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Perspective

Metal−Ligand Bifunctional Catalysis: A Nonclassical Mechanism for Asymmetric Hydrogen Transfer between Alcohols and Carbonyl Compounds

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Question: Is substrate/metal complexation essential for hydrogenative saturation of unsaturated compounds? *Answer*: No, it is not always necessary. The metal−ligand bifunctional mechanism allows for direct reduction of carbonyl compounds with an 18-electron transition metal hydride without C═O/metal interaction. Asymmetric transfer hydrogenation of aromatic carbonyl compounds using a 2-propanol/alkaline base system in the presence of RuCl[(*S*,*S*)-YCH(C_6H_5)CH(C_6H_5)NH_2](η^6-arene) (Y = O, NTs) or its analogues gives the corresponding *S* chiral alcohols of high enantiomeric purity. The reaction proceeds via a coordinatively saturated 18-electron complex, RuH[(*S*,*S*)-YCH(C_6H_5)CH(C_6H_5)NH_2]-(η^6-arene). The hydridic RuH and protic NH are simultaneously delivered to a C═O linkage via a six-membered pericyclic mechanism, giving an *S* alcohol and Ru[(*S*,*S*)-YCH(C_6H_5)CH(C_6H_5)NH](η^6-arene). The latter 16-electron Ru amide complex dehydrogenates 2-propanol to regenerate the Ru hydride species. A formic acid/triethylamine mixture serves as a better reducing agent. The recognition of carbonyl enantiofaces in the hydrogen transfer is made largely by the attractive CH/π interaction between the η^6-arene ligand and the aromatic substituent in carbonyl substrates.

Introduction

The significance of asymmetric catalysis is growing rapidly in the areas of pharmaceuticals, agrochemicals, flavors, and fragrances as well as advanced materials.[1,2] The organometallic approach using a molecular catalyst consisting of a metal atom or ion and a chiral organic ligand(s) is a general approach for this purpose and is widely used in research laboratories and industry. Ideal asymmetric catalysis is achievable only by suitable architectural and functional molecular engineering of chiral metal complexes and selection of appropriate reaction conditions. Designing an efficient asymmetric catalyst is an integrated molecular approach. It has been considered that the catalytic activity is generated by the central metal and that the stereoselectivity is controlled by the surrounding chiral ligand. However, the effects of the metal and ligands often interact with each other more strongly than in this notion, generating high reactivity and desired stereoselectivity. In certain catalysts, any of the steric and electronic details cooperate in achieving a stereocontrolled chemical reaction. Here, we present an example of metal−ligand bifunctional catalysis, where (1) both metal and ligand simultaneously participate in the bond-forming and -breaking processes,

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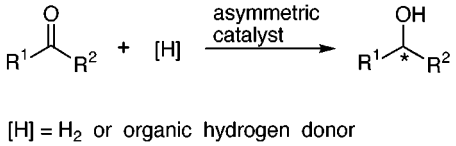
Scheme 1



(2) a coordinatively saturated metal complex reacts with an unsaturated substrate directly without metal ligation, and (3) not only the chiral ancillary but an achiral ligand plays a pivotal role in obtaining high enantioselectivity. This might provide a more general strategy for developing efficient molecular catalysts.

Mechanistic Background of Carbonyl Hydrogenation

Hydrogenative reduction of prochiral ketones to chiral alcohols (Scheme 1) is a powerful tool for precise stereocontrolled organic synthesis.[2] Although this transformation looks very simple, its usefulness is still limited. Homogeneous hydrogenation of unsaturated compounds with transition-metal complexes proceeds in a stepwise manner via metal hydride species. Molecular hydrogen readily reacts with various transition-metal complexes resulting in metal monohydrides (MH) or dihydrides (MH_2); however, their use for catalytic hydrogenation of simple ketones is not easy for various mechanistic reasons.[3] The C=O linkage has chemical characteristics that are distinct from C=C bonds. Reaction between a C=O function and a metal hydride species has been conceived to take place by a $\pi^2 + \sigma^2$ mechanism as illustrated in Figure 1. The coordinatively unsatuated MH would first form a C=O complex **1** that is then transformed to a metal alkoxide **2**. Protonolysis or hydrogenolysis of the M−O linkage gives an alcoholic

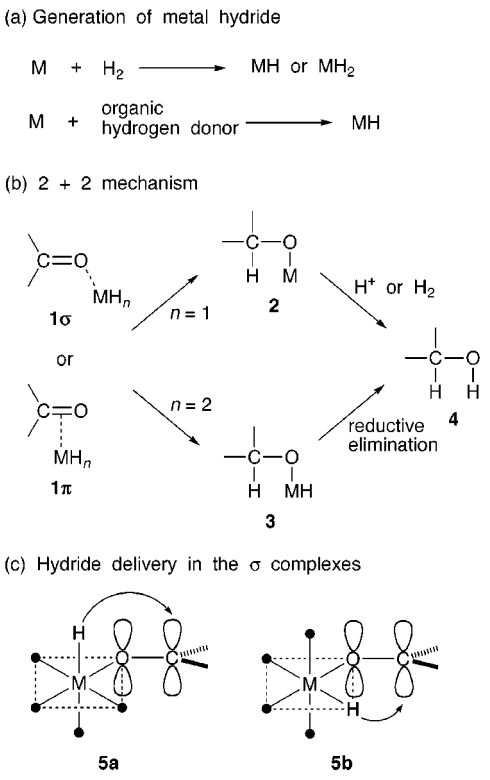


Figure 1. Putative mechanism for transition-metal-catalyzed hydrogenation of carbonyl compounds. M = transition metal.

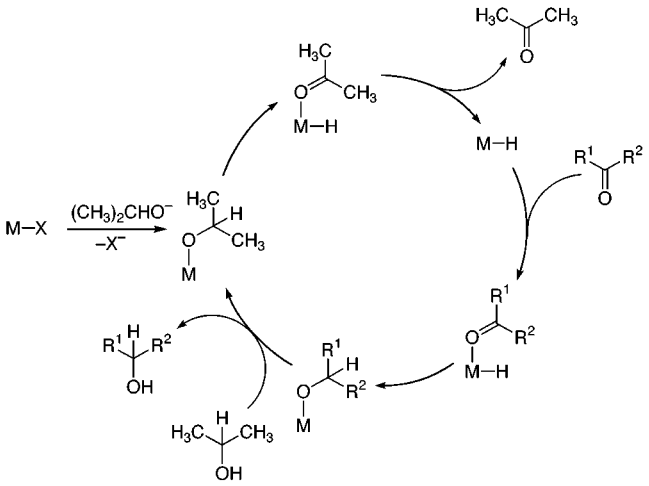


Figure 2. Conventional mechanism for transition-metal-catalyzed transfer hydrogenation with 2-propanol. M = transition metal.

product **4**. Alternatively, MH_2 reacts with a C=O moiety via **1** to give an alkoxymetal hydride **3**, which undergoes reductive elimination of the alcohol **4**. In both cases, the Lewis acidity and oxophilicity of M contribute to the C=O reduction. In addition, the capability of M to form the π complex $\mathbf{1}_\pi$, at least in the transition state, is crucial to achieve the 2 + 2 addition. However, usually electrophilic metals tend to form the σ complexes $\mathbf{1}_\sigma$ with a C=O function,[4] and hence, as illustrated in **5a** and **5b**, the relative locations of the hydride and carbonyl carbon are unsuitable for reaction. The hydride delivery needs some major geometrical change. The requisite π interaction between M−H and C=O, in addition to access to a sufficient concentration of the reactive complex, is often achieved with the assistance of a neighboring coordinative heteroatom of functionalized carbonyl substrates such as keto esters and hydroxy or amino ketones.[2] An additional electrophilic metal (Lewis acid catalysis or via bimetallic hydrides[5]) or protic species may play a similar role. In fact, only limited electropositive metals and C=O compounds with a low-lying LUMO form the requisite π complexes.[6] Thus, despite the notable development of stereoselective hydrogenation of functionalized olefins and ketones,[2] until recently,[3] homogeneous hydrogenation of simple ketones remained difficult.

Transfer hydrogenation using stable organic reducing agents, typically 2-propanol or formic acid, is another way to convert carbonyl compounds to alcohols. Certain late-transition-metal complexes, coupled with an inorganic base such as KOH, NaOH, or K_2CO_3, act as catalysts for transfer hydrogenation of ketones in 2-propanol.[7−9] The currently accepted mechanism for transfer hydrogenation is outlined in Figure 2, in which X is an anionic ligand, typically a halide.[7c,d,10−13] The role of the base is considered to be increasing the concentration of 2-propoxide ion, which coordinates with M and then β-eliminates forming an M−H reducing species and acetone. The mechanism of C=O reduction is basically the same 2 + 2 process as shown in Figure 1. Ligation of a chiral organic auxiliary to M results in asymmetric induction. Our and other research groups developed chiral complexes containing an Ir(I),[14,15] Rh(I),[14,15] or Ru(II) element[16−24] that catalyze asymmetric reduction of certain prochiral ketones to afford chiral secondary alcohols of high enantiomeric purity.[25]

