45
Rh

44
Ru

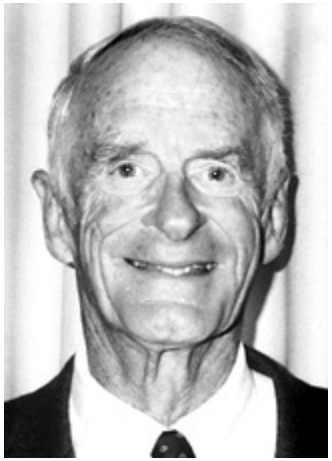
Asymmetric Hydrogenation

Pablo García-Reynaga
February 12, 2010

References:

Knowles, W; *Angew. Chem. Int. Ed.* **2002**, *41*, 1998.
Noyori, R.; *Angew. Chem. Int. Ed*. **2002**, *41*, 2008.
Ager, D.J.; Laneman, S.A. *Tetrahedron: Asymmetry*, **1997**, *8*, 3327.
Burk, *Acc. Chem. Res.*, **2000**, *33*, 363.
Noyori, *Angew. Chem. Int. Ed.*, **2001**, *40*, 40.

2001 Nobel Prize in Chemistry – Asymmetric Catalysis



William S. Knowles

1/4 of the prize

USA

St. Louis, MO, USA

b. 1917

Ryoji Noyori

1/4 of the prize

Japan

Nagoya University
Nagoya, Japan

b. 1938

K. Barry Sharpless

1/2 of the prize

USA

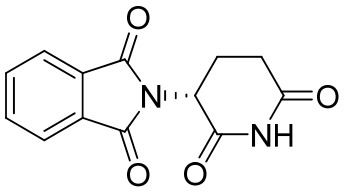
The Scripps
Research Institute
La Jolla, CA, USA

b. 1941

"for their work on chirally catalysed hydrogenation and oxidation reactions"

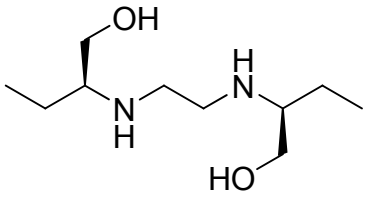
http://nobelprize.org/nobel_prizes/chemistry/laureates/2001/

Importance of Enantiopurity



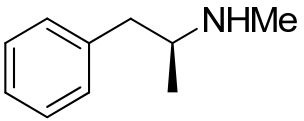
(R)-Thalidomide

Sedative



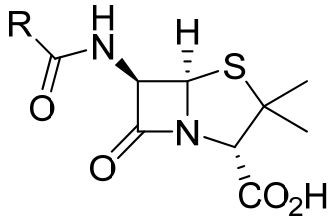
Ethambutol

Anti-TB



(S)-methanphetamine

Nasal decongestant

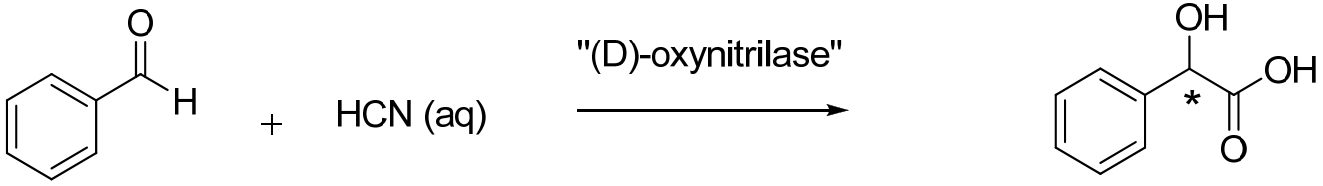


penicillin

- Chiral resolution is an expensive and wasteful process
- Selective crystallization of enantiomers is not a general process
- Traditionally through biochemical routes (specificity), although synthetic more efficient
- Enzymatic vs Molecular Catalysis

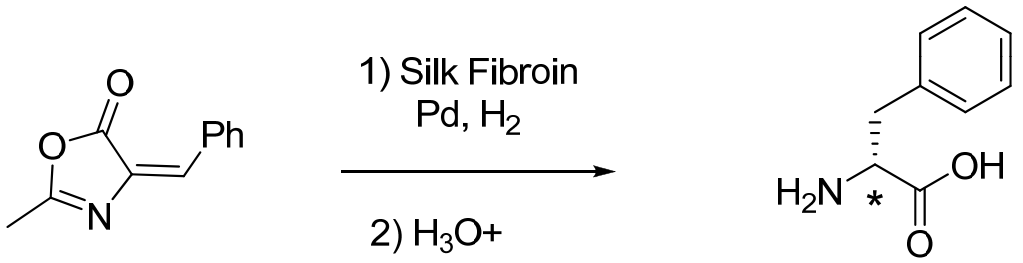
- Early 1990's – ca. 90% of synthetic chiral drugs were racemic.
- "Racemic Switching"

Early examples of asymmetric reactions

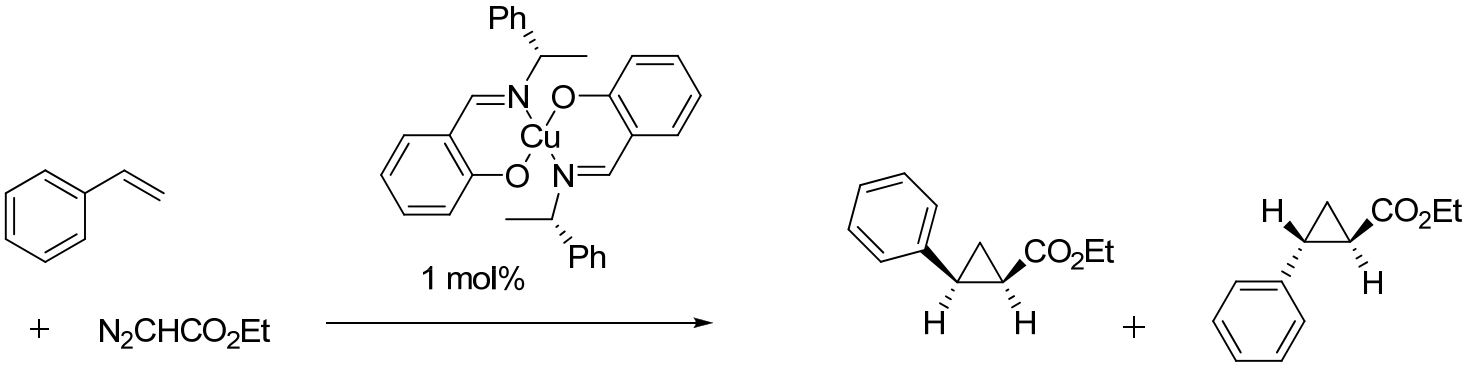


Krieble, V; *J. Am. Chem. Soc.,* **1913**, *35*, 1643.

