LIGAND DESIGN FOR CATALYTIC ASYMMETRIC REDUCTION

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1.1 INTRODUCTION

Molecular catalysts consisting of a metal or metal ion and a chiral organic ligand are widely used for asymmetric synthesis. Figure 1.1 illustrates a typical (but not general) scheme of asymmetric catalytic reaction.¹ The initially used chiral precatalyst **1A** is converted to the real catalyst **1B** through an induction process. An achiral reactant A and substrate B are activated by **1B** to form reversibly an intermediate **1C**. The chiral environment of **1C** induces asymmetric transformation of A and B to the chiral product A–B (*R* or *S*) through an intermediate **1D** with reproduction of catalyst **1B**. The absolute configuration of A–B is kinetically determined at the first irreversible step, **1C**→**1D**. The efficiency of catalysis depends on several kinetic and thermodynamic parameters, because most catalytic reactions proceed through such multistep transformation.

Catalytic asymmetric reduction of unsaturated compounds is one of the most reliable methods used to synthesize the corresponding chiral saturated products.^{2–4} Chiral transition metal complexes repeatedly activate an organic or inorganic hydride source, and transfer the hydride to olefins, ketones, or imines from one

Figure 1.1. The principal of asymmetric catalysis with chiral organometallic molecular catalysts (M = metal; A, B = reactant and substrate; X, Y = neutral or anionic ligand).

of two enantiofaces selectively, resulting in the enantio-enriches alkanes, alcohols, or amines, respectively. The three-dimensional (3D) structure and functionality of the chiral ligand, among other factors, are the obvious key for efficient asymmetric reduction. Rational design of chiral ligand can be done on the basis of full understanding of the corresponding catalytic reaction. This chapter presents successful examples of catalytic asymmetric reduction and the concepts of the ligand design. The description is brought to focus on the BINAP–transition metal chemistry.²

1.2 HYDROGENATION OF OLEFINS

1.2.1 Enamide Hydrogenation with Rhodium Catalysts

The discovery of Wilkinson complex, $\text{RhCl}[\text{P}(\text{C}_6\text{H}_5)_3]_3$,⁵ acting as an effective catalyst for hydrogenation of olefins opened the door for developing asymmetric reaction catalyzed by rhodium complexes with a chiral phosphine ligand.^{1,6–10} The enantioselective ability of chiral ligands has often been evaluated by hydrogenation of α -hydroxycarbonyl- or α -alkoxycarbonyl-substituted enamides. Figure 1.2

$R^1 = \text{H or CH}_3$

$R^2 = \text{CH}_3 \text{ or } \text{C}_6\text{H}_5$

Examples of chiral ligands:

(*R,R*)-DIPAMP

(*R,R*)-CHIRAPHOS

(*R*)-BINAP

BINAP: $\text{Ar} = \text{C}_6\text{H}_5$

TolBINAP: $\text{Ar} = 4\text{-CH}_3\text{C}_6\text{H}_4$

(*S,S*)-DIOP

(*S,S*)-DuPHOS

Me-DuPHOS: $\text{R} = \text{CH}_3$

Et-DuPHOS: $\text{R} = \text{C}_2\text{H}_5$

(*R,R*)-L1

(*R,R*)-*t*-Bu-BisP*

(*S*)-[2.2]PHANEPHOS

(*R*)-MonoPhos

Figure 1.2. Asymmetric hydrogenation of *N*-acylated dehydroamino acids and esters.

illustrates typical examples of phosphorus-based chiral ligands, with which Rh(I) catalyst selectively afforded (*S*)-amino acid derivatives in hydrogenation of (*Z*)-2-(acylamido)cinnamic acids and the methyl esters. Key factors for designing of these ligands are: (1) monodentate or bidentate, (2) steric effects (bulkiness, conformational flexibility, space coordinate, etc.), (3) electronic effects (alkylphosphine, arylphosphine, phosphite, phosphoramidite, etc.), (4) bite angle for bidentate

ligands, (5) C_1 or C_2 symmetry for bidentate ligands, and (6) chirality on the backbone or on phosphorus atoms. A DIPAMP–Rh-catalyzed hydrogenation of an enamide substrate is industrially used in the synthesis of L-dopa, a drug for the parkinsonian disease.⁸

