Asymmetric Transfer Hydrogenation of Ketones with Bifunctional Transition Metal-Based Molecular Catalysts†

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ABSTRACT

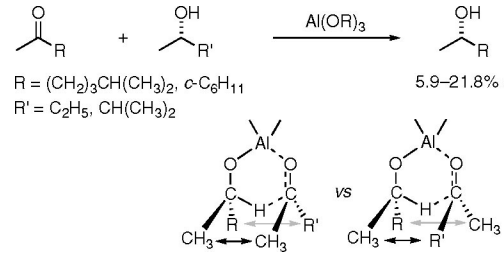
Recent development of conceptually new chiral bifunctional transition metal based catalysts for asymmetric reductive transformations is described. The chiral bifunctional molecular catalyst promoted reduction is now realized to be a powerful tool to access chiral compounds in organic synthetic procedures in both academia and industry. Based on structural investigation of the actual catalyst and its intermediates and a deep understanding of the reaction mechanism, this asymmetric reduction system can be widely used to produce valuable chiral alcohols and is now is applicable to commercial scale production.

Introduction

Asymmetric transfer hydrogenation of ketones and imines with chiral molecular catalysts is now realized to be one of the most powerful, practical, and versatile tools to access chiral alcohols and amines in organic synthesis because of its excellent selectivity, operationally simplicity, and wide substrate scope.[1] The selectivity in terms of stereo-, chemo-, and regioslectivity are often different from well-established asymmetric hydrogenation systems; therefore, asymmetric transfer hydrogenation may complement sophisticated asymmetric hydrogenation and other practical reduction systems.

The first report of a catalytic asymmetric transfer hydrogenation was by Doering and Young[2] who demonstrated an asymmetric version of the Meerwein–Ponndorf–Verley (MPV) reduction of ketones using a chiral alcohol, (*S*)-2-butanol or (*S*)-3-methyl-2-butanol, in the presence of *rac*-aluminum alkoxides giving chiral alcohols with 5.9–22% ee. Although the degree of enantioselection was not practically meaningful, these results strongly suggested that the hydrogen transfer proceeds through a six-membered transition state as shown in Scheme 1. Since then, there have been many chiral catalyst systems for the asymmetric reduction of ketones; however, notable successes have been limited to some transition metal and lanthanoid complexes reported by Pfalz for an Ir system, Genêt for a Ru system, Lemaire for a Rh complex, and Evans for a Sm system.[1a] In addition, Shvo and co-workers successfully developed the elegant and effective cyclopentadienyl ruthenium catalyst system for ketone reduction, in which hydrogen transfers in a concerted pathway.[3]

Scheme 1. Asymmetric Meerwein–Ponndorf–Verley Reduction



In 1995, Noyori and Ikariya and co-workers found a prototype of a conceptually new chiral Ru catalyst bearing N-sulfonylated 1,2-diamines and amino alcohols as chiral ligands for highly efficient asymmetric transfer hydrogenation of ketones and imines.[4] This finding inspired intense effort to extend the concept of the molecular catalyst and to explore new catalyst systems in academia and industry. In particular, Wills' tethered catalyst[5] and Carpentier, Wills, Andersson, and van Leeuwen's catalyst[6] with amino alcohol ligands are noteworthy catalyst systems because of their excellent catalytic performance. Detailed structural investigation on the real catalysts and a deep understanding of the mechanism of the hydrogen transfer revealed that excellent catalyst performance can be attributed to an amphiphilic property based on a metal/NH acid–base synergy in the active catalysts.[1a,e,7] Figure 1 lists some representative examples of well-defined bifunctional molecular catalysts. The reductive transformation with the bifunctional catalyst is characterized by high efficiency, a wide applicability, and practicality, which enables the catalyst system to develop successively into more general concepts for asymmetric molecular transformation.[1e] In this Account, we focus mainly on our recent progress in asymmetric transfer hydrogenation of functionalized ketones with bifunctional molecular catalysts based on ruthenium, rhodium, and iridium complexes bearing chiral diamine ligands as well as its commercial applications.[1f]

Takao Ikariya completed his Ph.D. degree in 1976 at 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 NKK corp. In 1991, he joined in the ERATO Molecular Catalysis Project of Japan Science and Technology Corporation, directed by Professor Ryoji Noyori. Ikariya was promoted to professor at Tokyo Institute of Technology in 1997.

John Blacker received his B.Sc. from the University of Sheffield 1984 in Biochemistry and Chemistry, then moved to Université Louis Pasteur, Strasbourg, to complete a DEA in Organic Chemistry and Ph.D. with Prof. Jean-Marie Lehn. Following postdoctoral studies with Prof. Alan Fersht in Cambridge; in 1990, he joined a part of ICI that is now NPIL Pharma and is now Technology Director responsible for chiral technology, process development, and commercial application.

† Dedicated to the late Professor Yoshihiko Ito.

