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Chemistry of *Concerto* Molecular Catalysis Based on the Metal/NH Bifunctionality#

Takao Ikariya

Department of Applied Chemistry, Graduate School of Science and Engineering, Tokyo Institute of Technology, 2-12-1-E4-1 O-okayama, Meguro-ku, Tokyo 152-8552

Received September 1, 2010; E-mail: tikariya@apc.titech.ac.jp

The development of conceptually new bifunctional transition-metal-based catalysts for a wide range of catalytic reactions is described. The bifunctional chiral molecular catalyst based on metal–ligand cooperation was originally developed for asymmetric transfer hydrogenation of ketones and imines and is now applicable to chemo- and stereoselective reductive and oxidative transformations as well as to enantioselective C–C and C–N bond formations with a wide scope and high practicability. The structural modification and electronic fine-tuning of the protic amine chelating ligands are crucial to develop unprecedented catalytic reactions. Cp*Ru complexes bearing a diamine (N–N) or aminophosphine (P–N) ligand readily activate H_2, and can effect hydrogenation of polar functionalities. The bifunctional Ir complexes promote aerobic oxidative transformation of alcohols into ketones and esters and are applicable to kinetic resolution of racemic secondary alcohols. A novel imido-bridged dirhodium complex, which is a dinuclear variant of the bifunctional mononuclear amido complexes, promotes aerobic oxidation of a secondary alcohol and H_2. In addition, the metal/NH bifunctional property also affects efficiently enantioselective conjugate additions. The present *concerto* molecular catalysts offer a great opportunity to open up new fundamentals for stereoselective molecular transformations.

1. Introduction

The chemistry of transition-metal catalysts has progressed significantly together with discoveries of novel catalytic transformations as well as understanding reaction pathways.[1] Approaches to clarify the chemical properties of key intermediates have led to the concept of a hitherto unknown elementary process, and an in-depth understanding of the reaction mechanism by kinetics and structural investigation of the catalytic species has enabled rational design of sophisticated molecular catalysts. Particularly, significant efforts have been continuously paid to develop bifunctional molecular catalysts having the combination of two or more active sites working in concert, to attain highly efficient molecular transformation for organic synthesis. We have recently developed metal–ligand cooperating bifunctional catalysts (*concerto* catalysts), in which the non-innocent ligands directly participate in the substrate activation and the bond formation. The concept of bifunctional molecular catalysis is now an attractive and general strategy to realize effective molecular transformation.[2]

In 1995, Noyori and co-workers reported an unprecedented effect of diamine ligands on the enantioselective hydrogenation of simple aromatic ketones with a BINAP–Ru(II) system [BINAP: 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl].[3] A combination of [$RuCl_2${(*S*)-binap}$(dmf)_n$], chiral 1,2-diamine, and KOH showed a much higher activity toward ketone hydrogenation than the classical coordinatively unsaturated BINAP–Ru catalyst. Subsequently, Noyori and Ikariya developed a prototype of a conceptually new phosphine-free Ru catalyst bearing *N*-sulfonylated 1,2-diamines as chiral ligands for highly efficient asymmetric transfer hydrogenation of ketones.[4] Detailed experimental and theoretical analyses of the real catalysts revealed that both an amidoruthenium complex of square-planar geometry and a coordinatively saturated hydrido(amine)ruthenium complex are involved in the catalytic cycle as depicted in Figure 1. This newly developed bifunctional catalysis is unique and simple. The amido complex generated by dehydrochlorination of the catalytic precursor, chloro(amine)ruthenium complex, readily dehydrogenates secondary alcohols including 2-propanol as well as formic acid to produce the hydrido(amine) complex. The NH unit bound to the metal center in the amine complex exhibits a sufficiently acidic character to activate ketonic substrates. During the interconversion between the amido and the amine complexes, the cooperative role of the metal/NH moiety stands up for the hydrogen delivery via a cyclic transition state where H^- and H^+ equivalents are transferred in a concerted manner from the hydrido(amine) complex to the C=O linkage or from 2-propanol to the amido complex without direct coordination to the metal center (outer-sphere mechanism). This unique concept of bifunctional transition-metal-

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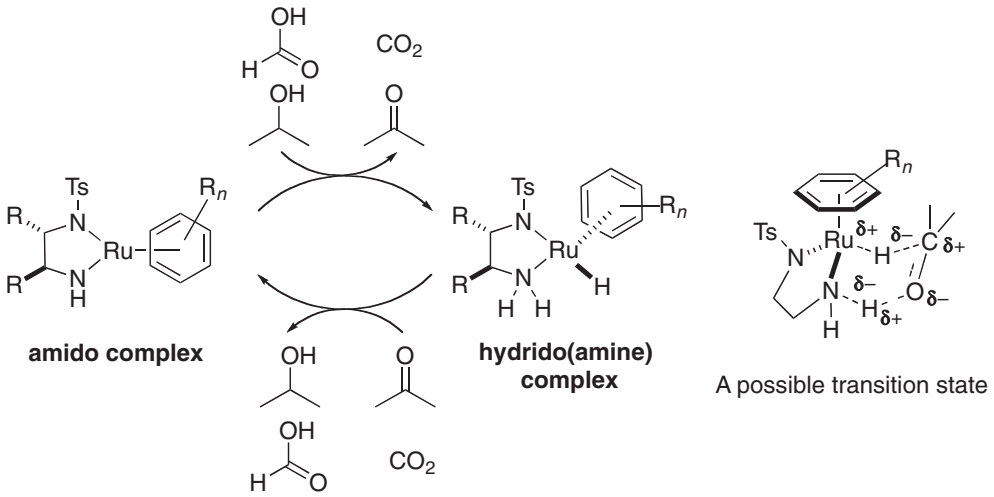


Figure 1. Interconversion of the amido and the amine hydrido Ru complex via a possible six-membered transition state.

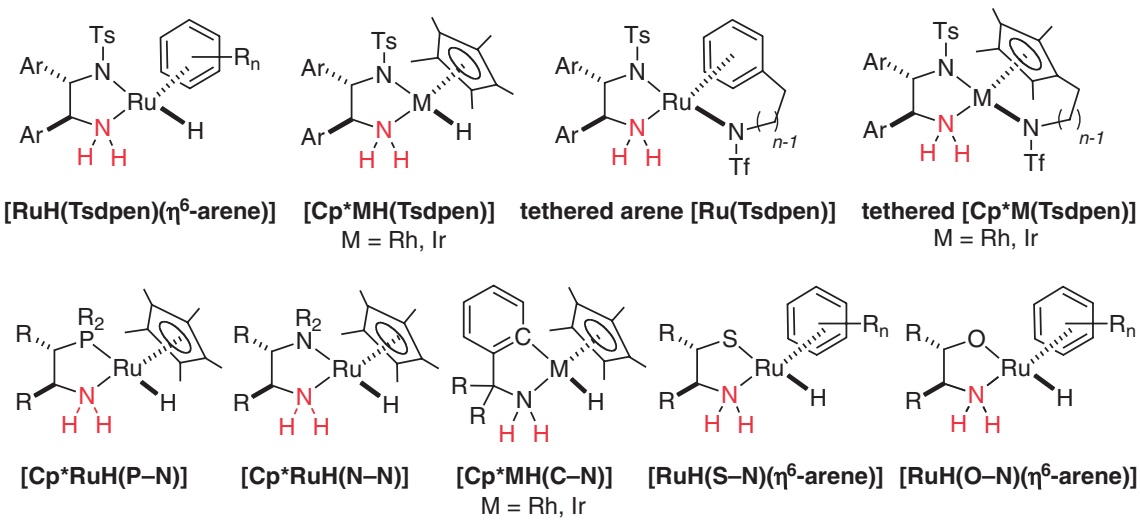


Figure 2. Schematic examples of hydrido(amine) complexes having a metal/NH bifunctionality.

based molecular catalysts leads to reactions with high rates and excellent stereoselectivities because the reactions proceed through a tight-fitting assembly of the reactants and chiral catalysts.

Figure 2 lists some representative examples of well-defined bifunctional molecular catalysts recently developed in our group. In addition to the *N*-sulfonylated diamines, *β*-amino alcohols (O–N),[5] diamines (N–N),[6] aminophosphines (P–N),[7] aminoethanethiols (S–N),[8] and *o*-aminomethylphenyl (C–N)[9] ligands were found to exhibit an excellent metal–ligand cooperating effect. In this article, I outline our recent progress in *concerto* molecular catalysts based on the metal/NH acid–base synergy, and their utilization to asymmetric redox transformations and related C–C and C–N bond formation reactions.

2. Asymmetric Transfer Hydrogenation of C=O and C=N Double Bonds Using *Concerto* Catalysts

The concept of the chiral bifunctional η^6-arene–Ru complexes, [RuCl(Tsdpen)(η^6-arene)], [Tsdpen: *N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine] has been successfully extended to analogous Cp*Rh and Ir complexes, [Cp*MCl(Tsdpen)] [Cp*: η^5-C(CH$_3$)$_5$, M = Rh and Ir].[10] These chiral *N*-sulfonylated diamine complexes as well as a new family of Cp*Ru complexes[11] bearing the protic amine chelating ligands serve as highly efficient catalysts for asymmetric transfer hydrogenation of simple alkyl aryl ketones and imines. Since early progress in the asymmetric reduction with the chiral Ru catalyst has been already reviewed,[2c–2e] this article focuses on asymmetric transfer hydrogenation of certain selected carbonyl compounds with chiral bifunctional catalysts.

