
Preface

The pioneers of hypervalent iodine chemistry have already realized that the chemistry of iodine(III) and iodine(V)-containing compounds offers multiple advantages over established methods. A wide range of reactions is possible, oxidations and C-C-coupling reactions under extremely mild reaction conditions and with a broad tolerance of other functional groups being the most prominent ones. The various findings in, and applications of, the chemistry with hypervalent iodine compounds has led, in recent years, to a tremendous growth which is reflected by the large number of publications in this field. However, the last comprehensive compilation of hypervalent iodine chemistry appeared more than five years ago. We felt that there is a need for an update. I am grateful to the distinguished scientists, who contributed, with their skill and expertise, the various chapters of this volume. By emphasizing the developments in hypervalent iodine chemistry over the last couple of years, this volume presents a comprehensive overview of the various facets, scope, and limitations of organic chemistry with hypervalent iodine compounds.

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Introduction and General Aspects

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Recent progress on hypervalent iodine chemistry is summarized in this book.

Keywords. Hypervalent iodine chemistry

Hypervalent iodine reagents were discovered a long time ago and (dichloro-iodo)benzene as the first member of this class was prepared by Willgerodt in 1886 [1]. He was also the author of the first comprehensive book in this field in 1914 [2]. A growing interest in the chemistry with these compounds was observed about 60 years later, although some reviews on hypervalent iodine compounds were published as early as in the 1960s [3, 4]. Several reviews appeared between then and 1990 [5–17] and these are summarized in Table 1. Recently many more reviews have been published on various parts of hypervalent iodine chemistry [18–29] and several books [30–32] on this topic have appeared covering many aspects of these reagents.

The purpose of this book is to address and summarize recent developments and synthetic applications in the field of hypervalent iodine chemistry. Therefore, emphasis is placed on the post 1990s literature with reference to earlier work where necessary and appropriate.

The concept of hypervalent molecules was established in 1969 [33]. Molecules containing elements of Groups 15–18 bearing more electrons than the octet in the valence shell are described as hypervalent molecules. Descriptions of such systems using molecular orbital theory led to the proposal of 3-center-4-electron (3c–4e) bonds (hypervalent bonds) [34, 35]. Supported by computational work this concept is now generally accepted [36, 37]. Its application to iodanes is detailed at the beginning of the chapter Structures, Properties and Reactivities by M. Ochiai. The most common hypervalent iodine compounds are aryl- λ^3 -iodanes (ArIL_2) with a decet structure and pseudotrigonal bipyramidal geometries and aryl- λ^5 -iodanes (ArIL_4) with a dodecet structure and square pyramidal geometries. The nomenclature for these molecules is not satisfactory and several names for the same compound are often in use. Therefore, throughout this book various names and abbreviations for the hypervalent iodine reagents have been used by the authors as we have not applied the sometimes lengthy IUPAC names. As we have tried to outline general principles and synthetic concepts in this book, the chapter by M. Ochiai describes the theoretical background of hypervalent iodine reagents as well as giving examples of their reac-

Table 1. Reviews on hypervalent iodine chemistry until 1990

Year	Authors	Title	Reference
1964	J. D. Roberts, M. C. Caserio	Basic Principles of Organic Chemistry	[3]
1966	D. F. Banks	Organic polyvalent iodine compounds	[4]
1980	J. C. Martin	Structural factors influencing stability in compounds of hypervalent carbon, silicon, phosphorus and iodine	[5]
1981	A. Vavoglīs	Aryliodine(III) dicarboxylates	[6]
1983	T. Umemoto	Perfluoroalkylation with (perfluoroalkyl)phenyliodonium trifluoromethanesulfonate (FITS) reagents	[7]
1983	G. F. Koser	Hypervalent halogen compounds	[8]
1984	A. Vavoglīs	Polyvalent iodine compounds in organic synthesis	[9]
1986	R. M. Moriarty, O. Prakash	Hypervalent iodine in organic synthesis	[10]
1986	S. Oae	Ligand coupling reactions through hypervalent and similar valence-shell expanded intermediates	[11]
1986	M. Ochiai, Y. Nagao	Hypervalent organoiodine compounds in organic synthesis: reaction with organosilicon and tin	[12]
1987	E. B. Merkushev	Organic compounds of polyvalent iodine. Derivatives of iodosobenzene	[13]
1989	I. I. Maletina, V. V. Orda, L. M. Yagupol'skii	Fluorine-containing organic derivatives of polyvalent halogens	[14]
1990	R. M. Moriarty, R. K. Vaid	Carbon-carbon bond formation via hypervalent iodine oxidations	[15]
1990	R. M. Moriarty, R. K. Vaid, G. F. Koser	[Hydroxy(organosulfonyloxy)iodo]arenes in Organic Synthesis	[16]
1990	D. Wang	Application of hypervalent organoiodine compounds in synthesis	[17]

tivities towards a variety of substrates including mechanistic concepts for these reactions. Many of these reactions are discussed in more detail in the following chapters, whereas the preparation of those reagents is described in the chapter by A. Vavoglīs. There are different routes of oxidizing iodine (I) to iodine (III) or iodine (V), but another general principle of generating hypervalent iodine molecules is a ligand exchange reaction on iodine (III) or iodine (V) compounds.

V. V. Zhdankin, in his chapter, summarizes the use of hypervalent iodine reagents for carbon-carbon bond formations. The generation of radicals with hypervalent iodine compounds is used in decarboxylative alkylations of organic substrates, whereas phenols and phenol ethers seem to be ideal substrates for

cyclizations and intermolecular coupling reactions. Significant research concerning transition metal-mediated reactions with hypervalent iodine reagents are included as well. This is followed by two chapters by G. F. Koser, another pioneer in hypervalent iodine chemistry. Carbon–Heteroatom and Heteroatom–Heteroatom bond formations are reviewed in these two chapters. In addition to the possible transformations using aryl- λ^3 -iodanes, the variety of reactions using diaryliodonium salts, alkenyl(aryl)iodonium salts and alkynyl(aryl)iodonium salts with heteroatom nucleophiles is described in detail. Aziridinations and amidation reaction are also summarized. In the penultimate chapter, oxidations and rearrangements using hypervalent iodine compounds are summarized by T. Wirth with emphasis on synthetic applications of these procedures. New reagents and polymer-supported versions are highlighted. Beside the traditional sulfide-to-sulfoxides and alcohols-to-ketone oxidations, the oxidation of activated carbon–hydrogen bonds of carbonyl compounds and the functionalization of only slightly activated carbon–hydrogen bonds in benzylic positions are discussed. New rearrangements using hypervalent iodine compounds are mentioned as well. In the last chapter of this book, H. Tohma and Y. Kita describe the application of hypervalent iodine reagents in total synthesis and natural product synthesis. Because of the low toxicity compared with heavy metal reagents, the mild reaction conditions usually employed and the easy handling of hypervalent iodine compounds, these reagents have been used in total syntheses of a variety of natural products including quinones, alkaloids, flavonoids, carbohydrate derivatives, and antibiotics.

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Reactivities, Properties and Structures

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Tri- and pentavalent iodine compounds are called λ^3 - and λ^5 -iodanes. Ligand exchange, i.e. displacement of heteroatom ligands of λ^3 - and λ^5 -iodanes with external nucleophiles, is a facile low energy process. A very high leaving group ability of λ^3 -iodanyl groups is among the most important features of λ^3 -iodanes, which makes it possible to generate highly reactive species such as carbenes, nitrenes, cations, and arynes under mild conditions and to oxidize a wide range of functionalities such as alcohols, amines, sulfides, alkenes, alkynes, and carbonyl compounds. The leaving process is termed reductive elimination, in which the λ^3 -iodanyl group eliminates with energetically preferable reduction to univalent iodides. The process is also associated with an increase in entropy. Pseudorotation and ligand coupling on iodine(III), and homolytic cleavage of hypervalent iodanes are also discussed. Finally, recent progress in the structural elucidations of λ^3 -iodanes is shown here.

Keywords. Iodane, Hypervalent, Reductive elimination, Ligand coupling, Ligand exchange

1	Introduction	6
2	General Reactivity Patterns	8
2.1	Ligand Exchange	8
2.1.1	Oxygen Nucleophiles	10
2.1.2	Nitrogen Nucleophiles	11
2.1.3	Other Heteroatom Nucleophiles	12
2.1.4	Carbon Nucleophiles	13
2.2	Hypernucleofuge: Reductive Elimination	15
2.3	Electronic Nature	18
2.4	Reductive α -Elimination	19
2.5	Reductive β -Elimination	20
2.5.1	C–C Multiple Bond Formation	20
2.5.2	Oxidation of Alcohols	23
2.5.3	Oxidations of Amines	24
2.5.4	Oxidations of Sulfides	25
2.6	Reductive Elimination with Fragmentation	26
2.7	Reductive Elimination with Substitution	29
2.8	Reductive Elimination with Rearrangement	31
2.9	Pseudorotation of λ^3 -Iodane	33
2.10	Ligand Coupling on Iodine(III)	35

2.11	Homolytic Cleavage	41
2.12	Single-Electron Transfer	44
3	λ^3-Iodanes with Two Carbon Ligands	46
3.1	Alkyl(aryl)- λ^3 -Iodanes	46
3.2	Alkenyl(aryl)- λ^3 -Iodanes	48
3.2.1	Generation of Alkylidene Carbenes	48
3.2.2	Nucleophilic Vinylic Substitution	51
3.3	Alkynyl(aryl)- λ^3 -Iodanes	52
3.3.1	Michael-Carbene Insertion Reaction	52
3.3.2	Michael-Carbene Rearrangement Reaction	56
4	Structure	57
4.1	In Solution	57
4.2	In the Solid State	59
5	References	63

1

Introduction

The term iodane refers to hydrogen iodide (HI), a colorless non-flammable gas. According to IUPAC rules, compounds with nonstandard bonding number are shown by the lambda notation; thus, H_3I is called λ^3 -iodane and H_5I λ^5 -iodane. The most common ArIL_2 (L: heteroatom ligands) with decet structure is named aryl- λ^3 -iodane and ArIL_4 with dodecet structure aryl- λ^5 -iodane.

Aryl- λ^3 -iodanes (ArIL_2) have a geometry of a pseudotrigonal bipyramid with an aryl group and lone pairs of electrons in equatorial positions and two heteroatom ligands (L) in apical positions. Bonding in ArIL_2 uses an essentially pure 5p orbital in the linear L-I-L bond. This is a hypervalent three-center four-electron bond (3c-4e bond) with two electrons from the doubly occupied 5p orbital on iodine and one electron from each of the ligands L. The aryl group is bound by a normal two-electron covalent bond with 5sp^2 hybridization to form $\text{C}_{\text{Ar}}\text{-I}$ σ -bond [1, 2].

The two lower energy molecular orbitals, bonding and nonbonding orbitals, of the three produced for hypervalent 3c-4e bond are filled (Fig. 1). Partial positive charge develops on the central iodine atom, while partial negative charge on the apical heteroatom ligands, because the filled nonbonding molecular orbital has a node at the central iodine. The partial positive charge on the iodine of the highly polarized 3c-4e bond makes the aryl- λ^3 -iodane an electrophilic agent. The inherent nature of 3c-4e bond explains the preferred orientation of more electronegative ligands in the apical positions. The presence of more electropositive central atoms is energetically favorable for hypervalent species: thus in general, λ^3 -iodanes are more stable than analogous λ^3 -bromanes and λ^3 -chloranes [1, 2].

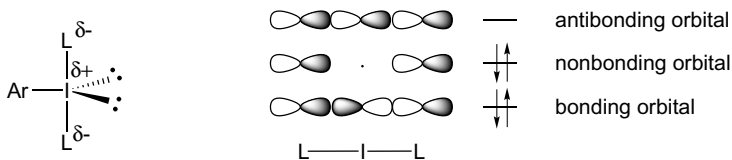
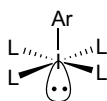


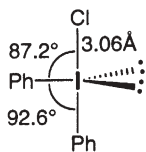
Fig. 1. Pseudotrigonal bipyramid structure and molecular orbital of the 3c – 4e bond

Aryl- λ^5 -iodanes ArIL_4 have a square pyramid structure with an aryl group in an apical position and four heteroatom ligands in basal positions. Two orthogonal hypervalent 3c – 4e bonds accommodate all of the heteroatom ligands and the apical aryl group has a character of a normal covalent bond using hybridized 5sp orbital [3].



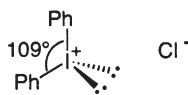
Structure A

Ar_2IL (L: heteroatom ligands such as halogens, OTs, BF_4 , OCOR, etc.) is usually called a diaryliodonium salt. Does this name reflect a real structure of Ar_2IL ? Our answer is “No”. For instance, Ph_2ICl is called diphenyliodonium chloride, probably because the I-Cl bond length (3.06 Å) is longer than the average covalent bond length (2.56 Å) [4]. The X-ray crystal structure determination, however, indicates that Ph_2ICl has a pseudotrigonal bipyramid structure **1** and, therefore, is a hypervalent [10-I-3] compound with good linearity for the axial triad Cl-I-C [5]. (The electronic structures are indicated by the [N-X-L] designation, in which N is the number of electrons formally associated with central atom X, and L is the number of ligands bonded to this atom [6].) The observed structure is far from the onium one **2** [8-I-2] expected from the name diphenyliodonium chloride. Onium salts such as ammonium, phosphonium, oxonium, sulfonium salts, etc. refers to compounds with tetrahedral geometry whose octet structure has eight electrons in the valence shell of the positively charged atom, and are not hypervalent compounds [7]. Therefore, we prefer the name chloro(diphenyl)- λ^3 -iodane instead of diphenyliodonium chloride, and diaryl- λ^3 -iodane for Ar_2IL . In fact, in the X-ray structural data reported for a large number of iodine(III) compounds, iodine(III) with a coordination number of 2 (as in iodonium salts) has never been observed [3].



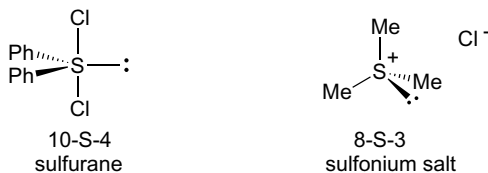
Structure 1

1 [10-I-3]
chloro(diphenyl)- λ^3 -iodane



2 [8-I-2]
diphenyliodonium chloride

In the case of the other hypervalent element compounds, these structural differences are strictly reflected in their terminology. For instance, sulfonium salts such as $\text{Me}_3\text{S}^+\text{Cl}^-$ are clearly differentiated from sulfuranes such as Ph_2SCl_2 . The latter is a hypervalent species of decet structure [10-S-4] and pseudotrigonal bipyramid with a linear Cl-S-Cl hypervalent bond; however, the former is not a hypervalent compound and has pseudotetrahedral geometry with octet structure [8-S-3].



In this chapter, the compounds R_2IL are termed λ^3 -iodanes, having a polarized hypervalent L-I-C bond, but not iodonium salts.

2 General Reactivity Patterns

Organo- λ^3 -iodanes are widely used reagents in organic synthesis. The number of carbon ligands and the heteroatom ligands on the iodine atom determines their reactivity. They are mostly divided into two classes: 1) RIL_2 with one carbon and two heteroatom ligands, 2) R_2IL with two carbon and one heteroatom ligands. The first class λ^3 -iodanes RIL_2 , in which the heteroatom ligands invariably occupy apical sites in the pseudotrigonal bipyramid, are useful agents for oxidation of various functional groups. The presence of two heteroatom ligands on iodine is essential for the oxidation reaction, one being used in ligand exchange step and the other being used in reductive elimination step. In these steps both heteroatom ligands serve as leaving groups. The second class λ^3 -iodanes R_2IL are not good oxidizing agents but transfer one carbon ligand (R) to a variety of nucleophiles. λ^3 -Iodanes R_3I with three carbon ligands are rare and generally unstable, because less electronegative carbon ligands are forced to occupy the apical positions [1, 8].

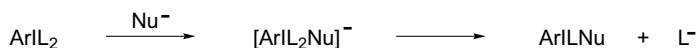
As described above, two fundamental modes of the reaction of organo- λ^3 -iodanes involve ligand exchange, occurring at iodine(III) with no change in the oxidation state, and reduction of hypervalent λ^3 -iodane to iodide, called reductive elimination. These processes are discussed in detail.

2.1 Ligand Exchange

Heteroatom ligands of λ^3 -iodanes are readily displaced with external nucleophiles. Detailed mechanism for ligand exchange on iodine(III) is not known, but two mechanistic pathways, associative and dissociative, are considered for the process [9]. There are many evidences supporting the associative mecha-

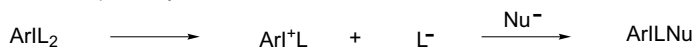
nism, while experimental results showing the dissociative pathway have not been reported, probably because dicoordinated [8-I-2] iodonium ion involved in a dissociative pathway is a highly energetic species. We believe that such a dicoordinated iodonium ion, if generated in solution, will be coordinated by a solvent molecule from apical sites to form hypervalent bonding.

associative pathway

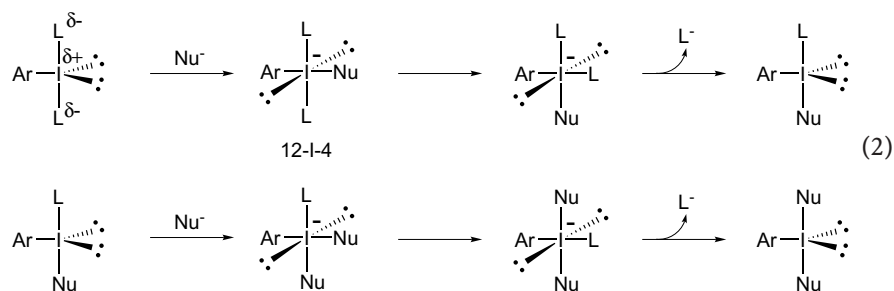


(1)

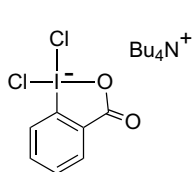
dissociative pathway



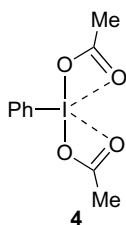
The iodine atoms of ArIL_2 are positively charged and, therefore, are electrophilic. A variety of nucleophiles react with the positively charged iodine towards the C-I σ^* orbital and result in the intermediate formation of a *trans* tetracoordinated [12-I-4] iodate with a square-planar arrangement. The *trans* iodate isomerizes to a *cis* iodate and elimination of a heteroatom ligand L from the tetracoordinated iodate produces a new aryl- λ^3 -iodane $\text{ArI}(\text{Nu})\text{L}$, as shown in Eq. (2). The overall process involves an exchange of a heteroatom ligand on iodine(III) with a nucleophile via addition-elimination sequence and is called ligand exchange. This process generally proceeds with a low-energy barrier, and hence is rapid and often reversible. Second ligand exchange of $\text{ArI}(\text{Nu})\text{L}$ may also occur through similar addition-elimination sequence, depending on the conditions, and affords ArINu_2 or $\text{ArINuNu}'$, if the second nucleophile (Nu') is different from the first one.



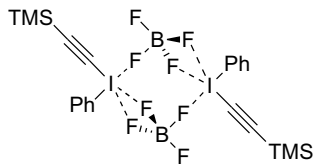
Involvement of the first step, addition of a nucleophile to λ^3 -iodanes, in ligand exchange is suggested by the isolation of tetracoordinated species. For instance, reaction of ICl_3 with benzyltrimethylammonium chloride afforded benzyltrimethylammonium tetrachloroiodate as a stable yellow crystal [10]. Its distorted square-planar configuration of ICl_4^- was determined by X-ray analysis [11]. Tetracoordinated square-planar arrangement was established for the cyclic tetra-*n*-butylammonium iodate 3 [12]. Tetra- or pentacoordination to a trivalent iodine is a generally observed phenomenon and structures of $\text{PhI}(\text{OAc})_2$ 4 [13] and $\text{TMSCC}(\text{Ph})\text{IBF}_4$ 5 [14] are shown as examples.



Structure 3 3



4

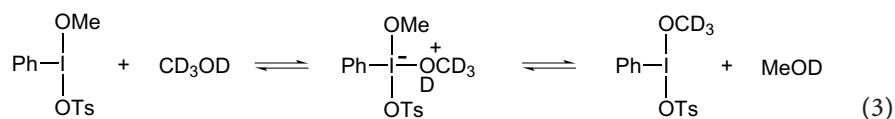


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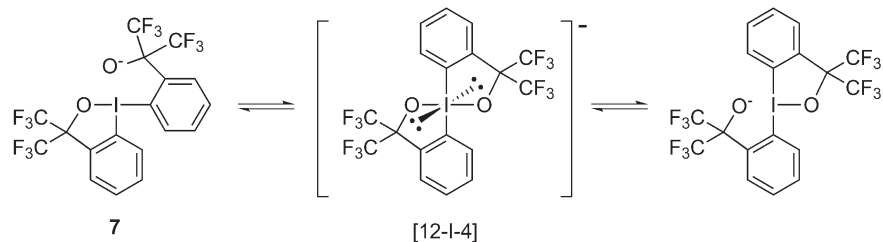
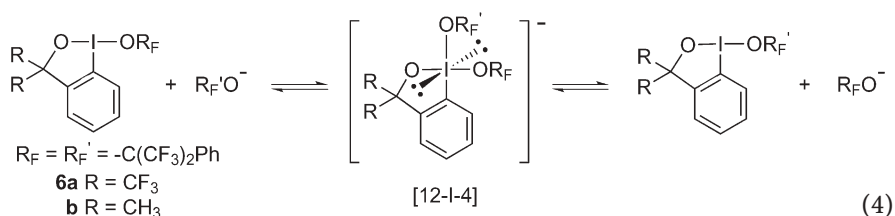
2.1.1

Oxygen Nucleophiles

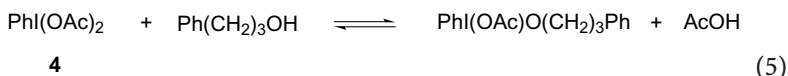
Rapid ligand exchange of [methoxy(tosyloxy)iodo]benzene with methanol- d_4 on the NMR (360 MHz) time scale was observed in CD_2Cl_2 at room temperature [15]. The formation of tetracoordinated species was assumed to be involved in this reaction.



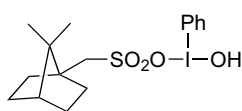
Bis(trifluoromethyl) λ^3 -iodane **6a** undergoes degenerate ligand exchange with added alkoxide $\text{PhC}(\text{CF}_3)_2\text{OK}$ more rapidly (second-order rate constant = $49 \text{ M}^{-1}\text{s}^{-1}$ at 56°C) than that of dimethyl λ^3 -iodane **6b** (second-order rate constant = $61 \text{ M}^{-1}\text{s}^{-1}$ at 93°C), in which an associative mechanism involving the formation of [12-I-4] species was proposed [16]. The CF_3 substituents, which lower the electron density on iodine(III) relative to the CH_3 substituents, make the iodine of **6a** more susceptible to attack by alkoxide ion. Dynamic ^{19}F NMR of λ^3 -iodane **7** showed an intramolecular ligand exchange via intermediacy of bicyclic tetracoordinated iodate with a ΔG^\ddagger of *ca.* 12 kcal/mol at -80°C [17].



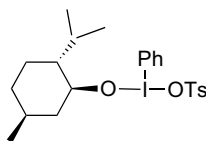
Equilibrium constant of ligand exchange of **4** with 3-phenylpropanol in CDCl_3 was measured by ^1H NMR to be 0.14 at 27°C [Eq. (5)] [18]. Phenolic oxidation with **4** yielding ligand exchange involves intermediate formation of phenoxy(acetoxy)- λ^3 -iodane via ligand exchange [19]. A variety of carboxylic acids (RCO_2H , $\text{R} = \text{Ar}$, $t\text{-Bu}$, CCl_3) undergo a facile ligand exchange with **4** in warm chlorobenzene to give $\text{PhI}(\text{OCOR})_2$ in high yields [20]. Equilibrium constants for ligand exchange of the λ^3 -iodane, *o*-iodoxybenzoic acid, with alcohols were measured [21].



Ligand exchange provides a route for the synthesis of chiral λ^3 -iodanes. [(+)-10-Camphorsulfonyl]oxy- λ^3 -iodane **8** was prepared from the reaction of **4** with (+)-10-camphorsulfonic acid in aqueous acetonitrile [22]. Concentration of a solution of [methoxy(tosyloxy)iodo]benzene and (+)-menthol in dichloromethane under vacuum results in facile ligand exchange on iodine to give the chiral λ^3 -iodane **9** [23].



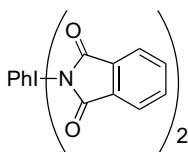
Structure 8

8**9**

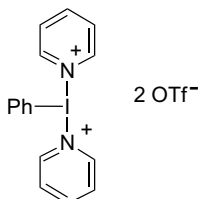
2.1.2

Nitrogen Nucleophiles

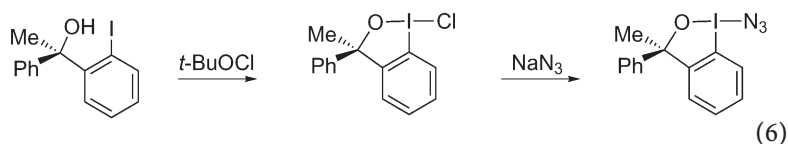
Amines and amides undergo a facile ligand exchange with λ^3 -iodanes (See Sects. 3.2.5.3, 3.2.7, and 3.2.8). λ^3 -Iodane **10** with two I-N bonds was prepared from [bis(trifluoroacetoxy)iodo]benzene **12** by the reaction with potassium phthalimide via ligand exchange [24]. The λ^3 -iodane **10** undergoes ligand exchange with acetic acid to give (diacetoxyiodo)benzene **4**. Reaction of **4** with pyridine in a mol ratio of 1 : 2 in the presence of TMSOTf gives a highly electron deficient bis(onio)- λ^3 -iodane **11** with the $E_{1/2}$ value of + 0.34 V [25].



Structure 10

10**11**

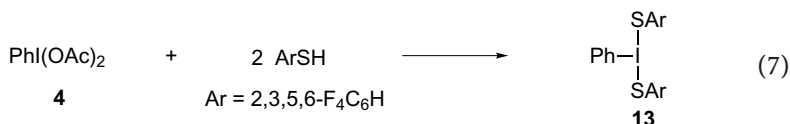
Oxidation of (*R*)-(+)-2-iodo- α -methylbenzhydrol with *t*-BuOCl gives chiral chloro- λ^3 -iodane, which on ligand exchange with NaN_3 affords (+)-azido- λ^3 -iodane [Eq. (6)] [26].



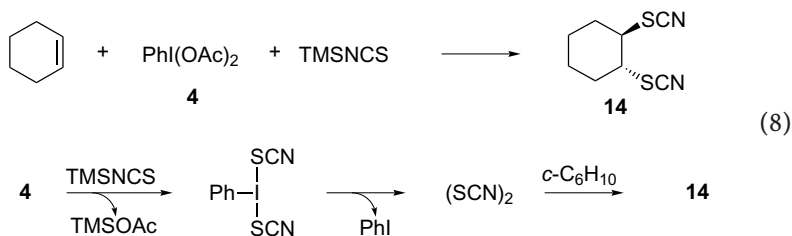
2.1.3

Other Heteroatom Nucleophiles

Formation of the λ^3 -iodane **13** with two I-S bonds was proposed when (diacetoxyiodo)benzene **4** was treated with electron deficient 2,3,5,6-tetrafluorothiophenol in pyridine [27]. The λ^3 -iodane **13** reacts with terminal alkynes to give 1,2-bis(arylthio)alkenes.



Exposure of alkenes to a combination of **4** and trimethylsilyl isothiocyanate leads to the formation of 1,2-dithiocyanates [Eq. (8)] [28]. The reaction involves the formation of bis(thiocyanato)- λ^3 -iodane by a ligand exchange. The decomposition of this iodane leads to the formation of thiocyanogen, which in turn undergoes the *anti* electrophilic addition to olefins.



Reaction of diarylhalo- λ^3 -iodanes with sodium *N,N*-dialkyldithiocarbamates results in the formation of yellow or orange dialkylcarbamoyl(diaryl)- λ^3 -iodanes, which are stable in the dark but decompose to aryl iodides and aryl dialkyldithiocarbamates in daylight via light-promoted homolytic pathway [29]. For ligand exchange of λ^3 -iodanes with sulfides, see Section 3.2.5.4.

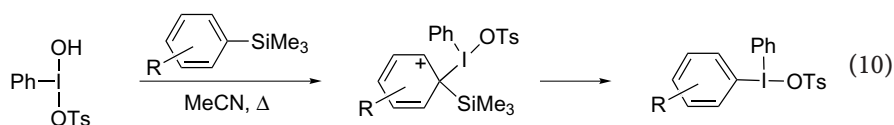
Exchange reaction between heteroatom ligands of λ^3 -iodanes probably occurs [Eq. (9)]: ^{13}C NMR spectra of a mixture of **4** and (dichloroiodo)benzene **15** in CDCl_3 showed a rapid ligand exchange and formation of a new λ^3 -iodane, presumably **16**, was detected as a major component in a nearly statistical ratio 1:1:2 of **4**:**15**:**16** [30].



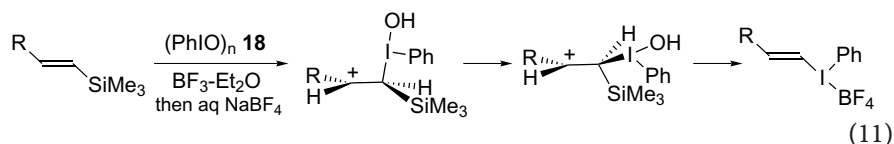
2.1.4

Carbon Nucleophiles

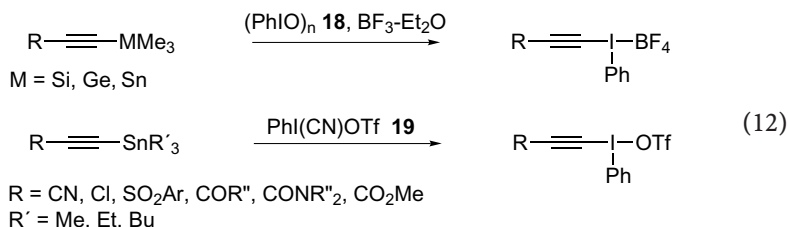
Ligand exchange on iodine(III) with carbon nucleophiles provides a useful method for synthesis of λ^3 -iodanes with two carbon ligands. Koser and co-workers found that exposure of aryltrimethylsilanes to [hydroxy(tosyloxy)-iodo]benzene **17** in refluxing acetonitrile allows the directed synthesis of diaryl- λ^3 -iodanes [31]. The reaction involves silicon-directed *ipso* carbon attack on the positively charged iodine and, therefore, is regioselective.



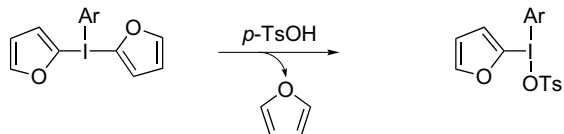
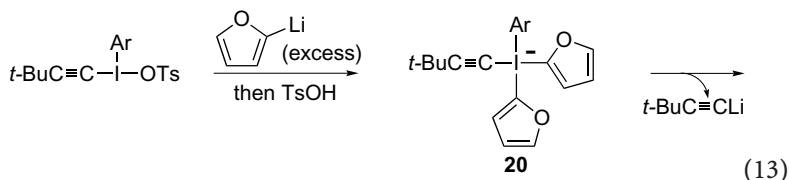
Similar ligand exchange with alkenyl(trimethyl)silanes provides a general and practical method for the synthesis of alkenyl(phenyl)- λ^3 -iodanes [Eq. (11)] [32]. Thus, reaction of (*E*)-alkenylsilanes with iodosylbenzene **18** or (diacetoxyiodo)benzene **4** in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ in dichloromethane at room temperature affords (*E*)-alkenyl- λ^3 -iodanes in high yields. Silicon β -effects [33] account for the observation that the reaction is exclusively regio- and stereospecific with retention of the olefin geometry. Alkenyl(tributyl)stannanes as well as alkenylboronic acids also undergo tin- and boron- λ^3 -iodane exchange, thus yielding alkenyl- λ^3 -iodanes stereoselectively [34, 35].



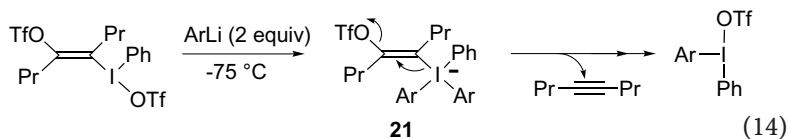
Alkynyl(trimethyl)silanes, germanes, and stannanes produce alkynyl(phenyl)- λ^3 -iodanes via ligand exchange on iodine under similar conditions [36]. Stang and co-workers developed a useful procedure for the preparation of diverse β -functionalized alkynyl- λ^3 -iodanes, which involves a ligand exchange of cyano- λ^3 -iodane **19** with alkynylstannanes [37].



When (*tert*-butylethynyl)aryl- λ^3 -iodanes were mixed with an excess of 2-lithiofuran or 2-lithiothiophene and subsequently treated with *p*-TsOH, (2-furyl)- or (2-thienyl)aryl- λ^3 -iodanes were obtained [38]. This carbon ligand exchange probably proceeds via selective elimination of the most stable alkynyl-lithium from the tetracoordinated iodate **20** [39].



Certain β -functionalized alkenyl ligands of λ^3 -iodanes can be displaced with an aryl group. Reaction of (*E*)-[β -(trifluoromethanesulfonyloxy)vinyl]- λ^3 -iodane with aryllithiums (2 equiv) at low temperature gave aryl(phenyl)- λ^3 -iodane selectively with concomitant formation of alkyne [Eq. (14)] [40]. Stereoelectronically preferable *anti* β -elimination of the intermediate iodate **21** and the presence of triflate leaving group with high nucleofugality (Section 3.2.2) are responsible for the facile ligand exchange of the vinyl group with an aryl group. The method was applied to ligand exchange of (*E*)-[β -(trifluoromethanesulfonyloxy)ethenyl]- λ^3 -iodane with alkynyllithiums yielding alkynyl- λ^3 -iodanes [41].

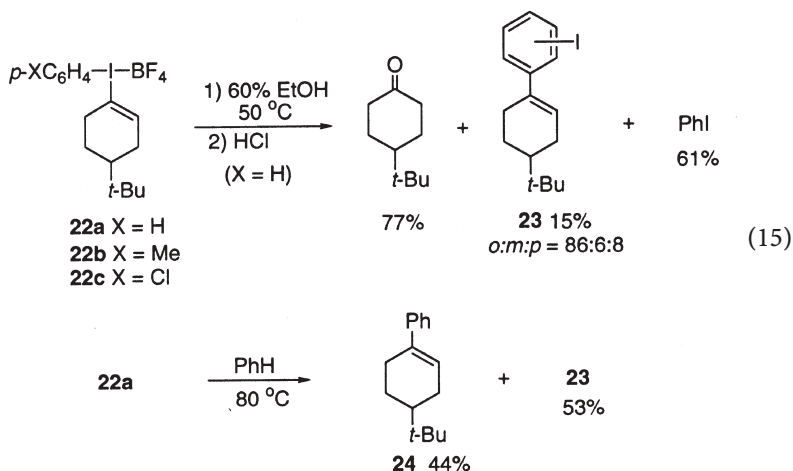


2.2

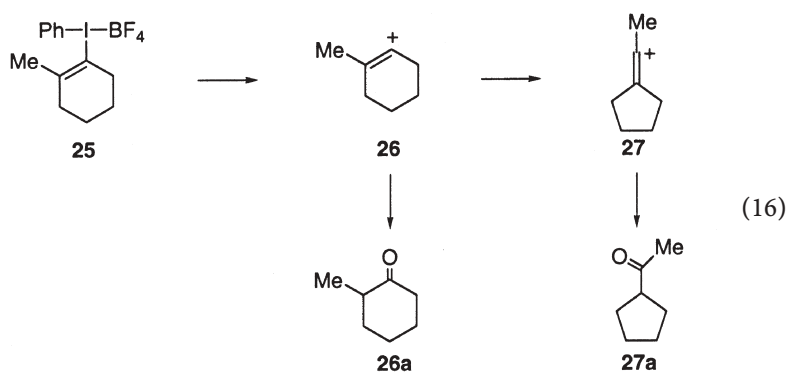
Hypernucleofuge: Reductive Elimination

Most important mode of reactions of hypervalent λ^3 -iodanes is their reductive transformation to univalent iodide. This process is very facile and energetically favorable, and often proceeds without the assistance of the added reagent. The rate of this unimolecular process was measured by solvolysis of alkenyl(aryl)- λ^3 -iodanes.

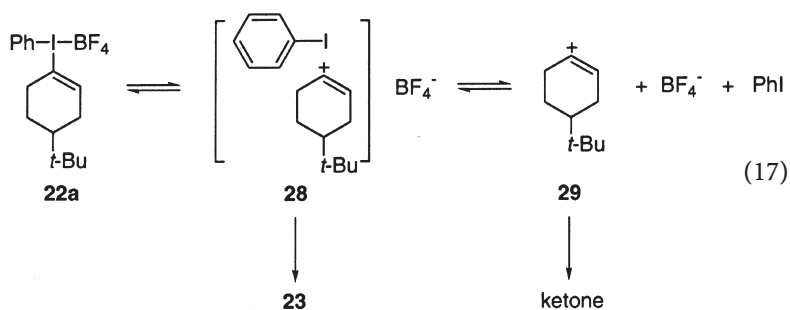
Solvolysis of (1-cyclohexenyl)phenyl- λ^3 -iodane **22a**, prepared by BF_3 -catalyzed ligand exchange of iododisylbenzene **18** with vinylsilane, proceeds at a reasonable rate in aqueous alcoholic solutions even at room temperature and generates cyclohexenyl cation with reductive elimination of iodobenzene [42]. The reaction in 60% aqueous ethanol at 50 °C affords 4-*tert*-butylcyclohexanone as a major product after acid workup, along with a mixture of rearranged products **23**, the *ortho* isomer being predominant. Heating of **22a** in benzene at 80 °C results in a Friedel-Crafts vinylation of benzene and affords a mixture of 1-phenylcyclohexene **24** and the rearranged products **23** [43].



The presence of cyclohexenyl cation intermediates was firmly established by the observation of carbocation rearrangement during the solvolysis of **25**, in which an initially generated bent vinyl cation **26** with sp^2 hybridization rearranges to a more stable linear vinyl cation **27** with sp hybridization [Eq. (16)]. The ratio of the rearranged to the unrearranged ketones depends on the nature of solvents used and changed from 14:86 (**27a**:**26a**) in 60% aqueous ethanol to 46:54 in the less nucleophilic 2,2,2-trifluoroethanol.



The mechanism for solvolysis of λ^3 -iodane **22a** involves generation of the intimate cyclohexenyl cation-iodobenzene pair **28**. Friedel-Crafts vinylation of iodobenzene within the intimate ion-molecular pair **28** will produce a mixture of rearranged products **23** with selective formation of the *ortho* isomer [Eq. (17)]. The fact that solvolysis of **22a** in methanol in the presence of an excess amount (50 equiv) of *p*-methyliodobenzene affords the exchanged vinyliodane **22b** (4%) in addition to the formation of **23** (*o*:*m*:*p* = 86:5:9) and the recovered vinyliodane **22a** (49%) suggests the reversible formation of the free cation **29** during solvolysis.



Pseudo-first-order rate constants for the solvolysis of **22** at 35–69°C are shown in Table 1. The leaving group ability of aryl- λ^3 -iodanyl groups increases with an increase in the electron-withdrawing nature of the ring substituents. Comparison of the solvolysis rate for **22a** with that of 1-cyclohexenyl triflate indicates that the phenyl- λ^3 -iodanyl group $\text{Ph}(\text{BF}_4)\text{I}-$ is a remarkably good nucleofuge with a leaving group ability about 10^6 times greater than triflate, a so-called “superleaving group”. The aryl- λ^3 -iodanyl groups are the most efficient leaving groups that have been evaluated quantitatively.

A leaving group such as the aryl- λ^3 -iodanyl group is termed a hypernucleofuge [44]. The hypernucleofuge must show a leaving group ability higher than that of a superleaving group such as TfO , and also be a hypervalent leaving group. As shown in [Eq. (18)], the leaving process of a hypernucleofuge must

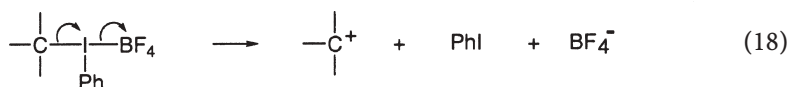
Table 1. Rate constants ($10^4 k_{\text{obsd}}/\text{s}^{-1}$) for solvolysis of **22** in 60:40 ethanol-water

Iodane 22	Temp/°C			ΔH^\ddagger kcal/mol	ΔS^\ddagger cal/mol deg
	35	50	69		
22a	0.229	2.32	26.9	28.7	13.3
22b	0.114	1.23	14.0	28.5	11.8
22c	0.594	5.74	60.3	27.9	12.8

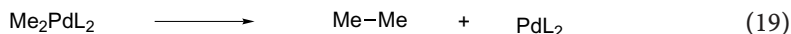
Table 2. Relative leaving group abilities

Nucleofuge	k_{rel}	Nucleofuge	k_{rel}
AcO	1.4×10^{-6}	I	9.1×10
F	9.0×10^{-6}	MsO	3.0×10^4
Me_2S^+	5.3×10^{-2}	TsO	3.7×10^4
Cl	1.0	TfO	1.4×10^8
F_3CCO_2	2.5	<i>p</i> -MePh(BF ₄)I	6.2×10^{13}
NO_3	7.2	Ph(BF ₄)I	1.2×10^{14}
Br	1.4×10	<i>p</i> -ClPh(BF ₄)I	2.9×10^{14}

involve an energetically preferable reduction of the hypervalent atom to the normal valency with octet structure, which is the origin of the high leaving group ability. The positively charged dimethylsulfonio group with tetrahedral geometry, and hence with no hypervalency, shows poor leaving group ability (Table 2). Furthermore, the leaving process of a hypernucleofuge is associated with an increase in entropy, since the hypervalent molecule decomposes into three components [Eq. (18)].

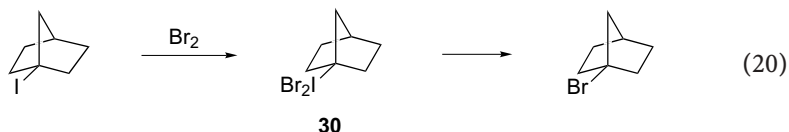


The process shown in Eq. (18) is termed *reductive elimination*, in which the λ^3 -iodanyl group eliminates with concomitant reduction to univalent iodide i.e. iodobenzene and simultaneously with elimination of a heteroatom ligand (BF₄) on iodine(III). The same term reductive elimination is widely used in organotransition metal chemistry in a somewhat different sense to describe reduction of transition metals with concomitant bond formation between two ligands [Eq. (19)].

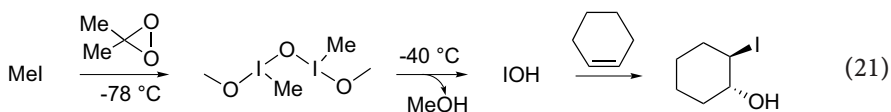


Reaction of 1-iodonorbornane with bromine in dichloromethane produces 1-bromonorbornane via the rapid formation of dibromo- λ^3 -iodane **30**. The observed rate constant ($k_{\text{obsd}} = 3 \times 10^{-4} \text{ s}^{-1}$ at 40 °C) for the unimolecular de-

composition of **30** shows that the dibromo- λ^3 -iodanyl group Br_2I - is a hypernucleofuge and its leaving group ability is 10^{10} times greater than that of iodine [45].



Because of the hypernucleofugality of λ^3 -iodanyl groups, alkyl- λ^3 -iodanes are generally unstable and can exist only as short-lived species. For instance, oxidation of iodomethane with dimethyldioxirane in acetone at -78°C produces polymeric iodosylmethane as a pale yellow precipitate (See Sect. 3.4.2) but it decomposes to hypoiodous acid and methanol even at -40°C , probably via nucleophilic substitution by water [Eq. (21)] [46]. Hypoiodous acid is trapped by olefins to give iodohydrines.



Introduction of an electron-withdrawing substituent into the alkyl moiety results in an increase in the stability of alkyl- λ^3 -iodanes: thus, $\text{ArSO}_2\text{CH}_2\text{ICl}_2$, $\text{R}_f\text{CH}_2\text{I}(\text{OCOCF}_3)_2$, $\text{Et}_3\text{N}^+\text{CH}_2\text{ICl}_2\text{BF}_4^-$, and $\text{Ph}_3\text{P}^+\text{CH}_2\text{ICl}_2\text{BF}_4^-$ can be obtained as relatively stable compounds [47, 48].

2.3

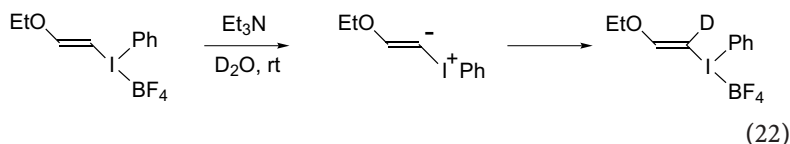
Electronic Nature

Phenyl- λ^3 -iodanyl groups show a highly electron-withdrawing nature. Hammett substituent constants of some λ^3 - and λ^5 -iodanyl groups have been estimated by ^{19}F NMR spectroscopy of *m*- and *p*-substituted fluorobenzenes (Table 3) [49]. As expected, the phenyl- λ^3 -iodanyl group, $\text{Ph}(\text{BF}_4)\text{I}$ -, is an inductively strong electron-withdrawing group with large σ_I (1.34) and small σ_R (0.03) values. It has been reported that the phenyl- λ^3 -iodanyl group increases the C-H acidity ($\text{p}K_a$ in aqueous solution) of malonic ester by 8 orders of magnitude [50].

α -Vinyl hydrogens of alkenyl- λ^3 -iodanes are quite acidic, because of the highly electron-withdrawing nature of λ^3 -iodanyl groups. Thus, weak bases such as amines can abstract the α -vinyl hydrogens of alkenyl- λ^3 -iodanes, generating vinyliodonium ylides [51, 52]. Treatment of (*E*)-(β -ethoxyvinyl)- λ^3 -iodane with triethylamine in D_2O -THF at room temperature undergoes deuterium exchange of the α -vinyl proton, indicating the generation of the vinyliodonium ylide via α -proton abstraction [Eq. (22)]. Interestingly, this reaction proceeds with exclusive retention of configuration.

Table 3. Hammett substituent constants

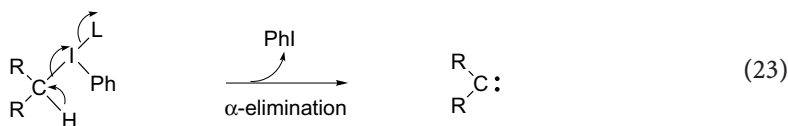
Substituent	σ_1	σ_R	σ_m	σ_p
I	0.47	-0.12	0.35	0.18
I(Ph)BF ₄	1.34	0.03	1.35	1.37
ICl ₂	1.17	0.03	1.18	1.20
I(OCOCF ₃) ₂	1.0	0.05	1.03	1.05
IF ₂	0.97	0.04	0.95	0.93
I(OAc) ₂	0.85	0.06	0.88	0.91
IO	0.56	0.06	0.59	0.62
IF ₄	1.05	0.14	1.12	1.19
IO ₂	0.66	0.10	0.71	0.76
N ₂ ⁺ (BF ₄) ⁻	1.48	0.31	1.65	1.79
NO ₂	0.64	0.16	0.71	0.78
SO ₂ Ph	0.59	0.12	0.62	0.68



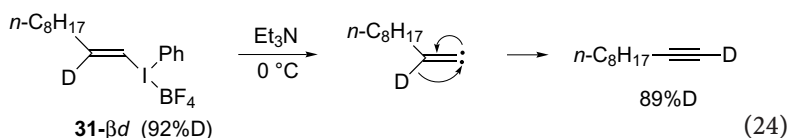
2.4

Reductive α -Elimination

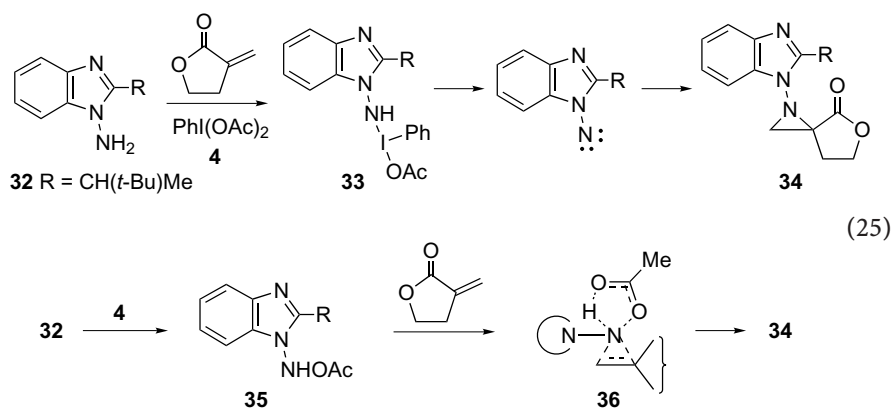
Reductive α -elimination of λ^3 -iodanes on carbon atoms provides a method for the generation of carbenes [Eq. (23)].



Reaction of (*E*)-alkenyl(phenyl)- λ^3 -iodane **31** with Et₃N at 0 °C leads to formation of the terminal alkyne quantitatively. Mechanistic studies with α - and β -deuterated λ^3 -iodanes indicate that the alkyne-forming reaction predominantly involves the generation of alkylidene carbenes via reductive α -elimination and their 1,2-hydrogen shift, but not direct *syn*- β -elimination [53]. The α -elimination of **31** consists of an α -hydrogen abstraction with Et₃N, followed by a rapid reductive elimination of the resulting vinylidonium ylide. Both the highly electron-withdrawing nature and the hyperleaving group ability of the phenyl- λ^3 -iodanyl group are responsible for the facile α -elimination. Generation of alkylidene carbenes from alkenyl- λ^3 -iodanes and their reactions will be discussed in detail in Sect. 3.3.2.1.

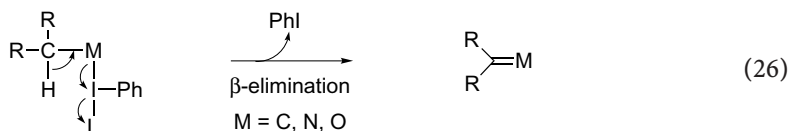


Oxidation of primary *N*-aminobenzimidazole **32** with $\text{PhI}(\text{OAc})_2$ **4** in the presence of olefins gives aziridines **34** [54]. Similar oxidations are effected by lead tetraacetate. The reaction was initially proposed to involve the intermediacy of *N*-nitrene as a reactive species, thought to be produced through reductive α -elimination of amino- λ^3 -iodane **33**. Recent mechanistic studies on lead tetraacetate oxidation, however, suggests that the acetoxamine **35** instead of *N*-nitrene is the aziridinating species, and the reaction proceeds through a transition state **36** similar to that of epoxidation using peracids [55].



2.5 Reductive β -Elimination

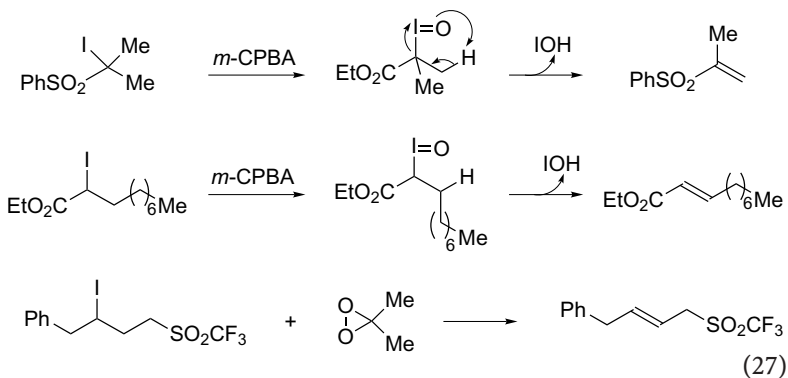
Reductive β -elimination of λ^3 -iodanes on carbon atoms ($M = \text{C}$) produces C–C double bonds, while that on oxygen and nitrogen atoms ($M = \text{O}$ and N), combined with the initial ligand exchange reaction, provides a method for oxidation of alcohols and amines to the corresponding carbonyl compounds and imines, respectively [Eq. (26)].



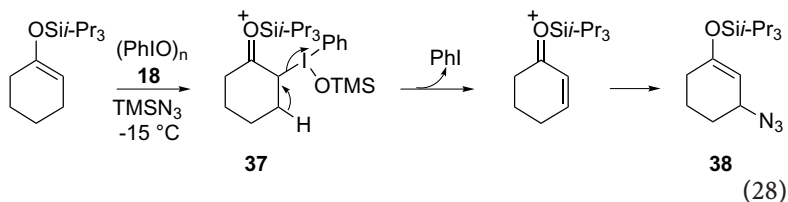
2.5.1 C–C Multiple Bond Formation

Oxidation of alkyl iodides, bearing electron-withdrawing groups such as carbomethoxy and sulfonyl at the α -carbon, with *m*-chloroperbenzoic acid results in clean elimination to give olefins [Eq. (27)]. This reaction involves reductive β -elimination of the intermediate iodosylalkanes, as observed in thermal pericyclic β -elimination of sulfoxides and selenoxides. Exclusive *syn* stereochemistry in the reductive β -elimination was established by deuterium labeling

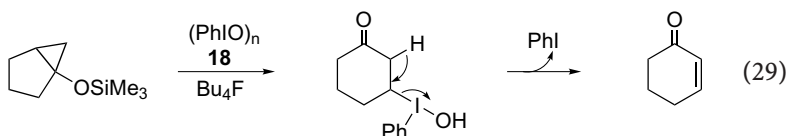
experiments using tetralins [56]. Reductive β -elimination of iodosylalkane derived from γ -iodo triflone proceeds regioselectively, probably because of a large inductive effect of the triflone [57].



Reaction of triisopropylsilyl enol ether with a combination of iodosylbenzene **18** and trimethylsilyl azide at -15°C gives directly the β -azido triisopropylsilyl enol ether **38** in a high yield. A mechanism involving the reductive β -elimination of α -iodanyl onium ion **37**, probably produced by ligand exchange of in situ generated $\text{PhI}(\text{N}_3)\text{OTMS}$ with silyl enol ether, was proposed. Addition of azide to the resulting α,β -unsaturated onium ion explains the formation of **38** [58, 59].

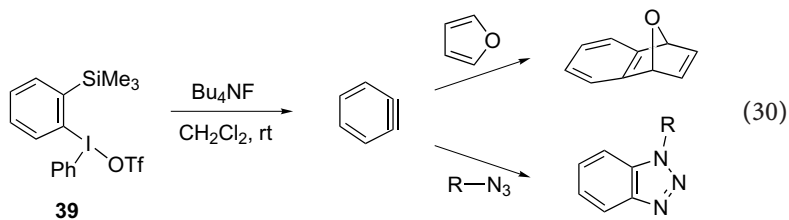


Ring opening of silyloxycyclopropanes with iodosylbenzene **18** in the presence of fluoride ion produces β - λ^3 -iodanyl carbonyl compounds, which undergo very facile reductive β -elimination to give α,β -unsaturated carbonyl compounds [Eq. (29)]. Since the starting silyloxycyclopropanes can be prepared from the corresponding silyl enol ethers, this reaction provides a method for ring expansion of ketones and lactones (See Sect. 3.2.6) [60].

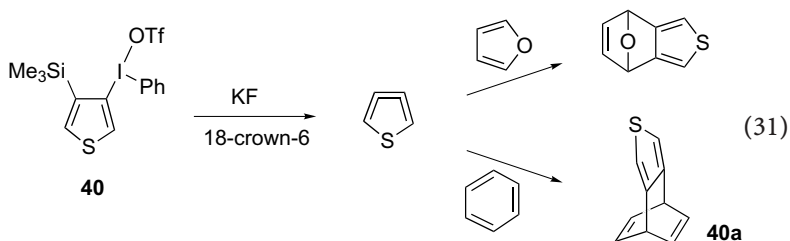


Kitamura and coworkers found that *o*-(trimethylsilyl)phenyl- λ^3 -iodane **39** acts as an excellent precursor of benzyne. Because of the high nucleofugality of the phenyl- λ^3 -iodanyl group, iodane **39** undergoes a fluoride ion-induced reduc-

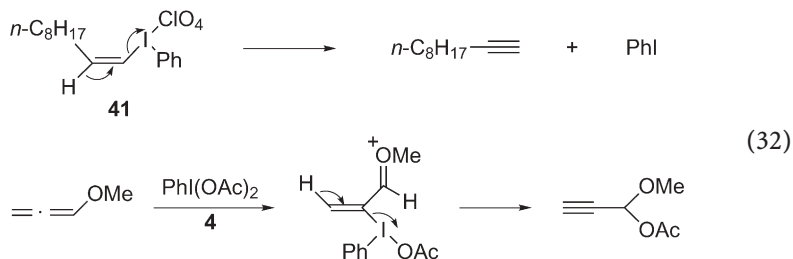
tive β -elimination under mild conditions (at room temperature) and generates benzyne, which undergoes Diels-Alder reactions with 1,3-dienes such as furans, anthracene, cyclopentadienone etc. affording cycloadducts in high yields [61]. Reaction with alkyl and aryl azides gives benzotriazoles [62].



The fluoride ion-induced reductive β -elimination makes it possible to generate highly strained olefins [Eq. (31)]. β -Silyl λ^3 -iodane **40** generates five-membered cumulene with remarkable reactivity at room temperature and affords Diels-Alder adduct **40a** (7% yield) by the reaction with benzene [63].



In contrast to the (*E*)-isomer, (*Z*)-alkenyl(phenyl)- λ^3 -iodane **41** is labile and decomposes with a half-life time of 20 min to terminal alkynes in chloroform solution at room temperature [64]. Stereoelectronically preferable reductive *anti* β -elimination accounts for this facile decomposition. In fact, the kinetic results for E2-type dehydrohalogenation of vinyl halides show that the relative rates of elimination decrease in the order *anti* β ->*syn* β -> α -elimination [65]. Similar *anti* β -elimination of vinyl- λ^3 -iodane was proposed in the oxidation of methoxyallene with (diacetoxyiodo)benzene **4** to 3-acetoxy-3-methoxypropyne [66].

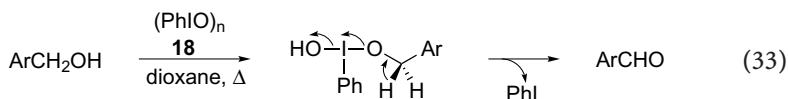


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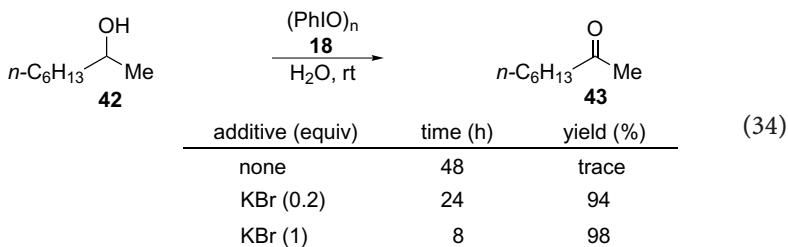
Oxidation of Alcohols

Aryl- λ^3 -iodanes with two heteroatom ligands undergo oxidation of alcohols to carbonyl compounds, one heteroatom ligand being used in ligand exchange step and the other being used in reductive β -elimination step. In these steps both heteroatom ligands serve as leaving groups. A detailed discussion and more examples can be found in Chapter 8 (Oxidations and Rearrangements).

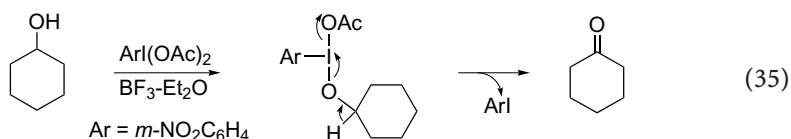
Benzyl and allyl alcohols are oxidized with iodosylbenzene **18** in refluxing dioxane to aldehydes [67]. Further oxidation of aldehydes to carboxylic acids does not take place. Aliphatic primary alcohols are not oxidized under the conditions. Ligand exchange of **18** with alcohols produces alkoxy- λ^3 -iodanes, which result in reductive β -elimination to give aldehydes [Eq. (33)].



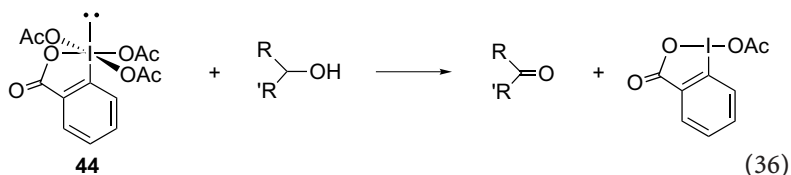
Interestingly, Kita and Tohma found that the addition of bromide catalyzes the oxidation of primary and secondary alcohols with iodosylbenzene **18** in water [68]. Use of a catalytic amount of KBr activates **18** and oxidizes alcohols to ketones at room temperature. Salts other than bromide (NaX: X = F, Cl, I, ClO₄, and NO₃) do not catalyze the reaction effectively. Iodosylbenzene **18** is depolymerized by the reaction with KBr and generates a reactive bromo- λ^3 -iodane via ligand exchange [Eq. (34)]. Further ligand exchange with an alcohol, followed by reductive β -elimination induced by intramolecular oxy anion, will explain the facile oxidation.



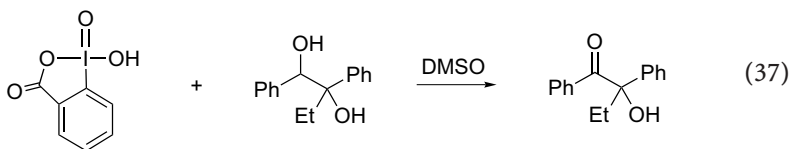
Lewis acids accelerate the oxidation of alcohols with aryl- λ^3 -iodanes. Treatment of cyclohexanol with *m*-nitrophenyl- λ^3 -iodane in the presence of BF₃-Et₂O at 30 °C afforded cyclohexanone in high yields [Eq. (35)] [69]. Both the ligand exchange and the reductive β -elimination are involved in the oxidation and accelerated by the coordination of BF₃ to the acetoxy ligand of the λ^3 -iodane. A relatively large primary kinetic deuterium isotope effect ($k_{\text{H}}/k_{\text{D}} = 4.84$) indicates that the α -C-H bond cleavage in reductive β -elimination is involved to a great extent in the rate-limiting step of the oxidation.



Dess-Martin λ^5 -iodane **44** is an extremely useful reagent for the conversion of primary and secondary alcohols to aldehydes and ketones at 25 °C [70]. It does not oxidize aldehydes to carboxylic acids under these conditions. It selectively oxidizes alcohols in the presence of furans, sulfides, and vinyl ethers. The oxidation mechanism involves a facile ligand exchange with alcohols, followed by reductive β -elimination.



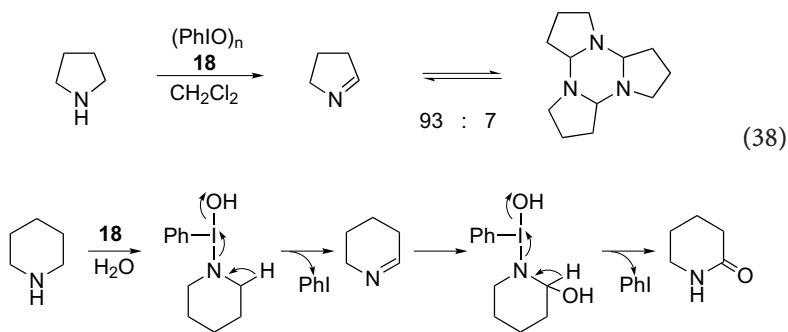
o-Iodoxybenzoic acid in DMSO smoothly oxidizes primary and secondary alcohols to aldehydes and ketones at 25 °C [71]. 1,2-Diols are converted to α -ketols or α -diketones without any oxidative cleavage of the glycol C-C bond [Eq. (37)]. Kinetic evidences suggest a two-step mechanism involving a fast pre-equilibrium ligand exchange with alcohols, followed by a rate-determining reductive β -elimination [21].



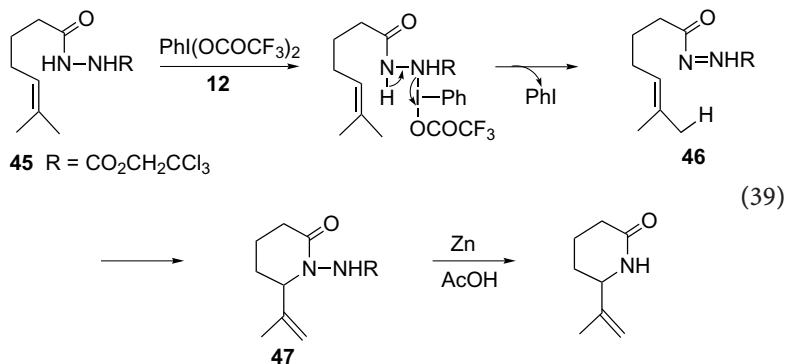
2.5.3

Oxidations of Amines

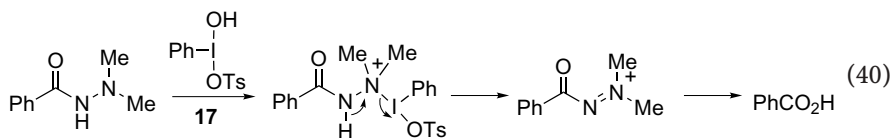
Aryl- λ^3 -iodane oxidation of amines to imines also involves a combination of ligand exchange and successive reductive β -elimination. Oxidation of pyrrolidine with iodosylbenzene **18** affords quantitatively an equilibrium mixture of 1-pyrroline and its trimer [72]. When oxidation of piperidine with **18** (2 equiv) was carried out in water, 2-piperidone was produced [73]. In the latter reaction, a sequence of ligand exchange and reductive β -elimination was repeated two times [Eq. (38)].



Reaction of hydrazide **45** with bis(trifluoroacetoxy)- λ^3 -iodane **12** gives the cyclic hydrazide **47**, which on zinc dust reduction affords δ -lactam [74]. The formation of **47** involves an intramolecular ene reaction of azodicarbonyl intermediate **46**, produced from a sequence of ligand exchange on iodine(III) and reductive β -elimination.



A similar reaction sequence is involved in the hydrolysis of *N,N'*-dimethylhydrazides [Eq. (40)] [75]. The hydrazide is efficiently cleaved to give benzoic acid upon treatment with $\text{PhI}(\text{OH})\text{OTs}$ **17** in water. The reaction occurs with the evolution of gas, probably nitrogen and methane.

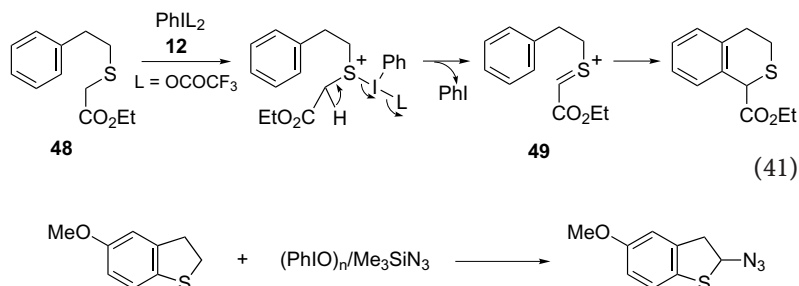


2.5.4

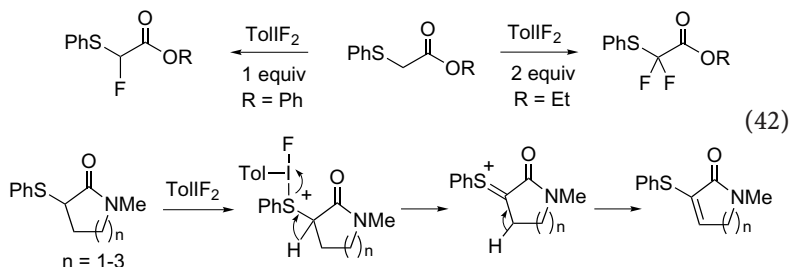
Oxidations of Sulfides

α -Thioacetate **48**, on treatment with λ^3 -iodane **12**, affords isothiochroman via Friedel-Crafts cyclization [76]. This reaction involves a combination of ligand exchange on iodine(III) and the successive reductive β -elimination, which gen-

erates Pummerer intermediate **49**. Intramolecular trapping of the cation **49** with a π bond yields 1-(ethoxycarbonyl)isothiochroman. α -Azidation of cyclic sulfides with a combination of $(\text{PhIO})_n$ **18** and Me_3SiN_3 proceeds via a similar reaction sequence [Eq. (41)] [77].

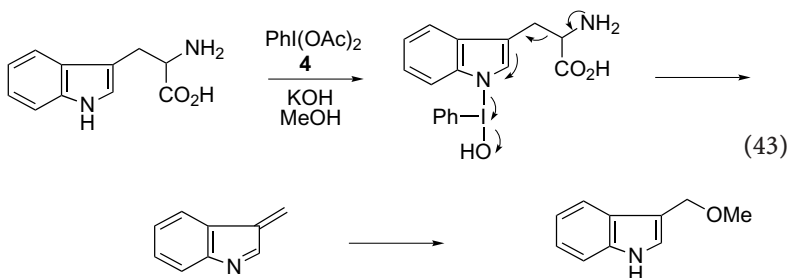


α -Sulfonyl esters and amides are fluorinated in the α -position through fluoro-Pummerer reaction when treated with (difluoroiodo)toluene [Eq. (42)] [78]. A second fluorination is possible with α,α -difluorosulfide being formed on treatment with two equivalents of the λ^3 -iodane. Reaction of lactams, however, resulted in the formation of α,β -unsaturated sulfides [79].

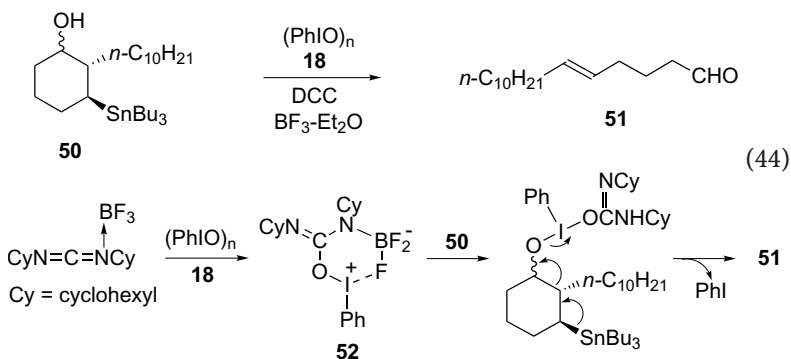


2.6 Reductive Elimination with Fragmentation

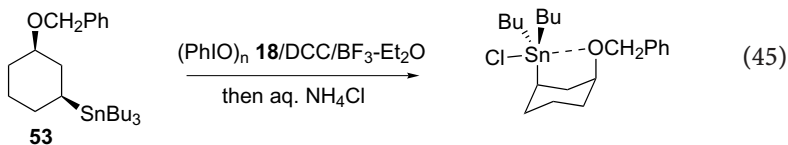
Moriarty found a specific side-chain cleavage of tryptophan [80]. Reaction of tryptophan and its derivatives with $\text{PhI}(\text{OAc})_2$ **4**/KOH in methanol afforded 3-(methoxymethyl)indole. Noncleavage observed for the reaction of 1-methyl- and α -*N*-acetyltryptophan indicates a mechanism involving the initial ligand exchange at ring nitrogen, followed by reductive elimination with synchronous fragmentation.



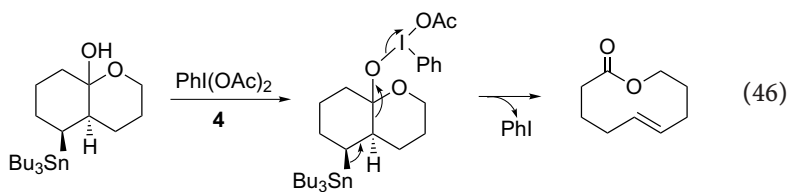
Exposure of the cyclic γ -stannyl alcohol **50** to a combination of $(\text{PhIO})_n$ **18**/DCC/ BF_3 undergoes an oxidative Grob fragmentation to give the unsaturated carbonyl compound **51** stereospecifically [81]. The γ -stannyl alcohol **50** is acid labile and, therefore, without DCC only decomposition of **50** was observed. Apparently, DCC not only decreases the Lewis acidity of BF_3 but also activates the λ^3 -iodane to give DCC- BF_3 -activated iodosylbenzene **52**. Ligand exchange of **52** with the alcohol **50** and then one-step synchronous fragmentation with reductive elimination of iodobenzene gives *trans* olefin **51** selectively.



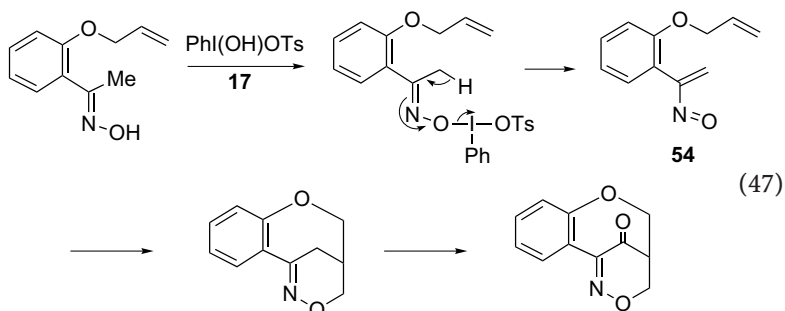
In contrast to the reaction of γ -stannyl alcohol **50**, the γ -stannyl benzyl ether **53** results in selective cleavage of the butyl-tin bond by reaction with $(\text{PhIO})_n$ **18**/DCC/ BF_3 and, after quenching of the reaction mixture with aqueous NH_4Cl , afforded the chlorostannane in high yield. Interestingly, the chlorostannane both in solution and in the solid state adopts a 1,3-diaxial conformation through Sn-O hypervalent interaction [82].



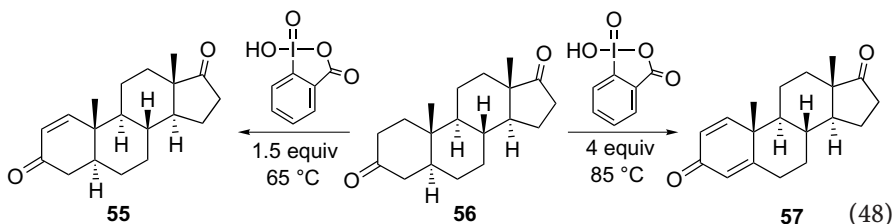
Similarly, exposure of stannyl lactol to $\text{PhI}(\text{OAc})_2$ **4** led to oxidative ring expansion yielding the *trans* unsaturated lactone stereoselectively, presumably via 1,4-fragmentation induced by reductive elimination of iodobenzene [Eq. (46)] [83].



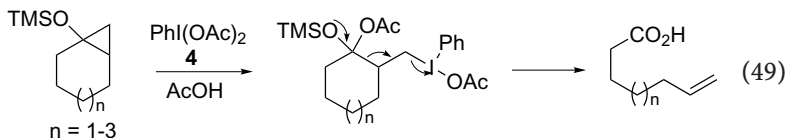
On addition of $\text{PhI}(\text{OH})\text{OTs}$ **17** to a solution of ketoxime in acetonitrile, the color changed to bluish green, indicating the formation of nitroso compound **54**. Formation of **54** involves a ligand exchange on iodine(III), followed by a vinylogous reductive β -elimination. The nitrosoalkene **54** undergoes intramolecular [4+2] cycloaddition and affords an 1,2-oxazinone derivative after oxidation [84].



A highly efficient method for dehydrogenation of carbonyl compounds was developed: for instance, oxidation of steroidal diketone **56** with *o*-iodoxybenzoic acid (1.5 equiv) in fluorobenzene-DMSO at 65 °C took place at six-membered ring selectively and gave the conjugated enone **55**, while with 4 equivalents of the λ^5 -iodane at 85 °C led to further oxidation yielding the dienone **57** in high yields. Primary alcohols are also converted into the corresponding α,β -unsaturated aldehydes in one pot. Although an ionic mechanism involving vinylogous reductive β -elimination of enoxy- λ^5 -iodane intermediates was originally proposed, many evidences suggest a single-electron transfer (SET) mechanism [85].



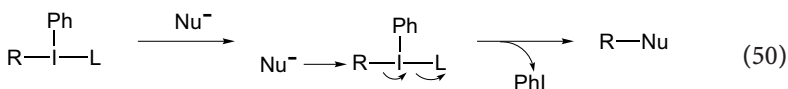
Exposure of cyclopropyl silyl ethers to **4** in acetic acid results in an oxidative Grob fragmentation to give unsaturated acids [Eq. (49)] [86].



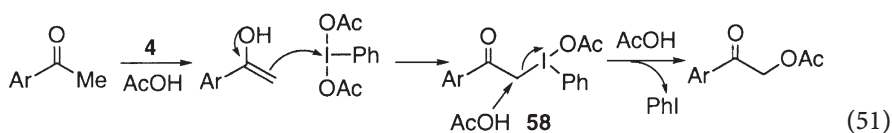
2.7

Reductive Elimination with Substitution

Reductive elimination of λ^3 -iodanes with two carbon ligands often accompanies attack of nucleophiles on the carbon atoms attached to the iodine(III) [Eq. (50)]. The reaction gives substitution products.

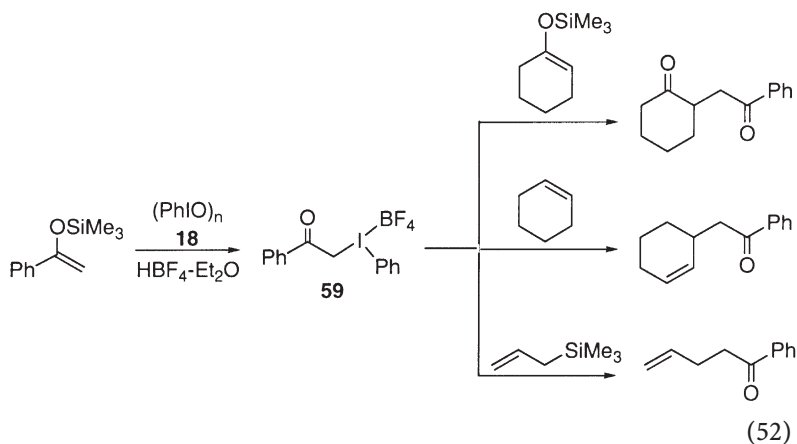


Oxidation of carbonyl compounds is among the most important reaction of organo- λ^3 -iodanes. Reaction of acetophenones with $\text{PhI}(\text{OAc})_2$ **4** in acetic acid and acetic anhydride in the presence of sulfuric acid results in α -oxidation of carbonyl compounds and affords α -acetoxy ketones directly [87]. Formation of α -(phenyl- λ^3 -iodanyl) ketones **58** by the ligand exchange with the enol tautomers is believed to be involved. The λ^3 -iodanyl ketones **58** appear to be highly reactive toward attack of nucleophiles, probably via an $\text{S}_{\text{N}}2$ pathway with reductive elimination of iodobenzene, because of the very high nucleofugality of the phenyl- λ^3 -iodanyl group.