The mechanism of hydrogenation of methyl (Z)-2-(acetamido)cinnamate catalyzed by a CHIRAPHOS–¹¹ or DIPAMP–Rh⁸ complex have been exhaustively studied by Halpern^{12–14} and Brown.^{7,15,16} They proposed the “unsaturated/dihydride mechanism” as illustrated in Figure 1.3. The Rh complex with the *R,R* ligand [(*R*)-**3A**] (solvate) and an enamide reversibly form the substrate complex **3B**, which undergoes irreversible oxidative addition of molecular H₂ to the Rh center, affording Rh(III) dihydride species **3C**. Both hydrides on Rh migrate onto the C–C double bond of the coordinated substrate. The first hydride migration to the C3 position forms a five-membered alkyl–hydride complex **3D**, and then reductive elimination of the hydrogenation product (second hydride migration) completes the cycle with regeneration of **3A**. The stereochemistry of product is determined at the first irreversible step, **3B** → **3C**, although a detailed theoretical investigation suggests the possibility that the process **3B** → **3C** is reversible and the step **3C** → **3D** constitutes the turnover-limiting step.¹⁷ The BINAP–Rh-catalyzed hydrogenation of enamides is proposed to proceed with the same Halpern–Brown mechanism.^{18–21}

Figure 1.3. Catalytic hydrogenation of *N*-acylated dehydroamino esters via an unsaturated/dihydride mechanism; the β substituents in the substrates are omitted for clarity [P–P = (*R,R*)-DIPAMP, (*R,R*)-CHIRAPHOS, or (*R*)-BINAP; S = solvent or a weak ligand].

Figure 1.4. Chiral environment of an (*R*)-BINAP–transition metal complex (*M* = metallic element, ax = axial, eq = equatorial; □ = coordination site in the P^1 –*M*– P^2 plane; ■ = coordination site out of the P^1 –*M*– P^2 plane).

CHIRAPHOS, DIPAMP, and BINAP are all chiral diphosphines with a C_2 symmetry (Figure 1.2) forming chelate complexes with transition metallic elements. DIOP developed by Kagan is the origin of this type of chiral ligand.²² Figure 1.4 illustrates the chiral template created by an (*R*)-BINAP–transition metal complex.^{18–21} The naphthalene rings are omitted in the side view for clarity. In this template, the chiral information of binaphthyl backbone is transmitted through the *P*-phenyl rings to the four coordination sites shown by □ and ■. The in-plane coordination sites, □, are sterically affected by the “equatorial” phenyl rings, whereas the out-of-plane coordination sites, ■, are influenced by the “axial” phenyl groups. Consequently, the two kinds of quadrant of the chiral template (first and third vs. second and fourth) are clearly differentiated spatially, where the second and fourth quadrants are sterically congested, while the first and third ones are relatively uncrowded. (*R,R*)-CHIRAPHOS²³ and (*R,R*)-DIPAMP²⁴ form a similar chiral environment with metals.

As shown in Figure 1.3, the Rh catalyst (*R*)-**3A** and a bidentate enamide substrate reversibly form the substrate complex **3B**. Figure 1.5 illustrates two possible diastereomeric structures of **3B**, depending on the *Si/Re*-face selection at C2, which leads to the *R* or *S* hydrogenation product. Therefore, the enantioselectivity is determined by the relative equilibrium ratio and reactivity of *Si*-**3B** and *Re*-**3B**. A ^{31}P NMR spectrum of the Rh complex and an enamide substrate in CH_3OH showed a single signal for thermodynamically more favored *Si*-**3B**.²⁰ Most importantly,

Figure 1.5. Molecular models of diastereomeric (*R*)-BINAP/enamide Rh complexes **3B** (not transition state) ($Z = \text{CO}_2\text{R}^1$; ax = axial, eq = equatorial).

the *Re*-**3B** which is less favored because of the nonbonded repulsion between an equatorial phenyl ring of the (*R*)-BINAP ligand and a carboxylate function of substrate reacts with H_2 much faster than the more stable *Si*-**3B**, leading to the *S* isomer as a major product. The observed enantioselectivity is a result of the delicate balance of the stability and reactivity of the diastereomeric **3B**. This inherent mechanistic problem requires careful choice of reaction parameters. For instance, the hydrogenation should be conducted under a low substrate concentration and low H_2 pressure to minimize reaction via the major diastereomeric intermediate *Si*-**3B**. Therefore, the hydrogenation of enamides catalyzed by BINAP-, CHIRAPHOS-, or DIPAMP-Rh complex, though giving amino acids in high enantiomeric excess (ee), is not ideal from the mechanistic standpoint. A Rh complex bearing Et-DuPHOS,²⁵ a C_2 -chiral diphosphines (see Figure 1.2), catalyzes the hydrogenation basically with the same mechanism.^{26,27}

This mechanistic problem can be solved when the more stable diastereomer of **3B** gives the major enantiomeric product. A Rh complex with a C_1 -chiral P/S mixed ligand, (*R,R*)-**L1** (see Figure 1.2), catalyzes hydrogenation of methyl (*Z*)-2-(acetamido)cinnamate to afford the *S* product in excellent ee.²⁸ The enamide substrate is reduced along with the catalytic cycle illustrated in Figure 1.3. However, unlike traditional catalyst systems, the stereochemistry of hydrogenation product suggests that the major *S* product is obtained via the most stable diastereomer of **3B**. A substrate complex, *Re*-**3B-L1**, is the only visible species among four possible diastereomers. Figure 1.6 illustrates the structure of an

Figure 1.6. Molecular models of (R,R)-**L1**/enamide metal complexes.

