Bifunctional Asymmetric Catalysis

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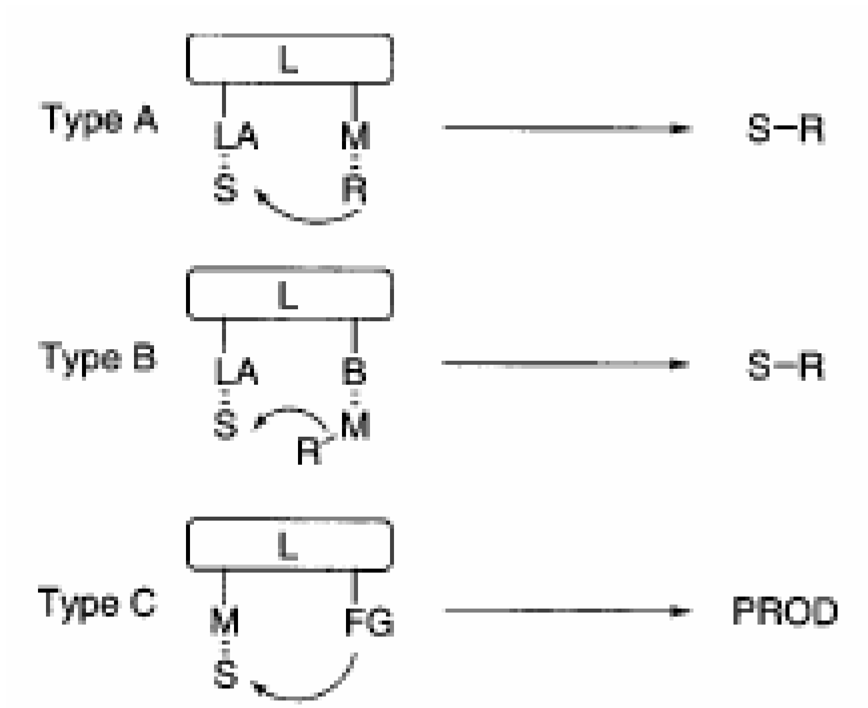
October 4, 2005

Why Bifunctional Catalysis?

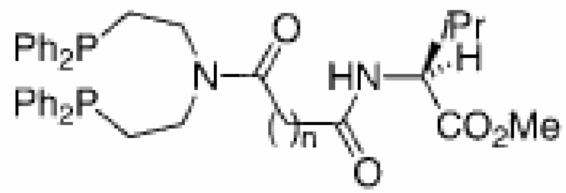
- Precise arrangement of 2 (or more) reacting species for high selectivity
- Simultaneous activation of multiple reactive species for high activity
- Can be regarded as simplified versions of enzymes

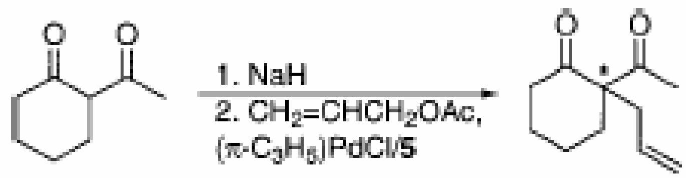
Classification System

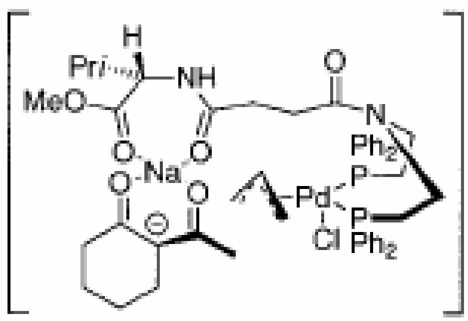


Rowlands, G. J., *Tetrahedron*, 57, **2001**, 1865

Type A Catalysts: Pd-allyl Substitutions



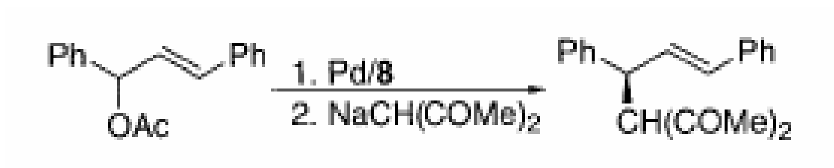




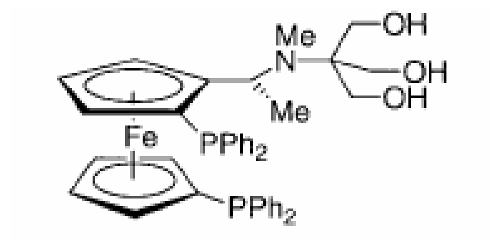
52% e.e. highest obtained

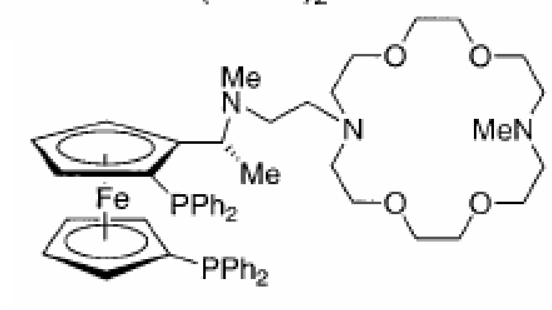
Kumada, M., *et. al., J. Chem. Soc., Chem. Commun.*, **1982**, 1162

More Systems For Pd-allyl Chemistry

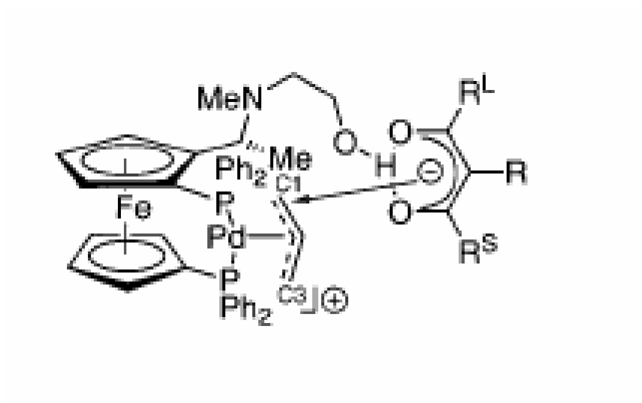


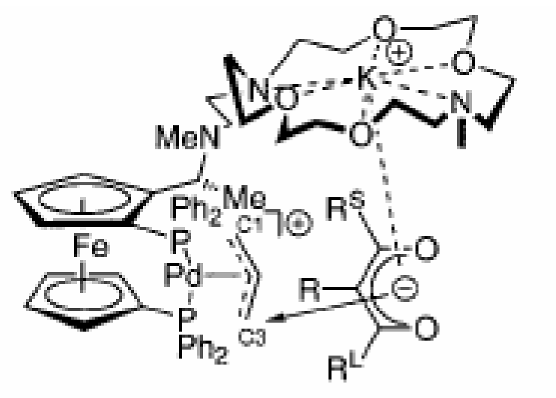
Up to 96% e.e.





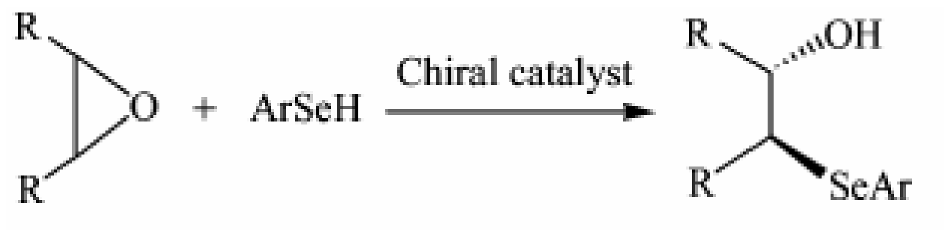
Up to 75% e.e.

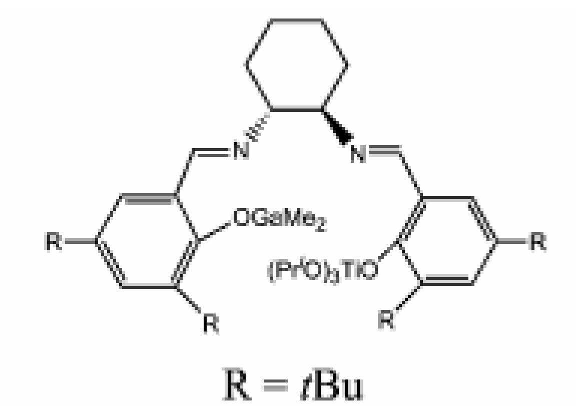


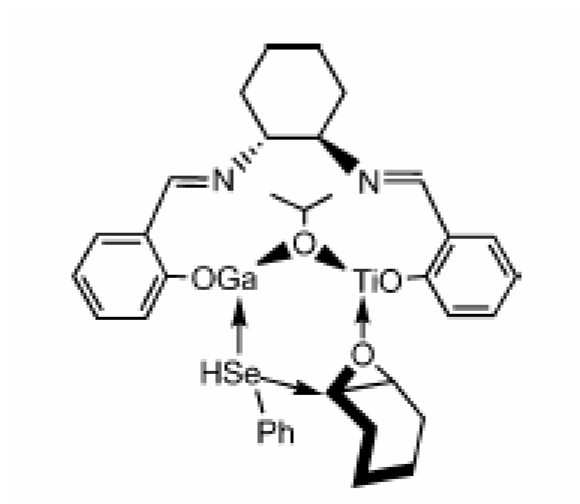


Ito, Y., *et. al.*, *Tetrahedron Lett.*, **1990**, *31*, 1743
Tetrahedron Lett., **1986**, *27*, 191
J. Am. Chem. Soc. **1992**, *114*, 2586

Epoxide Opening By Selenides



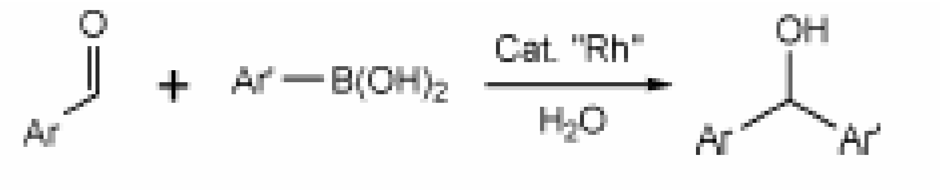


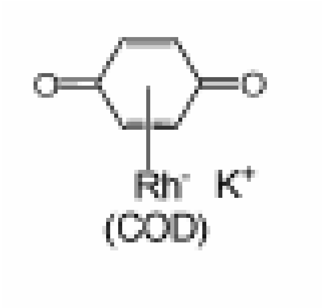


-High e.e.s and yields
-Corresponding mono-metallic and Bis-Ga complexes give poor e.e.

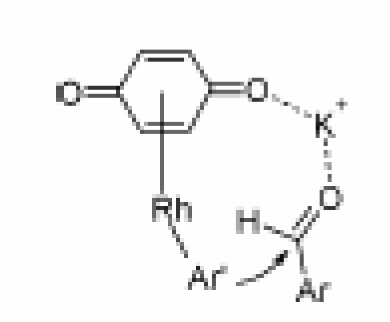
Zhu, C, *et. al.*, *Org. Lett.*, **2005**, *7*(10), 1927

Arylation of Aldehydes



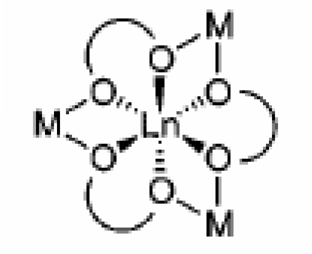


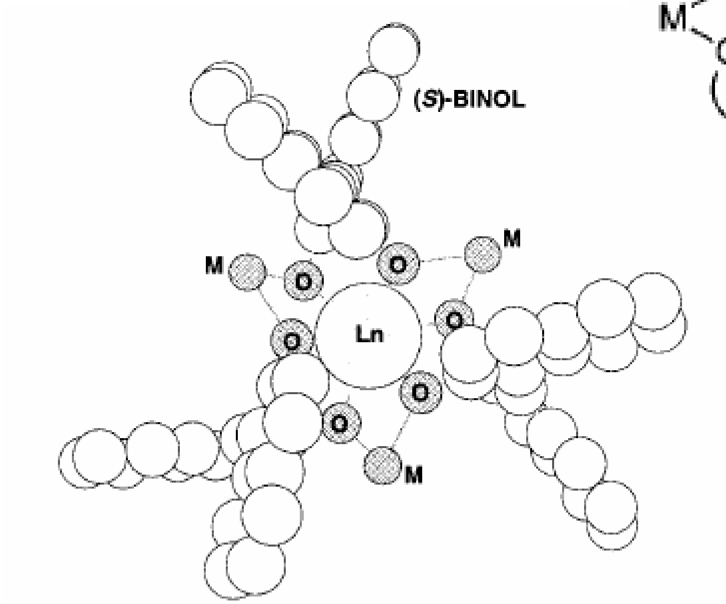
While this reaction is racemic,
it is a novel method of activating
aledhydes towards arylation

