
# Chem 652 Spring 2013

# Transition Metal Catalyzed Hydrogenation

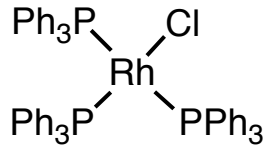
Prof. Donald Watson

Read Hartwig Chapters 14-16

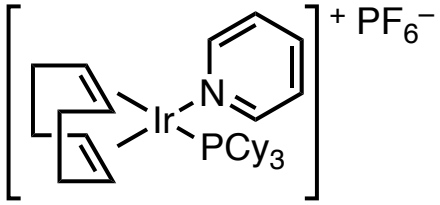
Note Chapter 14 and 16 not covered in lecture.

# *Soluble Transition Metal Catalyzed Hydrogenation*

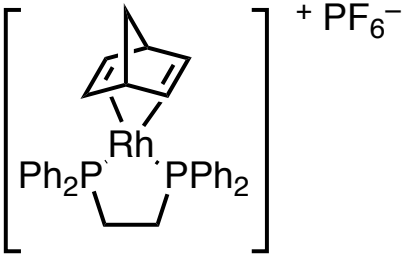
Several Classes of Catalysts:



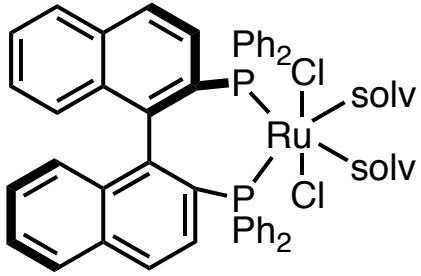

Neutral Rh Catalysts
(Wilkinson's Catalyst)



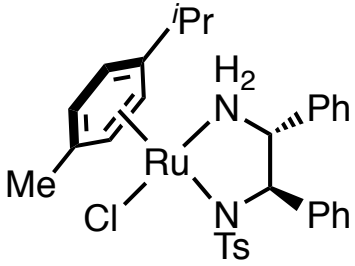

Cationic Ir Catalysts
(Crabtree's Catalyst)




Cationic Rh Catalysts




Ru(II) Catalysts
(Noyori's Catalyst)



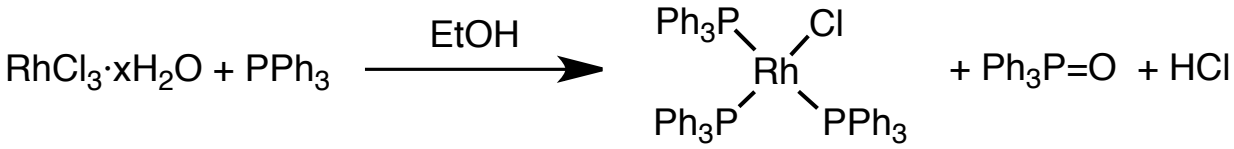

Transfer
Hydrogenation Catalysts


Early Metal Catalysts
(Buchwald Catalyst)

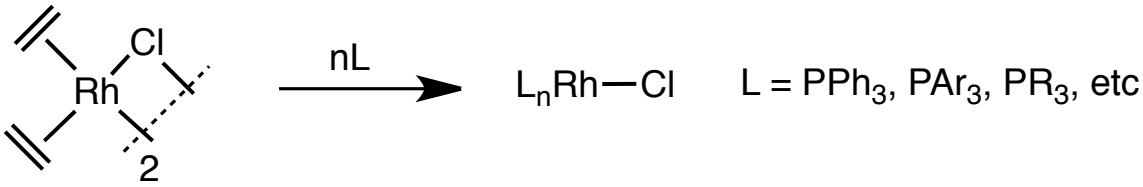
- More selectivity (chemo-, diastereo-, enantio-selectivity) than hetereogenous cats.
- Many, many variations on these catalysts.

# *Wilkinson's Catalyst*

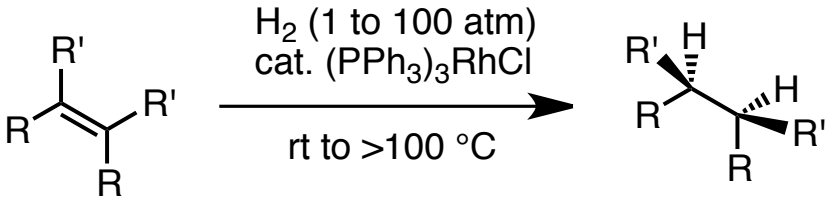
Synthesis:



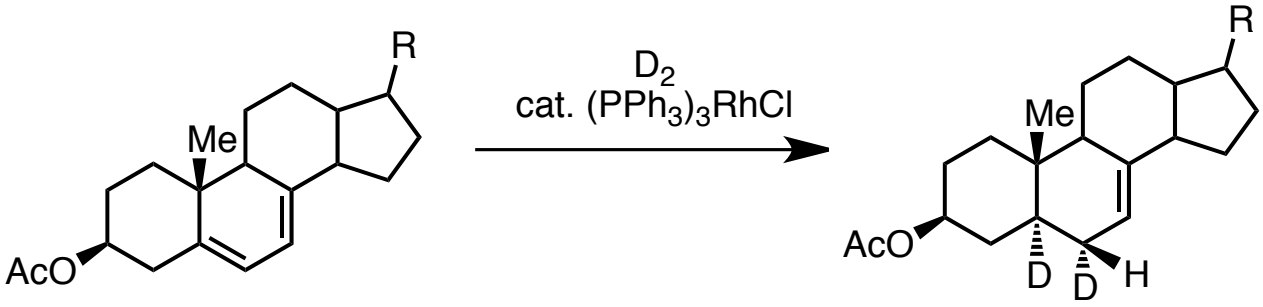

Most effective for simple $Ar_3P$.



# *Superfacial Addition of Hydrogen Across Alkene*



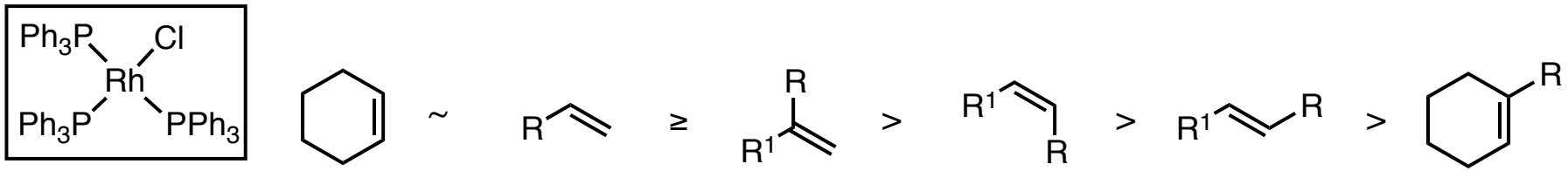

Example:




Note: No H/D scrambling.

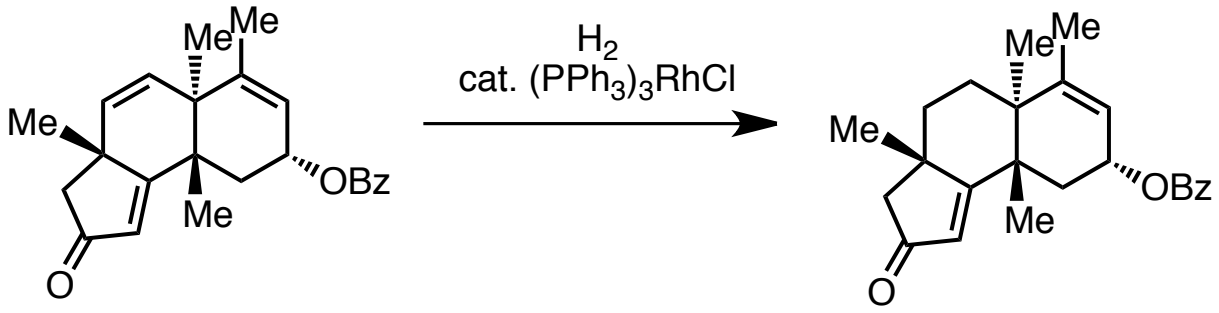
# *Rate Difference With Alkene Substitution*

- Approximately 50-fold rate difference depending on alkene substitution.
- In general, better ligand = faster rate.
- Some alkenes (e.g. ethylene, butadiene) bind so tightly they are slow to reduce.

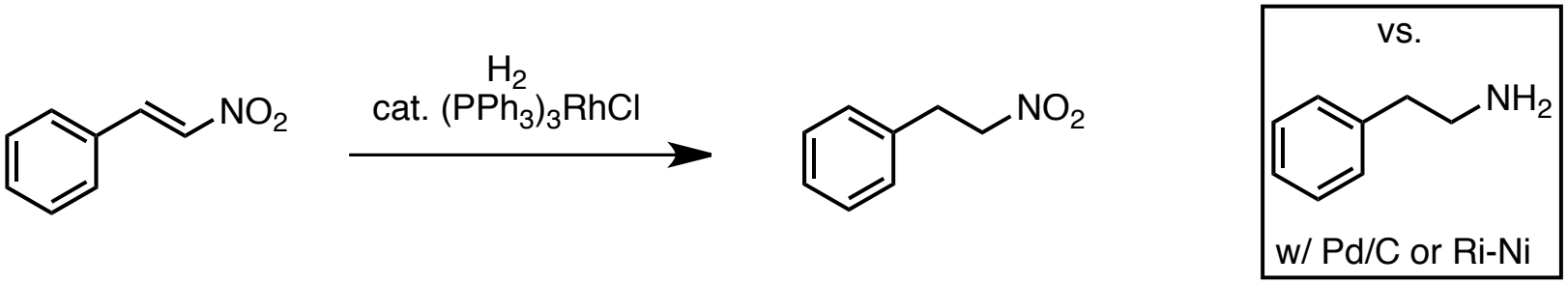


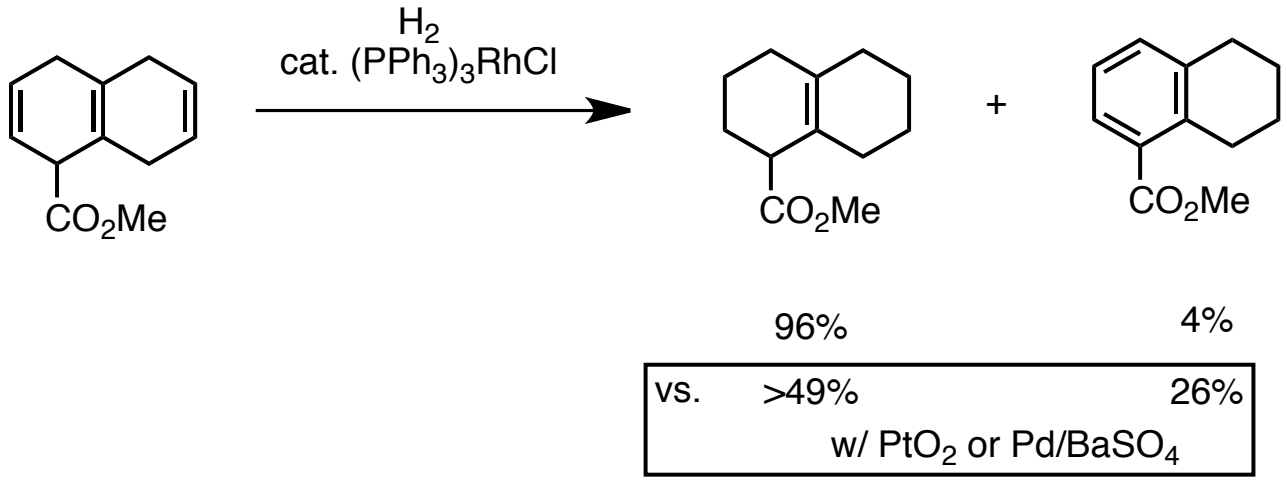

| $k^{25°C}$ (x $10^2$ $M^{-1}s^{-1}$) | 32 | 30 | 27 | 10 | 2 | 0.6 |
|---|---|---|---|---|---|---|

Example in synthesis:

