Toward efficient asymmetric hydrogenation: Architectural and functional engineering of chiral molecular catalysts

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Asymmetric hydrogenation uses inexpensive, clean hydrogen gas and a very small amount of a chiral molecular catalyst, providing the most powerful way to produce a wide array of enantio-enriched compounds in a large quantity without forming any waste. The recent revolutionary advances in this field have entirely changed the synthetic approach to producing performance chemicals that require a high degree of structural precision. The means of developing efficient asymmetric hydrogenations is discussed from a mechanistic point of view.

Asymmetric catalysis lies outside the realm of traditional organic synthesis. It is a pervasive, global endeavor involving synthetic organic chemistry, catalytic chemistry, structural chemistry, inorganic and coordination chemistry, physical chemistry, and theoretical chemistry, as well as chemical engineering.

Chiral Molecular Catalysts: Beyond the Shape

Asymmetric catalysis is four-dimensional chemistry (1). High efficiency can be achieved only by using a combination of both an ideal 3D structure (x, y, z) and suitable kinetics (t). Currently, efficient asymmetric catalysis primarily uses a molecular catalyst that consists of a metallic element and chiral organic ligand(s) (2). Fig. 1 illustrates a typical (but not general) catalytic scheme. Under reaction conditions, the initially used precatalyst **1** is converted to the true catalyst **2** (induction process) that activates achiral molecules A and B and transforms them to the chiral product A–B (catalytic cycle). Although the ligand must create a distinct enantio-differentiating environment in transition metal-based complexes, such an architectural design does not suffice to achieve asymmetric catalysis. Some of the steps in the multistep transformation are reversible, whereas the first irreversible step, for example **3→4**, kinetically determines the absolute stereochemistry of A–B. Efficient asymmetric catalysis requires a high turnover number and high turnover frequency, but the best way to generate high catalytic activity is not immediately apparent. First, the induction process of converting **1** to **2** is often not straightforward. Furthermore, to obtain a high turnover frequency, all of the transition metal-based entities **2–4** in this cycle must be neither very unstable nor very stable, avoiding substrate and/or product inhibition. Instead, **2–4** are required to interconvert one another smoothly by
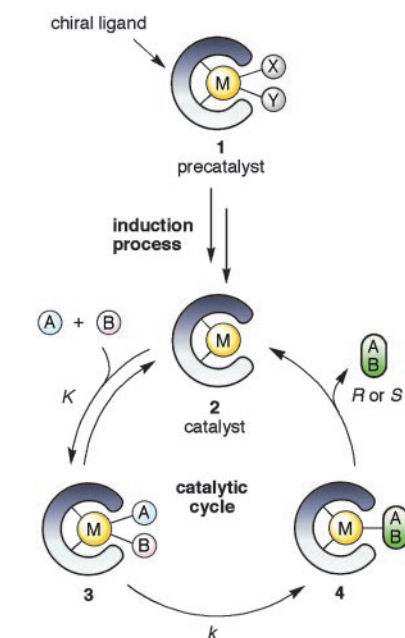

Fig. 1. The principle of asymmetric catalysis with chiral organometallic molecular catalysts. M, metal; A and B, reactant and substrate; X or Y, neutral or anionic ligand.

means of a low kinetic barrier, and without any destructive side reactions. The reaction conditions strongly influence the stability and reactivity of **1–4**. In general, both suitable architectural and functional engineering are crucial for obtaining sufficient catalytic efficiency. "Molecular catalysis" can cope with such requirements, because any molecules, by definition, can be designed and synthesized at will.

This perspective deals largely with the intrinsic mechanistic aspects of asymmetric hydrogenation developed in our laboratories (3–5). Although H—H bonds are readily cleaved by transition metal complexes, truly useful asymmetric hydrogenations are limited. 2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl (BINAP)–transition metal complexes are shaped in a manner

that is beneficial for chiral recognition (Fig. 2) (6, 7), and these complexes can act as hydrogenation catalysts. However, their efficiency highly depends on the structures of unsaturated substrates, the properties of the central metal and the auxiliary anionic or neutral ligands, and the reaction conditions (e.g., hydrogen pressure, temperature, solvent, and additive). No universal catalysts are known to exist, because of the diversity of unsaturated organic compounds.

