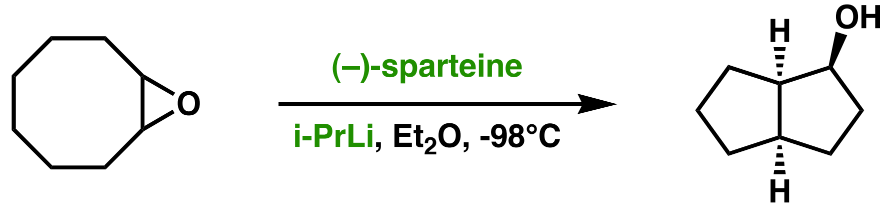
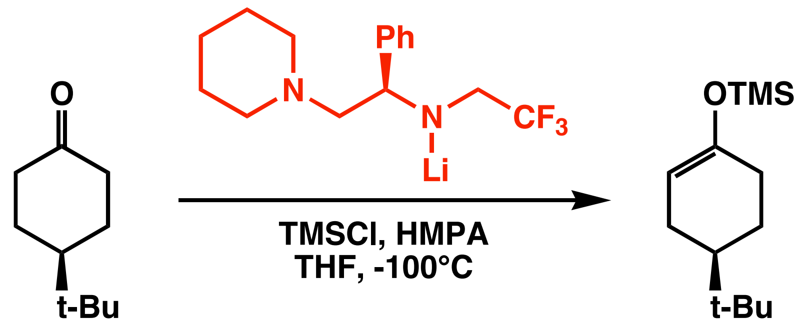


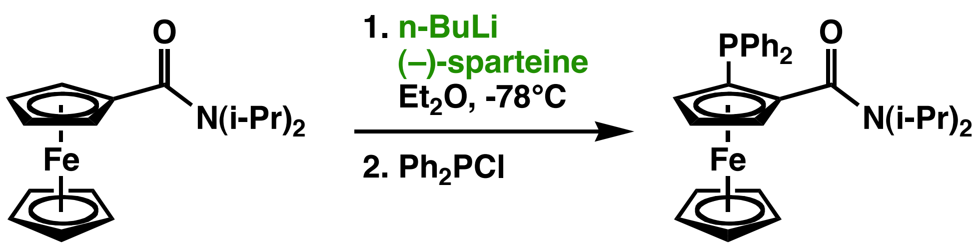
84% ee

Asymmetric Deprotonation

Ligands, Bases, and Applications



93% ee

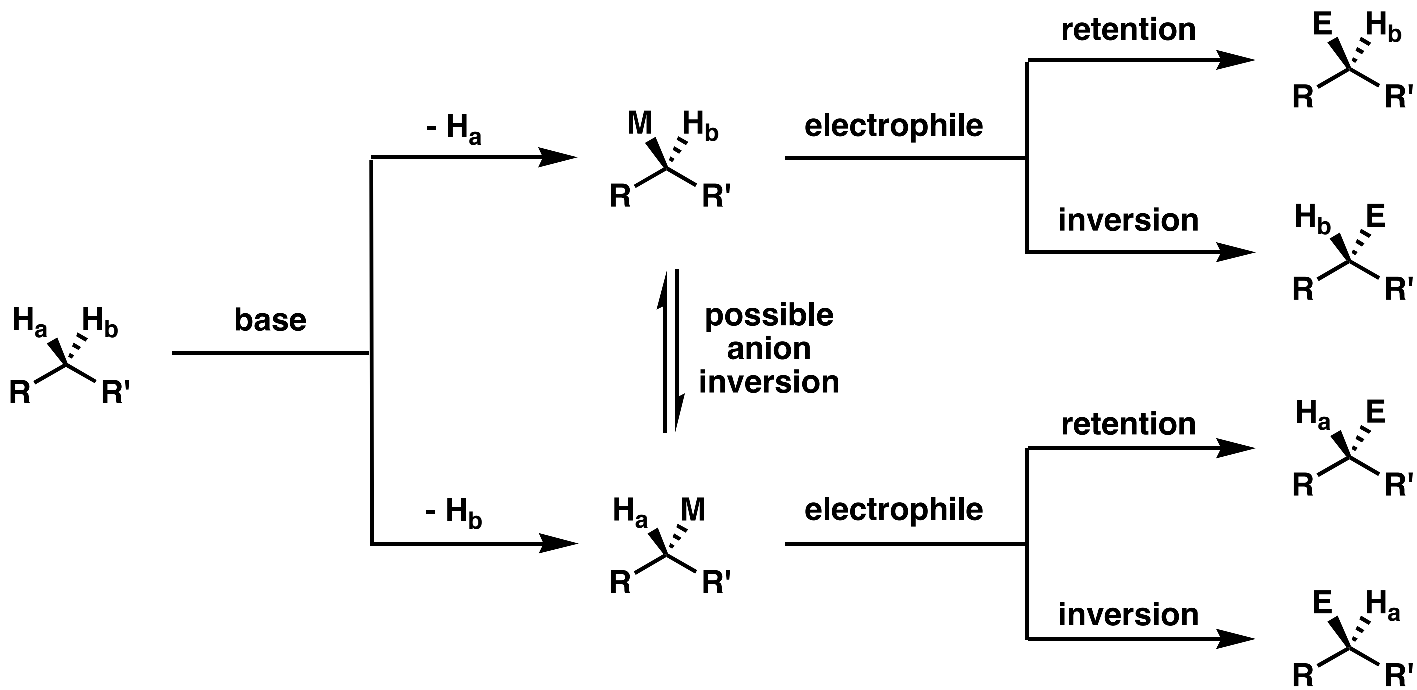


90% ee

David Ebner
Stoltz Group Literature Presentation
March 28, 2005

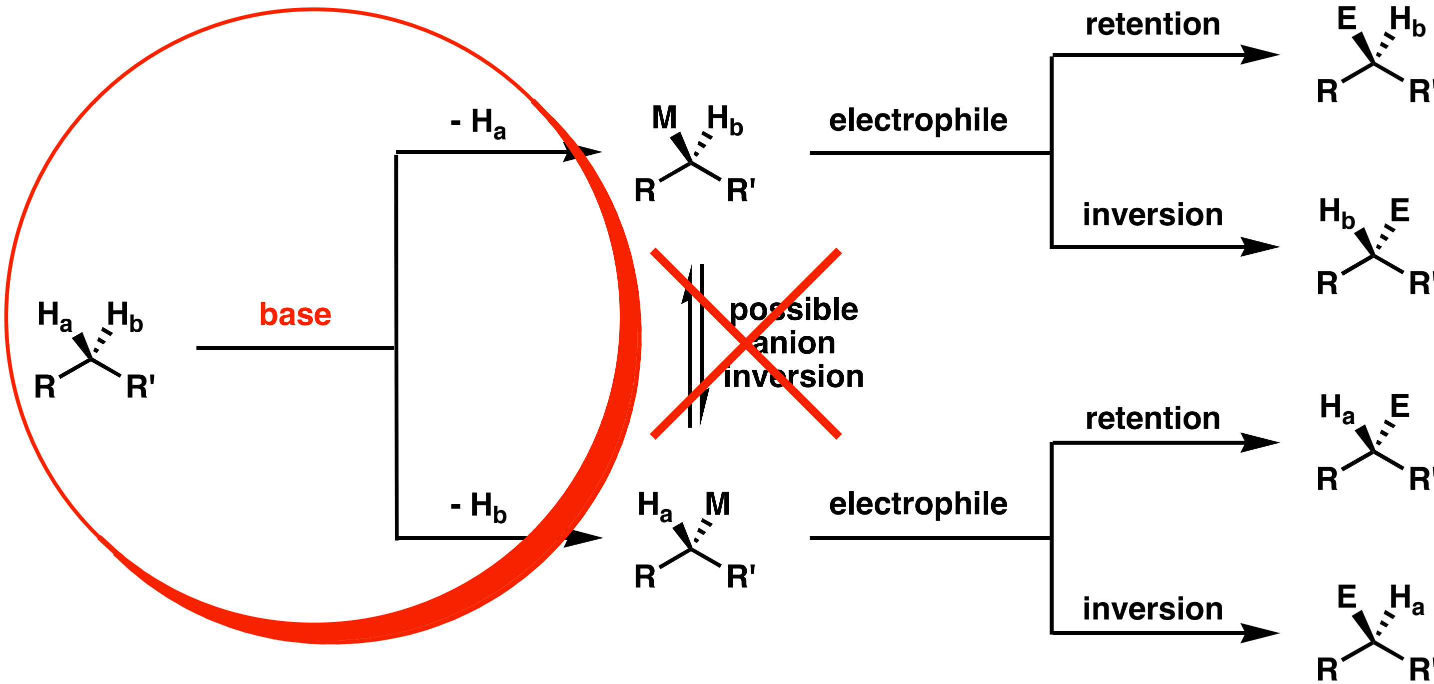
Enantioselective Deprotonation

Reaction Pathways



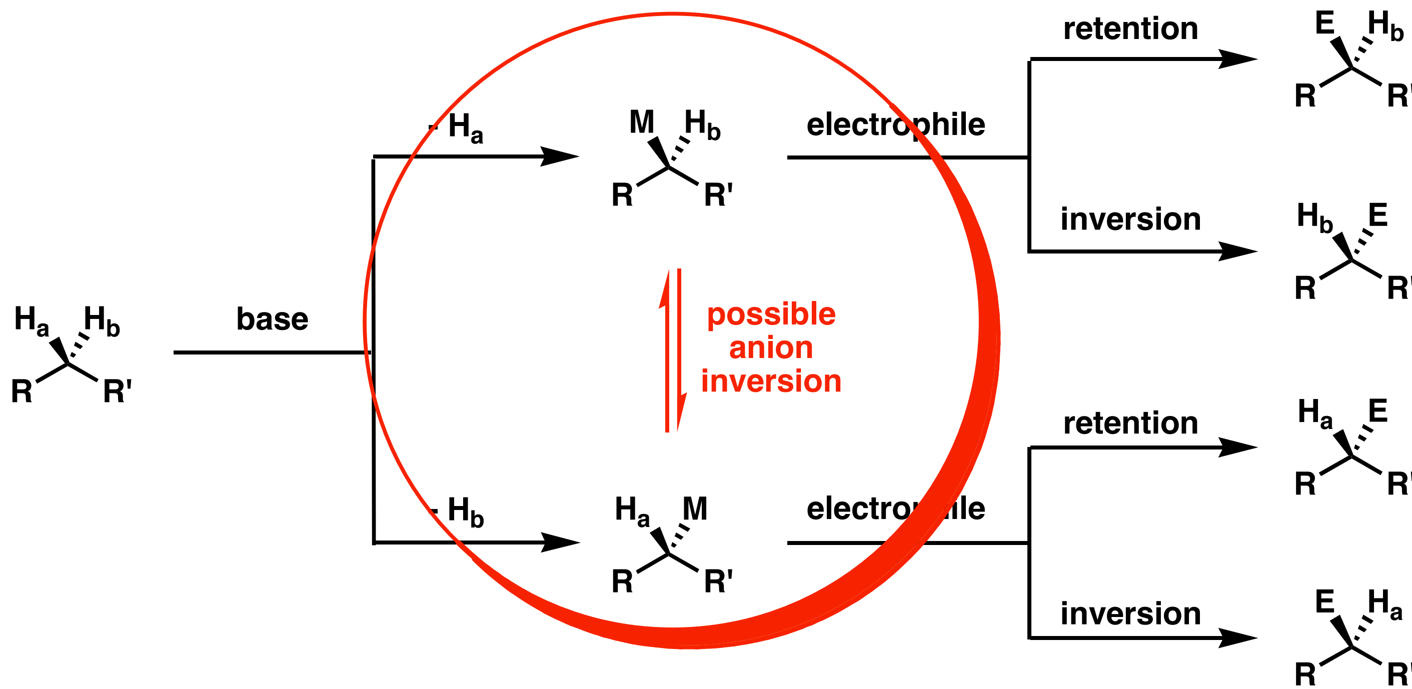
Enantioselective Deprotonation

Reaction Pathways



Enantioselective Deprotonation

What Will NOT Be Covered



Great Chemistry Not Covered Today:

- Chiral Auxiliary-Directed Deprotonation

- Enantioselective Additions of Achiral Anions to Chiral or Homochiral Electrophiles

- ***Aldols***
- ***Carbolithiations***
- ***Achiral Alkyllithium Additions to Electrophiles***

- Enantioselective Reactions of Racemic or Equilibrating Anions

- ***Deprotonation Adjacent to S, P, Se, Ph (usually)***
- ***Wittig Rearrangements***

Enantioselective Deprotonation

Outline and Key Players

I. meso-Ketone Deprotonations

II. meso-Epoxide Deprotonations

- ***a. β-Deprotonation***
- ***b. α-Deprotonation***

III. Deprotonation Adjacent to Heteroatoms

- ***a. O: Alkyl and Allylic Systems***
- ***b. N: Alkyl, Benzylic, and Allylic Systems***

IV. Other Enantioselective Deprotonations

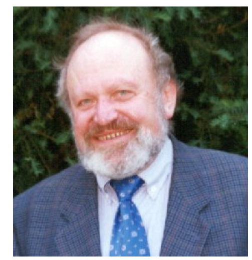
- ***a. Elimination of HX***
- ***b. Aromatic Lithiation***

K. Koga
Tokyo
Ketones

N. Simpkins
Nottingham
Ketones and Aromatics

M. Majewski
Saskatchewan
Ketones

D. Hodgson
Oxford
Epoxides



D. Hoppe
Muenster
Heteroatoms: O

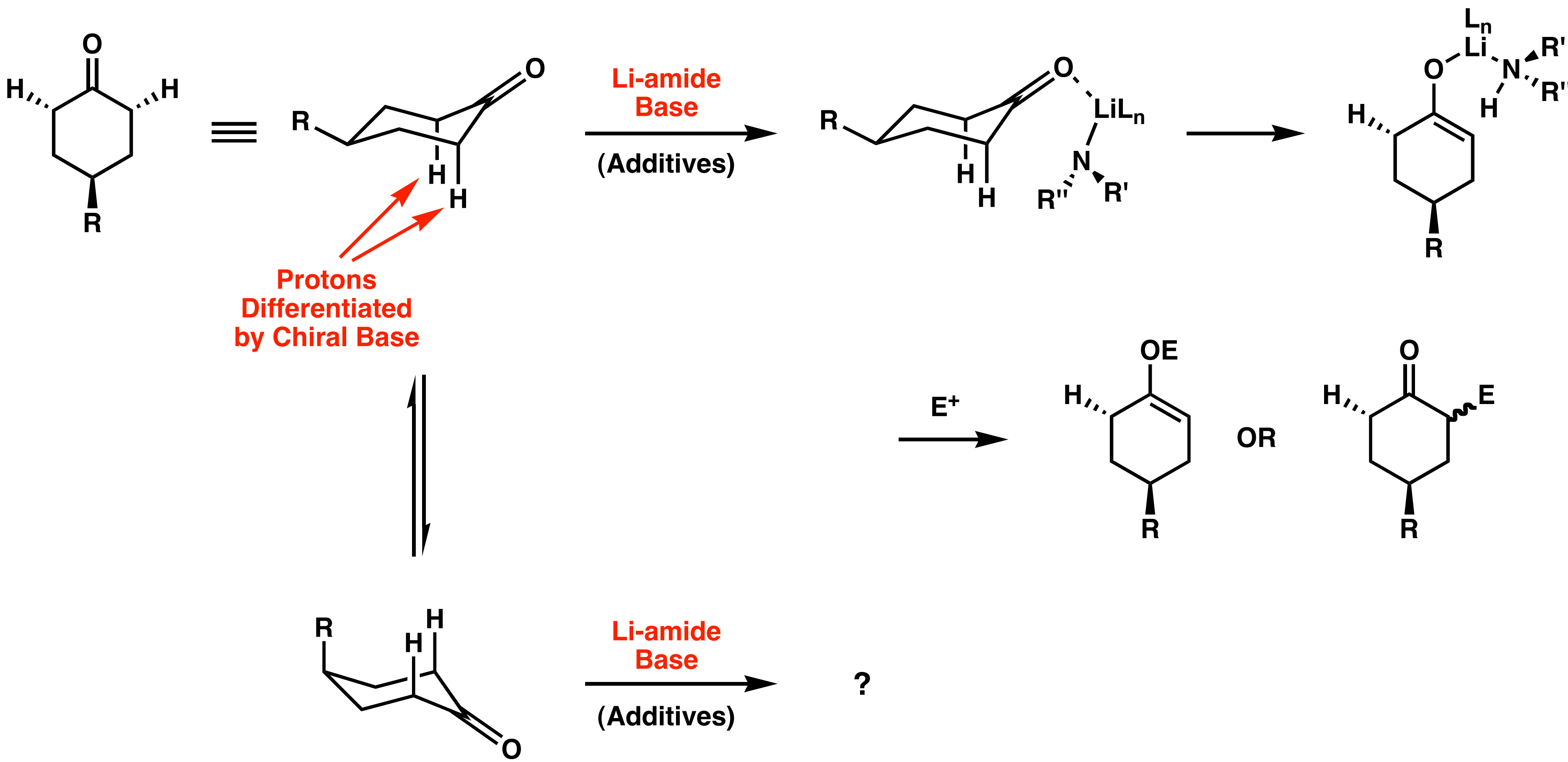
P. Beak
Illinois, Urbana-Champaign
Heteroatoms: N

