

Bifunctional Transition Metal-Based Molecular Catalysts for Asymmetric Syntheses

Takao Ikariya

Abstract The discovery and development of conceptually new chiral bifunctional molecular catalysts based on the metal/NH acid–base synergy effect are described. The chiral bifunctional molecular catalysis originally developed for asymmetric transfer hydrogenation of ketones is applicable in enantioselective hydrogenation of polar functionalities as well as practical oxidative reactions including aerobic oxidation of alcohols. The structural modification and electronic fine-tuning of the protic amine chelating ligands are crucial to develop unprecedented catalytic reactions. The present bifunctional transition metal-based molecular catalyst offers a great opportunity to open up new fundamentals for stereoselective molecular transformations.

Keywords Aerobic oxidation · Asymmetric reduction · Bifunctional molecular catalyst · Concerto catalysis · Cooperating ligand

Contents

1	Introduction	32
2	Asymmetric Transfer Hydrogenation of Simple and Functionalized Aromatic Ketones with the Bifunctional Catalysts	33
3	Catalytic Hydrogenation of Carboxylic Acid Derivatives Containing C=O Double Bonds with Bifunctional Molecular Catalysts	39
3.1	Heterolytic Cleavage of Molecular Hydrogen with Bifunctional Catalysts	39
3.2	Hydrogenation of Imides	41
3.3	Hydrogenation of <i>N</i> -Acylcarbamates and <i>N</i> -Acylsulfonamides	42
3.4	Hydrogenation of Esters and Lactones	43
3.5	Hydrogenolysis of Epoxides	44

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4	Oxidative Transformations with Bifunctional Molecular Catalysts	45
4.1	Dehydrogenative Oxidation of Alcohols with Cp [*] Ru(P–N) Catalysts	45
4.2	Aerobic Oxidation of Alcohols with Bifunctional Molecular Catalysts	48
5	Conclusions	51
	References	52

1 Introduction

A deep understanding of the mechanism of catalytic transformations as well as a great insight into the architecture of molecular catalysts has enabled rational design of sophisticated metal-based molecular catalysts [1–4]. Particularly, much effort has been recently paid to the development of bifunctional molecular catalysts based on the combination of two or more active sites working in concert, to attain highly efficient molecular transformations for organic synthesis. We have recently developed metal–ligand cooperating bifunctional catalysts (concerto catalyst), in which the non-innocent ligands directly participate in the substrate activation and in the bond formation. This bifunctional molecular catalysis is now an attractive and general strategy to highly realize effective molecular transformation [5–9].

The first metal-cooperating ligand bifunctional catalyst for reductive transformation of carbonyl compounds was reported by Shvo in 1985 [10, 11]. In 1995, Noyori and Ikariya found a prototype of the bifunctional ruthenium catalysts based on the M/NH acid base synergy effect, RuH(Tsdpn)(η^6 -arene), [TsDPEN: *N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine] [12–14] as shown in Fig. 1, for asymmetric transfer hydrogenation of ketones and imines. Milstein's pincer-type bifunctional catalysts based on the aromatization–dearomatization of the pyridyl ligand facilitate hydrogenation and transfer hydrogenation [15, 16]. Grützmacher's diolefinic amido Rh catalysts based on the Rh/NH bifunctionality promote hydrogenation and transfer hydrogenation of olefinic compounds [17, 18].

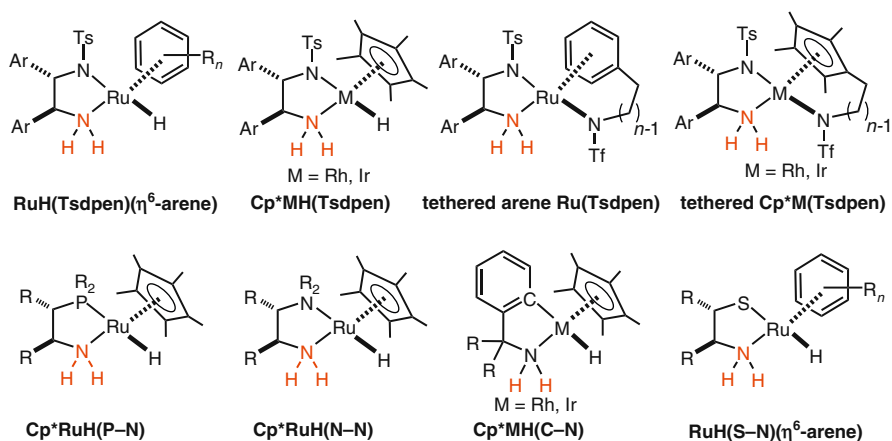


Fig. 1 A prototype and modified bifunctional catalysts bearing chelating amine ligands

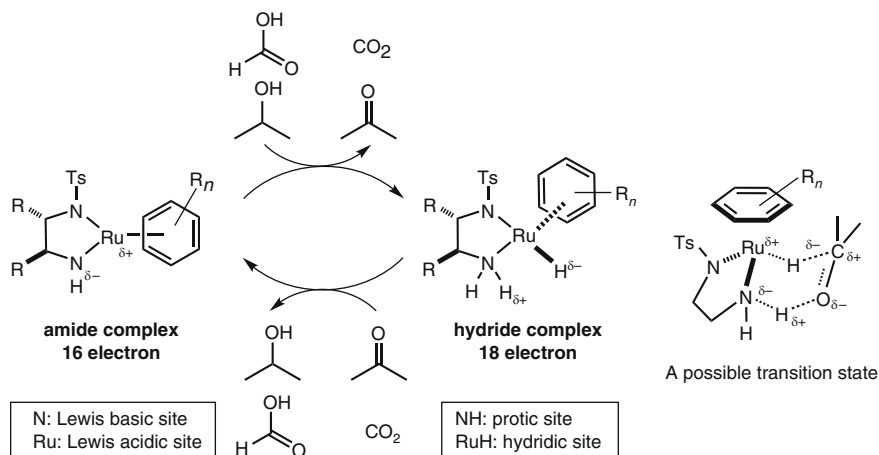


Fig. 2 Concept of bifunctional molecular catalysis based on M/NH acid–base synergy effect

Detailed structural studies on the active catalysts and kinetic studies as well as computational analysis for this hydrogen transfer revealed that an excellent catalytic performance is attributable to the metal–ligand cooperation based on a metal/NH bifunctionality [19]. This conceptually new bifunctional catalysis is unique and simple. Only the chiral amido and chiral amine hydrido ruthenium complexes are involved as catalysts and intermediates. The hydrogen transfer between an alcohol and a ketone takes place reversibly through a six-membered pericyclic transition state as shown in Fig. 2. An important and unprecedented aspect is that the carbonyl compound can be activated via outer-sphere mechanism, in which the metal and the amine ligand work in concert for its efficient activation, leading to high reaction rate and excellent stereoselectivities. The presence of an NH moiety in the ligands is crucially important to determine the catalytic performance in terms of reactivity and selectivity.

In this chapter, I outline our recent progress in asymmetric reductive and oxidative transformations with bifunctional molecular catalysts based on ruthenium, rhodium, and iridium complexes bearing chiral chelating amine ligands.

2 Asymmetric Transfer Hydrogenation of Simple and Functionalized Aromatic Ketones with the Bifunctional Catalysts

The concept of the chiral bifunctional η^6 -arene–Ru complexes, RuCl(Tsdpen)-(η^6 -arene), has been successfully extended to analogous Cp*Rh and Ir complexes, Cp*MCl(Tsdpen) (Cp* = η^5 -C(CH₃)₅, M = Rh, Ir) [20, 21], as well as a new family of Cp*Ru complexes bearing the protic amine chelating ligands (Fig. 1) for

hydrogenation [22], which will be discussed later. The chiral N-sulfonylated diamine complexes serve as highly efficient catalysts for asymmetric transfer hydrogenation of simple alkyl aryl ketones and imines [13]. Chiral N-tosylated diamines, β -amino alcohols (O–N) [23–25], diamines (N–N) [26], amino phosphines (P–N) [22], and aminoethanethiols (S–N) [27] serve as excellent cooperating ligands and lead to high reactivity and enantioselectivity in these asymmetric reactions.

In general, 2-propanol and formic acid can be used as very cheap hydrogen sources. Particularly, 2-propanol is a safe, nontoxic, environmentally friendly hydrogen source. Although the asymmetric reduction in 2-propanol gives satisfactory results, an inherent problem of the reaction using 2-propanol is the reversibility, leading to limited conversion determined by thermodynamic factors of the system and the deterioration of enantiomeric purity of the products upon the long exposure of the reaction mixture to the catalyst.

