NEW FRONTIERS IN ASYMMETRIC CATALYSIS

Edited by

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PREFACE

New Frontiers in Asymmetric Catalysis provides readers with a comprehensive perspective on understanding the concepts and applications of asymmetric catalysis reactions. Despite the availability of excellent comprehensive multivolume treatises in this field, we felt that researchers in pharmaceutical and chemical companies as well as university faculty and graduate students would benefit from a selection of some of the most important recent advances in this ever-growing area.

The key to efficient asymmetric catalysis lies in the creation of robust chiral catalysts by a suitable combination of chiral organic compounds and metal centers to which they are ligated. Many chiral organic ligands are *atropisomeric* ($a + tropos$ in Greek) compounds with C_2 symmetry, such as BINOL and BINAP. The use of C_2 symmetric ligands originally introduced by Kagan had a strong impact on subsequent ligands design for asymmetric catalysis. In recent years new nonsymmetric ligands that are more effective than their C_2 counterparts have been reported. The first chapters of this book are dedicated to ‘‘rational’’ ligand design, which is critically dependent on the reaction type (reduction, oxidation, and C–C bond formation). The concept of C_2 symmetry for bidentate ligands can be extended to the design of C_n symmetric multidentate ligands bearing phosphorous, nitrogen, and other coordinating elements.

Catalyst systems can be described as biomimetic assemblies of multifunctional or bimetallic catalysts. Ideally, their design can be based on quantitative analysis of the transition state for a given reaction. Alternatively, a combinatorial screening of metal centers and chiral ligands can also lead to new catalyst systems. The development of efficient high-throughput screening methods for finding a good lead or an optimized catalytic system is still in its infancy.

In asymmetric catalysis, Sharpless emphasized the importance of “ligand-accelerated catalysis” through the construction of an asymmetric catalyst from an achiral precatalyst via ligand exchange with a chiral ligand. By contrast, a dynamic combinatorial approach, where an achiral precatalyst combined with several multicomponent chiral ligands (L^1*, — —) and several chiral activator ligands (A^1*, — —) may selectively assemble into the most active and highest enantioselective activated catalyst ($ML^m* \ A^n*$).

In Chapters 4–6, recent findings on activation of C–H bonds, C–C bonds and small molecules (C=O, HCN, RN=C, and CO_2) are covered. The latest developments on C–C bond reorganization such as metathesis (which earned the Nobel prize in chemistry, 2005) are also described.

Studies on the origin of chirality generated from achiral or racemic “primitive earth” provide the basis for asymmetric catalysis starting from racemic or achiral catalysts. Asymmetric catalysis through enantiomeric fluctuation or discrimination by an external chiral bias and subsequent amplification of chirality can be developed through autocatalysis with nonlinear effects. One strategy for achieving this enantiomeric discrimination is the addition of a chiral source, which selectively transforms one catalyst enantiomer into a highly activated or deactivated catalyst enantiomer. Recent progress on “chirally economical” nonlinear phenomena, racemic catalysis, and autocatalysis are highlighted in Chapters 7–9.

Asymmetric catalysis in target- or diversity-oriented synthesis becomes an increasingly important tool. Desymmetrization of symmetric intermediates (asymmetric or enantioselective desymmetrization) is one important synthetic strategy reviewed in Chapter 10. Use of naturally occurring enzymes is one of the oldest and most important approaches employed in asymmetric desymmetrization, the so-called classic mesotrick process. Generally effective methods for highly enantioselective aziridination of olefins, reduction and C–C bond formation of aliphatic ketones, are also expected to become practical (often via a pseudodesymmetrization process) in the very near future. Asymmetric catalytic tendem (domino) reaction sequences are likely to remain at the forefront of future research efforts.

Finally in Chapters 11–13, some of the more recent discoveries that have led to a renaissance in the field of organocatalysis are described. Included in this section are the development of chiral Brönsted acids and Lewis acidic metals bearing the conjugate base of the Brönsted acids as the ligands and the chiral bifunctional acid–base catalysts.