General Reviews:

1. Majewski, "Enantioselective Deprotonation of Cyclic Ketones," in Advances in Asymmetric Synthesis, Vol. 3, pp 39-76, JAI Press, London: 1998.
2. Waldmann, "Enantioselective Deprotonation and Protonation," in Organic Synthesis Highlights II, H. Waldmann, ed. pp 19-28, VCH, Weinheim: 1995.
3. Organolithiums in Enantioselective Synthesis, D. Hodgson, ed. Springer, New York: 2003. (Whole book is good, especially pp 61-286.)
4. O'Brien, "Recent Advances in Asymmetric Synthesis Using Chiral Lithium Amide Bases," *J. Chem. Soc., Perkin Trans. 1*, **1998**, 1439-1457.
5. Hoppe and Hense, "Enantioselective Synthesis with Lithium/(–)-Sparteine Carbanion Pairs," *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2282-2313.
6. Hodgson, Gibbs, and Lee, "Enantioselective Desymmetrisation of Achiral Epoxides," *Tetrahedron*, **1996**, *52* (46), 14361-14384.
7. Cox and Simpkins, "Asymmetric Synthesis Using Homochiral Lithium Amide Bases," *Tetrahedron: Asymmetry*, **1991**, *2* (1), 1-26.
8. Eames, "Recent Developments in Enantioselective Deprotonation Mediated by Sub-Stoichiometric Quantities of Chiral Bases," *Eur. J. Org. Chem.*, **2002**, 393-401.
9. Beak, Basu, Gallagher, Park and Thayumanavan, "Regioselective, Diastereoselective, and Enantioselective Lithiation-Substitution Sequences: Reaction Pathways and Synthetic Applicaitons," *Acc. Chem. Res.* **1996**, *29*, 552-560.

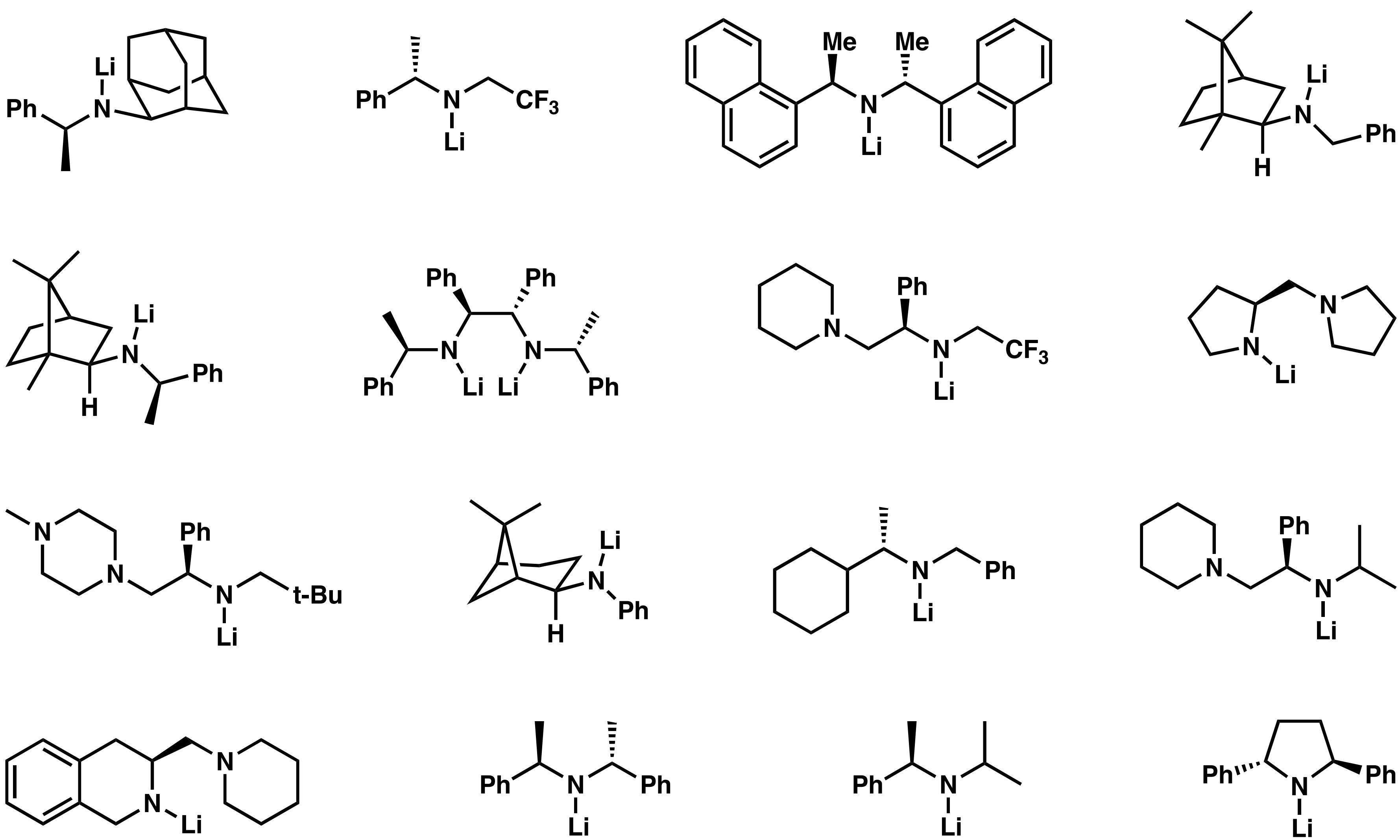
Asymmetric Deprotonation of meso Cyclic Ketones

General Considerations



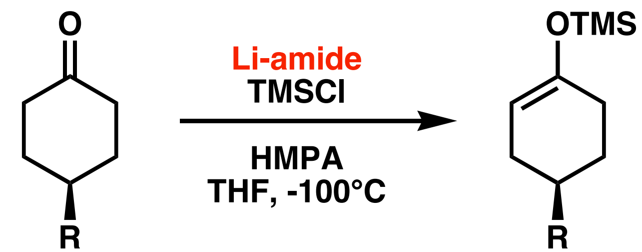
Chiral Lithium Amides Used in Ketone Deprotonations

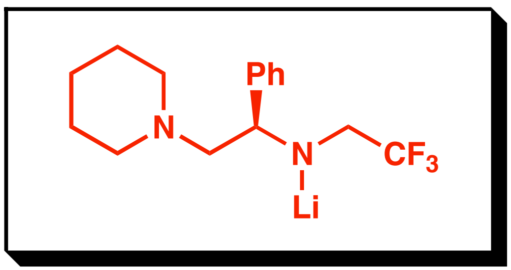
Only a Few of the Many!



Prochiral 4-Substituted Cyclohexanones

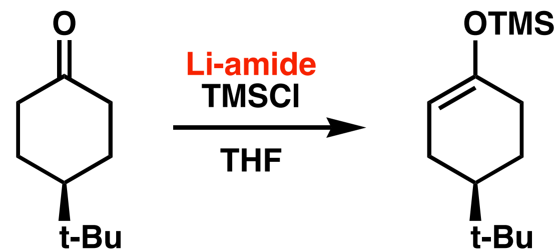
Enantioselective Deprotonation of Simple Substrates

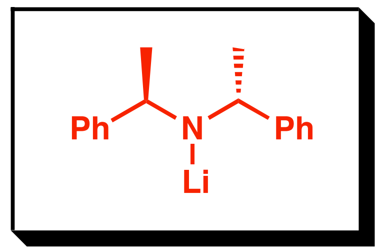




R	% Yield	% ee
Me	76	94
i-Pr	92	95
Ph	95	93
t-Bu	88	93

Koga, et. al. *Tetrahedron* **1997**, *53*, 13641



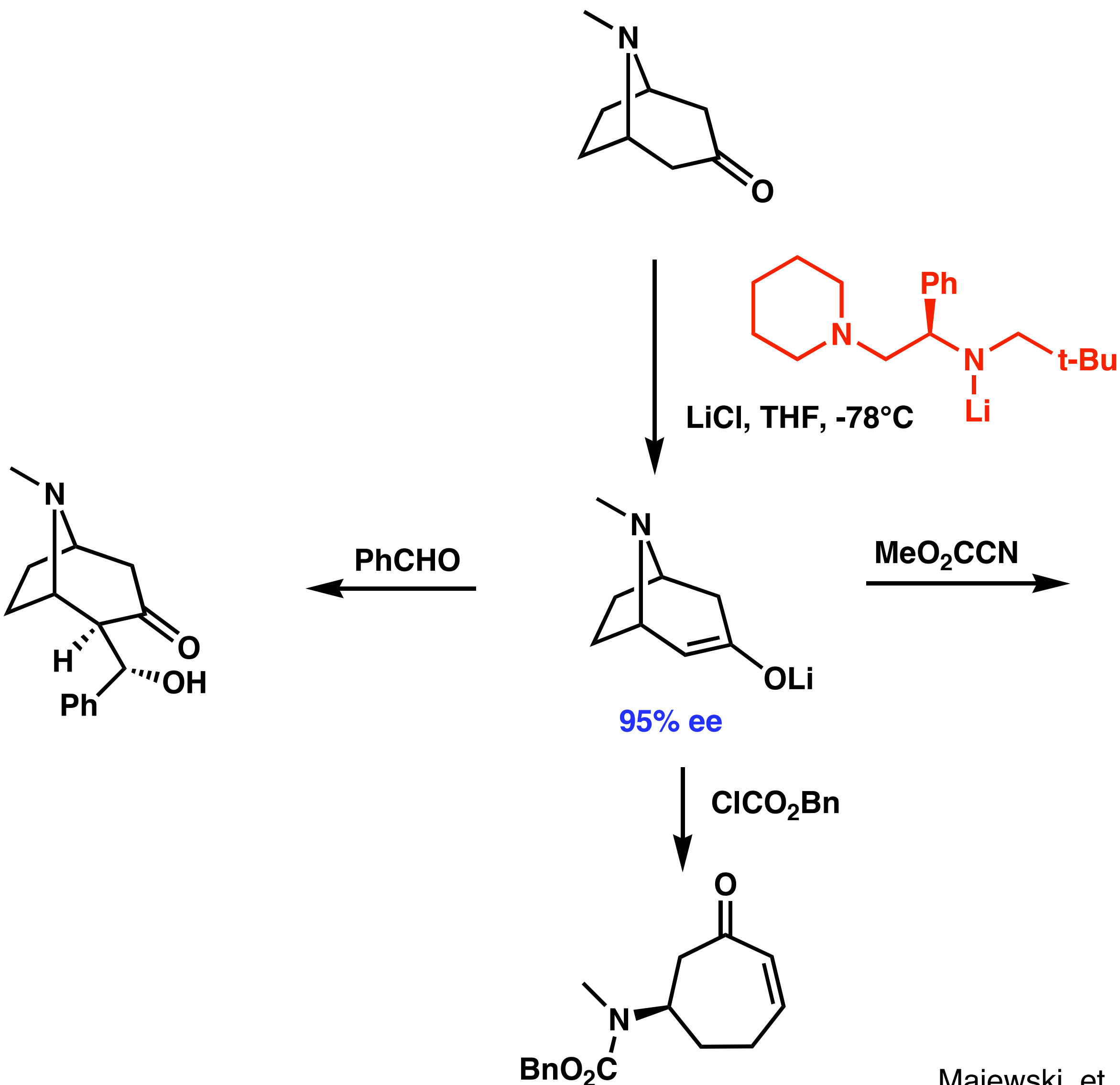


Temp (°C)	Quench	LiCl (equiv)	% ee
-78	Internal	0	69
-90	Internal	0	88
-78	External	0	23
-78	External	0.5	83

Simpkins, et. al. *J. Chem. Soc., Perkin Trans. 1* **1993**, 3113

Tropinone Derivatives

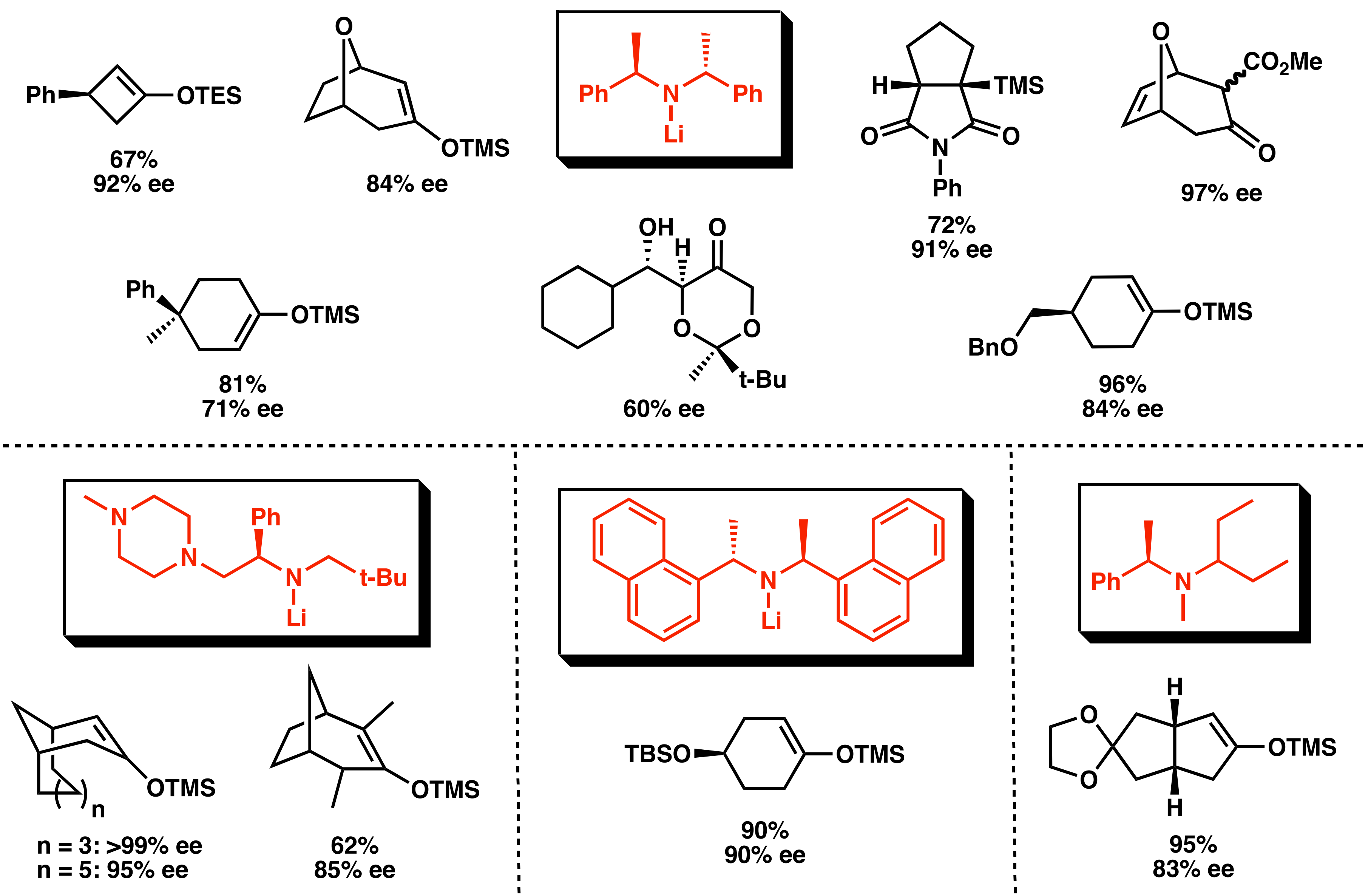
Different Conditions and Electrophiles Lead to a Variety of Products