(R,R)-**L1**–metal complex. The bulky *t*-butyl group on sulfur plays a crucial role in achieving high enantioface selectivity. This group is placed at the axial position to avoid steric hindrance with the ligand backbone. The two phenyl groups on phosphorus atom occupy the axial and equatorial positions. The high enantiodiscriminatory ability of the catalyst is rationalized by means of the quadrant model of *Re*-**3B-L1**.²⁸ The electron-donating olefin function of the enamide substrate preferably binds to Rh at the trans position to the less electron-donating sulfur atom instead of phosphorus, that is, the first and fourth quadrants are unfavorable for the olefinic function for electronic reasons. The third

Figure 1.7. Catalytic hydrogenation of *N*-acylated dehydroamino esters via dihydride/unsaturate mechanism; the β substituents in the substrates are omitted for clarity [P–P = (*R,R*)-*t*-Bu-BisP*^{*}; S = solvent or a weak ligand].

and fourth quadrants are blocked by equatorial *P*-phenyl and bulky *S*-*t*-butyl group, respectively. Therefore, only the second quadrant is available for approach of methoxycarbonyl group (Z).

The unsaturate/dihydride is not a sole mechanism for enamide hydrogenation. Its mechanistic problem can be resolved by a total change in catalytic cycle. *t*-Bu-BisP* is a *C*₂-symmetric, fully alkylated diphosphine with chiral centers at phosphorus (see Figure 1.2).^{29,30} Hydrogenation of enamides catalyzed by an (*R,R*)-*t*-Bu-BisP*–Rh complex gives the *S* product in excellent ee. The hydrogenation is revealed to proceed through the “dihydride/unsaturate mechanism” as shown in Figure 1.7.^{30–32} The major difference of this cycle from the unsaturate/dihydride cycle in Figure 1.3 is the order of reaction of the substrate and H₂. Now the catalyst (*R,R*)-**7A** first reversibly reacts with H₂, giving **7B**, followed by interaction with an enamide substrate to form a substrate–RhH₂ complex **7C**. The stereochemistry of product is determined at the first irreversible step, **7C** → **7D**. Because of the *C*₂-symmetric structure of (*R,R*)-*t*-Bu-BisP*, the quadrants of the chiral template are spatially differentiated into two kinds. The first and third quadrants are crowded by the location of bulky *P*-*t*-butyl groups, whereas the second and fourth ones are open for substrate approach owing to the presence of only small methyl groups. Therefore, two diastereomers of bidentate substrate–Rh(III)H₂ complex, *Re*-**7C** and *Si*-**7C**, are possible (Figure 1.8). Formation of *Si*-**7C** is

Figure 1.8. Molecular models of diastereomeric (R,R) - t -Bu-BisP*/enamide Rh complexes **7C** (not transition state).

unfavored because it suffers from serious steric repulsion between bulky P - t -butyl group and substrate amide function. On the other hand, only small methyl/amide repulsive interaction exists in *Re*-**7C**. The major *S* enantiomeric product is derived from the more stable diastereomeric species, *Re*-**7C**. The hydrogenation catalyzed by a [2.2]PHANEPHOS–Rh complex³³ (see Figure 1.2) is also suggested to proceed through the dihydride/unsaturate mechanism.³⁴

Chiral monodentate phosphites^{35,36} and phosphoramidites^{37,38} are also effective ligands for Rh-catalyzed asymmetric hydrogenation of enamide substrates. As seen in the structure of MonoPhos^{37,38} illustrated in Figure 1.2, combination of the modified BINOL backbone and the amine part gives a structural variety to this type of ligand.³⁹ Combinatorial methods are effective for optimization of the chiral structures.^{40,41} Elucidation of the hydrogenation mechanism catalyzed by the MonoPhos–Rh complex is in progress.^{42–44}

1.2.2 Hydrogenation of Functionalized Olefins with Ruthenium Catalysts

The BINAP–Rh catalyzed hydrogenation of functionalized olefins has a mechanistic drawback as described in Section 1.2.1. This problem was solved by the exploitation of BINAP–Ru(II) complexes.^{1,2} $\text{Ru}(\text{OCOCH}_3)_2(\text{binap})$ ¹⁸ catalyzes highly enantioselective hydrogenation of a variety of olefinic substrates such as enamides, α,β - and β,γ -unsaturated carboxylic acids, and allylic and homoallylic alcohols (Figure 1.9).^{6,7,45–48} Chiral citronellol is produced in 300 ton quantity in year by this reaction.⁹

It is worth noting that an opposite sense of enantioface selection is observed in going from the BINAP–Rh complex to the Ru catalyst. Hydrogenation of methyl (*Z*)-2-(acetamido)cinnamate with the (R) -BINAP–Ru catalyst in CH_3OH gives the *R* (not *S*) product selectively (Figure 1.9).^{1,18,21,45} Figure 1.10 illustrates the

Figure 1.9. Asymmetric hydrogenation of functionalized olefins catalyzed by BINAP-Ru complexes.