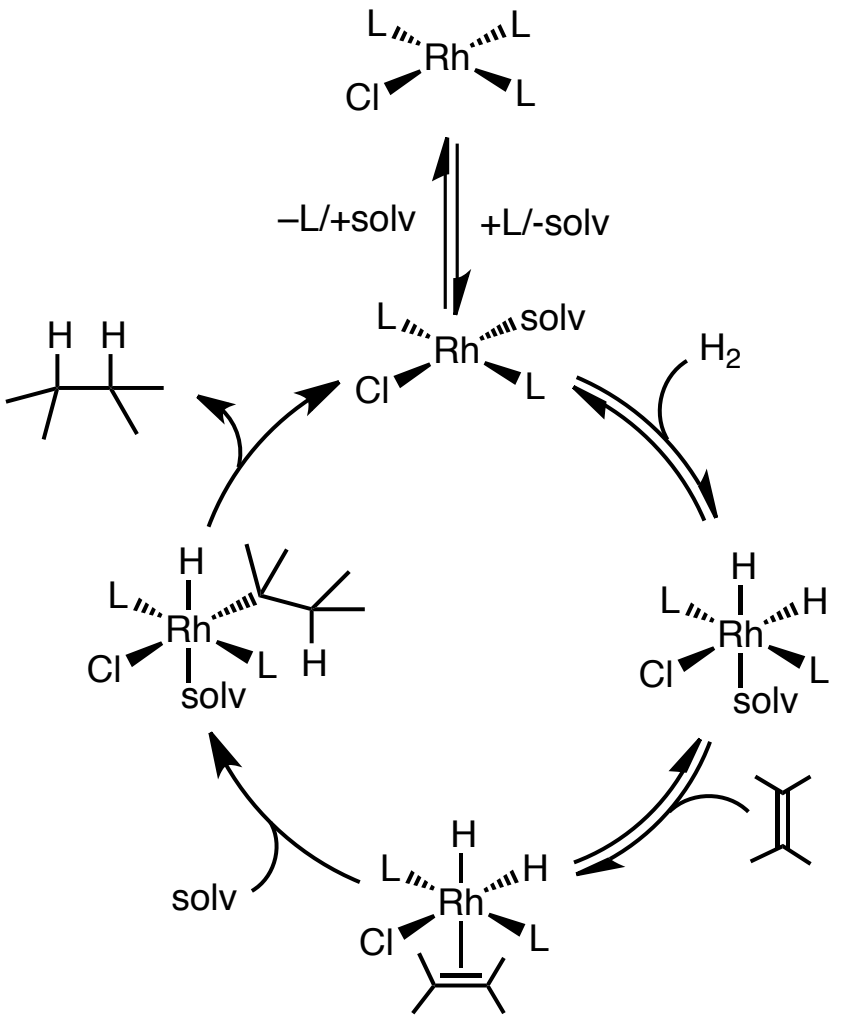


# *Good Chemoselectivity*



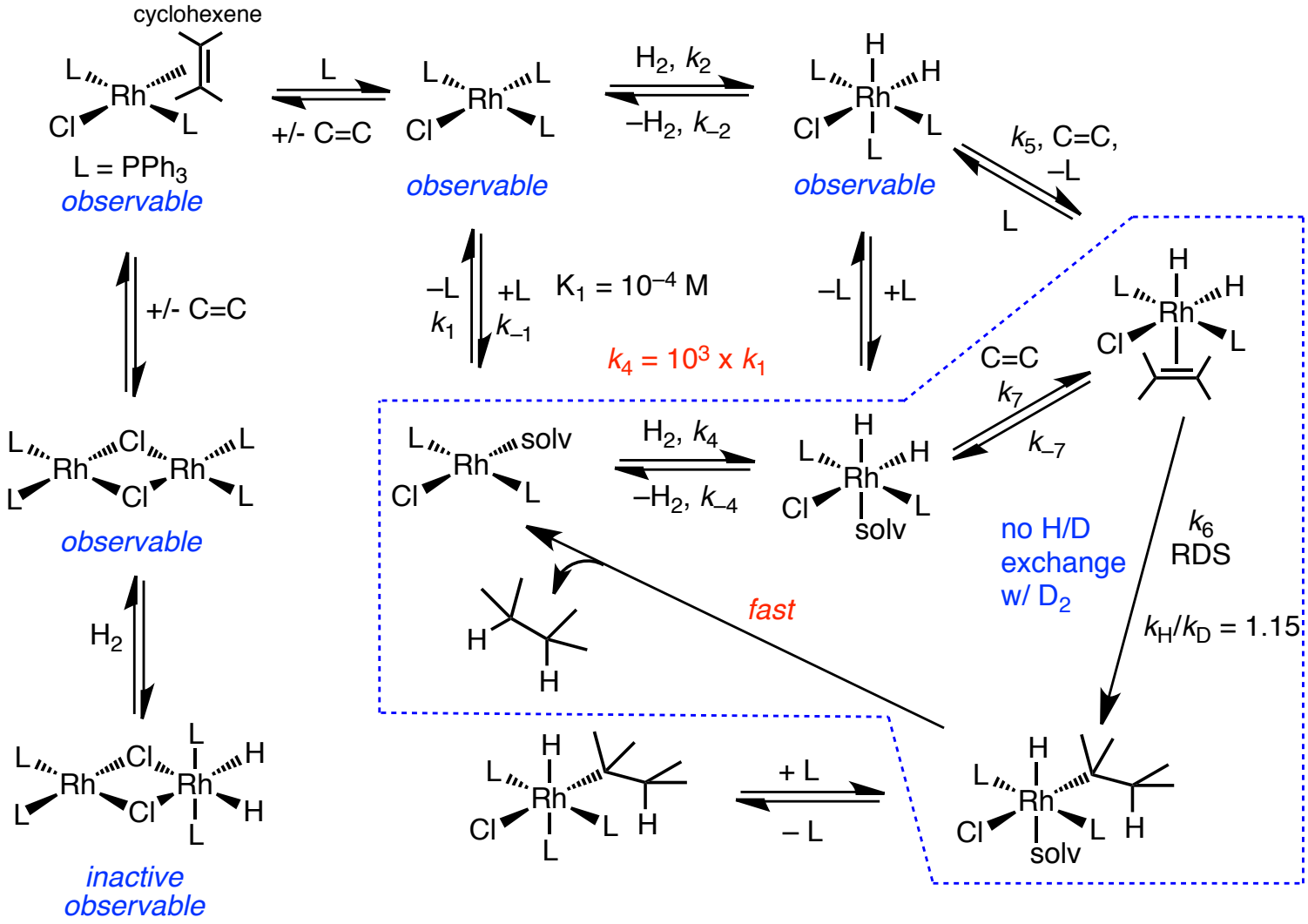
# *Mechanism: Hydrogen First*




Note: Neutral complexes less Lewis acidic and electron-rich.

Oxidative addition to hydrogen fast.

# *Actual Reaction Much More Complex*

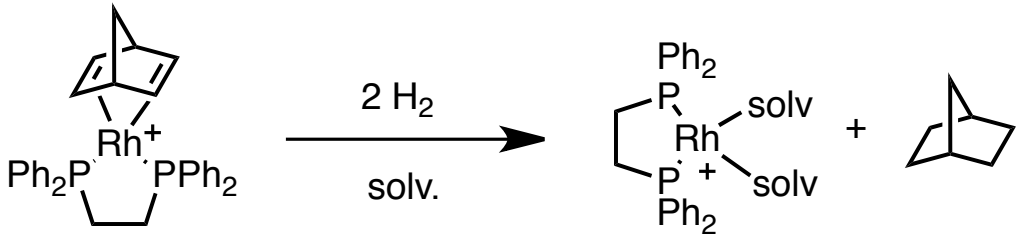



Note: The RDS in this pathway is substrate specific.

Halpern *et al. Science* **1982** *217* 401

# *Cationic Rhodium Complexes*

- Alkene or diene complexes are pre-catalysts:




- Most common type of catalyst for asymmetric alkene hydrogenation (with chiral ligands).
- Highly efficient. Often can use <<0.1% catalyst in reaction.
- Prepared with non-coordinating counter-ion ($BF_4^-$ , $PF_6^-$ , $B[3,5\text{-}C_6H_3(CF_3)]_4^-$.
- Less alkene scrambling than with neutral complexes.
- Because of Lewis-acidity of the complex, can be substrate directed… see more later.

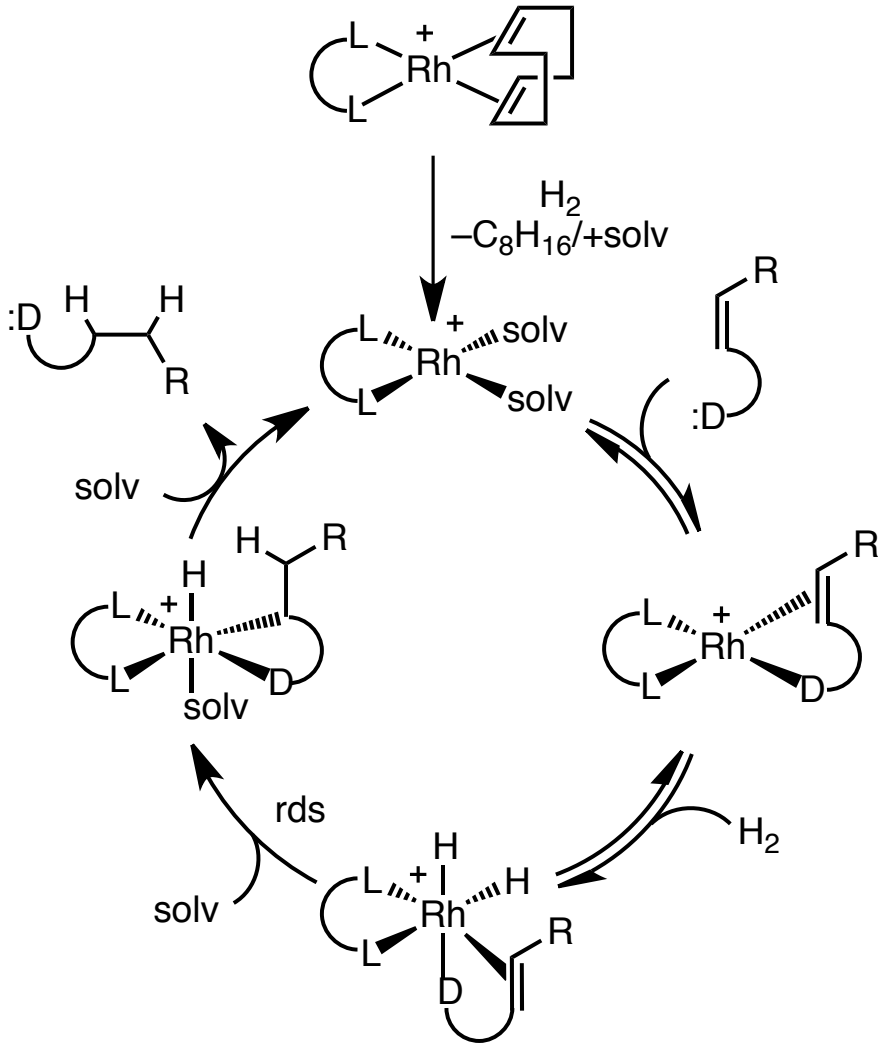
# *Cationic Rhodium Complexes*

- More active complexes from more electron-rich ligands.

| complex | [substrate] (mM) | $k_{int}$ x $10^4$ ($s^{-1}$) |
|---|---|---|
| $[Rh(NBD)(PPh_3)_2]^+$ | 5.3 | 0.1 |
| $[Rh(NBD)(PPh_2Me)_2]^+$ | 3.7 | 3.0 |
| $[Rh(NBD)(PPhMe_2)_2]^+$ | 3.5 | 6.0 |

- Complexes with bidentate ligand more active than those with mono-dentate ligands.
- Sensitive to acidity (basicity) of reaction… deprotonation can lead to neutral complex.

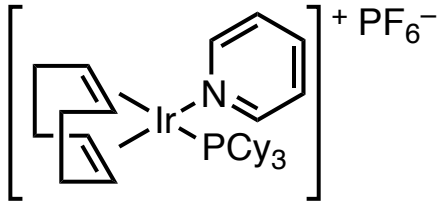
# *Mechanism: Olefin First*




- Cationic complexes are:
  - More electrophlic, therefore more likely to bind alkene or directing group.
  - Less likely to undergo oxidative addition.
- D = Directing Group, typically imine, alcohol, ether, carbonyl, etc.
- Note: $L_2Rh(solv)_2$ can react with $H_2$ but is not kinetically relevant.

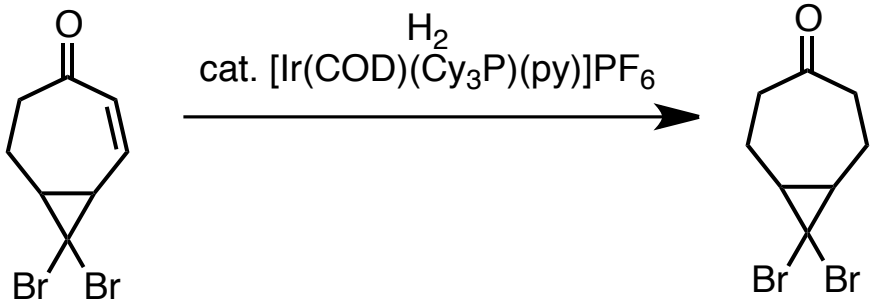
# *Cationic Iridium Catalysts*

- Prototypical (and first) example is Crabtree's catalyst:




Crabtree, *Acc. Chem. Res*. **1979**, *12*, 331.