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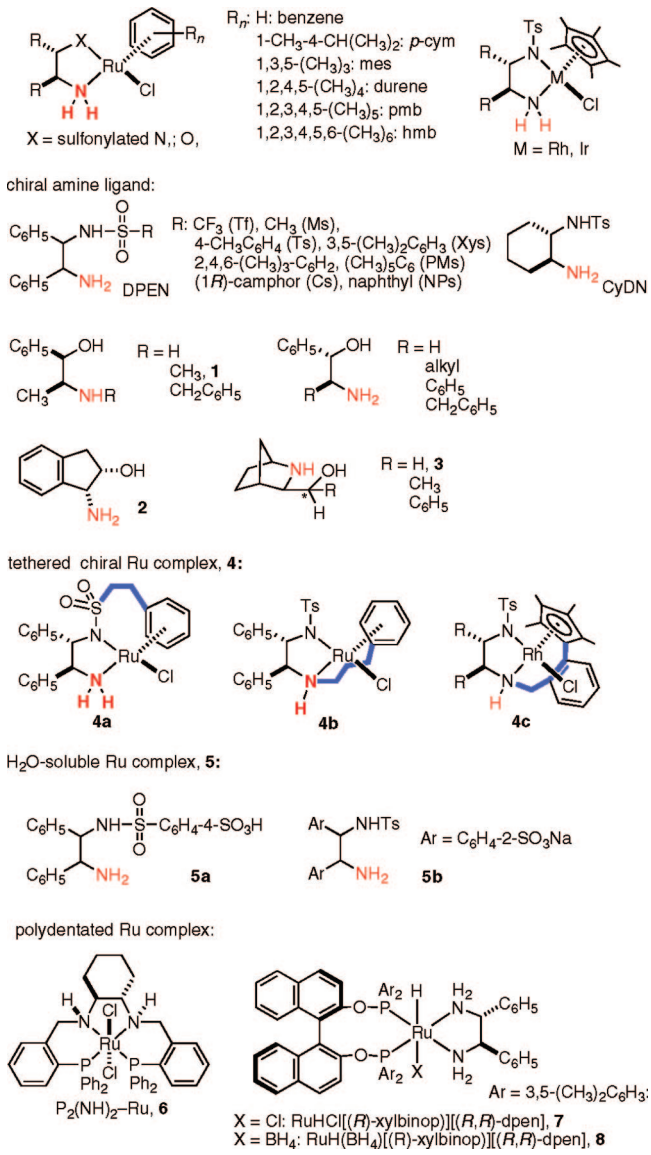
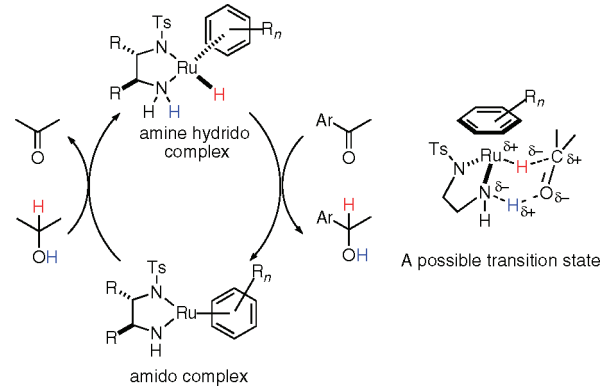


FIGURE 1. A prototype and representative modified bifunctional chiral Ru, Rh, and Ir complexes.

The Unique Mechanism of Hydrogen Transfer with Bifunctional Catalysts

Based on detailed structural analysis of the real catalyst and catalyst intermediate, both in the solid state and in solution, the real active catalyst, an amido Ru complex, has a 16-electron square-planar geometry, which has an intermediate bond length between the single and triple bond for the Ru–N bond.[8] Thanks to the nature of Ru–N bond, the amido Ru complex readily dehydrogenates 2-propanol to produce an amine hydrido Ru complex as a single diastereomer (Scheme 2). The resulting amine hydrido Ru complex has a coordinatively saturated octahedral configuration around the Ru center with a δ-configured five-membered N–N chelate ring. The NH unit bound to metal center exhibits a sufficiently acidic character to activate ketones. These unique structures of the real catalysts are responsible for the bifunctional molecular catalysis. During the interconversion of the amido and amine hydrido Ru complexes, the hydrogen

Scheme 2. Interconversion of the Amido and the Amine Hydrido Ru Complex via a Possible Six-Membered Transition State.



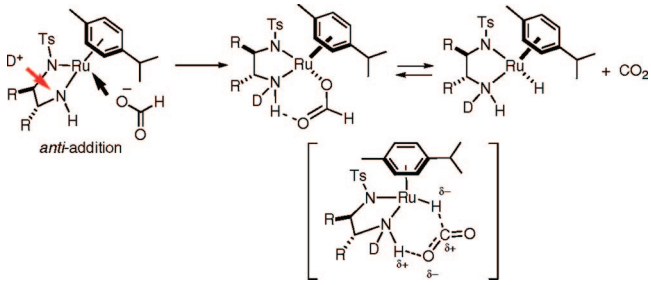
transfer between alcohols and carbonyl compounds occurs reversibly.

Ketone transfer hydrogenation with this system is characterized by an unprecedented unique reaction mechanism, which is different from the concerted mechanism for the aluminum alkoxide mediated MPV reduction,[2,9] and the conventional insertion mechanism with transition-metal hydride species generated from the alkoxide complexes.[1a] Careful kinetic studies and isotope labeling experiments,[8,10b] as well as computational analysis,[11] have confirmed that the bifunctional-catalyst-promoted hydrogen transfer between alcohols and ketones occurs reversibly through a six-membered pericyclic transition state.[7,12] The NH unit forms a hydrogen bond with the carbonyl oxygen atom to stabilize the transition state. Therefore, the presence of an NH moiety in the ligands is crucially important to determine the catalytic performance of the bifunctional catalysts.[4,7] An important and unprecedented aspect is that the carbonyl compound does not interact directly with the metal center for its own activation. A similar mechanism for the proton and hydride transfer to the ketone is proposed in Shvo's catalyst, $[2,3,4,5\text{-}(C_6H_5)_4(\eta^5\text{-}C_4COH)]RuH(CO)_2$, mediated transfer hydrogenation of ketones.[3,10a,13,14]

2-Propanol and formic acid can be used as very cheap hydrogen sources. 2-propanol is a particularly safe, nontoxic, and 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,[1a,b] an inherent drawback of the reaction is the reversibility, leading to limited conversion that is determined by thermodynamic factors of the system. As a result of the reversibility, there is a serious decrease in the enantiomeric purity of the products upon long exposure of the reaction mixture to the catalyst.[4e] Thus, the overall efficiency of the forward reaction is strongly dependent on the structures of the ketonic substrates and redox properties of product alcohols.

