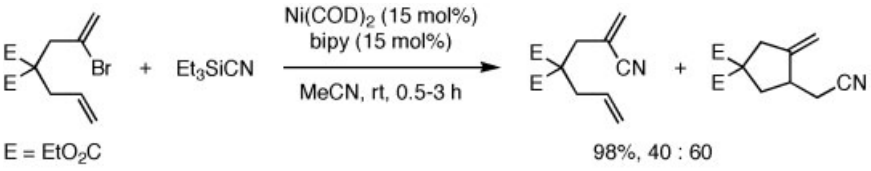


Scheme 10.244

10.5.4.5 **Transition Metal-catalyzed Reactions**

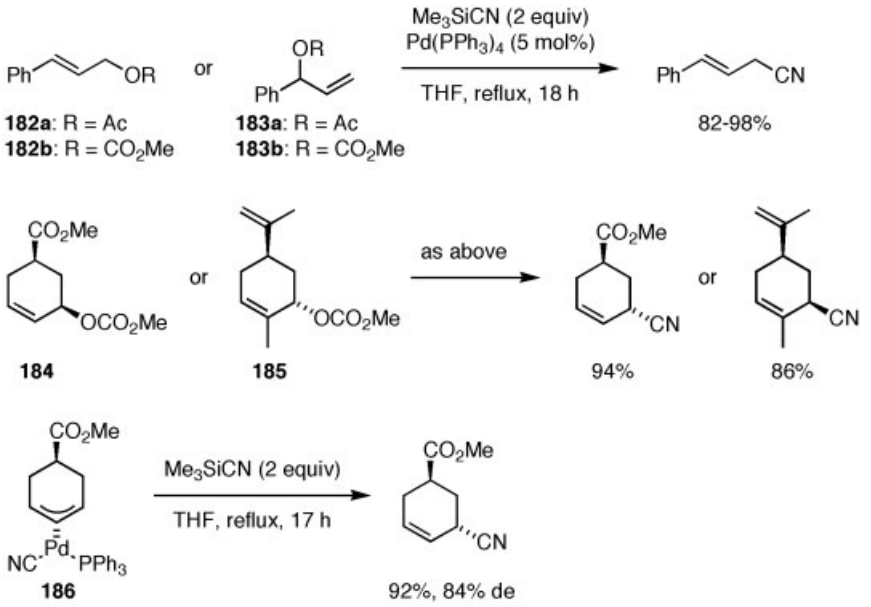
TMSCN has also been used as a convenient and reactive cyanide donor in transition metal-catalyzed processes. The Pd-catalyzed cyanation of aryl iodides with TMSCN is useful for the synthesis of aryl cyanides [667]. Anderson et al. recently found that TMSCN works as an efficient co-catalyst for the Pd-catalyzed cyanation of aryl iodides with KCN [668]. In this cyanation TMSCN should react with aryl iodides to give aryl cyanides and TMSI, and TMSCN would be regenerated by the reaction of TMSI with KCN.

The Ni-catalyzed reaction of 2-bromo-1,6-heptadienes with cyanosilanes affords cyclic and open chain adducts (Scheme 10.245) [669]. TMSCN and Et_3SiCN are available for this reaction whereas bulky cyanosilanes such as TBSCN and *i*-Pr_3SiCN result in sluggish or incomplete reactions leading to predominant formation of the open chain adducts. The product ratio is strongly affected by the substitution pattern of the substrate.



Scheme 10.245

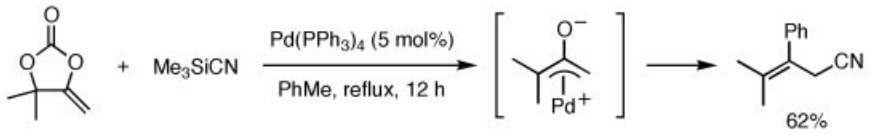
Tsuji et al. have reported that on catalysis by $Pd(PPh_3)_4$ allyl acetates and carbonates react with TMSCN to give β,γ-unsaturated nitriles in good to high yields (Scheme 10.246) [670]. Regioisomeric substrates such as **182** and **183** are converted into the same product, suggesting a π-allylpalladium intermediate. The cyanation of *cis*-alicyclic substrate **184** affords only the *trans* isomer of the corresponding nitrile, and *trans*-**185** is cyanated to the *cis* product. Thus, the cyanation proceeds with stereochemical inversion. A plausible mechanism involves oxidative addition of a substrate to a Pd(0) species, transmetalation of TMSCN with the resulting π-allylpalladium, and reductive elimination of the carbon ligands. Experiments using an isolated π-allylpalladium acetate and the corresponding cyanide indicate that the transmetalation step is facile, and that the reductive elimination step occurs only when excess TMSCN is present (Scheme 10.246). Conversion of π-allylpalladium cyanide **186** into the *trans* product suggests the overall inversion stereochemistry is probably because of an inversion–retention–retention process in the catalytic cycle. Pd-catalyzed cyanation with TMSCN is applicable to the synthesis of cyanoallenes from propargyl carbonates [671].



Scheme 10.246

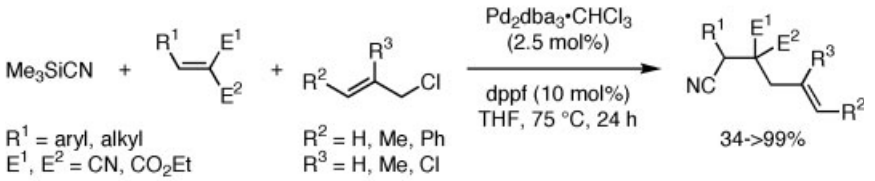
The Pd-catalyzed addition of TMSCN to 5,5-dimethyl-4-methylene-1,3-dioxolan-2-one forms a cyanated silyl enolate (Scheme 10.247). The cyanosilylation might proceed via an oxatrimethylenemethane-Pd complex [672].

In the presence of $Pd_2dba_3 \cdot CHCl_3$-4dppf the three-component coupling reaction of TMSCN, highly electron-deficient alkenes, and allyl chlorides proceeds smoothly to give cyanoallylation products in moderate to high yields (Scheme 10.248) [673]. It has been proposed that the reaction mechanism consists of oxidative addition of a



Scheme 10.247

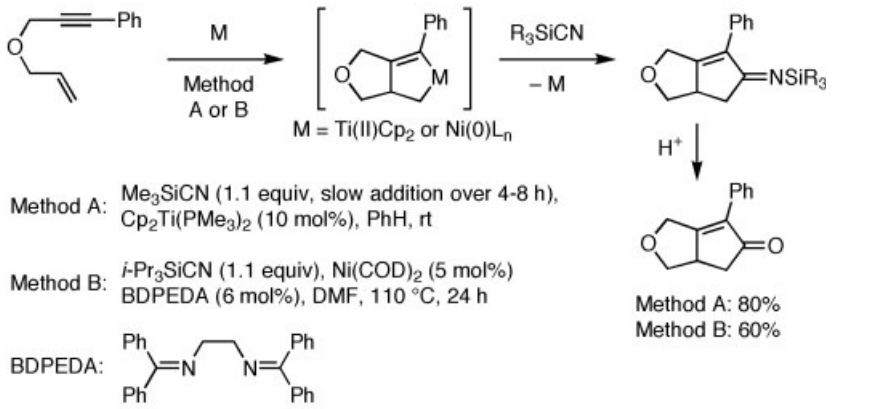
Pd(0) species to an allyl chloride, transmetalation of TMSCN with the resulting π-allylpalladium chloride, conjugate addition of the cyanide ligand of the π-allylpalladium cyanide to an activated alkene, and reductive elimination of the carbon ligands.



Scheme 10.248

Ito et al. have applied the Pd-catalyzed cyanosilylation of alkynes originally developed by Chatani et al. [674] to the stereodefined synthesis of tri- and tetra-substituted alkenes (Section 10.4.3.1, Scheme 10.212) [551 b].

Cyanosilanes serve as sources of isocyanide, because a tautomeric equilibrium exists between cyanosilanes and the corresponding isocyanides. Although the equilibrium largely favors the cyano tautomer, Buchwald et al. have successfully used the dilute isocyanide donors for the Ti(II)- and Ni(0)-catalyzed cyclizations of enynes to iminocyclopentenes (Scheme 10.249) [675]. Use of cyanosilanes achieves efficient imination of metallacyclopentene intermediates without deactivation of the active catalysts.



Scheme 10.249

Treatment of zirconacyclopentanes and -pentenes with TMSCN provides zirconocene-imine complexes which serve for carbon–carbon bond-forming reaction with a variety of unsaturated bonds [676].

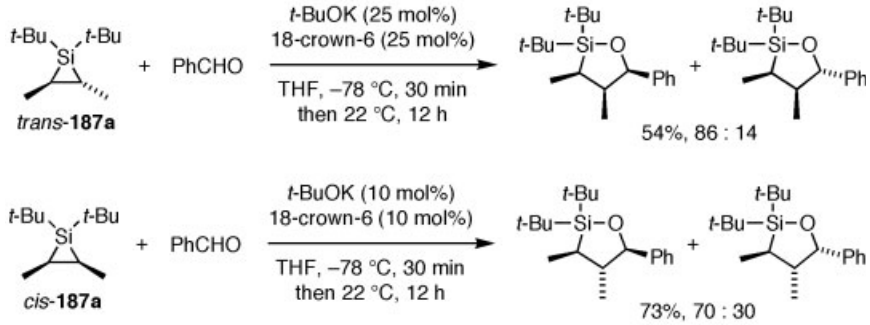
10.6 Silicon-containing Strained Molecules

The strain energy released on cleavage of three-membered ring compounds such as cyclopropanes, oxiranes, and aziridines can be used to accomplish powerful stereoselective transformations in organic synthesis. Although carbon–carbon bond-forming reactions using silacyclopropanes, three-membered ring silanes, were reported by Seyferth and Ando in the nineteen-eighties [677], the reactions were not extended to organic synthesis. In recent years the potential of silacyclopropanes as synthetic intermediates for stereoselective synthesis has been intensively studied by Woerpel et al. [678]. Silacyclobutanes as well as silacyclopropanes are known to have highly reactive carbon–silicon bonds. Until the end of the nineteen-eighties this reactivity had been used mainly for synthesis of polycarbosilanes by ring-opening polymerization and for generation of silenes by thermal decomposition [10]. The utility of silacyclobutanes for organic synthesis was systematically shown for the first time by Utimoto and Oshima in the nineteen-nineties [679]. This section describes carbon–carbon bond-forming reactions accompanied by cleavage of the strained silicon–carbon bond of silacyclopropanes and -butanes.

10.6.1 Carbon–Carbon Bond Formation with Silacyclopropanes

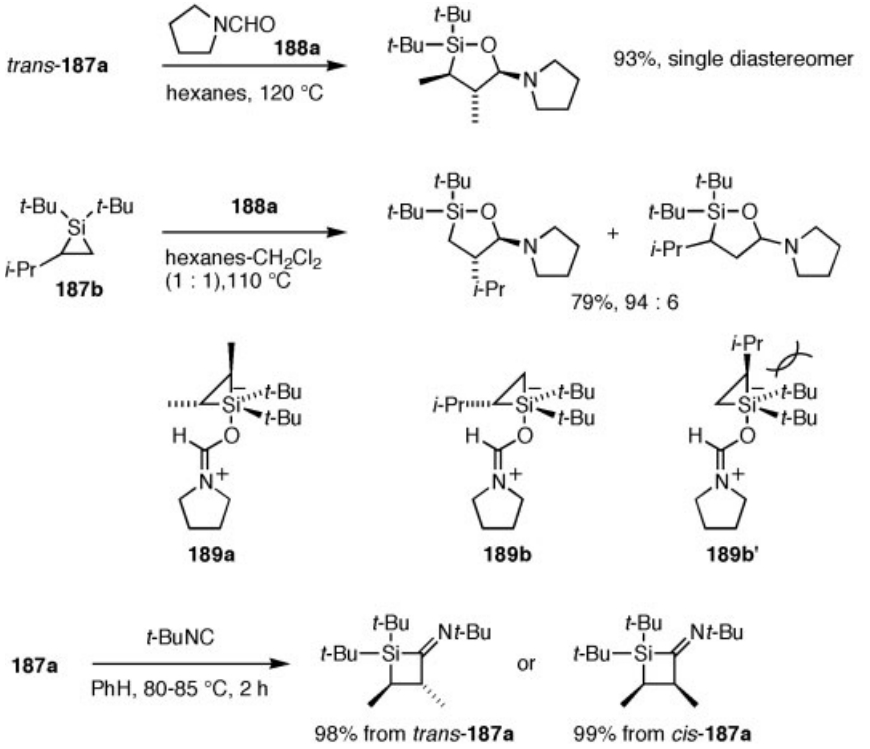
The thermal reactions of silacyclopropanes *cis*- and *trans*-**187a** with benzaldehyde give a stereoisomeric mixture of an oxasilacyclopentane product and significant quantities of by-products whereas the *t*-BuOK-catalyzed reactions proceed efficiently under mild conditions with inversion of silacyclopropane configuration (Scheme 10.250) [680]. The latter reactions might involve initial formation of a more reactive pentacoordinate siliconate intermediate. The base-catalyzed system is not applicable to insertion of enolizable aldehydes.

Under thermal conditions, formamide **188a** is inserted into *trans*-**187a** in high yield with high diastereoselectivity (Scheme 10.251) [681]. This reaction proceeds with retention of silacyclopropane configuration. The formation of siliconate **189a**, which activates the carbon–silicon bond and the formyl carbon, accounts for the high reactivity of **188** and the retention of stereochemistry. Use of *cis*-**187a** results in no insertion product, because of its rapid decomposition. The insertion into unsymmetrical silacyclopropane **187b** occurs exclusively on the more substituted side. This regioselectivity is probably because the insertion proceeds via the energetically more favorable siliconate intermediate **189b** rather than **189b′**, which suf-



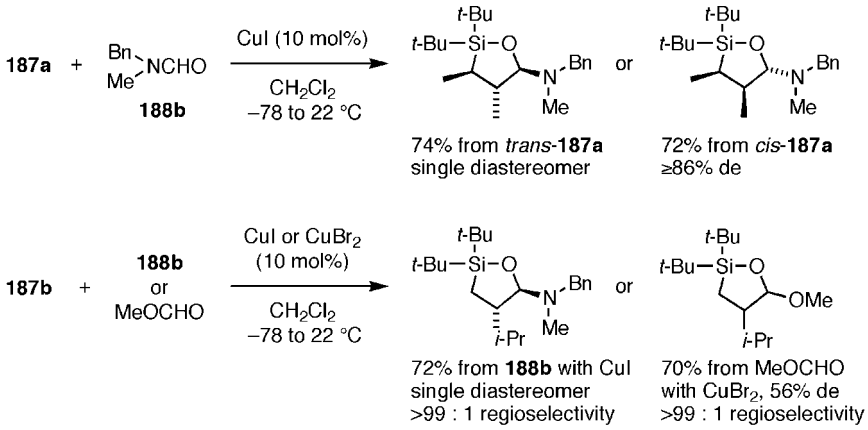
Scheme 10.250

fers from steric repulsion between the *t*-butyl group on silicon and the isopropyl group. Isocyanides also react with silacyclopropanes without any catalyst to give iminosilacyclobutanes (Scheme 10.251) [682]. Stereo- and regioselectivity are similar to those observed with formamides.



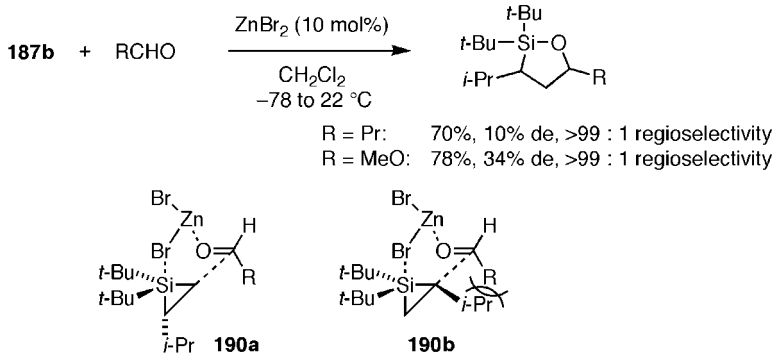
Scheme 10.251

Amide insertion into *trans*- and *cis*-**187a** is effectively catalyzed by a Cu salt at or below room temperature (Scheme 10.252) [683]. Aromatic aldehydes, *α,β*-unsaturated aldehydes, formates, and formamide can be used as the carbonyl donor. Carbonyl insertion into **187b** favors the more substituted side, and the regioselectivity is very high (Scheme 10.252). It has been proposed that the Cu-catalyzed reaction proceeds by transmetalation, forming an organocopper intermediate.



Scheme 10.252

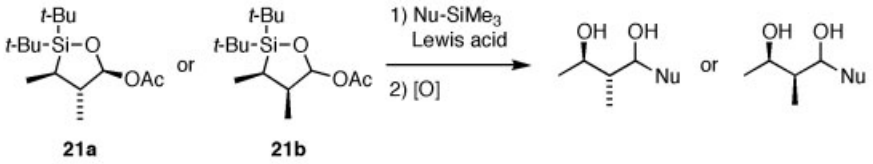
$ZnBr_2$ also work as an effective catalyst for the carbonyl insertion into **187b** (Scheme 10.253) [684]. The Zn-catalyzed system is valuable for insertion of aldehydes and ketones (including aliphatic compounds) as well as formates. In sharp contrast to the Cu-catalyzed reaction, the zinc-catalyzed reaction inserts these carbonyl compounds into the less substituted silicon–carbon bond of **187b** with high



Scheme 10.253

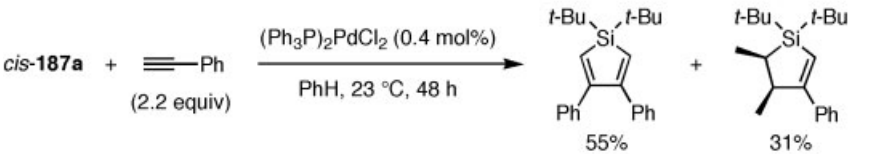
regioselectivity. $ZnBr_2$ most probably activates carbonyl compounds, and the bromine atom might coordinate to the silicon atom to enhance the nucleophilicity of the strained ring. The inverted regioselectivity can be rationalized by the unfavorable steric interaction in the transition structure **190 b**.

The insertion products from silacyclopropanes are valuable for stereoselective synthesis of 1,3-diols [55]. In particular, oxasilacyclopentanes **21 a** and **21 b**, derived from *trans*- and *cis*-**187**, can be converted into a variety of functionalized 1,3-diols by highly diastereoselective alkylation using silyl enolates (Section 10.2.1.1, Scheme 10.17) and allylsilanes, and subsequent oxidation of the silicon–carbon bond (Scheme 10.254).



Scheme 10.254

The Pd-catalyzed reaction of silacyclopropanes with terminal or electron-deficient alkynes gives siloles along with silacyclopentenes (Scheme 10.255) [685]. The mechanism for the formation of these products might involve oxidative addition of the carbon–silicon bond to a Pd(0) complex generated in situ.

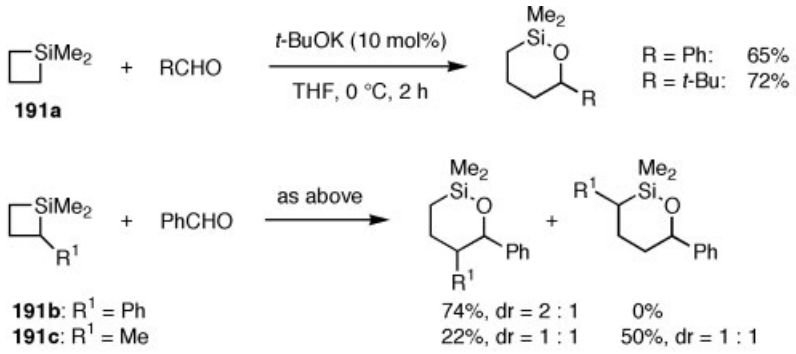


Scheme 10.255

10.6.2
Carbon–Carbon Bond Formation with Silacyclobutanes

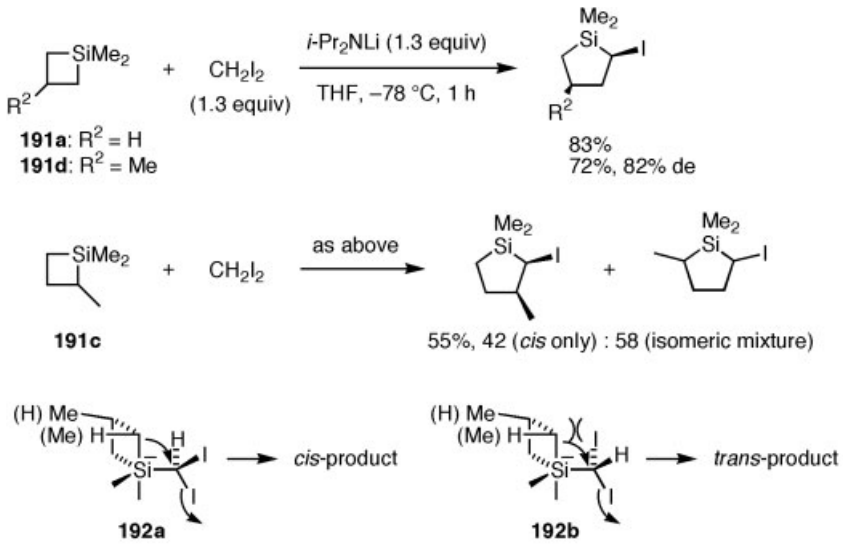
In the presence of a catalytic amount of *t*-BuOK, silacyclobutane **191 a** reacts with nonenolizable aldehydes to give cyclic silyl ethers in good yields (Scheme 10.256) [686]. Carbonyl insertion into **191 b** occurs across the benzylic carbon–silicon bond with high regioselectivity whereas **191 c** undergoes less regioselective insertion.

Silacyclobutanes react with lithium carbenoids to form silacyclopentanes by insertion of the C1 unit into the carbon–silicon bond (Scheme 10.257) [687]. The reaction with dihalomethyllithiums prepared from dihalomethanes and $LiN(i\text{-}Pr)_2$ affords 2-halosilacyclopentanes in moderate to good yields. With 3-methylsilacyclobutane **191 d** the ring-expansion reaction proceeds with high *cis*-selectivity. Although use



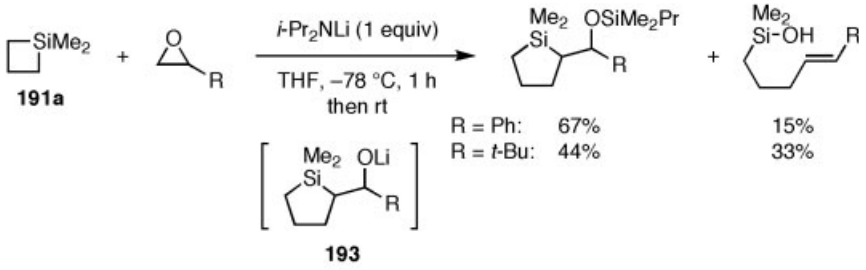
Scheme 10.256

of **191c** results in the formation of both regioisomers with low selectivity, the insertion leading to 2-halo-3-methylsilacyclopentanes is highly *cis*-selective. A plausible mechanism for the ring-expansion reaction involves 1,2-alkyl-migrative substitution of a pentacoordinate silicate intermediate such as **192**. The stereochemical outcome with **191c** and **191d** can be well explained by the transition structures **192a** and **192b**. The path via **192b** is disfavored by steric repulsion caused by the iodine inside the silacycle, and the 1,2-alkyl-migration proceeds via **192a** to provide predominantly *cis* products.



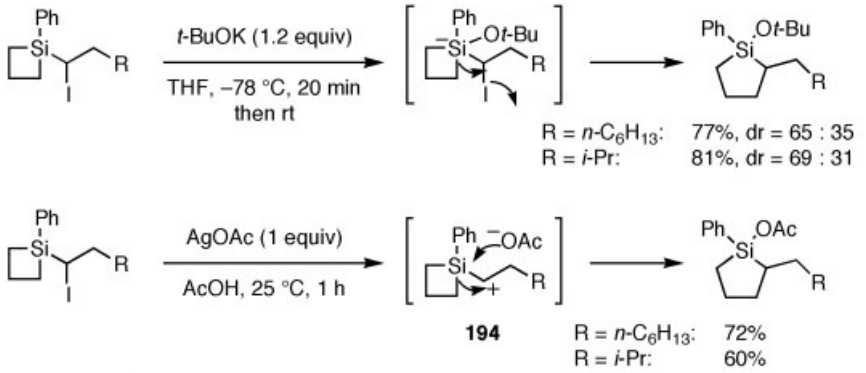
Scheme 10.257

The reaction of **191a** with oxiranyllithiums as lithium carbenoids gives 2-(1-siloxyalkyl)silacyclopentanes and 4-alkenylsilanols (Scheme 10.258) [686]. These products would arise from the initially formed silacyclopentane products **193**.



Scheme 10.258

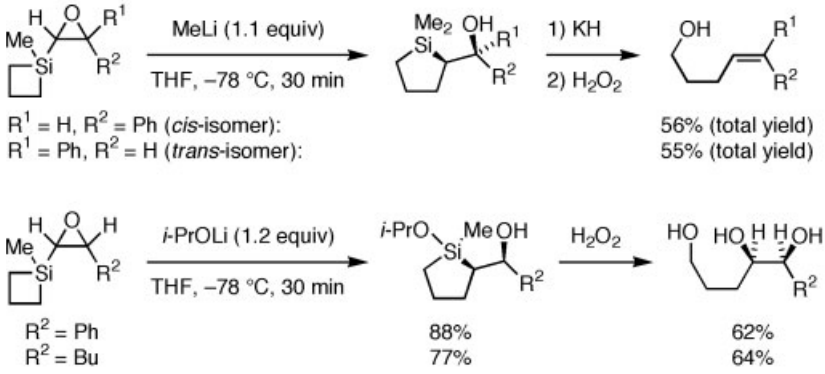
Treatment of 1-(1-iodoalkyl)silacyclobutanes with *t*-BuOK leads to 2-alkyl-1-*t*-butoxysilacyclopentanes (Scheme 10.259) [688]. The nucleophile-induced ring-expansion reaction might proceed via a pentacoordinate silicate intermediate similar to **192**. Silver acetate and *t*-BuOK induces the ring-expansion to afford 1-acetoxysilacyclopentanes (Scheme 10.259). The silver ion probably serves to abstract iodine from the substrate, and the resulting *α*-silylcarbenium ion **194** changes to the product via a cationic rearrangement. These products are easily converted into diols by oxidative cleavage of the carbon–silicon bonds.



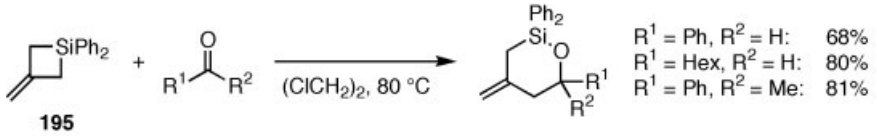
Scheme 10.259

1-Oxiranylsilacyclobutanes also undergo efficient stereospecific nucleophile-induced ring-expansion to give 1-(1-hydroxyalkyl)silacyclopentanes (Scheme 10.260) [689]. The products are available for the stereo-controlled synthesis of 4-alkenols and 1,2,5-triols.

3-Methylenesilacyclobutane **195** is more reactive to carbonyl compounds than silacyclobutanes (Scheme 10.261) [690]. The insertion of aldehydes and ketones into the carbon–silicon bond occurs at 80 °C without any catalyst. The allylsilane products can be used for further carbon–carbon bond formation in the presence of a Lewis acid. Compound **195** thus serves as a 2-methylene-1,3-dianion equivalent.

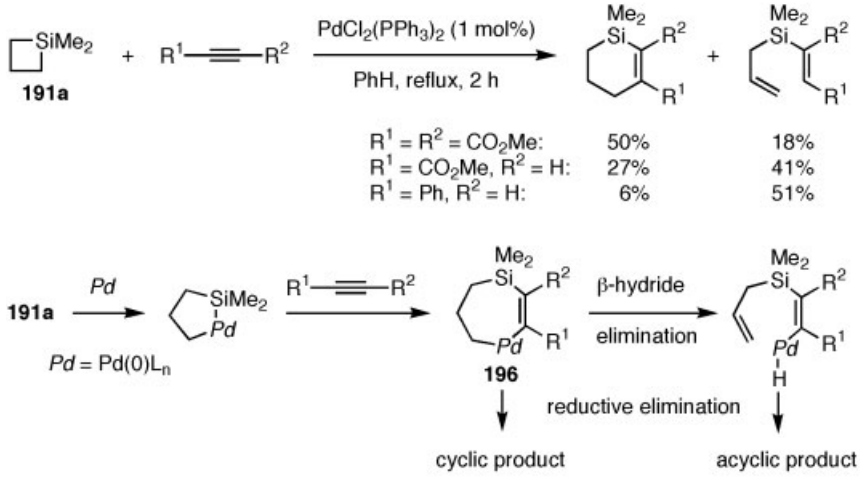


Scheme 10.260



Scheme 10.261

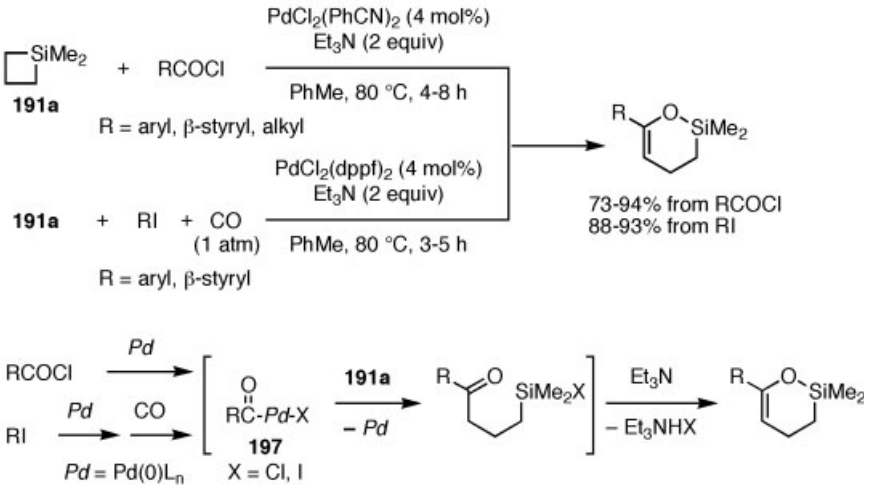
The silicon–carbon bonds of silacyclobutanes are readily activated by Pd and Pt complexes [691]. This notable characteristic has been used for carbon–carbon bond formation using silacyclobutanes [692–695]. The Pd-catalyzed reaction of **191 a** with alkynes affords silacyclohexenes and allylvinylsilanes (Scheme 10.262) [693]. A plausible mechanism for formation of the cyclic product involves three steps – oxidative addition of **191 a** to a Pd(0) species, alkyne insertion into the Si–Pd bond, and reduc-



Scheme 10.262

tive elimination of the carbon ligands in **196**. The acyclic product would arise from **196** by *β*-hydride elimination and the subsequent reductive elimination.

Under catalysis by $PdCl_2(PhCN)_2$, the reaction of silacyclobutanes with acyl chlorides in the presence of Et_3N produces cyclic silyl enolates in high yields (Scheme 10.263) [694]. A variety of acyl chlorides, including aromatic and aliphatic compounds, can be used for this reaction. The cyclic enolates are also obtained by using CO and organic iodides instead of acyl chlorides [695]. The mechanism proposed for these reactions involves formation of acylpalladium halide **197** from a Pd(0) species, ring-opening reaction of a silacyclobutane with the acylpalladium, and deprotonative cyclization of the resulting chlorosilane.



Scheme 10.263

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11
Germanium in Organic Synthesis

Takahiko Akiyama

11.1
Introduction

Germanium is a group 14 element, located between silicon and tin in the periodic table [1]. Whereas the synthetic utility of organosilicon [2] and organotin [3] compounds has been extensively studied, organogermanium compounds have attracted less attention of synthetic organic chemists. There are several reasons why organogermanium compounds have not been regarded as common synthetic reagents:

1. Organogermanium compounds are expensive.
2. Because chlorotrialkylgermanes, e.g. R_3GeCl [4], were not readily available commercially until recently [5], chlorogermanes had to be prepared from $GeCl_4$ [6], the cheapest commercial source of germanium.
3. Organogermanium compounds have properties between those of organosilicon and organotin compounds and this unique synthetic utility has not been extensively explored. Whereas organotin compounds prefer radical reactions, ionic reactions predominate with organosilicon compounds. Organogermanium compounds have both characteristics.

Although compilations of organogermanium chemistry are available [7, 8], most review articles focus on the structure and reaction of the organogermanium compounds. For this reason I wish to address the synthetic utility of organogermanium compounds focusing on articles published after 1990.

11.2
Allylgermanes

11.2.1
Preparation

Allylgermanes are readily prepared by the reaction of allylic Grignard reagents with chlorogermane. For example, addition of allyl magnesium bromide to chlorotriethylgermane occurs smoothly at room temperature in Et_2O to give allyltriethyl-

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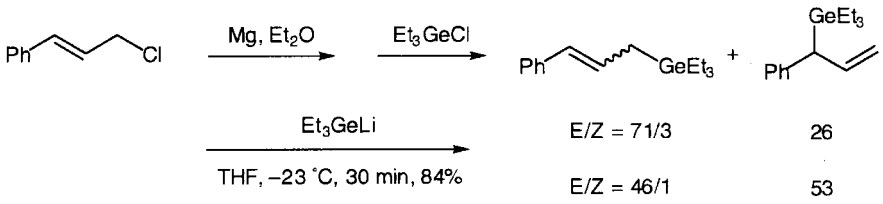
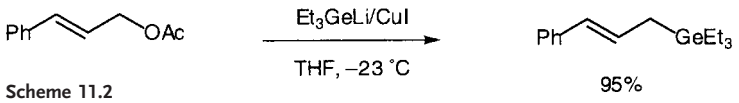
germane in high yield. For the preparation of cinnamylgermane, either treatment of a Grignard reagent derived from cinnamyl halide with Et_3GeCl or treatment of cinnamyl chloride with Et_3GeLi resulted in the formation of the mixtures of stereoisomers and regioisomers (Scheme 11.1). Takeda reported a stereoselective synthesis of cinnamylgermane starting from cinnamyl acetate by use of germyl anion in the presence of a Cu(I) salt (Scheme 11.2) [9].

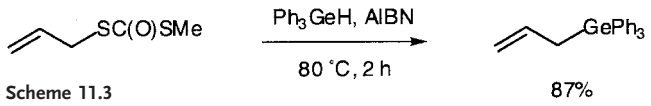


Scheme 11.1



Scheme 11.2

Allylgermane was also prepared by starting from allylic sulfur compound (Scheme 11.3) [10].



Scheme 11.3

Palladium-catalyzed germylation of allylic halides with germylstannanes also afforded allylic germanes [11].

11.2.2 Reaction

Allylic organometallic compounds are synthetic equivalents of allyl anions [12]. Mayr studied the kinetics of group 14 allylic organometallic compounds and found the order of nucleophilicity was Sn > Ge > Si [13]. Substituents on the metal also significantly affected the nucleophilicity. For instance, nucleophilicity increases in the order $SiPh_3 < GePh_3 < SiMe_3 < SnPh_3 < SnBu_3$.

The high nucleophilicity of group 14 organometallic compounds is because of their remarkable nonadjacent positive charge on the carbocation. The best known manifestation of the phenomenon is the β-effect of silicon [14] whereby a silicon

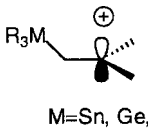
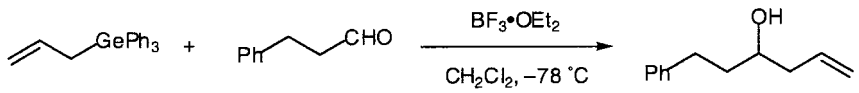


Fig. 11.1 The β-effect of silicon

atom two bonds from the nominal center of positive charge stabilizes the system by hyperconjugation (Fig. 11.1). The order of the β-effect is Sn >> Ge > Si [15].

Lewis acid-catalyzed allylation of allylgermane with an aldehyde was reported in 1986 for the first time (Scheme 11.4) [9].



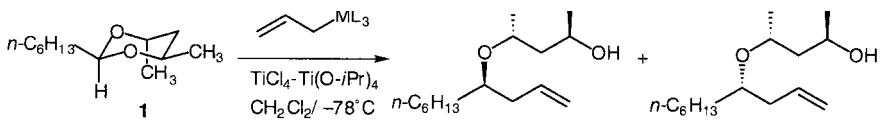
Scheme 11.4

Denmark studied the reactivity and stereoselectivity of group 14 allylic organometallic compounds toward chiral dioxane acetals [16]. Allylation with allyltributylstannane was significantly more selective than that with allyltrimethylsilane for several chiral dioxane acetals examined (Tab. 11.1).

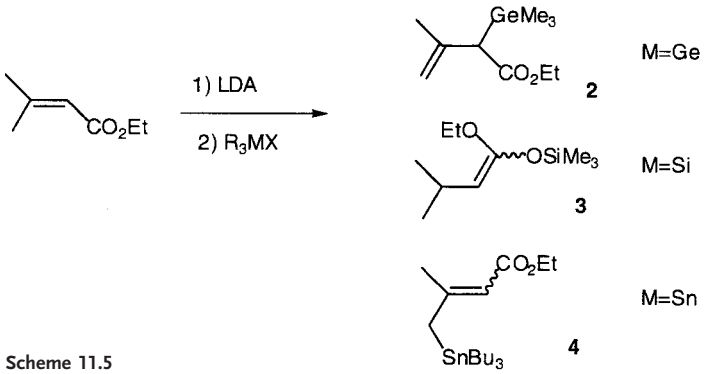
Yamamoto reported that trapping of a lithium enolate, derived from 3-methyl-2-butenoate, with Me_3GeX selectively gave α-germylated derivative (**2**) (Scheme 11.5) [17]. Trapping with Me_3SiCl or Bu_3SnCl afforded *O*-silylated product (**3**) or γ-stannylated compound (**4**) respectively.

The α-germylation is a reflection of kinetic control, whereas γ-stannylation is thermodynamic controlled. The C–Ge bond is stronger than the C–Sn bond. D(Ge–Et) = 237 kJ mol^{-1}, D(Sn–Et) = 193 kJ mol^{-1}. α-Germyl ester (**2**) played the role of a Ge-masked dienolate equivalent. Thus, Lewis acid-mediated addition of the α-germyl ester (**2**) to an acetal (Scheme 11.6) [17, 18], diethylazodicarboxylate

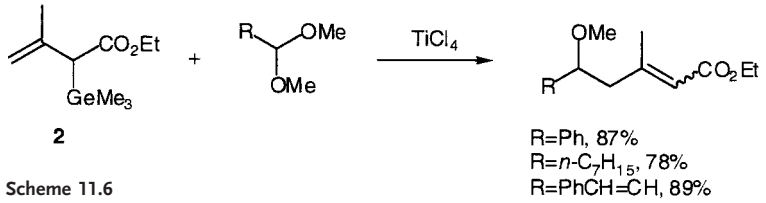
Tab. 11.1 The effect of the metal on diastereoselectivity



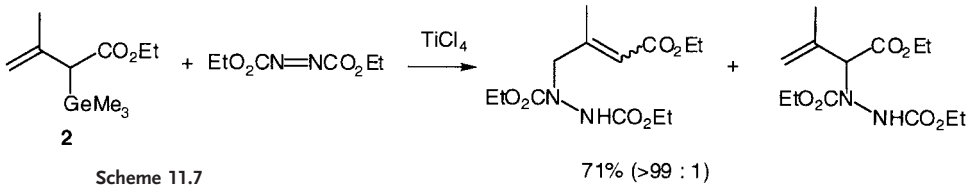
Entry	*ML_3*	*Ratio*
1	$SiMe_3$	58:1
2	$SiPh_3$	10:1
3	$GeMe_3$	100:1
4	Sn*n*-Bu_3	270:1
5	$SnPh_3$	90:1



Scheme 11.5



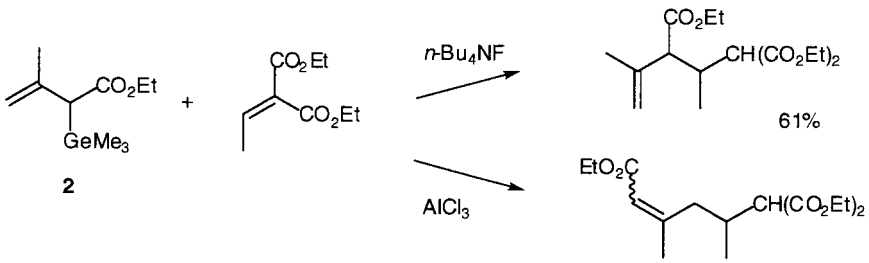
Scheme 11.6



Scheme 11.7

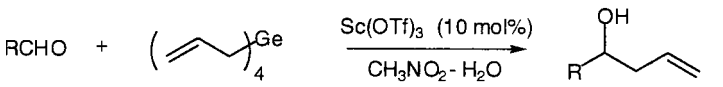
(Scheme 11.7) [19], or α,β-unsaturated carbonyl compounds furnished γ-adducts selectively (Scheme 11.7) [20].

Interestingly, use of tetrabutylammonium fluoride instead of Lewis acid resulted in the reversal of regioselectivity and the α adduct was obtained preferentially (Scheme 11.8).



Scheme 11.8

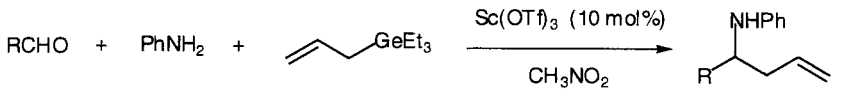
Allylation of carbonyl compounds with tetraallylgermane [21] is promoted by a catalytic amount of $Sc(OTf)_3$ in CH_3NO_2 to afford the corresponding homoallylic alcohols in high yields. It was found that addition of small amount of H_2O significantly increased the yields of the adducts (Scheme 11.9) [22].



R=Ph, 94%
R=$PhCH_2CH_2$, 92%
R= PhCO, 87%

Scheme 11.9

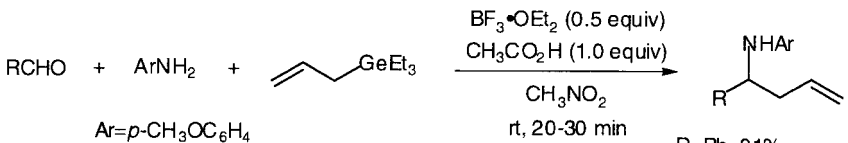
For the $Sc(OTf)_3$-catalyzed allylation of imines, use of allyltriethylgermane instead of tetraallylgermane turned out to be more effective and homoallylic amines were obtained in high yields. Because aldehydes were not reactive under these reaction conditions, a three-component synthesis starting from aldehyde, amine, and allylgermane was used and found to proceed smoothly, providing homoallylic amines in high yields (Scheme 11.10) [23].



R=Ph, 81%
R=*p*-$CH_3C_6H_5$, 86%
R=*c*-C_6H_{11}, 87%

Scheme 11.10

Combined use of $BF_3 \cdot OEt_2$ and AcOH was found to be effective for allylation of aldimines. The catalyst system is also effective for the three-component synthesis of homoallylic amines starting from aldehyde, amine, and allylgermane (Scheme 11.11) [24].

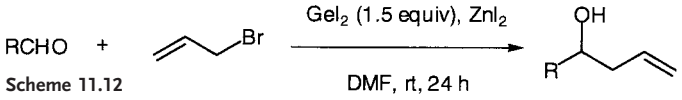


Ar=*p*-$CH_3OC_6H_4$

R=Ph, 81%
R=*c*-C_6H_{11}, 80%
R=PhCO, 88%

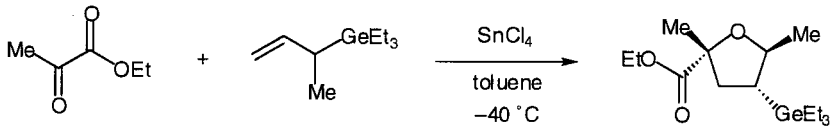
Scheme 11.11

Saigo reported germanium(II) halide-mediated Barbier-type allylation of carbonyl compounds. Addition of ZnI_2 improved the yields significantly (Scheme 11.12) [25]. Although the precise mechanism has not been clarified, the authors postulated an allylgermanium(IV) species as a reactive intermediate.



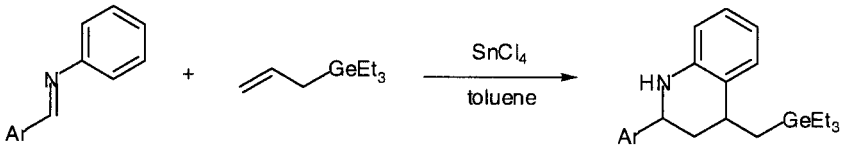
Scheme 11.12

Lewis acid-mediated cycloaddition reactions of allylgermane have been reported. Thus, [3+2] cycloaddition of α-keto ester to allylgermane occurred under the influence of tin(IV) chloride to afford germyl-substituted tetrahydrofurans stereoselectively (Scheme 11.13) [26]. Because the carbon–germanium bond is weaker than the carbon–silicon bond, yields of the cycloadducts were lower than those of the corresponding silicon analog [27].



Scheme 11.13

The Lewis acid-mediated aza Diels-Alder reaction of aldimine with allyltriethylgermane afforded tetrahydroquinoline derivatives, favoring the *cis* isomer (Scheme 11.14) [28].

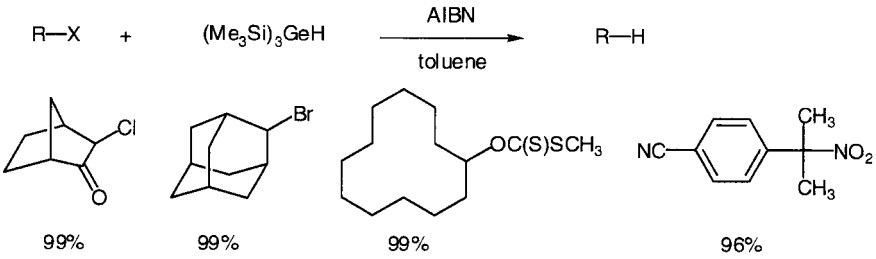


Scheme 11.14

11.3 Germanium–Hydrogen Bonds (Reductive Radical Chain Reactions)

Most radical reactions of interest to synthetic chemists are chain processes under reducing conditions. A feature associated with these reactions is hydrogen transfer from the reducing agent to a radical. Most hydrogen donors have been R_3SnH species. Because of increasing concern about the toxicity of organotin compounds, development of safe alternatives to R_3SnH is desired [29]. $(Me_3Si)_3SiH$ is an attractive alternative to the popular Bu_3SnH. Hershberger indicated that Bu_3GeH is superior to Bu_3SnH for some reductive alkylations. Bu_3GeH is significantly less reactive toward alkyl radicals than Bu_3SnH (a factor of approximately 10) and much less reactive than organomercury hydrides (a factor of at least 100). The reductive alkylation of acrylonitrile and of 2-cyclohexen-1-one by alkyl halide using Bu_3GeH was systematically evaluated [30].

Chatgilialoglu studied $(Me_3Si)_3GeH$ as a new radical hydrogen donor, and found that reduction of chlorides, bromides, and iodides, deoxygenation of secondary alcohols via a thiono ester (Barton-McCombie reaction), deamination of primary amines via isocyanides, removal of PhSe group, and replacement of a tertiary nitro group by hydrogen were extremely effective (Scheme 11.15) [31].



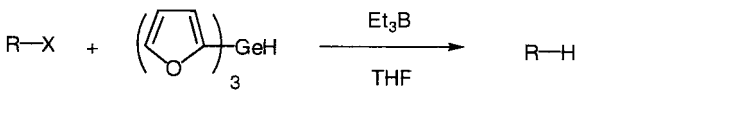
Scheme 11.15

Kinetic studies of the hydrogen donating ability showed that $(Me_3Si)_3GeH$ was superior not only to $(Me_3Si)_3SiH$ but also to Bu_3SnH (Fig. 11.2) [31].

The reactivity of group 14 organometallic hydride toward nitroxides [32], primary alkyl radicals [33], and cumylperoxyl radicals [34] has been studied.

Addition of $(Me_3Si)_3GeH$ to carbon–carbon triple bonds proceeded smoothly under radical conditions to give vinylgermane, although carbon–carbon double bonds are inert under identical conditions [35].

Oshima and co-workers developed tri(2-furyl)germane (**5**) as a novel and effective hydrogermane. Triethylborane-induced radical reduction of organic halides with **5** provided the corresponding reduced compounds in excellent yields (Scheme 11.16).



Scheme 11.16

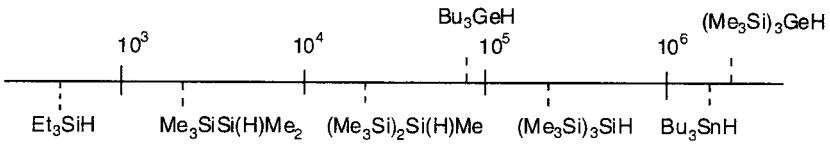
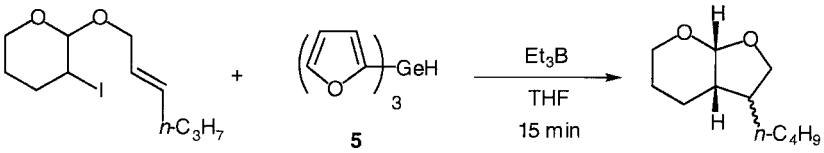


Fig. 11.2 Rate constants for hydrogen abstraction from a variety of group 14 reducing agents by primary alkyl radicals at 25 °C

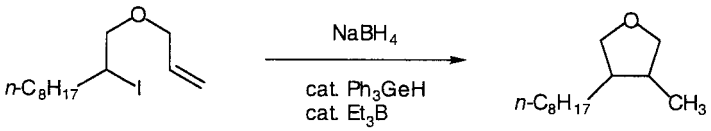
Radical cyclization of β-haloalkyl allyl ethers or 6-halo-1-alkenes afforded five-membered products under the same conditions (Scheme 11.17).



Scheme 11.17

These reactions proceeded with $NaBH_4$ in the presence of a catalytic amount of germanium hydrides (Scheme 11.18 and Tab. 11.2) [36].

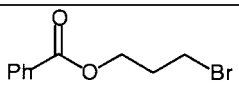
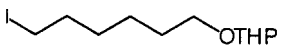
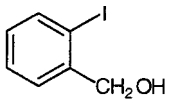
Oshima found Et_3B-induced hydrogermylation of alkenes (Schemes 11.19 and 11.20) and silyl enol ethers (Scheme 11.21) via radical processes [37]. Whereas Et_3B-induced reaction of tri(2-furyl)germane with 2-methyl-2-butene afforded the adduct in 90% yield, reaction of Ph_3GeH, n-Bu_3SnH, or $(Me_3Si)_3SiH$ gave the corresponding adduct in miserable yield, or failed to give the desired product (Scheme 11.20). Because stereospecific transformation of β-siloxygermanes to alkenes was achieved, this reaction provides a novel method for the stereoselective synthesis of alkenes starting from ketone by way of silyl enol ethers (Scheme 11.21).

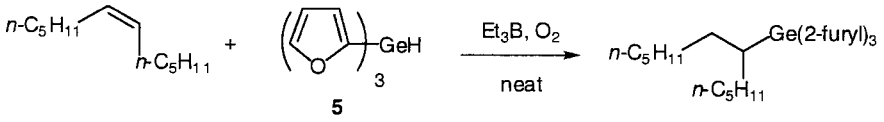


Scheme 11.18

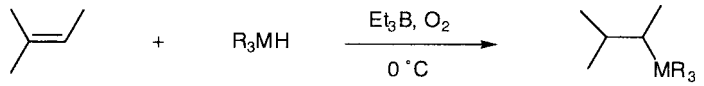
Tab. 11.2 Results obtained from catalytic reduction

$$RX \xrightarrow[\text{tri(2-furyl)germane(0.1 mmol)}\\ Et_3B\ (0.2\ \text{mmol})\quad THF]{NaBH_4\ (2.0\ \text{mmol})} RH$$

Entry	*Starting material*	*Reaction time (h)*	*Yield (%)*
1		4	90
2		1	97
3		7	77

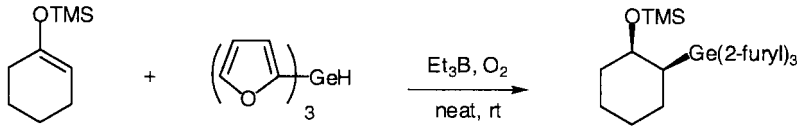


Scheme 11.19



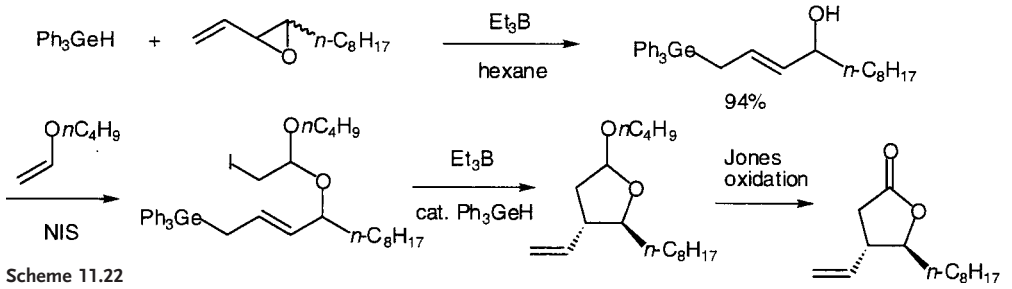
$(2\text{-Furyl})_3GeH$	90%
Ph_3GeH	11%
$(n\text{-}C_6H_{13})_3GeH$	0%
$n\text{-}Bu_3SnH$	0%
$(Me_3Si)_3SiH$	0%

Scheme 11.20



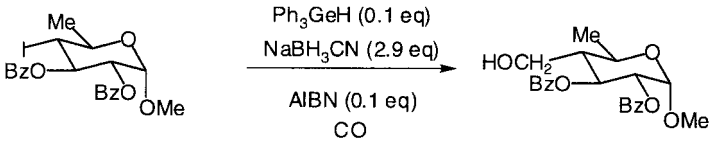
Scheme 11.21

Radical addition of triphenylgermane to vinyl oxiranes proceeded in the presence of triethylborane to yield 4-triphenylgermyl-2-buten-1-ol derivatives in good yield. Iodo acetals, prepared by iodoetherification of vinyl ethers with the allylic alcohol, underwent radical cyclization to give 2-alkoxy-4-vinyltetrahydrofurans which were converted into 4-vinyltetrahydro-2-furanones by Jones oxidation (Scheme 11.22) [38].



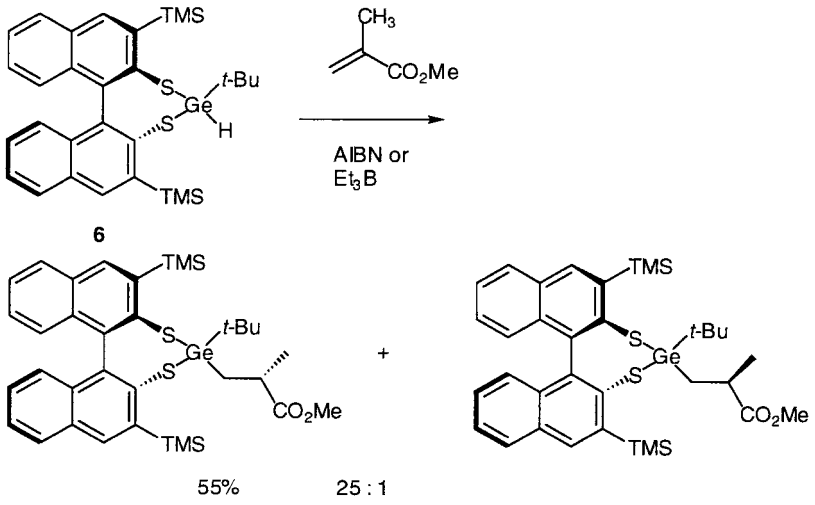
Scheme 11.22

Kahne developed a novel method for transformation of iodide to a CH_2OH group by treatment of an iodide with a catalytic amount of Ph_3GeH-$NaBH_3CN$-AIBN in benzene–THF under an atmosphere of CO at high pressure (Scheme 11.23) [39]. This methodology is used for synthesis of an analog of the B ring of the calicheamicin oligosaccharide in which the hydroxyl group at C4 is replaced by hydroxymethyl group by way of iodide.



Scheme 11.23

A new class of dithiogermanium hydride (**6**), based on a thiol analog of BINOL, has been prepared by Curran. Hydrogermylation of methyl methacrylate occurred with high stereoselectivity (Scheme 11.24) [40].



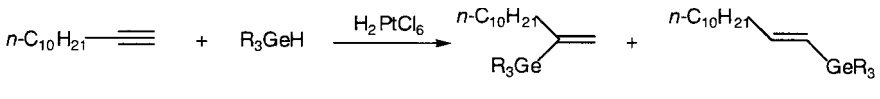
Scheme 11.24

11.4
Transition Metal-catalyzed Addition of Ge–X to an Unsaturated Bond

11.4.1
Hydrogermylation

Trialkylgermanes add to carbon–carbon triple bonds in the presence of transition metal catalyst [41]. A review on the addition + reaction of Ge-H functional organogermane compounds R_nGeH_{4-n} to unsaturated compounds (alkenes, alkynes, ketones, aldehydes) has been published [42].

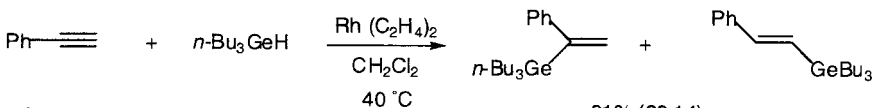
Hydrogermylation of terminal acetylenes was achieved by use of Pt catalyst to afford the corresponding vinylgermanes (Scheme 11.25) [43].



n-Pr3GeH 93% (13:87)
Ph3GeH 99% (25:75)

Scheme 11.25

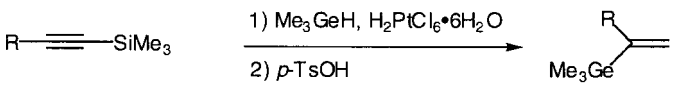
Rh(I) catalyst works in a complementary manner to give the α adduct preferentially (Scheme 11.26) [44].



91% (86:14)

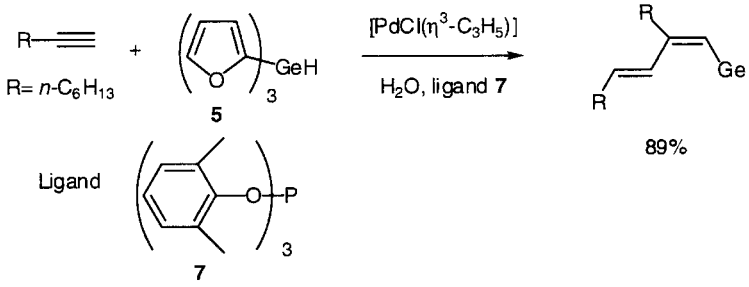
Scheme 11.26

A simple procedure for the preparation of 2-trimethylgermylalk-1-enes has been developed by Piers (Scheme 11.27) [45]. The method was successfully applied for the synthesis of 4-iodo-2-trimethylgermylbut-1-ene.



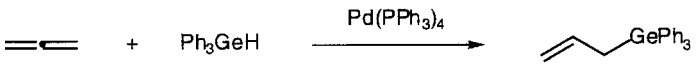
Scheme 11.27

Oshima recently observed a remarkable acceleration of the rate of Pd(0)-catalyzed hydrogermylation of alkynes and dienes in water [46]. Tri(2-furyl)germane (**5**) was found to be superior to Ph_3GeH, and the reaction was much faster in heterogeneous water than in homogeneous CH_2Cl_2. Use of a phosphite ligand **7** selectively furnished vinylgermanes in high yield. It was, furthermore, found that hydrogermylation was achieved at low catalyst loading in aqueous media by use of **7** (Scheme 11.28) [47].



Scheme 11.28

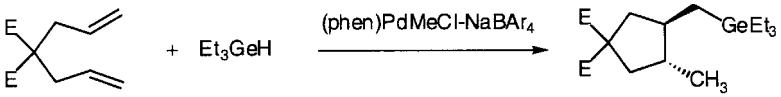
Hydrogermylation of allene was effected by means of Pd catalyst to afford allylic germanes in good yields (Scheme 11.29) [48].



Scheme 11.29

88%

Widenhoefer has reported that palladium complexes catalyze the cyclization/hydrogermylation of functionalized 1,6-dienes leading to R_3GeCH_2-substituted cyclopentanes in good yield with high *trans* selectivity (Scheme 11.30) [49]. Dienes which possessed olefinic substitution failed to undergo cyclization/hydrogermylation, in contrast to the corresponding protocol employing hydrosilanes.

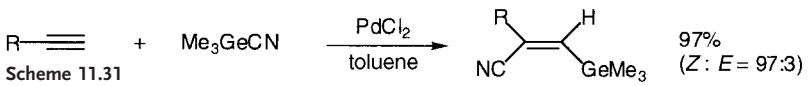


Scheme 11.30

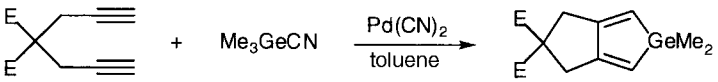
77%, >50:1

11.4.2
Carbogermylation

Palladium-catalyzed addition of trimethylgermyl cyanide to terminal acetylenes proceeded with high *Z* selectivity (Scheme 11.31) [50]. Application of this addition to the formation of germole derivatives has been reported (Scheme 11.32) [51].



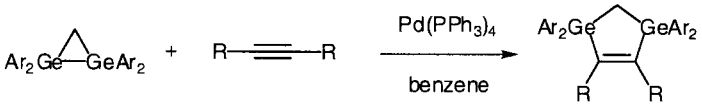
Scheme 11.31



Scheme 11.32

11.4.3
Germylmetalation

Double germylation of digermylanes with acetylenes afforded 3,5-digermacyclopentenes (Scheme 11.33) [52].

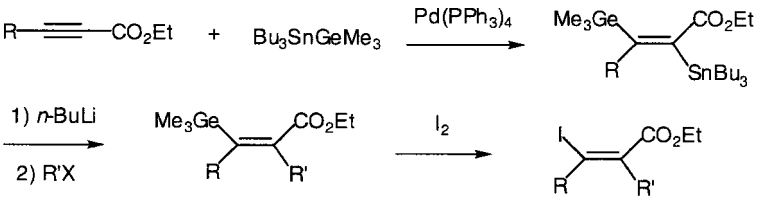


Ar=2,6-diethylphenyl

Scheme 11.33

Digermylation of alkenes and alkynes with 1,2-dichloro-1,1,2,2-tetramethylgermane proceeded in the presence of palladium catalysts [53].

Pd(0)-catalyzed insertion of acetylenes into germanium–tin bonds have been reported by Piers (Scheme 11.34) [54]. Because germyl groups attached to sp^2 carbon can be readily transformed into iodide with retention of the stereochemistry, this reaction is a novel method for the preparation of stereochemically defined tetra-substituted alkenes.

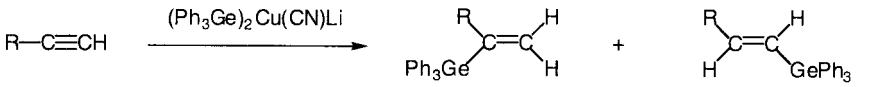


Scheme 11.34

11.5
Germanium–Metal Bonds

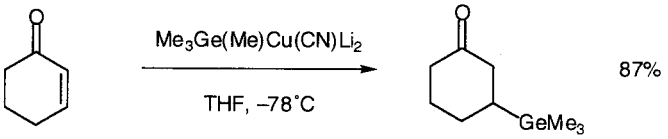
Terminal acetylenes react with $(Ph_3Ge)_2Cu(CN)Li$ or $(Et_3Ge)_2Cu(SMe_2)Li$ to afford vinylgermanes in good yield. Whereas germylcupration of 1-dodecyne gave 2-germyl-1-dodecene as a major product, germylcupration of phenylacetylene or 3-methyl-3-buten-1-yne furnished 1-germylalkene preferentially (Tab. 11.3) [55].

Tab. 11.3 Results from germylcupration



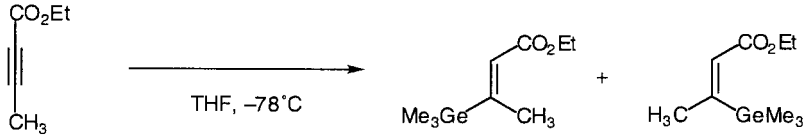
Entry	*R*	*Additive*	*Yield (%)*	*Ratio*
1	$C_{10}H_{21}$	*n*-BuOH	71	80:20
2	Ph	*n*-BuOH	85	<5:>95
3	$PhCH_2OCH_2CH_2$	*n*-BuCHO	82	5:95

Piers reported addition of (trimethylgermyl)copper (I) reagents to *α,β*-unsaturated carbonyl compounds (Scheme 11.35) [56].



Scheme 11.35

It was noted that by proper choice of the copper(I) reagent both *E* and *Z* isomers could be obtained stereoselectively in the addition to alkynyl ester (Scheme 11.36).

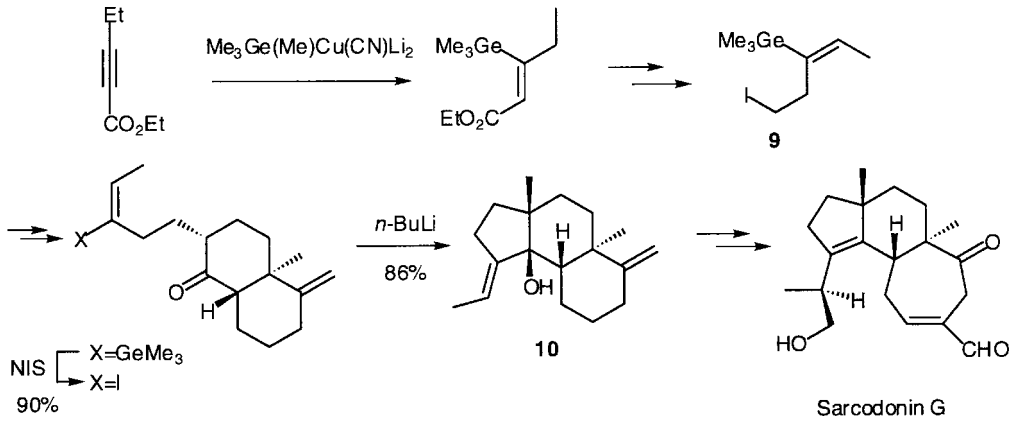


$Me_3GeCu(CN)Li$ 90% (>99:<1)
$Me_3Ge(Me)Cu(CN)Li_2$ 86% (20:80)

Scheme 11.36

Total synthesis of (±)-sarcodonin G was accomplished by using a stereochemically defined vinylgermane-bearing iodide moiety [57]. Thus, treatment of an alkenyltrimethylgermane with *N*-iodosuccinimide afforded clean iododegermylation. Rapid lithium–iodine exchange followed by intramolecular nucleophilic addition of the resulting alkenyllithium function to the carbonyl carbon provided tricyclic alcohol as a single isomer in an excellent yield (Scheme 11.37).

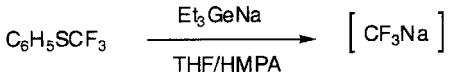
The germyl anion has been employed in conjunction with a metal salt [58]. It was found that a combination of Et_3GeNa and $LnCl_3$ works efficiently as a strong base for



Scheme 11.37

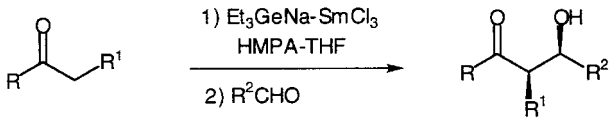
deprotonation of the α-hydrogen [59]. Thus stereoselective aldol condensation of ketones and amides was achieved by use of Et_3GeNa-$SmCl_3$ (Tab. 11.4) [60].

A novel method for generation of the CF_3 anion from $C_6H_5SCF_3$ under the action of Et_3GeNa in THF–HMPA has been reported (Scheme 11.38) [61]. Treatment of the CF_3 anion, generated in situ, with aldehydes (Scheme 11.39) [61], aldimines (Scheme 11.40) [62], and esters (Scheme 11.41) [63] afforded CF_3-substituted alcohols, amines, ketones, respectively in excellent yields. Appropriate choice of the counter ion is essential – Et_3GeLi and Et_3GeK were not effective in the transformation. The affinity of germanium for sulfur seems to be responsible for the reactivity.

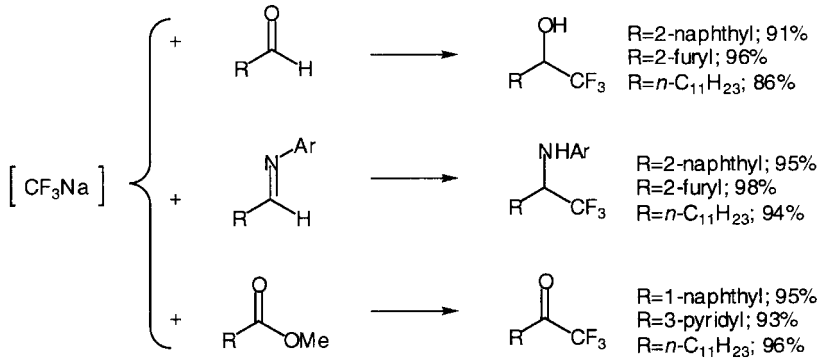


Scheme 11.38

Tab. 11.4 Results from the aldol reaction

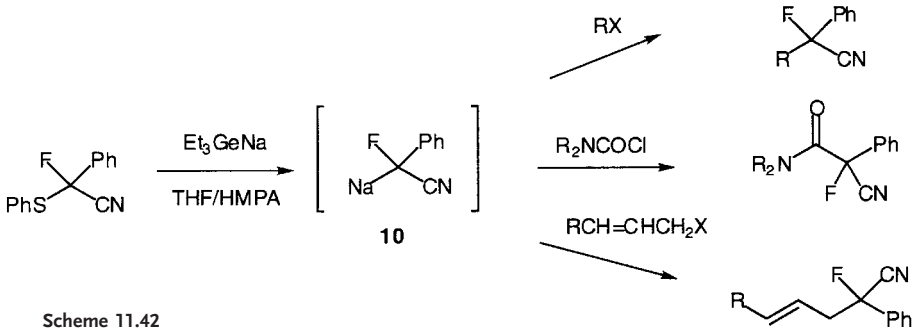


Entry	*R*	*R^1*	*R^2*	*Yield (%)*	*syn:anti*
1	Et	Me	Pr	97	95:5
2	*i*-Pr	Me	Pr	99	92:8



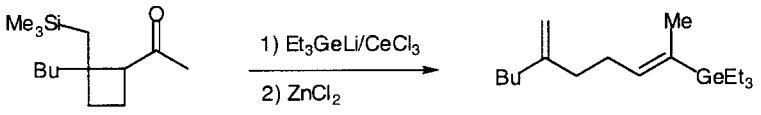
Schemes 11.39, 11.40, 11.41

This methodology has been successfully extended to the preparation of cyanofluoromethylene compounds. Thus the *α*-fluoro-*α*-cyano anion (**10**) generated in situ was trapped with RX [64], R_2NCOCl [65], and allylic halide [66] to afford the adducts in high yields (Scheme 11.42).



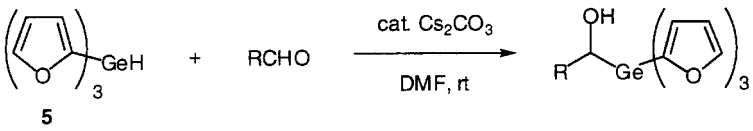
Scheme 11.42

(*E*)-Alkenylgermanes have been synthesized highly stereoselectively by addition of triethylgermyl lithium to cyclobutyl ketones and subsequent Lewis acid-promoted stereospecific ring opening of the resulting cyclobutylethanol derivatives (Scheme 11.43) [67].



Scheme 11.43

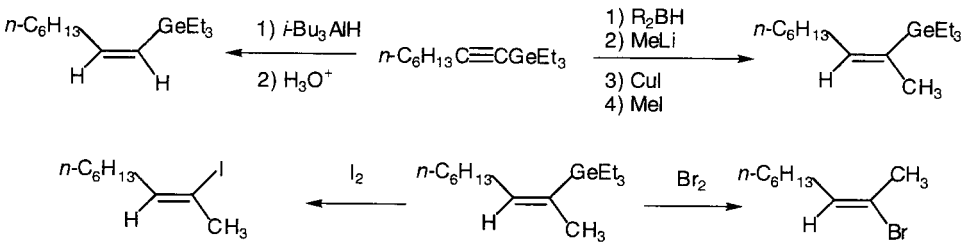
Nucleophilic addition of tri(2-furyl)germane (**5**) to aldehydes and *α,β*-unsaturated carbonyl compounds proceeded smoothly in the presence of a catalytic amount of base to give *α*-hydroxygermanes bearing a variety of functional groups (Scheme 11.44) [68].



Scheme 11.44

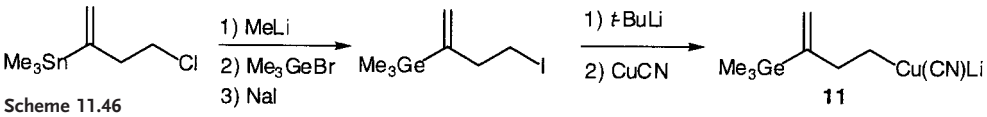
11.6 Vinylgermane [69]

Addition of organometallic compounds to alkynylgermanes is a useful method for stereoselective synthesis of vinyl halides (Scheme 11.45) [70]. Interestingly, vinylgermane was transformed into vinyl iodide with retention of stereochemistry whereas vinyl bromide was obtained with inversion of stereochemistry.



Scheme 11.45

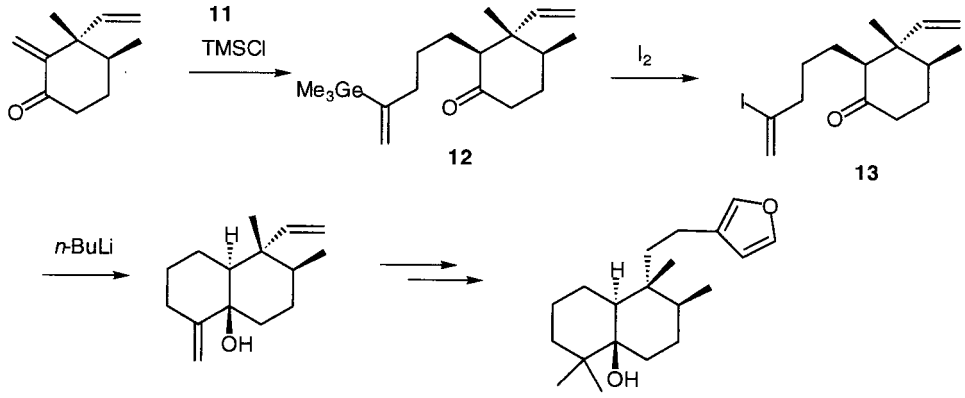
Piers extensively studied the synthetic usefulness of the vinylgermanes. For example, a lower order heterocuprate-bearing vinylgermane moiety (**11**) was prepared (Scheme 11.46).



Scheme 11.46

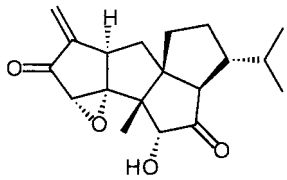
On treatment of an *α,β*-unsaturated ketone with the cuprate (**11**) in the presence of TMSCl, Michael reaction occurred smoothly to give the vinylgermyl-substituted compound (**12**). Treatment of **12** with I_2 in CH_2Cl_2 afforded a vinyl iodide

(**13**) (Scheme 11.47). This compound is used as an intermediate in the synthesis of (±)-ambliol B. It should be noted that use of germyl compounds is essential; an attempt to synthesize a structurally analogous cyanocuprate from a stannyl analog failed [70].



Scheme 11.47 (±)-Ambliol B

Total synthesis of the structurally novel tetraquinane diterpenoid (±)-crinipellin B [71] has also been accomplished on the basis of the vinylgermane strategy (Scheme 11.48).

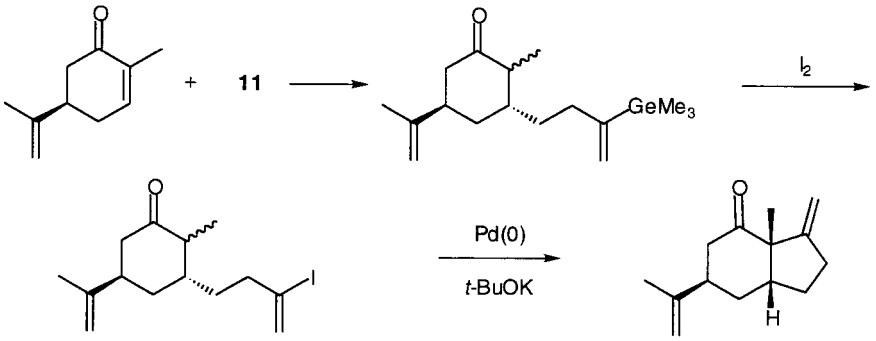


crinipellinB

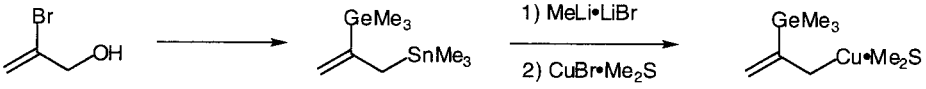
Scheme 11.48

A novel five-membered ring annulation reaction based on Pd(0)-catalyzed intramolecular coupling of vinyl iodide has been developed by taking advantage of the vinylgermane strategy (Scheme 11.49) [72].

The allylcuprate-bearing vinylgermane (**14**) has been prepared (Scheme 11.50) [73] and Michael addition of **14** to enones proceeded smoothly (Scheme 11.51).

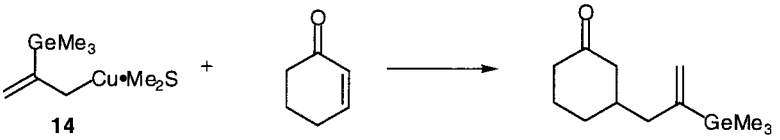


Scheme 11.49



Scheme 11.50

14

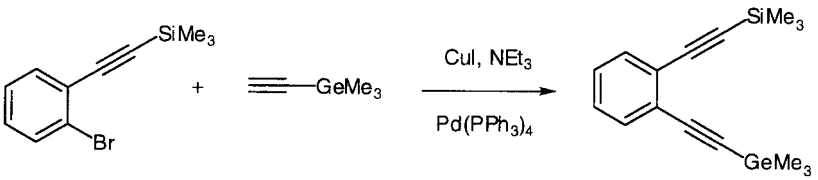


Scheme 11.51

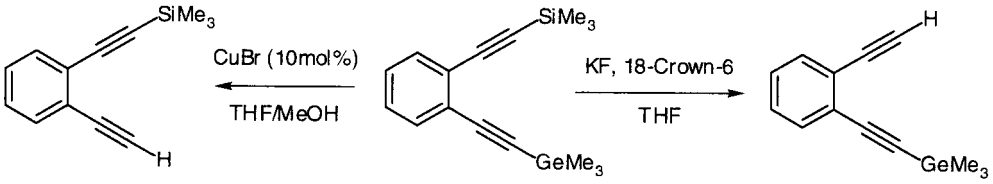
11.7 Alkynylgermanes and Arylgermanes [74]

The β-effect of Si, Ge, and Sn on the vinyl cation was investigated by kinetic study of the protiodemetalation of silyl-, germyl-, and stannylalkynes [75]. As expected, the order of the β-effect is Sn > Ge > Si.

Several C–$SiMe_3$- and C–$GeMe_3$-protected dialkynes have been synthesized (Scheme 11.52) and regioselectively deprotected by protodesilylation or protogermylation. Catalytic amount of CuBr in THF/MeOH or in aqueous acetone led exclusively to protogermylation (Scheme 11.53). The Me_3Si group was removed with KF/18-crown-6 in aqueous THF without affecting the $GeMe_3$ moiety. This method-



Scheme 11.52

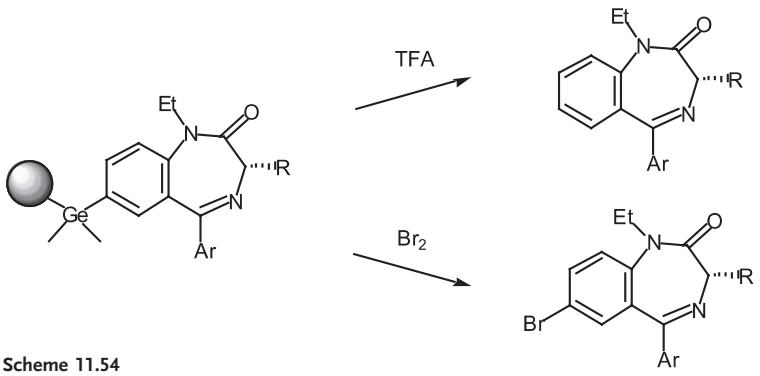


Scheme 11.53

ology has been used successfully in the synthesis of enediyne antibiotics and enzyme mimics [75].

