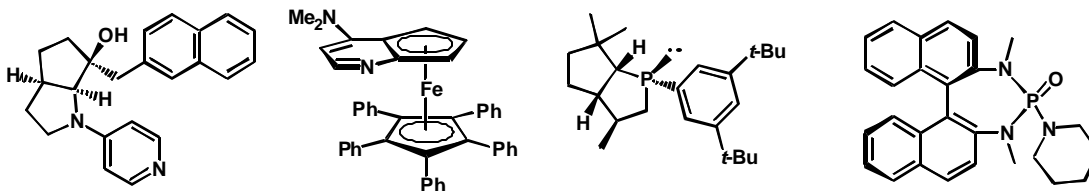


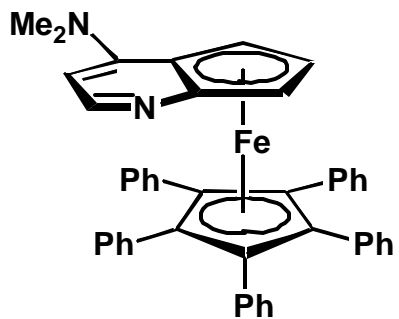
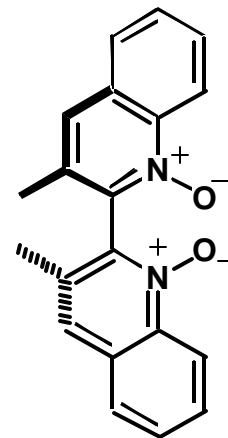
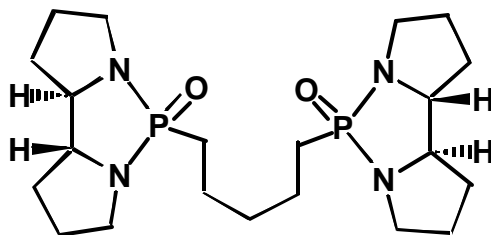
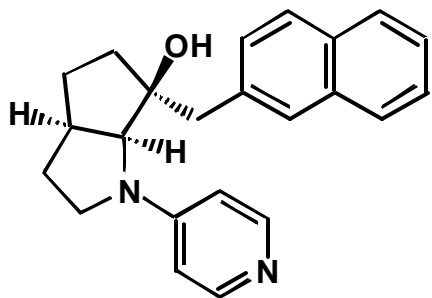
Chiral Lewis Bases in Asymmetric Synthesis

Enantioselective synthesis using chiral Lewis acids has evolved over the past 20 years to the state wherein today a diverse array of molecules can be synthesized efficiently and in very high enantioselectivities. With chiral Lewis acids having been successfully applied for asymmetric induction in key reactions such as the aldol, Diels-Alder reaction and aldehyde allylation, it is somewhat surprising that their chiral Lewis basic counterparts have only recently been explored. Despite its' relative infancy, asymmetric synthesis using chiral Lewis bases has been successfully demonstrated for several reactions including the kinetic resolution of alcohols, the stereospecific allylation of aldehydes and the aldol reaction of trichlorosilane enol ethers. This talk will examine the state of the art in asymmetric synthesis using chiral Lewis bases with focus on the mechanistic and conceptual differences of these reactions versus the conventional Lewis acid catalyzed processes.

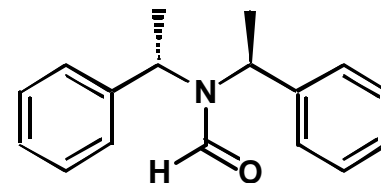
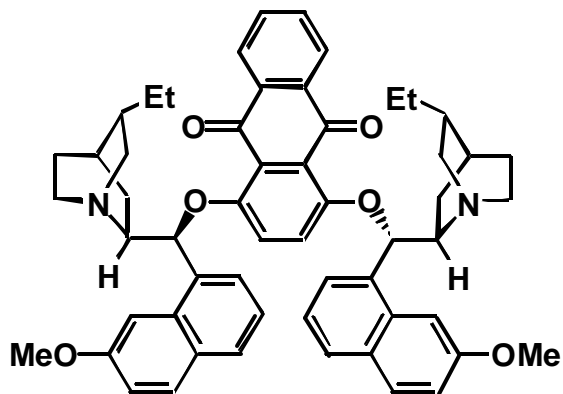
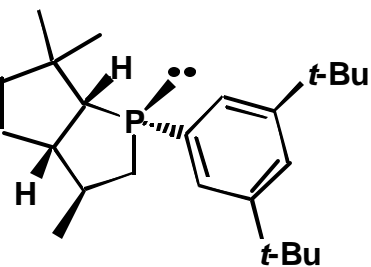


References:

- (1) Fu, G. C.; *Acc. Chem. Res.* **2000**, *33*, 412-420.
- (2) Denmark, S. E.; Stavenger, R. A. *Acc. Chem. Res.* **2000**, *33*, 432-440.
- (3) Iseki, K.; Kuroki, Y.; Takahashi, M.; Kishimoto, S.; Kobayashi, Y. *Tetrahedron* **1997**, *53*, 3513-3526.



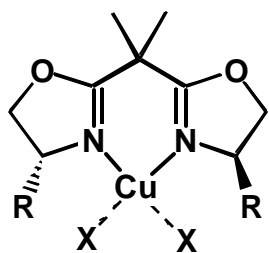
Chiral Lewis Bases in Asymmetric Synthesis



David Powell

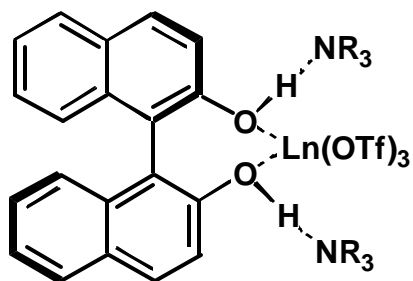
November 19th 2001

Chiral Lewis Acid Catalysis



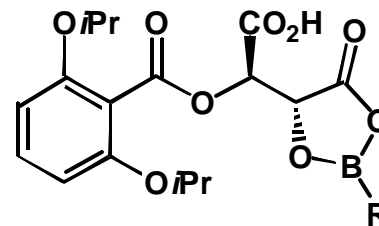
Evans

Aldol, Diels-Alder, Michael



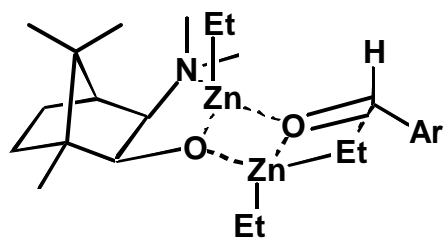
Kobayashi

Diels-Alder, [3+2] cycloadditions



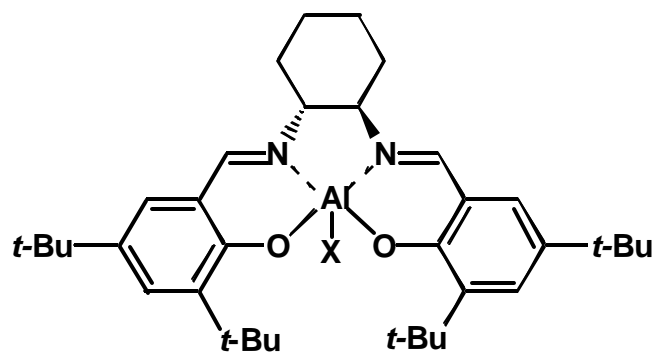
Yamamoto

Diels-Alder, aldol, allylation



Noyori

Addition of dialkylzincs to aldehydes



Jacobsen

Opening of epoxides, Michael, hetero Diels-Alder, addition to imines

What about Chiral Lewis Bases?

Why are chiral Lewis acids used so widely in organic chemistry?

- Many organic functional groups interact with Lewis acids.
- The interaction of L.A. with electron rich unsaturated functional groups is reasonably understood.
 - Schrieber *Angew Chem. Int. Ed. Engl.* **1990**, 29, 256-272.
 - Gladysz *Angew Chem. Int. Ed. Engl.* **1997**, 36, 550-583.
- The L.A. activated substrate reacts far faster than the unactivated substrate.

Why have chiral Lewis bases not enjoyed the same success as chiral Lewis acids?

- How do Lewis acids work to catalyze organic reactions?

Concepts behind Lewis Acid and Lewis Base Catalysis

Lewis Acids:

- Activation of electrophile
- Activation of nucleophile

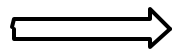
Lewis Bases:

- Activation of electrophile
- Activation of nucleophile
- Creation of chiral environment around transition metal

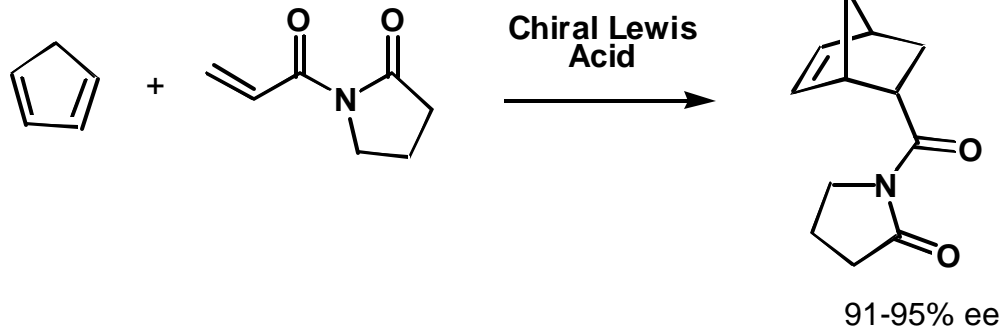
Concepts behind Lewis Acid and Lewis Base Catalysis

Lewis Acids:

- Activation of electrophile
- Activation of nucleophile

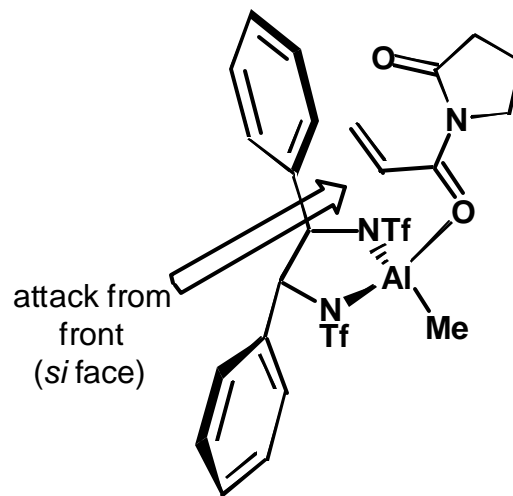


Asymmetric Diels-Alder



Lewis Bases:

- Activation of electrophile
- Activation of nucleophile



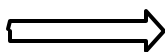
Corey and coworkers, *J. Am. Chem. Soc.* **1995**, 9616.

- Creation of chiral environment around transition metal

Concepts behind Lewis Acid and Lewis Base Catalysis

Lewis Acids:

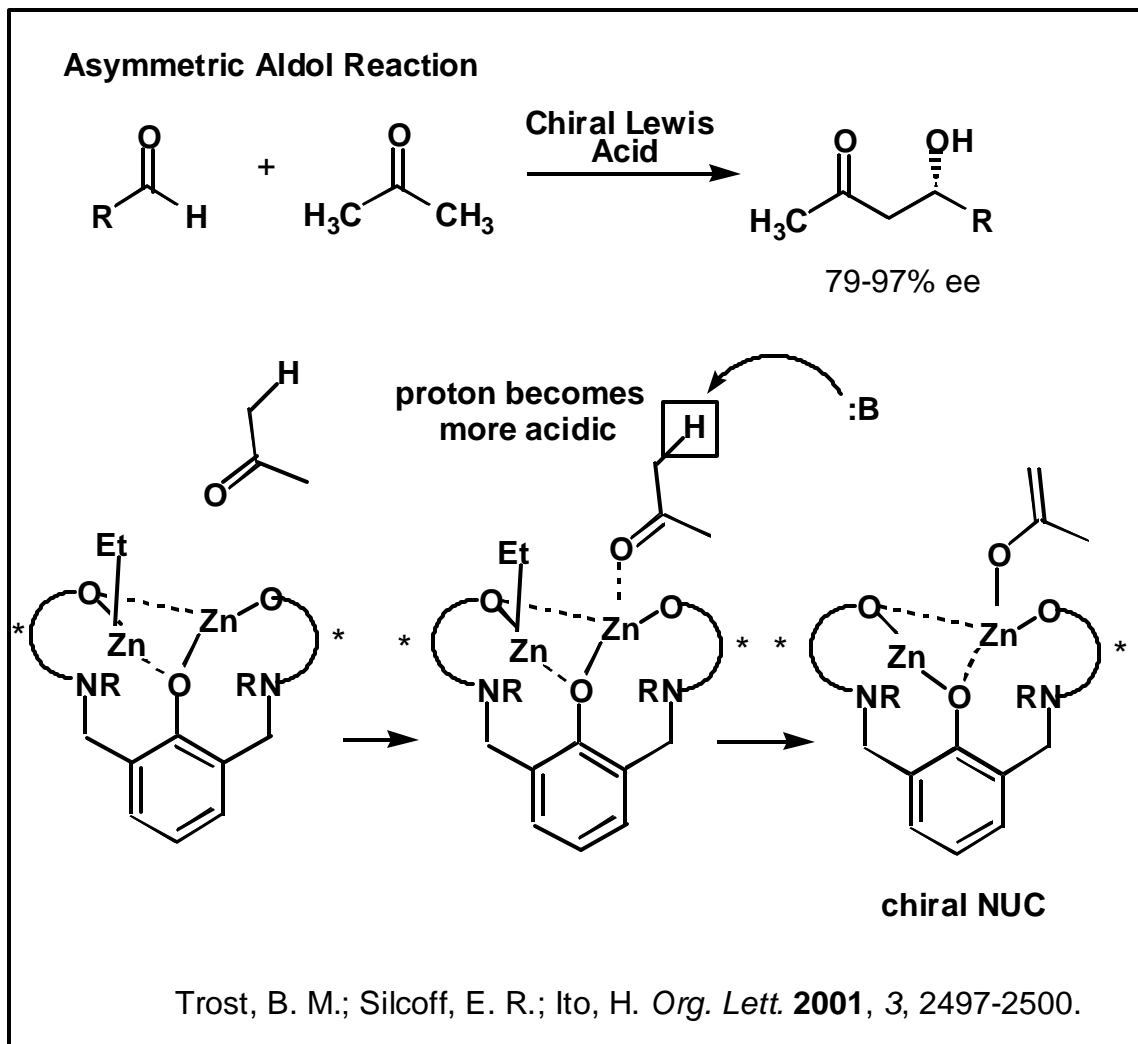
- Activation of electrophile
- Activation of nucleophile



Lewis Bases:

- Activation of electrophile
- Activation of nucleophile

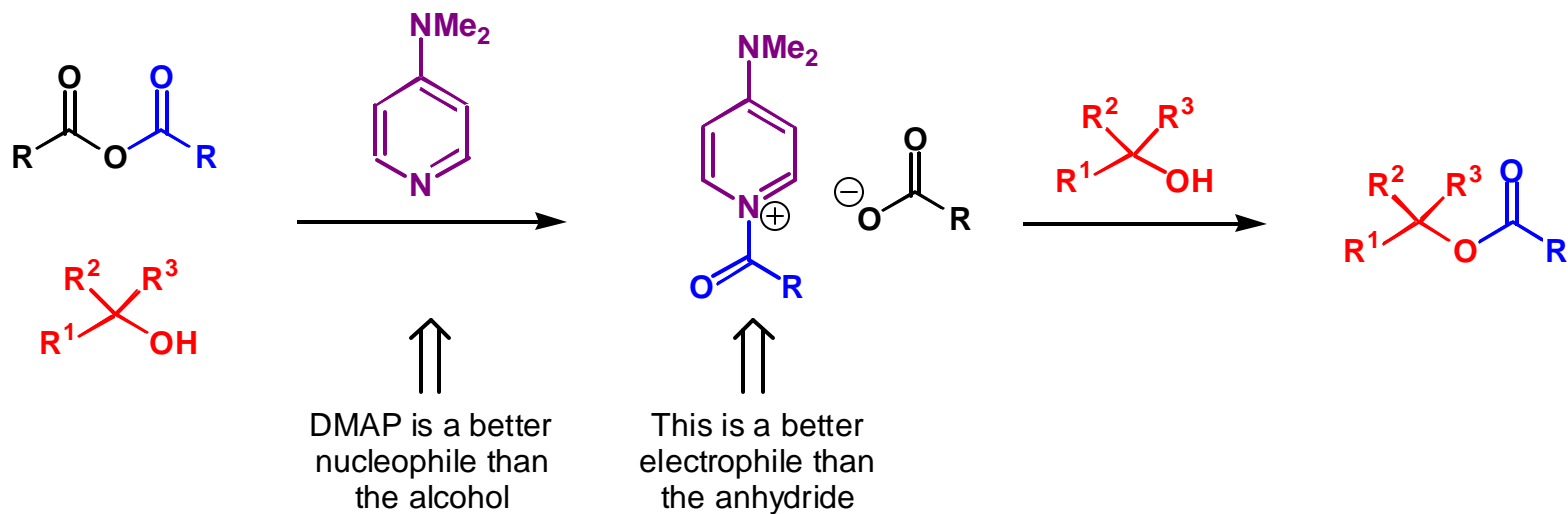
- Creation of chiral environment around transition metal