Majewski, et. al. *Tetrahedron Lett.* **1994**, *35*, 3653
Tetrahedron Lett. **1995**, *36*, 5465

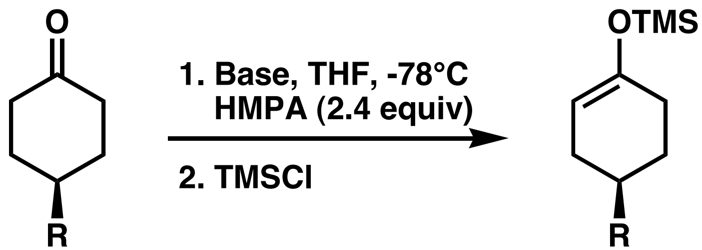
Other Prochiral Cyclic Substrates

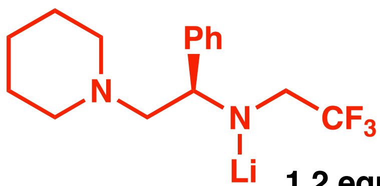
Similar Ligands Yield Good ee's with a Variety of Electrophiles



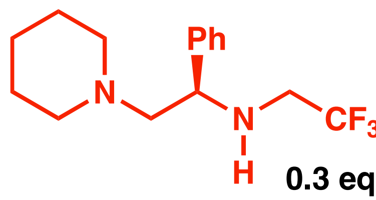
Catalytic Asymmetric Ketone Deprotonations

Early Efforts Lead to Moderate Selectivity

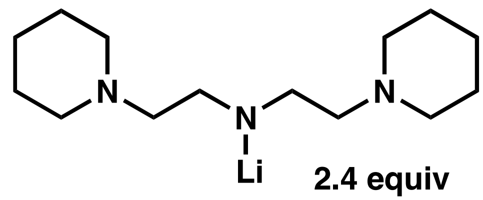




1.2 equiv



0.3 equiv



2.4 equiv

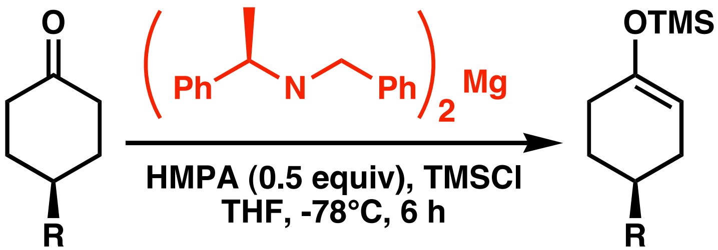
1.5 equiv DABCO

	Stoichiometric, 1 h		Catalytic, 1.5 h	
R	**% Yield**	**% ee**	**% Yield**	**% ee**
Me	**82**	**78**	**70**	**75**
i-Pr	**75**	**79**	**80**	**76**
Ph	**77**	**80**	**77**	**76**
t-Bu	**85**	**81**	**83**	**79**

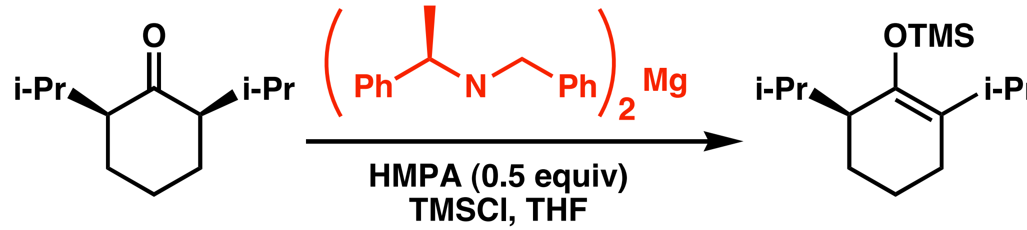
Koga, et. al. *Tetrahedron* **1997**, *53*, 1698

Chiral Magnesium Amides in Ketone Deprotonation

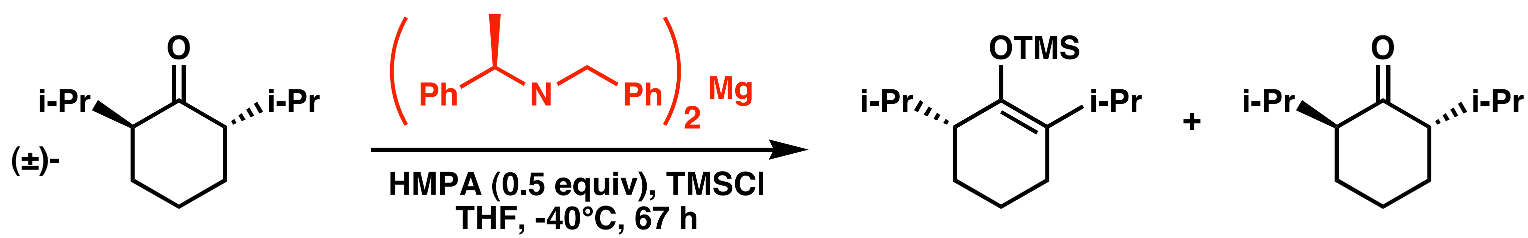
Less Reactive Alternative to Lithium Amides



R	% Conv.	% ee
Me	81	82
n-Pr	88	76
i-Pr	77	90
Ph	79	74
t-Bu	82	82



Temp (°C)	Time (h)	% Conv.	% ee
-78	39	54	>99
-60	6	66	99.4
-40	6	99	98.8
rt	2	100	82

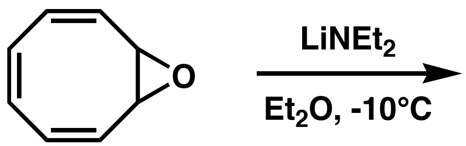


66%, 62% ee   34%, 88% ee

Kerr, Henderson, et. al. *Tetrahedron*, **2002**, *58*, 4573

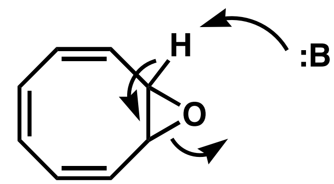
Deprotonation of Epoxides

Early Surprising Results



95%

Proposed Mechanism:

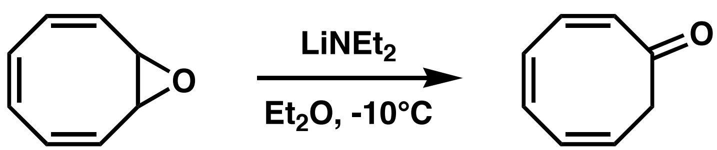


Cope and Tiffany, *J. Am. Chem. Soc.* **1951**, *73*, 4158

Cope, et. al. *J. Am. Chem. Soc.* **1958**, *80*, 2849

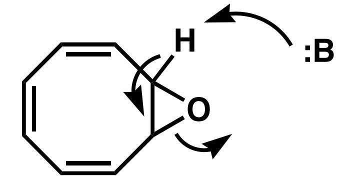
Deprotonation of Epoxides

Early Surprising Results

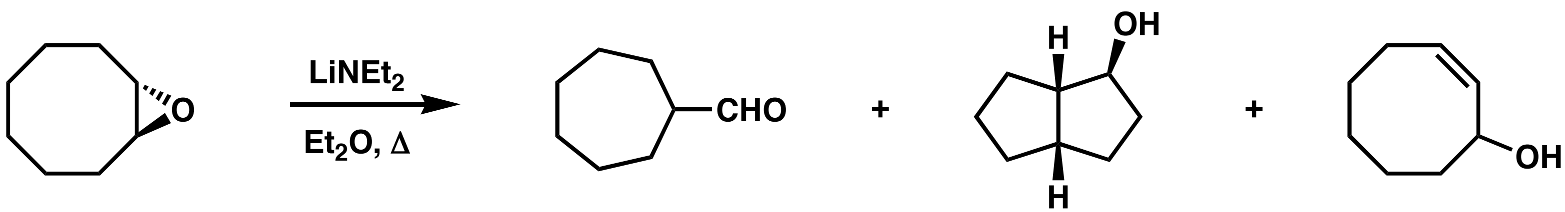


95%

Proposed Mechanism:



Cope and Tiffany, *J. Am. Chem. Soc.* **1951**, *73*, 4158

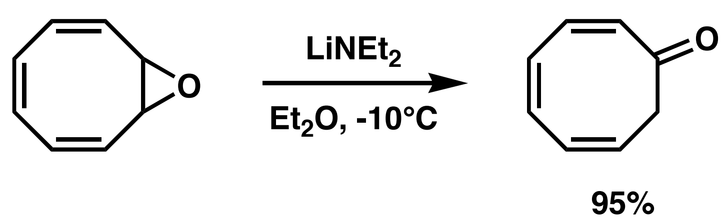


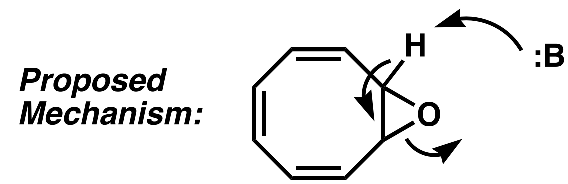
32% **55-60%** **10-15%**

Cope, et. al. *J. Am. Chem. Soc.* **1958**, *80*, 2849

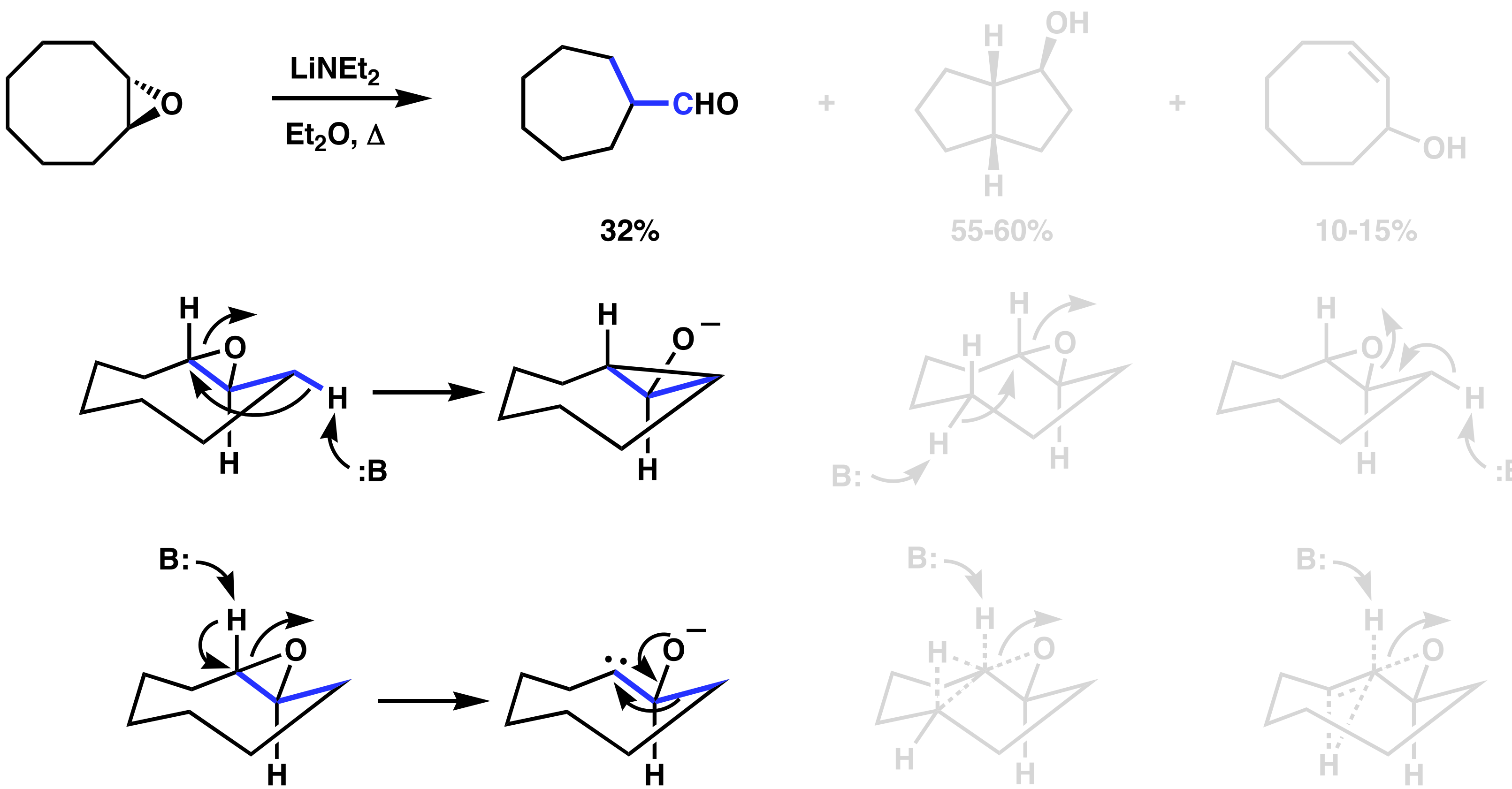
Deprotonation of Epoxides

Early Surprising Results





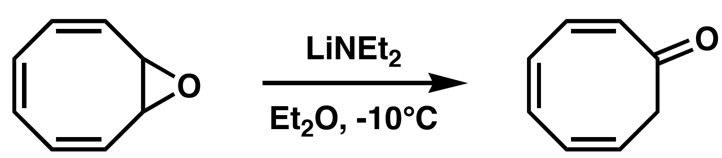
Cope and Tiffany, *J. Am. Chem. Soc.* **1951**, *73*, 4158



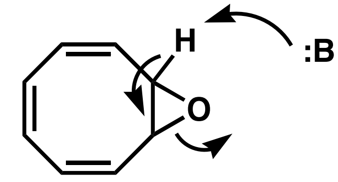
Cope, et. al. *J. Am. Chem. Soc.* **1958**, *80*, 2849

Deprotonation of Epoxides

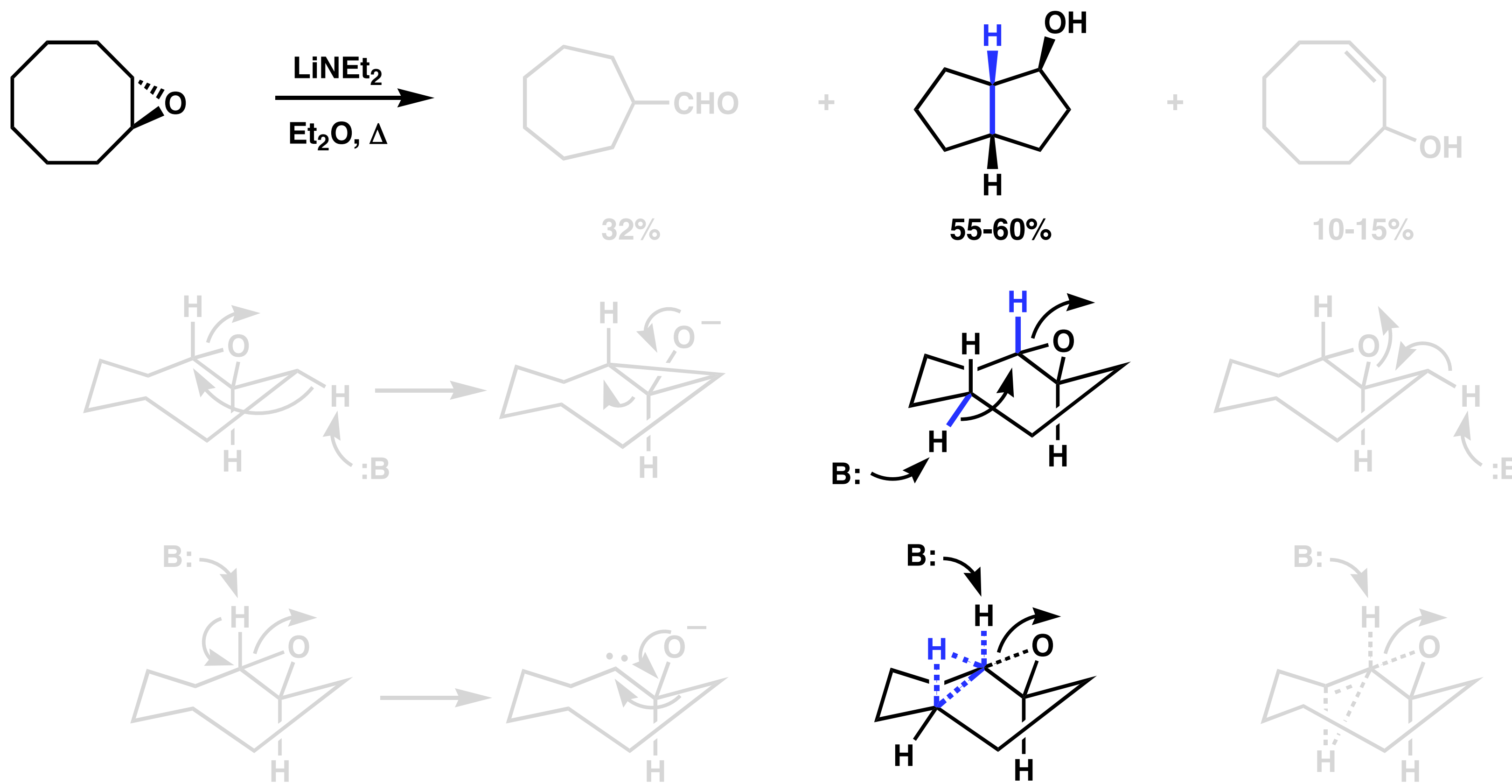
Early Surprising Results



Proposed Mechanism:



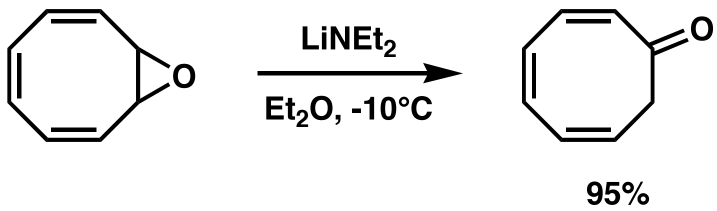
Cope and Tiffany, *J. Am. Chem. Soc.* **1951**, *73*, 4158

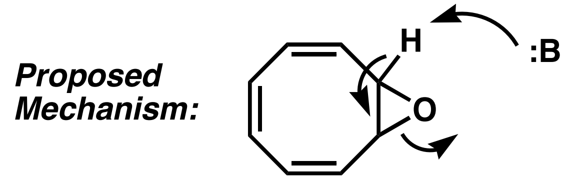


Cope, et. al. *J. Am. Chem. Soc.* **1958**, *80*, 2849

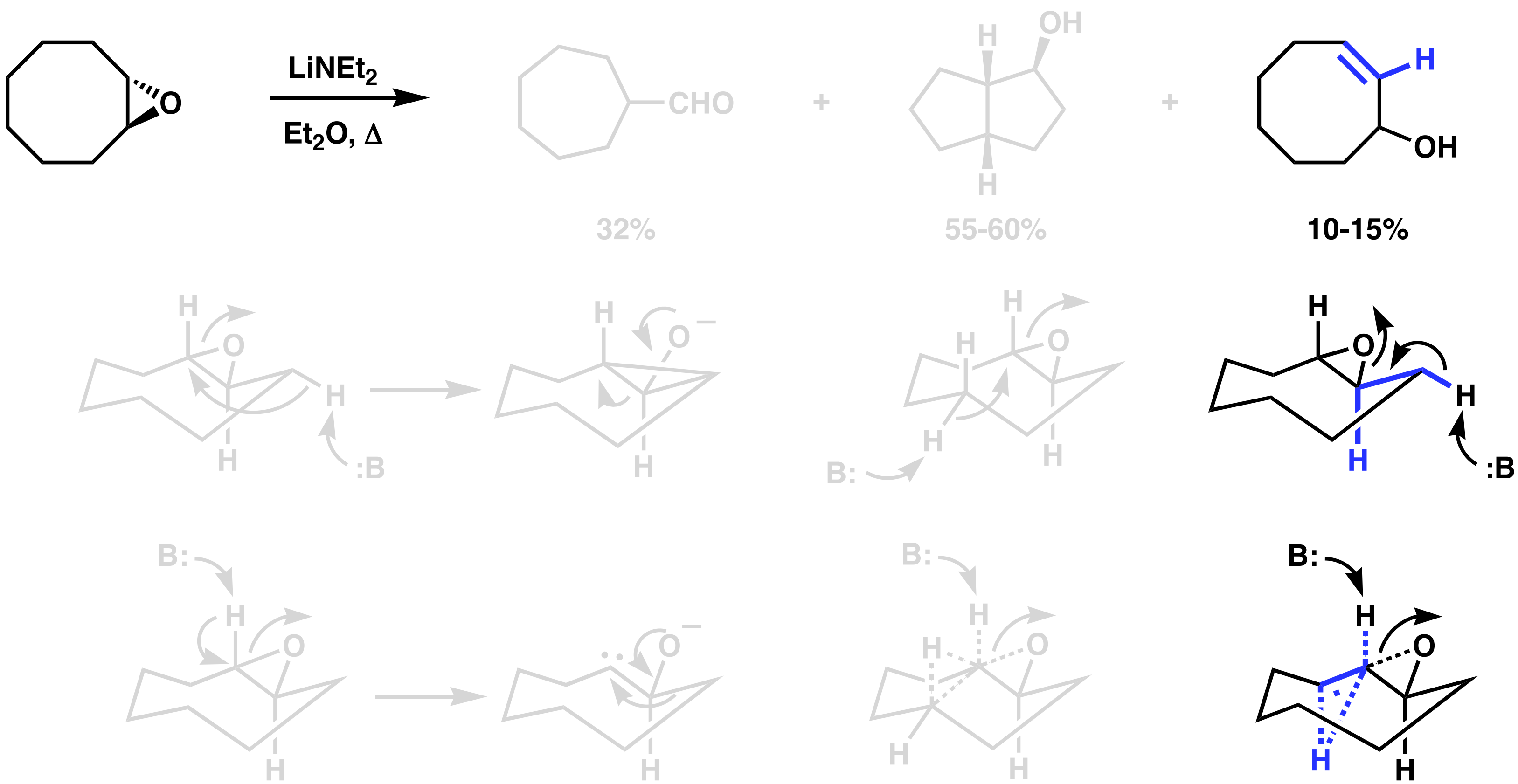
Deprotonation of Epoxides

Early Surprising Results





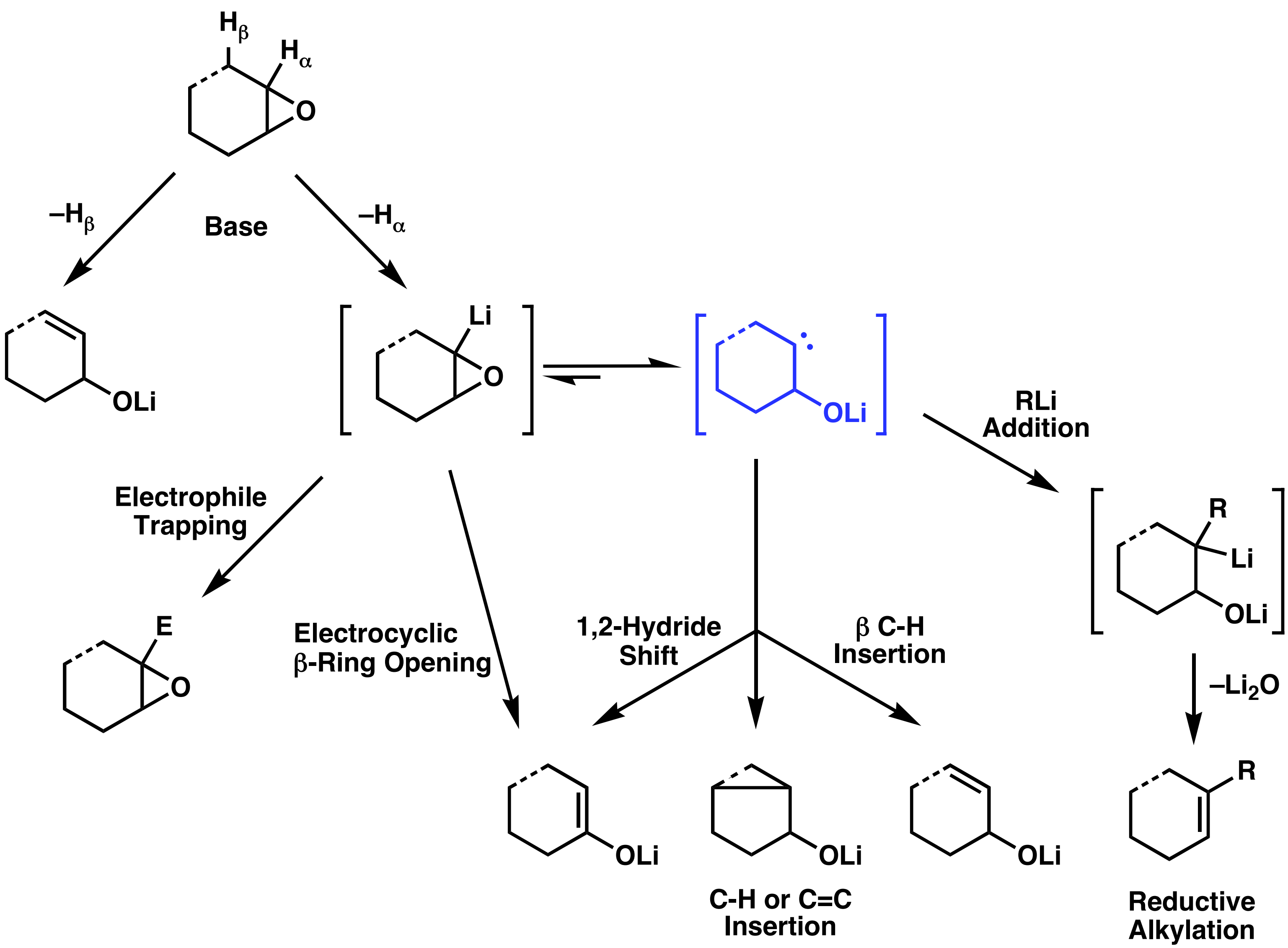
Cope and Tiffany, *J. Am. Chem. Soc.* **1951**, *73*, 4158



Cope, et. al. *J. Am. Chem. Soc.* **1958**, *80*, 2849

Asymmetric Deprotonation of Epoxides

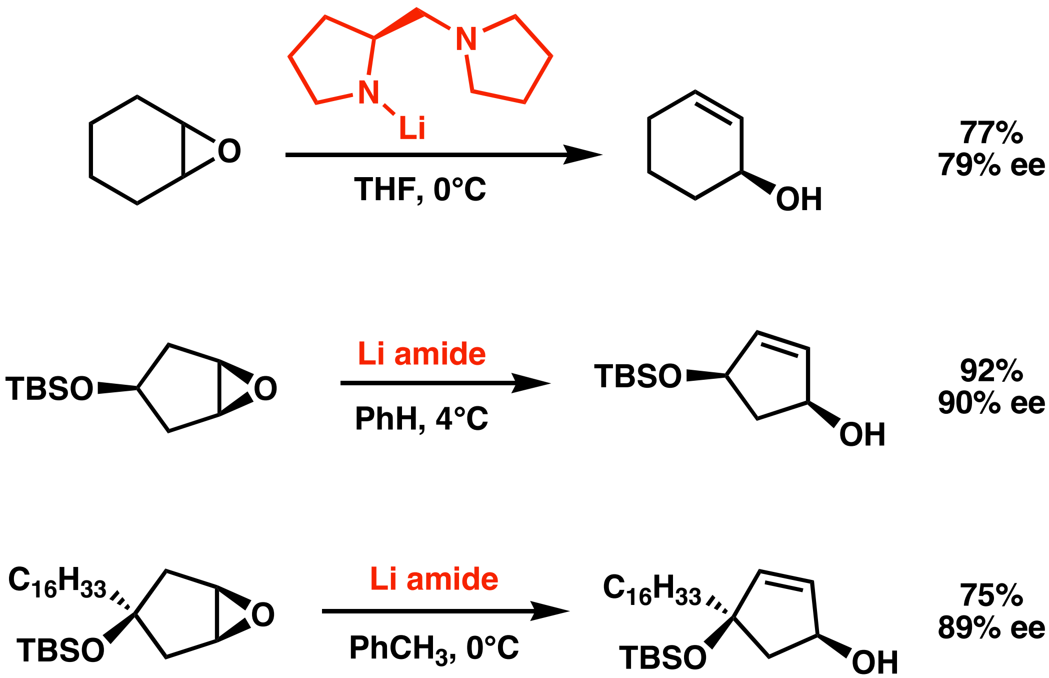
Can Reactivity Be Controlled?



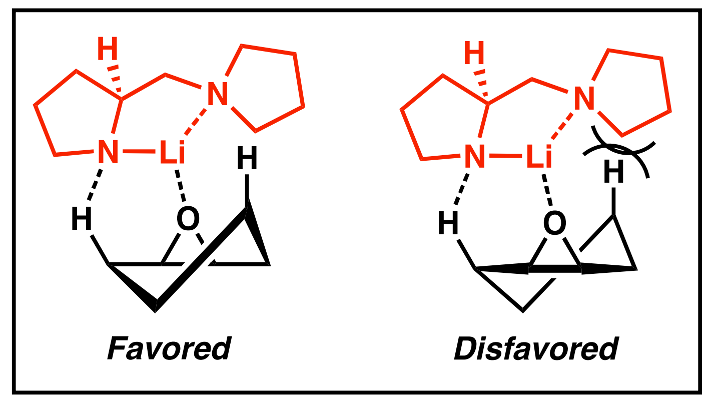
Hodgson and Gras, *Synthesis*, **2002**, *12*, 1625

Asymmetric β-Deprotonation of Epoxides

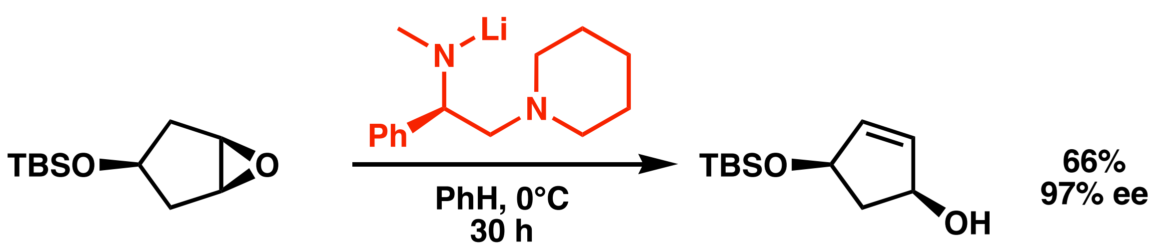
Allylic Alcohols Using Lithium Aminoamide Bases



Proposed Selectivity Model:



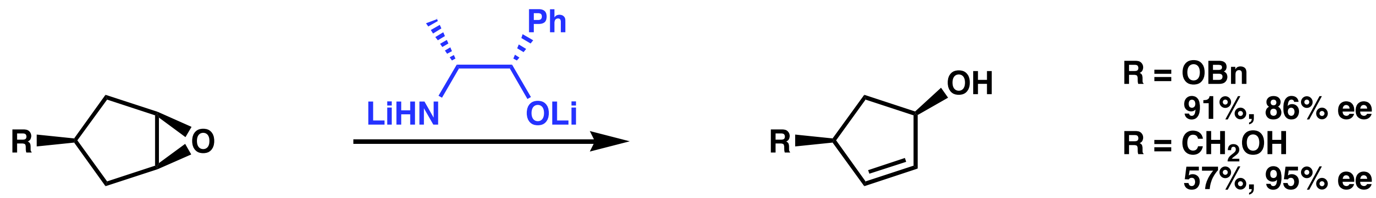
Asami, et. al. *Tetrahedron*, **1995**, *51*, 11725