Metallic Elements: Rhodium vs. Ruthenium in Asymmetric Hydrogenation of Enamides

In 1980, we reported that cationic BINAP–Rh(I) complexes catalyze the hydrogenation of α-(acylamino)acrylic acids and esters to give the amino acid derivatives in >90% enantiomeric excess (ee) (8). For example, in the presence of [Rh{(R)-binap}(CH$_3$OH)$_2$]$^+$ [(R)-**5**], (Z)-α-(benzamido)cinnamic acid is converted to (S)-N-benzoylphenylalanine in near 100% ee and 97% yield [substrate/catalyst molar ratio (S/C) = 100, 4 atm, room temp, 48 h, C$_2$H$_5$OH] (Fig. 3a). This reaction appeared to be excellent in terms of enantioselection, but proved to be less than ideal because of the "unsaturate/dihydride mechanism" that was thoroughly substantiated by Halpern, Brown, and coworkers (Fig. 3b) (9–11). When a C_2-chiral diphosphine ligand such as CHIRAPHOS or DIPAMP is used, the Rh complex **5** forms a mixture of two diastereomeric substrate complexes **6**, de-
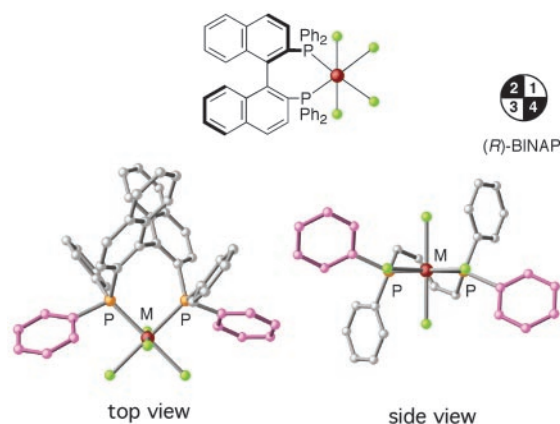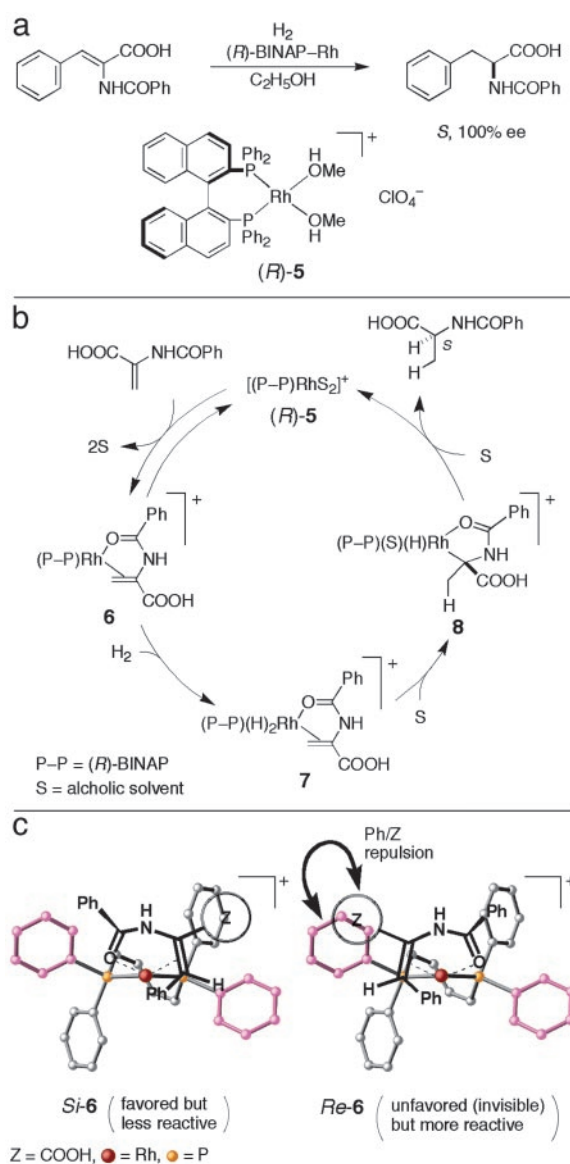
Fig. 2. Chiral environment of an (*R*)-BINAP–transition metal complex. The second and fourth quadrants are more crowded than the first and third quadrants because of shielding by the pink phenyl groups. M, metallic element.

tion remains far from ideal. Excellent enantioselection is obtainable only with Rh complexes of DuPhos, certain monodentate phosphites, or phosphoamidites (13–16) or by using the dihydride/unsaturate mechanism (17).

