Transition Metal-Catalyzed Asymmetric Conjugate Addition

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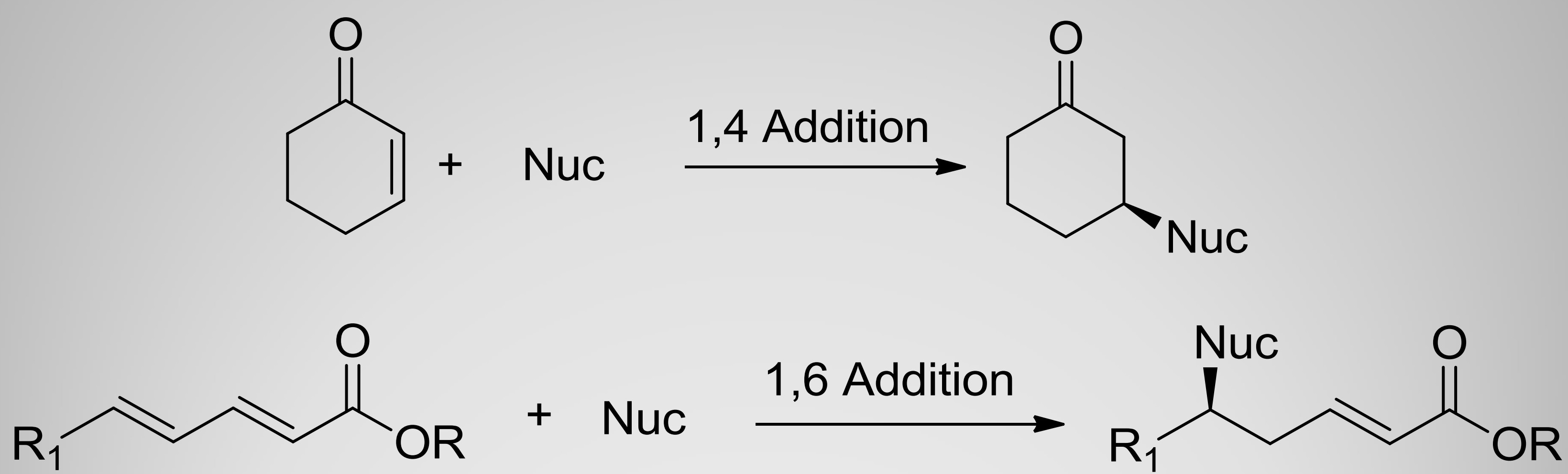
Dong Group
September 26, 2012

Overview

- Introduction
  - Background
  - History
- First Row TM Catalyzed
  - Copper
  - Nickel
- Second Row TM Catalyzed
  - Rhodium
  - Palladium
- Conclusions

What is Conjugate Addition?

- "Addition of a nucleophile to activated alkenes or alkynes, followed by protonation of the anionic intermediate."



Cordova, A. *Catalytic Asymmetric Conjugate Reactions*, **2010**, Wiley-VCH, Weinheim, Germany, 145.

1,2 vs 1,4

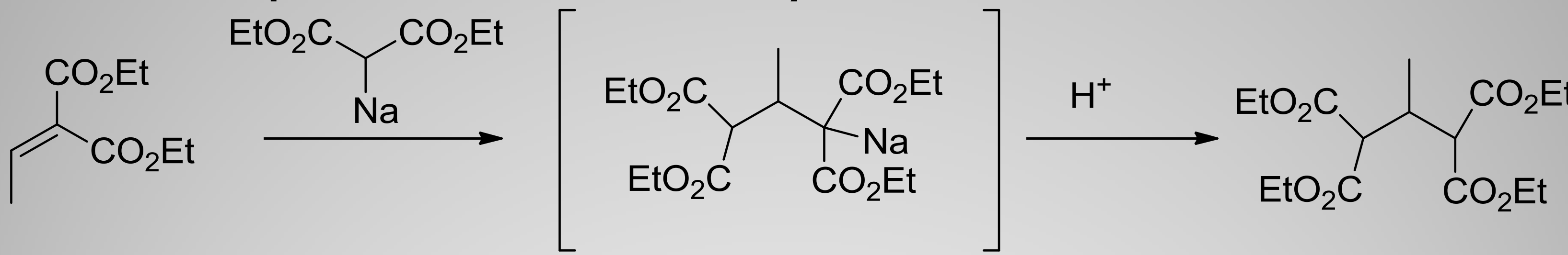
- Ways to Favor 1,4 Over 1,2:
  - Soft nucleophiles
  - Polar solvents (HMPA)
  - Sterics
  - Delocalization of carbanion
  - Higher temperatures
- With catalysts, tuning of structure/ligands also affects this

Why Asymmetric Conjugate Addition?

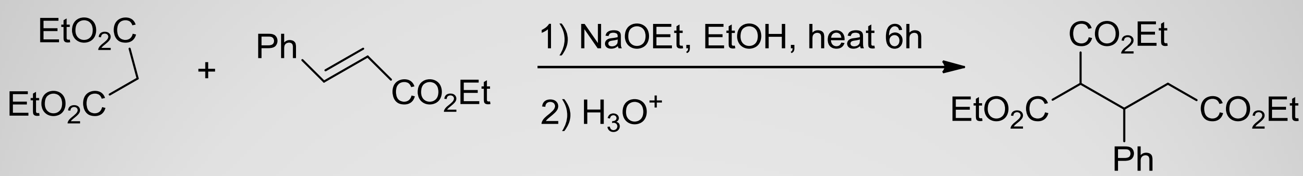
- Powerful method of forming C-C bonds with a new stereocenter
- Enantiopure compounds important in industry (pharmaceuticals and materials), as well as academia
- Tandem reactions lead to new functionality in surprising and useful ways

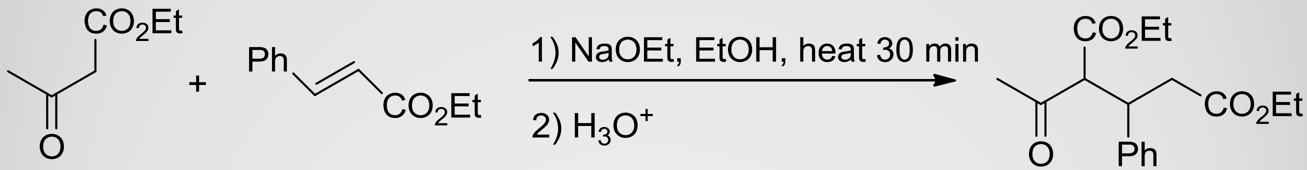
History

- First reported in 1883 by Komnenos



- Michael Reaction



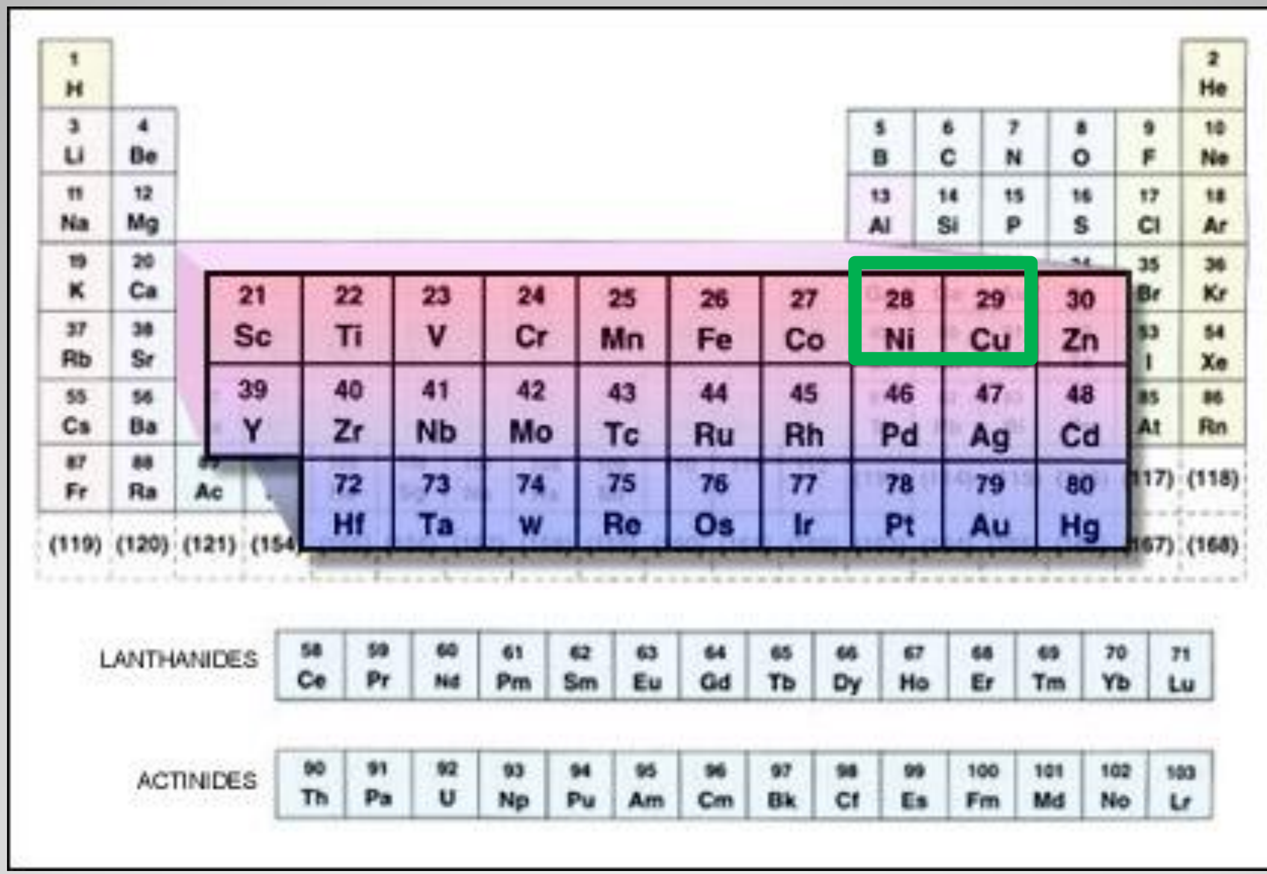


Komnenos, T., *Liebigs Ann. Chem.*, **1883**, *35*, 145.
Michael, A., *J. Prakt. Chem.*, **1887**, *3*, 349.

