Contents

Ruthenium in Organic Synthesis. Shun-Ichi Murahashi (Ed.)

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1
Introduction

Shun-Ichi Murahashi

Metal-catalyzed reactions have made a great contribution to the recent growth of organic synthesis, and a variety of synthetic methods have been reported using mainly Group 8 transition metal complexes in stoichiometric or catalytic amounts. In particular, useful transformations bearing high chemo- and stereoselectivities have been discovered in the field of palladium chemistry. Of all elements of the Periodic Table, ruthenium has the widest scope of oxidation states (from –2 valent in $Ru(CO)_4^{2-}$ to octavalent in RuO_4), and various coordination geometries in each electron configuration, which is in contrast to the narrow scope of oxidation states and simple square planar structure of palladium. For instance, in the principal lower oxidation states of 0, II, and III, ruthenium complexes normally prefer trigonal-bipyramidal and octahedral structures, respectively. Such a variety of ruthenium complexes has great potential for the exploitation of novel catalytic reactions and synthetic methods; however, as a consequence of the difficulties of matching the catalysts and substrates, ruthenium chemistry has lagged behind palladium chemistry by almost decade. Indeed, until the 1980s the reported useful synthetic methods using ruthenium catalysts are limited to a few reactions which include oxidations with RuO_4, hydrogenation reactions, and hydrogen transfer reactions. As the coordination chemistry of ruthenium complexes has progressed, specific characters of ruthenium have been made clear.

Ruthenium is relatively inexpensive in comparison with the other Group 8 transition metals such as rhodium, and a wide variety of ruthenium complexes have been prepared. $RuCl_3 \cdot nH_2O$ is frequently used as the starting material in the preparation of most of these ruthenium complexes [1]. The ruthenium complexes can be roughly divided into five groups according to their supporting ligands: carbonyl, tertiary phosphines, cyclopentadienyl, arena/dienes, and carbenes. These ligands have proven to serve effectively as the activating factors such as generation of coordinatively unsaturated species by the liberation of ligands, and stabilization of reactive intermediates. It has been understood that the precise control of coordination sites and redox sequences of the intermediacies are especially important in the case of ruthenium to design specific organic transformations. Moreover, ruthenium complexes also demonstrate a variety of useful characteristics, which include low redox potential, high electron transfer ability, high coordination ability to heteroatoms, Lewis acid acidity, unique reactivity of metallic species and intermediates such as

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oxo-metals, metallacycles, and metal carbene complexes. Therefore, a large number of novel, useful reactions have begun to be developed using catalytic amounts of ruthenium complexes [2,3]. The great influence of ruthenium chemistry on organic synthesis in recent years has now elevated the metal's importance to the same level as palladium, or even higher. Indeed, some ruthenium-catalyzed reactions have become industrial processes, with typical examples including a combination of the ruthenium-catalyzed asymmetric hydrogenation of 2-benzamidomethyl-3-oxobutanate via kinetic resolution [4] and the ruthenium-catalyzed oxidation of (1*R*′,3*S*)-3-[1′-(*tert*-butyldimethylsilyloxy)ethyl]azetidin-2-one. The latter process provides an important industrial scheme for the synthesis of 4-acetoxyazetidinone, which is a versatile and key intermediate in the synthesis of cabapenem antibiotics [5]. Grubb's ruthenium carbene complexes have also been used for industrial ring-opening metathesis polymerization (ROMP) [6]. Recent progress in the ruthenium carbene complex-catalyzed carbon-carbon double bond formation for organic synthesis is outstanding, and has become extremely important [7].

The 13 chapters of this book survey a range of fields of organic syntheses promoted by ruthenium catalysts, which involve hydrogenation, oxidation, various carbon–carbon bond formations, C–H activation, carbonylation, isomerization, bond-cleavage reaction, metathesis reaction, and miscellaneous nucleophilic and electrophilic reactions.

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2
Hydrogenation and Transfer Hydrogenation

M. Kitamura and R. Noyori

2.1
Introduction

Hydrogenation and transfer hydrogenation of unsaturated compounds are among the most important synthetic reactions in view not only of academic interest but also of industrial signifycance due to operational simplicity, environment-friendliness, and economics [1]. A hydrogen donor such as molecular hydrogen, alcohol, formic acid is catalytically activated by appropriate metals or metal complexes so that two hydrogen atoms are delivered to unsaturated bonds to give the corresponding reduction products. The discovery of RuO_2 [2] and $RuCl_2\{P(C_6H_5)_3\}_3$ [3] as selective hydrogenation catalysts provided an impetus to the development of Ru-based catalysts. Now, a number of Ru compounds are known to reduce, both in homogeneous and heterogeneous phases, a variety of substrates including unfunctionalized or functionalized olefins, ketones and aldehydes, other carbonyl compounds, imines, nitriles, and nitro compounds [4]. Ru complexes tend to be less reactive than the corresponding Rh, Ir, and Co complexes. Such mild reactivity sometimes realizes the chemoselective or regioselective reduction by appropriate combination with ligands as well as reaction conditions. Furthermore, the incorporation of well-shaped chiral ligands into Ru complexes led to the asymmetric version producing various optically active compounds that are useful and important in pharmaceutical and fine chemical industries [5]. Today, the significance of Ru chemistry in the field of asymmetric reduction is increasing exponentially. This chapter reviews Ru-catalyzed hydrogenation and transfer hydrogenation [4,5], focusing mainly on the asymmetric reactions, by classifying the substrates into olefins, ketones, imines, and others. Each section will be basically described in order of reactivity, chemo- and regioselectivity, and stereoselectivity.

The optically active organic ligands used in this chapter are broad ranging [6]. Some ligands **1–17** are listed in Figure 2.1, but for other abbreviated ligands the full names are described in the appropriate references.

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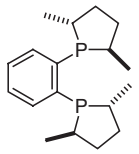
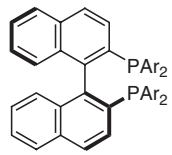
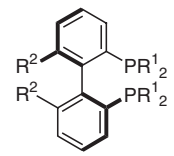


1, Me-DuPHOS



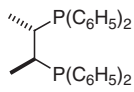
2, (*S*)-BINAP

BINAP: Ar = C_6H_5
TolBINAP: Ar = 4-$CH_3C_6H_4$
XylBINAP: Ar = 3,5-$(CH_3)_2C_6H_3$

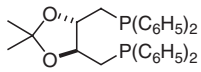


3, (*S*)-BIPHEMP

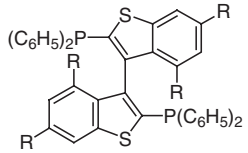
BIPHEMP: $R^1 = C_6H_5$; $R^2 = CH_3$
MeO-BIPHEP: $R^1 = C_6H_5$; $R^2 = CH_3O$
BICHEP: R^1 = *cyclo*-C_6H_{11}; $R^2 = CH_3$



4, (*S*,*S*)-CHIRAPHOS

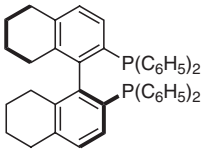


5, (*S*,*S*)-DIOP

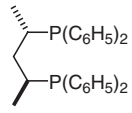


6, BITIANP

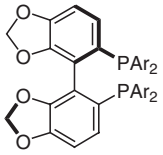
BITIANP: R = H
tetraMe-BITIANP: R = CH_3
(absolute configuration unknown)



7, (*S*)-H_8-BINAP

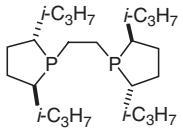


8, (*S*,*S*)-BDPP

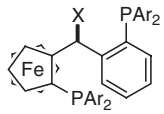


9, (*R*)-SEGPHOS

SEGPHOS: Ar = C_6H_5
DTBM-SEGPHOS:
Ar = 4-CH_3O-3,5-(*t*-$C_4H_9)_2C_6H_2$
(absolute configuration unknown)

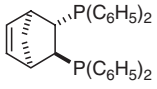


10, *i*-Pr-BPE

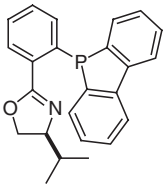


(*R*)-(*S*)-**11**

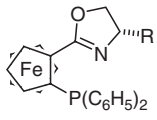
a: Ar = C_6H_5; X = $[(CH_3)_2CHCH_2]_2N$
b: Ar = 3,5-$(CH_3)_2C_6H_3$; X = $(CH_3)_2N$
c: Ar = C_6H_5; X = OCH_3



12, (*S*,*S*)-NORPHOS

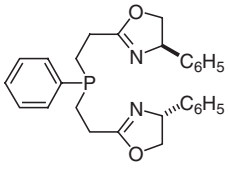


(*S*)-**13**

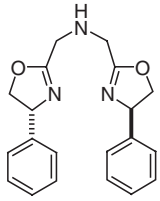


(*S*)-**14**

a: R = $(CH_3)_2CH$
b: R = C_6H_5



(*R*,*R*)-**15**



16, (*R*)-AMBOX

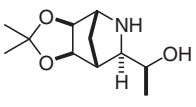


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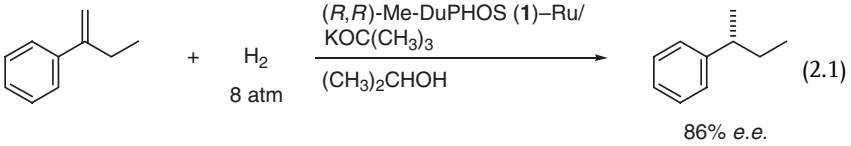
Figure 2.1 Ligands.

2.2 Hydrogenation

2.2.1 Unfunctionalized Olefins

$RuCl_2\{P(C_6H_5)_3\}_3$ is an active catalyst precursor for the homogeneous hydrogenation of 1-alkenes in the presence of methanol, ethanol, or triethylamine, which act as a base to generate $RuClH\{P(C_6H_5)_3\}_3$ [1e, 3, 4, 7]. The reactivity toward internal alkenes and cycloalkenes is lower than that for the terminal ones, attaining the selective saturation of terminal alkenes [8]. The catalyst activity is lost upon exposure to air or oxygen by formation of green-colored phosphine oxide complexes [7b,9]. The carboxylato analogues and the dihydride complex $RuH_2\{P(C_6H_5)_3\}_4$ show a similar tendency. Combination of noncomplexing strong acids with $RuH(OCOCH_3)\{P(C_6H_5)_3\}_3$, $Ru(OCOCH_3)_2\{P(C_6H_5)_3\}_2$, or $RuH_2\{P(C_6H_5)_3\}_4$ increases the activity, indicating the involvement of a cationic species [4a,10]. The anionic Ru cluster $[Ru_3(CO)_{10}(NCO)]^-$ acts as an efficient catalyst for the reduction of unfunctionalized alkenes under mild conditions [11]. $RuCl_2(CO)\{P(C_6H_5)_3\}_3$, $RuCl_2(CO)_2\{P(C_6H_5)_3\}_2$, $Ru(CO)_3\{P(C_6H_5)_3\}_2$, $Ru_3(CO)_{12}$, and $Ru(\eta^4\text{-cod})(\eta^6\text{-cot})$ have been studied in chemoselective hydrogenation of trans olefins in cyclic trienes or a number of dienes and in hydrogenation of 1-hexene. The rates decrease in the order of conjugated dienes > unconjugated dienes > terminal alkenes > internal alkenes [4a]. $Ru_4H_4(CO)_{12}$ hydrogenates 1-pentene under irradiation of near-UV to *n*-pentane [12]. The borohydride complex $RuH(\eta^1\text{-}BH_4)\{P(C_6H_5)_3\}_3$ is also active for 1-hexene hydrogenation, although the reactivity is less than the chloro complex [13]. A number of other Ru complexes including $RuCl(\eta^3\text{-}CH_2CHCH_2)(CO)_3$, $\{RuCl_2(\eta^6\text{-arene})\}_2$, $RuClH\{\eta^6\text{-}C_6(CH_3)_6\}\{P(C_6H_5)_3\}_3$, $Ru(\eta^4\text{-cod})(\eta^6\text{-cot})$, $\{Ru[\eta^4\text{-}(C_6H_5)_4C_4CO](CO)_2\}_2$, $\{Ru[\eta^4\text{-}(C_6H_5)_2(CH_3)_2C_4CO](CO)_2\}_2$ [4a], and $NiCpRu_3(\mu\text{-}H)_3(CO)_9$ [14] are catalyst precursors for alkene hydrogenation. Replacement of $P(C_6H_5)_3$ with $P(C_6H_5)_2(C_6H_4\text{-}3\text{-}SO_3Na)$ results in water-soluble Ru complexes which are effective for the hydrogenation of 1-hexene and styrene in two-phase system [15]. $Ru(OH)_2$ and Ru/C hydrogenate alkyl substituted cyclohexenes and the derivatives. Two hydrogen atoms are introduced onto the C=C bond in overall cis manner [16].

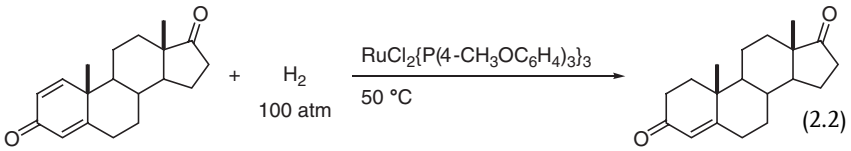
Control of the enantioselective hydrogenation of unfunctionalized olefins is not easy with chiral Ru complexes at the moment. Only a few successful examples have been reported. 2-Phenyl-1-butene, the simplest α-disubstituted prochiral olefin, is hydrogenated in 2-propanol by $RuCl_2\{(R,R)\text{-me-duphos}$ (**1**)$\}(dmf)_n/KOC(CH_3)_3$ system to give *R* product in 86% *e.e.* (Eq. 2.1) [17]. BINAP (**2**)-Ru complexes hydrogenate 1-methyleneindane in CH_2Cl_2 at 100 atm of H_2 to give 1-methylindane in 78% *e.e.* [18]. With the same Ru complex, α-alkylstyrenes are hydrogenated in only 10–30% optical yield. Though not a completely unfunctionalized olefin, 2,3-dihydrogeranylacetone is chemoselectively hydrogenated at the C=C bond in the presence of a Ru complex with MeO-BIPHEP (**3**) analogue containing four P-2-furyl groups to afford the saturated ketone in 91% *e.e.* [19].



(2.1)

2.2.2
Functionalized Olefins

The blue $Ru(OH)_2$ solution obtained by reduction of $RuCl_3$ in water catalyzes the hydrogenation of functionalized olefins such as maleic and fumaric acids [4a]. This is one of the first characterized examples of Ru-catalyzed homogeneous hydrogenation [20]. $RuCl_2(\eta^6\text{-}C_6H_6)/N(C_2H_5)_3$ combined system hydrogenates diethyl maleate, methyl sorbate in DMF in up to 49% yield [21]. With $RuCl_2\{P(C_6H_5)_3\}_3$, α,β-unsaturated ketones are reduced to saturated ketones [7a,b]. 3-Oxo-1,4-diene steroidal compounds undergoes selective saturation of C(1)-C(2) double bond (Eq. 2.2) [22].

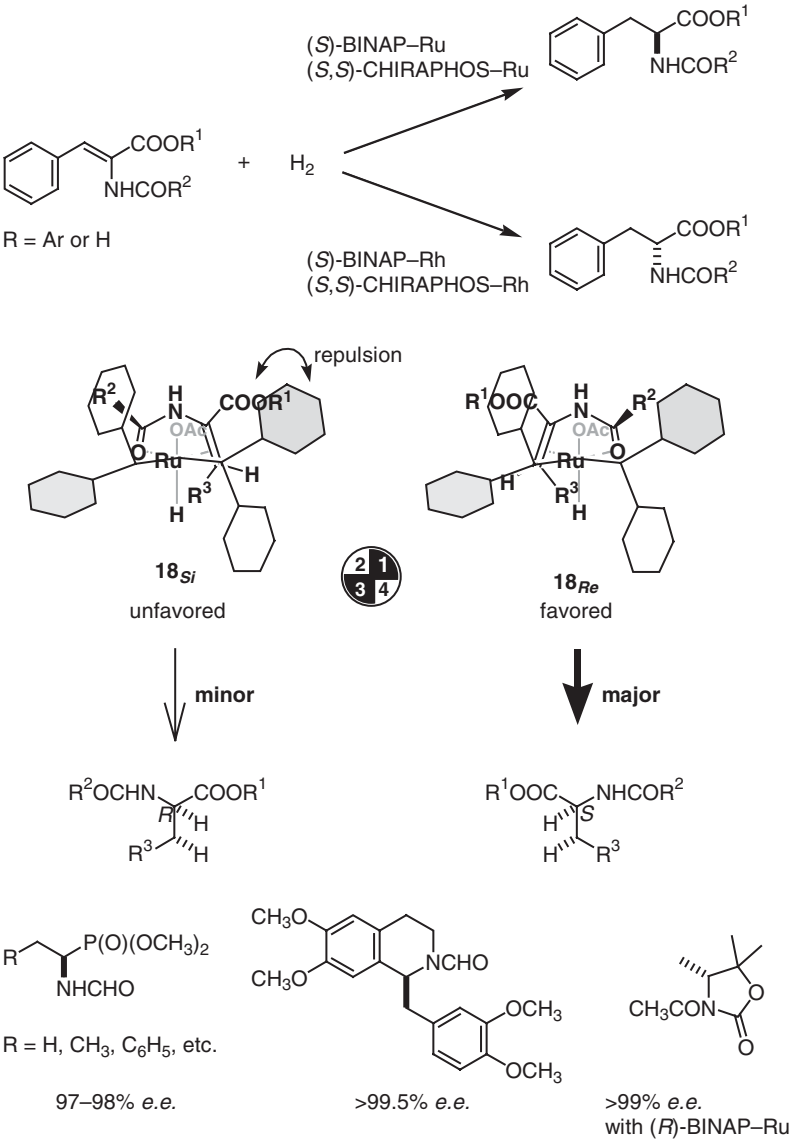


(2.2)

A considerable success has been realized for asymmetric hydrogenation of functionalized alkenes since the discovery of BINAP-Ru complexes in the mid-1980s [5]. The details are described in each of the following substrates, enamides, alkenyl esters and ethers, α,β- and β,γ-unsaturated carboxylic acids, α,β-unsaturated esters and ketones, and allylic and homoallylic alcohols.

The highly enantioselective hydrogenation of α-hydroxycarbonyl or α-alkoxycarbonyl substituted enamides is affected by a number of chiral Rh complexes, while the corresponding Ru complexes have not attracted much attention because the efficiency is usually lower than the Rh case. As shown in Scheme 2.1, (*S*)-BINAP (**2**)- and (*S*,*S*)-CHIRAPHOS (**4**)-Ru complexes, for example, catalyze the hydrogenation of (*Z*)-α-(acylamino)cinnamates to give the protected (*S*)-phenylalanine in 92 [23] and 97% *e.e.* [24], respectively, with the opposite enantioselectivity to that obtained with the corresponding Rh complexes. The mechanism of $Ru(OCOCH_3)_2\{(S)$-binap$\}$-catalyzed hydrogenation has been elucidated by kinetic experiments, rate law analysis, isotope labeling experiments, $^1H/^2H$ or $^{12}C/^{13}C$ isotope effect measurements, NMR studies, and X-ray crystallographic analysis [25]. The Ru diacetate complex is first converted to the Ru monohydride species [26], which interacts with enamide substrate. In the resulting catalyst-substrate (cat/sub) complex **18**, the hydride is intramolecularly transferred to α-carbon in exo manner to form five-membered metalacyclic intermediate. The Ru-C_β bond is cleaved mainly by hydrogen molecule to complete the catalytic cycle by liberation of the saturated *S* product.

The minor *R* enantiomer is also produced via the same, but diastereomorphic, reaction pathway as proved by a detailed analysis of isotope incorporation patterns of both enantiomeric products. The enantioselectivity is determined at the first irreversible hydrogenolysis step, but practically at the formation of the cat/sub complexes $\mathbf{18}_{Si}$ and $\mathbf{18}_{Re}$. $\mathbf{18}_{Si}$ is unfavored because of the existence of steric repulsion between alkoxycarbonyl group in the substrate and one of benzene rings on P atom of BINAP-Ru catalyst. In contrast to the Rh-catalyzed hydrogenation where the minor

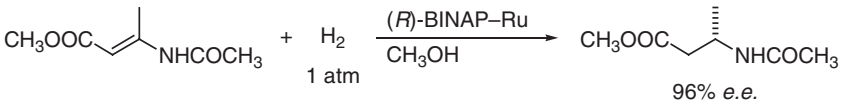


Scheme 2.1

cat/sub complex is far more reactive toward hydrogen molecule to produce the major product, the major product is generated from the major cat/sub complex $\mathbf{18}_{Re}$ in the Ru case. The difference in the mechanisms gives rise to an opposite sense of asymmetric induction between the Ru and Rh complexes with the same chiral phosphine ligand [23, 24, 27, 28].

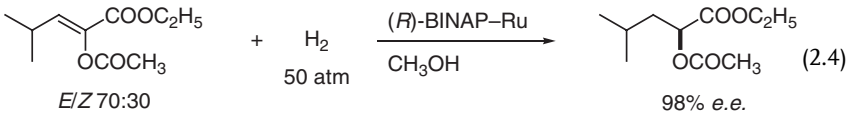
According to the above mechanism, replacement of alkoxycarbonyl group with a bulkier size of substituent is expected to increase the degree of enantioselectivity. 1-(Formamido)alkenylphosphonates and *N*-acyl-1-alkylidenetetrahydroisoquinolines, which have the sp^3-hybridized, tetrahedrally arranged phosphonic ester group and the constrained cyclic system, respectively, are hydrogenated at 1–4 atm of H_2 with almost perfect enantioselection by use of BINAP-Ru complexes (Scheme 2.1) [26a, 29]. BIPHEMP (**3**)-Ru-catalyzed hydrogenation is also effective for the asymmetric synthesis of 1-alkylated tetrahydroisoquinolines [30]. $Ru(OCOCH_3)_2$(binap)/CF_3COOH combined system can hydrogenate less reactive *N*-acyl-1-alkylidene-3,4,5,6,7,8-octahydroisoquinoline and *N*-acyl-1-alkylidene-4,5-dihydropyridine at 100 atm of H_2 with a 99:1 enantioselectivity [31]. α-Methyl-*N*-acyloxazolidinones with high *e.e.* are also obtained by the BINAP-Ru method using the methylene substrates [32].

BINAP-Ru-catalyzed hydrogenation of β-substituted (*E*)-β-(acylamino)acrylates gives β-amino acid derivatives with a high *e.e.* (Eq. 2.3) [33]. The *Z* double-bond isomers that have an intramolecular hydrogen bond between amide and ester groups are more reactive, but are hydrogenated with a poor enantioselectivity.



(2.3)

Alkenyl carboxylates and enamides are topologically analogous to each other. Both possess a carbonyl oxygen atom that is located three atoms from the olefin. The correct arrangement facilitates chelation to a metal center to realize high asymmetric induction. In fact, the BINAP-Ru complex is effective for hydrogenation of a 70:30 *E*/*Z* mixture of ethyl α-(acetoxy)-β-(isopropyl)acrylate in 98% optical yield (Eq. 2.4) [34]. The *E*/*Z* isomeric mixtures can be employed without detrimental effect on the selectivity.



(2.4)

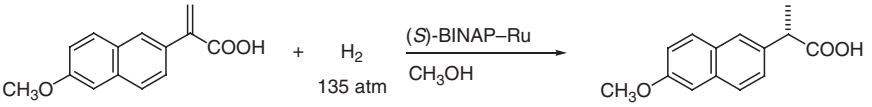
Without conjugation of the olefinic double bond to the alkoxycarbonyl function, high selectivity and high reactivity are attained in some cyclic systems. Even ester function can be replaced with ether. Thus, (*S*)-BINAP-Ru-catalyzed high-pressure hydrogenation of four- and five-membered cyclic lactones or carbonates having an exocyclic methylene bond gives (*R*)-β-methyl-β-propiolactone in 92% *e.e.*, (*R*)-γ-methyl-γ-butyrolactone in 95% *e.e.* [35], and the carbonate of (*R*)-3-methyl-2,3-buta-

nediol in 95% *e.e.* [36]. Considerable decrease in the enantioselectivity is observed with a six-membered substrate or an endo isomer of 4-methylene γ-lactone. Little success has been reported with acyclic α-alkyl-substituted acyl enolates. Alkenyl ethers such as 2-methylenetetrahydrofuran and the endo type substrate, 2-methyl-4,5-dihydrofuran can be converted by use of (*S*)-BINAP-Ru complexes in CH_2Cl_2 under 100 atm H_2 to (*R*)-2-methyltetrahydrofuran [35]. With an acyclic alkenyl ether, phenyl 1-phenylethenyl ether, the optical yield is moderate. The double chelation of olefin and oxygen atom to the Ru center may be important for high enantioface differentiation [35].

α-Phenylacrylic acid is hydrogenated in 40% optical yield by use of RuClH(diop (**5**))$_2$ [37]. The chiral Ru clusters such as $Ru_4H_4(CO)_8$(diop)$_2$ and $Ru_6(CO)_{18}$(diop)$_3$ hydrogenate a variety of α,β-unsaturated acids in up to 68% optical yield, although the rather severe conditions of 90–120 °C and 130 atm H_2 are required [38]. The efficiency has been significantly improved by use of BINAP-Ru complexes, which convert a wide range of substituted acrylic acids to the saturated products with high *e.e.* values [39]. The substitution pattern and reaction conditions – and particularly the hydrogen pressure – are the controlling factors for the efficiency. With geranic acid, only the double bond closest to the carboxyl group is saturated. In the Ru$(OCOCH_3)_2$-(binap)-catalyzed hydrogenation of tiglic acid, a monohydride mechanism is thought to operate, on the basis of deuterium-labeling experiments and kinetics [40, 41]. Other useful BINAP-Ru complexes and their derivatives include [RuX(η^6-arene)(binap)]Y (X = halogen, Y = halogen or BF_4) [42], Ru{η^3-$CH_2C(CH_3)CH_2$}$_2$(binap) [43], Ru(η^3-CH_2CHCH_2)(acac-F_6)(binap) [44], [$NH_2(C_2H_5)_2$][{RuCl(binap)}$_2$(μ-Cl)$_3$] [23a, 45, 46], Ru(acac)(mnaa)(binap)(CH_3OH) (MNAA = 2-(6′-methoxynaphth-2′-yl)acrylate anion) [47], [RuH(binap)$_2$]PF_6 [48], RuClH(binap)$_2$ [48], and Ru$(OCOCH_3)_2$(bitianp (**6**)) [49]. The hydrogenation of tiglic acid proceeds smoothly in supercritical carbon dioxide containing $CF_3CF_2CH_2OH$ and Ru$(OCOCH_3)_2${(*S*)-H_8-binap (**7**)} under 25–35 atm H_2 and 175 atm CO_2 at 50 °C to give (*S*)-2-methylbutanoic acid in over 99% yield and up to 89% *e.e.* [50].

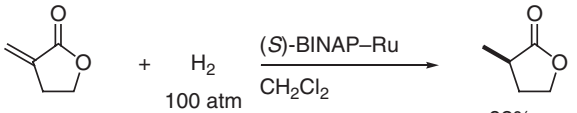
Enantioselective hydrogenation of α-aryl-substituted acrylic acids has been extensively studied because of the pharmaceutical importance of the saturated products. Anti-inflammatory (*S*)-naproxen of 97% *e.e.* is obtained by the high-pressure hydrogenation of 2-(6′-methoxy-2′-naphthyl)acrylic acid using Ru$(OCOCH_3)_2${(*S*)-binap} (Eq. 2.5) [39]. The hydrogenation rate is enhanced about 10-fold by use of Ru(acac)(mnaa){(*S*)-binap}(CH_3OH) [47]. H_8-BINAP-Ru complexes also show higher reactivity and selectivity [51], presenting a useful synthetic route to (*S*)-ibuprofen. The larger dihedral angle between the two aromatic rings of the tetralin moieties of H_8-BINAP than BINAP may be a reason for the high efficiency. The reactions have been refined by many technical methods using a continuously stirred tank reactor system [52], an ionic solvent [53], a catalyst-held film of ethylene glycol on a controlled porous hydrophilic support [54]. Asymmetric hydrogenation of 1-arylethenylphosphonic acid is also examined for the synthesis of phospho analogue of naproxen-type drugs, though the *e.e.* values are moderate with BINAP- or MeO-BIPHEP-Ru complexes [55]. Enantioselective hydrogenation of β,γ-unsaturated carboxylic acids is also possible with the aid of BINAP-Ru complexes [23, 39, 51, 56].

A Ru complex with a BINAP derivative covalently bonded to an aminomethylated polystyrene resin is also usable, though both the rate and enantioselectivity are decreased [57]. 2,3-Dimethylenesuccinic acid is hydrogenated by an (*R*)-BINAP-Ru complex at 3 atm of H_2 to give a 98.8:1.2 mixture of (2*S*,3*S*)-dimethylsuccinic acid with 96% *e.e.* and the *meso* isomer [58].



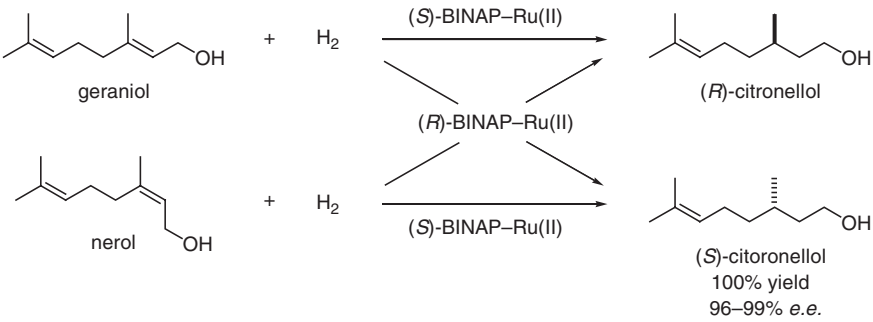
(2.5)

At the present stage, the successful results with α,β-unsaturated esters and ketones are limited to a small range of substrates. 2-Methylene- and -propylidene-γ-butyrolactones are converted to the corresponding γ-butyrolactones with greater than 92% *e.e.* (Eq. 2.6) [35]. The olefin geometry affects neither the sense nor degree of enantioselectivity. Itaconic anhydride as well as a 2-alkylidenecyclopentanone – though not an ester substrate – is similarly reduced by use of [RuCl(η^6-C_6H_6)(binap)]Cl, $[NH_2(C_2H_5)_2][\{RuCl(binap)\}_2(\mu\text{-}Cl)_3]$, and $Ru(OCOCH_3)_2$(binap) [35]. Endocyclic $\alpha\beta$-unsaturated ketones such as isophorone and 2-methyl-2-cyclohexenone are converted to the chiral ketones in up to 62% *e.e.* by use of RuClH(tbpc) [59] (TBPC = *trans*-1,2-bis(diphenylphosphinomethyl)cyclobutane), though the conversions are not satisfactory.



(2.6)

Prochiral allylic and homoallylic alcohols are hydrogenated in a highly enantioselective manner by use of BINAP-Ru complexes (Scheme 2.2) [60]. Geraniol or nerol is converted quantitatively to citronellol in 96–99% *e.e.* in methanol at an initial hydrogen pressure higher than 30 atm. The S/C approaches 50 000 in the reaction using the Ru bis(trifluoroacetate) catalyst. Only allylic alcohol double bond is hydro-



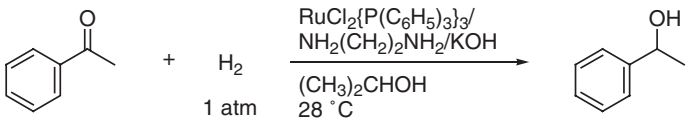
Scheme 2.2

genated, leaving the isolated C(6)-C(7) double bond intact. In this catalytic system, the BINAP-Ru complex isomerizes geraniol to γ-geraniol, which is hydrogenated to citronellol of opposite absolute stereochemistry [61]. Therefore, the low-pressure hydrogenation that decreases the hydrogenation rate relative to the isomerization rate results in a low enantioselectivity. Nerol is insensitive to changes in pressure. Hydrogenation of homogeraniol occurs regioselectively at the C(3)-C(4) double bond in a high optical yield with the same asymmetric orientation as observed with geraniol. Bishomogeraniol is not reduced. Similar dicarboxylate complexes having BIPHEMP and tetraMe-BITIANP (**6**, R = CH_3) ligands are also effective for asymmetric hydrogenation of allylic alcohols [30, 49]. The Ru hydrogenation method can be successfully applied to kinetic resolution of racemic acyclic and cyclic secondary alcohols [62]. Racemic 4-hydroxy-2-cyclopentenone is practically resolved on a multi-kilogram scale.

2.2.3
Unfunctionalized Ketones and Aldehydes

2.2.3.1 Reactivity

Homogeneous hydrogenation of aldehydes and ketones to the corresponding primary and secondary alcohols is catalyzed by a variety of mono- and polynuclear Ru complexes including $RuCl_2\{P(C_6H_5)_3\}_3$, $Ru(OCOCF_3)_2(CO)\{P(C_6H_5)_3\}_2$, $RuClH\{P(C_6H_5)_3\}_3$, $RuClH(CO)\{P(C_6H_5)_3\}_3$, $RuH_2\{P(C_6H_5)_3\}_4$, $RuH_2(CO)\{P(C_6H_5)_3\}_3$, $Ru_4H_4(CO)_{12}$, $Ru_4H_4(CO)_8\{P(n\text{-}C_4H_9)_4\}$, $RuCl_3/P(C_6H_4\text{-}3\text{-}SO_3Na)_3$, $Ru(CO)_3\{P(C_6H_5)_3\}_2$, $Ru(\eta^3\text{-}CH_2CHCH_2)Cl(CO)_3$ [4], although high hydrogen pressure and high temperature are usually required. Notably, an anionic complex, $K_2[Ru_2H_4\{P(C_6H_5)_2\}\{P(C_6H_5)_3\}_3]\cdot 2O(CH_2CH_2OCH_3)_2$, and 18-crown-6 combined system shows a much higher reactivity than other Ru complexes so far reported [63]. The high reactive species is proposed to be a neutral hydride complex, $RuH_4\{P(C_6H_5)_3\}_3$ [64]. The trinuclear Ru complex, $\{RuClH(dppb)\}_3$ (DPPB = 1,4-bis(diphenylphosphino)butane), catalyzes hydrogenation of acetophenone at atmospheric pressure [65]. Although $RuCl_2\{P(C_6H_5)_3\}_3$ is not very active for hydrogenation of ketones, the catalytic activity is remarkably enhanced when small amounts of $NH_2(CH_2)_2NH_2$ and KOH are added to this complex [66]. Acetophenone can be hydrogenated quantitatively at 1 atm of H_2 and at room temperature in 2-propanol (Eq. 2.7). At 50 atm of H_2, the turnover frequency (TOF) reaches up to 23 000 h^{-1}. The presence of both diamine and inorganic base as well as the use of 2-propanol as solvent is crucial to achieve the high catalytic activity. A preformed complex *trans*-$RuCl_2\{P(4\text{-}CH_3C_6H_4)_3\}_2\{NH_2(CH_2)_2NH_2\}$ and $KOC(CH_3)_3$ shows more than 20 times higher reactivity [67, 68]. Cyclohexanone is quantitatively reduced in the presence of the catalyst with an S/C of 100 000 at 60 °C under 10 atm H_2 to give cyclohexanol. The initial TOF is reached at 563 000 h^{-1}. The combination of RuClH(diphosphine)(1,2-diamine) and a strong base also shows high catalytic activity [69]. $RuH(\eta^1\text{-}BH_4)$(diphosphine)(1,2-diamine) [70] as well as the RuH_2 complexes [71] do not require an additional base to catalyze this transformation. A *trans*-$RuCl_2$(diphosphine)$(pyridine)_2$ promotes hydrogenation of acetophenone in the presence of $KOC(CH_3)_3$ [72].

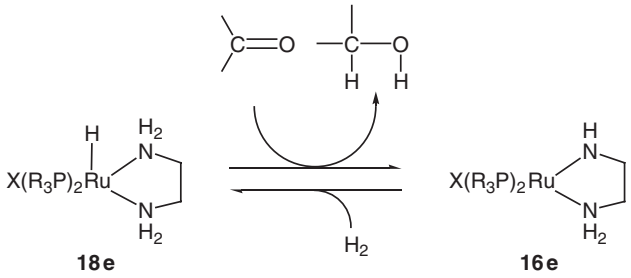


(2.7)

ketone:Ru:diamine:KOH = 500:1:1:2

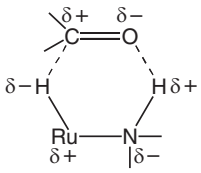
>99% yield
TOF = 880 h^{-1}

As shown in Scheme 2.3, the phosphine/1,2-diamine-Ru catalyst is supposed to hydrogenate a ketone through a pericyclic six-membered transition state **TS** [67], but not a conventional [$\sigma 2 + \pi 2$] transition state [9, 63, 73, 74]. $RuCl_2(PR_3)_2\{NH_2(CH_2)_2NH_2\}$ is first converted to $RuHX(PR_3)_2\{NH_2(CH_2)_2NH_2\}$ (X = H, OR, etc.) in the presence of an alkaline base and a hydride source. The coordinatively saturated 18-electron species interacts with a ketone to move **TS**. Because of the significant stabilization of **TS** by collaboration of the charge-alternating $H^{\delta-}$-$Ru^{\delta+}$-$N^{\delta-}$-$H^{\delta+}$ arrangement with the $C^{\delta+}$=$O^{\delta-}$ polarization, the 16-electron amido complex and a product alcohol are immediately generated. Heterolytic cleavage of the Ru-N bond by H_2 revives the 18-electron RuHX species. An alternative pathway via an N-protonated 16-electron cationic species and the η^2-H_2 complex is possible. The nonclassical metal-ligand difunctional mechanism has been supported both experimentally [75] and theoretically [76, 77] in the closely related transfer hydrogenation of ketones catalyzed by Ru complexes in 2-propanol [78] (see Scheme 2.6). Other transition state models have been also proposed [79, 80].



18e **16e**

X = H, OR, etc.

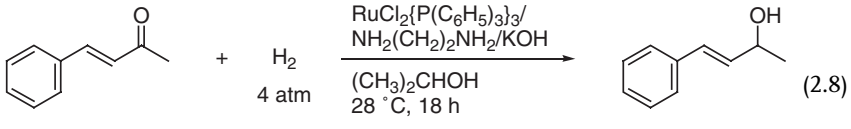


TS

Scheme 2.3

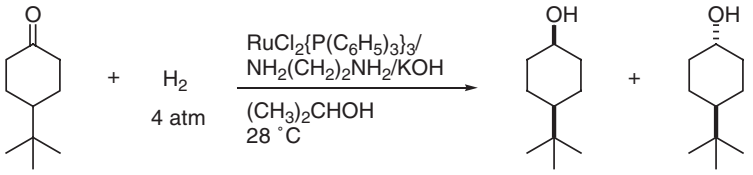
2.2.3.2 **Chemoselectivity**

Most existing heterogeneous and homogeneous catalysts using molecular hydrogen preferentially saturate carbon-carbon multiple bonds over carbonyl groups [1]. This selectivity is conceived to arise from the easier interaction of the metal center with an olefinic or acetylenic π bond than with a carbonyl linkage. $RuCl_2\{P(C_6H_5)_3\}_3$ hydrogenates 1-octene 250 times faster than heptanal in a competition experiment (S/C = 500, 6:1 2-propanol-toluene, 28 °C, 4 atm H_2). However, when 1 mol of $NH_2(CH_2)_2NH_2$ and 2 mol of KOH for the Ru complex are present in the above system, heptanal is hydrogenated 1500-fold faster than 1-octene [81]. Thus, as exemplified in Eq. 2.8, the phosphine/diamine-Ru catalyst system effects carbonyl-selective hydrogenation of a range of α,β-unsaturated aldehydes and ketones, leading to allylic alcohols. The chemoselectivity depends heavily on the pH of the reaction medium. Olefin-selective monohydride species exist at pH ≤3.3, while carbonyl-selective dihydride species exist exclusively at pH ≥7 [82]. Not only pH but also hydrogen pressure affects the equilibrium distribution of hydride complexes [83]. In the $RuClH\{P(C_6H_5)_3\}_3$-catalyzed hydrogenation of citral, the addition of 5 mol HCl increases both the reactivity and carbonyl-selectivity to give nerol predominantly [84]. Other Ru complexes such as $RuCl_2\{P(cyclo\text{-}C_6H_{11})_3\}_3$, $RuH(OCOCF_3)\{P(C_6H_5)_3\}_3$, $RuH_2\{P(C_6H_5)_3\}_4$, $RuCl_2(CO)_2\{P(C_6H_5)_3\}_2$, $RuCl_2(CO)_2\{P(cyclo\text{-}C_6H_{11})_3\}_2$, $Ru(OCOCF_3)_2(CO)\{P(C_6H_5)_3\}_2$, $RuCl_3(NO)\{P(C_6H_5)_3\}_2$ are also known to catalyze chemoselective hydrogenation of α,β-unsaturated aldehydes to the correspondding unsaturated primary alcohols [4]. A water-soluble $RuCl_3/P(C_6H_4\text{-}3\text{-}SO_3Na)_3$ in a toluene/buffer two-phase system is industrially used for production of allylic alcohols [85]. A Ru/C catalyst can be used for hydrogenation of ketones conjugated with trisubstituted olefinic bonds [86].



2.2.3.3 **Diastereoselectivity**

Diastereoselective hydrogenation of substituted cyclohexanones is attained by using the $RuCl_2\{P(C_6H_5)_3\}_3/NH_2(CH_2)_2NH_2/KOH$ catalyst system in 2-propanol [66, 81a]. 4-*tert*-Butylcyclohexanone is converted to *cis*-4-*tert*-butylcyclohexanol and the *trans* isomer in a 98:2 ratio (Eq. 2.9) [87]. Under similar conditions, 3-alkylcyclohexanone and 2-alkylcyclohexanone are reduced preferentially to the corresponding trans and cis alcohols, respectively. Bicyclo[2.2.1]heptan-2-one gives a 99:1 mixture of the endo and exo alcohols, while a conformationally flexible 1-phenylethyl ketones displays a high Cram selectivity. In all cases, the diastereoface tends to be kinetically discriminated from the less crowded direction. The tendency compares well with that of stoichiometric Selectride reduction [88].

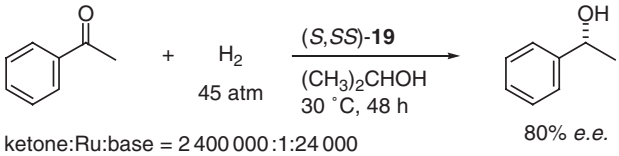


(2.9)

2.2.3.4 **Enantioselectivity**

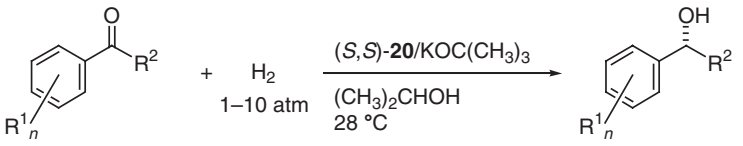
Replacement of the achiral phosphine of the homogeneous Ru complexes with a chiral ligand leads to the asymmetric version. In the early stage, only low optical yield was obtained in hydrogenation of ketones by use of $Ru_4H_4(CO)_8(diop)_2$ [89], but a breakthrough was provided by the invention of a remarkably highly reactive Ru catalyst system where phosphine-Ru(II) dichlorides, not very active catalyst precursor for ketone hydrogenation [4a, 5i], is further complexed with a 1,2-diamine ligand in 2-propanol containing a base [66, 68]. An excellent chemo-, diastereo-, and enantioselectivity are obtained with a wide variety of alkyl arylketones, fluoroketones, diarylketones, hetero-aromatic ketones, dialkylketones, unsaturated ketones, 1-deuterio aldehydes by using appropriate chiral diphosphine/diamine-Ru complexes.

Equation 2.10 illustrates the rapid, highly productive asymmetric hydrogenation of acetophenone using *trans*-$RuCl_2${(*S*)-tolbinap (**2**, Ar = 4-$CH_3C_6H_4$)}{(*S*,*S*)-dpen} ((*S*,*SS*)-**19**) or the *R*/*R*,*R* enantiomer [68] (DPEN = 1,2-diphenylethylenediamine). Only 2.2 mg of the Ru complex quantitatively produces 611 g of 1-phenylethanol under 45 atm H_2 at 30 °C. The turnover number (TON, moles product per mole catalyst) reaches 2 400 000 and the TOF may reach 228 000 h^{-1} [68, 90]. A wide variety of aromatic ketones can be hydrogenated quantitatively to give the corresponding secondary alcohols in high *e.e.* values (Scheme 2.4a) [66, 68, 81c]. Among many catalyst systems, *trans*-$RuCl_2${(*S*)-xylbinap (**2**, Ar = 3,5-$(CH_3)_2C_6H_3$)}{(*S*)-daipen} ((*S*,*S*)-**20**) or its *R*,*R* isomer (DAIPEN = 1,1-bis(4-methoxyphenyl)-3-methyl-1,2-butanediamine) exhibits the highest selectivity, up to 100:0, and generality in combination with $KOC(CH_3)_3$ [81c], while the reactivity slightly decreases. The reaction with an S/C ratio up to 100 000 is performed under 1–10 atm H_2. The influence of electronic and steric character of substituents on enantioselectivity is rather small. An increase in the bulk of the alkyl group and aromatic ring in the substrates tends to increase the extent of enantioselection. The sense of enantioselection is the same as that observed with simple acetophenone, unlike the case of chiral borane reduction [91].



(2.10)

a

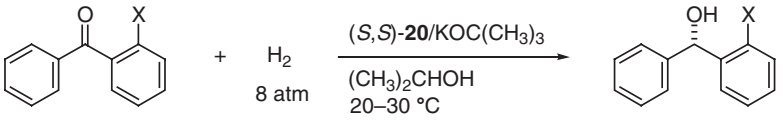


92–100% *e.e.*

R^1 = H, 3-CH_3, 2,4-$(CH_3)_2$, 2-F, 4-F, 4-Cl, 2-Br, 3-Br, 4-Br, 4-I, 2-CF_3, 3-CF_3, 4-CF_3, 2-CH_3O, 3-CH_3O, 4-CH_3O, 4-$(CH_3)_2CHOCO$, 4-NO_2, or 4-NH_2

R^2 = CH_3, C_2H_5, $(CH_3)_2CH$, *cyclo*-C_3H_5, or CF_3

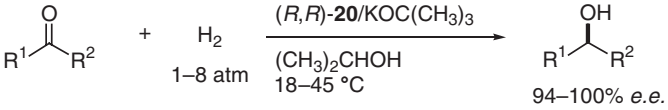
b



93–99% *e.e.*

X = CH_3, CH_3O, F, Cl, or Br

c

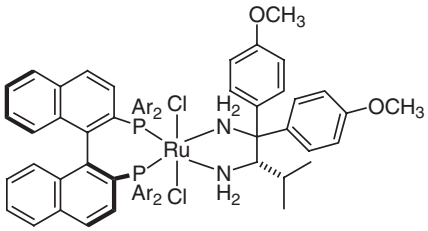


94–100% *e.e.*

R^1 = 2-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, or 4-pyridyl

R^2 = CH_3, *n*-C_5H_{11}, or $(CH_3)_2CH$

(*S*,*S*)-**20**:



Ar = 3,5-$(CH_3)_2C_6H_3$

trans-$RuCl_2${(*S*)-xylbinap}{(*S*)-daipen}

Scheme 2.4

Similar results to those of *trans*-Ru dihalogeno complexes with XylBINAP/DAIPEN or DPEN are obtained with other C_2 chiral diphosphine ligands including P-xylyl-substituted HexaPHEMP [92], P-Phos [93], and [2.2]Phanephos [94]. *trans*-RuClH{(*S*)-binap}{(*S*,*S*)-1,2-diaminocylcohexane} with $KOC(CH_3)_3$ also shows high catalytic activity [69]. The degree of enantioselectivity with $RuCl_2${(*S*,*S*)-bdpp (**8**)}{(*S*,*S*)-dpen}/$KOC(CH_3)_3$ [72] or in situ-generated $RuBr_2${(*R*,*R*)-bipnor}/(*S*,*S*)-

DPEN/KOH [95] catalyst system is decreased by 10–15% in the hydrogenation of acetophenone or 2′-acetonaphthone. Pivalophenone, a sterically demanding aromatic ketone, is hydrogenated by RuCp*Cl(η^4-cod)/(*S*)-(1-ethyl-2-pyrrolidinyl)-methylamine/KOH catalyst to afford the *R* alcohol in 81% *e.e.* [96]. $[NH_2(C_2H_5)_2]$-[{RuCl[(S)-tolbinap]}$_2$(μ-Cl)$_3$] hydrogenates 2′-halo-substituted acetophenones under 85 atm H_2 in up to >99% optical yield [97]. A stable six-membered intermediate where the Ru metal is chelated by carbonyl oxygen and halogen at the 2′ position is supposed [5c].

Highly base-sensitive ketonic substrates are not usable with the ternary catalyst systems, because a strong base is required to activate $RuCl_2$(diphosphine)(diamine) complexes. The disadvantage is overcome by use of *trans*-RuH(η^1-BH_4){(*S*)-xyl-binap}{(*S*,*S*)-dpen}, which generates an active species without an additional base [70]. For example, (*R*)-glycidyl 3-acetylphenyl ether is quantitatively hydrogenated at 8 atm of H_2 in the presence of the *S*/*S*,*S* catalyst to give the *R*,*R* product in a 99.5:0.5 diastereomer ratio, leaving the base-labile epoxy ring intact. In hydrogenation of ethyl 4-acetylbenzoate, no transesterification occurs at all.

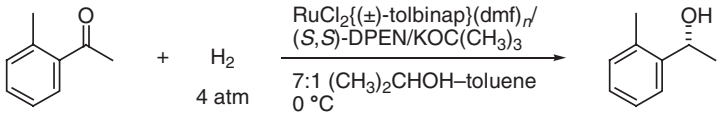
The homogeneous chiral phosphine/DPEN-Ru catalyst can be immobilized by use of polymer-bound phosphines such as polystyrene-anchored BINAP (APB-BINAP) [57, 98], Poly-Nap [99], and poly(BINOL-BINAP) [100], poly(BINAP) [101]. These complexes hydrogenate 1′-acetonaphthone and acetophenone with S/C of 1000–10 000 under 8–40 atm H_2 to give the corresponding secondary alcohols in 84–98% *e.e.* The recovered complexes are repeatedly used without significant loss of reactivity and enantioselectivity. Immobilization allows the easy separation of catalyst from reaction mixture, recovery, and reuse. These advantages attract much attention in combinatorial synthesis.

Enantioface selection of prochiral diaryl ketones is generally difficult because electronically and sterically similar two aryl groups are attached to the carbonyl group. Overreduction of diaryl methanols to diaryl methanes is also another problem, but these problems are overcome by use of the Ru ternary catalyst system (Scheme 2.4b). Thus, by using (*S*,*S*)-**20**/KOC$(CH_3)_3$, 2-substituted benzophenones are quantitatively reduced to the diaryl methanols without any detectable diaryl methanes [102]. With 3- or 4-substituted benzophenones, enantioselectivities are moderate. Benzoylferrocene is hydrogenated in the presence of *trans*-$RuCl_2${(*S*)-tol-binap}{(*S*)-daipen} and a base to afford the *S* alcohol in 95% *e.e.*

A variety of ketones possessing an electron-rich or -deficient heteroaromatic substituent are also good substrates for (*R*,*R*)-**20**/KOC$(CH_3)_3$ combined system (Scheme 2.4c) [103]. Hydrogenation of isopropyl 2-pyridyl ketone, 3- and 4-acetylpyridine proceeds smoothly, but the reaction is not completed with 2-(1-methyl)pyrrolyl ketone. The inhibition is avoided by protection of pyrrole nitrogen with a *p*-toluenesulfonyl group. Hydrogenation of 2-acetylthiazol and 2-acetylpyridine are also inhibited under the usual conditions, most likely due to the high binding capability of the products to the Ru metal, though the problem can be solved by the addition of B$[OCH(CH_3)_2]_3$ (ketone:Ru:borate = 2000:1:20) [103]. Double hydrogenation of 2,6-diacetylpyridine with the *R*,*R* catalyst gives *S*,*S* diol as a sole product. The (*R*)-Xylyl-Phanephos/(*S*,*S*)-DPEN-Ru(II) catalyst is also an excellent catalyst for

the hydrogenation of 3-acetylpyridine [94]. An in situ-prepared $RuCl_2$\{(*R*,*R*)-bicp\}(tmeda)/(*R*,*R*)-DPEN/KOH catalyst hydrogenates 2-acetylthiophene to afford the *S* alcohol in 93% *e.e.* [104]. $Ru(OCOCH_3)_2$\{(*R*)-binap\} can hydrogenate 1-deuterio benzaldehyde at about 10 atm of H_2 in the presence of 5 mol HCl, giving the *S* alcohol in 65% *e.e.* [105]. The introduction of a bromine atom at the 2′ position increases both the reactivity and enantioselectivity, probably because of a directing effect of the heteroatom interacting with the Ru metal. In contrast, *trans*-$RuCl_2$\{(*S*)-tolbinap\}\{(*S*)-daipen\}/$KOC(CH_3)_3$ hydrogenates 1-deuterio benzaldehyde with an opposite enantioselectivity in 46% optical yield [67a]. Introduction of methyl group at 2′ position doubles the *e.e.* value.

Enantiomer-selective interaction of a racemic metal complex with an appropriate nonracemic auxiliary sometimes activates the complex as a chiral catalyst. This methodology is viable for practical asymmetric catalysis whenever optically pure ligands are not easily obtained [106]. A racemic $RuCl_2$(tolbinap)$(dmf)_n$ is a poor catalyst for the hydrogenation of 2′-methylacetophenone. However, the aromatic ketone is transformed to the *R* alcohol in 90% *e.e.* when an equimolar amount of (*S*,*S*)-DPEN is added to the racemic complex (Eq. 2.11) [107]. Separate experiments show that the hydrogenation of the substrate with an enantiomerically pure (*S*)-TolBINAP/(*S*,*S*)-DPEN-Ru(II) complex gives the *R* alcohol in 97.5% *e.e.* and that reaction with the *S*/*R*,*R* catalyst affords the *R* product in only 8% *e.e.* [81b], indicating that the matched *S*/*S*,*S* cycle turns over 13-fold faster than the mismatched *R*/*S*,*S* cycle. In contrast to BINAP, DM-BIPHEP (**3**, R^1 = 3,5-$(CH_3)_2C_6H_3$; R^2 = H) is conformationally flexible and exists as an *R* and *S* equilibrium mixture [108]. Mixing of the $RuCl_2$(dm-biphep)$(dmf)_n$ complex with (*S*,*S*)-DPEN produces a 3:1 diastereomeric mixture of (*S*)-DM-BIPHEP/(*S*,*S*)-DPEN-Ru(II) and the *R*/*S*,*S* complex. As the major *S*/*S*,*S* species is more reactive and enantioselective, 1′-acetonaphthone is quantitatively reduced to the *R* alcohol in 92% *e.e.*, even with the mixed Ru complex.



S/C = 500

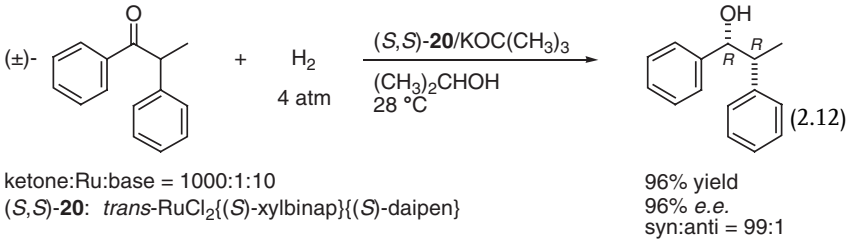
100% yield
90% *e.e.*

(2.11)

A chiral aromatic diamine, (*R*)-DM-DABN ((*R*)-3,3′-dimethyl-1,1′-binaphthyl-2,2′-diamine), selectively coordinates to $RuCl_2$\{(*R*)-xylbinap\}$(dmf)_n$, producing a catalytically inactive $RuCl_2$\{(*R*)-xylbinap\}\{(*R*)-dm-dabn\} complex [109]. The enantiomer-selective deactivation cooperates well with the asymmetric activation, giving a highly enantioselective catalyst system using a racemic XylBINAP-$RuCl_2$ complex. Thus, a catalyst system consisting of (±)-XylBINAP-$RuCl_2$ complex, (*R*)-DM-DABN, (*S*,*S*)-DPEN, and KOH in a 1:0.55:0.5:2 ratio hydrogenates 1′-acetonaphthone to the *R* alcohol in 96% *e.e.*

The hydrogenation of certain configurationally labile chiral ketones normally produces four possible stereoisomers of alcohols. However, owing to the configurational lability, in principle, a single stereoisomer with two contiguous stereogenic

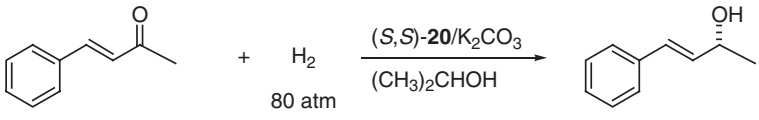
centers is obtainable in 100% yield under suitable conditions [110]. The rapid equilibration between the *R* and *S* enantiomers provides an opportunity for a chiral catalyst to reduce preferentially one of these. The combined effects of the catalyst-derived intermolecular chirality transfer and the substrate-controlled intramolecular asymmetric induction [111] determine kinetically the absolute configuration of the two stereogenic centers of the product. This dynamic kinetic resolution methodology can be applied to hydrogenation of racemic 2-phenylpropiophenone, which is enantiomerically labile under basic conditions. Thus, as shown in Eq. 2.12, $RuCl_2$\{(*S*)-xylbinap\}\{(*S*)-daipen\} ((*S*,*S*)-**20**)/$KOC(CH_3)_3$ system hydrogenates 2-phenylpropiophenone predominantly to the 1*R*,2*R* alcohol among four possible stereoisomers [67a]. $KOC(CH_3)_3$, a strong base, acts not only as a promoter of interconversion between the two enantiomeric ketones but also as a catalyst activator.



In the hydrogenation of both unconjugated and conjugated enones using most existing heterogeneous and homogeneous catalysts, the C=C bond is preferentially saturated over the C=O [1] because of the easier interaction of the metal center with an olefinic bond than with a carbonyl moiety (see Section 2.2.3.2). The use of *trans*-$RuCl_2$(binap)(1,2-diamine) and an inorganic base in 2-propanol has solved this problem, to realize carbonyl-selective and enantioselective hydrogenation [5i, 67]. For example, (*S*,*S*)-**20**/$KOC(CH_3)_3$ hydrogenates 1-(2-furyl)-4-penten-1-one, an unconjugated enone, to give quantitatively the *R* unsaturated alcohol in 97% *e.e.* [103], leaving the olefinic bond intact.

Replacement of $KOC(CH_3)_3$ or KOH with K_2CO_3, a weak base cocatalyst, expands the scope of the substrate even to simple α,β-unsaturated ketones with the conformational flexibility as well as the high sensitivity to basic conditions [68, 81, 103]. Conjugated enones having various substitution patterns are quantitatively transformed without any formation of undesired polymeric compounds. Thus, as shown in Eq. 2.13, benzalacetone is hydrogenated using *trans*-$RuCl_2$\{(*S*)-xylbinap\}\{(*S*)-daipen\} ((*S*,*S*)-**20**)/K_2CO_3 catalyst with an S/C of 100 000 under 80 atm H_2 to afford the *R* allyl alcohol quantitatively in 97% *e.e.* Thienyl ketone may also be used in this reaction. For highly base-sensitive 3-nonene-2-one, the (*S*)-XylBINAP/(*S*,*S*)-DAIPEN-Ru and $KOC(CH_3)_3$ ternary system requires a high dilution condition (0.1 *M*) to obtain high yields, but the concentration can be increased to 2.0 *M* by using *trans*-$RuH(\eta^1\text{-}BH_4)$\{(*S*)-xylbinap\}\{(*S*,*S*)-dpen\} under base-free conditions, thereby giving the *R* alcohol in 99% *e.e.* and in 95% yield. More substituted, less base-sensitive substrates are hydrogenated more rapidly and conveniently by using $KOC(CH_3)_3$ or KOH. Hydrogenation of 1-acetylcycloalkenes resulted in almost perfect enantio-

selectivity. β-Ionone, a dienone, is also converted to β-ionol in a highly chemoselective and enantioselective manner with an (*R*)-BINAP/(*R*,*R*)-1,2-dicyclohexylethylenediamine-Ru(II) and KOH system. The (*R*)-Xylyl-PhanePhos/(*S*,*S*)-DPEN-Ru catalyst also provides high enantioselectivity in the hydrogenation of benzalacetone [94].

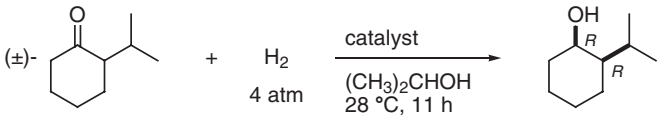


(2.13)

Carbonyl-selective asymmetric hydrogenation of 2-cyclohexenone – a simple cyclic conjugated enone – is still difficult, but some substituted 2-cyclohexenones such as 2,4,4-trimethyl-2-cyclohexenone, (*R*)-carvone, a chiral dienone, and (*R*)-pulegone, an s-*cis* chiral enone have been used successfully [66, 68, 81b, 107].

Highly enantioselective hydrogenation of simple dialkyl ketones is limited to a specific case. Cyclopropyl methyl ketone or methyl 1-methylcyclopropyl ketone, for example, can be hydrogenated in 95–98% optical yield in the presence of *trans*-S)-xylbinap}{(*S*)-daipen}",4>$RuCl_2${(*S*)-xylbinap}{(*S*)-daipen}/$KOC(CH_3)_3$ [67a, 81c]. The degree of enantioselectivity is decreased with cyclohexyl methylketone. Methyl is sterically different from other primary, secondary, tertiary alkyls, and cyclopropyl carbon has higher s character than the usual sp^3 carbon, which results in a strong electron-donative character [112].

Chiral cyclic dialkyl ketones having a configurationally labile α stereogenic center can be hydrogenated through dynamic kinetic resolution, producing a single hydroxy compound among four possible stereoisomers. For example, when racemic 2-isopropylcyclohexanone is hydrogennated with a $RuCl_2${(*S*)-binap}$(dmf)_n$/(*R*,*R*)-DPEN/KOH combined system, (1*R*,2*R*)-2-isopropylcyclohexan-1-ol is predominantly obtained (Eq. 2.14) [67a, 87]. The hydrogenation of the *R* ketone is 36-fold faster than that of the *S* enantiomer, and stereochemical inversion at the α position occurs 47-fold faster than hydrogenation of the less-reactive *S* substrate. Although not a simple aliphatic ketone, racemic 2-methoxycyclohexanone is hydrogenated with the (*S*)-XylBINAP/(*S*,*S*)-DPEN-Ru and KOH combined catalyst to give (1*R*,2*S*)-2-methoxycyclohexanol in 99% *e.e.* (*cis*:*trans* = 99.5:0.5) [113]. Similarly, racemic 2-(*tert*-butoxycarbonylamino)cyclohexanone is converted with (*S*)-XylBINAP/(*R*)-DAIPEN-Ru catalyst under basic conditions to the 1*S*,2*R* alcohol in 82% *e.e.* (*cis*:*trans* = 99:1) [81c, 114]. The $RuCl_2$ complex with a strong base catalyst is not suitable for the static kinetic resolution of racemic α-substituted ketones, but the use of *trans*-RuH(η^1-BH_4){(*S*)-xylbinap}{(*R*,*R*)-dpen} makes this possible [70]. With this complex, and without an additional base, racemic 2-isopropylcyclohexanone is hydrogenated to give, after 53% conversion, the 1*R*,2*R* alcohol in 85% *e.e.* (*cis*:*trans* = 100:0) together with unreacted *S* ketone in 91% *e.e.*



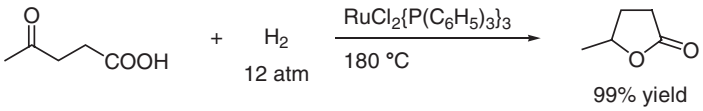
(2.14)

ketone:Ru:diamine:KOH = 500:1:1:20
catalyst: $RuCl_2\{(S)\text{-binap}\}(dmf)_n/(R,R)\text{-DPEN/KOH}$

93% *e.e.*
cis:trans = 99.8:0.2

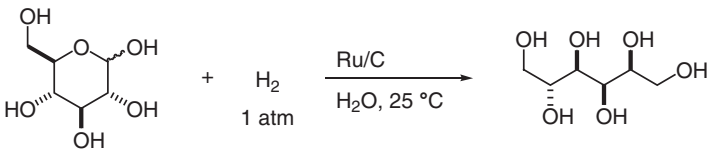
2.2.4
Functionalized Ketones

The reactivity of achiral Ru compounds for the hydrogenation of functionalized ketones has not been extensively studied. $RuCl_2\{P(C_6H_5)_3\}_3$ reduces γ-keto carboxylic acid at 180 °C to the corresponding γ-lactone (Eq. 2.15) [115]. Heterogeneous Ru/C catalyzes the atmospheric pressure hydrogenation of furfural in water at 25 °C [86]. Under such mild conditions, glucose is industrially converted to sorbitol (Eq. 2.16) [116]. At elevated temperature and pressure, tetramethyl-1,3-cyclobutanedione can be converted to a 98:2 diastereomer mixture of the diol (Eq. 2.17) [117].

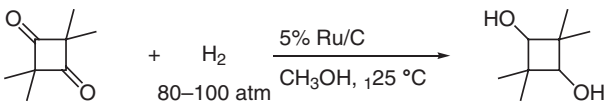


99% yield

(2.15)



(2.16)



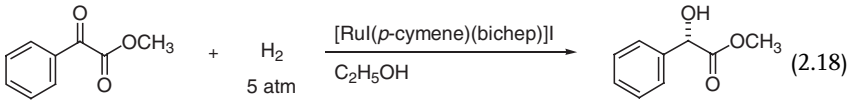
98:2

(2.17)

In contrast, many chiral phosphine-metal complexes have been investigated in the enantioselective hydrogenation of functionalized ketones because of the synthetic significance of the corresponding alcoholic products [5]. A high catalytic activity and an excellent level of enantioselectivity have been achieved by means of chiral phosphine-Ru complexes, as shown below. The presence of a functional group close to the carbonyl moiety efficiently accelerates the reaction and also controls the stereochemical outcome. The heteroatom-metal interaction is supposed to effectively stabilize one of diastereomeric transition states and/or key intermediates in

the hydrogenation. Hydrogenation of α-, β-, or γ-keto esters with Ru complexes having C_2-chiral diphosphines can be achieved with a high enantioselectivity and a high reaction rate [5i, 118–122].

Methyl 4′-methylbenzoylformate is hydrogenated to the hydroxy ester in 93% *e.e.* with a cationic BINAP-Ru complex in the presence of aqueous HBF_4 [120], whereas a neutral BINAP-Ru complex gives lower optical yield [119]. A cationic Ru complex of BICHEP (**3**, R^1 = *cyclo*-C_6H_{11}; R^2 = CH_3), an electron-rich biaryl ligand, shows >99% *e.e.* in hydrogenation of methyl benzoylformate and its benzylamide derivative (Eq. 2.18) [123]. A MeO-BIPHEP-Ru complex shows a higher reactivity in the presence of HBr [124]. A tetraMe-BITIANP (**6**, R = CH_3) ligand having heteroaromatic rings is also effective in the hydrogenation of methyl pyruvate [49]. Aliphatic α-keto esters are hydrogenated by use of a halogen-bridged Ru complex consisting of $\{RuCl_2[(R)\text{-segphos}\ (\mathbf{9})]\}_2$ and $(C_2H_5)_2NH_2Cl$ with an S/C of >1000 to give the *R* alcohols in >95% *e.e.* [125].

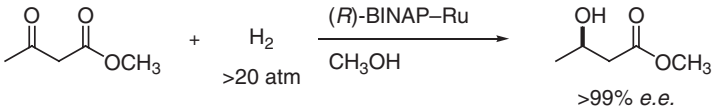


(2.18)

>99% *e.e.*

A wide variety of β-keto esters are hydrogenated with the BINAP-Ru complexes, RuX_2(binap) (X = Cl, Br, or I; empirical formula with a polymeric form) or $RuCl_2$(binap)$(dmf)_n$ (oligomeric form) [126], to give chiral β-hydroxy esters in a near-perfect optical yield [5c, 67a,b, 118–122]. *R* complexes convert methyl 3-oxobutanoate to (*R*)-methyl 3-hydroxybutanoate quantitatively in >99% *e.e.* at >20 atm of H_2 with an S/C of up to 10 000 in an alcoholic solvent (Eq. 2.19) [118]. The hydrogen pressure can be decreased to 1–5 atm when strongly acidic and/or high-temperature conditions are adopted [126b, 127a,b]. The method is applicable to α,α-difluoro-β-keto esters [128], β-keto amides and thioesters without significant loss of enantioselectivity [119, 128a, 129]. The same enantiofaces are selected. Because of the high utility of the BINAP-Ru catalysis, many preparation methods for the complexes have been reported [23a, 30, 45, 46, 72, 120, 124, 127]. The Ru complexes with other C_2 symmetric biaryl diphosphines such as BIMOP [130], BIPHEMP (**3**, R^1 = C_6H_5; R^2 = CH_3) [124], MeO-BIPHEP (**3**, R^1 = C_6H_5; R^2 = CH_3O) [131], C4TunaPhos [132], BIFAP [133], BisbenzodioxanPhos [134], P-Phos [93, 135], tetraMe-BITIANP (**6**, R = CH_3) [49], and steroid-modified BINAP [136] also exhibit excellent enantioselection in the hydrogenation of β-keto esters. A Ru complex with electron-rich *i*-Pr-BPE (**10**) effectively promotes the hydrogenation under low pressure [127a,b, 137]. $Ru(OCOCF_3)_2$([2.2]-phanephos) [94] shows high activity in the presence of $(n\text{-}C_4H_9)_4NI$ at low temperature and low hydrogen pressure, without strong acids [138]. A Ru complex with chiral 1,5-diphosphanylferrocene **11a** [139] is also excellent for asymmetric hydrogenation of β-keto esters. Examples of highly enantioselective hydrogenation of benzoylacetic acid derivatives are limited in number. An (*R*)-SEGPHOS (**9**)-Ru complex hydrogenates the ethyl ester with an S/C of 10 000 under

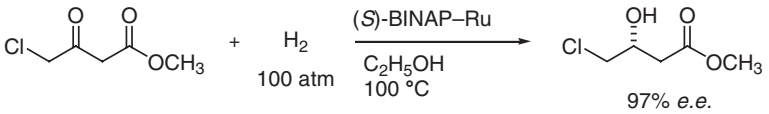
30 atm H_2 to give the *S* alcohol in 97.6% *e.e.* [125]. MeO-BIPHEP [131], Tol-P-Phos [93, 140], and a chiral ferrocenyl diphosphine **11c** [141] are also excellent ligands for this purpose. The hydrogenation of *N*-methylbenzoylacetamide in the presence of an (*R*)-BINAP-Ru catalyst affords the *S* alcohol in >99.9% *e.e.*, although the yield is 50% [128a]. β-Keto esters are effectively hydrogenated by some recyclable catalysts including oligomeric (*R*)-Poly-NAP-Ru [142], a Ru complex with polyethyleneglycol-bound BINAP, PEG-Am-BINAP [143], a water-soluble 6,6′-diaminomethyl-BINAP-Ru [144], and immobilized BINAP-Ru in a polydimethylsiloxane membrane matrix [145] or on a polystyrene resin [57].



(2.19)

Excellent enantioselectivity is also attained by the BINAP-Ru method in hydrogenation of γ-keto esters and *o*-acylbenzoic esters, giving γ-lactones and *o*-phthalides, respectively [146, 147].

In the asymmetric hydrogenation of bifunctionalized ketones, competitive interaction of the functionalities to the Ru center of the catalyst at the enantioface-differentiating stage significantly affects the degree and sense of enantioselection, depending on the steric and electronic nature of the coordinative groups. (*S*)-BINAP-Ru-catalyzed hydrogenation of methyl 5-benzyloxy-3-oxopentanoate affords the *S* alcohol in 99% *e.e.* with the same enantioselectivity as that with simple β-keto esters [119]. On the other hand, 4-benzyloxy- and 4-chloro-3-oxobutanoate are hydrogenated with the same *S* catalyst at room temperature to give the *R* alcohols with moderate *e.e.* values. When the reaction is conducted at 100 °C, the *e.e.* values are dramatically increased to up to 97% (Eq. 2.20) [5c, 148]. The introduction of a bulky triisopropylsilyloxy group at the C4 position achieves a high enantioselectivity, even at room temperature [119]. 4-Trimethylammonium chloride functionality does not interfere with the enantioselection [124]. The Ru complexes modified by other C_2-symmetric chiral diphosphines such as MeO-BIPHEP (**3**, $R^1 = C_6H_5$; $R^2 = CH_3O$), SEGPHOS (**9**), BisbenzodioxanPhos [134], and P-Phos [93] similarly exhibit high enantioselectivity in hydrogenation of ethyl 4-chloro-3-oxobutanoate at higher temperature [125, 131, 134, 135, 137]. Ru complexes having *i*-Pr-BPE (**10**) and Ph,Ph-oxoProNOP [149] show a moderate selectivity, even at room temperature.



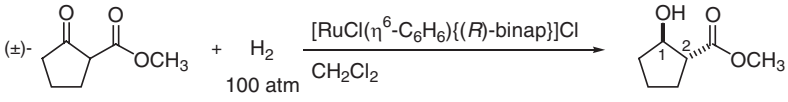
(2.20)

A series of the *N*-Boc-protected (*S*)-γ-amino β-keto esters are hydrogenated by the (*R*)-BINAP-Ru complex to give predominantly the *syn* alcohols [150]. The use of the *S* catalyst preferentially gives the anti isomer. *N*-Acetyl- or *N*-Boc-protected γ-amino γ,δ-unsaturated β-keto esters are hydrogenated by a mixture of an (*S*)-BINAP-Rh and -Ru catalyst to give predominantly 3*R*,4*R* products [151]. In this tandem hydrogenation, the BINAP-Rh catalyst selectively saturates the C=C bond under low-pressure hydrogen, after which the BINAP-Ru catalyst then saturates the C=O bond at high pressure. Hydrogenation of an *N*-Boc-protected (*S*)-δ-amino β-keto ester with an (*R*)-BINAP-Ru complex, followed by cyclization affords the trans-substituted lactone and its cis isomer in a 96:4 ratio [152].

A variety of keto esters other than keto carboxylic esters are usable for the substrates. β-Keto phosphonates are hydrogenated in the presence of a BINAP-Ru complex, giving β-hydroxy phosphonates in up to 99% *e.e.* [153]. The reactivity of the phosphonates is much higher than that of the carboxylic esters, so that the hydrogenation proceeds even at 1–4 atm of H_2 at room temperature. The sense of enantioface selection is the same as that with β-keto carboxylic esters. A BDPP (**8**)-Ru complex is also effective [154]. Similarly, in the presence of a MeO-BIPHEP-Ru complex β-keto thiophosphates are transformed to the β-hydroxy thiophosphates in high optical yield [153b]. Sodium β-keto sulfonates can be reduced to the *R* β-hydroxy sulfonates in up to 97% *e.e.* under atmospheric pressure and at 50 °C in the presence of a (*R*)-BINAP-Ru catalyst and HCl (Ru:HCl = 1:50) [155]. A (*R*)-MeO-BIPHEP-Ru complex is applied to hydrogenation ofβ-keto sulfones and sulfoxides. β-Alkyl-substituted β-keto sulfones are reduced at 1 atm of H_2, while the β-aryl-substituted substrate requires 75 atm [156]. (*R*)-β-Keto sulfoxides are hydrogenated in a highly diastereoselective manner [157]. The *R* substrate is well matched with the *S* catalyst to give the corresponding *S*,*R* alcohols predominantly. Combination of *R* catalyst/*R* substrate, however, gives a 6:94–10:90 mixture of *S*,*R* and *R*,*R* alcohols. The catalyst control dominates over the substrate control in this reaction.

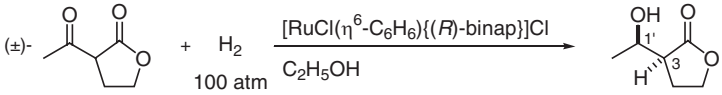
As described in Section 2.2.3.4, a single alcoholic compound among four possible stereoisomers is accessible from certain configurationally labile chiral ketones through dynamic kinetic resolution on the basis of asymmetric hydrogenation. The α position of α-monosubstituted β-keto esters is configurationally much more labile in comparison with that of unfunctionalized simple ketones. The significant lability realizes rapid equilibration between *R* and *S* enantiomer without any additional base [5c, 110]. In fact, as shown in Eq. 2.21, a racemic 2-alkoxycarbonylcycloalkanone, cyclic β-keto ester, is hydrogenated in CH_2Cl_2 containing [RuCl(η^6-C_6H_6){(*R*)-binap}]Cl to give the 1*R*,2*R* hydroxy ester with a high anti diastereoselectivity and a high enantioselectivity [158, 159]. Ru complexes with *i*-Pr-BPE (**10**) [137], tetraMe-BITIANP (**6**, R = CH_3) [49], and a chiral ferrocenyl diphosphine **11b** [139] are usable in alcoholic solvents. The degree of stereoselectivity is highly dependent on the substrates, the catalyst preparation procedure, and reaction conditions [120, 159]. In particular, the selection of solvent is crucial. The kinetic behavior of the stereoselective hydrogenation of racemic 2-methoxycarbonylcycloheptanone with Ru($OCOCH_3$)$_2$\{(*R*)-binap\} and 2 mol HCl is fully understood by use of computer-aided quantitative analysis [110, 160]. Thus, hydrogenation of the *R* keto ester in

CH_2Cl_2 occurs 9.8-fold faster than that of the *S* isomer, and the equilibration between the enantiomeric substrates is 4.4-fold faster than hydrogenation of the slow-reacting *S* substrate. On the other hand, hydrogenation of racemic 3-acetyltetrahydrofuran-2-one catalyzed by the cationic (*R*)-BINAP-RuCl(η^6-C_6H_6) complex gives the 3*S*,1′*R* (*syn*) alcohol in up to 97% *e.e.* (Eq. 2.22) [120, 158b]. A similar result is obtained by use of a tetraMe-BITIANP-Ru complex [49].



(2.21)

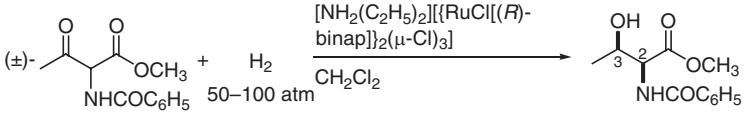
anti/syn = 99:1
92% *e.e.*



(2.22)

syn/anti = 98:2
97% *e.e.*

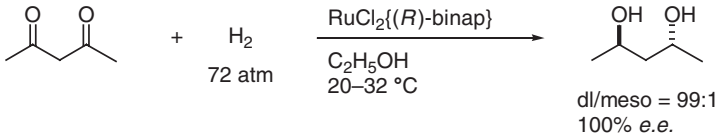
The hydrogenation of certain acyclic α-substituted β-keto esters via dynamic kinetic resolution also shows an excellent enantio- and diastereoselectivity [120, 158a, 161]. α-Acylamino and α-amidomethyl substrates are converted to 2*S*,3*R* (syn) alcohols in up to 98% *e.e.* with an (*R*)-BINAP-Ru complex (Eq. 2.23), and this method has been industrialized (Takasago Int. Corp.) [5c, 162]. By using sterically hindered DTBBINAP (**2**, Ar = 3,5-(*t*-C_4H_9)$_2$$C_6H_3$) [120] and DTBM-SEGPHOS (**9**, Ar = 4-CH_3O-3,5-(*t*-C_4H_9)$_2$$C_6H_2$) ligands, the α-amidomethyl keto ester is hydrogenated with almost perfect stereoselectivity, albeit at a lower rate [120, 125]. Interestingly, hydrogenation of an α-chloro substrate in the presence of a Ru{η^3-$CH_2C(CH_3)CH_2$}$_2$(η^4-cod)/BINAP system gives exclusively the anti-chlorohydrin in 99% *e.e.* [161b]. High diastereoselectivity is not accessible in BINAP- [158] or *i*-Pr-BPE-Ru [137] -catalyzed hydrogenation of simple α-methyl β-keto esters, although the reaction proceeds with a high level of enantioselection. α-Acylamino or α-halogeno β-keto phosphonates, α-substituted noncarboxylic esters, are also stereoselectively converted, with a BINAP-Ru complex, to the corresponding syn alcohols in up to >98% *e.e.* [153a, 163] with the same sense of enantio- and diastereoface discrimination as that in the case of α-substituted β-keto carboxylic esters.



(2.23)

syn/anti = 94:6
98% *e.e.*

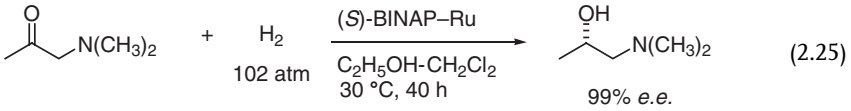
2,3-Butanedione is quantitatively hydrogenated at 26 °C and 80 atm of H_2 in ethanol containing $RuCl_2$\{(*R*)-binap\} (S/C = 2000) to give optically pure (*R*,*R*)-2,3-butanediol and the meso diol in a 26:74 ratio [119]. In contrast to the low diastereoselectivity with α-diketones, excellent diastereo- and enantioselectivities are attained in hydrogenation of β-diketones to the correspondding anti diols by use of a C_2-chiral diphosphine-Ru complex. (*R*)-BINAP-Ru complex converts 2,4-pentanedione to optically pure (*R*,*R*)-2,4-pentanediol in 99% yield (Eq. 2.24). With the same catalyst, 5-methyl-2,4-hexanedione and 1-phenyl-1,3-butanedione are reduced to the anti diol in a high optical yield [119, 164]. A BIPHEMP (**3**)- [165] or BDPP (**8**)-Ru complex [166] also shows high stereoselectivity for 2,4-pentanedione. In the hydrogenation of methyl 3,5-dioxohexanoate with an (*R*)-BINAP-Ru complex, an 81:19 mixture of an anti (3*S*,5*R*, 78% *e.e.*) and syn dihydroxy ester is obtained [167]. The absolute configurations suggest that the C(3) carbonyl group is more easily reduced than the C(5) carbonyl. An (*S*)-MeO-BIPHEP-Ru complex hydrogenates ethyl 2,4-dioxopentanoate to the corresponding diols, which then undergoes in-situ cyclization to give an 84:16 mixture of (3*R*,5*S*)-3-hydroxy-5-methyltetrahydrofuran-2-one with 98% *e.e.* and the 3*R*,5*R* isomer with 87% *e.e.* [168]. Ethyl 2-hydroxy-4-oxopentanoate is the only detectable intermediate. A Ru complex with a chiral ferrocenyl diphosphine (*S*)-(*R*)-**11c** exhibits almost perfect diastereo- and enantioselectivity in the hydrogenation of 1,3-diphenyl-1,3-propanedione [141]. In the same reaction system, BIPHEMP-Ru complex shows lower efficiency [169]. 1,5-Dichloro-2,4-pentanediol is obtained by hydrogenation of a dichloro diketone using $[NH_2(C_2H_5)_2][\{RuCl[(R)\text{-binap}]\}_2(\mu\text{-}Cl)_3]$ complex [170]. The same complex hydrogenates 1-phenyl-1,3-butanedione in CH_3OH at 50 °C and at 50 atm of H_2 to give a 98:2 mixture of (*R*)-1-phenyl-3-hydroxybutan-1-one in 98% *e.e.* and the diol [164]. With 2,5-hexanedione, a γ-diketone, (*R*,*R*)-2,5-hexanediol in >99.5% *e.e.* is obtained in 72% yield by an (*R*)-BINAP-Ru complex under acidic conditions (Ru:HCl = 1:4) [171]. The addition of HCl is essential to obtain high catalytic activity.



(2.24)

BINAP-Ru complexes show an excellent enantioselectivity in the hydrogenation of α-, β-, or γ-amino, -hydroxy, and -alkoxy ketones. Thus, α-dialkylamino ketones are effectively converted by (*S*)-BINAP-$RuCl_2$ complexes to the chiral β-amino alcohols with up to 99% *e.e.* (Eq. 2.25) [119, 120]. A normally unreactive Ru diacetate complex may be used for the hydrogenation of α-dimethylaminoacetone [119]. With a *trans*-$RuCl_2$\{(*R*)-xylbinap\}\{(*R*)-daipen\} ((*R*,*R*)-**20**)/$KOC(CH_3)_3$ catalyst system, a variety of α- and β-amino ketones are hydrogenated in high optical yields [114]. Thus, α-(dimethylamino)acetone is converted to the *S* amino alcohol in 92% *e.e.* with an S/C of 2000 under 8 atm H_2, whereas α-(dimethylamino)acetophenone is converted to the *R* alcohol in 93% *e.e.* with the same catalyst. The reversed sense of

enantioselection indicates the order of enantio-directing ability in this reaction is phenyl > (dimethylamino)methyl > methyl. 2-Dimethylamino-acetophenone is reduced with the *R,R* catalyst to give the *R* alcohol in 99.8% *e.e.* Even β-(dimethylamino)propiophenone, which is unstable under basic conditions, may be used as the substrate by minimizing the amount of $KOC(CH_3)_3$. The *S,S* catalyst gives the *R* γ-amino alcohol in 97.5% *e.e.* in 96% yield, although this is accompanied by 2% of 1-phenyl-1-propanol. Generation of this side product is completely suppressed by use of *trans*-RuH(η^1-BH_4){(*S*)-xylbinap}{(*S,S*)-dpen} under base-free conditions [70]. Dimethylaminomethyl thienyl ketone is also reduced selectively [103]. A γ-amino ketone is reduced by using the (*S*)-XylBINAP-Ru/(*S*)-DAIPEN/$KOC(CH_3)_3$ combined catalyst to give the *R* alcohol in 99% *e.e.* [114].



(2.25)

The hydrogenation of α- and β-hydroxy ketones with an (*R*)-BINAP-Ru catalyst gives *R* 1,2- and 1,3-diols in up to 98% *e.e.* [119, 172]. The sense of enantioface differentiation is the same as that in the hydrogenation of keto ester analogues. The asymmetric hydrogenation of 1-hydroxy-2-propanone leads to its industrial production (50 tons per year at Takasago Int. Corp.) [121g, 162]. A SEGPHOS (**9**)-Ru complex gives higher enantioselectivity in hydrogenation of hydroxyacetone to yield the diols in 99.5% *e.e.* [125]. The smaller dihedral angle of SEGPHOS than that of BINAP is thought to be responsible for the high level of enantioselectivity.

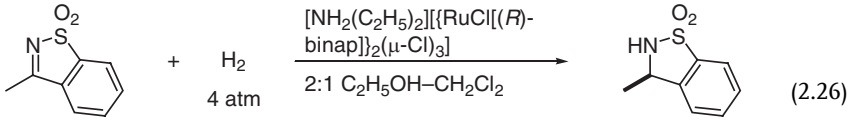
(*R*)-XylBINAP/(*R*)-DAIPEN-Ru, in the presence of a base, hydrogenates 2-methoxyacetophenone to give the *R* alcohol in 95% *e.e.* [67a] with the same sense of enantioselection as that in the hydrogenation of acetophenone. By contrast, the *R,R* complex-catalyzed hydrogenation of pyruvic aldehyde dimethylacetal affords the *S* alcohol in 98% *e.e.* The dimethoxymethyl group has a higher enantio-directing effect than the phenyl group.

β-Phenylthio ketones are also enantioselectively hydrogenated with a BINAP-, MeO-BIPHEP (**3**)-, or BDPP (**8**)-Ru complex without any deactivation of catalyst to give the chiral thio alcohols in up to 98% *e.e.* [173]. The reactivity and selectivity are somewhat decreased when a γ-phenylthio analogue is used as substrate, however.

A BINAP-Ru catalyst effectively discriminates between a hydroxy group and an alkoxy or aryloxy group, and even between *n*-octadecyl and triphenylmethoxy groups [174]. The *S* enantiomer of racemic 1-hydroxy-1-phenyl-2-propanone is selected by (*R*)-BINAP-Ru complex to be hydrogenated to the corresponding 1*S*,2*R* diol in 92% *e.e.* (50.5%, *syn*:*anti* = 98:2) [5c]. The unreacted *R* hydroxy ketone in 92% *e.e.* (49.5%) is recovered, and the relative hydrogenation rate of the enantiomers, k_S/k_R, is calculated to be 64:1.

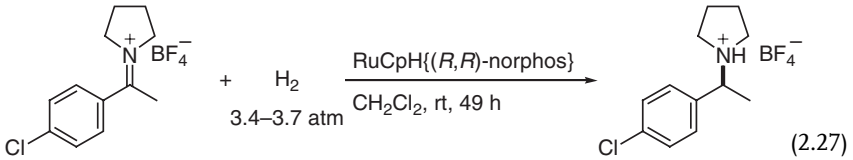
2.2.5
Imines

The catalytic activity of achiral Ru complexes for hydrogenation of C=N bonds has not been studied extensively, and reports on the asymmetric version are limited to sulfonimides and pyrrolidinium salts. Thus, a *p*-toluenesulfonimide derived from propiophenone is hydrogenated with $Ru(OCOCH_3)_2\{(R)\text{-binap}\}$ in THF to give the *R* product in 84% *e.e.*, albeit with a very low activity [175]. The degree of enantioface differentiation is highly dependent on the structure of substrate. A cyclic sulfonimide is hydrogenated with $[NH_2(C_2H_5)_2][\{RuCl[(R)\text{-binap}]\}_2(\mu\text{-Cl})_3]$ under 4 atm H_2 to give the almost enantiomerically pure *R* sultam (Eq. 2.26) [176]. $RuCpH[(R,R)$-norphos (**12**)] hydrogenates 4-chlorophenyl methyl pyrrolidinium salt to the *S* product in 60% *e.e.* (Eq. 2.27) [177]. The rate-determining step of this reaction was thought to be the hydride transfer from the catalyst to the $C=N^+$ group.



(2.26)

84% yield
>99% *e.e.*



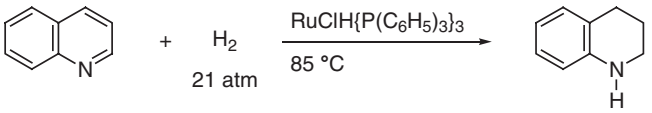
(2.27)

82% yield
60% *e.e.*

2.2.6
Others

Ruthenium complexes are effective catalysts for the chemoselective hydrogenation of aromatic and heteroaromatic rings. Using a $\{RuCl_2[\eta^6\text{-}C_6(CH_3)_6]\}_2/Na_2CO_3$ combined system, one molecule of the Ru catalyst converts 9000 molecules of benzene to cyclohexane at 50 °C under 50 atm H_2 for 36 h [178]. Anisole, methyl benzoate, acetophenone and benzophenone are hydrogenated to methoxycyclohexane, cyclohexanecarboxylic acid methyl ester, methyl cyclohexyl ketone, and dicyclohexyl ketone, respectively. Under these conditions, the ketone moiety is left intact. $RuClH\{\eta^6\text{-}C_6(CH_3)_6\}\{P(C_6H_5)_3\}$ also catalyzes the hydrogenation of benzenes, although high pressure is required [179]. *p*-Xylene is hydrogenated to *cis*-1,4-dimethylcyclohexane in the presence of $Ru\{\eta^6\text{-}C_6(CH_3)_6\}\{\eta^4\text{-}C_6(CH_3)_6\}$ [180]. $RuClH\{P(C_6H_5)_3\}_3$ and $[RuH_2\{P(C_6H_5)_2C_6H_4\}\{P(C_6H_5)_3\}_2]^-$ can selectively reduce the heteroaromatic rings of polyaromatic compounds such as quinoline and phe-

nanthridine to give 1,2,3,4-tetrahydroquinoline and 9,10-dihydrophenanthridine (Eq. 2.28) [181, 182]. Partial catalytic hydrogenation of benzene to cyclohexene is an important process for the production of nylons. A bilayer system including Ru metal, ZrO_2, and $ZnSO_4$ under 50 atm H_2 affords a mixture containing 60% of cyclohexene after 90% conversion of benzene (50 000 tons per year; Asahi Chemical Co.) [183].

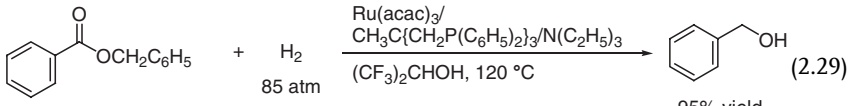


(2.28)

Ru complexes can be used for the selective conversion of alkynes to alkenes. Terminal and internal alkynes are hydrogenated by a cationic $[RuH\{P(CH_3)_2(C_6H_5)\}_5]PF_6$ complex to the corresponding terminal and cis alkenes without hydrogenation of C=C bonds and isomerization [184]. $RuCl_2\{P(C_6H_5)_3\}_3$ may also be used [185], while $RuClH\{P(C_6H_5)_3\}_3$ hydrogenates alkenes 10-fold faster than alkynes [186].

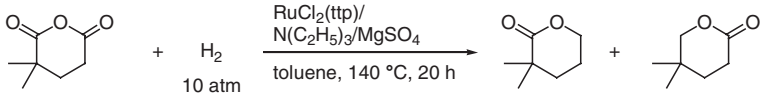
Carboxylic acids and their derivatives are less reactive toward hydrogenation than aldehydes and ketones, and hence drastic reaction conditions are required [1b]. The hydrogenation of carboxylic acids by RuO_2 or Ru/C in water requires about 150 °C and 500–700 atm [187]. The Ru/C catalyst converts arabinoic acid to arabitol under 100 atm H_2 and at 80 °C in water [188]. A bimetallic Ru-Sn/Al_2O_3 catalyst prepared by a sol-gel method preferentially hydrogenates the carboxylic acid functionality of oleinic acid over the C=C bond under 55 atm H_2 at 250 °C to give (*E*)- and (*Z*)-9-octadecen-1-ol [189]. The hydrogenation of succinic acid with $Ru_4H_4(CO)_8\{P(n\text{-}C_4H_9)_3\}_4$ in dioxane under 130 atm H_2 at 180 °C gives γ-butyrolactone in 100% yield [190]. Carboxylic esters are efficiently hydrogenated to the corresponding alcohol. The use of $Ru(acac)_3/CH_3C\{CH_2P(C_6H_5)_2\}_3$ in fluorinated alcohol solvent is a key issue for securing the high reactivity (Eq. 2.29) [191]. The Ru-Sn/Al_2O_3 system also promotes the hydrogenation of methyl laurate in DME under 97 atm H_2 at 280 °C to give lauryl alcohol [192], though contamination by chloride significantly reduces the reactivity. With this bimetallic system, olefinic groups are also hydrogenated, but a Ru-Sn-B/Al_2O_3 ternary catalyst preferentially saturates ester groups [193]. Methyl 9-octadecenoate is hydrogenated at 43 atm of H_2 and at 270 °C to produce a 77:23 mixture of 9-octadecen-1-ol and 1-octadecanol at 80% conversion. A potassium hydrido(phosphine)ruthenate complex is also known as an effective catalyst [63]. $Ru(acac)_3/CH_3C\{CH_2P(C_6H_5)_2\}_3/Zn$ catalyst system can be used for conversion of dimethyl oxalate to ethylene glycol [194]. With $Ru(OCOCH_3)_2(CO)_2\{P(n\text{-}C_4H_9)_3\}_2$, the reduction is stopped at methyl glycolate [195]. γ-Butyrolactone, δ-valerolactone, and ε-caprolactone are effectively saturated to the corresponding diols in the presence of $Ru(acac)_3/P(n\text{-}C_8H_{17})_3$ and an acidic promoter such as NH_4PF_6, H_3PO_4, or its derivative [196]. $RuCl_2\{P(C_6H_5)_3\}_3$ hydrogenates succinic anhydride in toluene under 10 atm H_2 at 100 °C to afford a mixture of γ-butyrolactone and succinic acid [197], while $Ru_4H_4(CO)_8\{P(n\text{-}C_4H_9)_3\}_4$ gives γ-butyrolactone in 100% yield [190]. A $Ru(acac)_3/P(n\text{-}C_8H_{17})_3/p$-TsOH system gives γ-butyrolactone from succinic

anhydride with a 98:2 selectivity at 97% conversion [198] and ethyl acetate from acetic anhydride with 99:1 selectivity. Regioselective hydrogenation of 2,2-dimethylglutaric anhydride to 2,2-dimethyl-δ-valerolactone is possible with $RuCl_2(C_6H_5P(CH_2CH_2CH_2P(C_6H_5)_2)_2)$ and $RuCl_2\{P(C_6H_5)_3\}_3$ (Eq. 2.30) [199, 200]. By using chiral Ru complexes such as BINAP-Ru(II) or DIOP-Ru(II), 3-substituted glutaric anhydrides are enantioselectively hydrogenated to give 3-substituted δ-valerolactone in up to 60% *e.e.* [201].



95% yield (2.29)

ester:Ru:ligand:amine = 2170:1:1.15–1.65:200



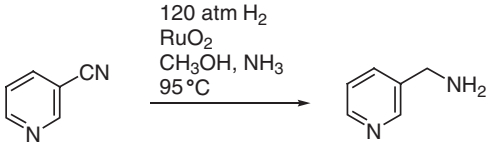
29% yield
99:1 (2.30)

anhydride:Ru = 25–50:1

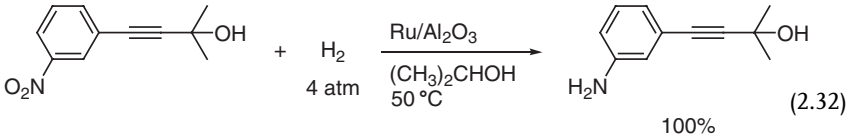
TTP = $C_6H_5P(CH_2CH_2CH_2P(C_6H_5)_2)_2$

Nitriles can be converted to the corresponding primary amines. Anionic Ru hydride complexes such as $K[RuH_2\{(C_6H_4)P(C_6H_5)_2\}\{P(C_6H_5)_3\}_2]C_{10}H_8 \cdot O(C_2H_5)_2$, $K_2[Ru_2H_4\{P(C_6H_5)_2\}\{P(C_6H_5)_3\}_3] \cdot 2O(CH_2CH_2OCH_3)_2$ are effective catalysts [63]. Chemoselective reduction of 3-cyanopyridine to 3-aminomethylpyridine is attainable by use of RuO_2-catalyzed hydrogenation under 120 atm H_2 and at 95 °C in a methanol-ammonia mixed solvent (Eq. 2.31). In ammonia, the pyridine ring is also saturated [202].

Both Ru carbonyl complexes and Ru phosphine complexes are used for the reduction of nitro compounds under H_2, H_2/CO, or water shift gas H_2O/CO [4a]. $RuCl_2\{P(C_6H_5)_3\}_3$ catalyzes the hydrogenation of aromatic and aliphatic nitro compounds to the corresponding primary amines. The complex performs highly chemoselective reduction of nitro compounds in the coexistence of carbonyl moieties [203]. Ru/C or Ru/Al_2O_3 preferentially reduces the aromatic nitro group in (3-nitrophenyl)acetylene (Eq. 2.32) [204]; this nitro group reduction is important not only in the laboratory-scale organic synthesis, but also in industrial production [4c].



(2.31)



(2.32)

Carbon monoxide (CO) and carbon dioxide (CO_2) are key compounds in C1 chemistry. The vaporization of coals produces synthesis gas (CO and H_2), which is widely used in the chemical industry. Carbon monoxide is hydrogenated to hydrocarbons (Fischer-Tropsch synthesis) [205] and oxygen-containing C1 and C2 molecules such as methanol, methyl formate, ethanol, and ethylene glycol by using a variety of Ru carbonyl or Ru oxide complexes [206]. The combination of $Ru_3(CO)_{12}$ or RuO_2 with CH_3COOOH [207], KI [208], 1-alkylbenzenimidazole [209], or $(n\text{-}C_4H_9)_4PBr$ [210] tends to make the reaction conditions milder. $Ru_3(CO)_{12}$/$(n\text{-}C_4H_9)_4PBr$ catalyst converts synthesis gas and ammonia into formamide [211]. Selectivity in the formation of small molecule products is well controlled by the use of bimetallic catalysts. Ethyleneglycol, for example, is produced with a good selectivity by using Ru-Rh [212, 213] and Ru-Re [214] systems. The Ru-Co catalyst prefers the generation of ethanol [215], while Ru-Mn or Ru-Ti catalyst is methanol-selective [216]. Ru-Co [217] and Ru/CH_3I [218] catalysts are able to homologate methanol, to produce ethanol.

CO_2 fixation attracts much attention with regard to global warming or environmental protection. The hydrogenation of CO_2 to formic acid or its derivative is one of the possible future fixation technologies. However, the high thermodynamic stability of CO_2 requires well-designed conditions, including catalysts as well as reaction media [219]. Ru complexes are among the most effective catalysts [220–223]. The addition of $N(C_2H_5)_3$ is crucial to attain a high TON, this being due to increase in the reaction enthalpy by forming ammonium formate as product [219]. An accelerating effect of a small amount of water is also observed [220, 221, 224], probably due to a donating effect of H_2O towards the carbon atom of CO_2 [219]. $RuX_2\{P(CH_3)_3\}_4$ (X = H or Cl) hydrogenates CO_2 with a TON of 7200 and a TOF of 1400 h^{-1} in supercritical CO_2 (sc-CO_2) containing $N(C_2H_5)_3$ and H_2O [221, 225]. The high solubility of hydrogen molecules in sc-CO_2 is the reason for this high reactivity [226]. Even higher reactivity (TOF = 95 000 h^{-1}) is attainable in sc-CO_2 in the presence of $RuCl(OCOCH_3)\{P(CH_3)_3\}_4$, $N(C_2H_5)_3$ and C_6F_5OH, a highly acidic alcohol [227]. The use of methanol rather than $N(C_2H_5)_3$ affords methyl formate. A $RuCl_2\{P(C_6H_5)_3\}_3$/basic Al_2O_3 combined system, $RuCl_2\{P(CH_3)_3\}_4$, and $RuCl_2(dppe)_2$ (DPPE = 1,2-bis(diphenylphosphino)ethane) achieves TON = 470 [228], 3500 and 12 900, respectively [229, 230]. Hydrogenation of CO_2 in the presence of $NH(CH_3)_2$ under appropriate conditions produces *N,N*-dimethylformamide. $RuCl_3$/DPPE/$Al(C_2H_5)_3$ and $RuCl_2\{P(C_6H_5)_3\}_3$ may be used for this purpose in hexane, realizing TONs of 3400 and 2650, respectively [231]. Use of these Ru complexes in sc-CO_2 showed remarkable TONs of 370 000 [232] and 740 000 [230]. Immobilization of Ru complexes facilitates the separation of catalysts from products. A Ru complex polymerized $RuCl_2\{P(CH_3)_2(CH_2)_2Si(OC_2H_5)_3\}_3$ with $Si(OC_2H_5)_4$ exhibits

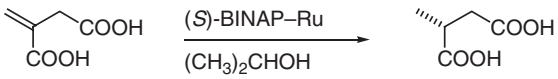
TON = 110 800 for DMF production in sc-CO_2 [233]. $RuCl_2$ and RuH_2 complexes with resin-supported diphosphine ligands are also effective for the hydrogenation in sc-CO_2 [234].

2.3 Transfer Hydrogenation

2.3.1 Olefins

A variety of phosphine-Ru complexes can transfer hydrogens from primary or secondary alcohol, formic acid, and a hydroaromatic compound to olefinic double bonds [1, 4]. For example, $RuCl_2\{P(C_6H_5)_3\}_3$ reduces cycloheptene by use of indoline as hydrogen donor to cycloheptane in toluene at 120 °C [235]. Monohydride or dihydride complexes such as $RuClH\{\eta^6\text{-}C_6(CH_3)_6\}\{P(C_6H_5)_3\}$ and $RuH_2\{P(C_6H_5)_3\}_4$ also act as a transfer hydrogenation catalyst for alkenes at 80–100 °C in combination with 2-phenylethanol or 2-propanol [179, 236]. With the phosphine-$RuCl_2$ and -RuClH complexes, the C=C bond of α,β-unsaturated ketones and esters are chemoselectively reduced [237–240]. When isopropylidene-1,2-α-D-glucofuranose is used as a chiral hydrogen donor, the olefin-selective asymmetric reduction of $CH_2{=}C(C_6H_5)(COC_6H_5)$ or isophorone is attained although the optical yields are less than 34%. Allylic or propargyl alcohols undergo an intramolecular transfer hydrogenation to give the corresponding aldehydes and ketones [22, 241, 242].

In the enantioselective reduction of olefins using chiral Ru complexes, formic acid, a 5:2 $HCOOH/N(C_2H_5)_3$ azeotrope, and 2-propanol are most frequently used. Other hydrogen donors such as ascorbic acid, benzyl alcohols, hydroaromatics, H_2O/CO combination have rarely been utilized. In an early attempt, tiglic acid is reduced in 2-propanol or 2-octanol containing $Ru_4H_4(CO)_8(diop)_2$ or $Ru_2Cl_4(diop)_3$ at 120–190 °C, although the optical purity of the obtained product is up to 15% [243, 244]. Chiral Ru complexes of the general formula $Ru(\eta^3\text{-}CH_2CHCH_2)(acac\text{-}F_6)$-(diphosphine) effectively catalyze hydrogen transfer from $HCOOH/N(C_2H_5)_3$ azeotrope to itaconic acid in THF to afford the saturated carboxylic acids in up to 93% *e.e.* [245]. The most active and selective catalyst for this transformation is formed with BINAP. $[RuH\{(S)\text{-binap}\}_2]PF_6$, a cationic five-coordinate complex, catalyzes saturation of the same unsaturated carboxylic acids with 2-propanol in 97% optical yield (Eq. 2.33) [246]. In all cases, the sense of enantioselection is identical to that of the reaction with molecular hydrogen. The use of a ligand that forms a seven-membered metal chelate ring is crucial for obtaining high efficiency in the Ru-catalyzed reaction using the $HCOOH/NR_3$ system. Kinetic resolution of racemic 1-phenylpropan-1-ol is attempted by DIOP- or neomenthyldiphenylphosphine-Ru-catalyzed transfer hydrogenation of $C_6H_5CH{=}CHCOCH_3$. 1-Phenylpropan-1-ol in about 11% *e.e.* is recovered after 57% conversion [247–249].



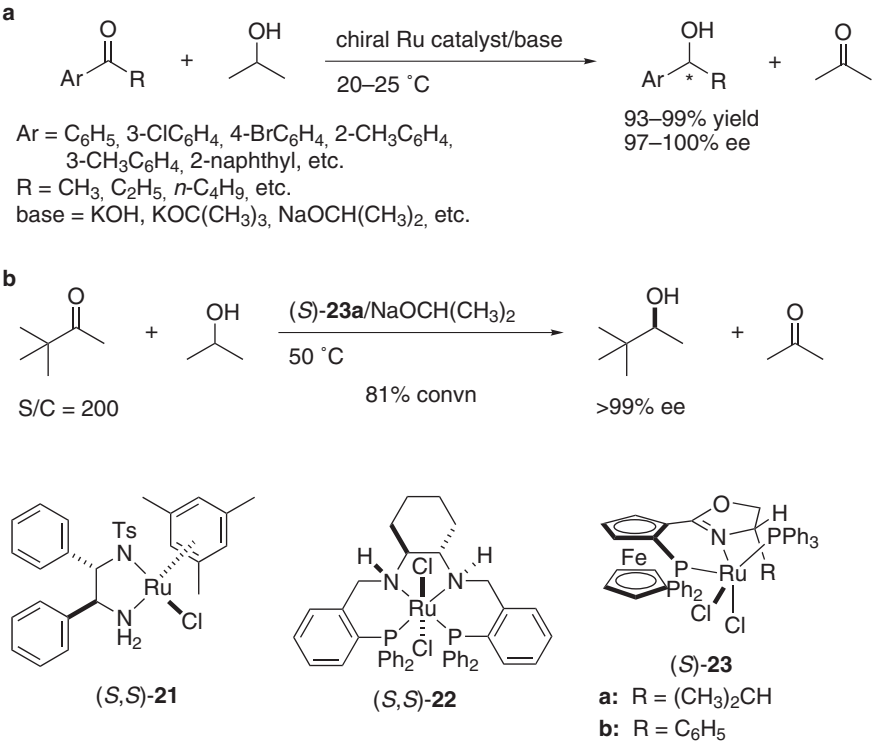
97% *e.e.* (2.33)

2.3.2 Ketones and Aldehydes

Transfer hydrogenation of ketones and aldehydes is catalyzed by a variety of Ru complexes, including $RuCl_2\{P(C_6H_5)_3\}_3$, $RuCl_2(pta)_4$ (PTA = 1,3,5-triaza-7-phosphaadamantane), $Ru(OCOCF_3)_2(CO)\{P(C_6H_5)_3\}_3$, $RuClH(CO)\{P(C_6H_5)_3\}_3$, $RuH_2(CO)\{P(C_6H_5)_3\}_3$, and $RuH_2\{P(C_6H_5)_3\}_4$ [250, 251]. 2-Propanol [252–254] and formic acid [255] are most preferably used as hydrogen donors, but methanol, tetrahydrofuran, and tetrahydronaphthalene are also utilized [256]. The addition of a strong base in the reaction using an alcoholic hydrogen donor increases the reactivity, because the time required to attain equilibrium between the ketonic substrate and the alcoholic product is shortened. The equilibrium position is highly dependent on the concentration of the substrate and the reduction potential difference between the two alcohols. The use of formic acid or its salt makes the reaction irreversible by the liberation of CO_2, thus increasing the efficiency. Transfer hydrogenation is a simple operation that does not require special apparatus, and may also prefer carbonyl-selective reduction. These advantages and characteristics induce chemists to investigate asymmetric versions by introducing a variety of chiral ligands into divalent Ru complexes [5h,i, 252e, 257]. To date, the extent of enantioselectivity obtained with chiral phosphine ligands has not been satisfactory [251], while highly reactive and enantioselective reactions are realized by use of chiral nitrogen-based ligands [252c]. A variety of aromatic, olefinic, and acetylenic carbonyl compounds can now be converted to the corresponding chiral alcohols, with high *e.e.* values.

2.3.2.1 Unfunctionalized Ketones and Aldehydes

As illustrated in Scheme 2.5a, aromatic ketones are reduced in high optical yields in an alkaline base containing 2-propanol by use of divalent Ru complexes possessing nitrogen-containing chiral ligands such as amido amines, diamines, amino alcohols, amino imines, amino or imino phosphines [258–260]. For example, the Ru complex (*S*,*S*)-**21**, which is prepared from TsDPEN (*N*-(4-toluenesulfonyl)-1,2-diphenylethylenediamine) and $\{RuCl_2(\text{mesitylene})\}_2$ precursor [261], effectively reduces acetophenone using a 0.1 *M* solution in 2-propanol containing KOH at room temperature to give (*S*)-1-phenylethanol in 95% yield and in 97% *e.e.* [78, 258]. The electronic properties and the steric bulk of aromatic ketones exert significant effects on the reaction rate and enantioselectivity. An *N*-arenesulfonylated derivative of chiral cyclohexanediamine can be similarly used as a chiral auxiliary [262].



Scheme 2.5

Appropriate combinations of $\{RuCl_2(\eta^6\text{-arene})\}_2$ complexes and a chiral proline-derived acylamino amine [263], the diamine [264], a chiral ferrocenyl diamine [262, 265], and a variety of β-amino alcohols [266–269] are effective and, in some cases, have a higher reactivity than a TsDPEN-Ru complex. The amino alcohol **17** shows a remarkably high catalytic activity in comparison with the original 2-azabornylmethanol [268]. The reaction is performed with an S/C as high as 5000 and a TOF of 8500 h^{-1}. The existence of an NH_2 or NH end-group in the chiral auxiliaries is essential in order to achieve a high efficiency. Sterically hindered pivalophenone is reduced with a 90:10 enantioselectivity by use of a Ru complex with a chiral oxazoline containing β-amino alcohol [270]. The chiral bisthiourea derivative of DPEN is a useful ligand for enantioselective reduction of isobutyrophenone [271].

$RuCl_2\{P(C_6H_5)_3\}_3$ is used as a precursor in combination with a pyridine-containing derivative of 2-amino-2′-hydroxy-1,1′-binaphthyl [272], and an amino bisoxazoline ligand, AMBOX (**16**) [273], effecting the enantioselective reduction of several aromatic ketones with up to 98% *e.e.* The enantioselectivity is decreased by increasing the bulkiness of alkyl groups.

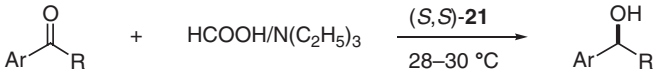
Although simple phosphine-Ru catalysts are not very effective for asymmetric transfer hydrogenation of ketones, Ru complexes with chiral phosphine ligands combined with oxazoline or secondary amine realize high reactivity and enantio-

selectivity. For example, a $RuCl_2$(**13**)$\{P(C_6H_5)_3\}$/NaOH catalyst system acts as an extremely active catalyst for the reduction of acetophenone in 2-propanol to give a TOF of 42 600 h^{-1} at 82 °C [274, 275]. In situ-prepared diastereomeric complexes consisting of $RuCl_2\{P(C_6H_5)_3\}_3$ and oxazolylferrocenylphosphines **14** may also be used in the reduction of aromatic ketones, providing the alcohols in up to 96% *e.e.* [276]. The presence of $P(C_6H_5)_3$ is crucial to achieve a high optical yield. The isolated complexes (*S*)-**23** convert a variety of aromatic ketones to the corresponding *R* alcohols in up to >99.9% *e.e.* (Scheme 2.5) [277]. The *S* catalyst dehydrogenates an enantiomer of racemic aromatic alcohols by transferring the hydrogen atoms to acetone with the k_{fast}/k_{slow} ratio of up >368:1, recovering the *R* alcohol in high *e.e.* at the appropriate conversion [75, 277]. A coordinatively saturated 18-electron Ru complex **22**, which is prepared from *trans*-$RuCl_2(dmso)_4$ and the C_2-symmetrical diphosphine/diamine ligand, catalyzes transfer hydrogenation of various acetophenone derivatives in 2-propanol containing $KOCH(CH_3)_2$ (Ru:base = 1:0.5) to substituted 1-phenylethanols in up to 97% *e.e.* (Scheme 2.5) [278]. The corresponding diphosphine/diimine-Ru complex is much less reactive, indicating the significance of the NH function for the catalytic activity.