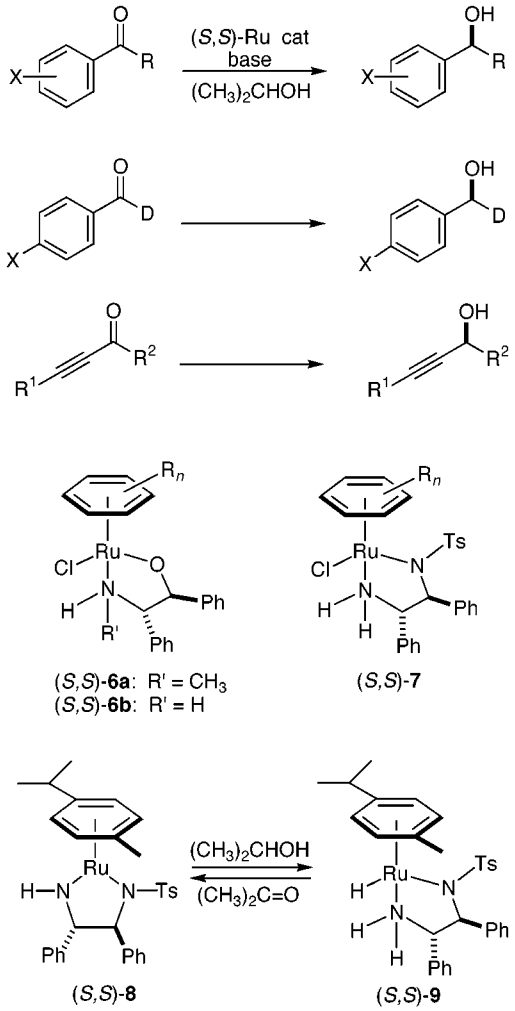
Here we describe a new mechanism-based efficient asymmetric transfer hydrogenation of carbonyl compounds. An efficient asymmetric catalyst requires a suitable three-dimensional architecture. In addition, to generate a novel catalytic activity, the organometallic complex should also have a unique functionality. Most existing hydrogenation catalysts utilize aprotic neutral ligands (tertiary phosphines, phosphites, tertiary amines, ethers, etc.), π donors (olefins, arenes, cyclopentadienide, etc.), and anionic heteroatom ligands (halides, alkoxides, carboxylates, etc.). However, these are not effective enough for the asymmetric reaction of Scheme 1. Little attention has been given to the possibility of using protic neutral ligands for catalysis. Alcohols, for example, are considered as mere spectators or weak donors, whose dissociation from a central metal generates a coordinatively unsaturated catalytic metal species. We have been interested in utilizing the chemical characteristics of primary or secondary, but not tertiary, amine ligands with the hope of seeing a novel mechanism using an "NH effect". Primary and secondary amines are relatively weak acids. However, upon complexation with a Lewis acidic metal, NH acidity is increased and the formation of an NH···O=C hydrogen bond in a transition state (TS) should facilitate the otherwise difficult metal to C=O hydride delivery. Intuitively, we paid attention to η^6-arene−Ru complexes as catalysts because (1) the aromatic spectators automatically occupy three adjacent coordination sites in an octahedral Ru coordination environment, leaving three sites with a *fac* relationship for other functions; (2) arene ligands may provide a unique reactivity and selectivity to the metallic center; and (3) the substitution pattern on the arene ring is flexible. The remaining three sites would accommodate an NH ligand and hydride among others. 2-Propanol was chosen as the hydrogen source because it has the most favorable chemical properties.[26]

Asymmetric Transfer Hydrogenation

Reduction with 2-Propanol. In our search for high reactivity in the reduction of acetophenone in 2-propanol containing $[RuCl_2(\eta^6\text{-benzene})]_2$ and KOH ([ketone] = 0.1 M, ketone/Ru/KOH = 200:1:2), a significant ligand acceleration was noted with ethanolamine (5 equiv to Ru).[19] The reaction showed a turnover frequency (TOF, moles of product per mole of Ru per hour) of 227 h^{-1} at 28 °C, giving 1-phenylethanol in 45% yield after 1 h and in 93% yield after 5 h. Without ethanolamine, the reaction at the same temperature gave the alcohol in only 1% yield with a TOF of only 3 h^{-1}. The TOF of the ethanolamine-aided reaction was increased to 4700 h^{-1} at 80 °C. Ethylenediamine and ethylene glycol were ineffective.

The marked ligand acceleration with ethanolamine led to the use of chiral β-amino alcohols, such as *threo*- and *erythro*-2-amino-1,2-diphenylethanol, ephedrine, and Ψ-ephedrine, for asymmetric reduction of aromatic ketones.[19] High enantioselectivity was obtained only when an appropriate arene and chiral amino alcohol were combined. Thus, when a 0.1 M solution of acetophenone was treated with a combination of $[RuCl_2(\eta^6\text{-hexamethylbenzene})]_2$ and (1*S*,2*S*)-2-methylamino-1,2-diphenylethanol at 28 °C for 1 h, (*S*)-1-phenylethanol was produced in 92% ee and 95% yield.[27,28] The octahedral complex **6a** (arene = hexamethylbenzene) acts as a catalyst precursor in the asymmetric reaction (Scheme 2).[24,28] The analogue **6b** is more reactive but less enantioselective.[27] Notably,

Scheme 2



the NH_2 or NH end of the amino alcohols is crucial for the catalytic activity; the dimethylamino analogues are totally ineffective. The extent of enantioselection is affected as well by the ketone substsituent.

N-Sulfonylated ethylenediamines are also excellent accelerators of Ru-catalyzed transfer hydrogenation.[19] For instance, as shown in Scheme 2, the chiral Ru complex (*S*,*S*)-**7** (arene = mesitylene) was found to catalyze asymmetric reduction of various aromatic ketones to the *S*-enriched secondary alcohols ([ketone] = 0.1 M, ketone/Ru/KOH = 200:1:2, 28 °C).[18,27] The reaction of acetophenone proceeds with an excellent enantioface differentiation, $k_{Re}/k_{Si} = 99$, while the resulting *S* alcohol is more susceptible to the reverse dehydrogenation than the *R* enantiomer by a factor of 99. Because of the occurrence of the reverse process,[7] the level of enantioselection decreases with increasing conversion of the ketone. Reaction of benzaldehyde-*1-d* and its derivatives using the Ru catalyst (*S*,*S*)-**7** (arene = *p*-cymene) and *t*-C_4H_9OK (aldehyde/Ru/base = 200:1:5) at 22 °C for 30 min gave the benzyl alcohols-*1-d* with a consistently high ee and with >99% isotopic purity (Scheme 2).[24] The high enantioselectivity is due to the favorable alcohol/carbonyl thermodynamic balance.[29] Similarly, certain alkynyl alkyl ketones were also reduced to the *S* propargylic alcohols with >95% ee in the presence of (*S*,*S*)-**7** (arene = mesitylene or *p*-cymene) and KOH ([ketone] = 0.1−1 M, ketone/Ru = 100−1000:1) (Scheme 2).[23] The C≡C bonds were left intact.

Structures and Reactivities of Intermediary Metal Complexes. A combined system of the chiral Ru complexes **6** or **7** and an alkaline base catalyzes asymmetric transfer hydrogenation of a range of prochiral ketones or aldehydes in 2-propanol. The precatalyst (*S*,*S*)-**7** (arene = *p*-cymene), true catalyst (*S*,*S*)-**8**, and hydride intermediate (*S*,*S*)-**9** (Scheme 2) were isolated and characterized by X-ray crystallography.[21,30] The *S*,*S* configuration of the diamine auxiliary forms a δ five-membered chelate ring, which determines the *R* configuration at the Ru stereogenic center in octahedral (*S*,*S*)-**7** and (*S*,*S*)-**9**. The purple 16e complex (*S*,*S*)-**8** that possesses a short Ru−N bond (1.897 Å) shows distinct dehydrogenative activity for methanol, ethanol, and 2-propanol, but not *tert*-butyl alcohol, giving the yellow RuH complex (*S*,*S*)-**9**. Reaction of **8** and H_2 gave **9** but only under high pressure. Most significantly, both the 18e and 16e complexes catalyzed the transfer hydrogenation of ketones at room temperature without alkaline bases. Asymmetric transfer hydrogenation of acetophenone in a 0.1 M 2-propanol solution containing (*S*,*S*)-**8** (ketone/**8** = 100:1) proceeds in the absence or presence of *t*-C_4H_9OK (**8**/base = 1:20) at the same rate and with the same enantioselectivity (*S*/*R* = 98:2). Similar 16e and 18e complexes would be involved when chiral ethanolamine derivatives are used as auxiliaries.[28] An alkaline base is used only for formation of **7** from $RuCl_2(\eta^6$-arene) and $HYCH(C_6H_5)CH(C_6H_5)NH_2$ (Y = O or NTs) and **8** from **7** by elimination of HCl.[31] The electronegative tosyl group in the 1,2-diamine is necessary to increase the acidity of the proton attached to the same nitrogen atom and also to stabilize the five-membered chelate ring.

A kinetic study of the steady-state 2-propanol/acetone catalytic cycle showed that the interconversion between **8** and **9** takes place either directly or via a very short-lived intermediate and that no other complexes limiting the catalytic turnover are involved.[21] Hydrogenation of acetone with **9** and reverse dehydrogenation of 2-propanol with **8** were equally facile. The rate of reaction of $(CD_3)_2CO$ and $(CH_3)_2CHOH$ with **9** is first order in $(CH_3)_2CHOH$ and the catalyst, eliminating the possibility of participation of two Ru complexes. The reduction of $(CH_3)_2CO$ and $(CD_3)_2CHOH$ in the presence of **8** or **9** was zero order in $(CH_3)_2CO$ (saturation kinetics) at high concentrations, whereas at low concentrations of acetone the rate was first order in $(CH_3)_2CO$. Thus, the reaction of **8** with 2-propanol is the turnover-limiting step in the steady-state catalytic hydrogen transfer, and the reverse reaction between **9** and acetone is more facile. Reduction of acetophenone with $(CH_3)_2CDOH$ catalyzed by (*S*,*S*)-**8** gave (*S*)-$C_6H_5CD(OH)CH_3$ (0.936 D at C-1) in 95% ee. Experiments using a mixture of $(CH_3)_2CHOH$ and $(CH_3)_2CDOH$ revealed a k_H/k_D value of 1.5 ± 0.1.