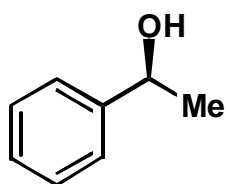
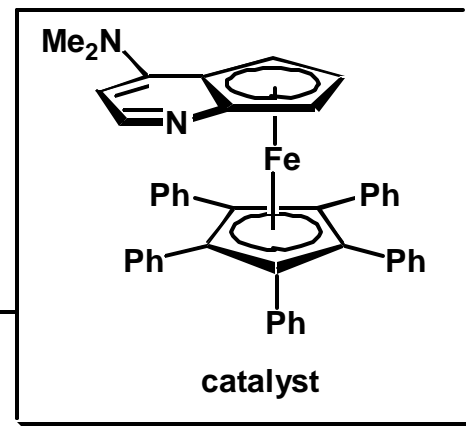
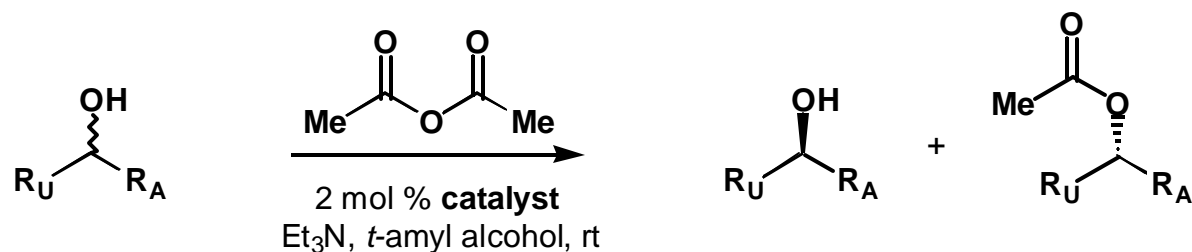
Lewis Base Activation of Electrophiles:



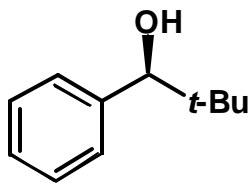
- the **ELEC** and **NUC** are generally slow to react.
- the **Lewis base** is more nucleophilic than **NUC**.
- the **Lewis base** reacts with the **ELEC** to give a more electrophilic species.
- the **NUC** reacts with this highly electrophilic **Lewis base**•**ELEC** complex.



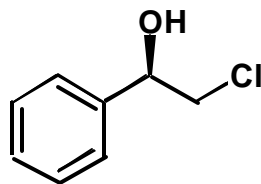
Lewis Base Activation of Electrophiles: Kinetic Resolution of Alcohols



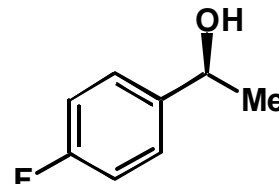
99 %ee
55 %conv.



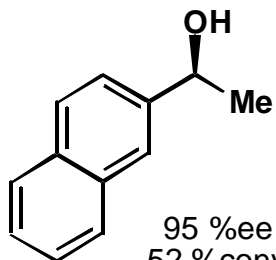
96 %ee
51 %conv.



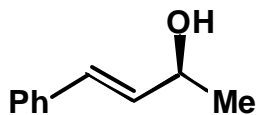
98 %ee
56 %conv.



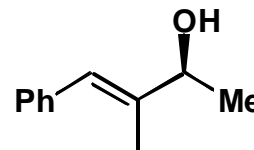
99 %ee
54 %conv.



95 %ee
52 %conv.



99 %ee
67 %conv.
(Et₂O)



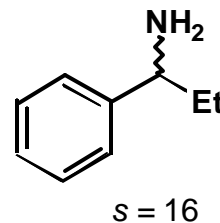
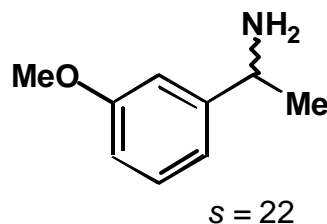
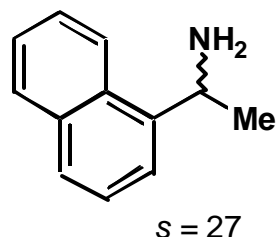
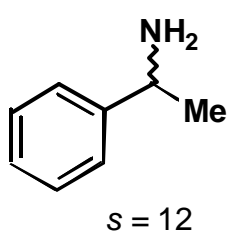
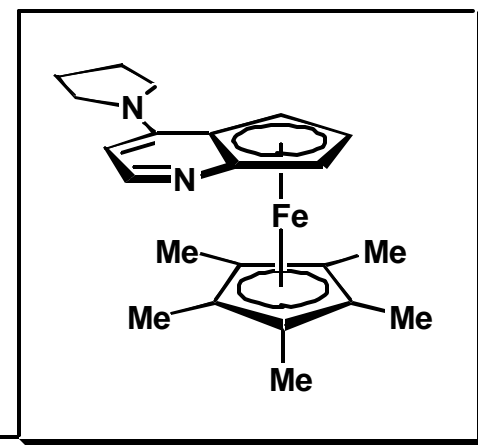
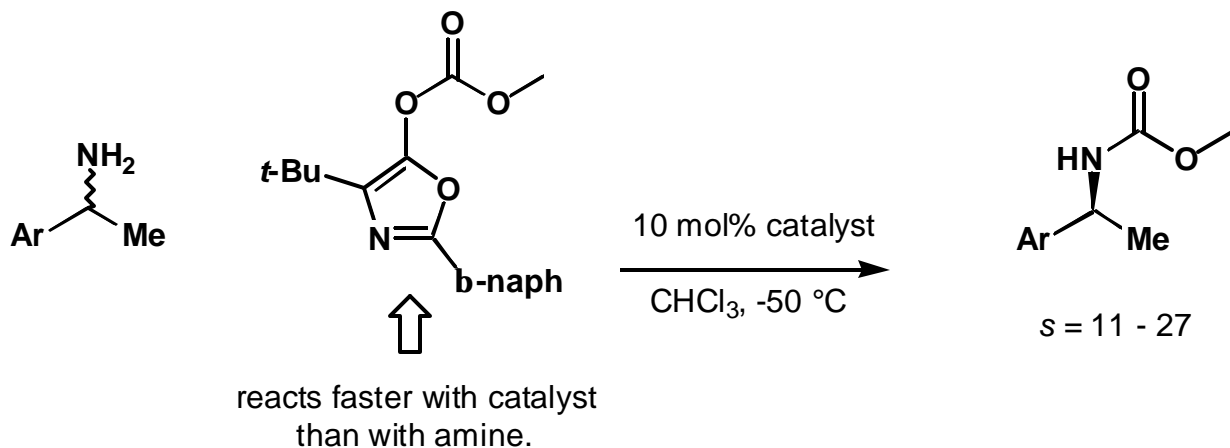
99 %ee
61 %conv.
(Et₂O)

Ruble, J. C.; Latham, H. A.; Fu, G. C. *J. Am. Chem. Soc.* **1997**, *119*, 1492-1493.

Ruble, J. C.; Tweddell, J.; Fu, G. C. *J. Org. Chem.* **1998**, *63*, 2794-2795.

Lewis Base Activation of Electrophiles: Kinetic Resolution of Amines

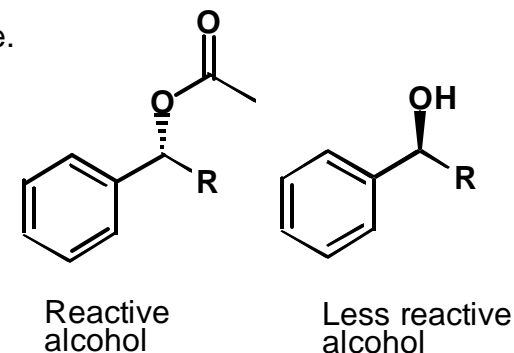
- the first effective nonenzymatic acylation catalyst for kinetic resolution of amines.
- under standard conditions the amine is nucleophilic enough to add directly to most acylating reagents



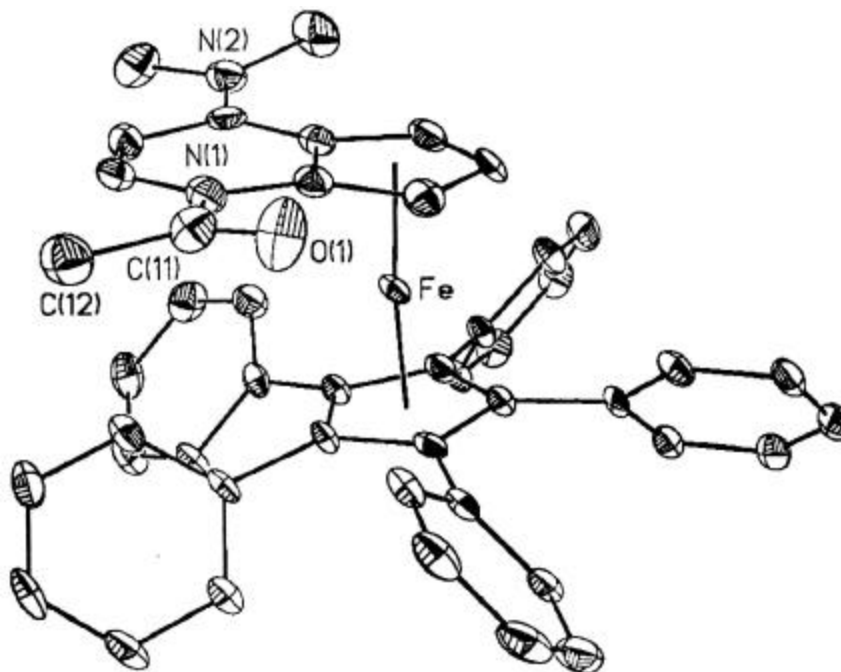
Arai, S.; Laponnaz-Bellemin, S.; Fu, G. C. *Angew. Chem. Int. Ed. Engl.* **2001**, *40*, 234-236.

Lewis Base Activation of Electrophiles: Chiral DMAP : Origin of Enantioselectivity

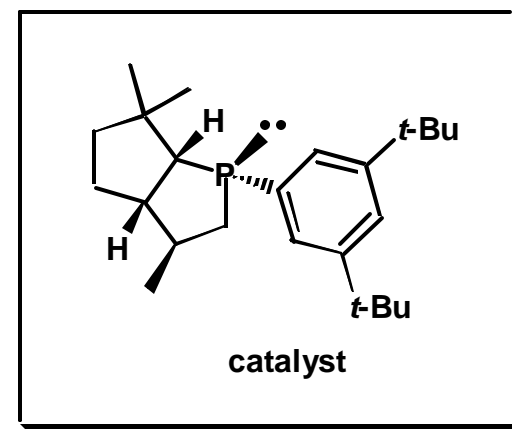
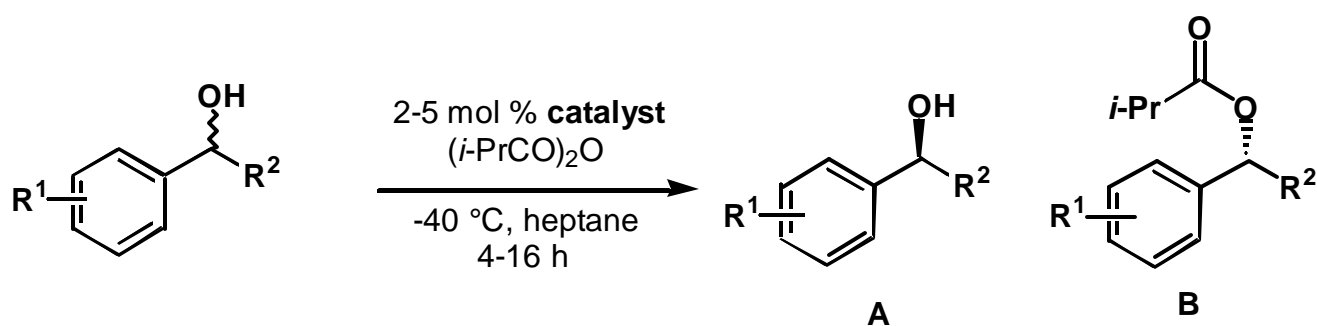
- Acetyl group rotamer consistent with minimization of sterics with methyl group and ferrocene.
- Nucleophile approaches from top face of DMAP* catalyst.
- Selectivity improves as size of alkyl group increases.



R = Me, $s = 43$
R = Et, $s = 59$
R = *i*-Pr, $s = 87$
R = *t*-Bu, $s = 95$



Lewis Base Activation of Electrophiles: Kinetic Resolution of Alcohols with Phosphines



R ¹	R ²	conv.	%ee A	%ee B	s
H	Me	29.2	38	93	42
H	<i>n</i> -C ₄ H ₉	51.3	93	89	57
H	<i>i</i> -C ₃ H ₇	46.9	84	88	100
4-Me	Me	50.1	95	95	145
4-MeO	Me	28.7	39	97	81

- Acylation rates were proportional to [catalyst] and [anhydride].

Lewis Base Activation of Electrophiles: Parallel Kinetic Resolution of Alcohols

In kinetic resolutions, the enantioselectivity of the resolution degrades as the reaction proceeds with time.

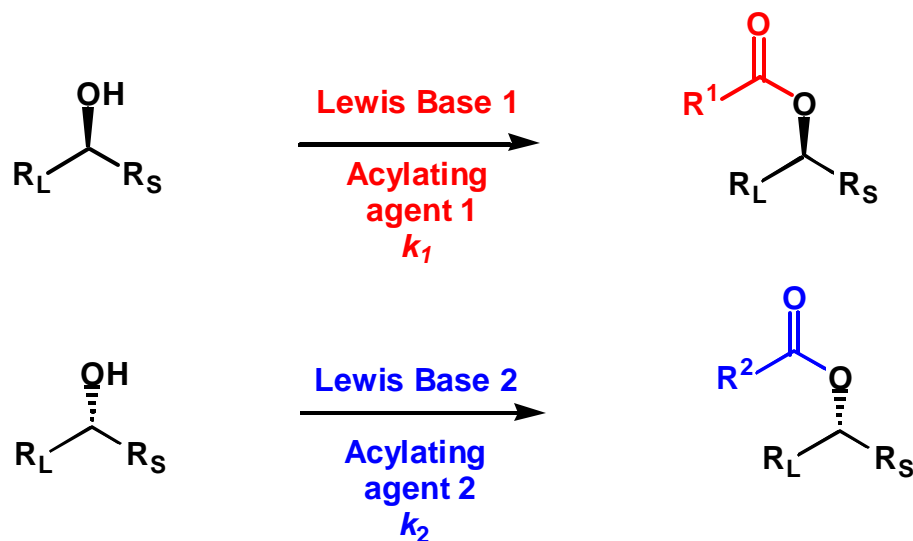
$$\frac{[\text{slow}]}{[\text{fast}]} \text{ increases exponentially with } t$$

In order to get very high ee of product need a large excess of reagent.

