Bifunctional transition metal-based molecular catalysts for asymmetric syntheses

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The discovery and development of conceptually new chiral bifunctional transition metal-based catalysts for asymmetric reactions is described. The chiral bifunctional Ru catalyst was originally developed for asymmetric transfer hydrogenation of ketones and imines and is now successfully applicable to enantioselective C–C bond formation reaction with a wide scope and high practicability. The deprotonation of 1,3-dicarbonyl compounds with the chiral amido Ru complexes leading to the amine Ru complexes bearing C- or O-bonded enolates, followed by further reactions with electrophlies gives C–C bond formation products. The present bifunctional Ru catalyst offers a great opportunity to open up new fundamentals for stereoselective molecular transformation including enantioselective C–H and C–C as well as C–O, C–N bond formation.

Introduction

Recently, much attention has been given to the design of chiral molecular catalysts with a bifunction based on the combination of Lewis acid and Lewis base working in concert, to attain highly efficient molecular transformation for organic synthesis.[1] Many sophisticated metal-based bifunctional catalyst systems have been reported, and excellent reviews on the concept and wide applications have been recently reviewed.[2] Since the bifunctional catalysts contain two or more active sites for activation of the electrophiles and nucleophiles, they can efficiently effect a wide range of molecular transformations including C–H, C–C, C–O, or C–N bond formation by cooperative activation and

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Takao Ikariya completed his PhD degree in 1976 at the Tokyo Institute of Technology and then he was appointed as an assistant professor at the University of Tokyo. He spent one and a half years in 1979–1981 as a postdoctoral fellow in Professor Robert H. Grubbs' group at Caltech. In 1985 he moved to the central research center of the NKK corp. In 1991 he joined in the ERATO Molecular Catalysis Project of the Japan Science and Technology Corporation, directed by Professor Ryoji Noyori. Takao Ikariya was promoted to professor at the Tokyo Institute of Technology in 1997.

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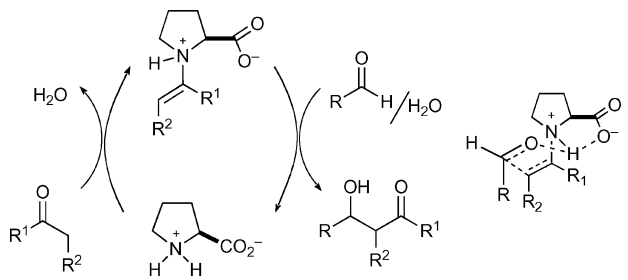
effective accumulation of reacting substrates on neighboring active centers in the same molecules. Although these molecular catalysts efficiently promote asymmetric reactions, they often suffer from acid–base neutralization mainly for structural reasons, leading to the deactivation of the catalysts. Therefore, careful and precise tuning of the structures of the molecular catalysts as well as the spatial organization of the functionality is required to achieve the best catalysis performance.

Organocatalysts bearing bifunctional properties also offer attractive and practical options in the recent development of asymmetric transformations mainly because organic molecular catalysts consist of readily available chiral molecules and structurally tunable molecules.[3] For example, in the proline-promoted aldol reaction shown in Scheme 1,[4] the zwitterionic proline molecule readily reacts with ketones and aldehydes to form an enamine derivative, which has an activated nucleophile. Therefore, certain electrophile, aldehyde or α·β-unsaturated carbonyl compounds readily react with the enamine, possibly through a metal-free Zimmerman–Traxler type transtion state, to give the corresponding C–C bond formation product in which the electrophile can be effectively activated by the Brønsted basic site in the same molecule. After hydrolysis, the proline molecule can be recovered and recycled. The most attractive aspect, which however is still not sufficiently clarified, is the catalytic cycle with proline, in which only the catalyst and its intermediates are involved. The catalyst activates nucleophiles with the formation of reactive compounds that further activate electrophiles. The reaction mechanism promoted by organocatalysts is very informative for designing bifunctional metal-based molecular catalysts.



Scheme 1 A possible catalytic cycle of proline-promoted aldol reaction.

We have recently developed chiral transition metal complexes bearing optically active N-sulfonylated 1,2-diamine ligands for asymmetric transfer hydrogenation of ketones and imines,[5] in which both chiral amido metal and chiral amine hydrido metal complexes with a metal/NH bifunctional synergetic effect are involved as catalysts and intermediates.[6] During interconversion between both the catalyst and the intermediate, highly efficient hydrogen transfer between ketones and alcohols reversibly takes place. Catalyst deactivation due to the acid–base neutralization or destructive aggregation can be minimized. This unique concept of the bifunctional transition metal based-molecular catalysts leads to high reaction rates and excellent stereoselectivies because the reactions proceed through a tight-fitting assembly of the reactants and chiral catalysts. This bifunctional catalyst can also provide a wide substrate scope and applicability in organic synthetic chemistry. In this perspective article, we outline our recent progress in bifunctional molecular catalysts based on ruthenium, rhodium, and iridium complexes bearing chiral diamine ligands and their utilization to asymmetric catalysis including enantioselective reduction and C–C bond formation.

What is the bifunctional transition metal-based molecular catalyst?

We have demonstrated that chiral η⁶-arene-Ru complexes, RuCl(Tsdpen)(η⁶-arene), and chiral η⁵-pentamethylcyclopentadienyl (Cp*)–Ru,[7] Rh, and Ir complexes, Cp*MCl(Tsdpen) (TsDPEN: *N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine), M = Rh, Ir (Fig. 1),[8] which have a structure isoelectronic to the arene–Ru complex, effected highly efficient asymmetric reductive transformation of ketones or imines. Chiral *N*-tosylated diamines, β-amino alcohols, diamines, and amino phosphines serve as excellent ligands and lead to high reactivity and enantioselectivity in these asymmetric reactions. We were able to isolate the catalyst precursor, real catalyst, and catalyst intermediate and determined their structures in the solid state[5] as well as in solution. A preformed catalyst precursor, for example, RuCl(Tsdpen)(η⁶-arene) as shown in Fig. 2, can be prepared as orange crystals in almost quantitative yield from the reaction of $[RuCl_2(\eta^6\text{-arene})]_2$ with TsDPEN in 2-propanol containing triethylamine. This chloride complex readily converts with a base in 2-propanol to the real active catalyst, an amido Ru complex. As shown in Fig. 3a, the Ru amido complex is formally a 16-electron neutral complex with a square-planar geometry,[5f] and the metal center is bound to two anionic nitrogen atoms and to an η⁶-arene. The amide complex has a relatively short Ru–N bond, 1.89 Å, which is intermediate between the N–Ru single and triple bond reported in the literature.[9] The lone-paired electrons on the nitrogen atom participate in formation of the N to Ru partial double bond. This purple-colored amido Ru complex readily reacts with

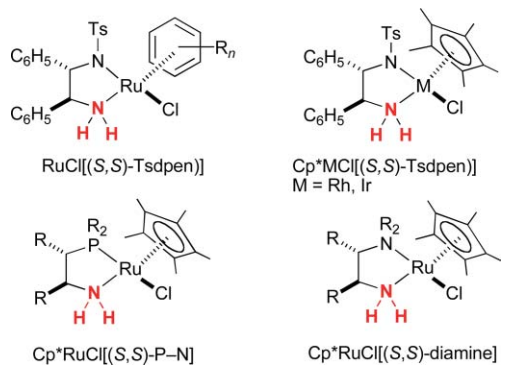


Fig. 1 Precursors of bifunctional molecular catalysts.

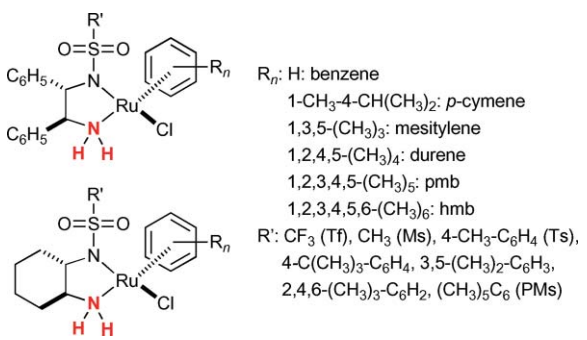


Fig. 2 Chiral Ru complexes bearing *N*-tosylated diamines.

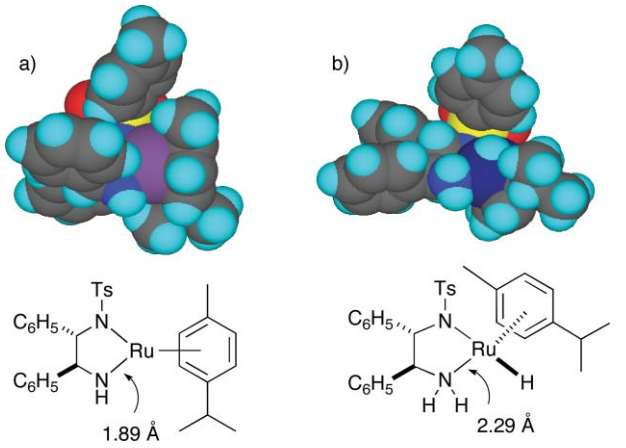
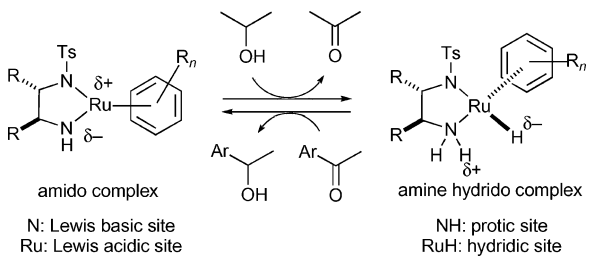


Fig. 3 Bifunctional molecular catalysts, (a) chiral amido Ru complex, (b) chiral amine hydrido Ru complex.