A successful example of highly enantioselective transfer hydrogenation of aliphatic ketones is limited only to *tert*-alkyl ketones (Scheme 2.5b). With a Ru complex (*S*)-**23a**/$NaOCH(CH_3)_2$ system in 2-propanol, pinacolone and 2,2-dimethylcyclohexanone are reduced in >99% and 98% optical yields [277], respectively. A Ru catalyst, prepared from $\{RuCl_2(\eta^6\text{-}C_6H_6)\}_2$, tridentate bisoxazoline phosphine ligand **15**, and a base, reduces pinacolone in 92% optical yield [279]. Only moderate optical yields of 60–75% are attainable with cyclohexyl methyl ketone or 5-methyl-3-hexanone in the presence of (*S*)-**23b**, $\{RuCl_2(\eta^6\text{-}C_6H_6)\}_2$/(*R,R*)-**15**, $\{RuCl_2[\eta^6\text{-}C_6(CH_3)_6]\}_2$/(*S,S*)-pseudoephedrine [259] or $RuCl_2\{(S)\text{-}\mathbf{13}\}\{P(C_6H_5)_3\}$ [274] system.

2-Propanol, a convenient and useful hydrogen donor, has an inherent ketone/alcohol equilibrium issue [280]. The reverse process often prevents a high conversion, particularly in the reduction of highly stable ketones to thermodynamically unfavorable alcohols. For example, reduction of acetophenone in 2-propanol requires a substrate concentration as low as 0.1 *M* to obtain a high yield. Furthermore, the product *e.e.* tends to deteriorate as the reaction proceeds, even if the catalyst has an excellent enantioface-discriminating ability. These thermodynamic problems are solved by the use of formic acid, another inexpensive hydrogen donor [255]. Formic acid, viewed as an adduct of H_2 and CO_2 [219], irreversibly reduces ketones to alcohols in the presence of a catalyst, in principle, in 100% conversion, giving better results than 2-propanol [281]. The enantioface of ketones can be discriminated under fully kinetic control. Actually, by using a 5:2 $HCOOH/N(C_2H_5)_3$ azeotropic mixture [282], the Ru complex (*S,S*)-**21** quantitatively transforms various aromatic ketones to the alcohols with high *e.e.* values at room temperature, and even in a 2–10 *M* solution (Eq. 2.34) [78, 281]. The presence of $N(C_2H_5)_3$ is essential to achieve a high reactivity, but alkaline bases are not required. The reduction of a benzophenone derivative having a methoxy and cyanide group at the 4- and 4′-positions gives the chiral alcohol in 66% *e.e.* [281]. A Ru complex generated from $\{RuCl_2(p\text{-cymene})\}_2$ and *N*-1-naphthylsulfonated (*R,R*)-1,2-diaminocyclohexane also shows a

high enantioselectivity for the reduction of aryl methyl ketones with a HCOOH/$N(C_2H_5)_3$ mixture [262].

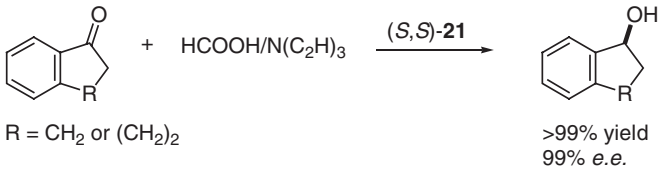


(2.34)

Ar = C_6H_5, 4-$CH_3OC_6H_4$, 2-naphthyl, or 2-furyl
R = CH_3 or C_2H_5

96–>99% yield
96–98% *e.e.*

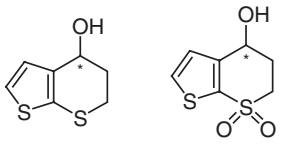
The low oxidation potential of α-tetralone or -indanone prevents completion of the reaction using 2-propanol as a hydrogen donor [258, 280]. Only moderate yields, though with excellent enantioselectivities, are attained with 2-propanol containing a Ru catalyst with a chiral amino alcohol [259, 266] or an amino bisoxazoline ligand AMBOX (**16**) [259, 266, 273a, 283, 284]. The use of a HCOOH/$N(C_2H_5)_3$ system achieves almost perfect transfer hydrogenation of these substrates in the presence of the Ru complex **21** [281], giving the corresponding chiral cyclic alcohols in up to 99% *e.e.* (Eq. 2.35) [78, 258, 281]. The sense of enantioface discrimination is the same as that in the reduction of acyclic aromatic ketones. The complex (*R*,*R*)-**21** is applicable to reduction of sulfur-containing cyclic ketones and a multi-functionalized ketone to give the desired *R* alcohols **24**, **25**, and **26** in 99, 98, and 92% *e.e.*, respectively [281]. The olefinic bond, halogen atom, quinoline ring, and ester group in **26** are not affected.



(2.35)

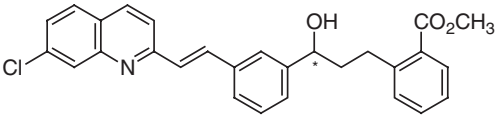
R = CH_2 or $(CH_2)_2$

>99% yield
99% *e.e.*



24

25



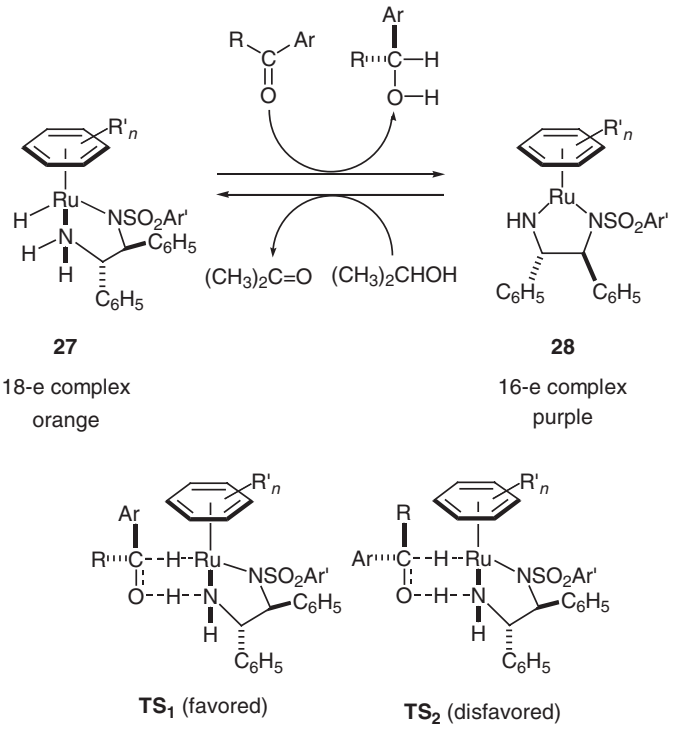
26

(*R*,*R*)-TsDPEN-RuCl(*p*-cymene) complex catalyzes the deuteration of benzaldehydes by using only a stoichiometric amount of the deuterium source, DCOOD/$N(C_2H_5)_3$, to give the *S* deuterio alcohols in up to 99% *e.e.* [285]. The d_1 content in

the product alcohol was >99%. The introduction of electron-donating and -accepting groups at the 4′ position little affected the enantioselectivity. The same catalyst reduces benzaldehydes-*d* in 2-propanol containing $KOC(CH_3)_3$, giving (*R*)-benzyl-1-*d* alcohol quantitatively in 98% *e.e.* [285].

Recycling of the catalyst has been investigated by using Ru complexes with a chiral water-soluble ligand [286, 287], a dendritic ligand [288], or a TsDPEN immobilized on a polystyrene resin [289, 290].

The supposed mechanism of asymmetric transfer hydrogenation of ketones by a TsDPEN-RuCl(η^6-arene) complex and base in 2-propanol is shown in Scheme 2.6. This is supported by theoretical calculation [76, 77] and detailed experimental investigations such as kinetic studies, X-ray crystallographic analysis of **27** and **28** (η^6-arene = *p*-cymene; Ar′ = 4-$CH_3C_6H_4$) [75]. First, an alkaline base eliminates HCl from the 18-electron (*S*,*S*)-TsDPEN-RuCl(*p*-cymene) catalyst precursor to generate the purple 16-electron species **28**. The coordinatively unsaturated Ru-amide complex **28** generates an orange-colored 18-electron RuH species **27** with dehydrogenation of 2-propanol. This then reduces the C=O bond of ketone via a six-membered pericyclic transition state, which is close to that of BINAP-Ru/DPEN/base-catalyzed hydrogenation of ketones [250, 291]. Liberation of the alcoholic product regenerates the 16-electron Ru species. The isolated complexes (*S*,*S*)-**27** and **28** (η^6-arene = *p*-cymene; Ar′ = 4-$CH_3C_6H_4$) show a reasonable activity for asymmetric reduction of acetophe-

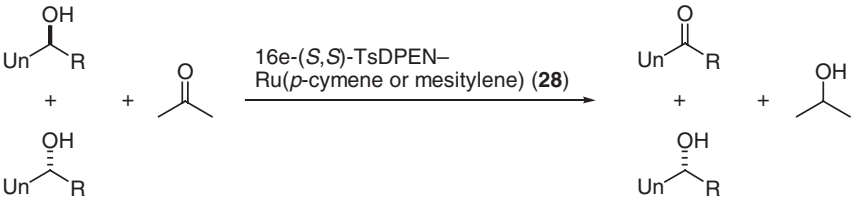


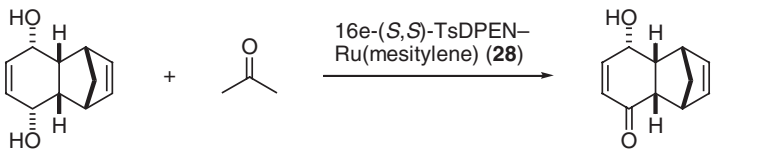
Scheme 2.6

none in 2-propanol without any base to give (*S*)-1-phenylethanol in 95% *e.e.* The *S,S* catalyst gives the *S* alcohol via the favored $\mathbf{TS_1}$ that is stabilized by the CH/π attractions between the η^6-arene ligand and the aromatic ring of the substrate [76]. The metal-ligand bifunctional mechanism contrasts sharply with that of many other systems mediated by metal complexes [292].

The reversibility of transfer hydrogenation of ketones with 2-propanol makes it possible to oxidize a secondary alcohol with acetone [250, 253b]. Under appropriate conditions, and using a chiral catalyst, a racemic secondary alcohol is kinetically resolved in an enantiomer-selective manner to give a mixture of an unreacted chiral alcohol and a ketonic product by the generation of 2-propanol. This process is especially advantageous for the resolution of racemic alcohols having a lower oxidation potential than that of 2-propanol [280]. Actually, as shown in Scheme 2.7, a variety of racemic aromatic or unsaturated alcohols are efficiently resolved in acetone containing a diamine-based TsDPEN-Ru(II) complex **28** (η^6-arene = *p*-cymene or mesitylene; Ar′ = 4-$CH_3C_6H_4$) [75]. The excellent enantiomer-discriminating ability of the catalyst achieves a k_{fast}/k_{slow} ratio of >100:1. Even at 50% conversion, almost optically pure secondary alcohols are recovered. Notably, racemic 2-cyclohexenol – a simple cyclic allylic alcohol – is also successfully resolved by this method. Such high optical yields are not attainable in the corresponding asymmetric transfer hydrogenation of ketones in 2-propanol, while the efficiency of resolution of 4-phenyl-3-butene-2-ol – a flexible allylic alcohol – is only moderate. The Ru catalyst system can be applied to desymmetrization of the meso unsaturated diol (Scheme 2.7) [75].

The kinetic resolution of racemic secondary alcohols by enzymatic acylation is a well-established method for obtaining optically pure alcohols or their esters in near-50% yield [293]. Coupling the enzymatic method with a catalytic redox ability of a Ru complex makes the process a dynamic kinetic resolution, increasing the theoretical yield from 50 to 100% [294]. Thus, a reaction system consisting of an achiral Ru catalyst for the chemical racemization of an alcoholic substrate, a suitable enzyme,

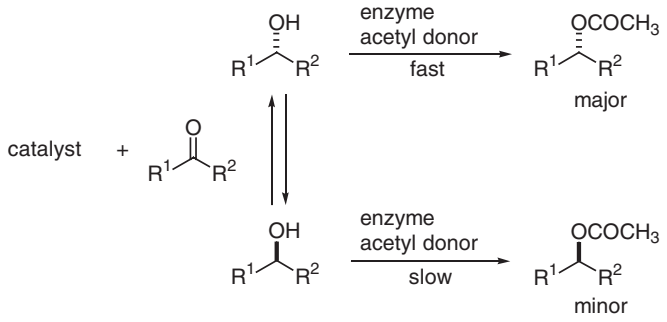




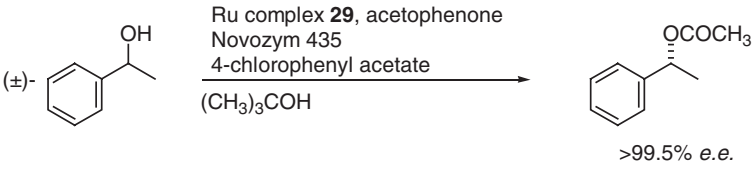
Scheme 2.7

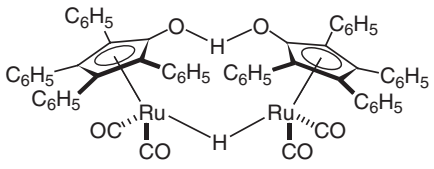
acetophenone, and an acetyl donor allows the transformation of racemic 1-phenylethanol to the *R* acetates with an excellent *e.e.* (Scheme 2.8) [295]. The presence of 1 equiv. acetophenone is necessary to promote the alcohol racemization catalyzed by the Ru complex **29** [295b, 296]. 4-Chlorophenyl acetate is a suitable acetyl donor, because the 4-chlorophenol produced does not interfere with the catalytic racemization. With the combined biological/chemical method, stereoisomeric mixtures of diols are converted to chiral diacetates in high optical purity [297]. The reaction of aliphatic diols such as 2,4-pentanediol and 2,5-hexanediol produces a lower dl:meso ratio, while the *e.e.* of the corresponding *R,R* diacetate is kept at >99%. Nitrogen-containing substrates are also usable in this procedure.

Only a very limited number of catalytic systems are available for the chemoselective and enantioselective transfer hydrogenation of unsaturated ketones. The use of the chiral Ru(II) complex **21** and KOH, or the isolated catalyst **28** (η^6-arene = *p*-cymene; Ar′ = 4-$CH_3C_6H_4$) has realized the highly enantioselective transfer hydrogenation of α,β-acetylenic ketones in 2-propanol [260]. Regardless of the size of alkyl groups in the substrates, a variety of propargylic alcohols are formed in up to 99% *e.e.* and in >99% yield. Unlike the reduction of alkyl aryl ketones, the use of $HCOOH/N(C_2H_5)_3$ diminishes the catalytic activity. The favorable ynone/ynol ther-



example:





29

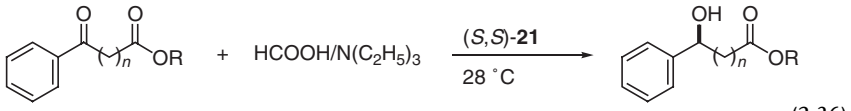
Scheme 2.8

modynamic balance leads to a high conversion with a 0.1–1 *M* ynone solution. Highly diastereoselective transfer hydrogenation of a chiral acetylenic ketone is also attained with **28** (η^6-arene = *p*-cymene; Ar′ = 4-$CH_3C_6H_4$) in 2-propanol [260, 298]. The degree and sense of diastereoface differentiation are mostly controlled by the chirality of the Ru catalyst.

2.3.2.2 Functionalized Ketones

Keto esters, pyridyl ketones, α-hetero-substituted acetophenones

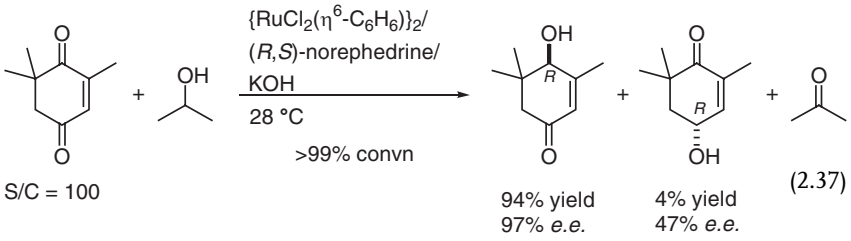
The reduction of some aromatic keto esters using the Ru complex (*S*,*S*)-**21** and $HCOOH/N(C_2H_5)_3$ mixture gives the corresponding *S* alcohols in up to 95% *e.e.* (Eq. 2.36) [78, 281] with the same sense of enantioselection as that in the reduction of simple aromatic ketones. The extent of enantioselectivity increases in the order of α-, β-, and δ-keto esters. A Ru complex prepared from $\{RuCl_2(p\text{-cymene})\}_2$ and an amino alcohol (*S*,*R*)-ephedrine effects reduction of ethyl 3-phenyl-3-oxopropanoate in 2-propanol containing $KOCH(CH_3)_2$ to afford the *S* alcohol in 94% *e.e.* [299, 300]. Methyl 2-acetylbenzoate is reduced with a 16-electron Ru catalyst, (*S*,*S*)-TsDPEN-Ru(*p*-cymene) [75], in 2-propanol to afford (*S*)-3-methylphthalide in 97% *e.e.* and in 93% yield contaminated with 1% of 3-(2-isopropoxy)-3-methylphthalide [301]. A $\{RuCl_2(p\text{-cymene})\}_2$/*N*-benzyl derivative of (*S*,*R*)-ephedrine/base catalyst system in 2-propanol as well as TsDPEN-RuCl with $HCOOH/N(C_2H_5)_3$ reduces several pyridyl ketones to give the pyridyl alcohols in up to 95% *e.e.* [302, 303]. Double reduction of 2,6-diacetylpyridine gives a 91:9 mixture of the *S*,*S* diol in 99.6% *e.e.* and the meso isomer. The isolated or in-situ-prepared (*S*,*S*)-TsDPEN-RuCl(*p*-cymene) transfers hydrogen atoms from $HCOOH/N(C_2H_5)_3$ to acetophenone possessing, at C2, hetero-atom-containing functional groups such as CN, N_3, NO_2 [304], *t*-$C_4H_9OCON(CH_3)$ [305], and Cl [306], giving the corresponding alcohols in up to 99% *e.e.* with the same enantioselectivity as that observed with acetophenone [281]. The chiral Ru complex (*S*,*S*)-TsDPEN-RuCl(*p*-cymene) in combination with $HCOOH/N(C_2H_5)_3$ hydrogen donor is usable for the highly enantioselective reduction of a variety of α-, β-diketones and α-hydroxy ketones [304, 307–309].



n = 0,1, or 3
R = C_2H_5 or $(CH_3)_2CH$

94–99% yield
75–95% *e.e.* (2.36)

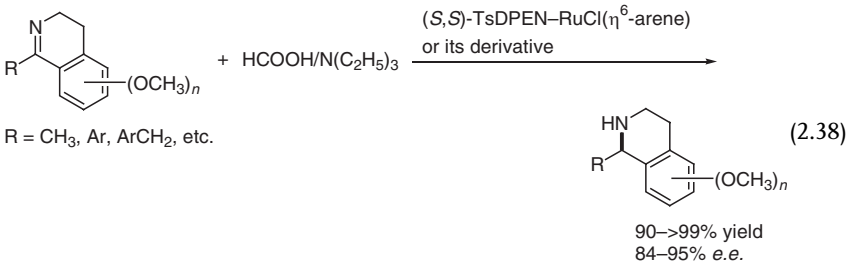
The $\{RuCl_2(\eta^6\text{-}C_6H_6)\}_2$/(*R*,*S*)-norephedrine/KOH catalyst system shows high chemo- and enantioselectivities in the reduction of 4-oxoisophorone in 2-propanol. Reduction of the sterically hindered carbonyl group is preferred over that of the less-hindered group (94:4) to give (*R*)-4-hydroxyisophorone in 97% *e.e.* as the major product (Eq. 2.37) [310]. No saturation of the double bond occurs.



(2.37)

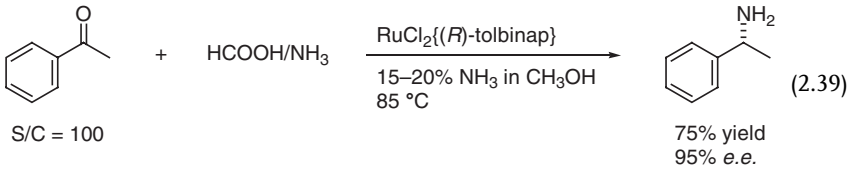
2.3.3 Imines

$Ru_3(CO)_{12}$ transfers hydrogen atoms from 2-propanol to *N*-phenylbenzaldimine at 82 °C to give benzyl phenyl amine in 80% yield [311]. A ketimine is reduced by use of $RuCl_2\{P(C_6H_5)_3\}_3$ in 2-propanol containing K_2CO_3, although the yield is less than 60% [312]. The asymmetric version using 2-propanol as a hydrogen donor has not been reported. However, high catalytic activity as well as enantioselectivity is now obtainable by use of 18-electron TsDPEN-RuCl(η^6-arene) complexes and HCOOH/$N(C_2H_5)_3$ as a hydrogen source, as illustrated in Eq. 2.38. A six-membered cyclic imine with R = CH_3 is reduced in the presence of *S,S* catalyst in CH_3CN at 28 °C to give quantitatively (*R*)-salsolidine in 95% *e.e.* [78, 313]. The reaction proceeds in aprotic polar solvents such as CH_3CN, DMF, DMSO, and CH_2Cl_2, and the reactivity and enantioselectivity are highly sensitive to the structures of the η^6-arene and 1,2-diamine ligands. The presence of NH_2 and $ArSO_2$ groups is crucial to achieve a high reactivity. The structure of the Ar group and substitution pattern of the $ArSO_2$ group can be flexibly changed towards the imine substrates. Cyclic imines substituted by alkyl, benzyl, and aryl groups are transformed to the amines in a high optical yield. An indol in 97% *e.e.* is also obtainable [78, 313]. The enantioselectivity in reduction of the imines derived from cyclic and acyclic ketones tends to decrease [314]. A remarkable feature of this reduction is the excellent chemoselectivity for the C=N bond. The reaction of a cyclic imine is >1000-fold faster than that of a structurally related ketone [78, 313], and the C=N/C=O selectivity is even higher than that observed in $NaB(CN)H_3$ reduction (98:1) [315]. Structurally similar aromatic olefins such as α-methylstyrene are inert under the standard conditions.



(2.38)

Chemoselective primary amine synthesis is directly from ketones and ammonia, and is a very challenging project [316]. TolBINAP-Ru complex can catalyze the reductive amination of certain ketones to give the corresponding amines in up to 95% *e.e.* (Eq. 2.39) [317].



(2.39)

2.3.4 Others

Reports on Ru-catalyzed transfer hydrogenation of substrates other than olefins, ketones, aldehydes, and imines are few in number. Carbon tetrachloride is reduced at 80 °C by benzyl alcohol in the presence of $RuCl_3/(n\text{-}C_{10}H_{21})_2(CH_3)_2NBr/Na_2CO_3$ combined catalyst to give chloroform in 93% yield [318]. $RuCl_2\{P(C_6H_5)_3\}_3$ can reduce quinoline and nitrobenzene by using HCOOH as a hydrogen source to give 1,2,3,4-tetrahydroquinoline in 76% yield and aniline in 94% yield, respectively [319].

2.4 Concluding Remarks

In this chapter, we have focused on the Ru-catalyzed hydrogenation and transfer hydrogenation of unsaturated compounds, especially olefins, ketones, and imines to produce alkanes, alcohols, and amines, respectively. Among a variety of Ru catalysts, homogeneous complexes constructed with Ru metal and a phosphorus- and/or nitrogen-containing ligand have the greater potential for control of reactivity, selectivity, and circularity, because molecular catalysts can be basically endowed with any chemical function and three-dimensional structure. Thus, the appropriate installation of a chiral environment on a Ru complex realizes chiral multiplication. Due to such a strong possibilities and the highly basic organic reactions involved, asymmetric hydrogenation or transfer hydrogenation will continue to be a major topic in organic synthesis. During the past two decades, a variety of chiral Ru molecular catalysts have been devised – as described above – and a variety of natural and unnatural chiral compounds are now accessible, in practical purpose, for asymmetric hydrogenations and transfer hydrogenations [5]. There is, however, much room for further development.

Ideal catalysis requires perfect chemo-, regio-, diastereo-, and enantioselectivity, eternal life, no substrate specificity, operational simplicity, safety, and environmental cleanness. Furthermore, the cost of catalysts and substrates, the ease of catalyst recovery, and the product value are also important items when evaluating catalysis.

As catalysis itself is a matter of producing important and useful compounds, it is strongly connected not only with science and technology but also with economy. Ru-catalyzed hydrogenation and transfer hydrogenation have been significantly developed since the first discovery of BINAP-Ru complexes and TsDPEN-Ru complexes, respectively. Although TON of >1 000 000 and a TOF of >100 s^{-1} have been attained with almost perfect selectivity, the scope is still limited. No universal catalyst can exist because unsaturated organic compounds that require selective reduction are so diverse. In addition, the discovery of higher-performance and more powerful catalysts is essential in order to expand the scope of their use, and this will require not only an accumulation of chemical knowledge but also a combinatorial approach using robotics, while computational methodology will also be of great assistance. In this respect, a variety of problems remains to be solved in this field, though undoubtedly great strides will be made in the future.

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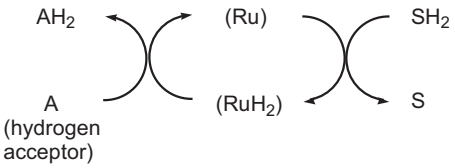
3
Oxidation Reactions

Shun-Ichi Murahashi and Naruyoshi Komiya

3.1
Introduction

Oxidation is one of the most fundamental reactions in organic synthesis. Owing to the current need to develop forward-looking technology that is environmentally acceptable with respect to, for example, negligible formation of inorganic salts and efficient, highly selective formation of products, many aspects must be considered in the search for new catalytic oxidation reactions. Ruthenium catalysts have played an extremely important role in the recent development of such oxidation reactions. The ruthenium-catalyzed oxidation can be classified mainly into two categories: (i) dehydrogenative oxidation; and (ii) oxygenation with metal-oxo and metal-hydroperoxo species [1, 2].

Dehydrogenative oxidation of organic substrates with ruthenium catalysts is important from both biological and industrial aspects. Low-valent ruthenium complexes are excellent catalysts for the dehydrogenation of alcohols because of their low redox potential and high affinity towards oxygen atoms [3]. The basic concept of the catalytic dehydrogenative oxidation of alcohols is shown in Scheme 3.1. Oxidative addition of low-valent ruthenium complex to substrates and β-ruthenium hydride elimination produces dehydrogenated compounds and ruthenium dihydride species, which react with a hydrogen acceptor (A) to afford hydrogenated products (AH_2) and a ruthenium complex catalyst to complete the catalytic cycle.



Scheme 3.1

Oxygenation of a variety of organic compounds can be carried out upon treatment with ruthenium(VIII) tetraoxide (RuO_4), which is generated on treatment of $RuCl_3$ or RuO_2 with an oxidant (XO) such as $NaIO_4$, HIO_4, NaOCl, and $NaBrO_3$ (Scheme 3.2) [4]. In contrast, middle-valent oxo-ruthenium complexes such as porphyrin oxo-ruthenium and nonporphyrin oxo-ruthenium complexes, which can be generated in

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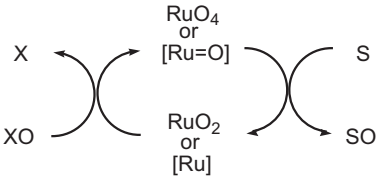
situ upon treatment of low-valent ruthenium complexes with oxidants such as PhIO, R_3NO, *t*-BuOOH, CH_3CO_3H, and H_2O_2 have been used for specific biomimetic, catalytic oxidation reactions [5,6], and often show different reactivities from that of RuO_4. This chapter reviews general and useful ruthenium-catalyzed oxidation reactions.



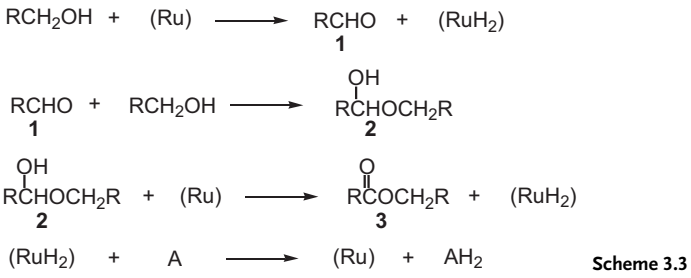
Scheme 3.2

3.2 Dehydrogenative Oxidation

3.2.1 Oxidation of Alcohols

Alcohols are activated with low-valent ruthenium complexes such as $RuH_2(PPh_3)_4$, $RuCl_2(PPh_3)_3$, $Ru_3(CO)_{12}$, $RuClCp(PPh_3)_2$, $[(C_4Ph_4COHOCC_4Ph_4)(\mu\text{-H})][Ru_2(CO)_4]$, and $(\eta^4$-tetracyclone$)(CO)_3Ru$ to give the carbonyl dihydridoruthenium intermediates. Capture of the intermediates with nucleophiles provides novel catalytic oxidative condensation of alcohols. In 1981, Murahashi discovered ruthenium-catalyzed oxidative transformation to esters [7]. Thus, primary alcohols undergo oxidative condensation upon treatment with a low-valent ruthenium complex catalyst to give the corresponding esters along with evolution of molecular hydrogen.

This reaction is simply formulated as shown in Scheme 3.3.

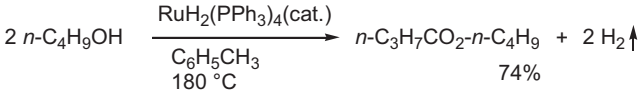


Scheme 3.3

Oxidative addition of primary alcohols to low-valent ruthenium followed by β-ruthenium hydride elimination would give the aldehyde **1** and ruthenium hydride, which reacts with another alcohol to give hemiacetal **2**. Further dehydrogenation of **2** gives the ester **3**. At the same time, reductive elimination from ruthenium dihydride would generate molecular hydrogen and regenerate low-valent ruthenium species to complete the catalytic cycle. When hydrogen acceptor (A) is present in the

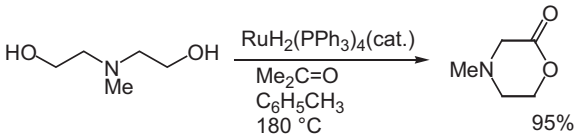
catalytic system, low-valent ruthenium species can be regenerated along with the formation of AH_2, and the reaction proceeds under milder conditions.

The reaction of primary alcohols with $RuH_2(PPh_3)_4$ catalyst gives the corresponding esters with evolution of molecular hydrogen (Eq. 3.1) [7,8]. $Ru(CO)_3(\eta^4$-tetracyclone) [9], $[Ru_2(OAc)_4Cl]$-$PEtPh_2$ [10], and $RuH_2(N_2)(PPh_3)_3$ [11] also catalyze the reaction without hydrogen acceptors, while $Ru_3(CO)_{12}$ requires a stoichiometric amount of diphenylacetylene [12].

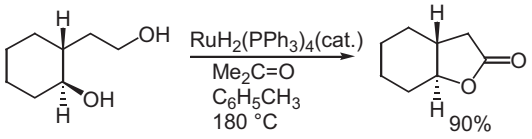


(3.1)

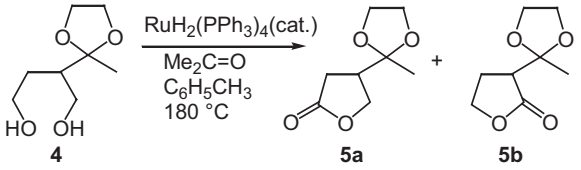
The $RuH_2(PPh_3)_4$-catalyzed reaction is applied to lactone synthesis from 1,4- and 1,5-diols in the presence of a hydrogen acceptor. Murahashi first demonstrated that acetone is an excellent hydrogen acceptor for synthetic purposes [8], although diphenylacetylene [12] and benzylideneacetone [13] are used as hydrogen acceptors. Diethanol amines can be converted very efficiently to morpholine derivatives in the presence of $RuH_2(PPh_3)_4$ catalyst and acetone (Eq. 3.2) [8].



(3.2)



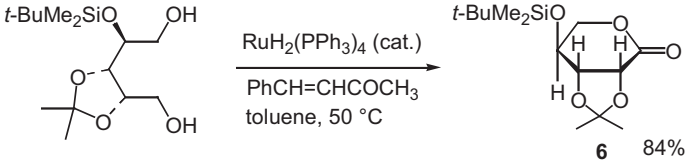
(3.3)



(3.4)

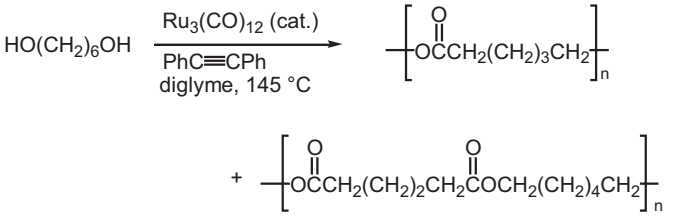
The dehydrogenation reaction is considerably affected by the steric bulkiness around the reaction sites, and generally favors the oxidation of primary hydroxyl groups with extremely high chemoselectivity [14]. Thus, the reaction of *trans*-2-(2-hydroxyethyl)cyclohexanol with $RuH_2(PPh_3)_4$ catalyst in the presence of acetone gives *trans*-hexahydro-2-benzofuranone exclusively (Eq. 3.3) [8]. The treatment of α-substituted diol **4** affords lactone **5** in a ratio of 97:3 (Eq. 3.4) [8]. Since the starting

unsymmetrical diols can be readily prepared by the α-substitution of lactones followed by reduction, the present reactions provide an efficient method for the preparation of β-substituted γ-butyrolactones from α-substituted γ-butyrolactones. This method is applied to the regioselective synthesis of aryl naphthalene ligands such as retrochinensin, justicidin E [15], and L-lyxose derivatives (**6**) (Eq. 3.5) [16].



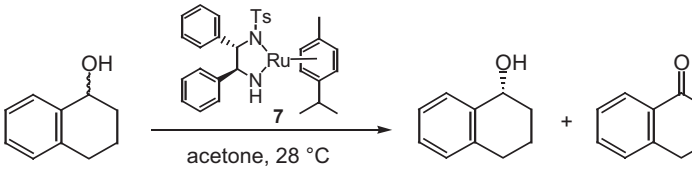
(3.5)

The reaction of a α,ω-diol, which has a longer methylene chain than 1,4- and 1,5-diols, gives the corresponding polyesters (Eq. 3.6) [12b].

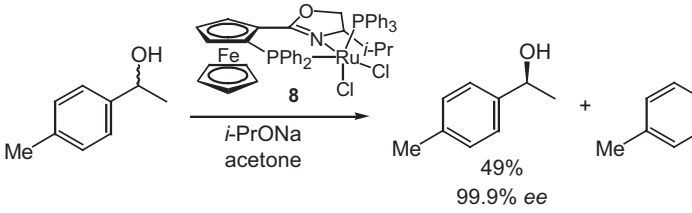


(3.6)

Asymmetric lactonization of prochiral diols has been performed with chiral phosphine complex catalysts $(Ru_2Cl_4((-)\text{-DIOP})_3$ and $[RuCl((S)\text{-BINAP})(C_6H_6)]Cl$ [17, 18]. Kinetic resolution of racemic secondary alcohol was also carried out with chiral ruthenium complexes **7** and **8** in the presence of a hydrogen acceptor, and optically active secondary alcohols were obtained with >99% *e.e.* (Eqs. 3.7 and 3.8) [19, 20].

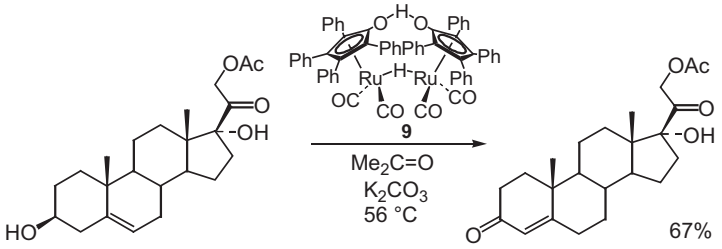


(3.7)



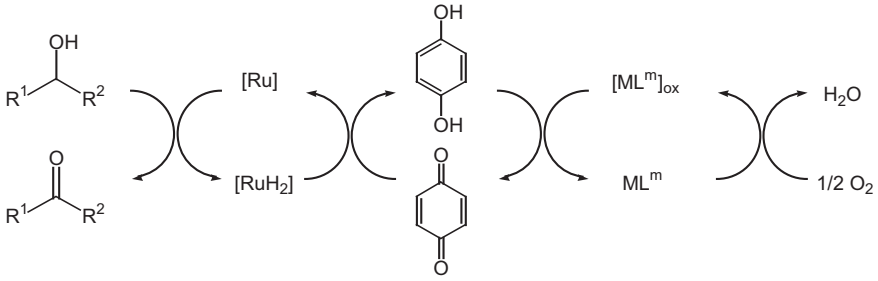
(3.8)

Various aliphatic and alicyclic alcohols are converted into the corresponding ketones and aldehydes upon heating with low-valent ruthenium catalysts such as $RuCl_2(PPh_3)_3$, $RuH_2(PPh_3)_4$, and $[(C_4Ph_4COHOCC_4Ph_4)(\mu\text{-}H)][(CO)_4Ru_2]$ (**9**) and hydrogen acceptors such as benzylideneacetone [21] and acetone [22, 23]. The reaction proceeds under mild conditions, when an inorganic base such as K_2CO_3 is used (Eq. 3.9) [23].



(3.9)

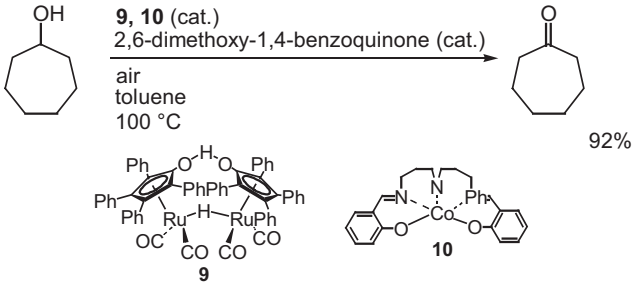
The present hydrogen transfer reaction is extended to the aerobic oxidation of alcohols. Thus, the oxidation of alcohols can be carried out with a catalytic amount of hydrogen acceptor under an O_2 atmosphere by a multistep electron-transfer process. As shown in Scheme 3.4, the ruthenium dihydrides formed during the hydrogen transfer can be regenerated by a multistep electron-transfer process including hydroquinone, ruthenium complex, and molecular oxygen.



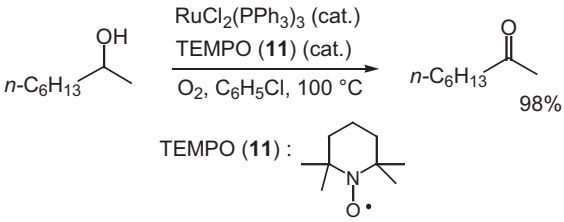
Scheme 3.4

Thus, the reaction of low-valent ruthenium complex [Ru] with alcohol gives ruthenium dihydride $[RuH_2]$, which undergoes hydrogen transfer from quinone to give hydroquinone and [Ru]. The reaction of hydroquinone with second catalyst $[ML_m]_{ox}$ affords quinone and ML_m which regenerates $[ML_m]_{ox}$ with molecular oxygen to complete the catalytic cycle. On the basis of this process, aerobic oxidation of alcohols is performed at ambient pressure of O_2 in the presence of ruthenium–cobalt bimetallic catalysts and hydroquinone [24–26]. Typically, cycloheptanol is oxidized to cycloheptanone under O_2 atmosphere (or MnO_2) with a catalytic system consisting of ruthenium complex **9**, cobalt complex **10**, and 1,4-benzoquinone (Eq. 3.10) [25, 26]. 2,2,6,6-Tetramethylpiperidine-1-oxyl (TEMPO) seems to oxidize ruthenium hydride species to make a multistep electron transfer system. The oxidation of secondary alcohols by a $RuCl_2(PPh_3)_3$-BzOTEMPO-O_2 system gives the corresponding ketones [27]. The combination of $RuCl_2(PPh_3)_3$-TEMPO (**11**) affords a more efficient catalytic

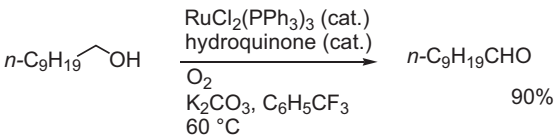
system for the aerobic oxidation of a broad range of primary and secondary alcohols at 100 °C, giving the corresponding aldehydes and ketones, respectively, in >99% selectivity (Eq. 3.11) [28]. The reoxidation of the ruthenium hydride species with TEMPO was proposed in the latter system [28c]. Using trifluoromethyltoluene as a solvent, the aerobic oxidation of primary alcohol was performed by the $RuCl_2(PPh_3)_3$/hydroquinone system (Eq. 3.12) [29].



(3.10)



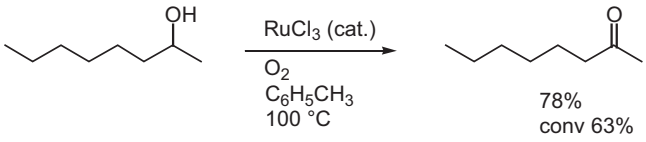
(3.11)



(3.12)

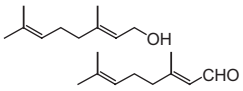
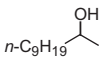
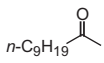
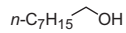
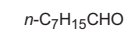
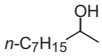
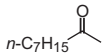
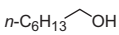
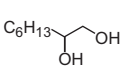
A hydroxycyclopentadienyl ruthenium chloride, (η^5-Ph_4C_4COH)$(CO)_2$RuCl-catalyzed oxidation of alcohols in the presence of chloroform occurs to give carbonyl compounds along with CH_2Cl_2 and HCl [30].

Compared to the multistep electron-transfer process shown in Scheme 3.4, more simple aerobic oxidations of alcohols were reported with various homogeneous and heterogeneous ruthenium catalysts. The aerobic oxidation of alcohols with metal catalysts is an attractive method for economical and environmental reasons. Aerobic oxidation of alcohols can be carried out using $RuCl_3$ catalyst with moderate conversion and selectivities (Eq. 3.13) [31]. Since this reaction was first reported, an arduous search for suitable catalysts has been continuing using various ruthenium complexes (Table 3.1).



(3.13)

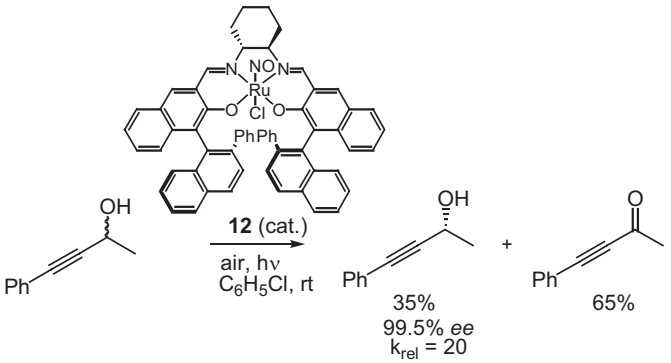
Table 3.1 Aerobic oxidation of alcohols

Entry	Catalyst	Oxidant	Condition	Alcoohol	Product	Yield (%)	Reference
1	$RuCl_2(PPh_3)_3$	O_2	$ClCH_2CH_2Cl$ rt			67	32a
2	RuO_2	O_2	*o*-$C_6H_4Cl_2$ 180 °C			92	33
3	$Ru_3O(O_2CCH_2CH_3)_6(PPh_3)_3$	O_2 (2.7 atm)	65 °C			TON=904	34
4	(*n*-Pr_4N)(RuO_4)	O_2	MS4A $C_6H_5CH_3$ 70 °C			88	35
5	PSP (polymer supported perruthenate)	O_2	$C_6H_5CH_3$ 85 °C			91	36c
6	$[RuCl_2\{p\text{-cymene}\}]_2$	O_2	$CsCO_3$ $C_6H_5CH_3$ 100 °C		PhCHO	91	37a
7	$Bi_{2+x}Ru_{2-x}O_{7-y}$	O_2 (6.8 atm) NaOHaq	40 °C		$NaO_2C(CH_2)_4CO_2Na$	70	38
8	RuHAP	O_2	$C_6H_5CH_3$ 80 °C			96	39c
9	RuO_2-FAU	air	80 °C		*n*-$C_6H_{13}CHO$	98	41
10	$[Ru(dmso)_3Mo_7O_{24}]^{4-}$	O_2 (2 atm)	120 °C			99	42
11	$RuCl_2(PPh_3)_3$/C	O_2	$PhCF_3$ 60 °C		$C_6H_{13}CHO$	77 conv. 92	45

By using $RuCl_2(PPh_3)_3$ [32] and RuO_2 [33] catalysts, activated alcohols such as allyl alcohols and α-ketols can be oxidized aerobically under mild and ambient conditions (Table 3.1; entries 1–2). Trinuclear ruthenium carboxylate, $Ru_3O(O_2CR)_6L_n$ ($L = H_2O$, PPh_3) is an effective catalyst for the aerobic oxidation of aliphatic alcohols (entry 3) [34]. Catalytic activities of these complexes are approximately 10-fold higher than those of $RuCl_3$ and $RuCl_2(PPh_3)_3$. Griffith and Ley and colleagues found that (*n*-Pr_4N)(RuO_4) (TPAP) is highly efficient for the selective oxidation of alcohols with tertiary amine *N*-oxide as an oxidant [36a]; however, the same catalyst was also found to be efficient for the aerobic oxidation of alcohols (entry 4) [35]. A variety of primary and secondary alcohols such as aliphatic, allylic, benzylic, and keto-alcohols can be oxidized at 70–80 °C under an O_2 atmosphere using TPAP as a catalyst. A polymer-supported perruthenate (PSP) and a perruthenate immobilized within MCM-41 can

be used for the heterogeneous oxidation of alcohols (entry 5) [36]. A catalytic system consisting of $[RuCl_2(p\text{-cymene})_2]_2$ and Cs_2CO_3 can be used for the aerobic oxidation of benzylic and allylic alcohols (entry 6) [37]. Vicinal diols undergo rare aerobic oxidative cleavage when heated with a mixed ruthenium metal oxide catalyst [Bi_{2+x}-$Ru_{2-x}O_{7-y}$; $0 < x < 1$; $0 < y < 5$] under high O_2 pressure (entry 7) [38]. Heterogeneous catalysts such as Ru-Al-Mg-hydrotalcites, Ru-Co-Al-hydrotalcites, Ru-hydroxyapatite (RuHAP) (entry 8) [39], Ru-Al_2O_3 [40], RuO_2-FAU (zeolite) (entry 9) [41], and ruthenium-containing polyoxometalate $[Ru(DMSO)_3Mo_7O_{24}]^{4-}$ (entry 10) [42] are highly efficient catalysts for the aerobic oxidation of alcohols. In these oxidation reactions, the key step is postulated to be the reaction of Ru-H with O_2 to form Ru-OOH; this is analogous to Pd-OOH that has been shown to operate in the palladium-catalyzed Wacker-type asymmetric oxidation reaction [43]. RuHAP is also effective for the oxidation of organosilanes to the corresponding silanols [44]. Catalytic oxidative cleavage of vicinal-diols to aldehydes with dioxygen was reported with $RuCl_2(PPh_3)_3$ on active carbon (entry 11) [45]. Ionic liquids such as tetramethyl ammonium hydroxide and Aliquate® 336 can be used as a solvent for the $RuCl_2(PPh_3)_3$-catalyzed aerobic oxidation of alcohols [46]. The heterobimetallic complex ($[(Bu_4N)(M(N)(CH_2SiMe_3)_2(\mu\text{-}O)_2CrO_2)]$ (M = Ru or Os) catalyzes the selective oxidation of alcohols with molecular oxygen [47].

Kinetic resolution of secondary alcohols is performed by asymmetric oxidation using an optically active (nitroso)(salen)ruthenium(II) chloride **12** (Eq. 3.14) [48]. The ruthenium catalyst **12** is also effective for asymmetric imidation of alkyl aryl sulfide [48c].

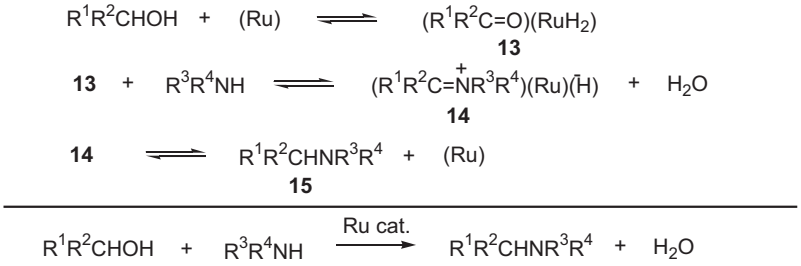


(3.14)

3.2.2 Oxidative Amination of Alcohols

Trapping the carbonyl compound **1** in Scheme 3.3 with various nucleophiles provides various catalytic oxidative transformations of alcohols. When a primary or secondary amine is employed as a nucleophile, intermediate **13** undergoes nucleophilic reaction with amine to give iminium ion complex **14** along with water. Intramolecular hydride transfer of **14** gives the corresponding *N*-alkylated amine **15** with regen-

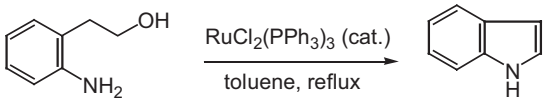
eration of ruthenium active species (Scheme 3.5) [49–56]. Representative results for oxidative amination of alcohols are summarized in Eqs. 3.15 to 3.18.



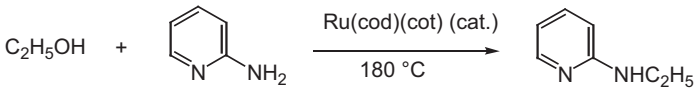
Scheme 3.5

$$n\text{-}C_7H_{15}OH + n\text{-}C_8H_{17}NH_2 \xrightarrow[180\ ^\circ C]{RuH_2(PPh_3)_4\ (cat.)} n\text{-}C_8H_{17}NH\text{-}n\text{-}C_7H_{15} \quad 92\% \qquad (3.15)$$

$$n\text{-}C_3H_7OH + PhNH_2 \xrightarrow[180\ ^\circ C]{RuCl_2(PPh_3)_3\ (cat.)} PhN(n\text{-}C_3H_7)_2 \quad 88\% \qquad (3.16)$$

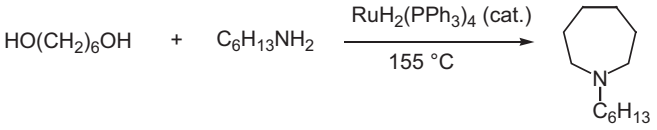


100% (3.17)



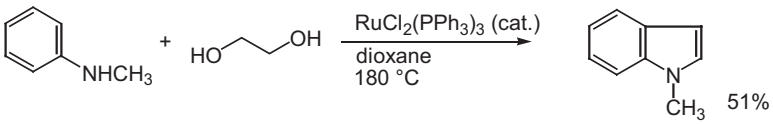
85% (3.18)

The reaction of primary alcohols with aliphatic amines proceeds efficiently with $RuH_2(PPh_3)_4$ catalyst (Eq. 3.15) [49], while $RuCl_2(PPh_3)_3$ is a good catalyst for the reaction with aromatic amines (Eqs. 3.16 and 3.17) [50, 56]. Intramolecular version of this reaction provides a method for synthesis of cyclic amines (Eq. 3.17). Selective *N*-monoalkylation of heteroaromatic primary amines occurs, when Ru(cod)(cot) is used as a catalyst (Eq. 3.18) [52], while similar treatment with $RuCl_2(PPh_3)_3$ or $RuCl_3$-PR_3 catalyst gives the corresponding *N,N*-dialkylated amines. Seven-membered ring can be readily obtained due to the template effect of ruthenium complexes to the difunctional substrates (Eq. 3.19) [49].

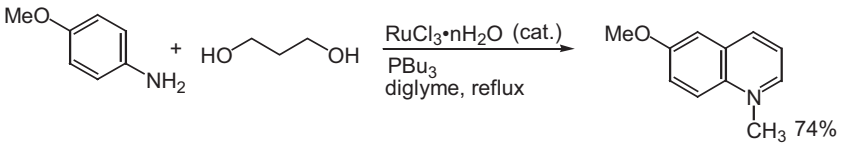


(3.19)

When aromatic amines are allowed to react with allylic alcohols [57], 1,2- [58], and 1,3-diols [59], the corresponding indole and quinoline derivatives are formed (Eqs. 3.20 and 3.21).

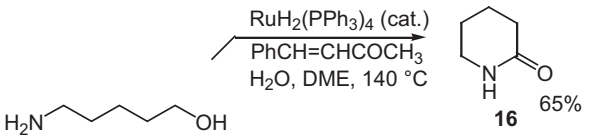


(3.20)

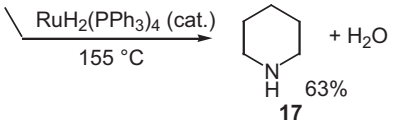


(3.21)

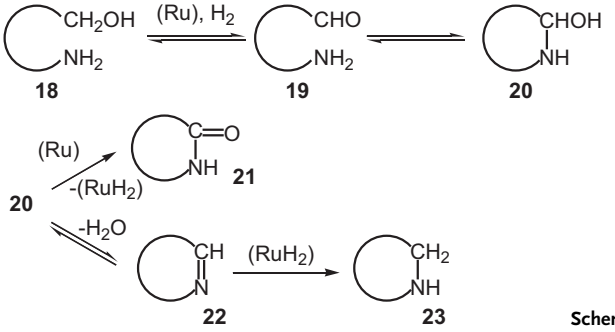
The $RuH_2(PPh_3)_4$-catalyzed reaction of amino alcohols in the presence of a hydrogen acceptor gives the corresponding lactams **16** (Eq. 3.22) [60]. This is principally in contrast to the oxidative cyclization of aminoalcohols without a hydrogen acceptor to afford cyclic amines **17** (Eq. 3.23) [49]. This difference can be rationalized by assuming the mechanism shown in Scheme 3.6. The dehydrogenation of amino alcohol **18** would give amino aldehyde **19**, which undergoes condensation to give intermediate **20**. Further dehydrogenation of **20** in the presence of a hydrogen acceptor gives lactams **21**. In contrast, the reaction without a hydrogen acceptor leads to dehydrogenation of **20**, giving imine **22** which undergoes hydrogenation with (RuH_2) to afford amine **23**.



(3.22)



(3.23)



Scheme 3.6

Primary amides undergo *N*-alkylation by the $RuCl_2(PPh_3)_3$-catalyzed reaction with alcohols (Eq. 3.24) [61, 62]. The $RuH_2(PPh_3)_4$-catalyzed reaction of phenylacetonitrile with ethanol proceeds in the presence of inorganic base to give the corresponding α-ethylated product (Eq. 3.25) [63].

$$\mathrm{Ph{-}C(=O){-}NH_2} + n\text{-}\mathrm{C_8H_{17}OH} \xrightarrow[180\ ^\circ\mathrm{C}]{\mathrm{RuCl_2(PPh_3)_3\ (cat.)}} \mathrm{Ph{-}C(=O){-}NH}\text{-}n\text{-}\mathrm{C_8H_{17}} \quad 76\% \tag{3.24}$$

$$\mathrm{PhCH_2CN} + \mathrm{C_2H_5OH} \xrightarrow[\mathrm{Na_2CO_3,\ reflux}]{\mathrm{RuH_2(PPh_3)_4\ (cat.)}} \mathrm{PhCH(C_2H_5)CN} \quad 92\% \tag{3.25}$$

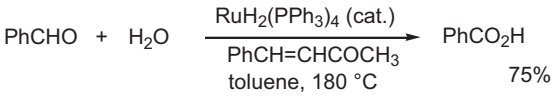
The present principle of the dehydrogenation of alcohols can be applied to catalytic transformations of aldehydes. Esters can be obtained from the reactions of aldehydes with alcohols using $RuH_2(PPh_3)_4$ as catalyst (Eq. 3.26) [8].

$$\mathrm{C_3H_7CHO} + \mathrm{C_4H_9OH} \xrightarrow[\text{toluene, 180 °C}]{\mathrm{RuH_2(PPh_3)_4\ (cat.)}} \mathrm{C_3H_7CO_2C_4H_9} + \mathrm{H_2} \quad 100\% \tag{3.26}$$

A Cannizzaro-type reaction occurs upon treatment of aldehydes with water to give the corresponding esters (Eq. 3.27) [8] or carboxylic acids and alcohols (Eq. 3.28) [64]. In contrast, a similar reaction in the presence of a hydrogen acceptor such as benzylideneacetone affords carboxylic acid selectively (Eq. 3.29) [8].

$$\mathrm{C_3H_7CHO} + \mathrm{H_2O} \xrightarrow[\text{toluene, 180 °C}]{\mathrm{RuH_2(PPh_3)_4\ (cat.)}} \mathrm{C_3H_7CO_2C_4H_9} \quad 65\% \tag{3.27}$$

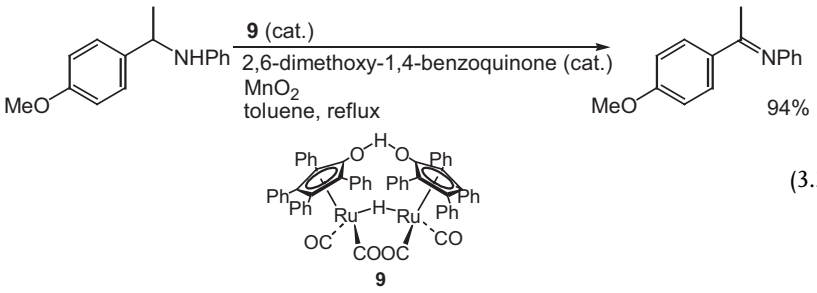
$$\mathrm{CH_3CHO} + \mathrm{H_2O} \xrightarrow[45\ ^\circ\mathrm{C}]{\mathrm{[\{Ru(C_6Me_6)\}_2(OH)_3]Cl\ (cat.)}} \mathrm{CH_3CO_2H} + \mathrm{CH_3CH_2OH} \quad \mathrm{TN{=}2395} \quad \mathrm{TN{=}462} \tag{3.28}$$



(3.29)

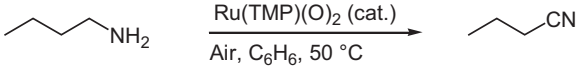
3.2.3
Oxidation of Secondary and Primary Amines

The oxidation of secondary amines to imines can be carried out by hydrogen transfer reaction under mild conditions using a catalytic amount of **9**/2,6-dimethoxy benzoquinone/MnO_2 (Eq. 3.30) [65].



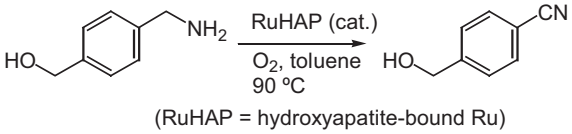
(3.30)

James et al. reported that aerobic oxidation of primary amines in the presence of a ruthenium porphyrin complex Ru(TMP)$(O)_2$ (TMP = tetramesitylporphyrinato) gives nitriles (100%) (Eq. 3.31) [66].

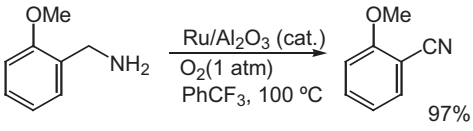


(3.31)

Heterogeneous catalysts such as hydroxyapatite-bound Ru complex [67] and Ru/Al_2O_3 [68] can be also used for the aerobic oxidation of primary amines to nitriles (Eqs. 3.32 and 3.33).



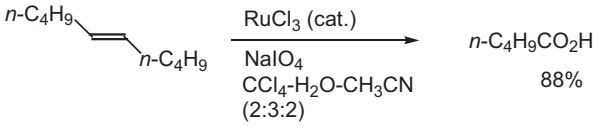
(3.32)



(3.33)

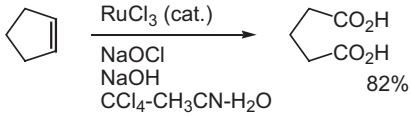
3.3 Oxidation with RuO_4

RuO_4 is a strong oxidant, and is efficient for the oxidation of various substrates such as alcohols, olefins, aromatic rings, and even aliphatic C–H bonds. However, problems such as very slow and incomplete reactions have often been encountered in the oxidations with RuO_4. These sluggish reactions are due to inactivation of ruthenium catalysts by forming low-valent ruthenium carboxylate complexes. The inactivation can be prevented by addition of CH_3CN. Thus, various oxidations with RuO_4 are remarkably improved by employing a solvent system consisting of CCl_4-H_2O-CH_3CN [4c]. Typically, oxidative cleavage of (*E*)-5-decene with $RuCl_3/NaIO_4$ in CCl_4-H_2O-CH_3CN gave pentanoic acid in 88% yield (Eq. 3.34), while the same reaction in a conventional CCl_4-H_2O system gave pentanal (17%) along with 80% of the recovered starting material.

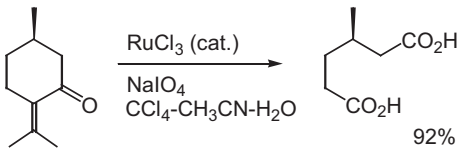


(3.34)

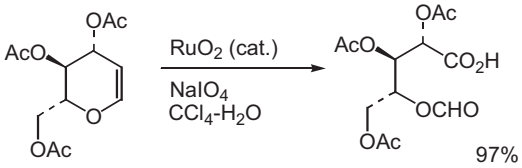
Various substrates such as allyl alcohols, α,β-unsaturated carbonyl compounds, and enol ethers undergo oxidative cleavage to afford the corresponding carbonyl compounds (Eqs. 3.35–3.37) [69–71]. *cis*-Dihydroxylation occurs selectively, when the reaction is carried out in a very short time (0.5 min) at 0 °C in EtOAc-CH_3CN-H_2O (Eq. 3.38) [72].



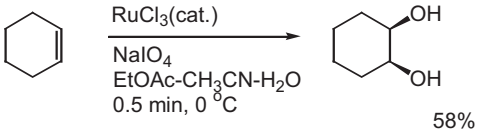
(3.35)



(3.36)

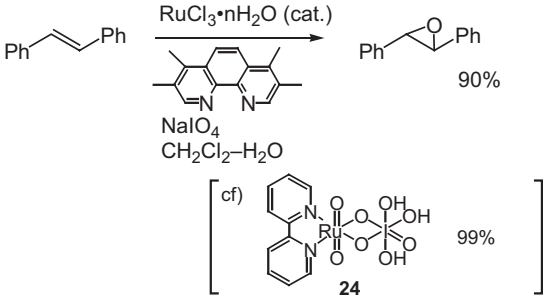


(3.37)



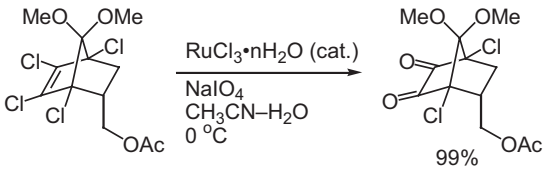
(3.38)

Octavalent RuO_4 generated from $RuCl_3$/hypochlorite or periodate system is usually too reactive, and the C=C bond cleavage is often a major reaction; however, the addition of a bipyridine ligand enables the epoxidation of alkenes, because an electron-donating ligand enhances the electron density on the metal and modulates the reactivity of RuO_4 [73–75]. $RuCl_3$ associated with bipyridyl and phenanthrolines catalyzes the epoxidation of alkenes with sodium periodate (Eq. 3.39) [73]. Dioxoruthenium complex $[RuO_2(bpy)\{IO_3(OH)_3\}]\cdot 1.5H_2O$ (**24**) was isolated by the reaction of RuO_4 with bipyridyl in the presence of $NaIO_4$, and the complex acts as an efficient epoxidation catalyst under similar conditions (Eq. 3.39) [74].



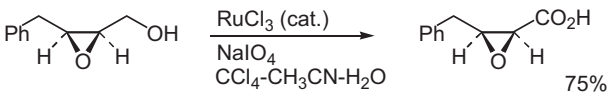
(3.39)

1,2-Dihaloalkenes are oxidized to α-diketones on a variety of norbornyl derivatives, which have been serving as highly potent and inextricable templates for strained polycyclic unnatural compounds (Eq. 3.40) [76].

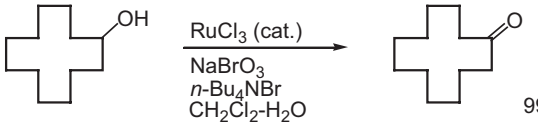


(3.40)

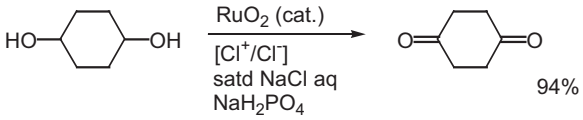
Primary and secondary alcohols are oxidized to the corresponding carboxylic acids and ketones, respectively (Eqs. 3.41 and 3.42) [4c, 77]. Electrooxidation using a double mediatory system consisting of RuO_4/RuO_2 and Cl^+/Cl^- redox couples is also effective for oxidation of alcohols (Eq. 3.43) [77e].



(3.41)

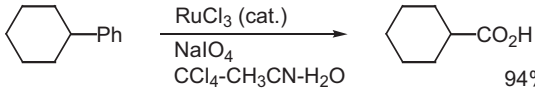


(3.42)

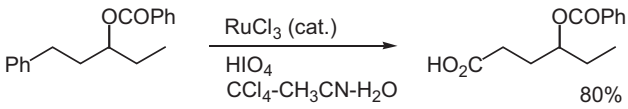


(3.43)

Aromatic rings are smoothly converted to carboxylic acids (Eq. 3.44) [4c, 78]. An alkylphenyl group can be oxidized selectivity in the presence of an electron-deficient phenyl group such as a benzoyl group (Eq. 3.45) [78a].

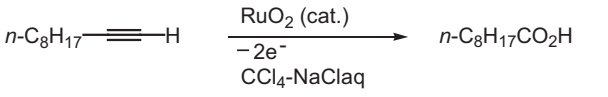


(3.44)

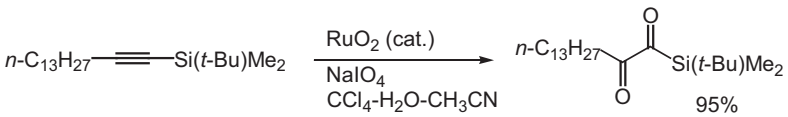


(3.45)

Terminal alkynes undergo the similar oxidative cleavage to afford carboxylic acids (Eq. 3.46), while internal alkynes are converted to diketones (Eq. 3.47) [79].



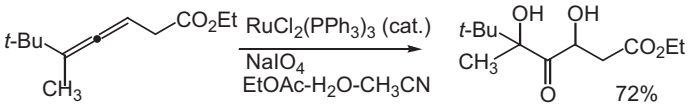
(3.46)



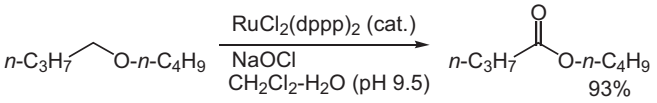
(3.47)

The oxidation of allenes gives α,α'-dihydroxy ketones (Eq. 3.48) [80]. Various heteroatom-containing compounds undergo oxidation of methylene groups at the α-position. Ethers are converted into esters and lactones [81]. The efficiency of the

α-oxidation of ethers was improved by pH control using hypochlorite in biphasic media (Eq. 3.49) [81a].

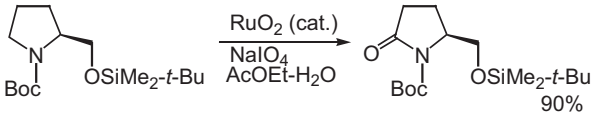


(3.48)

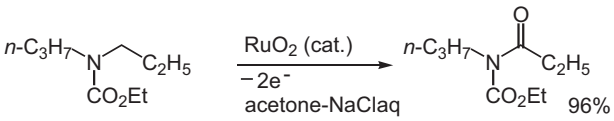


(3.49)

Tertiary amines [82] and amides [83] undergo similar oxygenation reactions at the α-position of nitrogen to afford the corresponding amides and imides, respectively. Oxidation of *N*-protected piperidine derivative using RuO_2 catalyst and $NaIO_4$ in AcOEt gave the corresponding lactam derivative (Eq. 3.50) [83b]. Electrooxidation is useful for the reaction of *N*-protected amines (Eq. 3.51) [82c].

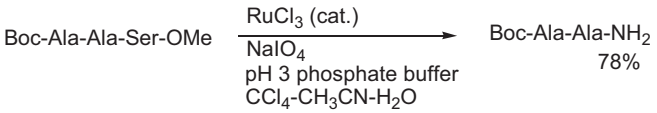


(3.50)



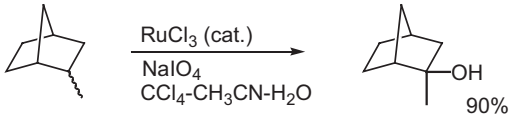
(3.51)

The method is successfully applied to selective N–C bond scission of peptides at serine or threonine residues (Eq. 3.52) [84].

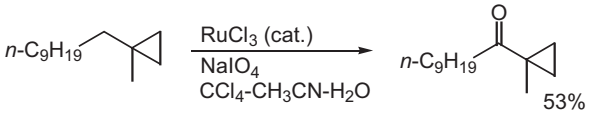


(3.52)

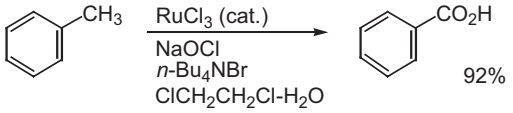
Unactivated alkanes can be oxidized with the $RuCl_3/NaIO_4$ system [85–91]. Tertiary C–H bonds undergo chemoselective hydroxylation to afford the corresponding tertiary alcohols (Eq. 3.53) [85].



(3.53)



(3.54)



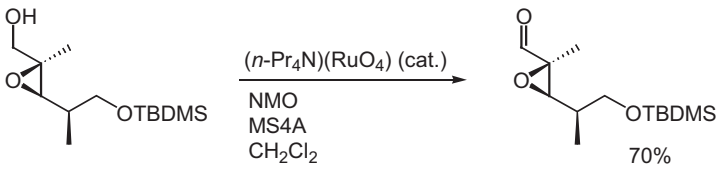
(3.55)

Bridgehead carbons of adamantane [86], pinane [87], and fused norbornanes [85a, 88] undergo selective hydroxylation under similar reaction conditions. Alkyl-substituted cyclopropane is oxidized selectively at the α-position to cyclopropane ring (Eq. 3.54) [89]. The methyl group of toluene can be converted into the corresponding carboxylic acids (Eq. 3.55) [91].

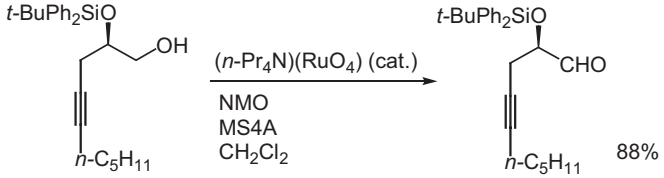
3.4
Oxidation with Ruthenium Complex Catalysts and Oxidants

3.4.1
Oxidation of Alcohols

The oxidizing power of ruthenium complexes can be finely tuned by varying the oxidation state and also the nature of the ligands. The salt of perruthenate ion (Ru(VII)) with a quaternary ammonium salt (n-Pr_4N)(RuO_4) (TPAP), which is soluble in a variety of organic solvents, shows far milder oxidizing properties than RuO_4 [92]. One of the key features of the TPAP system is its ability to tolerate other potentially reactive groups. For example, double bonds, polyenes, enones, halides, cyclopropanes, epoxides, and acetals all remain intact during TPAP oxidation. The oxidation of primary alcohols with TPAP gives the corresponding aldehydes (Eqs. 3.56 and 3.57), whereas RuO_4 oxidation results in the formation of carboxylic acid. NaOCl can be also used as an oxidant for the TPAP-catalyzed oxidation of secondary alcohols [93].



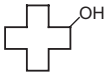
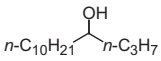
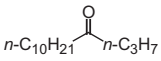
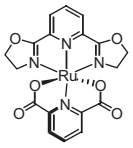
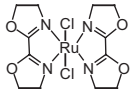
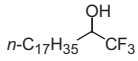
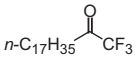
(3.56)



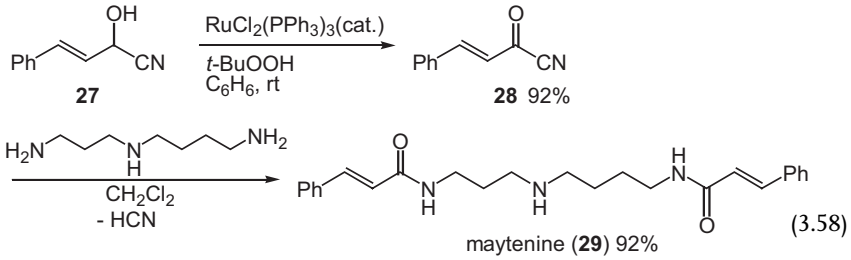
(3.57)

The ruthenium-catalyzed oxidation of alcohols has been reported using various catalytic systems (Table 3.2) which include $RuCl_2(PPh_3)_3$ catalyst with oxidants such as *N*-methylmorpholine *N*-oxide (NMO) (Table 3.2; entry 1) [94], iodosylbenzene (entry 2) [95], TMSOOTMS (entry 3) [96], $RuCl_3$ with hydrogen peroxide (entry 4) [97] and peracetic acid (entry 5) [98], K_2RuO_4 with potassium persulfate (entry 6) [99], Ru(pybox)(Pydic) complex (25) with diacetoxyiodosylbenzene (entry 7) [100], and $RuCl_2(biox)_2$ (26) with $NaIO_4$ (entry 8) [101]. The oxidation of alcohols in water can be carried out using ruthenium-sulfophthalocyanine and oxidants such as hydrogen peroxide or mono-persuflate [102].

Table 3.2 Ruthenium-catalyzed oxidation of alcohols with oxidant

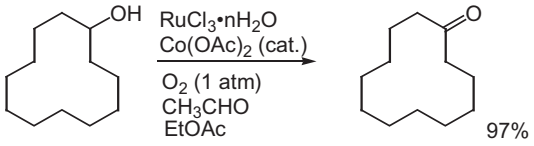
Entry	Catalyst	Condition	Substrate	Product	Yield (%)	Reference
1	$RuCl_2(PPh_3)_3$	NMO acetone			100	94
2	$RuCl_2(PPh_3)_3$	PhIO CH_2Cl_2			84	95
3	$RuCl_2(PPh_3)_3$	$Me_3SiOOSiMe_3$ CH_2Cl_2			83	96
4	$RuCl_3$	H_2O_2 $(n\text{-}C_{10}H_{21})_2(CH_3)_2NBr$ CH_2Cl_2			90	97a
5	$RuCl_3$	CH_3CO_3H AcOEt			95	98
6	K_2RuO_4	$K_2S_2O_8$ Adogen 464 CH_2Cl_2 NaOH aq		PhCHO	92	99b
7	 **25**	$PhI(OAc)_2$ CH_2Cl_2			98	100
8	 **26**	$NaIO_4$ CH_2Cl_2			96	101

The $RuCl_2(PPh_3)_3$-catalyzed reaction of secondary alcohols with *t*-BuOOH gives ketones under mild conditions [103, 104]. This oxidation can be applied to the transformation of cyanohydrins into acyl cyanides [103], which are excellent acylating reagents. Typically, the oxidation of cyanohydrin **27** with 2 equiv. of *t*-BuOOH in dry benzene at room temperature gives benzoyl cyanide (**28**) in 92% yield (Eq. 3.58). It is worth noting that the acyl cyanides thus obtained are excellent reagents for the chemoselective acylation reaction. The reaction of amino alcohols with acyl cyanides gives *N*-acylated amino alcohols selectively. Furthermore, primary amines are selectively acylated in the presence of secondary amines [105]. The use of this reaction has been illustrated by the short-step synthesis of maytenine (**29**) (Eq. 3.58). Ruthenium complexes such as $[Cn^*Ru(CF_3CO_2)_3(H_2O)]$ (Cn^* = *N*,*N*′,*N*″-trimethyl-1,4,7-triazacyclononane) and *cis*-$[Ru(6,6'\text{-}Cl_2bpy)_2O_2](ClO_4)_2$ can be also used for the oxidation of alcohols with *t*-BuOOH [106].



(3.58)

The generation of peracetic acid in situ provides an efficient method for the aerobic oxidation of alcohols. The oxidation of various aliphatic and aromatic alcohols can be carried out at room temperature with molecular oxygen (1 atm) in the presence of acetaldehyde and $RuCl_3$–$Co(OAc)_2$ bimetallic catalyst (Eq. 3.59) [107]. This method is highly convenient, because the products can be readily isolated simply by removal of both acetic acid and the catalyst by washing with a small amount of water. Under the same reaction conditions, primary alcohols are oxidized smoothly to the corresponding carboxylic acids. The present aerobic oxidation can be rationalized by assuming the following two sequential pathways: (i) formation of peracid by a cobalt-catalyzed radical chain reaction of aldehyde with molecular oxygen; and (ii) ruthenium-catalyzed oxidation of alcohol with peracetic acid thus formed.



(3.59)

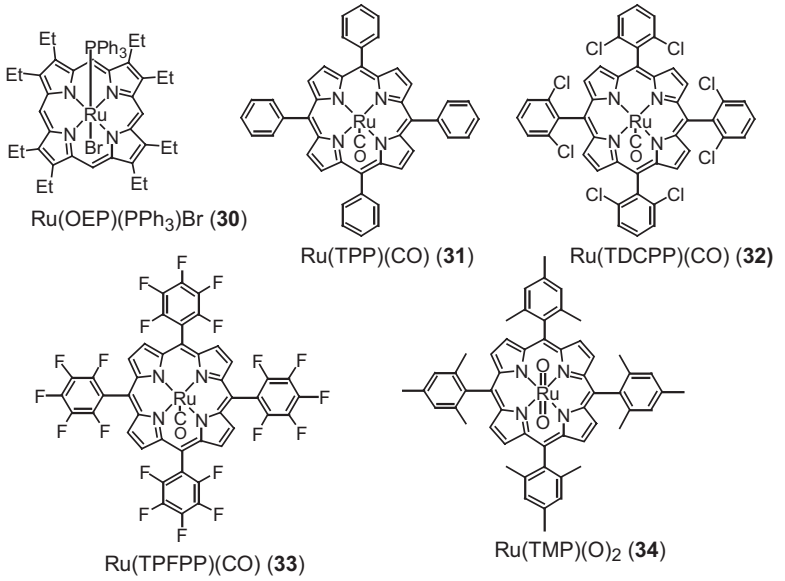
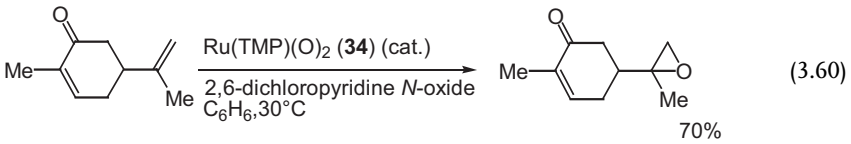
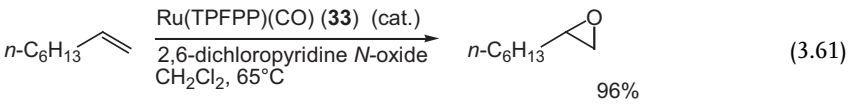


Figure 3.1

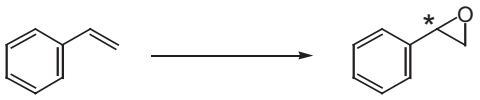
3.4.2 Oxidation of Alkenes

The epoxidation of alkenes with ruthenium porphyrins have been studied as model reactions of cytochrome P-450 (Figure 3.1) [108]. Ruthenium porphyrins such as Ru(OEP)(PPh_3)Br (OEP = octaethylporphyrinato) (**30**) have been examined for the catalytic oxidation of styrene with PhIO [109]. Hirobe et al. [110] and Groves et al. [111] reported that the ruthenium porphyrin-catalyzed oxidation of alkenes with 2,6-dichloropyridine *N*-oxide gives the corresponding epoxides in high yields (Eqs. 3.60 and 3.61). The substituents at the 2 and 6 positions on pyridine *N*-oxide are necessary for high efficiency, because simple pyridine coordinates to the ruthenium more strongly to retard the catalytic activity.

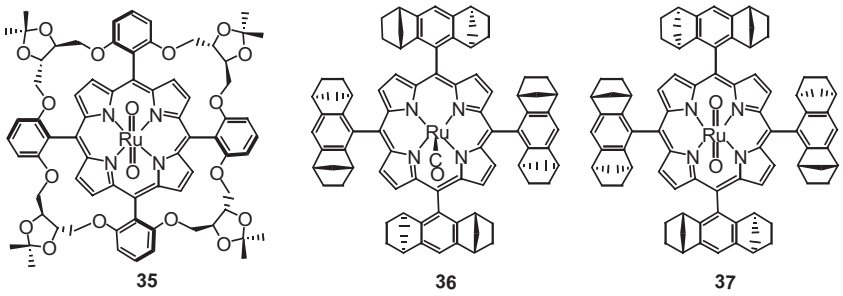




A ruthenium porphyrin complex immobilized in a polymer can be used for catalytic epoxidation with 2,6-dichloropyridine *N*-oxide [112]. Nitrous oxide (N_2O) can be also used as oxidant for the epoxidation of trisubstituted olefins in the presence of ruthenium porphyrin catalyst [113]. Asymmetric epoxidations have been reported using chiral ruthenium porphyrin complexes **35** [114], **36** [115], and **37** [116] (Eq. 3.62).



35 (cat.), 2,6-dichloropyridine *N*-oxide 57% *ee* (*S*)
36 (cat.), 2,6-dichloropyridine *N*-oxide 70% *ee* (*S*)
37 (cat.), O_2 (8 atm) 70% *ee* (*R*)

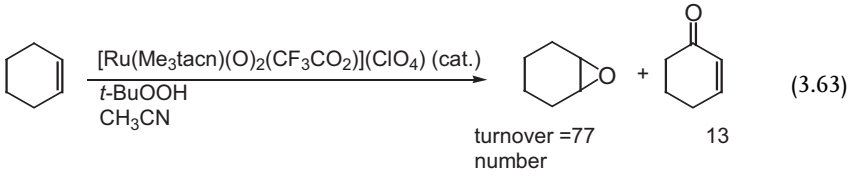


35 **36** **37**

(3.62)

Aerobic oxidation of alkenes with a ruthenium catalyst has been explored by several groups. Groves et al. reported that Ru(TMP)$(O)_2$ (**34**)-catalyzed aerobic epoxidation of alkenes proceeds under 1 atm of molecular oxygen without any reducing agent [111b].

Nonporphyrin ruthenium complexes such as $[RuCl(dpp)_2]$, $[Ru(Me_3tacn)(O)_2(CF_3CO_2)](ClO_4)$, and $[Ru(6,6\text{-}Cl_2bpy)_2(H_2O)_2]$ catalyze the oxidation of alkenes with PhIO [117] or *t*-BuOOH [118] to give the corresponding epoxides in moderate yields (Eq. 3.63).

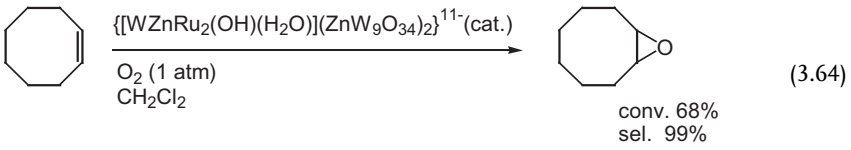


$[Ru(Me_3tacn)(O)_2(CF_3CO_2)](ClO_4)$ (cat.)
t-BuOOH
CH_3CN

turnover number = 77 13

(3.63)

A Ru-containing polyoxometalate, $\{[WZnRu_2(OH)(H_2O)](ZnW_9O_{34})_2\}^{11-}$ (Eq. 3.64) [119] and a sterically hindered ruthenium complex, $[Ru(dmp)_2(CH_3CN)_2](PF_6)$ (dmp = 2,9-dimethyl-1,10-phenanthroline) [120] are effective for the epoxidation with molecular oxygen.



(3.64)

Aqua(phosphine)ruthenium(II) complexes [121] are useful for activation of molecular oxygen, and catalytic oxidation of cyclohexene can be carried out with 1 atm of O_2 [121a,b]. The ruthenium catalyst bearing perfluorinated 1,3-diketone ligands catalyzes the aerobic epoxidation of alkenes in a perfluorinated solvent in the presence of *i*-PrCHO [122]. Asymmetric epoxidations of styrene and stilbene proceed with 56–80% *e.e.* with ruthenium complexes **38**–**40** (Figure 3.2) and oxidants such as $PhI(OAc)_2$, PhIO, 2,6-dichloropyridine *N*-oxide, and molecular oxygen [123–125].

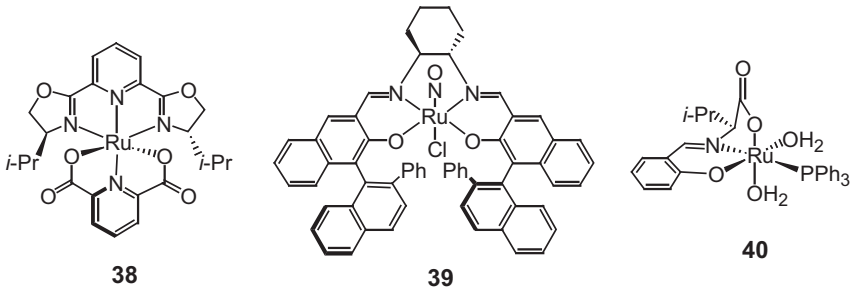
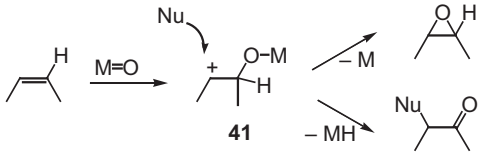


Figure 3.2

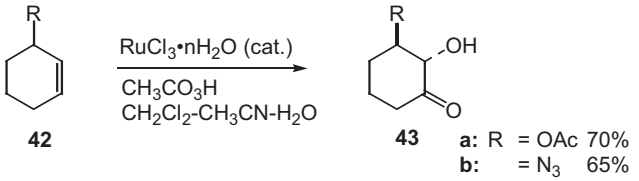
It was postulated that one possible intermediate for metalloporphyrin-promoted epoxidation is intermediate **41** (Scheme 3.7) [126]. If it were possible to trap intermediate **41** with external nucleophiles such as water, a new type of catalytic oxidation of alkenes could be performed.



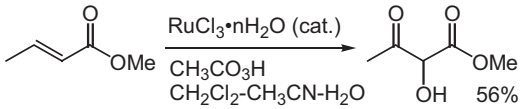
Scheme 3.7

Indeed, a transformation of alkenes to α-ketols was found to proceed highly efficiently. Thus, the low-valent ruthenium-catalyzed oxidation of alkenes with peracetic acid in an aqueous solution under mild conditions gives the corresponding α-ketols, which are important key structures of various biologically active compounds [127]. Typically, the $RuCl_3$-catalyzed oxidation of 3-acetoxy-1-cyclohexene (**42a**) and 3-azide-1-cyclohexene (**42b**) with peracetic acid in CH_2Cl_2-CH_3CN-H_2O (1:1:1) gave (2*S**,3*R**)-3-acetoxy-2-hydroxycyclohexanone (**43a**) and (2*S**, 3*R**)-3-azide-2-hydroxycyclohexanone (**43b**) chemo- and stereoselectively in 70% and 65% yield, respectively

(Eq. 3.65). Similarly, the reaction of methyl crotonate gave the corresponding 2-hydroxy-1,3-dicarbonyl derivative (Eq. 3.66).

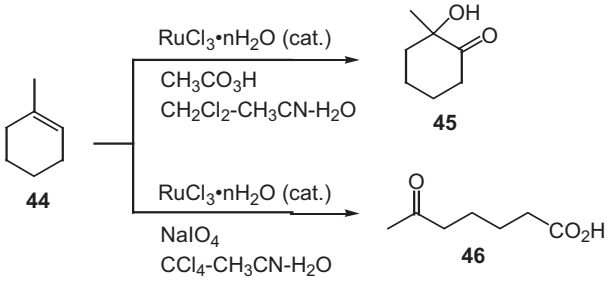


(3.65)



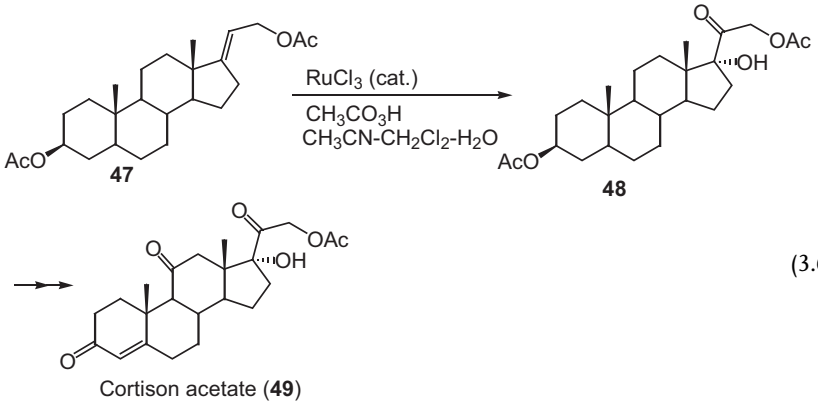
(3.66)

The oxidation, which is quite different from that promoted by RuO_4, is highly useful. Indeed, the oxidation of 1-methylcyclohexene **44** under the conditions gives 2-hydroxy-2-methylcyclohexanone (**45**) (67%), while oxidation of the same substrate **44** under the conditions in which RuO_4 is generated catalytically gives 6-oxoheptanoic acid (**46**) (91%) (Eq. 3.67).



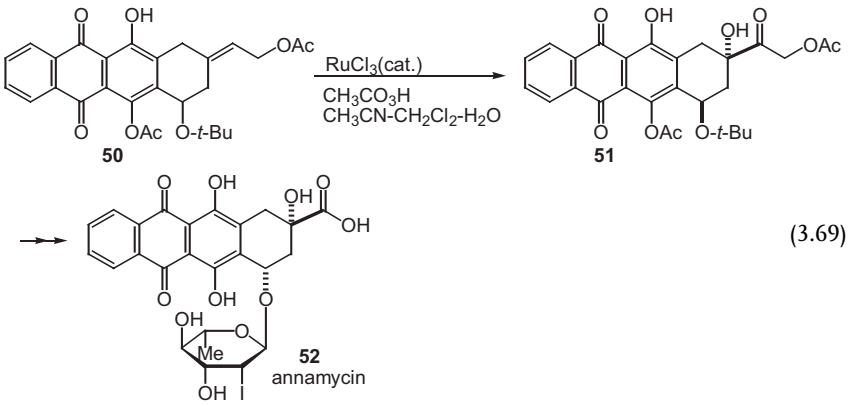
(3.67)

The efficiency of the present reaction has been demonstrated by the synthesis of cortisone acetate **49**, which is a valuable anti-inflammatory agent. The oxidation of 3β,21-diacetoxy-5α-pregn-17-ene (**47**) proceeds stereoselectively to give 20-oxo-5α-pregnane-3β,17α,21-triol 3,21-diacetate (**48**) (57%) (Eq. 3.68). Conventional treatment of **48** followed by microbial oxidation with *Rhizopus nigricaus* gave cortisone acetate **49** [128].



(3.68)

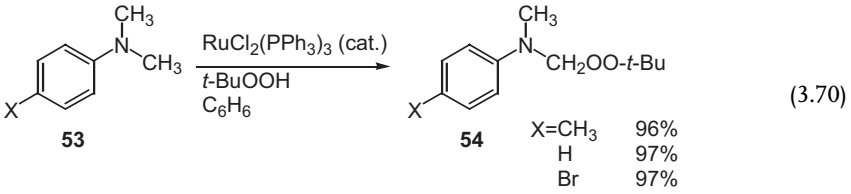
Furthermore, the method can be applied to the synthesis of 4-demethoxyadriamycinone, which is the key structure of the anti-cancer drugs, the adriamycins such as idarubicin and annamycin (**52**) (Eq. 3.69). The ruthenium-catalyzed oxidation of allyl acetate **50** gives the corresponding α-hydroxyketone **51** in 60% yield (Eq. 3.69) [129].



(3.69)

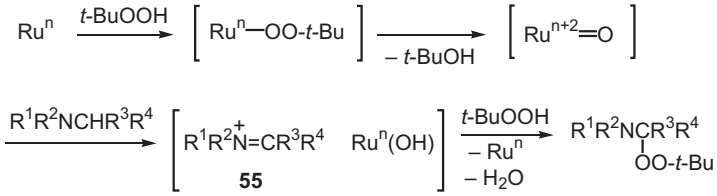
3.4.3 Oxidation of Amines

Selective oxidative demethylation of tertiary methyl amines is one of the specific and important functions of cytochrome P-450. Novel cytochrome P-450-type oxidation behavior with tertiary amines has been found in the catalytic systems of low-valent ruthenium complexes with peroxides. These systems exhibit specific reactivity toward oxidations of nitrogen compounds such as amines and amides, differing from that with RuO_4. It was discovered in 1988 that low-valent ruthenium complex-catalyzed oxidation of tertiary methylamines **53** with *t*-BuOOH gives the corresponding α-(*t*-butyldioxy)alkylamines **54** efficiently (Eq. 3.70) [130]. The hemiaminal type **54** product has a similar structure to α-hydroxymethylamine intermediate derived from the oxidation with cytochrome P-450.



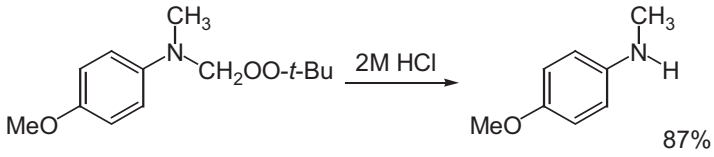
(3.70)

As shown in Scheme 3.8, the catalytic oxidation reactions can be rationalized by assuming the formation of oxo-ruthenium species by the reaction of low-valent ruthenium complexes with peroxides. The C–H activation at the α-position of amines and the subsequent electron transfer gives iminium ion ruthenium complex **55**. Trapping **55** with *t*-BuOOH would afford the corresponding α-*tert*-butylhydroxyamines, water, and low-valent ruthenium complex to complete the catalytic cycle.



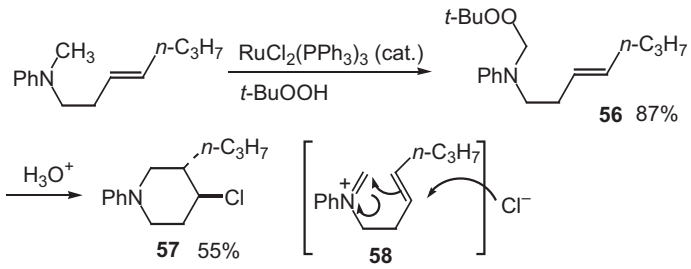
Scheme 3.8

The oxidation of *N*-methylamines provides various useful methods for organic synthesis. Selective demethylation of tertiary methylamines can be carried out by the ruthenium-catalyzed oxidation and subsequent hydrolysis (Eq. 3.71). This is the first synthetically practical method for the *N*-demethylation of tertiary amines. The methyl group is removed chemoselectively in the presence of various alkyl groups.



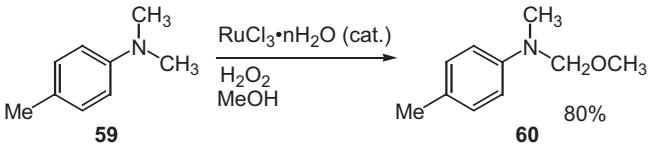
(3.71)

The biomimetic construction of piperidine skeletons from *N*-methylhomoallylamines is performed by means of the ruthenium-catalyzed oxidation and subsequent olefin-iminium ion cyclization reaction. *trans*-1-Phenyl-3-propyl-4-chloropiperidine **57** was obtained from *N*-methyl-*N*-(3-heptenyl)aniline stereoselectively via **56** upon treatment with a 2 *N* HCl solution (Eq. 3.72). This cyclization is the first demonstration of biomimetic formation of piperidine structure using *N*-methyl group, and can be rationalized by assuming the formation of iminium ion **58** by protonation of the oxidation product **56**, subsequent elimination of *t*-BuOOH, nucleophilic attack of an alkene, giving a carbonium ion, which is trapped with Cl^- nucleophile from the less hindered side.



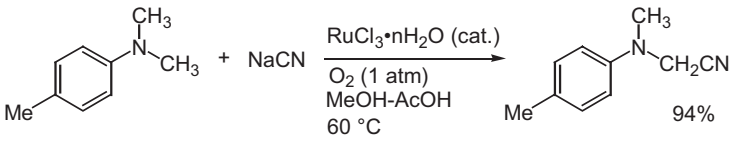
(3.72)

α-Methoxylation of tertiary amines can be carried out upon treatment with hydrogen peroxide in the presence of $RuCl_3$ catalyst in MeOH [131]. Thus, the oxidation of tertiary amine **59** gave the corresponding α-methoxyamine **60** in 80% yield (Eq. 3.73).



59 60 (3.73)

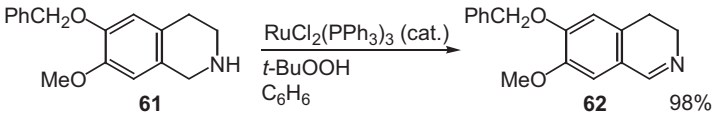
Recently, a new type of reaction – that is, aerobic oxidative cyanation of tertiary amines – was discovered. In this reaction, oxidation with molecular oxygen in place of peroxides, in addition to direct carbon–carbon bond formation by trapping of the iminium ion intermediates with a carbon nucleophile under oxidative conditions, is accomplished simultaneously. The ruthenium-catalyzed oxidation of tertiary amines with molecular oxygen (1 atom) in the presence of sodium cyanide gives the corresponding α-aminonitriles (Eq. 3.74) [132], which are useful for synthesis of α-amino acids and 1,2-diamines.



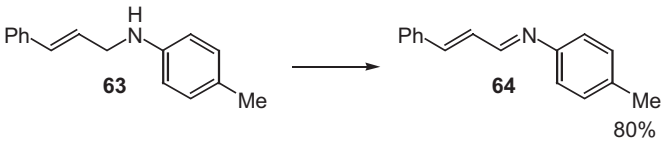
(3.74)

Tertiary amine *N*-oxides can be prepared from the corresponding tertiary amines by $RuCl_3$-catalyzed oxidation with molecular oxygen [133].

Secondary amines can be converted into the corresponding imines, in a highly efficient single step, upon treatment with 2 equiv. of *t*-BuOOH in benzene in the presence of $RuCl_2(PPh_3)_3$ catalyst at room temperature [134]. This is the first catalytic oxidative transformation of secondary amines to imines, which are hardly accessible by conventional methods. A 4Å molecular sieve is needed to prevent the hydrolysis of product imines in some cases. The oxidations of tetrahydroisoquinoline **61** and allylamine **63** gave the corresponding cyclic imine **62** and azadiene **64** in 98% and 80% yields, respectively (Eqs. 3.75 and 3.76).



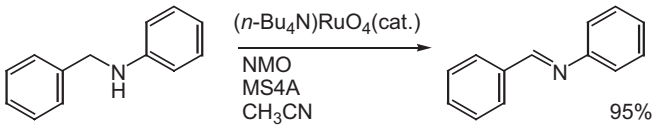
61 62 (3.75)



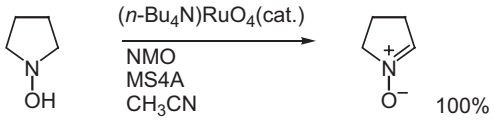
63 64 (3.76)

The catalytic system consisting of (n-Pr_4N)RuO_4 and *N*-methylmorpholine *N*-oxide (NMO) can be also used for oxidative transformation of secondary amines to im-

ines (Eq. 3.77) [135a]. Potassium ruthenate (K_2RuO_4) was used as a catalyst for oxidation of benzylamine with $K_2S_2O_8$ to give benzonitrile [99a]. The ruthenium-catalyzed oxidation of *N*-hydroxyl amines with NMO to nitrones occurs (Eq. 3.78) [135b], although these reactions can be carried out upon treatment with palladium catalyst without oxidant [136].



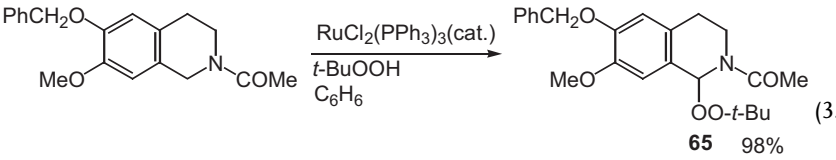
(3.77)



(3.78)

3.4.4
Oxidation of Amides and β-Lactams

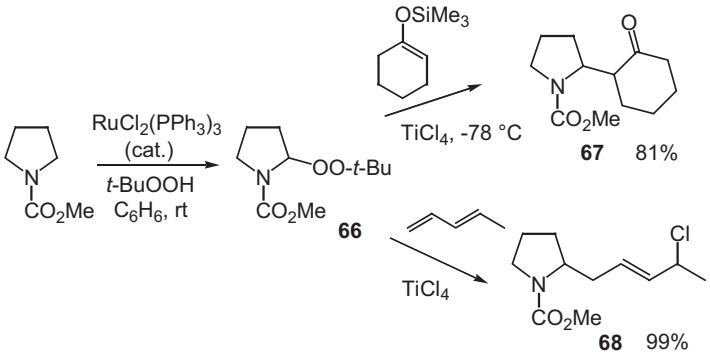
The C–H activation of amides by oxidation is an attractive strategy for the synthesis of biologically active nitrogen compounds. The oxidation of amides is difficult because of low reactivity in comparison with amines. However, the $RuCl_2(PPh_3)_3$-catalyzed oxidation of amides with *t*-BuOOH proceeds under mild conditions to give the corresponding α-(*t*-butyldioxy)amides in a highly efficient manner (Eq. 3.79) [137]. The *t*-butyldioxy amide of the isoquinoline **65** is an important synthetic intermediate of natural product.



65 98%

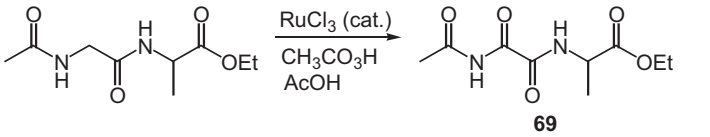
(3.79)

Since the Lewis acid-promoted reactions of the oxidized products with nucleophiles give the corresponding *N*-acyl-α-substituted amines efficiently, the present reactions provide a versatile method for selective C–H activation and C–C bond formation at the α-position of amides [138]. Typically, $TiCl_4$-promoted reaction of α-*t*-butyldioxypyrrolidine **66**, which can be obtained by the ruthenium-catalyzed oxidation of 1-(methoxycarbonyl)pyrrolidine with *t*-BuOOH, with a silyl enol ether gave keto amide **67** (81%), while the similar reaction with less reactive 1,3-diene gave α-substituted amide **68** (Eq. 3.80).



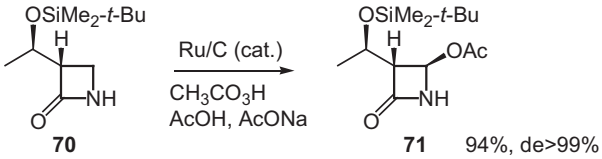
(3.80)

The oxidative modification of peptides is a most interesting topic, but there is no suitable method available. The ruthenium-catalyzed oxidation with peracetic acid provides a useful method for modification. For example, the reaction of *N*,*C*-protected peptides containing glycine residues with peracetic acid in the presence of $RuCl_3$ catalyst gives α-ketoamides **69** derived from oxidation at the C^{α} position of the glycine residue selectively (81%, conv. 70%) (Eq. 3.81) [139].



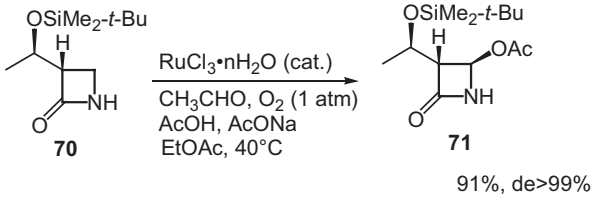
(3.81)

One of the most challenging topics among the oxidation of amides is the catalytic oxidation of β-lactams. Such an oxidation requires specific reaction conditions because of the high strain of the four-membered rings. The first direct oxidation of β-lactams was discovered in 1990 [137], when the ruthenium-catalyzed oxidation of β-lactams with peracetic acid in acetic acid was successfully carried out under mild conditions. The products obtained are highly versatile and key intermediates for the synthesis of antibiotics. Thus, the ruthenium-catalyzed oxidation of (1′*R*,3*S*)-3-[1′-(*tert*-butyldimethylsilyloxy)ethyl]azetidin-2-one (**70**) with peracetic acid in acetic acid in the presence of sodium acetate at room temperature gives the corresponding 4-acetoxy-2-azetidinone **71**, which is a versatile and key intermediate for the synthesis of carbapenem antibiotics, with extremely high diastereoselectivity (94%, >99% *d.e.*) (Eq. 3.82) [137]. This reaction has been used as an industrial process to produce **71** (60 t/year), and has also been applied to the stereoselective synthesis of 3-amino-4-acetoxyazetidinones [140].



(3.82)

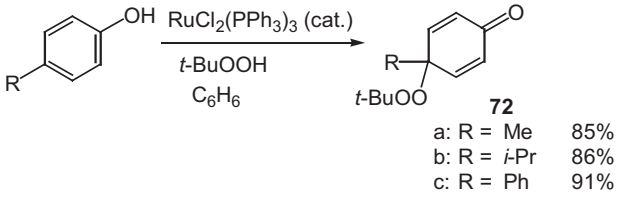
The oxidation reaction of β-lactams can be extended to the aerobic oxidation reaction [141]. Typically, the $RuCl_3$-catalyzed oxidation of β-lactam **70** with molecular oxygen (1 atm) in the presence of acetaldehyde and sodium carboxylate gave the corresponding 4-acyloxy β-lactam **71** in 91% yields (*d.e.* >99%) (Eq. 3.83). This aerobic oxidation gives peracetic acid in situ by ruthenium-catalyzed reaction of acetaldehyde with molecular oxygen, and hence similar results with those obtained by the oxidation with peracetic acid.



(3.83)

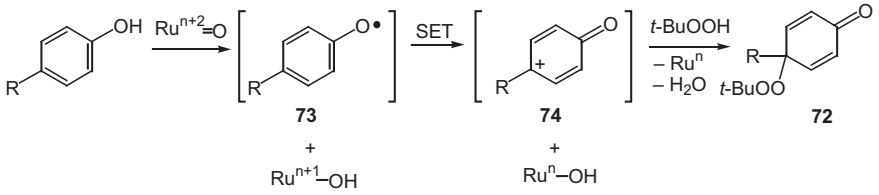
3.4.5 Oxidation of Phenols

The oxidative transformation of phenols is of importance in view of biological and synthetic aspects. However, the oxidation of phenols generally lacks selectivity because of coupling reactions caused by phenoxyl radicals, and selective oxidation of phenols is limited to the phenols bearing bulky substituents at the 2- and 6-positions [142]. It was discovered in 1996 that a biomimetic and selective oxidation of phenols can be carried out using ruthenium catalysts. Thus, the oxidation of *p*-substituted phenols bearing no substituent at the 2- and 6-positions with *t*-BuOOH in the presence of $RuCl_2(PPh_3)_3$ catalyst gives the corresponding 4-(*tert*-butyldioxy)cyclohexadienones selectively (Eq. 3.84) [143].



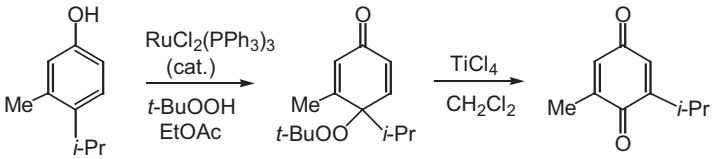
(3.84)

The reaction can be rationalized by assuming the mechanism which involves oxo-ruthenium complex (Scheme 3.9). Hydrogen abstraction with oxo-ruthenium species gives phenoxyl radical **73**, which undergoes fast electron transfer to the ruthenium to give a cationic intermediate **74**. Nucleophilic reaction with the second molecule of *t*-BuOOH gives the product **72**.



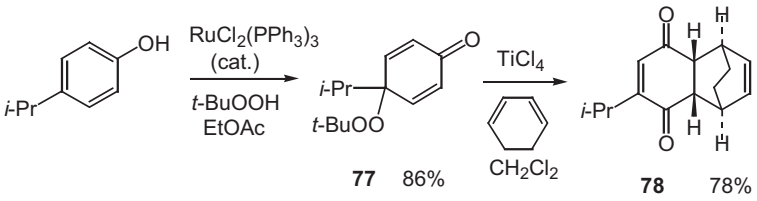
Scheme 3.9

The 4-(*tert*-butyldioxy)-4-alkylcyclohexadienones **72** thus obtained are versatile synthetic intermediates. The $TiCl_4$-promoted transformation of **75**, obtained from the oxidation of 3-methyl-4-isopropylphenol gives 2,6-disubstituted quinone **76** (93%), which is derived from the rearrangement of *i*-Pr group of **75** (Eq. 3.85).



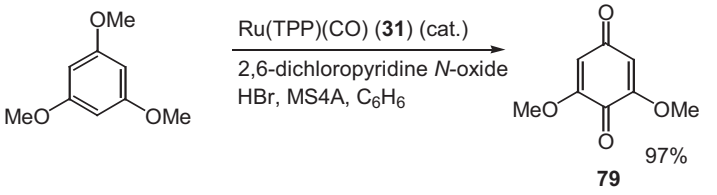
(3.85)

Interestingly, sequential migration-Diels–Alder reactions of *tert*-butyldioxy dienone **77** in the presence of 1,3-cyclohexadiene gave *cis*-fused octahydroanthraquinone **78** stereoselectively (78%) (Eq. 3.86).



(3.86)

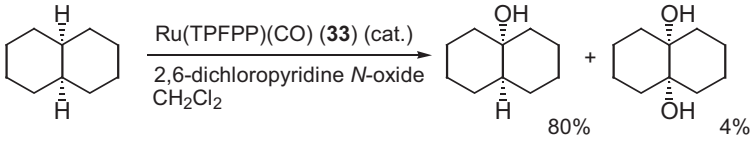
The oxidation of aromatic rings bearing methoxy groups was performed using a ruthenium porphyrin catalyst. The Ru(TPP)(CO) **31** (TPP = 5,10,15,20-tetraphenylporphyrinato)-catalyzed oxidation of polymethoxybenzene with 2,6-dichloropyridine *N*-oxide gives the corresponding *p*-quinone derivatives **79** (Eq. 3.87) [144]. The ^{18}O labeling experiments showed that the reaction proceeds via selective hydroxylation of the aromatic ring by oxo-ruthenium porphyrins to afford phenol derivatives, which undergo subsequent oxidation to afford the corresponding quinones.



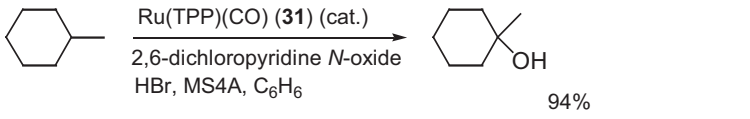
(3.87)

3.4.6
Oxidation of Hydrocarbons

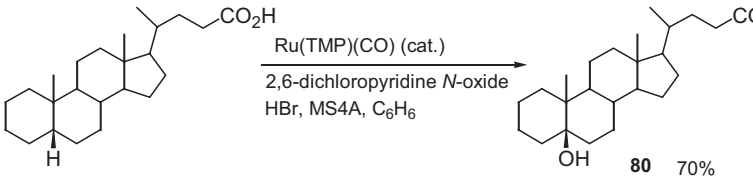
The catalytic oxidation of hydrocarbons can also be performed by ruthenium catalyzed oxidations with peroxides. Ruthenium porphyrins such as $Ru(OEP)(PPh_3)_3$ shows the catalytic activity for the oxidation of alkanes with PhIO [109]. The oxidation of alkanes with 2,6-dichloropyridine *N*-oxide in the presence of $Ru(TMP)(O)_2$ (**34**)/HBr [145] and Ru(TPFPP)(CO) (**33**) [111a] gives the corresponding oxidized compounds (Eqs. 3.88 and 3.89). These reactions are useful for oxidation of tertiary C–H bond, and the addition of small amounts of acids such as HCl and HBr enhances the efficiency of the reaction. For example, hydroxylation of methylcyclohexane was achieved with high selectivity and high efficiency (Eq. 3.89) [145a]. The oxidation of steroids such as 5β-cholan-24-oic acid proceeds selectively to give **80**, with retention of the configuration at the 5-position (Eq. 3.90) [145b].



(3.88)



(3.89)

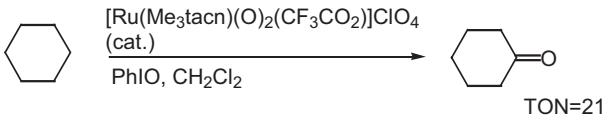


(3.90)

Zeolite-encapsulated perfluorinated ruthenium phthalocyanines catalyze the oxidation of cyclohexane with *t*-BuOOH [146]. A dioxoruthenium complex with a D_4-chiral porphyrin ligand has been used for the enantioselective hydroxylation of ethylbenzene to give α-phenylethyl alcohol with 72% *e.e.* [147].