Development and Advances

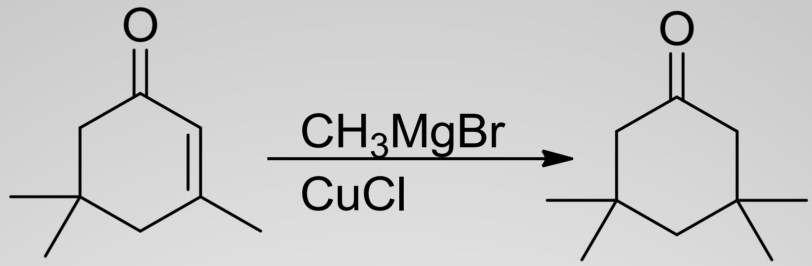
- Field has developed quickly due to need of C-C bond formation and stays relevant
- Asymmetric conjugate addition still relatively young field
- Split into two broad sections:
  - Transition metal catalysts (esp. Cu and Rh)
  - Organocatalysts (commonly a heterocycle)

First Row Transition Metals

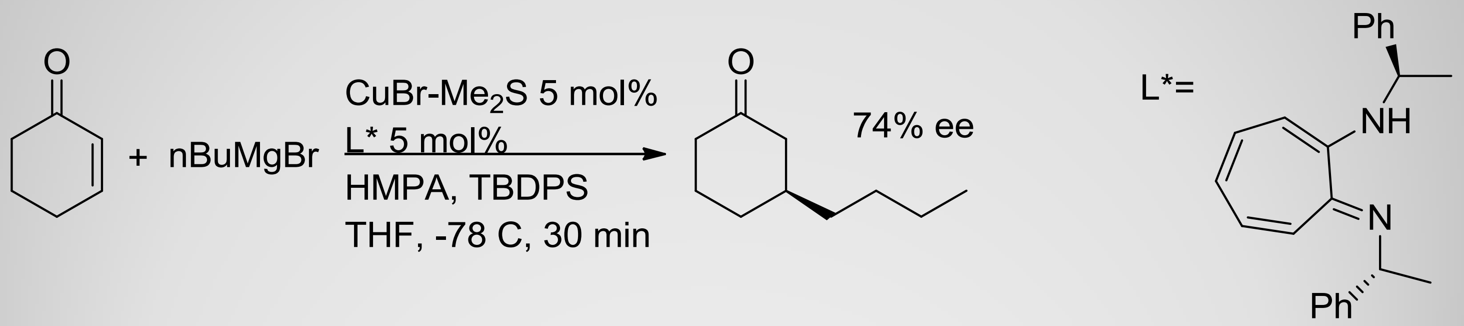


History

- Kharasch group discovered trace amounts of Cu salts led to 1,4 addition

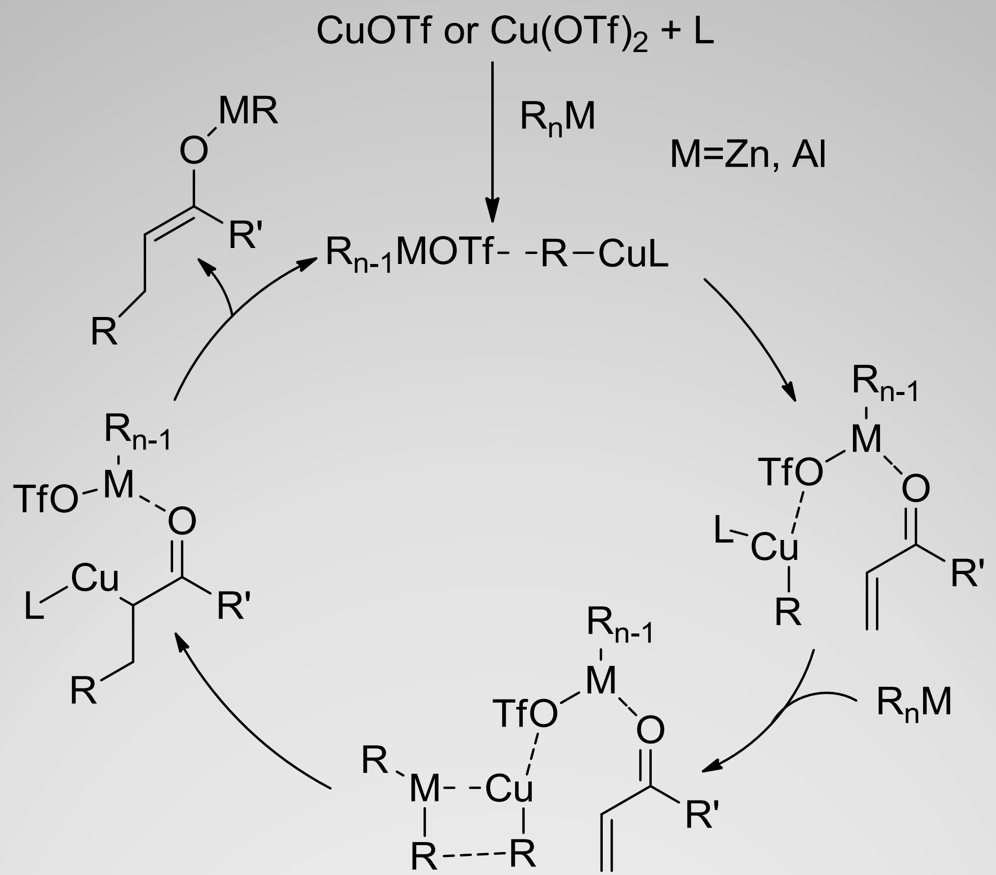


- Lippard was the first enantioselective example



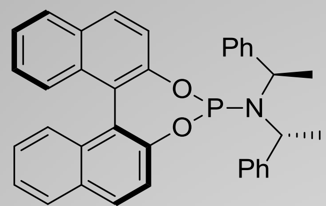
Kharasch, M.S., Tawney, P.O., *J. Amer. Chem. Soc.*, **1941**, *63*, 2308.
Lippard, S.J., *Organometallics*, **1990**, *9*, 3178.

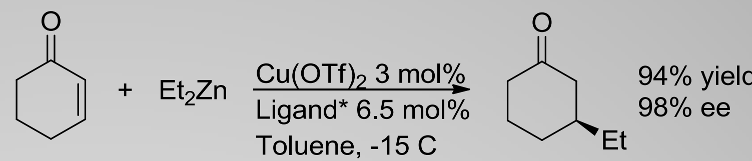
Cu Catalytic Cycle



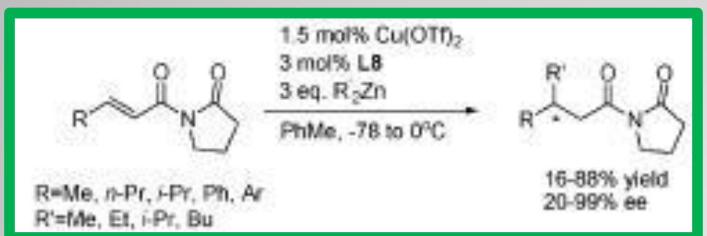
Cordova, A. *Catalytic Asymmetric Conjugate Reactions*, **2010**, Wiley-VCH, Weinheim, Germany, 73.
Nakamura, E., *Chem. Rev.*, **2012**, *112*, 2339.

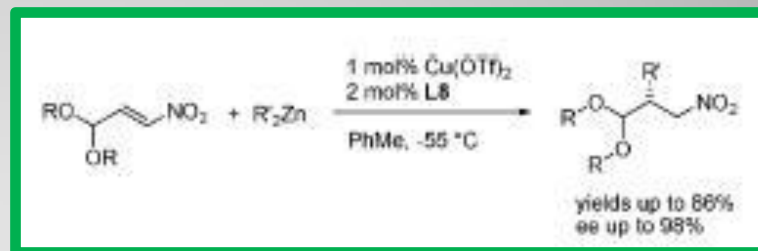
Organozinc/Organoaluminum

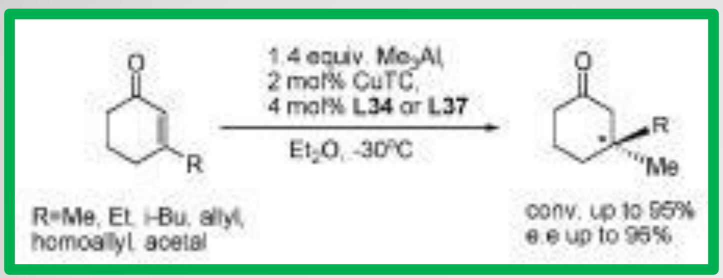


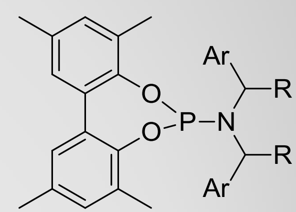


Me, Hep, iPr, $Ph(CH_2)_3$ also showed good ee's





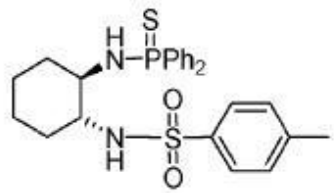




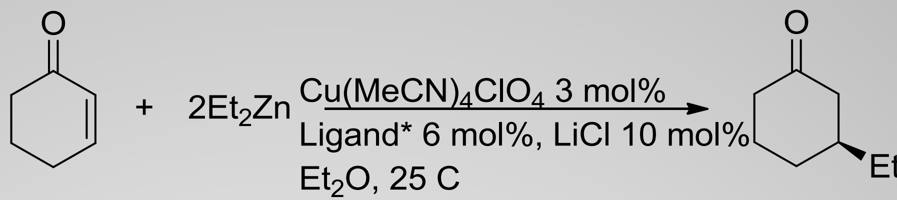
Ar= Ph, 2-Naph
R=(S)-Me, (R)-Me

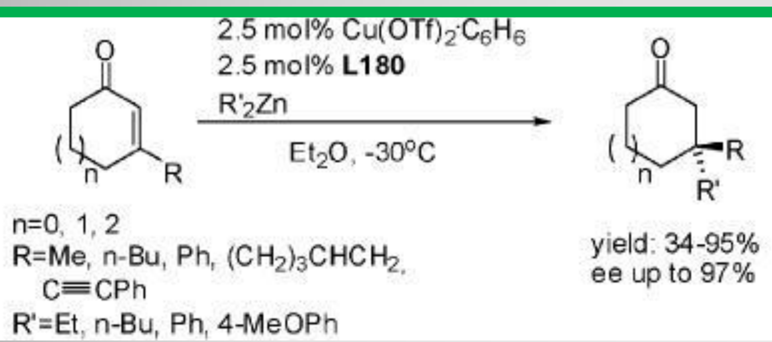
Feringa, B., *Chem. Soc. Rev.*, **2009**, *38*, 1039.

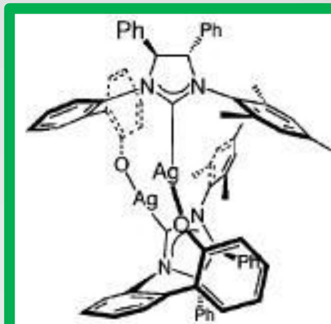
More Organozinc Ligands



L118

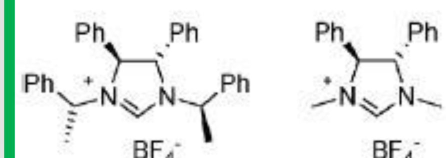






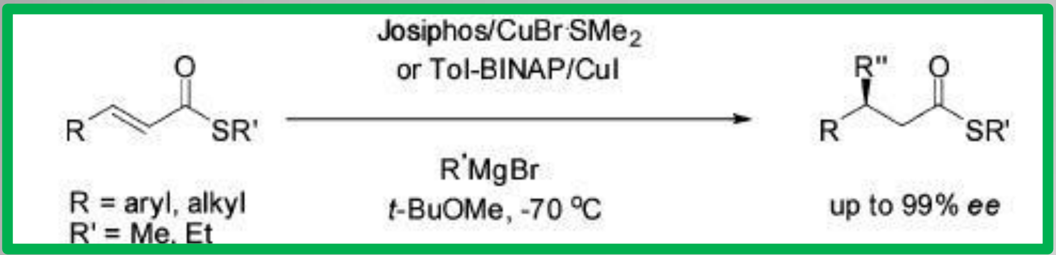
L180

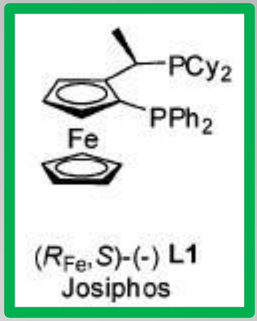
Other NHC Ligands

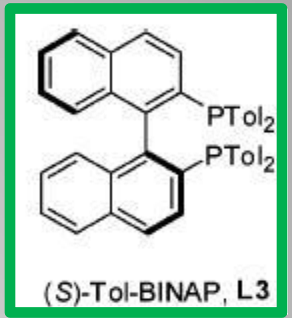


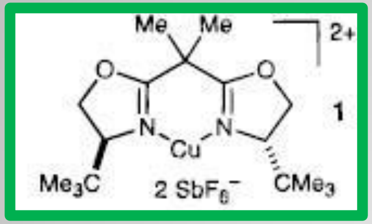
Shi, M., *Adv. Synth. Catal.*, **2005**, *347*, 535.
Hoveyda, A.H., *J. Am. Chem. Soc.*, **2006**, *128*, 7182.

