2. LUMO Activation

2.1 Lewis and Brønsted acids activation of carbonyl and imines

2.1.1 Aldol Reaction

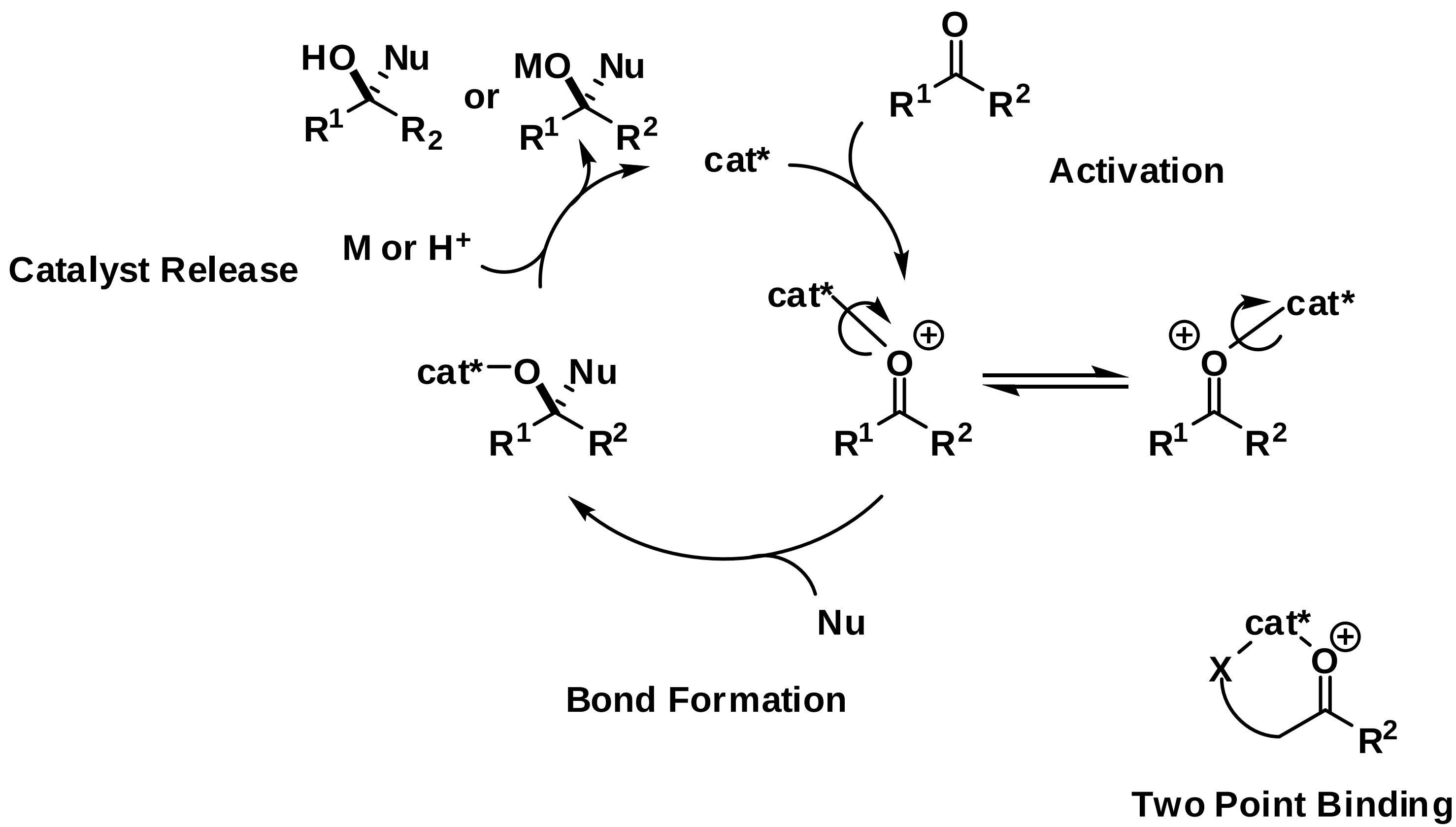
2.1.2 Allylation and Ene Reactions

2.1.3 Other Nucleophiles for Carbonyl Addition

2.1.4 Mannich Reaction

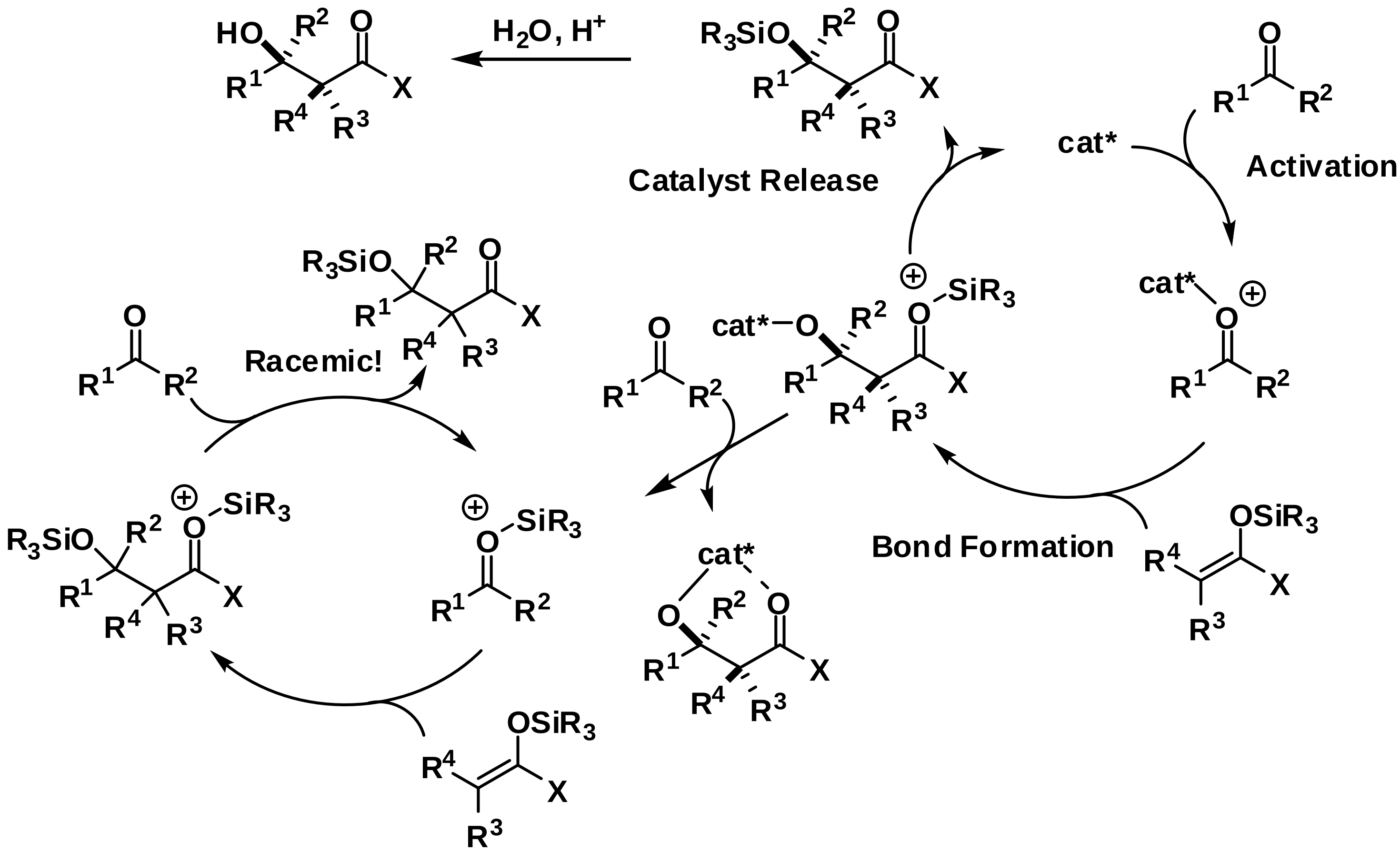
2.1.5 Other Nucleophiles for Imine Addition

2.1 Carbonyl and Imine Activation: Introduction



2.1.1 Aldol Reaction: General Scheme

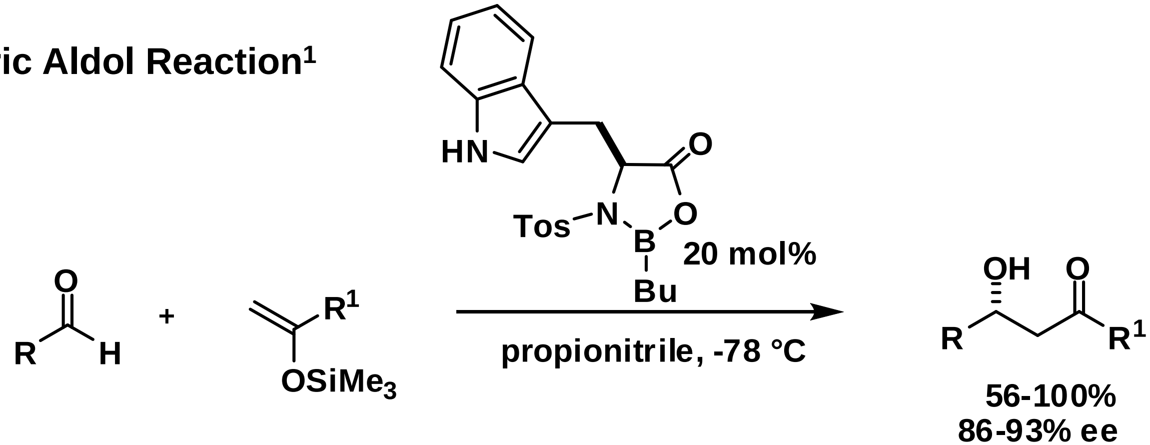
General Catalytic Cycle for Asymmetric Mukaiyama Aldol Reaction



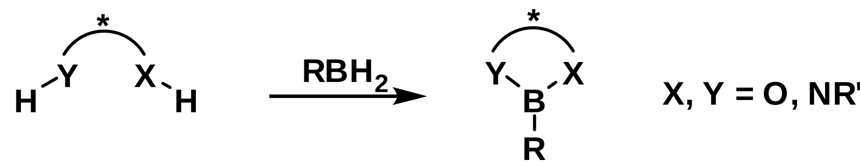
For aldol reactions: difficult to prevent competing racemic cycle!

2.1.1 Aldol Reaction: Early Examples

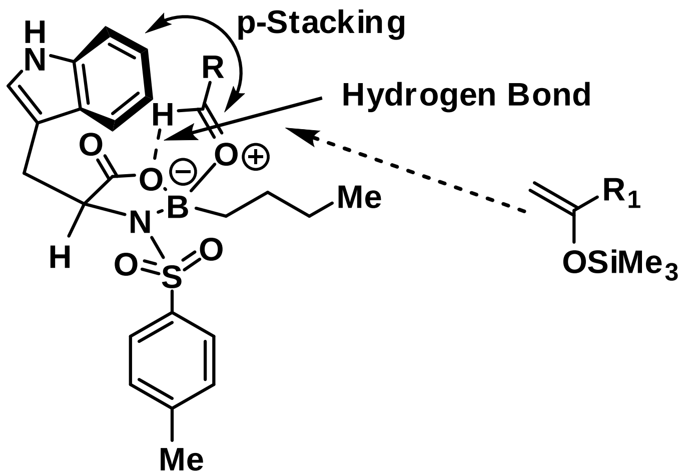
Corey Asymmetric Aldol Reaction[1]



Chiral Boranes: Design of ”Chiral BF_3 ”



Model for Selectivity



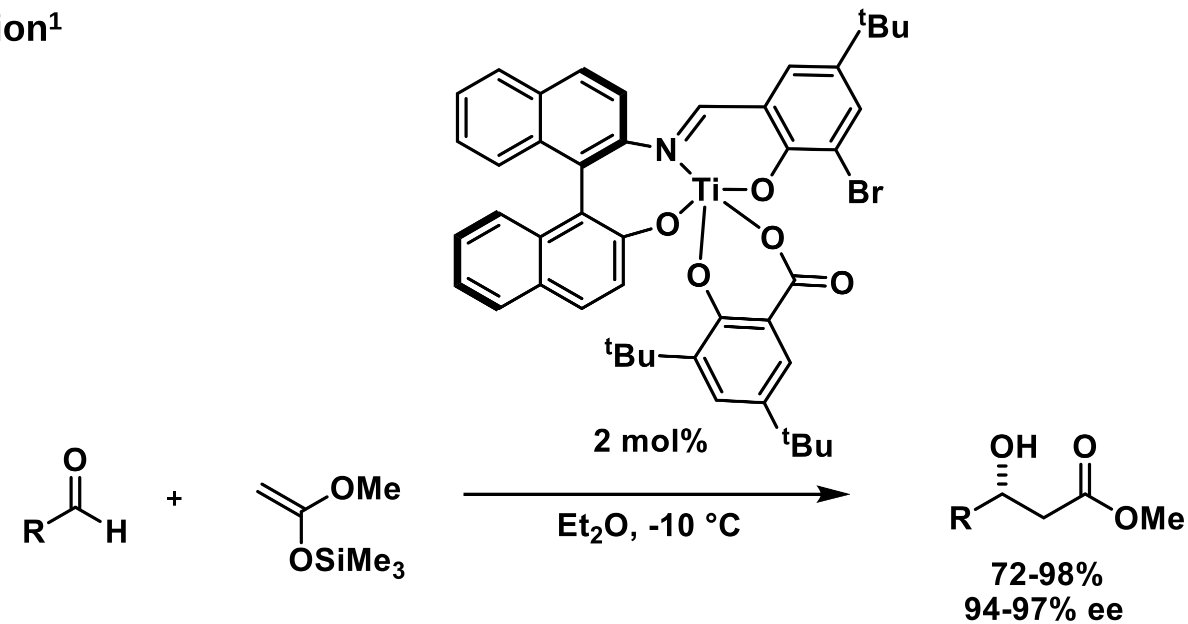
- 2 interactions to fixe substrate: hydrogen bond and π stacking
- One face blocked by indole of tryptophane

(1) E. J. Corey, C. L. Cywin, T. D. Roper, *Tetrahedron Lett.* **1992,** *33,* 6907-6910**.**

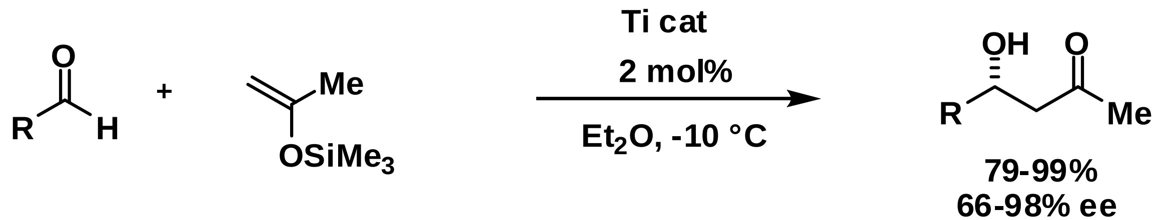
2.1.1 Aldol Reaction: Early Examples

Carreira Asymmetric Aldol Reactions

Acetate Aldol Reaction[1]



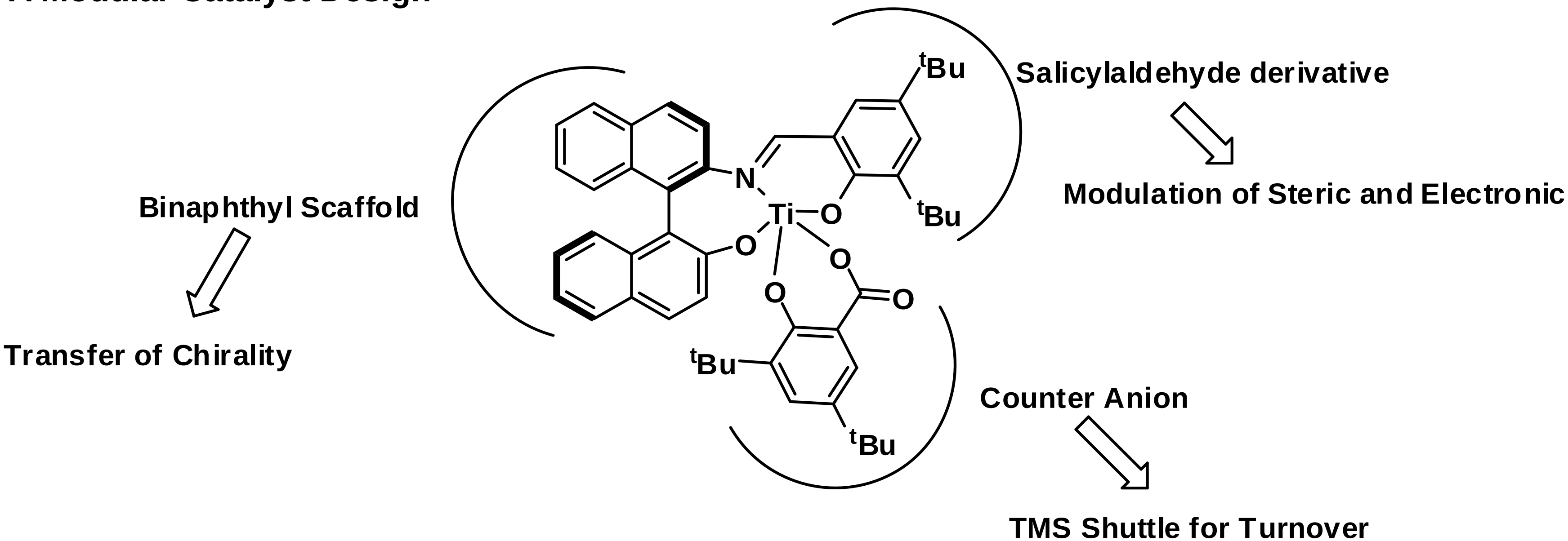
Acetone Aldol Reaction[2]



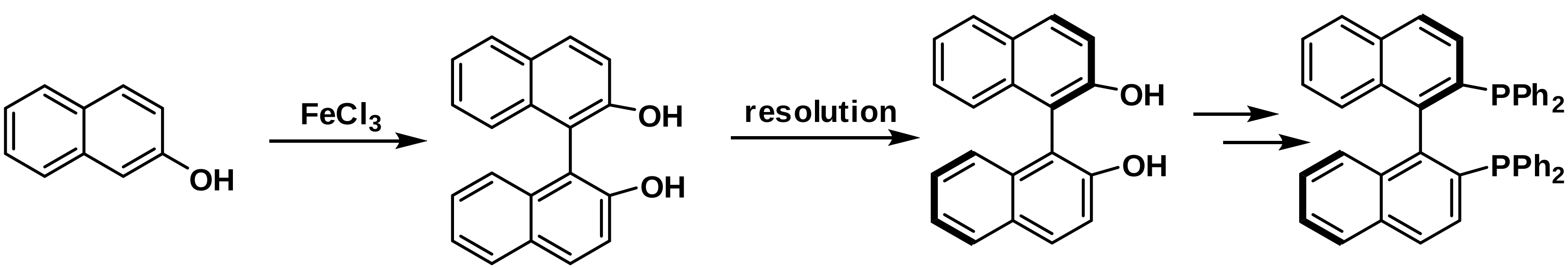
(1) Carreira, E. M.; Singer, R. A.; Lee, W. S. *J. Am. Chem. Soc.* **1994,** *116,* 8837-8838.
(2) Carreira, E. M.; Lee, W.; Singer, R. A. *J. Am. Chem. Soc.* ***1995,*** *117,* 3649-3650.