In general, 2-propanol can be used as a safe, nontoxic, and environmentally friendly hydrogen source. Although the asymmetric reduction in 2-propanol gives satisfactory results, an inherent drawback of the hydrogen-transfer reaction is its reversibility, leading to limited conversion determined by thermodynamic factors of the system and the deterioration of enantiomeric purity of the products upon a long exposure of the reaction mixture to the catalyst. On the other hand, formic acid is applicable to the asymmetric reduction in an irreversible fashion with in principle 100% conversion.[12] However, the bifunctional Ru catalyst also efficiently promotes hydrogena-

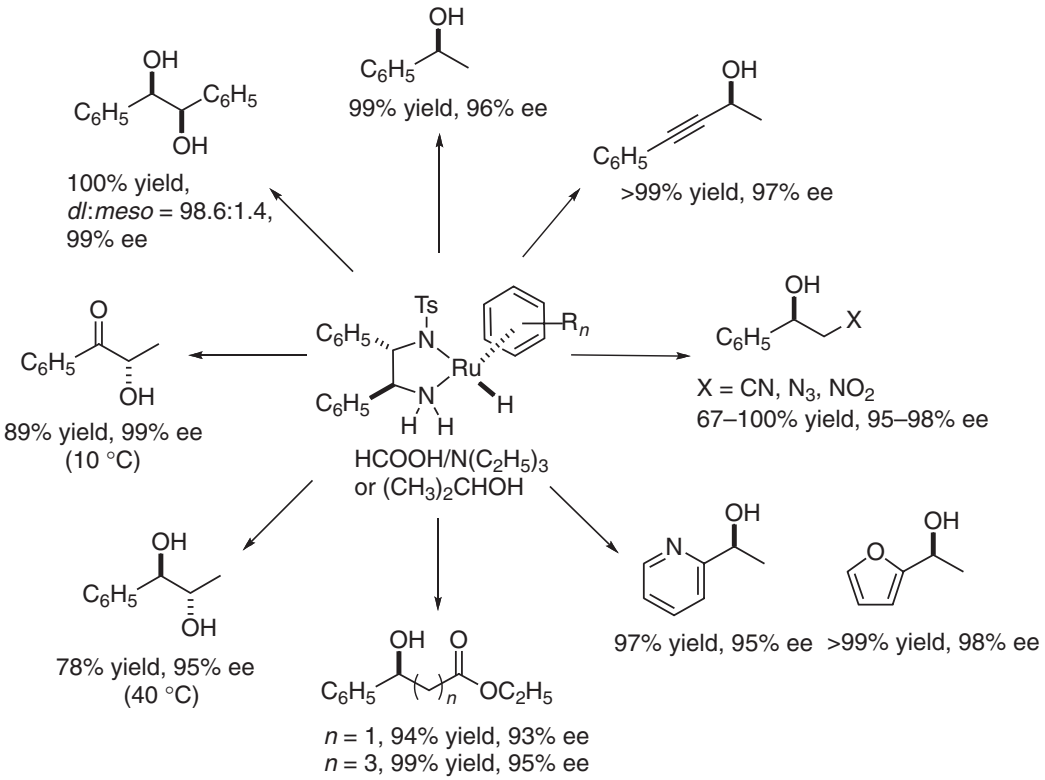


Figure 3. Asymmetric transfer hydrogenation of ketonic compounds with Ru–TsDPEN catalysts.

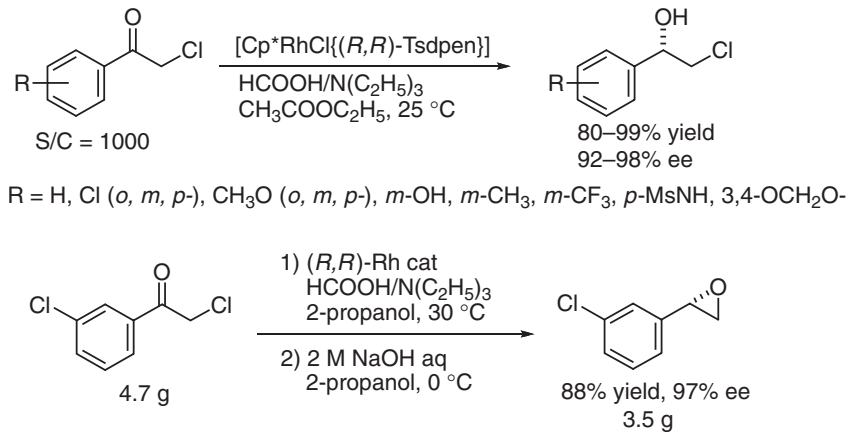


Figure 4. Asymmetric reduction of α-chloroacetophenones and one-pot procedure for synthesis of chiral epoxide.

tion of CO_2 to give formic acid and its derivatives.[13] Therefore, effective removal of CO_2 with inert gas can 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 substrate scope, and practicability. The bifunctional hydrido(amine)–Ru complex is coordinatively saturated, and the catalyst system tolerates amino, ester, cyano, nitro, azide, and chloro groups as well as heteroaromatic rings and the alkyne linkage,[2e] as summarized in Figure 3.

The reactions of acetophenones bearing CN, N_3, and NO_2 at the α-position with an azeotropic 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 (Figure 3).[14] These alcohols can be easily transformed by the conventional reduction of the functional groups to chiral β- and γ-amino alcohols with high ee.

1,2-Diaryldiketones are stereoselectively reducible with the chiral Ru–*p*-cymene complex in a mixture of $HCO_2H/N(C_2H_5)_3$ to give the chiral 1,2-diols with an excellent ee as shown in Figure 3.[15] Notably, a reaction of racemic benzoin with the (*S*,*S*)-Ru catalyst gives (*R*,*R*)-diol with >99% ee throughout the reaction, indicating that the reduction of benzil analogs proceeds through a dynamic kinetic resolution (DKR) of the intermediary benzoins. 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 obtained.[16] 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.

A variety of ring-substituted α-chloroacetophenones is also reducible with a chiral Cp*Rh complex, [Cp*RhCl{(*R*,*R*)-Tsdpen}], to provide quantitatively chiral alcohols with an excellent ee.[17] A more appealing feature is that one-pot synthesis of a chiral styrene oxide can be performed by sequential asymmetric reduction of chloroacetophenone with the chiral Rh in 2-propanol followed by treatment of the reaction mixture with NaOH aqueous solution, leading to the desired products in an isolated yield of 80–90% with 96–98% ee in a single reactor (Figure 4).[18] For example, (*S*)-*m*-chlorostyrene oxide, which is a key intermediate for the preparation of several β3-adrenergic receptor agonist compounds, is easily obtained through this the one-pot procedure.

Carbon–nitrogen double bonds are also reducible with a mixture of formic acid and triethylamine containing chiral Ru catalyst to the corresponding amines with a high level of enantiomeric excesses.[19] Besides, the related Cp*Rh system was demonstrated as an effective catalyst for transfer hydrogenation of prochiral cyclic imines, leading to chiral amines as useful pharmaceutical and agrochemical targets.[20]

3. Catalytic Hydrogenation of Polar Substrates with *Concerto* Catalysts

3.1 Hydrogenation of Ketones and Aldehydes. Although pioneering studies by Fryzuk and co-workers revealed that the amido–metal framework can promote the heterolytic splitting of molecular hydrogen,[21] the catalytic potential for hydrogenation was not examined until the discovery of the metal/NH cooperative effects in 1995. Noyori and co-workers reported that *trans*-[Ru(H)$_2$(diphosphine)(diamine)] complex serves as a highly efficient catalyst for the hydrogenation of ketones and aldehydes, in which excellent chemo- and stereoselectivity originates from its Ru/NH bifunctionality.[3,22,23] In 2001, we reported a similar effect for basic 2-propanol which can facilitate the heterolytic cleavage of H_2 bound to the 16-electron [Cp*Ru{Me$_2$N(CH$_2$)$_2$NH$_2$}]$^+$ (Cp*Ru(N–N)) fragment as shown in Figure 5.[6] Extensive isotope labeling experiments using D_2, Me$_2$CDOH and Me$_2$CHOD, led us to propose the preferential formation of the hydrogen-bonding network of η^2-H_2, ligated NH_2 and 2-propanol, thus preventing dehydrogenation of 2-propanol. Subsequently, Brandt, Andersson, and co-workers confirmed this reaction pathway by using theoretical calculations.[24]

Noyori, our group, and others reported that some isolable cationic amine Ru and Ir complexes, [Ru(OTf)(Tsdpen)(η^6-*p*-cymene)] and [Cp*Ir(Tscydn)(CH$_3$CN)]$^+$SbF$_6^-$ (Tscydn: *N*-(*p*-toluenesulfonyl)-1,2-cyclohexanediamine) are highly effective for the asymmetric hydrogenation of ketones or imines in methanol or 2-propanol even in the absence of base.[25–27] A key step is the heterolytic H_2 cleavage, which is promoted by the Ru(OTf) or Ir(SbF$_6$) system. It generates an active hydrido complex such as [RuH(Tsdpen)(η^6-*p*-cymene)] with simultaneous release of HOTf in highly polarized media like methanol. After the hydrido/proton transfer from the hydrido complex to substrates in a concerted manner, the 16-electron amido Ru complex is regenerated and then reacts with HOTf to complete the catalytic cycle. These experimental results have

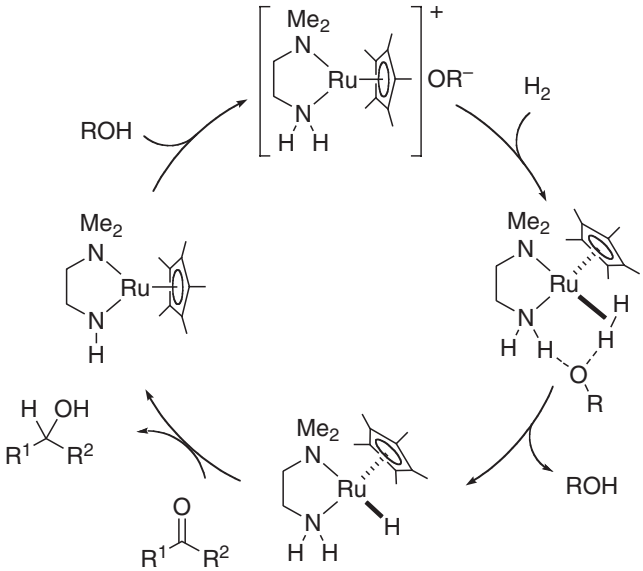


Figure 5. A possible mechanism of hydrogenation with [Cp*Ru{Me$_2$N(CH$_2$)$_2$NH$_2$}]$^+$.