Arylgermanes undergo electrophilic *ipso*-demetalation on treatment with Br_2, or Cl_2, and are more susceptible than arylsilanes [76]. This is because germanium has a greater β-effect in the rate-determining step [15].

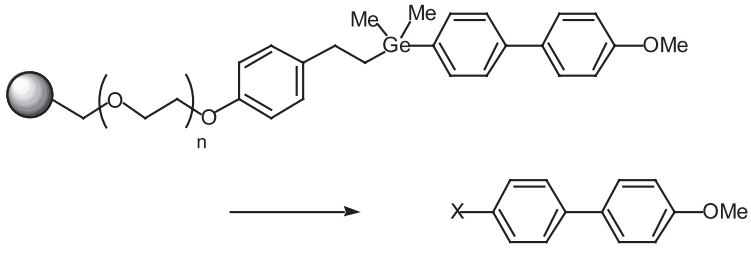
Ellman demonstrated that his arylgermane linker was more readily cleaved by electrophiles (TFA, Br_2) than the corresponding arylsilane linker and that his linker was compatible with a range of transformations associated with the introduction and manipulation of a diverse array of functional groups (Scheme 11.54) [77].



Scheme 11.54

A new germanium-based linker has been developed for solid-phase synthesis of aromatic compounds. Cleavage from the polymer support via *ipso*-degermylation with TFA, ICl, Br_2, and NCS provides protio, bromo, and chloroaryl compounds, respectively (Scheme 11.55) [78].

Another germanium-based linker has been developed for solid-phase synthesis of a pyrazole library [79]. A new iterative synthesis of regioregular oligothiophenes has been developed in which "double-coupling" after each iteration minimizes deletion sequences. The method exploits the susceptibility of α-silyl- but not α-germyl-substituted thiophene derivatives towards nucleophilic *ipso* protodemetalation and features an unusual "base-free" Suzuki-type coupling product. The strategy



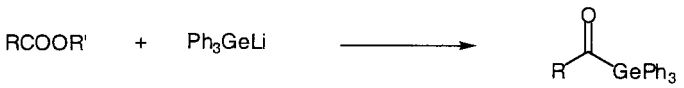
Scheme 11.55

has been designed for the solid-phase synthesis of highly pure oligothiophenes by use of a germanium-based linker [80].

11.8 Acylgermanes [81]

11.8.1 Preparation

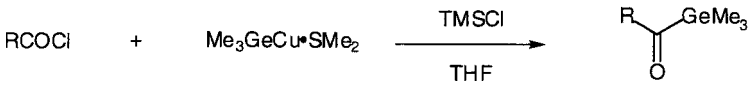
Acylgermanes are prepared by the reaction of ester with germyl lithium reagents (Scheme 11.56) [82].



R= CH_3, 76%
R=CH_2CH_3, 82%
R=$PhCH_2$, 81%

Scheme 11.56

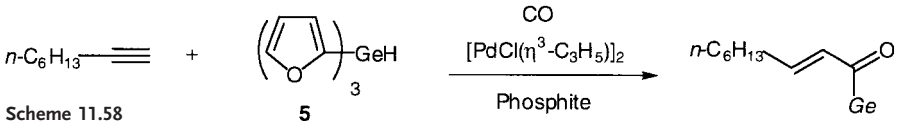
Addition of a germyl copper(I) reagent to acyl halides has afforded acylgermanes in excellent yield (Scheme 11.57) [83].



Scheme 11.57

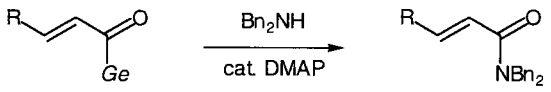
Acylgermanes have been obtained by treatment of benzoyl chloride with $Me_3GeGeMe_3$ in the presence of Pd catalyst [84].

Pd(0)-catalyzed hydrogermylcarbonylation of alkynes has been reported quite recently by Oshima (Scheme 11.58) [85]. *α,β*-Unsaturated acylgermanes were prepared starting from terminal alkynes. The reaction is considered to proceed by way of a vinylpalladium intermediate followed by CO insertion and subsequent reductive elimination.

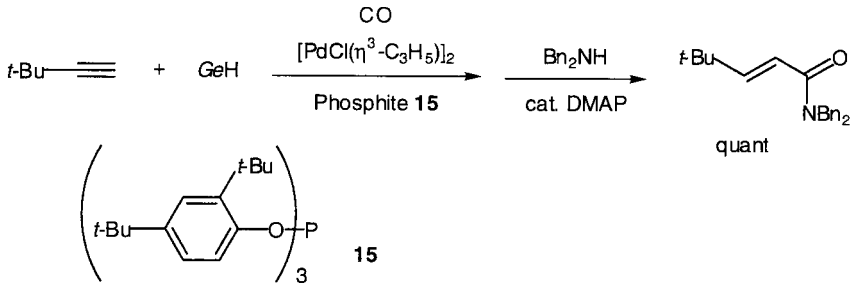


Scheme 11.58

The acylgermanes were transformed into *α,β*-unsaturated amides (Scheme 11.59). One pot transformation of an alkyne to *α,β*-unsaturated amides has been achieved successfully (Scheme 11.60).



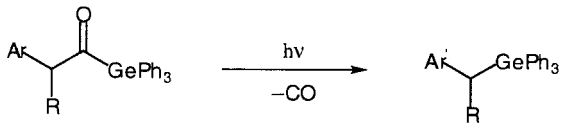
Scheme 11.59



Scheme 11.60

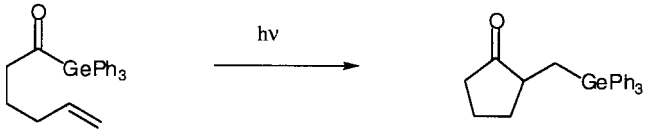
11.8.2
Reactions

Photochemical decarbonylation of the acylgermanes prepared as described above has been reported (Scheme 11.61) [86].



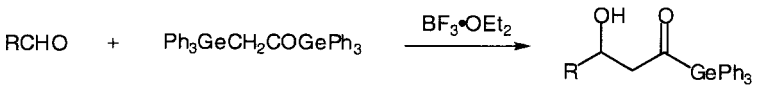
Scheme 11.61

Atom-transfer cyclization proceeded smoothly (Scheme 11.62) [87] as did radical cyclization of acylgermanes [88].



Scheme 11.62

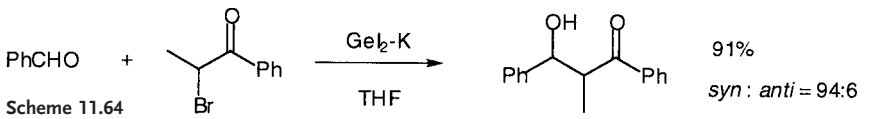
$Ph_3GeCH_2COGePh_3$ reacts with aldehydes in the presence of $BF_3 \cdot OEt_2$ to afford the corresponding aldol products in good yields (Scheme 11.63) [89].



Scheme 11.63

11.9 Germanium Enolate

The Reformatsky reaction with activated germanium metal proceeds highly diastereoselectively to give aldol adducts in high yields (Scheme 11.64) [90].



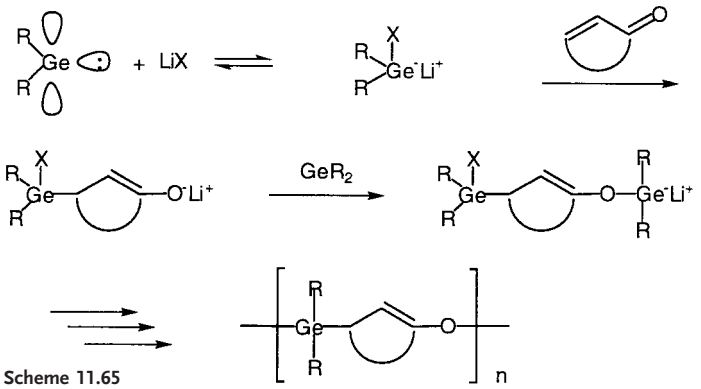
Scheme 11.64

Kobayashi prepared a novel germanium-containing polymer, poly(germanium enolate), by reaction of a divalent germanium compound, germylene, with a cyclic α,β-unsaturated ketone in the presence of a catalytic amount of a lithium compound (Scheme 11.65) [91].

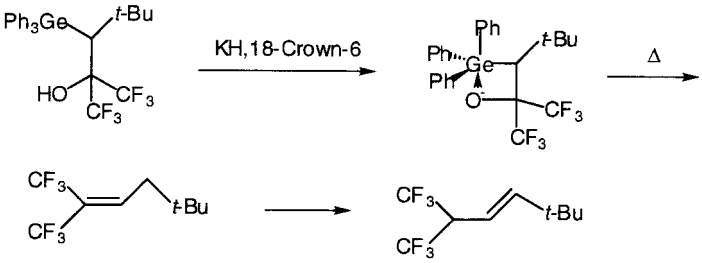
11.10 Miscellaneous

A Peterson-type reaction employing β-hydroxygermane has been reported (Scheme 11.66) [92].

The combined use of $GeCl_4$ and Ph_3P has been found to be effective for reduction of α-bromo esters [93].



Scheme 11.65



Scheme 11.66

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12
Tin in Organic Synthesis

Akihiro Orita and Junzo Otera

12.1
Introduction

The low polarity of the tin–carbon bond – the electronegativity of tin is larger than that of other main group elements – gives organotin compounds stability toward heat, hydrolysis, and oxidation. This is of great advantage, because they can usually be readily synthesized and handled in the open air, but also a disadvantage, because they are not as reactive as other organometallic species. As a result, the tin–carbon bond does not usually act as a nucleophile without activation of either the bond or the substrate. For example, simple alkyl groups attached to tin never have Grignard-like reactivity. In this respect, synthetic applications of organotin compounds rely heavily on discovering effective means of activating tin–carbon bonds.

Among a variety of organotin compounds, allylstannanes, in conjunction with activation of the carbonyl substrates by means of a Lewis acid, are known to be reactive enough for a wide range of synthetic applications. Because excellent and extensive review articles are already available [1], only progress made after publication of these articles is discussed in this chapter (Section 12.2).

When vinyl- or *α*-alkoxyalkyltin compounds are exposed to alkyllithium, unique tin–lithium exchange occurs, conveniently generating organolithium species that are otherwise difficult to obtain. Although it is a long time since the discovery of these procedures by Seyferth [2] and Still [3], respectively, their usefulness has never faded. Recent applications will be covered in Section 12.3.

Section 12.4 also deals with transmetalation, in which a metal–carbon bond is transferred from tin to palladium(II). The organic residues moved on the palladium are coupled with a variety of electrophiles. This reaction, which was first discovered by Migita-Kosugi [4] and later developed by Stille [5], is now recognized as one of the most useful methods for cross-coupling.

Radical chemistry has experienced a renaissance over the last two decades. A variety of transformations is feasible under neutral conditions, enabling synthetically useful chemoselective reactions. A significant breakthrough has, furthermore, repudiated the conventional belief that radical reactions are not stereoselective. We are now in a position to achieve a high level of stereoselectivity, and even

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enantioselectivity, in radical reactions [6]. Organotin hydrides have played the central role in these developments; and such great advances might not have been achieved without these reagents. Characteristic features of, and recent progress in, this field of chemistry are highlighted in Section 12.5.

Tin–oxygen bonds are also of great synthetic use. Because tin is more electropositive than silicon, a stannyloxy group is a more powerful electron-donating group. Hence, stannyl enolates occasionally work as better nucleophiles when use of the silyl analogs is not satisfactory [7]. This chemistry is discussed in Section 12.6.

Another important facet of organotin compounds is their Lewis acidic character. As described above, the electronegativity of tin is larger than that of most of other main group elements and thus the Lewis acidity of organotin compounds is not usually sufficient to trigger synthetically useful reactions. Bonding of electron-withdrawing atoms such as oxygen and halogens to tin increases the acidity of the tin, however [8]. The use of organotin alkoxides and halides in Lewis acid chemistry is the final topic of this chapter (Section 12.7).

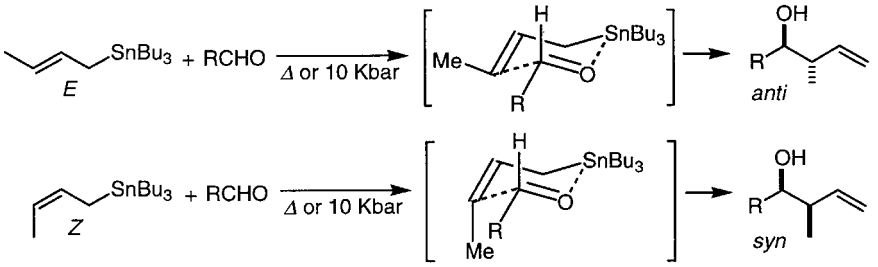
12.2 Allylstannanes

Since the discovery of thermally promoted allylation of aldehydes [9], allylstannanes have been widely used in organic synthesis as stable and stereodefined reagents for C–C bond formation. Although it had been reported that activated aldehydes [10] or allylstannanes with chloride on the tin [11] could be used for allylation, remarkably innovative technology for allylation was advanced by Naruta and by Sakurai and Hosomi [12]. They disclosed that allylation was promoted by addition of a Lewis acid; this substantially expanded the versatility of the allylstannane procedure. Because many allylation reactions have already been documented [1], the most recent progress in this field will be described after brief description of fundamental aspects.

12.2.1 Mechanistic Aspects of Allylation of Aldehydes with Allylic Stannanes

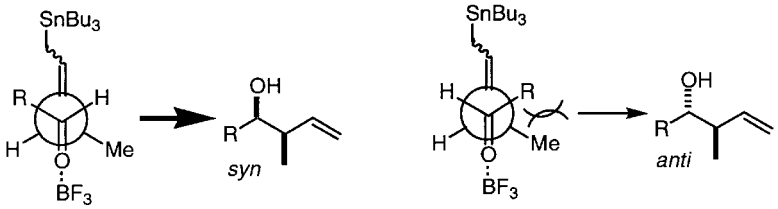
In thermally accelerated or high-pressure-promoted allylation using crotylstannane, the geometry of product reflects the 2-butenyl moiety of starting stannanes, and *E* and *Z* isomers furnish *anti* and *syn* isomers, respectively (Scheme 12.1) [9, 13]. This stereochemistry can be explained by invoking a six-membered cyclic transition state and a concerted bond-breaking and bond-making mechanism.

In sharp contrast, in $BF_3 \cdot Et_2O$-promoted allylation both *E*- and *Z*-crotylstannanes afford a *syn* homoallylic alcohol as the major diastereomer. An acyclic transition state with an antiperiplanar arrangement of the double bond was invoked



Scheme 12.1

to account for this stereoselectivity (Scheme 12.2) [14]. In these reactions, boron trifluoride is coordinated to the carbonyl oxygen and accelerates C–C bond formation by enhancing the electrophilicity of the carbonyl carbons.



Scheme 12.2

Denmark (Fig. 12.1) [15] and Keck (Fig. 12.2) [16], on the other hand, independently designed allylstannanes bearing a formyl group to study the relationship between the transition state geometry and product stereochemistry. On the basis of the stereochemistry of the products they concluded that allylation proceeds mostly through synclinal rather than antiperiplanar transition states (Scheme 12.3).

It was also revealed that the *syn*-synclinal orientation is preferable to the *anti*-synclinal geometry, because secondary orbital interaction of the LUMO of the aldehyde with the HOMO of the stannane led to a bonding effect (Scheme 12.4) [15 b].

Mechanistic studies of the allylic transfer have been performed, and synthetic application of allylstannanes in organic synthesis has been investigated. $B(C_6F_5)_3$ has been shown to catalyze discriminative allylation of aldehydes with an *ortho* donor substituent in preference to the *para* isomer, and the role of $B(C_6F_5)_3$ has

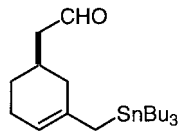


Fig. 12.1

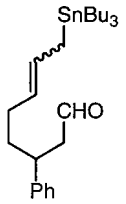
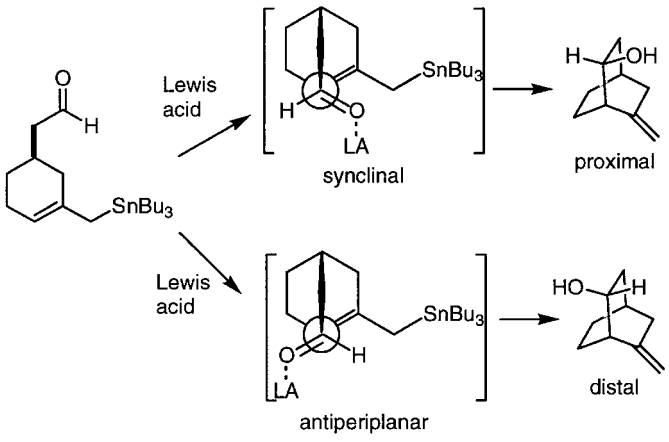
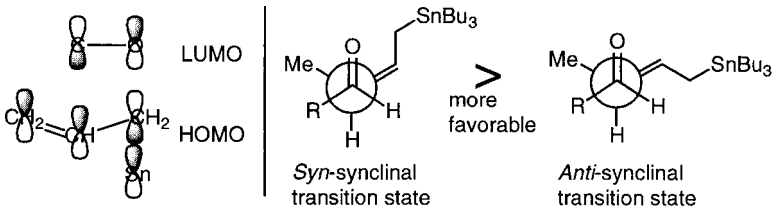


Fig. 12.2



Lewis acid	proximal/distal
$BF_3\,OEt_2$	87/13
$SnCl_4$	93/7

Scheme 12.3

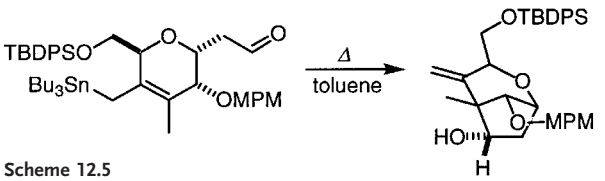


Scheme 12.4

been investigated thoroughly [17]. Systematic investigation of stereoselectivity of the Mukaiyama aldol reaction of α- or β-substituted and α,β-disubstituted aldehydes was performed in the presence of several typical Lewis acids [18]. Although it was known that carbonyls with greater coordinating power are more reactive as electrophiles [19], the phenomenon was systematically exemplified again in comparison with thermal and Lewis acid-catalyzed carbonyl transformations [20].

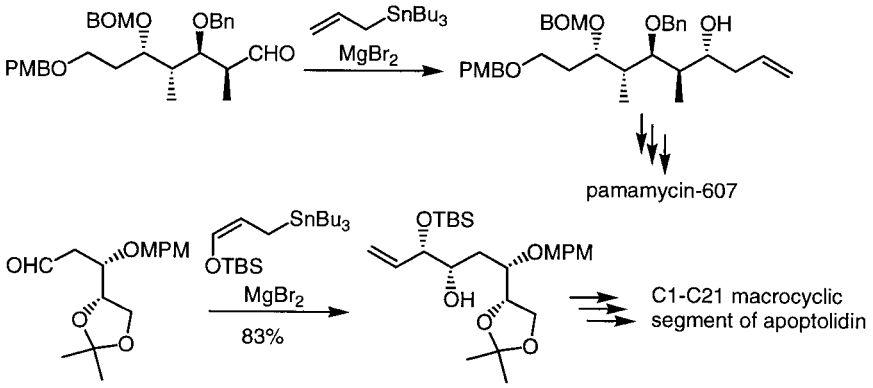
12.2.2
Allylic Stannanes as Allylating Reagents

Diverse allylic stannanes have been successfully used to gain access to complicated compounds. An intramolecular thermal allylation of a ω-formylallylstannane was used to construct the bicyclic BC array of verrucarol (Scheme 12.5) [21].



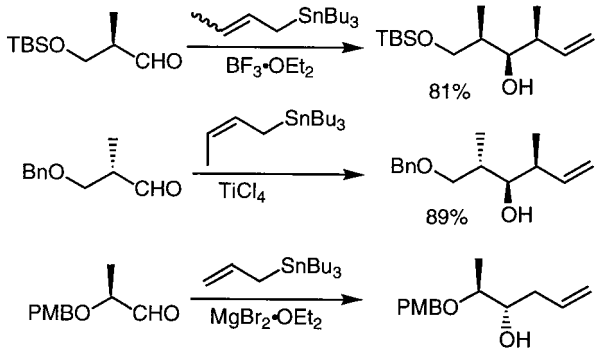
Scheme 12.5

Lewis acid-catalyzed allylation is widely used for incorporation of allyl moieties in the total synthesis of biologically active and pharmaceutically important compounds. Magnesium bromide-catalyzed allylation has been used in the total synthesis of pamamycin-607 (Scheme 12.6) [22] and the convergent synthesis of the C_1–C_{21} macrocyclic segment of apoptolidin (Scheme 12.6) [23].

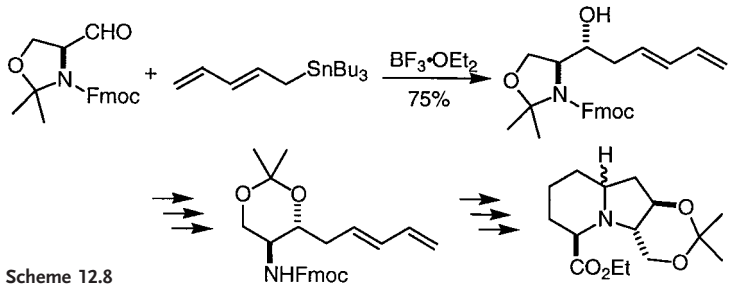


Scheme 12.6

In the synthesis of the C_3–C_8 segment of rutamycin B the *syn,syn* stereotriad at C_4–C_6 was synthesized by $BF_3 \cdot OEt_2$-catalyzed allylation with a *cis* and *trans* mixture of crotylstannanes (Scheme 12.7) [24]. In contrast with this stereocontrol, in the total synthesis of (–)-pironetin *anti,syn* homoallyl alcohol was obtained by $TiCl_4$-promoted addition of *Z*-crotylstannane to benzyloxy aldehyde (Scheme 12.7) [25]. Allylation of lactaldehyde proceeded smoothly in the presence of $MgBr_2 \cdot OEt_2$ to give a *syn* adduct which could be converted into β-rhodinosyl acetate, which is involved in the angucycline antibiotic family landomycin A



Scheme 12.7



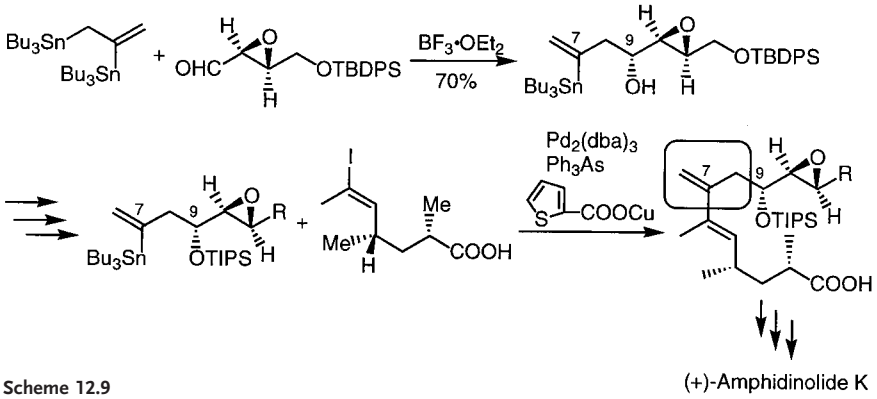
Scheme 12.8

(Scheme 12.7) [26]. Access to an indolizidine was realized by starting from a pentadienylstannane and chiral aldehyde (Scheme 12.8) [27].

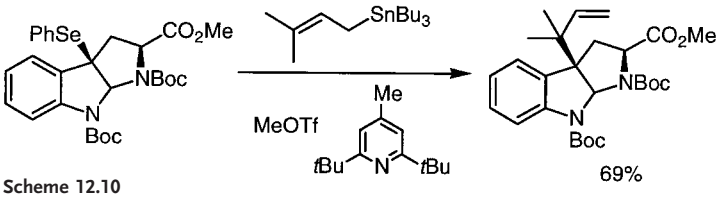
Allylstannanes with another stannyl group proved of great utility for further C–C bond formation [28]. Consecutive allylation of a non-racemic epoxy-aldehyde with the allylic bis-stannane followed by palladium-catalyzed coupling of the resulting ethenyltin with vinyl iodide was exploited in a total synthesis of (+)-amphidinolide K (Scheme 12.9) [29].

Lewis acid-promoted allylation of imines [30] and allylative substitution of selenides have been reported [31]. Displacement of selenide results in formation of a contiguous quaternary C–C bond with retention of configuration (Scheme 12.10).

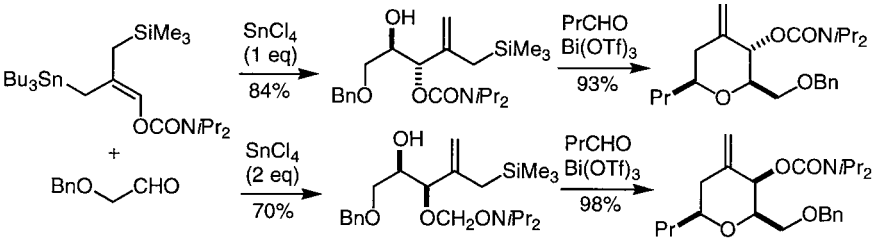
Several methodologies enabling access to polysubstituted tetrahydropyrans, which take advantage of allylation of aldehyde as a key step, were recently presented. A sequence of enantioselective allylation of aldehydes with allylstannanes having a silyl group, then diastereoselective cyclization, afforded stereocontrolled pyrans [32]. The stereocontrolled synthesis of substituted hydropyrans with functionality was achieved by starting from a functionalized allylstannane and an α-alkoxyaldehyde. The stereochemistry of the *syn,syn* and *syn,anti* relationship of the product depends on the nature and the amount of Lewis acids used for allylic transfer (Scheme 12.11) [33].



Scheme 12.9



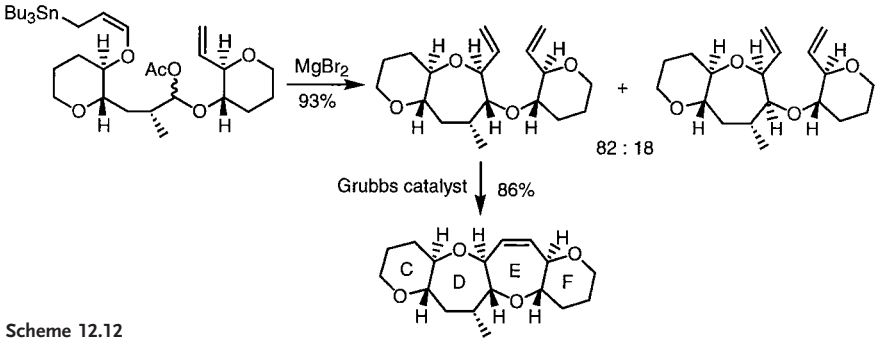
Scheme 12.10



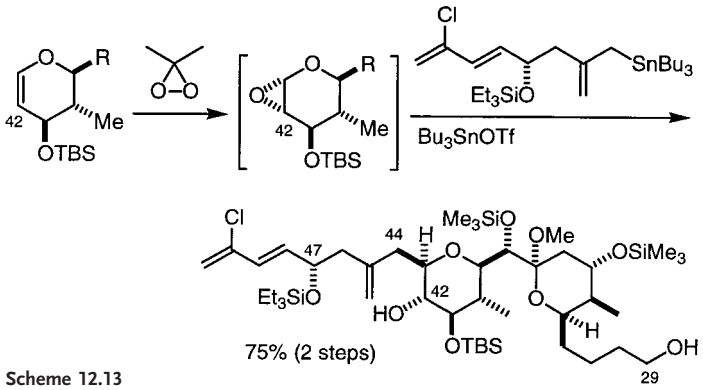
Scheme 12.11

Treatment of acetoxylacetones [34], cyclic acetals [35], silylated hemiaminals [36] and ethoxy carbamates [37] with allylstannanes in the presence of a Lewis acid afforded the corresponding allylated products. As shown in Scheme 12.12, when a γ-alkoxyallylstannane bearing α-acetoxy ether was treated with Lewis acid cyclization occurred by intramolecular allylic transfer to give seven-membered rings with high stereoselectivity. Subsequent ring-closing metathesis with Grubbs catalyst provided the polycyclic ethers, e.g. the CDEF ring segment of brevetoxin B and the CDEFG ring segment of gambierol [38]. Oxidation of a cyclic enol ether followed by allylation of the resulting epoxide under the influence of Bu_3SnOTf furnished the desired β-allylic adduct C_{29}–C_{51} fragment of spongistatin as the sole product (Scheme 12.13) [39].

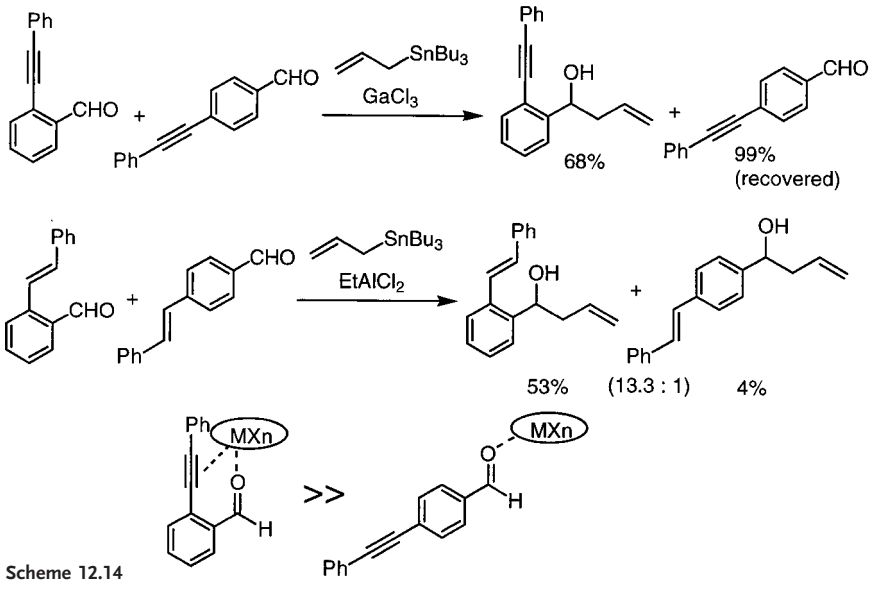
With recourse to the interaction between a Lewis acid and a π-bond, Yamamoto realized Lewis acid-activated selective allylation of an aldehyde located in proximi-



Scheme 12.12



Scheme 12.13



Scheme 12.14

ty to π-bonds (Scheme 12.14) [40, 41]. It should be noted that the strong chelating effect of $GaCl_3$ on the alkyne π-bond led to the high chemoselectivity [40]. With alkenyl aldehyde, however, $EtAlCl_2$-promoted allylation resulted in lower chemoselectivity [41].

12.2.3
For Easy Separation from Tin Residues

In conventional allylation the (allyl)SnR_3 usually employed are those with one allyl moiety and three alkyl groups which are not transferred to electrophilic carbon. Thus removal of the R_3Sn residue is unavoidable if pure compounds are to be obtained. To overcome this drawback several technologies have been developed. Curran developed a new technology for concise separation of allylation products from the tin residue by attaching fluoroalkyl chains to tin (Fig. 12.3) [42]. Higher affinity of fluorinated organic compounds for fluorous solvents rather than organic solvents enabled the fluorotin to transfer from organic to fluorous phase only by simple organic-fluorous liquid-liquid extraction method. Synthetic utilities of fluorous phase separation have been established so far, and this technology has been widely utilized in organic synthesis [43].

A novel monoorganotin reagent has been prepared and its allyl transfer properties assessed in several types of C–C bond formation reaction (Scheme 12.15) [44]. In these reactions aqueous work-up hydrolyzes the $SnBr(NTMS_2)_2$ moiety giving water-soluble or volatile compounds; this enabled easy purification of the allylation products.

Nokami reported allylation of carbonyl compounds by use of allyl halides and tin powder in the presence of water [45]. In this reaction, water obviously accelerates the addition, and the allylating reagent prepared in situ reacted with ketones

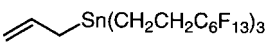
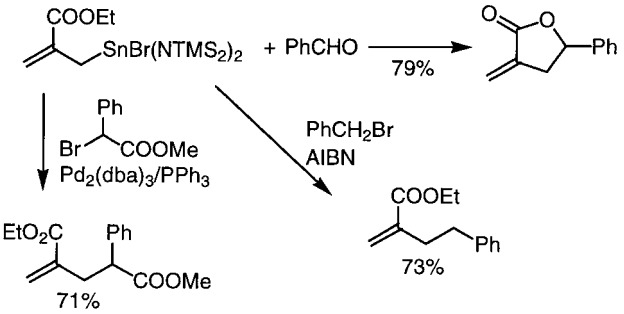
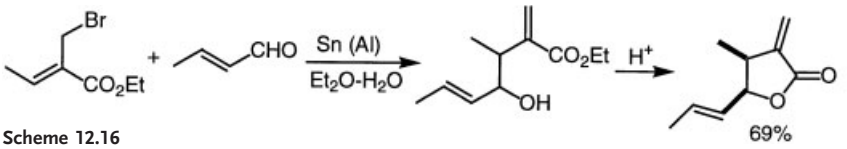


Fig. 12.3



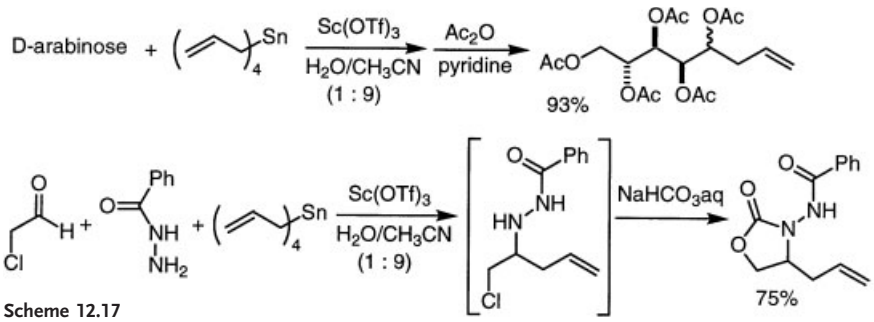
Scheme 12.15

and aldehydes to give the desired compounds. This procedure was applied to synthesis of substituted lactones (Scheme 12.16) [46]. Since this discovery many examples of allylation starting from allyl halide and different metals in aqueous media have appeared [47, 48]. Allylation in aqueous media is very useful, because water-soluble substrates can be used directly and there is no need to protect highly reactive functional groups such as carboxylic and hydroxy functions [47a].



Scheme 12.16

Tetraallyltin is of great advantage for allylation because all four allyl parts are usable as nucleophiles and, after work-up, no organotin residues are produced [48]. Allylation using allylic organostannane can be performed in aqueous media catalyzed by water-tolerant Lewis acids such as scandium and lanthanide triflates [49]. This procedure is applicable to imines and hydrazones as well as carbonyl compounds (Scheme 12.17) [49d]. To expand the utility and applicability of allylation reactions, more efficient and active Lewis acids have been pursued [50] and the mechanism of allylation in protic solvents has been investigated [51].

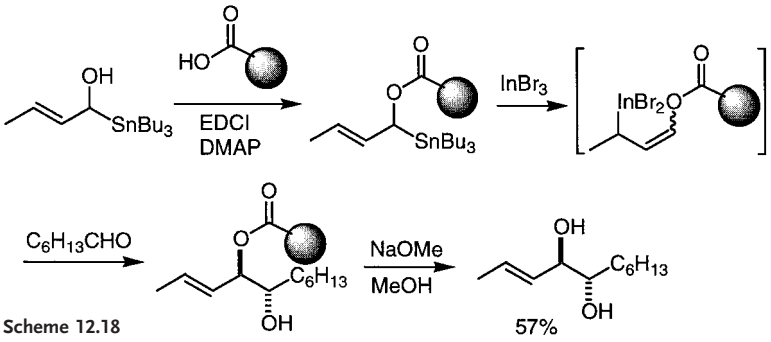


Scheme 12.17

α-(Hydroxy)crotylstannane supported on commercially available carboxylic polystyrene resin has been developed to overcome the difficulty of separating the allyl adduct from tin residues (Scheme 12.18) [52].

12.2.4
Activation of Allylstannanes by Transmetalation

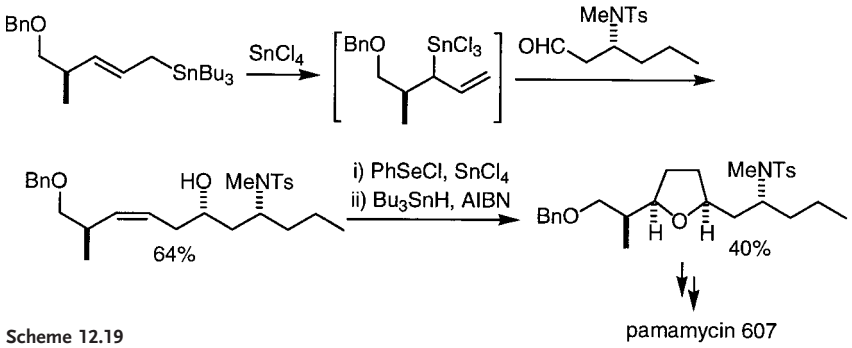
Allylic trialkylstannanes are, in general, stable and easily handled in air without special techniques or apparatus. Because of this innate stability of organotin com-



Scheme 12.18

pounds, however, activation of allylation reagents is necessary for allyl transfer. To this end transmetalation of the allyl moiety from tin to more acidic metal center is effective. Allyl transfer from allyltin to another metal center has been utilized successfully in organic synthesis [53].

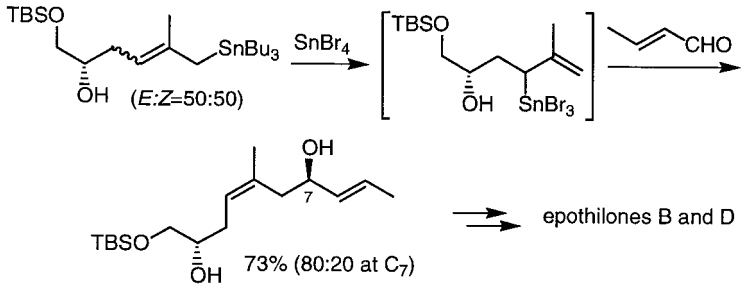
Consecutive treatment of an allylic stannane with $SnCl_4$ and hexanal derivative provided the corresponding homoallylic alcohol. Subsequent cyclization of this alcohol, promoted by phenylselenyl chloride and tin chloride, followed by reduction with Bu_3SnH afforded a disubstituted tetrahydrofuran as a single stereoisomer. Repetition of this procedure enabled access to pamamycin 607 which has three 2,5-*cis*-disubstituted tetrahydropyran moieties (Scheme 12.19) [54].



Scheme 12.19

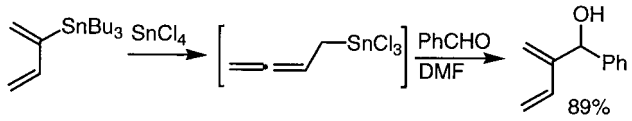
Transmetalation of allylstannanes using $SnBr_4$ and subsequent allylation of aldehyde resulted in 1,6-stereocontrol with moderate diastereoselectivity (Scheme 12.20) [55]. This procedure was applied in the total synthesis of epothilones B and D.

Regioselective butadienylation has been achieved by consecutive treatment of 2-butadienylstannane with $SnCl_4$ and aldehyde; in this procedure addition of a Lewis base dramatically improved the chemical yield (Scheme 12.21) [56]. For access to reactive allylmetal species, several new methods have been advanced, including the $SnCl_2$-NCS-promoted retro aldol reaction of homoallyl alcohol [57], the Pd(0)-



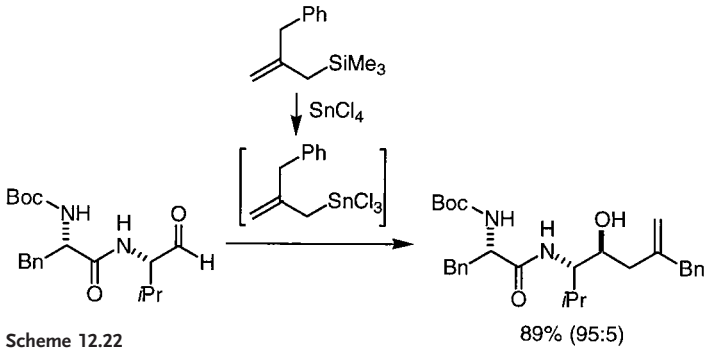
Scheme 12.20

catalyzed addition of HCl and $SnCl_2$ to allenes [58], and transmetalation between allylstannanes and $InCl_3$ [59].



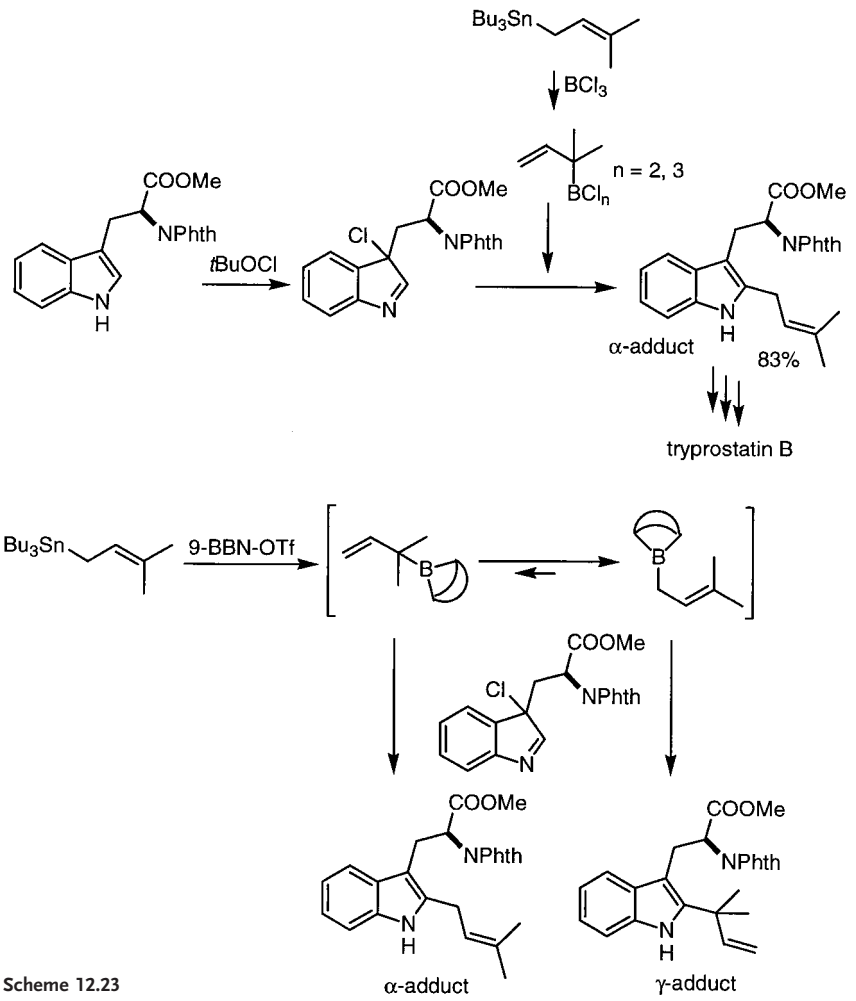
Scheme 12.21

The corresponding allylsilane can be used for access to allyltrichlorostannane. Consecutive transmetalation with $SnCl_4$ and exposure of a dipeptide aldehyde to the resulting allyltrichlorostannane led to a 1,2-*syn* adduct with high stereoselectivity (Scheme 12.22) [60].



Scheme 12.22

A total synthesis of tryprostatin B was achieved by regioselective prenylation of chloroindolenine with prenylborane dichloride, which was prepared from prenylstannane and BCl_3 (Scheme 12.23) [61]. In sharp contrast with this result, prenylborane derived from prenylstannane and 9-BBN-OTf afforded both *α*- and *γ*-adducts in a 1 : 1 ratio and the combined yield of prenylated indole was low.

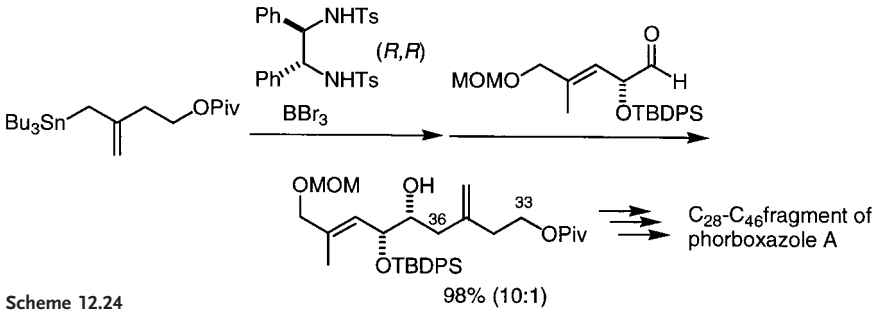


Scheme 12.23

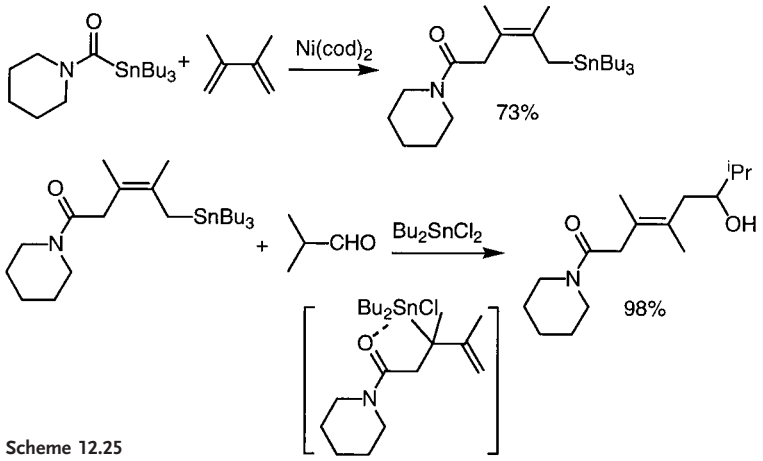
Stereoselective synthesis of the C_{28}–C_{46} fragment of phorboxazole A has been achieved. In this approach the correct relative stereochemistry at C_{37}/C_{38} was established by use of allylborane which was prepared by transmetalation between allylstannanes and a boron bromide reagent derived from homochiral diamine and BBr_3 (Scheme 12.24) [62].

When ε-oxoallylstannanes, prepared from carbostannation of 2,3-dimethylbutadiene, were reacted with aldehydes in the presence of Bu_2SnCl_2, α-adducts were obtained exclusively and no γ-adducts were observed. This complete regioselectivity is ascribable to intramolecular coordination of carbonyl group to γ-stannyl group (Scheme 12.25) [63].

Palladium-catalyzed carbostannation [64] and silastannation [65] are powerful tools for access to allylstannanes. Exposure of allene aldehydes or ketones to these



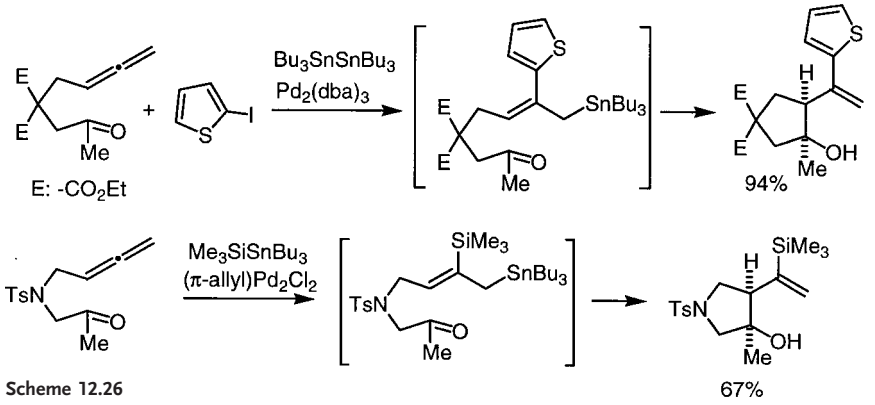
Scheme 12.24



Scheme 12.25

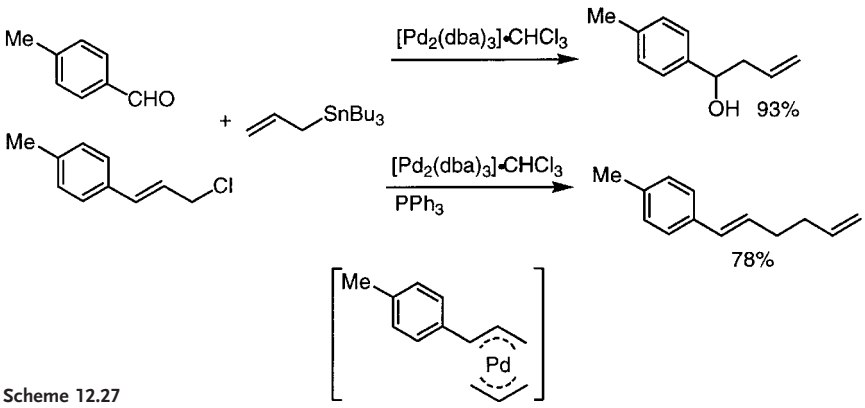
procedures enables tandem carbostannation or silastannation/carbonyl allyl addition to form *cis* cyclopentanols selectively (Scheme 12.26).

It has been reported that bis-π-allylpalladium, generated in situ, catalyzes allylation of aldehydes [66], imines [67], isocyanates [68], olefins [69], benzene [70], and



Scheme 12.26

benzyne [71] with allylstannanes. Although allyl addition to aldehydes proceeded irrespective of the presence of allyl chloride, addition of triphenylphosphine to this procedure retarded allylic transfer to the electrophile and promoted Migita-Kosugi-Stille coupling (Scheme 12.27) [72].

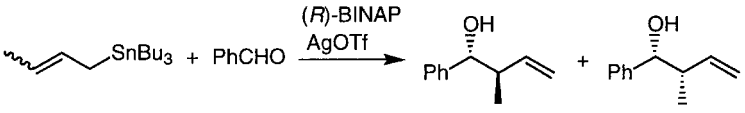


Scheme 12.27

12.2.5 Asymmetric Allylation

To accelerate allylation with allylstannanes, addition of a Lewis acid is often required, because coordination of the Lewis acid to the carbonyl can enhance the electrophilicity of the substrate and facilitate the coupling reaction. Since Yamamoto showed that a nonracemic Lewis acid, chiral (acyloxy)borane (CAB), catalyzed enantioselective allylation [73], chiral Lewis acid catalysts have been extensively developed. Above all, easily available chiral compounds such as BINOL and BINAP have been most frequently used as chiral auxiliaries [74], and enantioselective allylations of C–N double bonds and of carbonyl groups have been achieved [48a, 75].

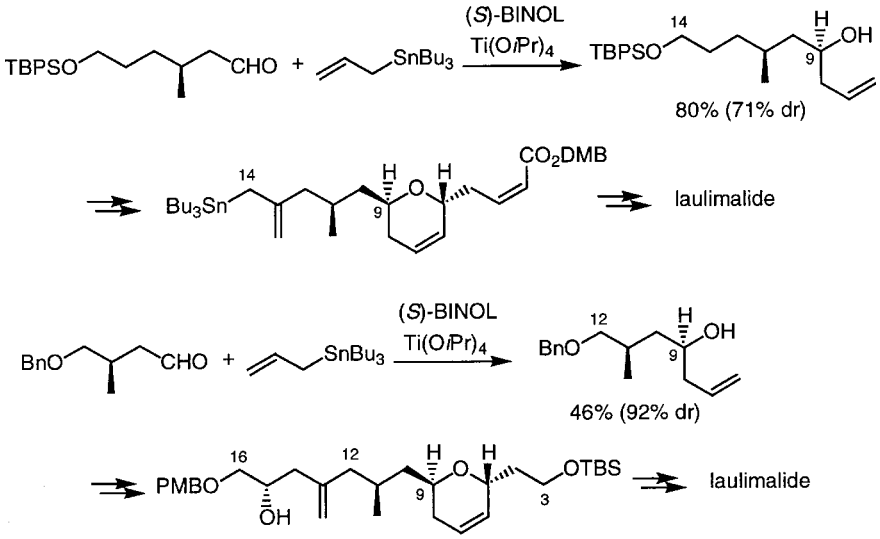
A chiral phosphine–silver(I) complex generated from BINAP and AgOTf-catalyzed asymmetric allylation of aldehydes with allylstannanes, resulting in high enantioselectivity. With 2-butenylstannane, the *anti* adduct was obtained preferentially irrespective of the double-bond geometry of the stannane (Scheme 12.28) [76].



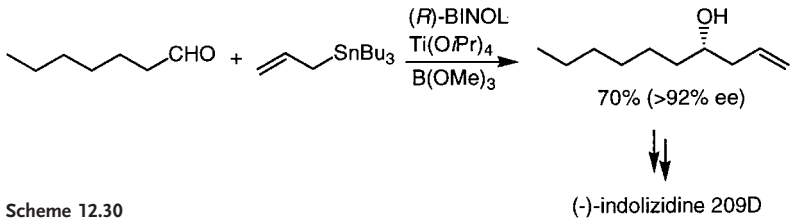
E/Z	yield	*anti* (% ee)/*syn* (% ee)
95/5	56%	85 (94)/15 (64)
2/98	72%	85 (91)/15 (50)

Scheme 12.28

Keck's asymmetric allylation has been employed independently by two research groups in the construction of the C_1–C_{14} and C_3–C_{16} fragments of the paclitaxel-like antimicrotubule agent laulimalide (Scheme 12.29) [77, 78]. It has been reported that addition of synergetic reagents improves the efficiency of the Keck procedure [79], and one variant was used for access to (–)-indolizidine 209D (Scheme 12.30) [80].



Scheme 12.29

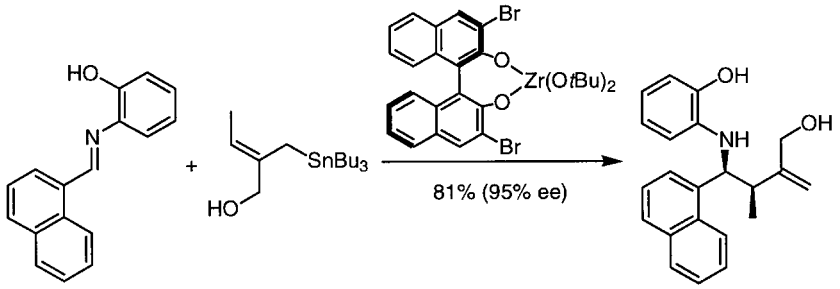


Scheme 12.30

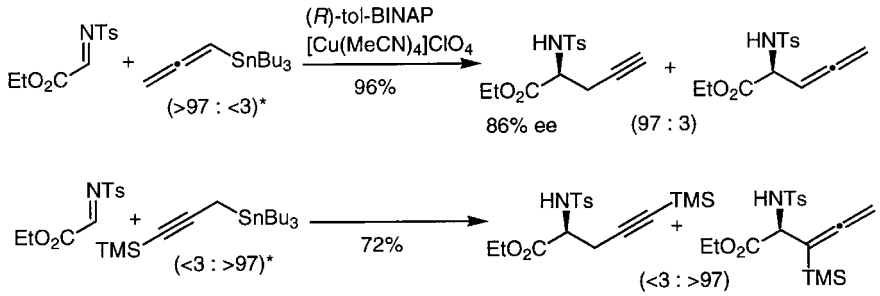
The catalysts generated from $Zr(OtBu)_4$ and BINOL derivatives enabled high efficiency allylation of aldehydes [81] and imines [82], respectively (Scheme 12.31).

A cationic copper complex with (*R*)-tol-BINAP as chiral auxiliary catalyzes asymmetric addition of allenyltin and propargyltin compounds to *α*-iminoesters to produce, preferentially, propargyl and allenyl adducts, respectively, in moderate to high enantioselectivity (Scheme 12.32) [83].

Bis(oxazolinyl)phenylrhodium(III) aqua complexes have been shown to act as asymmetric catalysts for enantioselective allylation of aldehydes (Scheme 12.33) [84]. Exposure of aromatic aldehydes to these catalysts resulted in moderate enan-

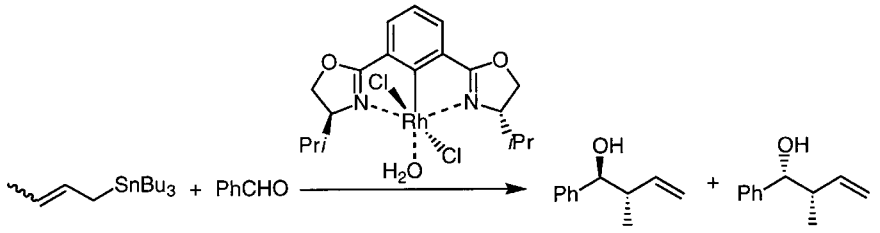


Scheme 12.31



Scheme 12.32

tioselectivity. When a crotylstannane was employed as nucleophile, an *anti* homoallyl alcohol was obtained predominantly, irrespective of the *E*/*Z* ratio of the crotylstannane. In this procedure antiperiplanar transition states were invoked to account for the diastereo- and enantioselectivity.

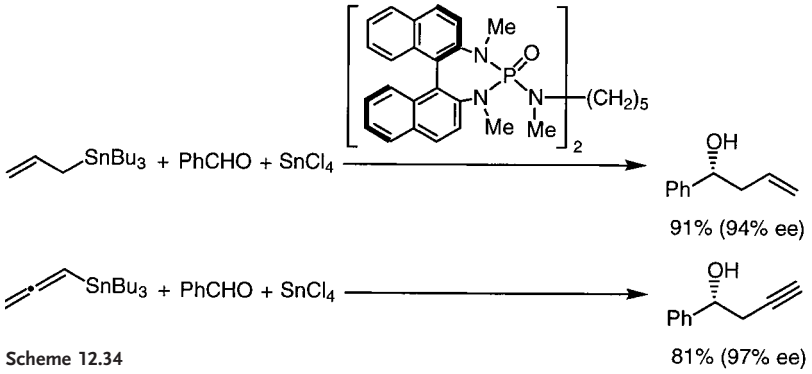


E/*Z*	yield	*anti* (% ee)/*syn* (% ee)
95/5	77%	71 (57)/29 (8)
2/98	85%	63 (60)/37 (7)

Scheme 12.33

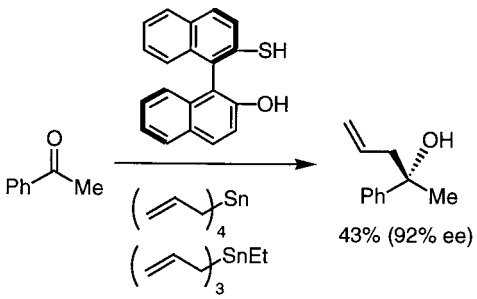
Denmark discovered that coordination of a chiral Lewis base to a Lewis acid enhances its acidity in the promotion of aldol [85] and allylation reactions [86]. This concept is efficient in asymmetric allylation of aldehydes with allylstannanes

(Scheme 12.34) [87]. In this procedure bis-phosphoramides with a methylene tether prove more advantageous for achieving high enantioselectivity than the mono-phosphoramides, strongly supporting a two-phosphoramide pathway [88].



Scheme 12.34

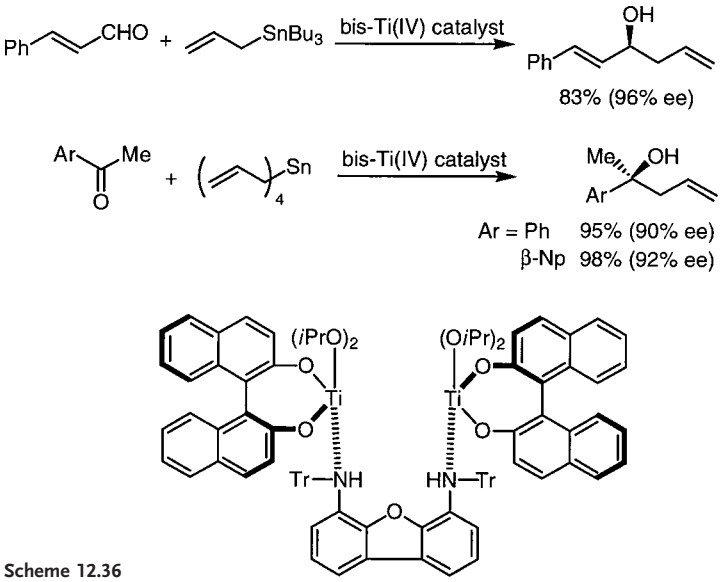
Allylation of ketones is a fundamental and important transformation, and therefore, efficient catalysts promoting addition of allylstannanes to ketones have been investigated [89]. Enantioselective allylation of ketones is a very challenging topic. It has been disclosed that asymmetric allylation of ketones with allylstannanes was promoted by addition of BINOL/$TiCl_2(OiPr)_2$ catalyst [90] or by premixing of BINOL with tetraallyltin [91]. In these reactions, however, enantioselectivity was not sufficient for practical purposes (acetophenone: <65% ee). It was recently discovered that acetophenone was allylated by a mixture of tetraallyltin and an alkyltriallyltin in the presence of monothiobinaphthol to furnish the desired chiral homoallyl alcohol with high enantioselectivity (Scheme 12.35) [92].



Scheme 12.35

Maruoka developed bidentate Lewis acids, with BINOL as chiral auxiliary, which can form double coordination complexes with carbonyls enabling more controlled enantioface discrimination (Scheme 12.36) [93]. This category of Lewis acids-catalyzed allylation of different aldehydes achieved high chemical yield and high enan-

tioselectivity. When cinnamaldehyde, recognized as a tough substrate for conventional enantioselective allylation, was subjected to the Maruoka system, allylation proceeded quite smoothly resulting in 96% ee. When acetophenone and methyl β-naphthyl ketone were subjected to the reaction, the desired homoallylic tertiary alcohols were obtained in excellent chemical yields and high enantioselectivity.

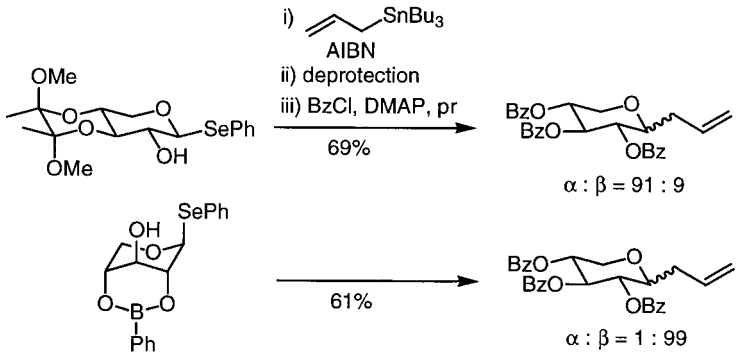


Scheme 12.36

12.2.6
Free Radical Reactions using Allylstannanes

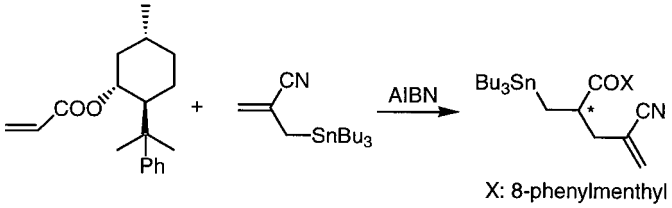
Allylstannanes work as allylating reagents under free-radical reaction conditions. Free-radical reactions have several advantageous features in organic synthesis – neutral reaction conditions, compatibility with Lewis acids, and no need to protect reactive functional groups such as hydroxy and amino groups. In these days, therefore, free radical allylation procedures have been widely used in organic synthesis and several reviews on free radical reactions are available [94].

Exposure of an allylstannane to halopyranoses in the presence of AIBN enables access to the corresponding allyl adducts [95]; this procedure is useful for *C*-allyl glycosidation [96]. To enhance the practical utility of *C*-glycosidation, the effect of conformational restriction on α- and β-selectivity was studied in free-radical allylation at the anomeric positions of phenylselenoxylose derivatives of fixed conformation (Scheme 12.37) [97]. Treatment of a phenylthionocarbonate of 2′-deoxynucleoside [98] and an iodopyrrolidine [99] to allyltributyltin/AIBN resulted in substitution of the allyl moiety.



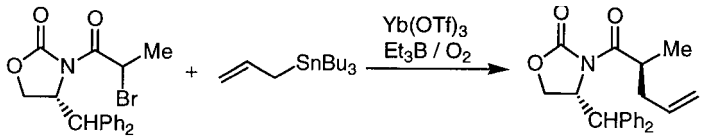
Scheme 12.37

When allylstannanes bearing an electron-withdrawing group were reacted with olefins and aromatic carbonyl compounds, with AIBN as radical-initiator, allylstannation occurred via radical chain process on the C=C and C=O double bonds, respectively [100]. On treatment of homochiral acrylates with a chiral auxiliary on the carbonyl with an allylstannane in the presence of initiators such as AIBN and Et_3B, the desired allylstannation products were obtained with moderate to high diastereoselectivity (Scheme 12.38). When acetylenes were subjected to this procedure, allylstannylation also occurred, leading preferentially to *anti* adducts.



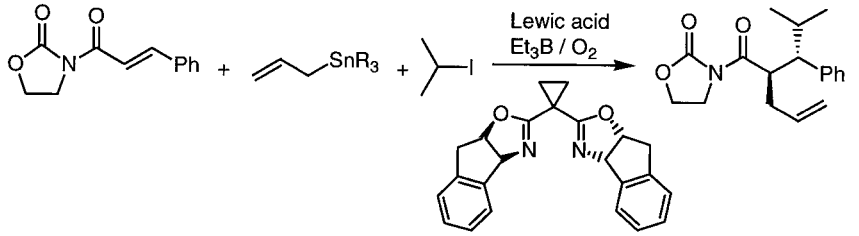
Scheme 12.38

It has been observed that addition of Lewis acids to the free radical allylation improved the chemical yield [101]. When substrates with a chiral auxiliary were subjected to free radical allylation in the presence of a Lewis acid, the desired allylated products were obtained with high stereoselectivity [94 d]. In these reactions the Lewis acid plays a pivotal role in fixing the conformation of radical intermediates. Recently Sibi indicated that an elevated reaction temperature accelerated inversion of the stereochemistry of the radical-centered carbon giving rise to greater diastereoselectivity (Scheme 12.39) [102]. When enantiomerically pure Lewis acids were employed as chiral auxiliaries enantioselective free radical allylation of sulfones [103] and oxazolidinones [104] were realized. In the latter reaction two contiguous chiral centers were generated successfully in a single operation with excellent stereoselectivity via tandem C–C bond formation; both enantiomers can be se-



temp	yield	dr
-78 °C	46%	2 : 1 (S)
0 °C	95%	50 : 1 (S)
RT	92%	>50 : 1 (S)

Scheme 12.39



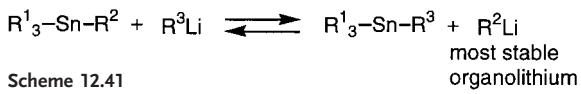
Lewis acid	R	temp	yield	dr	ee
MgI_2	Bu	-78 °C	93%	37 : 1	93
$Cu(OTf)_2$	Ph	-78 °C	93%	30 : 1	-79

Scheme 12.40

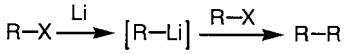
lectively obtained from the same chiral auxiliary by changing the metal center of the Lewis acids (Scheme 12.40).

12.3 Sn–Li Exchange

Since the transmetalation reaction between Sn and Li was discovered by Seyferth [105] the procedure has been used in preparative organic chemistry. Although the reaction involved is an equilibrium, appropriate combination of the substituents on tin, the organolithium compound used, and the solvent enables the equilibrium to be biased in the desired direction, giving rise to quantitative generation of the target organolithium (Scheme 12.41) [106]. By use of this technique different types of organolithium reagent such as vinyl [107], allyl [108], benzyl [109], *α*-hetero-substituted alkyl- [110], and aryllithium [111] have been successfully prepared. Tin–lithium transmetalation, in particular, is quite useful for preparation of allyl and benzyllithium derivatives, because conventional straightforward preparation starting from the corresponding halides and lithium results in low yields, because of the high reactivity of allyl and benzyl halides with the organolithium generated in situ (Scheme 12.42).

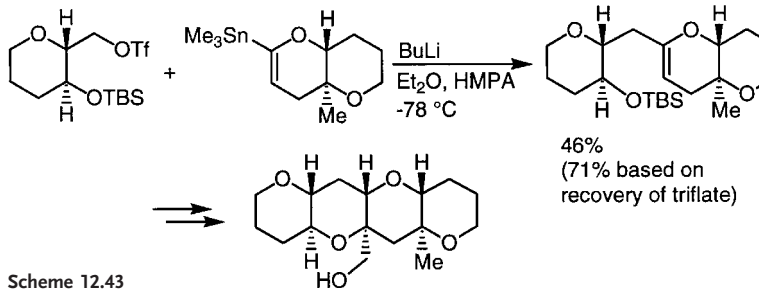


Scheme 12.41



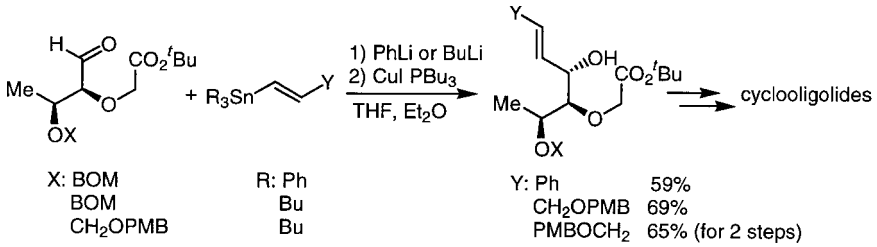
Scheme 12.42

This Sn–Li exchange is widely used for the construction of very complicated structures. A vinyllithium derived from vinylstannane by Sn–Li exchange has been used for synthesis of a polycyclic ether (Scheme 12.43) [112]. This synthetic process relies on the tendency of triflates to undergo S_N2 substitution with the cycloalkoxyvinyllithium generated in situ.



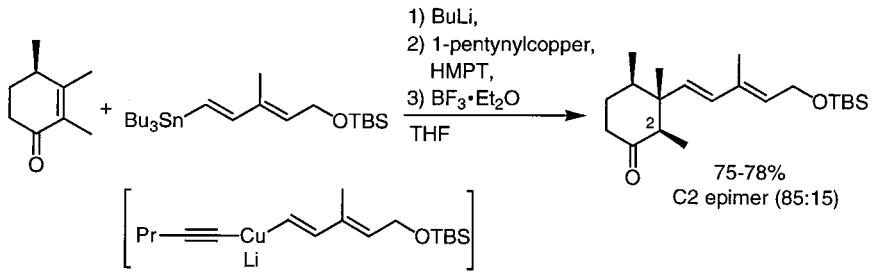
Scheme 12.43

The tin–lithium exchange methodology for access to vinyllithium derivatives has been used for synthesis of C_3-symmetric hydropyran cyclooligolides (Scheme 12.44) [113]. In this process, an aldehyde derived from readily available ethyl (*S*)-lactate was treated with cuprate which had been prepared by addition of organolithium and CuI to vinylstannanes, and various types of building block were successfully constructed.

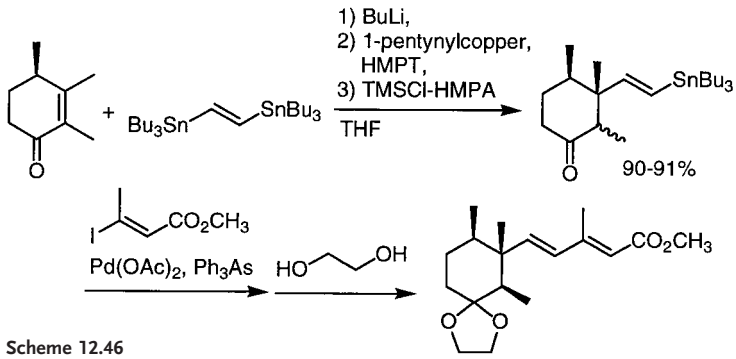


Scheme 12.44

Danheiser used vinylstannane derivatives as precursors in the preparation of a key sesquiterpenyl alcohol in the total synthesis of (–)-ascochlorin (Schemes 12.45 and 12.46) [114]. In the first synthetic route a dienylstannane is used to introduce a C_6 fragment, in which Lewis acid-promoted conjugate addition was performed by use of a mixed cuprate reagent derived from treatment of dienyllithium with pentynylcopper (Scheme 12.45). An alternative approach took advantage of bis(tributylstannyl)ethylene which served as a C_2 fragment and two Sn–C bonds were cleaved selectively, enabling C–C bond formation by Sn–Li exchange and Migita-Kosugi-Stille coupling (Scheme 12.46).

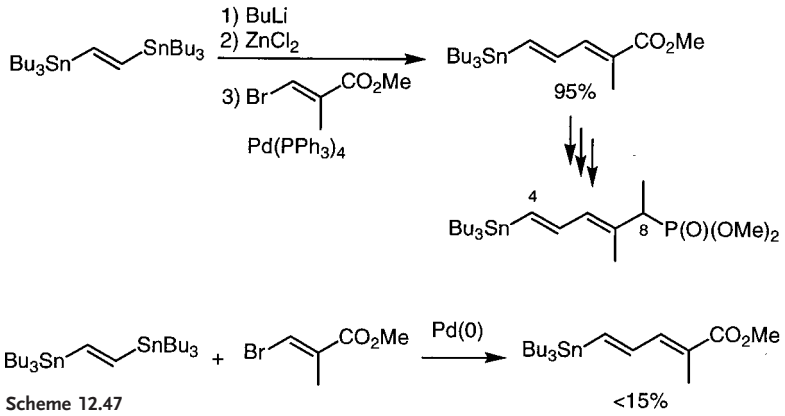


Scheme 12.45



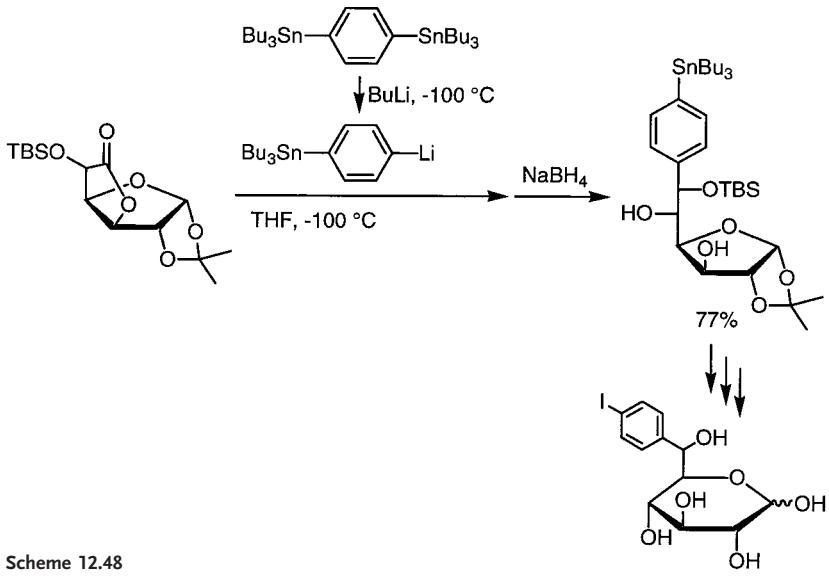
Scheme 12.46

It is noteworthy that stepwise transformation of Sn–C bonds of distannyl compound to C–C bonds is quite a powerful means of assembling functionalized components. Koskinen developed an efficient route to the key building block of the C1–C9 tetraene of calyculins and calyculinamides by sequential Sn–Li exchange of distannylethene and Negishi coupling (Scheme 12.47) [115]. Although Stille coupling between distannylethene and vinyl halides was sluggish and afforded a poor yield, despite a prolonged reaction time, Negishi coupling proceeded without incident to furnish the desired product in 95% yield; in this reaction the vinyltin moiety underwent four consecutive transfer reactions (Sn → Li → Zn → Pd → C).



Scheme 12.47

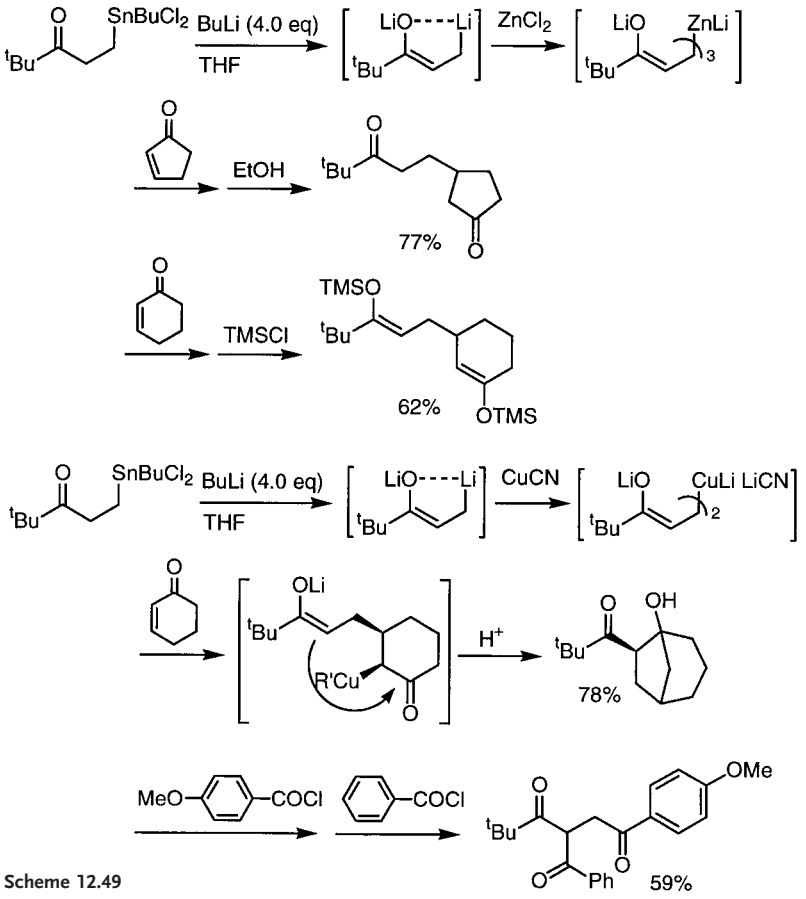
The usefulness of selective lithiation of 1,4-distannylbenzene was exploited to prepare 6-*C*-iodophenyl-D-glucose, expected to be a promising compound for SPECT medical imaging (Scheme 12.48) [116]. Sequential treatment of 1,4-distannylbenzene with BuLi and conformationally-locked glucuronolactone derivative at –100 °C supplied lactol which could be reduced by $NaBH_4$ to give a diol in 77% yield.



Scheme 12.48

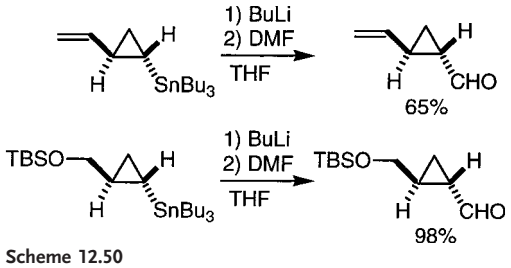
On consecutive deprotonation and Sn–Li exchange with a *β*-stannyl ketone, Ryu succeeded in generating an *α*,*β*-dianion in situ. This anion, which is difficult to obtain by other methods, underwent transformations with different types of elec-

trophile (Scheme 12.49). For example, consecutive treatment of β-stannylketone with four equivalents of BuLi, $ZnCl_2$, and α,β-unsaturated enones furnished 1,6-diketones in moderate yields, and addition of TMSCl to the resulting dienolate enabled access to disilyl enol ether [117]. By use of a similar procedure dianion cuprates provided bicyclo compounds [118] and 1,4-diketones [119], depending on the electrophile employed.



