



The most important practical difference between oxidation and reduction is that the reduction of unsymmetrical ketones generates chiral secondary alcohols. Reduction is treated extensively in most organic text and reference books.

Hydrogen/Metal catalysts

- H₂, Raney-Ni
- H₂, PtO₂
- H₂, Rh
- H₂, Pd/C
- H₂, Lindlar-Catalyst

Hydrides and Mixed Hydrides

- AlH₃ (LAH+AlCl₃)
- LAH
- DIBAL-H
- Li(OMe)₃AlH (LTMA)
- Li(O+Bu)₃AlH (LTBA)
- NaH₂Al(O(CH₂)₂OMe)₂ (Red-Al, vitride, SMEAH; with CuBr→1,4-reductions)
- B₂H₆; BH₃SMe₂; BH₃•THF; BH₃•NH₃
- LiBH₄ (LBH)
- LiEt₃BH (super hydride)
- K(i-PrO)₃BH (KIPBH)  
- Li, Na, K, LS-Selectride

Hydrides and Mixed Hydrides (cont.)

- NaBH₄ (SBH)
- NaCNBH₃ (stable at pH 3-4)
- NaBH₄, CeCl₃ (Luche reagent, 1,2-reduction of enones)
- NaBH(OAc)₃
- Zn(BH₄)₂
- Sia₂BH
- Bu ₃SnH

Dissolving Metal Reagents

- Na/NH₃/ROH (Birch)
- Li/NH₃/ROH
- Li/NH₃
- Zn/HOAc
- Zn/HCl (Clemmensen)
- Na/Hg
- Zn/Hg

Miscellaneous Reductants

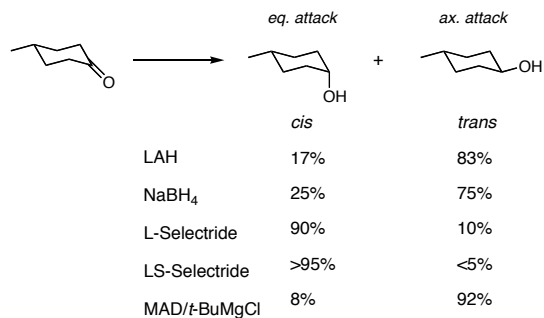
- NH₂NH₂/KOH
- Meerwein-Ponndorf-Verley, *i*-PrOH, Al(*i*-Pro)₃
- Diimide (H-N=N-H, prepared *in situ* from KOCON=NCOOK; adds to nonpolarized double bonds)

- Et ₃SiH/BF₃

Broad spectrum of selective reducing agents

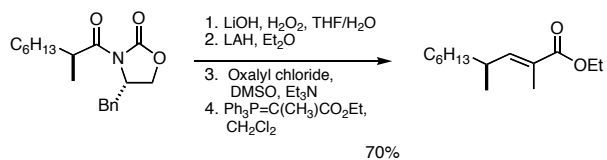
	KIPBH	NaBH ₄	LTBA	LiBH ₄	Al(BH ₂) ₃	BH ₃ •THF	Sia ₂ BH	9-BBN	AlH ₃	LTMA	LiAlH ₄	LiEt ₃ BH
RCHO	+	+	+	+	+	+	+	+	+	+	+	+
R ₂ CO	+	+	+	+	+	+	+	+	+	+	+	+
RCOCl	+	+	+	+	+	+	+	+	+	+	+	+
RCO ₂ R'	+	+	+	+	+	+	+	+	+	+	+	+
RCO ₂ H	+	+	+	+	+	+	+	+	+	+	+	+
RCONR' ₂	+	+	+	+	+	+	+	+	+	+	+	+
RCN	-	-	-	-	-	+	-	+	+	+	+	+
RNO ₂	-	-	-	-	-	-	-	+	+	+	+	+
RCH=CH ₂	-	-	-	-	-	+	+	+	-	-	-	-

The reduction of hindered halides with LAH proceeds predominantly by a single electron transfer pathway (Ashby, E. C.; Weider, C. O. *J. Org. Chem.* **1997**, *62*, 3542).



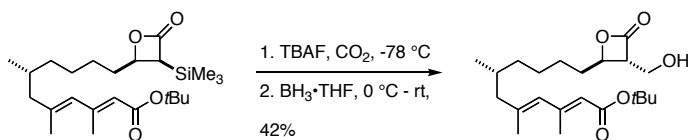
Acid to Alcohol [LAH]

Wipf, P.; Kim, Y.; Fritch, P. C. *J. Org. Chem.* **1993**, *58*, 7195.