"85% active"



Akabori, *Nature,* **1956**, *178*, 323.

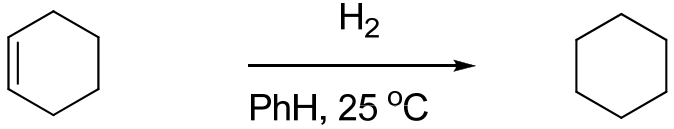


Nozaki et. al. *Tet. Lett.* **1966**, 5239.

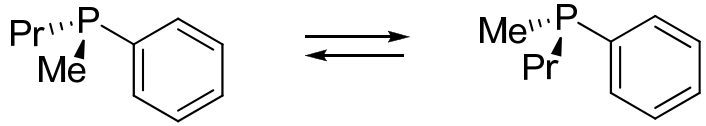
10% *ee*

6% *ee*

Reactions leading up to asymmetric hydrogenation



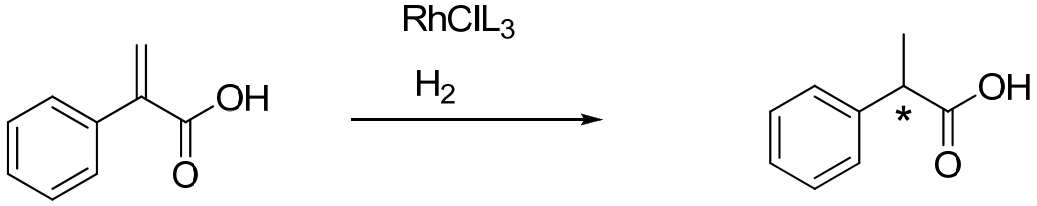
Wilkinson, *J. Chem. Soc. A,* **1966**, 1711



$t_{1/2}$ ~ 2 hrs @ 115 °C

Horner, *Tet. Lett.*, **1961**, *5*, 161.

Mislow, *J. Am. Chem. Soc*, **1967**, *89*, 4784.

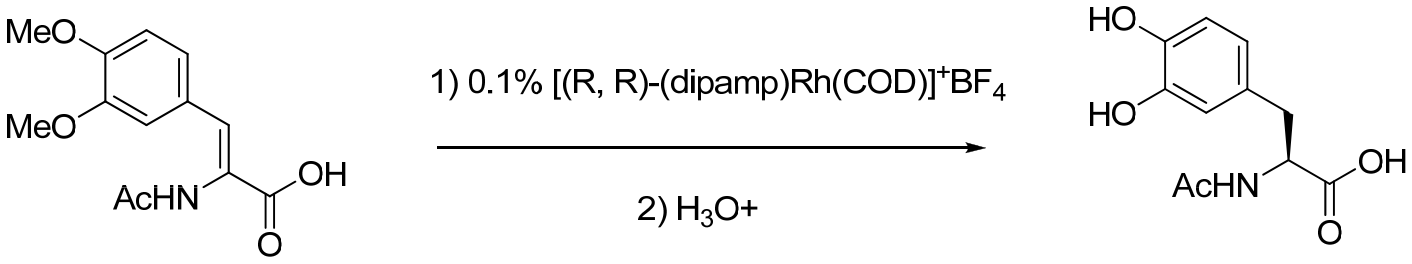


15% *ee*

Knowles*, Chem. Commun*, **1968**, 1445

1st example of asymmetric homogenous catalysis with chiral phosphine ligands

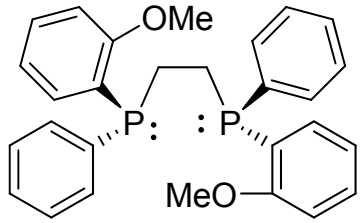
Rh(I) Hydrogenation - Further Development and Scope



L-DOPA

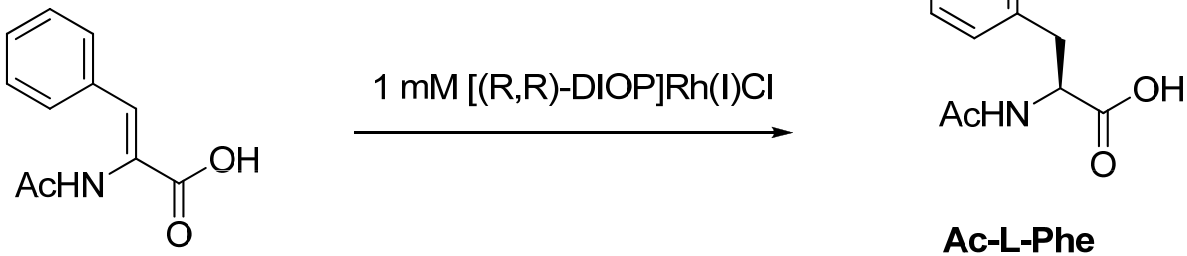
95% ee

Knowles, *J. Chem. Educ.*, **1986**, *63* (3), 222



(R,R)-DiPAMP

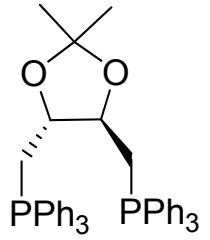
(Kagan) Ligands with backbone chirality also effective:



Ac-L-Phe

ca. 80% ee

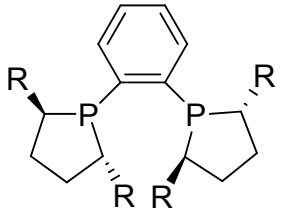
Kagan, *J. Chem. Soc. Chem. Comm*, **1971**,481