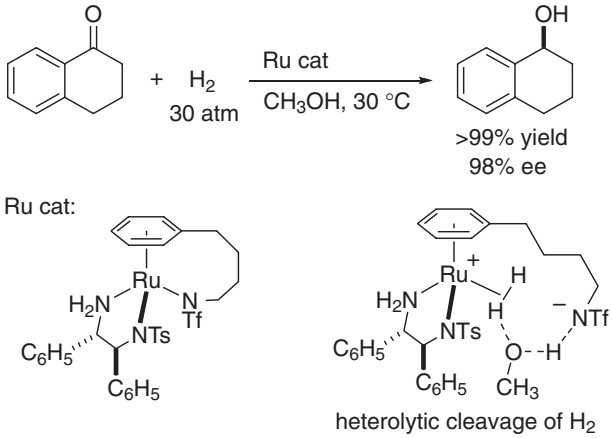


Figure 6. Hydrogenation of aromatic ketone with NTf-tethered Ru complex.

led us to develop new chiral hydrogenation catalysts, [{η^6:η^1-C$_6$H$_5$(CH$_2$)$_n$NTf}Ru{(*S*,*S*)-Tsdpen}] and [{η^5:η^1-(CH$_3$)$_4$C$_5$-(CH$_2$)$_n$NTf}M{(*S*,*S*)-Msdpen}] (M = Rh and Ir) complexes in which an NTf unit linked to a η^6-arene or η^5-tetramethylcyclopentadienyl ring (Figure 2). The introduction of a suitable tether unit dramatically facilitates the heterolytic cleavage of H_2 suggesting that the hemilabile NTf group on the tether can participate in the proton-transfer processes from a coordinating H_2 as shown in Figure 6.[28]

Although the prototype of bifunctional Ru–TsDPEN catalysts cannot efficiently promote hydrogenation of ketonic substrates, the ligand modification by changing the chelating amine ligands and by linking the triflylamide ligand to the innocent ligands causes a drastic change in the catalytic performance. Both [Cp*Ru(N–N)] and [Cp*Ru(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 leading to efficient catalysts for hydrogenation of a variety of carbonyl compounds.

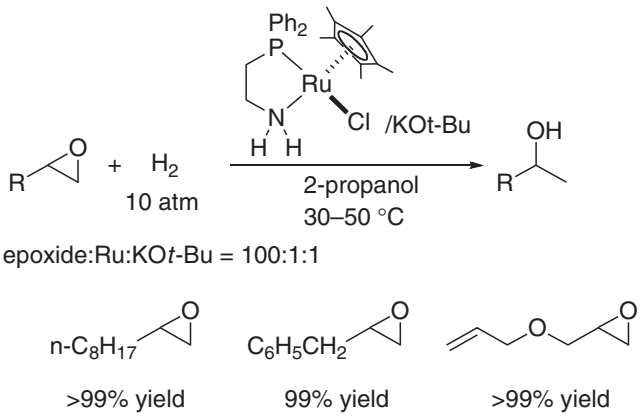


Figure 7. Hydrogenation of terminal epoxides with a [Cp*Ru(P–N)] catalyst.

3.2 Hydrogenolysis of Epoxides. Whereas the [Cp*Ru(N–N)] complex serves as an efficient catalyst for the chemoselective hydrogenation of ketones, the replacement of its tertiary amino group with a tertiary phosphino group has led to the expansion in the scope of the Ru/NH bifunctionality. A [Cp*Ru(P–N)] complex, $[Cp^*Ru\{Ph_2P(CH_2)_2NH_2\}]^+$, selectively delivers hydrogen to the non-substituted C–O bond in a variety of terminal epoxides, leading to the formation of the corresponding *sec*-alcohols, while [Cp*Ru(N–N)] complexes are totally inactive (Figure 7).[29] The [Cp*Ru(P–N)] catalyst can also discriminate the polarized C–O bonds in the epoxides from less polarized C=C bonds to allow chemoselective hydrogenation leading to alkenyl alcohols. Although stereospecific hydrogenolysis of optically active terminal epoxides was hampered by the competing racemization of the product alcohols, this catalytic hydrogenolysis provides a new alternative to stoichiometric metal hydride reduction.

3.3 Hydrogenation of Imides. A variety of imides are chemoselectively convertible to the corresponding alcohols and carboxamides in 2-propanol containing the [Cp*Ru(P–N)] catalyst under mild conditions as summarized in Figure 8.[30] This unprecedented 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. For example, *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. The chiral version of the [Cp*Ru(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 δ-hydroxyamides with excellent ee values and in high yields. Notably, the substituents on nitrogen in the cyclic imides significantly influence the outcome of the reaction; the *N*-3,4-$(OCH_2O)C_6H_3$ group has led to high enantioselectivity. Further synthetic elaboration of the chiral δ-hydroxyamides including bromination, base-induced cyclization, and CAN-mediated dearylation has furnished chiral piperidinone derivatives, which serve as important synthetic intermediates for a number of physiologically active chiral compounds including the antidepressant paroxetine. When symmetrically structured bicyclic imides were used, the enantioselective hydrogenation with the chiral catalyst proceeded via desymmetrization to give multiply functionalized chiral cyclic hydroxyamides with excellent ee's. The resulting chiral products including 1,3- and 1,2-*cis*-disubstituted cyclic compounds, which would be otherwise less accessible, are convertible to a variety of chiral cyclic compounds.[30b]

The bifunctional [Cp*RuCl(P–N)] complex allows the straightforward catalytic hydrogenation of *N*-acylcarbamates and *N*-acylsulfonamides to afford N-protected amines and alcohols selectively. Notably, hydrogenation was applicable to the reductive transformation of chiral *N*-acyloxazolidiones, which are useful synthetic intermediates in the asymmetric synthesis developed by Evans et al.[31] The resulting chiral alcohol and the original chiral auxiliary are obtainable without any loss in the optical purity as shown in Figure 9.[32]

3.4 Hydrogenation of Esters and Lactones Catalyzed by [Cp*Ru(P–N)] Complexes. [Cp*Ru(P–N)] catalysts also promote the hydrogenation of esters under more forcing conditions. For example, phthalide is cleanly hydrogenated to *o*-xylyleneglycol under 50 atm of H_2 at 100 °C as shown in Figure 10.[11b] Aprotic solvents including THF, dioxane, and toluene can be equally used as alcoholic solvents under these. The amount of base has a significant influence on the reaction rate and the addition of more than 25 equivalents of base to the [Cp*RuCl(P–N)] complex gives the highest catalytic performance. A variety of esters and lactones undergo hydrogenation to give the corresponding alcohols and diols, respectively. Notably, in the hydrogenation of chiral *N*-acylcarbamates bearing ester group on the lactam ring, no measurable loss of optical purity was observed despite the basic reaction conditions. The ester group in both substrates was also hydrogenated after a prolonged reaction time, leading to the formation of (*S*)-*N*-Boc-2-amino-1,5-pentanediol and (*S*)-*N*-Boc-2-amino-1,4-butanediol, respectively (Figure 10).[32]

4. Oxidative Transformation with *Concerto* 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 like acetone and molecular oxygen are used, the reverse reaction, dehydrogenative oxidation of alcohols is possible. This would attract much attention in organic synthesis.[33] The ligand modification is also crucial to determine the catalytic performance for oxidative transformation.

