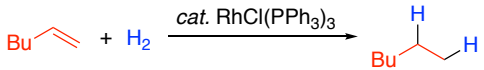
3. Reactions catalyzed by transition-metal complexes

3-1. Hydrogenation

(1) Hydrogenation of alkenes

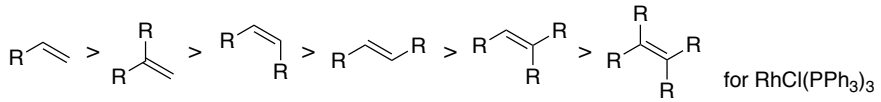


G. Wilkinson, *Chem. Commun.*, 131 (1965); *Nature*, **208**, 1203 (1965).

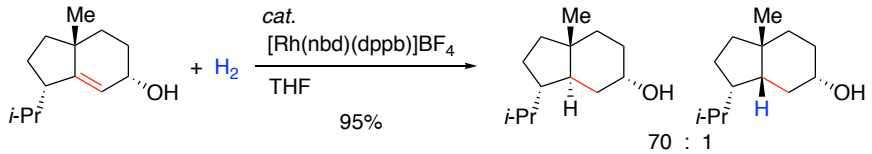
- As with metal-particle catalysts such as palladium on charcoal, Wilkinson complex, $RhCl(PPh_3)_3$, catalyzes the hydrogenation of alkenes.
- Some other metal complexes also work as catalysts for the hydrogenation.
- The homogeneous metal-complex catalysts are as useful for organic synthesis as the heterogeneous metal-particle catalysts, because the former exhibits setreo- and/or site-selectivity different from the latter.

(a) Reactivity of C–C double bond

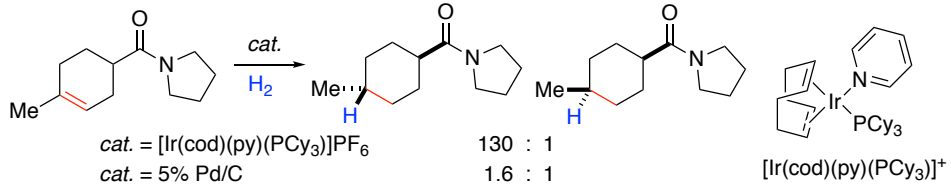
- Reaction rate of the rhodium-catalyzed hydrogenation is sensitive to the steric effect of the substituents on the C–C double bond.
- The reactivity depends on the binding constant of olefin to the metal atom.



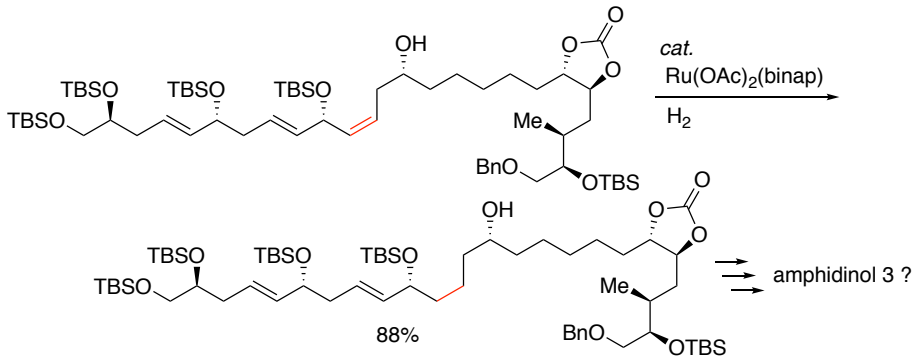
- An electron-withdrawing group enhance the reactivity.
- Lewis basic functional group neighboring on the alkene often works as the directing group to facilitate the hydrogenation.



D. A. Evans, *J. Am. Chem. Soc.*, **106**, 3866 (1984).

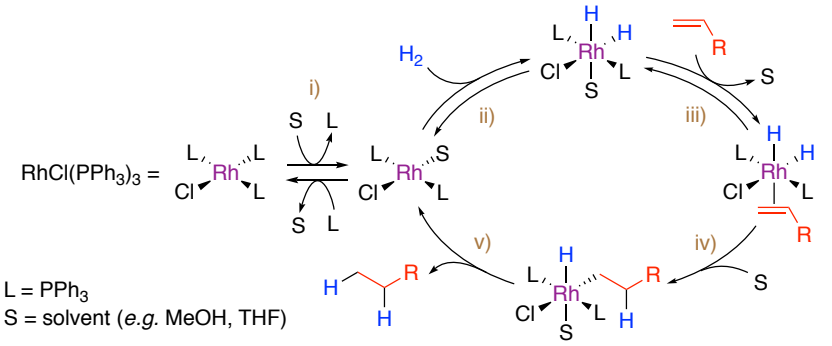


A. G. Schultz, *J. Org. Chem.*, **50**, 5905 (1985).



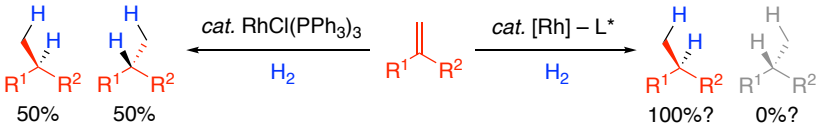
W. R. Roush, *Org. Lett.*, **7**, 1411 (2005).