On the other hand, the use of formic acid, a formal adduct of H_2 and CO_2, for asymmetric reduction can overcome the drawbacks of the reaction in 2-propanol, leading to irreversible kinetic enantioselective transfer hydrogenation with, in principle, 100% conversion.[4d] In contrast to the concerted process with 2-propanol, the

Scheme 3. A Possible Mechanism for the Reaction of the Amido Ru with Formic Acid



reaction of HCO_2H with the amide complex proceeds in a stepwise manner via a deprotonation of formic acid followed by formation of an ion pair intermediate, leading to the kinetically favorable formate complex (Scheme 3).[15] The resulting formate complex gives rise to the amine hydrido Ru complex through the decarboxylation of the intermediate. Notably, this hydrido Ru complex rapidly reacts with CO_2 to regenerate the formate complex and efficiently catalyzes the hydrogenation of CO_2 to give formic acid, in which the CO_2 molecule can be activated by the M/NH bifunctional moiety, as observed in the ketone reduction (Scheme 3).[4] On account of the reversibility, the CO_2 generated in the asymmetric reduction with formic acid should be effectively removed from the catalyst system.

Asymmetric Transfer Hydrogenation of Simple Aromatic Ketones with the Bifunctional Catalysts

The concept of the bifunctional catalyst developed for the chiral η^6-arene-Ru complexes, RuCl(Tsdpen)(η^6-arene), has been successfully extended to chiral η^5-pentamethylcyclopentadienyl-Ru,[16] Rh, and Ir complexes, Cp*MCl(Tsdpen) (Tsdpen: *N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine, Cp* = η^5-$C(CH_3)_5$, M = Rh, Ir; Figure 1),[17] which have a structure isoelectric to the arene-Ru complex. These complexes serve as highly efficient catalysts for asymmetric transfer hydrogenation of simple alkyl aryl ketones.[1a,e] Table 1 summarizes some examples of the bifunctional catalysts for asymmetric reduction of acetophenone.[18] 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.[1e]

The reactivity and enantioface selectivity of the chiral Ru complex, RuCl(N-tosylated diamine)(η^6-arene), are the consequences of 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. Although a wide range of N-sulfonylated diamines has been examined for the asymmetric reduction, only a small change in the enantioselectivity of the reaction is observed. In general, the $ArSO_2$ group in the diamine is important for attaining high reactivity.

It is noteworthy that the ligand modification by linking the amine ligand to the arene or cyclopentadienyl (Cp) ligands (Figure 1) causes a drastic change in the catalyst performance; in particular, the reactivity is significantly improved possibly due to an increase in the stability of the three leg piano stool structured Ru hydride complex.[5]

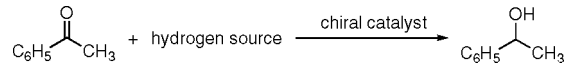
Asymmetric Transfer Hydrogenation of Functionalized Aromatic Ketones with Bifunctional Catalysts

Among the notable features of this asymmetric transfer hydrogenation with bifunctional catalysts is the carbonyl group selectivity. As a result of the coordinatively saturated nature of the amine hydrido Ru complex (Scheme 2), the reaction proceeds chemoselectively without the interference of amino, ester, hydroxyl, carbonyl, sulfido, sulfone, nitro, azide, and chloride groups, neither furan, thiophene, and quinoline rings, nor the olefinic linkage. For example, a reaction of the keto esters with a mixture of HCO_2H/$N(C_2H_5)_3$ containing Ru-Tsdpen complexes gives the corresponding chiral alcohols with moderate to excellent ee's (Scheme 4).[1a,19] Benzoylacetate esters and β-keto esters bearing phenyl substitutents are also efficiently reduced with 2-propanol containing chiral Ru complexes having a chiral β-amino alcohol, (1*S*,2*R*)-ephedrine, to give chiral alcohols with up to 94% ee. β-(3,4-Dimethoxyphenyl)serine methyl ester is obtainable in high diastereomeric and enantiomeric excesses from similar stereoselective transfer hydrogenation of β-keto-α-methylamino acid ester with a mixture of $HCO_2H/N(C_2H_5)_3$ and chiral arene-Ru catalysts bearing an *N*-perfluorosulfonyl-1,2-diamine ligand.[20] Notably, 2-acylbenzoates are successfully reduced by an isolable Ru-Tsdpen amide complexes to chiral phthalides with up to 97% ee, which are intermediates of several alkaloids (Scheme 5).[1c]

Asymmetric reduction of 1,2-diketones, for example, benzils, is noteworthy since these are not easily reduced by the currently available hydrogenation catalysts, Ru-BINAP complexes, Ru_2Cl_4[(*R*)-tolbinap]$_2$·$(C_2H_5NH_2)$,[21] $RuCl_2$[(*R*)-binap][(*R*,*R*)-dpen].[7] Asymmetric reduction of 1,2-diaryldiketones with the chiral Ru-*p*-cymene complex in a mixture of $HCO_2H/N(C_2H_5)_3$ gives the chiral 1,2-diols with an excellent ee (Scheme 6).[22]