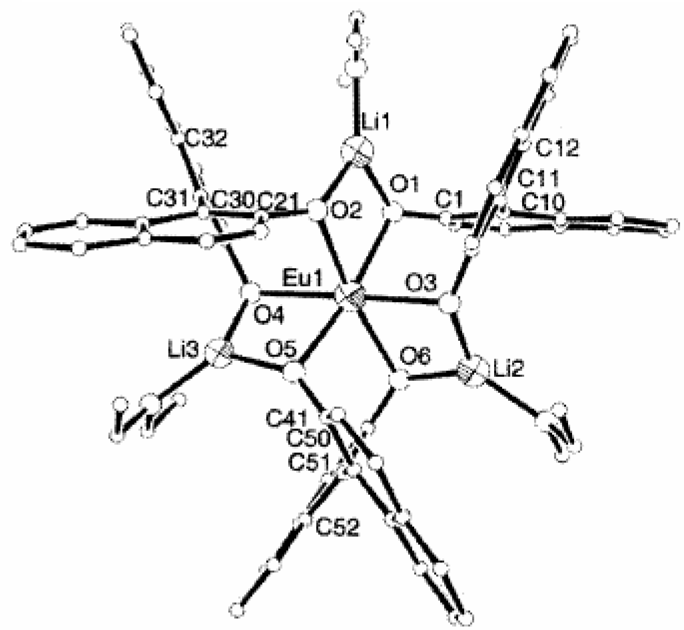


Sweigart, D. A., *et. al.*, *J. Am. Chem. Soc.*, 2005***,*** *127(35)****,*** 12239

Shibasaki's Heterobimetallic System



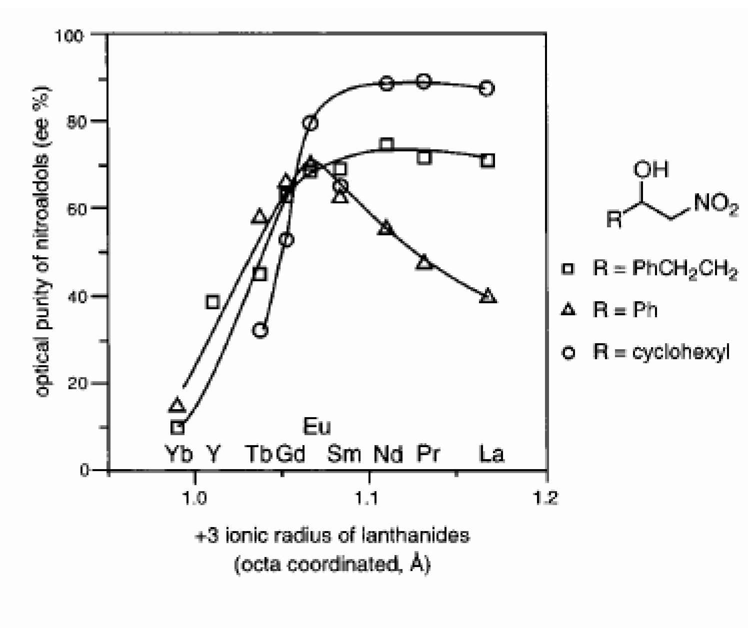




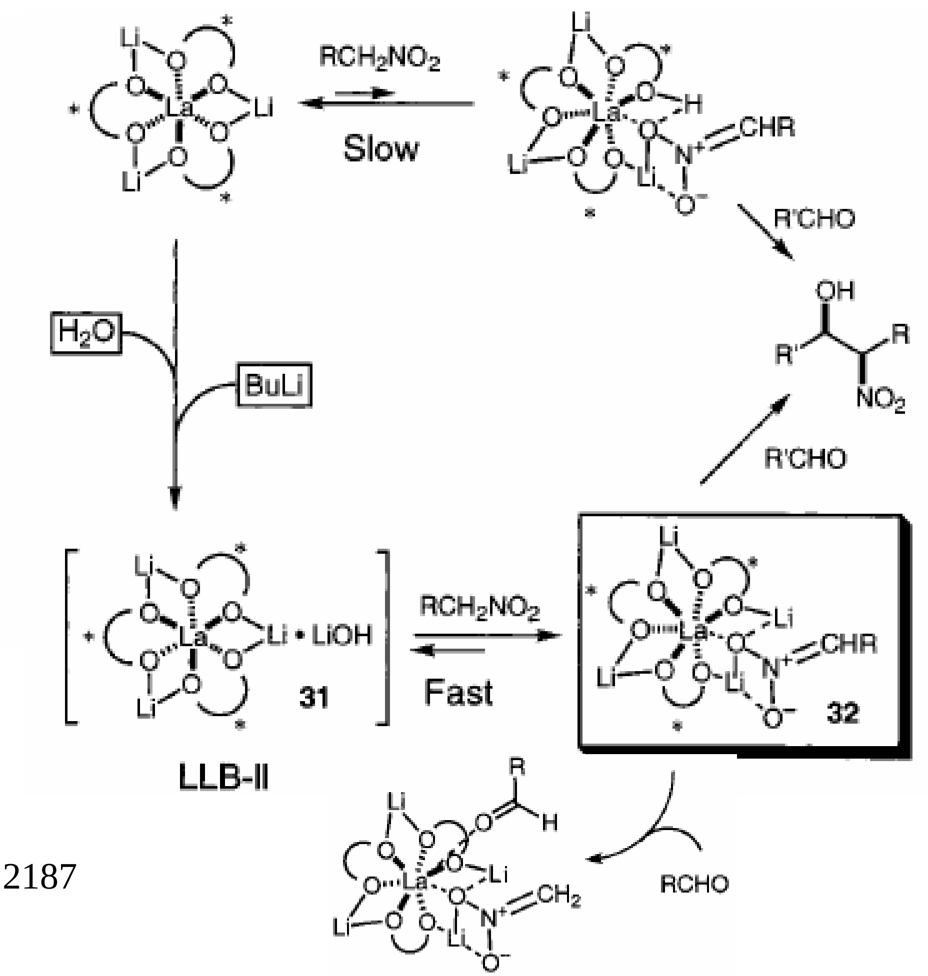
Shibasaki, M., Yoshikawa, N., *Chem. Rev.*, **2002**, *102*, 2187

Shibasaki's System Continued: Optimization

Interesting Example of "Lanthanide Contraction"



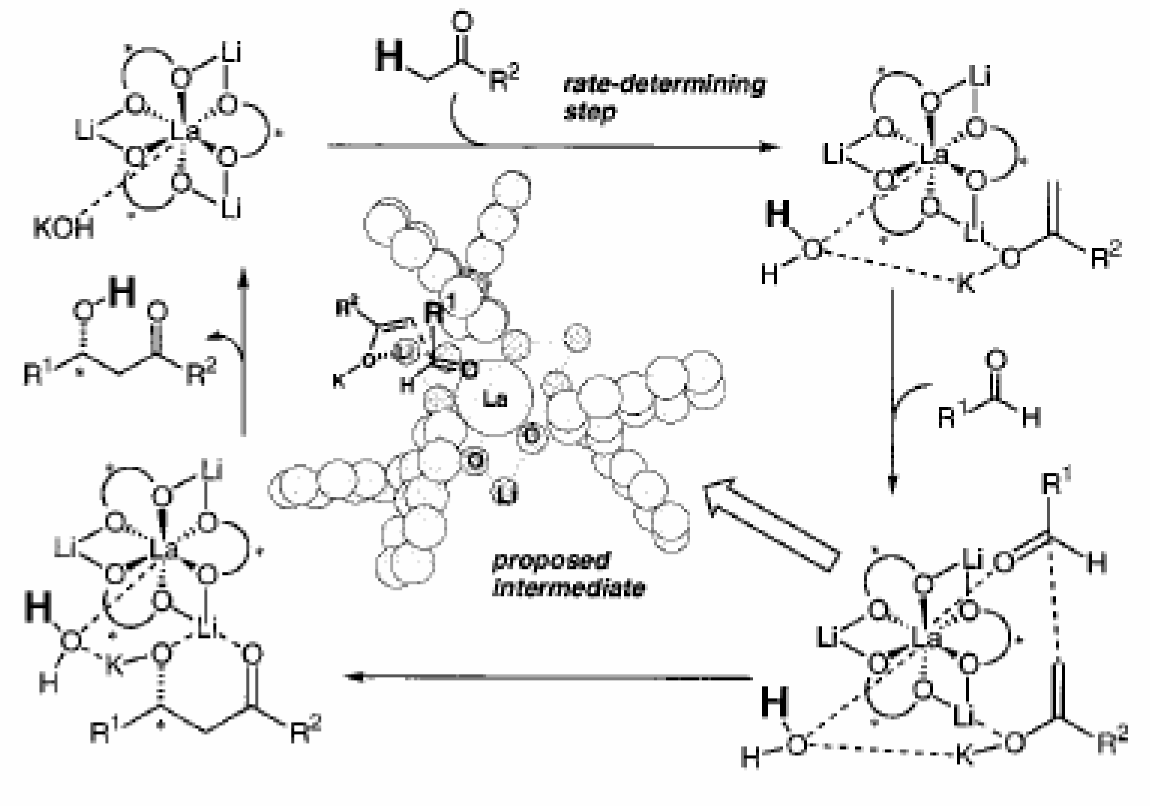
Mechanistic considerations led to more active second generation catalyst



Shibasaki, M., Yoshikawa, N., *Chem. Rev.*, **2002**, *102*, 2187

Shibasaki's System Continued

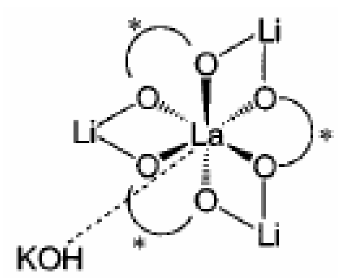
Extension of LLB to direct ketone aldol reactions
Initially required >20mol% of the catalyst
Catalytic base additives were found to greatly enhance the reactivity

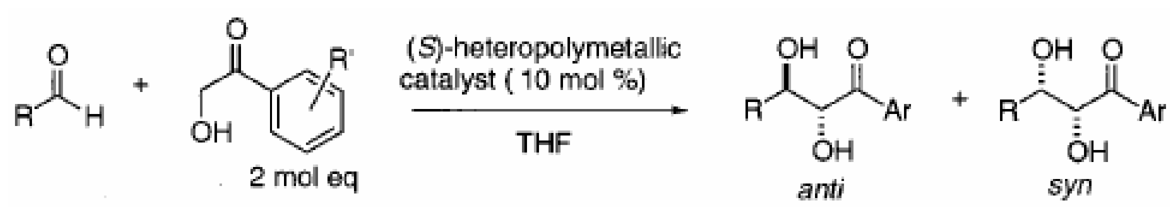


Mechanistic Evidence

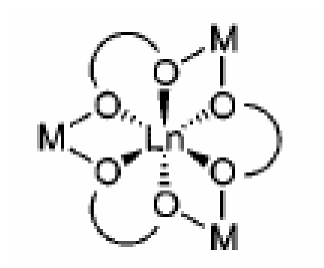
-"LPB" gives racemic pdt.
- $k_H/k_D = 5$ for d_3 ketone
-Coordination of aldehyde Confirmed by NMR