On the other hand, the asymmetric reduction using formic acid proceeds irreversibly with kinetic enantioselection and, in principle, 100% conversion. However, this bifunctional Ru catalyst also efficiently promotes hydrogenation of CO₂ to give formic acid and its derivatives [28]. Therefore, effective removal of CO₂ with inert gas allow complete conversion, in particular, in a large-scale reaction.

Asymmetric reduction of simple aromatic ketones with a mixture of formic acid and triethylamine containing the bifunctional catalyst is characterized by high efficiency in terms of activity, selectivity, wide applicability, and practicability. As a result of the coordinatively saturated nature of the bifunctional amine hydrido Ru complex, the reduction proceeds chemoselectively without the interference of amino, ester, hydroxyl, carbonyl, sulfido, sulfone, nitro, azide, and chloride groups, neither furan, thiophene, and quinoline rings, nor the olefinic linkage. For example, a reaction of the keto esters with a mixture of HCO₂H/N(C₂H₅)₃ containing Ru–TsDPEN complexes gives the corresponding chiral alcohols with moderate to excellent ee's (Fig. 3) [8, 29].

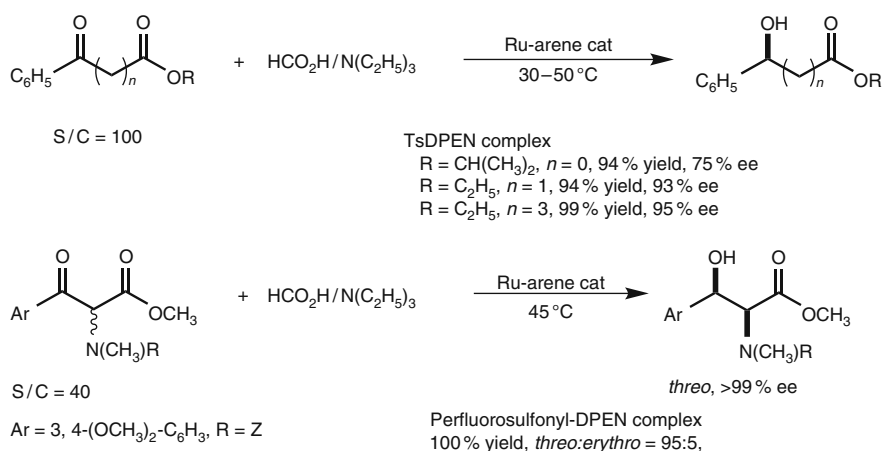


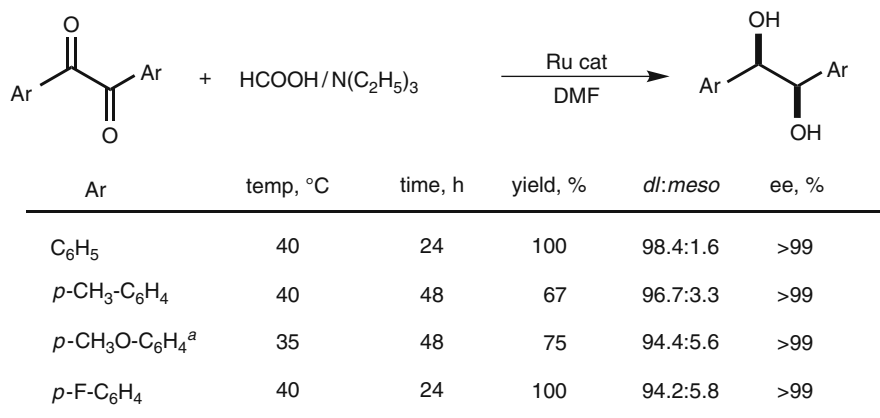
Fig. 3 Asymmetric reduction of benzoylacetate esters and β -keto esters

β -(3,4-Dimethoxyphenyl)serine methyl ester is obtainable in high diastereomeric and enantiomeric excesses from similar stereoselective transfer hydrogenation of β -keto- α -methylamino acid ester with a mixture of $\text{HCO}_2\text{H}/\text{N}(\text{C}_2\text{H}_5)_3$ and chiral arene-Ru catalysts bearing *N*-perfluorobutanesulfonyl-1,2-diamine ligand [29].

1,2-Diaryldiketones are stereoselectively reducible with the chiral Ru-*p*-cymene complex in a mixture of $\text{HCO}_2\text{H}/\text{N}(\text{C}_2\text{H}_5)_3$ to give the chiral 1,2-diols with excellent ee's (Fig. 4) [30, 31]. Notably, the outcome of the asymmetric reduction of benzils relies strongly on the property of the benzoin intermediates and the reactivity of the chiral Ru complex. For example, a reaction of racemic benzoin with the (*S,S*)-Ru catalyst gives (*R,R*)-diol with >99% ee at the early stage of the reaction (4% yield), while after 24 h, a chiral diol with the same de's and ee's as observed at the initial stage of the reaction is quantitatively obtainable, indicating that the reaction proceeds through a DKR of the intermediary benzoin [31]. This chiral diol can be readily converted to the corresponding chiral diphenylethylenediamine by the conventional procedure. Similarly, the reaction of 1,3-diphenylpropane-1,3-dione produces the corresponding chiral diol with 99% ee and in 99% yield (*dl:meso* = 94:6). The reduction of 1,3-pentanedione gives no reduction product under the same conditions [32, 33].

Asymmetric reduction of unsymmetrically substituted 1,2-diketones with the chiral Ru catalyst gives a partly reduced chiral α -hydroxy ketone at 10°C, while at higher temperature, 40°C, chiral *anti*-1,2-diols with an excellent ee is obtainable (Fig. 5) [34]. This method can be applied to access (1*R*,2*S*)-1-(4'-methoxyphenyl)-1,2-propanediol (98% ee), which is a major metabolite of *trans*-anethole in the rat.

Another valuable class of functionalized ketones is acetophenones bearing a functional group at the α -position. The reactions of acetophenones bearing CN, N₃,



Conditions: Ru cat = RuCl[(*S,S*)-Tsdpen](*p*-cymene), S/C = 1000, $\text{HCOOH}/\text{N}(\text{C}_2\text{H}_5)_3 = 4.4/2.6$. ^aS/C = 200, $\text{HCOOH}/\text{N}(\text{C}_2\text{H}_5)_3 = 4.4/4.4$ in 1.2M DMF.

Fig. 4 Asymmetric reduction of benzils with chiral Ru catalyst

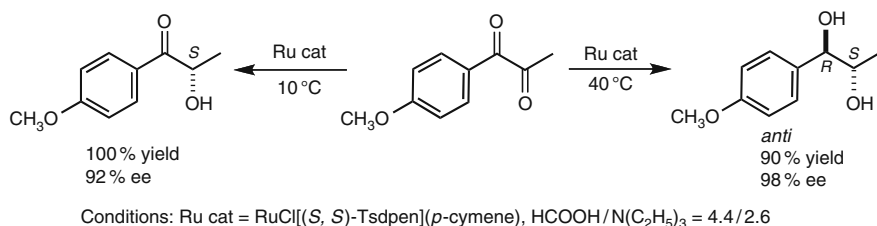


Fig. 5 Asymmetric reduction of unsymmetrically substituted 1,2-diketone

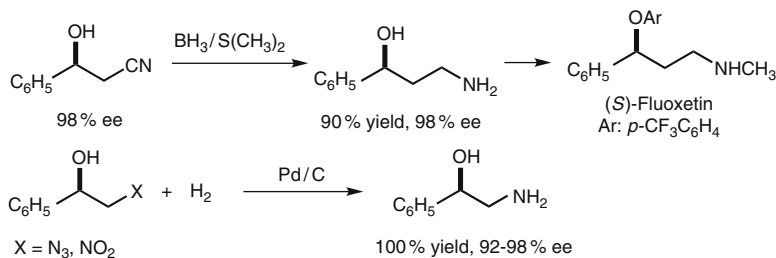
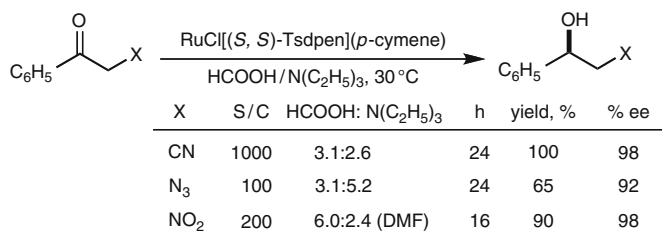


Fig. 6 Asymmetric reduction of acetophenones bearing CN, N_3 , and NO_2 groups

and NO_2 with a mixture of $HCO_2H/N(C_2H_5)_3$ containing the chiral Ru catalysts smoothly proceed to give the corresponding chiral alcohols with an excellent ee (Fig. 6) [32]. These alcohols can be easily transformed by the conventional reduction of the functional groups to chiral β - and γ -amino alcohols with high ee.