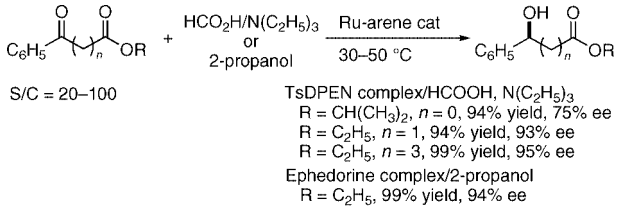
The outcome of the asymmetric reduction of benzils relies strongly on the property of the benzoin intermediates as well as the enantiomeric discrimination of the chiral Ru complex. A reaction of racemic benzoin with the (*S*,*S*)-Ru catalyst gives (*R*,*R*)-diol with >99% ee at the early stage of the reaction (4% yield), while after 24 h, a chiral diol with the same de's and ee's as observed at the initial stage of the reaction is quantitatively obtainable, indicating that the reaction proceeds through a dynamic kinetic resolution (DKR) of the intermediary benzoin (Scheme 7).[22b] Thus, the asymmetric reduction of 1,2-diketones with the chiral bifunctional Ru catalyst is characterized by high practicability and high selectivity. Enantiomerically pure (*R*,*R*)-hydrobenzoin is obtainable on a 100 g scale reaction by simple evaporation of triethylamine, washing with water, and crystallization from ethanol.

Table 1. Asymmetric Transfer Hydrogenation of Acetophenone with Bifunctional Catalysts

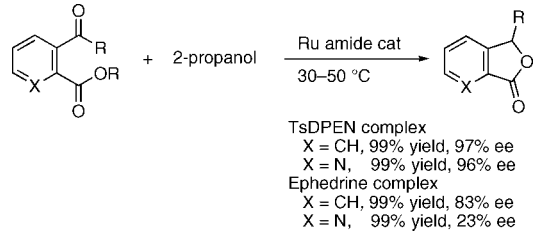


catalyst	hydrogen source	S/C	yield, %	% ee	ref
RuCl(Tsdpen)(mes)	$HCO_2H/N(C_2H_5)_3$	200	>99	98	4d
RuCl(Tsdpen)(*p*-cym)	$HCO_2H/N(C_2H_5)_3/H_2O$	1000	>99	96	34
RuCl(Tsdpen)(*p*-cym)	HCO_2Na/H_2O/CTAB	100	99	95	39a
RuCl(Csdpen)(*p*-cym)	HCO_2Na/H_2O	1000	95	96	40
Cp*RhCl(Csdpen)	HCO_2Na/H_2O	1000	89	99	40
Cp*IrCl(Csdpen)	HCO_2Na/H_2O	1000	97	98	40
tethered Ru, **4a**	$HCO_2H/N(C_2H_5)_3$	200	>99	96	5a
tethered Ru, **4b**	HCO_2Na/H_2O	200	100	96	5b
tethered Rh, **4c**	HCO_2Na/H_2O	200	100	98	5c
immobilized RuCl(Tsdpen)	$HCO_2H/N(C_2H_5)_3$	100	>99	97	36a
dentridic RuCl(Tsdpen)	$HCO_2H/N(C_2H_5)_3$		95	97	36c
H_2O-soluble RuCl(**5b**)(*p*-cym)	HCO_2Na/H_2O	200	>99	95	39b
RuCl(Tscydn)(*p*-cym)	HCO_2Na/H_2O	1000	99	85	38a
Cp*RhCl(Tscydn)	HCO_2Na/H_2O	1000	>99	95	38a
Cp*IrCl(Tscydn)	HCO_2Na/H_2O	1000	99	93	38a
RuCl(Tsdpen)(mes)/base	2-propanol	200	95	97	4a
$RuCl_2[P_2(NH)]_2$, (**6**)/base	2-propanol	200	93	97	4c
RuCl[(1R,2S)-**1**](hmb)/base	2-propanol	200	94	92	4b
RuCl(**3**)(*p*-cym)/base	2-propanol	200	92	94	6c
RuCl(**2**)(*p*-cym)/base	2-propanol	100	70	91	6b
tethered Ru, **4b**/base	2-propanol	200	>99	96	5a
Cp*RhCl(Tsdpen)/base	2-propanol	100	80	90	17b
Cp*RhCl(Tscydn)/base	2-propanol	200	85	97	17c
Cp*IrCl(Tscydn)/base	2-propanol	200	36	96	17c
H_2O-soluble RuCl(**5a**)(*p*-cym)	2-propanol	100	96	94	39c
RuHCl(xylbinop)(dpen), (**7**)/base	2-propanol	100	97	92	18a
$RuH(BH_4)$(xylbinop)(dpen), **8**	2-propanol	100	92	93	18b

Scheme 4. Asymmetric Reduction of Benzoylacetate Esters and *β*-Keto Esters

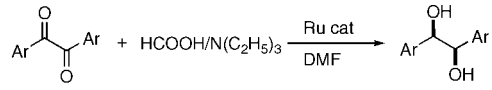


Scheme 5. Asymmetric Reduction of 2-Acylbenzoates to Chiral Phthalides



On the other hand, asymmetric reduction of unsymmetrically substituted 1,2-diketones with the chiral Ru catalyst gives a partly reduced chiral α-hydroxy ketone at lower temperature (10 °C), in which the reduction occurs at the less hindered carbonyl group of the diketone for steric reasons.[22c] At higher temperature (40 °C), full reduction of the diketones produces chiral *anti*-1,2-diols

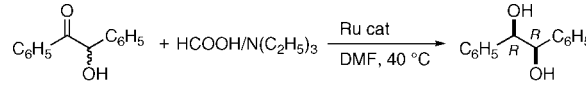
Scheme 6. Asymmetric Reduction of Benzils with Chiral Ru Catalysts