Methanol, ethanol, (±)-2-butanol, (*R*)-2-butanol, and (*S*)-2-butanol could also be used as hydrogen donors in place of 2-propanol in the reaction catalyzed by the *p*-cymene−Ru complex.[21] The consistently high enantioselection, regardless of the structures of the hydrogen donors, giving the *S* alcohol in 95 ± 0.5% ee, confirmed the involvement of a common Ru hydride species (*S*,*S*)-**9** as the reducing agent. Thus, the possibility of a Meerwein−Ponndorf-type mechanism[26] involving a Ru 2-propoxide is eliminated.

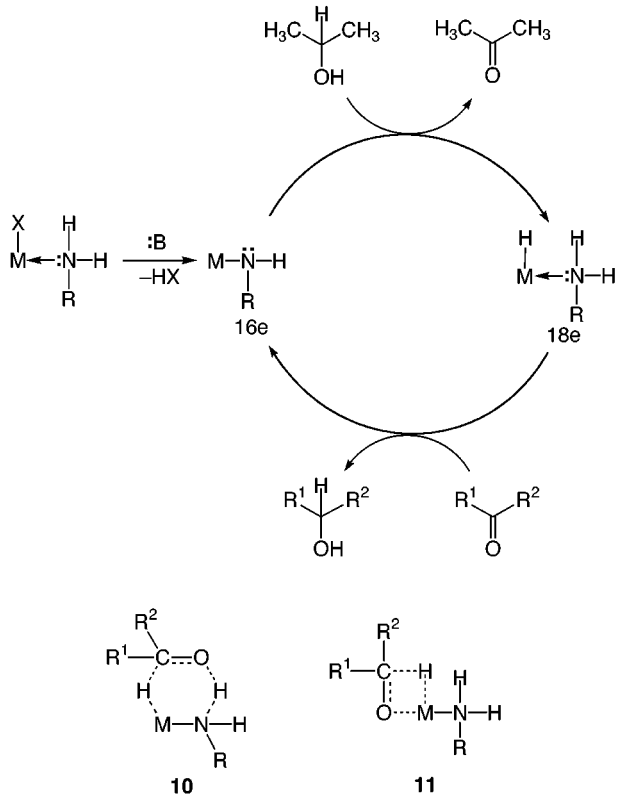


Figure 3. Metal−ligand bifunctional catalysis. M = transition metal.

Metal−Ligand Bifunctional Catalysis

Theoretical calculations[32] are very helpful to deeply understand this asymmetric catalysis, although the reaction environment is totally different, vacuum phase for calculation vs solution or solid phase for experiments. A range of experimental findings, combined with a theoretical study, show that this transfer hydrogenation takes place by a novel metal−ligand bifunctional mechanism outlined in Figure 3.[16o,32,33] The high catalytic activity of MH for a C=O function is generated by the NH unit in the auxiliaries attached to the metal center. This mechanistic model is in sharp contrast to the putative metal-centered pathway of Figure 2. Saturation of a C=O function with an MH species takes place via a six-membered pericyclic TS **10**[34] utilizing an "NH effect" instead of $\pi^2 + \sigma^2$ insertion of the C=O bond into the M−H linkage via TS **11**. The 18e MH complex is regenerated by dehydrogenation of 2-propanol with the 16e Ru amide via a similar cyclic TS. This nonclassical mechanism is characterized by the direct participation of the metal and the surrounding ligand in the bond-forming and -breaking steps of the dehydrogenative and hydrogenative processes.[35] Neither a carbonyl oxygen atom nor an alcoholic oxygen interacts with the metallic center throughout the hydrogen transfer processes. The carbonyl reduction occurs in an outer coordination sphere of the metal hydride complex.

A detailed theoretical study using ab initio MO calculation at the MP4//MP2 level predicted the pathway shown in Figure 4 for the model methanol/formaldehyde transformation.[32] An alternative β-elimination/insertion mechanism and its reverse reaction via **11** type TSs (Scheme 2) are much more difficult, because they require the unfavorable partial decoordination of the η^6-arene

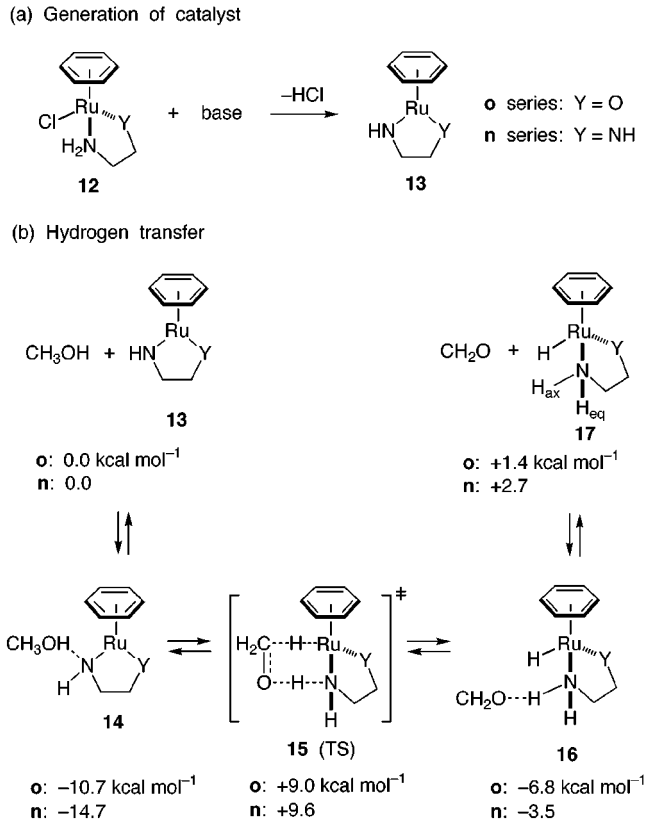


Figure 4. Calculated mechanism for Ru(II)-catalyzed hydrogen transfer between methanol and formaldehyde (MP4//MP2).

ligand from Ru. The calculation reveals that the complexes of the **o** (Y = O) and **n** series (Y = NH, a model of the *N*-sulfonyl derivatives) behave similarly. Figure 5 shows the detailed structures of some ground-state Ru complexes and TSs in some relevant reactions. A density functional theory based (DFT) calculation at the B3LYP level led to the same conclusion.[32]

KOH or other alkaline bases are necessary for the generation of the formal 16e Ru complex **13** (catalyst) from the 18e Ru chloride **12** (precatalyst) by a Dcb elimination of HCl,[36] and not for increasing alkoxide concentration, as is consistent with experiments.[21] Without base, the process **12o** → **13o** is even endothermic by 36.5 kcal mol^{-1}. The square-planar structure **13o** possesses a hexagonal benzene ring and anionic nitrogen and oxygen ligands. The η^6-arene ligand has a bis-allylic character. The Ru−amide bond, 1.839 Å, is much shorter than the normal Ru−N distance of 2.16 Å. Thus, the electron deficiency of the Ru center in the formal 16e complex is mitigated by substantial electron donation from the nonbonding orbital of the nitrogen.[37] The catalytic complex **13o** dehydrogenates methanol to form formaldehyde and the 18e Ru hydride **17o** possessing normal Ru−N (2.151 Å) and Ru−H (1.585 Å) distances. The dehydrogenation is endothermic by 1.4 kcal mol^{-1}. The equilibrium point of hydrogen transfer between alcohols and carbonyl compounds is dependent on the properties of the donors and acceptors. The ΔE value varies going from methanol to ethanol, −3.8 kcal mol^{-1}, and 2-propanol, −6.8 kcal mol^{-1}, and the reaction becomes exothermic. The activation energy of dehydrogenation varies from 19.7 to 17.2 and to 16.6 kcal mol^{-1}, respectively. Thus, dehydrogenation of 2-propanol is facile on both thermodynamic and kinetic grounds.

The alcohol dehydrogenation process and reverse hydrogen delivery from **17** to formaldehyde occurs by way of the transient hydrogen-bonded intermediates **14** and **16** and by a pericyclic mechanism through a six-membered TS **15**.[34] The C=O oxygen interacts with NH on Ru and the alcohol OH function with the amido nitrogen both via hydrogen bonds. The Ru complexes **14** and **16** are the only ground-state complexes present in this redox reaction. The activation energy of the hydrogenation via **16o**, 15.8 kcal mol^{-1}, is lower than that for methanol dehydrogenation in **14o**, 19.7 kcal mol^{-1}.