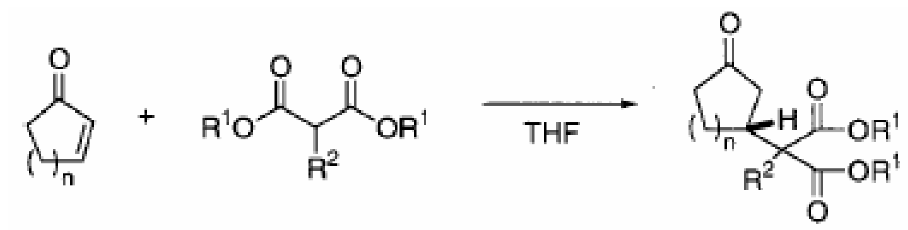
Shibasaki’s System: More Reactions





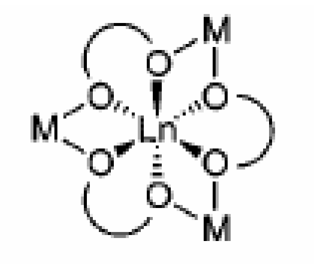
~4:1 anti:syn
e.e. of anti usually >90%

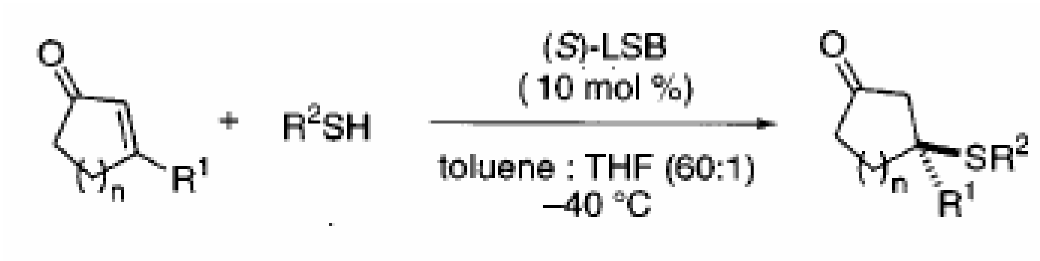




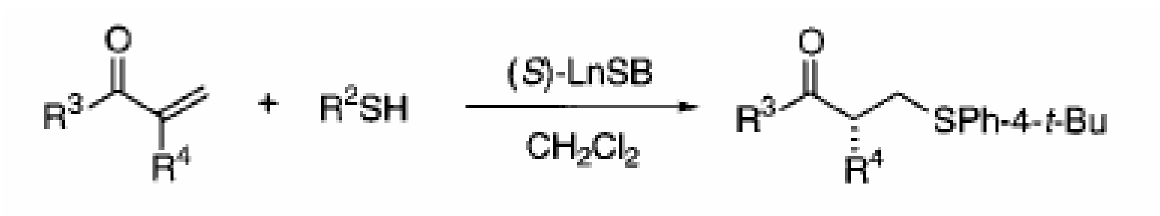
M = Na, Ln = La
High Yield, good e.e.

Shibasaki's System: Conjugate Addition of Thiols





Ln = La
High yields,
Good e.e.

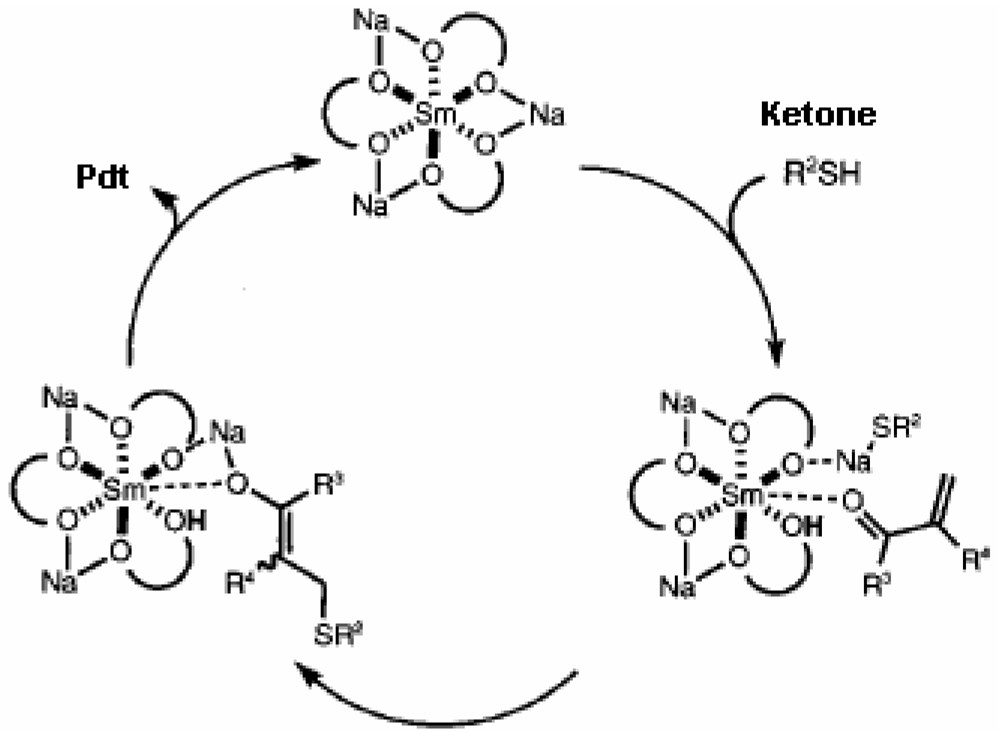


Ln = Sm or La
High Yields,
Good e.e.

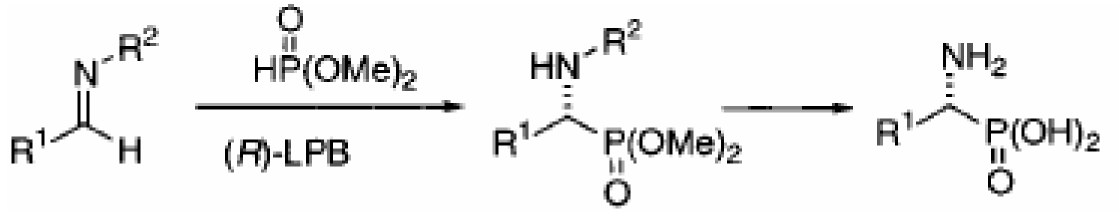
In the second reaction type selectivity comes from asymmetric protonation