4.1 Dehydrogenative Oxidation of Alcohols with [Cp*Ru(P–N)] Catalysts. As a result of excellent catalytic activity of the bifunctional catalysts toward the hydrogen transfer between alcohols and ketones, [Cp*Ru(P–N)] has proven to be an excellent catalyst for the racemization of chiral non-racemic *sec*-alcohols, in which facile intramolecular hydrogen transfer on the catalyst proceeds rapidly.[34] This redox process can be successfully applied to isomerization of allylic alcohols. Allylic alcohols undergo sequential dehydrogenation and transfer hydrogenation as shown in Figure 11 to give saturated carbonyl compounds in toluene containing

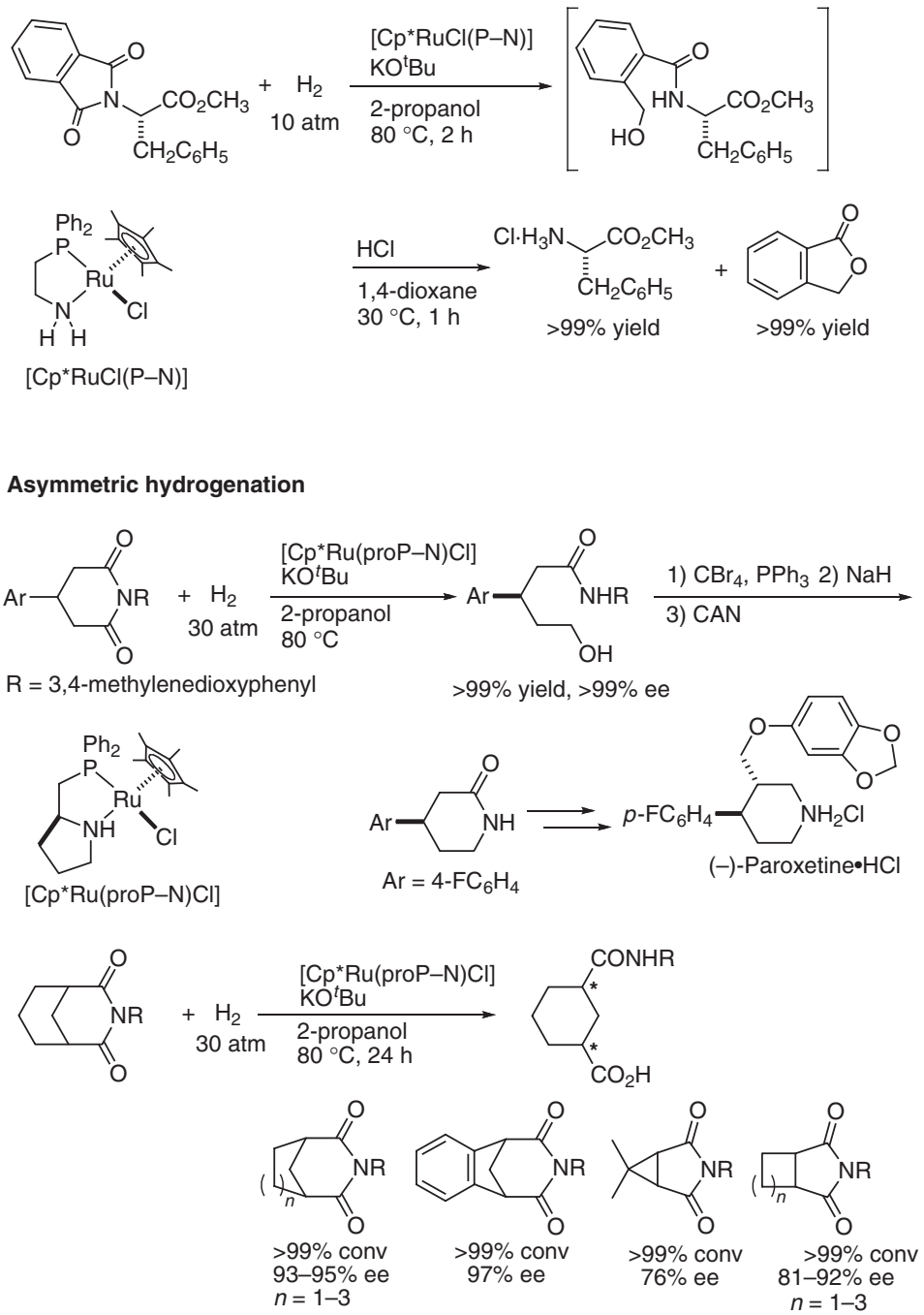


Figure 8. Hydrogenation of imides catalyzed by [Cp*Ru(P–N)] complexes and its applications to asymmetric hydrogenations.

[Cp*Ru(P–N)] catalysts; and the TOF (h^{-1}) of the reaction at 30 °C exceeds over 2500 h^{-1}.[35] This catalyst system can discriminate olefins with an allylic hydroxy group from other olefinic groups as a result of Ru/NH bifunctionality as shown in Figure 11. This unique chemoselectivity is applicable in the preparation of chiral macrocyclic ketones starting from readily available acyclic allylic alcohols equipped with two isolated C=C double bonds. Asymmetric isomerization with chiral [Cp*Ru(P–N)] catalysts followed by the ring-closing metathesis gave chiral muscone with a moderate ee.

Second, 1,4-diols undergo intermolecular hydrogen transfer, giving γ-lactones efficiently in acetone containing [Cp*Ru(P–N)] catalysts; the TOF (h^{-1}) of this reaction at 30 °C exceeding over 1000 h^{-1} (Figure 12).[36] 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 enables 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

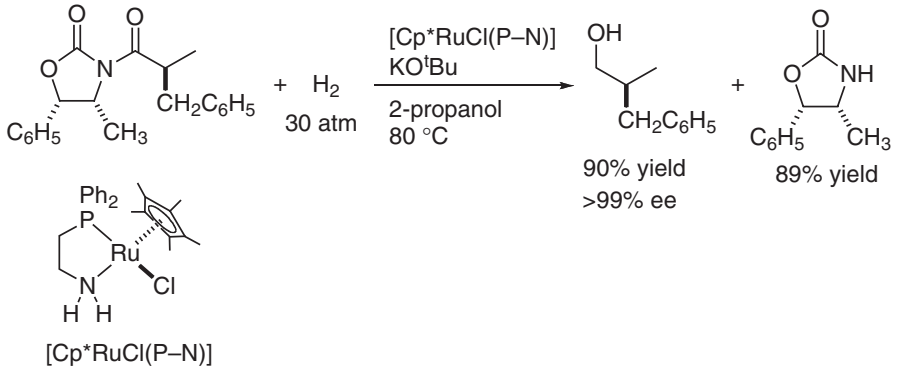


Figure 9. Hydrogenative deprotection of a chiral oxazolidinone.

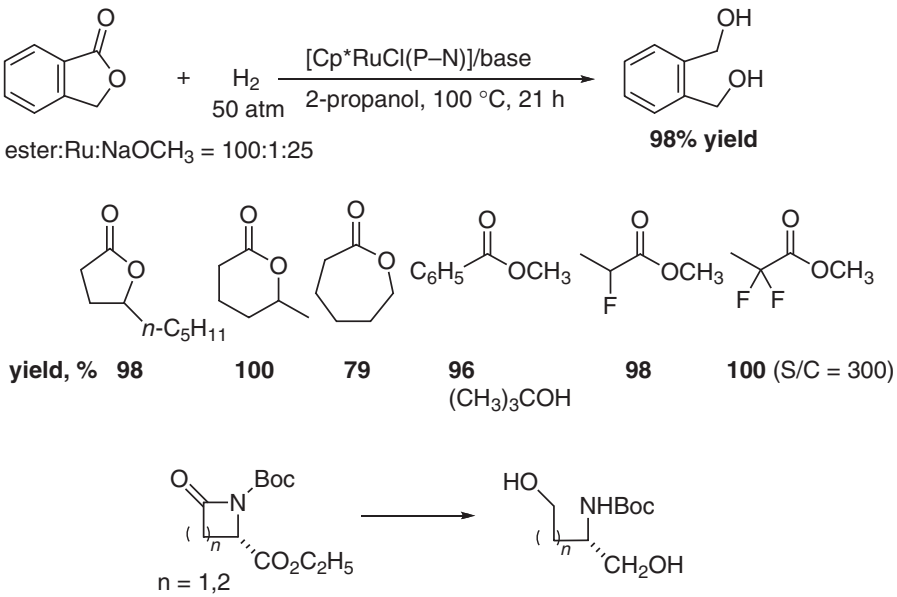


Figure 10. Hydrogenation of esters and lactones with [Cp*Ru(P–N)] catalyst.

provides a powerful and environmentally benign alternative for Fétizon oxidation.

4.2 Aerobic Oxidation of Alcohols.[37] 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. Fortunately, we found a new family of isolable bifunctional amido–Ir complexes bearing C–N chelating amine ligands, [Cp*Ir{κ^2(*N*,*C*)-(NHCR$_2$-2-C$_6$H$_4$)}] (R = C$_6$H$_5$ and CH$_3$), and the corresponding hydrido(amine) complexes, [Cp*IrH{κ^2(*N*,*C*)-(NH$_2$CR$_2$-2-C$_6$H$_4$)}], which serve as efficient catalysts for transfer hydrogenation of ketones, promote catalytic aerobic oxidation of alcohols. Separate experiments revealed that the hydrido(amine)–Ir complexes readily reacted with molecular oxygen under mild conditions to generate the corresponding amido Ir complexes [Cp*Ir{κ^2(*N*,*C*)-(NH$_2$CR$_2$-2-C$_6$H$_4$)}] as shown in Figure 13.[9a,38] 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. These results imply that the reaction of the hydrido complex with O_2 may 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.

The catalytic reaction of 1-phenylethanol proceeds smoothly under atmospheric pressure of air containing amido–Ir complex, [Cp*Ir{κ^2(*N*,*C*)-[NHC(C$_6$H$_5$)$_2$-2-C$_6$H$_4$]}] (Figure 14).[39] The hydrido(amine)–Ir complex, [Cp*IrH-{κ^2(*N*,*C*)-[NH$_2$C(C$_6$H$_5$)$_2$-2-C$_6$H$_4$]}], also gives the oxidation product acetophenone, whereas the hydrido complex bearing an *N*,*N*-dimethylamino group, [Cp*IrH{κ^2(*N*,*C*)-[N(CH$_3$)$_2$C-(C$_6$H$_5$)$_2$-2-C$_6$H$_4$]}], do not exhibit catalytic activity under otherwise identical conditions indicating that the M/NH bifunctional unit is also crucial for O_2 activation and that the aerobic dehydrogenation proceeds through the interconversion between the amine/amido catalyst intermediates. Binary catalyst systems, including the chloro(amine)–Rh and –Ru complexes and KOC(CH$_3$)$_3$, are also applicable to the aerobic oxidation.