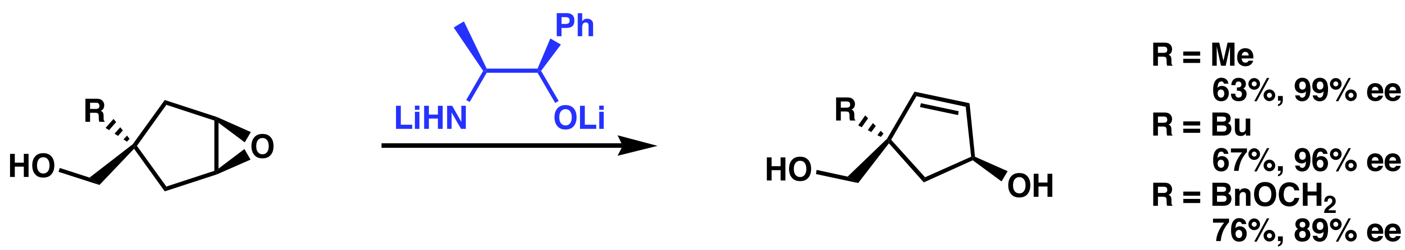
Singh, et. al. *J. Org. Chem*, **1996**, *61*, 6108

Asymmetric ß-Deprotonation of Epoxides

Use of Commercially-Available Ephedrine-Based Aminoalcohols



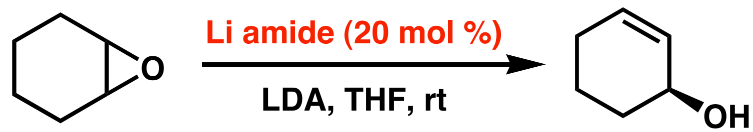
Murphy, et. al. *J. Chem. Soc., Chem. Commun.*, **1993**, 884

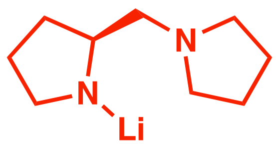


Hodgson, et. al. *Tetrahedron: Asymmetry*, **1996**, *7*, 407

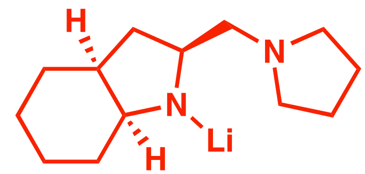
Catalytic Asymmetric Examples

Recent Studies Allow Similar Levels of Selectivity



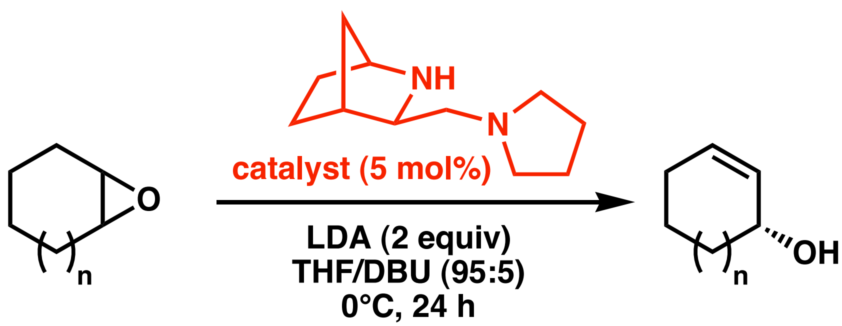


+ 1 equiv LDA + 6 equiv DBU
12 h, 71%, 75% ee



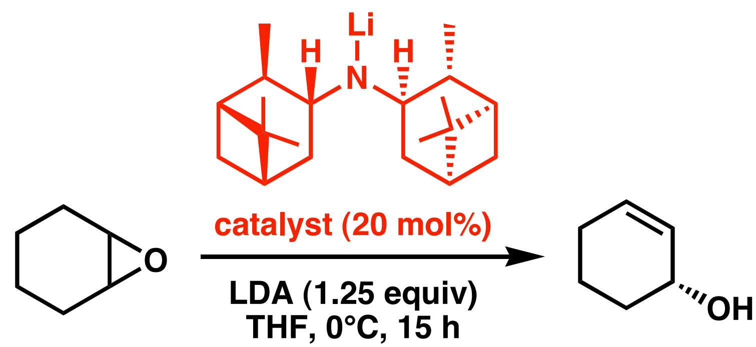
+ 1.8 equiv LDA
6 h, 95%, 88% ee

Asami, et. al. *Tetrahedron: Asymmetry* **1994**, *5*, 793
Tetrahedron Lett. **1997**, *38*, 6425



n = 1
91%, 96% ee
n = 2
89%, 96% ee
n = 3
81%, 78% ee

Andersson, et. al. *J. Am. Chem. Soc.*, **1998**, *120*, 10760

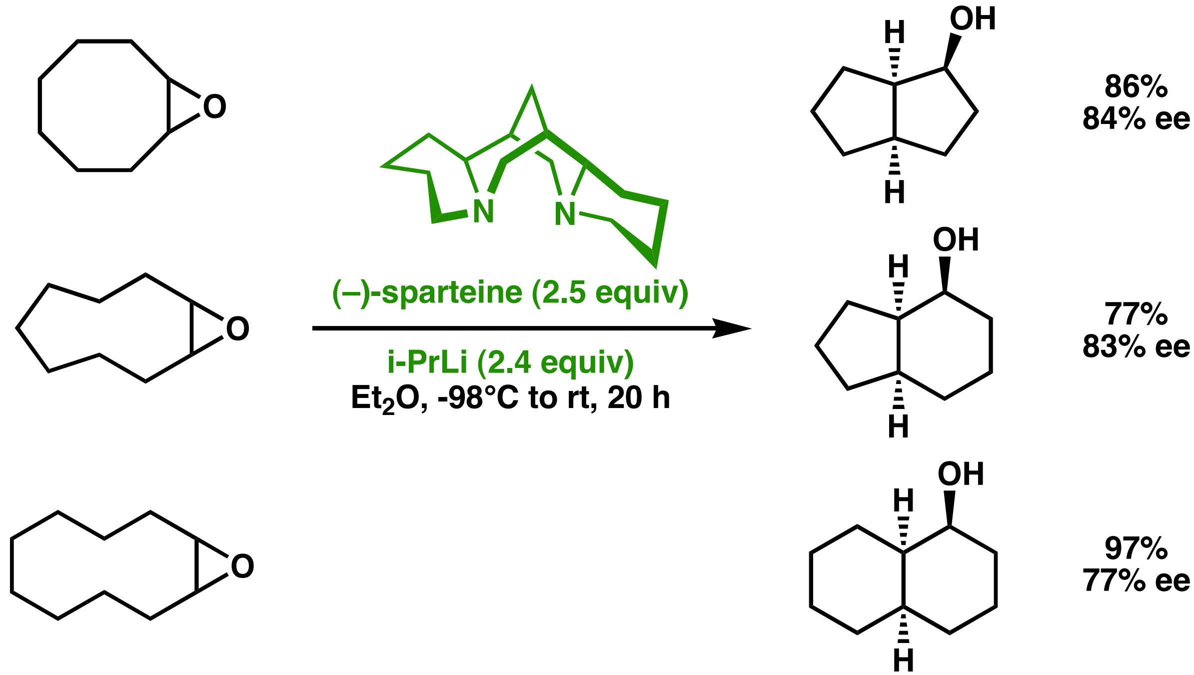


77%
95% ee

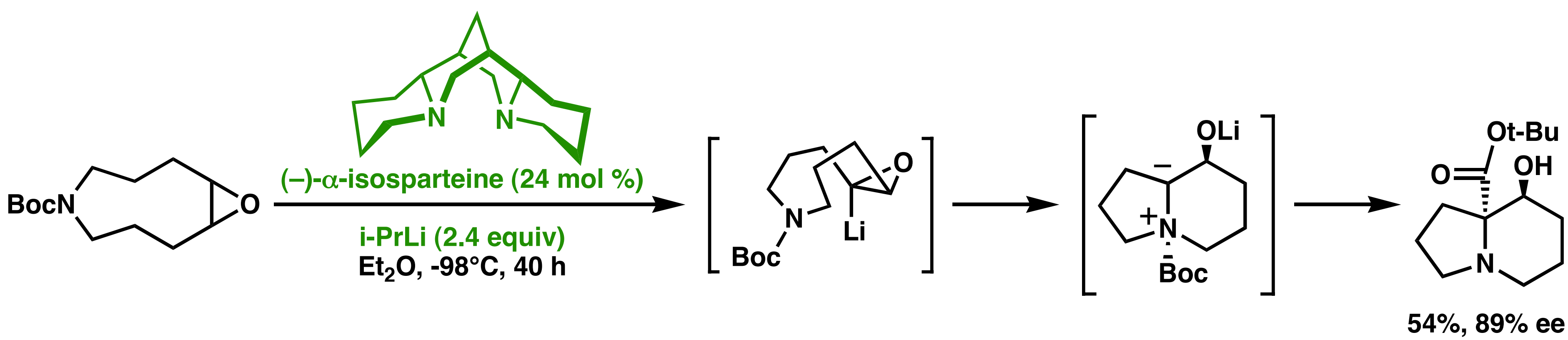
Malhotra, *Tetrahedron: Asymmetry*, **2003**, *14*, 645

Enantioselective α-Deprotonation of Epoxides

Transannular C-H Insertion With Alkyllithium Diamine Complexes



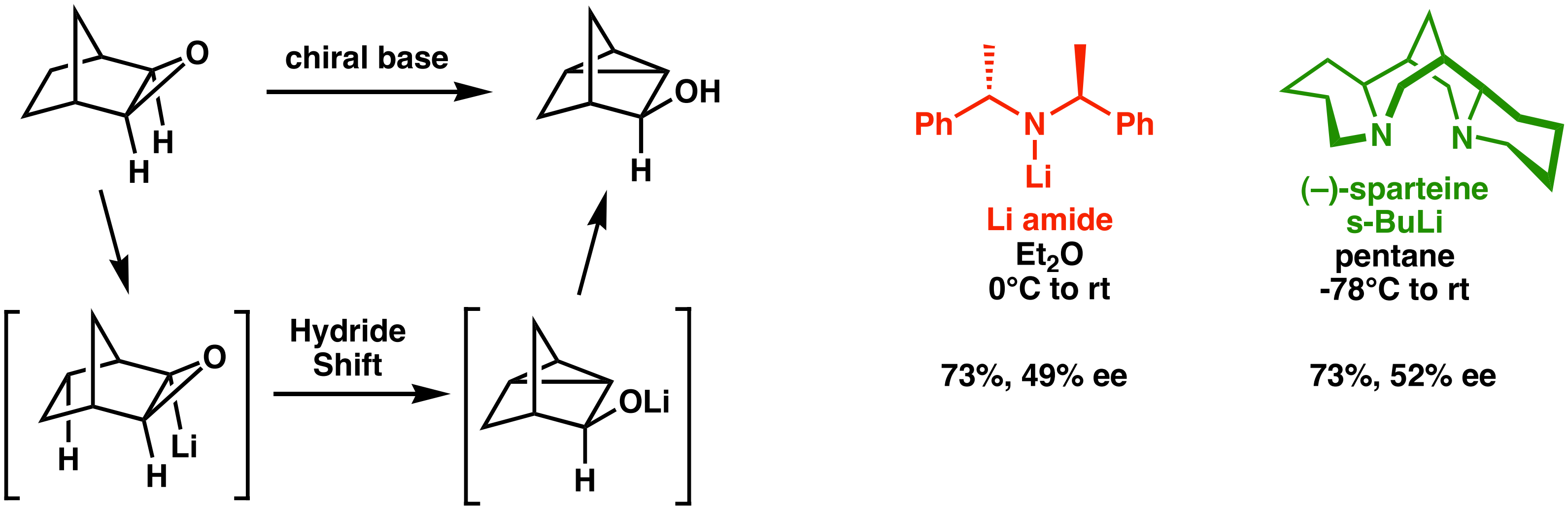
Hodgson and Lee, *Chem. Commun.* **1996**, 1015