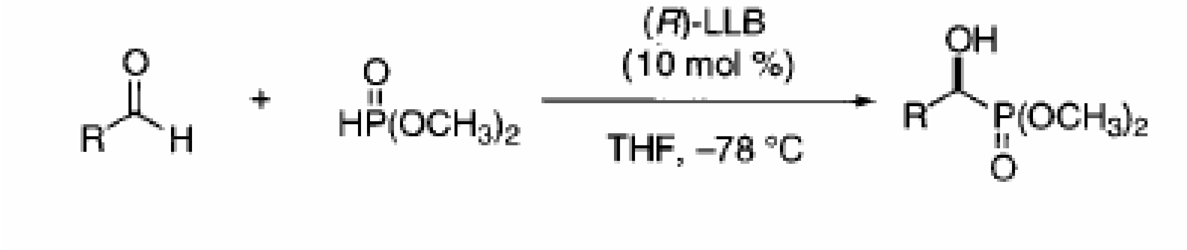
Mechanism of Thiol Conjugate Addition

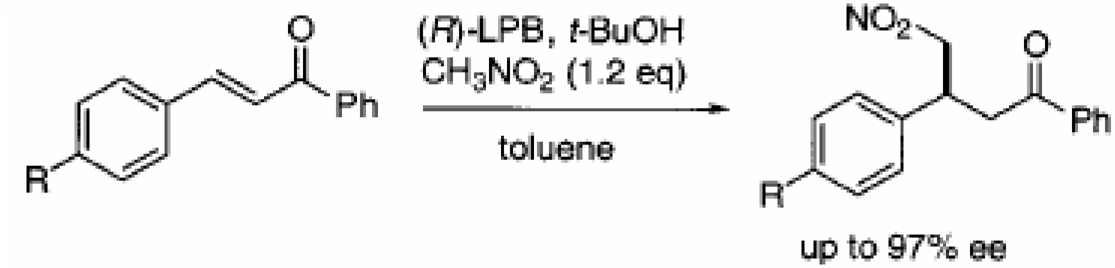
Asymmetric protonation by naphthol



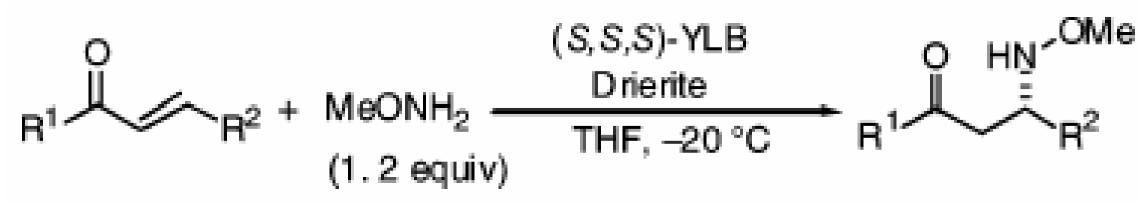
A Few More Examples

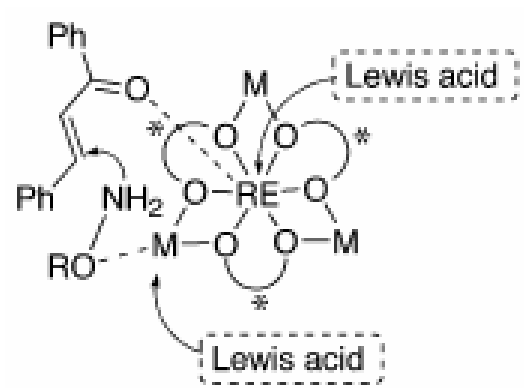


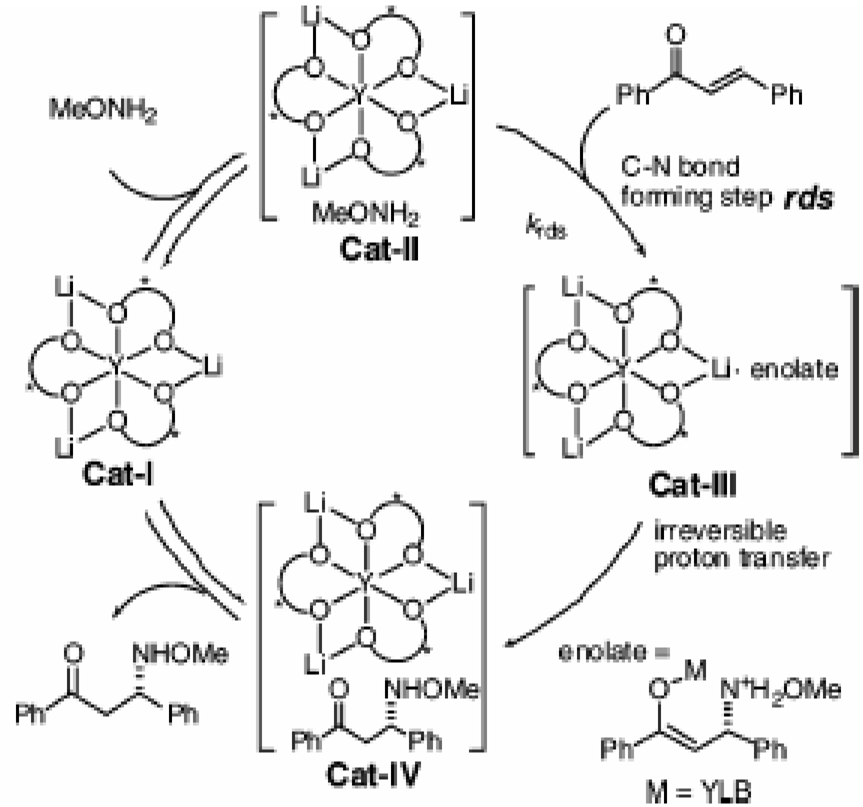




Most Recent Example

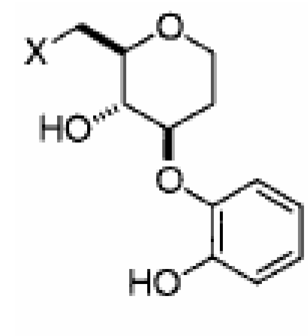




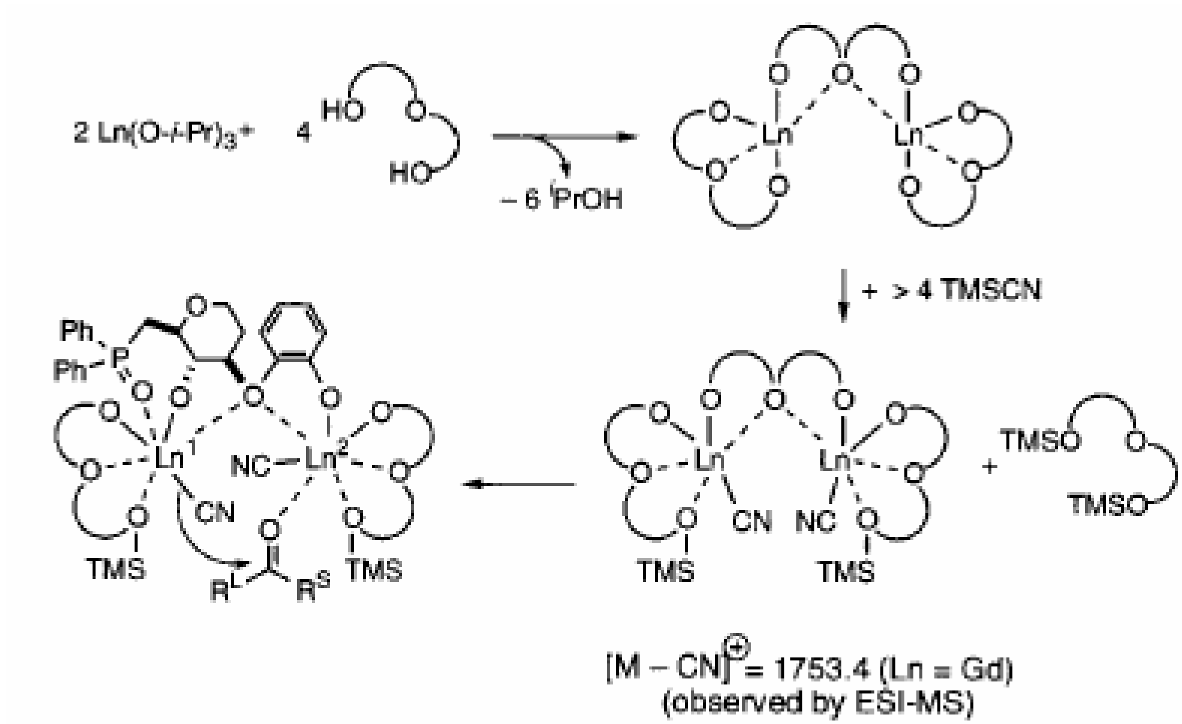


J. Am. Chem. Soc., **ASAP**

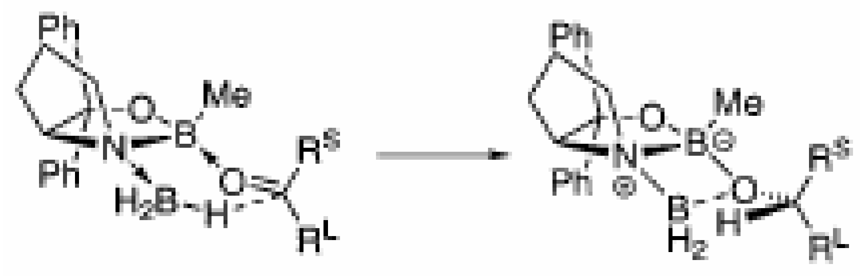
Ln-Ln Bimetallic System

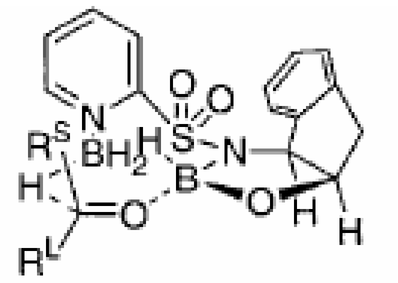


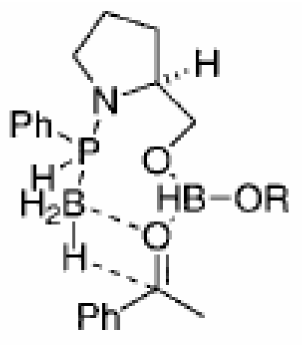
X = $Ph_2P(O)$
X = Ph_2CH

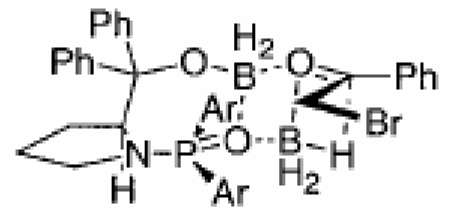


Type B Catalysts: CBS Reduction



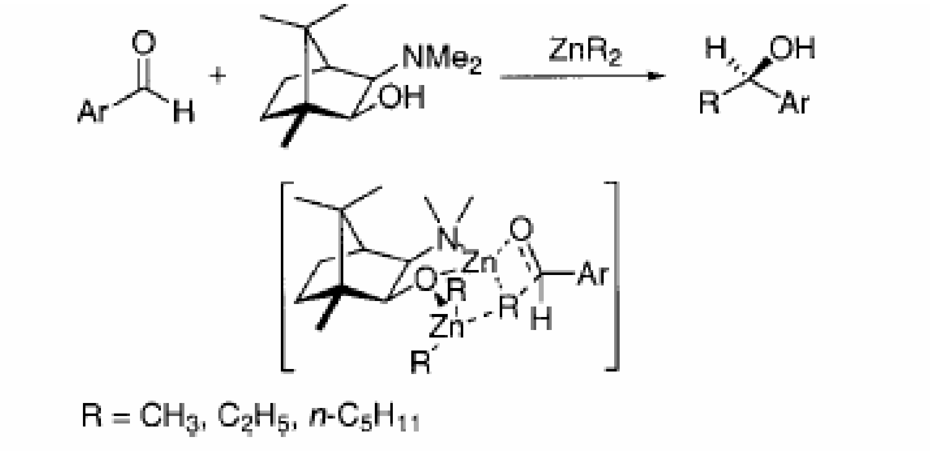


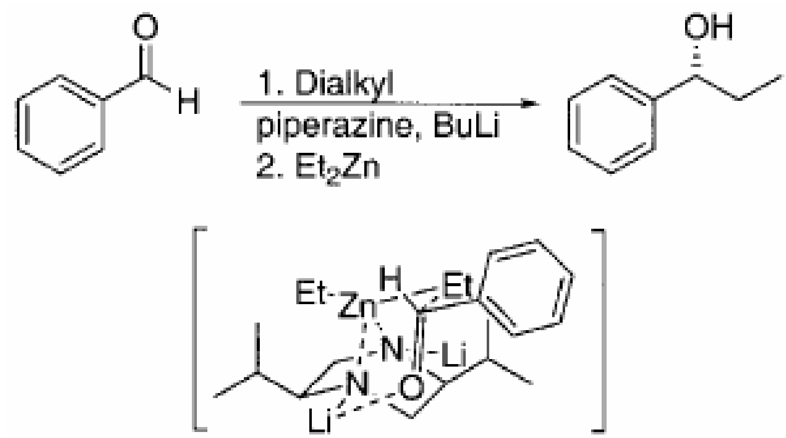




Corey, E. J., *et. al.*, *J. Am. Chem. Soc.*, **1987**, *109*, 5551
Sibi, M. P., *et. al.*, *Tetrahedron Lett.*, **1999**, *40*, 2477
Brunel, J. M., *et. al.*, *J. Chem. Soc. Chem. Comm.*, **1992**, 287
Wills, M., *et. al.*, *J. Chem. Soc. Perkins Trans. 1*, **1998**, 1027

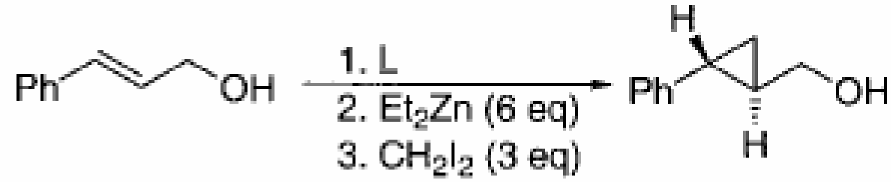
Dialkylzinc Additions

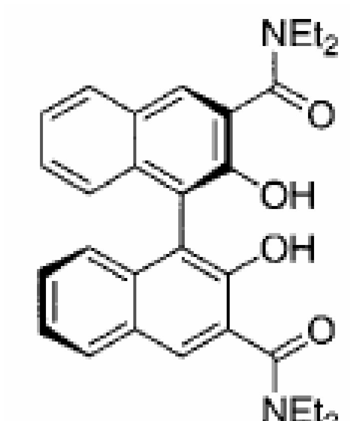




Noyori, R., Kitamura, M., *Angew. Chem. Int. Ed. Engl.*, **1991**, *30*, 49
Niwa, S., Soai, K. J., *J. Chem. Soc. Perkin Trans. 1*, **1991**, 2717

Asymmetric Simmons-Smith





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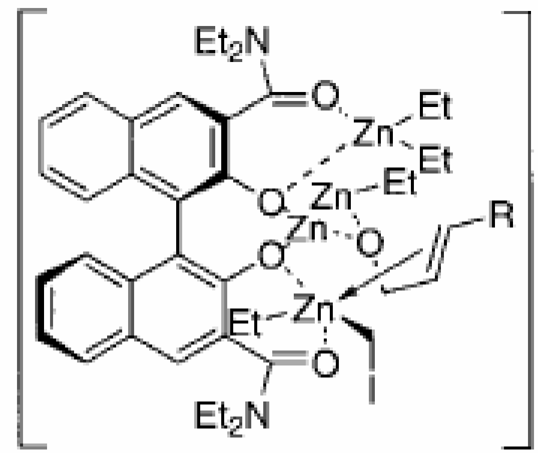
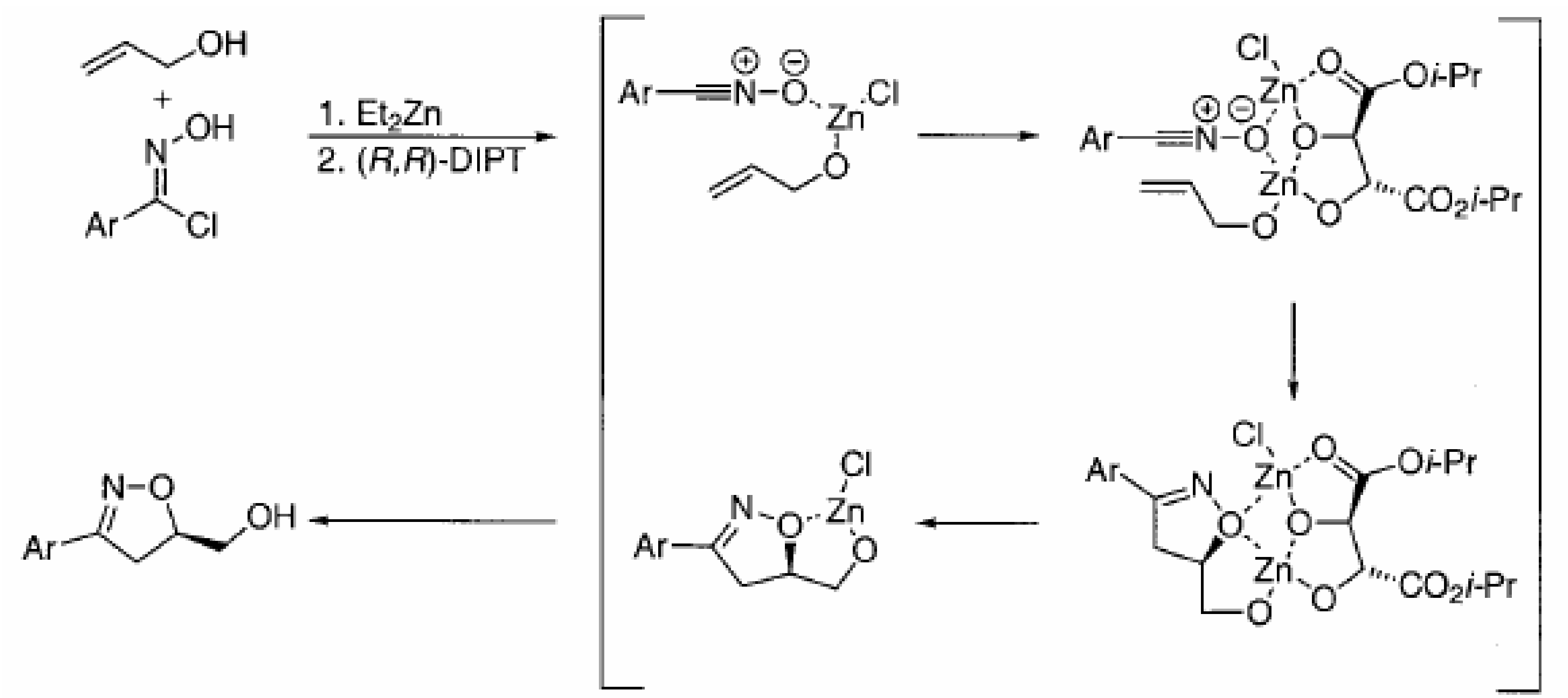


Up to 92% e.e.