2-propanol at room temperature to produce a yellow amine hydrido Ru complex as a single diasteromer with concomitant formation of acetone. This amine hydrido Ru complex, the other real catalyst intermediate, is an 18-electron complex with a distorted octahedral configuration around the Ru center with a ring in a δ-configurated five membered chelate ring, an η^6-arene, and a hydrido ligand as shown in Fig. 3b. The relatively short NH···HRu bond distance indicates an electrostatic interaction possibly due to the NH proton on the diamine being highly protic. These unique structures of the true catalyst and the intermediate are responsible for the *bifunctional molecular catalysts.*

In the catalytic reaction, thanks to the nature of the Ru–N bond, the amido Ru complex dehydrogenates an alcohol leading to the amine hydrido Ru complex. This complex in turn reacts with carbonyl compounds to transfer the hydride and proton to the C=O function giving the alcoholic product. Here, the amine hydrido complex converts to the amido complex. Thus, the hydrogen transfer between alcohols and carbonyl compounds occurs reversibly as shown in Scheme 2. The efficiency of the catalytic reduction is strongly influenced by the reactivities of these Ru complexes as well as redox potentials of the alcohols and carbonyl compounds.



Scheme 2 Interconversion between the amido and the amine hydrido Ru complexes.

Kinetic studies and isotope labeling experiments[5f,10] as well as computational analysis[11] for the hydrogen transfer between alcohols and ketones promoted by the Ru complexes revealed that the reaction takes place reversibly through a six-membered pericyclic transition state as shown in Fig. 4. The NH unit forms a hydrogen bond with the carbonyl oxygen atom to stabilize the transition state. An important and unprecedented aspect is

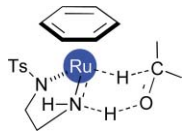


Fig. 4 A transition state for hydrogen transfer between ketones and alcohols.

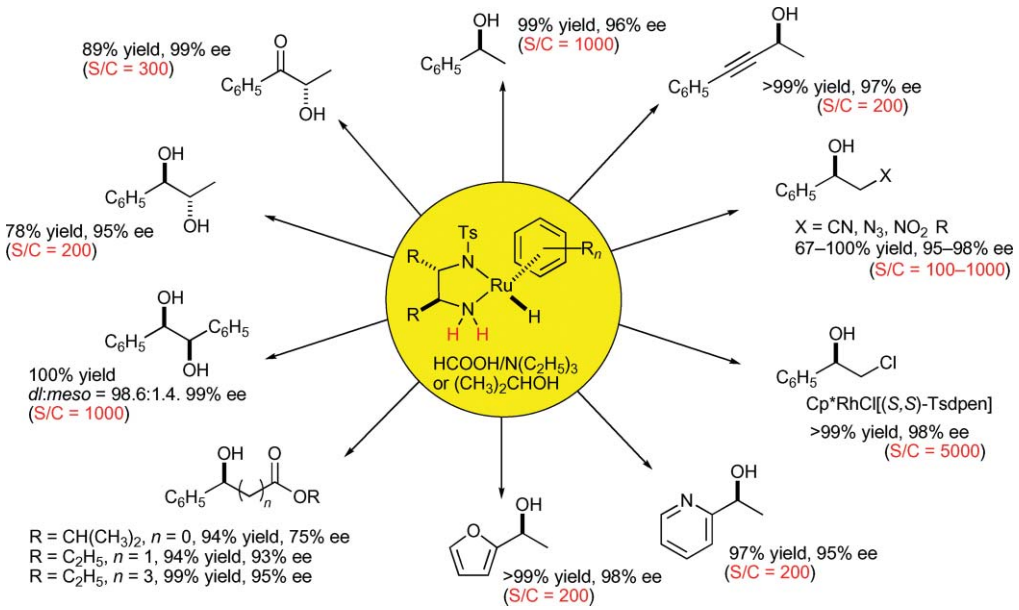
that the carbonyl compound does not interact directly with the metal center for its own activation. Therefore, the presence of an NH moiety in the ligands is crucially important to determine the catalytic performance of the bifunctional catalysts.[12] Thus, the present bifunctional catalyst system provides a practical and wide scope for asymmetric catalysis including enantioselective reduction and C–C bond formation, giving chiral compounds with excellent ee's.

Asymmetric transfer hydrogenation of acetophenones bearing substituents at the α position with the bifunctional molecular catalysts

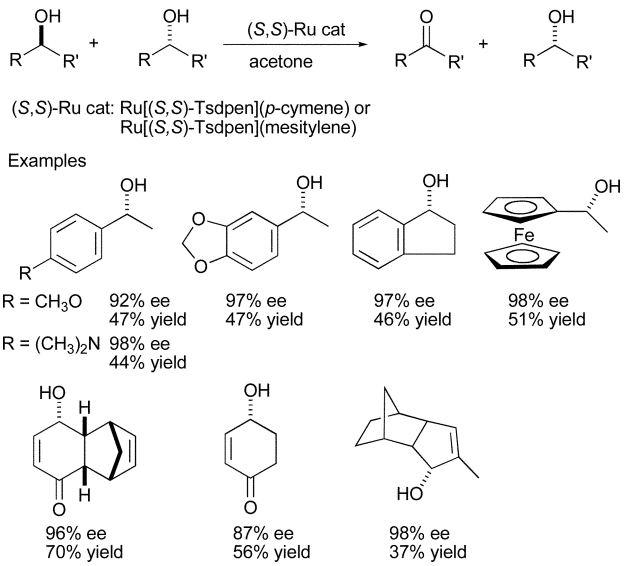
Since we found a prototype of the bifunctional Ru catalyst in 1995,[5] we have developed a very practical asymmetric transfer hydrogenation process with a series of chiral catalysts having the M/NH units in the same molecule as shown in Figs. 1 and 2. A wide variety of chiral alcohols are now accessible with excellent ee's from the reaction under mild conditions. Some representative results are summarized in Scheme 3.

Since early progress in asymmetric reduction with the chiral Ru catalyst has been already reviewed,[5i,13] this perspective review focuses on recent advances in asymmetric transfer hydrogenation of certain selected carbonyl compounds with chiral bifunctional catalysts. In general, 2-propanol and formic acid can be used as very cheap hydrogen sources. In particular, 2-propanol is a safe, nontoxic, environmentally friendly hydrogen source. Although the reactions with the chiral Ru catalysts in 2-propanol give satisfactory results in terms of both reactivity and selectivity,[5i] 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 the enantiomeric purity of the products upon long exposure of the reaction mixture to the catalyst. The efficiency of the forward reaction is dependent on the redox properties of product alcohols in addition to the chiral recognition ability of the catalysts as discussed above. The aromatic ketones having electron-withdrawing groups on the aromatic ring are readily reduced to the corresponding chiral alcohols with excellent ee's. On the other hand, when chiral alcohols with electron-donating groups are synthetically useful, the reverse reaction, enantiomer selective dehydrogenative oxidation of chiral racemic alcohols using acetone, becomes a practical process.[5g] In fact, chiral alcohols, (*R*)-1-arylethanols with an electron-donating group[5g] and 2-cyclopentenol derivatives,[14] are readily accessible by the kinetic resolution of racemic and meso alcohols with the chiral amido Ru complexes, Ru[(*S*,*S*)-Tsdpen](η^6-arene) (arene = *p*-cymene and mesitylene) as shown in Scheme 4.

The asymmetric reduction using formic acid, a formal adduct of H_2 and CO_2, proceeds irreversibly with kinetic enantioselection and, in principle, 100% conversion.[5d,15] Thus, the asymmetric



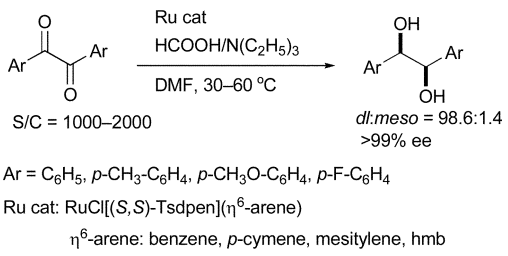
Scheme 3 Asymmetric transfer hydrogenation of ketones with chiral Ru and Rh catalysts.



Scheme 4 Kinetic resolution of *rac*-alcohols and desymmetrization of *meso*-alcohols with chiral Ru catalysts.

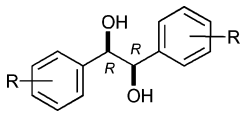
reduction of simple aromatic ketones with a mixture of formic acid and triethylamine containing the bifunctional catalyst is characterized by high efficiency in terms of activity, selectivity, wide applicability, and practicability as summarized in Scheme 3. Simple aromatic ketones with both electron-withdrawing and -donating substituents can be reduced to chiral alcohols with excellent ee's. The reactivity and enantioface-selectivity of the chiral Ru complex, RuCl(*N*-tosylated diamine)(η^6-arene), are the consequences of a compromise between the steric and electronic factors of the arene and *N*-tosylated diamine ligands. The reactivity decreases in the order benzene > *p*-cymene, mesitylene > hexamethylbenzene probably due to steric reasons. The $ArSO_2$ group in the diamine is important for attaining high reactivity, while the CF_3SO_2 analogue significantly reduces the reactivities.