The hydrogenation of CH_2O is viewed as a nucleophilic reaction of the hydride on Ru with a carbonyl carbon assisted by the C=O···H−N hydrogen bond. It should be noted that the H, N, and Y ligands in the octahedral complex **17** have a *fac* relationship. The five-membered ring is highly skewed and has two diastereotopic nitrogen-bonded hydrogens, H_{ax} (axial) and H_{eq} (equatorial) (Figure 5). Here, only H_{ax} is used for reaction with formaldehyde for a stereoelectronic reason. The hydrogenative reactivity of **17o** originates from the charge-alternating H−Ru−N−H_{ax} arrangment, where the NPA charges are −0.002 (H), +0.26 (Ru), −0.80 (N), and +0.42 (H_{ax}).[38] The hydrogenative complex **17** acts as a 1,4-dipole that fits well with the C=O dipole. The H−Ru−N−H_{ax} dihedral angle is 21.7° (cf. 10.9° in (*S*,*S*)-**9**[21]). The hydride interacts with the carbonyl carbon using its antibonding orbital with a Ru···H···C angle of 150° by hydrogen-bond assistance with an N···H···O angle of 164°. The C=O group utilizes the π face instead of the σ plane in the TS. The migrations of the hydridic RuH and protic NH_{ax} occur simultaneously via **15**, but this bond reorganization is not completely synchronous. The hydride delivery to the carbon precedes the proton transfer to the oxygen to some extent, as judged from the charge distribution and geometries. The six-membered TS structure is different from the Ru hydride **17** and also the Ru amide **13**. Its nature is understood by the conventional resonance hybrid, **18a** ↔ **18b** ↔ **18c** (Scheme 3), in which the contribution of **18b** is significant.[34] The reacting formaldehyde in **15o** has a significant methoxide ion character, but not a protonated formaldehyde character, whereas the Ru and N−H atoms have large positive charges. The values are larger than in the starting hydride **17o**, suggesting a polar nature of the TS.

The dehydrogenative activity of **13o** relies on the polarized Ru−N bond, as indicated by the NPA charges of +0.53 at Ru and −0.73 at N.[38] The reaction is concerted in nature but, as seen from the polar resonance structure **18b**, movement of the methanol proton to the amide nitrogen slightly precedes the α-hydrogen delivery to Ru. The Ru−N bond polarity in **13o** is significantly enhanced in TS **15**. The 16e Ru complex **13o** dehydrogenates 2-propanol, the best hydrogen-donating alcohol, via **19** (Figure 5). This TS has structural characteristics similar to **15o** for methanol, although it is located somewhat earlier in the reaction coordinate.

The complex **13o** can cleave an H_2 molecule to give the same RuH species **17o** with an exothermicity of 20.9 kcal mol^{-1}.[39] However, the reaction via TS **20** (Figure 5) occurs with an activation energy of 25.2 kcal mol^{-1}, a value significantly larger than for the reaction with 2-propanol, 16.6 kcal mol^{-1}. Elimination of H_2 from **17o** is kinetically very difficult, requiring E_a = 46.1 kcal mol^{-1}. These trends have been noticed in experiments with (*S*,*S*)-**8** and (*S*,*S*)-**9**.[21] The Ru hydride **17o** reduces H_2C=NH by way

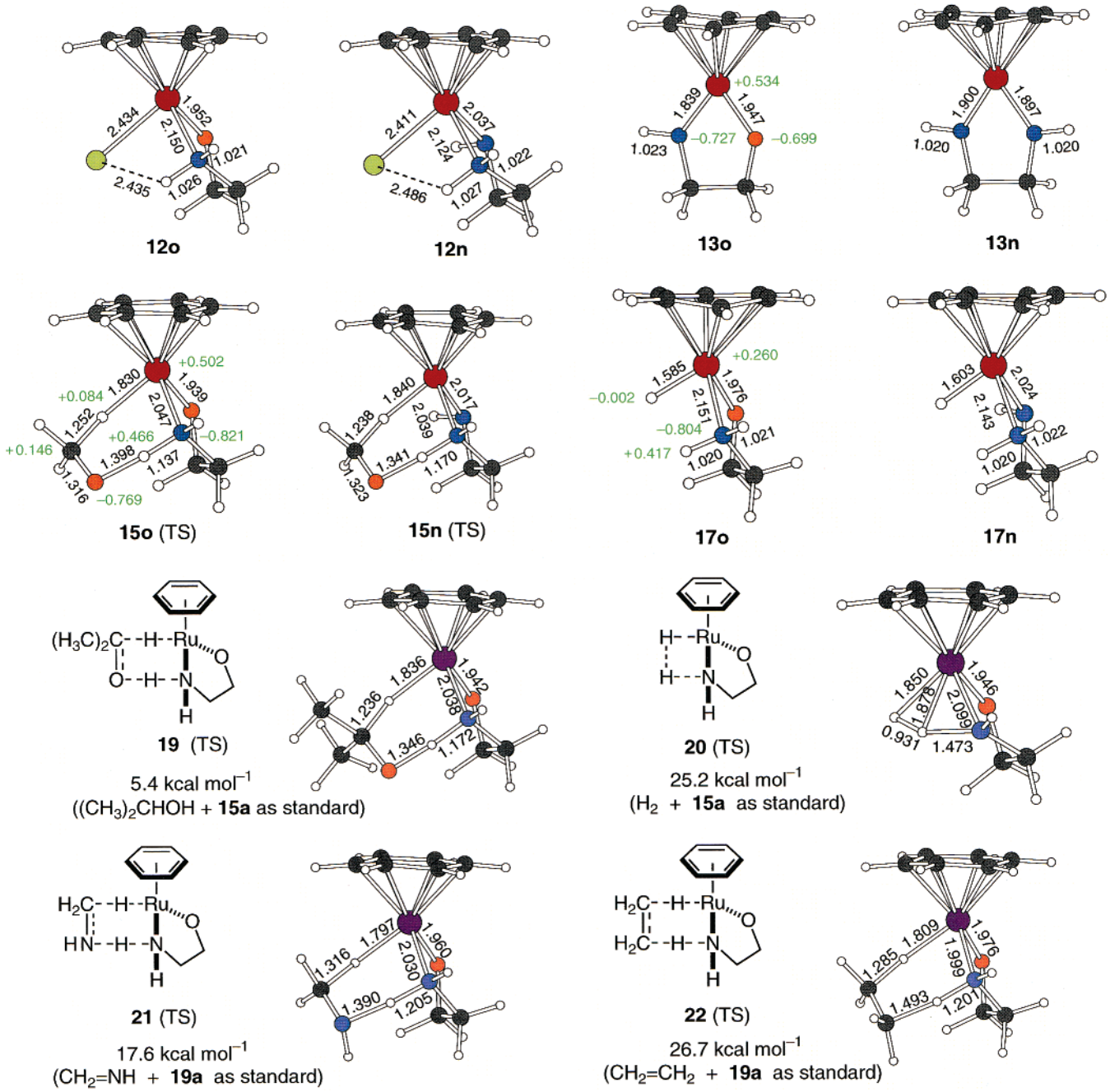
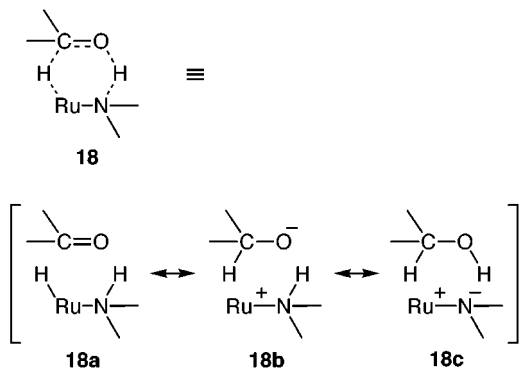


Figure 5. Calculated structures of Ru complexes and transition states in the model methanol/formaldehyde conversion and related reactions (MP2). NPA charges are given in green (B3LYP).

Scheme 3



of **21**,[34] affording CH_3NH_2 and **13o**, with an exothermicity of 8.8 kcal mol^{-1}. However, the activation energy is 26.9 kcal mol^{-1}, which is 11.1 and 4.9 kcal mol^{-1} higher than that for reduction of $H_2C{=}O$ to CH_3OH and $(CH_3)_2C{=}O$ to $(CH_3)_2CHOH$, respectively. Ethylene could accept two hydrogens from **17o** via the six-membered TS **22**[34] with E_a = 26.7 kcal mol^{-1}. Thus, the reactivity of the unsaturated substrates reflects the extent of the polarity of the double bond. Reduction of the polar C=X bonds involves the initial NH···X hydrogen-bonded species, while the C=C linkage is saturated by a direct bimolecular mechanism which is entropically much less favorable.

The ethanolamine- and ethylenediamine-based complexes behave similarly. The Ru-promoted alcohol/ketone and reverse conversion occur much more easily via a direct pericyclic mechanism than by a multistep, β-elimination or a 2 + 2 pathway (Figure 3 vs Figure 2). The NH effect plays a pivotal role in this hydrogen transfer