A breakthrough in this respect came when the Rh(I) element was replaced by Ru(II). When methyl (*Z*)-α-(acetamido)-cinnamate was hydrogenated in the presence of Ru(OCOCH$_3$)$_2$[(*R*)-binap] [(*R*)-**9**] (18, 19) (S/C = 200, 1 atm, 30°C, 24 h, CH$_3$OH), methyl (*R*)-α-(acetamido)cinnamate was obtained in 92% ee and 100% yield (Fig. 4*a*) (20). Most notably, the sense of the asymmetric induction was the opposite of that obtained with the (*R*)-BINAP–Rh catalyst (Fig. 3*a*), namely, *R/R* vs. *R/S* (20, 21). This contrasting
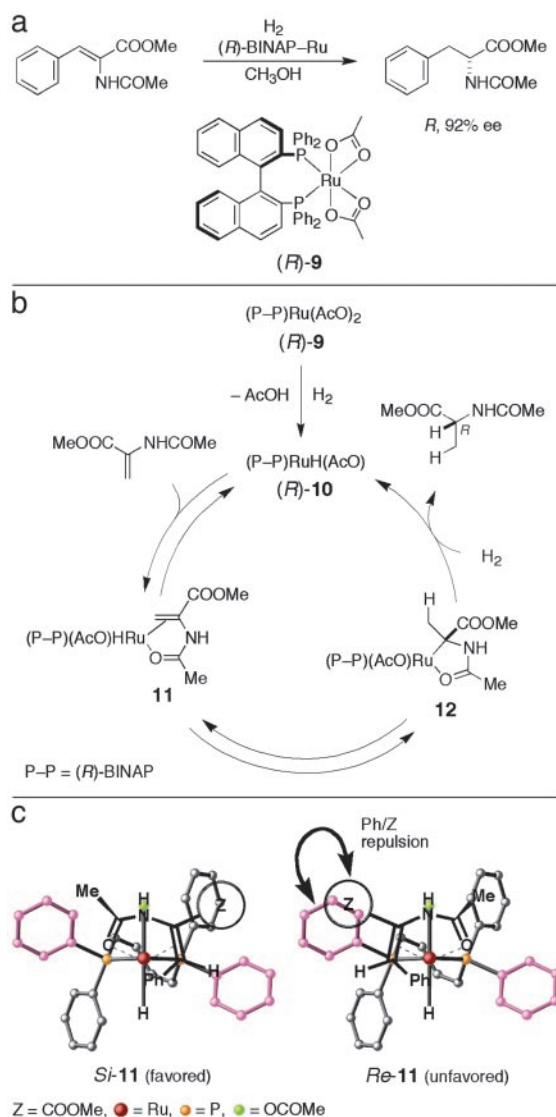
pending on the *Re/Si* face selection at C(2), which lead to the *S* or *R* hydrogenation product. Therefore, the enantioselectivity is determined by the relative equilibrium ratio and reactivity of diastereomeric **6**. Most importantly, under these reaction conditions, the more stable, major diastereomer is consumed much more slowly than the less stable, minor isomer because of the lower reactivity toward H$_2$, giving **7**, or, if this step is reversible, this leads to the more difficult migratory insertion of the Rh dihydride species, **7**→**8**. This situation can be monitored by ^{31}P NMR. Because of the superior chiral recognition ability of BINAP, the ^{31}P-NMR spectrum of a 6:1 mixture of (*Z*)-α-(benzamido)cinnamic acid and (*R*)-BINAP–Rh catalyst **5** in CH$_3$OH showed a single eight-line signal for *Si*-**6**, whereas the signal of the minor *Re*-**6** was undetectable (Fig. 3*c*) (12). Thermodynamically favored *Si*-**6**, leading to the *R* product, is only weakly reactive and, before hydrogenation, is converted to the NMR-invisible but highly reactive diastereomer *Re*-**6**, giving the *S* product, via decoordination and recoordination of the substrate. Therefore, the observed enantioselectivity is a result of the delicate balance of the stability and reactivity of diastereomeric **6**. Because of this inherent mechanistic problem, the optimum conditions leading to near 100% enantioselectivity are obtainable only by a very careful choice of reaction parameters. The reaction must be conducted under a low substrate concentration and low hydrogen pressure. The BINAP–Rh-catalyzed reaction occurs very slowly, because the reactive substrate/Rh complex **6** is present in a very low concentration under these hydrogenation conditions. The scope of the olefinic substrates is narrow. Thus, BINAP–Rh-catalyzed hydrogenation suffers from such a serious mechanistic limitation that this particular asymmetric reac-

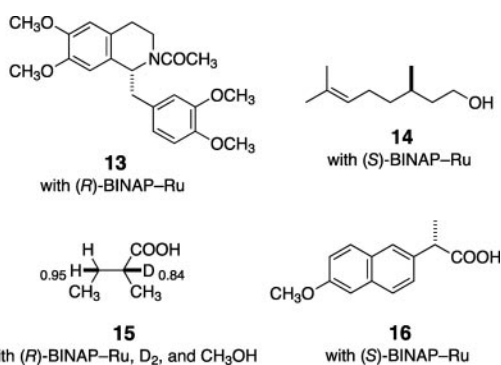
Fig. 3. Hydrogenation of (*Z*)-α-benzamidocinnamic acid catalyzed by an (*R*)-BINAP–Rh complex. (*a*) Reaction scheme. (*b*) Catalytic cycle, where the β-phenyl group in the substrate is omitted for clarity. (*c*) Diastereomeric Rh complexes.

Fig. 4. Hydrogenation of methyl (*Z*)-α-acetamidocinnamate catalyzed by an (*R*)-BINAP–Ru complex. (*a*) Reaction scheme. (*b*) Catalytic cycle, where the β-phenyl group in the substrate is omitted. (*c*) Diastereomeric Ru complexes.

standard Rh-catalyzed reaction, which uses only one H_2 molecule per product.

Replacement of Rh by Ru has greatly extended the reaction scope, allowing for the asymmetric hydrogenation of many kinds of olefinic substrates (Fig. 5) (6, 7). For example, the reaction with N-acylated benzylidene-tetrahydroisoquinolines gives chiral benzyl-tetrahydroisoquinolines such as N-protected tetrahydropapaverine (**13**) in near 100% ee, providing a general method of asymmetric synthesis of iso-quinoline alkaloids (23). Hydrogenation of geraniol possessing two olefinic bonds occurs only at the allylic alcohol part, thereby affording citronellol (**14**) in >95% ee (24).