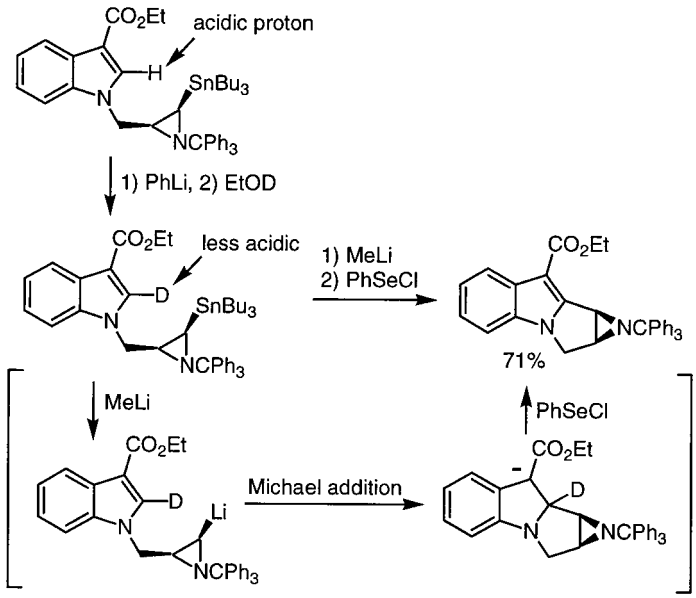
Scheme 12.49

Because cyclopropyl groups are found as basic structural units in a wide range of naturally occurring biologically active compounds, chiral cyclopropylstannane has been made use of as versatile precursor of a stereochemically defined cyclopropyl anion. Synthesis of dictyopterene A was achieved by using chiral cyclopropylstannanes as key intermediates in which Sn–Li exchange and subsequent formylation of the resulting anions played a pivotal role in the construction of continuous stereogenic centers (Scheme 12.50) [120].



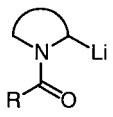
Scheme 12.50

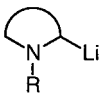
Aziridine groups are also often observed in biologically active compounds. Again the Sn–Li exchange procedure can be used to generate a chiral aziridinyl anion from aziridinylstannane; this has sufficient reactivity for C–C bond formation (Scheme 12.51) [121]. Although tin–lithium exchange often proceeds rapidly to provide the desired anion in good to excellent yield, Vedejs encountered a serious obstacle – in a synthetic study of a leucoaziridinomitosene derivative – competitive deprotonation on an indolyl ring prevented clean generation of the desired aziridinyl anion. To solve this problem, he developed novel methodology taking advantage of deuterium as a blocking group; substitution of the labile proton on the indole ring with deuterium by previous deprotonation–deuteration completely prevented the undesired side reaction, furnishing the desired aziridinyl anion by Sn–Li exchange. Eventually subsequent intramolecular Michael addition, selenylation, and elimination gave the desired leucoaziridinomitosene derivative in 71% yield.



Scheme 12.51

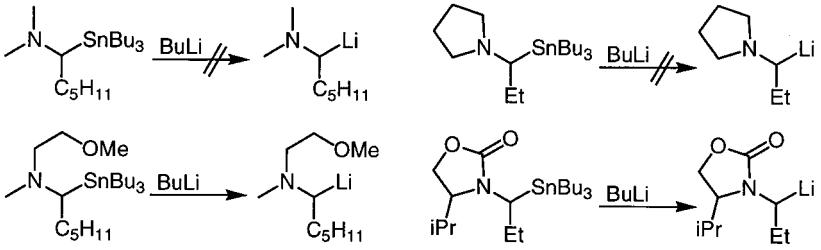
α-Aminoorganolithium species have been extensively studied and used as building blocks in the construction of numerous biologically and pharmaceutically important compounds bearing amino groups. To enable efficient access to α-aminoorganolithium, tin–lithium exchange on the corresponding α-aminoorganostannanes has been widely employed since the first report of a tin–lithium exchange procedure furnishing dimethylaminomethyllithium [122]. α-Aminoorganolithium compounds can be classified as dipole-stabilized and unstabilized species with distinctive reactivity (Scheme 12.52). As is often observed, the tin–lithium exchange proceeds smoothly to afford the desired organolithium compound. Recently, however, several examples have been reported in which tin–lithium exchange failed to occur (Scheme 12.53) [123]. In these reactions minor structural modification enables facile transmetalation on organostannanes. For example, with recourse to intramolecular chelating groups such as methoxy and carbonyl carbonates, tin–lithium exchanges on less reactive secondary stannanes can be facilitated by treatment with BuLi. Gawley found that rigid stannylpiperidines undergo smooth transmetalation when the tin is located in equatorial position, but fails to transmetalate when the stannyl group is present in the axial position (Scheme 12.54) [124]. This phenomenon suggests that a nitrogen lone pair plays an important role in tin–lithium transmetalation in which a synclinal relationship is required between the nitrogen lone pair and the carbon–tin bond.



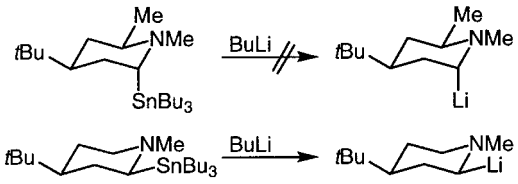


	dipole-stabilized	unstabilized
racemization	rapid	slow
reactivity		
RR'C=O	high	high
RX	low	high

Scheme 12.52

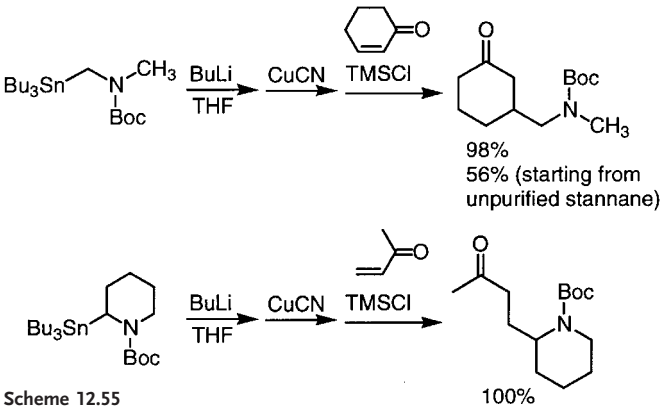


Scheme 12.53



Scheme 12.54

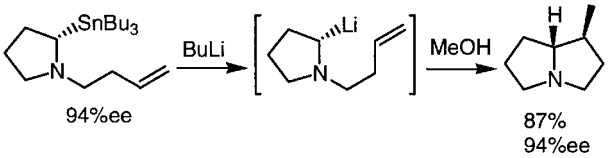
An α-aminoalkyllithium compound derived from the corresponding stannane can be converted into an α-aminoalkylcuprate by treatment with copper reagents such as CuI, CuCN, CuCN + 2LiCl, and RCu(CN)Li. The resulting α-aminoalkylcuprate undergoes conjugate addition with a variety of α,β-enones and enals in which addition of TMSCl is necessary to activate carbonyl electrophiles. In this reaction, the yield of conjugate adduct is sensitive to impurities in the organostannane employed. Use of unpurified stannane that had seemed clean on the basis of both TLC and spectroscopy resulted in lower yields than were obtained by use of the purified stannane (Scheme 12.55) [125].



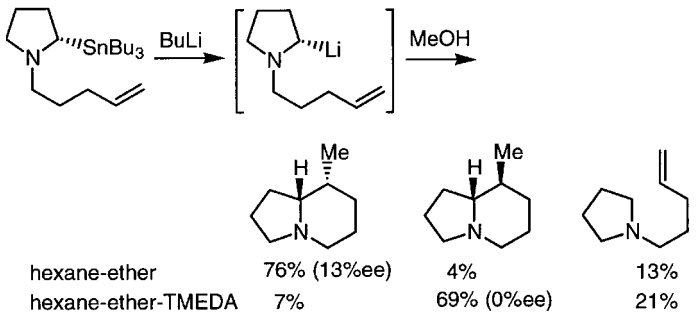
Scheme 12.55

Because tin–lithium exchange and anionic cyclization are known to occur with retention of configuration at the metal-bearing carbon center [126], enantiomerically enriched organostannanes can serve as promising precursors for access to chiral heterocycles. On the basis of this idea Coldham prepared the optically active hexahydro-1*H*-pyrrolizine alkaloid (+)-pseudoheliotridane with complete diastereoselectivity and enantiospecificity (Scheme 12.56) [127]. In sharp contrast with this success, six-membered ring formation by the same strategy resulted in a diastereomeric mixture of racemates (Scheme 12.57) [128].

It is noteworthy that consecutive tin–lithium exchange and intramolecular carbolithiation is effective in construction of the three nitrogen-positional isomers of the azabicyclo[2.2.1]heptane ring system starting from the corresponding α-amino-

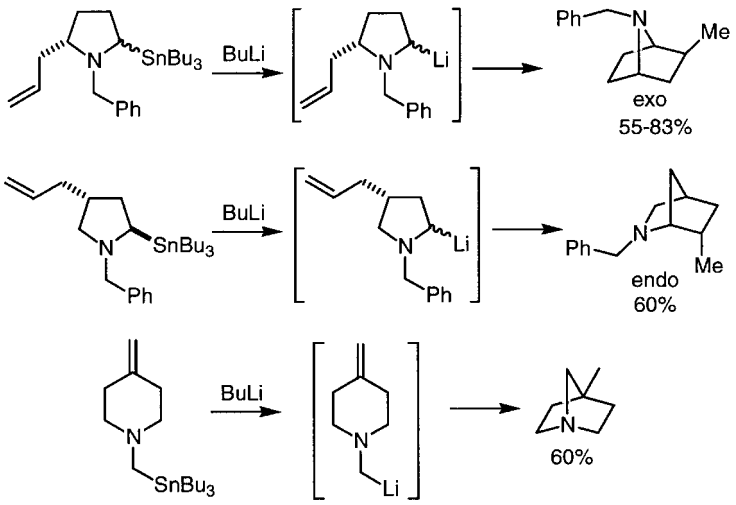


Scheme 12.56



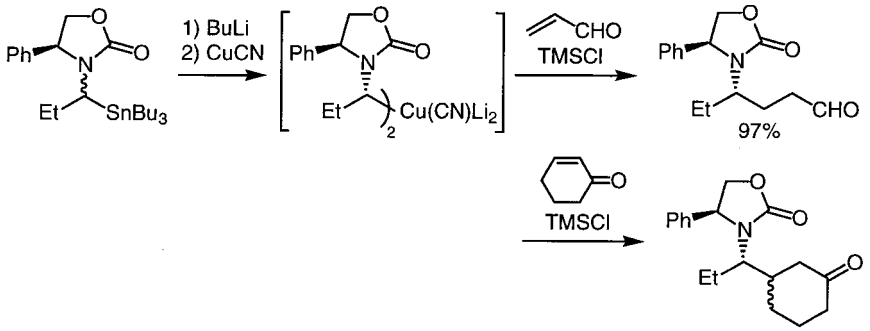
Scheme 12.57

organostannanes (Scheme 12.58) [129]. In these cyclization reactions, the stereochemistry of the carbon attached to the stannyl group is not important because each epimer can produce the target azabicyclo compound by retentive generation of organolithium and subsequent epimerization.



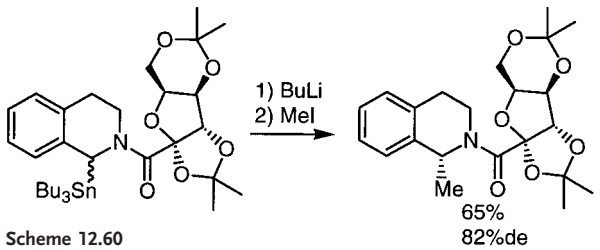
Scheme 12.58

As described above, α-aminoorganolithium compounds are configurationally unstable, undergoing facile epimerization. Introduction of a coordinatively stabilizing chiral auxiliary to the α-aminoorganostannane can, however, fix the stereocenter to produce configurationally stable chiral α-aminoorganolithium. When a chirally *N*-protected α-aminopropylstannane was treated with BuLi and CuCN, enantio-enriched α-aminopropylcyanocuprate was generated irrespective of the stereochemistry at the carbon bearing stannyl group (Scheme 12.59) [130]. The resulting cuprate underwent Michael addition, and it was concluded that transmetalation of the organic moiety from Li to Cu and conjugate addition proceeded with complete retention of configuration at the carbanion center.



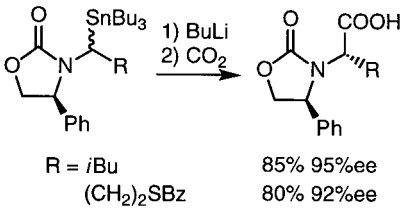
Scheme 12.59

Asymmetric syntheses based on the same strategy have been reported – both sugar-derived (Scheme 12.60) [131] and oxazolidine auxiliaries (Scheme 12.61) [132] enable dynamic kinetic resolution. Application of α-thioorganostannanes to this procedure enables access to an enantio-enriched α-thio anion to furnish alcohols in high enantiomeric excess by reactions with a variety of carbonyl compounds [133].



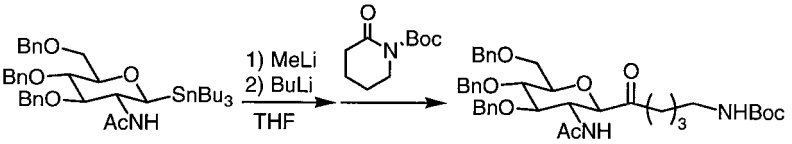
Scheme 12.60

α-Alkoxyorganostannanes have been widely used as conventional precursors of α-alkoxyorganolithium with a configurationally stable stereocenter on the anionic carbon [134]. The inherent configurational stability of α-alkoxyorganolithium re-



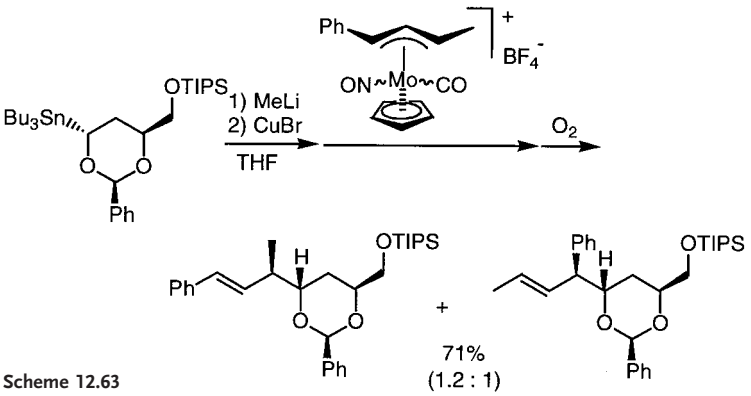
Scheme 12.61

sults in synthetic routes to a wide range of biologically and pharmaceutically important compounds. Westermann recently took advantage of a glycosylstannane for diastereoselective synthesis of a difficult-to-obtain *C*-glycosylated amino acid (Scheme 12.62) [134]. In this synthesis an α-alkoxycarbanion generated from the α-configured glycosylstannane was not susceptible to subsequent ring opening C–C bond formation, yielding the destannylated product only.



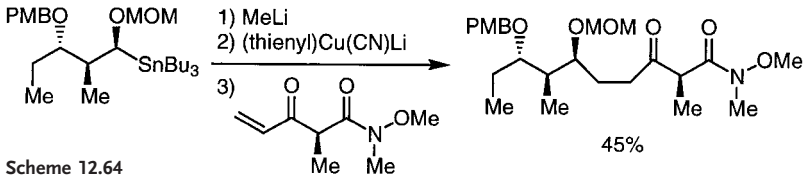
Scheme 12.62

Kocienski succeeded in the total synthesis of Cryptophycin 4, which has strong antitumor activity, by exploiting a key coupling between a cationic allyl complex and an α-alkoxy anion prepared by treatment of the corresponding organostannane with MeLi and CuBr (Scheme 12.63) [135]. Although regiocontrol was poor, and furnished an almost 1:1 mixture of regioisomers in this allylation, the stereochemistry of the axial C–Cu bond was retained and enantiofacial control was ex-



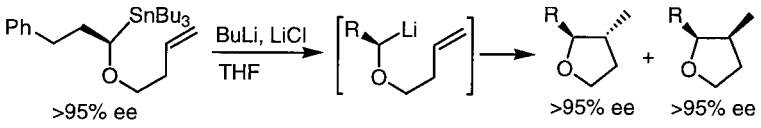
Scheme 12.63

cellent. It has been shown that a higher-order cuprate accessed by consecutive treatment of MeLi and (thienyl)Cu(CN)Li undergoes conjugate addition to an *α,β*-unsaturated ketone (Scheme 12.64) [136].



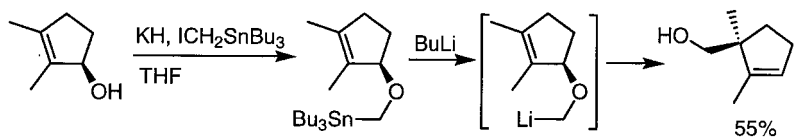
Scheme 12.64

Use of cyclization for access to optically active heterocycles has been studied extensively (Scheme 12.65) [137]. When an enantiomerically defined homoallyloxy stannane was treated with BuLi the desired cyclization occurred to afford the optically active furan derivative and the destannylated compound. Addition of LiCl to this cyclization procedure enhanced the yield to furnish *trans* and *cis* products in high enantio excess.

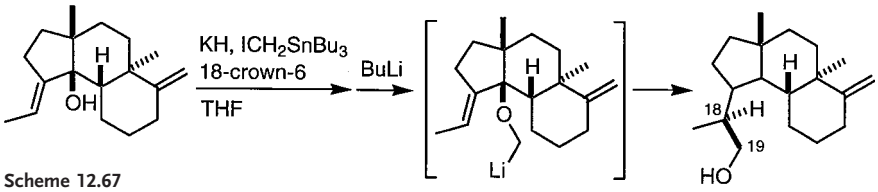


Scheme 12.65

Iodomethyltributylstannane [138] is a versatile tool for introduction of a homoallyl alcohol component by means of the Still-Mitra [2,3]-sigmatropic rearrangement [139]. This procedure has been studied in depth by Nakai [140] and is, nowadays, widely used as a routine transformation method for construction of the fragments bearing many stereogenic centers in the total synthesis of natural products. Mulzer made extensive use of the Still-Mitra [2,3]-sigmatropic rearrangement to build up the D-ring fragment of cobyric acid (Scheme 12.66) [141]. Piers treated a tertiary allyl alcohol with tributylstannylmethyl iodide in the presence of KH and 18-crown-6, and subjected the resultant stannane to [2,3]-sigmatropy achieving C–C bond formation between C-18 and C-19 in a synthetic study of the cyathane diterpenoid sarcodonin G (Scheme 12.67) [142].



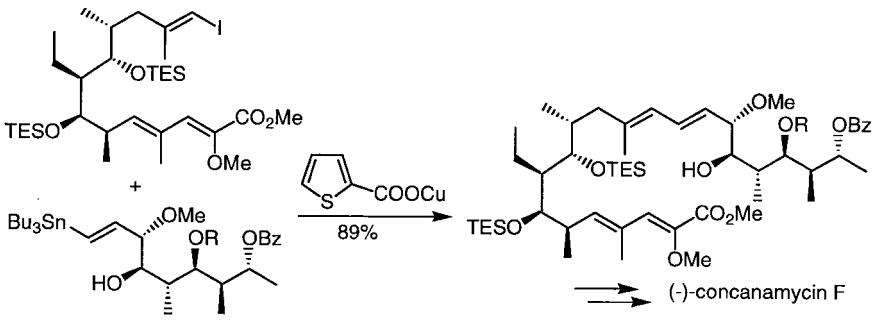
Scheme 12.66



Scheme 12.67

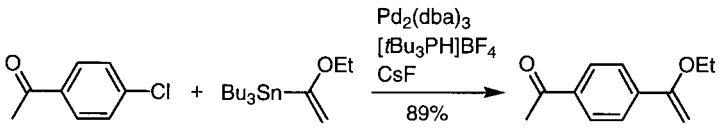
12.4 Migita-Kosugi-Stille Coupling

The palladium-catalyzed coupling of organotin compounds with organic halides is a powerful method for carbon–carbon bond formation. This procedure is called Migita-Kosugi-Stille coupling [4, 5] and has been widely used for organic synthesis [143]. Because of the easy accessibility and stability of the organotin components and mild reaction conditions, this coupling reaction is frequently performed in the synthesis of biologically active and pharmaceutically important compounds [144]. To advance its synthetic utility new variants of this coupling procedure have been investigated. It has been disclosed that addition of Cu(I) cocatalyst enabled carbon–carbon bond formation in otherwise nonproductive or sluggish palladium-catalyzed coupling reactions [145]. After this discovery, it was shown that copper(I) thiophene-2-carboxylate (CuTC) promotes coupling under mild conditions forming a $C(sp^2)$–$C(sp^2)$ bond from the corresponding organotin and organic halide [146]. This CuTC-catalyzed coupling was used for macrocyclization in a total synthesis of concanamycin F (Scheme 12.68) [147]. A copper-catalyzed Migita-Kosugi-Stille type coupling enables straightforward synthesis of substituted benzenes. When 3-bromo-2-trimethylbenzonorbornadiene derivatives were treated with copper(I) halide, hexasubstituted benzenes were obtained as cyclotrimerization products [148]. Treatment of siloxyvinylstannanes with alkenyl iodide in the presence of CuCl at room temperature produced the corresponding silyl dienol esters, which were readily hydrolyzed to enones [149].



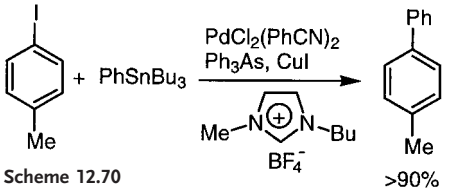
Scheme 12.68

Despite their stability and ready availability, aryl chlorides have rarely been employed as substrates for cross-coupling reactions because of their innate low reactivity. To overcome this drawback strongly electron-donating and sterically demanding ligands such as P*t*Bu$_3$ [150] and iminium salt [151] were used, and in these reactions the desired cross-coupling proceeded smoothly. The notable phosphine P*t*Bu$_3$, however, has an unavoidable drawback – it is difficult to handle because of its sensitivity to oxidation, ascribed to its strong electron-donor properties. It was recently reported that complexation of P*t*Bu$_3$ with BF_3 resulted in the formation of an air-stable complex which can serve as the original phosphine in the presence of Brønsted base (Scheme 12.69) [152]. In these reactions, addition of CsF was necessary to enhance the reactivity of the organostannane by formation of a hypervalent species [153]. As stated already, the ligands and additives play pivotal roles in the cross-coupling reaction, whereas a ligand-free coupling was used in a total synthesis of (–)-amphidinolide P [154]. When phosphines or polar solvents such as DMF, THF and NMP were used, this C–C bond formation does not occur.



Scheme 12.69

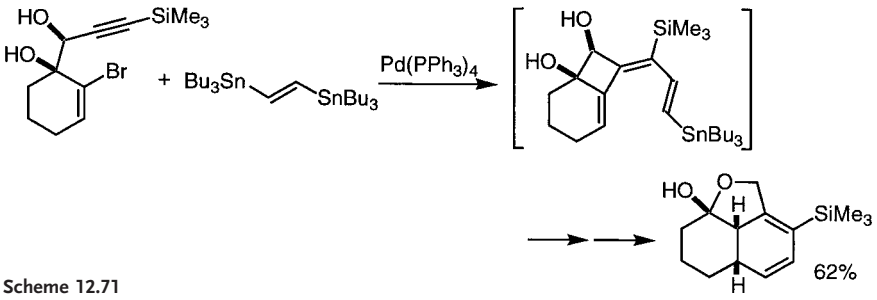
It has been reported that palladium-catalyzed cross-coupling can be performed in ionic liquids such as 1-butyl-3-methylimidazolium tetrafluoroborate. In this coupling procedure the solvent and catalyst system could be recycled, keeping the same levels of catalyst activity (Scheme 12.70) [155].



Scheme 12.70

When a distannyl ethylene was used in this coupling procedure, two C–C bonds were formed in a single operation [156]. The distannyl ethylene was useful for a total synthesis of macrocycle rapamycin, in which a triene array was installed by the coupling reaction between the distannyl ethylene and a diiodide component, giving rise to the formation of macrocycle array [157]. It was recently reported that polycyclic ring systems could be readily constructed by use of consecutive carbopalladation and cross-coupling between ethenyl bromides bearing a silyl acetylene and a distannyl ethylene, followed by a six-electron disrotatory electrocyclization (Scheme 12.71)

[158]. Use of this cascade cyclization procedure enabled facile access to a *cis*-fused decalin backbone which is involved in ascosalipyrrolidinone. When an ethenylstannane having a germyl group at the β position was subjected to this cross-coupling reaction C–C bond formation occurred at the stannyl side only, affording aryl or heteroarylgermanes [159].

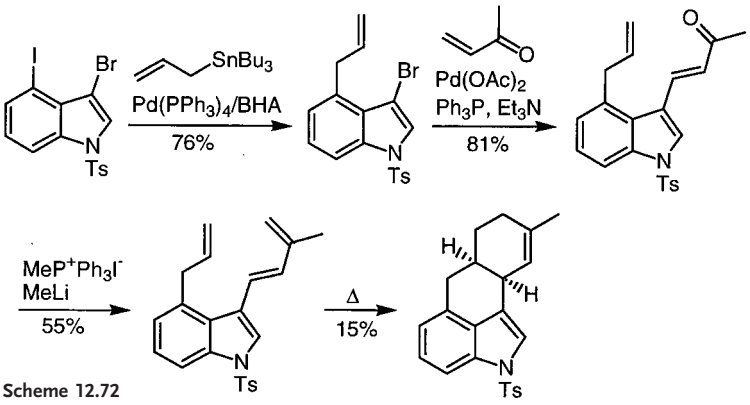


Scheme 12.71

When 1,2-diiodoalkenes were subjected to the coupling reaction monofunctionalization occurred successfully and the new C–C bond was formed preferentially at the less hindered iodide [160]. Migita-Kosugi-Stille coupling occurs preferably at iodide and bromide leaving fluoride intact – treatment of fluoroethenyl iodide [161] and bromide [162] with arylstannane in the presence of palladium catalyst afforded the corresponding ethenyl fluoride products, respectively.

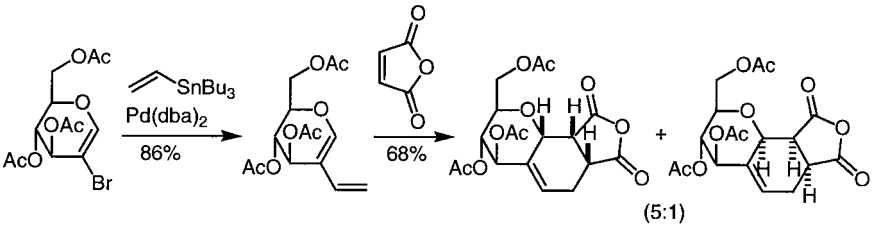
Palladium-catalyzed coupling can be used for allylation of aryl halide. For example, when iodoindole derivatives were treated with allylstannanes in the presence of palladium catalyst, the corresponding allyl adducts were obtained in good yield [163]. Subjection of a dibromoindole to the palladium-catalyzed allylation afforded a 3,4-diallyl derivative in a modest yield [164]. Discriminative allylation between iodine and bromine was realized, and the subsequent Mizoroki-Heck reaction with methyl vinyl ketone, methylenation, and intramolecular Diels-Alder reaction afforded the tetracyclic hapalindoles (Scheme 12.72) [165]. This palladium-catalyzed allylation procedure was used for incorporation of an allyl component in a synthesis of the FGHI ring system of azaspiracid [166]. In this transformation a catalyst system involving $[Pd_2(dba)_3] \cdot CHCl_3$ and tri-2-furylphosphine effected the smooth displacement of the triflate derived from a lactone with the methallyl side chain leading to the desired enol ether.

It is worthy of note that cyclobutene derivatives can be coupled to form a new C–C bond with recourse to the mild reaction conditions of the Migita-Kosugi-Stille cross-coupling procedure [167]. This cross-coupling can be used to incorporate an ethenyl group into carbohydrates, and treatment of a 2-bromo-D-glucal derivative with a vinylstannane under the influence of palladium catalysis provided a dieno-pyranoside product which was subjected to Diels-Alder reaction with dienophiles such as maleic anhydride and *N*-phenylmaleimide, furnishing the corresponding carbocyclic systems (Scheme 12.73) [168]. In the synthesis of new ana-



Scheme 12.72

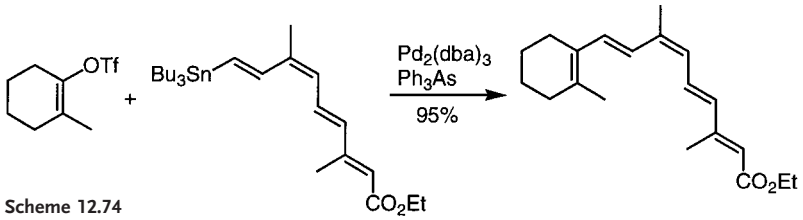
logs of the antibiotic novobiocin, this cross-coupling procedure was used to gain access to an arylcoumarin array [169]. When the tosylate which had been prepared by Mitsunobu coupling between L-rhamnopyranoside and the coumarin was subjected to cross-coupling with 4-stannylcatechol derivatives substitution of tosylate moiety occurred successfully, irrespective of high levels of functionality and the presence of unprotected groups, to give the desired analogs of novobiocin.



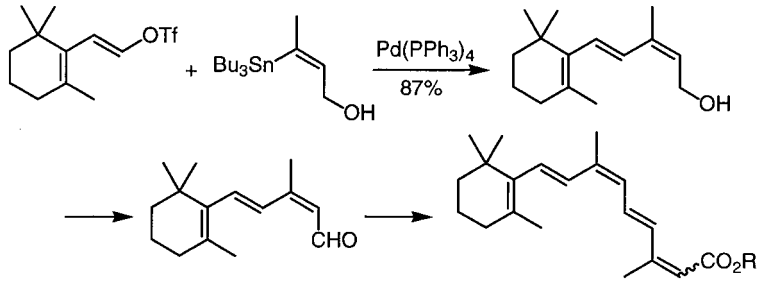
Scheme 12.73

Because its mild conditions are greatly advantageous for the construction of highly conjugated π-backbones, this coupling procedure has been widely used to gain access to retinol and retinoic acid derivatives. Exposure of the triflate which had been regioselectively prepared from 2-methylcyclohexanone to the cross-coupling reaction with a tetraenylstannane provided the desired 1,1-bisdemethylretinoate, and the geometry of the retinoid side-chain was preserved completely (Scheme 12.74) [170]. In the total syntheses of a series of 9*Z*-9-substituted retinoic acids the palladium-catalyzed coupling reaction between vinyl triflates and stannanes played a pivotal role in C_8–C_9 bond formation, in which vinylstannanes bearing electron-withdrawing groups such as formyl and enoate could not be employed because of their low reactivity [171]. Upon subjection of a vinyl triflate to cross-coupling with vinylstannanes bearing a hydroxy group, however, the desired C–C bond formation proceeded readily. In this triflate substitution protection of the hydroxy group was not necessary, and subsequent oxidation and the Horner-

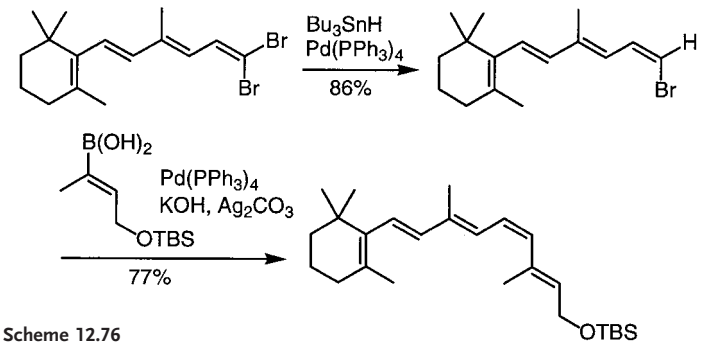
Emmons olefination of the resulting aldehyde furnished the target 9*Z*-9-substituted retinoic acids (Scheme 12.75). Use of palladium-catalyzed coupling has enabled access to a variety of retinoic acid derivatives whose 2,2,6-trimethylcyclohexene ring was replaced by a heteroaromatic ring [172]. In this process, use of *E* and *Z* triflates as starting compounds selectively produced all-*E* and 9*Z* products, respectively, because the coupling reaction proceeded stereospecifically with retention of the configuration of the double bonds. In a stereocontrolled synthesis of (11*Z*)-retinal stereoselective hydrogenolysis of the geminal-dibromo terminus of a tetraene plays an important role – treatment of dibromotetraene with Bu_3SnH under the influence of palladium catalysis gave rise to preferable reduction at the sterically less hindered position affording a (*Z*)-bromoalkene component (Scheme 12.76) [173]. Subsequent Suzuki-Miyaura coupling of the resulting tetraene with a (*Z*)-alke-



Scheme 12.74



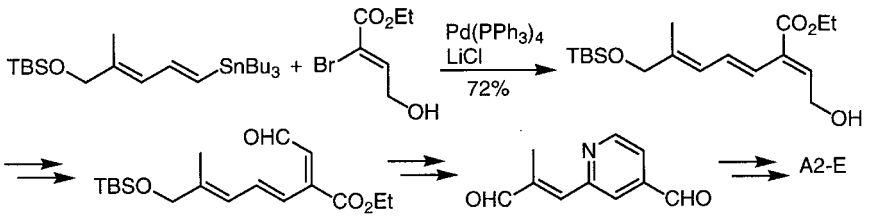
Scheme 12.75



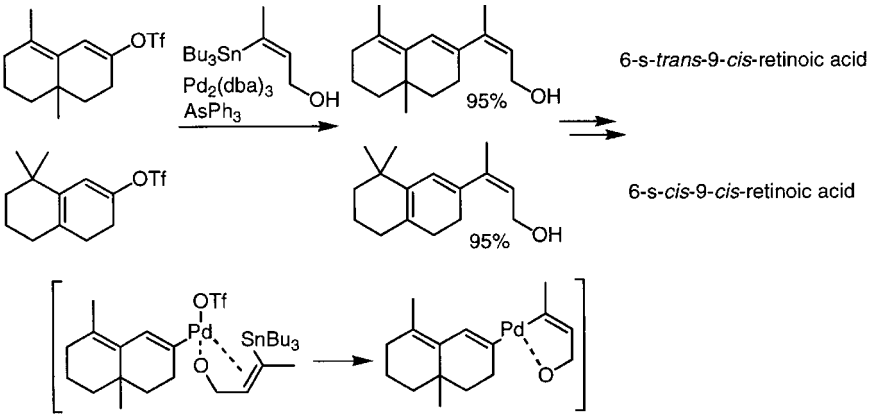
Scheme 12.76

nylboronic acid proceeded smoothly without loss of the stereochemical purity of the pentaene, and (11*Z*)-retinal was obtained in a pure form.

Because a lipofuscin "A2-E" might be involved in the process of age-related macular degeneration (AMG), A2-E has been selected as a potential target compound for remedy of AMG. In the course of synthetic study on A2-E a highly conjugated bis-aldehyde was prepared as a key intermediate by Nakanishi [174]. The highly conjugated compound is also accessible by use of Migita-Kosugi-Stille coupling followed by pyridine synthesis and incorporation of functional groups (Scheme 12.77) [175]. For access to analogs of 9-*cis*-retinoic acid with locked 6-*s*-*cis* and 6-*s*-*trans* conformations palladium-catalyzed cross-coupling between bicyclic dienyl triflates and (*Z*)-tributylstannylbut-2-en-1-ol was performed to give the desired triene product with perfect retention of the configuration of the double bond (Scheme 12.78) [176]. Consecutive oxidation of the resulting alcohols and side chain elongation resulted in the formation of the desired 6-*s*-*cis* and 6-*s*-*trans* locked analogs of 9-*cis* retinoic acid. In sharp contrast with these results the direct cross-coupling of the bicyclic dienyl triflate and a trienylstannane gave rise to unavoidable double bond isomerization leading to loss of the stereochemical integrity of the labile *cis* double bond. It should be noted that *cis*-stannylpropenol is by far more reactive than the *trans* isomer in this cross-coupling; this remarkable rate difference is ascribable to internal coordination of palladium to the hydroxy

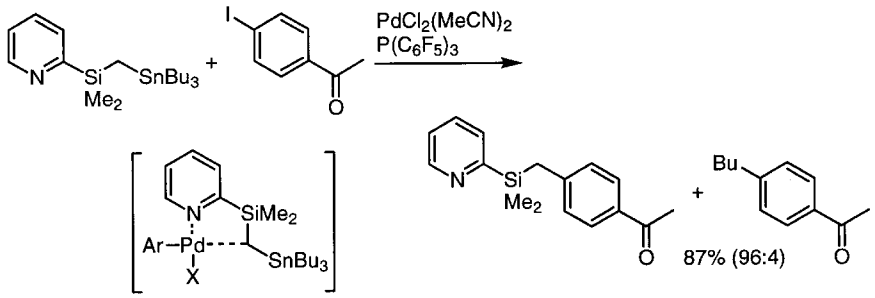


Scheme 12.77

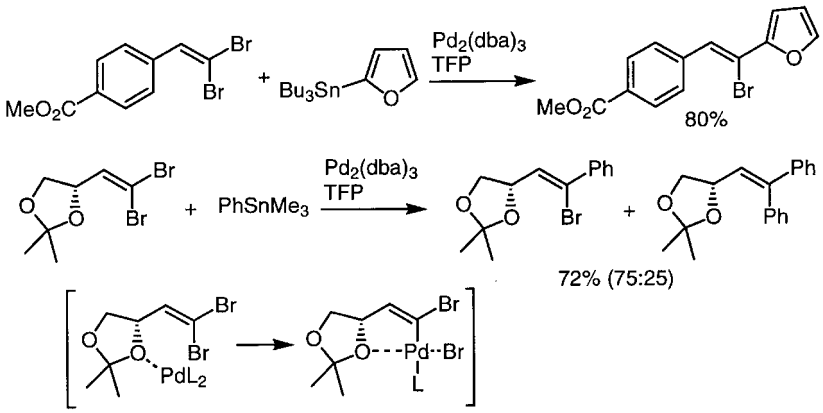


Scheme 12.78

group which enhances transmetalation (Scheme 12.78). Coordination of nitrogen to palladium also enhances transmetalation to enable the transfer of a 2-$PyMe_2SiCH_2$ group, whereas the Me_3SiCH_2 group has been regarded as a "dummy" ligand in this cross-coupling reaction, because of its low migration tendency [177]. When iodobenzene was treated with 2-$PyMe_2SiCH_2SnBu_3$ in the presence of $PdCl_2(CH_3CN)_2$ the cross-coupling proceeded smoothly, and the 2-$PyMe_2SiCH_2$ group was selectively transferred from tin to the aromatic ring (Scheme 12.79). A similar directing effect of oxygen atoms was observed in the coupling of 1,1-dibromo-1-alkenes. This coupling procedure provides (*Z*)-monobromide as the sole product (Scheme 12.80) [178]. When, however, a dibromoalkene with an oxygen function was used a 1,1-disubstituted-1-alkene was obtained as a byproduct by formation of the (*E*)-monobromide by coordination of palladium(0) to the oxygen atom before oxidative addition (Scheme 12.80).



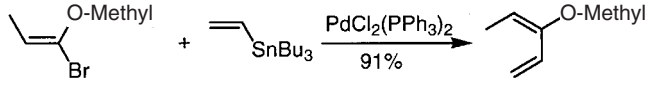
Scheme 12.79



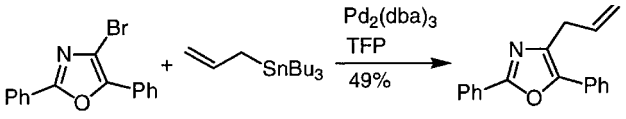
Scheme 12.80

α- and *β*-Halo vinyl ethers can be used for Migita-Kosugi-Stille coupling. When *β*-bromoethenyl ethers are treated with an organostannane in the presence of a palladium catalyst, cross-coupling proceeds smoothly, irrespective of the electron-

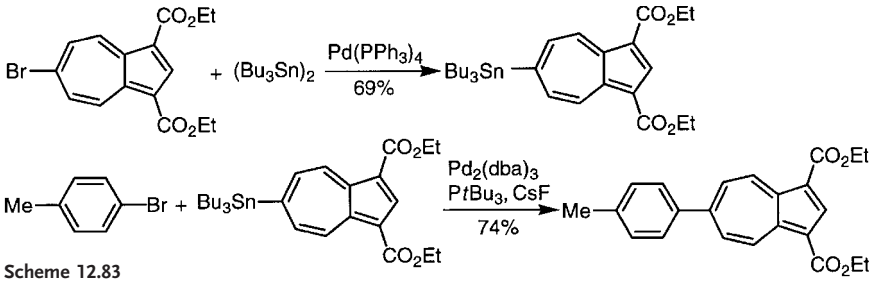
donating group at the β position, and the coupled ethenyl ether derivative is obtained. Although when a (*Z*) isomer was subjected to this coupling a 1:1 mixture of *E*/*Z* isomers was obtained, the resulting ethenyl ether could be converted to the corresponding ketone by treatment with acid [179]. When an α-bromoethenyl ether was employed in the coupling procedure with tributylvinyltin the bromoether underwent the desired cross-coupling to give the functionalized 1,3-diene. It was observed that the geometry of the double bond was completely inverted in this reaction, and an (*E*)-bromide provided the (*E*)-vinyl ether (Scheme 12.81) [180]. α-Bromoethenyl sulfide was also amenable to this procedure, but the corresponding adduct was afforded as a 1:1 mixture of the (*E*) and (*Z*) isomers [181]. The construction of 1,3-dienes by Migita-Kosugi-Stille cross-coupling is synthetically versatile. The formation of a 1,3-diene followed by Diels-Alder reaction with a dienophile was applied to the synthesis of a partial back-bone of Palau'amine and achieved practical levels of stereoselectivity [182]. Treatment of (*Z*)-3-iodoprop-2-enoic acid with an allenylstannane in the presence of a catalytic amount of palladium acetate afforded an α-pyrone derivative efficiently [183]. Oxazole heterocyclic units, which are often present in biologically active compounds, can be incorporated by the cross-coupling approach [184]. It is interesting that for access to an allyloxazole derivative coupling between a bromomethyloxazole and a vinylstannane and coupling of a bromooxazole with an allylstannane were both useful (Scheme 12.82). As an alternative it is possible to incorporate an oxazole component from stannyloxazoles and from oxazolic bromides (Scheme 12.82) [184]. In a study on the total synthesis of phorboxazole A, cross-coupling of 4-trifloyloxazole with a vinylstannane was used to form the C26–C31 subunit. For construction of this array, a trimethylvinylstannane reagent was more efficient than a tributylstannyl derivative. Such different reaction rates might be explained in terms of enhanced transmetalation as a result of reduced steric hindrance [185]. This coupling procedure is useful for functionalization of azulene [186]. Because azulene derivatives are sensitive to organolithium and magnesium reagents, a stannylazulene was prepared by a palladium(0)-catalyzed stannylation of 6-bromoazulene with bis(tributyltin) and the resulting stannylazulene was subjected to the coupling procedure, giving rise to the desired 6-arylazulenes (Scheme 12.83). Treat-



Scheme 12.81



Scheme 12.82

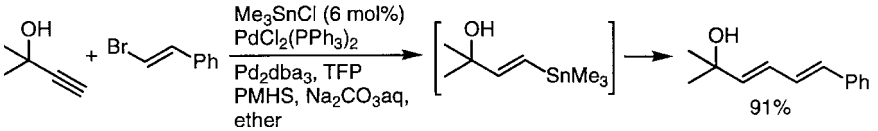


Scheme 12.83

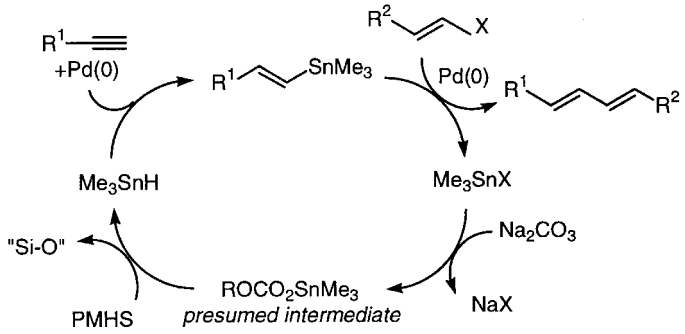
ment of the stannylazulene with 6-bromoazulenes under the influence of palladium catalyst successfully provided 6,6′-biazulenes [186].

Although Migita-Kosugi-Stille coupling is quite powerful for C–C bond formation, it suffers from an avoidable drawback – toxic R_3SnX is liberated in an equimolar amount to the desired product. To minimize this serious "tin problem" several palladium(0)-catalyzed hydrostannation/cross-coupling procedures have been successfully developed; in these only a catalytic amount of tin component is loaded and is utilized repeatedly in a catalysis cycle. Syringe-pump addition of vinyl, aryl or benzyl bromides or iodides to an ethereal solution, under reflux, of alkynes, aqueous Na_2CO_3, polymethylhydrosiloxane (PMHS), palladium catalyst and 6 mol% Me_3SnCl over a period of 15 h provided the desired cross-coupling products (Scheme 12.84) [187]. When allyl bromide, methyl iodide, and arylnonaflate were used in this procedure, no coupling product was obtained. This tandem hydrostannation/cross-coupling is supposed to proceed as shown in Scheme 12.85, and this catalysis cycle requires the trimethyltin component to undergo four types of transformation. A mixture of aqueous KF and a catalytic amount of tetrabutylammonium fluoride (TBAF) is usable instead of aqueous Na_2CO_3 [188]. This procedure enables the formation of a diene, which is a key intermediate in the preparation of kuehneromycin A. When tributyltin chloride was used instead of trimethyltin chloride this reaction proceeded sluggishly and provided poor yields. When the procedure was performed with microwave flash heating, however, consecutive hydrostannation and cross-coupling occurred quite readily a reaction was complete in several minutes only (Scheme 12.86) [188]. Microwave-irradiation is quite versatile for acceleration of palladium-catalyzed C–C bond formation. Although microwave-assisted coupling was complete within 10 min the same reaction gave no coupling product after reflux for 24 h.

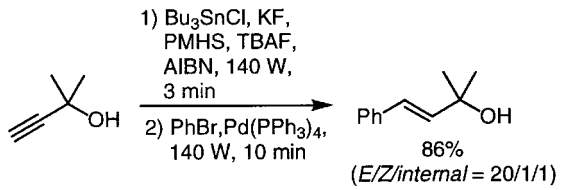
C–C bond formation by Migita-Kosugi-Stille cross-coupling has been widely used for the construction of pharmaceutically important and biologically active



Scheme 12.84



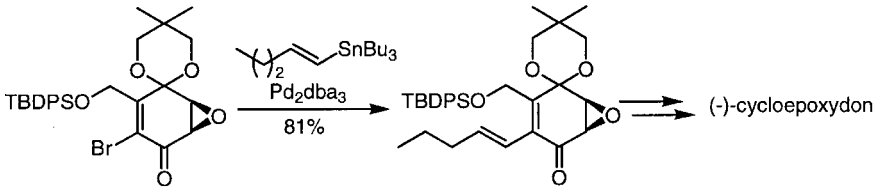
Scheme 12.85



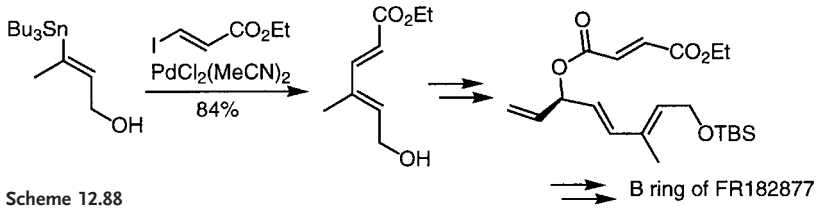
Scheme 12.86

compounds. Cross-coupling between a vinylhalide and a vinylstannane was performed in a synthesis of NF-κB inhibitor (–)-cycloepoxydon (Scheme 12.87) [189] and in a synthetic exploration of FR182877 (Scheme 12.88) [190], affording the expected diene products in good yields.

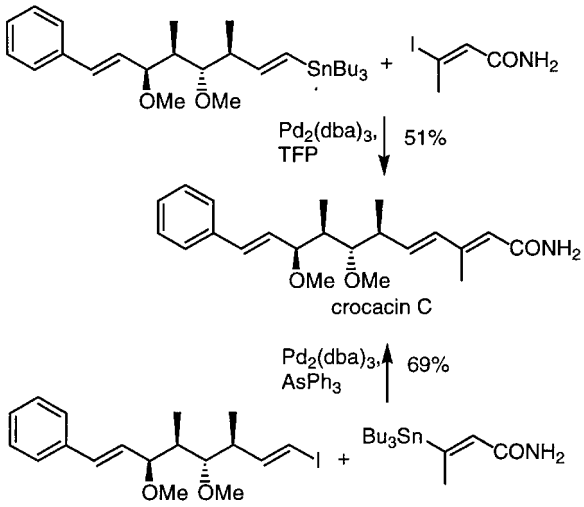
This cross-coupling procedure for access to diene components plays a pivotal role in a total synthesis of (+)-crocacins C (Scheme 12.89) [191] and D (Scheme 12.90)



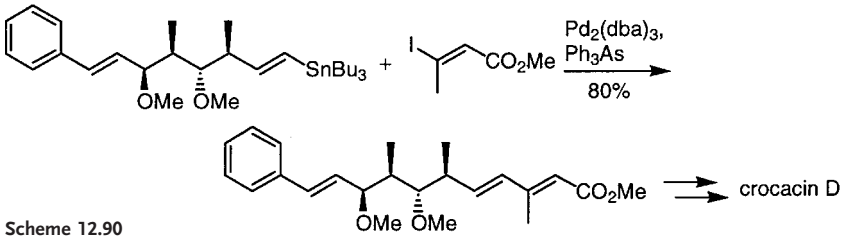
Scheme 12.87



Scheme 12.88



Scheme 12.89



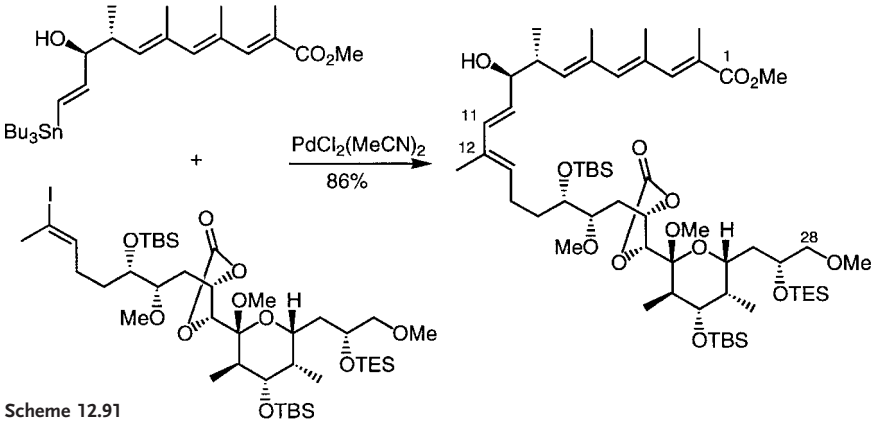
Scheme 12.90

[192]. In these coupling reactions, tri(2-furyl)phosphine or Ph_3As/palladium catalyst system in *N*-methylpyrrolidinone (NMP) promoted the construction of trisubstituted olefins quite smoothly.

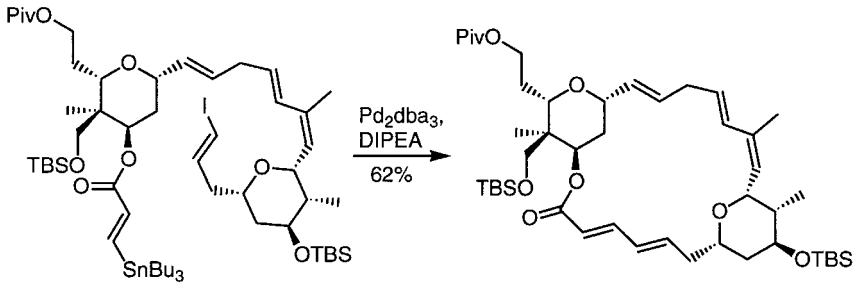
It is worthy of note that palladium-mediated cross-coupling between a vinyl halide and a vinylstannane has been used in synthesis of a macrolide. For access to apoptolidin a C11–C12 bond was formed by use of the C1–C11 and C12–C28 vinyl components to give the desired C1–C28 segment (Scheme 12.91) [193]. Intramolecular coupling under the influence of palladium catalyst resulted in the formation of the desired macrolactone, which was converted to (–)-lasonolide (Scheme 12.92) [194].

Triflate and halides can be used in this coupling procedure. For example, (*S*)-ipsenol was obtained by coupling an ethenylstannane and an enoltriflate which had been prepared from an optically active alcohol (Scheme 12.93) [195]. An alkaloid, (±)-ipalbidine, was synthesized from the corresponding vinyl triflate and *p*-methoxyphenylstannane (Scheme 12.94) [196].

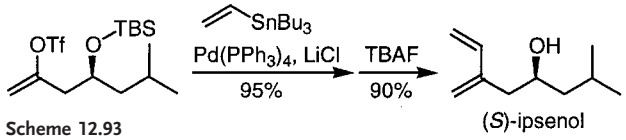
Treatment of a triflate, derived from a butenolide, with a variety of organostannanes in the presence of palladium catalyst furnished the corresponding coupling



Scheme 12.91



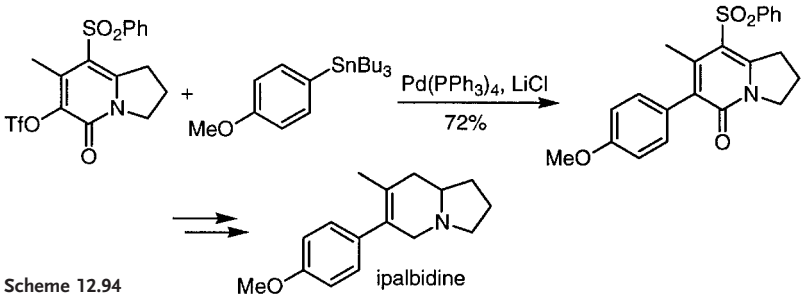
Scheme 12.92



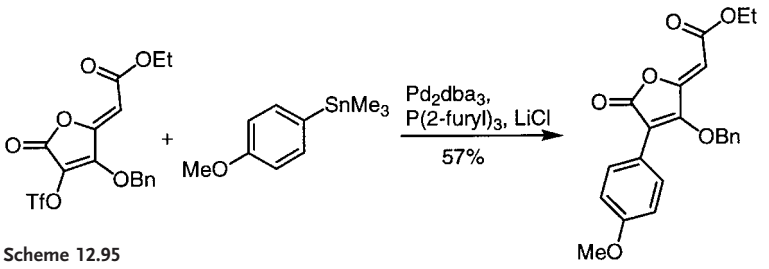
Scheme 12.93

products (Scheme 12.95) [197]. Although it was difficult to separate the desired products from Bu_3SnCl after the coupling the problem could be solved by use of $ArSnMe_3$ because the resulting Me_3SnCl was water-soluble, enabling easy separation.

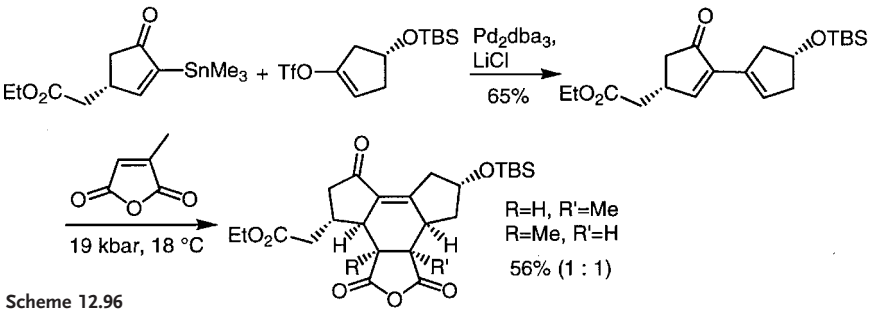
In a synthetic study of spinosyns A and D palladium-mediated coupling of a cyclopentenyltriflate and a cyclopentenylstannane was followed by Diels-Alder cycloaddition of the resulting diene with maleic anhydride (Scheme 12.96) [198]. This sequence achieved the construction of the ABC-ring system of the target compounds with control of several stereocenters.



Scheme 12.94



Scheme 12.95



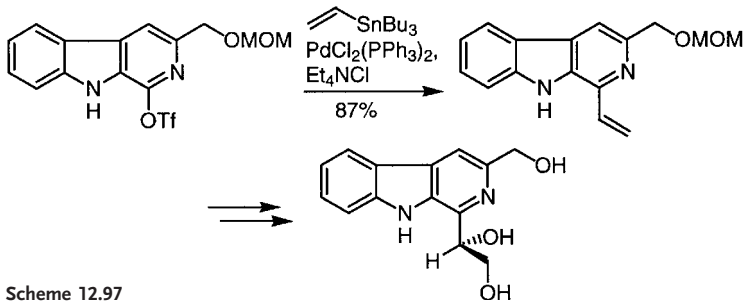
Scheme 12.96

Functionalization of indole derivatives can be achieved by this coupling procedure. Subsequent incorporation of ethenyl group and 1,2-dihydroxylation furnished the *β*-carboline alkaloids (*R*)-(–)-pyridindols (Scheme 12.97) [199].

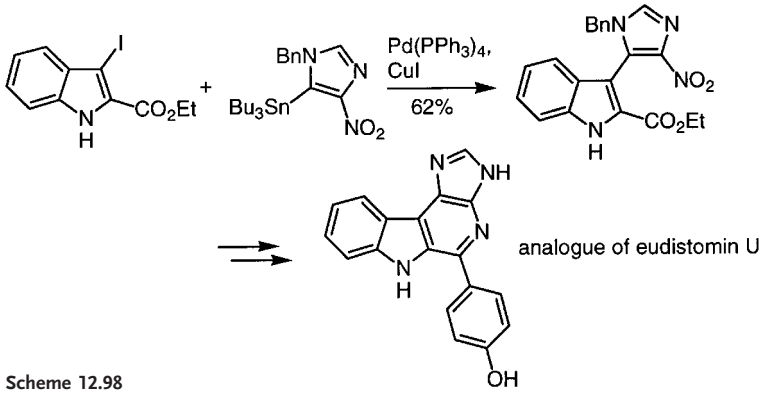
The coupling of 3-imidazolostannane then cyclization realized the synthesis of analogs of antimicrobial alkaloid eudistomin U (Scheme 12.98) [200].

Acid halides can also be used in Migita–Kosugi–Stille coupling; in this C–C bond formation the corresponding ketone is produced. Subjection of a benzoyl chloride derivative prepared in situ to cross-coupling with a vinylstannane provided the desired vinyl ketone which was successfully transformed to a potent COX-2 inhibitor (Scheme 12.99) [201].

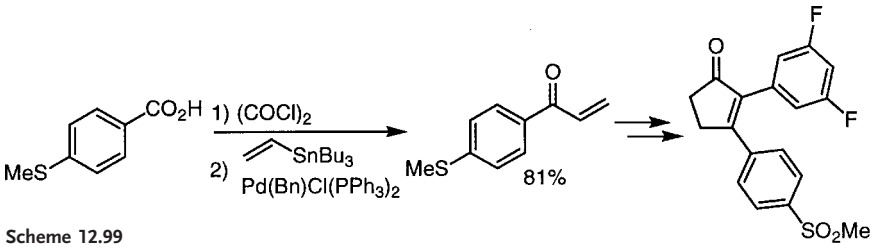
Alternatively, when palladium-mediated coupling was performed under an atmosphere of carbon monoxide, the corresponding ketone had carbon monoxide



Scheme 12.97



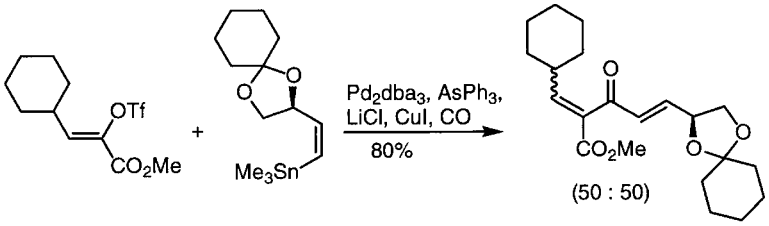
Scheme 12.98



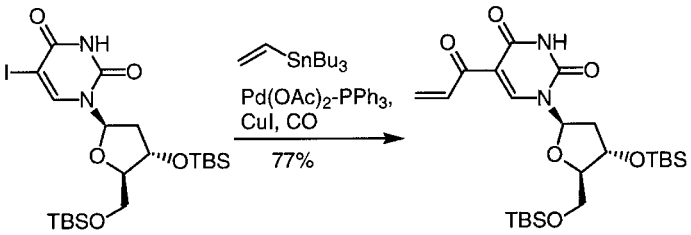
Scheme 12.99

incorporated between newly formed C–C bonds. In an attempt to gain access to sarcodictyin A a divinyl ketone array was constructed by use of this coupling protocol. In this reaction, the use of a soft ligand ($AsPh_3$) and CuI strongly accelerated insertion of carbon monoxide, rather than transmetalation, to accomplish the exclusive formation of ketones without formation of 1,3-diene, despite the electron-poor system used (Scheme 12.100) [202].

An iodopyrimidine nucleoside has been converted to the corresponding ketone by palladium-catalyzed carbonylative C–C bond formation (Scheme 12.101) [203].

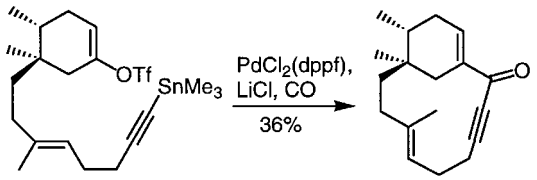


Scheme 12.100



Scheme 12.101

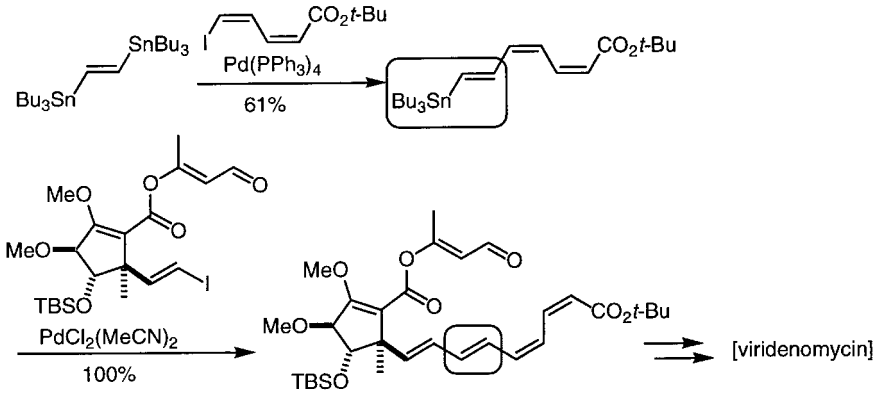
This carbonylative coupling procedure is applicable to macrocyclization. The core structure of phomactins C and D has been successfully assembled by palladium-catalyzed cyclization of a stannyl triflate under an atmosphere of carbon monoxide (Scheme 12.102) [204].



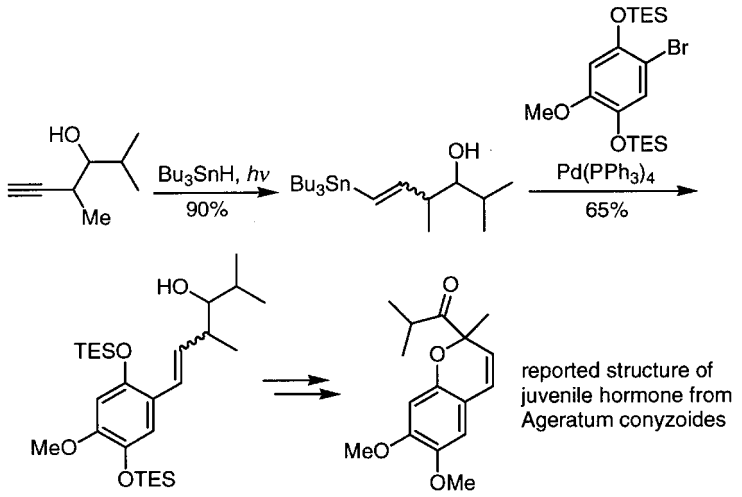
Scheme 12.102

This coupling procedure utilizing 1,2-distannylethene has proved quite versatile for installation of an ethenylene component in a synthetic study on the macrocyclic antibacterial agent viridenomycin (Scheme 12.103) [205]. In this explorative process consecutive coupling of distannylethene with a dienyl iodide and a highly functionalized ethenyl iodide accomplished the formation of the desired tetraene component. When a bromophenol and a vinylstannane derivative were subjected to palladium-catalyzed coupling the desired C–C bond formation proceeded smoothly to provide the corresponding ethenylphenol derivative. The ethenylphenol derivative was successfully converted to the reputed Ageratum juvenile hormone by thermal 6π-electrocyclization (Scheme 12.104) [206].

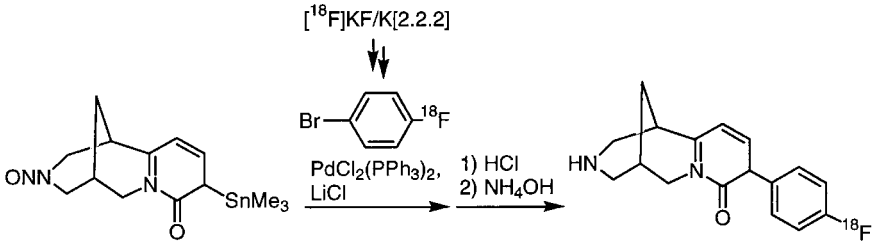
It is worthy of note that this cross-coupling enables rapid access to 9-(4′-[^{18}F]fluorophenyl)cytizine (^{18}F: $\tau_{1/2}$ = 109.7 min; Scheme 12.105), which is promis-



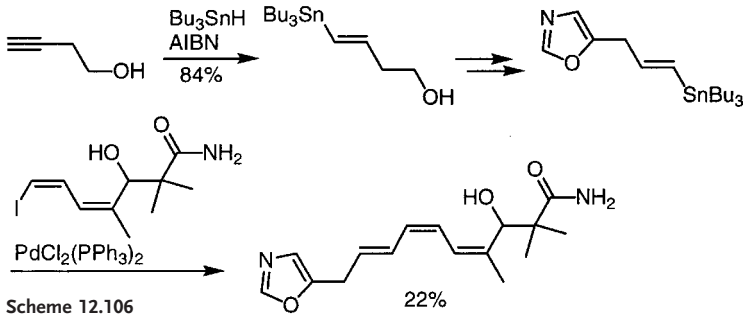
Scheme 12.103



Scheme 12.104



Scheme 12.105

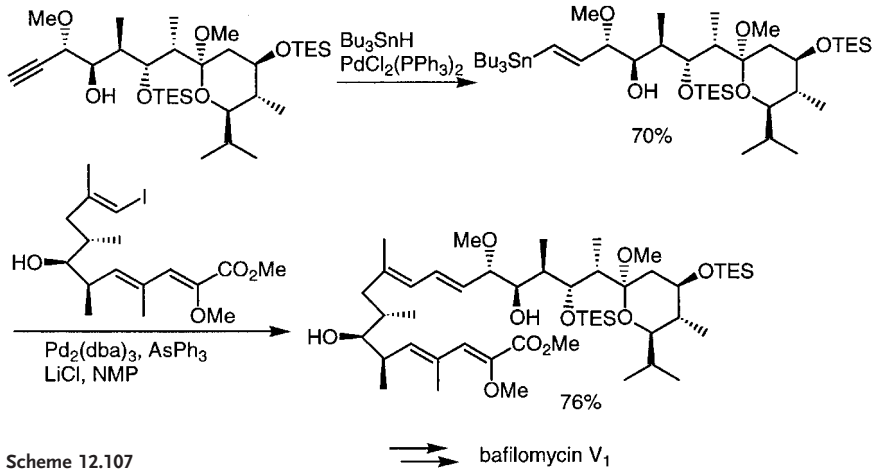


Scheme 12.106

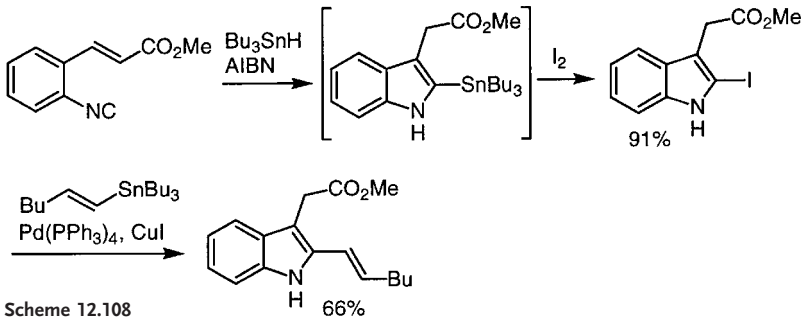
ing as a radioligand for positron emission tomography (PET) of $\alpha_4\beta_2$ nicotinic receptors [207]. For synthesis of a radioligand rapid incorporation of radioactive element and purification are crucial. Consecutive palladium-mediated cross-coupling of stannylcytizine with 4-[^{18}F]fluorobromobenzene, prepared in two steps from [^{18}F]KF/Kryptofix 222, and rapid denitrosation of the resulting [^{18}F]-adduct afforded the desired [^{18}F]cytizine derivative in 6–10% radiochemical yield.

Tandem hydrostannation/cross-coupling is a powerful tool for C–C bond formation starting from acetylenes. A vinylstannane derived from butynol by AIBN-mediated hydrostannation underwent the cross-coupling with a dienyl iodide under the influence of palladium catalyst to furnish racemic phthoxazolin A (Scheme 12.106) [208]. In this total synthesis a *Z,Z,E*-triene unit was efficiently assembled by exploiting this hydrostannation/cross-coupling procedure.

This tandem procedure is useful for synthesis of the highly functionalized vacuolar ATPase inhibitor, bafilomycin V_1 (Scheme 12.107) [209]. Coupling was effected with Pd(0), $AsPh_3$, and LiCl in NMP and proceeded to completion in 5 h at room temperature. Although the indole nucleus occurs in a wide range of natural products, consecutive cyclization of 2-isocyanocinnamate by hydrostannation, de-



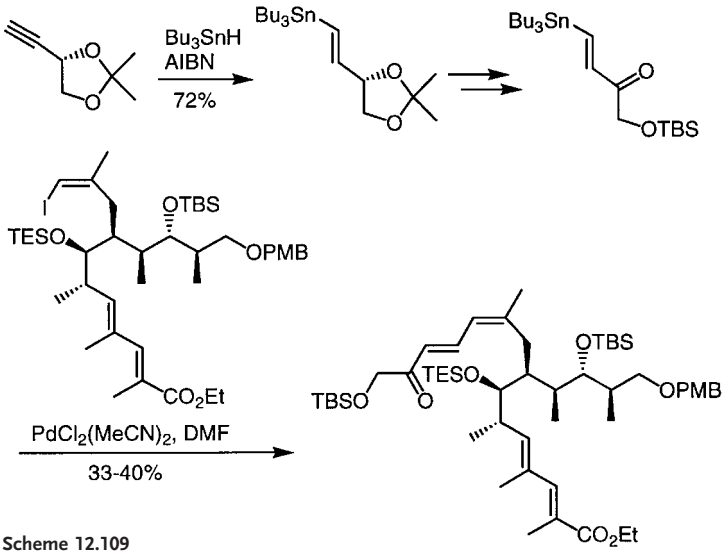
Scheme 12.107



Scheme 12.108

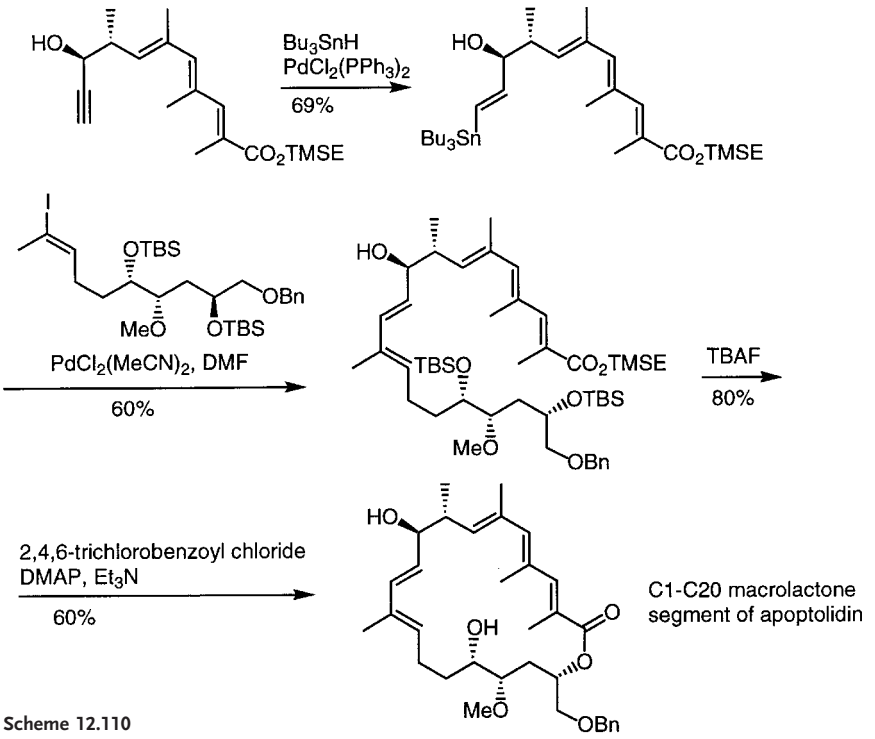
stannyliodination, and palladium-catalyzed cross-coupling of the resulting iodide with vinylstannane enabled access to 2,3-disubstituted indole derivatives (Scheme 12.108) [210].

Halichomycin is a structurally unprecedented tricyclic hemimacrolactam with strong antitumor effects. In the course of a synthetic study on a putative intermediate of halichomycin, tandem hydrostannation/coupling was exploited. On cross-coupling, however, a significant amount of homocoupling product of the stannane was produced, and the yield of the desired adduct was not satisfactory (Scheme 12.109) [211].



Scheme 12.109

This tandem $C(sp^2)$–$C(sp^2)$ bond formation is a versatile approach for a variety of macrolides. The macrolide component of apoptolidin has been successfully constructed by cross-coupling of a stannylcarboxylic acid and an iodoalcohol followed by intramolecular lactonization (Scheme 12.110) [212].



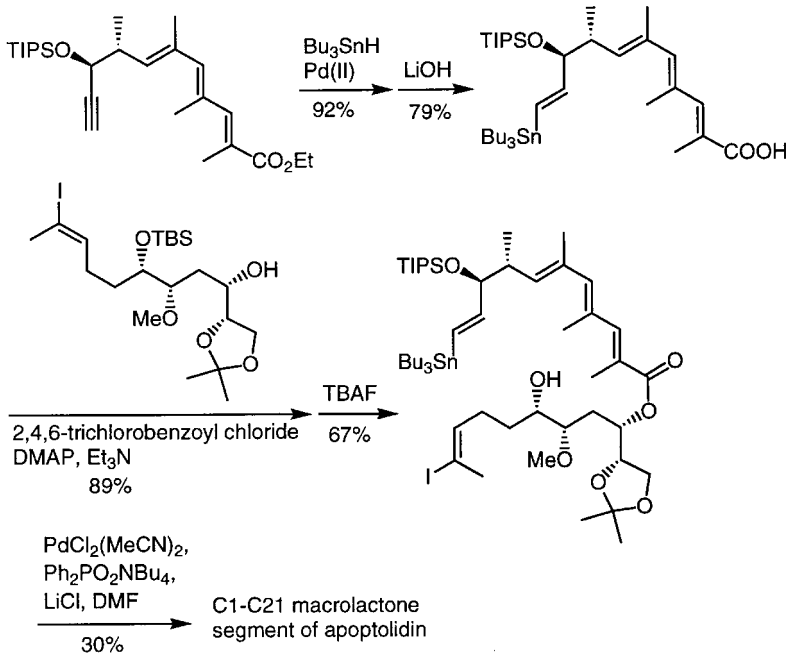
Scheme 12.110

It has also been established that consecutive esterification and cross-coupling affords the same macrolide segment (Scheme 12.111) [213]. This tandem cross-coupling procedure is an efficient means of assembly of a C2–C5 diene in (–)-macrolactone A (Scheme 12.112) [214]. In this reaction a bromoethyne was used as the starting component; otherwise a mixture of regioisomers (7 : 3 β/α) was obtained on hydrostannation.

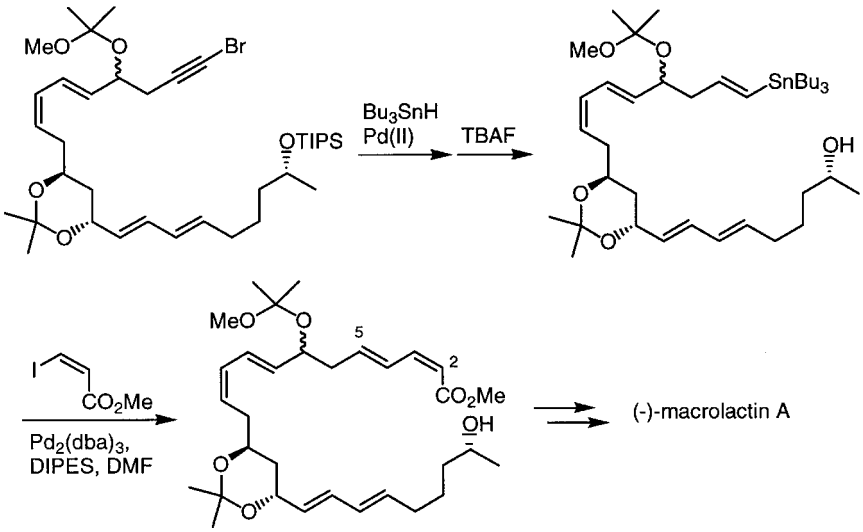
This hydrostannation/coupling/lactonization approach has been used in the synthesis of macrolactone component of apicularen derivatives (Scheme 12.113) [215].

12.5 Organotin Hydrides

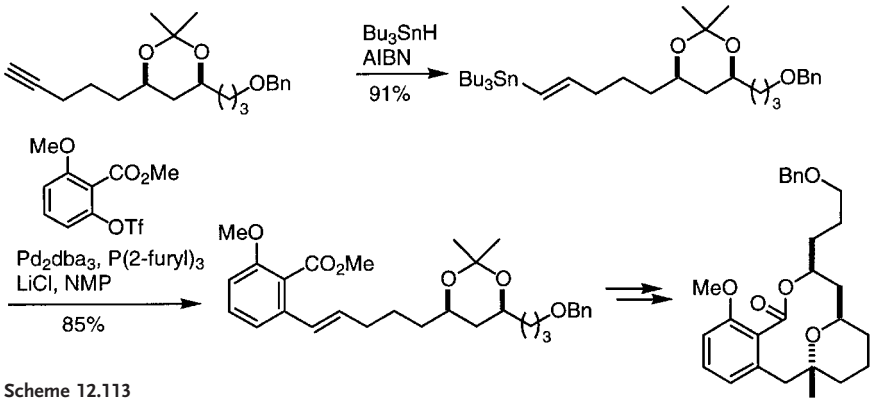
Organotin hydrides have been widely used as reductants in organic synthesis, because they have the advantages of ready availability, ease of handling, and high reactivity [216]. Because this organotin hydride reduction proceeds with high chemoselectivity it is applicable to the synthesis of highly functionalized compounds. Organotin hydride reduction is triggered by use of azobisisobutylonitrile (AIBN) or UV irradiation, and the reaction proceeds by a radical mechanism. When ole-



Scheme 12.111



Scheme 12.112



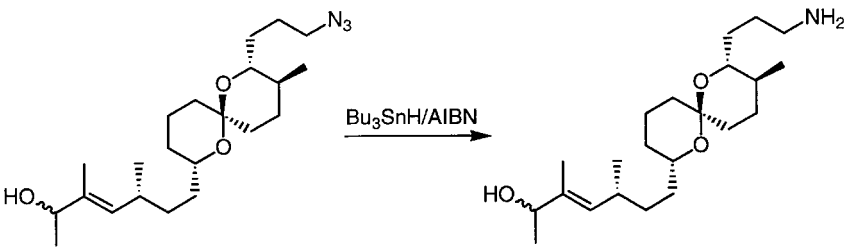
Scheme 12.113

fins or acetylenes containing halogen, organoselenyl, or carbonyl groups are employed hydride reduction followed by cyclization often occurs giving rise to the formation of kinetically favored cyclic compounds. In sharp contrast to this radical-mediated reduction it has been revealed that tin hydride serves as a hydride donor under ionic reaction conditions. When reduction is performed in polar solvent and/or in the presence of catalyst such as a Lewis acid and base, hydride transfer occurs under mild reaction conditions without halogen reduction or cyclopropane ring opening. Such versatile ionic reduction with organotin hydride has been also extensively studied and well reviewed so far [217].