Figure 1.10. Catalytic cycle of BINAP-Ru-catalyzed hydrogenation of methyl (Z)-α-acetamidocinnamate involving a monohydride/unsaturated mechanism. The β substituents in the substrates are omitted for clarity.

Figure 1.11. Molecular models of diastereomeric (*R*)-BINAP/enamide Ru complexes **10C** (not transition state).

“monohydride/unsaturate mechanism,” in which the RuH(AcO) species **10B**, formed by the heterolytic cleavage of H₂ by the precatalyst **10A**, acts as a real catalyst.^{21,49–53} Thus, the Ru hydride species is generated before the substrate coordination forming **10C**. The migratory insertion giving **10D**, in which the Ru–C bond is cleaved mainly by H₂, but also by CH₃OH solvent to some extent. The irreversible step determines the absolute configuration of the product. Because the diastereomers of **10D** would have a similar reactivity, the enantioselectivity well corresponds to the relative stability of the diastereomeric substrate–RuH(AcO) complexes, *Re*-**10C** and *Si*-**10C** (Figure 1.11). In order for **10C** to undergo migratory insertion, the Ru–H and C2–C3 double bond must have a *syn*-parallel alignment. As discussed above, the intermediate *Re*-**10C** is unfavored relative to *Si*-**10C** because of existence of *P*-Ph/COOCH₃ repulsion. Therefore, the major *Si*-**10C** is converted to the *R* hydrogenation product through **10D**. The two hydrogen atoms incorporated in the product are from two different H₂ molecules, or H₂ and protic CH₃OH.

1.2.3 Hydrogenation of Simple Olefins with Iridium Catalysts

Phosphinodihydroxazole (PHOX) compounds, **L2–4**, act as P/N bidentate ligands showing excellent enantioselectivity in Ir-catalyzed hydrogenation of simple α,α -disubstituted and trisubstituted olefins (Figure 1.12).^{54–58} The use of tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (BAr_F) as a counter anion achieves high catalytic efficiency due to avoidance of an inert Ir trimer

Figure 1.12. Asymmetric hydrogenation of simple olefins catalyzed by chiral Ir complexes.

formation. A chiral carbene–oxazoline ligand **L5** is also useful for this purpose.⁵⁹ The mechanism of this reaction is to be elucidated by experimental^{60–63} and theoretical^{64,65} studies. Chiral titanocene catalysts also show high enantioselectivity for hydrogenation of simple olefins.⁶⁶ This subject is discussed in Section 1.4.

1.3 REDUCTION OF KETONES

1.3.1 Hydrogenation of Functionalized Ketones

Although Ru(OCOCH₃)₂(binap) exhibits excellent catalytic performance on asymmetric hydrogenation of functionalized olefins, it is feebly active for reaction of ketones. This failure is due to the property of the anionic ligands. Simple replacement of the carboxylate ligand by halides achieves high catalytic activity for reaction of functionalized ketones.^{1,18,21,67} Thus, chiral precatalysts including RuCl₂[(*R*)-binap] (polymeric form),⁶⁷ RuCl₂[(*R*)-binap](dmf)_{*n*} (oligomeric form),⁶⁸ [RuCl{(*R*)-binap}(arene)]Cl,⁶⁹ [NH₂(C₂H₅)₂][{RuCl[(*R*)-binap]}₂-(μ-Cl)₃],⁶⁷ and other in situ formed (*R*)-BINAP–Ru complexes⁷⁰ are successfully used for hydrogenation of β-keto esters, resulting in the *R* β-hydroxy esters in >99% ee (Figure 1.13). An intermediate for the synthesis of carbapenem antibiotics is produced industrially by this method.¹⁸

Figure 1.13. Asymmetric hydrogenation of functionalized ketones catalyzed by BINAP–Ru complexes.