(b) Mechanism of the hydrogenation with Wilkinson catalyst



- A typical catalytic cycle of the hydrogenation of alkenes with Wilkinson complex is as follows:
  - i) Dissociation of L: One of phosphine ligands on Rh is replaced by a solvent molecule.
  - ii) Oxidative addition of H_2: The rhodium(I) species is inserted into the H–H bond.
  - iii) Coordination of alkene: The solvent on rhodium is replaced by the alkene substrate.
  - iv) Migratory insertion of alkene: One of the Rh–H bond adds to the C–C double bond.
  - v) Reductive elimination: The resulting alkyl group and hydride are eliminated from the Rh to form the C–H bond.
- The mechanism is affected by the substrate, catalyst, and reaction conditions. For example, the C–C double bond will interact with the rhodium(I) prior to the oxidative addition of H_2 when the substrate has an appropriate directing group. In some cases, monohydridometal species participates in the catalytic cycle.

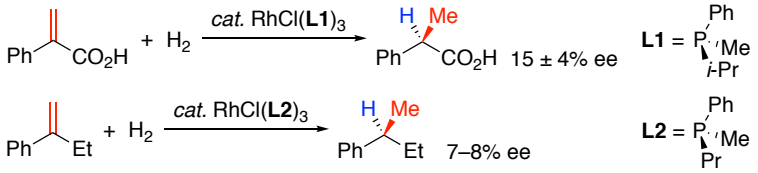
(c) Enantioselective hydrogenation of alkenes with asymmetric catalysis



L* = optically active phosphine

- The hydrogenation of prochiral alkenes must yield the racemic products when an achiral or racemic metal complex is employed as the catalyst, because the frontside attack of H2 equally takes place to the backside attack.
- The frontside (or backside) attack may be restricted when the metal complex has a well-designed phosphine ligand in place of PPh_3.

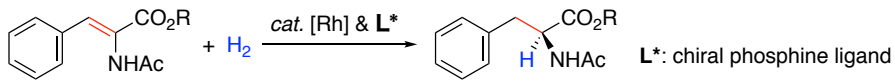
(i) Initial attempt



W. S. Knowles, *Chem. Commun.*, 1443 (1968); L. Horner, *Angew. Chem. Int. Ed.*, **7**, 942 (1968).

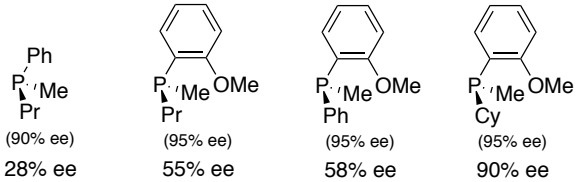
- To achieve the asymmetric catalysis, the PPh3 ligands in Wilkinson complex were replaced by the optically active phosphine bearing three different substituents.
- The chiral ligand possesses its stereogenic center on its phosphorus atom.
- These reports proved the chiral spectator ligand possible to control the stereochemistry in catalytic reactions. However, the enantioselectivities are very low and insufficient for organic synthesis.

(ii) Progress of asymmetric hydrogenation of 2-(*N*-acylamino)cinnamates



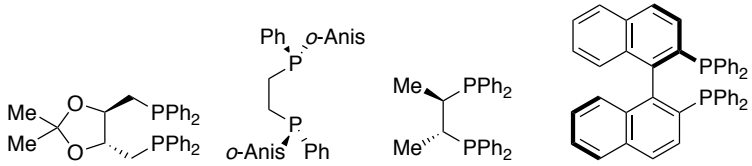
- The asymmetric hydrogenation transforms the substrate, 2-(*N*-acylamono)cinnamate or related compound, into the optically active protected phenylalanine.
- The C–C double bond and amide carbonyl oxygen in the substrate chelate the rhodium atom. The chelation restricts the conformation of the substrate–catalyst complex.

i) Optimization of *P*-chiral monophosphine (–1972)



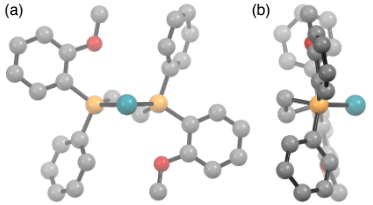
W. S. Knowles, *J. Chem. Soc., Chem. Commun.*, 10 (1972).

ii) Application and improvement of bidentate bisphosphine (1971–1980)

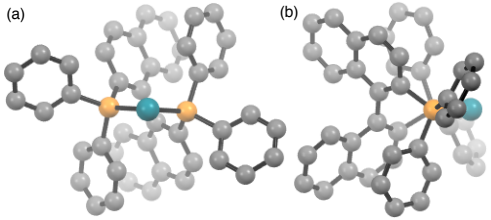


Review: W. S. Knowles, *Acc. Chem. Res.*, **16**, 106 (1983). 1) H. Kagan, *J. Chem. Soc., Chem. Commun.*, 481 (1971); *J. Am. Chem. Soc.*, **94**, 6429 (1972). 2) W. S. Knowles, *J. Am. Chem. Soc.*, **97**, 2567 (1975); *J. Am. Chem. Soc.*, **99**, 5946 (1977). 3) B. Bosnich, *J. Am. Chem. Soc.*, **99**, 6262 (1977). 4) R. Noyori, *J. Am. Chem. Soc.*, **102**, 2567 (1980).