To get a high ee of unreacted enantiomer need to run the reaction well past 50% conversion.

Diminished yields and low recovery of enantiopure products and starting material!

Parallel Kinetic Resolution: Basic Premise



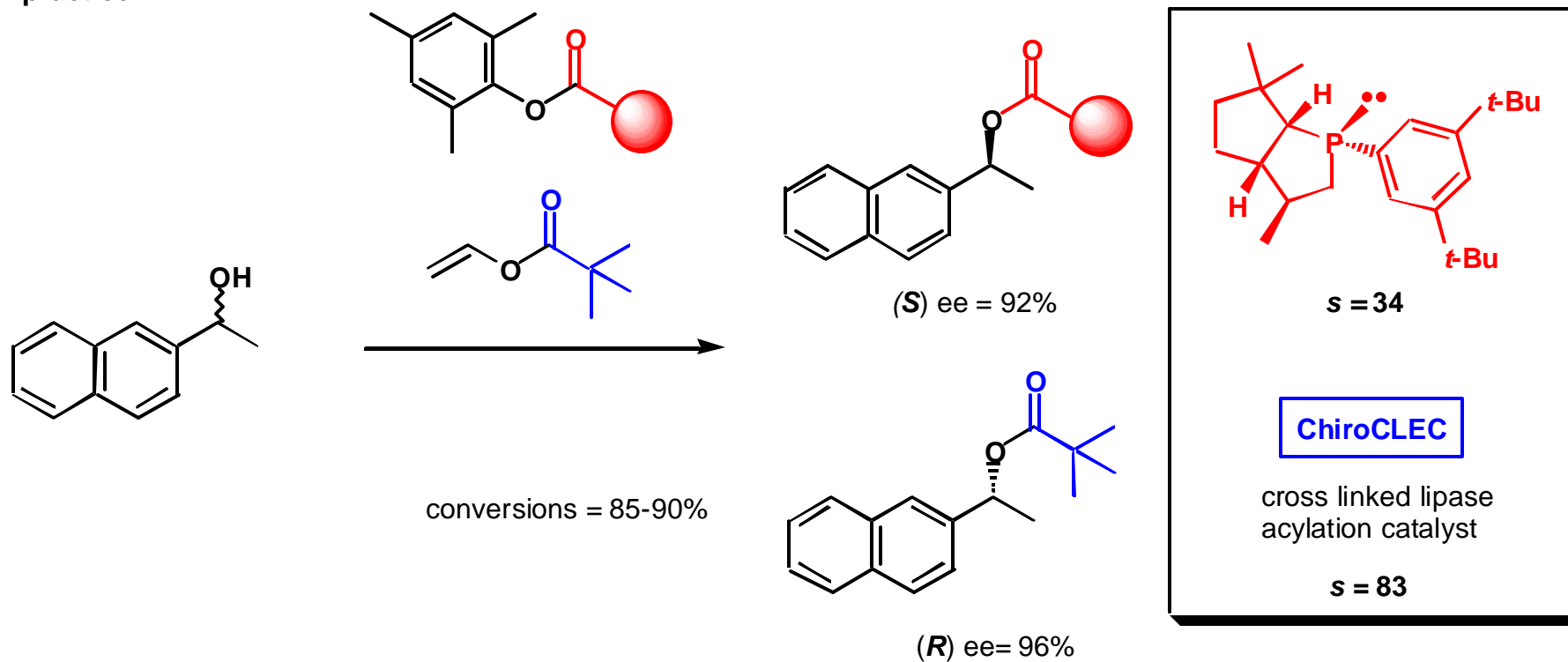
In the ideal case $k_1 = k_2$ and

$$\frac{[\text{slow}]}{[\text{fast}]} = 1$$

this gives the best selectivity

Lewis Base Activation of Electrophiles: Parallel Kinetic Resolution of Alcohols

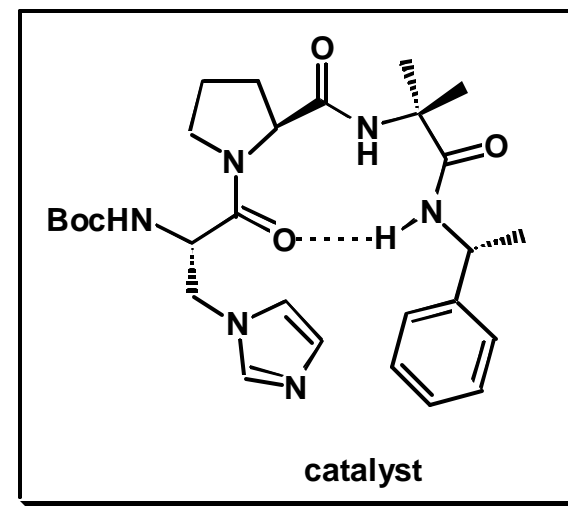
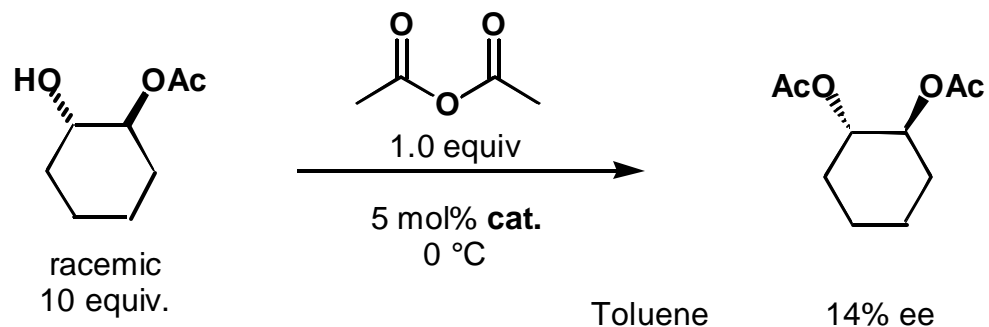
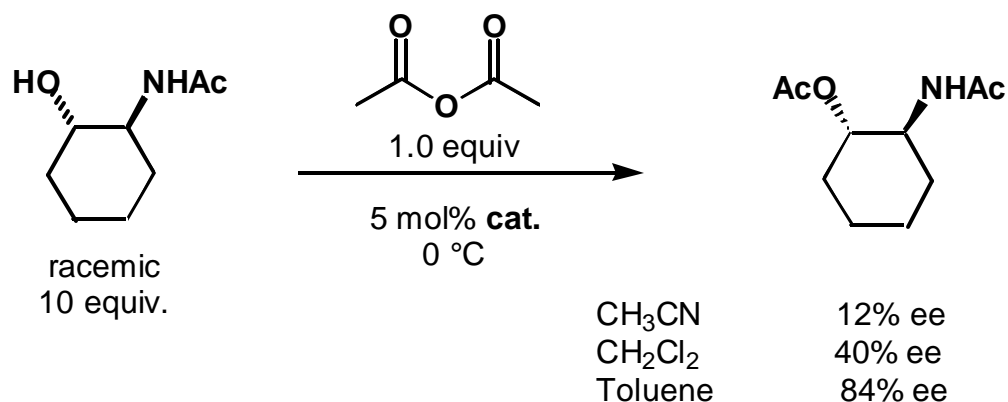
In practice:



- the obtained ee are close to the theoretical limits (<1 % conversion in simplified kinetic resolution)
 - (*S*) enantiomer $s = 34$ then ee% = 94%
 - (*R*) enantiomer $s = 83$ then ee% = 98%
- the kinetic resolution experiment at 50% conversion afforded 81% ee of both (*R*) and (*S*) enantiomers.

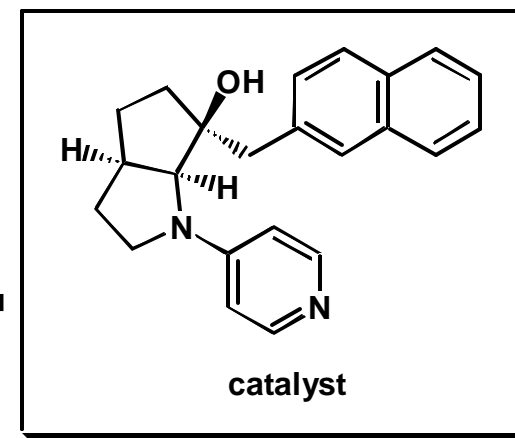
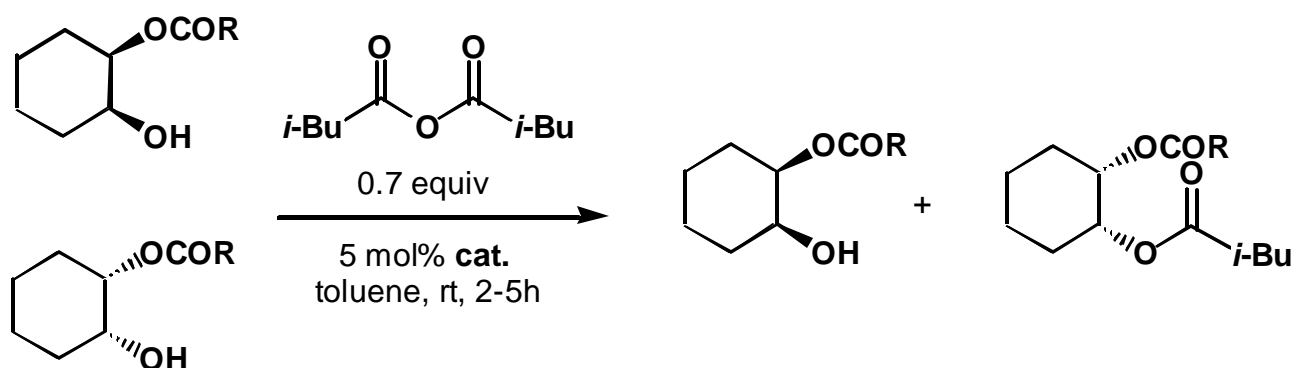
Vedejs, E.; Rozners, E.; *J. Am. Chem. Soc.* **2001**, 123, 2428-2429.

Lewis Base Activation of Electrophiles: Kinetic Resolution of Alcohols by Tripeptides



- involvement of the amide of the substrate with catalyst important for selectivity:
 - selectivity increases in solvents which favour H bonding.
 - replacement of the amide with an ester results in lower selectivities.

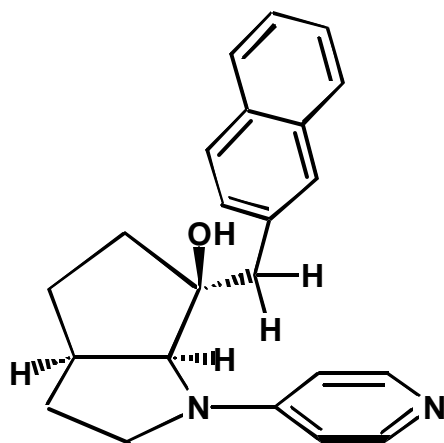
Lewis Base Activation of Electrophiles: Kinetic Resolution of Alcohols



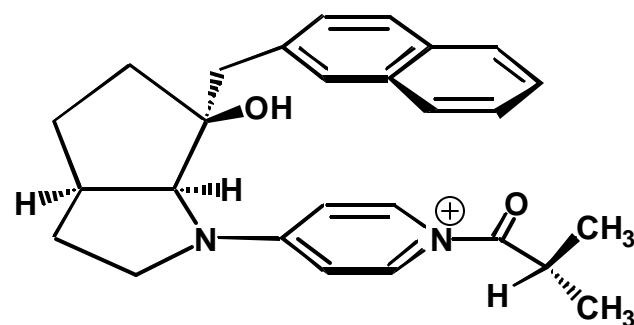
R	% Conv.	Optical purity of recovered substrate (%ee)	s
<i>t</i> Bu	68	94	8.3
Ph	71	81	4.5
4-MeOC ₆ H ₄	70	85	5.3
4-Me ₂ NC ₆ H ₄	72	>99	12.3

Lewis Base Activation of Electrophiles: Kinetic Resolution of Alcohols

Induced-fit Mechanism:



open conformation

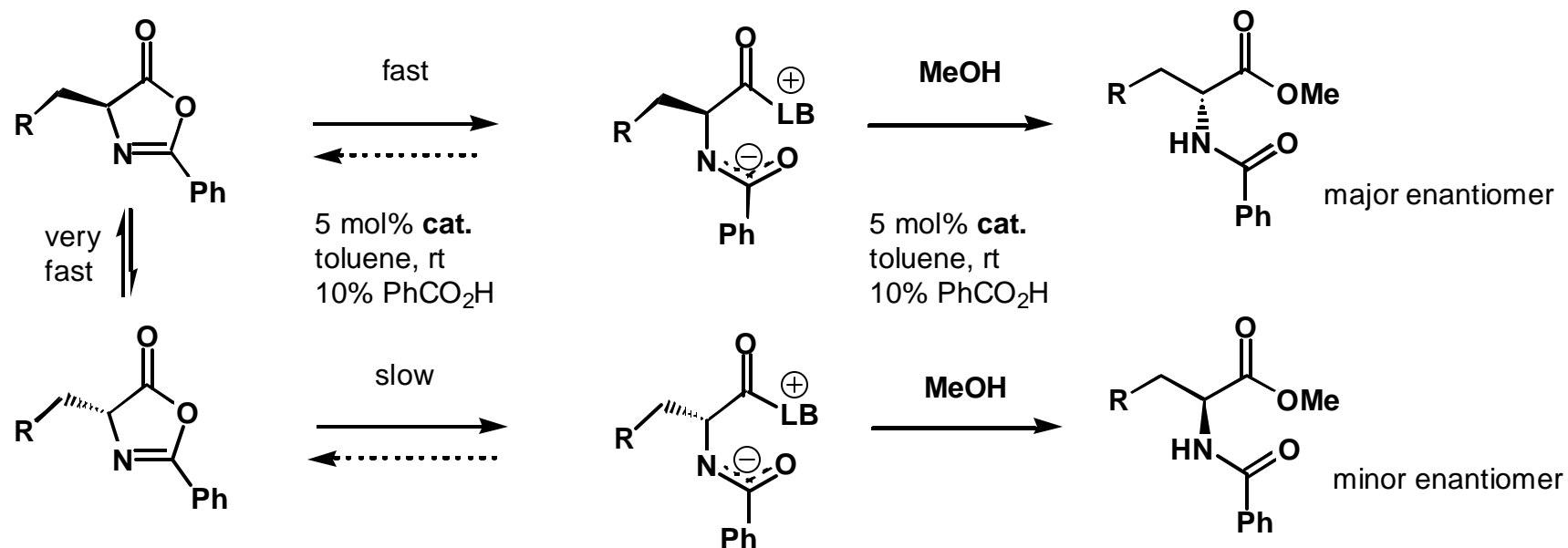


Nucleophile approaches
from bottom face

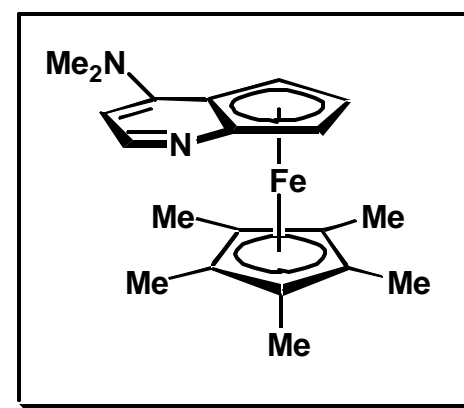
closed conformation

Kawabata, T.; Nagato, M.; Takasu, K.; Fujii, K. *J. Am. Chem. Soc.* **1997**, *119*, 3169-3170.