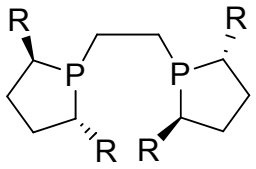
(R,R)-DIOP

- (E)- alkene hydrogenates slower and with low enantioselectivity
- β-disubstituted enamides hydrogenate with low enantioselectivities

Rh(I) Hydrogenation – DUPHOS and BPE Ligands

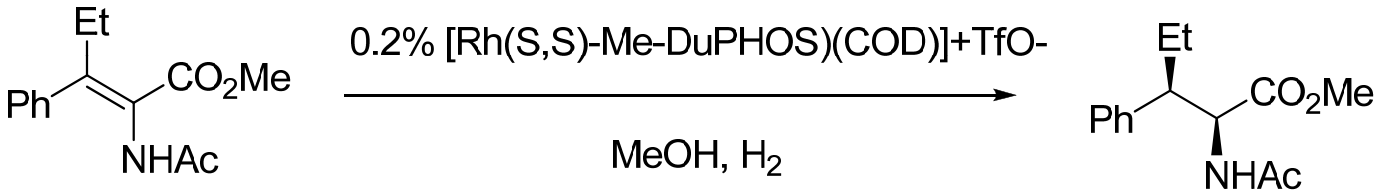


(R,R)-DuPHOS

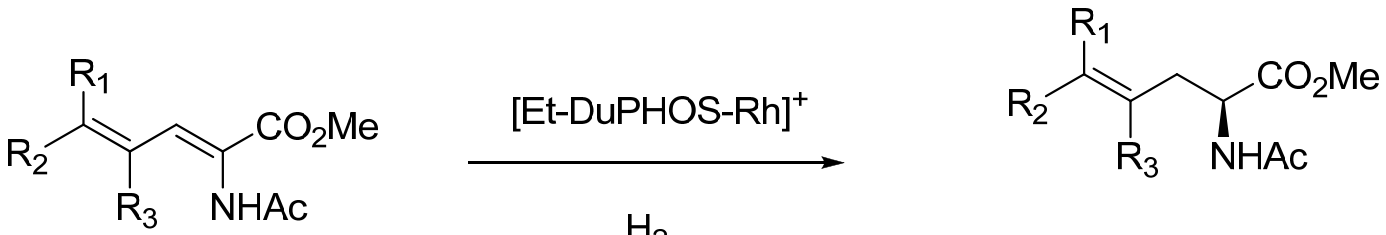


(R,R)-BPE

R=Me,Et, Pr



88% *ee*

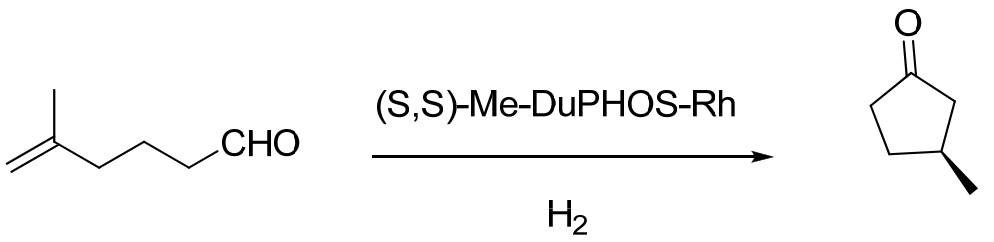


regioselectivity >98%
enantioselectivity > 98%

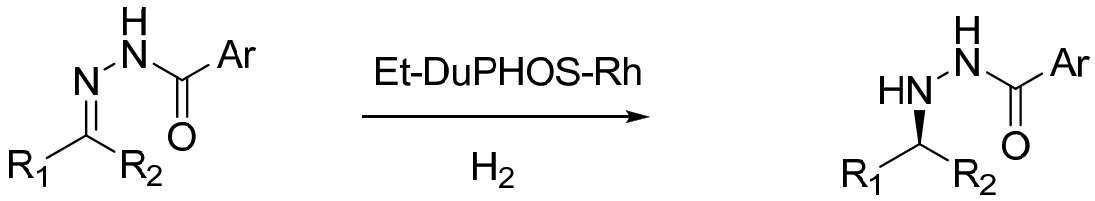
BPEPhos more flexible, so sometimes better for hindered alkenes

Burk, *Acc. Chem. Res.*, **2000**, *33*,363.

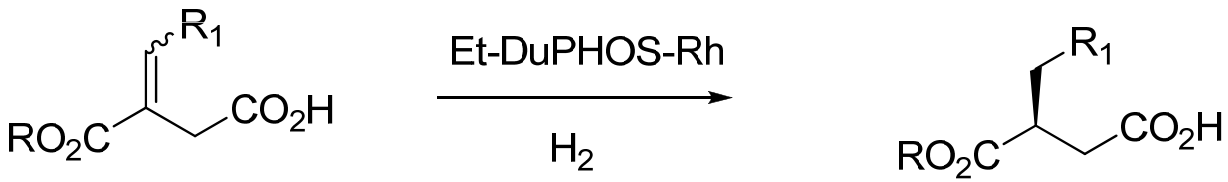
Rh(I) Hydrogenation – DUPHOS and BPEP Ligands