- The bidentate ligands form the chelate complex with various metal atom. The chelation restricts the position and arrangement of the *P*-substituents, which create rigid steric hindrance (chiral reaction field) around the rhodium atom.



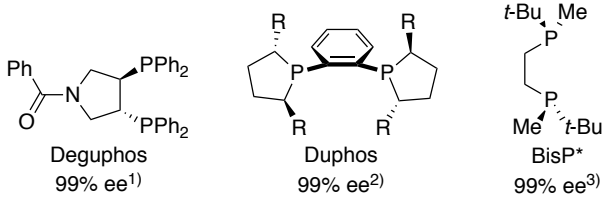
Crystal structure of {Rh(cod)[(*R*,*R*)-dipamp]}BF_4 (All H atoms, COD, and BF_4 are omitted for simplification). (a) Front view. (b) Side view.



Crystal structure of {Rh(nbd)[(*R*)-binap]}ClO_4 (All H atoms, NBD, and ClO_4 are omitted for simplification). (a) Front view. (b) Side view.

D. Heller, *Tetrahedron: Asymmetry*, **15**, 2139 (2004); R. Noyori, *J. Am. Chem. Soc.*, **102**, 2567 (1980).

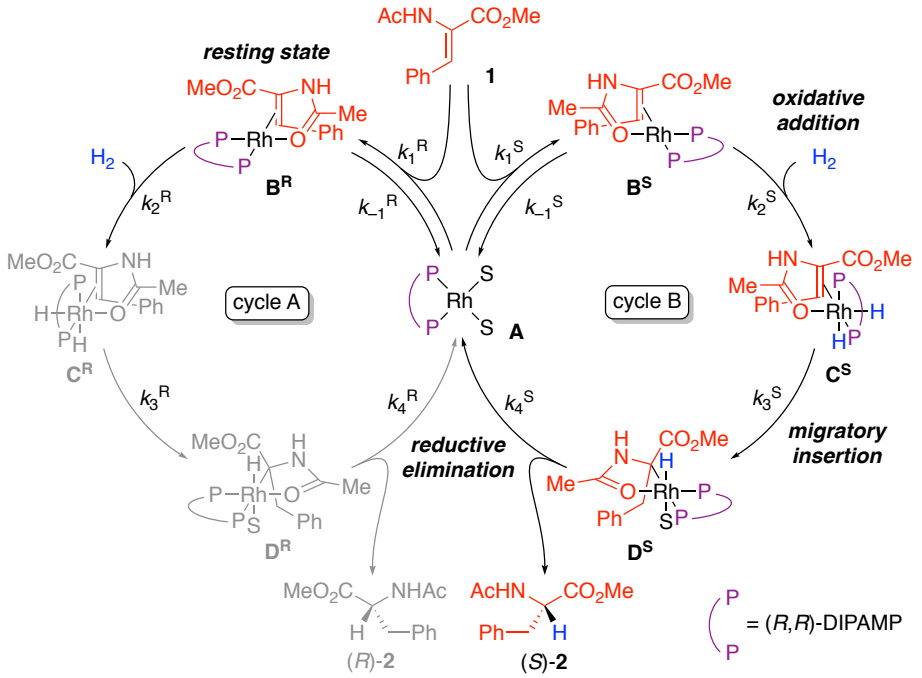
iii) Further improvement of chiral bisphosphine ligand



1) U. Nagel, *Chem. Ber.*, 119, 3326 (1986). 2) M. J. Burk, *J. Am. Chem. Soc.*, **113**, 8518 (1991); **115**, 10125 (1993). 3) T. Imamoto, *J. Am. Chem. Soc.*, **120**, 1635 (1998).

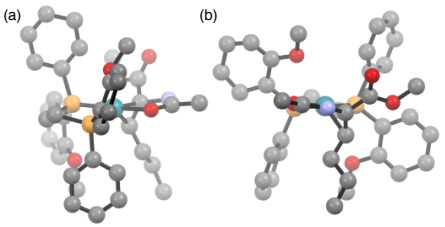
- Commonly, 5-membered chelation is favorable to the asymmetric hydrogenation of α-(*N*-acylamino)acrylates.
- Alkyl substituent, which is electron-donating, is preferable for enhancing the catalytic activity to aryl one, because the rate-determining oxidative addition is accelerated by the resulting electron-rich phosphorus. However, the alkyl group is disadvantageous to create the rigid chiral reaction field, because it is flexible.
- Nowadays, a broad range of chiral ligand, including monophosphine, amino-phosphine, phosphoramidite ones.

