

Stereoselective Organic Synthesis



INSTITUTE OF LIFE SCIENCES
(An Associate Institute of University of Hyderabad)

Prabhat Arya



I'll either find
a way...
or make one

Professor and Leader, Chemical Biology Program
Dean, Academic Affairs, Institute of Life Sciences
(An Associate Institute of University of Hyderabad Supported by Dr. Reddy's)
University of Hyderabad Campus
Gachibowli, Hyderabad 500046, India

Adjunct Professor, Biochemistry, McGill University
Member, Ottawa Institute of Systems Biology

tel: (+91) (40) 6657 1500
e mail: prabhata@ilsresearch.org
website: <http://www.ilsresearch.org>

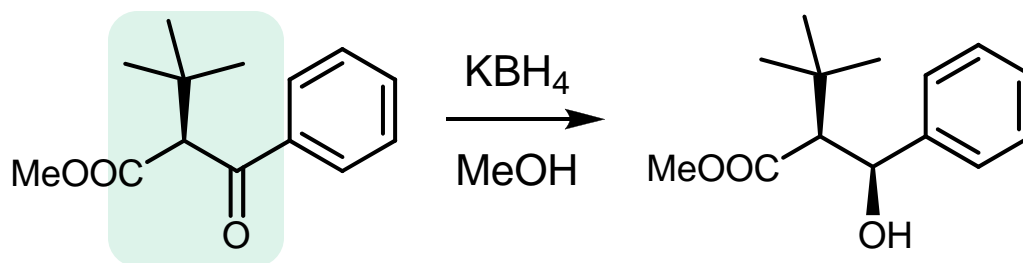
Day 4

Stereoselective Nucleophilic Addition to Carbonyl Group and Enantioselective Oxidation

Outline

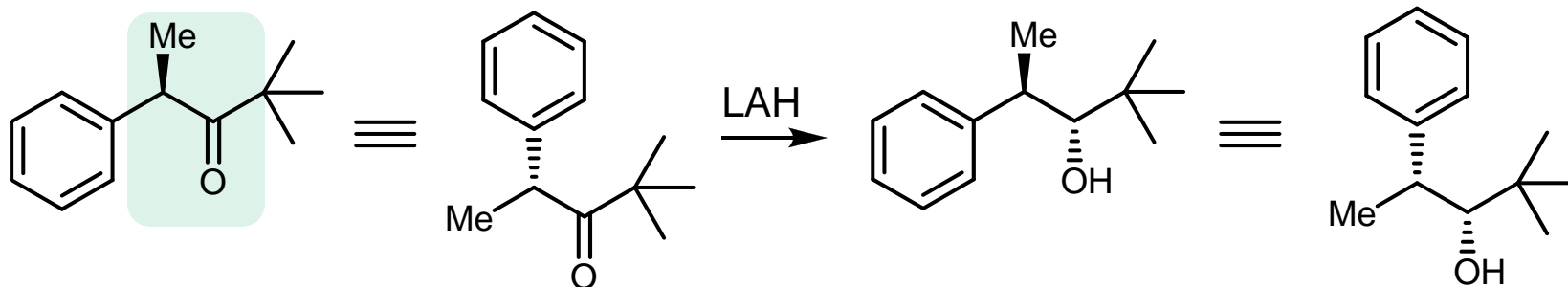
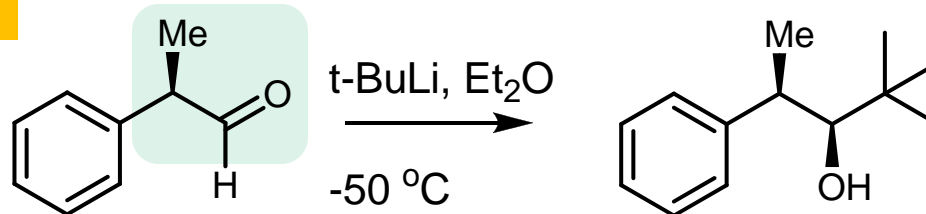
- Nucleophilic addition to carbonyl group
- Cram, Felkin-Anh, chelation and dipolar models
- 1,2 Asymmetric induction in carbonyl addition
- 1,3 Asymmetric induction in carbonyl addition
- enantioselective carbonyl reduction (Masamune, Corey)
- Diastereoselective oxidation
- Enantioselective oxidation (Sharpless and Jacobsen)
- Enantioselective synthesis examples

Examples of Stereoselective Nucleophilic Addition to Carbonyl Group



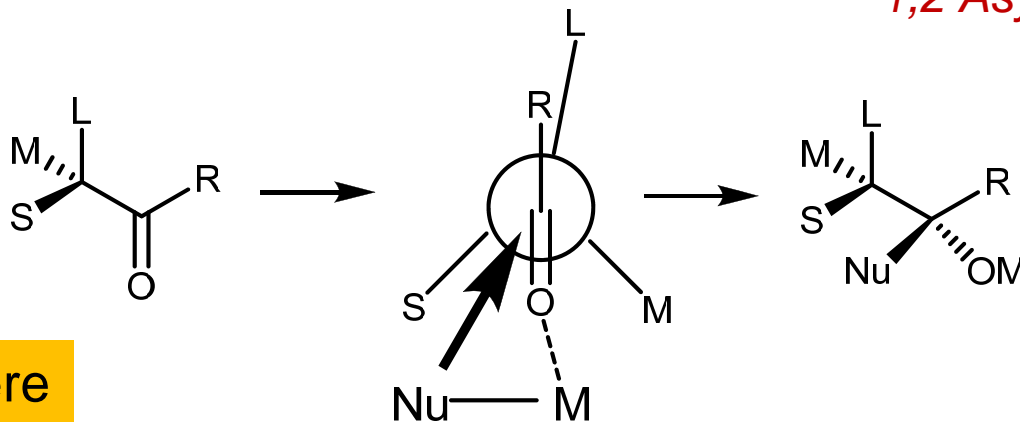
Use models here

1,2 Asymmetric Induction



Cram's Rule

1,2 Asymmetric Induction



Use models here

Increase in stereoselectivity

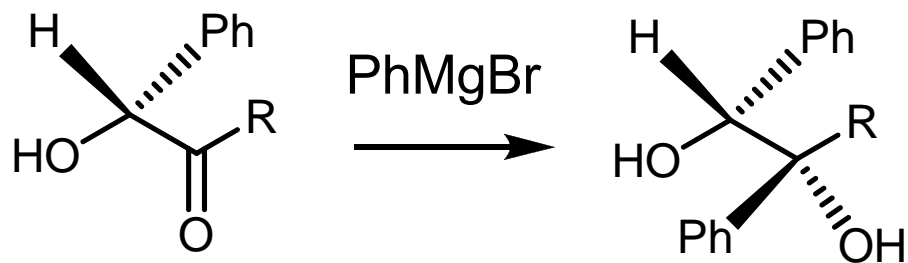
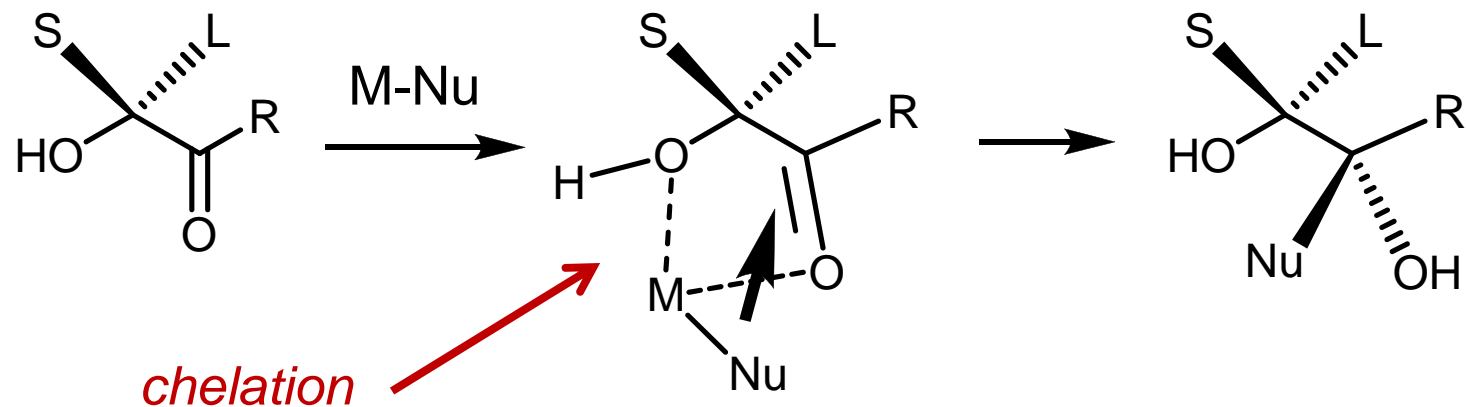
large difference between S and M

Decrease in stereoselectivity

increasing the size of R

- no chelating groups in the substrate other than the carbonyl group
- no polar group is attached to the chiral centre

The Cyclic Model for 1,2 Asymmetric Induction

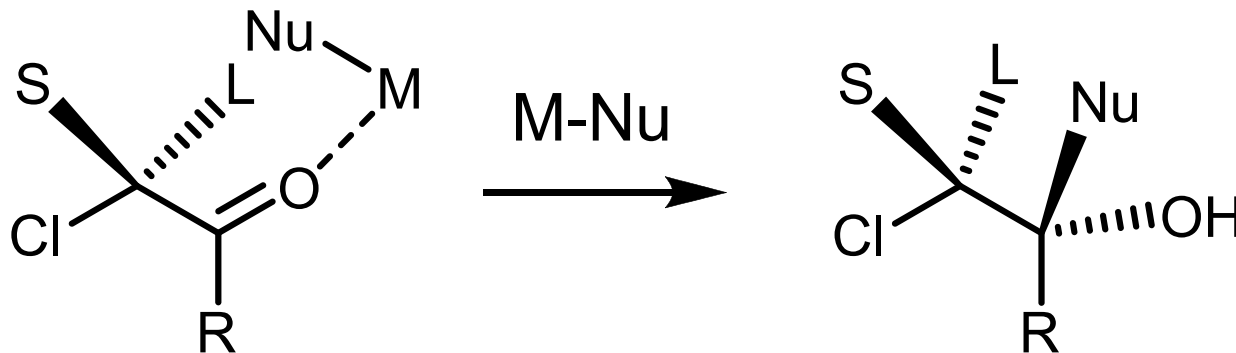


Use models here

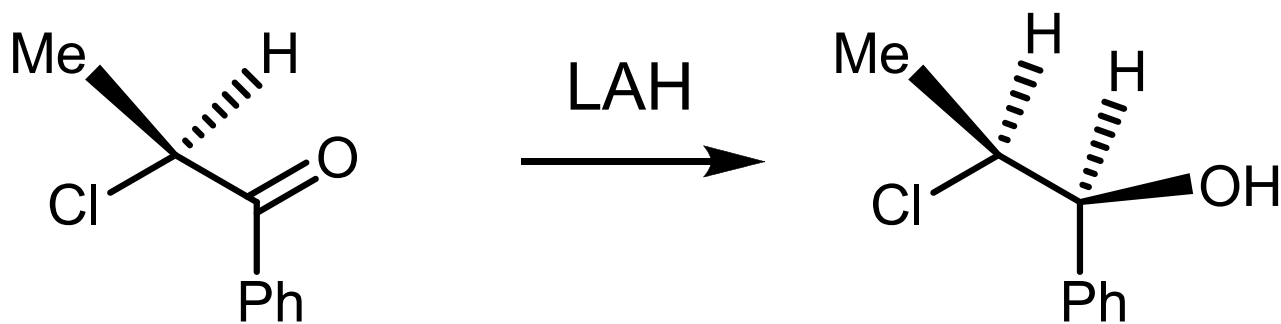
1,2 Asymmetric Induction

The Dipolar Model (Cornforth's Model)