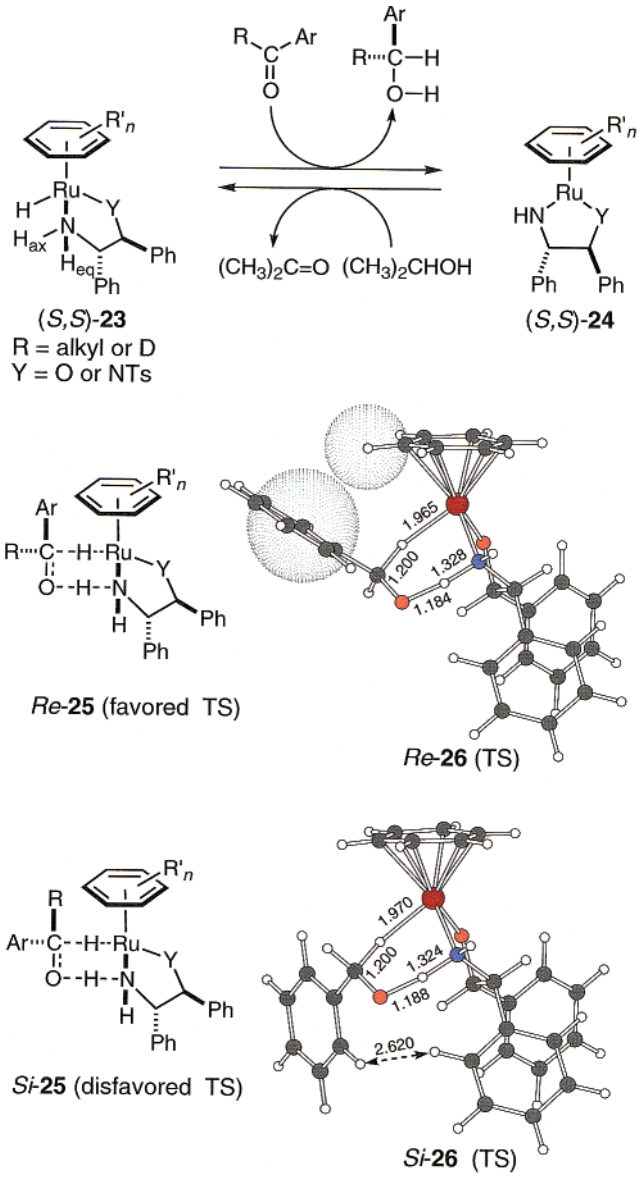


Figure 6. Sense of asymmetric induction and diastereomeric transition states (B3LYP).

reaction in accord with the high chemoselectivity for C=O functionality.[40]

Origin of Enantioselection

The kinetic asymmetric bias is generated by the combination of various steric and electronic factors. Chirality of the octahedral Ru complexes obviously originates from the structures of 2-amino alcohol or N-sulfonylated 1,2-diamine auxiliaries. The major role of the two phenyl groups in the chiral auxiliaries of (*S*,*S*)-**6** and (*S*,*S*)-**7** is to define the δ conformation of the skewed five-membered chelate ring by taking an equatorial orientation and then an *R* configuration at the Ru stereogenic center. This correlation was substantiated both experimentally and theoretically.[21,32]

Then why η^6-arene ligands? Intuitively, we selected η^6-arene−Ru(II) catalysts possessing a chiral amino ligand for the asymmetric reaction. A combined catalyst system of (*S*,*S*)-**6** or (*S*,*S*)-**7** and an alkaline base in 2-propanol catalyzes reduction of the aryl alkyl ketones or deuterated benzaldehydes to give the corresponding *S* alcohols

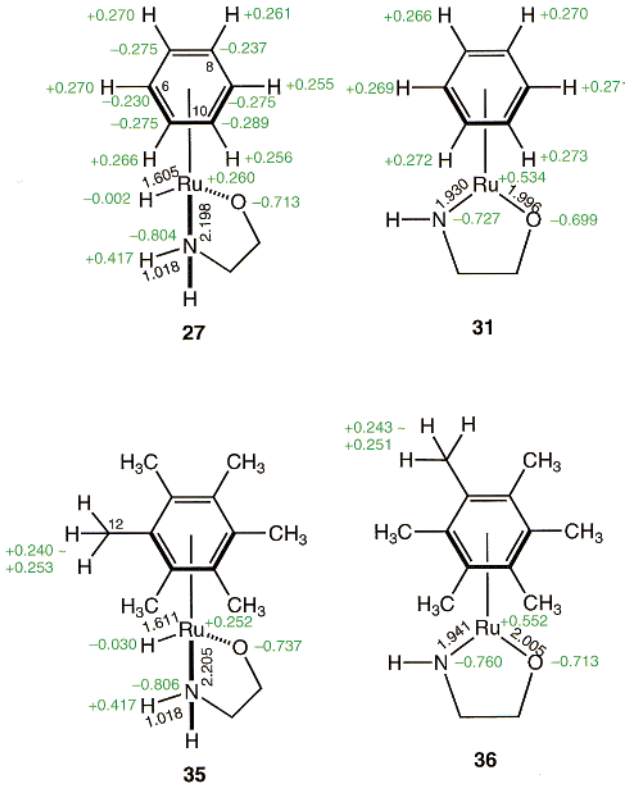


Figure 7. NPA charge (in green) distribution and selected bond lengths in the Ru hydride and amide complexes (B3LYP). **27** and **35** have a δ conformation for the N,O-chelate ring and an *R* conformation at Ru.

with fair to excellent enantiomeric purity (Scheme 2).[17−19,24] The mechanistic investigation[32] described above indicates the operation of the simple two-component catalytic cycle shown in Figure 6. The general stereochemical outcome suggests that the Ru hydride (*S*,*S*)-**23** reacts with the carbonyl substrates preferentially via the "sterically congested" TS, *Re*-**25**, rather than the uncrowded *Si*-**25**. The reverse process occurs via the same TS. In fact, a DFT calculation at the B3LYP level predicts *Re*-**26** and *Si*-**26** as the favored and unfavored TSs (ΔE_a = 2.1 kcal mol^{-1}), respectively, for the reaction of benzaldehyde and (*S*,*S*)-**23** (Y = O, arene = C_6H_6). The core structures of these diasteromeric TSs are geometrically very similar. Because no aggravating effects are seen in either structure, some factors that favor the proximity of the η^6-arene ligand and the carbonyl aromatic substituent must be operating in *Re*-**26**. A detailed theoretical scrutiny using a higher quality calculation[41] revealed that, in addition to the chiral geometry of the five-membered chelate ring,[32] the enantioselection originates from the CH/π attractive interaction between the η^6-arene ligand and aryl substituents in ketone or aldehyde substrates.

The reaction of RuH($OCH_2CH_2NH_2$)(η^6-benzene) (**27**) and benzaldehyde was selected as a model system (Figure 7) for the calculation at the MP2//B3LYP level. This model chiral Ru hydride, like (*S*,*S*)-**23**, is assumed to possess a δ conformation with respect to the N,O-chelate ring and then an *R* configuration at Ru. The hydrogenation of a C=O function utilizes the Ru−H linkage and the N−H_{ax} bond with a syn relationship. Figure 8 shows the calculated energy profile. Reaction of **27** and benzaldehyde proceeds via the hydrogen-bonded intermediate **28**, giving first **30** and then **31** and benzyl alcohol. This reaction is endothermic by 5.0 kcal mol^{-1}, while regen-

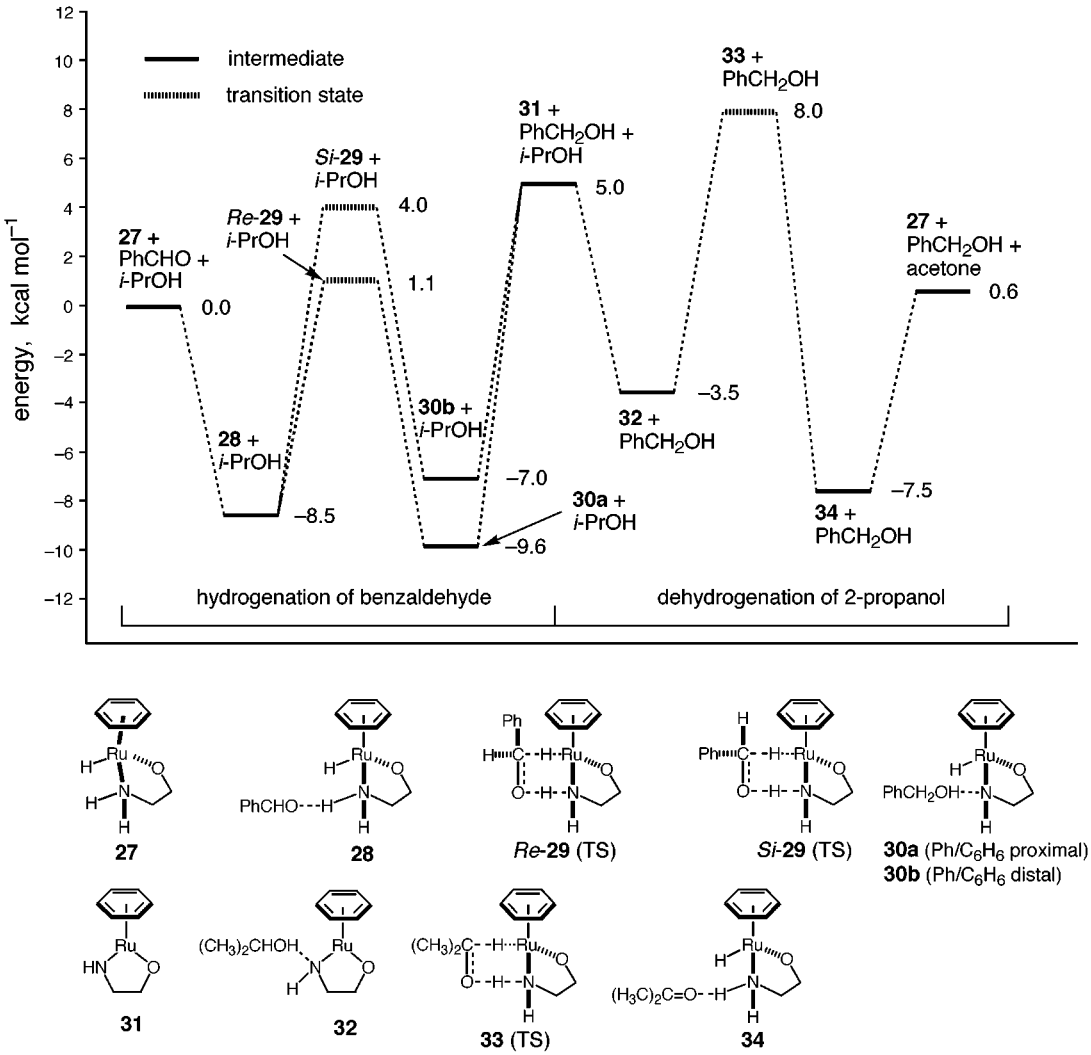


Figure 8. Energy diagram of the hydrogen transfer between benzaldehyde in 2-propanol promoted by **27** (MP2//B3LYP).

eration of **27** by reaction of **31** and 2-propanol is exothermic by 4.4 kcal mol^{-1}, making the overall reaction only 0.6 kcal mol^{-1} endothermic. In addition, the calculation predicts that the proximal TS, *Re*-**29**, is favored over the distal isomer, *Si*-**29**, by 2.9 kcal mol^{-1} (E_a = 9.6 vs 12.5 kcal mol^{-1}) (Figure 9). This TS model is very similar to the real system **26** (Figure 6) because the two phenyl rings omitted in the amino alcohol auxiliary do not exert any direct influence on other parts of the TS assemblies.