- Precatalyst. Diene reduced to give $L_nIr(III)H_2^+$.

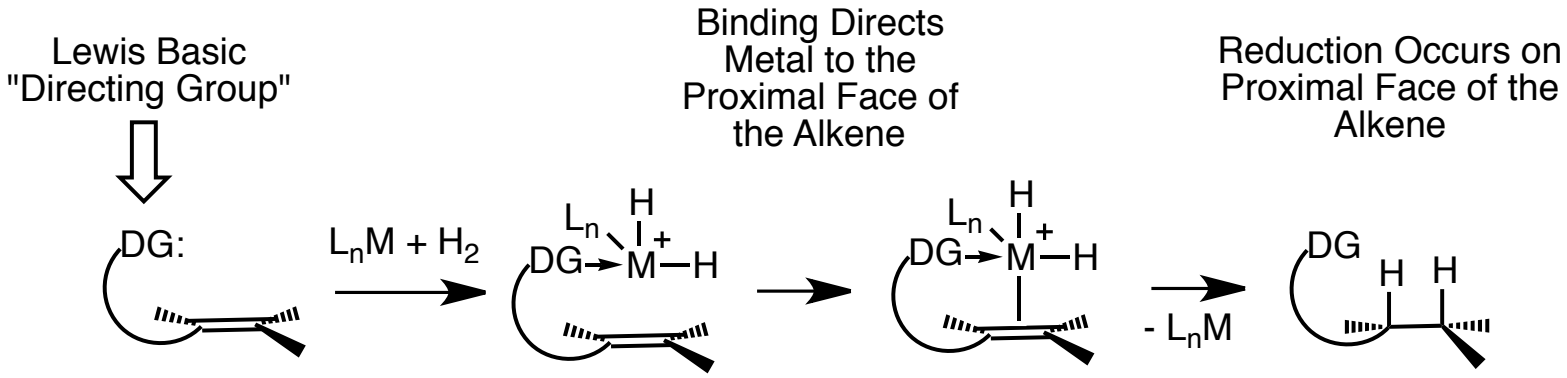


# *Cationic Iridium Catalysts Are Very Reactive*

| complex | T (°C) | Solvent | Turnover Frequency ($h^{-1}$) | | |
|---|---|---|---|---|---|
| | | | 1-hexene | cyclohexene | $Me_2C=CMe_2$ |
| $[Ir(COD)(PCy_3)(py)]^+$ | 0 | $CH_2Cl_2$ | 6,400 | 4,500 | 4,000 |
| $[Ir(COD)(PPh_2Me)_2]^+$ | 0 | $CH_2Cl_2$ | 5,100 | 3,800 | 50 |
| $[Ir(COD)(PPh_3)_2]^+$ | 0 | acetone | 10 | 0 | 0 |
| $[Rh(COD)(PPh_3)_2^+$ | 25 | $CH_2Cl_2$ | 4,000 | 10 | 0 |
| $[Ru(H)Cl(PPh_3)_3]$ | 25 | $C_6H_6$ | 9,000 | 7 | 0 |
| $[RhCl(PPh_3)_3]$ | 25 | $C_6H_6$/EtOH | 650 | 700 | 0 |
| $[RhCl(PPh_3)_3]$ | 0 | $C_6H_6$/EtOH | 50 | 70 | 0 |

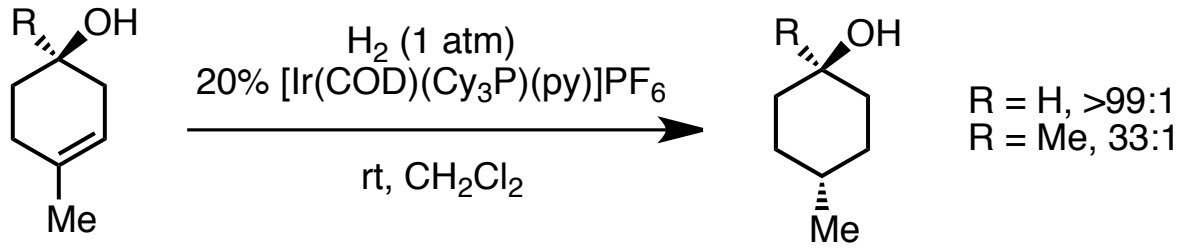
- Note: the fact that it reacts at all was surprising (3rd row).

# *Directed Hydrogenation*

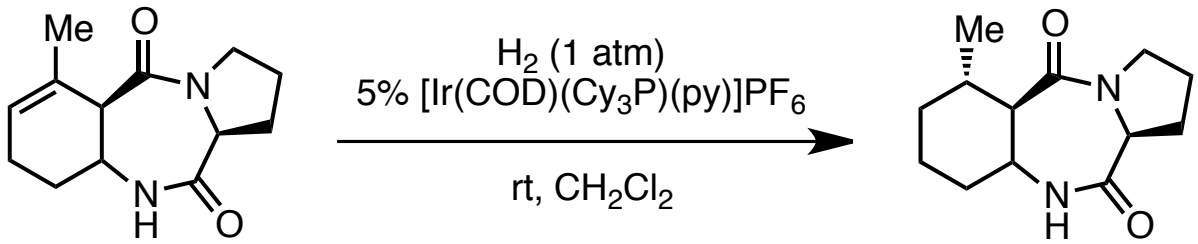



- Works best with highly Lewis Acidic Catalysts (ie cationic ones).
- Requires conformationally defined substrate.

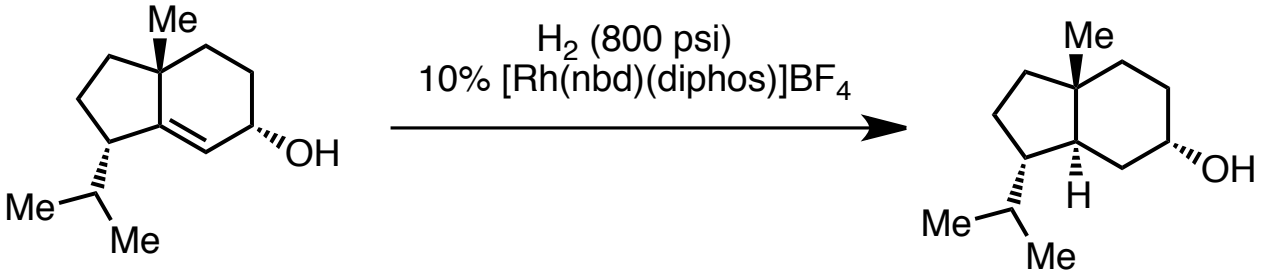
# *Directed Hydrogenation Examples*




R = H, >99:1
R = Me, 33:1



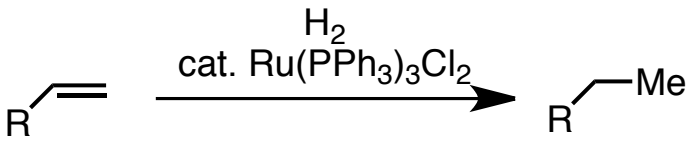

>99:1




70:1

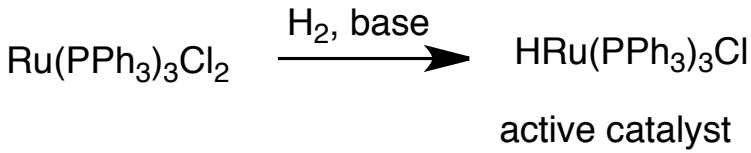
Note: reaction happens towards large isopropyl group!

# *Ruthenium Catalysts*

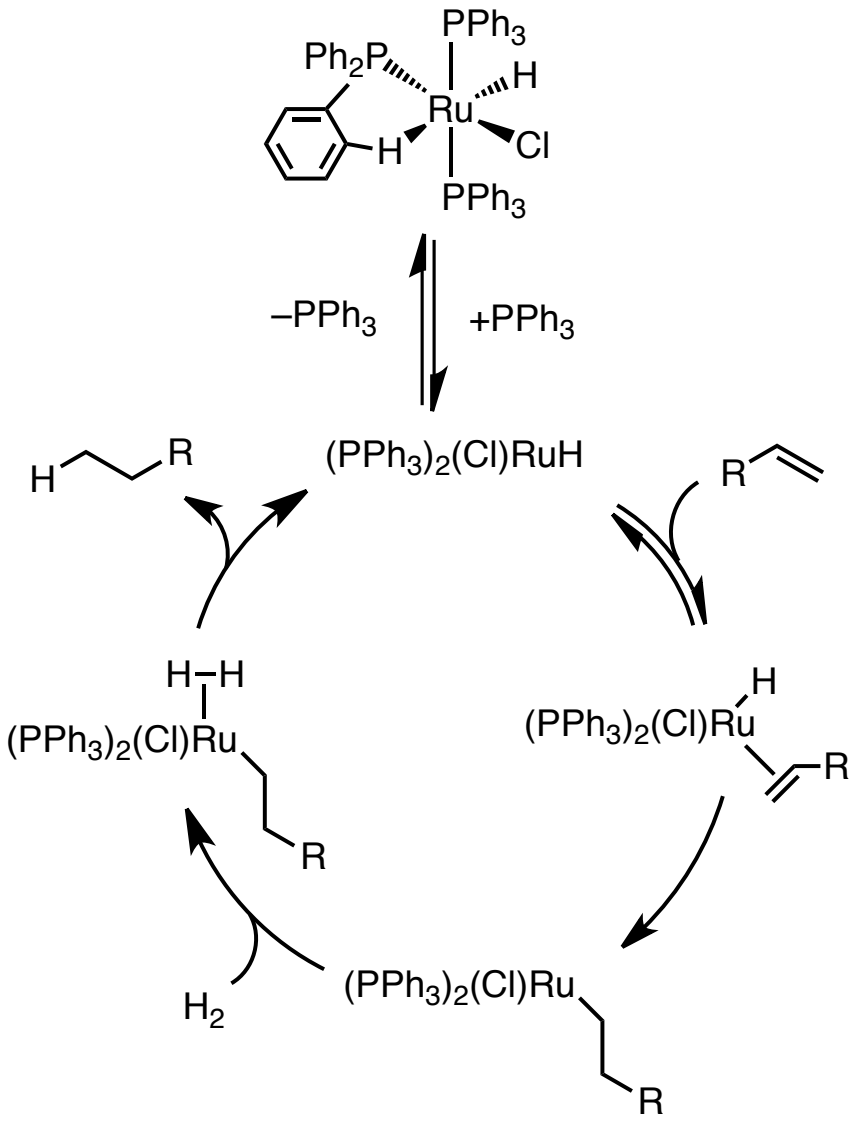



- Selective for terminal alkenes with simple alkenes ($k_{rel}$ ca. 1000).

Wilkinson *Nature* **1965**, *208*, 1203



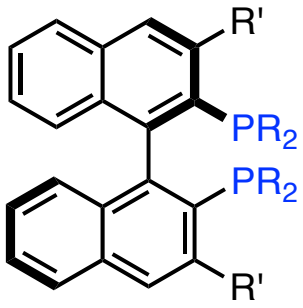
# *Monohydride Mechanism*



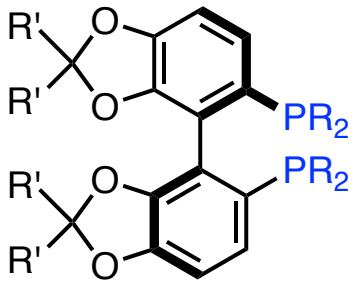
# *Asymmetric Catalysis*

- Chiral, single enantiomer ligands impart chirality of transition metal catalyst.
- Breaks symmetry in transition states leading to opposite enantiomers.
- Diastereomeric transitions states.
- Asymmetric catalysis is a ***kinetic*** phenomenon… we know this must be true because the enantiomeric product have identical thermodynamic properties.
- Enantiodetermining step must be first irreversible stereodetermining step.
- Before looking at reactions, we need to look at common chiral ligands.

