Asymmetric Transfer Hydrogenation Catalyzed by Chiral Ruthenium Complexes

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Introduction

Asymmetric reduction of C═O and C═N bonds forming chiral alcohols and amines, respectively, is among the most fundamental molecular transformations.[1] In nature, oxidoreductases such as horse liver alcohol dehydrogenase catalyze transfer hydrogenation of carbonyl compounds to alcohols using cofactors like NADH or NADPH.[2] Such biochemical reactions are normally very stereoselective. However, organic synthesis needs economically and technically more beneficial methods that are very general. A reaction using nonhazardous organic molecules (eq 1)

X = O, NR
DH_2 = hydrogen donor

provides a useful complement to catalytic reduction using molecular hydrogen, particularly for small- to medium-scale reactions. Transfer hydrogenation is operationally simple, and the selectivities including functional group differentiation may be different from those of hydrogenation. Unfortunately, catalytic asymmetric transfer hydrogenation has remained quite primitive.[3] It is only during recent years that some successful examples have been reported for the reduction of some activated olefins using alcohols or formic acid as the hydrogen source.[4] Historically, many scientists attempted the asymmetric Meerwein−Ponndorf−Verley reaction of ketone substrates without any great success.[5] Notable exceptions are the enantioselective reductions using 2-propanol accomplished with some transition metal and lanthanoid complexes, where pioneering efforts were made by Pfaltz (Ir),[6] Genêt (Ru),[7] Lemaire (Rh),[8] and Evans (Sm)[9] among others.[3,10] However, these processes can still be improved for practical use in organic synthesis, being limited by low catalytic activity, insufficient enantioselectivity, low substrate/catalyst molar ratio (S/C), or narrow scope.

In the reaction of eq 1 catalyzed by a metallic species, M, the stereo-determining hydrogen transfer takes place either from MDH or by way of the metal hydride, MH, formed by elimination of DH, depending on the nature of the metal catalyst and hydrogen donor. Main group elements can promote reaction of MDH,[11] whereas transition metal complexes prefer the hydride mechanism.[10a,12]

Asymmetric Transfer Hydrogenation of Ketones in 2-Propanol

2-Propanol is the conventional hydrogen source having favorable properties; it is stable, easy to handle (bp 82 °C), nontoxic, environmentally friendly, and inexpensive and dissolves many organic compounds.[13] The acetone product is readily removable.[3] The excellent catalytic performance of amine-based transition metal complexes[6,8,14] as well as the effectiveness of certain C_2 symmetrical ligands in chiral recognition[1,15] prompted us to develop new chiral Ru(II) complexes with well-shaped C_2-chiral ligands. To this end, we first prepared Ru complexes having a tet-

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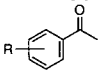
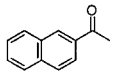
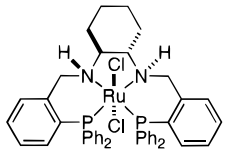
Table 1. Asymmetric Transfer Hydrogenation of Aromatic Ketones[a]

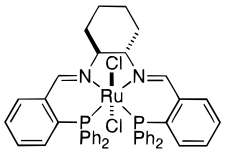
substrate	hydrogen donor and catalyst: $(CH_3)_2CHOH$ (*S,S*)-**1**[16]	$(CH_3)_2CHOH$ **4** + **6b** or **8**[20]	$(CH_3)_2CHOH$ (*S,S*)-**9a**[22]	HCO_2H (*S,S*)-**9a**[28]
				
R = H	93 (*R*, 93)	94 (*S*, 92)	95 (*S*, 97)	>99 (*S*, 98)
R = C_2H_5	78 (*R*, 96)	95 (*S*, 82)	94 (*S*, 97)	96 (*S*, 97)
R = $CH(CH_3)_2$		93 (*S*, 5)	22 (*S*, 84)[b]	41 (*S*, 83)[b]
R = $C(CH_3)_3$		22 (*R*, 40)	<1[b]	<1
				