Among the notable features of this asymmetric transfer hydrogenation is the carbonyl group selectivity. The functional groups at the α or β position do not interact with the metal center because of the coordinatively saturated nature of the amine hydrido Ru complexes. The reaction proceeds chemoselectively without influence of the olefinic linkage and amino, ester, hydroxyl, carbonyl, sulfido, sulfone, nitro, azide, and chloride group, and furan, thiophene, and quinoline rings. Asymmetric reduction of 1,2-diketones, benzils, is worthy of note.[17] Although benzils cannot be reduced by the currently available hydrogenation catalysts, Ru–BINAP complexes (BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl), $Ru_2Cl_4[(R)\text{-tolbinap}]_2\cdot(C_2H_5NH_2)$,[16] $RuCl_2[(R)\text{-binap}][(R,R)\text{-dpen}]$,[6] the reduction of 1,2-diketones with the chiral Ru complex in a mixture of formic acid and triethylamine gives the chiral 1,2-diols with an excellent ee as illustrated in Scheme 5. Various benzil derivatives are stereoselectively reduced to the chiral hydrobenzoins with high ee's and in good yields. Table 1 lists some examples.[17b] The benzils with electron-donating substituents are reduced with excellent enantioselectivity but lower reactivity, while the reduction of *p*-fluorobenzil proceeds rapidly as expected, giving a product with a high ee. The *p*-cymene and mesitylene complexes effect the reaction equally well, while the sterically congested hexamethylbenzene complex shows extremely high stereoselectivity although less reactivity at 40 °C.



Scheme 5 Asymmetric reduction of benzils with chiral Ru catalysts.

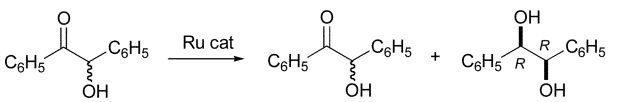
Table 1 Asymmetric reduction of benzil derivatives



R	Temp/°C	Time/h	Yield (%)	*dl* : *meso*	ee (%)
H	40	24	100	98.4 : 1.6	>99
p-CH_3	40	48	67	96.7 : 3.3	>99
p-OCH_3[a]	35	48	75	64.4 : 5.6	>99
p-F	40	24	100	94.2 : 5.8	>99

Conditions: Ru cat = RuCl[(*S*,*S*)-Tsdpen](*p*-cymene), S/C = 1000, $HCOOH/N(C_2H_5) = 4.4/2.6$.[a] S/C = 200, $HCOOH/N(C_2H_5)_3 = 4.4/4.4$ in 1.2 m DMF.

The success of the asymmetric reduction of benzils with a formic acid and triethylamine mixture relies strongly on the property of the benzoin intermediates as well as the enantiomer discrimination ability of the chiral Ru complexes. As shown in Scheme 6, a reaction of racemic benzoin with the (*S*,*S*)-Ru catalyst gives (*R*,*R*)-diol with >99% ee at the early stages of the reaction in 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. These results imply that the reaction proceeds through a DKR (dynamic kinetic resolution) of the intermediary benzoin, in which the (*S*,*S*)-catalyst favors the reaction of (*R*)-benzoin. Product distribution analysis shows that the rate of the reduction of (*R*)-benzoin proceeds 55 times faster than that of the *S* isomer. The slow-reacting *S* isomer undergoes rapid racemization under the basic conditions (Scheme 7).[17b] Similarly, the reactions of 1,3-diphenylpropane-1,3-dione and 2,6-diacetylpyridine with the RuCl[(*S*,*S*)-Tsdpen](*p*-cymene) catalyst produce the corresponding chiral diols with 99% ee and in 99% yield (*dl* : *meso* = 94 : 6), and with 99.6% ee and in 100% yield (*dl* : *meso* = 91 : 9), respectively (Scheme 8).[18,19]

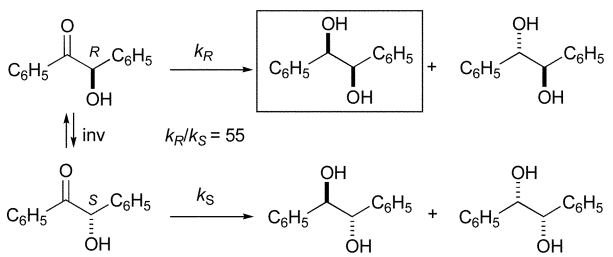


S/C = 1000

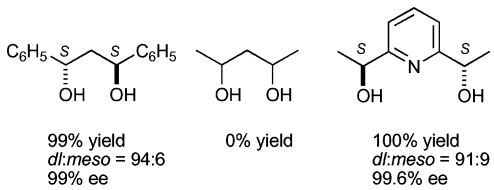
	benzoin		hydrobenzoin		
time, h	yield, %	ee, %	yield, %	*dl*:*meso*	ee, %
0.25	96	0	4	98.2:1.8	100
24	0	–	100	98.1:1.9	100

Ru cat = RuCl[(*S*,*S*)-Tsdpen](*p*-cymene) 0.005 mmol, $HCOOH/N(C_2H_5)_3$ = 3.1/2.6, 0.95 M in DMF, 40 °C.

Scheme 6 Asymmetric reduction of *rac*-benzoin with chiral Ru catalysts.



Scheme 7 Dynamic kinetic resolution of benzoin.



99% yield
dl:*meso* = 94:6
99% ee

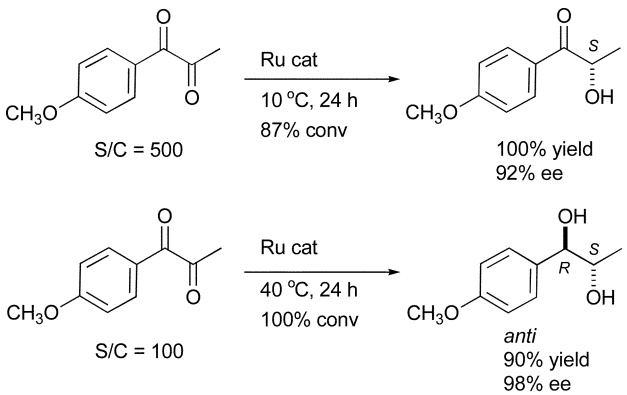
0% yield

100% yield
dl:*meso* = 91:9
99.6% ee

Conditions: Ru cat = RuCl[(*S*,*S*)-Tsdpen](*p*-cymene), $HCOOH/N(C_2H_5)_3$ = 8.6:5.0, 27 °C

Scheme 8 Asymmetric reduction of 1,3-diketones and 2,6-diacetylpyridine.

When asymmetric transfer hydrogenation of unsymmetrically substituted 1,2-diketones with the chiral Ru catalyst is carried out at a lower temperature (10 °C), chiral α-hydroxy ketones are obtainable with an excellent optical purity, in which the reduction occurs at the less hindered carbonyl group in the diketones for the steric reasons.[17c] At a higher temperature (40 °C) under otherwise identical conditions, the reduction of the ketones produces chiral *anti*-1,2-diols with an excellent ee. As shown in Scheme 9, the diketone bearing a methoxy group on the aromatic ring is steroselectively reduced to give (1*R*,2*S*)-1-(4′-methoxyphenyl)-1,2-propanediol, which is a major metabolite of *trans*-anethole in the rat, with 98% ee and in 90% yield.



S/C = 500
Ru cat
10 °C, 24 h
87% conv
100% yield
92% ee

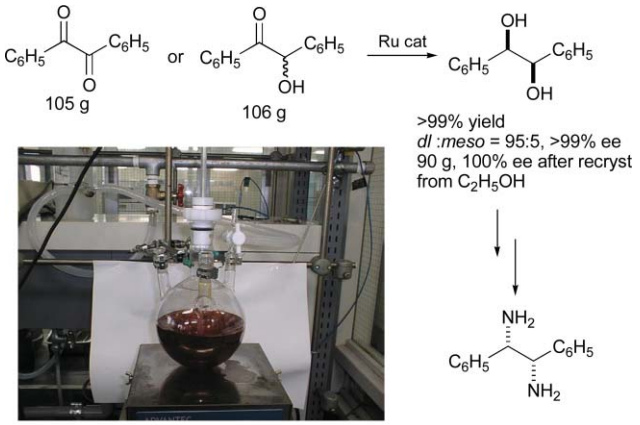
S/C = 100
Ru cat
40 °C, 24 h
100% conv
anti
90% yield
98% ee

Conditions: Ru cat = RuCl[(*S*,*S*)-Tsdpen](*p*-cymene), $HCOOH/N(C_2H_5)_3$ = 4.4/2.6

Scheme 9 Asymmetric reduction of unsymmetrically substituted 1,2-diketones.