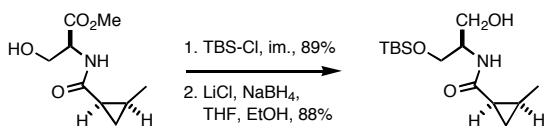
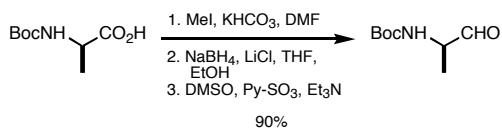
Acid to Alcohol [BH₃]

Dymock, B. W.; Kocienski, P. J.; Pons, J.-M., "A synthesis of the hypocholesterolemic agent 1233A via asymmetric [2+2] cycloaddition." *Synthesis* **1998**, 1655.

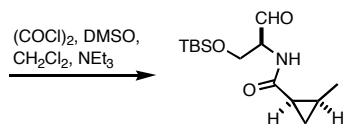


Ester to Alcohol [LiBH₄]

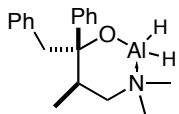
Hamada, Y.; Shibata, M.; Sugiura, T.; Kato, S.; Shioiri, T. *J. Org. Chem.* **1987**, *52*, 1252.



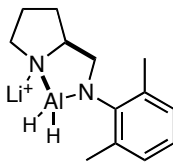
Wipf, P.; Xu, W. *J. Org. Chem.* **1996**, *61*, 6556.



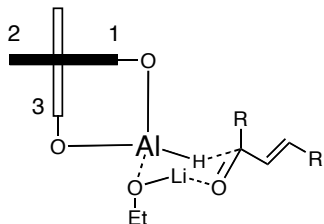
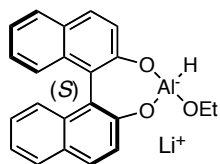
-LAH modified reagents: Mosher: LAH + darvon alcohol



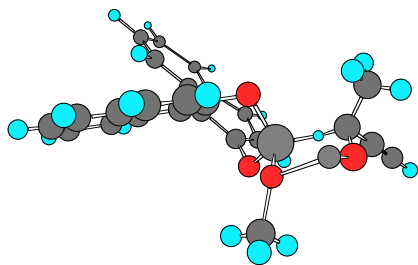
Mukaiyama: LAH + chiral diamine



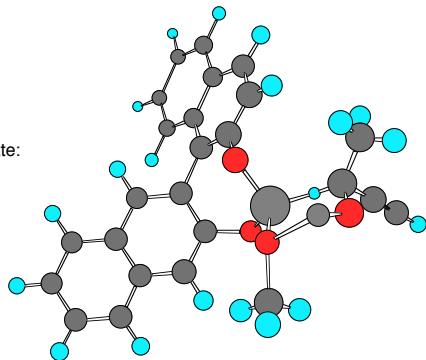
Noyori: Binal-H



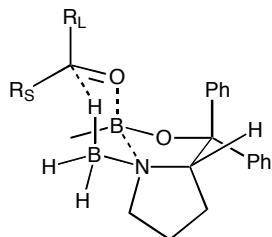
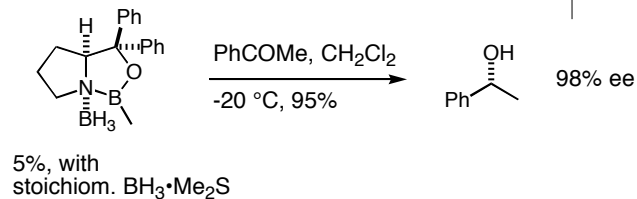
- (S)-Binal-H transition state:



- (R)-Binal-H transition state:

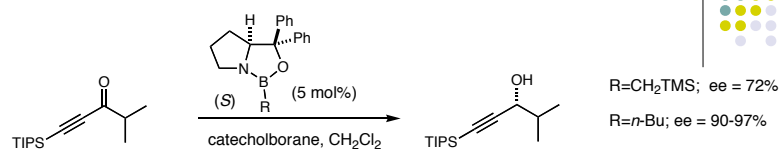


Oxazaborolidines: The systematic studies of Hirao, Itsuno, and coworkers revealed the catalytic nature of the aminoalcohol-borane system. Corey and co-workers identified the catalyst as oxazaborolidine (CBS = Corey-Bakshi-Shibata, diphenyloxazaborolidine). The transition state model shown below was proposed by Liotta (*J. Org. Chem.* **1993**, 58, 799; Ph or alkene substituents occupy R_L positions).