2.1.1 Aldol Reaction: Early Examples

A Modular Catalyst Design



Binaphthyl, a Privileged Scaffold for Asymmetric Catalysis

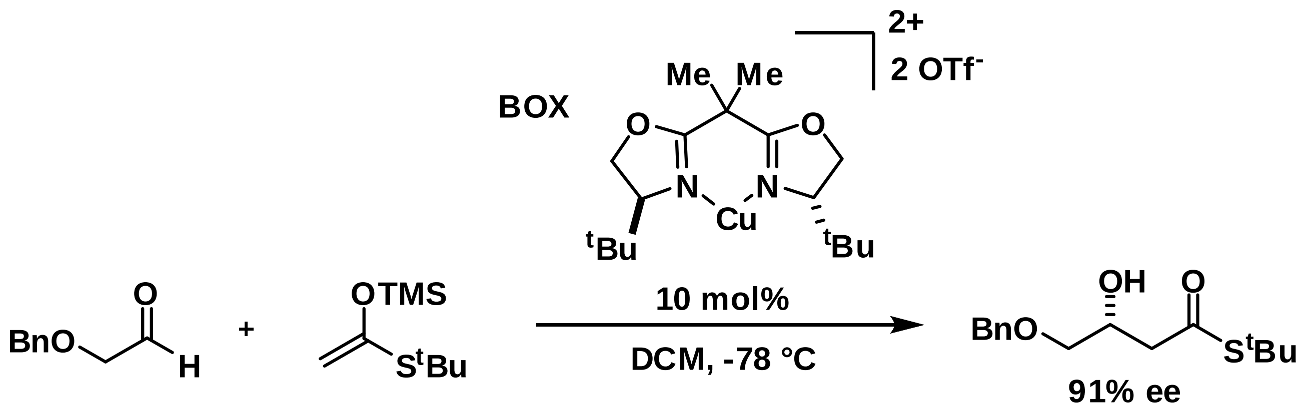


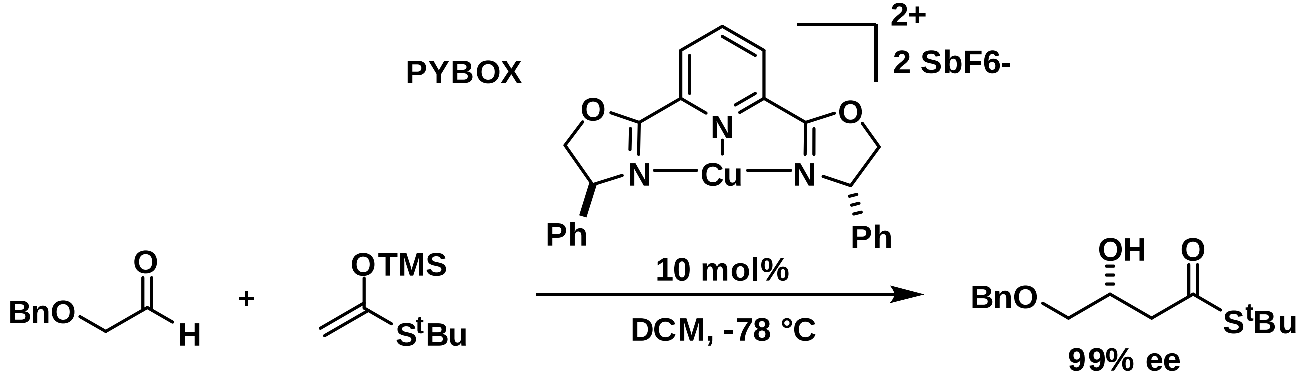
(R)-Binol

(R)-Binap

2.1.1 Aldol Reaction: Two Points Binding

Evans Aldol with (Benzyloxy)acetaldehyde[1]



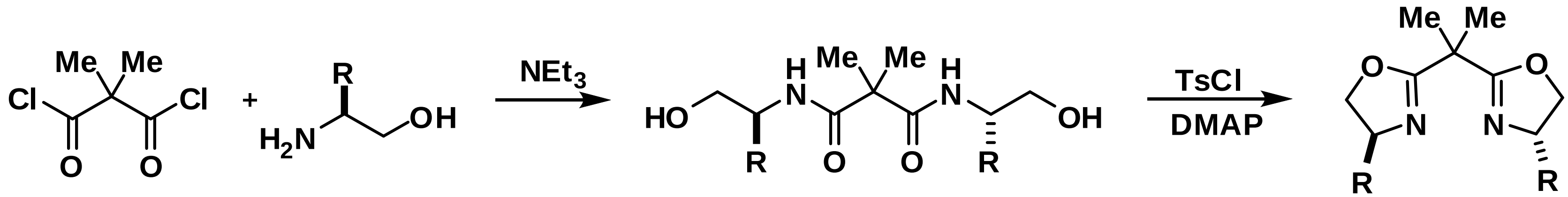


(1) Evans, D. A.; Kozlowski, M. C.; Murry, J. A.; Burgey, C. S.; Campos, K. R.; Connell, B. T.; Staples, R. J. *J. Am. Chem. Soc.* **1999,** *121***,** 669-685**.**

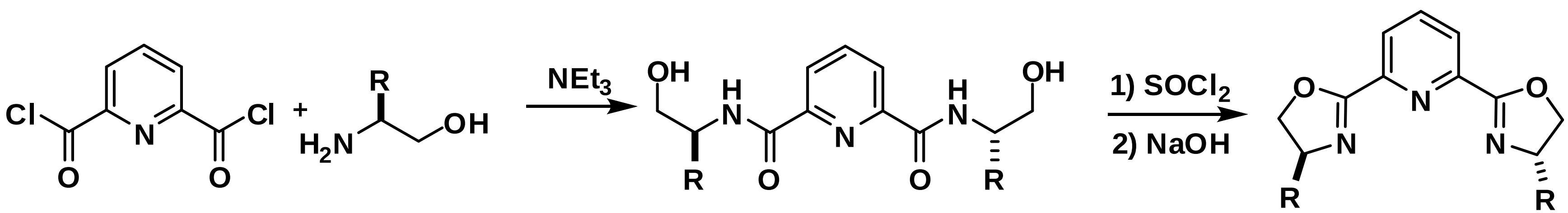
2.1.1 Aldol Reaction: Two Points Binding

BOX and PYBOX: Privileged ligands

BOX (BisOXazoline)



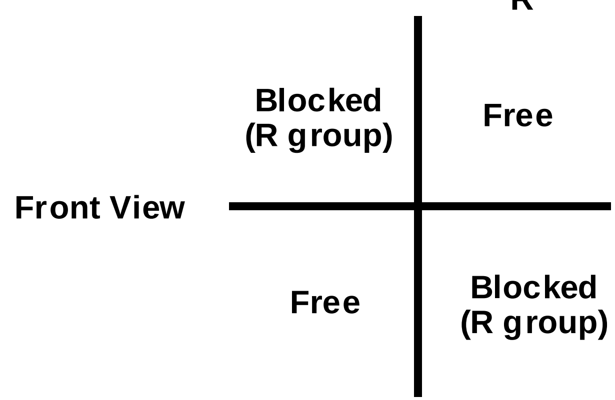
PYBOX (PYridineBisOXazoline)



C_2 – Symmetric Ligands

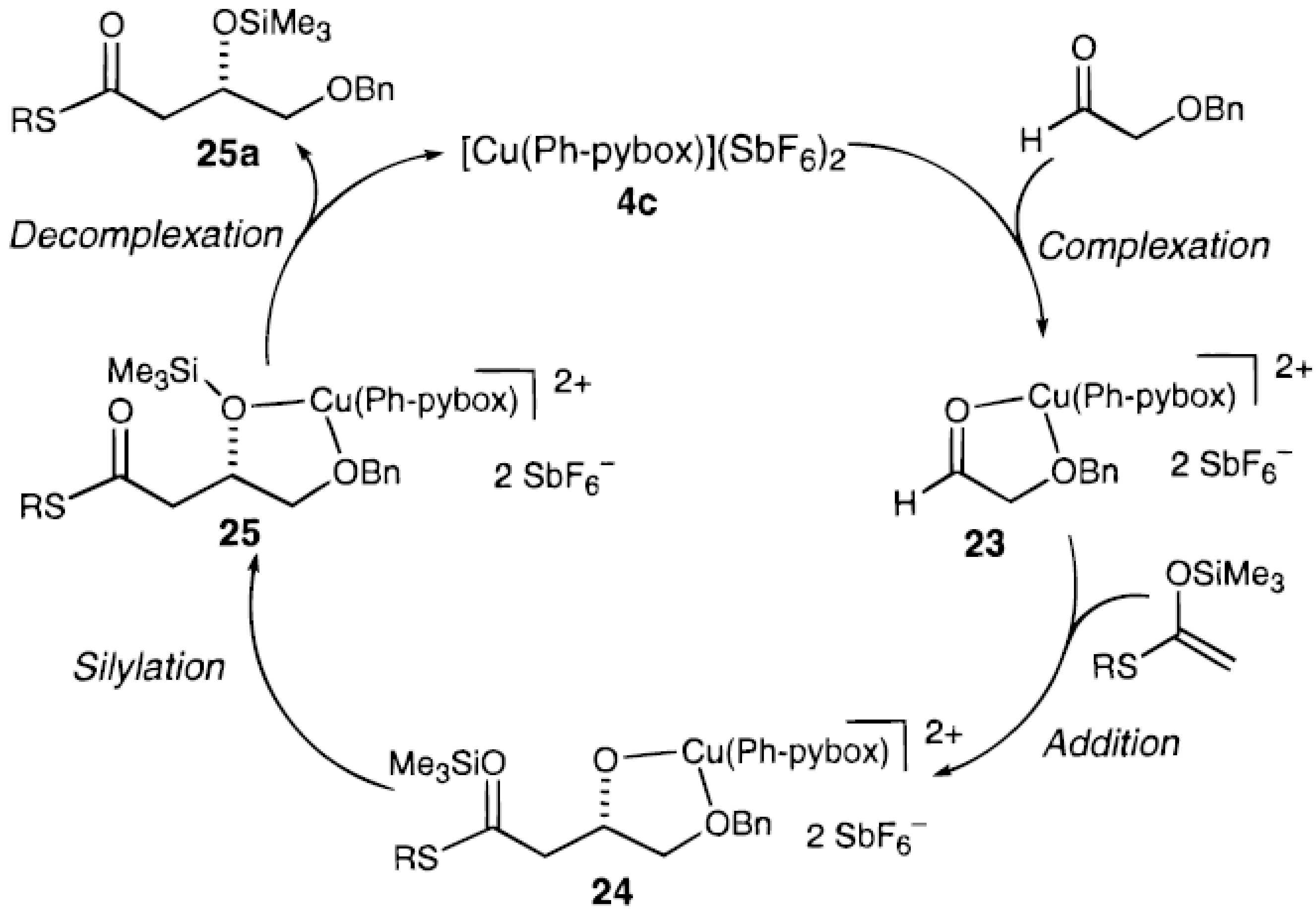
⬇

Well-Defined Steric Disposition



2.1.1 Aldol Reaction: Two Points Binding

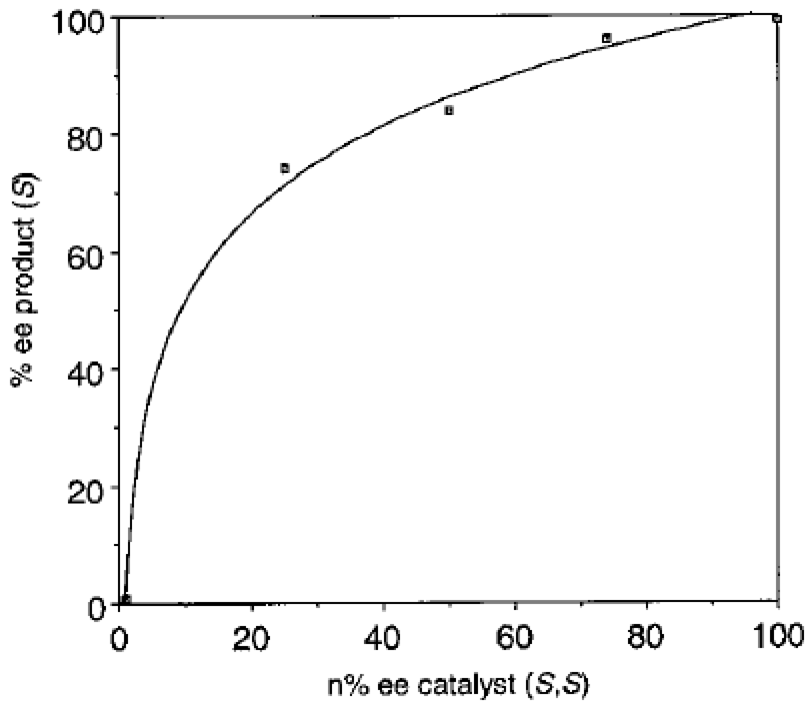
Mechanism Proposed by Evans[1]

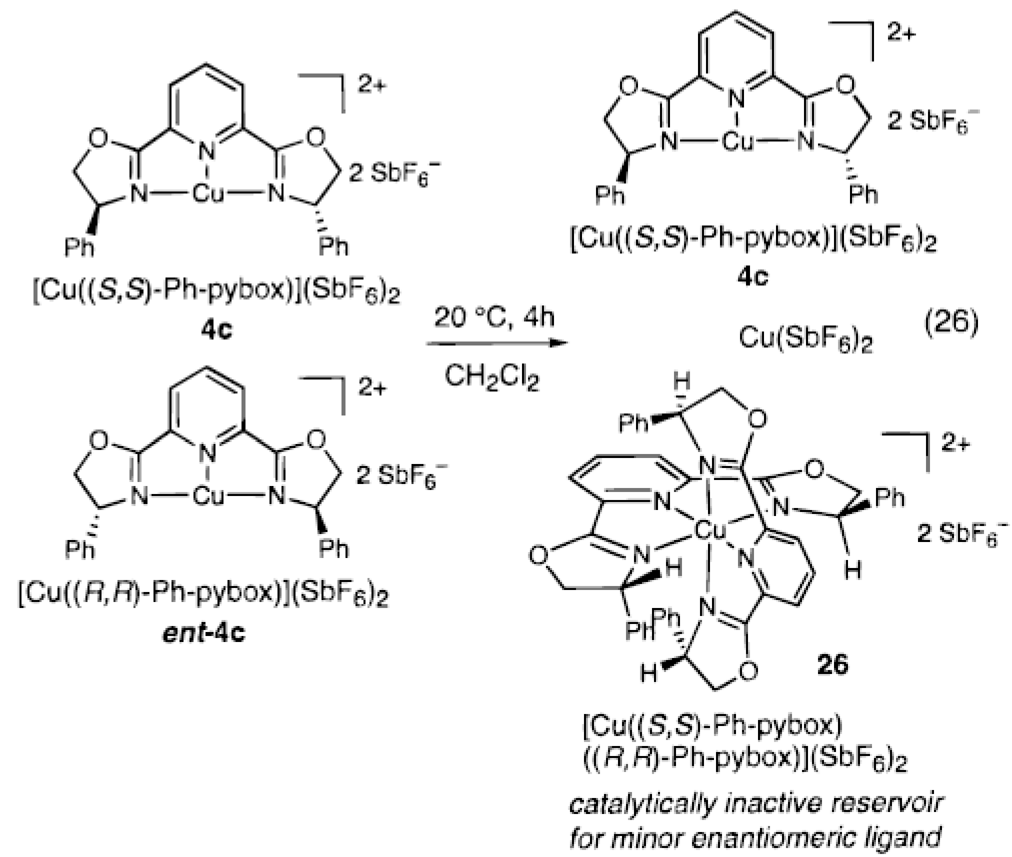


(1) Evans, D. A.; Kozlowski, M. C.; Murry, J. A.; Burgey, C. S.; Campos, K. R.; Connell, B. T.; Staples, R. J. *J. Am. Chem. Soc.* **1999,** *121*, 669-685.

2.1.1 Aldol Reaction: Two Points Binding

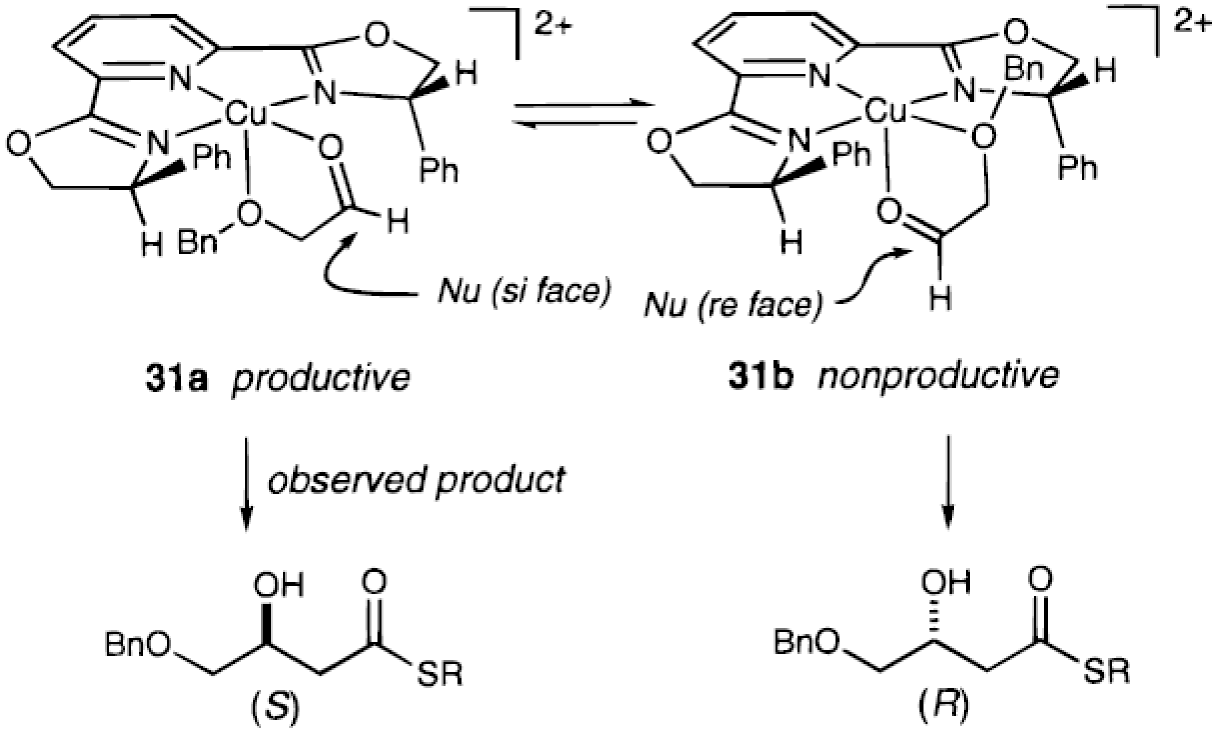
Observed Non-Linear Effect: Reservoir Effect





2.1.1 Aldol Reaction: Two Points Binding

Model for Selectivity

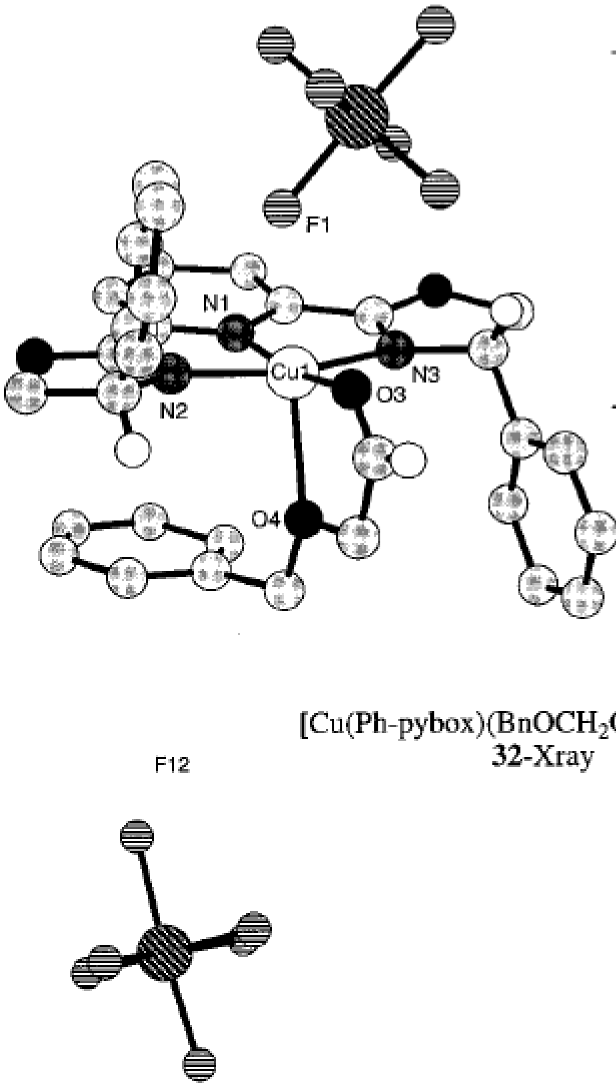


Based on the structure of similar copper complexes, a square planar pyramidal coordination is expected, but how to rationalize the binding mode of the substrate?