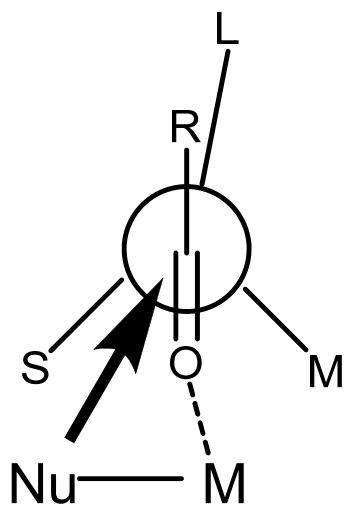
1,2 Asymmetric Induction



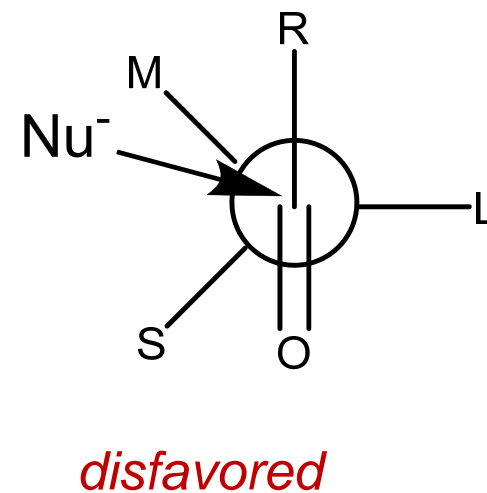
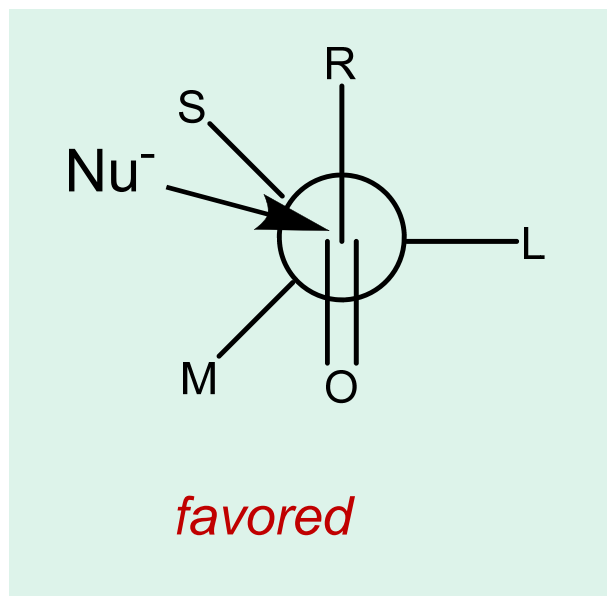
Use models here



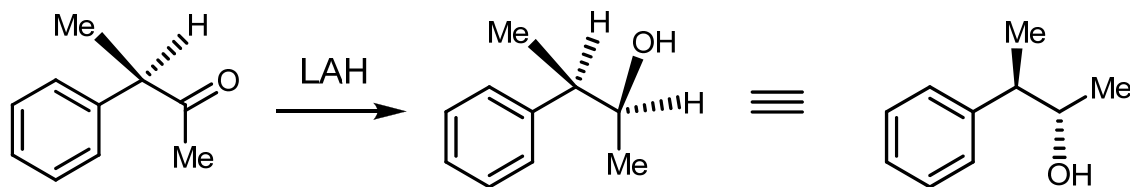
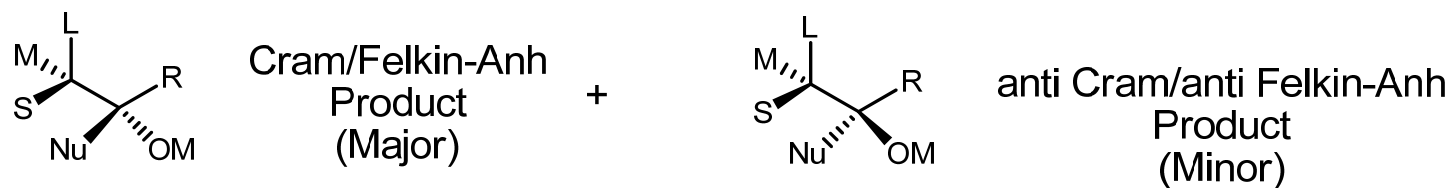
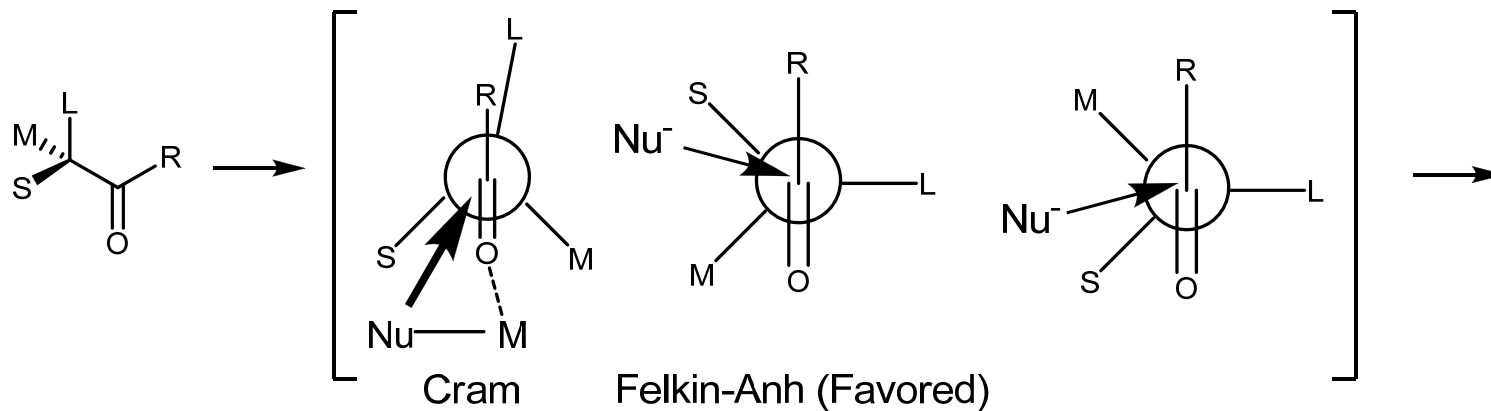
Cram Model



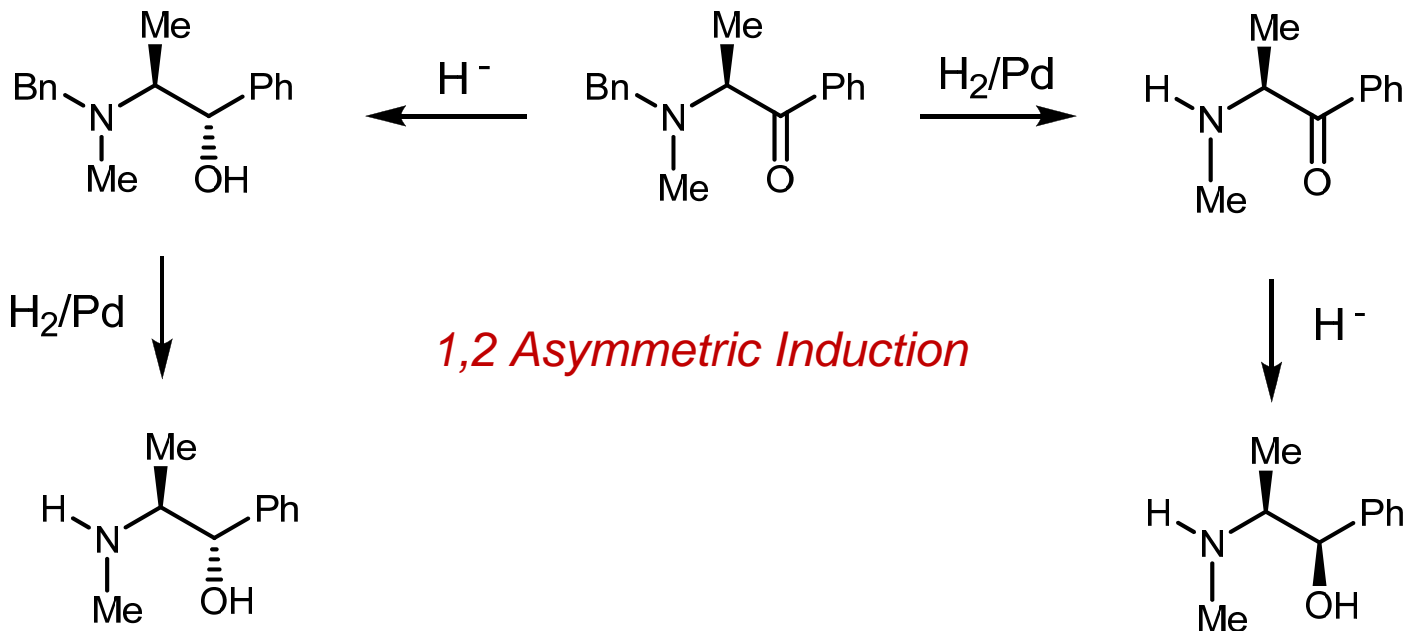
Felkin-Anh Model



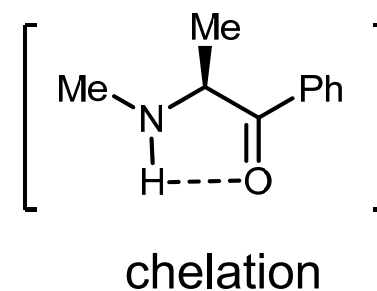
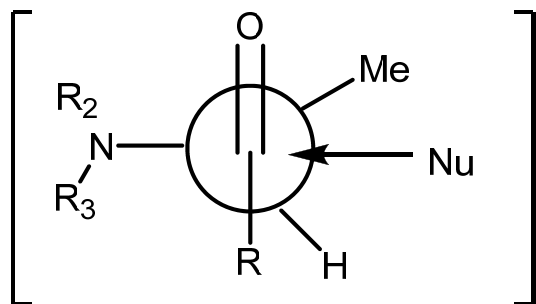
Use models here