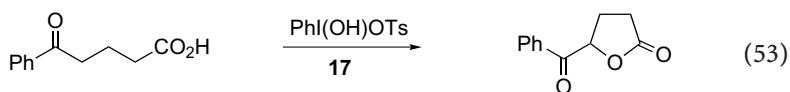


The oxidation of carbonyl compounds at the α -carbon atom by λ^3 -iodanes under acidic and basic conditions has broad synthetic utility and is extensively developed by Moriarty and Koser [9, 88, 89]. It is generally accepted that the α - λ^3 -iodanyl ketones are involved as key intermediates in the oxidation. The α - λ^3 -iodanyl ketones $[\text{RCOCHR}'\text{I}(\text{Ph})\text{L}]$ with various heteroatom ligands (L) such as OH [90], OMe [91], OCOCF_3 [92], OTs [93], OMs [94], $\text{OP}(\text{O})(\text{OPh})_2$ [95], $\text{OP}(\text{O})\text{R}_2$ [96], and N_3 [97] can be generated in situ from carbonyl compounds or silyl enol ether derivatives by the reaction with λ^3 -iodanes. In most of these α - λ^3 -iodanyl ketones, the ligand L is introduced to the α -carbon atom of the carbonyl compounds regioselectively with reductive elimination of iodobenzene.

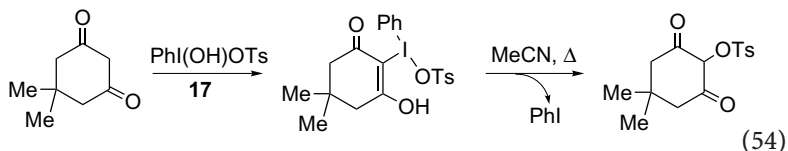
α - λ^3 -Iodanyl ketone **59** with a less nucleophilic ligand BF_4 reacts with a variety of external carbon nucleophiles including silyl enol ethers, olefins, and allyl silanes [98]. Ligand coupling pathways are proposed for the reactions of **59** with these nucleophiles, but bimolecular nucleophilic substitution of **59** with reductive elimination of iodobenzene also accounts for the formation of the products.



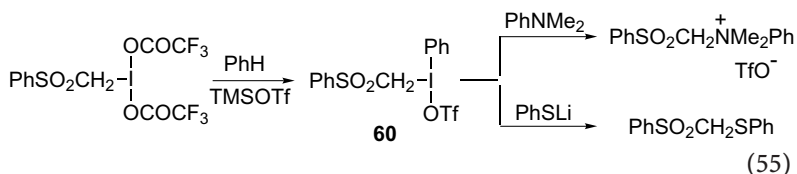
Intramolecular carboxy groups can participate as a nucleophile toward α - λ^3 -iodanyl ketones: for instance, oxidation of 5-oxocarboxylic acids with $\text{PhI}(\text{OH})\text{OTs}$ **17** affords a keto- γ -lactone in good yields [Eq. (53)] [99].



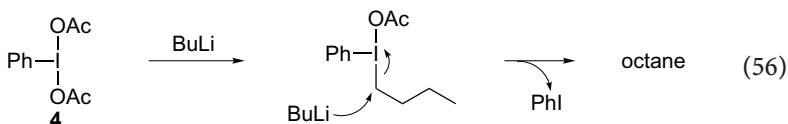
Simple α -(phenyl- λ^3 -iodanyl) ketones have never been isolated; however, α - λ^3 -iodanyl β -diketones are known. 2-Dimedonyl(phenyl)- λ^3 -iodane has been prepared from dimedone by the reaction with iodane **17** in a good yield as a white solid, which on heating in acetonitrile affords 2-tosyloxydimedone [Eq. (54)] [93].



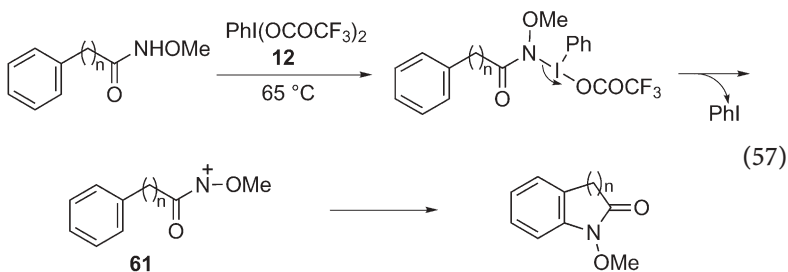
In contrast to α -(phenyl- λ^3 -iodanyl) ketones, it is possible to isolate α -(phenyl- λ^3 -iodanyl) sulfone **60** as a stable crystal [100]. The sulfone **60** undergoes substitutions with various nucleophiles with reductive elimination of iodobenzene.



Reaction of diacetoxy λ^3 -iodane **4** with butyllithium in THF at -5°C is very rapid and affords octane in high yields with concomitant formation of iodobenzene [Eq. (56)] [30]. This reaction probably involves a rapid ligand exchange with formation of butyl(phenyl)- λ^3 -iodane, which reacts with a second butyllithium on the carbon atom attached to the iodine(III) in an $\text{S}_{\text{N}}2$ process.



Electrophilic aromatic substitution takes place by the reaction of *N*-methoxyamides with λ^3 -iodanes. *N*-Methoxy lactams can be obtained in good yields by the reaction of *N*-methoxyamide with $\text{PhI}(\text{OCOCF}_3)_2$ **12** in chloroform at 65°C [Eq. (57)] [101]. This reaction involves generation of *N*-acylnitrenium ions **61**, which are stabilized by the *N*-methoxy group. Attack of the intramolecular phenyl group to the electron deficient nitrogen atom produces the nitrogen heterocycle.

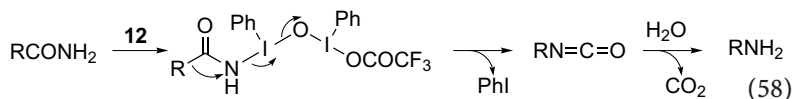


2.8

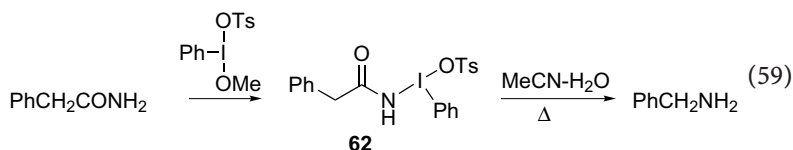
Reductive Elimination with Rearrangement

[Bis(trifluoroacetoxy)iodo]benzene **12** in acetonitrile-water brings about the facile Hofmann-type rearrangement of primary aliphatic amides to amines [Eq. (58)] [102]. Aromatic amines are further oxidized by the reagent and therefore cannot be prepared by this method. The active iodine(III) species are suggested to be μ -oxo dimers, generated under the acidic conditions [103]. The fact that the rearrangement occurs with complete retention of configuration in the migrating group indicates the concerted nature of 1,2-migration of alkyl groups and reductive elimination of iodobenzene. It is possible to isolate the interme-

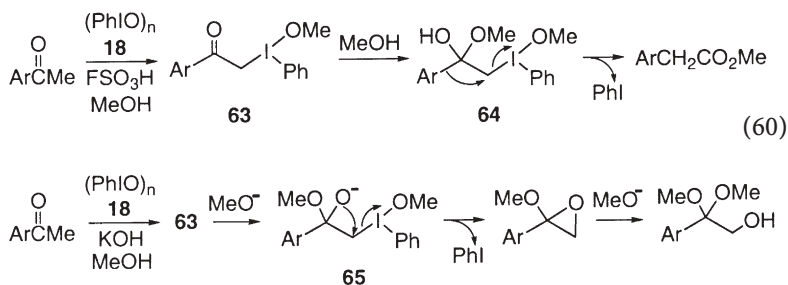
diolate isocyanates. When the reaction was applied to β -hydroxypropionamides, oxazolidin-2-ones were formed via intramolecular trapping of isocyanates [104].



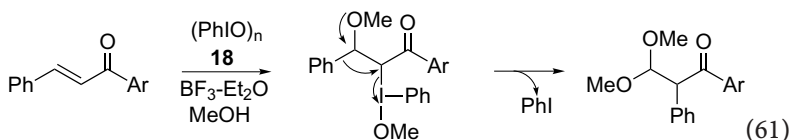
Koser isolated the intermediate N - λ^3 -iodanyl carboxamide **62** as a moderately stable solid by the reaction of α -phenylacetamide with [methoxy(tosyloxy)iodo]benzene in acetonitrile, and demonstrated that the hydrolytic decomposition of **62** in acetonitrile-water affords an alkylamine with one less carbon atom [105].



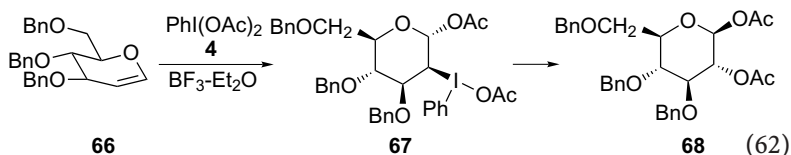
In the oxidation of acetophenones with iodosylbenzene **18** in MeOH, two distinct reaction pathways are followed depending upon the conditions [9, 106]: in the presence of fluorosulfonic acid, the reaction afforded the rearranged arylacetates, whereas α -hydroxy dimethyl acetals were obtained under basic conditions. α - λ^3 -Iodanyl ketones **63**, formed by ligand exchange of the active iodine(III) species $\text{PhI}(\text{OMe})_2$, are common intermediates. Reductive elimination of **64** with concomitant 1,2-aryl shift gives the rearranged arylacetates. On the other hand, intramolecular nucleophilic attack of alkoxide anion of **65** with reductive elimination is responsible for the formation of α -hydroxy dimethyl acetals. This mechanism has been established by isotopic labeling experiments using $\text{C}_6\text{H}_5\text{C}^{18}\text{OCH}_3$.



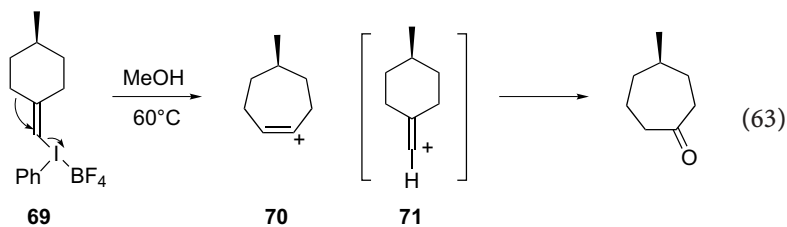
Chalcones under acidic conditions are known to undergo 1,2-aryl migrations with concomitant reductive elimination of iodobenzene yielding rearranged acetals [Eq. (61)] [106].



A one-pot procedure for oxidative glycosylation that effects the stereoselective installation of a carboxylate functionality onto the C2-position of glycol donor **66** with glycosidic bond formation was developed [107]. Glycol activation to generate 1,2-*trans*-diacetoxylglycoside **68** probably involves β -approach of BF_3 -activated $\text{PhI}(\text{OAc})_2$ yielding the intermediate λ^3 -iodane **67**, which undergoes migration of the C1-ester group to the C2-position with concomitant reductive elimination of iodobenzene and substitution of the second acetoxy group onto C1. Neighboring group participation of C2-acetoxy group will account for good anomeric selectivity.



Primary vinyl cations are highly labile species. Detailed study on solvolysis of chiral λ^3 -iodane (*R*)-**69** in methanol was carried out by Okuyama and Fujita [108]. They concluded that the solvolysis does not involve the generation of the primary vinyl cation **71**, but instead the chiral secondary vinyl cation **70**, produced via the reductive elimination of iodobenzene with concomitant *trans* β -C-C migration. Lodder and coworkers, however, found that photochemical solvolysis of 2-phenyl-1-propenyl(phenyl)- λ^3 -iodane produces a primary vinyl cation via an $\text{S}_{\text{N}}1$ pathway [109].

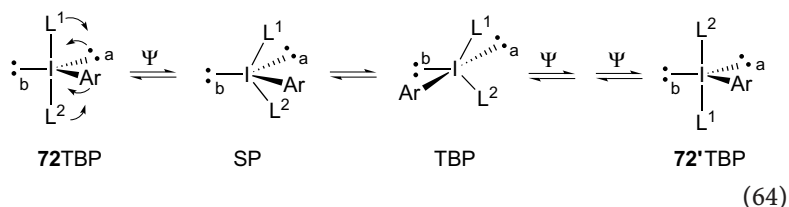


2.9

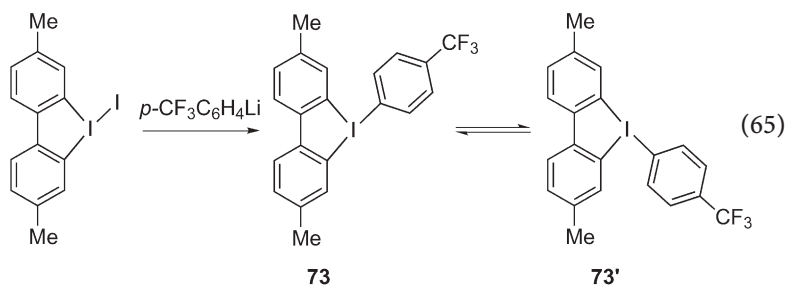
Pseudorotation of λ^3 -Iodane

In general, organo- λ^3 -iodanes are configurationally unstable and undergo facile stereomutation ($72 \rightleftharpoons 72'$). Apical heteroatom ligands L^1 and L^2 of **72** with trigonal bipyramid (TBP) structure mutually exchange their sites with formation of λ^3 -iodane **72'** via repeated pseudorotation (Ψ) on iodine(III). Berry pseudo-

rotation results in an exchange between the apical and equatorial ligands through bond bending [110]: during a Berry pseudorotation, two equatorial bonds become apical bonds, while two apical bonds move concertedly to form equatorial bonds through square pyramid (SP) structure. In some cases, dimerization is believed to be a mechanism for stereomutation (changing positions) of λ^3 -iodanes: a fluorine exchange between the apical and equatorial ligands in ClF_3 and BrF_3 , observed in their ^{19}F NMR spectra, probably occurs through the formation of bridged dimers [111].

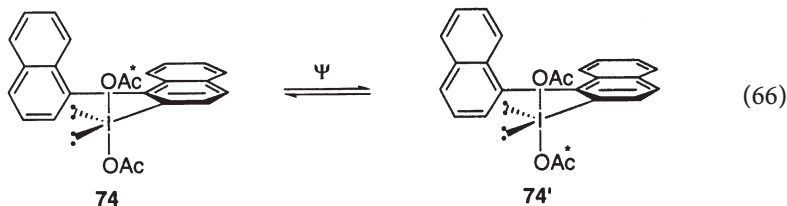


Low-temperature NMR spectrum of triaryl- λ^3 -iodane **73**, prepared from iodo- λ^3 -iodane by the ligand exchange with aryllithium, shows two methyl singlets at δ 2.24 and 2.41 [112]. Simultaneous broadening of the methyl and biphenyl aromatic resonances at higher temperatures demonstrates that the temperature dependence is caused by the degenerate isomerization of *p*-trifluoromethylphenyl substituent between two equivalent sites ($\mathbf{73} \rightleftharpoons \mathbf{73}'$). The barrier for the isomerization was measured to be 15 kcal/mol (40°C) with a relatively large negative entropy of activation ($\Delta S^\ddagger = -18$ eu). Both pseudorotation on iodine(III) and intermolecular ligand exchange mechanism may account for the isomerization of **73**; however, detailed studies are needed to clarify the mechanism for the degenerate isomerization.

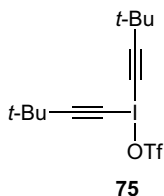


Rapid pseudorotation on iodine(III) was observed for chiral (diacetoxyiodo)binaphthyl **74** [113]. The two acetoxy groups of **74** are anisochronous in CDCl_3 at -10°C and appear at 1.52 and 2.0 ppm as sharp singlets. These two singlets coalesce at 34°C to one singlet at 1.73 ppm with a free activation energy of 15.1 kcal/mol. Similar temperature dependence was observed in the ^{13}C NMR. All line shape changes are reversible. These results can be rationalized in terms of the degenerate isomerization of the acetoxy groups of **74** between two apical

sites in keeping with the equatorial binaphthyl group ($74 \rightleftharpoons 74'$). Both the isomerization process via the rotation about the binaphthyl-iodine(III) single bond and bimolecular ligand exchange process can be ruled out, and the degenerate isomerization of **74** is attributed to rapid pseudorotation pathways on the iodine.



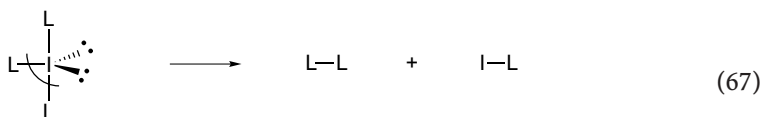
IR spectra of dialkynyl- λ^3 -iodane **75** differentiate the two alkynyl groups, occupying apical (2187 cm^{-1}) and equatorial (2152 cm^{-1}) sites, while the ^1H and ^{13}C NMR spectra display only single resonances for each of the different protons and carbons, probably due to degenerate isomerization by rapid pseudorotation on the iodine [114].

Structure **75**

2.10

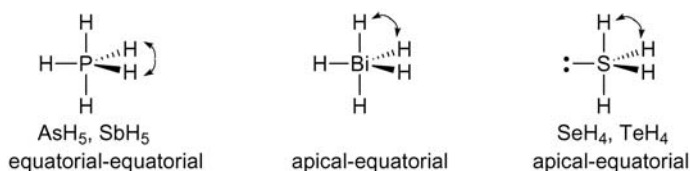
Ligand Coupling on Iodine(III)

The term ligand coupling is introduced by Oae to describe an intramolecular coupling of two ligands bonded to a hypervalent atom, as shown in Eq. (67) [115–117]. The same type of reaction is called reductive elimination in transition metal chemistry (see Section 3.2.2). We prefer the use of ligand coupling for the reaction of Eq. (67). Although the mechanism is still poorly understood, ligand coupling is a concerted reaction and proceeds with retention of configuration of the ligands. Its occurrence was clearly demonstrated in the case of hypervalent sulfur and phosphorus compounds [115].



L: carbon and heteroatom ligands

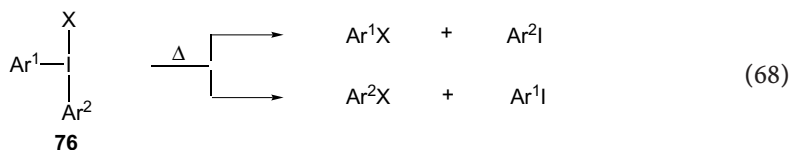
There are three types of ligand coupling modes for [10-X-5] and [10-X-4] compounds. Hoffmann and his coworkers suggested that for fragmentation of phosphorane ($\text{PH}_5 \rightarrow \text{PH}_3 + \text{H}_2$) both apical-apical and equatorial-equatorial couplings are symmetry-allowed, while apical-equatorial coupling is symmetry-forbidden [118]. Recent ab initio molecular orbital study by Moc and Morokuma showed that the transition states for H_2 elimination from XH_5 are equatorial-equatorial interaction for $\text{X} = \text{P}, \text{As},$ and Sb , whereas zwitterionic apical-equatorial interaction for $\text{X} = \text{Bi}$ [119]. Similarly for ligand coupling of XH_4 ($\text{X} = \text{S}, \text{Se},$ and Te), a highly polarized apical-equatorial transition state was calculated to be the lowest energy process [120]. This is probably due to the presence of lone pair electrons at the central hypervalent atoms.



Structure C

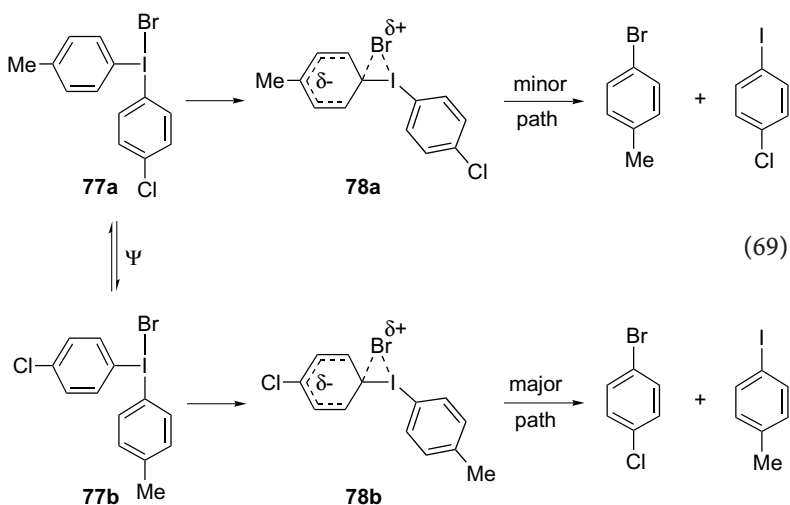
The experimental study of the mechanism of ligand coupling reactions is very limited, probably because of a very fast stereomutation of trigonal bipyramid structure by Berry pseudorotation and of occurrence of facile intermolecular ligand exchange reactions. Mechanism of ligand coupling of pentaarylantimony compounds was investigated in detail by Akiba and Yamamoto [117], and they concluded that the apical-apical coupling is a sole reaction path in the presence of stereoisomers generated by very fast Berry pseudorotation.

Thermolysis of diaryl(halo)- λ^3 -iodanes in solution or in the molten state has been extensively studied and affords a mixture of haloarenes and iodoarenes. The halogen ligand attacks the *ipso* carbon atom of one of the aryl groups. Unsymmetrically substituted halo- λ^3 -iodanes **76** shows interesting regioselectivity upon thermolysis [Eq. (68)]. The halogen ligand X preferentially combines with the aryl groups bearing *ortho* methyl groups, so called *ortho*-effect, and with the more electron-deficient aryl groups [121 – 123]. For the thermolysis of diaryl(halo)- λ^3 -iodanes, ligand coupling mechanism was suggested by Lancer and Wiegand in 1976 [121], and later by Grushin [124].



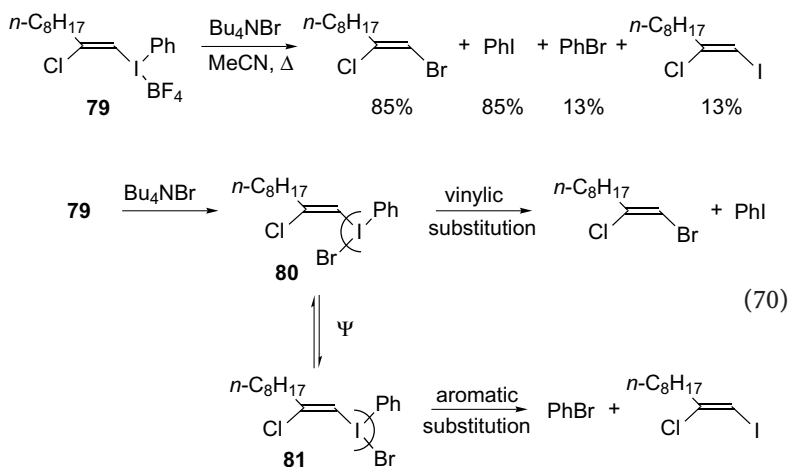
We propose a mechanism of carbon-halogen bond-forming ligand coupling of diaryl(halo)- λ^3 -iodanes, which involves a highly polarized apical-equatorial transition state. Ligand coupling mechanism of *p*-chlorophenyl(*p*-methylphenyl)bromo- λ^3 -iodane **77**, which exists as an equilibrium mixture of **77a** and

77b through rapid pseudorotation, is shown as an example [Eq. (69)]. Of the two possible transition states, in which the nucleophilic heteroatom ligand Br has an interaction with an *ipso* carbon atom of the aryl group that acts as an electrophile, 78b is more favorable than 78a, because both of the negative charge on the aromatic ring and the enhanced positive charge on iodine(III) are stabilized by the substituents more effectively. These polarized transition states account for the preferred coupling with the more electron-deficient aryl groups. The *ortho*-effect is probably due to steric acceleration.

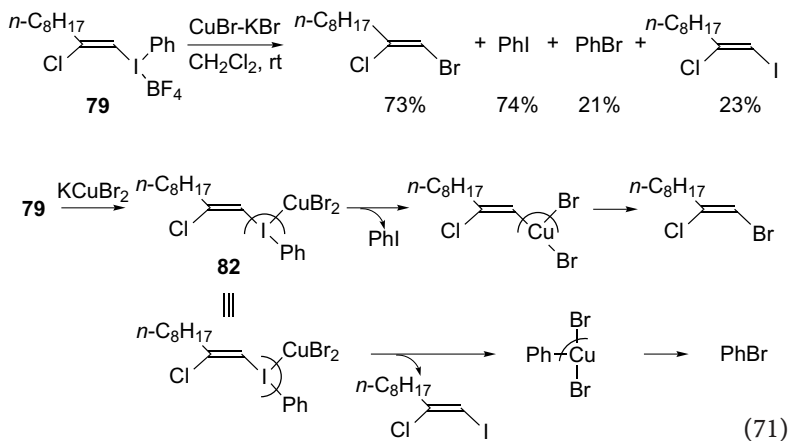


Recently, Widdowson and coworkers reported the *ab initio* MO calculations for the ligand coupling of diaryl(fluoro)- λ^3 -iodanes [125].

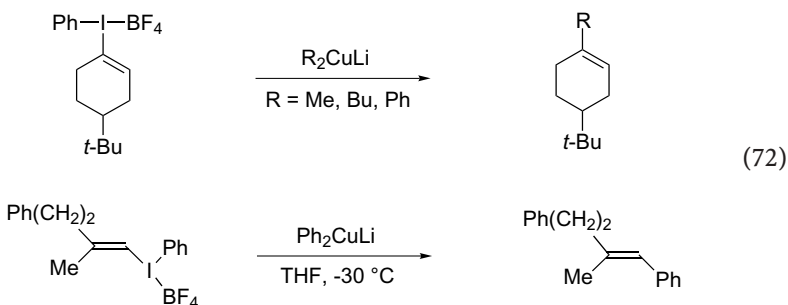
In nucleophilic substitutions of (*Z*)-(β -halovinyl)phenyl- λ^3 -iodanes with Bu_4NX , vinylic and aromatic substitutions compete with each other [126,127]; thus, treatment of β -chlorovinyl- λ^3 -iodane 79 with Bu_4NBr in refluxing MeCN gave a mixture of the vinylic substitution products, the (*Z*)-vinyl bromide and iodobenzene, as major products and the aromatic substitution products, bromobenzene and the (*Z*)-vinyl iodide, as minor products. The vinylic substitution was exclusively stereoselective with retention of configuration. The rate of substitutions decreases in the order of $\text{Bu}_4\text{NI} > \text{Bu}_4\text{NBr} > \text{Bu}_4\text{NCl}$. The product profiles, the stereochemical outcome as well as the detailed kinetic analyses suggest a ligand coupling mechanism: the ligand coupling of bromoiodane 80, produced by ligand exchange, yields products of the vinylic substitution, while the ligand coupling of bromoiodane 81, generated by rapid pseudorotation on iodine(III), produces the aromatic substitution products. The stereochemistry of the vinyl group was retained during the ligand coupling reaction.



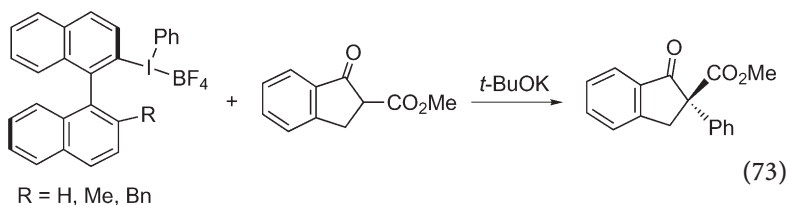
Cuprous halide-catalyzed vinylic substitutions of (*Z*)-(β -halovinyl)phenyl- λ^3 -iodanes with potassium halides also compete with nucleophilic aromatic substitutions. For instance, reaction of β -chlorovinyl- λ^3 -iodane **79** with CuBr-KBr gave the vinylic substitution products [(*Z*)-vinyl bromide (73%) and iodobenzene (74%)] as well as the aromatic substitution products [bromobenzene (21%) and (*Z*)-vinyl iodide (23%)] [126]. The reaction probably involves the following three steps [34]: 1) Oxidative addition of cuprates with formation of **82**, in which copper(III) ligand occupies an equatorial site because of its low electronegativity. 2) Two kinds of ligand coupling on iodine(III). 3) Reductive elimination (ligand coupling) of vinylcopper(III) or phenylcopper(III).



Reaction of alkenyl- λ^3 -iodanes with alkyllithiums gave a complex mixture of products; however, dialkyl- and diarylcuprates undergo clean vinylic substitutions at the *ipso* position of the alkenyl group. Representative examples are shown in Eq. (72) [34]. The reaction is stereospecific and gives products of exclusive retention of configuration through ligand coupling.



Diaryl- λ^3 -iodanes transfer the aryl group to carbonyl compounds to afford the α -C-arylated compounds. Studies by Beringer and coworkers on arylation of enolate anions derived from 1,3-dicarbonyl compounds suggested that the generation of the aryl radicals by electron transfer from enolates to λ^3 -iodanes is involved in this arylation reaction [128]. Barton's spin trapping experiments using 1,1-diphenylethylene, however, clearly demonstrated that the reaction involves two competing mechanisms: an induced radical-chain process producing aromatic hydrocarbons and a non-radical process, probably ligand coupling reaction, yielding arylation products. 1,1-Diphenylethylene is an efficient aryl radical trap that inhibits the radical-induced decomposition of diaryl- λ^3 -iodanes into arenes; thus, use of this trap in the reaction with enolate anions improves the yields of α -C-arylated products [129]. Chiral 1,1'-binaphthyl-2-yl(phenyl)- λ^3 -iodanes undergo direct asymmetric α -phenylation of cyclic β -keto esters with 40–50% enantiomeric excess [Eq. (73)] [130].

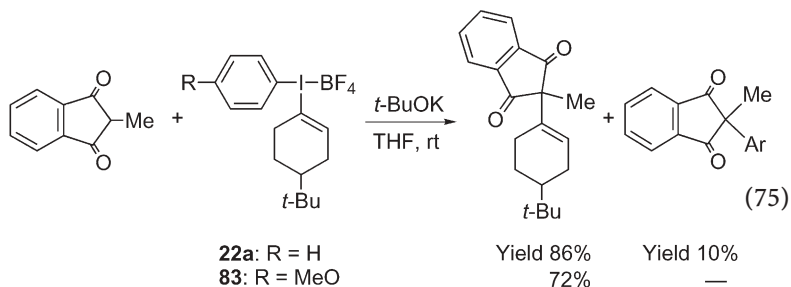


Reaction of diphenyl(fluoro)- λ^3 -iodane with silyl enol ethers in THF results in a regioselective α -phenylation [Eq. (74)] [131].

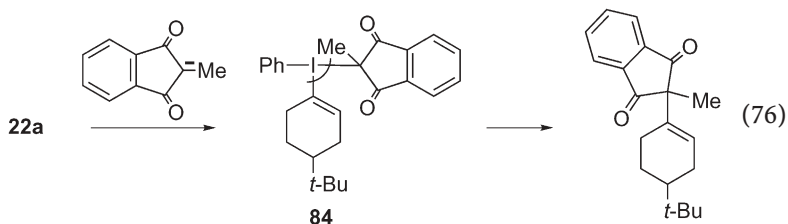


Cyclic vinyl- λ^3 -iodanes undergo direct α -vinylation of 1,3-dicarbonyl compounds [132]. In these reactions, the desired α -vinylation was accompanied by α -arylations as a competing side reaction; thus, reaction of the potassium enolate of 2-methyl-1,3-indandione to cyclohexenyl(phenyl)- λ^3 -iodane 22a afforded 2-cyclohexenyl-1,3-indandione in 86% yield and 2-phenyl-1,3-indandione in

10% yield. The use of the *p*-methoxyphenyl derivative **83** results exclusively in α -vinylation.

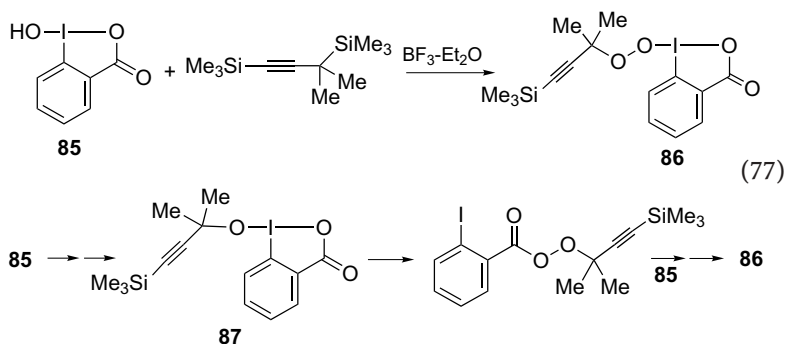


This reaction involves the formation of an intermediate α - λ^3 -iodanyl ketone **84** via ligand exchange, followed by ligand coupling yielding the vinylation and arylation products. A similar type of ligand exchange of $\text{PhI}(\text{OH})\text{OTs}$ **17** with dimedone is known [See Eq. (54)] [93]. Highly polarized transition state of ligand coupling such as **78** accounts for the electronic effects of *p*-methoxy group in **83** on the selectivity for vinylation versus arylation.



The α - λ^3 -iodanyl ketone **84** does undergo ligand coupling on iodine, but not nucleophilic substitutions on the α carbon atom of the carbonyl group. On the other hand, for the α - λ^3 -iodanyl ketone **58** (Section 3.2.7) the nucleophilic substitution is a preferred pathway. This is due to the presence of a heteroatom ligand on the iodine(III) of **58**, acting as a leaving group during the reductive elimination (in the $\text{S}_{\text{N}}2$ reaction). Thus, λ^3 -iodane **84** with no heteroatom ligand can not undergo the nucleophilic substitution.

BF_3 -Catalyzed reaction of 1-hydroxy-1 λ^3 ,2-benziodoxol-3(1*H*)-one **85** with propynylsilane unexpectedly afforded the peroxy- λ^3 -iodane **86** [133]. There is no direct evidences, but oxygen-oxygen bond forming ligand coupling of the intermediate **87** was proposed for the formation of the peroxy- λ^3 -iodane **86**. A similar O-O ligand coupling reaction was suggested in the thermal decomposition of λ^3 -iodane, yielding a dialkyl peroxide [134].



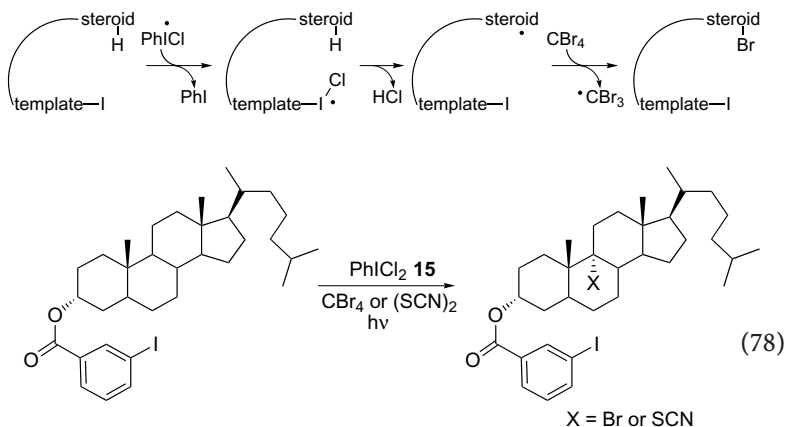
In solution, (dichloroiodo)arenes have been shown to exist as an equilibrium mixture with dichlorine and iodoarenes [135]. Ligand coupling is probably responsible for the formation of dichlorine.

2.11

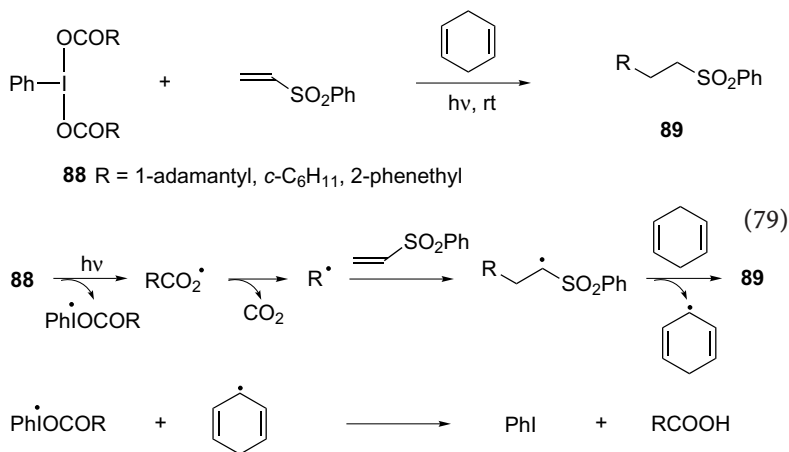
Homolytic Cleavage

Bond dissociation energies of organic iodides are relatively small: 56 kcal/mol (Me-I), 53.5 (Et-I), 40 (PhCH₂-I), 65 (Ph-I), and 47 (O-I). Those of organo- λ^3 -iodanes are not known, but assumed to be smaller compared to organoiodine(I) compounds. In fact, iodobenzene is a stable liquid with a boiling point of 188 °C, whereas triphenyl- λ^3 -iodane decomposes even at -10 °C into biphenyl and iodobenzene [136]. Recently, decomposition of triphenyl- λ^3 -iodane was suggested to proceed via ligand coupling reaction [124].

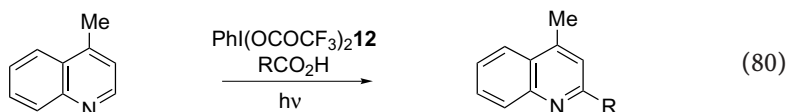
Breslow's template-directed remote oxidation of steroids utilizes an aryl iodide as a template to direct the oxidation of steroid tertiary carbons by the radical relay mechanism, in which a chlorine radical is transferred from a [9-I-2] [PhICl][•] radical to the iodine atom of the template and then relayed to a geometrically accessible hydrogen atom. This method allows a highly regioselective functionalization of nonactivated carbon atoms of steroids [Eq. (78)] [137, 138].



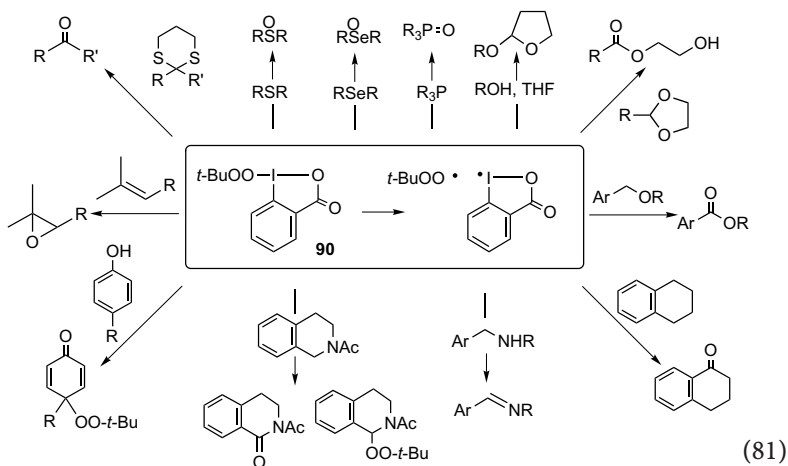
(Diacloxyiodo)arenes on heating or irradiation with a mercury lamp result in homolytic cleavage of hypervalent I-O bond and generate acyloxy radicals, which decompose to carbon-centered alkyl radicals with loss of CO₂. When a mixture of a (diacyloxyiodo)arene **88** and vinyl phenyl sulfone in the presence of 1,4-cyclohexadiene was irradiated with a high-pressure mercury lamp, the reductive alkylation product **89** was obtained via Michael addition of an alkyl radical [139, 140]. Yields of products decrease with decreasing stability and nucleophilicity of the alkyl radicals, tertiary > secondary > primary. The generation of alkyl radicals was established by trapping experiments using TEMPO.



Photochemical decomposition of (diacyloxyiodo)arenes provides a method for decarboxylative alkylation of heteroaromatic bases such as lepidine [Eq. (80)] [141, 142].

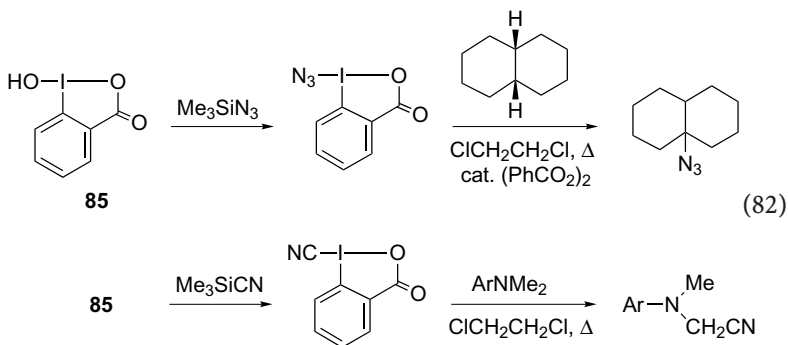


Alkylperoxy- λ^3 -iodanes are highly labile. [Bis(*tert*-butylperoxy)iodo]benzene decomposes homolytically even at -80°C to give *tert*-butylperoxy radical and iodobenzene [143]. This ready decomposition is attributed to the small dissociation energy of the apical hypervalent peroxy-iodine(III) bond, and is facilitated by conjugative overlap of the breaking hypervalent bond with π -orbitals of the aromatic nucleus. The stable, crystalline alkylperoxy- λ^3 -iodane **90**, in which fixation of an apical peroxy ligand and an equatorial aromatic ligand on iodine(III) by the formation of a five-membered heterocycle leads to enhanced stability of the alkylperoxyiodanes, was prepared by Lewis acid-catalyzed ligand exchange of 1-hydroxy-1 λ^3 ,2-benziodoxol-3(1*H*)-one **85** with *tert*-butyl hydroperoxide in chloroform [144]. The iodane **90** is stable in the solid state and can be safely stored at room temperature for an indefinite period of time.

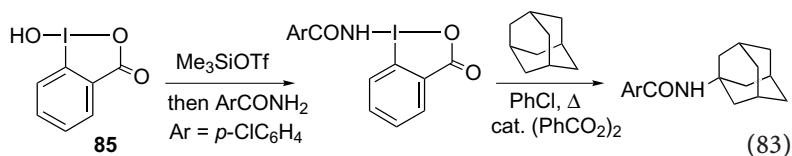


Alkylperoxy- λ^3 -iodane **90** generates *tert*-butylperoxy radical even at room temperature in solution via homolytic I-O bond cleavage and oxidizes benzyl ethers to the esters in the presence of alkali metal carbonates, thus offering a method for the deprotection of benzyl ethers [145]. A large value of deuterium isotope effects indicates that the rate-determining step of the reactions involves a high degree of benzylic C-H bond breaking. A mechanism involving the intermediacy of *tert*-butylperoxyacetals and/or hydroperoxyacetals is proposed. The iodane **90** undergoes oxidation of sulfides [146], selenides, amines [147], amides [148], and phenols [149], and oxidative ring cleavage of cyclic acetals [150]. 1-(*tert*-Butylperoxy)-3,3-dimethyl-1*H*-1 λ^3 ,2-benziodoxole can also generate *tert*-butylperoxy radicals in solution [151].

Cyclic azido- λ^3 -iodane prepared by ligand exchange of λ^3 -iodane **85** with trimethylsilyl azide is a useful reagent for direct azidation of anilines and alkanes [Eq. (82)]. Alkane azidation occurs in the presence of a radical initiator benzoyl peroxide at 80–132 °C [152, 153]. Cyano- λ^3 -iodane serves as an efficient cyano transfer agent toward *N,N*-dialkylanilines [154].

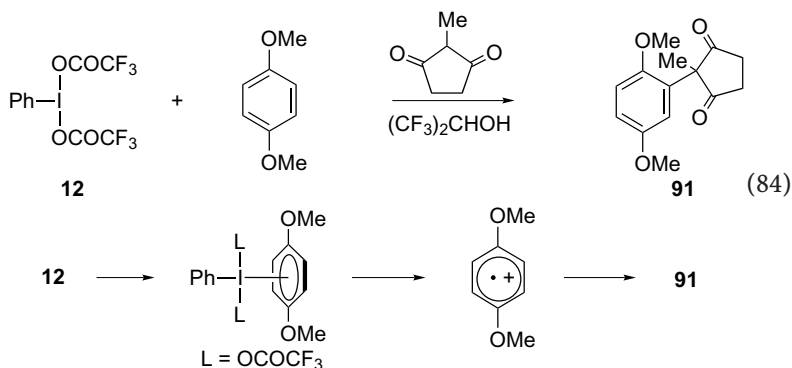


Cyclic amido- λ^3 -iodane prepared from **85** in one step can be used as a direct amidating reagent toward polycyclic alkanes under radical conditions [Eq. (83)] [155].

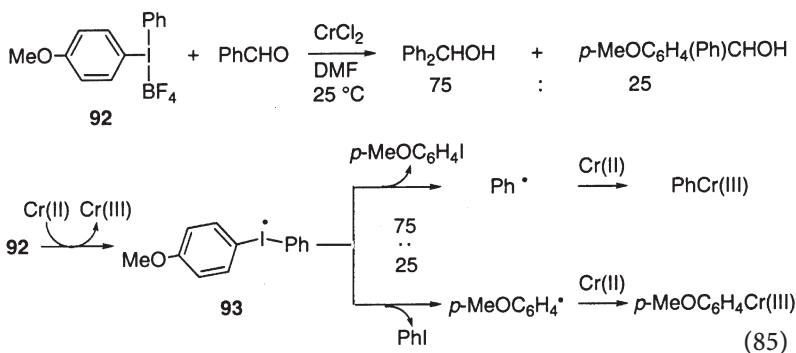


2.12 Single-Electron Transfer

Kita and Tohma found that exposure of *p*-substituted phenol ethers to [bis(trifluoroacetoxy)iodo]benzene **12** in the presence of some nucleophiles in polar, less nucleophilic solvents results in direct nucleophilic aromatic substitution [Eq. (84)] [156]. Involvement of a single-electron transfer (SET) from phenol ethers to λ^3 -iodane **12** generating arene cation radicals was suggested by the detailed UV-vis and ESR studies. SET was involved in the oxidative biaryl coupling of phenol ethers by **12** in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ [157].



The method for reactivity umpolung of diaryl-, alkenyl(aryl)-, and alkynyl(aryl)- λ^3 -iodanes was developed, which involves generation of organochromium(III) species via the reaction of the λ^3 -iodanes with anhydrous chromium dichloride, followed by their nucleophilic addition to aldehydes to yield alcohols [158]. Diaryl- λ^3 -iodanes are good electron acceptors (for instance, Ph_2I^+ : $E_{1/2}(\text{red}) = -0.7 \text{ V vs SCE}$) [159] and thus SET from Cr(II) produces short-lived [9-I-2] iodanyl radicals such as **93**. Substituent effects of unsymmetrically substituted diaryl- λ^3 -iodanes on the product profiles are in good agreement with the reported mode of decomposition of the intermediate unsymmetrical diaryliodanyl radicals [Eq. (85)]. Alkenyl(mesityl)- λ^3 -iodanes undergo exclusive alkenylation of aldehydes with no signs of the formation of an arylation product. Yb also undergoes SET to diaryl- λ^3 -iodanes [160].



In the atom-transfer reactions of iodine from aryl iodides to phenyl radical, intervention of [9-I-2] aryl(phenyl)- λ^3 -iodanyl radicals is proposed [Eq. (86)] [3]. The ab initio molecular orbital study indicates that the diaryl- λ^3 -iodanyl radicals are transition states in the atom-transfer reactions, but not intermediates [161]. Examples obtained by ab initio molecular orbital calculations with the B3LYP/6-31G(d) level are shown in Fig. 2.

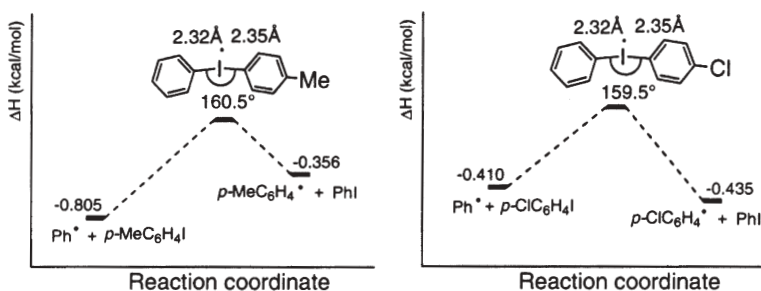
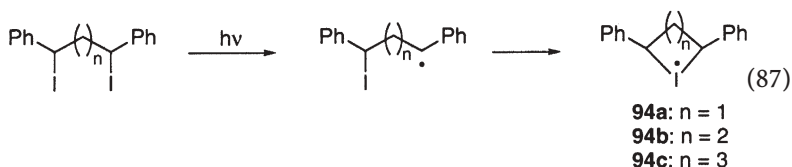
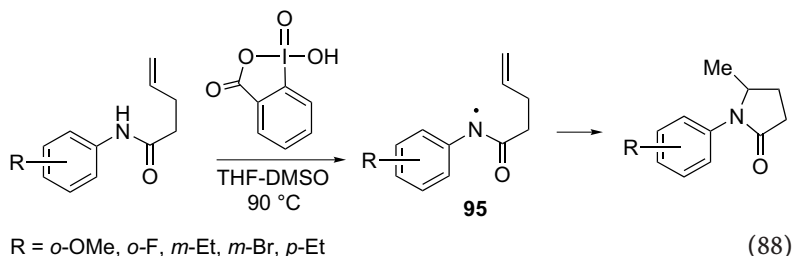


Fig. 2. Predicted coordinates for atom-transfer of iodine from aryl iodides to phenyl radical

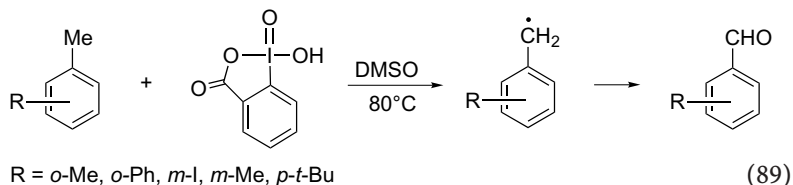
In contrast to diaryl- λ^3 -iodanyl radicals, cyclic dialkyl- λ^3 -iodanyl radicals seem to be intermediates in the atom-transfer [Eq. (87)]. In the laser photolysis of diiodoalkanes, formation of the cyclic hypervalent iodanyl radicals **94** was detected by UV absorption spectra as intermediates with lifetimes around 9.5×10^{-6} s (**94a**), 1.4×10^{-5} s (**94b**), and 4.4×10^{-6} s (**94c**) [162].



Exposure of unsaturated anilides to *o*-iodoxybenzoic acid in THF-DMSO at 90 °C results in cyclization to give γ -lactams [Eq. (88)] [163]. A mechanism involving an intermediacy of amidyl radical **95**, produced by SET and then deprotonation, was proposed for the formation of γ -lactams.



Oxidation of benzylic positions with *o*-iodoxybenzoic acid in DMSO proceeds via a similar mechanism involving the formation of benzyl radicals by SET [Eq. (89)] [164]. A variety of aromatic aldehydes were obtained in good yields with no over-oxidation to carboxylic acids.



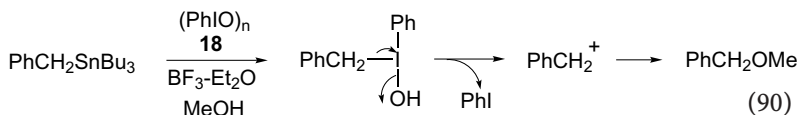
3 λ^3 -Iodanes with Two Carbon Ligands

In contrast to organo- λ^3 -iodanes with two heteroatom ligands (ArIL₂) that serve as efficient oxidizing agents towards a variety of functional groups, λ^3 -iodanes with two carbon atom ligands (RARIL) transfer the carbon ligand (R) to nucleophiles with reductive elimination of ArI (See also Section 3.2.7).

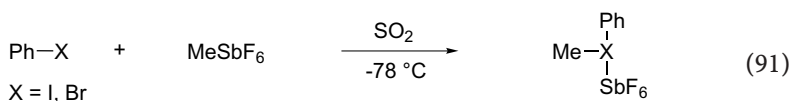
3.1 Alkyl(aryl)- λ^3 -Iodanes

Because of the hypernucleofugality of λ^3 -iodanyl groups, alkyl(aryl)- λ^3 -iodanes are generally labile and decompose readily via heterolysis of the C-I bond with reductive elimination of aryl iodide. For example, reaction of benzyltributylstannane with iodobenzene **18** and boron trifluoride-etherate in methanol at room temperature affords benzyl methyl ether in high yield [81]. This reaction involves ligand exchange on iodine(III) with benzyl group yielding benzyl- λ^3 -iodane, which probably decomposes to benzyl cation with reductive elimination of iodobenzene and affords benzyl methyl ether. Since benzyltributylstannane

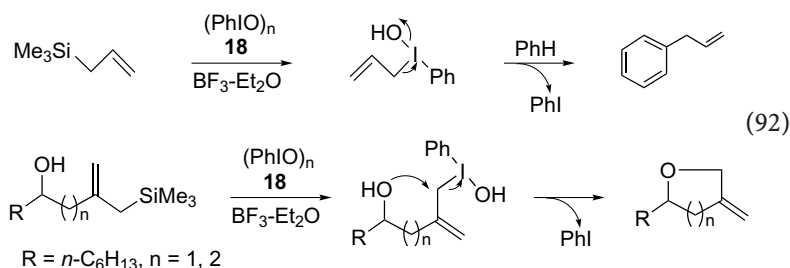
acts as an equivalent species of benzyl anion and reacts with electrophiles, this reaction provides a method of reactivity umpolung of benzylstannane.



Methyl(phenyl)- λ^3 -iodane and λ^3 -bromane were formed at low temperature (-78°C) in liquid SO_2 by the reaction of halobenzenes with methyl hexafluoroantimonate [Eq. (91)] [165]. These iodanes are stable at -20°C in SO_2 solution, but the methyl- λ^3 -iodane decomposes at room temperature.

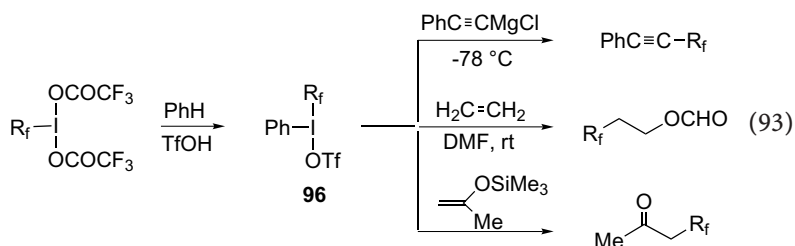


BF_3 -catalyzed reactions of allyltrimethylsilane, germane, and stannane with iodosylbenzene **18** generate allyl- λ^3 -iodane via ligand exchange. The allyl- λ^3 -iodane is a highly reactive species and acts as an allyl cation equivalent. When the reaction was carried out in the presence of electron-rich arenes, monoallylarenes were obtained via Friedel-Crafts alkylation [Eq. (92)] [166]. The use of oxygen and nitrogen nucleophiles such as alcohols, carboxylic acids, and trimethylsilyl azide gives allyl ethers, esters, and azides, respectively [167]. The allylation of alcohols was applied to intramolecular cyclization, and 5- or 6-membered β -methylene cyclic ethers were obtained in good yields [168].



Aryl- λ^3 -iodanes bearing an electron-deficient alkyl ligand such as aryl(sulfonylmethyl)- λ^3 -iodanes (Section 3.2.7) and aryl(perfluoroalkyl)- λ^3 -iodanes are relatively stable. A series of (perfluoroalkyl)phenyl- λ^3 -iodanes **96** were synthesized in good yields by treating bis(trifluoroacetoxy)- λ^3 -iodanes with benzene in the presence of triflic acid [47]. The λ^3 -iodanes **96** transfer the perfluoroalkyl groups to a variety of nucleophiles with reductive elimination of iodobenzene. The nucleophiles involve Grignard reagents, alkylolithiums, enolate anions, alkenes, alkynes, trimethylsilyl enol ethers, arenes, phenols, and thiols. In these reactions, the λ^3 -iodane **96** serves as a source of the perfluoroalkyl cation and, in

certain cases, of the perfluoroalkyl radical. (α,α -Dihydroperfluoroalkyl)phenyl- λ^3 -iodanes are known and similarly serve as highly reactive, electrophilic α,α -dihydroperfluoroalkylating agents [47, 169].



3.2

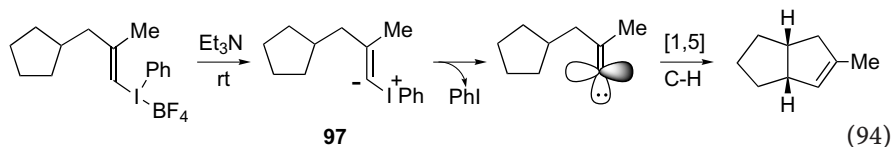
Alkenyl(aryl)- λ^3 -iodanes

3.2.1

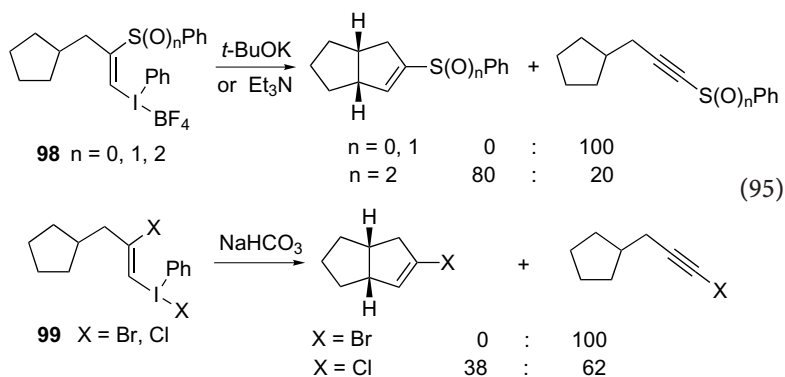
Generation of Alkylidene Carbenes

Alkenyl(aryl)- λ^3 -iodanes serve as good progenitors for the generation of alkylidene carbenes, because of the hyperleaving group ability of aryl- λ^3 -iodanyl groups and their highly electron-withdrawing nature (Section 3.2.4) [39, 44].

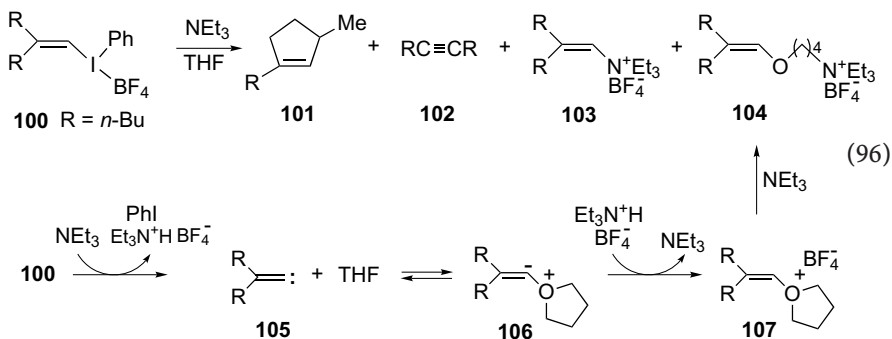
Triethylamine readily abstracts an acidic α -hydrogen of alkenyl- λ^3 -iodane at room temperature generating vinylidonium ylide **97** [Eq. (94)]. Attempted trapping of the ylide **97** with aldehydes or acid chlorides was found to be fruitless, and the ylide **97** undergoes very rapid reductive elimination of iodobenzene to give a singlet alkylidene carbene, which in turn results in an intramolecular 1,5-carbon-hydrogen insertion yielding the bicyclo[3.3.0]octene in good yields [170].



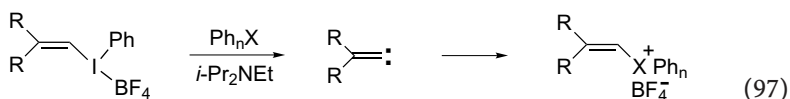
α -(Phenylsulfenyl) and α -(phenylsulfinyl) groups of alkylidene carbenes tend to show an excellent migratory aptitude. Thus, the reaction of sulfenyl- and sulfinyl λ^3 -iodanes **98** ($n = 0, 1$) with *t*-BuOK leads exclusively to formation of the rearranged alkynes (Eq. 95). In marked contrast, α -(phenylsulfonyl)alkylidene carbene predominantly undergoes 1,5-C-H insertions, yielding synthetically useful 1-sulfonylcyclopentene. The tendency of α -sulfur groups to migrate appears to depend to some extent on the availability of lone pair electrons at the sulfur atom [170]. In contrast to the reaction of α -chloroalkylidene carbenes, which give a mixture of the 1,5-C-H insertion product and the rearranged alkyne, exclusive formation of the bromoalkyne from λ^3 -iodane **99** ($X = \text{Br}$) is attributable to the migratory aptitude of the α -bromine atom, being higher than that of the α -chlorine atom [171].



When alkylidene carbenes are generated in ethereal solvents, formation of the solvent-alkylidene carbene complex (i.e. oxonium ylide) is observed. The alkylidene carbene **105** generated by Et_3N -induced α -elimination of **100** in THF undergoes regioselective 1,5-C-H insertions, 1,2-shifts of the butyl group, and electrophilic attack on the tertiary amine to give **101**, **102**, and **103**, respectively. In addition to these carbene-derived products, the reaction affords the three-component coupling product **104** produced through nucleophilic attack of THF on **105** generating the oxonium ylide **106**, followed by protonation with subsequent ring-opening of the resulting oxonium salt **107** by nucleophilic attack of Et_3N . The reactions were found to be temperature dependent: lowering the reaction temperature tended to decrease the yields of alkylidene carbene-derived products **101**–**103** and to increase those of the vinyloxonium ylide-derived product **104** [172]. This temperature dependence is explained in terms of reversible oxonium ylide formation.



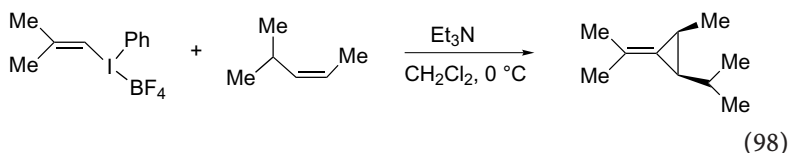
Preparation of group 15 alkenyl(triphenyl)onium (P, As, Sb) tetrafluoroborates and group 16 alkenyl(diphenyl)onium (S, Se, Te) tetrafluoroborates involves the base-induced reductive α -elimination, followed by nucleophilic trapping of the resulting free alkylidene carbenes with group 15 and 16 element-centered nucleophiles [Eq. (97)] [173].



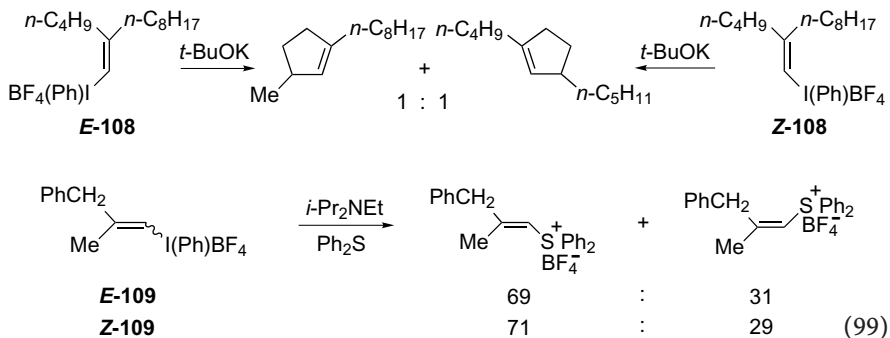
R,R = (CH₂)₅, or Me

Ph_nX = Ph₃P, Ph₃As, Ph₃Sb, Ph₂S, Ph₂Se, Ph₂Te

2-Methyl-1-propenyldiene, generated from 2-methylpropenyl-λ³-iodane, undergoes addition reaction to olefins to give methylenecyclopropanes. The addition to *cis*- and *trans*-4-methyl-2-pentenes is stereospecific with retention of the olefin geometry, implying that the alkylidene carbene generated has a singlet electronic state [Eq. (98)] [174]. Small negative ρ value (−0.56) for the addition to substituted styrenes shows that the alkenyl-λ³-iodane derived alkylidene carbene is mildly electrophilic and, therefore, a free carbene. Free alkylidene carbenes have been shown to be mildly electrophilic in nature and show a relatively small negative ρ value, whereas carbenoids show a very large degree of electrophilicity and a large negative ρ value.



Both the lack of regioselectivity observed for the intramolecular insertion of alkylidene carbenes derived from (*E*)- and (*Z*)-λ³-iodanes **108** and the high degree of stereoconvergence of the olefin geometry of vinylsulfonium salts indicate the intermediacy of the free alkylidene carbene [Eq. (99)] [53, 172].



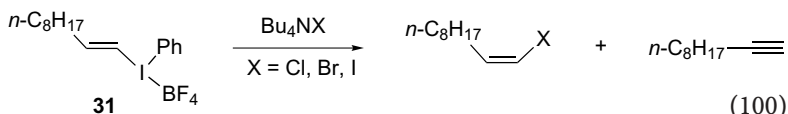
Strong bases like alkyllithiums or drastic reaction conditions are required to generate carbenic species from vinyl halides, thus precluding the presence of many functional groups in the substrate. The vinyl-λ³-iodane method produces free alkylidene carbenes under mild conditions, making the reaction compatible with a variety of functional groups.

3.2.2

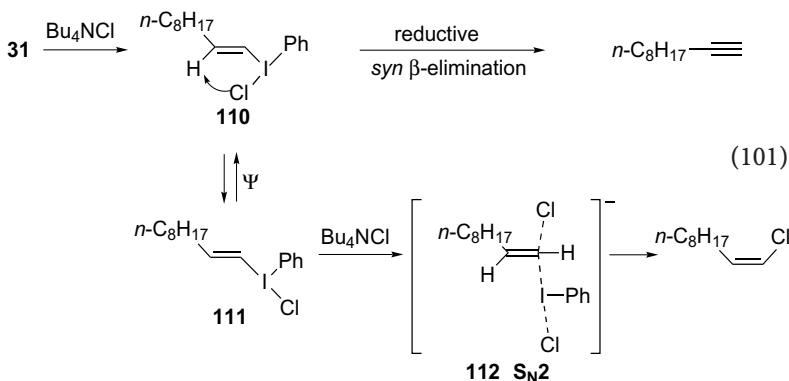
Nucleophilic Vinylic Substitution

The S_N2 reaction involves the attack of a nucleophile from the side opposite the leaving group and proceeds with exclusive inversion of configuration in a concerted manner. In contrast to the popular bimolecular nucleophilic substitution at the aliphatic carbon atom, the S_N2 reaction at the vinylic carbon atom has been considered to be a high-energy pathway. Textbooks of organic chemistry reject this mechanism on steric grounds [175].

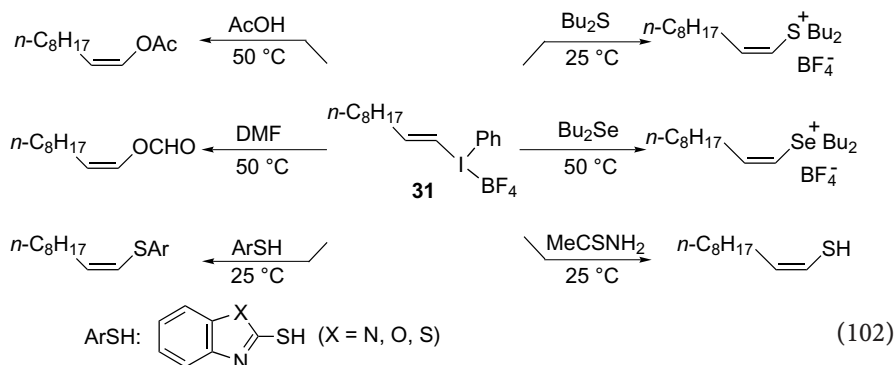
In 1991, we reported that a nucleophilic vinylic substitution of (*E*)- β -alkylvinyl- λ^3 -iodanes with halides (Bu_4NX , $X = Cl, Br, I$) in dichloromethane, methanol, or acetonitrile at room temperature proceeds with exclusive inversion of configuration [Eq. (100)] [176, 177]. This is the first clear example of a vinylic S_N2 reaction. This reaction competes with an alkyne-forming reductive *syn* β -elimination.



Detailed kinetic analysis and deuterium labeling experiments suggest the mechanism shown in Eq. (101). A very rapid ligand exchange on iodine(III) produces chloro- λ^3 -iodanes **110** and **111**. Stereoisomerization between these iodanes via pseudorotation will be very fast (Section 3.2.9). The isomer **110** with an equatorial alkenyl group undergoes intramolecular reductive *syn* β -elimination via five-membered cyclic transition state yielding 1-decyne, whereas **111** with an apical alkenyl group undergoes vinylic S_N2 reaction by the rear side attack of external halides via the transition state **112** yielding (*Z*)-alkenyl chloride with inversion of configuration. The hyperleaving group ability of the phenyl- λ^3 -iodanyl group would be the origin of this unusual inversion of configuration in the nucleophilic vinylic substitutions [178].



Nucleophiles that undergo vinylic S_N2 reaction involve sulfides, selenides [178], carboxylic acids [179], amides [180], thioamides [181], and phosphoroselenoates [Eq. (102)] [182]. All of these reactions proceed with exclusive inversion of configuration. These nucleophiles are only weakly basic or non-basic. More basic nucleophiles would result in a facile α -elimination of vinyl- λ^3 -iodanes generating alkylidene carbenes instead of the vinylic S_N2 reaction.



The ab initio MO calculations of vinyl- λ^3 -iodane indicate that the σ^* orbital for the $C_{\text{vinyl}}\text{-I}$ bond is lower in energy than the π^* orbital: for chloro(divinyl)- λ^3 -iodane, the σ^* orbital (1.81 eV) for the $C_{\text{vinyl}}\text{-I}$ apical bond is the LUMO, and the π^* orbital (3.34 eV) of the apical vinyl group is the third lowest vacant orbital (LUMO + 2) [183, 184]. The low-lying σ^* orbital is an important feature of the vinyl- λ^3 -iodanes and makes the bimolecular nucleophilic substitution (S_N2) at the vinylic carbon possible.

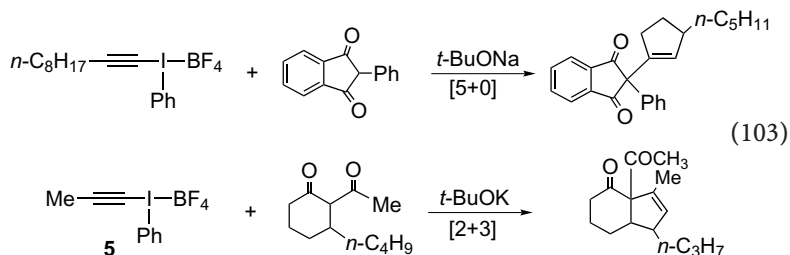
3.3

Alkynyl(aryl)- λ^3 -iodanes

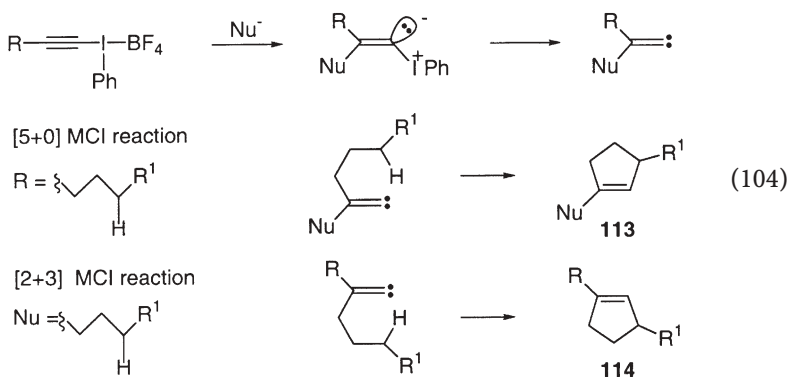
3.3.1

Michael-Carbene Insertion Reaction

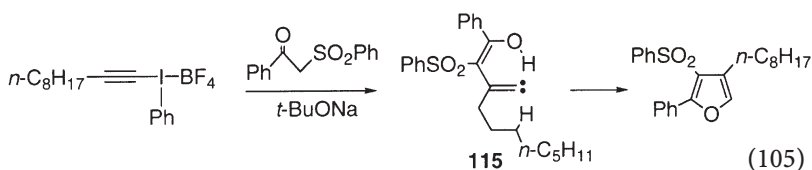
In 1986, we found that alkynyl- λ^3 -iodanes serve as good Michael acceptors toward soft nucleophiles, because of the highly electron-deficient nature of the β -acetylenic carbon atom. This conjugate addition of nucleophiles constitutes a key step of a highly versatile cyclopentene annulation of alkynyl- λ^3 -iodanes via the tandem Michael-carbene insertion (MCI) reaction [Eq. (103)] [185].



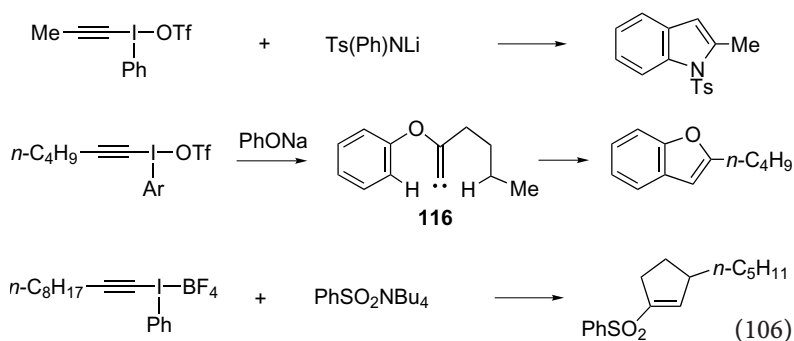
In contrast to hard carbanions like 2-lithiofuran, which attack the positively charged iodine of alkynyl- λ^3 -iodanes (See Section 3.2.1.4), soft carbanions such as β -dicarbonyl enolates (Nu^-) undergo *anti* Michael addition generating the labile vinylidonium ylides, which result in facile formation of alkylidene carbenes via reductive elimination of iodobenzene [Eq. (104)]. The intramolecular regioselective 1,5-C-H insertion gives the cyclopentene **113**. Since all carbon atoms of the cyclopentene ring of **113** come from the alkynylidanes, the reaction is termed a [5+0] cyclopentene annulation. The tandem MCI reaction also becomes valuable as a [2+3] cyclopentene annulation, in which two sp^2 and three sp^3 carbon atoms of the cyclopentene ring of **114** originate from acetylenic carbons of the alkynylidanes and the carbon nucleophiles, respectively.



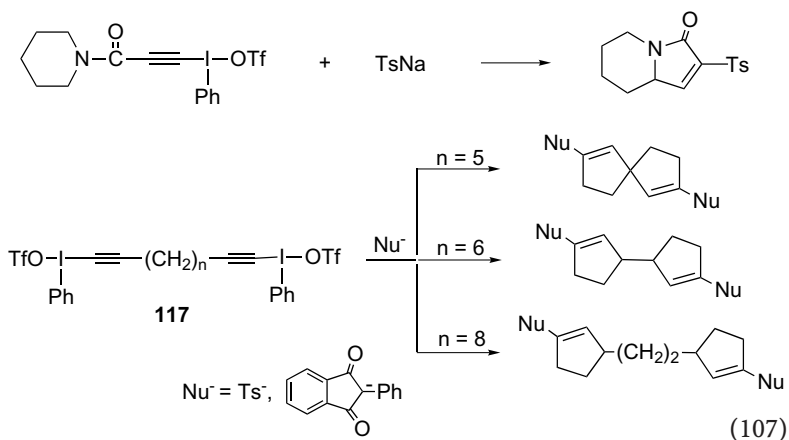
The MCI reaction provides a direct route to polysubstituted furans [185]. Exclusive formation of a furan in Eq. (105) implies that the intramolecular 1,5-insertion into C-H bonds of methylene groups cannot compete with that into O-H bonds of the enol carbene **115**.



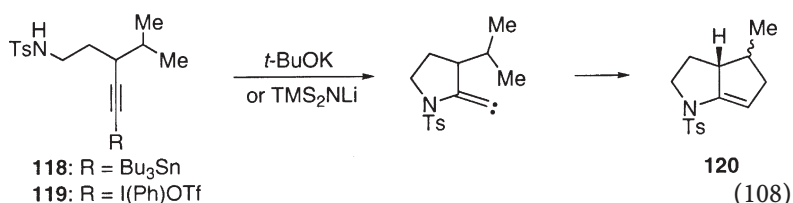
Nitrogen [186], oxygen [187], and sulfur nucleophiles [170] also act as nice Michael donors in the tandem MCI reactions [Eq. (106)]. The α -oxyalkylidene carbene **116**, generated by the reaction with phenoxide anion, shows a high selectivity for 1,5-insertion to the aromatic over the aliphatic C-H bonds to give the benzofuran.



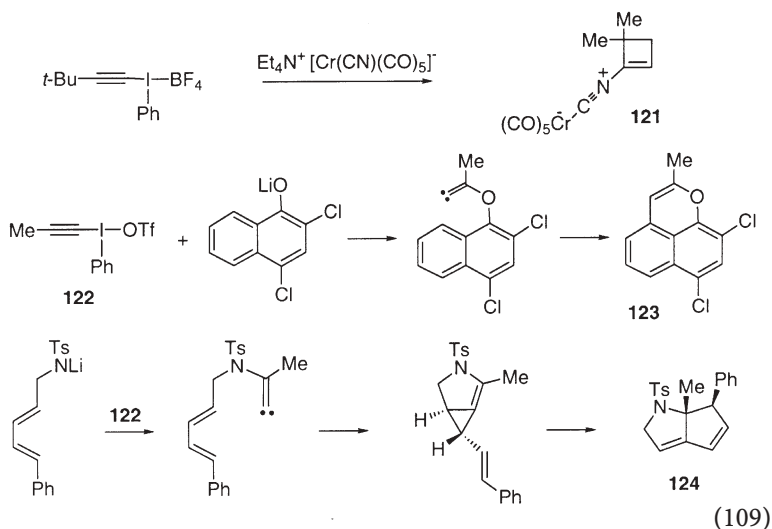
The tandem MCI reaction of β -ketoethynyl- and β -amidoethynyl- λ^3 -iodanes with sulfinate anion was demonstrated by Stang and co-workers [Eq. (107)] [188]. They further showed that the bis(alkynylidane) **117** undergoes the double MCI reaction yielding the bis(cyclopentene) products [189].



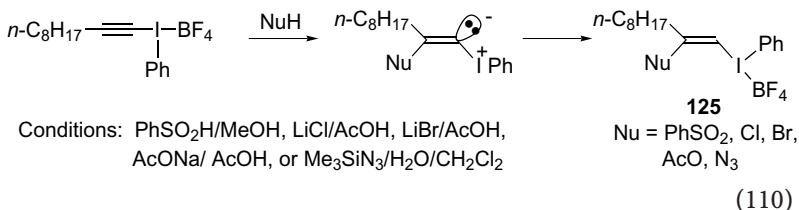
Feldman and co-workers developed a nicely designed intramolecular version of the MCI reaction [Eq. (108)] [190]. Treatment of the tosylamide-bearing alkynylstannane **118** with $\text{PhI}(\text{CN})\text{OTf}$ **19** gave via ligand exchange a labile alkynylidane **119**, which on exposure to a base undergoes an intramolecular tandem MCI reaction to afford the amide **120**. Hydroxyalkynyl- λ^3 -iodanes similarly undergo the intramolecular MCI reaction [191].



As shown above, insertion of alkylidene carbenes is highly regioselective. However, when the normal 1,5-C-H insertion pathway is blocked, 1,4- or 1,6-C-H insertion takes place [Eq. (109)]. Thus, the cyclobutene **121** [192] and the six-membered enol ether **123** [193] were obtained in modest yields. Intramolecular insertion into carbon-carbon double bond provides a method for synthesis of cyclopenten-annulated dihydropyrrole **124**, which results from homolytic scission of a methylenecyclopropane intermediate [194].



It is possible to isolate the intermediate of the first step in the tandem MCI reaction, when the reaction was carried under acidic conditions [Eq. (110)]. This method provides a convenient and stereoselective approach to β -functionalized (*Z*)-alkenyl- λ^3 -iodanes **125**, because Michael addition proceeds in an exclusively stereoselective manner. Thus, (*Z*)- β -sulfonyl [170], (*Z*)- β -halo [195], (*Z*)- β -acetoxy [196], and (*Z*)- β -azidoalkenyl- λ^3 -iodanes [197] were synthesized stereoselectively in high yields. These results provide firm evidence for the tandem MCI pathway.