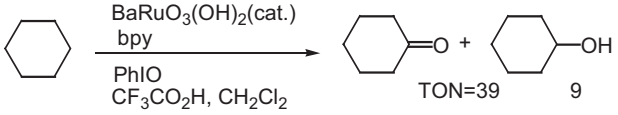
Nonporphyrin ruthenium complexes can be used for the catalytic oxidation of alkanes with peroxides. The combinations of *cis*-$[Ru(Me_3tacn)(O)_2(CF_3CO_2)]^+$/PhIO (Eq. 3.91) [118a], $BaRuO_3(OH)_2$/PhIO (Eq. 3.92) [148], *cis*-$[Ru(dmp)_2(MeCN)_2]^{2+}$/H_2O_2 (Eq. 3.93) [120a], *cis*-$[Ru(6,6\text{-}Cl_2bpy)_2(OH_2)_2]^{2+}$/*t*-BuOOH [118b], and $[RuCl(dpp)_2]^+$/PhIO (or LiClO) [117] are efficient for the oxidation of cyclohexane and adamantane. Ruthenium(III) complexes such as $[RuCl_2(TPA)]^+$ and $[RuCl(Me_2SO)(TPA)]^+$ bearing tripodal ligand TPA (TPA = tris(2-pyridylmethyl)amine) were synthesized, and catalytic oxidation of adamantane with *m*-chloroperbenzoic

acid was reported [149, 150]. Polyoxometalate $[SiRu(H_2O)W_{11}O_{39}]^{5-}$ also functions as an oxidation catalyst with $KHSO_5$ [151a] and H_2O_2 [151b].



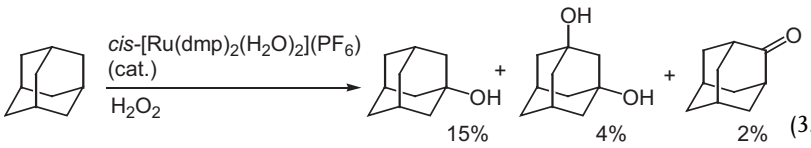
(3.91)

Me_3tacn = 1,4,7-trimethyl-1,4,7-triazacyclononane



(3.92)

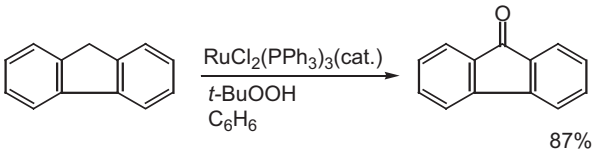
bpy = 2,2'-bipyridine



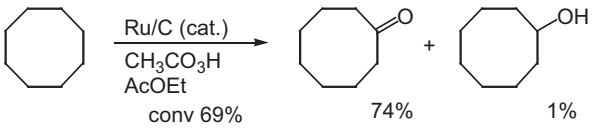
(3.93)

dmp = 2,9-dimethyl-1,10-phenanthroline

The oxidation of hydrocarbons with ruthenium catalysts bearing a simple ligand is highly effective. Thus, the oxidations of hydrocarbons with peroxides such as *t*-BuOOH and peracetic acid in the presence of ruthenium catalysts such as $RuCl_2(PPh_3)_3$ [152a,b] or Ru/C [152a,c] gave the corresponding ketones and alcohols efficiently. The former catalytic system is effective for oxidation of arylhydrocarbons, while the latter system is convenient to aliphatic hydrocarbons. For example, the $RuCl_2(PPh_3)_3$-catalyzed oxidation of fluorene with *t*-BuOOH gives fluorenone in 87% yield (Eq. 3.94). The Ru/C-catalyzed oxidation of cyclohexane with peracetic acid in ethyl acetate gives cychohexanone and cyclohexanol in 74% yield (Eq. 3.95).



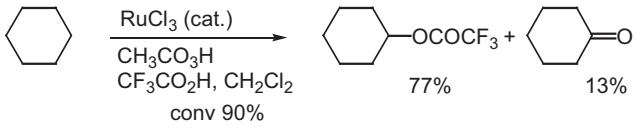
(3.94)



(3.95)

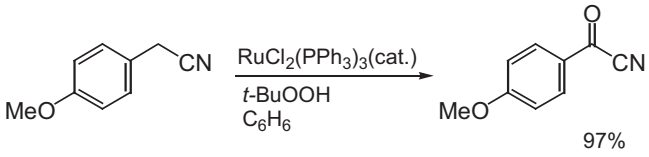
It is expected that more reactive species will be generated in the presence of a strong acid. Indeed, the $RuCl_3 \cdot nH_2O$-catalyzed oxidation of cyclohexane in trifluoro-

acetic acid and dichloromethane (5:1) with peracetic acid gives cyclohexyl trifluoroacetate in 77% yield along with cyclohexanone (13% yield) (Eq. 3.96) [152a]. The total yield of the oxidized products is 90%.

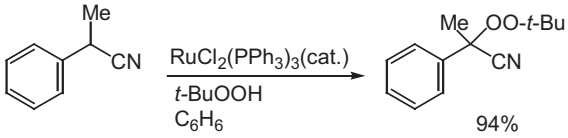


(3.96)

The ruthenium-catalyzed oxidation of nitriles takes place at the α-position to nitriles. For example, the $RuCl_3 \cdot nH_2O$-catalyzed oxidation of *p*-methoxybenzylcyanide with *t*-BuOOH gives the corresponding benzoylcyanide in 97% yield (Eq. 3.97) [153]. Oxidation of nitriles bearing α-substituents gives the corresponding 2-(*tert*-butyldioxy)alkanenitriles (Eq. 3.98).

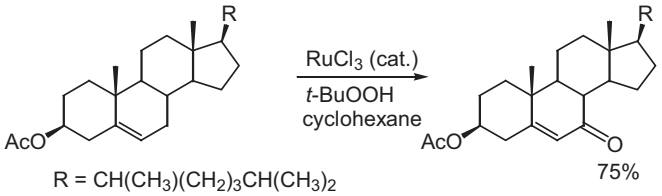


(3.97)



(3.98)

The allylic position of steroidal alkene can be oxidized with *t*-BuOOH in the presence of $RuCl_3$ catalyst (Eq. 3.99) [154].

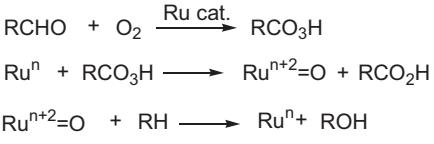


(3.99)

The catalytic oxidation of alkanes with molecular oxygen under mild conditions is an especially rewarding goal, as the direct functionalization of unactivated C–H bonds of saturated hydrocarbons usually requires drastic conditions such as high temperature.

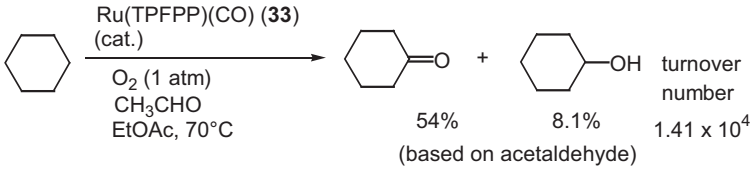
Nonporphyrin-based oxo-metal species can be generated by the reaction of a low-valent ruthenium complex with molecular oxygen in the presence of an aldehyde [141]. Thus, the ruthenium-catalyzed oxidation of alkanes with molecular oxygen in the presence of acetaldehyde gives alcohols and ketones efficiently [155]. These aerobic oxidations can be rationalized by assuming the sequence shown in Scheme 3.10.

The metal-catalyzed reaction of an aldehyde with molecular oxygen affords the corresponding peracid. The reaction of low-valent ruthenium catalyst with the peracid thus formed would give an oxo-ruthenium intermediate, followed by oxygen atom transfer to afford the corresponding alcohols. The alcohol is further oxidized to the corresponding ketone under the reaction conditions.



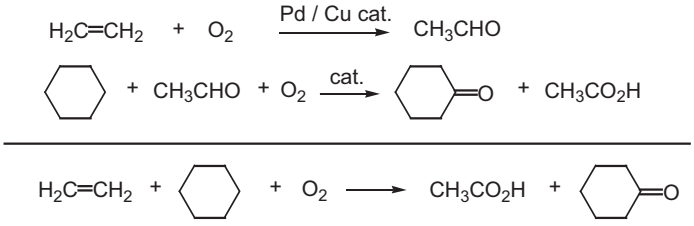
Scheme 3.10

We prepared Ru(TPFPP)(CO) (**33**) complex for the first time, and showed it to be an efficient catalyst for the aerobic oxidation of alkanes using acetaldehyde [156]. Thus, the **33**-catalyzed oxidation of cyclohexane with molecular oxygen in the presence of acetaldehyde gave cyclohexanone and cyclohexanol in 62% yields based on acetaldehyde with high turnover numbers of 14 000 (Eq. 3.100).



(3.100)

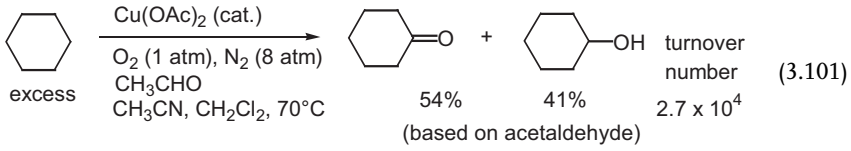
These oxidation reactions provide a powerful strategy for the synthesis of cyclohexanone by a combination of Wacker oxidation of ethylene with the present metal-catalyzed oxidation of cyclohexane (Scheme 3.11).



Scheme 3.11

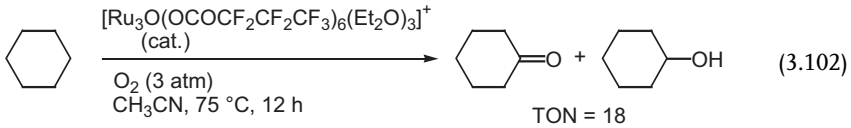
Recently, we found that a copper catalyst – as well as ruthenium – is effective for the oxidation of alkanes with molecular oxygen in the presence of acetaldehyde [157]. The catalytic system $CuCl_2$ and 18-crown-6 has proved to be efficient [157c]. Furthermore, we found that specific copper complexes derived from copper salts and acetonitrile are convenient and highly useful catalysts for the aerobic oxidation of unactivated hydrocarbons [158]. For example, oxidation of cyclohexane with molecular oxygen (1 atm of O_2 diluted with 8 atm of N_2) in the presence of acetaldehyde and $Cu(OAc)_2$ catalyst (0.0025 mol%) in CH_3CN/CH_2Cl_2 (3:2) at 70 °C in an

autoclave proceeded efficiently (95% based on acetaldehyde), with an extremely high turnover number (27 000) (Eq. 3.101) [158].

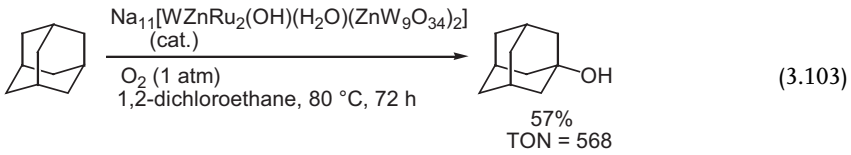


(3.101)

Very few methods have been reported for direct aerobic oxidation of alkanes using a perfluorinated ruthenium catalyst $[Ru_3O(OCOCF_2CF_2CF_3)_6(Et_2O)_3]^+$ [120c] and a ruthenium-substituted polyoxometalate $[WZnRu_2(OH)(H_2O)(ZnW_9O_{34})_2]^{11-}$ (Eqs. 3.102 and 3.103) [159, 160].



(3.102)



(3.103)

3.5 Conclusions

This chapter highlights the ruthenium-catalyzed dehydrogenative oxidation and oxygenation reactions. Dehydrogenative oxidation is especially useful for the oxidation of alcohols, and a variety of products such as ketones, aldehydes, and esters can be obtained. Oxygenation with oxo-ruthenium species derived from ruthenium and peroxides or molecular oxygen has resulted in the discovery of new types of biomimetic catalytic oxidation reactions of amines, amides, β-lactams, alcohols, phenols, and even nonactivated hydrocarbons under extremely mild conditions. These catalytic oxidations are both practical and useful, and ruthenium-catalyzed oxidations will clearly provide a variety of future processes.

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4
Carbon–Carbon Bond Formations via Ruthenacycle Intermediates

Yoshihiko Yamamoto and Kenji Itoh

Abstract

Metallacycles, which are carbocyclic system with at least one atom being replaced by a metal element, are fascinating building blocks, as they have two or more reactive metal-carbon bonds in their cyclic frameworks. Numerous transition metal-catalyzed multi-component coupling reactions have been developed utilizing metallacycle intermediates. Within the past decade, selective and atom-economical C–C bond-forming reactions have also been realized by means of ruthenium catalysis involving ruthenacycle intermediates. Ruthenacyclopentadienes and -trienes are key intermediates for recently developed Ru-catalyzed alkyne cyclotrimerizations, cyclocotrimerizations of alkynes with other unsaturated molecules, and other alkyne coupling reactions. The [2 + 2] cycloaddition and the Alder-ene reaction of alkynes and alkenes, and the Pauson-Khand reaction were explained in terms of the intermediary of ruthenacyclopentenes. Ruthenacyclopentanes and ruthenacyclopentenediones have also been considered to play central roles in recently reported alkene coupling reactions or the cycloaddition of cyclobutenediones and cyclopropenones. This chapter outlines the recent advances in the catalytic carbon-carbon bond formations via ruthenacycle intermediates.

4.1
Introduction

Metallacycles have been claimed to play pivotal roles in many transition metal-mediated multi-component coupling reactions [1]. For example, [2 + 2 + 2] alkyne cyclotrimerization leading to benzenes – the Reppe reaction – has been considered to proceed via metallacyclopentadiene and elusive metallacycloheptatriene intermediates ("common mechanism"), while metallacyclopentenes have been proposed as intermediates for the [2 + 2 + 1] cyclo-coupling reactions of an alkyne, an alkene, and CO leading to a cyclopentenone (the Pauson-Khand reaction). A metallacyclic compound – which is defined here as a carbocyclic system with one atom replaced by a transition metal element – can be generally formed by oxidative cyclization of two unsaturated molecules with a low-valent transition metal fragment [2–4]. Alter-

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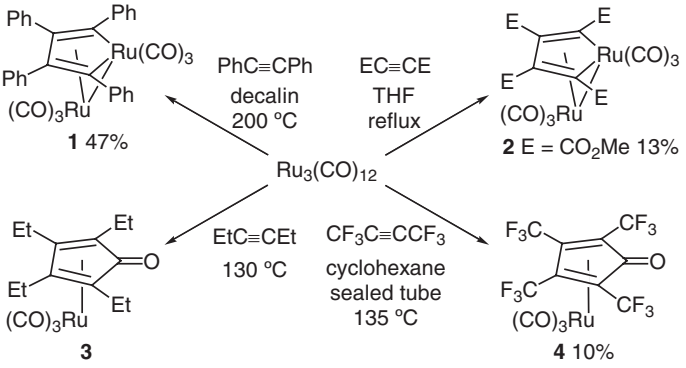
natively, the reaction of an anionic complex with a dielectrophile such as dihalides or disulfonates, and the transmetallation of a dimetallic reagent with transition metal elements give rise to a metallacycle that cannot be obtained from the oxidative cyclization [3, 4]. The insertion of a transition metal complex into a small carbocyclic ring also generates a metallacycle species via carbon-carbon bond fission [3–5]. Metallacycles generated thereby can be further transformed into useful organic materials, with or without the participation of other organic molecules. In this context, numerous synthetic technologies have been developed by utilizing a broad range of reactive metallacycles. However, synthetic potentials of ruthenacycles have remained less explored until quite recently [6], except for metathesis reactions involving ruthenacyclobutane intermediates [7]. This chapter outlines the recent advances in the catalytic carbon-carbon bond formations via ruthenacycle intermediates. Ruthenium-catalyzed metathesis reactions were not included, as many excellent reviews on metathesis reactions have been produced [8].

4.2
C–C Bond Formations Involving Ruthenacyclopentadiene/Ruthenacyclopentatriene

4.2.1
Alkyne Cyclotrimerizations

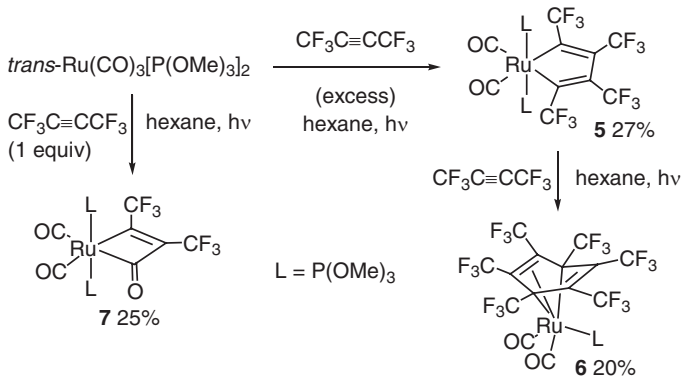
As mentioned above, the intermediary of metallacyclopentadienes has been widely recognized in many [2 + 2 + 2] cyclotrimerizations of alkynes and related cyclocotrimerizations [9]. Metallacyclopentadienes are generally produced by the oxidative cyclization of two alkyne molecules on a low-valent metal center. Various ruthenacyclopentadienes were synthesized by this method. For example, heating a decalin solution of $Ru_3(CO)_{12}$ and diphenylacetylene at 200 °C gave rise to the dinuclear ruthenacyclopentadiene complex **1** (Scheme 4.1) [10]. The similar dinuclear complex **2** was obtained from dimethyl acetylenedicarboxylate (DMAD) at lower temperature [11]. Dinuclear ruthenacyclopentadienes were also obtained, when conjugated



Scheme 4.1

dienes were reacted with $Ru_3(CO)_{12}$ at 140 °C in isooctane [12]. On the other hand, 3-hexyne or hexafluoro-2-butyne gave rise to cyclopentadienone complexes **3** [10] and **4** [13], respectively, probably via CO insertion/reductive elimination from the corresponding ruthenacyclopentadienes (Scheme 4.1).

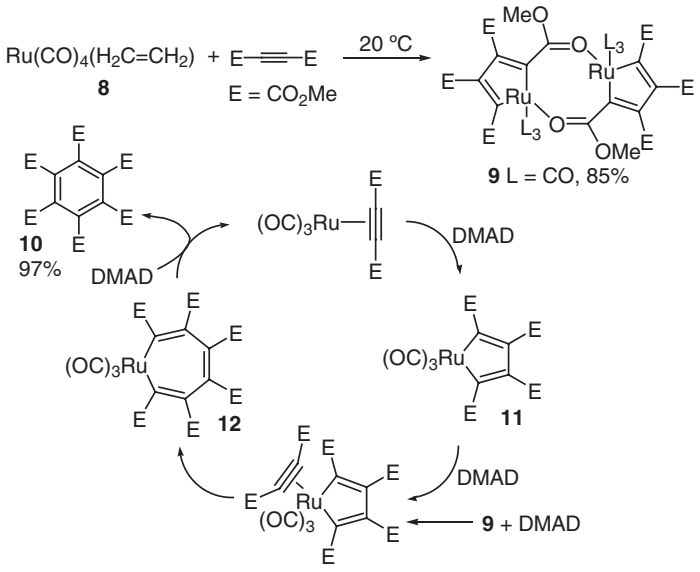
In contrast to the above thermal reactions, [*trans*-$Ru(CO)_3\{P(OMe)_3\}_2$] was irradiated in the presence of excess hexafluoro-2-butyne to afford the mononuclear ruthenacyclopentadiene **5**, which was further converted into the arene complex **6** upon irradiation with the alkyne (Scheme 4.2) [14]. Thus, the stoichiometric cyclotrimerization of hexafluoro-2-butyne was accomplished in a stepwise manner. By contrast, only 1 equiv. of the alkyne gave the ruthenacyclobutene **7** under similar conditions.



Scheme 4.2

Since the first discovery of Reppe [15], numerous transition-metal elements have been found to catalyze alkyne cyclotrimerizations [9]. In particular, much attention has focused on Group 9 and 10 transition elements such as Co, Rh, Ni, and Pd. With respect to Group 8 triads, some stoichiometric [14, 16] and catalytic [17–19] cyclotrimerizations with limited scope have been reported to date. Ru^0 and Os^0 catalysts have been confined to cyclotrimerizations of electron-deficient alkynes such as acetylenedicarboxylic acid esters and propiolates [17, 18], while the Fe^0-catalyzed cyclotrimerization of some electronically neutral alkynes was reported relatively recently [19]. The ruthenium(0) ethylene complex **8** was reacted with DMAD to give rise to the dimeric ruthenacyclopentadiene complex **9** (Scheme 4.3) [18]. Using **9** as catalyst precursor, the catalytic cyclotrimerization of DMAD proceeded at 80 °C to afford hexamethyl mellitate **10** almost quantitatively. Coordinatively unsaturated monomeric ruthenacyclopentadiene **11** and ruthenacycloheptatriene **12** might be involved in the catalytic cycle.

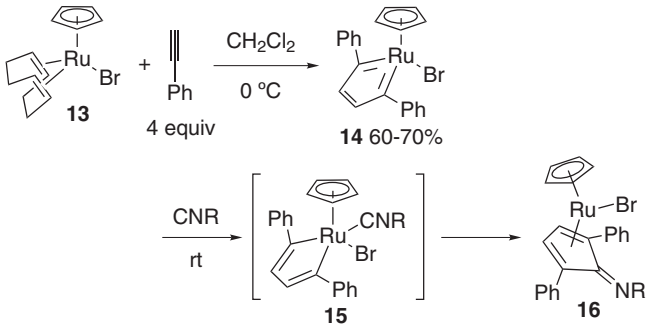
In contrast to the above ruthenium(0) complexes, the reaction of the Ru(II) complex **13**, bearing a cyclopentadienyl (Cp) ligand, with electronically neutral phenylacetylene gave rise to the coordinatively unsaturated ruthenacycle **14** (Scheme 4.4) [20]. On the basis of X-ray structural analysis, the original authors claimed that **14** is the first formally 18-electron ruthenium(II)-*metallacyclopentatriene*. In accordance with this claim, the ^{13}C NMR resonance corresponding to the metal-carbene α car-



Scheme 4.3

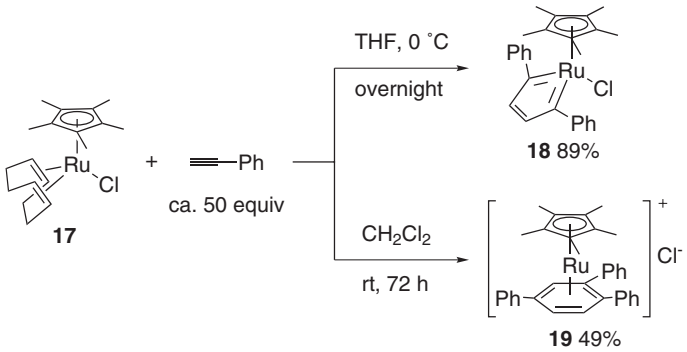
bons was observed at δ 271.1 ppm. However, **14** may be better described as a five-membered aromatic metallole, because it has a planar metallacycle structure with the Ru–Cα bond length of 1.942(6) Å, which is slightly longer than those of the typical Ru=C double bonds (1.83–1.91 Å). The Cα–Cβ and Cβ–Cβ bond lengths of 1.403(8) and 1.377(12) Å, respectively, are very close to that of benzene (1.40 Å). Such a highly delocalized structure is distinct from other metallacyclopentatriene complexes [21].

Upon treatment with 1 equiv. of ligand (L) in $CDCl_3$ at 25 °C, **14** was converted into saturated 18-electron metallacyclopentadiene complexes, [CpRu(L)($C_4Ph_2H_2$)Br] (L = morpholine, $P(OMe)_3$, PMe_2Ph) [20]. Consequently, the resonance of the metallacycle α carbons moved to upfield (δ 201.3 ppm for L = morpholine). On the other hand, the reaction of **14** with a stoichiometric amount of isocyanides at room temperature gave imino-2,5-diphenylcyclopentadiene complexes **16** instead of isocyanide complexes **15** (Scheme 4.4) [22]. Similarly, the reaction with CO gave rise to the corresponding cyclopentadienone complex [22].



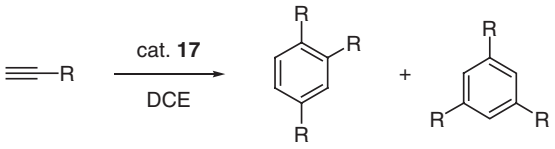
Scheme 4.4

The pentamethylcyclopentadienyl (Cp*) analogue of the ruthenacyclopentatriene was also obtained from [Cp*RuCl(tmeda)] (tmeda = $Me_2NCH_2CH_2NMe_2$) and phenylacetylene [23]. Similarly, the 1,5-cyclooctadiene (cod) complex **17** afforded the ruthenacyclopentatriene **18** in 89% yield, upon treatment with excess phenylacetylene at 0 °C in THF (Scheme 4.5) [24]. The X-ray analysis of **18** showed that it has a highly delocalized ruthenacycle structure quite similar to **14**: the Ru–Cα, Cα–Cβ and Cβ-Cβ bond lengths are 1.969(4), 1.402(7), and 1.37(1) Å, respectively. Moreover, the prolonged reaction of **17** with excess phenylacetylene in CH_2Cl_2 at room temperature gave rise to the cationic arene complex **19** in 49% yield (Scheme 4.5) [24]. The coordinated arene moiety was probably formed by [2 + 2 + 2] cyclotrimerization of phenylacetylene via the ruthenacycle **18**.



Scheme 4.5

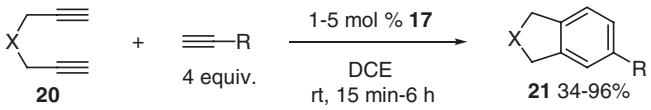
The formation of **19** suggests that alkyne cyclotrimerization might take place under mild conditions, although a catalytic reaction was not realized by means of the combination of **17** and phenylacetylene. This is because the formation of the stable cationic arene complex prevents the restoration of a catalytically active species under these conditions. However, more reactive alkynes would undergo catalytic cyclotrimerization without forming the corresponding stable arene complexes. Indeed, hexamethyl mellitate was obtained in 88% yield, when highly active DMAD was treated with 1 mol% **17** in 1,2-dichloroethane (DCE) even at room temperature for 1 h [25]. Similarly, ethyl propiolate gave both 1,2,4- and 1,3,5-regioisomers of triethyl benzenetricarboxylate in 61 and 28% yields, respectively (Scheme 4.6). The practical advantage of the ruthenium(II) catalyst is elucidated by these cyclotrimerizations proceeding without heating. In contrast, cyclotrimerization of a nonactivated alkyne, methyl propargyl ether, resulted in the decrease of the total yield, as well as the complete loss of regioselectivity even with a higher catalyst loading and elevated temperature of 50 °C. This inferior efficacy might be ascribed to the inefficient oxidative cyclization of the nonactivated alkyne with lower electron-accommodating ability than those of DMAD or ethyl propiolate.



R = CO_2Et: 1 mol % Ru, rt, 1 h; 61% + 28%
R = CH_2OMe: 5 mol % Ru, 50 °C, 1 day; 19% + 20%

Scheme 4.6

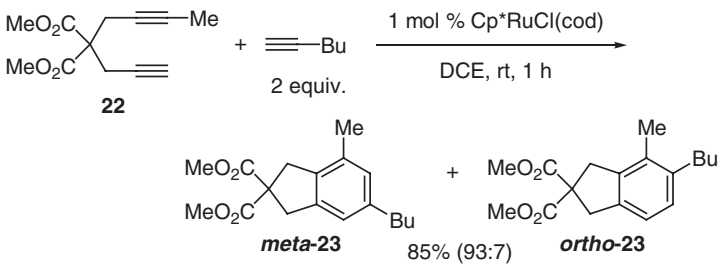
In order to improve the catalytic efficiency, 1,6-diynes **20** were employed together with a variety of monoalkynes (Scheme 4.7) [25]. Such 1,6-diynes were expected to make the oxidative cyclization step entropically favorable. In fact, the malonate-derived diyne **20** (X = $C(CO_2Me)_2$) and 4 equiv. of 1-hexyne was reacted in the presence of 1 mol% **17** at ambient temperature to afford selectively the desired indan derivative **21** (X = $C(CO_2Me)_2$, R = *n*-Bu) in 94% yield. This partially intramolecular cyclotrimerization was successfully applied to various monoalkynes possessing ether, alcohol, amine, and chloride functionalities, as well as parent acetylene (1 atm). The wide functional group compatibility of [Cp*RuCl(cod)] precatalyst **17** was also well exemplified by the reaction of various diynes **20** having ester, ketone, nitrile, amine, ether, and sulfide functionalities.



X = $C(CO_2Me)_2$, $C(COMe)_2$, $C(CN)_2$, NBn, NTs, O, S etc
R = H, Bu, *t*-Bu, Ph, CH_2OH, CH_2NMe_2, $(CH_2)_3Cl$

Scheme 4.7

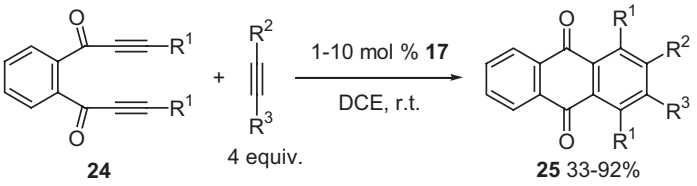
In a similar manner, the cycloaddition of the 1,6-octadiyne **22** with 1-hexyne proceeded in the presence of 1 mol% **17** at ambient temperature for 1 h (Scheme 4.8) [25]. As a consequence, the desired cycloadduct **23** was obtained in 85% yield with the excellent regioselectivity of *meta*:*ortho* = 93:7. A similar yield and regioselectivity (81%, *meta*:*ortho* = 94:6) were obtained, when a ruthenium(III) complex, $[(Cp^*RuCl_2)_2]$, was employed. Replacement of the Cp* ligand in **17** by a less sterically demanding and less electron-releasing Cp ligand in [CpRuCl(cod)] decreased



Scheme 4.8

the regioselectivity (*meta*:*ortho* = 87:13), as well as the reactivity. In contrast, the cycloaddition of **22** and 1-hexyne by means of readily available precatalysts based on Rh, Ni, and Co resulted in lower selectivity. These results showed that the excellent regioselectivity predominantly furnishing the *meta*-isomer is the significant merit of the [Cp*RuCl] catalyst.

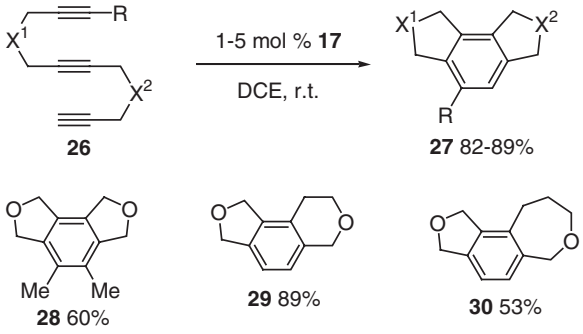
The ruthenium catalysis also proved to be effective for the anthraquinone annulation by means of the cycloaddition of 1,2-bis(propiolyl)benzene **24** with a monoalkyne (Scheme 4.9) [26]. Such an anthraquinone annulation was first realized by the stoichiometric reaction of isolated naphthoquinone-fused rhodacyclopentadiene complexes with monoalkynes [27], or the direct coupling of diketodiyne and monoalkynes with highly toxic [$Ni(CO)_4$] in large excess [28]. From the viewpoint of environmental safety, an alternative *catalytic* protocol is highly desirable. In this context, some research groups reported catalytic versions of anthraquinone annulations using Ni [29], Co [30], and Rh [31] precatalysts. These existing examples, however, have some disadvantages: (1) sub-stoichiometric amounts of precatalysts (20–33 mol%) or a reaction temperature above 60 °C were required; (2) the diyne substrate was almost confined to the internal diketodiynes; and (3) the product yields were not higher than 80%. In contrast, the cycloaddition of both terminal (R^1 = H) and internal (R^1 = Me) diketodiynes **24** with monoalkynes took place even at ambient temperature in the presence of 1–10 mol% **17** to afford substituted anthraquinones **25** in 33–92% yield.



Scheme 4.9

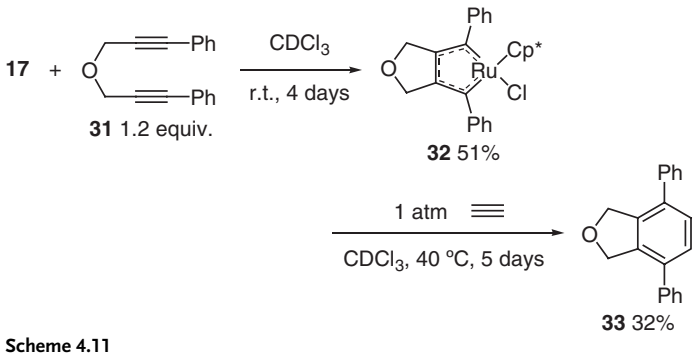
The completely intramolecular [2 + 2 + 2] alkyne cyclotrimerization of triynes **26** took place at ambient temperature under the ruthenium catalysis (Scheme 4.10) [25]. Tricyclic products **27** possessing carbo- (X = $C(CO_2Me)_2$) or heterocyclic (X = O, NTs) rings were obtained in over 80% isolated yields. A corresponding triyne bearing only internal alkynes was cyclized in refluxing chlorobenzene to afford the fully substituted benzene **28**. Tricyclic products **29** and **30** containing a six- or a seven-membered ring were also obtained under high-dilution conditions.

The above ruthenium(II)-catalyzed intramolecular alkyne cyclotrimerizations probably proceeded via a ruthenacycle intermediate similar to the aforementioned ruthenacyclopentatriene complex **18** reported by Dinjus (see Scheme 4.5) [24]. This was confirmed by the isolation of a bicyclic ruthenacycle intermediate and its reaction with acetylene (Scheme 4.11) [25]. The stoichiometric reaction of **17** with the internal diyne **31** possessing phenyl terminal groups in $CDCl_3$ at ambient temperature afforded the expected ruthenacycle complex **32** in 51% yield as single crystals. X-ray analysis of **32** disclosed that its Ru-Cα bond distances of 1.995(3) and



Scheme 4.10

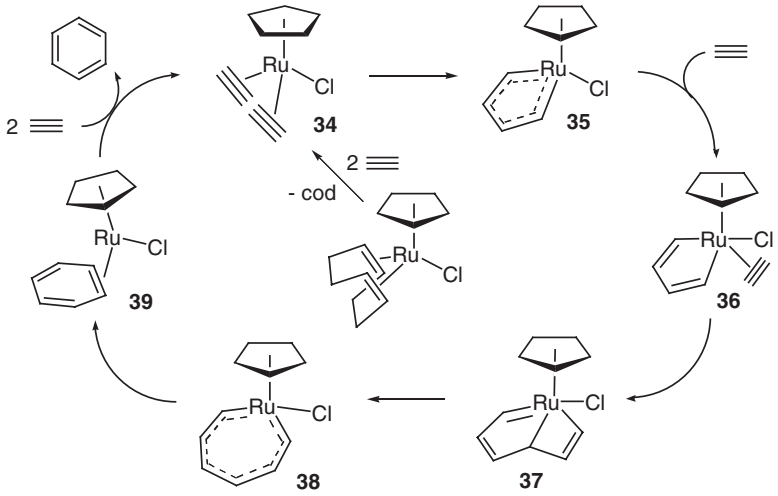
1.985(3) Å were intermediate between those of the precedent ruthenacyclopentatrienes **18** [24] and those of the related ruthenacyclopentadiene(phosphine) complex [32], indicative of these bonds having double bond character in part. In accord with this observation, the ^{13}C NMR spectrum (500 MHz, $CDCl_3$) showed the characteristic carbene resonance of Cα at δ 245.80 ppm. The C–C bond lengths of the ruthenacycle (1.425(4), 1.387(4), and 1.412(4) Å for C1–C2, C2–C3, and C3–C4, respectively) are closer to that of the delocalized bond in benzene (1.40 Å) rather than those of the typical Csp^2–Csp^2 single bond (1.48 Å) or the typical Csp^2=Csp^2 double bond (1.32 Å). These facts indicate that **32** has a highly delocalized structure. The isolated **32** was heated in $CDCl_3$ at 40 °C under the acetylene atmosphere for 5 days to give the expected terphenyl **33** in 32% isolated yield (Scheme 4.11).



Scheme 4.11

In addition to isolation and characterization of the ruthenacycle complexes **18** or **32**, the detailed reaction mechanism of the [2 + 2 + 2] cyclotrimerization of acetylene was analyzed by means of density functional calculations with the Becke's three-parameter hybrid density functional method (B3LYP) [25, 33]. As shown in Scheme 4.12, the acetylene cyclotrimerization is expected to proceed with formal insertion/reductive elimination mechanism. The acetylene insertion starts with the formal [2 + 2] cycloaddition of the ruthenacycle **35** and acetylene via **36** with almost no activation barrier, leading to the bicyclic intermediate **37**. The subsequent ring-

expansion gives rise to a highly delocalized seven-membered ruthenacycle **38**. Its ring closure finally gives the η^2-benzene complex **39**. In contrast to the cobalt-catalyzed reaction [34], the [4 + 2] cycloaddition between **35** and acetylene is found to be less favorable. All elementary steps are estimated as exothermic. The rate-determining step is the oxidative cyclization to form the ruthenacycle key intermediate **35**, and the bisalkyne complex **34** might be in equilibrium with solvated species $[CpRuCl(solvent)_n(acetylene)_{2-n}]$ and the starting cod complex. In this respect, 1,6-diynes are excellent substrates compared to monoalkynes for the Ru-catalyzed alkyne cyclotrimerization, because the formation of a diyne complex is entropically more favorable than that of a bisalkyne complex. Moreover, the activation barriers for the oxidative cyclization of 1,6-diynes were expected to be much smaller than those for monalkynes, because the three-atom tether places the alkyne termini in closer proximity to each other.



Scheme 4.12

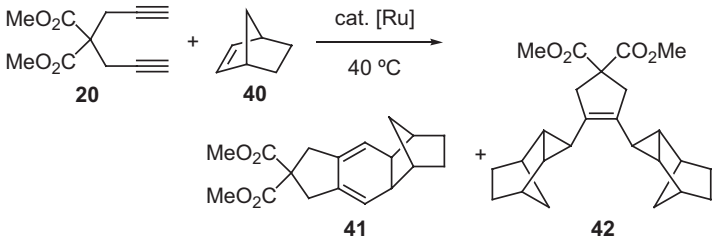
4.2.2
Cyclocotrimerizations of Alkynes with Other Unsaturated Molecules and Related Reactions

The transition metal-catalyzed [2 + 2 + 2] cyclocotrimerization of two molecules of an alkyne with an alkene has studied to a lesser degree compared to the parent alkyne cyclotrimerization [9], although the resultant cyclohexadiene is a valuable synthetic intermediate (e.g., a diene component for the Diels-Alder reaction). This is because a 2:1 coupling of an alkyne and an alkene is generally difficult to compete with the more facile alkyne cyclotrimerization. The success of the selective coupling depends on the electronic balance between the employed alkyne and alkene components; the combinations of an *electron-deficient alkene* with a neutral alkyne [35] or an *electron-deficient alkyne* with a neutral alkene [36] were successful in the previous

examples. Therefore, the intermolecular coupling employing electronically nonactivated alkene and alkyne components has remained a challenging subject [37].

In this context, Ru(II) complexes possessing a Cp-type ligand were examined as precatalysts with respect to the cycloaddition of 1,6-diynes with a strained cycloalkene, norbonene **40**, and its derivatives [38]. As shown in Scheme 4.13, the malonate-derived diyne **20** and 10 equiv of **40** was reacted at 40 °C in the presence of the Cp* complex **17** gave a [2 + 2 + 2] cycloaddition product **41** in 47% yield. Interestingly, the unexpected 1,2-dicyclopropylcyclopentene **42** was also obtained, albeit in 15% yield. The product selectivity was inverted using the analogous Cp complex instead of **17**, and the yield of **42** was further increased up to 78% with an (η-indenyl)ruthenium phosphine complex. These results suggested that the haptotropic flexibility of the cyclopentadienyl type ligands ($\eta^5 \leftrightarrow \eta^3$) [39] plays an important role for the formation of **42**. A plausible mechanism for the reaction of the 1,6-diynes with norbornene is outlined in Scheme 4.14. The tandem cyclopropanation might start with the [2 + 2] cycloaddition of the cyclic biscarbene form of the ruthenacycle intermediate (**43A**) and **40**, which produces the polycyclic complex **44**. The following reductive elimination of a cyclopropane moiety gives the vinyl carbene **45**, which reacts with another molecule of **40** to furnish **42** finally. On the other hand, the normal alkene insertion into the ruthenacyclopentadiene intermediate **43B** gives rise to the ruthenacycloheptadiene **46**, from which a [Cp′RuCl] fragment was reductively eliminated to give **41**.

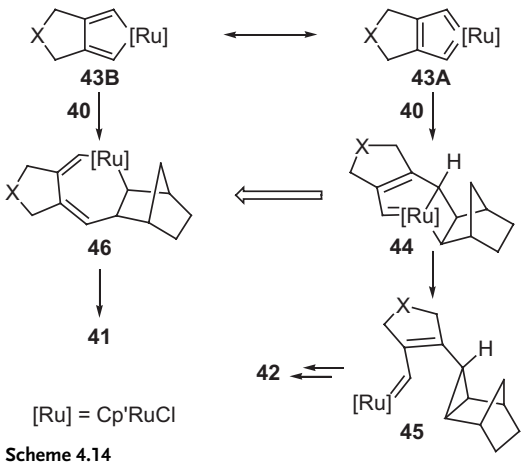
The formation of **44** is reminiscent of that of **37** from the ruthenacycle **35** and acetylene (Scheme 4.12). With the above acetylene cyclotrimerization mechanism in mind, the cleavage of the central Ru–C bond in **44** is expected to give rise to the intermediate **46**. This possibility was also examined by means of density functional calculations [25].



10 mol % Cp*RuCl(cod), CH_2Cl_2, 17 h: 47%/15%
10 mol %CpRuCl(cod), CH_2Cl_2, 7 h: 20%/45%
5 mol %(η^5-C_9H_7)RuCl(PPh_3)$_2$, DCE, 24 h: 12%/78%

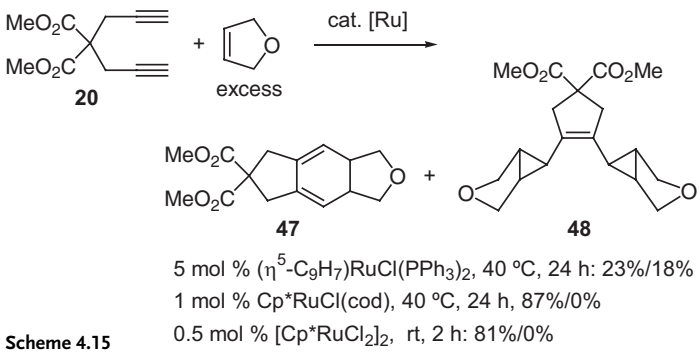
Scheme 4.13

The strained bicyclic structure of norbornene is essential for the tandem cyclopropanation. Less strained cyclopentene furnished the corresponding tandem cyclopropanation product only in 25% yield [38]. Similarly, 2,5-dihydrofuran gave **48** in low yield (18%), but in this case, a normal [2 + 2 + 2] cycloadduct **47** became a major product (23%) (Scheme 4.15). Employing Cp*RuCl(cod) **17** in place of the indenyl



Scheme 4.14

complex exclusively gave **47** in 87% yield. Moreover, a dinuclear Ru^{III} complex having a Cp* ligand, $[(Cp^*RuCl_2)_2]$, proved to be more effective, and the [2 + 2 + 2] cycloaddition proceeded even at room temperature for 2 h to afford **47** in a similar yield. It is noteworthy that cyclopentene never gave rise to the corresponding cycloadduct under the same reaction conditions. On the other hand, *N*-tosyl pyrroline and 3-sulfolene were found to be effective alkene components. These facts show that a heteroatom functionality on the alkene component plays a critical role in the ruthenium-catalyzed [2 + 2 + 2] cycloaddition leading to the cyclohexadienes. The pre-coordination of the oxygen lone pairs may contribute to the selective formation of **47**.

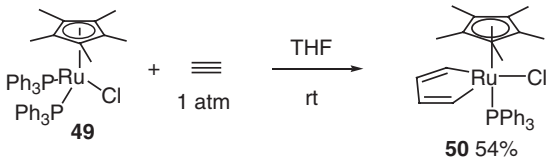


Scheme 4.15

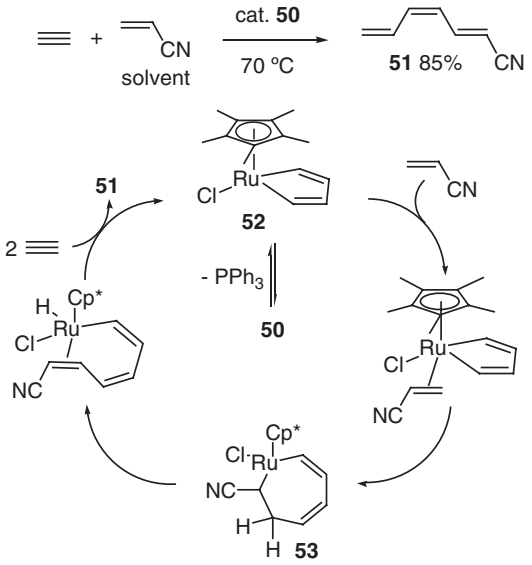
The ruthenacycle-phosphine complex **50** was prepared from the bis(phosphine) complex **49** under acetylene atmosphere at room temperature (Scheme 4.16) [32]. Its ruthenacyclopentadiene structure was unambiguously confirmed by X-ray analysis. The Ru–Cα bond distances of 2.092(4) and 2.059(5) Å are longer than those of the typical Ru=C double bonds (1.83–1.91 Å), and the Cα–Cβ bonds (1.321(6) and 1.338(7) Å) were obviously shorter than the Cβ–Cβ bond (1.414(8) Å). The ^{13}C NMR

resonance of the metallacycle α carbons at δ 200.9 ppm is similar to that of [CpRuBr($C_4Ph_2H_2$)(morpholine)] [22].

In addition to the cyclocotrimerizations described above, the linear cotrimerization of acetylene with acrylonitrile leading to the conjugated triene **51** was accomplished using ruthenacycle-phosphine complex **50** as a precatalyst (Scheme 4.17) [32]. According to the proposed mechanism, the reaction starts with the dissociation of the phosphine ligand from **50**, which generates the coordinatively unsaturated ruthenacycle species **52**. The insertion of acrylonitrile into the Ru–Cα bond of **52** gives rise to the ruthenacycloheptadiene intermediate **53**, which undergoes β-H elimination followed by the reductive elimination to finalize **51**.



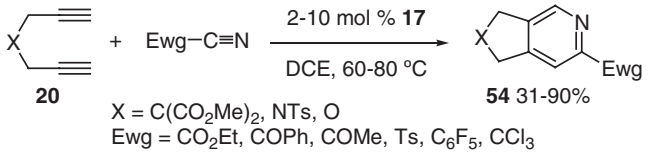
Scheme 4.16



Scheme 4.17

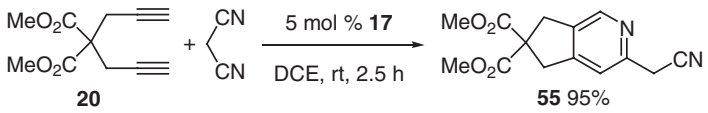
The transition metal-mediated [2 + 2 + 2] cyclocotrimerization of two alkynes and a nitrile is a powerful and straightforward route to substituted pyridines [9]. In particular, catalytic cyclocotrimerization is undoubtedly desirable as a metal-atom economically and environmentally benign process. Effective catalysis, however, has been confined to cobalt [40], although a variety of transition metals (Ti [41], Zr/Ni [42], Ta [43], Co [44], and Rh [45]) have been found to mediate the stoichiometric cyclocotrimerization. With respect to ruthenium, pyridine formation from acetoni-

trile and monoalkynes was reported, but this required near-stoichiometric amounts of a Ru^0 complex [46]. In this context, the Ru^{II}-catalyzed partially intramolecular cycloaddition of diynes with nitriles is expected to produce bicyclic pyridines effectively. Indeed, in the presence of 2–10 mol% **17**, electron-deficient nitriles such as ethyl cyanoformate and pentafluorobenzonitrile underwent cycloaddition with various 1,6-diynes **20** at 60–80 °C to give the desired pyridines **54** in moderate to good yields (Scheme 4.18) [47]. The cobalt-catalyzed cycloaddition of diynes with nitriles has been reported to furnish bicyclic pyridines [48]. Electron-deficient nitriles such as ethyl cyanoformate and pentafluorobenzonitrile, however, gave the desired pyridine in only poor yields.

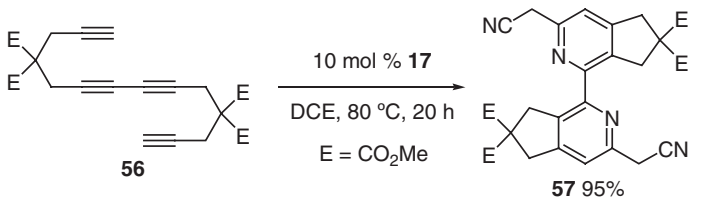


Scheme 4.18

Under the same reaction conditions, acetonitrile or benzonitrile hardly afforded the corresponding cycloadducts, indicative of electron-withdrawing groups on the nitrile components being essential for the ruthenium catalysis. Surprisingly, malononitrile unexpectedly gave rise to a bicyclic cyanomethylpyridine **55** in 95% yield, even at ambient temperature, upon treatment with the malonate-derived diyne **20** and 5 mol% **17** (Scheme 4.19) [49]. It is interesting to note that one of the two cyano groups remains intact after the completion of the reaction. In addition to malononitrile, other dicyanides including succinonitrile, *o*-phthalonitrile, and fumaronitrile also proved to be effective for the pyridine annulation. When an unsymmetrical 1,6-diyne having one internal alkyne was used, the corresponding 2,3,4,6-substituted isomer was formed with excellent regioselectivity. Taking advantage of such regioselectivity, a 2,2′-bipyridine **57** was synthesized in 95% yield from a tetrayne **56** and malononitrile in a single step (Scheme 4.20) [49].



Scheme 4.19

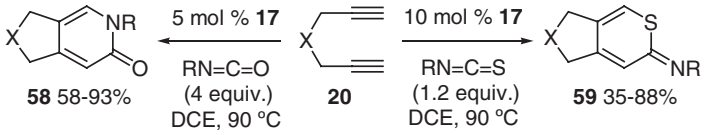


Scheme 4.20

Related cyclocotrimerizations of two alkyne molecules with isocyanates have also been achieved using cobalt and nickel catalysts [9]. With respect to intramolecular versions, two examples of the cobalt(I)-catalyzed cycloaddition of α,ω-diynes with isocyanates have been reported to afford bicyclic pyridones only in low yields, although 2,3-dihydro-5(1*H*)-indolizinones were successfully obtained from isocyanatoalkynes and several silylalkynes with the same cobalt catalysis [50]. On the other hand, the cycloaddition of 1,6-diynes **20** with 4 equiv. of isocyanates proceeded in refluxing DCE under the ruthenium catalysis to afford bicyclic pyridones **58** in 58–93% yield (Scheme 4.21) [51]. Both aryl and aliphatic isocyanates can be widely employed in this pyridone annulation.

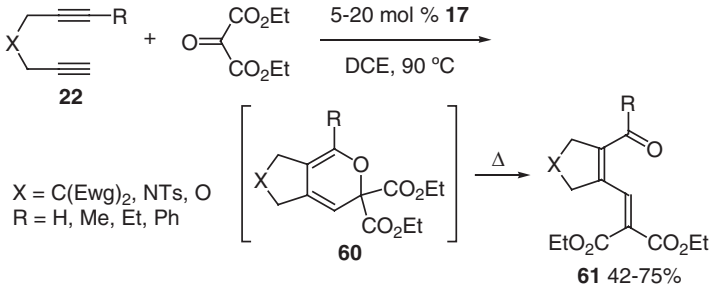
In contrast to isocyanates, isothiocyanates have rarely been examined as cycloaddition components, because their strong coordination of organosulfur compounds frequently deactivates catalytic species. Some organoruthenium complexes, however, recently proved to be efficient catalysts for the formation of carbon-sulfur bonds [52]. The catalytic cycloaddition of diynes **20** with isothiocyanates was also successfully achieved using **17** as a precatalyst [53]. Importantly, the cycloaddition took place across the C=S double bonds of the isothiocyanates to afford thiopyranimines **59** (Scheme 4.21). This reaction requires 10 mol% of **17**, as well as the diynes possessing a quaternary carbon center at the 4-position. When excess amounts of carbon disulfide were also employed in place of the isothiocyanates, a bicyclic dithiopyrone was obtained.

The recent DFT calculations on model reactions support the regiochemistry difference observed for the above cyclocotrimerizations of heterocumulenes [33].



Scheme 4.21

A highly electron-deficient carbon-oxygen double bond can also participate in the cyclocotrimerization with diynes under ruthenium catalysis. The cycloaddition of commercially available diethyl ketomalonate with the unsymmetrical diynes **22** proceeded at 90 °C in the presence of 5–10 mol% **17** (Scheme 4.22) [54]. The expected

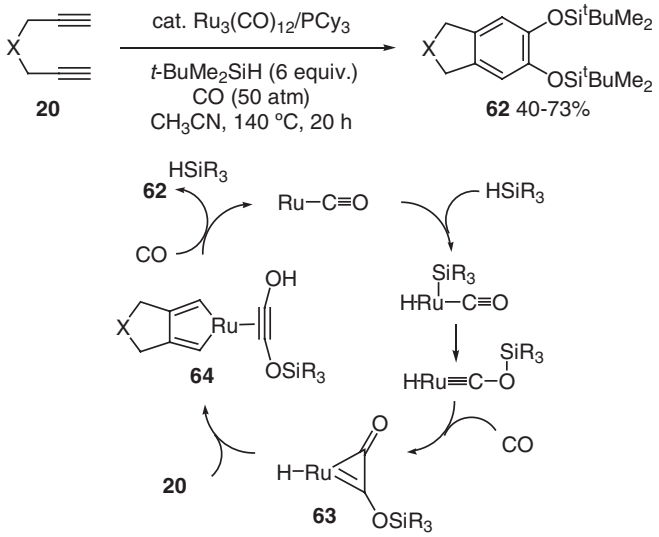


Scheme 4.22

fused 2*H*-pyrans **60**, however, underwent thermal electrocyclic ring opening immediately to produce cyclopentene derivatives **61** in 35–88% yields. The cyclopentadienylcobalt(I)-mediated stoichiometric cycloaddition of alkynes with ketones was also reported previously [55], but its catalytic version was realized for the first time by means of ruthenium catalysis.

4.2.3
Miscellaneous Reactions

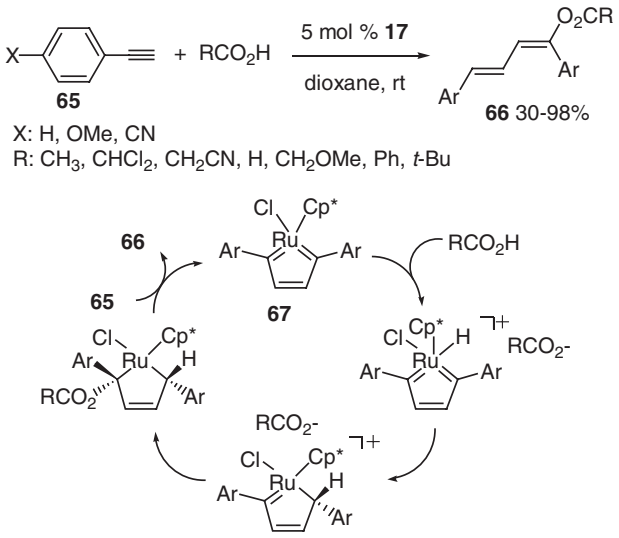
In the presence of catalytic amounts of $[Ru_3(CO)_{12}]$ and PCy_3, the reaction of 1,6-diynes **20** and *t*-$BuMe_2SiH$ under 50 atm CO in CH_3CN at 140 °C afforded bicyclic catechol derivatives **62** in moderate to good yields (Scheme 4.23) [56]. This novel benzannulation was claimed to proceed via the ruthenacyclopropenone **63** and the ruthenacyclopentadiene(dialkoxyacetylene) complex **64**, as shown in Scheme 4.23.



Scheme 4.23

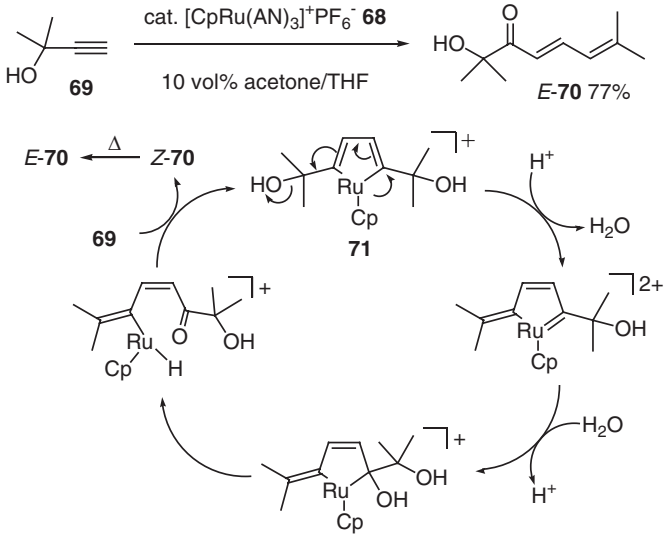
The precatalyst **17** was reported to promote a coupling reaction of two molecules of phenylacetylene or its derivatives **65** with carboxylic acids, leading to (1*E*,3*E*)-1,4-diaryl-1-acyloxybuta-1,3-dienes **66** in various yields (Scheme 4.24) [57]. Amino acids, as well as diacids, can also be employed as carboxylic acid components. A mechanism involving the addition of a carboxylic acid to the ruthenacyclopentatriene intermediate **67** was proposed for this stereoselective coupling.

A mechanistically relevant dimerization of the propargyl alcohol derivative **69** resulting in **70** was also promoted by a cationic complex **68** (Scheme 4.25) [58]. The reaction was considered to start with the regioselective formation of the ruthenacyclopentadiene **71** from **68** and **69**, and the subsequent migration of the hydroxy

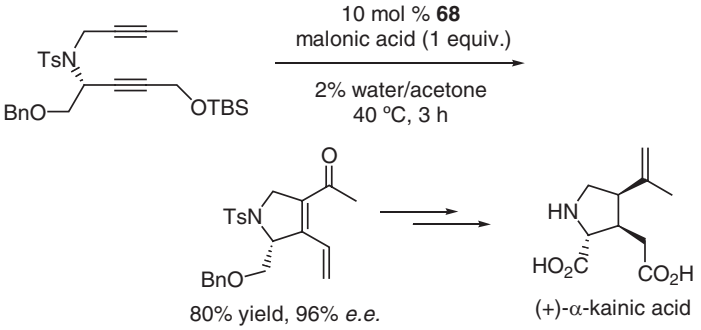


Scheme 4.24

group followed by β-H elimination and reductive elimination would give rise to the *Z*-**70**, which isomerizes to the *E*-**70** under the reaction conditions. The intramolecular variant with diynol substrates furnished cyclopentene derivatives [59]. This novel cycloisomerization of protected diynols was successfully applied to the total synthesis of (+)-α-kainic acid (Scheme 4.26) [60].

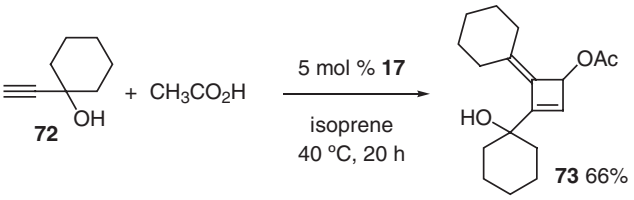


Scheme 4.25



Scheme 4.26

In contrast to these linear couplings of propargyl alcohol derivatives, a three-component cyclo-coupling of **72** proceeded in the presence of **17** and acetic acid to give rise to an alkylidenecyclobutene **73** in 66% yield (Scheme 4.27) [61]. The four-membered ring skeleton was considered to be derived from the ruthenium(II) cyclobutadiene complex, which might be formed via the corresponding ruthenacyclopentadiene.



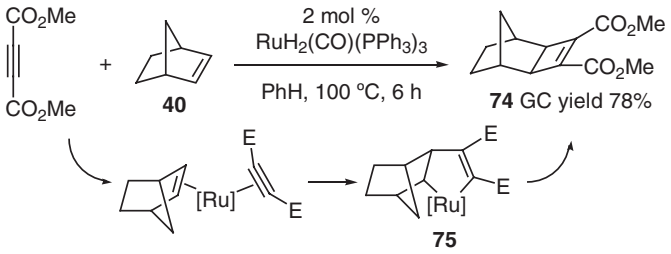
Scheme 4.27

4.3
C–C Bond Formations Involving Ruthenacyclopentene

4.3.1
Coupling Reactions Between Alkynes and Alkenes

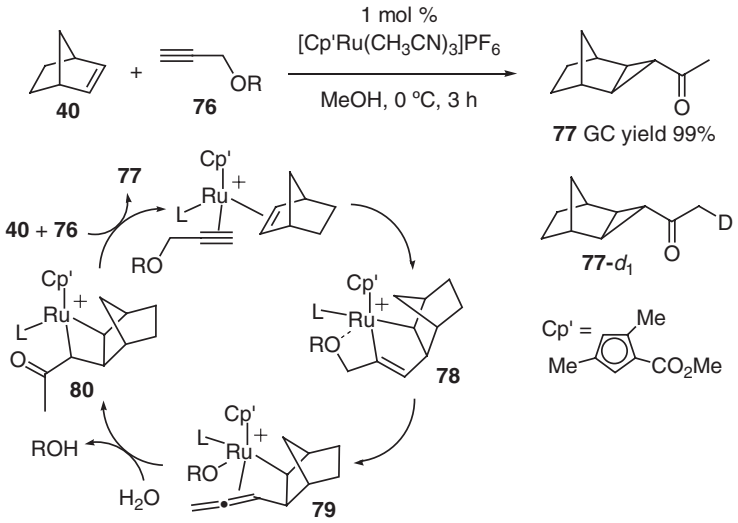
The [2 + 2] cycloaddition of an alkene and an alkyne is a valuable route leading to cyclobutene derivatives. The ruthenium(0)-catalyzed [2 + 2] cycloaddition of a strained cycloalkene, norbornene **40**, with highly electron-deficient DMAD afforded the cyclobutene **74** (Scheme 4.28) [62]. As expected, the reaction took place at the *exo* face of **40** via the ruthenacyclopentene intermediate **75**, that was formed by the oxidative cyclization of DMAD and norbornene. In addition to the parent **40**, various norbornene derivatives can also be used as alkene components. When the Ru^{II} precatalyst **17** was employed, electronically neutral alkynes participated in the [2 + 2] cycloaddition with norbornene and its derivatives [63]. A similar [2 + 2] cycloaddi-

tion of DMAD with ethylene was realized by employing a cationic alkylidene complex, $[(PCy_3)_2(CO)(Cl)Ru{=}CHCH{=}(CH_3)_2]^+BF_4^-$ as a precatalyst [64].



Scheme 4.28

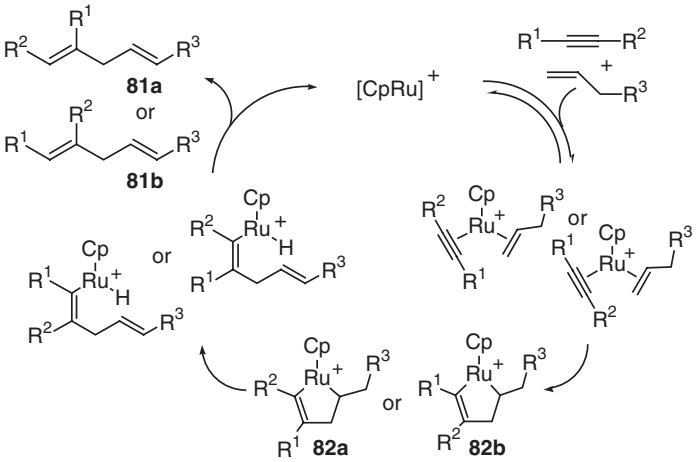
Propargyl alcohol derivatives behave differently to other alkynes toward the cycloaddition with norbornene **40**. As summarized in Scheme 4.29, the reaction of **40** with propargyl alcohol or its methyl ether (R = H or Me) **76** proceeded even at 0 °C in MeOH in the presence of a cationic ruthenium complex to give rise to the cyclopropyl ketone **77** in high yields [65]. When a MeOD/D_2O mixed solvent was employed instead of MeOH, **77**-d_1 was exclusively obtained. On the basis of these results, a plausible mechanism was proposed as follows: (1) the oxidative cyclization of **40** and **76** gives the ruthenacyclopentene **78**; (2) its β-oxygen elimination affords the allene complex **79**; (3) the central carbon of the coordinated allene is attacked by H_2O to give rise to the ruthenacyclobutane **80**; and (4) finally, the reductive elimination of **77** regenerates the catalyst.



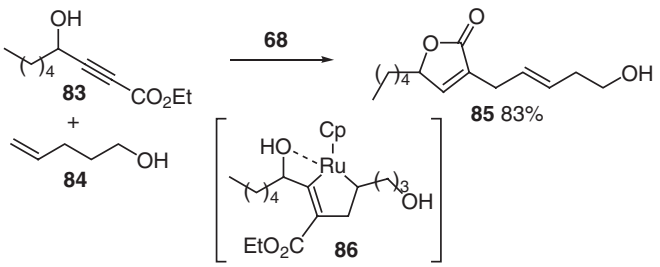
Scheme 4.29

In the case of using alkenes which have an allylic proton to undergo β-H elimination, Alder-ene type couplings with alkynes took place to afford 1,4-dienes **81a** and/or **81b** (Scheme 4.30) [66]. Such a linear coupling is also believed to involve a ruthenacyclopentene intermediate. The oxidative cyclization of unsymmetrical alkynes and alkenes might give rise to the ruthenacyclopentenes **82a** and/or **82b**, depending on the nature of the substituents. When the propargyl alcohol derivative **83** was used as an alkyne component, coupling with the alkenol **84** selectively furnished the butenolide **85** via the Alder-ene reaction through the ruthenacyclopentene **86** with the hydroxyl oxygen being coordinated, and subsequent lactonization (Scheme 4.31) [67]. On the other hand, unsaturated aldehydes and ketones were obtained using allylic alcohols as alkene components [68]. Similarly, allyl *t*-butyldimethylsilyl ether and *N*-allylamides gave silyl enol ethers [69] and enamides [70], respectively. The ruthenium-catalyzed alkene-alkyne coupling was successfully combined with the palladium-catalyzed intramolecular asymmetric allylic alkylation [71] to provide a novel one-pot heterocyclization method [72].

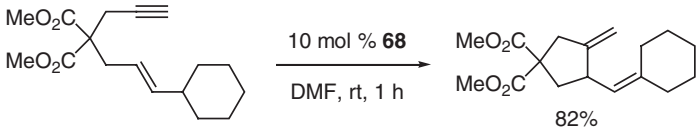
Intramolecular variants of the Alder-ene type couplings between alkynes and alkenes have been extensively explored by means of palladium catalysis [73]. Recently, such a cycloisomerization of enynes was also accomplished with ruthenium catalysis (Scheme 4.32) [74].



Scheme 4.30



Scheme 4.31

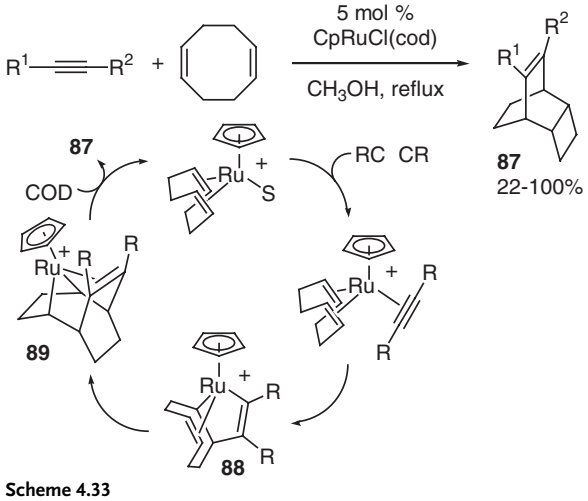


Scheme 4.32

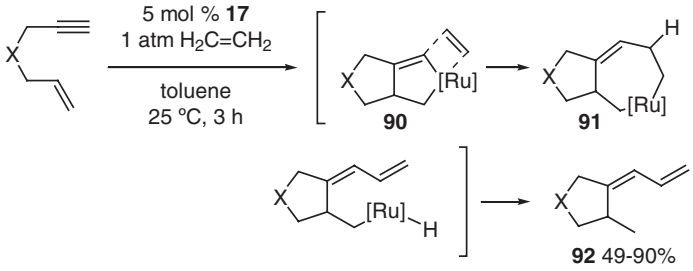
4.3.2

Three-Component Couplings of Alkynes, Alkenes, and Other Unsaturated Molecules

Ruthenacyclopentene intermediates would be transformed into various valuable cyclic molecules by subsequent reactions with other unsaturated molecules. Various terminal and internal alkynes were heated with 1,5-cyclooctadiene (COD) in refluxing MeOH containing a catalytic amount of CpRuCl(cod) to afford tricyclic compounds **87** in 22–100% yields (Scheme 4.33) [75]. This [2 + 2 + 2] cycloaddition was considered to start with the oxidative cyclization of an alkyne and one of the two alkene moieties of COD to give the ruthenacyclopentene intermediate **88**. Subsequent insertion of the remained alkene into the Ru–Csp^2 bond would give ruthenatricycle **89**. Finally, the reductive elimination of **87** restored the cationic ruthenium species. On the other hand, dienylidenecyclopentane **92** was obtained from 1,6-enynes upon treatment with 5 mol% **17** under ethylene atmosphere at 25 °C (Scheme 4.34) [76]. The insertion of ethylene into the Ru–Csp^2 bond of bicyclic ruthenacyclopentenes **90** was proposed to give rise to the ruthenacycloheptene **91**, which undergoes subsequent β-H elimination/reductive elimination steps finally to afford **92**.

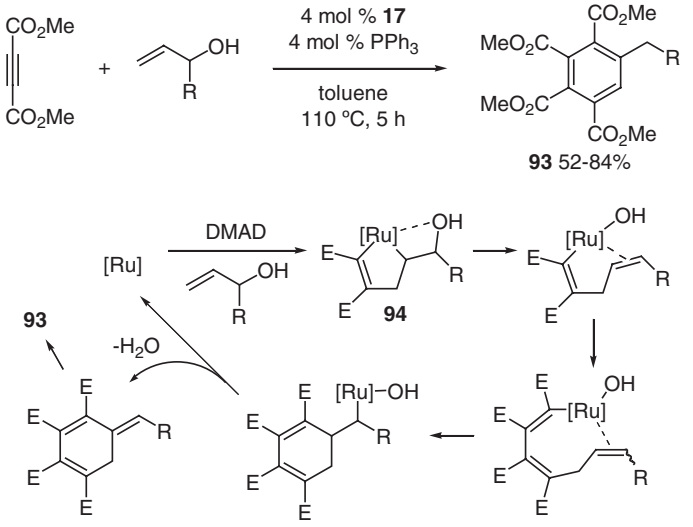


Scheme 4.33



Scheme 4.34

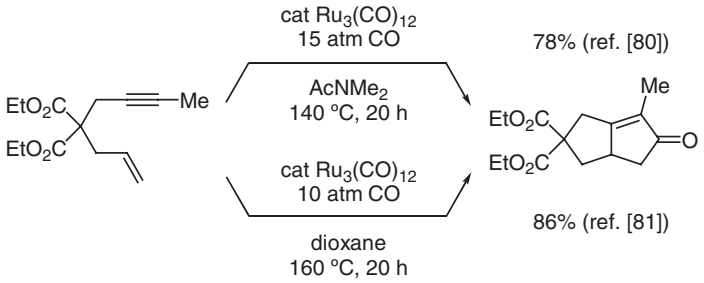
The catalyst generated in situ from **17** and PPh_3 proved to be effective in the annulation of highly substituted benzenes **93** from DMAD with allylic alcohols (Scheme 4.35) [77]. In contrast to the cycloaddition of 1,6-diynes with heterocycloalkenes (see Section 4.2.2) [38], the regioselective formation of the ruthenacyclopentene intermediate **94** was claimed to be involved in this benzannulation. Again, pre-coordination to the oxygen functionality is suggested to be important to determine the reaction pathways (cf. Schemes 4.15 and 4.31). Subsequent β-oxygen elimination followed by the sequential insertion of DMAD and the resultant alkene in this order would assemble the six-membered framework.



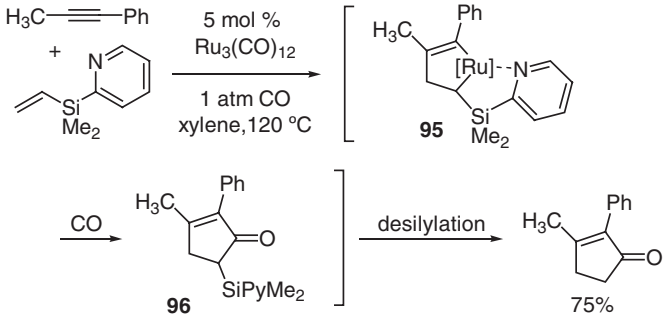
Scheme 4.35

The cobalt-mediated cycloaddition of an alkyne, an alkene, and CO leading to a cyclopentenone has been known as the Pauson-Khand (PK) reaction [78]. Due to its synthetic importance, numerous variants – especially catalytic reactions – have been developed to date [79]. The first ruthenium-catalyzed PK reaction of enynes has been achieved using $Ru_3(CO)_{12}$ by two research groups independently (Scheme

4.36) [80,81]. Bicyclic ruthenacyclopentenes are considered to be intermediates for these ruthenium-catalyzed PK reactions. The catalytic intermolecular PK reaction was recently realized by a combination of the ruthenium catalysis with alkenes possessing dimethylpyridylsilyl group (Scheme 4.37) [82]. With the directive aid of the pyridylsilyl group, putative ruthenacyclopentene key intermediates such as **95** were expected to be formed selectively and, as a result, the PK reaction took place even under 1 atm CO to afford regioselectively the desired cyclopentenone after facile concomitant desilylation via **96**.



Scheme 4.36

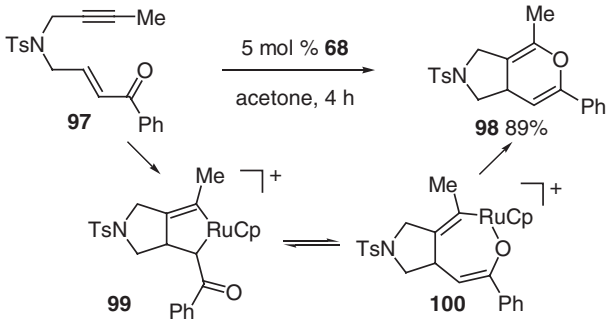


Scheme 4.37

4.3.3
Intramolecular Coupling of Alkynes with Enones and Vinylcyclopropanes

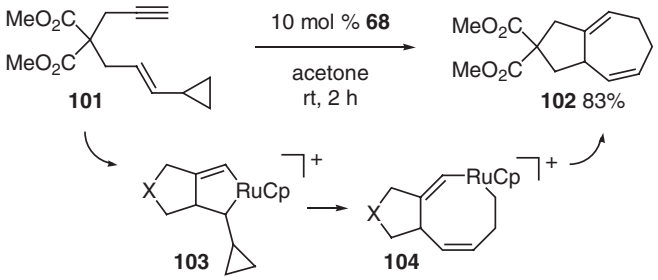
Diels-Alder type [4 + 2] cycloadditions of nonactivated coupling partners have been effected by various transition-metal catalyses [1]. Interestingly, the cationic ruthenium complex **68** catalyzed the intramolecular [4 + 2] cycloaddition between alkyne and enone moieties of **97** leading to **98** (Scheme 4.38) [83]. Such a formal hetero Diels-Alder reaction might proceed via a ruthenacyclopentene **99** and an oxaruthenacycloheptadiene **100**, which is an ruthenium enolate species.

Transition metal-catalyzed higher-order cycloadditions offer a powerful approach for the construction of medium-sized rings [1]. In this context, Wender and co-workers have developed catalytic cycloadditions of vinylcyclopropanes with alkynes,

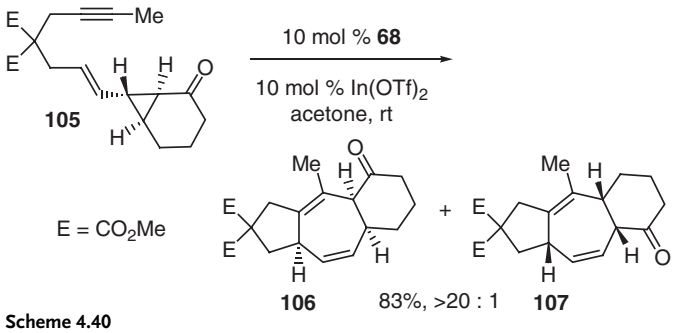


Scheme 4.38

allenes, and alkenes leading to seven-membered rings [84]. For these [5 + 2] cycloadditions, rhodium-based precatalysts are employed, with the rhodium catalysis frequently requiring high temperatures and long reaction times. Alternatively, recently reported ruthenium catalysis transformed more elegantly the cyclopropylenyne **101** into the desired bicyclo[5.3.0]decadiene **102**, even at room temperature for 2 h (Scheme 4.39) [85]. The ruthenium-catalyzed cycloaddition possibly proceeds via the mechanism involving the ruthenacyclopentene **103** and its ring-expansion product, ruthenacyclooctadiene **104**, as outlined in Scheme 4.39. The enyne substrate **105** possessing an unsymmetrical cyclopropyl moiety gave the regioisomer mixture of tricyclic products **106** and **107** (Scheme 4.40) [86]. However, the major isomer **106** was predominantly obtained when 10 mol% [$In(OTf)_2$] was used as an additive.



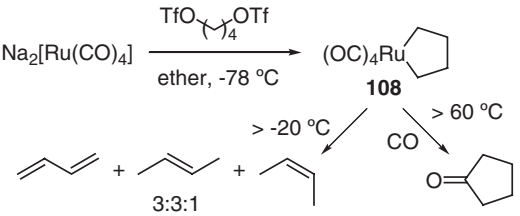
Scheme 4.39



Scheme 4.40

4.4
C–C Bond Formations Involving Ruthenacyclopentane

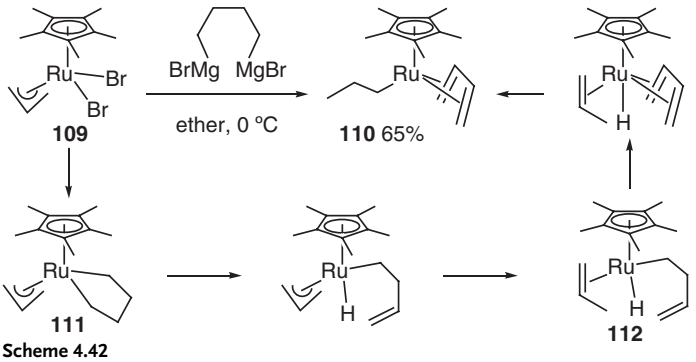
Ruthenacyclopentane **108** was synthesized by the reaction of $Na_2[Ru(CO)_4]$ with butanediylbis(trifluoromethanesulfonate) at –78 °C (Scheme 4.41) [87]. These ruthenacycle complexes are air-sensitive and thermally unstable. In fact, **108** decomposed even at –20 °C in the absence of CO to give rise to 1,3-butadiene, *trans*- and *cis*-2-butene in a ratio of 3:3:1. Under a CO atmosphere, this compound decomposed above 60 °C to afford cyclopentanone.



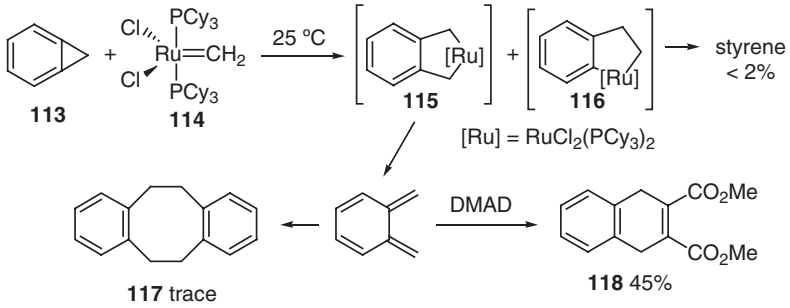
Scheme 4.41

The instability of ruthenacyclopetanes is also demonstrated by the following example (Scheme 4.42) [88]. The treatment of a dibromoruthenium(IV) π-allyl complex **109** with $BrMg(CH_2)_4MgBr$ at 0 °C furnished an unexpected alkylruthenium(IV) butadiene complex **110**, the formation of which was explained as follows. Substitution of the bromide ligands of **109** with Grignard reagent might give a ruthenacyclopentane **111**, which undergoes β-H elimination followed by the reductive elimination of an alkene to afford **112**. Subsequent second β-H elimination to coordinated butadiene and the insertion of the coordinated alkene into the Ru-H bond finally gave rise to the alkyl-diene complex **110**.

The stoichiometric reaction of proparene **113** and the carbene complex **114** at 25 °C gave rise to trace amounts of styrene, dibenzocyclooctadiene **117**, and other polymeric products (Scheme 4.43) [89]. Dibenzocyclooctadiene **117** was considered to be formed from the ruthenacycle **115** via a quinodimethane intermediate, while styrene was formed by the decomposition of the isomeric ruthenacycle **116**. The qui-



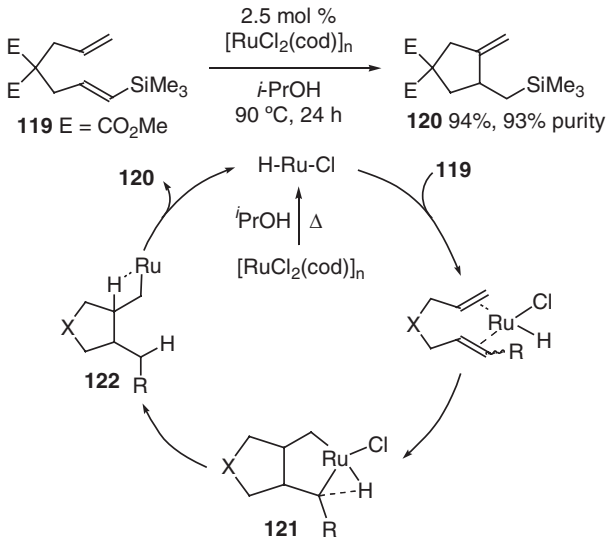
Scheme 4.42



Scheme 4.43

nodimethane intermediate was confirmed by the trapping experiment to afford a Diels-Alder adduct **118** in 45% yield.

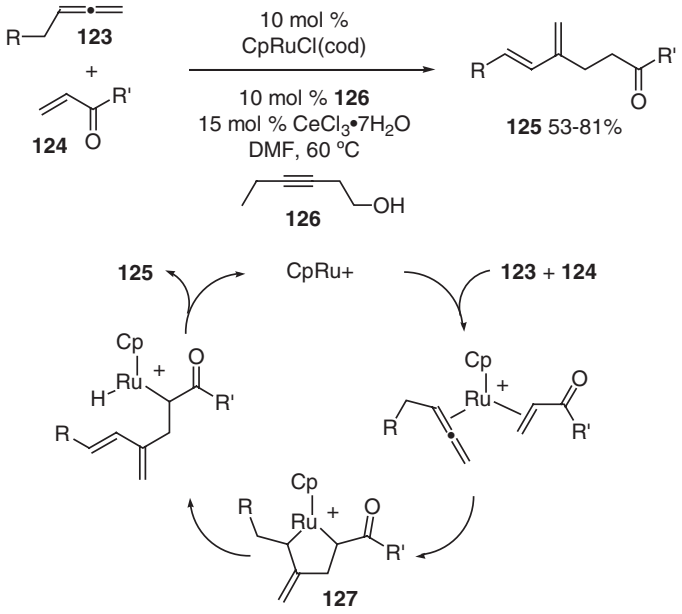
Such a labile ruthenacyclopentane was proposed as an intermediate for alkene coupling reactions. As depicted in Scheme 4.44, the intramolecular alkene coupling was accomplished by means of a novel ruthenium(II) catalyst system [90]. In the presence of a catalytic amount of insoluble polymeric complex, $[RuCl_2(cod)]_n$, 1,6-dienes were heated at 90 °C in *i*-PrOH to afford *exo*-methylenecyclopentanes with excellent isomer selectivity. It is noteworthy that the ruthenium catalysis also transformed an unsymmetrical diene **119** into the corresponding *exo*-methylenecyclopentane **120**, whereas the previous method using $[RhCl(PPh_3)_3]$ was reported to give a complex isomer mixture from a similar unsymmetrical diene substrate [91]. On the basis of this selectivity and some deuterium-labeling studies, unprecedented cyclization mechanism was proposed: (1) the polymeric complex is heated in *i*-PrOH to generate a chlororuthenium hydride species; (2) the oxidative cyclization of **119** on



Scheme 4.44

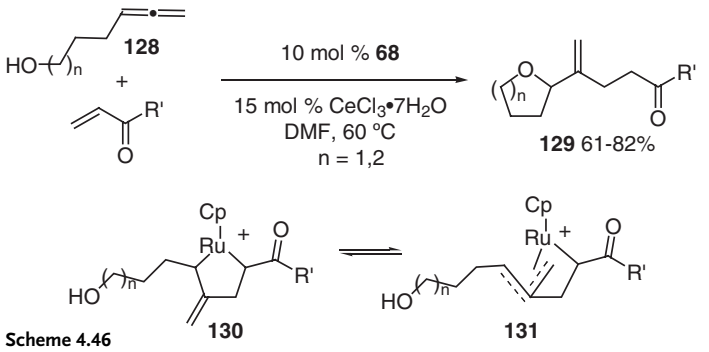
its ruthenium center generated the ruthenacyclopentane(hydrido) complex **121**; and (3) subsequent reductive elimination at the more substituted site followed by β-**H** elimination via **122** restored the ruthenium hydride active species. The ruthenium catalysis was further applied to the diastereoselective cycloisomerization of diallyllactones into spirolactones [92].

The intermolecular coupling of allenes **123** and enones **124** selectively afforded dienones **125** in 53–81% yields (Scheme 4.45) [93]. As a catalyst precursor, [CpRuCl(cod)] was employed with $CeCl_3 \cdot 7H_2O$ and an alkynol **126** as activators. The proposed reaction mechanism involves the regioselective oxidative cyclization of the two components on a cationic ruthenium center, leading to the ruthenacyclopentane intermediate **127**. When allenyl alcohols **128** were employed under otherwise identical conditions, the final products were cyclic ethers **129** (Scheme 4.46) [94]. As a catalyst precursor, the cationic ruthenium complex **68** can be used in the absence of the alkynol **126**. The ether ring was considered to be formed directly via the ruthenacyclopentane **130** or alternatively through its π-allyl form **131**.

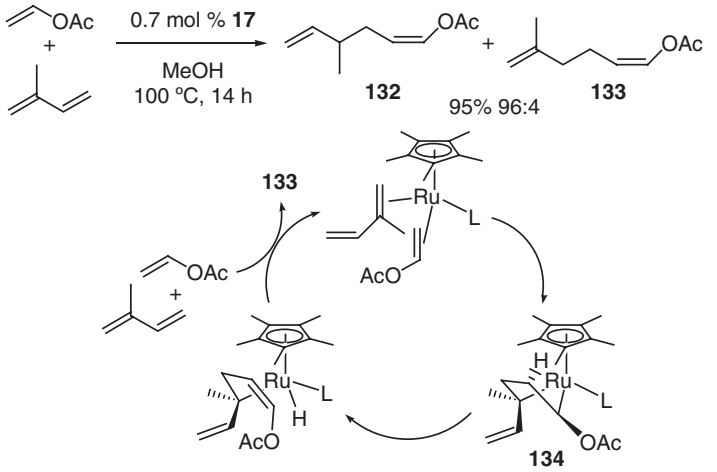


Scheme 4.45

Isoprene also underwent the intermolecular coupling with vinyl acetate (Scheme 4.47) [95]. In the presence of 0.7 mol% **17**, isoprene and vinyl acetate were heated at 100 °C in MeOH for 14 h to give dienes **132** and **133** with a ratio of 96:4. The present selectivity was attributed to the regioselective oxidative cyclization of the more substituted alkene moiety of isoprene and vinyl acetate giving rise to the ruthenacyclopentane intermediate **134**.



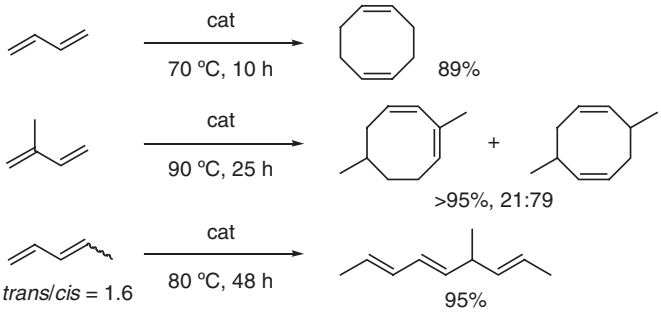
Scheme 4.46



Scheme 4.47

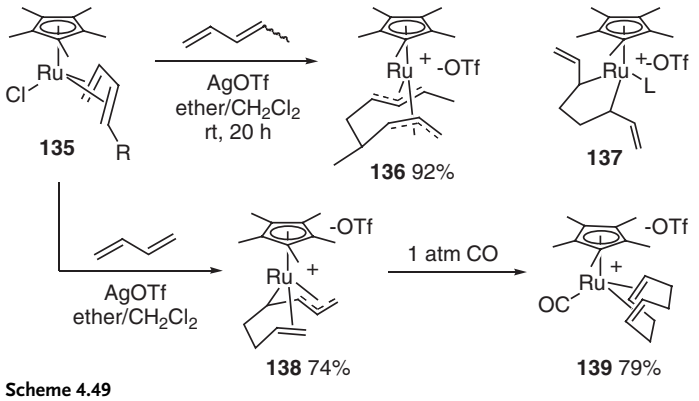
Cyclo- and linear-dimerizations of 1,3-dienes were accomplished by means of a cationic ruthenium catalyst derived from [Cp*RuCl(1,3-diene)] and AgOTf (Scheme 4.48) [96]. In THF, 1,3-butadiene was treated with the cationic ruthenium catalyst at 70 °C for 10 h to afford 1,5-cyclooctadiene in 89% yields. Similarly, isoprene underwent [4 + 4] cycloaddition in a head-to-tail fashion to yield quantitatively 2,6-dimethyl-1,3-cyclooctadiene and 3,7-dimethyl-1,5-cyclooctadiene in a ratio of 21:79. On the other hand, a head-to-tail linear dimer was obtained in 95% yield from 1,3-pentadiene.

These diene dimerizations might start with the formation of cationic Ru(IV) bis(π-allyl) complexes rather than ruthenacyclopentanes such as **137** (Scheme 4.49). This was confirmed by the stoichiometric reaction of the 1,3-pentadiene complex **135** (R = Me) with 1,3-pentadiene and AgOTf, giving rise to the bis(π-allyl) complex **136** in 92% yield. In contrast, the similar reaction of the 1,3-butadiene complex **135** (R = H) furnished a complex **138** in 74% yield, that was further converted into the 1,5-cyclooctadiene complex **139** in 79% yield upon exposure to 1 atm CO. On the basis of these studies, the mechanism of the dimerization of 1,3-butadiene was postulated as outlined in Scheme 4.50. The oxidative cyclization of 1,3-butadiene on the

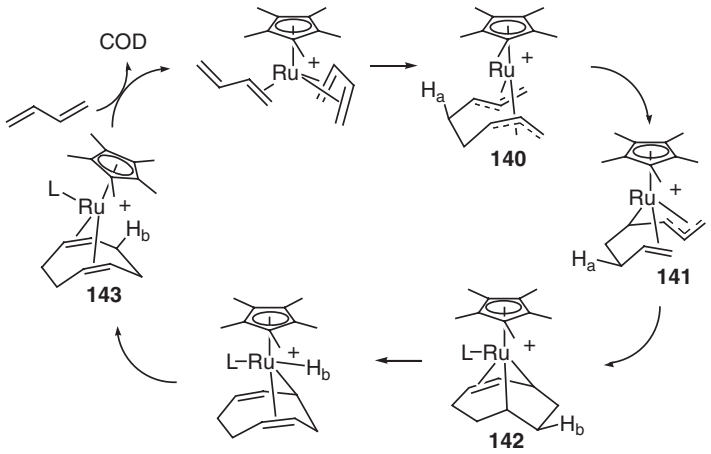


Scheme 4.48

cationic ruthenium center to give the bis(π-allyl) complex **140**, which undergoes 1,3-H migration to afford **141**. Further oxidative cyclization of terminal alkene moieties in **141** would give the ruthenabicyclooctene intermediate **142**. The 1,3-H shift via β-H elimination/reductive elimination occurs in **142** to give the 1,5-cyclooctadiene complex **143**.



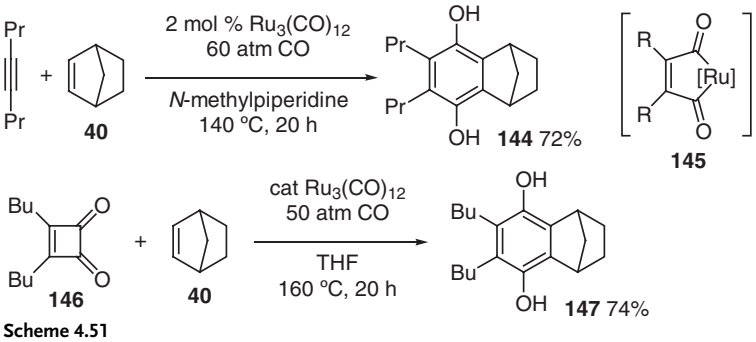
Scheme 4.49



Scheme 4.50

4.5
C–C Bond Formations Involving Ruthenacyclopentenedione and Ruthenacyclobutenone

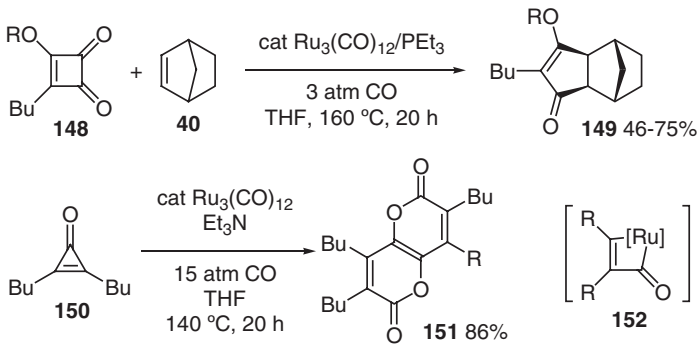
Transition-metal maleoyl and phthaloyl complexes have been used as building blocks for the synthesis of quinone derivatives [97]. These complexes were usually obtained by the reactions of low-valent transition metal elements with phthaloyl chloride or cyclobutenedione derivatives, and by the double carbonylation of *o*-diiodobenzene. With respect to Group 8 triads, quinones [98], cyclobutenediones [99], and cyclic imides [100] were synthesized utilizing maleoyliron complexes, which were generated by the Fe^0-mediated double carbonylation of alkynes [101]. All of these examples were, however, stoichiometric reactions, whereas the catalytic carbonylation reaction via a maleoyl complex is synthetically desirable. In this context, the catalyzed cocyclization of alkynes, alkenes, and two CO molecules was recently developed by means of ruthenium catalysis (Scheme 4.51) [102]. As an alkene component, norbornene **40** was heated with 4-octyne and catalytic amounts of $Ru_3(CO)_{12}$ in *N*-methylpiperidine at 140 °C under 60 atm CO to selectively afford a hydroquinone **144** in good yield. When other solvents such as *N*,*N*-dimethylacetamide, acetonitrile, and toluene were employed in place of *N*-methylpiperidine, a benzoquinone was obtained as a byproduct as a result of the cocyclization of each two molecules of an alkyne and CO. A maleoylruthenium complex **145** was considered to be a key intermediate. The maleoylruthenium intermediate could be formed by the oxidative addition of the corresponding cyclobutenedione to a low-valent ruthenium species. Indeed, 3,4-dibutyl-3-cyclobutene-1,2-dione **146** and norbornene **40** were treated with $[Ru_3(CO)_{12}]$ in THF at 160 °C under 50 atm CO to give rise to the expected hydroquinone **147** in 74% yield (Scheme 4.51) [103].



Scheme 4.51

Cyclobutenediones **148** possessing an alkoxy substituent reacted with norbornene **40** in quite a different way, in which CO molecule was extruded from the dione substrates (Scheme 4.52) [103]. In the presence of catalytic amounts of $Ru_3(CO)_{12}$ and PEt_3, **148** and **40** was heated at 160 °C under 3 atm CO to regioselectively afford cyclobutenones **149**. Such a novel reconstructive cycloaddition was further extended to the carbonylative dimerization of a cyclopropenone **150** resulting in the formation of a pyranopyrandione **151** in high yields [104]. These novel transformations of

small ring ketone substrates were considered to proceed via ruthnacyclopentenediones **145** and ruthenacyclobutenones **152** as key intermediates.



Scheme 4.52

4.6 Conclusion

During the past decade, ruthenium-catalyzed selective and atom-economical carbon–carbon bond-forming reactions have been developed on the basis of the mechanistic rationale focusing on ruthenacycle key intermediates. Several ruthenium(II) and ruthenium(III) complexes possessing a cyclopentadienyl-type planar spectator ligand dramatically expanded the scope of the [2 + 2 + 2] cyclotrimerization of alkynes and related cocyclizations. These reactions are believed to proceed via ruthenacycle intermediates formed by the oxidative cyclization of two alkyne molecules on [Cp*RuCl] fragments. X-ray diffraction and density functional studies on such ruthenacycle complexes disclosed that they have a novel cyclic biscarbenoid structure, which is formally regarded as ruthenacyclopentatriene. Ruthenacyclopentatrienes are also considered to be intermediates for unprecedented coupling reactions such as the tandem cyclopropanation between 1,6-diynes and bicycloalkenes, the stereoselective coupling of arylalkynes with carboxylic acids, and the dimerization of propargyl alcohols involving the hydroxyl group migration. Catalytic reactions, which might involve ruthenacyclopentene intermediates, have also been developed extensively, although the structural and theoretical studies on ruthenacyclopentenes have been remained unexplored. They involve [2 + 2] cyclobutene formation, Alderene type coupling, the Pauson-Khand reaction, [5 + 2] cycloaddition of cyclopropylenynes, and so on. In addition, other fascinating catalytic C–C bond formations have been accomplished utilizing relatively uncommon ruthenacycle intermediates such as ruthenacyclopentanes and ruthenacyclopentenediones. An increasing number of new catalytic C–C bond-forming reactions will be discovered by taking advantage of the synthetic potential of ruthenacycle intermediates as well as ruthenium precatalysts with unexplored ligand fields or oxidation states.

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5
Carbon–Carbon Bond Formation via π-Allylruthenium Intermediates

Teruyuki Kondo and Take-aki Mitsudo

5.1
Introduction

Recently, transition-metal complex-catalyzed organic synthesis with chemo-, regio- and stereoselectivity has been extensively studied. A variety of catalytic systems, which enable the introduction of a desired functional group into organic molecules and the selective transformation of many functional groups, have been designed and widely applied in organic synthesis [1]. In particular, palladium-catalyzed reactions have found widespread use in several important chemical processes [2]. Among these, palladium complex-mediated or -catalyzed allylic substitution reactions have been especially studied in detail. Since 1965, when Tsuji and coworkers first reported that π-allylpalladium chloride reacts with carbonucleophiles, such as malonates, acetoacetates, and enamines [3], the palladium complex-catalyzed allylic substitution reaction has become a well-established methodology in organic synthesis, and is now used to construct complex organic molecules [4]. Although a wide range of transition-metal complexes have recently been used in this reaction [5], the general use of ruthenium catalysts has not been forthcoming. In the early 1970s, the chemistry of ruthenium catalysis lagged far behind that of other transition-metal complexes, such as rhodium and palladium. Indeed, the chemistry of π-allylruthenium complexes has also been relatively under-developed. However, with recent progress in organometallic chemistry, organic synthesis catalyzed by ruthenium complexes has attracted much attention, and a large number of useful catalytic reactions have been discovered [6]. In ruthenium catalysis, the appropriate matching and tuning of the ruthenium catalysts with the ligands, substrates, and solvents used are always important. Under optimized reaction conditions, ruthenium complexes often show novel and interesting catalytic activities, which have not yet been observed in other transition-metal complexes.

In this chapter, the synthesis, structure, and reactivity of several π-allylruthenium complexes, and characteristic C–C bond-forming reactions mediated and catalyzed by ruthenium complexes via π-allylruthenium intermediates are described.

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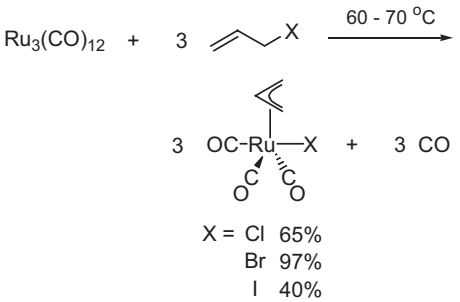
5.2
Synthesis, Structure, and Reactivity of π-Allylruthenium Complexes

5.2.1
π-Allylruthenium(II) Complexes

To date, several π-allylruthenium complexes have been prepared and reported. The representative methods for introducing an allyl group to a ruthenium complex are quite similar to those for other transition metals; for example, (1) the reaction of ruthenium halides with allyl Grignard reagents; (2) the insertion of conjugated dienes into a hydrido-ruthenium bond; and (3) the oxidative addition of several allylic compounds to low-valence ruthenium complexes.

The first π-allylruthenium(II) carbonyl complex to be reported was Ru{η^3-$CH(CH_3)CHCH_2$}$(CO)_3Cl$, which was prepared by treating the 1,3-butadiene ruthenium complex Ru(η^4-C_4H_6)$(CO)_3$ with hydrochloric acid in CCl_4 or hexane [7]. Subsequently, in a pioneering study by Pino and coworkers, the reaction of a suspension of $Ru_3(CO)_{12}$ in isooctane with allyl halides was shown to give yellow crystalline complexes, (π-C_3H_5)RuX$(CO)_3$ (X = Cl, Br, I), in high yields (Eq. 5.1) [8].



(5.1)

The photochemistry of (π-C_3H_5)RuX$(CO)_3$ was investigated by Wrighton and coworkers [9]. The complex (π-C_3H_5)RuX$(CO)_3$ exists in solution in a conformational equilibrium between *endo* and *exo* isomers that differ principally in the orientation of the allyl group (Figure 5.1). At room temperature, the two isomers interconvert slowly ($t_{1/2}$ >10 min) and the *endo* isomer predominates (>95%). The primary photoprocess of this complex is the loss of CO to yield the 16e intermediate, (π-C_3H_5)RuX$(CO)_2$. In the absence of reactive molecules such as a two-electron donor ligand, it dimerizes to give [(π-C_3H_5)Ru(μ-X)$(CO)_2]_2$, which back-reacts with CO to give only *exo*-(π-C_3H_5)RuX$(CO)_3$. However, thermal isomerization again gives an *endo*-rich distribution (>95%) of this complex.

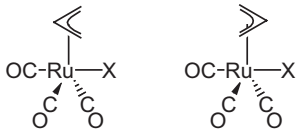
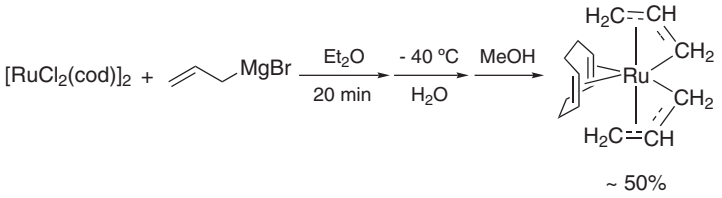


Figure 5.1 The two geometric isomers of (π-C_3H_5)RuX$(CO)_3$.

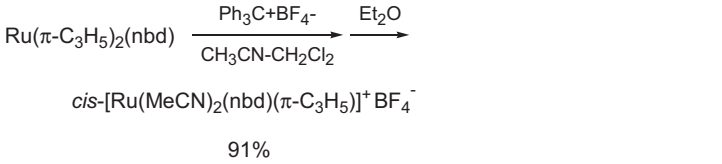
The reaction of the polymeric diene complexes, $[RuCl_2(diene)]_n$ [diene = cod (1,5-cyclooctadiene), nbd (2,5-norbornadiene)], with allylic Grignard reagents gives white bis(allylic) complexes, $Ru(allyl)_2(diene)$ (allyl = C_3H_5, 2-methylallyl), which contain asymmetrically bonded allyl ligands (Eq. 5.2) [10].



(5.2)

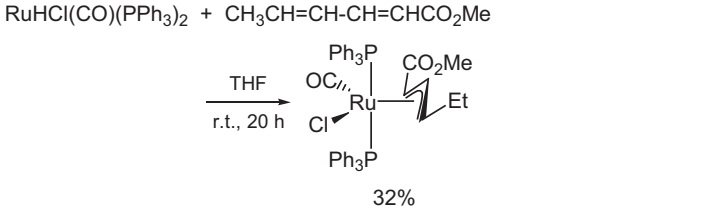
The cod complexes react with allyl halides to give yellow, crystalline, halo-bridged complexes, $Ru_2X_2(allyl)_2(cod)_2$ (X = Cl, Br), and in boiling methanol a suspension of $Ru(2\text{-methylallyl})_2(cod)$ reacts with triphenylphosphine with displacement of the diene ligand to give poorly soluble, pale yellow $Ru(2\text{-methylallyl})_2(PPh_3)_2$ [10].

One of the allyl groups in $Ru(\pi\text{-}C_3H_5)_2(diene)$ is readily removed by electrophiles in acetonitrile to give *cis*-$[Ru(MeCN)_2(diene)(\pi\text{-}C_3H_5)]^+$ (Eq. 5.3). The labile acetonitrile ligands are readily replaced by neutral chelating ligands (L_2 = 2,2′-bipyridine, 1,10-phenanthroline, 1,2-bis(dimethylarsino)benzene) or by acetylacetonate to yield $[RuL_2(diene)(\pi\text{-}C_3H_5)]^+$ and $Ru(acac)(nbd)(\pi\text{-}C_3H_5)$, respectively [11].



(5.3)

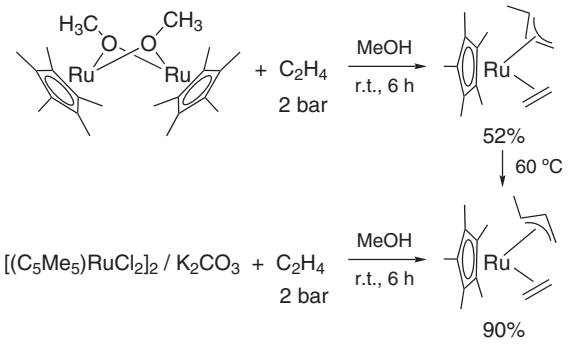
Methyl sorbate reacts with $RuHCl(CO)(PPh_3)_3$ by insertion into the Ru–H bond to give yellow $RuCl(CO)(PPh_3)_2\{CH(CO_2Me)CH{=}CHC_2H_5\text{-}1\text{-}3\text{-}\eta\}$ (Eq. 5.4) [12].



(5.4)

Although simple olefin addition products of $[(C_5Me_5)Ru(OMe)]_2$ are unstable at ambient temperature, under slightly more forcing conditions, the allyl complexes, $(C_5Me_5)Ru(\pi\text{-}C_3H_4Me)(C_2H_4)$ and $(C_5Me_5)Ru(\pi\text{-}C_3H_5)(C_3H_6)$, are formed by the reaction with ethylene and propylene, respectively [13]. When $[(C_5Me_5)Ru(OMe)]_2$ is treated with ethylene (under 2 bar pressure) in MeOH or hexane at room tempera-

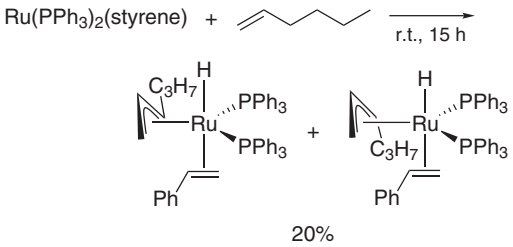
ture, a slow reaction occurs, as evidenced by a color change from cherry red to light brown, to give a yellow, air-stable complex, $(C_5Me_5)Ru(\pi\text{-}C_3H_4Me)(C_2H_4)$, which can be crystallized from pentane. If the mixture is heated to 60 °C, or alternatively if the reaction is conducted as a one-pot synthesis starting from $[(C_5Me_5)RuCl_2]_2/K_2CO_3$ in MeOH in the presence of ethylene, a second isomer is obtained (Eq. 5.5).



(5.5)

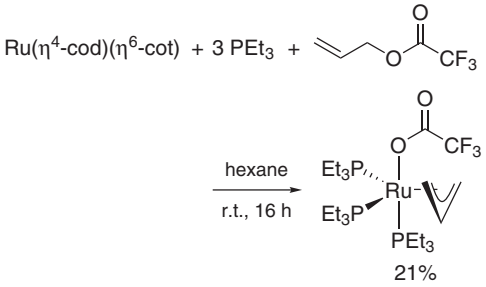
The oxidative addition of an allylic carbon–hydrogen bond to a transition-metal complex has been frequently invoked in the mechanism of the catalytic isomerization of olefins under hydride-free conditions.

The zerovalent ruthenium complex, $Ru(PPh_3)_2(styrene)_2$ reacts with hex-1-ene, either neat or in solution in petroleum, to give a yellow complex with a stoichiometry of $[RuH(PPh_3)_2(styrene)(C_6H_{11})]\cdot C_7H_8$ after recrystallization from toluene. On the basis of spectroscopic data (^1H, ^{31}P NMR) this has been suggested to be a mixture of *syn*- and *anti*-$RuH(PPh_3)_2(styrene)(1\text{-}3\text{-}\eta\text{-}C_6H_{11})$ (Eq. 5.6) [14].

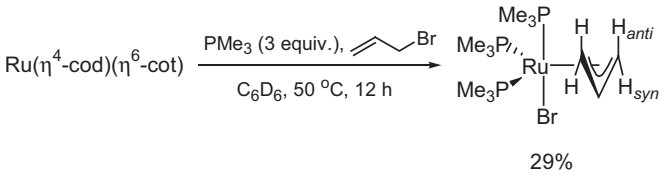


(5.6)

As mentioned above, the oxidative addition of allyl halides, carboxylates, ethers, and sulfides to Ru(0) complexes is a powerful tool for synthesizing π-allylruthenium(II) complexes (Eqs. 5.7 and 5.8) [15, 16].

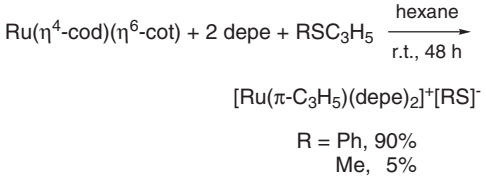


(5.7)



(5.8)

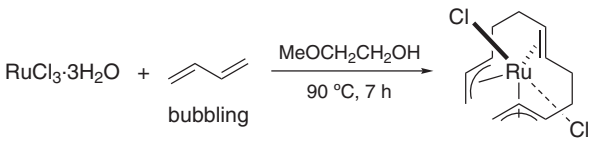
For example, allyl carboxylates or ethers react with Ru(η^4-cod)(η^6-cot) [cot = 1,3,5-cyclooctatriene] in the presence of monodentate tertiary phosphines to give a series of neutral π-allylruthenium(II) complexes, such as Ru(π-C_3H_5)(OCOR)(PR′$_3$)$_3$ [R = CF_3, Me, Ph; PR_3 = PMe_3, PEt_3, PMe_2Ph, $PMePh_2$] and Ru(OAr)(π-C_3H_5)-(PMe_3)$_3$ [Ar = Ph, C_6H_4-*o*-Me, C_6H_4-*o*-Et, C_6H_4-*o*-OMe], whereas similar reactions of these allyl ethers, sulfides, and carboxylates in the presence of the bidentate depe [depe = 1,2-bis(diethylphosphino)ethane] ligand give cationic π-allylruthenium(II) complexes, [Ru(π-C_3H_5)(depe)$_2$]$^+$RY$^-$ [RY = PhS, MeS, PhO, CF_3CO_2, CH_3CO_2] (Eq. 5.9).



(5.9)

5.2.2
π-Allylruthenium(IV) Complexes

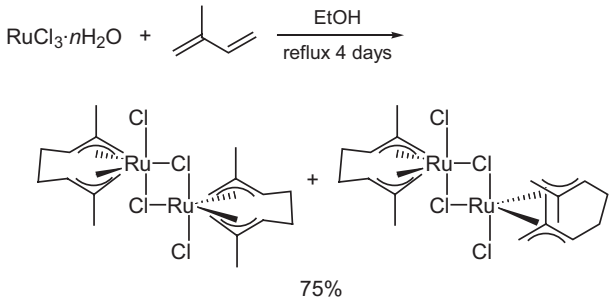
Methods for preparing bis(π-allyl)ruthenium(IV) complexes were first reported in the mid-1960s by Shaw, Allegra, and their coworkers. These complexes were obtained by the trimerization of butadiene or by tail-to-tail dimerization of isoprene with $RuCl_3$ in alcoholic solvents. For example, passage of butadiene through a solution of $RuCl_3$ in 2-methoxyethanol at 90 °C gives yellow-brown prisms of the complex $RuCl_2(C_{12}H_{18})$ (Eq. 5.10) [17]. X-ray crystallography has shown that this compound is dichloro(dodeca-2,6,10-triene-1,12-diyl)ruthenium(IV), which contains a ligand formed by cyclo-trimerization of butadiene and coordinated to ruthenium by a double bond and two π-allyl groups [18].