Hydrogen Source

In the hydrogenation of enamides, the Ru—C bond of **12** is cleaved mainly by H_2 (Fig. 4*b*) but to some extent (≈14%) also by protic CH_3OH (20). The pro-tonolysis pathway becomes conspicuous when α,β-unsaturated carboxylic acids are used as a substrate because of a change in the mechanism or a subtle difference in the properties of the Ru—C bond (25, 26). Reaction of (*Z*)-2-methyl-2-butenoic acid with D_2 and (*R*)-**9** in CH_3OH (S/C = 100, 4 atm, room temp) afforded (*R*)-2-methylbutanoic acid-2*d* (**15**) in 91% ee and 100% yield (Fig. 5). The hydrogen at C(3) comes mainly from hydrogen gas and the C(2) hydrogen is from CH_3OH. The reaction is net hydrogenation, whereby both H_2 and protic agents can serve as the hydrogen source. This hydro-genation reaction can be performed in supercritical CO_2 as well (27). In fact, the sense and degree of the asymmetric hy-drogenation of α,β-unsaturated carboxylic acids highly depends on the structure of the substrates and the hydrogen pressure, indicating the existence of various cata-lytic pathways. High-pressure (>100 atm) hydrogenation of an α-arylacrylic acid in CH_3OH affords (*S*)-naproxen (**16**), an important antiinflammatory agent, in 97% ee (Fig. 5) (28).

behavior was found to be caused by a "monohydride/unsaturate mechanism" (20, 22), in which the Ru monohydride **10**, formed by the heterolytic cleavage of H_2 by the precatalyst **9**, acted as true catalyst (Fig. 4*b*). Importantly, unlike in the Rh chemistry involving the "unsaturate/dihy-dride mechanism" (9–12), the metal hy-dride species in this reaction is generated before the substrate coordination. The stereochemistry of the product is deter-mined by the cleavage of the Ru—C bond in **12** largely by H_2. The enantiomer ratio corresponds well to the relative stability of the diastereomeric substrate/RuH com-plexes *Si*- and *Re*-**11** (Fig. 4*c*). Here, the major *Si*-**11** is converted to the *R* hydroge-nation product in a straightforward man-ner, i.e., the migratory insertion followed by hydrogenolysis. Notably, the two hydro-

gen atoms incorporated in the product are from two different H_2 molecules, as proven by isotope labeling experiments, and this result stands in contrast to the

Fig. 5. Examples of BINAP–Ru-catalyzed asymmetric hydrogenation of olefins.

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Significance of Anionic Ligands: Asymmetric Hydrogenation of Functionalized Ketones

Ru(OCOCH$_3$)$_2$(binap) (**9**) (18, 19), although excellent for the asymmetric hydrogenation of functionalized olefins, is totally ineffective in reactions of structurally similar ketones such as β-keto esters. This failure is caused by the properties of the anionic ligands, in particular, the carboxylates. On the other hand, when the carboxylates are simply replaced by halides, very high catalytic activity can be generated for functionalized ketones. Thus, the useful chiral precatalysts include RuX$_2$(binap) (**17**) (X = Cl, Br, I; polymeric form) (29, 30), [RuX(binap)(arene)]Y (X = halogen, Y = halogen or BF$_4$) (31), [NH$_2$(C$_2$H$_5$)$_2$][{RuCl(binap)}$_2$-(μ-Cl)$_3$] (32, 33), and other *in situ*-formed halogen-containing BINAP–Ru complexes (34, 35). Various β-keto esters are hydrogenated in alcoholic solvent with an S/C of up to 10,000 to give chiral β-hydroxy esters in high ee (Fig. 6a).

Fig. 6b presents a mechanistic model, in which the actual catalyst is RuHCl **18**, formed by the reaction between **17** and H$_2$ (36). First, **18** interacts reversibly with the β-keto ester to form the σ-type chelate complex **19**, in which metal-to-carbonyl hydride transfer is geometrically difficult. Then, protonation occurs at the oxygen to increase the electrophilicity of the carbon and convert the geometry from σ to π, thereby facilitating the hydride migration. The hydroxy ester ligand in the resulting product **20** is liberated by solvent molecules. The cationic Ru complex **21** once again cleaves H$_2$, thus regenerating **18**. This catalytic cycle takes place repeatedly. Enantioselection of a ratio of >99:1 is achieved in the hydride transfer step **19**→**20**. Here, the key is the carbonyl protonation in **19**, which is caused by HCl (37, 38) generated in the induction step **17**→**18**. When Ru(OCOCH$_3$)$_2$(binap) (**9**) is used, acetic acid is produced in place of HCl. The weak carboxylic acid is unable to generate high catalytic activity. Thus, even achiral anionic ligands in the precatalyst are not innocent in catalytic hydrogenation (39).