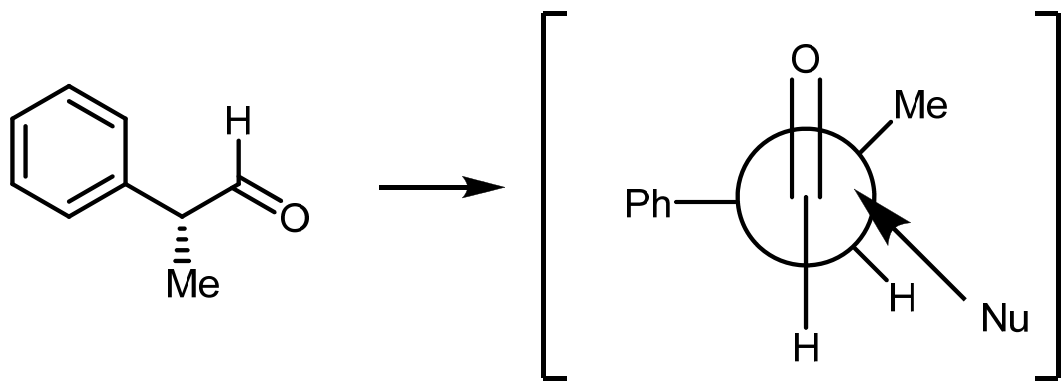
1,2 Asymmetric Induction



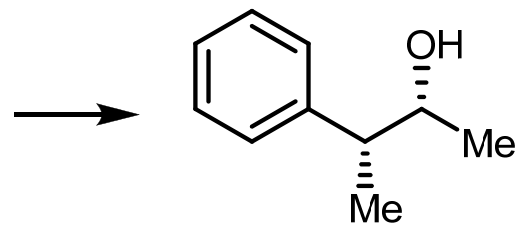
Felkin-Anh (favored)



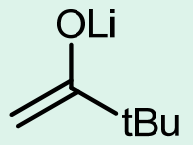
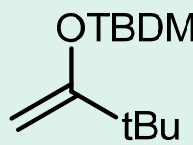
Use models here

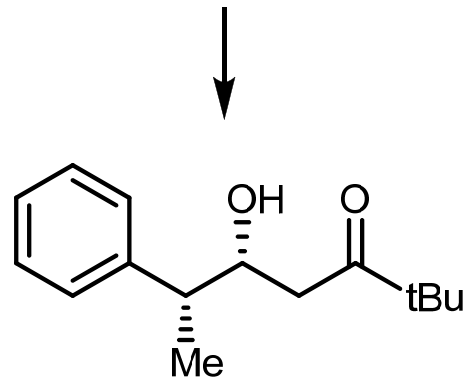


Felkin Anh Products



MeLi or MeMgBr dr: 2:1
MeTi (OiPr)₃ dr: 88:12

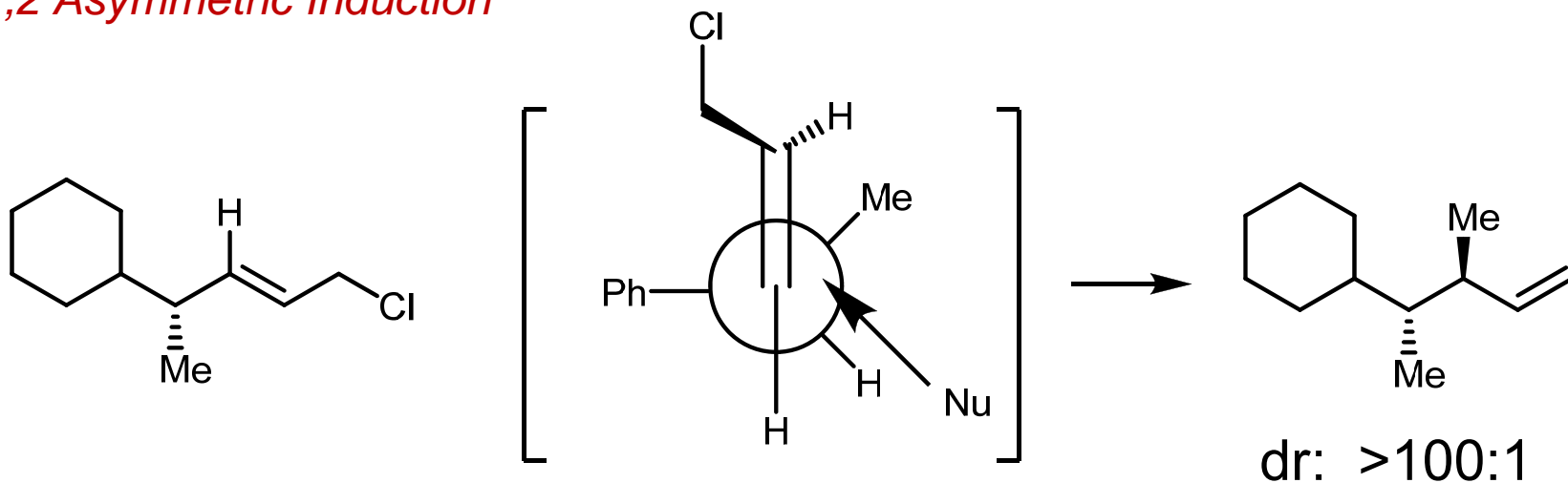
 dr: 4:1
 dr: 24:1



1,2 Asymmetric Induction

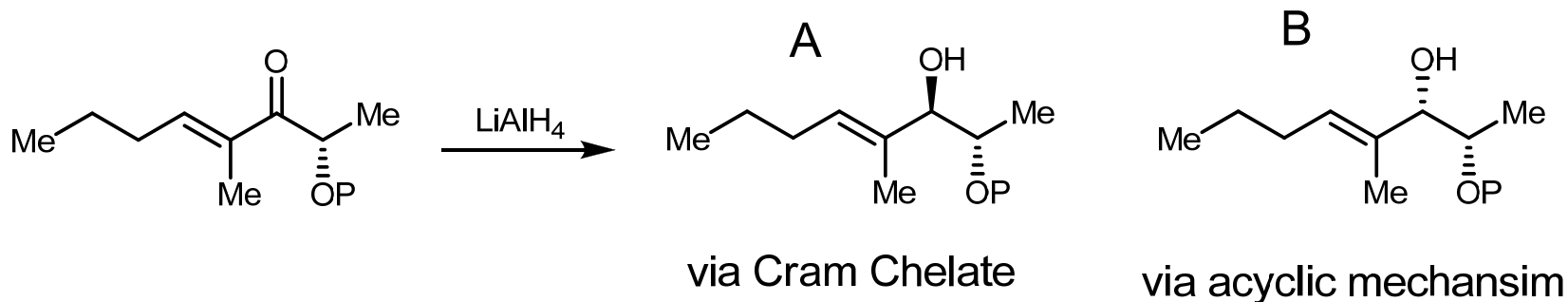
Felkin Anh Like

1,2 Asymmetric Induction



Use models here

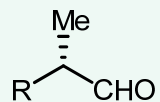
1,2 Asymmetric Induction



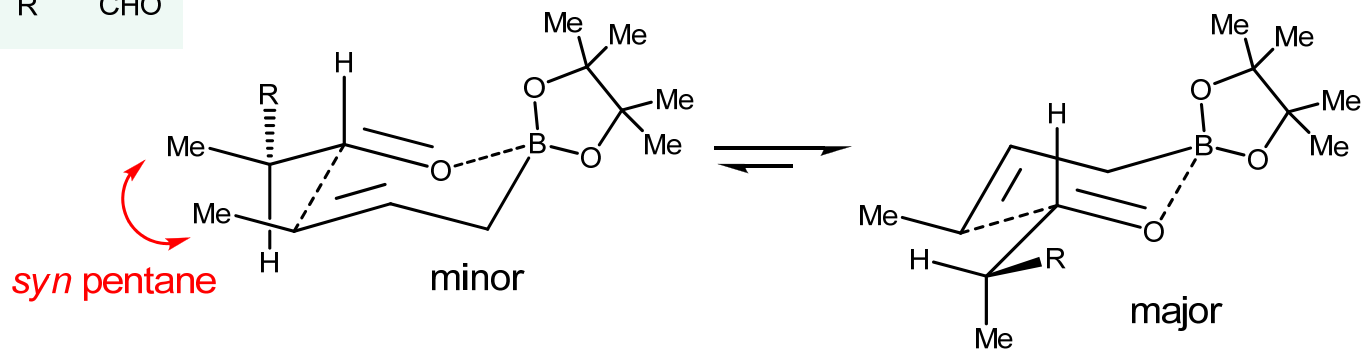
P	solvent	dr ratio A:B
Bn	Et ₂ O	98:2
TBDPS	THF	5:95
MOM	THF	70:30
MOM	Et ₂ O	98:2

1,2 Asymmetric Induction: Diastereoselective Allylation with Chiral Boron Reagents