Figure 1.14 illustrates a mechanistic model of this hydrogenation.^{21,71} The true catalytic RuHCl species **14B** is generated by the reaction of the RuCl_2 precatalyst **14A** and H_2 by releasing HCl . The catalyst **14B** reversibly interacts with the β -keto ester to form the σ -type chelate complex **14C**. Protonation of **14C** at the carbonyl oxygen increases electrophilicity of the carbonyl carbon, inducing conversion of the geometry from σ to π . Consequently, the hydride on Ru smoothly migrates to the substrate carbonyl carbon. The hydroxy ester ligand in the resulting complex **14D** is replaced by solvent molecule. The Ru cationic species **14E** cleaves H_2 , reproducing the catalyst **14B**. Enantioface selection of the reaction occurs in the hydride transfer step, **14C** $\rightarrow$ **14D**. The carbonyl protonation with HCl in **14C** is crucial for the transformation to **14D**.^{72–74} When $\text{Ru}(\text{OCOCH}_3)_2(\text{binap})$ is used, acetic acid is produced instead of HCl . Such a weak acid does not sufficiently protonate the carbonyl oxygen. Thus, even achiral anionic ligands in the precatalyst are important to achieve high catalytic efficiency.

Figure 1.15 illustrates two diastereomeric transition states *Re*-**15A** and *Si*-**15A** in the hydride migration step in the (*R*)-BINAP–Ru-catalyzed hydrogenation.²¹ The protonated carbonyl group, $\text{C}=\text{O}^+\text{H}$, becomes parallel to the H –Ru linkage, bringing the “R” group close to the *P*-phenyl ring of the (*R*)-BINAP ligand. Thus, transition state *Re*-**15A** producing the *S* alcohol is unfavored because of the R/Ph repulsive interaction in the fourth quadrant. Therefore, the (*R*)- β -hydroxy ester is obtained selectively through *Si*-**15A**.

Figure 1.16 lists other chiral ligands useful for asymmetric hydrogenation of α - and/or β -keto esters.^{6,75–77} A Ru complex with BPE, a fully alkylated diphosphine,

shows very high activity for reaction of β -keto esters.^{78,79} Its electron-donating character may accelerate the hydride transfer in **14C** $\rightarrow$ **14D** (see Figure 1.14). An axially chiral SEGPHOS efficiently discriminates two enantiofaces of α - and β -keto esters in the Ru-catalyzed hydrogenation.⁸⁰ The small angle, 65°, between

Figure 1.16. Chiral ligands useful for hydrogenation of keto esters.

the two aryl planes (dihedral angle) of the SEGPPOS–Ru complex may cause the high stereoselectivity. BPPM⁸¹ and JOSIPHOS⁸² are original for the design of C_1 -chiral diphosphines, whereas the origin of their efficiency is hard to rationalize. Rh complexes with oxoProNOP ligands achieve high catalytic activity and enantioselectivity in hydrogenation of α -keto esters.⁸³

1.3.2 Hydrogenation of Simple Ketones

β -Keto esters are highly reactive for the BINAP–RuCl₂-catalyzed hydrogenation (Figure 1.13).^{18,67,68} However, simple unfunctionalized ketones are totally inert to this catalyst system, because the substrates are unable to stabilize the transition state by forming a chelate structure (Figure 1.15).²¹ A combined system of *trans*-RuCl₂(binap)(dppe) and alkaline base^{84–86} or *trans*-RuH(η^1 -BH₄)-(binap)(dppe)⁸⁷ with or without a base exhibits excellent catalytic performance in asymmetric hydrogenation of a variety of simple ketones.^{21,86} For example, acetophenone is hydrogenated in the presence of an (*S*)-XylBINAP/(*S,S*)-DPEN–Ru catalyst (ketone:Ru = 100,000:1) in 2-propanol to give (*R*)-1-phenylethanol in 99% ee (Figure 1.17).^{85,87} Notably, now the reaction conditions are slightly basic.

The excellent catalytic activity is rationalized by a nonclassical metal–ligand bifunctional mechanism using an “NH effect.”^{86,88–90} As shown in Figure 1.18, *trans*-RuH(η^1 -BH₄)(tolbinap)(dppe) (**18A**) (TolBINAP; see Figure 1.2), a precatalyst, is converted to 16-electron cationic species **18B** in 2-propanol.^{88,91,92} It accepts an H₂ molecule to form **18C**, which undergoes deprotonation with an alcoholic solvent giving the Ru dihydride **18D**. This step is accelerated by a base. Ketonic substrate is rapidly reduced by **18D** to give the alcohol and 16-electron Ru amide **18E**. This complex is easily protonated by alcoholic media to recover the amino

Figure 1.17. Asymmetric hydrogenation of simple ketones catalyzed by BINAP/1,2-diamine–Ru complex.

complex **18B**, while it partially gives **18D** by reaction with H_2 . The reducing species **18D** has a *fac* structure for the hydride and two nitrogen atoms, allowing reaction with a ketone via the six-membered pericyclic transition state **18F**. Ketone is reduced in the outer coordination sphere of **18D**, where neither ketone/Ru nor alkoxy/Ru interaction is involved. This hydrogenation is carbonyl-selective. Alkenyl and alkynyl groups, which are normally reduced through a substrate/metal complex, are left intact under the hydrogenation conditions.^{85,87,93}