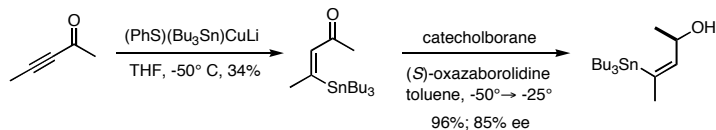


Preparation of the catalyst: Xavier, L. C.; Mohan, J. J.; Mathre, D. J.; Thompson, A. S.; Carroll, J. D.; Corley, E. G.; Desmond, R. *Org. Syn.* **1996**, 74, 51.
Corey, E. J.; Helal, C. J. *Angew. Chem. Int. Ed.* **1998**, 37, 1986 (review).

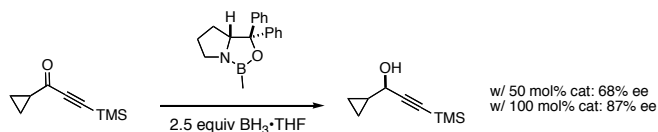
Corey, E. J.; Helal, C. J. *Tetrahedron Lett.* **1997**, *38*, 7511. Enantioselective: Corey, E. J.; Helal, C. J. *Angew. Chem. Int. Ed.* **1998**, *37*, 1986 (review).



Wipf, P.; Lim, S. *J. Am. Chem. Soc.* **1995**, *117*, 558; Wipf, P.; Lim, S. *Chimia* **1996**, *50*, 157.

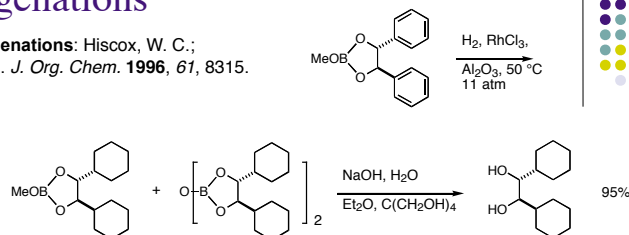


Wipf, P.; Weiner, W. *J. Org. Chem.* **1999**, *64*, 5321-5324.

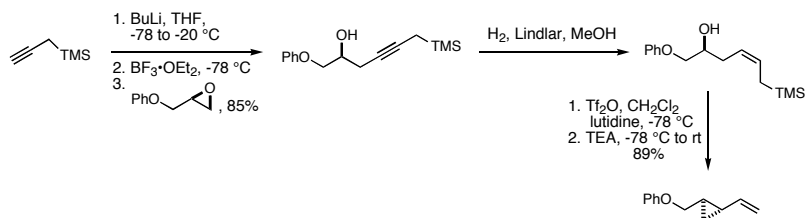


Hydrogenations

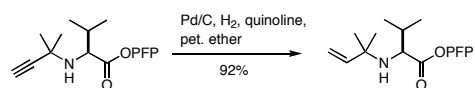
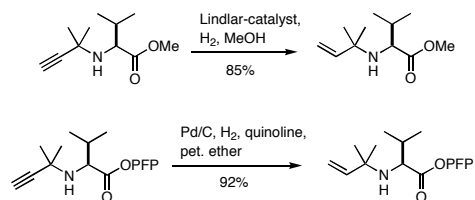
Arene Hydrogenations: Hiscox, W. C.; Matteson, D. S. *J. Org. Chem.* **1996**, *61*, 8315.



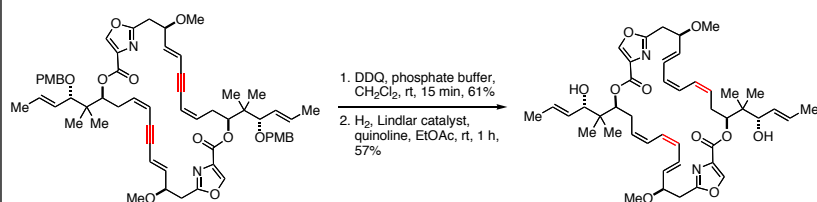
Lindlar Hydrogenation: Taylor, R. E.; Ameriks, M. K.; LaMarche, M. J. *Tetrahedron Lett.* **1997**, *38*, 2057.



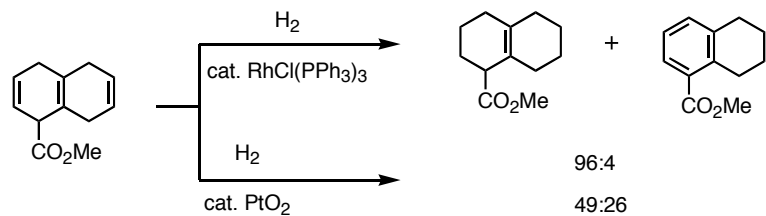
Lindlar Hydrogenation: Wipf, P.; Venkatraman, S. *J. Org. Chem.* **1996**, *61*, 6517.