A chiral Cp^*Rh complex, $Cp^*RhCl[(R,R)\text{-Tsdpen}]$, is the most reactive catalyst for the asymmetric reduction of a variety of ring-substituted α -chloroacetophenones. The reduction with an azeotropic mixture of $HCO_2H/N(C_2H_5)_3$ and the Rh catalyst proceeds rapidly to give almost quantitatively the corresponding chiral alcohol with 96% ee and an initial turnover frequency (TOF) exceeding $2,500\text{ h}^{-1}$ (0.7 s^{-1}) [35].

The use of a Wills' tethered Ru catalyst gives significant improvement in the reactivity; the reaction with an S/C = 200 gives the reduction product quantitatively with 95% ee after 1.5 h [36]. The resulting chiral 2-chlorophenylethanol is easily convertible to chiral styrene oxide with NaOH in water without loss of ee.

A more appealing feature is that one-pot synthesis of chiral styrene oxides can be performed by sequential asymmetric reduction of chloroacetophenones with the chiral Rh in 2-propanol followed by treatment of the reaction mixture with NaOH aqueous solution, leading to the desired products in isolated yields of 80–90% with 96–98% ee in a single reactor (Fig. 7) [37]. For example, (*S*)-*m*-chlorostyrene oxide, which is a key intermediate for the preparation of several β 3-adrenergic receptor agonist compounds, is easily obtained from a one-pot procedure.

Diastereoselective reduction of enantiomerically enriched aliphatic chlorinated ketones bearing another stereogenic center, *N*-substituted (3*S*)-3-amino-1-chloro-4-phenyl-2-butanones with the chiral Rh catalyst gives the corresponding chiral alcohols in excellent yields with high de's. Using Cp**Rh*Cl[(*S,S*)-Tsdpen] as a catalyst, the (2*S*,3*S*)-alcohol can be obtained with an excellent de, while the antipodal (*R,R*)-Rh catalyst gives rise to the (2*R*,3*S*)-alcohol (Fig. 8) [38]. A sequential asymmetric reduction of *N*-(*tert*-butoxycarbonyl)-(3*S*)-3-amino-1-chloro-4-phenyl-2-butanone with a mixture of HCO₂H/N(C₂H₅)₃ in 2-propanol containing the (*S,S*)-Rh catalyst followed by treatment of the reaction mixture with 1 M NaOH aqueous solution at 0°C gives (2*S*,3*S*)-*N*-(*tert*-butoxycarbonyl)-3-amino-1,2-epoxy-4-phenylbutane with 90% de, as crystals after the addition of water (Fig. 8). These chiral epoxides serve as potential chiral building blocks for the synthesis of pharmaceuticals such as inhibitors of HIV protease and of β -secretase in Alzheimer's disease.

Sulfur- or oxygen-containing ketones are also reducible with a mixture of formic acid and triethylamine containing chiral Ru catalyst to the corresponding chiral alcohols with 97–99% ee (Fig. 9) [8]. The resulting chiral alcohols are key intermediates for the synthesis of MK-0417, a carbonic anhydrase inhibitor. In a similar manner, asymmetric reduction of acetylpyridine and its derivatives bearing an electron-withdrawing group at 10°C gives chiral pyridylethanols in almost quantitative yield and with up to 92% ee [39], one of which is an intermediate of

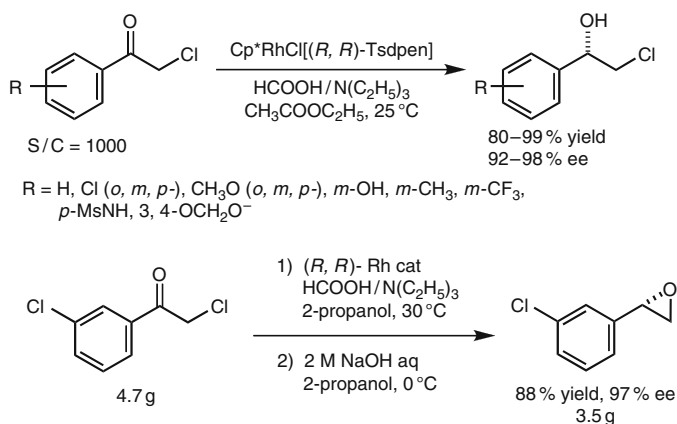
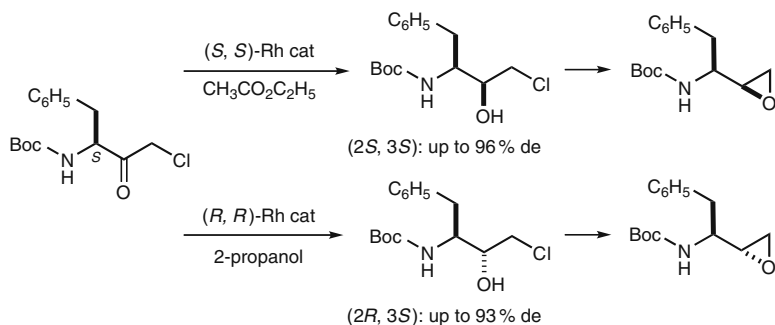


Fig. 7 Asymmetric reduction of α -chloroacetophenones and one-pot procedure for the synthesis of chiral epoxide



Reduction: Rh cat = Cp^{*}RhCl(Tsdpn), S/C = 1000, HCOOH/N(C₂H₅)₃, 1.0M solution, 25 °C, 2 h. **Epoxidation:** 2M NaOH aq in 2-propanol, 0 °C

Fig. 8 Asymmetric reduction of *N*-(*tert*-butoxycarbonyl)-(3*S*)-3-amino-1-chloro-4-phenyl-2-butanone and one-pot procedure for the synthesis of chiral epoxide

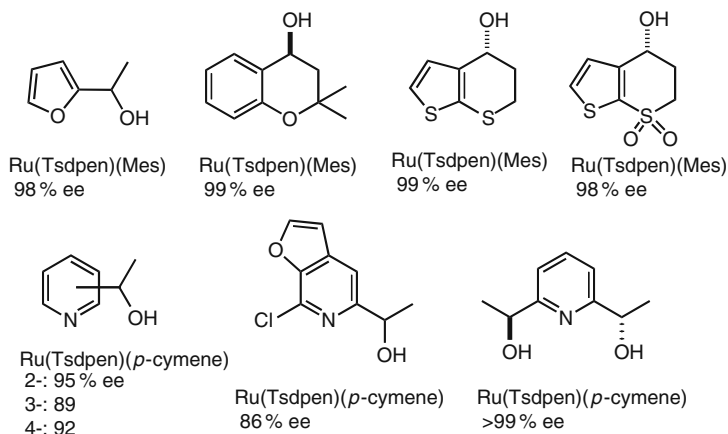


Fig. 9 Asymmetric reduction products of hetero atom containing ketones

PNU-142721, a potent *anti*-HIV medicine. Willis reported that his tethered version of the Ru(TsDPEN) catalyst is also highly effective for asymmetric reduction of 2,6-diacetylpyridine with a mixture of HCO₂H/N(C₂H₅)₃ to a chiral diol with 99.6% ee in 91% yield [36].

Both aryl- and alkylethynyl ketones are also reducible with 2-propanol containing the (*S,S*)-Ru catalyst to give chiral propargylic alcohols with an excellent ee and in good yield (Fig. 10). The asymmetric reduction of chiral acetylenic ketones with a pre-existing stereogenic center leads to diastereomeric propargylic alcohols. Using (*R,R*)- or (*S,S*)-catalyst for the reduction of the (*S*)-ketone with 98% ee leads to (3*S*,4*S*)-alcohol in 97% yield and with >99% ee and (3*R*,4*S*)-isomer in 97% yield and with >99% ee [40]. Similarly, functionalized acetylenic ketones bearing chiral centers can be reduced with excellent diastereoselectivity [41].