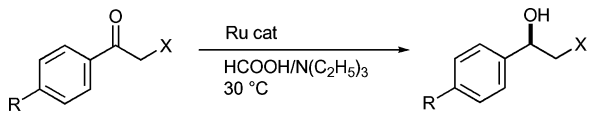
Thus, the asymmetric reduction of 1,2-diketones is characterized by high practicability and high selectivity in terms of chemo, regio-, diastereo-, and enantioselectivity. The coordinatively saturated nature of the amine hydrido Ru complex as well as the structural and electronic factors of the substrate are responsible for the stereoselective outcome of the asymmetric reduction. The reaction of 100 g of benzil or racemic benzoin with the Ru catalyst gives about 90 g of enantiomerically pure hydrobenzoin after single recrystallization from ethanol as shown in Scheme 10. This chiral diol can be readily converted to the corresponding chiral diphenylethylenediamine by the conventional procedure.[20]

Similarly, acetophenones bearing CN, N_3, and NO_2 groups at the α-position can be effectively reduced with a mixture of formic acid and triethylamine containing the chiral Ru catalysts to give the corresponding chiral alcohols with an excellent ee, as shown in Scheme 11.[18] The neighboring functional groups do not



Conditions: Ru cat = RuCl[(*S*,*S*)-Tsdpen](*p*-cymene) 1.6 g, HCOOH 102 g, $N(C_2H_5)_3$ 198 g, S/C = 200, DMF 100 mL, 30 °C, 48 h.

Scheme 10 A 100 gram-scale synthesis of enantiomerically pure hydrobenzoin.

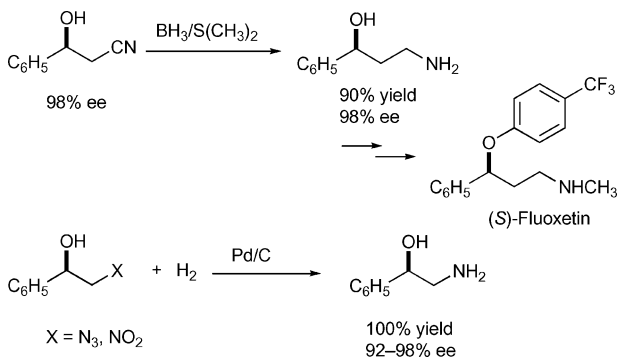


X	R	S/C	HCOOH:$N(C_2H_5)_3$	h	yield, %	% ee
CN	H	1000	3.1:2.6	24	100	98
N_3	H	100	3.1:5.2	24	65	92
NO_2	H	200	6.0:2.4[a]	16	90	98
NO_2	F	200	6.0:2.4[a]	16	95	96
NO_2	CH_3	200	6.0:2.4[a]	16	67	95

Ru cat = RuCl[(*S*,*S*)-Tsdpen](*p*-cymene). [a] In DMF.

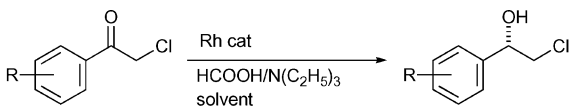
Scheme 11 Asymmetric reduction of acetophenones bearing CN, N_3, and NO_2 groups at the α position.

affect seriously the outcome of the reaction for the same reasons discussed above. These alcohols can be easily transformed by the conventional reduction of the functional groups to chiral β- and γ-amino alcohol with high ee (Scheme 12). In a similar manner, asymmetric reduction of acetylpyridine and its derivatives bearing a electron-withdrawing group in CH_2Cl_2 containing a mixture of formic acid and triethylamine and chiral Ru catalyst at 10 °C gives chiral pyridylethanols in almost quantitative yield and with 86% ee,[21] one of which is an intermediate of PNU-142721, a potent *anti*-HIV medicine.



Scheme 12 Synthesis of chiral amino alcohols.

α-Chlorinated acetophenones, which are hardly hydrogenated by conventional asymmetric hydrogenation catalysts, for example, Ru–BINAP catalysts,[6,16] are also smoothly reducible with chiral metal complexes. Notably, a chiral Cp*Rh complex, Cp*RhCl[(*R*,*R*)-Tsdpen],[8] which has a structure isoelectronic with a chiral Ru–arene complex, is the most reactive catalyst for the asymmetric reduction of chlorinated acetophenones as shown in Scheme 13.[22] The reaction with a substrate/catalyst molar ratio (S/C) = 5000 proceeds rapidly to give almost quantitatively the corresponding chiral alcohol with 96% ee and an initial turnover frequency (TOF) exceeding 2500 h^{-1} (0.7 sec^{-1}). Despite the structural similarity between the Cp*Rh(III) and the (η^6-arene)Ru(II) complexes, the significant difference in the reactivity toward 2-chloroacetophenones may be attributed to the electronic properties of the central metals. Ethyl acetate, CH_3CN, acetone, and DMF can be used as convenient solvents for the reaction. Recently, it has been reported that H_2O serves a good solvent for the same asymmetric reduction in H_2O containing the chiral Rh catalysts with HCO_2Na as a hydrogen source.[23] An analogous Ir complex, Cp*IrCl[(*R*,*R*)-Tsdpen], exhibits reasonably high reactivity but poor enantioselectivity. A variety of ring-substituted α-chloroacetophenones listed in Scheme 13, can be transformed to the corresponding chiral chlorinated alcohols with an excellent ee using a 5 : 2 formic acid : triethylamine azeotropic mixture as a hydrogen donor and the Rh catalyst.

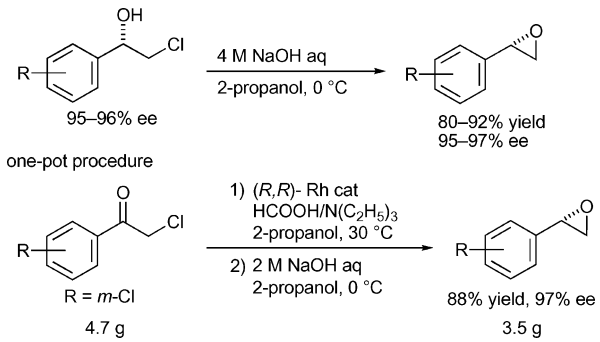


R	S/C	yield, %	ee, %	R	S/C	yield, %	ee, %
H	5000	99	96	*m*-OH	1000	93	95
o-Cl	1000	81	88	*m*-CH_3	1000	92	96
m-Cl	1000	93	95	*m*-CF_3	1000	80	96
p-Cl	1000	90	92	*p*-MsNH	1000	80	97
o-CH_3O	1000	90	95	3'4'-OCH_2O	1000	93	98
m-CH_3O	1000	90	95				
p-CH_3O	1000	94	94				

Conditions: Rh cat = Cp*RhCl[(*R*,*R*)-Tsdpen], 1.0 M $CH_3COOCH_2CH_3$ solution, at 25 °C.

Scheme 13 Chiral Rh complex-promoted asymmetric reduction of α-chlorinated acetophenones.

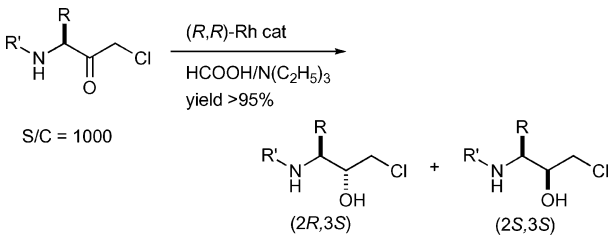
Chiral 2-chlorophenylethanol is easily convertible to chiral styrene oxide *via* Williamson's ether synthesis in water without loss of ee, as shown in Scheme 14. In particular, (*S*)-*m*-chlorostyrene oxide, which is a key intermediate for the preparation of several β3-adrenergic receptor agonist compounds, is readily obtained from



Scheme 14 Synthesis of chiral epoxides.

the reduction product. A more appealing feature is that one-pot synthesis can be performed by sequential asymmetric reduction of chloroacetophenone with the chiral Rh in 2-propanol and treatment of its reaction mixture with NaOH aqueous solution. Non-racemic styrene oxide can be synthesized in an isolated yield of 80–90% with 96–98% ee in a single reactor as shown in Scheme 14. This reaction is also very practical. A simple 1 : 1 mixture of 98% formic acid and triethylamine can also be used instead of its azeotrope. Even commercially available reagents and solvents can be used in this reaction without special purification. This epoxide synthetic process in either a one- or two-pot procedure is particularly useful for a gram-scale production of optically active epoxides; about 3.5 g styrene oxide being obtainable from 4.7 g of the chlorinated ketone (Scheme 14).

