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Ruthenium in Organic Synthesis

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Contents

Preface

In the recent past, transition metals have contributed extensively to organic synthesis, and this trend will continue in the future. Although ruthenium chemistry has lagged somewhat behind that of the other transition metals such as palladium, ruthenium complexes have a variety of useful characteristics including high electron transfer ability, high coordination ability to hetero-atoms, Lewis acid activity, low redox potentials, and unique reactivity of metal species and intermediates such as oxo-metals, metallacycles, and carbene complexes. Consequently, a large number of novel, useful reactions have begun to be developed using both stoichiometric and catalytic amounts of ruthenium complexes. Although several organic reactions using ruthenium catalysts have been reviewed separately, there is at present no comprehensive book available which details the field of ruthenium chemistry. Hence, the publication of this volume, *Ruthenium in Organic Synthesis*, is both interesting and timely, bearing in mind the recent developments in ruthenium chemistry and the practical application of ruthenium compounds. I hope that this book will provide valuable information to those researchers currently working on the chemistry of ruthenium – both in academia and industry – and will stimulate new developments in this fascinating area of chemistry.

I would like to thank the authors of the individual chapters, each of whom is acknowledged as a world expert in their area of ruthenium chemistry, for their cooperation in writing within the limited number of pages available. I would also like to thank the team at Wiley-VCH, especially Dr. Elke Maase and Dr. Romy Kirsten for their help and cooperation, not only for editing the manuscripts but also for providing valuable assistance during the publishing process.

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Okayama,
February 2004

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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

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.

References

1 (a) W. P. Griffith, *The Chemistry of the Rare Platinum Metals: Os, Ru, Ir, and Rh*, Wiley-Interscience, New York, **1967**; (b) F. A. Cotton, G. Wilkinson, C. A. Murillo, M. Bochman, *Advanced Inorganic Chemistry*, 6th ed., John Wiley & Sons, New York, **1999**; (c) S. Komiya, M. Hirano, *Synthesis of Organometallic Compounds*, S. Komiya (Ed.), John Wiley & Sons, New York, **1997**; (d) *Comprehensive Inorganic Chemistry*, Volume 3, J. C. Bailar, H. J. Emeléus, R. Nyholm, A. F. Trotman-Dickenson (eds.), Pergamon Press, Oxford, **1973**.

2 T. Naota, H. Takaya, S.-I. Murahashi, *Chem. Rev.* **1998**, *98*, 2599.

3 B. M. Trost, F. Đ. Toste, A. B. Pinkerton, *Cem. Rev.*, **2001**, *101*, 2067.

4 R. Noyori, T. Ikeda, T. Ohkuma, M. Widhalm, M. Kitamura, H. Takaya, S. Akutagawa, *J. Am. Chem. Soc.*, **1989**, *111*, 9134.

5 S.-I. Murahashi, T. Naota, T. Kuwabara, T. Saito, H. Kumobayashi, S. Akutagawa, *J. Am. Chem. Soc.*, **1990**, *112*, 7820.

6 R. H. Grubbs (Ed.), *Handbook of Metathesis, Volume 2*, Applications in Organic Synthesis, Wiley-VCH, **2003**.

7 R. H. Grubbs (Ed.), *Handbook of Metathesis, Volume 3*, Applications in Polymer Synthesis, Wiley-VCH, **2003**.

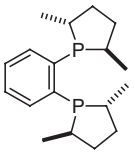
2
Hydrogenation and Transfer Hydrogenation

M. Kitamura and R. Noyori

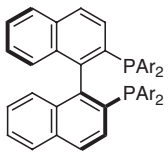
2.1
Introduction

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.

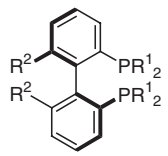


1, Me-DuPHOS



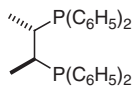
2, (*S*)-BINAP

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

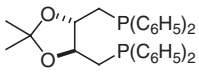


3, (*S*)-BIPHEMP

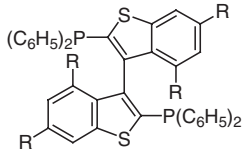
BIPHEMP: $R^1 = C_6H_5$; $R^2 = CH_3$
MeO-BIPHEP: $R^1 = C_6H_5$; $R^2 = CH_3O$
BICHEP: R^1 = *cyclo*-C_6H_{11}; $R^2 = CH_3$



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

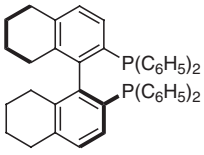


5, (*S*,*S*)-DIOP

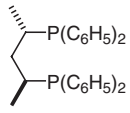


6, BITIANP

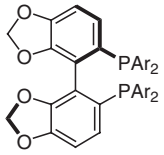
BITIANP: R = H
tetraMe-BITIANP: R = CH_3
(absolute configuration unknown)