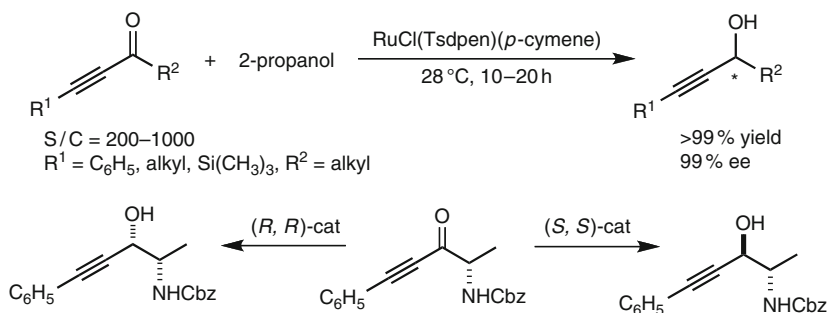


Fig. 10 Asymmetric reduction of α,β -acetylenic ketones

3 Catalytic Hydrogenation of Carboxylic Acid Derivatives Containing C=O Double Bonds with Bifunctional Molecular Catalysts

3.1 Heterolytic Cleavage of Molecular Hydrogen with Bifunctional Catalysts

Direct hydrogenation using molecular hydrogen with bifunctional molecular catalyst is a straightforward, practical, and environmentally benign process. In 1995, Noyori and coworkers discovered that a combined catalyst system including *trans*-[RuCl₂(diphosphine)(diamine)] and a base serves as a highly efficient catalyst for the hydrogenation of ketones and aldehydes, in which excellent chemo- and stereoselectivity originates from the Ru/NH bifunctional property [5, 42, 43]. The active catalyst, the amido Ru complex, undergoes heterolytic H₂ cleavage to generate the hydrido Ru complex. NMR studies of *trans*-[RuH(η^2 -H₂)(diphosphine)(diamine)]⁺ in 2-propanol-*d*₈ have revealed that subtle interplay between ligated η^2 -H₂ and solvated 2-propoxide is responsible for the heterolytic cleavage of H₂ in 2-propanol [44, 45].

In 2001, we found that H₂ bound to the coordinatively unsaturated Cp^{*}Ru[(CH₃)₂N(CH₂)₂NH₂]⁺(OR)⁻ complex (*N,N*-dimethylaminoethylamine, N–N) undergoes heterolytic cleavage through a hydrogen-bonding network in 2-propanol to give coordinatively saturated Cp^{*}RuH[(CH₃)₂N(CH₂)₂NH₂], on the basis of very careful isotope labeling experiments [26]. The alcohol-assisted H₂ activation on the amido Ru complex is a key step for hydrogenation with half-sandwich type of bifunctional catalysts (Fig. 11). Later, this reaction pathway was confirmed by Brandt and Andersson using theoretical calculations [46]. Similarly, Cp^{*}Ru(P–N) complexes (2-phosphinoethylamines: P–N) can also facilitate heterolytic cleavage of H₂ with the help of conjugate base of acidic compounds under mild conditions [22].

Noyori [47], our group [48, 49], and others [50–53] reported that some isolable cationic amine Ru and Ir complexes, $\text{Ru}(\text{OTf})[\text{Tsdpen}](\eta^6\text{-}p\text{-cymene})$ and $[\text{Cp}^*\text{Ir}(\text{Tscyd})](\text{CH}_3\text{CN})^+\text{SbF}_6^-$, are highly effective for the asymmetric hydrogenation of ketones or imines in methanol or 2-propanol containing no base. A key step is the heterolytic H_2 cleavage, which is promoted by the Ru (OTf) or Ir(SbF₆) system. It generates an active hydride complex, $\text{RuH}[\text{Tsdpen}](\eta^6\text{-}p\text{-cymene})$ with simultaneous release of HOTf or HSbF₆ in highly polarized media like methanol. After the concerted hydride/proton transfer from the hydride complex substrates, the 16-electron amido Ru complex is regenerated and then reacts with HOTf to complete the catalytic cycle.

These results led us to design a new type of bifunctional molecular catalysts having a triflylamide tethers linked to $\eta^6\text{-arene}$ or Cp* ring for asymmetric hydrogenation of ketones, in which tethered anion might work as a conjugate base [54]. The tethered arene–Ru complex, $\text{Ru}[\text{Tsdpen}][\eta^6:\eta^1\text{-C}_6\text{H}_5(\text{CH}_2)_n\text{NTf}]$ (Tf = CF₃SO₂) (Figs. 1 and 11), and tethered Cp* bound Rh complex, $[\eta^5:\eta^1\text{-}(\text{CH}_3)_4\text{C}_5(\text{CH}_2)_n\text{NTf}]\text{M}[\text{Msdpen}]$ (M = Rh, Ir, Ms = CH₃SO₂), which have been structurally modified based on the hydrogen transfer catalyst, $\text{Ru}[(S,S)\text{-Tsdpen}](\eta^6\text{-arene})$ and $\text{Cp}^*\text{M}[\text{Msdpen}]$ can effect efficiently asymmetric hydrogenation of aromatic ketones to give chiral alcohols with an excellent ee [55].

Thus, the ligand modification by changing the amine chelating ligands and by linking the triflylamide ligand to the innocent ligands causes a drastic change in the catalyst performance. Both $\text{Cp}^*\text{Ru}(\text{N–N})$ and $\text{Cp}^*\text{Ru}(\text{P–N})$ complexes as well as the tethered ones can facilitate heterolytic cleavage of H_2 with help of conjugate base of acidic compounds under mild conditions and can efficiently effect hydrogenation of a variety of carbonyl compounds.

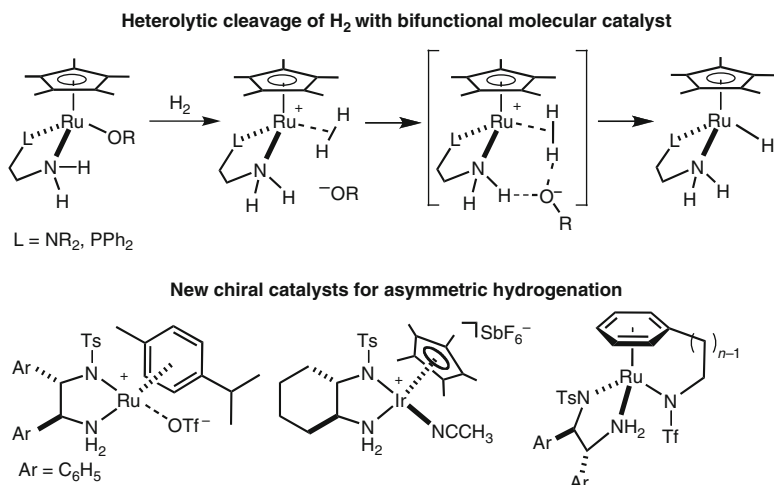


Fig. 11 H_2 activation with bifunctional molecular catalysts

3.2 Hydrogenation of Imides

The newly developed half-sandwich-type bifunctional catalysts $\text{Cp}^*\text{Ru}(\text{N}-\text{N})$, $\text{Cp}^*\text{RuCl}[(\text{CH}_3)_2\text{N}(\text{CH}_2)_2\text{NH}_2]$, $\text{Cp}^*\text{Ru}(\text{P}-\text{N})$, and $\text{Cp}^*\text{Ru}[(\text{C}_6\text{H}_5)_2\text{P}(\text{CH}_2)_2\text{NH}_2]$ serve as efficient catalysts for the chemoselective hydrogenation of ketones, as a result of its ability to perform alcohol-assisted heterolytic cleavage of H_2 and the Ru/NH bifunctionality. The use of the electron-donating $\text{N}-\text{N}$ and the $\text{P}-\text{N}$ ligand causes a positive effect on H_2 activation on the amido complexes. Since the electronic effect of the chelating amine ligands on both amido and amine complexes might conflict each other, even a slight change in the electronic properties of the amine ligands causes a significant change in the catalytic performance [22, 56]. In fact, $\text{Cp}^*\text{Ru}(\text{P}-\text{N})$ complex efficiently catalyzes the hydrogenation of imides, while $\text{Cp}^*\text{Ru}(\text{N}-\text{N})$ is totally inactive [57]. The electron-withdrawing nature of the $\text{P}-\text{N}$ ligand might enhance the Lewis acidity of the NH proton in the hydrido complex $\text{Cp}^*\text{RuH}[(\text{C}_6\text{H}_5)_2\text{P}(\text{CH}_2)_2\text{NH}_2]$, leading to facile activation of polar functionalities imides with the hydride complex.