Although tremendous progress has been made in the field of asymmetric catalysis, very few systems have become widely applicable on an industrial scale because of challenges of catalyst efficiency (turnover number (TON) and frequency (TOF), catalyst loading, applicability to a wide range of systems and with feedstocks of varying purity and the levels of enantioselectivity). The best known are the Takasago menthol process, the Novartis imine hydrogenation for metolachlor, the Sumitomo cyclopropanation for cilastatine, and the Firmenich process of fragrant paradisone. For many asymmetric reactions, the recovery and recycling of the catalysts are a serious concern for both industry and society in order to limit the amount of waste, and impurities, that affect the overall costs of the processes.

Thus, the use of catalysts in new "green" reaction media such as ionic liquids, fluorous solvents, and supercritical carbon dioxide has become a viable alternative to those discussed within the chapters.

We hope that readers will find helpful and thought-provoking information in this book written by frontrunners in their respective fields, including the areas recognized by recent Nobel prizes in chemistry.

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December 25, 2006

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1

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 synthsize 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

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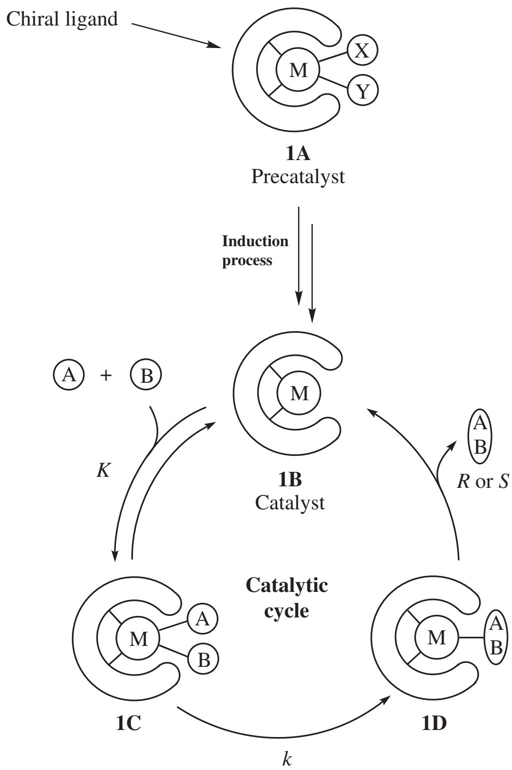


Figure 1.1. The principal of asymmetric catalysis with chiral organometallic molecular catalysts (M = metal; A, B = reactant and substrate; X, Y = neutral or anionic ligand).

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, $RhCl[P(C_6H_5)_3]_3$,[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