7, (*S*)-H_8-BINAP

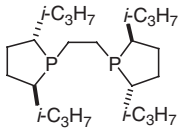


8, (*S*,*S*)-BDPP

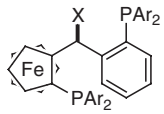


9, (*R*)-SEGPHOS

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

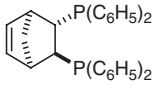


10, *i*-Pr-BPE



(*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



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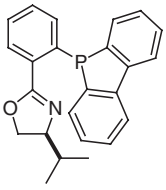
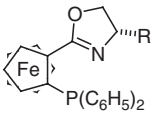
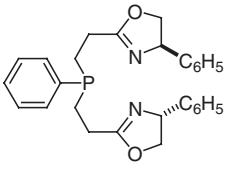


(*S*)-**13**

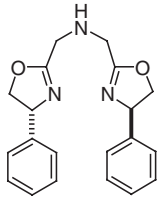


(*S*)-**14**

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



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



16, (*R*)-AMBOX

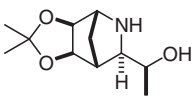


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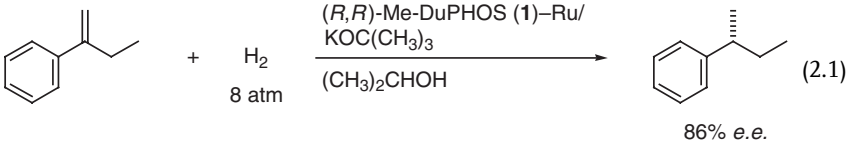
Figure 2.1 Ligands.

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].

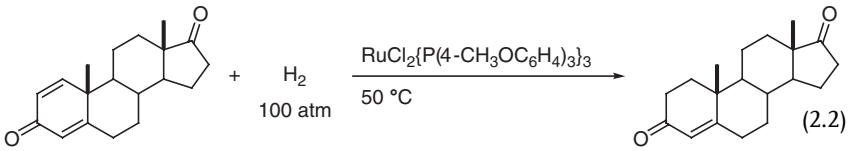
Control of the enantioselective hydrogenation of unfunctionalized olefins is not easy with chiral Ru complexes at the moment. Only a few successful examples have been reported. 2-Phenyl-1-butene, the simplest α-disubstituted prochiral olefin, is hydrogenated in 2-propanol by $RuCl_2\{(R,R)\text{-me-duphos}$ (**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].

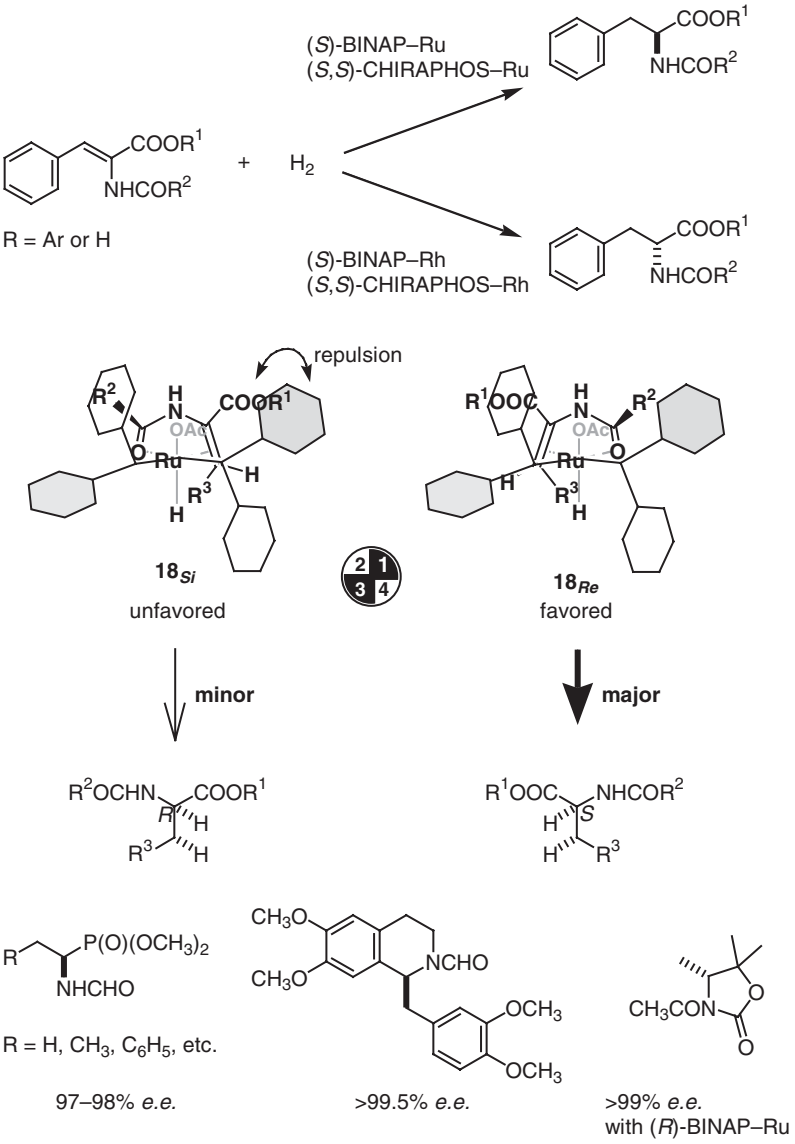


(2.2)

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

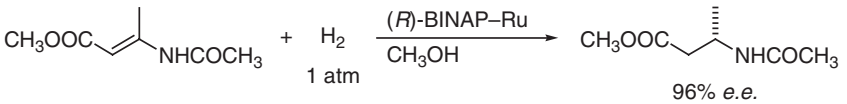


Scheme 2.1

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].