(5.10)

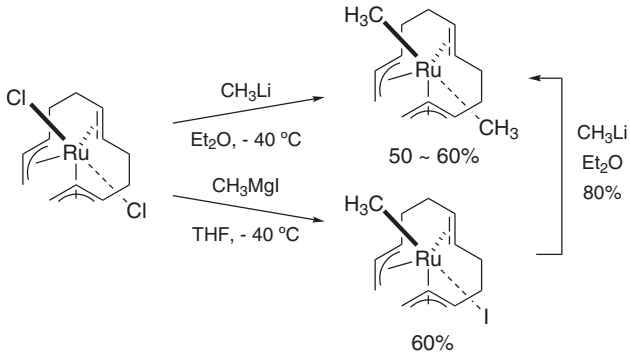
In contrast, isoprene undergoes tail-to-tail dimerization upon reacting with $RuCl_3$ and an excess of isoprene in ethanol to give a chloro-bridged 2,7-dimethylocta-2,6-diene-1,8-diyl complex, [RuCl(μ-Cl)(η^3:η^3-$C_{10}H_{16}$)]$_2$ [19], which exists in solution as a

pair of diastereomers, the meso form and the racemic form (Eq. 5.11). Black crystals of the meso form can be isolated by slow crystallization and their ^{1}H NMR spectra measured separately at ~200 K in a solution prepared at that temperature [20].



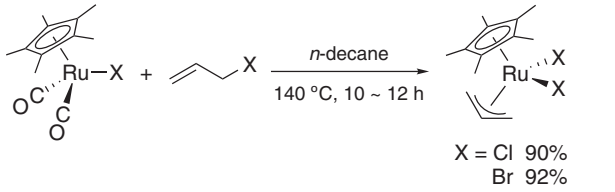
(5.11)

Itoh and co-workers prepared the first Ru(IV) alkyl-allyl complexes by the alkylation of $RuCl_2[(1\text{-}3\text{-}\eta\text{:}6,7\text{-}\eta\text{:}10\text{-}12\text{-}\eta)\text{-}C_{12}H_{18}]$ by means of CH_3MgX or an equimolar amount of CH_3Li (Eq. 5.12) [21].



(5.12)

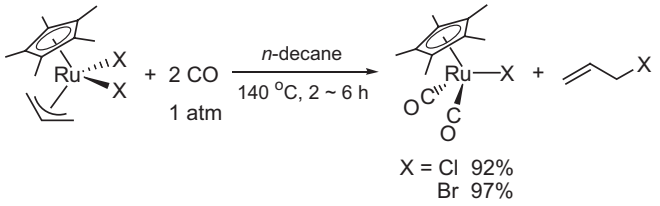
Other examples include the synthesis of π-allylruthenium(IV) complexes by the oxidative addition of allylic halides to $(C_5R_5)RuL_2X$ (R = H, Me; L = CO, PPh_3) (Eq. 5.13) [22, 23].



(5.13)

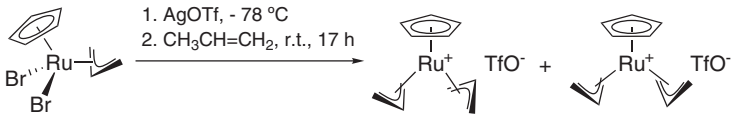
An X-ray structure determination was carried out on $(C_5Me_5)RuBr_2(\pi\text{-}C_3H_5)$, and showed a pseudo-piano-stool structure with two Br atoms and two terminal carbons for the *endo*-π-allyl ligand located at the basal positions. A crystal mirror plane bisects the pentamethylcyclopentadienyl and π-allyl ligands. The oxidative addition of allylic halides to $(C_5R_5)Ru(CO)_2X$ is reversible, since the reductive elimination of

allylic halides from Ru(IV)-allyl complexes proceeded under a CO atmosphere to reform the Ru(II)-carbonyl compounds (Eq. 5.14).



(5.14)

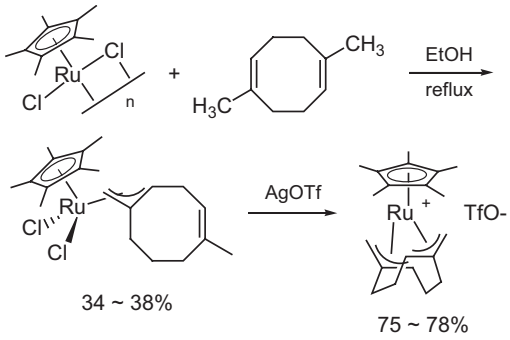
When $(C_5H_5)RuBr_2(\pi\text{-}C_3H_5)$ is treated with silver trifluoromethanesulfonate (silver triflate, AgOTf) and then reacted the reaction with propylene (1 atm), a new bis-allylic Ru(IV) cationic complex $[(C_5H_5)Ru(\pi\text{-}C_3H_5)_2]OTf$ is obtained in 95% yield as a mixture of two isomers, in which the allyl ligands have different configurations; *exo, endo* form and *endo,endo* isomer (Eq. 5.15) [24].



(5.15)

solvent	yield (%)	ratio
CH_2Cl_2	95	70 : 30
CH_2Cl_2-MeOH (7:3)	70	15 : 85

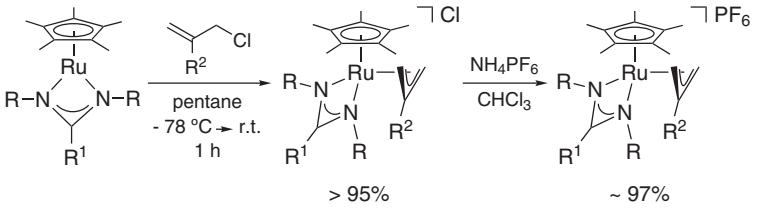
The former stereoisomer is predominant (70:30) in dichloromethane, whereas the latter prevails in the presence of alcohols (15:85). Interconversion did not occur in solution at ambient temperature. Although intermolecular allylic C–H bond activation of propylene did not occur in the case of pentamethylcyclopentadienyl analogues, it occurs readily in the case of the π-allylruthenium(IV) complex, (C_5Me_5)-$RuCl_2(\eta^3\text{-}C_{10}H_{15})$, obtained from 1,5-dimethyl-1,5-cyclooctadiene and $[(C_5Me_5)$-$RuCl_2]_2$, to result in the formation of the new bis-allylic complex $[(C_5Me_5)Ru(\eta^3,\eta^3$-$C_{10}H_{14})]OTf$ (Eq. 5.16).



(5.16)

The first oxidative addition of allylic substrates to the isolable coordinatively unsaturated complex $(C_5Me_5)Ru(\eta\text{-amidinate})$ has been observed, and this leads to a

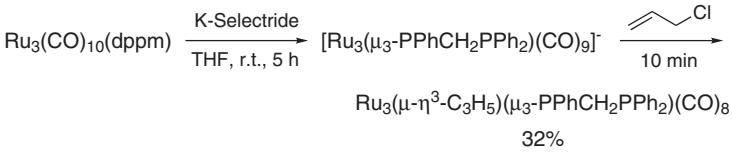
new cationic organoruthenium(IV) complex $[(C_5Me_5)Ru(\pi\text{-allyl})(\eta\text{-amidinate})]^+$ stabilized by a nitrogen-donor ligand (Eq. 5.17) [25].



(5.17)

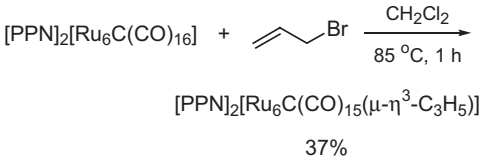
5.2.3
π-Allylruthenium Clusters

The reaction between $[Ru_3(\mu_3\text{-}PPhCH_2PPh_2)(CO)_9]^-$ and allyl chloride gives the yellow complex $Ru_3(\mu\text{-}\eta^3\text{-}C_3H_5)(\mu_3\text{-}PPhCH_2PPh_2)(CO)_8$, which has been shown by an X-ray study to contain a C_3H_5 ligand symmetrically bridging two metal atoms, a hitherto undescribed mode of attachment for an allyl group to a ruthenium metal cluster (Eq. 5.18) [26].



(5.18)

On the other hand, the reaction of $[PPN]_2[Ru_6C(CO)_{16}]$ (PPN = $(PPh_3)_2N^+$) with allyl bromide at 85 °C gives the allyl cluster, $[PPN][Ru_6C(CO)_{15}(\mu\text{-}\eta^3\text{-}C_3H_5)]$, in which the allyl ligand coordinates to one of the edges of the metal octahedron in a μ,η^3-manner. The structure of this complex has also been determined unequivocally by X-ray diffraction studies (Eq. 5.19) [27].



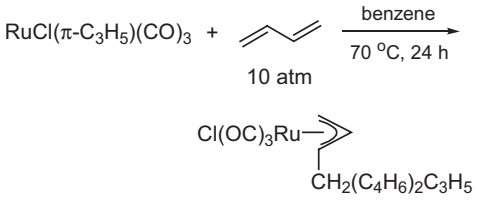
(5.19)

5.2.4
Reactivity and Catalytic Activity of $(\pi\text{-}C_3H_5)Ru(CO)_3X$ (X = Cl or Br)

Representative reactions with $(\pi\text{-}C_3H_5)Ru(CO)_3X$ are as follows. Alkynes, such as acetylene, phenylacetylene, and diphenylacetylene, react with $(\pi\text{-}C_3H_5)Ru(CO)_3Cl$ at 60–90 °C in aromatic hydrocarbons to give acyl complexes with a formula of

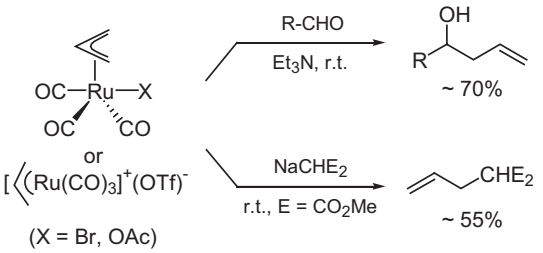
$[RuCl(OCCR{=}CR'C_3H_5)(CO)_2]_2$ arising from insertion of alkyne and CO into an allyl-ruthenium bond [28].

An analogous insertion reaction into the allyl-ruthenium bond occurs when $(\pi\text{-}C_3H_5)Ru(CO)_3Cl$ is treated with butadiene at 70–80 °C in hydrocarbon solution. A product arising from the addition of three molecules of butadiene to $(\pi\text{-}C_3H_5)Ru(CO)_3Cl$, corresponding to an empirical formula of $RuCl(C_{12}H_{18}C_3H_5)(CO)_3$, was separated and identified (Eq. 5.20) [28].



(5.20)

The ambiphilic character of π-allylruthenium complexes is in remarkable contrast to palladium chemistry [29]. A series of $(\pi\text{-}C_3H_5)RuX(CO)_3$ (X = Br, OAc or OTf) complexes prefer the attack of electrophiles such as aldehydes as well as the attack of nucleophiles such as $NaCH(CO_2Me)_2$, while π-allylpalladium complexes react exclusively with nucleophiles. Thus, stoichiometric reactions of π-allylruthenium complex with benzaldehyde and the sodium salt of diethyl malonate afford the corresponding homoallyl alcohol and allylmalonate, respectively (Scheme 5.1). The carbonyl ligand plays a very important role, and ambiphilic reactivity is realized only in ruthenium complexes bearing a carbon monoxide ligand.



Scheme 5.1 Ambiphilic reactivity of $(\pi\text{-}C_3H_5)Ru(CO)_3X$.

Other π-allylruthenium complexes bearing phosphine ligands, such as $Ru(OCOCF_3)(\pi\text{-}C_3H_5)(PEt_3)_3$ [15] and $RuBr(\pi\text{-}C_3H_5)(PMe_3)_3$ [16], did not react with $NaCH(CO_2Me)_2$, but did react with benzaldehyde at an elevated temperature (50–80 °C) to give the corresponding homoallyl alcohol. This is one reason why carbon monoxide is needed for catalytic reactions (vide infra). The allylation reaction of formaldehyde with $RuBr(\pi\text{-}C_3H_5)(CO)_3$, and the reactivity of formaldehyde complexes of $[Ru(\pi\text{-}C_3H_5)(HCHO)(CO)_3]^+$ and $RuBr(\pi\text{-}C_3H_5)(HCHO)(CO)_2$ were theoretically investigated with ab initio MP2-MP4(SDQ), CCSD(T), and DFT (B3LYP) methods [30].

The regioselectivity of the attack of the π-allyl moiety of ruthenium complexes by nucleophiles is also notable, since the reaction exclusively occurs at the more-substituted allylic terminus in π-allylruthenium complexes [29]. These reactions can be carried out catalytically by choosing appropriate ruthenium catalysts and reaction conditions (vide infra).

$(\pi\text{-}C_3H_5)Ru(CO)_3Cl$ is an effective catalyst for the hydrogenation of terminal and cyclic alkenes at a temperature of 80–100 °C under a hydrogen pressure of 1–20 atm. The substrate undergoes very rapid isomerization during the hydrogenation; isomerization also takes place in the absence of hydrogen [28].

The polymer-anchored catalyst $(\pi\text{-}C_3H_5)Ru(CO)_3X$ (X = Cl, or Br) on poly(4-vinylpyridine) has also been investigated, and has been shown to be an active catalyst for alkene isomerization (Figure 5.2) [31].

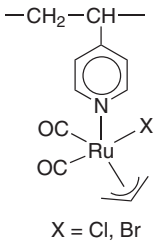


Figure 5.2 The polymer-anchored catalyst $(\pi\text{-}C_3H_5)Ru(CO)_3X$ on poly(4-vinylpyridine).

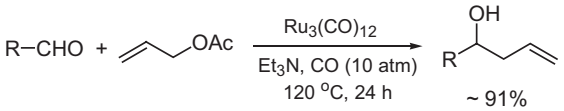
$(\pi\text{-}C_3H_5)Ru(CO)_3X$ (X = Cl, or Br) are also effective catalysts for the oligomerization of alkenes. A high proportion of straight-chain hexanes are obtained from ethylene. On the other hand, oligomers of ethylene ($>C_6$) and oligomerization products of propylene and 1-butene are mainly branched compounds due to the high isomerization activity of these catalysts. The catalytic activity of these complexes can be remarkably enhanced by adding organoaluminum halides [32].

5.3 Catalytic Reactions via π-Allylruthenium Intermediates

5.3.1 C–C Bond Formation via π-Allylruthenium Intermediates

Palladium-catalyzed allylic substitution reactions with carbon- and nitrogen-nucleophiles have been successfully applied to synthetic organic chemistry [4]. In this process, allylic esters can be considered an allylic cation synthon, which can react with nucleophiles. Recently, more attention has been paid to the umpolung [33] of these electrophilic π-allylpalladium intermediates in the reaction of palladium-catalyzed allylation reactions of aldehydes and ketones. However, these reactions require a stoichiometric amount of SmI_2 [34] or $SnCl_2$ [35] to generate nucleophilic allylic species. In the case of ruthenium, allylic acetates smoothly react with aldehydes to give homoallylic alcohols in high yields via a *nucleophilic* π-allylruthenium intermediate

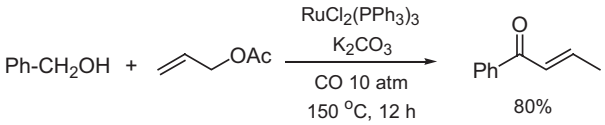
(Eq. 5.21) [36]. Notably, this reaction proceeds without the aid of additional metal compounds such as SmI_2 or $SnCl_2$.



(5.21)

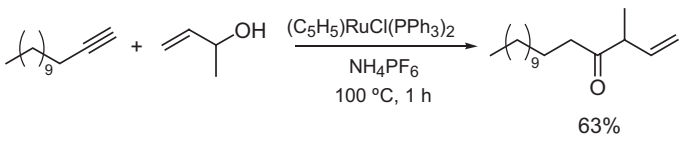
Carbon monoxide is essential for the present reaction (vide supra), and no reaction occurred at all under an argon atmosphere. The addition of base is also indispensable, and Et_3N is the most effective base, which should be a hydrogen source for the products. Allylic carbonates and allylic halides did not give products in good yield.

This nucleophilic reactivity of π-allylruthenium intermediates can be applied to the synthesis of enones. In general, primary alcohols react smoothly with allylic acetates in the presence of a catalytic amount of $RuCl_2(PPh_3)_3$ and an excess of K_2CO_3 under carbon monoxide to give the corresponding α,β-unsaturated ketones in high yields (Eq. 5.22) [37]. This addition occurred regioselectively at the more substituted carbon atom of the π-allyl ligand.



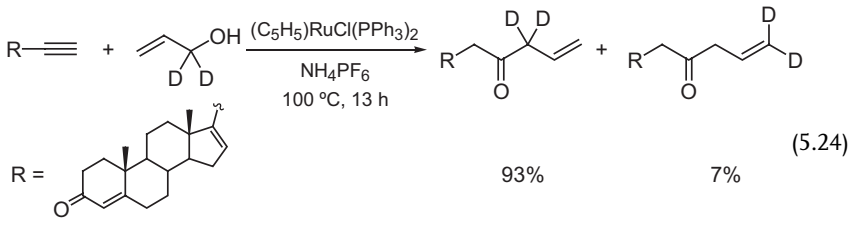
(5.22)

The ruthenium complex $(C_5H_5)RuCl(PPh_3)_2$ with NH_4PF_6 catalyzes the addition of allylic alcohols to terminal alkynes, yielding β,γ-unsaturated ketones (Eq. 5.23) [38]. This process involves the nucleophilic attack of allylic alcohols to a (vinylidene)ruthenium intermediate, leading to the formation of an (acyl)(π-allyl)ruthenium intermediate.

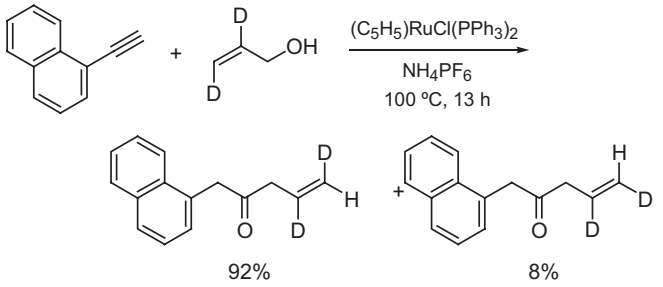


(5.23)

Insight into the mechanism involved was obtained in two labeling studies, as shown in Eqs. 5.24 and 5.25. The former indicates that the carbon bearing the hydroxyl group preferentially forms the new C–C bond to the terminal alkyne carbon. The latter indicates that the alkene geometry is largely retained. These studies support the intervention of a π-allyl species in which rotation around the ruthenium-allyl axis is slow relative to the rate of reductive elimination and the absence of a σ-allyl intermediate.



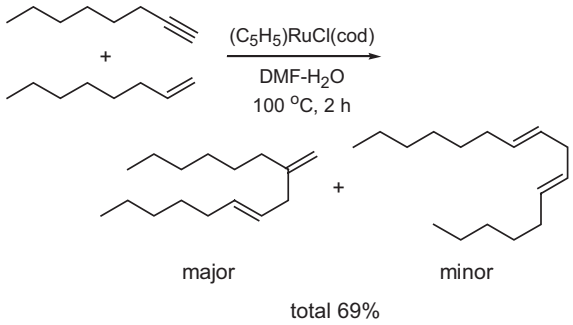
(5.24)



(5.25)

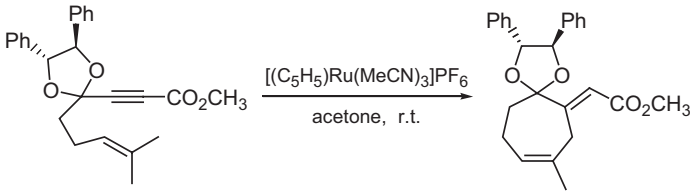
A similar ruthenium complex $(C_5H_5)RuCl(cod)$ catalyzes a totally different reaction pathway for alkynes and allylic alcohols to produce γ,δ-unsaturated ketones, which involves a ruthenacyclopentene intermediate, rather than a π-allylruthenium intermediate [39].

On the other hand, the ruthenium-catalyzed addition of alkenes to alkynes involves a π-allylruthenium intermediate [40]. Heating a 1:1 mixture of 1-octene and 1-octyne in 3:1 DMF-water at 100 °C with 5 mol% of ruthenium complex $(C_5H_5)RuCl(cod)$ for 2 h gave a 1:1 adduct, the spectroscopic properties of which clearly showed it to be a branched 1,4-diene with a small amount of the regioisomeric linear adduct (Eq. 5.26).



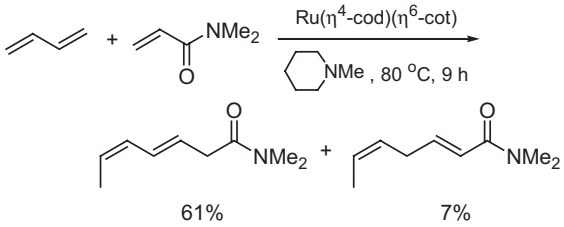
(5.26)

Cycloisomerization of 1,6-enynoate catalyzed by $[(C_5H_5)Ru(MeCN)_3]PF_6$ proceeds smoothly under mild reaction conditions to give a seven-membered ring compound in excellent yield (Eq. 5.27) [41]. In this reaction, the insertion of a C–H to form a π-allylruthenium intermediate is supported by deuterium-labeling studies.



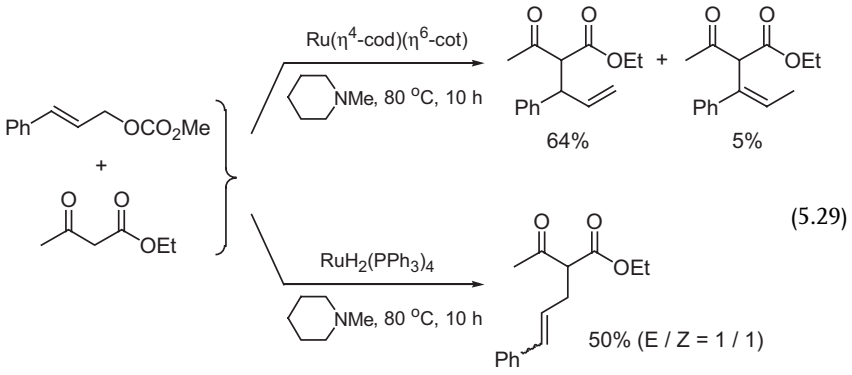
(5.27)

Ruthenium-catalyzed highly selective carbon-carbon bond-forming reactions involving the codimerization of alkenes and alkynes have been developed. Ru(η^4-cod)(η^6-cot) has turned out to be an excellent catalyst for these reactions [42]. The first and highly selective synthesis of 3,5-dienoic acid derivatives by the catalytic codimerization of 1,3-dienes with acrylic compounds has been developed (Eq. 5.28) [43]. 1,3-Butadiene, isoprene, 1,3-pentadiene, and 2,3-dimethylbutadiene reacted smoothly with acrylic compounds in the presence of a catalytic amount of Ru(η^4-cod)(η^6-cot) in *N*-methylpiperidine to give the corresponding linear codimers, 3,5-dienoic acid derivatives, in high yields. The stereochemistry of (5*Z*) in the products strongly suggests that the reaction proceeds via an *anti*-π-allylruthenium intermediate.



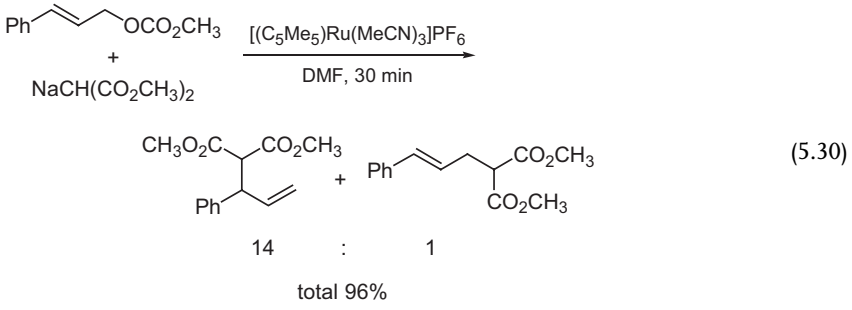
(5.28)

One of the benefits of allylic substitution reactions is the prospect that with unsymmetrical allylic substrates, the regioselectivity can be controlled by the catalyst. In ruthenium-catalyzed allylic substitution reactions, the regioselectivity can be controlled by choosing the appropriate ruthenium catalysts combined with ligands. The reaction of ethyl acetoacetate with cinnamyl methyl carbonate in the presence of a catalytic amount of Ru(η^4-cod)(η^6-cot) gave the corresponding cinnamylated products in high yield with high regioselectivity accompanied by the liberation of CO_2 and MeOH [44]. The reaction proceeds smoothly in *N*-methylpiperidine under mild reaction conditions (at 80 °C for 10 h). Notably, Ru(η^4-cod)(η^6-cot) and $RuH_2(PPh_3)_4$ [45] gave products with quite different regioselectivities. In the reaction of cinnamyl methyl carbonate with ethyl acetoacetate catalyzed by $RuH_2(PPh_3)_4$, ethyl 2-acetyl-5-phenyl-4-pentenoate was obtained as the sole product due to α-attack by the nucleophile. Using Ru(η^4-cod)(η^6-cot) catalyst with ethyl acetoacetate, only the product derived by selective γ-attack, ethyl 2-acetyl-3-phenyl-4-pentenoate was obtained as a major product. Thus, the regionselectivity of the products was remarkably influenced by the ruthenium catalyst used (Eq. 5.29).



(5.29)

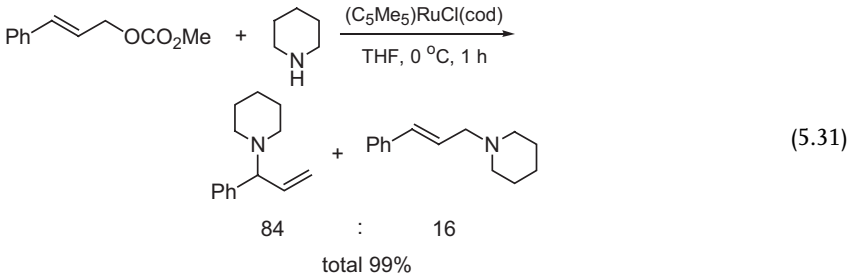
Recently, a new ruthenium catalyst that also provides regioselective allylic alkylation has been reported. In DMF, a highly branched alkylation product of cinnamyl carbonate with malonate anion was obtained in quantitative yield (branched/linear = 14/1) within 30 min in the presence of 1 mol% of $[(C_5Me_5)Ru(MeCN)_3]PF_6$ catalyst (Eq. 5.30) [46].



(5.30)

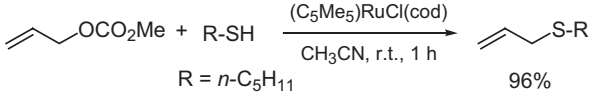
These ruthenium-catalyzed allylic alkylations differ from previous catalytic systems (Pd, Mo, W, and Rh) in several important respects, and nicely complement the previous systems. In particular, heteroatom nucleophiles that fail with Mo and W succeed with these ruthenium systems

For example, $(C_5Me_5)RuCl(cod)$ showed high catalytic activity for allylic substitution by amines (heteroatom nucleophiles that fail with Mo and W catalysts) under extremely mild reaction conditions (0 °C, for 1 h; >99% yield). The reaction is also highly regioselective to give branched *N*-allylamines as a major product (Eq. 5.31) [29].



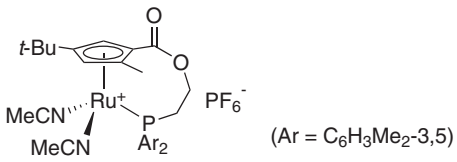
(5.31)

Furthermore, sulfur nucleophiles such as thiols can be used for ruthenium-catalyzed allylation reactions. Recent progress in the transition-metal complex-catalyzed synthesis of allylic sulfides without poisoning of the catalyst has included: (1) rearrangement of *O*-allylphosphoro- or phosphonothionates [47]; (2) conversion of *O*-allyl or *S*-allyl dithiocarbonates with liberation of carbon oxide sulfide (COS) [48]; and (3) allylic substitution by silylated thiols [49], heterocyclic sulfur nucleophiles [50], sodium thiophenoxides [51], and aromatic thiols [52]. The ruthenium complex seems to be one of the most promising catalysts for the transformation of sulfur-containing compounds [53]. In fact, the first ruthenium-catalyzed allylation of both aliphatic and aromatic thiols with various allylic reagents including allylic alcohols under extremely mild reaction conditions has been developed [54]. Treatment of aliphatic and aromatic thiols, represented by pentanethiol and benzenethiol, with allyl methyl carbonate in the presence of 5 mol% $(C_5Me_5)RuCl(cod)$ in CH_3CN at room temperature for 1 h under an argon atmosphere gave the corresponding allylic sulfides, allyl pentyl sulfide and allyl phenyl sulfide, respectively, in high yields (Eq. 5.32).



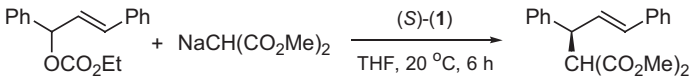
(5.32)

Enantioselective allylic substitutions catalyzed by transition-metal complexes are a powerful method for constructing complex organic molecules [4f,55]. Palladium-based catalysts have often given excellent results. To expand the scope of the reaction, a new enantioselective allylic alkylation catalyzed by planar-chiral ruthenium complexes was developed [56]. For example, the reaction of 1,3-diphenyl-2-propenyl ethyl carbonate with sodium dimethyl malonate in the presence of 5 mol% of a planar chiral (*S*)-ruthenium complex (Figure 5.3) at 20 °C for 6 h in THF resulted in the formation of the corresponding chiral allylic alkylated product of dimethyl 2-((2*E*)(1*S*)-1,3-diphenylprop-2-enyl)propane-1,3-dioate in 99% yield with 96% *e.e.* (Eq. 5.33).



(*S*) - (1)

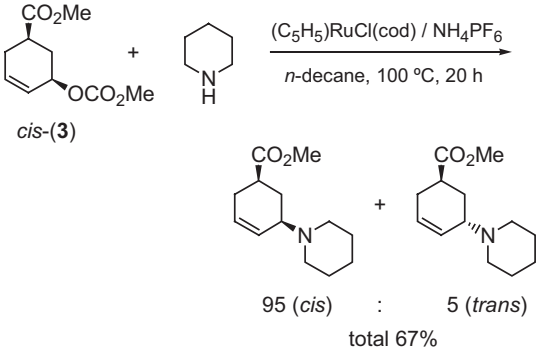
Figure 5.3 A planar chiral ruthenium complex, (*S*)-(**1**).



(5.33)

99% yield, 96% ee (*S*)

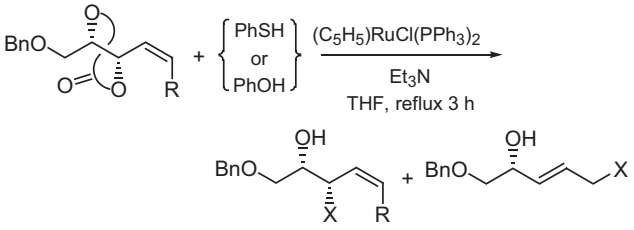
$(C_5Me_5)RuCl(cod)$ is a highly effective catalyst for regioselective allylic amination and alkylation reactions of *acyclic* allyl carbonates (vide supra) [29], but it was totally ineffective for allylic substitution of *cyclic* allyl carbonates. To investigate the stereoselectivity of ruthenium-catalyzed allylic substitution reactions, the development of a new catalyst system, which is highly effective for the allylic substitution of *cyclic* allyl carbonates, is needed. A novel ruthenium catalyst system of $(C_5H_5)RuCl(cod)/NH_4PF_6$ is effective for the allylic substitution of *cyclic* allyl carbonates, and enables the first investigation of the stereochemical course of ruthenium-catalyzed allylic substitution [57]. Treatment of *cis*-5-methoxycarbonylcyclohex-2-enyl methyl carbonate with piperidine in the presence of 5 mol% $(C_5H_5)RuCl(cod)$ and 10 mol% NH_4PF_6 in decane at 100 °C for 20 h predominantly gave methyl *cis*-5-piperidylcyclohex-3-enecarboxylate (total yield = 67%, *cis*:*trans* = 95:5) (Eq. 5.34).



(5.34)

Although few investigations have been made to determine the stereochemical course of the reaction of π-allylruthenium complexes with nucleophiles, Harman and coworkers recently reported that the reaction with soft nucleophiles exclusively proceeded via an *anti* mechanism [58]. The observations described here, together with information in the literature, suggest that the ruthenium-catalyzed allylic substitution reaction proceeds via a double inversion (i.e., a net retention) mechanism.

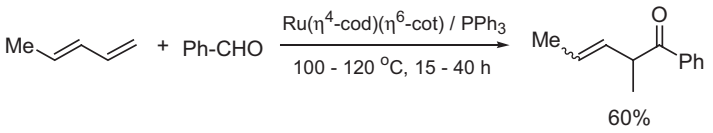
Allylic substitution of allylic cyclic carbonates with PhSH or PhOH is also catalyzed by $(C_5H_5)Ru(PPh_3)_2Cl$ complex (5 mol%) to afford (*E*)-allylic alcohol and erythro-*β*-hydroxy thiophenoxide or phenoxide, respectively, where the substitution proceeds by the external attack of a π-allylruthenium complex by nucleophiles with an overall net retention of configuration (Eq. 5.35) [59].



R = H, X = SPh (38%) X = SPh (37%)
X = OPh (40%) X = OPh (37%)
R = Me, X = SPh (60%)

(5.35)

The first ruthenium-catalyzed intermolecular hydroacylation of 1,3-dienes with aldehydes via a π-allylruthenium intermediate has been reported (Eq. 5.36) [60].

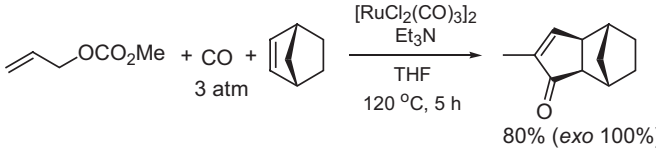


(5.36)

General palladium-catalyzed reactions of 1,3-dienes with aldehydes give tetrahydropyran derivatives and/or open-chain homoallyl alcohols [61]. Thus, the present reaction offers a novel method for preparing β,γ-unsaturated ketones from readily available 1,3-dienes and aldehydes.

In this reaction, carbon monoxide is not needed. The key intermediate is an (acyl)(π-allyl)ruthenium complex that undergoes reductive elimination to give the corresponding β,γ-unsaturated ketones.

Ruthenium-catalyzed carbonylations of allylic compounds [62] were described in Chapter 11. Here, ruthenium-catalyzed carbonylative cyclization of allylic carbonates with alkenes, not alkynes, which offers a new route to cyclopentenones is revealed [63]. Treatment of allyl methyl carbonate with 2-norbornene in the presence of 2.5 mol% $[RuCl_2(CO)_3]_2$ and 10 mol% Et_3N in THF at 120 °C for 5 h under 3 atm of carbon monoxide gave the corresponding cyclopentenone, *exo*-4-methyltricyclo[5.2.1.$0^{2,6}$]dec-4-en-3-one, in 80% yield with high stereoselectivity (*exo* 100%) (Eq. 5.37).



(5.37)

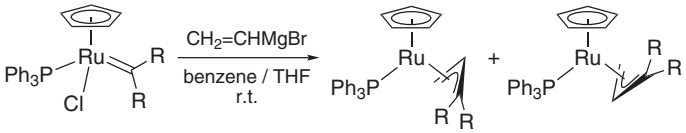
To clarify the intermediacy of a π-allylruthenium complex, the stoichiometric reaction of $RuBr(\pi\text{-}C_3H_5)(CO)_3$ with an equimolar amount of 2-norbornene was examined, and the corresponding cyclopentenone was obtained in an isolated yield of 47%. This π-allylruthenium complex also showed high catalytic activity in the presence of Et_3N for the carbonylative cyclization of allyl methyl carbonate with 2-norbornene to give the corresponding cyclopentenone in 65% yield. Consequently, the π-allylruthenium complex, an analogue of $RuBr(\pi\text{-}C_3H_5)(CO)_3$, appears to be the key intermediate as well as an active catalyst precursor in the present reaction.

5.3.2
Miscellaneous Reactions via π-Allylruthenium Intermediates

A series of easily prepared and exceptionally active ruthenium catalysts for ring-opening metathesis polymerization (ROMP) have been reported. As mentioned previously, the reaction of isoprene with $RuCl_3$ gave a bis(π-allyl)ruthenium(IV) complex of $[RuCl(\mu\text{-}Cl)(\eta^3\text{:}\eta^3\text{-}C_{10}H_{16})]_2$, which was converted into cationic bis(π-allyl)-ruthenium(IV) complexes by treatment with silver tetrafluoroborate. All of these complexes are stable in air and in solution for several hours. Although alone they

are almost completely ROMP-inactive, in the presence of aliphatic diazo compounds (e.g., ethyl diazoacetate), they show unusual catalytic activity with very short reaction times [64]. ROMP of 2-norbornene by this catalyst system gave a yield of up to 99% with a turnover frequency (TOF) of 24 000 h^{-1} within 2.5 min. Based on ^1H NMR and gel-permeation chromatography (GPC) analyses of the generated polymer, ethyl ester end groups could be identified, and this result clearly indicated that the ruthenium complex and diazoalkane initially form a carbene complex.

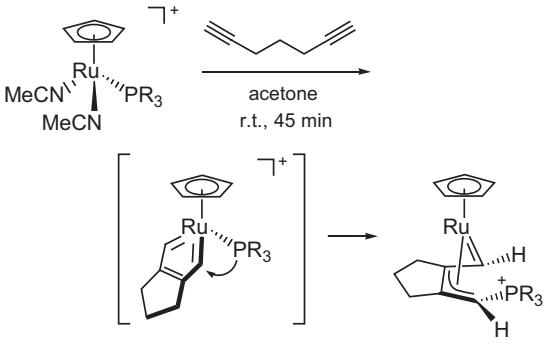
Furthermore, a ruthenium-mediated [C_1 + C_2] coupling leading to the formation of π-allylruthenium complexes has been reported (Eq. 5.38) [65]. The reaction of (carbene)ruthenium complexes of composition [$(C_5H_5)RuCl(=CR_2)(PPh_3)$] (R = Ph, *p*-$C_6H_4Cl$, *p*-$C_6H_4OMe$) with vinyl Grignard reagent leads, in benzene/THF at room temperature, to the displacement of chloro ligand and the formation of 1,1-diarylallyl complexes in 45~65% yield.



R = Ph
p-C_6H_4Cl
p-C_6H_4OMe

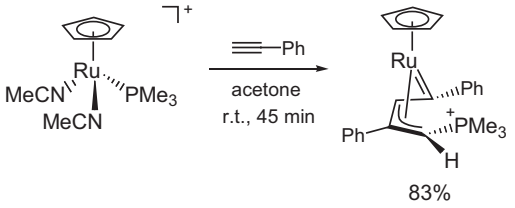
(5.38)

Selective C–C bond formation between alkynes mediated by the $[(C_5H_5)Ru(PR_3)]^+$ fragment leading to ruthenium allyl carbene complexes has recently been reported by Kirchner and coworkers [66]. The complexes $[(C_5H_5)Ru(PR_3)(MeCN)_2]PF_6$ (R = Me, Ph, Cy) react with 1,6-heptadiyne and HC≡CR′ (R′ = Ph, C_6H_9, *n*-Bu, H), most likely via a ruthenacyclopentatriene intermediate, to give the ruthenium allyl carbene complexes $[(C_5H_5)Ru\{=CH\text{-}\eta^3\text{-}C(CH_2)_3CCHPR_3\}]PF_6$ and $[(C_5H_5)Ru\{=C(R')\text{-}\eta^3\text{-}CHC(R')CHPMe_3\}]PF_6$, respectively (Eqs. 5.39 and 5.40). It was further demonstrated that these ruthenium allyl carbene complexes are acting as pseudo-16e species, reacting with both nucleophiles (PPh_3) and electrophiles (CF_3CO_2H) and being able to dehydrogenate a cyclohexyl group of the bulky PCy_3 ligand.



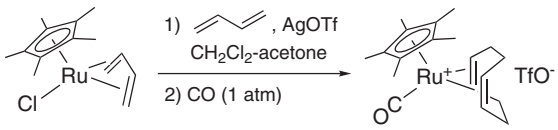
R = Me 85%
Ph 90%

(5.39)

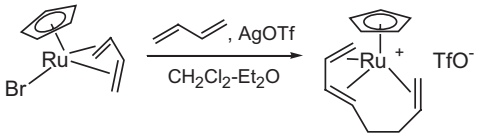


83% (5.40)

The oligomerization and cooligomerization of conjugated dienes are representative reactions that proceed via transition-metal π-allyl intermediates. When $(C_5Me_5)RuCl(\eta^4$-butadiene) in dichloromethane was treated with an acetone solution of an equimolar amount of silver trifluoromethanesulfonate (AgOTf) in the presence of excess butadiene at ambient temperature, after which the mixture was allowed to react with carbon monoxide (1 atm), a cationic 1,5-cyclooctadiene carbonyl complex, $[(C_5Me_5)Ru(CO)(\eta^2{:}\eta^2\text{-}1,5\text{-}C_8H_{12})]OTf$, was isolated in 95% yield (Eq. 5.41), whereas selective linear dimerization took place upon similar treatment with $(C_5H_5)RuBr(\eta^4$-butadiene), which gave $[(C_5H_5)Ru(\eta^4{:}\eta^2\text{-}1,3,7\text{-octatriene})]OTf$ (Eq. 5.42) [67].

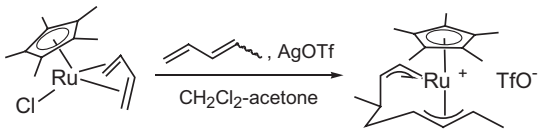


95% (5.41)



71% (5.42)

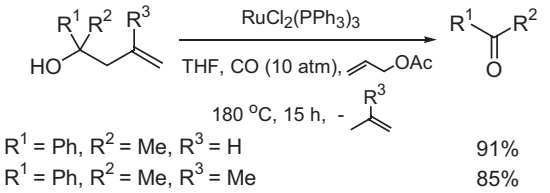
The intermediacy of bis(π-allyl)ruthenium complexes has been strongly suggested by the fact that a similar reaction of $(C_5Me_5)RuCl(\eta^4$-1,3-pentadiene) with 1,3-pentadiene in the presence of AgOTf affords $[(C_5Me_5)Ru\{4\text{-methyl-}(1\text{-}3\text{-}\eta^3{:}6\text{-}8\text{-}\eta^3)\text{-nonadienediyl}\}]OTf$ via a regioselective tail-to-head dimerization reaction (Eq. 5.43).



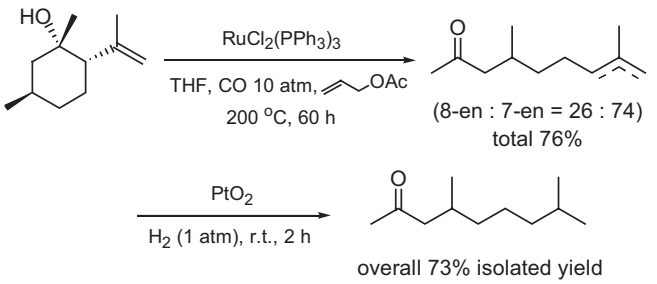
92% (5.43)

Catalytic cyclodimerization of dienes can also be performed selectively. 1,5-Cyclooctadiene, dimethylcyclooctadienes, and 6-methyl-2,4,7-nonatriene can be obtained from butadiene, isoprene, and 1,3-pentadiene, respectively, upon treatment with a catalytic amount of $(C_5Me_5)RuCl$(diene) and AgOTf.

The development of efficient methods for the selective formation and cleavage of C–C bonds catalyzed by transition-metal complexes is a central and challenging subject of modern organic synthesis [68]. Recently, the selective deallylation of tertiary homoallyl alcohols by ruthenium catalyst has been developed as an example of a ruthenium-catalyzed selective carbon-carbon bond-cleaving reaction [69]. For example, the treatment of tertiary homoallyl alcohols with an excess of allyl acetate in the presence of 5 mol% $RuCl_2(PPh_3)_3$ in THF under 10 atm of carbon monoxide at 180 °C for 15 h gave a deallylated product, the corresponding ketones and alkenes, in high yields (Eq. 5.44). The formation of a stable π-allylruthenium intermediate by β-allyl elimination should contribute significantly to the driving force of this catalytic reaction. The present reaction also offers a novel method for the catalytic ring-opening of general 2-vinylcycloalkanols (Eq. 5.45).



(5.44)



(5.45)

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6
Ruthenium-Catalyzed Olefin Metathesis

Robert H. Grubbs and Tina M. Trnka

6.1
Introduction

The olefin metathesis reaction is an elegant chemical transformation that entails the metal-carbene-catalyzed cleavage and reassembly of carbon-carbon double bonds. Although simple at first glance, this reaction can be applied in an enormous variety of synthetically useful permutations, such as ring-closing metathesis (RCM), cross metathesis (CM), acyclic diene metathesis polymerization (ADMET), and ring-opening metathesis polymerization (ROMP) (Figure 6.1). For this reason, olefin metathesis has become a valuable tool for the preparation of molecules in organic, inorganic, biochemical, medicinal, polymer, and materials chemistry.

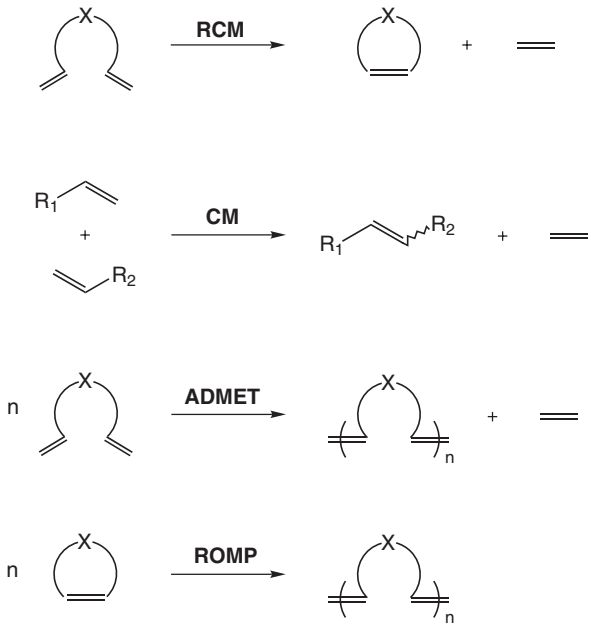

Figure 6.1 Examples of olefin metathesis processes. Ring-closing metathesis (RCM), cross metathesis (CM), acyclic diene metathesis polymerization (ADMET), and ring-opening metathesis polymerization (ROMP).

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This chapter is concerned specifically with olefin metathesis reactions catalyzed by ruthenium-carbene complexes, mainly because of their great success during recent years. We begin with an overview of these catalysts, and then focus on mechanistic considerations that are important for understanding the reactivity profiles of various catalyst derivatives. The second part of the chapter deals with applications of ruthenium-catalyzed olefin metathesis, especially RCM, CM, and combination processes in organic synthesis.

6.2
Ruthenium Olefin Metathesis Catalysts

It is interesting to recall the history of olefin metathesis and the origins of ruthenium-based catalysts. During the 1960s and 1970s, most metathesis catalysts consisted of early transition metal salt-alkylating reagent mixtures or supported metal oxides [1]. Although these multicomponent systems were limited in substrate scope, their catalytic activity was quite high, and this feature resulted in the commercialization of olefin metathesis (e.g., in the SHOP and Phillips triolefin processes). There were few advances in catalyst design, however, until the isolation of well-defined, metathesis-active complexes in the late 1970s. In particular, the Tebbe reagent $Cp_2Ti[(\mu\text{-}CH_2)(\mu\text{-}Cl)AlMe_2]$ [2] and Schrock's molybdenum and tungsten alkylidene catalysts $(NAr)(OR)_2M{=}CHR'$ [3] were responsible for revealing new possibilities in olefin metathesis chemistry. These complexes enabled several groundbreaking achievements, including the first living ROMP reactions, the first ROMP reactions with sterically hindered substrates, and the first RCM applications [4].

However, once again, the main obstacle to further development was one of limited substrate scope resulting from the oxophilic titanium, molybdenum, and tungsten metal centers. The problem is illustrated in Figure 6.2, which summarizes the reactivity of early and late transition metal olefin metathesis catalysts with common

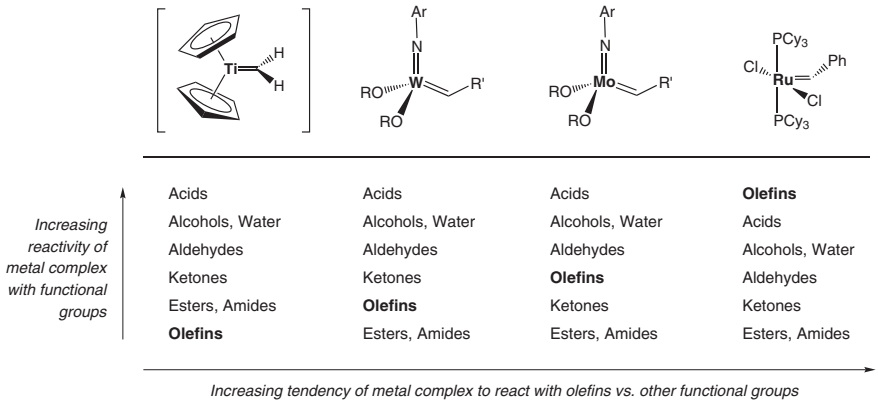


Figure 6.2 The reactivity of titanium-, molybdenum-, tungsten-, and ruthenium-carbene complexes with various functionalities.

functional groups. The titanium complex, for instance, reacts with protic functionalities and carbonyl-containing substrates in preference to olefins. In comparison, the molybdenum complex displays some compatibility with ketones, esters, and amides, but it is deactivated by aldehydes, alcohols, and water.

On the other hand, late transition metal-based catalyst systems that had been identified by the early 1990s were characterized by low activity but high functional group tolerance, especially toward water and other protic solvents. These features led to reinvestigations of ruthenium systems and, ultimately, to the preparation of the first well-defined, ruthenium-carbene olefin metathesis catalyst $(PPh_3)_2(Cl)_2Ru{=}CHCH{=}Ph_2$ (Ru-1) in 1992 [5].

Since that time, a wide variety of ruthenium-based catalysts have been prepared and studied [6]. The derivatives most commonly used in synthetic applications are the so-called "first-generation" bis(phosphine) complex $(PCy_3)_2(Cl)_2Ru{=}CHPh$ (Ru-2) and the "second-generation" *N*-heterocyclic carbene complex $(H_2IMes)(PCy_3)(Cl)_2Ru{=}CHPh$ (Ru-4) (H_2IMes = 1,3-dimesityl-imidazolidine-2-ylidene) (Figure 6.3). These catalysts have many merits with respect to their preparation, use, functional group compatibility, catalytic activity, tunability, and applications.

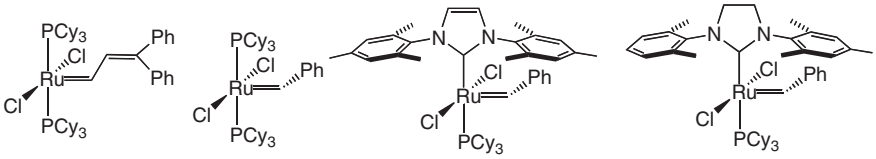


Figure 6.3 Ruthenium olefin metathesis catalysts. Cy = cyclohexyl.

Catalysts Ru-2 and Ru-4 are readily accessible for laboratory and industrial use because they are convenient to prepare through relatively short synthetic procedures. The development of large-scale preparations has also made these catalysts commercially available at increasingly lower costs. Although the syntheses of Ru-2 and Ru-4 must be performed under inert atmosphere conditions, these complexes are air-stable once isolated, and can be stored on the bench top. For applications in organic and polymer chemistry, Ru-2 and Ru-4 are easily handled using standard laboratory techniques. Another advantage is that these catalysts operate under mild reaction conditions, usually 40–80 °C and at atmospheric or slightly reduced pressures, and it is usual to obtain high product conversions with 1 to 5 mol% catalyst loadings. As illustrated in Figure 6.2, ruthenium-carbene complexes are compatible with most common functional groups, and thus can operate on diverse substrates. This point is described further in Section 6.3 with examples and applications from organic synthesis.

Furthermore, ruthenium-carbene complexes are highly tunable, well-defined, single-site, homogeneous catalysts. These characteristics provide the ability to access all catalytically active sites and thus to influence catalyst initiation, propagation, and stability properties. The relatively simple ligand environment of Ru-2, Ru-4, and

related derivatives has provided the opportunity systematically to alter their steric and electronic properties and observe the impact on catalytic performance. These studies have provided valuable mechanistic information and made it possible to tailor catalysts for specialty applications (e.g., enantioselective catalysis, solid-supported catalysis). All of these features make Ru-2 and Ru-4 high-performing and flexible catalysts, which are the primary reasons for their success.

6.2.1 Mechanistic Considerations

Mechanistic studies have played a particularly important role in the development of new ruthenium-carbene catalysts for olefin metathesis. The most critical aspects of their chemistry include: (i) the formation of the catalytically active species from the starting ruthenium-carbene complex; (ii) the propagation of this species in the catalytic cycle; and (iii) the ultimate decomposition of the active species. A range of mechanistic studies have revealed that the profiles of Ru-2 and Ru-4 differ significantly with respect to these points.

Catalyst initiation involves the formation of a metathesis-active ruthenium species from the starting precatalyst and its entry into the catalytic cycle. For both Ru-2 and Ru-4, the initiation event consists of phosphine (PCy_3) dissociation to produce the 14-electron intermediate [$(L)(Cl)_2Ru{=}CHR'$], where L = PCy_3 for Ru-2 and L = H_2IMes for Ru-4) (Figure 6.4). Although this proposed species has not been observed in solution, it has been identified in the gas phase [7], and the ligand dissociation step has been studied by ^{31}P NMR magnetization transfer experiments,

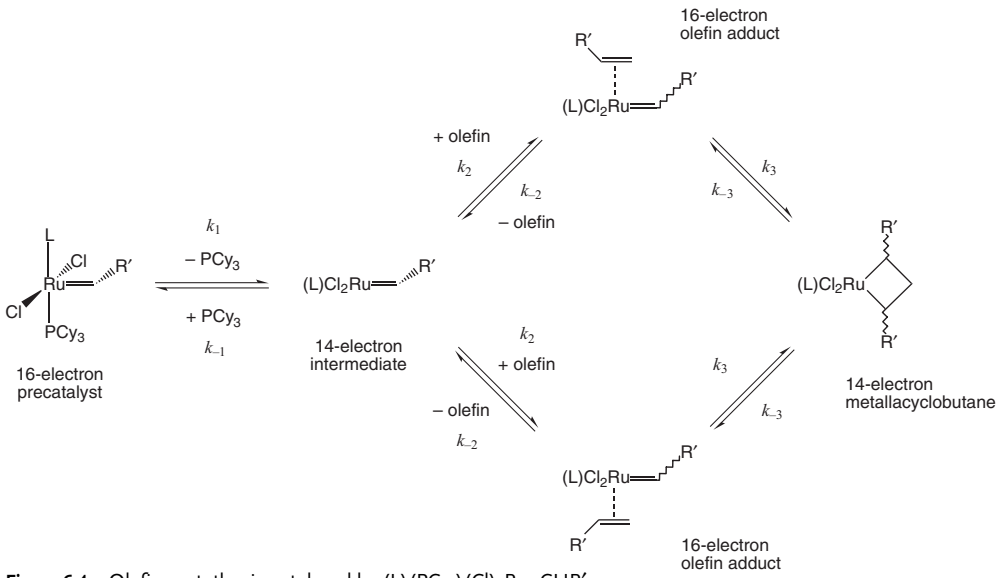


Figure 6.4 Olefin metathesis catalyzed by $(L)(PCy_3)(Cl)_2Ru{=}CHR'$ complexes (L = PCy_3 for Ru-1, Ru-2, Imes for Ru-3, H_2Imes for Ru-4).

^{1}H NMR and UV-visible kinetics, and mass spectrometry [8]. Consistent with a dissociative mechanism, catalytic turnover is inhibited by the addition of free phosphine, and enhanced by the addition of phosphine scavengers [8].

The rate of catalyst initiation – and thus the concentration of the catalytically active 14-electron species in solution – is determined by the lability of the ligand that must dissociate from the ruthenium center. In turn, the lability of this ligand is directly related to the strength of the ruthenium-ligand bond, a function of the stereoelectronic characteristics of both the ligand and the entire ruthenium-carbene moiety. For example, the effect of differentiating the L-type ligands in Ru-4 is to slow the initiation rate constant (k_1) by two orders of magnitude compared to that of Ru-2. A proposed explanation of this effect involves the strong electron-donating power of the H_2IMes ligand, which increases the electron density of the ruthenium center and thus the strength of the Ru-PCy_3 interaction in Ru-4 compared to Ru-2.

Once the [(L)$(Cl)_2$Ru=CHR′] intermediate forms, it has the potential to enter the catalytic cycle by coordinating with an olefinic substrate (Figure 6.4). Then, the resulting 16-electron olefin adduct can undergo [2 + 2] cycloaddition to form a 14-electron metallacyclobutane species. Subsequent metallacycle cleavage regenerates an olefin adduct, and productive propagation is completed by liberation of the coordinated olefin and regeneration of the 14-electron intermediate.

The overall metathesis activity of this class of ruthenium-carbene catalysts is determined by the relative magnitudes of several rate constants: (i) the rate constant of phosphine dissociation (k_1), which dictates the rate at which the precatalyst complex enters the catalytic cycle; (ii) the ratio of k_{-1}/k_2, which dictates the rate of catalyst deactivation (by re-coordination of phosphine) versus catalytic turnover (by coordination of olefinic substrate and subsequent steps); and (iii) the rate constant of metallacyclobutane formation (k_3), which dictates the rate of carbon-carbon bond formation.

Catalyst Ru-4 exhibits overall superior activity and improved substrate scope relative to catalyst Ru-2. For example, Ru-4 completes simple metathesis reactions, such as the RCM of diethyl diallylmalonate or the ROMP of cyclooctadiene, at rates several orders of magnitude greater than with Ru-2. In addition, whereas catalyst Ru-2 is unreactive toward sterically congested or electronically deactivated substrates, Ru-4 successfully mediates the formation of tetra-substituted olefins in five- and six-membered rings systems [9], as well as CM to form tri-substituted olefins and products containing electron-withdrawing substituents [10].

These differences in activity between Ru-2 and Ru-4 originate from a combination of effects. Although Ru-4 initiates more slowly than Ru-2 (vide supra), and hence less of the active 14-electron species is present, the *N*-heterocyclic carbene-coordinated species [(H_2IMes)$(Cl)_2$Ru=CHR′] is far more active for olefin metathesis than the corresponding phosphine-coordinated derivative [(PCy_3)$(Cl)_2$Ru=CHR′]. Once [(H_2IMes)$(Cl)_2$Ru=CHR′] forms, it can bind olefins at a rate proportional to k_2, or can be deactivated by re-coordination of phosphine at a rate proportional to k_{-1}. The ratios of these rate constants reveal that k_{-1}/k_2 for Ru-2 is four orders of magnitude larger than that for Ru-4 [8]. The relative magnitudes of k_1 (10^2 smaller) and k_{-1}/k_2 (10^4 larger) for Ru-4 relative to Ru-2 translate into the observed 10^2 to 10^3-fold over-

all higher rate of catalytic activity observed with Ru-4. In other words, rapid turnover in the catalytic cycle occurs in situations where the active species exhibits high selectivity for binding to the olefinic substrate relative to free phosphine (a small k_{-1}/k_2 value), as well as fast metallacyclobutane formation (a large k_3 value). Both of these effects are maximized by *N*-heterocyclic carbene ligands that stabilize the two critical electron-deficient, coordinatively-unsaturated intermediates {i.e., $[(L)(Cl)_2Ru{=}CHR']$ and the metallacyclobutane species} through steric and electronic influences.

An additional mechanistic consideration is catalyst deactivation by thermal decomposition routes. Studies show that the decomposition of Ru-2 and Ru-4 is inhibited by the addition of free phosphine, which suggests that degradation involves phosphine dissociation followed by bimolecular coupling of $[(L)(Cl)_2Ru{=}CHR']$ [8]. For this reason, the use of phosphine scavengers to increase the concentration of $[(L)(Cl)_2Ru{=}CHR']$ in solution and thereby increase the overall rate of olefin metathesis also results in accelerated catalyst decomposition. This effect is manifested in the temporarily high activity but limited longevity of Ru-2 and Ru-4 in the presence of CuCl or HCl. Alternatively, the ligand environment can be tuned to simultaneously increase the rate of catalysis and decrease the rate of decomposition, as in catalyst Ru-4. The particularly high thermal stability of this complex appears to result from the slow rate of phosphine dissociation from this complex, as well as steric and electronic stabilization of $[(H_2IMes)(Cl)_2Ru{=}CHR']$ by the H_2IMes ligand. This combination of effects makes Ru-4 especially robust and capable of accomplishing challenging metathesis transformations.

6.2.2
Case Study: Developing a Ruthenium-Carbene Catalyst for Acrylonitrile Metathesis

Some of the most difficult metathesis transformations involve olefins directly functionalized with electronically deactivating substituents, such as acrylonitrile. This substrate is challenging, because the mechanism of olefin metathesis requires the formation of α-substituted carbene intermediates. As illustrated in Figure 6.5, once Ru-4 undergoes turnover with 1 equiv. of acrylonitrile, the propagating species become the cyano-substituted carbene $[(H_2IMes)(Cl)_2Ru{=}CH(CN)]$ alternating with the methylidene derivative $[(H_2IMes)(Cl)_2Ru{=}CH_2]$.

Such α-carbene substituents can have a large impact on the olefin metathesis reactivity and stability of the resulting species. For example, studies have shown that the reaction of Ru-4 with acrylonitrile cleanly provides the cyanosubstituted carbene complex $(H_2IMes)(PCy_3)(Cl)_2Ru{=}CH(CN)$ [11]. Even in the presence of a large excess of acrylonitrile, no metathesis beyond the initial turnover occurs – that is, no fumaronitrile H(CN)C=CH(CN) or ethylene forms. These results suggest that the 14-electron species $[(H_2IMes)(Cl)_2Ru{=}CH(CN)]$ is trapped out of the catalytic cycle by reassociation of the PCy_3 ligand to yield $(H_2IMes)(PCy_3)(Cl)_2Ru{=}CH(CN)$ (Figure 6.6). Due to the electron-withdrawing properties of the cyano functionality, this complex initiates extremely poorly compared to Ru-4 and cannot re-enter the catalytic cycle.

This problem can be overcome by tuning the ligand sphere of catalyst Ru-4. For example, both the isopropoxy-tethered ruthenium complex $(H_2IMes)(Cl)_2Ru{=}CH$-

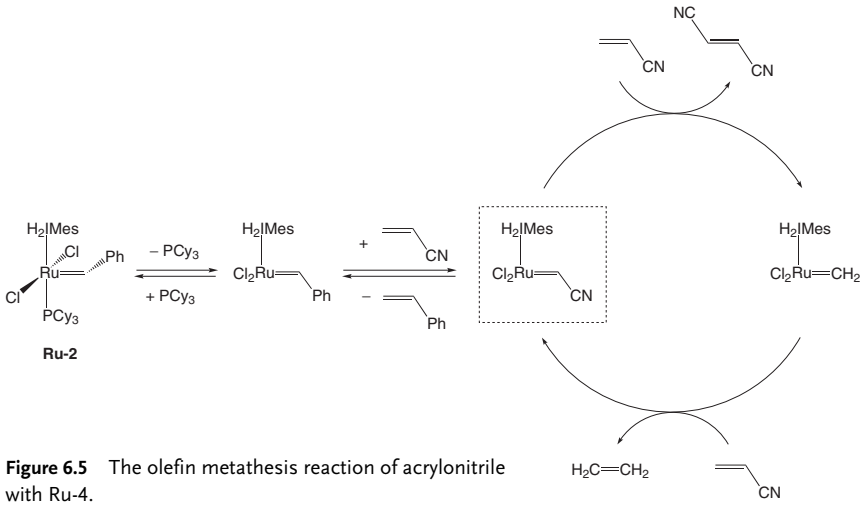


Figure 6.5 The olefin metathesis reaction of acrylonitrile with Ru-4.

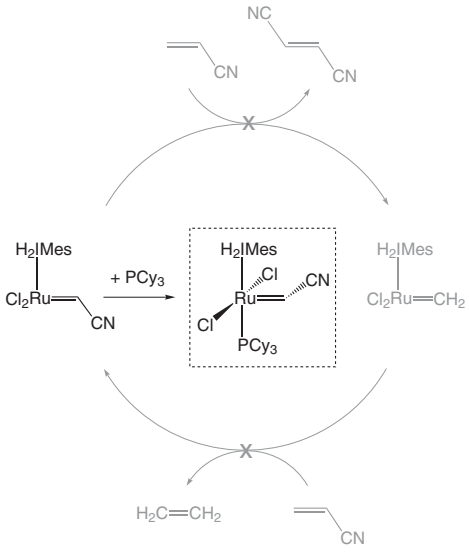


Figure 6.6 Formation of the catalytically inactive ruthenium-carbene complex $(H_2Imes))(PCy_3)(Cl)_2Ru{=}CH(CN)$ during the reaction of acrylonitrile with Ru-4.

$(C_6H_4OPr^i)$ [12] and the 3-bromopyridine derivative $(H_2IMes)(3\text{-}BrPy)(Cl)_2Ru{=}CHPh$ [12] (Figure 6.7) are capable of reactions such as CM between acrylonitrile and allylbenzene. This improvement in activity is presumably because the corresponding cyano-carbene species are less likely to remain trapped by the more weakly bound ether and pyridine ligands.

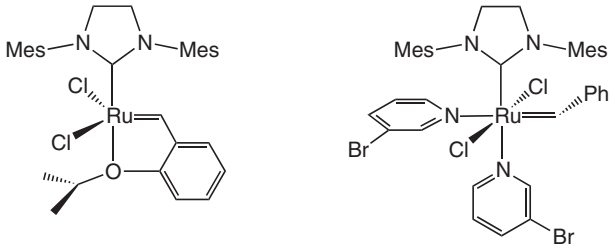


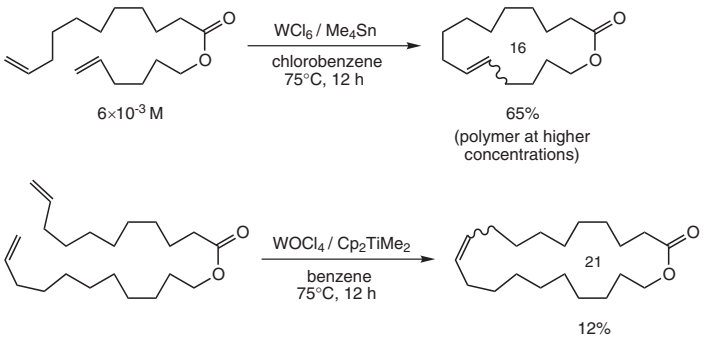
Figure 6.7 Two ruthenium-carbene complexes that are active for cross-metathesis reactions.

6.3 Applications of Ruthenium-Catalyzed Olefin Metathesis in Organic Synthesis

Olefin metathesis reactions are attractive transformations in organic synthesis for many reasons. Chief among them are: (i) the reliability of the reactions and the catalysts; and (ii) the relative simplicity of these transformation, as they normally involve readily available substrates and do not require protecting groups for reactive functionalities.

6.3.1 Ring-Closing Metathesis

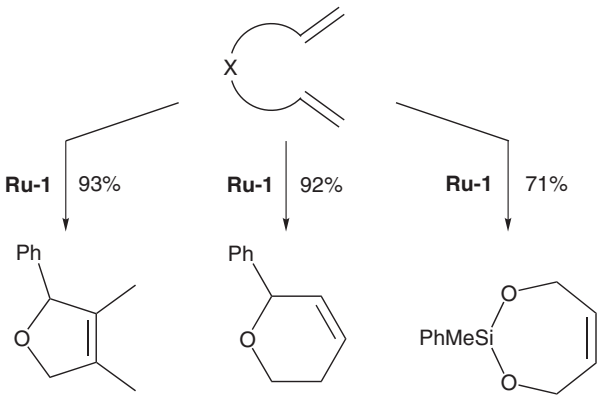
Ring-closing metathesis (RCM) has become a major reaction in organic chemistry for exactly these reasons. The first demonstrations that RCM could be used to prepare interesting, functionalized, cyclic olefins occurred during the early 1980s. At that time, the available catalysts consisted of tungsten halides combined with alkylating agents. For example, Villemin demonstrated that high yields of cyclic metathesis products could be obtained under conditions of high dilution [13]. In the same year, Tsuji and Hashiguchi prepared a large ring system by RCM and noted the need for improved catalysts with the statement, "In order to exploit the metathesis reaction as a truly useful synthetic methodology, it is essential to discover a new catalyst system which can tolerate the presence of functional groups in olefin molecules." (Eq. 6.1) [14].



(6.1)

Key to the advancement of this field was the development of well-defined catalysts that could be added to the reaction mixture instead of depending on in-situ creation of the catalyst, as in the classical systems used by Tsuji and Villemin. The classical systems required strong Lewis acid components that would react with most organic functionality. Although some success was achieved using the titanium-based Tebbe Complex [15], the development of general applicability resulted from the synthesis of the family of molybdenum and tungsten alkylidene complexes in the Schrock laboratory [16]. These catalysts were used in the synthesis of a variety of cyclic heterocyclic compounds with a range of double bond substitutions. Although the molybdenum complex remains the catalyst of choice for some applications [17], the ruthenium systems – due to their broad range of functional group compatibilities and stability under normal conditions – have become the major workhorses in the area of RCM. These ruthenium-based catalysts now allow the metathesis reaction to be fully exploited in organic synthesis [4].

When Professor Greg Fu was a postdoctoral at Caltech, he demonstrated the applicability of the molybdenum catalysts in ring-closing olefin metathesis reactions [18]. His results alerted the organic community to the power of olefin metathesis. As he was completing his stay at Caltech, the first of the ruthenium-based systems Ru-1 was prepared, and Fu demonstrated that these ruthenium systems could successfully carry out the basic ring-closing metathesis reactions, as well as highlighting their improved functional group tolerance and ease of use (Eq. 6.2) [19].



(6.2)

6.3.1.1 General Features of RCM

The major byproduct of RCM is the dimer of the substrate. The problem of controlling RCM versus dimerization or oligomerization (ADMET) can be analyzed from a number of different points of view; however, the most informative for organic applications is to consider the instantaneous concentration of rings and oligomers.

The equation in Figure 6.8 outlines all of the major competing reactions in an RCM reaction:

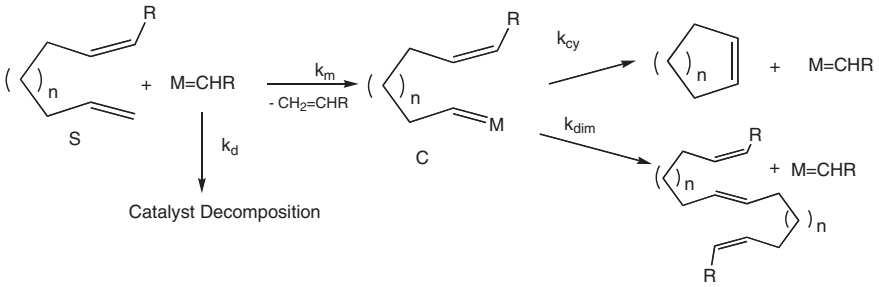


Figure 6.8 The ratio of cyclic to dimer product in ring-closing metathesis (RCM).

The instantaneous concentration of the desired cyclic product relative to the byproducts is shown below. In this analysis, the rate of dimerization k_{dim} is independent of ring size, and is only determined by the substitution on the double bond. As the rate of cyclization, k_{cy}, decreases due to substrate structure, the concentration of substrate must be decreased in order to maintain a high ratio of product to oligomers since, for most situations, the competing rate is a constant and the only variable is the concentration of substrate.

$$\frac{\left[\left(\right)_n\right]}{\left[\left(\right)_n \quad \left(\right)_n\right]} = \frac{k_{cy}\ [C]}{k_{dim}\ [C]\ [S]} = \left[\frac{1}{[S]}\right]\left[\frac{k_{cy}}{k_{dim}}\right] \tag{6.3}$$

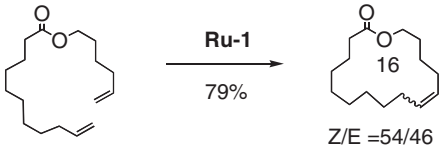
Unfortunately, since the metathesis rate is first order in substrate, a decrease in substrate concentration also decreases the rate of metathesis. To maintain adequate rates and to allow the rate of the second-order reaction – metathesis – to compete with decomposition, the concentration of catalyst must often be raised. As a consequence of the decrease in substrate concentration and an increase in catalyst concentration, the mol% catalyst can be quite high in some cases. The increased stability of the newer generations of catalysts has helped to improve this deficiency. In addition, since the ring-closing reaction is unimolecular and the oligomerization is second order, higher temperatures often favor RCM reactions.

RCM has been embraced by the organic community, and its utility has been demonstrated in a number of applications. A limited selection of these reactions is outlined below to demonstrate special features of the transformations.

6.3.1.2 Synthesis of Medium-Sized Rings using RCM

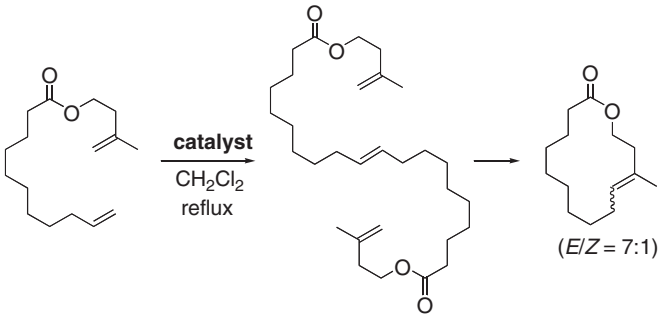
As indicated above, the classical systems were able to close medium-sized rings in reasonable yield, while the well-defined systems are even more effective.

Soon after publication of the original methods using well-defined catalysts, the groups of Hoveyda [20] Martin [21] and Fürstner [22] exploited the reaction in the synthesis of a wide variety of medium-sized rings (Eq. 6.4).



(6.4)

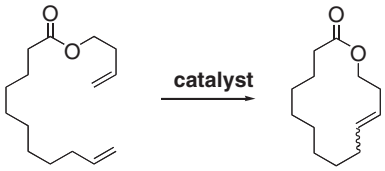
As more active members of the ruthenium catalyst family were developed, more complex systems could be prepared. For example, the first generation of ruthenium catalysts were very selective for less-substituted double bonds, and would not close tri-substituted double bonds in medium-ring systems. As demonstrated below, Ru-1 would only react with the unsubstituted terminal double bond. However, the newer catalyst will convert the intermediate into the desired ring system containing a tri-substituted double bond (Eq. 6.5) [23].



(6.5)

catalyst			
	Ru-2 (10%), 17 h	69%	0%
	Ru-3 (10%), 40 h	trace	65%
	Ru-4 (6%), 40 h	trace	57%

An additional problem that has been partially overcome with the newer catalysts is the control of the *E*:*Z* stereochemistry of the resulting products. For example, in the synthesis of epotholone, the Danischefsky group examined the stereochemistry as a function of the substituents around the ring [24]. With Ru-2, the *E*:*Z* stereochemistry of the product was found to be controlled by subtle conformational changes induced by substituents. That the Ru-2 and other bisphosphine catalysts gave the kinetically controlled product was demonstrated in a simple system (Figure 6.9).

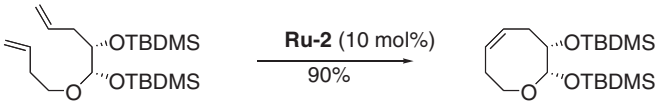


Catalyst	time	conversion	*E*:*Z*
Ru-4 (1 mol%)	40 min.	Quant	11.5:1
Ru-4 (1 mol%)		20%	5:1
Ru-2 (5 mol%)	5 h	97%	4.5:1

Figure 6.9 Stereochemistry of ring closing metathesis as a function of catalyst structure.

It was found that the bisphosphine system gave a 4.5:1 *E*:*Z* ratio of products, independently of the time of exposure to the catalyst. The 4.5:1 mix of products could be exposed to more Ru-2 without change. However, when the more active catalyst Ru-4 was used in the reaction, the products were equilibrated. At low conversions, the *E*:*Z* ratio was near that obtained with Ru-2, but at higher conversions the ratio increased to 11.5:1. If the product mixture of 4.5:1 was reacted with Ru-4, it was equilibrated to the equilibrium mixture of 11.5:1 [25].

Eight-membered rings pose special problems [26], and only systems with some steric constraints give acceptable yields of products (Eq. 6.6) [27].

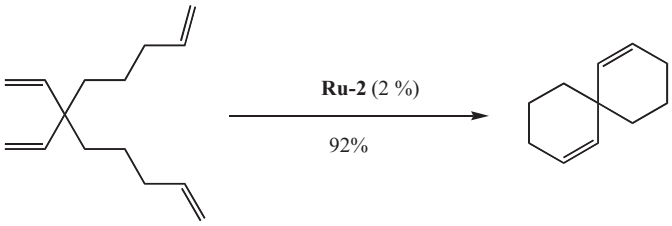


(6.6)

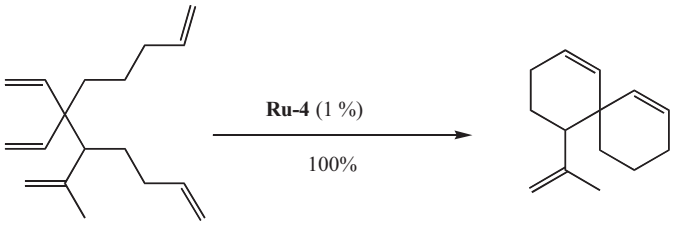
With the larger rings, the more difficult the ring is to close, the lower the concentration of substrate that can be used to provide a good yield. As the concentration of substrate decreases, the concentration of catalyst must be maintained at a concentration to give acceptable rates. As a result, the mol% catalyst is higher for more difficult RCM reactions.

6.3.1.3 Synthesis of Small Rings using RCM

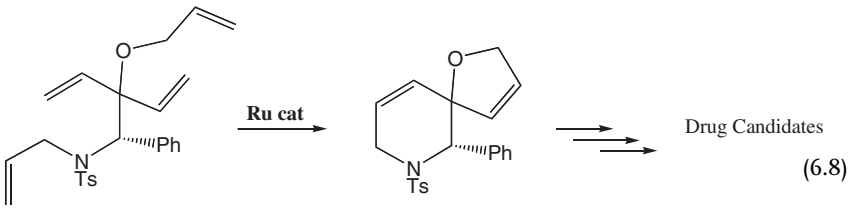
The formation of five-, six- and seven-membered rings using RCM is very favorable, and can be used to generate complexes systems in one step. For example, spiro compounds are readily prepared by RCM of precursors that are straightforward to synthesize. In the examples below (Eq. 6.7), the six-membered ring formation is favored [28].



(6.7)

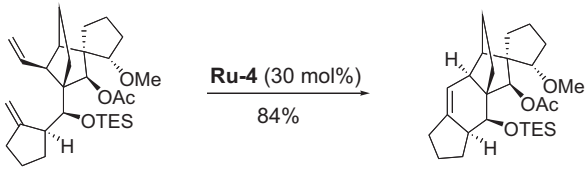


The second case in these examples demonstrates that high yields can be obtained for rather complex systems when using low catalyst loadings. An example of the rapid generation of a spiro-ring system for use as a pharmaceutical scaffold has been demonstrated by the Merck group. In this example, the starting materials are easily prepared in three steps (Eq. 6.8) [29].



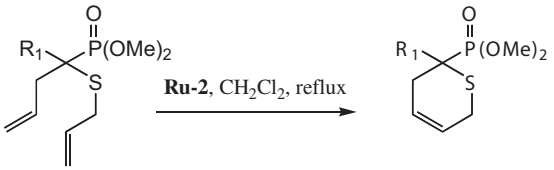
(6.8)

A particularly challenging case involves the formation of highly substituted, highly congested ring systems. In this example, the favorable formation of the six-membered ring allows this steric hindrance to be overcome (Eq. 6.9) [30].



(6.9)

Highly functionalized heterocycles can be easily generated using RCM reactions. The Hanson group has demonstrated that a family of highly functionalized sulfur and phosphorous compounds can be prepared in good yield using the ruthenium catalysts (Eq. 6.10) [31].

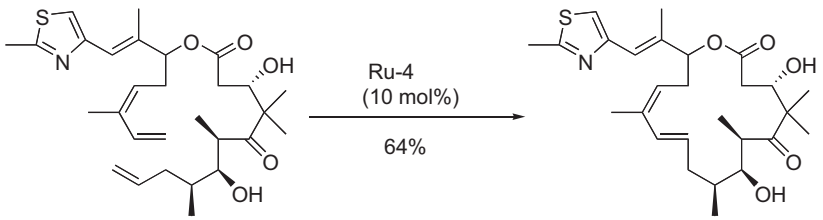


(6.10)

$R_1 = CO_2Me$, catalyst (5 mol%), 1.5 h 78%
$R_1 = CO_2{}^tBu$, catalyst (5 mol%), 20 h 99%

6.3.1.4 Complex and Highly Functionalized Systems

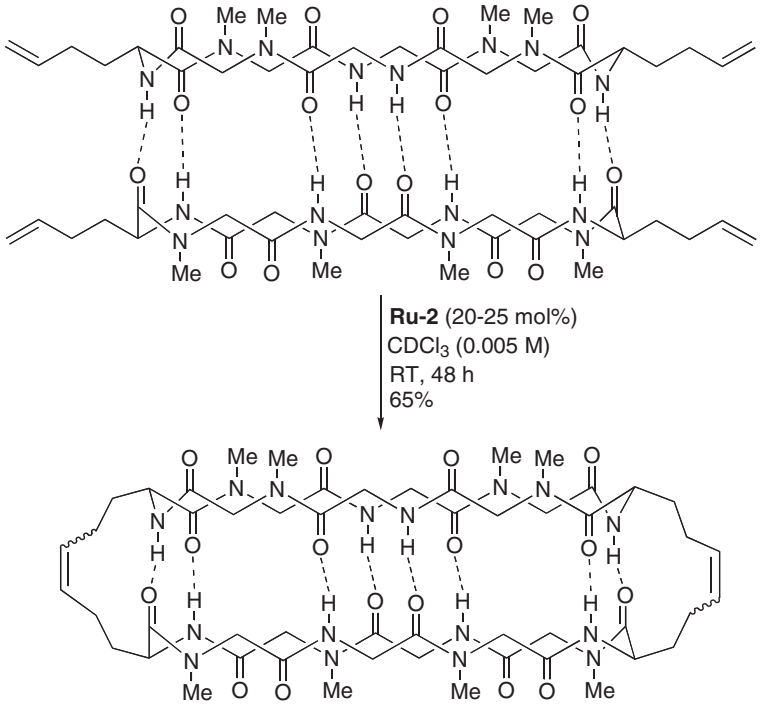
The functional group compatibility has been demonstrated in a number of cases, and the following were chosen to demonstrate the complexity and high level of functionality that can be tolerated. The Danischefsky group has finessed the stereochemistry problem in the synthesis of epotholone by closing a diene system in which the stereochemistry of the required double bond is already set [32]. The double bond formed by metathesis is selectively reduced to give the desired product (Eq. 6.11).



(6.11)

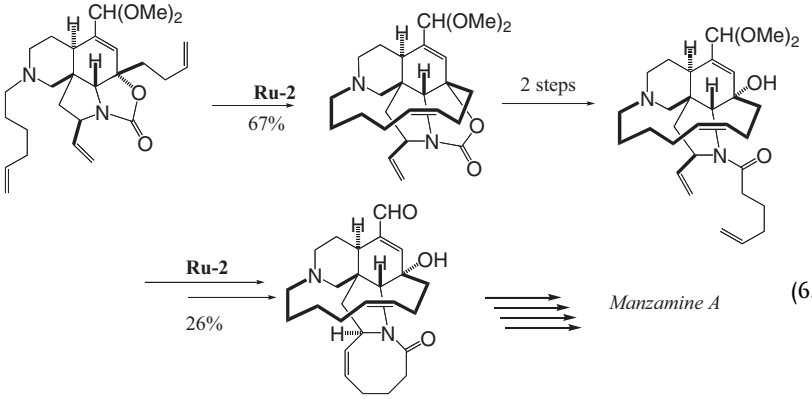
The example in Eq. 6.11 demonstrates the compatibility of the catalyst system with a variety of protic and basic groups that were not possible to use in metathesis reactions until the advent of the ruthenium systems.

The Ghadiri group used metathesis to "fix" a system formed by self-assembly. In this cyclic peptide system, the dimer is formed by complimentary hydrogen bonds [33], after which the metathesis reaction "stitches" the two halves together to form a stable structure (Eq. 6.12).



(6.12)

The Martin group was one of the first to use RCM in complex molecule synthesis, and have recently used two RCM reactions in the total synthesis of Manzamine A (Eq. 6.13) [34]

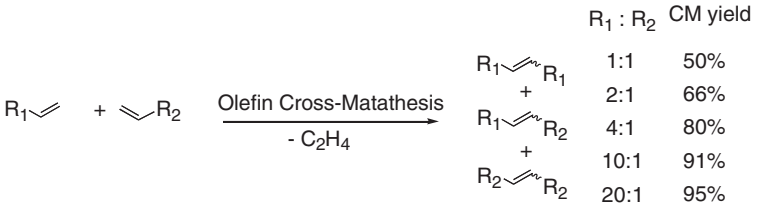


(6.13)

The above examples demonstrate the utility of the ruthenium-based metathesis catalyst systems in the synthesis of complex, highly functionalized molecules.

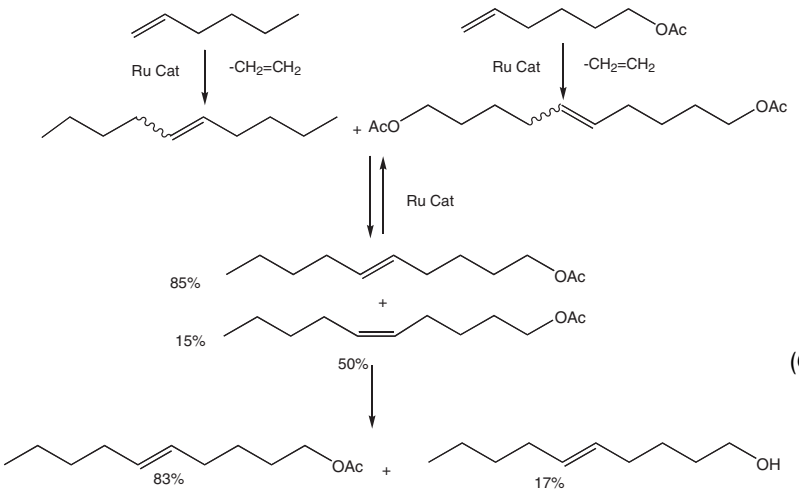
6.3.2 Cross Metathesis

The reaction of two acyclic olefins to produce a mix of new products is finding use in organic synthesis. The reaction under many circumstances produces the statistical mixture of products. High yields of the cross product can sometimes be obtained by either stoichiometric control or by the use of functional groups. When unfunctionalized olefins are used in the reaction, all the products are of similar stability and reactivity. Under these conditions, a 1:2:1 mixture of olefins will lead to only a 50% yield of the cross product. However, as shown below, if an excess of one of the olefins is used, the percentage yield based on the minor olefin may be much higher (Eq. 6.14) [1].



(6.14)

Although the desired product is often produced in low yield, cross metathesis does not result in the loss of double bonds, and the olefin fragments remain intact; hence, the byproducts can be recycled. Recycling is demonstrated in the application below, where cross metathesis is used to prepare an insect pheromone for the peach twig borer, an insect that attacks a variety of fruits (Eq. 6.15). The pheromone can be used to control the population of the insect through disruption of the insect's mating process [35].

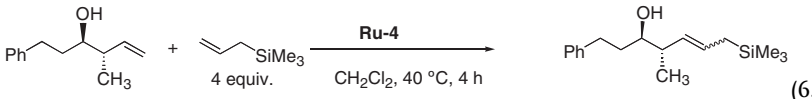


(6.15)

Pheromone for the Peach Twig Borer

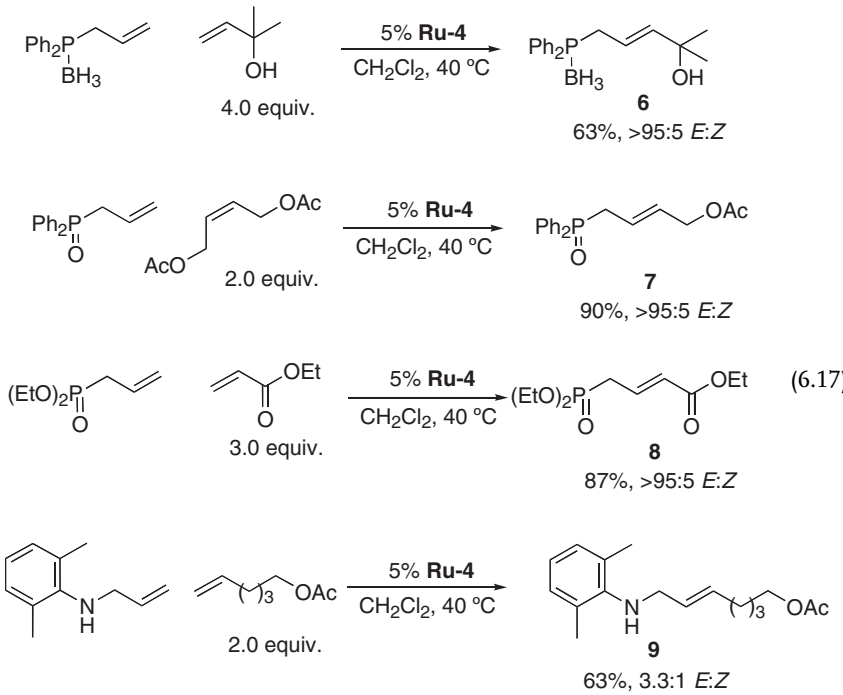
In this application, the byproducts can be recycled to produce very high yields of the desired products (Eq. 6.16). Unlike RCM, cross metathesis is favored by high concentrations of substrates, and consequently lower catalyst loadings are generally required for cross metathesis. In many cases, the reactions are best run without solvents.

In many complex syntheses, good yields can be obtained by combining a sterically hindered olefin with a readily available cross partner, and allyl silanes have proven to be very valuable cross partners in such processes [36].



(6.16)

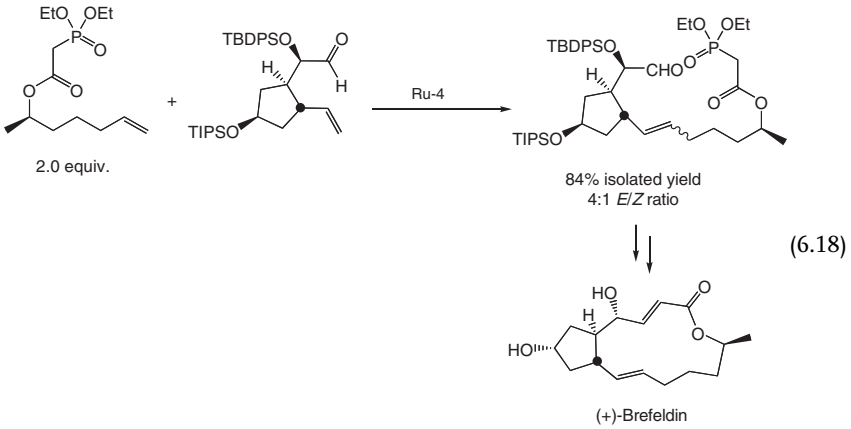
The tolerance of ruthenium catalysts to a variety of functionality, and the efficiency of the reaction, have led to cross metathesis being used to prepare a variety of highly functionalized molecules. The examples in Eq. 6.17 demonstrate the array of functionality that can be tolerated [37].



(6.17)

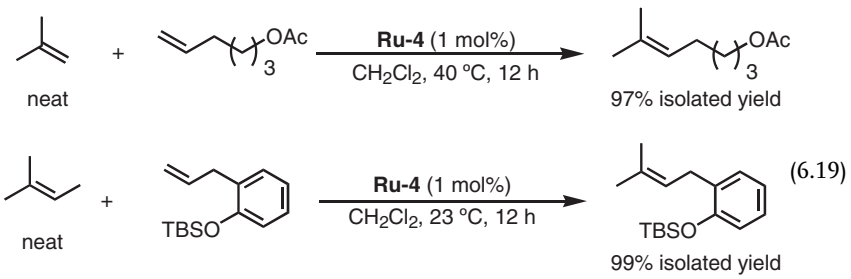
There are now sufficient examples to guide the use of cross metathesis in the synthesis of complex molecules in multi-step synthesis. The following is an excellent

example of the efficiency of the assembly of highly functionalized structures using cross metathesis (Eq. 6.18) [10].



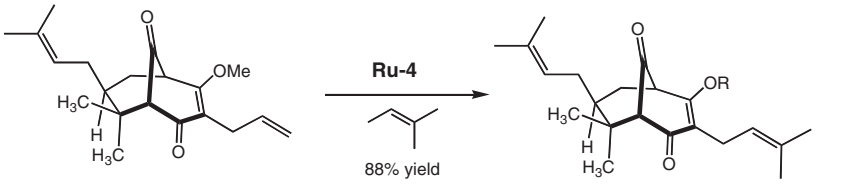
(6.18)

Although the first generations of the ruthenium catalysts were selective for less-substituted double bonds, the latest generations of catalyst allow for more highly substituted double bonds to be prepared. For example, the use of excess isobutylene – an olefin that is reluctant to homodimerize – with a simple olefin results in the formation of the corresponding isoprenoid structure in good yield [38].



(6.19)

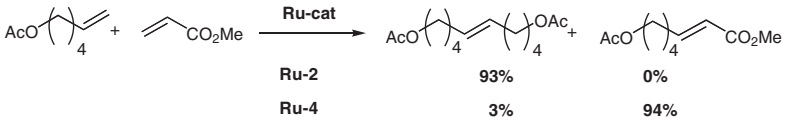
In an approach to the synthesis of Garsubellin A, the Stoltz group used cross metathesis to install a difficult-to-place isoprenoid group (Eq. 6.20) [39].



(6.20)

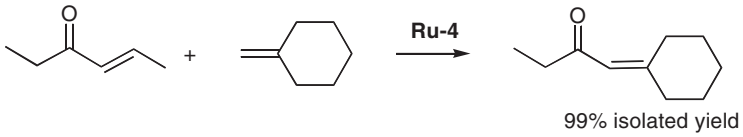
This points to a general approach to the installation of functionalized allyl groups in synthesis. The symmetrical parent allyl group can be used in the synthesis and then cross metathesis can be used to introduce any required structural complexity.

A significant breakthrough in cross metathesis was the discovery of general catalysts for reactions with directly functionalized olefins. The modification of the basic catalyst structure with *N*-heterocyclic carbene ligands opened this area of research. The bisphosphine catalyst Ru-2 would react only slowly with electron-deficient olefins in RCM reactions. As shown below, the reaction between a terminal olefin and an acrylate using Ru-2 gave none of the cross product. With the more electron-donating ligand in Ru-4, the same reaction gave the substituted acrylate as the major product [40].

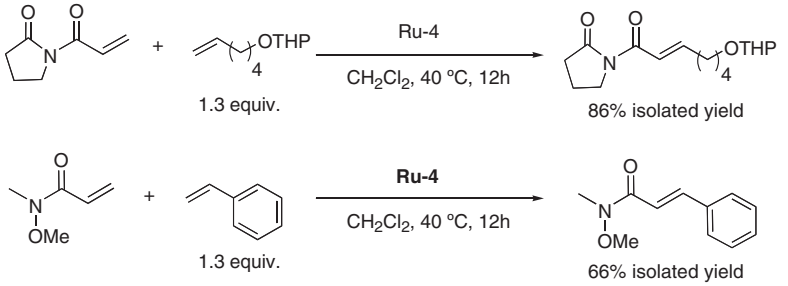


(6.21)

This cross-reaction is general for unsaturated esters, ketones, aldehydes and amides. In these cases, the dominant product is the cross-product even when the reactions are run with a 1:1 stoichiometry. In general, if one of the cross partners is slow to homodimerize but will take part in metathesis, the reaction is driven to the cross product. This observation holds for a wide variety of electron-deficient (and sterically hindered) olefins. For example, α,β-unsaturated ketones, aldehydes and amides all undergo clean and efficient cross metathesis reactions, [41] with the dominant product in all cases being the *E* isomer (Eqs. 6.22 and 6.23).



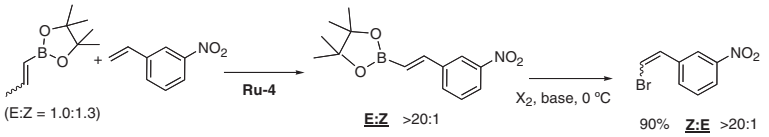
(6.22)



(6.23)

The vinylboronates represent an especially useful set of cross partners [42]. These electron-deficient olefins give excellent yields of cross metathesis products, and also

provide a rapid route to intermediates that are capable of being transformed into a variety of useful target molecules.



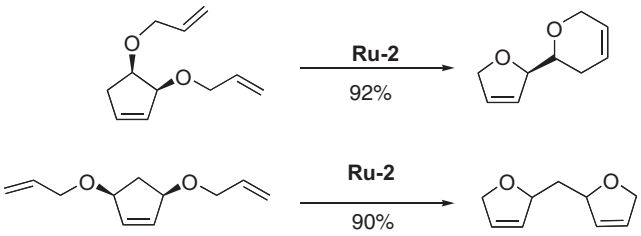
(6.24)

The ability of the ruthenium catalysts to tolerate functional groups, and recognition of the rules required to obtain high yields of cross metathesis products, will now allow the promise of this powerful reaction to be recognized [43]. A major outstanding problem is control of the stereochemistry of the formed double bond. In the case of electron-deficient olefins, the stereochemistry of the cross product is the *E* isomer, whereas in other cases, the *E*:*Z* ratio varies greatly based on the substituents. The development of a ligand-controlled synthesis that would allow the formation of unfunctionalized double bonds with high stereoselectivity would allow the full exploitation of this reaction.

6.3.3
Combination Metathesis Processes

Ring closing and cross metathesis allow the rapid synthesis of simple cyclic and acyclic systems. The metathesis activity that is now possible using well-defined catalysts allows for the rapid generation of complexity from simple starting materials by relay processes and combinations of metathesis steps. Many of these reactions have been recognized only recently, are now beginning to be used in complex synthetic transformations. A few of these types of reactions will be outlined here to demonstrate the power of these multistep, relay processes. In these processes, an initial metathesis step leads to a new carbene that results in further transformations of the substrate.

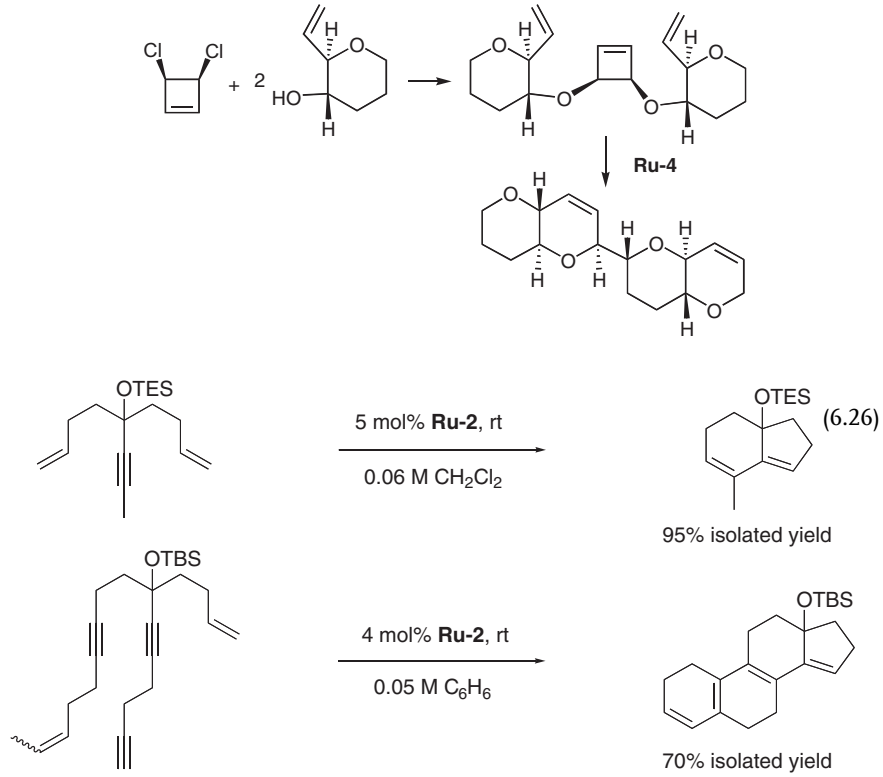
One of the simplest of these transformations is the ring opening-ring closing process. In this reaction, a terminal double bond undergoes metathesis to generate a new carbene that then opens a ring to generate a new carbene. The resulting carbene can then react with a second olefin to complete the process and form a new ring system. The examples in Eq. 6.25 demonstrate the rapid generation of multiple ring systems from one simple ring. The relative stereochemistry of the two rings is set in the starting simple ring [44].



(6.25)

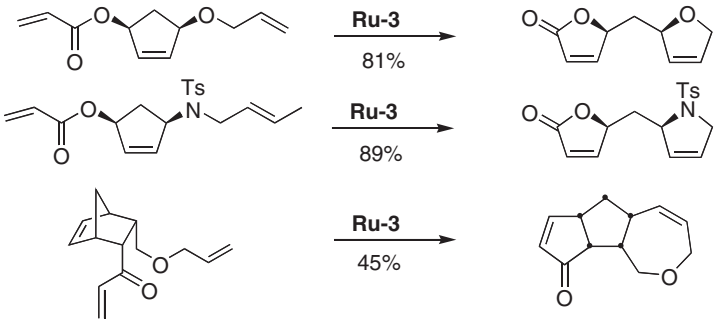
Sufficient examples have been demonstrated for this reaction to move into the synthesis of complex molecules. For example, the Nicolaou group has recently demonstrated that such a process can be used for the rapid generation of complex polycylic ethers (Eq. 6.26(a)) [45].

In a similar way, acetylenes can serve as the relay elements in a tandem metathesis process, and such reactions result in polycyclic dienes. The starting materials are easy to prepare through standard techniques (Eq. 6.26(b)) [46].



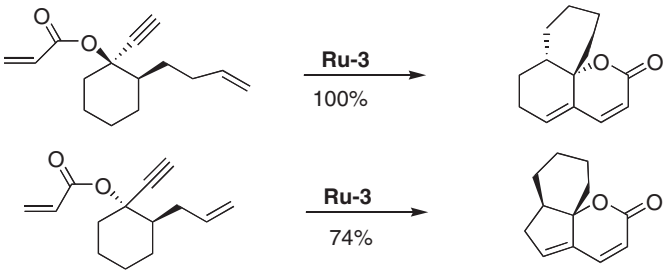
(6.26)

With the advent of the new catalysts systems that will undergo efficient reactions with electron-deficient olefins, the tandem process can be extended to the synthesis of a variety of polycyclic lactones (Eq. 6.27) [47].



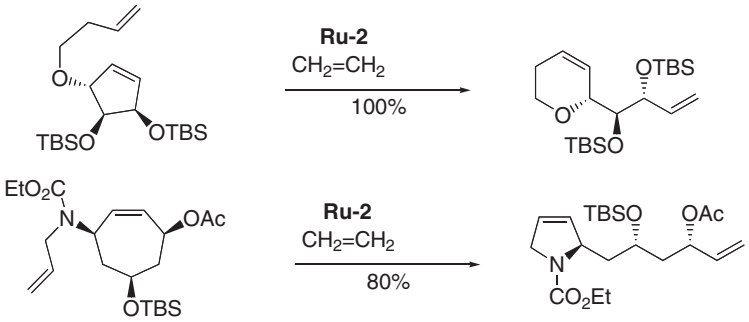
(6.27)

As indicated in the following examples, very complex ring systems can be generated by using such processes, with the release of ethylene being used to drive the formation of highly congested structures (Eq. 6.28).



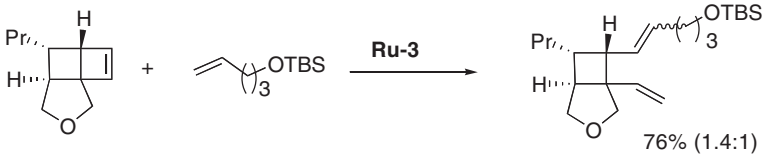
(6.28)

If a capping group is not installed in the substrate, the reaction turns over through the generation of a terminal double bond (Eq. 6.29). In some cases, the reaction is much cleaner if ethylene is added to the system, as this prevents dimerization of the product. Blechert has explored the types of ring systems that can be prepared using this process, and has defined the parameters that control the equilibrium between starting material and product [48].



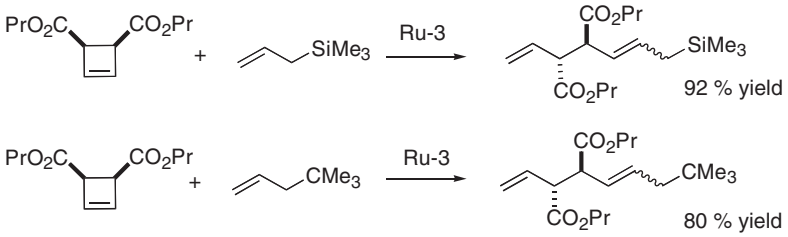
(6.29)

The intermolecular version of this reaction results in the formation of complex systems with fewer rings. The group of Snapper has used this reaction in a number of routes to obtain complex natural products. Many of these processes involve the opening of cyclobutenes, and the bicyclic cyclobutenes (Eq. 6.30) provide excellent control of stereochemistry, with the products being highly strained so that they will undergo further thermal reactions [49].



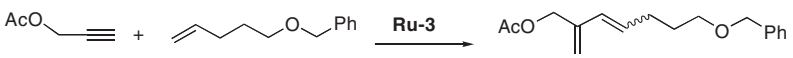
(6.30)

In order to obtain high yields, the cyclic partner should be strained so that it can compete with the acyclic olefin to yield a selective cross-reaction (Eq. 6.31) [50].



(6.31)

As discussed above, acetylenes can react in a similar way to cyclic olefins. When this concept is applied in "ring-opening" cross-reactions, an acetylene undergoes such a reaction with a simple olefin to produce a diene. Indeed, recent advances have suggested that this might become an excellent method for the formation of a variety of functionalized dienes [51].



(6.32)

6.4 Summary

Although olefin metathesis had been recognized as a potentially useful reaction in organic synthesis, the applications had to await the creation of families of catalysts that were well defined and would tolerate a variety of organic functional groups. The family of ruthenium-based olefin metathesis catalysts provides the functional group tolerance, as well as the thermal and environmental stability required for their use under standard organic conditions. As such, the ruthenium catalysts have finally allowed many of the promises of olefin metathesis as a general reaction in organic synthesis to be realized.

References

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7
Ruthenium-Catalyzed Cyclopropanation

Hisao Nishiyama

7.1
Introduction

Ruthenium-catalyzed reactions of olefins and diazoacetates have been investigated during the past decade, and found to be an efficient catalysis producing cyclopropanecarboxylates with high stereoselectivity and enantioselectivity. In most cases, newly designed nitrogen-based ligands proved to be efficient auxiliaries of the catalysts to attain high performance compared to phosphine ligands.

7.2
Asymmetric Catalytic Cyclopropanation

7.2.1
Styrene

Although, in the early 1990s, the catalytic activity of several ruthenium complexes was recognized in the cyclopropanation of olefins and diazoacetates, the activity was seen to be either comparable to, or perhaps lower than, that of rhodium, palladium, or copper catalysts. In 1994, an asymmetric version of ruthenium catalysts with chiral bis(oxazolinyl)pyridine (Pybox) was seen to demonstrate strong catalytic activity at ambient temperature, with extremely high *trans*-selectivity and high enantioselectivity by the reaction of styrene and diazoacetates (Scheme 7.1; Table 7.1) [1]. Pybox was first reported in 1989 by the present authors as a nitrogen-based ligand for the asymmetric hydrosilylation of ketones with rhodium catalysts [2]. In situ, both catalyst **2** and the ethylene-complex **3a** are highly effective, and provide 65–87% yields of the cyclopropane mixture **1*t*** + **1*c*** in up to 95% *e.e.* for *trans* and *cis*, respectively (Scheme 7.1). The bulky ester enables the *trans*:*cis* ratio to exceed 97:3. In order to attain the highest *e.e.* value, the *l*-menthyl group proved to be the better choice for the *trans* product when (*S*,*S*)-Pybox was used. During the study of isolation of the corresponding carbene-Ru(Pybox) complexes, bulky phenyl esters provided the highest *trans* selectivity, ranging from 98:2 to 100:0 (Table 7.1) [3].

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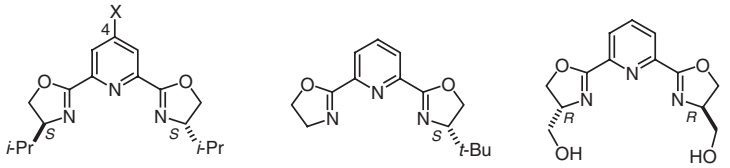
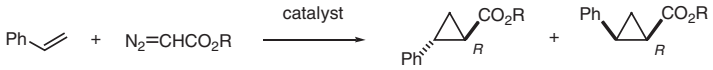


Pybox-*ip* (X = H) Pybox-*mtb* Pybox-*hm*

Chart 7.1



1*t* *trans* **1*c*** *cis*

Catalyst

2 [$RuCl_2$(*p*-cymene)/$_2$ + Pybox-*ip*]
3 $RuCl_2$(Pybox-*ip*-4X)(C_2H_4): X =, **a** H, **b** CO_2Me, **c** OMe, **d** NMe_2
4 [$RuCl_2$(*p*-cymene)/$_2$ + Pybox-*mtb*]
5 [$RuCl_2$(*p*-cymene)/$_2$ + Pybox-*hm*]

Scheme 7.1

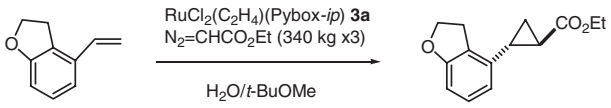
Table 7.1 Catalytic asymmetric cyclopropanation of styrene and diazoacetates with Ru-Pybox catalysts.

Catalyst	Diazoacetate R =	Solvent	Temp (°C)	1*t* + 1*c*		%*e.e.* (ds)		Reference
				Yield (%)	Ratio	1*t*	1*c*	
2[a]	Et	CH_2Cl_2	25	69	92:8	89	75	1
3a[a]	Et	CH_2Cl_2	25	73	91:9	89	79	
3a[a]	*t*-Bu	CH_2Cl_2	25	65	97:3	94	87	
3a[a]	*l*-Menthyl	CH_2Cl_2	40	83	97:3	96	80	
3a[a]	*d*-Menthyl	CH_2Cl_2	40	82	97:3	87	97	
3b[a]	*l*-Menthyl	CH_2Cl_2	40	95	96:4	97	85	3
3c[a]	*l*-Menthyl	CH_2Cl_2	40	89	96:4	90	67	
3d[a]	*l*-Menthyl	CH_2Cl_2	40	79	94:6	84	38	
3a[a]	2,6-(*i*-Pr)$_2$$C_6H_3$	benzene	60	92	100:0	92	–	4
3a[a]	2,4,6-$Me_3C_6H_2$	benzene	50	95	98:2	93	>98	
4[a]	*l*-Menthyl	CH_2Cl_2	30–35	84	99:1	94	64	5
5[b]	*d*-Menthyl	Toluene	40	38	89:11	8	28	6
5[b]	*d*-Menthyl	Toluene-H_2O (4:1)	40	57	97:3	94	76	
5[b]	*d*-Menthyl	Toluene-EtOH (4:1)	40	67	96:4	35	2	
5[b]	*d*-Menthyl	Toluene-*i*-PrOH (4:1)	30	52	97:3	96	88	

a Catalyst loading of 2 mol% (Ru to diazoacetate). Absolute configuration, (1*R*,2*R*) for **1*t*** and (1*R*,2*S*) for **1c**. Ds = diastereoselectivity.
b Catalyst roading of 5 mol% (Ru to diazoacetate). Absolute configuration: for **1*t***, *S* = (1*S*,2*S*), *R* = (1*R*,2*R*); *for* **1c**, *S* = *(1S,2R)*, *R* = *(1R,2S)*.

Remote substituents at the 4-position of the pyridine skeleton influenced the % *e.e.* value [4]. The electron-withdrawing ester of **3b** accelerated the catalysis, and increased the *e.e.* value to 93~97%. While, methoxy or amino groups of **3c** and **3d** decreased the activity (yields) and % *e.e.* value. On the basis of hypothetical considerations of the reaction course, single chiral Pybox-*mtb* was found to attain similarly higher stereochemical outcomes to Pybox-*ip* [5].