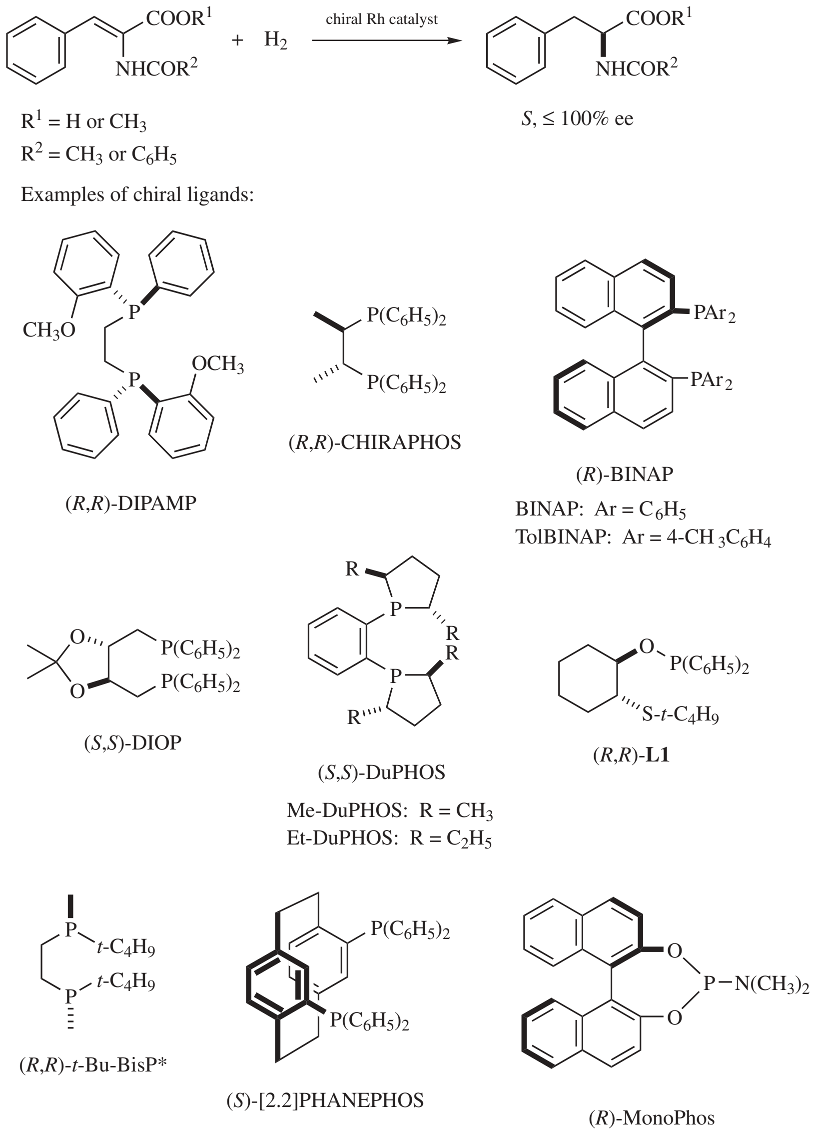


Figure 1.2. Asymmetric hydrogenation of *N*-acylated dehydroamino acids and esters.

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–Rh[8] complex have been exhaustively studied by Halpern[12–14] and Brown.[7,15,16] They proposed the "unsaturate/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 H_2 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]

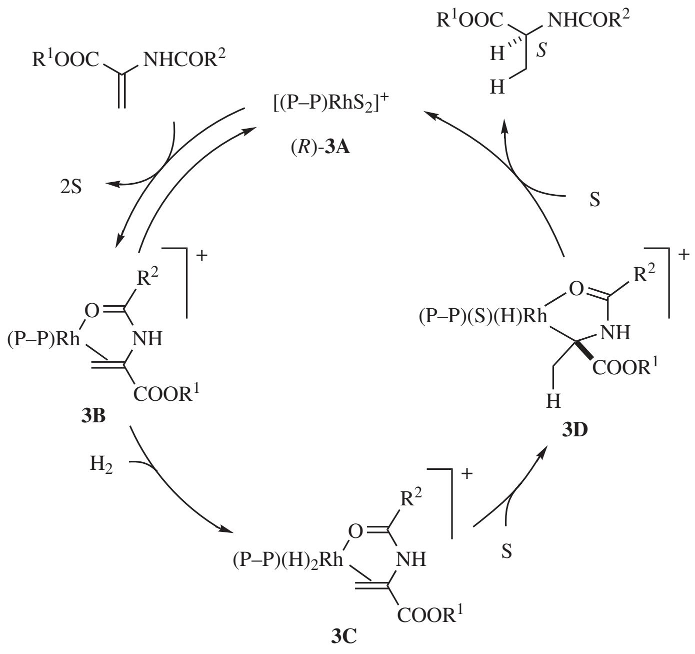


Figure 1.3. Catalytic hydrogenation of *N*-acylated dehydroamino esters via an unsaturated/dihydride mechanism; the β substituents in the substrates are omitted for clarity [P–P = (*R*,*R*)-DIPAMP, (*R*,*R*)-CHIRAPHOS, or (*R*)-BINAP; S = solvent or a weak ligand].