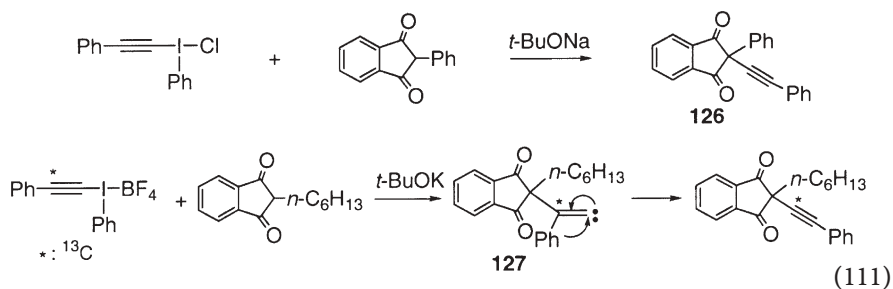


Conditions: $\text{PhSO}_2\text{H}/\text{MeOH}$, LiCl/AcOH , LiBr/AcOH , AcONa/AcOH , or $\text{Me}_3\text{SiN}_3/\text{H}_2\text{O}/\text{CH}_2\text{Cl}_2$
 Nu = PhSO_2 , Cl, Br, AcO , N_3

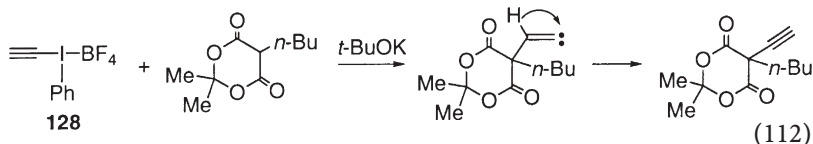
3.3.2

Michael-Carbene Rearrangement Reaction

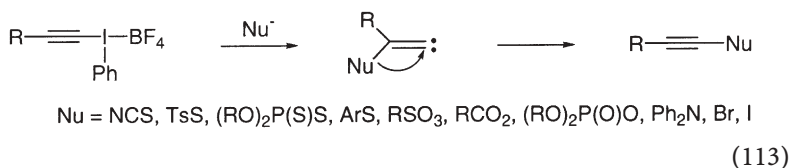
In 1965, Beringer and Galton reported an alkyneylation of the anion derived from phenylindandione with phenylethynyl- λ^3 -iodane, yielding the alkyne **126** [198]. Twenty years later, based on the ^{13}C -labeling experiments, we demonstrated that this reaction proceeds via Michael addition, followed by 1,2-phenyl rearrangement of the resulting alkylidene carbene [Eq. (111)] [185]. The migratory aptitude of a phenyl group is so high that the 1,5-C-H insertion of carbene **127** cannot compete with the 1,2-phenyl migration.



Similarly, ethynylation of β -dicarbonyl enolates via the tandem Michael-carbene rearrangement (MCR) pathway occurs smoothly by the reaction with the parent ethynyl- λ^3 -iodane **128**. High migratory aptitude of α -hydrogens of alkylidene carbenes is responsible for this facile ethynylation [199].

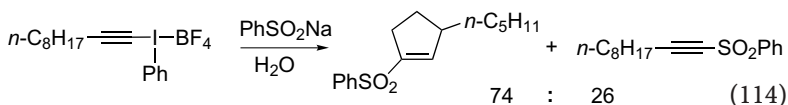


Nucleophiles with high tendency to migrate preferentially undergo the tandem MCR reaction, providing a useful route for the synthesis of substituted 1-alkynes. Examples of the MCR reaction with little or no tendency to compete with the MCI pathway are summarized in Eq. (113): Nu = thiocyanate [200, 201], thiotosylate [202], thiolate [203], phosphorodithioate [204], tosylate [205], carboxylate [206], phosphate [206], lithium diphenylamine [207], and halide [171]. It appears likely that, because of the electron-deficient nature of the carbenic



center of alkylidene carbenes, the electron-rich substituent, especially when the migrating atoms have lone pair electrons, tends to migrate readily.

When migratory aptitudes of α -substituents of alkylidene carbenes are relatively poor, the MCI pathway competes with the MCR reaction. Reaction of the alkynylidene with benzenesulfinate anion in water leads to a mixture of the MCI and the MCR products, because of a moderate migratory aptitude of aryl-sulfonyl groups [Eq. (114)] [170].



For other very useful reactions of alkynyl- λ^3 -iodanes involving Diels-Alder reactions, 1,3-dipolar cycloadditions, and reactions with transition metal complexes, see the excellent reviews of Koser [39] and Stang [208, 209].

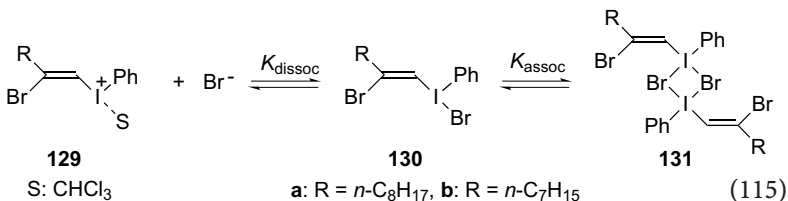
4 Structure

Solid state structures of λ^3 -iodanes are extensively discussed in the reviews by Koser [1, 39] and in the monograph by Varvoglis [3]. Recent progress in the structural elucidation is shown here.

4.1 In Solution

Studies on the solution structure of λ^3 -iodanes are relatively limited. In polar solvents, cryoscopic and conductance measurements have shown extensive dissociation of diaryl- λ^3 -iodanes (Ar_2IL ; $\text{L} = \text{BF}_4, \text{Cl}, \text{Br}, \text{OAc}$) into the solvated iodonium ions ($\text{Ar}_2\text{I}^+\text{S}$; $\text{S} = \text{polar solvents such as H}_2\text{O, MeOH, and DMSO}$) [3, 210]. Even in dichloromethane, bis(4-methylphenyl)- λ^3 -iodane (Ar_2IBF_4 ; $\text{Ar} = p\text{-MeC}_6\text{H}_4$) dissociates into the solvated iodonium ions with dissociation constant $K_{\text{dissoc}} = 4.7 \times 10^{-6} \text{ M}$ [211].

Vapor pressure osmometric and spectroscopic studies on the molecular association and dissociation of (*Z*)-vinyl(bromo)- λ^3 -iodane **130** in chloroform solution indicate the equilibrium formation of the dimer **131** as well as the iodonium ion **129**, which is stabilized by the coordination of the solvent chloroform via the hypervalent interaction between the positively charged iodine and a chlorine atom [212].



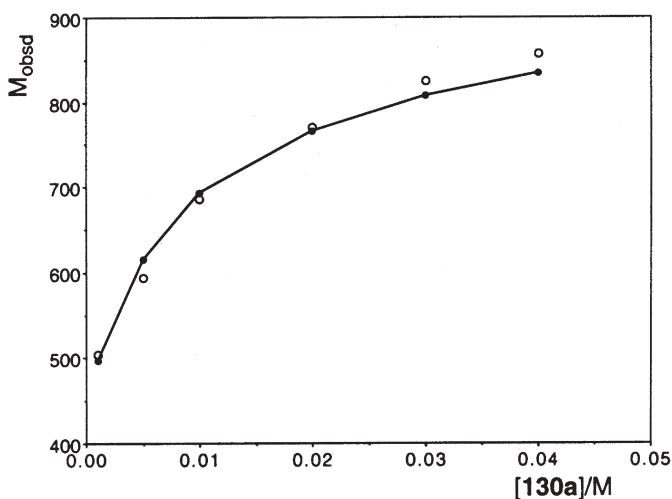


Fig. 3. Molecular weights of **130a** in CHCl_3 , measured by VPO at 25°C (○). Calculated (●)

The molecular weight of the vinyl(bromo)- λ^3 -iodane **130a** in chloroform solution was measured by vapor pressure osmometry. The average molecular weights (M_{obsd}) were concentration dependent: i.e. increasing the concentration of **130a** tended to gradually increase the average molecular weight, approaching twice the molecular weight of the monomer, which suggests formation of the dimer **131a** at higher concentrations (Fig. 3). The data obtained nicely fit the dissociation-association equilibrium model shown in Eq. (115), and dissociation and association constants were calculated by least squares estimation to yield $K_{\text{dissoc}} = 2.66 \times 10^{-5} \text{ M}$ and $K_{\text{assoc}} = 2.6 \times 10^2 \text{ M}^{-1}$, respectively.

^1H NMR chemical shifts of the vinylic and aromatic protons of λ^3 -iodane **130a** in CDCl_3 are concentration dependent. The resonances of the vinylic proton move increasingly downfield with increasing concentration of **130a**, whereas the signals of the *meta* and *para* protons shift upfield. The chemical shift data can be simulated by a nonlinear least-squares method by using the parameters given in Table 4 [212].

Further evidence for the aggregation of the vinyl(bromo)- λ^3 -iodane **130** to the dimeric form **131** was obtained from FAB mass spectrometry [212]. In the spectrum of FAB-MS of **130a**, in addition to the $\text{M}^+ - \text{Br}$ peaks, prominent peaks of $2 \times \text{M}^+ - \text{Br}$ were observed. Furthermore, when a solution of a 1:1 mixture of

Table 4. Chemical shift parameters (ppm) used for the curve fittings

	vinylic H	<i>ortho</i> H	<i>meta</i> H	<i>para</i> H
ion 129a	8.39	8.36	7.26	7.39
monomer 130a	6.61	8.02	7.55	7.70
dimer 131a	7.65	8.10	7.35	7.48

(*Z*)-(2-bromo-1-decenyliodane **130a** and (*Z*)-(2-bromo-1-nonyliodane **130b** was analyzed by FAB-MS, formation of a heterodimer (**130a** – **130b**) was clearly observed in addition to homodimers **131a** (i.e. **130a** – **130a**) and **131b** (i.e. **130b** – **130b**). These results are indicative of dimeric structure **131** even in the gas phase, in which the strength of the coordination bonds in **131** is close to the scope of mass spectroscopy.

In the solid state of halo- λ^3 -iodanes, halogen-bridged dimeric structures similar to **131** were reported: for instance, diphenyl(halo)- λ^3 -iodanes (Ph_2IL : L = Cl, Br, I) are isomorphous centrosymmetric dimers, held together by halogen bridges [5].

Detailed studies on the UV absorption spectra of alkenyl- λ^3 -iodane **133** (X = Cl, Br, I) in acetonitrile solutions in the presence of tetrabutylammonium halides show the equilibrium formation of the iodate **134** (Sect. 2.1), in addition to the iodonium ion **132** coordinated by acetonitrile via hypervalent bonding. [Eq. (116)] [213]. The equilibrium constants are summarized in Table 5. Determinations of the equilibrium constants by UV spectra were carried out at a low concentration of the λ^3 -iodane ($<10^{-4}$ M), without considering the formation of the corresponding dimers. The magnitudes of the equilibrium constant K_1 clearly decrease in the order Cl > Br > I, which reflects the differences in the stability of alkenyl- λ^3 -iodane **133**.

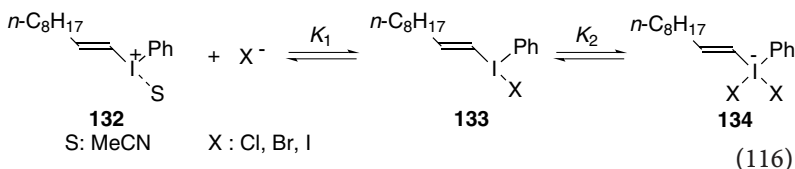


Table 5. Equilibrium constants in acetonitrile at 25 °C^a

133 (X = Cl)	133 (X = Br)	133 (X = I)	
K_1 M ⁻¹	46600 (7160)	11550 (2130)	2490 (439)
K_2 M ⁻¹	16.8 (15.1)	21.7 (20.4)	14.6 (17.1)

^a Values in parentheses are those obtained at the ionic strength of 0.10 (Bu_4NClO_4).

4.2

In the Solid State

Iodosylbenzene **18** is a pale yellow, amorphous powder and essentially insoluble in all nonreactive media. X-Ray powder diffraction and EXAFS spectroscopy showed a zigzag polymeric structure of **18** with the two I-O distances (2.04 and 2.377 Å) and the I-O-I bond angle (114°) (Fig. 4) [214]. A similar polymeric structure was determined for the imido analogue, (tosyliminoiodo)benzene PhINTs [214, 215]. Polymeric iodosylbenzene is likely to be terminated by addition of water, i.e. $\text{HO}(\text{PhIO})_n\text{H}$ [216].

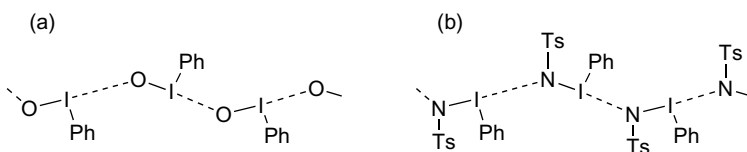


Fig. 4. Schematic solid state structures of $(\text{PhIO})_n$ 18 (a) and PhINTs (b)

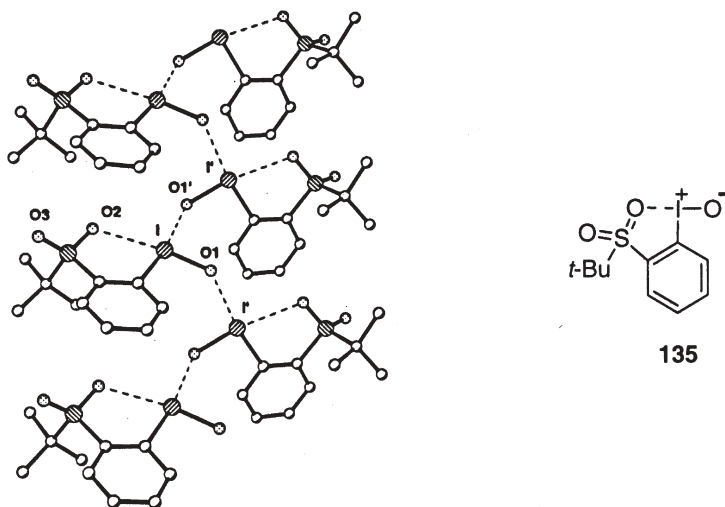
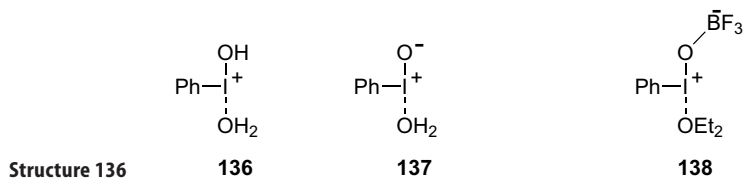


Fig. 5. Polymeric structure of *o*-sulfonyl iodosylbenzene 135

Polymeric structure of *o*-sulfonyl iodosylbenzene 135 with tetracoordinated iodine of pseudo square planar geometry was obtained by the single crystal X-ray analysis (Fig. 5) [217]. The bright yellow λ^3 -iodane 135 is soluble in chloroform because of the weaker intermolecular hypervalent interaction ($\text{I}-\text{O}1'$, 2.665 Å) compared to that of iodosylbenzene 18 [218].

Detailed studies on the solution structure of [hydroxy(mesyloxy)iodo]benzene and [hydroxy(tosyloxy)iodo]benzene 17 suggest that in aqueous solution iodosylbenzene 18 exists as a monomeric iodonium ion form 136, if the pH is < 2.3 , and as a neutral species 137 at $\text{pH} > 5.3$ through mildly alkaline conditions [216]. The monomer 137 is soluble only to the extent of about 3×10^{-3} M. Based on these finding, we propose a structure of 138 as a reactive species in the reaction using a combination of $(\text{PhIO})_n$ 18 and $\text{BF}_3\text{-Et}_2\text{O}$.



Structure 136

136

137

138

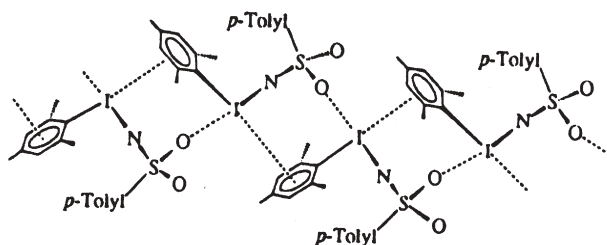


Fig. 6. Solid state structure of MesINTs 139

X-Ray analysis indicated a zigzag polymeric structure of MesINTs (Mes = 2,4,6-trimethylphenyl) 139 (Fig. 6). In contrast to PhINTs, the polymeric structure uses I-O secondary bonds (2.857 Å) [215]. An intermolecular secondary bonding of iodine(III) to the mesityl ring of a neighboring unit of MesINTs was also observed. The centroid-to-iodine distance is 3.46 Å, and below the sum of the van der Waals radii for the groups (~3.66 Å) [219].

In the solid state structure of λ^3 -iodane 140, BPh₄ acts as a bidentate π -ligand towards the iodine(III); thus, the two phenyl groups of BPh₄ coordinate to the iodine with keeping parallel arrangement to the phenyl groups attached to the iodine (Fig. 7) [220, 221]. The interatomic distance between the iodine and the center of the associated phenyl ring attached to the boron is 3.49 Å.

In the solid states of Ph(CF₃CH₂)INTf₂ and Ph₂INTf₂, the sulfonyl oxygen atoms of NTf₂ group instead of the nitrogen atom coordinate to the iodine(III) [222]. *o*-Substituted chiral λ^3 -iodane 141 was synthesized. The X-ray analysis showed a tetracoordinated iodine structure with a strong interaction (2.47 Å) between the oxygen of the methoxy group and the iodine [223]. The λ^3 -iodane 141 and its derivatives serve as enantioselective oxidizing agents of alkenes and ketones [224].

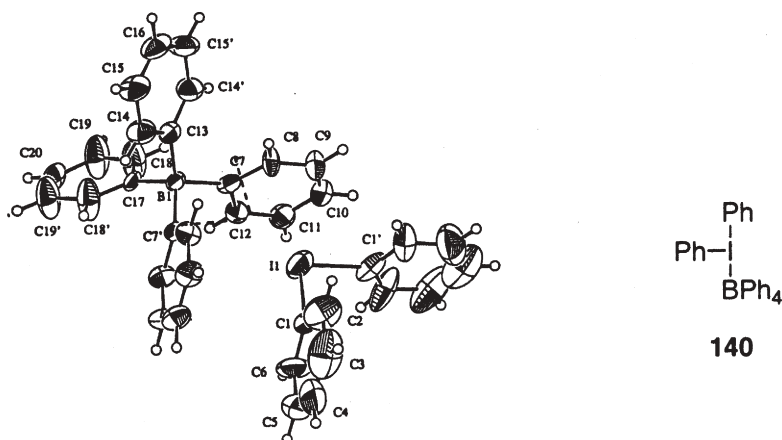
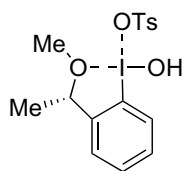


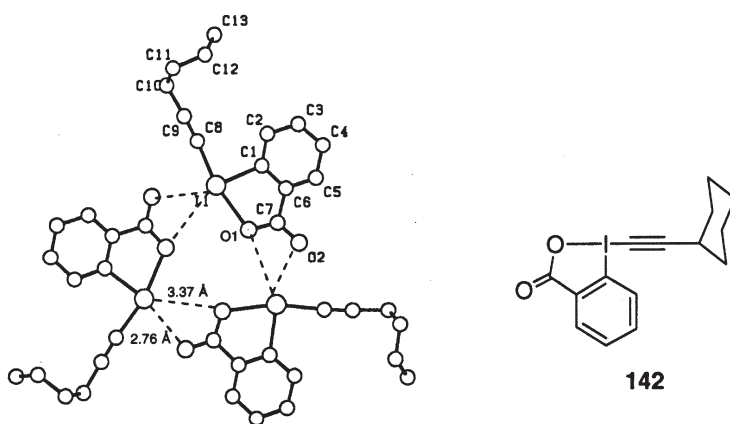
Fig. 7. Molecular arrangement of λ^3 -iodane 140



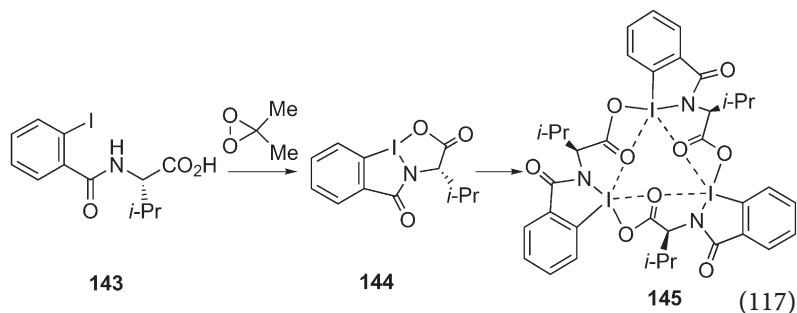
Structure 141

141

Interestingly, trimer was formed through secondary bonds between the iodine(III) and the two oxygen atoms (O1 and O2) in the solid state of 1-alkynyl-1 λ^3 ,2-benziodoxol-3(1*H*)-one 142 (Fig. 8) [225]. In the solid state the ethynyl substituent occupies an axial position of the cyclohexane chair conformer.

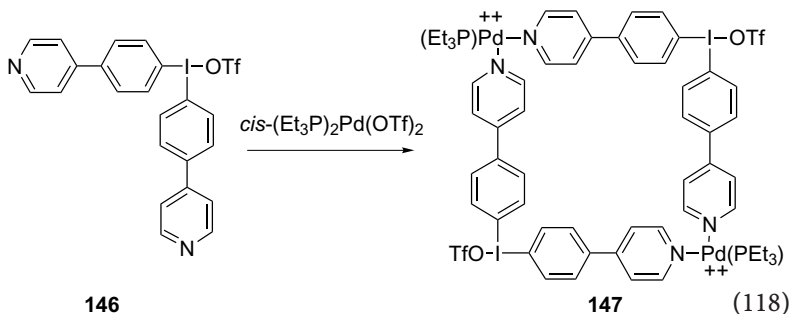
Fig. 8. Molecular arrangement of λ^3 -iodane 142

Macrocyclic hypervalent iodine trimer 145 was prepared directly from the oxidation of amino acid 143 [Eq. (117)] [226]: self-assembly of the monomeric λ^3 -iodane 144 directed by secondary bonding between iodine and oxygen atom of the amino acid fragment is responsible for the formation of the trimer 145, in which iodine atoms have the pentagonal planar geometry.



(117)

Stang and coworkers found that the interaction of bis[4-(4'-pyridyl)phenyl]- λ^3 -iodane **146** with *cis*-(Et₃P)₂Pd(OTf)₂ in acetone at room temperature results in hybrid λ^3 -iodane-Pd tetranuclear macrocyclic square **147** via self-assembly [Eq. (118)] [227]. Its X-ray structure shows a planar rhomboid-like geometry rather than a perfect square.



1 λ^3 ,2-Iodoxetane **149** was prepared by Kawashima and coworkers from the diol **148** by the oxidation with *t*-BuOCl [228]. X-Ray crystallographic analysis indicated a dimeric structure with hypervalent O-I-O bond angle of 144.5° and with planar four-membered ring (Fig. 9). Thermolysis of **149** in acetonitrile results in reductive *anti* β -elimination (Sect. 3.2.5.1) yielding 1,1,1,6,6,6-hexafluoro-2,5-bis(trifluoromethyl)-3-hexyne-2,5-diol quantitatively.

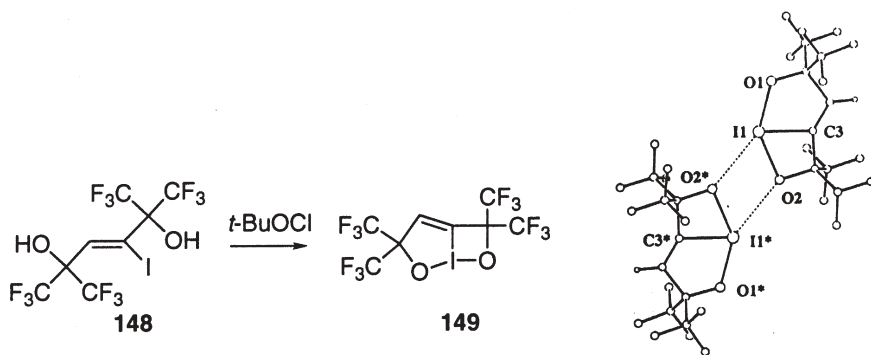


Fig. 9. Structure of λ^3 -iodane **149**

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Preparation of Hypervalent Iodine Compounds

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All synthetically useful methods for the preparation of a multitude of hypervalent iodine compounds are discussed, with an emphasis on those methods developed over the last decade. In addition, special approaches of mechanistic interest and others suitable for the synthesis of individual compounds of interest are also briefly mentioned.

Keywords. [Bis(acyloxy)iodo]arenes, Dialkoxyiodanes, (Dichloroiodo)arenes, (Difluoroiodo)arenes, Iminoiodanes, Iodanes, Iodonium salts, Iodosyl compounds, Iodyl compounds, Ylides

1	Introduction	70
2	Iodanes with One Iodine–Carbon Bond	71
2.1	Iodanes with Only Iodine–Chlorine Bonds	71
2.2	Iodanes with Only Iodine–Fluorine Bonds	72
2.3	Iodanes with Only Iodine–Oxygen Bonds: Non-Cyclic	73
2.3.1	[Bis(acyloxy)iodo]arenes	73
2.3.2	Iodosyl and Iodyl Compounds	74
2.3.3	Dialkoxyiodanes	75
2.3.4	Iodanes with Two Different Ligands: (Hydroxy, Sulfonyloxy)iodanes and Analogs	75
2.3.5	Oxygen-Bridged Iodanes with Two Iodine(III) Centers (μ -Iodanes)	76
2.4	Iodanes with only Iodine–Oxygen Bonds: Cyclic	76
2.4.1	λ^3 -Iodanes	77
2.4.2	λ^5 -Iodanes	78
2.5	Iodanes with Only Iodine–Nitrogen Bonds	79
2.5.1	<i>N</i> -Carboxamido-iodonium Salts	79
2.5.2	Bis(imidyl)iodanes	80
2.5.3	Bis(azonio)-Substituted Iodanes	80
2.5.4	Iminoiodanes	80
2.5.5	1-Azido-2-acetoxy-1,2-benziodazol-3(<i>H</i>)-one	81
2.6	Iodanes with Two Different Element–Iodine Bonds	81
2.7	Iodanes with One Iodine–Boron Bond	83
2.8	Polymer-Supported Iodanes	83
2.9	Unstable Compounds	84

3	Iodanes with Two Iodine–Carbon Bonds	84
3.1	Iodonium Salts	85
3.1.1	Diaryliodonium Salts	85
3.1.2	Alkenyl(phenyl)iodonium Salts	88
3.1.3	Alkynyl(phenyl)iodonium Salts	89
3.1.4	Alkyl(phenyl)iodonium Salts	90
3.1.5	Miscellaneous Iodonium Salts	91
3.2	Phenyliodonium Ylides	91
3.3	Phenyliodonium Dipoles	92
3.4	Cyclic Iodanes	93
3.5	Iodates of Iodine(I)	94
4	Iodanes with Three Iodine–Carbon Bonds	94
5	References	94

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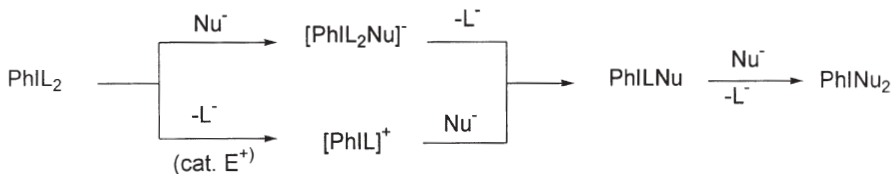
Introduction

A multitude of hypervalent iodine compounds belonging to a range of types have been prepared over the years since 1914, when Willgerodt's book summarised the state of the art in the field [1]. Their number, some 40 years later, was 426, as catalogued by Beringer and Gindler [2]. Presently, hypervalent iodine compounds are too numerous to count, but most of them belong to well-defined families; for most of them reliable methods of preparation have been developed. An exhaustive presentation of preparative ways for many individual compounds appeared in 1992 [3], whereas selected methods of preparative value are also available [4].

The general approach for the preparation of the most common hypervalent iodine compounds is the initial oxidation of iodine(I) to iodine(III) or (V). This requires the correct choice of strong electrophilic reagents as well as conditions which will lead to the formation of either one, for iodine(III), or two, for iodine(V), hypervalent bonds. Such reactions are possible in principle with the nucleophilic iodine of all sorts of iodides but actually take place mostly in aromatic iodides. Of practical importance is the direct attachment of chlorine, fluorine and acetoxy or trifluoroacetoxy groups. Apart from elemental chlorine and fluorine, other strong halogen electrophiles for such reactions include IF_5 , ClF_3 , CF_3OF , SO_2Cl_2 and $t\text{-BuOCl}$, whereas the pertinent peracids are used for the attachment of acetoxy- and trifluoroacetoxy- groups.

Once formed, hypervalent iodine compounds, i.e. λ^3 - and λ^5 -iodanes, can exchange readily their ligands with nucleophiles, sometimes with assistance from electrophiles. When only nucleophiles are involved, reactions follow an associative pathway, in which an iodate(III) or (V) species is formed. The "mixed" iodane initially formed is sometimes isolable but usually this procedure takes place with both ligands so that eventually the new species has two

new ligands. The other pathway is dissociative and usually requires catalysis by a good electrophile which helps the removal of one ligand with formation of a cationic iodonium species which subsequently combines with the nucleophile. In Scheme 1 is summarized the reactivity pattern for the most common λ^3 -iodanes of the general formula PhIL_2 .



Scheme 1 L is normally F, Cl, OAc, OTs and Nu is a variety of mainly oxygen nucleophiles

This chapter presents methods of preparation for hypervalent iodine compounds with an emphasis on those which serve as reagents. In order to facilitate classification the families of compounds have been divided according to the type of bonds attached to iodine. Procedures described in *Organic Syntheses* will be only briefly mentioned.

2 Iodanes with One Iodine–Carbon Bond

This category contains many families of compounds including reagents such as (dichloroiodo)arenes and (difluoroiodo)arenes as well as a plethora of compounds with iodine-oxygen bonds such as (diacetoxyiodo)benzene (DIB), Koser's and Dess-Martin's reagents, iodosylbenzene and "o-iodoxybenzoic acid" (IBX). Here belong also compounds containing one or two iodine-nitrogen bonds, some of which are emerging as promising new reagents, especially iodine-nitrogen ylides.

The conditions for the preparation of most iodanes of this category when is performed through exchange reactions are especially mild, since no heating is required. Also, protection from daylight is not necessary and the use of an inert atmosphere is rarely mandatory. However, for the initial oxidation of iodides very powerful oxidants are often used which should be handled with great care.

2.1 Iodanes with Only Iodine-Chlorine Bonds

The most useful compounds of this type are (dichloroiodo)arenes. The method of choice for their preparation remains the old, direct combination of elemental chlorine with the corresponding iodide, as originally applied by Willgerodt. The usual procedure for iodoarenes is to dissolve them in a suitable solvent (preferably chloroform or dichloromethane) and pass chlorine at 0°C (Scheme 2) [5].



The method has been applied for the large scale preparation of PhICl_2 which was obtained in 94 % yield from 20 kg of iodobenzene [6]. In order to avoid the use of elemental chlorine, its generation in situ was effected upon oxidation of hydrochloric acid by $\text{NaBO}_3 \cdot 4\text{H}_2\text{O}$ in CH_3CN or CCl_4 at room temperature [7]. Variants of this approach used as oxidants the biphasic system KClO_3 and CCl_4 [8] or CrO_3 in AcOH [9] or $\text{Na}_2\text{S}_2\text{O}_8$ [10]. Iodoarenes with electrophilic groups were readily chlorinated by these methods.

One-pot introduction of the dichloroiodo group to several arenes has also been reported. Upon treatment with $\text{I}_2/\text{CrO}_3/\text{AcOH}/\text{Ac}_2\text{O}/\text{H}_2\text{SO}_4$ iodoarenes are formed first and then oxidized to $\text{ArI}(\text{OSO}_3\text{H})_2$. Subsequently hydrochloric acid is added in an one-pot, two- or three-stage procedure, depending on the nature of the arene [11].

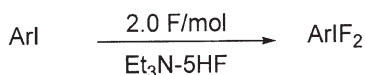
Although most aliphatic analogs are unstable, (dichloroiodo)perfluoroalkanes are stable. For their preparation only chlorine is necessary, without any solvent; the reaction may take place at low or room temperature, with various techniques, depending on the substrate [12]. Some iodides from aryl or alkyl iodomethyl sulfones afford also upon chlorination stable *I,I*-dichloro derivatives, $\text{RSO}_2\text{CH}_2\text{ICl}_2$. Similarly, quaternary ammonium and phosphonium iodomethyl salts, such as $\text{Et}_3\text{N}^+\text{CH}_2\text{I BF}_4^-$ and $\text{Ph}_3\text{P}^+\text{CH}_2\text{I BF}_4^-$, gave upon chlorination the corresponding dichloroiodanes, stabilized because of the presence of the electron-withdrawing ammonium or phosphonium groups [13].

2.2

Iodanes with Only Iodine-Fluorine Bonds

The direct fluorination of iodoarenes and iodoalkanes, even MeI , is possible with either diluted elemental fluorine or the expensive XeF_2 . However, the best method for the preparation of the useful ArIF_2 is the reaction of ArICl_2 with fluoride coming from $\text{HgO}/\text{hydrofluoric acid}$ [14, 15]. Recently, an efficient electrochemical route has been introduced involving anodic oxidation of iodoarenes in presence of fluoride; in this way the in situ generation of *p*-tolyl IF_2 was achieved by employing the novel electrolyte $\text{Et}_3\text{N}\cdot 5\text{HF}$ (Scheme 3) [16].

Fluorination of $\text{C}_6\text{H}_5\text{I}$, $\text{C}_6\text{F}_5\text{I}$ and $\text{C}_3\text{F}_7\text{I}$ with an excess of XeF_2 or ClF_3 can lead directly to the corresponding tetrafluoroiodo compounds. Also, arylsilanes such as Ar_4Si and PhSiF_3 have been converted by IF_5 -pyridine into ArIF_4 [3a, 17].



Scheme 3

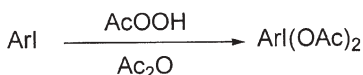
2.3

Iodanes with Only Iodine-Oxygen Bonds: Non-Cyclic

2.3.1

[Bis(acyloxy)iodo]arenes

These important compounds are prepared either directly from iodoarenes and peroxyacids or through ligand exchange reactions. The first method is suitable mainly for diacetoxy-derivatives which are readily formed upon oxidation of iodoarenes with $\text{H}_2\text{O}_2/\text{AcOH}/\text{Ac}_2\text{O}$. A detailed procedure for the parent (diacetoxyiodo)benzene can be found in *Organic Syntheses* (Scheme 4) [18].



Scheme 4

Alternative approaches use other oxidizing agents, either the system $\text{NaBO}_3 \cdot 4\text{H}_2\text{O}$ in AcOH [19] or $\text{NaBO}_3 \cdot \text{H}_2\text{O}$ in Ac_2O [20]. The former method was used, among others, for the preparation of *I,I*-diacetoxy derivatives of the isomeric 2- and 3-iodothiophenes and some *N*-protected iodopyrazoles [21]. Also, the use of $\text{NaIO}_4/\text{AcONa}/\text{Ac}_2\text{O}$ and $\text{CrO}_3/\text{AcOH}/\text{Ac}_2\text{O}/\text{H}_2\text{SO}_4$ leads to satisfactory results [22]. It should be pointed out that considerable economy can be achieved by employing CrO_3 oxidation. Not only this reagent is cheaper than $\text{NaBO}_3 \cdot 4\text{H}_2\text{O}$ but also the procedure avoids chloroform extraction and use of excess acetic acid. Overall, for the preparation of one mole of (diacetoxyiodo)benzene it has been estimated that using the CrO_3 method the cost is reduced by 80% [23]. The direct approach served also for the preparation of some bis trifluoroacetoxy analogs such as $\text{C}_6\text{F}_5\text{I}(\text{O}_2\text{CCF}_3)_2$ and other [bis(acyloxy)iodo]arenes from iodoarenes bearing strong electron-withdrawing groups; in these cases peroxytrifluoroacetic acid (from 80% H_2O_2 and CF_3COOH) was used. Also, in some instances arenes were converted into $\text{ArI}(\text{O}_2\text{CCF}_3)_2$ upon treatment with $\text{I}(\text{O}_2\text{CCF}_3)_3$ [3b].

The second method involves ligand exchange, usually between (diacetoxyiodo)benzene and a carboxylic acid. The reaction is best performed in mildly heated chlorobenzene under reduced pressure. This simple approach is suitable for the preparation of several [bis(acyloxy)iodo]arenes including dibenzoyloxy derivatives and also 1-adamantylcarboxy derivatives which are formed in high yields (Scheme 5) [24, 25].



Scheme 5

Another possibility is to use [bis(trifluoroacetoxy)iodo]benzene (BTI) and the sodium salt of a carboxylic acid. This method does not require heating because of the good nucleofugality of the trifluoroacetoxy group. When stoichiometric quantities of reagents are used, mixed [bis(acyloxy)iodo]arenes may be obtained [26]. In order to prepare [bis(trifluoroacetoxy)iodo]benzene itself,

it is enough to simply dissolve (diacetoxyiodo)benzene in trifluoroacetic acid and evaporate to a small volume. In a related method, used for the preparation of a series of $\text{PhI}(\text{OCOCOR})_2$, (diacetoxyiodo)benzene was allowed to react with oxalyl chloride in alcohol [27].

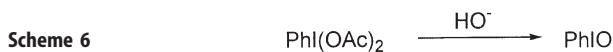
(Dichloroiodo)arenes may also be converted to (diacetoxyiodo)arenes upon treatment with mercuric acetate. This approach and also perborate oxidation of iodides were used for the preparation of some chiral 1,1'-binaphthyl derivatives [28].

Some aliphatic bis(trifluoroacetoxy)iodides are stable, like their dichloro analogs. Direct oxidation of $\text{ArSO}_2\text{CH}_2\text{I}$ with peroxytrifluoroacetic acid gave the corresponding iodanes, $\text{ArSO}_2\text{CH}_2\text{I}(\text{O}_2\text{CCF}_3)_2$ [29]. Similarly, perfluoroalkyl iodides afforded isolable iodanes [30, 31]. A polymeric iodane (actually an oligomer comprising 10–11 monomer units) was obtained upon reaction of (diacetoxyiodo)benzene or iodosylbenzene and dibenzoyl-L-tartrate [32].

2.3.2

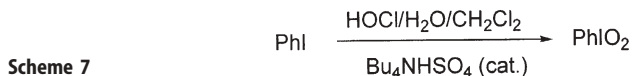
Iodosyl and Iodyl Compounds

Although written usually as monomeric, $\text{PhI}=\text{O}$ or PhIO , iodosylbenzene is actually polymeric, $[-(\text{Ph})\text{I}-\text{O}]_n$. It is conveniently obtained upon alkaline hydrolysis of (diacetoxyiodo)benzene, as detailed in *Organic Syntheses* [33]. Iodosylbenzene is practically insoluble in water and is formed through the unstable intermediate $\text{PhI}(\text{OH})_2$ (Scheme 6). Other iodosylarenes have been obtained similarly.



By introduction of the *t*-BuSO₂ group at the ortho position of (diacetoxyiodo)benzene and subsequent alkaline hydrolysis, the corresponding monomeric iodosyl sulfone was formed, which was soluble in chloroform because of intramolecular I-O bonding [34]. Some polymeric iodosylperfluoroalkanes have been obtained by careful hydrolysis (NaHCO_3 in ice for a short time) of $\text{R}_f\text{I}(\text{O}_2\text{CCF}_3)_2$ [35].

Apart from some aliphatic iodides, which have been oxidized directly to iodosyl derivatives with ozone or dimethyldioxirane [3], iodoarenes give directly iodylarenes with strong oxidants. From a synthetic point of view, potassium bromate in sulfuric acid has been used for the preparation of several members. The parent PhIO_2 can also be obtained by overoxidation of iodobenzene with peracetic acid, followed by hydrolysis as detailed in *Organic Syntheses* [36]. Another good method is oxidation of ArI by hypochlorite, at room temperature under phase transfer catalysis (Scheme 7) [37].



2.3.3

Dialkoxiodanes

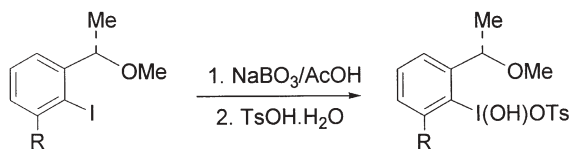
When dissolved in methanol iodosylbenzene undergoes methanolysis to give, under strictly anhydrous conditions, the isolable (dimethoxyiodo)benzene, $\text{PhI}(\text{OMe})_2$. However, this compound is dangerous because it may explode spontaneously [38]. Therefore, it has been used in some reactions as formed in situ in ordinary dry methanol.

A less stable but isolable iodane of this family, $\text{C}_6\text{F}_5\text{I}[\text{OC}(\text{CF}_3)_3]_2$, was prepared from oxidation of the iodide with perfluoro *tert*-butyl hypochlorite, $(\text{CF}_3)_3\text{COCl}$ [39]. The aliphatic $\text{CF}_3\text{I}(\text{OMe})_2$ was obtained from CF_3IF_2 and Me_3SiOMe [40].

2.3.4

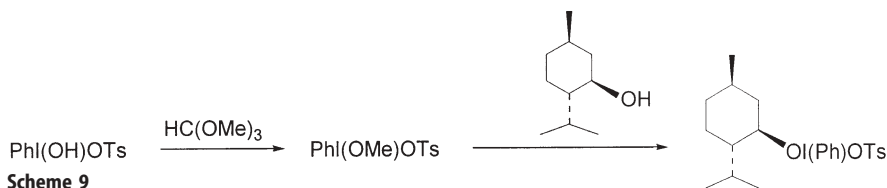
Iodanes with Two Different Ligands: (Hydroxy, Sulfonyloxy)iodanes and Analogs

The best known member among the various classes of these iodanes is undoubtedly [hydroxy(tosyloxy)iodo]benzene (HTIB), sometimes called Koser's reagent. It is prepared readily from (diacetoxyiodo)benzene and *p*-toluenesulfonic acid monohydrate in acetonitrile. The same method using *p*-nitrobenzenesulfonic acid or 10-camphorsulfonic acid leads to the corresponding sulfonyloxy analogs [41, 42]. Of special interest are some iodanes of this type coming from a chiral ether. Their preparation was effected by direct oxidation with sodium perborate and the isolated diacetoxy derivatives were separately treated with *p*-toluenesulfonic acid in acetonitrile (Scheme 8) [43].



Scheme 8

[Methoxy(tosyloxy)iodo]benzene is obtained from [hydroxy(tosyloxy)iodo]benzene and trimethyl orthoformate. This iodane has been used for the preparation of the (-)-menthyloxy analog by simple alcohol exchange upon mixing in dichloromethane equimolar quantities of it with (-)-menthol and concentrating under reduced pressure (Scheme 9) [44].



Scheme 9

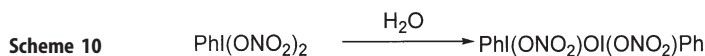
Some [hydroxy(tosyloxy)iodo]perfluoroalkanes, $\text{R}_\text{F}\text{I}(\text{OH})\text{OTs}$, were prepared from $\text{R}_\text{F}\text{I}(\text{O}_2\text{CCF}_3)_2$ by reaction with either a sulfonic acid, e.g. *p*-TsOH, or a silyl sulfonate, e.g. Me_3SiOTf [30, 31]. Several organic acids derived from phosphorus

behave like sulfonic acids, affording analogous iodanes. Thus, diphenyl phosphate upon reaction with (diacetoxyiodo)benzene in acetonitrile–water gave $\text{PhI}(\text{OH})\text{OP}(\text{O})(\text{OPh})_2$ [45]. Other similar iodanes were obtained using iodosylbenzene and phosphinic acids (Me_2POOH and Ph_2POOH) as well as phenyl methylphosphonic acid, $(\text{MeP}(\text{OPh})\text{OH})$ [46].

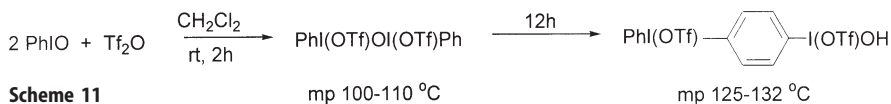
2.3.5

Oxygen-Bridged Iodanes with Two Iodine(III) Centers (μ -Iodanes)

Iodanes containing two groups coming from almost any acid except the carboxylic acids, are generally labile. Traces of moisture suffice to convert them into oxo-bridged bis iodanes, containing two iodine(III), as exemplified for $\text{PhI}(\text{ONO}_2)_2$ (Scheme 10) [3].



Reaction of iodosylbenzene with triflic anhydride gives an isolable, hygroscopic μ -compound, sometimes called Zefirov's reagent; upon longer reaction time (12 h), this isomerizes to a derivative of *p*-diiodobenzene which is also an iodonium salt (Scheme 11). The same compound was obtained directly from iodosylbenzene and triflic acid [47].



Analogs of Zefirov's reagent have been prepared from (diacetoxyiodo)benzene and some strong acids according to the general overall equation (Scheme 12) [48].



Scheme 12

A remarkable dual way to obtain $\text{PhI}(\text{O}_2\text{CCF}_3)\text{OI}(\text{O}_2\text{CCF}_3)\text{Ph}$ involved either solvolysis of iodosylbenzene by trifluoroacetic acid or nucleophilic attack by a strong base to the carbonyl group of [bis(trifluoroacetoxy)iodo]benzene [49]. Another unusual reaction leading to the formation of the same iodane has been reported between iodobenzene and xenon bistrifluoroacetate [50].

2.4

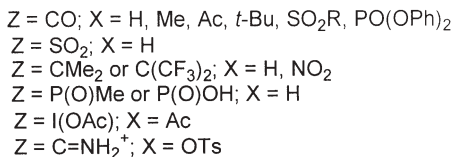
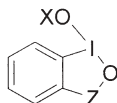
Iodanes with Only Iodine-Oxygen Bonds: Cyclic

Cyclic iodanes derived mostly from ortho-substituted iodoarenes in general are of special interest because of their reduced reactivity in comparison to their non-cyclic analogs. This property permits the preparation of some otherwise unstable iodanes which serve as good reagents for a range of transformations.

2.4.1

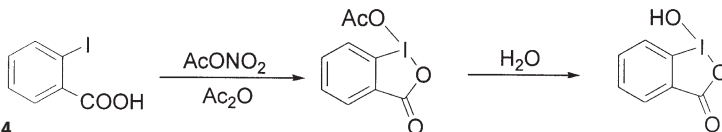
 λ^3 -Iodanes

Several cyclic λ^3 -iodanes of diverse structure have been reported over the years since Victor Meyer's *o*-iodosobenzoic acid, IBA, whose systematic name is 1-hydroxy-1,2-benziodoxol-3(1*H*)-one. A recent review on benziodoxoles presents in detail their preparation and interconversions [51]. In Scheme 13 appears a collection of the main types of λ^3 -iodanes which contain either a benziodoxole ring or a 5-membered-ring with iodine, oxygen and another atom.



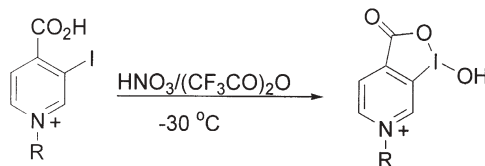
Scheme 13

Many of these iodanes are formed by oxidation of *ortho*-iodobenzoic acids or certain *ortho*-iodophenylated alcohols with Cl₂, AcOOH, *t*-BuOCl, CF₃OF or magnesium monoperoxyphthalate. Among λ^3 -iodanes more important are those derived from *o*-iodosobenzoic acid which is obtained from the mild oxidation of *o*-iodobenzoic acid. An improved yield for *o*-iodosobenzoic acid was obtained by hydrolysis of its acetyl derivative which in turn was prepared from *o*-iodobenzoic acid and acetyl nitrate in acetic anhydride, at room temperature (Scheme 14) [52].



Scheme 14

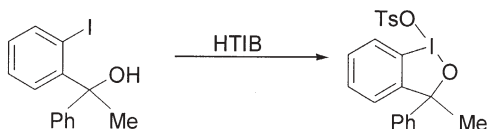
More drastic conditions, i.e. fuming HNO₃ in (CF₃CO)₂O were required for the preparation of some zwitterionic pyridinium analogs of *o*-iodosobenzoic acid (Scheme 15) [53].



Scheme 15

The oxidation with [hydroxy(tosyloxy)iodo]benzene or other oxidants of the chiral alcohol *o*-IC₆H₄C(Me)(C₆H₅)OH is of interest because it provides a chiral benziodoxole (Scheme 16); with *t*-BuOCl a *I*-chloroiodane is formed first and then it undergoes substitution with nucleophiles [54].

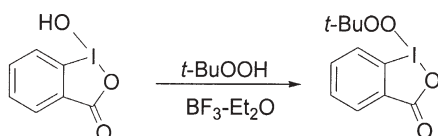
In the same way *I*-chloro-*o*-iodosobenzoic acid reacted with AgOPO(OPh)₂ to provide the *O*-(diphenylphosphoryl) derivative of *o*-iodosobenzoic acid [55].



Scheme 16

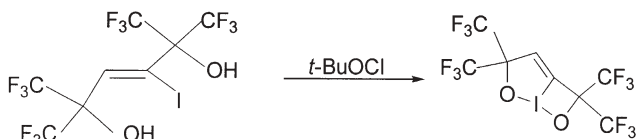
Another type of reactivity is due to the enhanced nucleophilicity of the hydroxyl group of *o*-iodosobenzoic acid. For example, *o*-iodosobenzoic acid reacts with silyl triflate or other silyl sulfonates to afford *O*-substituted sulfonates [56].

The *O*-*tert*-butyloxy derivative of *o*-iodosobenzoic acid is of interest because of its synthetic utility. In contrast to the facile reaction of *tert*-butyl hydroperoxide with iodosylbenzene (at -80°C), no ligand exchange was observed with this hydroperoxide and *o*-iodosobenzoic acid, even at room temperature. Treatment of *o*-iodosobenzoic acid with $\text{BF}_3 \cdot \text{Et}_2\text{O}$, however, provided enough activation for the exchange to take place (Scheme 17) [57].



Scheme 17

Some iodoxyloles coming from aliphatic precursors are also known [58]. A unique 1,2-iodoxetane fused to a dihydroiodoxole was obtained upon oxidation of an iodinated unsaturated bis alcohol (Scheme 18) [59].



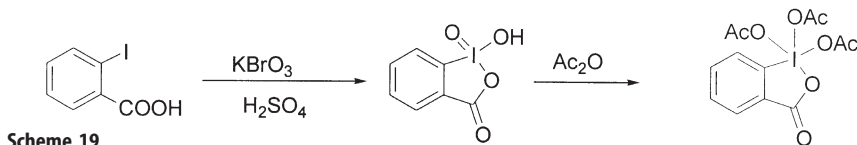
Scheme 18

2.4.2

λ^5 -Iodanes

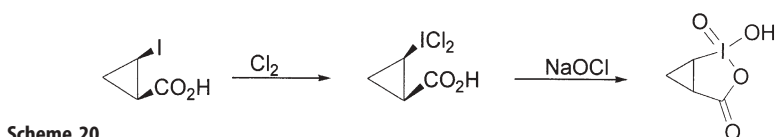
This special category comes mainly from *o*-iodobenzoic acids, the direct oxidation of which leads first to "*o*-iodosobenzoic acids" and then to "*o*-iodoxybenzoic acids", also cyclic. The parent compound, named 1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide, has been dubbed IBX acid and has become lately a useful reagent in many types of oxidation. For its preparation, among various oxidants, best results gave potassium bromate in 2*M* sulfuric acid at 65°C [60]. It was recommended to use microcrystalline *o*-iodoxybenzoic acid, because sometimes it is formed in the form of macrocrystals, and then it is less reactive; a simple procedure was given for the conversion of the latter to the former [61]. In order to overcome KBrO_3 , a known carcinogen which in addition evolves bromine upon reduction, the use of oxone in water was found advantageous [62]. A water-soluble analog of *o*-iodoxybenzoic acid bearing a carboxy

group was obtained from 3-iodophthalic acid upon KBrO_3 oxidation [63]. Another widely used oxidant derived from *o*-iodoxybenzoic acid is Dess-Martin reagent. This is prepared upon treatment of *o*-iodoxybenzoic acid with acetic anhydride. Both these preparations have recently appeared in *Organic Syntheses* (Scheme 19) [64].



The tris trifluoroacetoxy analog of Dess-Martin reagent is formed from *o*-iodoxybenzoic acid and trifluoroacetic anhydride. Curiously, no reports about the reactivity of this interesting oxidant are available [65].

A non-aromatic λ^3 -iodane was obtained by a combination of chlorination and oxidation with NaOCl of *cis*-iodocyclopropanecarboxylic acid (Scheme 20). Its λ^3 -analog has also been prepared by hydrolysis of the dichloride [58].



2.5

Iodanes with Only Iodine-Nitrogen Bonds

A variety of compounds belong to this category, in which are included some interesting phenyliodonium ylides and salts.

2.5.1

N-Carboxamido-iodonium Salts

This purely ionic class of compounds has several members; they are prepared from amides of carboxylic acids and $\text{PhI}(\text{OMe})(\text{OTs})$ in acetonitrile, at room temperature as *N*-phenyliodonio amide tosylates (Scheme 21) [66].

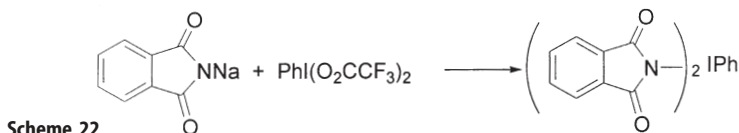


It is noted that these compounds do not give stable ylides with alkali. An exception was CF_3CONH_2 which upon reaction with (diacetoxyiodo)benzene in methanolic KOH at -40°C afforded directly the isolable ylide $\text{PhI}=\text{NCOCF}_3$ [3c].

2.5.2

Bis(imidyl)iodanes

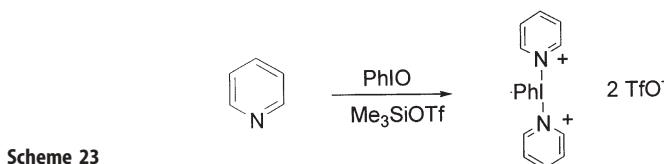
A whole class of iodanes with two iodine-nitrogen bonds comes from the reaction of [bis(trifluoroacetoxy)iodo]benzene with sodium salts of cyclic imides, such as phthalimide, saccharin and 2-pyridone (Scheme 22) [67]. Aliphatic analogs of imides failed to give isolable iodanes.



2.5.3

Bis(azonio)-Substituted Iodanes

This relatively unexplored class of iodanes is obtained by either (diacetoxyiodo)benzene or iodosylbenzene and a nitrogen heterocycle, such as substituted pyridines, quinoline or 1-methylimidazole, in presence of trimethylsilyl triflate (Scheme 23) [68]. Very dry conditions were required because of the highly hygroscopic character of the products, not permitting the determination of their melting points.



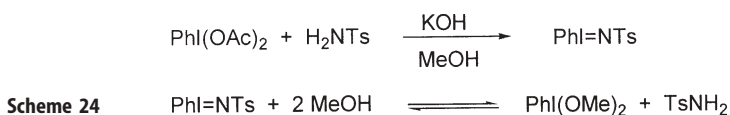
Scheme 23

2.5.4

Iminoiodanes

This class, also described as phenyliodonium ylides, has several members, notably those coming from sulfonamides, of the general formula PhI=NSO₂R, where R is an aromatic, aliphatic or heterocyclic group.

The original method, with some slight modifications concerning purity, is still used for the preparation of [*N*-(*p*-toluenesulfonyl)iminoiodo]benzene, PhI=NTs. (Diacetoxyiodo)benzene is treated with the sulfonamide in methanolic KOH at -10 °C. The reaction mixture is poured into water and the ylide precipitates; it can be recrystallized from methanol or methanol-water (4:1), although in both these solvents it undergoes partial solvolysis (Scheme 24) [69].



Scheme 24

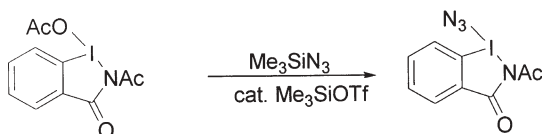
In a subsequent study it was reported that the initial precipitate was only 56% pure, when assayed iodometrically. The product was purified by dissolving it in a large volume of methanol, and adding an equal amount of water; the solution was allowed to crystallize at -20°C [70]. Similar procedures were followed for the preparation of several substituted iminoiodanes, of the general formula $\text{ArI}=\text{NSO}_2\text{R}$, where R was aryl [71], heteroaryl [72] or 2-trimethylsilylethyl [73]. In a variation, used for the preparation of a series of $\text{PhI}=\text{NSO}_2\text{Ar}$, alkali was avoided: the sulfonamides were simply treated with PhIO in methanol and molecular sieves [74]. Iminoiodanes are normally polymeric but a monomeric compound, *o*-*t*- $\text{BuSO}_2\text{C}_6\text{H}_4\text{I}=\text{NTs}$, was obtained from *o*-*t*- $\text{BuSO}_2\text{C}_6\text{H}_4\text{I}(\text{OAc})_2$ upon treatment with $\text{TsNH}_2/\text{KOH}/\text{MeOH}$ [34].

In a variation, ArIF_2 and $\text{PhSO}_2\text{N}(\text{SiMe}_3)_2$ or $\text{CF}_3\text{SO}_2\text{N}(\text{SiMe}_3)_2$ in organic solvents gave the corresponding ylides. Similarly, some double ylides of iodine(V), of the general formula $\text{ArI}(=\text{NSO}_2\text{Ph})_2$, were obtained from ArIF_4 and an *N,N*-silylated sulfonamide [75].

2.5.5

1-Azido-2-acetoxy-1,2-benziodazol-3(H)-one

Normally, iodanes with one or two azido groups attached to iodine(III) are very labile. Two cyclic iodanes, however, 1-azido-1,2-benziodazol-3(1*H*)-one and its 2-acetoxy derivative, are stable. They are prepared from the corresponding 1-acetoxybenziodazoles by reaction with trimethylsilyl azide (Scheme 25) [76, 77].

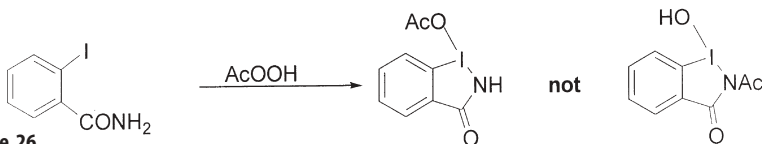


Scheme 25

2.6

Iodanes with Two Different Element–Iodine Bonds

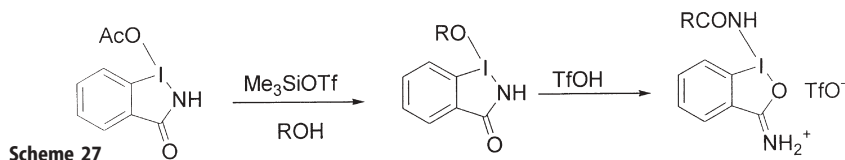
This category includes several heterocyclic iodanes coming mainly from benziodazoles or benziodoxoles or a combination of both. Among them, 1-hydroxy-1,2-benziodazole and its derivatives are of considerable interest. It is noted that the first iodane of this type, prepared in 1965 by peracetic acid oxidation of *o*-iodobenzamide, is not *N*- (as originally proposed) but *O*-acetyl (Scheme 26) [77].



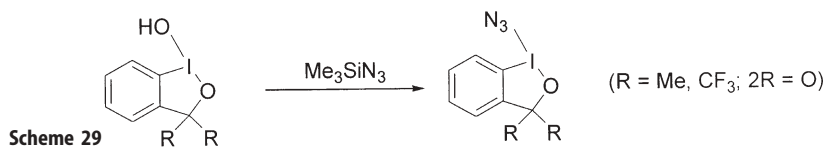
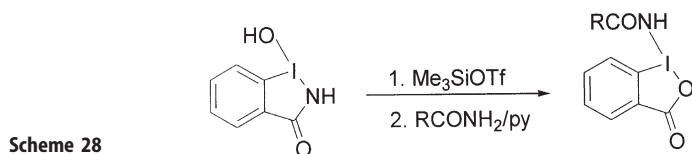
Scheme 26

This benziodazole reacts not only with Me_3SiN_3 , as already mentioned, but also with *p*-toluenesulfonic acid hydrate or methanesulfonic acid in acetic anhy-

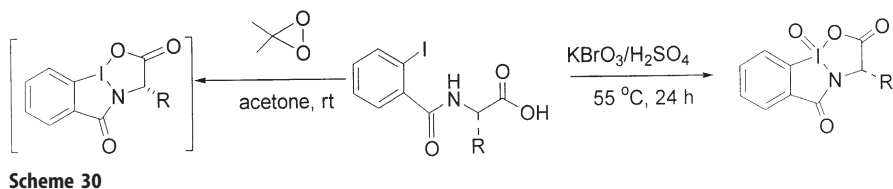
dride or trimethylsilyl triflate in acetonitrile; these reagents displace the acetoxy group to give, respectively, *O*-tosyl or mesyl or triflyliodanes. An interesting aspect of the chemistry of 1-triflyl-benziodazole is that upon reaction with carboxamides the initially formed 1-carboxamido derivative reacts further with TfOH undergoing ring-opening and recyclization leading to a rearranged *I*-carboxamido-derivative. An analogous rearrangement was observed with the similarly obtained *I*-alkoxybenziodazoles (Scheme 27) [77].



Related compounds are the *I*-carboxamido-benziodoxoles which were obtained from *o*-iodosobenzoic acid upon reaction with trimethylsilyl triflate and the amides (Scheme 28) [78]. Similarly, with trimethylsilyl azide, the azido-analogs were formed as described recently (Scheme 29) [76, 79, 80].



Oxidation of the *N*-(iodobenzoyl) derivatives of some α -amino acids gave interesting results: with dimethyldioxirane at 0°C non-isolable monomeric tricyclic products were apparently formed which underwent spontaneous self-assembly to afford trimeric macrocycles [81]. The same substrates, either with oxone in water at 70°C or with KBrO₃/H₂SO₄ were converted to the monomeric tricyclic λ^5 -iodanes (Scheme 30) [82].



Among non-cyclic iodanes of this category, the mixed $\text{ArI}(\text{F})\text{Cl}$ are mentioned which were generated electrochemically [83]; also, two labile aliphatic iodanes have been reported, $\text{CF}_3\text{I}(\text{Cl})\text{F}$ from CF_3IF_2 and $\text{CF}_3\text{I}(\text{Cl})\text{OMe}$ from $\text{CF}_3\text{I}(\text{Cl})\text{F}$ and Me_3SiOMe [40].

2.7

Iodanes with One Iodine-Boron Bond

The only compounds of this type are some phenyliodonium salts with a carbonyl group, obtained from 9-*o*-, 9-*m*- and 2-*p*-iodocarboranes which were converted into (dichloroiodo) and then into [bis(trifluoroacetoxy)iodo]carboranes; these were coupled with benzene in presence of acid [84].

2.8

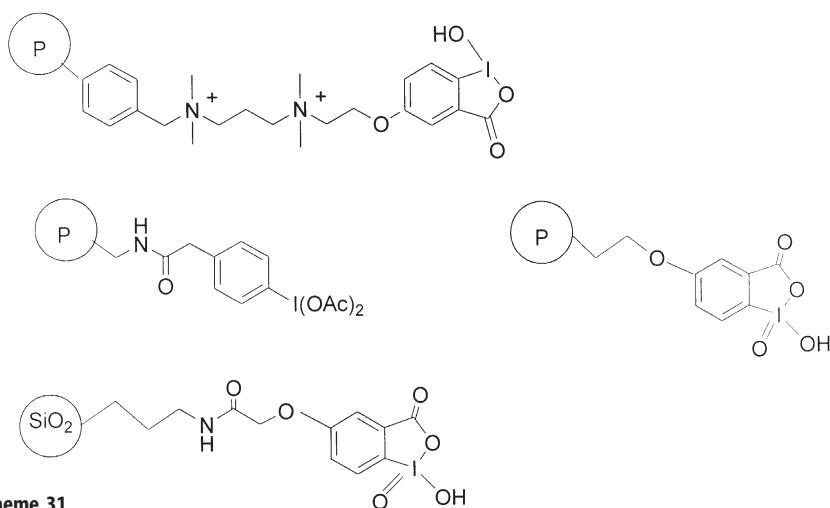
Polymer-Supported Iodanes

Polymer-supported hypervalent iodine compounds in general are readily prepared and they have gained recently considerable popularity as reagents for clean oxidations. However, they are not newcomers since they have been known since 1961. A detailed procedure for the iodination of polystyrene and its conversion to poly[(diacetoxyiodo)styrene] appeared in 1972 [85]. However, this and other related methods were time consuming and despite encouraging results did not gain popularity.

New types of polymer-supported reagents appeared recently accompanied by numerous applications. In one of them polystyrene of molecular weight = 45,000 was iodinated and subsequently converted first into poly[(diacetoxyiodo)styrene] and subsequently into poly{[hydroxy(tosyloxy)iodo]styrene}; an analogous conversion was effected using poly[(α -methylstyrene)] of low molecular weight (6000) [86]. Also, polymer-bound [bis(trifluoroacetoxy)iodo]benzene was prepared and employed in oxidations [87]. In a different approach, in order to overcome the tedious iodination step, the commercially available poly[(aminomethyl)styrene] was used as starting material; this was coupled with either *p*-iodobenzoic acid or *p*-iodophenylacetic acid. The resulting conjugates were subsequently acetoxyated at iodine as usual [88].

Several solid supports have been employed for the attachment of *o*-iodosobenzoic acid, including silica gel, titania and nylon [89]. Two polymer-supported *o*-iodoxybenzoic acid reagents have recently been reported. The first was obtained by attaching a carboxymethyloxy derivative of *t*-butyl *o*-iodobenzoate to an aminopropylated silica gel and oxidation with oxone [90]. The second involved chloromethylated polystyrene which was coupled with methyl 5-hydroxy-2-iodobenzoate and eventually oxidized by $\text{Bu}_4\text{NSO}_5\text{H}/\text{MeSO}_3\text{H}$ [91]. Some of these polymeric reagents appear in Scheme 31.

Reagents of this kind have been used in various reactions, at the end of which could be recovered by simple addition of ether or other solvents. Then they were converted again to their active form without measurable loss of activity.



Scheme 31

2.9

Unstable Compounds

Several λ^3 -iodanes are too labile to be isolated but there is some evidence suggesting their transient formation. Among them are compounds of the PhIL_2 type bearing one or two azido [92], arylthio [93] or thiocyanato [94] groups. Another unstable iodonium salt is $\text{PhI}^+\text{F TfO}^-$, formed directly upon oxidation of PhI by FXeOTf (from XeF_2 and TfOH) [95] and the zwitterionic $\text{PhI}^+\text{OSO}_2^-$, from iodosylbenzene and SO_3 [96], as well as the related $\text{PhI}^+\text{OBF}_3^-$, from iodosylbenzene and BF_3 [3d].

3

Iodanes with Two Iodine–Carbon Bonds

This category contains predominantly compounds belonging formally to either iodonium salts or λ^3 -iodanes of various kinds. Actually these range from purely ionic, e.g. $\text{Ph}_2\text{I}^+ \text{BF}_4^-$, of the [8-I-2] type, to covalent dimers, e.g. $[\text{Ph}_2\text{ICl}]_2$ of the [10-I-3] type, at least in the crystalline state. Analogous compounds of the [10-I-4] and [12-I-5] type are few and without special interest. In a number of iodonium salts the positive charge is internally compensated so that zwitterionic compounds are formed, either 1,2-iodonium compounds (ylides) or other dipoles. These three categories will be dealt with separately. It is mentioned that several variations have been developed for their preparation, because there are so many iodine(III) reagents which can be combined with a lot of arenes, alkenes and alkynes or derivatives thereof.

3.1

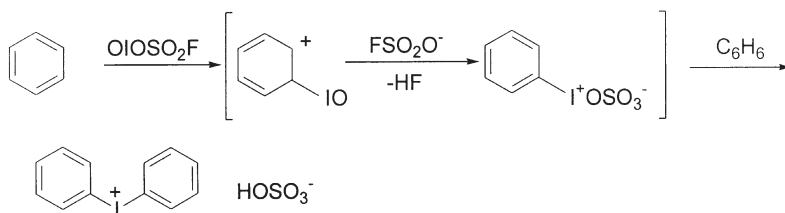
Iodonium Salts

3.1.1

Diaryliodonium Salts

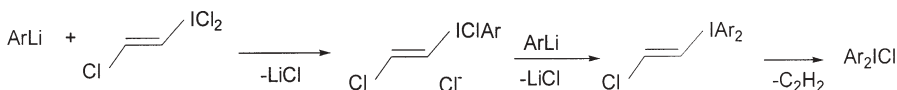
The first preparations of diaryliodonium salts have been reported in the 19th century, but refinements and improvements keep appearing to date. In most cases an iodoaryl species containing iodine(III) is coupled with an arene or a derivative of it in a typical electrophilic aromatic substitution. Lithiated, stannylated or silylated aryls and arylboronic acids or borates have been introduced recently in order to avoid harsh conditions and to improve yields. The iodoaryl species may be also formed in situ from arenes and iodine(III) reagents.

Symmetrical iodonium salts. Arenes, including non-activated compounds such as nitrobenzene, react with the powerful electrophile iodosyl fluorosulfate (FSO_2OIO , obtained from iodine, iodine pentoxide and fluorosulfonic acid) to give directly diaryliodonium hydrosulfates. The reaction is performed at low temperature (Scheme 32) [97].



Scheme 32

A similar electrophile, iodosyl triflate, $\text{CF}_3\text{SO}_2\text{OIO}$, was employed with arylsilanes [98]. The same reagent upon reaction with Me_3SiCN formed $(\text{CN})_2\text{I}^+ \text{TfO}^-$ which was coupled with tributyltin substituted arenes or heterocycles to afford bis(heteroaryl)iodonium triflates, e.g. dithienyl and difuryl derivatives [99]. However, this method gave poor results with nitrogen heterocycles. For them another approach was developed based on the reaction of the appropriate lithium compound with β -(dichloroiodo)chloroethylene (Scheme 33). Pyridine and quinoline compounds were formed in this way in moderate yield (23–71 %) [100].

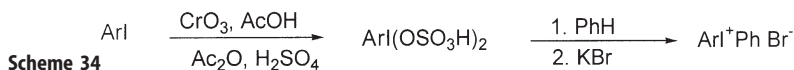


Scheme 33

A special method was needed for the synthesis of bis(pentafluorophenyl)-iodonium salts; this was achieved either by reaction of pentafluoroiodobenzene with $\text{C}_6\text{F}_5\text{Xe}^+ \text{TfO}^-$ or, more conveniently, from pentafluorobenzene and $\text{I}(\text{OOC}-\text{CF}_3)_3$ in strongly acidic conditions [101].

Unsymmetrical iodonium salts. The methods for the preparation of unsymmetrical iodonium salts are also suitable for symmetric iodonium salts, since a preformed or in situ generated aryl iodine(III) species coming also from deactivated arenes may react with any arene or derivative of it, provided it is not strongly deactivated. In this way, the dipolic intermediate of Scheme 32 i.e. $\text{PhI}^+\text{IOSO}_5^-$, also formed from PhIO and SO_3 , can serve for the preparation of unsymmetrical iodonium salts [96].

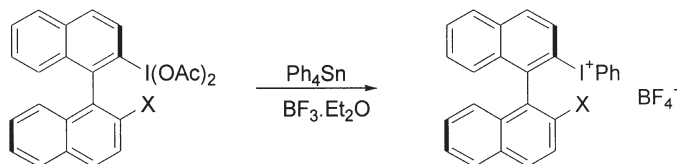
Improvements of the old methods have been reported recently. For example, when iodoarenes were oxidized with CrO_3 in acetic acid/acetic anhydride/sulfuric acid and then coupled with arenes, upon final addition of $\text{KBr}_{(\text{aq})}$ several diaryliodonium bromides were obtained in good yield (Scheme 34) [102].



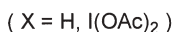
Oxidation of iodoarenes was also effective with $\text{NaBO}_3 \cdot \text{H}_2\text{O}$ in $\text{Ac}_2\text{O}/\text{H}_2\text{SO}_4$. The bromides were converted into the more useful ionic nitrates, trifluoroacetates or tetrafluoroborates by oxidative anion metathesis, using the corresponding acid and 30% hydrogen peroxide, and refluxing the mixtures in methanol; any liberated bromine was trapped by cyclohexene [20].

An inherent weakness of using arenes is that regio-isomers may be formed. This drawback is avoided by using organometallic precursors, since the reaction is confined to ipso-demetalation. In this way, 4-acetamido- and also 4-dimethylaminophenyl(phenyl)iodonium salts were prepared in much improved yield from reaction of the appropriate organomercurials with PhICl_2 [103]. Aryltri-alkylsilanes and also furyl and thienyl analogs reacted readily with [hydroxy-(tosyloxy)iodo]benzene to afford a range of iodonium tosylates [3e]. Similarly, some ring-fluorinated phenyltributylstannanes gave with the same reagent the corresponding fluorinated iodonium tosylates under mild conditions, in moderate yield [104]. This method was more efficient and versatile in comparison with another one involving treatment of (dicyano)iodonium triflate with aryltributylstannanes for the preparation of symmetrical iodonium salts [105].

Tetraphenylstannane was the reagent of choice for the conversion of two chiral precursors, i.e. 2-(diacetoxyiodo)- and 2,2'-bis(diacetoxyiodo)-1,1'-binaphthyls, into chiral iodonium salts (Scheme 35) [106].



Scheme 35

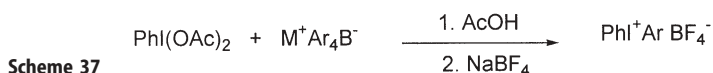


Reaction of some β -triflyloxy-vinyl(phenyl)iodonium triflates with aryllithiums can lead to the synthesis of diaryliodonium salts in a manner analogous to

the reaction of β -(dichloroiodo)chloroethylene. These methods involve the intermediacy of a diaryl(vinyl)iodane (Scheme 36) [107].

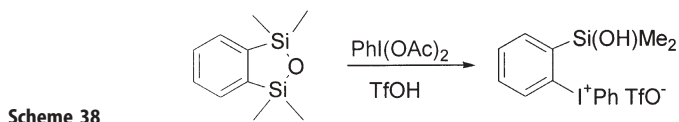


Aryl and heteroaryl (furyl, thienyl) boronic acids are especially suitable for the preparation of their iodonium salts, having the added advantage of better yields and lack of toxicity [108]. Tetraarylborates (sodium or potassium) reacted with (diacetoxyiodo)arenes in acetic acid to afford diaryliodonium salts in excellent yield (Scheme 37). It appears that triarylboranes formed upon reaction of the borates with acetic acid serve actually as the real arylating agents [109].

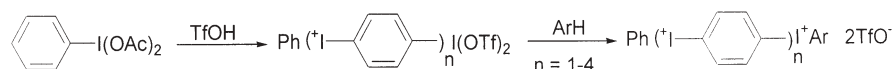


The electrosynthesis of diaryliodonium salts has been recently reported, based upon electrochemical oxidation of ArI in $\text{Ac}_2\text{O}/\text{AcOH}/\text{H}_2\text{SO}_4$ in presence of an arene [110].

Special iodonium salts. A range of *o*-trimethylsilyl-phenyliodonioarenes [111] and heteroarenes [112] as well as some similar *vic*-compounds coming from norbornadiene [113] and *o*-carborane [114] have been obtained from the corresponding bis trimethylsilyl precursors upon reaction with one equivalent of (diacetoxyiodo)benzene. These compounds are useful for their facile in situ conversion into benzyne-type intermediates; for benzyne itself the whole procedure is available in *Organic Syntheses* [115]. A recent improvement involved the synthesis of a new benzyne precursor illustrated in Scheme 38 [116].



The self-condensation of iodosylbenzene was the first reported synthesis of a diaryliodonium salt back in 1892. The mechanism of the reaction was delineated only recently. This approach served for the synthesis of *p*-(phenylene)bis-(aryliodonium) salts [47], as well as some oligomers from (diacetoxyiodo)benzene and triflic acid [117], followed by coupling with an arene (Scheme 39). Under suitable conditions the same reaction can lead to simple phenyl(aryl)-iodonium triflates [118].



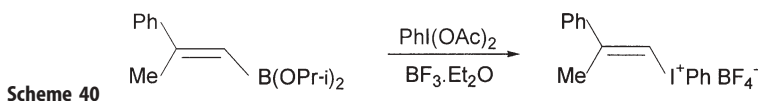
A new type of iodonium salts constitute the conformationally rigid, tetranuclear macrocyclic ring systems dubbed molecular boxes. The relatively simpler tetraaryltetraiodonium salts were obtained from 4,4'-bis(diacetoxyiodo)biphenyl and 4,4'-bis(trimethylsilyl)biphenyl [119]. The iodonium salt derived from 4-(4'-lithiophenyl)pyridine was made using the method of β -(dichloroiodo)chloroethylene and it was used for the construction of hybrid iodonium-platinum (or palladium) cationic tetranuclear macrocyclic squares including some in which the ligand of the metal was a chiral biphosphine [120, 121].

3.1.2

Alkenyl(phenyl)iodonium Salts

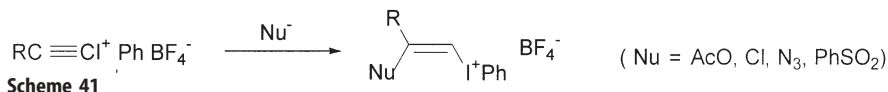
There are two approaches for the preparation of alkenyl(phenyl)iodonium salts: reaction of an activated alkene with an iodine(III) species and addition to a triple bond, either of simple alkynes or of alkynyl(phenyl)iodonium salts.

The newest and perhaps best method of general application in which the double bond already exists is the reaction of alkenylboronic acids or their esters with (diacetoxyiodo)benzene in presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$. Since the precursors are readily available from alkynes in a well defined stereochemistry, the alkenyliodonium salts may be obtained in pure *E*- or *Z*-form without difficulty and in high yield (Scheme 40) [122].

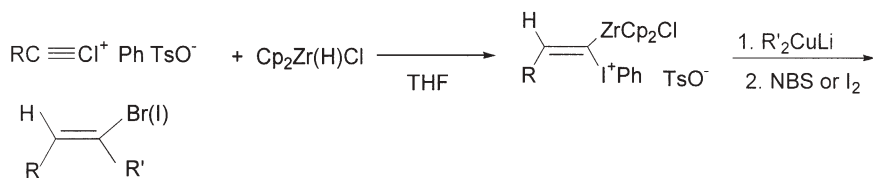


Other similar approaches have used alkenylsilanes and $\text{PhIO}/\text{Et}_3\text{O}^+ \text{BF}_4^-$ and also alkenylstannanes and $\text{PhI}^+ \text{CN TfO}^-$ [123, 124]. The reactions proceed also stereoselectively. The parent ethenyl(phenyl)iodonium triflate as well as several trisubstituted alkenyl members were obtained in this way. In an analogous manner *E*-alkenylzirconium compounds upon reaction with (diacetoxyiodo)benzene afforded *E*-alkenyl(phenyl)iodonium salts stereoselectively [125].

Alkynyl(phenyl)iodonium salts are transformed into their functionalized alkenyl analogs by reactions involving addition of nucleophiles to their triple bond which is a strong Michael acceptor. In most of them the stereochemistry is normally *Z* (Scheme 41). The choice of solvent, e.g. methanol, is crucial in some cases for the exclusive and almost quantitative formation of the *Z*-product [126, 127].