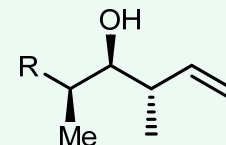
Use models here



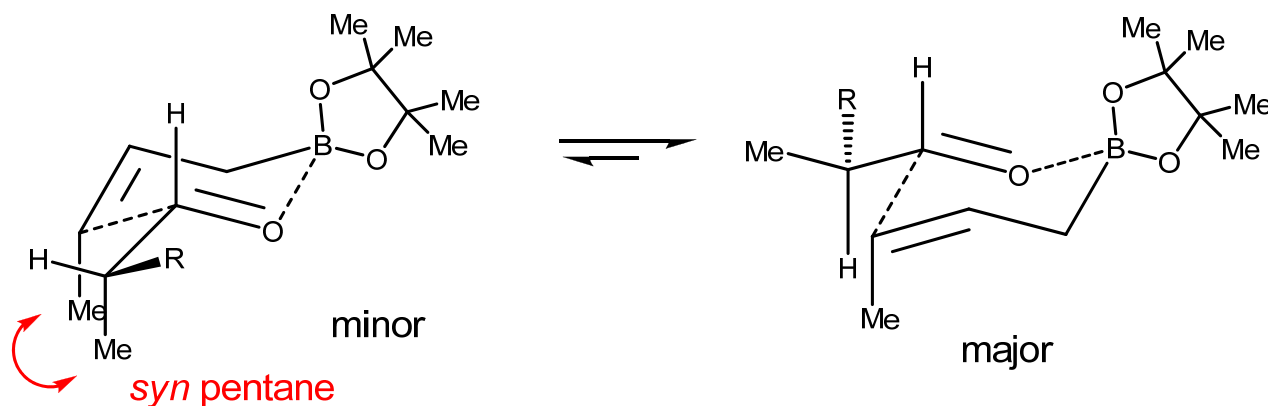
E-crotyl



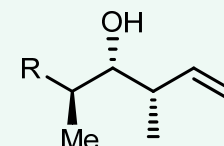
Felkin



Z-crotyl

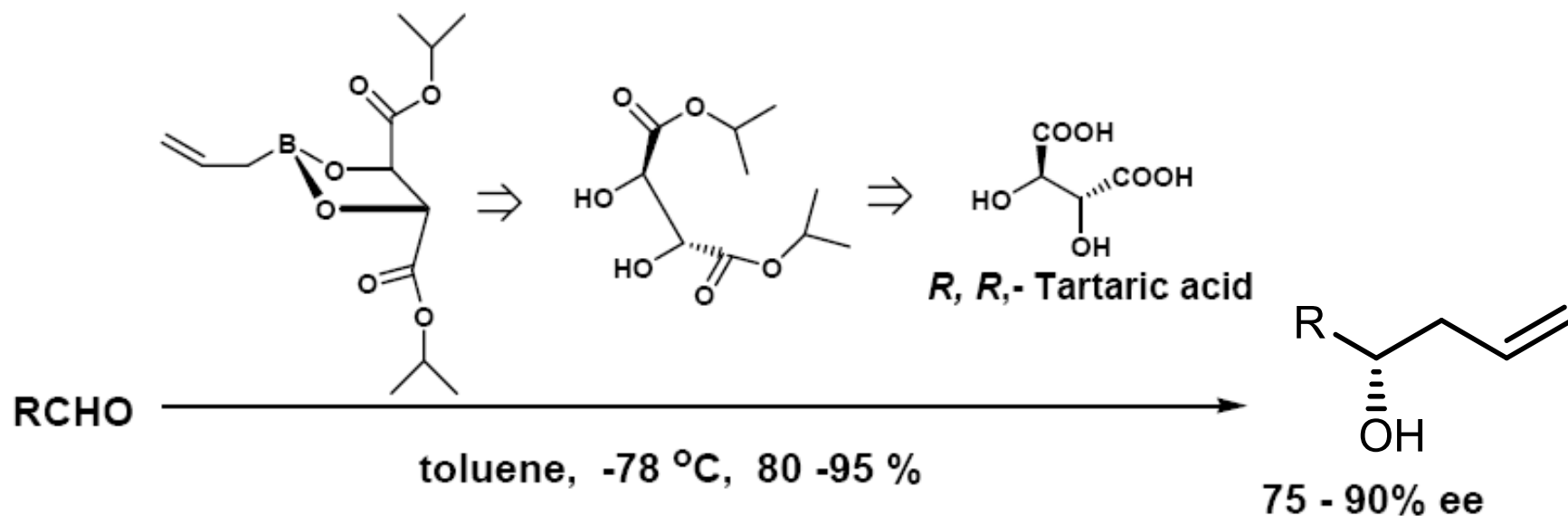


anti Felkin

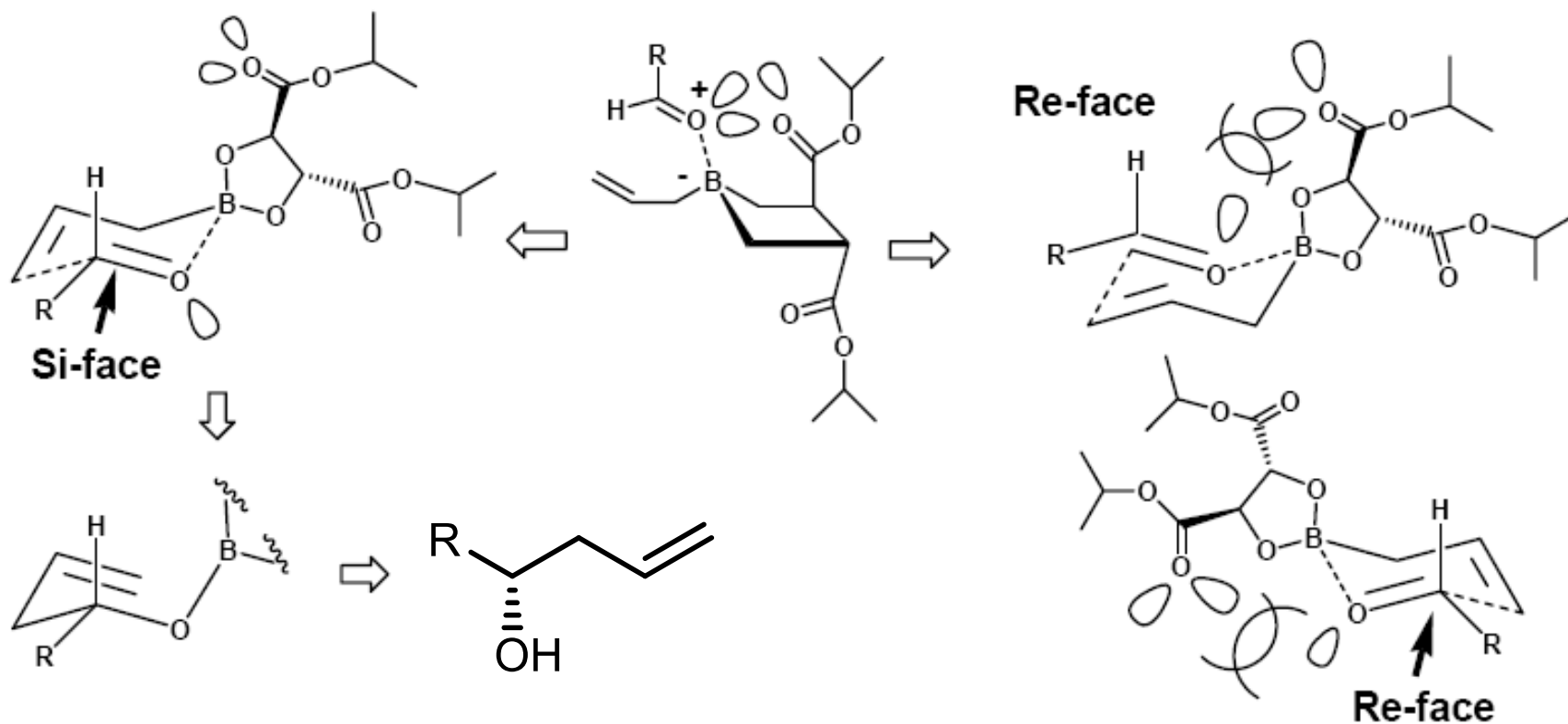


1,2 Asymmetric Induction: Diastereoselective Allylation with Chiral Boron Reagents

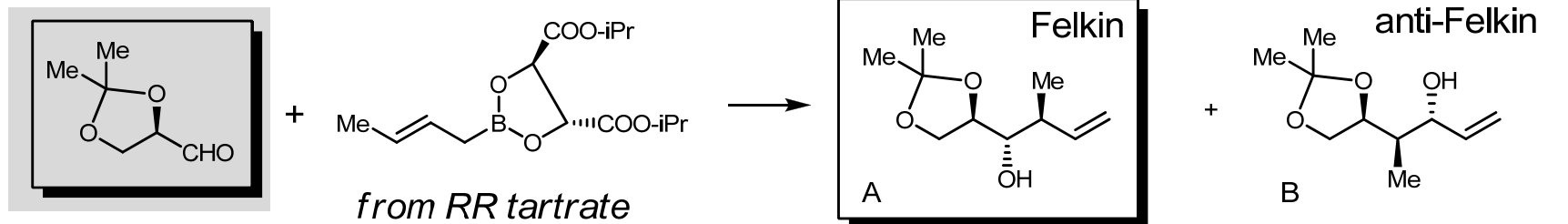
Enantioselective Organoborane Approach to Carbon-Carbon Bond Formation