93-98% *ee*



>90% *ee*

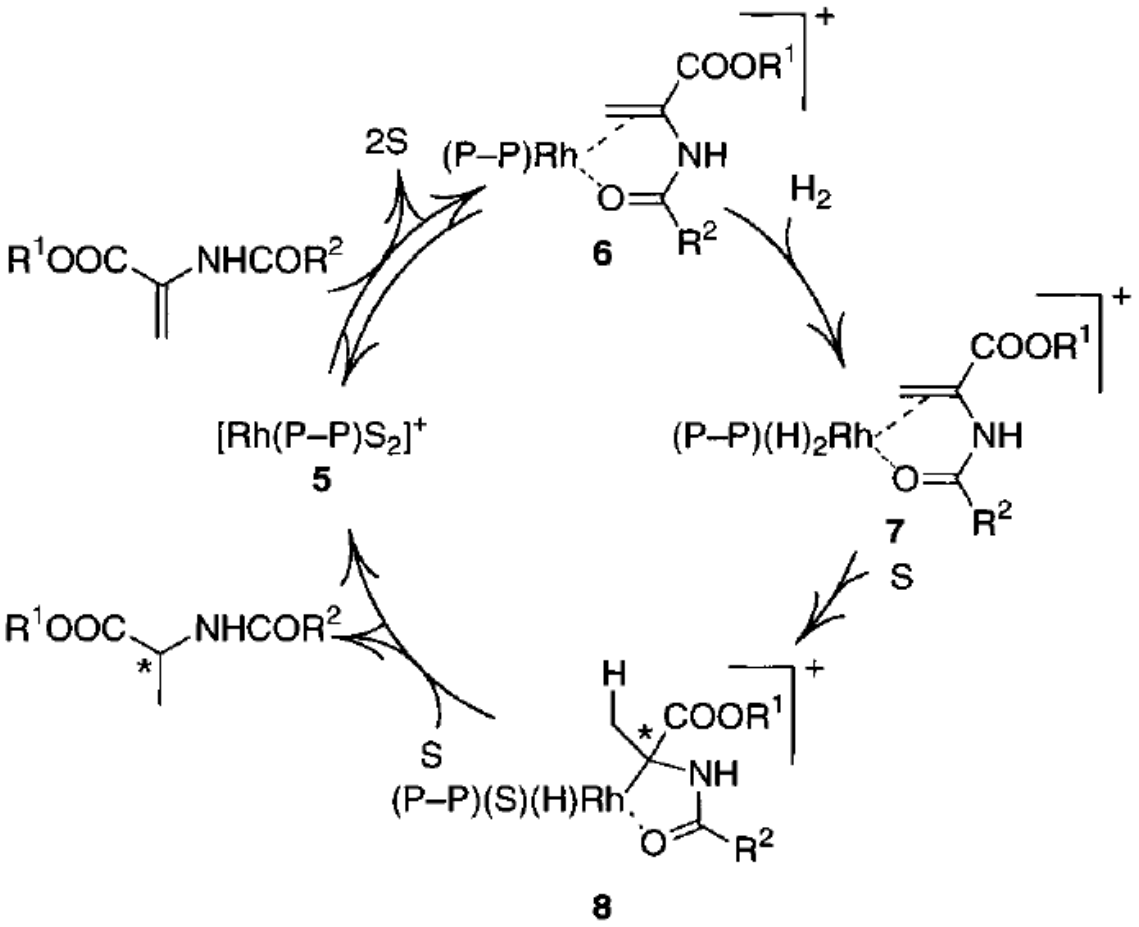


E/Z mixture

>97% *ee*

Burk, *Acc. Chem. Res.*, **2000**, *33*, 363.

General Reaction Mechanism

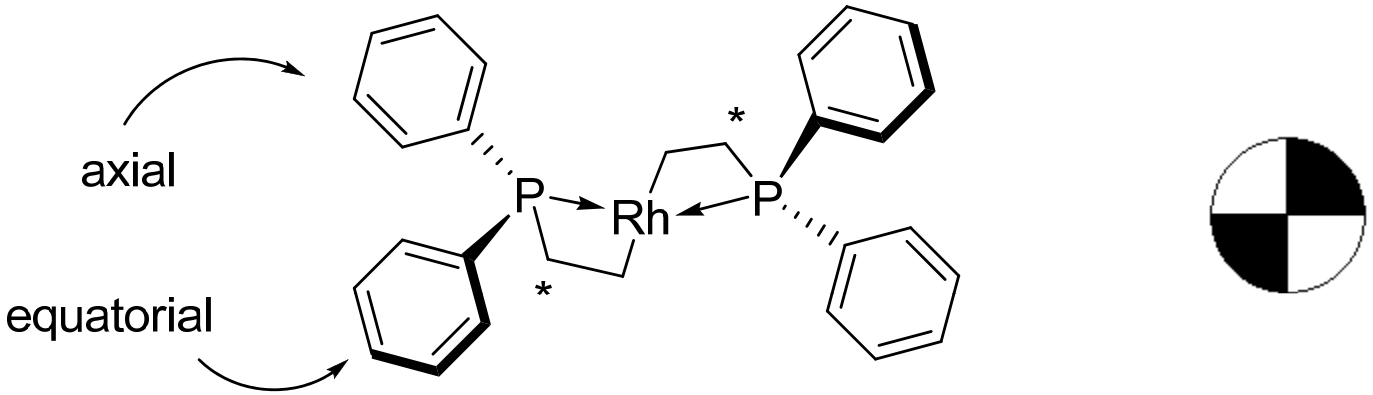


S = solvent, substrate as monodentate ligand, product, etc.

P–P = chiral diphosphine ligand

Noyori, *J. Am. Chem. Soc.*, **2002**, *124*, 6649.
Imamoto, *Chem. Commun.*, **2009**, 7447.