(iii) Reaction mechanism of the asymmetric hydrogenation with Rh–DIPAMP catalyst

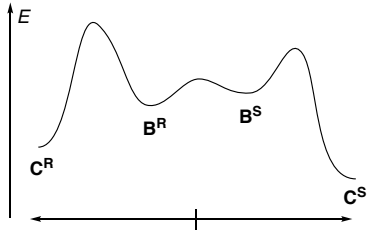


J. Halpern, *J. Am, Chem. Soc.*, **109**, 1746 (1987).

- The hydrogenation of **1** with (*R*,*R*)-DIPAMP–rhodium catalyst yields (*S*)-**2** as the major enantiomeric product.
- The hydrogenation starts from the coordination of substrate **1** on the solvated rhodium(I) cation **A**. Then, the **1**–rhodium(I) **B** undergoes the oxidative addition of H_2 to give dihydridorhodium(III) **C**. The C–C double bond on rhodium inserts into one of the Rh–H bonds. The remaining hydride and alkyl ligand are eliminated from intermediate **D** to form another C–H bond.
- The diastereoisomeric intermediates $\mathbf{B^R}$ and $\mathbf{B^S}$ are in equilibrium. The alkene–rhodium(I) $\mathbf{B^S}$ is less thermodynamically stable than $\mathbf{B^R}$, which leads to the formation of the minor enantiomer (*R*)-**2**.



Crystal structure of {Rh(substrate)[(*R*,*R*)-dipamp]}BF_4 $\mathbf{B^R}$ (All H atoms and BF_4 are omitted for simplification). (a) View adjusted to $\mathbf{B^R}$ in the above scheme. (b) Front view.



Energy diagram for the oxidative addtions of diastereoisomeric intermmediates $\mathbf{B^R}$ and $\mathbf{B^S}$.

J. Halpern, C. R. Landis, *Organometallics.*, **9**, 1392 (1990).

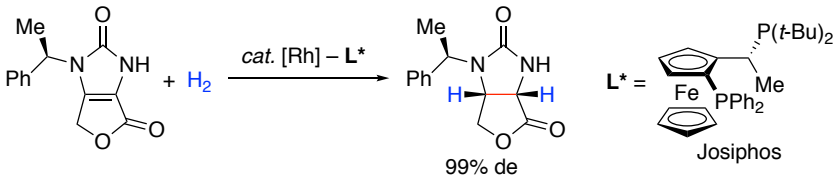
- However, $\mathbf{B^R}$ is too inert to undergo the oxidative addition of H_2. Therefore, molecular hydrogen preferentially reacts with $\mathbf{B^S}$, leading to the selective formation of (*S*)-**2**.
- When $\mathbf{B^S}$ is consumed, the remaining $\mathbf{B^R}$ isomerizes to the more reactive $\mathbf{B^S}$ to keep the equilibrium between $\mathbf{B^R}$ and $\mathbf{B^S}$.

- **Caution! Don't generalize the above mechanism for asymmetric hydrogenation.** Profile of the asymmetric hydrogenation strongly depends on chiral ligand and reaction conditions.

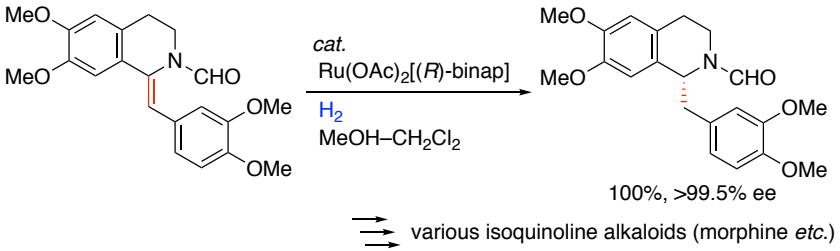
T. Imamoto, *J. Am. Chem. Soc.*, **122**, 7183 (2000); **130**, 2560 (2008); *ACS Catal.*, **5** 2911 (2015).

(iv) Asymmetric hydrogenation of other alkenes

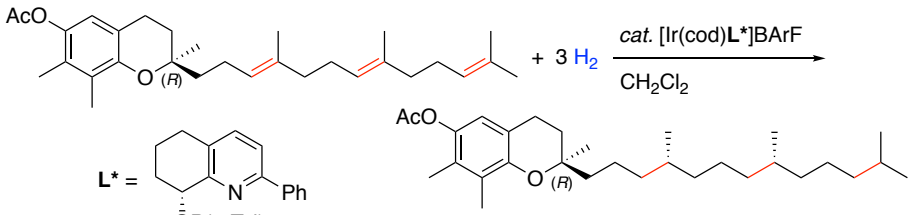
- Nowadays, a broad range of prochiral alkenes can be hydrogenated with high enantioselectivities through asymmetric catalysis. The highly enantioselective catalysts have been applied to the synthesis of various useful compounds.