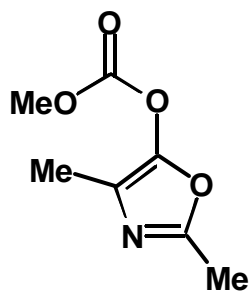
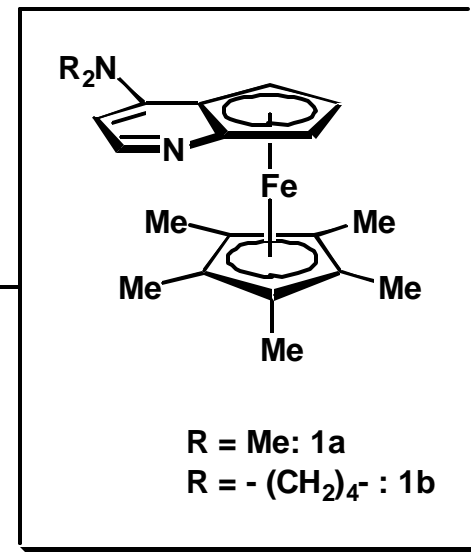
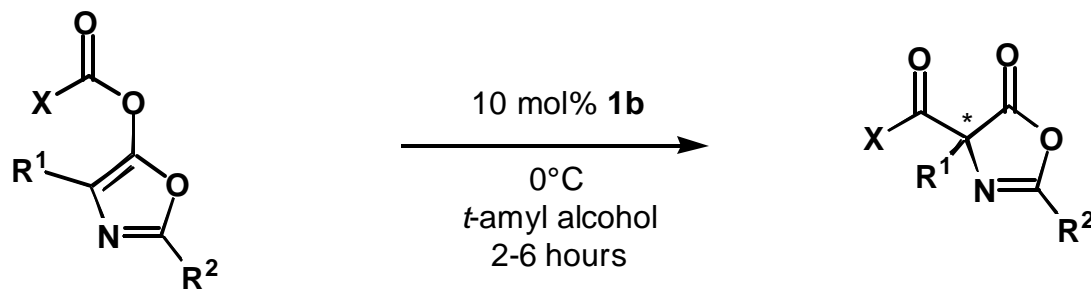
Lewis Base Activation of Electrophiles: Dynamic Kinetic Resolution of Azlactones



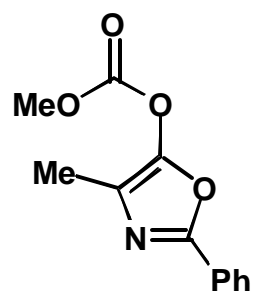
R	% ee	% Yield
H	54	98
Me	44	94
CH ₂ =CH ₂	61	94
<i>i</i> -Pr	55	95



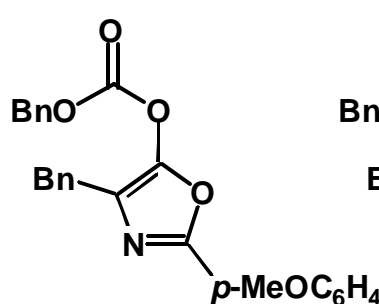
Lewis Base Activation of Electrophiles: Rearrangement of *O*-Acylated Azlactones



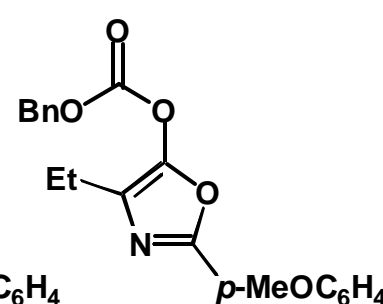
54% ee



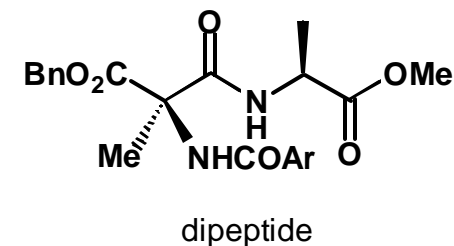
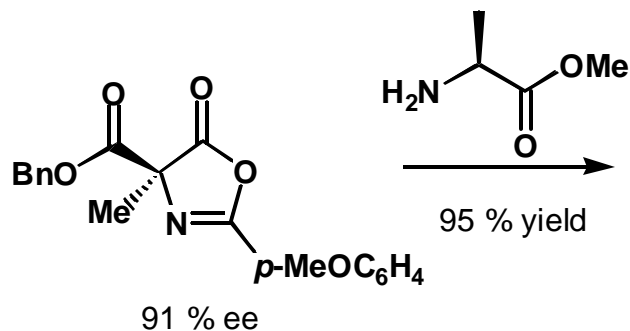
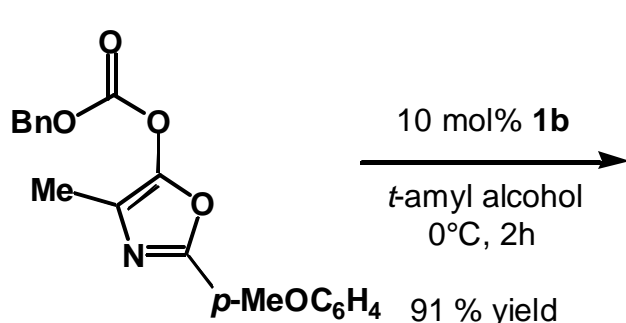
82% ee



90% ee



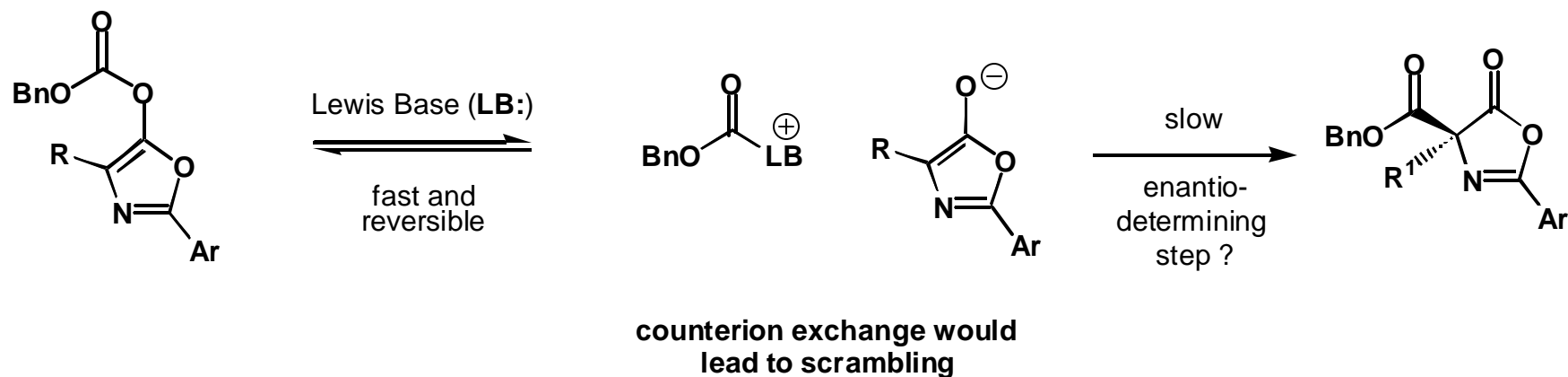
90% ee



Lewis Base Activation of Electrophiles: Rearrangement of *O*-Acylated Azlactones

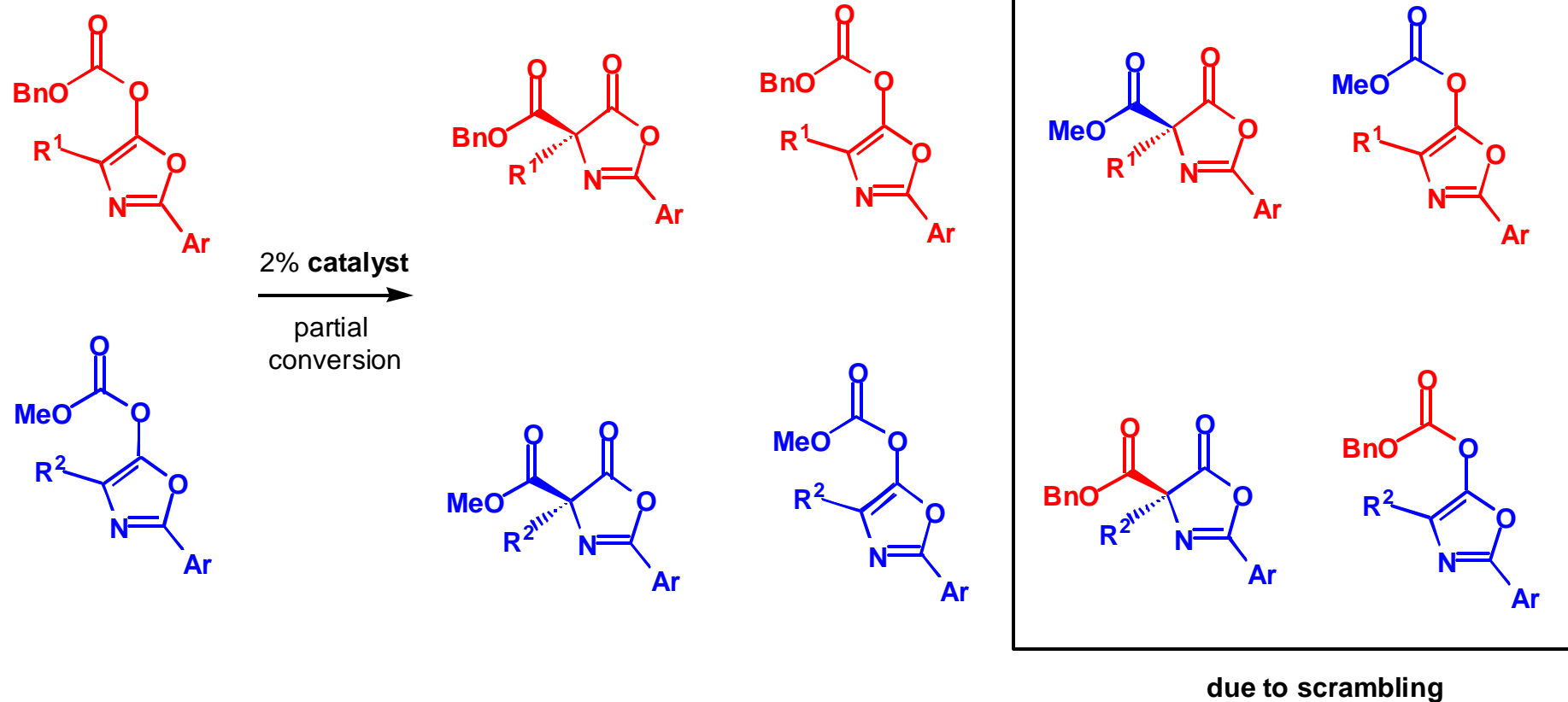
Mechanistic Insights:

- the rate of rearrangement is zero order in substrate.
- products are configurationally stable under the reaction conditions.

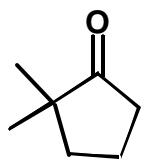
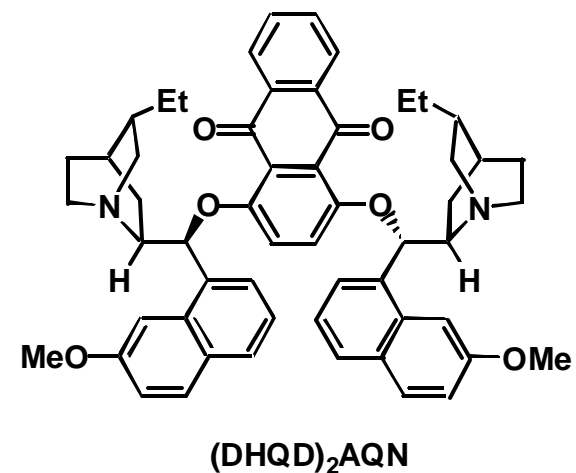
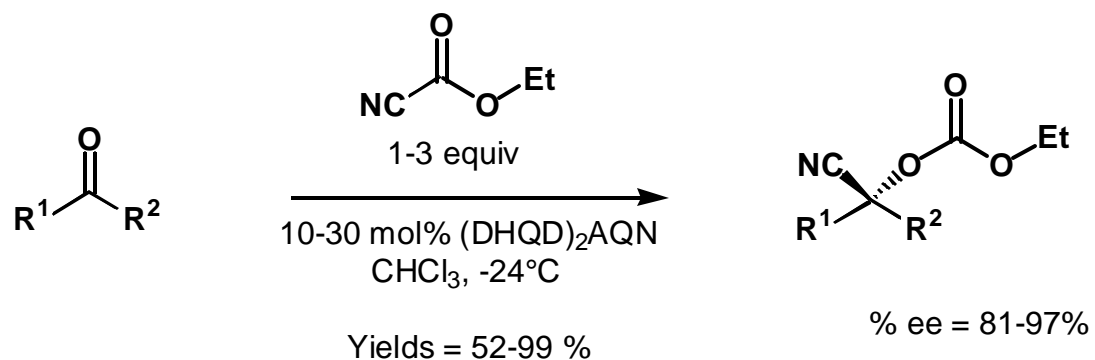


Lewis Base Activation of Electrophiles: Rearrangement of *O*-Acylated Azlactones

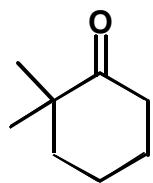
Mechanistic Insights:



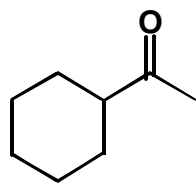
Lewis Base Activation of Electrophiles: Asymmetric Cyanation of Ketones



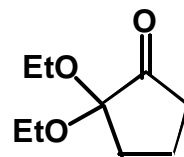
% ee = 95
yield % = 66



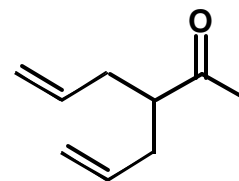
% ee = 91
yield % = 62



% ee = 87
yield % = 52

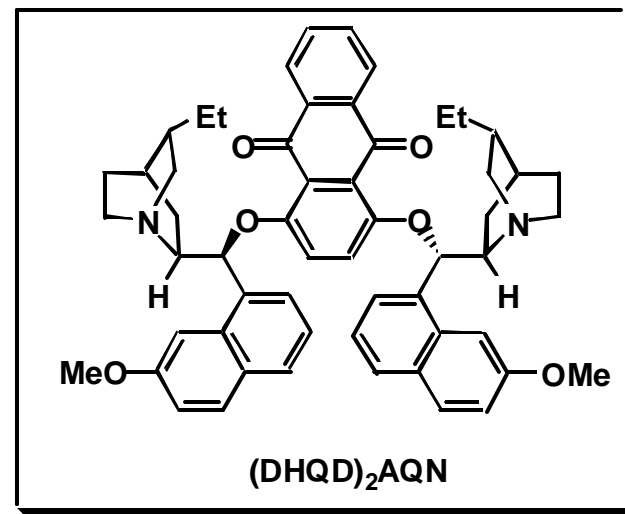
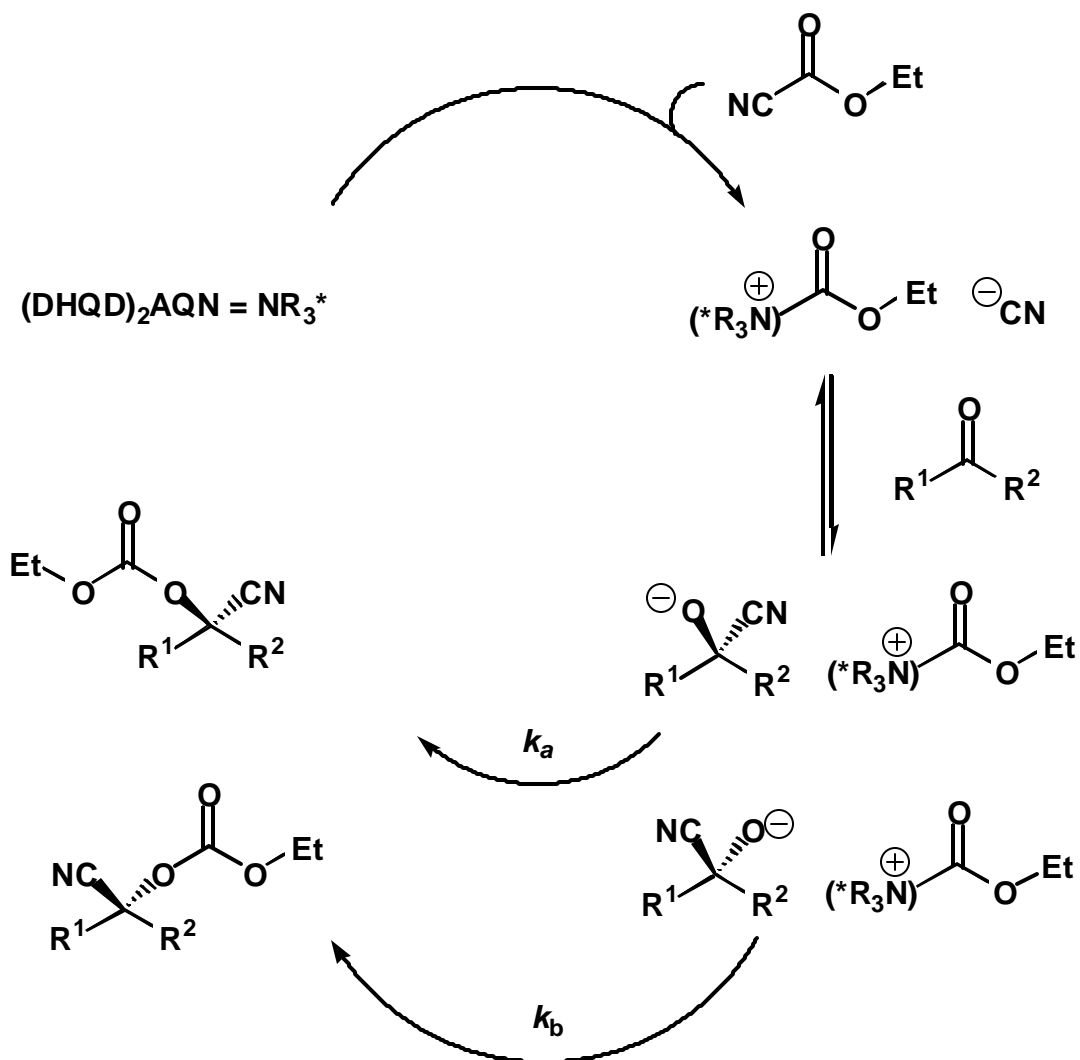