The reaction of primary alcohols under identical conditions affords the oxidative dimerization product, esters. When a mixture of benzyl alcohols containing combined catalyst of the chloro complex, [Cp*IrCl{κ^2(*N*,*C*)-[NH$_2$C(C$_6$H$_5$)$_2$-2-C$_6$H$_4$]}], with an equimolar amount of KOC(CH$_3$)$_3$ in THF was stirred

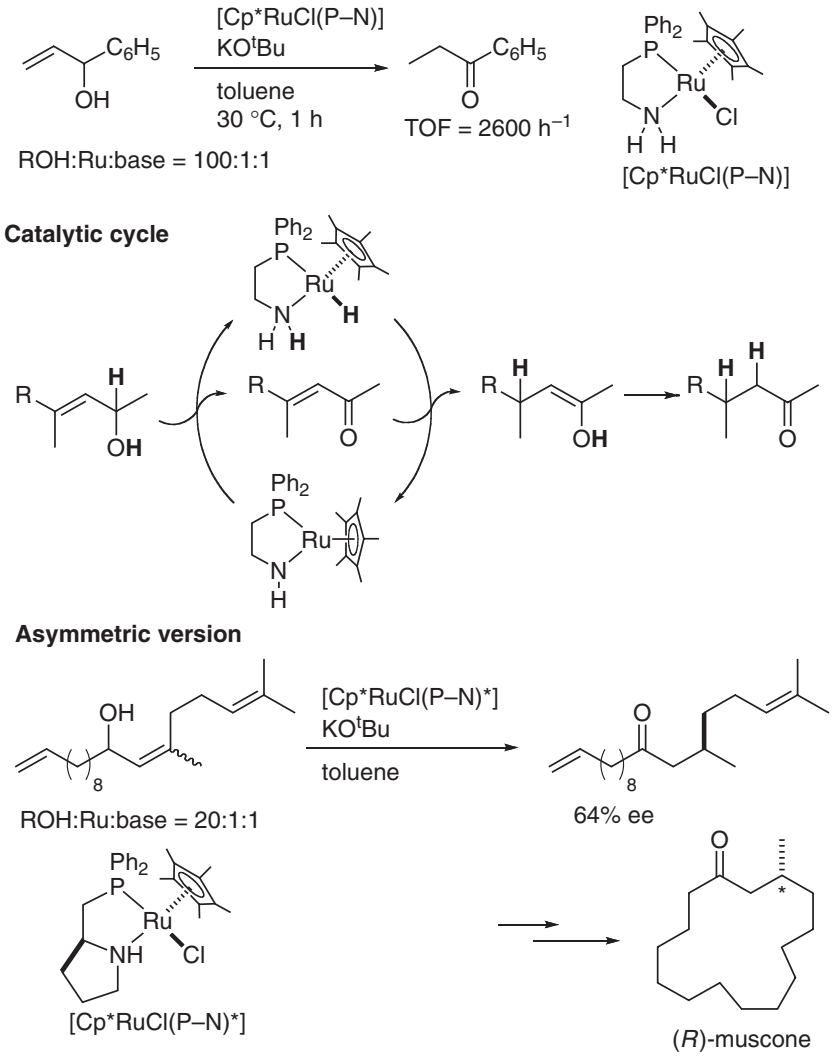


Figure 11. Isomerization of allylic alcohols with [Cp*Ru(P–N)] complexes and its application to (*R*)-muscone synthesis.

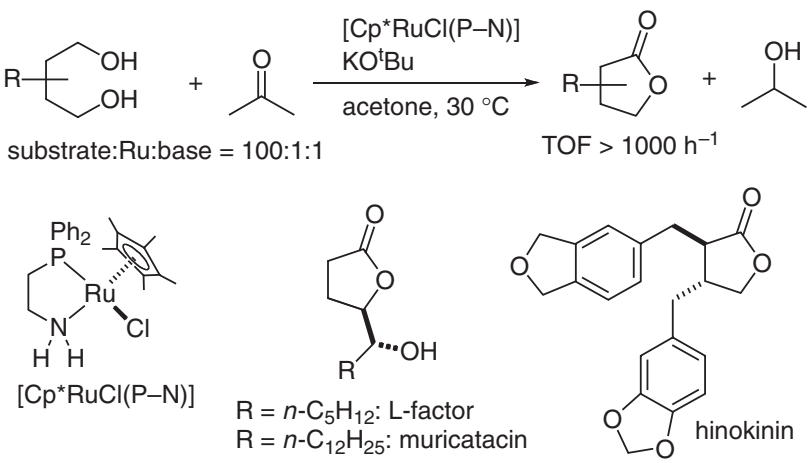


Figure 12. Oxidative lactonization of diols with [Cp*Ru(P–N)] complexes.

under air at 30 °C, the corresponding benzyl benzoate derivatives were obtained. A plausible mechanism is shown in Figure 15. In the presence of O_2, 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 catalysts (Figure 16). A racemic 1-phenyl-

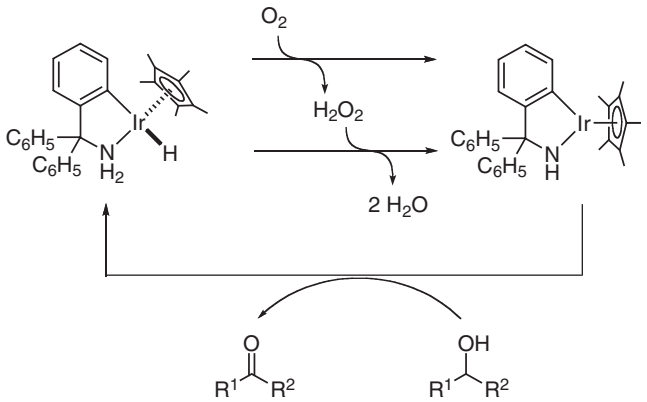


Figure 13. Mechanism of aerobic oxidation with [Cp*Ir(C–N)] complexes.

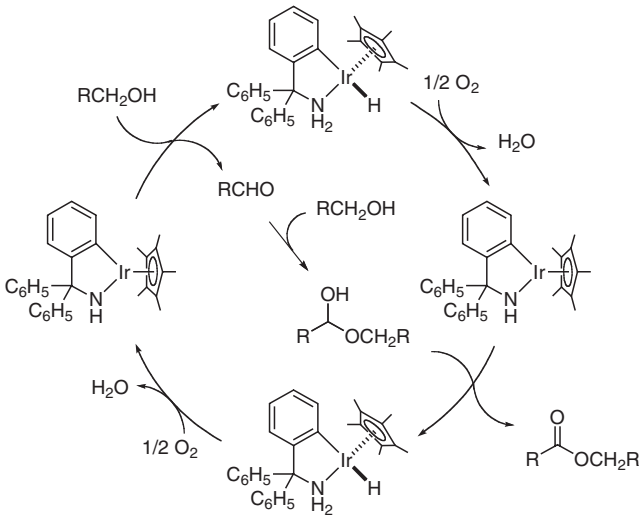


Figure 15. A possible catalytic cycle of aerobic oxidation of primary alcohols with [Cp*Ir(C–N)] complex.

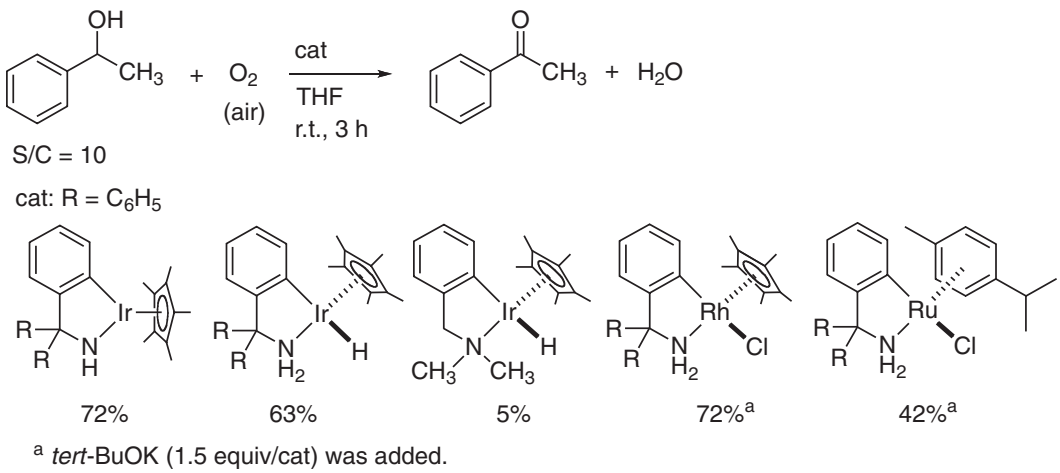


Figure 14. Aerobic oxidation of secondary alcohols with C–N chelate complexes.

ethanol is efficiently resolved by the chiral Ir complex, [Cp*Ir{(*S*,*S*)-Msdpen}] (Ms: methanesulfonyl), under the aerobic condition to give (*R*)-1-phenylethanol with a 48% yield and 98% ee; the k_f/k_s ratio being up to 100. Similarly, the reactions of 1-indanol and 1-tetralol at ambient temperature provide the *R*-enantiomers with >99% ee and with 46–50%. In contrast to previously reported kinetic resolution of alcohols with a combined system of [Ru{(*S*,*S*)-Tsdpen}(η^6-arene)] and acetone,[33a] aerobic kinetic resolution with binary catalyst systems including chiral Ir and Rh complexes, [Cp*MCl{(*S*,*S*)-Tsdpen}] (M = Ir, Rh) and a base proceed smoothly to give the desired chiral alcohols.