Katsuki, T., *et. al., Bull. Chem. Soc. Jpn.*, **1997**, *70*, 207

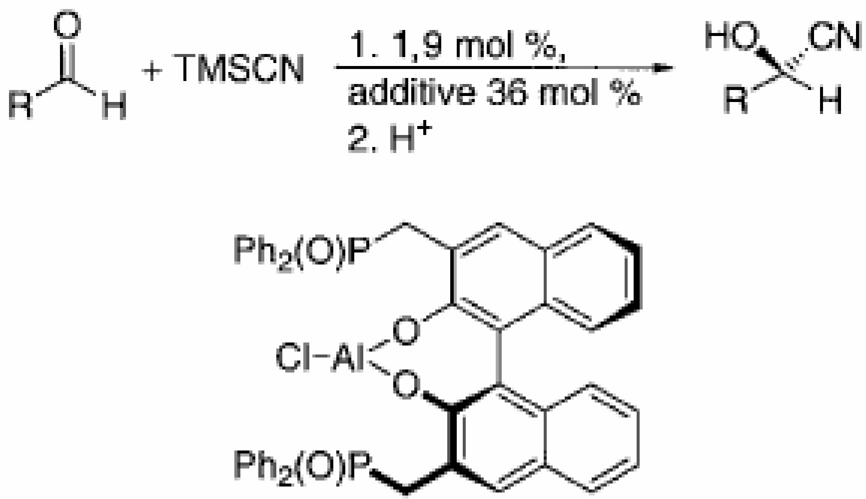
Synthesis of Isoxazolines



Asymmetric [3+2] cycloaddition

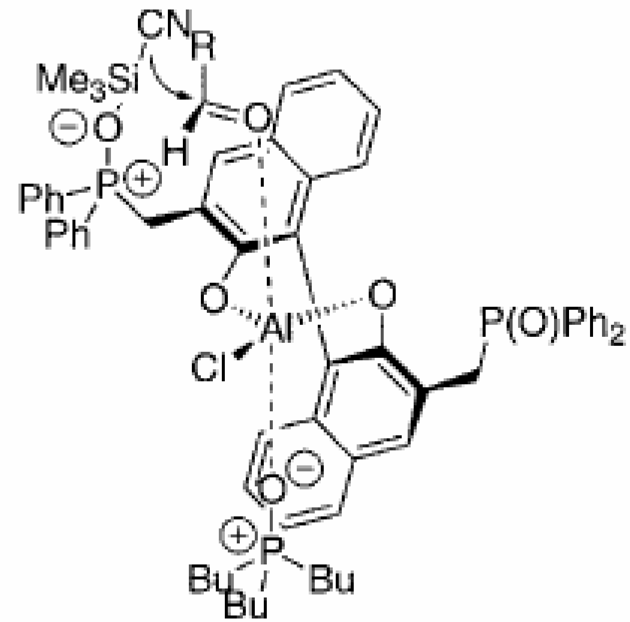
Inomata, K. *et. al.*, *Chem. Lett.*, **1993**, 1847

Cyanosilylation Reactions

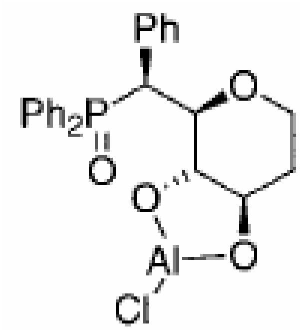


1

R = $Ph(CH_2)_2$, $CH_3(CH_2)_5$, $(CH_3)_2CH$, Ph
additive = $Bu_3P(O)$ or $CH_3P(O)Ph_2$

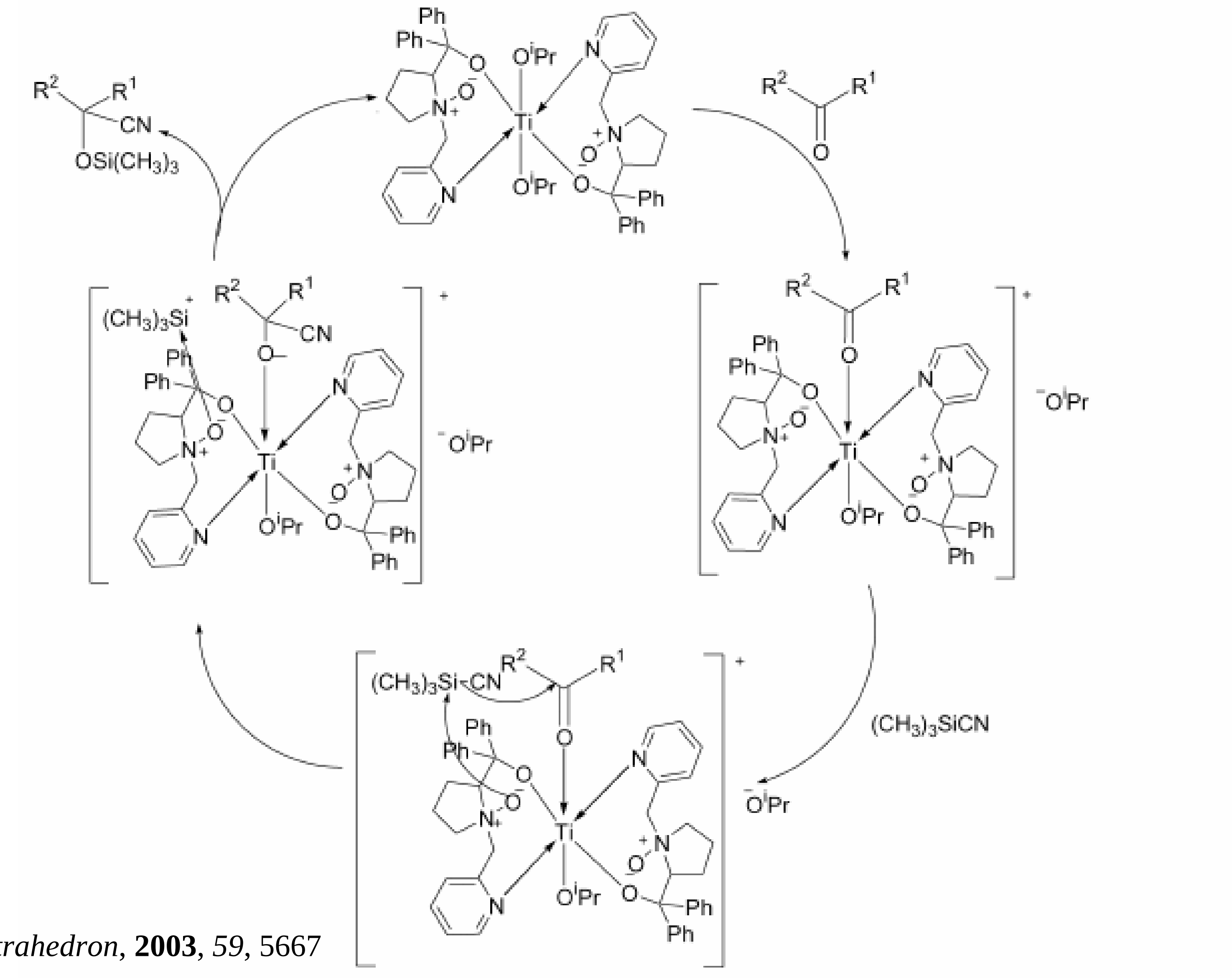


R = $Ph(CH_2)_2$,
$CH_3(CH_2)_5$, $(CH_3)_2CH$



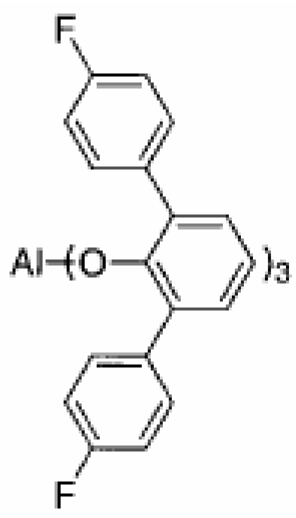
Shibasaki, M., *et. al.*, *J. Am. Chem. Soc.*, **1999**, *121*, 2641
Strecker reaction (not shown): *Angew. Chem. Int. Ed. Engl.*, **2000,** *39*, 1650
Tetrahedron Lett., **2000**, *41*, 2405