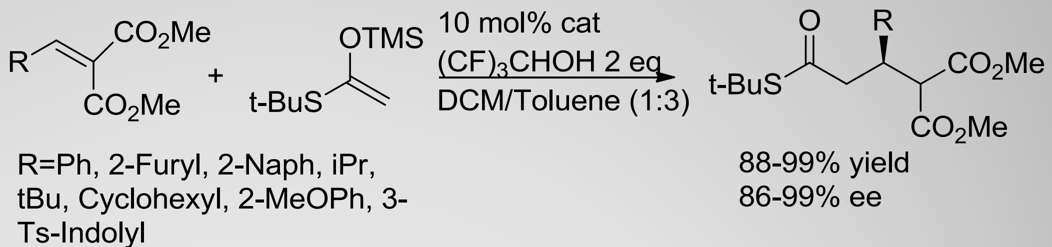
Other Cu Reagents

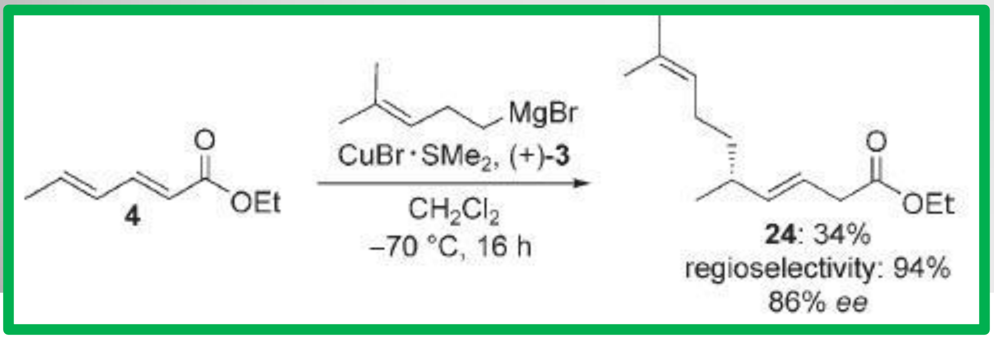


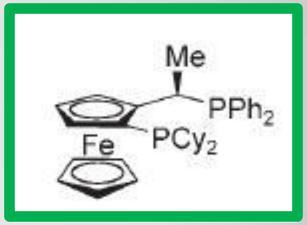








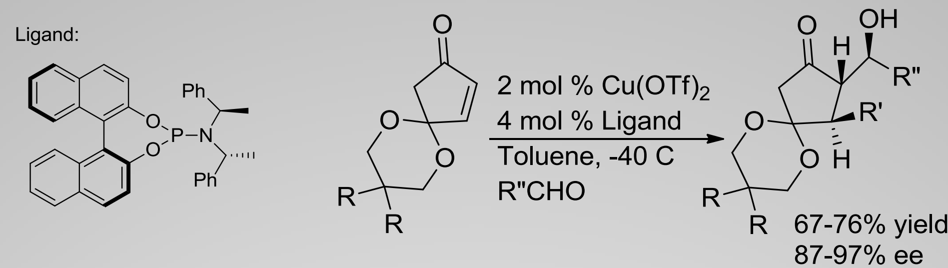




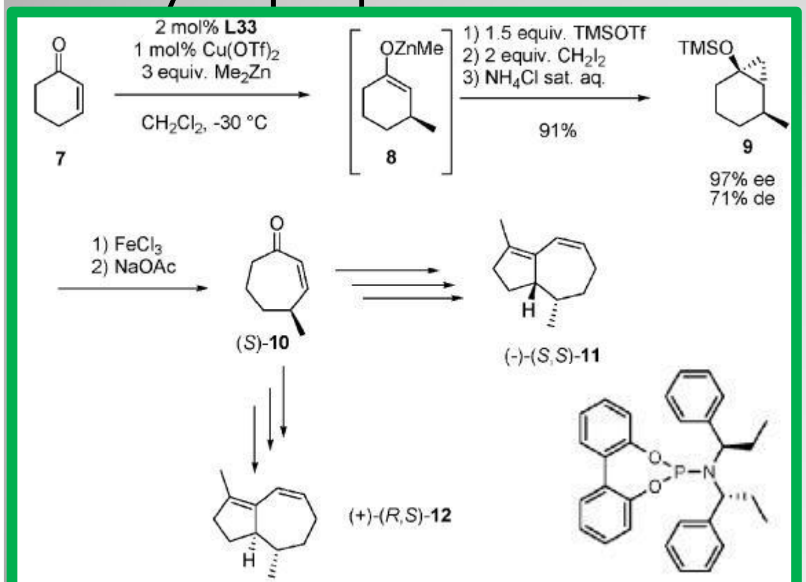
Feringa, B., *Org. Lett.*, **2007**, *9*, 5123.
Evans, D.A., *J. Am. Chem. Soc.*, **1999**, *121*, 1994.
Feringa, B., *Angew. Chem. Int. Ed.*, **2008**, *47*, 398.

Applications: Tandem Reactions

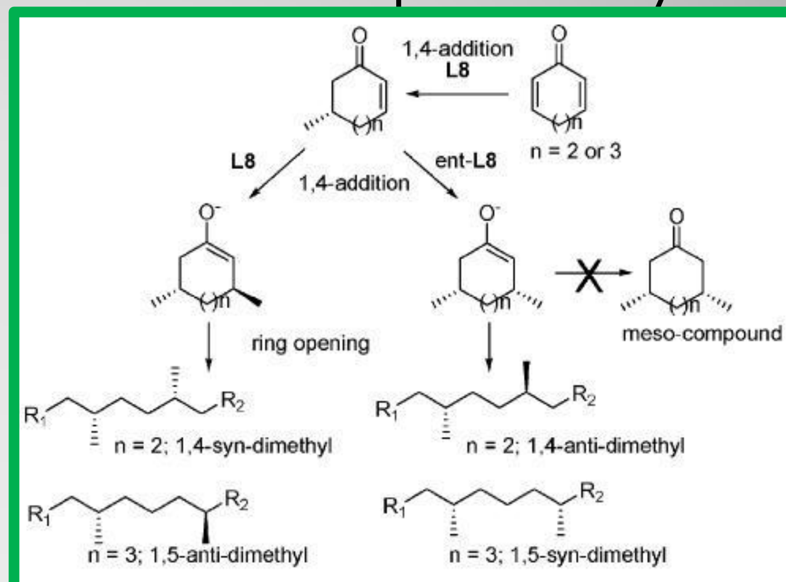
1,4-addition-aldol reactions



Cyclopropanations

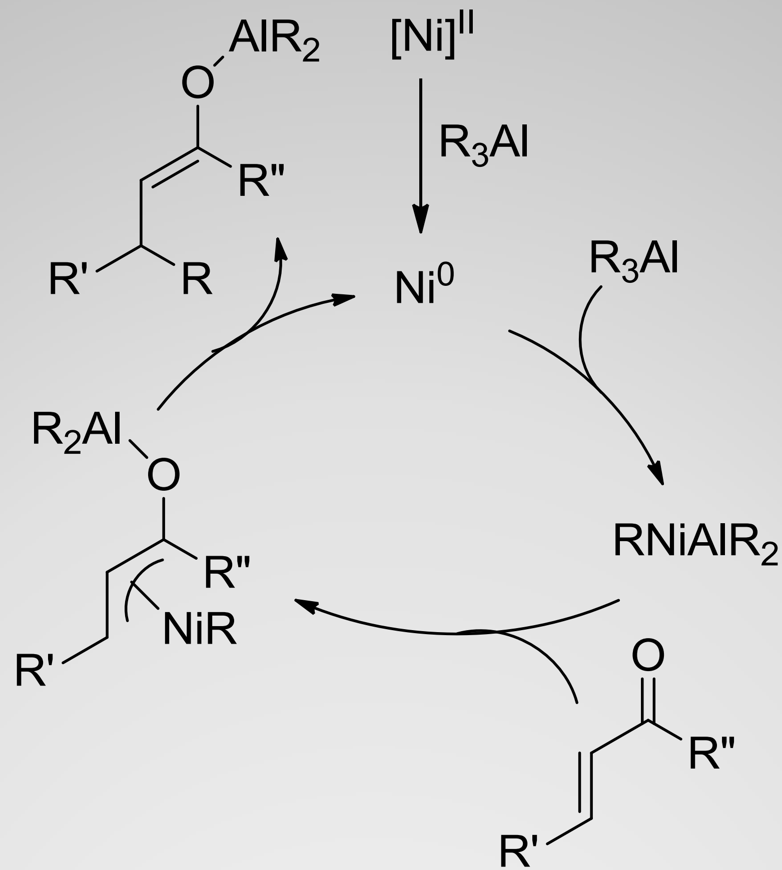


Saturated Isoprenoid Synth



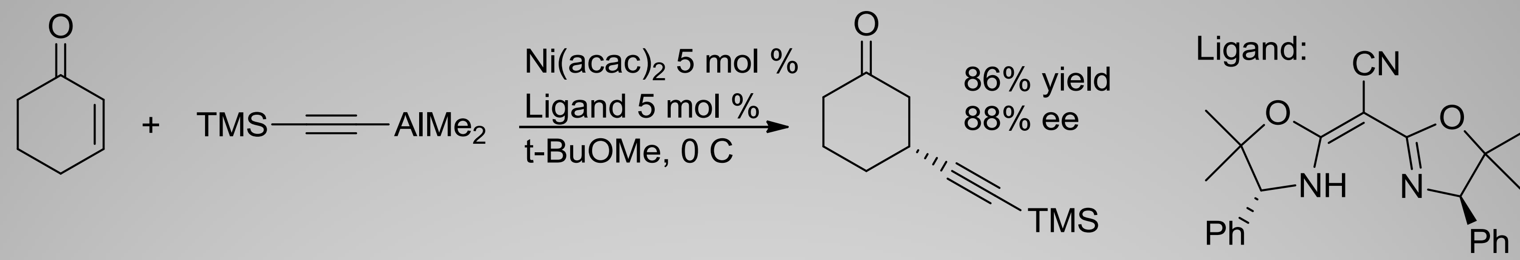
Feringa, B., *J. Am. Chem. Soc.*, **2001**, *123*, 5841.
Alexakis, A., *J. Org. Chem.*, **2002**, *4*, 3835.
Feringa, B., *Chem. Commun.*, **2005**, 1387.