A variety of imides are chemoselectively convertible to the corresponding alcohols and carboxamides in 2-propanol containing $\text{Cp}^*\text{RuCl}(\text{P}-\text{N})$ and KOt-Bu as the catalyst under mild conditions as shown in Fig. 12 [57]. This hydrogenation method is characterized by its excellent chemoselectivity, substrate scope, and controllable stereoselectivity by the chiral modification of the ligand structures. In fact, it is applicable to the deprotection of primary amines from *N*-phthaloyl-protected amino acid ester derivatives. *N*-phthaloyl-*L*-Phe methyl ester undergoes hydrogenation to generate *N*-(*o*-hydroxymethylbenzoyl)-*L*-Phe methyl ester, whose acid-promoted cyclization liberates the HCl salt of *L*-Phe methyl ester with concomitant formation of phthalide in high yields (Fig. 12) [57].

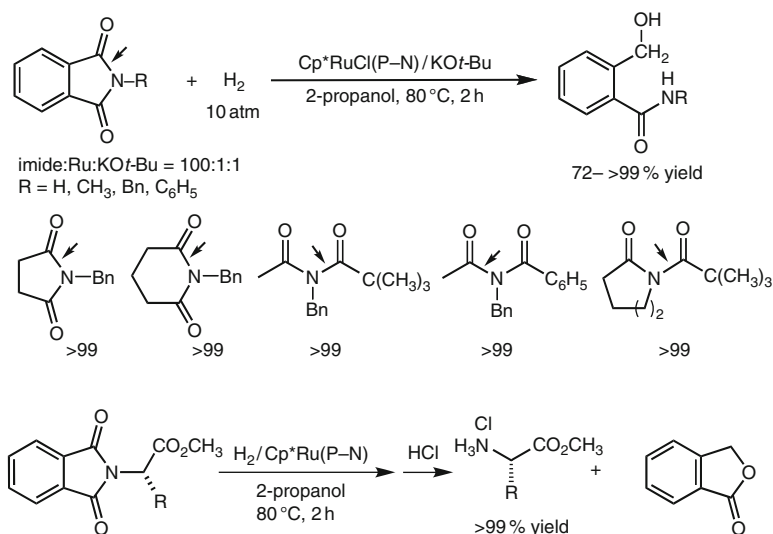


Fig. 12 Chemoselective hydrogenation of imides with bifunctional $\text{Cp}^*\text{Ru}(\text{P}-\text{N})$ catalyst

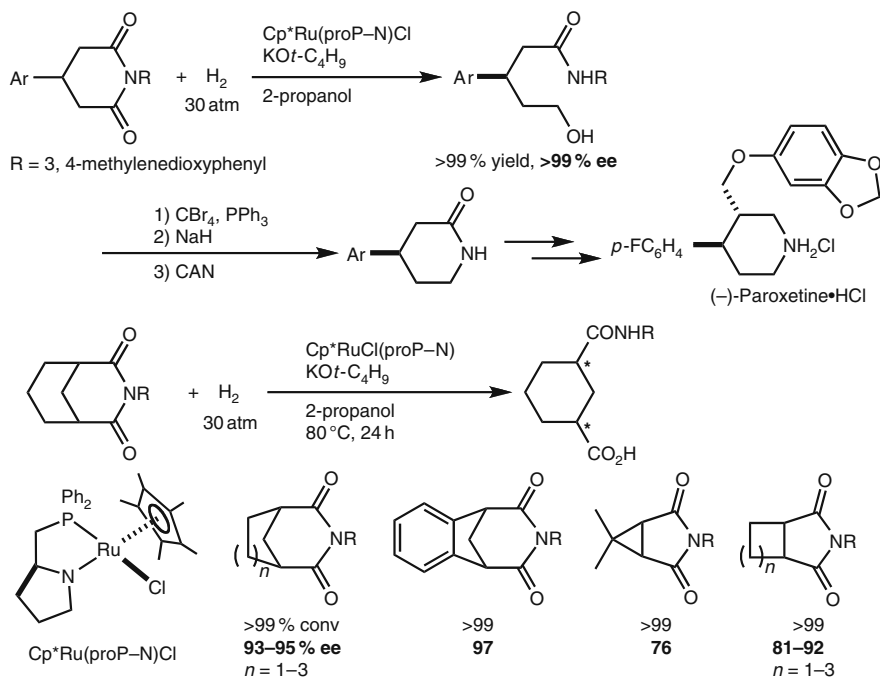


Fig. 13 Enantioselective hydrogenation of prochiral cyclic imides via desymmetrization

The chiral version of the $\text{Cp}^*\text{Ru}(\text{P-N})$ catalyst bearing the chiral P–N ligand derived from L-proline promotes the enantioselective hydrogenation of prochiral 4-arylglutarimides via desymmetrization to provide the corresponding hydroxyamides with excellent ees and in high yields as shown in Fig. 13 [57]. Further synthetic transformation of the chiral hydroxyamides provides chiral piperidinone derivatives which serve as important synthetic intermediates for a number of physiologically active chiral compounds including the antidepressant paroxetine. Similarly, readily accessible *sym*-glutar- or succinimides with the N -3,4-(OCH_2O) C_6H_3 group undergo highly enantioselective hydrogenation via desymmetrization to give the corresponding hydroxyamides with excellent ee's (Fig. 13) [58]. The present hydrogenation method would provide highly functionalized chiral hydroxyamides, which would otherwise require tedious multistep synthesis. Thus, this imide hydrogenation with bifunctional catalyst provides a versatile synthetic method in organic synthesis.

3.3 Hydrogenation of *N*-Acylcarbamates and *N*-Acylsulfonamides

The $\text{Cp}^*\text{Ru}(\text{P-N})$ catalyst promotes the hydrogenation of acyl moieties in *N*-acylcarbamates and *N*-acylsulfonamides under 30 atm of H_2 (Fig. 14) [59]. It is

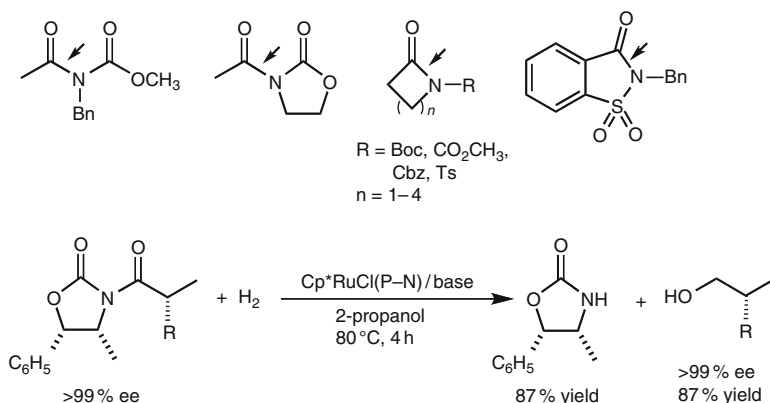


Fig. 14 Hydrogenation of *N*-acylcarbamates and related compounds

preferable to use *t*-BuOH for the hydrogenation of substrates with an adequately electrophilic acyl group, because sterically small alcoholic solvents sometimes cause undesired alcoholysis of the substrates. Moreover, the rates of the reaction strongly rely on the electron-withdrawing nature of substituents on nitrogen in the substrates. In fact, the acceleration effect of the *N*-substituents of pyrrolidinone derivatives has been found to increase in the following order: Cbz < Boc < CO₂CH₃ < SO₂CH₃ ≈ SO₂C₆H₄-*p*-CH₃. The present hydrogenation is applicable to the reductive treatment of chiral *N*-acyloxazolidinones, which are useful synthetic intermediates in the asymmetric synthesis developed by Evans (Fig. 14). For example, *N*-acyloxazolidinone undergoes selective hydrogenation in the presence of Cp^{*}RuCl(P–N) and KO*t*-Bu, to furnish the corresponding chiral alcohol without any damage to the stereochemistry, along with the original chiral auxiliary in high yields. This method may be an environmentally benign catalytic alternative to the method using LiAlH₄, which sometimes causes difficulty in the recovery of the chiral auxiliaries.

3.4 Hydrogenation of Esters and Lactones

In 1997, Teunissen and Elsevier reported the first homogeneous hydrogenation of unactivated esters to their corresponding alcohols catalyzed by a Ru(acac)₃/CH₃C[CH₂P(C₆H₅)₂]₃ system in dry methanol [60]. In 2006, Milstein and coworkers reported that a new mode of bifunctional catalysts based on the metal–ligand cooperation via aromatization–dearomatization of pyridine-based pincer-type ligands in the RuH(PNN)(CO) pincer catalyst can facilitate hydrogenation of esters to alcohols under mild conditions (Fig. 15) [61]. Since then, a few groups reported that some combined bifunctional catalysts based on the metal–NH cooperating effect, RuCl₂(P–N)₂, PNNP-tetradentate Ru catalyst with a base [62], and RuH₂(diphosphine)(diamine) [63] promoted efficiently hydrogenation of esters in reasonably good reactivity.