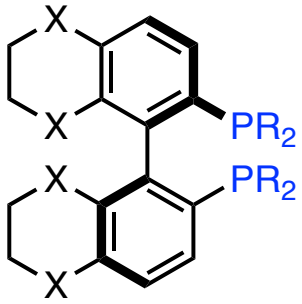
# *Chiral Biaryls*



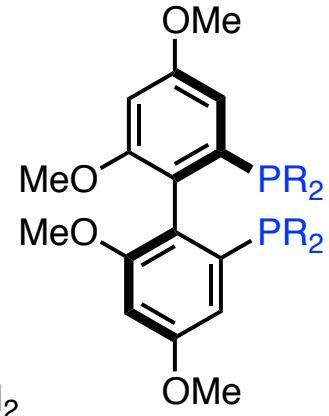

BINAP
3,3'-$(OR)_2$-BINAP
3,3'-diAlkyl-BINAP
3,3'-diAr-BINAP



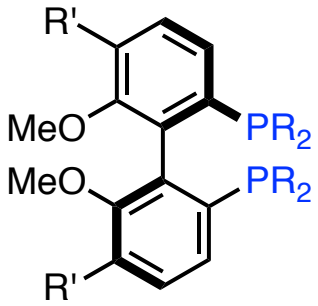

SEGPHOS, R' = H
Difluorphos, R' = F
SunPhos, R' = Me



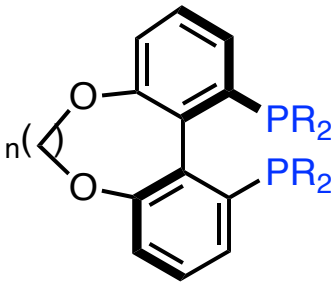

H8-BINAP, X = $CH_2$
SYNPHOS, X = O



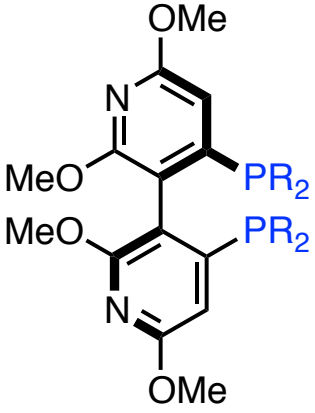

Garphos



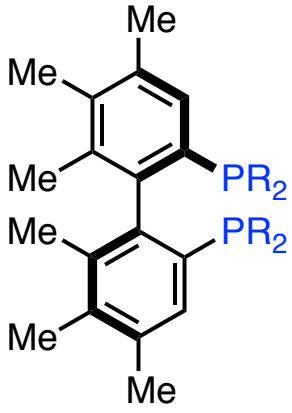

MeO-BIPHEP, R' = H
Cl-MeO-BIPHEP, R' = Cl




TUNEPHOS
(n = 1-6)



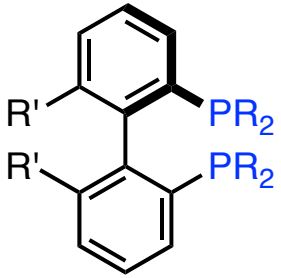

P-Phos



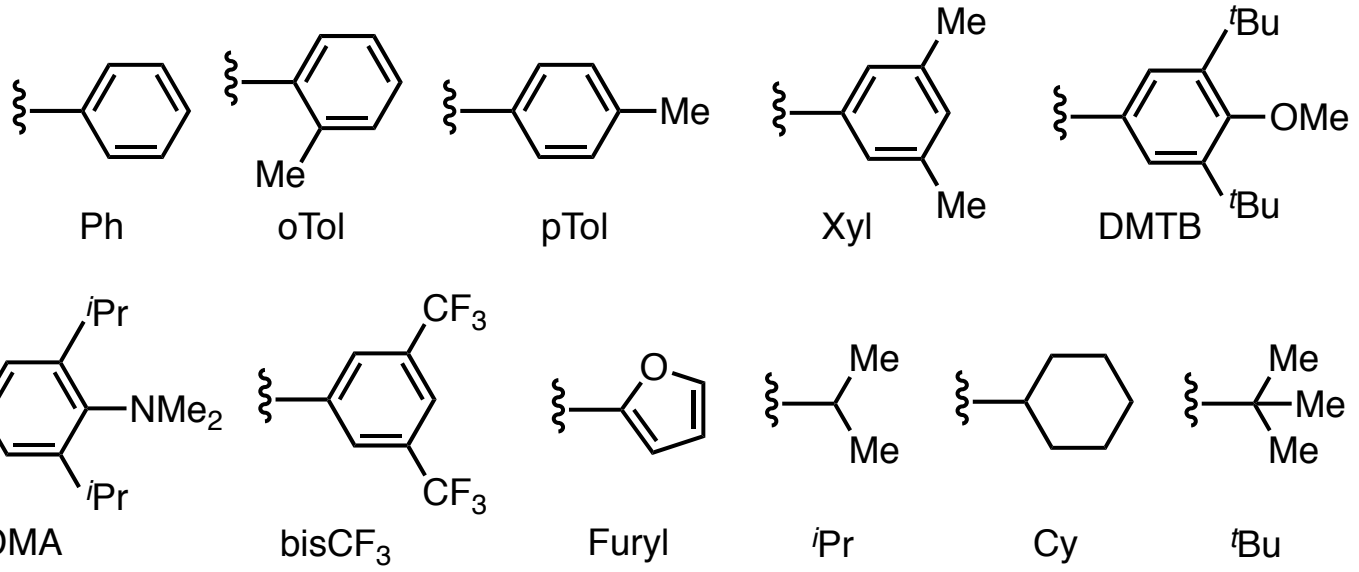

HexaPHEMP

- BINAP first example in class, reported by Noyori.
- Biaryl axis in tetra-sub. biaryls stable to racemization (to >100 °C).

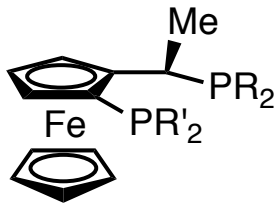
# *Lots of Phosphine Substituents!*



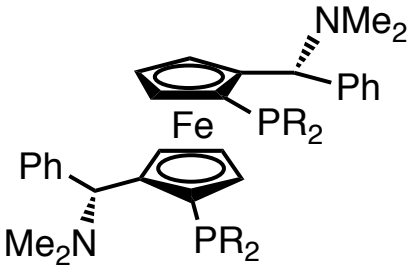

**R =**



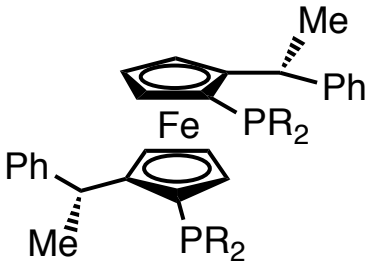
# *Ferrocene Backbones*



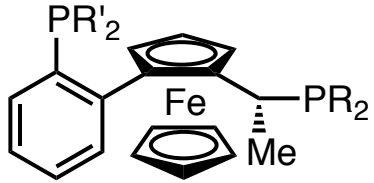

Josiphos




Mandyphos

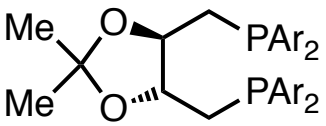



Mandyphos

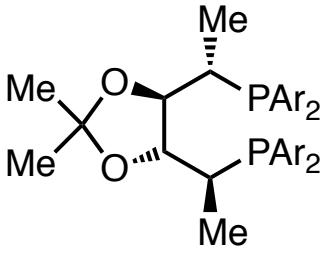



Walphos

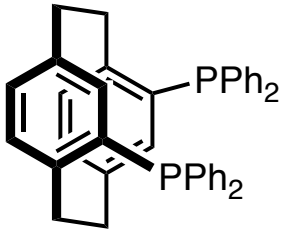
# *Chiral Backbones*



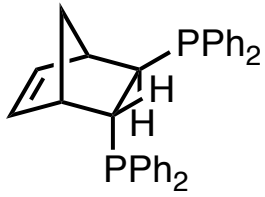

DIOP



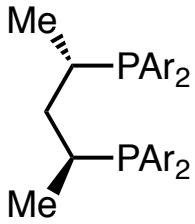

MeDIOP



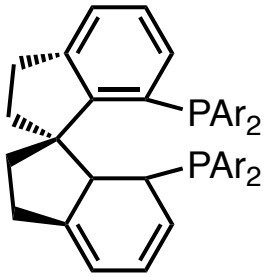

Phanephos



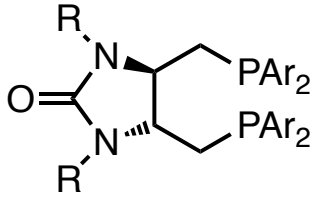

NorPhos




BDPP

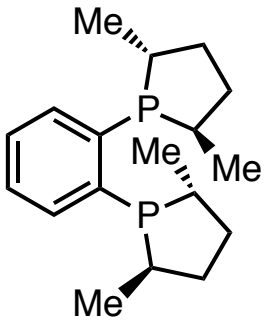



SPIROPhos

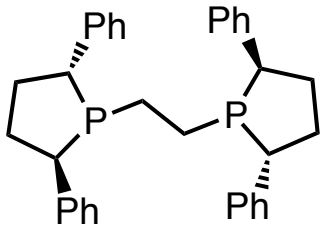



BDPMI

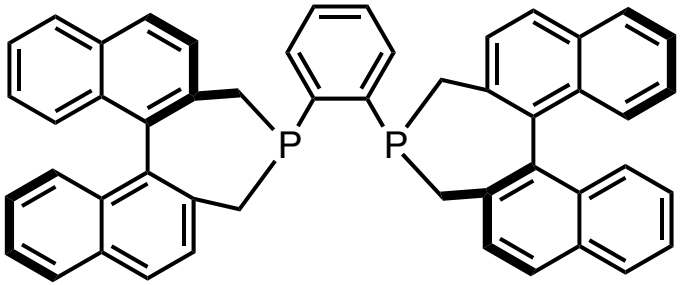
# *Aliphatic Bisphosphines*




Me-DuPHOS

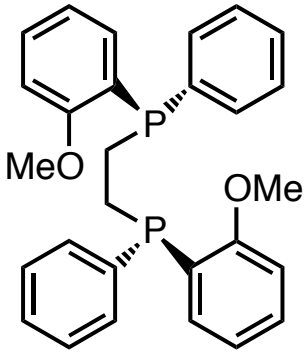



Ph-BPE

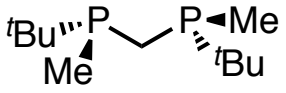



BINAPHANE

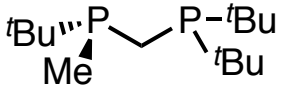
# *P-Chiral Phosphines*



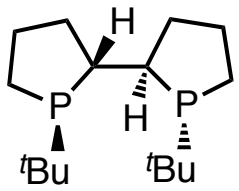

DIPAMP



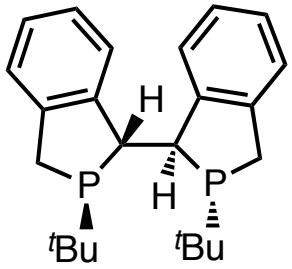

*t*Bu-MiniPhos




Tri-chicken-foot Phos

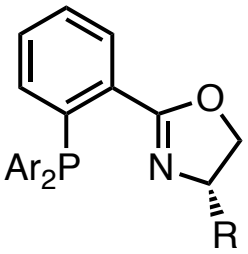



TangPhos

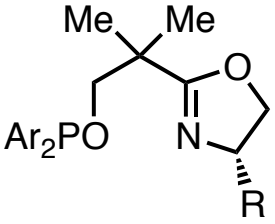



DuanPhos

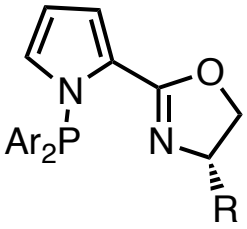
# *Chiral P,N Ligands*



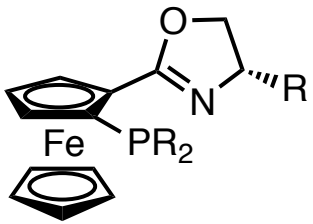

PHOX




SimplePhox

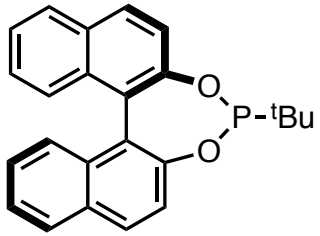



PryPHOX

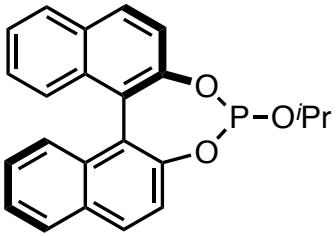


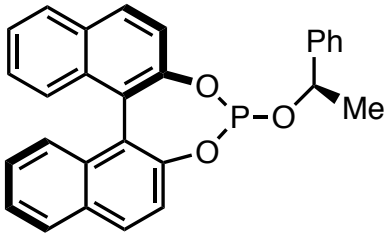
# *Phosphites, Phosphates,Phosphoramidites*