The introduction of a hydroxymethyl group on the oxazoline ring of Pybox (Pybox-*hm*) can provide a water-soluble catalyst of ruthenium **5** (Table 7.1) [6]. Compared to a toluene solution, toluene-water in a double-phase system improves the yield and also the *trans*:*cis* ratio. Dramatically, the *e.e.* value for *trans* and *cis* were increased to 94% and 76%, respectively. In these cases, *d*-menthyl ester was selected as a sterically matching ester to (*R*,*R*)-Pybox-*hm*. Because the active catalyst remains in the aqueous phase after separation of the organic phase, the catalysis can be carried out repeatedly. In the presence of protic solvents – and especially in *iso*-propyl alcohol – the catalysis can be performed to give 52–78% yields, 95:5~97:3 of *trans*:*cis* ratio, and 92~96% *e.e.* for *trans* and 65~88% *e.e.* for *cis*. Thus, Ru-Pybox catalysts proved to be both water- and alcohol-tolerant [7]. This advantage as an environmentally benign process was demonstrated in the large-scale production of the cylcopropane derivative by Bristol-Myers Squibb (Scheme 7.2) [8], the cyclopropanation being conducted in *t*-BuOMe and water.

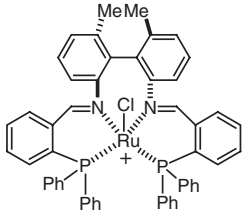


175-kg batches x3

Scheme 7.2

Following the discovery of Ru-Pybox catalysts, several chiral Ru-porphyrins, Ru-salens, and Ru-diimines were applied to the cyclopropanation of styrenes, especially using readily available ethyl diazoacetate. The diimino-diphosphine complexes **6** and **7** yielded selectively *cis*-products (Chart 7.2) [9,10]. Ru-porphyrin **8** showed very high efficiency by 0.05 mol% of low catalyst loading to give a 92:8~97:3 high *trans*:*cis* ratio, with up to 91% *e.e.* at 0 °C and 98% *e.e.* at 40 °C with ethyl diazoacetate (EDA) [11]. This catalyst was extended to dendritic structure [12]. Ru-salen **9** also gave *cis*-selectivity with a high *e.e.* value under light irradiation [13]. Ru-diimine **10** derived from axially chiral diamine exhibited high selectivity with EDA in 94%, 98:2 of *trans*:*cis*, and 95% *e.e.* for *trans* [14]. Ru-diiminopyridine **11** also exhibited 96% *e.e.* for *trans* with EDA [15]. Pyridine complexes **12** and **14** of Ru-salen attained 96~99% *e.e.* for both *trans* and *cis* with EDA [16]. An immobilized Pybox-Ru **15** was synthesized to give 85% *e.e.* with EDA (Chart 7.2) [17].

The absolute configuration of the products **1*t*** + **1c**, *trans* and *cis* isomers, is explained by the connection between the prochiral face of styrene to the prochiral face of the intermediate carbenoid center (Scheme 7.3). The *re*-face of styrene attacks



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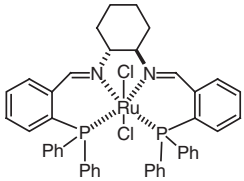
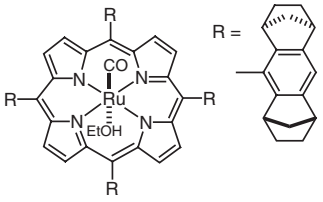


7 (AgOTf, 2,4,6-collidine)



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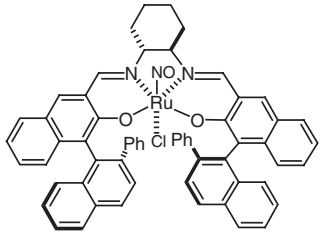
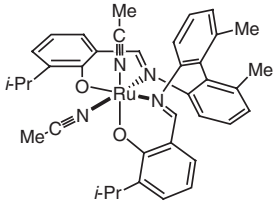


9 (Irradiation of light)



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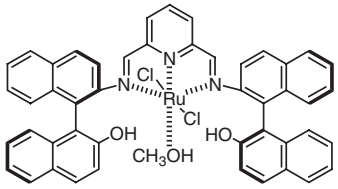

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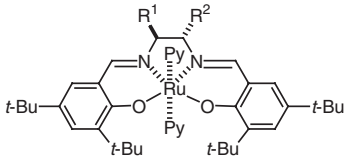
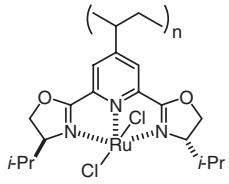


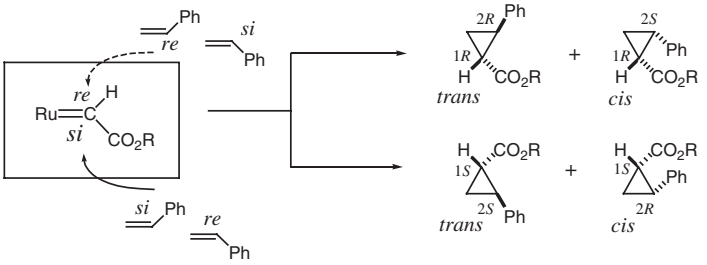
12 $R^1 = R^2 = Ph$
13 $R^1 = R^2 = Me$
14 $R^1, R^2 = (CH_2)_2$



15

Chart 7.2

the *re*-face of the carbene carbon to the *trans*-isomer **1*t*** of (1*R*,2*R*) absolute configuration. The chiral environment around the active Ru-carbene is able to open its less-hindered side, for example the *re*-face, to make 1*R* configuration. The attack of the *re*-face of styrene gives the 2*R* configuration.



Scheme 7.3 Prochiral face selection for asymmetric cyclopropanation.

7.2.2
Other Olefins

Substituted styrenes **16** were readily cyclopropanated with chiral Ru-catalysts **3a**, **5**, **6**, **8**, **9**, **10** and **11**. In the case of **3a**, **5**, **6**, and **9**, electron-withdrawing groups at the para-position led to a decrease in yield. This tendency appeared most drastic for **6**, with yields falling from 71% to 23% [9]. However, the *e.e.* value was increased from 71 to 94% by the adoption of *p*-CF_3-styrene. The apparent increase on *e.e.* from 86 for *p*-MeO to 98 for *p*-Cl was observed with Ru-diimine **10** catalyst [14]. The lower catalyst loading of 0.05 mol% for **8** was also noteworthy [11]. In addition, the important choice of readily available EDA for large-scale application was realized in the reactions with **6**, **8**, and **10**–**13**. The monosubstituted olefins **17**–**20**, and 1,1-disubstituted olefin **21** were readily cyclopropanated in up to 97% *e.e.* with Ru-Pybox **5** (Chart 7.3). Interestingly, methacrylic ester **23** gave a 95% yield with high *trans*-selectivity of >99% and 95% *e.e.* with the catalyst **13** (Chart 7.3) [16].

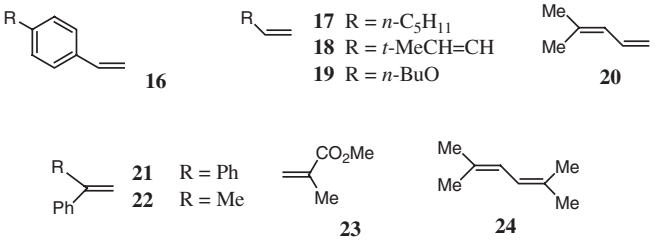
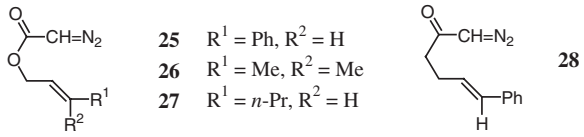


Chart 7.3

The intramolecular cyclopropanation of the diazoesters **25**–**27** was catalyzed to produce the bicyclic compounds up to 91% *e.e.* with **3**, **9**, and **10** [11]. The reaction of diazoketone **28** was catalyzed by **9** to produce the bicyclic ketone **30** in 78% yield with 94% *e.e.* (Chart 7.4) [13].

Substrate:



Product:

Chart 7.4

7.3 Non-Asymmetric Catalytic Cyclopropanation

In 1980, a ruthenium-catalyzed cyclopropanation with $Ru_2(OAc)_4Cl$ was reported in comparison with rhodium, palladium, or copper [19]. $Ru_3(CO)_{12}$ showed the catalytic activity for styrene and EDA at 60 °C [20]. In addition, $Ru_2(OAc)_4$ [21], Ru-polyethylene carboxylates [22], ruthenacarborane clusters [23], $Ru_2(CO)_4(\mu\text{-}OAc)_{2/n}$ [24], and $RuCl_2(Ph_3P)_3$ [25] catalyzed the cyclopropanation at 60~100 °C to give moderate to higher yields and 60:40 to 70:30 ratios of the *trans*:*cis* isomers.

Between 1995 and 2000, the catalytic activity of several ruthenium complexes bearing cyclopentadienyl Cp, arene, and pyridine ligands **31**–**37** was examined (Chart 7.5) [26–31]. At the relatively higher reaction temperatures of 45–100 °C, the catalysts **31**–**36** gave yields of 68 to 96%, but only moderate isomeric ratios of 60:40 to 70:30. The Cp-catalyst **31** produced the *cis*-product in 68% yield [26], while the diiminocarbene complex **36** [30] and the dipyridine-diimine complex **37** [31] gave a high *trans*-ratio. Among these complexes, only **37** was found to catalyze the reaction at room temperature.

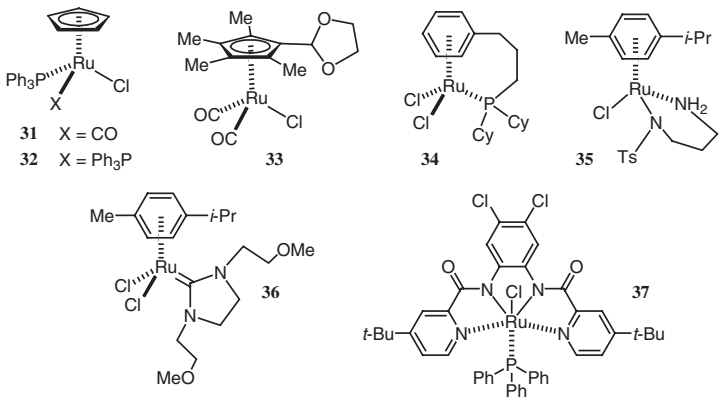
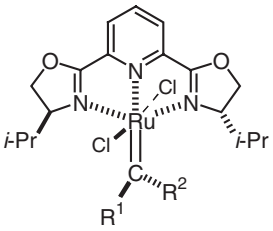


Chart 7.5

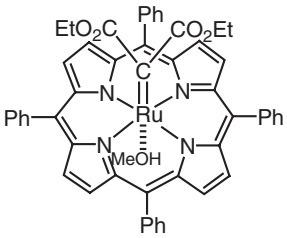
7.4
Carbene-Complexes and Mechanisms

In order to clarify the mechanism of cyclopropanation, several carbene-complexes of ruthenium have been isolated by reaction with diazocompounds. In the case of Pybox, the corresponding ruthenium-carbene complexes **38** were isolated and characterized using either NMR or X-ray analysis [32]. Similar ruthenium-carbene complexes, such as porphyrin-ruthenium carbene complex **39** [33] and pyridine-diimine-ruthenium complex **40** [34] were isolated and characterized (Chart 7.6).
[Chart 7.6]



38

R^1	R^2
H	$SiMe_3$
H	CH=CHPh
CO_2Me	CO_2Me
H	C_6H_2(2,6-di-*t*-Bu)(4-Me)



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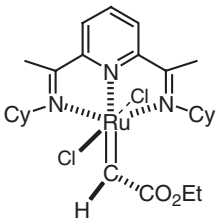

40

Chart 7.6

7.5
Conclusions

The catalytic activity of ruthenium complexes for the cyclopropanation of olefins and diazoacetates has been well investigated and, depending on the ligands utilized, the complexes have a high potential to produce high yields, stereoselectivities and enantioselectivities that are almost comparable to those of rhodium or copper catalysts [35]. Moreover, related carbene complexes of ruthenium have been isolated in order to clarify the mechanism of cyclopropanation [32–34]. It is likely that further improvements in these reactions will lead to the development of industrial processes utilizing cyclopropanation.

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8
Nucleophilic Additions to Alkynes and Reactions via Vinylidene Intermediates

C. Fischmeister, C. Bruneau, and P. H. Dixneuf

8.1
Introduction

Modern chemistry requires the continuous discovery of new synthetic methods allowing transformations with higher efficiencies and selectivities and performing new combinations of substrates into high-value chemicals. For cost and environment issues, the catalytic processes need to be efficient under mild conditions, and to give atom economy transformations with no byproducts and no separation processes. Catalytic reactions promoted by transition metal complexes have an increasing ability to fulfill these goals. Among the Group 8 transition metal complexes, ruthenium catalysts are attracting attention, as they appear able to promote a diversity of new transformations never observed with classical metal catalysts. Indeed, ruthenium catalysts can now promote carbon-carbon or carbon-heteroatom bond formation via a wide range of activation processes involving inert bonds or a variety of functional groups.

Recent reviews on olefin metathesis [1, 2], nonmetathesis [3], asymmetric hydrogenation [4] and organic synthesis reactions [5] have shown the potential of selected ruthenium catalysts. Among the emerging topics in which ruthenium catalysts play a crucial role are the selective transformations of multiple carbon-carbon bonds.

Here, we shall focus on ruthenium-catalyzed nucleophilic additions to alkynes. These additions have the potential to give a direct access to unsaturated functional molecules – the key intermediates for fine chemicals and also the monomers for polymer synthesis and molecular multifunctional materials. Ruthenium-catalyzed nucleophilic additions to alkynes are possible via three different basic activation pathways (Scheme 8.1). For some time, Lewis acid activation type (i), leading to Markovnikov addition, was the main possible addition until the first *anti*-Markovnikov catalytic addition was pointed out for the first time in 1986 [6, 7]. This regioselectivity was then explained by the formation of a ruthenium vinylidene species with an electron-deficient Ru=C carbon site (ii). Although currently this methodology is the most often employed, nucleophilic additions involving ruthenium allenylidene species also take place (iii). These complexes allow multiple synthetic possibilities as their cumulenic backbone offers two electrophilic sites (iii).

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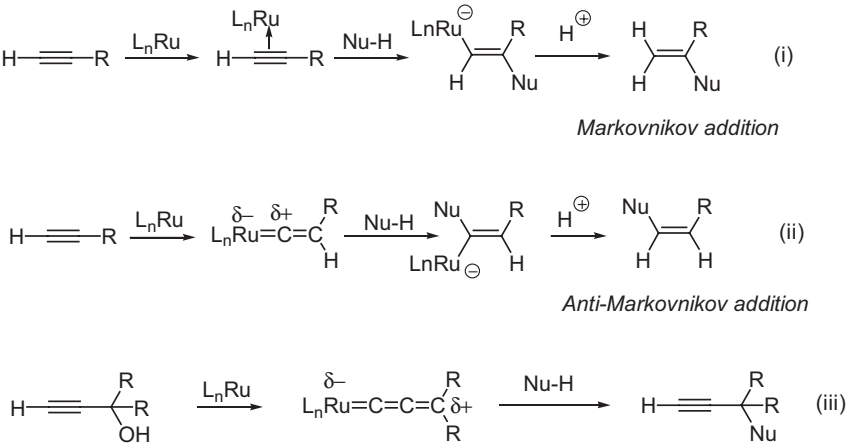


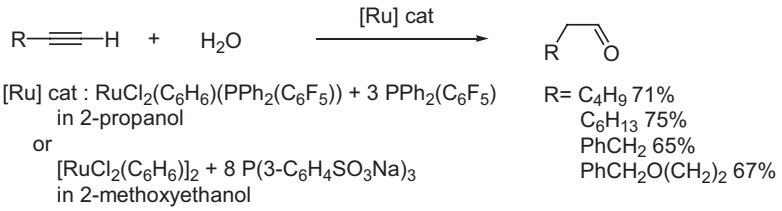
Scheme 8.1 Alkyne activation pathways.

This chapter will describe various additions to alkynes as a way to generate functional intermediates. In the first section, general additions of *O*, *N*, and *P* nucleophiles will be presented. Ruthenium-catalyzed hydrosilylation of alkynes will be described as an addition reaction to alkynes followed by ruthenium-catalyzed addition of *C* nucleophiles.

8.2
Addition of O-Nucleophiles

8.2.1
Addition of Water: Synthesis of Aldehydes from Terminal Alkynes

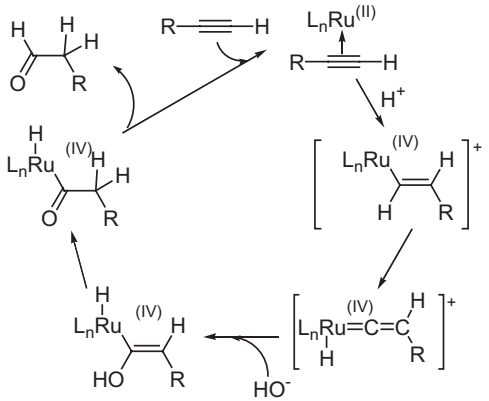
The addition of water to terminal alkynes catalyzed by ruthenium(III) complexes leads to ketones following Markovnikov's rule [8–10]. By contrast, the use of $RuCl_2(C_6H_6)(PPh_2(C_6F_5))$ in the presence of 3 equiv. of $PPh_2(C_6F_5)$, or $[RuCl_2(C_6H_6)]_2$ with a large excess of the water-soluble ligand $P(3\text{-}C_6H_5SO_3Na)_3$ (TPPTS) in alcohol at 65–100 °C provides the selective formation of aldehydes resulting from *anti*-Markovnikov addition [11] (Scheme 8.2).



Scheme 8.2 Ruthenium-catalyzed hydration of alkynes.

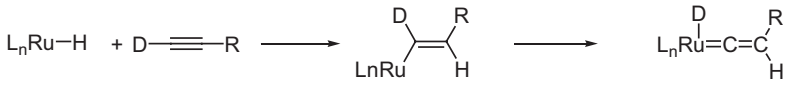
A variety of linear aliphatic terminal alkynes were transformed into aldehydes with good selectivity. The efficiency, regioselectivity of the addition, tolerance to functional groups were improved by using $RuCl(Cp)(phosphine)_2$ or RuCl(Cp)(diphosphine) as catalyst precursors [12]. The best results were obtained with diphenylphosphinomethane (dppm) as ligand, which made possible the preparation of aldehydes from bulky aliphatic alkynes (*tert*-$BuCH_2CHO$; 81%), aromatic alkynes ($PhCH_2CHO$; 90%), diynes ($OHCCH_2(CH_2)_6CH_2CHO$; 89%) and functional terminal alkynes ($NC(CH_2)_3CH_2CHO$; 88%; $PhCH_2O(CH_2)_2CH_2CHO$; 94%).

The mechanism of this reaction was investigated in detail by Wakatsuki [13] by isolation of intermediates, deuterium-labeling experiments and theoretical calculations. The postulated catalytic cycle involves first the protonation of a Ru(II)-alkyne species to give a Ru(IV)-vinylidene intermediate via a Ru(IV)-vinyl species. The nucleophilic addition of water to the α-carbon of the vinylidene ligand followed by reductive elimination affords the aldehyde (Scheme 8.3).



Scheme 8.3 Ruthenium-catalyzed hydration of alkynes; mechanism.

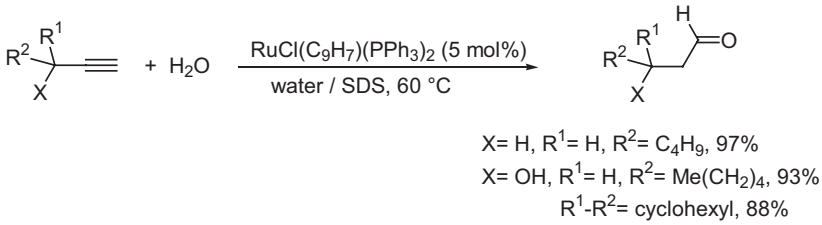
It is noteworthy that computational and experimental studies have shown that the formation of ruthenium-vinylidenes from terminal alkynes and ruthenium hydride complexes also proceeds via the formation of η^1-vinyl intermediate (Scheme 8.4) [14]. Thus, in this case the vinylidene ligand is not formed directly from the alkyne, and its β-hydrogen atom arises from the hydrido ligand.



Scheme 8.4 Vinylidene via η^1-vinyl intermediate.

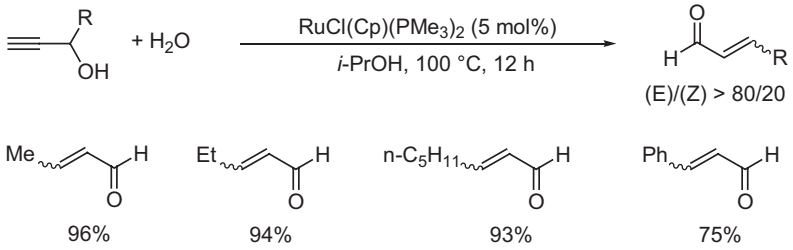
The indenyl complex $RuCl(\eta^5\text{-}C_9H_7)(PPh_3)_2$ also provides an efficient catalyst precursor for the *anti*-Markovnikov hydration of terminal alkynes including propargylic alcohols, in aqueous media and micellar solutions in the presence of surfactants

such as sodium dodecylsulfate (SDS) or hexadecyltrimethylammonium bromide (CTAB) [15] (Scheme 8.5).



Scheme 8.5 Hydration of alkynes with $RuCl(\eta^5\text{-}C_9H_7)(PPh_3)_2$.

In contrast, the reaction of secondary propargyl alcohols in 2-propanol/H_2O at 100 °C in the presence of 5 mol% of the more electron-rich $RuCl(Cp)(PMe_3)_2$ leads to isomerization and conjugated enals with (*E*)-stereoselectivity (Scheme 8.6) [16].

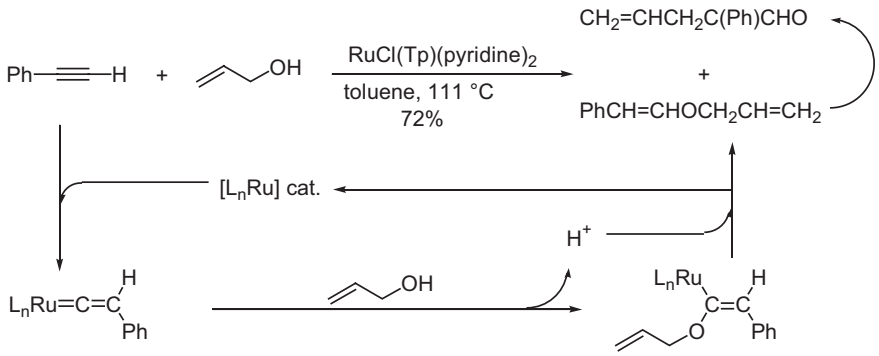


Scheme 8.6 Isomerization of propargyl alcohols.

8.2.2 Addition of Alcohols

8.2.2.1 Intermolecular Addition

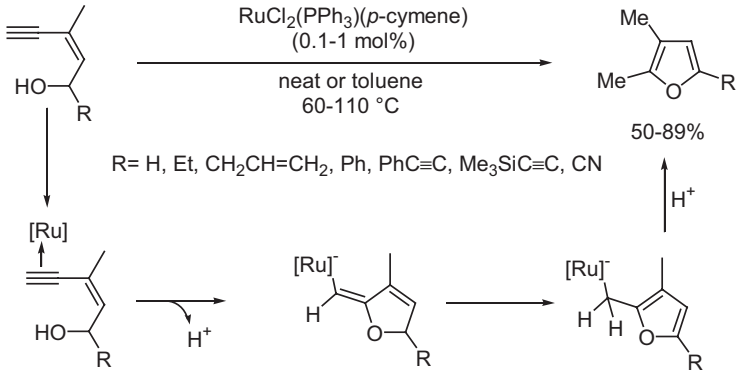
Although the addition of methanol to electron-deficient alkynes such as acetylene dicarboxylates is easy, the intermolecular addition of alcohol to unactivated alkynes in the presence of ruthenium catalysts to form enol ethers is not straightforward, and the only reported examples concern the addition of allylic alcohols to terminal alkynes. Thus, in the presence of a catalytic amount of RuCl(tris(pyrazolyl)borate)-$(pyridine)_2$, allyl alcohol adds to phenylacetylene in refluxing toluene to produce a 1:1 mixture of allyl β-styryl ether and 2-phenylpent-4-enal (resulting from Claisen rearrangement) (Scheme 8.7) [17].



Scheme 8.7 Addition of allyl alcohol to terminal alkynes.

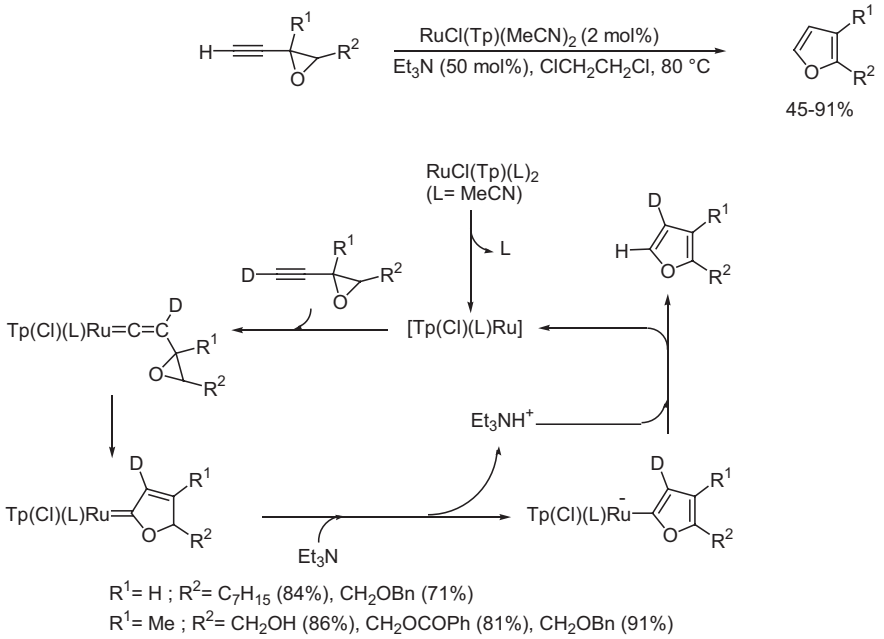
8.2.2.2 **Intramolecular Addition**

The intramolecular addition of a hydroxy group to a triple bond has been performed successfully in the presence of $RuCl_2(PPh_3)$(*p*-cymene) as catalyst precursor under mild conditions [18, 19]. The Lewis acid property of the ruthenium active species provides the activation of the triple bond and the Markovnikov addition of the hydroxy group to form 2-methylfuran derivatives after 1,5-proton shift and aromatization (Scheme 8.8).



Scheme 8.8 Intramolecular addition of the hydroxy group.

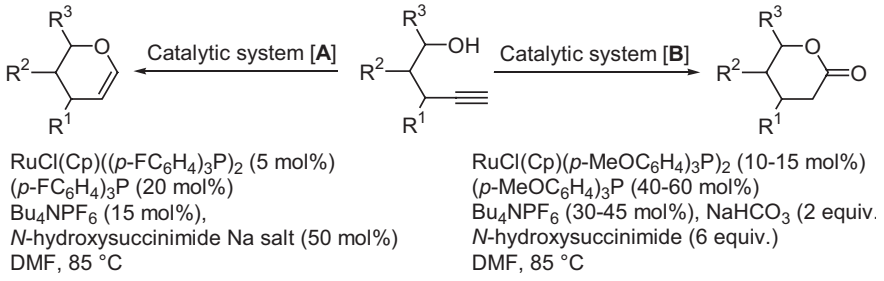
Furans have also been obtained via a related isomerization of terminal epoxyalkynes catalyzed by $RuCl(Tp)(MeCN)_2$ in the presence of a base at 80 °C in 1,2-dichloroethane. However, in this case their formation is explained by an intramolecular nucleophilic addition of the oxygen atom of the epoxide onto the α-carbon atom of a ruthenium-vinylidene intermediate (Scheme 8.9) [20]. For this reason, the reaction is specific of terminal alkynes. A large variety of functional groups such as ether, ester, acetal, tosylamide, nitrile, are tolerated by the reaction conditions and allow the formation of functionalized furans.



Scheme 8.9 Furans via isomerization of terminal epoxyalkynes.

The catalytic system [**A**] based on RuCl(Cp)(tris(*p*-fluorophenyl)phosphine)$_2$ (5 mol%), tris(*p*-fluorophenyl)phosphine (20 mol%), (Bu_4NPF_6, 15 mol%) and *N*-hydroxysuccinimide sodium salt (50 mol%) led to the selective transformation of pent-4-yn-1-ols into cyclic enol ethers via intramolecular *anti*-Markovnikov addition of the hydroxy group to the terminal carbon of the triple bond [21].

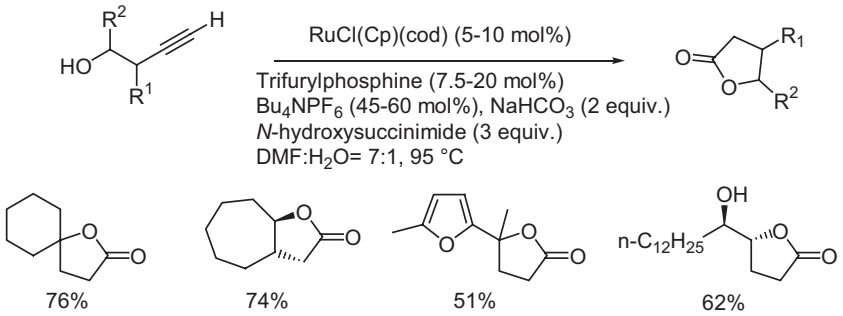
However, in the presence of (cyclopentadienyl)ruthenium complexes bearing an electron-rich ligand such as tris(*p*-methoxyphenyl)phosphine in the presence of a large excess of the same ligand, the selective formation of lactones was achieved. The recovery of the organic ligand as a lactone was made possible by oxidation with *N*-hydroxysuccinimide, a mild oxidant which does not destroy the catalyst (Scheme 8.10) [21].



Scheme 8.10 Enones and lactones via intramolecular addition of the hydroxy group.

Both oxidative cyclization and cycloisomerization were applied to a variety of substrates, including sugar derivatives. The only restriction for the formation of lactones was the presence of a tertiary alcohol functionality. The presence of a heteroatom at the propargylic position also inhibited both catalytic reactions.

Homopropargylic alcohols as well as propargylic epoxides and pentynols readily form cyclic ruthenium alkoxycarbenes upon intramolecular nucleophilic addition of the OH group to the electrophilic α-carbon of ruthenium-vinylidene species. Their oxidation in the presence of *N*-hydroxysuccinimide leads to the formation of pentalactones. The best catalytic system reported until now for this transformation of but-3-ynols is based on $RuCl(C_5H_5)(cod)$, tris(2-furyl)phosphine, $NaHCO_3$ as a base, in the presence of nBu_4NBr or nBu_4NPF_6, and *N*-hydroxysuccinimide as the oxidant in DMF-water at 95 °C (Scheme 8.11) [22].



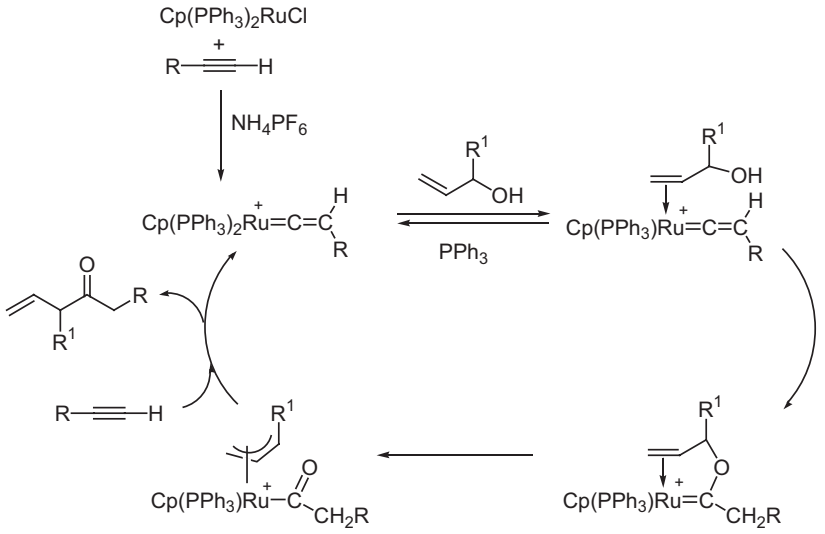
Scheme 8.11 Pentalactone derivatives by intramolecular *O*-addition.

8.2.2.3 Addition of Allylic Alcohol followed by Skeleton Rearrangement

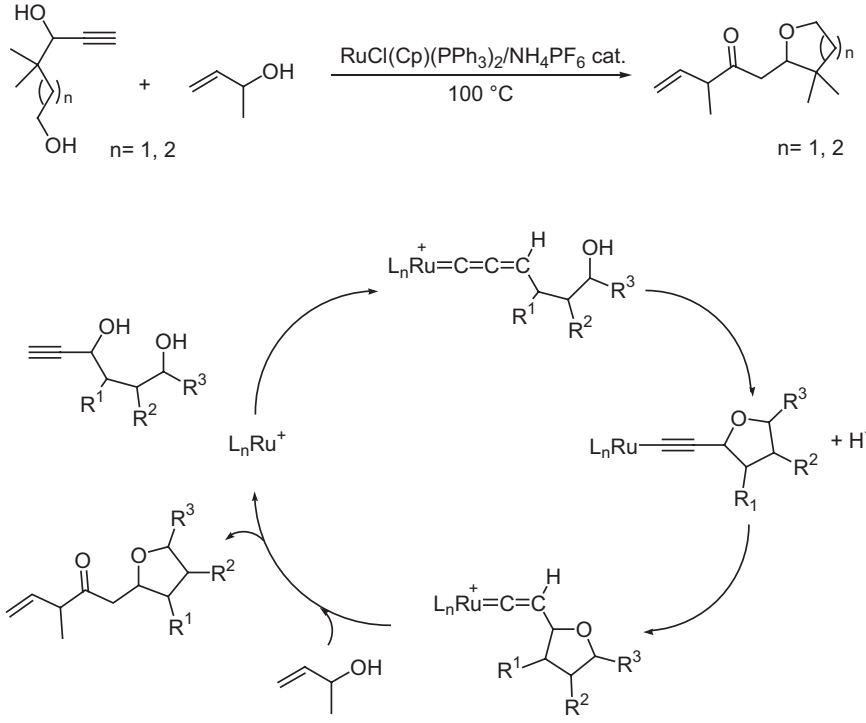
A remarkable selective reaction involving first C-O bond formation followed by rearrangement and C–C bond formation occurs with $RuCl(Cp)(PPh_3)_2$ as catalyst precursor. $RuCl(Cp)(PPh_3)_2$ in the presence of NH_4PF_6, AgOTf or $In(OTf)_3$ – additives which are known to facilitate chloride dissociation from the metal center – catalyzes the addition of allylic alcohols to terminal alkynes, affording unsaturated ketones [23, 24]. The key steps of this reconstructive coupling reaction are the nucleophilic addition of the allylic alcohol to a ruthenium-vinylidene species followed by formation of an allyl-metal intermediate via sigmatropic rearrangement (Scheme 8.12) [24].

This transformation of terminal alkynes via coupling with allylic alcohol with atom economy has been applied to the synthesis and modification of natural compounds such as rosefuran and steroids [25, 26].

As an extension of this reaction, the selective intramolecular nucleophilic addition of a hydroxy group at Cγ of a ruthenium allenylidene species generated by activation of propargylic alcohol by $RuCl(Cp)(PPh_3)_2/NH_4PF_6$ provides a ruthenium-vinylidene intermediate. The latter compound reacts with allylic alcohol via a second nucleophilic addition (Scheme 8.13) [27]. This unprecedented tandem reaction makes possible the construction of tetrahydrofuran derivatives in good yields, and has been used in the multistep synthesis of (–)calyculin A [28].



Scheme 8.12 Unsaturated ketones via addition of allylic alcohols to terminal alkynes.

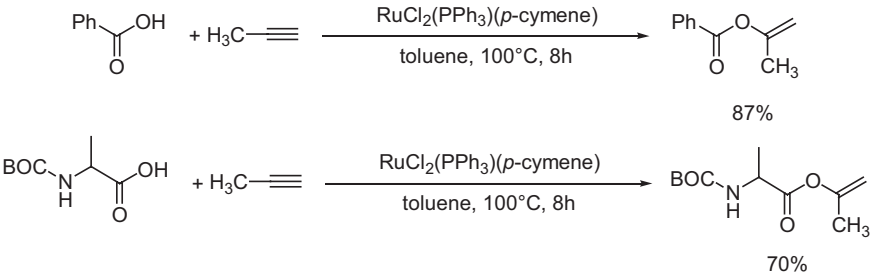


Scheme 8.13 Cascade intra- and intermolecular addition of allylic alcohols to activated triple bonds.

8.2.3 Addition of Carboxylic Acids

8.2.3.1 Markovnikov Addition

Initial studies showed that $Ru_3(CO)_{12}$ and $[Ru(CO)_2(O_2CCH_3)]_n$ were able to promote the addition of carboxylic acids to diphenylacetylene at 145 °C in toluene [29, 30]. Subsequently, a number of catalytic systems based on ruthenium catalysts have been discovered, and these have made possible – under mild conditions – the Markovnikov addition of carboxylic acids to terminal alkynes according to Scheme 8.14 to produce enol esters used as acylating reagents.



Scheme 8.14 Markovnikov addition of carboxylic acids to terminal alkynes.

The first generation of efficient and selective catalyst precursors for the Markovnikov addition were based on a multicomponent system composed of Ru(η^5-cyclooctadienyl)$_2$ in the presence of a trialkylphosphine (PBu_3 or PCy_3) and maleic anhydride [31–35], and subsequently on simple ruthenium complexes such as $RuCl_2(PPh_3)$(arene) [36–41] and $[Ru(O_2CH)(CO)_2(PPh_3)]_2$ [42, 43]. A variety of enol esters have been prepared from aromatic, aliphatic alkynes and enynes [39], and functionalized carboxylic acids such as aromatic and unsaturated acids [33–38], N-protected amino acids [40, 41], diacids [42], and α-hydroxy acids [43]. It is noteworthy that the addition takes place with retention of configuration from optically pure amino acids and hydroxy acids, and that polymers containing enol ester units have been obtained by addition of diacids to diynes [44]. These activated enol esters show interesting acylating properties as they liberate a ketone as byproduct under neutral conditions, and they have been used for the acylation of amines and alcohols [45, 46], the preparation of dipeptides [41], formates [47], acylamides, acylcarbamates, acylureas [48, 49], and oxalic acid derivatives [42].

Recently, new types of ruthenium catalyst precursors that perform the Markovnikov addition of carboxylic acids to terminal alkynes have been developed. The most representative examples are $[RuCl_2(p\text{-cymene})]_2$/P(furyl)$_3$/base [50], Ru-vinylidene complexes such as $RuCl_2(PCy_3)_2$(=C=CH*t*-Bu), $RuCl_2(PCy_3)$(bis(mesityl)imidazolylidene)(=C=CH*t*-Bu), $[RuCl(L)_2$(=C=CH*t*-Bu)$]BF_4$ [51], and the ruthenium complexes shown in Figure 8.1 [52–54].

In the presence of $RuCl_2(PPh_3)$(arene) or $[Ru(O_2CH)(CO)_2(PPh_3)]_2$, propargylic alcohols do not afford hydroxy enol esters but β-ketoesters according to Scheme 8.15

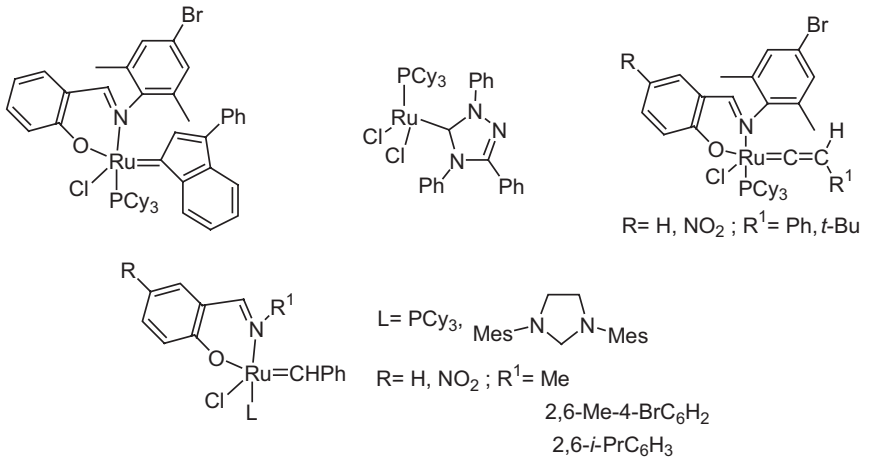
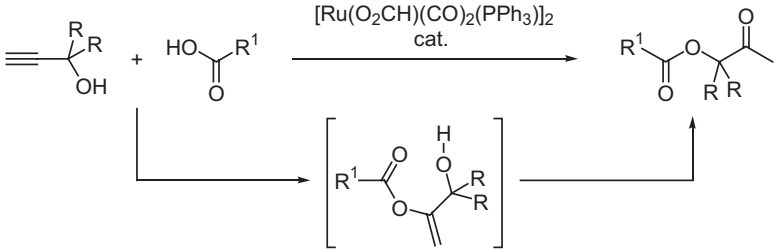


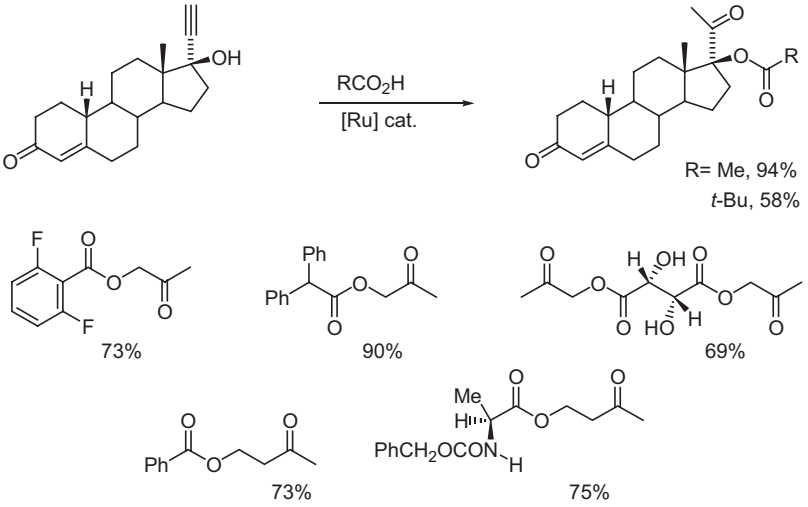
Figure 8.1

[33, 55]. It has been shown that the first step of the reaction is actually the nucleophilic Markovnikov addition of the carboxylate to the triple bond, followed by an intramolecular transesterification [56].



Scheme 8.15 Synthesis of β-ketoesters from propargylic alcohols and carboxylic acids.

The best catalyst to perform this reaction is the stable binuclear $[Ru(O_2CH)(CO)_2(PPh_3)]_2$ complex, which makes possible the transformation of bulky alcohols such as steroid derivatives with retention of configuration at the propargylic carbon atom [57], and the preparation of β-oxopropyl esters from propargylic alcohols as well as γ-oxobutyl esters from butynol (Scheme 8.16) [56].



Scheme 8.16 Examples of products obtained by addition of carboxylic acids to propargylic alcohols.

This catalyst is also very efficient for performing the addition of bulky acids to simple alkynes, as shown in the synthesis of the ferrocenylcarboxylic styryl ester [58]. It is worthwhile noting that various catalysts immobilized on polystyrene [59] and inorganic supports [60, 61] have been prepared, as well as thermomorphic catalysts (Figure 8.2) [62], which offer the possibility of recycling the catalyst.

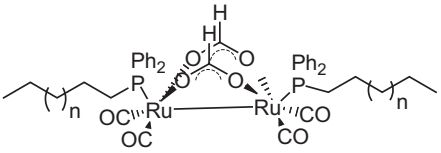
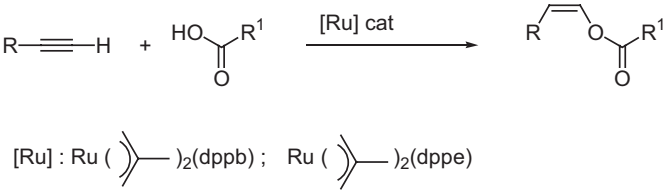


Figure 8.2

8.2.3.2 *Anti*-Markovnikov Addition

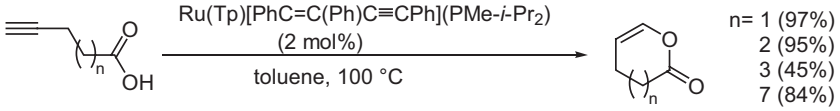
In contrast to the previous ruthenium catalysts, some π-allyl ruthenium complexes containing a chelating diphosphine ligand were the first metal complexes which favored the *anti*-Markovnikov addition of carboxylic acids to terminal alkynes to form (*Z*) and (*E*)-enol esters with high regio- and stereoselectivity [63–65] according to Scheme 8.17. It is postulated that the catalytic cycle accounting for this regioselectivity involves a ruthenium-vinylidene intermediate.



Scheme 8.17 *Anti*-Markovnikov addition of carboxylic acids to terminal alkynes.

The best catalyst precursors are Ru(methallyl)$_2$(dppb) (**A**) and Ru(methallyl)$_2$-(dppe) (**B**). The choice of the appropriate complex is dependent upon the steric demand of both alkyne and carboxylic acid. A large variety of carboxylic acids such as N-protected amino acids, α-hydroxy acids and functionalized alkynes such as enynes and propargylic ethers have been used in this respect [66, 67].

The regioselective *anti*-Markovnikov addition of benzoic acid to phenylacetylene has also been carried out successfully at 111 °C in the presence of ruthenium complexes containing a tris(pyrazolyl)borate (Tp) ligand, (RuCl(Tp)(cod), RuCl(Tp)(pyridine), RuCl(Tp)(tmeda)) with a stereoselectivity in favor of the (*E*)-enol ester isomer [17]. The σ-enynyl complex Ru(Tp)[PhC=C(Ph)C≡CPh)](PMe-*i*-Pr$_2$) efficiently catalyzes the regioselective cyclization of α,ω-alkynoic acids to give endocyclic enol lactones (Scheme 8.18) [68].



Scheme 8.18 Synthesis of enol lactones.

Very recently, new catalysts precursors derived from [RuCl$_2$(*p*-cymene)]$_2$ such as the RuCl$_2$(triazol-5-ylidene)(*p*-cymene) (**C**, **D**) (Figure 8.3) [69] or the in-situ-generated catalytic system based on [RuCl$_2$(*p*-cymene)]$_2$/P(*p*-C$_6$H$_4$Cl)$_3$/DMAP [50] have revealed their potential to perform the *anti*-Markonikov addition of a variety of carboxylic acids to phenylacetylene and terminal aliphatic alkynes.

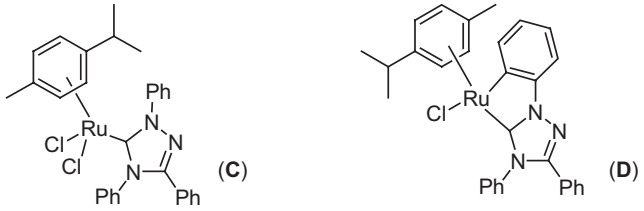
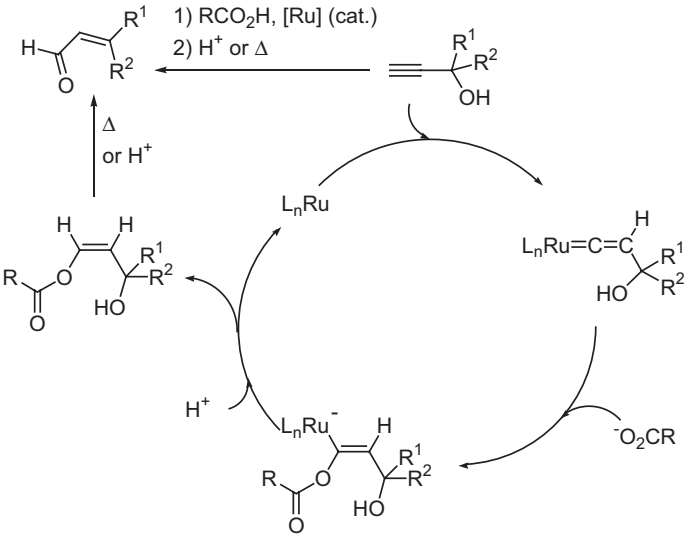


Figure 8.3

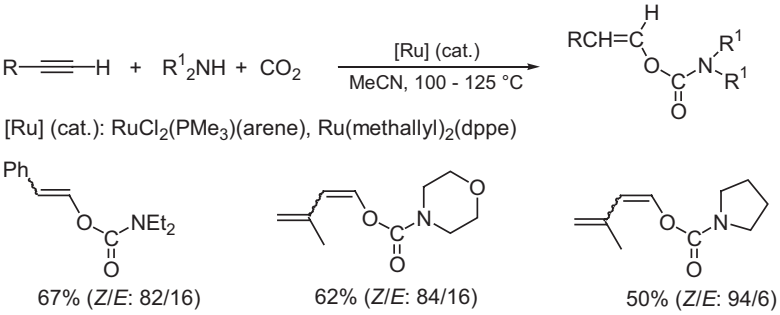
The addition to propargylic alcohols in the presence of Ru(methallyl)$_2$(dppe) (**B**) at 65 °C leads to hydroxylated alk-1-en-1-yl esters via the formation of a hydroxy vinylidene intermediate [70, 71]. These esters can easily be cleaved under thermal treatment or in the presence of *p*-toluenesulfonic acid or HBF$_4$ to give conjugated enals, corresponding to the formal isomerization products of the starting alcohols (Scheme 8.19).



Scheme 8.19 Two-step isomerization of propargylic alcohols.

8.2.4
Addition of Carbamates

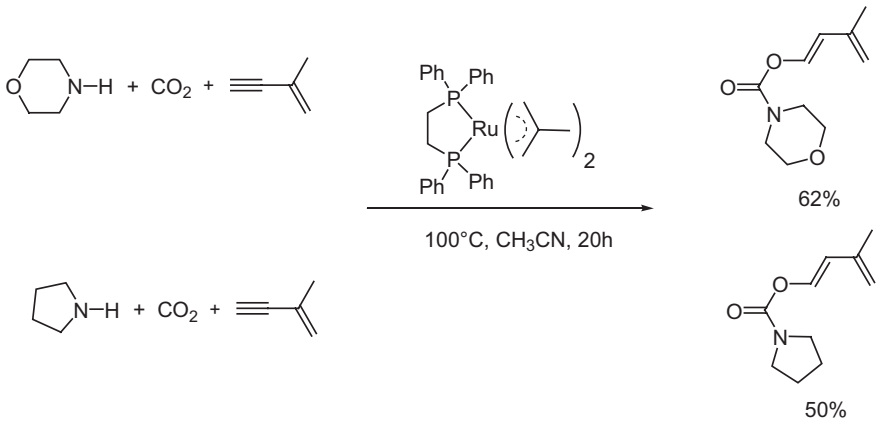
The first example of *anti*-Markovnikov addition of O-nucleophiles to terminal alkynes was actually the catalytic addition of ammonium carbamates generated in situ from secondary amines and carbon dioxide to give vinylcarbamates. This was also the first suggestion of a ruthenium-vinylidene intermediate as a catalytic active species for organic synthesis (Scheme 8.20) [6, 7].



Scheme 8.20 Addition of in-situ-generated carbamates to terminal alkynes.

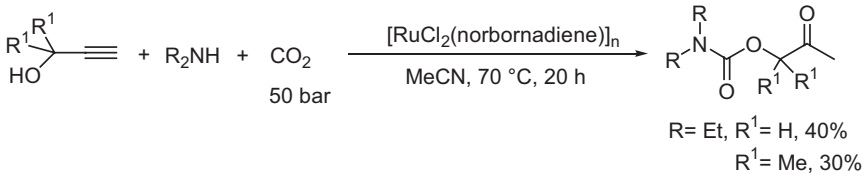
The most efficient catalyst precursors were then found in the $RuCl_2$(arene)(phosphine), $[RuCl_2(diene)]_n$ [72–74] and Ru(cod)(cot)/phosphine series [75]. Dienylcarbamates could also be selectively prepared from conjugated enynes and secondary

aliphatic amines, but in this case the best catalyst precursor was Ru(methallyl)$_2$(diphenylphosphinoethane) (Scheme 8.21) [76].



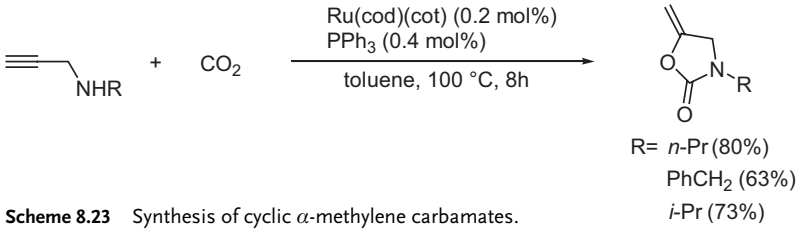
Scheme 8.21 Addition of in-situ-generated carbamates to conjugated enynes.

The formation of vinylcarbamates is restricted to secondary amines and terminal alkynes, which is in line with the formation of a metal-vinylidene intermediate. However, with propargylic alcohol a Markovnikov addition of carbamate initially takes place followed by transcarbamatation in the presence of secondary amines, leading to β-oxopropylcarbamates in moderate yields (Scheme 8.22) [77].



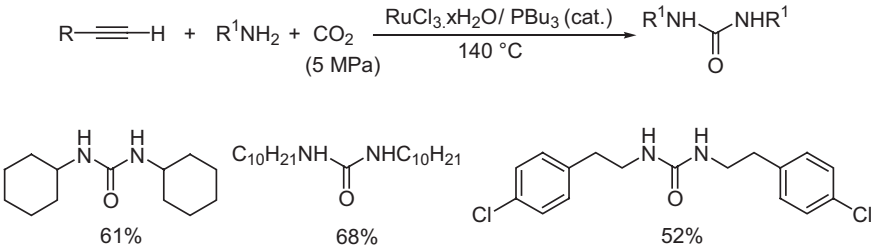
Scheme 8.22 Markovnikov addition of carbamates to propargylic alcohols.

It is worth mentioning the synthesis of cyclic α-methylene carbamates, which were also produced *via* Markovnikov intramolecular nucleophilic addition of O-carbamates, generated in situ from a propargylic amine and CO_2, in the presence of Ru(cod)(cot)/phosphine as catalyst precursor (cod: cyclooctadiene; cot: cyclooctatriene) (Scheme 8.23) [75].



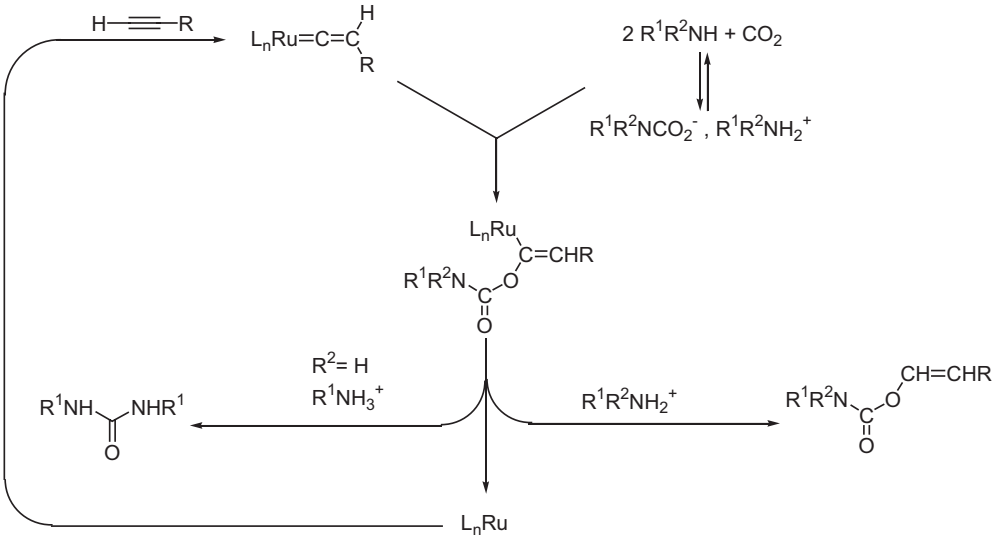
Scheme 8.23 Synthesis of cyclic α-methylene carbamates.

From primary aliphatic amines, a catalytic reaction actually takes place under similar conditions, but this leads to the formation of symmetrical ureas (Scheme 8.24) [78]. The catalytic system generated in this case is also thought to proceed via a ruthenium-vinylidene active species.



Scheme 8.24 Ureas from primary aliphatic amines.

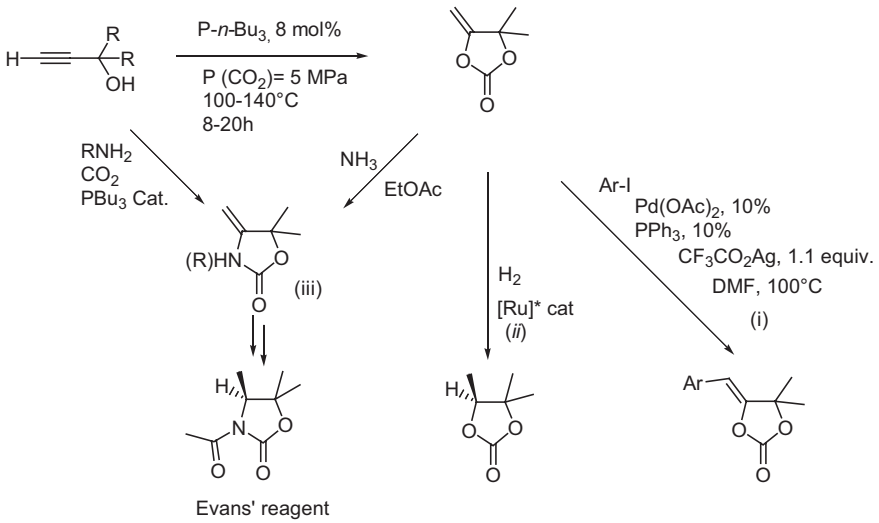
The proposed general catalytic cycle, which is applied to the formation of vinylcarbamates and ureas is shown in Scheme 8.25 [79].



Scheme 8.25 Proposed mechanism accounting for the formation of vinylcarbamates and ureas.

8.2.5
Addition of Carbonates

The intramolecular catalytic addition of propargylic carbonates to the C≡CH bond to give cyclic carbonates was first discovered with a ruthenium complex [80], but appeared to be more efficiently catalyzed by a simple phosphine such as P-*n*-Bu_3 (Scheme 8.26) [81].



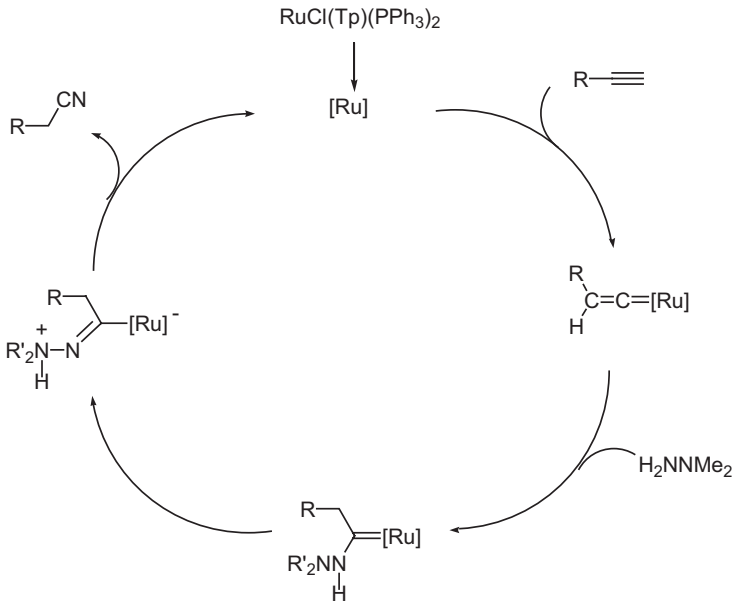
Scheme 8.26 Synthesis and some uses of cyclic of carbonates.

These easily-made carbonates have become useful intermediates for: (i) the direct synthesis of cyclic carbonates via the Heck reaction [82]; (ii) optically active carbonates by enantioselective hydrogenation [83]; and (iii) to oxazolidinones [84, 85] as an alternative route to the Evans reagent [86–88].

8.3 Addition of N-nucleophiles

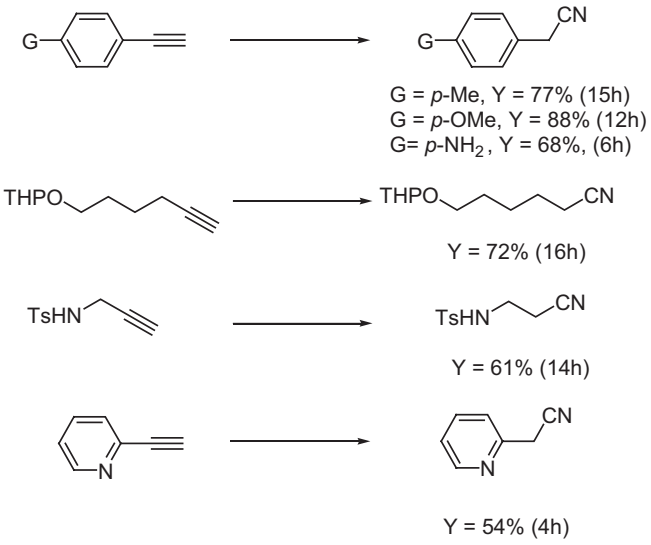
8.3.1 Addition of Hydrazines

Cyano-derivatives can be readily obtained by a ruthenium-catalyzed addition of various hydrazines to terminal alkynes [89] in which the cyano carbon atom arises from the terminal alkyne carbon atom. The tris(pyrazolyl)borate (Tp) complex $RuCl(Tp)(PPh_3)_2$ (1 mol%) was found to be the most active catalyst, and *N,N*-dimethylhydrazine (5 equiv.) the best nitrogen source. The proposed mechanism involves the nucleophilic attack of the nitrogen nucleophile on the α-carbon of a vinylidene intermediate (Scheme 8.27). Proton migration in the resulting α-hydrazinocarbene, followed by deamination, would give the nitrile derivative and regenerate the catalytic species.



Scheme 8.27 Addition of hydrazines to alkynes: postulated mechanism.

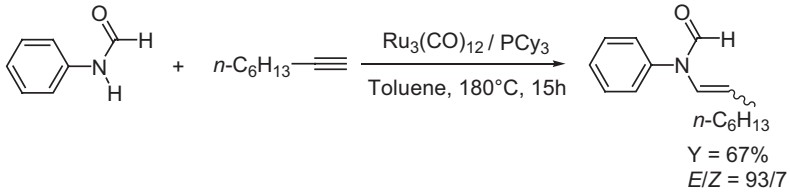
This catalytic reaction has been applied to several alkyne derivatives, and was found to be compatible with various functional groups (Scheme 8.28).



Scheme 8.28 Nitrile derivatives by addition of hydrazines to terminal alkynes.

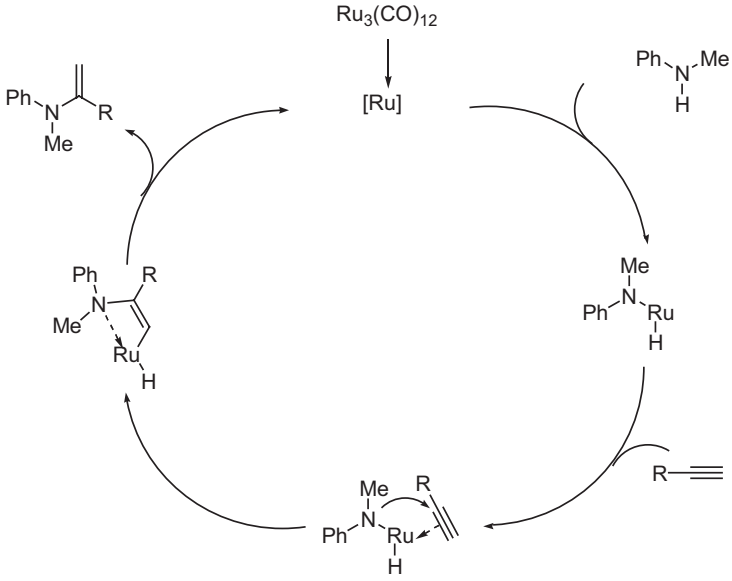
8.3.2
Hydroamination

Catalytic hydroamination of unsaturated carbon-carbon bonds has a strong potential for the access to a large variety of amines, enamines or imines [90]. The first addition of a N–H bond to alkynes catalyzed by a ruthenium catalyst was described in 1995 by Watanabe et al. [91], and involved a ruthenium-catalyzed addition of the N–H bond of N-formyl anilines to terminal alkyne (Scheme 8.29).



Scheme 8.29 The first ruthenium-catalyzed addition of a N–H bond to alkynes.

Since this report, $Ru_3(CO)_{12}$ has been found to be a good catalyst precursor for the addition of secondary amines to alkynes. The mechanism proposed so far involves the preliminary activation of the N–H bond with $Ru_3(CO)_{12}$ followed by an intramolecular nucleophilic addition of the amine to the η^2-coordinated alkyne to give a vinyl-ruthenium species. Reductive elimination of the enamine regenerates the ruthenium(0) catalytic center (Scheme 8.30) [92].

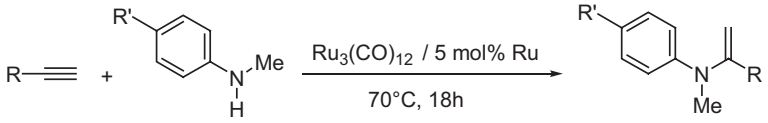


Scheme 8.30 Proposed hydroamination mechanism.

Although this mechanism is based on known activation of the N-H bond of aniline by $Ru_3(CO)_{12}$, a mechanism involving the activation of the carbon-carbon triple bond followed by a nucleophilic attack of the amine cannot be discarded. Indeed, typical Lewis acids such as Zn(II) or Cu(I) salts have been shown to be efficient catalysts for the intramolecular hydroamination of alkyne [93]. However, contrary to ruthenium(II) complexes, ruthenium(0) catalysts are not expected to electrophilically activate alkynes.

8.3.2.1 **Intermolecular Hydroamination**

The first intermolecular hydroamination of an alkyne was reported by Uchimaru in 1999 [92]. It was found that $Ru_3(CO)_{12}$ catalyzes the reaction of *N*-methylaniline derivatives with phenyl-substituted acetylenes in good yields (76–88%)(Scheme 8.31).



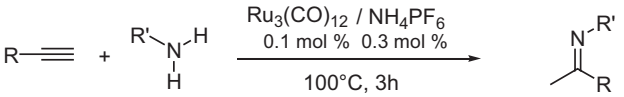
R = Ph, *p*-MeC_6H_4, *p*-FC_6H_4, Cyclohex-1-enyl
R' = H, Me

Y: 76-88%

Scheme 8.31 Addition of *N*-methylaniline to phenyl acetylene derivatives.

It is worth mentioning that the reaction proceeds regioselectively to give the Markovnikov addition product. The only drawback of this process is the necessity to use a 10-fold excess of the amine derivative to ensure high yields. Using only a five-fold excess of the amine resulted in a dramatic reduction of the yields, typically lower than 26%. Several other ruthenium complexes have been tested ($[RuCl_2(p\text{-cymene})]_2$, $RuCl_2(PPh_3)_3$, $[RuCl_2(cod)]_n$) but none of them was effective for this transformation.

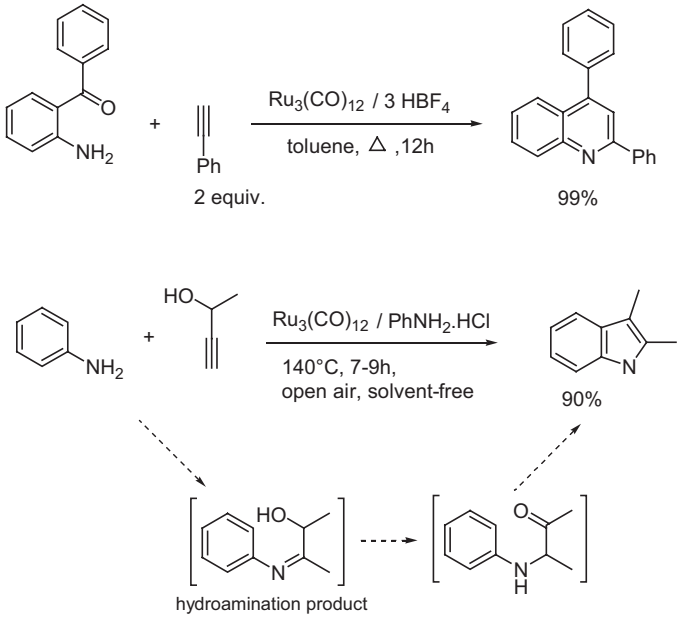
Almost simultaneously, Wakatsuki reported the catalytic addition of primary amine to terminal alkyne in the presence of strong acids, leading to imines. He observed a rate enhancement and high yields obtained when acidic additives such as HPF_6 and HBF_4 or their ammonium salts were used in combination with $Ru_3(CO)_{12}$ [94, 95]. It was thus possible to lower the catalyst loading to 0.3 mol% of ruthenium, and it is noteworthy that the reaction could be run in the open air, without solvent. Several substrates have been tested showing very good yields when phenylacetylene was used and moderate yields upon using an aliphatic terminal alkyne (Scheme 8.32).



R = C_6H_5, R' = *p*-$MeOC_6H_4$ Y = 95%
R = C_6H_5, R' = *p*-ClC_6H_4 Y = 88%
R = n-C_6H_{13}, R' = C_6H_5, Y = 63%

Scheme 8.32 Hydroamination leading to imines.

A huge number of additives have been tested, highlighting not only the necessity for a proton source but also the influence of the conjugated base and its coordinating ability. For example, aqueous HPF_6 allows high yield synthesis contrary to aqueous HCl, and the mechanism accounting for the influence of the additive has still to be elucidated. Nonetheless, this methodology has found application for the synthesis of quinolines [94] and 2,3-disubstituted indoles (Scheme 8.33) [96].



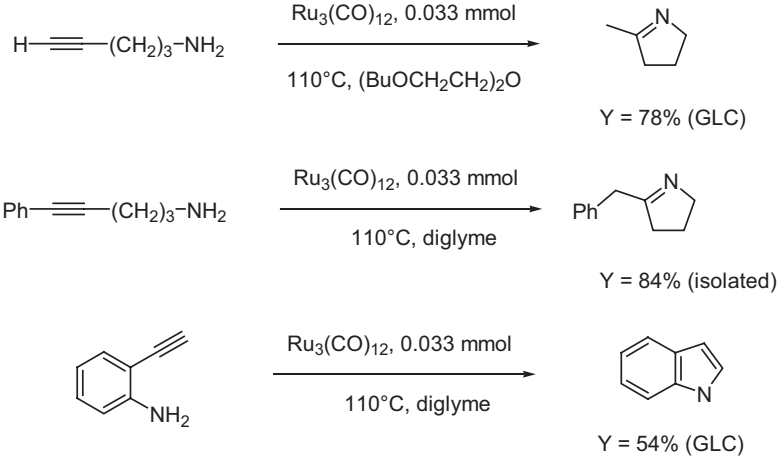
Scheme 8.33 Synthesis of quinolines and 2,3-disubstituted indoles via hydroamination.

For indole synthesis, the best additive both for yield and regioselectivity was found to be the anilinium hydrochloride ($PhNH_2 \cdot HCl$). The formation of the indole product can be explained by the isomerization of the hydroamination product, in which it has been clearly shown that the ruthenium catalyst is not involved.

8.3.2.2 **Intramolecular Hydroamination**

In 1999, Müller reported an extensive study on late transition metals as hydroamination catalysts [93]. The first ruthenium-catalyzed intramolecular hydroamination of an alkyne was demonstrated [93]. The complex $Ru_3(CO)_{12}$ was found to be an active catalyst, although the yield obtained was low. The ruthenium(II) complex $RuCl_2(PPh_3)_3$ was not active at all for the same transformation. This catalyst screening gave some indications on the reaction mechanism in favor of the initial activation of the alkyne rather than the oxidative addition of the N–H bond to the metallic center. Later, the activity of $Ru_3(CO)_{12}$ was demonstrated by Mitsudo and colleagues [97] for the conversion of 5-phenyl-4-pentynyl-1-amine into a cyclic imine (Scheme 8.34). The difference obtained by these two groups can be explained by the experimental conditions. The high conversion was obtained by heating for 4 h at 110 °C in

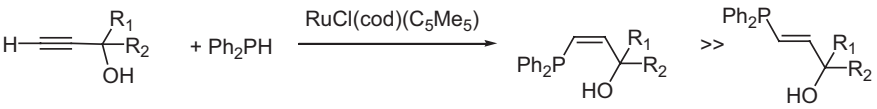
diglyme, which contrasts with the conditions used by Müller – that is, 40 °C in dichloromethane for 20 h. By using $Ru_3(CO)_{12}$ at high temperature it has been possible to perform the intramolecular hydroamination not only of terminal alkynes but also of internal alkynes. The synthesis of indole has also been performed with a moderate yield (Scheme 8.34).



Scheme 8.34 Intramolecular hydroamination of terminal and internal alkynes.

8.4
Addition of P-Nucleophiles: Hydrophosphination

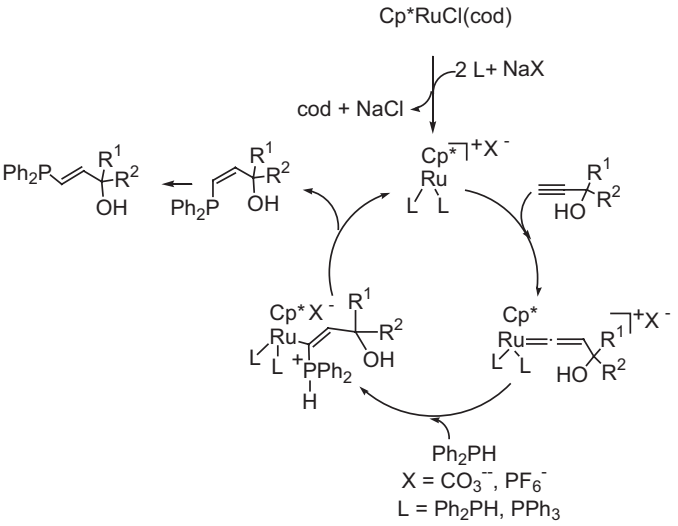
Metal complex chemistry, homogeneous catalysis and phosphane chemistry have always been strongly connected, since phosphanes constitute one of the most important families of ligands. The catalytic addition of P(III)-H or P(IV)-H to unsaturated compounds (alkene, alkyne) offers an access to new phosphines with a good control of the regio- and stereoselectivity [98]. Hydrophosphination of terminal nonfunctional alkynes has already been reported with lanthanides [99, 100], or palladium and nickel catalysts [101]. Ruthenium catalysts have made possible the hydrophosphination of functional alkynes, thereby opening the way to the direct synthesis of bidentate ligands (Scheme 8.35) [102].



	Yield (*Z*+*E* %)	*Z*/*E*
R_1= R_2= -$(CH_2)_5$-	70	95/5
R_1= R_2= -CH_3	81	75/25
R_1= R_2= -CH_2CH_3	55	75/25
R_1= -CH_3, R2= -$CH(CH_3)_2$	50	80/20

Scheme 8.35 Hydrophosphination of propargylic alcohols.

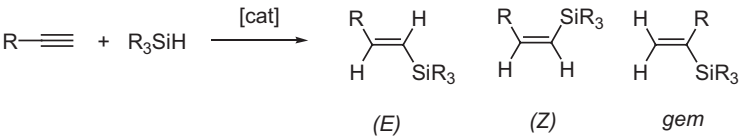
Contrary to the previous pathway of P-H addition to alkyne – that is, via alkyne insertion into the M-P bonds – this reaction has been shown to proceed via the nucleophilic attack of the phosphine to a ruthenium-vinylidene intermediate to yield the *anti*-Markovnikov product with a predominant *(Z)*-stereoisomer (Scheme 8.36). Indeed, it has been shown that $[Cp^*RuL_2]^+X^-$ intermediate gives vinylidene species with propargyl alcohols. The (*Z*)-isomer is formed as the major product, but isomerizes easily into the (*E*)-isomer upon isolation by chromatography over silica gel.



Scheme 8.36 *Anti*-Markovnikov hydrophosphination via a vinylidene intermediate.

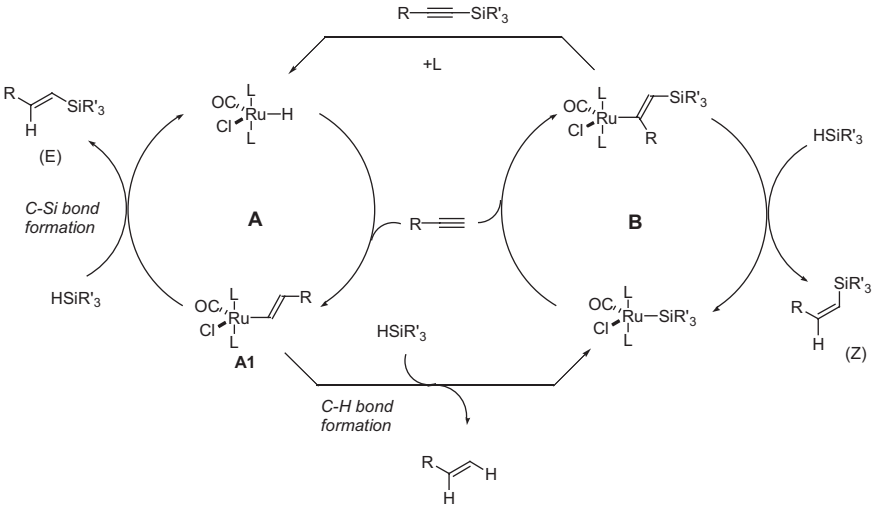
8.5
Hydrosilylation

The addition of a Si-H bond to a carbon-carbon double or triple bond is one of the most important transformations in organosilicon chemistry. The catalytic hydrosilylation of terminal alkynes yields three isomers, as shown in Scheme 8.37. Regioselectivity, as well as stereoselectivity, are therefore important issues, and are the driving forces to select active new catalysts.



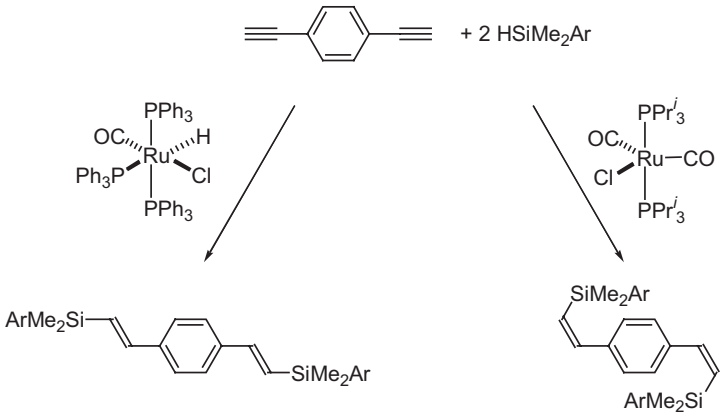
Scheme 8.37 Hydrosilylation of alkynes.

Since 1957 and the discovery of the Speir's catalyst $H_2PtCl_6/^iPrOH$, considerable efforts have been made to find new catalysts with high activity and selectivity. Along with the platinum-based catalysts, the Wilkinson's complex [103] $Rh(Ph_3P)_3Cl$ is one of the most popular hydrosilylation catalysts. Ruthenium catalysts are also able to promote the addition of silanes to unsaturated carbon-carbon bonds, and several reports have shown during the past decade that the well-defined ruthenium complexes of type $Ru(H)(Cl)(CO)L_n$ can provide excellent activity and selectivity [104–108]. The latest development has established two catalytic cycles involving monometallic species accounting for the formation of (*E*) and (*Z*)-alkenylsilanes (Scheme 8.38) [109], but the role of in-situ-formed polynuclear aggregates has also been considered [110].



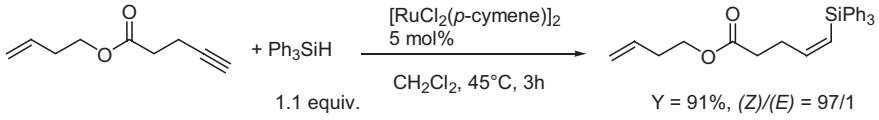
Scheme 8.38 Proposed mechanism accounting for the formation of (*Z*) and (*E*) isomers.

The crucial point to control the selectivity depends on the ability of the complex **A1** to favor C-Si bond formation to give the (*E*)-isomer or the C–H bond formation to shift to cycle **B** leading to the (*Z*)-isomer. This preference for one or the other pathway can be obtained by a judicious choice of the catalyst. For example, $RuHCl(CO)(PPh_3)_3$ catalyzes the formation of the (*E*)-isomer with excellent activities and selectivity over 99% in most cases. Using an excess of silane further increased the reaction rate. On the other hand, $Ru(SiMe_2Ph)Cl(CO)(PPr^i_3)_2$ has shown very high selectivity for the (*Z*) isomer formation. $RuHCl(CO)(PPr^i_3)_2$ [104] and $RuHCl(CO)(PCy_3)_2$ also promote the formation of the (*Z*) isomer, but with lower catalytic activities. These features have been used for the stereocontrolled synthesis of poly(*p*-phenylene-vinylene)s (PPVs) requiring the synthesis of alkenylsilane intermediates (Scheme 8.39) [111].



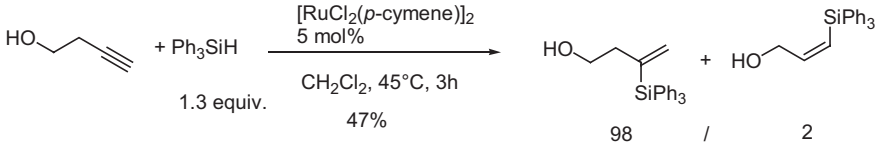
Scheme 8.39 Poly(*p*-phenylenevinylene)s (PPVs) precursors by hydrosilylation of alkynes.

(*Z*)-Vinylsilanes are also accessible by using $[RuCl_2(p\text{-cymene})]_2$ precatalyst [112]. High activities and stereoselectivity have been achieved with very good tolerance to functional groups such as chloro, alkoxy, or ester in the alkyl chain. It must be mentioned that this complex selectively hydrosilylates triple bonds in the presence of an olefinic bond (Scheme 8.40).



Scheme 8.40 Selective hydrosilylation of alkynes.

The presence of a hydroxy group at the homopropargylic position proved to modify dramatically the regioselectivity of the reaction. Indeed, 3-butyn-1-ol is selectively converted, to 3-(triphenylsilyl)-3-buten-1-ol (Scheme 8.41).



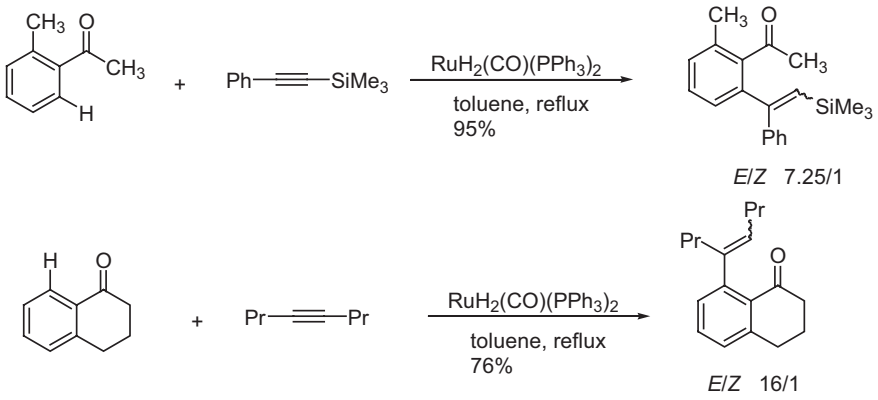
Scheme 8.41 Hydroxy group directed synthesis of *gem*-isomers.

In this case, the regioselectivity of the reaction leading to the Markovnikov addition product is thought to be due to the coordination of the hydroxy group to the ruthenium intermediate. However, the same selectivity for the Markovnikov product has been obtained without a directing group by using sterically demanding ruthenium complexes such as $Cp^*Ru(MeCN)_3^+PF_6^-$ [113].

Under the same conditions, the hydrosilylation of internal alkynes has been made possible with a nonclassical *trans*-addition of the silane which has been further used for the synthesis of trisubstituted vinylsilanes [114, 115]. Another complex, the trihydride $Cp^*RuH_3(PPh_3)$, is also able to provide selectively the internal hydrosilylation product. However, the use of chlorosilanes is here necessary in order to obtain clean reactions [116].

8.6 Addition of C–H Bond to Alkynes

The addition of carbonucleophiles to alkynes promoted by ruthenium complexes is not documented. However, several examples of C–H bond addition to alkynes with C–C bond formation have been performed. These involve the ruthenium activation of a C–H bond of aromatic ketones [117, 118] such as 2-methylacetophenone, tetralone [119] (Scheme 8.42), and enones [120, 121].



Scheme 8.42 Addition of C–H bonds to alkynes.

Many methods of ruthenium-promoted C–C bond formation implicating alkynes have been discovered. Most of these have involved oxidative coupling at a ruthenium(0) or (II) site, rather than addition of carbonucleophiles to electrophilically activated alkynes. These methods have been reported in several reviews [3, 122].

8.7 Conclusions

The above results show that the ruthenium-catalyzed activation of alkynes towards nucleophiles has first led to classical electrophilic activation, leading to Markovnikov additions as observed for addition of carboxylic acids and the synthesis of enol esters. In 1986, the regioselective *anti*-Markovnikov addition of in-situ-generated

ammonium carbamates led to the suggestion that ruthenium-vinylidene was in fact the active species. Subsequently, efforts were made to control the in-situ formation of vinylidene-ruthenium intermediates from terminal alkynes, and this led to the regioselective formation of vinylcarbamates, (*Z*)-enol esters or lactones, unsaturated ketones, aldehydes, nitriles and phosphines via the respective addition of ammonium carbamates, carboxylic acids, allylic alcohols, water, hydrazines, and secondary phosphines.

Whereas the catalytic hydrosilylation of alkynes was one of the first methods of controlled reduction and functionalization of alkynes, the ruthenium-catalyzed hydroamination of alkynes has emerged only recently, but represents a potential for the selective access to amines and nitrogen-containing heterocycles. It is also noteworthy that, in parallel, the ruthenium activation of inert C–H bonds allowing alkyne insertion and C–C bond formation also represents innovative aspects that warrant future development. Among catalytic additions to alkynes for the production of useful products, the next decade will clearly witness an increasing role for ruthenium-vinylidenes in activation processes, and also for the development of ruthenium-catalyzed hydroamination and C–H bond activation.

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9
Ruthenium-Catalyzed Reactions via sp C–H, sp^2 C–H, sp^3 C–H, and C–Halogen Bond Activations

Fumitoshi Kakiuchi and Naoto Chatani

9.1
Introduction

The manipulation of unreactive carbon-hydrogen bonds (C–H bonds) is one of the most attractive and potentially useful research areas in organic synthesis [1]. A promising result in this area was reported by Chatt and Davidson [2], who showed that a C–H bond in naphthalene, in the presence of a low-valent ruthenium complex, can be cleaved. This phenomenon held great appeal for inorganic chemists, especially in the area of organometallic chemistry. Since these studies were conducted, a large number of examples of C–H bond cleavage using a stoichiometric amount of transition metal complexes have been reported in the literature [3]. In almost all cases, the focus of the studies was on the isolation and characterization of metal-hydride species, formed by the oxidative addition of a C–H bond to a low-valent transition metal complex. During the 1980s, a few examples of catalytic reactions involving C–H activation appeared in the literature, in addition to the stoichiometric reactions. At the end of 1993, the situation with respect to catalytic methods for C–H bond functionalization had changed dramatically. Murai and colleagues reported on the highly efficient addition of C–H bonds in aromatic ketones to olefins using ruthenium catalysts [4a]. Their results stimulated studies of the catalytic functionalization of unreactive C–H bonds using a transition metal complex. To date, several types of catalytic reactions involving the cleavage of C–H bonds have been developed [1].

An important factor in the success of these reactions involves chelation-assistance by a heteroatom. Thus, the coordination of the heteroatom to the metal, brings the metal closer to the C–H bond and stabilizes the thermally unstable C–M–H species formed by the oxidative addition of a C–H bond to a low-valent transition metal complex. In addition, the use of the chelation-assistance leads to a high regioselectivity, which is an essential factor in organic synthesis. For reactions, a number of transition metal complexes – including ruthenium, rhodium, and iridium – are used as a catalyst, and ruthenium-catalyzed reactions will be described in this chapter [5].

The chapter will broadly survey the literature dealing with ruthenium-catalyzed reactions involving the cleavage of an otherwise unreactive carbon-hydrogen and carbon-halogen bonds in organic synthesis up to the early stages of 2003. Only limited

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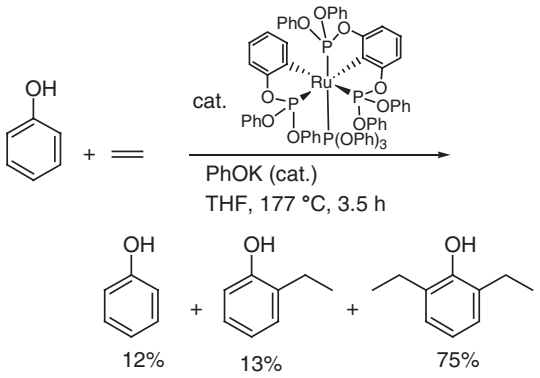
numbers of examples which involve unusual significance, originality, or complexity will be presented in equation form. Several areas – for example, reactions involving transition metal-carbenoids and transition metal-vinylidenes, and oxidations of C–H bonds – will be dealt with in other chapters in this book.

9.2 Activation of sp^2 C–H Bonds

9.2.1 Addition of Aromatic C–H Bonds to Olefins

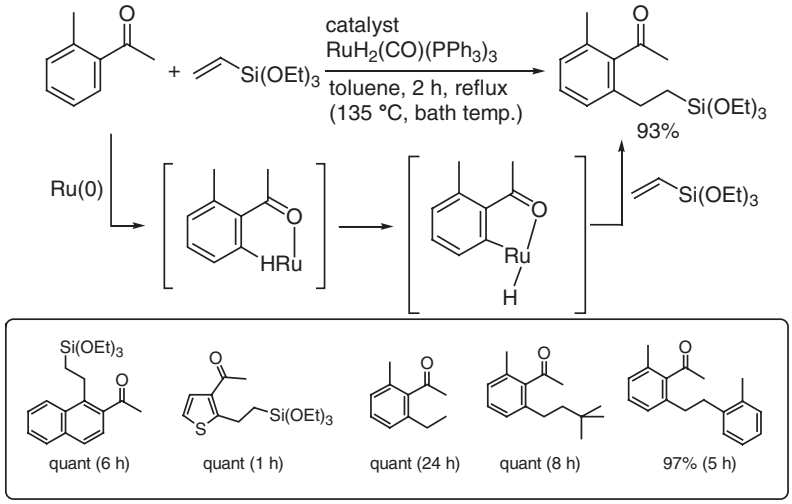
Catalytic additions of sp^2 C–H bonds in arenes to olefins are highly useful reactions, because they permit the alkylation of an aromatic ring without being converted into reactive but sacrificing functional groups, such as a halogen and triflate. One of the most promising results with respect to ruthenium-catalyzed functionalization of C–H bonds via C–H bond cleavage was reported by Lewis. The reaction of phenols with ethylene in the presence of a ruthenium catalyst gave the corresponding *ortho*-ethylated phenols (Eq. 9.1) [6]. In this case, the coordination of the phosphorus atom in the triphenylphosphite is important, and the use of potassium phenoxide is essential. The key of this reaction is an efficient exchange of the alkylated phenoxy moiety on the phosphite ligand with phenol. These pioneering results indicated that substituents which were able to coordinate to transition metal complexes had the potential to function as a directing group.



(9.1)

At the end of 1993, Murai reported on the first example of a highly efficient, selective alkylation of aromatic ketones with olefins using $RuH_2(CO)(PPh_3)_3$ as a catalyst [4a]. In this reaction, the coordination of an oxygen atom in a ketone carbonyl group to a ruthenium center was proposed to be highly important for attaining a catalytic reaction. The coordination of the ketone oxygen to the ruthenium facilitates the approach of the ruthenium to an ortho C–H bond and stabilizes the metalacycle intermediate which should be formed by an oxidative addition of the ortho C–H

bond to the ruthenium (Eq. 9.2). The reaction involves the cleavage and addition of an ortho C–H bond of acetophenone to an olefin.

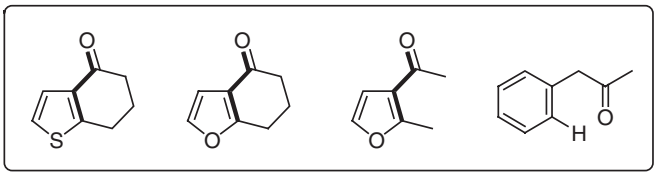


(9.2)

Several ruthenium complexes such as $RuH_2(CO)(PPh_3)_3$, $Ru(CO)_2(PPh_3)_3$, $Ru(CO)_3(PPh_3)_2$, and $RuH_2(PPh_3)_4$ show catalytic activities [4a,c]. Among these, $RuH_2(CO)(PPh_3)_3$ is the best catalyst for the reaction of aromatic ketones with olefins. The versatility of this reaction is wide. A variety of aromatic and heteroaromatic ketones can also be used in this coupling reaction [4] and, in many cases, the corresponding coupling products are obtained in excellent yields. Terminal olefins such as vinylsilanes, *tert*-butylethylene, styrenes, and allylsilanes show a high reactivity, but containing having allylic hydrogens such as 1-hexene result in low yields due to the isomerization of the double bond to an internal position.

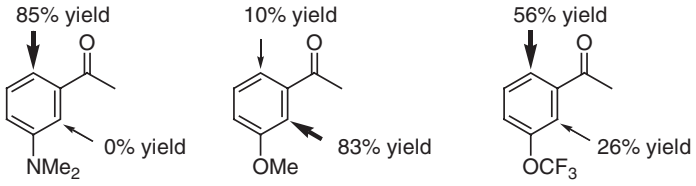
The relationship between the structure and the reactivity of the ketones has been studied [4c]. When 3-acetylthiophene was used in the coupling reaction, the alkylation took place only at 2-position (Eq. 9.2). In the cases of reactions of the ketones, shown in Scheme 9.1, no coupling product was obtained. Based on these results, Murai proposed that the α,β-conjugate enone framework is important in the C–H/olefin coupling reaction.

The $RuH_2(CO)(PPh_3)_3$-catalyzed coupling of aromatic ketones with olefins is tolerant of several functional groups [4f]. In the reaction of *m*-substituted acetophenones, two different reaction sites are present. The C–C bond formation, generally,



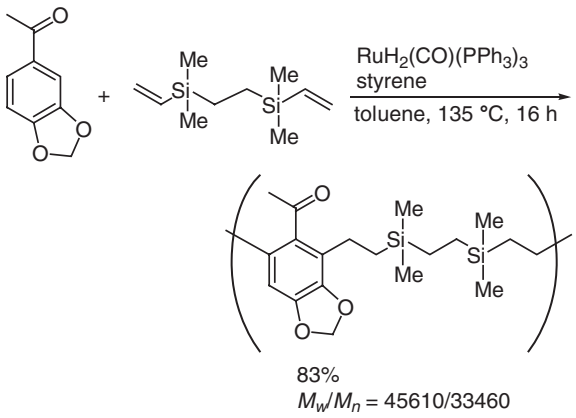
Scheme 9.1 Unreactive ketones.

takes place at the less-congested (6′) position) (Scheme 9.2). Interestingly, however, reaction of *m*-methoxyacetophenones with triethoxyvinylsilane takes place at the more congested ortho position – that is, the 2′-position (Scheme 9.2). When a strong electron-withdrawing CF_3 group, which should decrease the electron density of the adjacent atom, is attached to the ether oxygen, the alkylation took place preferentially at the less congested position. These results suggest that methoxy and fluoro groups may additionally assist in the regioselectivity determination step.



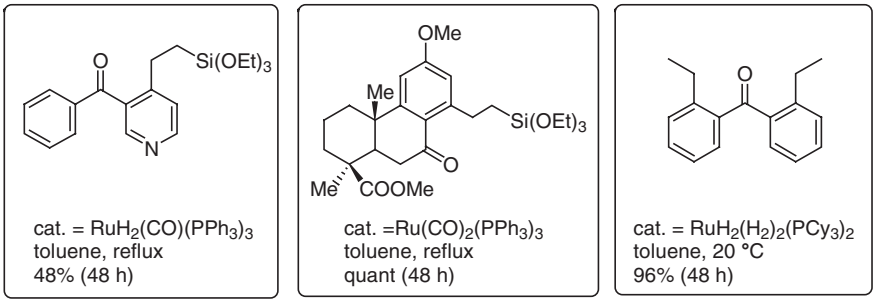
Scheme 9.2 Effect of substituents towards site selectivity.

Several related examples of the ruthenium-catalyzed addition of C–H bonds in ketones to olefins have been reported [7–9]. The coupling reaction of aromatic ketones with olefins has been examined extensively for polymer synthesis. Weber reported that the $RuH_2(CO)(PPh_3)_3$-catalyzed polymerization of aromatic ketones having two vacant ortho positions with 1,ω-dienes takes place with the aid of $RuH_2(CO)(PPh_3)_3$ [7]. This procedure provides high molecular weight polymers (M_w/M_n = 45610/33460) (Eq. 9.3).



(9.3)

Grigg reported that the alkylation of phenyl 3-pyridyl ketone using $RuH_2(CO)(PPh_3)_3$ as a catalyst proceeds exclusively at the pyridine ring (Scheme 9.3) [8]. This result indicates that C–C bond formation takes place preferentially at the electron-deficient aromatic ring. Aromatic ketones having a terpene framework can be alkylated by an olefin using $Ru(CO)_2(PPh_3)_3$ as a catalyst (Scheme 9.3) [9]. To improve the efficiency and versatility of the C–H/olefin coupling, a number of new catalyst systems have been developed. Chaudret reported that the $RuH_2(H_2)$-

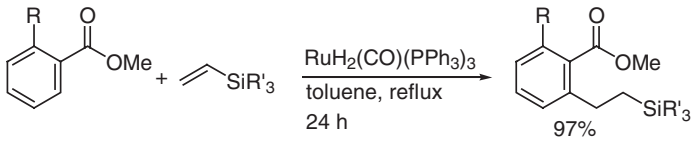


Scheme 9.3

$(CO)(PCy_3)_2$ complex catalyzes the alkylation of aromatic ketones at room temperature [10]. The reaction of benzophenone with ethylene using this ruthenium complex as a catalyst gave the corresponding 1:2 coupling product in 96% yield. Leitner subsequently reported on a similar room-temperature C–H/olefin coupling reaction using Chaudret's catalyst [11].

In Murai's reaction, $RuH_2(CO)(PPh_3)_3$, $RuH_2(PPh_3)_4$, $Ru(CO)_2(PPh_3)_3$, and $Ru(CO)_3(PPh_3)_2$ show catalytic activity, but $Ru_3(CO)_{12}$ does not [4a,c]. These results suggest that neither H nor CO is a necessary ligand and that a zero-valent ruthenium having at least two phosphine ligands (PPh_3 or PCy_3) constitutes the essential part of the catalyst [4c].

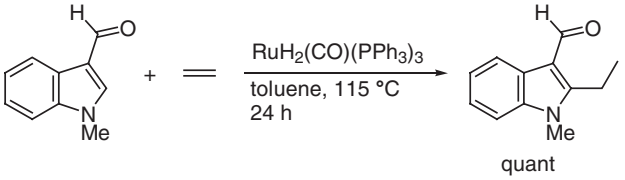
In the case of the reaction of aromatic esters with triethoxyvinylsilane, an unusual electronic effect of a substituent is found. In general, a reductive elimination step is usually accelerated by the introduction of an electron-releasing group on the leaving group. Interestingly, however, in this case, the reductive elimination step is facilitated by an introduction of an electron-withdrawing group such as CF_3, CN and CO_2Me groups on the aromatic ring (leaving group) [12]. The reactions of methyl *o*-toluate with triethoxyvinylsilane in the presence of $RuH_2(CO)(PPh_3)_3$ as a catalyst result in no reaction (Eq. 9.4, run 1)[12a]. The electronic effect of the reactions of methyl *o*-trifluoromethylbenzoate gave the corresponding alkylation product in 97% yield (Eq. 9.4, run 2). The substituent on the silicon atom is also important in this coupling reaction. The use of trimethylvinylsilane led to a high activity compared with the triethoxyvinylsilane. Methyl *o*-toluate, which is an ineffective ester for the reaction with triethoxyvinylsilane, reacted with trimethylvinylsilane to give the coupling products in 61% yield (Eq. 9.4, run 3) [12b].



(9.4)

run 1	$R = CH_3$	$SiR'_3 = Si(OEt)_3$	no reaction
run 2	$R = CF_3$	$SiR'_3 = Si(OEt)_3$	97%
run 3	$R = CH_3$	$SiR'_3 = SiMe_3$	61%

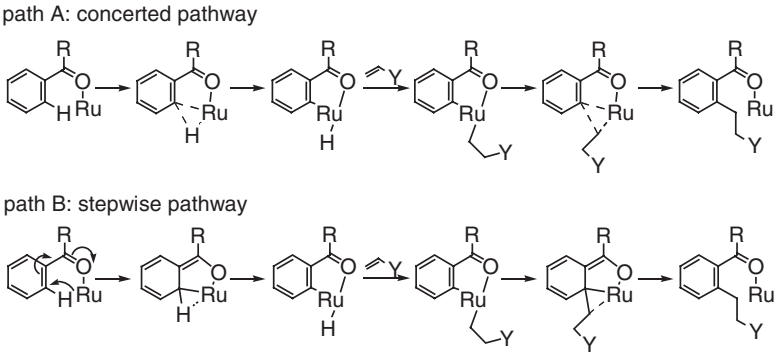
The use of a formyl group as a directing functionality is challenging because, in the case of the low-valent transition metal-catalyzed reaction of aldehydes with an olefin, aldehydes are prone to undergo decarbonylation or hydroacylation of the olefins. The following protocol to suppress the decarbonylation, one being steric and the other electronic in nature, can be used. In the case of the reaction of 1-methylindole-3-carboxaldehyde with ethylene, the ethylation product is also obtained in quantitative yield (Eq. 9.5) [13].



(9.5)

Information with respect to the rate-determining step is important for conducting the catalytic reaction under optimal reaction conditions. The rate-determining step in the reaction of aromatic ester was determined by means of deuterium-labeling experiments and natural abundance ^{13}C kinetic isotope effects [12b]. The reaction of methyl benzoate-d_5 with triethoxyvinylsilane with the aid of $RuH_2(CO)(PPh_3)_3$ as a catalyst did not give any coupling product, even after refluxing for 24 h [12b]. Interestingly, however, the ^1H NMR spectra of the recovered starting materials (the benzoate and the vinylsilanes) indicated that complete H/D scrambling occurred among two ortho positions of the benzoate and the three vinylic positions of the vinylsilane. Thus, the C–H bond cleavage using the ruthenium complex is facile and reversible. From these results, C–H bond cleavage is not rate-determining, and a rapid equilibrium occurs prior to the reductive elimination. The ^{13}C KIE of ortho carbon of the aromatic ester (^{13}C KIE = 1.033) suggests that the C–C bond formation – that is, reductive elimination – is rate-determining for this coupling reaction. Similar results were observed in the case of the reaction of aromatic ketones [12b].

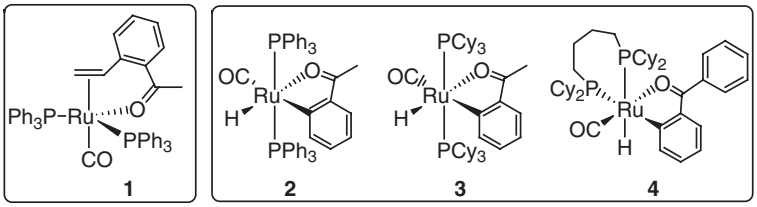
There are two possible pathways for a reductive elimination. One is a concerted pathway (path A), and the other is a stepwise pathway (path B) (Scheme 9.4). The



Scheme 9.4 Possible reaction pathways for C–H/olefin coupling.

kinetic studies and the electronic effect of the substituent on the aromatic ring suggest that the stepwise pathway (path B) is reasonable for the $RuH_2(CO)(PPh_3)_3$-catalyzed alkylation of aromatic ketones and esters with olefins. An ab initio theoretical calculation of the ruthenium-catalyzed reaction of benzaldehyde with ethylene by Morokuma and Koga also supports the stepwise reaction pathway (path B) [14].

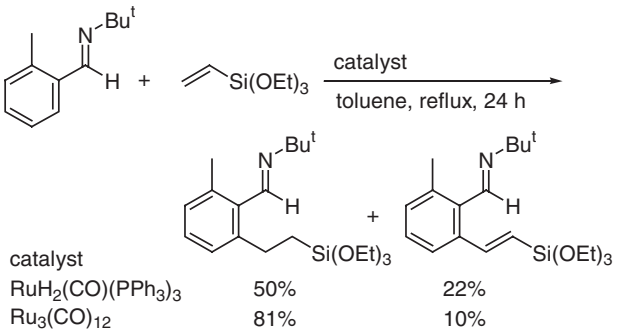
Several attempts have been made to understand the reaction mechanism and the intermediates involved in the catalytic reaction. Weber reported that Ru(*o*-vinylacetophenone)$(CO)(PPh_3)_2$ (**1**) [15] showed catalytic activity for the reaction of aromatic ketones with olefins (Scheme 9.5). To identify the plausible intermediate of the ruthenium-catalyzed reaction of aromatic ketones with olefins, three *ortho*-ruthenated complexes, $RuH(o\text{-}C_6H_4C(O)CH_3)(CO)(PPh_3)_2$ (**2**) [16], $RuH(o\text{-}C_6H_4C(O)CH_3)(CO)(PCy_3)_2$ (**3**) [10], and $RuH(o\text{-}C_6H_4C(O)Ph(CO)(dcypb)$ (**4**) (dcypb = $Cy_2P(CH_2)_4PCy_2$) [17], were synthesized and their catalytic activities examined (Scheme 9.5). However, these three complexes were found to be ineffective for this coupling reaction. In these cases, the authors claimed that the CO ligand suppresses the catalytic reactivity of these complexes, as Trost reported that a CO atmosphere completely inhibited the $RuH_2(CO)(PPh_3)_3$-catalyzed C–H/olefin coupling [18]. Hiraki studied the catalytic reaction of aromatic ketones with olefins by means of ^1H and ^{31}P NMR spectroscopy. In this study, the authors claimed that the CO ligand was bound to the ruthenium throughout the catalytic reaction [19]. These mechanistic studies suggest that the relationship between the structures of the catalyst precursor and the catalytic activity is currently poorly understood, and it is premature to conclude that the presence of a CO ligand on the ruthenium center retards catalytic activity.



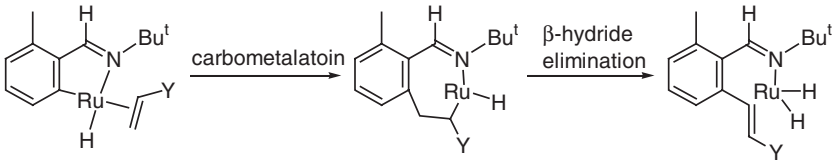
Scheme 9.5 Plausible intermediates involved in C–H/olefin coupling.

Chelation-assistance by nitrogen-containing functional groups such as amines, imines, hydrazones, and N-heterocycles is also effective for the alkylation of aromatic C–H bonds. A variety of coupling reactions by means of chelation-assistance by a nitrogen atom have been developed. In the case of the reaction of aromatic compounds having an sp^2 nitrogen directing group, $Ru_3(CO)_{12}$ exhibits a higher activity for C–H/olefin coupling. The reaction of aldimines yields a mixture of the corresponding 1:1 coupling product and the dehydrogenation product (Eq. 9.6) [20a]. The dehydrogenative coupling product is believed to form through carbometallation followed by a β-hydride elimination pathway, as shown in Scheme 9.6. Interestingly, the reaction of an aromatic ketimine derived from acetophenone affords the corresponding 1:1 coupling product as a sole product. Similar product selectivity was ob-

served, when the reaction of ketimines with olefins was carried out using $[RhCl(coe)_2]_2$-PCy_3 as a catalyst [21]. This result suggests that the structure of the substrate largely affects product selectivity. Hydrazones are also applicable to this type of alkylation reaction [20c].

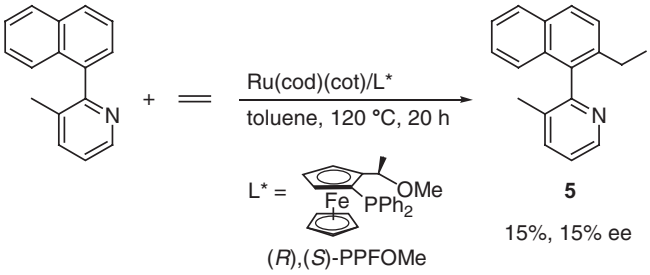


(9.6)



Scheme 9.6 Plausible pathway for the formation of a dehydrogenative coupling product.

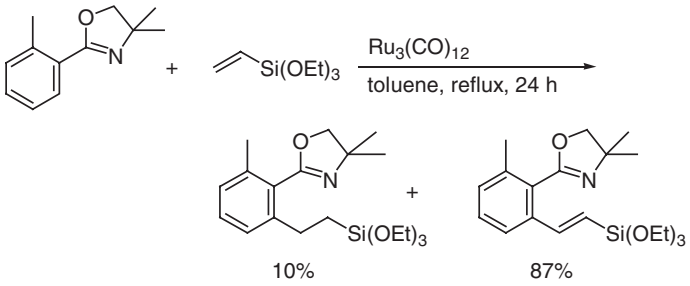
When the alkylation of 2-arylpyridines with olefins via a C–H bond cleavage was carried out with the aid of Ru(COD)(COT) (COD = 1,5-cyclooctadiene; COT = 1,3,5-cyclooctatriene) and the chiral phosphine (*R*),(*S*)-PPFOMe ((*R*),(*S*)-PPFOMe = (*R*)-1-[(*S*)-2-(diphenylphosphino)ferrocenyl]ethyl methyl ether), the alkylation product **5** was obtained in 15% yield with 15% *e.e.* (Eq. 9.7) [22]. Although the chemical and optical yields are inadequate, this result suggests that the atropselective alkylation of a biaryl compound is possible by means of a chelation-assisted C–H/olefin coupling.



(9.7)

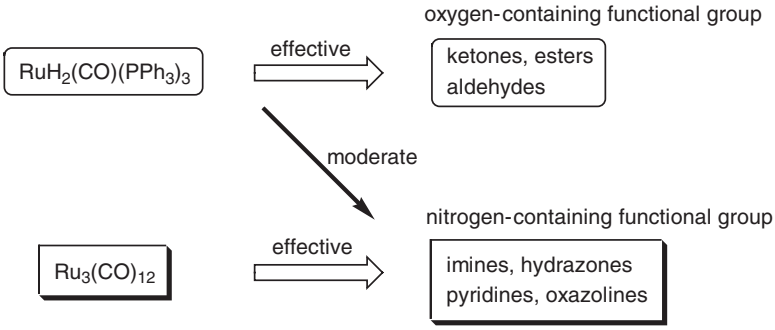
Aryloxazolines (five-membered N,O-heterocycle) show reactivity for coupling reactions with olefins [23]. In the case of the reaction of aryloxazalines, the coupling reaction proceeded with unusual product selectivity. In this case, alkenylation products were obtained as the major isomer (Eq. 9.8), and two hydrogen atoms generated

were trapped by olefins. Aryloxazines (six-membered N,O-heterocycles) can also be used for this coupling reaction.

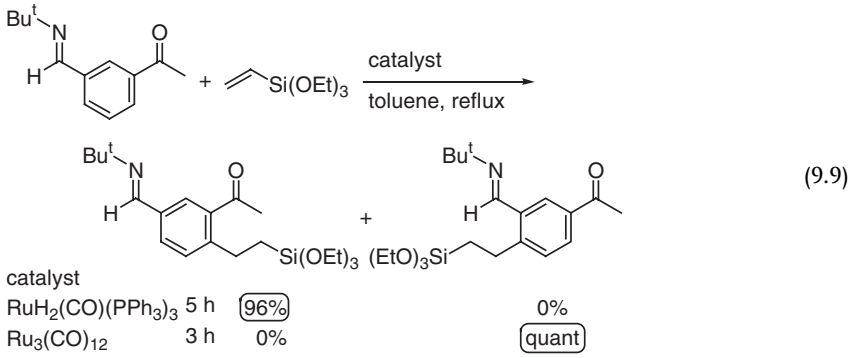


(9.8)

In the reaction of aromatic carbonyl compounds, $RuH_2(CO)(PPh_3)_3$ shows a high activity. In the case of aromatic compounds having a nitrogen-directing group, $Ru_3(CO)_{12}$ is a highly effective catalyst and $RuH_2(CO)(PPh_3)_3$ is a moderate one. By taking advantage of these different catalytic activities of $RuH_2(CO)(PPh_3)_3$ and $Ru_3(CO)_{12}$ with respect to ketones and imines (Scheme 9.7), unique site-selective alkylations can be attained. When the reaction of 1-[3-(*tert*-butyliminomethyl)phenyl]ethanone of triethoxyvinylsilane was conducted in the presence of the $RuH_2(CO)(PPh_3)_3$-catalyst, which shows a high catalytic activity for ketones, alkylation exclusively occurred at the position ortho to the acetyl group (6-position) (Eq. 9.9) [20b]. On the other hand, in the case of the reaction using $Ru_3(CO)_{12}$, which is an effective catalyst for imines, the alkylation proceeds predominantly at the imino group side (Eq. 9.9). This catalyst-specific reaction can be applied to C–H/acetylene coupling. The reaction of the 3-iminoacetophenone with 1-trimethylsilyl-1-propyne in the presence of $RuH_2(CO)(PPh_3)_3$ as catalyst resulted in an alkenylation of the C–H bond at the acetyl side. On the other hand, the use of $Ru_3(CO)_{12}$ as catalyst led to alkenylation at the ortho position of the imino group.