R. Imwinkelried, *Chimia*, **51**, 300 (1997); EP 602653 (1994).



R. Noyori, H. Takaya, *J. Am. Chem. Soc.*, **108**, 7117 (1986); *J. Org. Chem.*, **59**, 297 (1994).



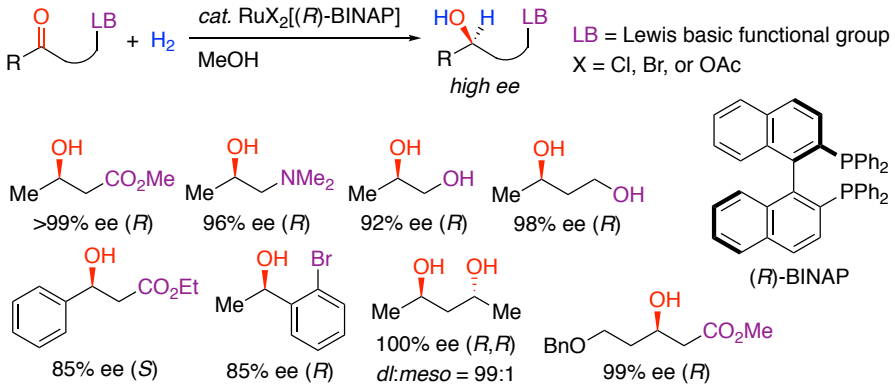
A. Pfaltz, *Science*, **311**, 642 (2006).

(2) Catalytic asymmetric hydrogenation of ketones

- Ketone carbonyl groups can be reduced with molecular hydrogen by transition-metal complex catalysts, such as $RhCl(PPh_3)_3$ and $RuCl_2(PPh_3)_3$.
- The reaction pathway depends on the catalyst or conditions. In most cases, the monohydridometal species seems to participate in the catalytic cycle.

(a) Asymmetric hydrogenation of functionalized ketones

(i) General

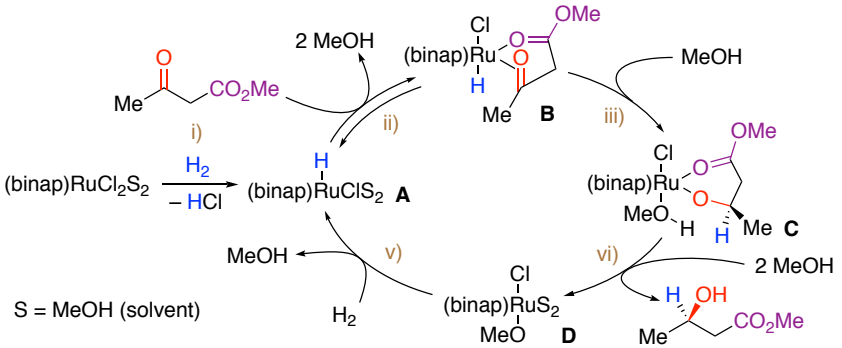


R. Noyori, H. Takaya, S. Akutagawa, *J. Am, Chem. Soc.*, **109**, 5856 (1987); **110**, 629 (1988).

- Various ketones bearing a Lewis basic functional group at α-, β-, or γ-position are converted the corresponding chiral secondary alcohols with high enantiomeric excesses through the chiral BINAP–ruthenium catalysis.

(ii) Mechanism

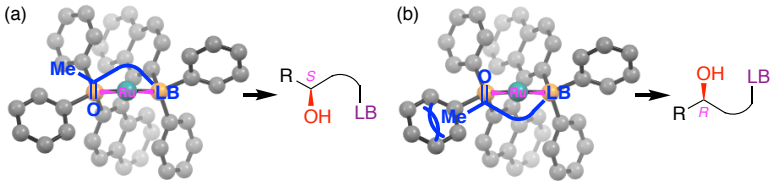
- The following catalytic cycle was proposed for the ruthenium-catalyzed asymmetric hydrogenation of functionalized ketones.



R. Noyori, *Angew. Chem. Int. Ed.*, **40**, 40 (2001); *Proc. Nat. Acad. Sci.*, **101**, 5356 (2004).

i) Generation of monohydridoruthenium(II) species **A** from the catalyst precursor
ii) Coordination of the substrate: The ketone carbonyl coordinates to the ruthenium through its π-bond in η^2 manner because of the following migratory insertion.
iii) Migratory insertion of ketone: The stereoselectivity is determined in this process.
iv) Methanolysis of the ruthenium alkoxide **C**: The product is eliminated from Ru.
v) Regeneration of **A**: The ruthenium methoxide **D** induces the heterolysis of molecular hydrogen.

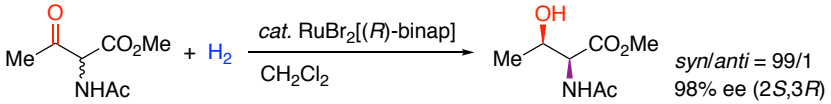
- In the intermediate **B**, the ester carbonyl oxygen, which is Lewis basic, coordinates to the ruthenium and works as the directing group. The coordination results in restricting the conformation of the substrate in the TS of the following migratory insertion.