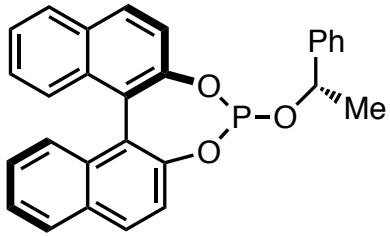
Phosphite



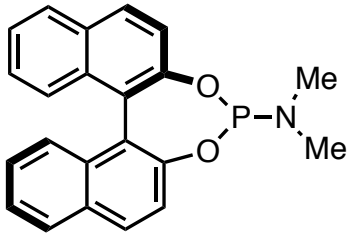

Phosphate



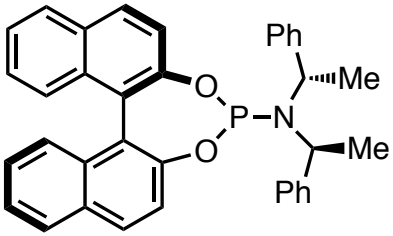



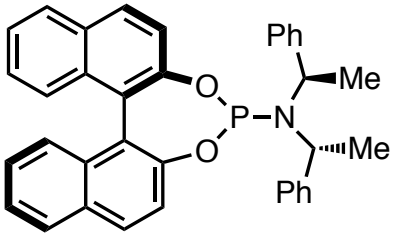



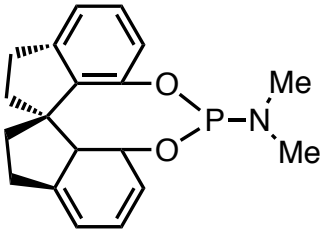

Phosphoramidite




MonoPhos

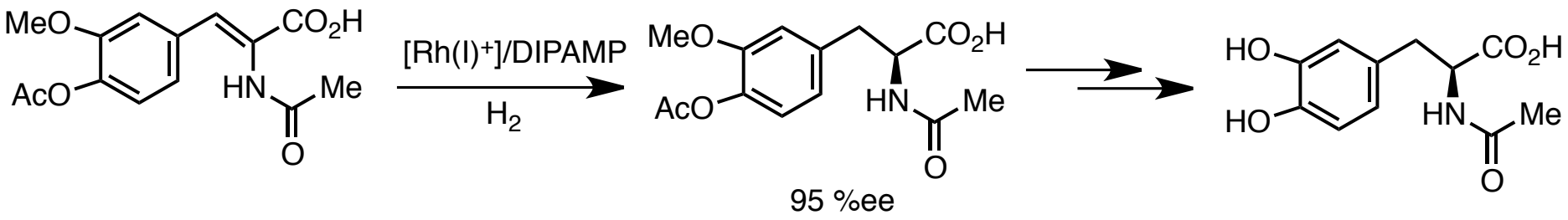


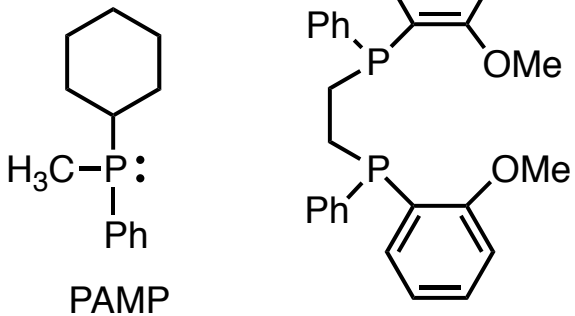




SIPhos

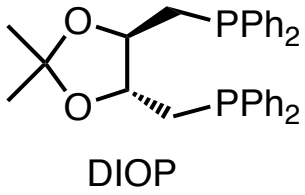
# *Monsanto L-Dopa Process: Entry Into Asymmetric Reductions*

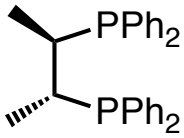


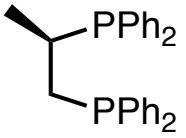









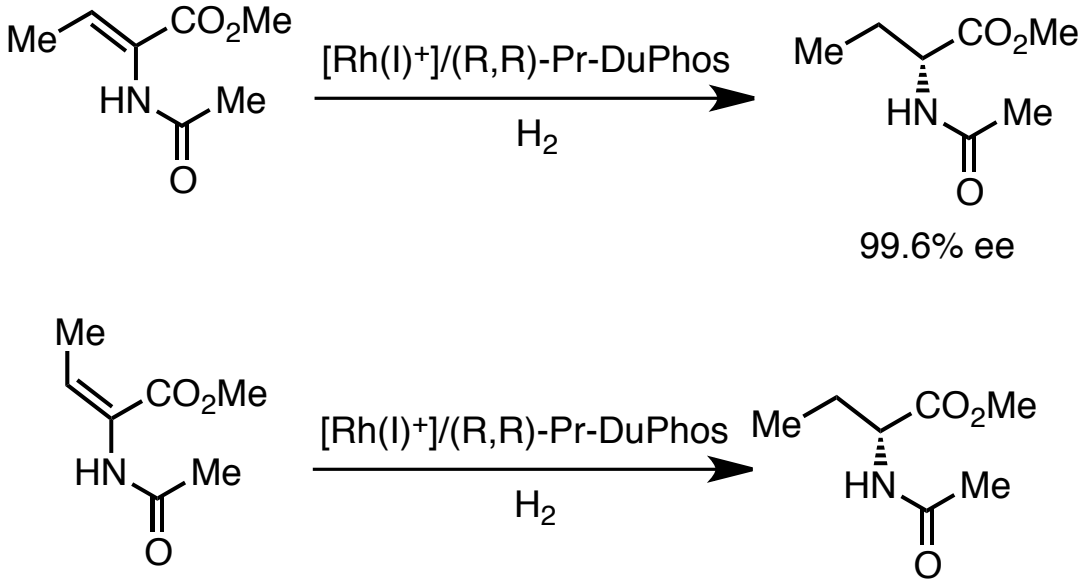

- Over 57 different ligands have been shown to be effective in this reaction.

William Knowles, Nobel Prize 2001

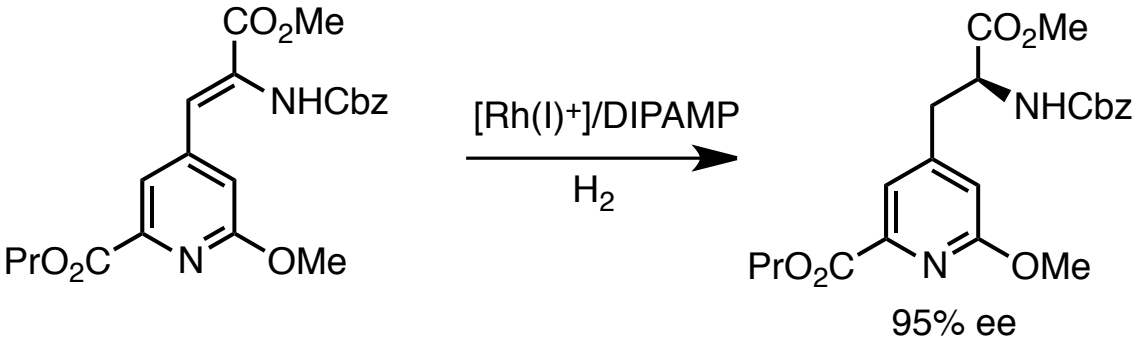
Knowles, W. S. *Angew. Chem. Int. Ed.* **2002**, *41*, 1998.

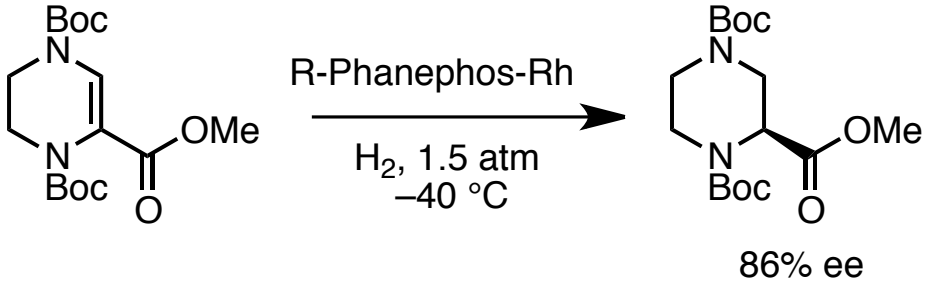
Tang, W.; Zhang, X. *Chem Rev* **2003**, *103*, 3029.

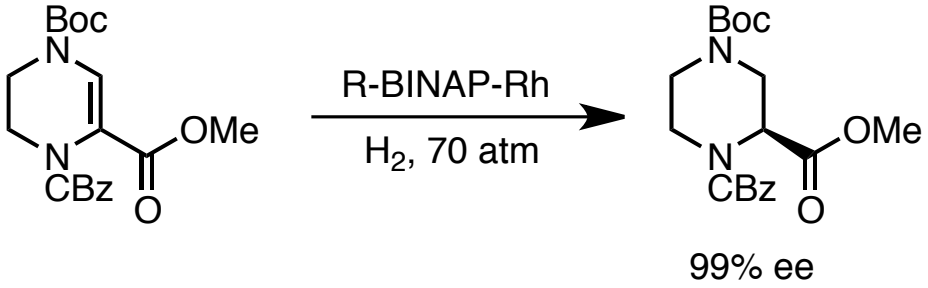
# *Alkene Geometry Often Does Not Matter With Some Catalysts*