R = *o*-Cl		99 (*S*, 89)	95 (*S*, 91)	
R = *m*-Cl	99 (*R*, 94)		98 (*S*, 98)	>99 (*S*, 97)
R = *p*-Cl	95 (*R*, 94)		95 (*S*, 93)	>99 (*S*, 95)
R = *p*-F	97 (*R*, 80)			
R = *o*-OCH_3		91 (*S*, 78)	24 (*S*, 89)	
R = *m*-OCH_3	74 (*R*, 93)		96 (*S*, 96)	>99 (*S*, 98)
R = *p*-OCH_3	67 (*R*, 58)	73 (*S*, 79)	53 (*S*, 72)	>99 (*S*, 97)
R = *p*-NO_2				100 (*S*, 86)
R = *p*-CN	99 (*R*, 94)			>99 (*S*, 90)
R = *o*-CH_3		96 (*S*, 83)	53 (*S*, 91)	
				
R = CH_2			45 (*S*, 91)	>99 (*S*, 99)
R = $(CH_2)_2$		62(*S*, 94)	65 (*S*, 97)	>99 (*S*, 99)
		99(*S*, 93)	92 (*S*, 93)	93 (*S*, 83)
			93 (*S*, 98)	>99 (*S*, 96)

[a] % yield (configuration, % ee). [b] Reaction at 40 °C.

radentate diphosphine/diamine ligand, **1**, or a diphosphine/diimine ligand, **2**.[16] The catalytic reduction of

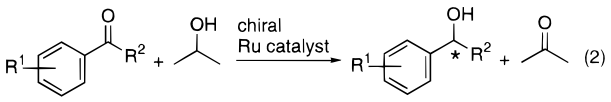


(*S,S*)-**1**



(*S,S*)-**2**

acetophenone derivatives proceeds from room temperature to 45 °C with an S/C of 200 using a 0.1 M solution in 2-propanol containing the Ru complex **1** and a molar equivalent of $(CH_3)_2CHOK$ as cocatalyst. Various substituted 1-phenylethanols are obtainable by this method in high yields and with up to 97% ee (eq 2). Some examples



(2)

are given in Table 1. The rate and enantioselectivity are sensitive to the steric crowding of the substrates[17] as well as the electronic properties of the ring substituents. The transfer hydrogenation is reversible, because 2-propanol and the products are secondary alcohols. The reduction of acetophenone with (*S,S*)-**1** appears to occur with excellent enantioface differentiation, $k_{Si}/k_{Re} \approx 100$. Although (*S,S*)-**1** catalyzes dehydrogenation of (*R*)-1-phenylethanol ca. 100 times faster than that of the *S* enantiomer, fortunately, this reverse process is much slower than the forward reaction, giving an excellent level of enantioselectivity. Thus the reaction, at least for those substrates which have a high oxidation potential,[18] is basically under kinetic control.

The diphosphine/diamine ligand in complex **1** has soft phosphine and hard nitrogen ligands as well as the NH functions. The diphosphine/diimine-based complex **2** has similar structural parameters as confirmed by X-ray crystallographic analysis.[16] However, because of the lack of an NH function, it is much less effective. For example, reaction of acetophenone in a 0.1 M 2-propanol solution containing (*S,S*)-**2** and $(CH_3)_2CHOK$ (S/C = 200, 23 °C, 48 h) gave the (*R*)-alcohol in only 3% yield and in 18% ee.