12.5.1
Selective Reduction of Functional Groups

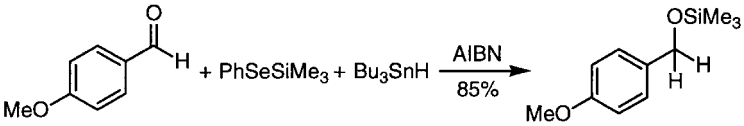
Organotin hydrides can be used for the reductive transformation of a variety of functionalities. When an azide was treated with Bu_3SnH in the presence of AIBN the azide group was converted to the desired amino group while spiroketal and allyl alcohol components remained intact (Scheme 12.114) [218].

On treatment of an aldehyde with Bu_3SnH and $PhSeSiMe_3$ in the presence of catalytic amount of AIBN as radical initiator hydrosilylation gave rise to the corre-

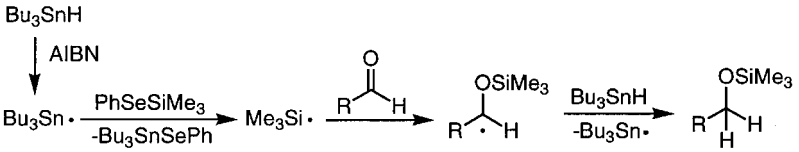


Scheme 12.114

sponding silyl ether (Scheme 12.115) [219]. This procedure enabled reduction of ketones, and reactive ketones such as acetophenone were converted into the desired silyl ether in good yield. On treatment of less reactive ketones such as 2-octanone, however, this reaction proceeded only sluggishly to give a poor yield, despite a prolonged reaction time. Although the reaction mechanism is ambiguous, a plausible reaction pathway was proposed (Scheme 12.116).

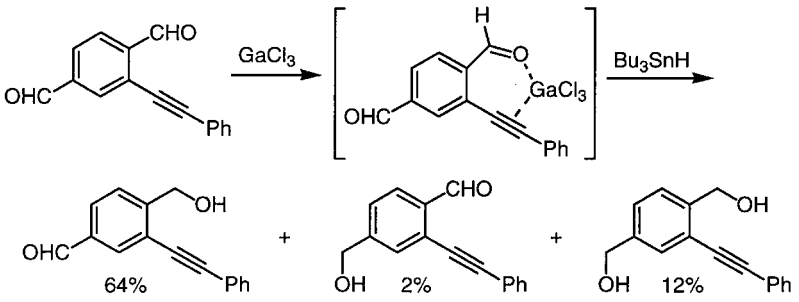


Scheme 12.115



Scheme 12.116

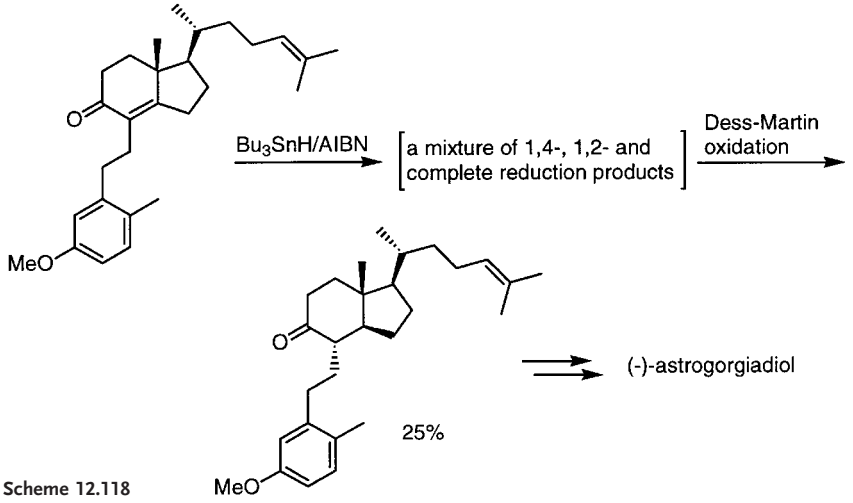
A carbonyl compound can be successfully converted into an alcohol by treatment with Bu_3SnH in the presence of a Lewis acid. When a Lewis acid able to chelate strongly with alkyne π-bond was employed, e.g. $GaCl_3$, the formyl group located on the *ortho* position to the alkynyl group was regioselectively reduced with Bu_3SnH (Scheme 12.117) [220].



Scheme 12.117

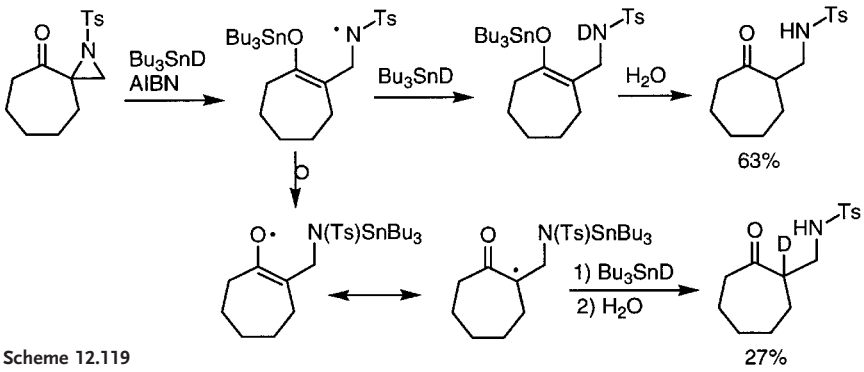
When subjected to organotin hydride reduction mediated by AIBN, an *α,β*-unsaturated ketone undergoes 1,4-reduction. In a synthetic study of the secosteroid (–)-astrogorgiadiol it was shown that the Bu_3SnH–AIBN reduction procedure

affords the desired *trans*-fused ketone, and that regio- and stereoselectivity are satisfactory (Scheme 12.118) [221].



Scheme 12.118

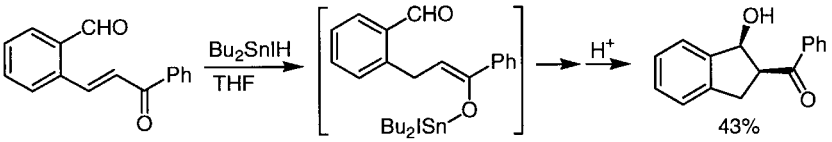
When a keto-aziridine was treated with Bu_3SnD–AIBN, an aminoketone was obtained by ring opening of the aziridine (Scheme 12.119) [222]. Interestingly, 1,5-Bu_3Sn group transfer competes with a direct hydrogen abstraction on the nitrogen-centered radical intermediate giving rise to the formation of *α*-deuterated amino ketone.



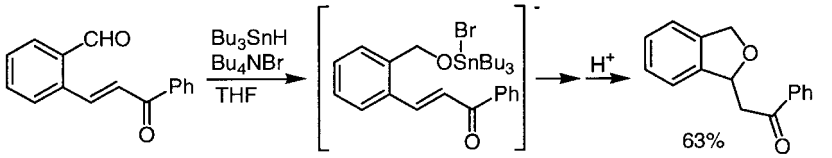
Scheme 12.119

Reduction of an enone, in preference to a formyl group, with Bu_2SnIH was realized under ionic reaction conditions to give an organotin enolate. The resulting organotin enolate attacks the remaining formyl group and the corresponding cyclic *β*-hydroxy ketone was produced (Scheme 12.120) [223]. In sharp contrast to

this result, when Bu_3SnH-Bu_4NBr reduction was used as a reductant, selective reduction of a formyl group then Michael addition of the resulting alkoxystannane to the enone produced a five-membered cyclic ether (Scheme 12.121).

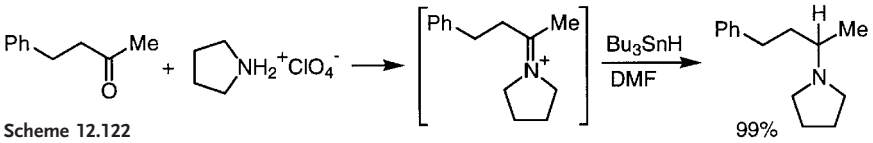


Scheme 12.120



Scheme 12.121

Ionic reduction enables efficient reductive amination of carbonyls. Although several reductive amination procedures have been developed, drawbacks had to be addressed – the requirement of excess amine to bias the equilibrium to the imine side and the unavoidable formation of overalkylation products. In sharp contrast, on treatment of a 1:1 mixture of carbonyl and amine hydroperchlorate with Bu_3SnH in DMF, the desired amines were prepared in satisfactory yield without contamination by overalkylation products (Scheme 12.122) [224].

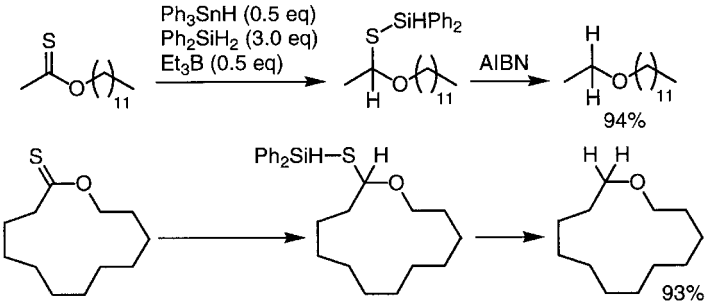


Scheme 12.122

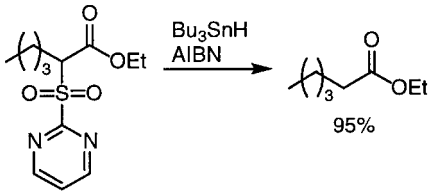
Organotin hydride reduction of thionoesters and thionolactones affords the corresponding ethers by hydrosilylation then desulfurization (Scheme 12.123) [225]. In this desulfurization process a catalytic amount only of triphenyltin hydride works well; use of a stoichiometric amount of expensive organotin hydride is thus avoided.

Organotin hydride/AIBN desulfurization enabled efficient desulfonylation of π-deficient heterocyclic sulfones, which cannot be removed by a conventional method such as use of Al(Hg) and Na(Hg) (Scheme 12.124) [226].

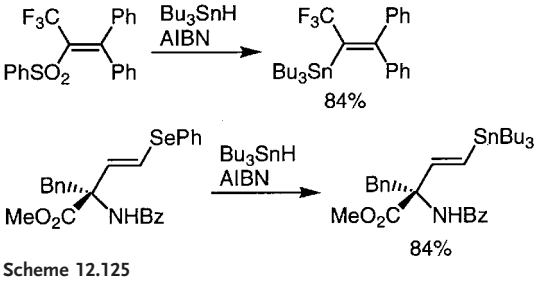
In sharp contrast with these results, when ethenylenesulfones [227] and selenides [228] are heated with Bu_3SnH in the presence of AIBN, desulfonylative and deselenative stannylation, respectively, occur, producing vinylstannanes (Scheme 12.125).



Scheme 12.123

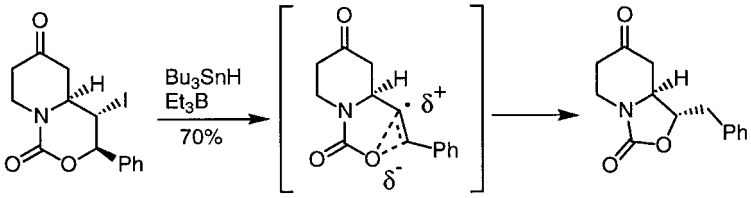


Scheme 12.124



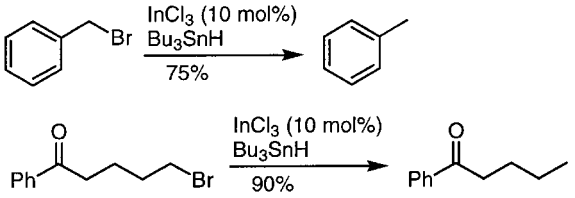
Scheme 12.125

Radical reactions with organotin hydrides have been valuable for dehalogenation of organic halides. Bu_3SnH/AIBN dehalogenation of a bicyclic carbamate furnished the ring-contracted product by carbamate rearrangement (Scheme 12.126) [229].



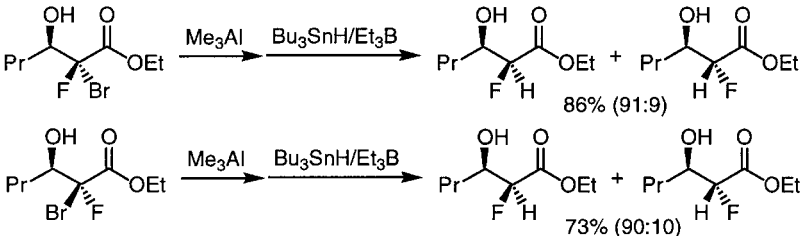
Scheme 12.126

Despite the utility of radical dehalogenation, development of more stable and milder initiators than AIBN, Et_3B, and Et_2Zn is still required. It has recently been reported that $InCl_3$, which is easy to handle because of its stability in the air, can serve well as an initiator of free-radical dehalogenation with Bu_3SnH at room temperature, enabling carbonyl groups to remain intact (Scheme 12.127) [230].



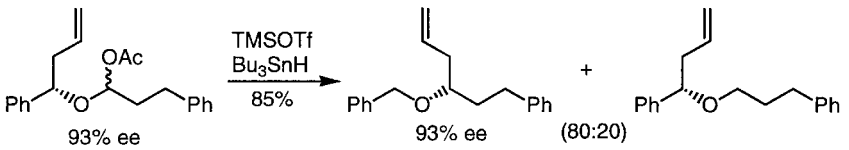
Scheme 12.127

Addition of Me_3Al to Bu_3SnH/AIBN-promoted dehalogenation of *α*-bromo-*α*-fluoro-*β*-hydroxy esters with high stereoselectivity, leading to *threo*-fluoro-*β*-hydroxy esters, irrespective of stereochemistry of the starting esters (Scheme 12.128) [231].



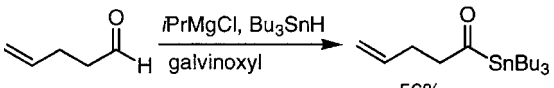
Scheme 12.128

Tributyltin hydride has been used as a hydride donor to produce stabilized carbenium ions in 2-oxonia Cope rearrangement; use of the less nucleophilic triethylsilane resulted in poor chemical and optical yields (Scheme 12.129) [232].



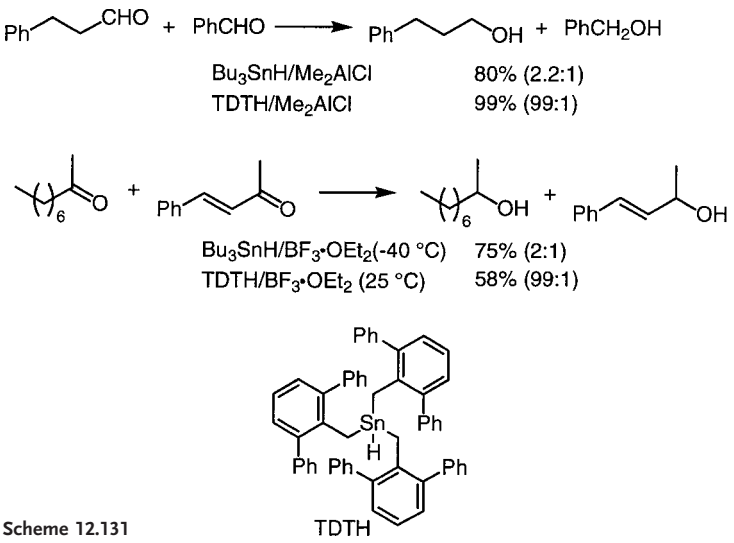
Scheme 12.129

Treatment of tributyltin hydride with a Grignard reagent enables preparation of the corresponding organotin anion, which undergoes the Cannizarro reaction with pentanal providing an acyl stannane (Scheme 12.130) [233].



Scheme 12.130

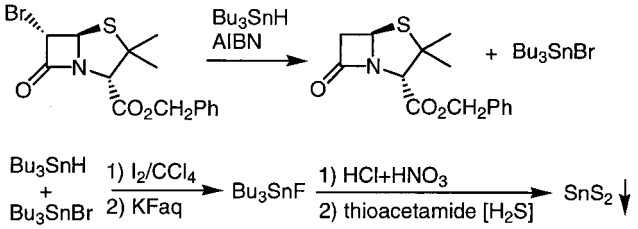
Several functionalized trialkyltin hydrides have been prepared and used in organic synthesis. For example, an optically active organotin hydride with binaphthyl as chiral center underwent hydrostannylation with methyl methacrylate leading to a β-stannyl ester; diastereoselectivity, however, was not sufficient [234]. Although a bowl-shaped organotin hydride with bulky aromatic substituents was prepared, the structurally novel tin hydride resulted in quite high chemoselectivity. When tris(2,6-diphenylbenzyl)tin hydride (TDTH) was used for competitive reduction of carbonyls under the influence of a Lewis acid it was observed that unsaturated carbonyl compounds such as benzaldehyde and α,β-enones are highly resistant to TDTH reduction (Scheme 12.131) [235].



Scheme 12.131

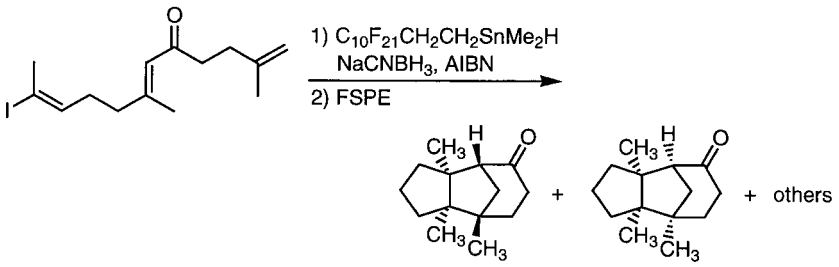
Although organotin hydrides have been widely used as powerful reagents for organic synthesis, separation of the desired product from excess tin reagent and other tin products is often tedious and time-consuming. Although several technologies have been advanced to overcome this drawback [236], easier, more practical and widely applicable technology is still in demand. For instance, exposure of a

crude mixture containing organotin compounds to an aqueous solution of inorganic fluorides such as KF [237] and CsF [238] causes precipitation the organotin compounds as insoluble organotin fluorides enabling easy purification of the desired products. After dehalogenation of a bromopenicillinate by use of Bu_3SnH/AIBN, treatment of the crude mixture with iodine then aqueous KF solution enabled facile separation of the dehalogenated product from the resulting insoluble Bu_3SnF. Subsequent treatment of Bu_3SnF with HCl/HNO_3 then thioacetamide afforded nontoxic SnS_2 as a yellow solid; this inorganic precipitate could be easily separated by filtration (Scheme 12.132) [239].



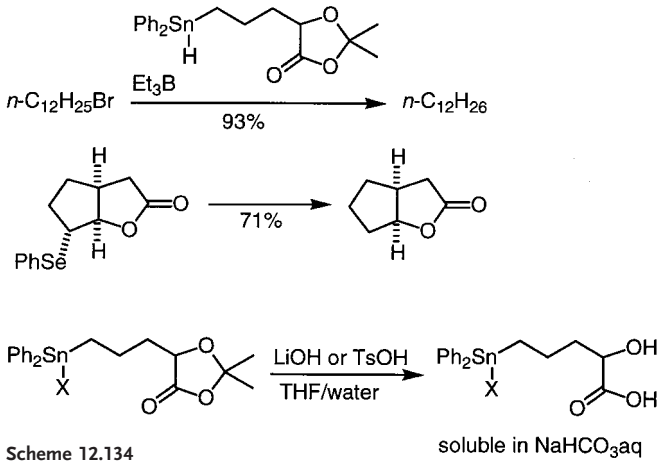
Scheme 12.132

A tin hydride attached to fluorous ponytails is quite versatile in respect of easy separation of the desired products from organotin compounds. When an iodoalkene was treated with $NaCNBH_3$ in the presence of a catalytic amount of fluoroalkyltin hydride, the desired tricyclic ketones were produced (Scheme 12.133) [240]. Application of the crude mixture to a small plug of fluorous reversed-phase silica gel enabled facile separation of the cyclic ketone obtained (fluorous solid-phase extraction, FSPE). In contrast, when tris(trimethylsilyl)silane (TTMSH) was employed as a hydride source chromatographic purification of the nonpolar and somewhat volatile products was impossible because of contamination by nonpolar silicon-containing byproducts.

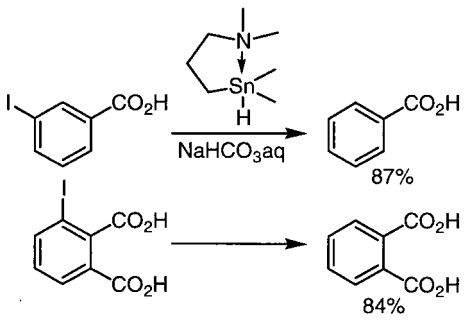


Scheme 12.133

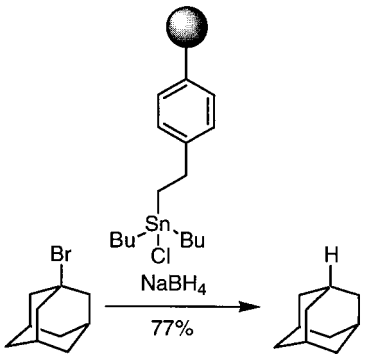
An organotin hydride which can be converted to a water-soluble form after use has been developed. An organotin hydride with a dioxolanone component reacted with organic halides, organoselenides, etc., with performance comparable with that of common organotin hydrides such as Bu_3SnH and Ph_3SnH. Subsequent mild hydrolysis (LiOH or TsOH in water/THF) converted the organotin compounds into base-soluble materials, and washing the crude mixture with $NaHCO_3$(aq) enabled removal of almost all the tin compounds (Scheme 12.134) [241]. Synthesis of a unique organotin hydride which is water-soluble and recyclable has been achieved. An organostannatrane hydride has been used to reduce iodobenzoic acid derivatives successfully in water without an initiator such as AIBN and Et_3B, forming the corresponding deiodinated products. The resulting organostannatrane halide was readily recycled by removal of water in vacuo (Scheme 12.135) [242]. A combination of poly-HIPE (high-internal-phase emulsion)-supported organotin hydride and $NaBH_4$ effected dehalogenation of alkyl bromide to prevent tin contamination and facilitate facile product separation (Scheme 12.136) [243].



Scheme 12.134



Scheme 12.135

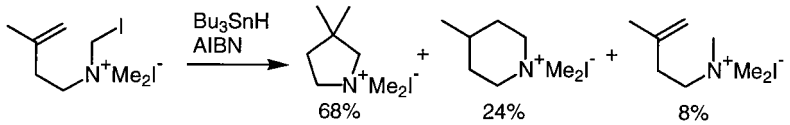


Scheme 12.136

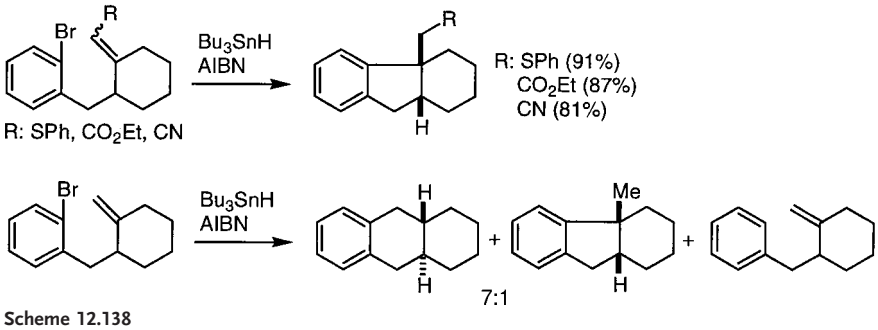
12.5.2
Free-radical C–C Bond Formation

Although various types of functional group transformations have been described in the proceeding section, these reactions frequently proceed with C–C bond formation [244]. Treatment of a 2-azoniaalkyl iodide with Bu_3SnH/AIBN led to the formation of an 8:3:1 mixture of 5-*exo*, 6-*endo* and acyclic ammonium salts by radical addition to a double bond (Scheme 12.137) [245]. Aryl radical cyclization to methylenecycloalkane bearing electron-withdrawing groups such as a phenylthio, an ester and a nitrile group at the terminus afforded exclusively *exo* cyclization products (Scheme 12.138) [246]. In sharp contrast to these results, on cyclization of bromomethylenecycloalkane without an electron-withdrawing group the 6-*endo* cyclization product was obtained perfectly, with a small quantity of 5-*exo* cyclization product [246]. Radical cyclization of sp^2 carbon on to an olefin attached to an electron-withdrawing group was employed in a total synthesis of (±)-merrilactone A [247]. This radical cyclization procedure is applicable both to alkynes and alkenes. When an acyclic iodoalkyne derived from D-glucose was subjected to the Bu_3SnH/AIBN cyclization procedure, the 7-*exo-dig* carbocyclization occurred whereas the cyclization of an iodoalkene derivative produced exclusively an 8-*endo-trig* product (Scheme 12.139) [248].

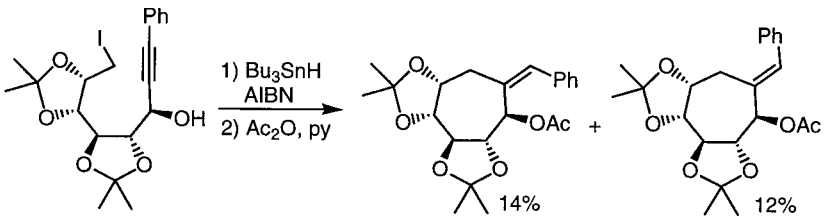
It has been reported that subjection of an 11-membered macrocycle involving an alkyne and alkenes to a radical cyclization procedure leads to a tandem cyclization giving rise to the formation of a fused 6,7-bicyclic framework [249]. It should be mentioned that the "in situ" methodology for generation of organotin hydride works



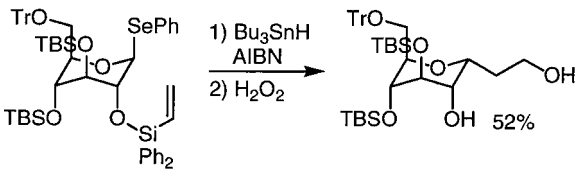
Scheme 12.137



Scheme 12.138



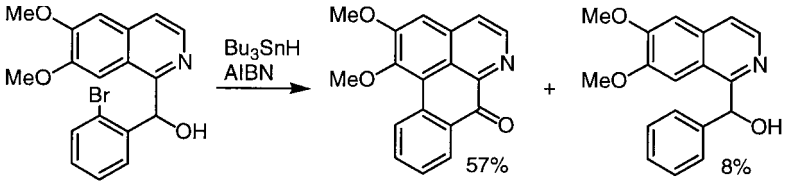
Scheme 12.139



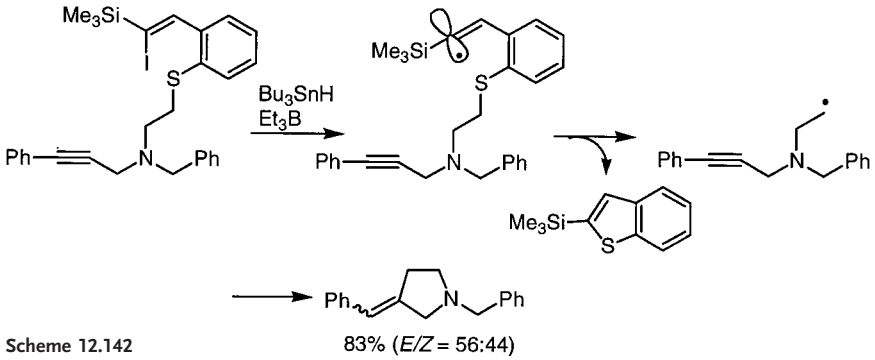
Scheme 12.140

well in radical cyclization of decalinic allylic alcohol [250] and propargyl ether derived from D-manno lactone [251]. The former procedure can prevent overreduction and improve the tedious work-up of the organotin compounds. A radical cyclization promoted by Bu_3SnH/AIBN was also useful for access to bicyclic sugars, whereas use of $Ph_4Si_2H_2$/AIBN greatly suppressed the formation of dehalogenated product [252]. A radical cyclization with a temporary connecting vinylsilyl tether on D-glucose followed by Tamao oxidation successfully gave access to a *C*-glycosidic product (Scheme 12.140) [253]. Radical cyclization is useful for C–C bond formation between sp^2 carbons to produce a biaryl compound (Scheme 12.141) [254].

Recently a new method for generation of carbon-centered radicals has been advanced by use of radical cyclization [255]. Treatment of *o*-[(*E*)-2-trimethylsilyl-2-iodovinyl]phenylthio derivatives with Bu_3SnH/Et_3B afforded the corresponding reduction product diagnostic of a facile formation of the desired radical (Scheme 12.142) [255].

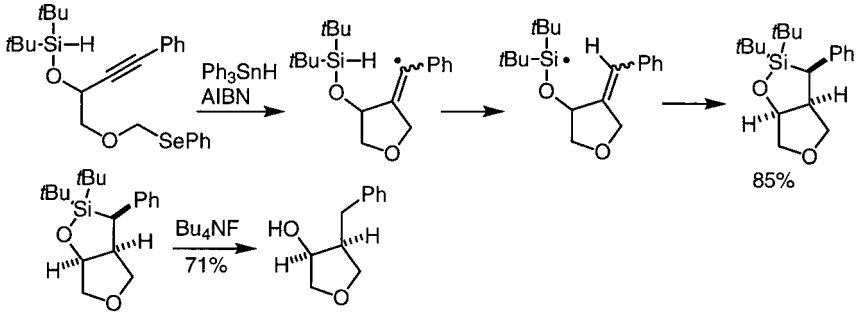


Scheme 12.141



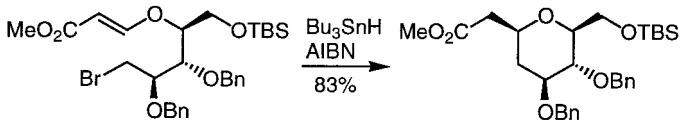
Scheme 12.142

On generation of a radical on propargyl hydrosilyl ether, a bicyclic compound was formed by sequential cyclization, 1,5-hydrogen transfer from silicon, and another cyclization (Scheme 12.143) [256]. This cyclization procedure proceeded leaving functional groups such as pyridine, Boc-N, and contiguous stereo centers untouched [256]. It has been reported that consecutive 1,5-hydrogen transfer and intermolecular C–C bond formation also proceeds smoothly [257].

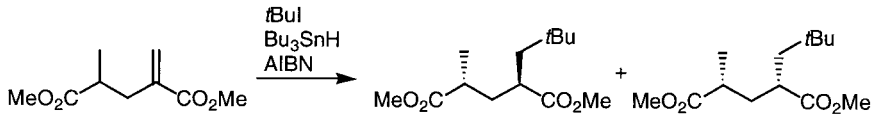


Scheme 12.143

Dehalogenative C–C bond formation is useful for construction of a tetrahydropyran array (Scheme 12.144) [258]. On treatment of a bromoenoate with Bu_3SnH/AIBN, the desired six-membered ring derivative was produced via intramolecular



Scheme 12.144



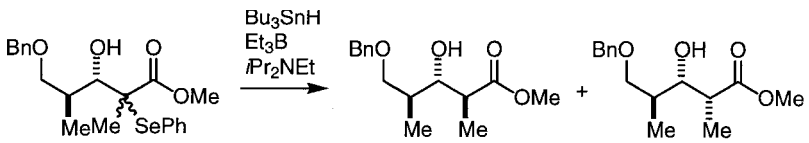
Lewis acid	yield (*anti/syn*)
none	81% (52:48)
$Sc(OTf)_3$	58% (1:99)
MgI_2	77% (2:98)

Scheme 12.145

radical Michael addition. C–C bond formation mediated by organotin hydrides undergoes stereoinduction by Lewis acid chelation on oxygen atoms. Although addition of an alkyl radical to an alkene then hydrogen transfer from Bu_3SnH yielded a mixture of diastereomeric products unselectively, addition of chelating Lewis acids such as $LiClO_4$, $Sc(OTf)_3$, and MgI_2 resulted in high stereoinduction (Scheme 12.145) [259]. Incorporation of alkyl substituents had a remarkable effect on the stereochemistry. When a bulky group, *tert*-butyl was employed, *syn* selectivity was observed whereas small substituents such as methyl and ethyl groups resulted in *anti* selectivity [259].

Addition of Lewis acid results in high diastereoselectivity in deselenidation performed by use of Bu_3SnH/Et_3B (Scheme 12.146) [260]. Addition of Lewis acid also improved diastereoselectivity in free radical-mediated intermolecular conjugate addition to a chiral *α,β*-unsaturated *N*-enoyl oxazolidinone (Scheme 12.147) [261].

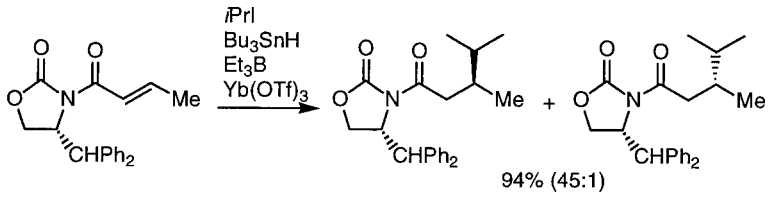
Taking advantage of this C–C bond-formation procedure followed by diastereoselective alkylation and lactonization gave rise to the formation of (–)-enterolactone (Scheme 12.148) [262]. In thorough research on factors affecting the relative stereochemistry at *β* and *γ* chiral centers, remarkable effects of Lewis acids on en-



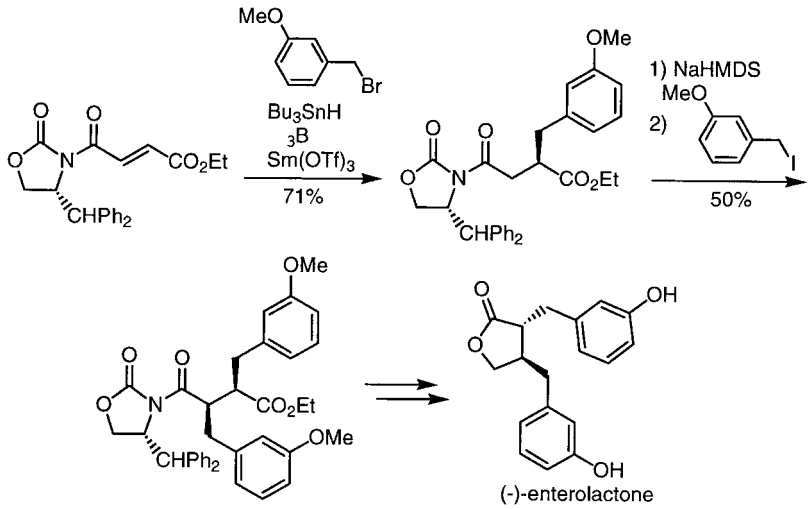
anti/syn (>20:1)
anti/syn (1:1.2)

Lewis acid	yield (*anti/syn*)
Bu_2BOTf	75% (>>20:1)
Et_2BOTf	65% (>>20:1)

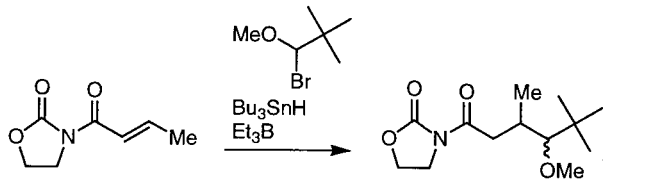
Scheme 12.146



Scheme 12.147



Scheme 12.148

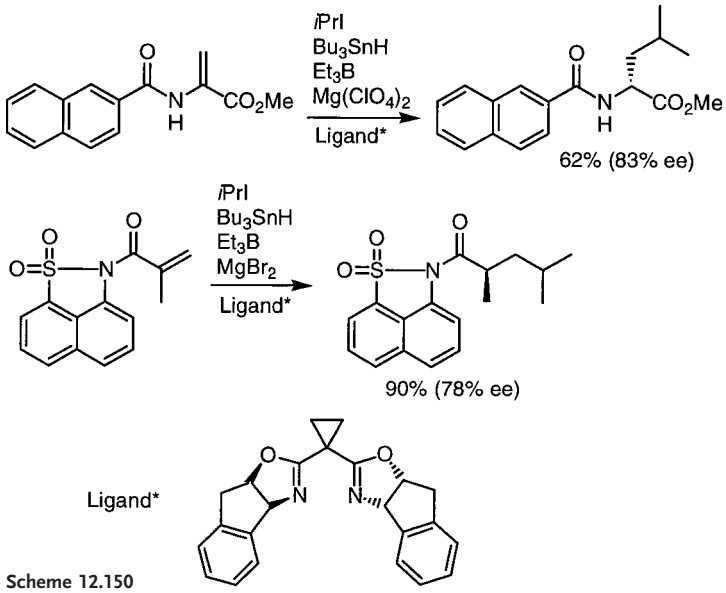


Lewis acid	yield (*syn/anti*)
none	10% (1:1)
$Yb(OTf)_3$	89% (6:1)
$Sm(OTf)_3$	90% (4:1)

Scheme 12.149

hancement of radical addition and on stereoselectivity were observed (Scheme 12.149) [263]. When a chiral Lewis acid was employed in this radical alkylation procedure high enantioselectivity was achieved (Scheme 12.150) [264].

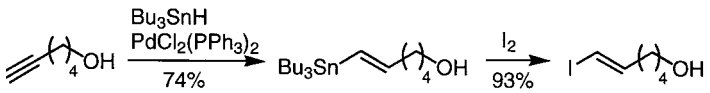
Hydrostannation is one of the most important transformations of functional groups. When subjected to hydrostannation, acetylenes and olefins are converted to vinylic- and alkylstannanes, respectively, and the resulting organostannanes can



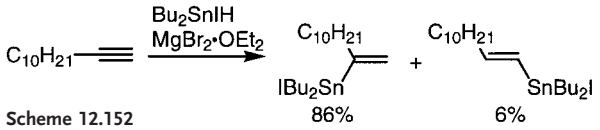
Scheme 12.150

be converted to other functions [265]. Because hydrostannation of acetylenes proceeds in a *syn* fashion to form a *trans* product stereoselectively, hydrostannation followed by tin–iodine exchange produces *trans* vinylic iodides (Scheme 12.151) [266]. In sharp contrast to conventional hydrostannation, it has been reported that $MgBr_2$-catalyzed hydrostannation of Bu_2SnIH on alkynes furnishes α adducts preferentially (Scheme 12.152) [267]. Acidic destannylation and ozonolysis of vinylic stannanes prepared by hydrostannation enabled access to *cis* olefins [268] and diols [269], respectively.

The resulting vinylic stannanes can be transformed to the corresponding vinylic lithium by tin–lithium exchange, and consecutive hydrostannation and tin–lithium exchange have been used in total syntheses of (±)-*iso*-caulerpenyne [270] and PGE_2-1,15-lactone [271]. Hydrostannation of alkyne followed by Migita-Kosugi-Stille coupling of the resulting vinylic stannane is quite a powerful tool for C–C

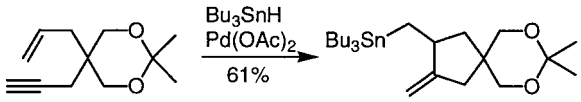


Scheme 12.151



Scheme 12.152

bond formation, as shown in Section 12.4. Concurrent hydrostannation and C–C bond formation are also versatile, as is tandem C–C bond formation leading to the formation of cyclized compounds. When treated with Bu_3SnH in the presence of a catalytic amount of palladium acetate, 1,6-enynes led to the formation of *exo*-methylenecyclopentanes with a tributylstannylmethyl group (Scheme 12.153) [272]. This procedure of cyclization by hydrostannation is applicable to the synthesis of a bicyclic β-lactam [273].



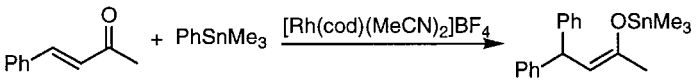
Scheme 12.153

Concurrent hydrostannation and addition of the resulting vinylic radical to a carbonyl have also been exploited in the synthesis of (+)-quercitol derivatives [274] and the carbocyclic core of CP-263,114 [275].

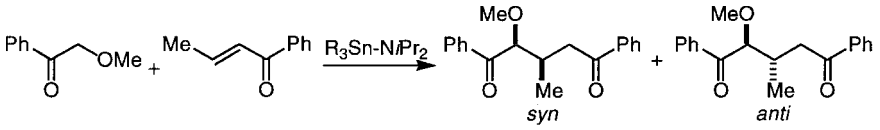
12.6 Organotin Enolate

Organotin(IV) enolates are a versatile means of mild and selective C–C bond formation [276], and several methods have been advanced for access to organotin enolates [277]. Concurrent formation of a C–C bond and organotin enolate by Michael addition have recently been reported (Scheme 12.154) [278]. Organotin enolates have characteristic stereoselectivity – the stereoselectivity in the aldol reaction [279] and in Michael addition can be tuned facilely by changing substituents on tin [280]. When a tributyltin enolate, prepared in situ from the corresponding ketone and $Bu_3SnNiPr_2$, was reacted with an enone, 1,4-addition proceeded regio- and stereoselectively to afford the *anti* adduct as a sole product (Scheme 12.155). In contrast, substitution on tin with chloride enhanced *syn* selectivity, and Cl_2BuSn enolate resulted in 91 : 9 selectivity of *syn*/*anti* isomers.

The nucleophilicity of organotin enolate can be enhanced by addition of appropriate ligands which coordinate with the organotin d-orbital to form a five-coordinated organotin enolate. Loading with Bu_4NF substantially accelerated a reaction between an organotin enolate and a nitroalkene to furnish the corresponding Michael addition product (Scheme 12.156) [281]. Lewis acids can significantly promote addition

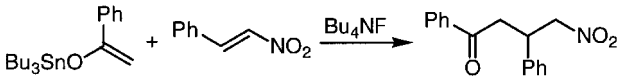


Scheme 12.154



tin amide	yield (*syn/anti*)
Bu_3Sn-N*i*Pr_2	64% (0:100)
Cl_2BuSn-N*i*Pr_2	84% (91:9)

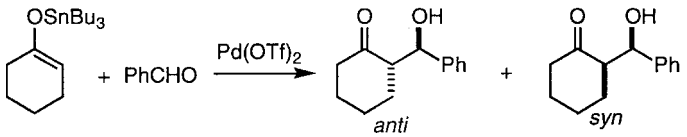
Scheme 12.155



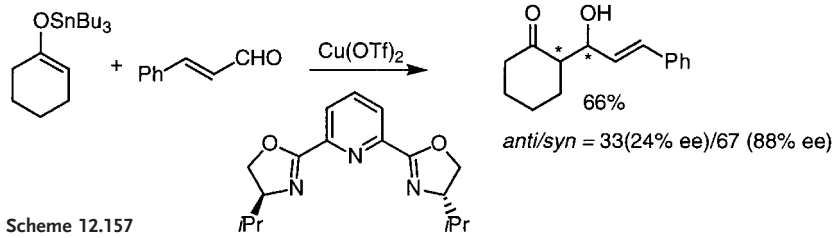
94%

Scheme 12.156

of organotin enolates to aldehydes. A tributyltin enolate of cyclohexanone reacted smoothly with benzaldehyde in the presence of metal triflates as Lewis acids, and when $Pd(OTf)_2$ was added the reaction resulted in remarkably high *anti* stereoselectivity. In contrast with this result, combination of (*S,S*)-*i*Pr-pybox and $Cu(OTf)_2$ resulted in *syn* selectivity, enabling high enantioselectivity (Scheme 12.157) [282].



77% (92:8)

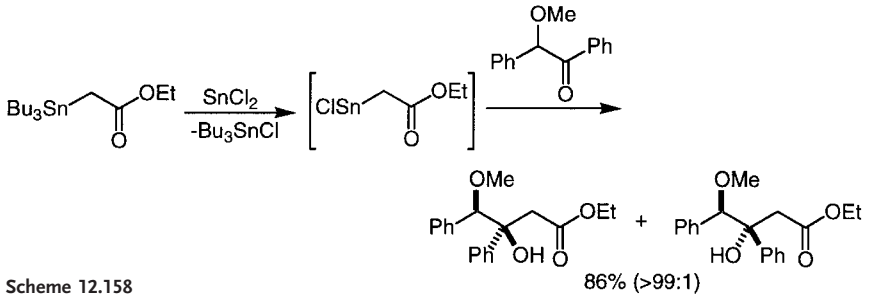


anti/syn = 33(24% ee)/67 (88% ee)

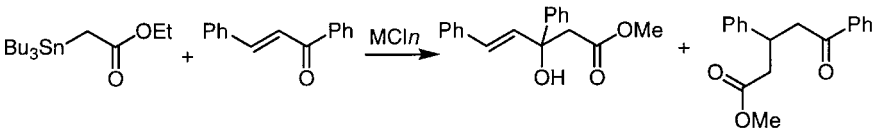
Scheme 12.157

It has been observed that *α*-silyl-*α*-stannylacetate serves as a nucleophile in the same way as stannyl enolate in the presence of a Lewis acid [283]. When an *α*-stannyl ester was reacted with *α*-alkoxyaldehydes in the presence of $SnCl_2$, enolate addition was successfully achieved in good yields and with high stereoselectivity (Scheme 12.158) [284]. This $SnCl_2$ activation of an *α*-stannyl ester is applicable to Michael addition. Use of Me_3SiCl as catalyst results in complete the opposite regioselectivity (Scheme 12.159) [285]. The mechanisms of these reactions are unclear, but it is assumed that an active species, chlorinated stannous ester, is generated by trans-

metalation between an organotin enolate and a metal chloride. Organotin enolates are useful as precursors of chlorosilyl enolates, which are activated by addition of chiral phosphoramides to afford enantioselectivity in reactions with aldehydes [286]. Organotin enolates can be used for C–C bond formation under free-radical conditions. When a stannyl enolate was reacted with alkyl halides in the presence of AIBN the desired alkylation proceeded efficiently; this procedure is applicable to three-component coupling of a stannyl enolate, alkenes, and alkyl halides (Scheme 12.160) [287]. This C–C bond-formation procedure mediated by AIBN can achieve cyclization in the reaction of enyne with a tin enolate (Scheme 12.161) [288].



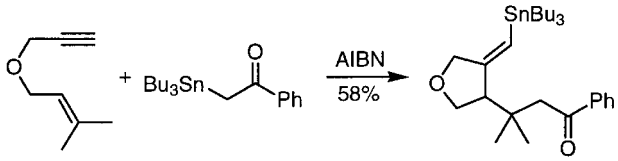
Scheme 12.158



MCl*n*	yield (1,2/1,4)
$SnCl_2$	63% (>99:1)
Me_3SiCl	95% (<1:99)

Scheme 12.159

Scheme 12.160

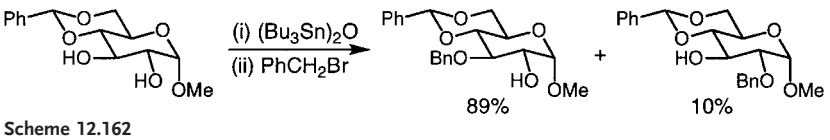


Scheme 12.161

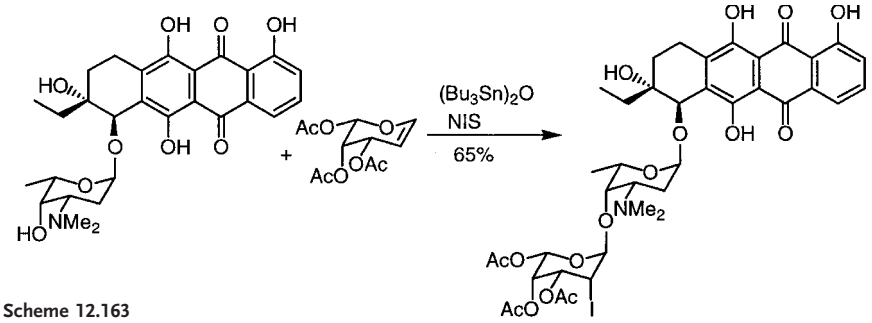
12.7
Organotin Alkoxides and Halides

12.7.1
Utilization of Sn–O Bonds in Synthetic Organic Chemistry

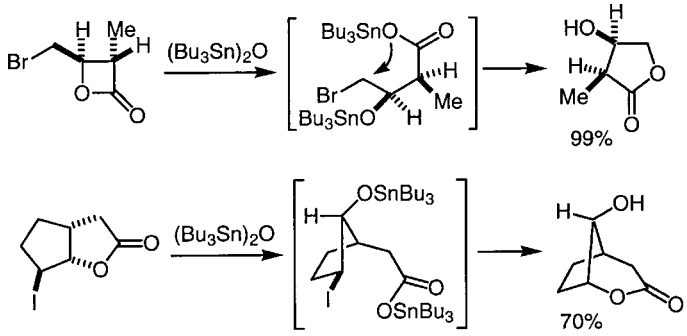
Tin–oxygen bonds are quite useful in preparative organic chemistry because the Sn–O bond can react with a variety of electrophiles, e.g. alkyl and acyl halides, under mild reaction conditions giving rise to new C–O bond formation. The organotin alkoxides needed can be prepared easily by reaction of alcohol, carboxylic acid, or ester with commercially available $(Bu_3Sn)_2O$, R_2SnO, or R_3SnOMe. Although the oxygen nucleophiles in organotin alkoxides are more reactive than the starting materials, it should be noted that a variety of functional groups can survive these transformations, because of the mild reaction conditions used. The synthetic utility of organotin alkoxides has been reviewed [289]. For example, when methyl 4,6-*O*-benzylidene-*α*-D-glucopyranoside was treated consecutively with $(Bu_3Sn)_2O$ and benzyl bromide, the 2-*O*-benzyl ether was obtained regioselectively in high yield (Scheme 12.162) [290]. The increased nucleophilicity of organotin-substituted oxygen derivatives is useful in glycosylation, and deoxyiodo disaccharides were obtained from treatment of glycal with a variety of organotin alkoxides in the presence of *N*-iodosuccinimide (Scheme 12.163) [291]. When halo lactones were treated with bis(tributyltin)oxide, ring expansion occurred, furnishing hydroxy lactones in good yields (Scheme 12.164) [292]. Use of an *α,β-trans*-substituted *β*-lactone gave rise to the formation of an *α-cis*-substituted *β*-hydroxy-*γ*-lactone, and a bicyclic compound was also transformed to the corresponding bicyclic lactone. This lactonization methodology is applicable to epimerization of the C_4-stereogenic center of iodolactones (Scheme 12.165) [293]. This reaction involves two



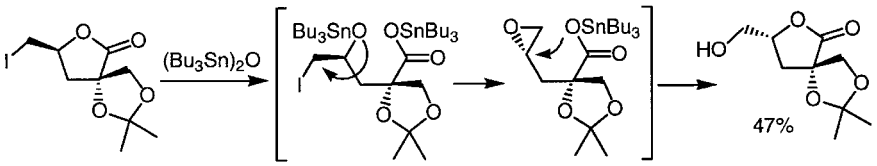
Scheme 12.162



Scheme 12.163



Scheme 12.164

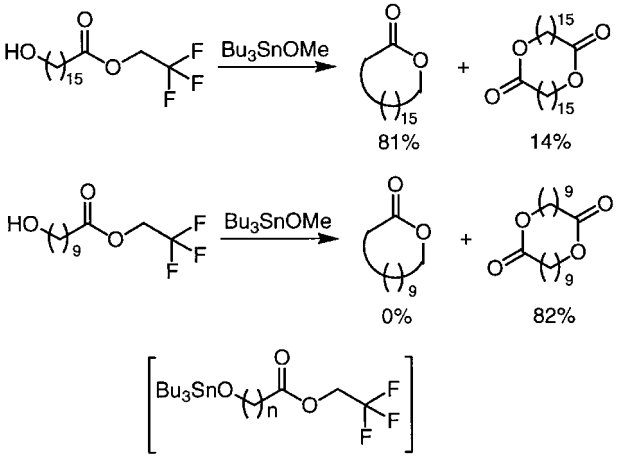


Scheme 12.165

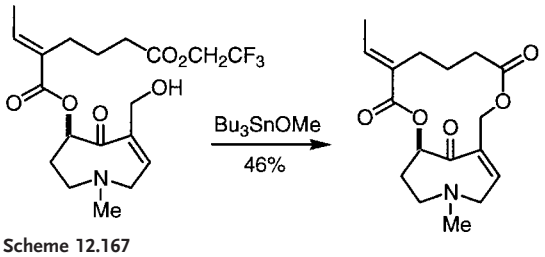
types of C–O bond formation in consecutive epoxidation and lactonization induced by nucleophilic substitution with organotin alkoxide and carboxylate. The lactonization occurred via 5-*exo* ring enclosure, and the δ-lactone produced by 6-*endo* ring closure was not obtained.

Although Bu_2SnO is a powerful catalyst for cyclization of ω-hydroxy and ω-amino carboxylic acids [294], treatment of ω-hydroxy trifluoroethyl esters with Bu_3SnOMe catalysis resulted in macrolactonization and/or diolide formation in different ratios, depending on chain lengths and reaction conditions (Scheme 12.166) [295]. In this reaction inter- and/or intramolecular transesterification occurred between trifluoroethyl esters and alkoxytrialkyltin generated by rapid exchange of the alkoxytin catalyst with the terminal alcohol. By use of this procedure as a final key step a 12-membered macrocyclic otonecine diester was obtained (Scheme 12.167) [296].

Diastereoselective functionalization of hydroxy groups in polyols has been of great importance in organic chemistry. Since it was disclosed that stannylene acetals undergo monofunctionalization on selective activation of the primary hydroxy group [297], the chemistry of stannylene acetal has been extensively developed and is well documented [289, 298]. The useful species, stannylene acetals, are easily accessible by treatment of diols with stoichiometric amounts of Bu_2SnO or $Bu_2Sn(OMe)_2$ with azeotropic removal of water or MeOH. The resulting stannylene acetals react with a variety of electrophiles to provide the corresponding product [299]. It has been reported that formation of stannylene acetals from polyols can be accelerated by microwave heating [300]. It was recently revealed that a catalytic amount of tin reagents such as Bu_2SnO, $Bu_2Sn(OMe)_2$ [301] and Me_2SnCl_2 [302] can activate hydroxy groups in the presence of a base to provide the corre-

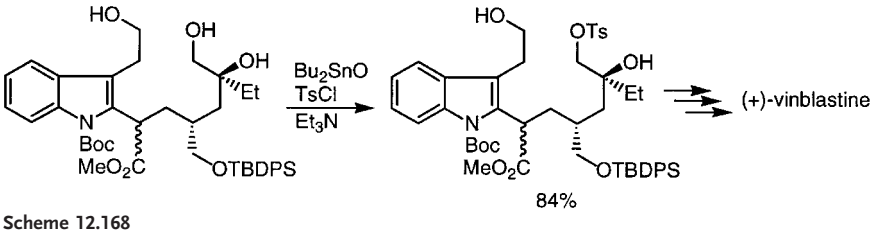


Scheme 12.166



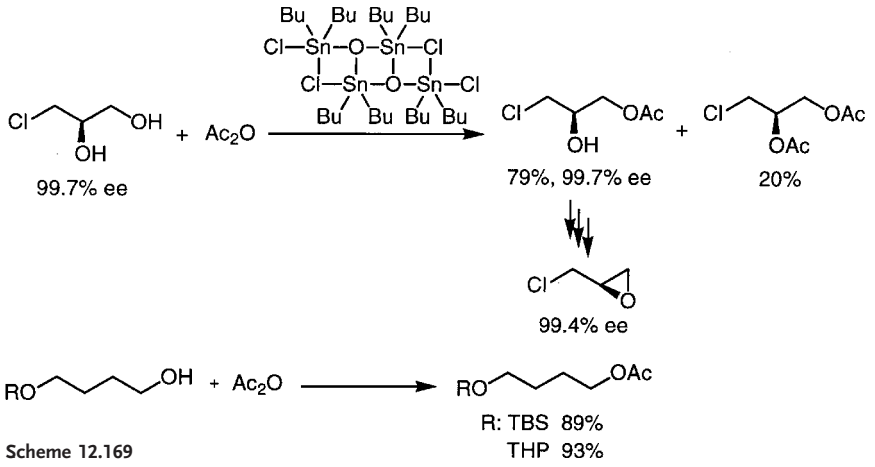
Scheme 12.167

sponding products with regioselectivity similar to those of stoichiometric versions of the reaction. Fluoroalkyltin oxide also effected regioselective sulfonylation of polyols and, after the reaction, the tin oxide was recovered by fluorous biphase technology [303]. The fluorotin oxide can, in the same way as the dibutyltin derivatives, be used catalytically. The monofunctionalization procedure via stannylene acetal was applied in a total synthesis of (+)-vinblastine in which the primary alcohol of a 1,2-diol was regioselectively tosylated under the influence of dibutyltin oxide (Scheme 12.168) [304].



Scheme 12.168

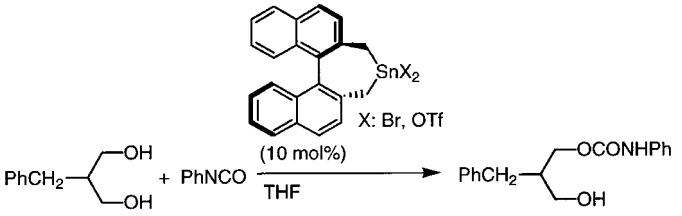
1,3-Disubstituted tetraalkyldistannoxanes with a dimeric structure are mild Lewis acids that can promote a variety of carbonyl transformations under extremely mild reaction conditions [305]. The distannoxane can effect selective acetylation of a primary alcohol in the reaction of enantiomerically pure 3-chloropropan-1,2-diol with acetic anhydride (Scheme 12.169) [306]. The distannoxane/Ac_2O procedure is effective for acetylation of alcohols with acid-labile functional groups, providing the corresponding acetates in good yields (Scheme 12.169) [307]. It has been reported that cationic organotin clusters such as $[Bu_2Sn(OH)(H_2O)]_2^{2+} \cdot 2\,TfO^-$ and $[(BuSn)_{12}O_{14}(OH)_6]^{2+} \cdot 2\,Cl^- \cdot 2\,H_2O$ promote efficient acetylation of alcohols with acetyl anhydride, and their activity is far higher than that of the corresponding neutral organotin compounds [307b]. Cationic organotin dimers are extremely active in acetylation and a loading of 0.001 mol% of this organotin catalyst was sufficient for quantitative acetylation. Although the cationic Sn_{12} cluster was slightly less active than the organotin dimer, high chemoselectivity was realized – an acid-labile alcohol with TBS-ether and geraniol could be successfully acetylated with Ac_2O under the influence of this Sn_{12} cluster; discriminative acetylation was also feasible in competitive reaction of primary and secondary alcohols with Ac_2O.



Scheme 12.169

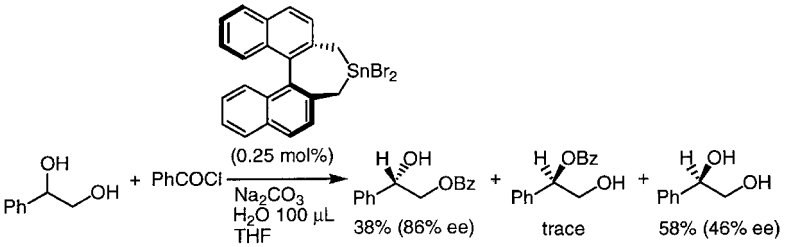
In chiral organotin dibromide- and bistriflate-catalyzed desymmetrization of 2-substituted 1,3-propandiols with phenyl isocyanate the enantiomeric excess of the product was uniquely dependent on the reaction temperature. The chirality of the product was inverted from one enantiomer to another upon changing the reaction temperature from 0 to –78 °C (Scheme 12.170) [308]. When, on the other hand, this nonracemic organotin dihalide was employed as a catalyst for benzoylation of racemic 1,2-diols, nonenzymatic kinetic resolution was achieved under sophisticated reaction conditions (Scheme 12.171) [309].

Dibutyltin oxide-promoted formation of dioxanones by reaction of optically active diols with *t*-butyl bromoacetate was utilized successfully for access to KDO, a



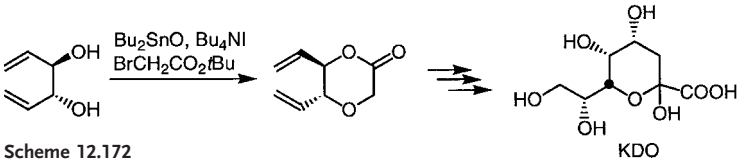
X	reaction temp	yield	%ee
TfO	0 °C	85%	(*S*) 32%ee
TfO	-78 °C	37%	(*R*) 24%ee

Scheme 12.170



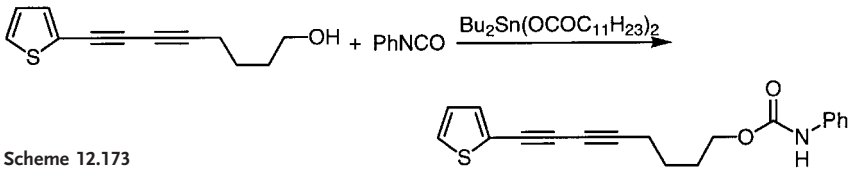
Scheme 12.171

key component of the cell-wall lipopolysaccharide (LPS) of Gram-negative bacteria (Scheme 12.172) [310]. In this cyclization procedure no decrease in enantiopurity was observed.



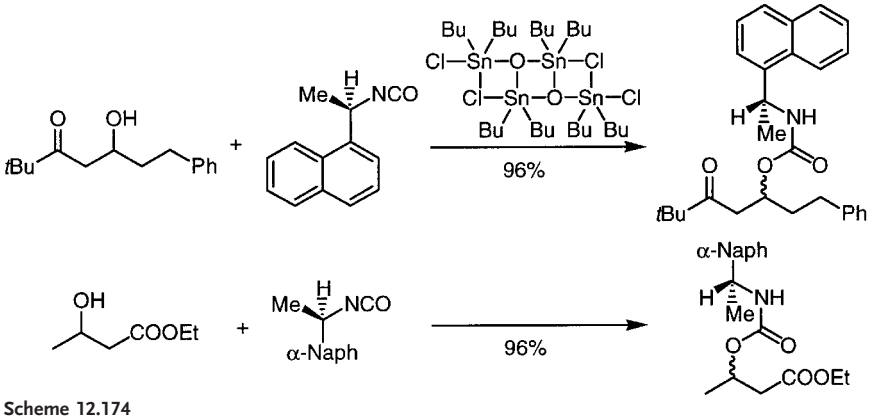
Scheme 12.172

It has been recognized that organotin compounds such as $Bu_2Sn(OAc)_2$ [311] and dibutyltin dilaurate [312] are excellent catalysts in the reaction of alcohols with isocyanates. Dibutyltin dilaurate can activate *N*-nucleophiles and alcohols [313], and bis(tributyl)tin oxide catalyzes the reaction with isothiocyanate to give the corresponding thionocarbamate [314]. It is noteworthy that organotin-catalyzed coupling between alcohols and isocyanates proceeds under mild conditions, and thus this coupling procedure is suitable for an acid-labile alcohol with a π-conjugated backbone. On treatment with phenylisocyanate in the presence of dibutyltin dilaurate, the alcohol-bearing thienylbutadiyne was smoothly converted to the corresponding carbamate, which was subsequently subjected to solid-state polymerization to give a polydiacetylene with third-order nonlinear optical properties (Scheme 12.173) [315].



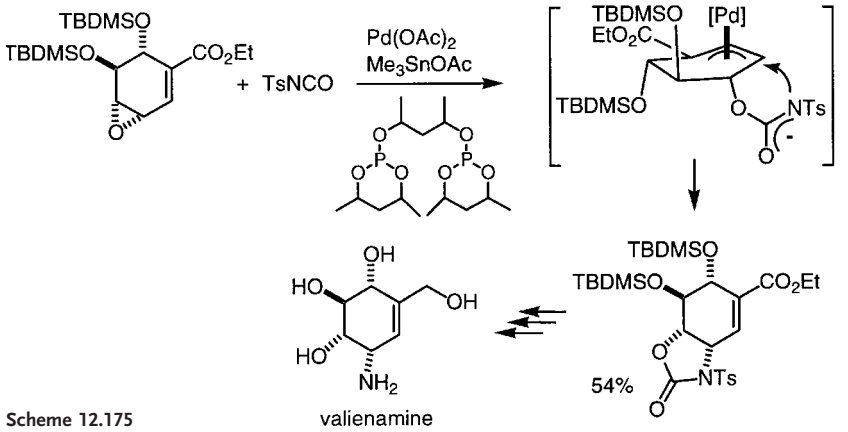
Scheme 12.173

Combination of a nonracemic isocyanate and a 1,3-disubstituted distannoxane has provided a new method for determination of the optical purity of chiral alcohols (Scheme 12.174) [316]. When a chiral alcohol was reacted with commercially available (*R*)-1-(1-naphthyl)ethyl isocyanate in the presence of 1,3-disubstituted distannoxane, formation of the desired carbamates occurred rapidly, with acid-labile functional groups such as ester, THP and *β*-hydroxyketone remaining intact. Subsequent HPLC analysis of the resulting carbamate revealed a pair of well-separated peaks of diastereomers derived from both enantiomeric alcohols.



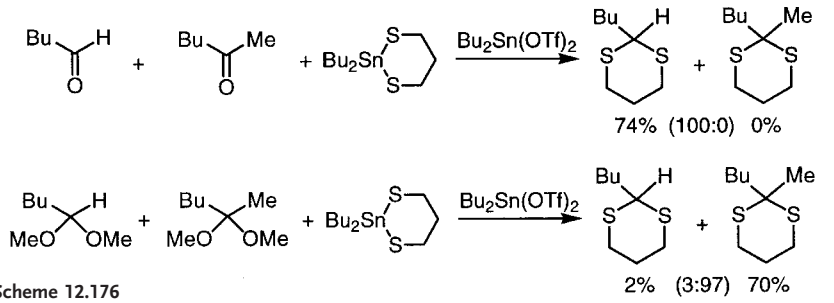
Scheme 12.174

Cyclic ethers [317] and lactones [318] are used as oxygen nucleophile components in reactions with isocyanates, producing the corresponding carbamates in good yield. A procedure for formation of cyclic carbamates by use of 2-aminoethanol and carbon dioxide in the presence of Bu_2SnO was recently reported [319]. Significantly, use of trimethyltin acetate as an additive in palladium-catalyzed coupling of vinyl epoxide and isocyanates enables regioselective formation of the cyclic carbamate whereas addition of a Brønsted acid (*p*-TsOH) instead of the organotin additive led to a carbonate derivative as the major product, indicative of preferential cyclization of the *O*-nucleophile (Scheme 12.175) [320]. The cyclic carbamate obtained was successively converted to (±)-valienamine. When an optically active vinyl epoxide was employed as starting compound, (+)-valienamine was accessible in the same sequence as used for the racemate.



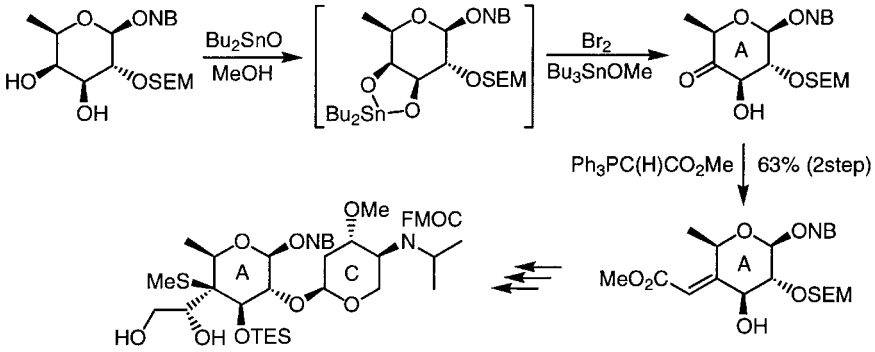
Scheme 12.175

Thiostannane can work as an S-nucleophile in the presence of a Lewis acid [321]. Thiostannanes are also useful in thioacetalization (Scheme 12.176) [322] and thioglycosidation [323] promoted in combination with the mild Lewis acid $Bu_2Sn(OTf)_2$. Differentiated thioacetalization has been achieved in competition reactions between carbonyls, acetals, and a carbonyl and an acetal. Thioglycosidation of acetyl and methyl glycosides proceeds smoothly under the influence of $Bu_2Sn(OTf)_2$, giving rise to almost identical stereochemistry irrespective of solvent polarity. This procedure is applicable to selenoglycosidation also [323].



Scheme 12.176

Trialkyltin alkoxides prepared by evacuation of methanol from a mixture of an alcohol and trialkyltin methoxide are easily oxidized by bromine in the presence of trialkyltin alkoxide as HBr scavenger, producing the desired aldehyde and ketone efficiently [324]. This oxidation is more feasible on organotin alkoxides derived from secondary alcohols than those from primary alcohols, and enables regioselective oxidation of polyols [325]. The regioselectivity in oxidation of vicinal secondary alcohols was also examined [326], and the empirical informative results were invoked for access to namenamicin A–C disaccharides (Scheme 12.177) [327].

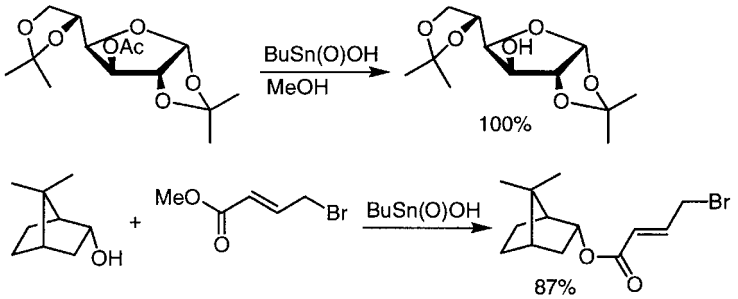


Scheme 12.177

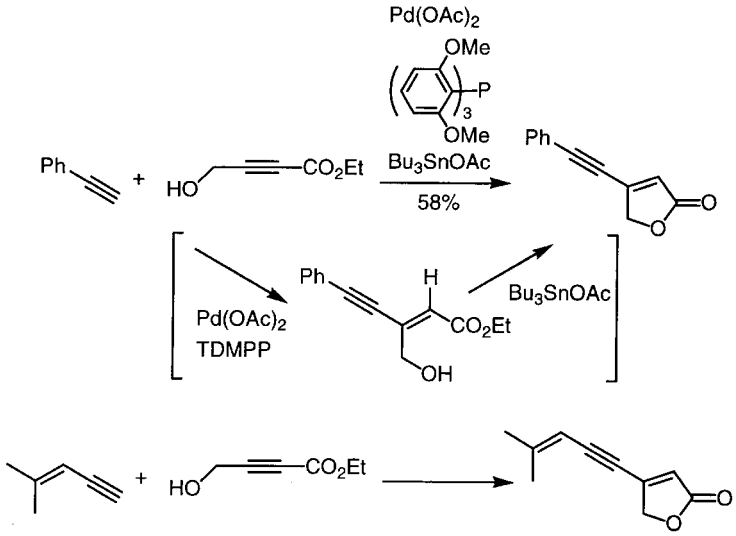
12.7.2
Transesterification

Transesterification is a fundamental functional group transformation widely used in synthetic organic chemistry [328]. It is well-recognized that organotin compounds can promote transesterification efficiently under the mild reaction conditions which enable a variety of functional groups to survive. Because of these attractive features, new procedures for transesterification mediated by organotin have been still extensively sought [329]. It has, for example, recently been shown that butylstannoic acid can serve as an excellent transesterification catalyst in the presence of diverse functions such as *β*-lactam, *α,β*-unsaturated ester, peptide, acetal, and halide (Scheme 12.178) [330]. Transesterification promoted by organotin can be performed in parallel with palladium-catalyzed C–C bond-forming reactions (Scheme 12.179) [331]. This procedure enabled access to cleviolide which is difficult to obtain from natural resources. The organotin-catalyzed cyclization was useful for construction of pyrrolinones which was not accessible under conventional basic conditions (Scheme 12.180) [332].

It has been disclosed that 1,3-disubstituted tetraalkyldistannoxanes are extremely effective catalysts for transesterifications of carboxylic esters in which secondary

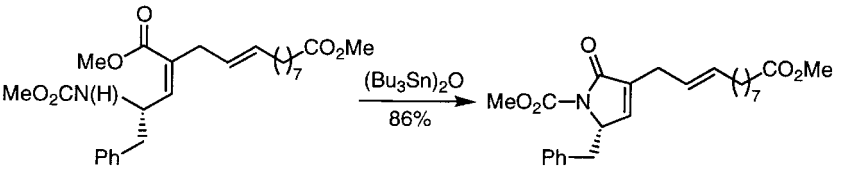


Scheme 12.178



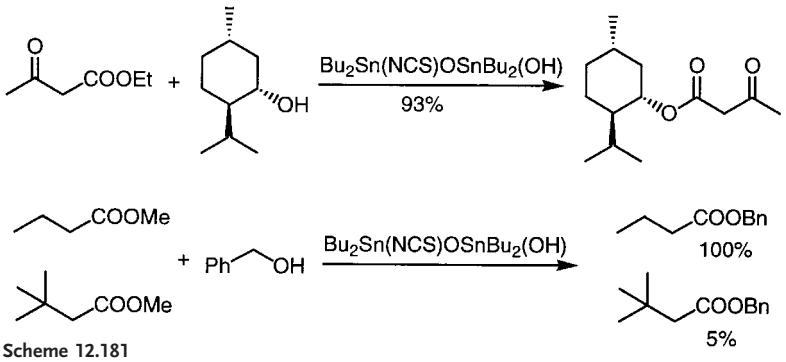
Scheme 12.179

cleviolide

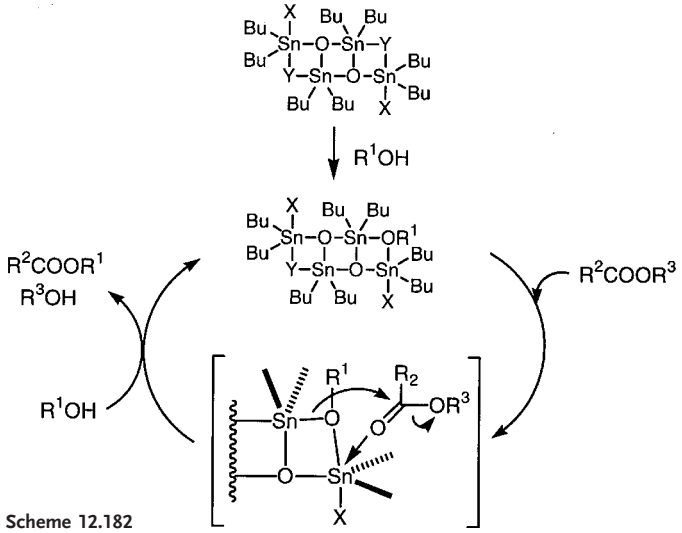


Scheme 12.180

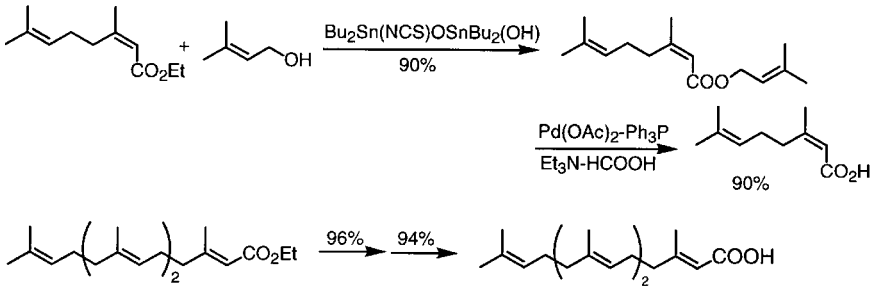
alcohols were employable; the reaction proceeded sluggishly with sterically demanding esters (Scheme 12.181) [333]. The 1,3-disubstituted tetraalkyldistannoxane adopts a dimeric ladder structure which, presumably, accelerates transesterification through the template effect with two tin atoms working synergistically (Scheme 12.182). Transesterification occurred under essentially neutral conditions, enabling a variety of functional groups to remain intact. Because of these novel advantages distannoxanes have been applied to a variety of organic syntheses. Transesterification of α,β-unsaturated esters with prenol furnished the corresponding prenyl esters in good yield without detectable isomerization of the double bonds, and palladium-catalyzed deprotection of the resulting allyl ester provided α,β-unsaturated carboxylic acids (Scheme 12.183) [333a]. The synthetic utility of transesterification promoted by use of 1,3-disubstituted distannoxane has been exemplified by syntheses of brefeldin derivatives [334], (–)-colletol [335] and bicyclic lactones [336]. In the synthesis of (–)-roccellaric acid, transesterification by 1,3-diisothiocyanato distannoxane played a pivotal role in the liberation of cyclopropyl alcohol followed by retroaldol ring opening and lactonization to furnish a key precursor for access to (–)-roccellaric acid (Scheme 12.184) [337].



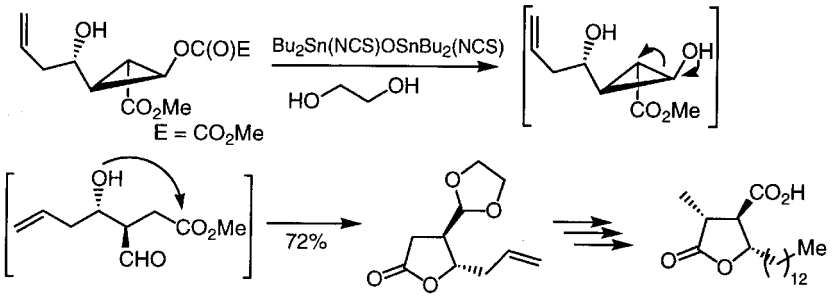
Scheme 12.181



Scheme 12.182

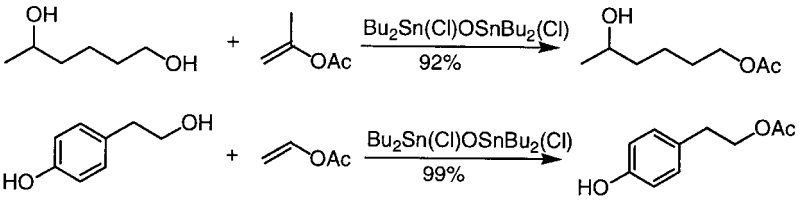


Scheme 12.183



Scheme 12.184

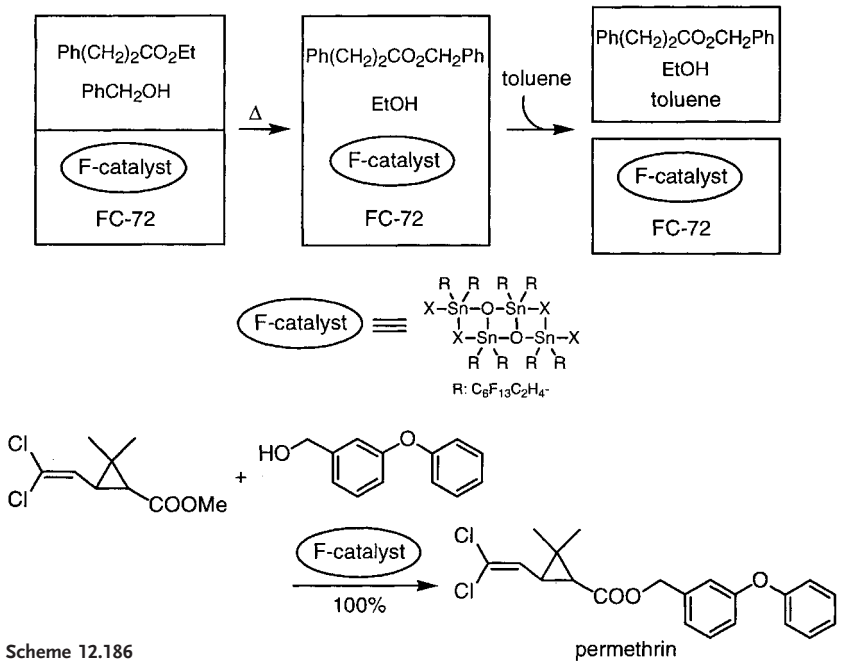
In transesterification it is difficult to achieve high conversion because of the reversibility of the reaction. This drawback is overcome by employing enol esters such as vinyl and isopropenyl acetates. On transesterification these enol esters are converted to acetaldehyde and acetone, respectively, and removed from the equilibrium enabling irreversible acylation (Scheme 12.185) [307a, 338]. This procedure enables preferential acylation of primary alcohols to secondary alcohols and phenols.