4.3 Extension to Dinuclear Bifunctional Catalysts Bearing Metal–Nitrogen Bond.[40] The metal–ligand bifunctional effect realized for the mononuclear half-sandwich amido complex is expected to be operative in imido-bridged dinuclear complexes with M–N bonds. Careful structural analysis and NMR studies revealed that the electron-withdrawing sulfonyl group stabilizes the imido-bridged dinuclear complexes,[41] also has an acid/base bifunctional property originated from the M–N bond nature.

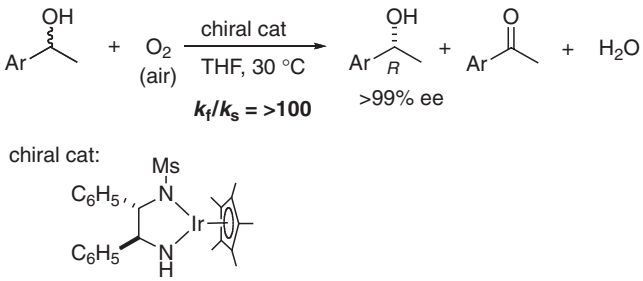


Figure 16. Aerobic oxidative kinetic resolution of racemic secondary alcohols.

A coordinatively unsaturtated bis(imido)-bridged dirhodium(III) complex, [(Cp*Rh)$_2$(μ-NTs)$_2$] (Ts: $SO_2C_6H_4CH_3$-*p*), prepared by the reaction of [Cp*RhCl$_2$]$_2$ with 2 equiv of TsNH$_2$ in the presence of KOH, reacts smoothly with H_2 (1 atm) in CH_2Cl_2 for 24 h at room temperature to afford the bis(amido)-bridged dirhodium(II) complex, [(Cp*Rh)$_2$(μ-NHTs)$_2$], in 82% yield as shown in Figure 17. An X-ray diffraction analysis of [(Cp*Rh)$_2$(μ-NHTs)$_2$]·TsNH$_2$ revealed the presence of intra-

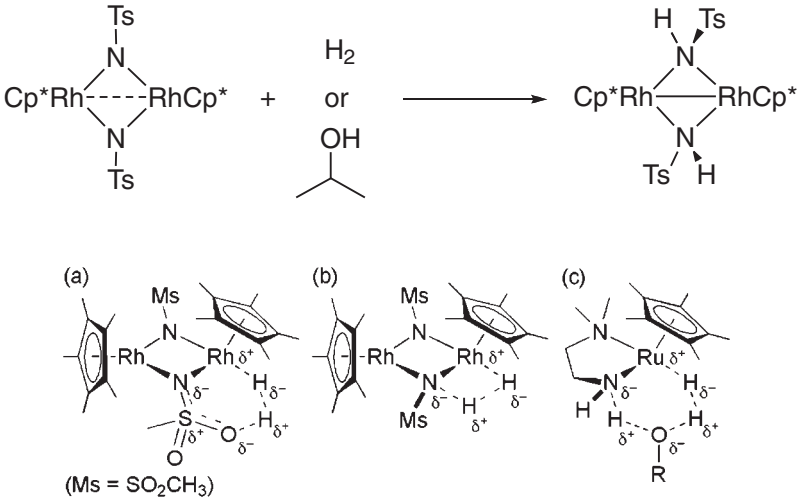


Figure 17. Reductive transformation of bis(imido)-bridged dirhodium(III) complex into bis(amido)-bridged dirhodium(II) complex.

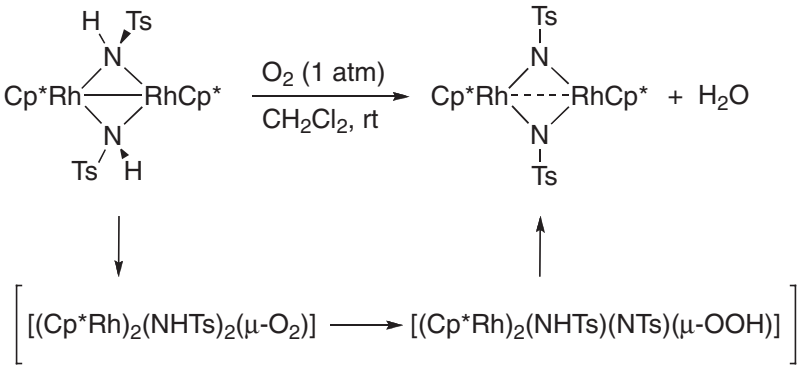


Figure 18. Aerobic oxidation of bis(amido)-bridged dirhodium(II) complex to bis(imido)-bridged dirhodium(III) complex.

and intermolecular hydrogen bonds between the amido protons and the sulfonyl O atoms. The Rh–Rh distance in the product bis(amido)-bridged complex is much shorter than that in $[(Cp^*Rh)_2(\mu\text{-}NTs)_2]$ (2.6004(12) vs. 2.7992(4) Å)[42] in agreement with the presence of an Rh(II)–Rh(II) single bond. It should be noted that in this reaction, H_2 is formally converted into two amido protons and two electrons for the reduction of the dirhodium(III) core in $[(Cp^*Rh)_2(\mu\text{-}NTs)_2]$. Such H_2 oxidation on dinuclear platforms remains quite rare.[43]

The bis(amido) complex is also obtainable upon treatment of the bis(imido) complex with an excess of 2-propanol. The generation of two NH protons associated with two-electron reduction of the metal center is in sharp contrast with the dehydrogenation of primary and secondary alcohols by unsaturated mononuclear amido complexes, which leads to the formation of hydrido–amine complexes without formal reduction of the metal, as described above. The DFT calculations for the reaction of the mesylimido analog, $[(Cp^*Rh)_2(\mu_2\text{-}NMs)_2]$, and H_2 revealed that heterolytic cleavage of H_2 assisted by the sulfonyl O atom (Figure 17a) is a favorable pathway rather than the direct addition of H_2 to the Rh–N bond (Figure 17b). Noteworthy is the similarity between the six-membered pericyclic transition state in this pathway and that proposed in related H_2 heterolysis, e.g., by mononuclear amido complexes with a solvent alcohol molecule (Figure 17c). The proton relay from the sulfonyl O atom to the imido N atom and the following spontaneous hydrido migration in the hydrido–amide intermediate highlights the significance of the Brønsted basicity of the two bridging sulfonylimido nitrogen atoms in this transformation.

The bis(amido)-bridged dirhodium(II) complex rapidly reacts with O_2 to form the bis(imido)-bridged dirhodium(III) complex and water as shown in Figure 18.[44] Although the precise mechanism has yet been clarified, the oxidation seems to occur via initial insertion of O_2 into the Rh(II)–Rh(II) bond in the amido complex followed by intramolecular proton shift from the amido ligand to the μ-peroxo ligand. Regeneration of the bis(imido) complex from this hydroperoxo intermediate may be explained by scission of the Rh–OOH bond aided by the NHTs proton to yield H_2O_2, which reacts with the bis(amido) complex to give the bis(imido) complex and H_2O, as described above.

The facile redox interconversion between the dinuclear imido and amido complexes (Figures 17 and 18) can be applied to catalytic aerobic oxidation of H_2 and alcohols. When a CD_2Cl_2 solution of $[(Cp^*Rh)_2(\mu\text{-}NTs)_2]$ is treated with a 1:1 mixture of H_2 and O_2 (total pressure: 1 atm), water is produced catalytically. In the reaction mixture, the sole rhodium species detectable by ^1H NMR spectroscopy is the bis(imido) complex, suggesting that the rate-determining step is the hydrogenation of $[(Cp^*Rh)_2(\mu\text{-}NTs)_2]$.