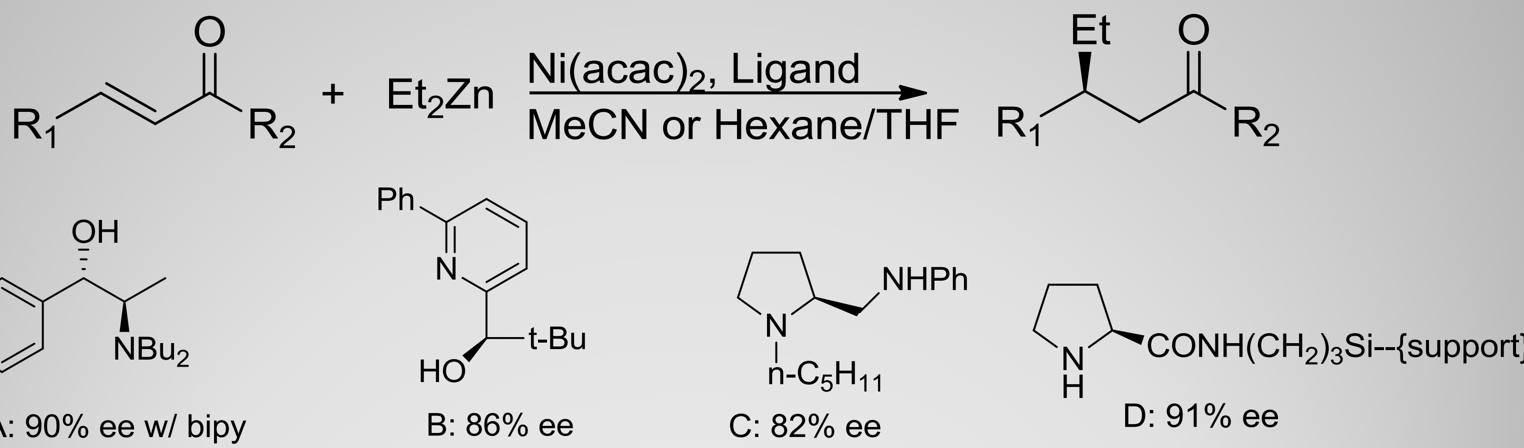
Ni Catalytic Cycle



Bagnell, L., *Austr. J. Chem.*, **1975**, *28*, 817.

Ni ECA



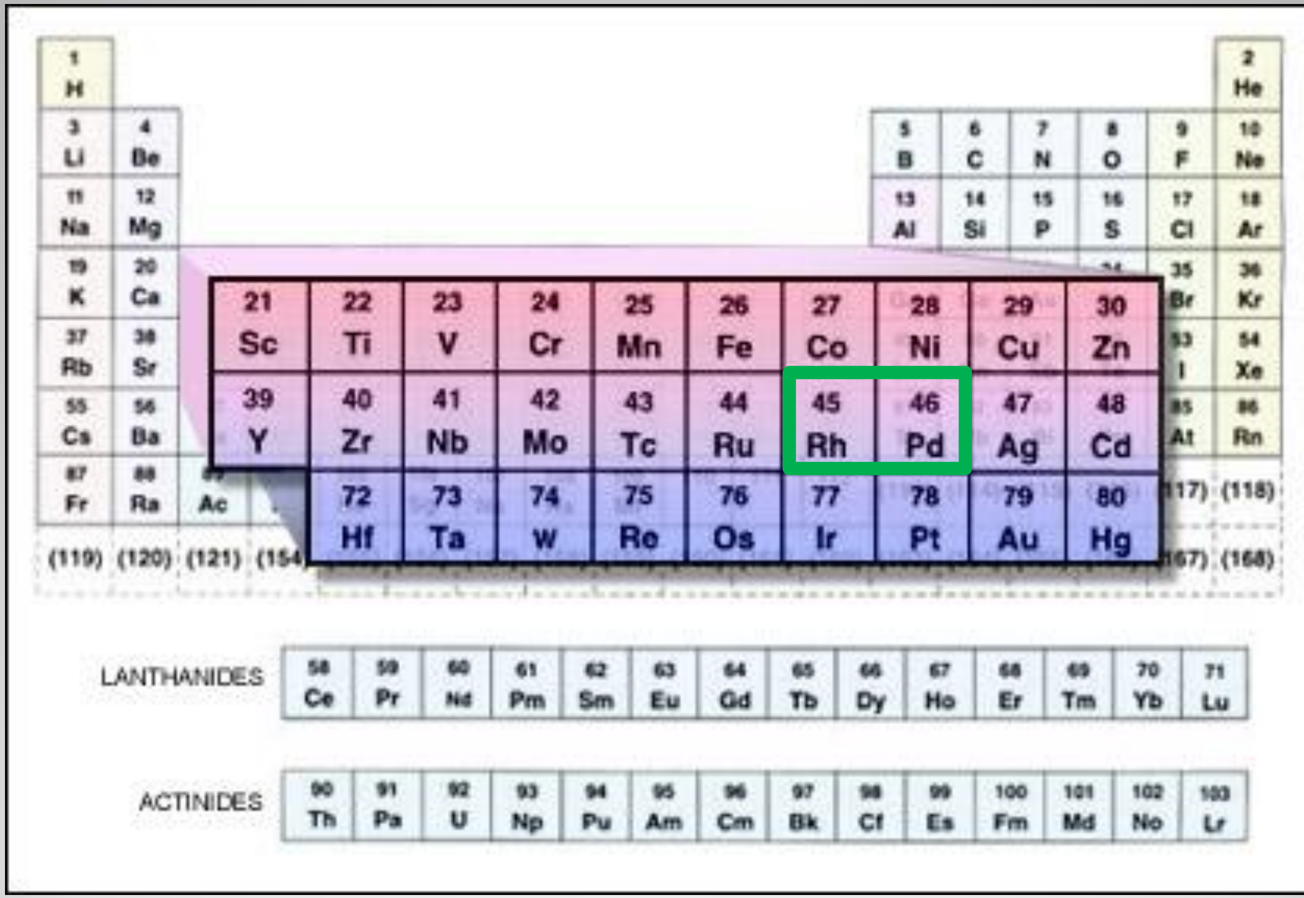


Corey, E.J., *Org. Lett.*, **2004**, *6*, 3385.
Yokoyama, S., *J. Chem. Soc., Chem. Commun.*, **1989**, 516.
Bolm, C., *Tetrahedron: Asymmetry*, **1991**, *2*, 701.
Asami, M., *Chem. Lett.*, **1994**, 297.
Sanchez, F., *Tetrahedron: Asymmetry*, **1992**, *3*, 845.

- Cu is well developed and can be used with primarily organozinc, aluminum, or magnesium reagents
- Many functional groups are tolerated
- Primarily used to deliver alkyl groups
- Less is known about Ni, and it tends to be less enantioselective

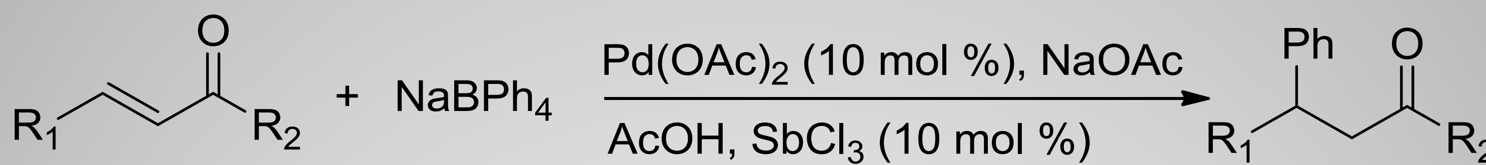
Summary

Second Row Transition Metals

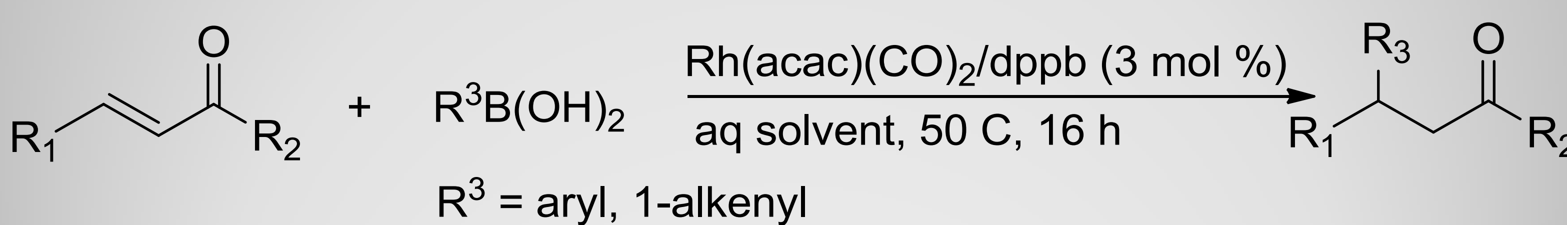


History

- Uemura-1994

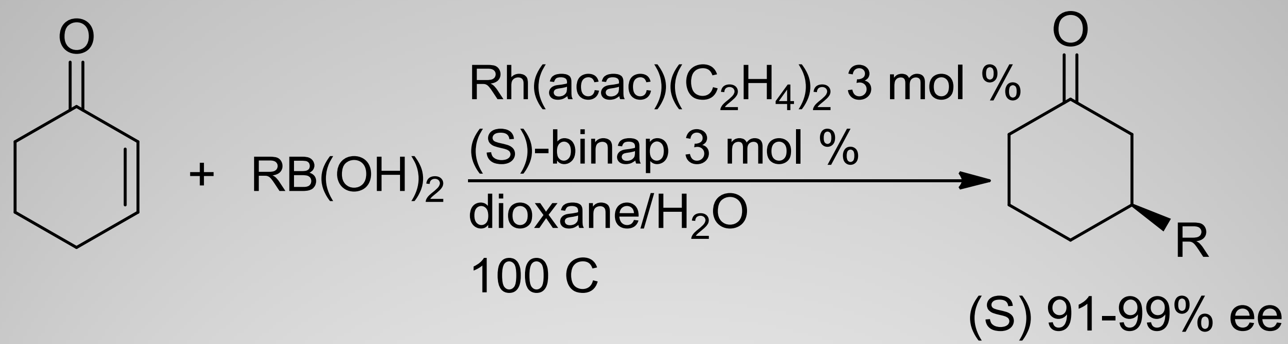


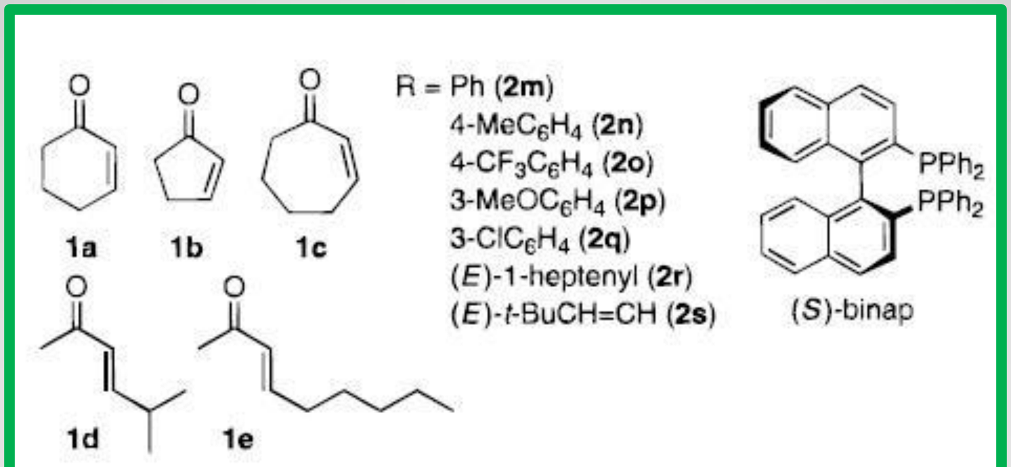
- Miyaura-1997



Miyaura, N., *et. al.*, *Organometallics*, **1997**, *16*, 4229.