Stereoelectronic Effect

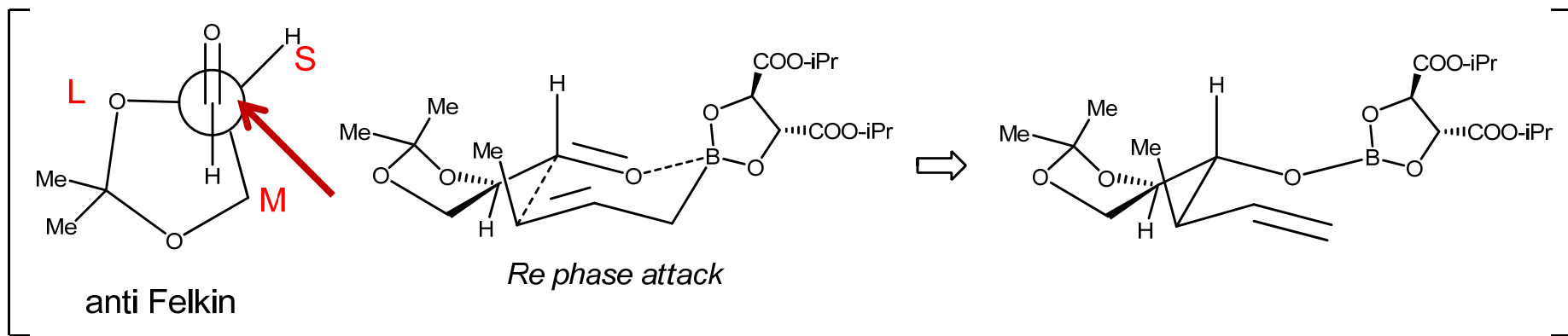
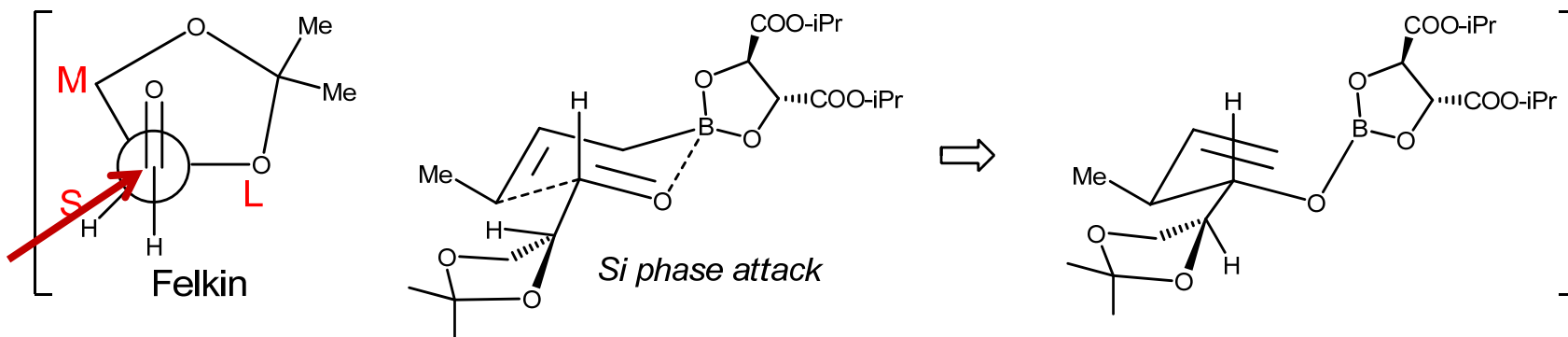


Use models here

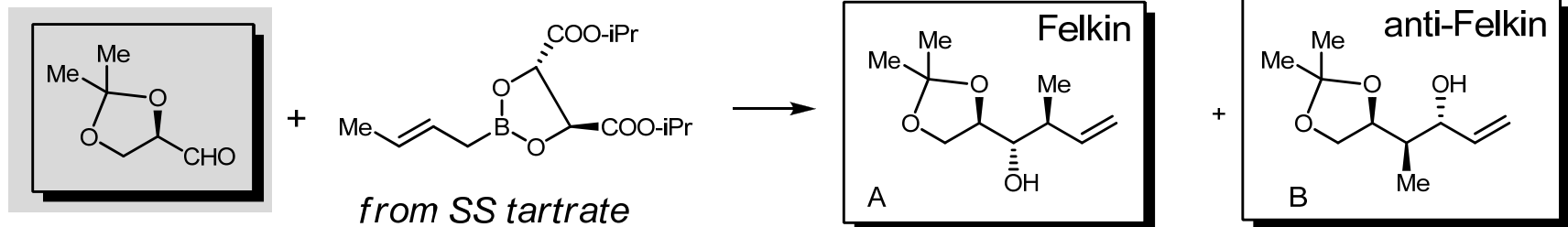


Use models here

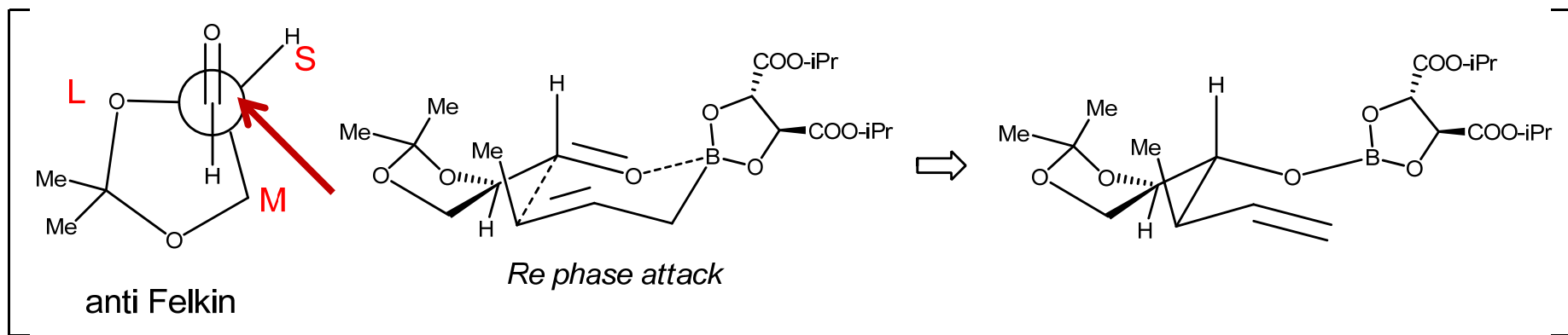
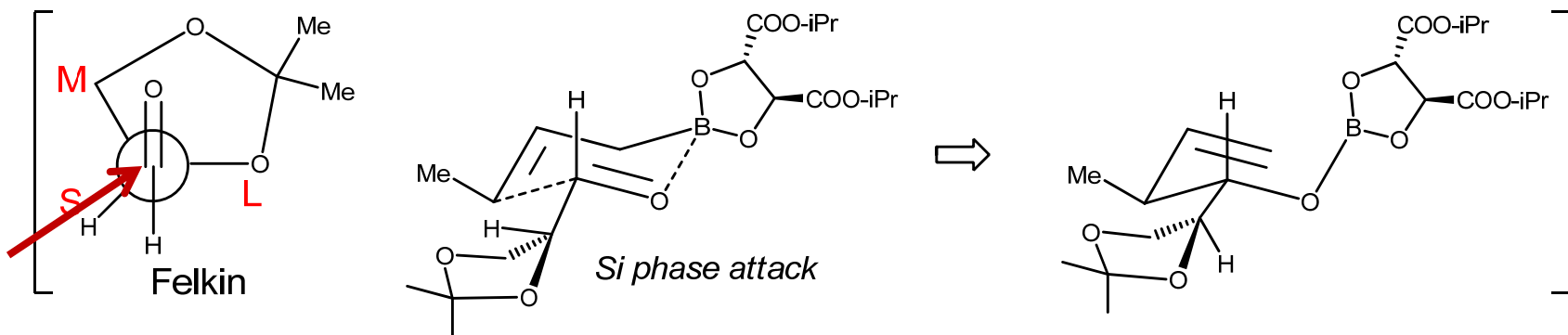
matched case (with RR tartrate), dr (A+B) = 91 : 9

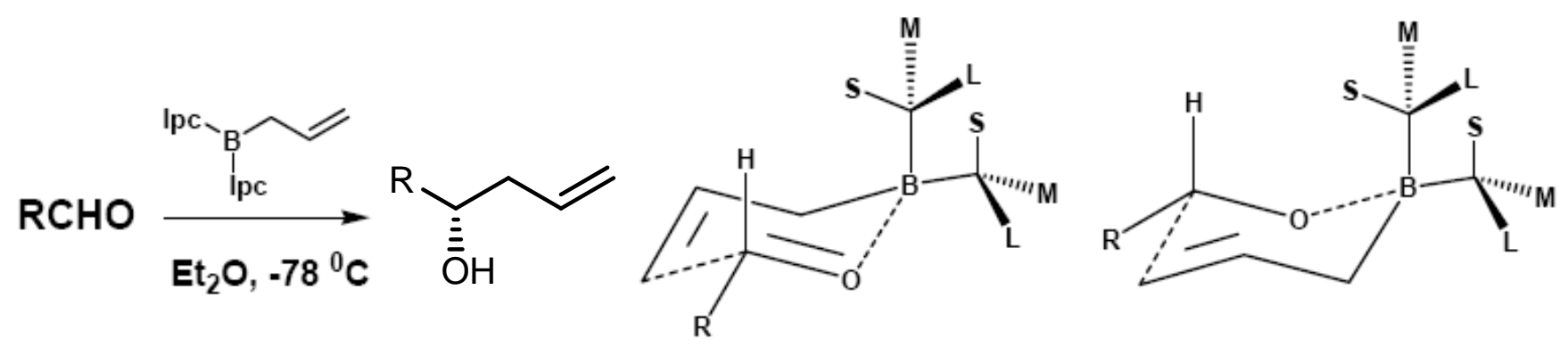
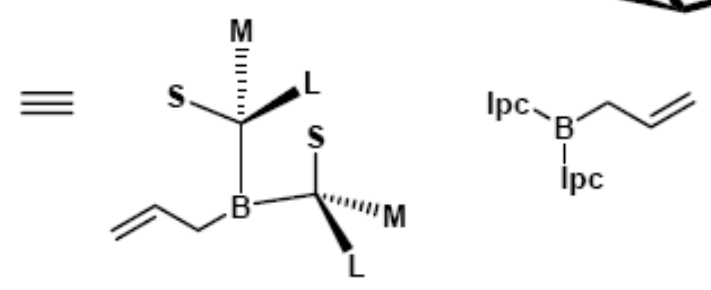
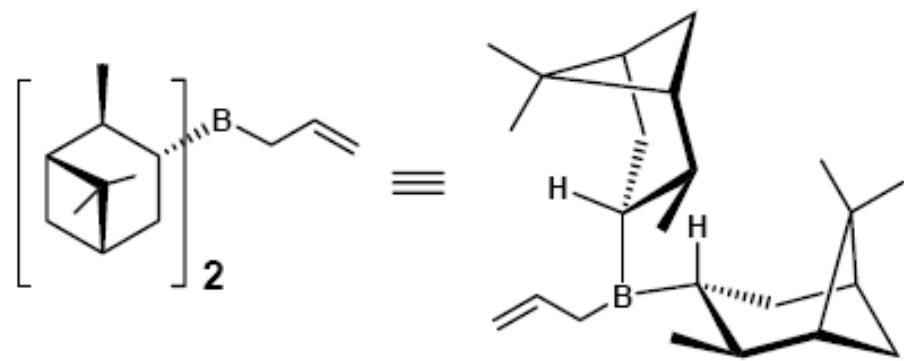