Ligation of the ester C=O to the Ru center stabilizes the transition states (TSs) in the hydride transfer step. Thanks to the shape of (R)-BINAP, diastereomeric *Si*- and *Re*-**22** are clearly differentiated (Fig. 6c). The *R*-generating *Si* structure is highly favored over the *S*-generating *Re* isomer, which suffers from the phenyl/R repulsive interaction. In addition, the oxygen/Ru interaction in **22** is crucial for catalytic activity as well. Notably, the BINAP–Ru-catalyzed hydrogenation of β-keto esters can be performed even in acetone containing a small amount of wa-
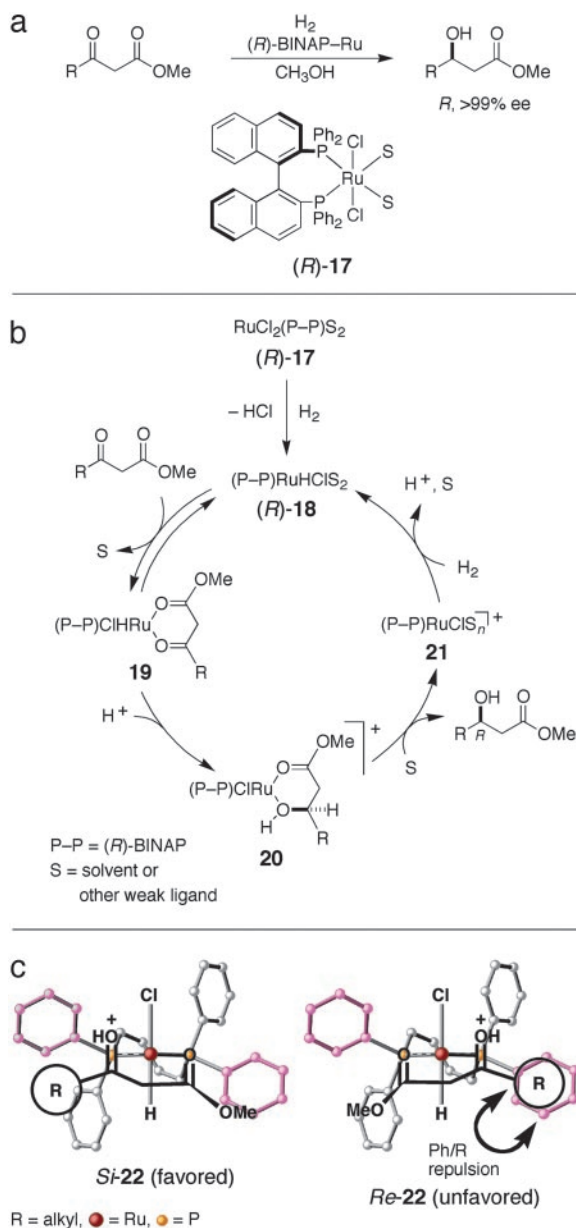
ter. Acetone, the simplest ketone used as a solvent, is almost inert to the hydrogenation, whereas the structurally more complex β-keto ester substrates are easily hydrogenated. This difference proves to be an important distinction.

The list of potential substrates can be extended to include various ketones possessing a directive functional group such as a dialkylamino, hydroxyl, alkoxyl, siloxyl, keto, halogeno, alkoxycarbonyl, alkylthiocarbonyl, dialkylaminocarbonyl, phosphoryl, and sulfoxyl group, among other possibilities (3–7). This asymmetric hydrogenation has been used for the synthesis of a large variety of biologically or pharmaceutically important chiral com-

pounds (3–5). For example, the simple asymmetric hydrogenation of acetol to (R)-propanediol (40) is used for industrial synthesis of levofloxacin (**23**) (Fig. 7), a quinolone antibacterial agent.

Solvent Effects on Stereoselectivity in Dynamic Kinetic Resolution

Although BINAP–Ru-catalyzed hydrogenation is normally best conducted in alcoholic solvents, sometimes different solvents must be used to achieve a high degree of stereoselectivity. In a chiral environment, enantiomers react at different rates. Therefore, if one chooses the appropriate chiral catalyst and reaction conditions, racemic β-keto esters possessing a
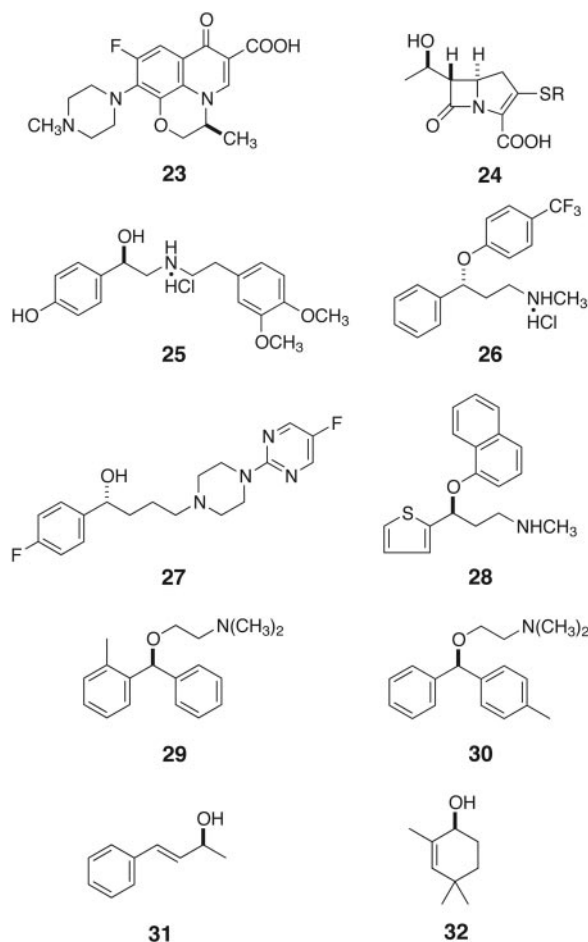