We have also been interested in developing nonphosphine-based chiral Ru catalysts because of the higher structural permutability. We paid particular attention to arene ligands,[19] because (1) the spectator ligands automatically occupy three adjacent coordination sites of Ru in an octahedral coordination environment, leaving three sites with a *fac* relationship for other functions, (2) arene ligands that are relatively weak electron donors may provide a unique reactivity on the metallic center, and (3) the substitution pattern on the ring is flexible. In this context, we first tested the ligand acceleration effects on the reaction of acetophenone in 2-propanol containing $[RuCl_2(\eta^6\text{-benzene})]_2$ (**3**) and KOH.[20] Although the Ru−KOH system was almost inert to the reduction at room temperature, various non-phosphine, hard additives were found to accelerate the transfer hydrogenation. The observed initial turnover frequency (TOF, moles of 1-phenylethanol per mole of Ru per hour; initial 20-min period at 28 °C) is given in Figure 1. The screening experiments revealed that simple ethanolamine (but not ethylenediamine[17] or ethylene glycol) displayed the highest rate enhancement (TOF of 227 per hour), giving 1-phenylethanol in 45% yield after 1 h at 28 °C or in 93% yield after 5 h at the same temperature. Without ethanolamine, the reaction at 28 °C gave the alcohol in only 1% yield. The highest TOF, up to 4700 per hour, was obtained with a higher S/C at 80 °C.

The marked rate enhancement with ethanolamine naturally led to the use of chiral β-amino alcohols for asymmetric catalysis.[20] 2-Amino-1,2-diphenylethanols **5** and **6**, ephedrine (**7**), and ψ-ephedrine (**8**) have been tested. The chiral Ru complexes were prepared *in situ* by heating a mixture of $[RuCl_2(\eta^6\text{-arene})]_2$ and β-amino alcohols with a *threo* or *erythro* relative configuration and different nitrogen-substitution patterns. A model reaction using acetophenone (eq 2; $R^1 = H$, $R^2 = CH_3$) indicated that various structural parameters including the alkyl substituents on the arene ligands markedly, but not straightforwardly, affect the rate of the reaction and the

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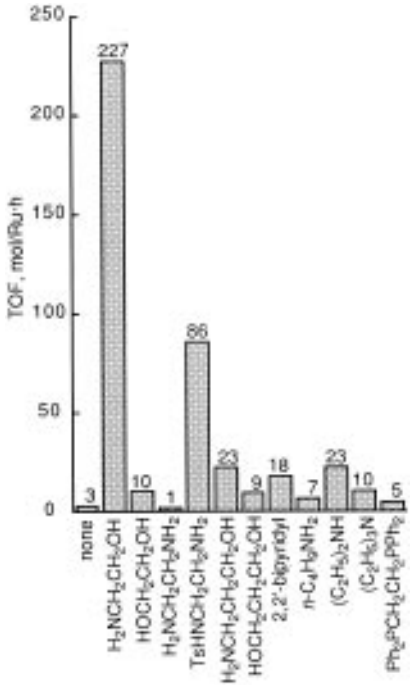
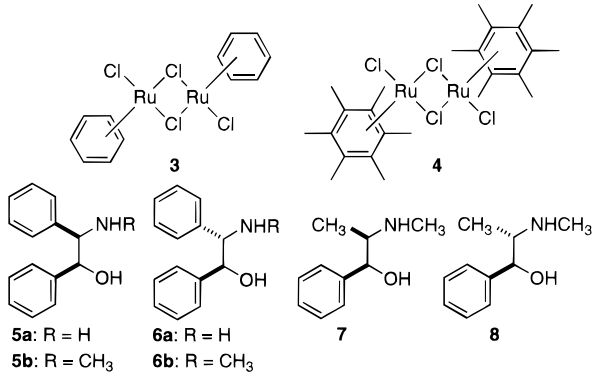
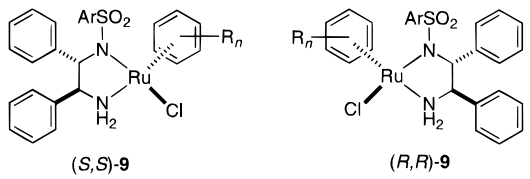


FIGURE 1. Ligand acceleration effects on transfer hydrogenation of acetophenone in a 0.1 M 2-propanol solution containing [$RuCl_2(\eta^6$-benzene)]$_2$ (3) and KOH (acetophenone:Ru:KOH:ligand = 200:1:2:5, 28 °C).