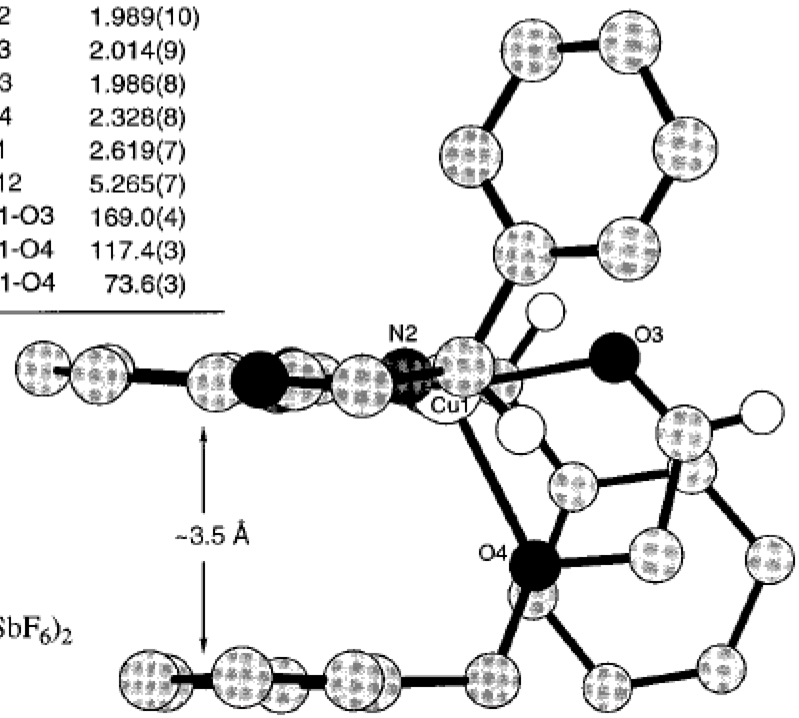
2.1.1 Aldol Reaction: Two Points Binding

Crystal Structure of Substrate-Catalyst Adduct

Selected bond lengths (Å) and angles (deg)	
Cu1-N1	1.952(10)
Cu1-N2	1.989(10)
Cu1-N3	2.014(9)
Cu1-O3	1.986(8)
Cu1-O4	2.328(8)
Cu1-F1	2.619(7)
Cu1-F12	5.265(7)
N1-Cu1-O3	169.0(4)
N1-Cu1-O4	117.4(3)
O3-Cu1-O4	73.6(3)

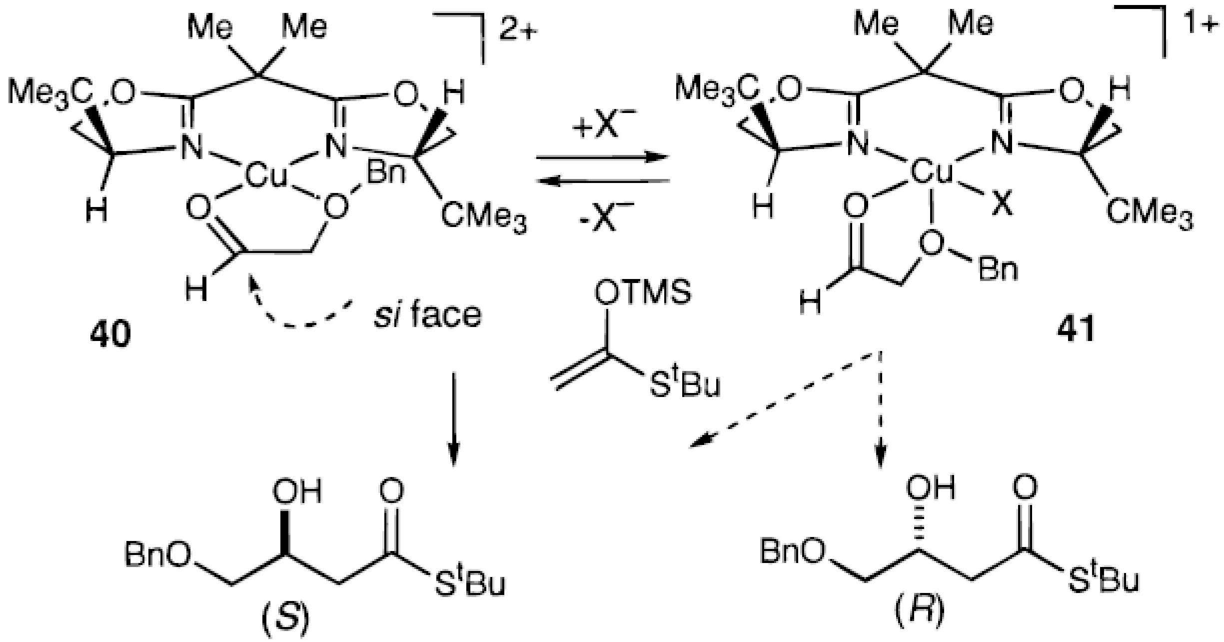


$[Cu(Ph\text{-}pybox)(BnOCH_2CHO)](SbF_6)_2$
32-Xray



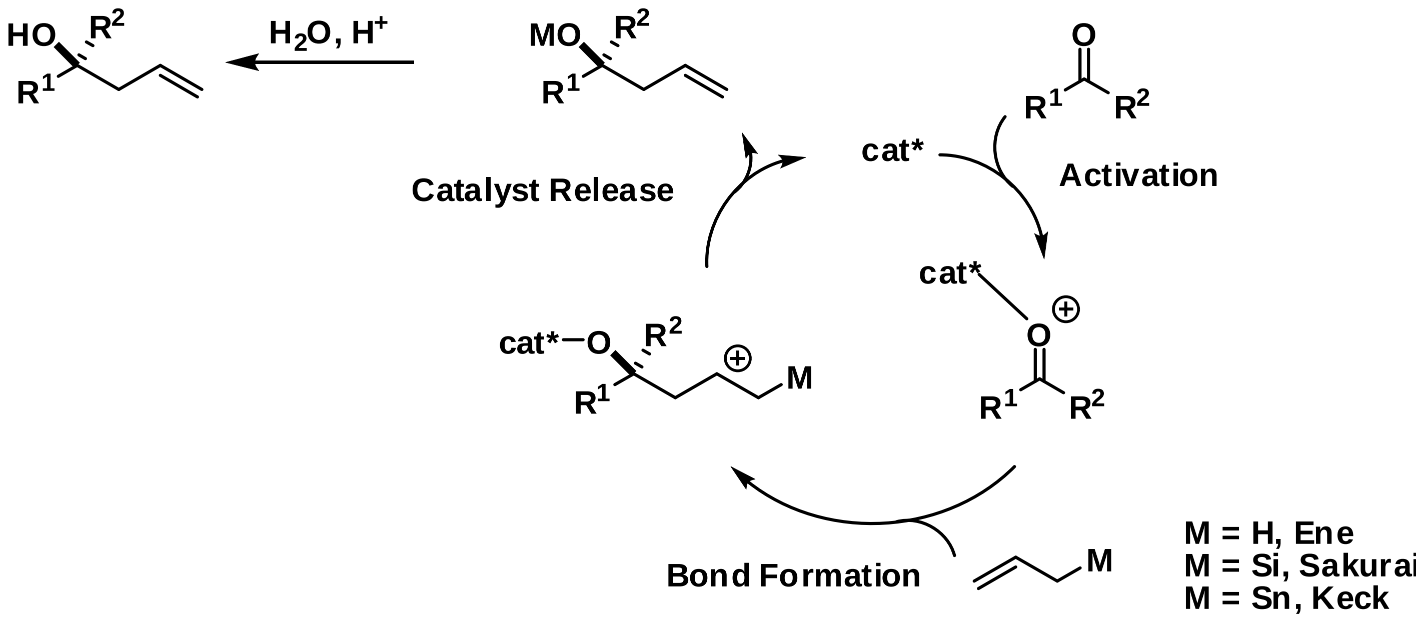
2.1.1 Aldol Reaction: Two Points Binding

BOX ligand: absolute stereochemistry of product is dependent of counter anion!

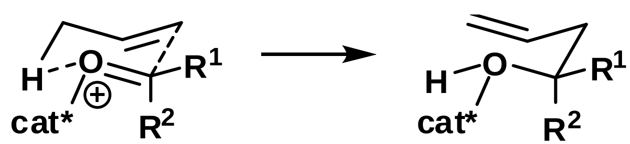


Observed with X = SbF_6 Observed with X = OTf

2.1.2 Allylation Reactions: Sakurai and Ene Reactions

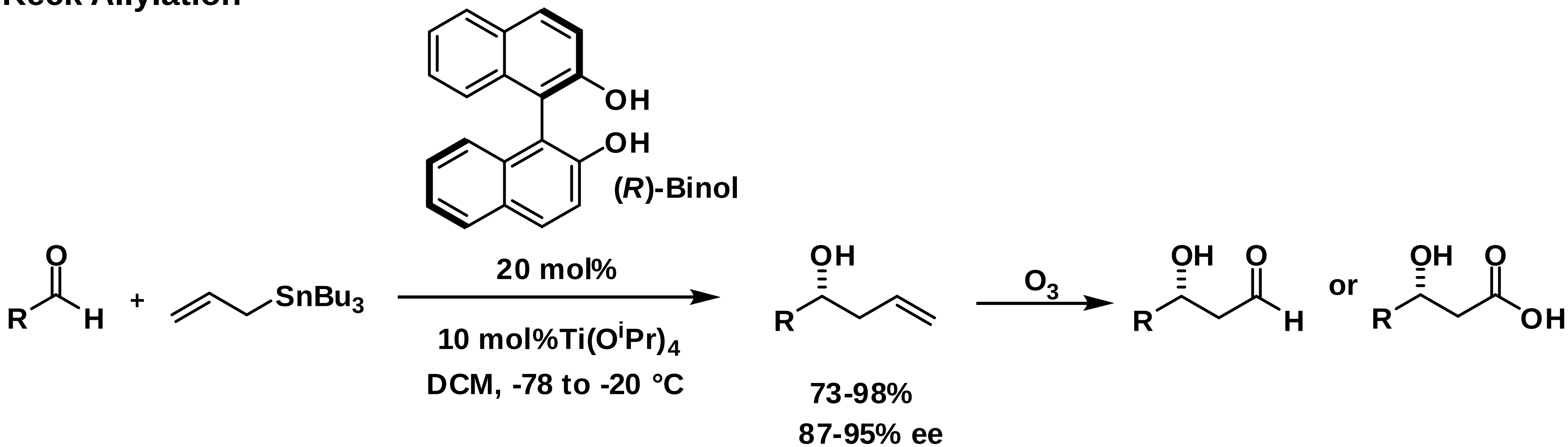


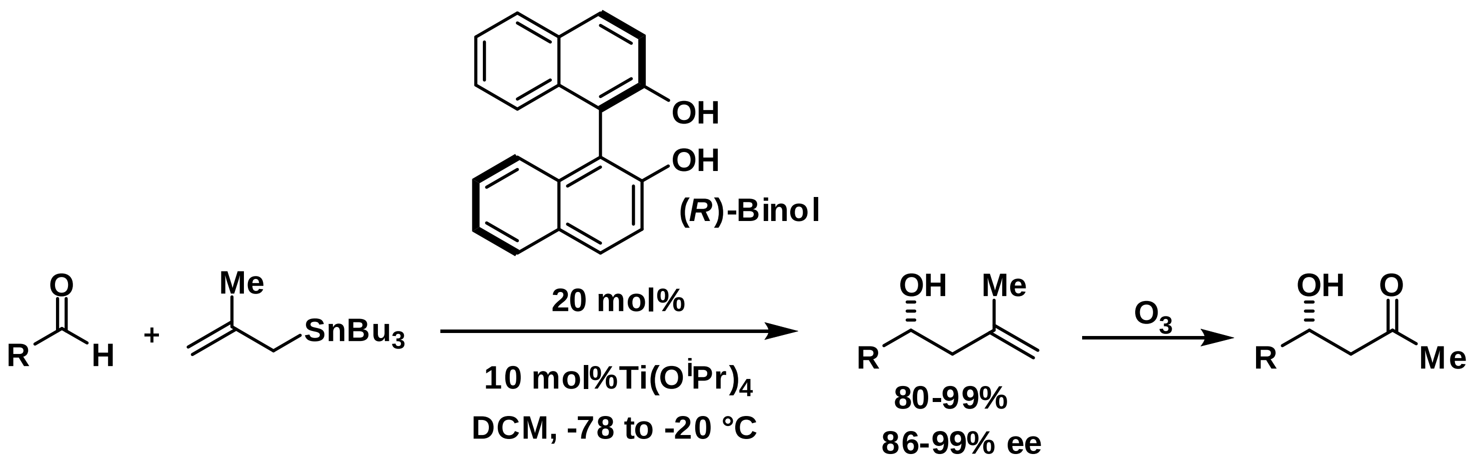
For the ene, the reaction is usually synchronous via a chair transition state



2.1.2 Allylation Reactions: Keck Allylation

Keck Allylation[1,2]



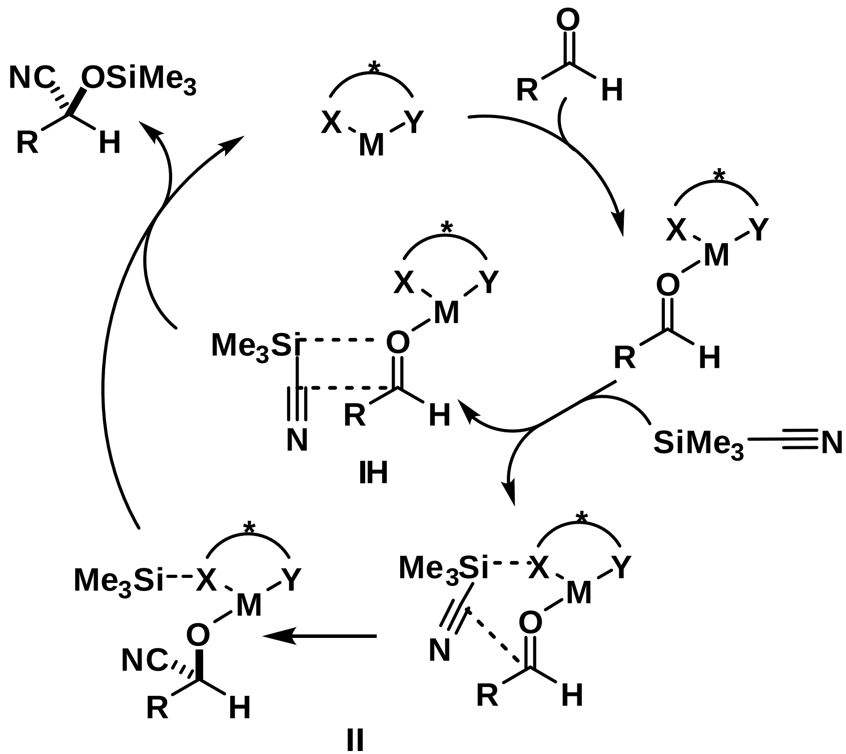


The catalyst (unknown structure!) is prepared directly before reaction

(1) Keck, G. E.; Tarbet, K. H.; Geraci, L. S. *J. Am. Chem. Soc.* **1993,** *115*, 8467-8468. (2) Keck, G. E.; Krishnamurty, D.; Grier, M. C. *J. Org. Chem.* **1993,** *58*, 6543-6544.