Scheme 12.185

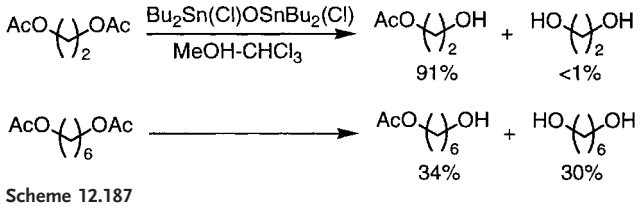
Although the distannoxanes are easily separable from organic compounds by column chromatography or distillation, irrespective of their high solubility in organic solvents, incorporation of fluoroalkyl pendants enabled much easier separation and re-use of fluoroalkyltin catalysts by use of fluorous biphase technology, giving rise to convenient and practical transesterification (Scheme 12.186) [339]. When an ester derived from volatile alcohol was employed in this procedure, transesterification proceeded perfectly even by use of 1:1 ratio of ester and alcohol to afford the desired ester in quantitative yield. The synthesis of the pyrethroid permethrin was performed successfully by use of this procedure.

It has been reported that the distannoxanes can also promote transformation of the carbonyl function, e.g. esterification [333b], lactonization [340a], polymerization [340b,c], acetalization [341], deacetalization [342], and desilylation [342] as well as transesterification, and in each reaction the mild conditions enable survival of a variety of acid-labile functions. With recourse to organotin-catalyzed transesterification, a variant of deacylation can be performed under mild conditions while conventional deacylation demands acidic or basic conditions. When 1,*n*-diol diacetate was treated



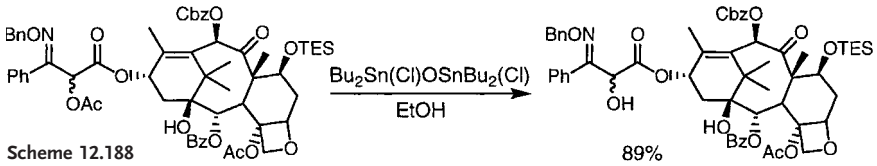
Scheme 12.186

with methanol in the presence of 1,3-disubstituted distannoxane the desired deacylation occurred to give the monoacetate or liberated diol depending on n. When $n<5$, formation of the monoacetate was favored whereas use of the diacetate with $n\geq5$ gave a mixture of monoacetate and free diol (Scheme 12.187) [343].

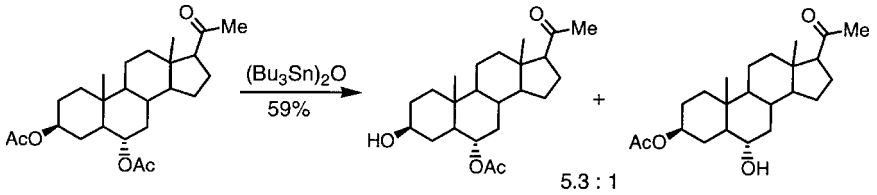


Scheme 12.187

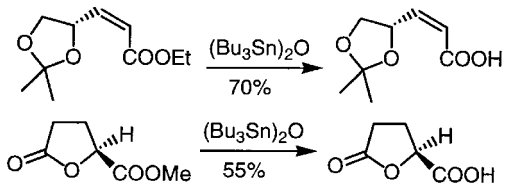
In the semisynthesis of paclitaxel from the 10-deacetylbaccatin III derivative, 1,3-disubstituted distannoxane-mediated deacetylation played a pivotal role, giving rise to the formation of the desired secondary alcohol even in the presence of several functional groups (Scheme 12.188) [344]. Bis(tributyltin)oxide [329] and 1,3-disubstituted distannoxane are excellent deacylation catalysts, and the synthetic utility of bis(tributyltin)oxide has been revealed in regio- [345] and chemoselective deacylation (Schemes 12.189 and 12.190) [346].

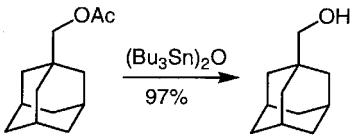


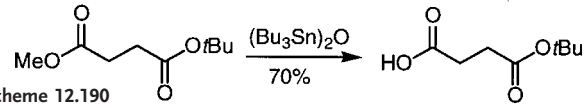
Scheme 12.188



Scheme 12.189



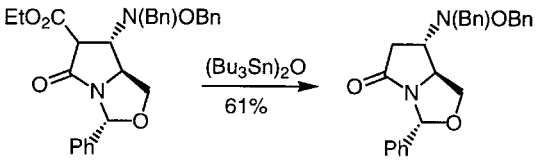




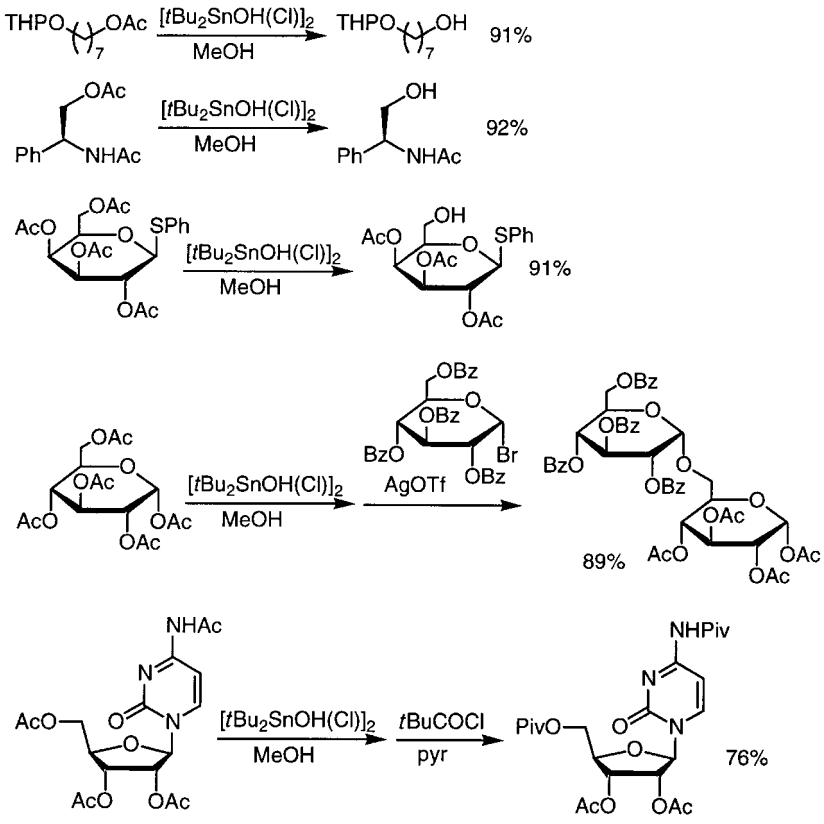
Scheme 12.190

This procedure enabled versatile hydrolysis of pyrrolidinones followed by decarboxylation (Scheme 12.191) [347]. It has been disclosed that a neutral organotin dimer $[t\mathrm{Bu_2SnOH(Cl)}]_2$ is an efficient catalyst for deacetylation (Scheme 12.192) [348]. When an MeOH solution of an acetate was heated at 30 °C in the presence of a catalytic amount of the organotin dimer deacetylation proceeded quite smoothly to furnish the parent alcohol, in which a variety of acid-labile functional groups remained intact. Acetates of primary alcohols and phenols underwent rapid deacetylation whereas acetates of secondary alcohols reacted only sluggishly. When this deacetylation procedure was applied to acetates derived from tertiary alcohols they remained intact, and decomposed under harsher conditions. When nonracemic acetates derived from chiral alcohols and aminoalcohols were treated with $[t\mathrm{Bu_2SnOH(Cl)}]_2$ in MeOH, the desired deacetylation proceeded, and no racemization was observed. Exclusive deacetylation of primary alcohols in the reaction of peracetates of carbohy-

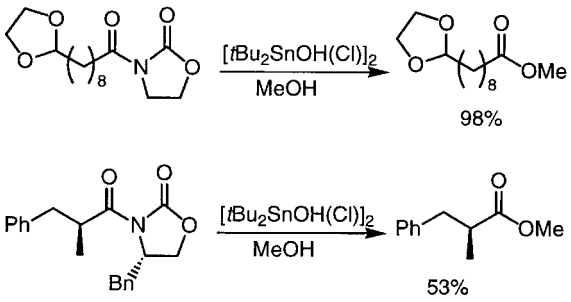
drates and nucleosides attests to the chemoselectivity of this deacetylation procedure. The resulting crude deacetylated products can be subjected to the subsequent acylation or glycosylation. This procedure is applicable to transesterification of *N*-acyl oxazolidinones, affording the corresponding esters (Scheme 12.193) [349]. When this transesterification was promoted by $[t\mathrm{Bu_2SnOH(Cl)}]_2$ acid-labile functional groups such as acetal and silyl ether remained intact, and no racemization or epimerization was observed; in $\mathrm{Sc(OTf)_3}$-catalyzed transesterification, however, subsidiary transformation, e.g. acetal exchange to dimethyl acetal and desilylation providing the parent alcohol, was unavoidable.



Scheme 12.191



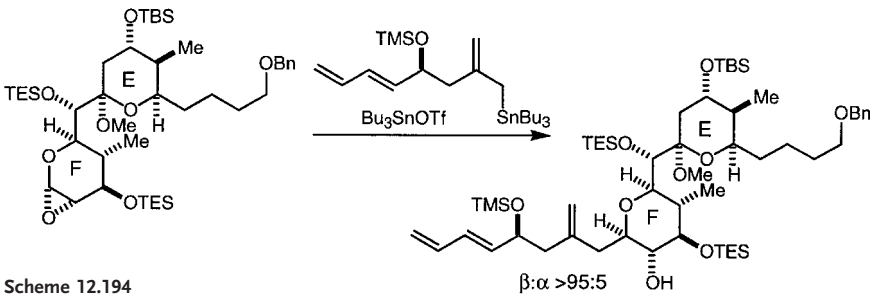
Scheme 12.192



Scheme 12.193

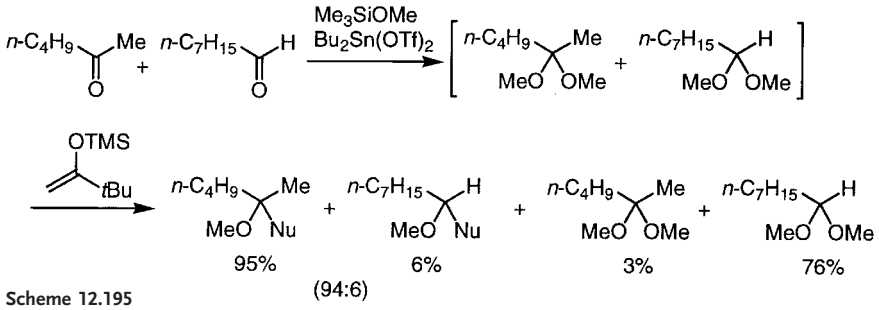
12.7.3
Organotin in Lewis Acids

Organotin compounds R_nSnX_{4-n} (where X is an electron-withdrawing group) and $SnCl_4$ are known to be efficient Lewis acids. The Lewis acidity of $SnCl_4$ and several organotin halides has been assessed by virtue of frequency shift of triphenylphosphine oxide, and it has been shown that the Lewis acidity of the tin increases in proportion to the number of electron-withdrawing group X [8]. As shown in the previous section, organotins act as excellent catalysts of a variety of carbonyl transformations. The mild Lewis acidity of organotins enables versatile transformation of other functionality. Dehydration between amine and carbonyl proceeds smoothly under the influence of Bu_2SnCl_2 leaving other functional groups intact [350]. Although organotin halides are useful, because of their stability in air and mild reactivity, they are not sufficiently acidic to trigger synthetically useful reactions such as C–C bond formation. Precedents of C–C bond formation by use of catalytic amounts of organotin halides involve transmetalation, producing reactive allyltin derivatives [351]. Incorporation of strong electron-withdrawing groups such as triflate [352, 353] and perchlorate [354, 355], instead of halide, substantially enhances the Lewis acidity, however, enabling C–C bond formation. Although tributyltin triflate catalyzes coupling between thioacetals and allyltin [352b–d], this organotin catalyst is still mild and effects allylation of bicyclic acetals with high stereoselectivity without damaging a variety of functional groups and stereogenic centers (Scheme 12.194) [352a].

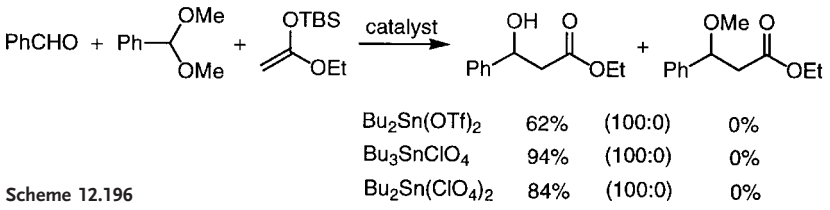


Scheme 12.194

The chemoselectivity of dibutyltin ditriflate is strikingly high. When enol silyl ethers were used as nucleophiles, $Bu_2Sn(OTf)_2$ activated ketals in preference to acetals, whereas aldehydes were more susceptible to activation by $Bu_2Sn(OTf)_2$ than ketones [353 g]. This novel preference realized discriminative C–C bond formation of ketones in the presence of aldehydes by acetalization then treatment with a silicon-based nucleophilic reagent (Scheme 12.195). When an equimolar mixture of aldehyde and acetal was exposed to ketene silyl acetal in the presence of organotin catalysts such as $Bu_2Sn(OTf)_2$ [353 b], Bu_3SnClO_4 [353 b], and $Bu_2Sn(ClO_4)_2$ [354], unprecedented chemoselectivity was observed – only aldehydes reacted with ketene silyl acetal, exclusively, leaving acetal components unchanged, despite use of excess nucleophile (Scheme 12.196). In sharp contrast with these results, however, it has been disclosed that silyl triflate activates acetal preferentially on treatment of a mixture of acetal and aldehyde with enol silyl ether derived from cyclohexanone [356].

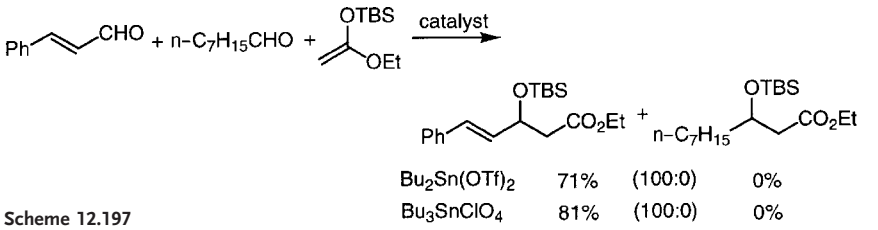


Scheme 12.195



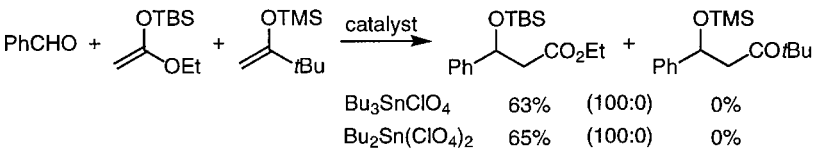
Scheme 12.196

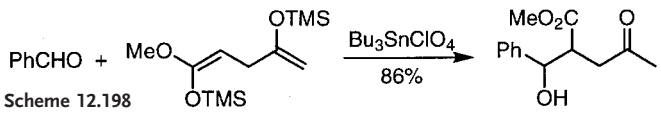
Dibutyltin ditriflate promotes Michael addition of enol silyl ethers and ketene silyl acetals to enones; acid-labile methyl vinyl ketone is usable because of the mild Lewis acidity of $Bu_2Sn(OTf)_2$ [353 c, d, f]. Bu_3SnClO_4 and $Bu_2Sn(OTf)_2$ accelerate the Michael-type Mukaiyama aldol reaction; both promoters enable addition of silyl nucleophiles to enones in preference to aldehydes [353 a, 354]. When these catalysts were employed in competition reactions between aldehydes bearing different substituents the substrates with electron-donating groups reacted more rapidly. In these reactions, the reactivity of carbonyl groups became greater with increasing coordinating capacity (Scheme 12.197); these results are obviously contrary to the conventional relationship between reactivity and the electron density on the carbonyl group.



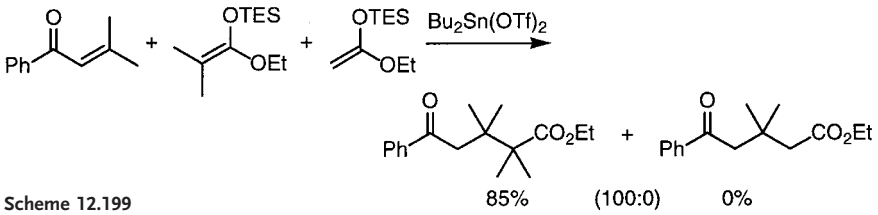
Scheme 12.197

With organotin perchlorates as promoters, discriminative activation of nucleophiles was achieved, giving rise to the exclusive formation of ketene silyl acetal adducts in preference to enol silyl ether adducts (Scheme 12.198) [353a, 354]. It should be noted that in the competitive Mukaiyama-Michael reaction between ketene silyl acetals, sterically demanding nucleophilic reagents reacted preferentially with hindered α-enones, producing contiguous quaternary carbon centers in good yield. This novel selectivity can be interpreted on the basis of single electron-transfer mechanism (Scheme 12.199) [353e].



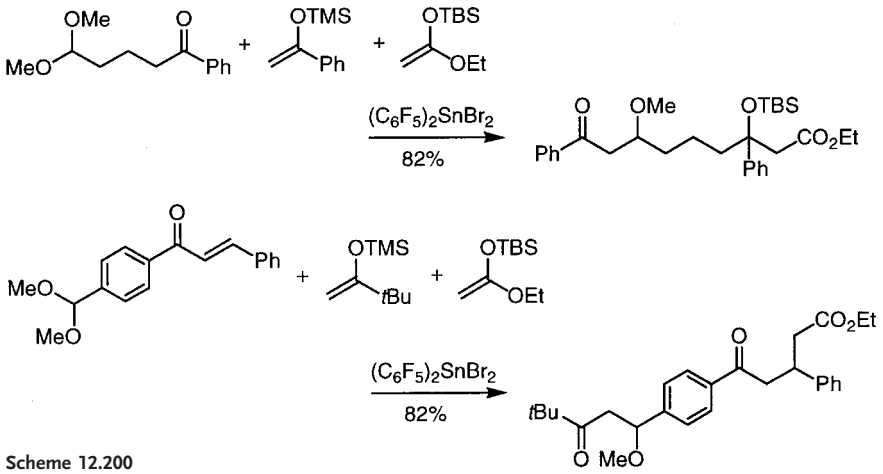


Scheme 12.198



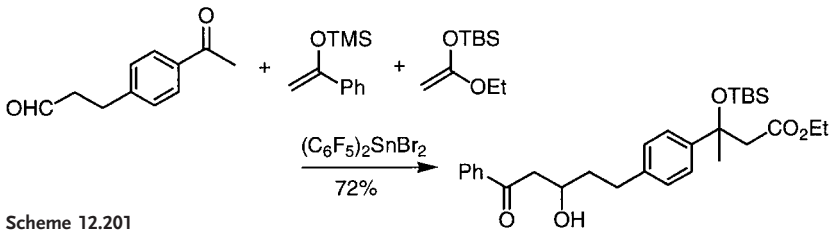
Scheme 12.199

As described above, incorporation of a strong electron-withdrawing group (X) in R_nSnX_{4-n} can enhance the Lewis acidity of the tin. For the same reason an organotin compound R_nSnX_{4-n} with electron-withdrawing organic moieties is expected to have intense Lewis acidity, sufficiently to catalyze C–C bond formation. This is so, and addition of silicon-based nucleophiles to carbonyls is triggered by $(C_6F_5)_2SnBr_2$, because of strong electron-withdrawal by the C_6F_5 substituents [357]. In the $(C_6F_5)_2SnBr_2$-catalyzed competitive Mukaiyama aldol reaction, ketene



Scheme 12.200

silyl acetal reacted with ketones more rapidly than with acetals, whereas enol silyl ethers undergo facile coupling with acetals rather than ketones [357a, b, d]. By taking advantage of this characteristic feature of $(C_6F_5)_2SnBr_2$ as a catalyst, multifold reactions can be promoted by the same Lewis acid in a one-pot method (Scheme 12.200). This parallel recognition process is applicable to C–C bond formation with unsubstituted ketones and aldehydes (Scheme 12.201) [357a–c].



Scheme 12.201

12.8 References

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13
Lead in Organic Synthesis

Taichi Kano and Susumu Saito

13.1
Introduction

13.1.1
General Aspects

After the organolead compound hexaethyldilead was first synthesized in 1858 [1] further development in this area was sparse and spasmodic. During the long history of the study of organolead compounds, what must be regarded as the single most important milestone was the discovery of the antiknock properties of Et_4Pb when added to motor gasoline [2]. Subsequently, other organolead compounds also found broader applicability in the fields of polymerization catalysts, polymer stabilizers, etc. Unfortunately, however, high toxicity causing serious environmental hazards and damage to the human body were found. It is not surprising that since then they have rarely attracted the worldwide attention of chemists and been profoundly investigated and produced industrially. There is, however, far more misleading information on toxicity than might be expected – surprisingly, *lead is approximately one tenth as toxic as palladium, despite public perception to the contrary* [3].

Lead is the largest and heaviest element in Group 14, and its chemistry resembles that of the other members of the Group, particularly tin. C–Pb bonds are, however, significantly weaker and thus organolead compounds (e.g. $Me_3Pb–CH_3$, bond length 2.24 Å, dissociation energy 204 kJ mol^{-1}) [4] are much less thermally and photochemically stable than the corresponding organotin compounds (e.g. $Me_3Sn–CH_3$, bond length 2.14 Å, dissociation energy 297 kJ mol^{-1}) [5]. Long bonds are associated with low bond dissociation energies [6], which facilitate homolytic reactions more readily. Homolytic cleavage of Pb(IV)–C σ bonds is thus more feasible with concomitant change in the oxidation state of lead from +4 to +2. Accordingly, R–Pb(IV) compounds are extremely effective oxidizing agents via radical ($R^{\bullet}$) and, occasionally, non-radical (R^{+}) pathways. Whether these two pathways are involved relies on the nature of the R group and the reaction conditions examined. Nucleophilic properties (R^{-}) have also been observed for the R–Pb(IV) species under conditions such as those in which alkylation of carbonyl carbons and metal–metal exchange are involved. It is thus conceivable that lead(IV) com-

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pounds enable versatile organic transformation. Their synthetic utility has, however, been underestimated, because of difficulties in controlling the high reactivity of the compounds and the diverse nature of the reaction products. Furthermore, the ligand coordination number of lead ranges from 4 [4] to 7 [7], and even higher (8 [8] and 9 [9] are also known). This structural and geometrical diversity of lead species makes elucidation of mechanistic aspects of the reactions elusive.

Despite their diverse nature, organic and inorganic lead compounds have, in fact, found broad application in selective organic synthesis. For example:

- typical Pb(IV) reagents of synthetic significance: $Pb(OAc)_4$ [10], $Pb(OCOCF_3)_4$ [10], $Pb(OAc)_4$–$Cu(OAc)_2$ [10], $Pb(OAc)_4$–I_2 [10], $Pb(OAc)_4$–$BF_3 \cdot Et_2O$ [11a], $Pb(OAc)_4$–MX [11b], PbO_{2-4}–$BF_3 \cdot Et_2O$ [11b]; and
- typical Pb(II) reagent: $Pb(OAc)_2 \cdot H_2O$ [10].

Relatively older applications (ca. 1990) of these reagents are summarized in appropriate books and reviews.

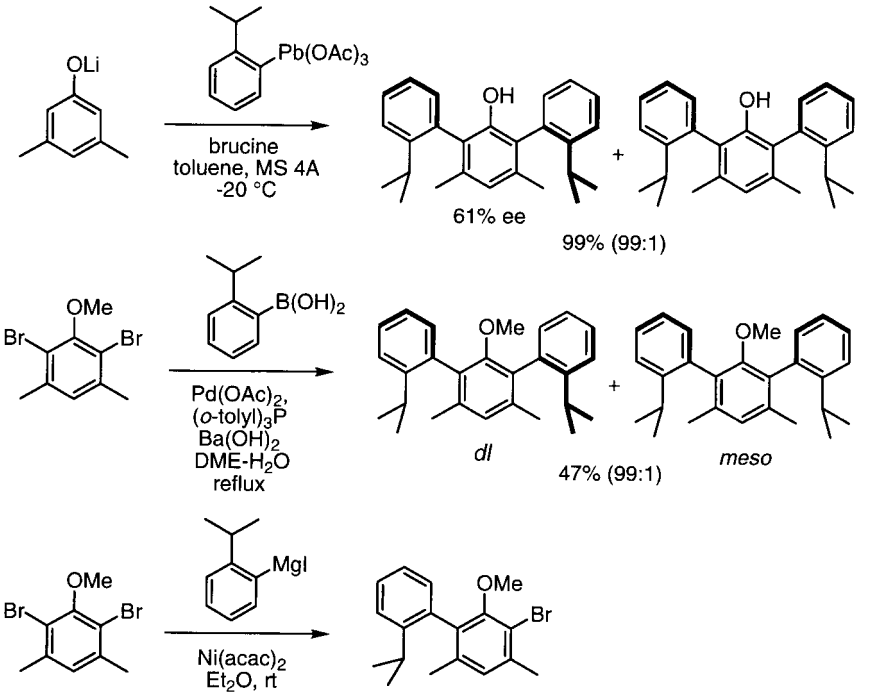
13.1.2 Preparation of Organolead Compounds

$Pb(OAc)_4$ is among the most widely used organolead compounds because of its use as a powerful oxidizing catalyst and as a precursor to other organolead compounds. For the latter purpose, several methods have been developed [12]. The most frequently used involves metal–metal exchange reactions – $Pb(OAc)_4$ reacts readily with R–Hg [12], R–Sn [13], R–Si (with an acid) [14], R–Zn [15] or R–$B(OH)_2$ (with $Hg(OAc)_2$ as catalyst) [16] to give $RPb(OAc)_3$. The preferred metal for the exchange depends on the nature of the R group. For example, the only general routes to vinyllead [13a–d] and 1-alkynyllead tricarboxylates [13e–g] are by Hg–Pb and Sn–Pb exchange. The synthesis of aryllead triacetates is also facilitated by direct plumbation, by means of $Pb(OCOCF_3)_4$ [17] or by means of $Pb(OAc)_4$ in strongly acidic media [18], of aromatic nuclei substituted with electron-donating groups. Diorganolead dicarboxylates were similarly prepared by the B–Pb exchange method [19].

13.1.3 Outstanding Features of Lead Compounds

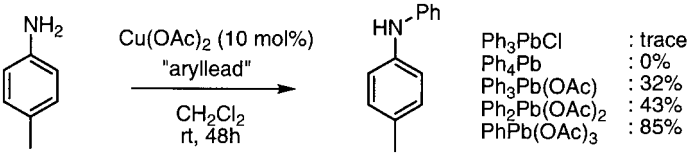
Recent progress on fundamental operations using organolead compounds has been made by Pinhey [20], Moloney [21], and Barton [22, 27] et al., in particular; these workers have greatly expanded the synthetic scope of this field. Unlike aryl–aryl coupling involving Ni and Pd catalysts [23], aryl–Pb(IV) can be used to create a carbon-carbon bond between two arenes even when both are in a sterically congested environment. Aryllead compounds can also be used to construct quaternary carbon centers *bimolecularly*, which otherwise is difficult to achieve. Although sterically crowded sp^3 carbon atoms are readily created by Pd-catalyzed intramolec-

ular Heck reactions [24], the intermolecular version of this reaction is exceedingly rare. This is at least in part because of the exceedingly high oxidation potential of lead (~1.69 V) which is nearly double that of palladium (0.92 V). It is good to look at the examples below (Scheme 13.1) [25]. Higher productivity was eventually achieved by use of aryllead compounds under milder conditions (–20 °C). This rapid reaction might involve a reductive elimination-type process, rather than a radical mechanism. High diastereo- and enantioselectivity are consistent with this possibility. Pinhey [26] and Moloney [21] and their colleagues also suggested the important contribution of non-radical processes involving aryllead compounds.



Scheme 13.1

It is interesting to note that the number of an aryl groups attached to lead has a large effect on the oxidizing strength of the corresponding aryllead species (Scheme 13.2) [27]. The yield of *N*-arylated product decreased with increasing num-



Scheme 13.2

ber of phenyl groups on the lead. The reactivity of aryllead species is altered substantially merely by changing the acyloxy group to chlorine.

Another advantage of lead compounds is their ability to tolerate a variety of functional groups. This is noticeable from their usefulness in modern syntheses of complex natural products, one of the main subjects of this chapter. In early studies, for example, $Pb(OAc)_4$ found particular application in alkaloid synthesis [28]. Donnelly and Finet have focused on the compact array of aromatic rings found in several members of the flavonoid family [29] by use of organolead species. A review of this new approach to arylation reactions with aryllead compounds can also be found in the total synthesis of natural products [30].

Overall, this chapter is confined to the lead compounds, including both organic and inorganic lead species, used in recent developments in synthetic organic chemistry. For more specialized and mechanistic information, including chemophysical, spectroscopic, and structural data about organolead compounds, more comprehensive understanding can be gained from excellent reviews or monographs [4, 12a, 21a, 31], to which readers are referred.

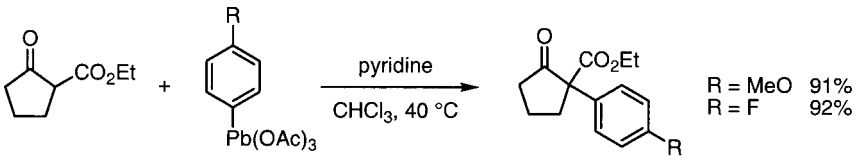
13.2
Pb(IV) Compounds as Oxidizing Agents [Pb(IV) is Reduced to Pb(II)]

13.2.1
C–C Bond Formation (Alkylation, Arylation, Vinylation, Acetylenation, C–C Coupling, etc.)

13.2.1.1 Arylation of Enolate Equivalents

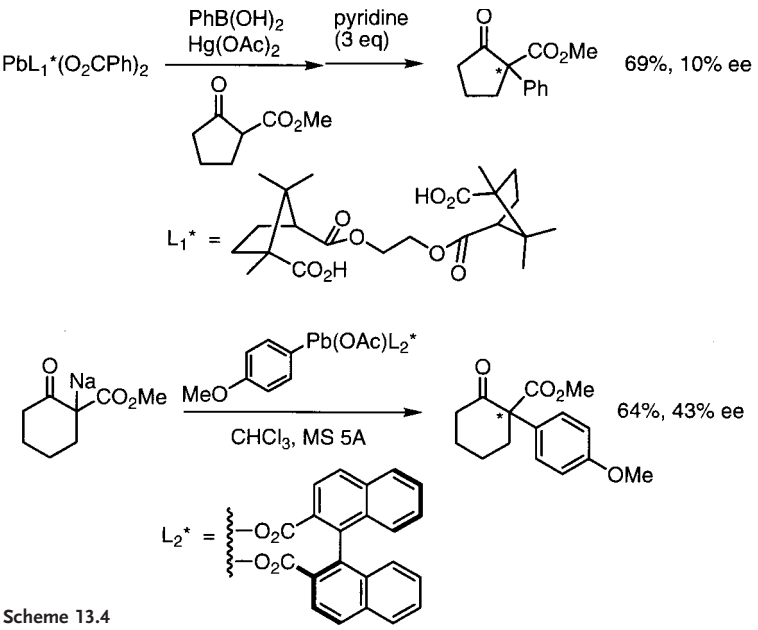
Aryllead, vinyllead, and alk-1-ynyllead tricarboxylates behave as aryl, vinyl and alkynyl cation equivalents to react with a variety of nucleophiles, especially soft carbon nucleophiles such as β-dicarbonyl compounds, phenols, and nitroalkanes. In these reactions, unique regioselectivity is obtained in which there is a preference for the generation of quaternary carbon centers. This aspect of reactivity has been put to use in a number of natural product syntheses and can result in the formation of highly hindered structures.

β-Keto esters and aryllead tricarboxylates react in chloroform in the presence of pyridine to give α-arylated products (Scheme 13.3) [32]. A variety of substrates can be used in this arylation reaction; an exception is keto esters with two α-hydrogen atoms.

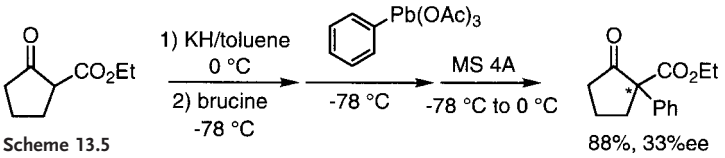


Scheme 13.3

There are only three examples of asymmetric coupling by this process. Two were performed by replacement of one or more labile acetate ligands with enantiomerically pure carboxylic acids (Scheme 13.4) [21c, 30]. The other, explored by our group, used brucine, although not under optimum conditions, as a chiral source albeit with moderate enantiomeric excess (Scheme 13.5) [33].

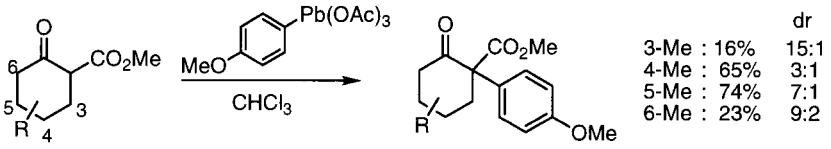


Scheme 13.4



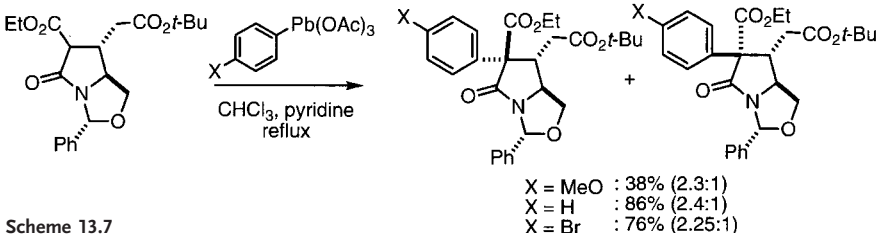
Scheme 13.5

A series of substituted methyl 2-oxo-1-cyclohexanecarboxylates has served as substrates for evaluation of diastereoselectivity in the sp^2–sp^3 bond forming reaction with *p*-methylphenyllead tricarboxylates. Selectivities ranged from poor to excellent depending on the position of the methyl substituent (Scheme 13.6) [34].



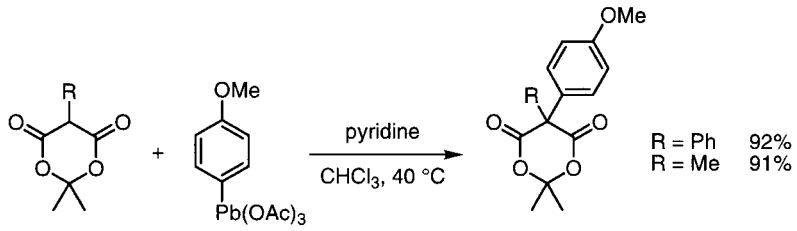
Scheme 13.6

This method has been also applied to the synthesis of a novel class of conformationally restricted glutamates with a ring substitution pattern similar to the kainoid group of amino acids. In all arylations a diastereomeric mixture was obtained; preferential addition of the aryl group to the *exo* face was predominant (Scheme 13.7) [35].



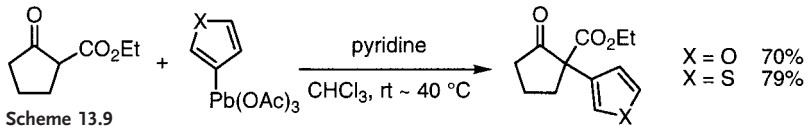
Scheme 13.7

Derivatives of 2,2-dimethyl-1,3-dioxan-4,6-dione (Meldrum's acid) and the sodium salts of substituted malonic esters undergo electrophilic *C*-arylation in high yield with aryllead triacetates; this provides a useful route to *α*-arylalkanoic acids, compounds of interest in the pharmaceutical industry and as synthetic intermediates (Scheme 13.8) [36].



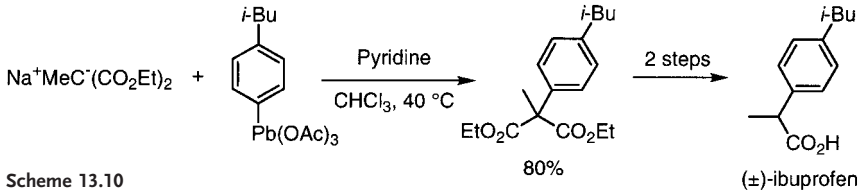
Scheme 13.8

The heteroaryllead tricarboxylates furyllead triacetate and thienyllead triacetate are much less stable than the benzenoid analogs and very sensitive to moisture. They were therefore prepared in situ and reaction with *β*-carbonyls yielded the *α*-furyl and thienyl *β*-keto esters in synthetically useful yields (Scheme 13.9) [37].



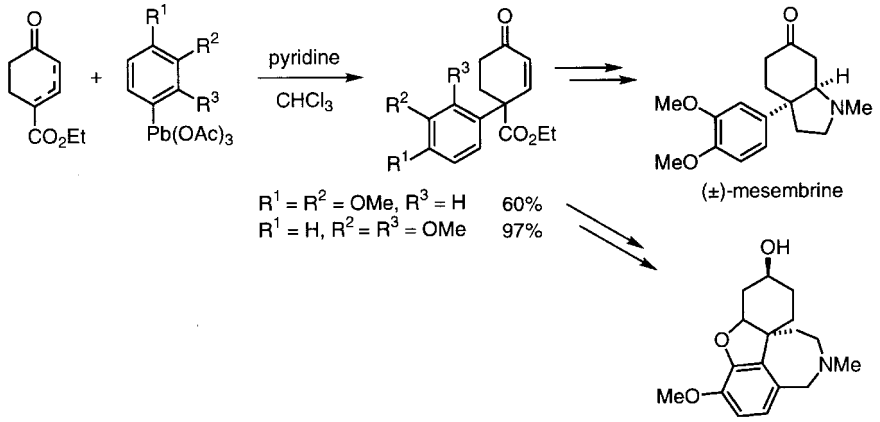
Scheme 13.9

Syntheses of the anti-inflammatory compound 2-(*p*-isobutylphenyl)propanoic acid (Ibuprofen) have been performed by use of this method (Scheme 13.10) [36].



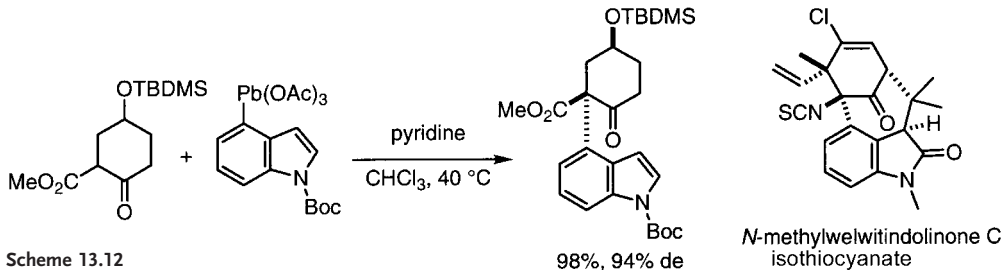
Scheme 13.10

Aryllead triacetates react with a mixture of isomeric vinylogous keto esters regiospecifically at C-1. In the synthesis of alkaloids such as (±)-mesembrine [39] and (±)-lycoramine [38], the central quaternary carbon center was installed by this electrophilic arylation reaction (Scheme 13.11).



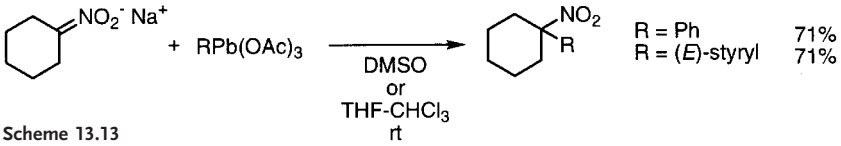
Scheme 13.11

The reaction of 4-indolyllead triacetate with substituted methyl 2-cyclohexanonecarboxylates, which has been investigated as a route to the natural product *N*-methylwelwitindolinone C isothiocyanate, afforded the desired coupled product in excellent yield and diastereoselectivity (Scheme 13.12) [40].



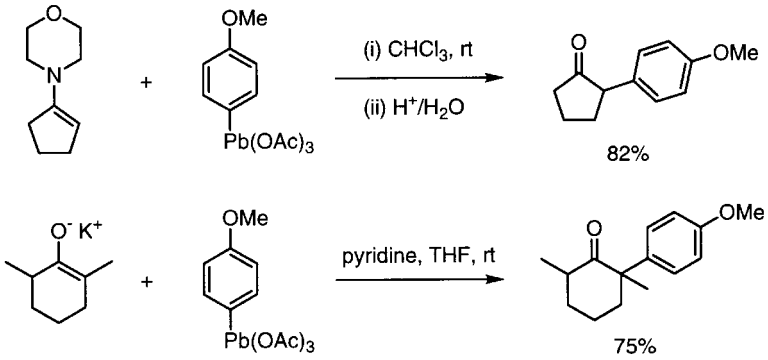
Scheme 13.12

Nitroalkanes, which have pK_a values within the range of reactive β-dicarbonyls, also react with aryllead triacetates to provide easy access to a wide range of α-aryl nitroalkanes in synthetically useful yields [41]. The reaction is, however, very slow under the conditions developed for β-dicarbonyl compounds, and pyridine has no effect on these reactions. The use of sodium salts of the nitro compounds accelerates reaction rates (Scheme 13.13).



Scheme 13.13

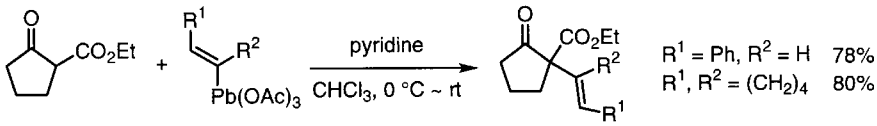
Enamines [42] and potassium enolates of ketones [43] can also be employed in the arylation reaction with aryllead triacetate to give α-arylated ketones (Scheme 13.14).



Scheme 13.14

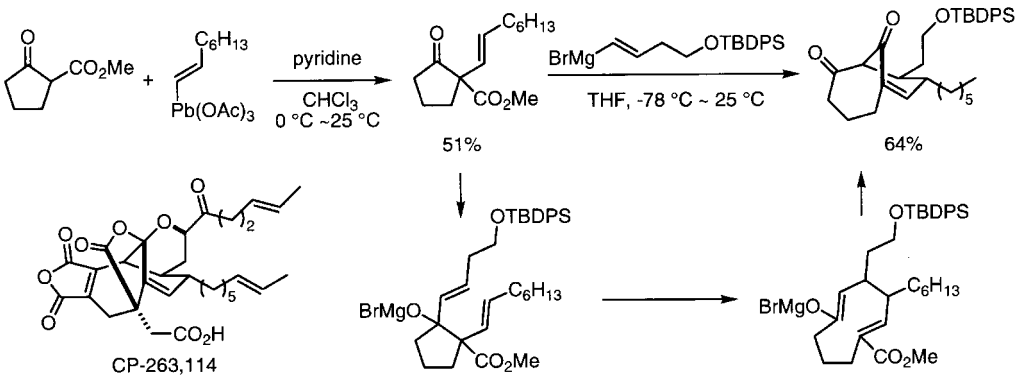
13.2.1.2 **Vinylation of Enolate Equivalents**

Unstable vinyllead triacetates, generated in situ, react with soft carbon nucleophiles such as β-dicarbonyl compounds to give moderate to good yields of *C*-vinylated products (Scheme 13.15). Thus, there is considerable potential for use of this vinylation in organic synthesis [12e, 41b].



Scheme 13.15

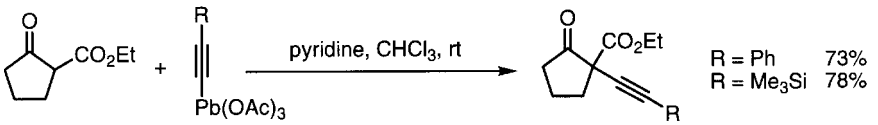
With this method a new bicyclic ring-forming process has been developed that results in direct construction of the CP-263,114 core system from a readily available β-keto ester (Scheme 13.16) [44].



Scheme 13.16

13.2.1.3 **Alkynylation of Enolate Equivalents**

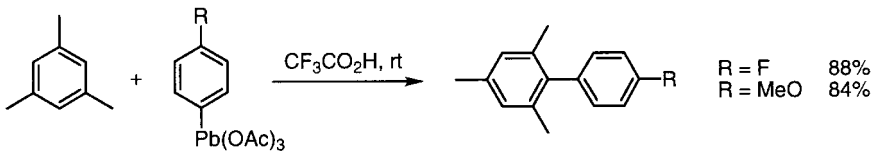
An analogous alkynylation reaction occurs when alk-1-ynyllead triacetates, which are also unstable, can be employed via in situ generation (Scheme 13.17) [13f].



Scheme 13.17

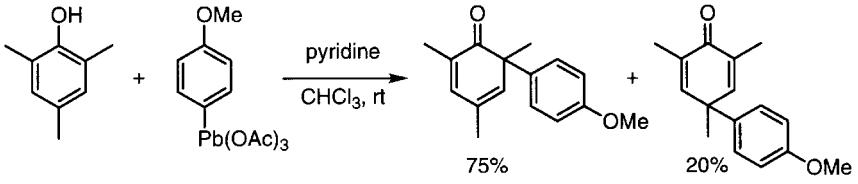
13.2.1.4 **Aryl–Aryl Coupling**

Aryllead tricarboxylates have been shown to react in trifluoroacetic acid with a range of aromatic compounds to give biaryls [31c]. With aromatic compounds that are more electron-rich than toluene the yields are generally good and the method is a useful synthesis of unsymmetrical biaryls (Scheme 13.18). It has been reported that a cationic intermediate generated from aryllead tricarboxylates was probably involved.



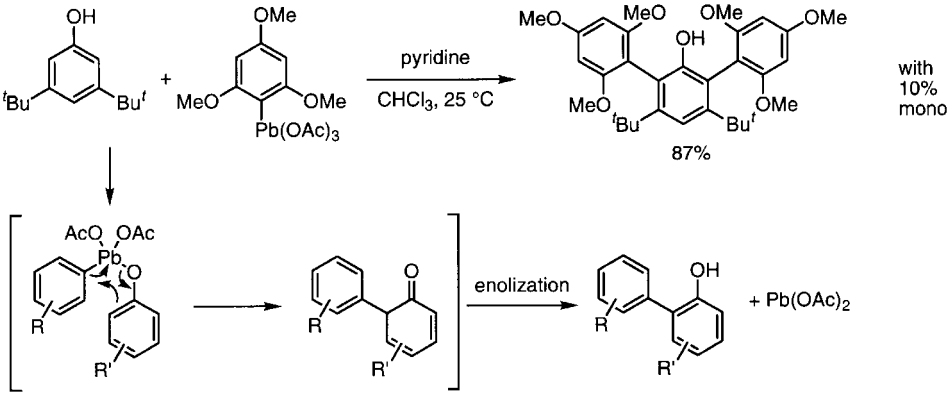
Scheme 13.18

A mixture of mesitol, *p*-methoxyphenyllead triacetate, and pyridine in equimolar quantities in chloroform gives an almost quantitative yield of the 6-arylcyclohexa-2,4-dienone and the 4-arylcyclohexa-2,5-dienone in a ratio of 4:1 (Scheme 13.19) [45]. There is a marked preference for *ortho* arylation.



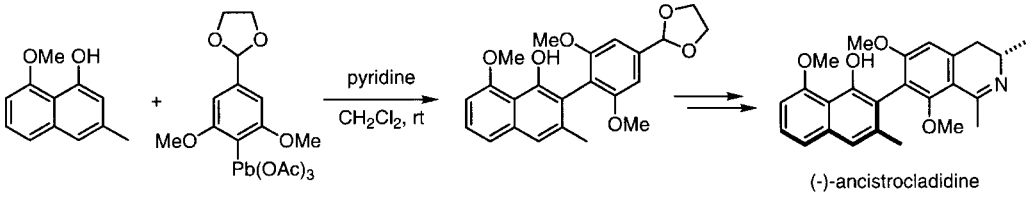
Scheme 13.19

The reaction of aryllead triacetate with 3,5-di-*tert*-butylphenol has been shown to yield very hindered di-arylated products (Scheme 13.20) [22a]. The favored pathway must involve the occurrence of covalent aryl(aryloxy)lead(IV) diacetate intermediates, although they have not been detected.



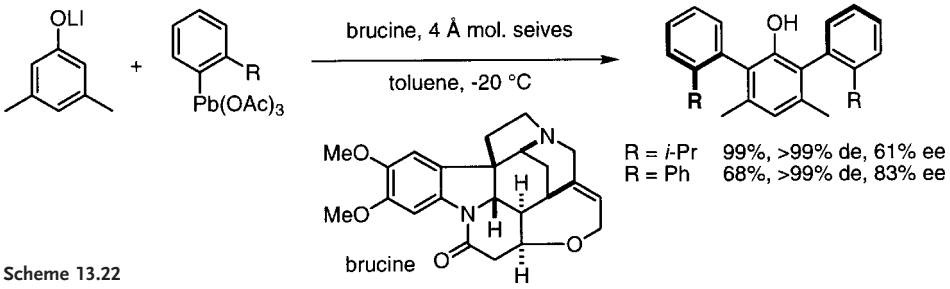
Scheme 13.20

Use of this method to form the extremely hindered biaryl linkage enabled completion of the first total synthesis of the rare 7,3′-linked naphthylisoquinoline alkaloid, ancistrocladidine (Scheme 13.21) [46].



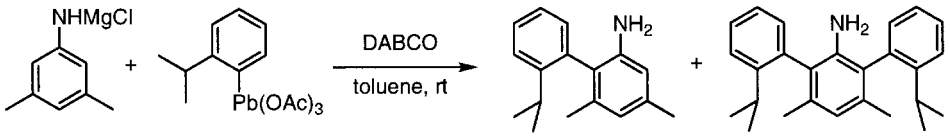
Scheme 13.21

The asymmetric coupling of a variety of phenol derivatives with bulky aryllead triacetates was achieved by use of the optically active amine brucine (Scheme 13.22) [25]. It was found that conformationally restricted tertiary amines, preformed lithium aryloxides, and addition of 4 Å molecular sieves were essential for accelerating the rate of phenol coupling. As a consequence the reaction could be performed at low temperature (–40 to –20 °C) with high diastereo- and enantioselectivity.



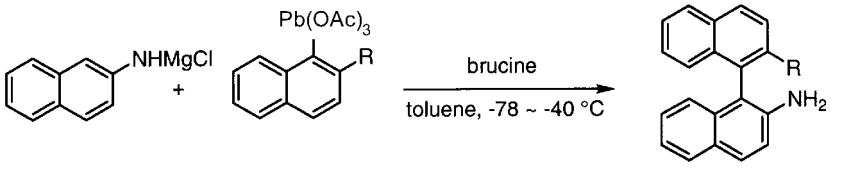
Scheme 13.22

In contrast with the reaction between phenol derivatives and aryllead triacetates, anilines and anilides do not undergo either *C*- or *N*-arylation with aryllead triacetate [27]. Aryl–aryl coupling of aryllead triacetates at the *ortho* position of anilines was, however, achieved by simple magnesation of the aniline nitrogen (Scheme 13.23) [47]. This method is advantageous with regard to the substitution pattern, because anilines are otherwise prone to electrophilic substitution at their *para* positions.



Scheme 13.23

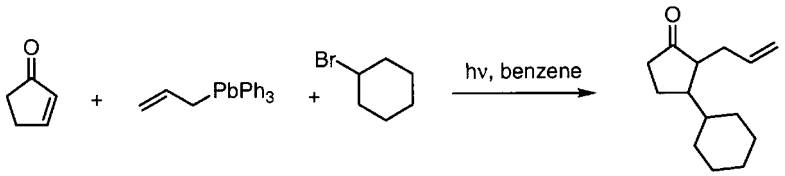
Investigation of an enantioselective version of this using brucine instead of DABCO showed that the coupling of *β*-naphthylamines with naphthyllead triacetate derivatives proceeded at even lower temperatures (–78 to –40 °C) to give the axially chiral biaryls with moderate enantioselectivity (Scheme 13.24) [25 b].



Scheme 13.24

13.2.1.5 **Other C–C Bond-forming Reactions (R–Pb as R• or R⁻)**

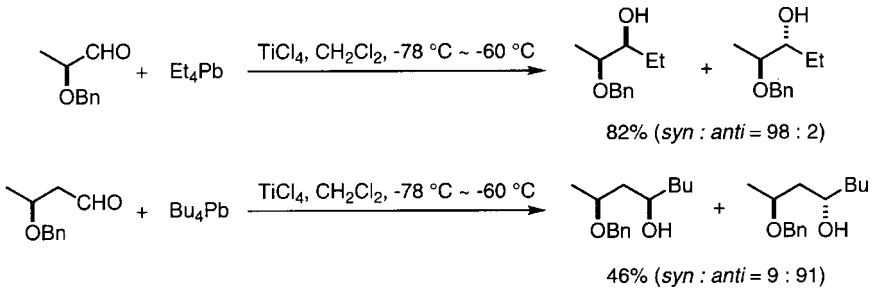
Three-component coupling in high yield has been achieved by irradiation of a mixture of *α,β*-unsaturated carbonyl compounds, alkyl halides, and allyltriphenyllead (Scheme 13.25) [48]. Addition of a catalytic amount of hexaphenyldilead accelerated the reaction, and alkyl bromides gave better yields than alkyl iodides. When allyltributyltin was used in the place of allyltriphenyllead, however, yields of the product did not exceed 60% under a variety of conditions.



Scheme 13.25

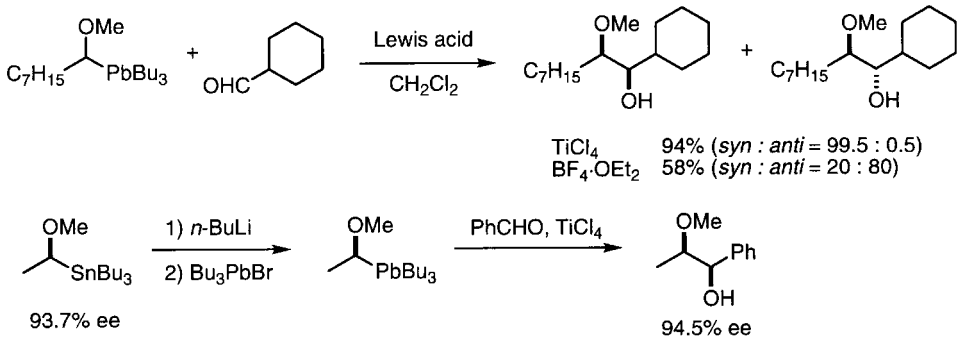
84% (*trans : cis* = 91 : 9)

Several air-stable, storable, and non-carbanionic reagents including allylic silanes and stannanes have been used for C–C bond formation with carbonyl compounds, usually under nonbasic conditions. Unfortunately, however, transferable groups are limited to allyl, alkyne, and enol groups. Tetraalkyllead compounds, on the other hand, reacted smoothly with aldehydes in the presence of $TiCl_4$ to produce the corresponding alcohols in moderate to good yield, with excellent diastereoselectivity (Scheme 13.26) [49].



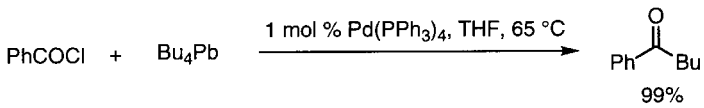
Scheme 13.26

The reaction of *α*-alkoxy organometallic compounds (lithium, magnesium, and copper) with benzaldehyde gave 1,2-diol derivatives with low *syn* diastereoselectivity, whereas condensation of *α*-alkoxy organoleads with aldehydes in the presence of $TiCl_4$ afforded very high *syn* selectivity. Furthermore, in the presence of $BF_3 \cdot OEt_2$, the *anti* isomer was afforded preferentially. It was found that the $TiCl_4$-mediated reaction of the optically active lead compound proceeded through retention to give the corresponding optically active 1,2-diol derivative (Scheme 13.27) [50].



Scheme 13.27

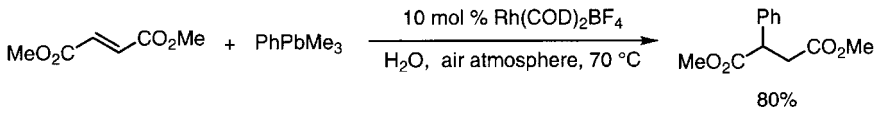
The palladium-catalyzed coupling of acid chlorides with tetraalkyllead derivatives gave the ketones in high yields under mild conditions (Scheme 13.28) [51]. Even with only 0.6 equiv. tetrabutyllead high yields (78–99%) were obtained.



Scheme 13.28

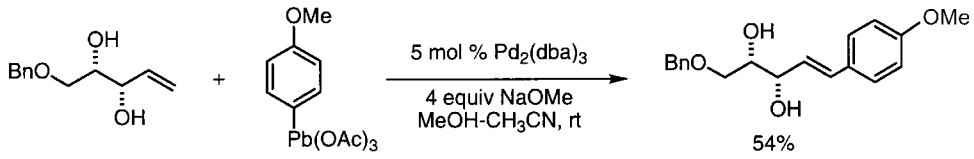
13.2.1.6 **Transition Metal-catalyzed Reactions**

In the presence of rhodium catalyst, α,β-unsaturated esters and ketones react with phenyltrimethyllead in aqueous media and under an air atmosphere to give the conjugated addition products in high yields (Scheme 13.29) [52]. Use of tetraphenyllead reduced the yield substantially (to 25%), and no reaction was observed with either chlorotriphenyllead or dichlorodiphenyllead.



Scheme 13.29

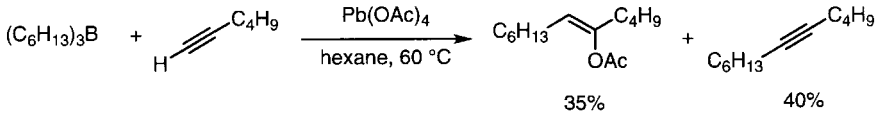
The palladium-catalyzed coupling reactions of organolead triacetates with olefins have been achieved under mild conditions [53]. Phenyllead triacetate undergoes facile coupling with the diol olefin without any formation of ketone resulting from β-PdH elimination to give the arylated diol (Scheme 13.30). The use of NaOMe as a base is critical in this type of coupling.



Scheme 13.30

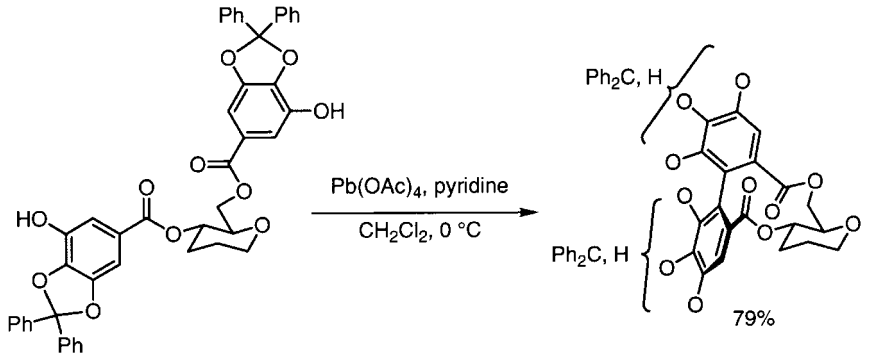
13.2.1.7 C–C Bond-forming Reactions using $Pb(OAc)_4$

In the reaction of trialkylborane with 1-alkyne and lead tetraacetate in hexane, one of the alkyl groups of the trialkylborane migrated to the terminal carbon atom of the triple bond, giving, regiospecifically, an internal enol acetate and an internal alkyne as the main products (Scheme 13.31) [54]. The former compound had the (*Z*) configuration.



Scheme 13.31

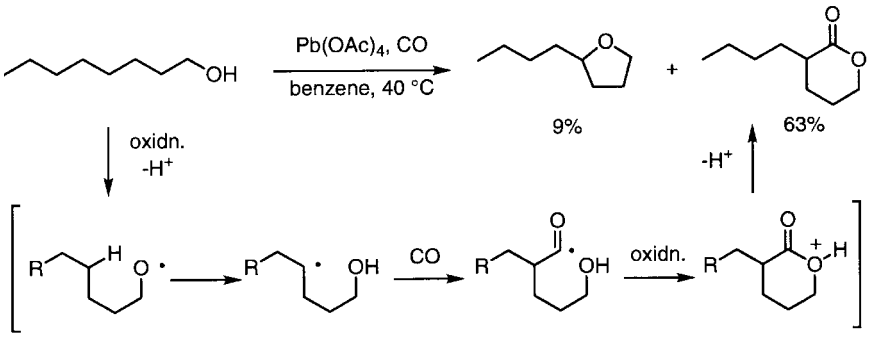
The construction of only the (*S*)-hexahydroxydiphenyl unit, a structural analog of secondary plant metabolite ellagitannins, by biomimetic cyclization of suitably protected glucose-derived digalloyl esters has been achieved by use of lead tetraacetate (Scheme 13.32). No quinone ketal-type product was detected, in contrast to the simpler system described below (Scheme 13.37).



Scheme 13.32

Carbonylation of saturated alcohols occurred to afford δ-lactones in moderate to good yields (Scheme 13.33) [56]. The mechanism of the remote carbonylation probably involves:

1. alkoxy radical generation via $Pb(OAc)_4$ oxidation of the saturated alcohol;
2. conversion of this alkoxy radical to a δ-hydroxyalkyl radical by a 1,5-hydrogen-transfer reaction;
3. CO trapping of the δ-hydroxyalkyl radical yielding an acyl radical; and
4. oxidation and cyclization of the acyl radical to give a δ-lactone.

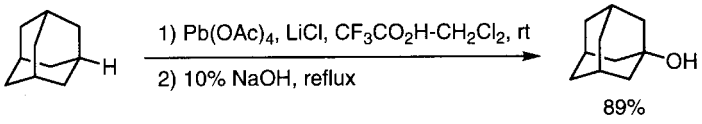


Scheme 13.33

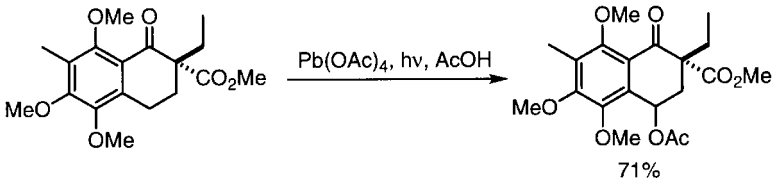
13.2.2

C–O Bond Formation (Acetoxylation, Including Oxidative Cleavage of a C–Si Bond, etc.)

Oxidation of hydrocarbons with a tertiary carbon, e.g. adamantane, with lead tetraacetate in trifluoroacetic acid–dichloromethane solution, in the presence of chloride ion, gave high yields of trifluoroacetate functionalized bridgehead alcohols [57]. Subsequent hydrolysis yielded the free bridgehead alcohols (Scheme 13.34). Another important advantage of this method is the feasible conversion of the intermediate trifluoroacetate into an amide with acetonitrile.



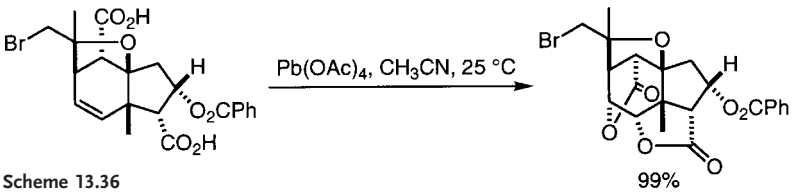
Scheme 13.34



Scheme 13.35

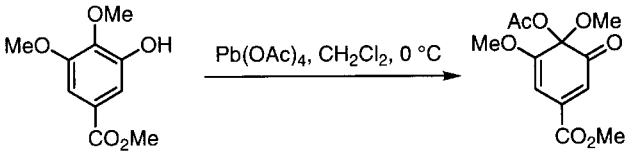
Aromatic compounds with a C–H group at the benzylic position are readily oxidized by lead tetraacetate to the corresponding benzyl acetates. Benzylic acetoxylation is preferably performed in acetic acid (Scheme 13.35) [58].

The reaction of olefins with lead tetraacetate has not been a useful method in organic synthesis, because reactions such as addition of an oxygen functional group to the double bond, substitution of hydrogen at the allylic position, and C–C bond cleavage can occur to give complex mixtures of products. With some specific alkenes, however, reaction with lead tetraacetate can afford synthetically important compounds cleanly. For instance, reaction of the diacid with 6 equiv. lead tetraacetate in acetonitrile gave the dilactone in excellent yield (Scheme 13.36) [59].



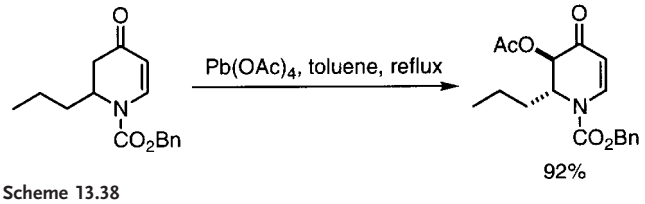
Scheme 13.36 99%

In acetic acid lead tetraacetate usually oxidizes phenols to the corresponding quinones or their derivatives. The product is highly dependent on the substituents on the aromatic ring. The reaction of dimethoxyphenol with lead tetraacetate furnished the monooxidation product quinone ketal in excellent yield (Scheme 13.37; compare with Scheme 13.32) [55].



Scheme 13.37 92%

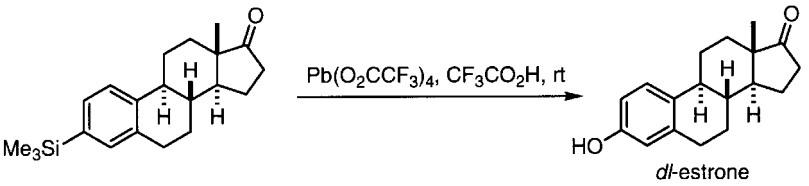
Carbonyl compounds, enol ethers, and enamines are acetoxylated by lead tetraacetate. By use of this method the enone could be *α*-acetoxylated stereoselectively and chemoselectively (Scheme 13.38) [60].



92%

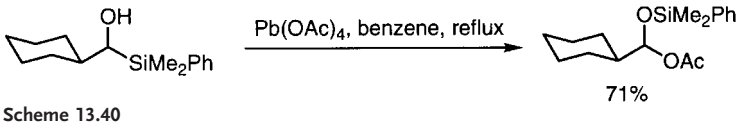
Scheme 13.38

Oxidative aryl–silicon cleavage [14a, 61a] occurred almost quantitatively on exposure to lead tetrakis(trifluoroacetate) to produce *dl*-estrone (Scheme 13.39) [61b]. It is likely that this process proceeds via aryllead tris(trifluoroacetate) and aryl trifluoroacetate as intermediates.



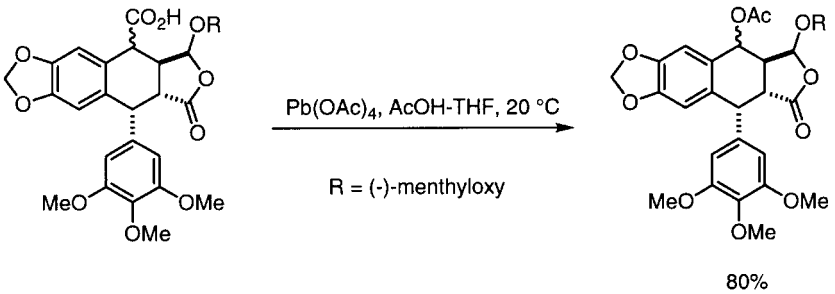
Scheme 13.39

Lead tetraacetate treatment of an α-silyl alcohol led to its rapid and efficient conversion into a mixed acetyl-silyl acetal under mild conditions (Scheme 13.40) [62].



Scheme 13.40

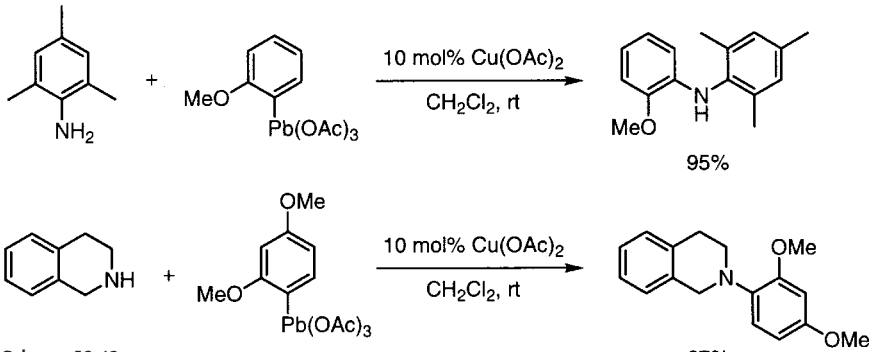
Because oxidative decarboxylation of carboxylic acids by lead tetraacetate depends on the reaction conditions, the co-reagents, and the structures of the acids, a variety of products such as acetate esters, alkanes, alkenes, and alkyl halides can be obtained. Mixed lead(IV) carboxylates are involved as intermediates; as a result of their thermal or photolytic decomposition decarboxylation occurs and alkyl radicals are formed. Oxidation of alkyl radicals by lead(IV) species gives carbocations; a variety of products is then obtained from the intermediate alkyl radicals and the carbocations. Decarboxylation of primary and secondary acids usually affords acetate esters as the main products (Scheme 13.41) [63].



Scheme 13.41

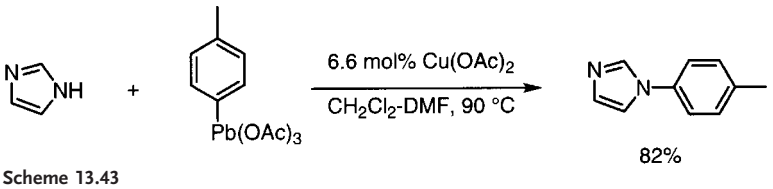
13.2.3
C–N Bond Formation (Aziridination, etc.)

Aryllead triacetates have been found to be regioselective reagents for the mono *N*-arylation of a range of aromatic heterocyclic and aliphatic amines under mild and neutral conditions in a reaction catalyzed by copper(II) acetate (Scheme 13.42) [27]. The arylation of arylamines is unaffected by the steric hindrance of the arylamine but depends on arylamine basicity. The arylation of heterocyclic amines proceeded in modest to good yields, whereas aliphatic amines were arylated in poor to modest yield. The mechanism proposed for these reactions involves transfer of the aryl group to copper, forming a copper(III) intermediate which subsequently undergoes ligand coupling to give the *N*-arylated amine.



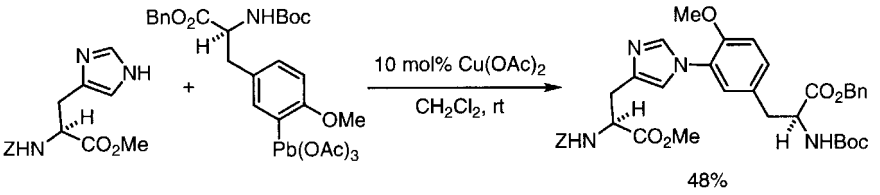
Scheme 13.42

N-arylimidazoles, important compounds in medicinal research, have been synthesized by nucleophilic aromatic substitution and Ulmann-type coupling. Aromatic substitution is, however, limited by the need for substrates activated by electron-withdrawing groups. The arylation of diazoles and triazoles, e.g. imidazole, by *p*-tolyllead triacetate compares very favorably with the Ullmann and related methods in that the conditions employed are much milder and the yields are usually excellent and reproducible (Scheme 13.43) [64].



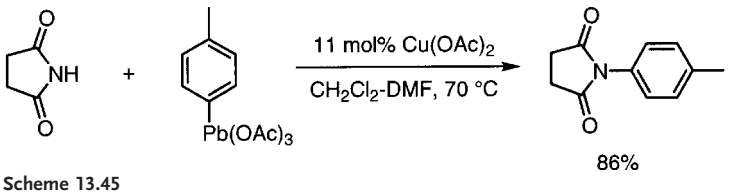
Scheme 13.43

Use of this method enabled synthesis of the histidine–tyrosine sidechain-coupled dipeptide found in the active site of cytochrome *c* oxidase (Scheme 13.44) [65].



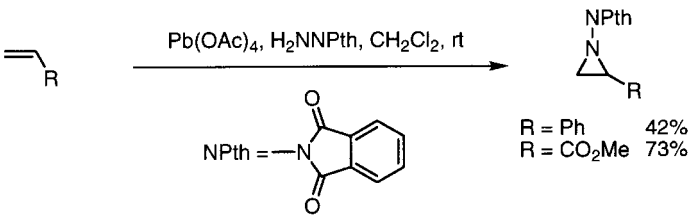
Scheme 13.44

It has, moreover, been found that *p*-tolyllead triacetate also efficiently arylated the nitrogen atom of carboxamides, sulfonamides, and imides (Scheme 13.45) [66].



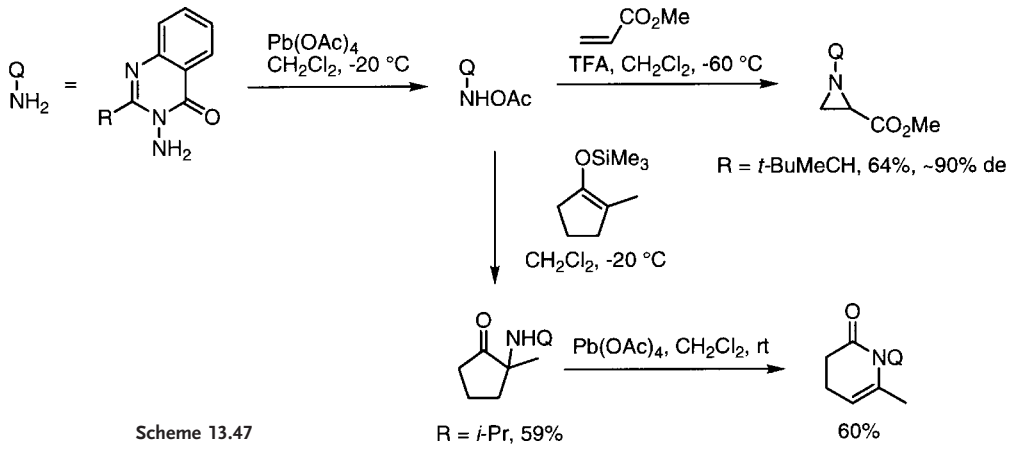
Scheme 13.45

The synthesis of aziridine derivatives has received much attention in recent years, because these are versatile building blocks for synthesis for a wide range of nitrogen-containing substrates. Oxidation of *N*-aminophthalimide with lead tetraacetate in the presence of a variety of electrophilic and nucleophilic olefins is a useful, stereospecific route to aziridines (Scheme 13.46) [67].



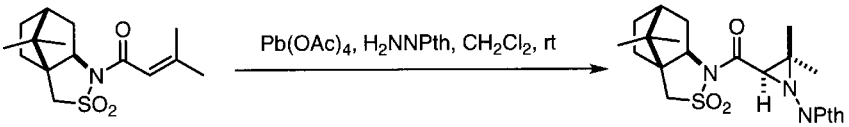
Scheme 13.46

Oxidation of 3-aminoquinazolones with lead tetraacetate at –20 °C gave *N*-acetoxyaminoquinazolones which were stable in solution at this temperature [68a]. These *N*-acetoxyaminoquinazolones functioned as aziridinating agents for alkenes, and diastereoselective aziridine formation was achieved by use of a 3-aminoquinazolone, which had a chiral center [68b]. Solutions of *N*-acetoxyaminoquinazolone also reacted with silyl enol ethers to give α-aminoketones, and further oxidation of these products with lead tetraacetate gave ring-expanded products (Scheme 13.47) [68c].



Scheme 13.47

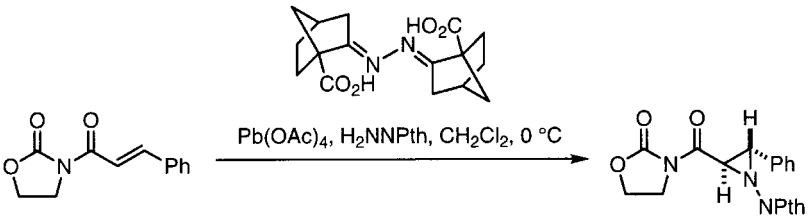
By use of a chiral auxiliary, diastereoselective aziridination could also be achieved [69]. Reaction of chiral *N*-enoylbornane[10,2]sultams with *N*-aminophthalimide in the presence of lead tetraacetate in CH_2Cl_2 proceeded smoothly and afforded excellent yields of the corresponding *N*-phthalimidoaziridines with high diastereomeric excess (Scheme 13.48) [69a].



Scheme 13.48

67%, >95% de

Enantioselective aziridination has also been achieved by use of an enantiopure ligand [70]. Reaction of a variety of *N*-enoyl oxazolidinones with *N*-aminophthalimide and lead tetraacetate in the presence of camphor-derived chiral ligands provided the *N*-phthalimidoaziridines in good to high enantiomeric excess (Scheme 13.49). The oxazolidinone moiety of the substrate played an indispensable role in this reaction. The use of aryl acrylates led either to low stereoselectivity or low chemical yield. Coordination of the ligand-mediated Lewis acid to the bidentate acyl oxazolidinone might account for these results.

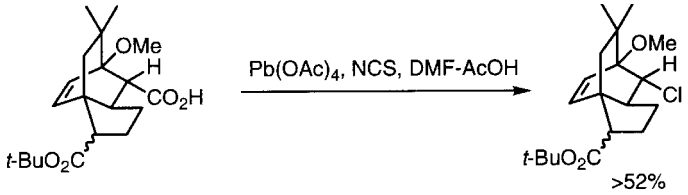


Scheme 13.49

83%, 95% ee

13.2.4
C–X (Cl, Br, I) Bond Formation

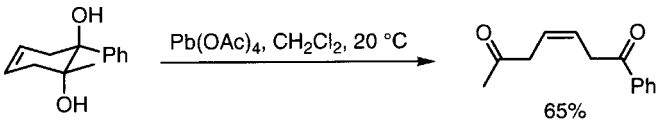
The preparation of chlorides by decarboxylation of carboxylic acids with lead tetraacetate and *N*-chlorosuccinimide as the chlorine donor in a 5:1 mixture of DMF and glacial acetic acid has been reported [71a]. The reaction has been applied particularly often to the preparation of secondary and tertiary chlorides when the classic Hunsdiecker reaction gives low yields (Scheme 13.50) [71b]. This reaction proceeds by a radical pathway.



Scheme 13.50

13.2.5
C–C Bond Cleavage (Fragmentation: Cyclic to Acyclic, etc.)

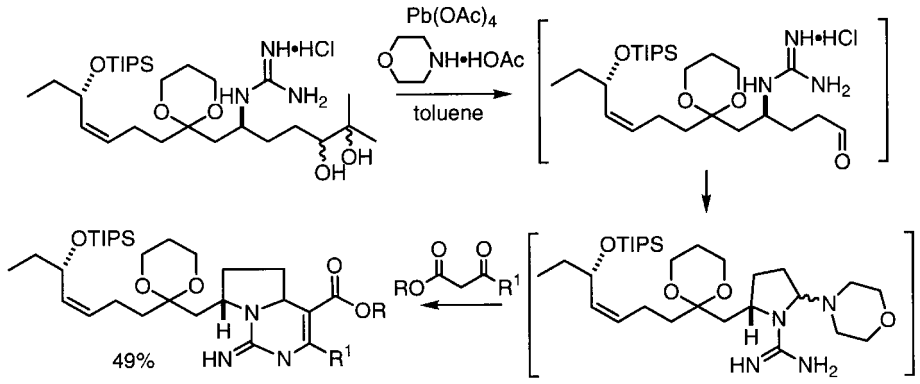
Lead tetraacetate is very frequently used for cleavage of 1,2-diols and preparation of the resulting carbonyl compounds. The rate of reaction is highly dependent on the stereochemistry of the substrate. There is usually correlation between the rate of oxidation and the spatial proximity of the hydroxy groups. For example, the rate of the oxidative cleavage of *cis*-cyclopentane-1,2-diol is much faster than that of *trans* isomer. It is, however, possible to oxidize *trans*-1,2-diol to diketone (Scheme 13.51) [72a].