3D models of the interaction between (*S*)-BINAP–Ru and the substrate. (a) The model leading to (*S*)-alcohol (major product). (b) The model leading to (*R*)-alcohol (minor product).

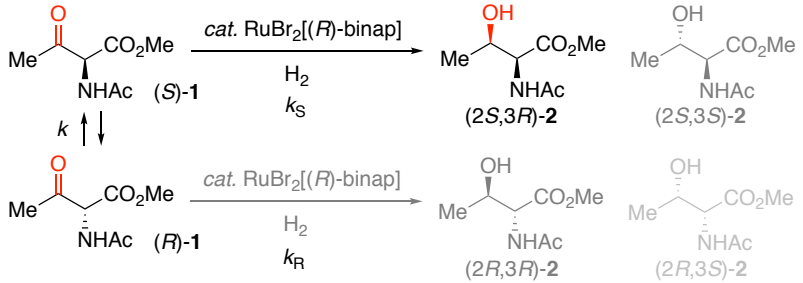
- In the model (b) leading to the minor enantiomer, the methyl group on the carbonyl carbon undergoes the steric repulsion from one of *P*-phenyl groups of BINAP. Therefore, the model (a) is preferable to the model (b).

(iii) Dynamic kinetic resolution in asymmetric hydrogenation



R. Noyori, S. Akutagawa, *J. Am. Chem. Soc.*, **111**, 9134 (1989); **115**, 144 (1993).

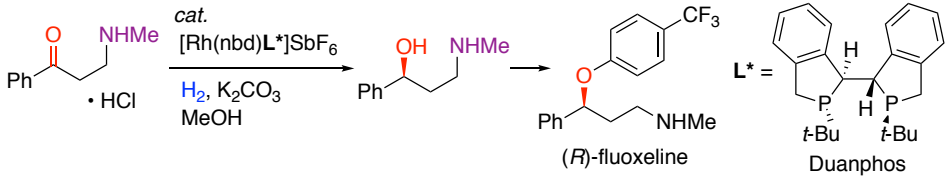
- Racemic α-substituted β-keto esters are converted to α-substituted β-hydroxy ester in high diastereoselectivities as well as high enantioselectivities.
- Commonly, the β-keto ester is possible to racemize through their enol during the hydrogenation.



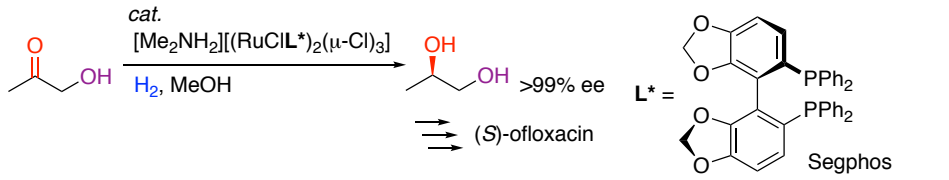
- The hydrogenation of **1** proceeds in similar manner to that of b-keto esters to give the product bearing *S* configuration at its α-carbon ($k_S >> k_R$).
- The major stereoisomer (2*S*,3*R*)-**2** will be selectively obtained from the asymmetric hydrogenation of racemic **1**, when its racemization is much faster than the hydrogenation of (*R*)-**1** with the chiral catalyst ($k >> k_R$).

(iv) Applications

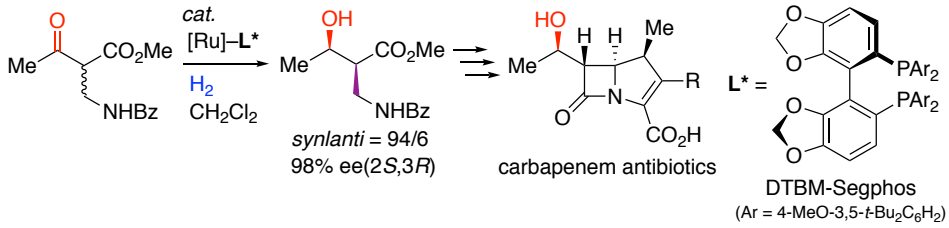
- The highly enantioselective hydrogenation of functionalized ketones has been applied to the synthesis of various useful biologically active compounds, including medicines.



X. Zhang, *Angew. Chem. Int. Ed.*, **44**, 1687 (2005).



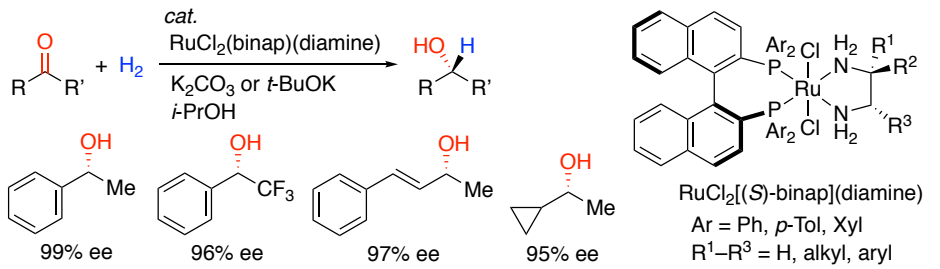
T. Saito, *Adv. Synth. Catal.*, **343**, 264 (2001).