Another example of the asymmetric reduction of chlorinated ketones is shown in Scheme 15.[24] The chiral Rh complex-catalyzed reduction of aliphatic chlorinated ketones bearing another chiral carbon attached to N-containing groups, N-substituted (3*S*)-3-amino-1-chloro-4-phenyl-2-butanones, gives the desired corresponding diastereomeric alcohols in excellent yields with high de. Interestingly, the diastereoselectivity of the reduction is controllable only by a simple change in the ligand chirality, while



ketone	(2*R*,3*S*):(2*S*,3*S*)
R = $C_6H_5CH_2$, R' = Boc	90:10
R = $C_6H_5CH_2$, R' = Cbz	90:10
R = $C_6H_5CH_2$, R' = Bz	97:3
R = $C_6H_5CH_2$, R' = Ts	91:9
R = $(CH_3)_2CHCH_2$, R' = Cbz	83:17
R = *p*-F-$C_6H_4CH_2$, R' = Cbz	87:13
R = 2-naphCH_2, R' = Cbz	91:9

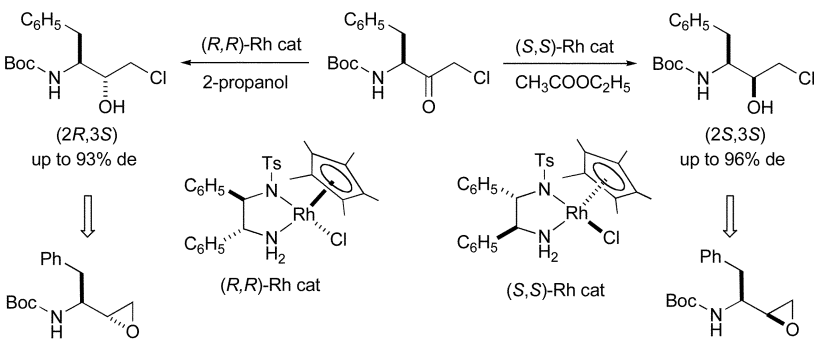
Conditions: (*R*,*R*)-Rh cat = Cp*RhCl[(*R*,*R*)-Tsdpen], 1.0 M $CH_3COOC_2H_5$ solution, 25 °C, 2 h.

Scheme 15 Asymmetric reduction of aminoalkyl chloromethyl ketones with (*R*,*R*)-Rh catalyst.

the chirality of the adjacent stereogenic center does not play a significant role. From the reaction with the (*S*,*S*)-Rh complex, the corresponding (2*S*,3*S*)-alcohol is obtained with an excellent de. The enantiomeric (*R*,*R*)-Rh catalyst gives rise to the (2*R*,3*S*)-alcohol which is the antipode of the product obtained with the (*S*,*S*)-catalyst as shown in Scheme 16. These diastereomers can be converted to epoxides in good yields without a decrease in the de value under basic reaction conditions. A sequential asymmetric reduction of *N*-(*tert*-butoxycarbonyl)-(3*S*)-3-amino-1-chloro-4-phenyl-2-butanone with a mixture of formic acid and triethylamine in 2-propanol containing the catalyst, Cp*RhCl[(*S*,*S*)-Tsdpen] or Cp*RhCl[(*R*,*R*)-Tsdpen], and treatment of its 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 in 86% yield with 90% de or its antipode (2*R*,3*S*)-diastereomer in 83% yield with 80% de as crystals after the addition of water. The important class of these compounds serves as potential chiral building blocks for synthesis of pharmaceuticals such as inhibitors of HIV protease and β-secretase in Alzheimer's disease.[25]

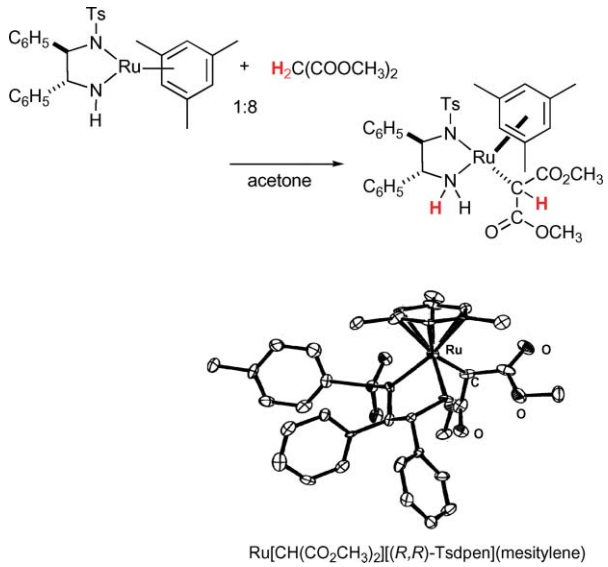
Asymmetric carbon–carbon bond formation with the bifunctional molecular catalysts

Deprotonation of acidic compounds with chiral amido complexes. The transfer hydrogenation with chiral amido metal complexes involves the deprotonation of alcohols and formic acid, which a have pK_a value ranging from 4 to 18, producing amine hydrido metal complexes (see Scheme 2). We envisaged that the amido nitrogen has a sufficient Brønsted basicity to effect deprotonation of certain acidic organic compounds, leading to an amino 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, 12.4) in toluene below −30 °C to give a yellow crystalline complex, Ru[$CH(CO_2CH_3)_2$][(*R*,*R*)-Tsdpen](η^6-mesitylene), as a single diastereomer, as shown in Scheme 17.[26] The single crystal X-ray analysis indicates that it has a three-legged piano stool coordination environment with mesitylene, amino, sulfonamino, and a C-bound malonato ligand. The chirality of the (*R*,*R*)-diamine ligand determines the *S* configuration around the central metal, as observed in the metal hydrido and chloro complexes. Notably, there is a short O···NH distance of 2.77 Å, which is possibly ascribed to intramolecular hydrogen bonding. A detailed



Conditions: Reduction; Rh cat = Cp*RhCl(Tsdpen), S/C = 1000, HCOOH/N(C_2H_5)$_3$, 1.0 M solution, 25 °C, 2 h. Epoxidation; 2M NaOH aq in 2-propanol, 0°C

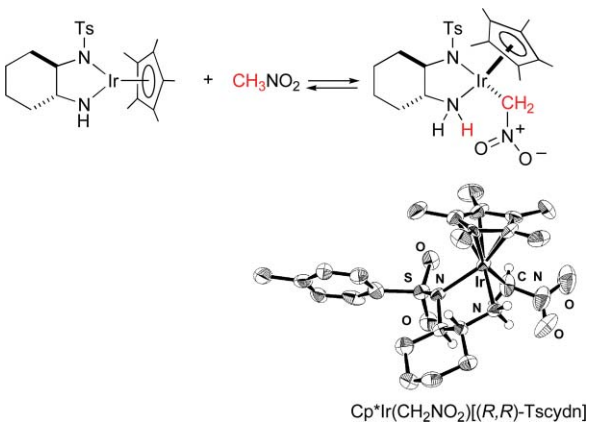
Scheme 16 Asymmetric synthesis of chiral epoxides *via* enantioselective reduction and epoxidation.



Scheme 17 Reaction of chiral amido Ru complex with dimethyl malonate.

NMR study of the malonate complex in CD_2Cl_2 shows that it exists in a temperature-dependent equilibrium with the amido complex and free malonate, in which no detectable formation of a metal enolato complex, the O-bound Ru complex, was observed in the solution.

In a similar way, the Ru amides can react with nitromethane (pK_a 10.2) and acetone (pK_a 20) to provide new organometallic compounds bearing a Ru–C bond.[27] Although the amido Ru complex reacts with 1 equiv of nitromethane to give an equilibrium mixture of the amido complex, nitromethane, and the nitromethyl complex, an analogous 16-electron amido Ir complex, Cp*Ir[(*R*,*R*)-Tscydn] ((*R*,*R*)-TsCYDN: (1*R*,2*R*)-*N*-(*p*-toluenesulfonyl)-1,2-cyclohexanediamine) readily reacts with 1 equiv of nitromethane at room temperature to give a pale yellow nitromethyl Ir complex, Cp*Ir(CH_2NO_2)[(*R*,*R*)-Tscydn], in quantitative yield as shown in Scheme 18.[27] Fig. 5 shows new amine Ir complexes having a C-bonded acetone or phenylacetylene group, which are obtained from the reactions of an amido Ir complex and acidic compounds. A detailed mechanistic investigation of the reaction of the amido complex and these compounds using NMR spectroscopy indicates that the reaction of the amido Ir complex and CD_3NO_2 in CD_2Cl_2 at low temperature possibly proceeds *via*



Scheme 18 Reaction of chiral amido Ir complex with nitromethane.

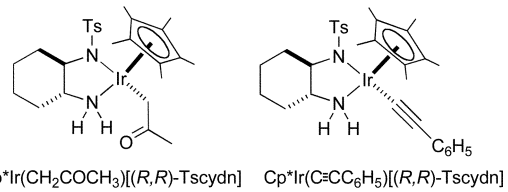
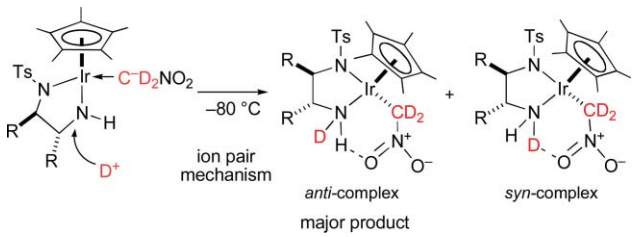


Fig. 5 Isolable Cp*Ir-acetone and Cp*Ir-phenylacetylene complexes.

an ion pair intermediate, leading to a predominant formation of the *anti* complex as shown in Scheme 19.[27]



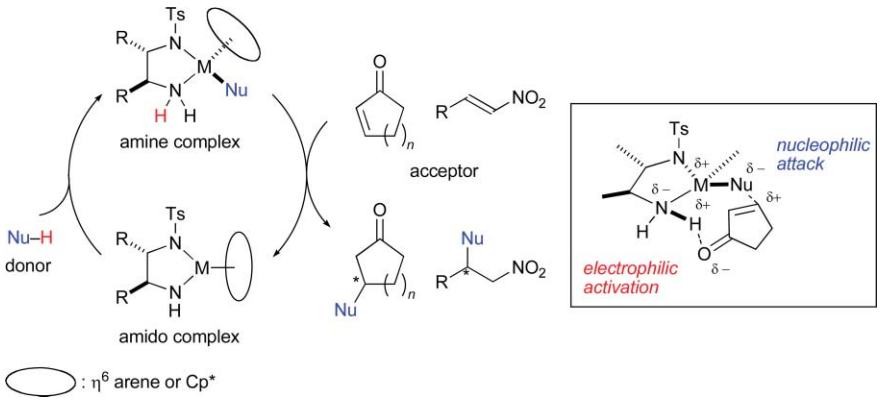
Scheme 19 Reaction mode of the C–H bond with amido Ir complex.