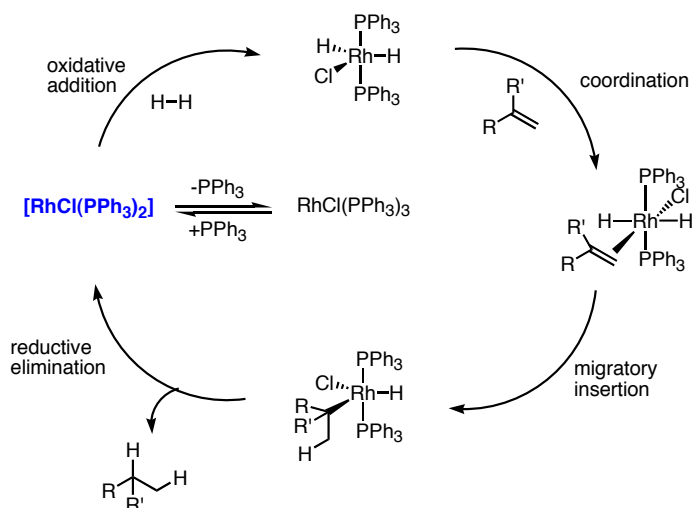
Wipf, P.; Graham, T. H., "Total synthesis of (-)-disorazole C1." *J. Am. Chem. Soc.* **2004**, *126*, 15346-15347.



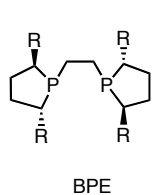
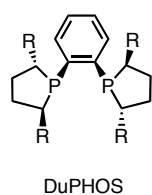
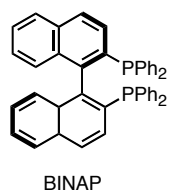
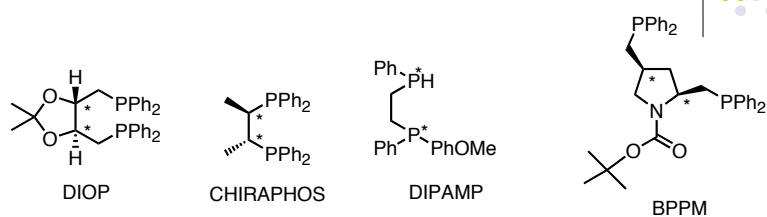
Alkene Hydrogenation with Wilkinson's Catalyst



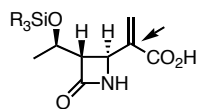
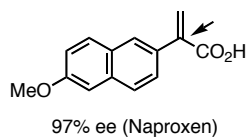
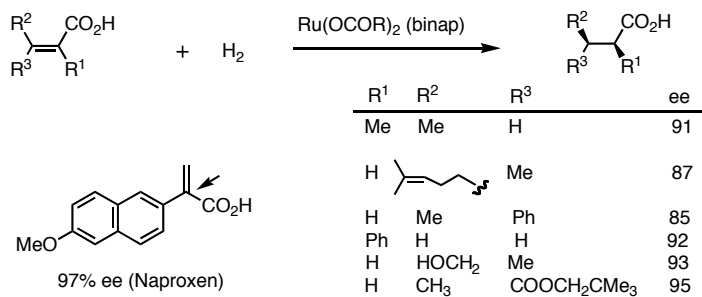
Mechanism