Ar	temp, °C	time, h	yield, %	*dl*:*meso*	ee, %
C_6H_5	40	24	100	98.4:1.6	>99
p-CH_3-C_6H_4	40	48	67	96.7:3.3	>99
p-CH_3O-C_6H_4[a]	35	48	75	94.4:5.6	>99
p-F-C_6H_4	40	24	100	94.2:5.8	>99

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

Scheme 7. DKR of *rac*-Benzoin with Chiral Ru Catalyst



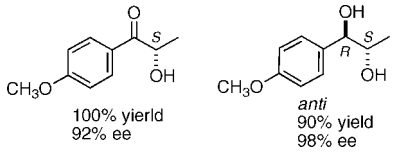
Ru cat = RuCl[(*S*,*S*)-Tsdpen](*p*-cymene)
S/C = 1000

time, h	yield, %	*dl*:*meso*	ee, %
0.25	4	98.2:1.8	100
24	100	98.1:1.9	100

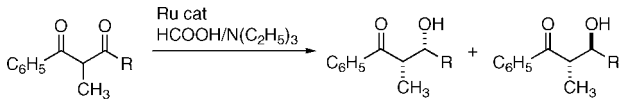
with an excellent ee. This method can be applied to access (1*R*,2*S*)-1-(4′-methoxyphenyl)-1,2-propanediol (98% ee), which is a major metabolite of *trans*-anethole in the rat (Scheme 8).

Similarly, asymmetric reduction of 2-methyl-1,3-diketones with the (*S*,*S*)-Ru catalyst proceeds smoothly via DKR of the ketones to give preferentially the *syn* isomers of chiral *β*-hydroxy ketones with a range of 88–98% ee (Scheme 9),[23] while the reaction of 1,3-diphenylpropane-1,3-dione produces the corresponding chiral diol with 99% ee and in 99% yield (*dl*/*meso* = 94:6). The reduction of

Scheme 8. Reduction Products of Unsymmetrically Substituted 1,2-Diketones



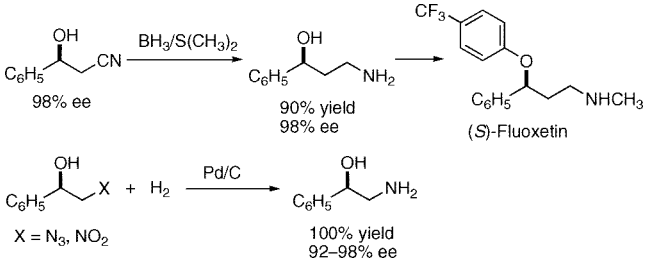
Scheme 9. Asymmetric Reduction of 2-Alkyl-1,3-diketones



R	yield, %	*syn*:*anti*	*syn*, % ee
CH_3	84	92:8	96
$(CH_2)_2NHBoc$	88	97:3	97

Ru cat = RuCl[(*S*,*S*)-Tsdpen](*p*-cymene), $HCOOH/N(C_2H_5)_3$ = 2:5, 50 °C

Scheme 10. Asymmetric Reduction of Acetophenones Bearing CN, N_3, and NO_2 Groups



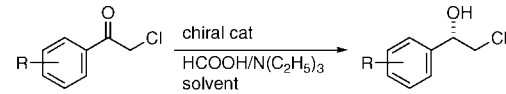
1,3-pentanedione gives no reduction product under the same conditions.[24,25]

Another valuable class of functionalized ketones is acetophenones bearing a functional group at the α-position. The reactions of acetophenones bearing CN, N_3, and NO_2 with a mixture of $HCO_2H/N(C_2H_5)_3$ containing the chiral Ru catalysts smoothly proceed to give the corresponding chiral alcohols with an excellent ee (Scheme 10).[24] These alcohols can be easily transformed by the conventional reduction of the functional groups to chiral β- and γ-amino alcohols with high ee.

α-Chlorinated acetophenones are also reducible with chiral bifunctional catalysts. Notably, a chiral Cp*Rh complex, Cp*RhCl[(*R*,*R*)-Tsdpen],[17c] is the most reactive catalyst for the asymmetric reduction of a variety of ring-substituted α-chloroacetophenones (Scheme 11).[26] The reduction with an azeotropic mixture of $HCO_2H/N(C_2H_5)_3$ and the Rh catalyst proceeds rapidly to give almost quantitatively the corresponding chiral alcohol with 96% ee and an initial turnover frequency (TOF) exceeding 2500 h^{-1} (0.7 s^{-1}). The use of a tethered Ru catalyst gives significant improvement in the reactivity; the reaction with a S/C = 200 gives the reduction product quantitatively with 95% ee after 1.5 h.[5d] Polymer-supported chiral Ru complexes also provide satisfactory results in terms of the selectivity and reactivity.[27]

Chiral 2-chlorophenylethanol is easily convertible to chiral styrene oxide with NaOH in water without loss of ee. A more appealing feature is that one-pot synthesis of chiral styrene oxide can be performed by sequential asymmetric reduction of chloroacetophenone with the

Scheme 11. Asymmetric Reduction of Ring-Substituted α-Chloroacetophenones with Chiral Catalysts



Cp*RhCl[(*R*,*R*)-Tsdpen]

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

S/C = 1000, 25 °C,
1.0 M $CH_3COOC_2H_5$ soln.

tethered Ru catalyst (4b)

R	yield, %	ee, %
H	100	95

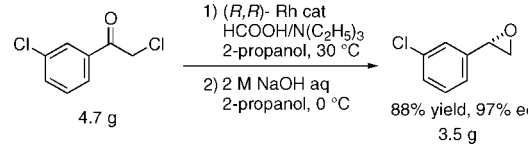
S/C = 200, 1.0 M ketone soln. 28 °C.