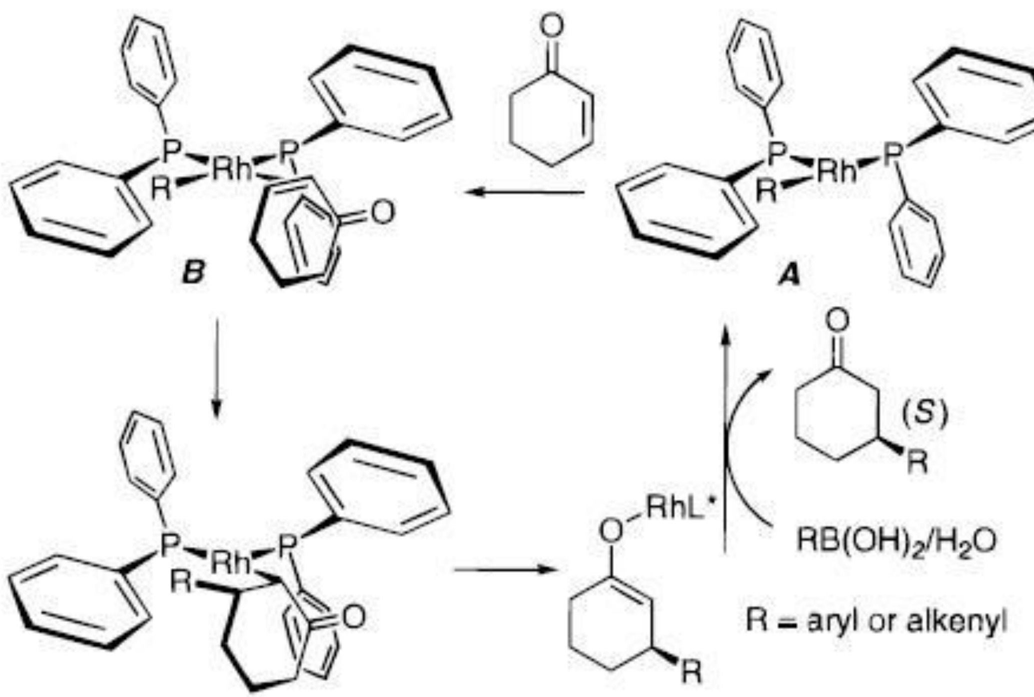
First Example of Enantioselctive Rh Catalyzed





Hiyashi, T., Miyaura, N., *J. Amer. Chem. Soc.*, **1998**, *120*, 5579.

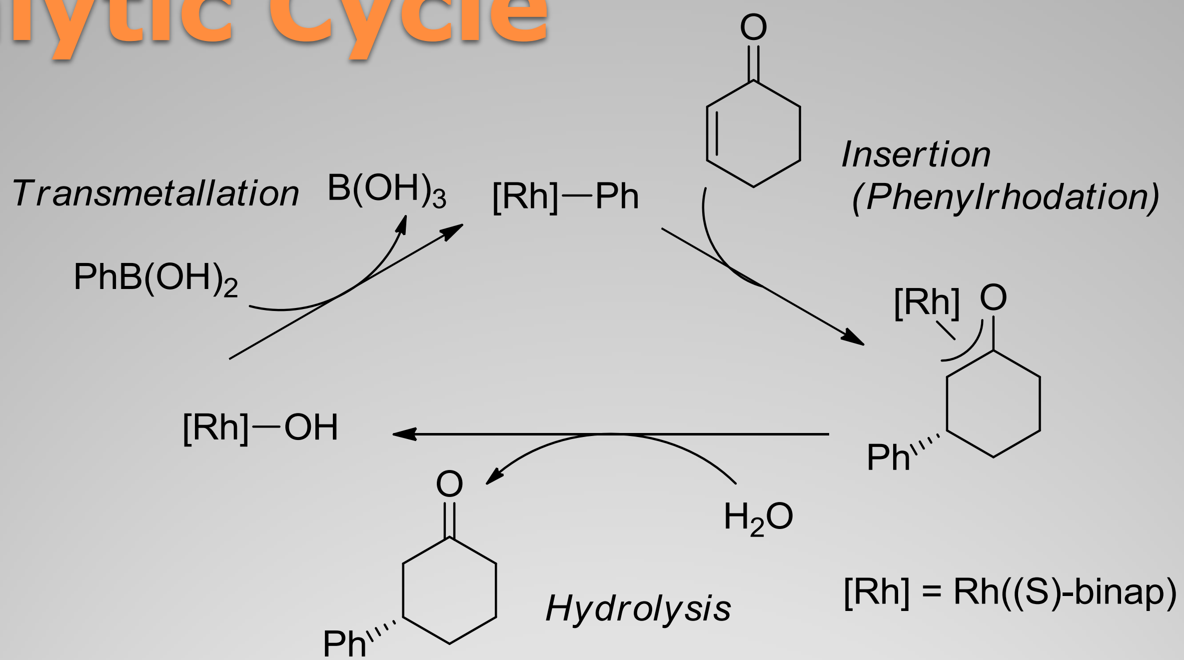
Why Is It Enantioselective?

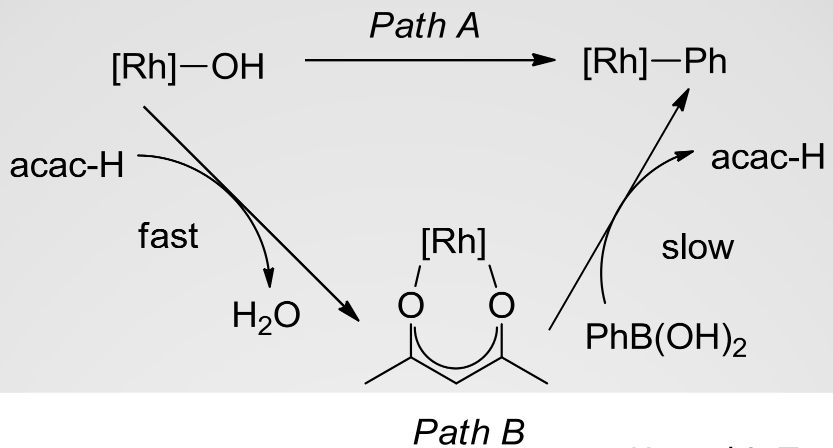


a The binaphthylene moiety in (S)-binap is omitted for clarity.

Hiyashi, T., Miyaura, N., *J. Amer. Chem. Soc.*, **1998**, *120*, 5579.

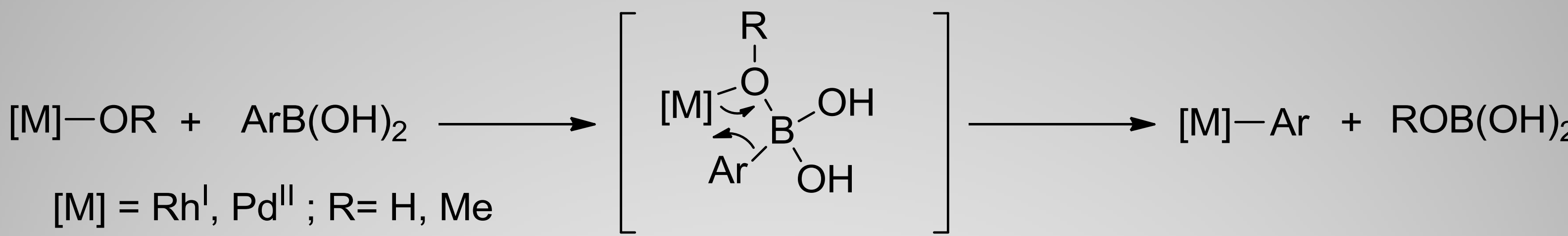
Catalytic Cycle

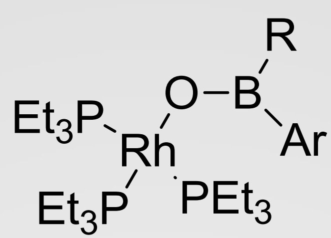




Hayashi, T., *J. Amer. Chem. Soc.*, **2002**, *124*, 5052.