The combination of (*S*)-TolBINAP and (*S,S*)-DPEN (or *R/R,R* combination) is crucial to achieve high enantioselectivity.^{94,95} Figure 1.19 illustrates a transition-state model in hydrogenation of acetophenone using an (*S*)-TolBINAP/(*S,S*)-DPEN– RuH_2 catalyst.^{88,89} Both (*S*)-TolBINAP and (*S,S*)-DPEN bind to a Ru center resulting in a C_2 -symmetric RuH_2 complex. The skewed five-membered DPEN chelate ring has two kinds of diastereotopic hydrogen at the nitrogen atoms. The axially arranged hydrogens, H_{ax} , are more reactive than the equatorial ones for stereoelectronic reasons. The $H^{\delta-}-Ru^{\delta+}-N^{\delta-}-H_{ax}^{\delta+}$ moiety with a small dihedral angle fits well with the $C^{\delta+}=O^{\delta-}$ function. Then a hydride on Ru smoothly migrates to the electrophilic carbonyl carbon, while the amine proton is transferred to the oxygen atom. Acetophenone approaches the reaction site in a way to minimize nonbonded repulsion and to maximize electronic attraction. The *Si*-**19A** is favored over the diastereomeric *Re*-**19A**, which suffers from significant nonbonded repulsion between the *P*-tolyl group of TolBINAP and the acetophenone phenyl ring. The *Si*-**19A** could further be stabilized by the secondary attractive interaction between an NH_{eq} and the phenyl ring of the substrate. This view is consistent with the fact that sterically less demanding alkenyl alkyl ketones are hydrogenated with equally high enantioselectivity.^{85,87,93}

Figure 1.18. Catalytic cycle of ToIBINAP/1,2-diamine-Ru-catalyzed hydrogenation of simple ketones.

The chiral environment of this catalyst system is easily modified by changing the combination of diphosphine and diamine ligands.^{77,96–98} Although the BINAP/1,2-diamine-Ru catalysts are feebly active for hydrogenation of 1-tetralones, this problem is solved simply by use of chiral 1,4-diamines instead of conventional 1,2-diamine ligands.⁹⁹ For example, hydrogenation of 5-methoxy-1-tetralone in the presence of an (*S*)-TolBINAP/(*R*)-IPHAN-Ru catalyst in 2-propanol results in the *R* alcohol in 98% ee (Figure 1.20). Hydrogenation of *tert*-alkyl ketones with the BINAP/1,2-diamine-Ru catalysts is also difficult obviously because of steric hindrance of the substrates. Ru catalysts wearing BINAP and α -picolylamine

Figure 1.19. (S)-TolBINAP/(S,S)-DPEN-RuH₂ species and diastereomeric transition states in the metal–ligand bifunctional catalysis; the equatorially oriented phenyl substituents in the DPEN ligands are omitted in the transition states *Si-19A* and *Re-19A* (Ar = 4-CH₃C₆H₄; ○ = Ru; ax = axial, eq = equatorial).

Figure 1.20. Asymmetric hydrogenation of 1-tetralones catalyzed by BINAP/1,4-diamine–Ru complex.

Figure 1.21. Asymmetric hydrogenation of *tert*-alkyl ketones catalyzed by BINAP/PICA–Ru complex.

(PICA) show excellent activity and enantioselectivity for reaction of such bulky ketones.¹⁰⁰ Selection of alcoholic solvent is important to achieve high catalytic performance. Thus, hydrogenation of pinacolone with the (*S*)-TolBINAP/PICA–Ru catalyst (*S*/*C* = 100,000) in $\text{C}_2\text{H}_5\text{OH}$ quantitatively gives (*S*)-3,3-dimethyl-2-butanol in 98% ee (Figure 1.21). The reaction in conventional 2-propanol with the same catalyst results in the *S* alcohol in only 36% ee.

Some chiral amino phosphine–Ru catalysts are also effective for asymmetric hydrogenation of simple ketones.¹⁰¹

A Rh complex with (*R,S,R,S*)-Me-PennPhos efficiently catalyzes asymmetric hydrogenation of simple ketones (Figure 1.22).¹⁰² Addition of catalytic amounts of 2,6-lutidine is crucial to achieve high enantioselectivity. This catalyst is also

Figure 1.22. Asymmetric hydrogenation of simple ketones catalyzed by a PennPhos–Rh complex.

effective for reaction of some aliphatic ketones. The origin of high stereoselectivity has not been elucidated yet.