Another Cyanosilylation

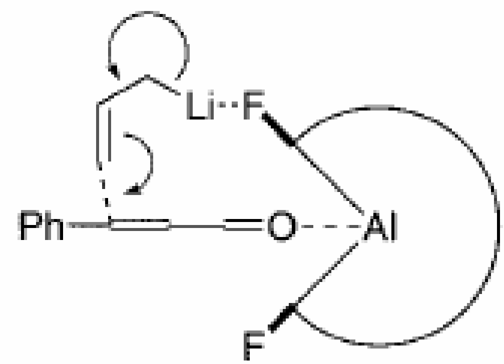


Feng, X., *et. al.*, *Tetrahedron*, **2003**, *59*, 5667

Conjugate Allylation

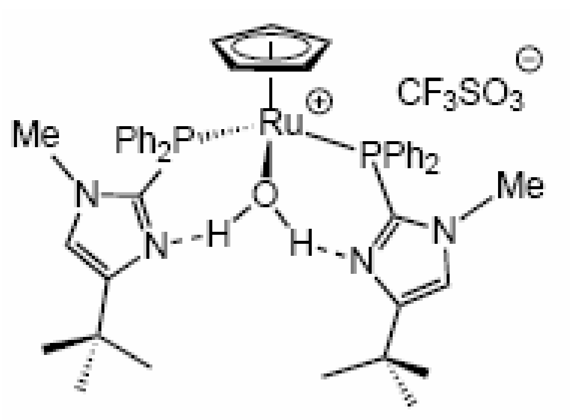


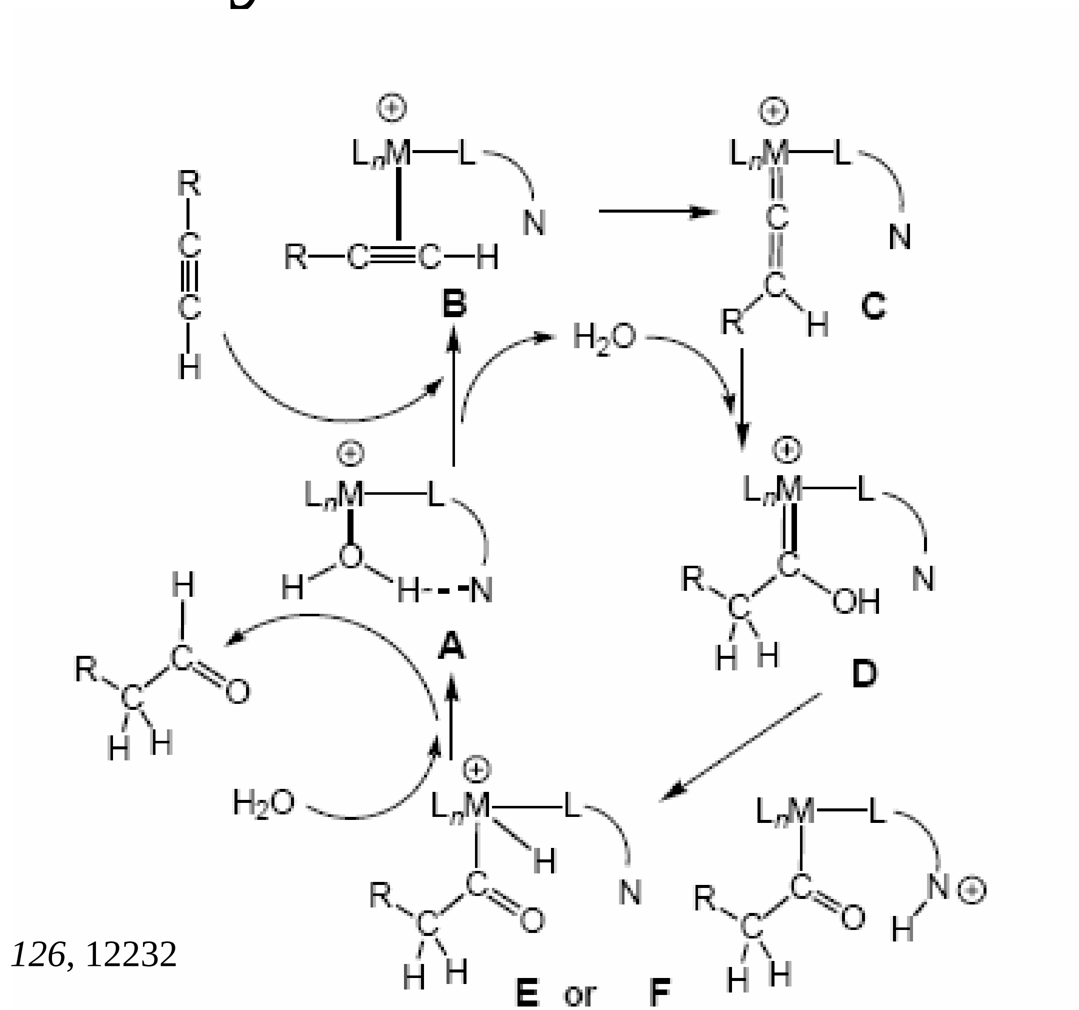
p-F-ATPH



Maruoka, K., *et. al., Angew. Chem. Int. Ed. Engl.*, **1997**, *38*, 1183

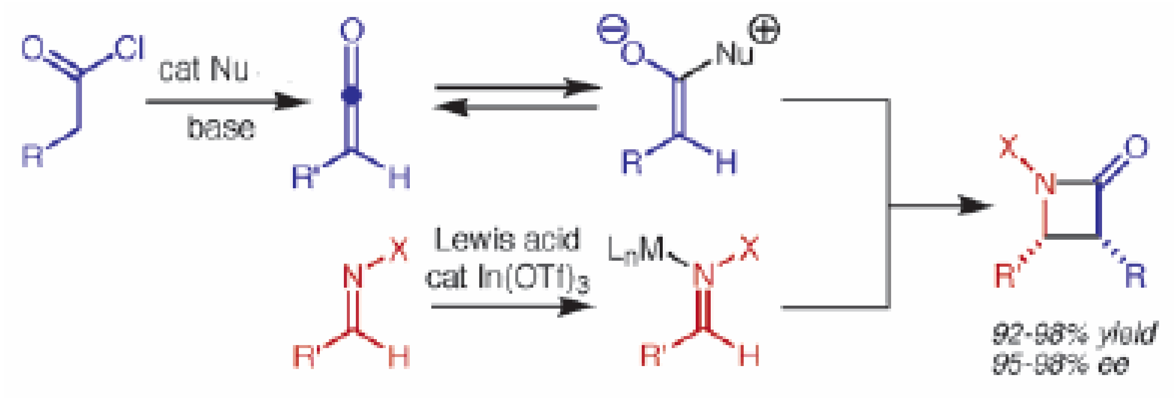
Anti-Markovnikov Hydration of Alkynes



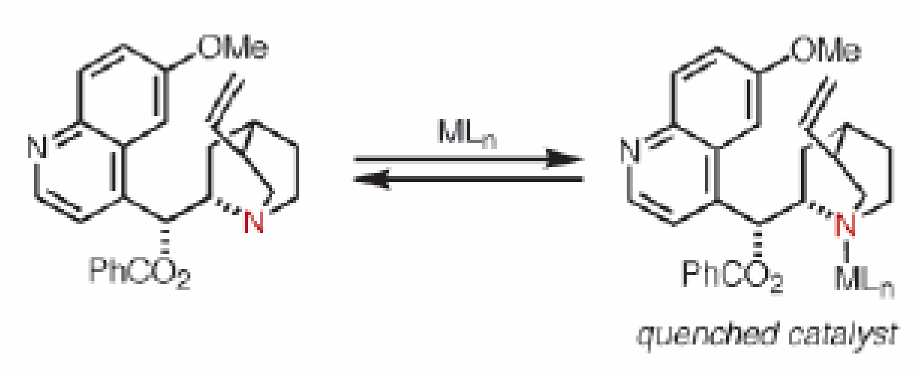


Angew. Chem. Int. Ed. Engl., **2001**, *40*, 3884
Grotjahn, D. B., *et. al.*, *J. Am. Chem. Soc.*, **2004**, *126*, 12232

β-Lactam Synthesis I

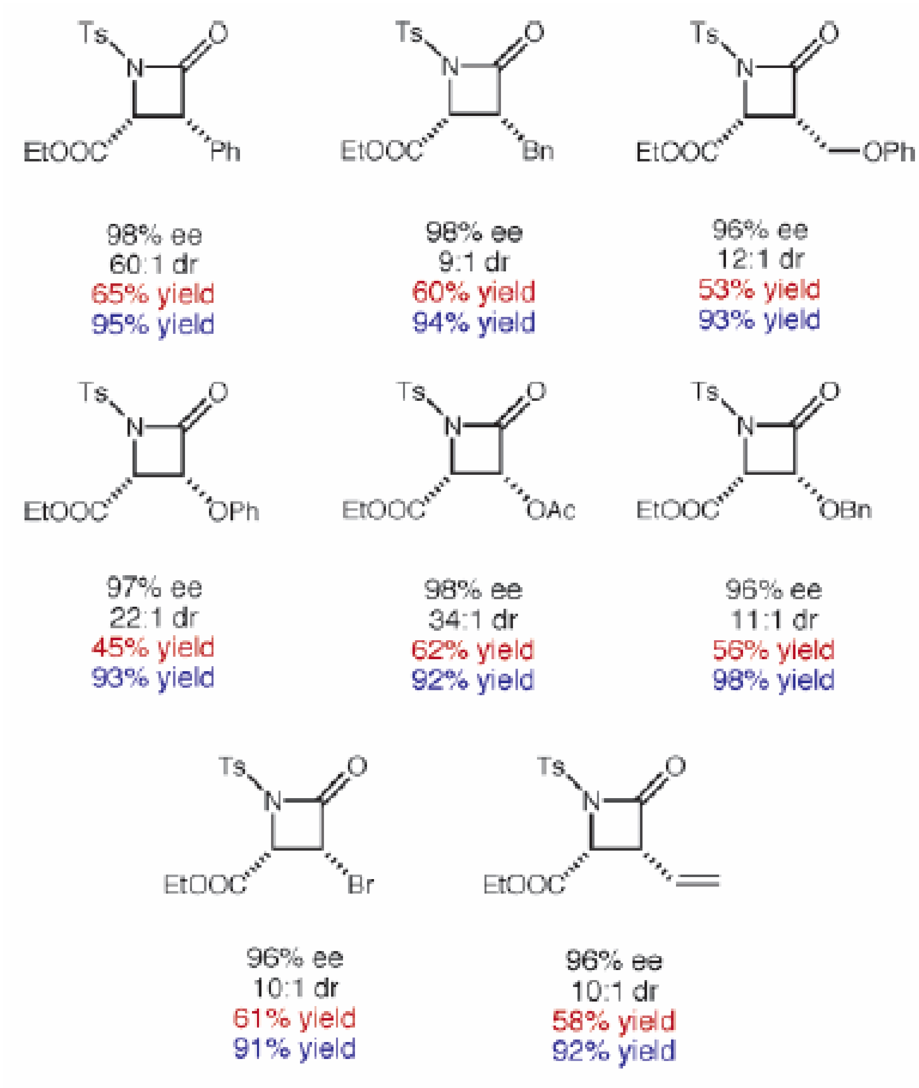


Initial metal screening showed a decrease in yield with late transition metals

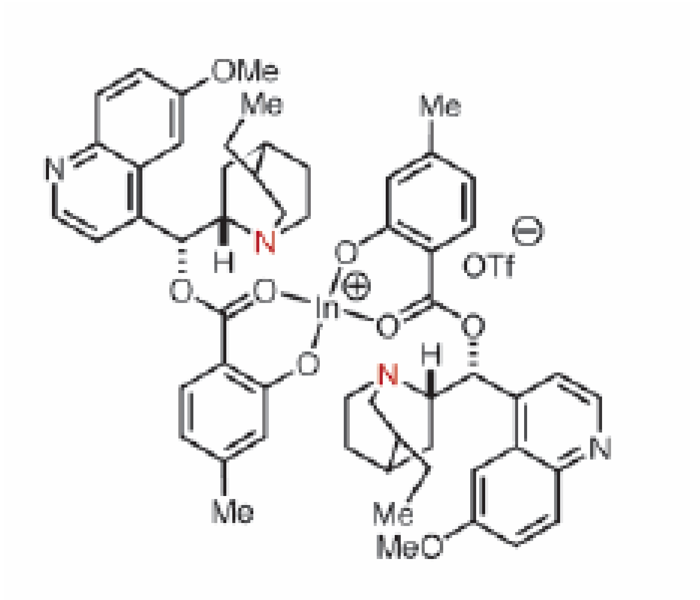


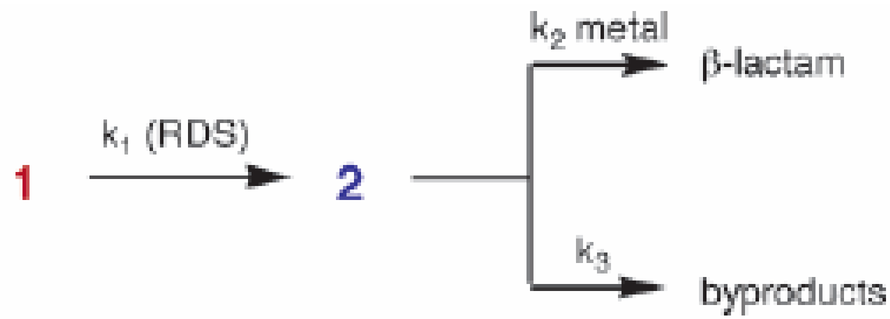
Leckta, T., *et. al.*, *J. Am. Chem. Soc.*, **2005**, *127*, 1206

β-Lactam Synthesis II

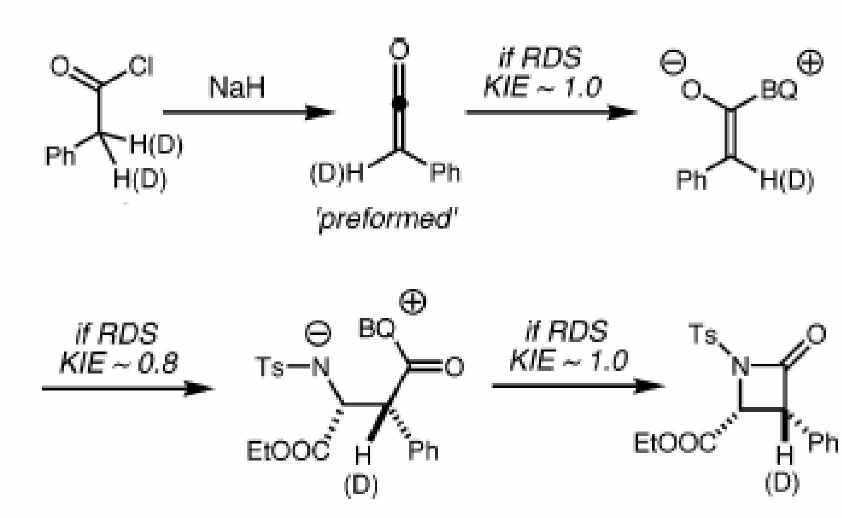


β-Lactam Synthesis III



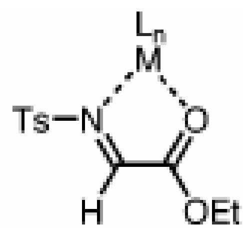


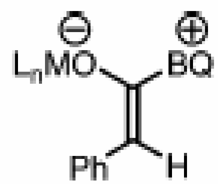
- Addition of metal salts does not increase rate of consumption of SMs
-Preformed ketene shows a large rate enhancement of product formation when metal salts are added

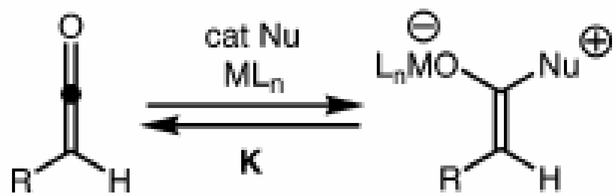


When ketene is preformed in the presence of BQ ligand, the observed RDS is the C-C bond forming step (KIE = 0.8).