extent of the enantioselectivity. High enantioselectivity was obtained only when an appropriate arene and chiral amino alcohol auxiliary were combined. Most notably, the presence of a primary or secondary amine end in the amino alcohols is crucial for the catalytic activity; the dimethylamino analogues are totally ineffective. Thus, the combined system consisting of [$RuCl_2(\eta^6$-hexamethylbenzene)]$_2$ (**4**) and **6b** gave (*S*)-1-phenylethanol in 92% ee and in 94% yield after 1 h of reaction at 28 °C. The second column of Table 1 lists examples of the asymmetric transfer hydrogenation using **4** and a chiral amino alcohol, **6b** or **8**. Reactions of alkyl phenyl ketones having a bulky alkyl substituent occur sluggishly. As the bulkiness increases, the ee is lowered and finally the sense is reversed with pivalophenone. 1-Naphthyl-1-ethanol, 1-tetralol, and 1-cyclohexylethanol were obtained in fair to high ee from the corresponding ketones by the use of **4** and an amino alcohol. In most cases, this reaction is reversible. Therefore, prolonged exposure of the product to the catalyst is detrimental to the asymmetric reaction.

Figure 1 indicates that N-tosylated ethylenediamine is also an excellent accelerator of the Ru catalyzed transfer hydrogenation of eq 2. In fact, we have found that a chiral Ru complex formulated as **9**[21] acts as an efficient catalyst



a: Ar = 4-$CH_3C_6H_4$; η^6-arene = mesitylene
b: Ar = 4-$CH_3C_6H_4$; η^6-arene = *p*-cymene
c: Ar = 4-$CH_3C_6H_4$; η^6-arene = benzene
d: Ar =2,4,6-$(CH_3)_3C_6H_2$; η^6-arene = *p*-cymene
e: Ar =2,4,6-$(CH_3)_3C_6H_2$; η^6-arene = benzene
f: Ar =1-naphthyl; η^6-arene = benzene

for asymmetric transfer hydrogenation of aromatic ketones in 2-propanol.[22] The third column of Table 1 illustrates some examples of the reduction performed in a 0.1 M 2-propanol solution containing (*S,S*)-**9a** and KOH (ketone:Ru:KOH = 200:1:2). The reaction at 28 °C is normally completed within 3 h. Separate experiments suggested that the (*S,S*)-**9a**-catalyzed reaction of acetophenone proceeds with an excellent enantioface differentiation, $k_{Re}/k_{Si} = 99$, and that the resulting (*S*)-alcohol is more susceptible to the reverse reaction by a factor of 99. Because of the occurrence of the reverse process, the level of enantioselection decreases with increasing conversion of the ketone.

Thus, an inherent problem of these potentially useful asymmetric catalyses is the reversibility of the reaction. The overall efficiency is strongly affected by the structures of the ketone substrates and the properties of the hydrogen donors as well as the reaction conditions. The equilibrium point is determined by the redox potentials of the hydrogen donors and acceptors present in the reaction system. Therefore, as seen from Table 1, *p*-methoxyacetophenone and 2,3-benzo-2-cycloalkenones which have low oxidation potentials[18,24] remain difficult to reduce with a high yield and satisfactory enantioselection. Even if the reduction proceeds with excellent kinetic enantioface differentiation, the reverse reaction frequently deteriorates the enantiomeric purity of the alcoholic products. Furthermore, the reverse process prevents complete conversion. In order to minimize the unfavorable reaction in 2-propanol, the reaction of acetophenone, for instance, must be performed with a substrate concentration as low as 0.1 M, because the calculated 1-phenylethanol:acetophenone equilibrium ratio in a 0.1, 1.0, 2.0, and 10 M 2-propanol solution decreases from 98:2 to 80:20, 70:30, and 37:63, respectively.[3d,18] Therefore, an unnecessarily long exposure of the reaction mixture to the catalyst must be avoided. The equilibrium point can be shifted by removing acetone, but this is technically difficult.