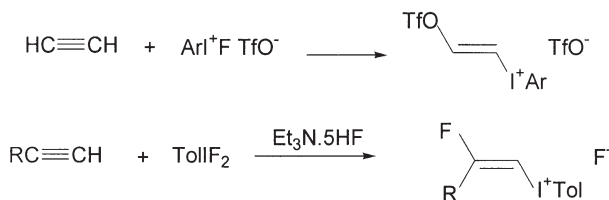


In some instances the iodonium salt is not isolated but may react in situ with nucleophiles, for example upon hydrozirconation of alkynyl(phenyl)iodonium salts with $\text{Cp}_2\text{Zr}(\text{H})\text{Cl}$ (Scheme 42); these salts were used for the stereoselective synthesis of some halogenated alkenes [128].



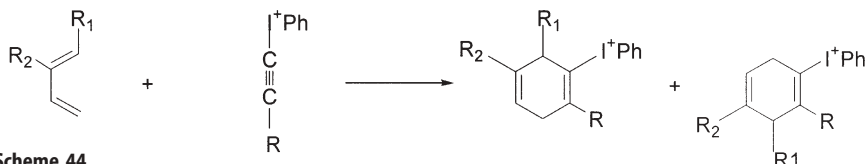
Scheme 42

Electrophilic addition of iodine(III) reagents to the triple bond of alkynes leading to alkenyl(phenyl)iodonium salts is also possible. It has been effected in some alkynes, including acetylene, with $\text{PhI}^+\text{F}^- \text{TfO}^-$ [95] or $\text{PhI}^+\text{OH}^- \text{TfO}^-$ [129] or PhI and XeF_2 in MeSO_3H [130] to afford 2-*E*-triflyloxy-alkenyl(phenyl)iodonium salts. Terminal alkynes reacted with *p*-TolylI F_2 in $\text{Et}_3\text{N}\cdot 5\text{HF}$ to afford similarly β -*E*-fluoroalkenyl(phenyl)iodonium fluorides (Scheme 43) [131].



Scheme 43

More conventional additions to alkynyl(phenyl)iodonium salts which served as dienophiles or dipolarophiles have led to a variety of alkenyl(phenyl)iodonium salts as exemplified in Scheme 44 [132, 133].



Scheme 44

3.1.3

Alkynyl(phenyl)iodonium Salts

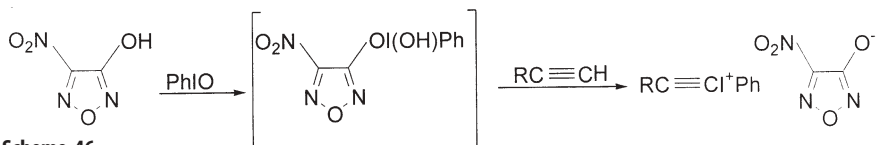
Alkynyl(phenyl)iodonium salts are known in great number and variety coming not only from acetylene itself but also from many alkynes, including various kinds of functionalized acetylenes, as reported in detail in an extensive review article [127]. These salts are best obtained from alkynylsilanes or alkynylstannanes upon reaction with a suitable phenyliodine(III) reagent such as (diacetoxyiodo)benzene and TfOH or Tf_2O [134]. Alkynylstannanes seem to be the substrates of choice and $\text{PhI}^+\text{CN}^- \text{TfO}^-$ (or its equivalent from $\text{PhI}(\text{O}_2\text{CCF}_3)_2$, Me_3SiCN and Me_3SiOTf) the most efficient iodine(III) reagent for the synthesis of a plethora of alkynyliodonium triflates (Scheme 45) [135].



Scheme 45

(X = alkyl, aryl, acyl, SiMe₃, etc)

Alkynylboronates are also suitable substrates when combined with the reagent obtained from PhIO and Tf₂O at 0°C, i.e. PhI(OTf)OI(OTf)Ph [136]. Another approach is the direct reaction of terminal alkynes with 3-hydroxy-4-nitrofurazan and PhIO (Scheme 46) [137].



Scheme 46

Chiral iodonium salts of the general type *p*-RC₆H₄C≡CI⁺Ph X⁻, where R was *S*-2-methylbutyloxy or *S*-2-methylbutyloxycarbonyl and X was TsO or TfO, were prepared from silylated alkynes with either [hydroxy(tosyloxy)iodo]benzene or PhI(OTf)OI(OTf)Ph [138].

Alkynyl(aryl)iodonium salts where aryl was the *o*-carboxyphenyl group were obtained from silylalkynes and *o*-iodosobenzoic acid [139]. It is noted that the first alkynyl iodonium salts were obtained in low yield from terminal alkynes. This approach was perfected recently, so that a range of substrates upon reaction with *p*-MeC₆H₄IO in aqueous HBF₄, with catalysis by HgO, afforded alkynyl (tolyl)iodonium salts [140].

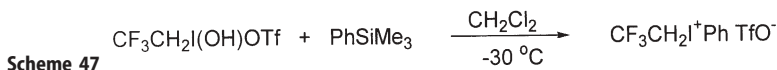
Polymer-bound alkynyl(phenyl)iodonium salts were prepared by refluxing polymer-bound [hydroxy(tosyloxy)iodo]benzene and some alkynes in dry chloroform [141].

3.1.4

Alkyl(phenyl)iodonium Salts

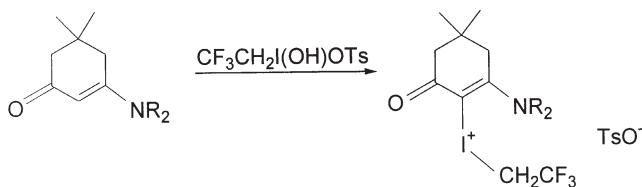
Simple alkyl(phenyl)iodonium salts are not stable. However, when there is in α -position the bulky, electron-withdrawing phenylsulfonyl group they are stabilized, like their precursors, i.e. ArSO₂CH₂I(OOCCF₃)₂. Iodanes of this type were coupled with benzene in presence of CF₃SO₂OTf to afford isolable ArSO₂CH₂I⁺Ph TfO⁻ [142].

A variety of perfluoroalkyl(phenyl)iodonium salts were obtained from precursors such as R_FI(OH)OTf, R_FI(OOCCF₃)₂ and others when coupled with benzene or arenes, as reported in a recent review article [143]. Similarly, a trifluoroethyl group attached to iodine(III) can also be coupled to the phenyl ring upon reaction with PhSiMe₃ as outlined in Scheme 47 [144].



Scheme 47

It is noted that $\text{CF}_3\text{CH}_2\text{I}(\text{O}_2\text{CCF}_3)_2$ reacted also with benzene in presence of the strong acid Tf_2NH to give the salt $\text{CF}_3\text{CH}_2\text{I}^+\text{Ph Tf}_2\text{N}^-$ which is stable in water [145]. Trifluoroethylidonium salts of a different kind were obtained from enamines and $\text{CF}_3\text{CH}_2\text{I}(\text{OH})(\text{OTs})$ (Scheme 48) [146].

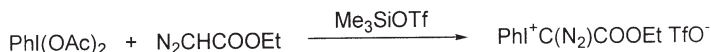


Scheme 48

3.1.5

Miscellaneous Iodonium Salts

Some phenyliodonium salts not belonging to the above types are of special interest because they have been used as reagents, e.g. $\text{PhI}^+\text{CN TfO}^-$ [135]. Another interesting iodonium salt not yet fully explored is the α -phenyliodonio-diazo compound which has been obtained from ethyl diazoacetate and (diacetoxyiodo)benzene in presence of Me_3SiOTf (Scheme 49) [147].



Scheme 49

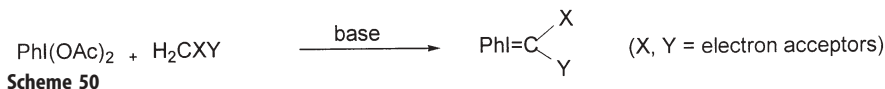
Among iodonium salts not containing an aryl group, the most interesting are those with two cyano and two alkynyl groups. The former was obtained from the reaction between Me_3SiCN and TfOIO leading to $(\text{CN})_2\text{I}^+\text{TfO}^-$, as already mentioned [105]. The latter, formed similarly from trimethylsilylalkynes and TfOIO , were of the general type $(\text{RC}\equiv\text{C})_2\text{I}^+\text{TfO}^-$, where $\text{R} = i\text{-Pr}, t\text{-Bu}$ or silyl [105, 148].

It is noted that although not stable, some purely aliphatic dimethyliodonium salts have been known, e.g. $\text{CH}_3\text{I}^+\text{CF}_3 \text{AsF}_6^-$, $\text{MeI}^+\text{CH}_2\text{I}^+\text{Me} 2\text{AsF}_6^-$ obtained by methylation of the corresponding iodides (CF_3I and CH_2I_2) using $\text{MeOSO}^+\text{AsF}_6^-$ in liquid SO_2 [149]. Also, the $(\text{CF}_3)_2\text{I}^+$ ion has been formed from CF_3IF_2 and $\text{Cd}(\text{CF}_3)_2$; it may be added that CF_3IF_2 with $\text{Hg}(\text{CF}_3)_2$ afforded the anion $[(\text{CF}_3)_2\text{IF}_2]^-$ [150].

3.2

Phenyliodonium Ylides

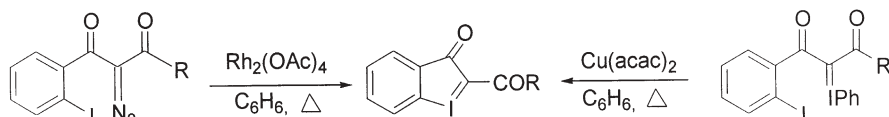
The standard method for the preparation of many phenyliodonium ylides is reaction of compounds having an active methylene group with an iodine(III) species, usually in aqueous alkali, to give iodonium ylides (Scheme 50) [151].



Scheme 50

This method has been used with slight variations for the preparation of a large number of phenyliodonium ylides which can serve as carbene or carbenoid precursors, especially those of the general formula $\text{PhI}=\text{C}(\text{COR})_2$ and $\text{PhI}=\text{C}(\text{SO}_2\text{R})_2$ [3f]. Also, more elaborate ylides coming from functionalized β -lactams [152, 153] and β -ketoesters [154] have been successfully obtained. When the active methylene compound is fairly acidic there is no need for alkaline conditions. Thus, $\text{PhI}=\text{C}(\text{COOEt})\text{SO}_2\text{C}_4\text{F}_9$ was prepared from (diacetoxyiodo)benzene and $\text{EtOOCCH}_2\text{SO}_2\text{C}_4\text{F}_9$ in CH_2Cl_2 at room temperature [155].

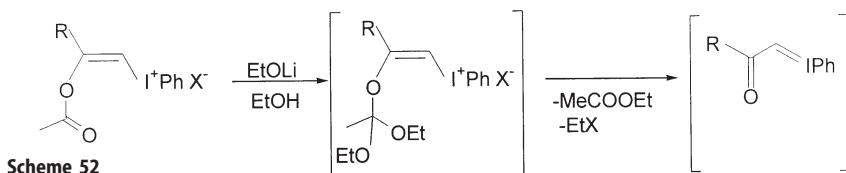
An alternative approach, suitable mainly for some heterocyclic ylides, is generation of an iodoarylated carbene, either from a diazo or a phenyliodonio precursor, which is trapped intramolecularly by iodine (Scheme 51) [156, 157].



Scheme 51

Ylides of the general formula $\text{Ph}_3\text{P}^+\text{C}(\text{R})=\text{I}^-\text{Ph X}^-$, where R is an electron withdrawing group (mainly COMe, COOMe, CN etc) and X is BF_4 , TsO or TfO can be obtained from $\text{Ph}_3\text{P}=\text{CHR}$ and various iodine(III) species [158, 159].

Among some unstable phenyliodonium ylides the most interesting are those with a monocarbonyl carbanionic moiety which are formed from β -acetoxyalkenyl(phenyl)iodonium precursors upon reaction with EtOLi (Scheme 52) [160]. These reagents are useful for the synthesis of α,β -epoxy ketones and 2-acylaziridines.

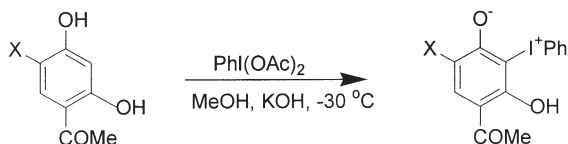


Scheme 52

3.3

Phenyliodonium Dipoles

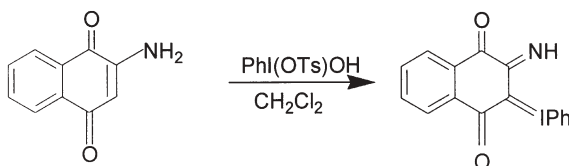
This category is assigned predominantly to 1,4-dipoles in which the negative charge is localized at an oxygen or nitrogen atom. Phenols bearing electron-withdrawing substituents react directly with iodine(III) reagents undergoing aromatic electrophilic substitution without the need of a catalyst. In this way, a series of substituted resorcinols gave the expected dipoles (Scheme 53) [161].



Scheme 53

An analogous reaction took place with some 6-substituted-2-methyl-4-quinolones and [hydroxy(tosyloxy)iodo]benzene [162] and also between 5-nitro-7-hydroxyquinoline and (diacetoxyiodo)benzene [163]. Depending on the solvent or the presence of alkali, either the iodonium salt or the 1,4-dipole could be isolated.

Hydroxylated 1,4-benzoquinones and 1,4-naphthoquinones gave similarly the corresponding dipoles [164]. The amino analogs reacted in the same way to afford first isolable iodonium salts and then the imino dipoles (Scheme 54) [165]. It is noted that the open-chain methyl 2-aminocrotonate gave with [hydroxy(tosyloxy)iodo]benzene only the iodonium salt, i.e. $E\text{-MeC}(\text{NH}_2)=\text{C}(\text{COOMe})\text{I}^+\text{Ph TsO}^-$ [166].

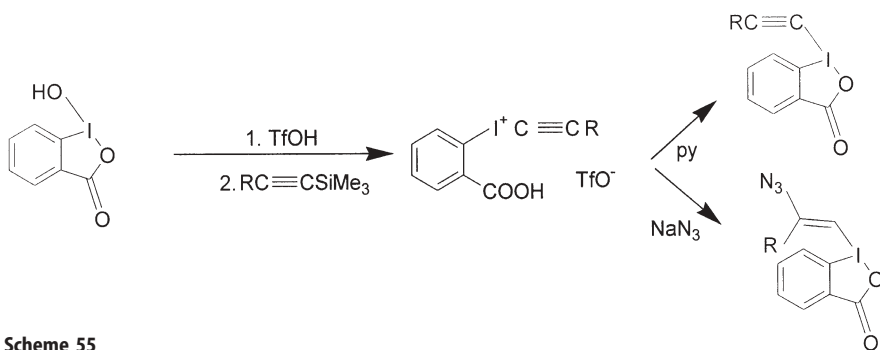


Scheme 54

3.4

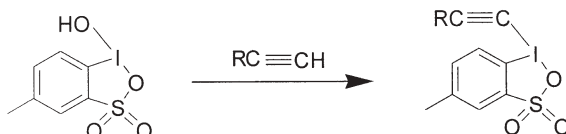
Cyclic Iodanes

A number of 1-hydroxybenziodoxoles and related heterocycles, more efficiently through their triflates, upon reaction with $\text{RC}\equiv\text{CSiMe}_3$ afforded either alkynyl iodonium salts or the corresponding cyclic iodanes, depending on the conditions. Some of these compounds reacted with NaN_3 , and were converted into β -azidoalkenyl derivatives as illustrated in Scheme 55 [127, 167, 168].



Scheme 55

A similar reaction occurred with Me_3SiCN to afford 1-cyanobenziodoxoles or their analogs in which the CO group of benziodoxole was CMe_2 or $\text{C}(\text{CF}_3)_2$ [169, 170]. Another heterocycle coming from an *o*-iodobenzenesulfonic acid gave with terminal alkynes 1-alkynyl derivatives as shown in Scheme 56 [171]. The cyclic structure of these iodanes was established by single-crystal X-ray analysis [76, 169, 170, 171].



Scheme 56

3.5

Iodates of Iodine(I)

There are only two compounds of this type, $(C_6F_5)_2I^- Li^+$ and $[C(CF_3)_3]I^- (Me_2N)_3S^+$ which were obtained from C_6F_5I or $(CF_3)_3CI$ and the appropriate carbanions [172].

4

Iodanes with Three Iodine – Carbon Bonds

Stable non-cyclic iodanes of this kind are rare. One of them is $PhI(CN)_2$, obtained from $PhIO$ and trimethylsilylcyanide at $-78^\circ C$ [173]. Recently, another stable iodane was reported, i. e. $(C_6F_5)_3I$ which was prepared from $C_6F_5IF_2$ and $Bi(C_6F_5)_3$ [174]. The stability of these compounds is due to their relatively strong axial bonds because of higher polar contribution from CN and C_6F_5 groups, whereas their low nucleophilicity prevents them from attacking the highly electrophilic iodine(III). Cyclic iodanes are generally more stable, although they decompose slowly upon standing; 5-aryl-5*H*-dibenziodoles have been obtained from benziodolium ion and aryllithiums [3g].

5

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C–C-Bond Forming Reactions

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The use of hypervalent iodine reagents in carbon-carbon bond forming reactions is summarized with particular emphasis on applications in organic synthesis. The most important recent methods involve the radical decarboxylative alkylation of organic substrates with [bis(acyloxy)iodo]arenes, spirocyclization of *para*- and *ortho*-substituted phenols, the intramolecular oxidative coupling of phenol ethers, and the reactions of iodonium salts and ylides. A significant recent research activity is centered in the area of the transition metal-mediated coupling reactions of the alkenyl-, aryl-, and alkynyliodonium salts.

Keywords. Hypervalent iodine, C–C bond formation, Iodonium, Cross-coupling

1	Introduction	100
2	Radical Decarboxylative Alkylation with [Bis(acyloxy)iodo]arenes	101
3	Oxidative Cyclization of Substituted Phenols and Phenol Ethers . .	103
4	Cyanation with Cyanobenziodoxoles	106
5	Reactions of Stabilized Alkylodonium Salts	107
6	Reactions of Alkenyliodonium Salts	110
6.1	Generation of Alkylidenecarbenes	110
6.2	Alkenylation of C-Nucleophiles	111
6.3	Transition Metal-Mediated Cross-Coupling Reactions	111
7	Reactions of Aryliodonium Salts	115
7.1	Arylation of C-Nucleophiles	116
7.2	Transition Metal-Mediated Reactions	117
7.3	Generation of Benzyne and Its Reactions	118
8	Reactions of Alkynyliodonium Salts	120
8.1	Alkynylation of C-Nucleophiles	120
8.2	Transition Metal-Mediated Reactions	121
8.3	Preparation of Five-Membered Carbocycles and Heterocycles via Intramolecular Carbene Insertion	123

8.3.1	Synthesis of Cyclopentenes	123
8.3.2	Synthesis of Cyclopentenones	125
8.3.3	Synthesis of Oxygen Heterocycles	125
8.3.4	Synthesis of Nitrogen Heterocycles	126
8.4	[4 + 2] Cycloaddition Reactions	128
9	Reactions of Iodonium Ylides	130
10	Conclusion	132
11	References	133

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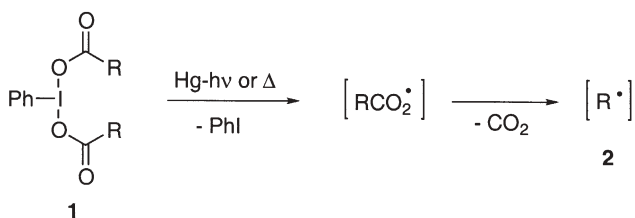
Introduction

Carbon-carbon bond forming reactions represent an important area of practical application of hypervalent iodine reagents. Evaluation of the available literature reveals that the formation of a new C-C bond in these reactions can be achieved by two general pathways. The first type of reactions involves the generation of carbon-centered reactive intermediates, such as free radicals, carbocations, cation-radicals, etc., from the appropriate hypervalent iodine precursors followed by their trapping with an organic substrate. The second general type of reactions proceeds via coupling of carbon ligands in the tricoordinate iodine intermediate, which can be generated by the addition of a carbon nucleophile to an iodonium salt. The first pathway is generally realized in various oxidations of organic substrates with [bis(acyloxy)iodo]arenes, while the second pathway is typical of the reactions of iodonium salts. Several less general approaches to C-C bond formation via the carbenoid reactions of alkynyliodonium salts and iodonium ylides and the cycloaddition reactions are also known.

The purpose of present review is to summarize the application of different classes of iodine(III) compounds in carbon-carbon bond forming reactions. The first two sections of the review (Sects. 2 and 3) discuss the oxidative transformations induced by [bis(acyloxy)iodo]arenes, while Sects. 4 through 9 summarize the reactions of iodonium salts and ylides. A number of previous reviews and books on the chemistry of polyvalent iodine discuss the C-C bond forming reactions [1 - 10]. Most notable is the 1990 review by Moriarty and Vaid devoted to carbon-carbon bond formation via hypervalent iodine oxidation [1]. In particular, this review covers earlier literature on cationic carbocyclizations, allylation of aromatic compounds, coupling of β -dicarbonyl compounds, and some other reactions of hypervalent iodine reagents. In the present review the emphasis is placed on the post 1990s literature.

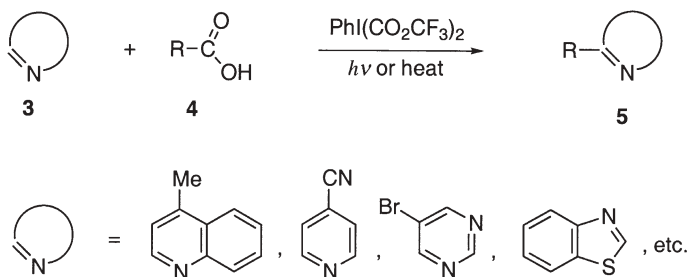
2 Radical Decarboxylative Alkylation with [Bis(acyloxy)iodo]arenes

[Bis(acyloxy)iodo]arenes **1** can serve as precursors to alkyl radicals **2** via decarboxylative radical decomposition initiated by irradiation with a mercury lamp (Hg-h ν) or heating (Scheme 1) [3]. Generated under these conditions alkyl radicals **2** can be effectively trapped with the appropriate organic substrates affording products with a new C-C bond. The starting [bis(acyloxy)iodo]arenes **1** can be prepared in situ from the readily available [bis(trifluoroacetoxy)iodo]benzene or (diacetoxy)iodobenzene and a carboxylic acid.



Scheme 1

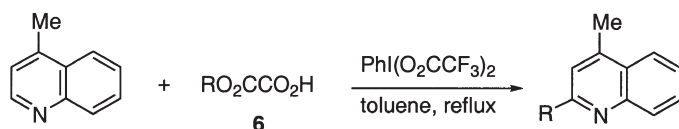
In a convenient experimental procedure, nitrogen heterocycles **3** are alkylated by a mixture of a carboxylic acid **4** and [bis(trifluoroacetoxy)iodo]benzene in boiling benzene or under irradiation in dichloromethane at room temperature (Scheme 2) [11, 12]. A similar procedure has been used for the stereoselective synthesis of C-nucleosides and their analogs via photolysis of the gulonic acid derivatives, (diacetoxy)iodobenzene, and the appropriate heteroaromatic bases [13].



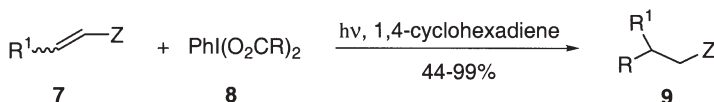
Scheme 2 R = 1-adamantyl, cyclohexyl, 2-PhCH₂CH₂, PhOCH₂, PhC(O), etc.

Further modification of this procedure allows the use of alcohols as the source of alkyl radicals. In this case, alcohols are first converted into the oxalic acid monoalkyl esters **6**, which are used as reagents in the radical alkylation of heteroaromatic bases (Scheme 3) [12, 14].

Similar experimental procedures can be used for the radical alkylation of electron-deficient alkenes **7** (Scheme 4). In this process, a mixture of alkene **7** and [bis(acyloxy)iodo]arenes **8** (prepared from PhI(OAc)₂ and the respective



Scheme 3 R = 1-adamantyl, cyclohexyl, 1-methylcyclohexyl, (-)-menthyl, etc.

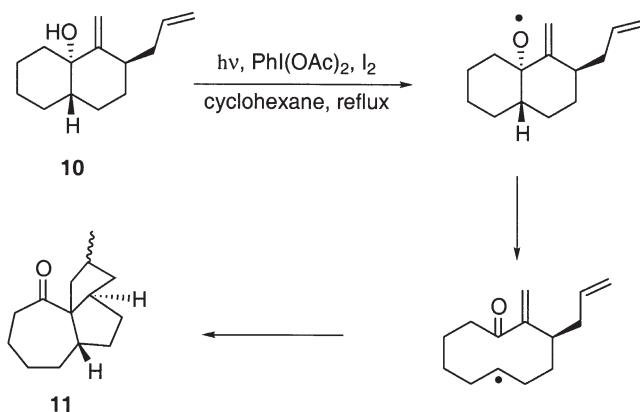


Z = SO₂Ph, SPh, CO₂Me, P(O)(OEt)₂; R¹ = H, Me

Scheme 4 R = 1-adamantyl, cycloalkyl, 2-PhCH₂CH₂, etc.

carboxylic acid or monoalkyl esters of oxalic acid) is irradiated with a high-pressure mercury lamp in dichloromethane in the presence of 1,4-cyclohexadiene to give a reductive addition product **9** [15, 16]. In these reactions, the yields of products (44–99%) depend on the stability and the nucleophilicity of the alkyl radicals (tertiary > secondary > primary) [3].

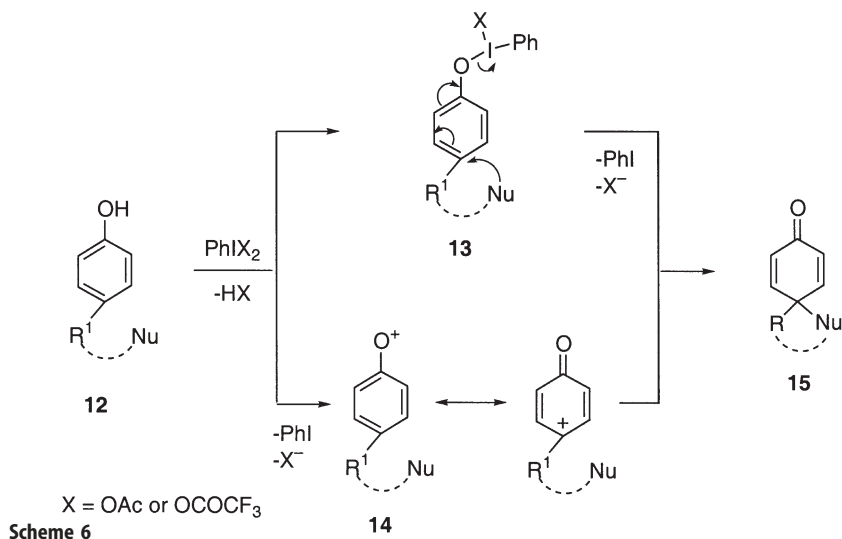
Photolysis of (diacetoxy)iodobenzene with cyclic alcohols in the presence of iodine leads to the generation of the respective alkoxy radical which can sequentially undergo fragmentation and rearrangement leading to the intermediate formation of a C-radical and subsequent cyclization. This methodology has been applied to the preparation of various synthetically interesting medium-sized ketones and lactones [5]. A specific example of such a reaction leading to a new C–C bond formation is shown in Scheme 5. The treatment of bicyclic dienol **10** with (diacetoxy)iodobenzene/I₂ in degassed cyclohexane under irradiation and reflux results in a cascade radical fragmentation-transannulation-cyclization sequence leading to ketone **11** in 81% yield [17].



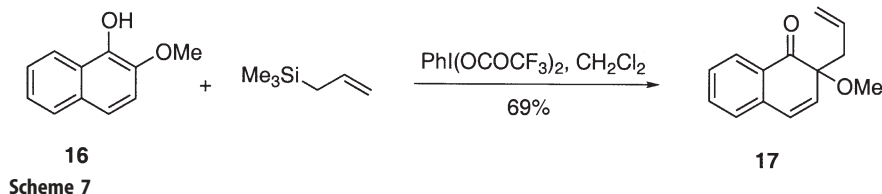
Scheme 5

3 Oxidative Cyclization of Substituted Phenols and Phenol Ethers

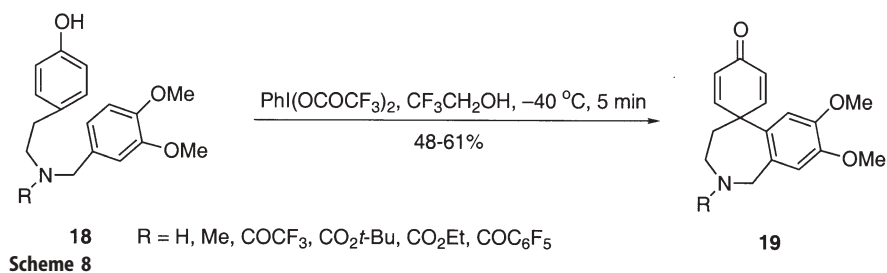
Intramolecular oxidative cyclizations in the appropriately substituted phenols and phenol ethers provide a powerful tool for the construction of various practically important polycyclic systems. Especially interesting and synthetically useful is the oxidation of the *p*-substituted phenols **12** with [bis(acyloxy)iodo]-arenes in the presence of an appropriate external or internal nucleophile (Nu) leading to the respective spiro dienones **15** according to Scheme 6. It is assumed that this reaction proceeds via concerted addition-elimination in the intermediate product **13**, or via phenoxenium ions **14** [18–21]. The recently reported lack of chirality induction in the phenolic oxidation in the presence of dibenzoyltartaric acid supports the hypothesis that of mechanism proceeding via phenoxenium ions **14** [18]. The *o*-substituted phenols can be oxidized similarly with the formation of the respective 2,4-cyclohexadienone derivatives.



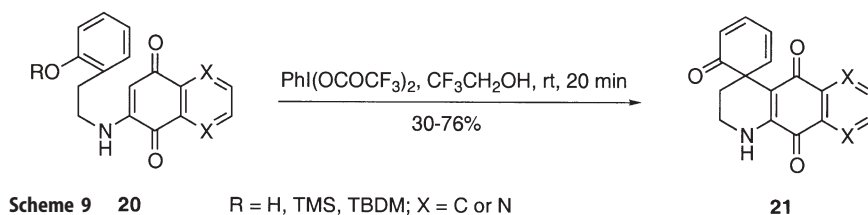
Various nucleophiles, such as alcohols, fluoride ion, amides, allylsilane, and electron-rich aromatic rings, have been successfully used in this reaction in either an inter- or intra-molecular mode. A recent example of a new C–C bond formation in this reaction in the inter-molecular mode includes the preparation of derivatives **17** by the oxidation of 2-alkoxynaphthols **16** in the presence of an allylsilane or a silyl enol ether as a carbon-based nucleophile (Scheme 7) [22].



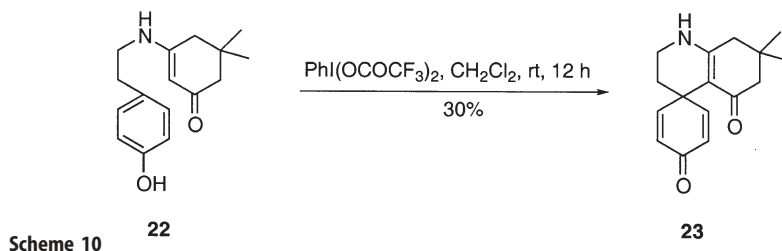
The phenolic oxidation in the intra-molecular mode has been widely exploited as a synthetic tool for the construction of a spirodienone fragment. Kita and coworkers applied the oxidative coupling of various phenolic derivatives towards the synthesis of several pharmacologically interesting natural products [21, 23, 24]. In a recent example, spirodienone compounds **19**, which are intermediates for the synthesis of an amaryllidaceae alkaloid, (+)-maritidine, were selectively obtained by the reaction of **18** and [bis(trifluoroacetoxy)iodo]benzene (Scheme 8) [24].



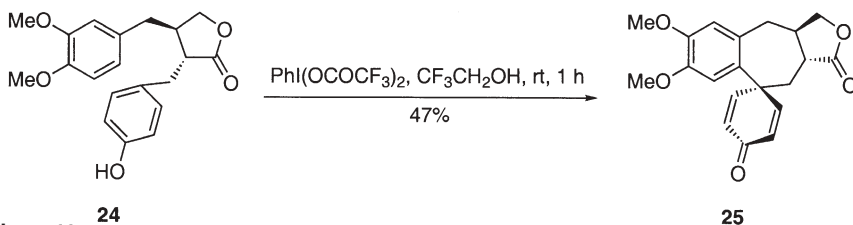
A similar oxidation of the phenol derivatives **20** bearing aminoquinones at the *ortho* positions affords the respective azacarbo-cyclic spirodienones **21** (Scheme 9) [23].



Likewise, the oxidation of phenolic enaminone derivatives **22** with [bis(trifluoroacetoxy)iodo]benzene under mild conditions leads to spirocyclohexadienone **23** (Scheme 10) [25].

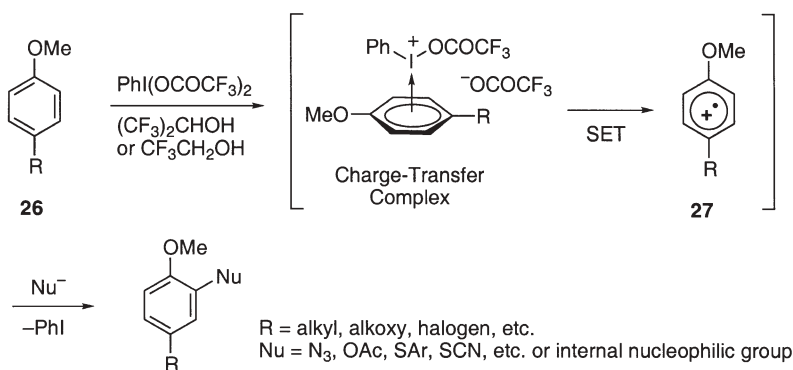


Treatment of dibenzylbutyrolactone **24** with [bis(trifluoroacetoxy)iodo]benzene in trifluoroethanol for one hour gives as the major product spirodienone **25**, which has been postulated as an intermediate in the biosynthesis of tetrahydrodibenzocyclooctene lignans [26] (Scheme 11).



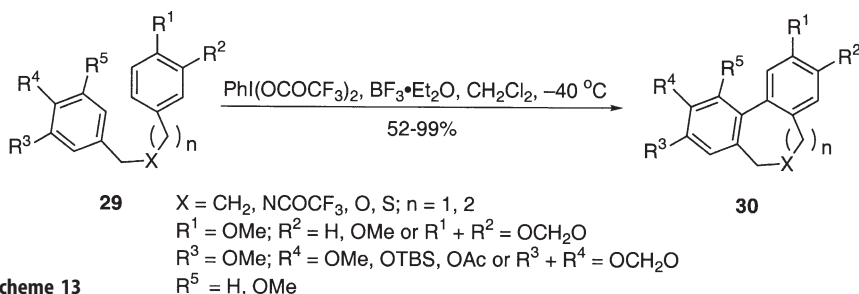
Scheme 11

The oxidation of phenol ethers **26** by [bis(trifluoroacetoxy)iodo]benzene in the presence of external or internal nucleophiles affords products of nucleophilic substitution **28** via the intermediate formation of the cation radical intermediate **27** according to Scheme 12 [21, 27–30].



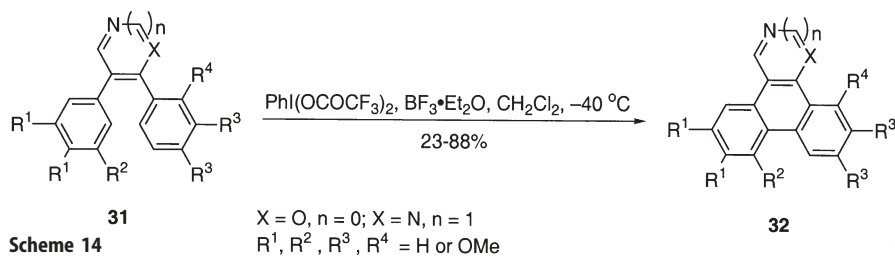
Scheme 12

In the intermolecular mode, this reaction has been utilized for the preparation of products **28** from various nucleophiles, including C-nucleophiles (e.g. β -dicarbonyl compounds). A similar reaction in the intramolecular mode provides a powerful synthetic tool for the preparation of various polycyclic compounds via oxidative biaryl coupling [21, 27–30]. Several examples of these C–C bond forming reactions are shown in Schemes 13–15. Specifically, various dibenzoheterocyclic compounds **30** have been prepared by the oxidation of phenol ether derivatives **29** with [bis(trifluoroacetoxy)iodo]benzene in the presence of BF_3 -etherate in dichloromethane (Scheme 13) [27–29].

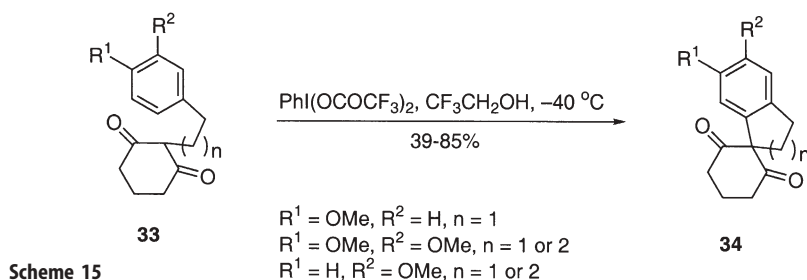


Scheme 13

Under similar conditions, the phenanthro-fused thiazoles, isoxazoles and pyrimidines **32** (Scheme 14) can be prepared by oxidative coupling of the respective phenol ethers **31** [31, 32].

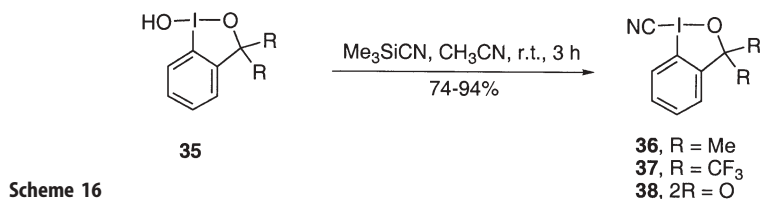


A novel hypervalent iodine-induced direct intramolecular cyclization of α -(aryl)alkyl- β -dicarbonyl compounds **33** has been recently reported (Scheme 15) [30]. Both *meta*- and *para*-substituted phenol ether derivatives containing acyclic or cyclic 1,3-dicarbonyl moieties at the side chain undergo this reaction in a facile manner affording spirobenzannulated compounds **34** that are of biological importance.



4 Cyanation with Cyanobenziodoxoles

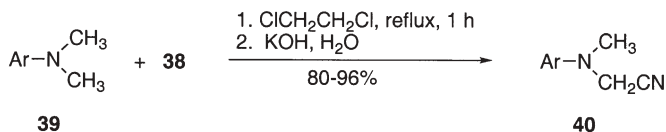
The five-membered hypervalent iodine heterocycles, benziodoxoles, are commonly used as convenient radical precursors [3, 33]. The main advantage of benziodoxoles over the non-cyclic hypervalent iodine reagents is the higher thermal stability allowing the preparation of otherwise unstable derivatives with I-Br, I-OOR, I-N₃, and I-CN bonds. The stable cyanobenziodoxoles **36**–**38** are prepared in one step by the reaction of cyanotrimethylsilane with the respective hydroxybenziodoxoles **35** (Scheme 16) [34, 35], or from acetoxybenziodoxole



Scheme 16

and cyanotrimethylsilane [36]. The structures of products **37** and **38** were unambiguously established by single-crystal X-ray analysis [35, 36].

Cyanobenziodoxoles **36–38** are used as efficient cyanating reagents toward *N,N*-dialkylarylamines. In a typical example, reagent **38** reacts with *N,N*-dimethylanilines **39** in 1,2-dichloroethane at reflux to afford the respective *N*-cyanomethyl-*N*-methylanilines **40** in good yield (Scheme 17) [34].



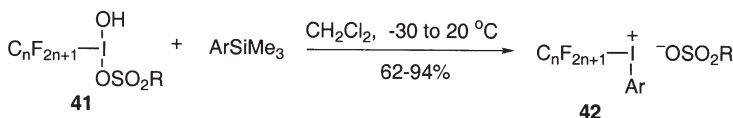
Scheme 17

Ar = Ph, 4-BrC₆H₄, 4-MeC₆H₄, 1-naphthyl, etc.

In a recent paper, cyanobenziodoxole **38** was applied to the synthesis of *N*-cyanomethyl-*N*-cyclopropylamine, which is an important metabolite of the cyclopropylamine derived drugs [37].

5 Reactions of Stabilized Alkylidonium Salts

Iodonium salts with one or two non-substituted aliphatic alkyl groups generally lack stability. The presence of electron-withdrawing substituents in the alkyl group of the iodonium salt has a pronounced stabilizing effect. The most stable and important derivatives of this type are fluoroalkyl(aryl)iodonium salts. The preparation of fluoroalkyl(aryl)iodonium salts and their application as electrophilic fluoroalkylating reagents was reviewed by Umemoto [8]. The triflate salts, PhI(C_nF_{2n+1})OTf, originally were synthesized by the reaction of [bis(trifluoroacetoxy)iodo]perfluoroalkanes with benzene in the presence of triflic acid [8]. A recent and more general method for the preparation of various perfluoroalkyl(aryl)iodonium sulfonates **42** involves the reaction of [hydroxy(sulfonyloxy)iodo]perfluoroalkanes **41** with arylsilanes under Lewis acid catalysis (Scheme 18) [38].

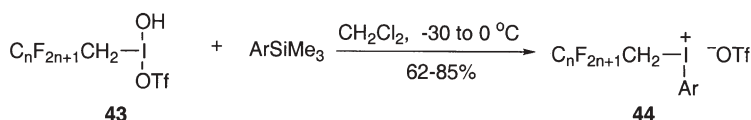


R = *p*-Tol, CH₃, CF₃; n = 4, 6

Scheme 18 Ar = Ph, 4-MeC₆H₄, 4-MeOC₆H₄, 2-MeC₆H₄, 4-Me₃SiC₆H₄

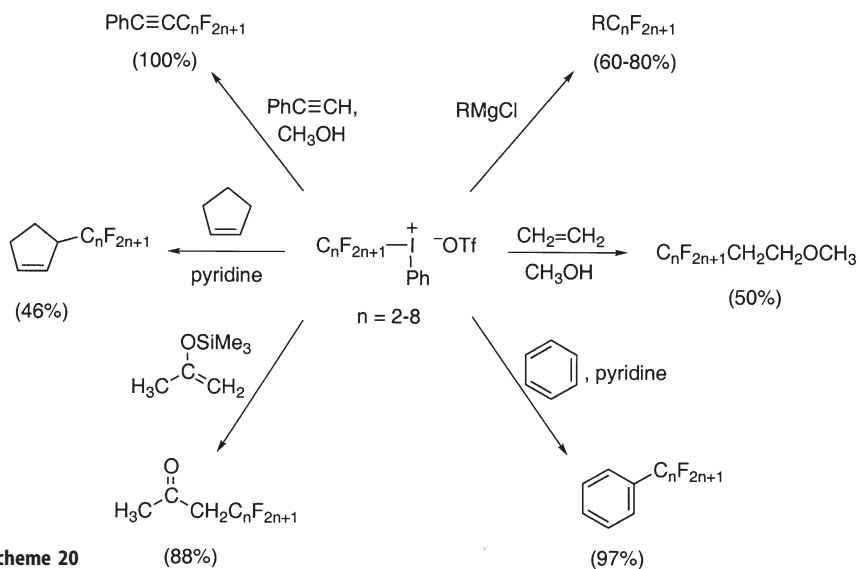
In a similar manner, 1*H*,1*H*-perfluoroalkyl(aryl)iodonium triflates **44** are best prepared by the reaction of triflates **43** with trimethylsilylarenes under mild conditions (Scheme 19) [39].

Perfluoroalkyl(phenyl)iodonium sulfonates **42** (also known as FITS reagents), as well as 1*H*,1*H*-perfluoroalkyl(aryl)iodonium triflates **44**, have found practical application as electrophilic fluoroalkylating reagents toward a

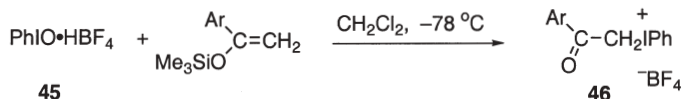


Scheme 19 $n = 1, 2$; Ar = Ph, 4-MeC₆H₄, 2-MeC₆H₄, 4-Me₃SiC₆H₄, 4-MeOC₆H₄

variety of organic substrates, such as carbanions, alkenes, alkynes, silyl enol ethers, and arenes [8]. Several specific examples of these reactions are shown in Scheme 20.

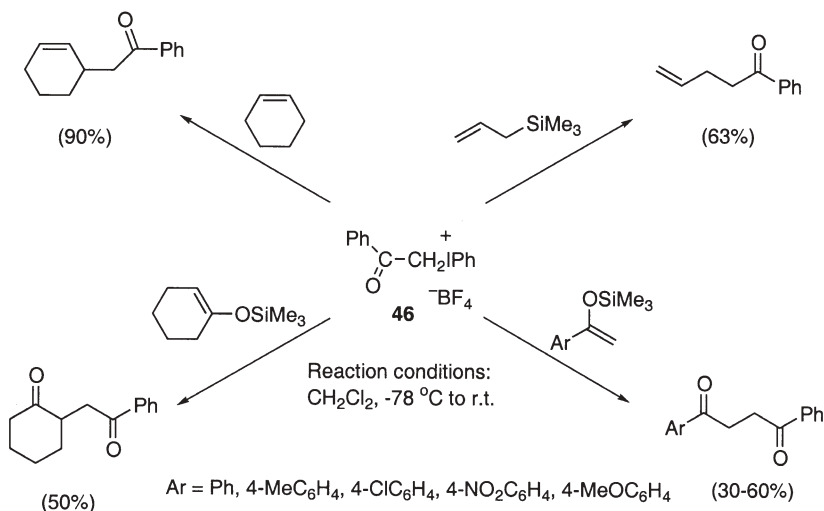


The relatively unstable β -oxoalkyl(aryl)iodonium salts **46** can be generated by a low temperature reaction of silyl enol ethers with reagent **45** (Scheme 21) [40].



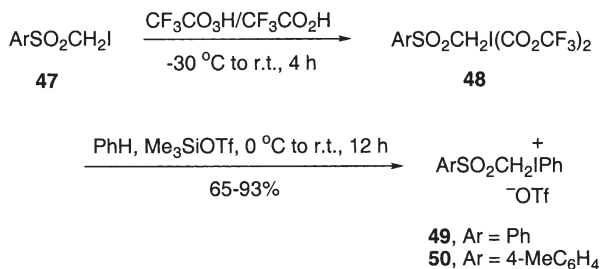
Scheme 21 Ar = Ph, 4-MeC₆H₄, 4-ClC₆H₄, 4-NO₂C₆H₄, 4-MeOC₆H₄

Iodonium salts **46** have been proposed as the reactive intermediates in several synthetically useful carbon-carbon bond forming reactions [1, 40]. Reactions of adducts **46** with various silyl enol ethers selectively afford 1,4-diones, while the reactions with alkenes lead to the products of alkylation at the allylic position (Scheme 22) [40].



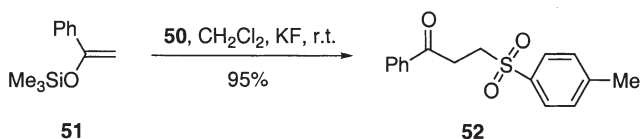
Scheme 22

The stable (arylsulfonylmethyl)iodonium salts **49** and **50** can be conveniently prepared in two steps starting from the readily available iodomethyl sulfones **47** (Scheme 23) [41]. Iodonium salts **49** and **50** are not moisture sensitive, can be purified by crystallization from acetonitrile, and can be stored for several months in a refrigerator. The structure of iodonium triflate **50** was unambiguously established by a single crystal X-ray analysis [41].



Scheme 23

Iodonium salts **49** and **50** are efficient electrophilic alkylating reagents towards a variety of organic nucleophiles, including silyl enol ethers. The reaction with silyl enol ether **51** proceeds under mild conditions and selectively affords the appropriate product of alkylation **52** along with iodobenzene as the by-product (Scheme 24) [41].



Scheme 24

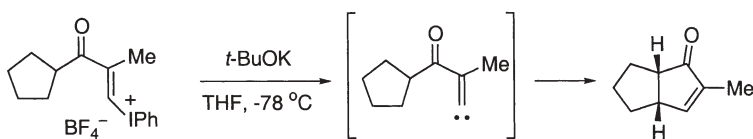
6 Reactions of Alkenyliodonium Salts

Alkenyl(phenyl)iodonium salts have attracted a significant interest recently as stable and readily available powerful alkenylating reagents. Several convenient, general procedures for the stereoselective synthesis of alkenyliodonium salts from silylated or stannylated alkenes and the appropriate hypervalent iodine reagents are known [5]. The chemistry of alkenyliodonium salts has been extensively covered in several recent reviews [42–45].

Numerous reactions of alkenyl(phenyl)iodonium salts leading to the formation of new C–C bond have been reported in the literature. The most important and synthetically useful reactions include the generation and subsequent cyclization of alkyldenecarbenes, alkenylation of carbon substrates via nucleophilic vinylic substitution, and transition metal-mediated coupling reactions.

6.1 Generation of Alkyldenecarbenes

Reactions of alkenyliodonium salts with strong bases may lead to the generation of an alkyldenecarbene via a base-induced α -elimination [42, 46, 47]. Alkyldenecarbenes generated by this method can undergo a 1,5-carbon-hydrogen insertion, providing a useful route for the construction of substituted cyclopentenes [46, 48, 49]. In a typical example, reaction of alkenyliodonium tetrafluoroborate **53** with potassium *tert*-butoxide affords bicyclic product **54** in high yield (Scheme 25) [46].



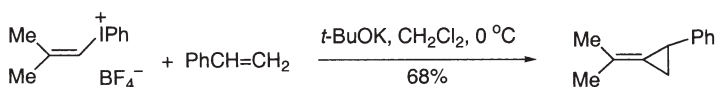
Scheme 25 **53**

54 (61%)

In some cases, such a cyclization is accompanied by alkyne formation due to 1,2-migration of a substituent in the intermediate alkyldenecarbene [46, 48, 49].

The alkyldenecarbenes generated via base-induced α -elimination can also be trapped by cycloaddition with external alkenes. For example, the treatment of alkenyliodonium salt **55** with a strong base in the presence of excess styrene gives methylenecyclopropane **56** in good yield (Scheme 26) [47].

The addition to *cis*- and *trans*-alkenes under these conditions is stereospecific with retention of the alkene geometry, implying that the intermediate alkyldenecarbene has a singlet electronic state [47].



Scheme 26 **55**

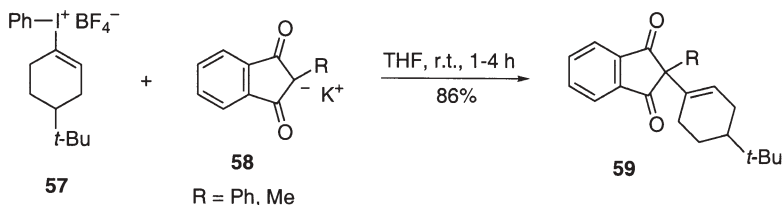
56

6.2

Alkenylation of C-Nucleophiles

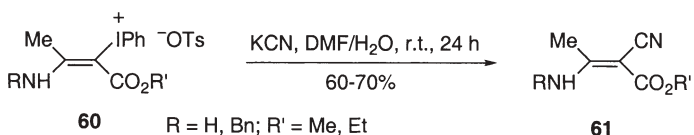
Alkenyl(phenyl)iodonium salts are highly reactive in vinylic nucleophilic substitution reactions because of the excellent leaving group ability of the phenyliodonium moiety. Only a few examples of non-catalytic alkenylation of carbon nucleophiles are known [50, 51]. In most cases these reactions proceed with predominant retention of configuration via the addition-elimination mechanism or ligand coupling on the iodine [42, 50].

Enolate anions derived from various 1,3-dicarbonyl compounds can be vinylylated with cyclohexenyl- and cyclopentenyl- iodonium salts (Scheme 27) [50]. The vinylation of enolate anions **58** in these reactions is frequently accompanied by the formation of the phenylated dicarbonyl compounds; however, the selectivity of these vinylation reactions can be improved by using alkenyl(*p*-methoxyphenyl)-iodonium salts instead of **57**.



Scheme 27

Iodonium salts **60** react with cyanide anion affording the cyano derivatives of crotonic acid **61** as single isomers retaining the initial configuration of the phenyliodonium tosylate (Scheme 28) [51].

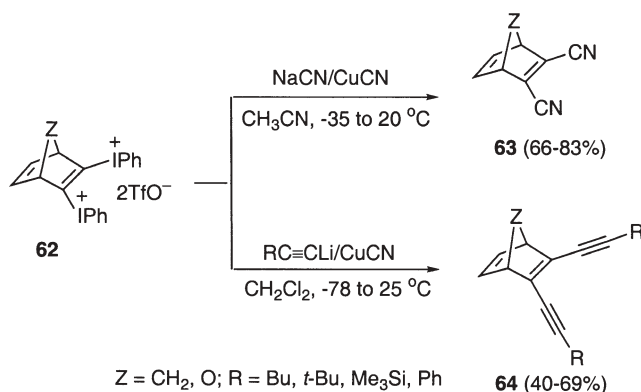


Scheme 28

6.3

Transition Metal-Mediated Cross-Coupling Reactions

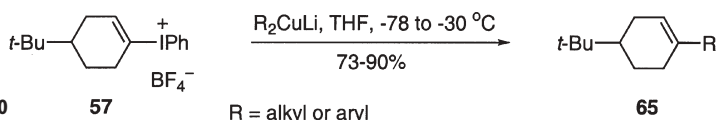
The selectivity of the alkenylation reactions and the yields of products can be dramatically improved by carrying out the reaction of alkenyliodonium salts with carbon nucleophiles in the presence of transition metal compounds in stoichiometric or catalytic amounts. Thus, the reactions of bicycloalkenyldiiodonium salts **62** with cyanide anion or with alkynyllithium in the absence of transition metals are non selective and lead to a wide spectrum of products, while the same reactions in the presence of the equimolecular amount of copper(I) cyanide afford the respective products of vinylic nucleophilic substitution in good yields (Scheme 29) [52, 53].



Scheme 29

Z = CH₂, O; R = Bu, *t*-Bu, Me₃Si, Ph**63** (66-83%)
64 (40-69%)

Likewise, the reaction of iodonium salt **57** with lithium organocuprate reagents affords products of coupling **65** in good yields (Scheme 30) [54].



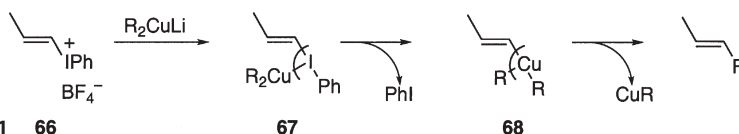
Scheme 30

57

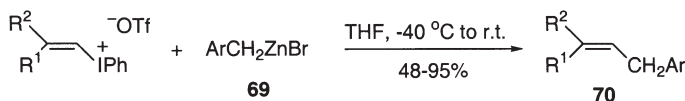
R = alkyl or aryl

65

Copper(I) mediated reactions of alkenyliodonium salts with nucleophiles proceed with complete retention of configuration, which is probably explained by the mechanism involving oxidative addition of cuprates, ligand coupling at the iodine center of **67**, and then ligand coupling at the copper(III) of **68** (Scheme 31) [42, 54].

Scheme 31 **66****67****68**

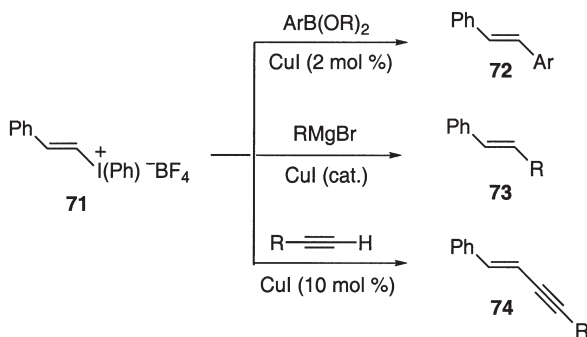
Organozinc reagents **69** can also be alkenylated with alkenyl(phenyl)iodonium salts affording the respective cross-coupling products **70** as single stereoisomers in excellent yields under very mild conditions (Scheme 32) [55].



Scheme 32

R¹, R² = alkyl or Ph; Ar = 2,6-Cl₂C₆H₃ or 3-CNC₆H₄

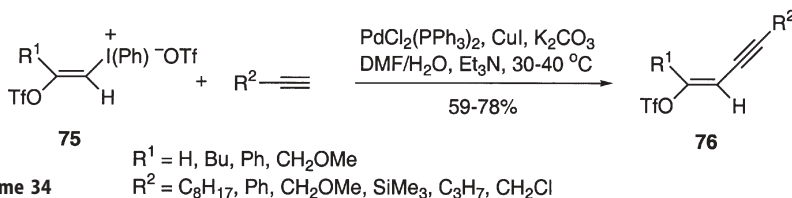
Alkenyliodonium salts can serve as highly reactive substrates in various transition metal-catalyzed reactions. In the presence of a copper(I) catalyst iodo-



Scheme 33

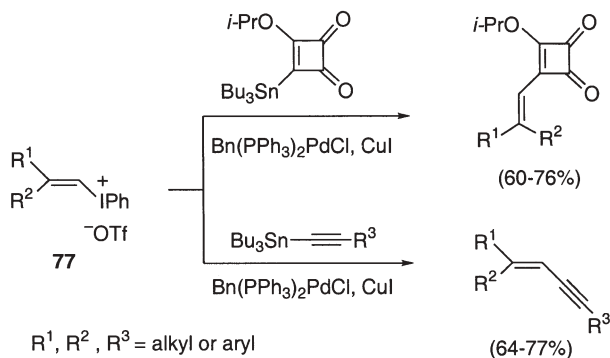
ium salt **71** selectively reacts with organoborates [56], Grignard reagents [57], and terminal alkynes [58] to afford the respective cross-coupling products **72-74** in high yields (Scheme 33).

Even higher selectivity is achieved in the palladium(II)/copper(I)-catalyzed cross-coupling reactions. Conjugated enynes **76** can be synthesized with high stereoselectivity by the reaction of alkenyliodonium triflates **75** with terminal alkynes in the presence of catalytic amounts of dichloro(triphenylphosphine)palladium(II) and CuI in aqueous medium (Scheme 34) [59].



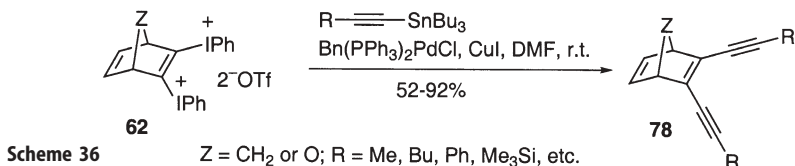
Scheme 34

The palladium/copper-cocatalyzed coupling of the readily available trisubstituted alkenyl(phenyl)iodonium triflates **77** with alkynyl- and alkenylstannanes proceeds under exceedingly mild conditions with retention of geometry of the alkenyl ligand of the iodonium salt (Scheme 35) [60].

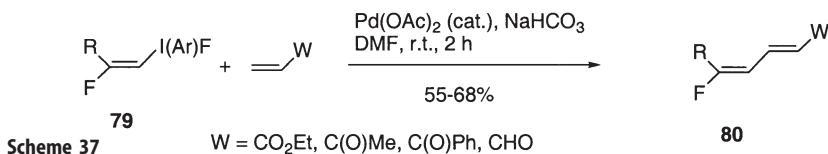


Scheme 35

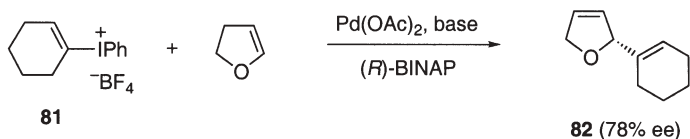
A similar procedure was used for the preparation of several bicyclic enediynes **78** from bis-iodonium salts **62** and alkynylstannanes (Scheme 36) [61]. This coupling reaction was recently utilized in the synthesis of novel dinuclear complexes with a photochromic bridge [62].



Alkenyliodonium salts can be used as highly reactive substrates for Heck-type olefination and similar palladium-catalyzed cross-coupling reactions [63–65]. In a recent example, a series of dienes **80** were stereo- and regioselectively prepared by a palladium-catalyzed Heck-type reaction of alkenyliodonium salts **79** with α,β -unsaturated carbonyl compounds (Scheme 37) [64].

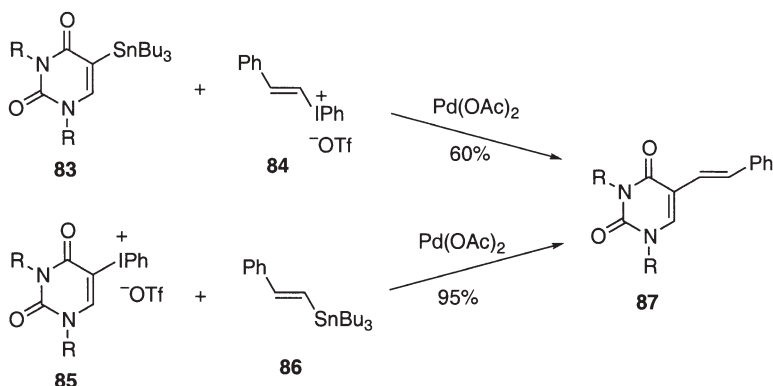


A similar procedure was employed in the asymmetric Heck-type coupling of iodonium salt **81** with 2,3-dihydrofuran (Scheme 38) [65]. When carried out in the presence of the chiral bidentate ligand (*R*)-BINAP, this reaction afforded optically active (up to 78% ee) coupling product **82** in moderate yield.



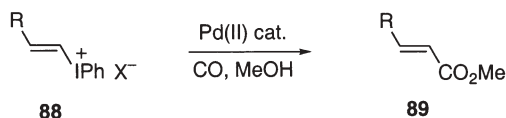
Scheme 38 (*R*)-BINAP = (*R*)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl

Organotin compounds can be effectively used as substrates in the palladium-catalyzed cross-coupling reactions of alkenyliodonium salts [66, 67]. For example, the reaction of alkenyliodonium triflate **84** with 5-stannylated uracil **83** proceeds smoothly to provide cross-coupled products **87** in moderate yield. The same products **87** are obtained in almost quantitative yield in the palladium-catalyzed cross-coupling of uracil iodonium triflate **85** and vinyltin **86** (Scheme 39) [67].



Scheme 39

The palladium-catalyzed carbonylation reaction of alkenyliodonium salts in the presence of alcohols proceeds at room temperature under one atmosphere of carbon monoxide to afford esters **89** in good yields (Scheme 40) [68].



Scheme 40

It is assumed that the mechanism of the palladium-catalyzed cross-coupling reactions of iodonium salts involves the initial oxidative addition step, followed by ligand coupling at the iodine and then at the palladium centers analogously to the mechanism shown in Scheme 31 [63, 66].

7 Reactions of Aryliodonium Salts

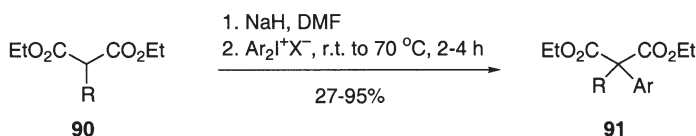
Aryl-, as well as heteroaryliodonium salts, belong to the most common, stable, and well investigated class of polyvalent iodine compounds. The preparation and chemistry of aryliodonium salts was extensively covered in several reviews [5, 7, 9, 10]. Diaryliodonium salts have found synthetic application as arylating reagents in reactions with various organic substrates.

Several reactions of aryliodonium salts leading to the formation of new C–C bond are known. The most important and synthetically useful reactions include the direct arylation of carbon nucleophiles, the transition metal mediated cross-coupling reactions, and the reactions involving the generation and trapping of the benzyne intermediates.

7.1

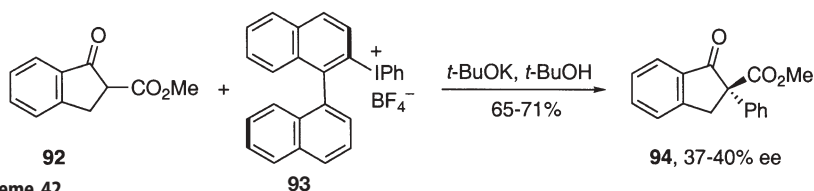
Arylation of C-Nucleophiles

Compounds containing an active methylene group, or the respective carbanions formed in situ, react smoothly with diaryliodonium salts to yield α -arylated products [1]. A recent example of arylation of carbanions under polar, non-catalytic conditions is represented by the reaction of diaryliodonium salts with malonates **90** (Scheme 41) [69].



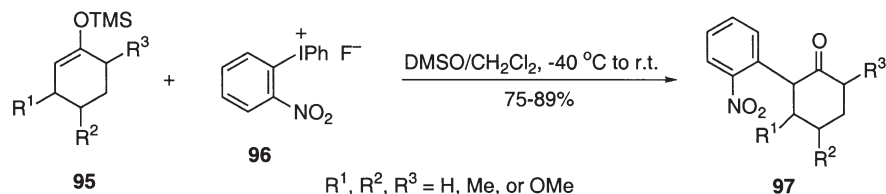
Scheme 41 R = H, CH₃, CH₂CH=CH₂; Ar = Ph, 4-MeC₆H₄; X = BF₄, OTf

Asymmetric phenylation of carbanions with chiral iodonium salts has recently been reported [70]. The chiral diiodonium salt **93** selectively reacts with potassium enolate of 1-oxo-2-indancarboxylate **92** to give the α -phenylated indanone **94** with moderate enantioselectivity (Scheme 42).



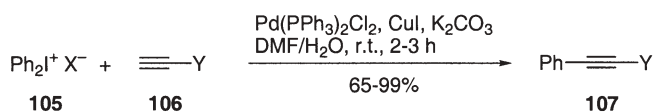
Scheme 42

Diaryliodonium fluorides can be used as efficient reagents for the arylation of silyl enol ethers [71, 72]. The reaction of silyl enol ethers **95** with *o*-nitrophenyliodonium fluoride **96** results in a regioselective arylation yielding arylketones **97** in good yields (Scheme 43) [72]. This arylation has been applied in a new, regiocontrolled synthesis of carbocycle-fused indoles [72].



Scheme 43

Palladium salts and complexes are efficient catalysts in the cross-coupling reaction of diaryliodonium salts with uracil nucleosides [67], organoboron compounds [79–81], organostannanes [82–84], silanes [85, 86], organolead triacetates [87], organobismuth(V) derivatives [88], organozirconium compounds [89], carbon monoxide [56, 90], allylic alcohols [91], functionalized allenes [92], β -substituted α,β -enones [93], Grignard reagents [94], 2,3-dihydrofuran [95], alkenes [96–98], and terminal alkynes [99–102]. A recent example of the synthetic application of the palladium-catalyzed coupling is illustrated by the reaction of diaryliodonium sulfonates **105** with enynes or electron-deficient alkynes **106** affording aryl alkynes **107** in good yields in a convenient single-pot procedure (Scheme 46) [102].

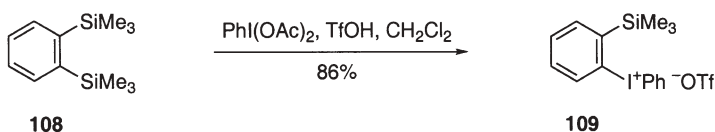


Scheme 46
 X = OTs or OTf
 Y = CO₂Et, CPh, CO-cyclohexyl, CO-adamantyl, MeC=CH₂

Cross-coupling reactions of iodonium salts with terminal alkynes or organostannanes can also be effectively catalyzed by CuI, MnCl₂·4H₂O, or Ni(acac)₂ [56, 58, 103, 104].

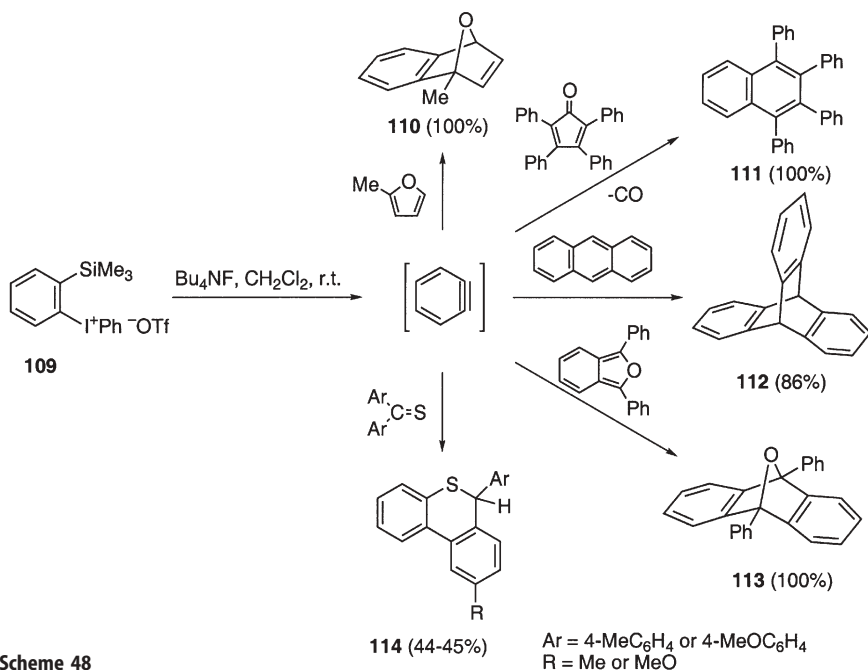
7.3 Generation of Benzyne and Its Reactions

Benzyne is an important reactive intermediate especially useful for the construction of polycyclic compounds via cycloaddition reactions with various dienes. Several benzyne precursors, including diphenyliodonium-2-carboxylate [1], have been previously used for the generation of benzyne by thermal decomposition. More recently, several new precursors that generate benzyne quantitatively under very mild conditions have been developed [105–108]. An efficient benzyne precursor, iodonium triflate **109**, can be readily prepared by the reaction of 1,2-bis(trimethylsilyl)benzene **108** with [(diacetoxy)iodo]benzene in the presence of trifluoromethanesulfonic acid (Scheme 47) [105].



Scheme 47

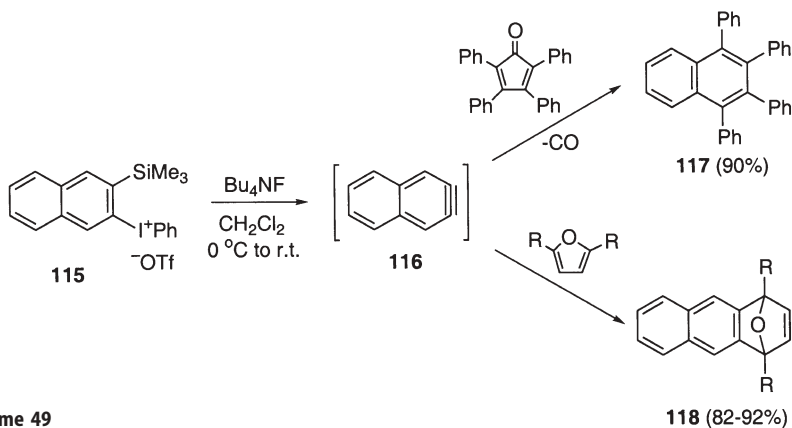
The treatment of reagent **109** with tetrabutylammonium fluoride in dichloromethane at room temperature generates benzyne, which can be trapped with the appropriate diene to afford the benzyne adducts **110–114** in high yields (Scheme 48) [105, 106]. Similarly, 3- and 4-methylbenzynes can be efficiently



Scheme 48

generated from the corresponding methyl-substituted (trimethylsilyl)phenyliodonium triflates and trapped by furan, 2-methylfuran, anthracene, or tetraphenylcyclopentadienone [105].

(Trimethylsilyl)naphthylidonium triflate **115** has been used as a precursor to 2,3-didehydronaphthalene **116**, which can be subsequently trapped with furans or tetraphenylcyclopentadienone to afford adducts **117** or **118**, respectively (Scheme 49) [107].

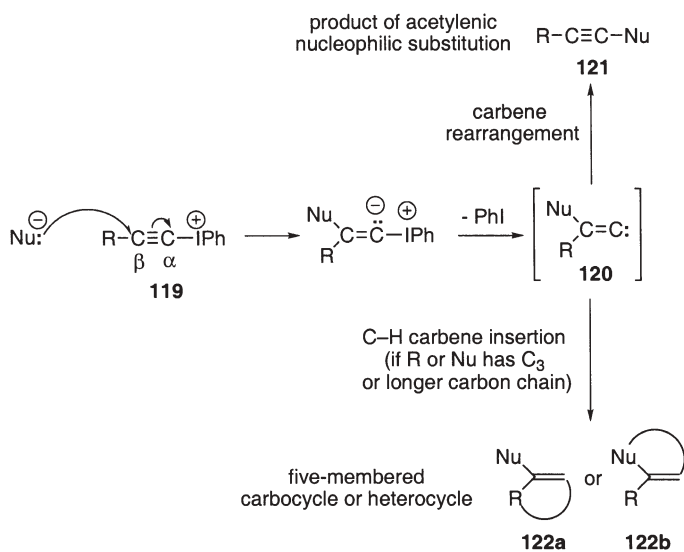


Scheme 49

8 Reactions of Alkynyliodonium Salts

Alkynyl(phenyl)iodonium salts have attracted a significant interest as stable and readily available powerful alkynylating reagents. The preparation, structure, and chemistry of alkynyliodonium salts was extensively covered in a recent review [4].

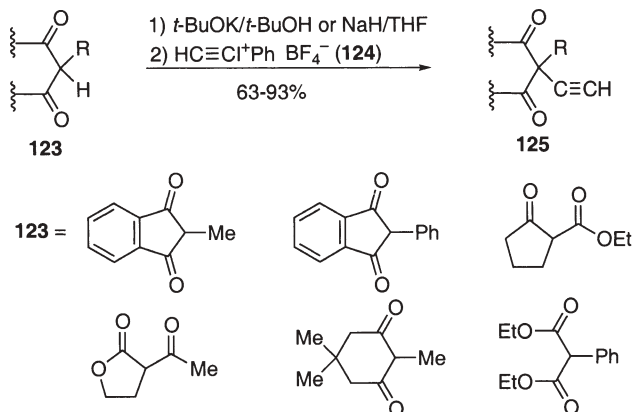
Reactions of alkynyliodonium salts **119** with nucleophiles proceed via an addition-elimination mechanism involving alkyldenecarbenes **120** as key intermediates. Depending on the structure of the alkynyliodonium salt, specific reaction conditions, and the nucleophile employed, this process can lead to a substituted alkyne **121** due to the carbene rearrangement, or to a cyclic product **122** via intramolecular 1,5-carbene insertion (Scheme 50). Both of these reaction pathways have been widely utilized as a synthetic tool for the formation of new C–C bonds. In addition, the transition metal mediated cross-coupling reactions of alkynyliodonium salts are increasingly used in organic synthesis.



Scheme 50

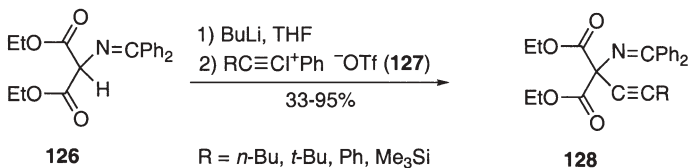
8.1 Alkynylation of C-Nucleophiles

Alkynyl(phenyl)iodonium salts can be used for the preparation of substituted alkynes by the reaction with carbon nucleophiles. The parent ethynyliodonium tetrafluoroborate **124** reacts with various enolates of β -dicarbonyl compounds **123** to give the respective alkynylated products **125** in a high yield (Scheme 51) [109]. The anion of nitrocyclohexane can also be ethynylated under these conditions. A similar alkynylation of 2-methyl-1,3-cyclopentanedione by ethynyliodonium salt **124** was applied in the key step of the synthesis of chiral methylene lactones [110].



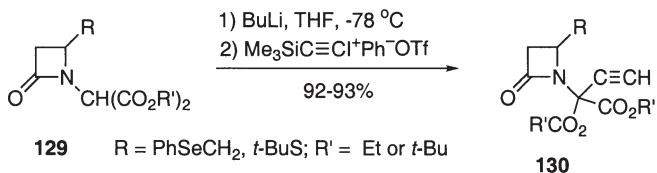
Scheme 51

Likewise, the reaction of the lithium enolate of aminomalonate **126** with alkynyliodonium triflates **127** affords alkyne malonates **128** in good yields (Scheme 52) [111]. The best yields in this reaction are observed when a freshly prepared solution of the lithium enolate in THF is added to a stirred cold solution of the iodonium salt. The use of potassium enolate instead of lithium, or addition of the reagents in a different order, results in lower yields of products **128**.



Scheme 52

Under similar conditions, (2-oxoazetidynyl)malonates **129** can be alkylated by (trimethylsilyl)ethynyl iodonium triflate (Scheme 53). In contrast to the previous reaction (Scheme 52), this alkylation directly affords the desilylated terminal alkynes **130** as the final isolated products [112]. This reaction (Scheme 53) allows ethynylation of malonates under milder conditions compared to the reaction shown in Scheme 51.

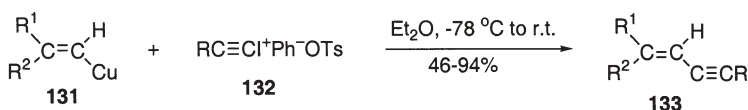


Scheme 53

8.2

Transition Metal-Mediated Reactions

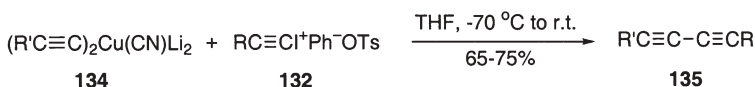
Alkynyl(phenyl)iodonium salts can be efficiently coupled with various organo-copper reagents. Direct coupling of alkynyliodonium tosylates **132** with vinyl-



Scheme 54

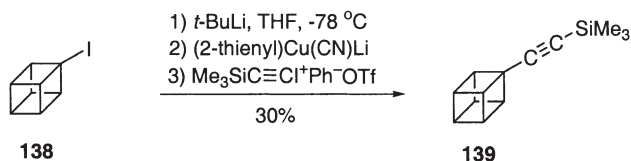
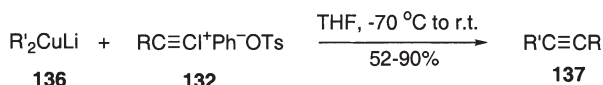
copper reagents **131** affords 1,3-enynes **133** in good isolated yields (Scheme 54) [113]. This reaction is highly stereoselective and proceeds with retention of the alkene geometry. It is assumed that this reaction proceeds through an oxidative addition of the alkynyl species to give a Cu(III) intermediate, followed by reductive elimination and coupling.

A similar coupling of alkynyliodonium tosylates **132** with dialkynylcuprates **134** leads to conjugated diynes **135** (Scheme 55) [114, 115]. This method can be used for the preparation of unsymmetrical diynes in moderate yield. Recently, this coupling was employed in the synthesis of various liquid-crystalline diaryl-diacetylenes [115].