2.1.3 Other Nucleophiles: TMSCN

General Considerations for the Silylcyanation of Aldehydes

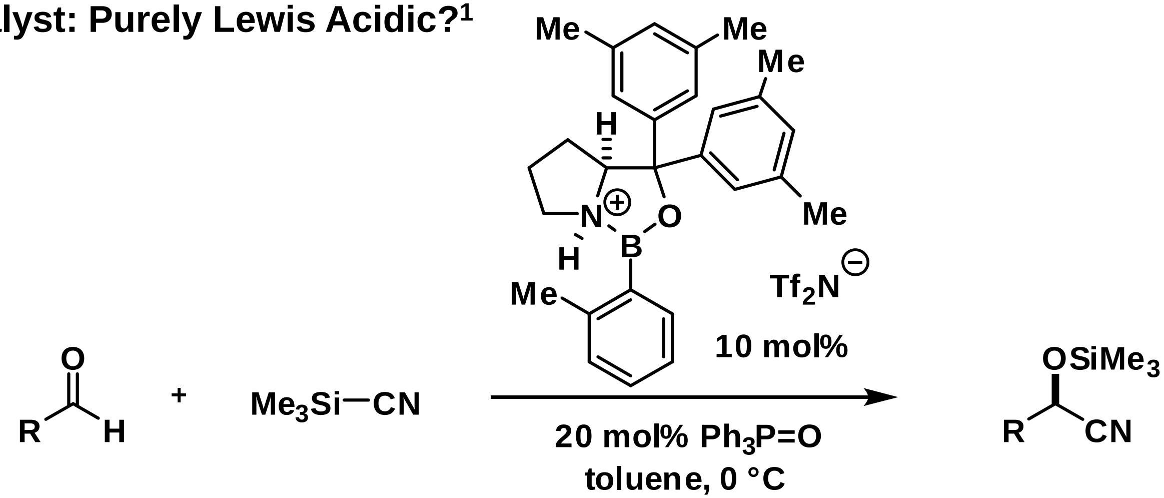


- Two Mechanisms can be envisaged
  - **I** Direct silylcyanation
  - **II** Activation of the silyl group via a heteroatom of the ligand

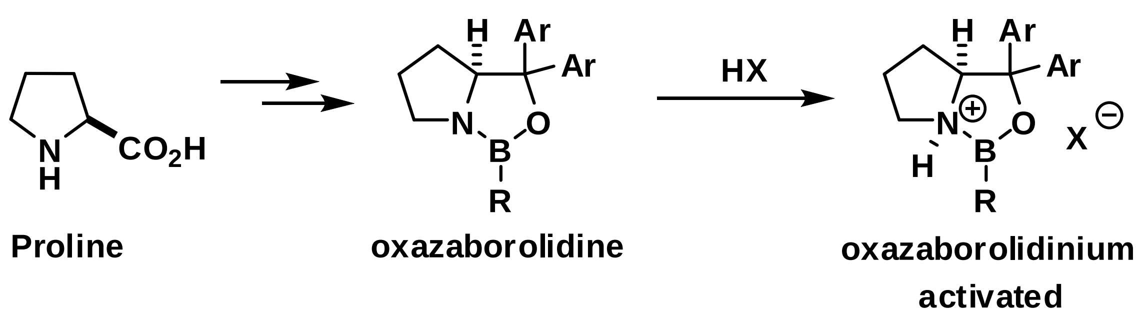
➡ Modern reactions are designed on dual activation

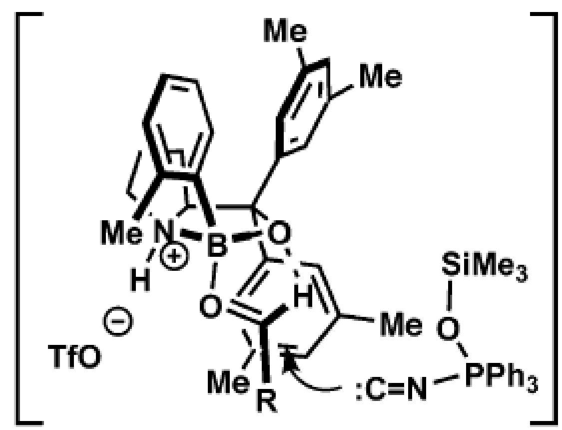
2.1.3 Other Nucleophiles: TMSCN

Corey Boron Catalyst: Purely Lewis Acidic?[1]

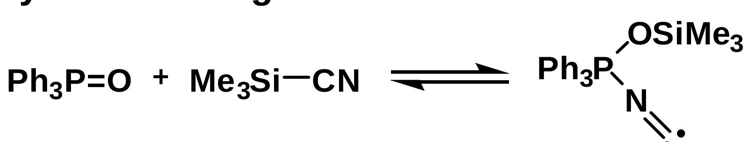


The Privileged Proline Scaffold and Bronsted Acid Activation of Lewis Acid





A New Cyanation Reagent?

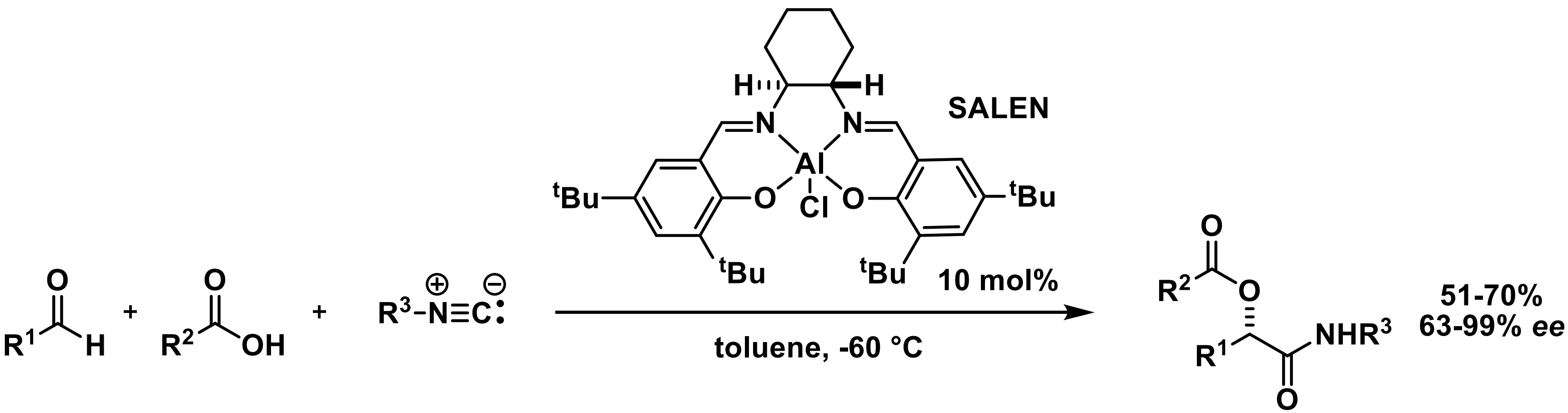


Without $Ph_3P=O$: Very low selectivity!

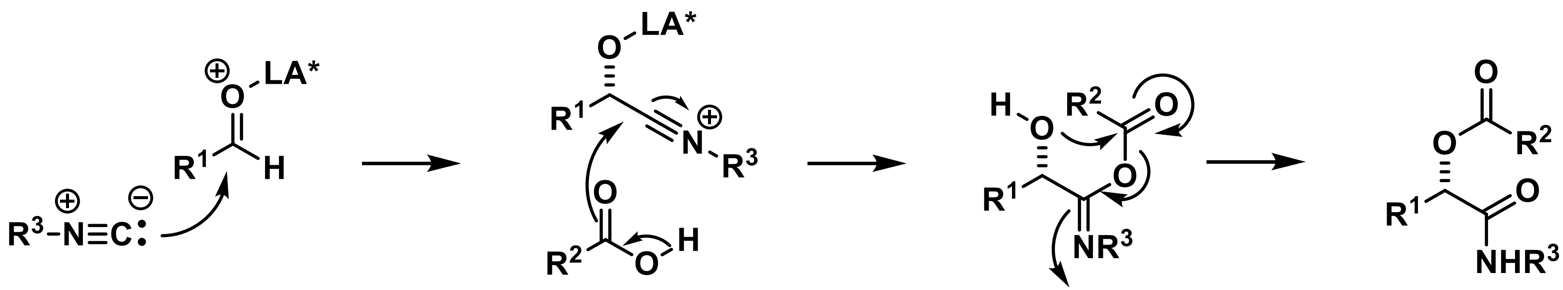
(1) Ryu, D. H.; Corey, E. J. *J. Am. Chem. Soc.* **2004,** *126,* 8106-8107. (2) Ryu, D. H.; Corey, E. J. *J. Am. Chem. Soc.* **2005,** *127,* 5384-5387.

2.1.3 Other Nucleophiles: Isonitriles

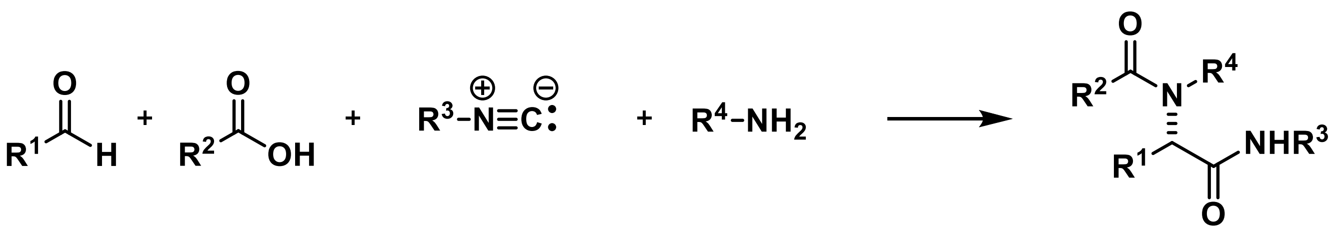
Asymmetric Passerini 3 Components Reaction[1]



Mechanism



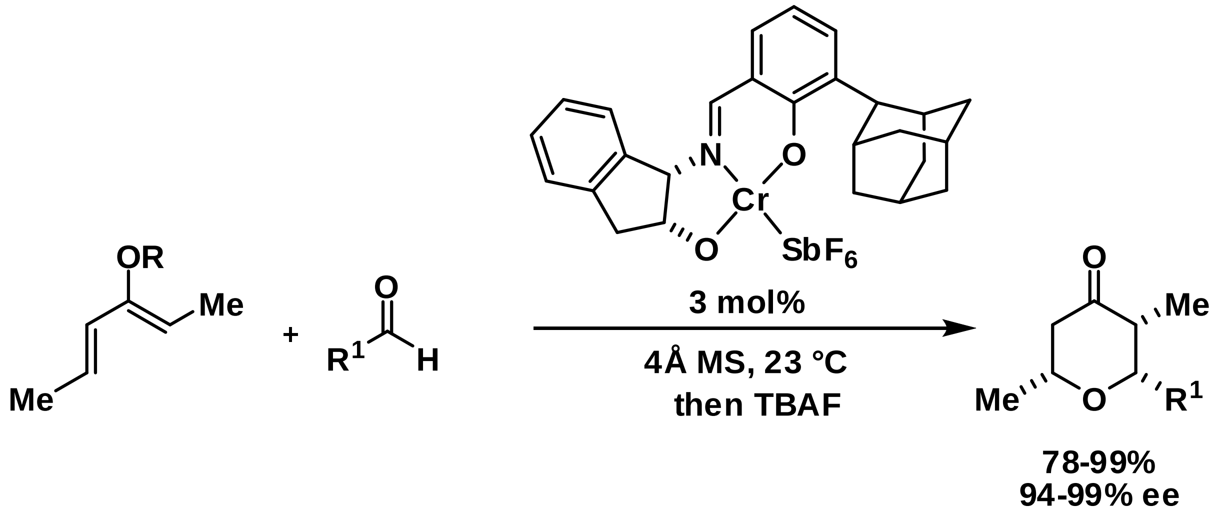
Other important multi-component reaction: Ugi 4 components reaction:



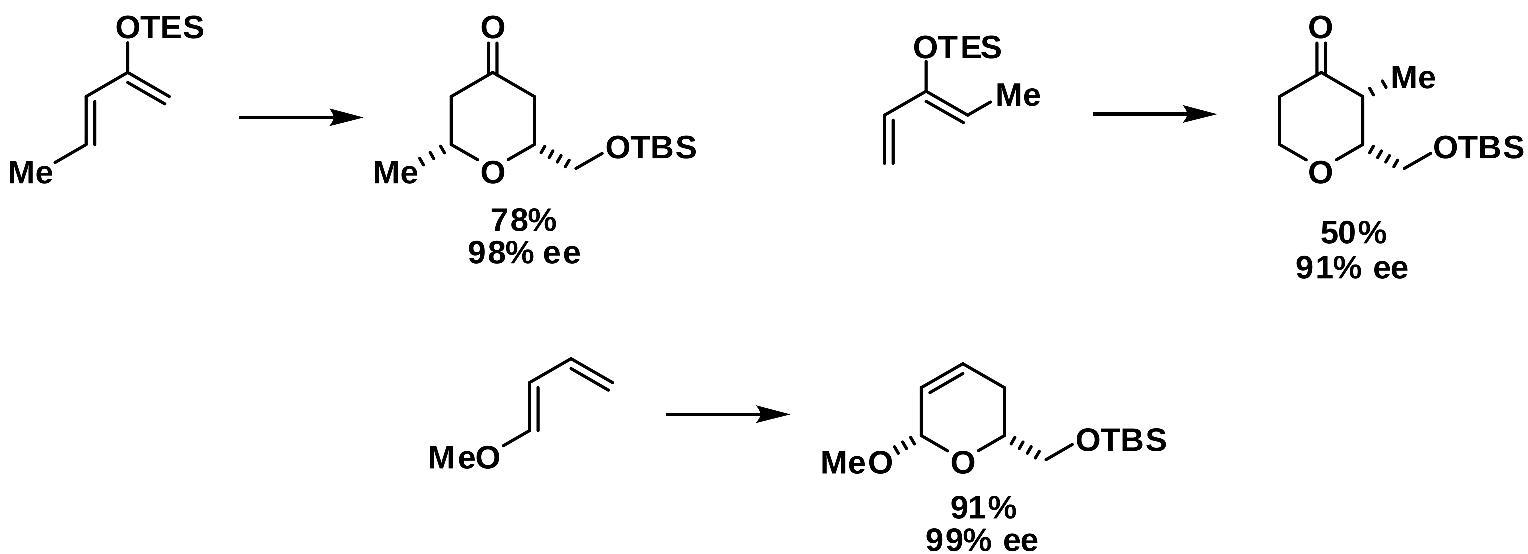
(1) Wang, S. X.; Wang, M. X.; Wang, D. X.; Zhu, J. P. *Angew. Chem., Int. Ed.* **2008**, *47*, 388.

2.1.3 Other Nucleophiles: Hetero Diels-Alder

Jacobsen: Cr-Catalyzed Hetero-Diels Alder Reaction with Aldehydes



Other Dienes



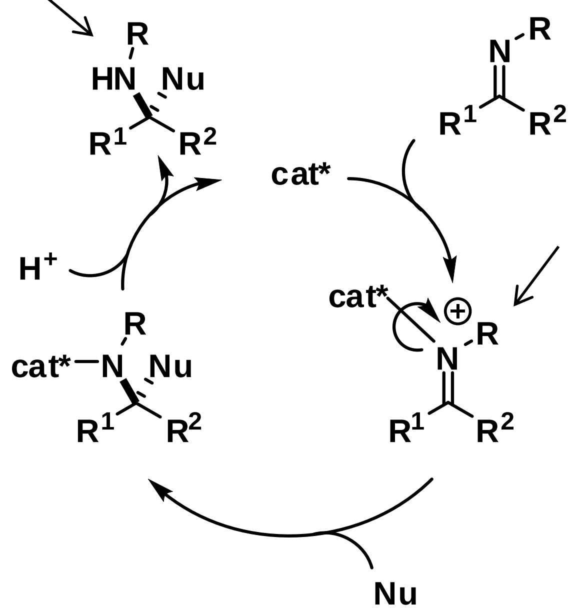
(1) Dossetter, A. G.; Jamison, T. F.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **1999,** *38,* 2398-2400.

2.1.4 Mannich: Introduction

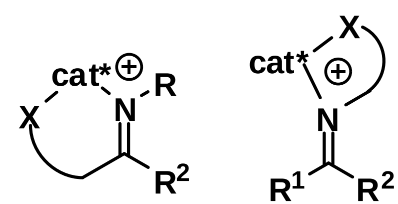
Comparison Imine - Carbonyl

Released Amine still very good ligand:
Catalyst release is more difficult

E or Z imine formed prior to reaction



Imine more basic: activation is easier

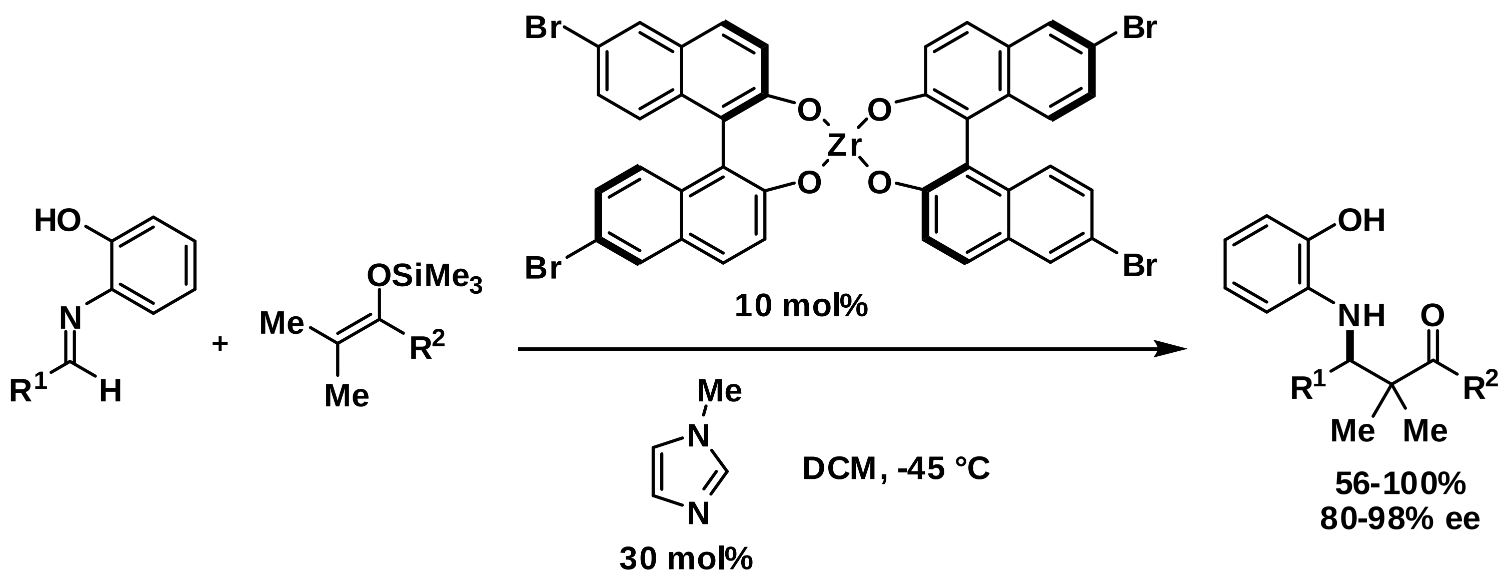


R group offers new possibilities for 2 points binding

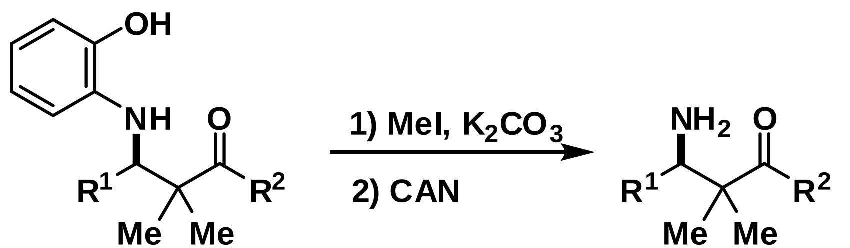
Choice of R group is essential to modulate activation and catalyst release!