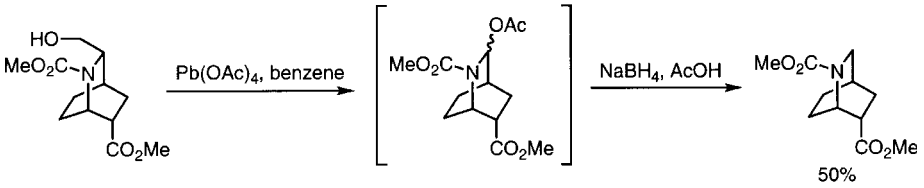
Scheme 13.51

The convenience of this reaction has been well demonstrated in the total synthesis of 13,14,15-isocrambescidin 800 (Scheme 13.52) [72b].

The oxidative cleavage of the carbon–carbon bond mentioned above is applicable not only to 1,2-diols but also to β-aminoalcohols and 1,2-diamines. For example, hydroxymethyl groups could be removed from β-aminoalcohols by treatment with lead tetraacetate in benzene then reduction with $NaBH_4$ (Scheme 13.53) [73a].

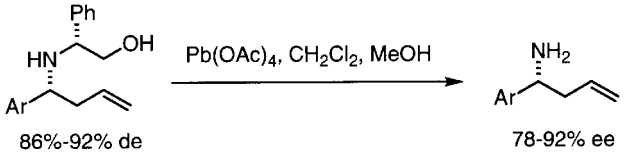


Scheme 13.52



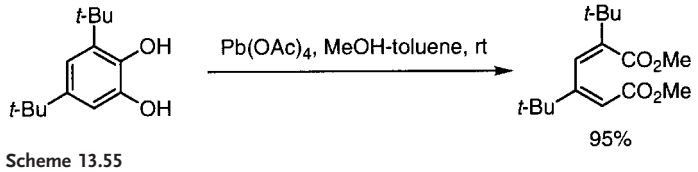
Scheme 13.53

When a β-aminoalcohol containing a secondary amino group was used the primary amine was obtained, with slight loss of optical purity (Scheme 13.54) [73 b].



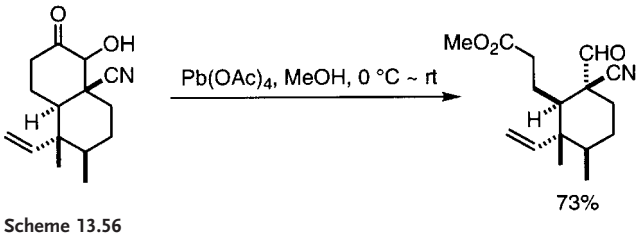
Scheme 13.54

Oxidative ring-opening of substituted catechols with lead tetraacetate provided the corresponding substituted *cis,cis*-2,4-diene-1,6-dioates in fair to good yields (Scheme 13.55) [74].



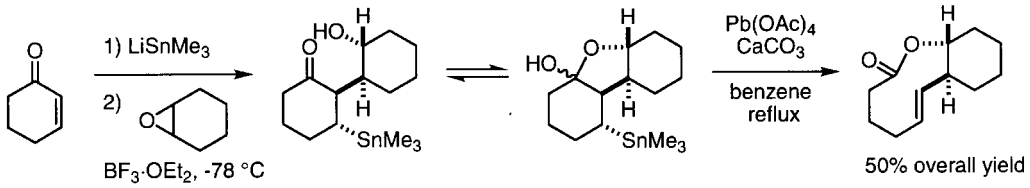
Scheme 13.55

Oxidation of α-hydroxyketones with lead tetraacetate gives α-diketones; reaction in the presence of water or alcohol affords the formyl carboxylic acid or its ester (Scheme 13.56) [75].



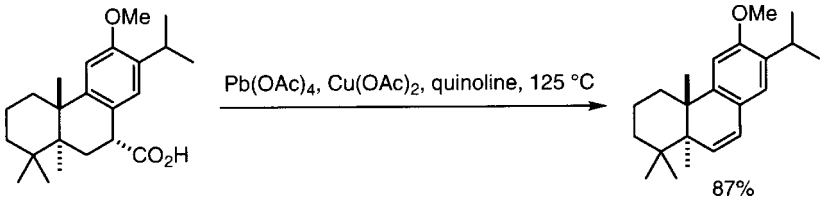
Scheme 13.56

Not only 1,2-di-functionalized substrates with heteroatoms but also tertiary alcohols and hemiketals undergo oxidative C–C bond cleavage at the α position on treatment with lead tetraacetate. For example, a γ-hydroxy ketone and the corresponding hemiketal have been fragmented by lead tetraacetate into a 9-membered olefinic lactone (Scheme 13.57) [76].



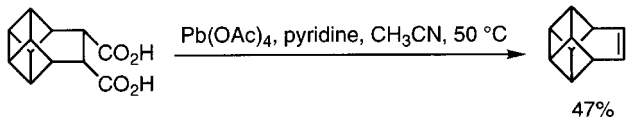
Scheme 13.57

As described above, decarboxylation of carboxylic acids gives a variety of products depending on the reaction conditions and substrates used. In the presence of a catalytic amount of copper(II) acetate reaction of carboxylic acids with lead tetraacetate affords olefins in good yields (Scheme 13.58) [77].



Scheme 13.58

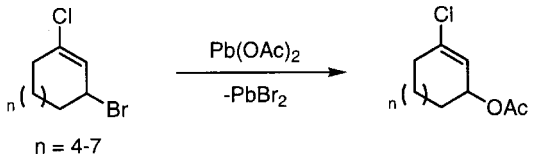
Treatment of 1,2-dicarboxylic acids with lead tetraacetate in pyridine, dimethylformamide, or acetonitrile leads to decarboxylation and the formation of olefins (Scheme 13.59) [78].



Scheme 13.59

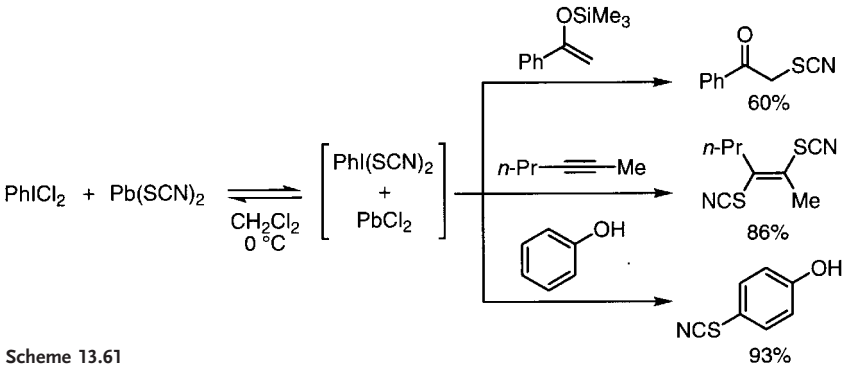
13.3
Pb(II) as a Lewis Acid

An interesting old reference dealing with the Lewis acidic properties of Pb(II) species is worth mentioning [79]. Pb(II) species behaved entirely differently from typical Lewis acids such as $AlCl_3$, $TiCl_4$, $SnCl_4$, and BF_3, etc., when used for the preferential replacement of a bromine atom in 1-chloro-3-bromocycloalkenes by an acetoxy group (Scheme 13.60). Established physical and experimental data show that M–O σ bonds are stronger than M–X σ bonds for several typical Lewis acids. Thus, in general, substitution of M–O σ bonds by C–X (X=halogen) σ bonds is highly unlikely and the reverse seems to be a common feature. It seems that the Pb–Cl bond is quite strong, in contrast to the Pb–C, Pb–Pb, and Pb–H bonds, although no data are available from direct comparison of Pb–O and Pb–X (X=halogen) bonds [4].



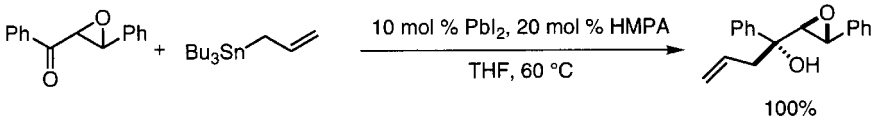
Scheme 13.60

A combination of $PhICl_2$ and $Pb(SCN)_2$ is an effective reagent for thiocyanation of silyl enol ethers [80a], alkynes [80b], and phenols [80c] (Scheme 13.61). Such reactions are thought to proceed via in-situ generation of $PhI(SCN)_2$. It has been reported that the presence of the weak Lewis acid $PbCl_2$ generated in situ seems to accelerate the reaction with phenol.



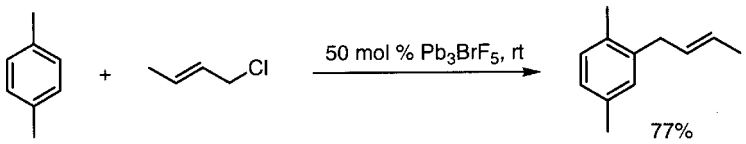
Scheme 13.61

Allyltri-*n*-butyltin usually requires activation to perform effective allylation of carbonyl compounds. Stereoselective reactions occasionally occur in the presence of the strong Lewis acids $TiCl_4$, $SnCl_4$, and $BF_3 \cdot OEt_2$. These conventional Lewis acids cannot, however, be used for chemoselective allylation of carbonyl compounds bearing other reactive functional groups, because of further transformation and decomposition of the products. It has been found that the lead diiodide–HMPA complex is a good catalyst for chemo- and diastereoselective allylation of *α,β*-epoxy ketones under mild neutral conditions (Scheme 13.62) [81].



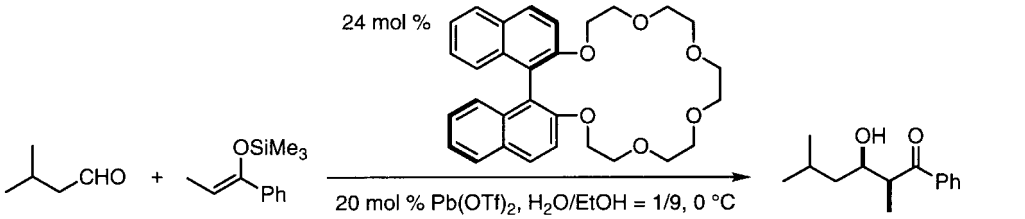
Scheme 13.62

The composite lead fluoride reagent Pb_3BrF_5, prepared from PbF_2 and NaBr, is a nonhygroscopic and efficient solid reagent for promoting selective Friedel-Crafts type reaction of aromatic compounds with allylic halides to afford the monoallylated compounds (Scheme 13.63) [82]. The Lewis acid catalysts $TiCl_4$ and $ZnCl_2$-Montmollironite K-10 were more reactive than the lead fluoride reagent but gave substantial amounts of the hydrogen chloride adducts as major by-products. Such by-products are rarely detected when the lead reagent is used.



Scheme 13.63

Lewis acid-catalyzed asymmetric aldol reactions of silyl enol ethers with aldehydes are among the most powerful carbon–carbon bond-forming methods; aprotic anhydrous solvents and low reaction temperatures are, however, usually needed for successful reaction. To perform the catalytic asymmetric aldol reaction in aqueous media a chiral crown ether–$Pb(OTf)_2$ complex was employed as a chiral catalyst stable in water–ethanol [9]. Good to high yields and high levels of diastereo- and enantioselectivity were obtained at 0 °C in aqueous media (Scheme 13.64).

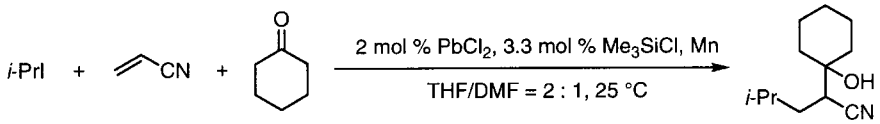


99% (*syn* : *anti* = 94 : 6), 87% ee

Scheme 13.64

13.4 Pb(0) Compounds as Reducing Agents [Pb(0) is Oxidized to Pb(II); Catalytic Use of Pb(II), etc.]

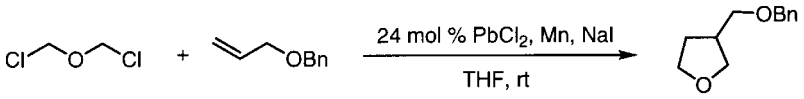
Several procedures for reducing Pb(II) to Pb(0) have been developed to expand the scope of Pb(II). These methods involve the use of an extra metal, e.g. Al, Mn, Ti, or Zn, as a reducing agent to prepare and regenerate Pb(0) species during the course of the reactions. This enables more efficient synthesis with catalytic amounts of Pb(II). Manganese–lead has been used as a reducing agent for three-component coupling of alkyl iodides, electron-deficient olefins, and carbonyl compounds (Scheme 13.65) [83]. Treatment of the alkyl iodide with the manganese metal, activated by addition of a catalytic amount of lead dichloride, afforded an alkyl radical which reacted with the electron-deficient olefin to form intermolecular 1,4-adducts. It is likely that a second one-electron reduction of the resulting radical adduct led to an alkylmanganese compound and that this anionic species was trapped by the carbonyl compound to give the three-component coupling product.



Scheme 13.65

86%

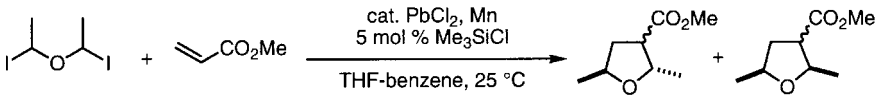
Combination of the manganese–lead reducing agent with a bis(chloromethyl) ether generated a carbonyl ylide which then reacted with a wide range of dipolarophiles – alkenes, alkynes, aldehydes, ketones, and aldimines – to yield [3+2] cycloadducts (Scheme 13.66) [84a].



Scheme 13.66

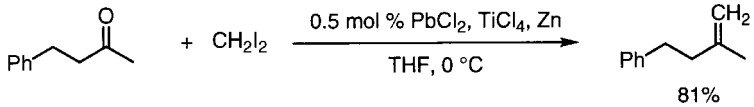
93%

When acrylate was employed the [3+2] cycloaddition proceeded without addition of lead dichloride; the diastereomeric ratios of the products of the reaction between acrylate and the carbonyl ylide depended, however, on the presence of lead dichloride [84b]. For example, a tetrahydrofuran derivative with the *trans* configuration between the 2 and 5 positions was the main product when lead dichloride was added whereas 2,5-*cis*-tetrahydrofuran was the main product when no lead dichloride was added (Scheme 13.67).



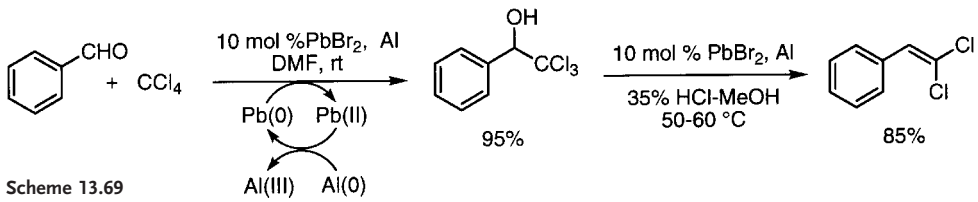
Scheme 13.67

Treatment of ketones with a mixture of CH_2I_2, $TiCl_4$, and zinc in THF at 0 °C for 90 min produced the methylenation product in 5–8% yield whereas when lead dichloride was added the reaction proceeded smoothly at 0 °C to give the product in 81% yield within 30 min (Scheme 13.68) [85]. A catalytic amount of lead dichloride probably promotes further reduction of zinc carbenoid (ICH_2ZnI) by zinc in THF to give a geminal dizinc compound ($CH_2(ZnI)_2$) which is a key intermediate for the methylenation of carbonyl compounds.



Scheme 13.68

When a mixture of tetrachloromethane and benzaldehyde in DMF was treated, at room temperature, with a catalytic amount of lead(II) bromide and a slight excess of aluminum as a stoichiometric reductant the coupled product was obtained in good yield (Scheme 13.69) [86]. Subsequent reductive 1,2-elimination of trichloromethyl carbinol by means of the Pb/Al bimetal system could be readily achieved by changing the reaction media. The mechanism of the Pb/Al bimetal redox system presumably involves lead(0) reduction of polyhalomethane to provide an organolead complex which then reacts with an aldehyde to give the coupling product. Regeneration of lead(0) by reduction of lead(II) with aluminum metal would complete the catalytic cycle.



Scheme 13.69

13.5 Conclusion

The purpose of this chapter was to consider and anticipate the scope and availability of lead compounds in selective organic synthesis. It should be pointed out that more effective structural design of lead species would be possible if one could control the number of coordination sites and complex ligand exchange. Carboxylate ligands are labile and rapidly undergo intermolecular exchange [21 b, 87]. In connection with this undesirable equilibrium, concomitant formation of oligomeric or polymeric structures as a result of complex intermolecular interactions imposes significant limitations on further development in this area of research. Very few systematic studies of relevance to organic synthesis are being conducted on the relationship between reactivity and the nature of ligand coordination. Because the synthetic power of lead should be manifold, however, because of its high oxidation potential and low cost, control of the reactivity of lead by structural and geometrical design, by use of hitherto unknown ligand, is among the most important issues in the future discovery of novel lead reagents. For reasons of atom economy, making Pb(IV) reactions catalytic is increasingly important. Moloney recently explored the use of electrochemical methods to effect reoxidation of Pb(II) to Pb(IV) [88], and another trial has also been reported [89], but much more needs to be done. Given this progress in lead-promoted reactions, unprecedented selectivities and efficiencies will be accommodated, thereby further expanding synthetic scope in this important field of chemistry.

13.6 References

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14
Antimony and Bismuth in Organic Synthesis

Yoshihiro Matano

14.1
Introduction

Antimony and bismuth lie in the 5th and 6th rows of the 15th group of the periodic table and have the electron structures $(Kr)(4d)^{10}(5s)^2(5p)^3$ and $(Xe)(4f)^{14}(5d)^{10}(6s)^2(6p)^3$, respectively. Antimony and bismuth therefore adopt normal oxidation states of 0, +3, and +5, and a variety of types of compound containing these elements have been used as reagents and catalysts in modern organic synthesis. Selected physical properties of antimony and bismuth are summarized in Table 14.1. Relatively small ionization potentials, electronegativities, and bond energies and large orbital radii are characteristics of these heavy elements.

A variety of relatively inexpensive inorganic antimony and bismuth salts are now commercially available. Most of the Lewis acidic metal salts are moisture-sensitive and corrosive; they must, therefore, be handled under dry conditions. Trivalent organic compounds of the types R_3Sb and R_3Bi can be prepared by the metathesis of SbX_3 and BiX_3 with appropriate organometallic reagents. Aliphatic compounds are rather reactive toward air and light, and great care is needed in the handling of the methyl and ethyl derivatives. In contrast, aromatic tertiary compounds are stable crystalline solids and are therefore easy to handle. Pentavalent organic compounds of the types R_3SbX_2 and Ar_3BiX_2 are generally prepared by the oxidation of the corresponding trivalent organic compounds (R_3Sb and Ar_3Bi). Stibonium salts ($R_3R'SbX$) and bismuthonium salts (Ar_3RBiX) can be synthesized by alkylation of R_3Sb and by metathesis of Ar_3BiY_2, respectively. The stability of pentavalent compounds is strongly dependent on the substituents. A limited number of organoantimony and organobismuth compounds are commercially available.

The CAS numbers and uses of antimony and bismuth and representative compounds of the metals in organic synthesis are summarized in Table 14.2. In Sections 14.2 and 14.3, respectively, the uses of antimony and bismuth reagents in organic synthesis are overviewed with selected examples. Each section is divided into four main subsections – metallic and trivalent inorganic reagents, pentavalent inorganic reagents, trivalent organic reagents, and pentavalent organic reagents. Each subsection is subdivided on the basis of reaction types – carbon–carbon bond-forming reactions, carbon–heteroatom bond-forming reactions, oxida-

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Tab. 14.1 Selected physical properties of antimony and bismuth

	Sb	*Bi*
Atom number	51	83
Atomic weight	121.757	208.980
Melting point (°C)	630.7	271.4
First ionization potential (eV)	8.64	7.287
Electronegativity (Allred-Rochow)	1.82	1.67
Ionic radius (Å)	0.90 (3+)	1.17 (3+)
	0.74 (5+)	0.90 (5+)
Covalent radius (Å)	1.41 (3+)	1.52 (3+)
Bond dissociation energy (kJ mol^{-1})	268 (Sb–C)	194 (Bi–C)

Tab. 14.2 CAS number and uses in organic synthesis of Sb, Bi, and their compounds

	CAS no.	*Uses*		*CAS no.*	*Uses*
Antimony					
Sb	7440-36-0	C, R	Bu_3Sb	2155-73-9	C, X, R
$SbCl_3$	10025-91-9	C, X, R, M	Ph_3Sb	603-36-1	C, X, O, R
$Sb(OEt)_3$	10433-06-4	C, X, R	Ph_3SbCl_2	594-31-0	C, X, O
SbF_5	7783-70-2	C, X, O, R, M	Ph_4SbI	13903-91-8	C, X
$SbCl_5$	7647-18-9	C, X, O, R, M			
Bismuth					
Bi	7440-69-9	C, X, O, R	Bu_3Bi	3692-81-7	C, X
$BiCl_3$	7787-60-2	C, X, R, M	Ph_3Bi	603-33-8	C, X, O
$Bi(OTf)_3$	88189-03-1	C, X, R, M	Ph_3BiCl_2	594-30-9	C, X, O
Bi_2O_3	1304-76-3	O	$Ph_3Bi(OAc)_2$	7239-60-3	C, X, O
$Bi(OAc)_3$	22306-37-2	X, O	Ph_3BiCO_3	47252-14-2	C, X, O
$Bi(NO_3)_3 \cdot 5H_2O$	10035-06-0	C, X, O, M	$Ph_4BiOCOCF_3$	83566-43-2	C, X, O
$NaBiO_3$	12232-99-4	O, M			

C = carbon-carbon bond-forming reactions; X = carbon–heteroatom bond-forming reactions; O = oxidation; R = reduction; M = miscellaneous reactions.

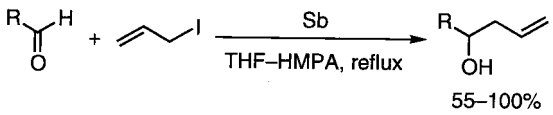
tion, reduction, and miscellaneous reactions. Because of space limitations detailed discussion of reactivity, selectivity, and reaction mechanisms are not provided. It is, therefore, recommended that readers refer to the original references for more detail when the reactions described in these chapters need to be performed. Further information is available in reviews and monographs summarizing the use of antimony and bismuth in organic synthesis [1–4], the specific uses of antimony [5, 6] and bismuth [7–10] in organic synthesis, and general aspects of organoantimony [11, 12] and organobismuth [13–16] chemistry. Doak and Freedman have produced annual surveys of antimony [17] and bismuth [18] chemistry in the *Journal of Organometallic Chemistry*, and Wardell has produced an annual survey in *Organometallic Chemistry* [19].

14.2
Antimony in Organic Synthesis

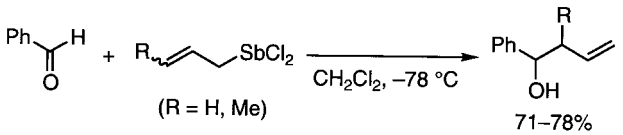
14.2.1
Elemental Antimony and Antimony(III) Salts

14.2.1.1 Carbon–Carbon Bond-forming Reactions

Elemental antimony [20] and $SbCl_3$–M (M = Fe, Al) binary systems [21] mediate the Barbier-type allylation of aldehydes by allylic halides or phosphates to afford homoallyl alcohols (Scheme 14.1). In the presence of fluoride salts a similar allylation with allyl bromide proceeds in H_2O [22]. Allylic dichlorostibanes, generated from allylic stannanes and $SbCl_3$, react with benzaldehyde to give homoallyl alcohols (Scheme 14.2) [23].

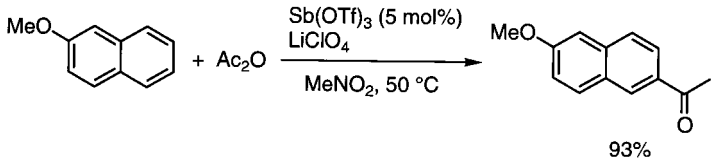


Scheme 14.1



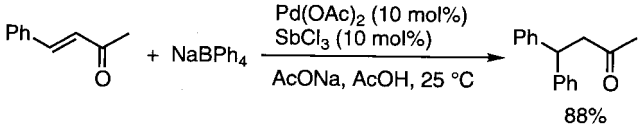
Scheme 14.2

The Friedel-Crafts acetylation of 2-methoxynaphthalene with Ac_2O is efficiently catalyzed by $Sb(OTf)_3$ [24]. When the reaction is conducted in the presence of $LiClO_4$ in $MeNO_2$, only the 6-acetylated isomer (thermodynamic product) is obtained (Scheme 14.3).



Scheme 14.3

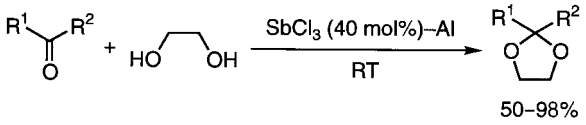
The $Pd(OAc)_2$-catalyzed hydrophenylation of α,β-unsaturated aldehydes and ketones with $NaBPh_4$ proceeds in the presence of a catalytic amount of $SbCl_3$ (Scheme 14.4) [25].



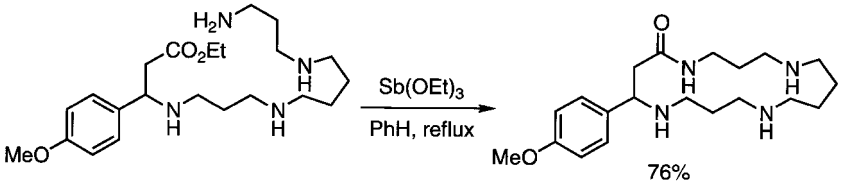
Scheme 14.4

14.2.1.2 **Carbon–Heteroatom Bond-forming Reactions**

The acetalization of aldehydes and ketones with alcohols is catalyzed by $SbCl_3$ in the presence of Fe or Al (Scheme 14.5) [21]. The selective acetalization of aldehydes can also be performed by combined use of $Sb(OR)_3$ (R = Et, *i*Pr) and allyl bromide [26]. $Sb(OEt)_3$ promotes intermolecular amidation between amines and esters or carboxylic acids [27]. When tetraamino esters are used as substrates, the antimony(III)-templated macrolactamization occurs to yield macrocyclic spermine alkaloids (Scheme 14.6).

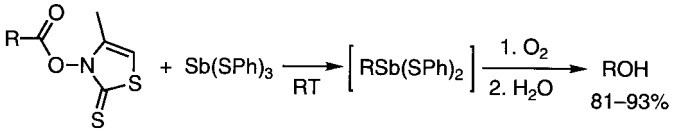


Scheme 14.5

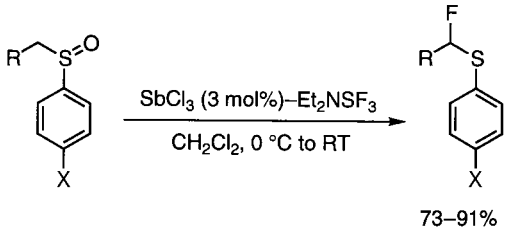


Scheme 14.6

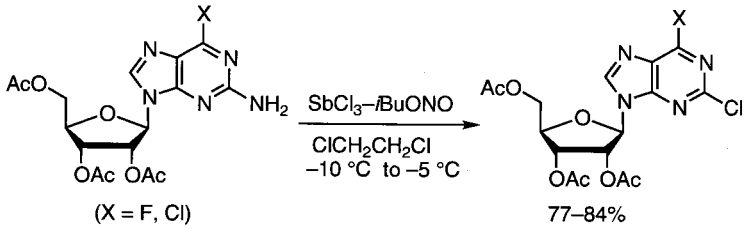
Mixed anhydrides of carboxylic acids (RCO_2H) and thiohydroxamic acid react with $Sb(SPh)_3$ in the presence of O_2 and water to give alcohols (ROH) via $RSb(SPh)_2$ intermediates (Scheme 14.7) [28]. Both thioethers and sulfoxides bearing *α* hydrogen atoms are converted to *α*-fluorothioethers by treatment with (diethylamino)sulfur trifluoride under $SbCl_3$ catalysis (Scheme 14.8) [29]. Treatment of 2-amino-6-halo nucleosides with *tert*-butyl nitrite in the presence of $SbCl_3$ affords the 2-chloro-6-halopurine nucleosides (Scheme 14.9) [30].



Scheme 14.7



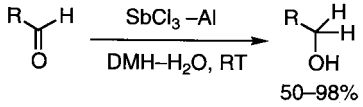
Scheme 14.8



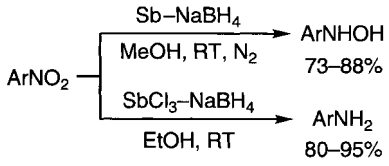
Scheme 14.9

14.2.1.3 **Reduction**

In the presence of molten $SbCl_3$, anthracene and naphthacene are selectively hydrogenated by tetralin to give 9,10-dihydroanthracene and 5,12-dihydronaphthacene, respectively [31]. Both $SbCl_3$–Al and $SbCl_3$–Zn binary systems reduce a variety of aldehydes to the corresponding primary alcohols in DMF–H_2O (Scheme 14.10) [32]. In the presence of a catalytic amount of $SbCl_3$, acetophenones are reduced to 1-arylethanols by an electrochemical method [33]. Nitroarenes are reduced by Sb–$NaBH_4$ in MeOH [34], and by $SbCl_3$–$NaBH_4$ in EtOH [35] to afford *N*-arylhydroxylamines (Scheme 14.11) and anilines (Scheme 14.12), respectively.



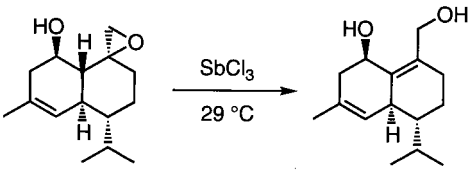
Scheme 14.10



Schemes 14.11, 14.12

14.2.1.4 Miscellaneous Reactions

In the presence of $SbCl_3$, khusinoloxide undergoes rearrangement of the oxirane ring to give an allylic diol (Scheme 14.13) [36]. Microwave irradiation of ketosemicarbazones with $SbCl_3$ in the presence of water produces the corresponding ketones within 6–15 s [37].

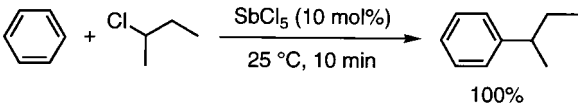


Scheme 14.13

14.2.2 Antimony(V) Salts

14.2.2.1 Carbon–Carbon Bond-forming Reactions

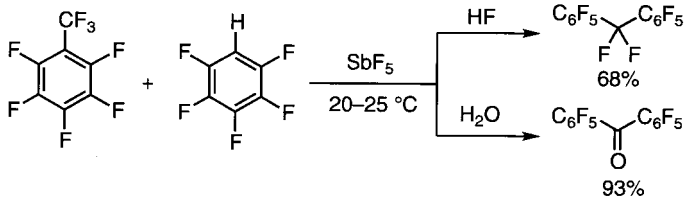
SbF_5 and $SbCl_5$ catalyze Friedel-Crafts alkylation of arenes (Scheme 14.14) [38, 39]. On the basis of the results from benzylation of benzene and toluene, SbF_5 is classified as a very active Lewis acid catalyst whereas $SbCl_5$ is classified as a moderately active catalyst.



Scheme 14.14

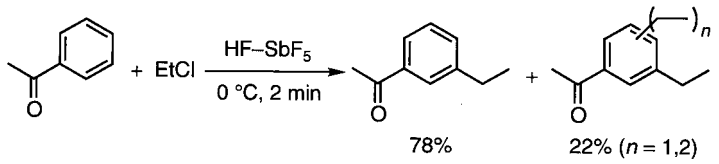
SbF_5 reacts with perfluoroindan and trifluoromethylbenzenes to generate benzylic cations which readily alkylate polyfluorinated arenes [40]. The polyfluorinated *α*-fluorodiphenylmethyl cations thus obtained can be transformed to perfluorinated diphenyldifluoromethanes by acidolysis (Scheme 14.15) or to benzophenones by hydrolysis (Scheme 14.16) [41]. In the presence of the SbF_5 catalyst, perfluorinated benzenes and olefins undergo electrophilic condensation with fluorinated olefins [42]. Pentafluorobenzene reacts with hexachlorobenzene in SbF_5 to give an unsymmetrical perhalogenated biphenyl via a radical cation intermediate [43].

Superacid systems such as HF–SbF_5, FSO_3H–SbF_5–SO_2ClF, and SbF_5–SO_2ClF can protonate a wide range of hydrocarbons, alcohols, and phenols to generate cationic species under mild conditions. In HF–SbF_5 Friedel-Crafts alkylation of aromatic nuclei bearing strong electron-withdrawing groups can be achieved to afford *m*-alkylated derivatives as major isomers (Scheme 14.17) [44]. The relative reactiv-



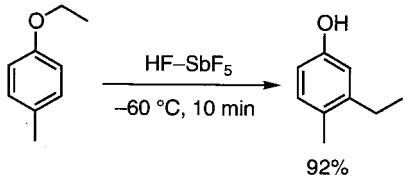
Schemes 14.15, 14.16

ity of the alkyl chlorides toward acetophenone is estimated to be EtCl > *n*PrCl, *i*PrCl, *n*BuCl, *s*BuCl ≫ *i*BuCl ≫ *t*BuCl. In the reactions with propyl and butyl chlorides, however, olefinic, alcoholic, condensation, and skeletal isomerization products complicate the alkylation.



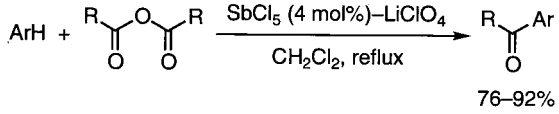
Scheme 14.17

In the HF–SbF_5 system the *O*-alkyl group of alkyl aryl ethers bearing *p*-alkyl or 2,6-dialkyl substituents rearranges to the *meta* position of the aromatic nucleus (Scheme 14.18) [45]. Diprotonation of *para*-substituted phenols with HF–SbF_5 occurs at the oxygen and *meta* carbon atoms, and the resulting diprotonated species undergo Friedel-Crafts alkylation with arenes [46].



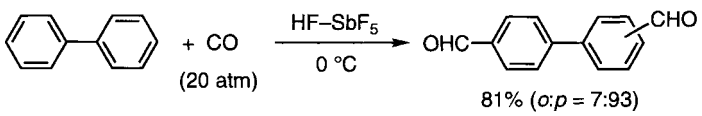
Scheme 14.18

In the presence of a stoichiometric amount of $SbCl_5$, Friedel-Crafts acylation proceeds with acyl halides and acid anhydrides [47]. $SbCl_5$ also promotes the Fries rearrangement of phenyl acetates [48]. The electrophilic acylation of fluoro-olefins with acetyl fluoride or benzoyl fluoride is promoted by SbF_5 in liquid SO_2 [49]. The Friedel-Crafts acylation of benzene and electron-rich arenes is successfully catalyzed by $SbCl_5$–$AgClO_4$ [50], $SbCl_5$–Ar_2BCl [51], $SbCl_5$–$LiClO_4$ [52], or $GaCl_3$–$AgSbF_6$ [53] (Scheme 14.19). Acyl chlorides, acid anhydrides, and acyl enolates are used as sources of acyl groups.

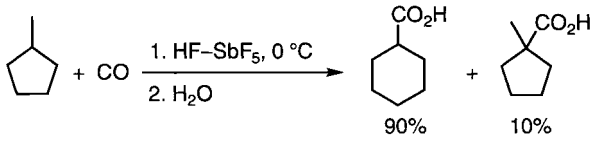


Scheme 14.19

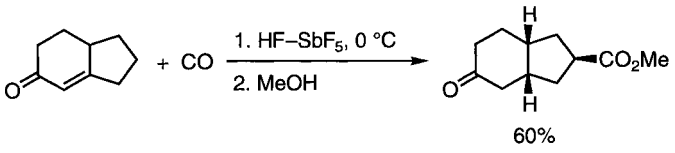
The HF–SbF_5 system works well in the Gattermann-Koch formylation of arenes and the Koch carbonylation of alkanes [54]. For instance, biphenyl is diformylated in HF–SbF_5–CO to afford 4,4′-diformylbiphenyl as a major isomer (Scheme 14.20). The carbonylation of alkanes with C5–C9 carbon atoms in the HF–SbF_5–CO system affords mixtures of C3–C8 carboxylic acids after hydrolysis of the generated secondary carbenium ions [55]. Successive treatment of methylcyclopentane with CO in HF–SbF_5 and with water produces cyclohexanecarboxylic acid as a major product (Scheme 14.21) [56]. It seems that a tertiary methylcyclopentyl cation readily isomerizes to the more stable cyclohexyl cation before being trapped by CO. Bicyclic α,β-unsaturated ketones are functionalized by HF–SbF_5 or FSO_3H–SbF_5 under a CO atmosphere to give saturated keto esters after methanolysis (Scheme 14.22) [57]. Alcohols with short carbon chains also react with CO in HF–SbF_5 to give the corresponding methyl esters [58]. γ-Butyrolactones are carboxylated under the same conditions to afford 1,5-dicarboxylic acids [59].



Scheme 14.20

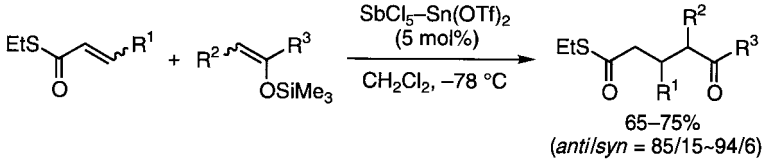


Scheme 14.21

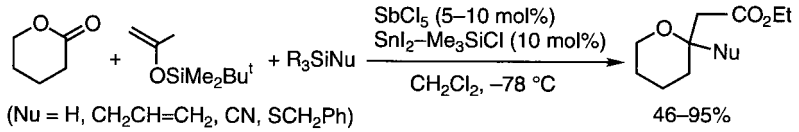


Scheme 14.22

The Mukaiyama-Michael addition of silyl enolates to α,β-unsaturated thioesters is promoted by an $SbCl_5$–$Sn(OTf)_2$ binary catalyst to afford δ-keto thioesters with high *anti* selectivity (Scheme 14.23) [60]. The successive treatment of lactones with a ketene silyl acetal and silyl nucleophiles in the presence of an $SbCl_5$–Me_3SiCl–SnI_2 ternary catalyst yields α-mono- and α,α-disubstituted cyclic ethers (Scheme 14.24) [61]. SbF_5 promotes the condensation of α,β-unsaturated aldehydes and ketones with α-diazocarbonyl compounds to give cyclopropane derivatives in high isomeric purity [62].

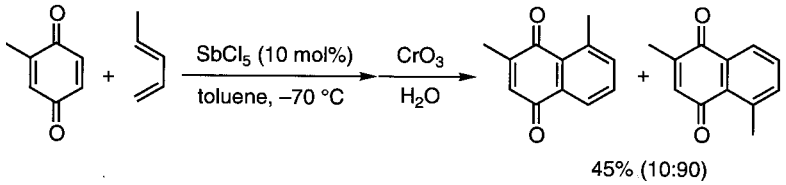


Scheme 14.23

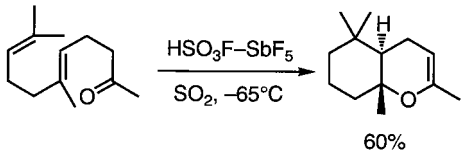


Scheme 14.24

$SbCl_5$ improves the regioselectivity in the Lewis acid-catalyzed Diels-Alder reaction of toluquinone with 1,3-dienes (Scheme 14.25) [63]. The greater steric demand of $SbCl_5$ compared with other Lewis acids would favor the less hindered transition state. Acyclic isopentenoids are cyclized under HF–SbF_5 catalysis to yield monocyclic or bicyclic derivatives (Scheme 14.26) [64].

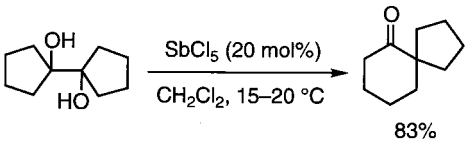


Scheme 14.25



Scheme 14.26

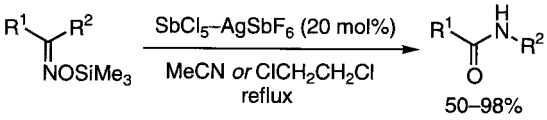
The isomerization of *endo*-trimethylenenorbornane to the *exo* isomer is efficiently catalyzed by superacid systems in cyclohexane or Freon-113 (1,1,2-trichloro-1,2,2-trifluoroethane) [65]. The CF_3SO_3H–SbF_5 system is also effective for isomerization of trimethylenenorbornane to adamantane, although a stoichiometric amount of the acid is necessary to obtain good results [66]. $SbCl_5$ and $SbCl_5$–$AgSbF_6$ promote the pinacol rearrangement of 1,2-diols and their trimethylsilyl ethers (Scheme 14.27) [67].



Scheme 14.27

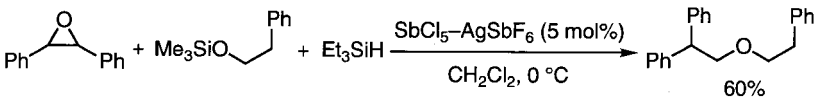
14.2.2.2 Carbon–Heteroatom Bond-forming Reactions

The catalytic Beckmann rearrangement of ketoxime trimethylsilyl ethers can be achieved with $SbCl_5$–$AgSbF_6$, affording the corresponding amides or lactams (Scheme 14.28) [68].



Scheme 14.28

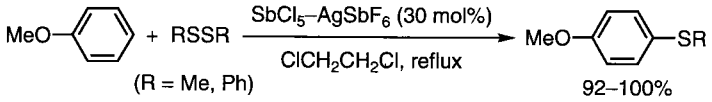
In the presence of a catalytic amount of $SbCl_5$–$AgSbF_6$ or $Ph_3C^+SbF_6^-$, the ring-opening rearrangement of epoxides proceeds to generate carbonyl compounds, which subsequently undergo catalytic reductive coupling with alkoxysilanes–Et_3SiH to yield unsymmetrical ethers (Scheme 14.29) [69].



Scheme 14.29

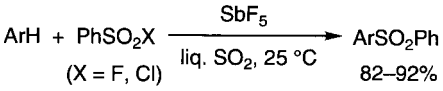
Pentafluorobenzene reacts with elemental sulfur and selenium in the presence of SbF_5 to yield $(C_6F_5)_2S$ and $(C_6F_5)_2Se$, respectively [70]. Diaryl disulfides are also used for sulfenylation with polyfluorobenzenes under SbF_5 catalysis [71]. The sulfenylation of arenes with diphenyl and dimethyl disulfides proceeds under $SbCl_5$–$AgSbF_6$ catalysis to afford the corresponding unsymmetrical sulfides (Scheme

14.30) [72]. The thiocyanation of benzene, alkylbenzene, and halobenzene can be performed with a mixture of $SbCl_5$ and $Pb(SCN)_2$ [73].

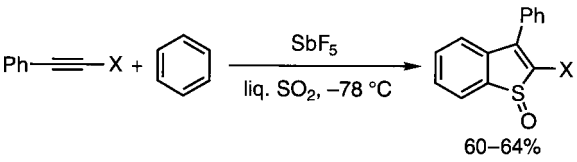


Scheme 14.30

Both RSO_2F–SbF_5 (R = Ph, Me) and $PhSO_2Cl$–$SbCl_5$ complexes are useful agents for the Friedel-Crafts sulfonylation of arenes (Scheme 14.31) [74]. Benzene and toluene are sulfonylated with alkyl- and arylsulfonyl halides or anhydrides in the presence of a catalytic amount of SbF_5 in Freon-113 [75]. When treated with SbF_5 and benzene in liquid SO_2, phenylacetylenes (PhC≡CX) are converted to 3-phenylbenzo[*b*]thiophene *S*-oxides (X = Cl, Ph) (Scheme 14.32) or 2,2-diphenylethenylsulfinic acids (X = H, Br) [76]. In the HSO_3F–SbF_5 magic acid medium, arenes react with SO_2 to give symmetrical diaryl sulfoxides [77].

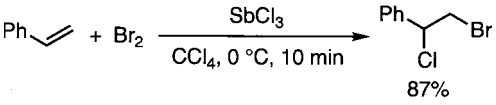


Scheme 14.31

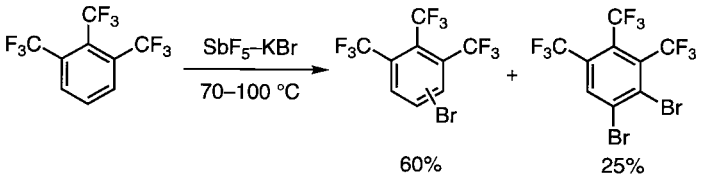


Scheme 14.32

$SbCl_5$–Br_2, $SbCl_5$–LiBr, and $SbCl_3$–Br_2 can be used for the chlorobromination of olefins (Scheme 14.33) [78]. The mixtures $SbCl_5$–Br_2 and $SbCl_5$–I_2 are also effective for the halogenation of both electron-rich and electron-deficient arenes [79]. 1,2,3-Tris(trifluoromethyl)benzene and polyfluorinated indan are brominated at the aromatic nuclei by the SbF_5–KBr binary reagent (Scheme 14.34) [80, 81]. Treatment of SbF_5 with CH_2X_2 (X = Cl, Br) generates halonium ions, which undergo halogenation of saturated alkanes [82].

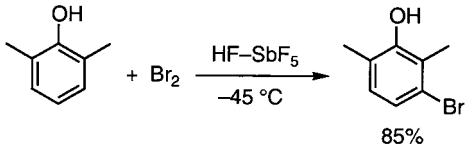


Scheme 14.33



Scheme 14.34

In HF–SbF_5 solution 4-alkyl- and 2,6-dialkylphenols and their methyl ethers (anisoles) are converted to the *O*-protonated forms, which react with Br_2 to afford *m*-bromophenol derivatives selectively (Scheme 14.35) [83, 84]. In HF–SbF_5 *o*- and *p*-bromophenols isomerize to *m*-bromophenol by a 1,2-Br shift in the protonated forms [85]. When NaBr or KBr is used instead of Br_2, the *meta* selectivity is reduced [86]. Electrophilic halogenation of arenes can also be performed with Ar_3SeCl [87].

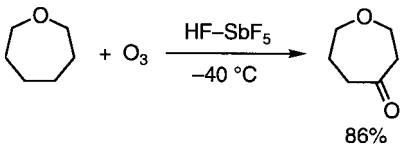


Scheme 14.35

Under $SbCl_5$ catalysis oxygen–bromine exchange between benzaldehyde and *o*-chlorobenzal bromide proceeds at 100 °C to give benzal bromide and *o*-chlorobenzaldehyde in moderate yields [88]. Isomeric transformation of perfluorinated epoxides to the corresponding carbonyl compounds occurs in the presence of SbF_5 [89]. Isomerization of polyfluorinated olefins, cyclohexadienes, and cyclopropanes is also promoted by the action of SbF_5 [90].

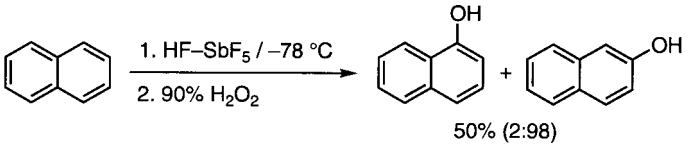
14.2.2.3 **Oxidation**

The oxyfunctionalization of hydrocarbons can be achieved by ozone or hydrogen peroxide in superacid media [91]. Nonactivated C_{sp3}–H bonds of alkanes, aliphatic alcohols, ethers, aldehydes, and ketones are readily oxygenated to the corresponding carboxonium ions [92–95]. The carbonyl products are usually obtained with high regioselectivity that is difficult to attain with other C–H activating reagents (Scheme 14.36).

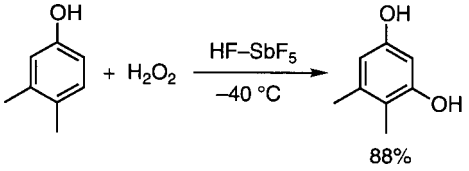


Scheme 14.36

The aromatic C–H bonds of benzene, alkylbenzenes, halobenzenes, and aromatic ketones can also be oxygenated by superacid–H_2O_2 systems, resulting in the formation of the corresponding phenol derivatives [96–98]. When naphthalene is treated with 90% H_2O_2 in HF–SbF_5, 2-naphthol is obtained almost exclusively (Scheme 14.37) [99]. This regioselectivity is in marked contrast with that observed for the reaction in HF alone, where 1-naphthol is formed via typical electrophilic substitution with $H_3O_2^+$. The unusual selectivity observed in the superacid medium has been explained by considering the oxygenation to the protonated naphthalene. Hydroxylation of phenols and anilines by H_2O_2 occurs readily in HF–SbF_5 to yield resorcinols and *m*-aminophenols, respectively (Scheme 14.38) [100].

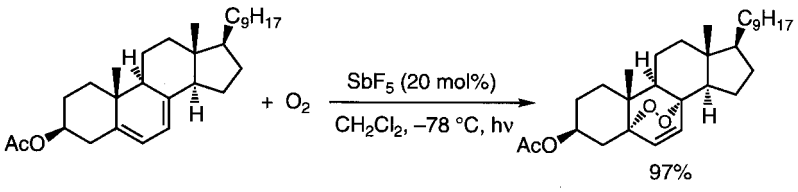


Scheme 14.37



Scheme 14.38

Ergosteryl acetate can be converted to its peroxide by triplet oxygen in the presence of a catalytic amount of SbF_5 or $SbCl_5$ under illumination (Scheme 14.39) [101].

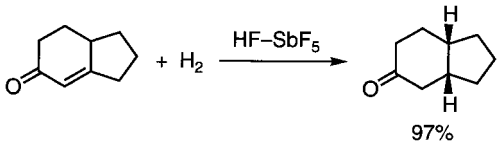


Scheme 14.39

14.2.2.4 **Reduction**

In HF–SbF_5 benzene is reduced by isopentane, affording cyclohexane, methylcyclopentane, and several C5-alkylated benzenes [102]. At the initial stage of the reaction the protonated benzene would abstract a hydride from isopentane to form cyclohexadiene and an isopentyl cation. The reduction becomes catalytic in both the superacid

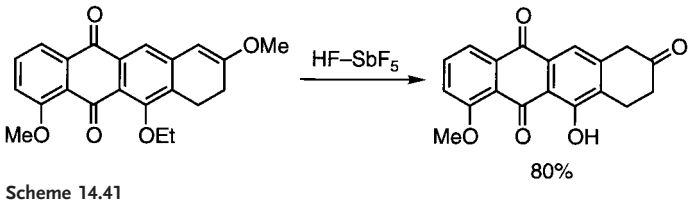
and isopentane under a hydrogen atmosphere. In $HF–SbF_5$ the carbon–carbon double bond in cyclic α,β-unsaturated ketones and steroidal enones is reduced by methylcyclopentane or H_2 to afford the corresponding saturated ketones (Scheme 14.40) [103].



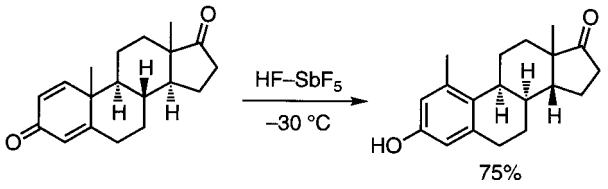
Scheme 14.40

14.2.2.5 Miscellaneous Reactions

Hydrolytic cleavage of the C–O bond of bicyclic, tetracyclic, and steroidal enolates with $HF–SbF_5$ induces their isomerization to the corresponding ketones (Scheme 14.41) [104]. Rearrangement of dienones to aromatic compounds is also promoted by $HF–SbF_5$ (Scheme 14.42) [105]. Ring expansion of methyl penicillinates is achieved by $SbCl_5$ to give thiazepine derivatives [106]. 1,3-Dithianes derived from ketones and aldehydes are deprotected with $SbCl_5$ by means of a single-electron-transfer mechanism [107].



Scheme 14.41



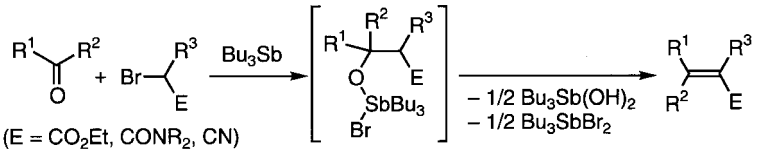
Scheme 14.42

14.2.3 Organoantimony(III) Compounds

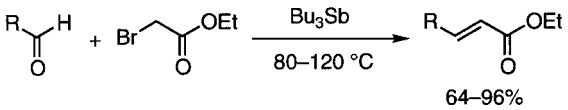
14.2.3.1 Carbon–Carbon Bond-forming Reactions

Tri-*n*-butylstibane (Bu_3Sb) mediates the olefination of aldehydes with activated haloalkanes such as α-halo esters, α-bromo amides, and haloacetonitriles under neat conditions to afford α,β-unsaturated esters, amides, and nitriles, respectively

(Scheme 14.43) [108]. With *α*-bromoacetates and *α*-bromoacetamide, the *E* isomers are formed exclusively (Scheme 14.44). In these reactions, the initially formed stibonium halides recombine to generate zwitterionic species which undergo nucleophilic addition to the carbonyl carbon.

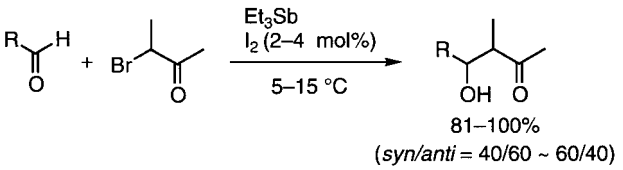


Scheme 14.43

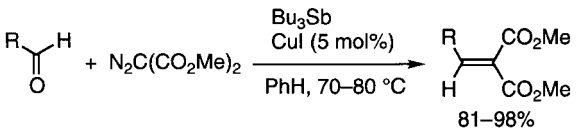


Scheme 14.44

Treatment of aldehydes with two equivalents of *α*-bromoketones and Bu_3Sb produces *α,β*-unsaturated ketones and debrominated ketones [109], whereas the I_2-catalyzed reaction with equimolar amounts of the ketones and R_3Sb gives *β*-hydroxyketones (Scheme 14.45) [110]. The olefination of carbonyl compounds with diazo esters is mediated by Bu_3Sb under copper catalysis (Scheme 14.46) [111].



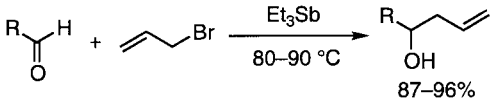
Scheme 14.45



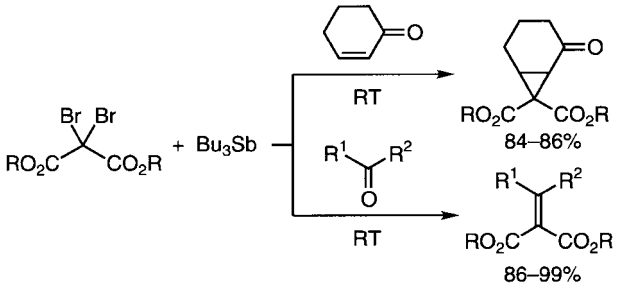
Scheme 14.46

The nucleophilic allylation of aldehydes can be achieved by combined use of R_3Sb and allyl iodide or bromide under neat conditions (Scheme 14.47) [112]. Trichloroacetonitrile also reacts with aldehydes in the presence of Bu_3Sb to yield *α,α*-dichloro-*β*-

hydroxynitriles [113]. Bu_3Sb promotes the cyclopropanation of electron-deficient olefins with α,α-dibromomalonic esters, ethyl α,α-dibromocyanoacetate, and ethyl α,α-dibromophenylacetate (Scheme 14.48) [114]. On the other hand, nonconjugated ketones react with α,α-dibromomalonic esters in the presence of Bu_3Sb to afford the corresponding alkylidenemalonic esters (Scheme 14.49) [115]. $(Ph_2Sb)_2Mg$ promotes olefination between α-bromoacetophenone and aldehydes; diphenylantimony(III) enolates are generated as active nucleophiles [116].

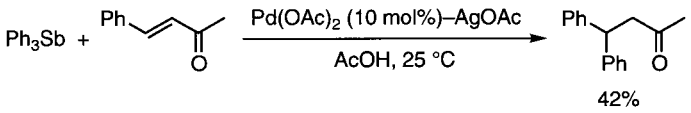


Scheme 14.47

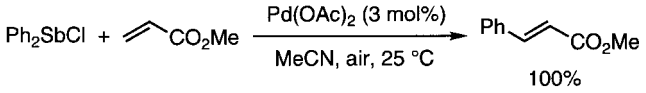


Schemes 14.48, 14.49

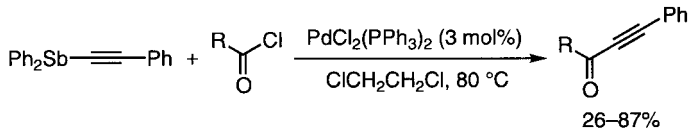
The treatment of Ph_3Sb with stoichiometric amounts of $Pd(OAc)_2$ and Et_3N results in the cleavage of all Sb–C bonds to afford biphenyl in high yield [117]. In AcOH in the presence of AgOAc and a catalytic amount of $Pd(OAc)_2$, α,β-unsaturated ketones and aldehydes undergo hydroarylation with Ar_3Sb to afford the corresponding conjugate addition products (Scheme 14.50) [118]. Ar_2SbCl, $ArSbCl_2$, and Ph_2SbOAc also react with α,β-unsaturated carbonyl compounds under $Pd(OAc)_2$ catalysis. In contrast, styrene and α,β-unsaturated esters undergo the Heck reaction with Ph_3Sb to give stilbene and β-phenyl-α,β-unsaturated esters, respectively. Ph_2SbCl and $PhSbCl_2$ react with a variety of olefins such as allylic alcohols, allylic acetates, and styrenes in the presence of a catalytic amount of $Pd(OAc)_2$, in air to give the corresponding Heck-type products (Scheme 14.51) [119]. Oxygen is believed to mediate the generation of PhPd(OAc) species from Ph_2SbCl and HPd(OAc) in the catalytic cycle. 1-Alkynyldiphenylstibanes react with acyl chlorides under Pd catalysis to afford alkynyl ketones (Scheme 14.52) [120].



Scheme 14.50

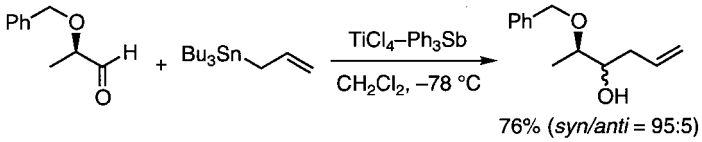


Scheme 14.51



Scheme 14.52

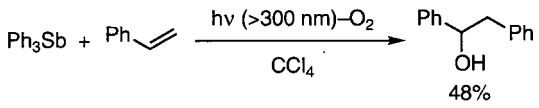
The Lewis acid–base complex $TiCl_4$–$SbPh_3$ mediates the Diels-Alder reaction of an acrylate of (*S*)-ethyl lactate with cyclopentadiene to afford an *endo*-adduct with high diastereoselectivity [121]. The same complex is also effective in the allylation of an *α*-alkoxy aldehyde with allyltributylstannane; a homoallyl alcohol is obtained with a high *syn* selectivity (Scheme 14.53).



Scheme 14.53

14.2.3.2 **Carbon–Heteroatom Bond-forming Reactions**

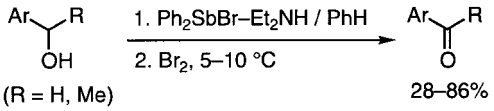
The photochemical reaction of Ar_3Sb with styrenes in the presence of O_2 results in the formation of 1,2-diarylethanols via peroxyantimony(V) intermediates (Scheme 14.54) [122]. The irradiation of a mixture of $Ph_2SbSbPh_2$ and iodoalkanes in air produces alcohols via alkyl diphenylstibonates [123]. Alkyl aryl sulfones are obtained by the Bu_3Sb-promoted reaction of tosyl chloride with alkyl halides [124].



Scheme 14.54

14.2.3.3 **Oxidation**

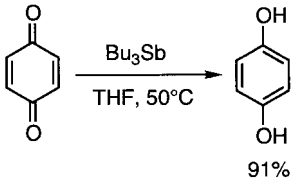
Substituted benzyl alcohols are oxidized to the corresponding carbonyl compounds by consecutive treatment with Ph_2SbBr and Br_2 in the presence of Et_2NH (Scheme 14.55) [125].



Scheme 14.55

14.2.3.4 **Reduction**

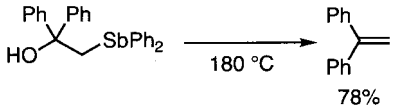
Nitroarenes, *p*-benzoquinone, *α*-bromoketones, *α*-bromophenylacetonitrile, and *α,β*-dibromostyrene are reduced by R_3Sb to azoxyarenes, hydroquinone, ketones, 2,3-diphenylsuccinonitrile, and styrene, respectively (Scheme 14.56) [126]. The combined use of Ph_2SbH and $AlCl_3$ reduces aldehydes to primary alcohols [48a].



Scheme 14.56

14.2.3.5 **Miscellaneous Reactions**

The pyrolysis of 2-hydroxy-2,2-diphenylethylstibane gives 1,1-diphenylethylene (Scheme 14.57) [127]. The optically active (*S*)-(+)- and (*R*)-(–)-2,2′-bis[di(*p*-tolyl) stibano]-1,1′-binaphthyls (BINASb) are used as chiral ligands in the Rh-catalyzed asymmetric hydrosilylation of acetophenone [128].



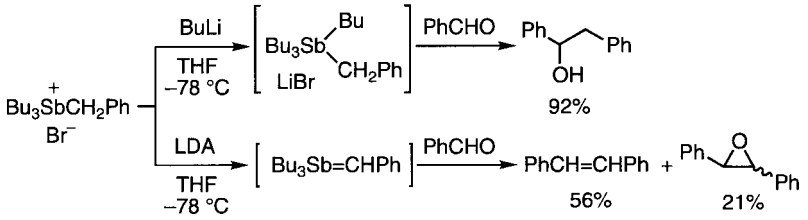
Scheme 14.57

14.2.4
Organoantimony(V) Compounds

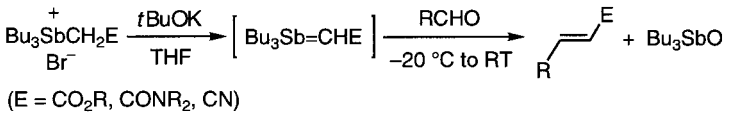
14.2.4.1 **Carbon–Carbon Bond-forming Reactions**

Nucleophilic reagents such as BuLi and PhLi preferentially attack the antimony(V) center of stibonium salts ($[Bu_3Sb^+R][X^-]$) to generate pentaorganylantimony compounds (Bu_3SbRR') which add one of their organyl groups nucleophilically to the carbonyl carbon (Scheme 14.58) [129]. In contrast, strong but less nucleophilic bases, e.g. *t*BuOK and LDA, abstract an *α*-proton of the stibonium salts to generate stibonium ylides ($Bu_3Sb{=}CHR''$), which undergo Wittig-type olefination or Corey-Chaycovsky-type epoxidation with carbonyl compounds (Scheme 14.59). Stibonium

ylides bearing an electron-withdrawing group (CO_2R, $CONR_2$, CN) produce exclusively the corresponding olefins with high *E*-selectivity (Scheme 14.60) [130].



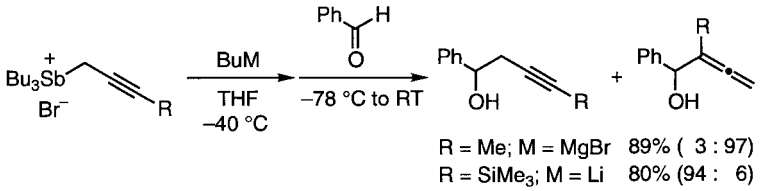
Schemes 14.58, 14.59



(E = CO_2R, $CONR_2$, CN)

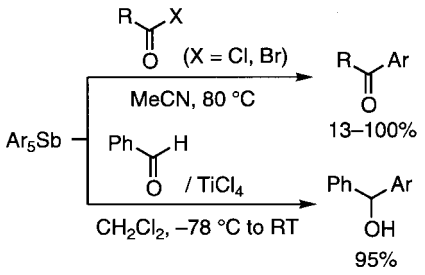
Scheme 14.60

Consecutive treatment of allenyltributylstibonium bromides with BuM (M = MgBr, Li) and aldehydes yields homopropargyl alcohols [131]. Similar treatment of 3-substituted propargyltributylstibonium bromides affords a mixture of homopropargyl and homoallenyl alcohols, the regioselectivity being dependent on the substituents and reaction conditions (Scheme 14.61). Tetrabutyl(prenyl)antimony reacts at the γ position with acid chlorides and an acetophenone–$AlCl_3$ complex to give allyl ketones and homoallyl alcohols, respectively [132]. Pentaorganylantimonys react with benzoyl chloride to give the corresponding phenyl ketones, in which the order of ligand-transfer is $MeCH{=}CHCH_2 > Ph > PhCH_2 > Me > Et > nBu$. In the absence of additives Ar_5Sb reacts with aroyl chlorides, cinnamyl chloride, and ethyl oxalyl chloride to give the corresponding aromatic ketones in good yields (Scheme 14.62) [133]. The phenylation of benzaldehyde, 1-hexanal, and cyclohexanone with Ph_5Sb is promoted by addition of $TiCl_4$ (Scheme 14.63).

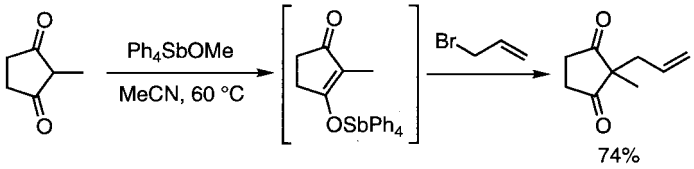


Scheme 14.61

Ph_4SbOMe abstracts an acidic α-proton from 1,3-dicarbonyl compounds to generate antimony(V) enolates which are readily alkylated by allyl, propargyl, and benzyl bromides and by ethyl bromoacetate (Scheme 14.64) [134].

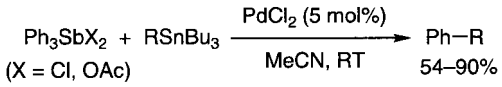


Schemes 14.62, 14.63

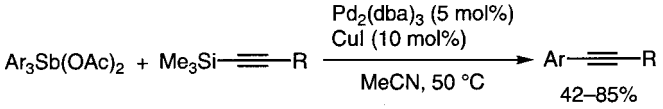


Scheme 14.64

Ph_3SbX_2 (X=Cl, OAc) undergoes cross-coupling reactions with vinyl- and arylstannanes under $PdCl_2$ catalysis to give styrenes and biaryls, respectively (Scheme 14.65) [135]. When the reactions are performed in the presence of CO the corresponding aromatic ketones are obtained. Alkynylsilanes can be used for Pd(0)–Cu(I)-catalyzed cross-coupling and carbonylative cross-coupling reactions with $Ar_3Sb(OAc)_2$ (Scheme 14.66) [136].



Scheme 14.65

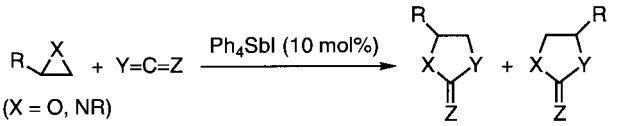


Scheme 14.66

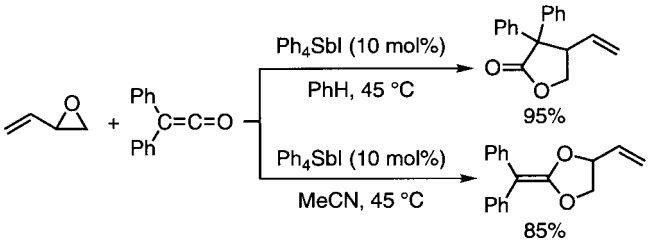
14.2.4.2 Carbon–Heteroatom Bond-forming Reactions

Ph_4SbI catalyzes [2+3] cycloaddition reactions of oxiranes and aziridines with heterocumurenes such as ketenes, isocyanates, isothiocyanates, carbodiimides, carbon dioxide, and carbon disulfide to produce the corresponding five-membered heterocyclic compounds (Scheme 14.67) [137–139]. The regioselectivity depends on the structure of the substituents and on the reaction medium, but *α*-cleavage

usually occurs predominantly. Ph_3SbF_2 also catalyzes the formation of cyclic carbonates from oxiranes and CO_2 [140]. Vinyl epoxide reacts with 1,1-diphenylketene in the presence of Ph_4SbI to give a lactone or an acetal, depending on the solvents employed (Schemes 14.68 and 14.69) [137]. When oxetanes are used in place of oxiranes under Ph_4SbI catalysis six-membered heterocycles are obtained



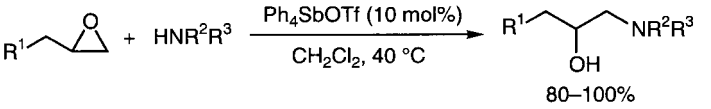
Scheme 14.67



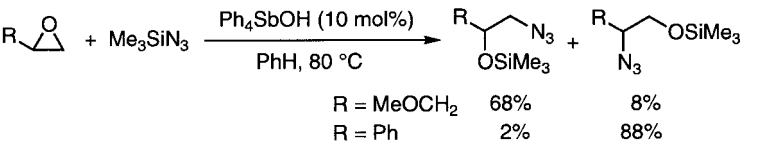
Schemes 14.68, 14.69

[141].

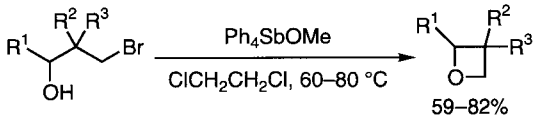
Ph_4SbOTf is an effective Lewis acid catalyst of nucleophilic addition of primary and secondary amines to oxiranes (Scheme 14.70) [142]. Ph_4SbOH catalyzes the azidation of oxiranes with Me_3SiN_3 [143], the regioselectivity being dependent on the substituents of the oxiranes (Scheme 14.71). Ph_4SbOMe promotes intramolec-



Scheme 14.70



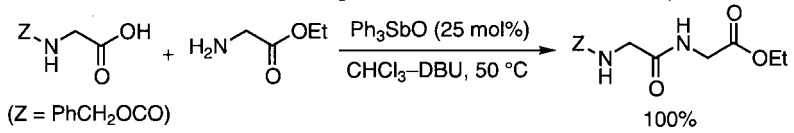
Scheme 14.71



Scheme 14.72

ular C–O bond formation with 1,2- and 1,3-halohydrins (Scheme 14.72) [144] and Ph_4SbOH mediates the β-lactam synthesis from β-halo amides [145].

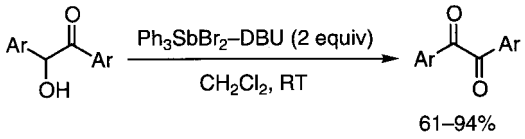
Ph_3SbO mediates the dehydrative condensation of carboxylic acids with amines via $Ph_3Sb(OCOR)_2$ as reactive intermediates [146]. This catalytic system has been applied to dipeptide synthesis (Scheme 14.73) [147]. Treatment of olefins with a mixture of AcOH and P_4S_{10} in the presence of Ph_3SbO affords alkylthio esters [148].



Scheme 14.73

14.2.4.3 **Oxidation**

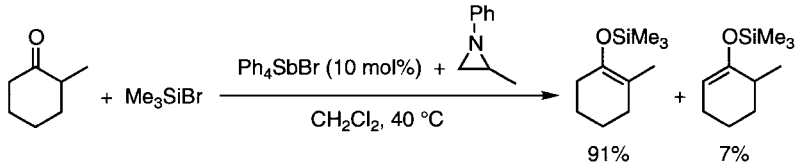
Benzoins are oxidized to benzils by combined use of Ph_3SbBr_2 and DBU (Scheme 14.74) [149].



Scheme 14.74

14.2.4.4 **Miscellaneous Reactions**

Cyclic ketones are transformed into silyl enol ethers by treatment with a mixture of Me_3SiBr and *N*-substituted aziridines under Ph_4SbBr catalysis (Scheme 14.75) [150].



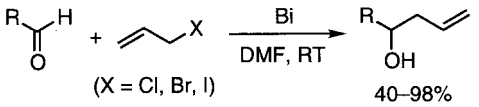
Scheme 14.75

14.3
Bismuth in Organic Synthesis

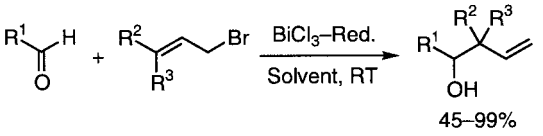
14.3.1
Elemental Bismuth and Bismuth(III) Salts

14.3.1.1 Carbon–Carbon Bond-forming Reactions

Elemental bismuth promotes the Barbier-type reaction between allylic halides and aldehydes to afford homoallyl alcohols in good yield (Scheme 14.76) [151]. Activated bismuth can be generated in situ from $BiCl_3$ and a reducing agent such as Zn [152], Fe [151, 152], Al [153], Mg [154], $NaBH_4$ [155], or, alternatively, by use of electrodes [156] (Scheme 14.77). The Bi-mediated Barbier-type allylation is compatible with hydroxyl and carboxyl groups (Scheme 14.78), and can be conducted in aqueous media [152b]. The allylation also proceeds with allyl alcohols in the presence of PBr_3 or Me_3SiCl–NaI [157]. Aldimines undergo the same type of C–C bond formation to give homoallyl amines [158]. The $BiCl_3$–Zn couple mediates the propargylation of cyclohexanecarboxaldehyde with an allenyl iodide [159].

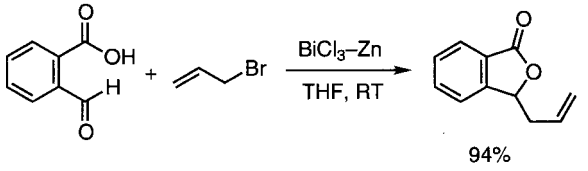


Scheme 14.76



Red./Solvent = Fe/THF, Zn/THF, Al/THF–H_2O, Mg/THF–H_2O, $NaBH_4$/THF–H_2O, $NaBH_4$–Bu_4NBr/DMF, electrolysis/CH_2Cl_2–H_2O

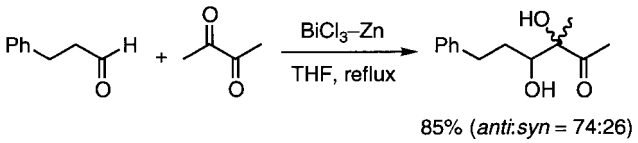
Scheme 14.77



Scheme 14.78

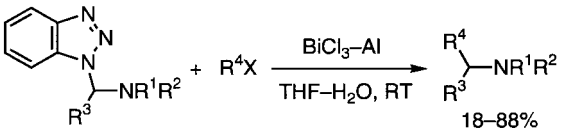
The $BiCl_3$–Al system is applicable to the Reformatsky-type reaction of aldehydes with *α*-bromoketones, although substantial amounts of dehalogenated by-products are formed [160]. In the presence of Zn and $BiCl_3$, the reductive coupling of *α*-di-

ketones with aldehydes occurs to yield *α,β*-dihydroxyketones (Scheme 14.79) [161]. Treatment of aldimines with a mixture of Bi and KOH in MeOH affords the corresponding vicinal diamines [162].



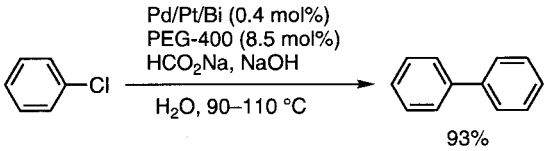
Scheme 14.79

The alkylation of immonium ions derived from 1-(aminoalkyl)benzotriazoles with alkyl halides is promoted by $BiCl_3$–Al in aqueous media (Scheme 14.80) [163].



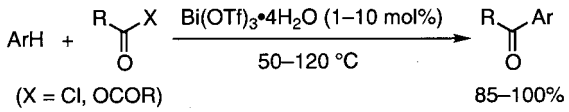
Scheme 14.80

The reductive homocoupling of chlorobenzene to biphenyl is efficiently catalyzed by a recyclable, heterogeneous trimetallic catalyst in the presence of PEG 400 in H_2O (Scheme 14.81) [164]. Bismuth is believed to trap the surplus hydrides and retard undesired side-reactions. A ternary metal redox system, $BiCl_3$–Al–$NiCl_2$(bpy), mediates the reductive coupling of *β*-bromostyrene [165].

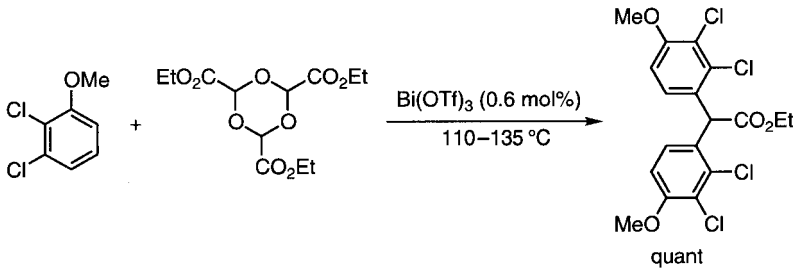


Scheme 14.81

Bismuth(III) salts such as $BiCl_3$, $BiBr_3$, $Bi(OCOR)_3$, and $Bi(OTf)_3$ [166] have been widely used as Lewis acid catalysts to mediate C–C bond formation. $Bi(OTf)_3$, Bi_2O_3, and $BiCl_3$ catalyze Friedel-Crafts acylation with acyl chlorides or acid anhydrides [167]. Both electron-rich and electron-deficient arenes are acylated in high yields under catalysis by $Bi(OTf)_3$ (Scheme 14.82). Under microwave irradiation the catalytic activity of BiX_3 (X=Cl, OTf) in the acylation of aromatic ethers is enhanced [168]. The *N*-acyl group of *p*-substituted anilides migrates to the *ortho* position of the aromatic nucleus under $BiCl_3$ catalysis [169]. Treatment of 2,3-dichloroanisole with the ethyl glyoxylate polymer in the presence of a catalytic amount of $Bi(OTf)_3$ affords an *α,α*-diarylacetic acid ester quantitatively (Scheme 14.83) [170].

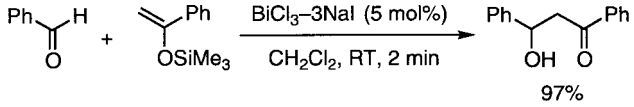


Scheme 14.82



Scheme 14.83

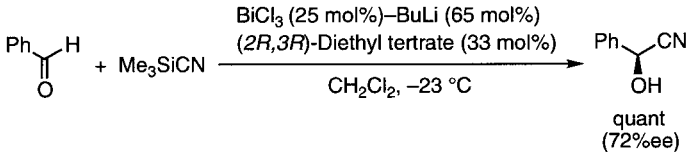
The Mukaiyama-aldol reaction of aldehydes, ketones, and acetals can be catalyzed by $BiCl_3$ [171] or by combined use of $BiCl_3$ and metal iodides (NaI, ZnI_2, SnI_2) [172] to afford the corresponding aldols (Scheme 14.84). The binary system works better than $BiCl_3$ alone. The Mukaiyama aldol reaction is also catalyzed by $Bi(OTf)_3$, the catalytic activity of which is greater than that of $Sc(OTf)_3$ and $Ln(OTf)_3$ [173]. In this reaction, however, the initially generated Me_3SiOTf is believed to be the true catalyst.



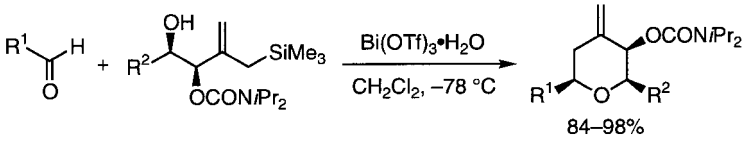
Scheme 14.84

The allylation and cyanation of aldehydes and ketones are mediated by $BiCl_3$ and $BiBr_3$ [174, 175]. When a chiral bismuth(III) catalyst is used for cyanation, cyanohydrins are obtained in up to 72% ee (Scheme 14.85) [175]. The $Bi(OTf)_3$-promoted intramolecular Sakurai cyclization of homoallylic alcohols is involved as a key step in the stereoselective synthesis of polysubstituted tetrahydropyrans (Scheme 14.86) [176]. In the presence of the $BiCl_3$–xMI_n binary catalyst, allyltrimethylsilane [177] and silyl enolates [178] are acylated to give allyl ketones and β-diketones, respectively.