As analyzed in Figure 9, *Re*-**29** is more stabilized by the CH/π attractions between the η^6-benzene ligand and the aldehyde phenyl substituent. The C(6)H···C(15) distance, 2.860 Å, is close to the sum of the van der Waals radii, 2.9 Å. The CH/π attractive force is based on both electrostatic and charge-transfer interactions.[42] In fact, the C(6)−H, C(15), and C(16) atoms in *Re*-**29** have special charge parameters; C(6)−H with a significant positive NPA charge interacts with highly negative C(15) and C(16) via largely electrostatic attractions. However, the charge-transfer character is not negligible, the Mulliken bond populations being +0.0080 and +0.0040, respectively. The high C−H acidity in benzene caused upon metal complexation[43] is the key for this effect, as already seen in the ground-state complexes **27** and **31** in Figure 7. The C(sp^2)H/π attractive interaction between the two aromatic rings becomes further conspicuous through the through-bond linkage via the Ru···H···C moiety, and this feature is different from the conventional T-shaped interaction.[42] First, in going from free benzene to *Re*-**29**, the positive charge of C(sp^2)H is increased from +0.24 au to +0.27−0.28 au, or even to +0.29 au at C(6)−H (Figure 9). The latter hydrogen is distinct in both *Re*-**29** and *Si*-**29** and is the most electron-deficient when compared with those in the starting Ru hydride **27** (+0.26 to +0.27 au) or even the 16e complex **31** (+0.27 au). On the other hand, the hydride approach to the C═O carbon renders an alkoxide character to the reacting benzaldehyde and, consequently, reverses the relative charge distribution at the ortho/para vs meta positions. This effect results in a significant increase in the C−H accepting ability at the ortho and para carbons. In particular, the negative charge at the interacting C(15) (−0.25 au) is much larger than in free benzaldehyde (−0.20 au), whereas C(16) is inherently electron-rich in both *Re*-**29** and C_6H_5CHO (−0.24 au). Notably, C(15) and C(16) in *Re*-**29** have higher negative charges (−0.25 and −0.24 au, respectively) than in *Si*-**29** (−0.23 au) in such a way as to interact with the highly positive C(6)−H atom. The same conclusion has been reached from the MP2 optimizations, which suggest a preference for *Re*-**29** over *Si*-**29** by 2.9 kcal mol^{-1} (E_a = 7.5 vs 10.3 kcal mol^{-1}). This calculation indicated a greater CH/π interaction in *Re*-**29** with the C(6)H···C(15) distance of 2.609 Å.

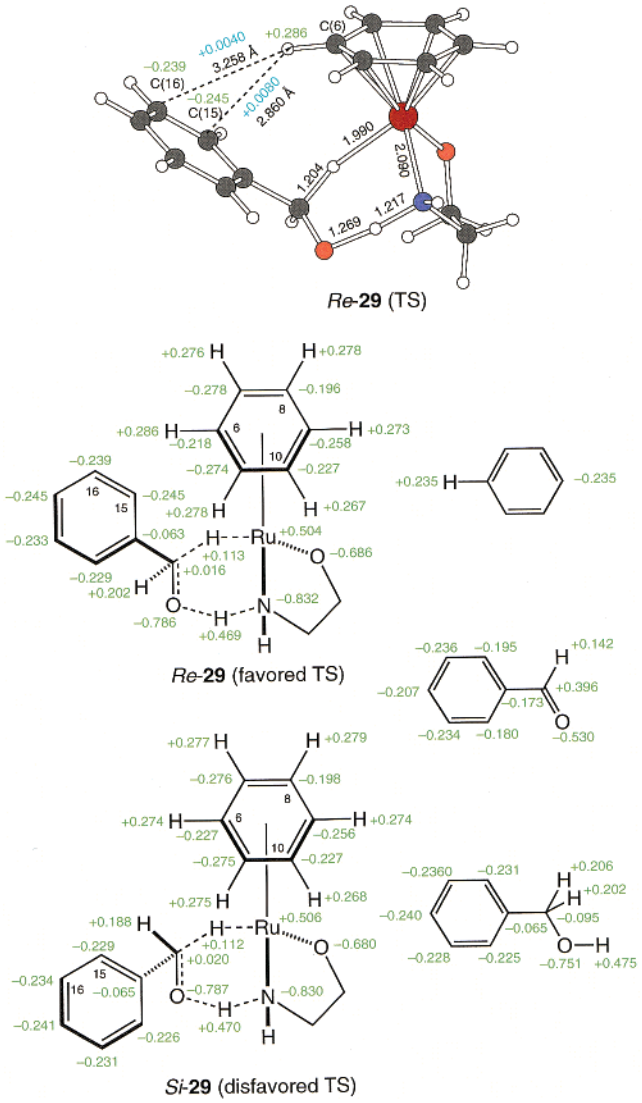


Figure 9. C(sp^2)H/π attractive interaction between the η^6-benzene ligand and the phenyl group in *Re*-**29**. NPA charges (B3LYP) in the diastereomeric TSs, benzene, benzaldehyde, and benzyl alcohol are given in green. The Mulliken bond population (RHF) is given in blue.

Thus, the TS chirality stems from the amino alcohol auxiliary but the CH/π attraction is the direct origin that stabilizes one of the diastereomeric TSs more. This TS stabilization is reminiscent of the origin of the endo stereoselection in the purely organic Diels−Alder reaction which is based similarly on an attractive secondary interaction between nonreacting sites.[44]

This view not only is consistent with the general asymmetric sense but also explains many other experimental findings. A systematic study of asymmetric reduction of deuterated benzaldehyde derivatives using (*S*,*S*)-**23** (Y = O, arene = C_6H_6) has revealed that the ee of the *S* products and the relative rates (in parentheses) are as follows: *p*-CH_3O, 61% (0.55); *p*-CH_3, 49% (0.96); H, 45% (1.0); *p*-Br, 37% (1.5); *p*-CF_3, 20% (1.6).[24] Electron-donating substituents tend to enhance the enantioselectivity due to the greater secondary interaction caused by the higher C−H accepting ability of the π-electron-rich aromatic ring, while electron-withdrawing substituents lower the extent of enantioselection. The electronic effects on the reactivity are also in accord with the nature of the calculated TS **15**, particularly the contribution of the polar formula **18b** (Scheme 3). As expected, the relative rate does not have a linear free-energy relationship. Furthermore, the reaction of *p*-cyano-*p*′-methoxybenzophenone, a skeletally symmetrical but electronically unsymmetrical diaryl ketone, gives (*S*)-*p*-cyano-*p*′-methoxybenzhydrol in 34% ee[41] due to the greater η^6-benzene/4-methoxyphenyl CH/π interaction.

Alkyl groups in the η^6-arene ligand change the properties of the Ru complexes. As illustrated in Figure 7, because of the electron-donating nature of methyl groups, the NPA charge of Ru−H in **27**, 0.002 au, is considerably increased to −0.03 au in the fully methylated complex **35**, while the positive charge at Ru is reduced from +0.26 to +0.25 au. The N−H_{ax} charge is little affected. In a similar manner, methylation increases the negative charges at the N and O atoms and the positive charges at Ru (−0.73, −0.70, and +0.53 au in **31** vs −0.76, −0.71, and +0.55 au in **36**). These perturbations affect the rate and stereoselectivity, where the influence can be either electronic or steric. Both *Re*-**29** and *Si*-**29** possess small negative NPA charges at C(6), C(8), and C(10) (Figure 9). The values for *Re*-**29** are −0.22, −0.20, and −0.23 au, respectively, which are to be compared to −0.26 to −0.28 au at other carbons. Therefore, introduction of electron-donating alkyl groups at these electron-deficient positions stabilizes the TSs. The DFT calculation predicts that reaction of the hexamethylbenzene analogue, (*S*,*S*)-**35**, and C_6H_5CHO proceeds with an activation energy 2.8 kcal mol^{-1} lower than that with the parent η^6-benzene complex **27**. Dehydrogenation of 2-propanol is also easier with **36**, which has a relatively high Ru−N polarity, as judged from the relative TS energies (6.8 vs 8.0 kcal mol^{-1}). Furthermore, the reaction occurs preferentially via TS *Re*-**37** instead of *Si*-**37**, resulting in the same sense of asymmetric induction (Figure 6). As analyzed in Figure 10, the operation of C(sp^3)H/π attractions[45] stabilizes the sterically congested *Re* TS more than the uncrowded *Si* isomer by 1.7 kcal mol^{-1} (E_a = 6.8 vs 8.5 kcal mol^{-1}). This is noteworthy because the presence of methyl groups distorts the core six-membered geometry significantly from that of nonmethylated *Re*-**29**. In addition, a slight rotation around the arene−Ru axis is seen in going from **35** to TS *Re*-**37**. In *Re*-**37**, the atomic distances between C(12)H and C(21) and C(22) in the aldehyde phenyl are 2.974 and 3.177 Å, respectively, and the bond populations are +0.0027 and +0.0030, respectively. The attraction reflects the distinct positive NPA charge at C(12)H (+0.26 au) (+0.237 to +0.239 au in free hexamethylbenzene) and the large negative charges at C(21) and C(22) (−0.247 and −0.241 au). The high hydridic character of Ru−H of **35** would facilitate the reduction. Experimentally, catalytic reduction of benzaldehyde-*1*-*d* with (*S*,*S*)-**6b** (arene = $C(CH_3)_6$) and *t*-C_4H_9OK in 2-propanol occurs 3.4 times faster than the reaction with the parent benzene complex but gives a somewhat lower ee (*S*, 32% vs 45%).[41]