PS-supported Ru catalyst

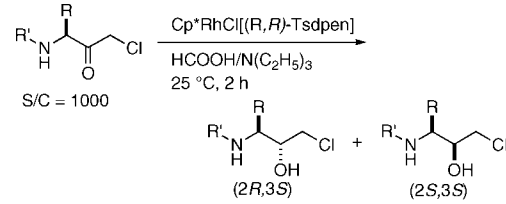
R	yield, %	ee, %
H	90	95.3

S/C = 100, DMF, 30 °C.

Scheme 12. One-Pot Procedure for Synthesis of Chiral Epoxide



Scheme 13. Asymmetric Reduction of Aminoalkyl Chloromethyl Ketones with (*R*,*R*)-Rh Catalyst

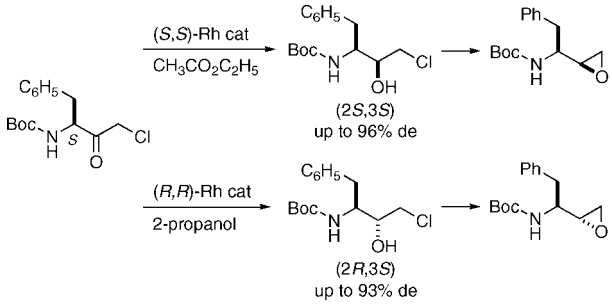


R = $C_6H_5CH_2$, $(CH_3)_2CHCH_2$, *p*-F-$C_6H_4CH_2$, 2-naphCH$_2$
R' = Boc, Cbz, Bz, Ts

chiral Rh in 2-propanol and treatment of its reaction mixture with NaOH aqueous solution, leading to the desired products in an isolated yield of 80–90% with 96–98% ee in a single reactor (Scheme 12). For example, (*S*)-*m*-chlorostyrene oxide, which is a key intermediate for the preparation of several β3-adrenergic receptor agonist compounds, is easily obtained from one-pot procedure.

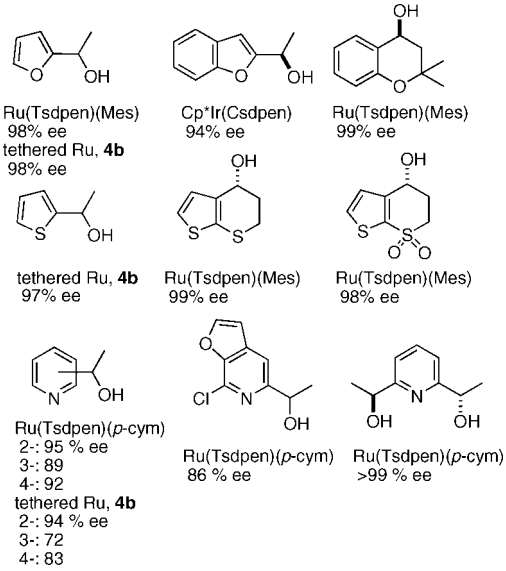
Asymmetric reduction of enantiomerically enriched aliphatic chlorinated ketones bearing another stereogenic center is also promising to provide access to valuable chiral alcohols (Scheme 13).[28] Even commercially available reagents and solvents can be used in this reaction without special purification. The chiral Rh complex catalyzed reduction of N-substituted (3*S*)-3-amino-1-chloro-4-phenyl-2-butanones gives the desired corresponding diastereomeric alcohols in excellent yields with high de's. With Cp*RhCl[(*S*,*S*)-Tsdpen] as a catalyst, the (2*S*,3*S*)-alcohol can be obtained with an excellent de, while the enantiomeric (*R*,*R*)-Rh catalyst gives rise to the (2*R*,3*S*)-alcohol (Scheme 14). A sequential asymmetric reduction of *N*-(*tert*-butoxycarbonyl)-(3*S*)-3-amino-1-chloro-4-phenyl-2-butanone with a mixture of $HCO_2H/N(C_2H_5)_3$ in 2-propanol

Scheme 14. One-Pot Synthesis of Chiral Epoxides



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 15. Asymmetric Reduction of Heteroaromatic Ketones with the Bifunctional Catalyst

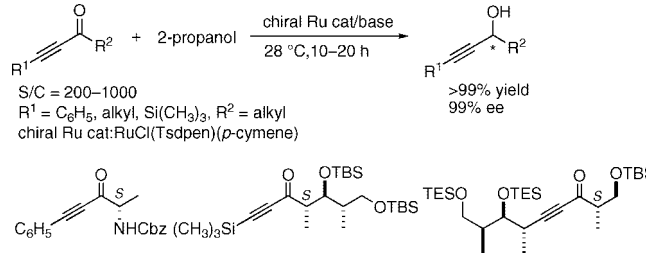


containing the (*S*,*S*)-Rh catalyst and treatment of the reaction mixture with 1 M NaOH aqueous solution at 0 °C give (2*S*,3*S*)-*N*-(*tert*-butoxycarbonyl)-3-amino-1,2-epoxy-4-phenylbutane with 90% de as crystals after the addition of water. These chiral epoxides serve as potential chiral building blocks for synthesis of pharmaceuticals such as inhibitors of HIV protease and β-secretase in Alzheimer's disease.[28]

Sulfur- or oxygen-containing ketones are also reducible with a mixture of formic acid and triethylamine containing chiral Ru catalyst to the corresponding chiral alcohols with 97–99% ee (Scheme 15).[1a] The resulting chiral alcohols are key intermediates for synthesis of MK-0417, a carbonic anhydrase inhibitor. In a similar manner, asymmetric reduction of acetylpyridine and its derivatives bearing an electron-withdrawing group at 10 °C gives chiral pyridylethanols in almost quantitative yield and with up to 92% ee (Scheme 15),[29] one of which is an intermediate of PNU-142721, a potent anti-HIV medicine. A tethered version of the Ru catalyst is also highly effective for asymmetric reduction of heteroaromatic ketones.[5d] The reaction of 2,6-diacetylpyridine with a mixture of $HCO_2H/N(C_2H_5)_3$ (8.6:5.2) gives a chiral diol with 99.6% ee in 91% yield.