Chiral amido Ru complex promoted enantioselective C–C bond formation

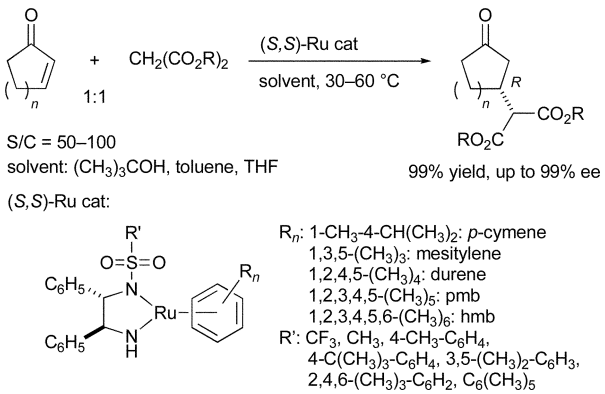
Michael addition of 1,3-dicarbonyl compounds to cyclic enones. Based on the detailed mechanistic studies of asymmetric hydrogen transfer between alcohols and ketone and the reactivity of the Ru amido complex toward acidic compounds, we explored a possible utility of the present bifunctional Ru amido complex in enantioselective C–C bond formation as illustrated in Scheme 20. As discussed previously, the amine hydrido complex stereoselectively reacts with ketonic substrates through a pericyclic six-membered transition state (Fig. 4) to transform to the amido complex, resulting in the catalytic enantioselective reduction of ketones in a highly efficient manner.[5] If an amido metal complex could react with certain acidic compounds to give the corresponding amine complex bearing a metal-bonded nucleophile, followed by further reactions with carbonyl compounds, catalytic enantioselective C–C bond formation could be achieved in a similar manner to the transfer hydrogenation. The M/NH bifunctional units possibly participate in the activation of carbonyl compounds *via* the cyclic transition state to facilitate the nucleophilic attack to the carbonyl compounds as shown in Scheme 20.

In fact, we found that a chiral Ru catalyst, Ru[(*S*,*S*)-Tsdpen](η^6-arene) efficiently effected the enantioselective Michael addition of malonates or acetoacetate to cyclic enones to give the corresponding adducts with excellent ee's.[26] A reaction of dimethyl malonate and cyclopentenone in a 1 : 1 molar ratio in *tert*-butyl alcohol containing the chiral amido complex (malonate:enone:Ru = 50 : 50 : 1) proceeds smoothly at 40 °C to provide the corresponding (*R*)-Michael adduct in an almost quantitative yield and with an excellent ee as shown in Scheme 21. *tert*-Butyl alcohol, toluene, and THF can be used as practical solvents, while CH_2Cl_2 gives a reasonably high ee albeit a slightly lower activity.

The outcome of the reaction in terms of reactivity and selectivity can be determined by the delicate balance between the steric and electronic properties of the diamine and arene ligands in the chiral Ru complexes as well as the reaction conditions.



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



Scheme 21 Asymmetric Michael addition of malonates to cyclic enones.

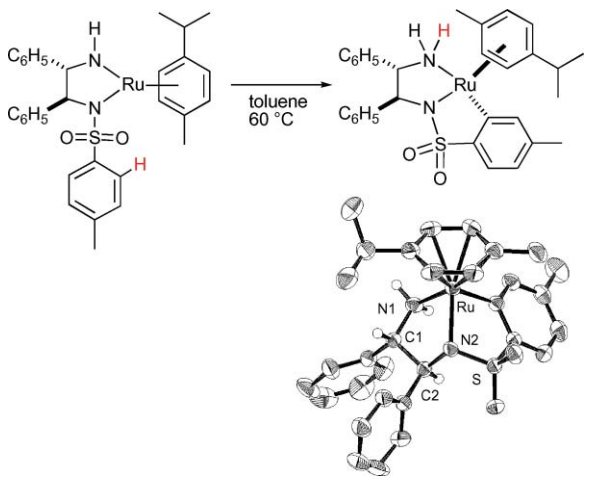
As listed in Table 2, enantioselection increases in the order *p*-cymene < mesitylene < durene < pentamethylbenzene and hexamethylbenzene as a ligand of the chiral amido Ru complexes. In contrast to the trend of the reactivity for the asymmetric reduction mentioned above, a more sterically congested complex with pentamethyl- or hexamethylbenzene displays better reactivity than the *p*-cymene complex, indicating the electron-donating ability of the multi-substituted arene ligands should cause an increase in nucleophilicity of the metal-bonded Michael donors. In addition, the use of the methanesulfonylated diamine (MsDPEN) instead of the TsDPEN greatly improves the catalyst performance in terms of reactivity and enantioselectivity as well as thermal stability as listed in Table 3. The reaction at an S/C = 100 with the MsDPEN complex proceeds rapidly to completion even at 60 °C to give the products without serious loss of the ee value. On the other hand, at higher temperature, the TsDPEN complexes

Table 3 Asymmetric Michael reaction with chiral amido Ru complex at 60 °C

Diamine	Arene	S/C	Temp/°C	Time/h	Yield (%)	ee (%)
Tsdpen	durene	100	60	24	90	94
	pmb	100	60	24	86	96
	hmb	100	60	24	54	96
Msdpen	hmb	100	60	24	99	97

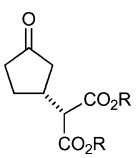
Conditions: Ru cat = Ru[(*S*,*S*)-diamine](η6-arene), $(CH_3)_3COH$ 1 ml.

readily convert to a new catalytically inactive metallacycle as shown Scheme 22.[28] Unnecessary heating of the TsDPEN catalyst solution should be avoided.



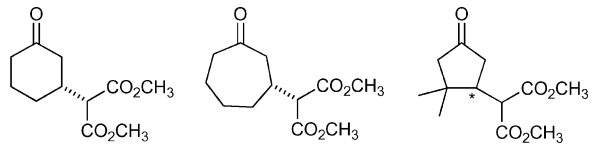
Scheme 22 Cyclometalation of amido Ru complex.

Table 2 Effect of arene ligand on the outcome of asymmetric Michael addition

	R = CH_3		R = C_2H_5		
	Arene	Yield (%)	ee (%)	Yield (%)	ee (%)
	*p*-Cymene	87	82	97	85
	Mesitylene	99	89	95	91
	Durene	99	94	94	94
	pmb	99	97	96	96
	hmb	98	98	96	96

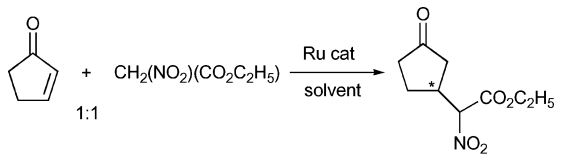
Conditions: Ru cat = Ru[(*S*,*S*)-Tsdpen](arene), S/C = 50, 30–40 °C, 24 h, acceptor : donor = 1 : 1, solvent $(CH_3)_3COH$.

A variety of cyclic enones as the acceptor and malonates and β-keto esters as the donor can be successfully transformed to the corresponding optically active Michael adducts with high ee's as shown in Scheme 23. Cyclohexenone and cycloheptenone react with dimethyl malonate in the presence of the MsDPEN complex as the catalyst to give 1,4-adducts with excellent ee's. The reaction of 4,4-dimethylcyclopentenone with malonate gives the product with >99% ee. The Michael adduct of α-methyl substituted dimethyl malonate to cyclopentenone is also obtainable with an excellent ee and in moderate yield (97% ee, 51% yield). Nitroacetate can be used as a donor, giving the Michael adducts in high yield and with 91% ee, although with a 1 : 1 diastereomer ratio as listed in Scheme 24.[29] The TfDPEN complex gives the best catalyst performance for the reaction of nitroacetate.



Conditions: Ru cat = Ru[(*S*,*S*)-Msdpen](hmb), S/C= 50, 30–40 °C, 24–72 h, acceptor:donor= 1:1, in $(CH_3)_3COH$ or toluene.

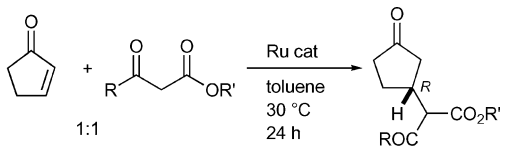
Scheme 23 Asymmetric Michael addition of dimetyl malonate to cyclic enones.