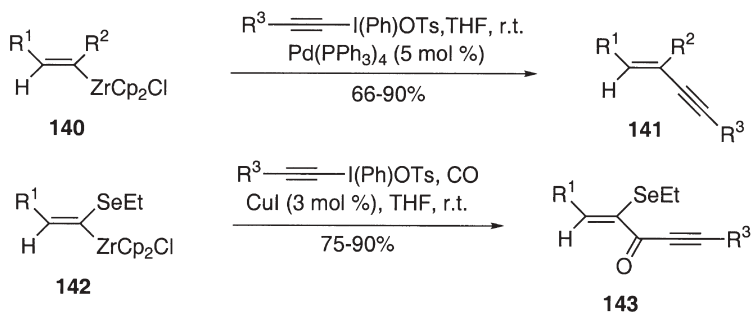
Scheme 55

Likewise, alkynyliodonium tosylates can be coupled with dialkyl- and diphenyl cuprates **136** to afford the respective alkyl- and phenyl-substituted alkynes **137** (Scheme 56) [114]. An interesting example of this reaction involves the coupling of (trimethylsilyl)ethynyl iodonium triflate with cubyl cuprate generated in situ from iodocubane **138** [116].



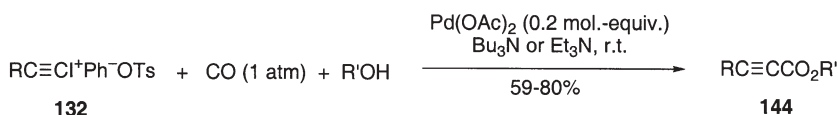
Scheme 56

Alkynyl(phenyl)iodonium salts can be effectively used in palladium(0) or copper(I) catalyzed coupling or carbonylative coupling reactions with various organozirconium complexes (Scheme 57) [117–119].



Scheme 57 $\text{R}^1 = \text{Ph, CH}_3\text{OCH}_2, \text{Pr, Bu, EtSe}; \text{R}^2 = \text{Bu}_3\text{Sn, Ph}_3\text{Sn, Et}_3\text{Sn, EtSe}$
 $\text{R}^3 = \text{Ph, CH}_3\text{OCH}_2, \text{C}_5\text{H}_{11}$

The palladium catalyzed alkoxyacylation of alkynylidonium tosylates 132 in methanol or ethanol in the presence of trialkylamine proceeds under mild conditions to give carboxylates 144 in good yield (Scheme 58) [120].



Scheme 58 $\text{R} = n\text{-Bu, Ph, } p\text{-MeOC}_6\text{H}_4; \text{R}' = \text{Me, Et}$

8.3

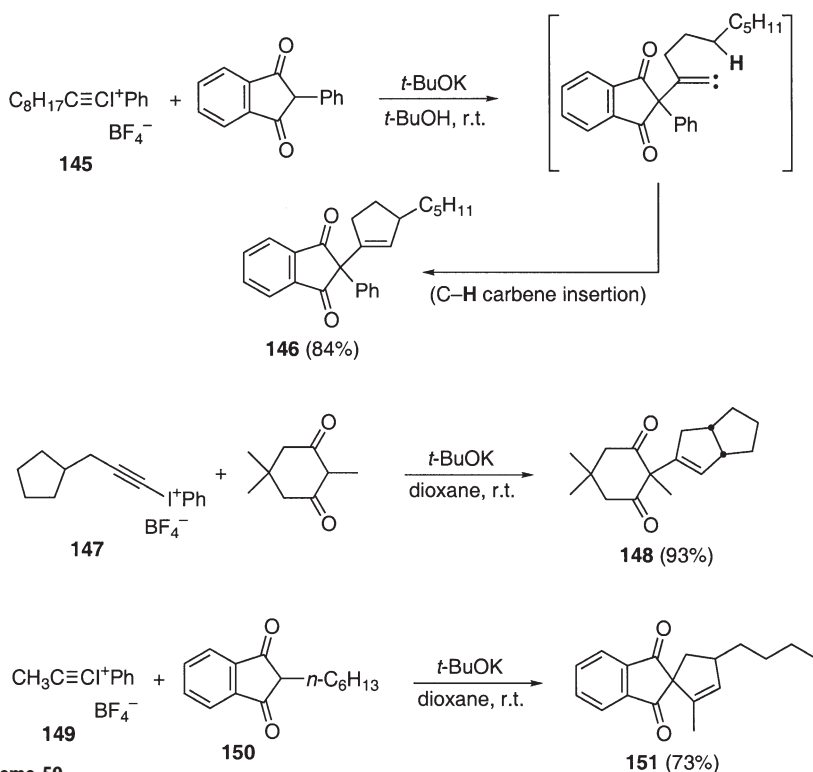
Preparation of Five-Membered Carbocycles and Heterocycles via Intramolecular Carbene Insertion

The predominant formation of five-membered carbocycles or heterocycles 122 (Scheme 50) via a sequential conjugate addition-carbene insertion pathway is generally observed in the reactions of the appropriate alkynylidonium salts 119 ($\text{R} =$ long alkyl chain or other group with C-H bond available at C5) with various relatively “hard” nucleophiles. Typical nucleophiles used to initiate these selective cyclizations are enolate, azide, sulfinate, tosylamide, thioamide and some other anions.

8.3.1

Synthesis of Cyclopentenes

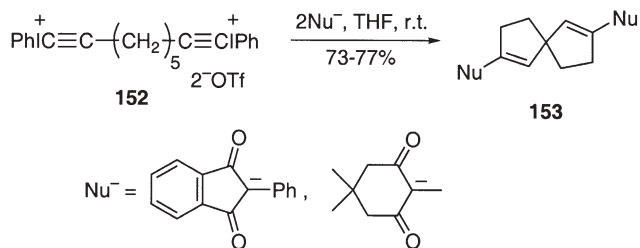
Cyclopentenes are commonly formed in the reaction of the appropriate alkynylidonium salts with enolate anions. Various alkynylidonium tetrafluoroborates interact with β -dicarbonyl enolates to give products of cyclopentene annulation in 50–90% yield [121]. Several examples of such annulations are shown in Scheme 59. The carbene cyclization can also occur when the long alkyl



Scheme 59

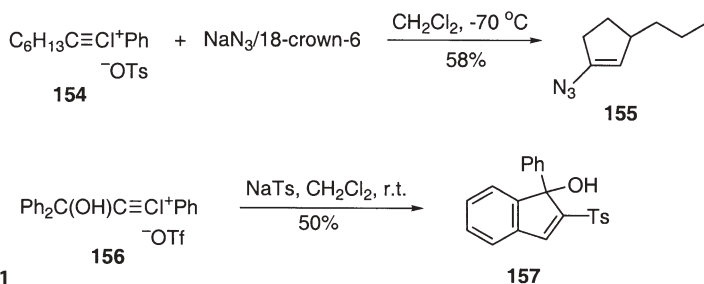
chain is part of the enolate nucleophile, as illustrated by the reaction of propynyliodonium salt **149** with β -diketone **150**.

The bis(alkynyliodonium) triflate **152** reacts with the enolate anions of β -diketones to afford the respective bis-insertion products **153** (Scheme 60) [122].



Scheme 60

The cyclopentene annulations can also occur in the reactions of alkyneiodonium salts with nitrogen- and sulfur nucleophiles (Scheme 61). Specifically, azidocyclopentene **155** is formed upon treatment of octynyliodonium tosylate **154** with sodium azide in dichloromethane [123]. The reaction of alkyneiodonium salt **156** with sodium toluenesulfonate results in the formation of substituted indene **157** via alkylidene carbene aromatic C-H bond insertion [124].

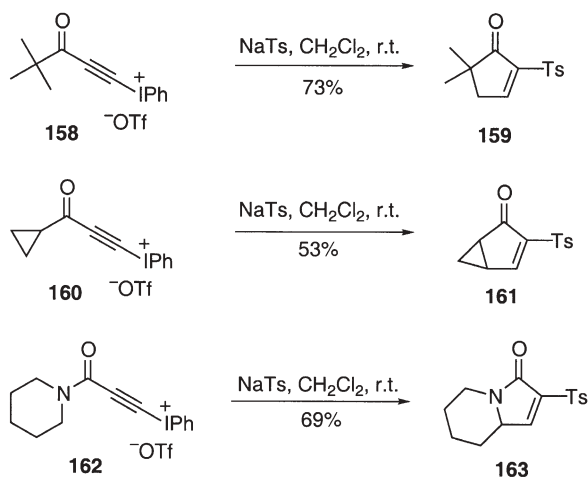


Scheme 61

8.3.2

Synthesis of Cyclopentenones

A variety of substituted 2-cyclopentenones are obtained in good yields by the reaction of sodium toluenesulfonate with β -ketoethynyl(phenyl)iodonium triflates [125]. Several specific examples of this reaction are shown in Scheme 62. This methodology readily affords not only simple cyclopentenones but also fused bicyclic systems **161** and γ -lactams **163**.

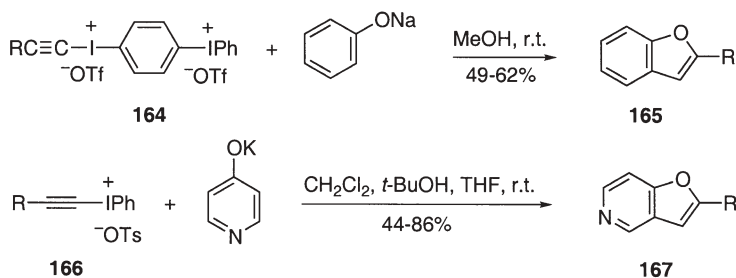


Scheme 62

8.3.3

Synthesis of Oxygen Heterocycles

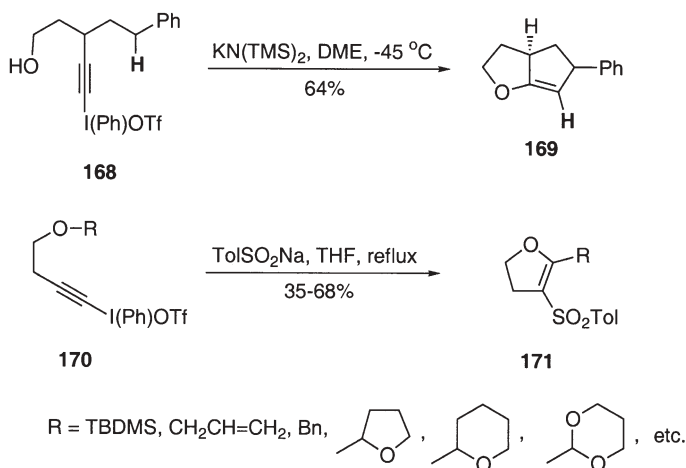
Various 2-substituted benzofurans **165** are obtained by the interaction of iodonium salts **164** with sodium phenoxide in methanol (Scheme 63) [126, 127]. This reaction proceeds via the intramolecular alkylidene carbene insertion into the *ortho*-CH bond of the phenoxy ring. Furopyridine derivatives **167** can be prepared similarly by the intramolecular aromatic C-H insertion of the alkylidenecarbenes generated by the reaction of alkynyliodonium tosylates **166** with potassium salts of 4- or 3-hydroxypyridines [128].



R = *n*-Bu, *t*-Bu, *n*-C₆H₁₃, *n*-C₁₀H₂₁, etc.

Scheme 63

Cyclopentannulated tetrahydrofurans **169** [129] and substituted dihydrofurans **171** [130] can be synthesized by the treatment of functionalized alkynyliodonium salts **168** and **170** with the appropriate nucleophile (Scheme 64). Alkynyliodonium salts **168** and **170**, the key precursors in these reactions, are conveniently prepared from the appropriate alkynylstannanes and can be used without additional purification.

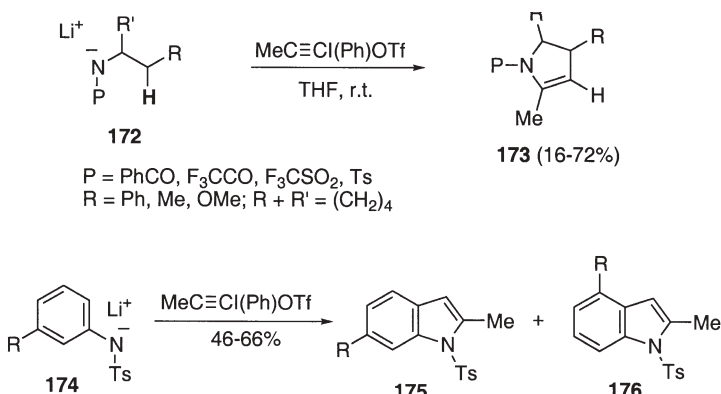


Scheme 64

8.3.4

Synthesis of Nitrogen Heterocycles

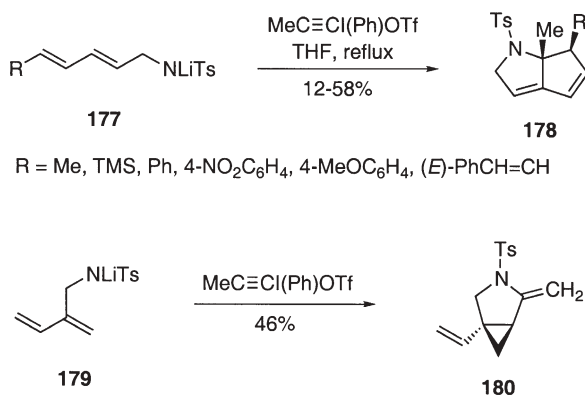
A variety of five-membered nitrogen heterocycles can be prepared efficiently by inter- or intramolecular addition/cyclizations of sulfonamide anions with alkynyliodonium salts. The intermolecular variant employs the combination of the amides **172** or anilides **174** with propynyl(phenyl)iodonium triflate (Scheme 65) [131, 132]. The yield of dihydropyrroles **173** in this cyclization is extremely sensitive to the nature of the protective group P; the tosyl group in **172** proved



Scheme 65 R = H, Me, OMe, CO₂Me, CO₂-*t*-Bu

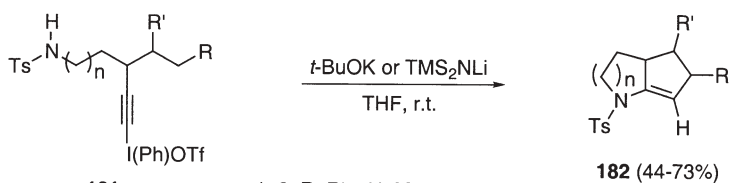
superior to the other carbonyl- or sulfonyl-based species [131]. The reaction of propynyl(phenyl)iodonium triflate with anilides **174** results in a non-regioselective formation of indoles **175** and **176** due to intramolecular alkylidene carbene insertion into the *ortho*-CH bonds [132].

A similar intermolecular cyclization was recently utilized in the synthesis of highly substituted dihydropyrrole derivatives [133–135]. In a specific example, the addition of pentadienyltosylamide derivatives **177** to propynyl(phenyl)iodonium triflate initiates a sequence of transformations that furnishes the complex, highly functionalized cyclopentene-annelated dihydropyrrole products **178** in moderate yields with complete stereoselection (Scheme 66). Under similar reaction conditions, the isomeric isoprene-derived tosylamide **179** reacts with propynyl(phenyl)iodonium triflate to give azabicyclo[3.1.0]hexane **180** as the final product [134].



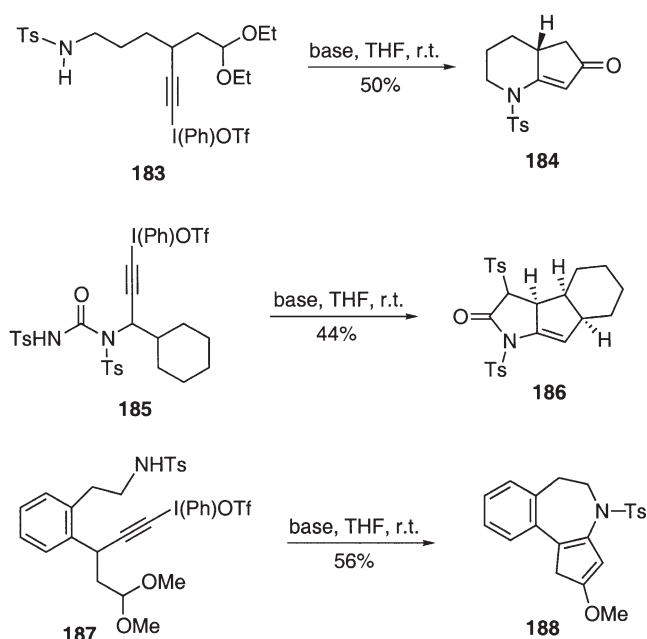
Scheme 66

The intramolecular variant of this cyclization is achieved by treatment of iodonium salts **181** with a base in THF (Scheme 67) [132].



Scheme 67 **181** $n = 1, 2; R, R' = H, \text{Me, etc.}$

These intramolecular bicyclizations can provide an efficient entry into polycyclic alkaloid skeleta; several specific examples of bicyclizations are shown in Scheme 68 [136]. Alkynyliodonium salts **181**, **183**, **185**, and **187**, key precursors in these reactions, are conveniently prepared from the appropriate alkynylstannanes and can be used without additional purification.



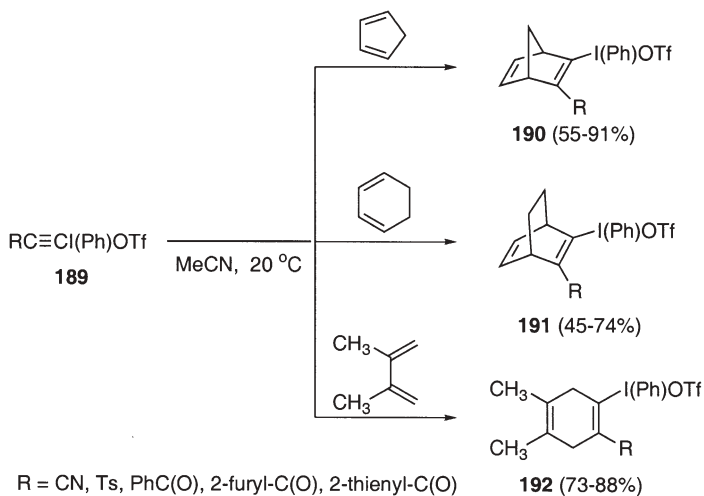
Scheme 68

8.4

[4 + 2] Cycloaddition Reactions

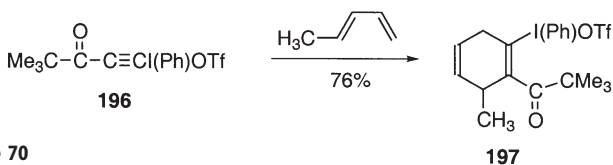
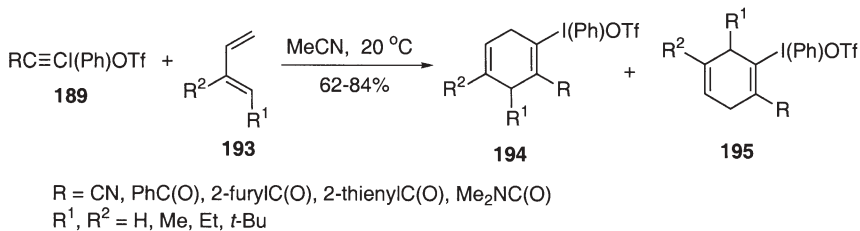
Alkynyliodonium salts functionalized with electron-withdrawing substituents in the β -position readily undergo [4 + 2] Diels-Alder cycloadditions with a wide range of dienes. Several examples of these cycloadditions are shown in Scheme 69 [137]. All adducts **190-192** are stable microcrystalline solids with two functionalities, the iodonium moiety and R, that may be used for further synthetic elaboration.

The reaction of alkynyliodonium salts **189** with unsymmetrically substituted dienes **193** results in a mixture of two regioisomeric cyclohexadienes **194** and



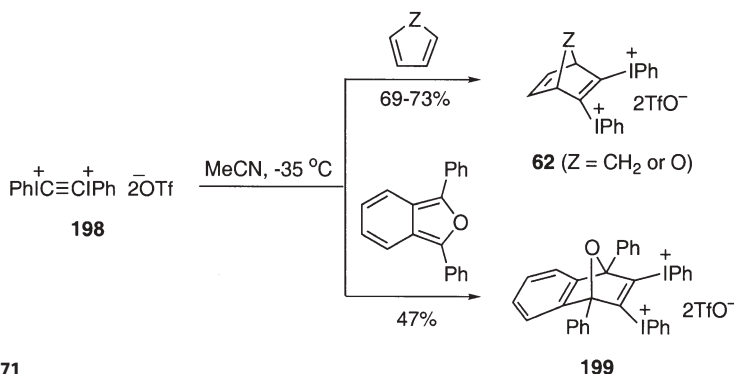
Scheme 69

195 (Scheme 70) [138]. In general, this cycloaddition shows low regioselectivity in the case of 2-substituted dienes and has a better degree of regioselectivity in the case of 1-substituted dienes. Moreover, the reaction of 1-methylbutadiene with alkyneiodonium salt **196** selectively affords a single regioisomer **197**, whose structure was established by X-ray analysis [138].



Scheme 70

The bis-iodonium acetylene **198** is even more reactive than **189** and undergoes Diels-Alder reaction with cyclopentadiene, furan and 1,3-diphenylisobenzofuran in acetonitrile under very mild conditions (Scheme 71) [139]. All adducts (**62**, **199**) are isolated in the form of stable microcrystalline solids; products **62** can be reacted further with nucleophiles or combined in a cross-coupling reaction with lithiated or stannylated alkynes [52, 53, 61].

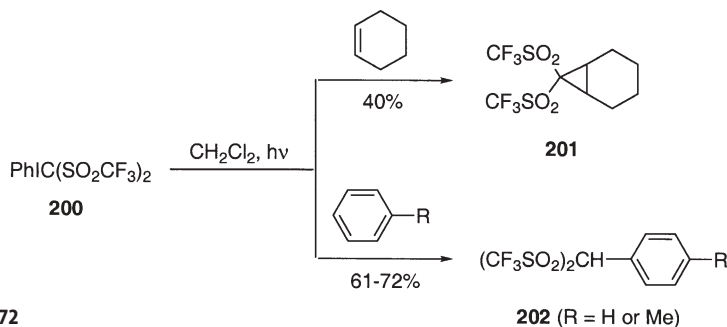


Scheme 71

9 Reactions of Iodonium Ylides

Iodonium ylides can serve as convenient precursors to the respective carbene intermediates under thermal, photochemical, or catalytic conditions. According to computational results, the thermal decomposition of iodonium ylides leading to carbenes should be facile, requiring an enthalpy change of no more than of 15 kcal/mol [140]. Iodonium ylide $\text{PhI}=\text{C}(\text{CO}_2\text{Et})_2$ readily decomposes in cyclohexane at 100°C affording the C–H insertion product together with iodobenzene as the major products. The thermal reaction of this ylide in the presence of *trans*- and *cis*-3-heptenes results in a stereospecific cyclopropanation. Under photochemical conditions this cyclopropanation is not stereoselective. These results indicate that the thermal decomposition of the iodonium ylides under mild conditions is an efficient source of a singlet carbene intermediate, uncontaminated with excited states of the precursor that would attend the photolysis [140].

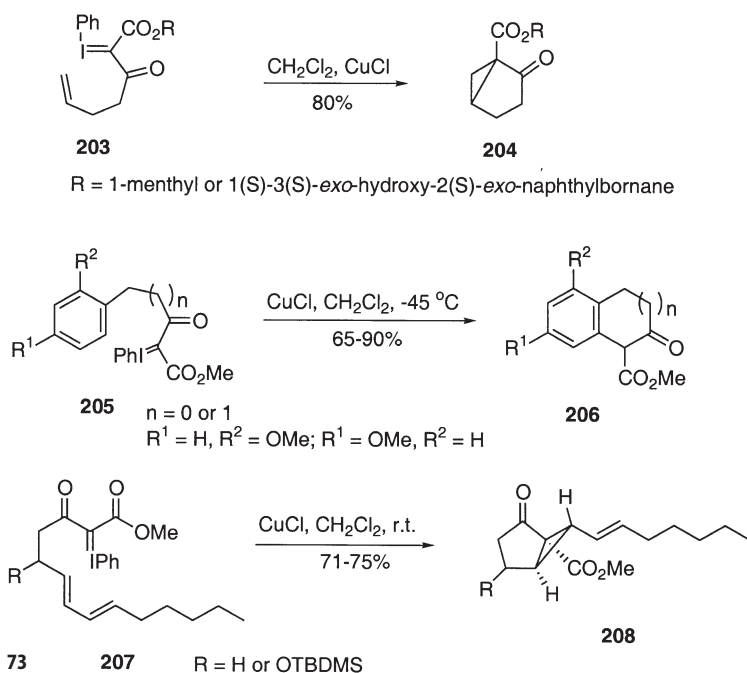
Phenyliodonium bis(perfluoroalkanesulfonyl)methide **200** can react with various organic substrates upon irradiation with UV light [141, 142]. For example, the reaction of **200** with cyclohexene affords cycloaddition product **201**, while the photolysis of **200** in benzene or toluene leads to the C–H insertion products **202** (Scheme 72) [142].



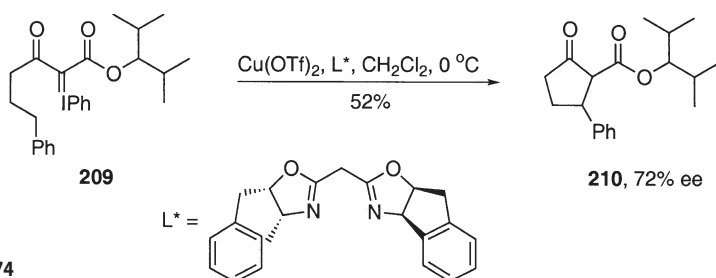
Scheme 72

A similar reaction of ylide **200** can also be carried out under thermal conditions or in the presence of catalytic amounts of $\text{Cu}(\text{acac})_2$ [143]. The carbenoid reactions of iodonium ylides can also be effectively catalyzed by rhodium(II) complexes [144, 145]. The product composition in the rhodium(II) catalyzed reactions of iodonium ylides was found to be identical to that of the corresponding diazo compounds, which indicates that the mechanism of both processes is similar and involves metalcarbenes as key intermediates as it has been unequivocally established for the diazo decomposition [144].

The catalytical decomposition of iodonium ylides is especially useful as a method of cyclization via intramolecular cycloaddition or bond insertion [146–148]. Several representative examples of these cyclizations are shown in Scheme 73. Specifically, the intramolecular cyclopropanation of ylide **203** leading to product **204** was used in the synthesis of the 3,5-cyclovitamin D ring A synthon [146]. The copper(I) catalyzed decomposition of phenyliodonium ylides **205** affords the corresponding substituted tetralones **206** in good preparative yields [147]. Under similar conditions, iodonium ylides **207** undergo regio- and stereoselective intramolecular cyclopropanation to form the key bicyclo[3.1.0]hexane intermediates **208** for prostaglandin synthesis [148].



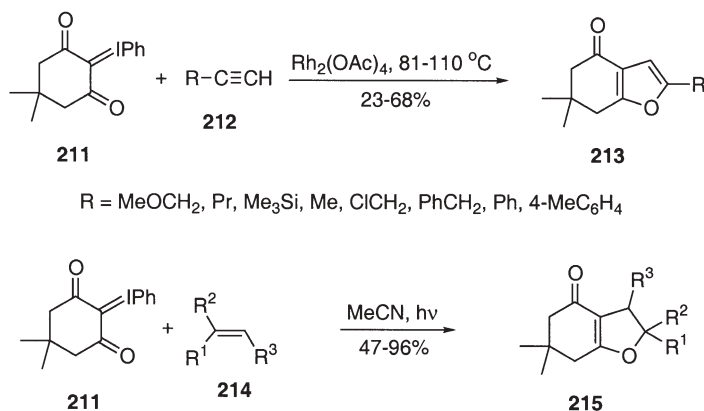
The metal-catalyzed carbenoid decomposition of iodonium ylides can be applied in asymmetric reactions [149–152]. For example, the copper(II)-catalyzed intramolecular C–H insertion of phenyliodonium ylide **209** in the presence of several chiral ligands affords product **210** (Scheme 74) [151]. Enantioselectivities in this reaction vary in the range of 38–72% for different chiral



Scheme 74

ligands, and are higher than those resulting from a similar reaction of the diazo compounds.

The cyclic β -dicarbonyl iodonium ylides can undergo [3+2] cycloaddition reactions with various substrates under catalytic or photochemical conditions, presumably via a stepwise mechanism [153–156]. In a recent example, iodonium ylide **211**, derived from dimedone, undergoes dirhodium(II) catalyzed thermal [3+2]-cycloaddition with acetylenes **212** to form the corresponding furans **213** (Scheme 75). Under photochemical conditions ylide **211** reacts with various alkenes **214** to form dihydrofuran derivatives **215** [156].



Scheme 75

R¹, R², R³ = H, Ph, PhCH₂, EtO, Me, Pr, OEt

10 Conclusion

The preceding survey of the application of iodine(III) compounds in carbon-carbon bond forming reactions reflects an active current interest in the chemistry of hypervalent iodine. Hypervalent iodine compounds are employed increasingly in organic synthesis as environmentally benign, efficient, and versatile reagents. The most important C–C bond forming reactions are based on the oxidative generation of carbon-centered reactive intermediates from the appropriate hypervalent iodine precursors, or on the ligand coupling reactions

of iodonium salts. The most valuable synthetic methods include the radical decarboxylative alkylation of organic substrates with [bis(acyloxy)iodo]arenes, the oxidative cyclization of substituted phenols and phenol ethers, and the reactions of iodonium salts and ylides. Significant recent research activity has been centered in the area of the transition metal-mediated coupling reactions of the alkenyl-, aryl-, and alkynyliodonium salts.

It can be anticipated that these areas of synthetic application will continue to attract significant research activity in the future. The increasing use of the transition metal-mediated coupling reactions of iodonium salts may add a new dimension to the field of polyvalent iodine chemistry.

We hope and anticipate that this review will provide added stimulus for the further development of the chemistry of polyvalent iodine compounds.

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C-Heteroatom-Bond Forming Reactions

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Recent progress on the use of hypervalent iodine reagents for the construction of carbon-heteroatom (N, O, P, S, Se, Te, X) bonds is reviewed. Reactions of aryl- λ^3 -iodanes with organic substrates are considered first and are loosely organized by functional group, separate sections being devoted to carbon-azide and carbon-fluorine bond formation. Arylations and alkenylations of nucleophilic species with diaryliodonium and alkenyl(aryl)iodonium salts, and a variety of transformations of alkynyl(aryl)iodonium salts with heteroatom nucleophiles are then detailed. Finally, the use of sulfonyliminoiodanes as aziridination and amidation reagents, and reactions of iodonium enolates formally derived from monoketones are summarized.

Keywords. C-heteroatom bond formation, Aryl- λ^3 -iodanes, Iodonium salts, Sulfonyliminoiodanes, Hypervalent iodine

1	Introduction	138
2	Aryl-λ^3-Iodanes	138
2.1	Azidation	139
2.2	Oxidative Additions to C,C-Multiple Bonds	142
2.2.1	The C,C-Double Bond	142
2.2.2	The C,C-Triple Bond	145
2.3	Functionalization of Aromatic Compounds	146
2.4	α -Functionalization of Carbonyl Compounds	149
2.5	C-Fluorine Bond Formation	150
3	Diaryliodonium Salts	154
4	Alkenyl(aryl)iodonium Salts	155
5	Alkynyl(aryl)iodonium Salts	158
5.1	Alkynylation	158
5.2	CH-Bond Insertions	159
5.3	C-Heteroatom Bond Insertions	161
5.4	Intramolecular Additions	162
5.5	Cyclocondensations	163

6	Sulfonylimino(aryl)iodanes	163
6.1	Aziridination	163
6.2	Amidation	166
7	Iodonium Enolates	167
8	References	168

1

Introduction

The formation of carbon-heteroatom bonds can be effected by reactions of hypervalent iodine reagents with a wide range of organic substrates and inorganic nucleophiles, and represents one of the most popular applications of organoiodine(III) compounds [1–10]. Except for C-I(III) bond forming reactions used for the synthesis of iodanes and iodonium salts, C-heteroatom bond formation is almost always accompanied by reduction of the hypervalent iodine reagents to iodine(I) compounds.

In this chapter, the use of aryl- λ^3 -iodanes, iodonium salts, and iodonium ylides for C-heteroatom (N, O, P, S, Se, Te, X) bond forming reactions is reviewed. Because an exhaustive coverage of this subject, even when confined to the past decade, could easily fill a book, emphasis is placed on major themes of the 5–7 year period ending in 2001, earlier literature being discussed when appropriate to set the historical context. For purposes of clarity in nomenclature, iodine(III) compounds possessing one arene and two heteroatom ligands are identified herein as aryl- λ^3 -iodanes or more simply as aryliodanes, while those possessing one heteroatom and two carbon ligands are generally identified as iodonium salts, unless the heteroatom species is covalently bound to iodine. The schemes in this chapter are meant to exemplify the transformations under consideration and, in many cases, show only specific examples or sub-sets of published reactions. The reaction conditions indicated in the schemes are usually taken from tables and representative procedures.

One of the most striking advances of the past decade, based on foundational studies in the 1970s and 1980s, is the development of methods for C-nitrogen bond formation. Although 1°- and 2°-amines are typically oxidized by iodine(III) reagents and of limited use for this purpose, iodine(III)-compatible species such as azide and arenesulfonylamidates can be readily incorporated into organic structures with hypervalent iodine compounds.

2

Aryl- λ^3 -Iodanes

Aryl- λ^3 -iodanes **1** are electrophilic at iodine and undergo ligand exchange with a variety of nucleophilic species, including organic functional groups (Scheme 1). Such reactions may be regarded as nucleophilic substitutions at trivalent

iodine or as electrophilic aryliodinations of nucleophilic substrates. The dissociative and associative mechanisms for ligand exchange, and electrophilic catalysis of the dissociative pathway, are discussed in the 1992 monograph by A. Vargolis [9]. Whether C-heteroatom bond forming reactions between aryliodanes and organic substrates proceed by heterolytic (more common) or homolytic pathways, ligand exchange at iodine is often involved in the overall transformation (Scheme 1).

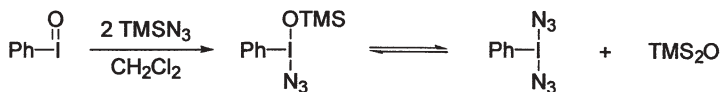


Scheme 1

2.1

Azidation

The treatment of iodosylbenzene (2) with two equivalents of trimethylsilyl azide in dichloromethane results in the formation of [azido(trimethylsilyloxy)iodo]benzene (3) and [bis(azido)iodo]benzene (4), (Scheme 2) [11–14]. Although the azidoiodanes are unstable and decompose in solution at temperatures above -30°C , they can be employed in situ for azidations of organic compounds. The addition of trimethylsilyl azide to iodosylbenzene/substrate mixtures enables such azidations to be effected at temperatures higher than -30°C .



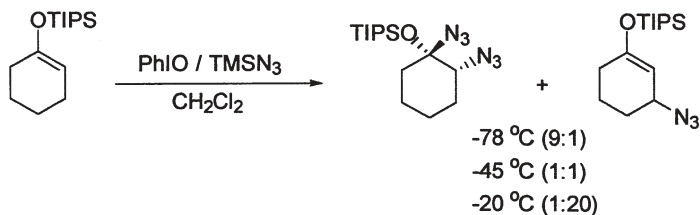
Scheme 2 2

3

4

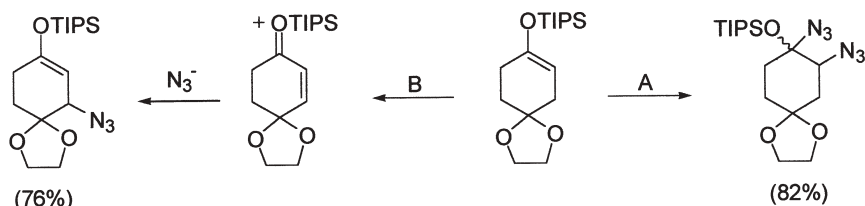
Applications of 3 and 4 during the past decade include azidations of triisopropylsilyl (TIPS) enol ethers, glycols and dihydropyrans, aryl *N,N*-dialkylamines, cyclic amides, and cyclic sulfides. Because the relative concentrations of 3 and 4 in solvents employed for their use are uncertain, the azidoiodanes are usually represented collectively as $\text{PhIO}/\text{TMSN}_3$.

The reactions of cyclic TIPS enol ethers with $\text{PhIO}/\text{TMSN}_3$ (1:2) have been examined in detail [12–14]. Two primary modes of reactivity have been identified, one leading to vicinal-diazides (α -pathway) and the other leading to allylic azides (β -pathway) (Scheme 3).



Scheme 3

In general, the formation of diazides from cyclic TIPS enol ethers occurs with high *trans*-stereoselectivity, and is favored by lower temperatures and the presence of TEMPO in the reaction medium. Homolytic decomposition of the azidoiodanes, and the addition of azido radicals to the enol ethers is believed to be responsible for product formation. Allylic azidation, on the other hand, is favored at higher temperatures and thought to occur via hydride-abstraction from the enol ethers by ion-pairs derived from 3 and 4 to give TIPS enonium intermediates. Thus, by an appropriate choice of reaction conditions, the outcome of azidonations of TIPS enol ethers with 3 and 4 can be almost completely controlled (Scheme 4). For example, in one publication, selective diazidonations of seven TIPS enol ethers and selective allylic azidonations of twenty TIPS enol ethers are tabulated [14].

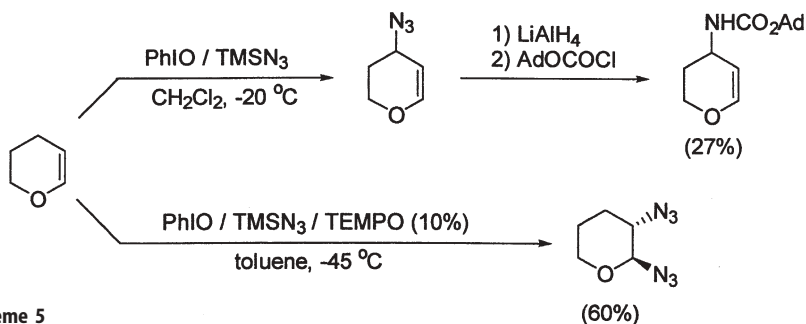


A : PhIO / TMSN₃ / TEMPO (cat), CH₂Cl₂, -45 °C

Scheme 4 B : PhIO / TMSN₃, CH₂Cl₂, -15 °C

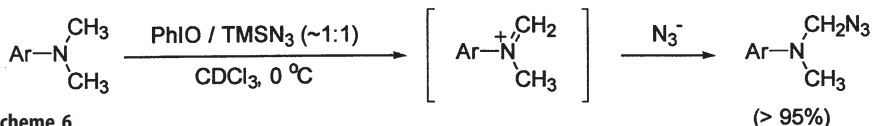
Synthetic applications of the β -pathway include conversions of the TIPS allylic azides to enones with tetrabutylammonium fluoride, ionization of the C-N₃ bond with alkylaluminum reagents and capture of the TIPS enonium ions with carbon nucleophiles, and development of a procedure for γ -lactamization [15–17]. Allylic azidonations of TIPS enol ethers have also been incorporated into syntheses of (+)-pancratistatin [18, 19] and the core structure of lycorane [20].

As observed with the TIPS enol ethers, dihydropyran undergoes either allylic azidation or *trans*-diazidation with PhIO/TMSN₃, depending on the reaction conditions (Scheme 5) [21]. These general modes of reactivity have been exploited for the synthesis of diaminopyrans from dihydropyran. Related conversions of *O*-protected 3-deoxy- and 3,6-dideoxyglycals to 3-azidoglycals (i.e., allylic azidation) and their 1-azido isomers have also been reported [22].



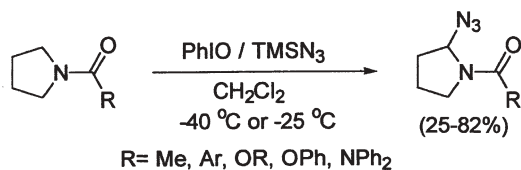
Scheme 5

N,N-Dimethylarylamines are rapidly converted to *N*-azidomethyl-*N*-methylarylamines with PhIO/TMSN₃ (ca. 1:1) in deuteriochloroform at 0 °C, presumably through aryliminium intermediates (Scheme 6) [23, 24]. When the quantity of the reagent is doubled, *N,N*-bis(azidomethyl)arylamines can be generated. Although the (azidomethyl)arylamines are generally too unstable for purification, they can be utilized without isolation as synthetic intermediates. This was demonstrated, for example, by the sequential conversion of *N,N*-dimethyl-*m*-anisidine to *N*-benzyl-*N*-methyl-*m*-anisidine with PhIO/TMSN₃ and phenylmagnesium bromide [24].



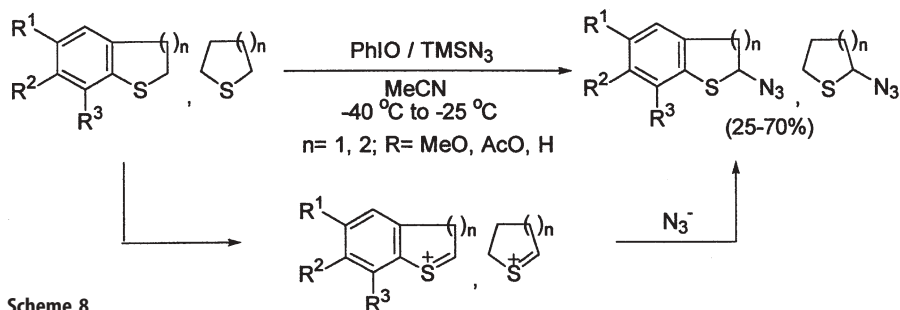
Scheme 6

The treatment *N*-carbonyl pyrrolidine derivatives with PhIO/TMSN₃ (1:2) leads to α -azidation of the pyrrolidine ring (Scheme 7) [25]. Similar results were obtained with the piperidine analogs, although product yields were much improved when iodosylbenzene was replaced with *o*-iodosylbenzoic acid and the reactions were conducted under reflux. Extension of the azidation methodology to carbonyl derivatives of L-proline methyl ester was successful, although the product mixtures were generally more complex [26].



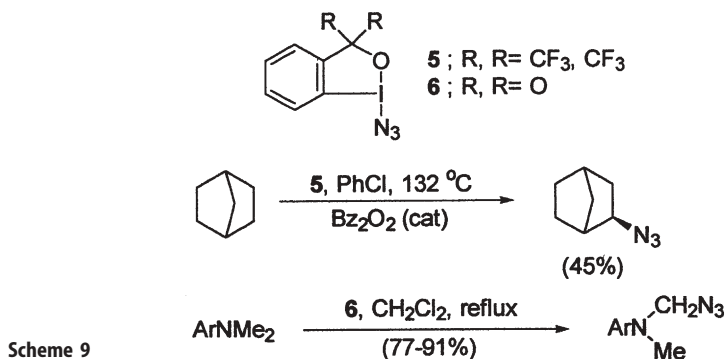
Scheme 7

Cyclic sulfides undergo similar α -azidations with PhIO/TMSN₃ (1:2) in acetonitrile (Scheme 8) [27]. A polar mechanism involving phenyliodination at sulfur and formation of an unsaturated sulfonium species was suggested to account for the introduction of the azide ion.



Scheme 8

Azidoiodanes, **5** and **6**, derived from the benziodoxole and benziodoxolone ring systems are thermally stable crystalline solids and can be employed at much higher temperatures than **3** and **4** [28–30]. This has been demonstrated with azidations of *N,N*-dimethylarylamines, and benzoyl peroxide catalyzed azidonations of cyclohexene and saturated hydrocarbons with **5** and **6** (Scheme 9) [29, 30].



Scheme 9

The related reagent combination, $\text{PhI}(\text{OAc})_2/\text{NaN}_3$, has been employed for direct conversions of aromatic aldehydes to aroyl azides, ArCON_3 [31]. These reactions were conducted in dichloromethane at room temperature and are thought to occur by a radical mechanism.

2.2

Oxidative Additions to C,C-Multiple Bonds

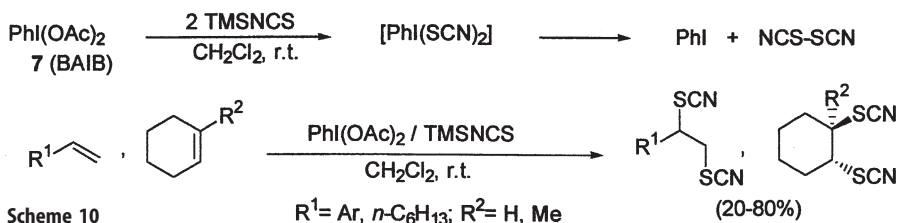
2.2.1

The C,C-Double Bond

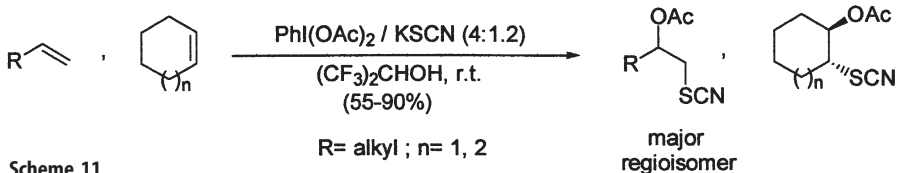
[Bis(acetoxy)iodo]benzene (**7**, BAIB) can be used in combination with various reagents for oxidative additions to C,C-double bonds. Recent publications in this area are focused on C-N, C-O, C-S, C-Se, and C-X bond formation with emphasis on the co-introduction of non-equivalent heteroatom groups. The role of BAIB in such reactions is diverse, ranging from addition of the iodane to the double bond to the generation of iodine(III) and non-iodine(III) species that react with the olefinic substrates.

Admixture of BAIB with two equivalents of trimethylsilyl isothiocyanate in dichloromethane leads to the rapid formation of thiocyanogen and iodobenzene, presumably via [bis(thiocyanato)iodo]benzene (Scheme 10) [32]. The addition of alkenes to such solutions affords *vicinal*-dithiocyanatoalkanes. Cyclohexene and its 1-methyl analog were converted exclusively to the *trans*-adducts under these conditions, while dihydropyran gave a 1:1 mixture of *cis*- and *trans*-isomers.

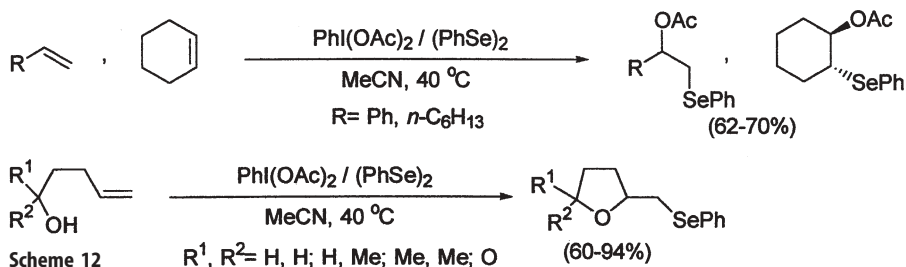
Dithiocyanations with the related system, BAIB/KSCN (1:2, MeCN), are restricted to activated substrates such as dihydropyran and α -methylstyrene,



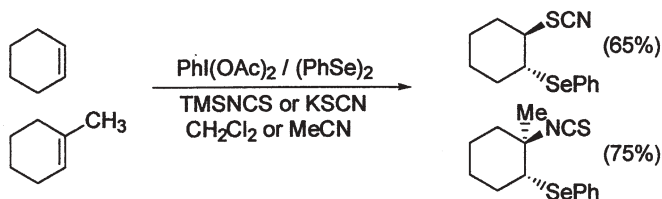
unless magnesium perchlorate or TEMPO is added to the reaction medium [33]. However, the use of BAIB in excess and the replacement of acetonitrile with hexafluoro-2-propanol (i.e., BAIB/KSCN (>3:1, HFP)) favors a phenyliodination process resulting in *trans*-acetoxythiocyanation of the double bond (Scheme 11) [34]. Terminal alkenes were converted primarily, but not exclusively, to 1-thiocyanato-2-acetoxyalkanes under these conditions.



Diphenyl diselenide is an especially useful co-reagent with [bis(acetoxy)-iodo]benzene. For example, the BAIB/PhSeSePh (2:1) combination has been employed for *trans*, Markovnikov additions of 'PhSeOAc' and 'PhSeOH' to alkenes [35]. Such formal additions appear to be regulated by seleniranium intermediates, and were extended to intramolecular cyclizations of olefinic alcohols, carboxylic acids, and β -dicarbonyl compounds (Scheme 12).



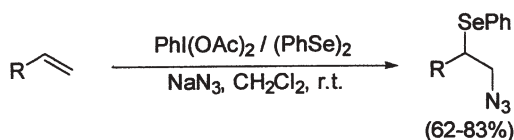
The addition of olefinic compounds to the three component system, BAIB/TMSNCS/PhSeSePh (2.5:1:5), or its KSCN variant, results in stereo- and regioselective (*trans*, Markovnikov) phenylselenenyl-thiocyanation (or -isothiocyanation) of the C,C-double bond (Scheme 13) [36]. Whether C-S or C-N bond formation occurs when the 'SCN' group is introduced seems to depend on the capacity of the alkene to stabilize carbocation-like intermediates. For example, C-S bond formation occurred with cyclohexene, while C-N bond formation



Scheme 13

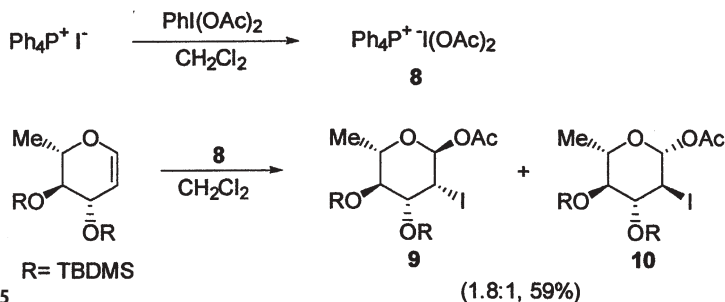
occurred with 1-methylcyclohexene. Based on NMR evidence, PhSe-SCN appears to be the species responsible for product formation in this system.

Azido-phenylselenenylations of olefinic compounds can be effected with BAIB/PhSeSePh/NaN₃ in CH₂Cl₂ (Scheme 14) [37]. Such additions proceed in anti-Markovnikov fashion and appear to be initiated by addition of the azido radical to the C,C-double bond. While cyclohexene and *cis*-4-octene gave 3:1 and 2:1 mixtures of diastereomeric adducts under these conditions, dihydropyran was converted cleanly to the *trans*-addition product. Regioselective azido-phenylselenenylations of dihydropyran derivatives and *O*-protected glycals with this reagent have also been documented [21, 38, 39].

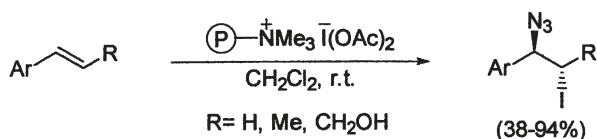
Scheme 14 R = Ph, *n*-C₆H₁₃, PhCH₂, CH₃COCH₂CH₂, MeO₂C(CH₂)_n (n=1-3)

Ligand-transfer oxidations of tetraethylammonium bromide and quaternary phosphonium iodides with BAIB in aprotic solvents afford the corresponding bis(acetoxy)halogenate(I) salts (e.g., **8**) [40, 41]. Such solutions have been utilized for stereo- and regioselective (*trans*, Markovnikov) haloacetoxylation of cyclic alkenes and glycals (Scheme 15). The reactions of glycals with these reagents lead to mixtures of α - and β -2-haloglycosyl acetates (e.g., **9** and **10**) and, in the case of bromoacetoxylation, are complicated by competitive *cis*-addition of 'AcOBr' to the C,C-double bond.

Tetraethylammonium bis(azido)halogenate (I) and (trimethylammonio)-polystyryl bis(azido)iodate (I) salts have been similarly employed for haloazido-



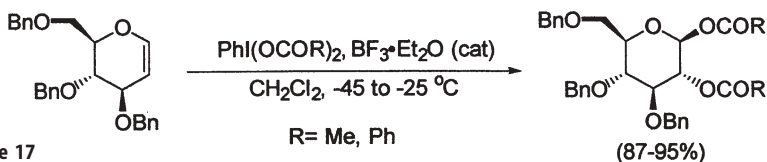
Scheme 15



Scheme 16

nations of alkenes and glycals (Scheme 16) [42, 43]. In general the same stereo- and regiochemical patterns were observed, the high selectivity of the polymeric reagent in both categories being noteworthy. The bis(azido)halogenate salts were prepared by the stepwise treatment of BAIB with trimethylsilyl azide and the ammonium halides, or by a reverse sequence.

The activation of [bis(acyloxy)iodo]arenes with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ enables the conversion of protected glycals to *trans*-1,2-bis(acyloxy)glycosides (Scheme 17) [44]. In the presence of triflic acid, these compounds are excellent 2-acyloxyglycosyl donors and can be utilized in situ with carbohydrate-based alcohols for the synthesis of disaccharides.



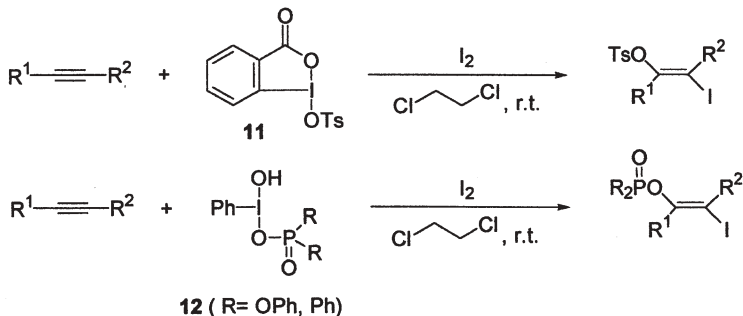
Scheme 17

Ligand exchange of BAIB with magnesium perchlorate in CH_2Cl_2 -MeCN, followed by the introduction of terminal and cyclic alkenes, has been reported to give *vicinal*-bis(perchlorato)alkanes [45]. The cyclic alkenes gave *cis*-adducts under these conditions.

2.2.2

The C,C-Triple Bond

The treatment of terminal and internal alkynes with 1-tosyloxybenziodoxolone (11) in the presence of molecular iodine results in *trans* iodo-oxytosylation of the C,C-triple bond, and in the case of unsymmetrical alkynes, leads to Markovnikov adducts (Scheme 18) [46]. Co-iodinations of alkynes with the

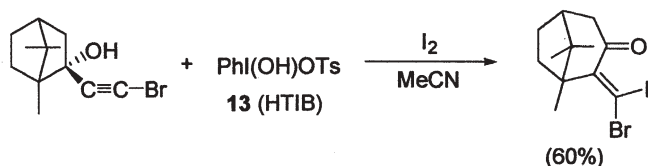


Scheme 18

R¹, R² = Ph, Ph; *n*-Pr, *n*-Pr; Ph, H; *n*-Bu, H; Ph, Me

iodine(III)-phosphate and -phosphinate reagents **12** similarly afford *trans*-iodo(phosphoryloxy)alkenes, although terminal alkynes are less efficient in this context (Scheme 18) [47].

Combinations of [hydroxy(tosyloxy)iodo]benzene (**13**, HTIB) with molecular iodine or *N*-iodosuccinimide in acetonitrile promote conversions of haloethynylcarbinols to β -halo- β -iodoenones (the McNelis rearrangement) [48–57]. When bromoethynylcarbinols are utilized, (*Z*)- β -bromo- β -iodoenones are generally formed with high stereospecificity. The McNelis rearrangement, exemplified in (Scheme 19) [15], has been demonstrated with a variety of cyclic and acyclic haloethynylcarbinols, and has recently been reviewed [8].



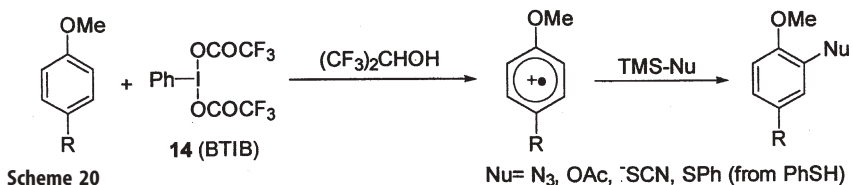
Scheme 19

The treatment of alkynes with the combined reagent, $\text{PhICl}_2/\text{Pb}(\text{SCN})_2$, in dichloromethane at 0–5°C provides access to *trans*-bis(thiocyanato)alkenes [58]. Whether thiocyanogen, thiocyanogen chloride, or [bis(thiocyanato)-iodo]benzene is responsible for dithiocyanation of the C,C-triple bond has not been established.

2.3

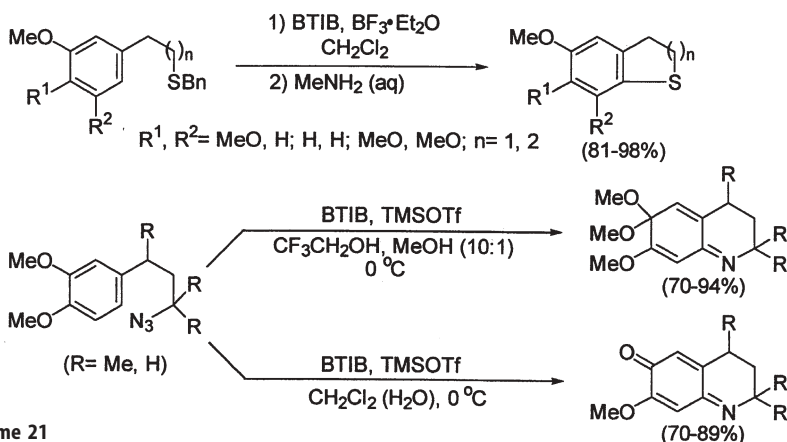
Functionalization of Aromatic Compounds

[Bis(trifluoroacetoxy)iodo]benzene (**14**, BTIB) can be utilized in hexafluoro-2-propanol for the installation of nucleophiles at the *ortho*-position of *para*-substituted alkoxyarenes [59–63]. Such reactions have been employed for the construction of carbon-carbon and carbon-heteroatom (N, O, S) bonds, trimethylsilyl compounds serving as useful progenitors of the heteroatom nucleophiles (Scheme 20). Oxidative substitutions of this type appear to proceed through arene radical-cations, generated by single electron-transfer within BTIB/substrate charge-transfer complexes.



Scheme 20

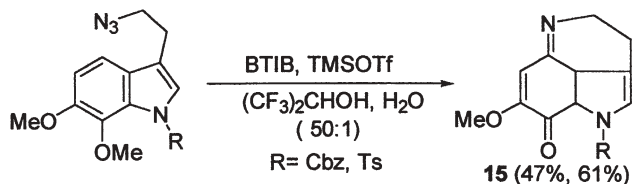
BTIB oxidations of aromatic ethers in which sulfido groups are tethered to the ring provide access to heterocyclic sulfides [64], while related oxidations of azido-tethered analogs lead to quinone imines and/or their dimethyl ketals



Scheme 21

(Scheme 21) [65, 66]. The function of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ and trimethylsilyl triflate in these reactions is to activate BTIB.

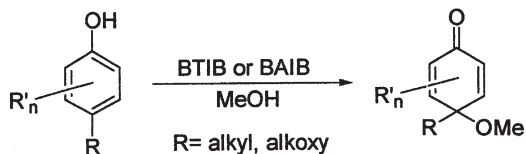
Oxidative cyclizations of 3-(β -azidoethyl)indoles with BTIB afford pyrroloiminoquinones **15**, compounds that appear as sub-structures in biologically active marine alkaloids such as the makaluvamines and discorhabdins (Scheme 22) [67–69]. In fact, BTIB-mediated sulfide and azide cyclizations, and α -azidation of the cyclic sulfide with PhIO/TMSN_3 , were incorporated into the first total synthesis of (\pm)-makaluvamine F [68, 69].



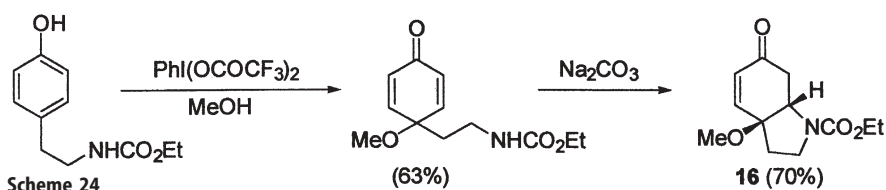
Scheme 22

Oxidations of variously-substituted 4-alkyl- and 4-alkoxyphenols with BAIB or BTIB in alcoholic solvents provide ready access to alkoxy(alkyl)- and dialkoxycyclohexadienones (Scheme 23) [70–72]. Dienone formation is generally attributed to the capture of aryloxyiodane and/or aryloxonium ion intermediates with the alcohol [73]. Related C–O bond forming oxidations of phenols with BAIB and BTIB, including intramolecular cyclizations leading to spirodienones, are summarized in several reviews [1–3, 74].

Phenols are sometimes used for the construction of C–N bonds by an oxidation-Michael addition sequence. A recent example is the two-step conversion of

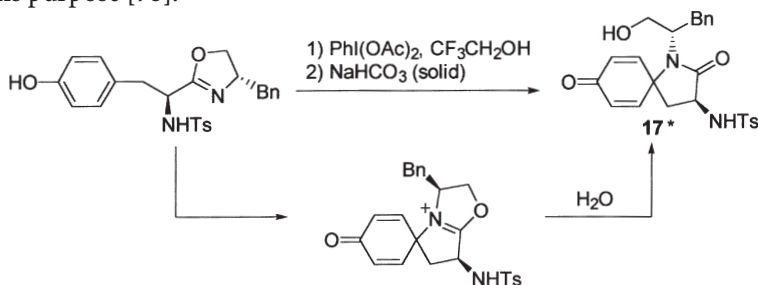


Scheme 23



protected 4-(β - or γ -aminoalkyl)phenols to *cis*-fused hydroindolenones such as **16**, in which BAIB was employed in methanol in the oxidation step (Scheme 24) [75].

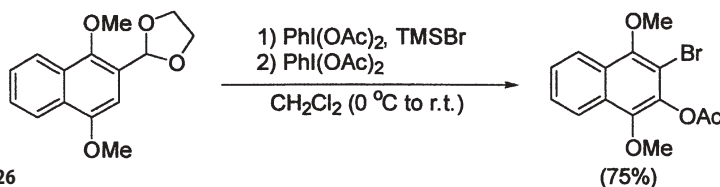
The more challenging task of direct C-N bond formation has recently been accomplished by utilization of the oxazoline ring as the nitrogen donor [76–78]. This approach was demonstrated by the preparation of spirolactams such as **17** from oxazoline derivatives of tyrosine and related phenolic acids by oxidation with BAIB in trifluoroethanol (Scheme 25), and similar conversions of indole-tethered oxazolones to tetracyclic products through spirolactam intermediates. It is noteworthy that phenolic amides, amines, and iminoethers were not useful for this purpose [78].



* converted immediately to acetate (41% overall yield) with Ac₂O, pyridine, DMAP

Scheme 25

Reactions of 1,4-dimethoxynaphthalene and its 2-chloro, 2-bromo, and 2-(1,3-dioxolanyl) derivatives with BAIB/TMSX (X=Cl, Br) combinations in dichloromethane result in acetoxylation, monohalogenation, or dihalogenation of the more activated ring (Scheme 26) [79]. Specific outcomes depend on the naphthalene derivative and reaction conditions. It is interesting that the 2-(1,3-dioxolanyl) derivative undergoes ipso-bromination with BAIB/TMSBr, and that this mode of reactivity was not observed with 2-(1,3-dioxolanyl)-1,4-dimethoxybenzene. These reactions are mechanistically diverse. Evidence was presented that bromination occurs after the formation of molecular bromine, and that chlorination probably follows a radical pathway involving the homo-

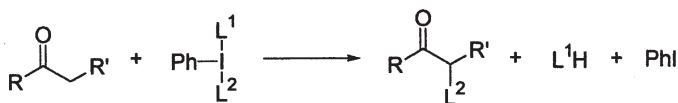


lytic decomposition of (dichloroiodo)benzene. Acetoxylation appears to require the prior formation of a phenyliodonium intermediate.

2.4

α -Functionalization of Carbonyl Compounds

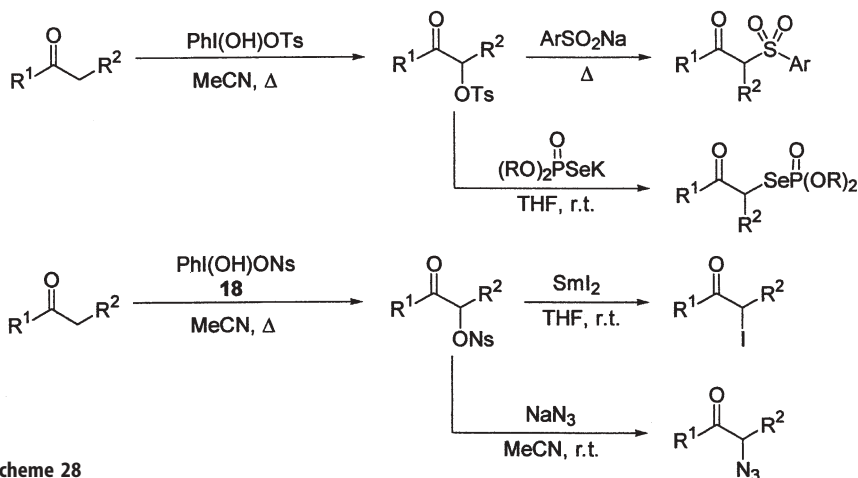
The use of aryl- λ^3 -iodanes for C-heteroatom bond formation at the α -carbon atoms of ketones and β -dicarbonyl compounds, and related transformations of silyl enol ethers and silyl ketene acetals, has been exhaustively summarized in recent reviews (Scheme 27) [5, 8]. Reactions of this type are especially useful for the introduction of oxygen ligands (e.g., $L^2 = \text{OH}$, OR, OCOR, OSO_2R , $\text{OPO}(\text{OR})_2$), and have been extensively utilized for the synthesis of α -sulfonyloxy ketones and α -hydroxy dimethyl ketals.



Scheme 27

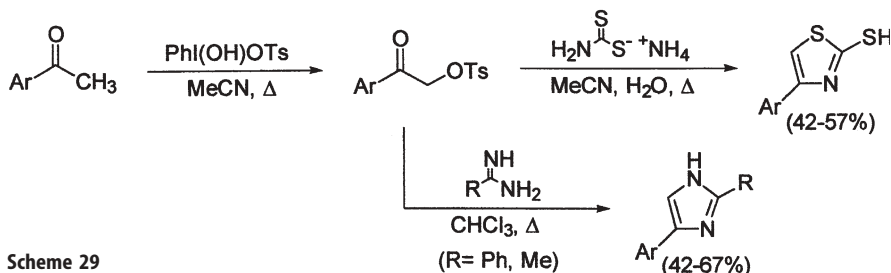
Recent developments in this area include the use of poly[hydroxy(tosyloxy)-iodo]styrenes [80], chiral 2-(α -alkoxyalkyl) analogs of [hydroxy(tosyloxy)-iodo]benzene [81–83], and iodine(III)-phosphonate and -phosphinate reagents [84] for C-oxygen bond formation at α -carbon. Oxy-sulfonylations at the α -carbon atoms of carboxylic anhydrides with [hydroxy(sulfonyloxy)iodo]arenes have also been documented [85].

The installation of heteroatom groups based on elements other than oxygen can be readily achieved by a two-step (usually one-pot) sequence in which ketones are first converted to tosyloxy ketones with HTIB, and nucleophilic reagents are then introduced [6, 8]. The nosylate analog **18** of HTIB can also be used for this purpose. Recent examples of C-S, C-Se, C-N, and C-I bond formation by this approach are shown in Scheme 28 [86–89].

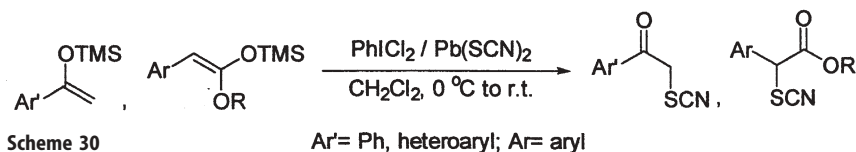


Scheme 28

Application of multidentate nucleophiles in this procedure provides access to a wide range of heterocyclic structures and is illustrated with recently published examples in Scheme 29 [90–92]. The 1990s literature on this subject has been reviewed [6, 8, 93].



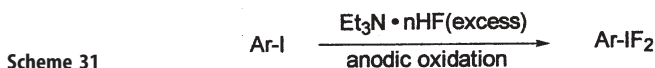
α -Thiocyanations of silyl enol ethers, silyl ketene acetals, and β -dicarbonyl compounds can be effected with the combined reagent, $\text{PhICl}_2/\text{Pb}(\text{SCN})_2$ (Scheme 30) [94,95].



2.5

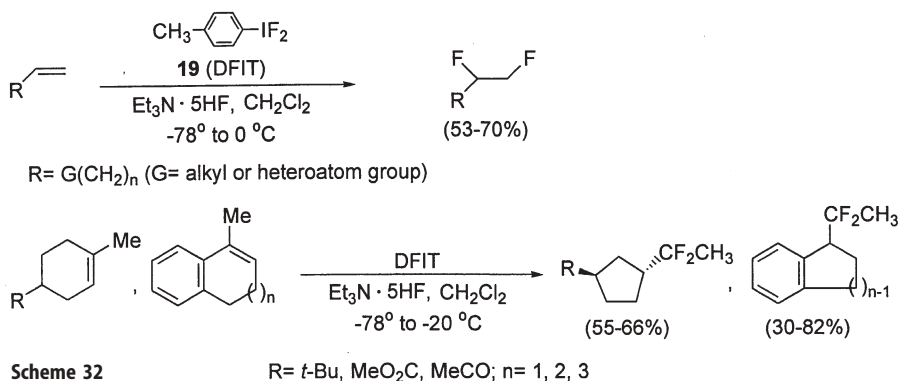
C-Fluorine Bond Formation

The generation of (difluoroiodo)arenes by anodic oxidations of aryl iodides in the presence of excess $\text{Et}_3\text{N} \cdot n\text{HF}$ is a notable recent development (Scheme 31) [96, 97]. Because the fluoroiodanes are activated by hydrogen-bonding with HF, such reagent combinations are especially useful for electrophilic fluorinations of organic compounds. When oxidation potentials of the aryl iodides are lower than those of the substrates, indirect anodic fluorinations of the latter can be achieved.



Among the (difluoroiodo)arenes, *p*-(difluoroiodo)toluene (**19**, DFIT) is the most popular reagent for C-fluorine bond-forming reactions. In a number of recent studies, DFIT was utilized in a 3-amine $\cdot n\text{HF}(\text{CH}_2\text{Cl}_2)$ medium, sometimes under electrochemical conditions.

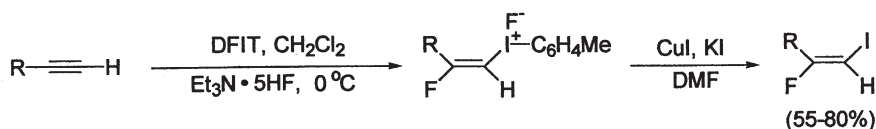
The use of DFIT in $\text{Et}_3\text{N} \cdot 5\text{HF}(\text{CH}_2\text{Cl}_2)$ for *vicinal*-difluorinations of variously functionalized terminal alkenes has recently been demonstrated (Scheme 32) [98]. Although fluorinative rearrangements of arylalkenes to 2,2-difluoro-1-arylalkanes with (difluoroiodo)arenes were documented decades ago [99–101],



Scheme 32

these are the first reported examples of 1,2-difluorinations of alkenes with difluoro(aryl)iodanes. However, while 4-carbomethoxycyclohexene gives a *cis*-difluoro adduct under these conditions, benzocycloalkadienes and 4-substituted-1-methylcyclohexenes undergo fluorinative ring contractions reminiscent of the arylalkene rearrangement, the methylcyclohexenes leading to *trans*-1,3-disubstituted cyclopentanes [102].

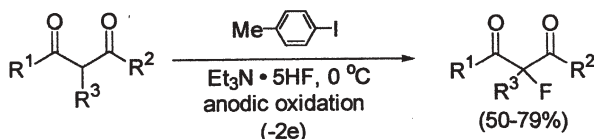
The treatment of terminal alkynes, including functionalized analogs, with electrochemically prepared DFIT/Et₃N·5HF affords (*E*)- β -fluoroalkenyl(*p*-tolyl)iodonium fluorides (Scheme 33) [103]. The crude iodonium salts can be extracted from the reaction mixtures with dichloromethane and used without purification for further synthetic transformations. For example, when the crude iodonium salts were mixed with CuI-KI (CH₂Cl₂), the corresponding (*E*)-1-iodo-2-fluoroalkenes were obtained.



Scheme 33

R = G(CH₂)_n (G = alkyl or heteroatom group)

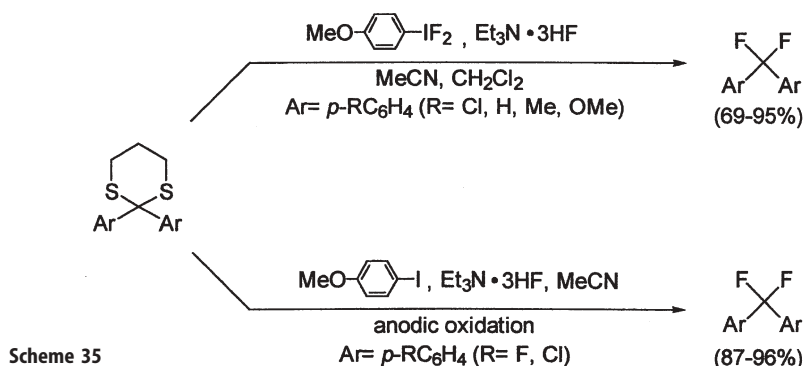
DFIT has been employed with pyridine·9HF for monofluorinations of β -ketoesters [104]. Similar α -fluorinations can be effected by electrolysis of Et₃N·5HF solutions, containing 1:1 mixtures of *p*-iodotoluene and β -dicarbonyl compounds, in an undivided cell at 0 °C. In this procedure, DFIT is generated in situ and mediates fluorination of the substrate (Scheme 34) [97].



Scheme 34

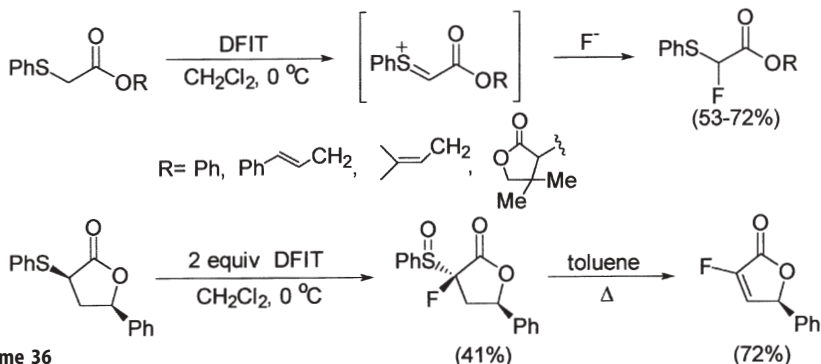
R¹ = alkyl, Ph; R² = alkyl, Ph, OR; R³ = Me, H

Organosulfur compounds are especially useful for C-fluorine bond forming reactions with (difluoroiodo)arenes. For example, dithioketal derivatives of benzophenones are readily converted to diaryldifluoromethanes with two equivalents of DFIT in dichloromethane [105]. This transformation has also been effected with electrochemically prepared *p*-(difluoroiodo)anisole/ $\text{Et}_3\text{N} \cdot 3\text{HF}$, and by anodic oxidations of *p*-iodoanisole in acetonitrile solutions containing $\text{Et}_3\text{N} \cdot 3\text{HF}$ and dithioketal substrates (Scheme 35) [96]. Under the latter conditions, *p*-(difluoroiodo)anisole is continuously regenerated, and the iodoarene was employed at catalytic levels for high yield conversions of the dithioketals to diaryldifluoromethanes.



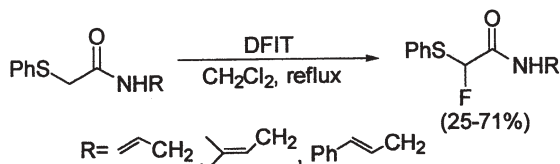
α -(Phenylsulfanyl)acetate esters undergo fluorination at the α -carbon atom upon treatment with DFIT in dichloromethane (Scheme 36) [106]. As demonstrated with the ethyl ester, the use of excess DFIT leads to difluorination (2 equiv), or difluoro-sulfoxidation (3 equiv) of the $-\text{CH}_2\text{S}-$ moiety. Similar treatment of α -(phenylsulfanyl)lactones with two equivalents of DFIT, and thermolysis of the resulting fluorosulfoxides in toluene gave the corresponding 2-fluoro-2-buten-4-olides (Scheme 36) [106].

The fluorinations of α -phenylsulfanyl esters and lactones with DFIT are noteworthy, since α -fluorinations of aliphatic esters and lactones, or their silyl ketene



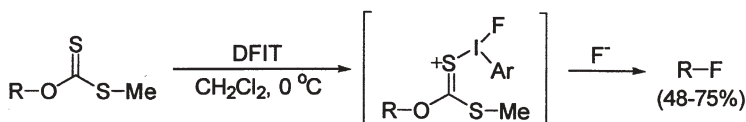
acetals, with (difluorido)arenes have not been documented. Such transformations appear to be examples of the fluoro-Pummerer reaction involving the formation of alkylidenesulfonium ion intermediates (Scheme 36).

DFIT-induced fluoro-Pummerer reactions of *N*-substituted-2-(phenylsulfanyl)acetamides have also been reported (Scheme 37) [107]. With some amides, cyclization of the Pummerer intermediate was competitive with fluorination, and in other cases, fluorination was preempted by sulfoxide formation.

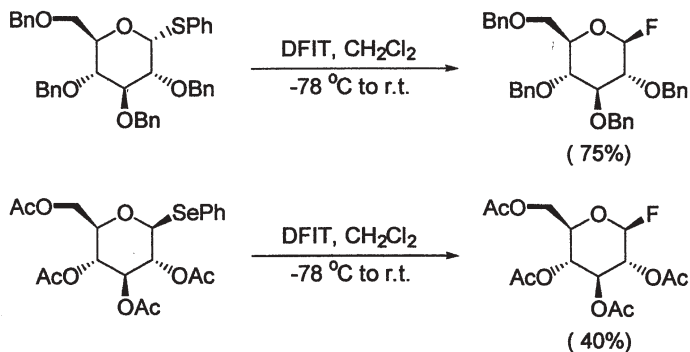


Scheme 37

The conversion of alcohols to xanthate esters, and treatment of the latter with DFIT provides access to 1°- and 2°-alkyl fluorides, probably through intermediates of the type shown in Scheme 38 [108].

Scheme 38 R = *n*-C₁₆H₃₃, PhCH₂, PhCHEt, adamantyl, cholestanyl, menthyl

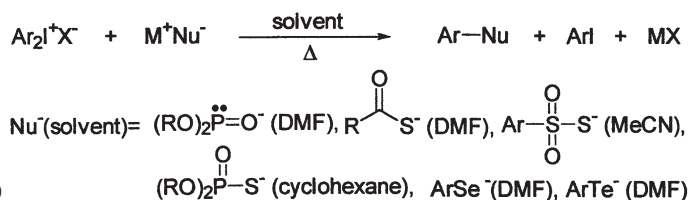
1-Arylthio- and 1-phenylselenoglycosides can be converted to 1-fluoroglycosides with DFIT in dichloromethane (Scheme 39) [109]. The stereochemistry of such reactions depends on several factors, including the nature of the glycosyl group, the identity (S, Se) of the C-1 heteroatom, the presence or absence of a C-2 acetoxy group, and in some cases, the configuration (α or β) of the anomeric carbon. A striking example of neighboring acetoxy participation is provided by DFIT fluorinations of β -1-phenylseleno-tetra-*O*-acetylglucose and its 2-deoxy analog, which occurred with complete retention and complete inversion of configuration, respectively.