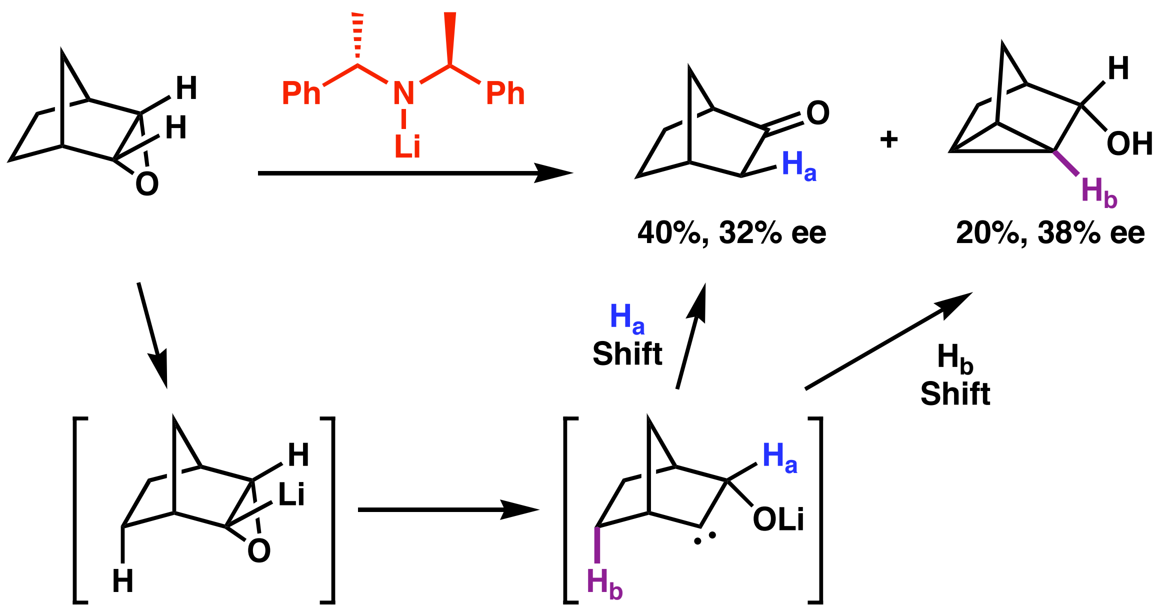


Hodgson, et. al. *J. Chem. Soc., Perkin Trans 1,* **2001**, 2161

More Transannular Epoxide Rearrangements

Reactivity Differences in Bicyclic Systems

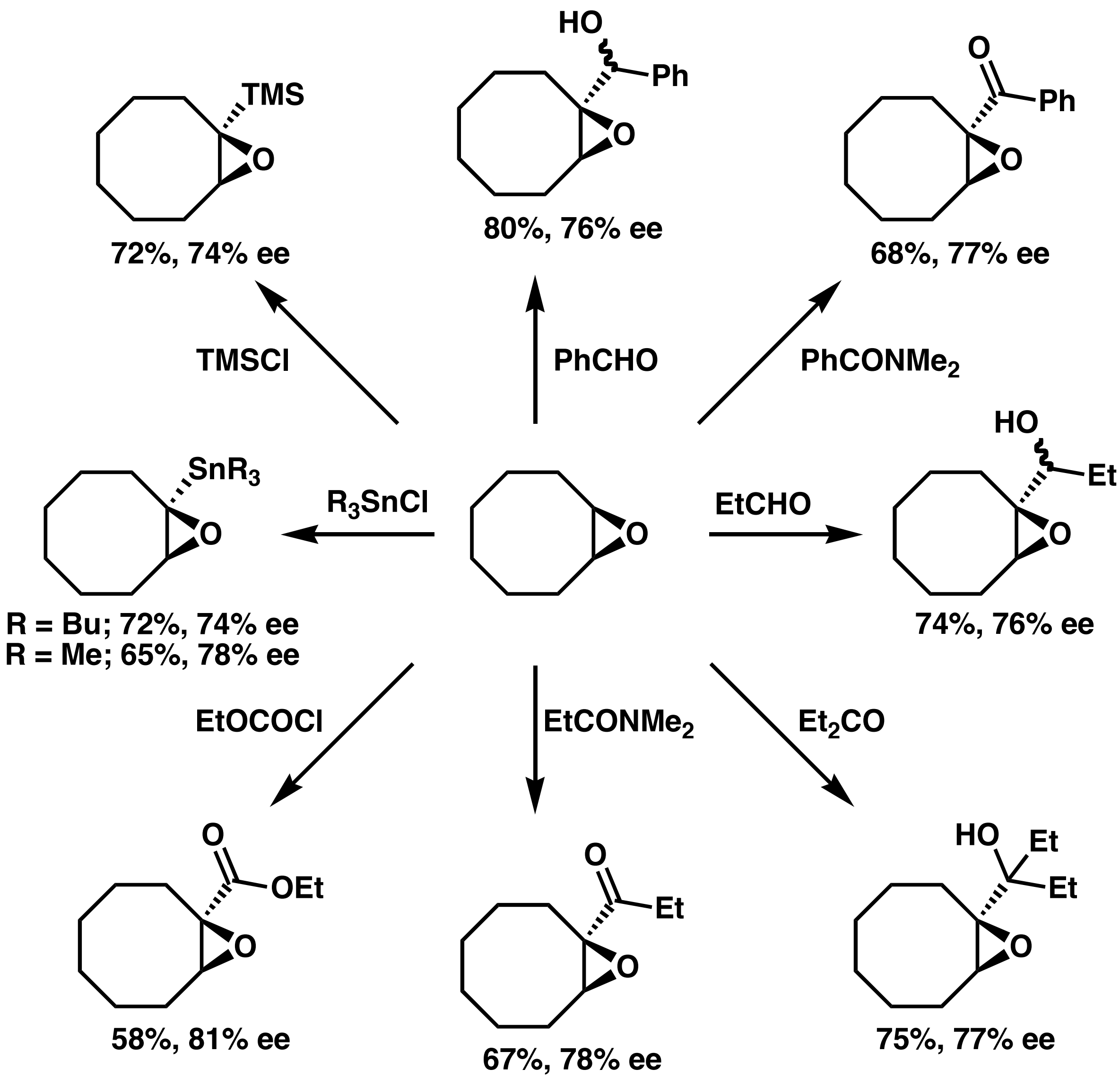




Hodgson and Marriott, *Tetrahedron: Asymmetry,* **1997**, *8*, 519

Trapping of Lithiated Epoxides

Enantioselective Epoxide Substitution with Various Electrophiles



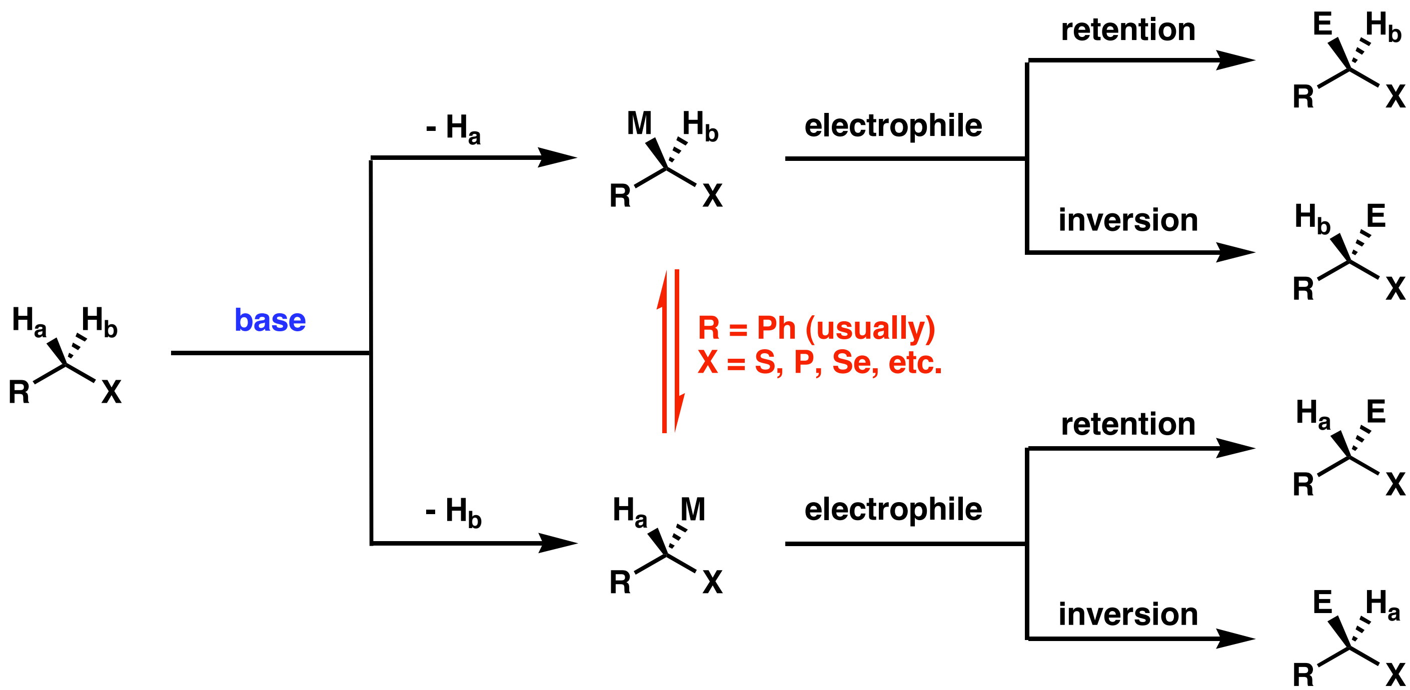
Conditions

s-BuLi (1.25 equiv)
(–)-sparteine (1.3 equiv)
Et_2O, -90°C, 3 h
then
electrophile (1.5 equiv)
-90°C to rt over 5 h

Hodgson, et. al. *Org. Biomol. Chem.* **2003**, *1*, 4293

Deprotonation Adjacent to Heteroatoms

A Return to Reaction Pathways

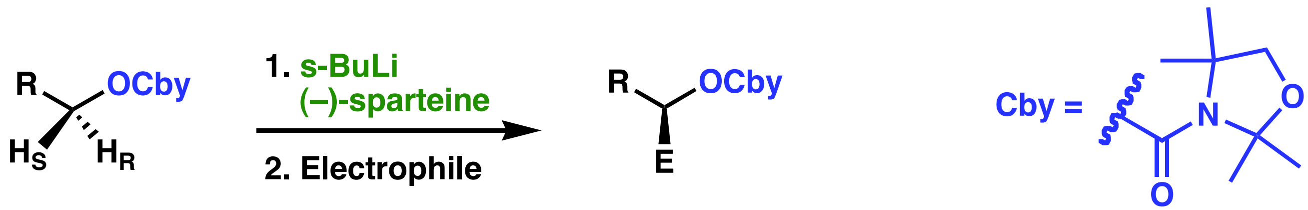


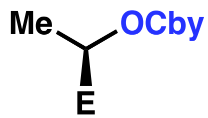
Asymmetric Deprotonation Adjacent to Heteroatoms

- ***X = O, R = Alkyl***
- ***X = CH=CR'OR'', R = Aryl, Alkyl***
- ***X = N, R = Alkyl, Aryl, Allyl***

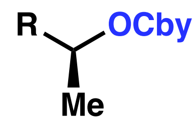
Deprotonation Adjacent to Oxygen

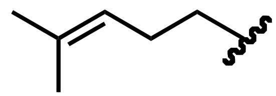
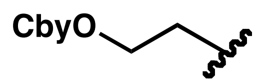
Alkyl Carbamates

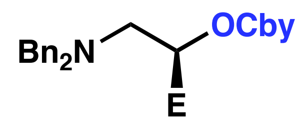




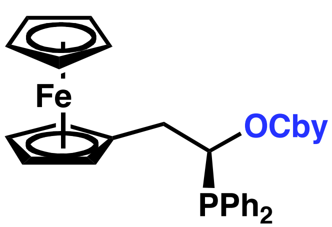
E	% Yield	% ee
D	86	> 96
$PbMe_3$	61	93
$CH_2CH{=}CH_2$	60	42



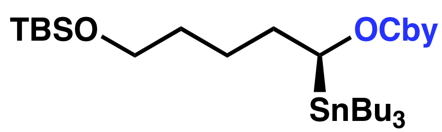
R	% Yield	% ee
$H_3C(CH_2)_{11}$	60	98
	64	92
	85	> 95



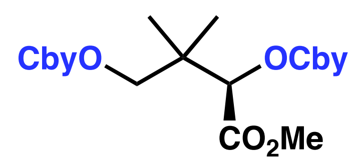
E	% Yield	% ee
CO_2Me	56	> 95
Bu_3Sn	70	> 95
Me_3Si	70	> 95
Me	72	> 95



80%
> 95% ee



85%
> 95% ee

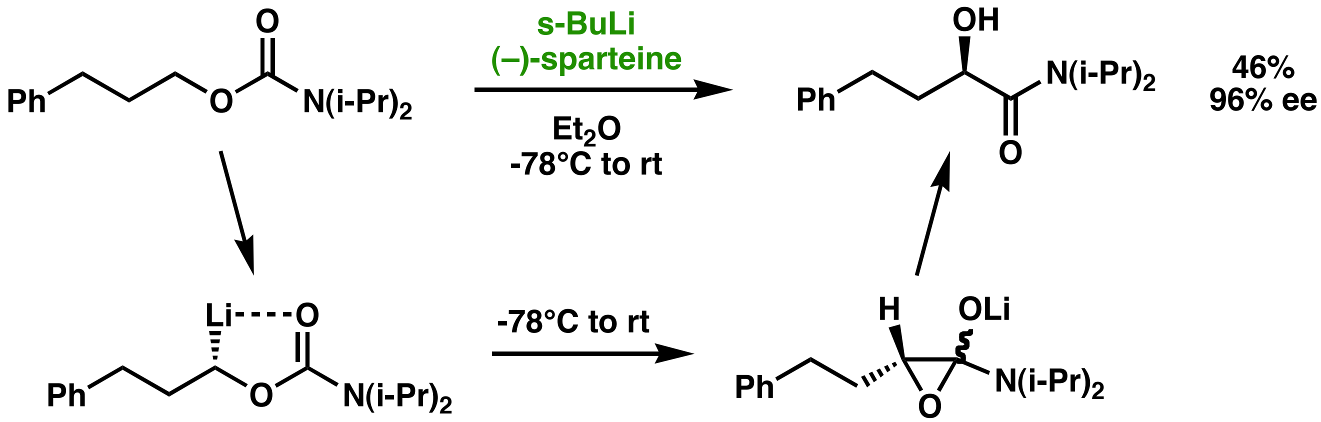


80%
> 95% ee

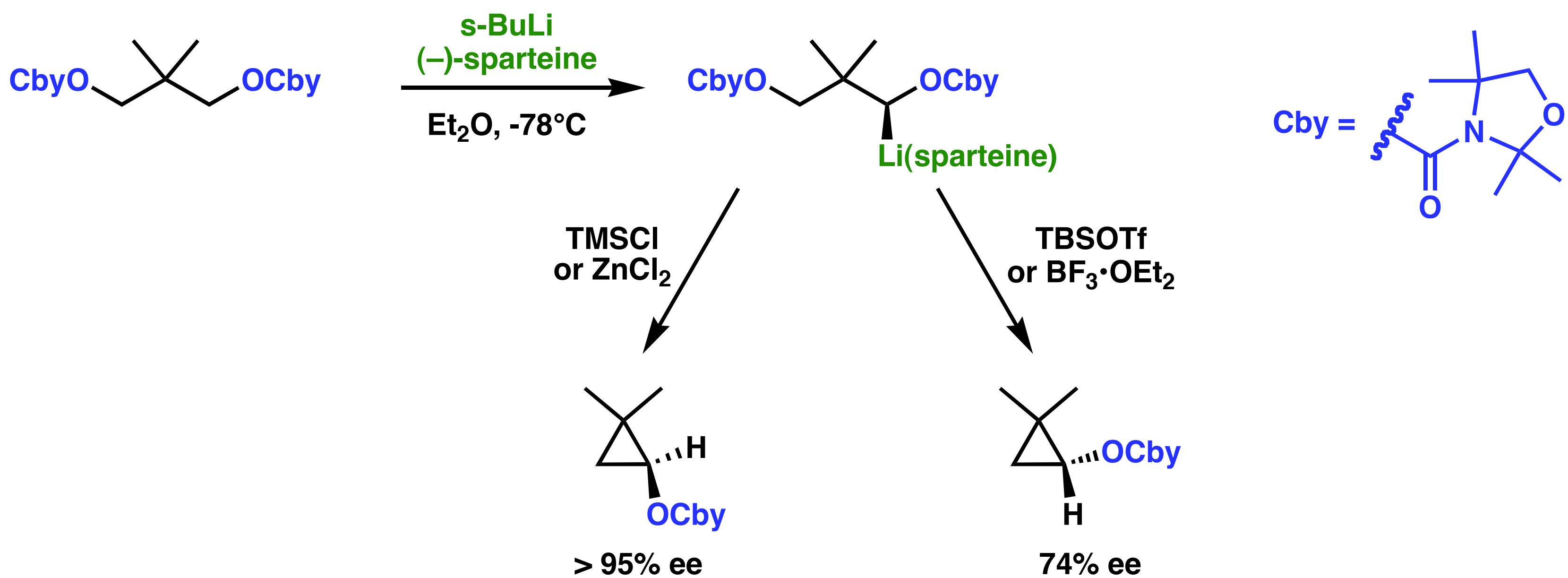
Hoppe, et. al. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1422
Angew. Chem., Int. Ed. Engl. **1992**, *31*, 1505
Synthesis **1999**, 1573
Org. Lett. **2002**, *4*, 2189

Asymmetric Deprotonation of Alkyl Carbamates

Intramolecular Reactions



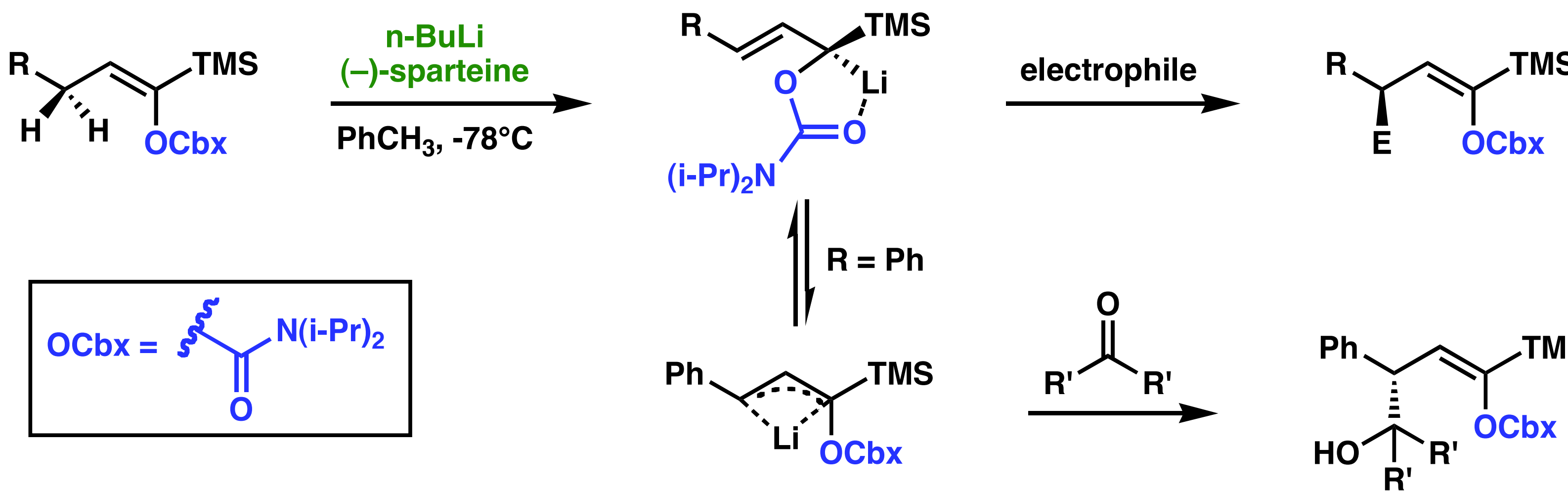
Tomooka, Shimizu, Inoue, Shibata,l Nakai, *Chem. Lett.* **1999**, 759

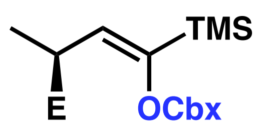


Hoppe, et. al. *Synlett* **1994**, 1034

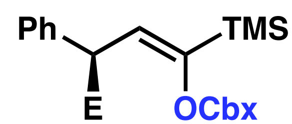
Silyl Alkenyl Carbamates

Configurationally Stable Allyllithiums

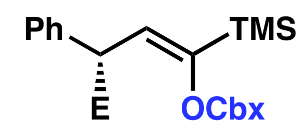




E	% Yield	% ee
Me_3Si	85	≥95
Bu_3Sn	80	≥95
Ph_3Sn	83	≥95
MeOC(O)	35	72
t-BuC(O)	66	83