Fig. 6. Hydrogenation of β-keto esters catalyzed by an (R)-BINAP–Ru complex. (a) Reaction scheme. (b) Catalytic cycle. (c) Diastereomeric transition states.

Fig. 7. Chiral compounds obtained by the asymmetric hydrogenation of ketones.

configurationally labile α-stereogenic center can be selectively transformed into one stereoisomer of the four possible stereoisomers (41). As illustrated in Fig. 8, (R)-BINAP–Ru-catalyzed the hydrogenation of racemic methyl α-(benzamidomethyl)-acetoacetate (33) in dichloromethane (not CH$_3$OH) ([33] = 0.2 M, [(R)-17] = 1.3 mM, 100 atm, 50°C, 40 h), which gives the 2S,3R hydroxy ester (S,R)-34 with 94:6 syn/anti diastereoselectivity and 99.5:0.5 enantioselectivity (42). This asymmetric synthesis via a dynamic kinetic resolution is used for the industrial production of chiral 4-acetoxyazetidinone, a synthetic intermediate for carbapenem antibiotics (24) (Fig. 7).

Computer-aided quantitative analysis has revealed the following results under these catalytic conditions: (i) the inherent, highest S,R/S,S/R,R/R,S selectivity at time $t = 0$ ($w/x/y/z$ partition parameter, where the starting S and R ketones are assumed to exist in equal amounts) is 93.8:0.1:5.6:0.49; (ii) (S)-33 is hydrogenated 15 times faster than (R)-33; (iii) the inversion of the slow-reacting (R)-33 to (S)-33 takes place 92 times faster than hydrogenation; (iv) the extent of the (R)-

BINAP catalyst-based asymmetric induction (C_{cat}) is calculated to be 104:1 in favor of the 3R isomer; and (v) the substrate-based asymmetric induction (C_{sub}) is 9:1 in favor of syn C(2)/C(3) stereochemistry (43). Thus, various steric and kinetic parameters can be beneficially combined to selectively produce the desired 2S,3R stereoisomer. When the reaction is conducted in CH$_3$OH ([33] = 0.2 M, [(R)-17] = 1.3 mM, 100 atm, 25°C, 20 h), the diastereoselectivity is drastically reduced to form a 1:1 mixture of (S,R)-34 in 93% ee and (R,R)-34 in 97% ee. Under such conditions, both (S)- and (R)-33 have comparable reactivity, leading to hydrogenation.

Metal–Ligand Bifunctional Catalysis: The NH Effect in the Asymmetric Hydrogenation of Simple Ketones

For the mechanistic reasons given in Fig. 6, simple unfunctionalized ketones are inert to hydrogenation in the presence of RuX$_2$(diphophine) (X = halogen). On the other hand, the newly devised RuCl$_2$-(diphosphine)(1,2-diamine) complexes including 35, 37, and 39 are excellent precatalysts for the asymmetric hydrogenation of simple ketones that lack heteroatom functionality capable of producing any interaction with the transition metal center (Fig. 9) (36). The use of BINAP and a suitably shaped chiral 1,2-diamine allows for the practical asymmetric hydrogenation of various ketones in 2-propanol containing an alkaline base cocatalyst such as KOH, KOCH(CH$_3$)$_2$, and KO-t-C$_4$H$_9$. Moreover, when RuH-(η^1-BH$_4$)(binap)(1,2-diamine), 36 and 38, is used as precatalyst, such a strong base is unnecessary (44). In these complexes, the presence of an NH$_2$ moiety in the diamine ligand is crucial for obtaining high catalytic activity. This type of hydrogenation tolerates many substituents, including halogen, CF$_3$, alkoxyl, ester, amide, NO$_2$, and NH$_2$, as well as various electron-rich and -deficient heterocycles (45, 46). In addition, this reaction is rapid and productive. The hydrogenation of acetophenone with RuCl$_2$[(R)-tolbinap][(R,R)-dpen] [DPEN=1,2-diphenylethylenediamine) [(R,RR)-37] proceeds with a high turnover number of 2,400,000 and a high turnover frequency of 63 s^{-1} (47). This asymmetric hydrogenation has been ap-
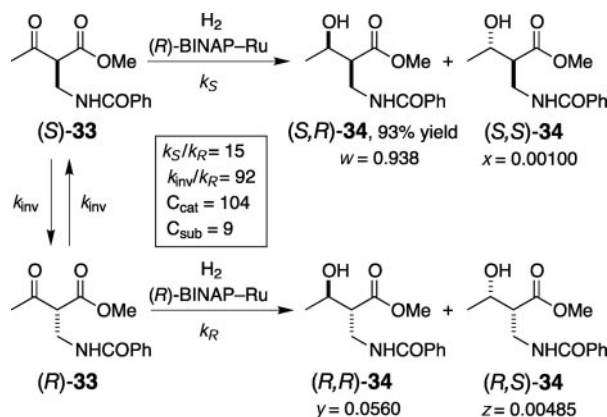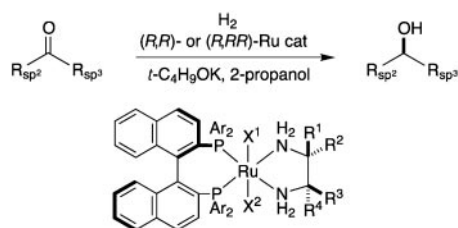