% ee = 94
yield % = 99



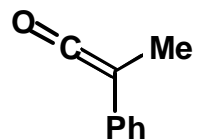
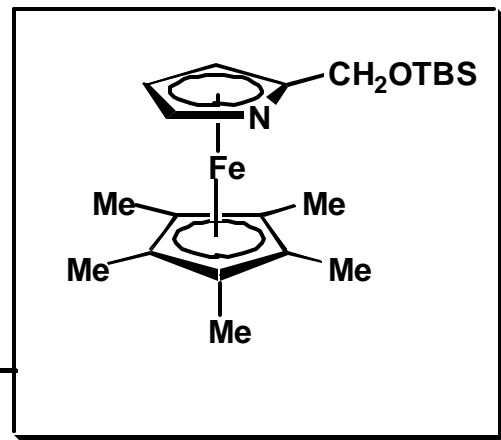
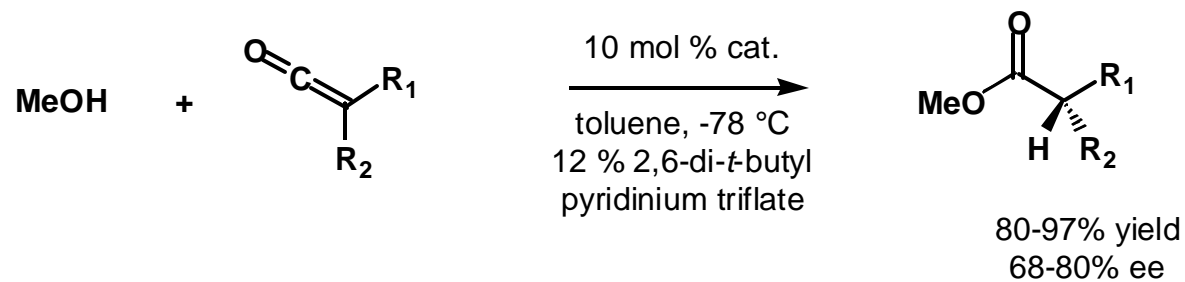
% ee = 81
yield % = 54

Lewis Base Activation of Electrophiles: Asymmetric Cyanation of Ketones

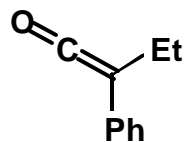


Dynamic Kinetic Resolution

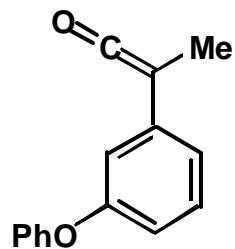
Lewis Base Activation of Nucleophiles: Addition of Alcohols to Ketenes



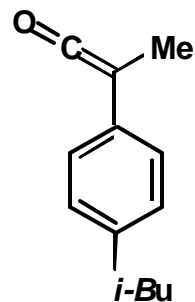
87% y, 77% ee



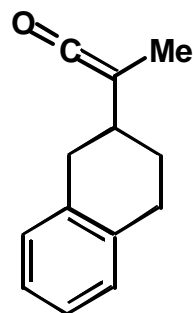
92% y, 68% ee



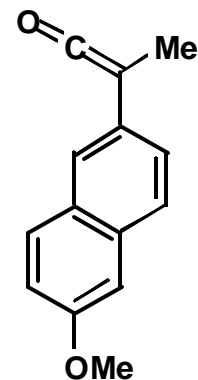
96% y, 74% ee



88% y, 77% ee

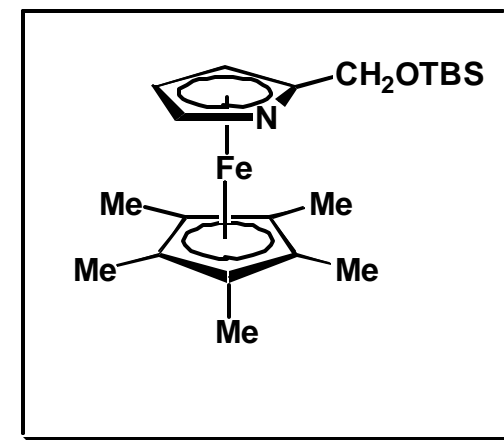
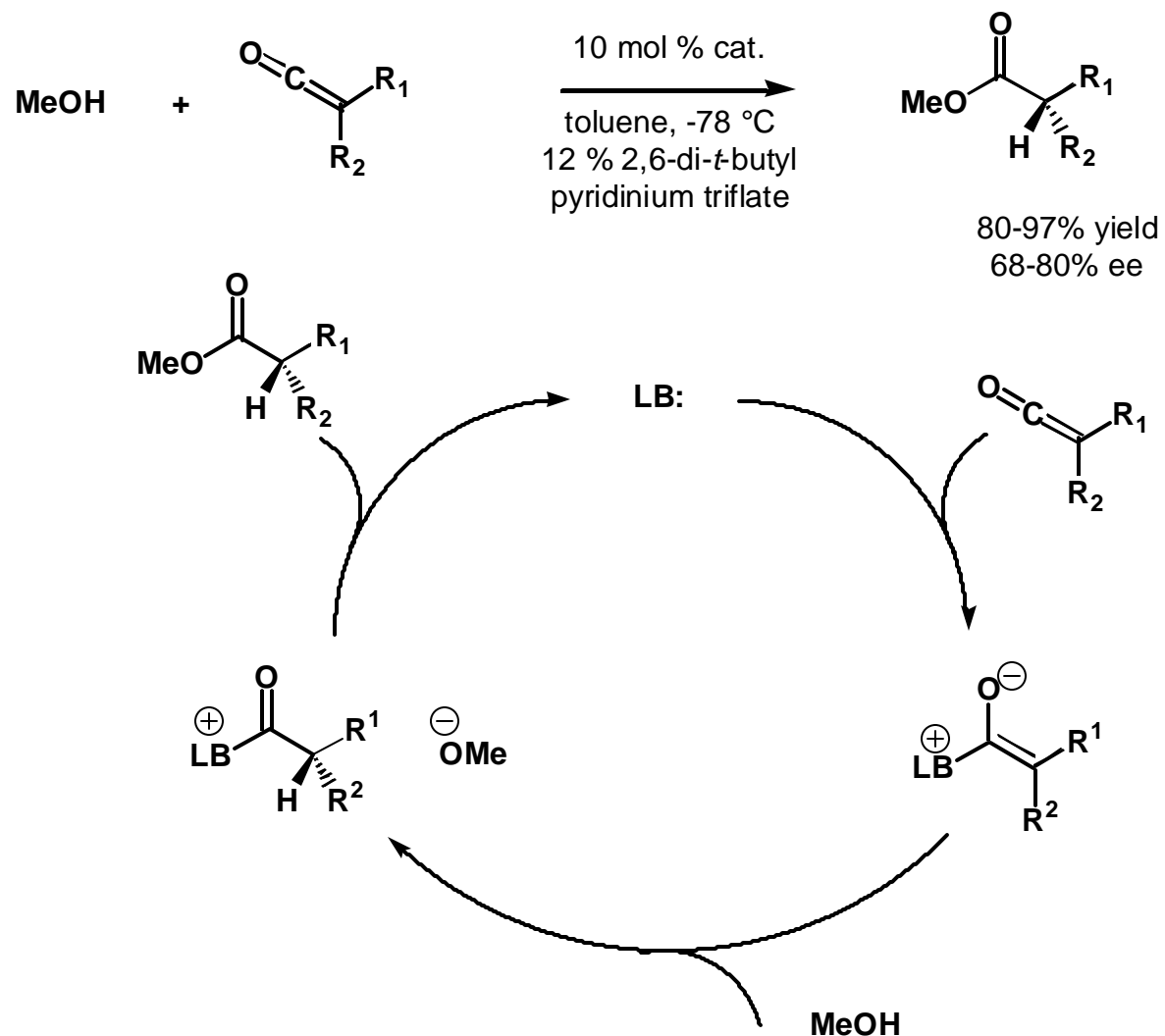


97% y, 80% ee



80% y, 75% ee

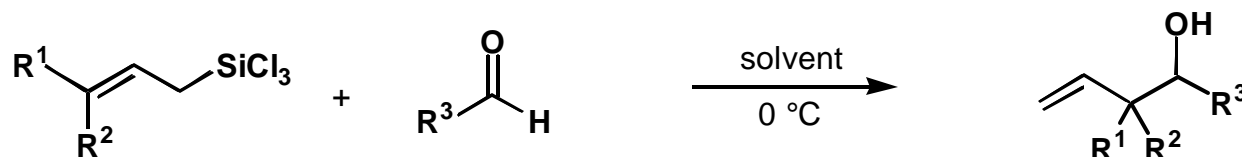
Lewis Base Activation of Nucleophiles: Addition of Alcohols to Ketenes



Lewis Base Activation of Nucleophiles: Allylation with allyltrichlorosilanes

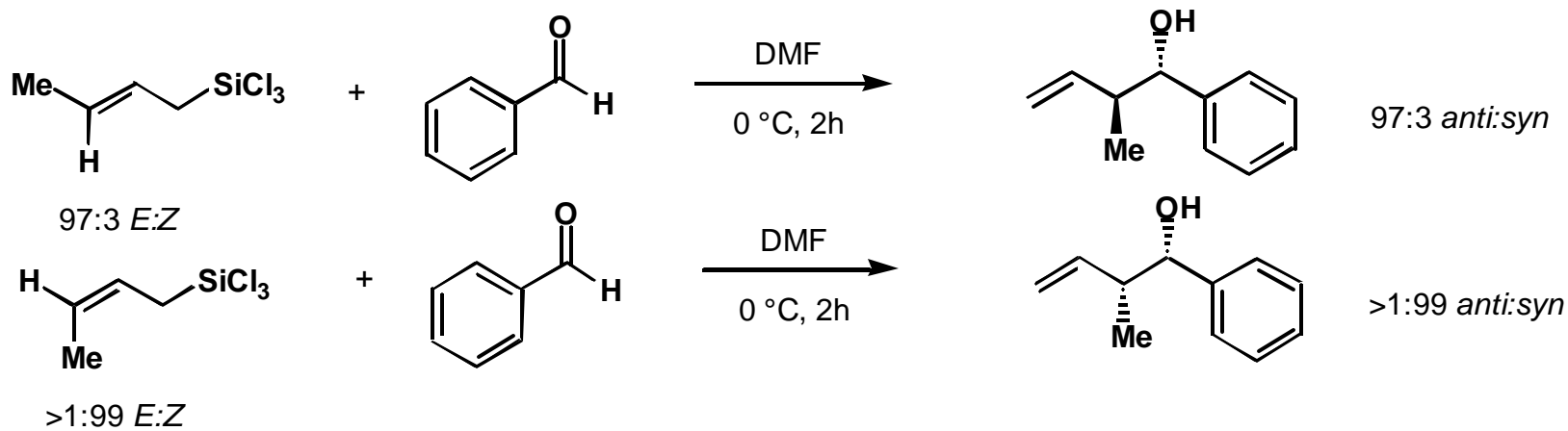
Achiral Reaction:

A Lewis Base is crucial for this reaction



Solvent	Yield (%)
CH_2Cl_2	trace
Et_2O	trace
benzene	trace
THF	trace
DMF	90
CH_2Cl_2 + 1 equiv DMF	68

The reaction is stereospecific

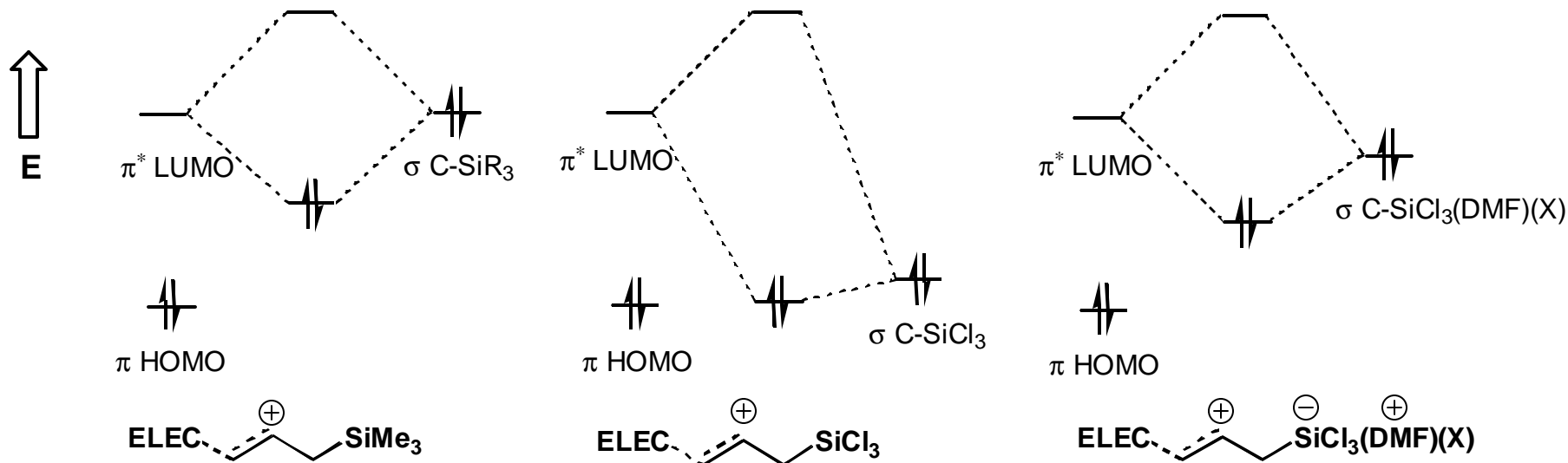
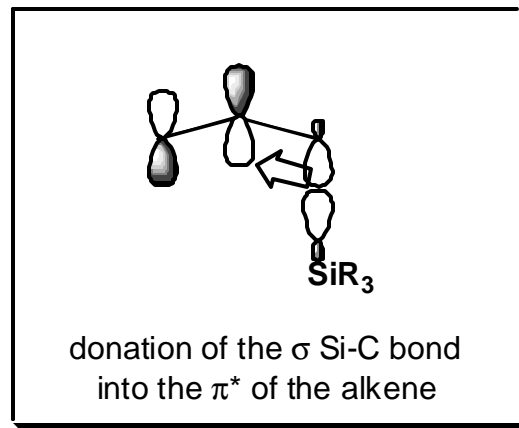
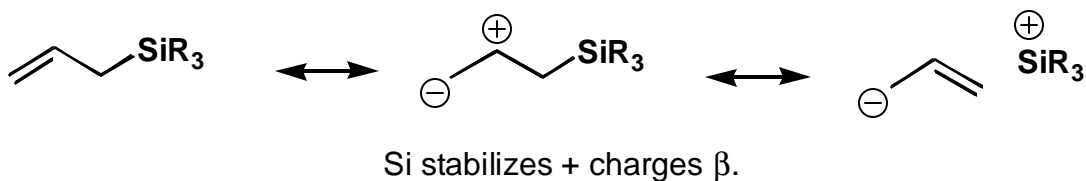


Kobayashi, S.; Nishio, K. *J. Org. Chem.* **1994**, *59*, 6620-6628.