This investigation has revealed previously unrecognized effects of arene ligands. The result implies that, in certain cases, though not always, ring alkylation could faciliate the reaction more and also generate a larger asymmetric bias, only if other perturbations remain similar. In fact, in transfer hydrogenation of certain aromatic ketones, the *p*-cymene or mesitylene Ru complexes exhibit higher enantioselectivities than the simple benzene complex.[17−19]

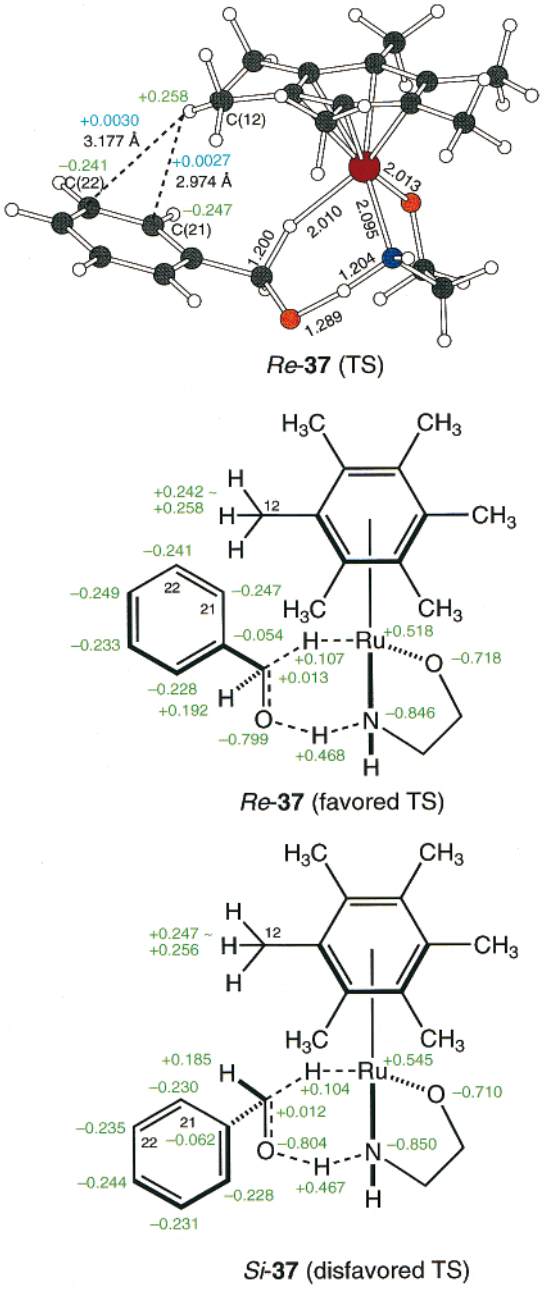
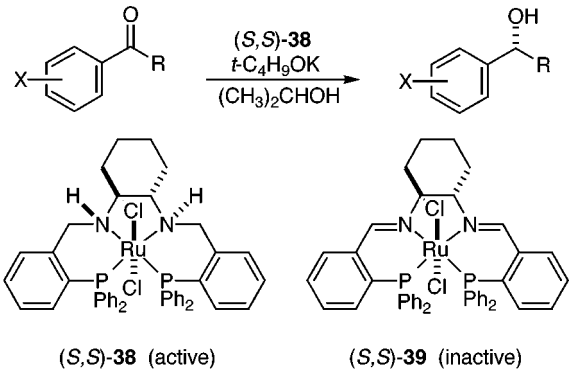


Figure 10. C(sp^3)H/π attraction between the η^6-hexamethylbenzene ligand and the phenyl group in *Re*-**37**. NPA charges (B3LYP) in the diastereomeric TSs and the Mulliken bond population (RHF) are shown in green and blue, respectively.

The CH/π attraction is the major origin of the stereoselective stabilization of a diastereomeric TS. However, the chiral structures of the Ru complexes are further influenced by the steric and electronic properties of ligand substituents. In the chiral ethanolamine-based Ru catalysts, the hydroxy-bearing carbon configuration is the primary determinant of the asymmetric sense in the reaction of acetophenone, suggesting the significance of the correlation between the chelate ring conformation and Ru configuration, δ,*R* and λ,*S*.[19] The N-methylated ethanolamine complex (*S*,*S*)-**6b** exhibits higher enantioselectivity than the nonmethylated analogue **6a** (Scheme 2).[19] The moderate stereoselectivity with **6a** is ascribable to the partial participation of the diastereomeric λ,*S* Ru hydride caused by the flipping of the N,O-chelate ring. The presence of the *N*-CH$_3$ group in **6b** would prevent such a possibility because of the unfavored interaction with the adjacent cis-oriented phenyl substituent. The *N*-tosyldiamine complex (*S*,*S*)-**23** (Y = NTs, arene = C$_6$H$_6$) gives higher ee's in the reaction of benzaldehyde-*1-d* derivatives (*S*, 99−96%) than the similar ethanolamine complex (*S*,*S*)-**23** (Y = O, arene = C$_6$H$_6$) (*S*, 61−20%).[24] The enhanced enantioselectivity is due to an additional *N*-Ts/η^6-arene interaction that destabilizes the *Si* TS more. This effect becomes more significant when the alkylated benzene−Ru complexes are used as catalysts.

Scheme 4



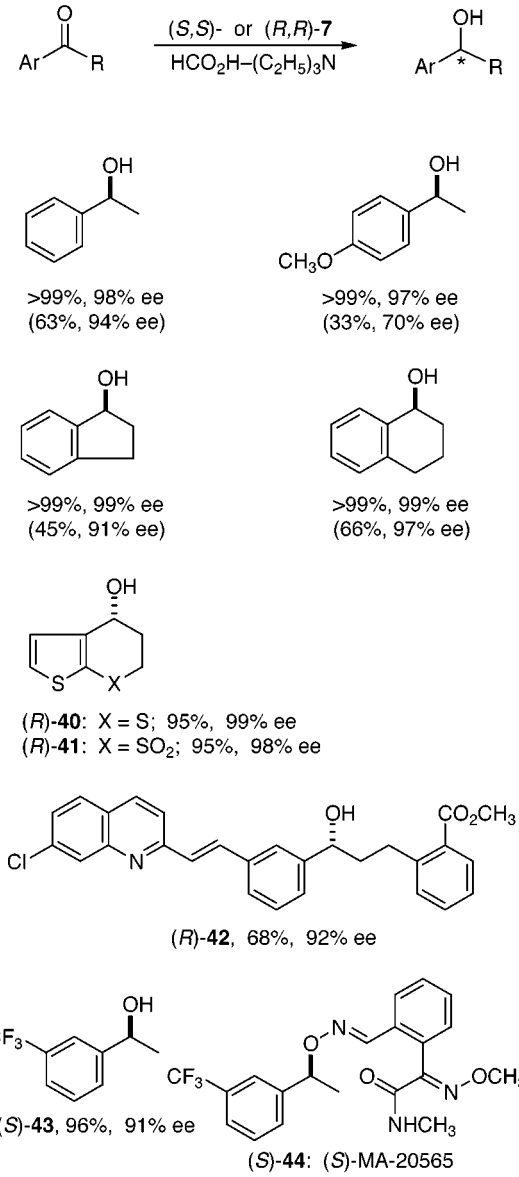
The high enantioselectivity observed with the structurally rigid α,β-ynones is interpreted in a similar manner.[23] The reaction of more flexible α,β-enones and -enals-*1-d* is less selective,[22,24] and aliphatic aldehyde-*1-d* gives poor enantioselectivity.[24]

Extension and Implications

The NH effect is the origin of the high activity of the Ru catalysts, while efficient ligands are not limited to arene complexes. The C_2 chiral Ru complex (*S*,*S*)-**38**, possessing a tetradentate diphosphine/diamine ligand, promotes highly enantioselective transfer hydrogenation of aromatic ketones in 2-propanol containing *t*-C$_4$H$_9$OK, giving the *R* alcohols in high ee (Scheme 4).[20a] Most notably, the structurally similar diphosphine/diimine complex (*S*,*S*)-**39** is almost inert to the catalytic reaction because of the lack of an NH function.