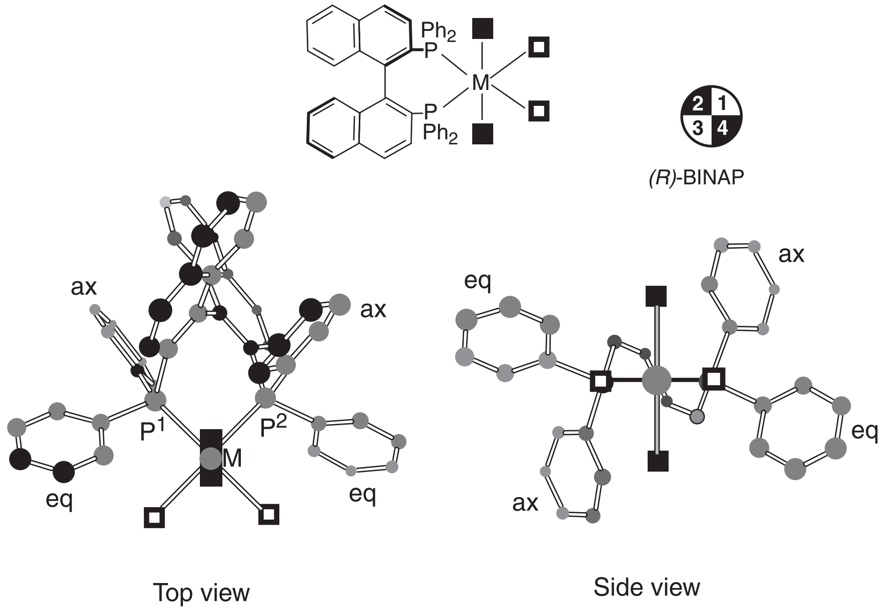


Figure 1.4. Chiral environment of an (*R*)-BINAP–transition metal complex (M = metallic element, ax = axial, eq = equatorial; □ = coordination site in the P^1–M–P^2 plane; ■ = coordination site out of the P^1–M–P^2 plane).

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*)-CHIRAPHOS[23] and (*R*,*R*)-DIPAMP[24] form a similar chiral environment with metals.

As shown in Figure 1.3, the Rh catalyst (*R*)-**3A** and a bidentate enamide substrate reversively 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,

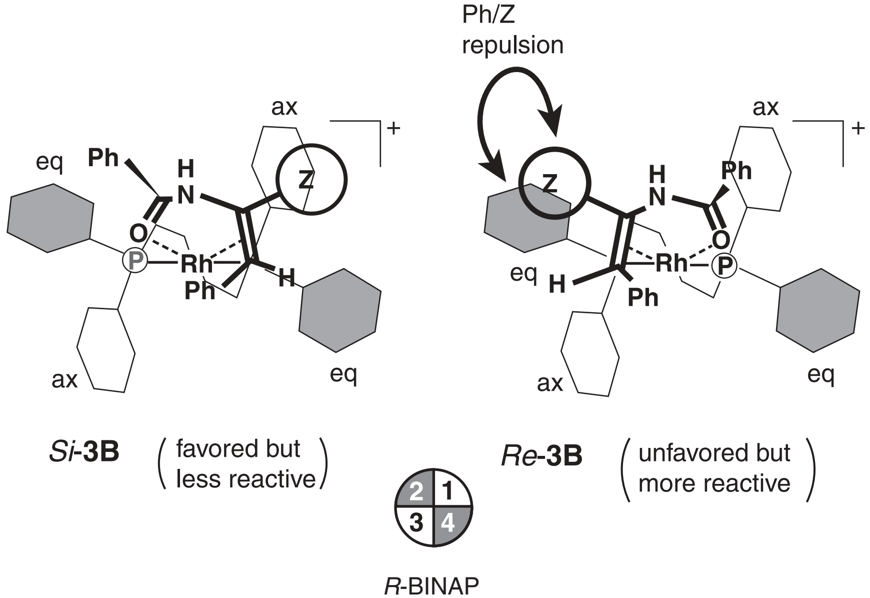
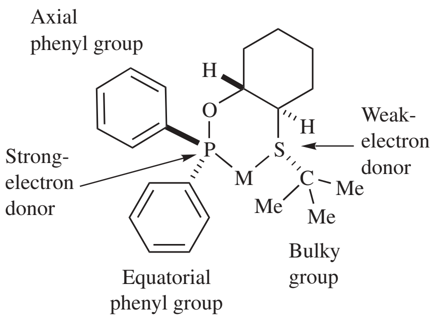


Figure 1.5. Molecular models of diastereomeric (*R*)-BINAP/enamide Rh complexes **3B** (not transition state) ($Z = CO_2R^1$; ax = axial, eq = equatorial).