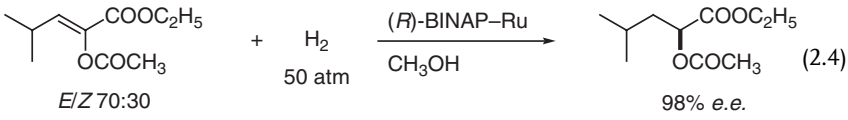
According to the above mechanism, replacement of alkoxycarbonyl group with a bulkier size of substituent is expected to increase the degree of enantioselectivity. 1-(Formamido)alkenylphosphonates and *N*-acyl-1-alkylidenetetrahydroisoquinolines, which have the sp^3-hybridized, tetrahedrally arranged 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)

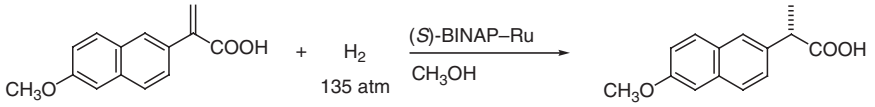
Without conjugation of the olefinic double bond to the alkoxycarbonyl function, high selectivity and high reactivity are attained in some cyclic systems. Even ester function can be replaced with ether. Thus, (*S*)-BINAP-Ru-catalyzed high-pressure hydrogenation of four- and five-membered cyclic lactones 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].

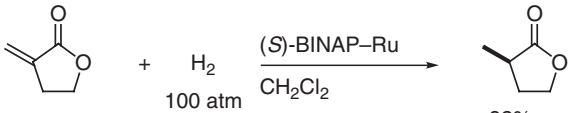
Enantioselective hydrogenation of α-aryl-substituted acrylic acids has been extensively studied because of the pharmaceutical importance of the saturated products. Anti-inflammatory (*S*)-naproxen of 97% *e.e.* is obtained by the high-pressure hydrogenation of 2-(6′-methoxy-2′-naphthyl)acrylic acid using 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].



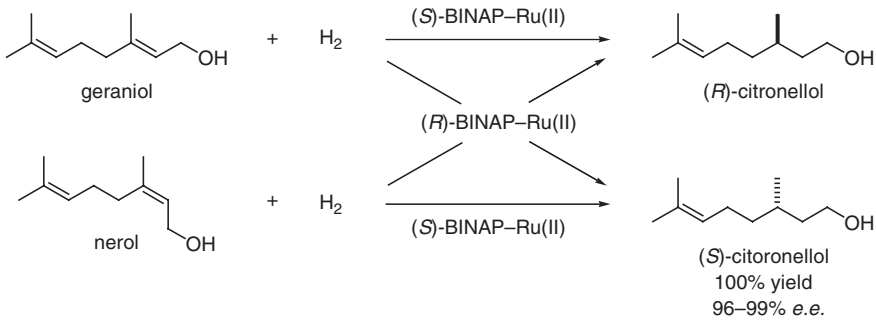
(2.5)

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-



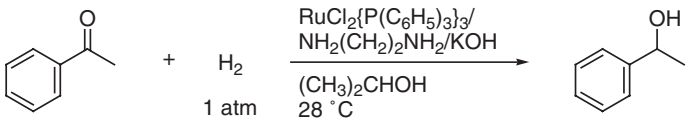
Scheme 2.2

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*-$RuCl_2\{P(4\text{-}CH_3C_6H_4)_3\}_2\text{-}\{NH_2(CH_2)_2NH_2\}$ 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].

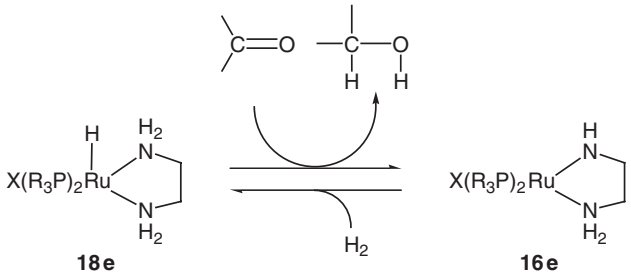


(2.7)

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

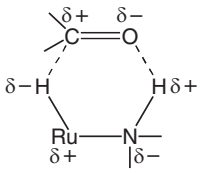
>99% yield
TOF = 880 h^{-1}

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