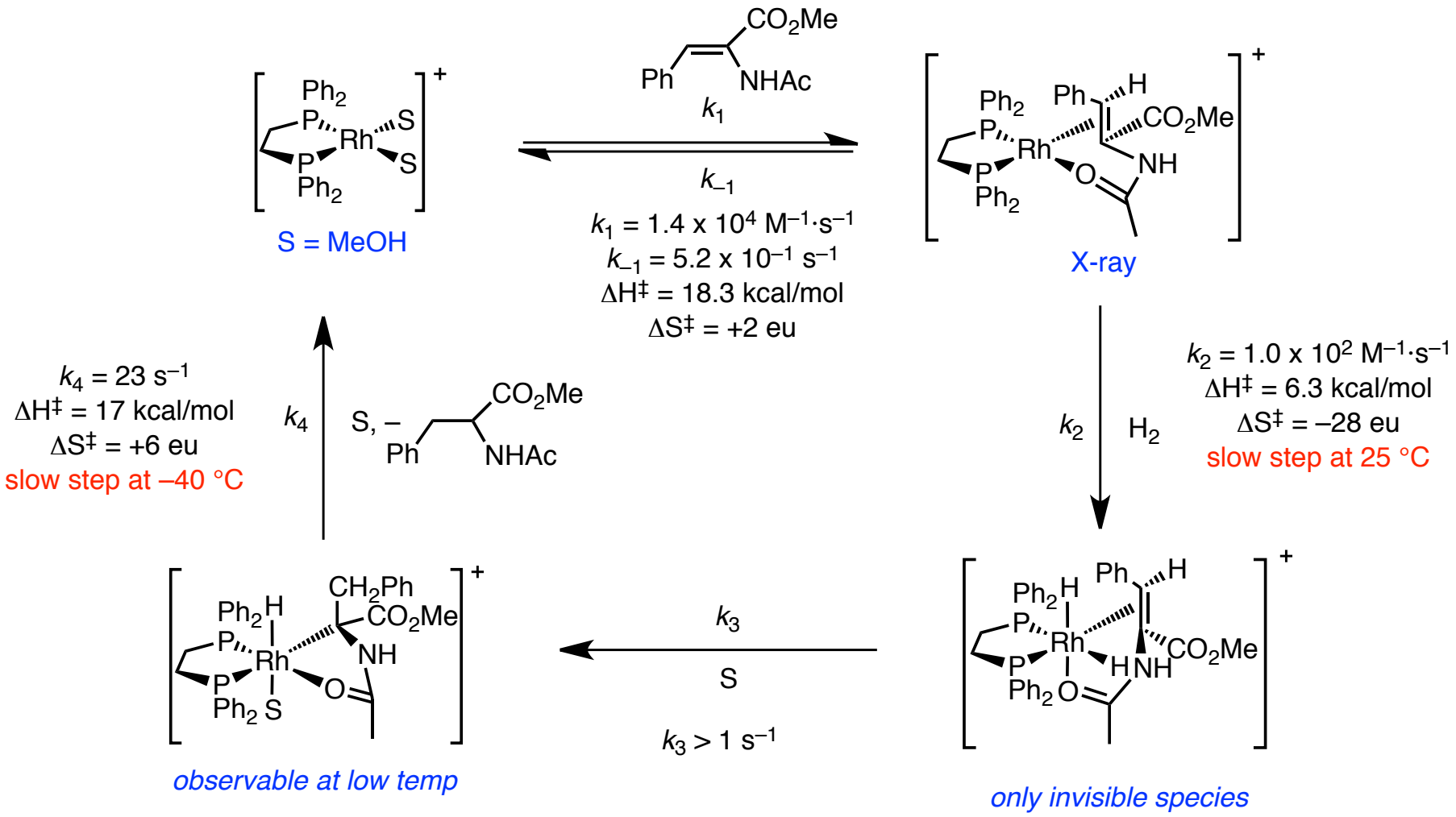
# *Other Examples*



# *Process Has Been Very Carefully Studied*




Halpern and Landis

# *Enantioselectivity with DIPAMP: A Surprise*

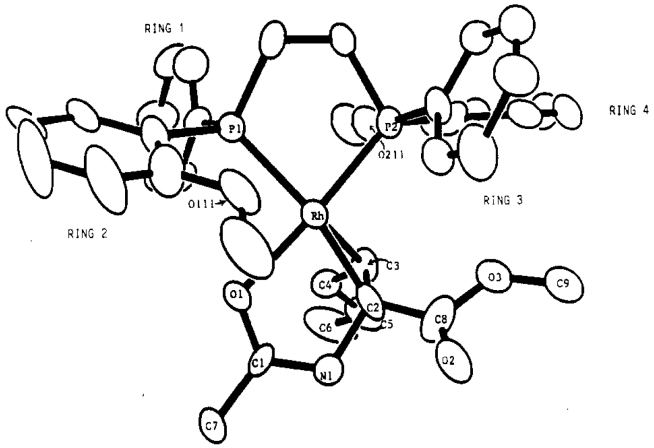
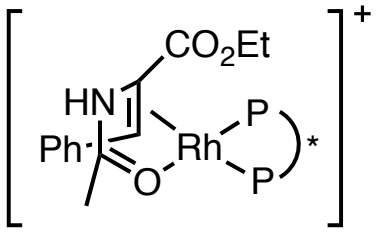
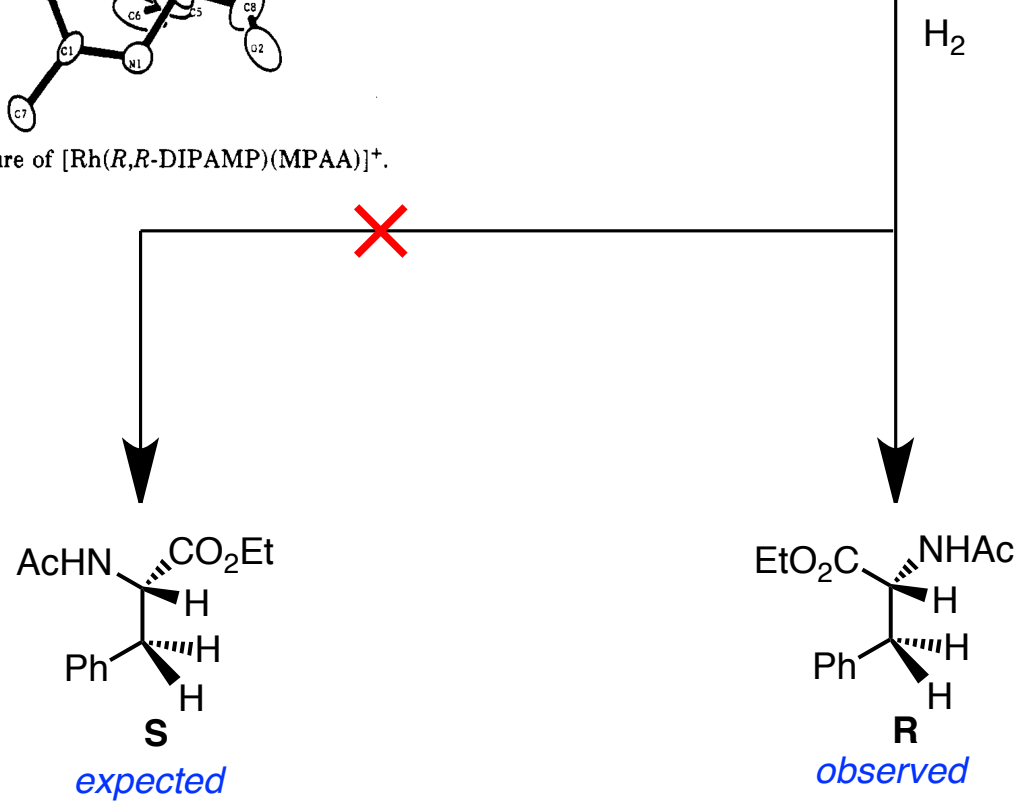
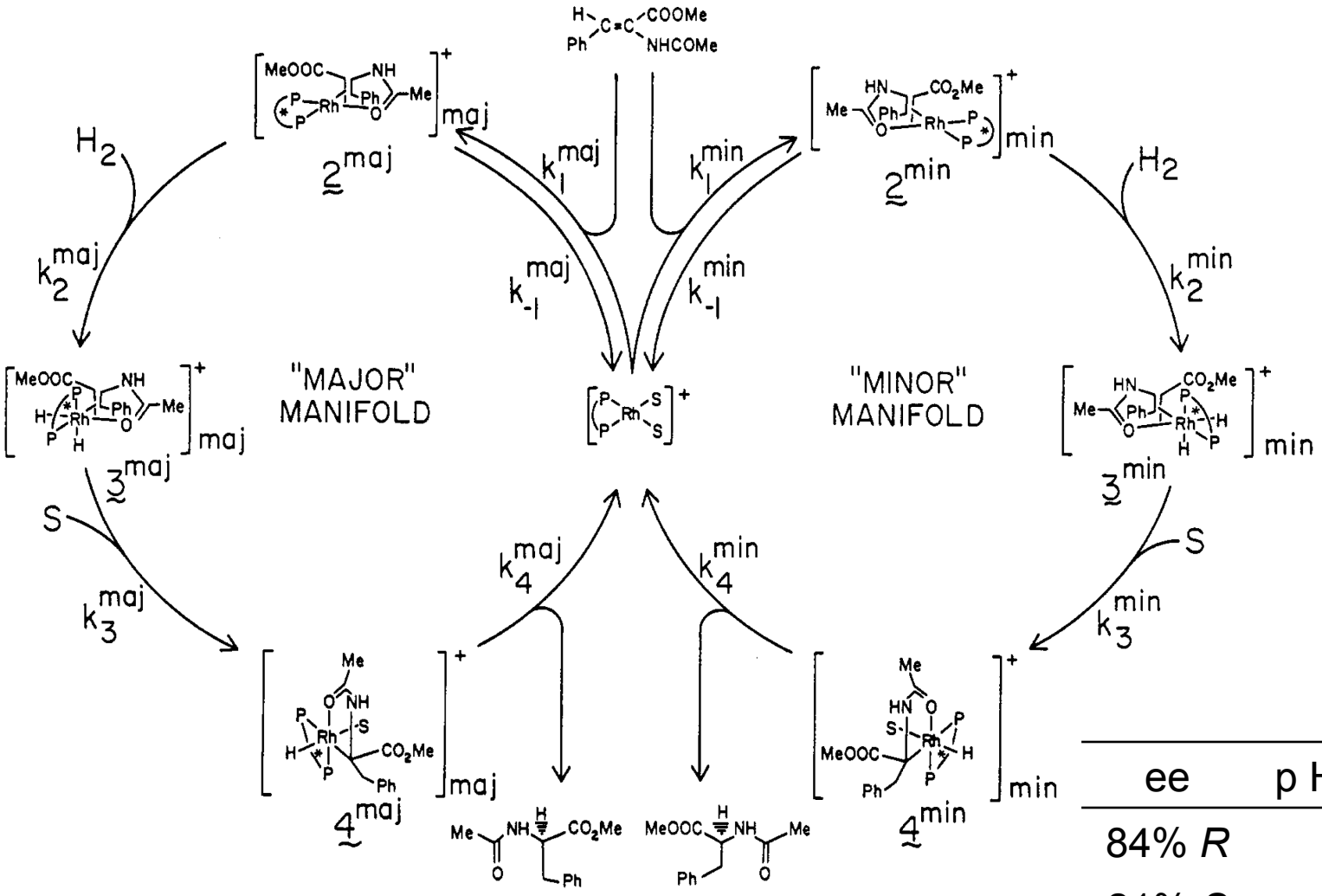



**Figure 1.** Structure of [Rh(*R*,*R*-DIPAMP)(MPAA)]$^+$.



# *Actual Mechanism*

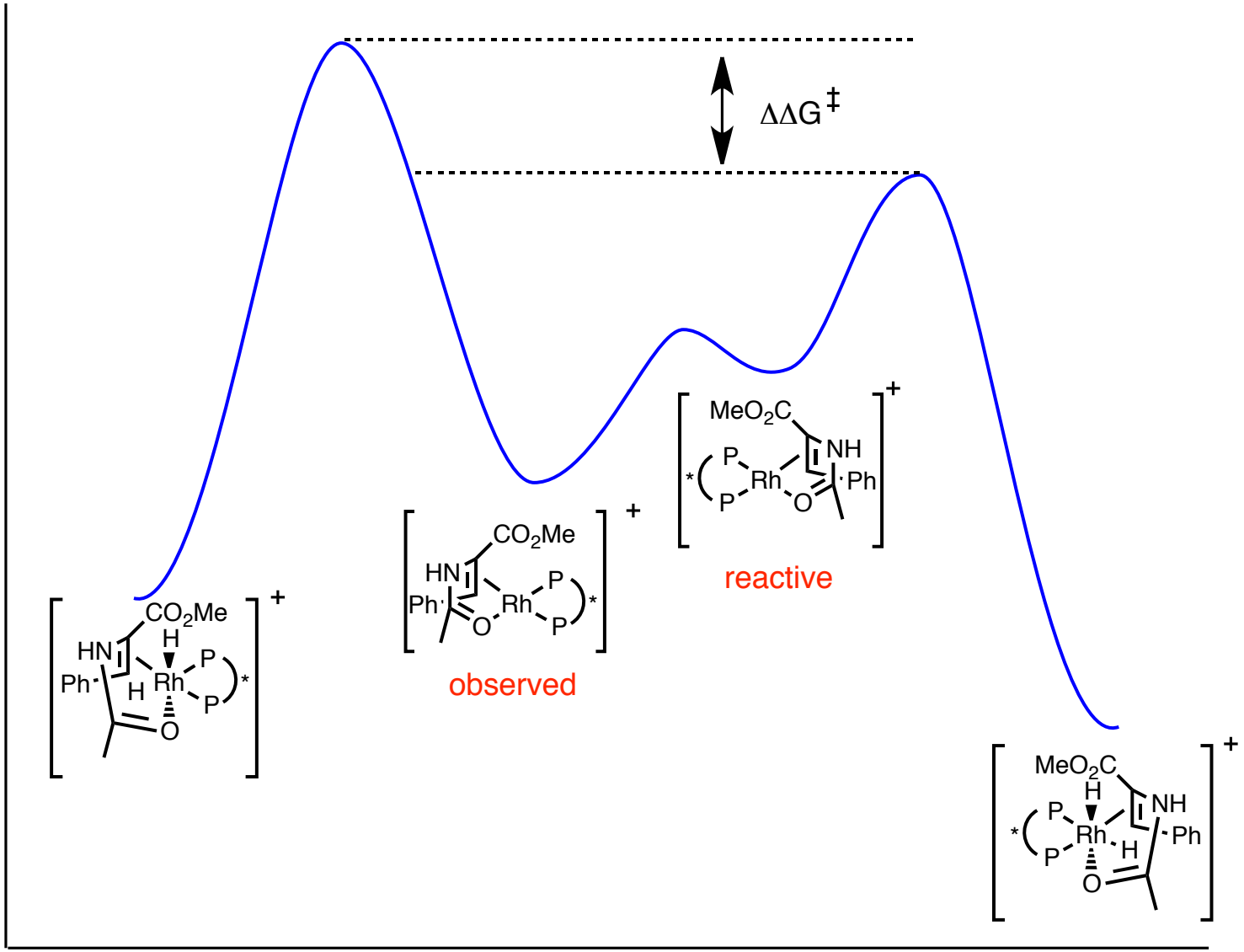



- Dependence on T and P

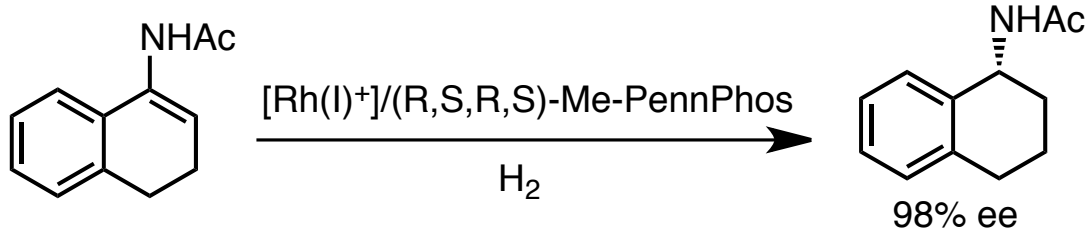
Landis and Halpern *JACS* **1987** *109* 1746

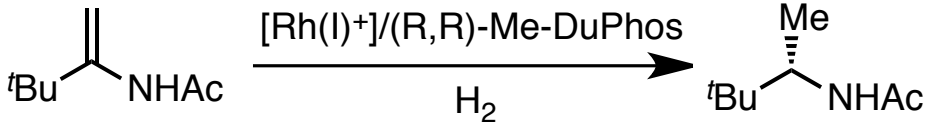
| ee | p $H_2$ (atm) |
|---|---|
| 84% *R* | 1 |
| 21% *S* | 20 |
| 8% *S* | 100 |