Fig. 8. Stereoselective hydrogenation of racemic methyl α-(benzamidomethyl) acetoacetate (33) with (R)-17 under dynamic kinetic resolution.

(R,R)-35: Ar = 3,5-(CH₃)₂C₆H₃; R¹ = R² = 4-CH₃OC₆H₄;
R³ = (CH₃)₂CH; R⁴ = H; X¹ = X² = Cl

(R,SS)-36: Ar = 3,5-(CH₃)₂C₆H₃; R¹ = R⁴ = C₆H₅; R² = R³ = H;
X¹ = BH₄; X² = H

(R,RR)-37: Ar = 4-CH₃C₆H₄; R¹ = R⁴ = H; R² = R³ = C₆H₅;
X¹ = X² = Cl

(R,RR)-38: Ar = 4-CH₃C₆H₄; R¹ = R⁴ = H; R² = R³ = C₆H₅;
X¹ = BH₄; X² = H

(R,SS)-39: Ar = 4-CH₃C₆H₄; R¹ = R⁴ = C₆H₅; R² = R³ = H;
X¹ = X² = Cl

Fig. 9. Asymmetric hydrogenation of simple ketones catalyzed by BINAP/1,2-diamine–Ru complexes.

plied to the synthesis of various pharmaceutically important chiral compounds such as denopamine hydrochloride (**25**) (β_1-receptor agonist), fluoxetine hydrochloride (**26**) (antidepressant), BMS 181100 (**27**) (antipsychotic), duloxetine (serotonin and norepinephrine inhibitor) (**28**), orphenadrine (**29**) (antihistaminic and anticholinergic), and neobenodine (**30**) (antihistaminic) (Fig. 7) (48, 49).

Furthermore, cyclic and acyclic α,β-unsaturated ketones can be selectively converted into allyllic alcohols of high enantiomeric purity (45, 46). This selectivity is in contrast with that of diamine-free RuX₂(binap) complexes (X = carboxylate or halide) (23) converting geraniol or nerol to **14** in high ee (Fig. 5). The chiral alcohol **32** (Fig. 7), a key intermediate leading to various bioactive compounds, is obtainable by the hydrogenation of the corresponding cyclohexenone in the presence of (R,SS)-**39**. In addition, various cyclic and acyclic ketones are hydrogenated with high diastereoselectivity by simply using RuCl₂(PAr₃)₂(en) and an alkaline base (50).

The high rate of the reaction and carbonyl selectivity are based on nonclassical metal–ligand bifunctional catalysis, which uses an "NH effect," as illustrated in Fig. 10 (51). Under the present hydrogenation conditions, the catalyst precursor **40** generates **41** equilibrating with **44**. The major cationic 16e species **41** is converted to **42** and then **43**, which in turn reacts with a ketonic substrate to form **44** and an alcohol product. The 16e Ru amide **44** returns largely to **41** by protonation, but gives some **43** caused by the reaction with H₂. The reducing 18e Ru dihydride **43** possesses the hydride and two nitrogen atoms with a *fac* relationship. When (R)-BINAP and (R,R)-DPEN are used as chiral ligands, two hydrogen atoms are asym-

metrically activated, as shown by hydridic RuH and protic NHax in (R,RR)-**43**. This 18e complex reacts with a simple ketone in its outer coordination sphere, where neither a ketone/Ru nor an alkoxy/Ru complex is involved. This mechanistic scheme is distinct from the conventional model shown in Fig. 1. The six-membered, pericyclic transition state is schematically shown by **45**.