Ru cat	solvent	temp, °C	yield, %	ee, %
Ru[(*R*,*R*)-Msdpen](hmb)	$(CH_3)_3COH$	30	99	82
Ru[(*R*,*R*)-Tfdpen](hmb)	$(CH_3)_3COH$	30	98	91
Ru[(*R*,*R*)-Tfdpen](hmb)	$(CH_3)_2CHCH_2OH$	0	95	92

Scheme 24 Asymmetric Michael addition of nitroacetate with TfDPEN complex.

It is noteworthy that the stereochemical outcome of the reaction with β-keto esters[30] is delicately influenced by the steric and electronic factors in the Ru complexes, acceptors, and donors and the solvent used.[30a] As summarized in Scheme 25, for the reaction of cyclopentenone and isobutyrylacetic acid methyl ester, a combination of Ru[(*S*,*S*)-Msdpen](hmb) as the catalyst and *tert*-butyl alcohol as the solvent is the best choice and (*R*)-4-methyl-3-oxo-2-(3-oxocyclopentyl)pentanoic acid methyl ester with 92% ee with a 1 : 1 mixture of two diastereomers with a single stereogentic center at the cyclopentenone ring is obtainable in 96% yield. The TsDPEN analogue in toluene also provides better results compared with those attained in *tert*-butyl alcohol; the ee value reaching up to 95% ee. An increase in the steric bulkiness of the acyl group in the β-keto esters causes an increase in the ee value of the products obtained from the reaction with the MsDPEN complex in the order $CH_3 < CH(CH_3)_2 < C(CH_3)_3$ except for the C_2H_5-substituted keto ester. The Michael addition of methyl benzoylacetate and ethyl benzoylacetate to cyclopentenone with the MsDPEN complex gives the corresponding adducts with 96



keto ester

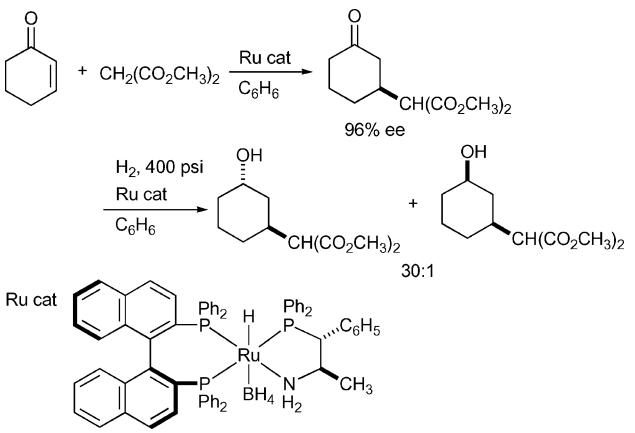
R	R'	Ru cat	yield, %	ee, %
CH_3	CH_3	Ru[Msdpen](hmb)	100	85
C_2H_5	CH_3	"	92	80
$CH(CH_3)_2$	CH_3	"	97	88
$C(CH_3)_3$	CH_3	"	100	97
CH_3	CH_3	Ru[Tsdpen](hmb)	99	91
C_2H_5	CH_3	"	99	89
$CH(CH_3)_2$	CH_3	"	95	95
$C(CH_3)_3$	CH_3	"	92	87
C_6H_5	CH_3	"	91	96
CH_3	$C(CH_3)_3$	"	93	72

As a 1:1 mixture of two diastereomers.

Scheme 25 Asymmetric Michael addition of β-keto esters.

and 97% ee, respectively. The steric bulkiness of the ester part in the β-keto esters exhibits a negative effect on the enantioselectivity of the reaction. Unfortunately, the reaction of acyclic enones is not stereoselective at all under the reaction conditions.

By using a similar chiral Ru catalyst bearing M/NH bifunctional units, Morris recently reported that *trans*-$RuH(\eta^1\text{-}BH_4)$-((*R*,*R*)-Pnor)((*S*)-binap) ((*R*,*R*)-Pnor = (1*R*,2*R*)-$P(C_6H_5)_2CH$-$(C_6H_5)CH(CH_3)NH_2$), which is an active catalyst for asymmetric hydrogenation, efficiently catalyzed Michael addition of dimethyl malonate to 2-cyclohexenone to give the chiral cyclic ketone, which is further enantioselectively hydrogenated with the same catalyst to provide the corresponding diastereomeric alcohols with reasonably high ee (Scheme 26).[31]

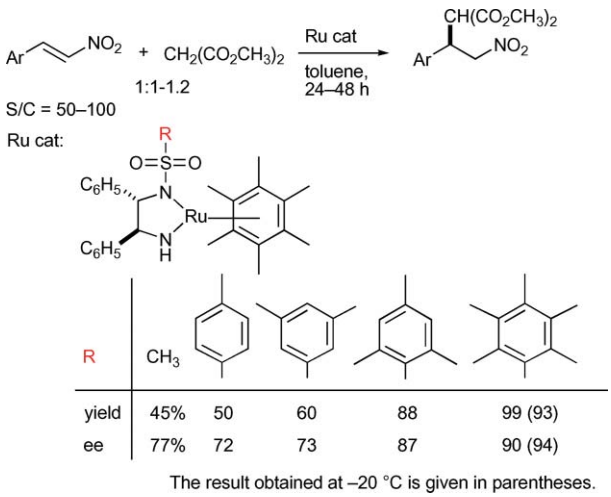


Scheme 26 Tandem Michael addition/hydrogenation with chiral Ru catalyst.

Michael addition of 1,3-dicarbonyl compounds to nitroalkenes

We have expanded the scope of the enantioselective C–C bond formation with chiral Ru catalysts to the reaction of acyclic Michael acceptors, nitroalkenes,[32] and found that nitroalkenes smoothly react with Michael donors, 1,3-dicarbonyl compounds

to provide the corresponding Michael adducts in high yields and with excellent ee's as shown in Scheme 27.[33] Again, fine-tuning of the structures of the arene and N-sulfonylated diamine ligands in the chiral Ru amide complexes leads to the achievement of the highly efficient enantioselective Michael addition to nitroalkenes. Chiral Ru catalysts bearing the TsDPEN and MsDPEN ligand, which are excellent catalysts for reaction of cyclic enones and dimethyl malonate, give unsatisfactory results for the reaction of *trans*-β-nitrostyrene. However, modification of the structure of the R group in the sulfonyl group, RSO_2, causes a significant improvement in the catalyst performance; the reactivity and enantioselectivity of the Ru[(*S*,*S*)-N-sulfonylated dpen](η⁶-hmb) (HMB = η⁶-hexamethylbenzene, $(CH_3)_6C_6$) tend to increase with the increase of the electron-donating ability of the N-substituents of the sulfonyl groups, namely, in the order *p*-$CH_3C_6H_4SO_2$ < 3,5-$(CH_3)_2C_6H_3SO_2$ < 2,4,6-$(CH_3)_3C_6H_2SO_2$ < 2,3,4,5,6-$(CH_3)_5C_6SO_2$ (PMBs). The Ru[(*S*,*S*)-PMBsdpen](η⁶-hmb) complex displays the best catalyst performance in terms of reactivity and selectivity, reaching up to 99% yield and 90% ee, respectively. Even at lower temperature, −20 °C, the reaction of dimethyl malonate with an S/C of 100 proceeds smoothly to give the Michael adduct with 95% ee and in 97% yield. The electron-withdrawing TfDPEN complex, which is an excellent catalyst for Michael addition of nitroacetate to cyclic enones, gives unsatisfactory results for reaction of nitroalkenes.



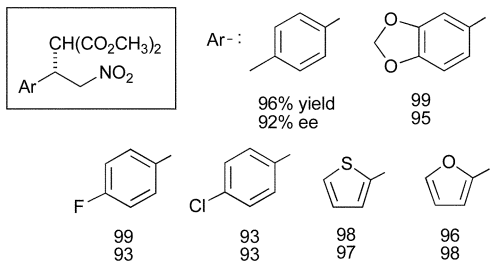
R	CH_3				
yield	45%	50	60	88	99 (93)
ee	77%	72	73	87	90 (94)

The result obtained at –20 °C is given in parentheses.

Scheme 27 Asymmetric Michael addition of dimethyl malonate to niroalkenes.