Scheme 39

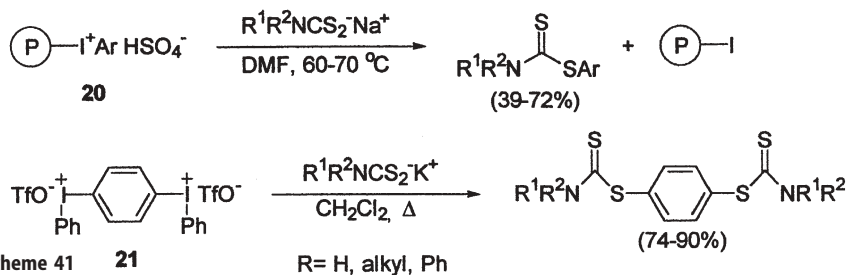
3 Diaryliodonium Salts

The use of diaryliodonium salts for direct arylations of nucleophilic species is a well-established practice. Examples of C-heteroatom bond formation by this approach, including uncatalyzed arylations of dialkyl phosphite, thiocarboxylate, arylthiosulfonate, dialkyl phosphorothiolate, arylselenolate, and aryltellurolate salts with symmetrical diaryliodonium halides, are shown in (Scheme 40) [110–115].



Scheme 40

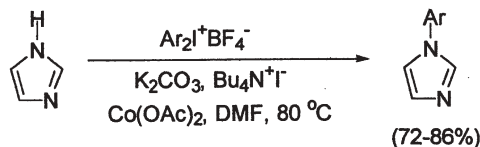
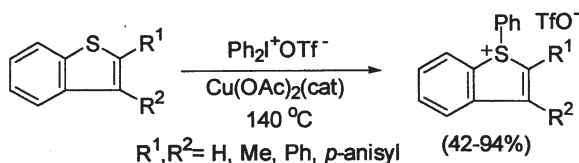
Sodium dithiocarbamates are similarly converted to aryl dithiocarbamates with polymeric aryliodonium bisulfates **20** derived from styrene (Scheme 41) [116]. The high regioselectivity of C-I bond cleavage in **20** is noteworthy, “only trace amounts of iodoarenes” [ArI] having been detected in “occasional cases”. Regioselective conversions of *p*-phenylenebis(phenyliodonium) ditriflate (**21**) to *p*-phenylenebis(dithiocarbamates) with dithiocarbamate salts have also been reported (Scheme 41) [117].



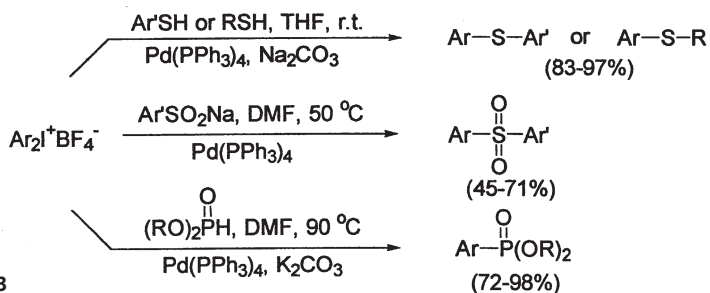
Scheme 41

Arylations of weak organic nucleophiles are best achieved with iodonium salts possessing nucleofugic anions and, in some cases, can be facilitated with transition metal catalysts. Recent examples include Cu(II)-catalyzed *S*-phenylations of 1-benzothiophenes with diphenyliodonium triflate [118], and Co(II)-catalyzed *N*-arylations of imidazoles with diaryliodonium tetrafluoroborates (Scheme 42) [119].

Palladium-catalyzed cross-coupling reactions of diaryliodonium tetrafluoroborates have recently been employed for conversions of mercaptans to aryl- and diaryl sulfides, sodium arenesulfonates to diaryl sulfones, and dialkyl phosphites to aryl phosphonates (Scheme 43) [120–122].

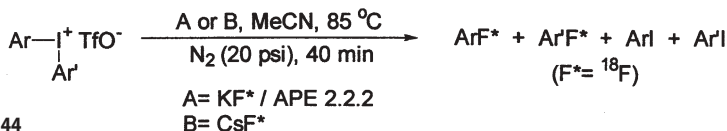


Scheme 42



Scheme 43

The catalytic influence of 18-crown-6 on the production of fluorobenzene from diphenyliodonium tetrafluoroborate and KF in dichloroethane was documented some years ago [123]. More recently, diaryliodonium salts have been used for direct syntheses of [^{18}F]-fluoroarenes [124, 125]. After an initial study in which various counterions were surveyed, this was finally accomplished by the treatment of diaryliodonium triflates and trifluoroacetates with $^{18}\text{F}^- \text{K}^+$ -APE 2.2.2 (i.e., the aminopolyether 4,7,13,16,21,24,27-hexaoxa-1,10-diazabicyclo-[8.8.8]hexacosane) or $\text{Cs } ^{18}\text{F}$ in acetonitrile (Scheme 44). An added feature of these studies is rather extensive confirmation that nucleophiles are preferentially directed to the more deactivated ring of unsymmetrical diaryliodonium ions, unless one of the rings possesses *ortho*-substituents [125].



Scheme 44

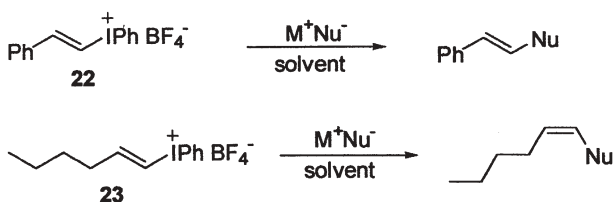
4

Alkenyl(aryl)iodonium Salts

Alkenylations of heteroatom nucleophiles with alkenyl(aryl)iodonium salts occur by a variety of mechanisms, including $\text{S}_{\text{N}}1$, $\text{S}_{\text{N}}2$, alkylidenecarbene, and addition-elimination pathways [126, 127]. Reactions that occur with retention of configuration at vinylic carbon are sometimes attributed to a ligand-coupling

(LC) mechanism in which iodobenzene (or ArI) is expelled from tricovalent intermediates, i. e., alkenyliodanes [126, 127].

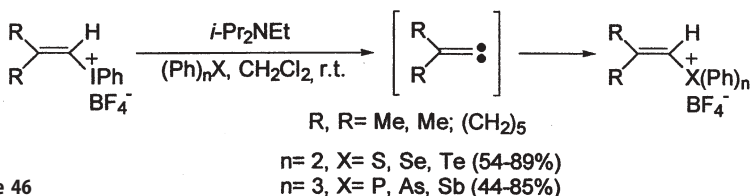
In a recent series of studies focused on the synthetic utility of alkenyliodonium salts, (*E*)- β -phenylethenyl(phenyl)- and (*E*)-1-hexenyl(phenyl)iodonium tetrafluoroborates, **22** and **23**, were utilized for alkenylations of a range of soft, anionic nucleophiles (Scheme 45) [128–135]. In all cases but one, alkenylations with **22** occurred with retention of configuration, while alkenylations with **23** occurred with inversion of configuration. Only the dialkyl phosphoroselenolate salts gave mixtures of (*Z*)- and (*E*)-products with **22** [132]. Furthermore, although cuprous iodide was used to catalyze the reactions of **22** and **23** with the phosphorothioate and -dithioate salts, the stereochemical results were the same [131, 133]. It was generally assumed that retention was an outcome of the ligand-coupling or addition-elimination pathways, while stereochemical inversion was attributed to the vinylic S_N2 mechanism.



MNu (conditions): $R^1R^2NCS_2Na$ (THF, r.t.); $ROCS_2K$ (THF, r.t.)
 $RSCS_2K$ (THF, r.t.); $(RO)_2P(O)SK$ (THF, r.t., Cul); $(RO)_2P(O)SeK$ (THF, r.t.);
 $(RO)_2PS_2K$ (THF, r.t., Cul); $ArSeNa$ (EtOH, 0 °C); $ArTeNa$ (EtOH, 0 °C)

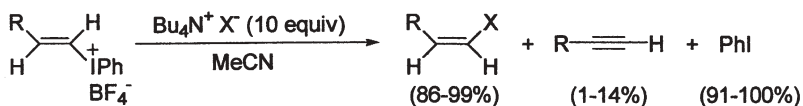
Scheme 45

The treatment of β , β -dialkylvinyl(phenyl)iodonium salts with an appropriate base leads to alkylidenecarbenes. When such carbenes are generated in the presence of neutral heteroatom nucleophiles, vinyl onium salts can be obtained [136]. Diisopropylethylamine is a useful base for this purpose, especially when further transformations of the onium salts are possible. α -Elimination reactions of this type have recently been employed for the synthesis of alkenyl(diaryl)- and alkenyl(triaryl)onium salts of Group 15 and Group 16 elements (Scheme 46) [137].



Scheme 46

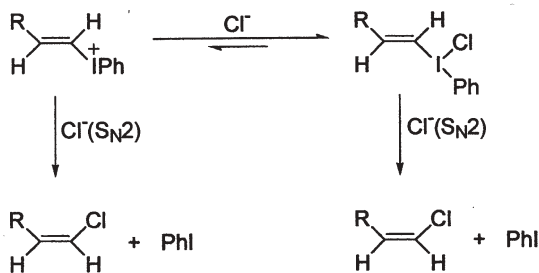
Studies of the conversion of (*E*)- β -alkylvinyl(phenyl)iodonium tetrafluoroborates to (*Z*)-haloalkenes (complete inversion) with tetrabutylammonium halides (Cl^- , Br^- , I^-) in acetonitrile provide convincing evidence for the vinylic



Scheme 47 R = $n\text{-C}_8\text{H}_{17}$, $\text{Ph}(\text{CH}_2)_3$; X = Cl^- , Br^- , I^-

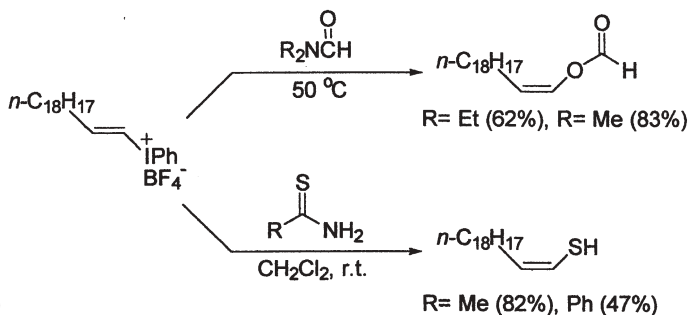
$\text{S}_{\text{n}}2$ mechanism (Scheme 47) [138, 139]. Concerted, in-plane nucleophilic substitutions of this type are facilitated by the exceptional nucleofugality of iodobenzene, and appear to be operative with weakly basic nucleophiles. Similar reactions of (*E*)- β -phenylvinyl(phenyl)iodonium tetrafluoroborate are slower, less stereoselective, and more prone to competitive alkyne formation.

Kinetic and spectroscopic studies of reactions of several (*E*)- β -alkylvinyl(phenyl)iodonium tetrafluoroborates with tetrabutylammonium chloride indicate that the vinyliodonium chlorides, generated by anion exchange, are present in equilibrium with the corresponding vinyl(chloro)iodanes (Scheme 48) [140]. Both species undergo vinylic $\text{S}_{\text{n}}2$ reactions with chloride ion, and although the chloroiodanes are less reactive, they are by far the dominant species at equilibrium and account for most of the (*Z*)-1-chloroalkene production.



Scheme 48

Vinylic $\text{S}_{\text{n}}2$ reactions of (*E*)- β -alkylvinyl(phenyl)iodonium tetrafluoroborates with such weakly basic nucleophiles as *N*, *N*-dialkyl formamides, thioamides, thioureas, and heterocyclic thiols have recently been documented, examples of which are shown in Scheme 49 [141, 142].



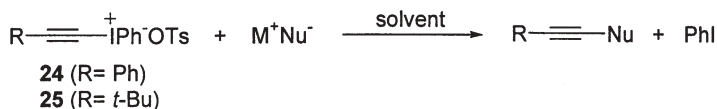
Scheme 49

5 Alkynyl(aryl)iodonium Salts

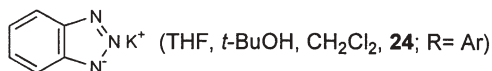
The treatment of alkynyl(aryl)iodonium salts with carbon and heteroatom nucleophiles often results in a Michael addition/ α -elimination sequence, and is an excellent method for the generation of alkylidenecarbenes, $R(\text{Nu})\text{C}=\text{C}$: [143, 144]. The carbenes may rearrange to alkynes, or undergo intramolecular 1,5-CH bond insertions leading to cyclopentene rings. Whether rearrangement or insertion is dominant depends on the migratory aptitudes of the R and Nu groups in the carbenes and the availability of γ -CH bonds in these groups. In recent years, alternate modes of carbenic reactivity, including intramolecular C-heteroatom bond insertions and intramolecular additions to C,C-double bonds, have been exploited to synthetic advantage.

5.1 Alkynylation

Recent examples of the rearrangement or alkynylation pathway include conversions of arylethynyl- and *tert*-butylethynyl(phenyl)iodonium tosylates **24** and **25** to alkynylphosphonates, -selenides, and -tellurides with the appropriate anion salts in DMF (Scheme 50) [145–147], and a similar synthesis of “push-pull” selenides and tellurides from alkynyliodonium triflates containing electron-withdrawing groups in the alkynyl moiety [148].



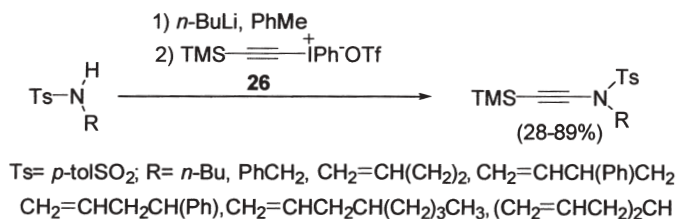
MNu (solvent) : (RO)₂PONa (DMF, EtOH), ArSeNa (DMF), ArTeNa (DMF),



Scheme 50

Arylethynylations of potassium benzotriazolate with iodonium tosylates **24** in THF/*t*-BuOH/CH₂Cl₂ have also been reported [149, 150]. However, when the *tert*-butylethynyl salt **25** was used instead, insertion of the intermediate alkylidenecarbene into the O-H bond of *tert*-butyl alcohol preempted rearrangement.

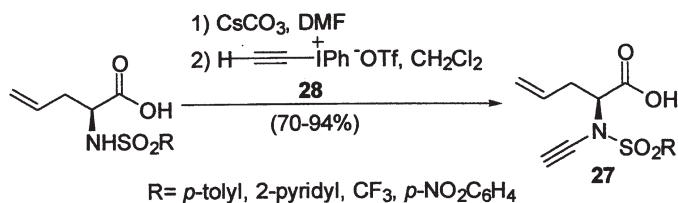
Anions of *secondary*-sulfonamides, especially *N*-substituted tosylamidate ions, have emerged as premier partners for C-N bond forming reactions with alkynyliodonium salts. To a much lesser extent *secondary*-carboxamidate ions have also been used for this purpose. For example, the sequential treatment of *N*-substituted tosylamides with *n*-butyllithium and phenyl(trimethylsilylethynyl)iodonium triflate (**26**) affords the corresponding *N*-trimethylsilylethynyl-*p*-toluenesulfonamides, which can be desilylated with tetrabutylammonium fluoride in “wet” THF (Scheme 51) [151]. It is noteworthy that the presence of such groups as *n*-Bu and CH₂=CH(CH₂)₂ in the tosylamidate ions did



Scheme 51

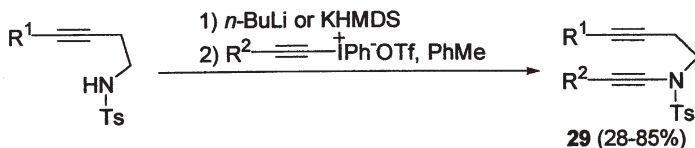
not lead to *N*-tosyldihydropyrroles (i. e., the insertion pathway). Similar alkynylations were demonstrated with *N*-benzylcarboxamides and the trifluoromethanesulfonamide analog.

This approach to *N*-alkynylsulfonamides has been applied to the synthesis of enantiomerically pure derivatives **27** of *N*-(ethynyl)allylglycine (Scheme 52) [152]. In this case, deprotonated sulfonamide derivatives of (*S*)-allylglycine were treated with ethynyl(phenyl)iodonium triflate (**28**), since the trimethylsilylethynyl salt **26** was not very effective for this purpose.



Scheme 52

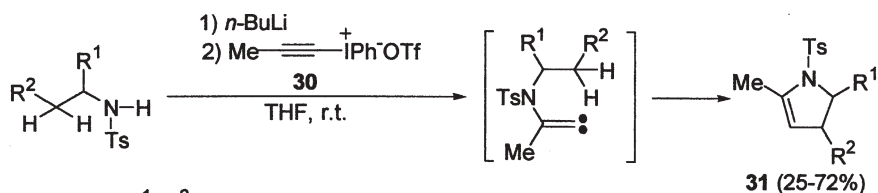
N-(1-Alkynyl)-*N*-(3-alkynyl)toluenesulfonamides **29** of considerable structural variety are accessible via reactions of *N*-(3-alkynyl)tosylamidate ions with alkynyliodonium triflates (Scheme 53) [153]. Selected compounds from this series were utilized for regiospecific Rh(I)-catalyzed syntheses of indolines.



Scheme 53

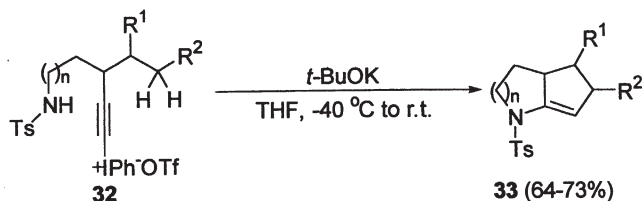
5.2 CH-Bond Insertions

Reactions of phenyl(propynyl)iodonium triflate (**30**) with tosylamidate ions possessing *N*-alkyl chains of two or more carbon atoms follow the carbene insertion pathway leading to *N*-tosyldihydropyrroles **31** (Scheme 54) [154, 155]. The *N*-cyclohexyl tosylamidate ion leads stereospecifically to the *cis*-fused bicyclic dihydropyrrole under these conditions.



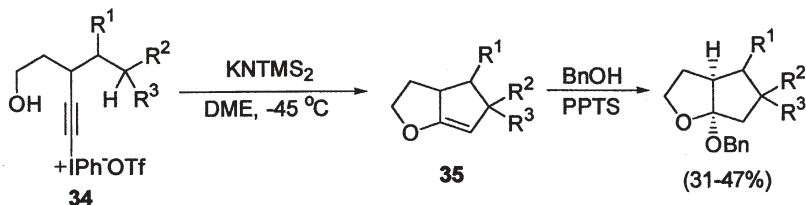
Scheme 54 $\text{R}^1, \text{R}^2 = \text{Ph, Me; H, Ph; H, Me; Me, CH}_2\text{OTBDMS, (CH}_2)_4$

The intramolecular version of the dihydropyrrole synthesis can be effected with starting compounds **32**, containing tosylamido and alkynyliodonio groups linked by two or three carbon atoms, and affords bi- and tricyclic tosylenamides **33** (Scheme 55) [155, 156]. Formation of the azabicyclo [n.3.0] nucleus ($n = 3, 4$) occurs with differing degrees of diastereoselectivity, but generally shows some preference for the *syn*-diastereomers. By an appropriate choice of starting compounds, carbonyl groups can be placed at different locations in the tosylenamide structures.



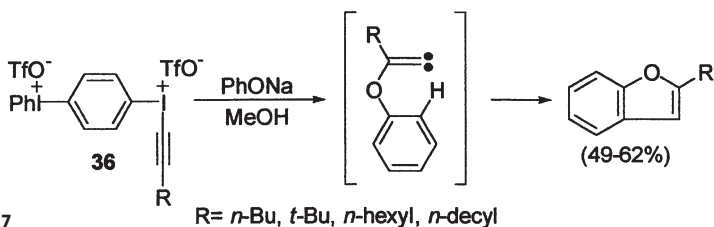
Scheme 55 $n = 1, 2; \text{R}^1, \text{R}^2(\text{examples}) = \text{H, Ph; Me, H; (CH}_2)_4; \text{H, OTBDMS}$

Bicyclizations of structurally analogous 5-hydroxy-1-pentynyliodonium triflates **34** to cyclopentene-annulated tetrahydrofurans **35** have also been reported (Scheme 56) [157]. Because the strained enol ether moiety in **35** is acid sensitive, these compounds were converted to their monobenzyl ketals. In general, bicyclizations of **34** are less efficient and less versatile than those of the tosylamido analogs.



Scheme 56 $\text{R}^1, \text{R}^2, \text{R}^3 = \text{Me, H, H; (CH}_2)_4; \text{H; H, Me, Me; H, H, Ph}$

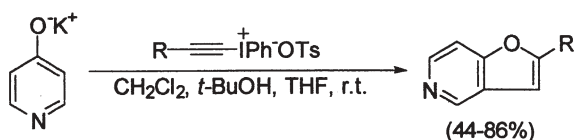
Admixture of alkynyl(*p*-phenylene)bisiodonium ditriflates **36** with sodium phenoxide in methanol results in the production of benzofurans (Scheme 57)



Scheme 57

[158, 159]. In such reactions, insertion of the intermediate alkylidene carbenes into the *ortho*-CH bonds of the aromatic ring is preferred over insertion into the γ -CH bonds of the aliphatic side chain.

Alkynyliodonium tosylates have been similarly employed with the potassium salts of 3- and 4-hydroxypyridines for the synthesis of furopyridines (Scheme 58) [160]. As expected, the 3-hydroxypyridines afford mixtures of regioisomeric furopyridines, corresponding to carbenic insertions into the non-equivalent *ortho*-CH bonds of the pyridine ring.



Scheme 58

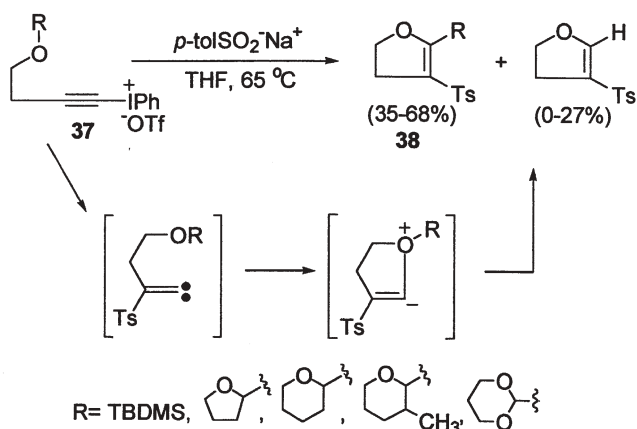
Additional examples of *ortho*-CH bond insertions can be found in reported preparations of *N*-tosyl-2-methylindoles from lithium tosylanilides and propynyliodonium triflate 30 [154, 156], and 2-aryloxybenzofurans from trimethylsilyliodonium triflate 26 and potassium salts of nitrophenols [161].

5.3

C-Heteroatom Bond Insertions

Reactions of silyl, pyranlyl, furanyl, and 1,3-dioxanyl ethers, 37, of 4-hydroxy-1-butynyl(phenyl)iodonium triflate with sodium *p*-toluenesulfinate in THF afford 2-substituted-3-tosyldihydrofurans 38, and, in the case of the *cis*- and *trans*-2-methyl-1-pyranlyl analogs, occur with high (but not complete) stereochemical retention (Scheme 59) [162, 163]. The furanyl and pyranlyl ethers also give rise to 3-tosyldihydrofuran. A mechanism for these reactions involving cyclization of alkylidene carbenes to vinyloxonium ylides has been proposed. Stevens rearrangement of the ylides would give 38, while protonation of the ylides and loss of the migrating group would give 3-tosyldihydrofuran.

Similar intramolecular capture of an alkylidene carbenoid intermediate with the lone-pair of a carbamate nitrogen atom in the novel bicyclization of an alkynyl-substituted *N*-tosylurea has been suggested [164].

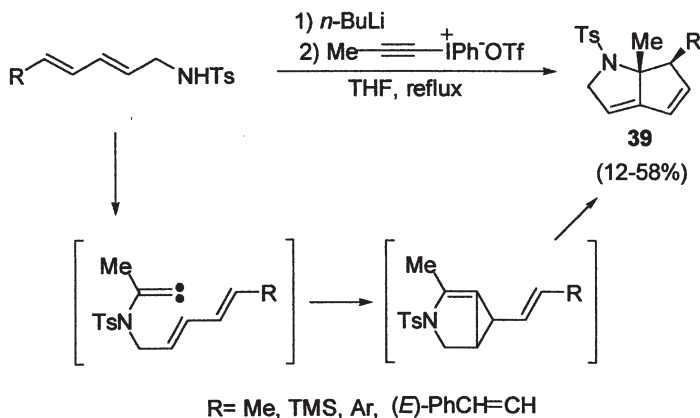


Scheme 59

5.4

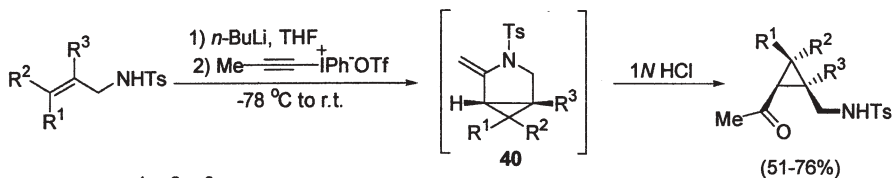
Intramolecular Additions

The sequential treatment of (*E,E*)-1-tosylamido-2, 4-alkadienes with *n*-butyllithium and propynyliodonium triflate **30** results in a cascade addition/bicyclization sequence leading to bicyclic *N*-tosyldihydropyrroles **39** (Scheme 60) [165, 166]. These transformations are completely stereoselective for the *cis*-isomers, and appear to proceed by intramolecular addition of alkylidenecarbene intermediates to the C₂-C₃ double bond of the pentadienyl chain to give azabicyclo[3.1.0]hexenes, which rearrange to **39** through diyl radical species.



Scheme 60

Similar reactions of allylic tosylamidate ions with **30** provide access to azabicyclo[3.1.0]hexanes **40**, possessing an exocyclic double bond [167]. Such compounds (generated in situ) have been utilized for the synthesis of *cis*-1-acetyl-2-tosylamidocyclopropanes (Scheme 61) [168].

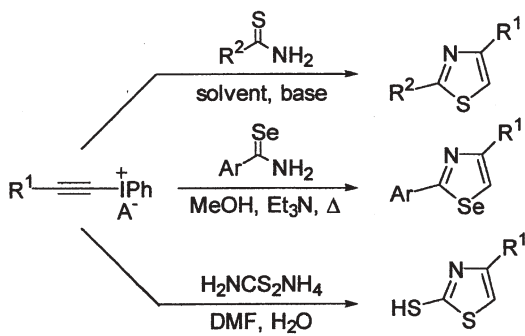


Scheme 61 $R^1, R^2, R^3 = H, H, H; H, Me, H; H, Et, H; Et, H, H; H, H, Me; Me, Me, H$

5.5

Cyclocondensations

Reactions of alkynyliodonium salts with multidentate nucleophiles can be employed for the synthesis of heterocyclic compounds. Recent examples include preparations of thiazoles, selenazoles, and 2-mercaptothiazoles by the treatment of alkynyliodonium mesylates or tosylates with thioamides, selenoamides, and ammonium dithiocarbamate (Scheme 62) [169–171]. A novel hetero-Claisen rearrangement of tricovalent iodine(III) intermediates was proposed to account for the 2, 4-disubstitution pattern of the thiazoles [169].



Scheme 62

$R^1 = \text{aryl, alkyl, CH}_2\text{OR}; A^- = \text{MsO}^- \text{ or } \text{TsO}^-$

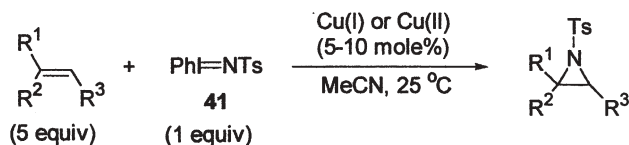
6

Sulfonylimino(aryl)iodanes

6.1

Aziridination

The use of sulfonylimino(aryl)iodanes, especially [(tosylimino)iodo]benzene (41), as nitrene-transfer agents has undergone considerable development during the past decade. Much of this effort is based on the finding in the early 1990s that tosylaziridinations of alkenes with $\text{PhI} = \text{NTs}$, previously demonstrated with Mn(III)- and Fe(III)-porphyrin catalysts, can be achieved more generally and efficiently with copper(I) and copper(II) salts; i. e., the Evans aziridination reaction [172, 173]. Standard conditions for preparative aziridinations of this type were developed, and applied to cyclic and acyclic alkenes, arylalkenes, and α, β -

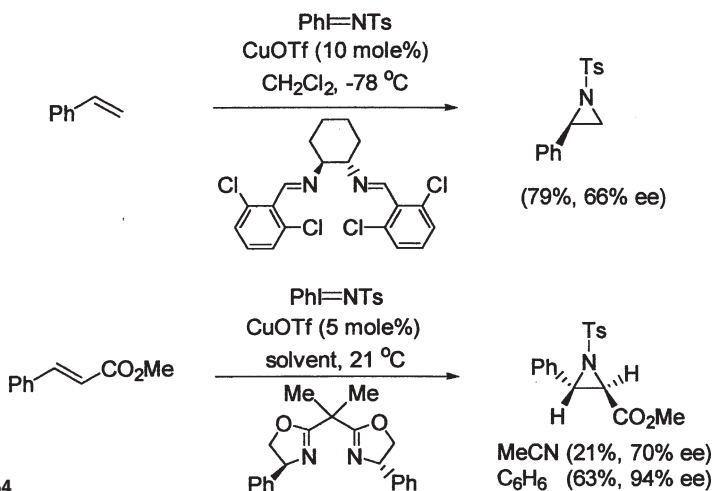


Scheme 63

$\text{R}^1, \text{R}^2, \text{R}^3 = \text{H, alkyl, aryl, CO}_2\text{Me}$

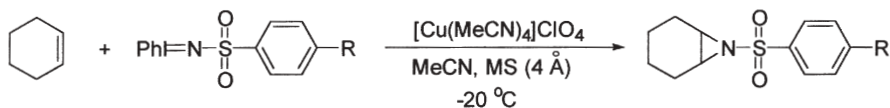
unsaturated esters (Scheme 63). Tosylaziridinations of *trans*-alkenes and *cis*-4-octene, under these conditions, were found to be highly stereoselective.

A parallel development during this period was the identification of chiral bis(oxazolines) and bis(benzylidene)diaminocyclohexanes as useful ligands for copper-catalyzed, asymmetric tosylaziridination reactions with $\text{PhI}=\text{NTs}$ (Scheme 64) [174, 175]. Evidence for the likely formation of copper(III)-nitrene intermediates, 'Cu(III)=NTs', in such reactions was also reported [176].



Scheme 64

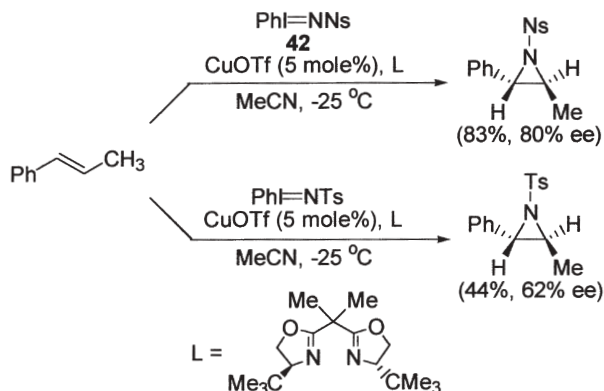
More recently, the effect of substituents in the arenesulfonyl moiety on Cu(I)-catalyzed aziridinations of cyclohexene with a series of [(arenesulfonylimino)iodo]benzenes was evaluated (Scheme 65) [177]. Iminoiodanes possessing *p*-OMe, *p*-CF₃, and *p*-NO₂ substituents gave higher yields of aziridines than the tosylimino analog. Product yields in these reactions are not simply related to relative rates of aziridination (*p*-MeO > *p*-Me > *p*-NO₂), and appear to reflect partitioning of the copper(III)-nitrene intermediates between aziridination of the C,C-double bond and reduction to the corresponding sulfonamides.



R(isolated yield) : Me(74%), CF₃(88%), NO₂(92%), MeO(98%), I(76%), F(69%)

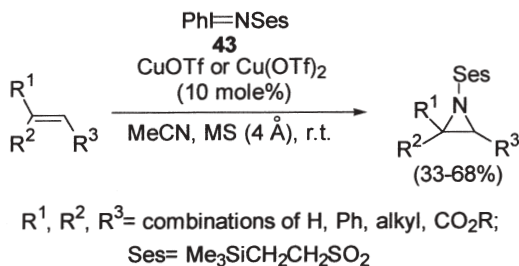
Scheme 65

The greater overall efficiency of [(nosylimino)iodo]benzene (**42**), $\text{PhI}=\text{NNs}$, and the *p*-methoxysulfonylimino analog has been demonstrated with various olefinic substrates and obviates the need for the five-fold excess of alkene in the standard aziridination procedure [177]. These iminoiodanes were also employed for asymmetric aziridinations of a series of olefinic compounds, and in most cases, gave higher enantioselectivities than the tosyliminoiodane (Scheme 66) [178]. Nosylaziridines offer some synthetic advantages over their tosyl counterparts [179]. They are more reactive with nucleophiles, and once ring-opening has occurred, the nosylamido group is more easily deprotected.



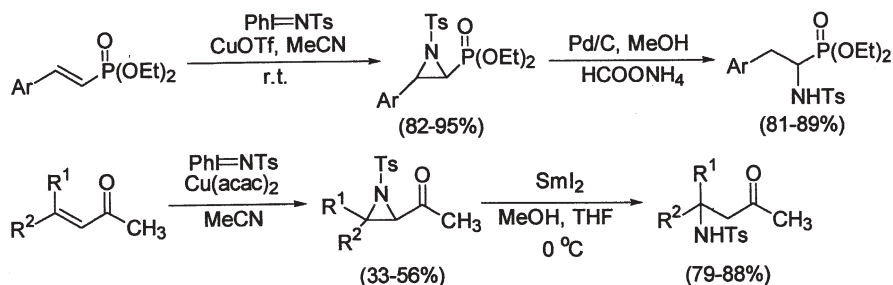
Scheme 66

Another recent innovation is the use of [(2-trimethylsilyl)ethanesulfonylimino]iodo]benzene (**43**), $\text{PhI}=\text{NSes}$, for Cu(I) and Cu(II)-catalyzed aziridinations of olefinic compounds (Scheme 67) [180]. This reagent was deliberately designed for facile deprotection of the *N*-sulfonylaziridines and products derived therefrom. For example, several *N*-(Ses)aziridines were converted to aziridines with TASF [$(\text{Me}_2\text{N})_3\text{S}^+ \text{SiMe}_3\text{F}_2^-$] in MeCN or DMF at room temperature.



Scheme 67

The availability of monofunctionalized *N*-sulfonylaziridines by the Evans aziridination method, and capacity of the aziridines to undergo regioselective ring-openings with various reducing agents have been exploited for the synthesis of bifunctional nitrogen compounds. Examples of such two-step sequences include syntheses of α -(tosylamido)alkylphosphonates [181], β -tosylamido



Scheme 68

 $\text{R}^1, \text{R}^2 = \text{H, Ph; H, H; Me, Me}$

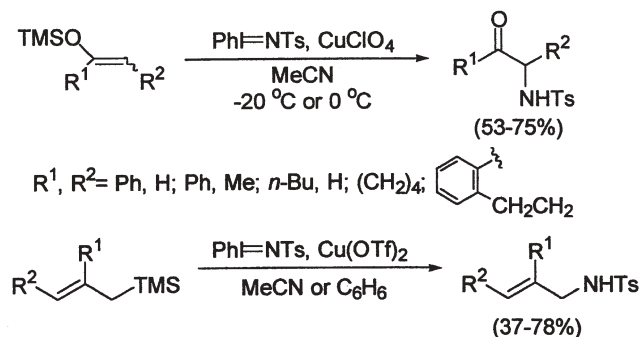
ketones, esters and amides [182, 183], and 2-substituted α - and β -(sulfonylamido)carboxylates [184], examples of which are shown in Scheme 68.

Copper-catalyzed tosylaziridinations with PhI=NTs have also been incorporated into multistep syntheses of α -vinylalanine [185], and the *trans*-decalin core of the marine alkaloid, kalihinol A [186]. Distereoselective tosylaziridinations of planar-chiral azoninones [187], and Ses-, nosyl-, and tosylaziridinations of 11-pregnene-3,20-dione have also been reported [188, 189].

6.2

Amidation

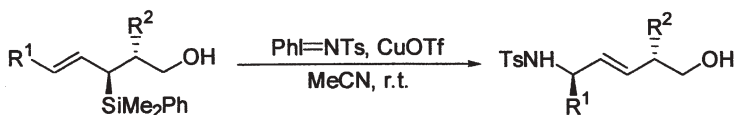
Copper-catalyzed reactions of [(tosylimino)iodo]benzene with unsaturated compounds sometimes lead to tosylamidation. Examples include conversions of silyl enol ethers to α -tosylamido ketones [173], and tosylamidation of allylic silanes with loss of the silyl group [190] (Scheme 69).



Scheme 69

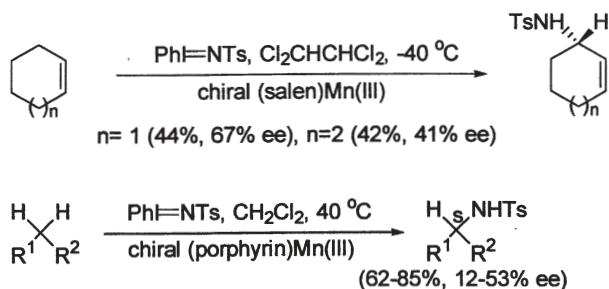
 $\text{R}^1, \text{R}^2 = \text{H, H; CH}_2\text{Cl, H; CH}_2\text{OAc, H; H, Ph}$

Chiral (*E*)-crotylsilanes have been utilized with PhI=NTs for Cu(I) -catalyzed syntheses of olefinic dipeptide isosteres, examples of which are shown in Scheme 70 [191]. In this case, tosylamidation occurs with allylic inversion, probably via asymmetric tosylaziridination of the C,C-double bond. The diastereoselectivity of product formation is high ($>30:1$) and appears to be strongly influenced by the hydroxyl group in the starting compounds.



Scheme 70 $R^1, R^2 = \text{Me, H (65\%); Me, Me (64\%)}$

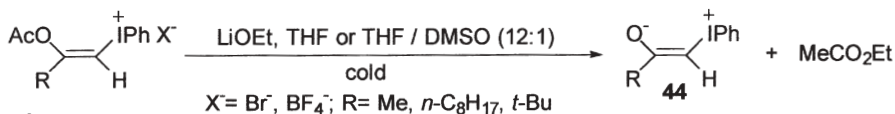
Several recent publications are focused on allylic and benzylic tosylation of a range of unsaturated hydrocarbons with $\text{PhI}=\text{NTs}$ [192–196]. Salen-Mn(III) complexes, Ru(II) and Mn(III)-porphyrins, and Ru(II)- and Ru(III)-amine complexes were employed as catalysts for this purpose, and issues pertaining to catalyst efficiency and enantioselectivity of tosylation were addressed. Examples are shown in Scheme 71 [192, 193].



Scheme 71 $R^1, R^2 = \text{Ar, Me; 1,2-C}_6\text{H}_4(\text{CH}_2)_n (n = 2, 3)$

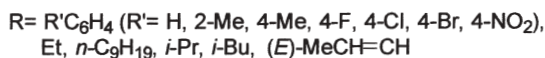
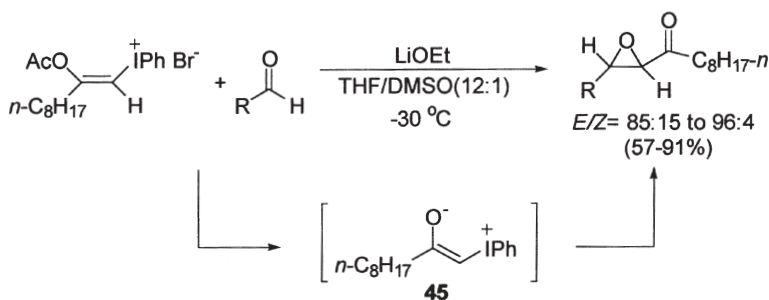
7 Iodonium Enolates

One of the most notable recent advances in iodonium ylide chemistry is the first demonstrable generation of iodonium enolates **44** formally derived from unactivated monocarbonyl compounds [197]. This was accomplished by the treatment of (*Z*)- β -acetoxyvinyl iodonium salts with lithium ethoxide, either in THF or in THF-DMSO (12:1) (Scheme 72).



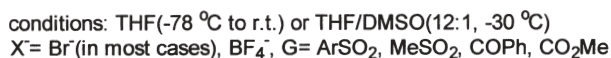
Scheme 72

Although the ylides are too unstable for isolation, they can be utilized in situ for stereoselective syntheses of α, β -epoxy and -aziridinyll ketones. For example, the generation of 1-phenyliodonium-1-decen-2-olate (**45**) in the presence of aliphatic and aromatic aldehydes affords the corresponding epoxy ketones with high *trans*-stereoselectivity (Scheme 73) [197]. Efforts to trap **45** with ketones were unsuccessful, leading instead to 10-eicosene-9, 12-dione, the formal ylide “dimerization” product.



Scheme 73

N-Phenylbenzaldimine is similarly unreactive with the decenolate ylide. However, when the iodonium enolates are employed with *N*-acyl- and *N*-sulfonylimines of aromatic aldehydes, aziridinyl ketones are obtained (Scheme 74) [198, 199].



Scheme 74

The diastereoselectivity of aziridine formation with **45** was examined in detail and depends on various factors, including the nature of the group attached to the imine nitrogen atom, the solvent, and even the counterion of the starting iodonium salt. Not all sulfonyl groups are the same. For example, reactions of **45** with the *N*-benzenesulfonyl- and *N*-methanesulfonylimines of benzaldehyde in THF-DMSO at -30 °C gave *trans*:*cis*-aziridine ratios of 61:39 and 36:64, respectively. In general, the use of *N*-(mesitylsulfonyl)imines with **45** in THF shows high preference for the production of *cis*-aziridines, while the use of *N*-acylimines with **45** in THF-DMSO favors the formation of *trans*-aziridines.

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8

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Heteroatom-Heteroatom-Bond Forming Reactions

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Recent progress on the use of hypervalent iodine reagents for the construction of heteroatom-heteroatom bonds is reviewed. Reactions of aryl- λ^3 -iodanes with heteroatom substrates derived from third-row elements and beyond are considered first, and an unusual example of heteroatom-heteroatom bond formation with diaryliodonium salts is then discussed. Finally, the use of sulfonylimino(aryl)iodanes for imidations of phosphorus, sulfur, selenium, and arsenic compounds, including enantioselective transformations (S,Se), and alternate hypervalent iodine approaches to *N*-sulfonylsulfilimines and *N*-sulfonylarsinimines are summarized.

Keywords. Heteroatom-heteroatom bond formation, Aryl- λ^3 -iodanes, Sulfonyliminoiodanes, Hypervalent iodine

1 Introduction	173
2 Aryl- λ^3 -Iodanes	174
3 Sulfonylimino(aryl)iodanes	177
4 Conclusion	182
5 References	182

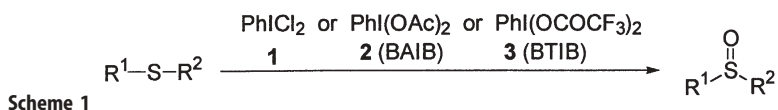
1 Introduction

The use of hypervalent iodine reagents for heteroatom-heteroatom bond forming reactions is well established in the context of classical oxidation chemistry [1–11]. For example, oxidations of anilines to azobenzenes, thiols to disulfides, and sulfides to sulfoxides with aryl- λ^3 -iodanes were documented decades ago [1–5]. During the last ten years, particular attention has also been given to oxidative transformations of compounds derived from heavier elements, including the interception of reaction intermediates or initially formed products with external nucleophiles. A second important development is the utilization of sulfonyliminoiodanes, $\text{ArI}=\text{NSO}_2\text{R}$, for heteroatom-nitrogen bond formation, especially for imidations of sulfur, selenium, phosphorus and arsenic com-

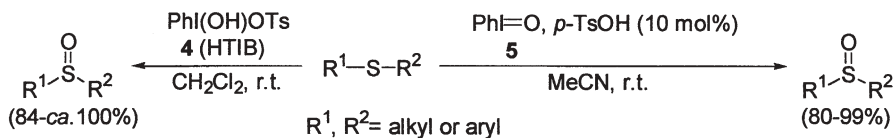
pounds. In this chapter, recent progress on heteroatom-heteroatom bond forming reactions of hypervalent iodine reagents with heteroatom substrates is reviewed [6–11]. Emphasis is placed on the five year period ending in 2001, but earlier literature is also discussed.

2 Aryl- λ^3 -Iodanes

Oxidations of sulfides to sulfoxides can be effected with various aryl- λ^3 -iodanes. For example, (dichloroiodo)benzene (**1**) in aqueous pyridine [12], [bis(ace-toxy)iodo]benzene (**2**, BAIB) in acetic anhydride (H_2SO_4) [13], and [bis(trifluoroacetoxo)iodo]benzene (**3**, BTIB) in chloroform [14] have all been utilized for this purpose (Scheme 1).



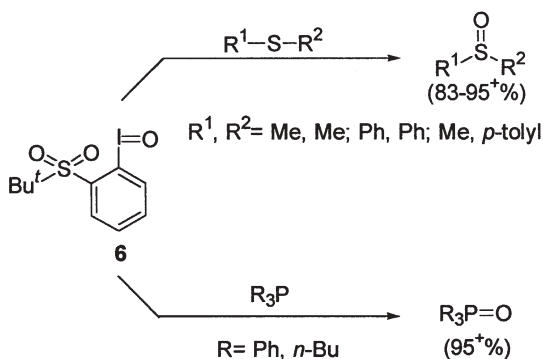
More recently, sulfide oxidations with [hydroxy(tosyloxy)iodo]benzene (**4**, HTIB) have been reported [15]. Such reactions proceed readily in dichloromethane at room temperature and stop at the sulfoxide stage (Scheme 2). HTIB can also be generated in situ from iodosylbenzene (**5**) and 10 mol% *p*-toluenesulfonic acid for catalytic oxidations of sulfides to sulfoxides [16]. Oxidations of unsymmetrical sulfides with the chiral (+)-10-camphorsulfonyloxy analog of HTIB afford the corresponding sulfoxides (82–92%) with low enantioselectivities (2.7–13.7% ee) [15].



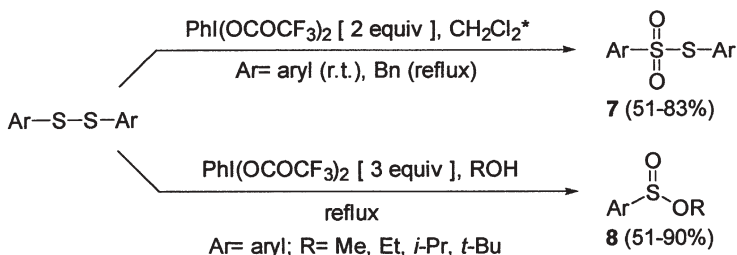
Because of its insolubility in common aprotic solvents, iodosylbenzene is of limited use for uncatalyzed oxidations in such media. The *o*-*tert*-butylsulfonyl derivative **6** of iodosylbenzene, on the other hand, is moderately soluble (0.08 M) in chloroform and has been employed for uncatalyzed oxidations of sulfides and phosphines to sulfoxides and phosphine oxides (Scheme 3) [17].

The treatment of diaryl disulfides with BTIB in dichloromethane leads to the production of *S*-aryl thiosulfonic esters **7** (Scheme 4) [18]. When such reactions are conducted in an alcoholic medium, arenethiolic esters **8** are obtained [19]. Similar conversions of arenethiols to **7** or **8** with BTIB can also be effected [18, 19].

Although examples were not documented, it has been reported that diaryl diselenides undergo oxidative cleavage with BTIB at the Se-Se bond to give are-



Scheme 3

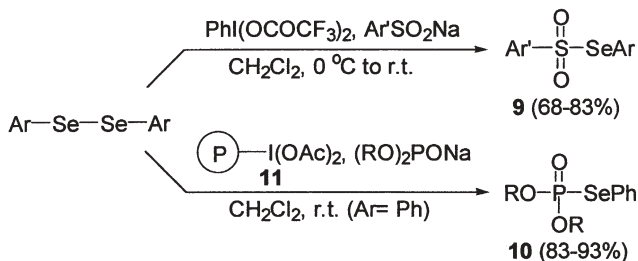


* oxidation of the *o*- $\text{HO}_2\text{CC}_6\text{H}_4$ derivative was conducted in MeCN at reflux

Scheme 4

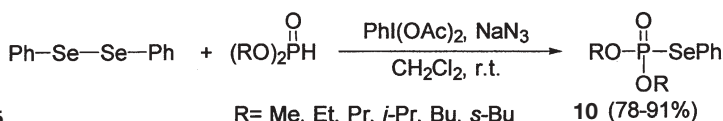
neselenyl trifluoroacetates [18, 20]. This mode of reactivity was exploited for Se-S bond formation [20]. More specifically, the treatment of diaryl diselenides with BTIB in the presence of sodium arenesulfonates provides access to the corresponding selenosulfonates **9** (Scheme 5). Se-phenyl-*O*, *O*-dialkyl phosphoroselenolates **10** (i.e., Se-P bond formation) have been similarly prepared by reactions of diphenyl diselenide with poly[bis(acetoxy)iodo]styrene (**11**) in the presence of sodium dialkyl phosphorates [21]. While mechanisms of the foregoing reactions have not been established, heterolytic processes initiated by phenyliodination of the diaryl diselenides with BTIB or **11** seem likely.

A related, but mechanistically different, approach to the dialkyl phosphoroselenolates **10** entails the treatment of diphenyl diselenide with BAIB and



Scheme 5

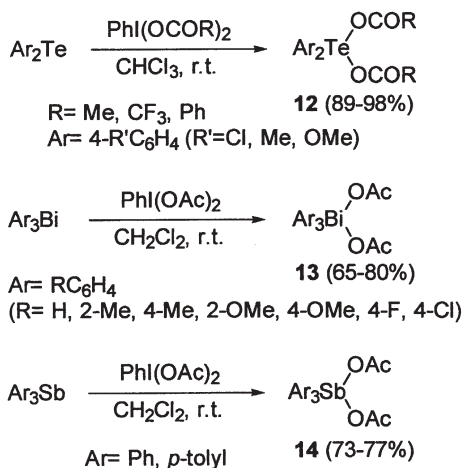
R = Me, Et, *n*-Pr, *i*-Pr, *n*-Bu, *s*-Bu



Scheme 6

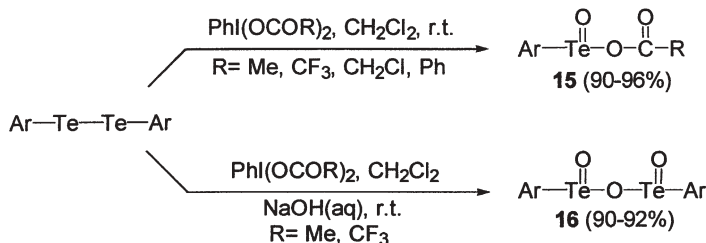
dialkyl phosphorous acids in the presence of sodium azide (Scheme 6) [22]. A radical mechanism, initiated by hydrogen atom abstraction from the dialkyl phosphorous acids by the azido radical was suggested for these reactions.

Diaryl tellurides undergo facile ligand-transfer oxidations with [bis(acyloxy)iodo]arenes in chloroform to give stable diaryltellurium dicarboxylates **12** (Scheme 7) [23]. Similar ligand-transfer oxidations of triarylbismuthanes and triarylstibanes with BAIB in dichloromethane leading to Bi(V) and Sb(V) diacetates **13** and **14** have also been reported [24,25]. The triarylbismuth diacetates were employed for high yield Cu(II)-catalyzed arylations of a series of arylamines [24].



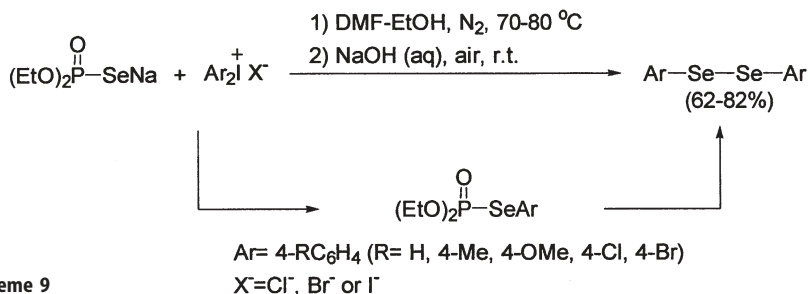
Scheme 7

Reactions of diaryl ditellurides with [bis(acyloxy)iodo]arenes, on the other hand, lead to oxidative cleavage of the Te-Te bond, and afford aryltellurinic mixed anhydrides **15** (Scheme 8) [26]. When such oxidations are conducted in a medium containing aqueous sodium hydroxide, aryltellurinic anhydrides **16** are obtained [16].



Scheme 8

In a rare example of the use of iodonium salts for heteroatom-heteroatom bond formation, diaryliodonium halides were employed with sodium *O*, *O*-diethyl phosphoroselenolate for a one-pot synthesis of diaryl diselenides (Scheme 9) [27]. These transformations probably occur via arylation of the phosphoroselenolate salt with the diaryliodonium ions, hydrolysis of the resulting aryl phosphoroselenolates with sodium hydroxide, and air oxidation of the arene-selenide ions thus produced.

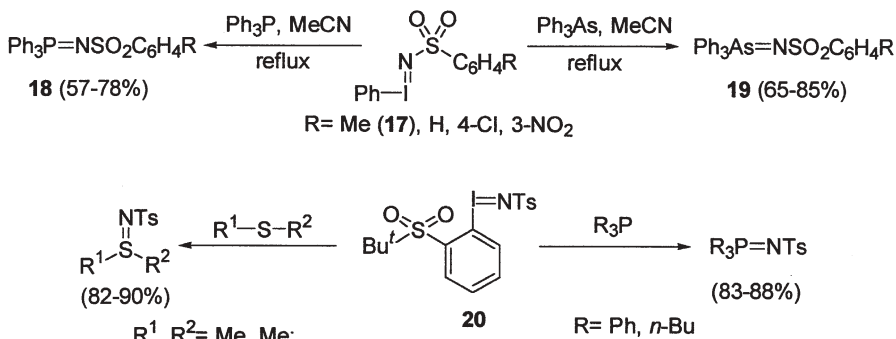


Scheme 9

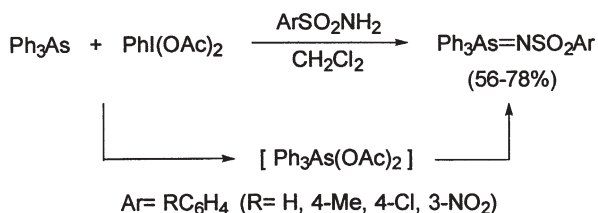
3 Sulfonylimino(aryl)iodanes

[(Tosylimino)iodo]benzene (17) and its analogs are excellent reagents for nitrene-transfer reactions with heteroatom substrates derived from third-row elements and beyond. In fact, transylidations of 17 with triphenylphosphine, dimethyl sulfide, and dimethyl sulfoxide were reported as early as 1975 [28]. Recent examples include similar uncatalyzed reactions of various sulfonyliminoiodanes with triphenylphosphine and triphenylarsine in acetonitrile, to give the corresponding phosphorus and arsenic ylides 18 and 19 (Scheme 10) [29]. Uncatalyzed tosylimidations of sulfides and phosphines can also be effected with the much more soluble *o*-*tert*-butylsulfonyliminiodane 20 [17].

The synthesis of *N*-sulfonylarsinimines 19 has been accomplished by a non-nitrene pathway involving the treatment of triphenylarsine with BAIB and the



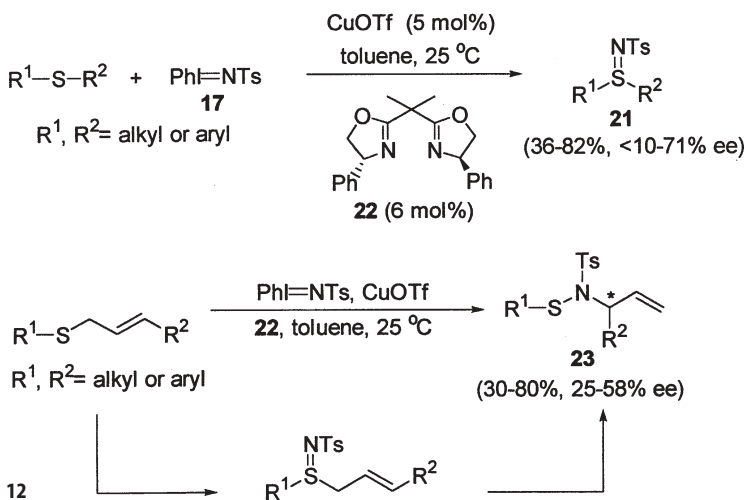
Scheme 10



Scheme 11

corresponding sulfonamides (Scheme 11) [29]. Production of the ylides is thought to occur via the intermediate formation of triphenylarsine diacetate.

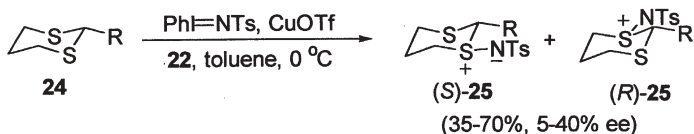
The treatment of various sulfides with $\text{PhI}=\text{NTs}$ in the presence of cuprous triflate leads to the corresponding *N*-tosylsulfimides (*N*-tosylsulfilimines) **21** [30]. The presence of the chiral bis(oxazoline) ligand **22** in the reaction medium results in coordination of the copper(III)-nitrene intermediate, $\text{L}^*\text{Cu}(\text{III})=\text{NTs}$, and enables the enantioselective production of **21** (Scheme 12). Similar copper-catalyzed reactions of allylic sulfides with $\text{PhI}=\text{NTs}$ lead to formal insertion of the 'NTs' group into the carbon-sulfur bond of the substrates, and proceed via a [2,3]-rearrangement with allylic inversion, to give sulfonamides **23** [30].



Scheme 12

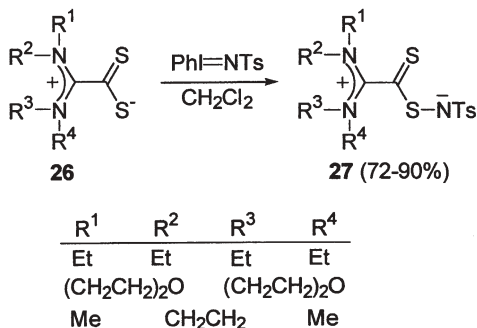
Asymmetric imidations of aryl alkyl sulfides with [(tosylimino)iodo]benzene, catalyzed by various chiral (salen)manganese(III) complexes, have been investigated in some detail [31, 32]. The influence of catalyst structure, solvent, temperature, 3°-amine *N*-oxides, and the presence of molecular sieves on product yields and the enantioselectivity of imidation with **17** was evaluated. Enantioselectivities as high as 90 % ee and 97 % ee with methyl 2-nitrophenyl sulfide and methyl 2,4-dinitrophenyl sulfide, respectively, were achieved.

Modestly enantioselective tosyylimidations of a series of 2-substituted -1,3-dithianes **24** with $\text{PhI}=\text{NTs}$, cuprous triflate, and the chiral bis(oxazoline) ligand

Scheme 13 R= Me, Bn, 2-MeC₆H₄CH₂, SiMe₂Ph, SiMe₃

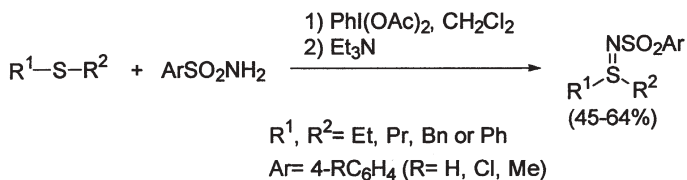
22 have also been reported (Scheme 13) [33]. Such reactions are highly stereoselective for the *trans*-sulfimides 25, only the methyl analog leading to some of the *cis*-isomers (i. e., *trans*:*cis* = 94:6). It was demonstrated with the parent dithiane (R = H) that the presence of the bis(oxazoline) ligand increased the yield of product from 9% to 77% at 20°C, probably because the ligated copper(III)-nitrene intermediate is a more efficient nitrene-transfer agent than its unligated counterpart. Similar tosyylimidations of 1,3-dithiolane and 5-alkyl derivatives of 1,3-dithiane were investigated.

Further examples of the functionalization of sulfur compounds with iodine(III)-nitrogen ylides include copper-catalyzed imidations of phenyl benzyl sulfide with [(sulfonylimino)iodo]benzenes possessing imidazole and pyridine rings in the sulfonyl moiety [34], and uncatalyzed tosyylimidations of diaminothiocarboxylate inner salts 26 (Scheme 14) with PhI=NTs to give 27 [35].



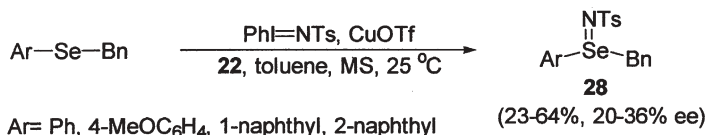
Scheme 14

Imidations of sulfides can also be achieved by BAIB-mediated condensation reactions similar to those employed for the synthesis of *N*-sulfonylarsinimines (Scheme 15) [36]. More specifically, the treatment of sulfides with BAIB and various sulfonamides, followed by the addition of triethylamine, affords moderate yields of the corresponding *N*-sulfonylsulfilimines.



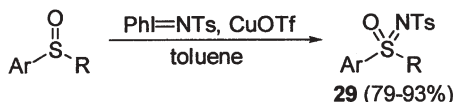
Scheme 15

Enantioselective conversions of aryl benzyl selenides to *N*-tosylselenimides **28** with [(tosylimino)iodo]benzene, cuprous triflate, and the chiral bis(oxazoline) **22** have recently been demonstrated (Scheme 16) [37, 38]. Because benzyl phenyl selenide undergoes uncatalyzed imidation with $\text{PhI}=\text{NTs}$ in acetonitrile (46% yield) or dichloromethane (trace yield), toluene was selected as the solvent for the asymmetric imidation reactions. Furthermore, in order to avoid racemization of **28** by moisture, molecular sieves were added to the reaction medium.



Scheme 16

Sulfoxides react with $\text{PhI}=\text{NTs}$ in the presence of cuprous triflate to give high yields of the corresponding *N*-tosylsulfoximines **29** (Scheme 17) [39]. It is noteworthy that the presence of vinyl and allyl groups in the starting sulfoxides does not lead to competing tosylaziridination of the C,C-double bond (i.e., the Evans aziridination reaction) [40]. Furthermore, enantiomerically pure *R*-(-)-methyl *p*-tolyl sulfoxide is converted to the corresponding sulfoximine with retention of configuration ($\geq 98\%$ ee) under these conditions.

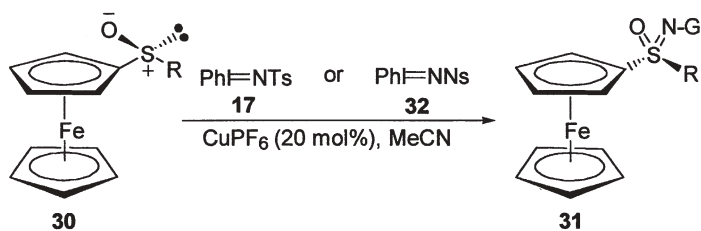


Ar= Ph, *p*-tolyl (one example);
R= Me, Et, *i*-Pr, vinyl, allyl, Bn

Scheme 17

Similar stereospecific conversions of chiral ferrocenyl sulfoxides **30** to ferrocenyl sulfoximines **31**, either with [(tosylimino)iodo]benzene or its nosylate analog **32** have been reported (Scheme 18) [41], including the synthesis of a planar-chiral ferrocenyl sulfoximine [42].

Copper (I)-catalyzed reactions of 3,4-di-*tert*-butylthiophene (**33**) with $\text{PhI}=\text{NTs}$ lead to several products, including the *N*-tosylsulfilimine **34**, the sulfone

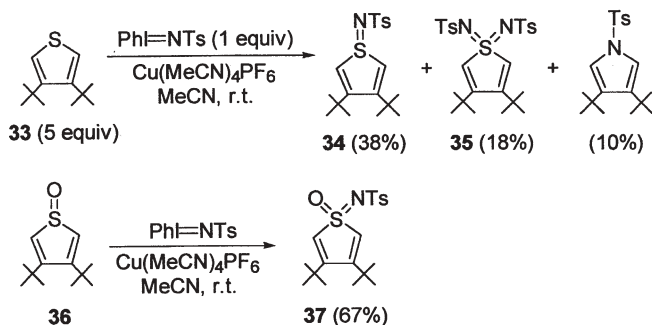


G= Ts; R= Me, *t*-Bu, Ph, *p*-tolyl; yield of **31** (43-53%)

G= Ns; R= Me, *t*-Bu, *p*-tolyl, 2-methoxynaphthyl; yield of **31** (62-74%)

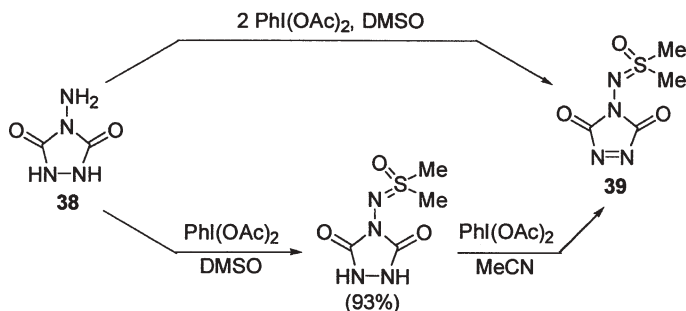
Scheme 18

bis(*N*-tosylimine) **35**, and 3,4-di-*tert*-butyl-*N*-tosylpyrrole (Scheme 19) [43, 44]. Similar treatment of 3,4-di-*tert*-butylthiophene oxide (**36**) with $\text{PhI}=\text{NTs}$ affords the sulfoximine **37** [44, 45]. Analogous reactions of **33** with $\text{PhI}=\text{NSO}_2\text{Ph}$, and of 2,4-di-*tert*-butylthiophene and its oxide with [(tosylimino)iodo]benzene have been demonstrated [44, 45].



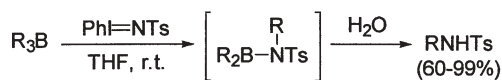
Scheme 19

The treatment of *N*-aminourazole (**38**) with two equivalents of BAIB in DMSO results in imidation of the sulfoxide and oxidation of the urazole ring to give the sulfoximine **39** (Scheme 20) [46]. The preparation of **39** from **38** can also be accomplished stepwise, by isolation of the dihydro sulfoximine intermediate and BAIB-oxidation of this compound in acetonitrile. The sulfoximine **39** was not isolated, but was generated in solution and employed for the synthesis of bicyclic diazenes.



Scheme 20

Although the foregoing studies are focused on imidations of P, S, Se, and As compounds with [(tosylimino)iodo]benzene, and related reactions, $\text{PhI}=\text{NTs}$ has also been utilized for conversions of trialkylboranes to *N*-alkyl-*p*-toluenesulfonamides (Scheme 21) [47]. Such reactions presumably occur through *N*-tosylaminoborane intermediates (i. e., B-N bond formation).



Scheme 21



4 Conclusion

In summary, recent investigations of reactions of aryl- λ^3 -iodanes, ArIL^1L^2 , with heteroatom substrates, derived from third-row elements and beyond, provide examples of P-O, S-O, Se-O, Se-P, Se-S, Te-O, Bi-O and Sb-O bond formation. Sulfonylimino(aryl)iodanes, $\text{ArI}=\text{NSO}_2\text{R}$, are especially useful as imidation reagents, and have been utilized for the construction of P-N, S-N, Se-N, and As-N bonds. Diaryliodonium salts have been employed indirectly for formation of the Se-Se bond.

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Oxidations and Rearrangements

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Oxidations and rearrangements using hypervalent iodine compounds are summarized in this review with emphasis on synthetic applications of these procedures. New reagents and polymer-supported versions are highlighted which facilitate the use of hypervalent iodine compounds in these reactions. Beside the more traditional oxidation of sulfides to sulfoxides and of alcohols to the corresponding ketones, the functionalization of activated carbon–hydrogen bonds in the oxidation in carbonyl compounds and the functionalization of only slightly activated carbon–hydrogen bonds in benzylic positions are discussed. New rearrangements using hypervalent iodine compounds are finally mentioned.

Keywords. Hypervalent iodine, Oxidation, Polymer-supported reagents, Rearrangement

1	Introduction	186
2	Reagents	186
2.1	Established Reagents	186
2.2	New Reagents	187
2.3	Polymer-Supported Reagents	188
3	Oxidations	189
3.1	Synthesis of Sulfoxides from Sulfides	190
3.2	Oxidations of Alcohols	192
3.3	Oxidations of Phenols	194
3.4	Oxidations to Heteroaromatic Compounds	197
3.5	Functionalizations of Carbonyl Compounds	198
3.5.1	Functionalization in the α -Position	198
3.5.2	Introduction of an α,β -Unsaturation	200
3.6	Oxidation of Carbon–Hydrogen Bonds	202
4	Rearrangements	203
5	References	205

1 Introduction

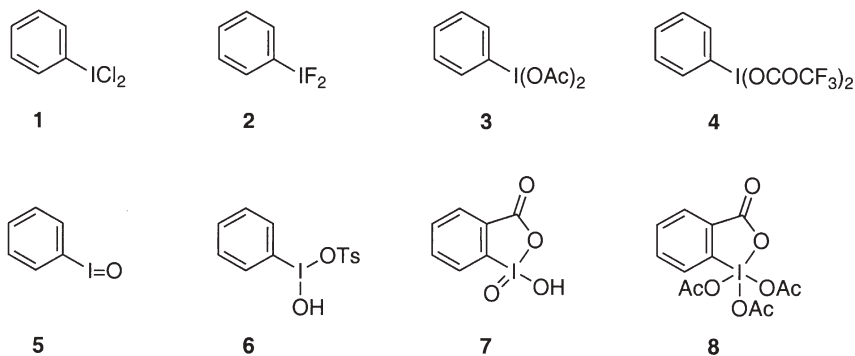
Hypervalent iodine reagents were discovered a long time ago. Within the last decade there has been an explosive growth in the use of these reagents in organic synthesis. The use of hypervalent iodine compounds as oxidizing agents has been widely investigated and has a very broad synthetic utility. This area has been reviewed in different forms and scope [1–8]. The purpose of this review is to address and summarize recent developments and synthetic applications. Section 2 highlights the hypervalent iodine reagents used in the various oxidations. The different oxidations which can be achieved using hypervalent iodine compounds are highlighted in Sect. 3. Possible rearrangements are finally covered in Sect. 4. Examples are given to demonstrate the usefulness of these reactions and emphasis is placed on the post 1990s literature.

2 Reagents

The use of hypervalent iodine compounds as oxidizing agents has seen an tremendous increase in recent years. Several classes of hypervalent iodine reagents are known and most of them can be used for oxidative transformations. The search for novel oxidizing agents, especially for reagents showing a high degree of selectivity by tolerating a variety of other functional groups, is a top priority in current research.

2.1 Established Reagents

The first hypervalent iodine compound, (dichloroiodo)benzene **1**, was prepared in 1886 by Willgerodt [9]. Since that time, several new reagents of iodine (III) and iodine (V) have been developed and are now frequently used in oxidative functionalizations. Scheme 1 shows a selection of the most frequently used hypervalent iodine oxidants.



Scheme 1. Established hypervalent iodine oxidants

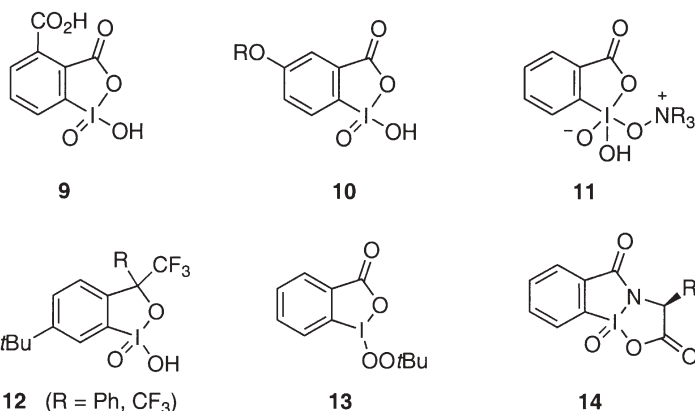
[Bis(acyloxy)iodo]benzenes **3** and **4** [10] can be used not only in oxidations but have also found broad applications in many other useful transformations as highlighted in other chapters of this volume. Iodosobenzene **5** is a polymeric reagent (PhIO)_n, but it depolymerizes in alcohols or acids. Because of its polymeric nature this reagent has not been employed so widely in oxidation reactions but it can easily be used together with catalysts like boron trifluoride or metal complexes. [Hydroxy(tosyloxy)iodo]benzene **6** was first reported in 1970 [11] and is often called Koser's reagent [12, 13]. It can be easily synthesized from **3** through a ligand exchange reaction. Another quite "old" reagent is 2-iodoxybenzoic acid (IBX) **7**, which was first reported in 1893 [14]. It had been rarely used in reactions, probably due to its low solubility in most organic solvents [15], but has received much attention recently [16]. Dess and Martin transformed **7** into the much more soluble Dess-Martin periodinane (DMP) **8**, which has been employed widely as a very mild oxidant with a broad functional group tolerance [15, 17].

2.2

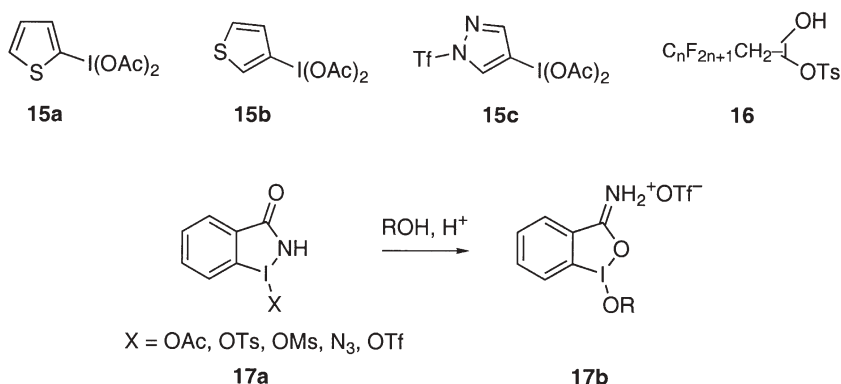
New Reagents

Based on the success and on the versatility of the established reagents, several attempts have been undertaken to further improve these oxidants. The recent attraction of IBX **7** has led to the synthesis of a more soluble compound. Starting from 3-nitrophthalic acid, the modified IBX reagent **9** can be synthesized in about 60% overall yield. It is now possible to oxidize allylic or benzylic alcohols to the corresponding aldehydes or ketones in water or in aqueous solvent mixtures in good yields [18]. The inability of the reagent **9** to oxidize non-allylic and non-benzylic alcohols led to the proposal of a SET (Single-Electron-Transfer) mechanism involved in the reaction. The development of electronically modified IBX reagents to tune electron transfer processes with different perspectives has been intensified recently. Different substituted IBX reagents like **10** have been synthesized [19] and a ligand exchange led to promising reagents **11** [20]. Not only *N*-oxides (as shown in **11**), but also DMSO or THF can act as a ligand to IBX altering its reactivity. The ability of *N*-oxides to coordinate to hypervalent iodine compounds was already known and has been used to tune the solubility of (tosylimidoiodo)arenes [21]. The reactivity of these reagents is, however, changed in stoichiometric [22] as well as in catalytic reactions [23–25]. Other cyclic hypervalent iodine reagents have been developed as well. Compounds of type **12** have been introduced as highly soluble and non-explosive oxidants, although their synthesis involves several steps [26]. Compound **13** can be obtained from iodosobenzoic acid by a Lewis acid-catalyzed ligand exchange reaction with *tert*-butyl hydroperoxide [27]. Even chiral derivatives of type **14** have been reported recently [28]. Compounds **9**–**14** are shown in Scheme 2.

(Diacyloxyiodo)benzenes like **3** and **4** have been especially popular for the oxidation of phenol derivatives. Recently some electronically modified reagents of this type have been synthesized, where the benzene moiety has been replaced by a heteroaromatic system. For compounds **15**–**17** see Scheme 3. The reagents **15** and **16** have been used for oxidations of hydroquinones and sulfides as well



Scheme 2. IBX related reagents



Scheme 3. New iodine (III) reagents

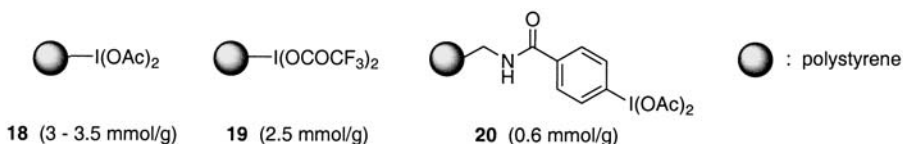
as for various rearrangements [29, 30]. Stable fluoroalkyl analogs **17** of [hydroxy(tosyloxy)iodo]benzene **6** have been prepared in two steps from the appropriate iodofluoroalkanes [31]. Like the Koser reagent **6** they are able to react with silyl enol ethers and the corresponding (fluoroalkyl)alkynyl iodonium salts have been prepared. Cyclic hypervalent iodine reagents are known to be stable compounds [32]. The structure and the chemistry of benziodazoles of type **17a** has been investigated. The triflate **17a** (X = OTf) reacts with alcohols (or amides) to the thermodynamically more stable 3-iminiumbenziodoxoles **17b** [33, 34]. The results of *ab initio* calculations are in good agreement with the X-ray structural data.

2.3

Polymer-Supported Reagents

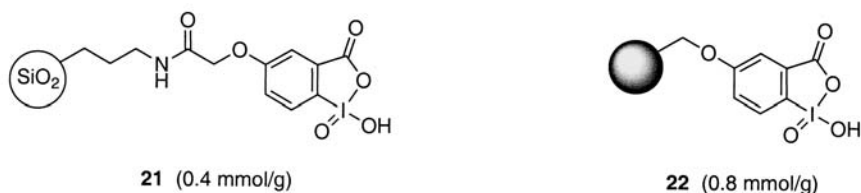
Solid phase organic synthesis have become quite popular recently with the demand of “clean” organic synthesis in agrochemical and pharmaceutical

industries [35]. The first examples of polymer supported hypervalent iodine compounds have already reported in the early seventies, but their potential remained almost unexplored [36, 37]. Recently, polystyrene supported (diacetoxy)benzene **18** has been prepared by iodination of polystyrene applying known conditions (iodine, periodic acid, sulfuric acid) [38] and subsequent oxidation. Using the same procedure, polymer-supported [bis(trifluoroacetoxy)-iodo]benzene **19** has also been synthesized [39], Scheme 4. These reagents with a quite high loading of around 3 mmol/g have then been used in rearrangements, coupling reactions, and oxidations with success [40–42]. A similar reagent can also be prepared using a linker technique and, although with a lower loading (0.3 mmol/g), reagent **20** has been employed in similar transformations [43]. All these polymer supported reagents can be very easily removed after the reaction by filtration. Furthermore, it is possible to reoxidize them and to reuse them with almost no loss of activity.



Scheme 4. Polymer bound (diacyloxy)benzene derivatives

The success of 2-iodoxybenzoic acid (IBX) **7** in oxidations and in the design of new reactions has prompted various research groups to develop polymer supported reagents of this type as well. This reagent has been immobilized through a phenoxide linker and both reagents reported so far have therefore only modest loading (0.4–0.8 mmol/g). Reagents **21** and **22** differ in the polymer, **21** uses mesoporous silica and **22** uses polystyrene as solid support, Scheme 5. Both reagents have been used in simple oxidation reactions with success [44, 45].