Lewis Base Activation of Nucleophiles: Allylation with Allyltrichlorosilanes

What role does the DMF play?

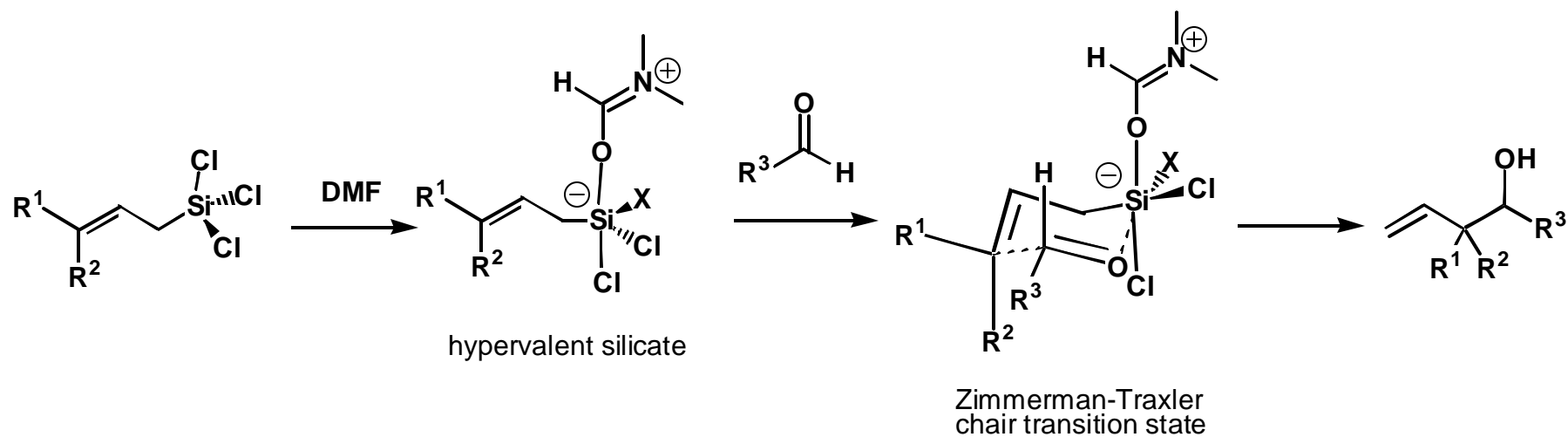
⊕



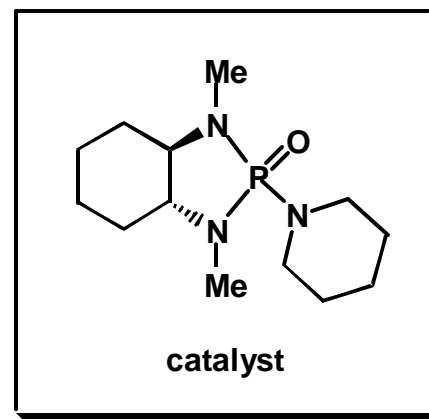
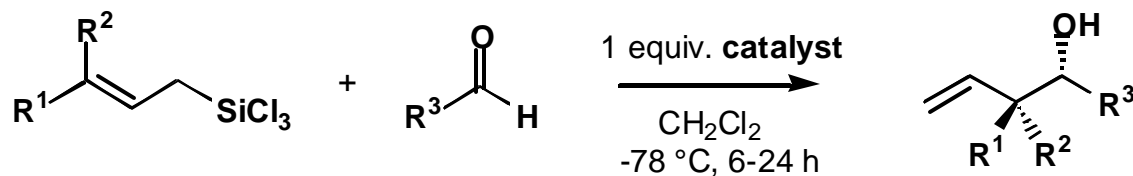
The DMF increases the nucleophilicity of the allylsilane

Lewis Base Activation of Nucleophiles: Allylation with Allyltrichlorosilanes

Achiral Reaction Mechanism:



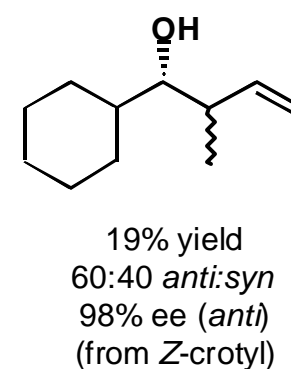
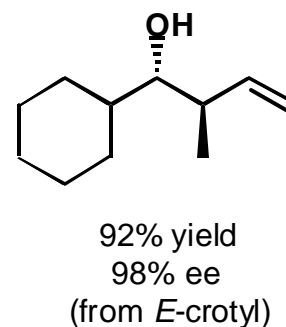
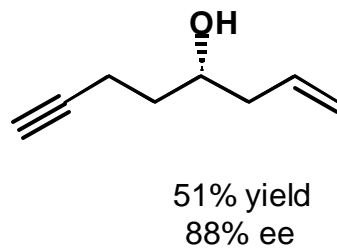
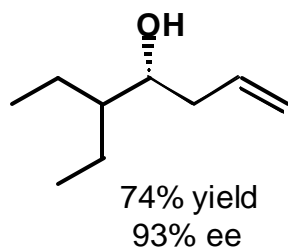
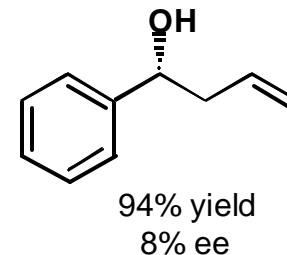
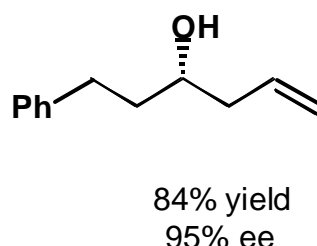
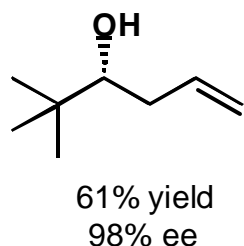
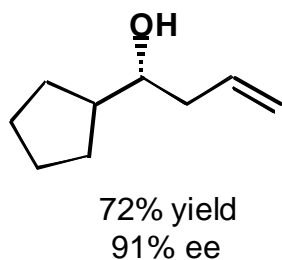
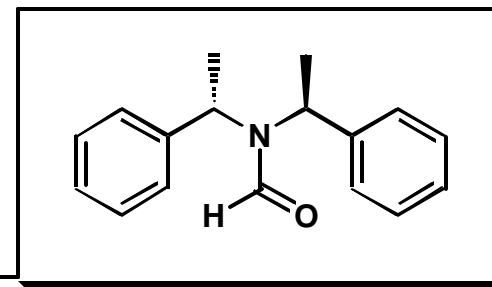
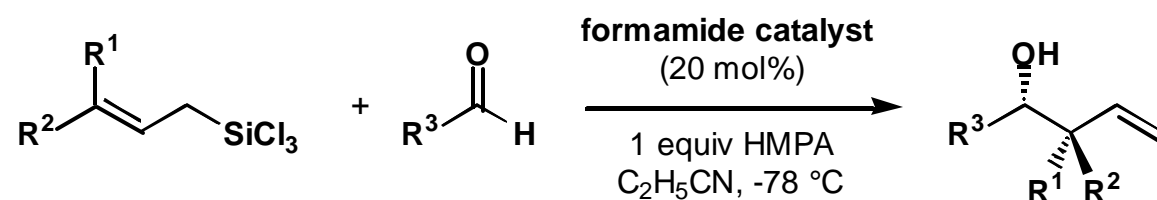
Lewis Base Activation of Nucleophiles: Allylation with Allyltrichlorosilanes: Phosphoramides



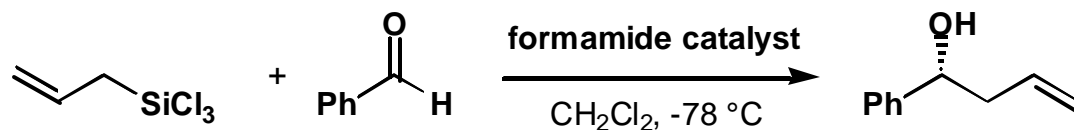
R ¹	R ²	R ³	Yield (%)	ee (%)
H	H	C ₆ H ₅	81	60
H	H	2-MeC ₆ H ₄	81	65
H	H	4-NO ₂ C ₆ H ₄	76	21
H	H	4-MeOC ₆ H ₄	80	50
Me	H	C ₆ H ₅	72 (98:2 anti:syn)	60
H	Me	C ₆ H ₅	68 (2:98 anti:syn)	66
H	H	C ₆ H ₅	74	59

using 25 mol% catalyst →

Lewis Base Activation of Nucleophiles: Allylation with Allyltrichlorosilanes

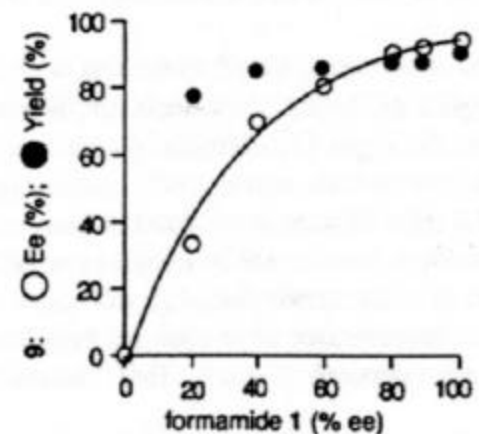
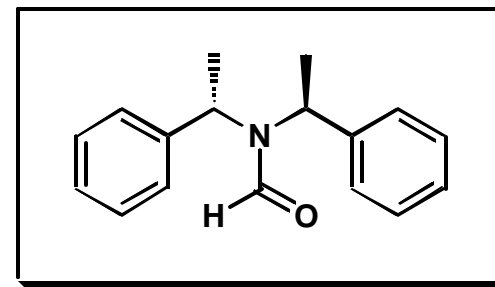


Lewis Base Activation of Nucleophiles: Allylation with Allyltrichlorosilanes

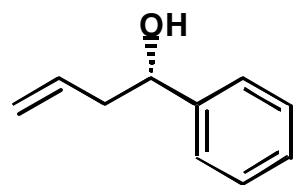
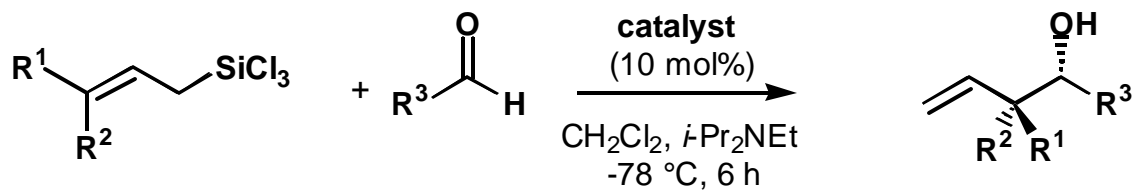


Formamide (mol%)	Yield (%)	% ee
100	81	68 (R)
50	45	40 (R)
25	20	30 (S)
10	12	32 (S)

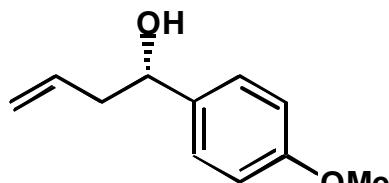
Observation of a positive non-linear effect suggests more than one formamide in the transition structure.



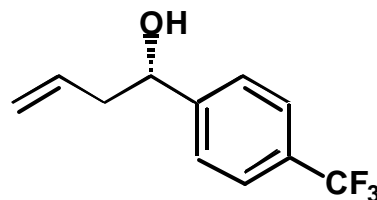
Lewis Base Activation of Nucleophiles: Allylation with Allyltrichlorosilanes



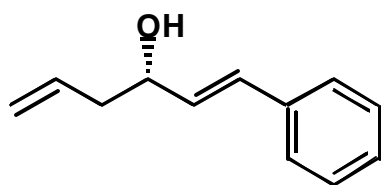
85% yield, 88% ee



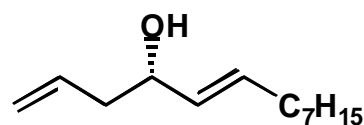
91% yield, 92% ee



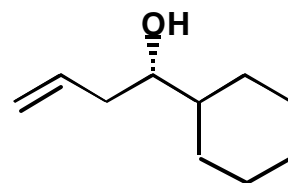
71% yield, 71% ee



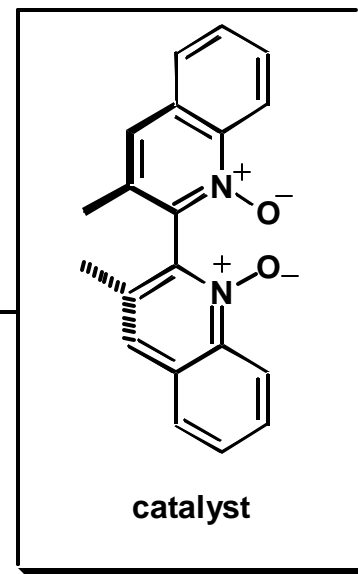
87% yield, 80% ee



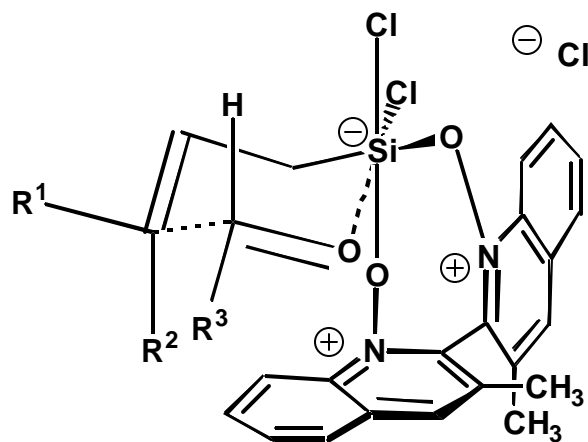
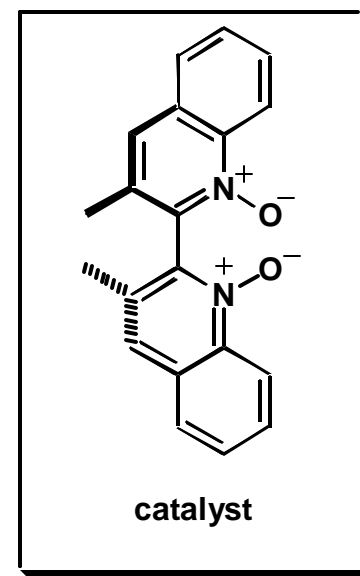
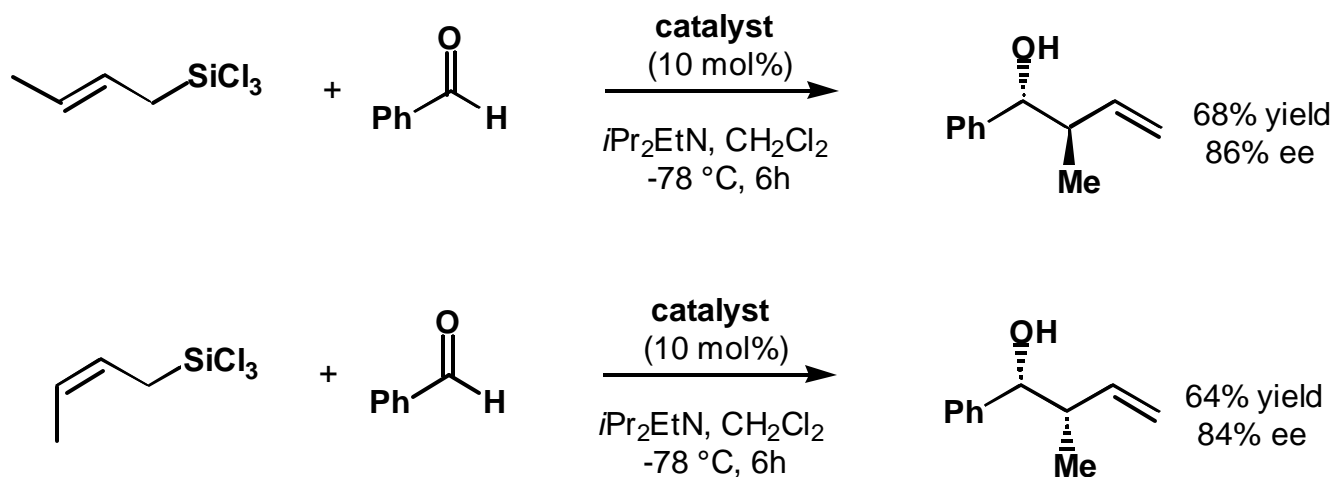
74% yield, 81% ee