α,β-Acetylenic ketones are also readily reducible to chiral propargylic alcohols with an excellent ee and in

Scheme 16. Asymmetric Reduction of α,β-Acetylenic Ketones



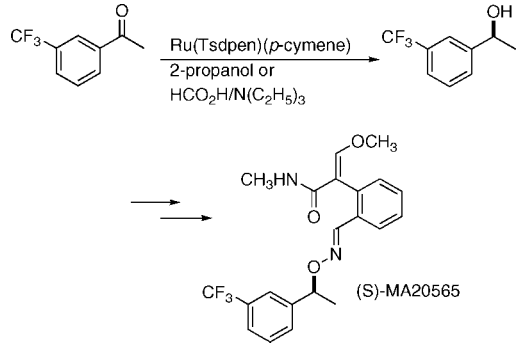
good yield (Scheme 16).[4f] Both aryl- and alkylethynyl ketones are reducible with 2-propanol containing the (*S*,*S*)-Ru catalyst. The precursor of the lower side chain unit of prostaglandins, (*S*)- or (*R*)-alcohol, $(CH_3)_3SiC{\equiv}CCH(n\text{-}C_5H_{11})OH$,[1a] can be prepared by this method. The asymmetric reduction of chiral acetylenic ketones with a preexisting stereogenic center leads to diastereomeric propargylic alcohols. Using (*R*,*R*)- or (*S*,*S*)-catalyst for the reduction of the (*S*)-ketone with 98% ee leads to (3*S*,4*S*)-alcohol in 97% yield and with >99% ee and (3*R*,4*S*)-isomer in 97% yield and with >99% ee, respectively (Scheme 16). In a similar manner, relatively complex ketones bearing chiral centers can be reduced with excellent diastereoselectivity.[30]

Catalytic Asymmetric Transfer Hydrogenation Used in Industry

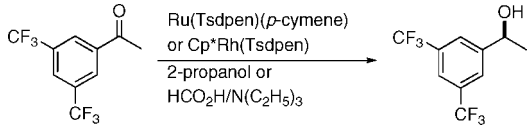
Catalytic asymmetric transfer hydrogenation is being increasingly used in industry because of its selectivity, efficiency, scope, simplicity, and economic viability.[1f] There are new developments in catalyst design, hydrogen donor, solvents, reactor, and substrate scope. In general, recent aims have been to improve catalyst turnover and selectivity, either through more active catalysts or ones that can be recycled, to enable lower costs and higher purity products, as well as more productive, less wasteful processes.

The most widely used or privileged precatalysts used in industry are the RuCl(Tsdpen)(*p*-cymene) or Cp*MCl(Tsdpen) (M = Rh, Ir) (Figure 1). An example of their industrial use is the intermediate of herbicide (*S*)-MA20565, (*S*)-1-(3-trifluoromethylphenyl)ethanol, in 91% ee using the Ru catalyst and both the 2-propanol and $HCO_2H/N(C_2H_5)_3$ systems developed by Okano's group (Scheme 17).[29,31] The use of optimal equimolar ratio of $HCO_2H/N(C_2H_5)_3$ enabled an S/C of 5000/1 with TOF of 167 h^{-1}, and the reaction was operated at the 100 kg scale. The reversibility of the 2-propanol system, and hence the slow erosion of optical purity, is overcome by distilling acetone/2-propanol from the system. Of note are the mesh or microchannel and rotating disk reactors that efficiently remove acetone and provide high and consistent optical purities of the products.[32] The mesh reactor employs a selective ceramic membrane that allows acetone and 2-propanol to pass and sets-up the reaction for continuous flow operation. The rotating disk reactor generates a high surface area thin film of reaction media from which the acetone can be efficiently stripped.

Scheme 17. Large Scale Asymmetric Reduction Used To Produce an Agrochemical



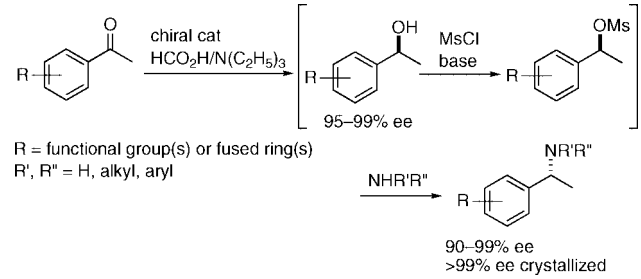
Scheme 18. Large Scale Asymmetric Reduction Used To Produce a Pharmaceutical Intermediate



Other studies have found that different optimal ratios of formic acid and triethylamine are of critical importance, as is the cosolvent, because this affects particularly the pK_a of formic acid.[1f,33] Statistical experimental design, varying catalyst, solvent, hydrogen donor, and mode of addition, is probably the best means of determining the optimal process. A noteworthy observation is that sparging nitrogen gas through the reaction solution resulted in a faster reaction rate and higher yields. It is now understood that this may at least in part be a result of the unexpected complexation or reduction of CO_2,[15] and using Le Châtellier's Principle removing the CO_2 prevents the back-reaction and shifts the equilibrium toward product formation. If excess formic acid is used in the reaction, this is slowly decomposed by the catalyst to CO_2 and H_2, which becomes more obvious when the substrate has been fully reduced. While bubbling nitrogen through a round-bottomed flask in the laboratory is effective at removing the unwanted gases including CO, when faced with operating at large scale, this presents an unusual set of issues, including defining the rate of gas sparge, the mixing required, and the avoidance of solvent stripping. The scaling-up of a reaction in which there is a gaseous second phase is nonlinear; in this case factors such as the liquid depth and mixing affect the ability to scrub both H_2, CO, and CO_2. Optimization of reaction conditions including the gas flow rate and mixing is required to attain the maximum catalyst performance in the reaction.