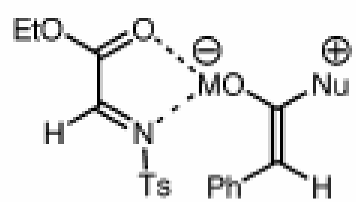
Identifying the Role of the Metal

A 
Lewis acid activation of the imine; consistent with IR and NMR evidence

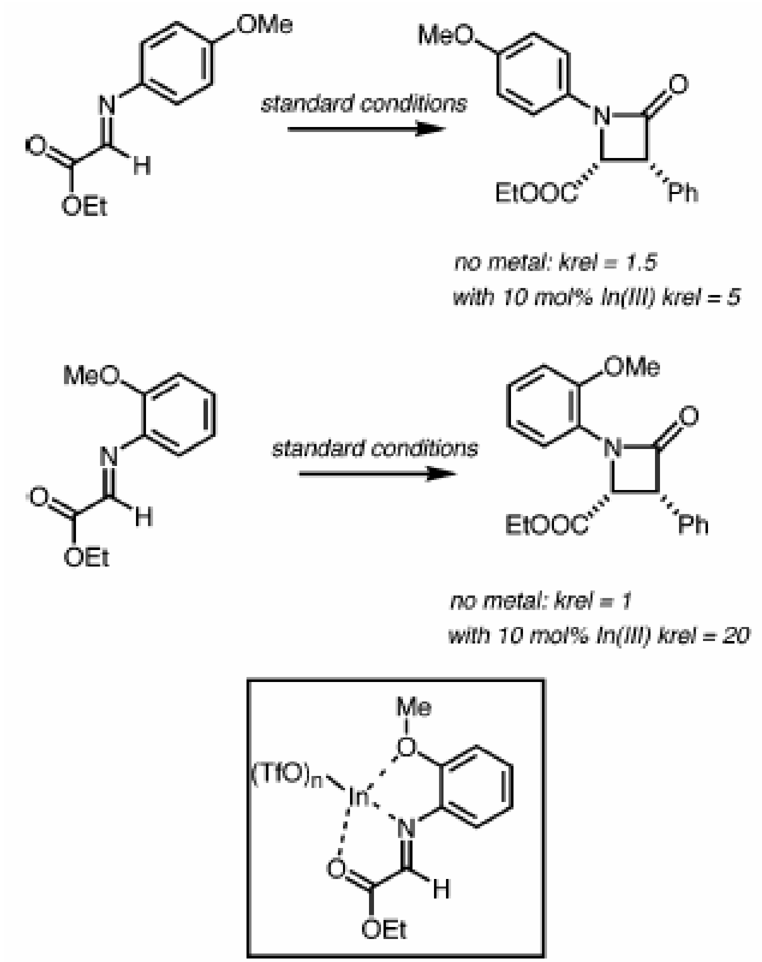
B 
stabilization of a metal enolate



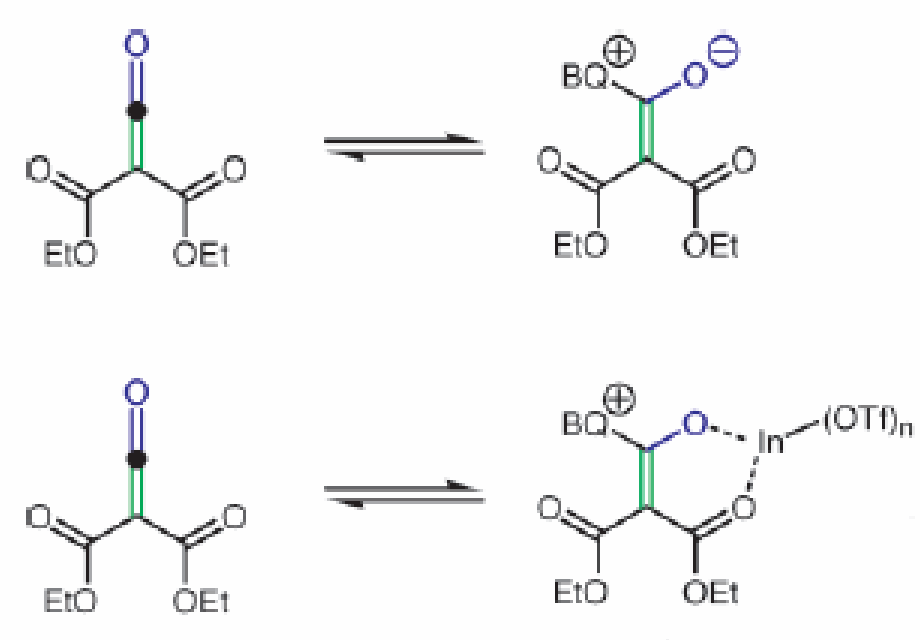
without metal **K** < 1

C 
a combination

Support for A (or C)

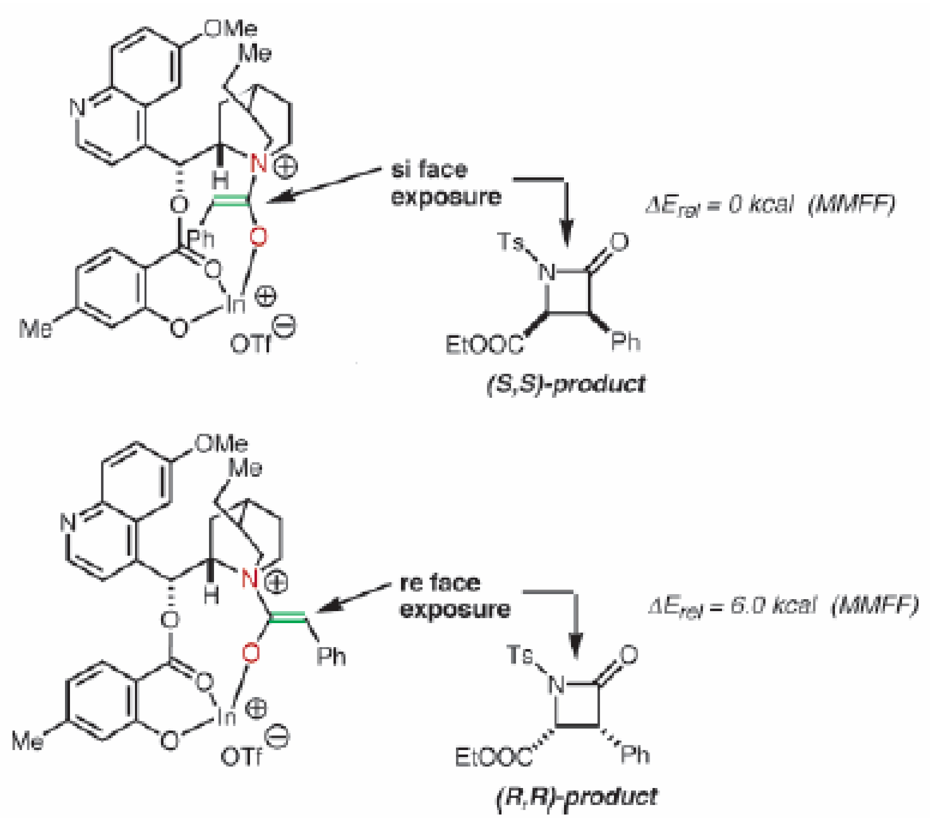


Ruling out Role "B"



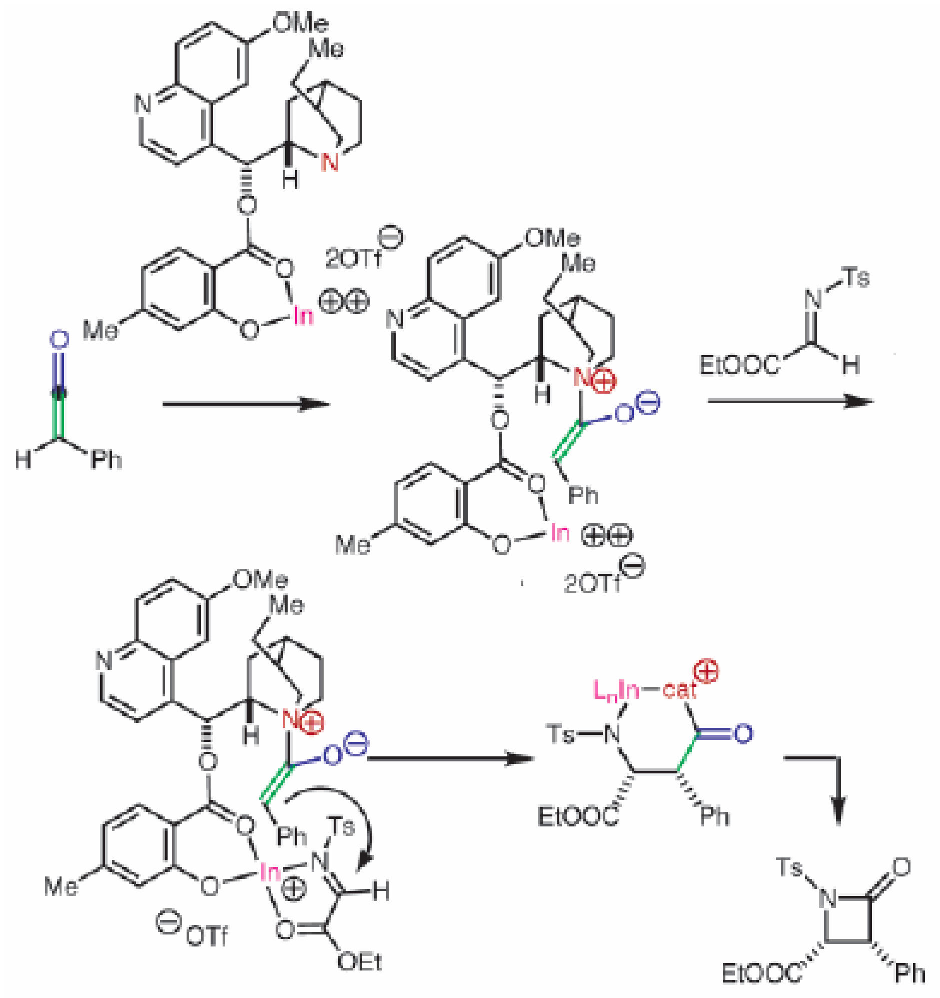
Addition of In(III) salt did not significantly increase the concentration of the enolate form

Ruling Out Double Binding of Enolate

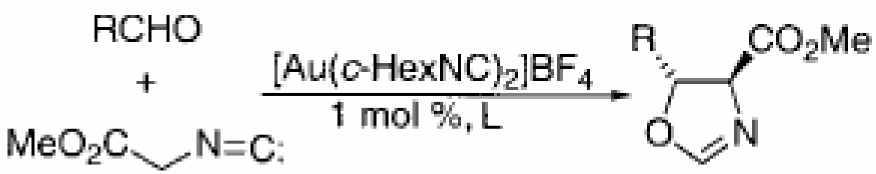


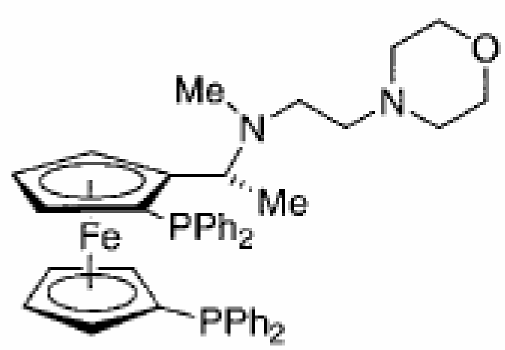
Selectivity is, in fact, for the (R,R) product, which is not consistent with this model.

Final mechanism!



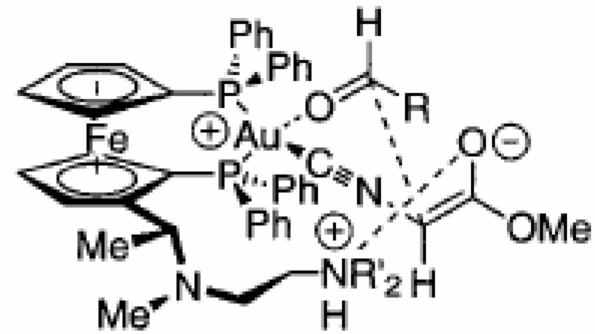
Type C reactions I





L

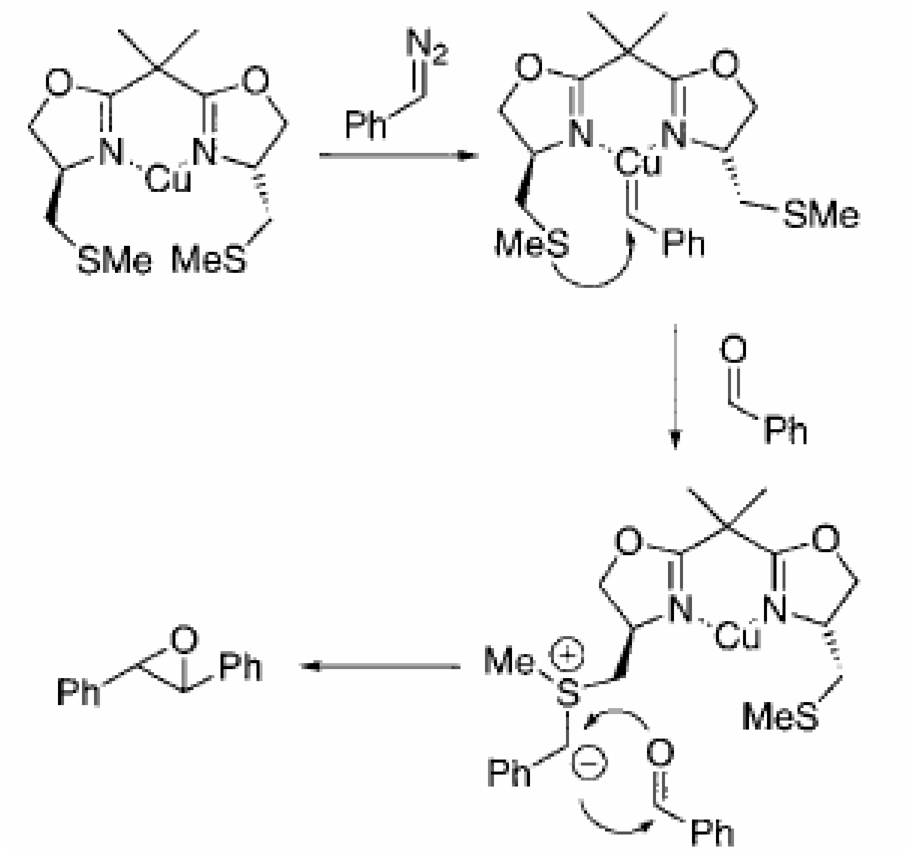
R = Ph, *o*-MeOPh, *p*-ClPh, *i*-Bu, *i*-Pr