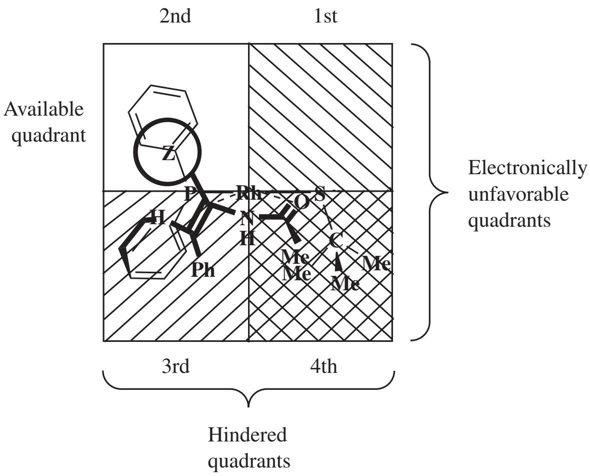
the *Re*-**3B** which is less favored because of the nonbonded repulsion between an equatorial phenyl ring of the (*R*)-BINAP ligand and a carboxylate function of substrate reacts with H_2 much faster than the more stable *Si*-**3B**, leading to the *S* isomer as a major product. The observed enantioselectivity 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



(*R*,*R*)-**L1**–metal complex

M = metal



Re-**3B**-**L1** (only one visible diastereomer)

Z = CO_2CH_3

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

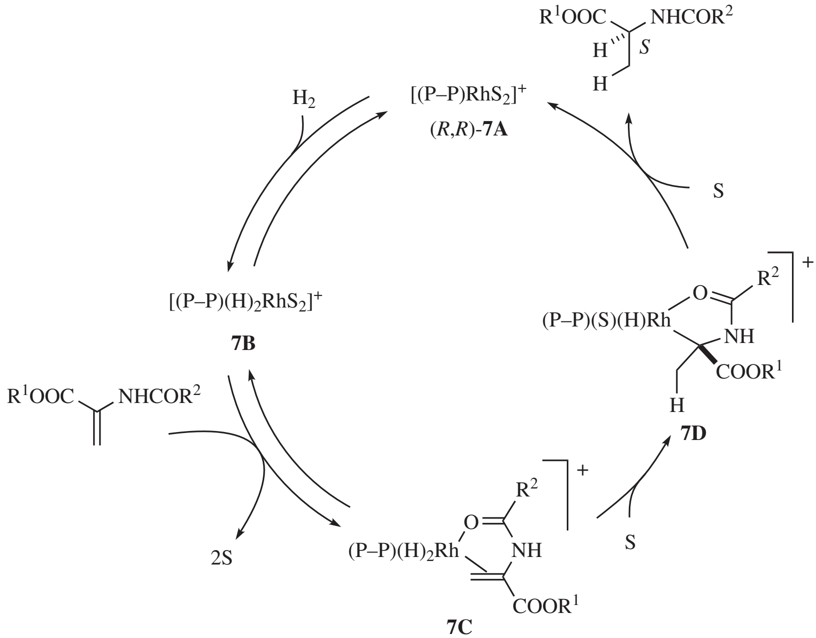


Figure 1.7. Catalytic hydrogenation of *N*-acylated dehydroamino esters via dihydride/unsaturate mechanism; the β substituents in the substrates are omitted for clarity [P–P = (*R*,*R*)-*t*-Bu-BisP*; S = solvent or a weak ligand].

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 H_2. Now the catalyst (*R*,*R*)-**7A** first reversibly reacts with H_2, giving **7B**, followed by interaction with an enamide substrate to form a substrate–RhH_2 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)H_2 complex, *Re*-**7C** and *Si*-**7C**, are possible (Figure 1.8). Formation of *Si*-**7C** is

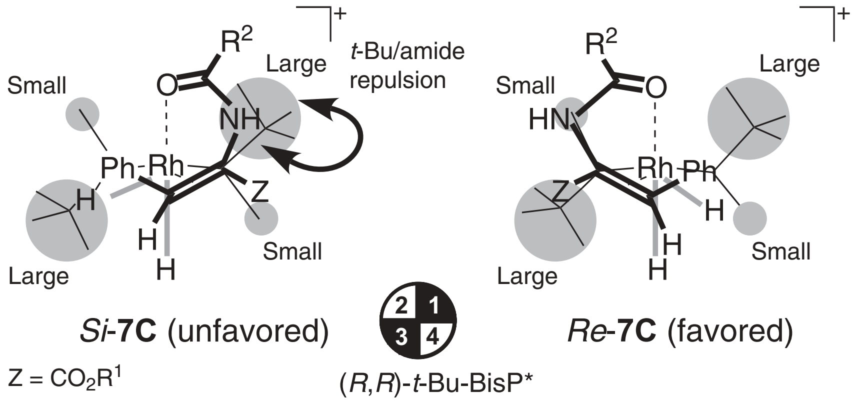


Figure 1.8. Molecular models of diastereomeric (*R*,*R*)-*t*-Bu-BisP*/enamide Rh complexes **7C** (not transition state).