# *Curtin-Hammett Kinetics*

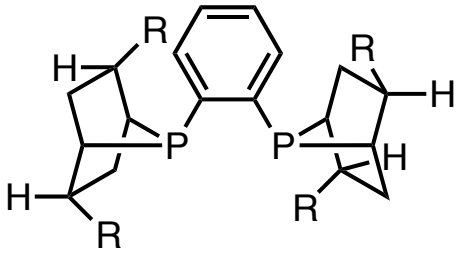


# *Other Enamines*



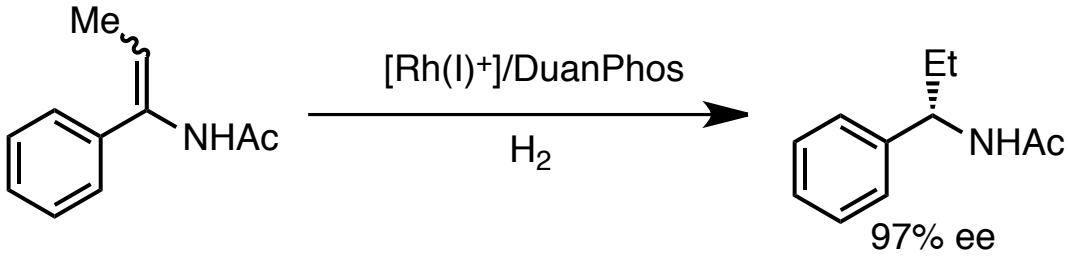




99% ee




PennPhos

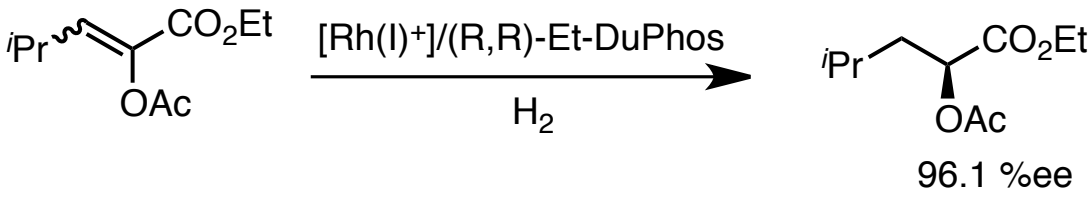
- Other enamines can also be reduced with these catalyst systems.
- In general, substrates need to have a stabilized N-carbonyl enamine tautomer.



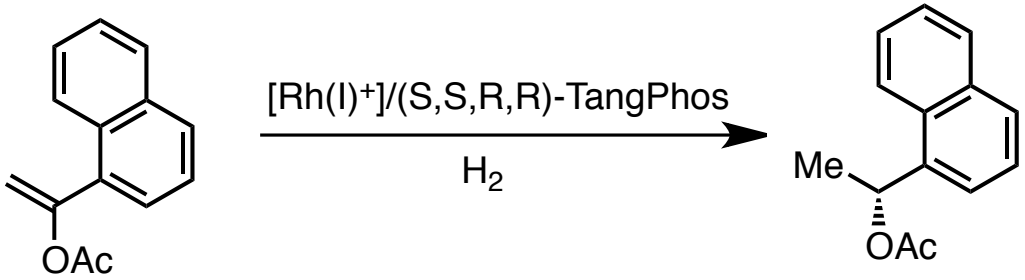

97% ee

- In *some* cases, both alkene isomers can be reduced to the same enantiomer.

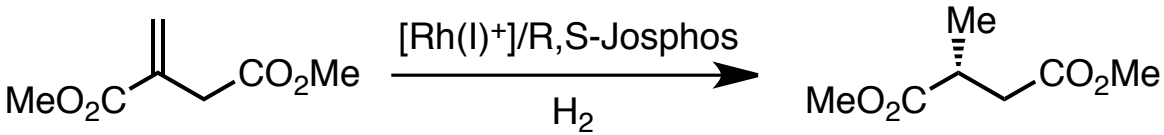
# *Examples of Other Substrate Classes*




96.1 %ee



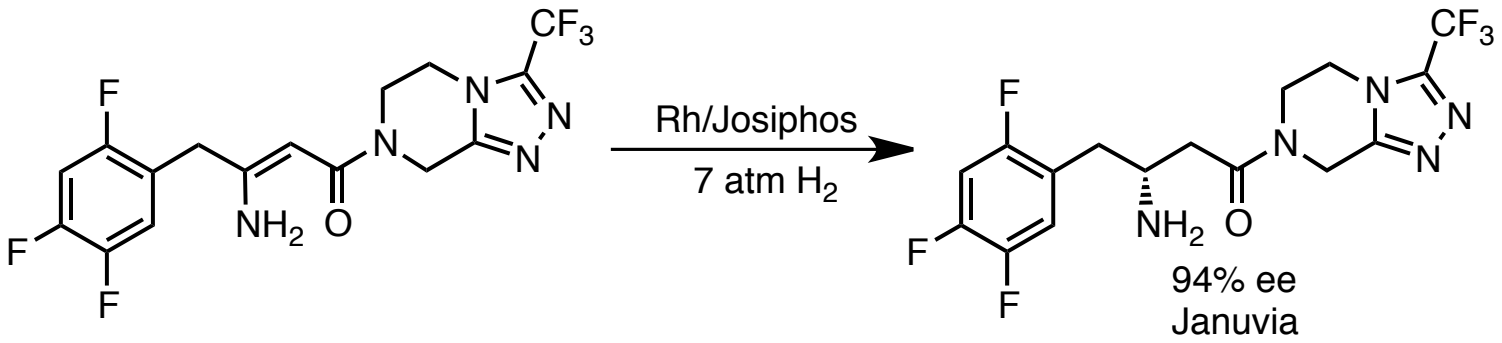

97 %ee




99 %ee

- Note: In all cases, alkene is substituted with a donor group to coordinate and orient catalyst.

# *Industrially Important Example*

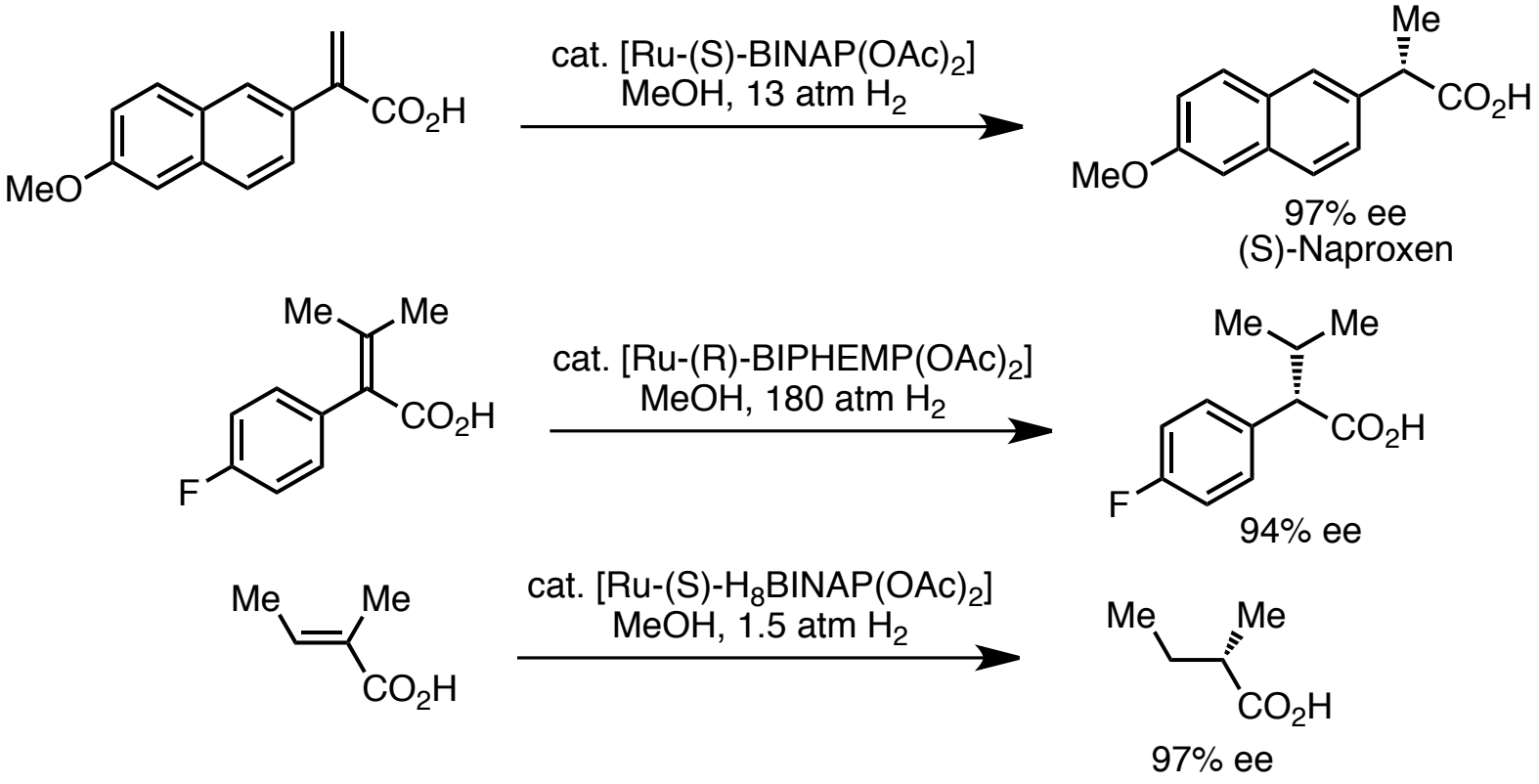



- Januvia is a Merck drug for the treatment of diabetes.

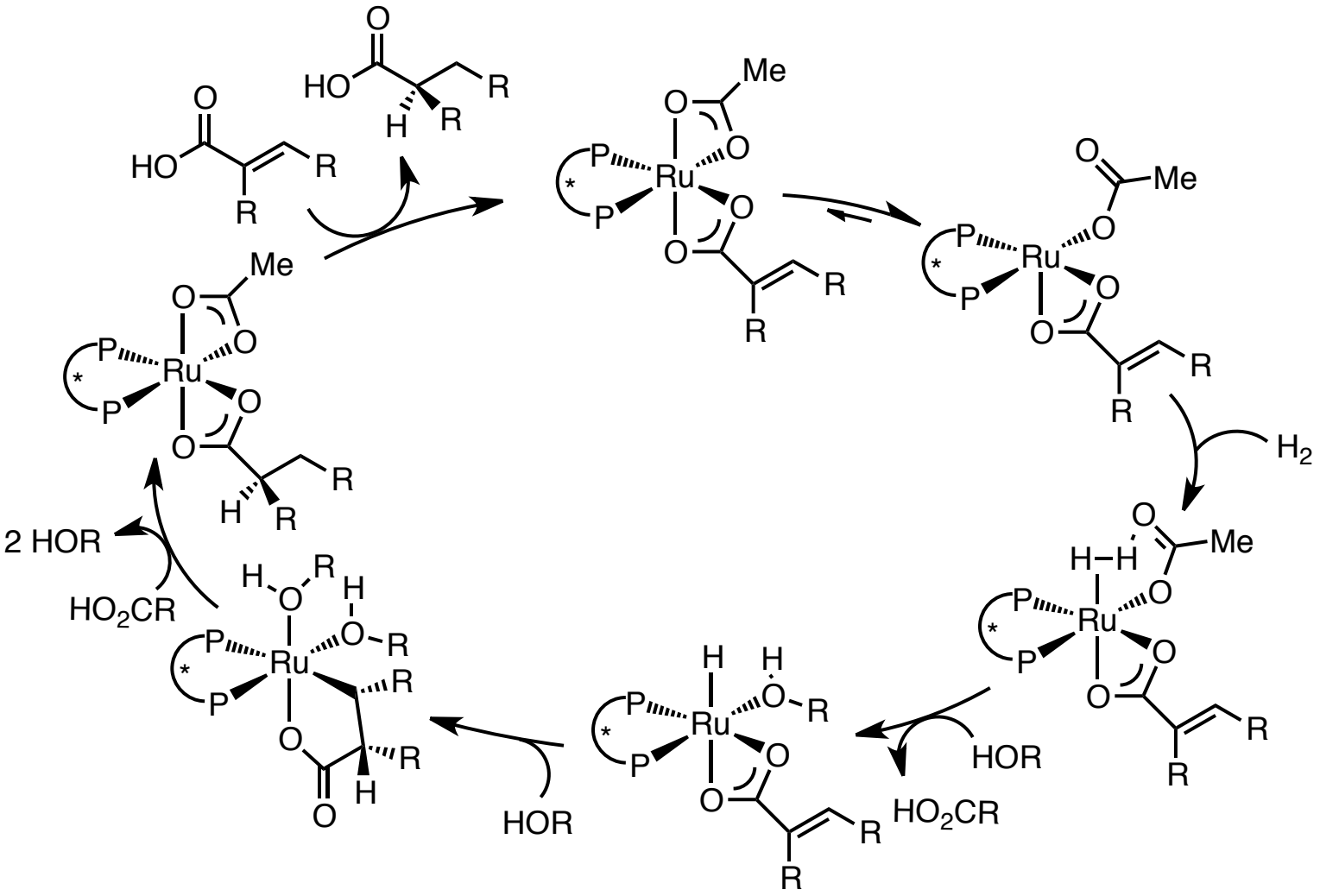
# *Enantioselective Alkene Hydrogenation Using Ruthenium*

- $L_2Ru(II)(OAc)_2$ are very effective at hydrogenating functionalized alkene.