The transfer hydrogenation catalyzed by a chiral amino alcohol- or 1,2-diamine-based Ru complex has been extended to various ketonic substrates.[15e,16p,28a,46] An inherent drawback of the reaction with 2-propanol as the hydrogen donor is the reversibility of the reaction, which arises from the structural similarities of the starting and product systems.[7] Although the above amino alcohol- or diamine-based Ru(η^6-arene) complexes **6** and **7** have excellent chiral recognition ability, the catalysis exhibits a significant erosion of the initial kinetic enantioselectivity as the reaction proceeds, particularly with a high substrate concentration.[18,19] The extent of the undesired effect is highly dependent on the properties of the ketone structures, since the equilibrium point is determined by the redox potential of the hydrogen donors and acceptors.[29] The reverse process prevents the complete conversion as well. Thus, the reaction of aromatic ketones is normally conducted in a 0.1 M 2-propanol solution. This long-standing problem was solved simply by using formic acid, a formal adduct of H$_2$ and CO$_2$, in place of 2-propanol.[47] The asymmetric reaction using a 2 M to even a 10 M solution of an aromatic ketone in a 5:2 formic

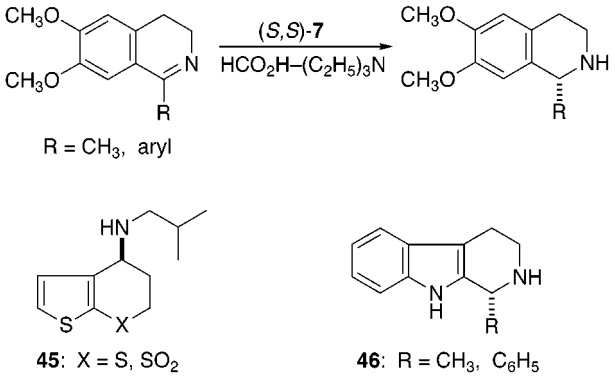
Scheme 5



acid−triethylamine mixture containing (*S*,*S*)-**7** (arene = mesitylene) (ketone/Ru = 200−1000:1) gave the *S* alcohol with excellent enantioselectivity. Scheme 5 shows examples of some secondary alcohols prepared by this procedure. The selectivity is to be compared with the values in parentheses obtained in 2-propanol. The ee value of 1-phenylethanol was consistently high, *S*/*R* = 99:1, throughout the reaction until its completion. Various substituted benzaldehydes-*1-d* were converted to chiral benzyl-*1-d* alcohols with high enantiomeric and isotopic purity.[24] In a similar manner, *p*-methoxyacetophenone, 1-indanone, and 1-tetralone with high reduction potentials were reduced to the chiral alcohols in 97−99% ee and high chemical yield.[47] *p*-Cyano-*p*′-methoxybenzophenone gave the (*S*)-benzhydrol in 66% ee. The reaction proceeds via the same Ru hydride species (*S*,*S*)-**23** (Y = NTs) but irreversibly under truly kinetic control even in a high concentration.

Thus, the asymmetric transfer hydrogenation now becomes synthetically very useful. This method using (*R*,*R*)-**7** (arene = mesitylene) allows for the highly enantioselective synthesis of (*R*)-**40** or (*R*)-**41** and (*R*)-**42**, which serve as intermediates for MK-0417 (a carbonic anhydrase inhibitor) and L-699,392 (a LTD4 antagonist), respectively.[46] This asymmetric method was successfully applied for the reduction of *m*-trifluoromethylacetophenone using a substrate/(*S*,*S*)-**7** ratio of 5000 and at a scale feasible industrially.[48,49] The product, (*S*)-**43**, is an important intermediate for (*S*)-**44**, a wide-spectrum agrochemical fungicide. Double reduction of α-diketones including benzil derivatives with (*S*,*S*)-**7** in a substrate/Ru molar ratio of 1000−2000 gave directly (*R*,*R*)-1,2-diols with high diastereo- and enantioselectivity.[50] The transfer hydrogenation is chemoselective for the C=O function, and the reaction is tolerant of olefinic, ester, sulfide, sulfone, nitro group, aryl chloride, cyanide, and many heteroaromatic cycles.[17,51,52]

Scheme 6

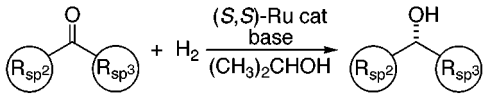


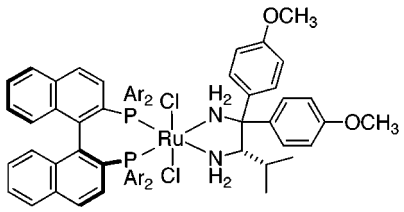
The reversibility of the reaction using 2-propanol is the greatest flaw of an otherwise very attractive redox process. However, this tendency can be utilized for kinetic resolution of racemic alcohols using acetone as a hydrogen acceptor.[22] Thus, various polyoxygenated 1-phenylethanols, *p*-(dimethylamino)-1-phenylethanol, 1-ferrocenylethanol, 1-indanol, and 1-tetralol, and some cyclic allylic alcohols were resolved directly without derivatization using (*S*,*S*)-**8** (arene = *p*-cymene or mesitylene) as catalyst. These alcohols have a low oxidation potential and hence are difficult to prepare in high enantiomeric purity by ketone reduction in 2-propanol. However, the reverse process makes it possible.

The Ru-catalyzed reaction using a formic acid−triethylamine mixture can be extended to asymmetric reduction of imines.[15c,53−55] The reaction of acetophenone benzylimine with (*S*,*S*)-**7** gave the corresponding *S* amine in 77% ee. The asymmetric sense is the same as that of acetophenone reduction (Figure 6) and can be understood by the mechanistic model based on the CH/π attraction. As generalized in Scheme 6, the highly enantioselective reaction catalyzed by (*S*,*S*)-**7** (arene = benzene or *p*-cymene) opens a new route for the synthesis of natural and unnatural isoquinoline alkaloids. The reaction using an imine/Ru molar ratio of 100−1000:1 afforded the chiral amines in up to 95% ee. The reaction exhibited an opposite asymmetric sense due to the nonbonded repulsion between the η^6-arene ligand and the CH_2 unit in the dihydroisoquinoline substrates. This reaction was applied to the synthesis of **45**, an intermediate for MK-0417. Certain chiral indoles, such as **46**, are also obtainable by this method. Unlike the reaction in 2-propanol, imines are more reactive than ketones under such conditions using an aprotic polar solvent such as DMF, DMSO, CH_3CN, and CH_2Cl_2.

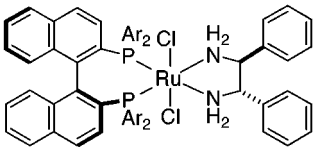
Utilization of the notable NH effect can be applied to carbonyl reduction using molecular hydrogen.[3] $RuCl_2$-

Scheme 7



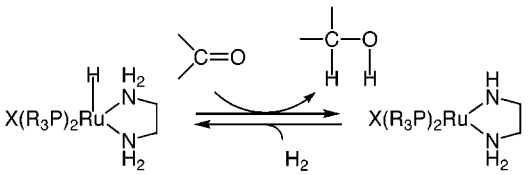


(*S,S*)-**47**: Ar = 3,5-$(CH_3)_2C_6H_3$



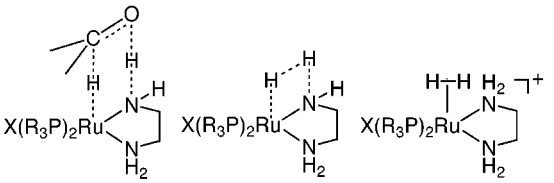
(*S,SS*)-**48**:
Ar = C_6H_5, 4-$CH_3C_6H_4$,
3,5-$(CH_3)_2C_6H_3$

Scheme 8



49 **50**

X = H, OR, etc.



51 (TS) **52** (TS) **53**

(phosphine)$_2$(1,2-diamine) complexes, coupled with an alkaline base in 2-propanol, catalyze hydrogenation of simple ketones to alcoholic products. Use of an appropriate chiral diphosphine and diamine ligands leads to rapid, productive, and highly enantioselective hydrogenation. A wide variety of aromatic, heteroaroamatic, and olefinic ketones can be converted chemoselectively to the corresponding chiral alcohols with high ee. Scheme 7 shows the general sense of asymmetric induction in reactions using the BINAP/diamine-based Ru catalyst (*S,S*)-**47**. Some other diphosphine/diamine combinations such as (*S,SS*)-**48** or diastereomeric (*S,RR*)-**48** are also appropriate, depending on the ketonic substrates. We have postulated that the reaction proceeds by way of the 18e Ru hydride **49** and 16e Ru amide intermediate **50** as outlined in Scheme 8.[3] Hydrogenation of a ketone occurs via the six-membered TS **51** by analogy to **10** in Figure 3. The reducing species **49** may be regenerated directly by reaction of **50** and H_2 via TS **52**[39,56–58] or in a stepwise fashion via N-protonation to **50** followed by deprotonation from the η^2-H_2 Ru complex **53**.[3,56]

Conclusion

Molecular designing of asymmetric catalysts is highly flexible. The nonclassical metal−ligand bifunctional mechanism provides a new insight for hydrogenative reduction of C=X compounds (X = O, N) catalyzed by transition-metal complexes possessing NH ligands, or more generally protic neutral ligands LH (L = heteroatom). The unsaturated bonds can be hydrogenated without ligation to the metallic center, where hydride and proton are simultaneously delivered from MH and NH, respectively. The chiral "molecular surface" of the coordinatively saturated metal hydride species recognizes the differences in ketone enantiofaces, in contrast to many other asymmetric hydrogenations where enantioface discrimination is made within a "metal template" via metal/substrate interactions. The stereodetermining TS structure is determined integrally by combining various steric and electronic factors. The secondery interaction between nonreacting sites is particularly important in generating the kinetic bias.

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