Use models here

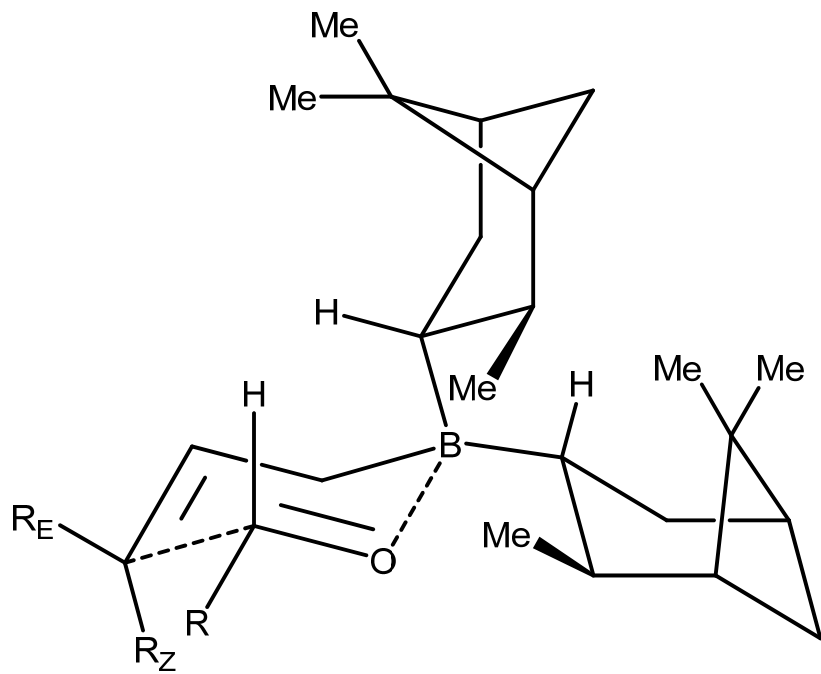


mismatched case (with *SS* tartrate), dr (A+B) = 2 : 98

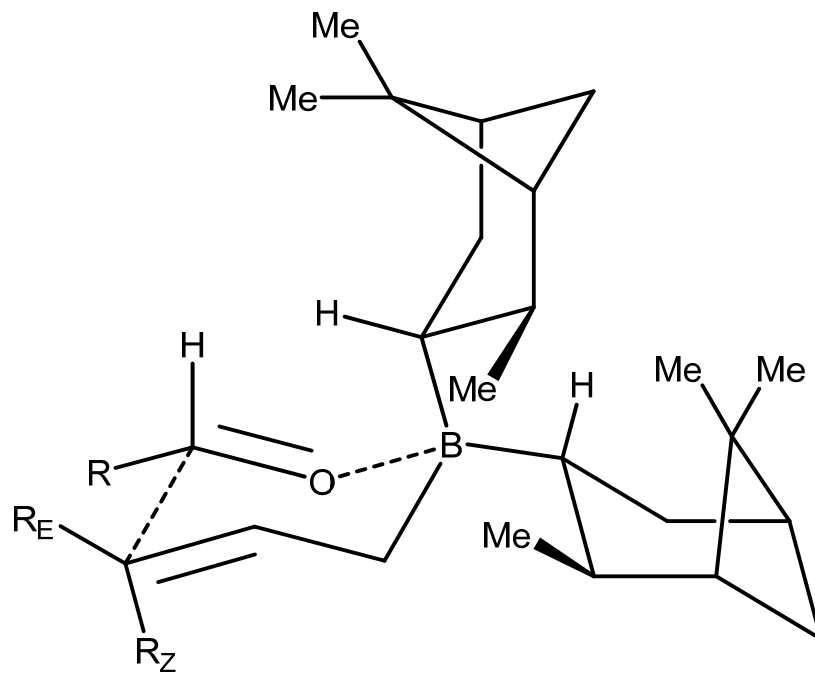




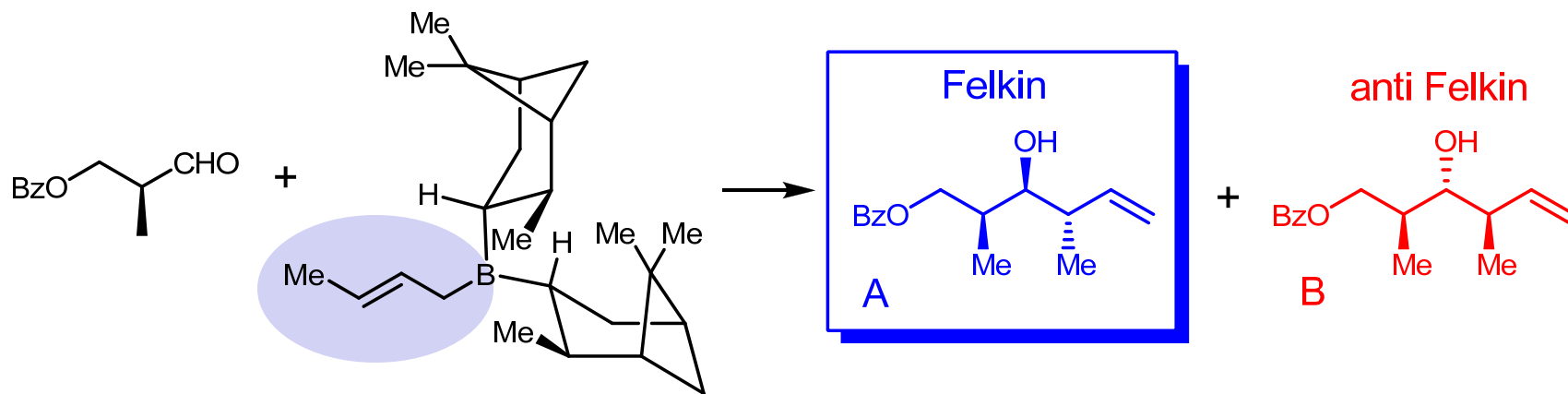
Favored Transition State



Disfavored Transition State



Derived from (+) pinene

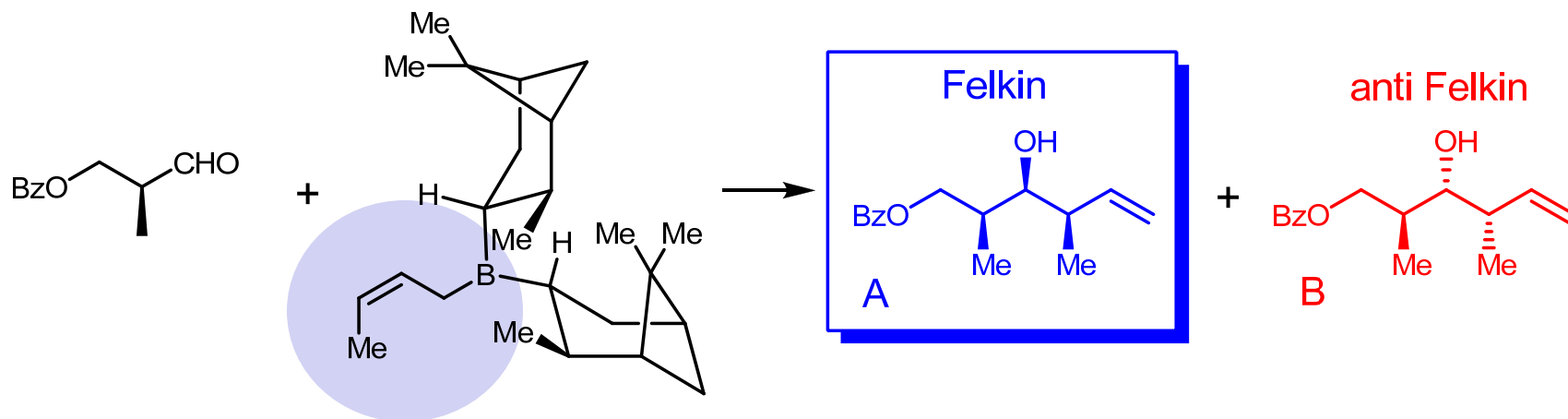


Use models here

matched case (+) pinene reagent
dr (A+B) = 98 : 2

mismatched case (-) pinene reagent
dr (A+B) = 5 : 95

Derived from (+) pinene

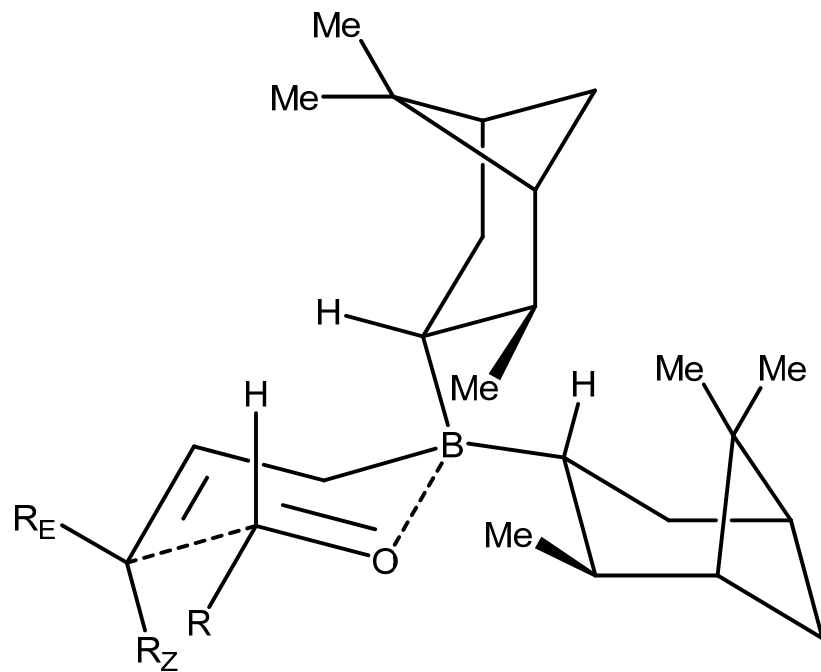


Use models here

matched case (+) pinene reagent
dr (A+B) = 92 : 8

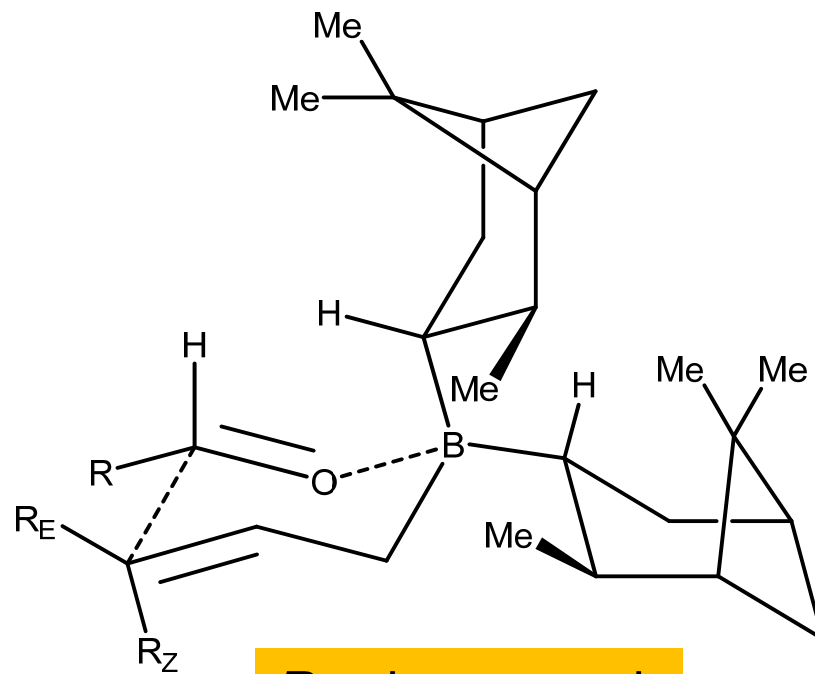
mismatched case (-) pinene reagent
dr (A+B) = 5 : 95