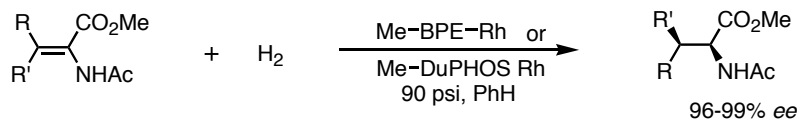
Enantiomerically Enriched Phosphines



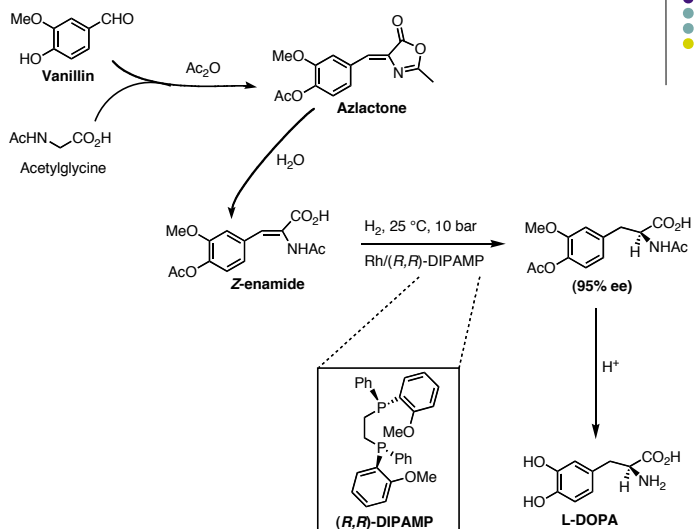
Asymmetric Hydrogenation

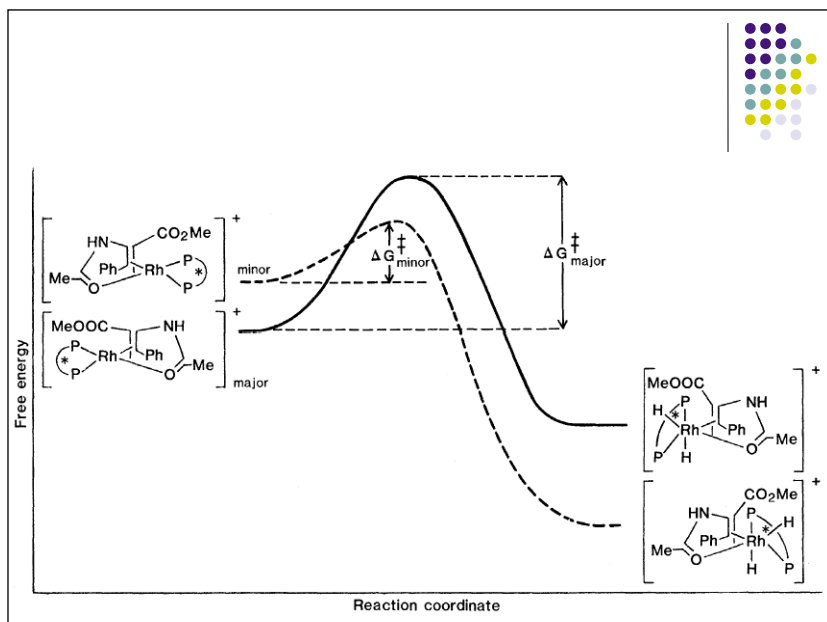
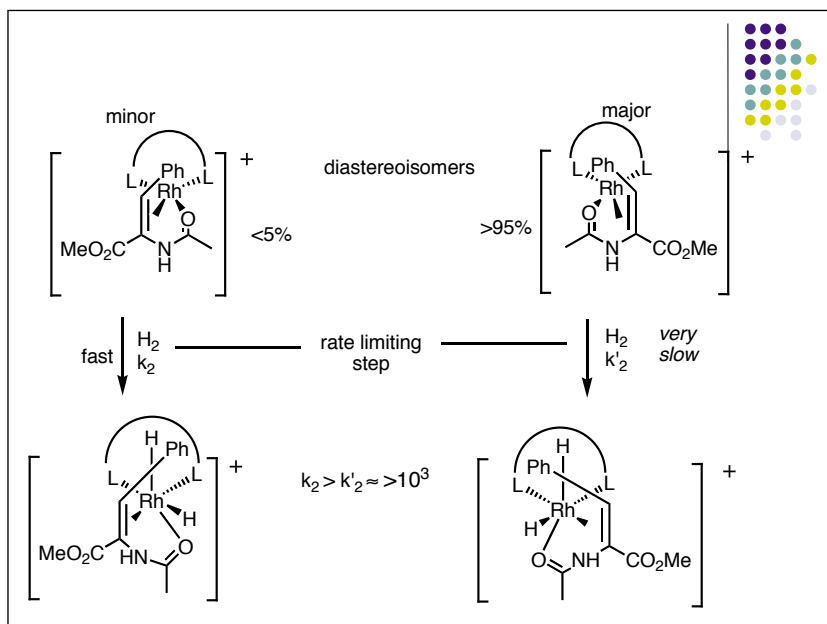
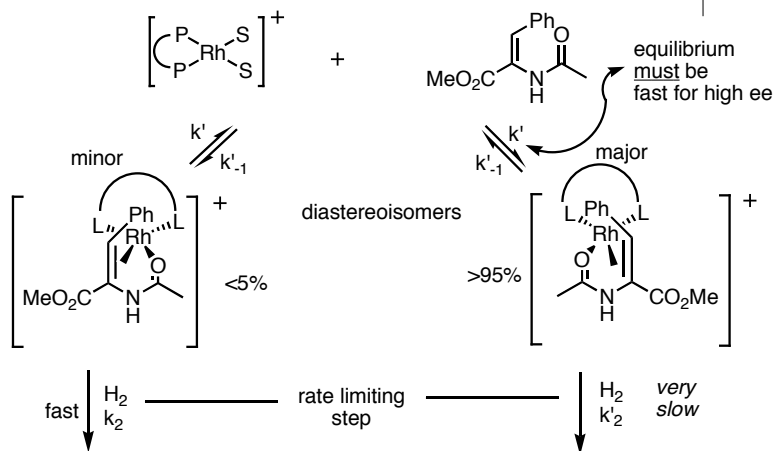