(21) The ligation of the *S,S*-configurated nitrogen ligand induces the *R* configuration at the Ru center.[22,23]

(22) Hashiguchi, S.; Fujii, A.; Takehara, J.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 7562−7563.
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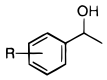
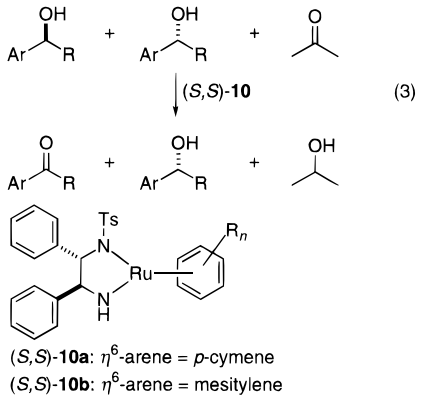
Table 2. Kinetic Resolution of Secondary Alcohols with (*S,S*)-10[a]

substrate	catalyst	time, h	unreacted alcohol: recovery, %	% ee	config.	k_f/k_s
						
R = H	**10a**	36	50	92	*R*	>80
R = *p*-OCH_3	**10a**	22	47	92	*R*	>30
R = *p*-$N(CH_3)_2$	**10b**	30	44	98	*R*	>30
						
R = CH_2	**10a**	6	47	97	*R*	>40
R = $(CH_2)_2$	**10a**	6	49	99	*R*	>50

[a] The reaction was carried out at 28 °C in a 2 M acetone solution of the substrate with S/C = 500. See ref 25.

Kinetic Resolution of Secondary Alcohols

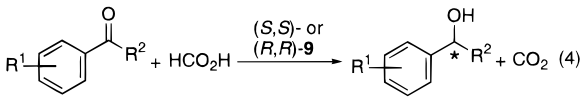
The reversibility of the reaction is the greatest flaw of the reduction using 2-propanol. However, this tendency in turn can be utilized for kinetic resolution of secondary alcohols via dehydrogenative oxidation (eq 3). In this



context, the preformed 16-electron Ru(II) diamide complex **10**[23] has proved to be an excellent catalyst. Thus, when a 2 M acetone solution of racemic 1-phenylethanol containing (*S,S*)-**10a** (S/C = 500) was allowed to stand at 28 °C for 36 h, the *S* enantiomer was consumed preferentially to recover the *R*-enriched alcohol in 50% yield and in 92% ee.[25] Various secondary alcohols, especially those with high reduction potentials are eligible for the asymmetric dehydrogenation. Some examples are listed in Table 2. This Ru-catalyzed asymmetric reaction using acetone as the hydrogen acceptor provides a chemical analogue of the biological oxidation of alcohols using alcohol dehydrogenase and NAD or NADP.[2]

Asymmetric Transfer Hydrogenation of Ketones Using Formic Acid

Formic acid is another well-behaving, inexpensive reducing agent.[26] The asymmetric reduction using this hydrogen donor, an adduct of H_2 and CO_2, in place of 2-propanol must proceed irreversibly with truly kinetic enantioselection and, in principle, 100% conversion. In fact the reaction with a 5:2 formic acid−triethylamine azeotropic mixture, bp 89 °C at 16 mmHg,[27] in the presence of the chiral Ru catalyst **9a** has provided a simple solution to this long-standing problem.[28] Although Ru(II) complexes generally catalyze the reversible process $HCO_2H \rightleftharpoons H_2 + CO_2$,[29] molecular hydrogen does not participate in the ketone reduction under these catalytic conditions. As summarized in Table 1 (the fourth column), many sterically uncongested aromatic ketones are reduced to the secondary alcohols with higher yield and ee as shown in eq 4.