E	% Yield	% ee
Me_3Si	18	92
Bu_3Sn	61	≥95
Ph_3Sn	96	≥95

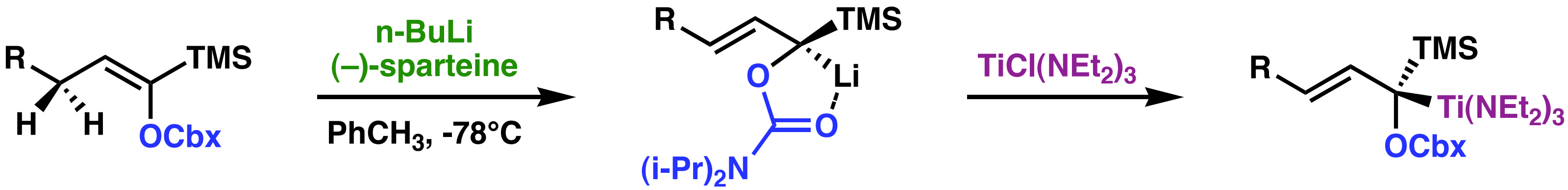


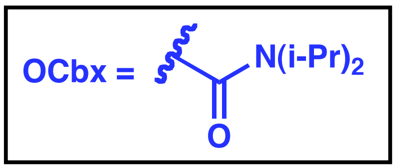
E	% Yield	% ee
MeOC(O)	72	≥95
t-BuC(O)	94	≥95
Me_2COH	92	≥95
c$C_6H_{11}OH$	82	90

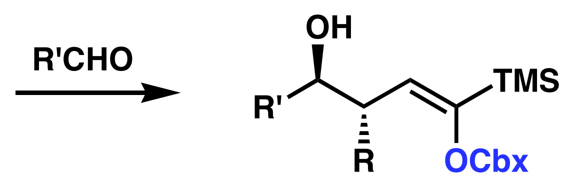
Hoppe, et. al. *Org. Lett.* **2004**, *6*, 783

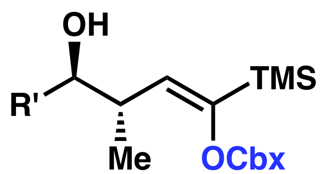
Enantioselective Homoaldols

Metal Exchange to Ti Leads to a Highly Diastereoselective Process

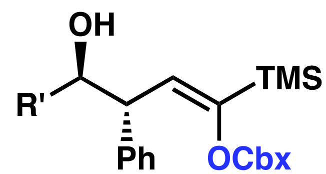








R'	% Yield	% ee
$CH_3(CH_2)_2$	70	≥95
$(CH_3)_2CH$	72	≥95
$(CH_3)_3C$	80	≥95
cC_6H_{11}	69	≥95
C_6H_5	71	89

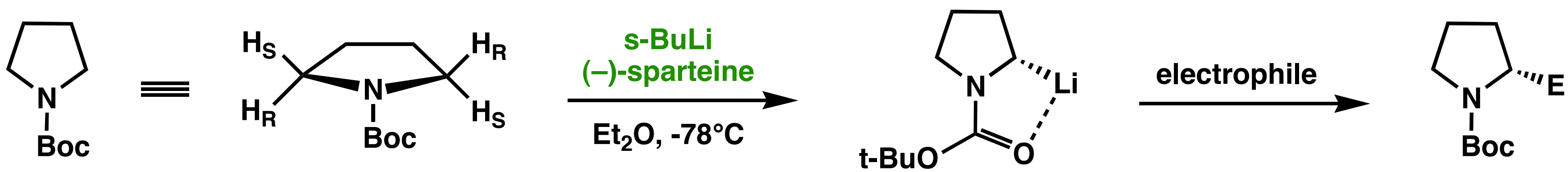


R'	% Yield	% ee
$CH_3(CH_2)_2$	98	91
$(CH_3)_2CH$	95	94
$(CH_3)_3C$	98	95
cC_6H_{11}	93	97
4-BrC_6H_4	99	≥95

Hoppe, et. al. *Org. Lett.* **2004**, *6*, 783

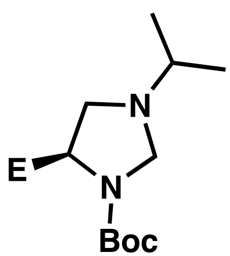
Deprotonation Adjacent to Nitrogen

Alkyl Carbamates Revisited



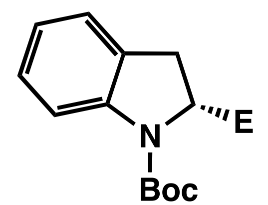
E	% Yield	% ee
Me	88	94
Me_3Si	71	94
Bu_3Sn	83	96
CO_2H	55	88

Beak, et. al. *J. Am. Chem. Soc.* **1994**, *116*, 3231



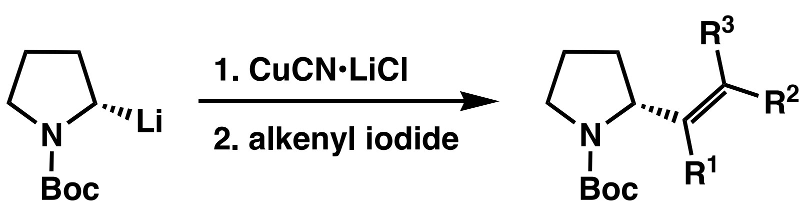
40-50%
0-88% ee

Coldham, et. al. *Org. Lett.* **2001**, *3*, 3799



15-70%
94-98% ee

Beak, et. al. *J. Org. Chem.* **1997**, *62*, 7679



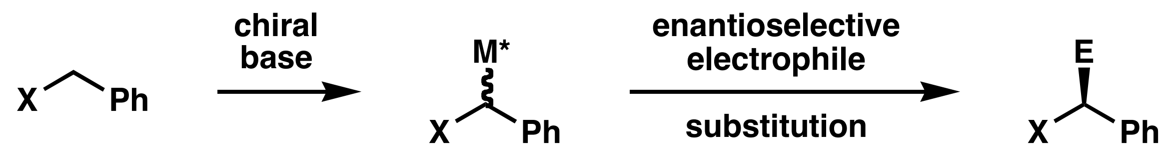
89-95%
86-90% ee

Dieter, et. al. *J. Am. Chem. Soc.* **2001**, *123*, 5132

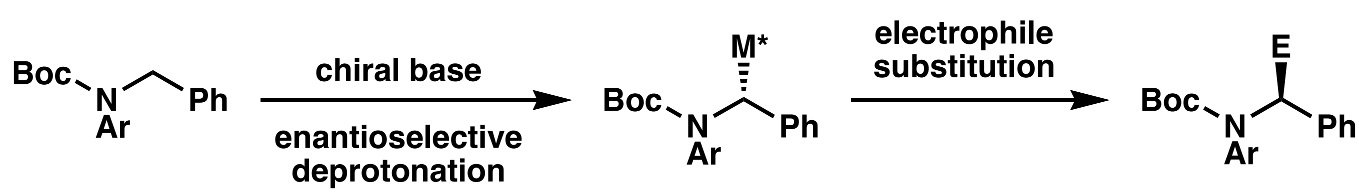
Benzylic Carbamates

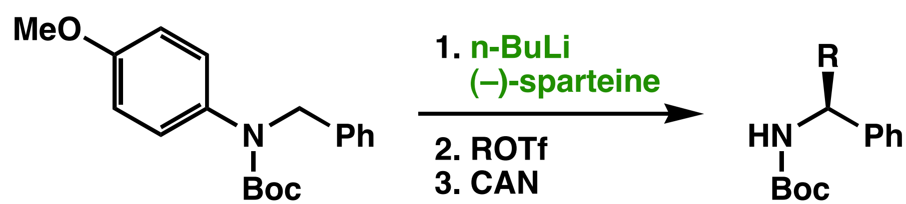
Configurationally Stable Benzyllithiums Possible

Most Benzylic Deprotonations: Configurationally Unstable Anions



X = NArBoc: Enantiomeric Anions Do Not Interconvert at Low Temp!



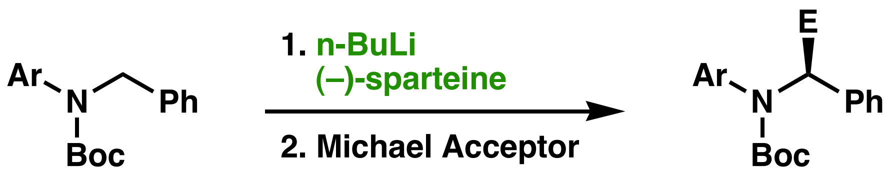


R	% Yield	% ee
Me	81	94
Et	78	94
Allyl	69	93
Bn	73	96

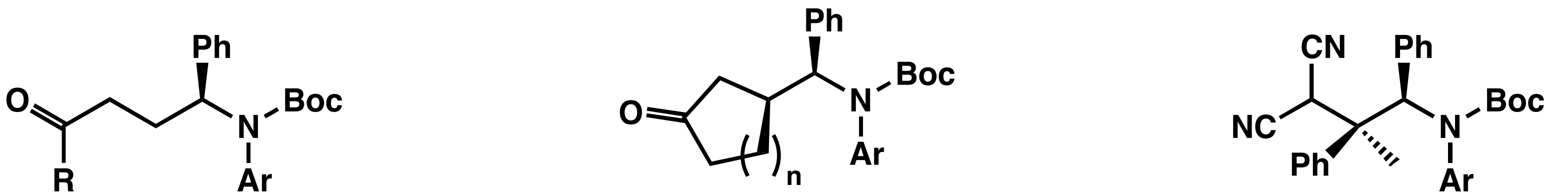
Beak, et. al. *J. Am. Chem. Soc.* **1996**, *118*, 3757

More Benzylic Carbamates

Applications and Electrophiles



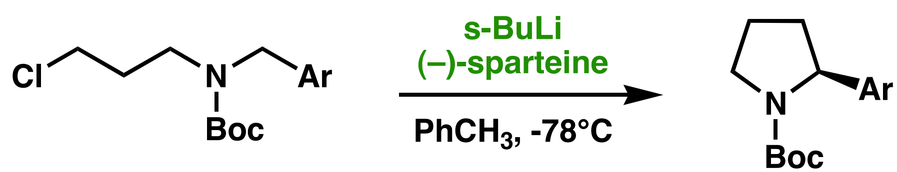
Ar = p-$MeOC_6H_4$



R = H: 72%, 94% ee | **n = 1: 86%, >99:1 dr, 92% ee** | **91%, 92:8 dr, 90% ee**

R = Me: 63%, 94% ee | **n = 2: 82%, >99:1 dr, 92% ee**

Beak, et. al. *J. Am. Chem. Soc.* **1997**, *119*, 10537
J. Org. Chem. **1999**, *64*, 2996

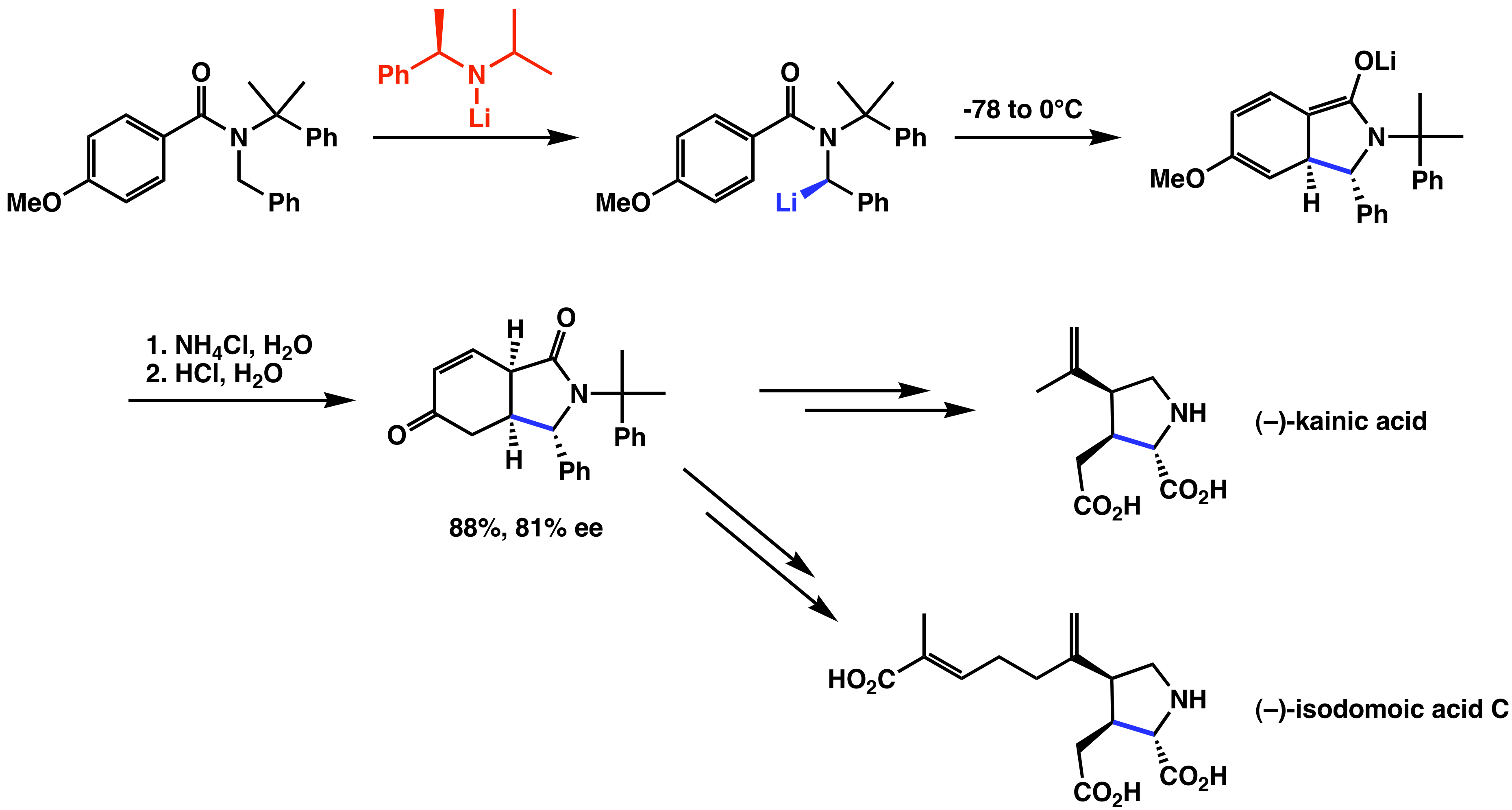


Ar	% Yield	% ee
Ph	72	96
1-Naphthyl	68	92
3-thienyl	52	92
3-furyl	21	96

Beak, et. al. *J. Am. Chem. Soc.* **1996**, *118*, 715

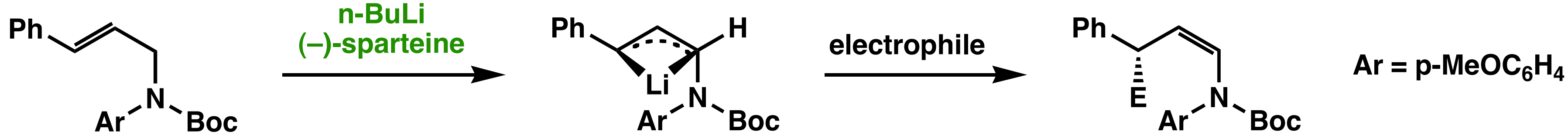
Lithium Amides in Benzylic Deprotonation

Cyclization of Arylamides Leads to Isoindolones

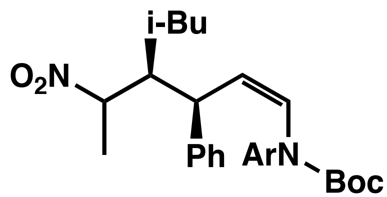


Clayden, et. al. *Tetrahedron* **2002**, *58*, 4727
J. Am. Chem. Soc. **2005**, *127*, 2412