2.1.4 Mannich: First Examples

Kobayashi: the First Efficient Catalytic System



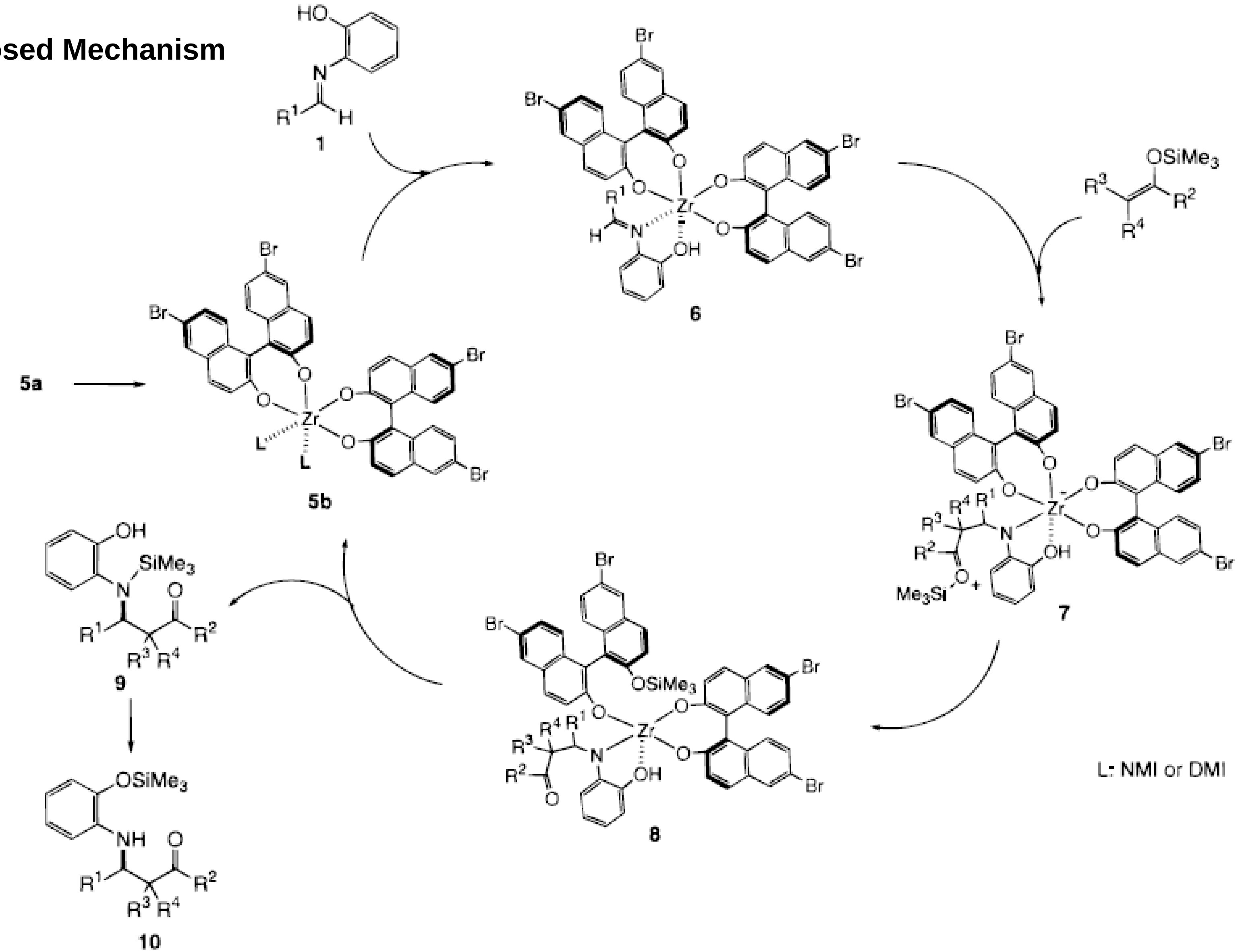
Deprotection of the Product



(1) Ishitani, H.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc.* **1997,** *119,* 7153-7154.

2.1.4 Mannich: First Examples

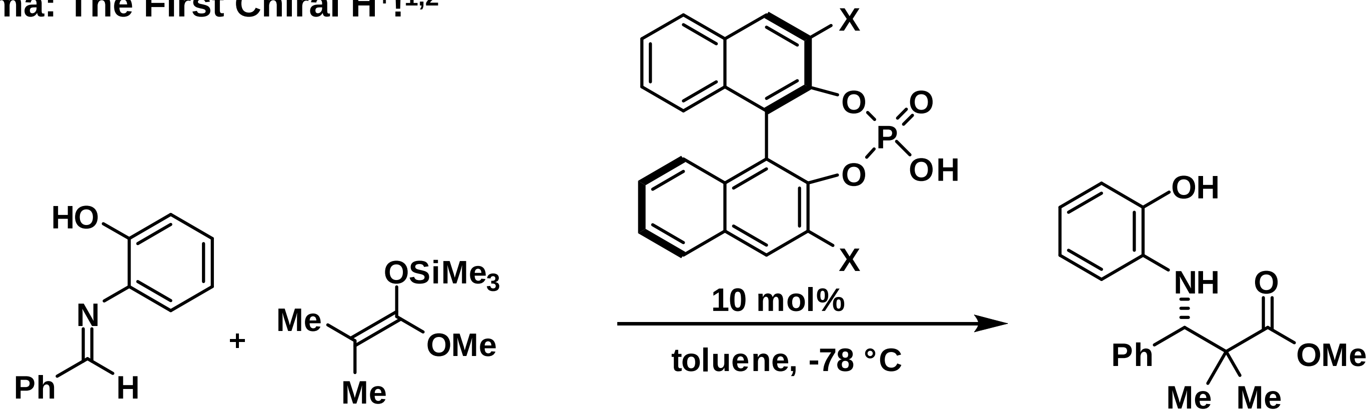
Proposed Mechanism

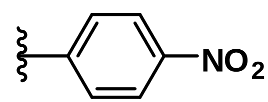


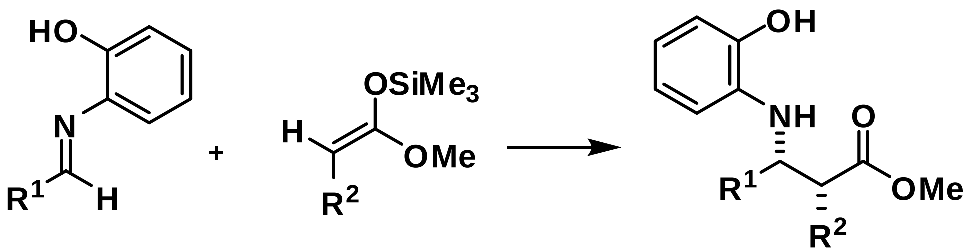
(1) Ishitani, H.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc.* **2000,** *122,* 8180-8186.

2.1.4 Mannich: Phosphoric acids

Akiyama: The First Chiral H+![1,2]



X	yield	ee
HH	57%	0%
Ph	100%	27%
	96%	87%

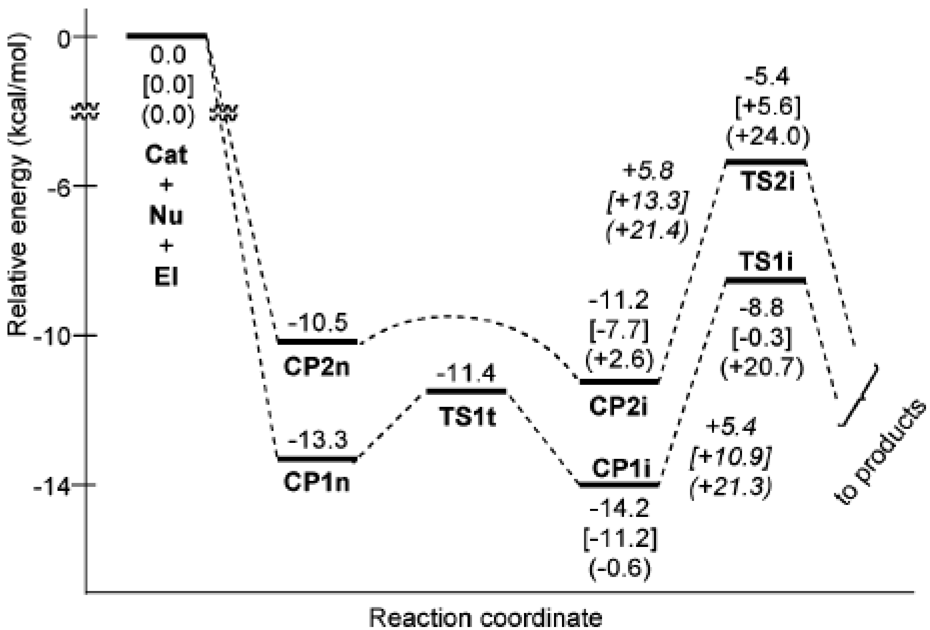


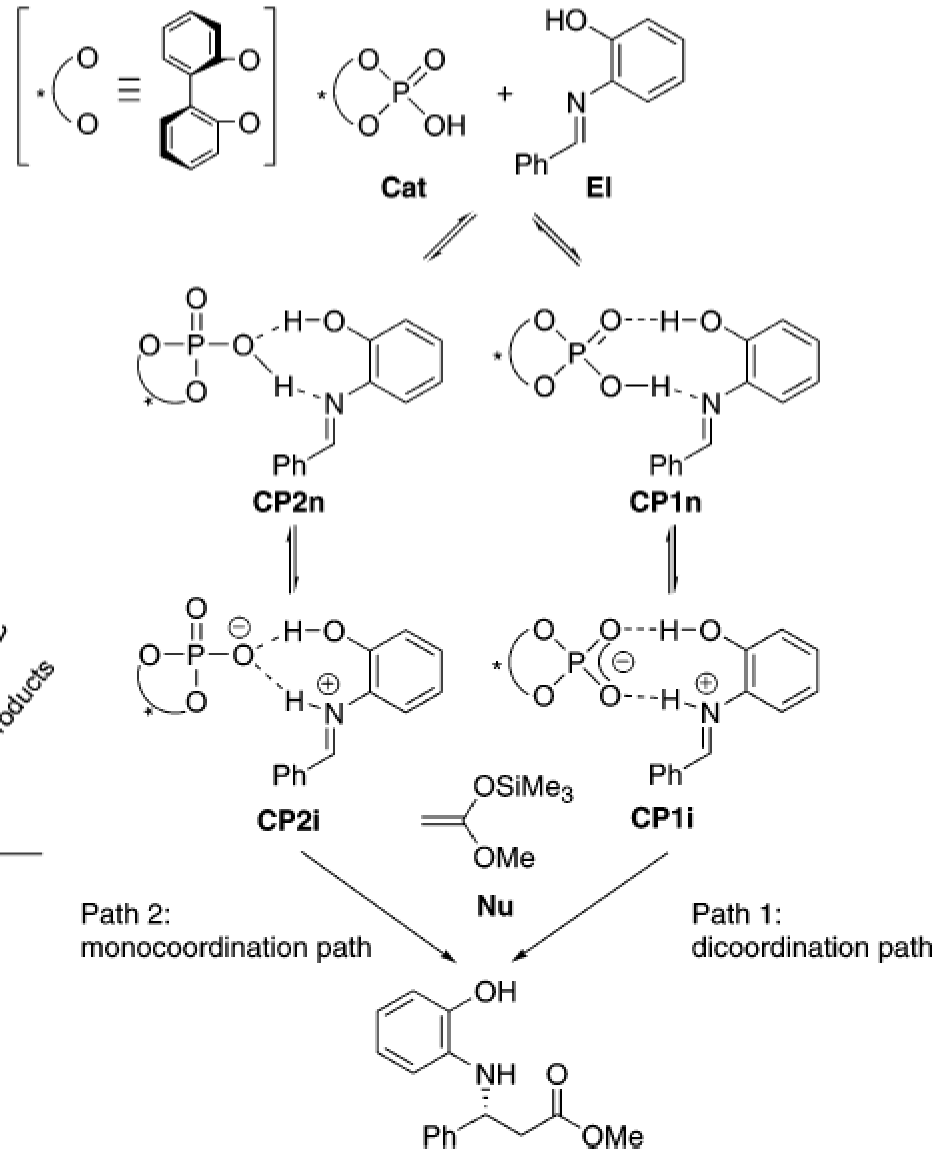
65-100%
85-96% ee
86:14-100:0 syn:anti

(1) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem., Int. Ed.* **2004,** *43,* 1566-1568. (2) Yamanaka, M.; Itoh, J.; Fuchibe, K.; Akiyama, T. *J. Am. Chem. Soc.* **2007,** *129,* 6756-6764.

2.1.4 Mannich: Phosphoric acids

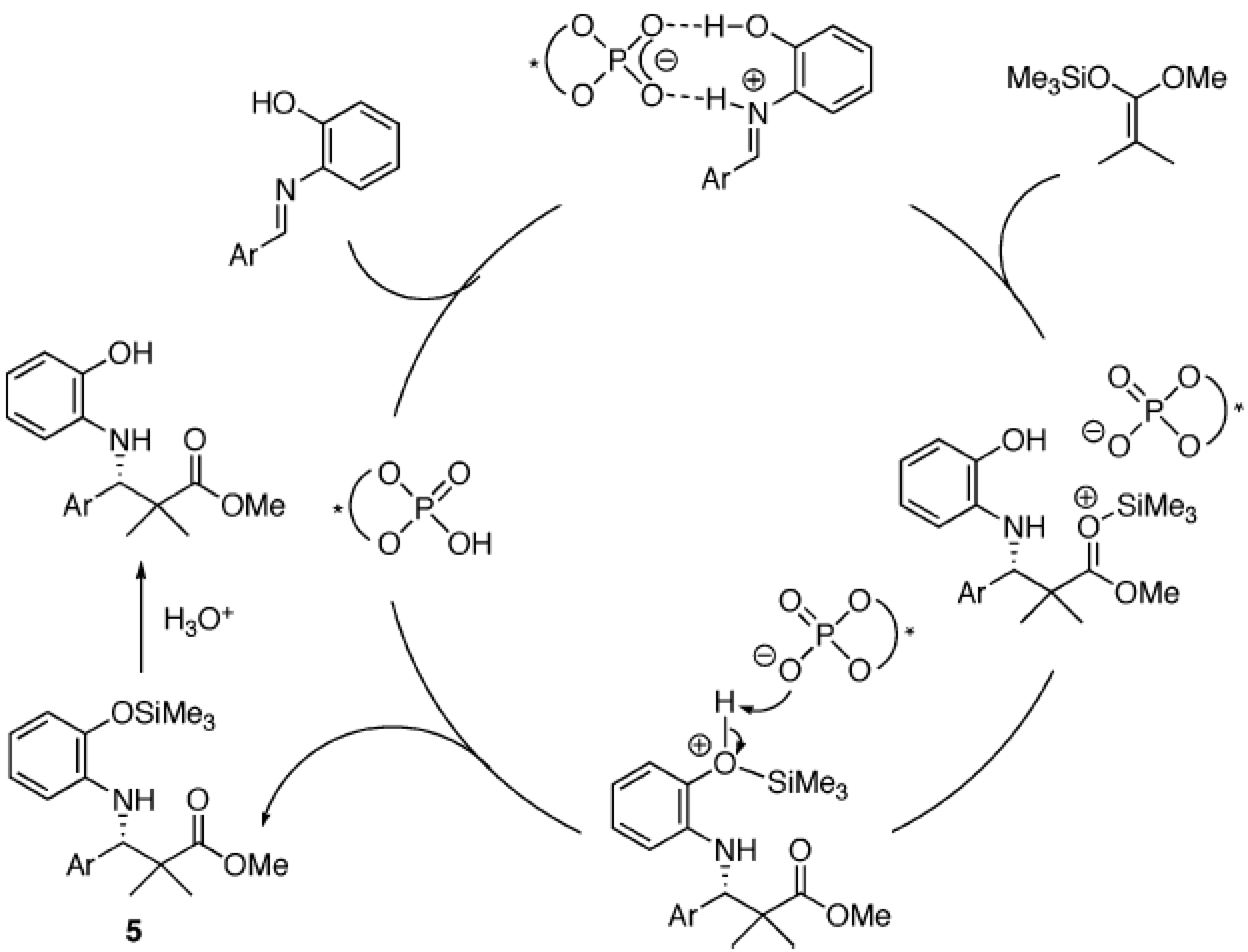
2 Pathways for Activation





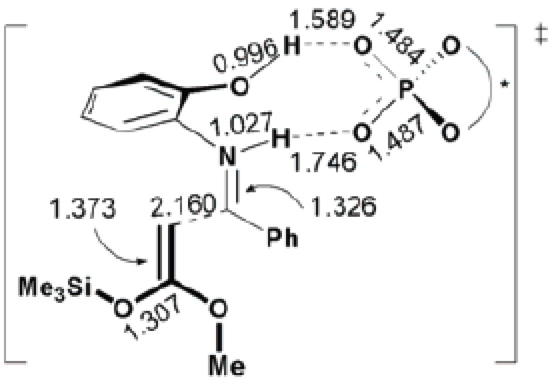
2.1.4 Mannich: Phosphoric acids

Proposed Mechanism

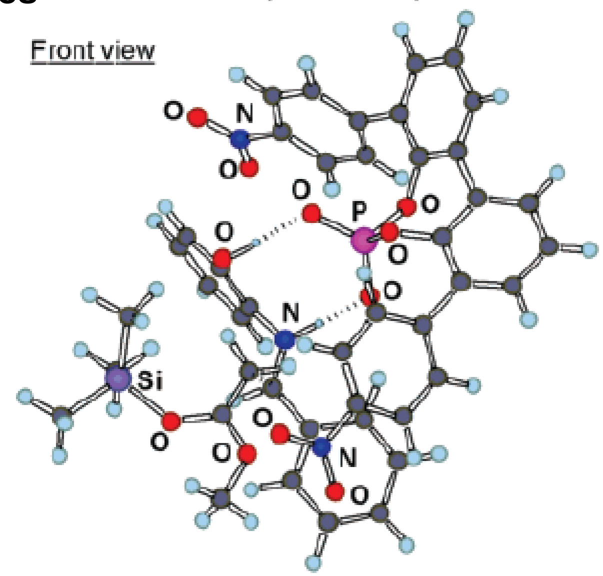


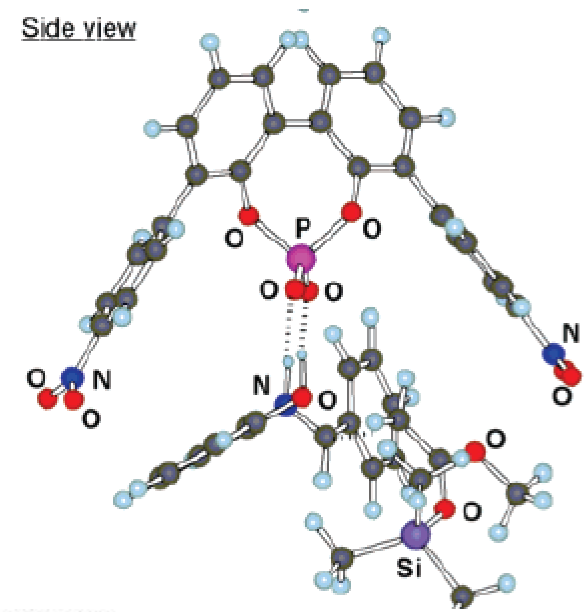
2.1.4 Mannich: Phosphoric acids

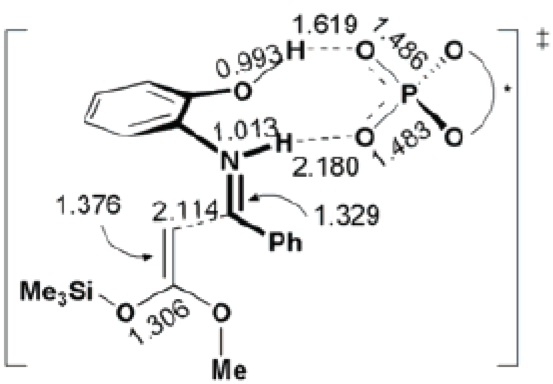
Calculation for Transition States



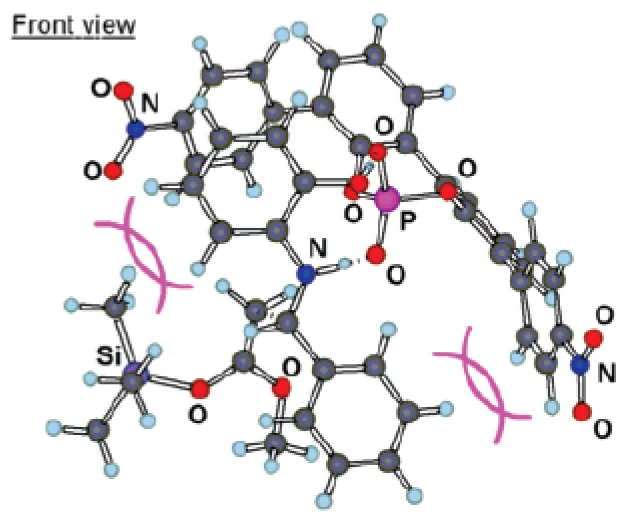
TS3r (0.0 kcal/mol)