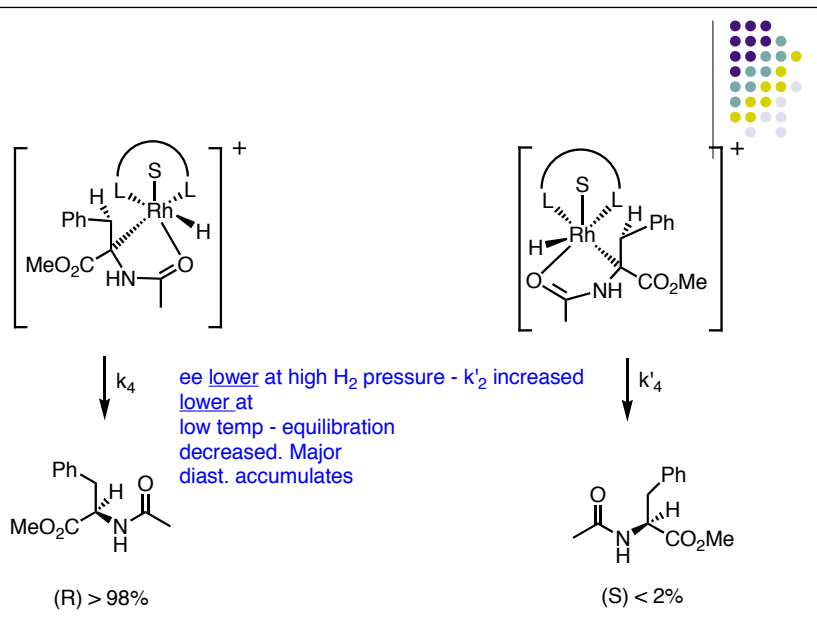
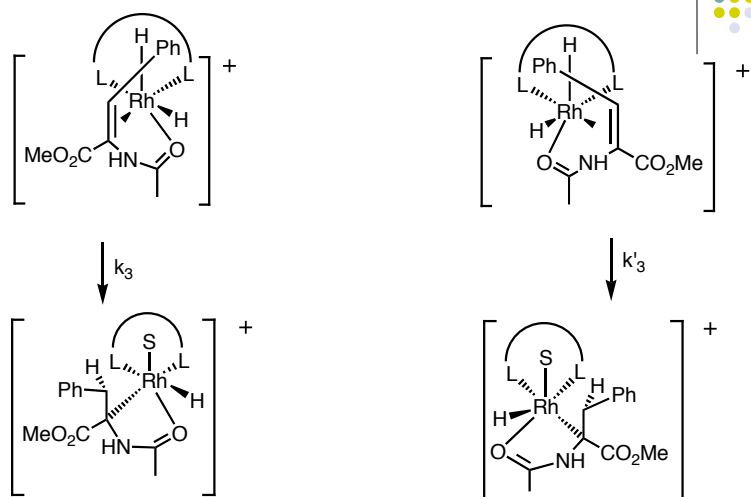
Asymmetric Hydrogenation



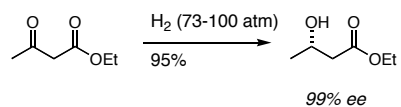
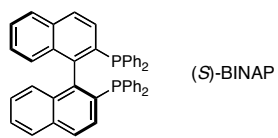
Monsanto L-DOPA Process



Mechanism: Halpern, J. Science 1982, 217, 401-407.Li, M.; Tang, D.; Luo, X.; Shen, W., "Mechanism of asymmetric hydrogenation of enamides with [Rh(bisp*)] + catalyst: Model DFT study." *Int. J. Quant. Chem.* **2005**, *102*, 53-63.