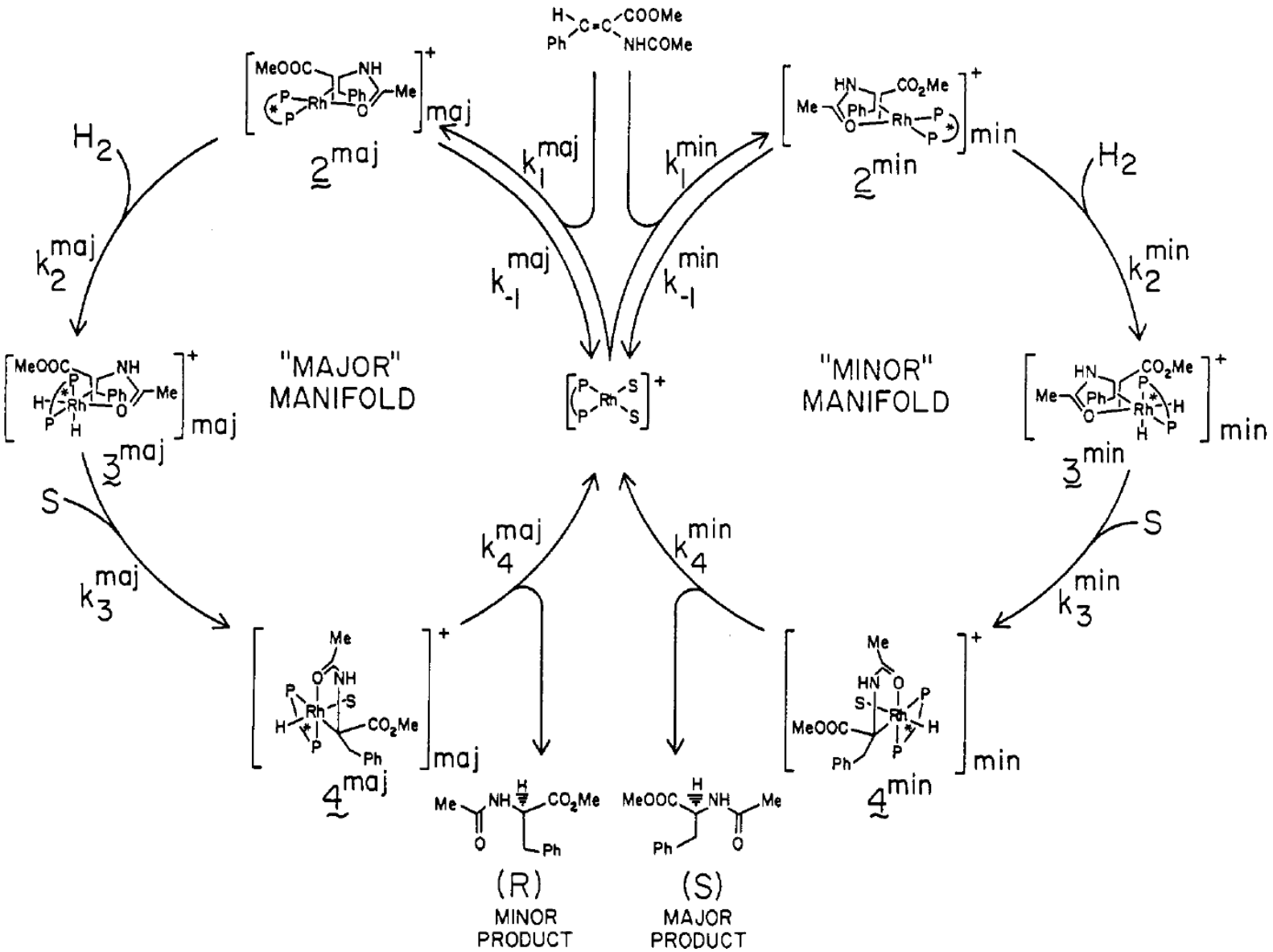
Source of Stereoselection



- Less stable diastereomeric complex reacts fastest with H_2
- Stereoselection mechanism changes with ligand type
    - Electron – Rich Phosphines, P-chiral, Sterically-Hindered Phosphines
- Electron – Donating substituents change regioselectivity of H addition

Imamoto, *Chem. Commun.*, **2009**, 7447.

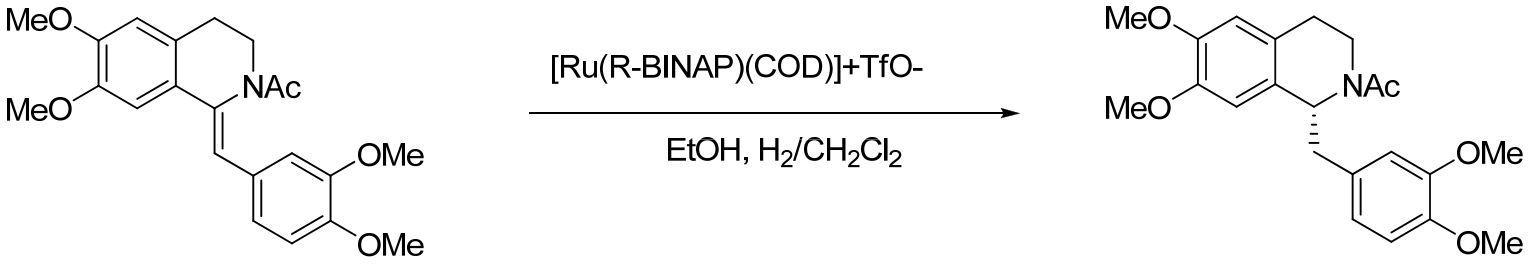
General Reaction Mechanism Revisited (Backbone Chiral Ls)