27% yield, 28% ee

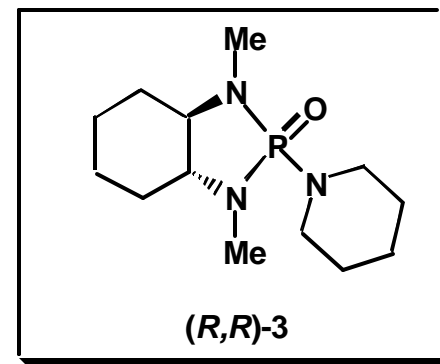
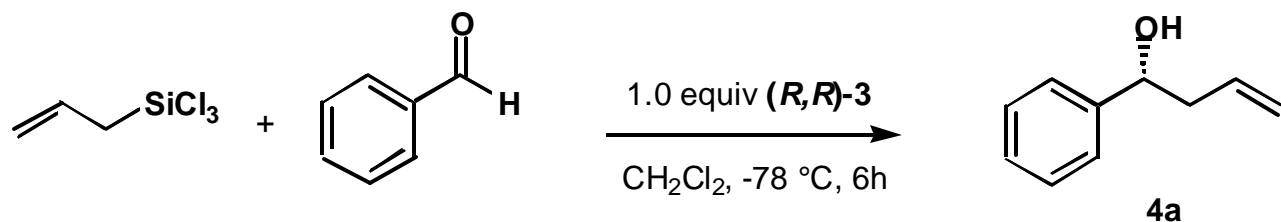


Lewis Base Activation of Nucleophiles: Allylation with Allyltrichlorosilanes

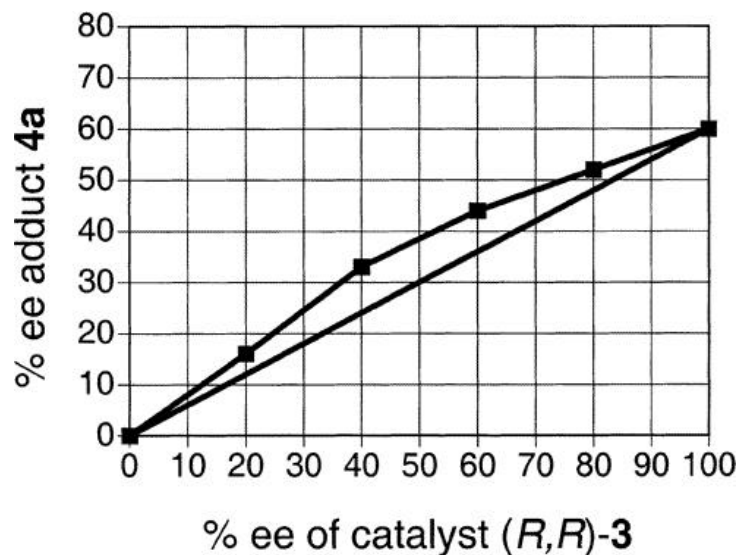


Lewis Base Activation of Nucleophiles: Allylation with Allyltrichlorosilanes

Mechanistic Insights:



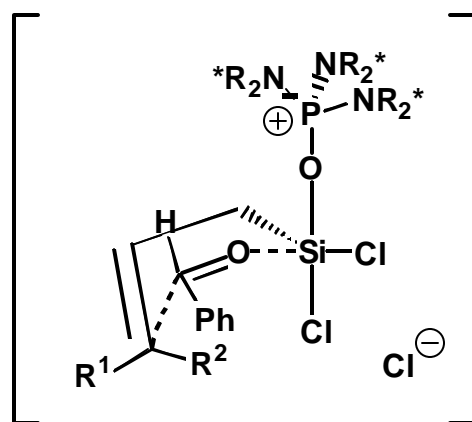
- at reduced catalyst loadings the % ee erodes despite the lack of a competitive uncatalyzed reaction.



- a modest ($g = 0.46$) positive non-linear effect was observed.
- the rate was determined to be 1st order in trichloroallylsilane, and benzaldehyde. (ReactIR)
- the displays a higher order dependance on catalyst (R,R) -3, with an order of 1.77

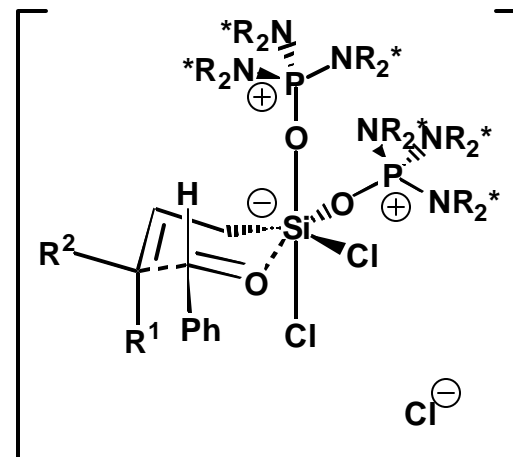
Lewis Base Activation of Nucleophiles: Allylation with Allyltrichlorosilanes: Mechanism

Possible Transition States:



trigonal bipyramidal boat

low ee
 $E = \text{syn}, Z = \text{anti}$



octahedral chair

high ee
 $E = \text{anti}, Z = \text{syn}$

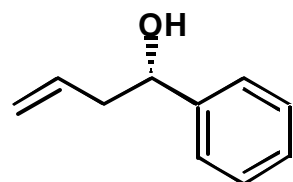
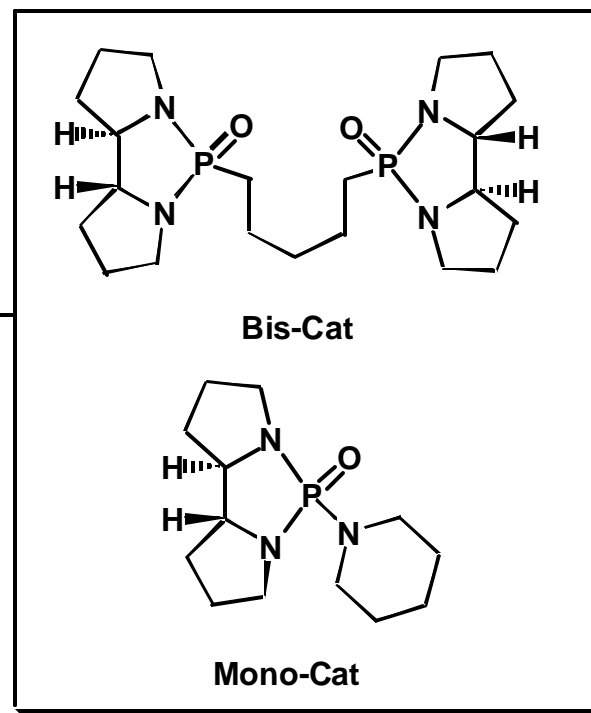
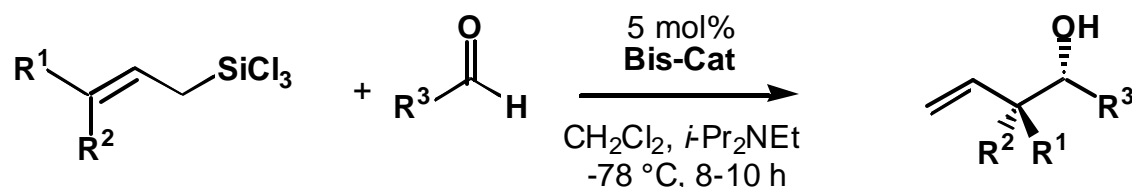
Denmark, S. E.; Fu, J. *J. Am. Chem. Soc.* **2000**, *122*, 12021-12022.

- octahedral chair mechanism would require ionization of a chloride ligand:

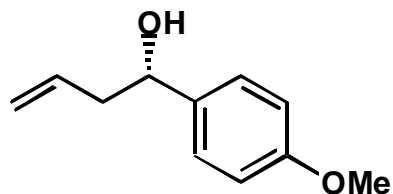
addition of AgOTf increases the rate of the reaction where addition of Cl^- dramatically decreases the rate.

Short, J. D.; Attenoux, S.; Berrisford, D. J. *Tetrahedron Lett.* **1997**, *38*, 2351-2354.

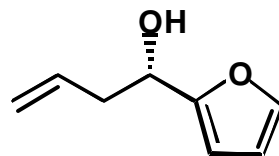
Lewis Base Activation of Nucleophiles: Allylation with Allyltrichlorosilanes : Bidentate LB



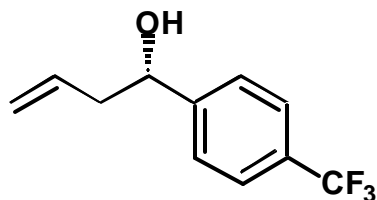
85% yield, 87% ee
(56% yield, 56% ee
from **Mono-Cat**)



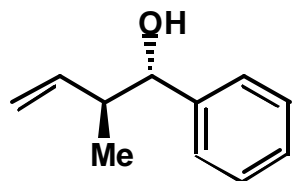
84% yield, 88% ee



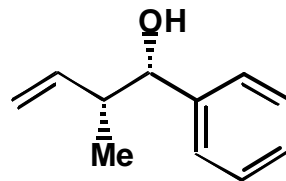
59% yield, 81% ee



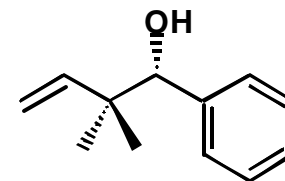
79% yield, 80% ee



82% yield, 86% ee
99:1 *anti:syn*
(from *E*-crotylsilane)



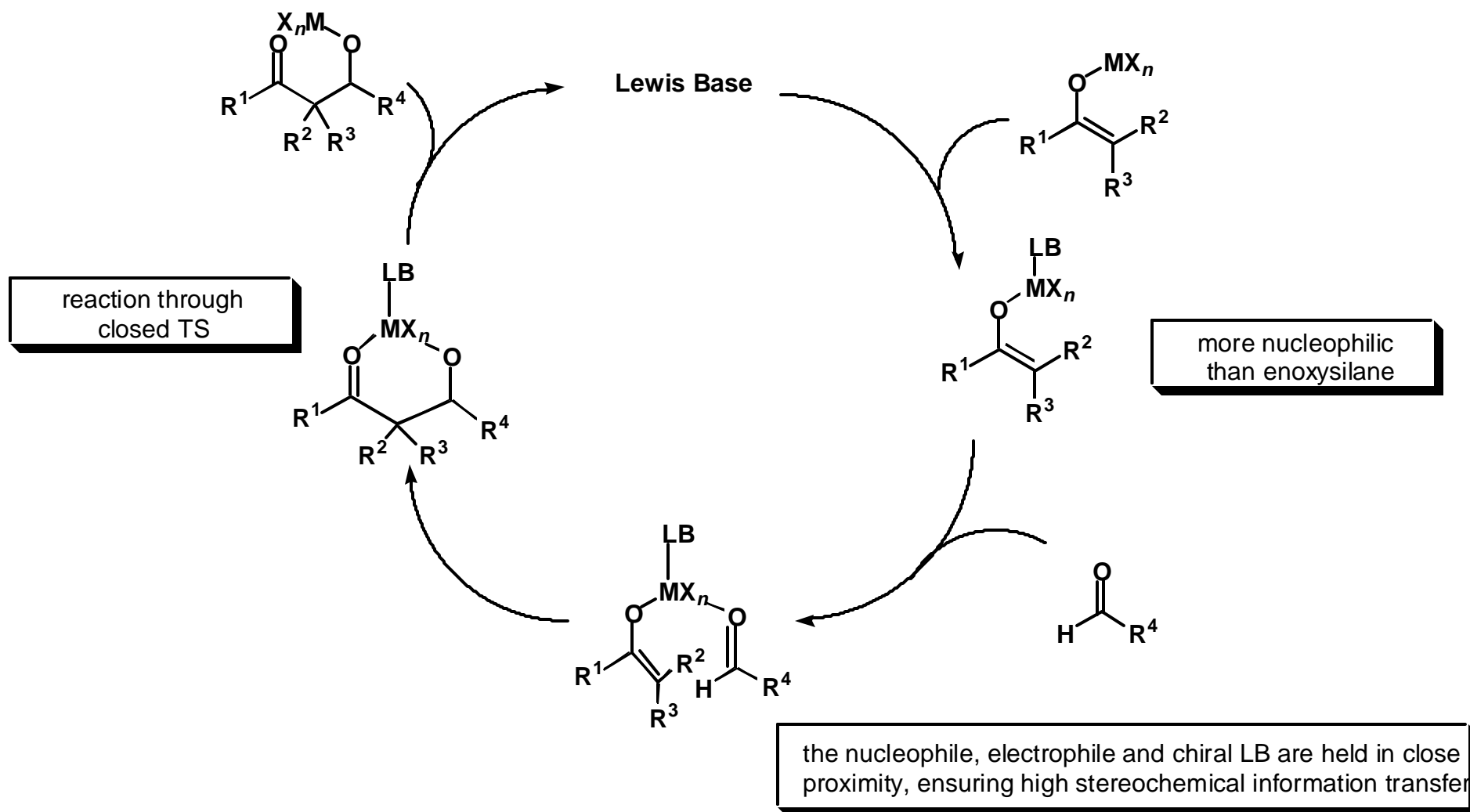
89% yield, 94% ee
1:99 *anti:syn*
(from *Z*-crotylsilane)



89% yield, 96% ee

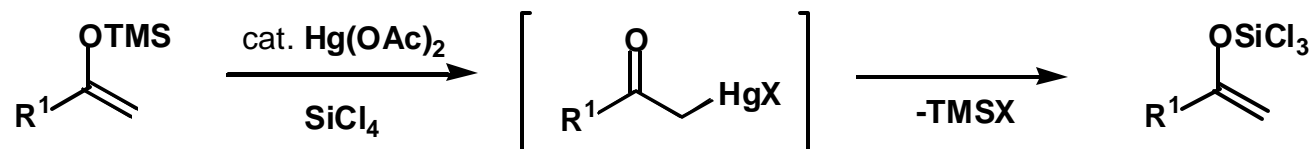
Lewis Base Activation of Nucleophiles: Aldol Reaction of Enoxysilanes