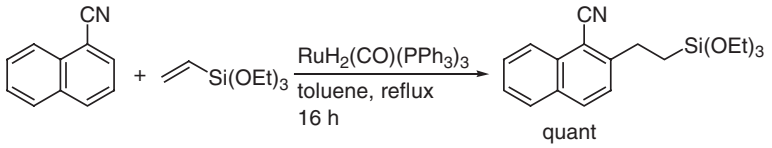


Scheme 9.7



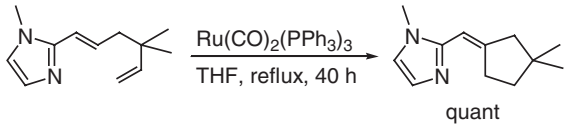
(9.9)

For the chelation-assisted catalytic reaction, π-electrons in a nitrile group are able to function as a directing group. The ruthenium-catalyzed alkylation of aromatic nitriles with triethoxyvinylsilane takes place predominantly at the ortho position (Eq. 9.10) [24]. This regioselectivity indicates the possibility of π-coordination of the CN group to the ruthenium in the catalytic cycle.

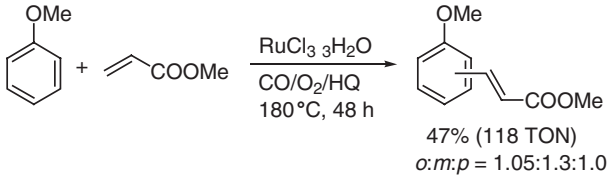


(9.10)

An intramolecular C–H/olefin coupling reaction can provide a cyclization product. Rhodium complexes involving $[RhCl(coe)_2]_2$-PR_3 and $(\eta^5\text{-}C_5Me_5)Rh(C_2H_3SiMe_3)_2$ complexes are superior as catalysts. Some ruthenium complexes are also reasonably effective for cyclization reactions. Intramolecular olefinic C–H/olefin coupling with the aid of $Ru(CO)_2(PPh_3)_3$, which is also effective for the reaction of aromatic ketones with olefins, yields the carbocyclic compounds in high yield (Eq. 9.11) [25].



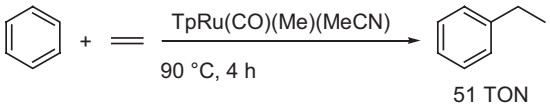
(9.11)



(9.12)

In 2001, Milstein reported on the oxidative alkenylation of arenes with olefins using a $Ru/O_2/CO$ catalyst system (Eq. 9.12) [26], but details of the reaction mechanism have not been elucidated. Very recently, Gunnoe reported ethylation and propylation of ben-

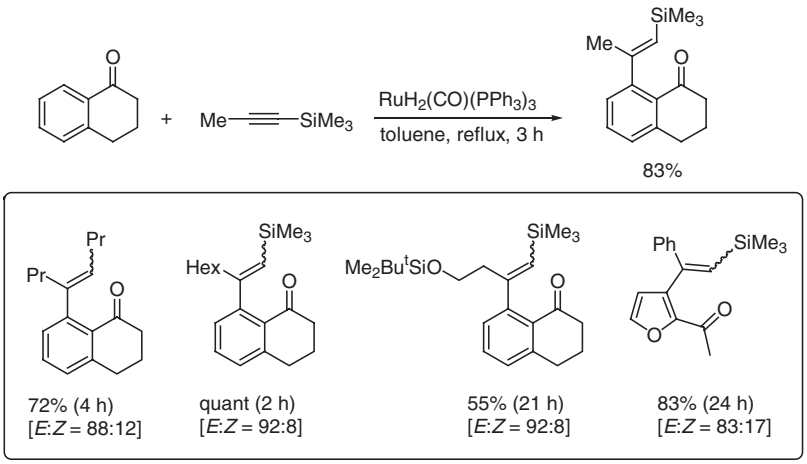
zene using TpRu(CO)(Me)(NCMe) (Tp = trispyrazole borate) as a catalyst (Eq. 9.13) [27]. This is a new entry for alkylation of benzene, though the applicability of this reaction is narrow. These authors proposed that a catalytic cycle involves olefin/acetonitrile ligand exchange followed by olefin insertion into the Ru-Ar bond. The C–H bond activation in another arene allows elimination of alkylbenzenes.



(9.13)

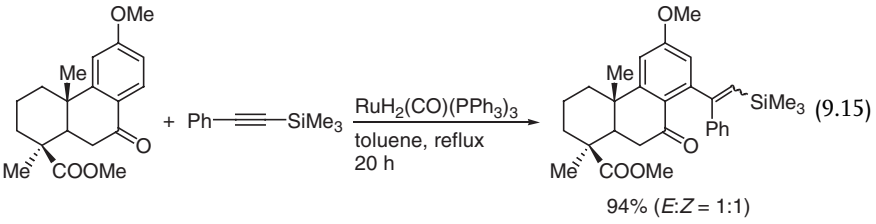
9.2.2
Addition of Aromatic C–H Bonds to Acetylenes

In the case of a reaction using acetylenes as an acceptor of the C–H bond, an alkenylation can be achieved. Pioneering work in this area was reported by Yamazaki. In this case, styrene derivatives were obtained by the reaction of arenes with disubstituted acetylenes using $Rh_4(CO)_{12}$ as a catalyst [28]. To date, several studies of the transition metal-catalyzed addition of C–H bonds to acetylenes have been reported [29–32]. Murai reported that the $RuH_2(CO)(PPh_3)_3$-catalyzed reaction of aromatic ketones with internal acetylenes gave the corresponding ortho vinylation product in high yields [29]. In the case of the reaction with 1-trimethysilylacetylenes, the C–C bond formation proceeded exclusively at the position β to the silyl group. When 1-trimethylsilylpropyne was used, the desired coupling product was obtained in excellent yield and the regio- and stereochemical outcomes are perfect (Eq. 9.14), the *E*-isomer being the predominant product. This stereochemistry indicates that the addition of C–H bonds to C–C triple bond proceeds with *syn* selectivity. These coupling reactions provide a new route to the preparation of trisubstituted styrene derivatives. The C–H/acetylene coupling can be applied to several aromatic compounds, and the corresponding alkenylation products were obtained in high yields.

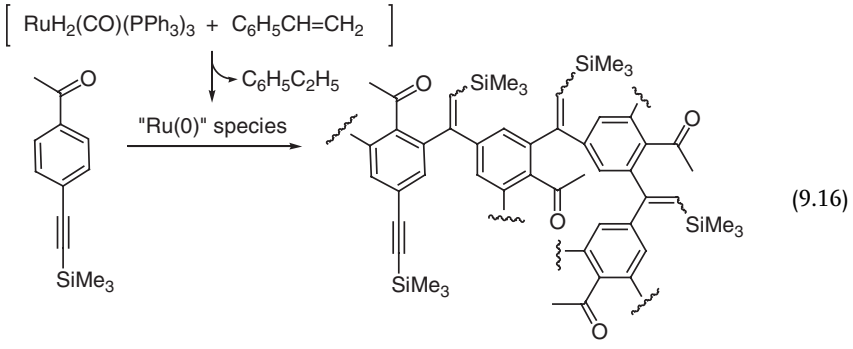


(9.14)

The C–H/acetylene coupling reaction was applied to fused aromatic ketones having a terpene framework. Alkenylation proceeded exclusively at the position ortho to the ketone carbonyl group (Eq. 9.15) [30]. The combination of acetophenone and diynes provides a new entry route to copolymerization of aromatic ketones with acetylenes. The step growth copolymerization of aromatic ketones and acetylenes was also studied (Eq. 9.16) [31].



(9.15)

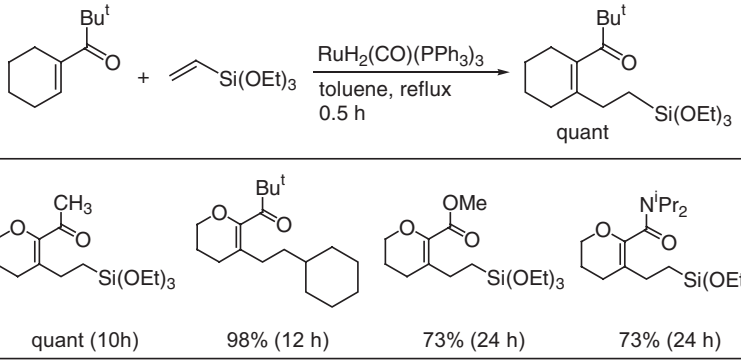


(9.16)

9.2.3

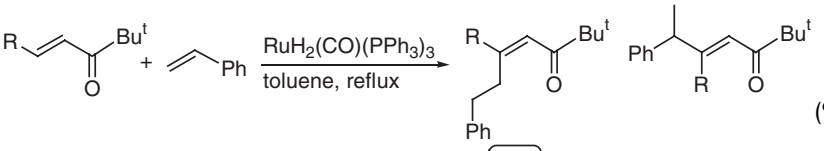
Addition of Olefinic C–H Bonds to Olefins and Acetylenes

Olefinic C–H bonds in conjugated enones are able to add across C–C double bonds with the aid of the $RuH_2(CO)(PPh_3)_3$ as a catalyst (Eq. 9.17) [18, 33]. Reactions of conjugated ketones [33a,b] with olefins provide the corresponding β-alkylation products in good to excellent yields. The applicability of olefins in this olefinic C–H/olefin coupling is widespread compared with those in aromatic C–H/olefin couplings. Vinylcyclohexane, α-methylstyrene, 2-vinylpyridine, and methyl methacrylate, which are ineffective olefins in the reaction of aromatic ketones, showed high reactivity.



(9.17)

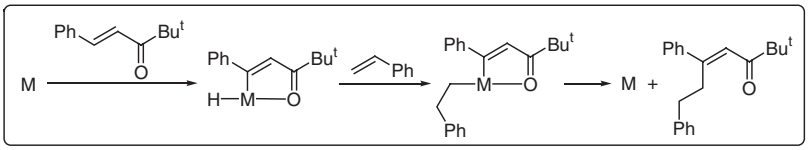
These reactions can also be applied to an acyclic system [33b]. When the reaction of *trans*-4,4-dimethyl-1-phenyl-1-penten-3-one with styrene was carried out using $RuH_2(CO)(PPh_3)_3$ as catalyst, the β-alkylation product was obtained (Eq. 9.18). On the other hand, when *trans*-2,2-dimethyl-4-hexene-3-one was used, the stereochemistry around the double bond of the enone moiety was completely changed, compared to the starting enone. In addition, C–C bond formation took place between the β-carbon of the enone moiety and the α-carbon of styrene. From these results, the substituent on the β-carbon of the enone has a significant effect on the reaction pathway. These authors claimed that the reaction of Eq. 9.18 (run 1) proceeded via the mechanism similar to that proposed in the reaction of aromatic ketones (the oxidative addition of a C–H bond, Scheme 8, mechanism 1) and the reaction in Eq. 18 (run 2) occurred through a hydrometallation pathway (Scheme 9.8, mechanism 2) because the stereochemistry around the double bond was converted to the opposite one. Conjugate esters and amides are also applicable for the olefinic C–H/olefin coupling [18, 33c]. Trost reported on a similar coupling reaction of a conjugated ester with olefins using $RuH_2(CO)(PPh_3)_3$ (Eq. 9.19) [18]. This coupling reaction tolerates a variety of functional groups on the ester moiety. Both cyclic and acyclic conjugated esters can be applied to the coupling reaction. In the case of the reaction of acyclic esters, the addition of a small amount of THF was effective in suppressing the undesired stereochemical isomerization.



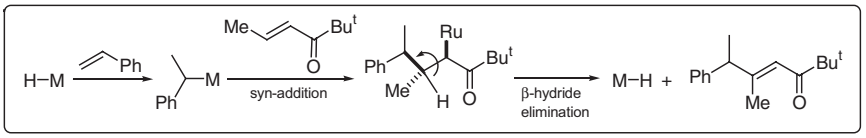
(9.18)

run 1	R = Ph	3 h	64%	0%
run 2	R = Me	1 h	0%	80%

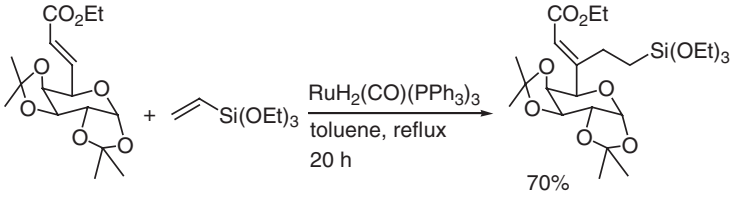
mechanism 1



mechanism 2

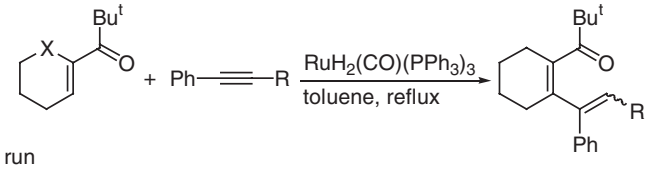


Scheme 9.8



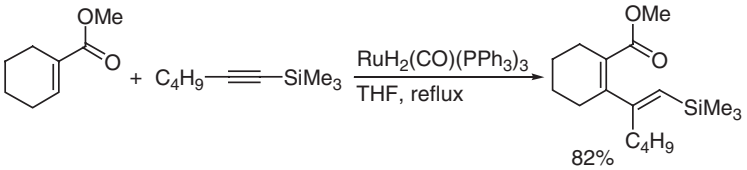
(9.19)

The C–H/acetylene coupling is also effective for the synthesis of conjugate dienones. The reaction of 1-(5,6-dihydro-4*H*-pyran-2-yl)-2,2-dimethylpropan-1-one with phenyl(trimethylsilyl)acetylene in the presence of $RuH_2(CO)(PPh_3)_3$ as a catalyst gave the β-alkylation product in 96% yield (Eq. 9.20) [29b]. This reaction gives highly congested conjugate dienones, whereas the reaction using phenyl(trimethylsilyl)acetylene results in regioselective alkenylation. This regionselectivity is analogous to those in the reaction of aromatic ketones. Trost reported the alkenylation of α,β-unsaturated esters with acetylenes using $RuH_2(CO)(PPh_3)_3$-catalyst (Eq. 9.21) [18].



(9.20)

run				
1	X = O	R = $SiMe_3$	1 h	96% (*E*:*Z* = 94:6)
2	X = O	R = Ph	1 h	71% (*E*:*Z* = 76:24)
3	X = CH_2	R = Ph	2 h	85% (60:40)

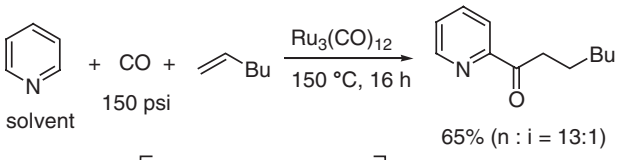


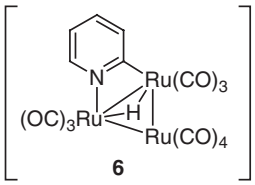
(9.21)

9.2.4
Carbonylation of C–H Bonds

Pioneering investigations by Moore and extensive studies by Murai and Chatani showed that various types of a three-component coupling reactions of C–H/CO/olefins can be catalyzed by $Ru_3(CO)_{12}$. In all cases, the presence of an sp^2 nitrogen in the substrate is required, indicating that the coordination of an sp^2 nitrogen to ruthenium is an important step for the reaction to proceed. The carbonylation reactions reported thus far can be classified into four types, depending on the position where the carbonylation takes place: (i) α to an sp^2 nitrogen; (ii) β to an sp^2 nitrogen; (iii) γ to an sp^2 nitrogen; and (iv) δ to an sp^2 nitrogen.

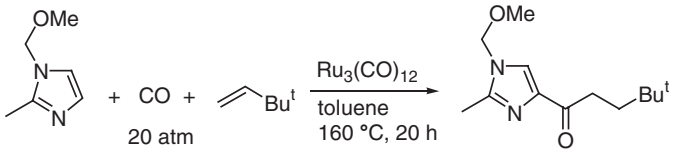
In 1992, Moore reported that the reaction of pyridine, alkenes, and CO catalyzed by $Ru_3(CO)_{12}$ results in a selective cleavage of a C–H bond α to the pyridine nitrogen to give pyridyl alkyl ketones (Eq. 9.22) [34], but no other pyridine-containing products were observed. The reaction of internal olefins such as 2-hexene, gave the same linear/branched ratio as 1-hexene. Although a variety of transition metal carbonyl complexes were examined for their ability to catalyze this new carbonylation reaction, only ruthenium carbonyl complexes showed catalytic activity. A trinuclear ruthenium cluster **6**, formed by the coordination of the pyridine nitrogen to the ruthenium catalyst followed by regiospecific activation of a C–H bond α to the pyridine nitrogen, is proposed as the key catalytic species. A kinetic study indicated a first-order rate with respect to pyridine and $Ru_3(CO)_{12}$ and zero order with respect to CO pressure and olefin concentration.





(9.22)

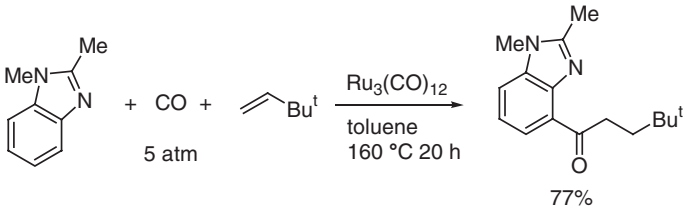
Murai found that C–H bonds in imidazoles also undergo carbonylation (Eq. 9.23). The coupling occurred regioselectively at the 4-position (α to the sp^2 nitrogen), with no 5-isomer being detected [35]. A variety of functional groups, such as ketone, ester, cyano, acetal, N,O-acetal, ketal, and silyl groups, were tolerated under the reaction conditions.



(9.23)

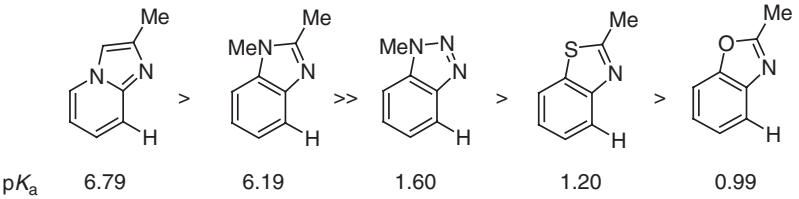
The carbonylation reaction is also applicable to other five-membered N-heterocycles, such as thiazoles, oxazoles, and pyrazoles [36]. The reactivity of the substrates increases with increasing pK_a values of the conjugate acids of the N-heterocycles according to the series: imidazole (pK_a 7.85) > thiazole (pK_a 3.37) > oxazole (pK_a 2.91) > pyrazole (pK_a 2.09). This indicates that the coordination of the substrates by the sp^2 nitrogen to the ruthenium center is the key step in the carbonylation of C–H bonds in N-heterocycles.

Murai reported that $Ru_3(CO)_{12}$ catalyzes carbonylation at a C–H bond β to the sp^2 ring nitrogen (Eq. 9.24). The $Ru_3(CO)_{12}$-catalyzed the reaction of 1,2-dimethylbenzimidazole with an alkene, and CO provided the corresponding β-acylated product in high yield with complete site selectivity [37].



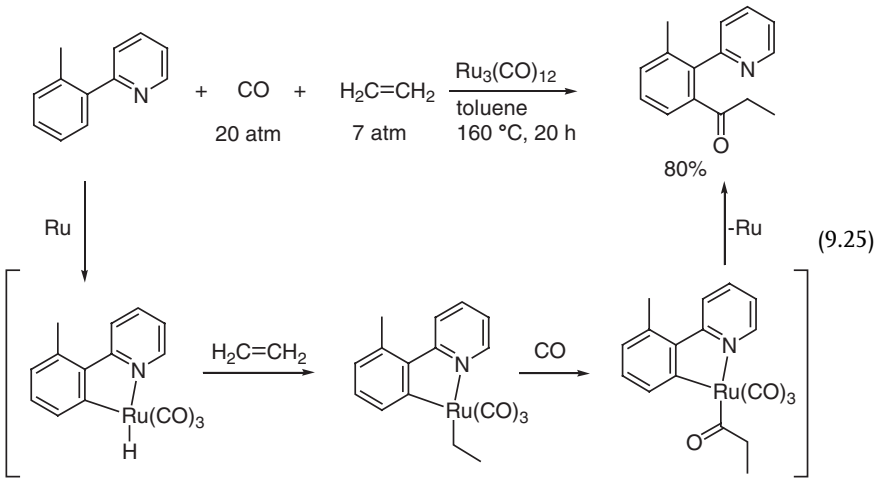
(9.24)

A similar basicity-dependent reactivity of substrates described in the α-carbonylation was observed in the case of carbonylation at C–H bond β to the sp^2 nitrogen, as shown in Scheme 9.9. Thus, the higher the pK_a of the substrate is, the higher is the reactivity.



Scheme 9.9 Reactivity of five-membered N-heterocyclic compounds.

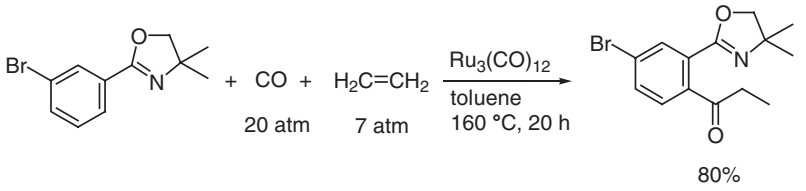
In contrast to the carbonylation of a parent pyridine, in which carbonylation takes place at C–H bonds α to the pyridine nitrogen, 2-phenylpyridine did not undergo α-carbonylation, but, instead, *ortho*-carbonylation took place. When the reaction of 2-*o*-tolylpyridine with CO (20 atm) and ethylene was conducted at 160 °C, the *ortho*-C–H bond (γ to the sp^2 nitrogen) in the benzene ring underwent carbonylation (Eq. 9.25) [38]. Carbonylation took place selectively at a C–H bond γ to the sp^2 nitrogen (*ortho*-C–H bond). C–H bonds in the pyridine ring and *meta*- and *para*-C–H bonds in the benzene ring are completely unreactive.



(9.25)

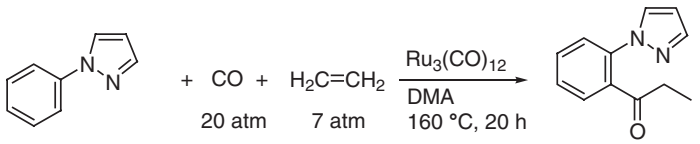
In the reaction of *m*-substituted substrates, carbonylation takes place exclusively at the less-congested position (i.e., the 6-position), irrespective of the electronic nature of the substituents, indicating that the regioselectivity is determined by steric factors. In the case of 2-naphthylpyridine, carbonylation takes place selectively at the 3-position, presumably because of steric hindrance by the peri-hydrogen on the naphthalene ring. In sharp contrast to the α and β carbonylations described above, this reaction is restricted to ethylene as the olefin partner. The use of 1-hexene resulted in no reaction.

The presence of a directing group is essential for the reaction to proceed, but it not limited to a pyridine ring. Some other N-heterocycles, which involve an sp^2 nitrogen can also function as an effective directing group. An oxazoline ring is also an effective directing group for γ carbonylation at a C–H bond in the benzene ring (Eq. 9.26) [39].



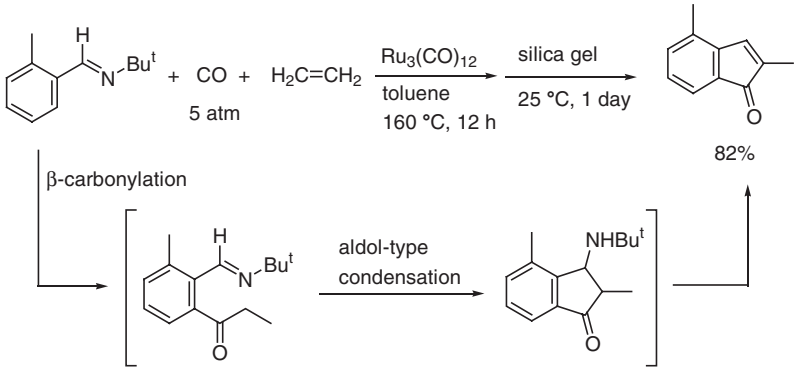
(9.26)

A pyrazole ring can also serve as a directing group (Eq. 9.27) [40]. The reactivity of *N*-phenylpyrazole is much higher that expected on the basis of the basicity of the pyrazole.



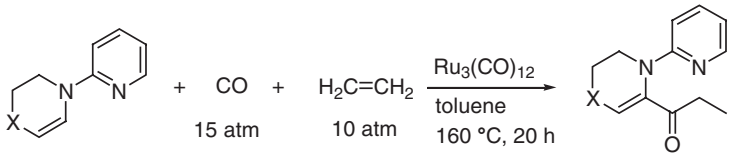
(9.27)

An imino group also directs the selective cleavage of *ortho*-C–H bonds. The reaction of aromatic imines with CO and ethylene in the presence of $Ru_3(CO)_{12}$ gave the expected ketones. However, the reaction did not stop at the carbonylation step, but an in-situ intramolecular aldol-type reaction proceeded to give indenone derivatives as the final products (Eq. 9.28) [41]. Treatment of the reaction mixture with silica gel selectively afforded indenones in good yields.



(9.28)

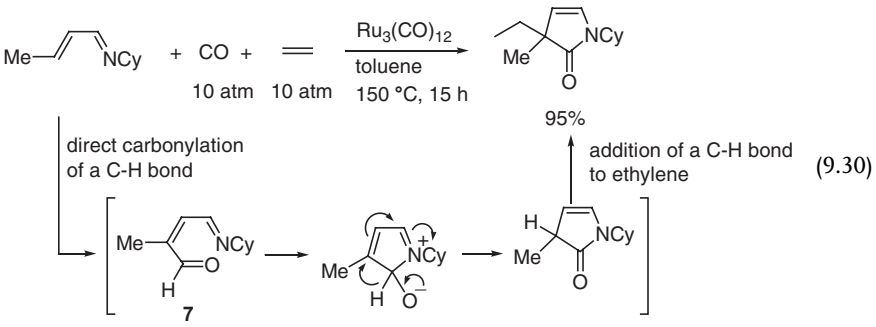
The three-component coupling reaction can be extended to olefinic C–H bonds (Eq. 9.29) [42]. Carbonylation of pyridylolefins is less efficient than that of pyridylbenzenes (Eq. 9.29) because of side reactions, that include isomerization of the olefin and hydrogenation of the C–C double bond. However, it was found that cyclic olefins involving a nitrogen in the ring gave high yields of carbonylation products. The reactivity is significantly affected by the nature of the X group in the ring.



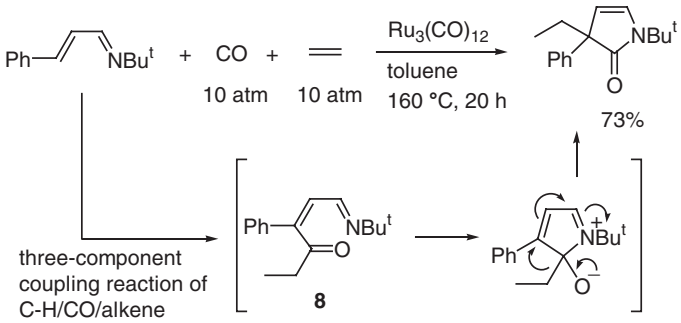
X = NMe	95%
X = O	91%
X = CH_2	13%

(9.29)

Imhof reported that the reaction of α,β-unsaturated imines with CO and olefins in the presence of $Ru_3(CO)_{12}$ gives γ-lactam derivatives instead of the expected ethyl ketone (Eq. 9.30) [43]. Chatani also reported that the $Ru_3(CO)_{12}$-catalyzed reaction of α,β-unsaturated imines with CO and ethylene results in a three-component coupling reaction to give unsaturated γ-lactams (Eq. 9.31) [44]. Imhof proposed that aldehyde **7**, formed by direct carbonylation at the C–H bond in the 3-position and the Ru-catalyzed addition of a C–H bond to ethylene are proposed as key intermediates. A different mechanism from that of Imhof was proposed in which the reaction proceeds via a two-step sequence involving an initial three-component coupling reaction at the olefinic C–H bonds leading to **8** and a non-catalyzed ethyl group rearrangement.

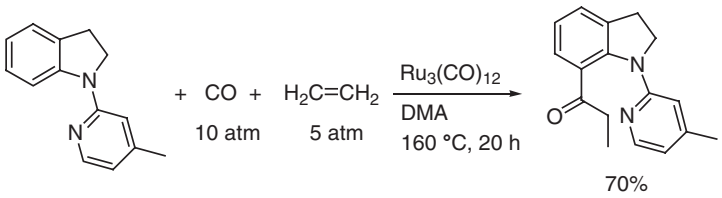


(9.30)



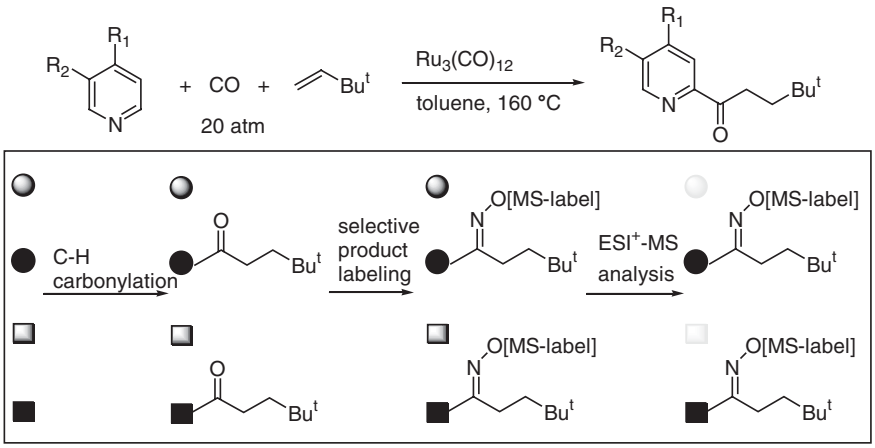
(9.31)

Chatani reported that the carbonylation of a C–H bond at the δ position to the sp^2 nitrogen also proceeds in the presence of $Ru_3(CO)_{12}$ (Eq. 9.32) [45]. The choice of *N,N*-dimethylacetamide (DMA) as the solvent is crucial for the reaction to proceed efficiently, and the available substrates are limited to an indoline skeleton.



(9.32)

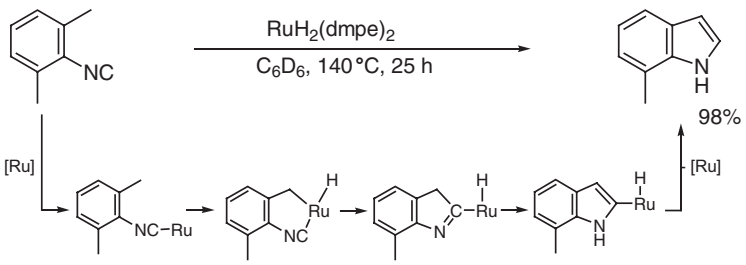
Several high-throughput protocols have recently been reported for determining optimal reaction conditions and applicable substrates, and these protocols are frequently used to optimize the reaction conditions in transition metal-catalyzed reactions. Electrospray ionization mass spectrometry (ESI-MS) has drawn increasing attention for the analysis of combinatorial libraries. Recently, Ellman and Bergman applied this method to exploit $Ru_3(CO)_{12}$-catalyzed carbonylation at C–H bonds in N-heterocycles [46]. The high-throughput strategy for optimizing of the carbonylation and the discovery of new products are shown in Scheme 9.10. A mixture consisting of aromatic N-heterocycles (33 different compounds) and *tert*-butylethylene was subjected to carbonylation at the C–H bonds catalyzed by $Ru_3(CO)_{12}$ (40 mol%)



Scheme 9.10 High-throughput reaction evaluation and optimization: exploring C–H activation.

under CO (20 atm) at 160 °C. The reaction mixture was treated with a peptide label, $H_2NOGlyArg_4$, to give oxime derivatives, which were then analyzed using ESI^+-MS.

The isonitrile group is a good coordinating group for transition metals. Jones reported on a unique transformation of an aromatic isocyanide having an alkyl group at the ortho position to indole derivatives [47]. When the reaction of 2,6-xylyl isocyanide was conducted in the presence of $RuH_2(dmpe)_2$, intramolecular cyclization leading to an indole derivative via C–H bond cleavage took place (Eq. 9.33). In this case, the isocyanide moiety was inserted into the benzylic C–H bond. These findings provided a new route to the synthesis of indoles.

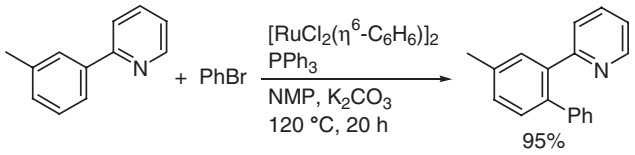


(9.33)

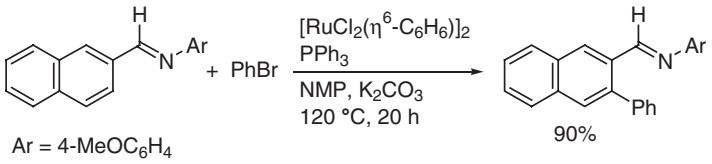
9.2.5
Arylation of Aromatic C–H Bonds

For the alkylation and alkenylation of C–H bonds, olefins and acetylenes are used as reactants. This type of coupling protocol is not applicable to arylation. Recently, a nitrogen-directed arylation of aromatic C–H bonds, leading to biaryl compounds has been developed. In 2001, Oi demonstrated that ruthenium(II)-phosphine can be used as a catalyst in the regioselective arylation of 2-arylpyridines using aryl halides (Eq. 9.34) [48]. The predominant ortho selectivity indicates that the coordination of

the pyridine nitrogen is the key for the reaction. The same catalyst-system is also effective for the arylation of aromatic imines (Eq. 9.35) [49]. Although mechanistic studies of these reactions have not been reported, these authors proposed that the catalytic reaction is initiated by the oxidative addition of bromobenzene to the ruthenium(II) species leading to a ruthenium(IV) species (i.e., $Ru(Ph)(Br)(Cl)_2(L)_n$), and the C–H bond is then cleaved by electrophilic attack by the ruthenium(IV) complex. Thus, the C–H bond is cleaved via an electrophilic substitution pathway.

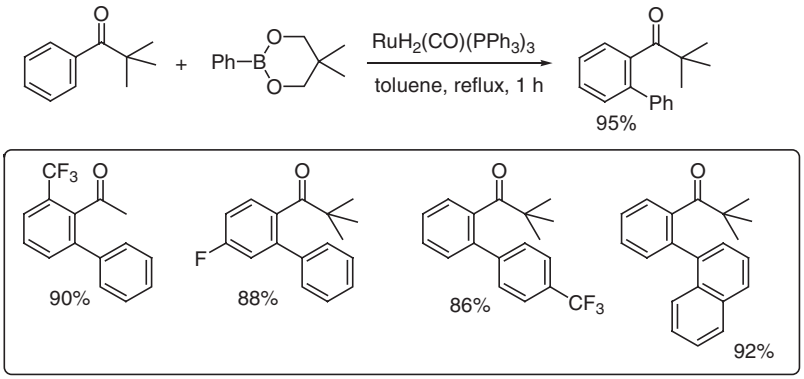


(9.34)



(9.35)

Very recently, Kakiuchi reported on the ruthenium-catalyzed arylation of C–H bonds using organoborane reagents. The reaction of aromatic ketones with arylboronates using a ruthenium catalyst resulted in the production of arylated aromatic ketones (Eq. 9.36) [50]. This arylation reaction using arylboronates can be applied to a variety of aromatic ketones and arylboronates. The authors proposed that this reaction involves the oxidative addition of a C–H bond to a Ru(0) species.



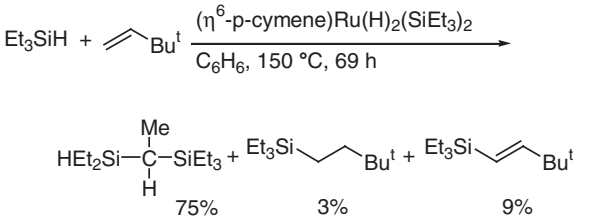
(9.36)

9.2.6
Silylation of Aromatic C–H Bonds

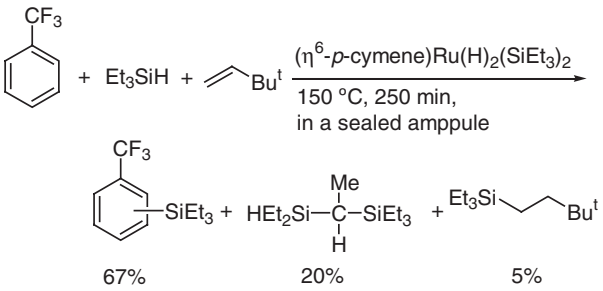
The catalytic conversion of C–H bonds to C–C bonds is one of the most attractive and potentially useful reactions in organic synthesis. The silylation of C–H bonds

via a C–H bond cleavage is another research topic in catalytic methods involving C–H bond cleavage. Pioneering studies on silylation reactions were reported by Curtis [51], who described the $IrCl(CO)(PPh_3)_3$-catalyzed silylation of benzene with pentamethyldisiloxane under thermal reaction conditions. Unfortunately, the efficiency and the selectivity of this reaction were low. Following this discovery, several attempts have been made to achieve a high efficiency and selectivity.

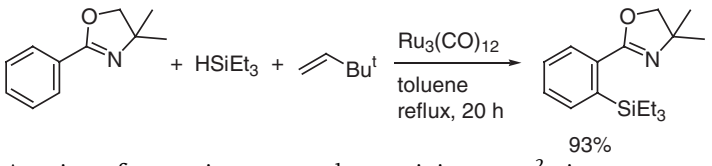
In 1994, Berry reported on the ruthenium-catalyzed silylation of arene C–H bonds with hydrosilanes [52]. In this study, it was reported that (η^6-arene)$Ru(H)_2(SiEt_3)_2$ and (η^5-C_5Me_5)$Rh(H)_2(SiEt_3)_2$ catalyze the transfer dehydrogenative coupling of triethylsilane in the presence of a hydrogen scavenger to give the dimer of the hydrosilane (Eq. 9.37) [52a]. The authors later applied this catalyst system to the silylation of arenes having an electron-withdrawing substituent (Eq. 9.38) [52b]. The relative ratio of the reactivity of the arylsilanes to phenylsilane are CF_3 (2.8) > F (1.4) > H (1.0) > CH_3 (0.32). This indicates that an electron-withdrawing group would enhance the C–H functionalization. Berry's silylation procedure is promising, but the low regioselectivity is an inevitable drawback. The chelation-assisted C–H bond cleavage protocol – one of the most reliable methods for attaining high regioselectivity – was applied to the silylation reaction [53]. The $Ru_3(CO)_{12}$-catalyzed silylation of aryloxazolines with hydrosilanes give the ortho-selective silylation products in good to excellent yields (Eq. 9.39) [53a]. In this silylation, the two hydrogen atoms generated must be trapped with a scavenger because the generation of molecular hydrogen from the RuH_2-species is usually a thermally unfavorable process. The use of an olefin as a hydrogen scavenger is required for the reaction to proceed in a catalytic manner. The functional group compatibility of this reaction is high, and it is tolerant of both electron-donating (Me, OMe, and NMe_2) and -withdrawing (CF_3 and F) groups.



(9.37)

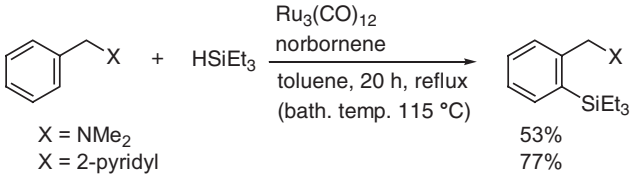


(9.38)



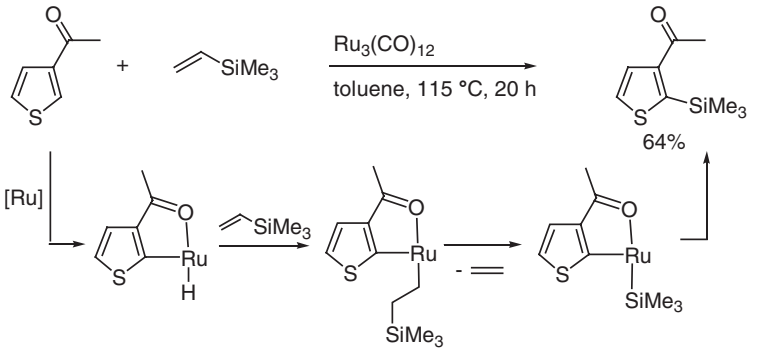
(9.39)

A variety of aromatic compounds containing an sp^2 nitrogen atom as a directing group can be used in this silylation of C–H bonds. The reaction of aromatic imines with triethylsilane provided the corresponding silylation product in a high yield [53b]. Several azoles such as phenyltetrazoles and pheylimidazoles are also effective. Though 2-(1-naphthyl)-3-methylpyridine attains a co-planar geometry with great difficulty, this naphthylpyridine gives the silylation product in quantitative yield. This indicates that in this step for the C–H/SiR_3 coupling, π-conjugation between the aromatic ring and the directing group is not so important. This result is contrast to the C–H/olefin coupling, in which π-conjugation between the aromatic ring and the directing groups seems to be important for attaining a catalytic reaction. This is an important feature of this silylation reaction. Even in the case of the reaction of *N,N*-dimethylbenzylamine, 2-benzylpyridine, and 2-pyridyl(phenyl)ether in which the directing group does not conjugate with π-electrons of the phenyl ring, silylation products are obtained in high yields in an ortho-selective manner (Eq. 9.40) [54]. These results suggest that predicting the relationship between the structures of substrates and reactivity remains a difficult task.



(9.40)

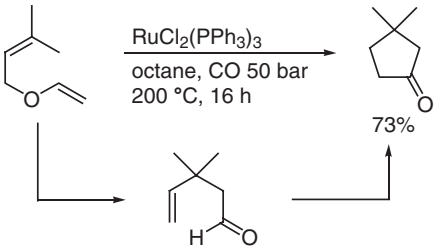
The combination of a substrate and a catalyst is important for a successful catalytic reaction. When the reaction of acetophenone with trimethylvinylsilane was conducted in the presence of $Ru_3(CO)_{12}$ as a catalyst, no reaction occurred. Interestingly, when the reaction of heteroaromatic compounds was carried out, such as 3-acetylthiophene and 2-*N,N*-diisopropylfuran amide, with vinylsilanes using $Ru_3(CO)_{12}$ as a catalyst, the regioselective silylation of a C–H bond took place efficiently [55] (Eq. 9.41). In this reaction, the vinyl moiety functions as a hydrogen acceptor. Thus, ethylene should be generated after the reaction. The generation of a Ru-SiR_3 species is the key to achieving a catalytic reaction. The hydroruthenation of vinylsilanes followed by *β*-silyl elimination [56] sequence was proposed for this reaction. The scope of this silylation is narrow, since only heteroaromatic compounds are applicable substrates.



(9.41)

9.3 Addition of C–H Bonds in Aldehydes to C–C Multiple Bonds and Related Reactions

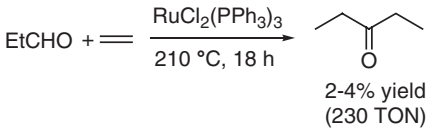
The addition of a C–H bond of a formyl group to a C–C multiple bond is highly useful method for synthesizing various types of ketones. The first example of a transition metal-catalyzed addition of a formyl group to olefins (i.e., the intramolecular hydroacylation of olefins) was reported by Miller, who used a rhodium catalyst [57]. After this study, the transition metal-catalyzed intramolecular cyclization of enals to the corresponding ketones was extensively studied, as this methodology provides a new route to the construction of a cyclopentanone framework from readily obtainable 4-pentanals [58]. The asymmetric version of this type of cyclization is of current interest in this field. For these reactions, rhodium complexes are often highly active. There is only one example of the ruthenium-catalyzed intramolecular hydroacylation of olefins. Eilbracht reported on the $RuCl_2(PPh_3)_3$-catalyzed intramolecular hydroacylation of 4-pentanals which was formed from allyl vinyl ether via Claisen rearrangement (Eq. 9.42) [59].



(9.42)

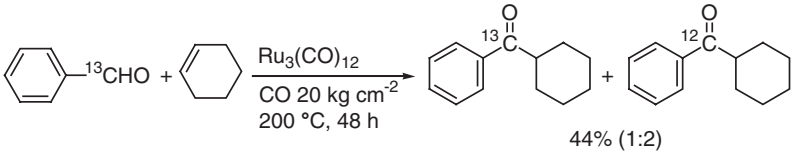
For the intermolecular hydroacylation of olefins and acetylenes, ruthenium complexes – as well as rhodium complexes – are effective [60–64]. In 1980, Miller reported the first example of an intermolecular hydroacylation of aldehydes with olefins to give ketones, during their studies of the mechanism of the rhodium-catalyzed intramolecular cyclization of 4-pentenal using ethylene-saturated chloroform as the solvent [60]. A similar example of the hydroacylation of aldehydes with olefins using ruthenium catalyst is shown in Eq. 9.43. When the reaction of propionaldehyde with ethylene was conducted in the presence of $RuCl_2(PPh_3)_3$ as the catalyst without

any solvent at 210 °C, the hydroacylation of ethylene leading to 3-pentanone in 2–4% yield occurred (turnover number (TON) = 230) [61].

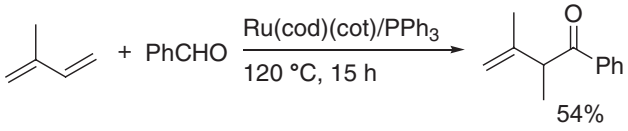


(9.43)

Watanabe reported that the addition of C–H bonds in aldehydes to olefins takes place efficiently with the aid of $Ru_3(CO)_{12}$ under a CO atmosphere at 200 °C (Eq. 9.44) [62]. In the case of the reaction with 1-hexene, a mixture of linear and branched ketones was obtained in 35% and 12% yields, respectively. The use of a CO atmosphere is the key to accomplishing this reaction in a catalytic manner. These authors revealed the role of CO by means of isotope-labeling experiments using ^{13}CO. The presence of CO is essential for suppressing the decarbonylation of aldehydes and for stabilizing the active catalyst species. Interestingly, the reaction using 1,3-dienes as an acceptor of the C–H bond proceeds in the absence of CO (Eq. 9.45) [63]. Aromatic and heteroaromatic aldehydes can also be used in this reaction.

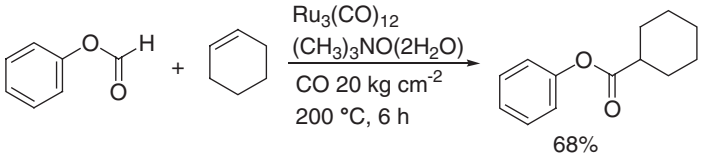


(9.44)



(9.45)

Formyl C–H bonds in formic acid esters and amides also add to C–C double bonds. Trimethylamine oxide, which is believed to offer a coordinatively unsaturated position, is indispensable to the success of the reaction [64]. For the reaction of alkylformates, a $Ru_3(CO)_{12}$-$(CH_3)_3NO(2H_2O)$ catalyst system showed a high activity (Eq. 9.46) [64a,b]. On the other hand, in the case of the hydroamidation of olefins, trimethyl amine oxide is not essential. The hydroamidation of cyclopentene takes place in the presence of $Ru_3(CO)_{12}$ (Eq. 9.47) [64c]. Internal olefins such as cyclohexene and cyclopentene exhibit a high reactivity compared with terminal olefins. These authors later reported that the [PPN][$HRu_3(CO)_{11}$]/PCy_3-catalyst (PPN = bis-(triphenylphosphoranylidene)ammonium; $[Ph_3P{=}N{=}PPh_3]^+$) system showed a high activity [64d]. The reaction of *N*-phenylformamide with norbornene in the presence of a [PPN][$Ru_3H(CO)_{11}$] catalyst gave the corresponding hydroamidation product in high yield (Eq. 9.48).



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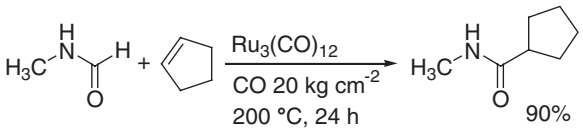
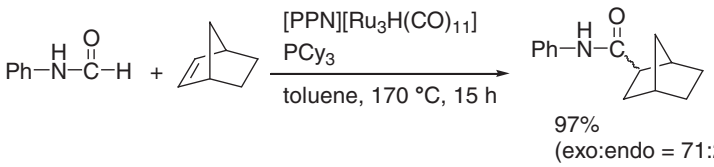
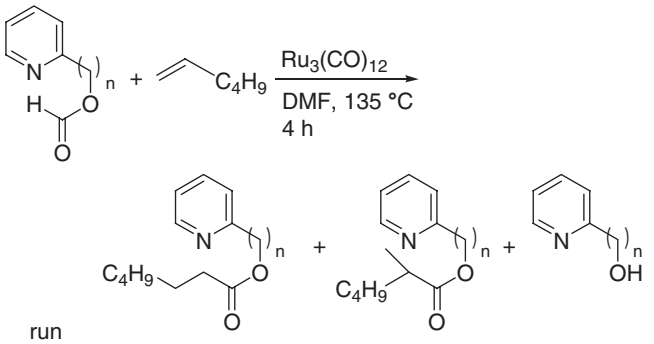


(9.47)



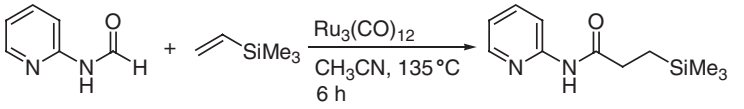
(9.48)

The chelation-assisted C–H/olefin coupling protocol can be used in the intermolecular addition of formyl C–H bonds to olefins. A new strategy for the hydroesterification and hydroamidation of olefins was reported by Chang [65]. The reaction of 2-pyridylmethyl formate with 1-hexene in the presence of a $Ru_3(CO)_{12}$-catalyst gave the hydroesterification product in 98% yield as a mixture of liner and branched isomers (Eq. 9.49). The chain length of the methylene tether is important for a successful reaction to occur. Thus, the reaction of 2-pyridyl formate (n = 0) afforded 2-hydroxypyridine, a decarbonylation product, and the reaction of 2-pyridylethyl formate (n = 2) resulted in a low conversion (7%) of the starting formate. From these results, the formation of a six-membered ruthenacycle intermediate appears to be crucial for this chelation-assisted hydroesterification. Interestingly, however, in the case of the reaction of formamide, *N*-(2-pyridyl)formamide showed a high reactivity (Eq. 9.50) [65a]. This indicates that the reaction proceeds through a five-membered ruthenacycle intermediate. Olefins having a bulky substituent such as *tert*-butyl and trimethylsilyl groups exhibited a high regioselectivity.



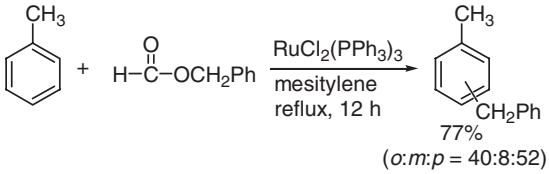
run			
1	n = 1	98% (liner:branch = 74:26)	<1%
2	n = 0		95%
3	n = 2		5%

(9.49)



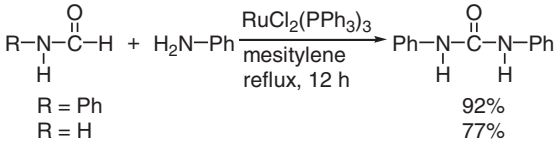
(9.50)

The reaction of alkyl formates with arenes gives alkylation products [66]. When the reaction of alkyl formates was conducted using $Ru_3(CO)_{12}$ as a catalyst, the decarboxylation of alkyl formate proceeded selectively and the subsequent alkylation of the arenes occurred with the evolution of molecular hydrogen (Eq. 9.51). This alkylation procedure is unique, even though the site-selectivity is low.



(9.51)

A transformation of formamides to ureas was reported by Watanabe [67]. In place of CO, formamide derivatives are used as the carbonyl source. The reaction of formanilide with aniline was conducted in the presence of a catalytic amount of $RuCl_2(PPh_3)_3$ in refluxing mesitylene, leading to *N*,*N*′-diphenylurea in 92% yield (Eq. 9.52) [68]. These authors proposed that the catalysis starts with the oxidative addition of the formyl C–H bond to the active ruthenium center, although they did not provide any experimental evidence for this. In the case of the reaction of formamide ($HCONH_2$) with amines, two molecules of the amine react with the amide to afford symmetrically substituted ureas in good yields. In this reaction, one molecule of NH_3 and one molecule of H_2 is evolved.

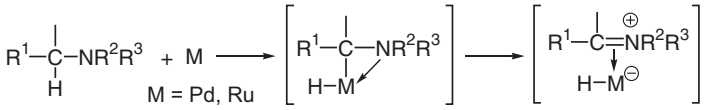


(9.52)

9.4 Activation of sp^3 C–H Bonds

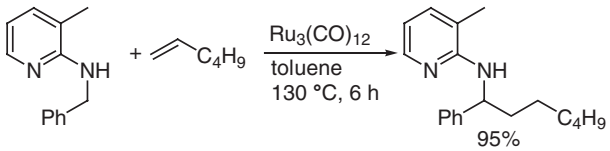
9.4.1 Reaction of C–H Bonds Adjacent to Heteroatoms

The direct functionalization of sp^3 C–H bonds in alkanes is an extremely difficult process [69], and only a limited number of studies have been reported. A much more practical – but still challenging – process is the functionalization of sp^3 C–H bonds adjacent to a heteroatom [70–73]. Murahashi reported the impressing example of an alkyl group exchange reaction and hydrolysis reaction of tertiary amines

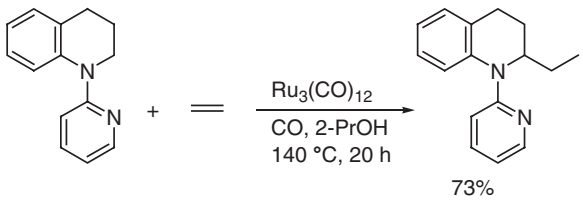


Scheme 9.11

using a palladium catalyst [70]. In this case, a coordination of nitrogen atom to a palladium facilitates a cleavage of a C–H bond (Scheme 9.11). The similar protocol of the C–H bond activation was used in the transition metal-catalyzed annulation of anilines with tertiary amines, giving substituted quinolines (M = Ru, Scheme 9.11) [71]. Recently, Jun succeeded in the $Ru_3(CO)_{12}$-catalyzed alkylation of an sp^3 C–H bond α to the nitrogen atom in benzyl(3-methyl-2-pyridinyl)amine by means of chelation-assistance (Eq. 9.53) [72]. In this case, the coordination of the pyridine nitrogen to the ruthenium complex followed by C–H bond cleavage, which allows the formation of a five-membered ruthenacycle, was proposed to be a feature of this catalytic reaction. Murai also reported on the ruthenium-catalyzed coupling of 1-(2-pyridinyl)1,2,3,4-tetrahydroquinoline (Eq. 9.54) [73]. The use of 2-propanol as a solvent was found dramatically to improve the yield of the product.



(9.53)

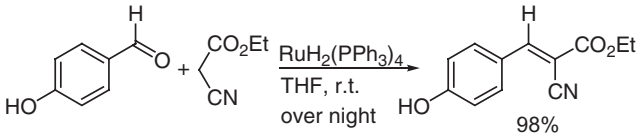


(9.54)

9.4.2
Reaction of Active Methylene Compounds

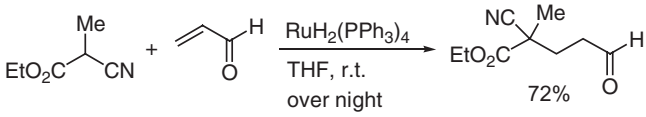
The C–H bond cleavage of active methylene compounds with a transition metal catalyst is another method for the functionalization of these C–H bonds. To date, several reactions have been developed. In particular, the asymmetric version of this type of catalytic reaction provides a new route to the enantioselective construction of quaternary carbon centers. One of the most attractive research subjects is the catalytic addition of active methylene C–H bonds to acetylenes, allenes, conjugate ene-ynes, and nitrile C–N triple bonds. The ruthenium-catalyzed reaction active methylene compounds with carbonyl compounds involving aldehyde, ketones, and α,β-unsaturated ketones and esters is described in this section.

Murahashi reported the first example of transition metal-catalyzed addition of activated nitriles to aldehydes and ketones, giving α,β-unsaturated nitriles (Eq. 9.55) [74]. In the case of the reaction of the nitriles with aldehydes and ketones, condensation products corresponding to a Knoevenagel reaction are obtained in high yields. This reaction does not require a base, and proceeds under neutral reaction conditions. Later, the analogous Knoevenagel reaction of aldehydes with cyanoacetate using $RuH_2(PPh_3)_4$ was reported by Lin in 1993 [75].

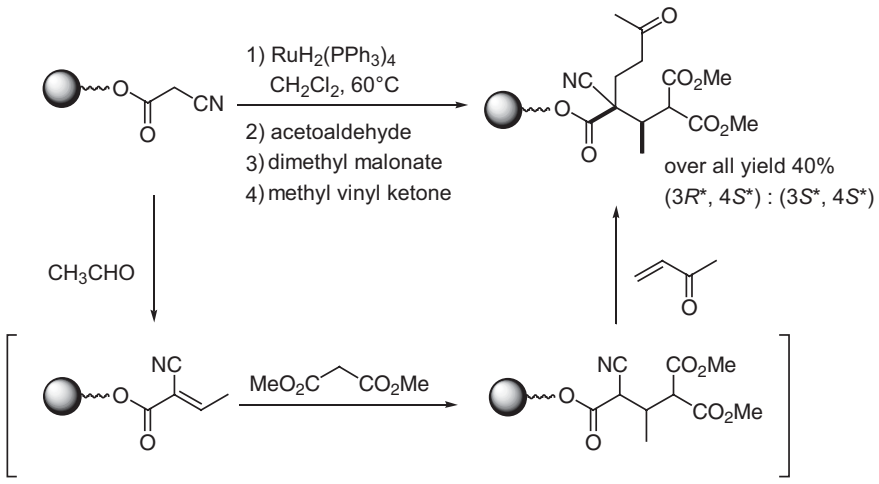


(9.55)

The $RuH_2(PPh_3)_4$-catalyzed addition of active methylene compounds can also be applied to conjugate additions to α,β-unsaturated carbonyl compounds (Michael additions). In 1989, Murahashi reported the first example of the transition metal-catalyzed Michael addition of active methylene compounds [74]. One of the notable advances of this catalytic reaction is that the addition of C–H bonds to α,β-unsaturated carbonyl compounds give Michael adducts without contamination by the corresponding aldol products (Eq. 9.56) [74]. Recently, Murahashi applied their aldol and Michael addition reactions to a solid-phase synthesis using polymer-supported nitriles (Scheme 9.12) [76]. In this case, four component reactions took place with high diastereoselectivity.

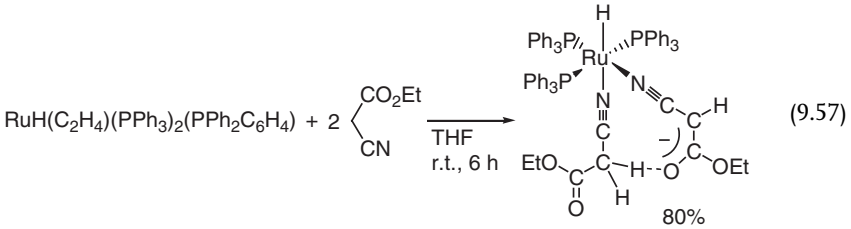


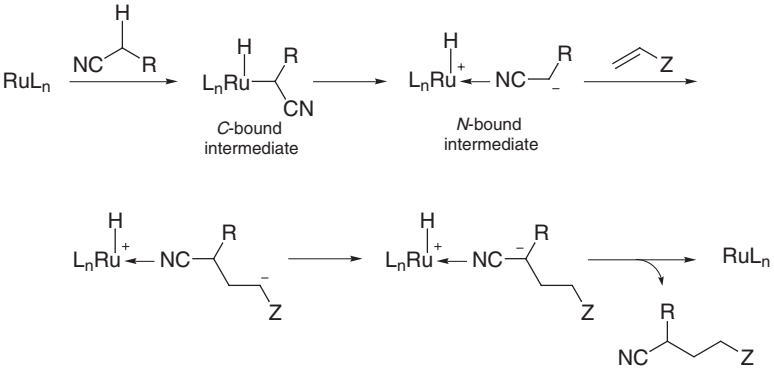
(9.56)



Scheme 9.12

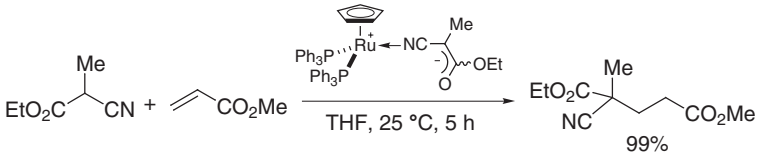
The pathway involved in the activation of active methylene compounds is a subject of considerable interest. Details of the mechanism of ruthenium-catalyzed aldol and Michael reactions of active methylene compounds containing a nitrile group have been studied by means of kinetic studies, X-ray analyses, and NMR studies [1b, 77]. Stoichiometric reactions provide important information concerning the structure of the plausible intermediate. For example, the reaction of $RuH(C_2H_4)(PPh_3)_2(P(o\text{-}C_6H_4)Ph_2)$ with ethyl cyanoacetates gave *mer*-$RuH(NCCHCO_2Et)(NCCH_2CO_2Et)(PPh_3)_3$, which has been characterized by spectroscopic and analytical methods, with the liberation of a quantitative amount of ethylene (Eq. 9.57) [77, 78]. As evidenced by NMR and IR spectral data and X-ray analysis, it was found that the intermediate contained a hydride ligand on the ruthenium atom, and both cyanoacetate molecules are bonded to the ruthenium center with a nitrogen atom of the cyano group. One cyanoacetate ligand is coordinated in the enolate form, and this enolate ligand interacted with a C–H bond of the methylene moiety of the other cyanoacetate. Kinetic studies of the reaction of ethyl cyanoacetate with benzaldehyde involved the use of the hydrido(enolate)ruthenium (II) catalyst. The results suggest that the rate is first order with respect to benzaldehyde and the ruthenium catalyst, and zero order with respect to ethyl acetate. The Michael reaction of nitriles with olefins having electron-withdrawing groups can be rationalized by the pathway shown in Scheme 9.13. The enolate ligand attacks the β carbon of the olefin, having an electron-withdrawing group. The carboanion generated then reacts with the Ru-H moiety to give the corresponding Michael adduct, regenerating the Ru(0) species.





Scheme 9.13 Proposed mechanism for Michael reaction of nitriles with olefins having electron-withdrawing groups.

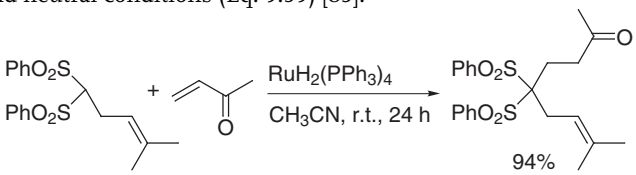
For aldol and Michael reaction of nitriles, cyclopentadienyl ruthenium enolate complexes shows catalytic activity. The reaction of 2-methylphenylacetonitrile with ethyl acrylate gave the corresponding Michael addition product in 99% yield (Eq. 9.58) [79]



(9.58)

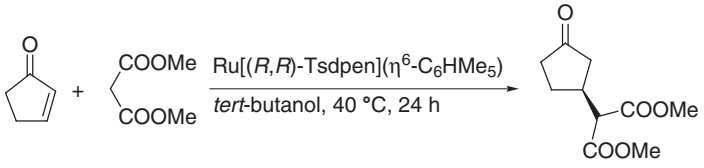
Murahashi and Naota studied the reaction mechanism of cyclopentadienyl ruthenium enolate complex-catalyzed aldol and Michael addition reactions [80–82]. This mechanistic study revealed that the cone angle of the tertiary phosphine ligands largely affects the stability of C- and N-bound complexes [80, 82]. Thus, ligation of bulky phosphine ligand would favor the N-bound complexes [80]

In place of active methylene compounds having a nitrile group, malonates, β-ketoesters, 1,3-diketones, 1,1-disulfones, nitro compounds, Meldrum acid, and anthrone can also be used as the Michael donors for these ruthenium-catalyzed aldol and Michael reactions. The reaction proceeds well in acetonitrile under mild and neutral conditions (Eq. 9.59) [83].



(9.59)

Very recently, Ikariya reported chiral amido ruthenium complex-catalyzed asymmetric Michael addition of dimethyl malonate with conjugate enones using Ru[(*R*,*R*)-TsDPEN](η^6-arene) ((*R*,*R*)-TsDPEN = (1*R*,2*R*)-*N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine) [84]. The reaction of cyclopentenone with dimethyl malonate gave the corresponding β-alkylation product in 99% yield with 97% *e.e.* (Eq. 9.60). For this ruthenium-catalyzed asymmetric Michael addition, the Brønsted basicity of the amido ligand is responsible for the excellent catalytic activity.



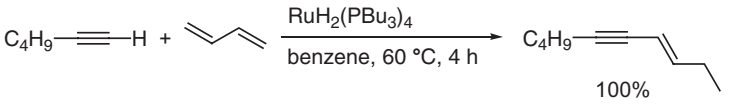
(9.60)

99% yield; 97% *e.e.*

9.5
Addition of sp C–H Bonds in Acetylenes to C–C Multiple Bonds

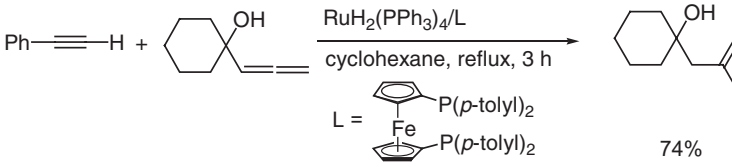
The addition of C–H bonds in terminal acetylenes to C–C double bonds in conjugate dienes and α,β-unsaturated carbonyl compounds can take place with the aid of a

ruthenium catalyst. The first selective linear codimerization of terminal acetylenes and 1,3-dienes using $RuH_2(PBu_3)_4$-catalyst was reported by Mitsudo and Watanabe [85]. The reaction of 1-hexyne with 1,3-butadiene in the presence of $RuH_2(PBu_3)_4$ as a catalyst gave the *E*-isomer of the linear conjugate enynes. This result suggests that this reaction proceeded with high stereoselectivity.

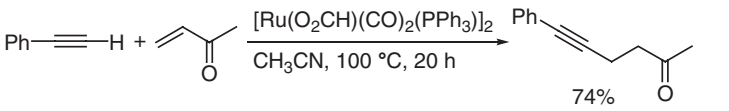


(9.61)

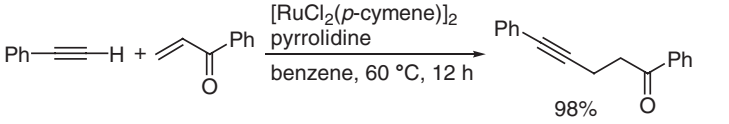
An example of addition of C–H bonds in terminal acetylene to allenes is shown in Eq. 9.62. The reaction of phenylacetylene with β-hydroxy allene using $RuH_2(PPh_3)_4$ as a catalyst gave conjugate enynes [65]. Dixneuf reported on a unique example of ruthenium-catalyzed Michael reaction using terminal acetylenes. The reaction of terminal alkynes with α,β-enones in the presence of $[Ru(O_2CH)(CO)_2PPh_3]_2$ or $[Ru(O_2CH)(CO)_2PMe_3]_2$ complex as a catalyst afforded γ,δ-ynones [87]. The reaction of phenylacetylene with but-3-en-2-one afforded the corresponding ynone in 74% yield (Eq. 9.63). When alkylacetylene is used for this coupling reaction, the use of $[Ru(O_2CH)(CO)_2PMe_3]_2$ as a catalyst is essential to attain an improved yield. The reaction with cyclohexenone was unsuccessful, which suggests that it is sensitive to steric hindrance at the β carbon. A similar conjugate addition of terminal acetylenes to α,β-enones was reported by Chang [88]. The reaction of 1-decyne with phenyl vinyl ketone in the presence of $[RuCl_2(p\text{-cymene})]_2$ and pyrrolidine as catalysts gave the γ,δ-ynones in 98% yield (Eq. 9.64), and was also seen to be sensitive to the steric factor. Amines are essential for the generation of catalytic active ruthenium-acetylide species. A variety of alkynes (e.g., trimehylsilylacetylene, 5-hexyn-1-ol, 5-chloropent-1-yne, and hex-5-ynenitrile) can be used for this addition reaction.



(9.62)



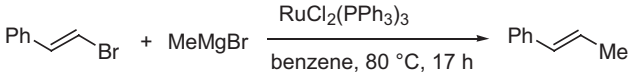
(9.63)



(9.64)

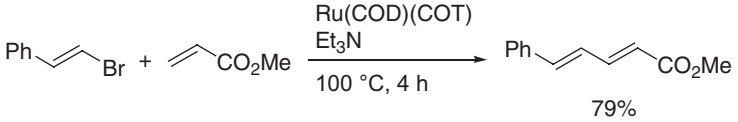
9.6
Catalytic Reactions Involving Carbon-Halogen Bond Cleavage

Catalytic reactions of organohalides using palladium, nickel, or rhodium catalysts are well investigated. Interestingly, however, in the case of ruthenium-catalyzed reactions, only a few examples involving carbon-halogen cleavage have been reported. The pioneering studies with respect to ruthenium-catalyzed reactions involving carbon-halogen bond cleavage were reported by Murahasahi in 1979 [89]. The reaction of *E*-β-bromostyrene with methyl Grignard reagent using $RuCl_2(PPh_3)_3$ as a catalyst gave *E*-1-phenyl-1-propene in high yield (Eq. 9.65). Organolithium reagents are also applicable to this coupling reaction.



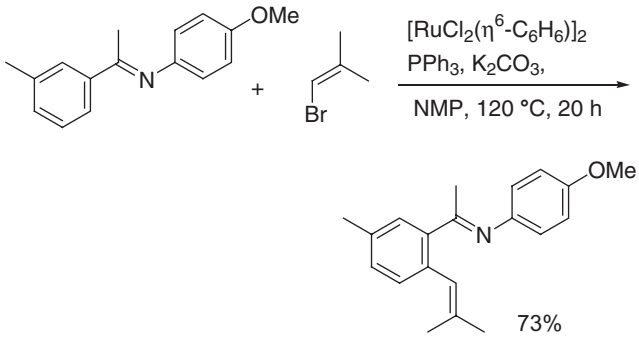
(9.65)

An example of this is a Heck-type reaction of β-bromostyrene with conjugated unsaturated ester using Ru(COD)(COT) as a catalyst (Eq. 9.66) [90].



(9.66)

An example of coupling of vinylhalides with aromatic imines is shown in Eq. 9.67. The reaction of an aromatic imine with 2-methyl-1-bromo-1-propene using $[RuCl_2(\eta^6\text{-}C_6H_6)]_2$ as a catalyst gave the corresponding ortho alkenylation product in high yield [49]. In this case, electrophilic Ru(IV)-species generated by the reaction of the halide with $[RuCl_2(\eta^6\text{-}C_6H_6)]_2$ reacted with the aryl imine to give the *ortho*-alkenylation product. Oi also reported the ruthenium-catalyzed arylation of aromatic imines and arylpyridines with arylbromide (see Eqs. 9.34 and 9.35) [48, 49].



(9.67)

9.7 Conclusions

The catalytic use of C–H bonds is clearly one of the simplest, most powerful methods in organic synthesis. Since the early 1960s, C–H bond cleavage – or so-called C–H bond activation – has been an intriguing research subject for both inorganic and organometallic chemists, but recently this situation has changed dramatically. A variety of catalytic reactions involving C–H bond cleavage have become popular, and various types of transformations such as C–H/olefin, C–H/acetylene, C–H/CO/olefin, C–H/aryl, and C–H/SiR_3 couplings, hydroacylation, aldol and Michael reactions using active methylene compounds have been presented in the literature. This research area has continued to expand rapidly, and ruthenium-catalyzed reactions in particular are highly attractive as they exhibit high selectivity and efficiency, and wide applicability – all of which are essential in practical organic synthetic procedures.

During the past decade, several fundamental transformations of C–H bonds to other synthetically valuable bonds have been developed, and some basic applications of the catalytic functionalization of C–H bond to synthesis of polymers and the catalytic functionalization of natural products have been studied. During the next decade however, it is likely that fascinating developments will continue to be made in the direct use of C–H bonds in organic synthesis.

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10
Ruthenium Lewis Acid-Catalyzed Reactions

Rodolphe F. R. Jazzar and E. Peter Kündig

10.1
Introduction

Lewis acids play key roles in a large number of reactions, and their use in organic synthesis continues to see rapid development, particularly in the field of asymmetric catalysis [1]. Late transition metal Lewis acid catalysts have emerged as a new class of compounds within this area. They offer neutral and mild conditions that are of interest for the needs of modern chemistry and its focus on economically and ecologically friendly methods.

In comparison with classic Lewis acids derived from main group halides (e.g., B, Al, Sn), f-elements, and early transition metal halides, late transition metal Lewis acids often are more inert to ubiquitous impurities such as water, offer higher stability, tunable properties by ligand modification, and a well-defined structure and coordination chemistry, thus allowing detailed studies of reaction mechanisms, and a rational basis for catalyst optimization. Among this new class of late transition metal Lewis acids, ruthenium complexes – the subject of this chapter – display remarkable properties

This review of Ru-based Lewis acids centers on in-situ procedures in which the metal activates a substrate by forming a σ-bond to a Lewis basic atom of the reacting substrate. Particular attention will be paid to stereoselective and catalytic reactions. We exclude from this survey the vast area of chemistry of transition metal complexes of π-bound unsaturated ligands, as details of these are described in other chapters of this book.

10.2
Ethers, Acetals, Carboxylic Acid Derivatives, and Epoxides

10.2.1
Cleavage and Formation of Ethers

Ito et al. reported the $RuCl_3$ **(1)** -catalyzed formation of allyl ethers from allylic alcohols and methanol (Scheme 10.1) [2]. The reaction, which is likely to pass via a

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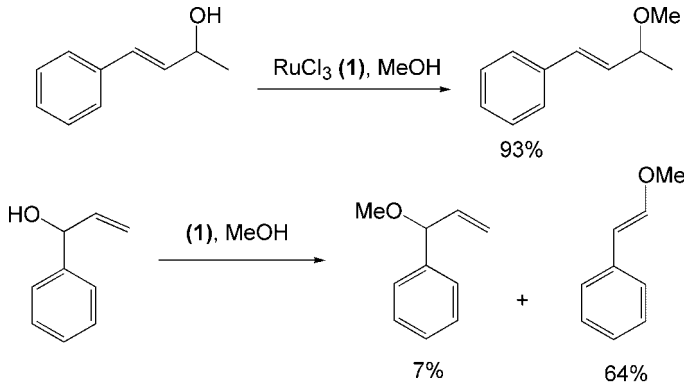
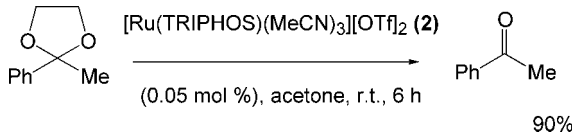


Scheme 10.1

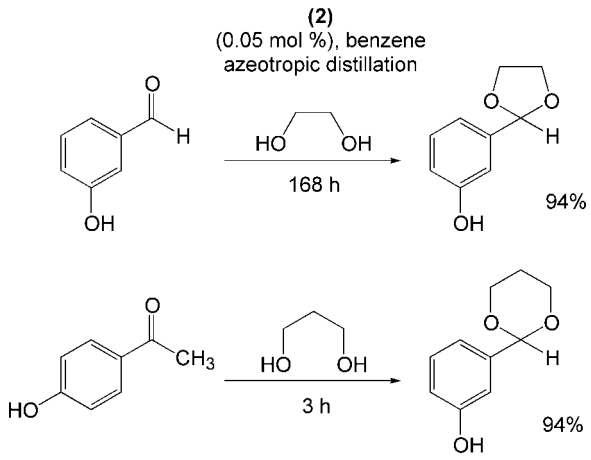
π-allyl Ru intermediate, tends to undergo allylic rearrangements to yield the thermodynamically more stable product. Racemization of optically active allylic alcohols was also observed.

10.2.2 Reactions Involving Acetals

The cleavage of acetals usually involves acidic conditions, incompatible with acid-sensitive substrates. $[Ru(TRIPHOS)(MeCN)_3][OTf]_2$ **(2)** in acetone offers a solution



Scheme 10.2



Scheme 10.3

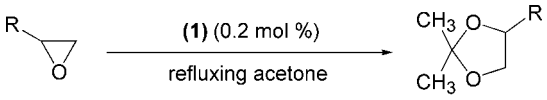
as it efficiently catalyzes the deprotection of 1,3-dioxolanes of ketones (Scheme 10.2) [3]. Moreover, competitive experiments show that while THP derivatives of phenols are cleaved, THP derivatives of benzyl alcohol resist under these conditions.

Conversely, the same catalyst **(2)** can be used for the protection of hydroxy benzaldehydes, substrates that usually need protection of the phenol function prior to acetal formation. Azeotropic distillation in benzene give good yields of the acetal product with both 1,2-ethanediol and 1,3-propanediol (Scheme 10.3) [4].

10.2.3
Catalytic Ring-Opening and Ring Transformations of Epoxides

10.2.3.1 Achiral Catalysts

In the presence of acetone, anhydrous $RuCl_3$ (**1**) catalyzes the transformation of epoxides to the correspondding 1,3-dioxolane derivatives in high yields (Scheme 10.4) [5]. Both, epoxides bearing electron-donating and -withdrawing groups are tolerated. The same authors report the same catalyst also to convert epoxides into thiiranes in the presence of ammonium thiocyanate. The reaction takes place with inversion of configuration, though some erosion of enantiomeric purity is observed: (*R*)-(+)-styrene oxide gave (*S*)-(–)-styrene sulfide of 78% optical purity (Scheme 10.5) [6].



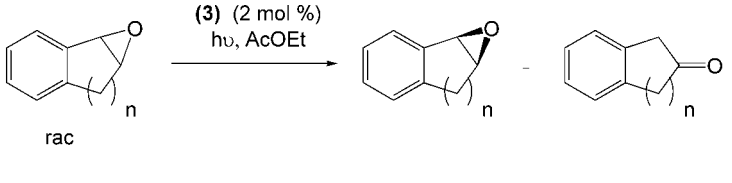
Entry	R	Time [h]	Yield [%]
1	Ph	5	90
2	CH_2O	2	87
3	CH_2Cl	2	91
4	CH_2OH	2	89

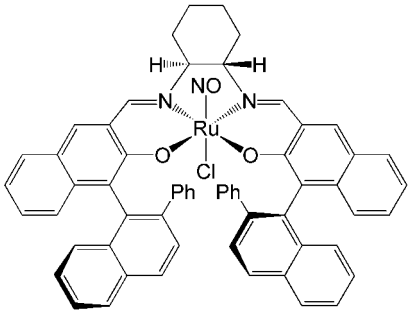
Scheme 10.4

Scheme 10.5

10.2.3.2 **Chiral Catalysts**

Kinetic resolution has been reported for dihydronaphthalene oxide and indene oxide upon irradiation in the presence of catalytic amounts of a Ru(salen)(NO) **(3)** complex (Scheme 10.6) [7].





(3)

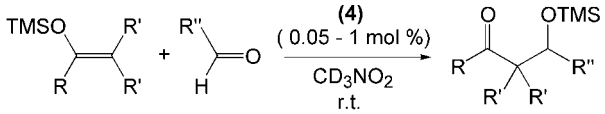
Entry	n	Yield [%]	*e.e.* [%]
1	1	52	89
2	2	54	98

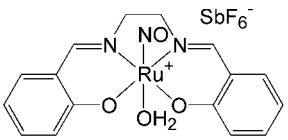
Scheme 10.6

10.3 Ru-Promoted Additions to C=O and C≡N Bonds

10.3.1 Mukaiyama and Sakurai Reactions

Lewis acids induce the reaction of silyl enol ethers with aldehydes and ketones via an aldol cross-coupling reaction commonly referred to as the Mukaiyama aldol reaction. This process, which involves carbon-carbon bond formation and the transfer of a silyl group from one oxygen atom to the other, is an exceptionally mild method of carbon-carbon bond formation. Additionally, this reaction is a powerful method for the preparation of β-hydroxy carbonyl compounds that have extensive application in organic synthesis [8]. In an analogous but yet less versatile reaction reported by Sakurai [9], Lewis acids promote the reaction of allyl silanes with aldehydes, ketones, and acetals. Amongst the variety of Lewis acids traditionally used in these reactions (e.g., Me_3SiOTf, $Me_3SiCl/SnC1_2$, Ph_3COTf), transition metal Lewis acids have emerged as a potentially powerful class of catalyst precursor for this reaction. Hollis et al. have established the use of $[Ru(salen)(NO)(H_2O)][SbF_6]$ **(4)** in both the Mukaiyama and the Sakurai reactions using low catalyst loadings (<1 mol%) (Scheme 10.7) [8, 10]. This catalyst has shown to obviate some the disadvantages encountered with conventional Lewis acids, which include ligand exchange and sensitivity to water.





(4)

R	R'	R''	Time [min]	Yield [%]
Ph	H	Ph	< 6	90 (NMR)
MeO	Me	Ph	< 3	90 (NMR)

Scheme 10.7

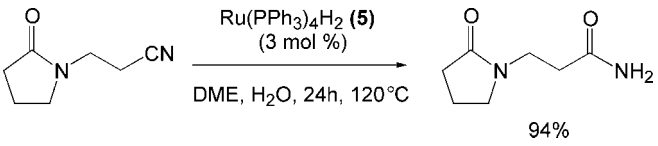
10.3.2 Lewis Acid Activation of Nitriles

Murahashi and coworkers have pioneered and extensively developed catalytic reactions of nitriles with low-valent Ru [11]. The transformation of a nitrile into an amide usually requires strong acids or bases, but in the presence of $Ru(PPh_3)_4H_2$ **(5)** as catalyst, the nucleophilic addition of water to nitriles to yield amides under neutral conditions. For a typical example, see Scheme 10.8 [12].

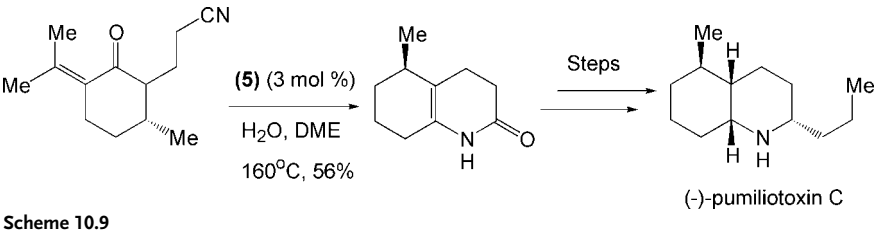
This Ru(II)-catalyzed hydration of nitriles is a highly useful transformation as demonstrated inter alia in the synthesis of (–)-pumiliotoxin C in a reaction sequence involving retro-aldol reaction, hydration, and cyclization (Scheme 10.9) [13].

When coupled with a reductive step, nitriles can be converted directly into alcohols using $Ru(P(i\text{-}Pr)_3)_2(CO)(H_2)H_2$ **(6)** (Scheme 10.10) [14].

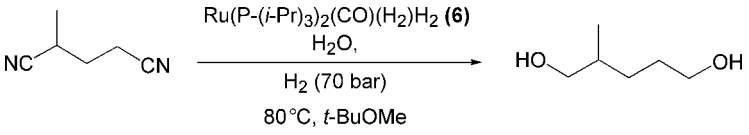
Analogous reactions with amines or alcohols afford amides (Scheme 10.11) [15], and esters in high yield (Scheme 10.12) [16].



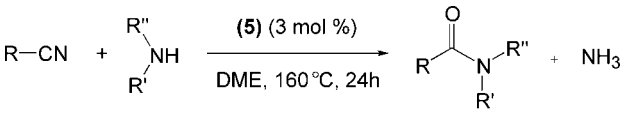
Scheme 10.8



Scheme 10.9

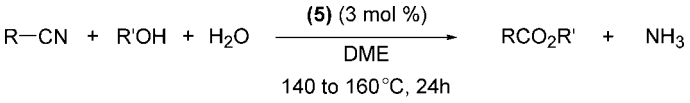


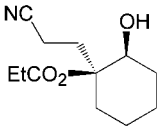
Scheme 10.10



R	R'	R''	Yield [%]
Me	*n*-Bu	H	93
Me	$(CH_2)_5$		97
Me	Bn	Me	95
$MeOCH_2$	*n*-Bu	H	93

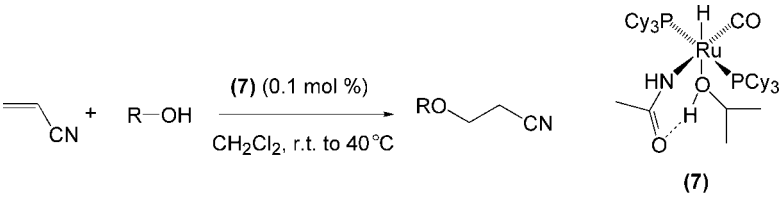
Scheme 10.11



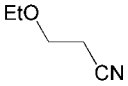
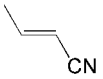
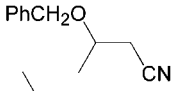
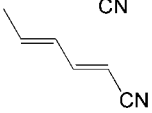
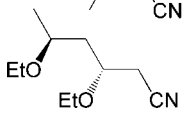
R	R'	yield [%]
Me	$Ph(CH_2)_2$	73
$C_{11}H_{23}$	Me	86
$PhCH_2$	*i*-$PrCH_2$	57
		73

Scheme 10.12

Mechanistically, two scenarios have been advanced. The first involves coordination of the nitrile to the Ru center which is followed by nucleophilic attack at the nitrile, while the second entails a sequence of events starting with oxidative addition of water, an alcohol or an amine to the metal center, followed by insertion of the nitrile into the Ru-OH bond. A recent report describes the conjugate addition of alcohols to acrylonitrile compounds catalyzed by a ruthenium-acetamido complex $[Ru(PCy_3)_2(CO)(CH_3CONH)$-(*i*-PrOH)H] **(7)** (Scheme 10.13) [17]. The mechanistic investigation of this reaction supports the proposal that the N-coordination of acrylo-



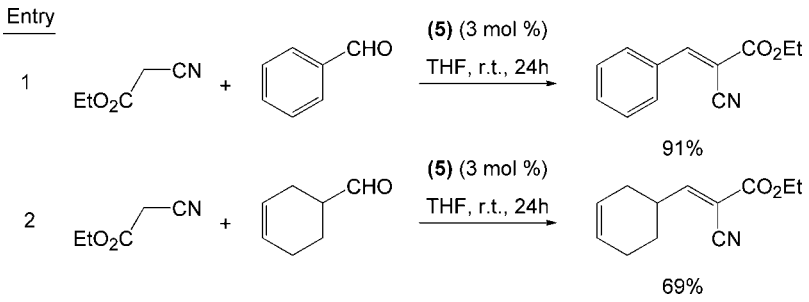
(7)

Entry	Substrate	Alcohol	Cat. [mol%]	Product	Time [h]	Yield [%]
1		EtOH	0.1		6	96
2		$PhCH_2OH$	1.0		20	93
3		EtOH	5.0		24	63
				d.r. = 2 : 1		

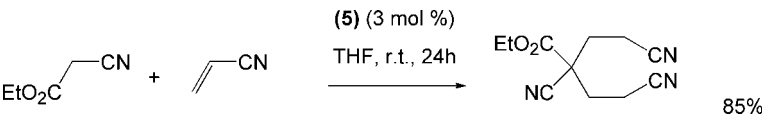
Scheme 10.13

nitrile promoted the nucleophilic addition of the alcohol substrate, and that the amido ligand serves as a base for the generation of the nucleophile.

Ru(II) complexes catalyze Michael reactions and Knoevenagel condensations of 2-nitrilo esters. The best catalysts are $Ru(Cp)(PPh_3)_2H$ and $Ru(Cp^*)(PPh_3)_2H$, but the reactions were first discovered when **5** was used [18, 19]. A selection of examples is shown in Schemes 10.14 and 10.15.



Scheme 10.14



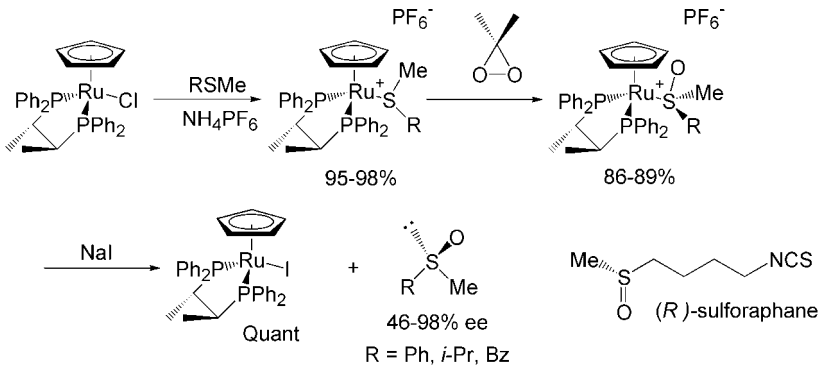
Scheme 10.15

A powerful feature of these reactions is that nitriles are selectively activated in the presence of other substrates that contain active C-H bonds. This is nicely demonstrated in that the reaction shown in entry 1 of Scheme 10.14 gives the same product when carried out in the presence of 2,4-pentanedione, even though both starting materials have the same pH. The same reaction, when carried out initiated by base, rather than Ru(II), gives mixtures of products. Mechanistically it is proposed that ruthenium coordinates the nitrile and that this activation ultimately results in a ruthenium hydride with a nitrile-complexed enolate. The latter then reacts by 1,2- or 1,4-addition to the electrophile. Established first with Ru, reactions involving nitrile activation were subsequently extended to enantioselective variants using chiral Rh complexes [20] and to the synthesis of glutarimides in a novel three-component reactions of nitriles, olefins, and water using Ir complexes [21].

10.4
Activation of Organo-Sulfur Derivatives

10.4.1
Stereoselective Sulfoxidation

Major interest has been expressed in the synthesis of chiral sulfoxides since the early 1980s, when it was discovered that chiral sulfoxides are efficient chiral auxiliaries that are able to bring about important asymmetric transformations [22]. Sulfoxides are also constituents of important drugs (e.g., omeprazole (Losec®, Prisolec®)) [23]. There is a plethora of routes of access to enantioenriched sulfoxides, and many involve metal-catalyzed asymmetric oxidations [24]. Examples of ruthenium metal-based syntheses of sulfoxides are scarce, presumably due to the tendency of sulfur atoms to bind irreversibly to a ruthenium center. Schenk et al. reported a diastereoselective oxidation of Lewis acidic Ru-coordinated thioethers with dimethyldioxirane (DMD) (Scheme 10.16) [25]. Coordination of the prochiral thioether to the metal is followed by diastereoselective oxygen transfer from DMD in high yield. The

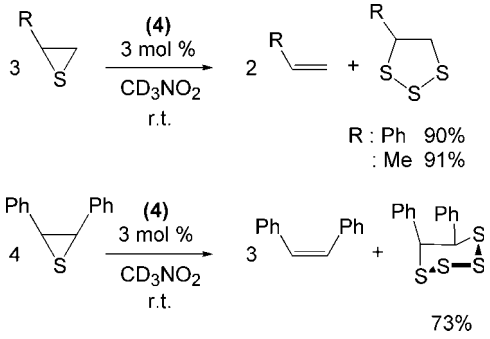


Scheme 10.16

generated sulfoxide is then freed from the metal center by treatment with a halide (e.g., NaI), and this makes it a stoichiometric procedure. Several aryl methyl sulfoxides derivatives have been obtained by this method in reasonable to high *e.e.* [26], and this method was applied to the synthesis of sulforaphane isolated in 43–48% yield and 80% *e.e.* [27].

10.4.2
Disproportionation of Thiiranes

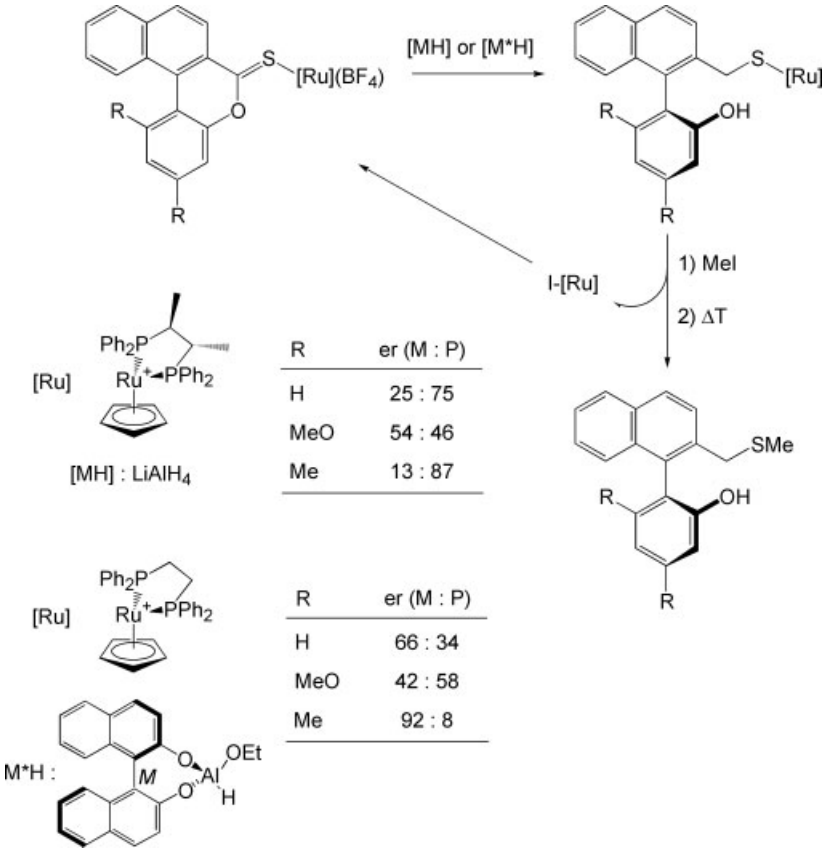
Scheme 10.17 shows an unusual disproportionation of thiiranes. These strained sulfides react, in the presence of catalytic amounts of **4**, to afford 1,2,3-trithiolanes and 1,2,3,4-tetrathianes and alkenes [28]. Monosubstituted thiiranes such as styrene sulfide and propene sulfide react to form the corresponding olefin and the 4-substituted 1,2,3-trithiolane in a 2:1 ratio in isolated yields in excess of 90% (Scheme 10.17). The reaction is thought to arise through initial thiirane coordination to the ruthenium center and subsequent nucleophilic attack of free thiirane on the carbon of coordinated thiirane.



Scheme 10.17

10.4.3
Transformation of Thionolactones Derivatives

Bringman et al. have investigated biaryl lactones and biaryl thionolactones as precursors to enantiomerically enriched axially chiral biaryls. Both, the lactones and the thionolactones are configurationally labile. In this method, biaryl products are obtained by coordination of a Lewis acid followed by reductive lactone ring cleavage. Asymmetric induction requires either the Lewis acid or the reducing agent to be chiral. Both approaches have been realized for biaryl thionolactones with mild Ru Lewis acids (Scheme 10.18) [29].



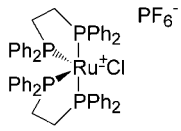
R	er (M : P)
H	25 : 75
MeO	54 : 46
Me	13 : 87

R	er (M : P)
H	66 : 34
MeO	42 : 58
Me	92 : 8

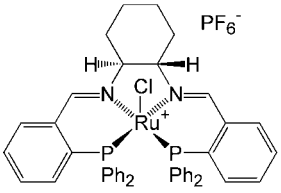
Scheme 10.18

10.5 Halide Substitution for Fluoride

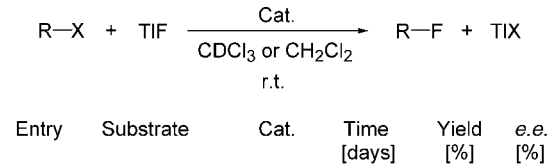
The importance of fluorinated organic compounds both in medicinal chemistry and biochemistry has resulted in much recent attention towards efficient carbon fluorine bond formation [30]. The reactions developed include a very successful electrophilic asymmetric mono-fluorination of 1,3-dicarbonyl compounds [31]. A nucleophilic variant was also investigated. In this context, the groups of Togni and Mezzetti have established that ruthenium Lewis acids could efficiently catalyze fluorination reactions [32]. In the presence of [Ru(1,2-bis(diphenylphosphino)ethane)$_2$Cl][PF_6] **(8)** (10 mol%), *tert*-butyl iodide reacted at room temperature with TlF (1.1 equiv.) to yield *tert*-butyl fluoride (84% yield). This reaction was extended successfully to a range of organic halides (Entries 1–3, Scheme 10.19). The use of the chiral complex [Ru((1*S*,2*S*)-*N*,*N*′bis[2-diphenylphosphino)benzylidene]diaminocyclohexane))Cl][PF_6] **(9)** showed modest chiral induction at the outset of the reaction (Entry 4, Scheme 10.17). The near-racemic mixture obtained at completion points to an S_N1-type process in this nucleophilic halide

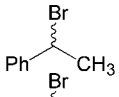
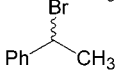


(8)



(9)



Entry	Substrate	Cat.	Time [days]	Yield [%]	*e.e.* [%]
1	$(CH_3)_3C—Br$	**(8)**	5	63	-
2	$(CH_3)_3C—I$	**(8)**	0.2	84	-
3		**(8)**	1	83	-
4		**(9)**	0.04 1	1 62	16 3

Scheme 10.19

exchange risks as being a serious obstacle in the goal of the development of catalytic asymmetric nucleophilic fluorination.

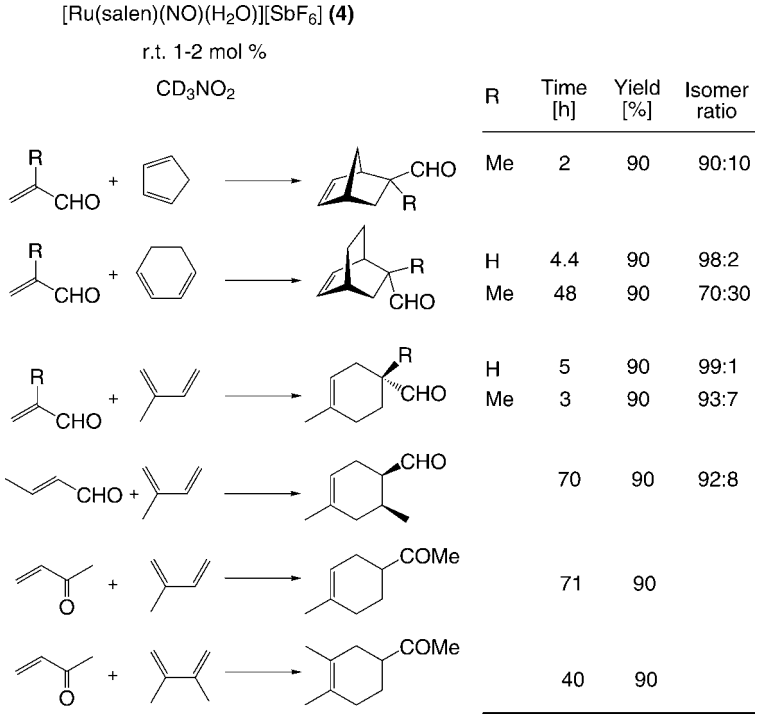
10.6 Cycloaddition Reactions

10.6.1 Diels–Alder Reactions

Diels–Alder reactions belong to the small and select group of classic organic reactions that add in a single step much complexity (two new C–C bonds, up to four new stereogenic centers) to a molecule. It is the most flexible and powerful method for the synthesis of six-membered ring compounds. Enantioselective catalysis as a means to control the stereogenic centers, as well as to increase the efficiency and diastereoselctivity of the reaction, is a very appealing concept. Lewis acid catalysis has demonstrated its ability to strongly contribute to reaching this target [1, 33].

The readily prepared and air-stable complex *trans* **4**, catalyzes Diels–Alder reactions between 1,3-dienes and α,β-unsaturated methyl ketones or enals. Nitromethane is the best solvent, and rate accelerations are up to a factor of 10^5 compared to the uncatalyzed reaction and up to 10^2 compared to catalysis by trifluoroacetic acid (Scheme 10.20) [34].

The strong donor ligands make the metal center in cationic $Ru(Cp)(PR_3)^+$ complexes electron-rich, despite the positive charge. This fragment prefers binding to alkenes rather than to an enal carbonyl. Thus, this complex does not promote the classical Diels–Alder reaction, and replacing one phosphine by a CO ligand does not alter this state of affairs [33, 35]. However, a few years later it was shown that $Fe(Cp)(R,R\text{-CYCLOP-F})^+$ and $Fe(Cp)(BIPHOP\text{-F})^+$, incorporating electron-poor

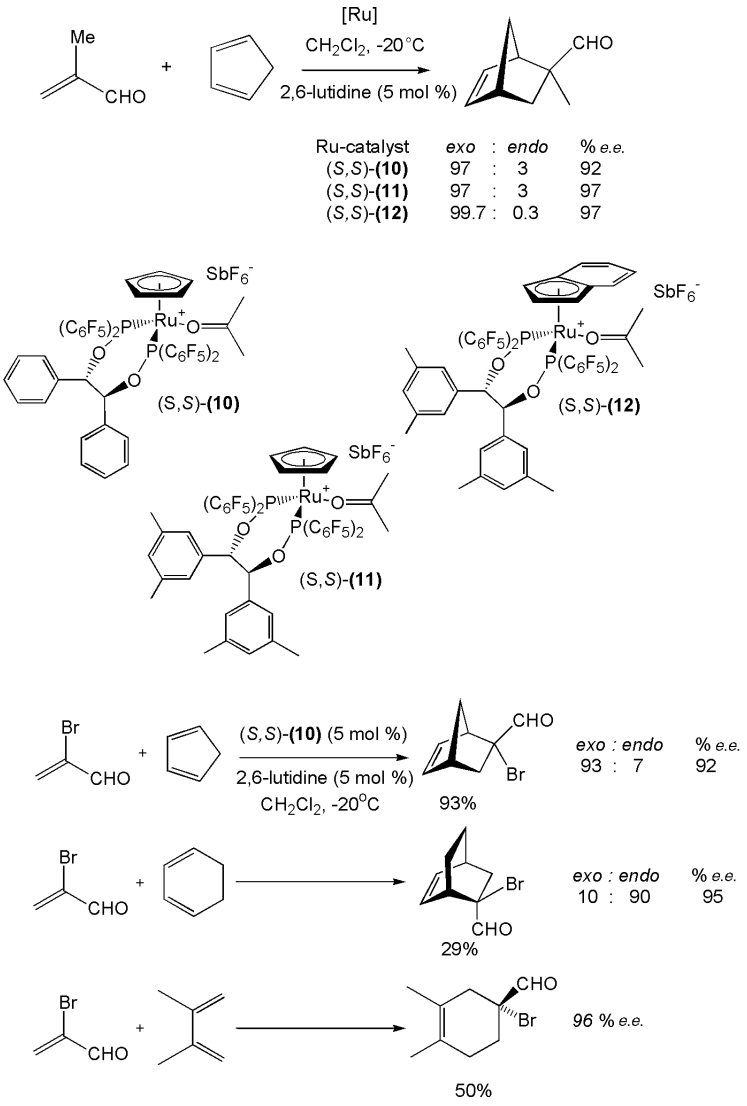


Scheme 10.20

C_2-chiral bidentate fluoroarylphosphinite ligands, efficiently catalyze the asymmetric Diels–Alder reaction between enals and 1,3-dienes [36]. Electronic factors apart, the catalyst creates a chiral contour that favors enal coordination, and subsequently this was extended to Ru Lewis acids [37]. These are stable at room temperature, and can be recycled almost quantitatively after the reaction. The immediate catalyst precursor, Ru(Cp)(BIPHOP-F)I is readily available via a one-pot synthesis from $Ru_3(CO)_{12}$. Although the Ru-catalysts were at first not quite as active as the Fe analogues and produced lower asymmetric induction than the Fe analogues, structural data showed the way to improve the situation (Scheme 10.21).

The cycloaddition product is thought to result from an *s-trans* conformation of the dienophile in the chiral pocket and a diene approach from the Cp side of the catalyst. The low yields obtained in the reactions with bromoacrolein appear to be linked to catalyst deactivation by halide abstraction in the product [37].

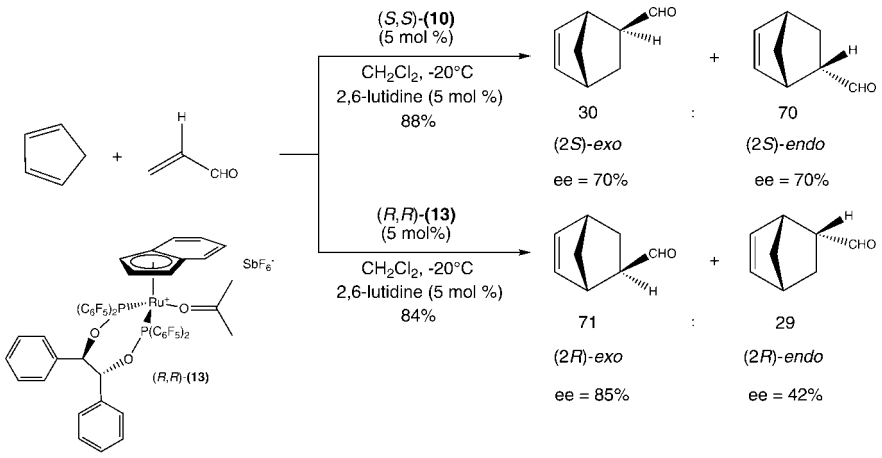
The nature of the counter ion has a large effect on the rate ($OTf^- < BF_4^- < PF_6^- < SbF_6^- < TFPB^-$), but not on the asymmetric induction. An X-ray structure of a catalyst-substrate adduct and NMR data revealed proximity of the anion to the catalyst and the substrate. Larger anions accelerate the reaction, presumably by forming a looser ion pair [36b, 37]. In the indenyl complex, the indenyl arene occupies the space where the anion resides in the Cp complex. This again results in a higher turnover frequency, and it also increases by a factor of 10 the *exo*/*endo* ratio. The



Scheme 10.21

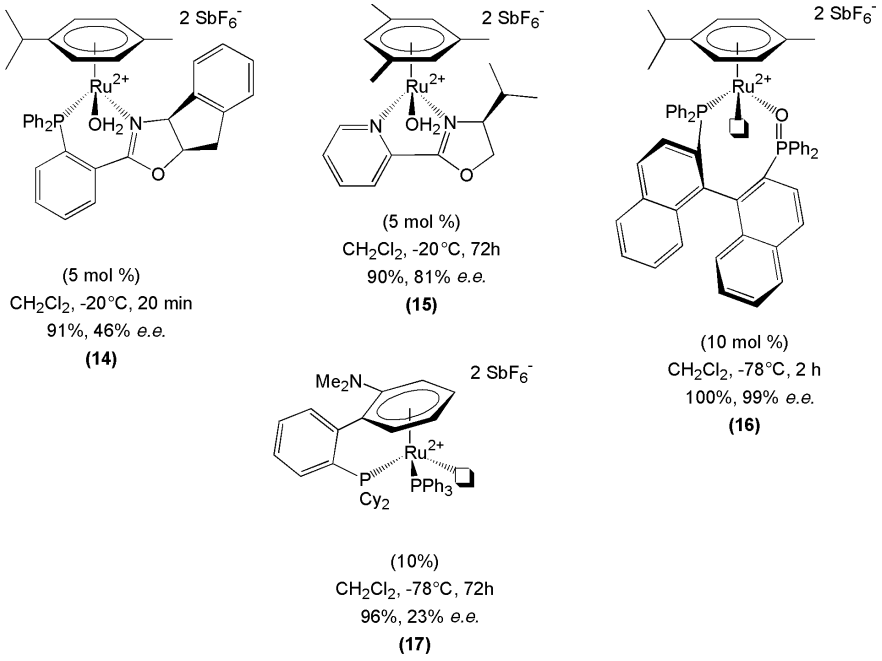
hypothesis advanced by the authors is that the *endo* transition state is disfavored because the diene collides with the catalyst roof (indene) [38]. A first example of reversal of diastereoselectivity is shown in Scheme 10.22. The concept may lead to the emergence of *exo* selective Diels–Alder catalysts.

Dicationic η^6-arene Ru half-sandwich complexes have also undergone development as Ru Lewis acids. Reaction of the readily available [Ru(η^6-arene)Cl_2]$_2$ with bidentate ligands affords [Ru(η^6-arene)(L-L′)Cl][Cl], and halide removal with a silver salt then yields the corresponding dicationic Lewis acid. With chiral dissymmetric



Scheme 10.22

ligands, diastereoisomers are formed with a pseudotetrahedral, stereogenic transition metal center [39]. Some of the halide complexes are configurationally stable, and diastereoisomers are often formed with large preferences of one diastereoisomer over the other. On halide removal, rapid equilibration occurs. Asymmetric induction in the Diels–Alder reaction then depends on the rate of diastereoisomer interconversion and relative rate of the catalysis by the two diastereoisomeric forms



Scheme 10.23

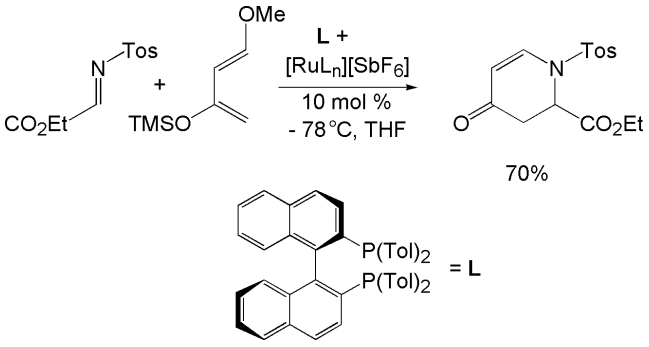
of the catalyst. Despite this complication, high enantioselectivities have been achieved. The 2+ charge makes these compounds strong Lewis acids, and reactions are often run at –78 °C. Catalysts that have found successful application incorporate dissymmetric P,N **(14)** [40], N,N [41], and P,P(O) [42] ligands. Scheme 10.23 lists examples and asymmetric induction achieved in the model reaction of cyclopentadiene and methyl acrolein. New strategies in this field include the use of racemic ligand in catalyst **16** and a chiral additive that deactivates one of the enantiomers of the catalyst (chiral poisoning). In the presence of L-proline and racemic **C**, the cycloadduct of methacrolein and cyclopentadiene was obtained with up to 54% *e.e.* [43]. The Faller group also demonstrated that planar chirality in tethered η^6:η^1-(phosphinophenylenearene-*P*)ruthenium(II) complexes could induce enantioselective Diels–Alder reaction, albeit with low asymmetric induction at this stage **(17)** [44].

10.6.2
Hetero Diels–Alder Reactions

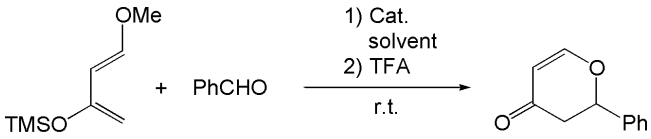
Asymmetric catalytic hetero Diels–Alder reactions give access to synthetically important substituted heterocycles [45]. Asymmetric oxa Diels–Alder reactions involving aldehydes and ketones and catalyzed by chiral Lewis acid catalysts can be performed with a high degree of chiral induction [46]. The field is much less advanced that of the corresponding catalytic enantioselective aza Diels–Alder reactions.

Jorgensen and coworkers probed the use of $[RuL_n][SbF_6]$ with chiral binap ligands for the synthesis of optically active non-natural α-amino acids of the piperidine type. The reaction of imines derived from ethyl glyoxylate with activated dienes afforded a 70% yield of the cycloadduct, but no asymmetric induction was observed (Scheme 10.24) [47].

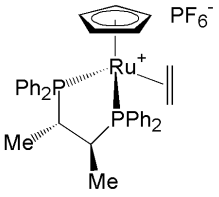
Several Ru-based transition metal complexes catalyze the hetero Diels–Alder reaction between aldehydes, in particular benzaldehyde and Danishefsky's diene. Using the $[Ru(Cp)(CHIRAPHOS)]^+$ **(18)** complex, a modest *e.e.* value of 25% is obtained (Entry 1, Scheme 10.25) [48]. This reaction is also catalyzed by irradiating the chiral complex **(3)** in the presence of the diene and the hetero-dienophile. The product is obtained with a good chiral induction (Entry 2, Scheme 10.25) [49, 50].