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 complex[33] (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] $Ru(OCOCH_3)_2$(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

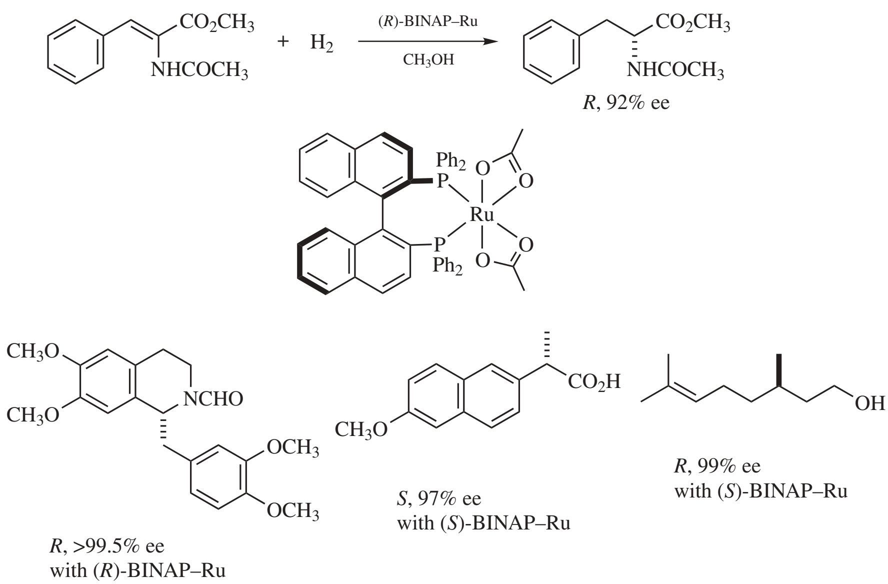


Figure 1.9. Asymmetric hydrogenation of functionalized olefins catalyzed by BINAP–Ru complexes.

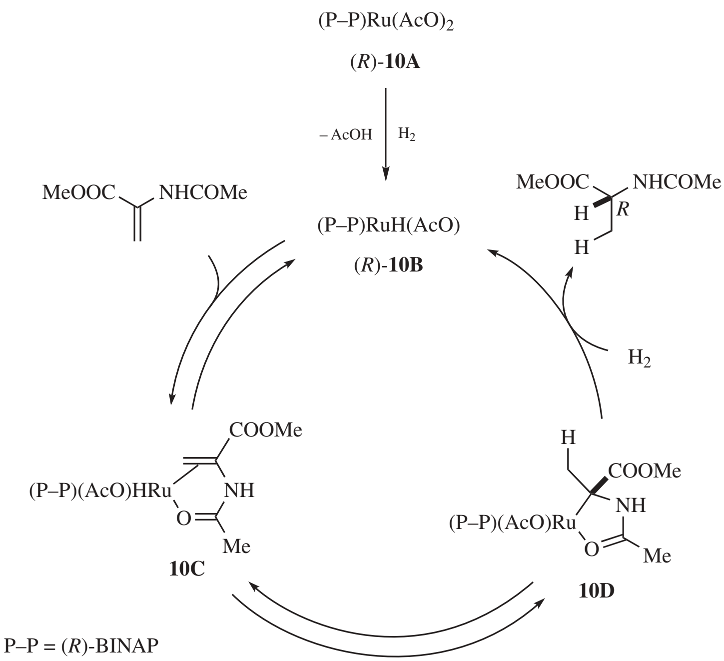


Figure 1.10. Catalytic cycle of BINAP–Ru-catalyzed hydrogenation of methyl (*Z*)-α-acetamidocinnamate involving a monohydride/unsaturated mechanism. The β substituents in the substrates are omitted for clarity.