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

Ru(I) catalyzed hydrogenations provides generality

Isoquinoline Alkaloids

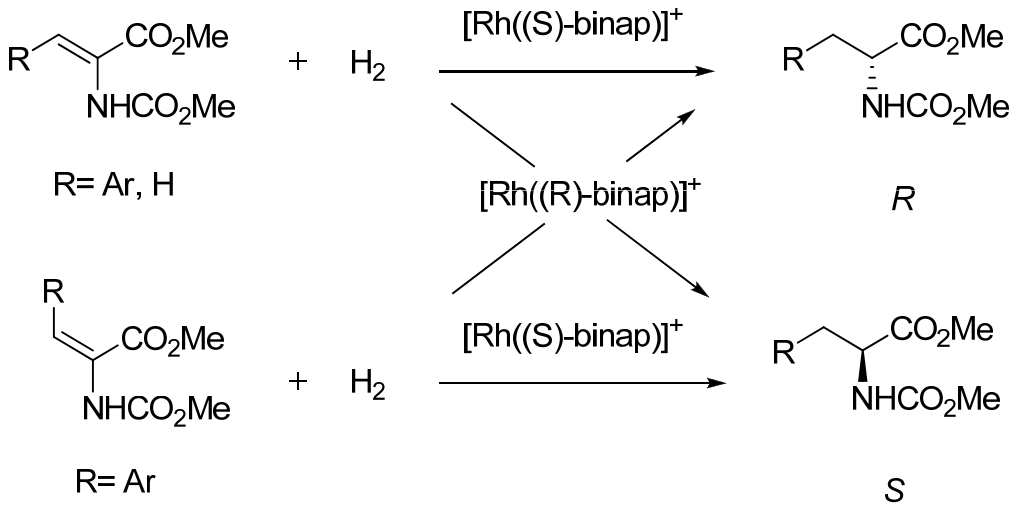


Noyori, *J. Am. Chem. Soc.,* **1986**, *108*, 7117

N-acetyl-tetrahydropapaverine

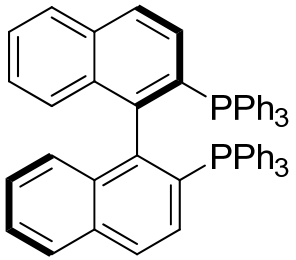
100%, 99.5% *ee*

Stereospecific enamide hydrogenation R vs S binap



Noyori, *J. Am. Chem. Soc.*, **2002**, *124*, 6649

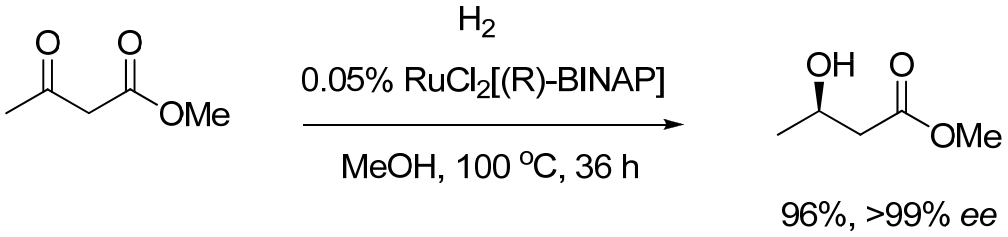
90-92% ee



(R)-BINAP

Ru-catalyzed Hydrogenation of β-keto esters

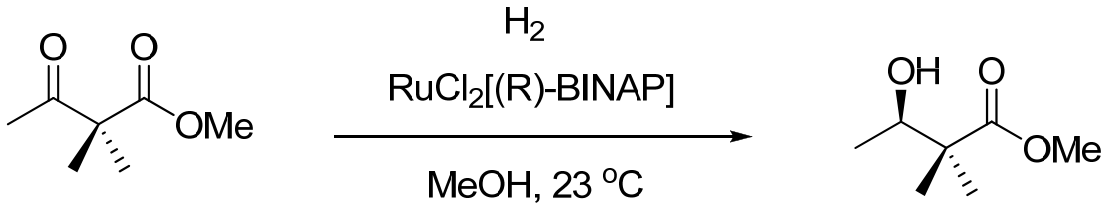
Beta-keto esters



96%, >99% *ee*

Noyori, *J. Am. Chem. Soc.* **1987**, *109*, 5856.

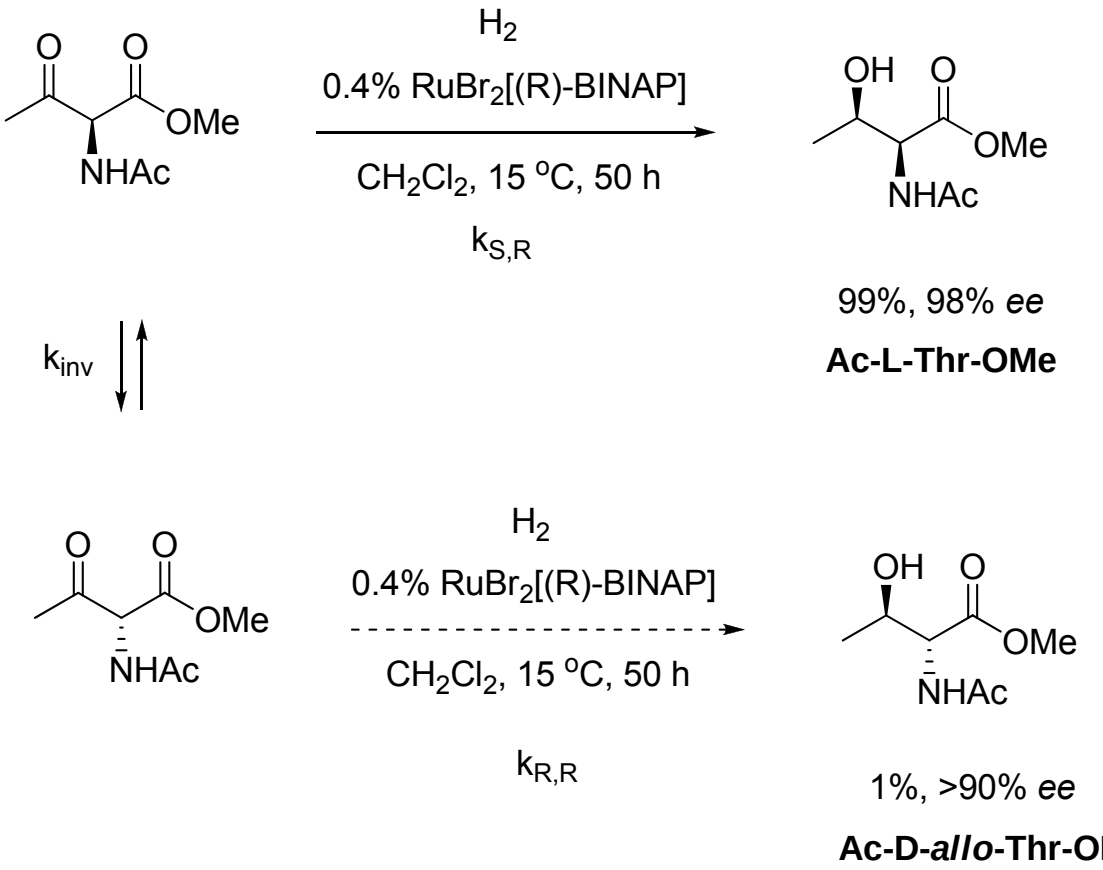
Reduction proceeds through keto form



99%, >96% *ee*

Noyori, *Acc. Chem. Res.*. **1990**, *23*, 345

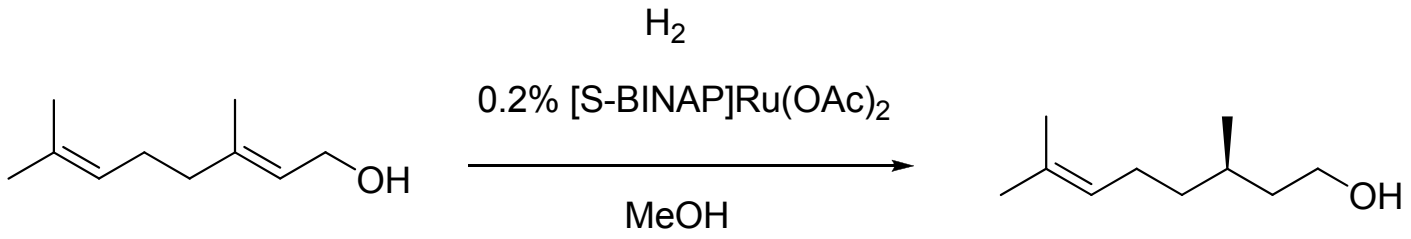
Dinamic Kinetic Resolution of β-keto esters