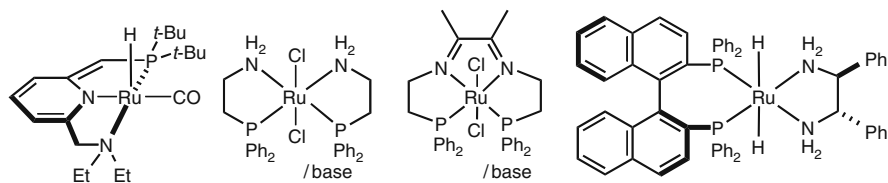


Fig. 15 Examples of efficient bifunctional catalysts for ester hydrogenation

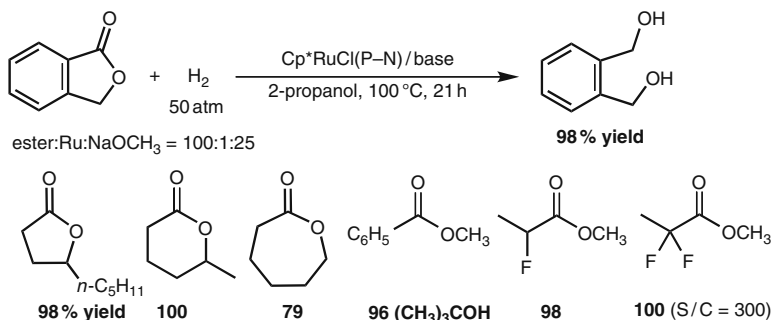


Fig. 16 Hydrogenation of esters and lactones with the Cp^{*}Ru(P-N) catalyst

We have also found that our bifunctional catalyst Cp^{*}Ru(P-N) and a large amount of base promote the hydrogenation of esters under more forcing conditions [22, 56]. For example, phthalide is cleanly reduced to *o*-xyleneglycol under 50 atm of H₂ at 100 °C in the presence of Cp^{*}Ru(P-N) catalysts (Fig. 16). A variety of esters and lactones undergo hydrogenation to give the corresponding alcohols and diols, respectively.

3.5 Hydrogenolysis of Epoxides

The Cp^{*}Ru(P-N) catalyst systems also efficiently facilitate hydrogenation of a variety of terminal epoxides, leading to the corresponding secondary alcohols preferentially in high yields for the steric reasons (Fig. 17). Alkenyl epoxides gave secondary alkenyl alcohols in quantitative yield without formation of saturated alcohols or epoxides. Terminal epoxides bearing another oxygen functionality on the side chain also undergo hydrogenolysis to afford the corresponding secondary alcohols in good yields, indicating that groups next to the epoxide group do not interact with the metal center because of the Ru/NH bifunctionality of the Cp^{*}Ru catalyst [64]. Although stereospecific hydrogenolysis of chiral terminal epoxides was hampered by the competing racemization of the chiral product alcohols (vide infra), this catalytic hydrogenolysis provides a new alternative to stoichiometric metal hydride reduction.

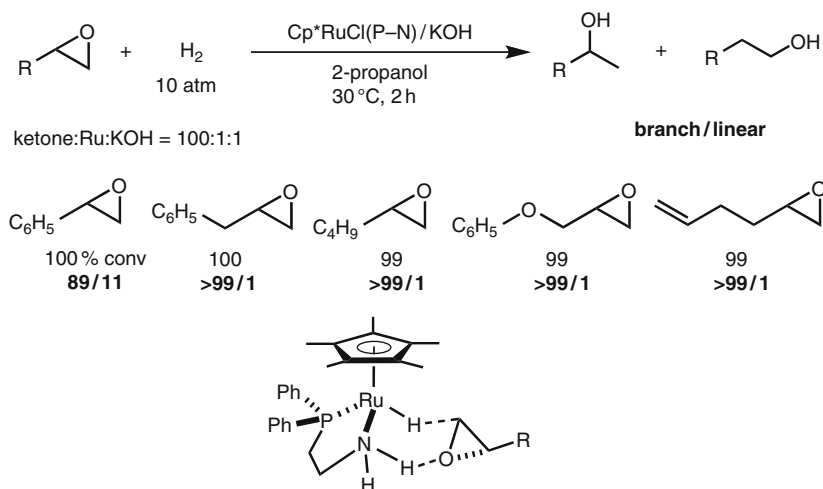


Fig. 17 Hydrogenation of terminal epoxides with the Cp^{*}Ru(P–N) catalyst

4 Oxidative Transformations with Bifunctional Molecular Catalysts

As mentioned in the introduction, the hydrogen transfer between alcohols and ketones with the bifunctional molecular catalyst occurs reversibly through a six-membered pericyclic transition state. When suitable hydrogen acceptors such as acetone and oxygen molecule can be used, the reverse reaction, dehydrogenative oxidation of alcohols would attract much attention in organic synthesis (Fig. 18). The ligand modification is also crucial to determine the catalytic performance for oxidative transformation. Noticeably, the bifunctional Cp^{*}Ru(P–N) catalyst exhibits excellent catalytic activity toward both hydrogenation and transfer hydrogenation, while the Cp^{*}Ru(N–N) complex serves as only hydrogenation activity. Therefore, the (P–N) complex is a choice of the catalyst for oxidative transformation.

4.1 Dehydrogenative Oxidation of Alcohols with Cp^{*}Ru(P–N) Catalysts

The bifunctional catalyst Cp^{*}Ru(P–N) but not with Cp^{*}Ru(N–N) is an excellent catalyst for the racemization of chiral non-racemic *sec*-alcohols [65]. In fact, asymmetric hydrogenation of prochiral ketones becomes possible with chiral Cp^{*}Ru(N–N) catalyst system, thanks to its reluctance to dehydrogenate alcohols, but not with chiral Cp^{*}Ru(P–N) systems since concurrent racemization of the product alcohols deteriorates the ee value of the alcoholic products regardless of whether the hydrogen source is H₂ or 2-propanol [64, 65].

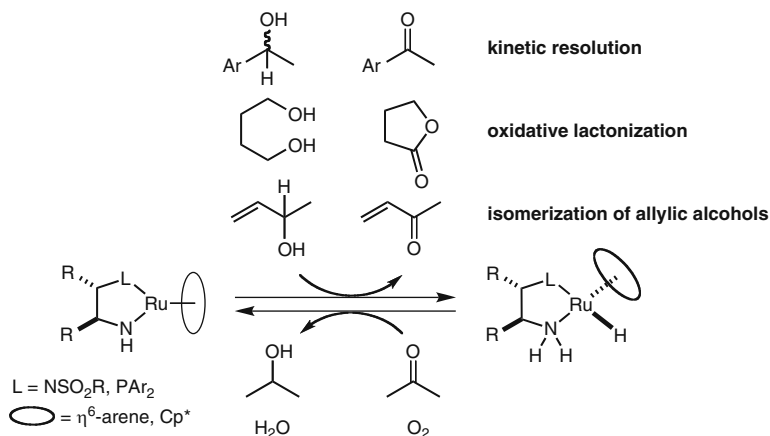


Fig. 18 Bifunctional catalyst promoted oxidative transformations

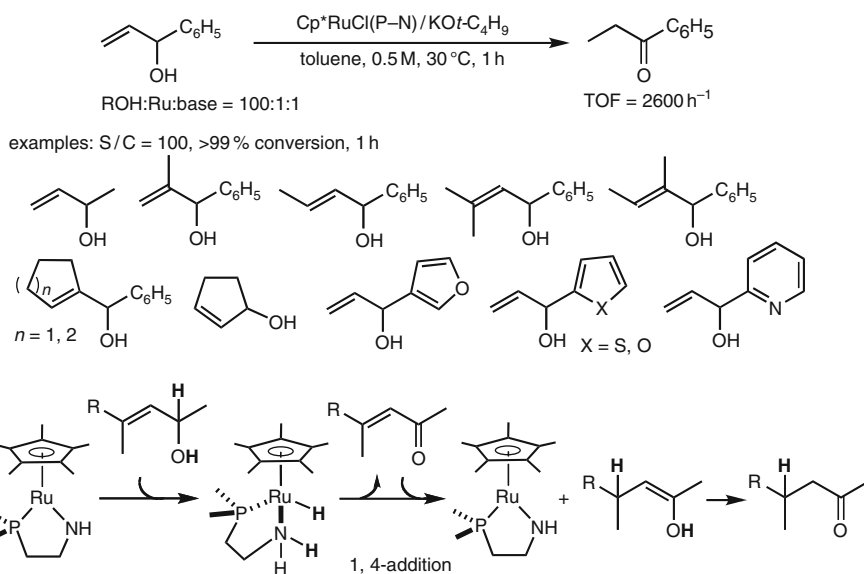


Fig. 19 Isomerization of allylic alcohols with bifunctional catalysts

Two synthetically viable, oxidative transformations of alcohols have been successfully developed. First, allylic alcohols undergo intramolecular hydrogen transfer to give saturated carbonyl compounds in aprotic media containing $\text{Cp}^*\text{Ru}(\text{P-N})$ catalysts; the TOF of the reaction at 30°C exceeds 2,500 h⁻¹ (Fig. 19) [66].