T. Saito, *Adv. Synth. Catal.*, **343**, 264 (2001).

(b) Asymmetric hydrogenation of simple ketones

(i) General

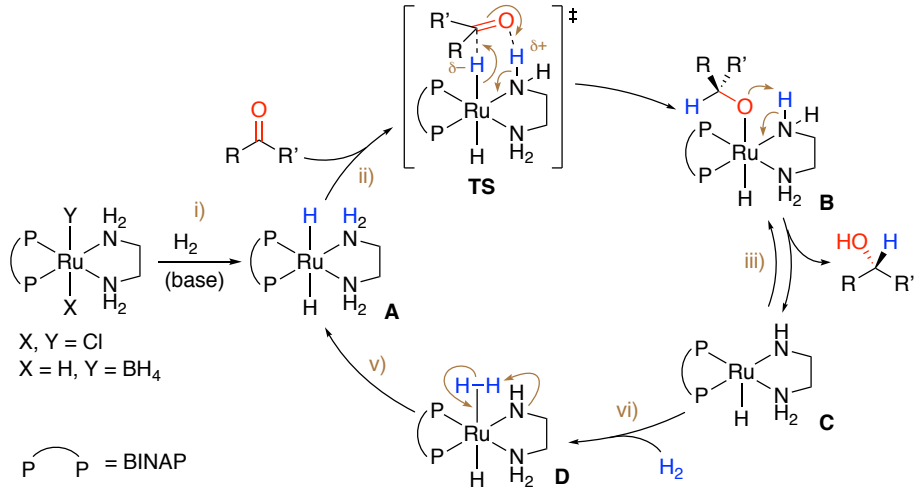


R. Noyori, *J. Am. Chem. Soc.*, **117**, 2675 (1995); **120**, 13529 (1998);.**124**, 6508 (2002).

- Simple ketones, which has no directing group, had been formidable substrates for the catalytic asymmetric hydrogenation as compared to the functionalized ketones.
- RuX2(bisphosphine)(1,2-diamine)-type catalyst allows the chemoselective hydrogenation of ketones. This catalyst is compatible with various functional groups, including nitro, olefin, and cyclopropane.

(ii) Mechanism

- The hydrogenation through the RuX_2(bisphosphine)(1,2-diamine)-type catalyst proceeds through an outer-sphere mechanism.



R. Noyori, *J. Am. Chem. Soc.*, **125**, 13490 (2003); S. H. Bergens, *J. Am. Chem. Soc.*, **130**, 11979 (2008).

i) Generation of dihydridoruthenium(II) species **A** (or **B**) from the catalyst precursor

ii) Transfer of hydride (on Ru) and proton (on N) to ketone: The nucleophilic attack of the hydride to the carbonyl carbon takes place simultaneously with the protonation of carbonyl oxygen through 6-membered transition state **TS**. The resulting alcoholic product is immediately converted to ruthenium alkoxide **B**.

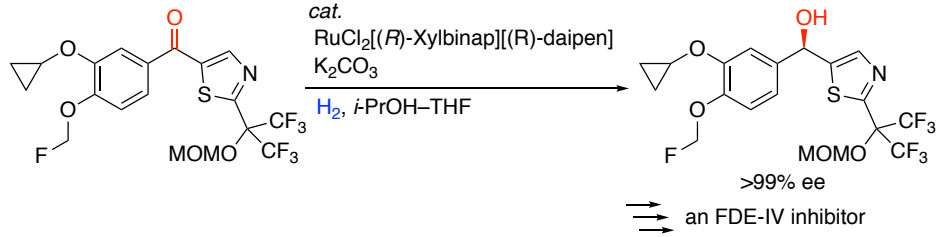
iii) Protonation of alkoxide on ruthenium: One of the protons on N reacts with the alkoxo ligand to release the desired product.

iv) Formation of molecular hydrogen complex: The coordination of H_2 on Ru leads to the decrease in its pK_a.

v) Regeneration of **A**: The H–H bond in D

(iii) Applications

- $RuCl_2$(binap)(diamine)-type catalysts are often used for the preparation of various biologically active compounds and drug candidates.

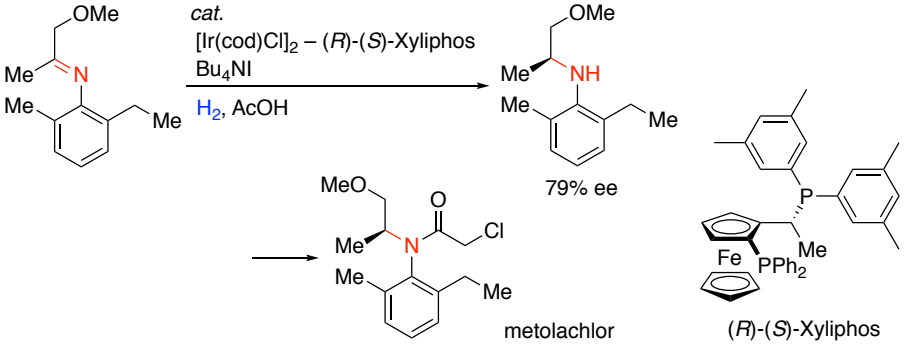


C.-y. Chen, *Org. Lett.*, **5**, 5039 (2003).