1.3.3 Transfer Hydrogenation of Ketones

As illustrated in Figure 1.23, chiral arene–Ru catalysts achieve high enantioselectivity in transfer hydrogenation of aryl, alkenyl, and alkynyl ketones.^{1,103} Various secondary alcohols are obtainable in >95% ee. The combination of TsDPEN (Ts = *p*-toluenesulfonyl) and arene ligands controls enantio-face selection. Importantly, selection of an achiral arene ligand is crucial for high stereoselection. In place of TsDPEN, some chiral β -amino alcohols are also usable.^{6,49,75,76,104} 2-Propanol or formic acid is selected as a hydride source. The reduction of ketones with 2-propanol is reversible, because the products are also secondary alcohols. In many cases, therefore, formic acid, an irreversible reducing agent, with

Figure 1.23. Asymmetric transfer hydrogenation of ketones catalyzed by chiral arene–Ru complexes.

Figure 1.24. Metal–ligand bifunctional mechanism in asymmetric transfer hydrogenation of ketones (R = alkyl; Un = alkenyl, alkynyl, or aryl).

(C₂H₅)₃N for tuning the acidity of reaction media gives higher conversion and better enantioselectivity.¹⁰⁵

Detailed experimental¹⁰⁶ as well as theoretical^{107–110} studies revealed the mechanism of the asymmetric transfer hydrogenation in 2-propanol. As summarized in Figure 1.24, the NH effect is evident. The 18-electron Ru complex, RuH[(S,S)-TsNCH(C₆H₅)CH(C₆H₅)NH₂](η⁶-arene), smoothly reduces ketonic substrate through a six-membered pericyclic transition state, in which Ru–H and N–H are simultaneously delivered onto the C=O function, giving an *S* alcohol and 16-electron Ru[(S,S)-TsNCH(C₆H₅)CH(C₆H₅)NH](η⁶-arene). The stereochemical outcome indicates that the *Re*-24A is much more favored than the diastereomeric *Si*-24A, due to stabilization caused by the CH–π interaction between the η⁶-arene ligand and the aromatic, olefinic, or acetylenic group in the substrates.¹⁰⁹

Figure 1.25 exemplifies the structures of certain efficient precatalysts for asymmetric transfer hydrogenation of ketones. Precatalysts **C1**–**C3** use the “NH effect” described above.^{111–113} A turnover frequency, defined as moles of product per mol of catalyst per hour, of 30,000 h^{–1} is achieved by using of **C2** and an alkaline base in 2-propanol.¹¹² A Rh complex **C3** is an isolobal to the corresponding arene–Ru complex (see Figure 1.23).¹¹³ The Ru complexes **C4**¹¹⁴ and **C5**¹¹⁵ without NH group in ligand catalyze the reaction by different mechanisms. A higher than 90% optical yield is achieved by using **C5** in reduction of certain aliphatic ketones.¹¹⁵

Figure 1.25. Examples of chiral precatalyst for asymmetric transfer hydrogenation of ketones.

As shown in Figure 1.26, a chiral Sm(III) complex catalyzes asymmetric reduction of aromatic ketones in 2-propanol with high enantioselectivity.¹¹⁶ Unlike other late-transition-metal catalysis, the hydrogen at C2 of 2-propanol directly migrates onto the carbonyl carbon of substrate via a six-membered transition state **26A**, as seen in the Meerwein–Ponndorf–Verley reduction.⁶

1.3.4 Hydroboration of Ketones

Borane reduction catalyzed by chiral oxazaborolidines (CBS reduction, CBS = Corey, Bakshi, and Shibata) exhibits excellent enantio- and chemoselectivity for a wide variety of ketonic substrates (Figure 1.27).^{117–119} This reaction was originally developed as a stoichiometric system consisting of diphenylvalinol and borane,¹²⁰ but was later extended to a useful catalytic method.¹²¹ Because of the high efficiency of this reaction, many chiral oxazaborolidines have been synthesized from β -amino alcohols.^{117–119} Among them the prolinol-derived oxazaborolidine is one of the most widely used catalysts.^{117,122}

Figure 1.26. Asymmetric Meerwein–Ponndorf–Verley-type reduction of ketones catalyzed by a Sm complex.

The proposed catalytic cycle for reduction of acetophenone is illustrated in Figure 1.28.¹¹⁷ The (*S*)-oxazaborolidine catalyst (*S*)-**28A** has both Lewis acidic and basic sites, and its borane adduct **28B** acts as a chiral Lewis acid. The B center in the borolidine ring selectively interacts with a sterically more accessible electron

Examples of chiral alcohol obtained by the CBS reduction:

Figure 1.27. Asymmetric reduction of ketones with borane catalyzed by oxazaborolidines.