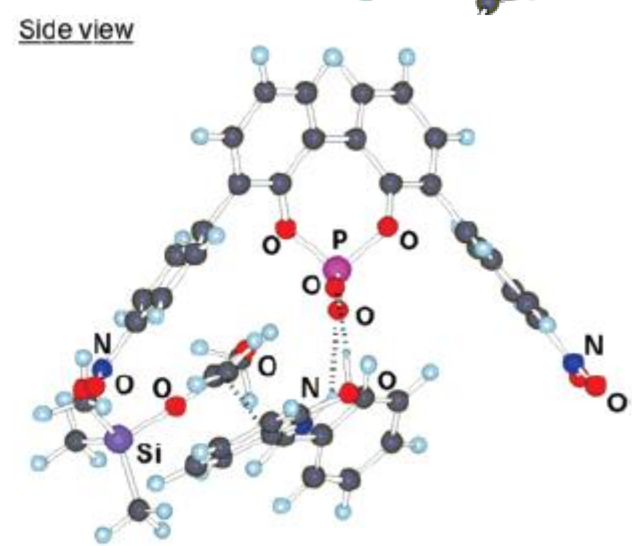






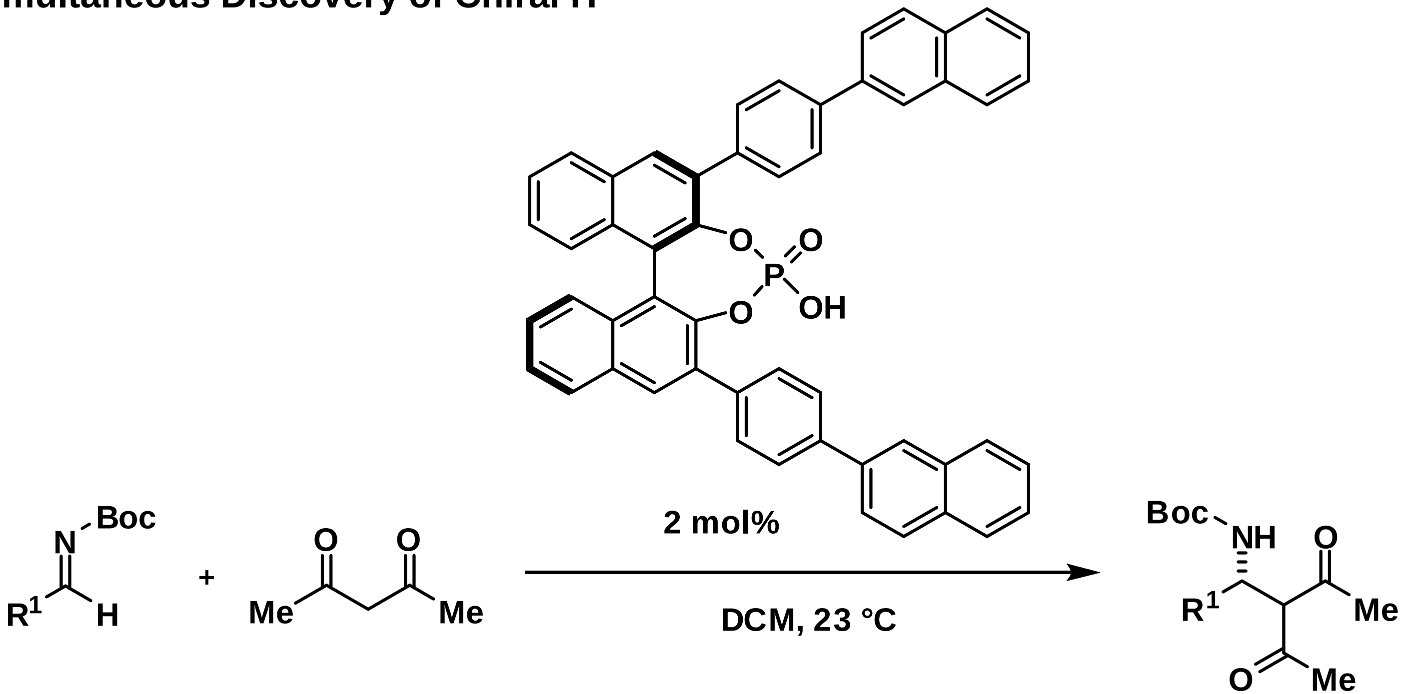
TS3s (+5.7 kcal/mol)



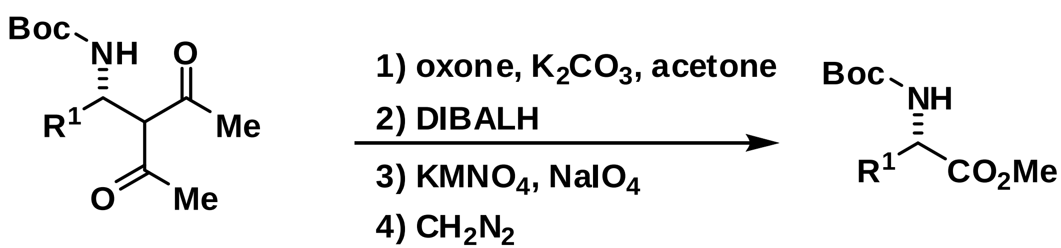


2.1.4 Mannich: Phosphoric acids

Terada Simultaneous Discovery of Chiral H+[1]



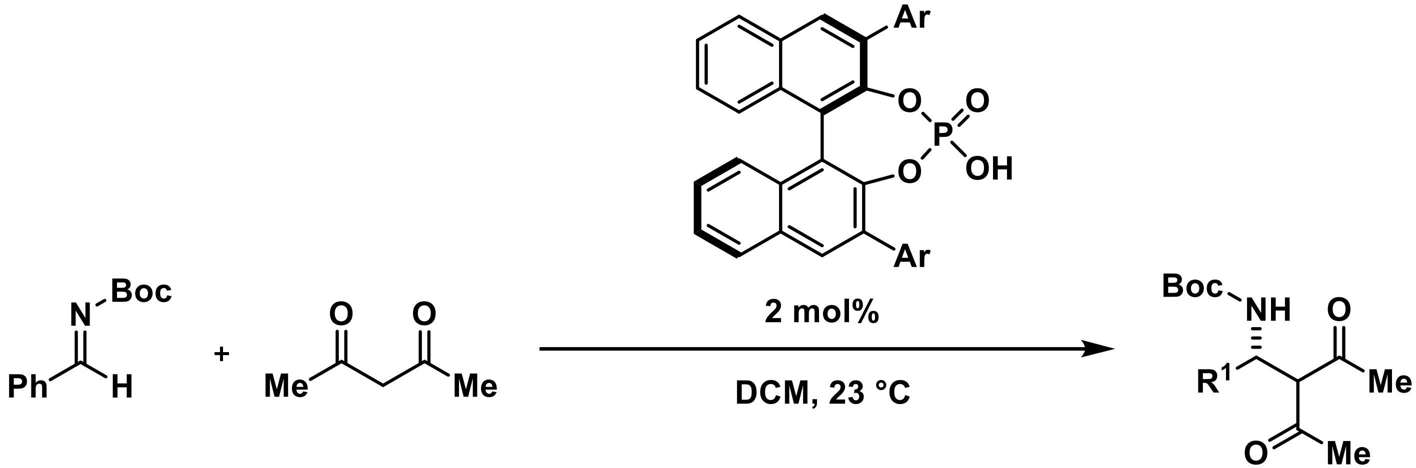
Transformation into Amino Acids



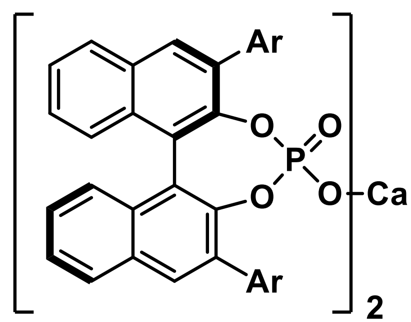
(1) Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004,** *126,* 5356-5357.

2.1.4 Mannich: Phosphoric acids

Is it really chiral Chiral H+[1]



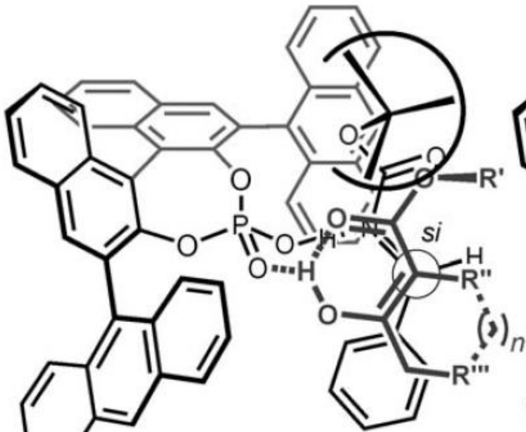
catalyst purified on SiO_2: 92% *ee*
catalyst washed with HCl: -93% *ee*



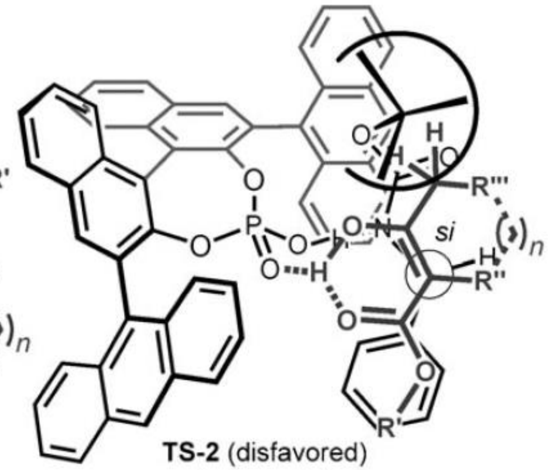
92% *ee*!

(1) Hatano, M.; Moriyama, K.; Maki, T.; Ishihara, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 3823-3826.

2.1.4 Mannich: Phosphoric acids



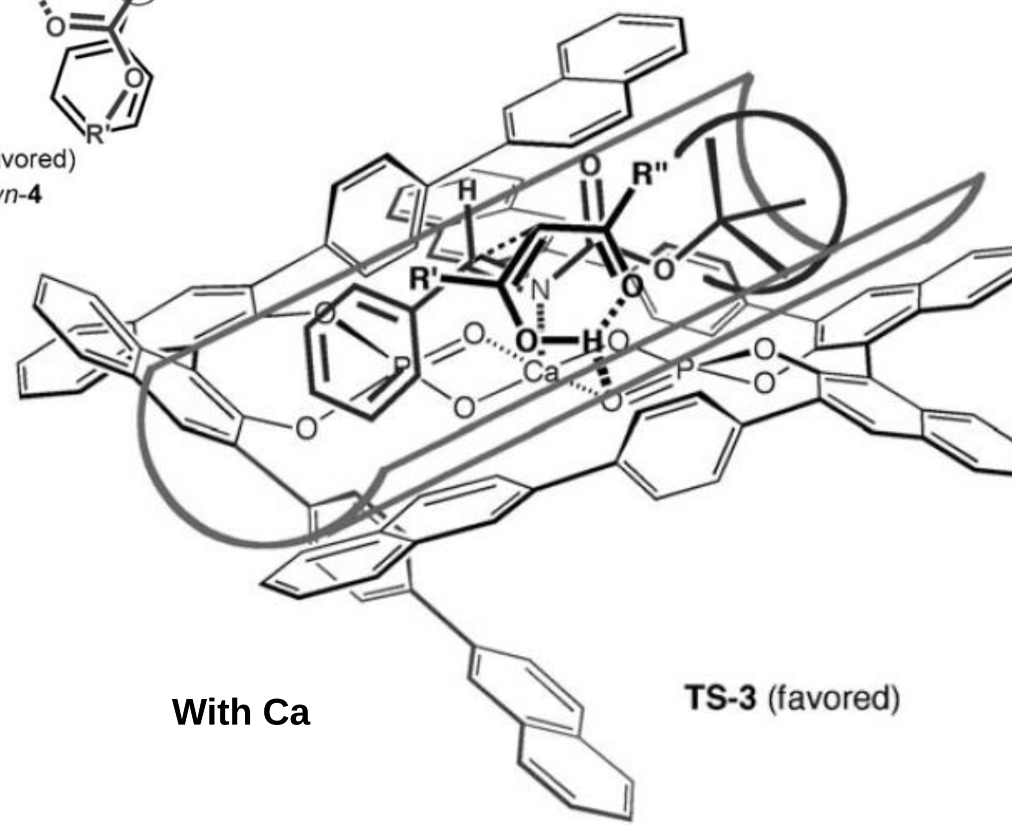
TS-1 (favored)
to be *anti*-**4**



TS-2 (disfavored)
to be *syn*-**4**

With H+

A more accurate model using bifunctional activation can explain these results (see chapter 4)!



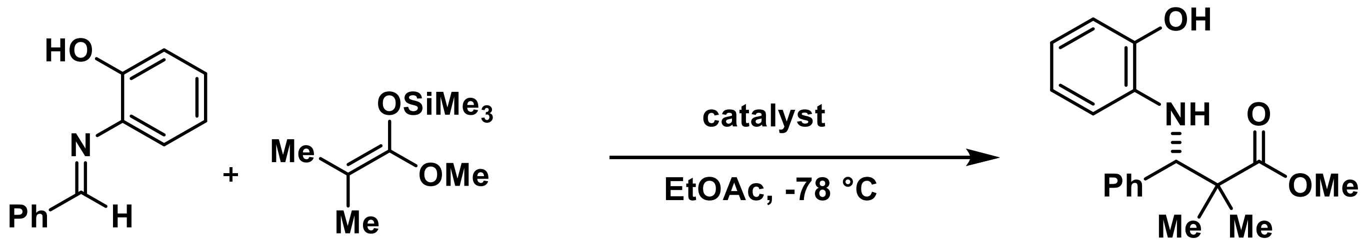
With Ca

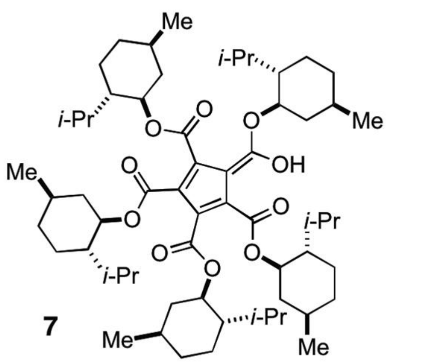
TS-3 (favored)

(1) Hatano, M.; Moriyama, K.; Maki, T.; Ishihara, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 3823-3826.

2.1.4 Mannich: Other acids

Lambert: New type of chiral Bronsted catalyst



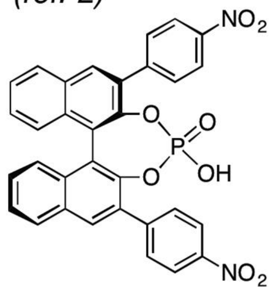


7

1 mol%
1 h
97% yield, 97% ee

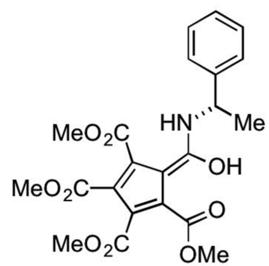
0.01 mol% (0.3 M)
48 h
90% yield, 97% ee

(ref. 2)



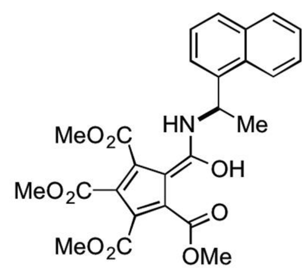
14

10 mol%, 24 h
98% yield, 89% ee
(toluene)



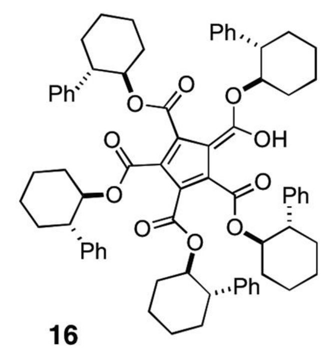
15

10 mol%, 6 h
88% yield, –30% ee



8

10 mol%, 8 h
85% yield, 44% ee



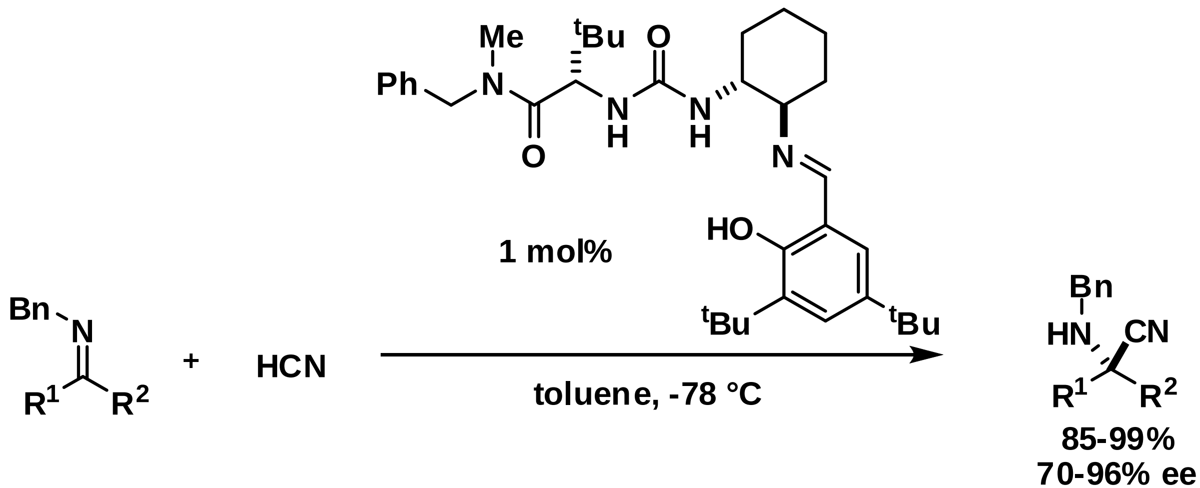
16

5 mol%, 5 min
90% yield, 89% ee

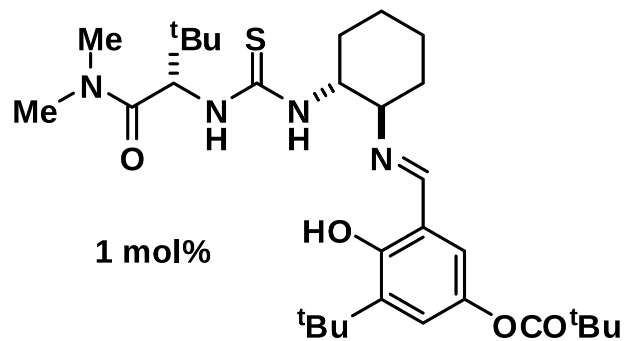
Gheewala, C. D.; Collins, B. E.; Lambert, T. H. *Science* **2016**, *351*, 961-965.