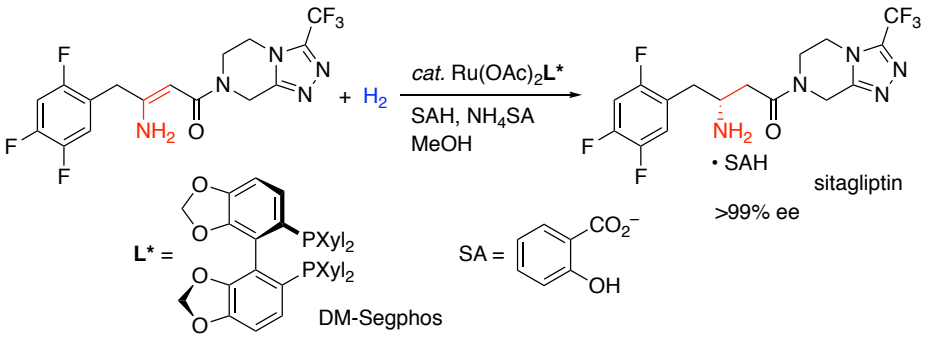
(3) Catalytic asymmetric hydrogenation of imines

- As with ketones, imines are also reduced with molecular hydrogen through transition-metal catalysis.
- Enantioselective hydrogenation of imines is useful for preparing optically active amines, which are often seen in many useful compounds.
- However, the hydrogenation of imines is more formidable than those of alkenes and ketones. The amine product commonly poisons the metal catalyst, because the lone pair on its N strongly interacts with the metal atom.
- Many excellent chiral catalysts have been developed for the asymmetric hydrogenation of specific imines, which can be converted into useful chiral compounds.

Examples



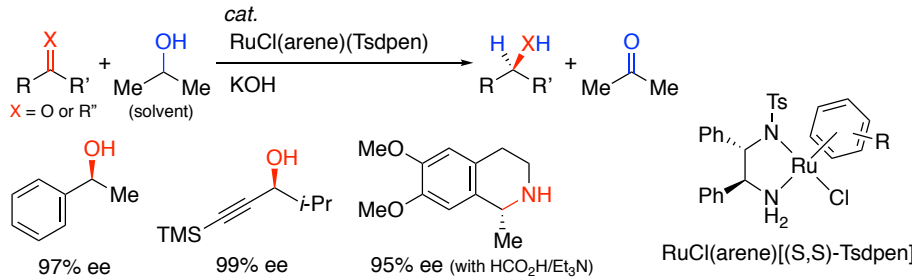
H.-U. Blaser, *Adv. Synth. Catal.*, **344**, 17 (2002).



D. Steinhuebel, K. Matsumura, *J. Am. Chem. Soc.*, **131**, 11316 (2009).

(4) Asymmetric reduction other than hydrogenation

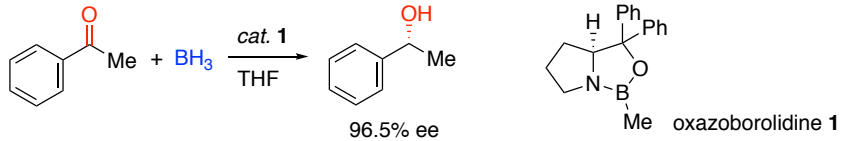
(a) Transfer hydrogenation of ketones and imines



R. Noyori, *J. Am. Chem. Soc.*, **117**, 7562 (1995); **118**, 4916 (1996); **119**, 8738 (1997).

- The transfer of hydrogen from secondary alcohols to ketones, Meerwein–Ponndolf–Varley-type reduction, is known to proceed in the presence of not only Lewis acid but also transition-metal complex catalyst.
- Optically active Ru(η^6-arene)(*N*-Ts-diamine) complexes work as useful catalysts for the enantioselective transfer hydrogenation of various ketones and imines with 2-propanol.
- The transfer hydrogenation with 2-propanol is an equilibrated reaction. Therefore, the prolonged reaction time and/or high concentration of substrate are disadvantageous for high enantioselectivity.
- A mixture of formic acid and triethylamine is also usable for the asymmetric transfer hydrogenation with Ru(η^6-arene)(*N*-Ts-diamine) catalyst. In this case, the reaction is irreversible.

(b) CBS (Corey–Bakshi–Shibata) reduction



E. J. Corey, *J. Am. Chem. Soc.*, **109**, 5551 (1987); **109**, 7925 (1987); *Angew. Chem. Int. Ed.* **37**, 1986 (1998).

- Various ketones are reduced to the chiral secondary alcohols with high enantiomeric excesses through CBS reduction.
- In the CBS reduction, oxazaborolidine **1** works as the Lewis acid catalyst for the borane reduction of the carbonyl.