Unlike conventional catalysts, this catalyst system discriminates olefins with an allylic hydroxy group from other olefinic groups as a result of Ru/NH bifunctionality as shown in Fig. 19. This unique chemoselectivity is applicable in the preparation of

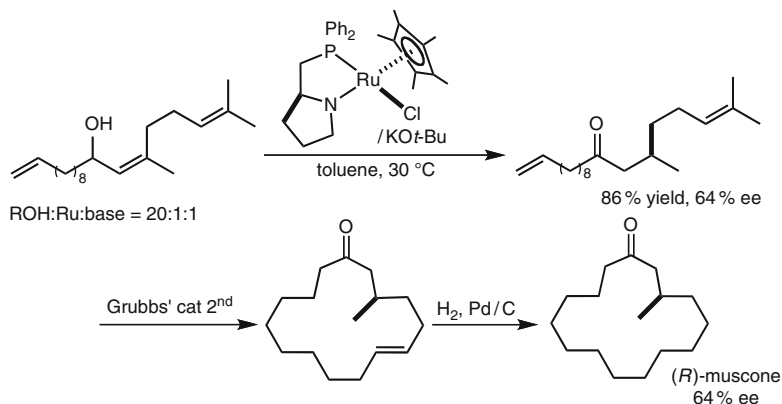


Fig. 20 Asymmetric isomerization of allylic alcohol and its application to muscone synthesis

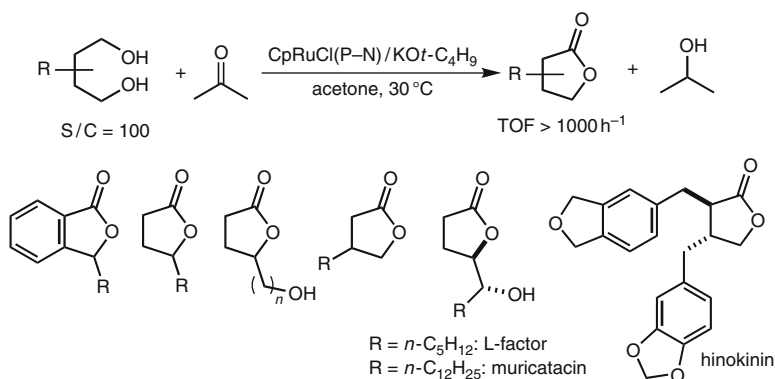


Fig. 21 Dehydrogenative oxidation of diols with bifunctional Cp*Ru(P-N) catalysts

macrocyclic ketones starting from readily available acyclic allylic alcohols equipped with two isolated C=C double bonds. For example, the present asymmetric isomerization provides a chiral ketone having two olefinic units suitable for ring-closing metathesis as shown in Fig. 20. Muscone can be conveniently prepared using asymmetric isomerization with chiral Cp*Ru(P-N) catalysts as a key step [66].

Second, 1,4-diols undergo intermolecular hydrogen transfer, giving lactones efficiently in acetone containing Cp*Ru(P-N) catalysts; the TOF of this reaction at 30 °C exceeds 1,000 h⁻¹ (Fig. 21) [67]. The catalytic oxidative lactonization of diols is characterized by its unique chemo- and regioselectivity. The significant rate difference between primary and secondary alcohols in dehydrogenation, and the rate difference between 1,4-diols and 1,5- or 1,6-diols enable unique oxidative lactonization of triols.

The oxidation of triols provides exclusively γ -butyrolactones including L-factor and muricatacin, where the remote OH groups remain intact regardless of whether

they are primary or secondary. Due to its high efficiency and experimental simplicity, the present catalytic oxidative transformation provides a powerful and environmentally benign alternative for Fétizon oxidation.

4.2 Aerobic Oxidation of Alcohols with Bifunctional Molecular Catalysts

When molecular oxygen can be used as a hydrogen acceptor for the dehydrogenative oxidation of alcohols with the bifunctional catalyst, aerobic oxidation becomes a simple and minimal organic waste process. We found that a new series of bifunctional hydrido(amine)-iridium complexes with electron-donating C–N chelate amine ligands $\text{Cp}^*\text{IrH}[\kappa^2(\text{N},\text{C})\text{-}\{\text{NH}_2\text{CR}_2\text{-}2\text{-C}_6\text{H}_4\}]$ ($\text{R} = \text{C}_6\text{H}_5, \text{CH}_3$) rapidly react with molecular oxygen under mild conditions to generate the corresponding amido Ir complexes $\text{Cp}^*\text{Ir}[\kappa^2(\text{N},\text{C})\text{-}\{\text{NH}_2\text{CR}_2\text{-}2\text{-C}_6\text{H}_4\}]$ as shown in Fig. 22 [68].

Other oxidants like hydroperoxides also effect the transformation of the hydrido complex to the amido complex. The reaction of the hydrido complex with an equimolar amount of H_2O_2 in THF generates the amido complex in an excellent yield in addition to a detectable amount of H_2O . The treatment of *tert*-BuOOH with the hydrido complex also clearly gives the amido complex and *tert*-BuOH [69]. These results clearly indicate that the reaction of the hydrido complex with O_2 may proceed through O_2 insertion into the metal hydride bond to form an amine–hydroperoxo complex, followed by the release of the amido complex and H_2O_2 . The resulting H_2O_2 product then reacts with the hydrido complex to provide the amido complex and water (Fig. 22).

On the basis of a combination of the reactions shown in Fig. 22, we successfully developed the aerobic oxidation of alcohols with bifunctional Cp^*Ir , Cp^*Rh , and

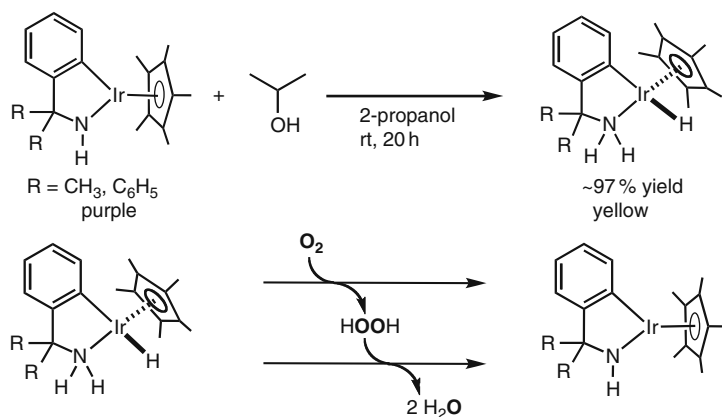


Fig. 22 Stoichiometric reactions of bifunctional $\text{CpIrH}(\text{C}-\text{N})$ complexes with O_2 and H_2O_2

(η^6 -arene)Ru catalysts bearing the C–N ligands [68, 70]. Although a wide variety of homogeneous and heterogeneous systems based on transition metals have been explored, limited examples of Rh- and Ir-catalyzed reaction have been reported (Fig. 23). For example, the reaction of 1-phenylethanol proceeded smoothly under atmospheric pressure of air at 30°C in THF containing amido Ir complex gives acetophenone in 72% yield. Notably, an analogous hydrido complex bearing an *N,N*-dimethylamino group did not exhibit catalytic activity under otherwise identical conditions, indicating that the M/NH bifunctionality is also crucial for O₂ activation and that the aerobic oxidation proceeds through the interconversion between the amine/amido catalyst intermediates. Binary catalyst systems, including the chloro(amine)-Rh and -Ru complexes and KOC(CH₃)₃, are applicable to the aerobic oxidation.