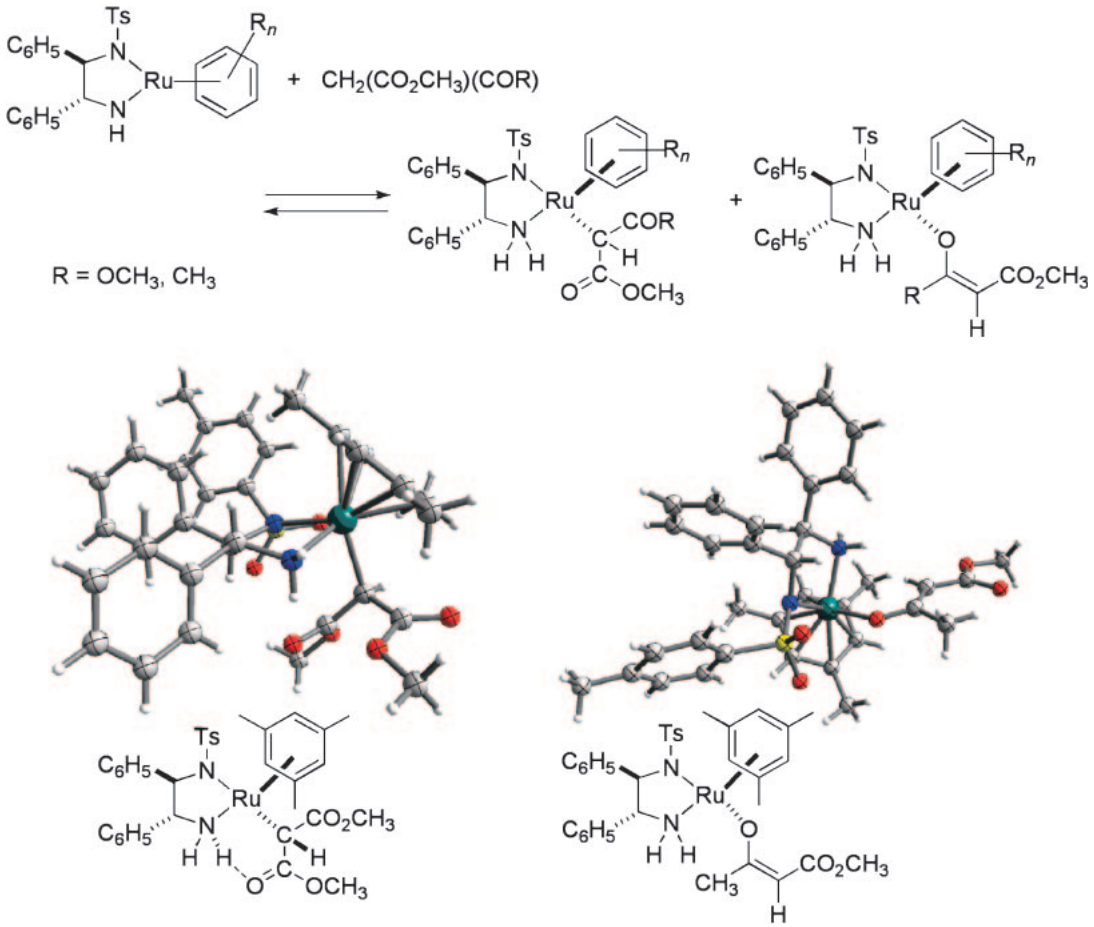


Figure 19. Reactions of [Ru{(*R*,*R*)-Tsdpen}(η^6-mesitylene)] with dimethyl malonate or acetoacetate and reaction products.

The sulfonylimido-bridged dirhodium complex also catalyzes the aerobic dehydrogenative oxidation of alcohols. Reaction of 2-octanol with O_2 (1 atm) proceeds very slowly in the presence of 1 mol % of [(Cp*Rh)$_2$(μ-NTs)$_2$] at 30 °C to give 2-octanone, the TON being up to 15 after 12 h-reaction. To the best of our knowledge, [(Cp*Rh)$_2$(μ-NTs)$_2$] represents the first well-defined dinuclear catalyst for this reaction without fragmentation throughout the catalysis.

5. Asymmetric Carbon–Carbon Bond Formation by Conjugate Addition with *Concerto* Catalysts[45]

Chiral bifunctional amido complexes have a sufficient Brønsted basicity to deprotonate alcohols and formic acid, which have pK_a value ranging from 4 to 18, producing amine hydrido metal complexes. We envisaged that the basic amido complexes could react with certain acidic organic compounds having a similar range of the pK_a value to lead to an amine complex bearing a metal-bonded carbon nucleophile. In fact, we have found that the purple-colored amido Ru complex, [Ru{(*R*,*R*)-Tsdpen}(η^6-mesitylene)], smoothly reacts with dimethyl malonate (pK_a, 13 in H_2O) in toluene below −30 °C to give an yellow crystalline complex, [Ru{CH(CO$_2$CH$_3$)$_2$}-{(*R*,*R*)-Tsdpen}(η^6-mesitylene)], as shown in Figure 19.[46] The single-crystal X-ray analysis indicates that it has a three-legged piano stool coordination environment with mesitylene, amino, sulfonamino, and C-bound malonato ligand. A detailed NMR study of the malonate complex in CD_2Cl_2 showed that it exists in a temperature-dependent equilibrium with the amido complex and free malonate, and that no detectable formation of an O-bound enolato complex was observed in the solution. In a similar way, the amido Ru complex react with β-keto esters (pK_a, 11 in H_2O) to give an equilibrium mixture of C- and O-bound complexes, which was determined by the NMR analysis of the temperature-dependent lineshape analysis together with 2D correlation and exchange experiments. The structure of the O-bound complex was determined by single-crystal X-ray analysis as shown in Figure 19.[47]

If the amine complexes bearing a metal-bonded nucleophile generated from an amido metal complex with certain acidic compounds can attack electron-deficient acceptors, the catalytic C–C bond formation shown in Figure 20 could be achieved. In fact, a chiral Ru catalyst, [Ru{(*S*,*S*)-Tsdpen}(η^6-arene)] efficiently promoted enantioselective Michael addition of dimethyl malonate to cyclopentenone to give the corresponding adducts with excellent ee's (Figure 21).[46] The variation of the catalyst structure showed the crucial role of the substituents in the arene ligand of the amido–Ru complex. The sterically congested complex with pentamethylbenzene or hexamethylbenzene ligand displays better reactivity than the *p*-cymene complex, indicating that the electron-donating ability of the multi-substituted arene ligands should cause an increase in nucleo-

philicity of the metal-bonded Michael donors. A variety of cyclic enones including cyclohexenone, cycloheptenone, and 4,4-dimethylcyclopentenone as well as pronucleophiles of malonates, β-keto esters, and nitroacetates can be successfully transformed to the corresponding chiral Michael adducts with high ee's.[47]

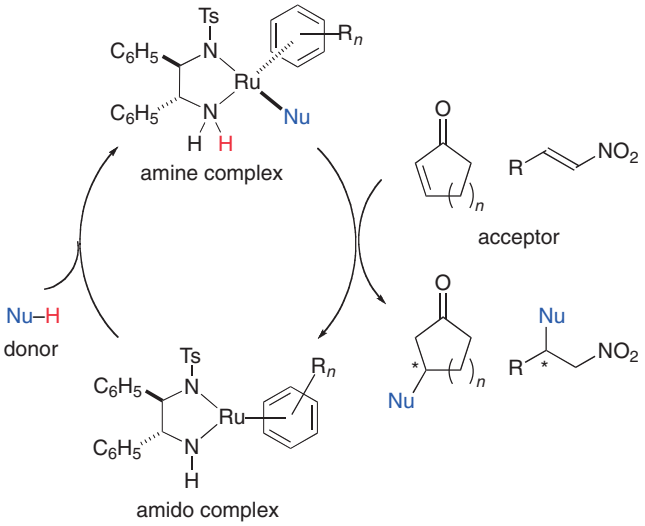


Figure 20. Enantioselective C–C bond formation catalyzed by the chiral amido complex.

The scope of the enantioselective C–C bond formation with chiral Ru catalysts is extensible to nitroalkenes as acyclic acceptors. Nitrostyrenes smoothly reacted with 1,3-dicarbonyl compounds in the presence of chiral (*S*,*S*)-Ru complexes affording high yields of corresponding (*R*)-Michael adducts with excellent ee values as shown in Figure 22.[48] The [Ru{(*S*,*S*)-PMBsdpen}(η^6-hmb)] [PMBs: 2,3,4,5,6-$(CH_3)_5C_6$-SO_2; HMB: η^6-hexamethylbenzene, $(CH_3)_6C_6$] complex displays the best catalytic performance in the reaction of dimethyl malonate, reaching up to 97% yield and 95% ee at −20 °C with a substrate/catalyst ratio (S/C) of 100. Other 1,3-dicarbonyl compounds such as β-keto esters and sterically bulkier 1,3-diketones can also be used as the Michael donors.

These Michael addition reactions are also characterized by high practicability in organic synthetic chemistry. For example, a gram-scale reaction of the substituted β-nitrostyrene (2.1 g) with dimethyl malonate with the chiral Ru catalyst (malonate:nitrostyrene:Ru = 100:100:1) at −20 °C for 48 h gave the chiral nitro compound in 94% yield (2.97 g) with 95% ee. After separation of the catalyst by simple column chromatography, single recrystallization from alcohol produces the enantiomerically pure Michael adduct, which is an intermediate of rolipram.

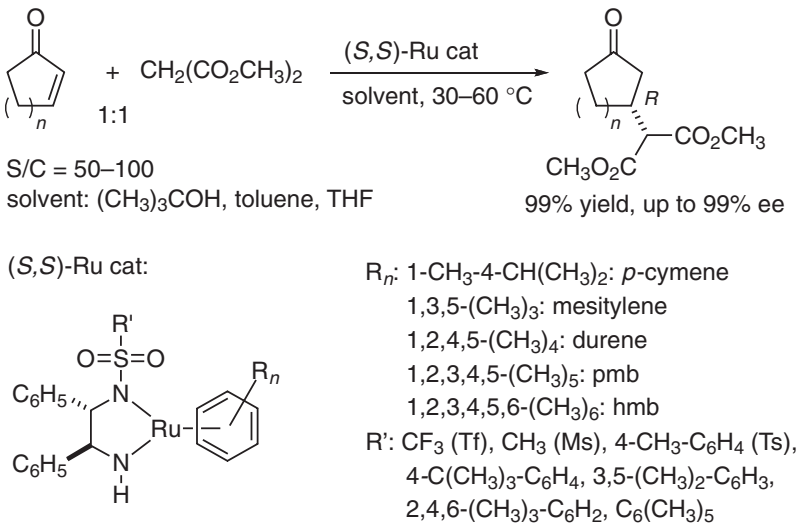


Figure 21. Asymmetric Michael addition of dimethyl malonate to cyclic enones.