Unsaturated Carboxylic Acids:

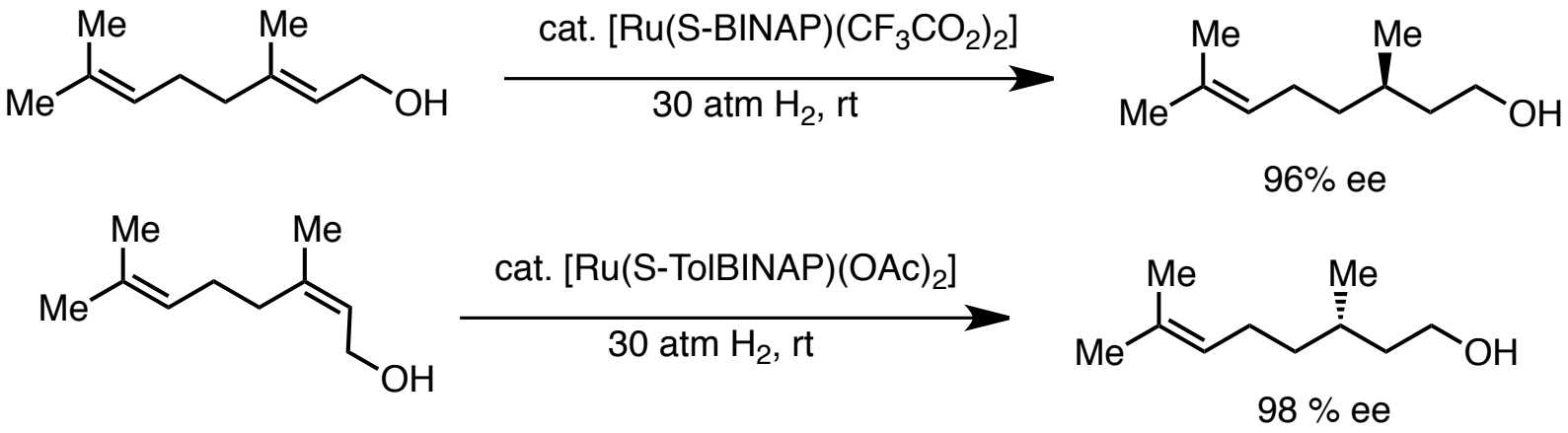


# *Mechanism for Ruthenium Cat. Hydrogenation of Alkenes*

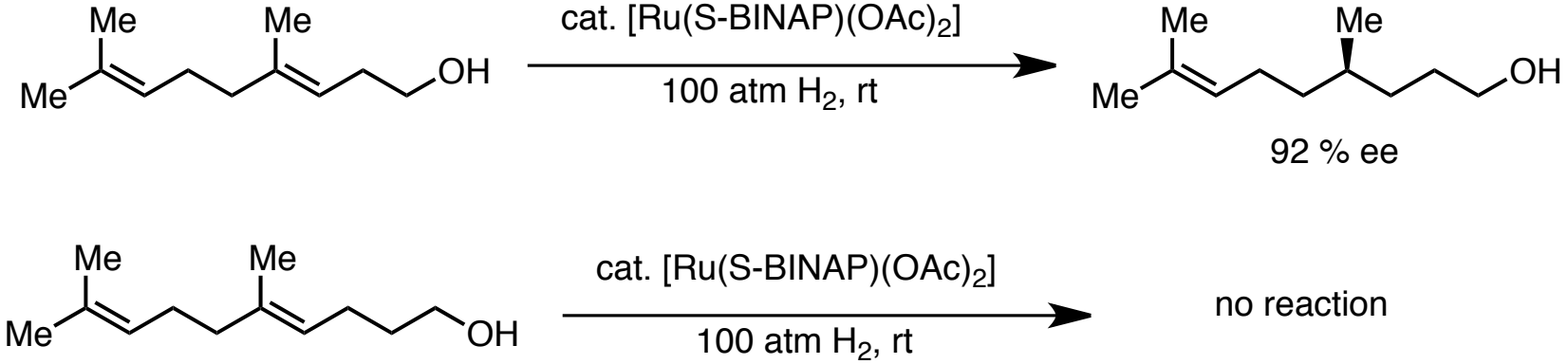



Halpern

# *Allylic Alcohols Also Effective Substrates*

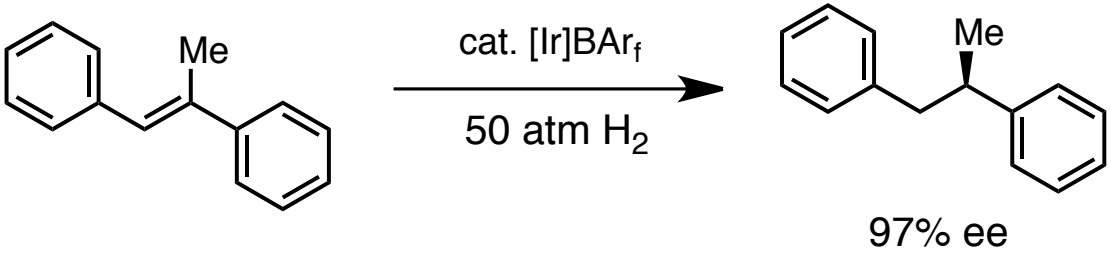



- Homoallylic alcohols are also reasonable substrates, but not longer homologues.

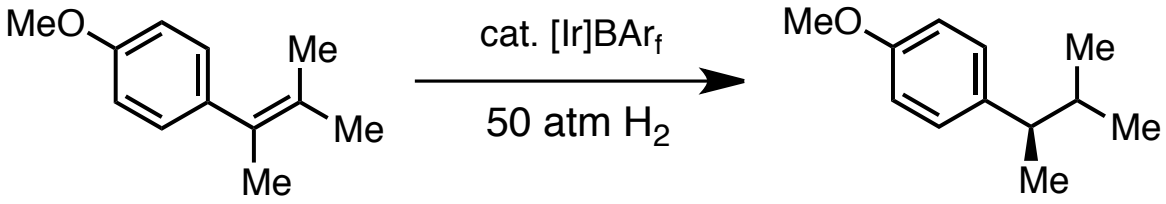



Noyori *JACS* **1987**,*109*,1596.

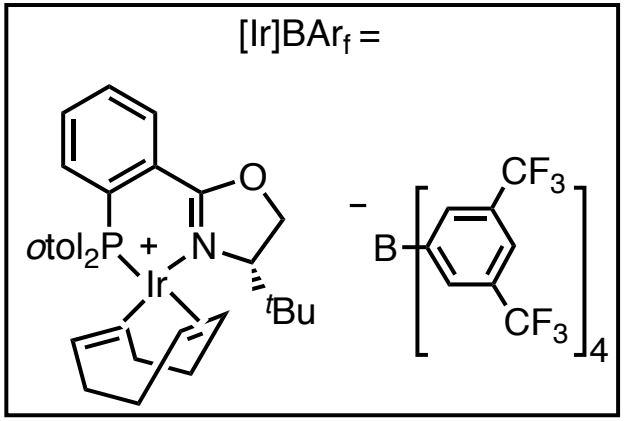
# *Enantioselective Alkene Hydrogenation with Iridium*

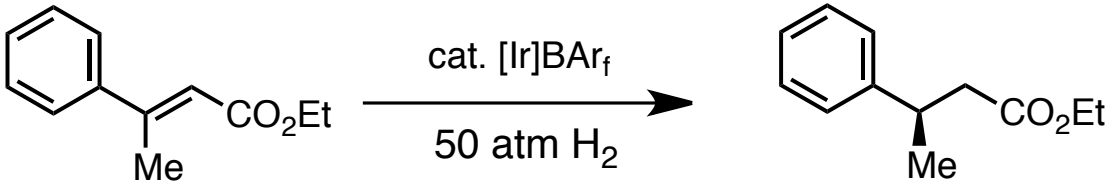



97% ee




81% ee



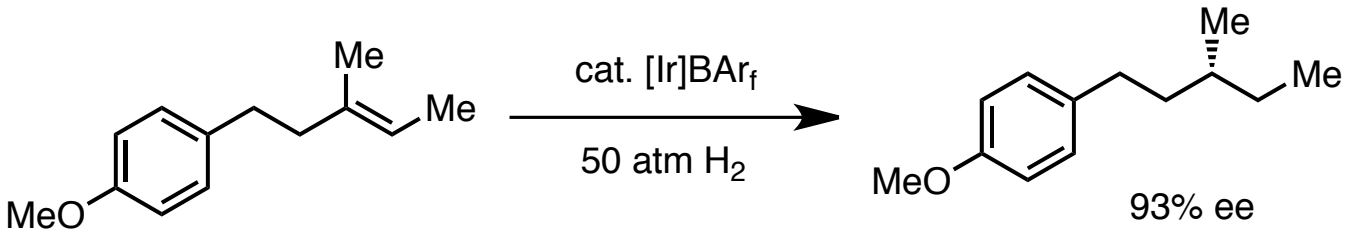



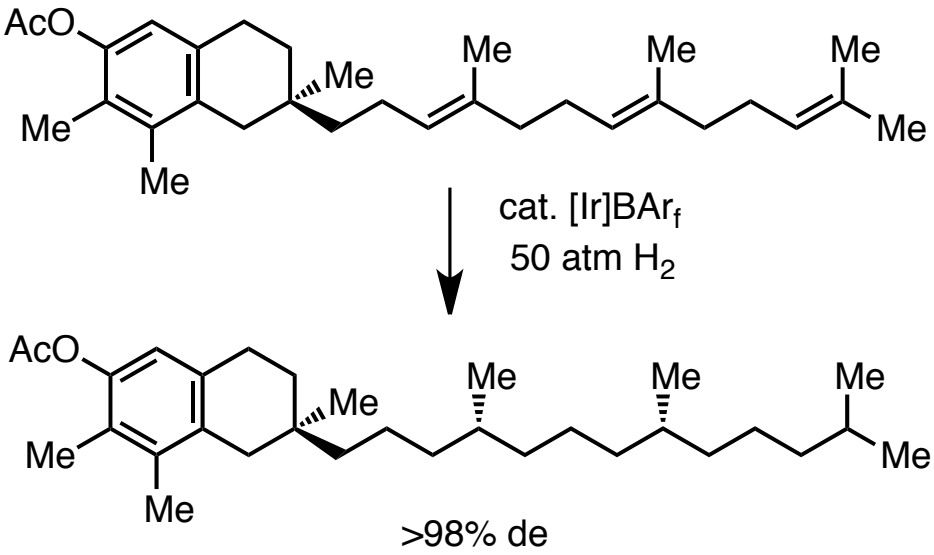

84% ee

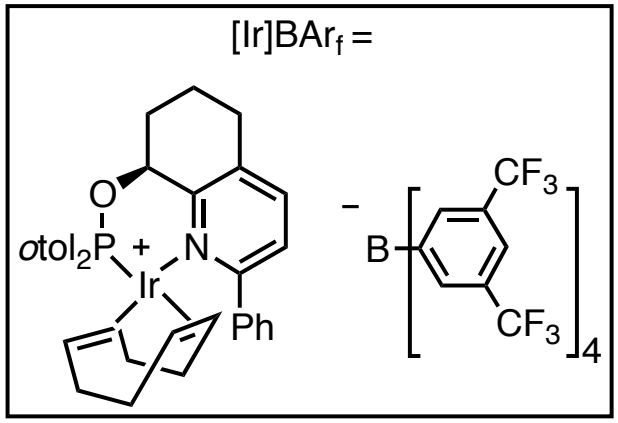
Pfaltz ACIE **1998**, 37, 2897

- Tri-substituted alkenes work best.
- First example of asymmetric tetra-substituted alkene hydrogenation.

# *Enantioselective Alkene Hydrogenation with Iridium*




Pfaltz *Science* **2006**, *311*, 642.