2.1.5 Other Reactions with Imines: Strecker

Jacobsen Urea Catalyst: The First Use of Urea in Asymmetric Catalysis[1,2]



Second Generation Catalyst:

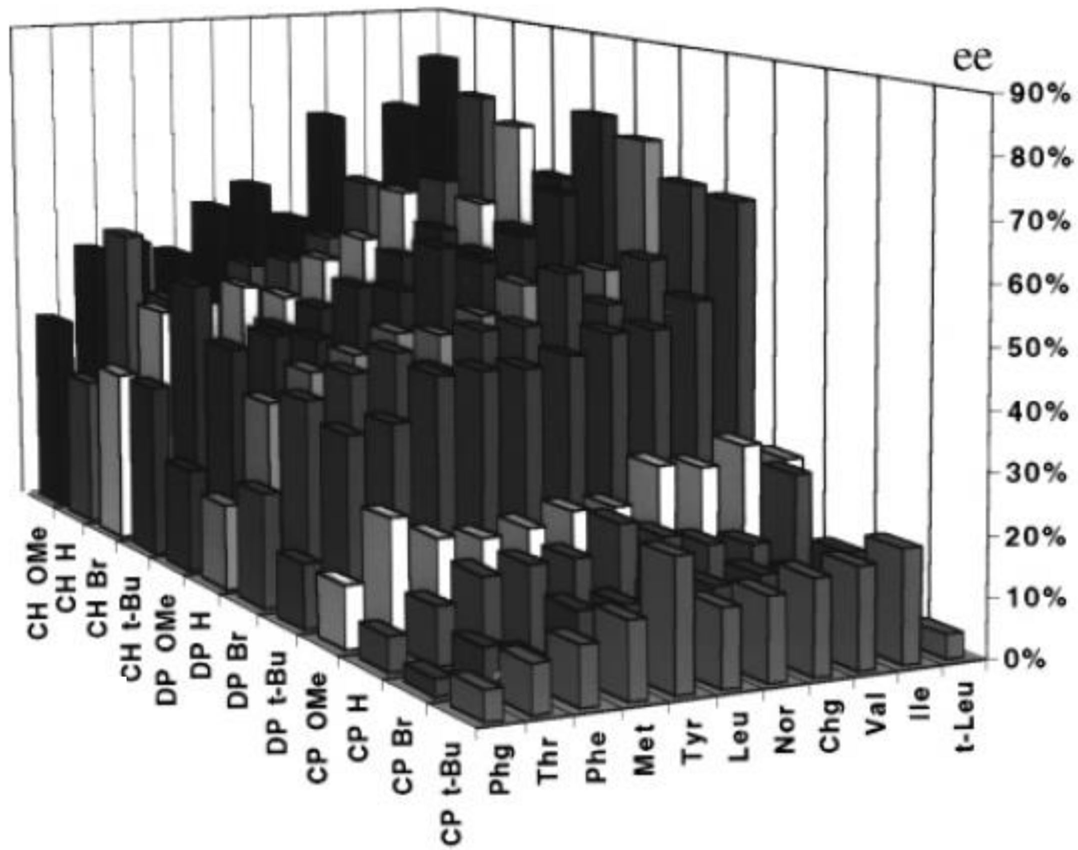


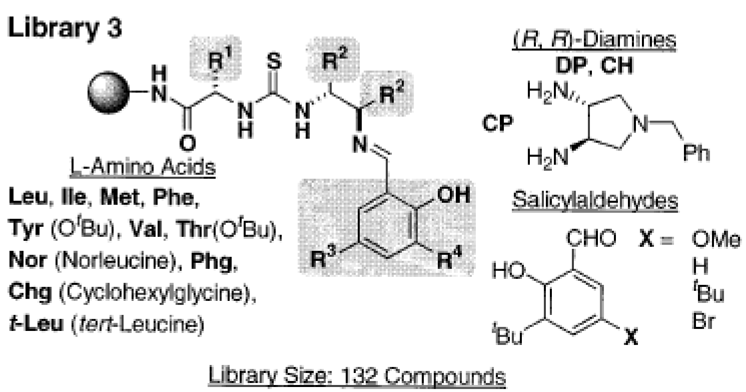
86-99.3% ee

(1) Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998,** ***120,*** 4901-4902. (2) Vachal, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002,** ***124,*** 10012-10014.

2.1.5 Other Reactions with Imines: Strecker

Discovery of the Urea Catalyst:
A Surprising Control Experiment.

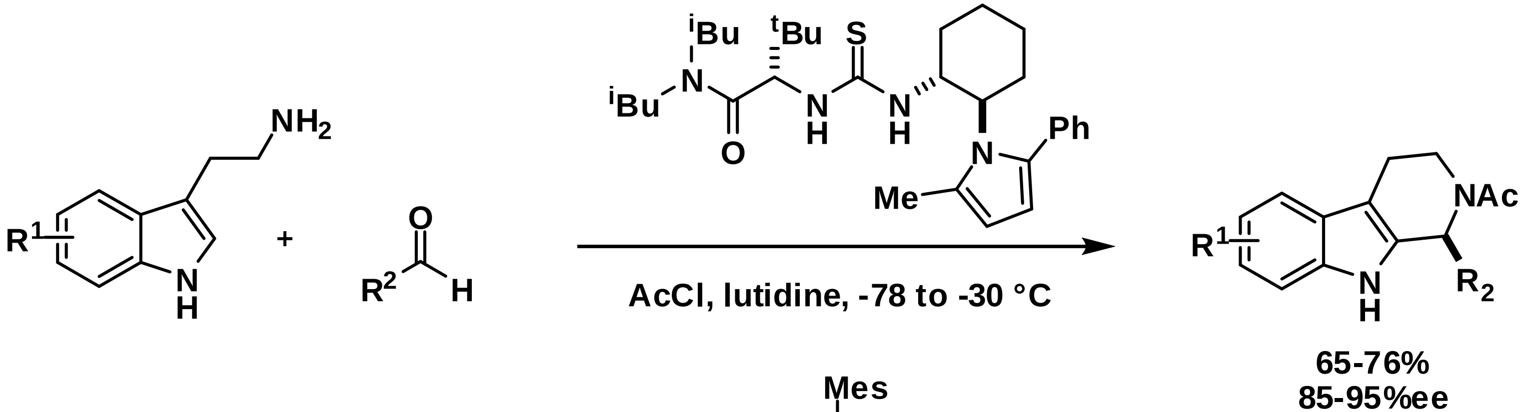




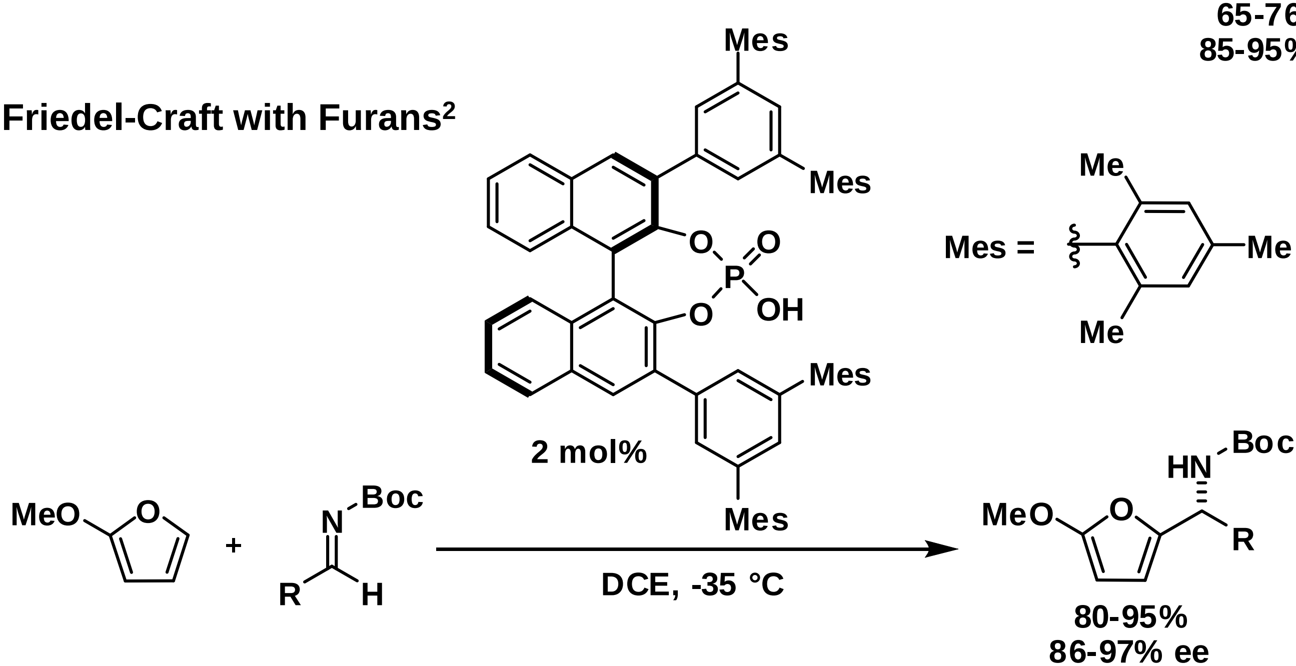
(1) Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998,** ***120,*** 4901-4902. (2) Vachal, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002,** ***124,*** 10012-10014.

2.1.5 Other Reactions with Imines: Aza-Friedel-Craft

Jacobsen: Catalytic Asymmetric Pictet-Spengler Reaction[1]



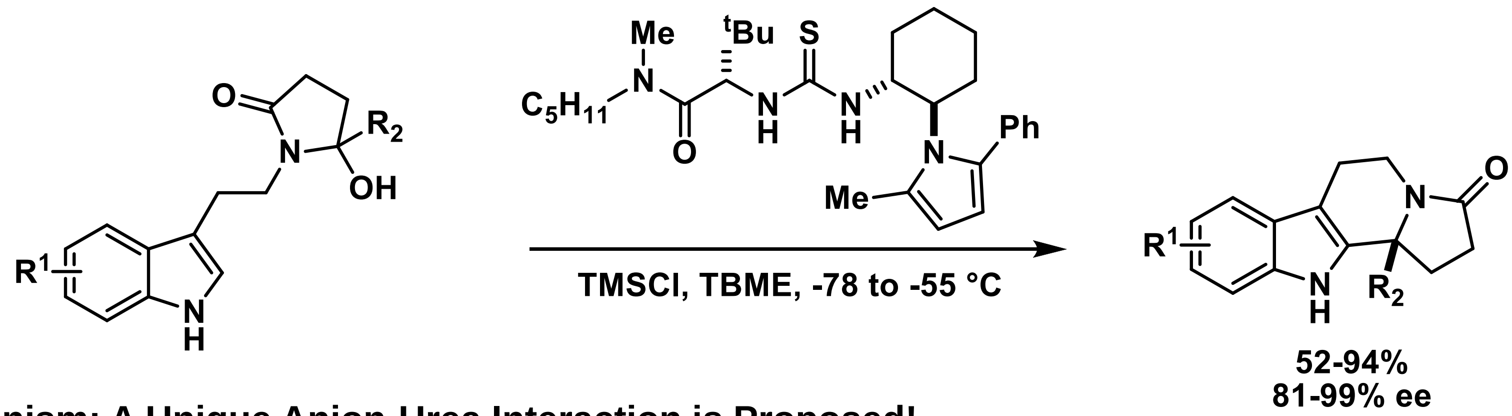
Terada: Aza-Friedel-Craft with Furans[2]



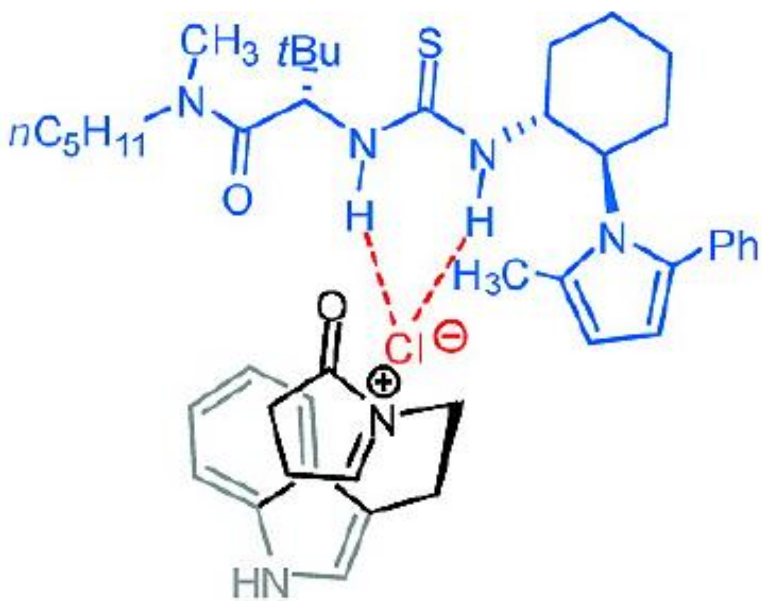
(1) Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004,** *126,* 10558-10559. (2) Uraguchi, D.; Sorimachi, K.; Terada, M. *J. Am. Chem. Soc.* **2004,** *126,* 11804-11805.

2.1.5 Other Reactions with Imines: Aza-Friedel-Craft

Jacobsen: Catalytic Asymmetric Pictet-Spengler Reaction for tetracyclic systems[1]



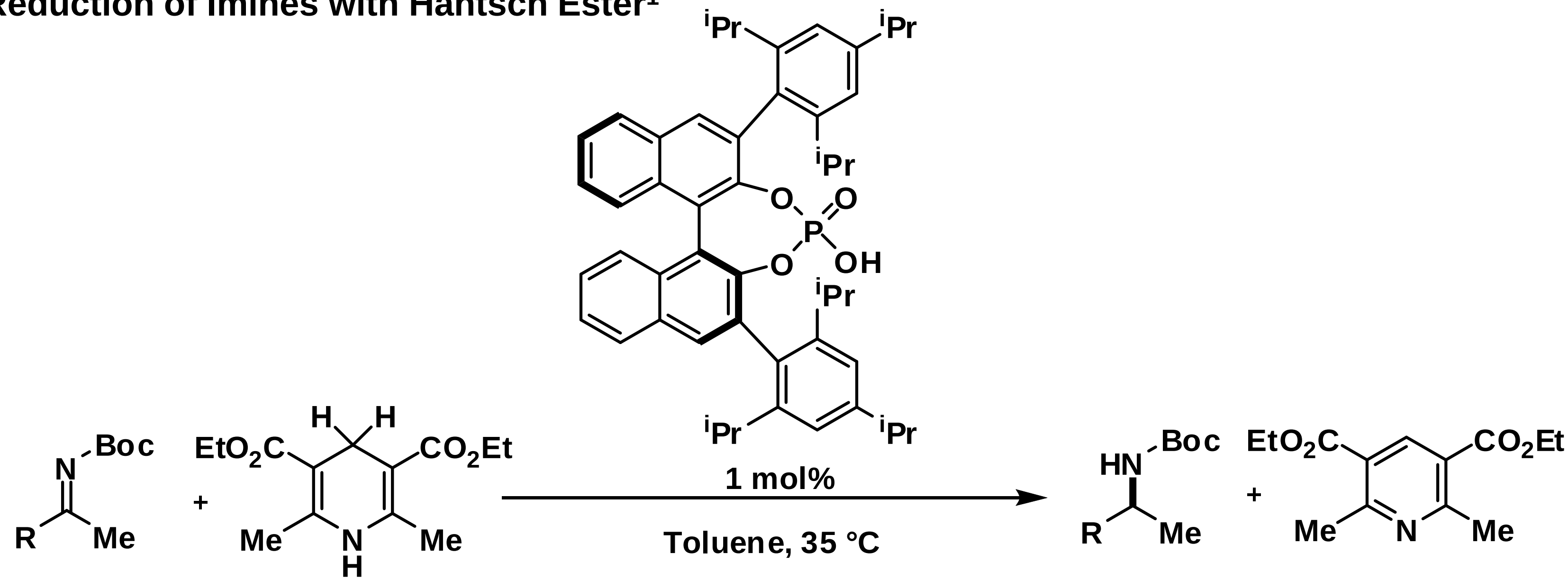
Mechanism: A Unique Anion-Urea Interaction is Proposed!



(1) Raheem, I. T.; Thiara, P. S.; Peterson, E. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* ***2007,*** *129,* 13404-13405.