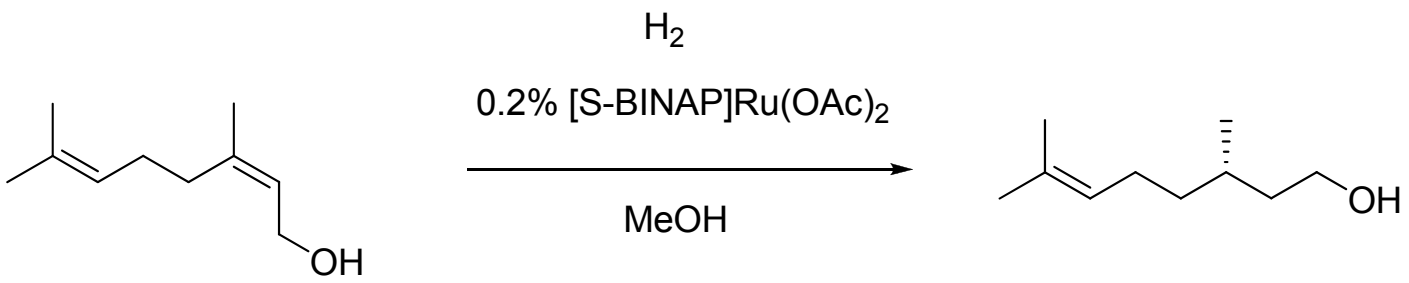
- Efficient reaction is obtained when $K_{inv} >> K_{S,R}$ and $K_{R,R}$
- Quick acces to β-hydroxy amino acids