Scheme 5. Polymer bound 2-iodoxybenzoic acid reagents

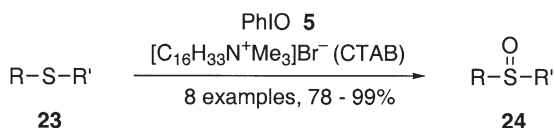
3 Oxidations

With many hypervalent iodine compounds oxidation reactions can be performed. This part highlights the most important transformations and is restricted to those transformations where a new oxygen atom is attached to the substrate.

3.1

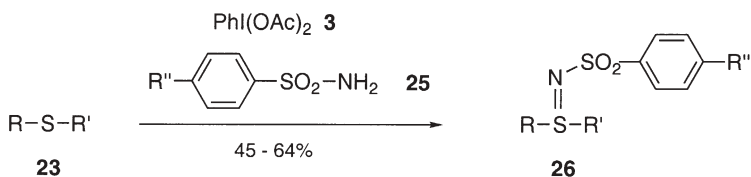
Synthesis of Sulfoxides from Sulfides

The oxidation of chalcogen compounds by hypervalent iodine reagents is a known procedure. The oxidation of sulfides only leads to the formation of mixtures of sulfoxides and sulfones under drastic conditions. Usually only sulfoxides are formed and can be obtained in excellent yields [46–48]. Recent investigations showed that sulfide oxidation can be catalyzed by quaternary ammonium salts in micellar systems. Iodosobenzene **5** is catalytically activated by cetyltrimethylammonium bromide (CTAB) and the sulfoxides **24** can be obtained in high yields under very mild conditions, Scheme 6 [49]. Other micelle forming surfactants have also been employed, but CTAB showed the best results in this reaction. It is also possible to perform such oxidations to sulfoxides with (*tert*-butylperoxy)iodanes of type **13** [50].



Scheme 6. Oxidation of sulfides to sulfoxides

In changing the oxidant to a mixture of (diacetoxyiodo)benzene **3** and a sulfonamide **25** the direct transformation of sulfides **23** to the corresponding *N*-sulfonylsulfinimines **26** is possible. Compounds **26** have been prepared in 45–64% yield, Scheme 7 [51].

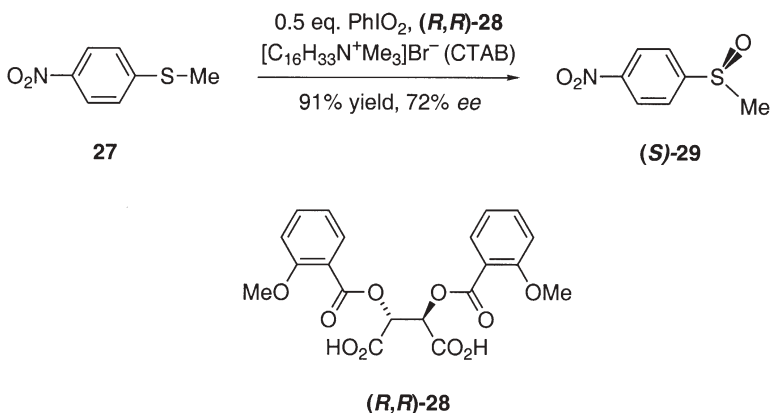


Scheme 7. Synthesis of *N*-sulfonylsulfinimines

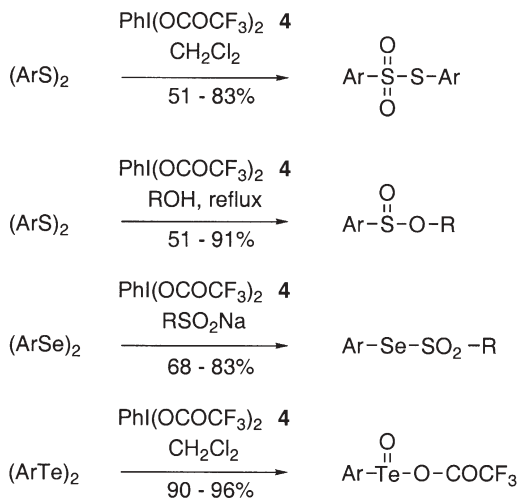
Using a chiral catalyst in stereoselective oxidations of sulfides was highly successful [52]. However, chiral hypervalent iodine compounds bearing the chiral information either on an oxygen ligand [44, 53–55] or on the aromatic moiety of the reagent [56] only led to low enantiomeric excess in the resulting sulfoxides. The approach of hypervalent iodine-induced oxidation mediated by reversed micelles seems to be a breakthrough in asymmetric sulfide oxidation. Only 10 mol% of the tartaric acid derivative (*R,R*)-**28** is needed for the synthesis of optically active sulfoxide (*S*)-**29** in up to 72% *ee* [57]. Several examples of asymmetric sulfoxide formation have been reported and an intensive screening of chiral catalysts and of reaction conditions have been performed. Recent reports from the same research group indicate that the CTAB is not necessary,

although slightly higher selectivities are obtained in its presence [58]. The use of iodosylbenzene **5** led to lower selectivities and lower yields than the use of iodylbenzene (PhIO_2).

Disulfides, diselenides, and ditellurides can be oxidized by hypervalent iodine compounds quite easily. Depending on the reaction conditions disulfides can be oxidized to sulfinic esters [59] or thiosulfonic *S*-esters [60, 61]. Diselenides can be transformed into selenosulfonates [62]. Arenetellurinic mixed anhydrides are mild oxidants and can be obtained by oxidation of the corresponding ditellurides as shown in Scheme 9 [63]. Recently it was shown that a thioacetal based linker for solid-phase synthesis can be cleaved oxidatively using [bis(trifluoroacetoxy)iodo]benzene **4** [64].



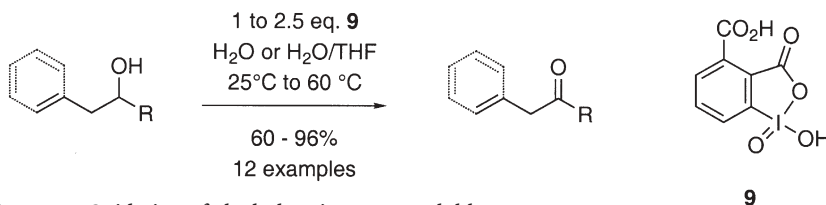
Scheme 8. Stereoselective sulfoxide formation



Scheme 9. Oxidation of disulfides, diselenides and ditellurides

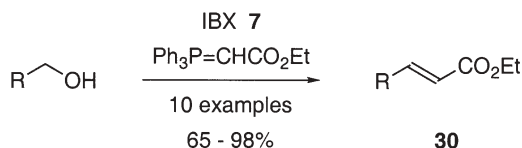
3.2 Oxidations of Alcohols

One of the prominent reagents for the oxidation of alcohols is the Dess-Martin periodinane (DMP) **8** [15, 17, 65, 66]. This reagent and its cyclic precursor, *o*-iodosylbenzoic acid (IBX) **7** [14, 16, 67] can be employed as iodine(v) reagents in various oxidations of alcohols to the corresponding carbonyl compounds. Although there are various alternative procedures available for the synthetic chemist, the mild reaction conditions and the broad functional group tolerance make these reagents highly attractive. Although in many syntheses the Dess-Martin reagent **8** is used as a very efficient oxidant, *o*-iodosylbenzoic acid **7** might be a cheaper alternative in some cases. It is beyond the scope of this article to list all the applications of these reagents in organic synthesis [68, 69]. With the development of new reagents like the water soluble derivative **9** milder reaction conditions can be applied. By using this reagent, a variety of different alcohols can be easily oxidized to the corresponding carbonyl compounds as shown in Scheme 10.



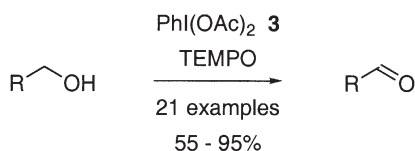
Scheme 10. Oxidation of alcohols using water-soluble reagent **9**

Benzylic, allylic, and propargylic alcohols can be oxidized by *o*-iodosylbenzoic acid (IBX) **7** in the presence of stabilized Wittig ylides to generate α,β -unsaturated esters **30** in a one-pot procedure, Scheme 11. This is useful when the intermediate aldehydes are unstable and difficult to isolate [70].



Scheme 11. One-pot oxidation and Wittig reaction to α,β -unsaturated esters

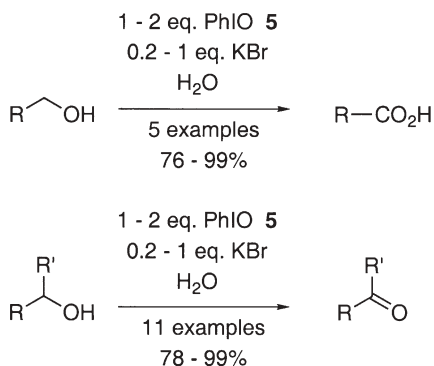
Mainly iodine(v) reagents have been used for such oxidations, but some iodine(III) reagents have also been successfully applied. The radical TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) is necessary in the oxidation of alcohols with (diacetoxyiodo)benzene **3**. With this combination highly selective oxidations of primary alcohols to the corresponding aldehydes in high yields are possible, Scheme 12. Secondary alcohols are not attacked under the reaction conditions providing a useful alternative to the widely used Dess-Martin reagent [71].



Scheme 12. Oxidation of primary alcohols by TEMPO/PhI(OAc)₂

However, longer reaction times can lead to the corresponding carbonyl compounds as well. An activation of (diacetoxyiodo)benzene **3** with boron trifluoride is also possible and can be used for a direct oxidation of carbazolylmethyl alcohols [72].

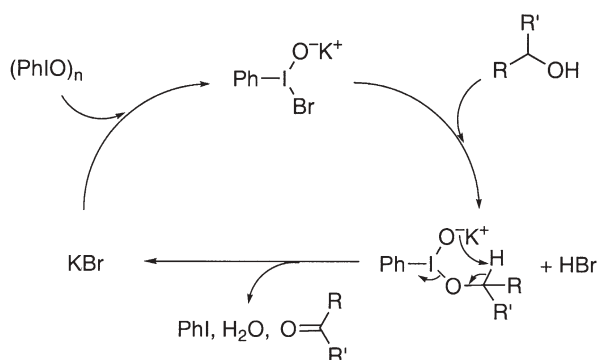
The combination of iodosobenzene **5** and potassium bromide in water generates a powerful oxidant for the oxidation of alcohols. Primary alcohols are converted exclusively to the carboxylic acids in very high yields, whereas secondary alcohols lead to the corresponding ketones, Scheme 13 [73].



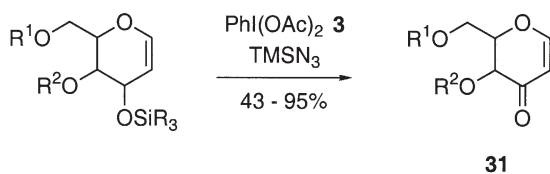
Scheme 13. PhIO/KBr reagent combination for oxidations in water

Interestingly, the same reaction can be performed with the polymer-supported reagent **18** in water, because the reagent **18** was found to be considerably stable in this solvent. A mechanistic rationale of the catalytic activation of iodosobenzene **5** by potassium bromide is given in Scheme 14. This reaction provides a very facile and environmentally benign method for the alcohol oxidation.

The reagent combination of (diacetoxyiodo)benzene **3** and trimethylsilyl azide was found to be a powerful method for desilylating and oxidizing glycals. The α,β -unsaturated compounds **31** are obtained in good yields and even sensitive groups like selenoethers are tolerated in this transformation (Scheme 15) [74]. The same transformation can, however, also be effected by [hydroxy(tosyloxy)iodo]benzene (Koser's reagent) **6** alone in good yields [75–77].



Scheme 14. Mechanism of the catalytic activation of PhIO by KBr

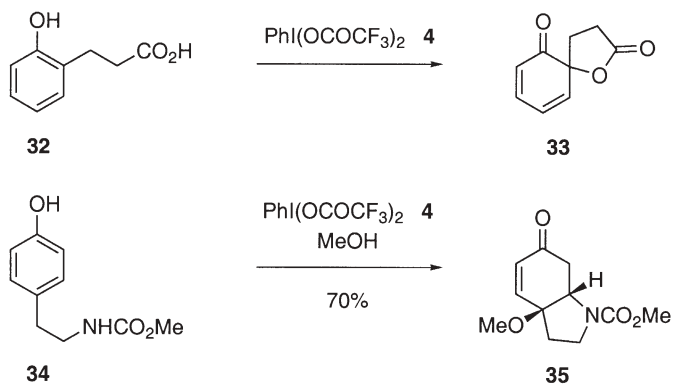


Scheme 15. Desilylation and oxidation of glycals

3.3

Oxidations of Phenols

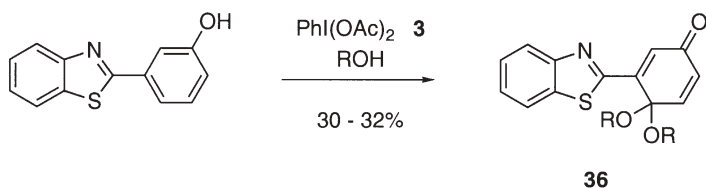
The oxidation of phenols with hypervalent iodine compounds has been used frequently and nucleophilic additions can be performed as well as cyclization reactions using this technique. The resulting quinone derivatives show high reactivity and they have been used in a various subsequent reactions. Substituted phenols like **32** [78] or **34** [79] have been oxidized by hypervalent iodine reagents and, depending on the substitution pattern, cyclizations have taken place as shown in Scheme 16. Product **33** is unstable and undergoes subsequent



Scheme 16. Oxidation of phenols with subsequent cyclizations

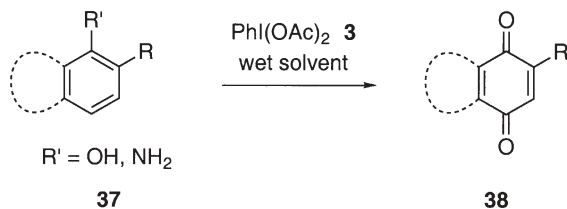
Diels-Alder reactions leading to polycyclic addition products in good yields. Some of such quinone oxidation products have also been used in Michael additions [80, 81] or in Diels-Alder reactions [82, 83].

Aromatic compounds substituted by a heteroatom can be oxidized to corresponding quinone derivatives using hypervalent iodine reagents. Phenols can be oxidized either in the *ortho* [84] or in the *para* position [85] by using iodine(III) reagents. By this route, benzothiazoles of type 36, Scheme 17, are accessible and they have been tested as antitumor compounds [86, 87].



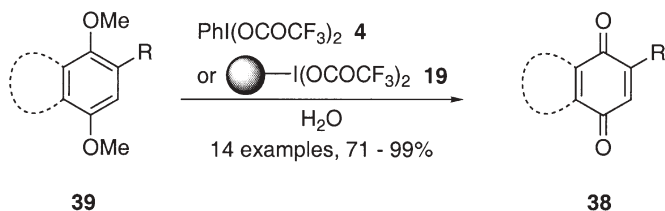
Scheme 17. Oxidation of phenols in the *para* position

Using small amounts of water in these reaction allows the efficient synthesis of *para*-quinones 38 as shown in Scheme 18, starting either from phenols 37 ($R' = \text{OH}$) [88–91] or from the corresponding anilines 37 ($R' = \text{NH}_2$) [92].



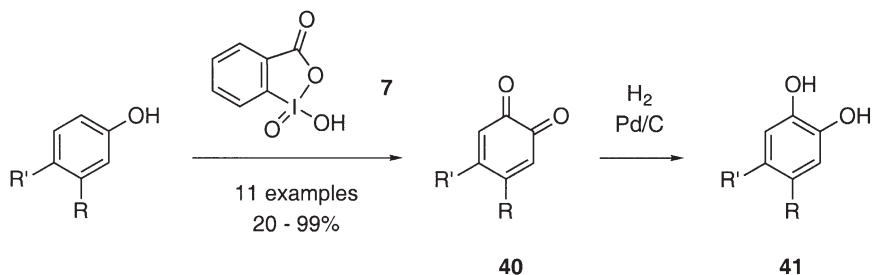
Scheme 18. Synthesis of quinones from phenols or anilines

Similar *para*-quinone derivatives can be obtained by oxidative demethylations of phenol ethers which can be performed in water. Either [bis(trifluoroacetoxy)iodo]benzene 4 or the polymer-supported reagent 19 can be used for the generation of *para*-quinones 38 from 1,4-dimethoxybenzene derivatives of type 39, Scheme 19 [93].



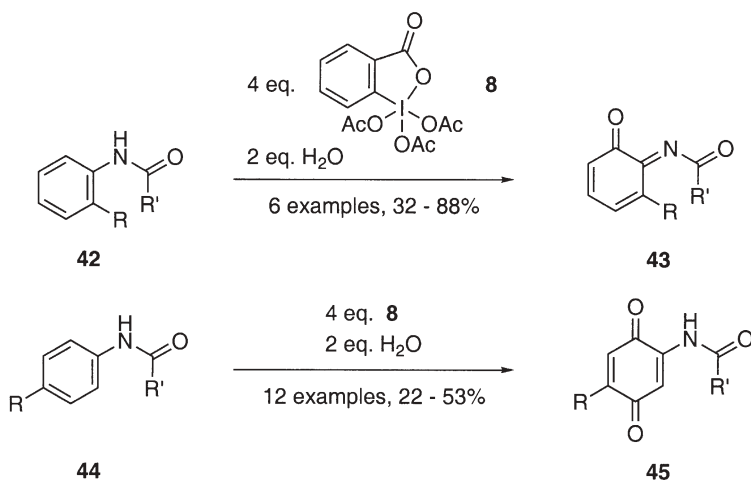
Scheme 19. Oxidative demethylations of phenol ethers

Recently it has been shown, that iodine(v) reagents can also be used for such transformations. An efficient regioselective method for the oxidation of phenols to *ortho*-quinones **40** can be achieved using 2-iodoxybenzoic acid (IBX) **7**. With a subsequent reduction this proves to be a useful procedure for the synthesis of a variety of catechols **41**, Scheme 20 [94].



Scheme 20. Regioselective oxidation of phenols in the *ortho* position

The Dess-Martin periodinane **8** is also able to oxidize aromatic compounds to the corresponding quinones. The presence of water is important and, starting from anilides **42** substituted in the 2-position, the rare class of *ortho*-imidoquinones **43** is accessible, Scheme 21. It has been shown that compounds of type **43** are interesting building blocks and can lead to polycyclic molecules of diverse molecular architecture [95, 96]. They can undergo subsequent Diels-Alder reactions and intramolecular versions have been used for a rapid access to natural products and for synthesis of scaffolds for further manipulation. *para*-Quinones **45** are also easily accessible, however, only in modest yields by reacting 4-substituted anilines **44** under the same reaction conditions, Scheme 21 [97].



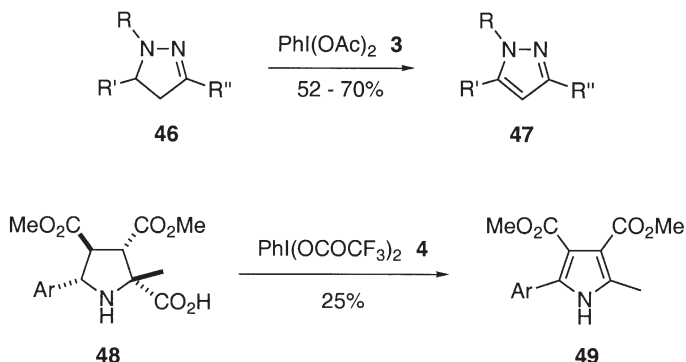
Scheme 21. Synthesis of *ortho*-imidoquinones and *para*-quinones by oxidation with Dess-Martin periodinane

The formation of the products **43** and **45** has also been studied from a mechanistic point of view. Labeling studies with H_2^{18}O revealed that two molecules of acetyl-2-iodoxybenzoic acid (formed by the reaction between Dess-Martin Periodinane **8** and water) are involved in *para*-quinone formation. It is suspected that the substituent in 2-position in **42** blocks another molecule of acetyl-2-iodoxybenzoic acid attacking the initially formed product leading to the formation of *ortho*-imidoquinones. Anilides substituted in the 3-position does lead to complex mixtures in the oxidation reaction.

3.4

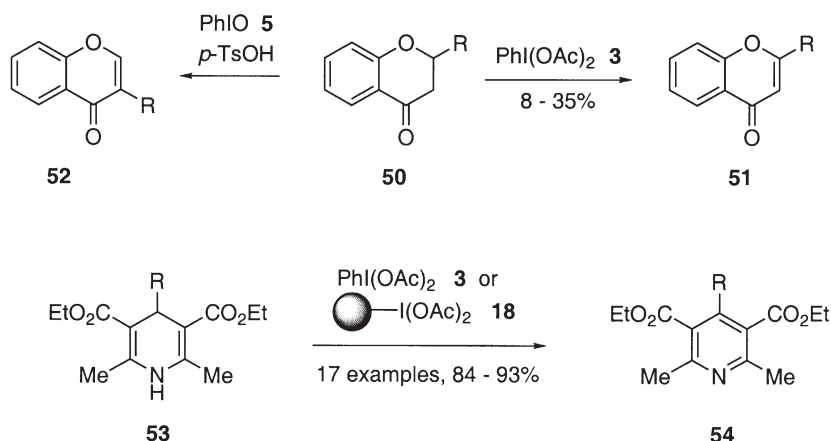
Oxidations to Heteroaromatic Compounds

Although the mechanism of the transformation of single into double bonds has not been investigated in detail, a heteroatom attached to the single bond is necessary for an efficient introduction of the double bond. Trisubstituted pyrazolines **46** can be oxidized with (diacetoxyiodo)benzene **3** to the corresponding pyrazoles **47** in good yields [98]. Two double bonds can be introduced in easy accessible proline derivatives **48** [99] by an oxidative decarboxylation with [bis(trifluoroacetoxy)iodo]benzene **4** yielding tetrasubstituted pyrroles of type **49**, Scheme 22 [100].



Scheme 22. Oxidation of five-membered ring systems

Tetrahydroquinolones can be transformed also by (diacetoxyiodo)benzene **3** to the aromatic arylquinolines, a structure found in various alkaloids [101]. Depending on the reagent, it is possible to oxidize flavanones **50** either into flavones **51** or into rearranged isoflavones **52** [102, 103]. (Diacetoxyiodo)benzene **3** or the polymer-supported reagent **18** were also efficient reagents for the oxidation of 1,4-dihydropyridines **53** to the corresponding pyridine derivatives **54**, Scheme 23 [104].

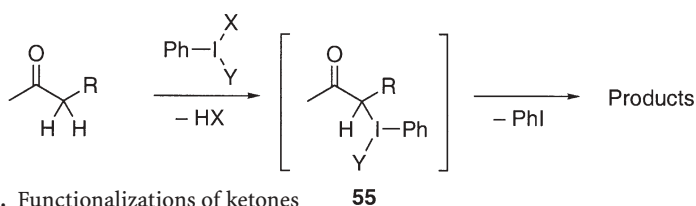


Scheme 23. Oxidation of six-membered ring systems

3.5

Functionalizations of Carbonyl Compounds

The oxidation of carbonyl compounds can be achieved with hypervalent iodine reagents quite easily. A general feature of these reactions is the electrophilic attack of the hypervalent iodine reagent at the α -carbon atom of a carbonyl group and a review on this chemistry has been published recently [6]. This leads to hypervalent iodine intermediates of type 55. These phenyliodinated intermediates are quite unstable and a variety of subsequent reactions are possible. Intermediates 55, Scheme 24, can be considered as unpoled substrates regarding the reactivity of the α -position of the initial carbonyl compounds. Major processes are the substitution by a nucleophile (see Sect. 3.5.1 Functionalization in the α -Position) or the introduction of a carbon-carbon double bond (see Sect. 3.5.2 Introduction of an α,β -Unsaturation).



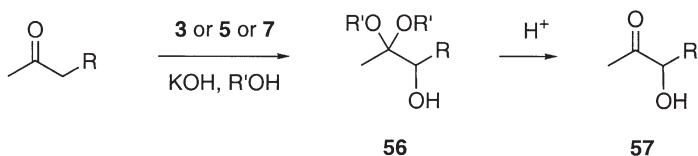
Scheme 24. Functionalizations of ketones

3.5.1

Functionalization in the α -Position

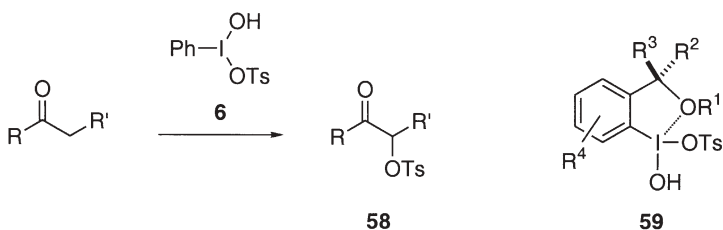
Carbonyl compounds can be functionalized in the α -position under various conditions. Treatment of ketones with (diacetoxyiodo)benzene 3, iodosobenzene 5, or 2-iodoxybenzoic acid (IBX) 7 under basic conditions provides effi-

cient routes to α -hydroxylated dialkylacetals **56** [2, 105, 106]. This reaction has also been applied for functionalization in natural product synthesis [107–109], because the α -hydroxylated dialkylacetals **56** can be easily hydrolyzed under acidic conditions to α -hydroxy ketones **57** in good overall yields, Scheme 25. Also silyl enol ethers and ketene silyl acetals can be oxidized under neutral or acidic conditions providing an alternative approach to α -hydroxy ketones of type **57** [110–112].



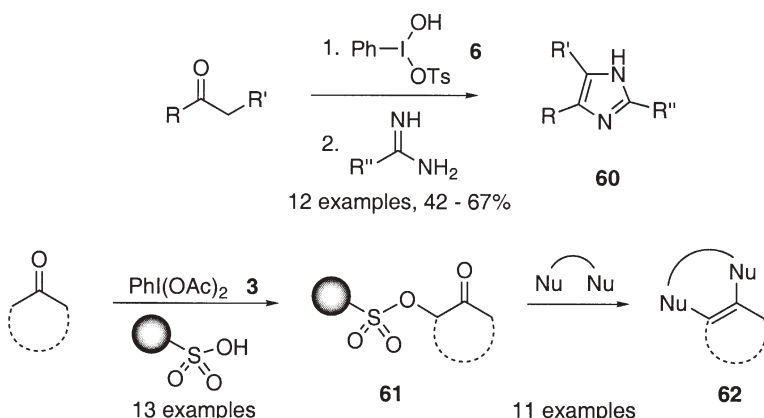
Scheme 25. Synthesis of α -hydroxy dialkylacetals from ketones

Using other hypervalent iodine compounds or different reagent combinations, various functional groups can be introduced in the α -position of ketones. α -Tosylations of ketones can be achieved directly using [hydroxy(tosyloxy)-iodo]benzene **6**. The major drawback is the low regioselectivity observed in these reactions, although the α -tosylation of silyl enol ethers circumvents this problem. In the last few years some efforts have been done in the synthesis of chiral hypervalent iodine compounds [48, 53–55, 113–117], but only a few of them have been used successfully in stereoselective synthesis. With chiral derivatives of type **59** it is possible to α -tosylate propiophenone with about 40% *ee* [56, 118, 119].



Scheme 26. α -Tosylation of ketones

The products **58** of this reaction are of high interest as they can be used in a variety of subsequent reactions, Scheme 26. They can be used in next condensation reactions [120, 121], which sometimes can be carried out as one-pot procedures [122]. Some examples are shown in Scheme 27. The combination of α -tosylation and reaction with amidines generates different substituted 1*H*-imidazoles **60** [123]. Also polymer bound sulfonic acids can be used to trap the hypervalent iodine intermediates and to transfer subsequent steps to solid-phase synthesis [124]. Products of type **61** can be reacted with a variety of different bisnucleophiles to generate polycyclic compounds **62**.

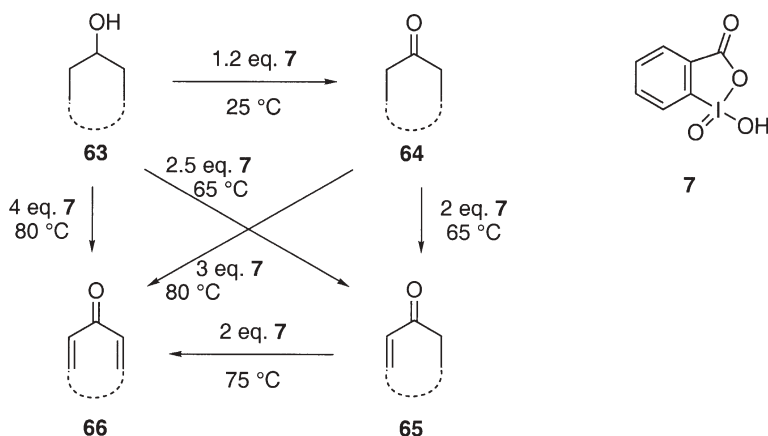


Scheme 27. α -Tosylations of ketones and subsequent reactions

3.5.2

Introduction of an α,β -Unsaturation

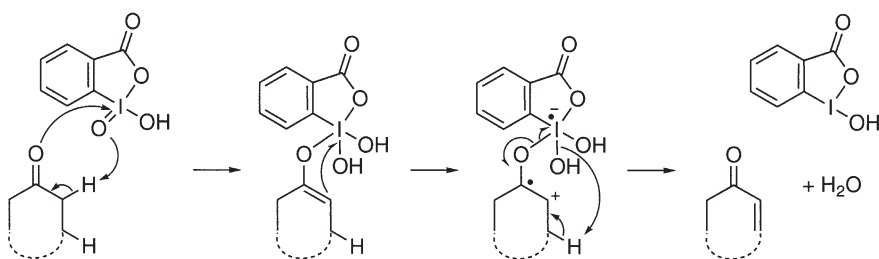
α,β -Unsaturated carbonyl compounds are widely used in organic synthesis and, despite of their versatility, their preparation is sometimes a challenging transformation. Several routes involving selenium or palladium chemistry have been developed and only recently it was found that hypervalent iodine compounds can serve as very versatile reagents in accomplishing this reaction [125, 126]. Depending on the amount of 2-iodoxybenzoic acid (IBX) **7** it is possible to introduce one α,β -unsaturation (**65**) or even two and generate dienones of type **66**. Taking into account that one can oxidize alcohols **63** to the corresponding carbonyl compounds **64** with **7**, 4 equivalents **7** are sufficient for a direct conversion of **63** into **66**, Scheme 28. The solvents for these reactions are toluene/DMSO mixtures.



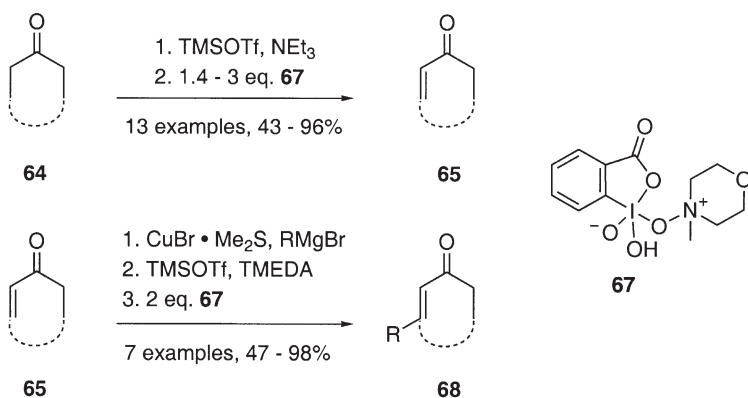
Scheme 28. Synthesis of α,β -unsaturated carbonyl systems

Although hypervalent iodine compounds are often used as oxidants and sometimes as electrophilic reagents, the dehydrogenation of carbonyl compounds is believed to proceed via a single electron transfer (SET) process. Although an ionic process was originally proposed, there has been experimental evidence for the involvement of radical species. Either **7** or an **7**•DMSO adduct serves as the oxidant to initiate the SET process. The subsequently generated radical cation finally cleaves off water and generates the dehydrogenated product.

Recently it was found that the reactivity of 2-iodoxybenzoic acid (IBX) **7** can be tuned efficiently by ligand complexation and the dehydrogenation of carbonyl compounds can then be achieved at room temperature [127]. The IBX•*N*-methylmorpholin-*N*-oxide complex **67** is not only an efficient reagent for the dehydrogenation of carbonyl compounds, it can also be used for the oxidation of silyl enol ethers [128]. The postulated mechanism for the 2-iodoxybenzoic acid (IBX) **7** mediated dehydrogenation reactions described in Scheme 29 proceeds through enolization with subsequent capture of the enolate moiety. The oxidation of silyl enol ethers might follow a similar mechanism and the procedure results in a new and complimentary oxidation method for the enone functionality. Additionally silyl enol ethers can be formed in situ from enones **65** and, after dehydrogenation with **67**, products **68** can be obtained in good yields, Scheme 30.



Scheme 29. Proposed SET mechanism of the dehydrogenation of carbonyl compounds



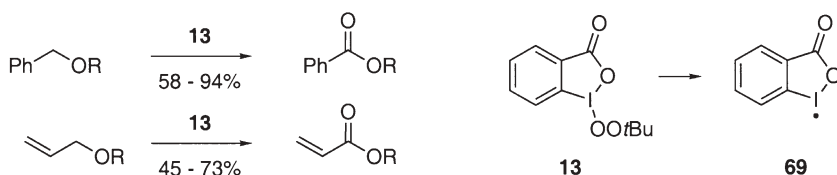
Scheme 30. Oxidation of silyl enol ethers

Very recently it has been shown that also the most simple iodine(v)-based reagents like iodic acid (HIO_3) and its anhydride iodine pentoxide (I_2O_5) can form complexes with ligands like DMSO and that these complexes can be used as simple and cheap alternatives for reagents of type 11 [129]. The complexes $\text{HIO}_3 \cdot \text{DMSO}$ and $\text{I}_2\text{O}_5 \cdot \text{DMSO}$ are mild and efficient oxidants and can be used for the dehydrogenation of aldehydes and ketones mentioned above.

3.6

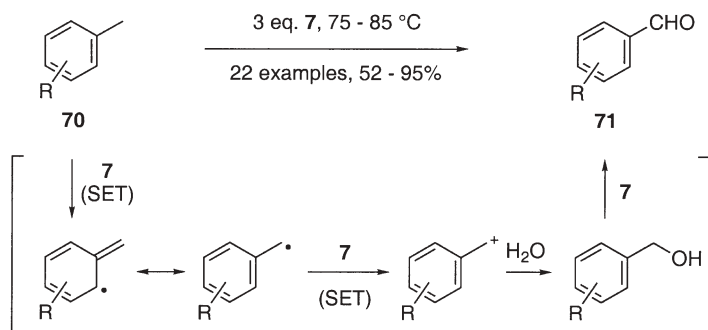
Oxidation of Carbon–Hydrogen Bonds

Compound 13 is a stable precursor for the corresponding iodine(III)-centered radical 69 [130] which can be used for the oxidation of amines [131] or for the oxidation of benzyl, allyl, or propargyl ethers to the corresponding esters [132]. Benzyl ethers are common protecting groups and usually removed under reducing conditions. If the substrate contains other reducible groups, the oxidative debenzoylation might be a possible alternative as shown in Scheme 31. Other oxidants can be used as well for the oxidative debenzoylation [133, 134].



Scheme 31. Oxidation of ethers to the corresponding esters

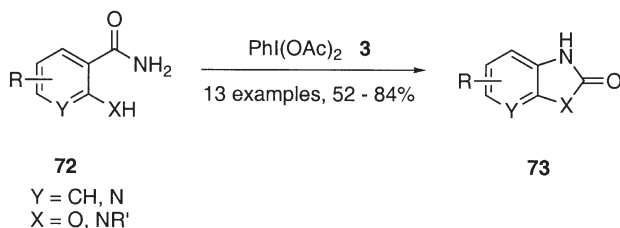
Recently it was found that iodine(v) compounds like 2-iodoxybenzoic acid (IBX) 7 can be used to affect selective oxidations at carbon atoms adjacent to aromatic systems. The mechanism of this transformation is believed to proceed via a SET (Single-Electron-Transfer) process. A postulated mechanism for the oxidation of benzylic positions is outlined in Scheme 32. This oxidation is quite general and proceeds efficiently in fluorobenzene/DMSO mixtures or in DMSO at 80 °C [135]. Starting from compounds 70, the corresponding aldehydes 71 can be obtained easily in good yields.



Scheme 32. Oxidations of carbons adjacent to aromatic systems

4 Rearrangements

A useful property of hypervalent iodine reagents is their ability to react first as an electrophile and then to be transformed into an excellent leaving group. This particular aspect has been used in different rearrangements for the construction of highly functionalized molecules. Various iodine(III) reagents have been employed in Hofmann-type rearrangements [136–139]. The presence of a nucleophile in the *ortho* position of aromatic amides of type **72** can lead to direct cyclizations and to the formation of heterocyclic compounds **73** as shown in Scheme 33 [140].



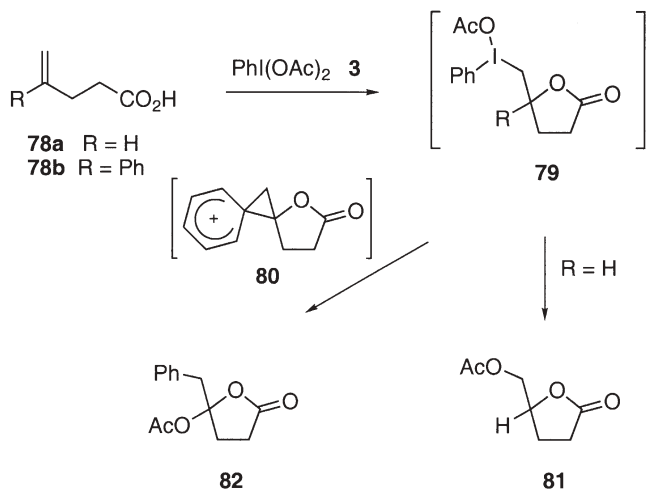
Scheme 33. Hofmann rearrangements with subsequent cyclizations to heterocycles

N-Substituted amidines **74** are transformed via the carbodiimide intermediate **75** into urea derivatives **76** as shown in Scheme 34 [141]. This reaction has been performed with a variety of aliphatic and aromatic substituents and in addition to (diacetoxyiodo)benzene **3** other hypervalent iodine compounds can also be used for this rearrangement. Phenyl substituted amidines **74** ($\text{R}' = \text{Ph}$) can lead to cyclized products of type **77**.



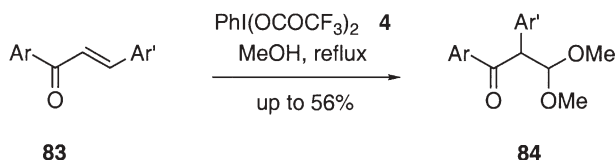
Scheme 34. Rearrangement of amidines

Treatment of aryl-substituted alkenes with hypervalent iodine compounds can lead to the formation of phenyliodinated intermediates, which can be stabilized by the aryl substituent via the formation of phenonium ions. Subsequent nucleophilic attack might then lead to rearranged products. This behavior can be nicely seen by comparing the unsaturated carboxylic acids **78** in their reaction with (diacetoxyiodo)benzene **3**. The substrate **78a** without the phenyl substituent is cyclized to the phenyliodinated intermediate **79**, which is then attacked by the acetate under the formation of lactone **81** [142]. Substrate **78b** is, however, then stabilized by the formation of an intermediate phenonium ion **80** and attack by the acetate is accompanied by a 1,2-phenyl migration and **82** is generated, Scheme 35 [143].



Scheme 35. Cyclization of unsaturated carboxylic acids

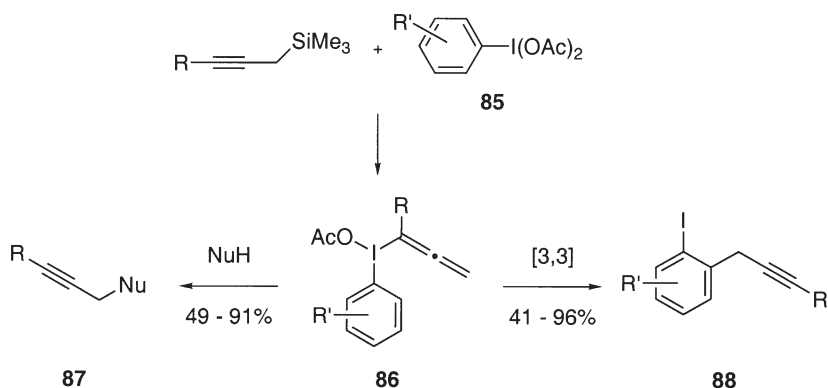
Similar intermediates might be involved in the rearrangement of chalcones **83** by [bis(trifluoroacetoxy)iodo]benzene **4** in refluxing methanol. Compounds of type **84** can be obtained, Scheme 36, which have been employed in the synthesis of isoflavones. The yield of this reaction is dependent on the electron density of the aromatic moieties [144].



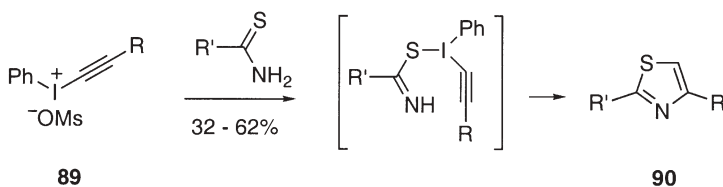
Scheme 36. Rearrangement of chalcones

Alkenyl(phenyl)iodine(III) compounds can also serve as starting materials in rearrangements. Allenyl(aryl)iodine(III) compounds of type **86** can be synthesized from (diacetoxyiodo) derivatives **85** and propargylsilanes [145]. It depends on the leaving group ability of the aromatic substituent on iodine in **86** as to whether the reaction proceeds via nucleophilic substitution to compounds of type **87** or by an iodonio-Claisen rearrangement to compounds **88**, Scheme 37 [146, 147]. The easy access to propynyl compounds **87** has been shown [148] and solvent effects in these reactions have been investigated as well [149, 150].

Alkynyl(aryl)iodine(III) compounds **89** can also be employed in hetero-Claisen rearrangements [151] after reaction with appropriate thioamides yielding thiazoles of type **90** in reasonable yields as shown in Scheme 38 [152]. Ring enlargement reactions of furan derivatives into pyranones by hypervalent iodine compounds were reported as well [153].

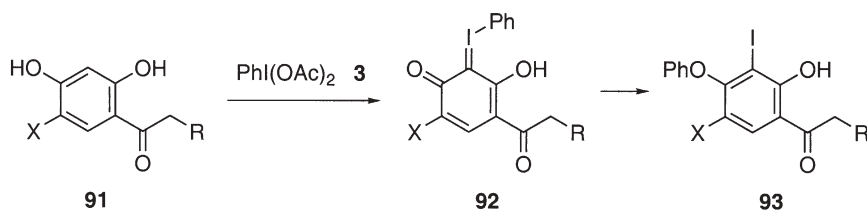


Scheme 37. Iodonio-Claisen rearrangement



Scheme 38. Thiazoles via hetero-Claisen rearrangements

The oxidation of α -substituted 2,4-dihydroxyacetophenones **91** with (diacetoxyiodo)benzene **3** can lead, under appropriate reaction conditions, to iodonio ylides **92**, which rearrange into the corresponding iodophenoxy ethers **93**, Scheme 39 [154].



Scheme 39. Synthesis of iodophenoxy ethers via rearrangement

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Synthetic Applications (Total Synthesis and Natural Product Synthesis)

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Recently, hypervalent iodine reagents have been used extensively in organic synthesis. In particular, (diacyloxyiodo)benzenes such as phenyliodine(III) diacetate (PIDA) and phenyliodine(III) bis(trifluoroacetate) (PIFA) have received a great deal of attention due to low toxicity, ready availability, easy handling, and reactivities similar to that of heavy metal reagents and anodic oxidation. A variety of available reactions for natural product syntheses have been developed using PIDA, PIFA, and other iodine(III or V) reagents. These reactions are expected to be utilized for pharmaceutical and agrochemical process due to their safety, mild reaction conditions and high yields. This review focuses on recent progress in the use of hypervalent iodine reagents toward total syntheses of various biologically active natural products involving quinones, alkaloids, flavonoids, sugars, and other antibiotics.

Keywords. Hypervalent iodine reagents, Total synthesis, Natural products

1	Introduction	210
2	Fundamental Reactions for Natural Product Synthesis	211
2.1	Oxidation Reactions of Aromatic Compounds	211
2.1.1	Oxidation of Phenol Derivatives to Quinone Monoacetals and Quinones	211
2.1.2	Oxidation of Phenol Derivatives to Spiroannulated Compounds	213
2.1.3	Oxidation of Phenol Ether Derivatives to Biaryls, Quinone-Imine Derivatives, and Sulfur-Containing Heterocycles	214
2.1.4	Oxidation of Anilides Using Iodine(V) Reagents	216
2.2	Phenyliodonium Salt-Mediated Reactions Leading to Diaryl Ether Derivatives and Nitrogen-Containing Heterocycles	217
2.3	Reactions of Unsaturated Bonds with Hypervalent Iodine Reagents	219
2.3.1	Oxidation of α,β -Unsaturated Ketones, Enols, and Alkenes	219
2.3.2	Oxidation of Alkynes	220
2.4	Others	221
3	Total Synthesis of Natural Products Using Hypervalent Iodine Reagents	222
3.1	Total Synthesis of Natural Products via Oxidation of Aromatic Compounds with Hypervalent Iodine Reagents	223
3.1.1	Total Synthesis via Oxidation Reactions of Phenol Derivatives with PIDA or PIFA	223

3.1.2	Total Synthesis via Oxidative Spiroannulation Reactions of Phenol Derivatives with PIDA or PIFA	228
3.1.3	Total Synthesis via Oxidation Reactions of Phenol Ether Derivatives with PIFA	235
3.1.4	Total Synthesis via Oxidation Reactions of Anilides with Iodine(V) Reagents	238
3.2	Total Synthesis via Phenyliodonium Salt-Mediated Reactions . . .	239
3.3	Total Synthesis via Hypervalent Iodine-Induced Reactions of Unsaturated Bonds	242
3.4	Total Synthesis via Other Hypervalent Iodine-Induced Reactions .	243
4	Conclusion	245
5	References	245

Abbreviations

PIDA	phenyliodine(III) diacetate
PIFA	phenyliodine(III) bis(trifluoroacetate)
DMP	Dess-Martin Periodinane
IBX	<i>o</i> -iodoxybenzoic acid
PDAIS	poly(diacetoxyiodo)styrene
PBTIS	polybis(trifluoroacetoxyiodo)styrene
CF ₃ CH ₂ OH	2,2,2-trifluoroethanol
(CF ₃) ₂ CHOH	1,1,1,3,3,3-hexafluoro-2-propanol
TMSOTf	trimethylsilyl trifluoromethanesulfonate
TMSN ₃	azidotrimethylsilane
ESR	electron spin resonance
SET	single electron transfer

1

Introduction

Recently, in consideration of the environment, heavy metal oxidants such as lead(IV), thallium(III), and mercury(II) cannot be used for industrial processes, especially for pharmaceutical and agrochemical processes, due to their high toxicity and serious amount of metal waste. Hypervalent iodine reagents are now extensively used in organic synthesis as a mild, safe, and economical alternative for heavy metal reagents (Fig. 1).

In particular, (diacyloxyiodo)benzene such as phenyliodine(III) diacetate (PIDA) and phenyliodine(III) bis(trifluoroacetate) (PIFA) have received a great deal of attention due to their reactivities similar to those of heavy metal reagents or anodic oxidation, low toxicity, ready availability and easy handling. Accordingly, a variety of useful oxidation reactions using iodine(III) or iodine(V) reagents have been developed recently. A number of previous review articles and

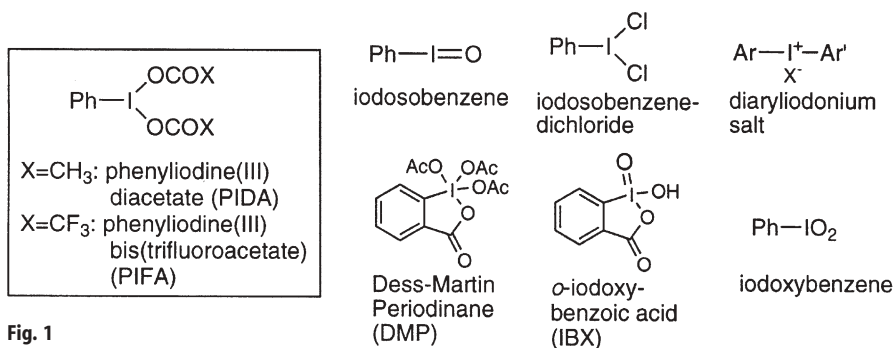


Fig. 1

other chapters of this book are also available for more detailed information about the unique properties and versatile utilities of hypervalent iodine reagents [1–26]. This review article will focus on recent aspects of hypervalent iodine-induced reactions that are used as the key reactions for total syntheses of natural products. From the viewpoint of natural product synthesis, the hypervalent iodine-induced reactions are classified into three major categories; (1) oxidation reactions of aromatic compounds (mainly, phenolic oxidation reactions), (2) phenyliodonium(III) salt-mediated reactions, and (3) oxidation reactions of unsaturated bonds. Thus, we will first briefly outline the fundamental hypervalent iodine-induced reactions, which have been used widely for natural product synthesis, and then illustrate by examples their application to total or formal syntheses of various biologically active natural products.

2 Fundamental Reactions for Natural Product Synthesis

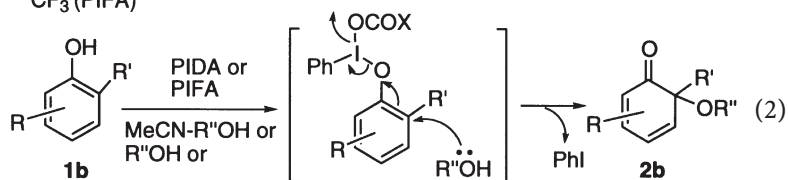
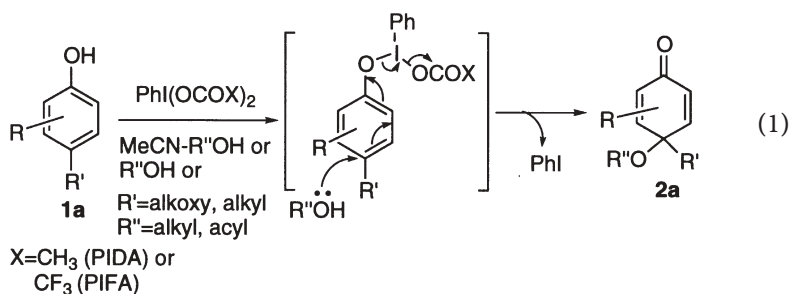
2.1 Oxidation Reactions of Aromatic Compounds

2.1.1 Oxidation of Phenol Derivatives to Quinone Monoacetals and Quinones

Hypervalent iodine oxidation of phenol derivatives has been used most widely for total synthesis of natural products. Phenolic oxidation leading to the corresponding quinone derivatives is a pivotal biological process, and a number of naturally occurring compounds having a quinone structure show biologically important activities such as antitumor, antibacterial, antifungal and antiprotozoan activities. Among a variety of quinone derivatives, quinone monoacetals are potentially attractive compounds as regiospecific quinone equivalents in organic synthesis. Thus, they serve as precursors to various types of natural products. They are generally prepared by (i) chemical oxidation of 4-alkoxy- or 4-(aryloxy)phenols with oxidizing reagents such as copper(II) species, ceric salts, thallium(III) salts, ferric chloride, and DDQ, (ii) electrochemical oxidation of *p*-methoxyphenols or their trimethylsilyl ethers, and (iii) monohydrolysis of

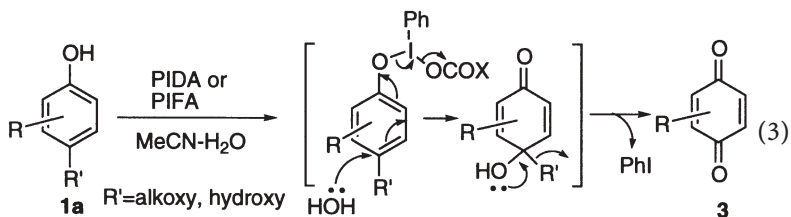
quinone bisacetals. Although the first method (i) is the most facile and shortest route to quinone monoacetals among methods, it often employs highly toxic oxidants, the yields are generally moderate to low, and the reactivity of the above oxidants is not so high and is dependent upon the substrate used.

In 1987, Kita and co-workers first developed a general and high yielding (59%~quant.) route to *p*-benzoquinone monoacetals (**2a**) and spirolactones from *para*-substituted phenols (**1a**) with PIFA in MeCN in the presence of alcohols (R''OH) [27]. Similar methods for preparing quinone monoacetals and quinol ethers have been developed independently by Lewis et al. (PIDA/CH₂Cl₂-R''OH (11~65% yields)) [28] and Pelter et al. (PIDA/R''OH (65~99% yields)) [29] [Eq. (1)].



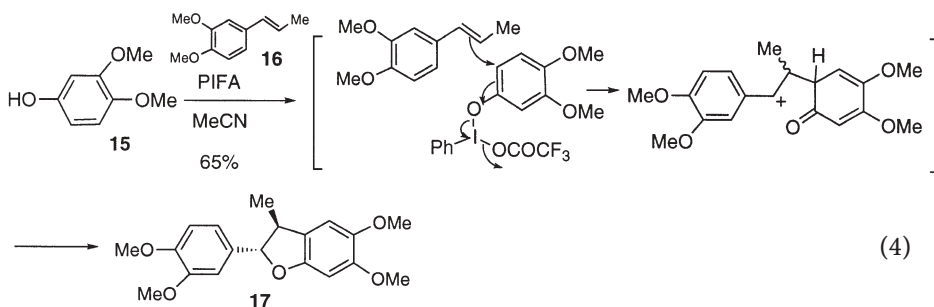
Thereafter, these methodologies were extended to the preparation of *o*-quinone monoacetals (**2b**) [32–34] [Eq. (2)], and have been utilized widely for total syntheses of natural products such as miroestrol (**4**), thielocin A1 (**5**), dynemicin A (**6**), manumycin (**7**), nisamycin (**8**), xestoquinone (**9**), calicheamicinone (**10**), and asatone (**11**).

In a similar manner, quinones (**3**) were prepared in high yields by oxidation of hydroquinones or alkoxyphenols (**1**) with PIDA or PIFA in alcohols or in the presence of water [29, 30] [Eq. (3)].



These reactions were applied to total syntheses of natural products such as **6**, ventiloquinone E (**12**), KW-2170 (**13**), and EO9 (**14**).

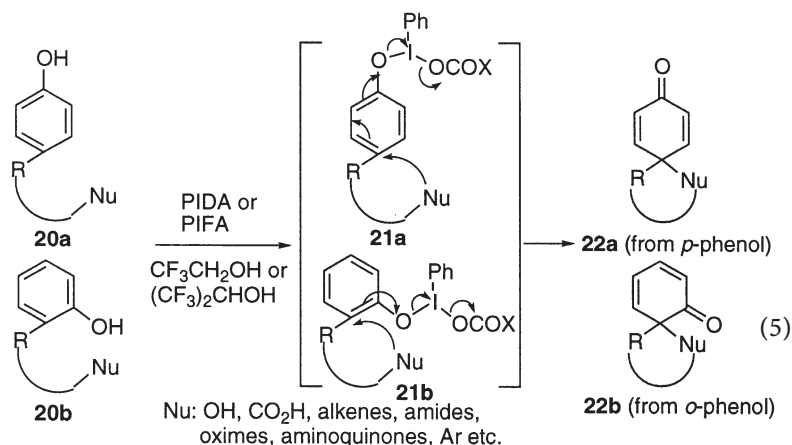
On the other hand, PIFA-induced oxidation of *p*-methoxy-substituted phenols (**15**) in the presence of electron-rich styrene derivatives (**16**) resulted in new carbon-carbon bond formation via an intermolecular 1,3-cycloaddition to afford *trans*-dihydrobenzofurans (**17**) stereoselectively [35, 36] [Eq. (4)]. A formal synthesis of neolignans such as kadsurenone (**18**) and denudatin B (**19**) was achieved by this methodology.



2.1.2

Oxidation of Phenol Derivatives to Spiroannulated Compounds

A variety of natural products bearing a spirocyclic system exist, and a considerable number of them are biosynthetically formed by oxidative spiroannulation reaction. Hypervalent iodine(III) oxidation of *para*- and *ortho*-substituted phenol derivatives (**20**) having a nucleophilic side-chain was found to be an efficient method to afford spirocyclohexadienone derivatives (**22**). The phenolic OH group of *para*- or *ortho*-substituted phenols initially reacts with iodine(III) species to form the intermediate (**21**). Then, intramolecular nucleophilic attack of the side chain nucleophile (alcohols [27, 37, 38], carboxylic acids [27], alkenes [39, 40], amides [41], oximes [42, 43], aminoquinones [44, 45], and electron-rich aromatic rings [46–48, 112, 113]) to the *ipso* position takes place to give the cross-conjugated cyclohexadienone (**22**) [Eq. (5)]. These reactions proceed under mild reaction conditions to give the corresponding spiro-compounds in moderate yields using standard polar solvents such as MeCN and CHCl₃. Kita and co-workers have also shown that the use of polyfluorinated alcohols, which are polar and weakly nucleophilic solvents such as 2,2,2-trifluoroethanol (CF₃CH₂OH) and 1,1,1,3,3,3-hexafluoro-2-propanol ((CF₃)₂CHOH), gave good to high yields of the same spiro compounds [41, 44, 45].

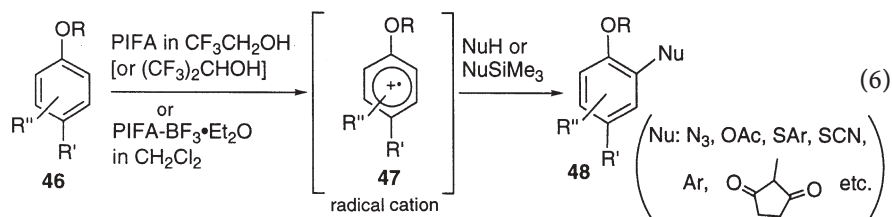


Utilizing this spiroannulation reaction of *para*- or *ortho*-substituted phenols with PIDA or PIFA, total syntheses of various natural products such as arnorosin (23), gymnastatin A (24), stenine (25), epoxysorbicillinol (26), bisorbicillinol (27), araplysillin-I (28), (\pm)-geodin (29), discorhabdin C (30), discorhabdin A (31), isosteganes (32), steganes (33), galanthamine (34), narwedine (35), norgalanthamine (36), sanguinine (37), lycoramine (38), (+)-maritidine (39), oxomaritidine (40), epimaritidine (41), palmarumycin CP₁ (42), deoxy-preussomerin A (43), FR901483 (44), and TAN1251 (45), have been achieved.

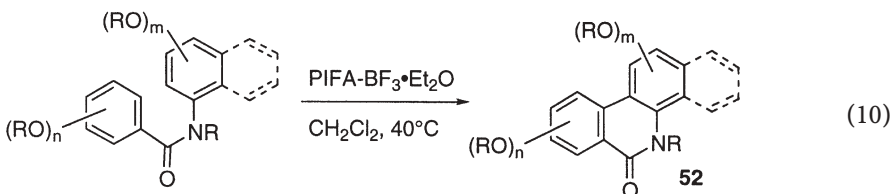
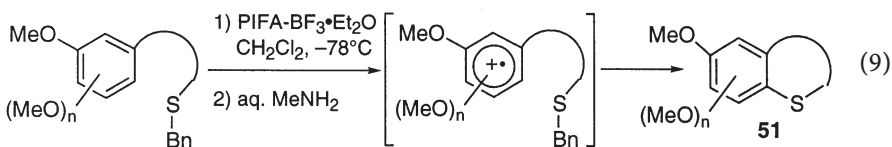
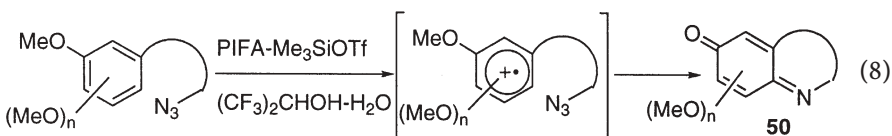
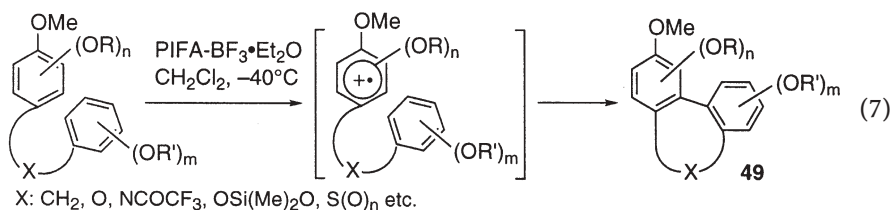
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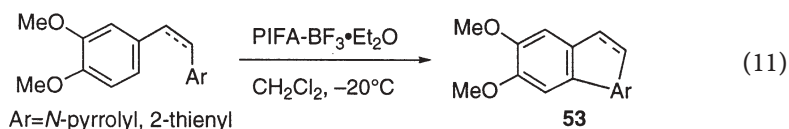
Oxidation of Phenol Ether Derivatives to Biaryls, Quinone-Imine Derivatives, and Sulfur-Containing Heterocycles

In contrast to phenolic oxidations, reactions of phenol ethers with hypervalent iodine reagents have been limited and have been reported only on the formation of diaryliodonium salts. It is well-known that diaryliodonium salts are obtained by the reaction of unsubstituted or *meta*-substituted phenol ethers with iodine(III) reagents, as reported by Beringer and co-workers [49]. However, Kita and co-workers found that the reaction of *ortho*- and *para*-substituted phenol ethers (46) with some nucleophiles in the presence of PIFA in polar and poorly nucleophilic solvents such as CF₃CH₂OH and (CF₃)₂CHOH caused nucleophilic substitution reactions [50, 51]. Various nucleophiles such as azide [50, 51], acetate [51], thiophenolate [52], thiocyanate ion [52], and β -dicarbonyl compounds [53] are introduced efficiently at the *ortho* positions of *o*- and *p*-substituted phenol ethers [Eq. (6)]. These reactions proceed with the formation of a charge-transfer complex of phenol ethers with PIFA, followed by single electron transfer leading to radical cations (47), which are subject to attack by nucleophiles to give 48. UV and ESR studies supported the generation of CT complexes and radical cations [51].



Similar types of nucleophilic substitutions have also been carried out when PIFA is activated by two equivalents of Lewis acids such as trimethylsilyl trifluoromethanesulfonate (TMSOTf) and $\text{BF}_3 \cdot \text{Et}_2\text{O}$ or heteropolyacid in standard solvents such as CH_2Cl_2 and MeCN. These reactions were applied to intramolecular reactions by the same authors leading to biaryls (49) [54–57], quinone imine derivatives (50) [58], and dihydrobenzothiophenes (51) [59], which are important structures of bioactive natural products [Eqs. (7)–(9)]. Domínguez and co-workers have expanded the above biaryl coupling reaction to the syntheses of benzo[*c*]phenanthridine system (52) [60] and heterobiaryl compounds (53) [61] [Eqs. (10, 11)].



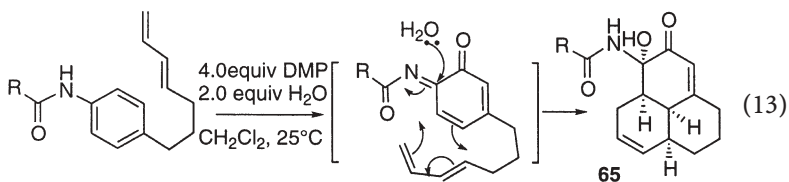
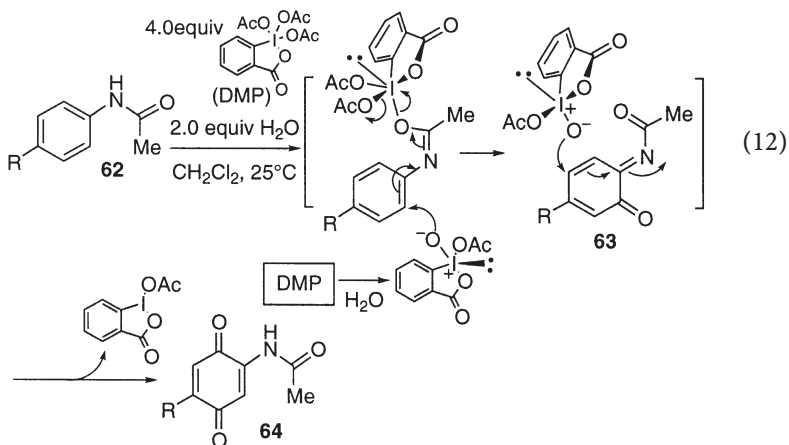


These related reactions have been utilized for total syntheses of natural products such as makaluvamine D (54), makaluvamine I (55), makaluvamine M (56), makaluvamine F (57), and michellamine A (58). Furthermore, synthetic studies on ellagitannin (59), benzo[*c*]phenanthridines (60), and rebeccamycin (61) have also been carried out.

2.1.4

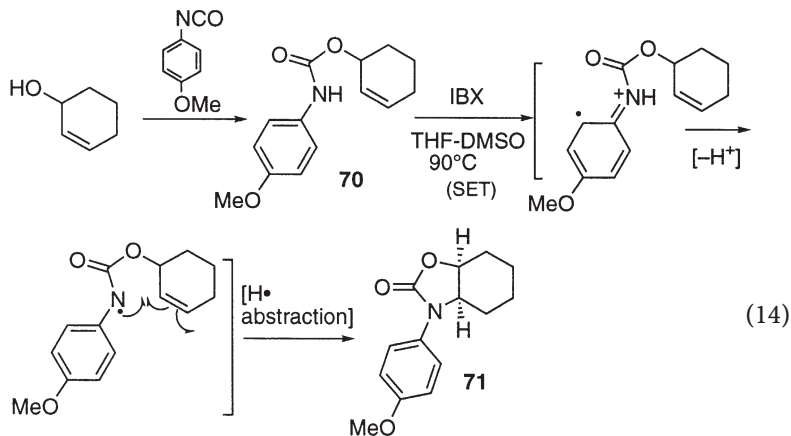
Oxidation of Anilides Using Iodine(V) Reagents

Iodine(V) reagents such as Dess-Martin periodinane (DMP) and *o*-iodoxybenzoic acid (IBX) are known as general reagents for oxidation of alcohols and have been utilized widely for natural product syntheses. Besides their general use for alcoholic oxidation, recently, the active studies on novel utilization of iodine(V) reagents such as DMP and IBX have been pursued mainly by Nicolaou and co-workers [26]. In particular, the versatile reactivities of anilides (62) with IBX or DMP are interesting and involve unprecedented features as follows. *o*-Imidoquinones (63) are prepared from 62 by the action of DMP and water. This reaction has been investigated extensively and was found to lead to *p*-quinones (64) [62] [Eq. (12)] and polycyclic systems (65) of diverse molecular architectures [63] [Eq. (13)].



This methodology was applied to the total synthesis of naturally occurring compounds, epoxyquinomycin B (**66**) and BE-10988 (**67**) and synthetic studies on pseudopterosin A aglycone (**68**) and elisabethin A (**69**).

Furthermore, Nicolaou and co-workers reported a SET-based IBX-mediated cyclization of anilides (**70**) leading to cyclic urethanes (**71**) [64] [Eq. (14)].

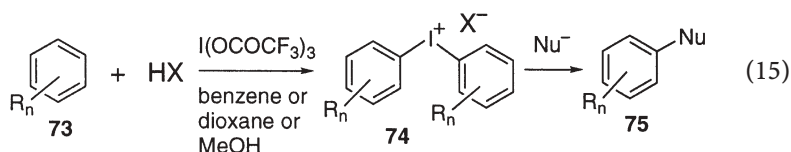


Application of this methodology to the synthesis of a variety of aminosugar derivatives involving *l*-vancosamine (**72**) has been performed.

2.2

Phenylidonium Salt-Mediated Reactions Leading to Diaryl Ether Derivatives and Nitrogen-Containing Heterocycles

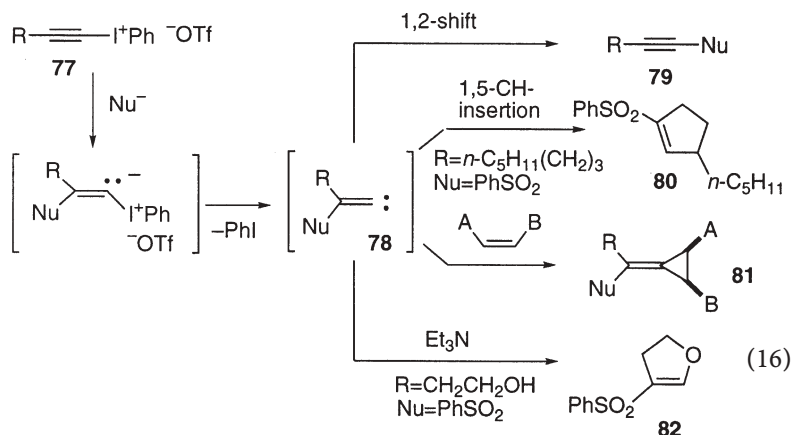
It is well-known that nucleophilic substitution reactions of diaryliodonium salts (**74**), prepared by the reaction of substituted arenes (**73**) with iodine(III) reagents such as PIDA, PIFA, $\text{PhI}=\text{O}$, and $\text{I}(\text{OCOCF}_3)_3$, smoothly proceed to yield various functionalized arenes (**75**) [49] [Eq. (15)].



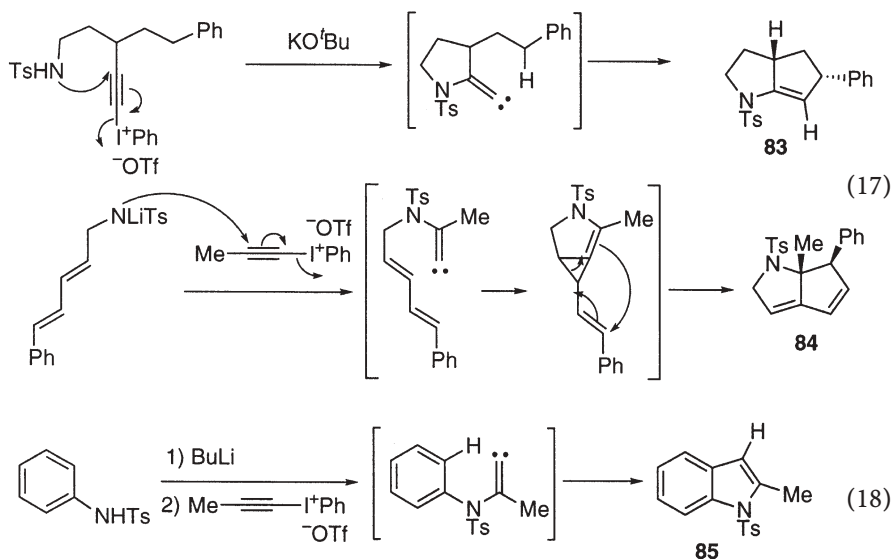
Total synthesis of a selective thyromimetic SK&FL-94901 (**76**) was accomplished by diaryl ether formation from symmetrical or unsymmetrical diaryliodonium salts.

The electrophilic phenyl(alkynyl)iodonium salts (**77**) have proven to be a ready participant in a wide range of complex transformations. That is, simple 1,2-shift of R or Nu can form new alkyne (**79**). As a more interesting feature for organic synthesis, Ochiai and co-workers have reported on a series of studies on

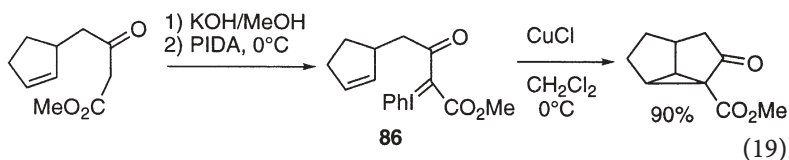
intra- and intermolecular alkylidenecarbene (**78**)-mediated reactions, starting from **77**, leading to **80**, **81**, and **82** [Eq. (16)].



Further applications to preparations of nitrogen-containing heterocycles such as pyrroles (**83**, **84**) and indoles (**85**) by Feldman and co-workers [Eqs. (17), (18)] made these reactions more important and useful for natural product synthesis [66, 67].



A high-yielding intramolecular cyclopropanation using β -dicarbonyl iodonium ylides (**86**) was reported by Moriarty and co-workers [68] [Eq. (19)]. This methodology is a viable alternative to diazo ketone route for intramolecular cyclopropanation.



These reactions have been applied to synthetic studies on biologically active compounds such as 1 β -methylcarbapenem (87), the antileukemic principle, pareitropone (88), and the potentially antiinflammatory marine alkaloid, halichlorine (89).

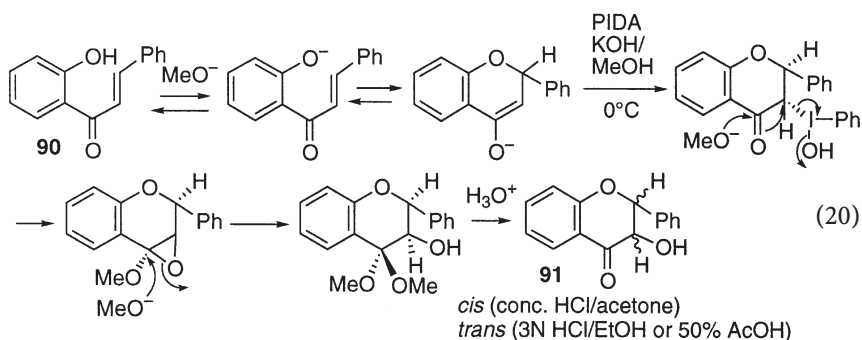
2.3

Reactions of Unsaturated Bonds with Hypervalent Iodine Reagents

2.3.1

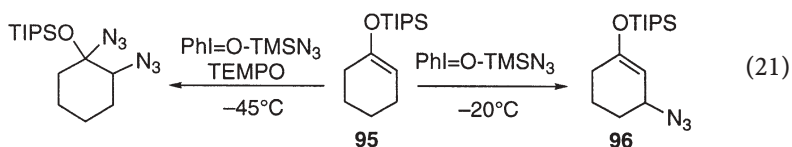
Oxidation of α,β -Unsaturated Ketones, Enols and Alkenes

Oxidation of *o*-hydroxychalcones (90) using PIDA under basic conditions (KOH-MeOH) affords *cis*- or *trans*-3-hydroxyflavanone (91) selectively via its dimethylacetal [69] [Eq. (20)].

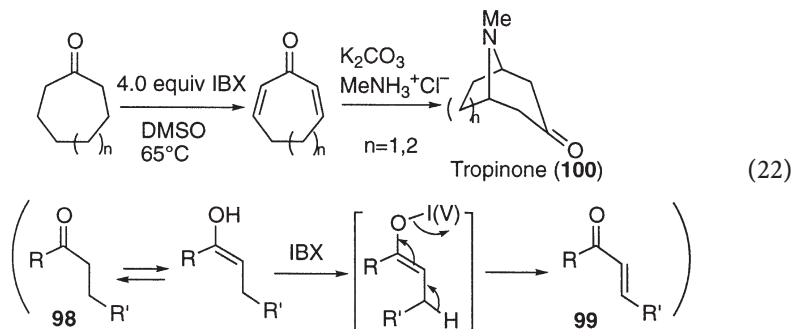


Utilizing this reaction, total syntheses of naturally occurring flavones, namely a phytoalexin, homopterocarpin (92), and chrysin (93) and luteolin (94), which are promising chemotherapeutics for AIDS, have been achieved.

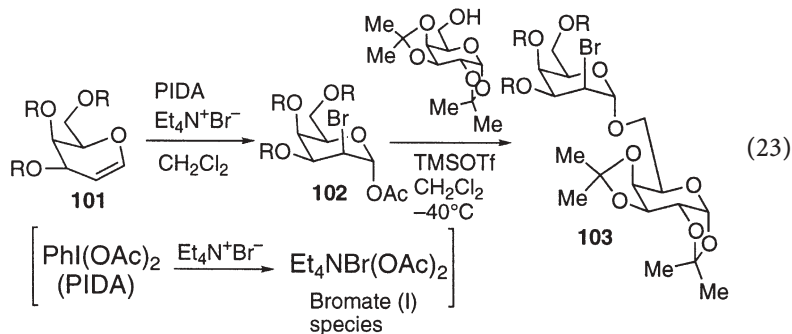
The β -azido triisopropylsilyl (TIPS) enol ether (96) functionalization developed by Magnus et al. from TIPS-enol ether (95) using iodosobenzene (PhI=O)-TMSN₃ [70–73] provides a unique strategy for the total synthesis of an anti-tumor agent, (+)-pancratistatin (97) [Eq. (21)].



A preparative method for α,β -unsaturated systems (**99**) from alcohols and ketones (**98**) using IBX via enol intermediates was developed by Nicolaou and co-workers. This methodology was found to be useful for selective dehydrogenation of steroid derivatives and the synthesis of tropinone derivatives (**100**) [74, 75] [Eq. (22)]



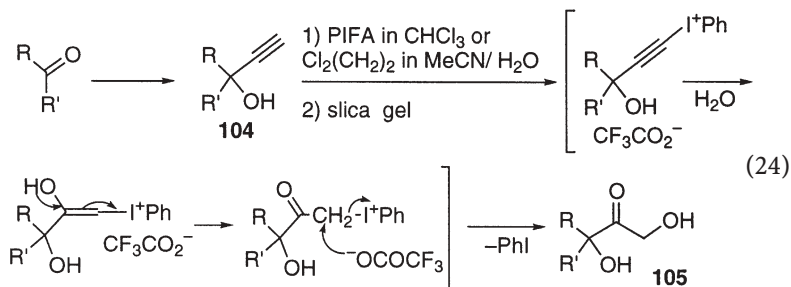
The 1,2-addition to carbohydrate-derived enol ethers (**101**) with tetraethylammonium [di(acetoxy)bromate (I)], prepared from PIDA and tetraethylammonium bromide in situ, resulted in 2-deoxy-2-bromopyranosyl acetates (**102**) which are versatile glycosyl donors for the synthesis of 2'-deoxy-2'-bromoglycosides (**103**) [76] [Eq. (23)].



2.3.2

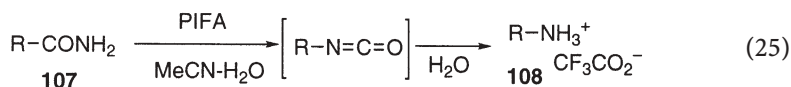
Oxidation of Alkynes

A useful direct transformation of ethynylcarbinols (**104**) into dihydroxyacetones (**105**) was developed by Kita and co-workers [77, 78] and was utilized for the syntheses of anticancer agents, adriamycin (**106**) analogs, and antiinflammatory drugs, corticosteroids [Eq. (24)].

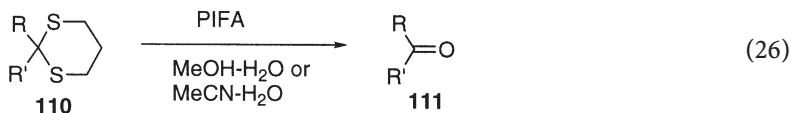


2.4 Others

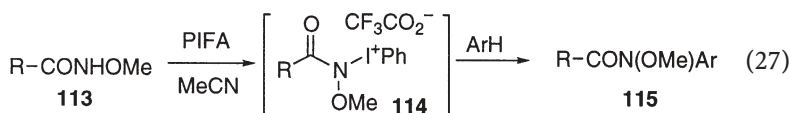
Hofmann-type rearrangement of primary amides (**107**) into the corresponding amines (**108**) using PIFA [79–81] was used for the initial reaction toward the total synthesis of the potent thrombin inhibitor cyclotheonamide A (**109**) [Eq. (25)].