Scheme 10.24

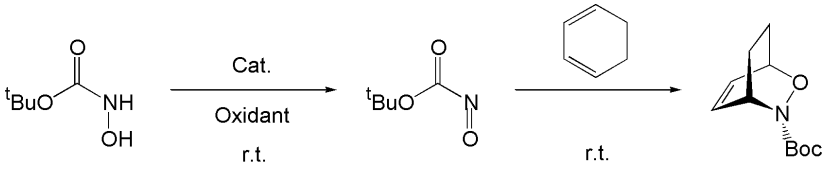


Entry	Cat.	Solvent	Time	Yield [%]	*e.e.* [%]
1	**(18)** (5 mol %)	$CHCl_3$	24h	60	25
2	**(3)** (2 mol %)/hν	TBME	7d	54	79

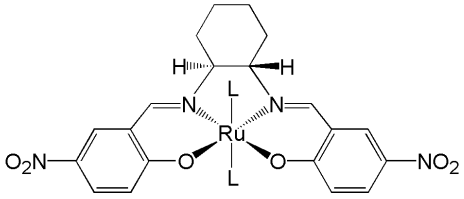


(18)

Scheme 10.25



Entry	Cat.	Solvent	*t*-BuOOH	Times/h	Yield [%]
1	$Ru(PPh_3)_4Cl_2$ (10 mol %)	CH_2Cl_2	300	72	69
2	**(1)** / P*P	MeOH	300	144	20
3	**(19)** (0.1 mol %)	CH_2Cl_2	100	1	81



L = PPh_3

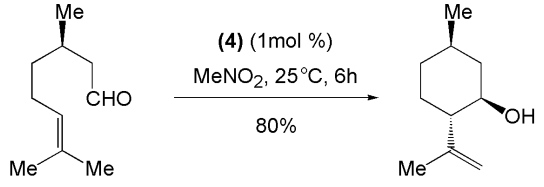
(19)

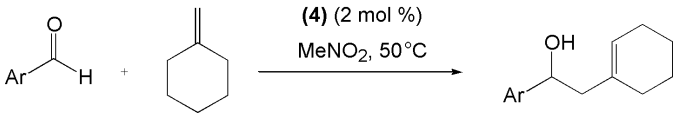
Scheme 10.26

Ruthenium(II) complexes may also be used to oxidize *N*-Boc hydroxylamine in the presence of *tert*-butylhydroperoxide (TBHP) to the corresponding nitroso dienophile, which is subsequently trapped by cyclohexa-1,3-diene to give the hetero Diels–Alder adduct (Entry 1, Scheme 10.26) [51]. A triphenylphosphine oxide-stabilized ruthenium(IV) oxo-complex was found to be the catalytically active species. Use of a chiral bidentate bis-phosphine-derived ruthenium ligand (BINAP or PROPHOS) result in very low asymmetric induction (8 and 11%) (Entry 2, Scheme 10.26). The low level of asymmetric induction is explained by the reaction conditions (in-situ oxidation) that failed to produce discrete, stable diastereomerically pure ruthenium complexes. It is shown that ruthenium(II) salen complexes also catalyze the oxidation of *N*-Boc-hydroxylamine in the presence of TBHP, to give the *N*-Boc-nitroso compound which can be efficiently trapped with a range of dienes from cyclohepta-1,3-diene (1 h, r.t., CH_2Cl_2, 71%) to 9,10-dimethylanthracene (96 h, r.t., CH_2Cl_2, 36%) (Entry 3, Scheme 10.26) [52]. However, the use of an enantiopure ruthenium salen complex **(19)** did not generate asymmetric induction, which suggests that the acyl nitroso dienophile intermediate readily dissociates from the chiral ruthenium complex involved in the oxidation step prior to Diels–Alder cycloaddition.

10.6.3
Hetero-Ene Reactions

The Lewis acid salen complex **4** (Scheme 10.7) readily catalyzes the conversion of (+)-citronellal to *l*-isopulegol via an intramolecular hetero-ene reaction. It is noteworthy to mention that this reaction is of importance in the industrial production of





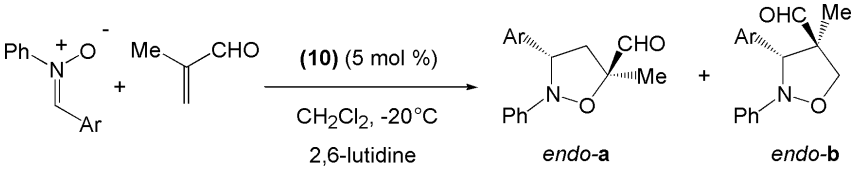
Ar	Time [h]	Yield [%]
C_6F_5	5	88
p-NO_2Ph	10	83
p-CNPh	50	82

Scheme 10.27

l-menthol. In addition, this complex also catalyzes the intermolecular hetero-ene reaction between activated enophiles and olefins to give homoallylic alcohols via a stepwise process (Scheme 10.27) [53].

10.6.4
1,3-Dipolar Cycloaddition Reactions

Kündig and co-workers reported the single-site Fe- and Ru-catalyzed enantioselective 1,3-dipolar cycloadditions of nitrones with α,β-unsaturated enals (Scheme 10.28) [54]. Normally, Lewis acids bind nitrones stronger than aldehydes and the coordination is irreversible [55]. The authors demonstrate that the Ru-catalyst (and the corresponding Fe-catalyst) in Scheme 10.28 is fine-tuned for aldehyde recognition. Nitrones coordinate, but in a readily reversible manner, and this allows the use of these catalysts for this cycloaddition reaction. The Fe-catalysts give products with *e.e.* values up to 96%, but the values for the Ru catalyst are somewhat lower. This synthetic method provides a new approach to the synthesis of enantiomerically enriched isoxazolidines of significant importance in the assembly of biologically active compounds such as lactams, amino acids, and alkaloids [56].



Entry	Ar	Yield [%]	*endo*-**a**/*endo*-**b**	*e.e.* [%]
1	Ph	92	60/40	76/94
2[a]	*p*-NO_2-Ph	80	100/0	66/-
3	*p*-CF_3-Ph	82	90/10	74/-

[a] Reaction at 0 °C

Scheme 10.28

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11
Ruthenium-Catalyzed Reactions with CO and CO_2

Take-aki Mitsudo and Teruyuki Kondo

11.1
Introduction

Transition metal-catalyzed conversion of carbon monoxide (CO) and carbon dioxide (CO_2) into high-value organic compounds is a very important process in synthetic organic chemistry, industrial chemistry and green or sustainable chemistry [1]. Among the transition metals, ruthenium shows very characteristic catalytic performance.

CO and syngas (a mixture of CO and H_2) are key compounds in organic synthesis and industrial chemistry as a C1 building block. CO is also commonly used in the chemistry of natural gas and petroleum and the chemistry of heavy carbon resources such as heavy oils and coals. Once natural gas, petroleum, heavy oil or coal is converted into syngas by reforming or gasification, hydrocarbons and oxygenates such as methanol, ethanol and ethylene glycol can be synthesized through C1 processes catalyzed by transition metals. In C1 chemistry, ruthenium provides very active and characteristic catalysis [2].

Carbonylation reactions of organic compounds such as alkenes, alkynes, alcohols and amines are very important in organic synthesis. Ruthenium catalysts show unique catalytic activities in these reactions [2c].

One of the most significant processes that involve CO in organic industrial chemistry is the hydroformylation of alkene, or the oxo process, in which rhodium and cobalt complex catalysts are used. Ruthenium is a strong candidate for replacing the very expensive rhodium catalyst. Further, ruthenium complexes are excellent catalysts for the addition of formyl groups of aldehydes, formates and formamides to alkenes.

Quite recently, novel cyclization reactions involving CO to give carbocyclic and heterocyclic compounds, which are characteristic for ruthenium catalysts, have been developed. Ruthenium complexes provide new avenues for cyclization reactions. In addition, CO is often used as a reducing agent, and reductive carbonylations of nitro compounds catalyzed by ruthenium complexes are very attractive reactions that provide phosgene-free processes [3].

Carbon dioxide is much more stable than CO. Transition metal-catalyzed CO_2 fixation is one of the most challenging subjects in both industrial and environmental chemistries [4]. If CO_2 can be efficiently converted into useful chemicals on a

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large scale, the problem of limited carbon resources and the greenhouse effect of CO_2 could be partly solved. Among transition metal complexes, ruthenium complexes show excellent catalytic performance in the conversion of CO_2 into CO and basic chemicals.

Extensive attempts have been made to utilize CO_2, which is a nontoxic and readily available raw material, in place of toxic CO. The underlying principle is the reduction of CO_2 to CO, that is, the reverse water gas shift reaction (RWGSR). In this reaction, ruthenium cluster anions exhibit high catalytic activity, and the resulting CO further reacts with hydrogen to give the products.

Hydrogenation of CO_2 to formic acid and its derivatives such as methyl formate and *N,N*-dimethylformamide is an attractive process. Among transition metal catalysts, homogeneous ruthenium catalysts are especially effective for these reactions.

The electrochemical or photochemical reduction of CO_2, when catalyzed by ruthenium complexes, also produces formic acid derivatives. Furthermore, ruthenium-catalyzed electrochemical reduction of CO_2 can provide carbon-carbon bond-forming reactions. Although at present the efficiency of such electrochemical and photochemical reactions does not appear to be satisfactory for use as a new tool in large-scale organic synthesis, the chemistry suggests that these methodologies may someday be useful in organic synthesis.

A distinctive reaction that uses CO_2 is the synthesis of enol carbamate, in which carbamic acid derived from CO_2 and amines is added to acetylenes, catalyzed by ruthenium complexes.

Thus, in the conversion of CO and CO_2 into useful chemicals, ruthenium catalysts can play essential roles.

11.2
Reactions with Carbon Monoxide

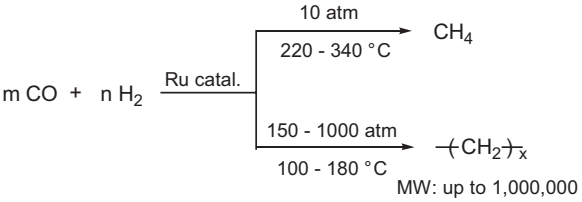
11.2.1
Ruthenium-Catalyzed Fischer-Tropsch Synthesis: Methane and Polymethylenes

The Fischer-Tropsch synthesis is the reductive oligomerization of carbon monoxide over heterogeneous catalysts (Eq. 11.1) [1, 5–7].

$$m\,CO + n\,H_2 \xrightarrow{\text{Fe, Co, Ni, or Ru catal.}} -(CH_2)_x- + y\,H_2O + z\,CO_2 \qquad (11.1)$$

This reaction produces paraffins, olefins, and oxygenates such as alcohols, and iron, cobalt, nickel, thorium, and ruthenium are known to be active catalysts. The chain length and products depend on the metal and reaction conditions.

Methane is formed over nickel and ruthenium catalysts, especially at low pressure (up to 10 atm) and high temperature (220–340 °C). Nickel and cobalt catalysts yield paraffins and olefins at milder temperatures (<200 °C) and a pressure of 1–10 atm. Over iron catalysts, olefins, paraffins and small amounts of alcohols are formed at medium pressure (10–100 atm) and a high temperature of 210–340 °C. Ruthenium



Scheme 11.1 Ruthenium-catalyzed Fischer-Tropsch synthesis.

catalysts give polymethylene with a molecular weight of up to 1 000 000 at elevated pressure (150–1000 atm) and low temperature (100–180 °C). Thus, ruthenium is a unique catalyst in Fischer-Tropsch synthesis (Scheme 11.1).

11.2.2
Synthesis of Oxygenates from Syngas by Homogeneous Catalysts

Oxygen-containing C1 and C2 molecules can be efficiently synthesized from CO and H_2 (syngas) using cobalt, rhodium, and ruthenium catalysts. Among these catalysts, ruthenium is very efficient and selectively provides products with less than C2 units [8,9]; this is in contrast to the Rh and Co catalysts, which produce byproducts with more than C3 units (Eq. 11.2).

$$m\,CO + n\,H_2 \xrightarrow{\text{Co, Rh, Ru catal.}} CH_3OH,\ CH_3CH_2OH,\ HOCH_2CH_2OH \qquad (11.2)$$

A $Ru_3(CO)_{12}/I^-$/acid/phosphine oxide catalyst [8, 9] or a $Ru_3(CO)_{12}/Cl^-$ catalyst [10] gives ethanol together with methanol (Eq. 11.3).

$$m\,CO + n\,H_2 \xrightarrow{Ru_3(CO)_{12}\,/\,Cl^-} CH_3CH_2OH \qquad (11.3)$$

When ethanol is produced, methanol is formed in the first step, and is then homologated. Dombek reported that ruthenium complexes are effective for the production of ethylene glycol at 340 atm and below, especially in the presence of iodide (Eq. 11.4) [11].

$$m\,CO + n\,H_2 \xrightarrow{\text{Ru catal.}} HOCH_2CH_2OH + CH_3OH \qquad (11.4)$$

Ru catal. : $Ru_3(CO)_{12}\,/\,I^-$ [11], $Ru(acac)_3\,/\,Bu_4PBr$ [12],
$Ru_3(CO)_{12}$ / benzimidazole [13, 14], Ru / Rh [15-17], Ru / Re [18]

Knifton reported that the combination of ruthenium complex/phosphonium salt, such as RuO_2/Bu_4PBr and $Ru(acac)_3/Bu_4PBr$, is a good catalyst for the synthesis of ethylene glycol together with methanol and ethanol [12].

$Ru_3(CO)_{12}$/1-alkylbenzimidazoles showed high selectivity for ethylene glycol [13]. A mechanistic study of this reaction showed that $RuH_2(CO)_3$(1-methylbenzimidazole) is formed, and this complex is considered to be the active species. 1-Methylbenzimidazole enhances both the rate of the formation of formaldehyde from syngas and the rate of the hydroformylation of formaldehyde [14].

Bimetallic catalysts, Ru/Rh [15–17] and Ru/Re [18], were found to be effective for the selective synthesis of ethylene glycol. A bimetallic Ru/Co catalyst gives ethanol [19], while Ru/Mn and Ru/Ti give methanol [20]. In the presence of ammonia, syngas can be converted into the corresponding formamide with the $Ru_3(CO)_{12}/Bu_4PBr$ catalyst (Eq. 11.5) [21].

$$CO + H_2 + NH_3 \xrightarrow{Ru_3(CO)_{12} / Bu_4PBr} HCONH_2 \qquad (11.5)$$

11.2.3 Carbonylation of Alcohols and Amines

Primary alcohols are carbonylated to esters with ruthenium catalysts (Eq. 11.6) [2b, 22a].

$$CH_3CH_2CH_2CH_2OH + CO \xrightarrow[450\ atm,\ 200\ °C,\ 2\ h]{RuCl_3 \cdot 3H_2O\ /\ I_2} \underset{51\%}{CH_3CH_2CH_2CH_2\overset{\overset{O}{\|}}{C}-OC_4H_9} \qquad (11.6)$$

Methanol reacts with CO in the presence of a $Ru_3(CO)_{12}$ catalyst to give methyl formate. Although methyl formate is produced in industry from methanol and CO using bases as catalysts, more efficient catalysts are needed [22b]. Formic or acetic esters of diols are carbonylated to give lactones or hydroxylic ester with $[Ru(CO)_3I_3]^-/I^-$ catalysts (Eq. 11.7) [23].

$$CH_3CO_2CH_2CH_2CH_2OCOCH_3 + CO \xrightarrow[200\ °C]{[Ru(CO)_3I_3]^- / CH_3I} \underset{60\%}{\text{  }} \qquad (11.7)$$

Primary and secondary amines react with CO in the presence of $Ru_3(CO)_{12}$ [24], $RuCl_3 \cdot 3H_2O$ [25] or Ru(II)(EDTA)(CO) [26] catalyst to give the corresponding N-substituted formamides (Eq. 11.8).

$$\left.\begin{matrix} RNH_2 \\ R_2NH \end{matrix}\right\} + CO \xrightarrow{Ru\ catal.} \left\{\begin{matrix} RNHCHO \\ R_2NCHO \end{matrix}\right. \qquad (11.8)$$

Ru catal.: $Ru_3(CO)_{12}$ [24], $RuCl_3 \cdot 3H_2O$ [25], Ru(II)(EDTA)(CO) [26]

In-situ high-pressure IR spectroscopy revealed that in the carbonylation of piperidine by $Ru_3(CO)_{12}$ catalyst under 0.1 to 1.0 MPa of CO, a mononuclear complex is the active reaction intermediate. A catalytic cycle involving $RuH(NC_5H_{10})(CO)_4$ and $RuH(CONC_5H_{10})(CO)_3$ has been proposed [27].

11.2.4
Homologation Reaction of Alcohols and Esters

Homologation is the one-carbon extension reaction of organic compounds such as alcohols and carboxylic esters, and is very important. Cobalt, rhodium, and ruthenium complexes are known to be efficient catalysts. Methanol and methyl ester can be converted to ethanol and ethyl ester, respectively, using Ru/I^- [28] and Ru/Co [29] catalysts (Eq. 11.9).

$$CH_3OH + CO + H_2 \xrightarrow[150\ atm,\ 200\ ^\circ C,\ 2\ h]{RuI_2(CO)_4\ /\ CH_3I\ /\ NaI} C_2H_5OH + C_2H_5OAc \qquad (11.9)$$

Synergistic effects are observed in the Ru/Rh [30] and Ru/Co [29, 31] catalytic systems. Ethanol is efficiently formed from methyl formate with a Ru/HCl catalyst. CO and hydrogen are produced in situ at pressures sufficiently high to induce homologation of the methyl group [32].

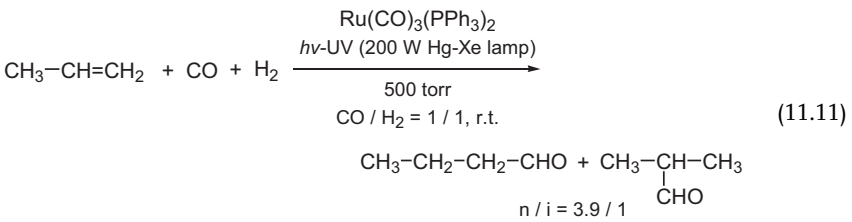
11.2.5
Hydroformylation and Related Carbonylation

The hydroformylation reaction or oxo process is an important industrial synthetic tool. Starting from an alkene and using syngas, aldehydes with one or more carbon atoms are obtained. In almost all industrial processes for the hydroformylation of alkenes, rhodium or cobalt complexes are used as catalysts [33]. A number of studies on ruthenium complex-catalyzed hydroformylation have been reported [34]. One of the reasons for the extensive studies on ruthenium complex catalysts is that, although the rhodium catalysts used in industry are highly active, they are very expensive, and hence the development of a less-expensive catalytic system is required. Since inexpensive ruthenium catalysts can achieve high selectivity for desired *n*-aldehydes or *n*-alcohols, if the catalytic activity can be improved to be comparable with that of rhodium catalysts, it is possible that a ruthenium-catalyzed oxo process would be realized.

The ruthenium complex-catalyzed hydroformylation of 1-alkene was first examined by Wilkinson's group. $Ru(CO)_3(PPh_3)_2$/phosphine catalysts were found to have moderate catalytic activity [35–37]. $Ru_3(CO)_{12}$ [38] and anionic hydridocluster complexes such as $[NEt_4][Ru_3H(CO)_{11}]$ [39] have also been shown to have catalytic activity. In molten phosphonium salt, $Ru_3(CO)_{12}$/2,2′-bipyridine has high catalytic activity [40]. The $Ru_3(CO)_{12}$/1,10-phenanthroline catalyst in *N,N*-dimethylacetamide (DMAC) shows excellent activity and selectivity for *n*-aldehydes (Eq. 11.10) [41].

$$R{-}CH{=}CH_2 + CO + H_2 \xrightarrow{Ru\ catal.} R{-}CH_2{-}CH_2{-}CHO + R{-}\underset{\displaystyle CHO}{\underset{|}{CH}}{-}CH_3 \qquad (11.10)$$

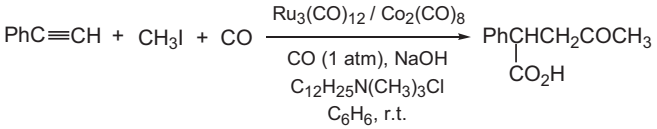
The hydroformylation of alkene proceeds under ultra-violet (UV) irradiation (200 W, Hg-Xe lamp) with a $Ru(CO)_3(PPh_3)_2$, $Ru(CO)_4(PPh_3)$ or $Ru_3(CO)_{12}$ catalyst system at a low pressure of CO at ambient temperature. In the reaction of propylene, the n/i ratio was 3.9 (Eq. 11.11) [42].



(11.11)

A bimetallic system of $Ru_3(CO)_{12}/Co_2(CO)_8$ shows high catalytic activity for the hydroformylation of cyclohexene. Synergistic effects may play an important role in the insertion of alkene into a hydrido-metal bond [43].

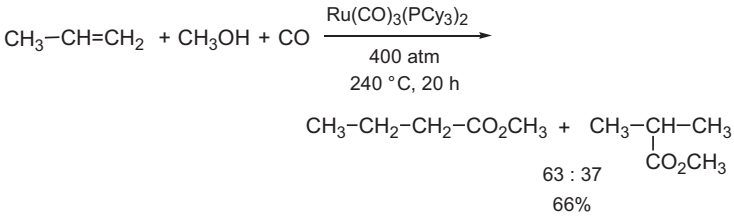
The bimetallic catalyst system $Ru_3(CO)_{12}/Co_2(CO)_8$ catalyzes the reaction of terminal acetylenes with methyl iodide and 1 atm of CO under phase-transfer conditions to give γ-oxocarboxylic acid (Eq. 11.12) [44].



(11.12)

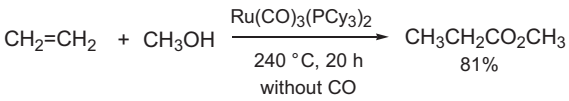
11.2.6
Hydroesterification, Hydroamidation, and Hydroacylation

The hydroesterification of alkenes is a versatile method for obtaining carboxylic esters from alkene, CO, and alcohol (Eq. 11.13) [45, 46].



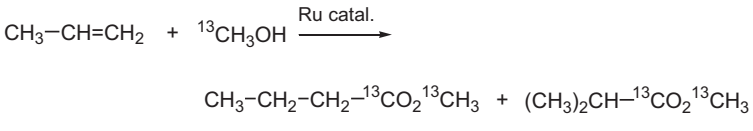
(11.13)

Ethylene reacts with methanol with the $Ru(CO)_3(PCy_3)_2$ catalyst even in the absence of CO to give methyl propionate (Eq. 11.14).



(11.14)

Keim and coworkers examined the mechanism of this reaction using $^{13}CH_3OH$ and propylene. Methyl butyrate was obtained as a product, and ^{13}C was found to be incorporated into both the carbonyl carbon and the methoxy group (Eq. 11.15) [47].



(11.15)

This result shows that the product is obtained upon the decomposition of methanol to CO and hydrogen (Eq. 11.16).

$$^{13}CH_3OH \overset{[Ru]}{\rightleftharpoons} {}^{13}CO + 2\,H_2 \qquad (11.16)$$

The hydroesterification of allenes with alcohol and CO, when catalyzed by ruthenium complexes, gives acrylates [48, 49]. In the presence of amines, acrylamides are formed in high yields (Eq. 11.17).

$$H_2C{=}C{=}CH_2 + C_2H_5OH + CO \xrightarrow[15\ atm,\ 100\ °C,\ 3\ h]{Ru_3(CO)_{12}} \underset{88\%}{H_2C{=}\overset{\overset{CH_3}{|}}{C}{-}CO_2C_2H_5} \qquad (11.17)$$

Hydroesterification can alternatively be performed via the addition of methyl formate to alkene [50–52]. Ethylene or alkenes react with methyl formate in the presence of catalytic amounts of ruthenium complexes, $RuCl_2(PPh_3)_3$ [53], $RuH_2(PPh_3)_4$ [54], $Ru_3(CO)_{12}$, $[Ru_3(CO)_{10}Cl]^-$ [55], and $RuCl_3/[Et_4N]I$ [56], to give methyl propionate or alkynoate in good to excellent yields. Halide ion was shown to promote the reaction, and $[PPN][Ru(CO)_3Cl_3]/NEt_3$ [PPN = bis(triphenylphosphine)iminium] was found to be an efficient catalyst (Eq. 11.18) [57].

$$CH_2{=}CH_2 + HCO_2CH_3 \xrightarrow{Ru\ catal.} CH_3CH_2CO_2CH_3 \qquad (11.18)$$

Ru catal.: $RuCl_2(PPh_3)_3$ [53], $RuH_2(PPh_3)_4$ [54], $Ru_3(CO)_{12}$, $Ru_3(CO)_{10}Cl^-$ [55], $RuCl_3$ / 2[Et_4N]I [56], [PPN]$Ru(CO)_3Cl_3$ / NEt_3 [57]

Benzyl formate reacts with cyclohexene in the presence of $Ru_3(CO)_{12}/(CH_3)_3NO\cdot 2H_2O$ catalyst under 20 atm of CO at 200 °C to give benzyl cyclohexanecarboxylate in 68% yield [58].

Further, alkene reacts with formamides in the presence of $Ru_3(CO)_{12}$ to give the hydroamidated products (Eq. 11.19).

$$R\text{-}CH{=}CH_2 + \overset{O}{\overset{\|}{H}}CNR'_2 \xrightarrow{Ru\ catal.} R{-}CH_2CH_2CONR'_2 + RCH(CH_3)CONR'_2 \qquad (11.19)$$

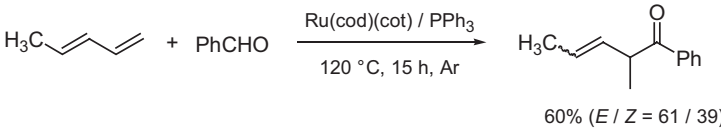
N-Methylformamide reacts with cyclohexene to give the corresponding adduct in high yield [59]. $[PPN][Ru_3H(CO)_{11}]/PCy_3$ catalyzes the addition of formanilide to alkenes such as ethylene or 2-norbornene. It should be noted that CO is not required in this reaction [60].

Aldehydes also react with alkenes to give hydroacylated products, unsymmetric ketones. Isnard and coworkers reported the first intermolecular hydroacylation, though the yields of the products were low (Eq. 11.20) [61].

$$R\text{-}CH{=}CH_2 + \overset{O}{\overset{\|}{H{-}C}}{-}R' \xrightarrow{Ru\ catal.} R{-}CH_2CH_2COR' + RCH(CH_3)COR' \qquad (11.20)$$

Intermolecular hydroacylation is difficult because decarbonylation of aldehyde is predominant, and ketone is not formed. However, this problem can be overcome by charging the pressure of CO [62].

1,3-Dienes react with aldehydes in the presence of a Ru(cod)(cot)/triphenylphosphine [cod = 1,5-cyclooctadiene, cot = 1,3,5-cyclooctatriene] catalyst to give hydroacylated products (Eq. 11.21) [63].

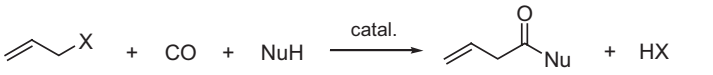


(11.21)

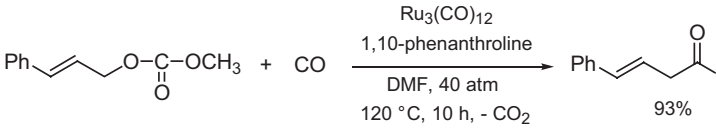
Usually hydroacylation reactions of alkenes requires CO to suppress decarbonylation of the aldehyde, but this reaction does not require CO. The key intermediate in the catalytic cycle is postulated to be a [Ru(η^3-allyl)(acyl)Ln] species.

11.2.7 Carbonylation of Allylic Compounds

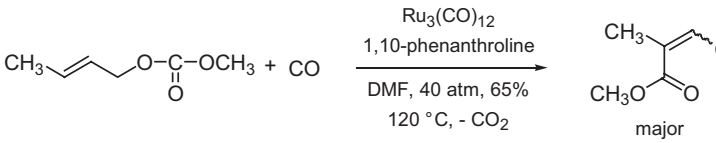
The carbonylation of allylic compounds by transition metal complexes is a versatile method for synthesizing unsaturated carboxylic acid derivatives (Eq. 11.22) [64]. Usually, palladium complexes are used for the carbonylation of allylic compounds [65], whereas ruthenium complexes show characteristic catalytic activity in allylic carbonylation reactions. Cinnamyl methyl carbonate reacts with CO in the presence of a $Ru_3(CO)_{12}$/1,10-phenanthroline catalyst in dimethylformamide (DMF) to give methyl 4-phenyl-3-butenoate in excellent yield (Eq. 11.23) [66]. The regioselectivity is the same as in the palladium complex-catalyzed reaction. However, when (*E*)-2-butenyl methyl carbonate is used as a substrate, methyl (*E*)-2-methyl-2-butenoate is the major product, with the more sterically hindered carbon atom of the allylic group being carbonylated (Eq. 11.24). This regioselectivity is characteristic of the ruthenium catalyst [66].



(11.22)

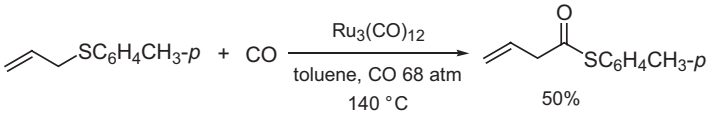


(11.23)



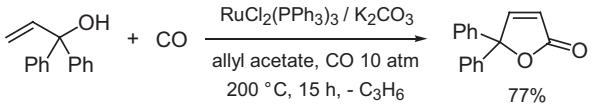
(11.24)

The insertion of CO into an allylic carbon-sulfur bond was first achieved using either a palladium or ruthenium catalyst (Eq. 11.25) [67].



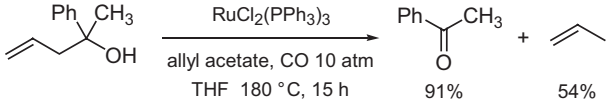
(11.25)

Oxidative cyclocarbonylation of 1,1-disubstituted allylic alcohols was accomplished with the $RuCl_2(PPh_3)_3$ catalytic system to form 2(5*H*)-furanones (Eq. 11.26). The presence of CO and an excess amount of allyl acetate, which is a hydrogen acceptor, is essential in this respect [68].



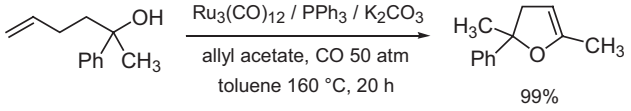
(11.26)

When homoallyl alcohols are treated under analogous reaction conditions, the carbonylation reaction does not occur; rather, a characteristic carbon-carbon bond cleavage occurs to give ketones and alkenes. During this reaction, β-carbon elimination occurs to give the products. The CO pressure is crucial for suppressing deactivation of the catalyst and stabilizing the active species by coordination to the metal center (Eq. 11.27) [69].



(11.27)

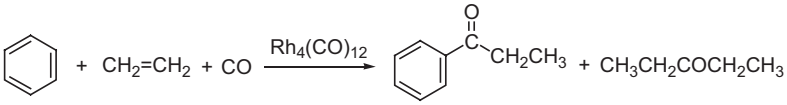
The homologues of the homoallyl alcohol in Eq. 11.27 react intramolecularly to give dihydrofurans quantitatively. Again, in this reaction, CO and allyl acetate are essential (Eq. 11.28) [70].



(11.28)

11.2.8
Carbonylation via Activation of C–H Bonds

The catalytic activation of a C–H bond and successive insertion of CO provides new tools for organic synthesis. Hong and Yamazaki reported that the rhodium-catalyzed reaction of benzene, ethylene and carbon monoxide gives propiophenone (Eq. 11.29) [71].

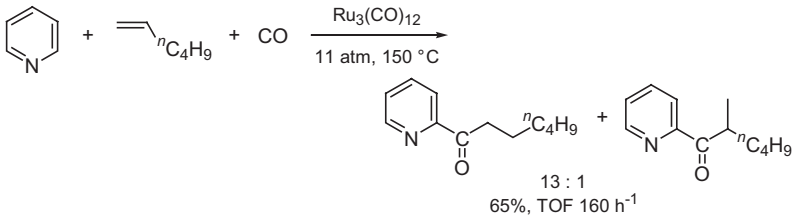


(11.29)

This reaction may proceed via activation of the C–H bond of benzene and oxidative addition, with subsequent insertion of CO and ethylene, and reductive elimination.

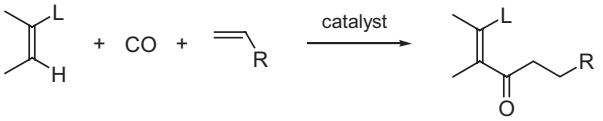
The photo-induced rhodium-catalyzed C–H activation of aliphatic and aromatic hydrocarbons and CO insertion has also been reported [72].

With regard to ruthenium complexes, in 1992 Moore and coworkers reported the ruthenium-catalyzed three-component coupling of pyridine, alkene, and carbon monoxide to produce 2-pyridyl alkyl ketone (Eq. 11.30) [73]. This reaction involves ruthenium-catalyzed C–H bond activation followed by the insertion of CO and alkene to give the product.



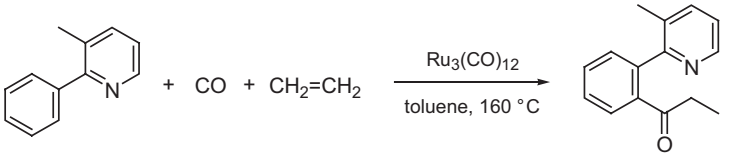
(11.30)

On the other hand, Murai and coworkers succeeded in the ruthenium-catalyzed activation of the C–H bonds of aromatic, heteroaromatic and olefinic compounds that had directing groups [74] (see Chapter 9), by applying Moore's concept to their catalytic systems (Eq. 11.31).

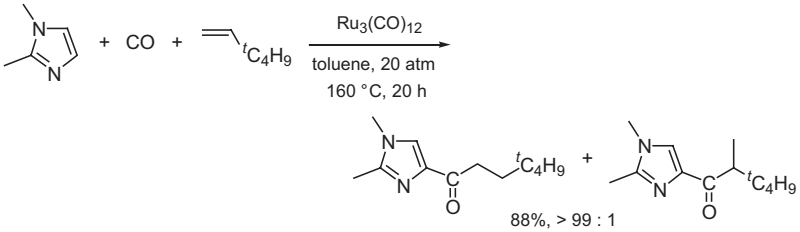


(11.31)

Typical reactions are shown in Eqs. 11.32 and 11.33, and the scope and details of the reactions are discussed in Chapter 9.

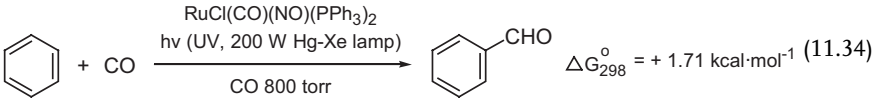


(11.32)



(11.33)

An example of ruthenium-catalyzed photo-induced C–H bond activation and successive carbonylation is the formation of benzaldehyde in the reaction of benzene and CO (800 torr) under UV irradiation (200 W, Hg-Xe) in the presence of RuCl(CO)(NO)$(PPh_3)_2$ (Eq. 11.34) [75].

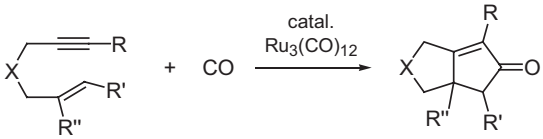


(11.34)

11.2.9
Cyclization Reaction with CO

The cyclization reaction of unsaturated compounds with CO is one of the most attractive reactions in organic synthesis. Recently, ruthenium complexes were shown to have outstanding potential for catalytic activity in these reactions.

The Pauson-Khand reaction is a well-known method for preparing cyclopentenones by the [2 + 2 + 1] cycloaddition reaction of alkyne, alkene and CO. While reactions using stoichiometric amounts of $Co_2(CO)_8$ were initially examined, catalytic versions with cobalt, titanium, rhodium, iridium, and ruthenium complexes have recently been developed. Whilst the intramolecular version is rather easy, the *intermolecular* version is a very difficult problem that has not yet been solved [76].
The intramolecular versions catalyzed by ruthenium complexes, and developed independently by the groups of Murai [77] and Mitsudo [78] in 1997, opened the door to the chemistry of noble metal-catalyzed Pauson-Khand reactions (Eq. 11.35).

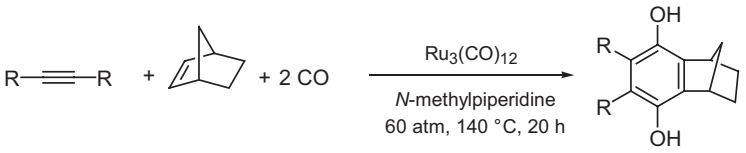


(11.35)

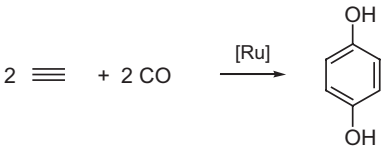
These two reports show the characteristics of ruthenium complex catalysts. Murai's group used $Ru_3(CO)_{12}$ catalyst in dioxane as solvent, while Mitsudo's group used the same catalyst in *N,N*-dimethylacetamide (DMAC) as solvent. Both catalyst systems work well for simple 1,6-enynes.

In dioxane, when X = O or RN, the reaction proceeds smoothly. However, when a methyl group is introduced into the olefinic moiety, the reaction is suppressed. On the other hand, in DMAC the introduction of a methyl group to the olefinic moiety does not affect the catalytic activity, though when X = O or RN, a deallylation reaction proceeds to disturb the cyclization reaction. In DMAC, oxidative addition of the allyl-X group to the ruthenium active species would occur, most likely due to the coordination of a more electron-donating amide solvent. Thus, the two reports are mutually supportive.

Considerable effort has been devoted to achieving the *intermolecular catalytic* Pauson–Khand reaction. The ruthenium complex-catalyzed reaction of an alkyne with an alkene such as ethylene or 2-norbornene under CO gave hydroquinone derivatives [79], with CO (2 mol) being introduced into the products (Eq. 11.36). This reaction is the first example of the preparation of hydroquinone derivatives by the reaction of alkynes and alkenes with CO, while hydroquinone is synthesized by the ruthenium-catalyzed reaction of 2 mol acetylene with 2 mol CO (Eq. 11.37) [80].

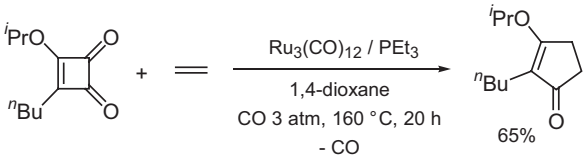


(11.36)



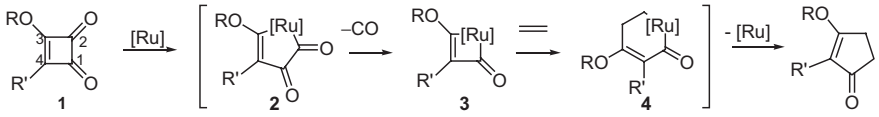
(11.37)

A reaction which corresponds to the intermolecular Pauson-Khand reaction was accomplished by the $Ru_3(CO)_{12}$-catalyzed reaction of cyclobutenediones with alkenes under CO (Eq. 11.38) [81].



(11.38)

A possible reaction mechanism for this is illustrated in Scheme 11.2. The reaction proceeds via C–C bond cleavage and the mono-decarbonylation of cyclobutenedione **1**. The presence of an alkoxy group at the 3-position is essential for this reaction. The alkoxy group probably acts as a directing group to cleave the C(2)–C(3) bond, giving **2**. The decarbonylation reaction in **2** gives **3**, followed by the insertion of alkene and the reductive elimination of the formed **4** to give the product.

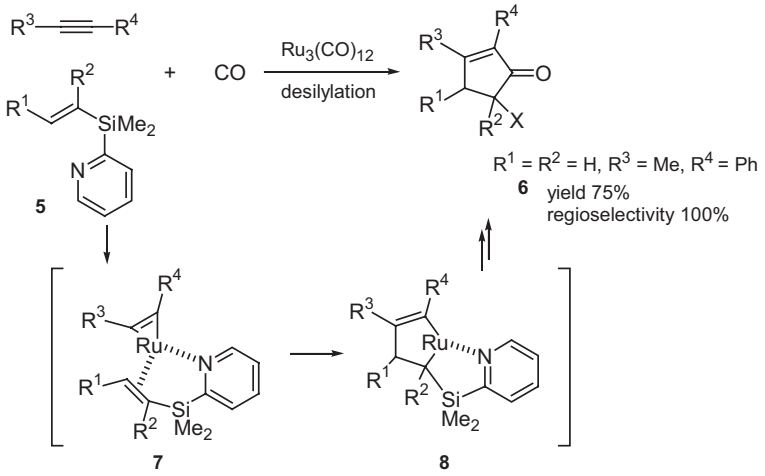


Scheme 11.2 A proposed mechanism for the reaction of cyclobutenedione with alkene and CO in Eq. 11.38.

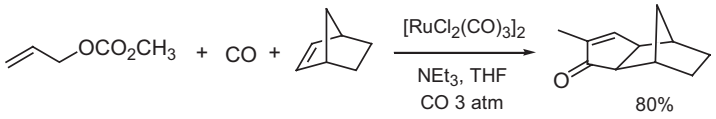
The reaction with ^{13}CO showed the partial scrambling of ^{13}CO with the carbonyl group of the cyclopentenones, which indicates that decarbonylation-carbonylation occurs in this reaction.

Quite recently, the intermolecular Pauson-Khand reaction was successfully performed using alkenes with a directing group. 2-Pyridylsilyl alkene **5** reacts with alkynes under a low pressure of CO in the presence of $Ru_3(CO)_{12}$ to give cyclopentenones **6** (Scheme 11.3). The directing group assists the coordination of alkene to form **7** and the ruthenacyclopentene complex **8**. During the reaction or work-up of the reaction solution, the pyridyl silyl group is detached [82].

The reaction of allyl carbonates with 2-norbornene under 3 atm of CO catalyzed by $[RuCl_2(CO)_3]_2$ gives cyclopentenones. A reaction mechanism involving successive insertion of 2-norbornene and CO into a π-allyl-ruthenium bond is proposed (Eq. 11.39) [83], the details of which discussed in Chapter 5.

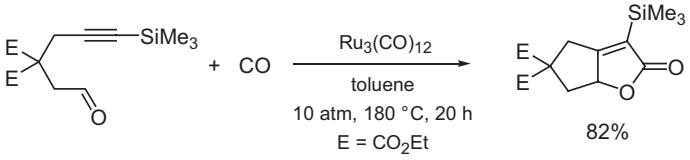


Scheme 11.3 Intermolecular Pauson-Khand reaction with alkyne and 2-pyridylsilylalkene.

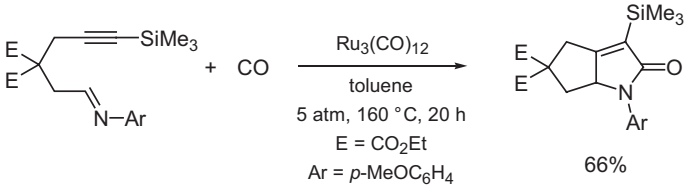


(11.39)

Murai's group developed a series of new $Ru_3(CO)_{12}$-catalyzed cycloaddition reactions involving CO. In the intramolecular Pauson-Khand reaction, the olefinic moiety is replaced by a carbonyl [84] or imine group [85] to give either γ-lactones or γ-lactams (Eqs. 11.40 and 11.41).

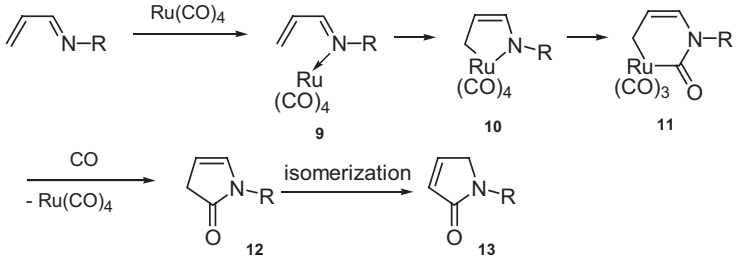


(11.40)

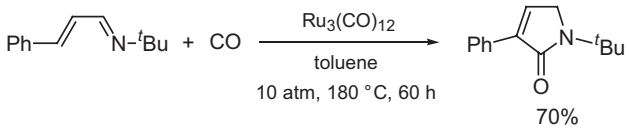


(11.41)

Further, replacement of the acetylenic part in the Pauson-Khand reaction by a carbonyl or imine group has been successfully achieved. α,β-Unsaturated imines react with CO in the presence of $Ru_3(CO)_{12}$ catalyst to give carbonylative [4 + 1] cycloadducts, γ-lactams, in high yields [86]. A possible mechanism is shown in Scheme 11.4. Coordination of α,β-unsaturated imine to "$Ru(CO)_4$" gives **9**, which is converted into **10** via oxidative cyclization. Subsequent carbonylation of **10** gives **11**, the reductive elimination of which gives **12** (Eq. 11.42).

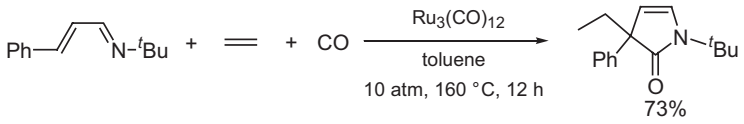


Scheme 11.4 A possible mechanism of the cyclic carbonylation of α,β-unsaturated imines.



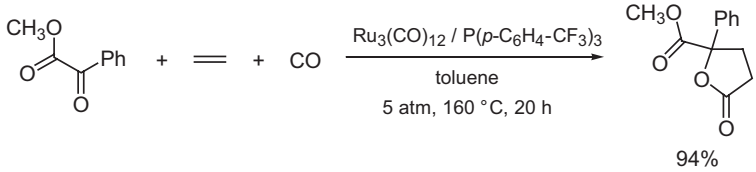
(11.42)

When the reaction is performed in the presence of an alkene, a three-component coupling reactions take place (Eq. 11.43) [87]. When this reaction is applied to cyclopropylimines, six-membered unsaturated lactams are obtained [88].



(11.43)

A completely new intermolecular [2 + 2 + 1] cycloaddition was achieved when α-ketoester was used as one component (Eq. 11.44) [89].

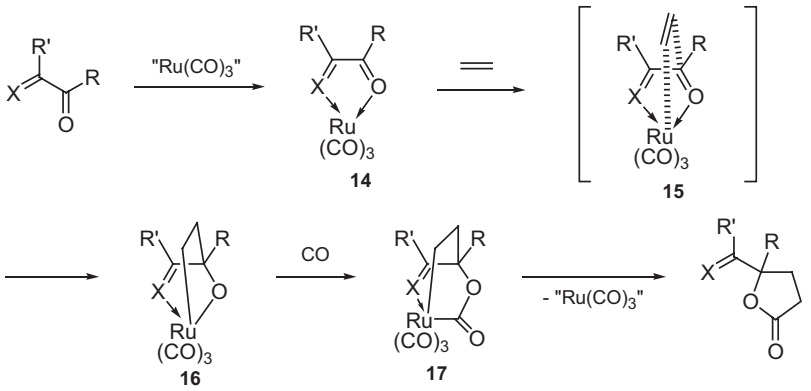


(11.44)

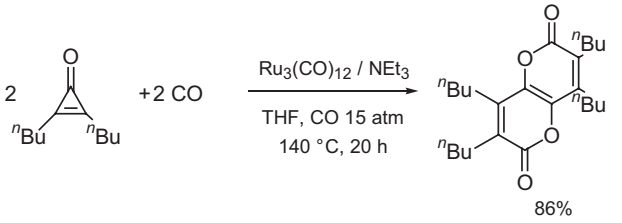
In this reaction, the addition of $P(p\text{-}C_6H_4\text{-}CF_3)_3$ was crucial to obtain the product in high yield. Furthermore, 2-acetylpyridines and 2-pyridylimines, together with ethylene and CO, give 2-pyridyl-γ-lactones [89] and 2-pyridyl-γ-lactams [90], respectively.

For these reactions, an interesting mechanism involving a [2 + 3] cycloaddition reaction is proposed (Scheme 11.5) [89]. The key reaction may be the [2 + 3] reaction of **14** with alkene to give **16** via **15**. The CO insertion reaction, followed by the reductive elimination of the formed **17**, gives the product. The [2 + 3] cycloaddition reaction has been found in the reaction of $Ru(CO)_3$(1,4-diazabutadiene) with dimethyl maleate [91].

Cyclopropenones react with CO in the presence of $Ru_3(CO)_{12}/NEt_3$ to give pyranopyrandiones. This reaction involves C–C bond cleavage and a successive reconstructive carbonylation reaction (Eq. 11.45).

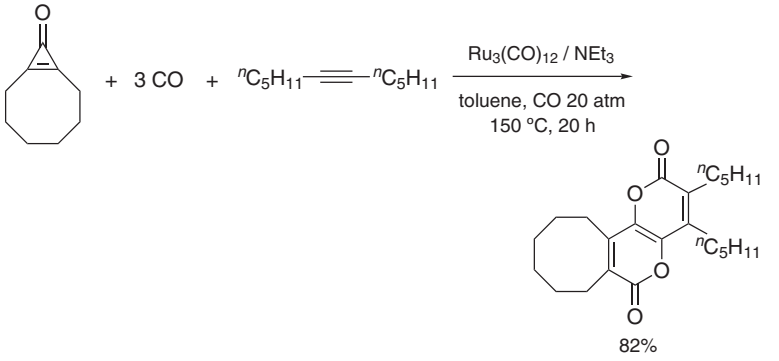


Scheme 11.5 A possible mechanism for the preparation of lactones in Eq. 11.44.



(11.45)

In the presence of acetylenes, the latter are incorporated into the products to give unsymmetric pyranopyrandiones (Eq. 11.46).



(11.46)

Based on the results of a mechanistic study using ^{13}CO, a reaction mechanism involving the carbonylation of a ruthenium-carbene intermediate has been proposed [92].

11.2.10
Carbonylation of Nitrogen-Containing Compounds

The oxidative carbonylation of amines has been performed using palladium complex catalysts. Rhodium and ruthenium complexes have also been shown to have catalytic activity in the preparation of carbamates and ureas [93, 94]. An example is shown in Eq. 11.47. The usual carbonylation of amines to give formamides was discussed in Section 11.2.3.

$$2\ PhNH_2 + CO + 1/2\ O_2 \xrightarrow[\text{CO 38 atm, } O_2\text{ 3 atm}\\ \text{170 °C, 2 h}]{Bu_4N[Ru(CO)_3I_3]} PhNHCNHPh \quad (67\%) \qquad (11.47)$$

The reductive carbonylation of nitroarenes with transition metal catalysts is a very important process in industry, as the development of a phosgene-free method for preparing isocyanate is required. Ruthenium, rhodium, and palladium complex catalysts have all been well studied, and ruthenium catalysts have been shown to be both highly active and attractive. The reduction of nitroarene with CO in the presence of alcohol and amine gives urethanes and ureas [95], respectively, both of which can be easily converted into isocyanates [3,96].

A typical reaction is the $Ru_3(CO)_{12}$ or $Ru(CO)_3(PPh_3)_2$-catalyzed reductive carbonylation of nitrobenzene to carbamates (Eq. 11.48) [97].

$$PhNO_2 + 3\ CO + CH_3OH \xrightarrow[Et_4NCl,\ \text{toluene}\\ \text{CO 82 atm}\\ \text{160 - 170 °C, 5 h}]{Ru_3(CO)_{12}} PhNHCOCH_3 \quad (93\%) + 2\ CO_2 \qquad (11.48)$$

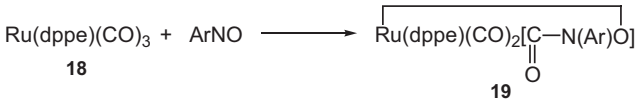
The $[Ru_3H(CO)_{11}]^-$-catalyzed reaction in CH_3CN directly gives phenylisocyanate (Eq. 11.49) [98], while the $Ru_3(CO)_{12}$ catalyst in aqueous alkali gives aniline (Eq. 11.50) [99].

$$PhNO_2 + CO \xrightarrow[CH_3CN,\ CO\ 21\ atm\\ 140\ °C,\ 3\ h,\ -\ CO_2]{[Ru_3H(CO)_{11}]^-} PhNCO \quad (95\%) \qquad (11.49)$$

$$PhNO_2 + CO \xrightarrow[CH_3O(CH_2)_2OH,\ PhCH_2NEt_3Cl\\ \text{r.t., 1 atm, } -\ CO_2]{Ru_3(CO)_{12},\ \text{aq NaOH}} PhNH_2 \quad (100\%) \qquad (11.50)$$

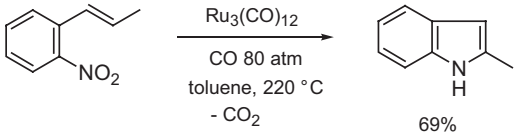
Mechanistic studies on the reaction involving ruthenium-nitrene complexes [100] or ruthenium-nitroso complexes [95] have also been reported. A stoichiometric reaction of Ru(dppe)$(CO)_3$ (**18**) with ArNO gives Ru(dppe)$(CO)_2$[CON(Ar)O] (**19**) (Eq. 11.51). In the first step of the catalytic reaction, nitroarene is reduced to nitrosoarene, while in the second step the complex **19** reacts with methanol and CO to give a

bis(methoxycarbonyl)ruthenium complex which reacts with $ArNH_2$ to give the carbamates (Eq. 11.51).

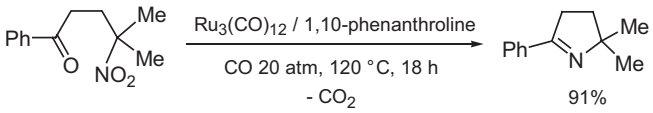


(11.51)

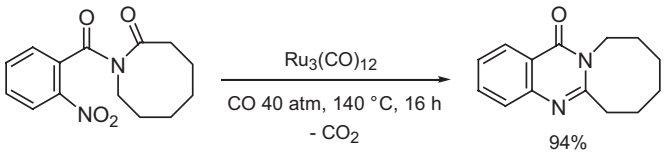
Reductive cyclization of 2-nitrostyrenes, γ-nitrocarbonyl compounds and *N*-(2-nitrobenzoyl)amides catalyzed by $Ru_3(CO)_{12}$ gives indoles (Eq. 11.52) [101], 1-pyrrolines (Eq. 11.53) [102], and 4(3*H*)-quinazolinones (Eq. 11.54) [103], respectively.



(11.52)

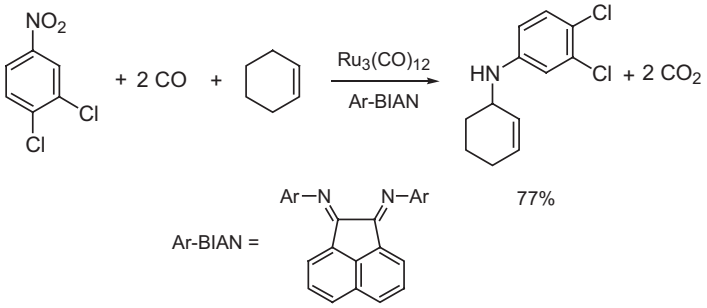


(11.53)



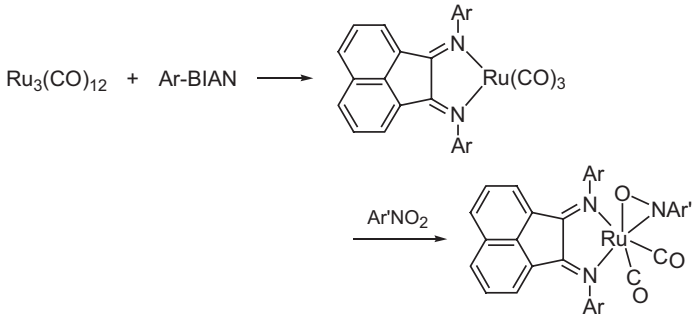
(11.54)

Reduction of nitroarenes with CO in the presence of alkenes with allylic hydrogen gives allyl amines (Eq. 11.55) [104].



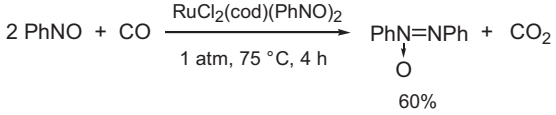
(11.55)

$Ru_3(CO)_{12}$ reacts with Ar-BIAN to give Ru(Ar-BIAN)$(CO)_3$, which in turn reacts with nitroarenes to give a Ru(Ar-BIAN)(nitrosoarene)$(CO)_2$ complex (Eq. 11.56) [104].



(11.56)

$Ru(II)Cl_2(cod)(PhNO)_2$, prepared by reacting $[RuCl_2(cod)]_n$ with nitrosobenzene, has been shown to be an active catalyst for the synthesis of azoxybenzene from nitrosoarene and carbon monoxide (Eq. 11.57) [105].

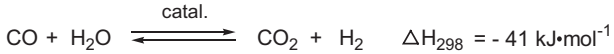


(11.57)

Syntheses of *N*-arylurethanes and *N,N′*-diarylureas for an approach to phosgene-free isocyanates could be accomplished by ruthenium complex-catalyzed dehydrogenative reactions of *N*-arylformamides, which are prepared by the carbonylation of aminoarenes (see Eq. 11.8), with alcohols [106] and aminoarenes [107], respectively.

11.2.11
Water-Gas Shift Reaction

The water-gas shift reaction (Eq. 11.58) is an industrially important equilibrium that controls the composition of hydrogen or CO in water-gas, syngas, or reformed gases.

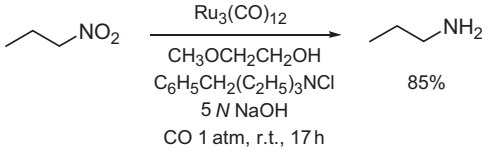


(11.58)

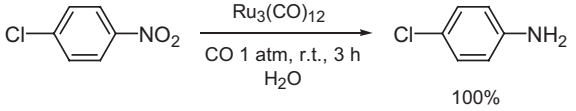
This reaction is slightly exothermic, and commercial plants operate with heterogeneous catalysts at elevated temperatures (200–450 °C) [108]. Quite recently, heterogeneous catalysts with ruthenium have been intensively studied to remove CO from the reformed gases for fuel cells [109].

On the other hand, several homogeneous transition metal complexes such as $Fe(CO)_5$, $FeH(CO)_4^-$, $Ru_3(CO)_{12}$, $[Ru(bipy)_2(CO)Cl]^-$, $FeH_2Ru_3(CO)_{13}$, K[Ru(H-EDTA)-(CO)], $[Rh(CO)_2I_2]^-$, and $Pt[P(i\text{-}Pr)_3]_3$, have been shown to catalyze the reaction at low temperature [108a]. Among them, ruthenium complexes are very efficient catalysts, and this reaction is used to reduce organic compounds without using molecular hydrogen.

Alkyl (Eq. 11.59) [99] and aryl (Eq. 11.60) [99, 110, 111] nitro compounds can be reduced to the corresponding amines in high yields under the water-gas shift reaction.



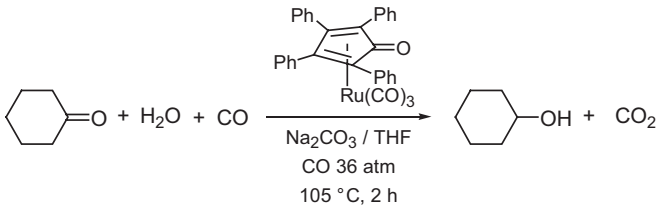
(11.59)



(11.60)

The hydroformylation of alkenes such as 1-pentene can be achieved under water-gas shift reaction conditions with ruthenium catalysts. Although the catalytic activity is not satisfactory, the n/i ratio of the produced alcohols is very high [112].

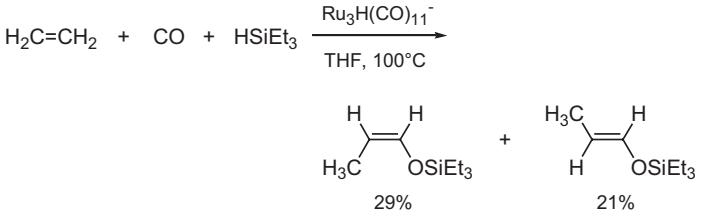
(η^4-Cyclopentadienone)(tricarbonyl)ruthenium(0) catalyzes the reduction of ketones under water-gas shift reaction conditions (Eq. 11.61) [113].



(11.61)

11.2.12
Reactions of Silanes with CO

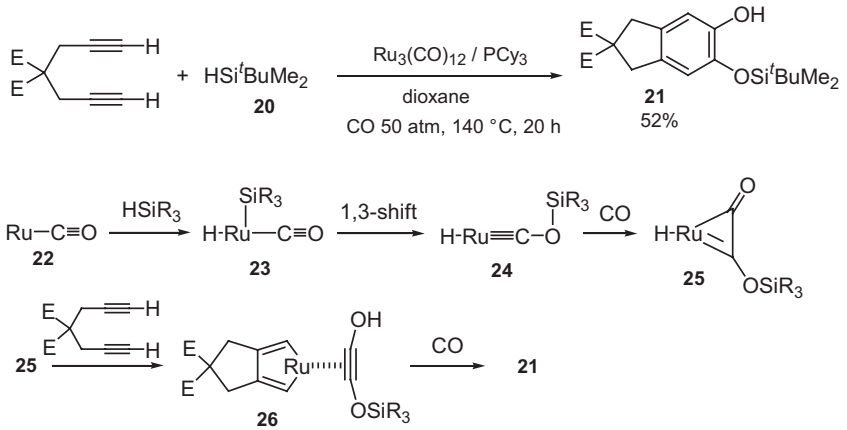
Terminal alkenes react with CO and trialkylsilane in the presence of transition metal catalysts to give the corresponding silyl enol ethers. $Ru_3(CO)_{12}$ and $Co_2(CO)_8$ each show high catalytic activity [114]. $Ru_3H(CO)_{11}^-$ [115] shows moderate catalytic activity with high selectivity for linear isomers (Eq. 11.62).



(11.62)

Interestingly, the reaction of 1,6-diynes with $HSiR_3$ **20** and CO catalyzed by $Ru_3(CO)_{12}/PCy_3$ gives catechol derivatives **21** [116]. A proposed reaction mechanism is also shown in Scheme 11.6.

The oxidative addition of trialkylsilane to the ruthenium carbonyl species **22** gives **23**, in which a 1,3-shift of R_3Si from the ruthenium to the carbonyl oxygen atom

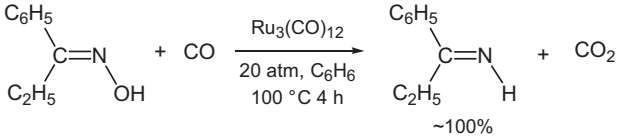


Scheme 11.6 Synthesis of catechols by the Ru-catalyzed reaction of 1,6-diynes with silane and CO.

gives the carbyne complex **24**. The insertion of CO into the ruthenium-carbon triple bond and a 1,3-hydrogen shift followed by the reaction with 1,6-diynes may give a siloxyhydroxyacetylene complex **26** via **25**, which in turn gives the products **21** via a [2 + 2 + 2] aromatization reaction.

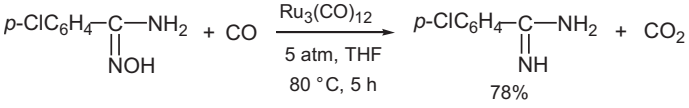
11.2.13 Miscellaneous Reactions

The reduction of ketoximes to ketimines can be performed with the $Ru_3(CO)_{12}$ catalyst under CO pressure (Eq. 11.63) [117].



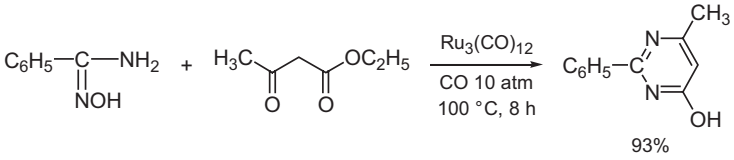
(11.63)

The reaction of amidoxime with CO using the $Ru_3(CO)_{12}$ catalyst gives amidines (Eq. 11.64) [118].



(11.64)

This reaction can also be applied to the synthesis of pyrimidines (Eq. 11.65) [118].



(11.65)

11.3
Reactions with Carbon Dioxide

11.3.1
Reduction of CO_2 to CO

The reduction of CO_2 to CO by molecular hydrogen – that is, the reverse water-gas shift reaction (RWGSR) (Eq. 11.66) – is an important process for using CO_2 via CO [4a,b,119]. Methanol (Eq. 11.67) [4b,120] or ethanol (Eq. 11.68) [4b,121] can each be synthesized from CO_2 using ruthenium catalysts.

$$CO_2 + H_2 \xrightarrow[[PPN]Cl]{Ru_3(CO)_{12}} CO + H_2O \tag{11.66}$$

$$CO_2 + 3\,H_2 \xrightarrow[KI]{Ru_3(CO)_{12}} CH_3OH + H_2O \tag{11.67}$$

$$2\,CO_2 + m\,H_2 \xrightarrow[KI]{Ru_3(CO)_{12}\,/\,Co_2(CO)_8} C_2H_5OH + n\,H_2O \tag{11.68}$$

11.3.2
Reduction of CO_2 to Formic Acid and its Derivatives

As described in Section 11.1, the transition metal-catalyzed hydrogenation of CO_2 to formic acid, methyl formate and *N,N*-dimethylformamide is a very attractive reaction with regard to CO_2 fixation to produce valuable chemicals on a large scale [4, 122].

Formic acid is a very important industrial chemical that is used as the simplest carboxylic acid and an organic reducing agent. Among transition metal complexes, ruthenium complexes have been found to be very efficient catalysts for the conversion for CO_2 to formic acid or formate.

In 1994, Noyori and coworkers discovered that $RuX_2(PMe_3)_4$ (X = H or Cl) are highly active catalysts for the hydrogenation of CO_2 to formic acid in a supercritical mixture of CO_2 (*sc*CO_2; *Tc* = 31 °C, *Pc* = 72.9 atm), H_2 and NEt_3. A turnover number (TON) of 7200 and a turnover frequency (TOF) of 1400 h^{-1} at 50 °C were achieved (Eq. 11.69) [123a].

$$sc CO_2 + H_2 + NEt_3 \xrightarrow[\substack{H_2\ 80\ atm,\ total\ 200\ atm\\ 50\ °C,\ 47\ h}]{RuCl_2(PMe_3)_4} \underset{\substack{TON\ 7,200\\ TOF\ 1,400\ h^{-1}}}{[HNEt_3]^+[HCO_2]^-} \tag{11.69}$$

Noyori's report had a major impact on research into the hydrogenation of CO_2, and many papers and reviews have subsequently been published on the subject. It should be noted that a trace amount of water or alcohol accelerates the reaction. This "water-effect" – which was first reported by Inoue and coworkers [124] – is often observed in the catalytic reduction of CO_2 with H_2.

The hydrogenation of CO_2 to formic acid is efficiently catalyzed by ruthenium complexes [125] such as *cis*-[Ru(6,6′-Cl_2bipy)$_2$(H_2O)$_2$][(CF_3SO_3)$_2$] [125a], TpRuH(PPh_3)(CH_3CN) (Tp = hydrotris(pyrazolyl)borate) [125b] in ethanol or RuH_2(CO)(PPh_3)$_3$ in ethanol/water [126]. Using the *cis*-[Ru(6,6′-Cl_2bipy)$_2$(H_2O)$_2$][(CF_3SO_3)$_2$] catalyst in ethanol, the TON was up to 5000 and the TOF was 625 h^{-1} at 150 °C.

The hydrogenation of CO_2 in water is an important topic in both industrial and environmental chemistries. Leitner and coworkers reported that RhCl(tppts)$_3$ (tppts = (C_6H_4-*m*-$SO_3^-Na^+$)$_3$P) is an efficient catalyst for the hydrogenation of CO_2 in water to form formate, with an initial TOF of 7260 h^{-1} at 81 °C and 1365 h^{-1} at 23 °C in the presence of $HNMe_2$ under 40 atm (CO_2/H_2 = 1/1) [122b,c].

[$RuCl_2$(tppms)]$_2$ [tppms = (C_6H_4-*m*-$SO_3^-Na^+$)(C_6H_5)$_2$P] was found to be an active catalyst under mild conditions without amine additives under 80 atm (CO_2/H_2 = 1/3) in 0.2–1.0 *M* aqueous $NaHCO_3$. Sodium formate (0.93 *M* HCO_2^-) was formed with a TON of 372 and a TOF of 27 h^{-1} at 24 °C (Eq. 11.70) [127]. Under the same reaction conditions, *trans*-[IrCl(CO)(tppms)$_2$] is also effective [127].

$$CO_2 + H_2 + NaHCO_3 \xrightarrow[80\ atm,\ H_2O,\ 24\ ^\circ C]{[RuCl_2(tppms)]_2} Na^+[HCO_2]^- \quad \text{TON 372, TOF 27 } h^{-1} \tag{11.70}$$

Methyl formate has been proposed to be a versatile intermediate in the synthesis of oxygenated base chemicals [128, 129]. One of the most interesting synthetic routes to methyl formate is the reduction of CO_2 with hydrogen in the presence of methanol. This reaction is exothermic, and has been referred to as the hydrocondensation of CO_2 with methanol. Since the first report of a successful transition metal-catalyzed reaction by a Russian group [130], several other reports have been published. However, the catalytic activity (i.e., the TOF) has not been satisfactory.

[$Ru(CO)_3Cl_3$]$^-$ [131] and anionic ruthenium carbonyl clusters such as $Ru_3H(CO)_{11}^-$, $Ru_3(OCOH)(CO)_{10}^-$, and $H_3Ru_4(CO)_{12}^-$ [132] each catalyze the hydrogenation of CO_2 in methanol to form methyl formate. When $Ru_3H(CO)_{11}^-$ is used as a catalyst at 125 °C, the TON was raised to 7.3 and the TOF was 0.3 h^{-1}. Even though this catalytic activity is low, a careful analysis of the catalytic activities of the clusters and recovered complexes after the reaction suggested that $H_3Ru_4(CO)_{12}^-$ is a catalytically active species [132].

In the presence of methanol, *sc*CO_2 can be hydrogenated to methyl formate with the $RuCl_2(PMe_3)_4$ catalyst. At 80 °C the TON was 3500, and formic acid was also formed (TON = 6800) (Eq. 11.71) [123c].

$$sc\ CO_2 + H_2 + CH_3OH \xrightarrow[H_2\ 80\ atm,\ total\ 200\ atm,\ 80\ ^\circ C,\ 64\ h]{RuCl_2(PMe_3)_4} HCO_2CH_3\ (TON\ 3{,}500) + HCO_2H\ (TON\ 6{,}800) \tag{11.71}$$

Since 1970, when Haynes reported the first example of the reduction of CO_2 with H_2 in the presence of amines and rhodium catalyst to give formamides [133], several other reports have been published on the preparation of formamides [135–137].

In 1994, Noyori and coworkers reported that the formation of DMF from *sc*CO_2, H_2, and dimethylamine was successfully catalyzed by $RuCl_2(PMe_3)_4$, with a TON of up to 370 000 within 37 h (Eq. 11.72) [123c, 138]. This TON value is greater than the largest TON of 3400 for the formation of DMF from CO_2 in a conventional liquid solvent, as reported by Kiso and Saeki [135].

$$CO_2 + H_2 + HN(CH_3)_2 \xrightarrow[sc\ CO_2]{RuCl_2(PMe_3)_4} HCON(CH_3)_2 + H_2O \quad \begin{matrix}\text{TON 370,000}\\ \text{TOF 10,000 h}^{-1}\end{matrix} \tag{11.72}$$

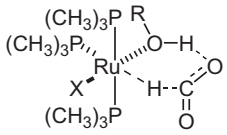
The reaction proceeds in two steps: the formation of formic acid (Eq. 11.73), which is catalyzed by a ruthenium complex, and the reaction of formic acid with dimethylamine (Eq. 11.74).

$$CO_2 + H_2 \xrightarrow{\text{Ru catalyst}} HCO_2H \tag{11.73}$$

$$HCO_2H + HN(CH_3)_2 \longrightarrow HCON(CH_3)_2 + H_2O \tag{11.74}$$

The high rate of the reaction in *sc*CO_2 is attributed to rapid diffusion, weak catalyst solvation, and the high miscibility of H_2 in *sc*CO_2. The key step in the catalytic cycle of the reaction in Eq. 11.71 may be the insertion of CO_2 into the Ru-H bond assisted by water or alcohol to form the formato complex $RuX(O_2CH)(ROH)L_3$ **27**. Hydrogenolysis of the Ru-O_2CH bond in **27** by molecular hydrogen leads to the formation of formic acid, and regenerates the catalytic species. Hydrogenolysis would be considerably accelerated under supercritical conditions because of the high concentration of H_2.

Water and methanol each promote the reaction. This promoting effect can be explained by coordination of the water or methanol to the metal, which stabilizes the key intermediate **28** by hydrogen bonding during CO_2 insertion.



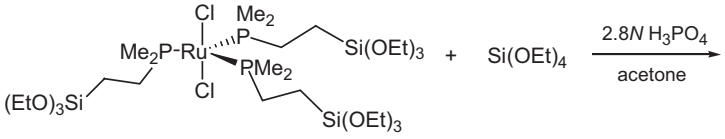
28

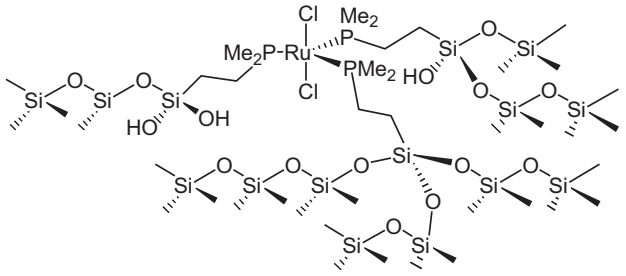
In 1997, Baiker and coworkers reported that $RuCl_2(dppe)_2$ is an excellent catalyst for the reaction of CO_2 with H_2 and $HN(CH_3)_2$ to give DMF, with a TON and TOF of 740 000 and 360 000 h^{-1}, respectively (Eq. 11.75) [139]. Changing the CO_2 pressure from 85 atm to 18 atm reduced the activity from 360 000 h^{-1} to 150 000 h^{-1}. The authors claimed that this result indicates that supercritical conditions may not be necessary for high catalytic activity.

$$CO_2 + H_2 + HN(CH_3)_2 \xrightarrow[\begin{matrix}H_2\ 85\ atm\\ CO_2\ 130\ atm\\ 100\ °C\end{matrix}]{RuCl_2(dppe)_2} HCON(CH_3)_2 \quad \begin{matrix}\text{TON 740,000}\\ \text{TOF 360,000 h}^{-1}\end{matrix} \tag{11.75}$$

Methyl formate was also synthesized in the presence of CH_3OH, with a TON of 12 900 and TOF of 830 h^{-1}. The catalytically active species has been proposed to be $[RuHCl(dppe)_2]$ [139].

The immobilization of Groups 8 and 9 metal complexes by silica hybrid gel has been successfully performed using the Sol-Gel process (Eq. 11.76) [140]. A ruthenium-containing gel catalyst derived from $RuCl_2[PMe_2(CH_2)_2Si(OEt_3)_3]_3$ and $Si(OEt)_4$ showed high catalytic performance for the preparation of DMF. The TON and TOF values were 110 800 and 1860 h^{-1}, respectively, which were the highest values among the heterogeneous catalysts. For the synthesis of methyl formate, TOFs of up to 115 h^{-1} were achieved [140].





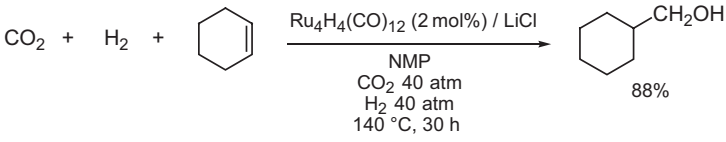
(11.76)

11.3.3

Hydroformylation of Alkenes with CO_2

The hydroformylation of alkenes using CO_2 instead of CO is an attractive target reaction. Since ruthenium complexes are active catalysts for the reduction of CO_2 to CO and also for hydroformylation, it is expected that the hydroformylation of an alkene with CO_2 would be successful. Indeed, Sasaki and coworkers found that $Ru_4H_4(CO)_{12}$/LiCl catalyzed the hydroformylation of cyclohexene to give (hydroxymethyl)cyclohexane in 88% yield [141].

In the hydroformylation of terminal alkene, hydrogenation proceeds and a considerable amount of alkane is formed, together with oxo alcohols (Eq. 11.77).



(11.77)

11.3.4
Reduction of CO_2 with Silanes

Although the transition metal-catalyzed hydrosilylation of carbonyl compounds has been studied extensively, few reports have been made on the hydrosilylation of CO_2, and ruthenium complexes such as $RuCl_3 \cdot nH_2O$ in CH_3CN [142], $RuCl_2(PPh_3)_3$ [143] and $[Ru_3H(CO)_{11}]^-$ [144] have been shown to catalyze the reaction to give silyl formate (Eq. 11.78).

$$CO_2 + HSiCH_3(C_2H_5)_2 \xrightarrow[100\ ^\circ C,\ 20\ h]{RuCl_2(PPh_3)_3\ (1\ mol\%)} \underset{14\%}{HCO_2SiCH_3(C_2H_5)_2} \qquad (11.78)$$

11.3.5
Electro- and Photochemical Reduction of CO_2

Organic synthesis via transition metal complex-catalyzed electrochemical and photochemical reduction of CO_2 has been developed [2, 122b, 145–147]. Among transition metal complexes, ruthenium bipyridine complexes show high catalytic activity; a typical reaction is shown in Eq. 11.79. $[Ru(bpy)_2(CO)_2]^{2+}$ and $[Ru(bpy)_2(CO)Cl]^+$ efficiently catalyze the electrochemical reduction of CO_2 to CO and HCO_2^-. The nature of the products is dependent upon the pH of the solution. A catalytic cycle involving $[Ru(bpy)_2(CO)]^0$, $[Ru(bpy)_2(CO)(CO_2^-)]^+$ and $[Ru(bpy)_2(CO)CO_2H]^+$ was proposed (Eq. 11.79) [146l].

$$CO_2 + e^- \xrightarrow[bpy = 2,2'\text{-bipyridine}]{[Ru(bpy)_2(CO)_2]^{2+}} CO + HCO_2^- \qquad (11.79)$$

$Ru(bpy)(CO)_2Cl_2$, $[Ru(bpy)(CO)_2(CH_3CN)_2]^{2+}$ and $[Ru(bpy)(CO)Cl_3]^-$ were also found to be effective catalysts [147].

Tanaka and coworkers found that carbon-carbon bond-forming reactions take place during the ruthenium complex-catalyzed electrochemical reduction of CO_2 [146g, 146h]. For example, the electrochemical reduction of CO_2 by $[Ru(trpy)(CO)L]^{2+}$ (trpy = 2,2′:6′2″-terpyridine) at –1.50 V (versus SCE) produces not only HCO_2H and CO but also HCHO, CH_3OH, HOOCCHO and $HOCH_2CO_2H$ in CH_3CN/H_2O at –20 °C. A mechanism via Ru-η^1-CO_2, Ru-CO_2H, RuCO, RuCHO and $RuCH_2OH$ intermediates is proposed (Eq. 11.80) [146g].

$$CO_2 + e^- \xrightarrow[\substack{-1\text{-}50\ V\ (vs\ SCE)\\ CH_3CN/H_2O,\ -20\ ^\circ C\\ trpy = 2,2':6',2''\text{-terpyridine}}]{[Ru(trpy)(CO)L]^{2+}} \begin{array}{l} HCO_2H,\ CO + HCHO \\ CH_3OH,\ HOOCCHO \\ HOCH_2CO_2H \end{array} \qquad (11.80)$$

The electrochemical reduction of CO_2 catalyzed by $[Ru(bpy)_2(qu)(CO)]^{2+}$ (qu = quinoline) in the presence of $(CH_3)_4N^+$ or CH_3I in dry CH_3CN produces CH_3COCH_3, $CH_3COCH_2CO_2^-$ and HCO_2^-. The four-carbon component $CH_3COCH_2CO_2^-$ is derived from acetone via a carboxylation reaction by $[Ru(bpy)_2(qu)(CO)]^{2+}$ [146e,f].

Acetone is formed by the double-alkylation of $[Ru(bpy)_2(L)(CO)]^{2+}$ (L = quinoline [146e] or naphthyridine [146d]) with CH_3I or $(CH_3)_4N^+$ (Eq. 11.81).

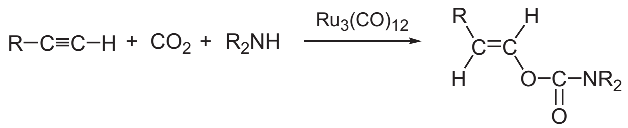
$$CO_2 + e^- + \begin{matrix}(CH_3)_4N+ \\ \text{or} \\ CH_3I\end{matrix} \xrightarrow[\text{qu = quinoline}]{[Ru(bpy)_2(qu)(CO)L]^{2+}} CH_3COCH_3 + CH_3COCH_2CO_2^- \quad (11.81)$$

In the photochemical reduction of CO_2, ruthenium complexes show efficient catalytic activity [148]. Simultaneous photogeneration of CO and H_2 takes place by the visible-light irradiation of systems containing the $[Ru(bpy)_3]^{2+}$ complex as a photosensitizer, the Co(II) species as a homogeneous catalyst, which mediates CO_2 and H_2O reduction via the formation of a Co(I) intermediate, and tertiary amines as electron donors (Eq. 11.82) [148b].

$$CO_2 + H_2O \xrightarrow[Et_3N]{\begin{matrix}[Ru(bpy)_3]^{2+} / Co(II) \\ h\nu \text{ (1000 W Xe-Hg lamp)}\end{matrix}} CO + H_2 \quad (11.82)$$

11.3.6
Addition of Carbamic Acid to Alkynes

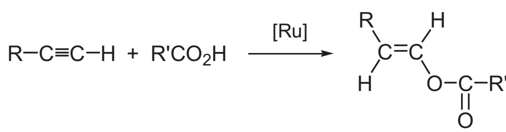
In 1986, Sasaki and Dixneuf reported the first example of the $Ru_3(CO)_{12}$-catalyzed formation of vinyl carbamate from terminal acetylene, CO_2 and secondary amines (Eq. 11.83) [149, 150].



(11.83)

Since CO_2 and R_2NH give carbamic acid and its salts, this reaction is an extension of the addition of carboxylic acids [151] to terminal acetylenes to give enol ester catalyzed by ruthenium complexes (Eqs. 11.84 and 11.85).

$$CO_2 + R_2NH \rightleftharpoons R_2NCO_2H \xrightarrow{R_2NH} [R_2NH_2]^+[R_2NCO_2]^- \quad (11.84)$$



(11.85)

Dixneuf suggested that this reaction proceeds via the nucleophilic attack of a carbamate anion to the ruthenium vinylidene intermediate generated by the reaction of ruthenium complexes with terminal acetylene. The details of this reaction are discussed in Chapter 8.

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12
Isomerization of Organic Substrates Catalyzed by Ruthenium Complexes

Hiroharu Suzuki and Toshiro Takao

12.1
Introduction

The catalysis of organic reactions is one of the most important applications of transition metal complexes, and has attracted the considerable attention of organometallic chemists. Typical reactions that are catalyzed by many transition metal complexes are hydrogenation, polymerization, cross-coupling, and isomerization. Among them, isomerization must be useful and efficient for transformation of functionalized organic compounds because the number of the functional groups generally remains unchanged, both before and after the reaction. This chapter focuses on the recent development of the ruthenium complex-catalyzed alkene isomerization and skeletal rearrangement of enynes and dienes, and racemization of secondary alcohols. In addition, a recent topic – olefin isomerization promoted by Grubbs' catalyst – is mentioned in the final section of the chapter.

The two established pathways for transition metal-catalyzed alkene isomerization are the π-allyl metal hydride and the metal hydride addition-elimination mechanisms. The metal hydride addition-elimination mechanism is the more common pathway for transition metal-catalyzed isomerization. In this mechanism, free alkene coordinates to a metal hydride species. Subsequent insertion into the metal-hydride bond yields a metal alkyl. Formation of a secondary metal alkyl followed by β-elimination yields isomerized alkene and regenerates the metal hydride. The π-allylhydride mechanism is the less commonly found pathway for alkene isomerization. Oxidative addition of an activated allylic C–H bond to the metal yields a π-allyl metal hydride. Transfer of the coordinated hydride to the opposite end of the allyl group yields isomerized alkene.

The fundamental differences between these two mechanisms are that: 1) the π-allyl metal hydride mechanism involves a 1,3-hydrogen shift while the metal hydride addition-elimination mechanism involves a 1,2-hydrogen shift; and 2) the hydrogen shift in the π-allylhydride mechanism proceeds in an intramolecular fashion while that in the metalhydride addition-elimination mechanism proceeds in an intermolecular fashion.

Generally, the product favors a thermodynamic equilibrium mixture of isomeric alkenes in case there are no functional groups capable of conjugation with the car-

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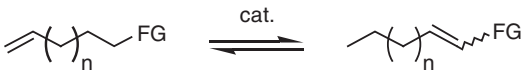
bon-carbon double bond. When there is a functional group (FG), such as an alkoxyl group or a hydroxyl group, in the molecule, the C=C group regioselectively moves along the chain of the molecule to the position adjacent to the functional group.



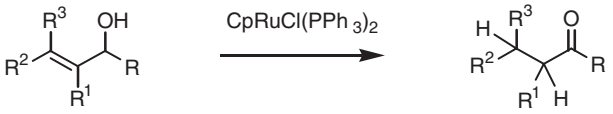
FG: functional group

(12.1)

12.2 Isomerization of Alkenyl Alcohols to Aldehydes and Ketones

Although thus far a number of reports have been made on ruthenium complex-catalyzed isomerization of alkenyl alcohols to saturated aldehydes or ketones, the mechanistic details of these reactions have not yet been fully elucidated. It has been generally accepted that isomerization of the alkenyl alcohol forming a carbonyl compound proceeds via an intermediate enol. However, developments in mechanistic studies have advanced recently, and a new mechanism which involves an intermediary ruthenium alkenylalkoxide is proposed by Trost et al. for isomerization of allylic alcohols catalyzed by $CpRuCl(PPh_3)_2$ ($Cp = \eta^5\text{-}C_5H_5$) [1]. Grubbs et al. also proposed a modified metal hydride addition-elimination mechanism which involves 1,3-hydrogen shifts [2].

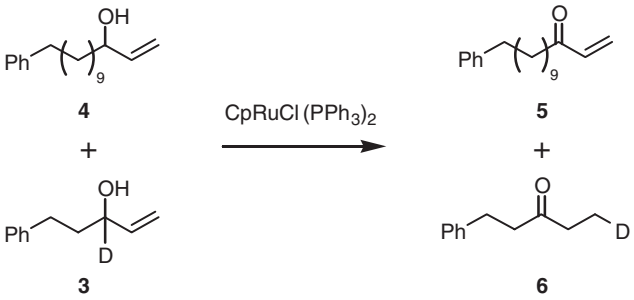
Chloro(cyclopentadienyl)bis(triphenylphosphine)ruthenium, $CpRuCl(PPh_3)_2$, effectively catalyzes isomerization of allylic alcohols **1** to saturated carbonyl compounds **2**, aldehydes or ketones, in the presence of NH_4PF_6 (Eq. 12.2).



1 **2**

(12.2)

The use of an indenyl complex as catalyst instead of the cyclopentadienyl analogue enhances the reactivity due to the opening of a coordination site by valence tautomerization. The reaction is highly chemoselective, and nonallylic alcohols and allyl ethers are not isomerized (Eq. 12.3).



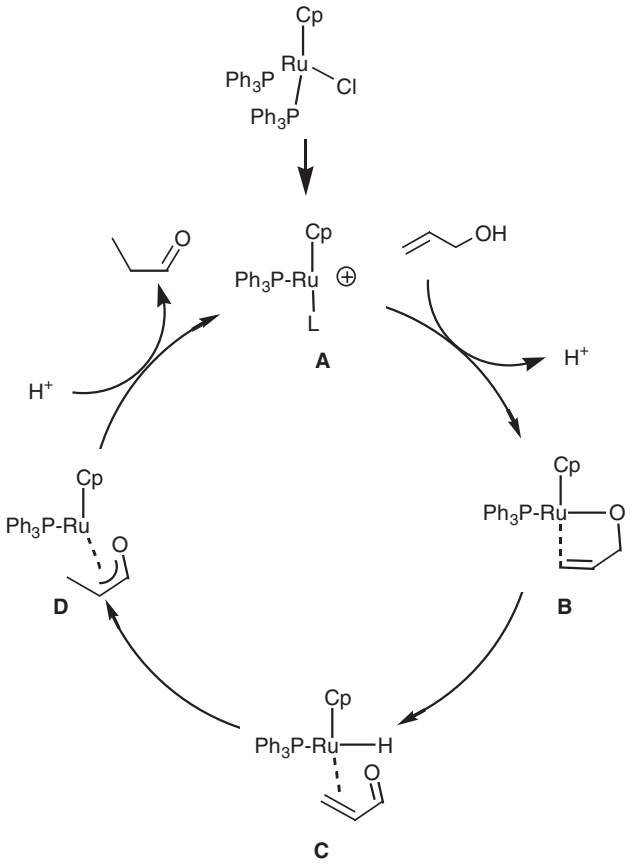
(12.3)

A crossover experiment using **3** and **4** under standard conditions demonstrated the intramolecularity of this hydrogen shift. Intramolecularity of the isomerization and the 1,3-hydrogen shift strongly indicates that the reaction proceeds via the π-allyl metal hydride mechanism as depicted in Scheme 12.1.

Allylic alcohols are isomerized via direct interaction of the ruthenium atom with alcohol. β-Elimination of ruthenium hydride from metal alkoxide yields a ruthenium-enone species **C** which undergoes insertion of the olefinic moiety into the Ru-H to form an oxyallylic intermediate **D**. As a result, the hydrogen atom shifts from the α- to γ-position of the allylalcohol. Protonolysis of the oxyallylic species leads to a saturated carbonyl compound and cationic unsaturated species, $[CpRu(PPh_3)_2]^+$ **A**.

The fact that allylic ethers are not isomerized to the corresponding enol ethers by this catalytic system is clearly consistent with the above mechanism involving the metal alkoxide intermediate.

Substitutionally labile complexes of the type $[CpRu(PR_3)(CH_3CN)_2]PF_6$ (R = Ph, Cy) **7** [3] greatly improve catalytic performance for the isomerization of allylic alcohols, $R^2HC{=}CHC(OH)HR^1$ [4]. The turnover number (TON) and turnover fre-



Scheme 12.1

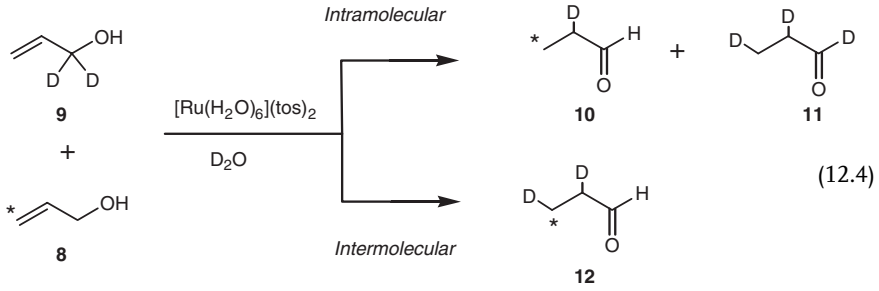
quency (TOF) for the isomerization of allylalcohol to propanal is found to be 1800 and 21 500 h^{-1}, respectively. However, these catalysts tolerate only a limited substitution pattern on the substrate. Only in the case of R^1 = H or alkyl, R^2 = H or Ph, does the reaction give satisfactory results.

Limitations of the reaction due to the substitution pattern of the allylic alcohols were overcome by the use of tetrapropylammonium perruthenate (TPAP) as a catalyst and monosubstituted, disubstituted and trisubstituted allyl alcohols were converted into the corresponding saturated aldehydes and ketones [5]. Intermediacy of the ruthenium alkoxide in this reaction was evidenced from the complete lack of reactivity of the trimethylsilyl ether derived from the allylic alcohol.

Although isomerization of common allylic alcohols to saturated carbonyl compounds by the use of slightly improved ruthenium catalysts, such as CpRuCl(dppb) and $RuH_2(PBu_3)_4$, have been reported recently [6, 7], there is nothing further to add to the outcome produced by Trost et al. as regards the mechanism.

The first example of fully aqueous metal catalysis of olefin isomerization was reported by Grubbs et al. in 1994 [2]. These authors adopted $[Ru(H_2O)_6](tos)_2$ (tos = *p*-toluenesulfonate) [8] as a catalyst, which is highly active for the ring-opening polymerization of strained cyclic olefin. Both allylic alcohol and allylic ethers undergo isomerization in the presence of $[Ru(H_2O)_6](tos)_2$.

The intra/intermolecularity of the allylic alcohol isomerization has been investigated through a $^{13}C/^{2}H$ crossover labeling study employing allyl-3-^{13}C alcohol **8**, allyl-1,1-d_2 alcohol **9**, and D_2O (Eq. 12.4).

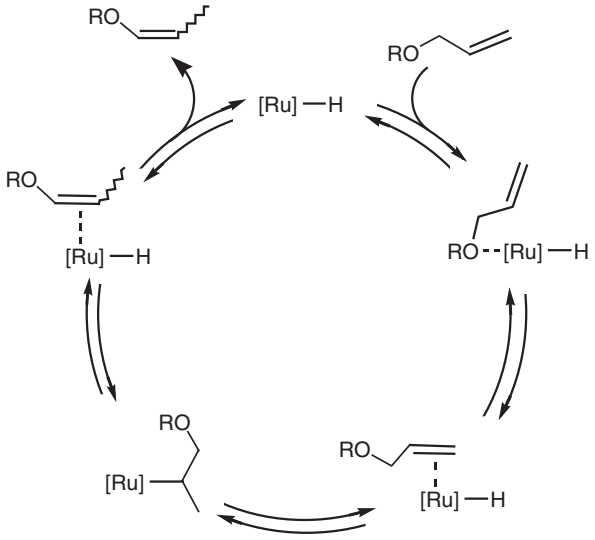


(12.4)

The crossover product, propionaldehyde-1,3-*d*-3-^{13}C **12**, clearly demonstrated that the isomerization occurred via intermolecular 1,3-hydrogen shift. These results are consistent with a modified metal hydride addition-elimination mechanism which involves exclusive 1,3-hydrogen shift through oxygen-directed Markovnikov addition of the metal hydride to the carbon-carbon double bond (Scheme 12.2). The directing effect of functional groups on the selectivity of transition metal catalysis is well presented [9], and an analogous process appears to be operative in the isomerization of allylamines to enamines [10].

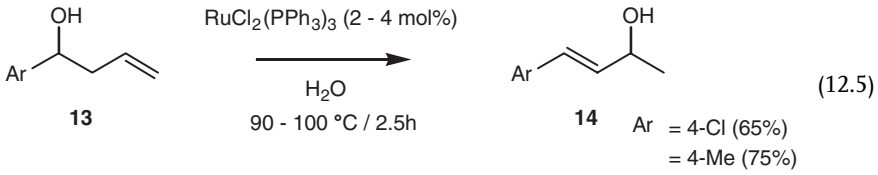
A transition metal cluster complex $[Ru_3H(CO)_{11}]^-$ catalyzes isomerization of allylic alcohols to saturated aldehydes [11].

A novel type of isomerization of alkenyl alcohol, repositioning of the carbon-carbon double bond, is catalyzed by $RuCl_2(PPh_3)_3$. In the presence of a catalytic amount



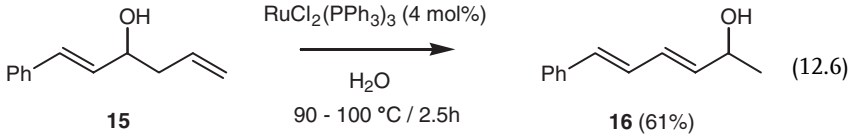
Scheme 12.2

of $RuCl_2(PPh_3)_3$, homoallylic alcohols and allylic alcohols undergo structural reorganization in which both the hydroxyl group and the olefin have been reshuffled (Eq. 12.5) [12].



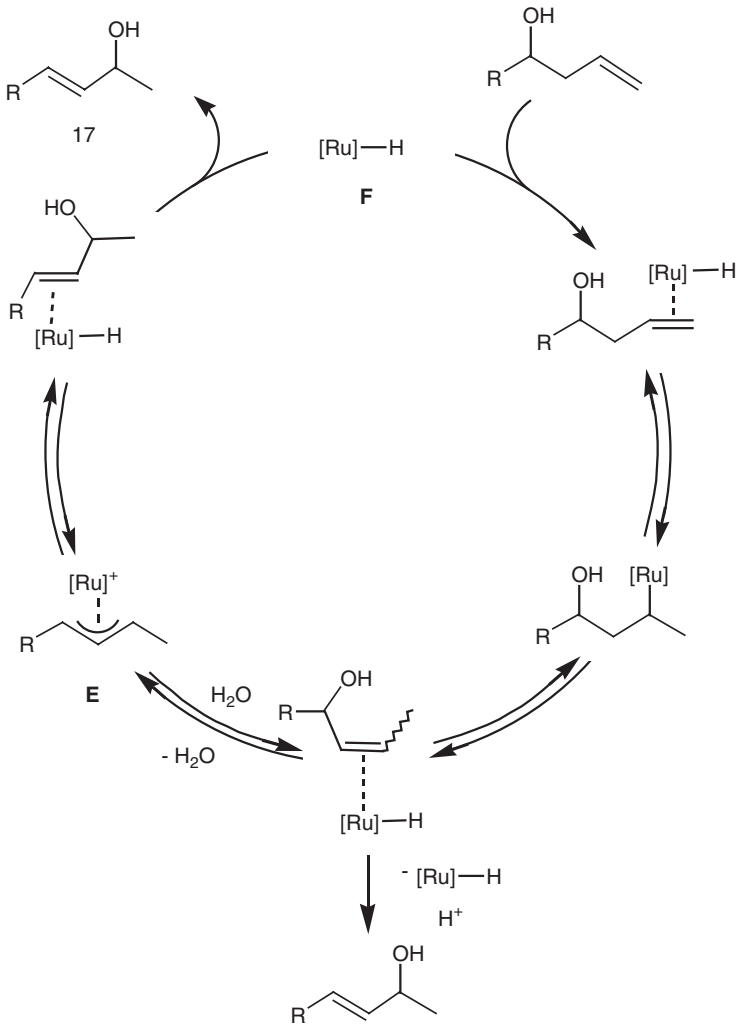
(12.5)

In the reaction of alcohol **15** in which both an allylic and a homoallylic functional groups are involved, the reaction occurs exclusively by rearrangement of the homoallylic group to give the conjugated dienol **16** (Eq. 12.6).



(12.6)

This reaction is unique, but is applicable to a limited substitution pattern on the substrate. Only in the case of R = aryl, the corresponding product is obtained cleanly. For this reaction, a catalytic cycle involving an intermediary π-allyl-ruthenium species is proposed (Scheme 12.3).

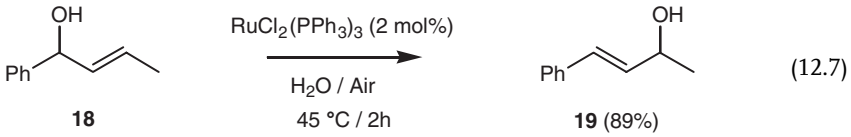


Scheme 12.3

π-Allylruthenium species **E** is formed through carbon-oxygen bond cleavage of the allylic alcohols. Attack of the π-allyl complex by H_2O gives the stable final product **17** and regenerates the catalyst **F**.

This catalytic system is also applicable to isomerization of allylic alcohols. Under reaction conditions which are the same as, or milder than, those for the rearrangement of homoallylic alcohols, the allylic alcohols isomerized rapidly [12b].

The driving force of these catalytic reactions is probably stabilization due to conjugation between the carbon-carbon double bond and the aryl group (Eq. 12.7).

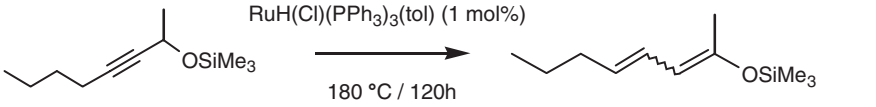


18 **19** (89%) (12.7)

12.3
Isomerization of Propargyl Alcohols and Ethers

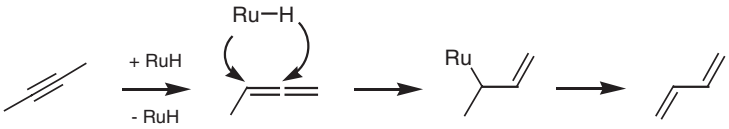
Ruthenium hydride complexes such as $RuH(Cl)(PPh_3)_3(tol)$ (*tol* = toluene) and $RuH(Cl)(CO)(PPh_3)_3$ can effect isomerization of propargyl alcohols and propargyl ethers to α,β-unsaturated carbonyl compound and dienol ether, respectively [13].

Acetylenic silyl ethers are converted to the conjugated dienol silyl ethers by the catalysis of ruthenium hydride complexes (Eq. 12.8).



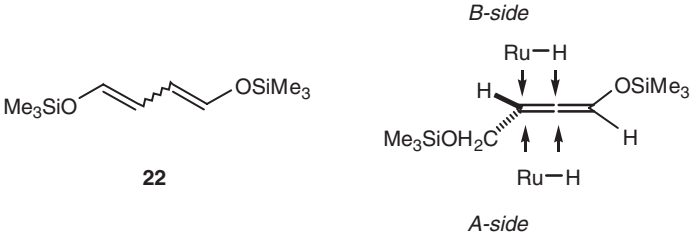
20 **21** (100%) (12.8)

For this reaction, a mechanism involving the addition-elimination of the ruthenium hydride is proposed. Allene derivatives are probably formed in the initial stage and the subsequent addition of the ruthenium hydride to the allene followed by the elimination of the ruthenium hydride forms a 1,3-diene derivative, which is stabilized due to conjugation with the siloxy group (Scheme 12.4).



Scheme 12.4

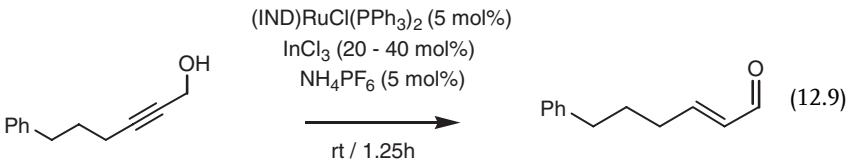
In the reaction of dienol silyl ether derived from butyn-1,4-diol, conjugated dienol silyl ether **22** was obtained as a 1:1 mixture of (*Z*,*Z*) and (*Z*,*E*) stereo isomers. The



22

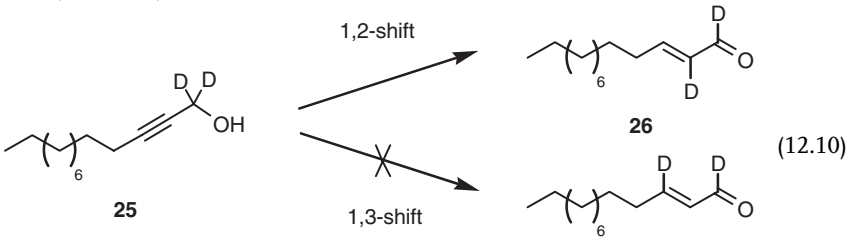
formation of the 1:1 mixture of (*Z*,*Z*) and (*Z*,*E*) isomers is reasonably explained by a face-selective addition of the ruthenium hydride to the intermediary allenyl silyl ether from side A, the opposite side of the siloxy group at C1 with respect to a plane defined by C2, C3, and C4. This is probably due to steric repulsion between the siloxy group and the ruthenium hydride species.

In contrast to the reaction mode of the propargyl ethers, α,β-unsaturated aldehydes and ketones are isolated in the catalytic isomerization of the propargyl alcohols. Trost et al. developed a new catalytic system, (IND)$RuCl(PPh_3)_2$/$InCl_3$/NH_4PF_6/THF (IND = η^5-indenyl), that efficiently effected such isomerization [14]. The reaction is cocatalyzed by a mixture of $NHEt_3PF_6$ and NH_4PF_6, and addition of indium trichloride accelerates the reaction (Eq. 12.9).



23 **24** (88%) (12.9)

The reaction exhibits extraordinary chemoselectivity and an isolated carbonyl group, ester, unprotected alcohol, alkyne and terminal alkene are unaffected by this catalytic system. Notably, the geometry of the resulting alkene moiety is controlled to be *E* (Eq. 12.10).

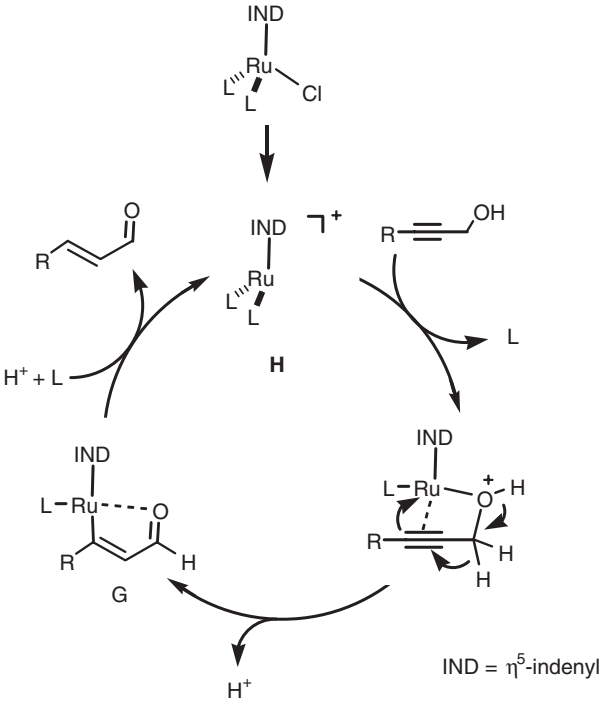


25 **26** **27** (12.10)

The mechanism of the isomerization was probed by using the deuterated propargyl alcohol **25**. The labeling pattern in the produced α,β-enone **26** showed that the isomerization proceeded via a 1,2-shift of a hydrogen atom attached at the propargylic carbon. On the basis of these results, a mechanism was proposed as depicted in Scheme 12.5.

The 1,2-hydrogen shift on the propargyl carbon concomitant with elimination of the proton from the hydroxyl group generates a vinylruthenium species **G**, which probably undergoes protonolysis to yield the conjugated aldehyde and unsaturated cationic ruthenium complex **H**.

A similar reaction was reported by Ma et al. in preference to Trost's work [15]. In the isomerization of 2-ynols to α,β-unsaturated aldehydes, the combination of a ruthenium catalyst, $RuCl_2(PPh_3)_3$, and 2 equiv. of an aliphatic phosphine ligand, such as P^nBu_3 or P^iPr_3, is effective.

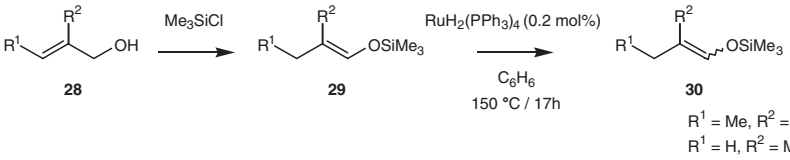


Scheme 12.5

12.4 Isomerization of Functionalized Alkenes

Isomerization of the functionalized olefins has, thus far, been applied to the efficient preparation of synthetic intermediates such as enol ethers and enamines [16].

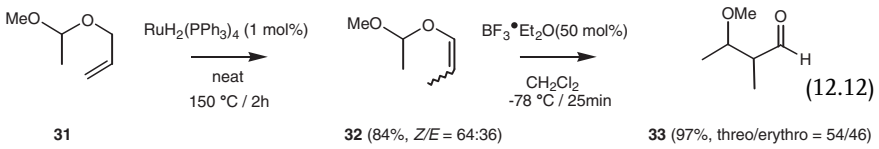
Allyl silyl ethers **29** derived from the corresponding allylic alcohols **28** are selectively isomerized to silyl enol ethers **30** via carbon-carbon double bond migration catalyzed by a ruthenium hydride complex, $RuH_2(PPh_3)_4$ (Eq. 12.11) [17]. The generality of the reaction was demonstrated for the silyl ethers of methallyl alcohol, cinnamyl alcohol, 2,4-pentadienyl alcohol, and so on.



(12.11)

Irrespective of the starting allylic silyl ethers, the products are a thermodynamically equilibrated mixture of *Z* and *E*-stereo isomers, and the *Z*/*E*-isomers ratio is in the range from 1.2 to 1.8.

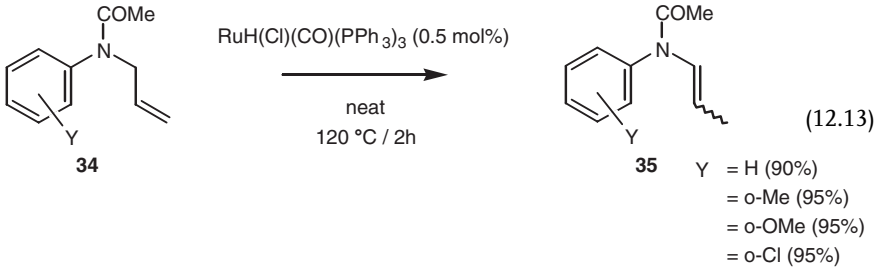
Ruthenium hydride-catalyzed carbon-carbon double bond migration is applicable to isomerization of allylic acetals and ketals **31** to vinylic ones **32**, which undergo selective cross-aldol type reaction by treatment with BF_3-Et_2O to yield **33** (Eq. 12.12) [18].



(12.12)

31 **32** (84%, *Z*/*E* = 64:36) **33** (97%, threo/erythro = 54/46)

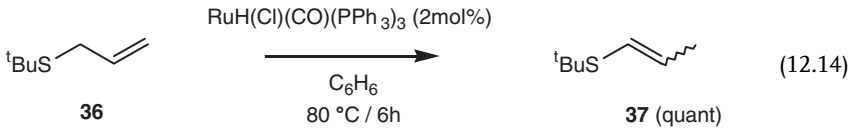
Isomerization of *N*-allyl amide to *N*-propenyl amide is a key step of the deprotection of an amino group. (*E*)-*N*-Aryl-*N*-(1-propenyl)ethanamides **35** are obtained via the double bond migration of *N*-aryl-*N*-allylamide **34** catalyzed by a ruthenium hydride complex [19]. The configuration of the *N*-propenyl moiety in the product is almost *E*, and the high *E* selectivity is probably due to the steric repulsion between the aryl group and the methyl substituent of the propenyl group (Eq. 12.13).



(12.13)

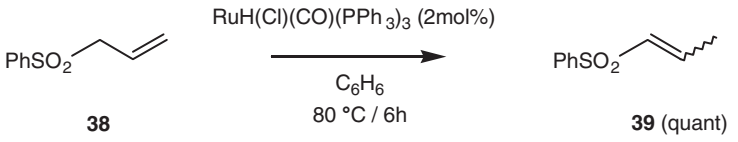
34 **35** Y = H (90%)
= o-Me (95%)
= o-OMe (95%)
= o-Cl (95%)

There are few reports of the transition metal complex-catalyzed isomerization of S-allyl sulfides and sulfones. This is clearly a consequence of the very strong coordinating ability of sulfur atoms and the resulting tendency for S-C (allyl) bond cleavage. In the case of a bulky substituent being present at the sulfur atom, the isomerization to 1-propenyl derivatives is successful (Eqs. 12.14 and 12.15) [20].



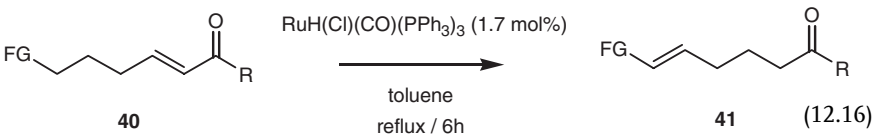
(12.14)

36 **37** (quant)



38 **39** (quant) (12.15)

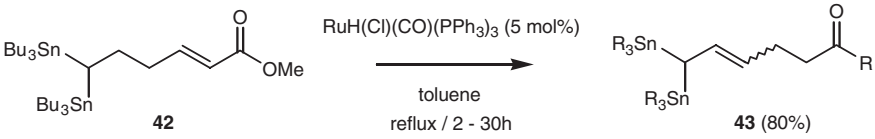
When an α,β-unsaturated carbonyl compound having a functional group at an appropriate position in a tether is treated with $RuH(Cl)(CO)(PPh_3)_3$ the double bond migrates from the α,β-position of the carbonyl group to the position conjugated with the functional group (Eq. 12.16) [21].



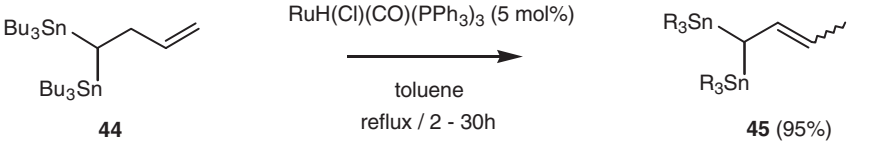
40 **41** (12.16)

FG = BnO, R = OMe (79%)
FG = TBDPSO, R = Ph (79%)

Alkene, alkyne, alkoxyl and siloxyl groups can be used as the functional moiety. Compounds having conjugation between a carbon-carbon double bond and the above-mentioned functional groups is likely to be thermodynamically more stable than the α,β-unsaturated carbonyl compound, and stabilization due to conjugation of the carbon-carbon double bond with the functional group is, therefore, the driving force of the isomerization. Trialkylsilyl and trialkylstannyl groups also stabilize olefin due to σ,π-conjugation (Eqs. 12.17 and 12.18).



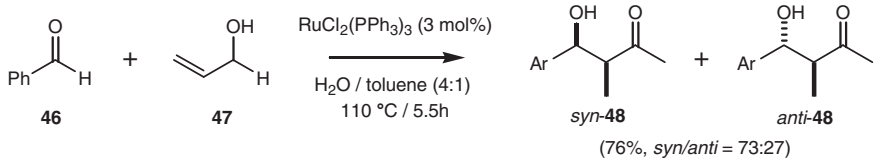
42 **43** (80%) (12.17)



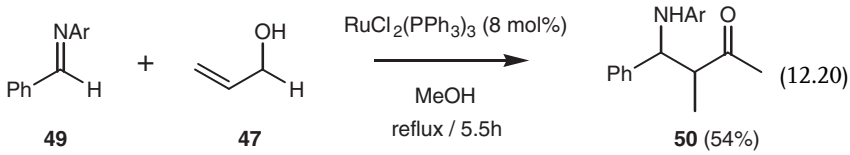
44 **45** (95%) (12.18)

Intermediary ruthenium-enol and -enol ether complexes generated in the isomerization of allylic alcohols and allylic ethers are often used as they are for the subsequent transformation.