Kinetic Resolution of Simple Ketones Under Basic and Neutral Conditions

The hydrogenation of racemic 2-isopropyl-cyclohexanone (**46**) in 2-propanol containing (R)-**17**, (S,S)-DPEN, and KOH ([**46**] = 0.8 M, [**17**] = [DPEN] = 1.6 mM, [KOH] = 32 mM, 28°C, 11 h) quantitatively gives the 1S,2S alcohol (S,S)-**47** in 93% ee with 99.8:0.2 cis selectivity (Fig.
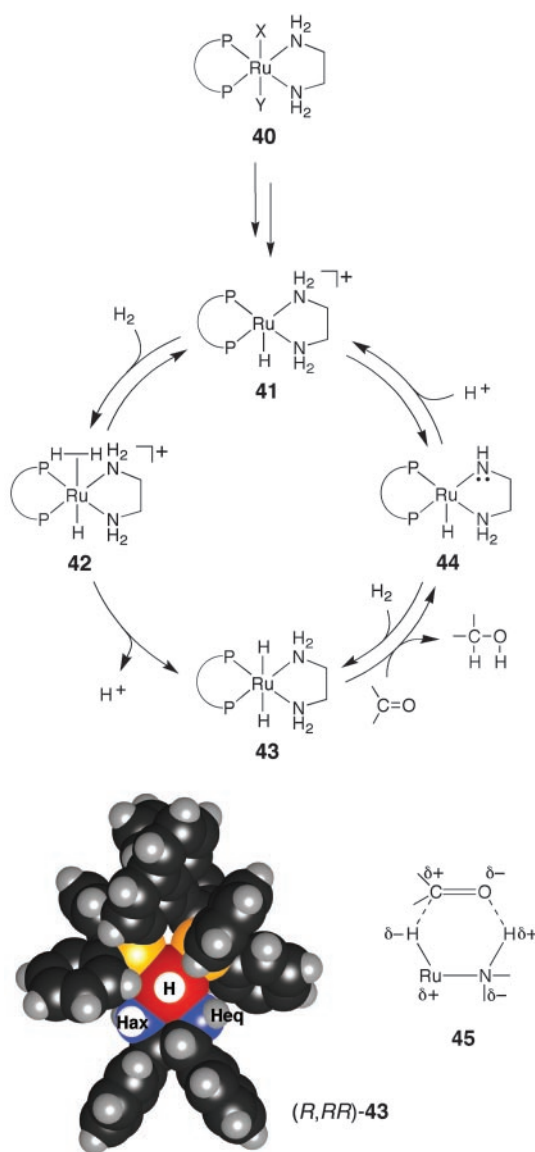

Fig. 10. Metal–ligand bifunctional mechanism in the Ru-catalyzed hydrogenation of ketones.
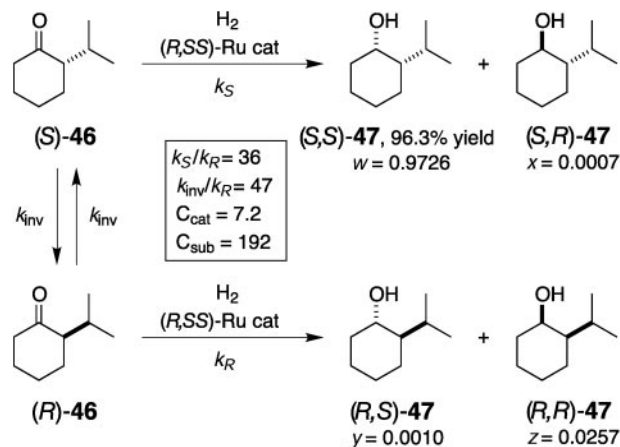
Fig. 11. Dynamic kinetic resolution of a racemic ketone by hydrogenation with (*R*)-**17**, (*S*,*S*)-DPEN, and KOH in 2-propanol.

11) (50). This dynamic kinetic resolution is based on the facile configurational inversion of the substrate caused by the alkaline base and a protic solvent. These conditions are appropriate for producing alcoholic products of high ee (50, 52) but

remain unsuitable for obtaining the configurationally labile starting ketones. However, when racemic **46** was hydrogenated in 2-propanol with (*R*,*SS*)-**36**, but without any base (S/C = 2,000, 8 atm, 25°C, 2 h), at 53% conversion, unreacted (*R*)-**46** with

91% ee was recovered together with the 1*S*,2*S* alcohol (*S*,*S*)-**47** in 85% ee (44).

Conclusion

Asymmetric hydrogenation is a core technology in modern chemical synthesis. High rates and selectivities are attainable only by the combination of structurally well designed catalysts and suitable kinetic parameters (2, 36). All of our Ru-based molecular catalysts commonly involve an octahedral BINAP–RuH species; however, the reactivity of these catalysts is remarkably influenced by the anionic or neutral auxiliaries present in the other three coordination sites. Deep mechanistic insight is indispensable for developing truly efficient asymmetric hydrogenation reactions. A diverse array of chiral compounds are accessible by this purely chemical means. The recent substantial expansion of this subject has given rise to enormous economic potential in the chemical manufacture of pharmaceuticals, animal health products, agrochemicals, fungicides, pheromones, flavors, and fragrances (53).

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