Transmetallation



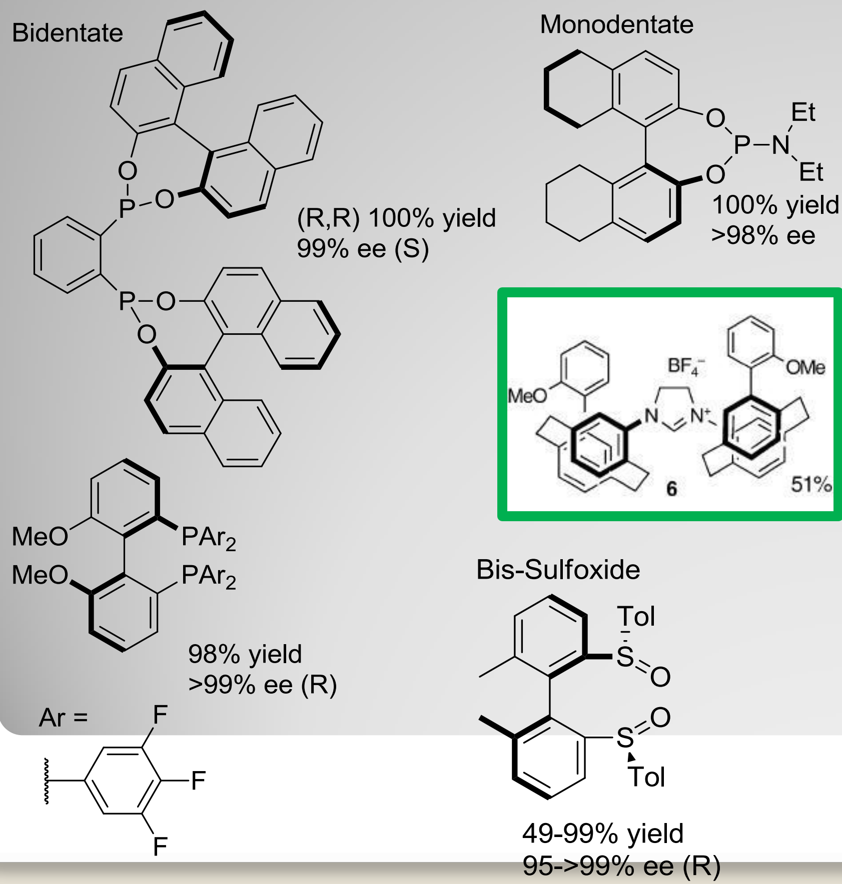


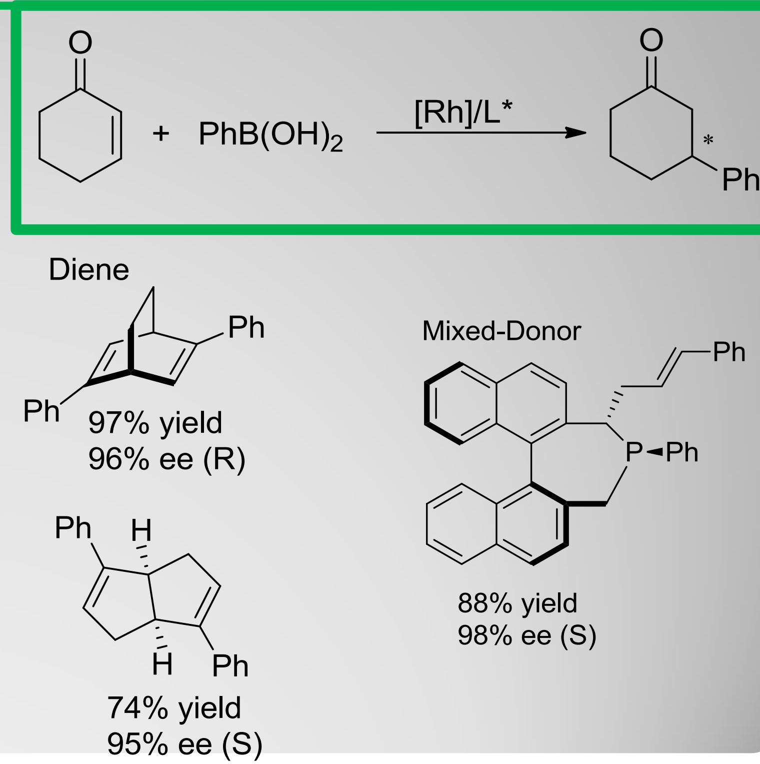
R=OH, Ar

Hartwig, J.F., *J. Am. Chem. Soc.*, **2007**, *129*, 1876.

Catalyst Precursors/ Organoboron Ligand Scope

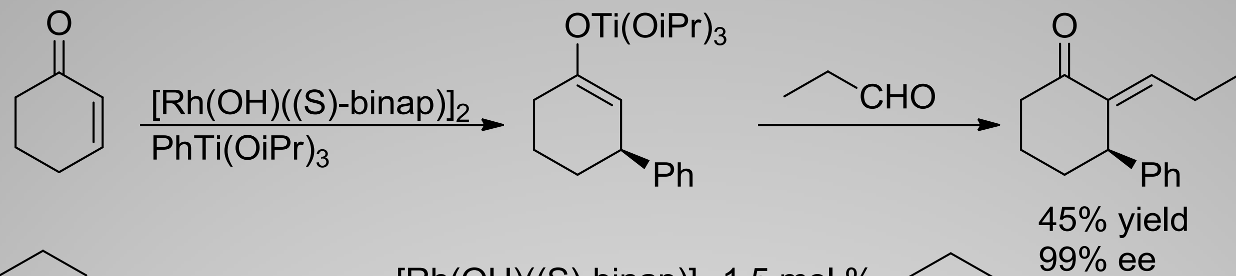
- Neutral and cationic Rh species work well
  - $[RhCl(C_2H_4)_2]_2$
  - $[Rh(nbd)_2]^+BF_4^-$

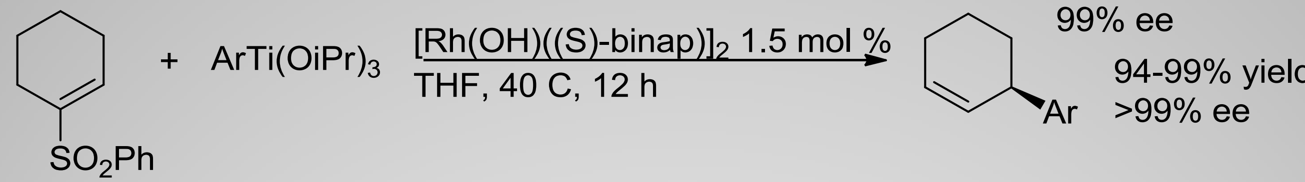


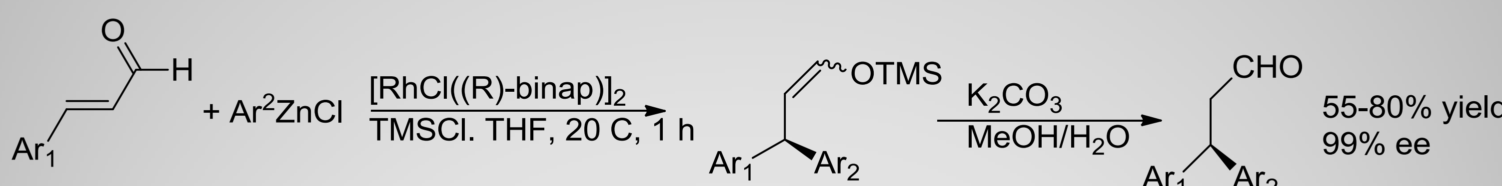


Cordova, A. *Catalytic Asymmetric Conjugate Reactions*, **2010**, Wiley-VCH, Weinheim, Germany, 11-19.

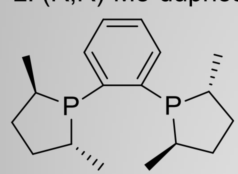
Organotitanium/Organozinc Reagents

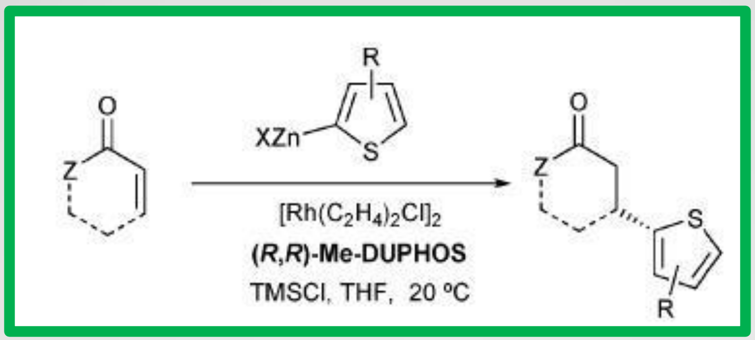


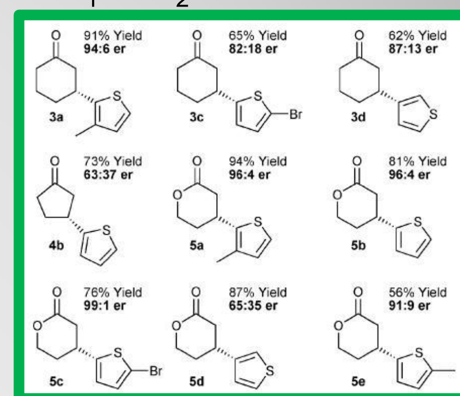




L: (R,R)-Me-duphos

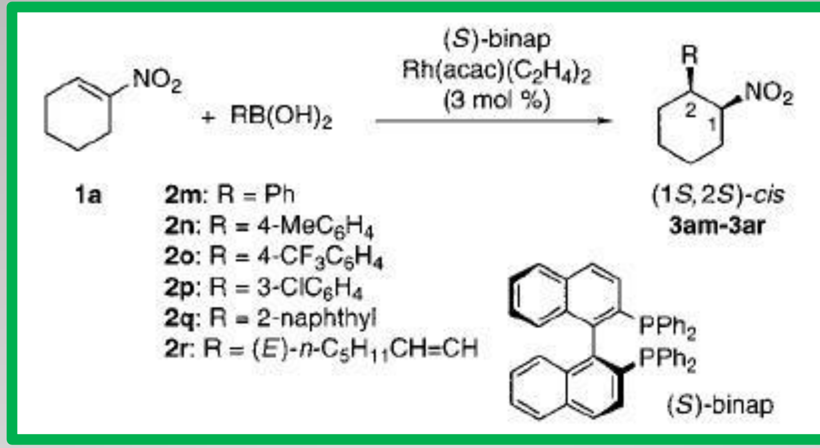




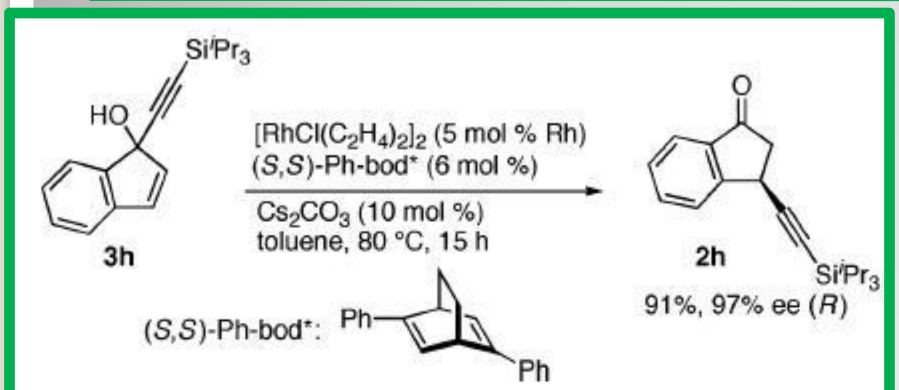


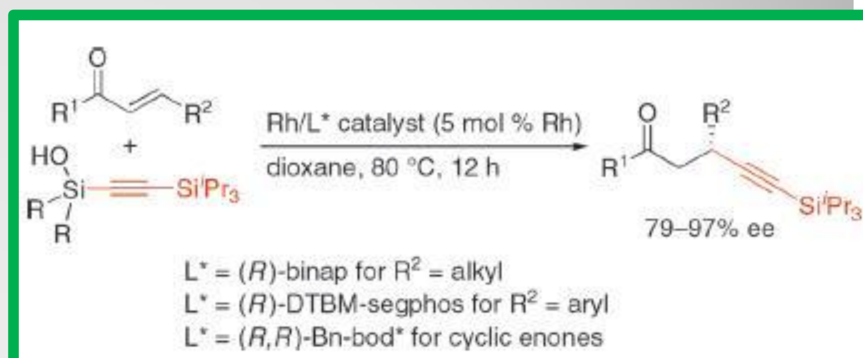
Cordova, A. *Catalytic Asymmetric Conjugate Reactions*, **2010**, Wiley-VCH, Weinheim, Germany, 38, 40.
Hayashi, T., *J. Am. Chem. Soc.*, **2003**, *125*, 2872.
Frost, C.G., *Chem. Commun.*, **2008**, 3795.