Cross-coupling between allylic alcohol and aldehyde is efficiently catalyzed by $RuCl_2(PPh_3)_3$ in water to form an aldol-type product **48** [22]. This reaction has limitations in the substituents of the aldehydes, and the use of aliphatic aldehydes provides complicated mixtures. Cross-coupling of imines with allylic alcohols under similar conditions generates Mannich-type reaction products **50** as major products, together with aldol-type products **48** [22]. The selectivity of the reaction was improved by using methanol as the solvent, whereupon no aldol-type product was observed (Eqs. 12.19 and 12.20).

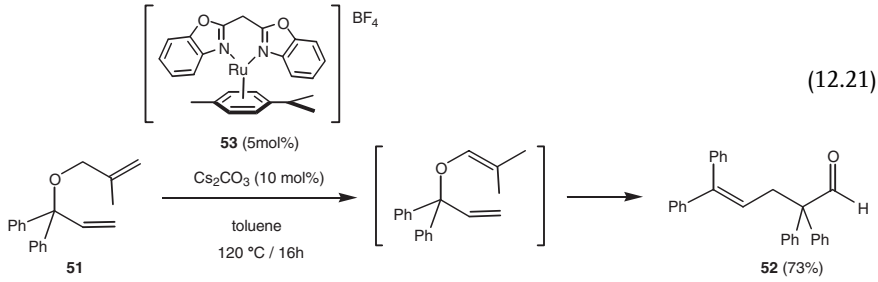


46 **47** (12.19)



49 **47** **50** (54%) (12.20)

Catalytic tandem isomerization/Claisen reaction of bis allyl ether was reported by Dixneuf et al. [23]. A cationic bis-oxazoline-ruthenium-arene complex **53** in the presence of both 1,3-bis(2,6-diisopylphenyl)imidazolinium chloride and Cs_2CO_3 catalyzes the selective transformation of bis-allyl ether **51** into γ,δ-unsaturated aldehyde **52** via successive alkene isomerization and Claisen rearrangement (Eq. 12.21).



53 (5mol%)

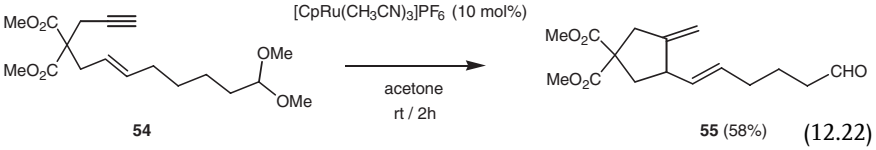
51 **52** (73%) (12.21)

12.5
Cycloisomerization of 1,6-Enynes and 1,6-Dienes

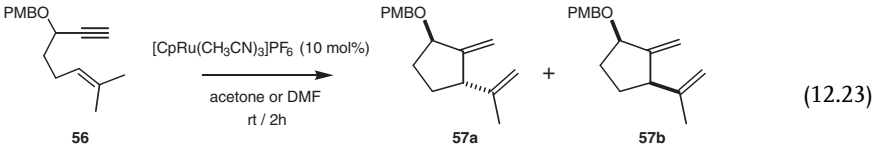
A number of cycloisomerization reactions of enynes to construct five-membered carbocycles with a variety of transition metal catalysts have been reported thus far [24]. The mechanisms that have been proposed for the cycloisomerization of enynes include: 1) hydrometallation of alkyne followed by carbometallation of the olefin;

2) initial formation of a metallacyclopentene followed by β-hydrogen elimination; 3) formation of a metallacyclopentene followed by reductive elimination to a cyclobutene and conrotatory cycloreversion; and 4) a metal alkylidene. Trost et al. proposed an alternative mechanism that involved allylic carbon-hydrogen bond activation for the isomerization of 1,6-diynes to 4-alkyliden-cycloheptenes.

1,6-Enynes which have the secondary or tertiary center at the propargylic position are isomerized to 2-alkenyl-methylenecyclopentane in moderate to high yield with a catalytic amount of $[CpRu(CH_3CN)_3]PF_6$ in acetone or dimethylformamide (DMF) [25]. This catalyst system is acidic, and an acid-labile group such as a dimethyl acetal **54** is hydrolyzed to aldehyde **55**.



54 **55** (58%) (12.22)

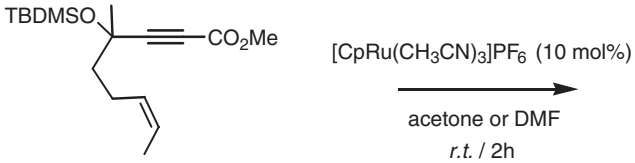


56 **57a** **57b** (12.23)

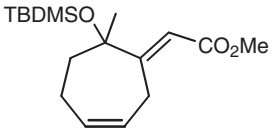
in acetone; 83%, a/b = 1.4:1
in DMF; 87%, a/b = 1.4:1

The mechanism which involves an intermediary ruthenacyclopentene **K** is proposed (Scheme 12.6). Coordination of the enyne to the coordinatively unsaturated cationic cyclopentadienylruthenium species **I**, tautomerization of the resulting ruthenium-enyne complex **J** to the ruthenacyclopentene **K**, β-hydrogen elimination to form a vinylruthenium **L**, followed by reductive elimination yields the 2-alkenyl-1-alkylidenecyclopentane **58** and regenerates the catalyst **I**.

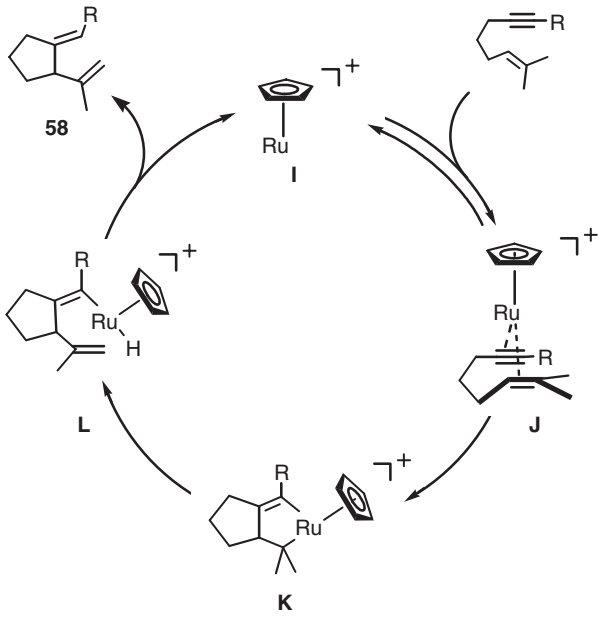
In contrast, the 1,6-enynes having a quaternary carbon at the propargylic position are isomerized to 4-alkylidenecyclohept-1-ene by treatment with a catalytic amount of $[CpRu(CH_3CN)_3]PF_6$ in acetone or DMF (Eq. 12.24) [26].



59 (12.24)



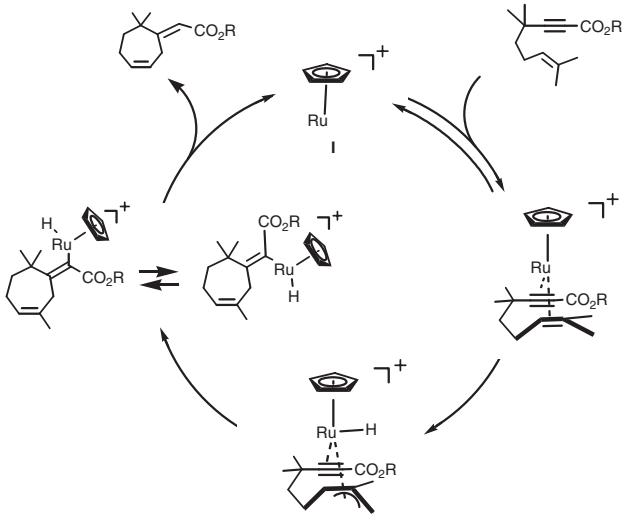
60 (77% in DMF, 83% in acetone)



Scheme 12.6

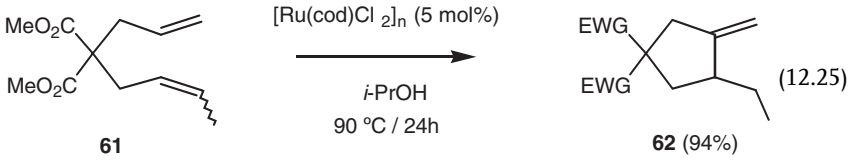
A mechanism which involved the allylic carbon-hydrogen bond activation of the alkene moiety was proposed for the cycloisomerization of 1,6-diyne to alkylidenecycloheptene on the basis of stereochemical consideration and deuterium labeling experiment (Scheme 12.7).

In the presence of a catalytic amount of a ruthenium complex, 1,6-diene **61** was effectively converted into the corresponding methylenecyclopentane **62** in *i*PrOH.



Scheme 12.7

The alcoholic solvent was essential for this catalytic cycloisomerization [27]. On the basis of studies using the known ruthenium hydrides and deuterium-labeling substrates, a mechanism involving an intermediary ruthenacyclopentane was proposed (Eq. 12.25).

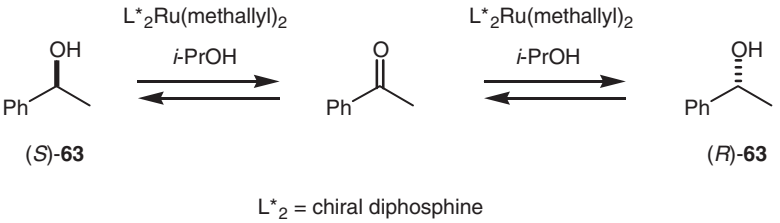


(12.25)

12.6 Racemization of Secondary Alcohols

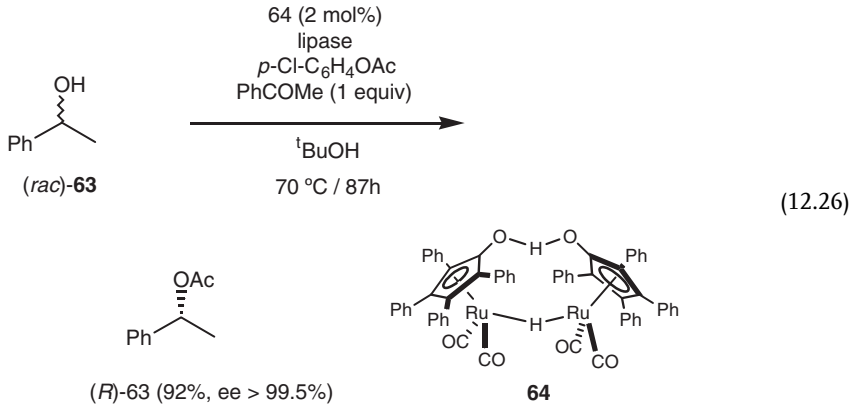
Racemization of an enantiomer which is undesirable for kinetic resolution is important from both an economical and an environmental point of view. Transition metal-catalyzed hydrogen transfer from alcohols to ketones has been recently used for racemization of secondary alcohols.

In the hydrogen transfer between propan-2-ol and acetophenone catalyzed by ruthenium catalyst $L^*_2Ru(methallyl)_2$ (L^*_2 = chiral diphosphine ligand), Genet et al. observed racemization of α-methylbenzyl alcohol **63** formed as a final product (Scheme 12.8) [28].



Scheme 12.8

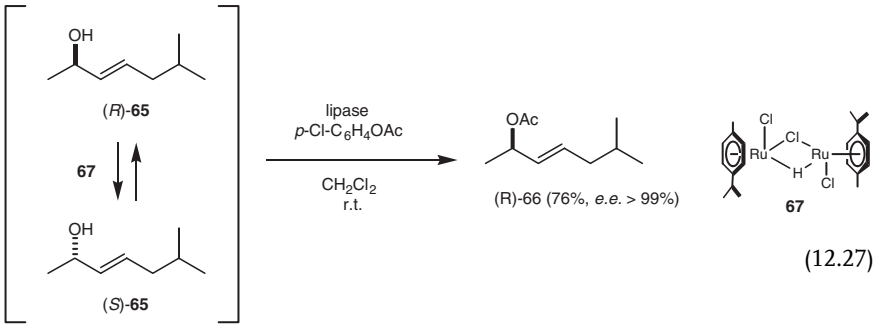
The ruthenium-catalyzed racemization of α-methylbenzyl alcohol was combined with an enzyme-catalyzed transesterification with lipase. Dinuclear ruthenium complex **64** effectively catalyzes the racemization of α-methylbenzyl alcohol and the combination of **64**, *p*-chlorophenyl acetate, and enzyme N-435 in the reaction of racemic amethylbenzyl alcohol gave enantiomerically pure (*R*)-α-methylbenzyl acetate in the excellent yield (Eq. 12.26) [29].



(12.26)

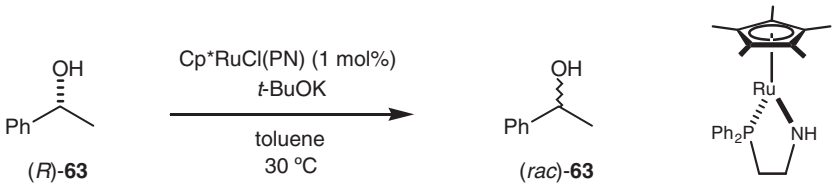
(η^5-Indenyl)RuCl(PPh_3)$_2$ was found to be a very reactive catalyst which can racemize (*S*)-a-methylbenzyl alcohol completely within 20 min at room temperature in the presence of 5 mol% KOH [30].

(*p*-Cymene)ruthenium(II) complex **67** is an excellent racemization catalysts for the dynamic kinetic resolution (DKR) of allylic alcohols, even at room temperature. Racemic allylic alcohol **65** was selectively transformed to (*R*)-**66** by the use of **67** and the immobilized lipase from *Pseudomonas cepacia* as the catalyst for the enantioselective acylation (Eq. 12.27) [31].



(12.27)

Ito et al. developed an effective catalyst for racemization of chiral non-racemic secondary alcohols. Catalytic system, Cp*RuCl(cod)/$Ph_2P(CH_2)_2NH_2$/*t*BuOK, effects extremely rapid racemization (Eq. 12.28). These authors proposed the in-situ formation of a coordinatively unsaturated (16 e) Cp*Ru(amido) complex **68** as an active species [32].

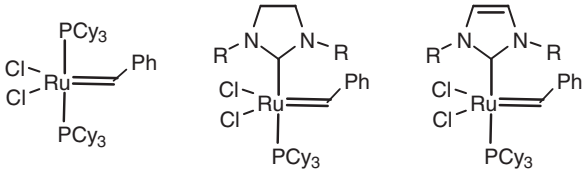


(12.28)

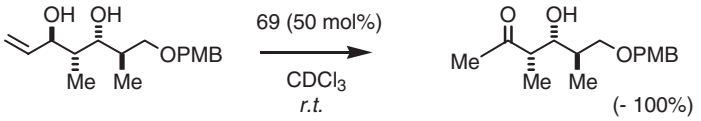
12.7 Olefin Isomerization Promoted by the Grubbs' Catalyst

Metathesis reactions by the use of ruthenium alkylidene complexes **69–71** – the so-called "Grubbs' catalyst" – were found to be highly useful for polymer syntheses and organic syntheses [33]. Recently, it has been shown that Grubbs's catalyst also catalyzes side reactions in some cases, and this resulted in olefin isomerization. Catalyst use is also prominent in the cross metathesis reactions of acyclic dienes (ADMET) and ring-closing metathesis (RCM) of macrocyclic molecules, in which cases the rate of metathesis reactions are relatively slow. Several different experimental conditions have been shown to affect the ratio of the isomerization, including reaction temperature, ring size, coordination ability of solvents, and proton source in the substrates. While substrates containing allylalcohol and allylamine moiety have shown to be susceptible to underwent isomerization, isomerization of olefin that has no functional group has also been reported.

Although it is not clear whether olefin isomerization is promoted by the metathesis catalyst itself, decomposition products, or impurities from the catalyst synthesis, it is generally concerned that a ruthenium hydride species, which is active for olefin isomerization, would be generated by the decomposition of the alkylidene complex. While olefin isomerization by the use of **69–71** has been reported, selectivity for the isomerization of **69** seems to be different from that of **70** and **71**, which contains N,N′-disubstituted 2,3-dihydro-1*H*-imidazol-2-ylidene ligand (or its fully saturated analogue). There are more reports upon the side reactions of the highly active compounds **70** and **71**. In contrast to the ruthenium complexes, olefin isomerization has never been observed during metathesis reactions catalyzed by the molybdenum alkylidene complex. Conversion of the secondary allylalcohol to ketone by the benzylidene complex $(PCy_3)_2Cl_2Ru{=}CHPh$ (**69**) has been reported in relation to the olefin isomerization (Eq. 12.29) [34].

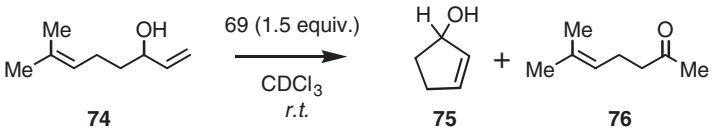


69 **70** **71**



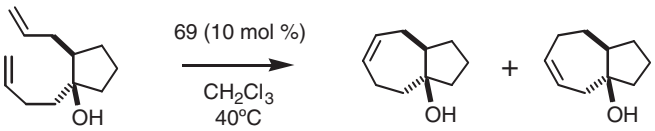
72 73 (12.29)

When the allylalcohol contains an additional olefinic part, the reaction competes with RCM (Eq. 12.30) [34b]. In the case of **74**, the activation barrier for the RCM pathway toward **75** would become higher because of the sterically hindered trisubstituted C=C double bond of **74**. For the RCM of such sterically demanding dienes, complexes **70** and **71** are generally used.



74 75 76 (12.30)

(75/76 =1/1.5)

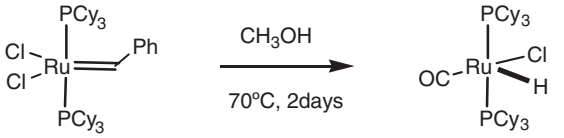


77 78 79 (12.31)

(78/79 =1.6/1)

Migration of the double bond of the cyclic olefin formed by the RCM has also been observed [35]. RCM of the diene **77** by **69** in refluxing dichloromethane resulted in the formation of considerable amounts of the unexpected cyclic olefin **79** in addition to **78** (Eq. 12.31) [35a]. It was also noted that the formation of **79** was effectively suppressed by the addition of amine to the dichloromethane solution or employment of diethylether as solvent, which implies participation of proton in the isomerization reaction. It was also noted that a terminal vinyl group with a free tertiary allylic hydroxyl group accelerates RCM, rather than its methyl ether derivative. These results suggested some interaction between the alkylidene complex **69** with hydroxyl proton in situ.

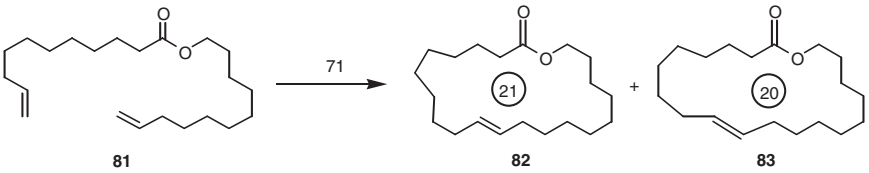
Hydrolysis [36], thermolysis [37], and alcoholysis (Eq. 12.32) [38] of the benzylidene complex **69** were investigated in relation to decomposition of **69**. In each case, formation of the hydride complex was confirmed by the use of ^{1}H NMR spectroscopy. Treatment of **69** with ethanol afforded a hydride complex $(PCy_3)_2(CO)Ru(Cl)(H)$ (**80**). Complex **80** has been shown to promote isomerization of 1-octene to 2-octene; reaction of 88 000 mol equiv. of 1-octene with **80** at 100 °C for 3 h gave 97% conversion with 92% selectivity for 2-octene [38].



69 **80** (12.32)

Since complexes **70** and **71** have been shown to be thermally stable in contrast to **69** [39], and hence their thermal degradation was negligible. Although reaction of **70** with 1-octene performed at room temperature in ADMET conditions afforded mainly C_{14}-olefin, significant amounts of C_7 and C_9-C_{13} olefins were observed in the reaction performed at 60 °C [40]. This result suggests that olefin isomerization is promoted to some extent at a higher temperature.

It has been reported that activities of the ruthenium alkylidene complexes, which contain mesityl groups at the N atoms, are highly influenced by solvent [41]. Reactions in toluene occur substantially faster than those in CH_2Cl_2. While treatment of diene **81** with 1.2 mol% of **71** in toluene led to essentially complete consumption of the starting material in 6.5 h, the same reaction took over 20 h in CH_2Cl_2 by use of 4 mol% of **71** (Eq. 12.33) [42].



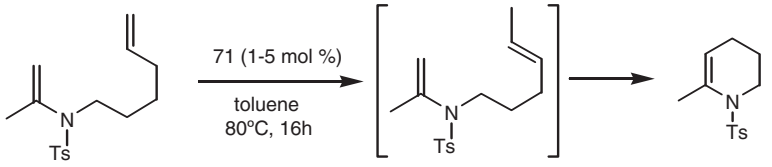
81 **82** **83**

Solvent	Temp	Catalyst	Time	Yield (%)	
				82	83
Toluene	40 °C	1.2 mol%	6.5h	65	10
CH_2Cl_2	40 °C	4 mol%	23h	71	2

(12.33)

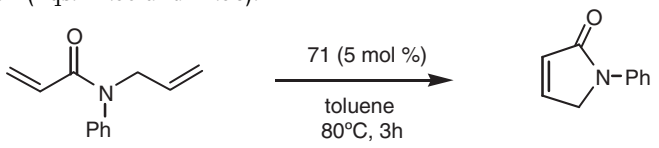
In the reaction shown in Eq. 12.33, unprecedented reactivity of **71** in toluene has been shown to promote simultaneous isomerization of the double bonds of the substrate. Treatment of **81** with **71** in toluene afforded significant amounts of the 20-membered ring **83**, in addition to the desired 21-membered lactone **82**. Compound **83** was probably formed by way of an initial isomerization of one of the double bonds in **81**, followed by elimination of propene instead of ethylene during ring closure. Although the reaction rate becomes slower, the ratio of the 21-membered ring **82** is increased by the use of CH_2Cl_2 as solvent.

It has been reported that RCM of enamides affording five- and six-membered cyclic enamides readily proceeds when the enamides contain a protective group on the N atom. However, an attempt to create a seven-membered cyclic enamide through RCM of **84** resulted in exclusive formation of a six-membered ring **86** (Eq. 12.34) [43]. This reaction was thought to proceed by way of ruthenium-catalyzed isomerization to the intermediary olefin **85**, followed by ring closure of the isomerized intermediate to the six-membered enamide **86**, which is a typical example of the ring-size effect.

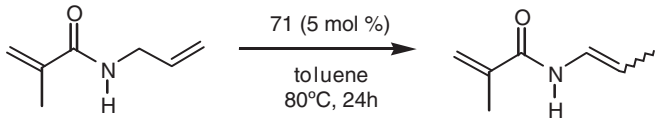


84 **85** **86** (62%) (12.34)

An H-atom on nitrogen significantly affects the reactivity of **71** [42]. By contrast, the acrylic acid amide containing a phenyl group on the N atom **87** underwent RCM, and treatment of **89** with complex **71** resulted in exclusive olefin isomerization (Eqs. 12.35 and 12.36).

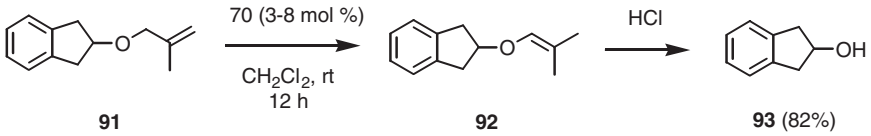


87 **88** (82%) (12.35)

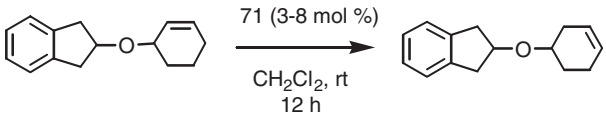


89 **90** (71%) (12.36)

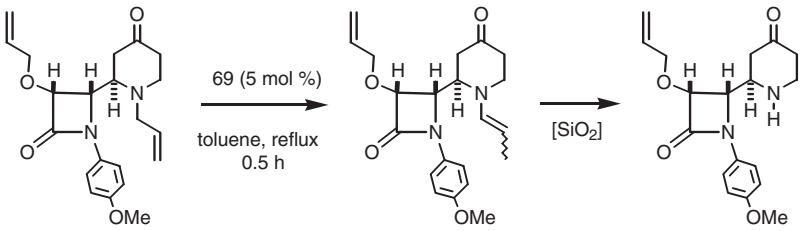
Olefin isomerization catalyzed by ruthenium alkylidene complexes can be applied to the deprotection of allyl ethers, allyl amines, and synthesis of cyclic enol ethers by the sequential reaction of RCM and olefin isomerization. Treatment of **70** with allyl ether affords corresponding vinyl ether, which is subsequently converted into alcohol with an aqueous HCl solution (Eq. 12.37) [44]. In contrast, the allylic chain was substituted at the C1 position, and allyl ether **94** was converted to the corresponding homoallylic **95** (Eq. 12.38). The corresponding enamines were formed by the reaction of **70** with allylamines [44, 45]. Selective deprotection of the allylamines in the presence of allyl ethers by **69** has been observed (Eq. 12.39), which is comparable with the π-allyl palladium deallylation methodology. This selectivity was attributed to the ability of the lone pair of the nitrogen atom to conjugate with a new double bond of the enamine intermediate.



91 **92** **93** (82%) (12.37)

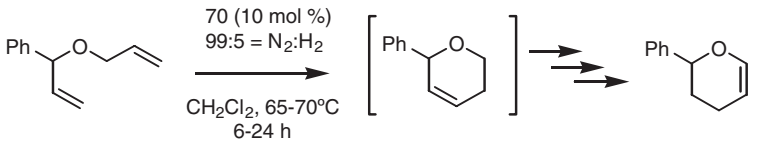


94 **95** (73%) (12.38)



96 **97** **98** (74 %) (12.39)

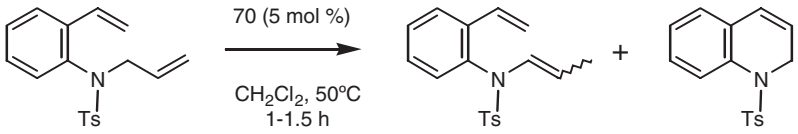
As vinyl ethers were known to be poor substrates in Ru-catalyzed olefin metatheses, it has been difficult to obtain cyclic enol ethers by RCM of the vinyl ethers. Recently, a novel method to obtain cyclic enol ethers has been reported, which afforded cyclic enol ethers directly from easily prepared dienes containing an allyl ether moiety [46]. Treatment of **70** with diene **99** in CH_2Cl_2 in the presence of small amount of H_2 resulted in a formation of dihydropyran **101** (Eq. 12.40). Treatment of **70** with H_2 has been thought to produce an active catalyst for the olefin isomerization, and only metathesis products are formed until a small amount of H_2 is introduced in the reaction. These results implied that this reaction most likely proceeded by way of a formation of the cyclic olefin **100**, which was subsequently converted to dihydropyran **101** by the newly formed isomerization catalyst. In addition to the tandem reaction shown in Eq. 12.40, another method for obtaining cyclic enol ethers from allyl ethers has also been demonstrated [46b]. This method included addition of the hydride donor, such as $NaBH_4$, to the reaction solution after the metathesis reaction had been completed. Although attempts to observe an active species for olefin isomerization in the presence H_2 failed, these results suggested participation of hydride species in the olefin isomerization.



99 **100** **101** (61%) (12.40)

It has been reported that treatment of **70** with silyl enol ether generates active species only toward olefin isomerization (Eq. 12.41) [47]. When vinyl acetate was added to the reaction instead of silyl enol ether, neither metathesis nor isomerization took place. Although details of the active species remain unclear, Fischer-type carbene complexes would be formed in the reaction of **70** with silyl enol ether. It has also been recognized that hydride-carbonyl complexes were formed by the thermolysis of

Fischer-type complexes containing an alkoxy group on the carbene carbon, which has been shown to promote olefin isomerization.



(12.41)

102	$OSiMe_3$	103	104
	0 equiv.	0 %	100 %
	1.0 equiv.	100 %	0 %

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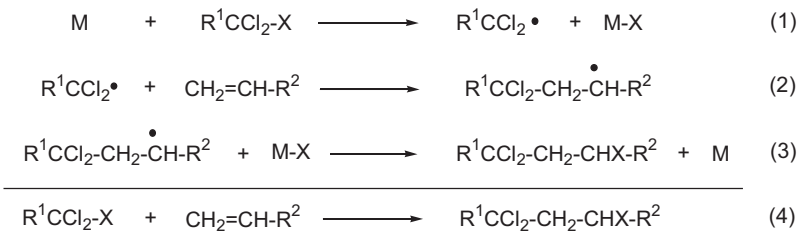
13
Ruthenium-Promoted Radical Reactions

Hideo Nagashima

13.1
Introduction and Historical Background

Reactions which occur through organic radical intermediates have often been seen in the catalysis of transition metal complexes [1–3]. In particular, the treatment of organic halides (R–X) with various low-valent transition metal complexes (M) results in abstraction of a halogen atom from the organic halides to produce organic radicals (R•) (equation 1 in Scheme 13.1). The formal oxidation state of the metal complex is increased by one, and M-X is formed by the halogen abstraction (equation 2). If the formed organic radicals are able to promote an addition reaction to unsaturated compounds (equation 3), and the resulting adduct radicals are capable of abstracting the halogen atom from the high-valent metallic species M-X (equation 4), then the full catalytic sequence shown in Scheme 13.1 is established.



Scheme 13.1 Metal-catalyzed Kharasch addition. M = transition metal compounds; X = halogen atom; R^1 = H, Cl, CO_2R, etc., R^2 = alkyl or aryl.

This catalytic sequence is known as Kharasch addition or atom transfer radical addition (ATRA) [4]. Various polyhalogenated compounds such as CCl_4 and CCl_3CO_2R are used as the organic halides, and transition metal salts or complexes are used as the catalyst [3]. Intramolecular version of the Kharasch addition reaction (atom transfer radical cyclization, ATRC) has opened novel synthetic protocols to the synthesis of carbocycle or heterocyles catalyzed by transition metals [5–7], and this has become a very important field in free radical cyclization in organic synthesis. Transition metal-catalyzed Kharasch reactions sometimes afford telomers or poly-

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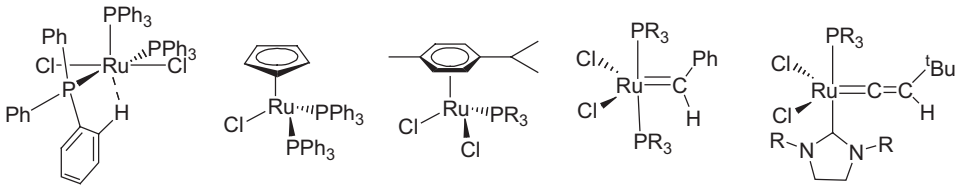


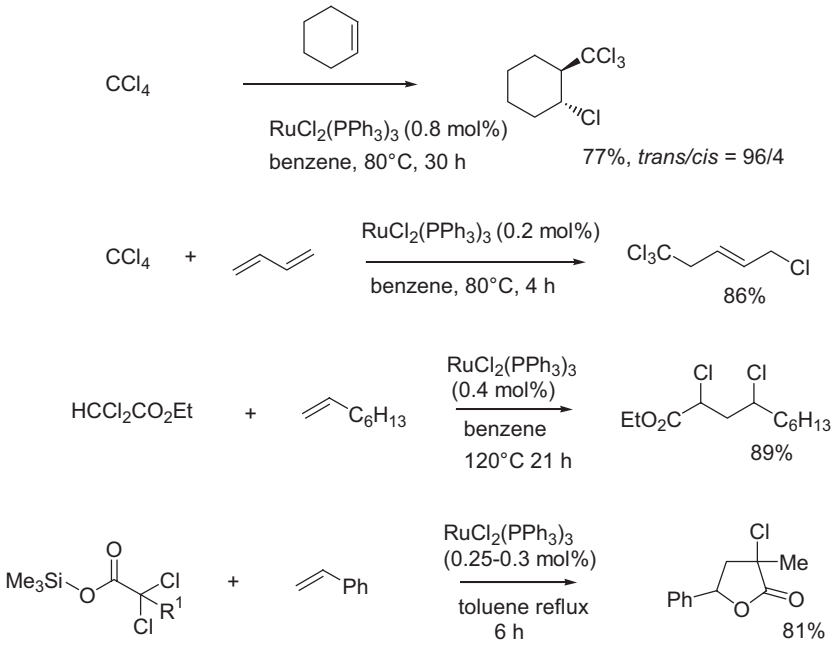
Figure 13.1 Representative ruthenium complexes active for Kharasch addition and atom transfer radical polymerization (ATRP).

mers [8]. Reinvestigations carried out by Sawamoto [9] and Matejaszewski [10] during the mid-1990s produced the epoch of discovery termed "controlled living radical polymerization" or atom transfer radical polymerization (ATRP), in which the judicious choice of transition metal complexes, monomers, and organic halide initiators eventually produced polymers and block copolymers with narrow molecular weight distributions.

These studies, and their long history, have provided numerous aspects of organic and polymer chemistry in which a variety of transition metal complexes and salts actually behave as efficient catalysts. In particular, certain ruthenium complexes, of which typical examples are illustrated in Figure 13.1, sometimes show distinctly different activity and/or selectivity from those available with other catalysts. The purpose of this chapter is to describe special features of ruthenium catalysts in these radical reactions, and to highlight the importance of ruthenium-catalyzed radical reactions in organic and polymer synthesis.

13.2
Ruthenium-catalyzed Kharasch Addition (ATRA) in Organic Synthesis

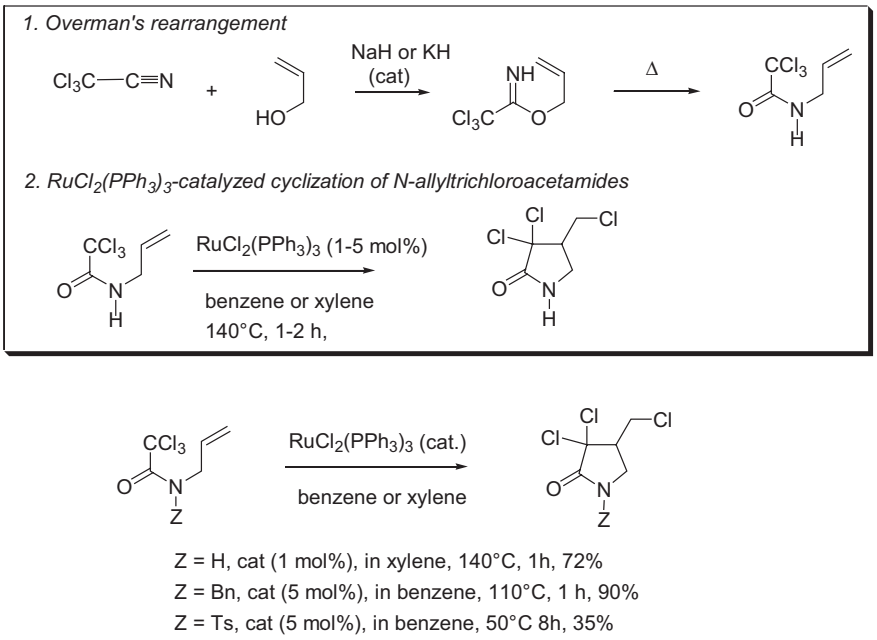
As the first ruthenium catalyst, Nagai and coworkers identified the efficient catalysis of $RuCl_2(PPh_3)_3$ in the addition reaction of CCl_4 or $CHCl_3$ to alkenes in 1973 [11], and expanded their results to the synthesis of several polyhalogenated organic compounds, as summarized in Scheme 13.2. Various alkenes undergo the addition reaction to form the corresponding 1:1 adducts. No telomerization occurs, even in the reaction with styrene. The addition of CCl_4 to cyclohexene affords the corresponding adduct as a mixture of isomers, of which the *trans*:*cis* ratio is 96:4 [12]. Selective 1,4-addition takes place in the reactions of CCl_4 with 1,3-dienes [13]. Methyl and ethyl tricholoroacetates or trichloroacetyl chloride are also activated by catalysis of $RuCl_2(PPh_3)_3$ to give the corresponding α,α,γ-trichlorinated esters [14]. The addition reaction of certain trichloroacetic acid derivatives to alkenes affords γ-lactones [15]. As further extension of the $RuCl_2(PPh_3)_3$-catalyzed Kharasch addition, addition of CF_2ClCCl_3 to silyl enol ethers was reported to give halogenated enones as the products [16]. A series of investigations by Boutevin and coworkers showed that the $RuCl_2(PPh_3)_3$-catalyzed addition of polychlorinated compounds to alkenes is applied to synthesis of telechelic oligomers [17].



Scheme 13.2 $RuCl_2(PPh_3)_3$-catalyzed reactions of polychlorinated compounds.

13.3
Ruthenium-catalyzed Intramolecular Kharasch Addition (ATRC) in Organic Synthesis

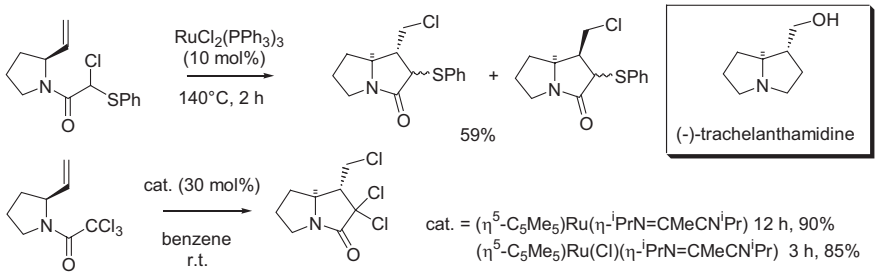
A variety of intramolecular Kharasch reactions, which may also be referred to as ATRCs, have been devised that provide effective synthetic methods for γ-lactams, cyclopentanones, and macrocyclic compounds [5–7, 18, 19]. Some of the reactions in fact applicable to the synthesis of natural product skeletons [25–28]. A ruthenium complex $RuCl_2(PPh_3)_3$ is generally a good catalyst for the cyclization of *N*-allyltrichloroacetamides [20–22]. Of particular importance in the catalysis of $RuCl_2(PPh_3)_3$ is the cyclization of secondary *N*-allyltrichloroacetamides (Z = H), though other catalysts are poisoned by complexation with the substrates or products [20, 21]. This has in fact brought about a two-step sequence of γ-lactam synthesis from allylic alcohols in combination with Overman's [3.3]-Sigmatropic rearrangement, which gives variously substituted *N*-allyltrichloroacetamides by way of 1,3-transposition of the OH group in allylic alcohols to a $NHCOCCl_3$ moiety (Scheme 13.3) [21]. Two types of tandem cyclization are also achieved to provide a one-step synthesis of bicyclic lactams. One type is a general tandem radical cyclization, in which the intermediate radical species is trapped by a carbon-carbon double bond intramolecularly. The other type is a stepwise reaction in which the first cyclization giving a α,α,γ-trichlorinated γ-lactam is followed by activation of a α-carbon-chlorine bond in the resulting lactam, leading to the second intramolecular Kharasch addition [21]. *N*-Allyltrichloroacetamides bearing the electron-withdrawing substituents such as tosyl and Cbz



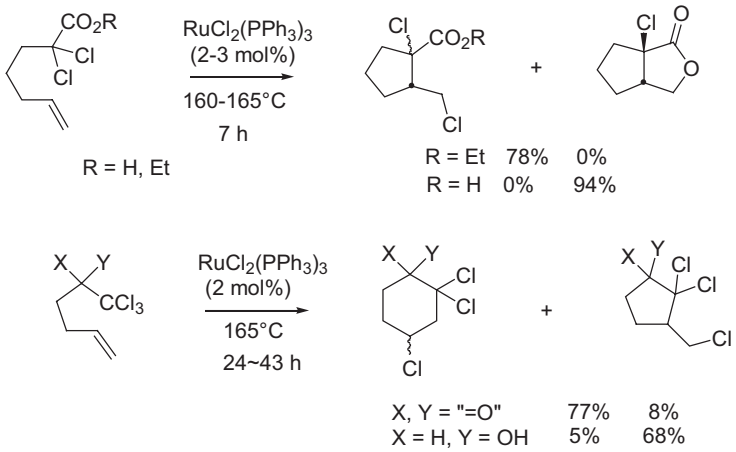
Scheme 13.3 Synthesis of trichlorinated γ-lactams.

groups react faster than those having electron-donating substituents, such as methyl and benzyl moieties [22]. Stereochemical features of the ruthenium-catalyzed cyclization of secondary *N*-allyltrichloroacetamides are similar to those seen in free radical cyclizations of analogous systems [22]. It is known that reactivity of polyhalogenated compounds in the Kharasch addition is dependent on the number of chlorine atoms in them (e.g., CCl_4 > $CHCl_3$, CCl_3CO_2R > $CHCl_2CO_2R$). Several N-tosylated *N*-allyldichloroalkanamides were subjected to the $RuCl_2(PPh_3)_3$-catalyzed cyclization, which involves ruthenium-catalyzed reversible C-Cl bond cleavage and reformation leading to rapid inversion of the radical intermediate [23, 24].

It has long been recognized that the importance of the intramolecular Kharasch reaction is attributable to its facile application to alkaloids and other natural product syntheses [5–7, 18, 19]. In the ruthenium-catalyzed cyclization, Ishibashi and coworkers reported a cyclization of *N*-allylic α-chloro-α-thioacetamides, and its application of this cyclization to precursors of (–)-trachelanthamidine, (±)-haemanthidine, and (±)-pretazettine was achieved [25]. Oxazolone derivatives having a trichloroacetoxy or bromodifluoroacetoxy group and a carbon-carbon double bond in the molecule reportedly undergo cyclization to form the corresponding 12-membered ring products with complete diastereoselectivity by catalysis of $RuCl_2(PPh_3)_3$ [26]. The products are precursors of enantiomerically pure statine analogues. The preparation of a trichlorinated bicyclic lactam, a precursor of (–)-trachelanthamidine and (–)-pseudoheliotridane, was earlier reported by Ishibashi and coworkers with $RuCl_2(PPh_3)_3$ [25], and also by a Spanish group using a stoichiometric quantity of CuCl in acetonitrile [27] (Scheme 13.4). Highly efficient ruthenium amidinate cata-



Scheme 13.4 Preparation of an alkaloid skeleton.

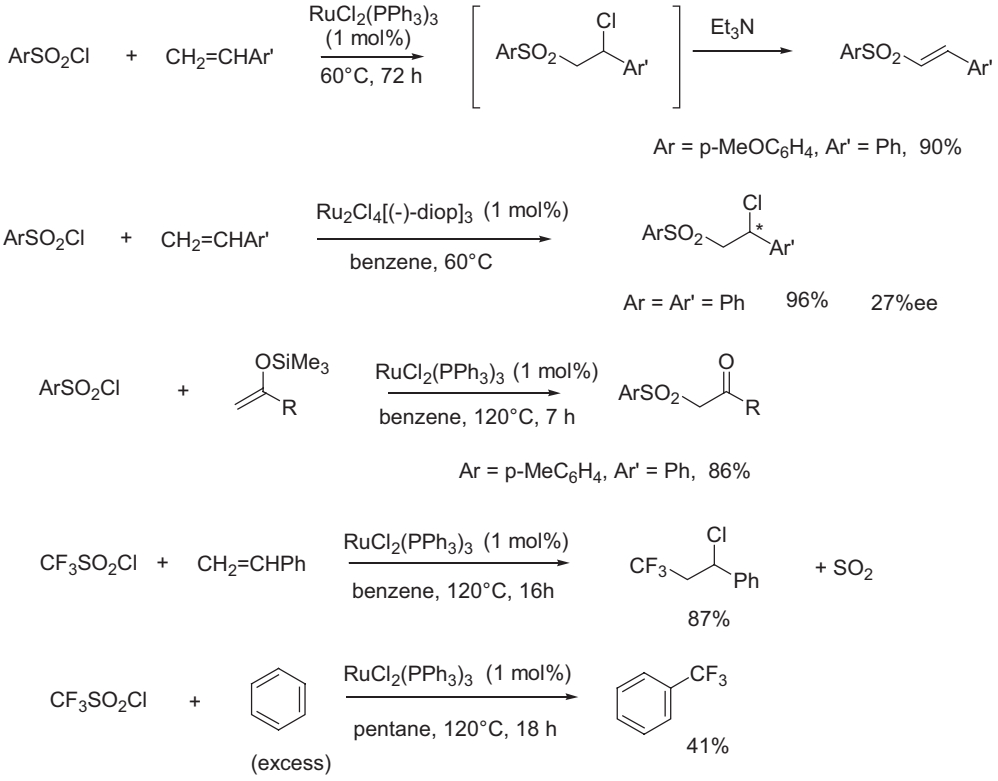


Scheme 13.5 Preparation of carbocycles.

lysts, (η^5-C_5Me_5)Ru(η-amidinate) and (η^5-C_5Me_5)RuCl(η-amidinate) have recently been discovered [28]. The preparation of carbocyclic compounds by intramolecular Kharasch addition was actively investigated by Weinreb and coworkers [29–32], and representative examples are shown in Scheme 13.5. Although the high reaction temperature is a drawback, these cyclizations represent a convenient pathway to five- or six-membered carbocycles.

13.4
Ruthenium-catalyzed Addition of Sulfonyl Chlorides to Alkenes in Organic Synthesis

Alkanesulfonyl chlorides are known to be a good source of alkanesulfonyl radicals or alkyl radicals with the aid of redox catalysts [3]. A series of studies using $RuCl_2(PPh_3)_3$ as the redox catalyst have been carried out by Kamigata and coworkers (Scheme 13.6) [33–39]. Arenesulfonyl chlorides add to styrene derivatives to form the corresponding adducts, which undergo dehydrochlorination of Et_3N to form the unsaturated sulfones [33]. When styrylsulfonyl chlorides are used as the precursor,



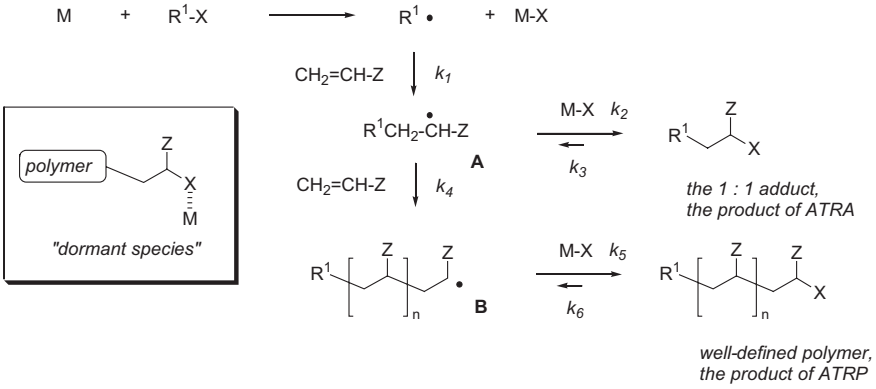
Scheme 13.6 Ruthenium-catalyzed addition of alkenesulfonyl chlorides.

the resulting adducts with styrene derivatives undergo dehydrochlorination and subsequent extrusion of SO_2 at elevated temperatures to form substituted butadienes [34]. The addition of CCl_3SO_2Cl or $RfSO_2Cl$ (Rf = CF_3 or perfluoroalkyl) to alkenes is accompanied by the elimination of SO_2 to form the corresponding tetrachlorinated or monochloroperfluorinated alkanes [35]. Asymmetric addition is investigated with chiral ruthenium phosphine catalysts, and some asymmetric induction (up to 40% *e.e.*) was attained [36, 37]. Additions to silyl enol ethers were also investigated to open the ways to access α-ketosulfones and β,β-dichlorinated α,β-unsaturated ketones [38]. Interestingly, $RfSO_2Cl$ reacts with aromatic or heteroaromatic compounds in the presence of $RuCl_2(PPh_3)_3$ to give rise to aromatic perfluoroalkylation [39]. These results clearly demonstrate the synthetic utility of ruthenium-phosphine complexes in organic synthesis with alkanesulfonyl chlorides.

13.5
Ruthenium-catalyzed Addition of Organic Halides and Sulfonylchlorides in Polymer Synthesis: ATRP

In 1995, Sawamoto and coworkers discovered that polymerization of methyl methacrylate (MMA) in the presence of CCl_4 and a catalytic amount of $RuCl_2(PPh_3)_3$ and aluminum alkoxides actually promoted the chain growth to give poly-MMA of $M_n = 10^3 \sim 10^4$, and with narrow molecular weight distributions [40]. This was the "dawn" of the metal-catalyzed polymerization methods referred to as "controlled living polymerization" or ATRP. This field of polymer chemistry has been one of the most actively investigated during the past few years, and two major reviews [9,10] detail over 400 related reports submitted up until the end of the year 2000.

The mechanisms of ATRP are analogous to those of ATRA (Scheme 13.7). However, one striking difference between the mechanisms of ATRA and ATRP is that the adduct radical A with another molecule of the vinyl monomer results in chain growth (k_4). The resulting radical species at the polymer end B also reacted with M-X to the polymer having a halogen atom at its terminus (k_5). An important feature of ATRP is that the halogen atom-terminated polymer is reactive with M to regenerate the radical species (k_6). In other words, the polymer bearing a halogen atom at its terminal behaves like a dormant species, which reversibly forms a low concentration of radical species ($k_5 > k_6$): this, in turn, is reactive with limited molecules of the vinyl monomer and regenerates the dormant species by rapid reaction with M-X. In well-controlled ATRP, formation of the dormant species predominates over the usual termination of the radical polymerization – that is, disproportionation or dimerization of the radical species. Thus, a combination of these elementary reactions results in successful living radical polymerization. Various catalyst systems containing Fe, Cr, Mo, Re, Rh, Ni, and Pd have been reported to be effective for ATRP, and several ruthenium complexes have also been studied for their performance as polymerization catalysts. Various organic halides including benzylic halides, α-haloesters, α-haloketones, α-halonitriles, and aryl and alkanesulfonyl chlorides have

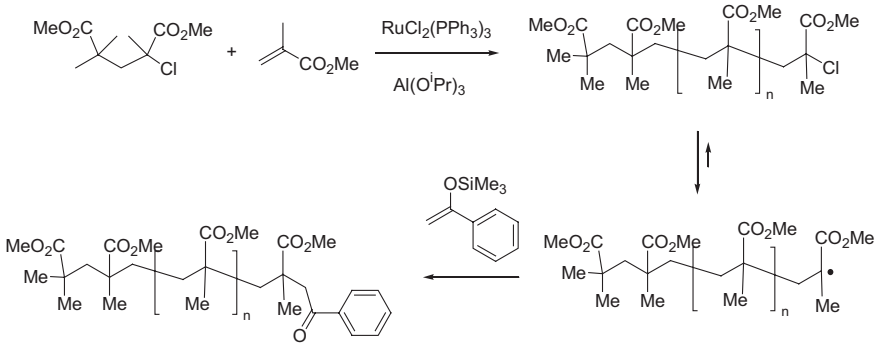


Scheme 13.7 Proposed mechanisms for ATRP. M = transition metal compounds.

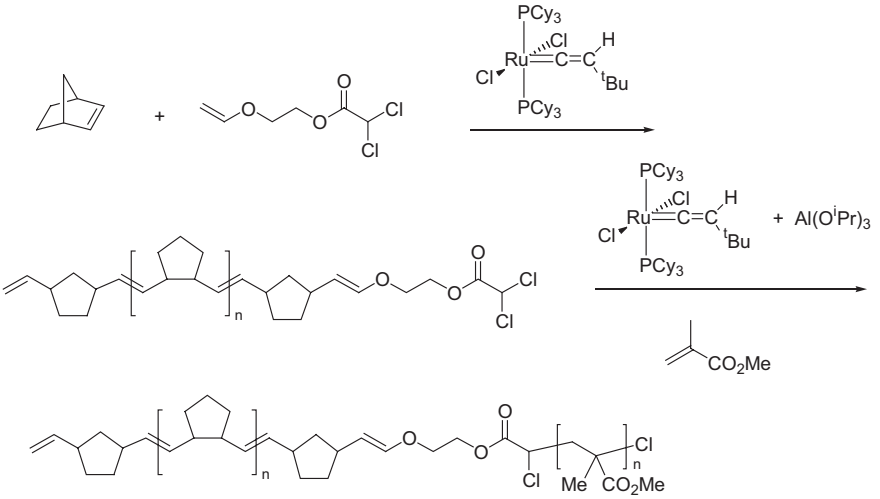
been proven to be useful as an initiator. As the investigations into ATRP have incorporated many areas of chemistry and physics, the reader may wish to examine the above-cited reviews [9,10] with regard to the details of this technique.

With regard to ruthenium-catalyzed ATRP, the $RuCl_2(PPh_3)_3$-catalyzed living polymerization of MMA was one of the earliest contributions to ATRP using various organic halides as the initiator [40, 41]. The addition of amines [42] or metal alkoxides such as $Al(O\textit{i}\text{-}Pr)_3$ and $Sn(O\textit{i}\text{-}Pr)_4$ [43] as the additive is often important for controlled living radical polymerization. Improvement is needed in the relatively high reaction temperatures (60–80 °C), limitation of the monomer which can be used for precisely controlled polymerization, and the requirement of additives to carry out the polymerization. More active catalysts may bring about the polymerization at lower temperatures without additives, and can be applicable to the polymerization of other monomers. Active searches for other catalyst systems have thus been made during the past few years. For example, the problems have been solved using $RuH_2(PPh_3)_4$ [44], Cp-based half-sandwich ruthenium(II) catalysts such as (η^5-C_5H_5)$RuCl(PPh_3)_3$ and its analogues [45, 46], (η^6-*p*-cymene)$RuCl_2(L)$, (L = PCy_3 or $P\textit{i}\text{-}Pr_3$) [47], and Grubbs's carbenes [48–50] as the catalyst. Many of these catalysts are also active towards ATRA [51, 52].

Concepts for the efficient production of structurally "well-defined" polymers have now become closely related to those for the efficient synthesis of complex organic molecules with high selectivity. In a typical example, "tandem catalysis" was described by the research group of Grubbs in 2000. In this process, a single component precatalyst can mediate three mechanistically distinct reactions, ring-opening metathesis polymerization (ROMP), ATRP, and hydrogenation to form well-defined block copolymers [48] (for details, see Chapter 00). One of the synthetic merits of living polymerization is the utilization of end functionality. The ATRP of MMA catalyzed by ruthenium complexes produces a poly-MMA bearing a halogen atom at the polymer end, which undergoes facile activation by the ruthenium catalyst existing in the reaction medium. The radical species at the polymer end is effectively trapped by silyl enol ethers (Scheme 13.8), and this is an effective method for end-capping of the polymer [53]. The active polymer terminal also serves as a source of block copo-



Scheme 13.8 End-capping of poly-methyl methacrylate (poly-MMA) formed by ATRP by silyl enol ethers.



Scheme 13.9 Preparation of macroinitiators for ATRP by ring-opening metathesis polymerization (ROMP).

lymerization, and several block copolymers were synthesized [54]. Other synthetic merits include the possible design of multifunctional initiators and the selection of appropriate monomers; a representative example for production of block copolymers is shown in Scheme 13.9 [50]. The application of living polymerization to production of star-shaped polymers [55] and polymer catalysts [56] was reported.

13.6 Summary and Perspective

Transition metal-mediated radical reactions lie not only in a boundary field between radical chemistry and organometallic chemistry, but also in a borderland of organic and polymer synthesis. As described in Section 13.1, many transition metal compounds capable of facile donation of one electron to organic halides are generally active towards metal-mediated radical reactions. However, $RuCl_2(PPh_3)_3$ and other ruthenium(II) complexes are both versatile and effective catalysts for those reactions involving activation of polyhalogenated compounds or sulfonylchlorides which lead to the successful preparation of fine organic compounds and well-defined polymers. As many of the ruthenium complexes that are useful catalytically in radical reactions are also thermally stable and not sensitive towards air and/or moisture, they can be handled in straightforward manner by synthetic chemists. Although the mechanisms of transition metal-catalyzed Kharasch additions have been regarded as controversial in relation to the possible involvement of free radical chain processes, one problem which has long been a topic of discussion is the possible coordination of radical intermediates in the catalytic cycle with the metallic species. Successful asymmetric induction (see Scheme 13.6) and the proposed existence of a dormant

species (see Scheme 13.7) are indicative of any metal-radical interaction in catalytic reactions. Nonetheless, further progress into metal-radical interactions should provide synthetic chemists with valuable clues into the opening of new fields of ruthenium-catalyzed reactions in organic and polymer synthesis.

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14
Ruthenium-Catalyzed Bond Cleavage Reactions

Sanshiro Komiya and Masafumi Hirano

Abbreviations

Acac	Acetylacetonato (MeCOCHCOMe)
COD	Cyclooctadiene (C_8H_{12})
COT	Cyclooctatriene (C_8H_{10})
DCyPE	1,2-bis(di*cyclo*hexylphosphino)ethane ($Cy_2PC_2H_4PCy_2$)
DCyPP	1,2-bis(di*cyclo*hexylphosphino)propane ($Cy_2PC_3H_6PCy_2$)
DEPE	1,2-bis(diethylphosphino)ethane ($Et_2PC_2H_4PEt_2$)
DMPE	1,2-bis(dimethylphosphino)ethane ($Me_2PC_2H_4PMe_2$)
DPPE	1,2-bis(diphenylphosphino)ethane ($Ph_2PC_2H_4PPh_2$)
DPPM	1,2-bis(diphenylphosphino)methane ($Ph_2PCH_2PPh_2$)
NBD	Norornadiene (C_7H_8)

14.1
Introduction

Ruthenium complexes have recently drawn attention as useful homogeneous catalysts for organic synthesis both in industry and in the laboratory, and now are considered to occupy a central position in organometallic chemistry. This is because many unique and interesting reactions including C–H and C–C bond cleavages have been continuously reported in ruthenium chemistry during the past few decades. One interesting feature of ruthenium-promoted reactions is that many are highly efficient but specific, and their activity and selectivity rely heavily on both the ancillary ligands and reaction conditions employed. This chapter deals with recent advances in bond cleavage reactions with ruthenium complexes. A comprehensive description of these reactions is avoided here, not only due to a diversity of facts, the mechanisms of which are still not well understood, but also to page limitation. Thus, Ru-mediated C–H and C–C bond cleavage reactions are mainly described, as these are likely to be of high value in the future, and promise new, environmentally benign organic molecular *trans*formations with high atom economy. Other important Ru-promoted cleavage reactions of relatively polarized bonds such as carbon-halogen and carbon-heteroatoms, acids, or nonpolar bonds such as dihydrogen and

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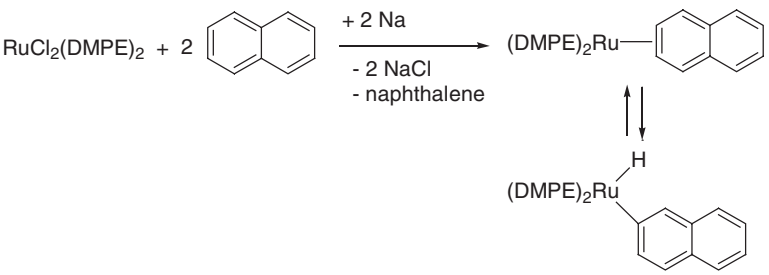
C–Si bonds are also described, but only briefly. Thus, the additional examination of reference materials and books describing general comprehensive descriptions of *trans*ition metal-mediated bond cleavage reactions would be advantageous to the reader [1].

14.2
C–H Bond Activation Reactions

Orthometallation of triarylphosphine and triarylphosphite at ruthenium has long been known as intramolecular C–H bond activation in ruthenium chemistry [2], but did not receive attention from organic chemists. In 1965, Chatt and Davidson documented that a Ru(0) complex, which was formed by two-electron reduction of Ru(II) by use of sodium naphthalene is capable of reversible cleavage of sp^2 C–H bonds of naphthalene by oxidative addition/reductive elimination processes (Scheme 14.1) [3].

This intermolecular oxidative addition of C–H bond to ruthenium became an epoch-making finding toward a brand-new research field in organometallic chemistry, namely *trans*ition metal-mediated cleavage of unactivated C–H bond directed toward organic synthesis [4]. Following this initial report, enormous effort was paid to the reactions of low-valent *trans*ition metal complexes, as oxidative addition is favored at electron-rich metal centers. However, catalytic functionalization processes of C–H bond were not well developed until recently, as seen in other *trans*ition metal-mediated organic reaction processes. In order to achieve C–H bond activation in general, several approaches including electrophilic and nucleophilic activations, electron *trans*fer, σ-bond metathesis, and oxidative addition are available. Regardless of the reaction mechanisms, coordinative unsaturation of ruthenium center and the proximity of the C–H bond with the metal are considered to be the most important factors. Although the cleavage reaction of the sp^3 C–H bond remains much less common than that of the sp^2 C–H bond, these modern strategies are also able to provide activation processes for the sp^3 C–H bond.

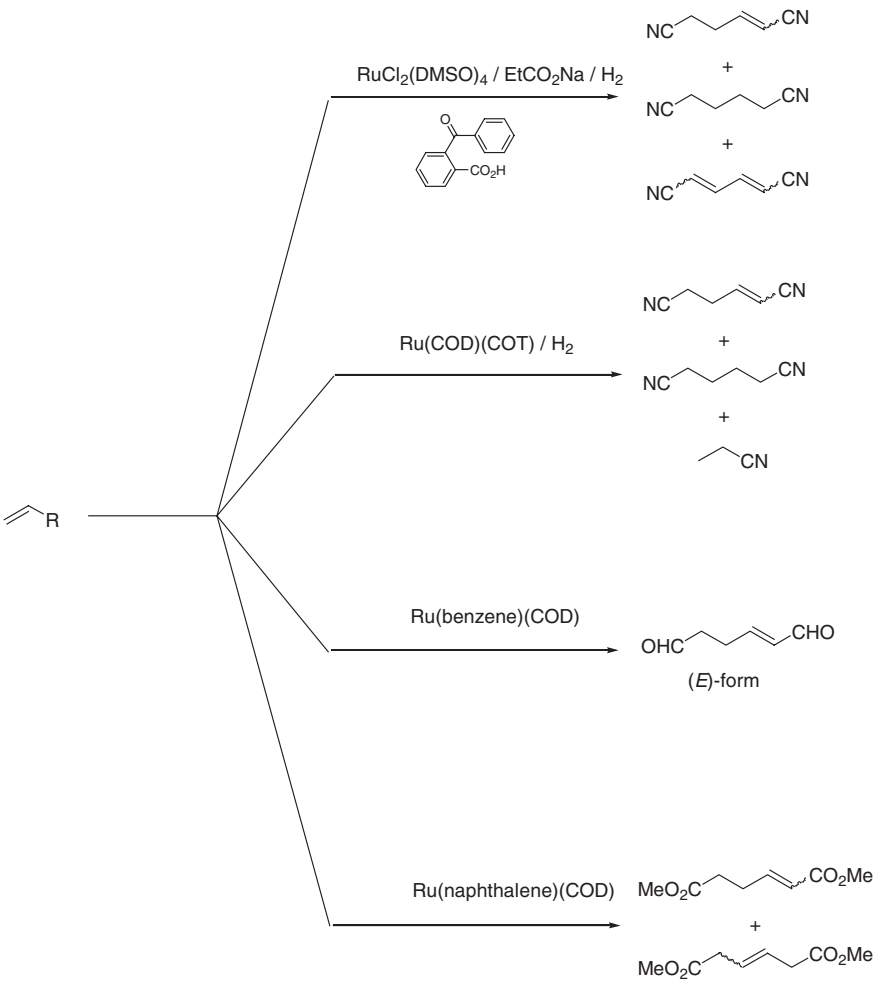
This section details selected catalytic C–H bond cleavage reactions, in addition to strategies for cleaving sp^2 and sp^3 C–H bonds. The activation of polar C–H bonds is also described.



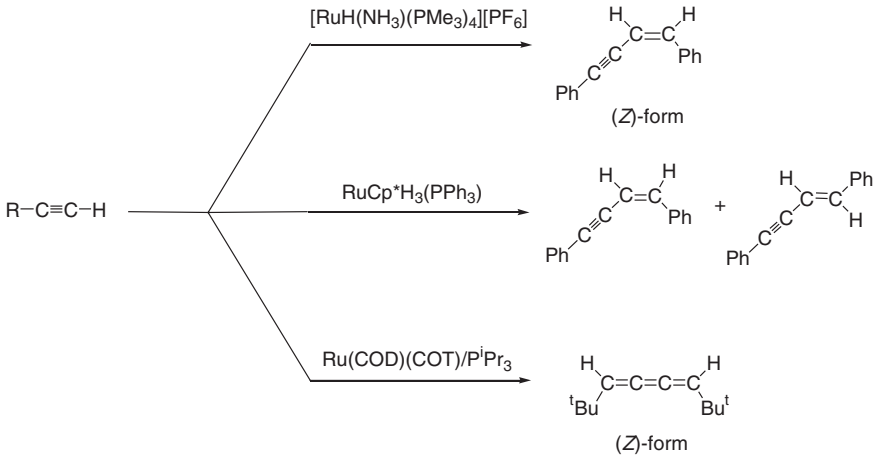
Scheme 14.1

14.2.1
Catalytic Reactions Involving a C–H Bond Cleavage Step

Molecular *trans*formations involving a nonpolar C–H bond cleavage step have recently attracted much attention due to their high atom economy as well as their simplification of the reaction process. One of the most characteristic catalyses by Ru complexes involving C–H bond cleavage reaction is the dimerization of substituted olefins. A common starting material of ruthenium complexes, $RuCl_3 \cdot 3H_2O$ is found to catalyze the dimerization of α-olefins [5]. Divalent $RuCl_2(DMSO)_4$ [6] and zerovalent complexes such as Ru(1,5-COD)(1,3,5-COT) [7], Ru(benzene)(COD) [8] and Ru(naphthalene)(1,5-COD) [9] also catalyze tail-to-tail dimerization of acrylonitrile, acrolein and methyl acrylate, respectively (Scheme 14.2). In these catalyses,



Scheme 14.2



Scheme 14.3

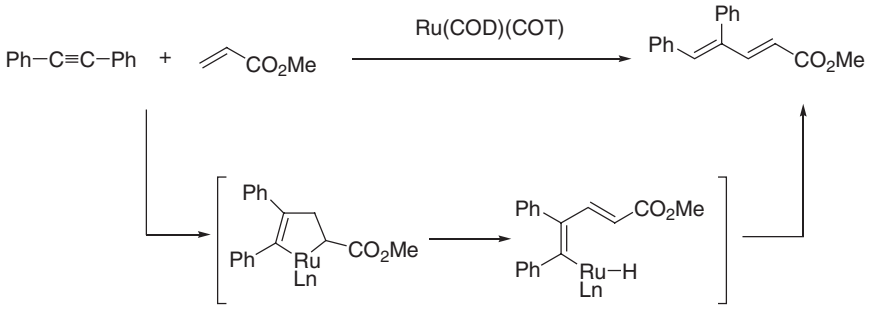
zerovalent ruthenium complex is considered to involve the C–H bond cleavage step to give (alkenyl)(hydrido)ruthenium(II) species.

Catalytic dimerization of terminal alkynes is also reported to give eneynes [10,11] or butatriene [12]. In both reactions, the activity and selectivity are sensitive to the substituents in the alkyne and tertiary phosphine ligands employed (Scheme 14.3).

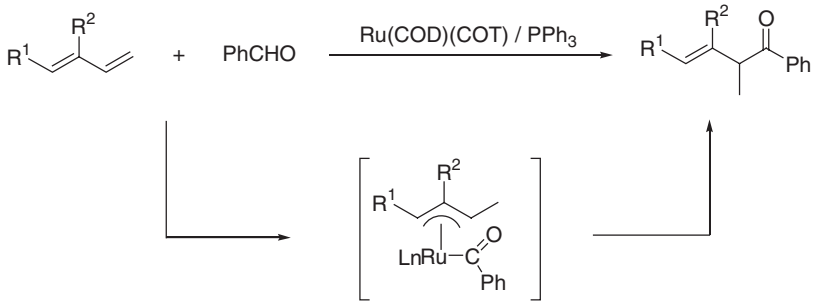
Similarly, dihydridoruthenium(II) complex $RuH_2(PBu_3)_4$ also catalyzes codimerization between terminal alkynes and dienes giving enynes [13]. Regioselective codimerization of internal alkynes with alkenes having an electron-withdrawing group also proceeds by Ru(1,5-COD)(1,3,5-COT) (Scheme 14.4) [14]. In this reaction, a ruthenacycle complex is considered to be involved as an intermediate.

Tischchenko-type dimerization of aldehyde is catalyzed by dihydridoruthenium(II) complexes. In this reaction, aldehyde is initially consumed to reduce Ru(II) to give Ru(0), to which aldehyde oxidatively adds to give a hydrido(acyl)ruthenium(II) active intermediate affording esters [15]. Hydroacylation of olefins [16] and dienes [17] is also catalyzed by ruthenium complexes (Scheme 14.5).

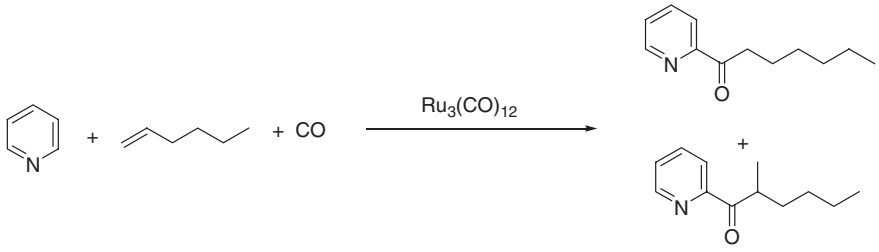
Catalytic C–H bond cleavage of arenes by ruthenium complexes is currently a major topic in organic synthesis. $Ru_3(CO)_{12}$ catalyzes a three-component coupling



Scheme 14.4



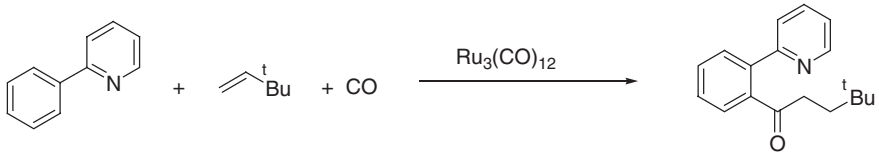
Scheme 14.5



Scheme 14.6

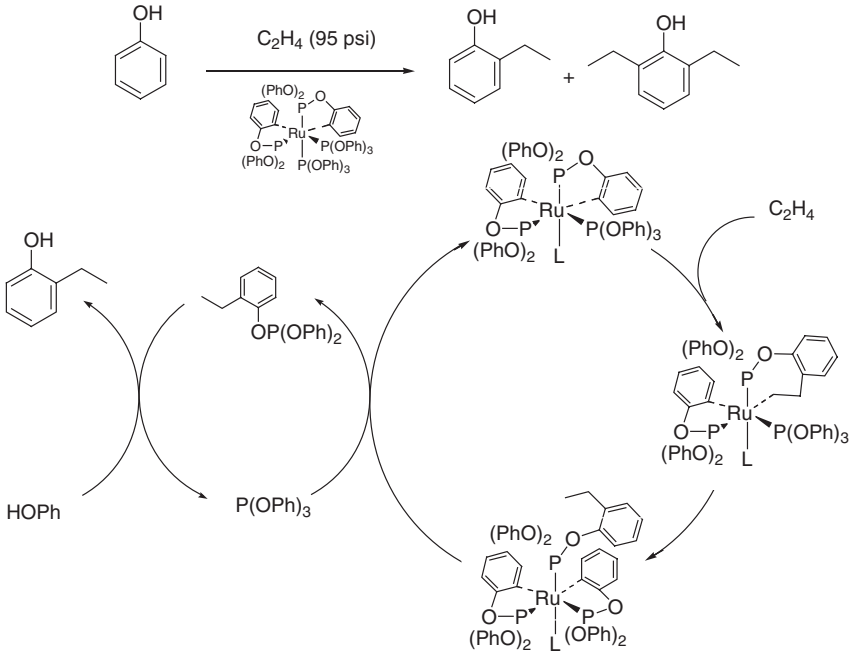
reaction of pyridine, 1-hexene and CO via C–H bond cleavage at the 2-position of pyridine (Scheme 14.6) [18].

This reaction is considered to proceed via initial coordination of pyridine to one of ruthenium centers, after which the adjacent ruthenium cleaves the *ortho* C–H bond followed by successive insertion of CO and olefin. When 2-phenylpyridine is employed in a similar system, acylation in the phenyl ring takes place via prior coordination of the N atom followed by cleavage of proximal C–H bond in the phenyl group (Scheme 14.7) [19].



Scheme 14.7

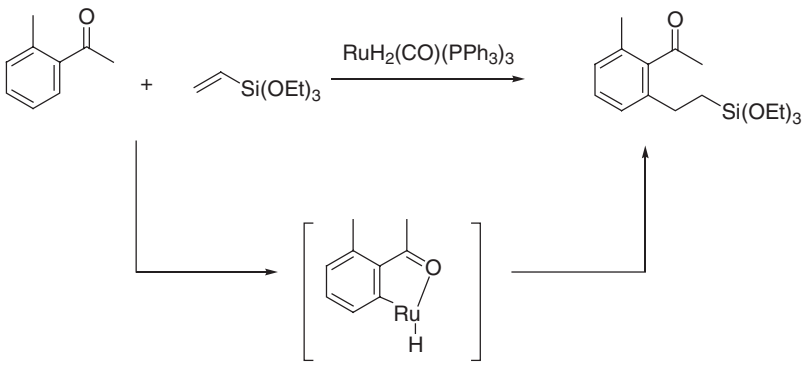
The coupling reaction between phenol and ethylene to give *ortho*-ethylphenol is catalyzed by (triphenylphosphite)ruthenium complex [20]. In this reaction, the *ortho* C–H bond of triphenylphosphite is cleaved by orthometallation, and then insertion of ethylene followed by reductive elimination lead to the formation of triarylphosphite having an *ortho*-ethylphenoxo group. Transesterification between the phosphite and phenol then releases *(ortho)*-ethylphenol by reproducing triphenylphosphite (Scheme 14.8).



Scheme 14.8

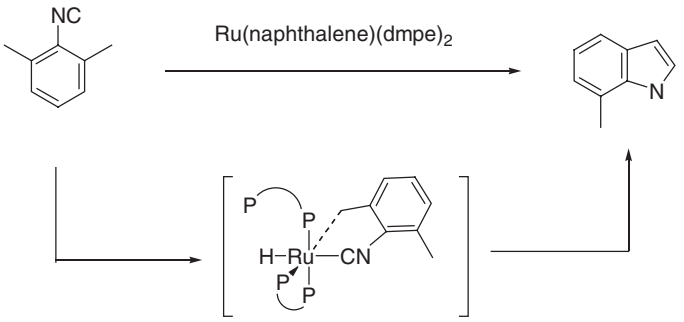
Various vinylsilanes, olefins or acetylenes insert into the *ortho* C–H bond of aromatic ketones in the presence of catalytic amount of ruthenium complexes in high yields [21,22]. The C–H bond cleavage reaction of aromatic ketones also involves orthometallation which is promoted by prerequisite coordination of the carbonyl group to ruthenium (Scheme 14.9) [21]. This type of reaction has a wide generality for aromatic and alkenyl ketones with a variety of alkenes.

Similar catalytic aromatic aldimine/olefin coupling reactions also proceed to give *ortho*-alkyl aromatic aldimine, where $Ru_3(CO)_{12}$ was found to show a higher catalytic activity for aldimine than $RuH_2(CO)(PPh_3)_3$ [22].



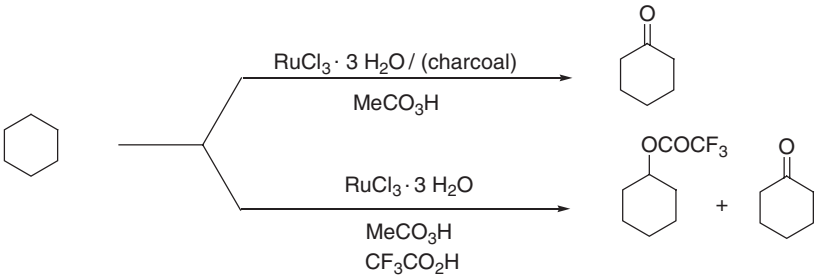
Scheme 14.9

On the other hand, the sp^3 C–H bond is much less reactive, and the catalytic cleavage reaction is still uncommon [23,24]. As a rare example, the sp^3 C–H bond in 2,6-dimethylbenzoisocyanide takes place by RuH(naphthyl)$(DMPE)_2$ to give 7-methylindole, though the efficiency is poor (TON = 3.5) (Scheme 14.10) [23]. In this reaction, isocyanide coordinates to the coordinatively unsaturated ruthenium(0) center, and the C–H bond cleavage reaction takes place.



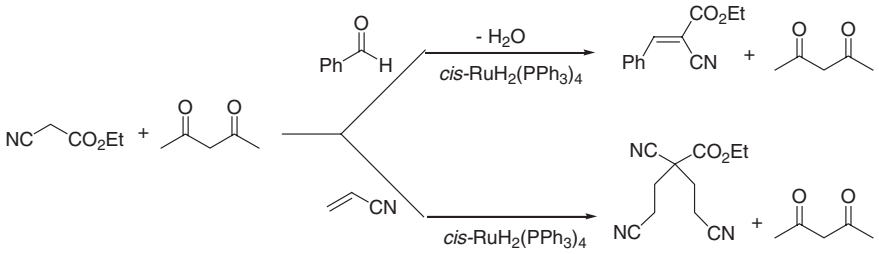
Scheme 14.10

A high-valent ruthenium complex is also reported to cleave the sp^3 C–H bond. $RuCl_3 \cdot 3H_2O$ catalyzes the *trans*formation of *cyclic* alkanes to the corresponding ketones in the presence of peracetic acid, where oxoruthenium species is considered to act as the active species. Alcohol, as a primary product in this oxidation reaction, is obtained as an intermediate in the presence of trifluoroacetic acid (Scheme 14.11) [25].



Scheme 14.11

Proton abstraction of the polar C–H bond with base is a well-established heterolytic C–H bond cleavage to obtain carbanion. Ruthenium complexes can act as a base in nonpolar media to provide highly selective catalyses, as in the Murahashi aldol and Michael reactions. These reactions are highly chemoselective under neutral and mild conditions, where cyanoesters preferentially react over 2,4-pentanedione with nucleophiles (Scheme 14.12) [26]. The mechanistic basis of this reaction is described in Section 14.2.2.



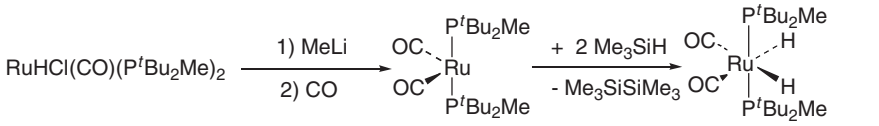
Scheme 14.12

14.2.2 Key Strategies for C–H Bond Cleavage Reactions

14.2.2.1 Coordinative Unsaturation

Coordinatively unsaturated zero-valent ruthenium complexes are capable of cleaving inactive C–H bonds. Since $RuH(C_{10}H_7)(DMPE)_2$ is in equilibrium with a Ru(0) complex having a weakly bound η^2-naphthalene ligand, Ru(naphthalene)$(DMPE)_2$, it can also be regarded as a useful precursor for a coordinatively unsaturated Ru(0) species. This complex reacts with a variety of aromatic compounds to form $RuHAr(DMPE)_2$. The introduction of electron-withdrawing groups into the aryl group is considered to stabilize the Ru-Ar bond [27].

The removal of H_2 from *cis*-$RuH_2(PPh_3)_4$ can also generate coordinatively unsaturated species. For example, treatment of *cis*-$RuH_2(PPh_3)_4$ with various olefins leads to an initial formation of a coordinatively unsaturated zero-valent ruthenium intermediate by stoichiometric facile hydrogenation of olefin. In fact, the reaction of *cis*-$RuH_2(PPh_3)_4$ with ethylene at room temperature gives an ethylene complex formally formulated as $Ru(C_2H_4)(PPh_3)_3$, which actually forms an orthometallated product $RuH(\textit{(ortho)}\text{-}C_6H_4PPh_2\text{-}\kappa^2C,P)(C_2H_4)(PPh_3)_2$ (vide infra) [28]. Similar treatment of *cis*-$RuH_2(PPh_3)_4$ with styrene results in the formation of an unusual example of a 16-electron square planar ruthenium(0) complex Ru(styrene)$_2(PPh_3)_2$, in which two phosphine ligands and the vinylic double bonds of two styrenes are coordinated to the metal [29]. Thermal reductive elimination of the precursor complexes of Ru(II) giving Ru(0) normally requires a high temperature: *cis*-$RuH_2(PMe_3)_4$ (>180 °C), *cis*-$RuHPh(PMe_3)_4$ (135 °C), and *cis*-$RuH(CH_2Ph)(PMe_3)_4$ (85 °C) [30]. However, once the unsaturated species are formed, they are sufficiently reactive toward the C–H bonds. Coordinatively unsaturated species can also be generated at low temperature by removal of HCl from $RuHCl(CO)(P^tBu_2Me)_2$ with *t*BuLi in the presence of propylene, leading to facile C–H bond activation of propylene to give an η^3-allyl complex



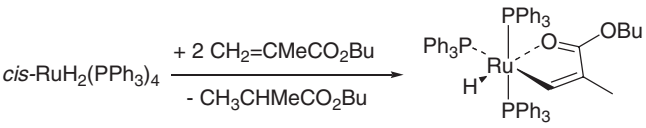
Scheme 14.13

even at –75 °C [31]. It is worth noting that the first isolated 16-electron Ru(0) complex, $Ru(CO)_2(PtBu_2Me)_2$ shows activity toward various bond activation reactions (Scheme 14.13) [32].

14.2.2.2 Close Proximity of C–H Bond

Close proximity of the C–H bond to ruthenium is also an important factor for the bond cleavage reaction. Indeed, prior coordination of a substrate through a tethered Lewis basic site renders a C–H bond in close proximity to the ruthenium center, leading to various facile bond-cleavage reactions. $RuCl_2(PPh_3)_3$ is formally regarded as a five-coordinate Ru(II) complex, but the X-ray structure analysis revealed that one of the *ortho* C–H bonds of the PPh_3 ligand has an agostic interaction, giving a pseudo six-coordinate structure [33]. When PPh_3 is replaced by $P(OPh)_3$, orthometallation smoothly takes place to form $RuCl\{P(OC_6H_4)(OPh)_2\}\{P(OPh)_3\}_3$. This complex catalyzes H/D exchange reaction of phenol at the *ortho* position under D_2 in the presence of KOPh as a cocatalyst [20,34].

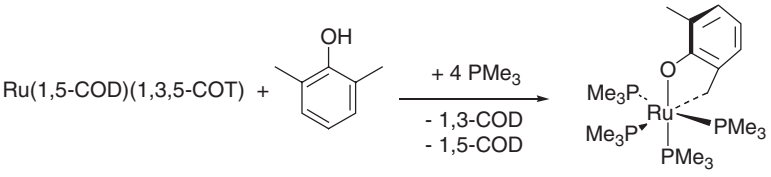
In the reaction of *cis*-$RuH_2(PPh_3)_4$ with alkyl methacrylate, regioselective sp^2 C–H bond cleavage takes place to give a ruthenacycle complex (Eq. 14.1) [35].



(14.1)

Since stoichiometric hydrogenation of alkyl methacrylate by the dihydride complex is observed, a coordinatively unsaturated ruthenium(0) complex is also believed to be formed in this reaction, as mentioned above. Coordination of olefin through carbonyl oxygen then takes place to force the sp^2 C–H bond close to the ruthenium center to cause C–H oxidative addition. A similar sp^2 C–H bond-cleavage reaction by use of acetophenone was also reported [36]. This concept of close proximity of the bond leading to C–H bond activation has been successfully applied to ruthenium-catalyzed C–H/olefin coupling reactions [1e,22]. sp^2 C–H bond cleavage is found to be a facile process, and the efficient trapping of such species is considered to be the key step for the catalysis.

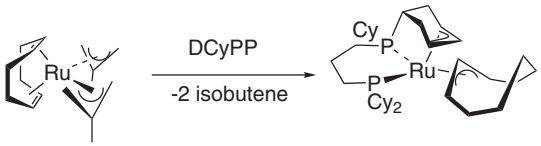
By virtue of the intramolecular anchoring bonding, sp^3 C–H bond activation may become possible. Treatment of Ru(1,5-COD)(1,3,5-COT) with *(ortho)*-substituted phenols resulted in the successive O–H and sp^3 C–H bond-cleavage reactions, giving



Scheme 14.14

an oxaruthenacycle complex *cis*-Ru[OC_6H_3(2-CH_2)(6-Me)](PMe_3)$_4$ with concomitant formation of 1,5- and 1,3-CODs (Scheme 14.14) [37].

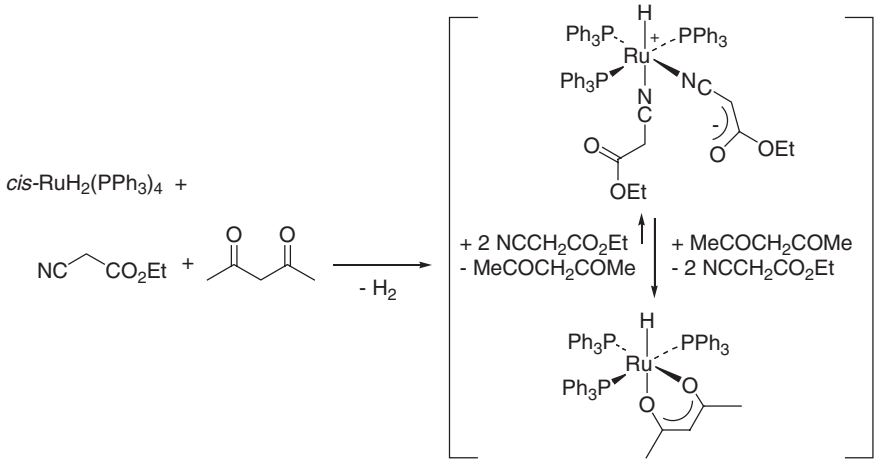
In this reaction, the allylic moiety – which is formed by initial protonation of COT – may behave as a good hydrogen acceptor for further C–H bond activation. Analogous ability of the allylic moiety as a hydrogen scavenger was also reported for Ru(η^3-2-metallyl)$_2$(1,5-COD) (Scheme 14.15) [38]. In this reaction, a *cyclo*hexyl fragment in the DCyPP ligand loses three hydrogen atoms, where two 2-methylallyl fragments and the 1,5-COD ligand act as hydrogen acceptors.



Scheme 14.15

14.2.2.3 **Cleavage of Polar C–H Bond**

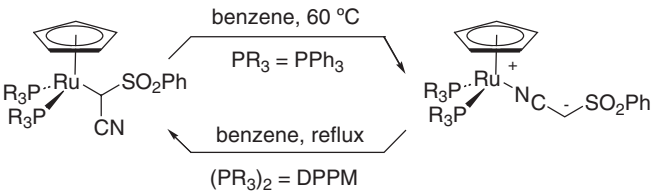
An electrophilic reaction of the acidic C–H bond to ruthenium is apparently expected, but is regarded as an intriguing process since it involves the formation of organometallic species that have potential applications for further C–C bond-forming reactions [39]. Active methylene compounds oxidatively added to Ru(0) to give hydrido(enolato)ruthenium(II) complexes. Reaction with ethyl cyanoacetate then produces zwitterionic enolato complexes *mer*-RuH(NCCHCO$_2$Et-κN)(NCCH$_2$CO$_2$Et-κN)(PPh_3)$_3$, the unique coordination mode of which is due to a strong coordinating ability of the cyano group towards the ruthenium center; in contrast, 2,4-pentanedione afforded chelating hydrido(acac-$\kappa O,O'$)ruthenium(II) complex RuH(OCMeCHCOMe-$\kappa^2 O,O'$)(PPh_3)$_3$ [40,41]. Although both ethyl cyanoacetate and 2,4-pentanedione have similar acidity (pK_a = 9.0), these enolato ligands show drastic differences in reactivity. The zwitterionic enolate smoothly reacts with electrophiles such



Scheme 14.16

as aldehyde and acrylonitrile, whereas the chelating enolate shows no tendency to react with these substances. These facts clearly explain the high chemoselectivity of the ruthenium-catalyzed Murahashi aldol (Knöevenagel) and Michael reactions, where cyanoesters preferentially react over 2,4-pentanedione with nucleophiles under neutral and mild conditions (Scheme 14.16) [42]. The selectivity of the reaction is considered to be kinetically controlled, as the equilibrium between these two enolato complexes lies on the inactive chelating enolate side.

Controlling factors for coordination modes of the enolato ligand derived from cyanoester have been examined. When sterically demanding ancillary ligands are employed, N-bonded zwitterionic compounds are preferentially formed. Relief of such steric congestion at Ru causes the coordination mode of the enolato ligand to change from N-bonded to C-bonded, thus producing a cyanoalkylruthenium complex (Scheme 14.17). In this case, the zwitterionic enolato ligand also shows a higher nucleophilicity than the C-bonded counterpart [43].



Scheme 14.17

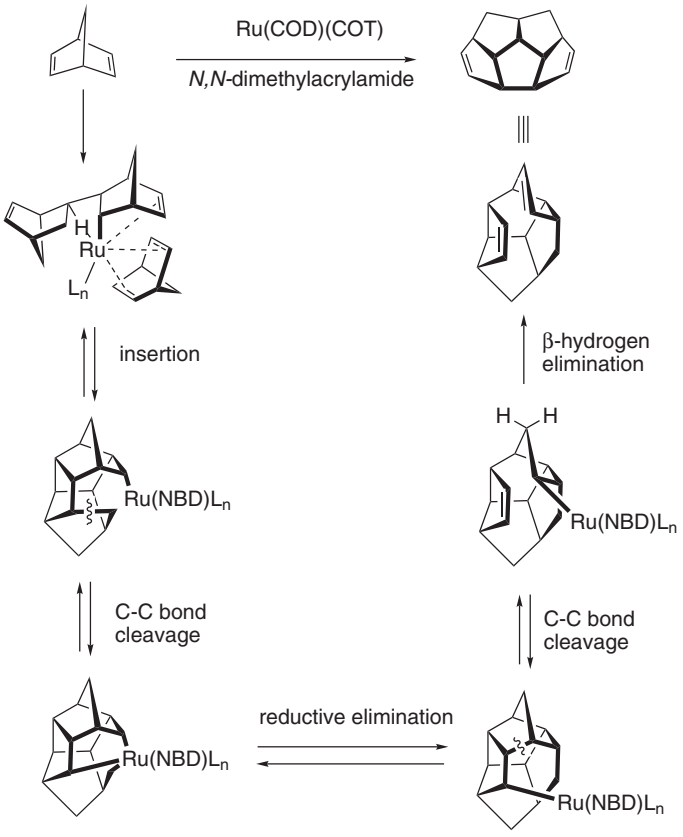
It is interesting to note that the deuterido ligand in *trans*-M(D)(NCCHCO$_2$Et)-(DEPE)$_2$ (M = Fe, Ru) was not consumed during the catalytic Michael reaction, indicating that the product-releasing step is not a reductive elimination but rather protonation by the incoming Michael acceptor [44]. This highlights the importance of initial C–H activation by Ru(0) as an entry step, although the actual catalytic cycle proceeds by a ruthenium(II) species.

14.3
C–C Bond-Activation Reactions

The activation of a carbon-carbon bond, which is the least reactive and the most fundamental bond in organic molecules, is one of the most difficult but challenging studies in organometallic chemistry. Difficulties in C–C bond activation are generally attributable to their thermodynamic stabilities and nonpolarizability, and so to date examples of catalytic C–C bond cleavage reactions are few in number. Nevertheless, several sophisticated reaction systems involving C–C bond-cleaving reactions have been documented. These examples may contribute greatly towards future research into organic synthesis, and are also regarded as model reactions for heterogeneous Pt-catalyzed naphtha-reforming reactions [45]. Some catalytic and stoichiometric C–C bond-activating reactions are described in this section.

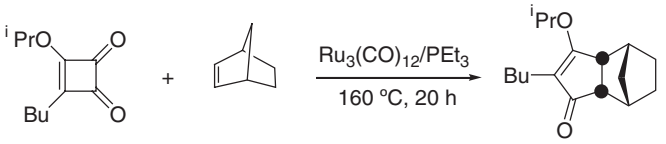
14.3.1
Catalytic C–C Bond-Cleavage Reaction

Examples of the catalytic C–C bond-cleavage reaction by Ru(0) complex are limited, though some examples have been reported. Under mild conditions, Ru(1,5-COD)(1,3,5-COT) catalyzes the conversion of 2,5-norbornadiene to a cage-shaped compound penta*cyclo*[6.6.0.$0^{2,6}$.$0^{3,13}$.$0^{10,14}$]tetradeca-4,11-diene. In this reaction, two norbornadienes dimerize, and at least two C–C bond cleavage reactions are involved to give the product, though the details of the mechanism are not clear (Scheme 14.18) [46].



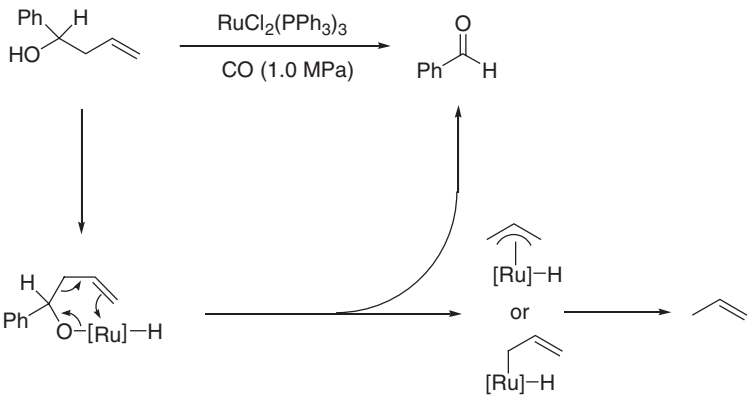
Scheme 14.18

The catalytic C–C bond cleavage of *cyclo*butenedione by $Ru_3(CO)_{12}$ in the presence of PEt_3 followed by insertion of olefin produces *cyclo*pentenone frameworks (Eq. 14.2) [47].



(14.2)

The catalytic formation of ketones and propylene from homoallylic alcohols by C–C bond cleavage is also documented by $RuCl_2(PPh_3)_3$. In this reaction, the formation of η^3- or η^1-allylhydridoruthenium(II) intermediate may be a major driving force for the C–C bond-cleavage reaction (Scheme 14.19) [48].



Scheme 14.19

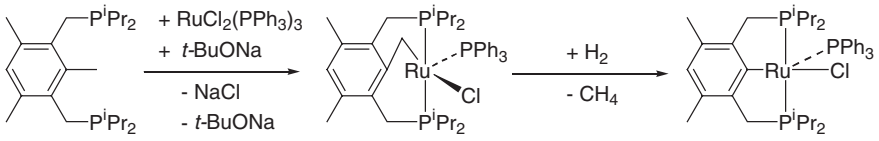
14.3.2
Key Strategies for C–C Bond-Cleavage Reactions

The two main strategies for C–C bond activation are first, the use of strained molecules and second, the close proximity of unactivated C–C bonds to the *trans*ition metal. Although the former point has been relatively well investigated [45], the latter point leads to major difficulties because an unactivated C–C bond has no inclination to interact with metal, there being no polarization and high steric congestion at the bond. Nonetheless, several examples of the latter problem have been recognized, and are described here.

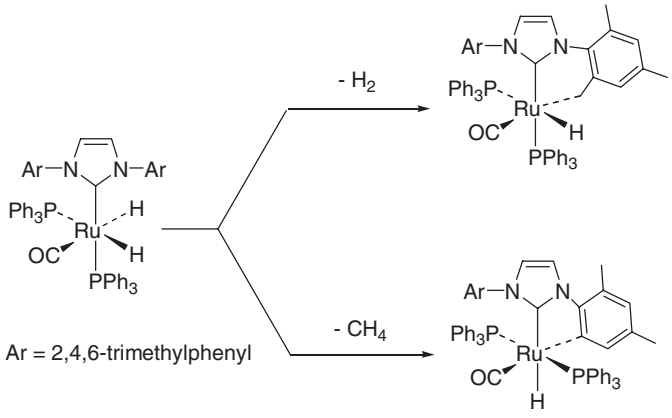
14.3.2.1 Close Proximity of C–C Bond

Close proximity of the C–C bond to the Ru metal is an important factor in the bond-cleavage reaction. A divalent ruthenium complex $RuCl_2(PPh_3)_3$ cleaves C–C bonds in a pincer-type PCP ligand under a H_2 atmosphere (Scheme 14.20) [49]. In this reaction, rapid prior C–H bond cleavage of the methyl group also occurs simultaneously. A similar cleavage of unstrained sp^2C–sp^3C bond by *cis,mer*-$RuH_2(CO)(PPh_3)_3$ has also been reported by Macgregor et al. [50]. The C–C bond activation product is also thermodynamically more favorable than C–H activation product (Scheme 14.21).

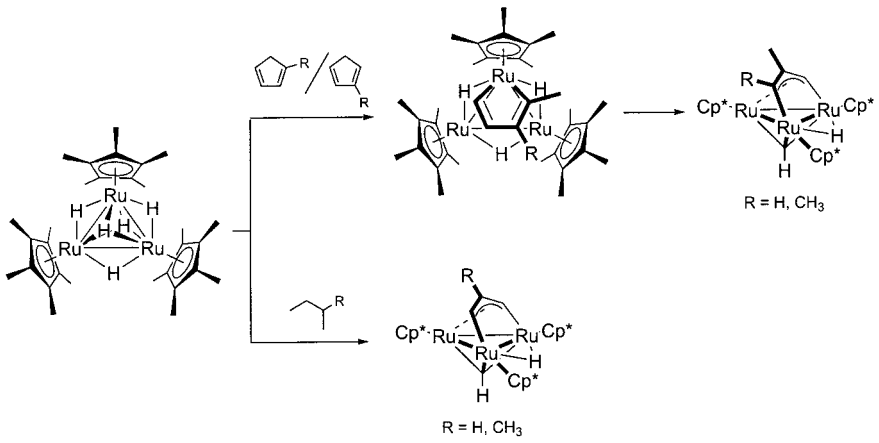
A trinuclear ruthenium cluster blocked by three pentamethyl*cyclo*pentadienyl ligands showed a unique reaction environment for C–C bond cleavage. C–C bonds in *cyclo*pentadiene and branched alkane are easily cleaved on the triruthenium cluster, giving organo(methylidyne)triruthenium complexes. For example, *cyclo*pentadiene coordinates to the trinuclear Ru cluster and cleaves a C–C bond to form ruthena*cy*-



Scheme 14.20



Scheme 14.21

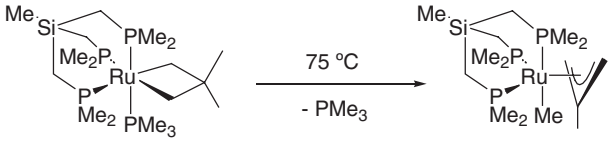


Scheme 14.22

*cyclo*hexadiene, which then *trans*forms to 2-methylruthena*cyclo*pentadiene complex (Scheme 14.22) [51]. Moreover, the final products are always thermodynamically stable. Clearly, the future application to catalysis of these reactions shows great promise.

14.3.2.2 β-Alkyl Elimination

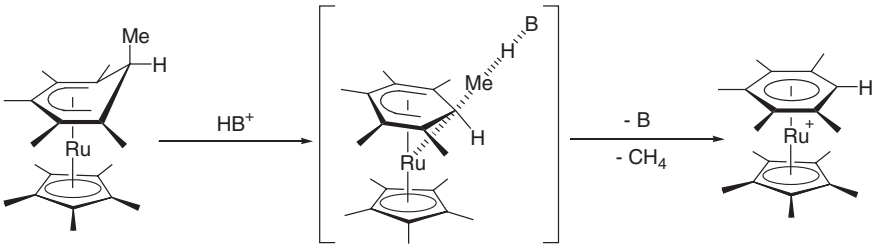
A ruthenacycle complex with a tridentate ligand $Ru(CH_2CMe_2CH_2)[(PMe_2CH_2)_3SiMe](PMe_3)$ was found to catalyze β-methyl elimination under mild conditions (75 °C) to give a (η^3-allyl)(methyl)ruthenium(II) complex (Eq. 14.3) [52]. Catalytic β-allyl elimination of homoallylic alcohol proceeds effectively to give the corresponding ketone, with the generation of propylene [53].



(14.3)

14.3.2.3 Aromatization of Ligand

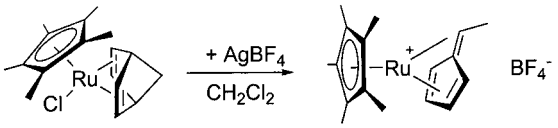
Aromatization of the ligand is a major driving force in the C–C bond-cleavage reaction. For example, sp^3C–sp^3 C bond cleavage in (pentamethyl*cyclo*hexadienyl)ruthenium is reported to give ruthenocene derivatives (Scheme 14.23) [54]. In this reaction, a Brønsted base is believed to promote demethylation from the *exo* face; similar reactions are documented for cationic ruthenium(II) complexes [55–57].



Scheme 14.23

14.3.2.4 Relief of Ring Strain

The relief of ring strain also encourages the C–C bond-cleavage reaction. For example, replacement of Cl in RuCp*(NBD)Cl by BF_4^- leads to the C–C bond cleavage of NBD to form 6-methylfulvene (Eq. 14.4) [58]. Since this reaction did not proceed in the presence of coordinating ligand such as tertiary phosphines, the major driving force in this reaction is considered to involve coordinative unsaturation.

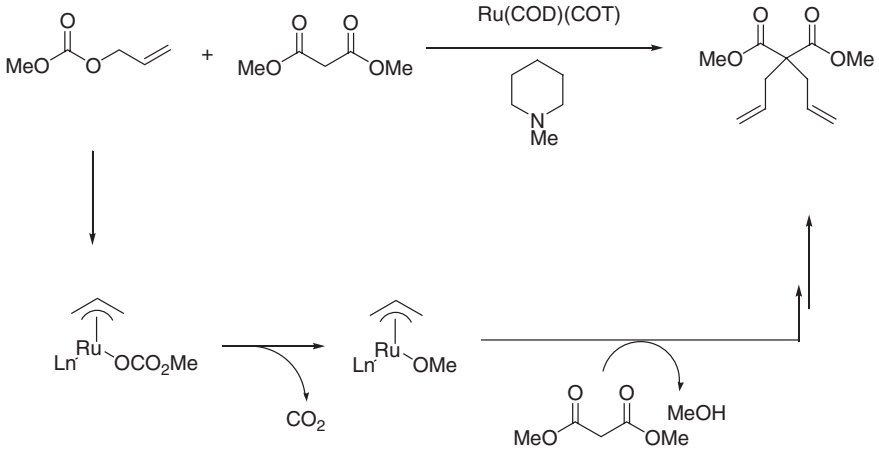


(14.4)

14.4
Cleavage Reactions of Other Single Bonds

Other bond-cleavage reactions are also important in *trans*ition metal-mediated chemical *trans*formations, and a variety of selected bond-cleavage reactions and catalysis are described in this section.

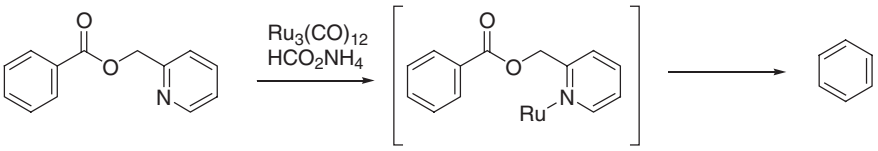
Transition-metal-mediated C–O bond cleavage reactions are interesting in view of environmentally benign halogen-free chemical processes [59]. Zerovalent ruthenium complexes are also active toward C–O bond-cleavage reactions, and a number of catalytic processes have been developed in this respect. For example, Ru(1,5-COD)(1,3,5-COT) catalyzes allylic alkylation of carbon nucleophiles with allylic carbonates in basic solvent (Scheme 14.24) [60].



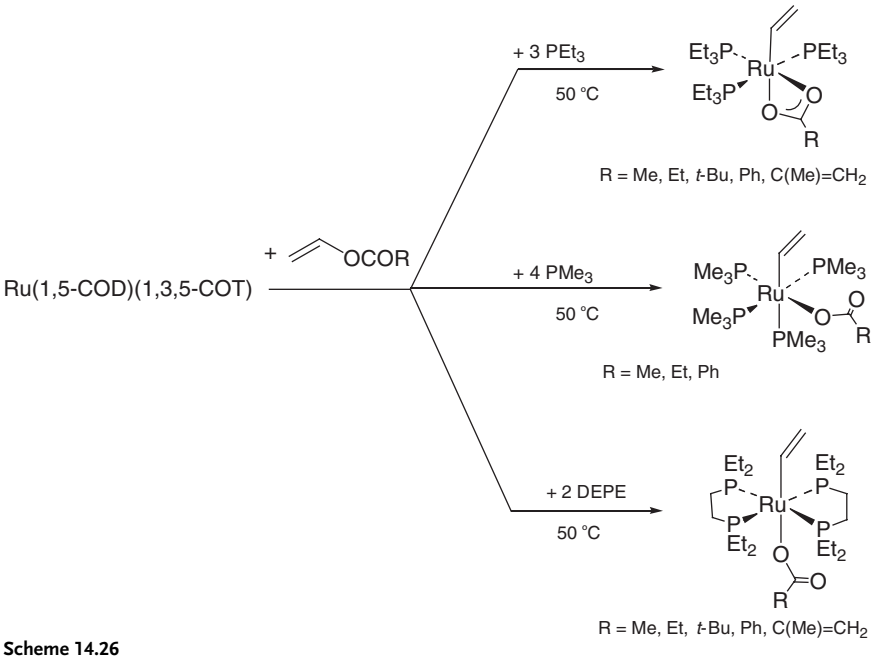
Scheme 14.24

Prerequisite coordination of the Lewis basic site to Ru complexes is known to promote bond-cleavage reactions via a so-called metallation process (Scheme 14.25) [61]. For example, the pyridinomethyl group effectively guides the C–O bond-cleavage reaction of the adjacent ester group.

The first clear example of oxidative addition of the C–O bond is the reaction of Ru(1,5-COD)(1,3,5-COT) with vinyl acetate in the presence of PEt_3, to give *mer*-$Ru(CH{=}CH_2)(OAc\text{-}\kappa^2O,O')(PEt_3)_3$ (Scheme 14.26) [62]. In this reaction, the introduction of a substituent at the alkenyl carbon discourages the reaction, but the bulky carboxylate promotes the oxidative addition. In the oxidative addition of vinyl carboxylate to Ru(1,5-COD)(1,3,5-COT) in the presence of DEPE, an intermediate



Scheme 14.25



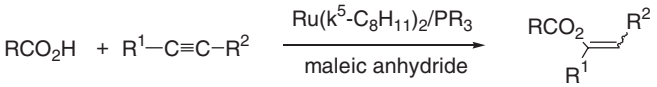
Scheme 14.26

complex formulated as Ru(η^2-CH_2=CHO_2CR)-(DEPE)(1,5-COD) was detected. When phenyl vinyl ether was employed as a reactant, a η^2-phenyl vinyl ether analogue Ru(η^2-CH_2=CHOPh)(DEPE)(1,5-COD) was isolated [63]. These facts suggest that the C–O bond oxidative addition needs prerequisite η^2-coordination of substrates. Allylic esters and ethers also oxidatively add to Ru to form a η^3-allylic complex *fac*-Ru(η^3-C_3H_5)(OR)L_3 [64]. This fact supports the oxidative addition mechanism in the catalytic allylation by use of allylic carbonates [65]. The reaction shows an ambiphilic character, and an independently prepared η^3-allylruthenium(II) complex Ru(η^3-C_3H_5)$X(CO)_3$ was in fact reactive with both electrophiles and nucleophiles to result in the C–C bond formation [66]. The reductive cleavage of allylic esters with formic acid to produce a terminal olefin is another example of this reaction [67].

As yet, the C-N bond-cleavage reaction is relatively rare. A (pentamethyl*cyclo*pentadienyl)ruthenium complex $RuCp^*X_2$ and a hydridoruthenium(II) complex $RuHCl(CO)(PPh_3)_3$ are reported to cleave the C-N bond in allylamine to give corresponding η^3-allylruthenium(II) complexes [68, 69]. The major driving force for this

reaction is likely to be the thermodynamic stability of the η^3-allyl complex formed. Stoichiometric P-C bond cleavage in *cis*-Ru$(OC_6H_4Me\text{-}4)_2(PMe_3)_4$ is also reported to give *mer*-Ru[$PMe_2(OC_6H_3Me\text{-}4)$-$\kappa^2C,P$]$(OC_6H_4Me\text{-}4)(PMe_3)_3$ [70].

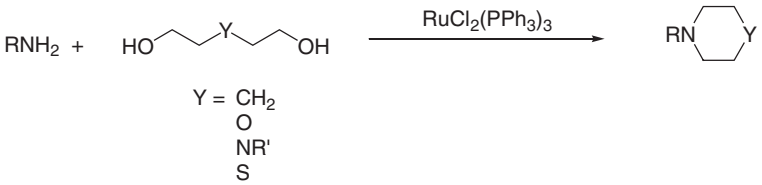
Acids can also react with ruthenium complexes by either protonation or oxidative addition. The catalytic addition of acidic compounds is also important; for example, a divalent ruthenium complex Ru(η^5-*cyclo*octadienyl)$_2$ catalyzes the addition reaction of carboxylic acid to alkynes in the presence of tertiary phosphines and maleic anhydride (Eq. 14.5) [71].



(14.5)

Another described example of bond cleavage is that of the O–H bond. Treatment of *cis*-$RuH_2(PMe_3)_4$ with phenol results in the formation of *cis*-RuH(OPh)$(PMe_3)_4$ [72]. A detailed analysis of this reaction revealed that protonation of the dihydrido complex takes place initially to provide a cationic hydrido(dihydrogen)ruthenium complex [*cis*-RuH$(H_2)(PMe_3)_4$]OPh, and this is followed by displacement of the dihydrogen ligand by the phenoxo anion. $RuH_2(PPh_3)_4$ shows a high activity toward the catalytic dehydrogenative oxidations of alcohol to ketone [73], primary alcohol to ester [74], and diol to lactone [75].

$RuCl_2(PPh_3)_3$ catalyzes coupling reactions of primary amines with 1,5-diols to give N-substituted piperidines, morpholines, and piperazines in high yields (Eq. 14.6) [76].



(14.6)

Jia and Morris reported that (dihydrogen)ruthenium(II) complex formulated as $[RuCp(H_2)L_2]^+$ produces a proton by heterolytic cleavage of the coordinated H-H bond [77]. Of particular interest is that the pK_a values of these complexes closely depend on the ancillary ligand employed (pK_a = 4.9-9.0 in THF), suggesting that a decrease in the electron density of the metal increases the acidity of the dihydrogen complex.

Oxidative addition of the carbon-halogen bond is a well-documented reaction for Group 10 *trans*ition metal complexes, but it is relatively limited for ruthenium. The example given here involves the reversible oxidative addition of allyl halide to $RuCp(CO)_2X$ to produce RuCp(η^3-allyl)X_2 [78]. Oxidative addition of allyl halide to a Ru(0) complex Ru(1,5-COD)(1,3,5-COT) is also reported, but the product yield was poor [79]. Nevertheless, a catalytic Heck-type alkenylation of bromostyrene with methyl acrylate by Ru(1,5-COD)(1,3,5-COT) proceeded smoothly [80]. A cross-coupling reaction of alkenyl halide with Grignard reagents or alkyl lithium also pro-

ceeded in moderate to good yields under ambient conditions by $RuCl_2(PPh_3)_3$, or by combination of $RuCl_2(PPh_3)_3$ with potassium or sodium amalgam [81].

The double oxidative addition of a *gem*-dihaloalkane such as CH_2Cl_2 or $PhCHCl_2$ to $Ru(H)_2(H_2)_2(PCy_3)_2$ or Ru(1,5-COD)(1,3,5-COT) affords $RuCl_2(=CH_2)(PCy_3)_2$ [82] and $Ru(=CHPh)Cl_2(PCy_3)_2$ [83] respectively, both of which are known to act as efficient metathesis polymerization catalysts. Catalytic dehalogenation of aryl chlorides by $RuH_2(H_2)_2(PCy_3)_2$ is also reported [84]. Coordinative unsaturation is also an important factor for the C-X bond-cleavage reaction. RuCp*(amidinato), which can formally be regarded as a 16-electron divalent coordinatively unsaturated complex, cleaves C–X bond of allyl halide to give a tetravalent allylruthenium complex [85].

Carbon-silicon bond cleavage is an important reaction in organosilane chemistry. The oxidative addition of a C-Si bond in $Me_3SiCCSiMe_3$ to Ru(0) complex $Ru(H_2)(CO)(PtBu_2Me)_2$ is reported to give a square-pyramidal Ru(II) complex $Ru(SiMe_3)(CCSiMe_3)(CO)(PtBu_2Me)_2$ [86]. C–Si Bond cleavage of vinylsilane was achieved by hydridoruthenium(II) complex $RuHCl(CO)(PPh_3)_3$ via β-silyl elimination of silylethylruthenium(II), evolving ethylene [87].

14.5 Conclusions

C–H and C–C bond activations by ruthenium complexes have formed the focus of this chapter, and consequently other important reactions to cleave chemical bonds such as dihydrogen, C–S and M–R have not been described. Today, ruthenium is regarded as a powerful tool for cleaving a variety of both activated and unactivated chemical bonds under homogeneous conditions. Important factors that provide these activities include: 1) coordinative unsaturation of the ruthenium center; 2) a close proximity of the bond to the ruthenium metal; and 3) kinetic preference and thermodynamic stability of the products. It is likely that the combined use of ruthenium complexes and modern strategies in organic synthesis and catalysis will provide many opportunities for the creation of new reaction processes in the future.

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