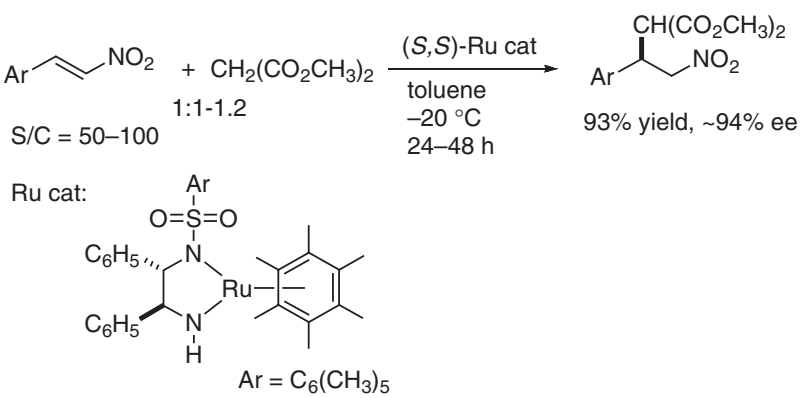


Figure 22. Asymmetric Michael addition of dimethyl malonate to nitroalkenes.

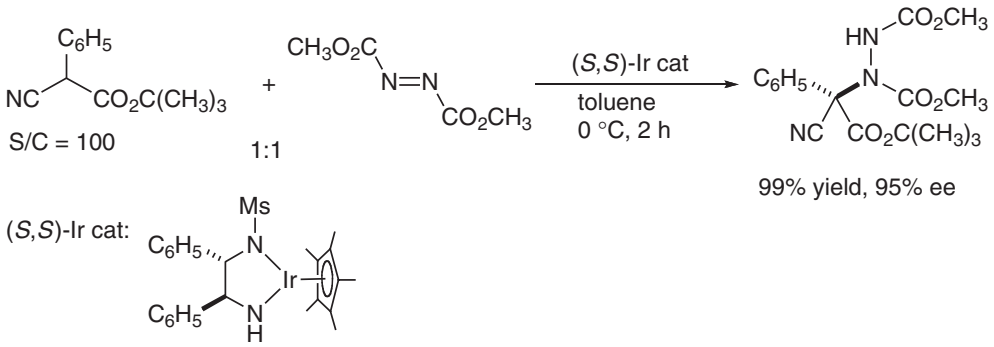
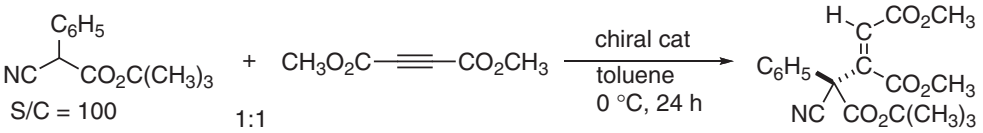


Figure 23. Asymmetric Michael addition of cyanoacetates to dimethyl azodicarboxylate.



chiral cat	isolated yield	$Z/E^{a)}$	ee, % $(Z/E)^{b)}$
[Ru{(*S*,*S*)-Tsdpen}(hmb)]	97	20	91/52
[Cp*Ir{(*S*,*S*)-Tsdpen}]	96	20	90/23

[a)]determined by ^{1}H NMR, [b)]determined by HPLC.

proposed mechanism

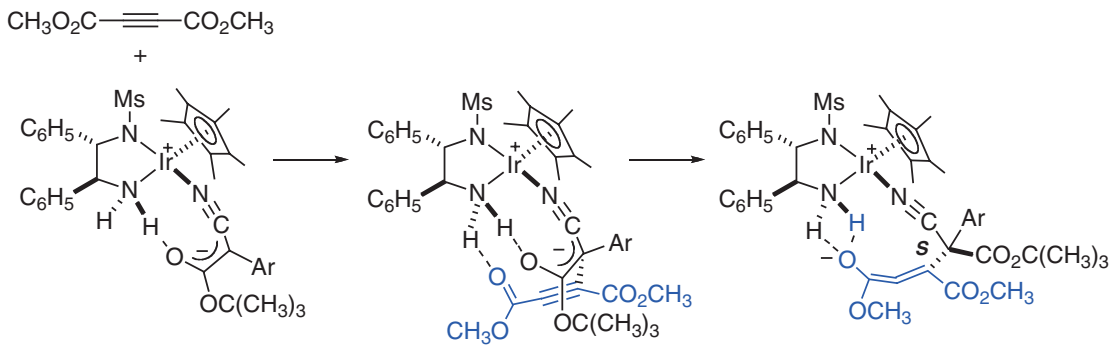


Figure 24. Asymmetric conjugate addition of α-cyanoacetates to acetylenic esters.

Analogous bifunctional Ir complexes were found to catalyze the reaction of α-cyanoacetates with dialkyl azodicarboxylates that yields the direct amination products, the hydrazine adducts, in excellent yields and with excellent ee's (Figure 23).[49] The significant rate of the non-catalytic background reaction requires the slow addition of azodicarboxylate to a toluene solution of cyanoacetate containing the chiral Ir catalyst with a syringe pump at the low temperature. The CsDPEN [Cs: (1*R*)-camphorsulfonyl] complex gave the best catalyst performance in terms of the selectivity, the ee value of the product reaching up to 98% ee.

When the acetylenic esters are used as electrophiles, enantioselective and *Z* selective conjugate addition of α-cyanoacetate with bifunctional chiral catalysts yields chiral adducts having a quaternary carbon center with an excellent ee. Both chiral Ru and Ir complexes works equally well in this C–C bond forming reaction at 0 °C to afford the corresponding chiral adducts with up to 95% ee and an excellent *Z*/*E* selectivity in almost quantitative yields as shown in Figure 24.[50]

A stoichiometric reaction of *tert*-butyl α-cyanoacetate with the amido Ir complex in CH_2Cl_2 proceeds rapidly to give a mixture of two *N*-bound nitrile complexes, [Cp*Ir{NCC-(C_6H_5)[COOC(CH_3)$_3$]}{(*S*,*S*)-Msdpen}], which was determined by single-crystal X-ray analysis and NMR study.[49,50] Based on the absolute configuration of the reaction products and the results of a combined NMR and computational (B3LYP/SDD) analysis, we proposed that the C–C bond forming reaction may occur from the *N*-bound cyanoester complex which is stabilized by the hydrogen bond as shown in Figure 24. The acetylenic diester might approach the *Si*-face of the *N*-bound cyanoester anion by interaction of the O atom of the ester unit with the NH proton of the amino group in the cyanoester complex for mainly the steric interaction of the loose carbomethoxy group with the substituents on the anion carbon. In addition, the high *Z*/*E* ratios of this C–C bond formation product suggests that the proton transfer occurs directly from nitrogen to carbon, since the protonation of the

oxygen atom would yield a hydroxyallene intermediate with equal potential for transferring the proton in two alternative positions (Figure 24). Thus, the cyanoester and dialkyl azodicarboxylate or acetylenic esters are activated by the bifunctional catalyst to facilitate the enantioselective C–N or C–C bond forming reactions.

Although possible catalytically active intermediates are isolated[45] or are detectable by spectroscopy as well as ESI-MS, the precise mechanism of the Michael reaction catalyzed by the metal complexes is still controversial. Further investigation including computational analysis on the reaction pathways for these conjugate additions should be required.

6. Conclusion

This article focuses on recent advances in chemistry of conceptually new bifunctional transition-metal-based molecular catalysts for stereo-, regio-, and chemoselective reductive or oxidative transformation as well as enantioselective C–C and C–N bond formations via Michael-type conjugate additions. The chiral amido Ru catalyst bearing a cooperating amido group, which was originally developed for asymmetric transfer hydrogenation of ketones, has a sufficient Brønsted basicity to react with hydrogen donors such as 2-propanol and formic acid to form the bifunctional hydrido(amine) complex. Thus, these complexes perform efficiently the hydrogen-transfer reactions between ketones and alcohols through an unprecedented outer sphere mechanism involving pericyclic transition states. The reacting unsaturated substrates are not necessarily bonded directly to the metal center. Judicious modification of cooperating ligands by changing the amine ligands from *N*-sufonylated diamines to other bidentate protic amines such as the *N*,*N*-dimethylaminoethylamines (N–N) and 2-phosphinoethylamines (P–N) causes a drastic change in the catalytic performance. For example, the [Cp*Ru(P–N)] complex exhibits an excellent catalytic activity for both hydrogenation of polar substrates including epoxides, imides, *N*-acylcarbamates, and esters as well as asymmetric isomerization of allylic alcohols by intramolecular transfer hydrogenation. The concept of *concerto* catalysis based on the metal/NH bifunctionality is also successfully applicable to aerobic oxidative dynamic kinetic resolution of racemic alcohols and enantioselective C–C and C–N bond formation reactions. Thus, the rational design of the cooperating amine ligand that adjusts the balance of the electronic factors on the M/NH units in the bifunctional catalysts is crucial to exploit characteristic catalyst performance with a wide scope and high practicability. I believe the present *concerto* molecular catalyst offers a great opportunity to open up new fundamentals for selective molecular transformation including asymmetric synthesis.

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Dedicated to Professor Akio Yamamoto on the occasion of his 80th birthday.

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Takao Ikariya completed his Ph.D. degree supervised by Prof. A. Yamamoto in 1976 at Tokyo Institute of Technology and then he was appointed as an assistant professor in the Department of Synthetic Chemistry at the University of Tokyo. He discovered a prototype of chiral Ru–BINAP complex and successfully developed asymmetric hydrogenation with the Ru–BINAP complexes. He spent Prof. R. H. Grubbs' group at Caltech for one and a half years in 1979–1981 as a postdoctoral fellow. In 1985, he moved to the central research center of NKK Co. In 1991, he joined in the ERATO Molecular Catalysis Project of JST, which was directed by Prof. R. Noyori. Then Ikariya was promoted to professor at Tokyo Institute of Technology in 1997. He received the Chemical Society of Japan Award in 2009. His current research interests include powerful and practical molecular catalysis in both liquid solvents and supercritical fluids.