R = Ph, *o*-MeOPh, *p*-ClPh, *i*-Bu, *i*-Pr
NR'$_2$ = morpholino

Hayashi, T., *et. al*., J. Am. Chem. Soc., **1986,** *108*, 6405

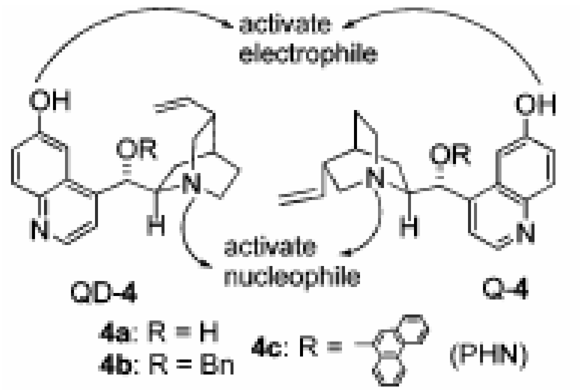
Type C reactions II

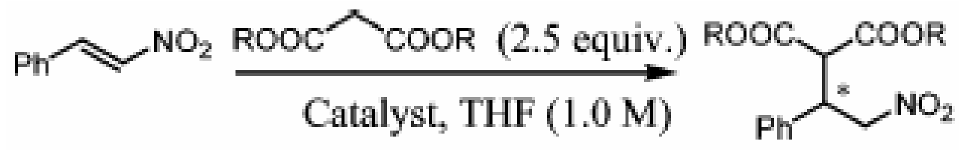


e.e. not great

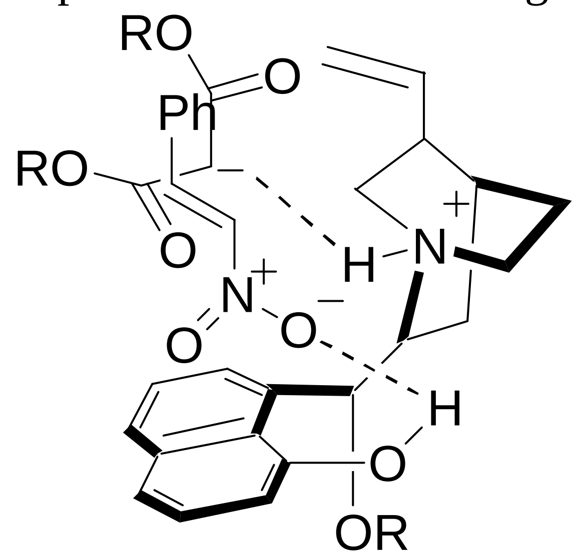
Aggarwal, V. K., *et. al.*, *J. Chem. Soc. Perkin Trans. 1*, **1998**, 2037

Other catalysts



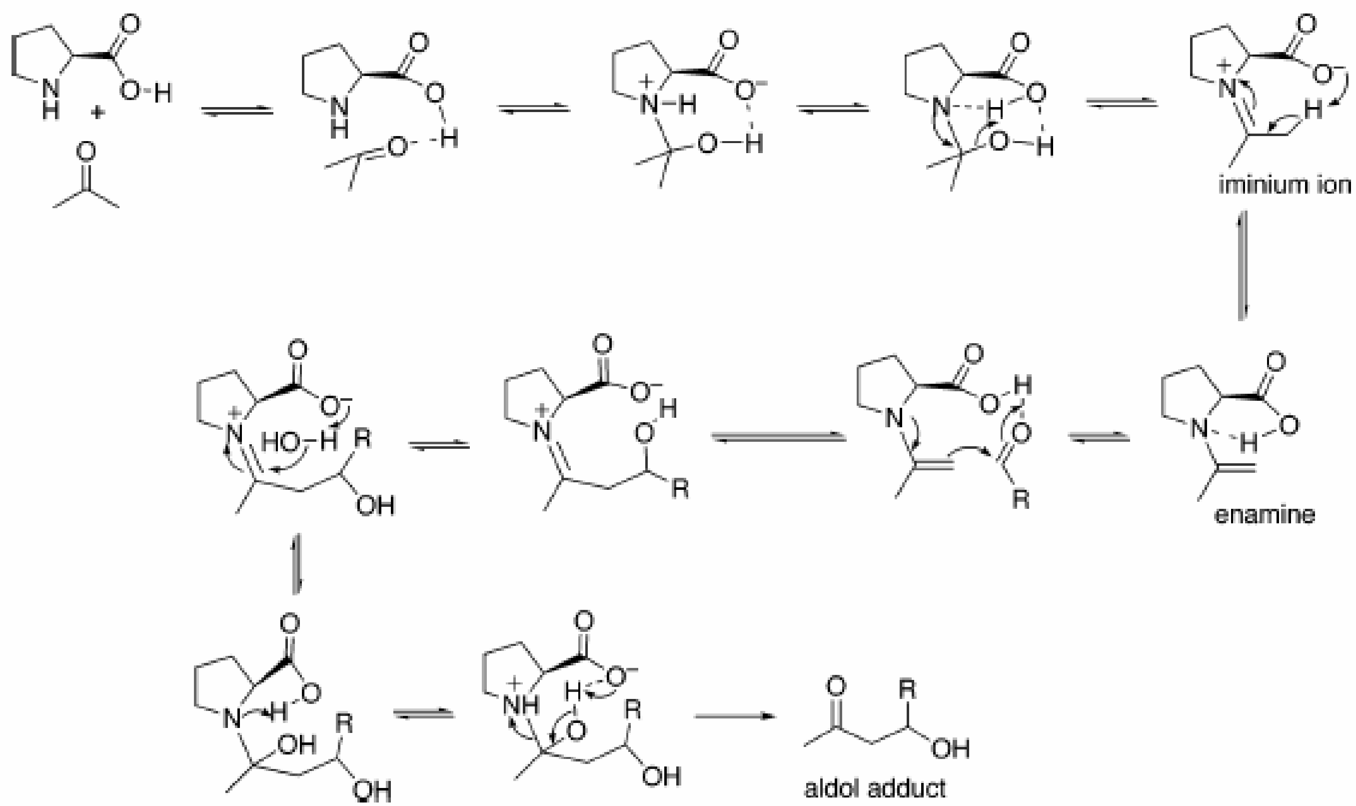


Quinuclidine nitrogen deprotonates malonate, phenolic proton H-bonds to nitro group

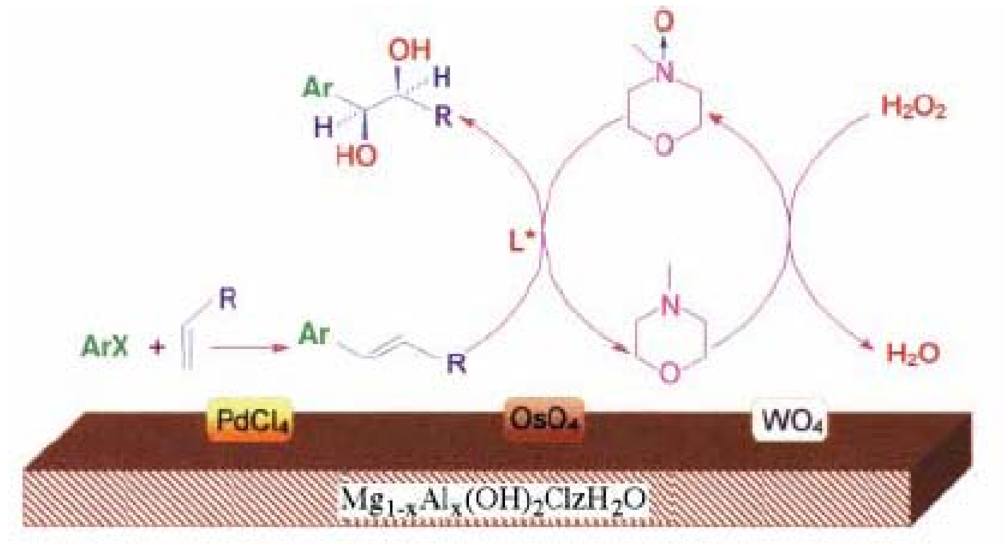


Deng, L., *et. al.*, *J. Am. Chem. Soc.*, **2004**, *126*, 9406
Wynberg, H., Hiemstra, H., *J. Am. Chem. Soc.*, **1981**, *103*, 417

Proline As a Multifunctional Catalyst: H as Metal



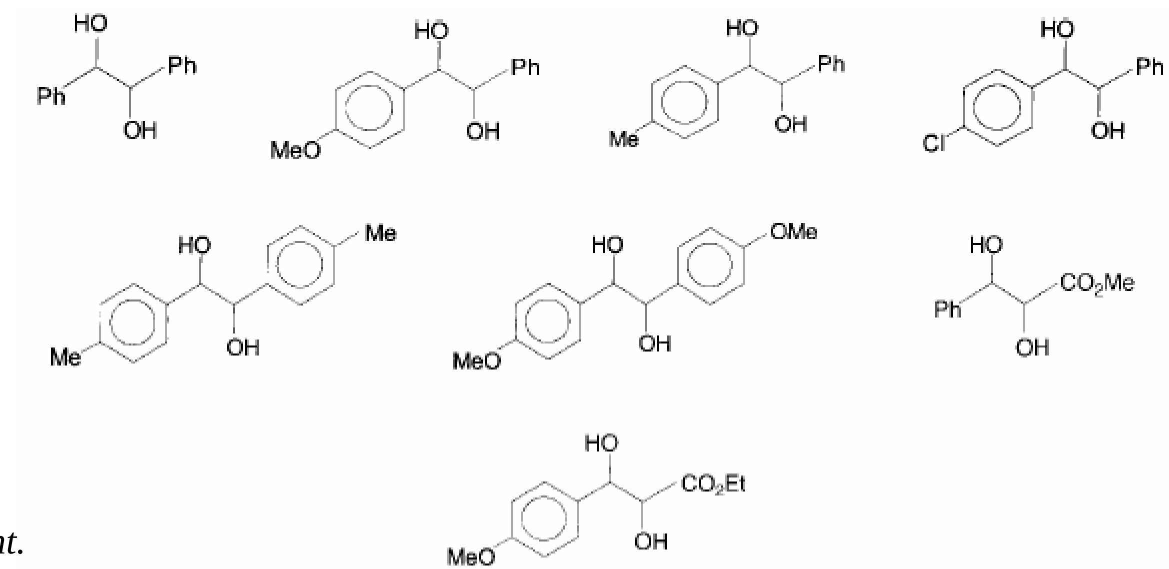
“Trifunctional Matrix”



L* is $(DHQD)_2$PHAL

-e.e.s of products shown are 95-99%!

-yields are 83-94%



Choudary, B. M., *et. al.*, *Angew. Chem. Int. Ed. Engl.*, **2001**, *40*, 4619

Conclusions

- Multifunctional catalysis allows for a great degree of control over reactivity and selectivity
- This is an area with a great deal of future possibilities, especially in “Type C” and organocatalytic versions.

Review Articles

- Cahard, D., Ma, J.-A., *Angew. Chem. Int. Ed. Engl.*, **2004**, *43*, 4566.
- Yamamoto, H., Futatsugi, K., *Angew. Chem. Int. Ed. Engl.*, **2005**, *44*, 1924
- Rowlands, G. J., *Tetrahedron*, **2001**, *57*, 1865
- Shibasaki, M., Yoshikawa, N., *Chem. Rev.*, **2002**, *102*, 2187