Various acetophenone derivatives and acetonaphthones can be reduced with a high ee using an S/C ratio of 200−1000 and a 2 M or even 10 M solution at 28 °C. The reaction occurs rapidly at 60 °C with a slight decrease in ee. Triethylamine is necessary. The ketone reduction is best effected with a ratio of <2:1. This method solves the energetic problem of the reduction process, where an unfavorable thermodynamic balance is expected in 2-propanol. Enantioselectivity of the reduction using a 2 M solution of acetophenone is kept consistently high, *S*:*R* = 99:1, throughout the reaction until completion.

The reactivity and enantioface-differentiation ability of the Ru complex **9** are consequences of the compromise between the steric and electronic properties of the arene ligand and the chiral diamine auxiliary. The high efficiency is based not only on the chirality of the N-sulfonylated 1,2-diamine but also on the presence of the polar functional groups as well as the alkyl substituents on the arene ligands. The reactivity decreases in the order benzene > *p*-cymene and mesitylene > hexamethylbenzene. The $ArSO_2$ group in the diamine terminus is important for the reactivity; the complexes with the CF_3SO_2, C_6H_5CO, and CH_3CO analogues were much less reactive. The presence of an NH_2 terminus is crucial. The $NHCH_3$ analogue showed a comparable enantioselectivity but with much lower reactivity; the $N(CH_3)_2$ derivative gave very poor reactivity and stereoselectivity.

Using the preceding method, *p*-methoxyacetophenone, 1-indanone, and 1-tetralone with a low oxidation potential are reduced to the chiral alcohols in 97−99% ee. 2-Tetralol (**11**) was obtained in 82% ee. The ester-containing alcohols **12**−**14** are obtainable in a moderate to excellent optical yield. The formation of the β-hydroxy ester **13** by reduction using (*S,S*)-**9c** at 60 °C is to be noted. 2-Acetylfuran can be reduced cleanly to the alcohol **15** without saturating the furan ring. The oxacyclic alcohol **16** can be prepared in a like manner. The sulfur-containing ketones **17** are reduced with (*R,R*)-**9a** to the alcohols **18** in 98−99% ee, which serve as key intermediates for the

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(26) (a) Watanabe, Y.; Ohta, T.; Tsuji, Y. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 2441−2444. (b) Nakano, T.; Ando, J.; Ishii, Y.; Ogawa, M. *Tech. Rep. Kansai Univ.* **1987**, *29*, 69−76.
(27) (a) Wagner, K. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 50−54. (b) Narita, K.; Sekiya, M. *Chem. Pharm. Bull.* **1977**, *25*, 135−140.
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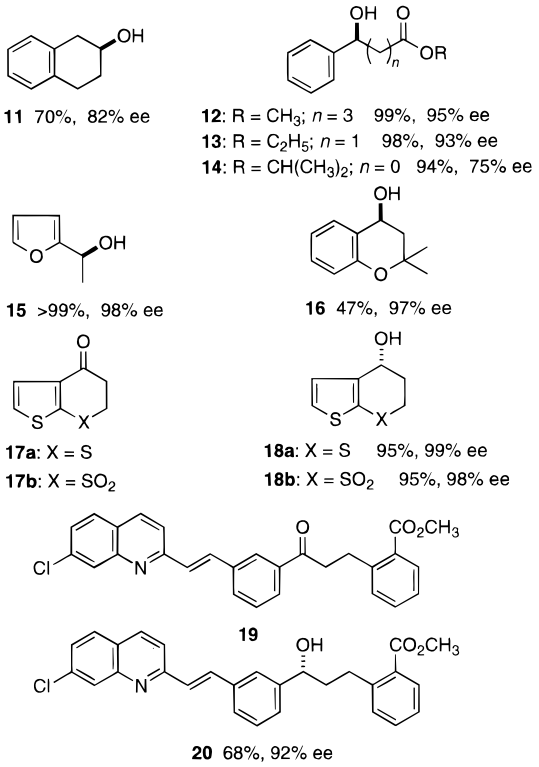
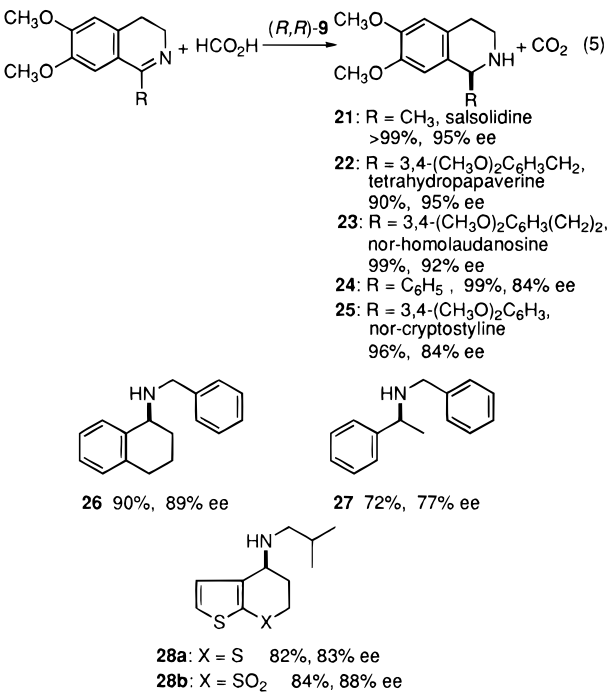
synthesis of MK-0417, a carbonic anhydrase inhibitor.[30] Reaction of the multifunctionalized ketone **19** catalyzed by (*R*,*R*)-**9a** gives the (*R*)-benzylic alcohol **20** in 92% ee, an intermediate for the synthesis of L-699,392 (a LTD_4 antagonist).[31]