Another industrial application is the synthesis of the pharmaceutical intermediate (*R*)-1-(3,5-bistrifluoromethylphenyl)ethanol used in a variety of NK1 antagonists, for example, as antiemetics (Scheme 18). This chiral alcohol has been prepared using each of the Ru-, Rh-, and Ir-based catalysts. The strong electron-withdrawing groups on the aromatic ring appear to have eluded attempts to prepare it with >99% ee, although this has been achieved using asymmetric molecular hydrogenation and dehydrogenase catalysts. A method to improve the ee value from 91% to >99% has been developed by Merck using asymmetric transfer hydrogenation with TsCYDN-Ru catalyst, followed by cocrystallization of the product alcohol with DABCO.[34] NPIL Pharma has developed successfully a hundreds of kilograms scale production of a derivative chiral secondary amine, with the opposite stereochemistry, which can be prepared from the corresponding chiral alcohol by Walden inversion of mesylated alcohol (Scheme 19).[35a] The process has been extended to produce other primary, secondary, and tertiary amines[35b,c] and might be more efficient than asymmetric transfer hydrogenation of the imine or related reductive amination of the ketone, due to higher selectivities and productivities. Other reactions that have been operated at large scale include a variety of phenacylhalides used in styrene oxides and β-amino alcohols, N-substituted (3*S*)-3-amino-1-chloro-4-hydrocarbyl-2-butanones described above that are used in HIV protease inhibitors, and 3-oxo-3-thien-2-ylpropanenitrile that can be used in the selective norepinephrine- and serotonin-reuptake inhibitor, duloxetine.[35d]

Scheme 19. Efficient Large Scale Process Used To Produce Chiral Amines



Immobilized Catalysts

There have been a number of studies in which ligands have been attached or bound to polymeric material to provide an immobilized asymmetric transfer hydrogenation catalyst.[27,36] The advantages of heterogeneous catalysts are that they are easily separable from the product and can be recycled such that economic and product quality benefits ensue. These should be realized through a high number of recycles that offsets the cost of the immobilized catalyst, along with metal levels that are below the industry guidelines of 10 ppm. Unfortunately, most examples illustrate the lability of the metal and polymer-supported ligand, especially with the Cp*Rh and Cp*Ir complexes, which has frustrated many attempts to have a highly active, selective, and recyclable immobilized catalyst by tethering through the ligand.

Use of Water as Reaction Medium

The use of water is particularly attractive because it has the potential of generating less process waste, is safer to operate, and is low cost. The standard arene-Ru and Cp*Rh and Cp*Ir catalysts are insoluble in water but are nevertheless stable in the presence of water because of the reversibility of the reaction of the amido complex with H_2O giving the amine hydroxo metal complex.[37] The

hydrogen donor, HCO_2Na or $HCO_2H/N(C_2H_5)_3$, can be used in the aqueous phase with catalyst dissolved in a second immiscible phase.[38,39] For example, asymmetric transfer hydrogenation of aryl ketones with HCO_2Na in water containing the chiral Csdpen complexes of Ru, Rh, or Ir (Csdpen = *N*-camphorsulfonyl-1,2-diphenylethylenediamine) proceeds smoothly to give the corresponding chiral alcohols with excellent ee. Of particular note is that the Ir-(*R*,*R*,*R*)-Csdpen complex is an efficient catalyst for the reduction of a wide range of ketones, giving the product with up to 98% ee at 40 °C.[40]

The process has been used to reduce a variety of ketones at >100 kg scale with high selectivity and efficiency. Alternatively water-soluble ligands with either a sulfonate group on the *N*-arylsulfonamide of the diamine or a sulfonate on the phenyl groups of diphenylethylenediamine (Figure 1) can be used to provide water-soluble catalysts.[39b,c]

Summary and Outlook

This Account has described recent advances in chemistry and commercial applications of chiral bifunctional transition metal catalyst promoted asymmetric reduction of ketones. An unprecedented aspect in the hydrogen transfer from the amine hydrido metal complex and ketones is that the acidic amine proton and the metal hydride cooperatively activate the reactant and are concertedly transferred to C=O double bonds via pericyclic transition states. Since the reacting substrate is not bonded directly to the central metal, the reduction with the bifunctional catalysts leads to high reaction rates and excellent stereoselectivies. Thus, this bifunctional catalyst can provide a wide substrate scope and applicability in organic synthetic chemistry. The industrial outlook for asymmetric reduction with bifunctional catalysts is bright because of their excellent catalyst performance, wide substrate scope, operational simplicity, and economic viability, as well as the growing awareness of the need for green chemistry.

The chiral bifunctional catalyst originally developed for asymmetric transfer hydrogenation of ketones, as discussed in this Account, is now successfully applicable to enantioselective C–C bond formation.[1e] We believe the present bifunctional molecular catalyst offers a great opportunity to open up new chemistry and industrial process for stereoselective molecular transformation in addition to the enantioselective reduction.

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