Noyori, *J. Am. Chem. Soc.* **1989**, *111*, 9134

Ru catalyzed stereospecific hydrogenation of allylic esters



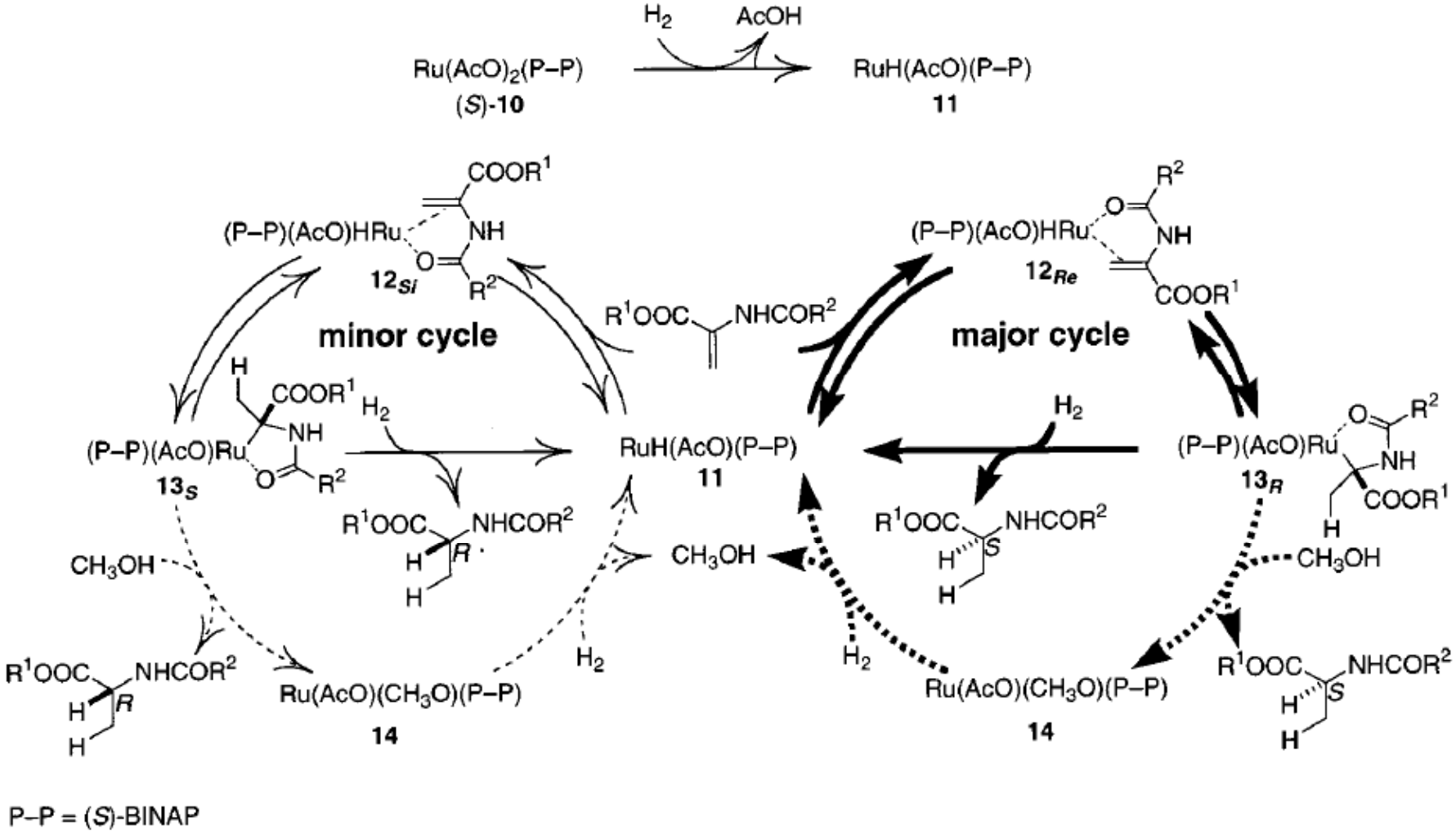
(*R*)-citronellol, 96% *ee*



(*S*)-citronellol, 98% *ee*

Noyori, *J. Am. Chem. Soc.* **1987**, *109*, 1596

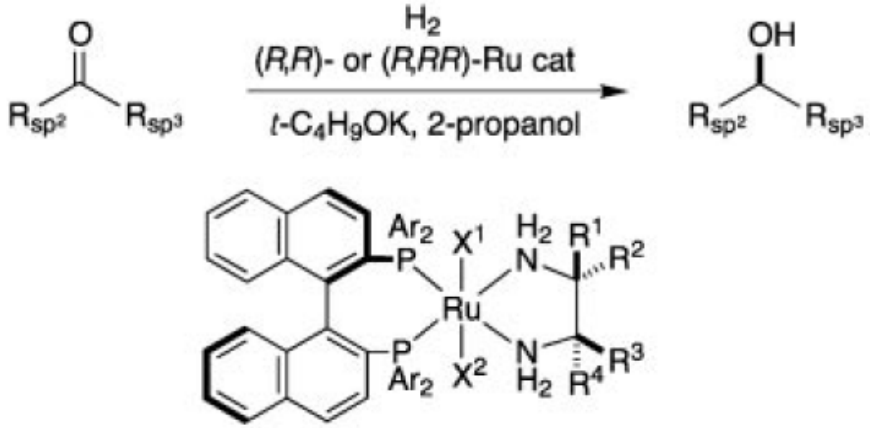
Mechanism of Ru(II)-catalyzed hydrogenation of enamides



• Change of mechanism relative to (Rh)-based hydrogenation allows excellent selectivity in favor of most stable Ru(II) complex

Noyori, *J. Am. Chem. Soc.*, **2002**, *124*, 6649.

Simple Ketones



(*R,R*)-35: Ar = 3,5-$(CH_3)_2C_6H_3$; $R^1 = R^2$ = 4-$CH_3OC_6H_4$; $R^3 = (CH_3)_2CH$; R^4 = H; $X^1 = X^2$ = Cl

(*R,SS*)-36: Ar = 3,5-$(CH_3)_2C_6H_3$; $R^1 = R^4 = C_6H_5$; $R^2 = R^3$ = H; $X^1 = BH_4$; X^2 = H

(*R,RR*)-37: Ar = 4-$CH_3C_6H_4$; $R^1 = R^4$ = H; $R^2 = R^3 = C_6H_5$; $X^1 = X^2$ = Cl

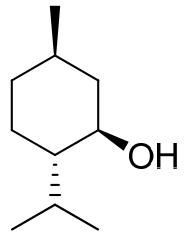
(*R,RR*)-38: Ar = 4-$CH_3C_6H_4$; $R^1 = R^4$ = H; $R^2 = R^3 = C_6H_5$; $X^1 = BH_4$; X^2 = H

(*R,SS*)-39: Ar = 4-$CH_3C_6H_4$; $R^1 = R^4 = C_6H_5$; $R^2 = R^3$ = H; $X^1 = X^2$ = Cl

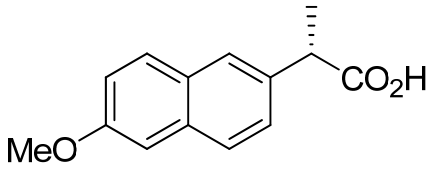
- Also works for Alkyl-Alkyl and functionalized ketones
- NH_2-type ligand is important for catalyst activity, “NH effect”
- Proceeds by different outersphere mechanism (no ketone-Ru coord involved)

Review: Noyori, *Angew. Chem. Int. Ed.*, **2001**, *40*, 40.

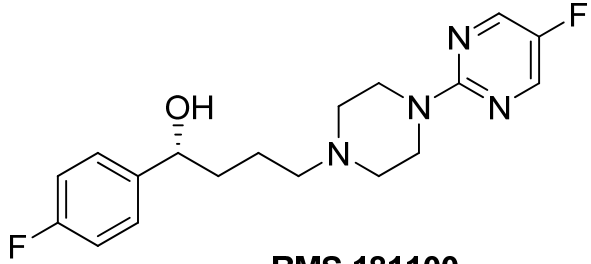
Application of Ru(II)-based Hydrogenation to Natural Products



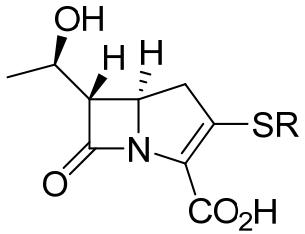
(-)-menthol



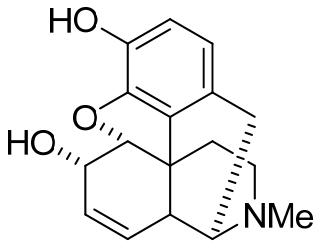
naproxen



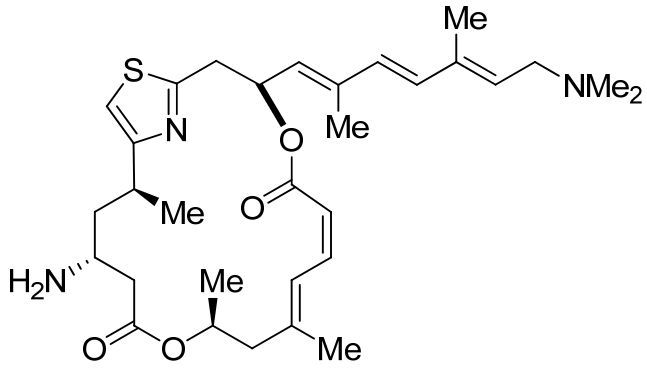
BMS 181100
(antipsychotic agent)



carbapenems



morphine



Pateamine A

Noyori, R. *Angew. Chem. Int. Ed.* **2002**, *41,* 2008.