Other Substrates



84-85% yield
98-99% ee
cis/trans= 88/15-82-12

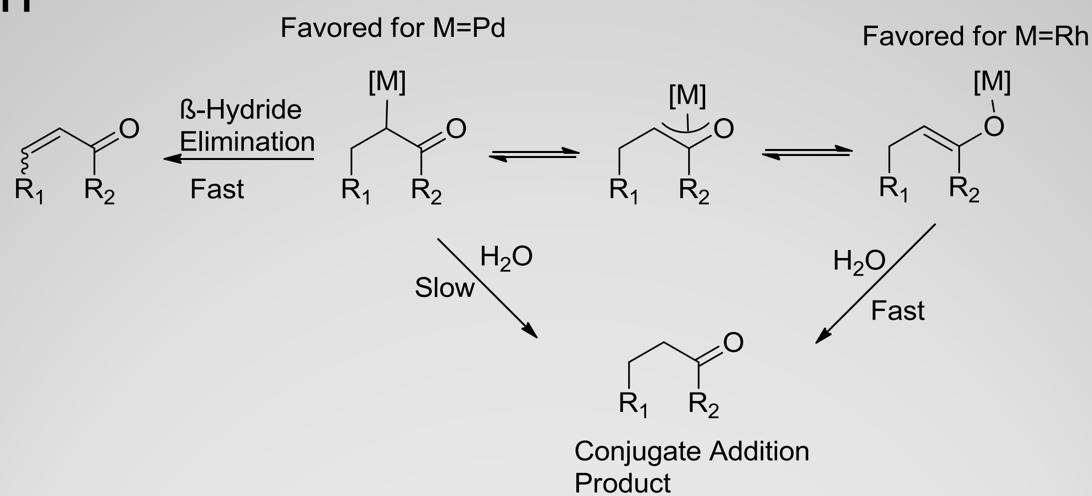




Hayashi, T., *J. Am. Chem. Soc.*, **2000**, *122*, 10716.
Hayashi,T., *J. Am. Chem. Soc.*, **2007**, *129*, 14158.
Hayashi, T., *Org. Lett.*, **2009**, *11*, 3222.

What About Palladium?

- Neutral Pd binds preferentially to carbon, unlike Rh, so β-hydride elimination to Heck-type products is common

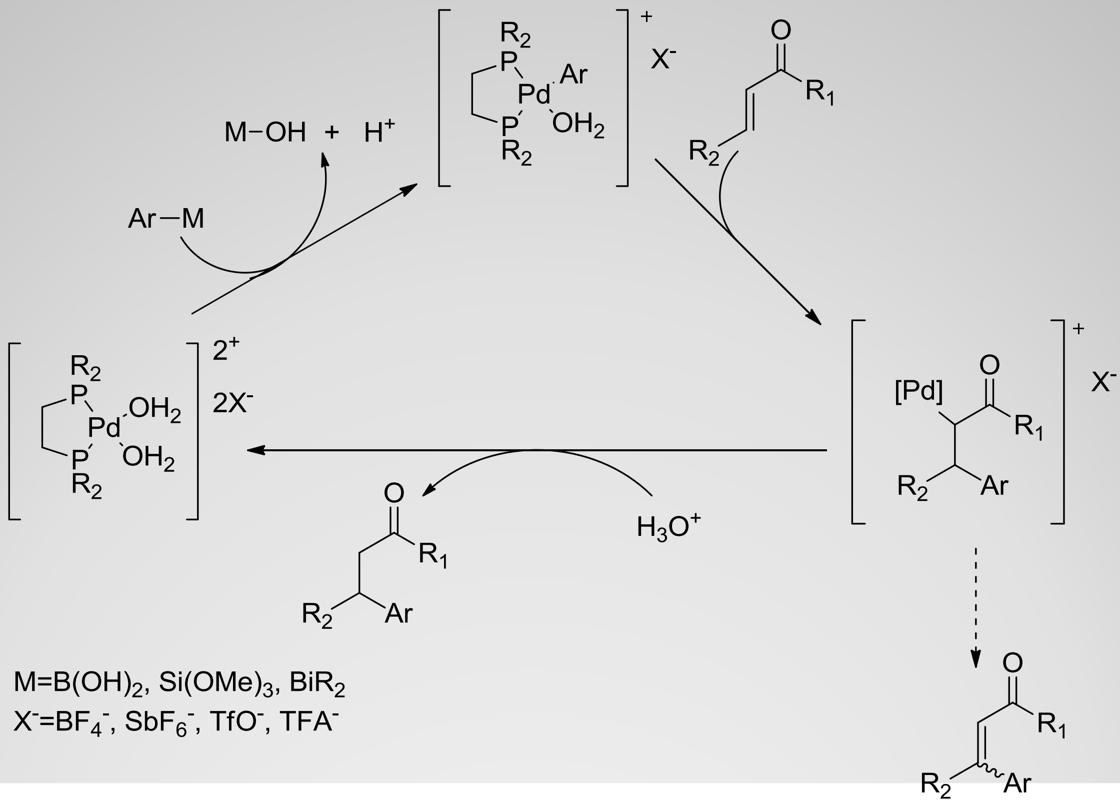


- Cationic Pd can be used to reduce this unwanted side reaction

Cordova, A. *Catalytic Asymmetric Conjugate Reactions*, **2010**, Wiley-VCH, Weinheim, Germany, 145.
Albeniz, A.C., *Organometallics*, **1999**, *18*, 5571.

Catalytic Cycle

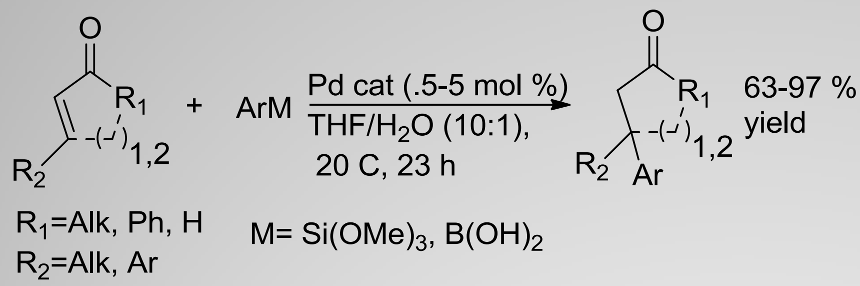
- Very similar to Rh, except cationic vs neutral species

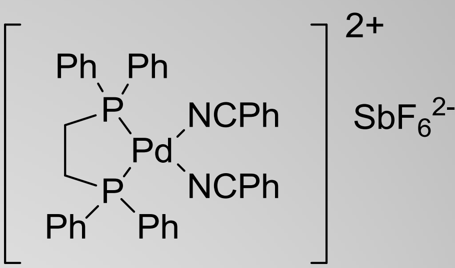


Cordova, A. *Catalytic Asymmetric Conjugate Reactions*, **2010**, Wiley-VCH, Weinheim, Germany, 63.

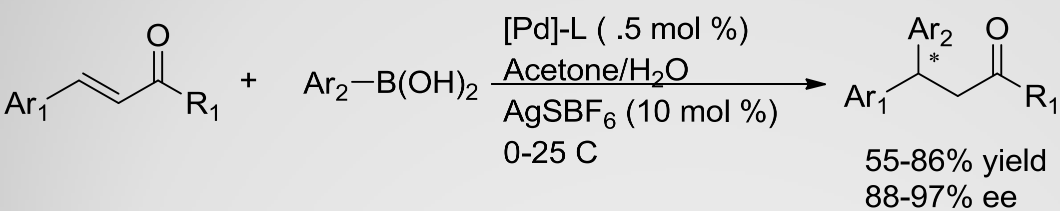
Cationic Pd Complexes

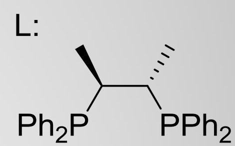
- $[Pd(dppe)(MeCN)_2](SbF_6)_2$ was developed by Miyaura.





- Using chiral ligand instead of dppe gave enantioselectivity

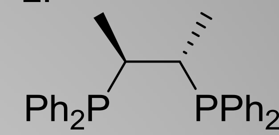


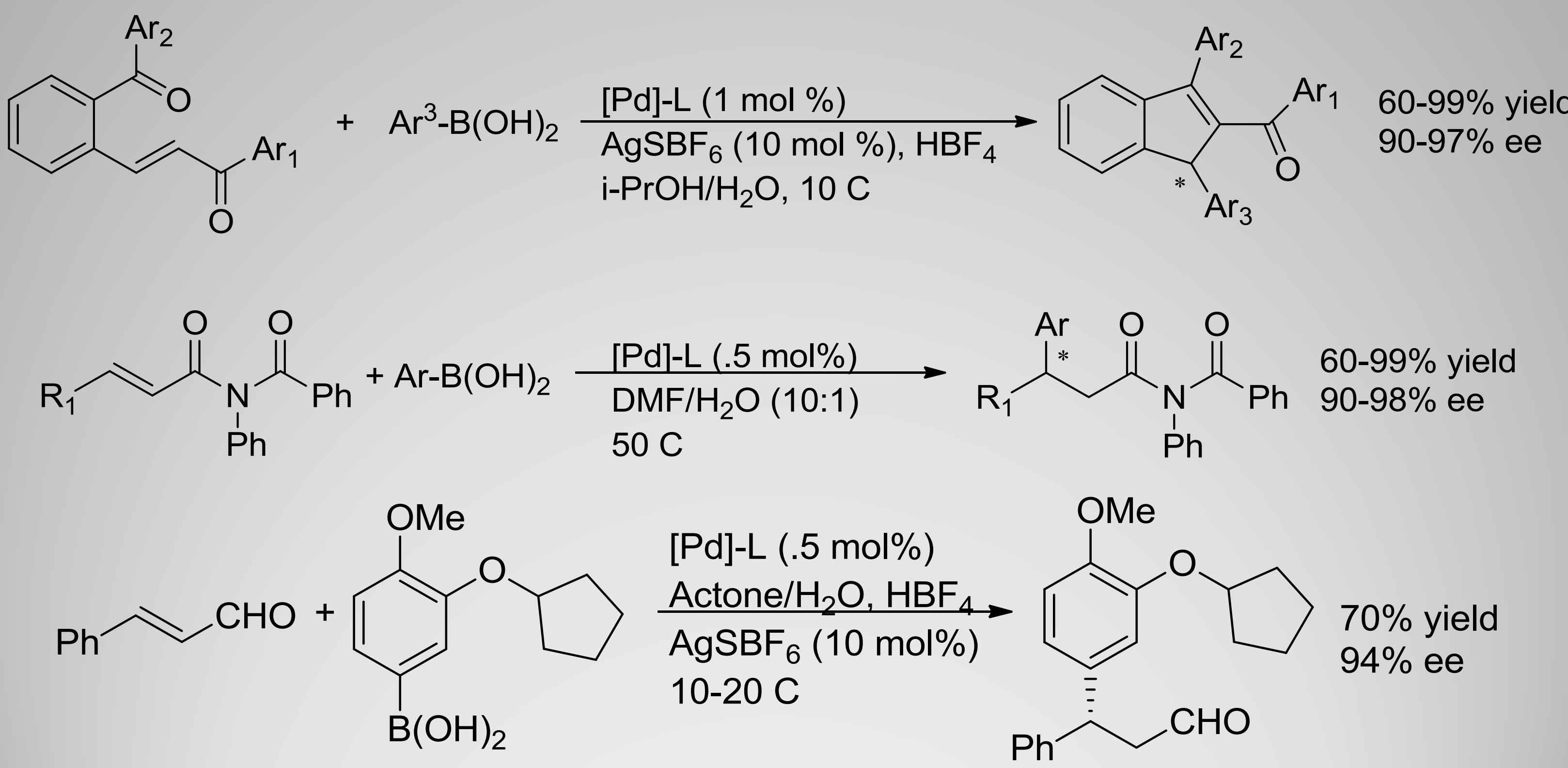


Miyaura, N., *Organometallics*, **2004**, *23*, 4317.
Miyaura, N., *Adv. Synth. Catal.*, **2007**, *349*, 1759.