Toluene is the best choice of solvent for conjugate addition to nitroalkenes, while the reaction in $CHCl_3$, THF, DMF, or CH_3CN gives unsatisfactory results. In a particular solvent, DMF or CH_3CN, the amide complex initiates the polymerization of nitroalkenes to produce polymers with high molecular weight, in which the reaction might proceed *via* 1,4-conjugate addition with a possible Ru–nitronato complex, as observed in the initial stage of the Michael addition.[33]

A variety of substituted aromatic nitroalkenes can be used as the Michael acceptor; both electron donating and withdrawing groups do not seriously affect the outcome of the reaction as shown in Scheme 28.[33] The reaction of *p*-methyl-, *p*-chloro-, *p*-fluoro-, and dioxolane-substituted β-nitrostyrene provides almost quantitatively the Michael adducts with 92, 93, 93, and 95% ee,

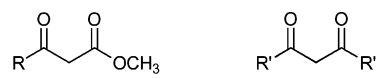


Conditions: Ru cat = Ru[(*S*,*S*)-PMBsdpen](hmb), S/C = 50, donor:acceptor = 1:1–1.2, –20 °C, 24–48 h

Scheme 28 Asymmetric Michael reaction of aromatic nitroalkenes.

respectively. An excellent enantioselectivity is also observed for nitroalkenes with hetero aromatic rings, thienyl, and furyl, the ee values of Michael adducts being 97 and 98%, respectively. Similarly, the nitroalkenes with aliphatic substituents also give the Michael adducts with an excellent ee in almost quantitative yield.[34]

Several 1,3-dicarbonyl compounds such as β-keto esters and 1,3-diketones can be used as the Michael donors.[33] Again, the stereochemical outcome of the Michael addition with Ru[(*S*,*S*)-PMBsdpen](η⁶-hmb) is significantly influenced by the structure of the Michael donors. The reaction of sterically more congested methyl-substituted dimethyl malonate with *trans*-β-nitrostyrene gives the corresponding adduct with 97% ee in 94% yield. Similarly, the conjugated addition of β-keto esters to the nitroalkene at −20 °C proceeds smoothly to give the corresponding adducts in 95–97% yield as shown in Scheme 29. As observed in the reaction of cyclic enones with β-keto esters, an increase in the bulkiness of the acyl group in the keto esters causes a significant improvement in the enantioselectivity of the reaction. Although the reaction of acetoacetate produces the Michael product with 58% ee, the enantiomeric purity of the adducts increases in the order CH_3 < C_2H_5 < $CH(CH_3)_2$ < C_6H_5, the ee value reaching up to 94% with benzoylacetate. This conjugate addition to nitroalkenes becomes even more appealing when 1,3-diketones are donors. Although acetylacetone provides the Michael adduct in a reasonably high yield but with poor ee, a sterically bulkier diketone gives satisfactory results in terms of yield and enantioselectivity, the ee value reaching up to 97%.



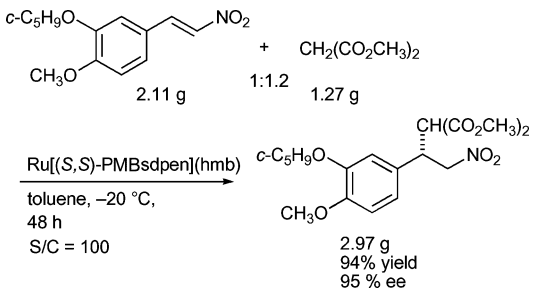
R	yield, %	ee, %
CH_3	95	58
C_2H_5	97	89
$CH(CH_3)_2$	97	94
C_6H_5	96	92

R'	yield, %	ee, %
CH_3	90	7
C_2H_5	98	97
$CH(CH_3)_2$	99	97

Conditions: Ru cat: Ru[(*S*,*S*)-PMBsdpen](hmb), S/C = 50, donor:nitroalkene = 1:1–1.2, –20 °C, 24–48 h

Scheme 29 Michael addition of β-keto esters and 1,3-diketones.

The conjugate addition to nitroalkenes is also characterized by high practicability in organic synthetic chemistry. A gram-scale reaction of the substituted β-nitrostyrene (2.1 g), as shown in Scheme 30, 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



Scheme 30 A gram-scale synthesis of the rolipram intermediate.

separation of the catalyst by simple column chromatography, single recrystallization from alcohol produces the enantiomerically pure Michael adduct, which is an intermediate of rolipram.[32a,b]

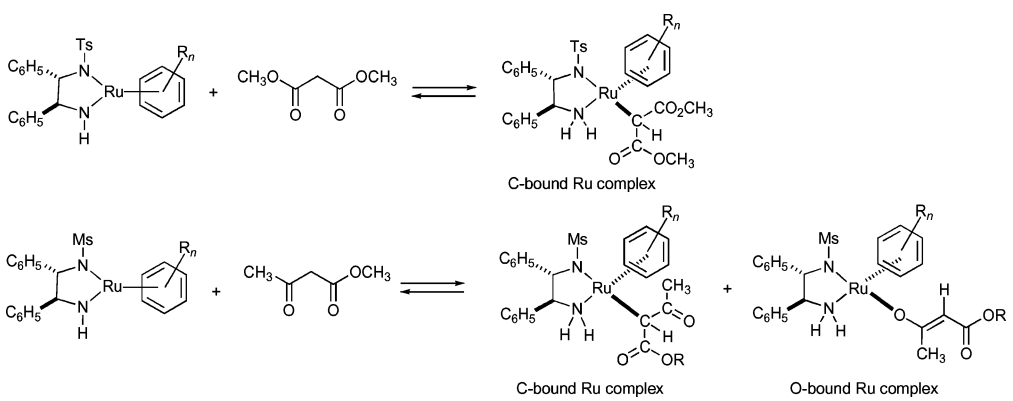
Mechanistic consideration of asymmetric Michael reaction with bifunctional Ru complexes

There have been many reports on catalytic enantioselective Michael addition promoted by metal-based catalysts.[35] In particular, the catalytic asymmetric Michael reaction is one of the most important organic synthetic procedures for a stereoselective C–C bond forming reaction partly due to its high atom economy. In general, most of the reactions reported in the literature proceed through the nucleophilic attack of metal-bonded O- or C-enolate to olefinic carbon in the Michael acceptor, except for olefin insertion into the Rh–C bond reported by Hayashi.[36] However, the precise mechanism of the Michael reaction catalyzed by the metal complexes is still controversial although possible catalytically active intermediates are isolated[37] or are detectable by spectroscopy as well as ESI-MS.[38] On the basis of NMR spectroscopy and X-ray structural analysis of the malonato Ru complex shown in Scheme 17, we demonstrated the possibility of the C-bound Ru complex as a catalytic intermediate for Michael addition of malonates to cyclic enones.[26] However, another possible reaction pathway through the oxygen bound Ru enolate intermediate cannot be ruled out. In contrast to the reaction of the Ru amido complex with dimethyl malonate, the chiral Ru complex having η^6-HMB reacts with methyl acetoacetat even at lower temperature (−30 °C) to give a mixture of a C-bound Ru complex, Ru[CH(COCH$_3$)(COOCH$_3$)][(*S*,*S*)-Msdpen](η^6-hmb), and an O-bound Ru complex, Ru[OC(CH$_3$)=CHCOOCH$_3$][(*S*,*S*)-Msdpen](η^6-hmb)) (Ru–O : Ru–C = 1 : 1.1), as shown in Scheme 31.[29,30a] The ^{1}H VTNMR spectra of a 1 : 1 reaction mixture of the amido complex and acetoacetate in CD_2Cl_2 revealed that no appreciable change in the molar ratio of the carbon bound Ru complex to the O-bound Ru complex was observed by the increase in the temperature and that both complexes independently existed in a temperature-dependent equilibrium with the amido complex and free acetoacetate.[29,30a] A direct interconversion between C-and O-bound Ru enolate complexes possibly through the oxo-π-allyl intermediate[39] was not observed in solution.

In addition, a positive effect of the steric hindrance in the acyl group of *β*-keto esters and an apparent negative effect of the temperature on the stereochemical outcome of the reaction as discussed above suggest that the reaction may proceed through the C-bound or O-bound Ru enolate depending on the structures of the Michael donors and the reaction conditions.[29,30a] However, with only these experimental data and NMR studies as well as indirect experimental results, no precise reaction mechanism for the Michael reaction with the chiral amido catalyst can be envisaged because it cannot be ruled out that the major product arises from the less-stable intermediate, which is undetectable by spectroscopic methods. Further investigation including computational analysis of the reaction pathways should be required.

Conclusions and Perspectives

This perspective review focuses on recent advances in our chemistry of chiral bifunctional transition metal molecular catalysts for asymmetric reduction and C–C bond formation. The present conceptually new chiral Ru amide catalyst was originally developed for asymmetric transfer hydrogenation of ketones and imines and is now successfully applicable to enantioselective C–C bond formation reaction with a wide scope and high practicability. A key step in the latter catalytic reactions is the deprotonation of 1,3-dicarbonyl compounds with the chiral amido Ru complexes, leading to the amine Ru complexes bearing C- or O-bonded enolates. An unprecedented aspect in the hydrogen transfer from the amine hydrido metal complex and ketones or imines is that the acidic amine proton and the metal hydride cooperatively activate the reactant and are concertedly transferred to C=O or C=N double bonds *via* pericyclic transition states. The reacting substrate is not bonded directly to the central metal. In contrast to the transfer hydrogenation, further understanding of the mechanism



Scheme 31 Reactions of chiral amido Ru complex with dimethyl malonate and acetoacetate.

of the C–C bond formation is demanded. Nevertheless, we believe the present bifunctional molecular catalyst offers a great opportunity to open up new fundamentals for stereoselective molecular transformation including C–O, C–N bond formation, in addition to the enantioselective C–H and C–C bond formation discussed in this article.

In addition, we have recently found that preliminary attempts at ligand modification by changing the amine ligands from N-sufonylated diamines to the *N*,*N*-dimethylaminoethylamines (N–N) and 2-phosphinoethylamines (P–N) (Fig. 1) causes a drastic change in the catalyst performance.[40] For example, in contrast to the inertness of Tsdiamine Ru complexes toward H_2 activation, both Cp*Ru(N–N) and Cp*Ru(P–N) complexes readily activate H_2 under mild conditions, and can efficiently effect hydrogenative transformation of ketones and epoxides to secondary alcohols. In addition, the Cp*Ru(P–N) complex also exhibits an excellent catalytic activity for both hydrogenation with H_2 and transfer hydrogenation with alcohols. 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 unprecedented catalyst performance.

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