Basic Premises: Simultaneous activation of nucleophile and electrophile

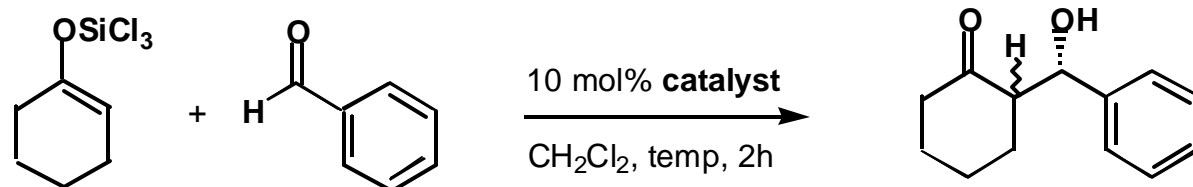


Lewis Base Activation of Nucleophiles: Aldol Reaction of Enoxysilanes

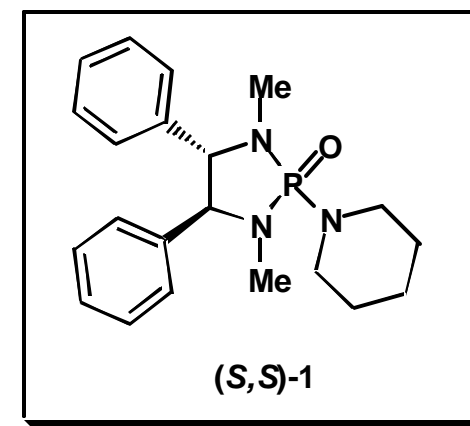
Formation of Enoxysilanes from Silylenol ethers:



Chiral phosphoramidate catalyzed addition:

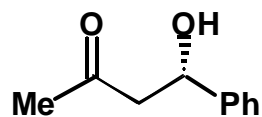
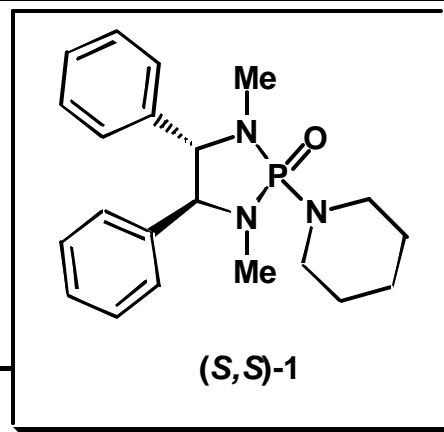
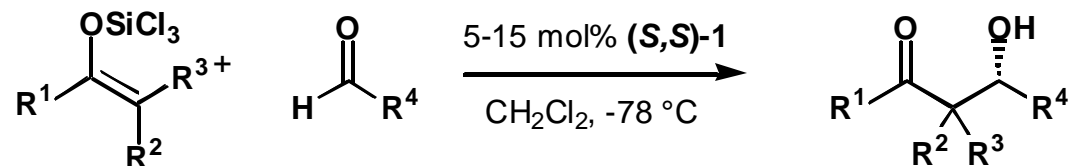


catalyst	temp (°C)	<i>syn/anti</i>	% ee	Yield (%)
(<i>S,S</i>)-1	-78	1/50	94 (<i>anti</i>)	94
none	-78	>50/1	-	19 (conv.)
none	0 (6 h)	49/1	-	92

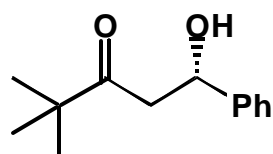


Lewis Base Activation of Nucleophiles: Aldol Reaction of Enoxysilanes

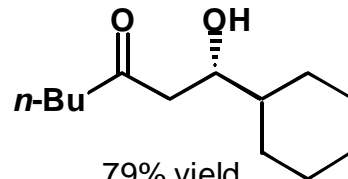
Enantioselective Aldol Reaction



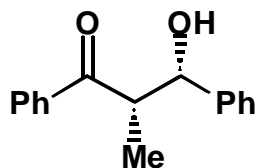
98% yield
88% ee



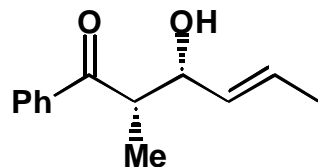
95% yield
52% ee



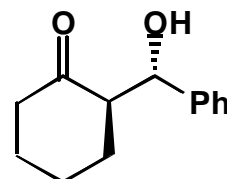
79% yield
90% ee



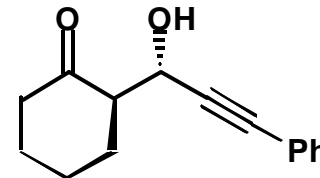
95% yield
95% ee
(from Z-silane)



94% yield
92% ee
(from Z-silane)



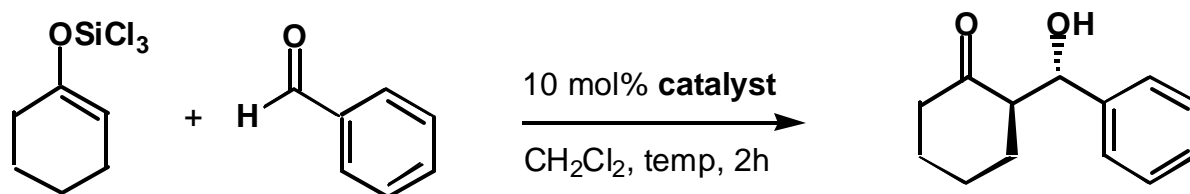
91% yield
92% ee



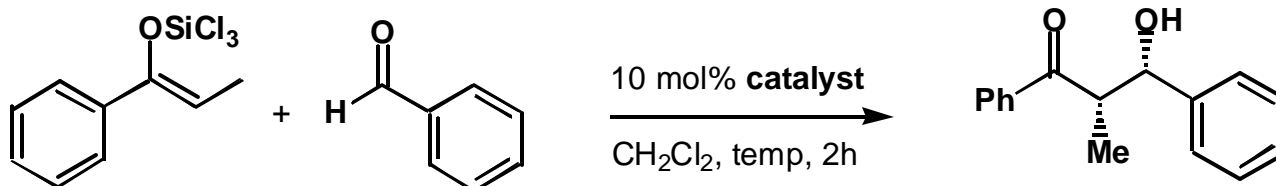
90% yield
82% ee

Lewis Base Activation of Nucleophiles: Aldol Reaction of Enoxysilanes

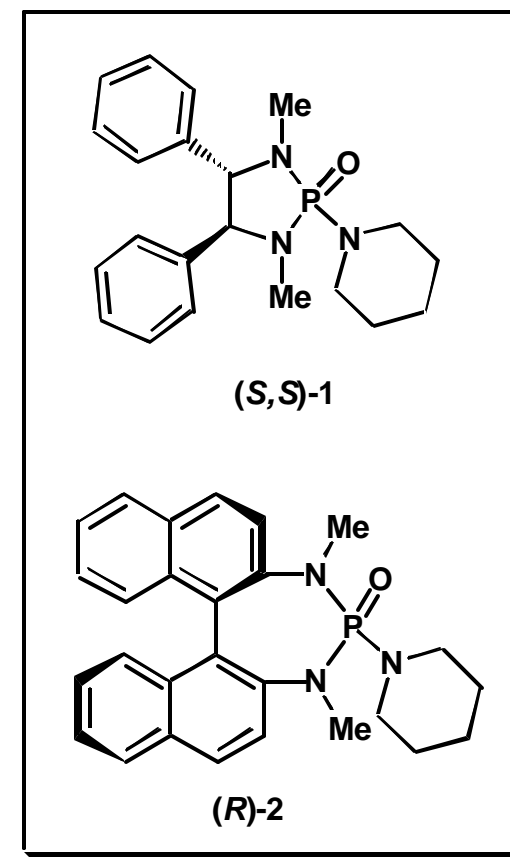
Catalyst Structure can effect ee and diastereoselectivity:



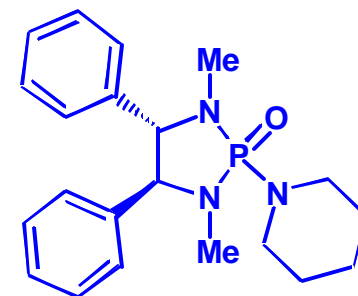
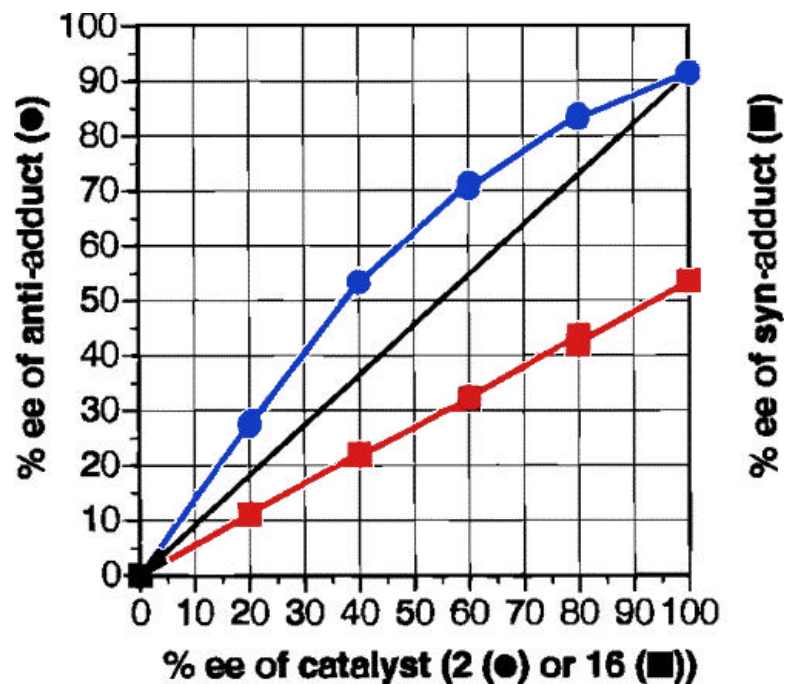
catalyst	temp (°C)	syn/anti	% ee	Yield (%)
(S,S)-1	-78	1/50	94 (<i>anti</i>)	94
(R)-2	-78	3.2/1	50 (<i>syn</i>) 56 (<i>anti</i>)	87



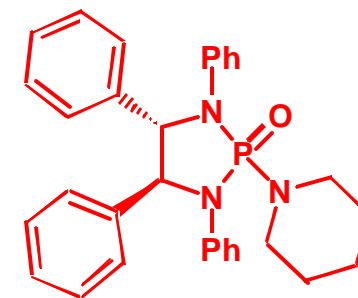
catalyst	temp (°C)	syn/anti	% ee	Yield (%)
(S,S)-1	-78	18/1	95 (<i>syn</i>)	95
(R)-2	-78	1/1.5	38 (<i>syn</i>) 6 (<i>anti</i>)	61



Lewis Base Activation of Nucleophiles: Aldol Reaction of Enoxysilanes: Non-Linear Effects

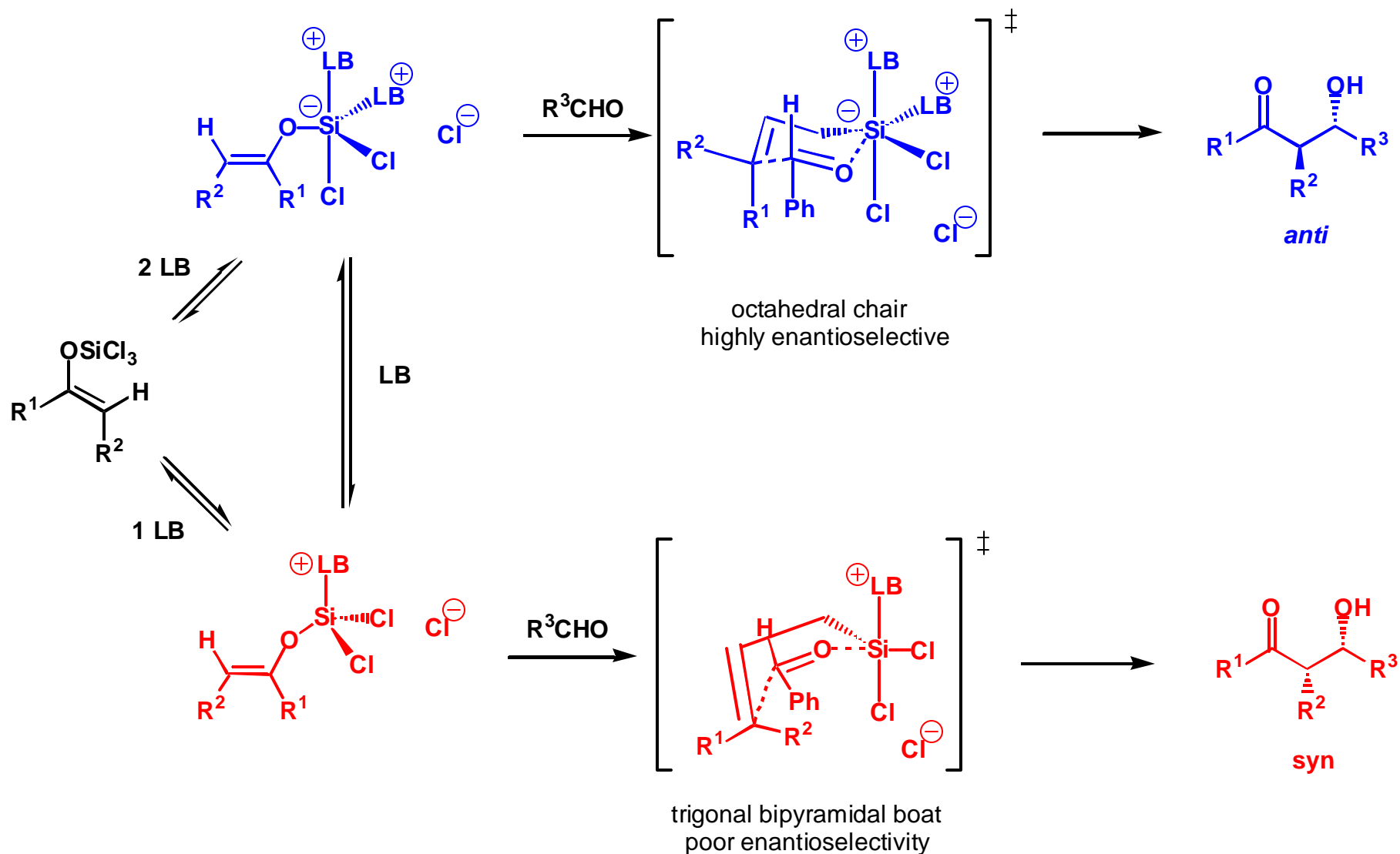


(S,S)-2- anti cat.



(R)-16 - syn cat.

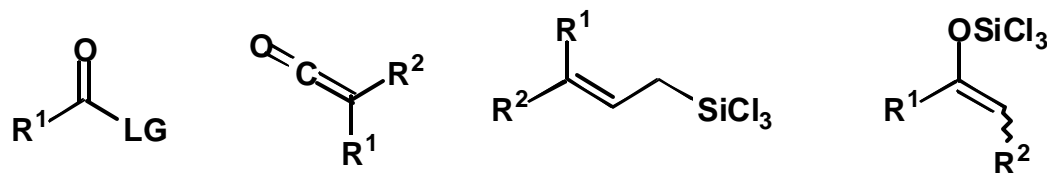
Lewis Base Activation of Nucleophiles: Aldol Reaction of Enoxysilanes: Unified Mechanism



Conclusions

The study of chiral Lewis bases has in general been neglected relative to chiral Lewis acids

- Many organic functional groups interact with Lewis bases.



- The interaction of L.B. with functional groups still needs to be better understood
- concepts are all based on well understood principles - FMO
- The L.B. activated substrate reacts far faster than the unactivated substrate.

Despite reports of a chiral Lewis base appearing over 50 years ago, this is still a relatively new area.

Chiral Lewis bases offer many advantages over chiral Lewis acid processes.

Future applications into imine additions, Michael reactions, epoxide ring opening and ?????

Acknowledgements

Dr. Robert Batey

Batey Group