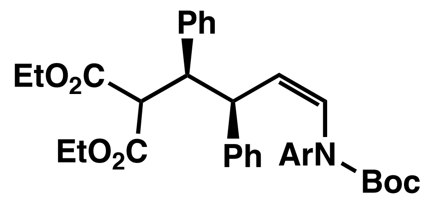
Enantioselective N-Allylcarbamate Deprotonation



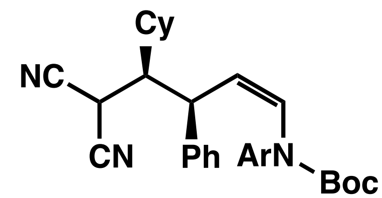
E	% Yield	% ee
Me	73	94
Bn	70	96
Allyl	72	94



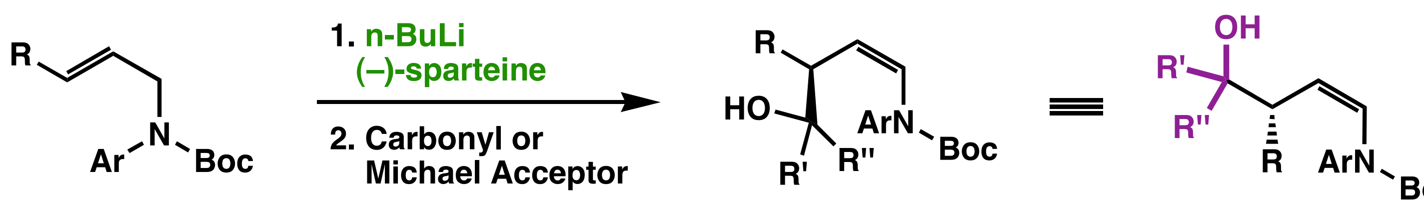
73%, >94% ee
98:2 dr

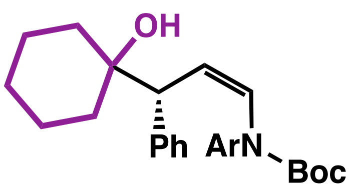


86%, 96% ee
94:6 dr

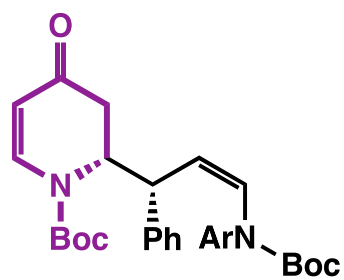


80%, 88% ee
63:44 dr

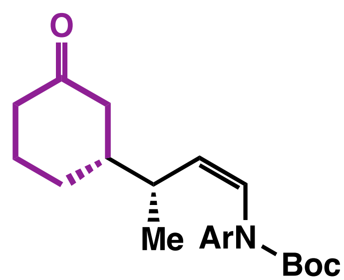




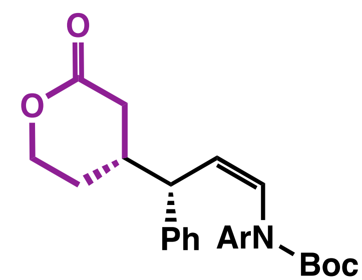
77%, 98% ee



80%, 86% ee
90:10 dr



62%, 96% ee
80:20 dr

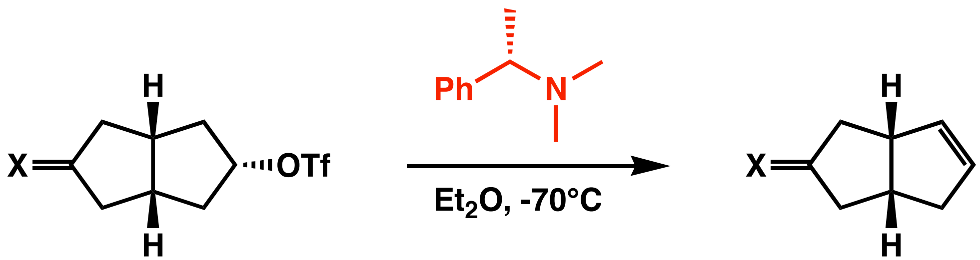


80%, 92% ee
89:11 dr

Beak, et. al. *J. Am. Chem. Soc.* **1996**, *118*, 12218
J. Am. Chem. Soc. **2001**, *123*, 1004

Enantioselective Synthesis by Loss of HX

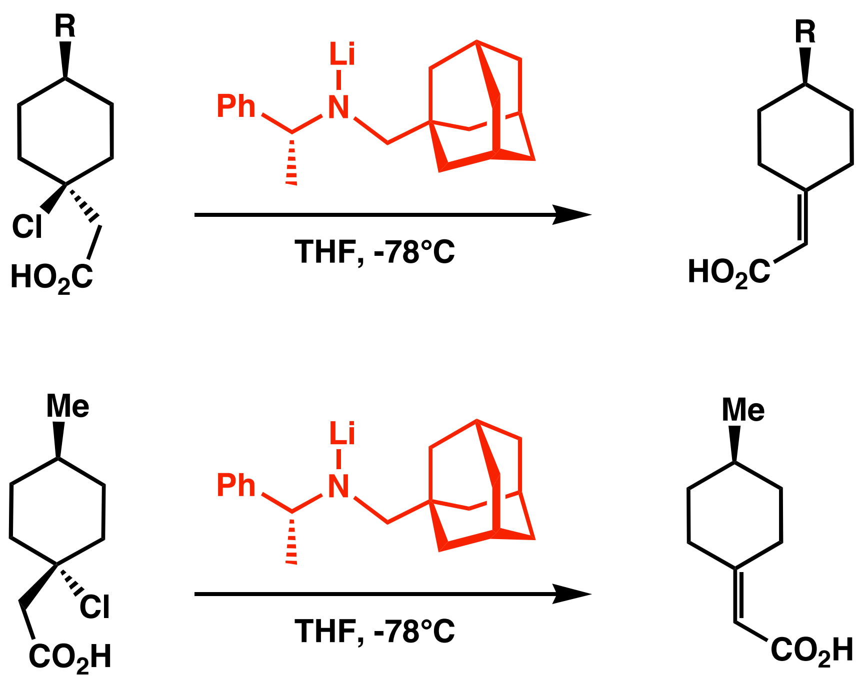
Chiral Amides Lead to Enantioenriched Alkenes



X = O
44% ee

X = –$O(CH_2)_2O$–
99% ee

Sakai, et. al. *Tetrahedron Lett.* **1987**, *28*, 6489



R = Me
80% ee

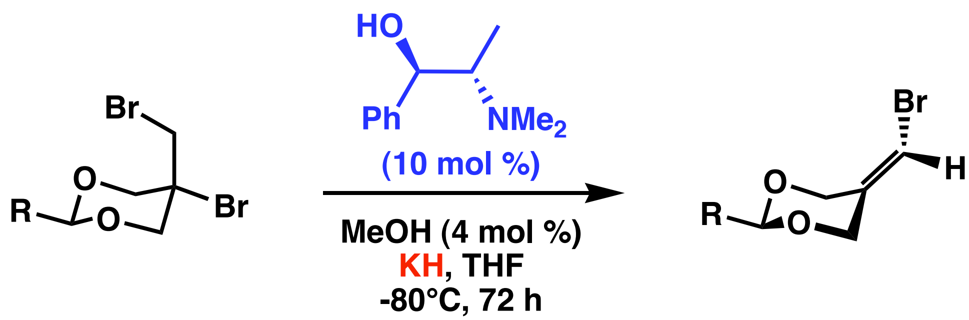
R = t-Bu
82% ee

75% ee

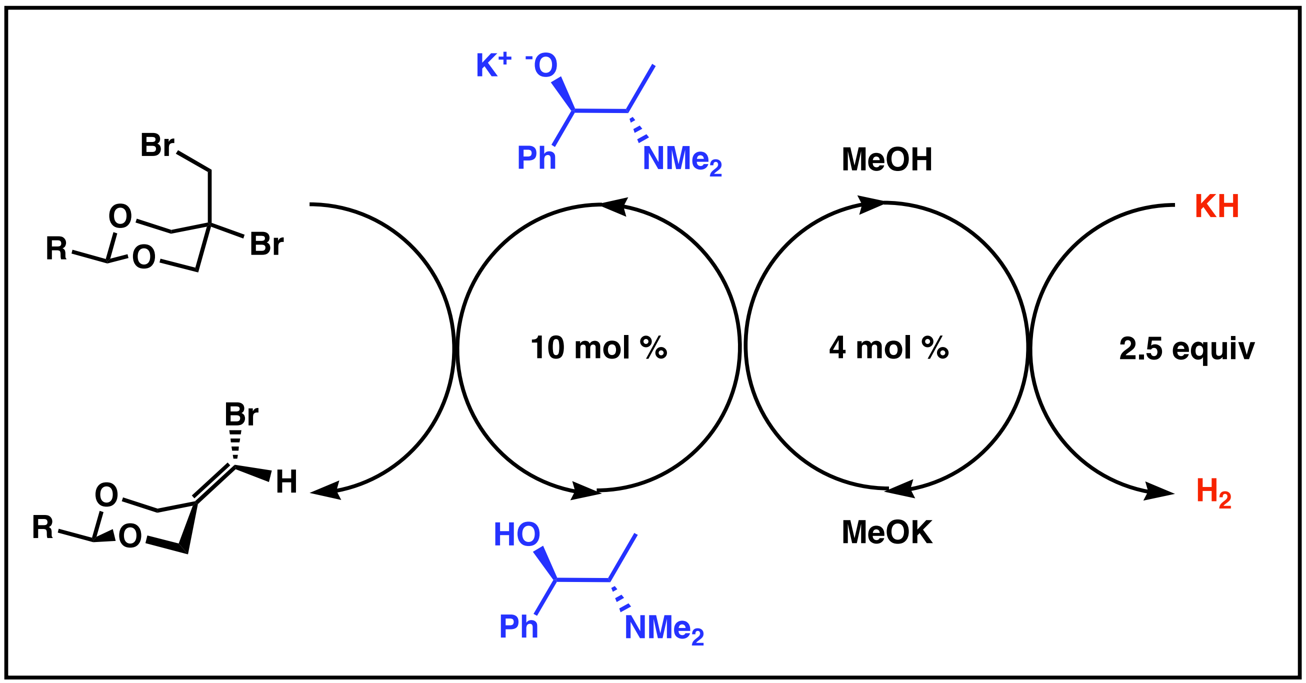
Duhamel, et. al. *Tetrahedron: Asymmetry*, **1990**, *1*, 347

More Enantioselective Loss of HX

Chiral Alkoxides Allow Catalytic Reactions



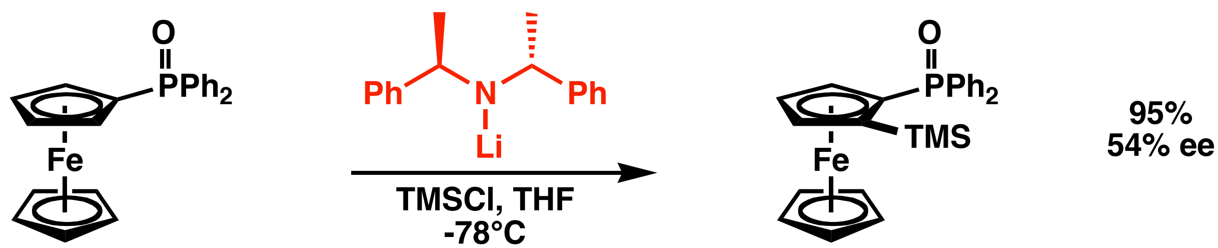
R	% Yield	% ee
t-Bu	83	90
n-Pr	78	77
i-Pr	79	65
Ph	82	94
p-$MeOC_6H_4$	79	>98
p-$NO_2C_6H_4$	78	>98
p-PhC_6H_4	81	96



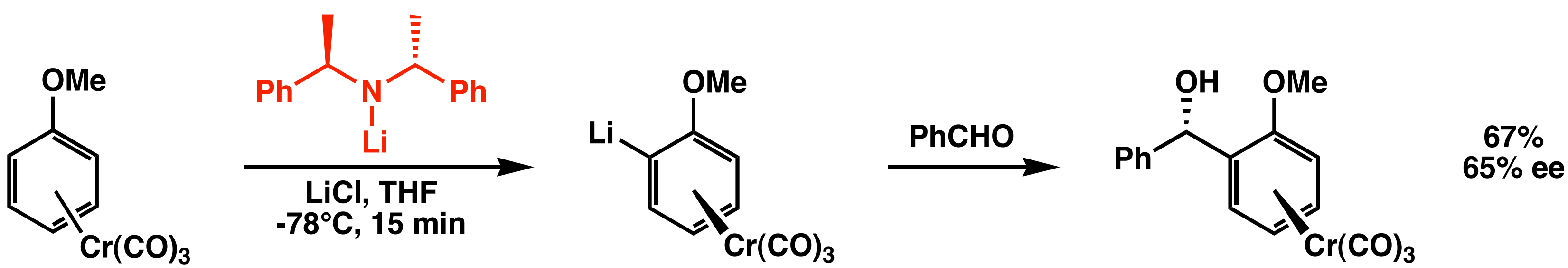
Duhamel, et. al. *J. Org. Chem.*, **1998**, *63*, 5541

Enantioselective Lithiation of Aromatics

Generation of Planar Chirality with Lithium Amide Bases



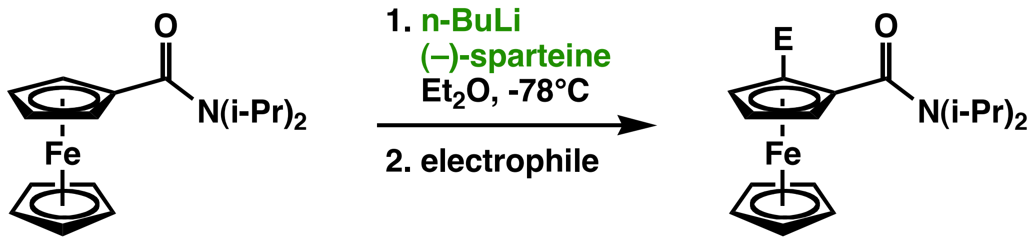
Simpkins and Price, *Tetrahedron Lett.,* **1995**, *36*, 6135



Simpkins, et. al. *J. Chem. Soc., Perkin Trans 1,* **1997**, 401

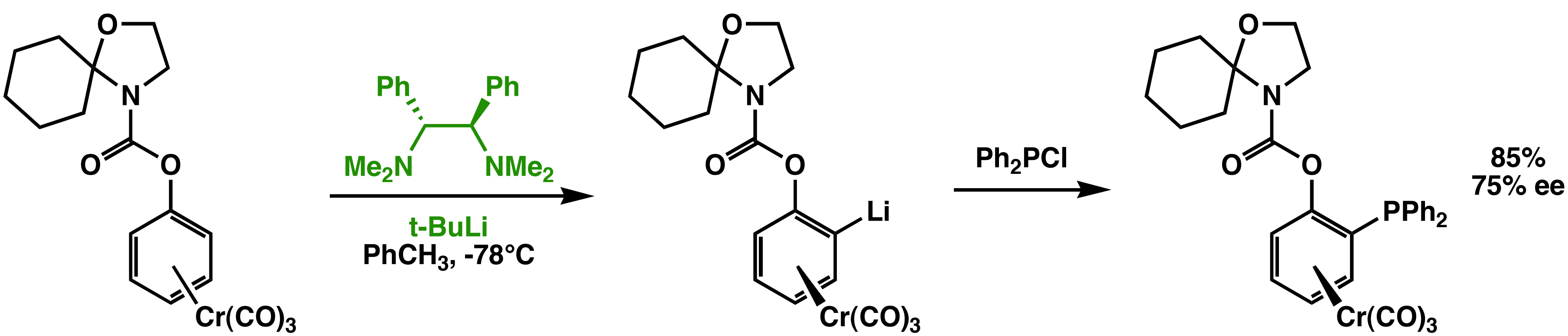
Enantioselective Lithiation of Aromatics

Generation of Planar Chirality with Alkyllithium / Sparteine



E	% Yield	% ee
TMS	96	98
Me	91	94
$Ph_2C(OH)$	91	99
I	85	96
Ph_2P	82	90
$B(OH)_2$	89	85

Snieckus, et. al. *J. Am. Chem. Soc.,* **1996**, *118*, 685



Uemura, et. al. *Tetrahedron: Asymmetry,* **1994**, *5*, 1427