Figure 1.28. Catalytic cycle of oxazaborolidine-catalyzed asymmetric reduction of ketones.

pair of the carbonyl oxygen to avoid steric repulsion between the R substituent on B and the acetophenone phenyl, leading to a favored six-membered transition state **28C**. Migration of the borane hydride to the carbonyl carbon gives **28D**, which is converted to **28A** directly or **28B** through a borane adduct **28E** with releasing of the *R* alkoxide product. For this reaction, borane–THF complex is most commonly used, whereas catecholborane gives better results for reaction of α,β -unsaturated ketones^{123,124} and alkynyl ketones.¹²⁴

The skeletally fixed prolinol ring gives the best performance for enantioface selection of substrates in **28C**.¹¹⁷ Furthermore, the substitution by *gem*-phenyl or -2-naphthyl groups at the carbinol center is recommended (see structure in Figure 1.27). More hindered groups and heteroaryl rings reduce the enantioselectivity. Methyl and *n*-butyl groups are commonly used as a substituent at the boron atom. The use of (trimethylsilyl)methyl group instead of simple alkyls gives better enantioselection in the reaction of (triisopropylsilyl)acetylenic ketones, which requires recognition of the bulky group located far from the reaction site.¹²²

A chiral β -keto iminato Co complex in the presence of tetrahydrofuryl alcohol (THFA) and ethanol (or methanol) results in high enantioselectivity in reduction of aromatic ketones using NaBH_4 as a hydride source (Figure 1.29).^{125,126} The in situ generated $\text{NaBH}_2(\text{OR})(\text{OC}_2\text{H}_5)$ ($\text{ROH} = \text{THFA}$) reduces the Co complex to form a true catalytic CoH species.

Figure 1.29. Asymmetric reduction of ketones with NaBH_4 catalyzed by a β -keto iminato Co complex.

1.4 REDUCTION OF IMINES

The Brintzinger-type C_2 -chiral titanocene catalysts¹²⁷ efficiently promote asymmetric hydrogenation of imines (Figure 1.30).^{128,129} A variety of cyclic and acyclic imines are reduced with excellent enantioselectivity by using these catalysts. The active hydrogenation species **30B** is produced by treatment of the titanocene binaphtholate derivative **30A** with *n*-butyllithium followed by phenylsilane.

Figure 1.31 illustrates a mechanism proposed for this hydrogenation. The titanocene hydride **31A** is expected to be a catalytic species. The imine substrate is inserted into the Ti—H bond of **31A** with a 1,2-fashion to form a titanocene amide complex **31B**. Then the hydrogenolysis of **31B** through a σ -bond metathesis produces the amine product with regeneration of **31A**. The enantioface selection

Figure 1.30. Asymmetric hydrogenation of imines with a chiral titanocene catalyst.

Figure 1.31. Reaction mechanism and diastereomeric transition states of titanocene-catalyzed hydrogenation of imines.

occurs at the first 1,2-insertion step **31A** $\rightarrow$ **31B**, in which two diastereomeric four-membered transition states **Re-31C** and **Si-31C** are possible.¹²⁹ **Re-31C** suffers from significant steric repulsion between the R substituent of the cyclic imine and the tetrahydroindenyl ligand. Thus the *R* amine product is predominantly produced via the favored transition state **Si-31C**.

Substituents on imino nitrogen influence both reactivity and enantioselectivity in hydrogenation of imino compounds.^{6,9,130} Figure 1.32 shows two successful examples. An f-BINAPHANE-Ir complex effects asymmetric hydrogenation of *N*-aryl aromatic imines.¹³¹ On the other hand, an Et-DuPHOS-Rh complex²⁵ (see Figure 1.2) is effective for hydrogenation of *N*-acylhydrazones.¹³²

Figure 1.33 illustrates asymmetric hydrogenation of a functionalized imine with a XYLIPHOS-Ir catalyst, occurring with a catalyst turnover number of 2,000,000.^{9,133} The presence of I^- under acidic conditions is crucial to achieve high catalytic performance. (*S*)-Metolachlor, a herbicide, is industrially produced in a >10,000-ton quantity per year by this reaction.

Asymmetric transfer hydrogenation of imines catalyzed by chiral arene-Ru complexes achieves high enantioselectivity (Figure 1.34).^{103,134} Formic acid in aprotic dipolar solvent should be used as a hydride source. The reaction proceeds through the "metal-ligand bifunctional mechanism" as shown in the carbonyl reduction (Figure 1.24).

Figure 1.32. Asymmetric hydrogenation of *N*-arylimines and *N*-acylhydrazones catalyzed by chiral Ir and Rh complexes.

Figure 1.33. Industrial asymmetric hydrogenation of a functionalized imine catalyzed by a XYLIPHOS-Ir complex.

Figure 1.34. Asymmetric transfer hydrogenation of imines catalyzed by chiral Ru complexes.

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