Other 1-phenylethanols with substituents on the arene ring, sterically congested diphenylmethanol, and an aliphatic secondary alcohol are convertible into the corresponding ketones using the amido Ir catalyst as shown in Fig. 24.

When primary alcohols are used for aerobic oxidation under identical conditions, the oxidative dimerization product, esters are obtainable as shown in Fig. 25. In fact, the reaction of benzyl alcohols gives the corresponding benzyl benzoate derivatives in a range of 62–64% yields. The oxidation of 1,2-benzenedimethanol

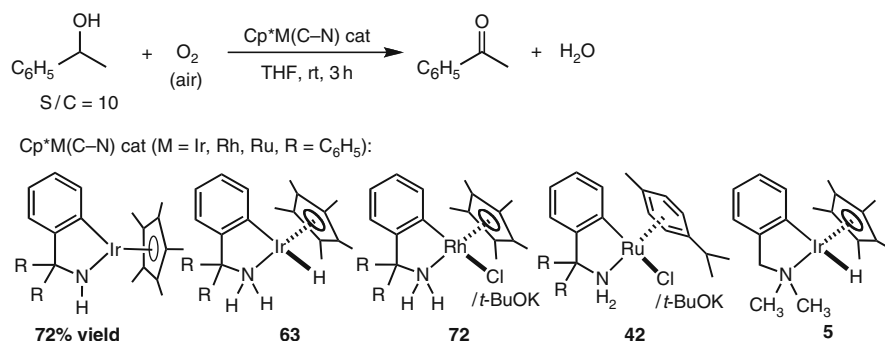


Fig. 23 Aerobic oxidation of 1-phenylethanol with bifunctional catalysts

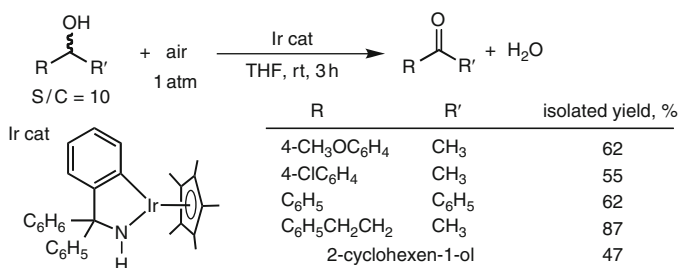


Fig. 24 Aerobic oxidation of secondary alcohols with bifunctional amido Ir catalyst

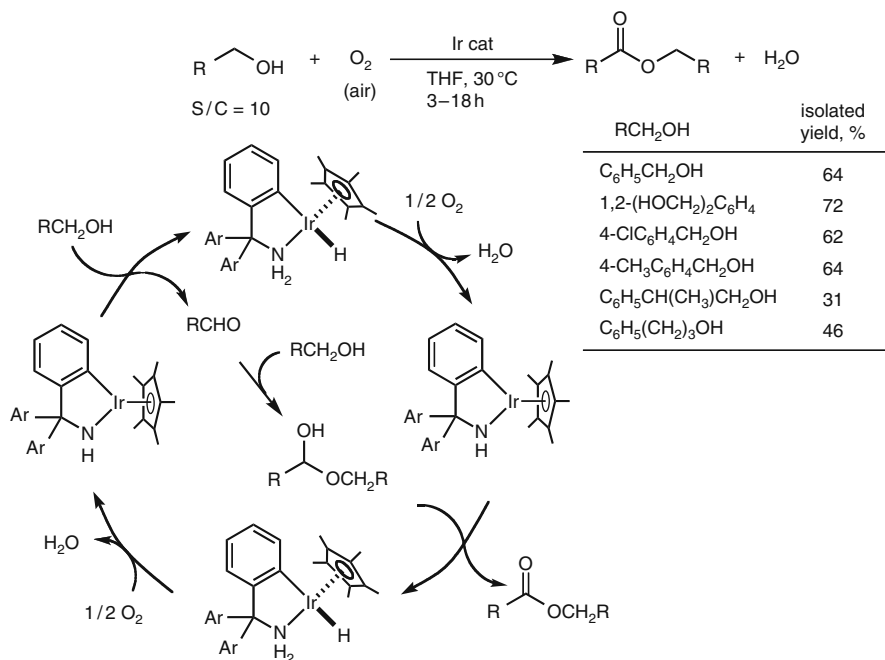


Fig. 25 Aerobic oxidation of primary alcohols with the Cp*Ir(C–N) catalyst

also affords phthalide in 72% yield by an intramolecular esterification. A plausible mechanism is shown in Fig. 25. In the presence of O₂, the oxidation of benzyl alcohol takes place smoothly to give benzaldehyde. Subsequent attack of the remaining alcohol affording the hemiacetal and its ready conversion into the ester is accomplished by the second oxidation.

This aerobic oxidation of alcohols is more appealing when applied to the kinetic resolution of racemic secondary alcohols with chiral amido complexes [69–76]. When a THF (1.0 M) solution of racemic 1-phenylethanol with the chiral Cp*Ir (C–N) was treated with air at 30°C for 4 h, (*R*)-1-phenylethanol was recovered with a 48% yield and 12% ee catalysts (Fig. 26). Noticeably, the use of the chiral amido Ir complex bearing the DPEN ligand, Cp*Ir[(*S,S*)-Msdpen] (Ms = methanesulfonyl), significantly improves the enantiomer discrimination ability, and desired (*R*)-1-phenylethanol is obtainable in 48% yield and 98% ee with a *k_f/k_s* ratio of up to 90. A 1-phenylethanol derivative having an electron-donating CH₃O group at the para position is efficiently resolved with catalyst. Similarly, the *R*-enantiomers with >99% ee and with 46–50% yields are readily obtainable from the reactions of 1-indanol and 1-tetralol at ambient temperature [69].

In contrast to previously reported kinetic resolution of alcohols with isolable chiral amido Ru using acetone [19], aerobic kinetic resolution with binary catalyst systems including chiral Ir and Rh complexes Cp*MCl[(*S,S*)-Tsdpen] (M = Ir, Rh) and a base proceeds smoothly to give the desired chiral alcohols.

$$\text{Ar-CH(OH)-CH}_3 + \text{O}_2 \xrightarrow[\text{THF, 30 }^\circ\text{C}]{\text{chiral cat}} \text{Ar-CH(OH)-CH}_3 + \text{Ar-CO-CH}_3 + \text{H}_2\text{O}$$

$$S/C = 10$$

chiral cat:	alcohol		time, h	unreacted alcohol		
	Ar	[M]		recover %	ee, %	k_t/k_s
	C ₆ H ₅	1	4	48	12	1.5
	C ₆ H ₅	1	24	39	86	9
	C ₆ H ₅	1	22	44	84	13
	C ₆ H ₅	0.2	38	48	98	91
	4-CH ₃ C ₆ H ₄	0.2	19	38	98	17
	1-indanol	1	2	42	98	18
	1-tetralol	0.1	6.5	46	>99	78
Cp*RhCl(Tsdpen)/t-BuOK	C ₆ H ₅	1	3.5	46	93	29

Fig. 26 Aerobic oxidative kinetic resolution of racemic secondary alcohols

5 Conclusions

This chapter has described mainly recent advances in chemistry of our chiral bifunctional transition metal molecular catalyst based on metal/NH acid–base synergy effect for stereoselective reductive and oxidative transformations. The concept of the bifunctional catalyst design is now successfully applicable to a new family for asymmetric hydrogenation of polar functionalities by the ligand modification and electronic fine-tuning. A key step in the hydrogenation is the alcohol-assisted heterolytic cleavages of molecular H₂ with the chiral amido complexes, leading to the amine hydrido Ru complexes. The acidic amine proton and the metal hydride activate polarized C–O bond through outer-sphere mechanism, in which the reacting substrate is not bonded directly to the central metal. Another unprecedented aspect is that the oxygen molecule can be readily activated by the bifunctional system leading to aerobic oxidation of alcohols. Thus, the present bifunctional molecular catalyses can provide a wide substrate scope and applicability in organic synthetic chemistry. Thus, the rational design of the amine ligand that adjusts the balance of the electronic factors on the M/NH units in the bifunctional catalysts is crucially important to exploit further unprecedented catalyst performance [9, 77–80]. Finally, the industrial outlook for asymmetric reduction with

bifunctional catalysts is bright, because of their excellent catalyst performance, wide substrate scope, operational simplicity, and economic viability as well as the growing awareness of the need for green chemistry [6].

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