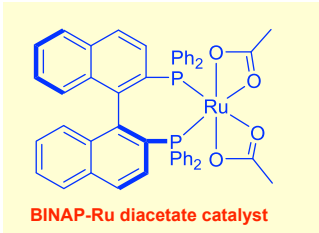


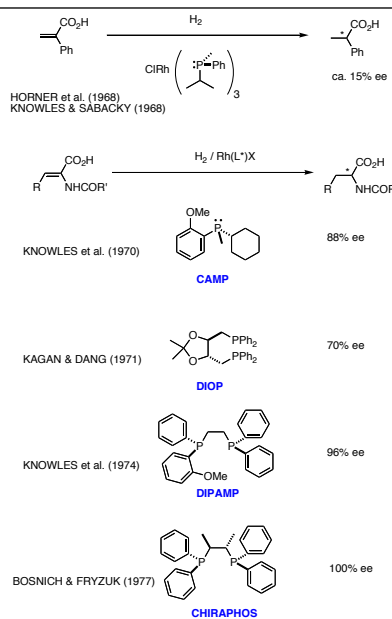
Noyori: BINAP-Ru(II)Cl₂



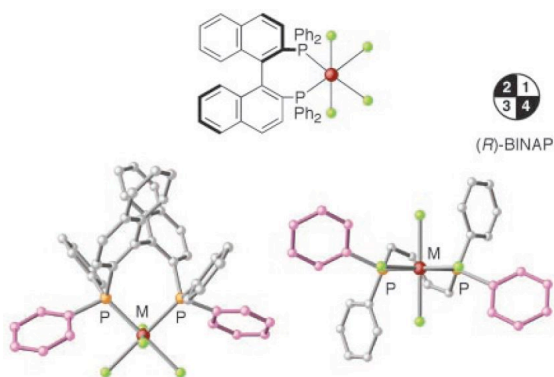
The Nobel Prize in Chemistry 2001
 "for their work on chiral catalysed hydrogenation reactions"

William S. Knowles	Ryoji Noyori	K. Barry Sharpless
1/4 of the prize USA	1/4 of the prize Japan	1/2 of the prize USA
St. Louis, MO, USA b. 1917	Nagoya University Nagoya, Japan b. 1938	The Scripps Research Institute La Jolla, CA, USA b. 1941





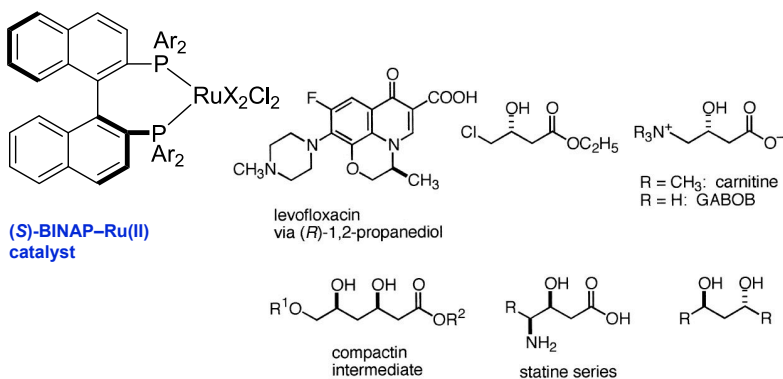
Chiral environment of the (R)-BINAP-transition metal complex

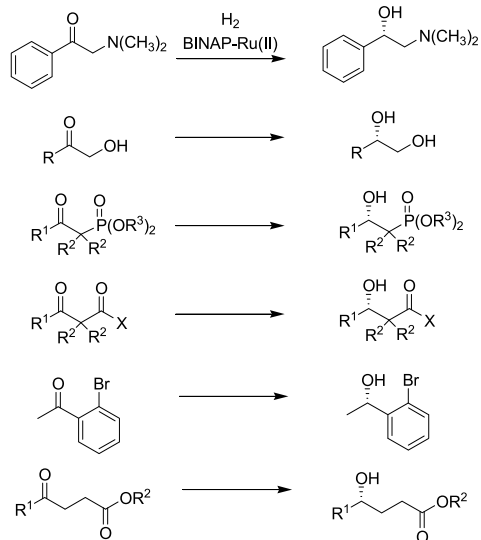


Asymmetric hydrogenation of ketones by BINAP-ruthenium complexes

Halogen-containing BINAP-Ru(II) complexes are efficient catalysts for the asymmetric hydrogenation of a range of functionalized ketones.

Coordinative nitrogen, oxygen, and halogen atoms near C=O functions direct the reactivity and stereochemical outcome in an absolute sense.

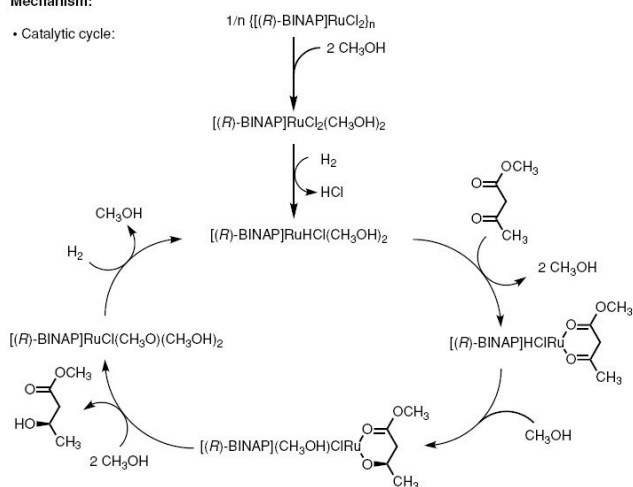




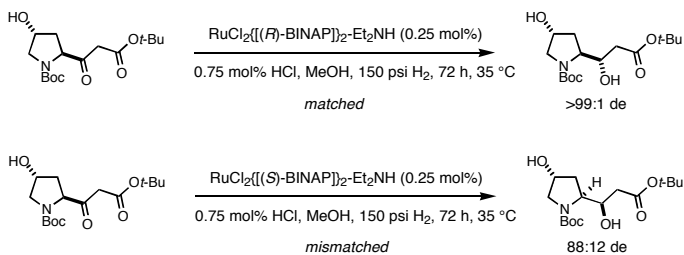
Asymmetric hydrogenation of β -keto esters