Favored Transition State



Si phase attack

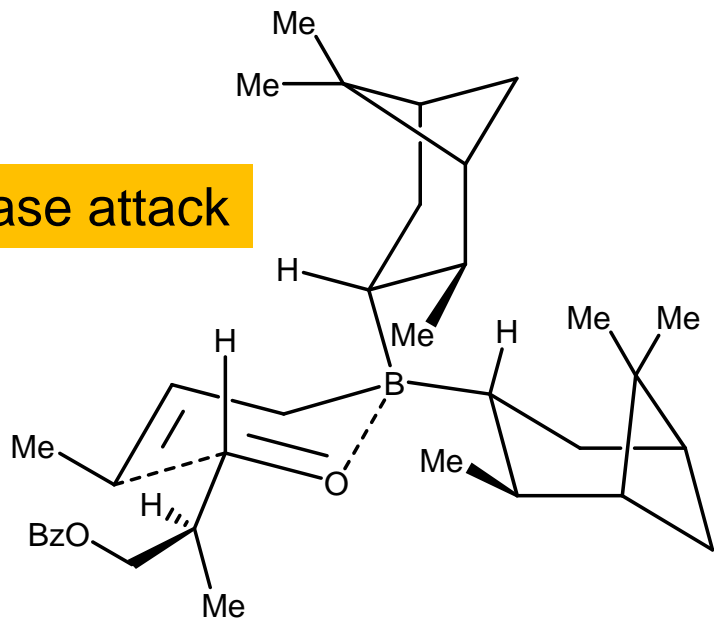
Disfavored Transition State



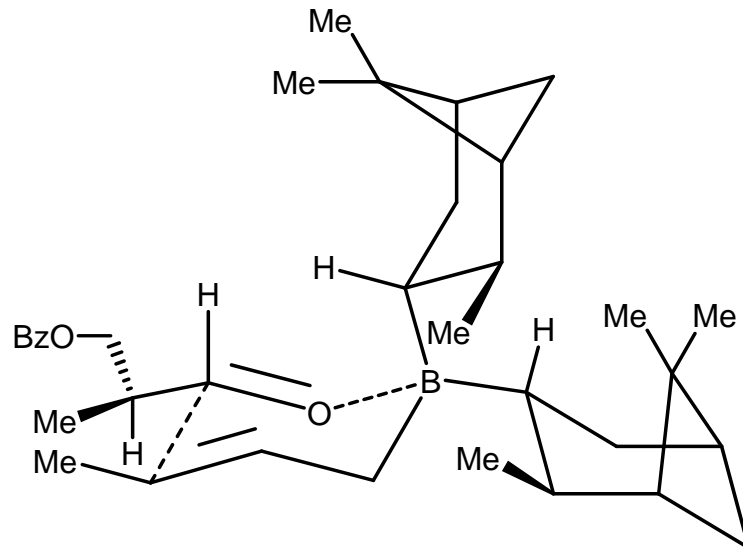
Re phase attack

Favored Transition State

Si phase attack

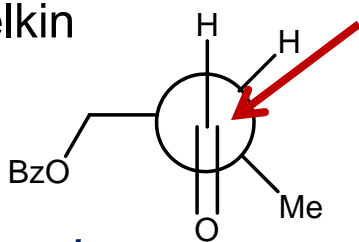


Disfavored Transition State



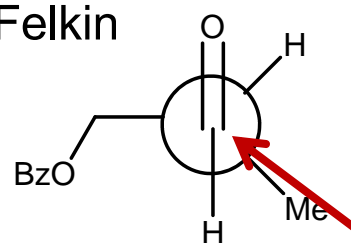
Re phase attack

Felkin



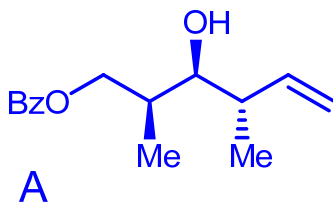
favored

anti Felkin



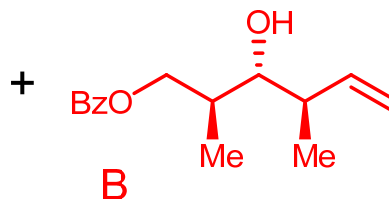
Use models here

Felkin



A

anti Felkin

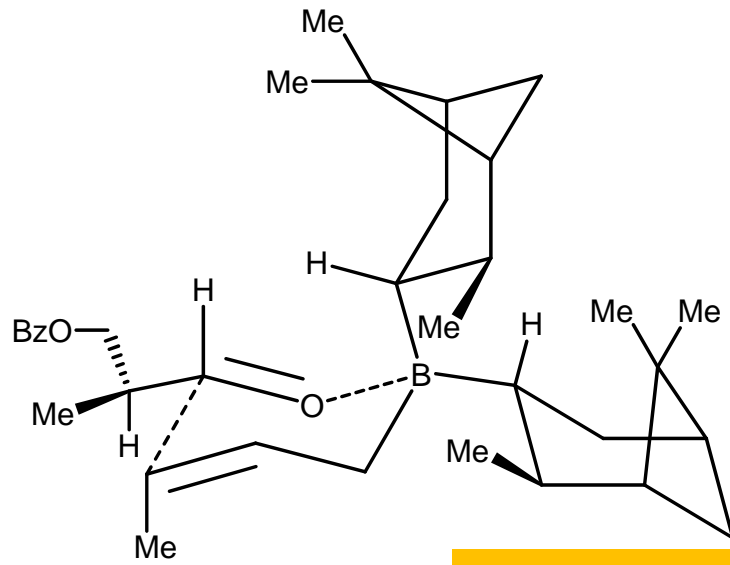
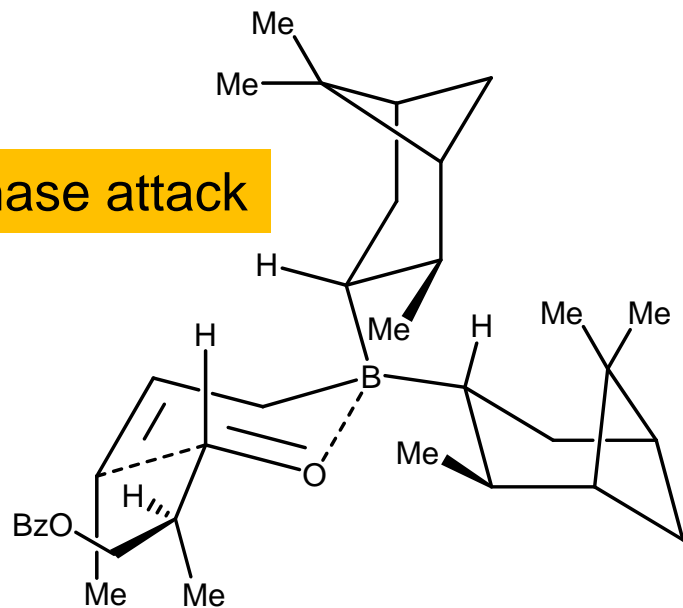