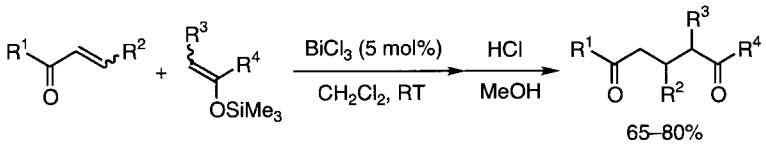
BiX_3 mediates the Mukaiyama-Michael addition of α,β-unsaturated carbonyl compounds (Scheme 14.87) [171, 172 b, c]. The $BiCl_3$-catalyzed Michael addition of 1,3-dicarbonyl compounds to methyl vinyl ketone and benzal acetophenone proceeds efficiently under microwave irradiation [179]. The Knovenagel condensation of aldehydes with active methylene compounds can also be promoted by $BiCl_3$ (Scheme 14.88) [180].



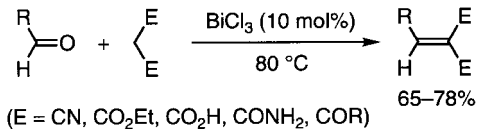
Scheme 14.85



Scheme 14.86

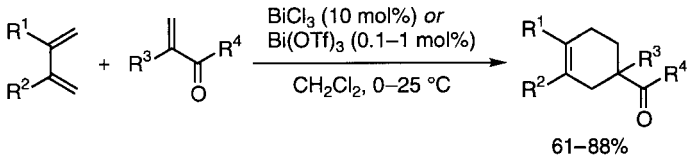


Scheme 14.87



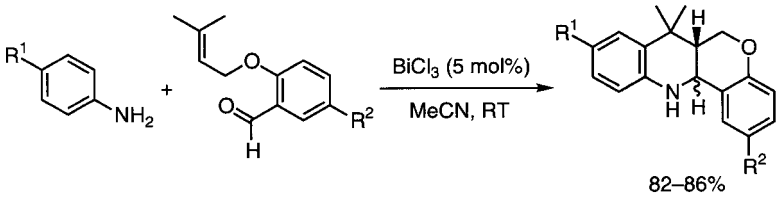
Scheme 14.88

$BiCl_3$ and $Bi(OTf)_3$ catalyze the carbonyl-ene reaction [181] and Diels-Alder reaction [182] without diene polymerization (Scheme 14.89). The tandem [4+2] cycloaddition reaction (Scheme 14.90) [183] and the Erlenmeyer synthesis of azalactones (Scheme 14.91) [184] are catalyzed by $BiCl_3$ and by $Bi(OAc)_3$, respectively.

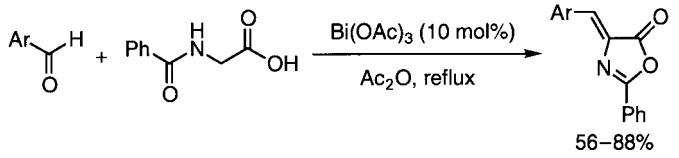


Scheme 14.89

In the presence of 0.01–0.1 mol% $Bi(OTf)_3 \cdot H_2O$, aryl-substituted epoxides rearrange to 2-arylketones with high regioselectivity (Scheme 14.92) [185]. $BiOClO_4 \cdot xH_2O$ is also used in the rearrangement of epoxides, although the cata-

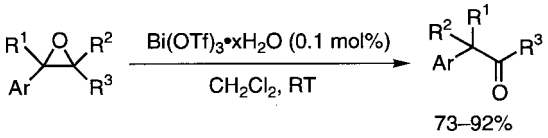


Scheme 14.90



Scheme 14.91

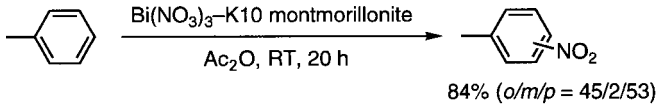
lyst loading is much higher (10–50 mol%) than for $Bi(OTf)_3$ [186]. $BiCl_3$ enhances the catalytic activity of the Pd-mediated hydroarylation of nitroolefins [187].



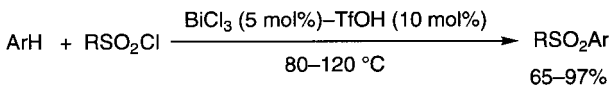
Scheme 14.92

14.3.1.2 Carbon–Heteroatom Bond-forming Reactions

In the presence of montmorillonite arenes are smoothly nitrated by $Bi(NO_3)_3 \cdot 5H_2O$ (Scheme 14.93) [188]. $BiCl_3$ and $Bi(OTf)_3$ are effective catalysts of the electrophilic phosphinylation of electron-rich arenes with PCl_3 [189]. The sulfonylation of arenes proceeds under catalysis by $Bi(OTf)_3$ or BiX_3–TfOH (Scheme 14.94) [190].

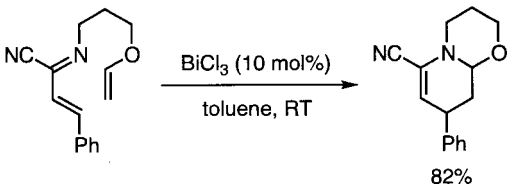


Scheme 14.93

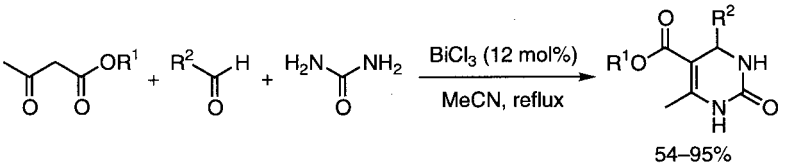


Scheme 14.94

Both the carbonyl- [191] and aza-Diels-Alder reactions [192] are catalyzed by $BiCl_3$ and $Bi(OTf)_3$ (Scheme 14.95). $BiCl_3$ mediates the Biginelli cyclocondensation of a mixture of β-keto esters, aldehydes, and urea to afford 3,4-dihydropyrimidin-2(1*H*)-ones (Scheme 14.96) [193].

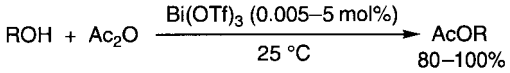


Scheme 14.95



Scheme 14.96

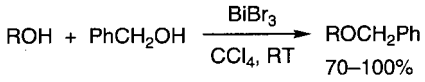
Acetylation, formylation, and benzoylation of a variety of primary and secondary alcohols with the respective acids (acetic acid or anhydride, ethyl formate, and benzoic anhydride) can be achieved under the catalysis of $BiCl_3$, $Bi(OCOCF_3)_3$, or $Bi(OTf)_3$ (Scheme 14.97) [194–196]. The *O*-acylation of phenols is also promoted by these Lewis acids. Among the bismuth(III) salts employed, $Bi(OTf)_3$ is the most effective in terms of reaction conditions and yields of the esters. The $Bi(OTf)_3$–acid anhydride procedure is applicable to the acylation of sterically demanding or tertiary alcohols and phenols. Treatment of tertiary or benzylic bromides with $Bi(OCOR)_3$ (R = Me, Ph) affords the corresponding esters [197]. In the presence of a catalytic amount of $Bi_2(SO_4)_3$, the esterification of *cis*-(–)-thujopsene with a series of C2–C8 acids proceeds in moderate yield [198].



Scheme 14.97

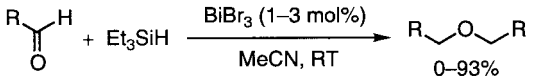
The *O*-benzylation of aliphatic alcohols with benzylic alcohols is promoted by $BiBr_3$ (Scheme 14.98) [199]. In the presence of $BiCl_3$, 1-glycosyl dimethylphosphite reacts with 3-phenylpropanol to give the corresponding glycoside [200].

The $BiCl_3$-catalyzed reductive heterocoupling of carbonyl compounds with unprotected alcohols is effected by Et_3SiH to afford unsymmetrical ethers [201]. Sim-



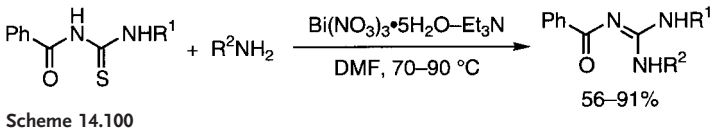
Scheme 14.98

ilarly, aromatic aldehydes undergo reductive homocoupling with Et_3SiH under $BiBr_3$ catalysis to afford dibenzyl ethers (Scheme 14.99) [202]. This method has been extended to the one-pot synthesis of crownophanes and homooxacalixarenes.



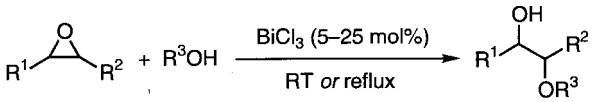
Scheme 14.99

Prolonged heating of $Bi(OAc)_3$ with amines, *N*-substituted formamides, and alcohols affords moderate yields of amides, *N*-acetylformamides, and esters [203]. $BiCl_3$ mediates the Beckmann rearrangement of ketoximes under microwave irradiation [204], and $Bi(NO_3)_3 \cdot 5H_2O$ mediates the guanidylation of *N*-benzoylthioureas (Scheme 14.100) [205].



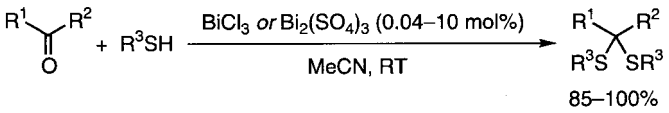
Scheme 14.100

$BiCl_3$ catalyzes the ring-opening addition of mono- and di-substituted epoxides to alcohols, acetic acid, and water (Scheme 14.101) [206]. Cyclic epoxides react with amines, Me_3SiN_3, and Me_3SiCl in the presence of $BiCl_3$ or $Bi(OTf)_3$ to afford the corresponding α-functionalized alcohols [207]. Both aromatic and aliphatic aldehydes are converted to acylals by Ac_2O in the presence of 0.1 mol% $Bi(OTf)_3 \cdot xH_2O$ [208]. BiX_3 (X = Cl, Br, I) and $Bi_2(SO_4)_3$ act as catalysts of the *S,S*-acetalization of aldehydes and ketones (Scheme 14.102) and the transacetalization of *O,O*-acetals to the corresponding *O,S*- and *S,S*-acetals [209]. Monosubstituted oxiranes and cyclohexene oxide are converted to the respective thiiranes under $BiCl_3$ catalysis with NH_4SCN as a source of sulfur atoms [210].



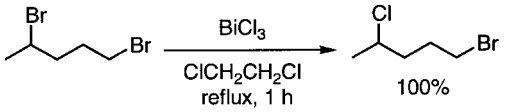
R^3 = H, 75–98%; R^3 = alkyl, 78–99%; R^3 = Ac, 79–96%

Scheme 14.101



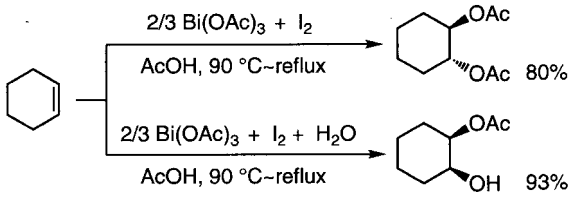
Scheme 14.102

Replacement of the hydroxyl group of secondary and tertiary alcohols by a chlorine atom can be achieved by use of $BiCl_3$ or Me_3SiCl–$BiCl_3$ [211, 212]. Secondary and tertiary alkyl bromides and iodides are converted to the corresponding chlorides and bromides by treatment with BiX_3 (X = Cl, Br; Scheme 14.103) [213]. The $BiBr_3$-promoted nucleophilic substitution of *O*-acetylated *β*-D-ribofuranose is used in the synthesis of *β*-D-nucleoside derivatives [214]. Cyclic carbonates are formed from terminal epoxides and DMF in the $BiBr_3$-catalyzed reaction under an O_2 atmosphere [215].



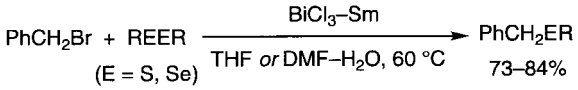
Scheme 14.103

The Prévost reaction of cyclohexene with $Bi(OAc)_3$ in the presence of I_2 in AcOH proceeds stereospecifically to give the *trans* diacetate under dry conditions and the *cis* monoacetate under wet conditions (Scheme 14.104) [216].

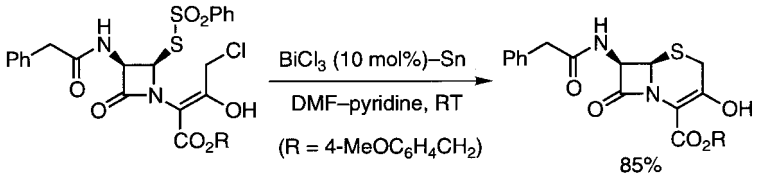


Scheme 14.104

The $BiBr_3$–Sm binary reagent promotes reductive C–S and C–Se bond formation between benzyl and allyl bromides and diorganyl disulfides and diselenides in aqueous media, affording the corresponding sulfides and selenides, respectively (Scheme 14.105) [217, 218]. Intramolecular reductive C–S bond formation by use of a $BiCl_3$–M (M = Sn, Zn) redox system is used in the synthesis of 3-hydroxycephems and 2-*exo*-methylenepenams (Scheme 14.106) [219]. Alkyl and arylsulfonyl chlorides couple with allylic halides in the presence of Bi to afford the corresponding allylic sulfones [220].



Scheme 14.105

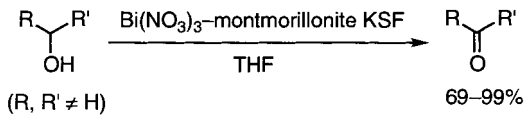


Scheme 14.106

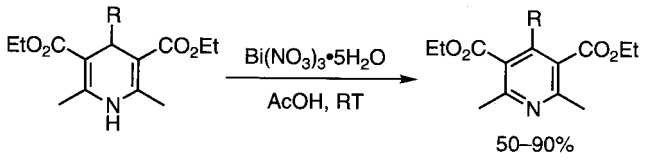
14.3.1.3 **Oxidation**

9-Decen-1-ol is oxidized by air to 9-decenoic acid in aqueous media in the presence of a supported platinum catalyst with bismuth atoms deposited on the surface of the platinum particles [221]. Metal-supported bismuth catalysts have been studied extensively for selective oxidation of hydrocarbons and alcohols for industrial use [222].

Benzyl and secondary alcohols are oxidized by $Bi(NO_3)_3$ supported on clays to afford aromatic aldehydes and ketones, respectively (Scheme 14.107) [223]. Benzoins are oxidized to benzils by treatment with a mixture of 40 mol% $Bi(NO_3)_3 \cdot 5H_2O$ and 4 mol% $Cu(OAc)_2$ in AcOH–H_2O [224]. Bi_2O_3 also oxidizes α-ketols and α-diols, in which the metallic bismuth is deposited after oxidation [225, 226]. When treated with Bi_2O_3–MoO_3, α-hydroxy esters are converted to α-keto esters [227]. $Bi(NO_3)_3 \cdot 5H_2O$ oxidizes several 4-substituted Hantzsch 1,4-dihydropyridines to the corresponding pyridines (Scheme 14.108) [228].

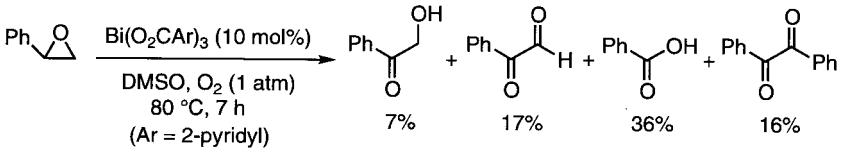


Scheme 14.107

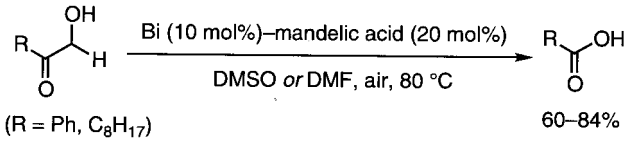


Scheme 14.108

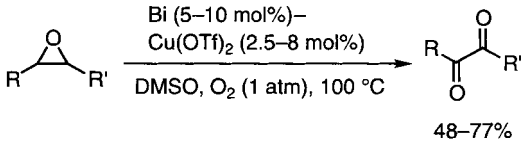
Some bismuth(III) carboxylates catalyze the oxidative C–C bond cleavage of epoxides into carboxylic acids in a DMSO–O_2 system (Scheme 14.109) [229]. In the initial stage DMSO transfers an oxygen atom to epoxides activated by $Bi(OCOR)_3$, producing α-hydroxy ketones [230]. α-Hydroxy ketones can be converted into carboxylic acids by O_2 under bismuth(III) mandelate catalysis (Scheme 14.110). In the presence of catalytic amounts of Bi and $Cu(OTf)_2$, 1,2-disubstituted epoxides are oxidized to α-diketones by a combination of O_2 and DMSO (Scheme 14.111) [231]. The mechanism presumably involves two catalytic cycles; the first oxidative ring-opening to α-hydroxy ketones is catalyzed by $Cu(OTf)_2$–DMSO, and the second oxidation to α-diketones is achieved by the Bi^0/Bi^{III} redox cycle under the action of O_2.



Scheme 14.109



Scheme 14.110

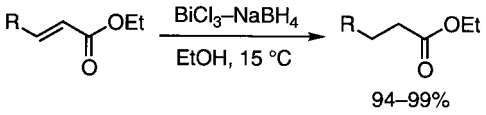


Scheme 14.111

Autoxidation of cyclohexene is mediated by $Bi_2(SO_4)_3$ to give 1-cyclopentene-1-carboxylic acid in 90–92% yield [232]. The selective oxidation of sulfides to sulfoxides is accomplished by $Bi(NO_3)_3$, both stoichiometrically [233] and catalytically with air [234].

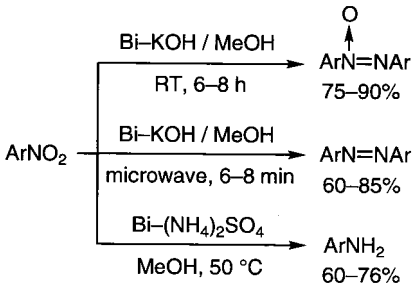
14.3.1.4 **Reduction**

The carbon–carbon double bond of α,β-unsaturated esters [235] and α,β-conjugated aldimines [236] is selectively reduced by the binary reagent $BiCl_3$–$NaBH_4$ to afford saturated esters and allylic amines, respectively (Scheme 14.112). Aryl-substituted olefins are also reduced by $BiCl_3$–$NaBH_4$, to the corresponding alkylbenzenes [237]. Aromatic α-halo ketones are dehalogenated by $BiCl_3$–$NaBH_4$ or $BiCl_3$–$NaBH_4$–NaI in THF–H_2O [238].



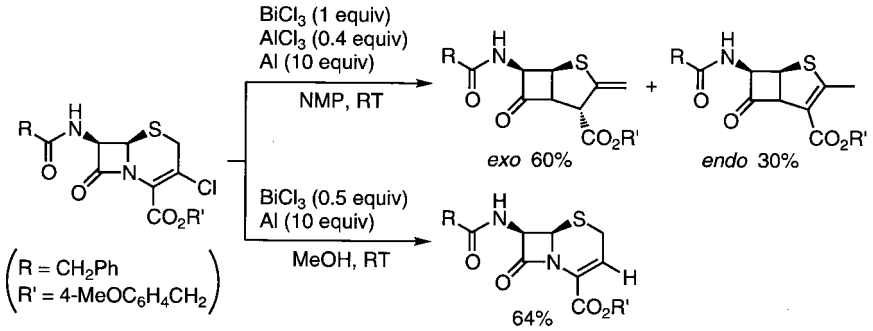
Scheme 14.112

Nitroarenes are reduced to azoxybenzenes by Bi–KOH or Bi–$NaBH_4$ in alcoholic solvents (Scheme 14.113) [239]. Under microwave irradiation the reduction proceeds much more rapidly to give azobenzenes (Scheme 14.114) [239 b]. *para*-Substituted nitrobenzenes are reduced to *para*-substituted anilines by Bi–$(NH_4)_2SO_4$ (Scheme 14.115) [240]. The combined use of $BiCl_3$ and a reducing agent converts nitroarenes into azoxybenzenes, *N*-hydroxyanilines, or anilines, depending on the reagents and reaction conditions employed [241–244].



Schemes 14.113–14.115

3-Substituted Δ^3-cephemes undergo sequential reductive ring-opening/recyclization with $BiCl_3$–Al–$AlCl_3$ in NMP to give 2-*exo*-methylenepenams and 2-methylpenems, and dehalogenation with $BiCl_3$–Al in MeOH to give 3-norcephalosporin (Scheme 14.116) [245].

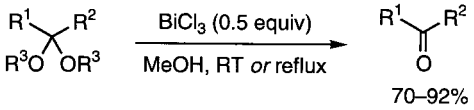


Scheme 14.116

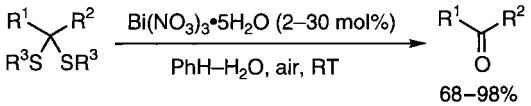
14.3.1.5 Miscellaneous Reactions

The deprotection of trimethylsilyl ethers derived from alcohols and phenols is catalyzed by BiX_3 (X = Cl, $OCOCF_3$, OTf) in MeOH [246]. *Tert*-butyldimethylsilyl (TBDMS) ethers are resistant to the action of $BiCl_3$ and $Bi(OCOCF_3)_3$ but are smoothly deprotected by use of a mixture of $BiCl_3$ and NaI (Scheme 14.117) [247]. Treatment of acetals with $BiCl_3$ in MeOH generates the parent carbonyl compounds in good yield (Scheme 14.118) [248]. $Bi(NO_3)_3 \cdot 5H_2O$ is also effective for the selective deprotection of acyclic acetals derived from ketones and conjugated aldehydes [249]. In the presence of a catalytic amount of $Bi(NO_3)_3 \cdot 5H_2O$, *O,O*-, *O,S*-, and *S,S*-acetals are readily deprotected in air (Scheme 14.119) [250, 251]. The active catalyst is believed to be the NO^+ ion generated from the nitrate. $Bi(OTf)_3$ is a highly efficient catalyst for the deprotection of acetals and ketals; TBDMS ethers remain intact [252]. The deprotection of 1,1-diacetates derived from aldehydes is catalyzed by $BiCl_3$ in $CHCl_3$ under reflux [253].

Scheme 14.117

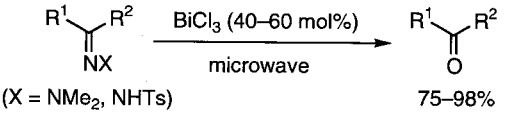


Scheme 14.118



Scheme 14.119

The C_{sp3}–O bond of 2-*tert*-butoxy-furan and -thiophene is cleaved catalytically by $BiCl_3$ or $Bi(OTf)_3$ to produce 2(5*H*)-furanone and -thiophenone, respectively [254]. The selective hydrolysis of aryl esters is catalyzed by bismuth(III) mandelate in DMSO [255]. In the presence of 50 mol% $Bi(NO_3)_3 \cdot 5H_2O$, 10 mol% $Cu(OAc)_2$, and Montmorillonite K10 ketoximes undergo facile deoximation in acetone–H_2O [256]. Under microwave irradiation the $BiCl_3$-promoted hydrolytic cleavage of the C=N bond of dimethylhydrazines, tosylhydrazines, semicarbazones, and oximes proceeds in wet THF (Scheme 14.120) [257–259].

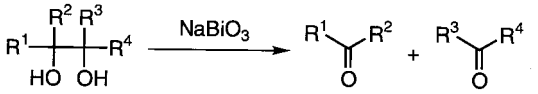


Scheme 14.120

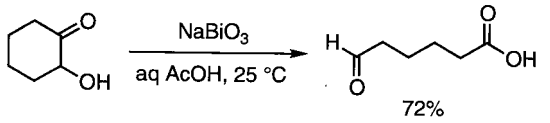
14.3.2 Bismuth(V) Salts

14.3.2.1 Oxidation

$NaBiO_3$ has been used in the oxidation of alcohols, phenols, and olefins. Allylic and benzylic alcohols are oxidized by $NaBiO_3$ to α,β-unsaturated and aromatic aldehydes, respectively [260]. In aqueous H_3PO_4 or AcOH, $NaBiO_3$ cleaves the C–C bond of vicinal diols to give two molecules of carbonyl compounds (Scheme 14.121) [261]. When treated with $NaBiO_3$ in aqueous AcOH, 2-hydroxycyclohexanone is converted to 6-oxohexanoic acid (Scheme 14.122) [262].



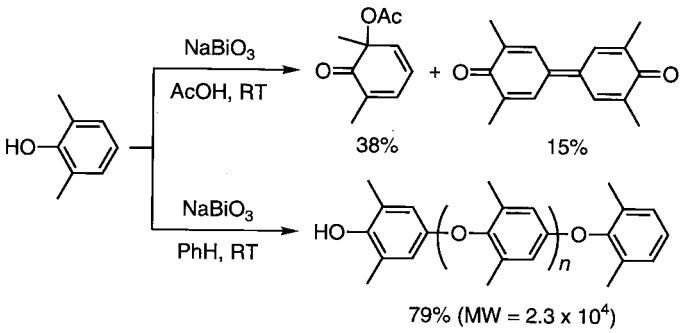
Scheme 14.121



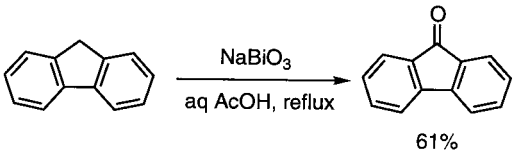
Scheme 14.122

Phenols are oxidized by $NaBiO_3$ to polyphenylene oxides, quinones, or cyclohexa-2,4-dienone derivatives, depending on the substituents and the reaction conditions [263]. For example, 2,6-xylenol is oxidized in AcOH to afford a mixture of cyclohexadienone and diphenoquinone derivatives (Scheme 14.123) [264] and is oxidatively polymerized in benzene under reflux to give poly(2,6-dimethyl-1,4-phenylene) ether (Scheme 14.124) [265]. Substituted anilines and a poly(phenylene oxide) are oxidatively depolymerized by $NaBiO_3$ to afford the corresponding anils [266]. $NaBiO_3$ oxidizes olefins to vicinal hydroxy acetates or diacetates in low to moderate yield [267]. Polycyclic aromatic hydrocarbons bearing a benzylic methylene group are converted to aromatic ketones in AcOH under reflux (Scheme 14.125) [268].

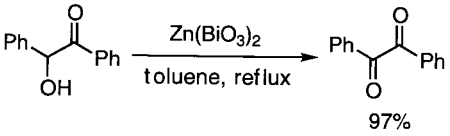
$Zn(BiO_3)_2$, readily available from $NaBiO_3$ and $ZnCl_2$, converts primary alcohols, secondary alcohols, benzoins, thiols, and sulfides to aldehydes, ketones, benzils, disulfides, and sulfoxides, respectively, in toluene under reflux (Scheme 14.126) [269].



Schemes 14.123, 14.124



Scheme 14.125



Scheme 14.126

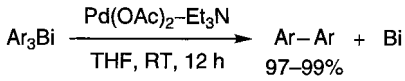
14.3.2.2 Miscellaneous Reactions

Microwave irradiation of ketoximes on wet silica-supported $NaBiO_3$ produces the original ketones within a few minutes [270]. The deoximation of allylic and benzylic oximes can also be achieved by use of $Zn(BiO_3)_2$ [271].

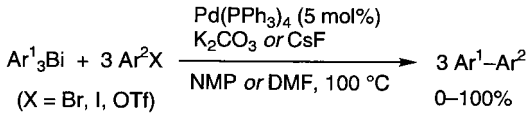
14.3.3 Organobismuth(III) Compounds

14.3.3.1 Carbon–Carbon Bond-forming Reactions

The Bi–C bonds of triarylbismuthanes (Ar_3Bi) are readily cleaved by palladium and rhodium under mild conditions. In the presence of stoichiometric amounts of $Pd(OAc)_2$ and Et_3N, Ar_3Bi is completely converted to biaryls and elemental bismuth (Scheme 14.127) [272]. When Ar_2BiX are used homocoupling proceeds with a catalytic amount of $Pd(OAc)_2$ [272b]. Pd-catalyzed biphenyl formation with Ph_3Bi is much improved under an O_2 atmosphere [273]. In the presence of a catalytic amount of $Pd(PPh_3)_4$ and a base, Ar_3Bi undergoes cross-coupling reactions with aryl bromides, iodides, and triflates to give unsymmetrical biaryls (Scheme 14.128) [274].

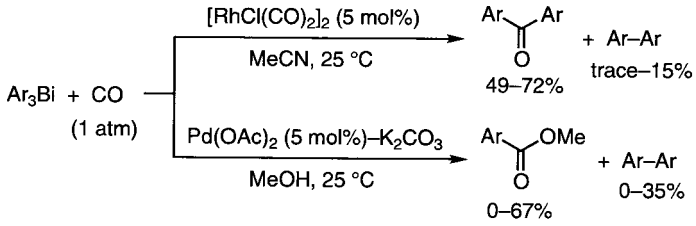


Scheme 14.127

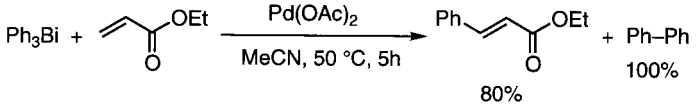


Scheme 14.128

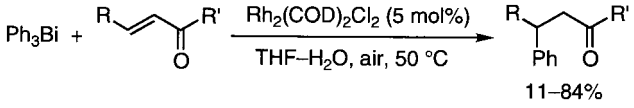
When treated with a Rh- or Pd-catalyst in a CO atmosphere, Ar_3Bi is converted to diaryl ketones or benzoic acid esters, depending on the catalysts and solvents employed (Schemes 14.129 and 14.130) [275]. Ph_3Bi reacts with acyl chlorides in the presence of $Pd(OAc)_2$ and Et_3N in HMPA to give phenyl ketones in good yields [272 b]. Ar_3Bi undergoes the Heck arylation or hydroarylation with α,β-unsaturated carbonyl compounds in the presence of $Pd(OAc)_2$ or a Rh catalyst (Schemes 14.131 and 14.132) [272 a, 276]. $PdCl_2$ catalyzes the arylation of vinyl epoxides with Ar_3Bi to afford arylated allylic alcohols [277].



Schemes 14.129, 14.130

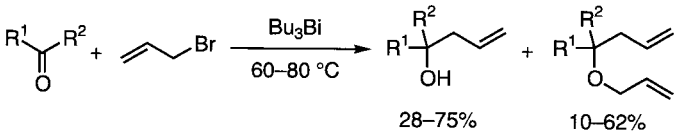


Scheme 14.131



Scheme 14.132

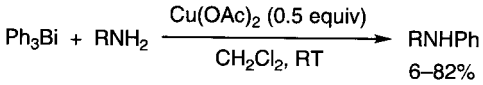
Bu_3Bi mediates the allylation of carbonyl compounds with allyl bromide to give a mixture of homoallyl alcohols and their allyl ethers (Scheme 14.133) [278]. Tris(4-methoxyphenyl)bismuthane catalyzes the cyanation of carbonyl compounds with Me_3SiCN [175]. In the presence of fluoride ions $(C_6F_5)_3Bi$ undergoes nucleophilic substitution with an activated C–F bond of perfluorinated compounds to transfer three C_6F_5 groups [279]. $(CF_3)_3Bi$ can also act as a trifluoromethyl anion equivalent [280].



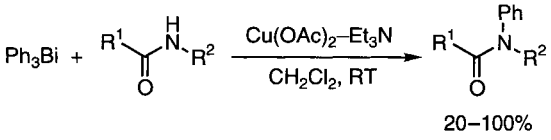
Scheme 14.133

14.3.3.2 Carbon–Heteroatom Bond-forming Reactions

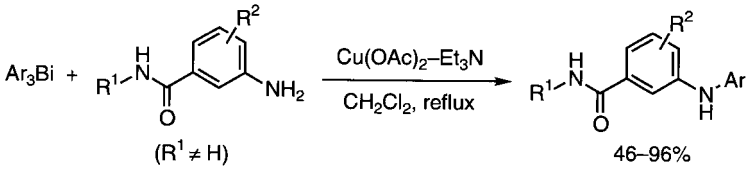
N-Arylaminophthalimides, hydrazines, hydrazones, and N–H containing heterocycles are *N*-arylated by combined use of Ar_3Bi and $Cu(OAc)_2$ (Scheme 14.134) [281] in which $Cu(OAc)_2$ oxidizes Ar_3Bi to $Ar_3Bi(OAc)_2$ and catalyzes the arylation via transmetalation (Section 14.3.4.2). The $Cu(OAc)_2$-promoted *N*-arylation of amides, sulfonamides, ureas, carbamates, and anilines with Ar_3Bi proceeds efficiently in the presence of Et_3N or pyridine (Scheme 14.135) [282]. *N*-Arylation occurs selectively on the primary amino group of aminobenzanilides (Scheme 14.136) [283]. A variety of amines are *N*-alkylated in moderate yields by use of alkylbismuthanes assisted by $Cu(OAc)_2$ [284].



Scheme 14.134

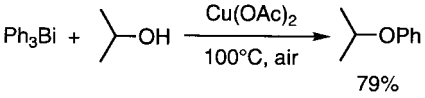


Scheme 14.135

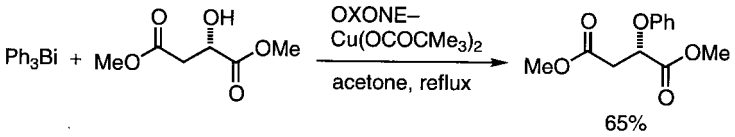


Scheme 14.136

In the presence of excess $Cu(OAc)_2$ Ph_3Bi reacts with alcohols to give *O*-phenyl ethers, and their yields are improved by the presence of O_2 (Scheme 14.137) [285]. The copper-mediated *O*-alkylation of alcohols with R_3Bi affords a mixture of alkyl ethers and aldehydes derived from the R group [286]. Dimethyl malate can be *O*-phenylated by combined use of Ph_3Bi and OXONE in the presence of copper(II) pivalate (Scheme 14.138) [287]. The *O*-phenylation of phenols with Ph_3Bi proceeds smoothly in the presence of $Cu(OAc)_2$ and Et_3N [281a].

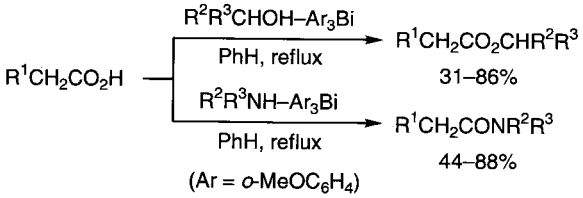


Scheme 14.137

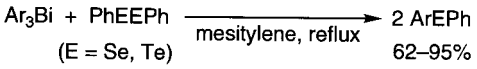


Scheme 14.138

Ar_3Bi bearing *ortho* methoxy groups mediates dehydrative condensation of *α*-monosubstituted carboxylic acids with alcohols and amines (Scheme 14.139) [288]. Macrocyclic esters can be synthesized by the Ar_3Bi-templated reaction of diols with dicarboxylic acid derivatives [289]. The Bi–C bonds of Ar_3Bi are cleaved by diphenyl diselenide and ditelluride to give aryl phenyl selenides and tellurides, respectively (Scheme 14.140) [290]. The reaction of Ar_3Bi with elemental chalcogen (E; Se, Te) affords a mixture of the respective dichalcogenides (ArEEAr) and monochalcogenides (ArEAr).



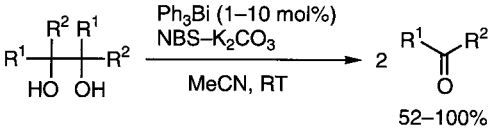
Scheme 14.139



Scheme 14.140

14.3.3.3 Oxidation

In the presence of a catalytic amount of Ph_3Bi, 1,2-glycols are oxidatively cleaved by NBS to afford the corresponding carbonyl compounds (Scheme 14.141) [291]. When treated with a mixture of Ph_3Bi and *t*BuOOH in CCl_4, bibenzyl is oxidized to benzoin in low yield [292].

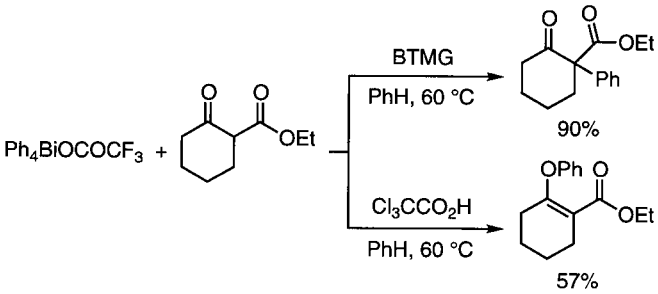


Scheme 14.141

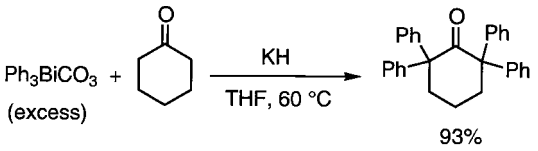
14.3.4 Organobismuth(V) Compounds

14.3.4.1 Carbon–Carbon Bond-forming Reactions

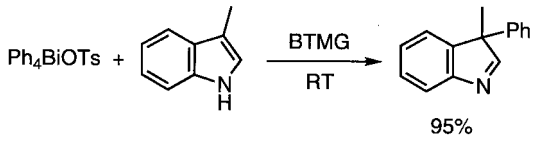
Arylbismuth(V) compounds such as Ar_3BiX_2, Ar_4BiX, and Ar_5Bi have been used in the arylation of a variety of enolic substrates. Under neutral or basic conditions 1,3-dicarbonyl compounds, *α*-nitrocarboxylic acid derivatives, alkyl ketones, and *α*-sulfonyl ketones are *C*-arylated at the active methyl, methylene, or methine carbon via intermediate arylbismuth(V) enolates (Scheme 14.142) [293–296]. Under acidic conditions the *O*-phenylation proceeds to give phenyl enol ethers (Scheme 14.143). When active methylene compounds are treated with excess arylbismuth(V) reagent, polyarylated products are formed in good yield (Scheme 14.144). Nitroalkanes and indoles can also be arylated at the carbon atom (Scheme 14.145) [293b, 297]. *C*-Arylation using the Ar_3BiX_2–base system has been used as a key step in the syntheses of *α*-phenylated amino acid derivatives, flavones, and some natural products [296, 298]. The regioselective *α*-arylation of *α,β*-unsaturated carbonyl compounds and 1-nitrocyclohexene is achieved by successive treatment with LDA–HMPA and Ph_3BiCl_2 (Scheme 14.146) [299].



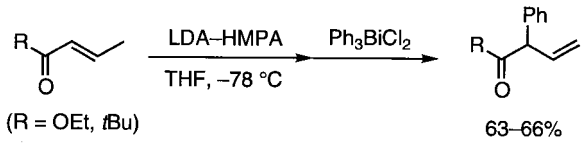
Schemes 14.142, 14.143



Scheme 14.144

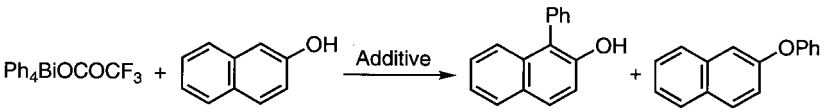


Scheme 14.145



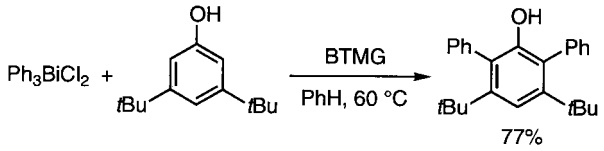
Scheme 14.146

The arylation of phenols with arylbismuth(V) compounds has been investigated extensively both synthetically and mechanistically [293 c, 300–302]. *C*-Arylation at the *ortho* position yields 2-arylphenols and *O*-arylation affords diaryl ethers. In general *C*-arylation occurs preferentially for phenols bearing electron-donating substituents and under basic conditions whereas the *O*-arylation occurs for phenols bearing electron-withdrawing substituents and under acidic conditions. Results from the phenylation of 2-naphthol are summarized in Scheme 14.147 [300 d]. When treated with excess arylbismuth(V) reagents both *ortho* positions of 2,6-unsubstituted phenols are phenylated (Scheme 14.148) [300]. 2,6-Disubstituted phenols, on the other hand, undergo oxidation, oxidative dimerization, or *para*-phenylation [303].



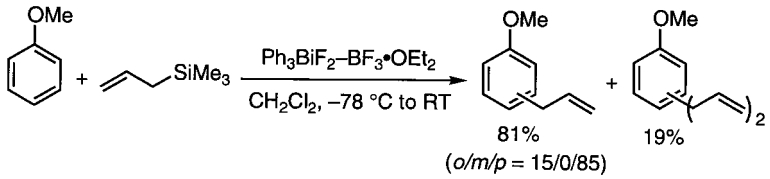
Additive	*C*-Phenyl	*O*-Phenyl
none	9%	67%
Cl_3CCO_2H	–	91%
BTMG	94%	–

Scheme 14.147

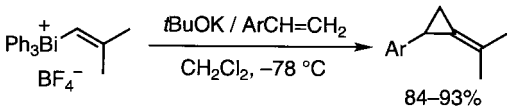


Scheme 14.148

2-Oxoalkylbismuthonium salts react with a sodium salt of dibenzoylmethane to alkylate the active methylene carbon [304]. Treatment of a mixture of Ph_3BiF_2 and allyltrimethylsilane with $BF_3 \cdot OEt_2$ in the presence of excess electron-rich arenes yields allylated arenes via the Friedel-Crafts reaction (Scheme 14.149) [305]. The action of *t*BuOK on a mixture of alkenylbismuthonium salt and styrenes gives alkylidenecyclopropanes in high yield (Scheme 14.150) [306]. Michael addition of sodium *p*-toluenesulfinate to a 1-hexynylbismuthonium salt results in the formation of 3-methyl-1-tosylcyclopentene [307].

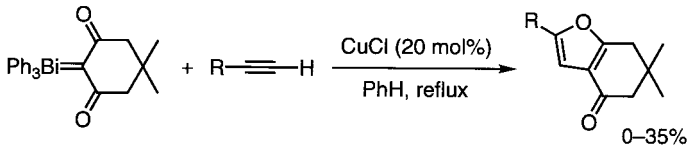


Scheme 14.149

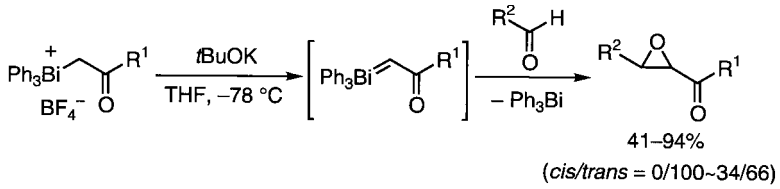


Scheme 14.150

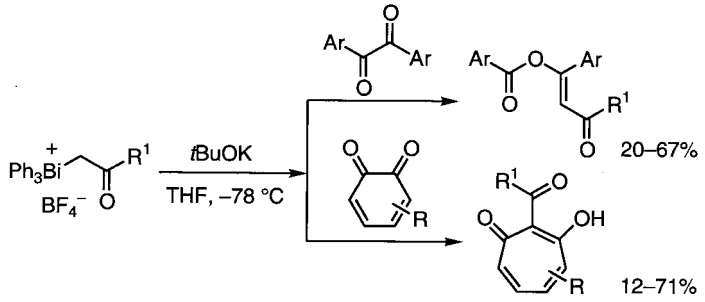
Stabilized bismuthonium ylides derived from cyclic 1,3-dicarbonyl compounds react with aldehydes to afford four kinds of coupling product [308]. In the presence of a copper catalyst the same ylide undergoes cycloaddition reactions with terminal acetylenes and phenyl isothiocyanate to afford furan and oxathiole derivatives, respectively (Scheme 14.151) [309, 310]. Monocarbonyl bismuthonium ylides (Ph_3Bi=CHCOR), generated from the corresponding bismuthonium salts and a base at low temperatures, react with a variety of aldehydes to yield *α,β*-epoxy ketones with high *trans* selectivity (Scheme 14.152) [311]. In the reaction with *N*-sulfonylaldimines, the *cis*/*trans* selectivity of the aziridines produced can be controlled by suitable choice of base and additive [312]. Ph_3Bi=CHCOR reacts readily with *α*-keto esters [313], benzils [314], and *ortho*-quinones [315] affording epoxides, *O*-aroyl enolates (Scheme 14.153), and 3-hydroxytropones (Scheme 14.154), respectively. In these reactions Ph_3Bi is recovered in good yield, indicating the high leaving ability of the triphenylbismuthonio group.



Scheme 14.151

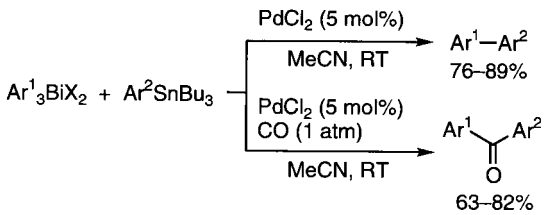


Scheme 14.152



Schemes 14.153, 14.154

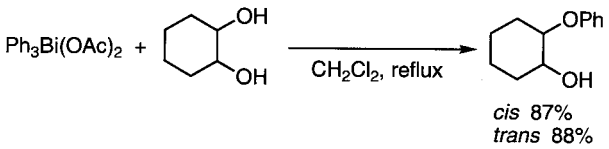
In the presence of a catalytic amount of $PdCl_2$, Ar_3BiX_2 (X=Cl, OAc) couples with arylstannanes to give biaryls (Scheme 14.155) or, under a CO atmosphere, diaryl ketones (Scheme 14.156) [316]. Unsymmetrical biaryls are also prepared by Pd-catalyzed reaction of diaryliodonium salts with Ar_3BiX_2 [317]. Terminal acetylenes are phenylated by Ph_3BiF_2 under CuCl catalysis to afford phenyl-substituted acetylenes [318].



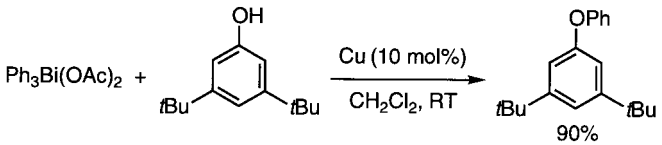
Schemes 14.155, 14.156

14.3.4.2 Carbon–Heteroatom Bond-forming Reactions

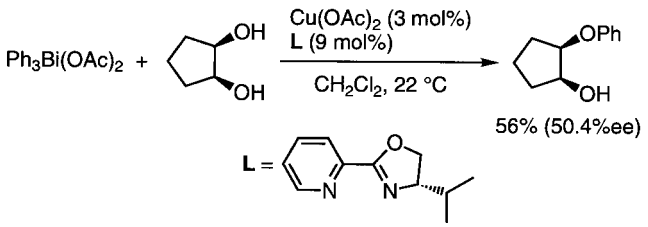
O-Arylation of alcohols can be achieved by use of arylbismuth(V) reagents [319, 320]. In the absence of a catalyst, primary and secondary alcohols are converted to phenyl ethers in low to moderate yields by $Ph_4BiOCOCF_3$ under neutral or acidic conditions. By contrast, both aliphatic and flexible alicyclic diols undergo selective monophenylation with $Ph_3Bi(OAc)_2$ to afford monophenylated ethers in good yields (Scheme 14.157) [321]. In the presence of copper or a copper salt *O*-arylation of enols, phenols, and alcohols proceeds more efficiently and under milder conditions than the uncatalyzed *O*-arylations (Scheme 14.158) [285, 322, 323]. The copper-catalyzed *O*-arylation has been applied to the synthesis of immunosuppressive macrolides [324]. The enantioselective monophenylation of vicinal diols has been attempted using $Ph_3Bi(OAc)_2$ and a chiral copper catalyst (Scheme 14.159) [325]. The kinetic resolution of racemic secondary alcohols via enantioselective benzoylation has been accomplished by use of $Ph_3Bi(OAc)_2$, CO, AgOAc, and a chiral Pd(II) catalyst [326].



Scheme 14.157



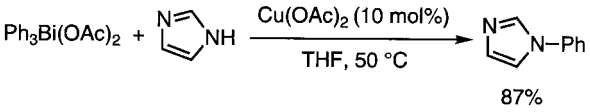
Scheme 14.158



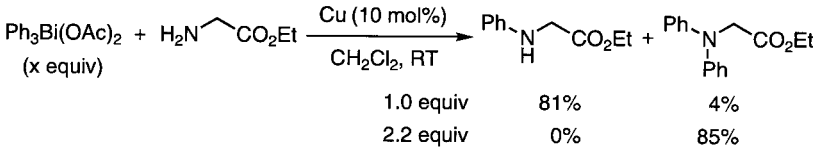
Scheme 14.159

A variety of aliphatic and aromatic amines, amides, and N–H-containing heteroarenes smoothly undergo *N*-arylation with $Ar_3Bi(OAc)_2$ in the presence of a copper catalyst (Scheme 14.160) [297, 327–329]. With copper(II) pivalate the *N*-arylation of amines proceeds more efficiently than with $Cu(OAc)_2$ [330]. Amino acid

derivatives are *N*-phenylated with $Ph_3Bi(OAc)_2$ under copper catalysis (Scheme 14.161) [331]. $Ar_3Bi(OAc)_2$, generated in situ from Ar_3Bi and $PhI(OAc)_2$, can be used directly for the one-pot *N*-arylation of 3,4-dimethylaniline [332].

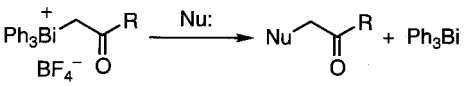


Scheme 14.160



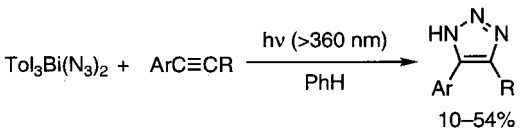
Scheme 14.161

Alkylbismuthonium salts smoothly transfer the alkyl group to a variety of nucleophiles, e.g. piperidine, triphenylphosphane, arylsulfinates, alcohols, arylthiolates, dimethyl sulfide, and halides, under mild conditions (Scheme 14.162) [304, 333]. Triarylbismuth diazides undergo nucleophilic azidation with aldehydes [334] and a photochemical azido transfer reaction with arylacetylenes (Scheme 14.163) [335]. Stabilized bismuthonium ylides undergo [2+3] cycloaddition with sulfenes (Scheme 14.164) [336]. Triarylbismuthane *N*-tosylimides react with aromatic aldehydes, phenyl isocyanate, and benzoyl chloride to form a C–N bond [337]. Triarylbismuthane *N*-acylimides react with dimethyl acetylenedicarboxylates to afford stabilized bismuthonium ylides; when heated or with the assistance of a copper salt these eliminate Ar_3Bi to produce trisubstituted oxazoles in good yields (Scheme 14.165) [338]. Ethyl bis(4-methyl-1-naphthyl)bismuthinate, prepared from the corresponding bismuthane and chloramine-T [339], promotes dehydrative condensation of AcOH and amides to afford *N*-acetylamides under mild conditions [340].

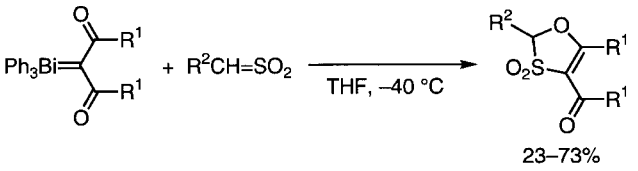


Nu: = Ph_3P, Me_2S, R_2NH, ArSNa, ArONa, KX

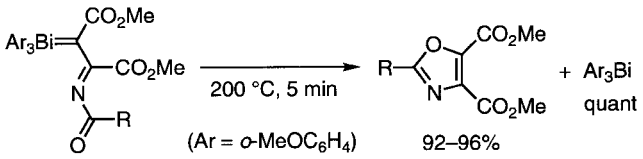
Scheme 14.162



Scheme 14.163



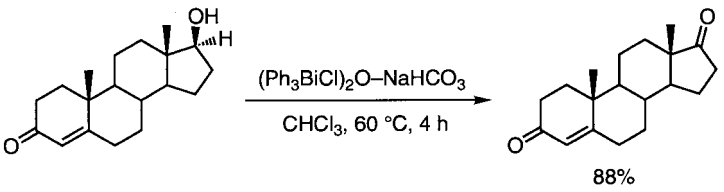
Scheme 14.164



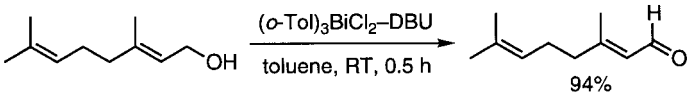
Scheme 14.165

14.3.4.3 **Oxidation**

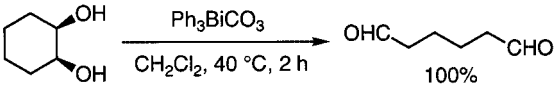
Organobismuth(V) compounds have remarkable oxidizing power. Primary and secondary alcohols are oxidized to aldehydes and ketones, respectively, by Ph_3BiCO_3 or a $(Ph_3BiCl)_2O$–base system (Scheme 14.166) [341]. The reaction is usually conducted under neutral or basic conditions, and further oxidation to carboxylic acids does not occur. Ph_3BiX_2 (X=Cl [342], OO*t*Bu [343], OCOR [344], and others), $Ar_3Bi{=}NR$ [345], $Ar_2Bi(O)OR$ [339], $(Ar_3BiO)_n$ [346], Ph_4BiX [320], and Ph_5Bi [347] have also been reported to oxidize alcohols to carbonyl compounds. *ortho* Substituents have been found to enhance the oxidizing ability of Ar_3BiCl_2 (Scheme 14.167) [348]. In the Bi(V)-based oxidation systems allylic and benzylic alcohols are oxidized much more rapidly than nonconjugated alcohols. The C–C bond of α-glycols is oxidatively cleaved by a variety of organobismuth(V) oxidants to yield two molecules of carbonyl compounds (Scheme 14.168) [291, 349].



Scheme 14.166



Scheme 14.167

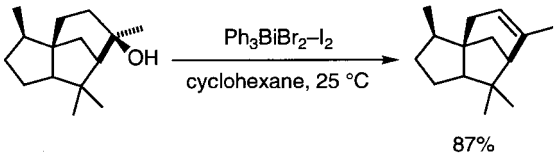


Scheme 14.168

$Ph_3Bi(OOtBu)_2$ oxidizes a methyl group in diethyl ether to afford ethoxyacetic acid as the initial product [350]. The peroxide also oxidizes toluene and ethylbenzene to benzaldehyde and acetophenone, respectively, via radical intermediates [343]. Thiophenol, benzophenone hydrazone, and hydrazobenzene are efficiently oxidized by organobismuth(V) compounds [341 a, c]. 2,6-Dialkylphenols are oxidatively dimerized by Ph_3BiCO_3 [300 e].

14.3.4.4 Miscellaneous Reactions

Sesquiterpinic alcohol is dehydrated by the Ph_3BiBr_2–I_2 system to give cedrene (Scheme 14.169) [351].



Scheme 14.169

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15
Selenium and Tellurium in Organic Synthesis

Akiya Ogawa

15.1
Introduction

Selenium and tellurium belong to group 16 of the periodic table, with oxygen and sulfur; these elements, especially sulfur, selenium, and tellurium, are often called "chalcogen" in a narrow sense. This is because these elements have d-orbitals, and their compounds sometimes have similar chemical properties. Selenium was discovered by Berzelius in 1817 and named from the Greek "*δελην η*", the moon. Tellurium was recognized as an element in 1782; its name was derived from the Latin "*tellus*", the earth. During the last few decades, the chemistry of selenium and tellurium has been growing; as a result organoselenium and tellurium compounds have recently attracted considerable attention in view of their importance as reagents and intermediates in organic synthesis.

Selenium and tellurium have a wide-range of oxidation states (–2 to +6) and form a variety of organic selenium and tellurium compounds. Several excellent books dealing with organoselenium and tellurium chemistry have been published and these provide a comprehensive overview of the preparation and reactivity of selenium and tellurium compounds [1].

This chapter deals with useful (or promising) synthetic reactions based on the characteristic features of selenium and tellurium compounds. Attention is mainly focused on the utility of selenium and tellurium compounds in organic synthesis.

15.2
Preparation of Parent Selenium and Tellurium Compounds

15.2.1
General Aspects of Selenium and Tellurium Compounds

Representative physical constants of selenium and tellurium are listed in Tab. 15.1, where they are compared with those of oxygen and sulfur [2]. As is apparent from the table, selenium and tellurium have physical properties similar to those of sulfur; in contrast, the physical properties of oxygen are different from

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those of the other group 16 elements. Oxygen functions are generally "hard" in character whereas sulfur, selenium, and tellurium functions have "soft" character. Selenium and tellurium therefore form a series of compounds similar to those of sulfur, although selenium and tellurium compounds are often unstable compared with the corresponding sulfur compounds, as expected from their bond-dissociation energies (e.g. bond dissociation energies D (kcal mol^{-1}) for diethyl chalcogenides are as: Se–C, 60; S–C, 70; and O–C, 87 [1f]). Although the bond dissociation energy for tellurium has not been specified, organotellurium compounds, especially in low oxidation states, are sometimes much more unstable than selenium compounds. On the other hand, tetravalent tellurium compounds are relatively stable, compared with the corresponding selenium compounds. In particular, the

Tab. 15.1 Physical constants of the group 16 elements

	O	*S*	*Se*	*Te*
Atomic number	8	16	34	52
Relative atomic mass (^{12}C = 12.0000)	15.9994	32.066	78.96	127.60
CAS Reg. No.	[7782-44-7]	[7704-34-9]	[7782-49-2]	[13494-80-9]
Electronic configuration	$2s^2 2p^4$	$3s^2 3p^4$	$4s^2 3d^{10} 4p^4$	$5s^2 4d^{10} 5p^4$
Radius (Å) (covalent/van der Waals)	0.66/1.40	1.04/1.85	1.17/2.00	1.37/2.20
Electronegativity (Pauling/Allred)	3.44/3.50	2.58/2.44	2.55/2.48	2.1/2.01
Bond length (Å)				
X–H	0.96	1.34	1.46	1.70
X–C	1.43	1.82	1.98	2.05
X–X	1.48	2.05	2.32	2.86
X–O	1.20	1.60	–	–
X=C	1.48	1.50	1.61	2.00
Bond energy (kcal mol^{-1})				
X–H	110	87	73	57
X–C	86	65	59	–
X–X [1e]	33	63	44	33
X=C	191	137	–	–
pK_a				
H_2X (aqueous)	16	7.0	3.8	2.6
Isotopes (natural abundance, %)				
	^{16}O (99.762)	^{32}S (95.02)	^{74}Se (0.9)	^{120}Te (0.09)
	^{17}O (0.038)	^{33}S (0.75)	^{76}Se (9.0)	^{122}Te (2.57)
	^{18}O (0.200)	^{35}S (4.21)	^{77}Se (7.6)	^{123}Te (0.89)
		^{36}S (0.02)	^{78}Se (23.6)	^{124}Te (4.76)
			^{80}Se (49.7)	^{125}Te (7.10)
			^{82}Se (9.2)	^{126}Te (18.89)
				^{128}Te (31.73)
				^{130}Te (33.97)

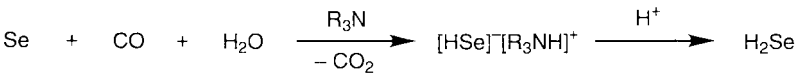
thermal instability of selenoxides as representative tetravalent selenium compounds leads to a useful synthetic method, i.e. "selenoxide *syn*-elimination".

To determine the structures of selenium and tellurium compounds, it is convenient to know natural abundance ratios of their isotopes. For selenium, for example, ^{80}Se and ^{78}Se are present in the ratio of 2:1, and this is indicative of the characteristic features of selenium compounds in mass spectra (i.e. monoselenides, $M^+:M^+-2=2:1$; diselenides, $M^+:M^+-2=1:1$). Furthermore, satellites based on the NMR-active ^{77}Se nuclei are helpful for assignment of carbon signals adjacent to Se in ^{13}C NMR.

15.2.2 Parent Selenium Compounds

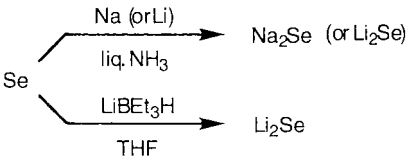
15.2.2.1 Hydrogen Selenide and its Metal and Amine Salts

Hydrogen selenide (H_2Se) can be regarded as an important selenium source for the synthesis of organic and inorganic selenium compounds. The practical use of H_2Se itself has, however, been limited, because of its high toxicity and instability in air. H_2Se can be generated in situ by hydrolysis of aluminum selenide, Al_2Se_3 [1a], or bis(trimethylsilyl) selenide, $(Me_3Si)_2Se$ [3]. Alternatively, reaction of metallic selenium with carbon monoxide and water in the presence of a tertiary amine such as *N*-methylpyrrolidine, and then acidification of the amine salts of hydrogen selenide formed, leads to the isolation of H_2Se (b.p. –41.3 °C) after trap-to-trap distillation (Scheme 15.1) [4].



Scheme 15.1

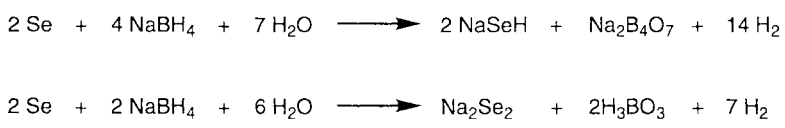
In place of hydrogen selenide itself, a variety of metal or amine salts of hydrogen selenide (M_2Se, M = Li, Na, K, AlR_2, SiR_3, or $[HSe]^-[R_3NH]^+$) have been used conveniently as the synthetic equivalents; these can be prepared by reduction of elemental selenium. Although sodium selenide (Na_2Se) and lithium selenide (Li_2Se) can be synthesized by the reduction of elemental selenium with Na and Li, respectively, in liquid ammonia, the procedure involves somewhat troublesome manipulation in terms of the use of liquid ammonia [5]. A one-pot, high-yield procedure based on the lithium triethylborohydride reduction of elemental selenium has been devel-



Scheme 15.2

oped as depicted in Scheme 15.2 [6]. Technically important is use of selenium shot – if selenium powder is used, the yield of Li_2Se decreases sharply.

Sodium hydrogen selenide, NaSeH, and bis(trimethylsilyl) selenide, $(Me_3Si)_2Se$, can be employed as useful hydrogen selenide equivalents. The former reagent can be prepared very easily by the reaction of elemental powdered selenium with two equivalents of sodium borohydride ($NaBH_4$) in water or ethanol [7]. In this system, the generation of sodium diselenide (Na_2Se_2) is also possible by equimolar reaction between elemental selenium and $NaBH_4$ (Scheme 15.3).



Scheme 15.3

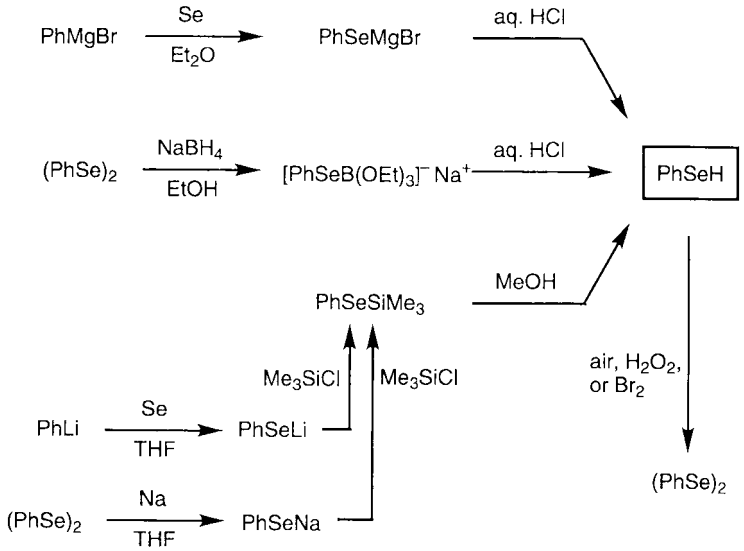
The latter reagent, $(Me_3Si)_2Se$, is conveniently synthesized by silylation of Li_2Se with Me_3SiCl in THF [3, 8]. Addition of a small amount of $BF_3 \cdot Et_2O$ (1.6 mol%) accelerates the silylation of Li_2Se [9]. Bis(trimethylsilyl) selenide, obtained as an air-sensitive, colorless oil, can be stored at –20 °C in an argon-flushed glass vessel for approximately a month. After this time, however, amorphous selenium (red color) is gradually deposited on the vessel. Because of its foul smell, bis(trimethylsilyl) selenide should be handled in a well-ventilated hood.

15.2.2.2 **Selenols and their Metal Salts**

Benzeneselenol, a representative selenol, is a colorless liquid of greater acidity than benzenethiol [$pK_a = 5.9$ (PhSeH); 6.5 (PhSH)]. Benzeneselenol is usually synthesized by the reaction of phenylmagnesium bromide with metallic selenium then quenching with aqueous hydrochloric acid [10]. Similar hydrolysis of the sodium phenylseleno(triethoxy)borate complex prepared by the reduction of diphenyl diselenide with sodium borohydride is a convenient alternative [11].

Phenyl trimethylsilyl selenide is also a useful precursor of benzeneselenol, which is formed on treatment of the former with methanol [12]. Phenyl trimethylsilyl selenide is conveniently prepared by the reduction of diphenyl diselenide with sodium in THF and then silylation of the thus formed PhSeNa with trimethylsilyl chloride. It can also be prepared by silylation of PhSeLi, which can be prepared in situ from metallic selenium and phenyllithium in THF (Scheme 15.4).

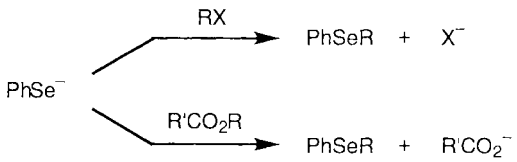
Because of its acidity benzeneselenol gives phenylselenolate ions in the presence of bases such as MeLi (in Et_2O) [13] and NaH (in THF) [14]. Sodium selenolate prepared by $NaBH_4$ reduction of $(PhSe)_2$ is believed to be a complex with triethyl borate [15] and indeed is less nucleophilic than uncomplexed PhSeNa generated by the reduction of $(PhSe)_2$ with Na [14a] (or by reaction of PhSeH with NaH). Selenolate ions are usually much more sensitive to air (molecular oxygen) than is PhSeH. Oxidation of PhSeH or its anions by air or other oxidizing agents such as H_2O_2 or Br_2



Scheme 15.4

provides a general method for synthesis of diphenyl diselenide [16], a key intermediate in the preparation of a variety of organoselenium reagents.

Selenolate ions are widely used as reagents for introducing a PhSe group into organic molecules. For example, nucleophilic substitution of organic halides by selenolate ions leads to the corresponding selenides in good yields [17]. On treatment of esters with selenolate ions, alkyl–oxygen cleavage occurs to provide carboxylic acids and alkyl selenides [14]. The use of lactones as the substrates leads to the synthesis of ω-phenylselenenyl carboxylic acids [15b, 18]. Ring-opening of epoxides by $PhSe^-$ gives β-hydroxy selenides [19], which can be converted into allylic alcohols *via* oxidative elimination of phenylseleno group [15a] (Scheme 15.5).

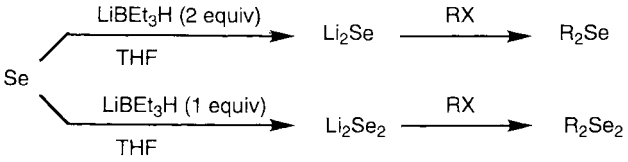


Scheme 15.5

15.2.2.3 Selenides and Diselenides

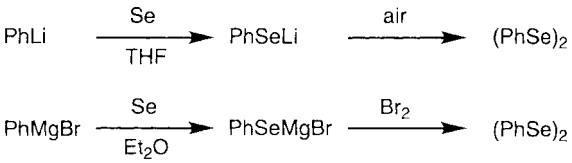
Because organic selenides and diselenides are regarded as some of the most important parent organoselenium compounds, much effort is devoted to accomplishing their preparation. One of the most straightforward means of access to symmetrical dialkyl selenides and diselenides is alkylation of the corresponding alkali

metal salts of hydrogen selenide (H_2Se) or hydrogen diselenide (H_2Se_2), which can be generated in situ by the reduction of elemental selenium with appropriate reducing agents, for example alkali metal–ammonia [5], alkali metal with ultrasound [20], Rongalite ($HOCH_2SO_2Na$) [21], sodium borohydride [7], and lithium triethylborohydride [6]. Among these, reduction systems using sodium borohydride or lithium triethylborohydride are superior to the others because they enable highly selective synthesis of selenides and diselenides without contamination with each other (Scheme 15.6). In addition to the alkali metal salts of H_2Se and H_2Se_2, amine salts of the same compounds can be generated selectively from selenium, carbon monoxide, and water by changing the tertiary amines used (to *N*-methylpyrrolidine and DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), respectively); alkylation of these leads to the corresponding diorganyl selenides and diselenides with excellent selectivity [22].



Scheme 15.6

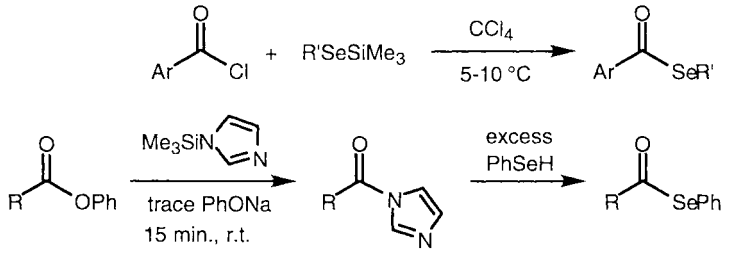
An alternative method for practical synthesis of symmetrical diselenides is reaction of organometallic reagents (e.g. organolithium and organomagnesium reagents) with elemental selenium and subsequent oxidation, with air or bromine, of the selenolate anions formed [16b, 23] (Scheme 15.7). In particular, large-scale synthesis of diphenyl diselenide, a parent compound for PhSe-containing reagents, is usually performed by oxidation of PhSeMgBr with Br_2 [23c, d]. Air-oxidation of selenols also gives rise to symmetrical diorganyl diselenides. For example, 2,2′-dipyridyl diselenide can be derived from 2-bromopyridine by the reaction with NaSeH and subsequent air-oxidation [24].



Scheme 15.7

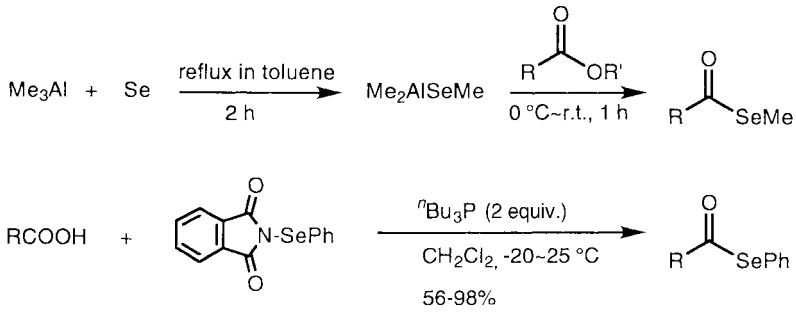
Unsymmetrical organic selenides, on the other hand, can be obtained by the alkylation of selenolate anions ($PhSe^-$) formed in situ by reduction of organic diselenides (Section 15.2.2.2) [25]. Allylic and benzylic selenides (e.g. PhSe-$CH_2CH{=}CH_2$ and PhSe-CH_2Ar) are prepared by allylation and benzylation of $PhSe^-$, respectively [26].

Instead of alkylating reagents, the use of acyl or aroyl halides in this reaction conveniently leads to the synthesis of selenoesters as useful acylating reagents in organic synthesis. A mild and convenient method is reaction of trimethylsilyl selenides with acyl halides [27] or reaction of selenols with imidazolide (or triazolide) of carboxylic acids (Scheme 15.8) [28].



Scheme 15.8

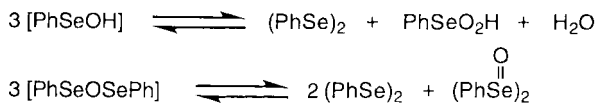
Conversion of *O*-alkyl esters to their corresponding methylselenoesters by treatment with dimethylaluminum methylselenolate has also been reported [29]. Preparation of selenoesters directly from carboxylic acids is accomplished by reaction with selenocyanates [30] or *N*-PSP (*N*-phenylselenophthalimide) [31] in the presence of trialkylphosphine. Yields of selenoesters prepared from *N*-PSP and Bu_3P are usually higher than those obtained by use of ArSeCN and Bu_3P (Scheme 15.9).



Scheme 15.9

15.2.2.4 **Selenenic Acids and their Derivatives**

Organic selenenic acids and their anhydrides are thermally unstable and readily disproportionate into the corresponding diselenides and seleninic acids (or their anhydrides) [15a, 32]. Because this process is believed to be reversible, these selenium compounds can be generated in situ by the comproportionation, i.e. the reverse processes (going right to left in the following equations), and used directly without isolation (Scheme 15.10) [32–34].



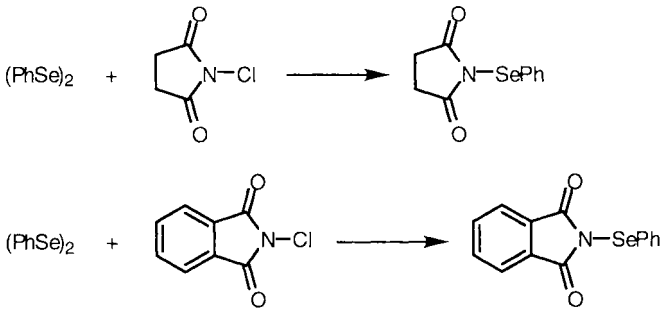
Scheme 15.10

Since seleninic acids and their anhydrides are much more stable than the corresponding selenenic compounds, they can be employed as starting materials for the synthesis of selenenic acids and their anhydrides. Reduction of seleninic acids and their anhydrides with appropriate reducing reagents such as hydrazines [35], hypophosphorous acid (H_3PO_2) [36], and thiols [37] is a useful alternative method for the synthesis of selenenic acids and their anhydrides.

Compared with selenenic acids, the corresponding selenenyl chlorides and bromides are relatively stable, and can be prepared by the direct halogenation of organic diselenides. In particular, benzeneselenenyl chloride and bromide (PhSeCl, PhSeBr) are commercially available, and widely employed as excellent electrophiles in organic synthesis [38]. Technically important in the bromination of diselenides is slow addition of one equivalent of bromine to a solution of diselenides in THF – rapid addition and/or use of excess bromine result in the formation of seleninyl bromides ($RSeBr_3$) as byproducts (Scheme 15.11).

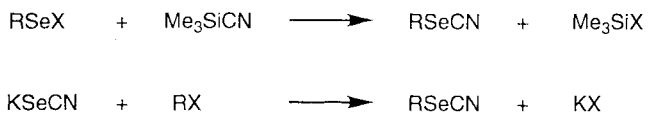
Scheme 15.11

As well as selenenyl halides, *N*-phenylselenosuccinimide (*N*-PSS) and *N*-phenylselenophthalimide (*N*-PSP) are widely used as powerful selenenylating reagents in organic synthesis. *N*-PSS and *N*-PSP are conveniently synthesized by reaction of diphenyl diselenide with *N*-chlorosuccinimide and *N*-chlorophthalimide, respectively (Scheme 15.12) [39].



Scheme 15.12

Selenocyanates (RSeCN), which are employed for the synthesis of selenides and selenoesters, are usually derived from selenenyl halides and cyanide ion (or silyl cyanate) [38k, 40]. Alkylation of potassium selenolate (KSeCN) with alkyl halides is an alternative means of preparation of aliphatic selenocyanates (Scheme 15.13) [41].

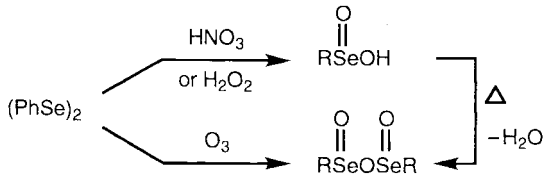


Scheme 15.13

15.2.2.5 Seleninic Acids and their Derivatives

Seleninic acids and their anhydrides, RSe(O)OH and RSe(O)OSe(O)R, are used as versatile and specific oxidizing reagents for a variety of organic compounds. In contrast with selenenic acids, seleninic acids (and their anhydrides) are stable, especially, benzeneseleninic acid, PhSe(O)OH, and benzeneseleninic anhydride, PhSe(O)OSe(O)Ph, which are commercially available.

Methods of synthesis of seleninic acids are based on oxidation of diselenides (or selenocyanates) with HNO_3 [38k, 42] or H_2O_2 [23a, 42d, 43]. Seleninic anhydrides are prepared by dehydration of seleninic acids [42e, 44] or by oxidation of diselenides with ozone (Scheme 15.14) [44, 45].



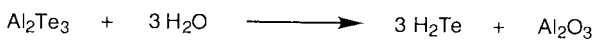
Scheme 15.14

The synthetic utility of selenonic acid ($RSeO_3H$) and its derivatives has, on the other hand, been limited, because of their lower thermal stability.

15.2.3 Parent Tellurium Compounds

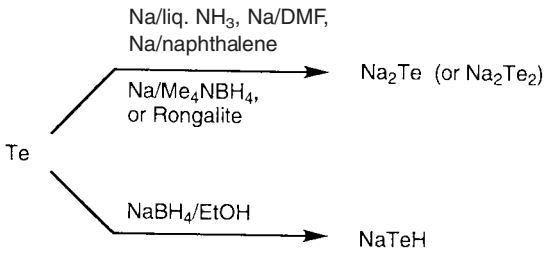
15.2.3.1 Hydrogen Telluride and its Metal Salts

Because hydrogen telluride (H_2Te) is much more sensitive than hydrogen selenide to air and light, it is usually prepared in situ by hydrolysis of aluminum telluride (Al_2Te_3) with excess water; it is then used directly without isolation (Scheme 15.15) [46].



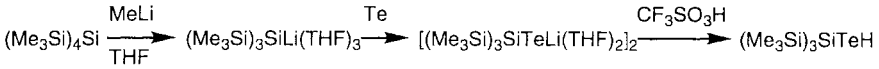
Scheme 15.15

Alkali metal tellurides, e.g. Na_2Te, are sometimes used as hydrogen telluride analogs; they are prepared by reduction of elemental tellurium with appropriate reducing agents, for example Na/liq. NH_3 [5], Na/DMF [47], Na/naphthalene [48], Na/Me_4NBH_4 [49], and Rongalite [50]. By changing the molar ratio of Te/reducing agent appropriately, sodium ditelluride (Na_2Te_2) can be synthesized by use of methods analogous to those mentioned for sodium telluride (Na_2Te) [48a, 51]. Reduction of elemental tellurium with $NaBH_4$ in ethanol, on the other hand, results in the formation of sodium hydrogen telluride, NaTeH (Scheme 15.16) [51d, 52].



Scheme 15.16

Thermally stable tris(trimethylsilyl)silyl hydrogen telluride, $(Me_3Si)_3SiTeH$, is isolated according to Scheme 15.17. On heating at 130 °C for 1 day in hydrocarbon solution $(Me_3Si)_3SiTeH$ is stable without decomposition; it readily decomposes on irradiation with sunlight, however, forming tellurium mirror [53].

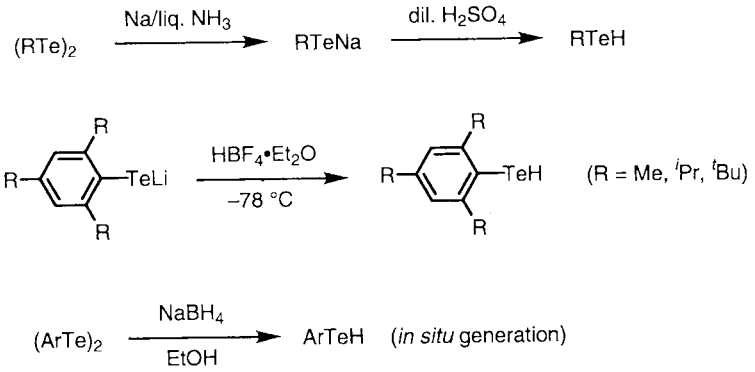


Scheme 15.17

15.2.3.2 **Tellurols and their Metal Salts**

Tellurols are much more sensitive than selenols to air and light and readily decompose to give the corresponding ditellurides. Aliphatic tellurols are prepared by reduction of the corresponding ditellurides with sodium in liq. NH_3, then protonation of the thus formed tellurolate ions; aromatic tellurols cannot usually be isolated in the pure form [54]. It has been reported that, exceptionally, arenetellurols bearing a sterically bulky substituent have been isolated as colorless crystals at low temperature (–78 °C) [55]. Aromatic tellurols are, therefore, usually prepared in situ by the reduction of ditellurides with $NaBH_4$, and employed directly for the synthesis of organic tellurium compounds without isolation (Scheme 15.18) [56].