2.1.5 Other Reactions with Imines: Reduction

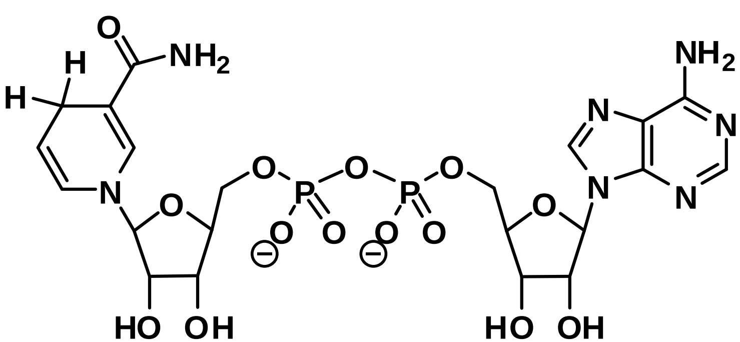
List: Reduction of Imines with Hantsch Ester[1]



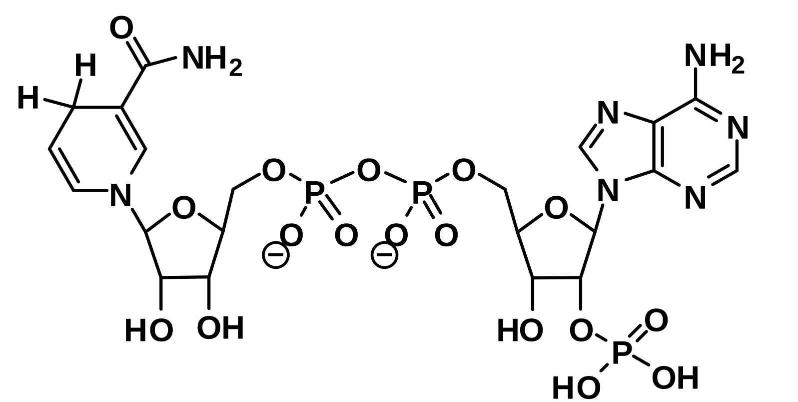
Hantsch ester

84-98%
80-93% ee

Hantsch ester: a simpler analog of the bioreductant NADH and NADPH



NADH (Nicotinamide Adenine Dinucleotide)

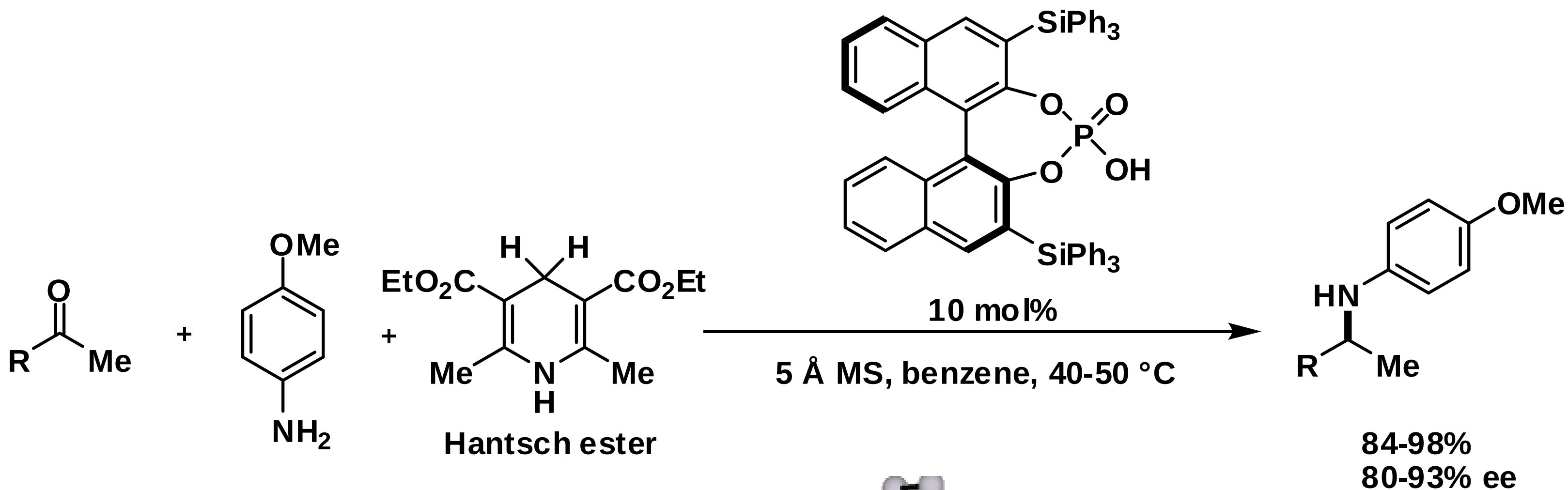


NADPH (Nicotinamide Adenine Dinucleotide Phosphate)

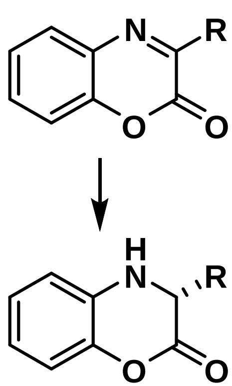
(1) Hoffmann, S.; Seayad, A. M.; List, B. *Angew. Chem., Int. Ed.* **2005,** *44,* 7424-7427.

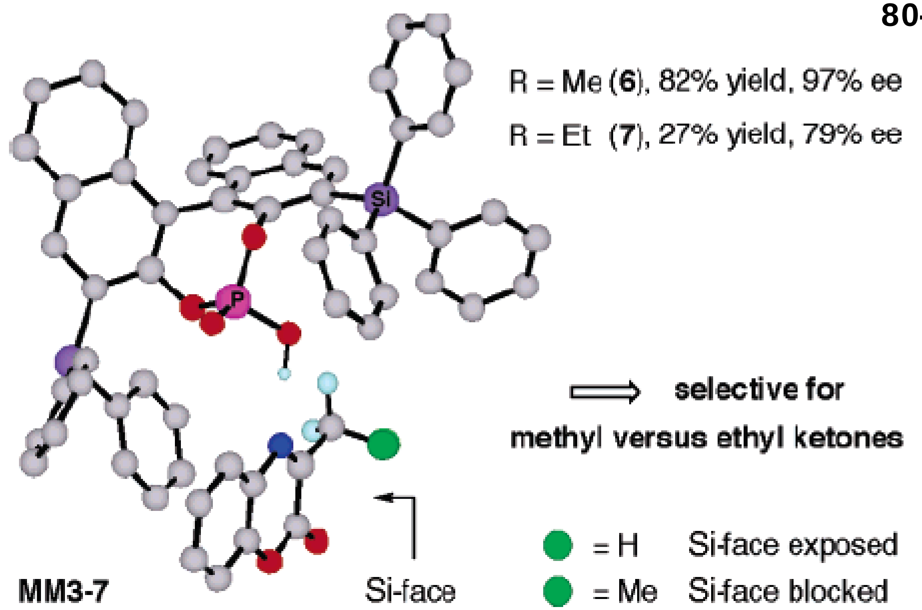
2.1.5 Other Reactions with Imines: Reduction

Mac Millan: Catalytic Asymmetric Reductive Amination



Reduction of Cyclic Imines

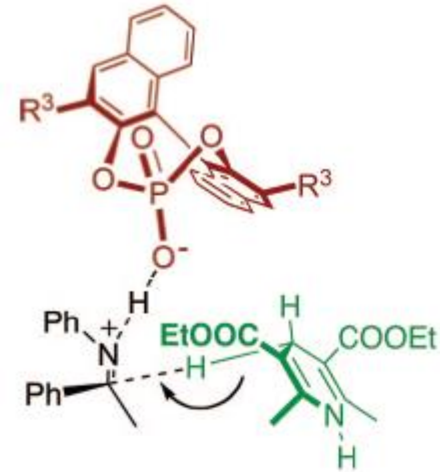




(1) Storer, R. I.; Carrera, D. E.; Ni, Y.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006,** *128,* 84-86.

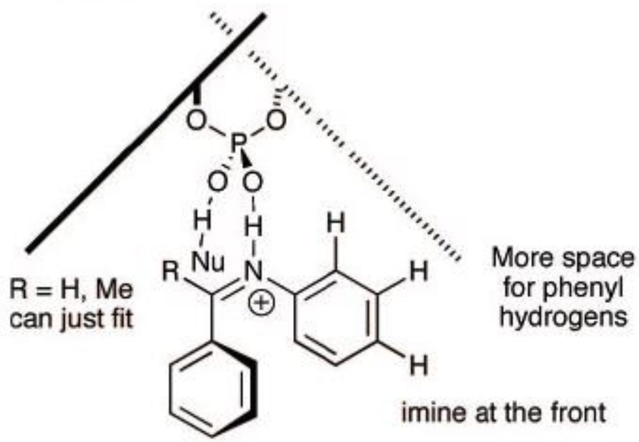
2.1.5 Other Reactions with Imines: Reduction

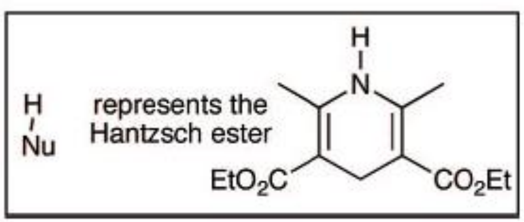
Reduction of Imines: Old Simple Mechanism

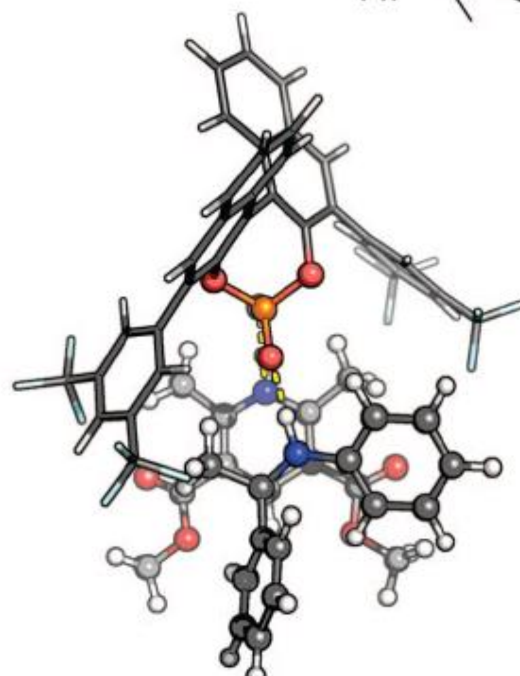


New Calculated Mechanism[1]

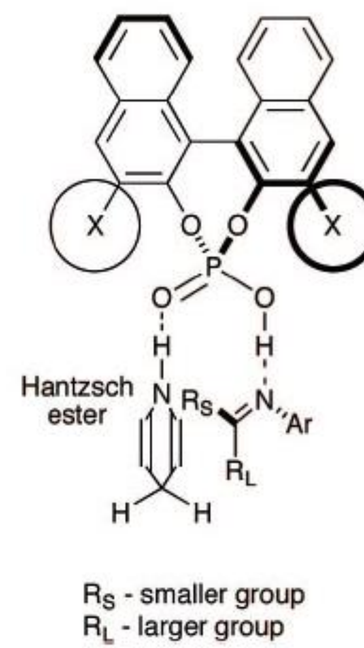
Front view:







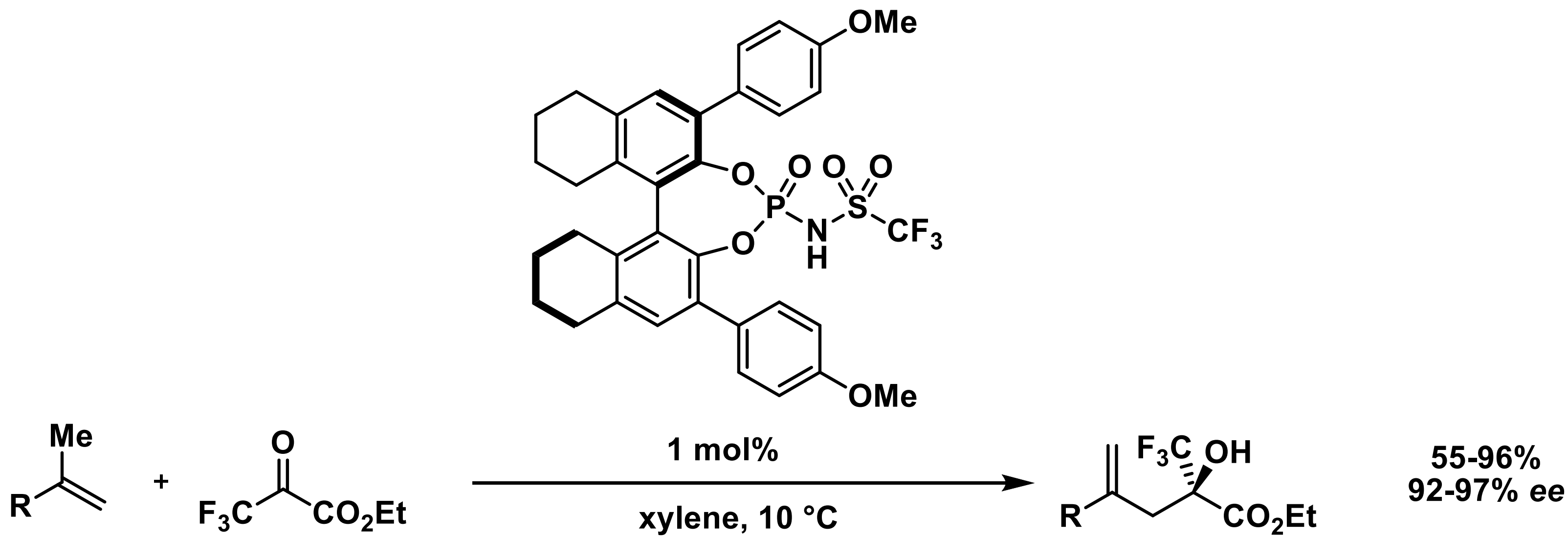
ew:



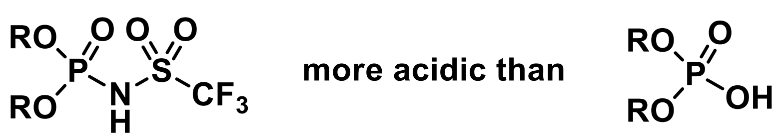
(1) Simon, L.; Goodman, J. M. *J. Am. Chem. Soc.* ***2008,*** *130,* 8741-8747.

2.1.5 Extension to Carbonyls Activation

Rueping: One of the First Examples of Activation of Carbonyles for Ene Reaction[1]



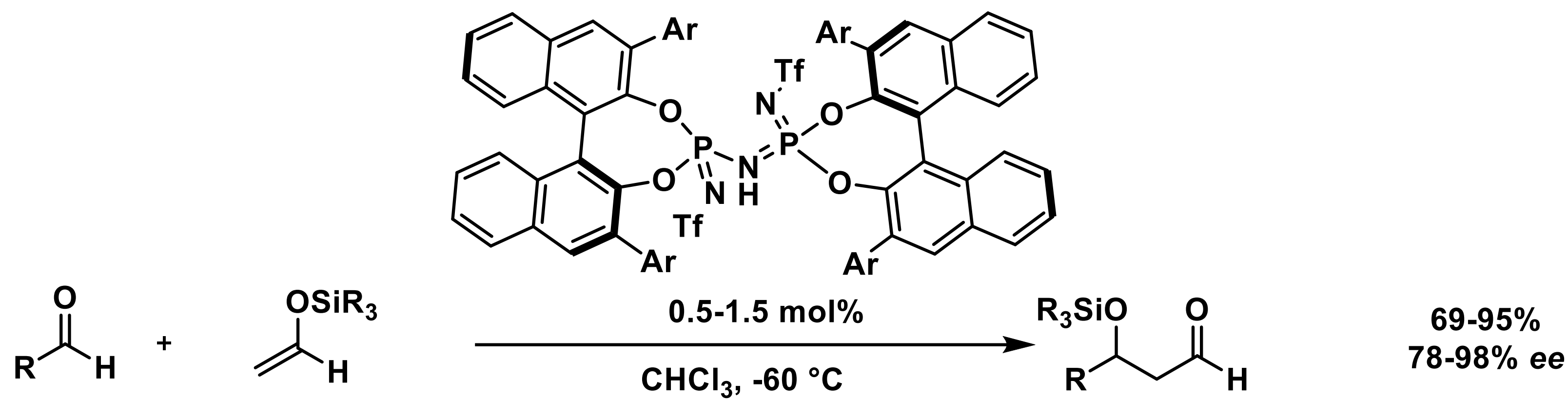
Key Discovery: Enhanced acidity of Trifluoromethansulfonyl Imides

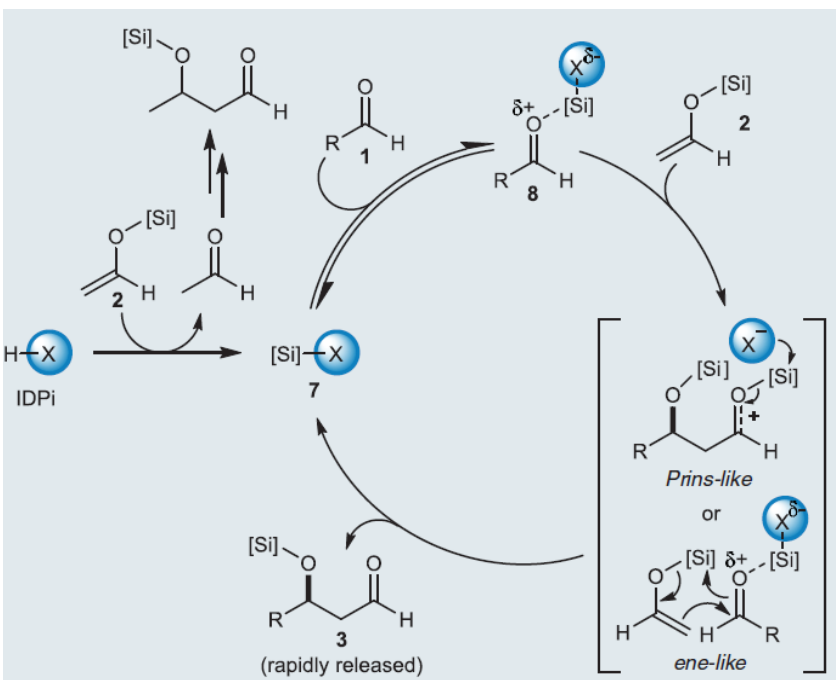


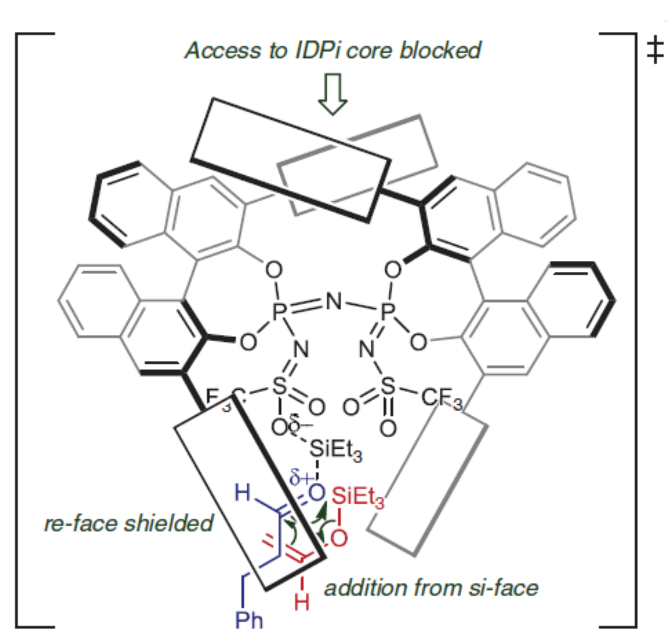
(1) Rueping, M.; Theissmann, T.; Kuenkel, A.; Koenigs, R. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 6798-6801.

2.1.5 Extension to Carbonyls Activation

List: Confined Lewis Acid catalysts for the Aldol reaction[1]







(1) Schreyer, L.; Kaib, P. S. J.; Wakchaure, V. N.; Obradors, C.; Properzi, R.; Lee, S.; List, B., Science **2018**, *362*, 216-219.