Mechanism:

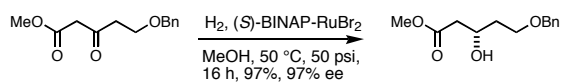
• Catalytic cycle:



Armstrong, J. D.; Keller, J. L.; Lynch, J.; Liu, T.; Hartner, F. W.; Ohtake, N.; Ikada, S.; Imai, Y.; Okamoto, O.; Ushijima, R.; Nakagawa, S.; Volante, R. P. *Tetrahedron Lett.* **1997**, *38*, 3203.



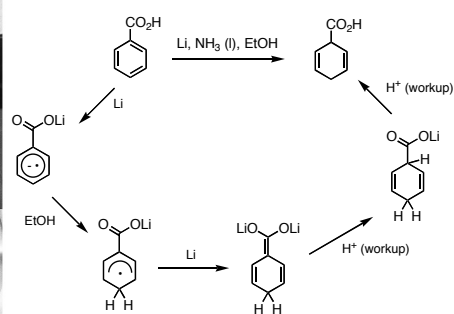
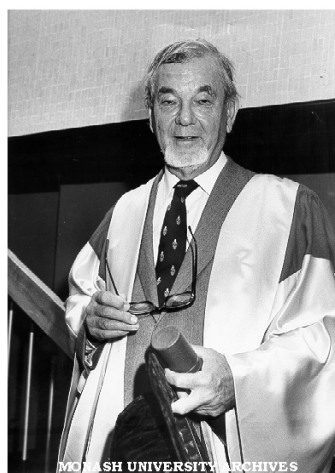
Ali, S. M.; Georg, G. I. *Tetrahedron Lett.* **1997**, *38*, 1703.



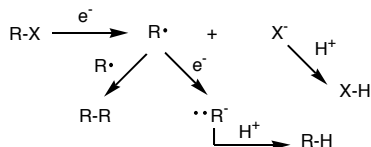
Significance of BINAP Chemistry

- ✚ Excellent enantioselectivity (90-100% ee).
- ✚ Wide scope of substrates (C=O, C=C, C=N).
- ✚ Rivals or exceeds enzymes: e.g. 2,400,000 (TON), 228,000 h⁻¹, 63 s⁻¹ (TOF).
- ✚ Development of pharmaceuticals and synthetic intermediates.
- ✚ Successful industrial applications.
- ✚ An enormous scientific or technological impact and even more general social benefits.

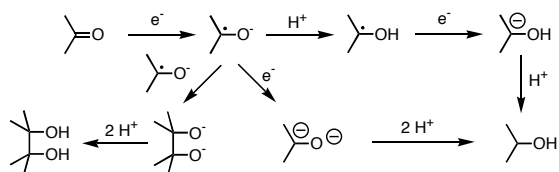
Birch and other (Dissolving) Metal Reductions



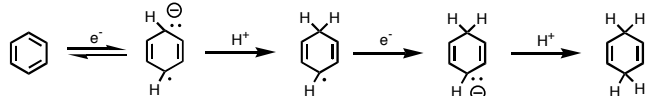
Mechanism of bond fission of single bonds with lithium-ammonia illustrated for alkyl halides:



Mechanism of multiple bond saturation with lithium-ammonia illustrated for ketones:



Mechanism of Birch reduction of benzene:



The acidity of the proton source used in the first protonation step is important to the outcome of the reduction. Sometimes, a more acidic proton source than NH_3 ($\text{pK}_a = 35$) is advantageous. According to House, *Modern Synthetic Reactions*, alcohols ($\text{pK}_a = 16-19$) or ammonium salts ($\text{pK}_a = 10$) may be added to the reaction mixture. Generally, the more acidic the proton source, the faster the reduction. If the protonation of the radical anion is the rate limiting step, NH_3 can be too weak an acid to allow reaction. An unactivated benzene ring is only slowly reduced without an added proton donor.

Reduction of an α,β -unsaturated ketone in NH_3 stops at the saturated ketone stage; in the presence of an added proton source, the saturated alcohol is obtained.