Isolated aliphatic tellurols, on the other hand, are usually insoluble in water but soluble in aqueous alkali, because of their acidic character.



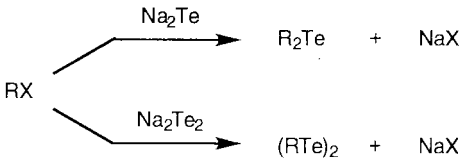
Scheme 15.18

Elemental tellurium reacts with organometallic compounds, i.e. RM, to furnish metal tellurolates (Scheme 15.19); these are widely used as useful sources of tellurium for synthesis of a variety of unsymmetrical tellurides [57].

Scheme 15.19

15.2.3.3 **Tellurides and Ditellurides**

In addition to the selective synthesis of selenides and diselenides, symmetrical dialkyl tellurides [5a, 47–49, 50a, 58] and ditellurides [48a, 51a, c, 59] can be prepared with high selectivity by alkylation of Na_2Te and Na_2Te_2, respectively, with alkyl halides (Scheme 15.20).

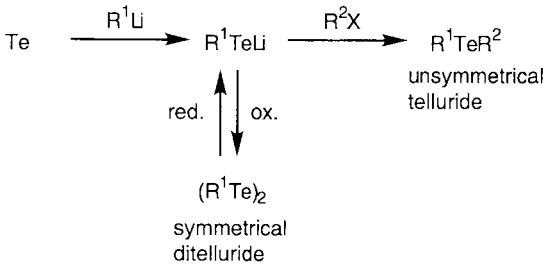


Scheme 15.20

Arylation of Na_2Te to prepare aromatic tellurides requires the use of aryl iodides [60] or arenediazonium fluoroborates, $[ArN_2^+]BF_4^-$ [61], relatively powerful arylating agents, and heating in DMF or NMP (*N*-methyl-2-pyrrolidone).

Although unsymmetrical tellurides are obtained by stepwise alkylation of Na_2Te with two different alkyl halides, product selectivity is not high [60c, 62]. A more

convenient method is alkylation of metal tellurolates, RTeM, easily generated in situ by reaction of organometallic reagents with elemental tellurium or by reduction of ditellurides with alkali metals (Scheme 15.21) [57g, 63].

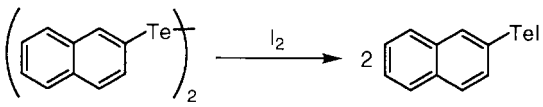


Scheme 15.21

Air-oxidation of metal tellurolates is another convenient synthesis of organic ditellurides [57a,c,d,g, 60c, 64].

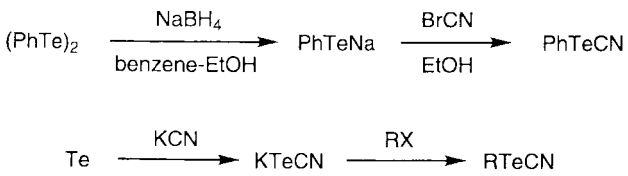
15.2.3.4 **Tellurenyl Compounds**

The reaction of organic ditellurides with halogen leads to the formation of tellurenyl halides [65]. 2-Naphthyltellurenyl iodide is isolated by using this method, as exemplified by Scheme 15.22.



Scheme 15.22

Aromatic tellurocyanates are prepared by the cyanation of metal tellurolates [66] and aliphatic tellurocyanates can be obtained by alkylation of potassium tellurocyanates (Scheme 15.23) [67].



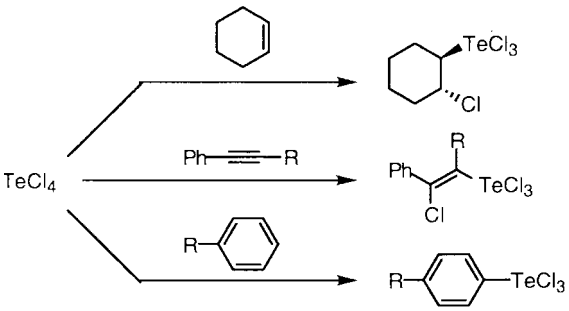
Scheme 15.23

Although these tellurenyl compounds are representative tellurenylating reagents, their synthetic utility is not as high as that of the corresponding selenenyl compounds.

15.2.3.5 Tellurinyl Compounds

One of the characteristic features of tellurium is that it forms a variety of tellurinyl derivatives; these can be roughly classified into four groups with the structures $RTeX_3$, R_2TeX_2, R_3TeX, and RTe(O)X.

One of the most general methods for synthesis of $RTeX_3$ is addition of tellurium tetrachloride ($TeCl_4$) to a variety of carbon–carbon unsaturated compounds such as alkenes and alkynes [68]. $TeCl_4$ also reacts with aromatic compounds to afford the corresponding substitution products, arenetellurium trichlorides ($ArTeCl_3$), in good yields (Scheme 15.24) [69].



Scheme 15.24

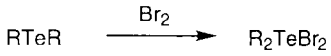
Alternatively, halogenation of organic ditellurides provides a convenient preparation of $RTeX_3$ (Scheme 15.25) [65a, 70].

$$(RTe)_2 + 3X_2 \longrightarrow 2RTeX_3$$

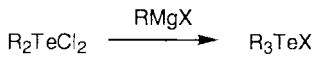
Scheme 15.25

Similarly to the synthesis of $RTeCl_3$, diorganyltellurium dichlorides (R_2TeCl_2) can be prepared by reaction of $TeCl_4$ with two equivalents of unsaturated compounds or aromatic compounds (Scheme 15.26) [68a, 69a, 70b, 71]. Equimolar reaction of $RTeCl_3$ with unsaturated compounds or aromatic compounds also provides diorganyltellurium dichlorides (R_2TeCl_2) [68b, 71e, 72]. Diorganyltellurium dibromides, R_2TeBr_2, readily prepared by bromination of diorganyl tellurides (Scheme 15.26), provide telluroxide on treatment with aq. NaOH [73].

Triorganyltellurium halides (R_3TeX) are prepared by the reaction of diorganyltellurium dichlorides (R_2TeCl_2) with organometallic compounds such as Grignard reagents (Scheme 15.27) [74].

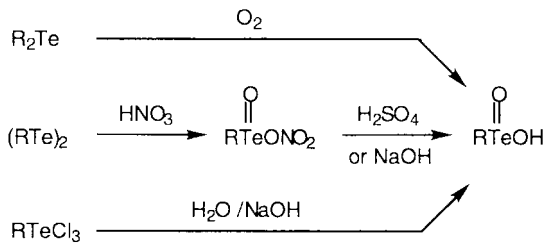


Scheme 15.26



Scheme 15.27

Tellurinic acids, on the other hand, are obtained by several methods, as shown in Scheme 15.28 [57e, 75].

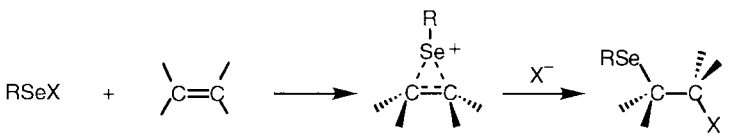


Scheme 15.28

15.3
Selenium Reagents as Electrophiles

15.3.1
Electrophilic Addition to Unsaturated Bonds

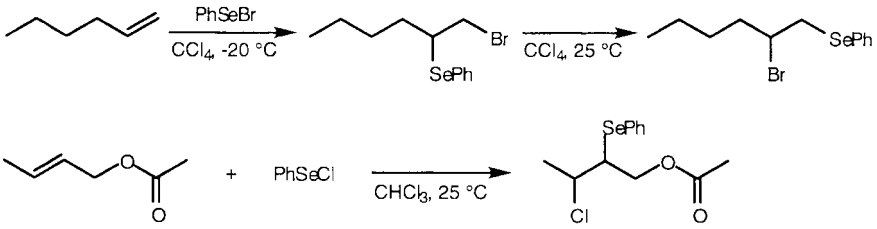
A series of selenenyl compounds – selenenic acids, selenenic anhydrides, selenenyl halides, selenocyanates, and selenenamides, etc. – act as excellent electrophilic selenenylation reagents toward a variety of carbon–carbon unsaturated compounds. For example, electrophilic addition of selenenyl halides to carbon–carbon double bonds proceeds stereospecifically in the *anti* conformation. This addition is first-order in both selenenyl halides and carbon–carbon unsaturated compounds,



Scheme 15.29

i.e. overall second order [76]. The addition usually involves the formation of seleniranium ions as rate-determining step, and subsequent backside attack of nucleophiles on the seleniranium ions leads to the *anti* addition (Scheme 15.29) [77].

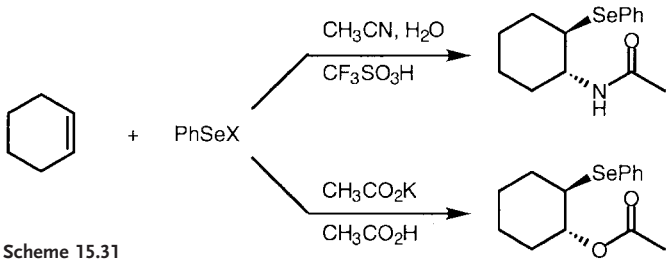
The regiochemistry of this addition, on the other hand, depends on the reaction conditions [78]. Under kinetically controlled conditions (CCl_4, –20 °C), reaction of PhSeBr with terminal alkenes provides *anti*-Markovnikov adducts predominantly. Interestingly, on standing at 25 °C for 2 days, the *anti*-Markovnikov adducts formed isomerize to provide Markovnikov adducts exclusively (Scheme 15.30).



Scheme 15.30

With internal alkenes, a mixture of Markovnikov and *anti*-Markovnikov adducts is usually obtained [76, 77]. Interestingly, the addition of PhSeCl to allylic acetates proceeds with excellent regioselectivity even for internal alkenes [79]. This is probably because of coordination of the acetate group to the seleniranium ion.

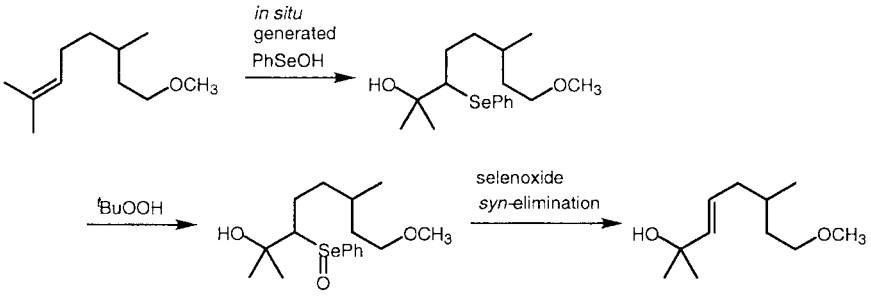
The adducts of selenenyl halides with alkenes are usually unstable both thermally and solvolytically. Thus, reaction of selenenyl halides with alkenes is conducted in the co-presence of nucleophiles such as CH_3CN [80], alcohols [81], water [82], CH_3CO_2K [38a], CF_3CO_2Ag [83], and $AgNO_2$ (Scheme 15.31) [84]; the corresponding selenenylation products, in which the halide groups have been substituted by the nucleophiles, are isolated as thermodynamically stable adducts.



Scheme 15.31

Selenenic acids generated in situ are also used for oxyselenation of a variety of alkenes [32, 33, 85]. The resulting *β*-hydroxyselenides can be easily converted into the corresponding allylic alcohols, by selenoxide *syn*-elimination, on treatment

with appropriate oxidizing reagents (Scheme 15.32). (Selenoxide *syn*-elimination is discussed in Section 15.7.2.2.)



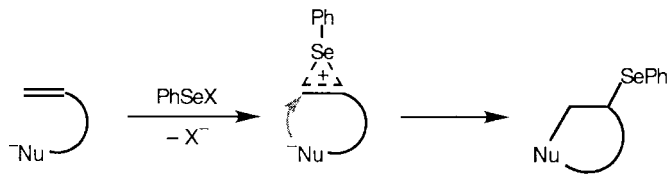
Scheme 15.32

The overall reactions thus provide a useful method for synthesis of allylic alcohols from alkenes.

Although little is known about the selenenylation of simple alkynes, reaction of propargyl alcohols with benzeneselenenyl halides leads successfully to the formation of the corresponding β-chloro-substituted vinylic selenides [86]. In this reaction, the regioselectivity depends on the substituents on the propargyl alcohols. For allenes the selenenylation generally occurs at both C–C double bonds, affording the corresponding RSeX adducts bearing the seleno group located predominantly on the central carbon of the allenes [87].

15.3.2
Cyclofunctionalization

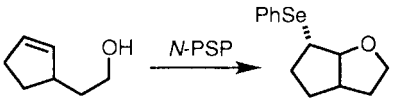
Electrophilic addition of phenylselenenyl groups ($PhSe^+$) to alkenes bearing a nucleophilic group (Nu^-), for example hydroxy, carboxy, and amino groups, proceeds via intramolecular ring-closure to provide stereospecifically cyclized products, for example cyclic ethers, lactones, and cyclic amines, respectively (Scheme 15.33). These types of cyclization reaction are well-characterized by the term "cyclofunctionalization" [88].



(Nu^- = OH, CO_2H, NHR, etc.)

Scheme 15.33

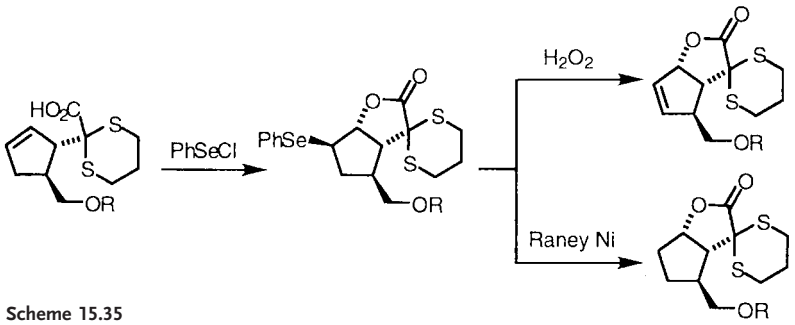
Many types of internal nucleophile, e.g. -Nu$^-$ = -CO_2H [88, 89], -CO_2R [90], -C(=O)R [91], -OH [39a, 90b, 92], -NHC(=O)R [93], -SH [94], and -CH=CHR [95], can be used for the cyclofunctionalization.



Scheme 15.34

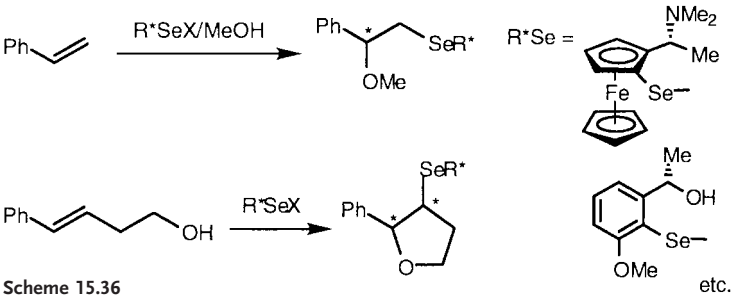
N-Phenylselenophthalimide (*N*-PSP) is a particularly excellent reagent for the cyclofunctionalization, because the low nucleophilicity of the phthalimide anion results in selective attack by these internal nucleophiles at the seleniranium ion intermediates (Scheme 15.34) [96]. Similarly, phenylselenenyl triflate (PhSeOTf) [97] and sulfate ($PhSeOSO_3^-$) [98] work as efficient electrophilic reagents toward unsaturated bonds.

As exemplified by Scheme 15.35, the resulting selenenylated lactones can be easily converted into the corresponding alkenes and alkanes, by selenoxide *syn*-elimination and reductive deselenation, respectively [89b, c].



Scheme 15.35

Several chiral selenenylating reagents, developed recently, are useful for the asymmetric oxyselenation and cyclofunctionalization of unsaturated compounds (Scheme 15.36) [99].

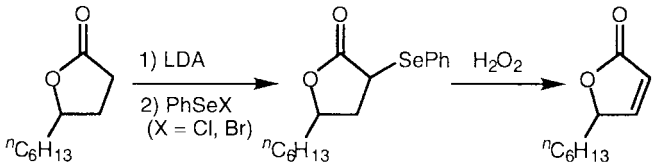


Scheme 15.36

15.3.3

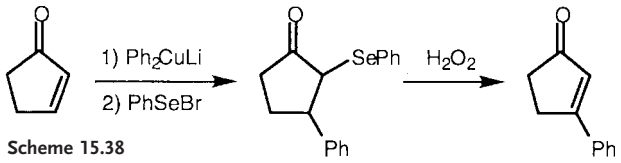
Synthesis of α,β-Unsaturated Carbonyl Compounds via α-Seleno Carbonyl Compounds

The reaction of carbonyl compounds (or their enolates) with selenenyl halides, then oxidative elimination from the α-seleno carbonyl compounds formed, is a representative method for the synthesis of α,β-unsaturated carbonyl compounds from the corresponding saturated carbonyl compounds (Scheme 15.37) [1c, i, 16b, 38a, c, 100].



Scheme 15.37

Selenenyl halides also react similarly with copper enolates, aluminum enolates, and zirconium enolates [101]. Scheme 15.38 illustrates the selenenylation of copper enolates generated by conjugate addition of lithium diphenylcuprate to cyclopentenone [100d].

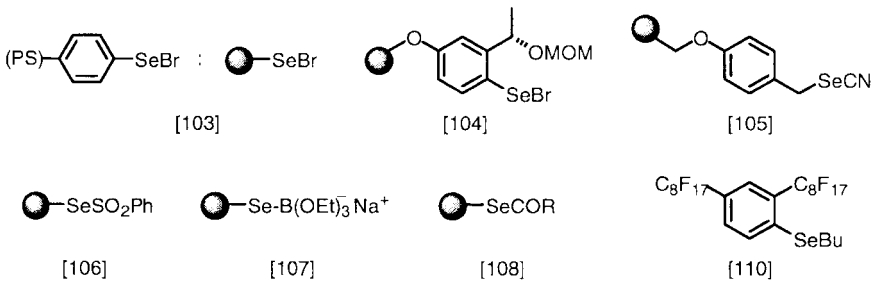


Scheme 15.38

15.3.4

Polymer-supported or Fluorous Selenium Reagents

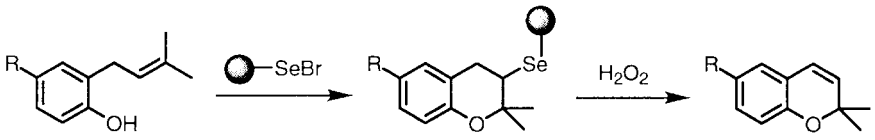
Recent advances in combinatorial chemistry has led to the development of several polymer-supported selenium reagents, exemplified by Scheme 15.39 [103–109].



[103] [104] [105] [106] [107] [108] [110]

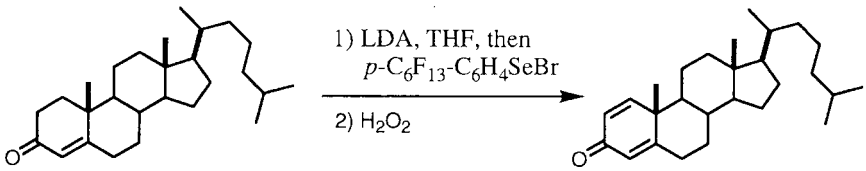
Scheme 15.39

Polymer-supported selenenyl halides are particularly useful, because both introduction of the desired substrates on to the polymers bearing the selenenyl halide groups, by cyclofunctionalization processes, and elimination of the products from the polymers, by oxidative cleavage processes (selenoxide *syn*-elimination), are readily achieved (Scheme 15.40) [103].



Scheme 15.40

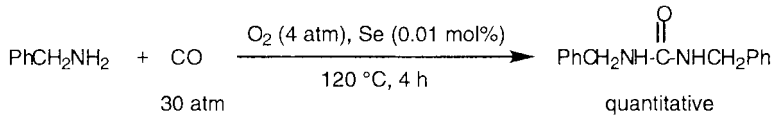
Selenium reagents with fluorous tags (e.g. fluorous aryl butyl selenide [110], *p*-C_6F_{13}-C_6H_4SeCl [111], $C_8F_{17}SeCl$ [112], etc.) have also been developed recently. For example, steroidal enone can be converted to the cross-conjugated dienone via the formation of the *α*-selenoketone (Scheme 15.41) [111]. In this reaction the resulting selenium species from the selenoxide elimination are readily reduced to fluorous diaryl diselenides on treatment with appropriate reducing agents, e.g. sodium metabisulfite ($Na_2S_2O_5$). By continuous fluorous extraction [113], the formed fluorous diaryl diselenides are then recovered in high yields.



Scheme 15.41

15.3.5
Selenium-catalyzed Carbonylation with CO

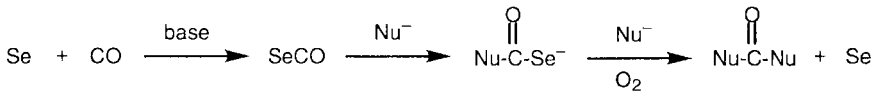
Elemental selenium is an excellent catalyst for the carbonylation of a variety of nucleophiles such as amines, alcohols, water, and carbon nucleophiles in the presence of oxygen under mild conditions [114]. In the synthesis of ureas from primary amines and CO, for example (Scheme 15.42), the turnover number reaches ca. 10^4, giving ureas in almost quantitative yields. Successful applications of this Se/CO system include not only synthetic reactions with a variety of carbamates, carbonates, and sulfur- or selenium-containing compounds but also metallurgical refining of selenium and several important processes as exemplified by isocyanate synthesis, the water-gas shift reaction, and separation of carbon monoxide [115].



Scheme 15.42

A possible reaction path is shown in Scheme 15.43 [116]. Selenium reacts with carbon monoxide in the presence of bases to generate carbonyl selenide (SeCO) as an active carbonylating species. Carbonyl selenide can be isolated by treatment of amine salts of selenolcarboxylic acids with sulfuric acid [117]. Nucleophilic attack at the carbon of SeCO leads to the formation of selenolcarboxylic acid derivatives, the pathways from which to give the desired carbonylation products involve several possibilities, depending on the nature of nucleophiles, i.e.:

- direct nucleophilic attack of Nu^- on the selenolcarboxylic acid derivatives;
- formation of isocyanates by elimination of HSe^- from selenolcarboxylic acid derivatives, followed by nucleophilic addition of Nu^-; and
- the formation of carbamoyl diselenides by air-oxidation, followed by nucleophilic attack by Nu^- at the diselenides.



Scheme 15.43

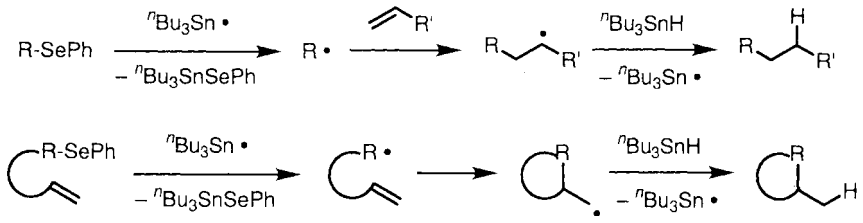
The reaction of selenium with CO and H_2O in the presence of tertiary amines generates amine salts of hydrogen selenides ($[HSe_n]^- \cdot [R_3NH]^+$, $n=1$ or 2), which can be used for the synthesis of selenium compounds such as selenides, diselenides, and selenocarbonyl compounds and for the selective reduction of carbonyl, nitro, and olefinic compounds [118].

15.4
Radical Reactions of Selenium and Tellurium Compounds

15.4.1
Organoselenium Compounds as Carbon Radical Precursors

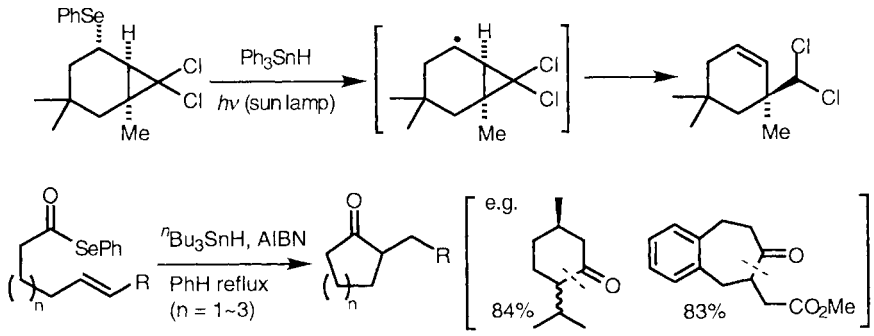
As shown in Scheme 15.44, organic selenides are employed as useful carbon radical precursors under tin hydride-mediated radical conditions [119]. In particular, combination of this carbon radical generation from selenides and the radical cyclization provides useful synthetic methods for a variety of cyclic compounds. Although similar transformations using alkyl halides such as R–I in place of R–SePh are possible,

nucleophilic substitution ($R–I + Nu^- \rightarrow R–Nu + I^-$) sometimes occurs in preference to the desired radical reactions in the presence of nucleophilic moieties such as nitrogen-containing functional groups.



Scheme 15.44

Similarly, the selenide in Scheme 15.45 generates the cyclopropylcarbinyl radical intermediate on photoirradiation with Ph_3SnH, giving the corresponding ring-opened product in 96% yield [119f]. Acyl radicals generated in situ from seleno-esters cyclize with intramolecular olefinic moieties to give cyclic ketones in good yields (Scheme 15.45) [120].



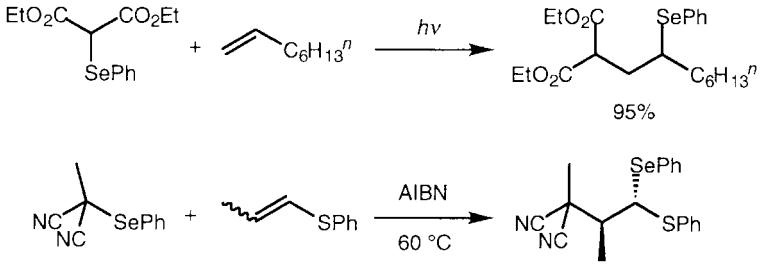
Scheme 15.45

15.4.1.1 Group-transfer Reactions of Organoselenium Compounds

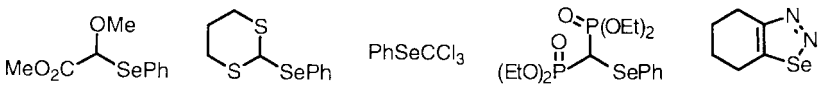
Under photoirradiation conditions 2-(phenylseleno)propanedioates add to a variety of olefins and acetylenes regioselectively in good yields via phenylseleno group transfer [121]. The group transfer addition of methyl(phenylseleno)malononitrile to a variety of alkenes has been investigated in detail; as depicted in Scheme 15.46 group transfer addition to phenyl 1-propenyl sulfide proceeds with high *anti* selectivity [122].

Similarly, group transfer addition using the selenides depicted in Scheme 15.47 has also been reported [123].

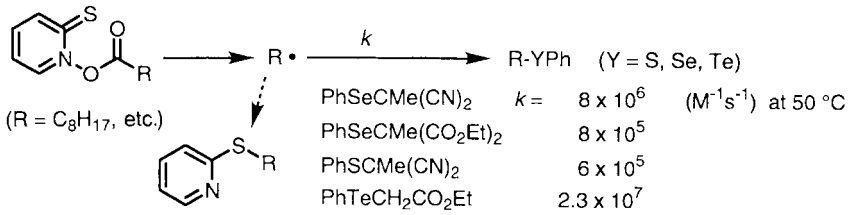
Rate constants for chalcogen group transfer in bimolecular substitution reactions with primary alkyl radicals are determined by competition kinetics using



Scheme 15.46



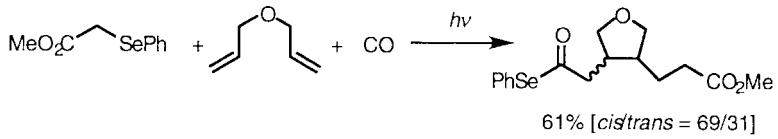
Scheme 15.47



Scheme 15.48

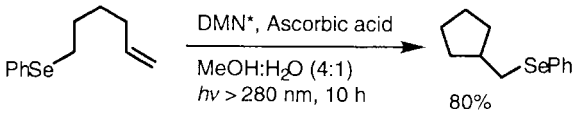
PTOC (pyridine thiocarbonyl) esters as the radical precursors and competing trapping agents (Scheme 15.48) [122c].

Photolysis of methyl *α*-(phenylseleno)acetate in the presence of diallyl ether and carbon monoxide leads to the acyl selenides via radical cyclization and group transfer carbonylation (Scheme 15.49) [124].



Scheme 15.49

Photosensitized one-electron reductive cleavage can also be used to achieve selective cyclization via phenylseleno group transfer radical chain processes (Scheme 15.50) [125].

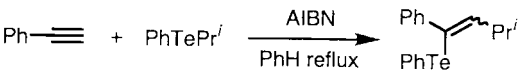


(DMN*: photoexcited 1,5-dimethoxynaphthalene)

Scheme 15.50

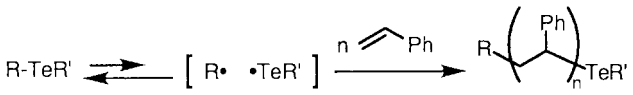
15.4.1.2 **Group-transfer Reaction of Organotellurium Compounds**

It is apparent from the rate constant for phenyltelluro group transfer from ethyl α-(phenyltelluro)acetate in bimolecular substitution reactions with primary alkyl radicals that organic tellurides have higher carbon radical trapping ability than the corresponding selenides. Indeed, non-activated carbon radicals can be generated from diorganyl tellurides under radical conditions. The carbotelluration of alkynes with diorganyl tellurides occurs regioselectively (Scheme 15.51) [126].



Scheme 15.51 97% [*E*/*Z* = 56/44]

Because sp^3 carbon–tellurium bonds are often unstable under photoirradiation conditions, carbotelluration producing sp^2-carbon–tellurium bonds occurs preferentially. Successful telluro group transfer cyclization has also been reported [119 g]. Carbonyl tellurides are useful precursors for carbonyl radicals, which are employed for cyclization and addition reactions [127]. The reaction of diorganyl tellurides with isocyanides leads to the formation of imidoyl tellurides in high yields [128]. The carbotelluration system has also recently been applied to living radical polymerization (Scheme 15.52) [129].



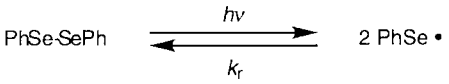
Scheme 15.52

15.4.2
Addition of Selenium- and Tellurium-centered Radicals

Organic selenols and diselenides are used as representative precursors for selenium-centered radicals. On exposure to air, selenols readily undergo hydrogen abstraction by molecular oxygen to generate seleno radicals even at room temperature or below. In the absence of substrates, seleno radicals generated in this way couple with each other to afford the corresponding diselenides [16]. Selenium-centered radicals are also generated by thermolysis of organic diselenides. For example, homolytic cleav-

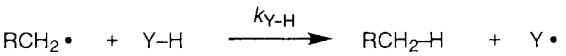
age of the selenium–selenium single bond of diphenyl diselenide occurs efficiently in organic solvent on heating above 140 °C, generating phenylseleno radical in situ [130]. In the absence of solvent $(PhSe)_2$ gradually decomposes at temperatures above its melting point (62 °C) with the deposition of amorphous selenium.

Organic diselenides usually have absorption maxima in the near-UV region, and irradiation with light of these wavelengths causes homolytic cleavage of the selenium–selenium single bonds to generate the corresponding selenium-centered radicals [131]. The seleno radicals thus formed are labile species and readily undergo recombination to re-form the starting dichalcogenides. The rate constant (k_r) for the recombination of PhSe• (Scheme 15.53) is reported to be close to the diffusion-controlled rate constant (e.g. $k_r = 7\times10^9$ $M^{-1}s^{-1}$ (CCl_4)) [132].

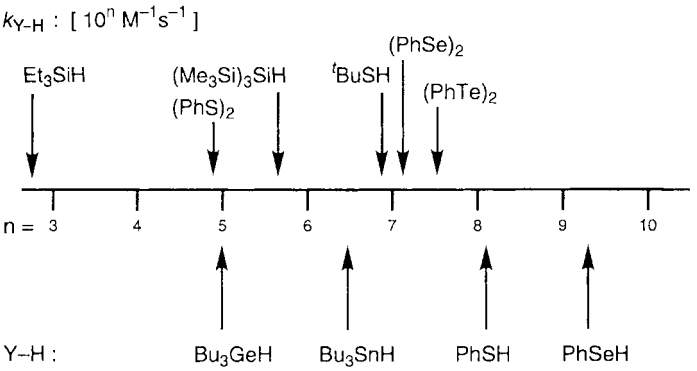


Scheme 15.53

The carbon radical-trapping behavior of benzeneselenol and diphenyl diselenide, in the reaction depicted in Scheme 15.54, is compared in Scheme 15.55 with that of other representative radical mediators.



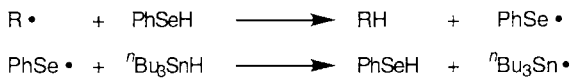
Scheme 15.54



Scheme 15.55

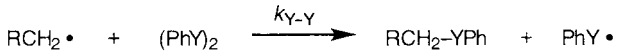
It is apparent from Scheme 15.55 that the reactivity of PhSeH toward carbon radicals is excellent and the rate constants for hydrogen abstraction from selenols by carbon radicals reach the diffusion-controlled rate constants ($k_{toluene} = 1.7\times10^9$ $M^{-1}s^{-1}$; $k_{THF} = 2.0\times10^9$ $M^{-1}s^{-1}$; 20 °C) [133].

Benzeneselenol can be used as a polarity-reversal catalyst for abstraction of hydrogen from tin hydrides by carbon-centered radicals (Scheme 15.56) [134].



Scheme 15.56

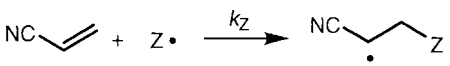
Scheme 15.55 also indicates the rate constants for the S_H2 reaction of alkyl radicals with diphenyl dichalcogenides. The rate constants for the S_H2 reaction with $(PhSe)_2$ are larger than those with $(PhS)_2$ by a factor of ca. 160 [135]. The carbon-radical-capturing ability of $(PhTe)_2$ (Scheme 15.57) is also excellent, a factor of 4 better than that of $(PhSe)_2$.



Scheme 15.57

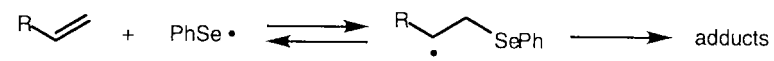
In Tab. 15.2 the relative reactivity of seleno radicals toward unsaturated bonds is compared with that of other heteroatom-centered radicals [132, 136].

Tab. 15.2 Rate constants for addition of heteroatom-centered radicals to acetonitrile



Z•	k_Z (M^{-1} s^{-1})
Et_3Si•	1.1×10^9
$^nBu_3Ge$•	1.8×10^8
$^nBu_3Sn$•	8.3×10^7
p-ClC_6H_4S•	4.6×10^5
PhSe•	1.4×10^4

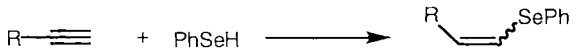
Seleno radicals are relatively less reactive toward olefins, and these kinetic data suggest that the reverse process from *β*-seleno alkyl radical intermediates contributes to the inefficiency of the radical addition reactions of selenium compounds (Scheme 15.58).



Scheme 15.58

15.4.2.1 Radical Addition of Selenols and Diselenides to Alkynes and Allenes

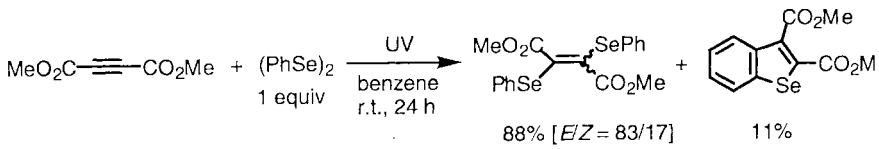
Under neutral conditions, organic selenols gradually add to alkynes at room temperature, via a radical mechanism, to give the corresponding *anti*-Markovnikov adducts in moderate yields with high stereoselectivity. For example, addition of PhSeH to 1-hexyne requires a longer reaction time (240 h) to afford 1-(phenylseleno)-1-hexene (*Z* isomer >95%) in 45% yield [137]. Diphenyl diselenide is found to promote the radical addition of PhSeH to inactivated acetylenes on irradiation with visible light (Scheme 15.59) [138]. In contrast with aliphatic acetylenes, the radical addition of PhSeH to aromatic acetylenes proceeds very rapidly, and is accomplished within 5 min. Small amounts of oxygen (or air) initiate the radical addition of PhSeH to acetylenes.



R =	$^{n}C_4H_9$	O_2, 240 h	45% [*Z*>95%]
	$^{n}C_4H_9$	*hv*, 10 mol% $(PhSe)_2$, 3.5 h	78% [*E*/*Z* = 18/82]
	Ph	Ar, 24 h	trace
	Ph	O_2, <5 min	83% [*Z*>95%]

Scheme 15.59

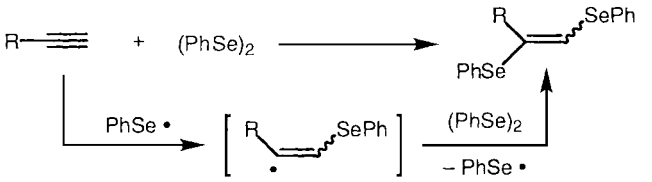
In the radical addition of organic diselenides to acetylenes, diphenyl diselenide adds to electron-deficient acetylenes such as dimethyl acetylenedicarboxylate to form the corresponding vicinal diselenides upon UV-irradiation in benzene (Scheme 15.60) [139]. The procedure cannot, however, be applied to usual alkynes such as 1-octyne. The lower concentration of the substrates might contribute to the inefficiency of the desired radical addition.



Scheme 15.60

In the absence of solvent (i.e. when concentrations of the substrates are higher), $(PhSe)_2$ adds to a variety of alkynes on irradiation with the light of wavelength >300 nm (Scheme 15.61) [140].

Because diphenyl diselenide undergoes thermolysis to generate a phenylseleno radical, thermal reaction of the diselenide with acetylenes occurs on heating at >150 °C in the dark, providing vicinal bis(phenylseleno)alkenes in good yields [141].



R =	$^{n}C_4H_9$	$h\nu$ >300 nm	40 °C	24 h	91% [E/Z = 95/5]
	Ph	$h\nu$ >300 nm	40 °C	4 h	93% [E/Z = 83/17]
	$^{n}C_6H_{13}$	dark	150 °C	10 h	74% [E/Z = 92/8]

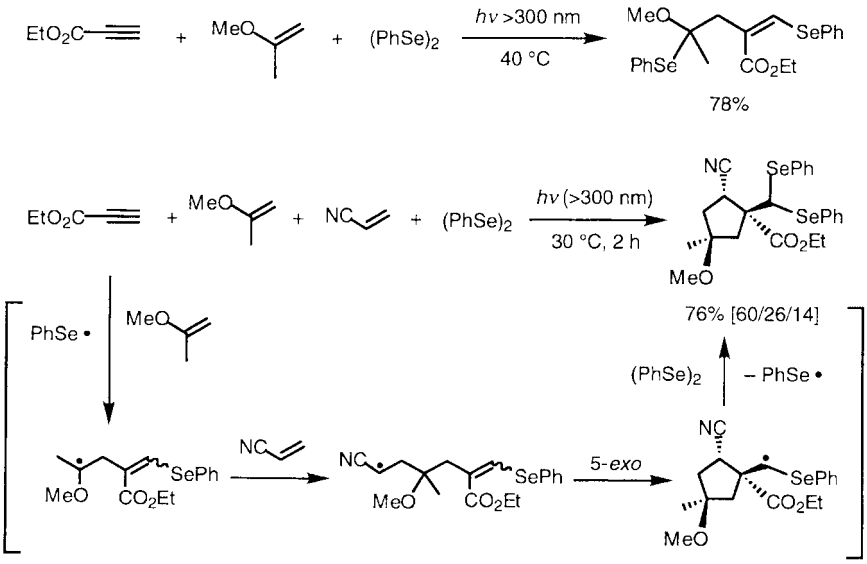
Scheme 15.61

This thermal addition is usually sluggish below 120 °C (e.g. for 1-octyne: 140 °C, 5 h, 42% adduct; 120 °C, 5 h, 11%; 100 °C, 5 h, 3%). Interestingly, the reaction with phenylacetylene occurs on heating even at 80 °C (76% of the desired adduct). The high reactivity of phenylacetylene is probably because vinyl radicals bearing a phenyl group at the α position of the radical center form π-radicals and are more stable than usual vinyl radicals, which are σ-radicals (Scheme 15.62) [142].

Scheme 15.62

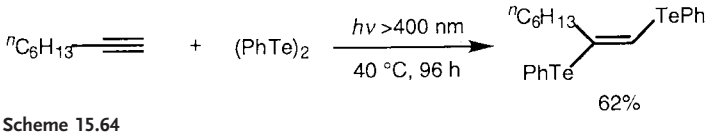
This bisselenation of alkynes has recently been applied to tandem radical addition to two or more unsaturated compounds. On irradiation through Pyrex by means of a tungsten lamp ($h\nu$>300 nm), $(PhSe)_2$ adds to electron-deficient alkynes such as ethyl propiolate and alkenes (or isocyanides) sequentially, to furnish the corresponding coupling products in moderate to high yields selectively, as exemplified in Scheme 15.63 [143]. The second equation in this scheme is an example of four-component coupling involving 5-*exo* radical cyclization. The appropriate strength of carbon-radical trapping by diphenyl diselenide facilitates this selective coupling.

As already mentioned, the rate of capture of carbon radicals by diphenyl ditelluride is even faster than that by the corresponding diselenide ($k_{PhTeTePh}/k_{PhSeSePh}$ = 4) [135], whereas the reactivity of the phenyltelluro radical toward carbon–carbon unsaturated bonds is presumably poor in comparison with that of the phenylseleno radical. It is inferred from these facts that it might be difficult to achieve addition of PhTe• to C–C multiple bonds. To achieve radical-addition of organic ditellurides to C–C unsaturated bonds, higher concentrations of substrates are essential. The stability of the products (vicinal bistelluroalkenes) to light is also important. Thus, upon irradiation through Pyrex with a tungsten lamp ($h\nu$>300 nm), the reaction of $(PhTe)_2$



Scheme 15.63

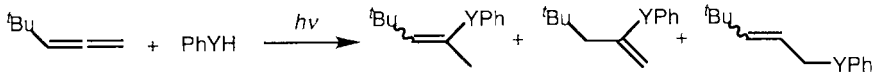
with 1-octyne in the absence of solvent at 70 °C provides 1,2-bis(phenyltelluro)-1-octene in 32% yield. The UV-visible spectrum of this adduct is indicative of absorption in the near-ultraviolet, which causes the reverse reaction of the adduct to the starting materials. Indeed, on near-UV irradiation in $CDCl_3$ at 40 °C for 6 h, the adduct decomposes to re-form 1-octyne (60%) and diphenyl ditelluride. Thus, reaction of $(PhTe)_2$ with 1-octyne and shading, with a filter, from near-ultraviolet light successfully affords satisfactory yields of the ditelluride adduct as a single stereoisomer (*E*) (Scheme 15.64) [144].



Scheme 15.64

In contrast with unactivated acetylenes such as 1-octyne, addition of ditellurides to activated acetylenes such as aryl group-substituted acetylenes and conjugate acetylenes proceeds even on irradiation with light of wavelength >300 nm. For example, reaction of phenylacetylene with $(PhTe)_2$ provides the desired 1,2-bis(phenyltelluro)styrene ($E/Z = 90:10$) in 97% yield on irradiation through Pyrex (>300 nm) at 40 °C for 24 h.

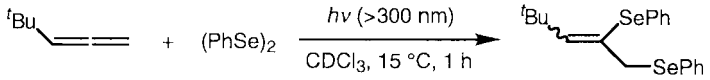
Radical addition of benzeneselenol to allenes occurs in the presence of oxygen (or upon photoirradiation) to give the vinylic selenides in good yields (Scheme 15.65) [145].



	Y =				
	S	UV	37%	38%	25%
Scheme 15.65	Se	>300 nm	70%	8%	0%

This addition proceeds via selective attack of PhSe• at the central carbon of allenes whereas the corresponding thiol addition to allenes occurs by attack of PhS• at both the central and terminal carbons of allenes.

Diphenyl diselenide can add to allenes very smoothly, providing *β*-(phenylseleno)allylic selenides in high yields, as depicted in Scheme 15.66 [146]. In contrast, the photoinduced reaction of $(PhS)_2$ with allenes affords a complex mixture, because the lower capturing ability of $(PhS)_2$ for carbon free radicals enables oligomerization of the allenes.

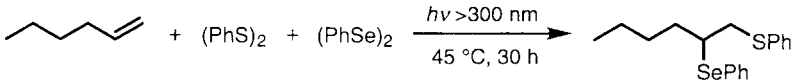


Scheme 15.66 — 82% [*E*/*Z* = 28/72]

Radical addition of $(PhTe)_2$ to allenes, on the other hand, does not proceed, because of the instability of the desired allylic tellurides under photoirradiation conditions.

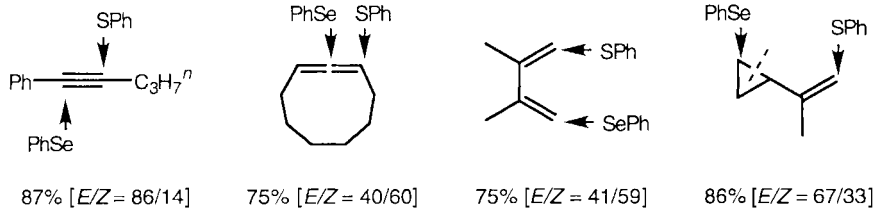
15.4.2.2 Radical Addition to Alkenes

To date, there have been no reported examples of efficient radical addition of organic diselenides or ditellurides to alkenes. The difficulty of radical addition of organic diselenides or ditellurides might arise from the lower reactivity of seleno or telluro radicals toward the carbon–carbon double bond. As already mentioned, rate constants for addition of PhS• to an olefinic double bond are greater than those of PhSe• by a factor of approximately 10–50. Rate constants for the S_H2 reaction of alkyl radicals with $(PhSe)_2$ are, on the other hand, greater than those with $(PhS)_2$ by a factor of ca. 160. Accordingly, when the addition is performed in the presence of both $(PhS)_2$ and $(PhSe)_2$, the high reactivity of PhS• toward olefins and the excellent capturing ability of $(PhSe)_2$ for carbon radicals realize simultaneous addition of two different heteroatom groups to the double bonds [147]. For example, reaction of 1-hexene with equimolar amounts of $(PhS)_2$ and $(PhSe)_2$ by irradiation with a tungsten lamp at 45 °C for 30 h furnishes 1-(phenylthio)-2-(phenylseleno)hexane as the sole product (Scheme 15.67).



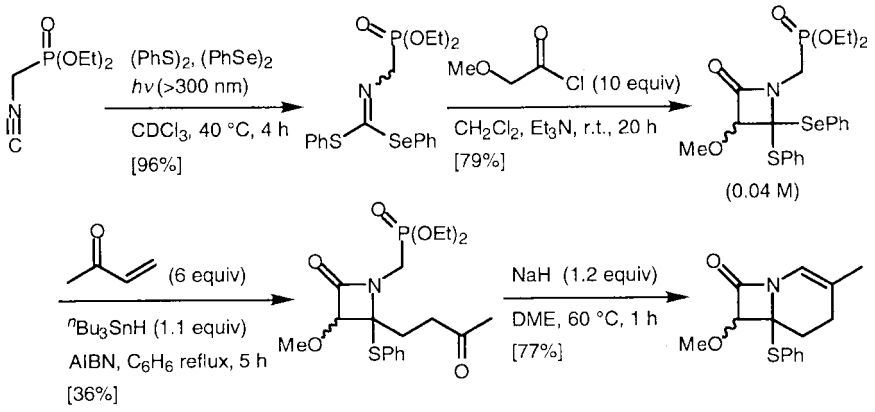
Scheme 15.67 — 89%

The procedure can be employed with alkenes, allenes, conjugated dienes, vinylic cyclopropanes, and isocyanides, and the corresponding thioselenation products are obtained regioselectively in good yields, as exemplified by the compounds in Scheme 15.68 [148].



Scheme 15.68

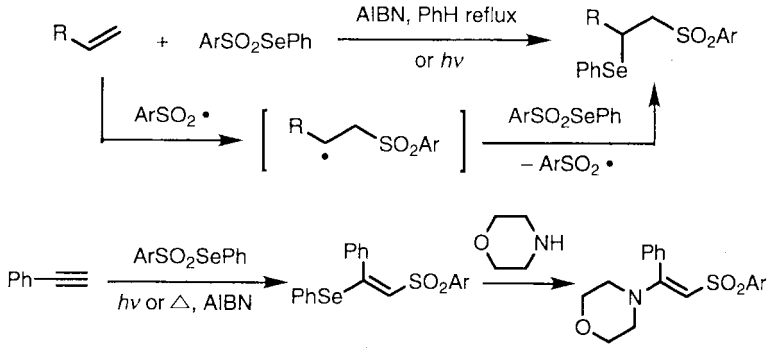
With vinylcyclopropanes thioselenation proceeds via ring-opening of cyclopropylcarbinyl radicals. An example of the thioselenation of isocyanides by means of a $(PhS)_2$–$(PhSe)_2$ mixed system is shown in Scheme 15.69; the product is a useful building block for β-lactam derivatives, e.g. carbacephems.



Scheme 15.69

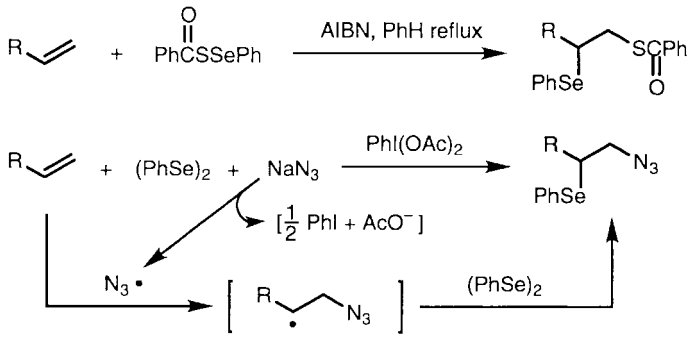
Simultaneous introduction of both sulfur and selenium functions into carbon–carbon unsaturated compounds via a radical mechanism is also demonstrated by "selenosulfonation" [149] and "selenothiocarboxylation" [150] (Scheme 15.70). In these addition reactions, attack of sulfur-centered radicals at the terminal position of alkenes and the subsequent S_H2 reaction on the selenium lead to the formation of *anti*-Markovnikov adducts regioselectively. The selenosulfonation can be applied to a variety of unsaturated compounds, for example alkynes, allenes, and vinylcyclopropanes, and combination with the selenoxide *syn*-elimination procedure

or nucleophilic substitution of selenium moieties affords a wide range of synthetically useful sulfone derivatives.



Scheme 15.70

Similarly, selenothiocarboxylation and azidoselenation [151] of alkenes proceed regioselectively via a radical mechanism in which benzoylthio and azide radicals, respectively, attack the terminal position of alkenes and a phenylseleno group is introduced into the inner position (Scheme 15.71).



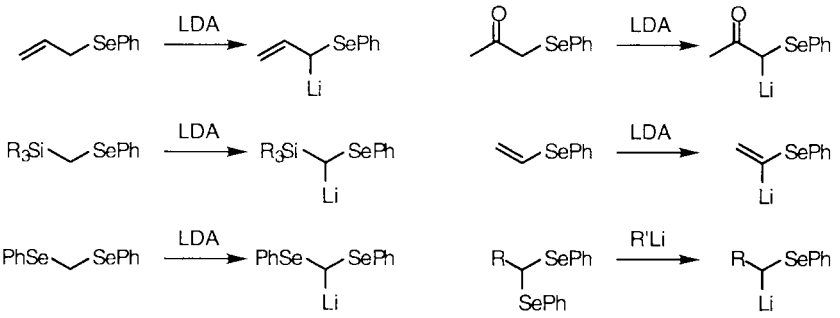
Scheme 15.71

15.5
Selenium and Tellurium Reagents as Nucleophiles

15.5.1
Selenium-stabilized Carbanions

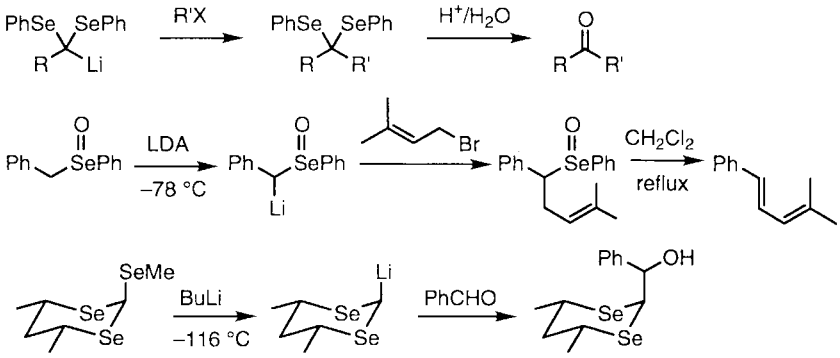
Selenium is well-known to stabilize anions on *α*-carbon atoms, and a variety of *α*-seleno-substituted carbanions has been used as useful building blocks in organic synthesis [152]. These selenium-stabilized carbanions can be prepared easily by

deprotonation with strong bases such as LDA, KDA, NaH, etc., or by selenium (or halogen)–metal exchange reactions. Representative examples are listed in Scheme 15.72.



Scheme 15.72

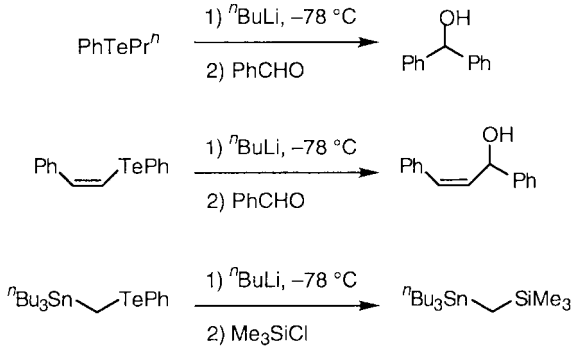
The selenium-stabilized carbanions formed react with a variety of electrophiles such as carbonyl compounds, alkyl halides, epoxides, etc., transforming them into several functional groups, as exemplified in Scheme 15.73 [153].



Scheme 15.73

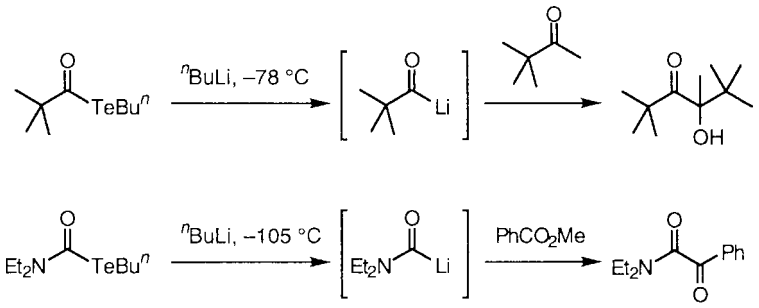
15.5.2
Tellurium-lithium Exchange Reaction

Diorganyl tellurides undergo tellurium–lithium exchange reactions very efficiently by reaction with organolithium reagents [154]. This tellurium–lithium exchange reaction has wide generality and can be applied to the generation of a variety of synthetically useful organolithium compounds such as aryl-, vinyl-, and alkyllithiums and allyl- and benzyllithiums, which cannot be generated by halogen–lithium exchange reaction (Scheme 15.74).



Scheme 15.74

This exchange reaction proceeds quite rapidly even at low temperatures and several carbonyllithium compounds which are unstable umpolung species can be generated successfully by use of this reaction (Scheme 15.75) [155].



Scheme 15.75

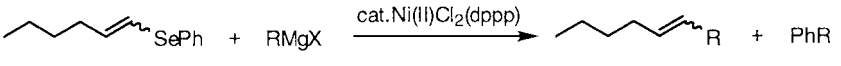
15.6
Transition Metal-catalyzed Reactions

Although the utility of transition metal catalysts for effecting a wide variety of synthetic transformations using heteroatom compounds such as organic silicon, tin, and boron compounds is well established, use of these catalysts for synthetic reactions of organic selenium and tellurium compounds has remained largely unexplored. This might be partly because of the widespread prejudice that selenium and tellurium compounds often bind strongly to the catalysts, thus poisoning them and making the catalytic reactions ineffective. A series of pioneering experiments on the transition-metal-catalyzed reactions of selenium compounds have, however, recently been reported [156]. These novel reactions are strongly suggestive of the promise of transition-metal-catalyzed systems in synthetic reactions of organic selenium compounds. Examples of transition-metal-catalyzed reactions of

organotellurium compounds are, on the other hand, still rare, partly because of the instability of carbon–tellurium bonds in the presence of transition metal catalysts.

15.6.1
Cross-coupling Reaction

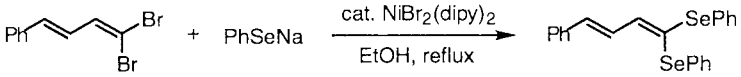
Alkyl, aryl, and allylic selenides are found to couple with Grignard reagents in the presence of catalytic amounts of nickel(II)-phosphine complexes such as $NiCl_2(PPh_3)_2$ and $NiCl_2$(dppp), as shown in Scheme 15.76 [157].



R =		
Ph	83%	100%
^{n}Bu	86%	49%

Scheme 15.76

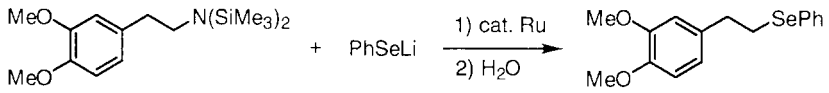
By use of nickel-catalyzed cross-coupling reactions, a variety of vinylic selenides can be synthesized from vinylic bromides and sodium benzeneselenolate (Scheme 15.77) [158].



89%

Scheme 15.77

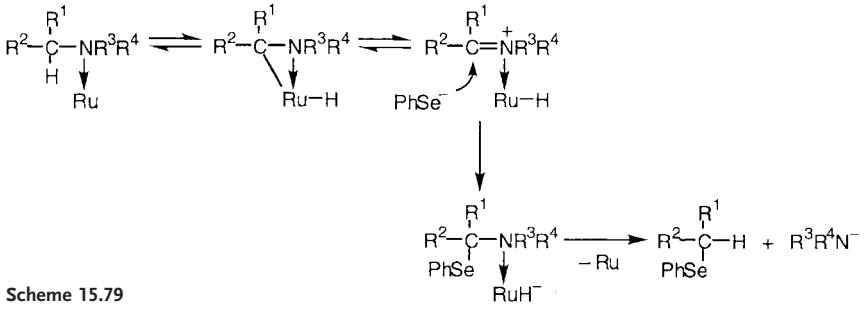
Interestingly, alkyl groups on amines can be employed for the synthesis of unsymmetrical selenides in the presence of ruthenium catalysts prepared by the reduction of $RuCl_3$ with potassium (Scheme 15.78) [159].



81%

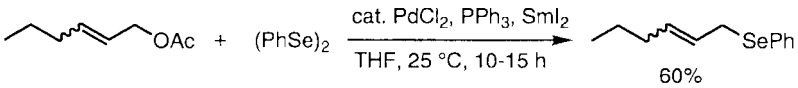
Scheme 15.78

Nucleophilic attack of selenolate anions on the iminium ion complex, generated by insertion of ruthenium into a carbon–nitrogen bond adjacent to the nitrogen, and subsequent reductive cleavage seem to operate as key steps (Scheme 15.79).



Scheme 15.79

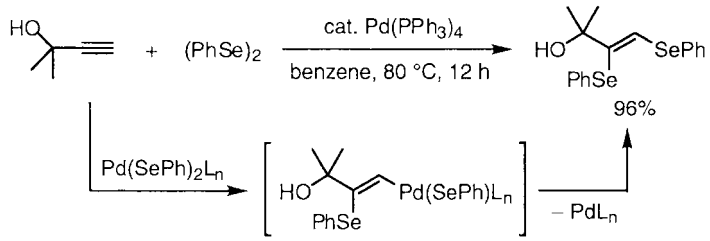
By using a Pd/SmI_2 system as catalyst, allylic acetates can be converted regioselectively to the corresponding allylic selenides, most probably by selenation of allylic anion intermediates (Scheme 15.80) [160].



Scheme 15.80

15.6.2
Transition Metal-catalyzed Addition Reaction

In the presence of low-valent palladium catalysts such as $Pd(PPh_3)_4$, diaryl diselenides are found to add stereoselectively to terminal alkynes, giving the corresponding vicinal bis(arylseleno)alkenes in good yields, as exemplified by Scheme 15.81 [161].

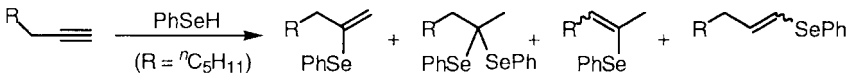


Scheme 15.81

This bisselenation might proceed via oxidative addition of $(PhSe)_2$ to low-valent palladium complexes, regioselective selenopalladation of alkynes to give vinylic palladium intermediates, and reductive elimination of the vicinal diselenoalkenes with regeneration of the catalyst.

The hydroselenation of alkynes with PhSeH also provides a simple route to vinylic selenides (Scheme 15.82). In contrast with radical addition of PhSeH to ter-

minal alkynes, which provides *anti*-Markovnikov adducts regioselectively [137, 138], $Pd(OAc)_2$-catalyzed hydroselenation of 1-octyne with PhSeH at 80 °C for 15 h gives rise to the corresponding Markovnikov adduct, 2-(phenylseleno)-1-octene, as the major product, with other addition products [162]. In this hydroselenation ligand-exchange of $Pd(OAc)_2$ with two equivalents of PhSeH occurs to give $Pd(SePh)_2$, which adds to terminal alkynes regioselectively generating in situ *β*-selenoalkenylpalladium intermediates. Subsequent protonation of the vinylpalladium intermediates with PhSeH affords the Markovnikov adducts with regeneration of the catalyst, i.e. $Pd(SePh)_2$.

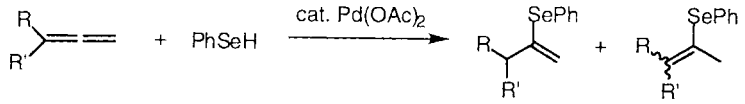


catalyst :	$Pd(OAc)_2$	62%	13%	7%	3%
	$PdCl_2(PhCN)_2$	4%	-	68%	-

Scheme 15.82

Sequential addition/isomerization occurs in the presence of $PdCl_2(PhCN)_2$, affording internal vinylic selenides selectively in good yields.

$Pd(OAc)_2$-catalyzed hydroselenation of alkynes with PhSeH can be applied to the hydroselenation of allenes (Scheme 15.83). Whereas radical addition of selenols to allenes leads to the formation of regioisomeric mixtures of vinylic selenides [145], the $Pd(OAc)_2$-catalyzed hydroselenation provides the corresponding vinylic selenides with moderate to high regioselectivity [163].



				yield [*E*/*Z*]
R = ^{t}Bu	R' = H	O_2	8%	70% [67/33]
^{t}Bu	H	cat. $Pd(OAc)_2$	74%	-
^{n}Bu	H	cat. $Pd(OAc)_2$	63%	16% [44/56]
cyclohexyl	H	cat. $Pd(OAc)_2$	69%	20% [50/50]

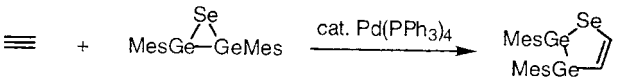
Scheme 15.83

A mechanistic proposal includes:

- ligand-exchange of the acetoxyl groups of $Pd(OAc)_2$ with PhSe groups to give the palladium selenide complex (as an active catalyst) with the concomitant formation of AcOH;
- coordination to the palladium species of the allene double bond bearing the higher electron density;

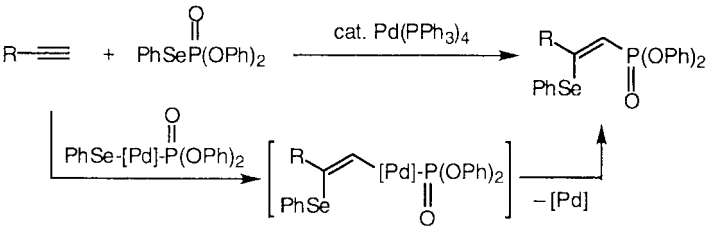
- *syn*-selenopalladation to form σ-allylpalladium; and
- without changing into π-allylpalladium, immediate quenching of the σ-allylpalladium intermediate by PhSeH to give the desired adduct with regeneration of the catalyst.

Although these reactions include activation of Se–Se or Se–H bonds by transition-metal catalysts, one of the most interesting applications of this methodology is the simultaneous introduction of two different heteroatoms into unsaturated compounds. The first example of the transition-metal-catalyzed simultaneous introduction of seleno- and other heteroatom-functions to alkynes is shown by use of selenadigermiranes as strained molecules (Scheme 15.84) [164]. Regio- and stereoselective addition to alkynes of heteroatomic compounds bearing an Se–Si or Se–Ge bond is also illustrated by the $Pd(PPh_3)_4$-catalyzed reaction of $PhSeSiMe_3$ and $PhSeGeMe_3$ with aromatic acetylenes; yields of the adducts are relatively low (e.g. (*Z*)-Ar(PhSe)C=CH($GeMe_3$), 35%) [165].



Scheme 15.84

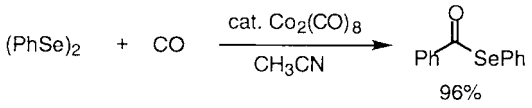
Palladium complexes such as $Pd(PPh_3)_4$, $Me_2Pd(PPh_3)_4$, and $Pd(PPh_3)_2$-(CH_2=CH_2) efficiently catalyze addition of *O,O,Se*-triphenyl phosphoroselenoate ($PhSeP(O)(OPh)_2$), which bears an Se–P linkage, to terminal alkynes to produce the corresponding selenophosphorylation products, (*Z*)-1-(diphenoxyphosphinyl)-2-(phenylseleno)alkenes, in high yields with high regio- and stereoselectivity (Scheme 15.85) [166].



Scheme 15.85

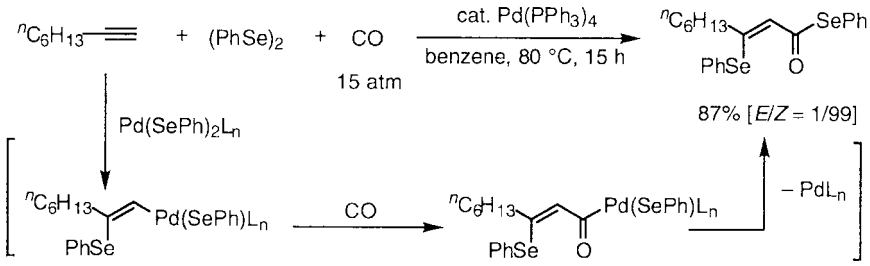
15.6.3
Transition Metal-catalyzed Carbonylation Reaction

It is of much interest that the transition-metal-catalyzed reactions of selenium and tellurium compounds are performed in the presence of carbon monoxide, because there is a possibility that this might cause simultaneous introduction of both seleno and carbonyl moieties into organic molecules. Diphenyl diselenide undergoes carbonylation with carbon monoxide (100 atm) in the presence of a catalytic amount of $Co_2(CO)_8$ (40 mol%) at 200 °C, providing selenoester in 96% yield (Scheme 15.86). Similar carbonylation of diphenyl ditelluride with CO (100 atm) also proceeds at 125 °C, successfully providing the corresponding telluroester in 40% yield [167].



Scheme 15.86

The palladium-catalyzed carbonylation of terminal alkynes with diphenyl diselenide under pressurized carbon monoxide (15 atm) proceeds successfully to give the corresponding selenoesters in high yields (Scheme 15.87) [161]. The carbonylation is completely regioselective and highly stereoselective. Similar carbonylation does not, unfortunately, proceed with ditellurides.



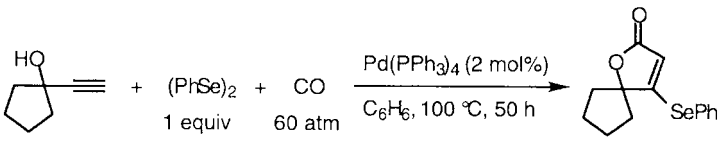
Scheme 15.87

A possible mechanism for this carbonylation might include:

- oxidative addition of $(PhSe)_2$ to low-valent palladium species;
- stereoselective *cis*-selenopalladation of acetylenes to form a *cis*-vinylpalladium intermediate;
- CO insertion to form an acylpalladium intermediate; and
- reductive elimination of the product with retention of the stereochemistry.

When the palladium-catalyzed carbonylation with $(PhSe)_2$ and CO is applied to propargyl alcohols, carbonylative lactonization occurs under higher CO pressure

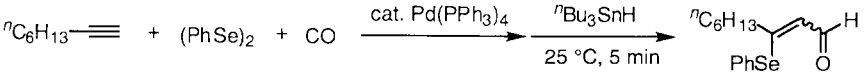
giving β-(arylseleno)-α,β-unsaturated γ-lactones in good yields (Scheme 15.88) [168].



Scheme 15.88

70%

Palladium-catalyzed carbonylative addition of terminal acetylenes and reduction of the thus formed selenoesters by means of $^{n}Bu_3SnH$ can be achieved successively without isolation of the selenoesters. This one-pot transformation from acetylenes to β-seleno-α,β-unsaturated aldehydes is synthetically the equivalent to regio- and stereoselective selenoformylation of acetylenes (Scheme 15.89) [169].



Scheme 15.89

86% [E/Z = 11/89]

15.7 Reduction and Oxidation Reactions

15.7.1 Reduction Reactions

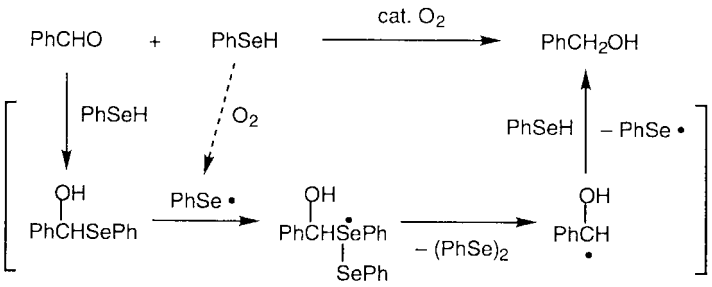
15.7.1.1 Reduction of Selenium and Tellurium Compounds

As already mentioned, the utility of organic selenium compounds for effecting a wide variety of synthetic transformations is now well-established; reductive cleavage reactions of C–Se bonds are, therefore, of great importance in utilizing these, because the final step always deals with the resulting organic selenides. Representative procedures for reduction of a C–Se bond to C–H include Raney-nickel reduction, metal boride reduction, and radical reduction by use of tin hydrides [170]. Tin hydride reduction is also used widely for reduction of C–Te bonds to C–H [171]. The reaction of diaryl tellurides (Ar_2Te) with Raney Ni leads to detellurative coupling to give biaryl (Ar–Ar) in good yields [172].

15.7.1.2 Reduction using Hydrogen Selenide and Selenols and their Tellurium Analogs

Hydrogen selenide and selenols are excellent hydrogen donors toward a variety of carbon radicals. The rate constant for hydrogen abstraction from H_2Se by photoexcited acetophene in THF is $4.7\times10^{8}\ M^{-1}s^{-1}$ [173]. Benzeneselenol reduces α,β-un-

saturated ketones and aromatic aldehydes to the corresponding saturated ketones and benzylic alcohols, respectively, by radical chain mechanism initiated by small amounts of oxygen (Scheme 15.90) [174].



Scheme 15.90

This reduction demonstrates the characteristic features of selenium in radical reactions, i.e. oxygen-induced generation of PhSe•, selective S_H2 reaction on the selenium, and the excellent hydrogen donating ability of PhSeH.

Hydrogen telluride (H_2Te) is known to reduce a variety of functional groups such as aldehydes, *α,β*-unsaturated ketones, nitroarenes, imines, and enamines [46, 175].

15.7.1.3 Reduction with Selenolates and Tellurolates

Selenolates such as Na_2Se, NaSeH, PhSeNa, etc., and tellurolates such as Na_2Te, NaTeH, PhTeNa, etc., are excellent nucleophiles and can reduce a variety of functional groups by nucleophilic attack or single electron-transfer. On treatment with alkali metal selenolates (or amine salts of H_2Se and PhSeH), reduction or reductive selenation of ketones and aldehydes, C=C reduction of *α,β*-unsaturated compounds, and reduction of nitrogen compounds such as nitro compounds occur successfully [118, 176]. Compared with these selenolate anions, the corresponding tellurium compounds are highly reactive not only toward the same substrates but also toward halo compounds such as *α*-bromo ketones and *vic*-dibromoalkanes [46, 52, 177].

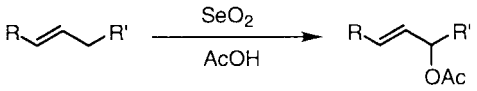
Other reductions using selenium compounds involve the stereospecific deoxygenation of epoxides by use of selenocyanates or selenoamides [178].

15.7.2 Oxidation Reactions

15.7.2.1 Selenium Dioxide Oxidation

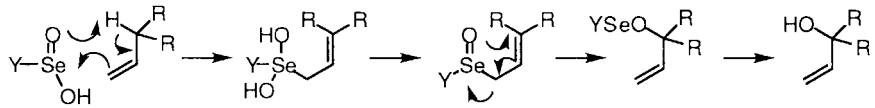
Owing to its characteristic behavior under oxidizing conditions, selenium dioxide (SeO_2) has been widely used as a useful oxidizing agent in organic synthesis, especially for oxidation of olefins and carbonyl compounds such as ketones and alde-

hydes [179]. Allylic oxidation of olefins occurs selectively on heating in acetic acid solution, giving the corresponding allylic acetates in high yields (Scheme 15.91).



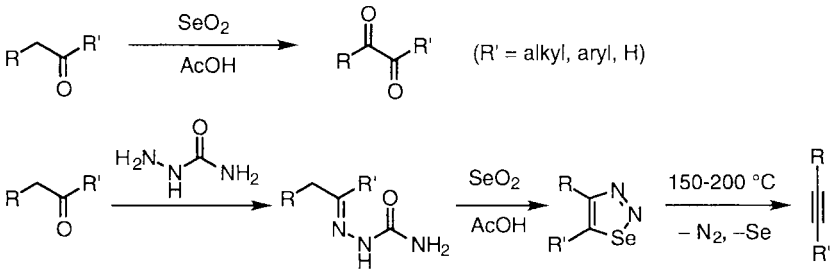
Scheme 15.91

The oxidation proceeds via sequential ene reaction, dehydration, [2,3]sigmatropic rearrangement, and hydrolysis (or solvolysis) (Scheme 15.92) [180]. Oxidation of trisubstituted olefins occurs at the *α* position of the more substituted vinylic carbon in the order $CH_2 > CH_3 > CH$. On combination with a slight excess, or more, of *t*-butyl hydroperoxide (^{t}BuOOH) allylic oxidation of olefins proceeds as a catalytic reaction of SeO_2.



Scheme 15.92

Ketones and aldehydes readily undergo oxidation of methylene groups adjacent to the carbonyl in one portion, providing *α*-diketones and *α*-keto aldehydes, respectively (Scheme 15.93).

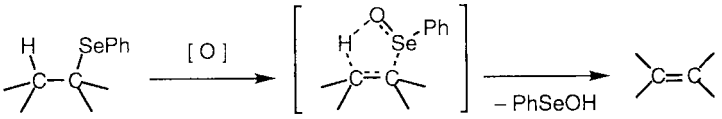


Scheme 15.93

Selenium dioxide reacts with semicarbazones to give selenadiazoles, the thermolysis of which provides a useful means of synthesis of acetylenes from the corresponding ketones. For example, highly strained acetylenes such as cyclohexyne can be prepared conveniently [181].

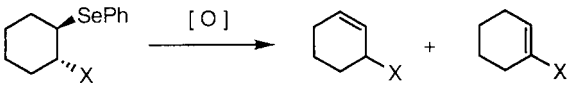
15.7.2.2 **Selenoxide *syn*-Elimination**

Selenoxide *syn*-elimination is widely accepted as one of the most expedient methods for olefin formation, because selenoxide elimination occurs at lower temperatures than the corresponding sulfoxide elimination [1c, 1i, 182]. The elimination is believed to occur via a cyclic transition state in which all five participating centers are located on the same plane; the selenoxide elimination is therefore stereospecific (Scheme 15.94).



Scheme 15.94

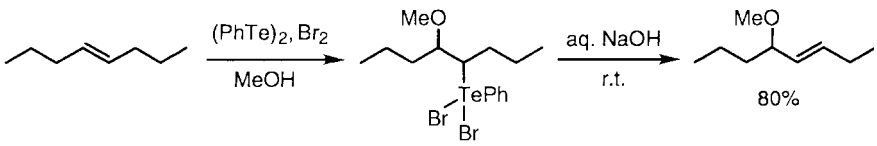
The regioselectivity of the elimination depends on the nature of the substituents. The presence of oxygen-containing functional groups such as hydroxy, alkoxy, and acetoxy leads to the selective formation of allylic compounds, whereas *β*-chloro alkyl selenides afford a mixture of vinylic and allylic chlorides, as shown in Scheme 15.95 [38a]. Asymmetric selenoxide elimination using optically active ferrocenyl selenides has also been reported [183].



X =		
OAc	97	3
OH	99.8	0.2
OMe	98	2
Cl	51	49

Scheme 15.95

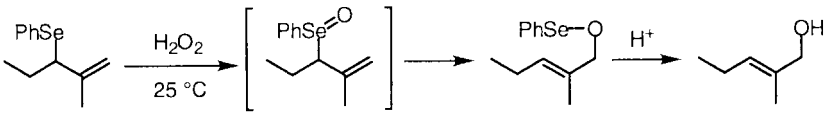
The telluroxide elimination is reported to occur on treatment of *s*-alkyl(phenyl)tellurium dibromides with aqueous NaOH, giving the corresponding olefins in good yields (Scheme 15.96) [184].



Scheme 15.96

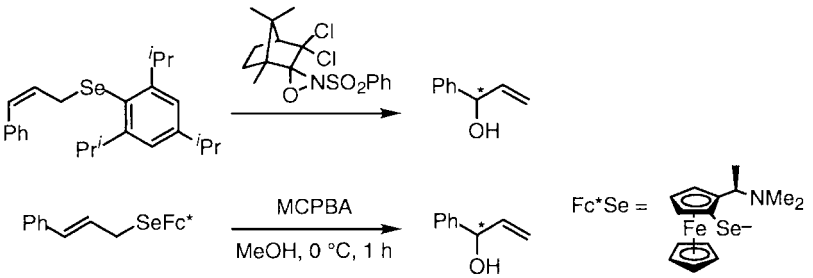
15.7.2.3 [2,3]Sigmatropic Rearrangement

In general, when a seleninyl group (PhSe(O)-) is present at the allylic position, the elimination proceeds *via* [2,3]sigmatropic rearrangement, providing the corresponding allylic oxidation products (Scheme 15.97) [185].



Scheme 15.97

The procedure can be applied to the synthesis of optically active allylic alcohols, as exemplified by Scheme 15.98 [186].



Scheme 15.98

15.7.2.4 Seleninic Acid Oxidation

Benzeneseleninic anhydride, $(PhSeO)_2O$, is a mild oxidizing agent for a variety of alcohols, giving high yields of the corresponding carbonyl compounds [187]. Similarly, benzeneseleninic anhydride is effective in the *α*-hydroxylation of ketones, oxidation of benzylic hydrocarbons, and dehydrogenation of steroidal ketones to *α,β*-unsaturated ketones [188]. Reaction of benzeneseleninic acid, PhSe(O)OH, with H_2O_2, moreover, generates in situ benzeneperoxyseleninic acid, PhSe(O)OOH, which epoxidizes olefinic double bonds [189].

15.8 References

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