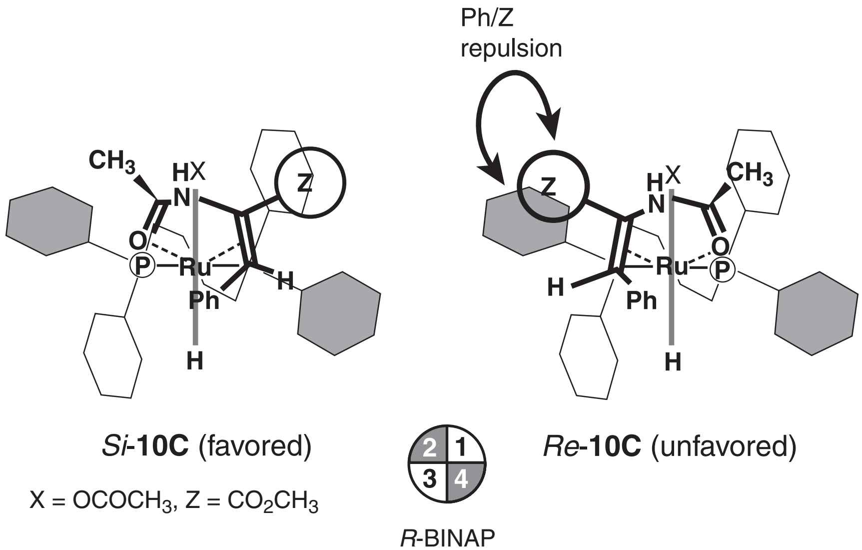


Figure 1.11. Molecular models of diastereomeric (*R*)-BINAP/enamide Ru complexes **10C** (not transition state).

"monohydride/unsaturate mechanism," in which the RuH(AcO) species **10B**, formed by the heterolytic cleavage of H_2 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 H_2, but also by CH_3OH 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/$COOCH_3$ 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 H_2 molecules, or H_2 and protic CH_3OH.

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

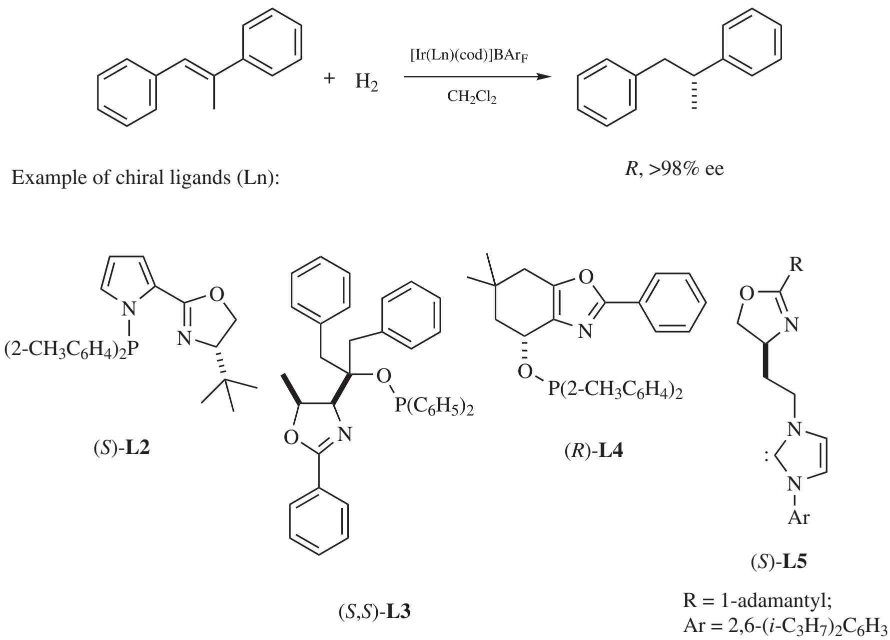


Figure 1.12. Asymmetric hydrogenation of simple olefins catalyzed by chiral Ir complexes.

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 $Ru(OCOCH_3)_2$(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 $RuCl_2$[(*R*)-binap] (polymeric form),[67] $RuCl_2$[(*R*)-binap]$(dmf)_n$ (oligomeric form),[68] [RuCl{(*R*)-binap}(arene)]Cl,[69] $[NH_2(C_2H_5)_2]$[{RuCl[(*R*)-binap]}$_2$-$(\mu\text{-Cl})_3$],[67] and other in situ formed (*R*)-BINAP–Ru complexes[70] 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]