Palladium with (*S*,*S*)-chiraphos

L:





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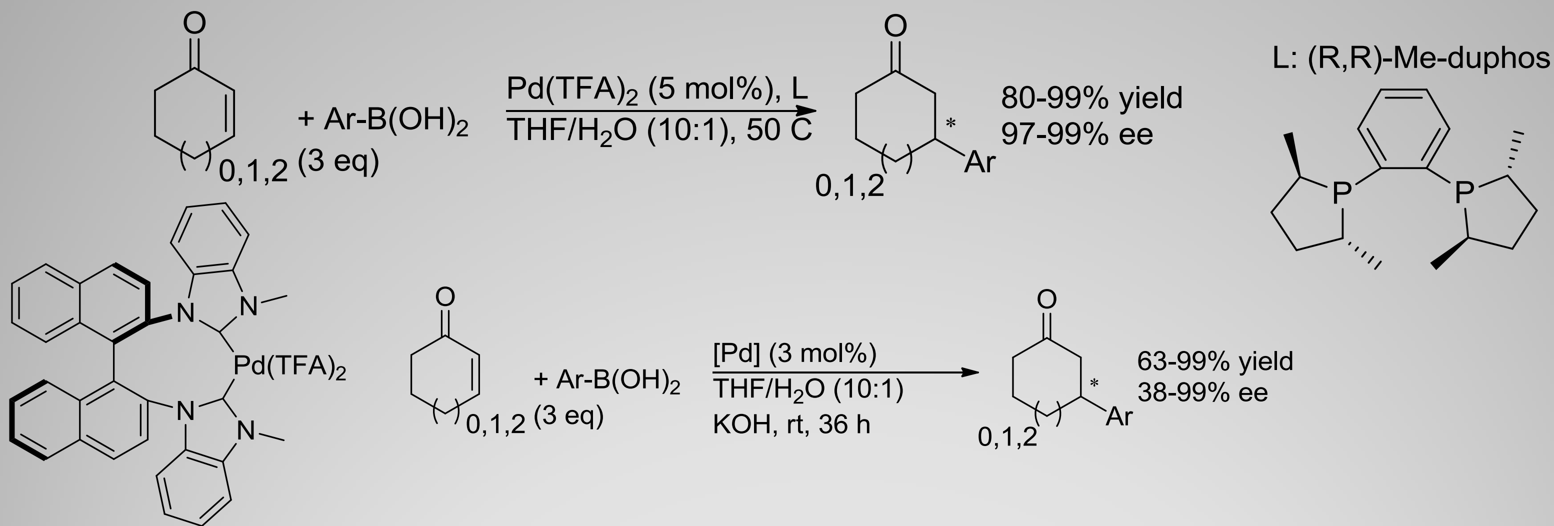
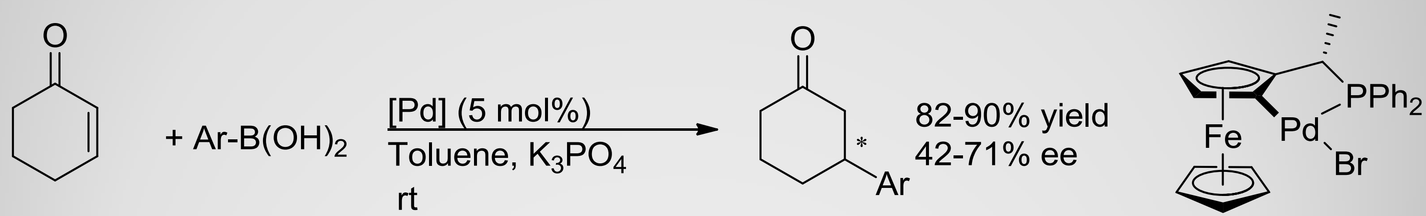
Other Pd Catalysts

- $Pd(TFA)_2$



- Palladacycles



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- Rhodium is expensive, but works well for conjugate addition, with few side reactions
- Palladium is cheaper, but lags behind Rh due to competing β-hydride elimination
- Both work well for aryl and alkenyl groups, but not for sp^3 carbons

Summary

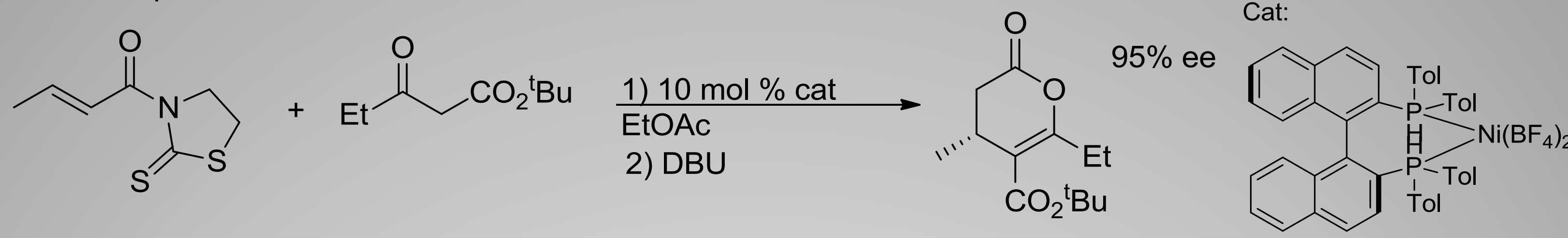
- First and second row TM’s complement one another
  - Cu/Ni are good for introducing alkyl groups
  - Rh/Pd are good for introducing aryl/alkenyl groups
- Relatively young field, but growing quickly
- Many catalyst/ligand options
- Tandem reactions allow for great diversity of products

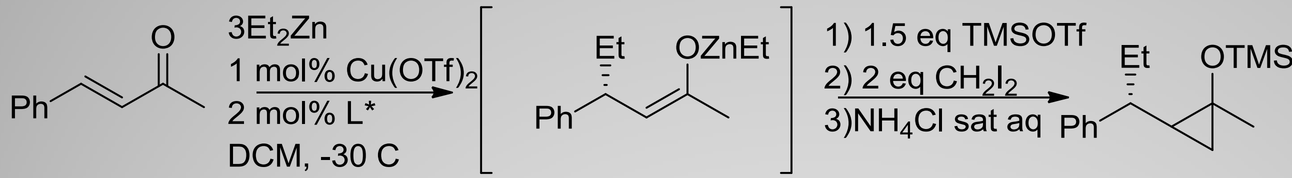
Conclusions

- Thank you for your attention!

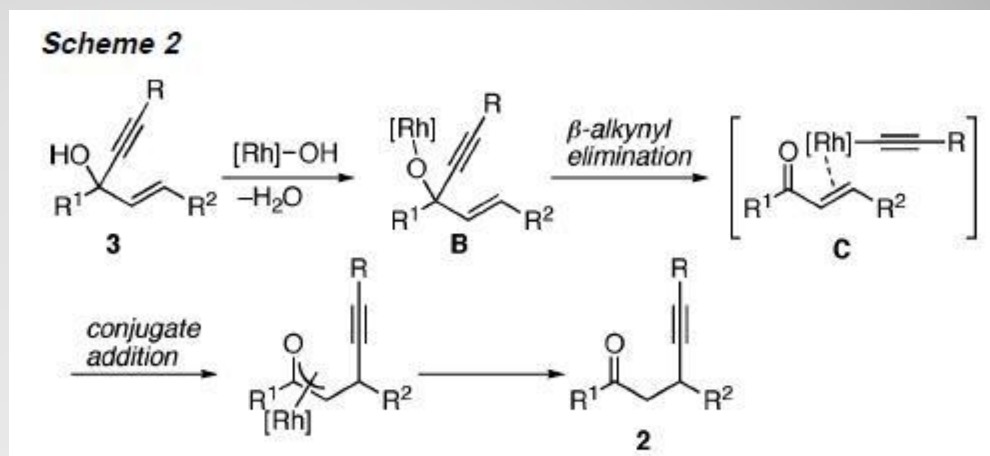
Questions?

1) Predict the products:



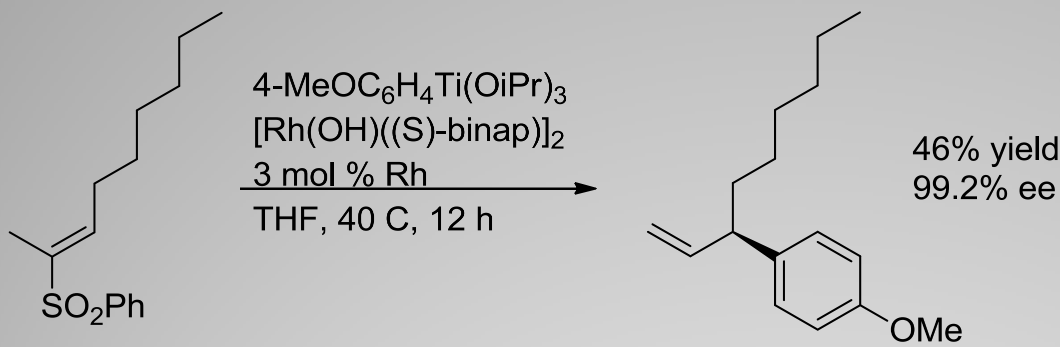


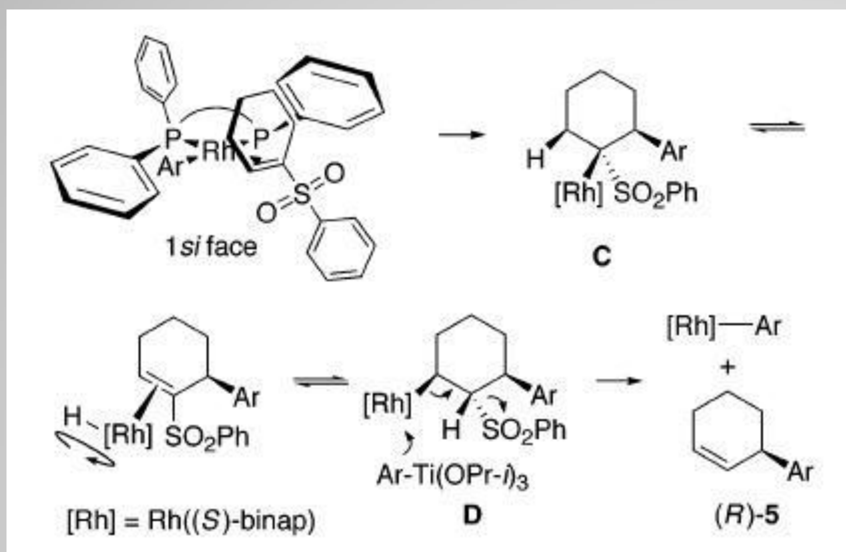
2) Propose a mechanism:



Question Answers

3) Predict the product and provide a reasonable mechanism:





Question Answers