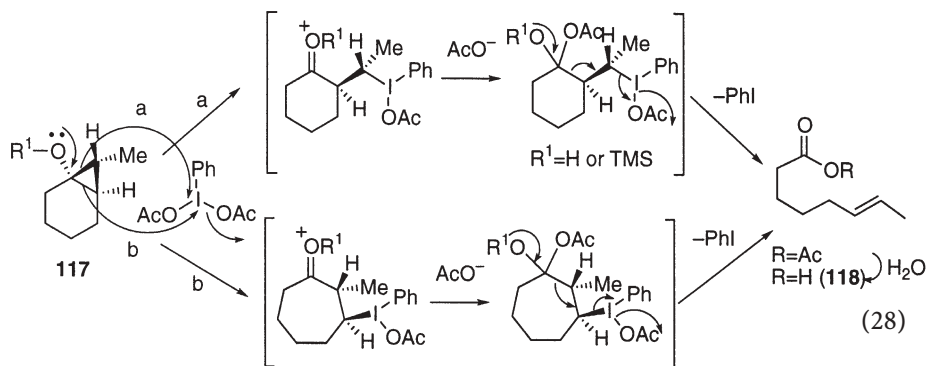
Mild deprotection of dithioacetals (**110**) to the corresponding carbonyl compounds (**111**) using PIFA [82] developed by Stork and co-workers was effective for the total synthesis of an antifungal agent, (+)-ambruticin (**112**) [Eq. (26)].



Treatment of *N*-methoxyamides (**113**) with PIFA generated electron deficient nitrogen species (**114**) which react intra- or intermolecularly with an aromatic group to give *N*-aryl-*N*-methoxyamides (**115**) in good yields [83] [Eq. (27)]. This reaction was applied to total synthesis of a potential agent for Parkinson's disease, PNU-95666E (**116**).



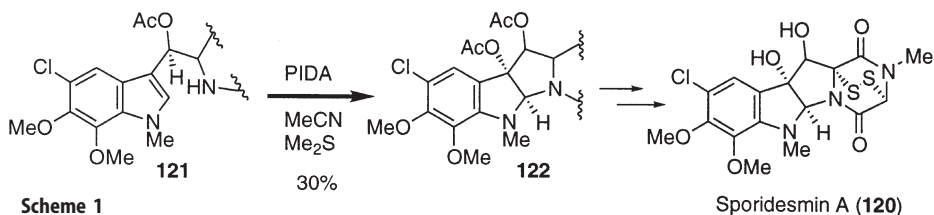
PIDA-mediated fragmentation reaction of tertiary cyclopropanols (**117**) afforded the corresponding alkenoic acids (**118**) in high yields [84]. This reaction was utilized for asymmetric total synthesis of a piperidine alkaloid, (-)-pinidine (**119**) [Eq. (28)].



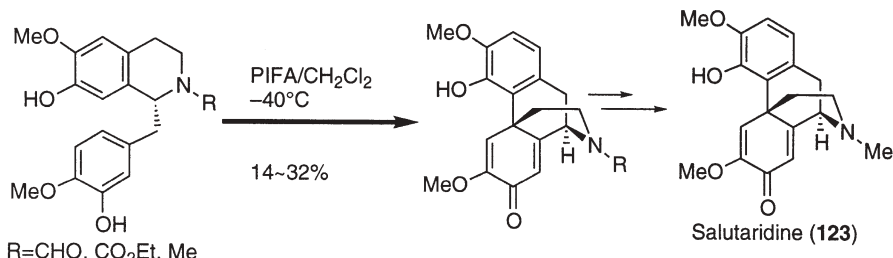
3

Total Synthesis of Natural Products Using Hypervalent Iodine Reagents

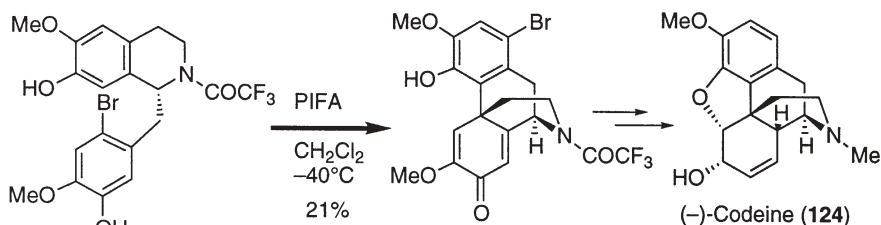
Pioneering studies on hypervalent iodine-induced reactions toward total syntheses of several natural products had been reported from the 1970s to the early 1980s. That is, Kishi and co-workers accomplished the total synthesis of sporidesmin A (**120**), which is a toxic metabolite of *Pithomyces chartarum*, by PIDA-mediated cyclization of tryptamine derivative **121**, but, the yield of tricyclic compound **122** was only 30% [85] (Scheme 1).



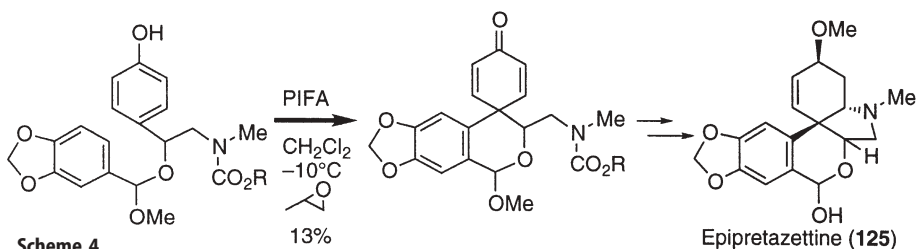
Other applications of iodine(III)-mediated reactions toward total syntheses of bioactive alkaloids such as salutaridine (**123**), (-)-codeine (**124**), and 6a-epipretazettine (**125**) were reported by White et al. and Szántay et al. in the early 1980s [46–48] (Schemes 2–4).



Scheme 2



Scheme 3



Scheme 4

Although these also involved pioneering studies on phenolic coupling reactions, they had not received much attention due to their low yields (up to 32% yield). This situation changed when an efficient phenolic oxidation reaction leading to *p*-quinone monoacetals and spirocyclohexadienones (spiro lactones and spiroethers) was developed by Kita and co-workers in 1987 [27], and several useful reactions leading to *p*- and *o*-quinones and their monoacetals have been reported since then [28–34] [Eqs. (1), (2)]. Furthermore, remarkable improvements of the yields have been performed by changing the solvent to polar and weakly nucleophilic solvents such as $\text{CF}_3\text{CH}_2\text{OH}$ and $(\text{CF}_3)_2\text{CHOH}$ [Eq. (5)] [41, 44, 45]. With these discoveries as a turning point, the hypervalent iodine-induced reactions, not only those such as phenolic oxidations but also other fundamental reactions as those described in the previous sections, have been utilized widely for natural product syntheses. In this section, we will illustrate by examples, classified on the basis of the type of reactions, their details leading to total or formal syntheses of various types of bioactive natural products.

3.1

Total Synthesis of Natural Products via Oxidation of Aromatic Compounds with Hypervalent Iodine Reagents

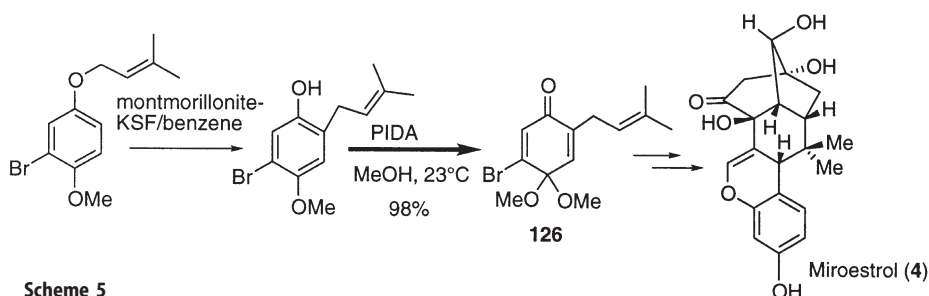
3.1.1

Total Synthesis via Oxidation Reactions of Phenol Derivatives with PIDA or PIFA

Mild and high yielding oxidation reactions of phenol derivatives to the corresponding quinone monoacetals, quinols, and quinones using PIDA or PIFA [Eqs. (1)–(3)] have been developed independently by Kita et al. [27], Lewis et al. [28], and Pelter et al. [29], and have been utilized extensively for the syntheses of

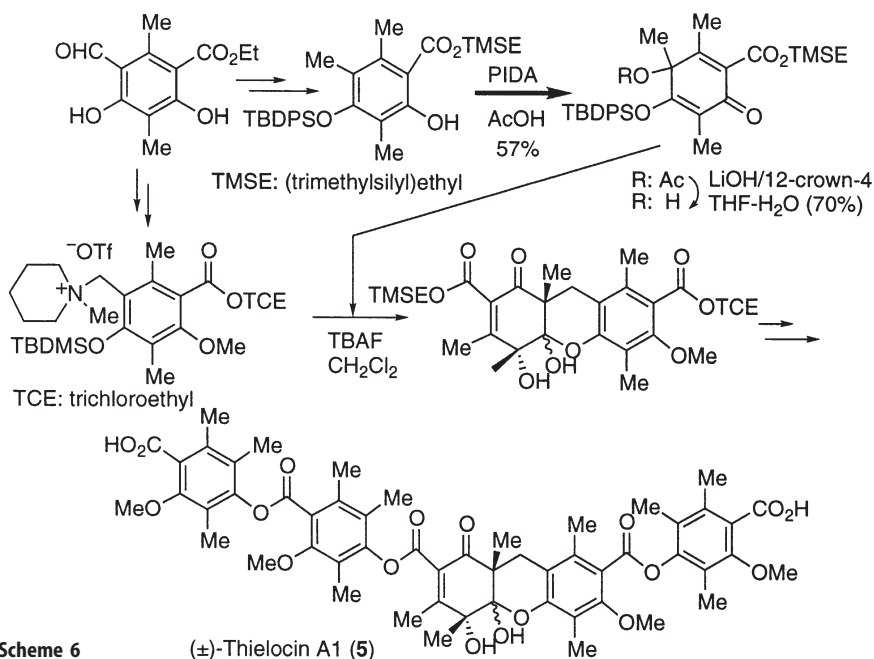
natural products and their key precursors such as Michael acceptors and regioselective dienophiles for Diels Alder reactions.

Corey and Wu utilized PIDA oxidation leading to the quinone monoacetal (**126**) for the initial step of enantioselective total synthesis of miroestrol (**4**), which is the folk medicine of southeast Asia, isolated from *Pueraria mirifica* (Thai *kwaok keur*) [86] (Scheme 5).

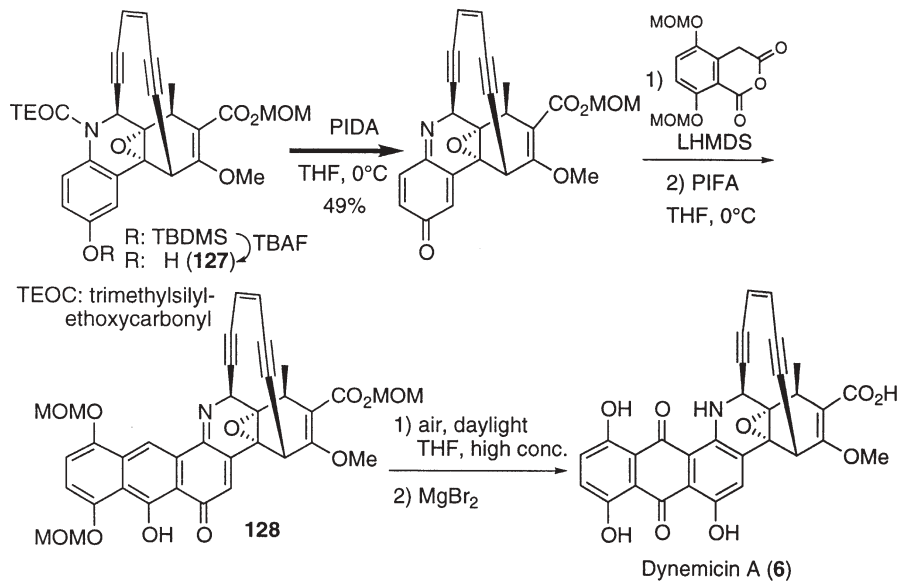


Total synthesis of an unusual pentameric dypside, thielocin A1b (**5**), which is a specific inhibitor of group II phospholipase A₂, was achieved via regioselective phenolic oxidation using PIDA [87] (Scheme 6).

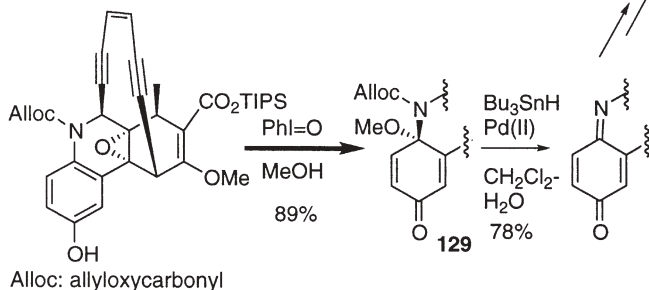
Double oxidation reactions of aminophenols (**127**) to the corresponding quinone-imines (**128**) using PIDA and PIFA were utilized for total synthesis of an enediyne antibiotic, (\pm)-dynemicin A (**6**), by Danishefsky and co-workers



Danishefsky's Approach



Myers's Approach



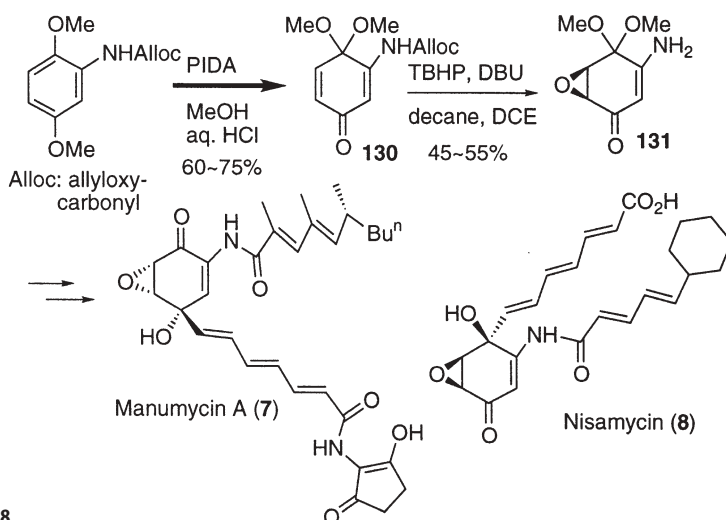
Scheme 7

[88] (Scheme 7). Another approach to quinone-imine moiety of 6 was carried out via quinone *N,O*-acetal (129) [31] by Myers and co-workers [89].

The manumycin family were isolated from *Streptomyces parvulus* (Tü 64) and possess a wide range of biological properties. Taylor and co-workers synthesized manumycin A (7) via the quinone monoacetal (131), which was prepared by PIDA oxidation, followed by epoxidation and alkylation on the cyclohexadienone (130) [90] (Scheme 8). Other members of the mamumycin family of antibiotics such as alisamycin, asukamycin, and (\pm)-nisamycin (8) have been synthesized by similar strategies [91].

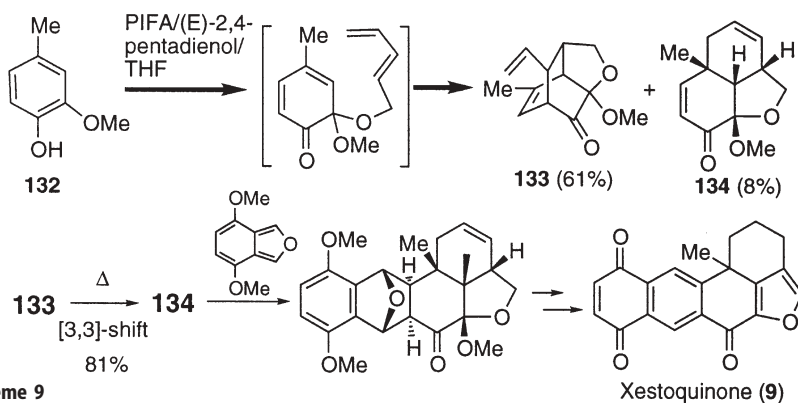
Similarly, *o*-alkoxyphenols are converted efficiently to *o*-quinone monoacetals, which have also been used as the key precursors for natural product synthesis using PIDA or PIFA.

Total synthesis of a pentacyclic antifungal marine natural product, xestoquinone (9) was achieved via tricyclic naphthofuranone (134) prepared by a



Scheme 8

procedure (PIDA-oxidation, intramolecular Diels-Alder reaction, and/or then, [3,3]-shift of 133 by heating in refluxing 1,2,4-trimethylbenzene) starting from the phenol (132) [92] (Scheme 9).

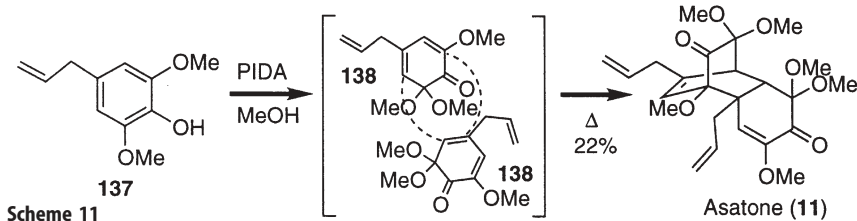
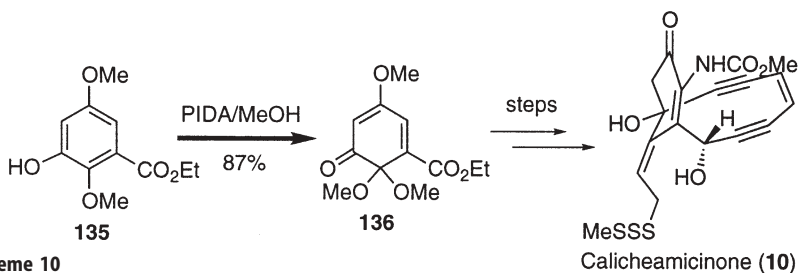


Scheme 9

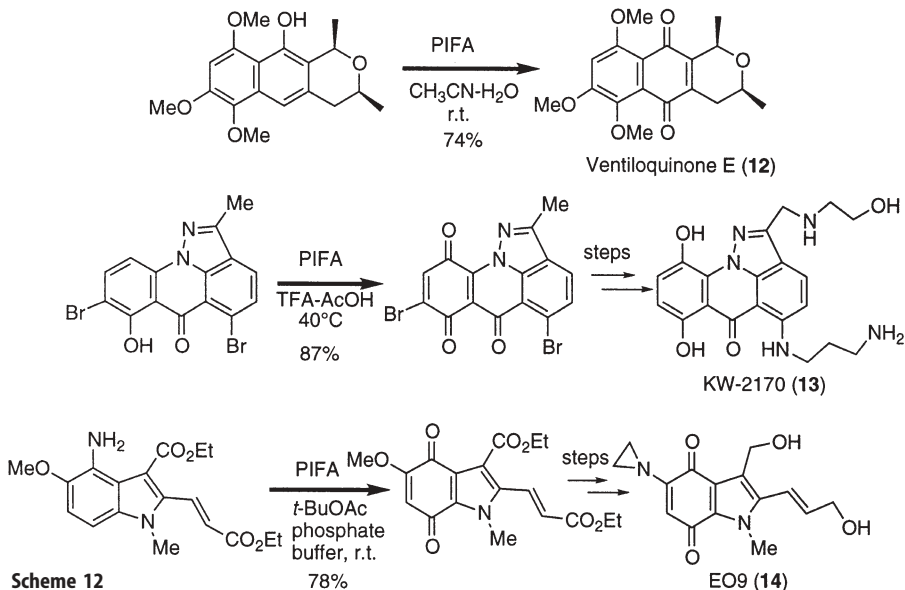
Transformation of *o*-methoxyphenol (135) into *o*-quinone monoacetal (136) using PIDA was used for the initial step of the synthesis of the enediyne aglycone, (\pm)-calicheamicinone (10), of the potent antitumor agent calicheamicin [93] (Scheme 10).

Potent antileukemic agent, asatone (11), which was isolated from *Asarum taitonense* Hayata, was synthesized via dimerization of cyclohexa-2,4-dienone (138) generated by PIDA oxidation of *o*-methoxyphenol (137) [94] (Scheme 11).

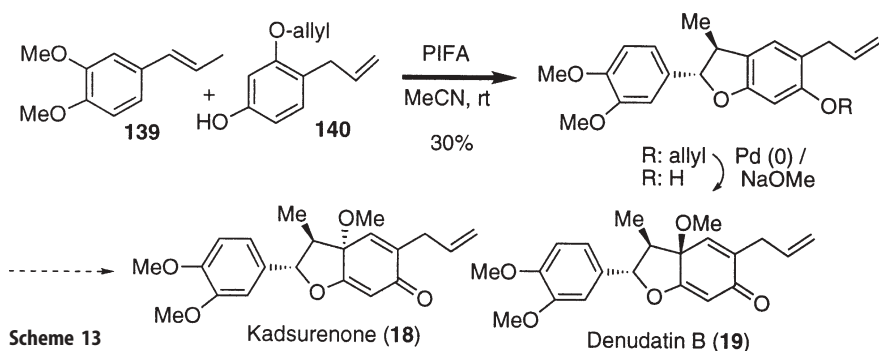
Total syntheses of natural products bearing a quinone structure have been accomplished efficiently by PIFA oxidation. That is, in the syntheses of antitu-



mor agents such as ventiloquinone E (12) [95], KW-2170 (13) [96], and EO 9 (14) [97], transformation of phenols into the corresponding quinones was the key step (Scheme 12). These iodine(III)-induced reactions proceeded in high yields under mild reaction conditions.



A convergent route to neolignans such as a potent and specific platelet-activating factor (PAF) antagonist, kadsurenone (18) and denudatin B (19), via a



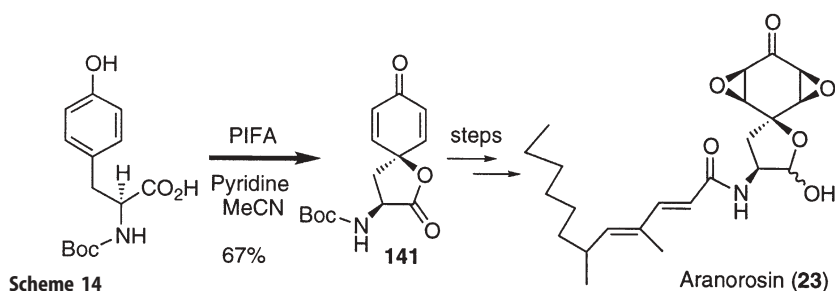
formal 1,3-cycloaddition of electron-rich styrene derivative **139** to oxidized phenols **140** was developed by Swenton and co-workers [35] (Scheme 13).

3.1.2

Total Synthesis via Oxidative Spiroannulation Reactions of Phenol Derivatives with PIDA or PIFA

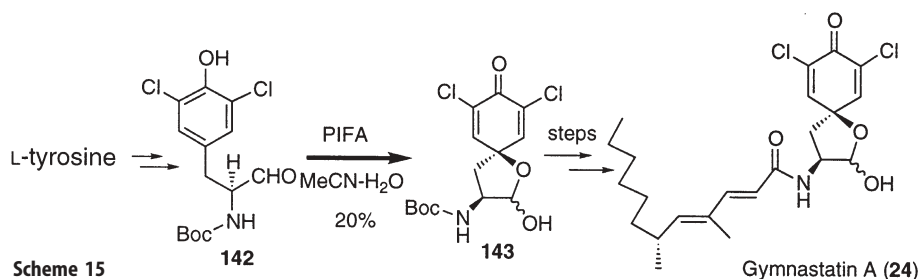
Iodine(III)-induced spiroannulation reactions of phenol derivatives have been applied widely to total syntheses of related natural products. These reactions have been usually carried out in MeCN, but recently polyfluorinated alcohols such as $\text{CF}_3\text{CH}_2\text{OH}$ and $(\text{CF}_3)_2\text{CHOH}$ are preferred.

Total synthesis of a novel antibiotic, aranosin (**23**), which was isolated from the fermentation broth of *Pseudoarachniotus roseus*, was accomplished by Rama Rao et al. [98], Wipf et al. [99], and McKillop et al. [100] via the construction of spiro lactone (**141**) using PIFA or PIDA (Scheme 14).

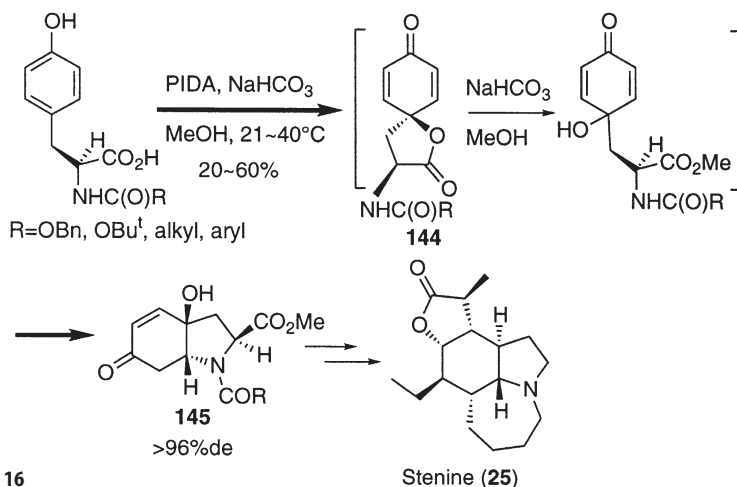


In an analogous fashion, total synthesis of cytotoxic marine alkaloid, gymnastatin A (**24**), which was isolated from the sponge *Halicondria japonica*, was accomplished via the spiro lactol (**143**) derived from the tyrosinal derivative (**142**) with PIFA [101] (Scheme 15).

An interesting approach toward the total synthesis of the *Stemona* alkaloid, (–)-stenine (**25**), which have been used in Chinese and Japanese folk medicine as insecticides, as drugs for the treatment of respiratory diseases, via spiro lactone



144 was reported by Wipf and co-workers. They accomplished asymmetric total synthesis of **25** via a bicyclic compound (**145**), which is obtained in an enantio- and diastereomerically pure form in a single step from L-tyrosine using PIDA-induced cyclization reaction [102] (Scheme 16).

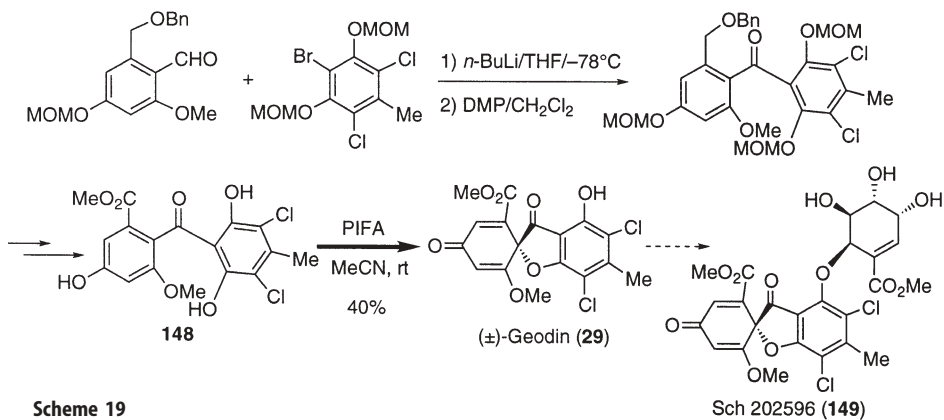
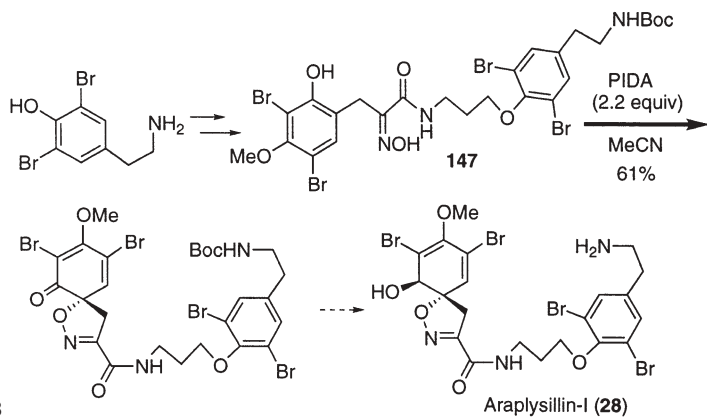
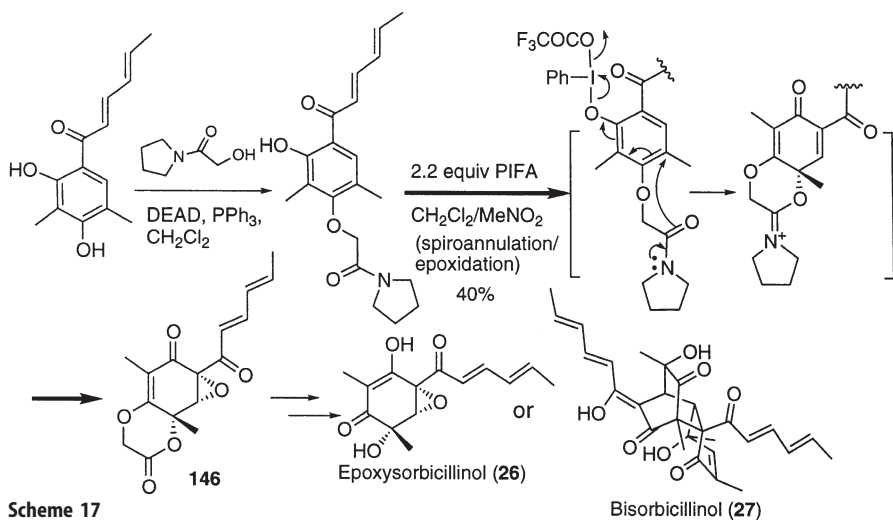


Efficient routes to epoxysorbicillinol (**26**) and bisorbicillinol (**27**) were developed by Pettus and co-workers [103]. The key step is the hypervalent iodine(III)-induced oxidative dearomatization to produce a stable and highly malleable *p*-quinol intermediate (**146**) (Scheme 17).

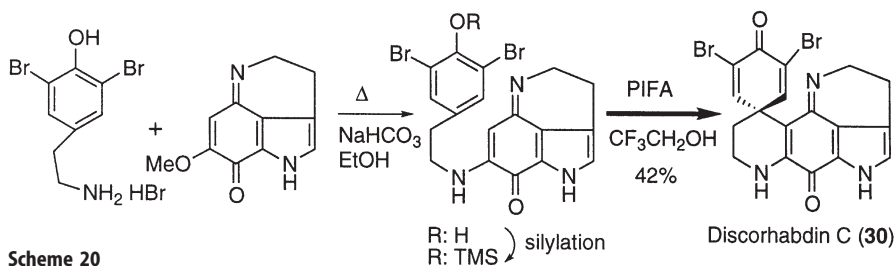
The key structure of antimicrobial marine natural product, araplysillin-I (**28**), which was isolated from *Psammaphysilla arabica*, was synthesized by spiroannulation of *o*-phenolic oxime-amide (**147**) with PIDA [104] (Scheme 18).

A facile synthesis of the known antifungal antibiotic (\pm)-geodin (**29**) corresponding to the spirocoumaranone part of Sch 202596 (**149**) was achieved by PIDA-induced spiroannulation reaction of the phenol (**148**) [105] (Scheme 19).

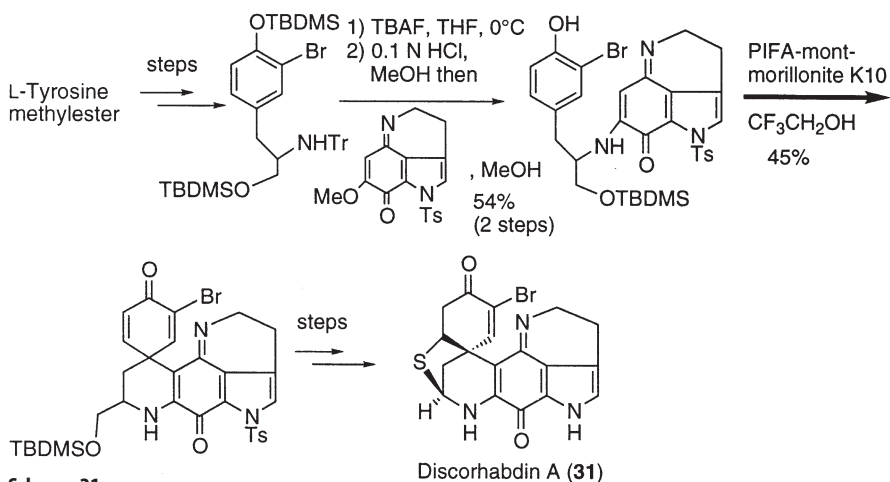
Carbocyclic spirohexadienone derivatives, which are important substructures of various bioactive alkaloids, have also been constructed efficiently by oxidative spiroannulation with hypervalent iodine(III) reagents in polar and weakly nucleophilic solvents such as $\text{CF}_3\text{CH}_2\text{OH}$ and $(\text{CF}_3)_2\text{CHOH}$ [Eq. (5)].



Several efficient methods for PIFA-induced spiroannulation reactions of silylated phenol derivatives [44] or phenols [45] toward total synthesis of discorhabdin alkaloids having potent cytotoxicities and unique structures have been developed by Kita and co-workers. Utilizing these methodologies, total syntheses of discorhabdin C (30) [106] and discorhabdin A (31) [107] have been accomplished (Scheme 20, 21).



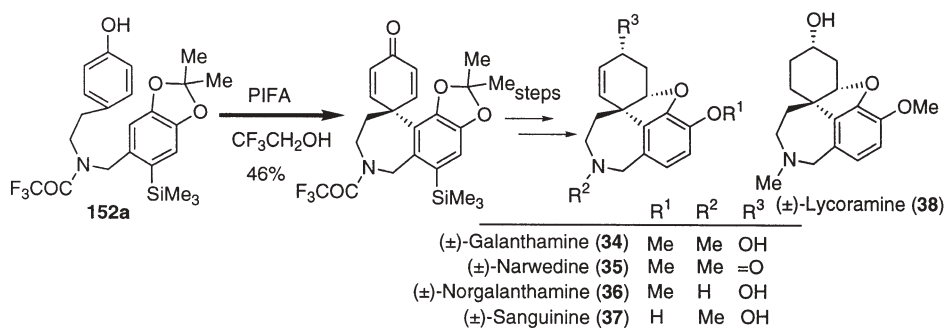
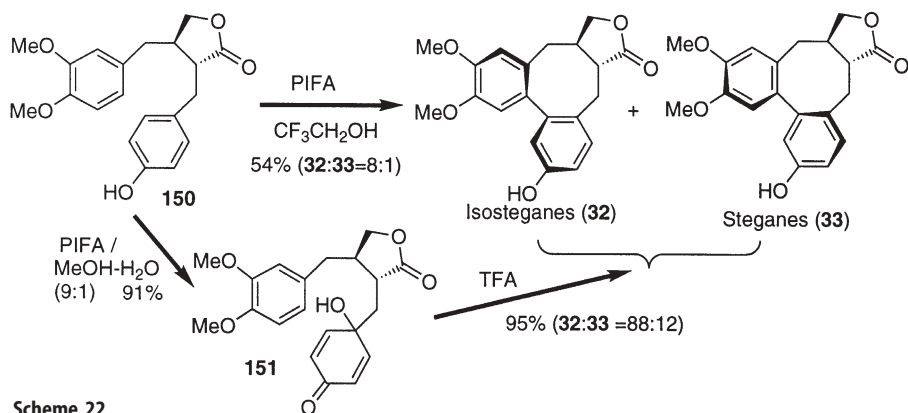
Scheme 20



Scheme 21

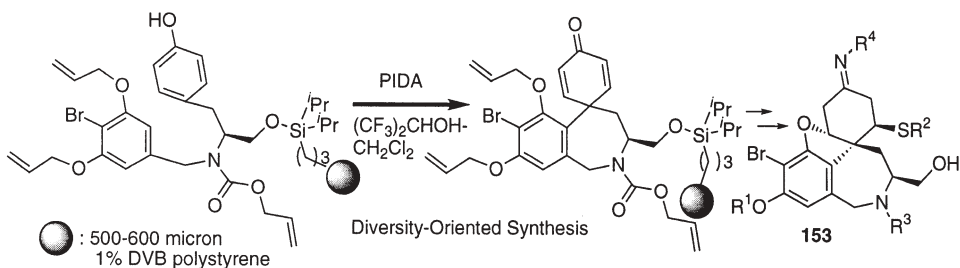
Analogously, Pelter and co-workers reported that PIFA reacts in $\text{CF}_3\text{CH}_2\text{OH}$ with readily available *trans*-2,3-dibenzylbutyrolactones (150) to produce isosteganes (32) and steganes (33) (Scheme 22). After that, they improved the yields of 32 and 33 by treating 150 with PIFA in aqueous MeOH followed by treatment with TFA via the quinol intermediate 151 [108]. Related synthetic studies toward lignans have also been performed by the same group [109–111].

(-)-Galanthamine (34), an alkaloid isolated from the *Amaryllidaceae* family, has been approved in Austria and the United Kingdom for the treatment of Alzheimer's disease as a selective acetylcholinesterase inhibitor. Oxidative spiroannulation of norbelladine derivative (152) using PIFA in $\text{CF}_3\text{CH}_2\text{OH}$ provides a mild and efficient method for preparing galanthamine (34) and related alkaloids such as narwedine (35), norgalanthamine (36), sanguinine (37), lycoramine (38), and maritidine (39) [112, 113] (Scheme 23).

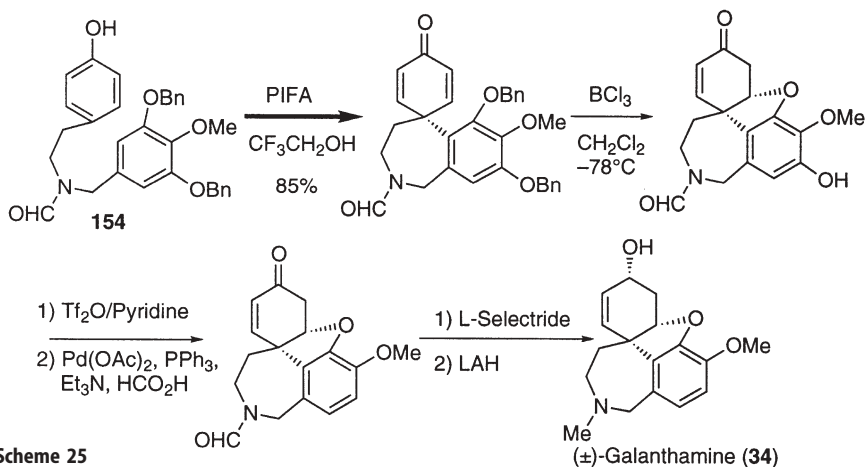


Scheme 23

This methodology was applied to biomimetic diversity-oriented synthesis to discover galanthamine-like molecules (153) with biological properties beyond those of the natural product by Shair and co-workers [114] (Scheme 24).



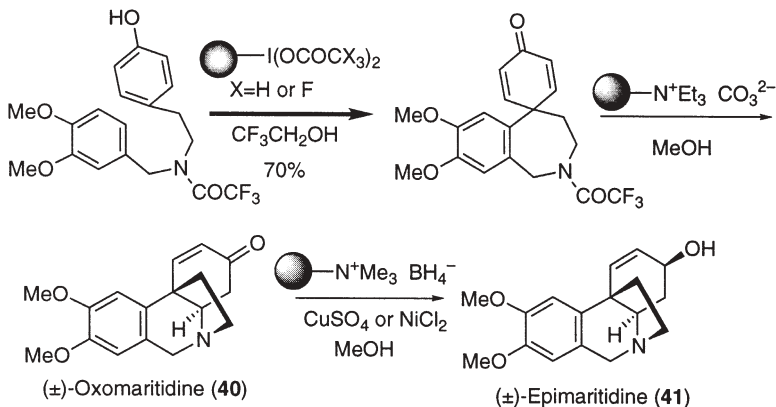
Scheme 24



Scheme 25

Toward the industrial production of 34, Node and co-workers improved the yield of this phenolic coupling reaction using the suitably protected norbelladine-type derivative (154) [115] (Scheme 25).

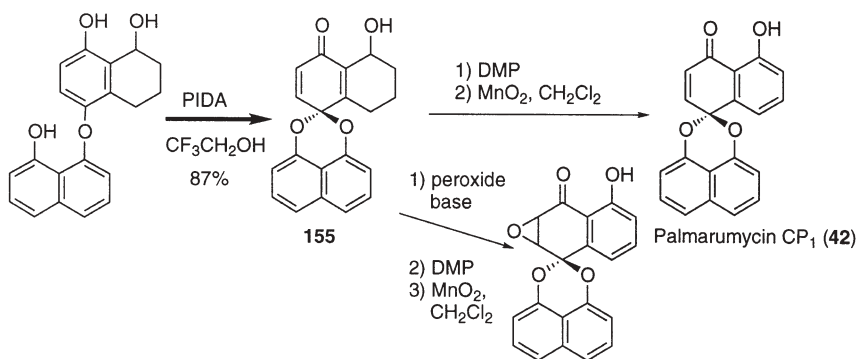
Ley and co-workers applied the polymer-supported hypervalent iodine reagents, poly(diacetoxyiodo)styrene (PDAIS) or polybis(trifluoroacetoxyiodo)styrene (PBTIS) to the above-mentioned spiroannulation reaction. They succeeded in the concise syntheses of (±)-oxomaritidine (40) and (±)-epimaritidine (41) using this methodology as the key steps [116] (Scheme 26).



Scheme 26

These reaction conditions using fluorinated solvents have also been applied to the construction of other spirocyclic systems.

Wipf and co-workers developed a general route for the construction of the spiroketal naphthodecalines (155) using PIDA in $\text{CF}_3\text{CH}_2\text{OH}$ and the first total syntheses of palmarumycin CP₁ (42) and (±)-deoxypreussomerin A (43), which are fungal metabolites showing antitumor and antibiotic activities [117, 118] (Scheme 27).

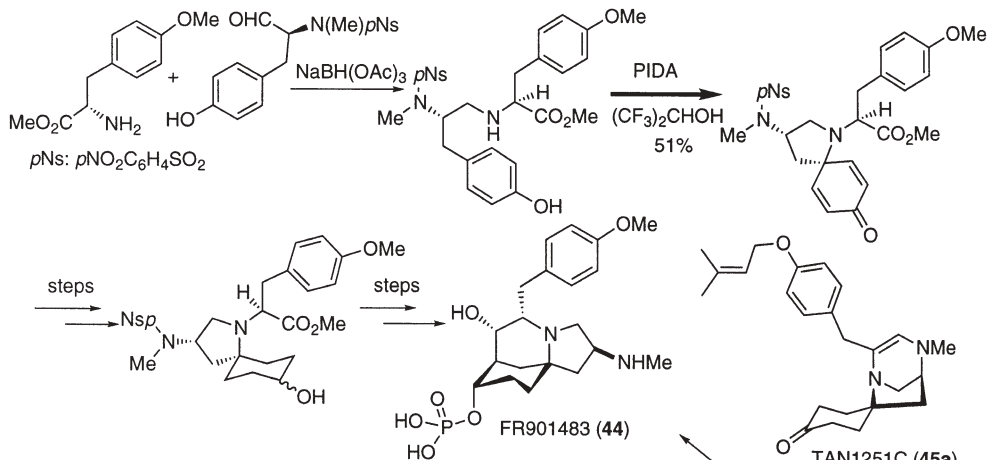


Scheme 27

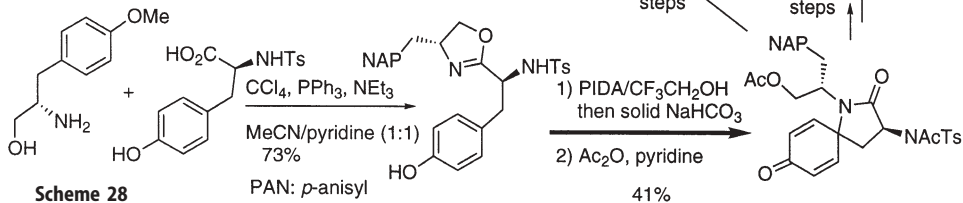
Deoxypreussomerin A (43)

Sorensen and co-workers reported the total synthesis of a powerful immunosuppressant, FR901483 (44), by oxidative azaspiroannulation with PIDA in (CF₃)₂CHOH and intramolecular aldol addition reactions [119]. About the same time, Ciufolini and co-workers also succeeded independently in the total syntheses of 44 and TAN 1251C (45a), which is a muscarinic antagonist of potential interest as an antispasmodic or antiulcer agent, utilizing a similar spiroannulation with PIDA [120] (Scheme 28).

Sorensen's Approach



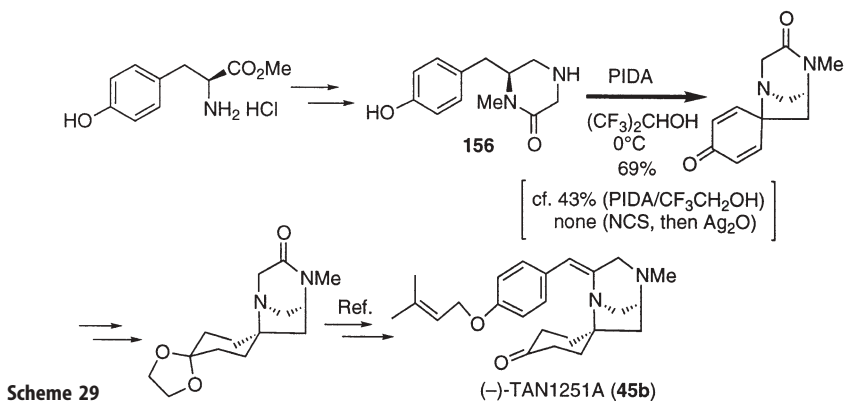
Ciufolini's Approach



Scheme 28

41%

Honda and co-workers applied the above procedure to the formal total synthesis of enantiopure (-)-TAN1251A (**45b**), a muscarinic M₁ receptor antagonist, isolated from a culture of *Penicillium thomii* RA-89 [121]. The best yield of the spiroannulation reaction of the phenol **156** using PIDA was achieved by the reaction in (CF₃)₂CHOH similar to the Sorensen's procedure [119]. Incidentally, none of the desired product was obtained by the typical stepwise procedure using chlorination with NCS followed by Ag₂O oxidation (Scheme 29).

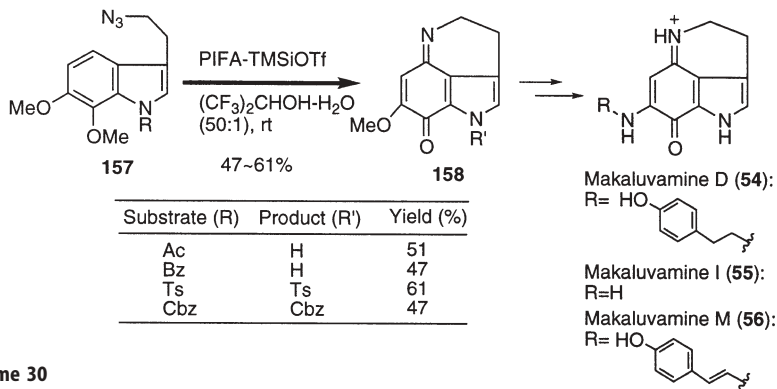


3.1.3

Total Synthesis via Oxidation Reactions of Phenol Ether Derivatives with PIFA

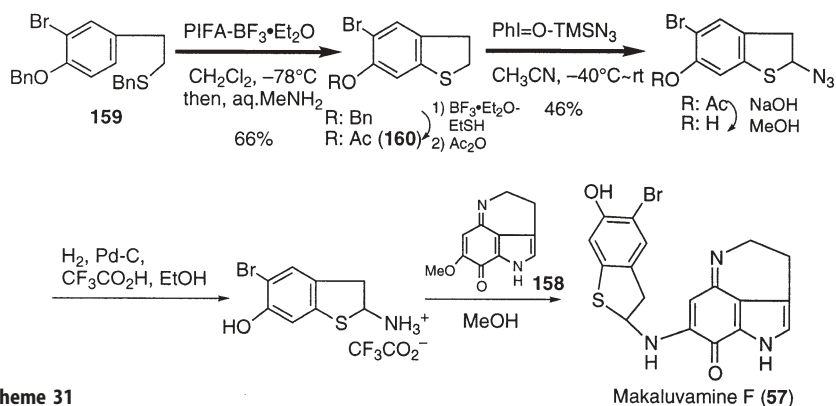
Intramolecular nucleophilic substitution reactions of phenol ether derivatives induced by activated iodine(III) reagents such as PIFA-TMSOTf and PIFA-BF₃·Et₂O [Eq. (7) – (11)] have been applied to total or formal synthesis of various types of bioactive natural products.

Kita and co-workers have developed a concise and high-yielding procedure for preparing the pyrroloiminoquinone derivatives (**158**), which are key precursors of antitumor marine alkaloids, makaluvamine D (**54**), I (**55**), and M (**56**), from the phenol ether derivatives (**157**) bearing an alkylazido side chain using PIFA-TMSOTf [122] (Scheme 30).



Scheme 30

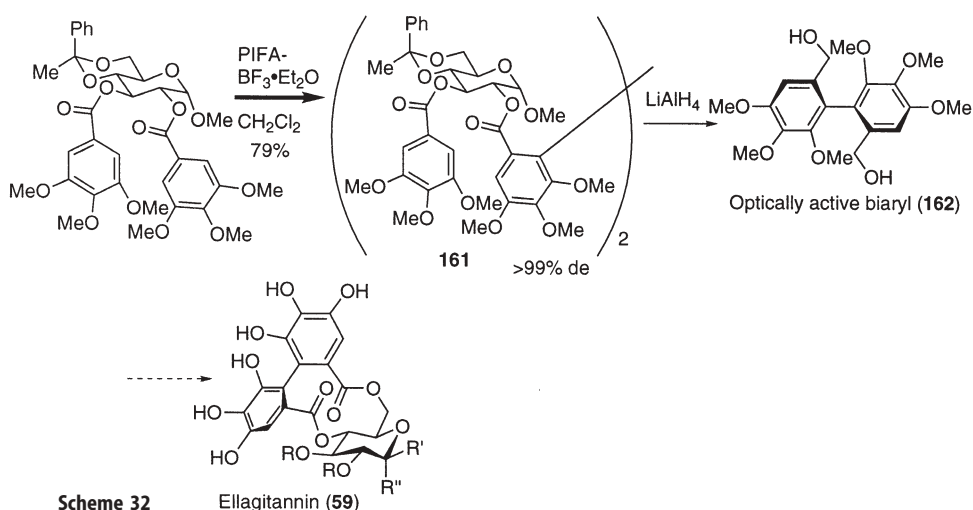
Combining this pyrroloiminoquinone formation [58, 122], the cyclic sulfide formation of phenol ether **159** using PIFA- $\text{BF}_3 \cdot \text{Et}_2\text{O}$ [59], and α -azidation of cyclic sulfide (**160**) using $\text{PhI}=\text{O}-\text{TMSN}_3$ [123], the first total synthesis of (\pm)-makaluvamine F (**57**), which is a potent inhibitor for DNA topoisomerase II, was achieved by Kita and co-workers [124, 125] (Scheme 31).



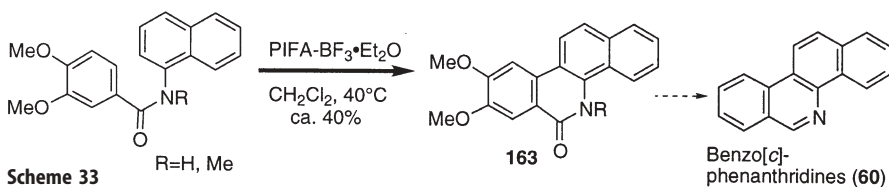
Scheme 31

Utilizing a chiral biaryl coupling reaction of phenol ethers with PIFA- $\text{BF}_3 \cdot \text{Et}_2\text{O}$, synthesis of a potential precursor (**162**) as its enantiomerically pure form for preparing of ellagitannin (**59**) was performed by an unexpected intermolecular biaryl coupling reaction [126] (Scheme 32). In this reaction, high diastereomeric excess of the biaryl (**161**) was observed when using α -D-glucose derivatives as chiral templates.

An extension of the intramolecular biaryl coupling with PIFA- $\text{BF}_3 \cdot \text{Et}_2\text{O}$ to a short and efficient access to benzo[*c*]phenanthridines (**60**) and phenanthri-

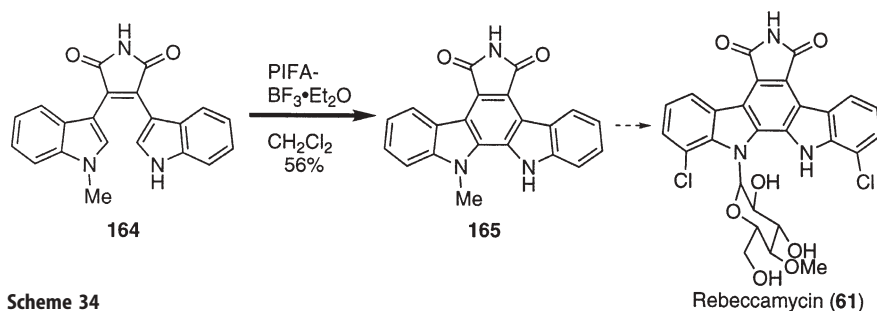


Scheme 32



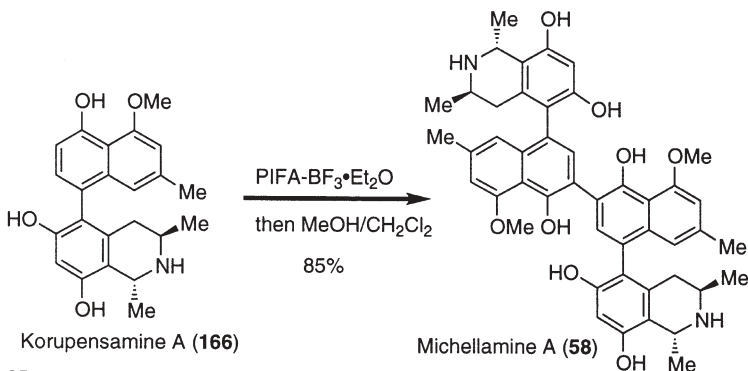
163, which are important core structures of biologically active isoquinoline alkaloids, have been achieved by Domínguez and co-workers [60] (Scheme 33).

Similar application to the construction of bisindole system was reported by Faul and co-workers. That is, the core structure (indole[2,3-*a*]carbazoles) (165) of rebeccamycin (61), which possesses potent antitumor and protein kinase C inhibitory properties, was synthesized by intramolecular coupling reaction of bisindolylmaleimides (164) with PIFA-BF₃·Et₂O [127] (Scheme 34).



Scheme 34

Concise total synthesis of a promising antiviral (anti-HIV) agent, michellamine A (58), was accomplished by Bringmann and Tasler via oxidative biaryl coupling reaction of korupensamine A (166) using PIFA (or Pb(OAc)₄-BF₃·Et₂O [128] (Scheme 35).



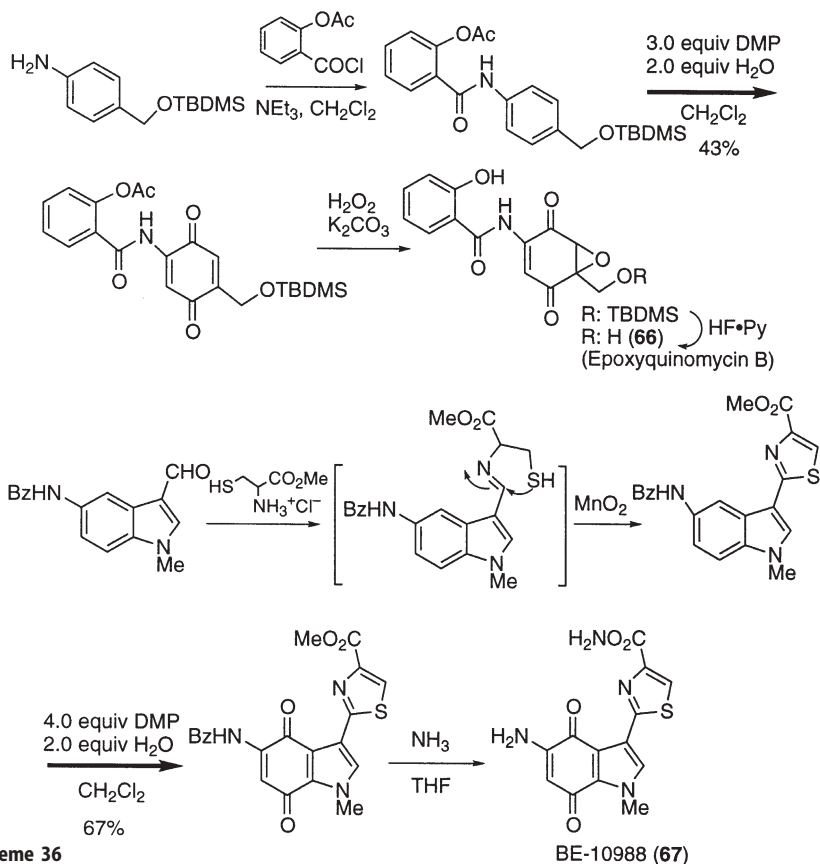
Scheme 35

3.1.4

Total Synthesis via Oxidation Reactions of Anilides with Iodine(V) Reagents

Nicolaou and co-workers have shown the versatile reactivities of anilides toward iodine(V) reagents under various reaction conditions.

Concise total syntheses of a promising antiinflammatory agent, epoxyquinomycin B (**66**), isolated from *amycolatopsis* sp. MK299–95F4, and a promising topoisomerase-II inhibitor, BE-10988 (**67**), isolated from the culture broth of a strain of *Actinomyces*, have been accomplished by a DMP-induced oxidation reaction of anilides [129] (Scheme 36).

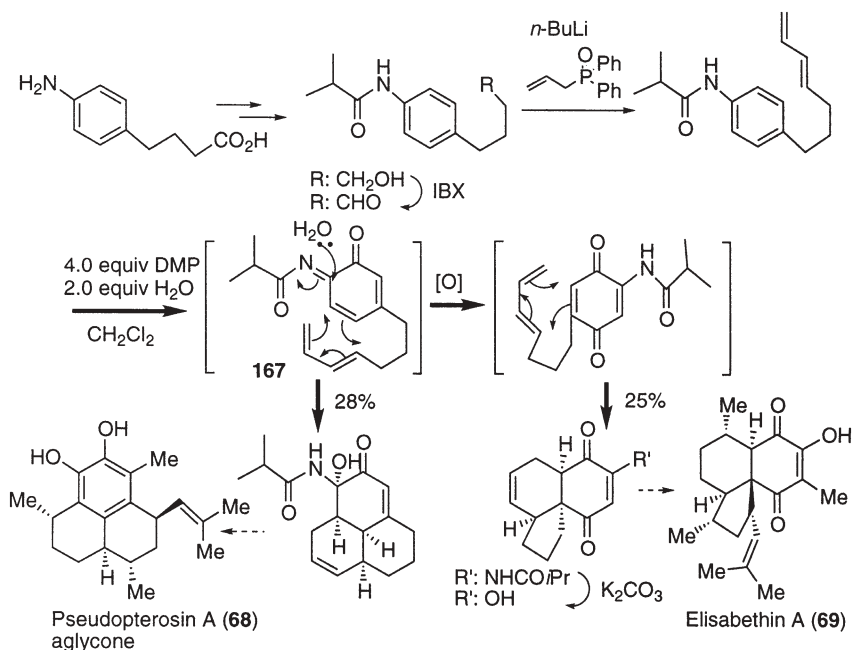


Scheme 36

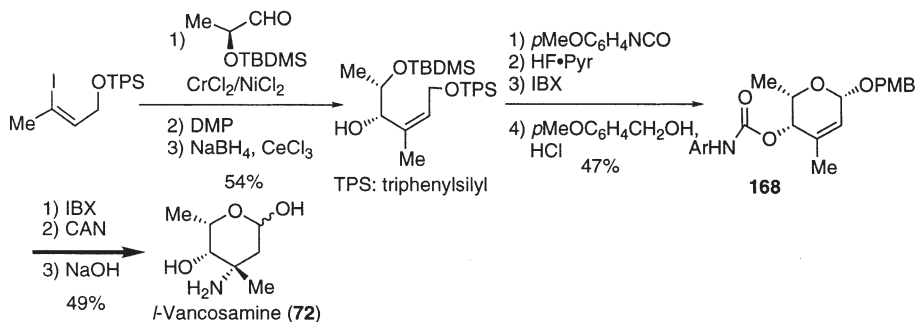
BE-10988 (**67**)

Similarly, construction of polycyclic structures by intramolecular Diels-Alder reactions via *o*-imidoquinones (**167**), prepared by DMP-induced oxidation, was revealed to be useful for the synthesis of pseudoterosin A (**68**), elisabethin A (**69**), and their structural analogues [129] (Scheme 37).

A stereocontrolled synthesis of *l*-vancosamine (**72**) was achieved by Nicolaou and co-workers starting from **168** via IBX-induced cyclization followed by CAN-mediated removal of PMB group and basic hydrolysis [130] (Scheme 38).



Scheme 37



Scheme 38

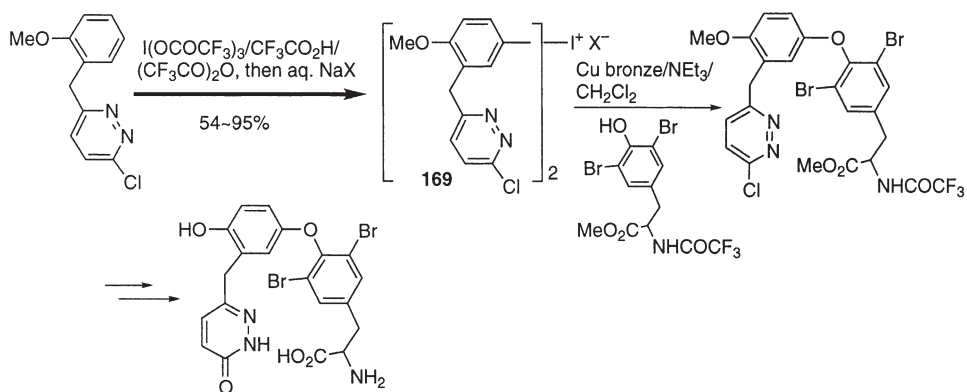
3.2

Total Synthesis via Phenyliodonium Salt-Mediated Reactions

Phenyliodonium salt-induced reactions are also applicable to total syntheses of several natural products having biaryl ether moieties and polycyclic nitrogen heterocycles.

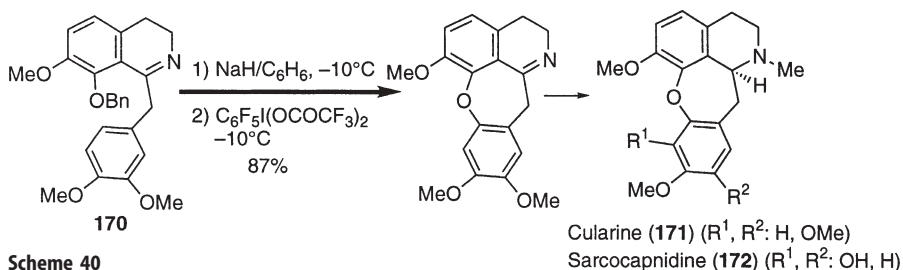
A large scale synthesis of SK&FL-94901 (76), which is a novel, selective, and potent thyromimetic, was established by construction of the hindered diaryl ether moiety via symmetrical iodonium salt 169 [131] (Scheme 39).

Cularines are isoquinoline alkaloids, which occur mainly in the *Fumaraceae* family, and are used as muscle relaxants. Total syntheses of (+)-cularine (171)



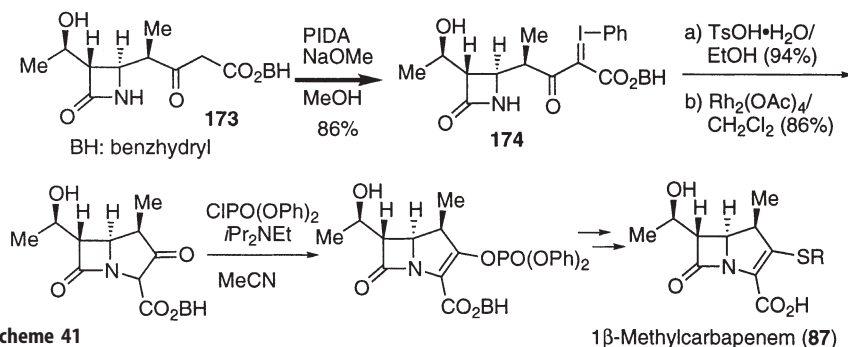
Scheme 39 SK & FL-94901 (**76**)

and (+)-sarcocapnidine (**172**) were performed by intramolecular diaryl ether formation from benzylphenyl ether **170** with $C_6F_5I(OCOCF_3)_2$ via $ArO-I^+-C_6F_5$ intermediate as the key step [132] (Scheme 40).



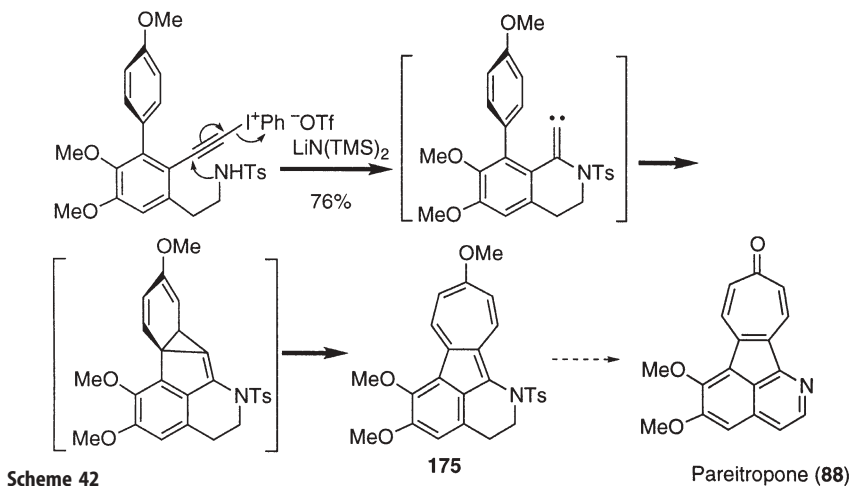
Scheme 40

An efficient construction of the 1β -methylcarbapenam nucleus (**87**) was established by Kume and co-workers utilizing acid- or rhodium (II)-catalyzed cyclization of the iodonium ylide derivatives (**174**), which were easily prepared from the corresponding β -ketoester derivatives (**173**) with PIDA [133] (Scheme 41).



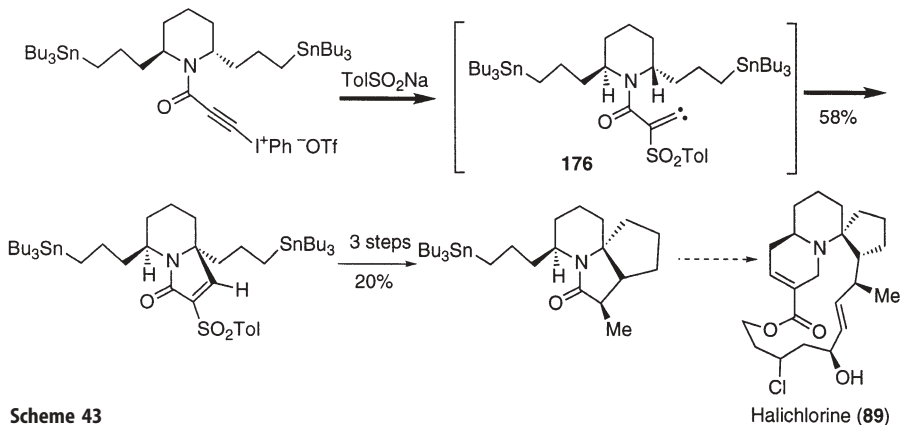
Scheme 41

1β -Methylcarbapenam (**87**)



The key structure (175) of a strongly antileukemic tropoloisoquinoline alkaloid, pareitropone (**88**), was synthesized by alkyldenecarbene salt-mediated intramolecular 1,5-CH insertion via alkyldenecarbene generation [134] (Scheme 42).

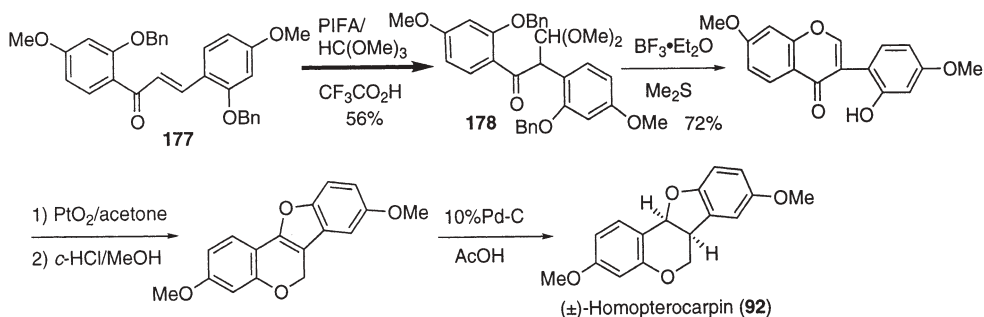
The polycyclic core of the marine alkaloid, halichlorine (**89**), which shows selective VCAM-1 induction inhibition, was synthesized by alkyldenecarbene salt-mediated intramolecular 1,5-CH insertion via alkyldenecarbene (176) generation [134] (Scheme 43).



3.3

Total Synthesis via Hypervalent Iodine-Induced Reactions of Unsaturated Bonds

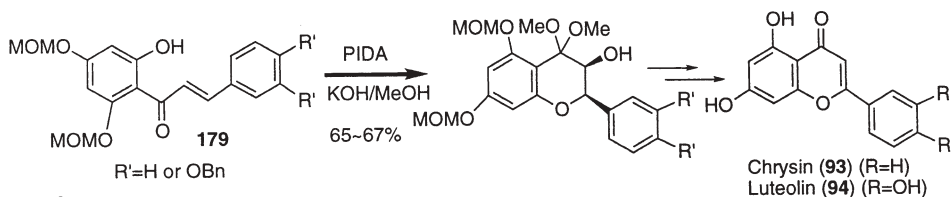
Hypervalent iodine oxidation reactions of unsaturated compounds such as α,β -unsaturated compounds, alkynes, and silylenol ethers afford the important substructures of several natural products.



Scheme 44

(\pm)-Homopterocarpin (92), a phytoalexin isolated from *Pterocarpus santalinus*, was synthesized from chalcone 177 via a rearrangement product (178) by treatment with PIFA in the presence of TFA by Miki and co-workers [135] (Scheme 44).

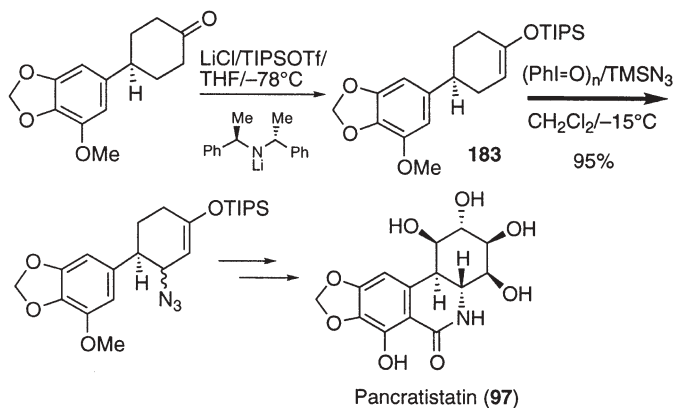
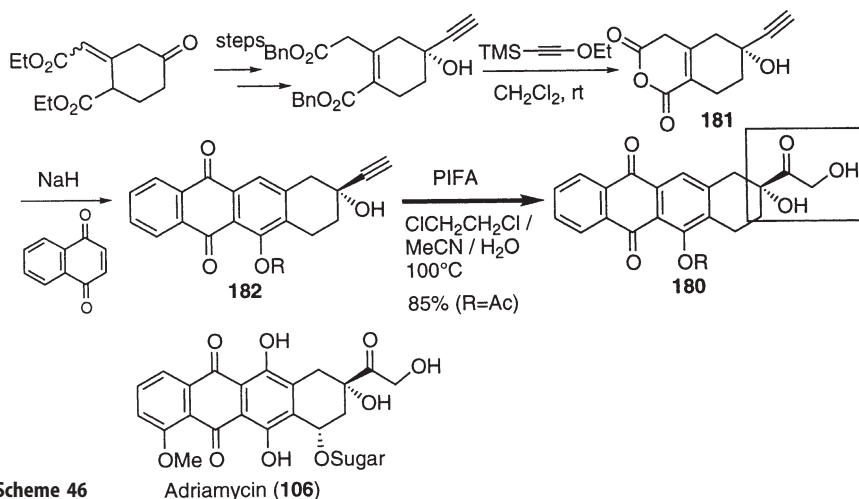
Total syntheses of chrysin (93) and luteolin (94), which are non-toxic potent inhibitors of reverse transcriptases from Rauscher murine leukemia (RLV) and the human immunodeficiency virus (HIV), were accomplished by Antus and co-workers via cyclodehydrogenation of the appropriately substituted 2'-hydroxychalcone (179) in the presence of PIDA/KOH in MeOH [136] (Scheme 45).



Scheme 45

An improved total synthesis of the aglycone (180) of 11-deoxyadriamycin-type antibiotics, which show stronger antineoplastic activity and/or less cardiotoxicity than daunomycin and adriamycin, was accomplished by applying the method to dihydroxyacetone (180) from ethynylcarbinol (182), prepared by strong base-induced cycloaddition of the substituted tetrahydrohomophthalic anhydride (181) [137], using PIFA [78] (Scheme 46).

Unique total synthesis of antitumor alkaloid, pancratistatin (97), which was isolated from the roots of the Hawaiian *Pancreatum littorale* Jacq., by β -azidation reaction of triisopropylsilylenol ether (183) with $\text{PhI}=\text{O} \cdot \text{TMSN}_3$ as the key reaction has been accomplished by Magnus and Sebhat [138] (Scheme 47).

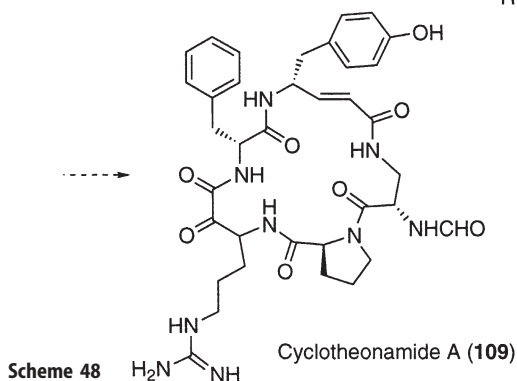
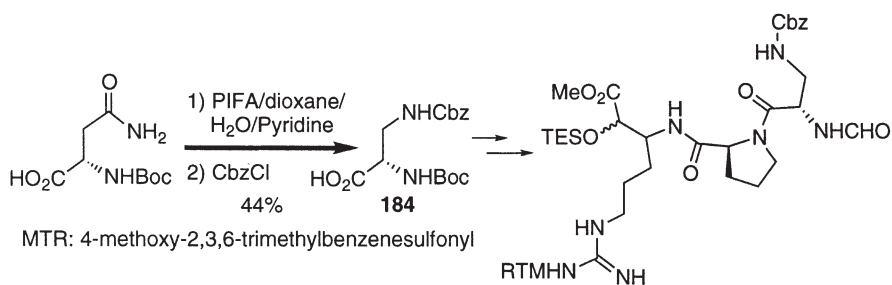


3.4

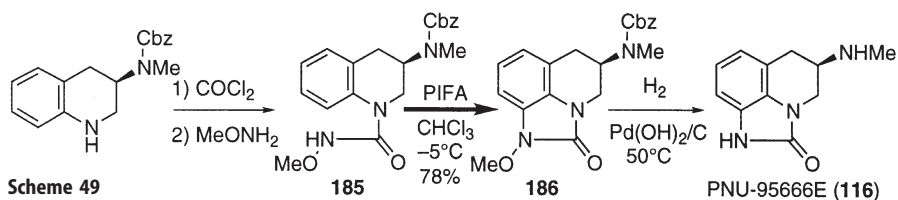
Total Synthesis via Other Hypervalent Iodine-Induced Reactions

The C(1) to N(14) segment of the potent thrombin inhibitor cyclotheonamide A (**109**) was prepared from L-arginine, L-proline, and L-asparagine. The arginine backbone was extended via a cyanohydrin, and the unusual diaminopropanoic acid residue (**184**) was obtained from hypervalent iodine oxidation of the asparagine side chain [139] (Scheme 48).

PNU-95666E (**116**) is a selective and high-affinity artificial agonist at the dopamine D₂ receptor subtype and is a potential agent for treating Parkinson's disease. The synthesis of the enantiomerically pure tricyclic structure (**186**) was achieved by PIFA-induced oxidative cyclization of **185**, starting from D-phenylalanine [140] (Scheme 49). This methodology was applied to a multikilo scale synthesis.



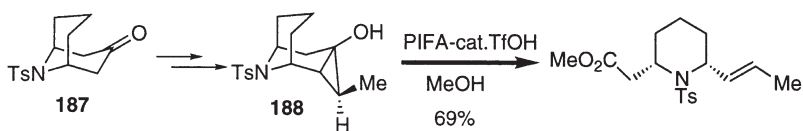
Scheme 48



Scheme 49

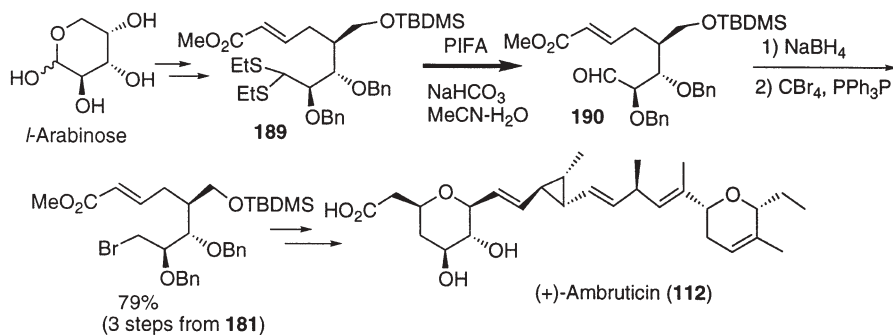
Asymmetric synthesis of the piperidine alkaloid (-)-pinidine (**119**) was accomplished by starting from norgranatanone (**187**) via asymmetric enolization, stereoselective cyclopropanation, and oxidative ring cleavage of the resulting cyclopropanol system (**188**) with PIFA as key steps [141] (Scheme 50).

Total synthesis of an orally active antifungal agent, ambruticin (**112**), which was isolated from fermentation extracts of *Myxobacteria* species *Polyangium*



Scheme 50

(-)-Pinidine (**119**)



Scheme 51

cellulosum var. *fulvum*, was accomplished by Lee and co-workers. Mild and high yielding transformation of dithioacetal moiety (**189**) into aldehyde (**190**) was carried out by the use of PIFA [142] (Scheme 51).

4 Conclusion

A variety of biologically active natural products have been synthesized by the use of hypervalent iodine-induced reactions. The development of fundamental reactions using hypervalent iodine(III or V) reagents, which are applicable to natural product syntheses, have become more and more important and useful in the practical fields of chemical, pharmaceutical, and agrochemical industries due to their versatility, mild reactivity, ready availability, high yields, and safety. Utilization of hypervalent iodine reagents, especially recyclable polymer-supported reagents, will have a growing demand in practical and industrial processes for natural product synthesis in the future.

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