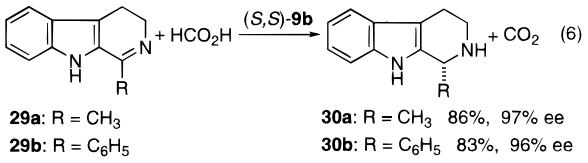
Thus, the reaction proceeds chemoselectively without affecting an olefinic linkage, ester, sulfide, sulfone, and nitro group, aryl chloride and cyanide, and furan, thiophene, and quinoline rings.

Asymmetric Transfer Hydrogenation of Imines

Asymmetric transfer hydrogenation of imines has remained undeveloped.[32−34] Now the arene−Ru(II) complexes of type **9** possessing some suitable chiral 1,2-diamine ancillaries efficiently catalyze asymmetric reduction of imines with a formic acid−triethylamine mixture (eq 5).[35] The reaction can be performed with a 5:2 formic acid−triethylamine mixture with an S/C ratio of 100−1000 at 28 °C in various polar solvents such as acetonitrile, DMF, DMSO, acetone, and dichloromethane. The same result was obtained when the reaction was done in an open vessel using a Ru complex *in situ* formed from $[RuCl_2(\eta^6\text{-arene})]_2$ and the N-sulfonylated diamine in the reaction media, without isolating the pure compound. Chiral amines obtained by this method are exemplified by **21**−**28**. This reaction is particularly useful for asymmetric reduction of cyclic imines, giving the amines **21**−**25** with 90−97% ee, to open a new, general route to natural and unnatural isoquinoline alkaloids. This method allows a convenient preparation of the chiral amines **28**, intermediates for the synthesis of MK-0417.[30]



Furthermore, this method can be extended to the synthesis of optically active indoles. The chiral amines **30** are accessible from the imines **29** as shown in eq 6.



The functional group selectivity of this catalyst system is noteworthy. The Ru catalyst **9b** does catalyze reduction of ketones in a formic acid−triethylamine mixture as described above, but imines are much more reactive than ketones. Thus, the imine **31** can be reduced even in acetone that contains formic acid, triethylamine, and **9b**. A competitive experiment using a mixture of **31** and the structurally similar ketone **32** revealed that the ketimine is >1000 times more reactive than the ketone. α-Methylstyrene (**33**) is inactive under the standard conditions.

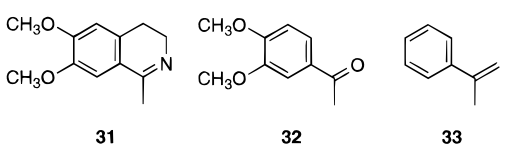


Figure 2 illustrates the general sense of asymmetric

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(34) Reviews on asymmetric reduction of imines: (a) Johansson, A. *Contemp. Org. Synth.* **1995**, 393−407. (b) James, B. R. *Chem. Ind.* (*Dekker*) **1995**, *62*, 167−180.

(35) Uematsu, N.; Fujii, A.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 4916−4917.

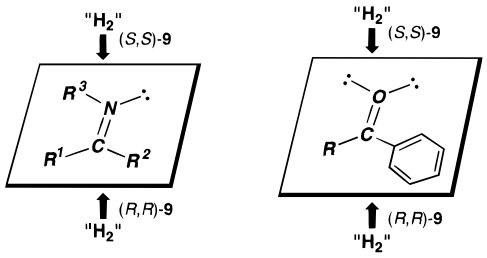
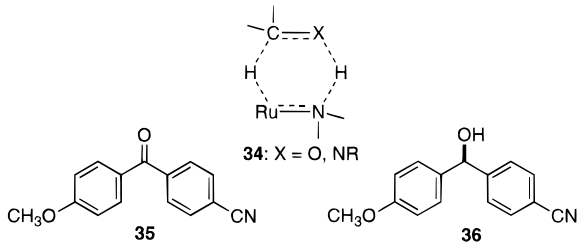


FIGURE 2. General sense of asymmetric transfer hydrogenation catalyzed by the Ru complex 9.

induction in transfer hydrogenation of imines, which is compared with that observed with aromatic ketones.

Perspective

The discovery of these reactive chiral Ru complex catalysts has allowed us to achieve highly efficient asymmetric transfer hydrogenation of ketones and imines. We are confident that such asymmetric catalysis provides a viable tool in organic synthesis together with catalytic hydrogenation[17,36] and stoichiometric and catalytic metal hydride reduction.[37] The transfer hydrogenation using 2-propanol or formic acid as the hydrogen source would proceed via reactive ruthenium hydride intermediates formed by elimination of acetone[23] or carbon dioxide, respectively.[3] The chiral elements on the Ru(II) center which control the stereochemical outcome are either phosphines or nonphosphines. The presence of an NH moiety in the ligands is crucially important throughout the three catalyst systems described above.[38] Hydride transfer from a ruthenium hydride species to a ketone or imine requires an out-of-plane interaction between the Ru−H moiety and the C═X bond (X = O, NR). We think that this hydrogen transfer occurs via metal−ligand bifunctional catalysis[23] and that the NH linkage can stabilize a transition state by forming a hydrogen bond with the X atom. The six-membered cyclic transition structure is schematically visualized by **34**. The steric course of the imine reduction (Figure 2) is determined by formal discrimination of the enantiofaces of the sp^2 nitrogen atom by this mechanism, while the enantiomeric bias in the ketone reduction could result from steric and electronic differentiation of the two nonbonding electron pairs of the carbonyl oxygen.[39] Consistent with this view, reaction of the benzophenone derivative **35** in a formic acid−triethylamine mixture containing (*S*,*S*)-**9a** gave the (*S*)-alcohol **36** in 66% ee.[28]



As a consequence of microscopic reversibility, the same transition state **34** (X = O) intervenes in the kinetic resolution of chiral secondary alcohols.[25] Thus, suitable molecular architecture of chiral transition metal complexes, coupled with appropriate selection of reaction conditions, leads to successful ketone and imine asymmetric reduction displaying a wide scope.

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(38) Various aprotic sp^2 nitrogen ligands have also been used for asymmetric transfer hydrogenation using 2-propanol.[6,10b,14]

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