B

Disfavored Transition State

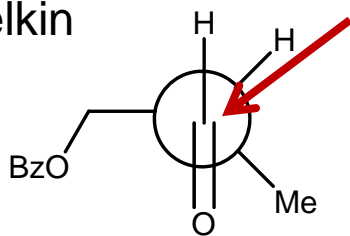
Favored Transition State

Si phase attack

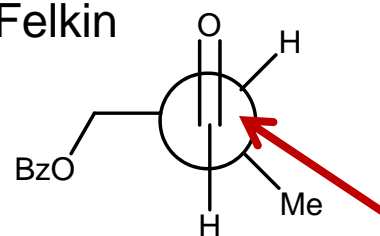


Re phase attack

Felkin

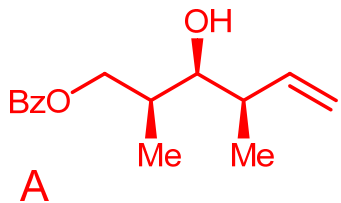


anti Felkin

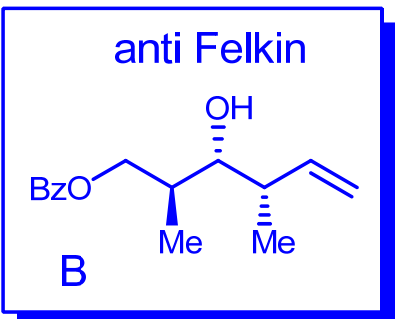


Use models here

Felkin

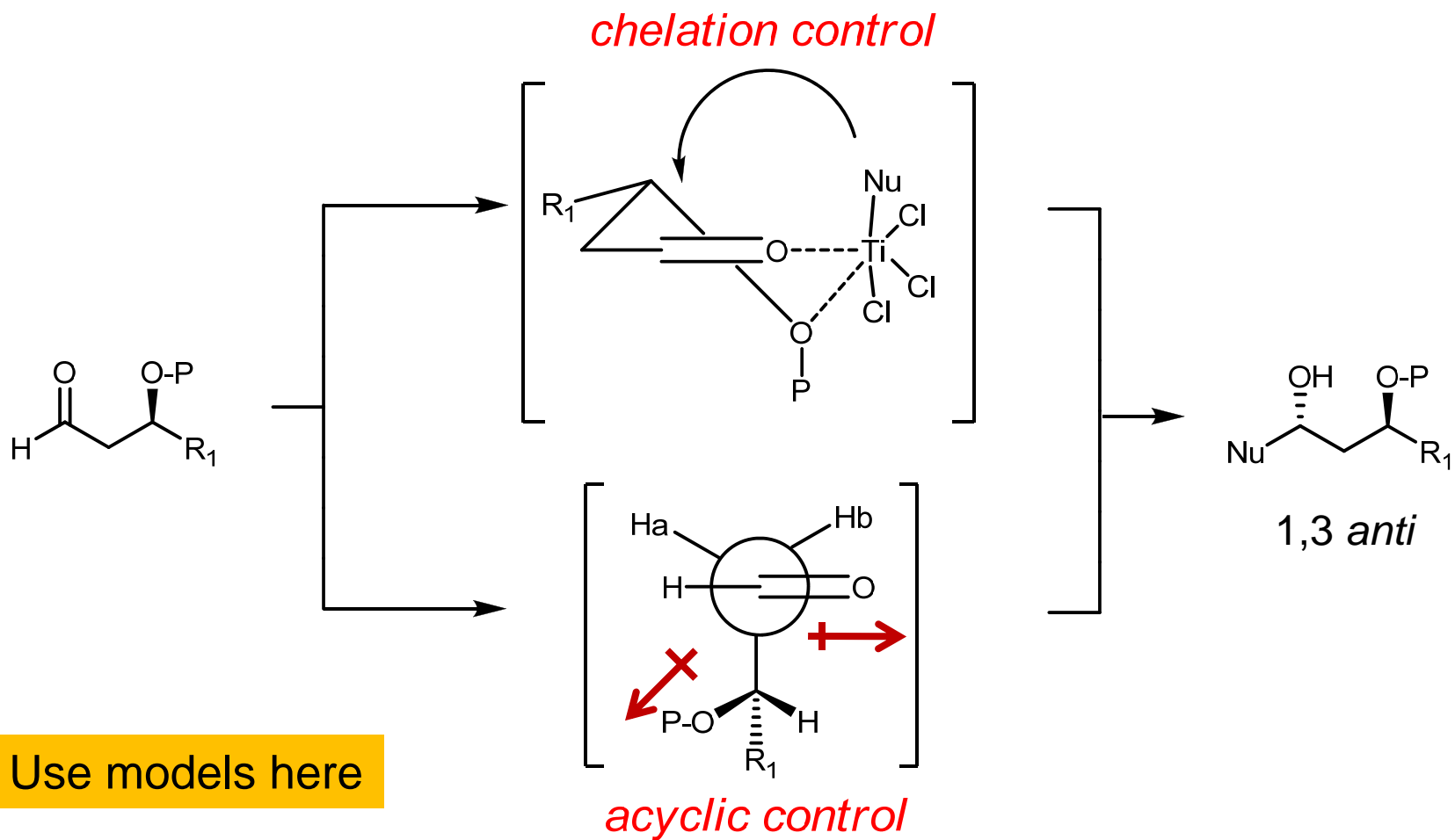


anti Felkin

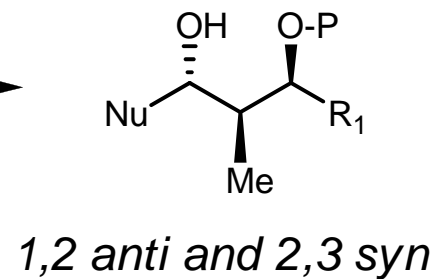
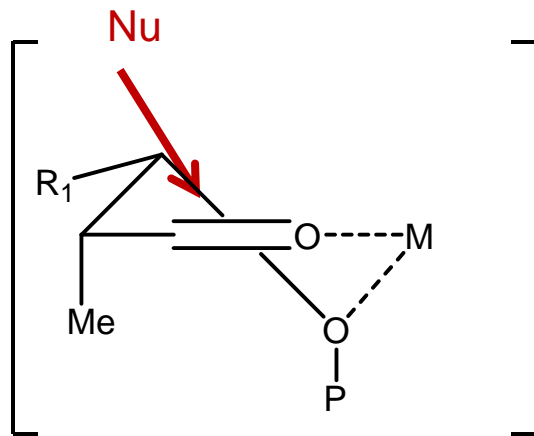
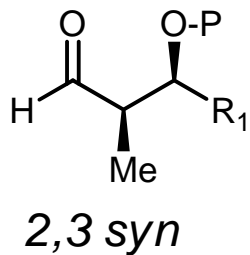
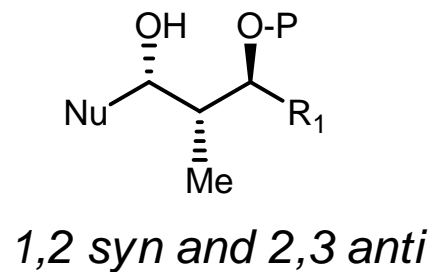
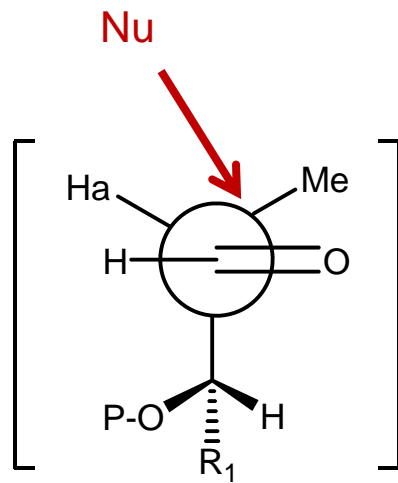
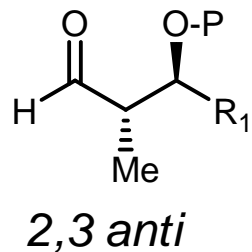


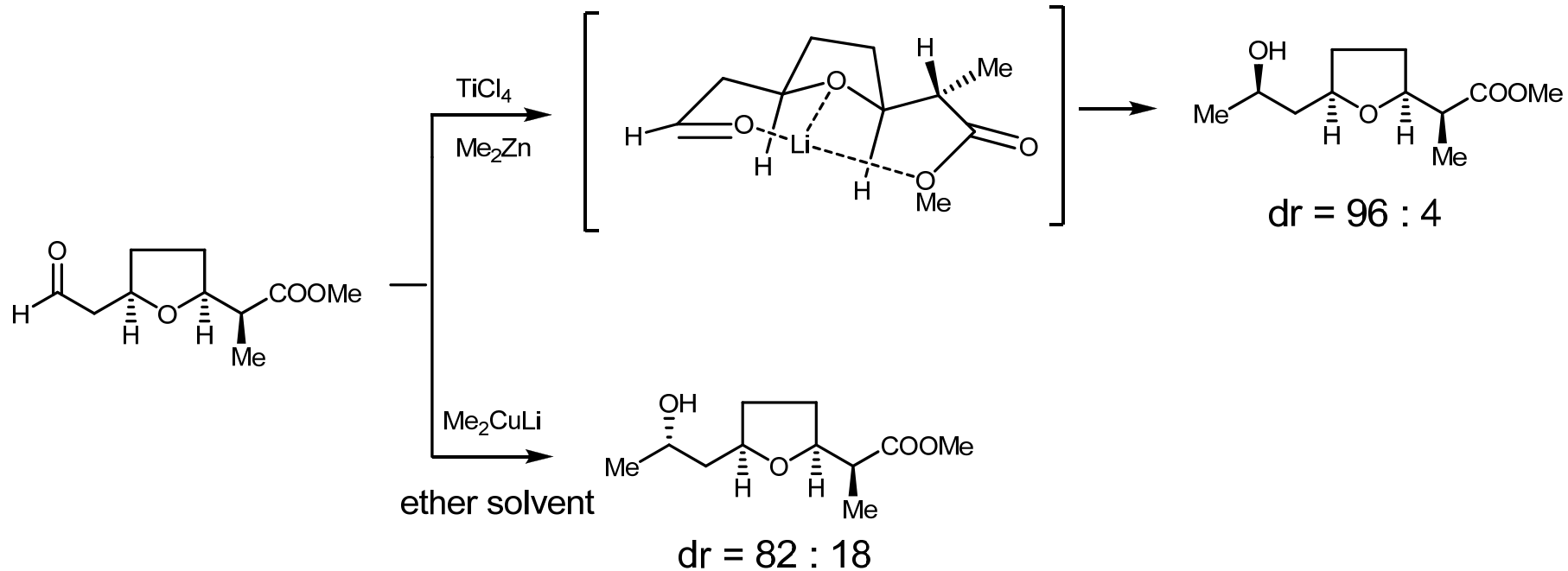
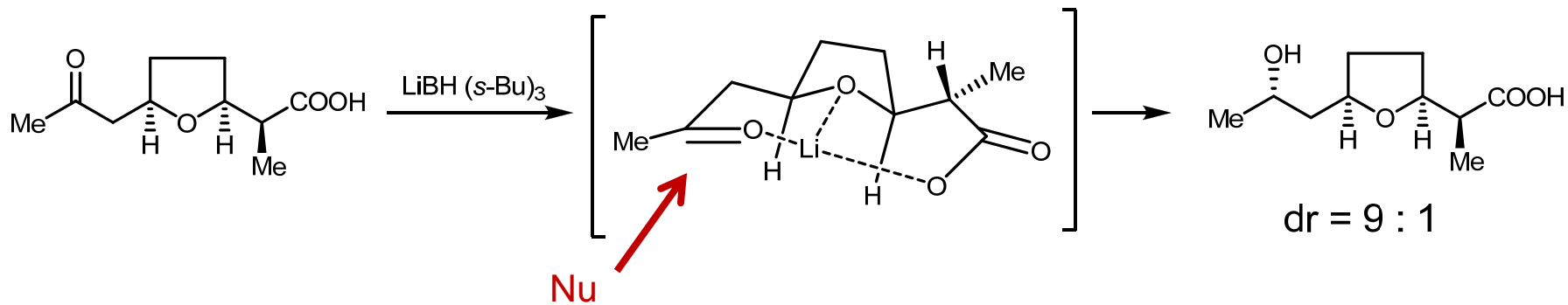
favored

1,3 Asymmetric Induction: Stereogenic Centre β to the Carbonyl Group



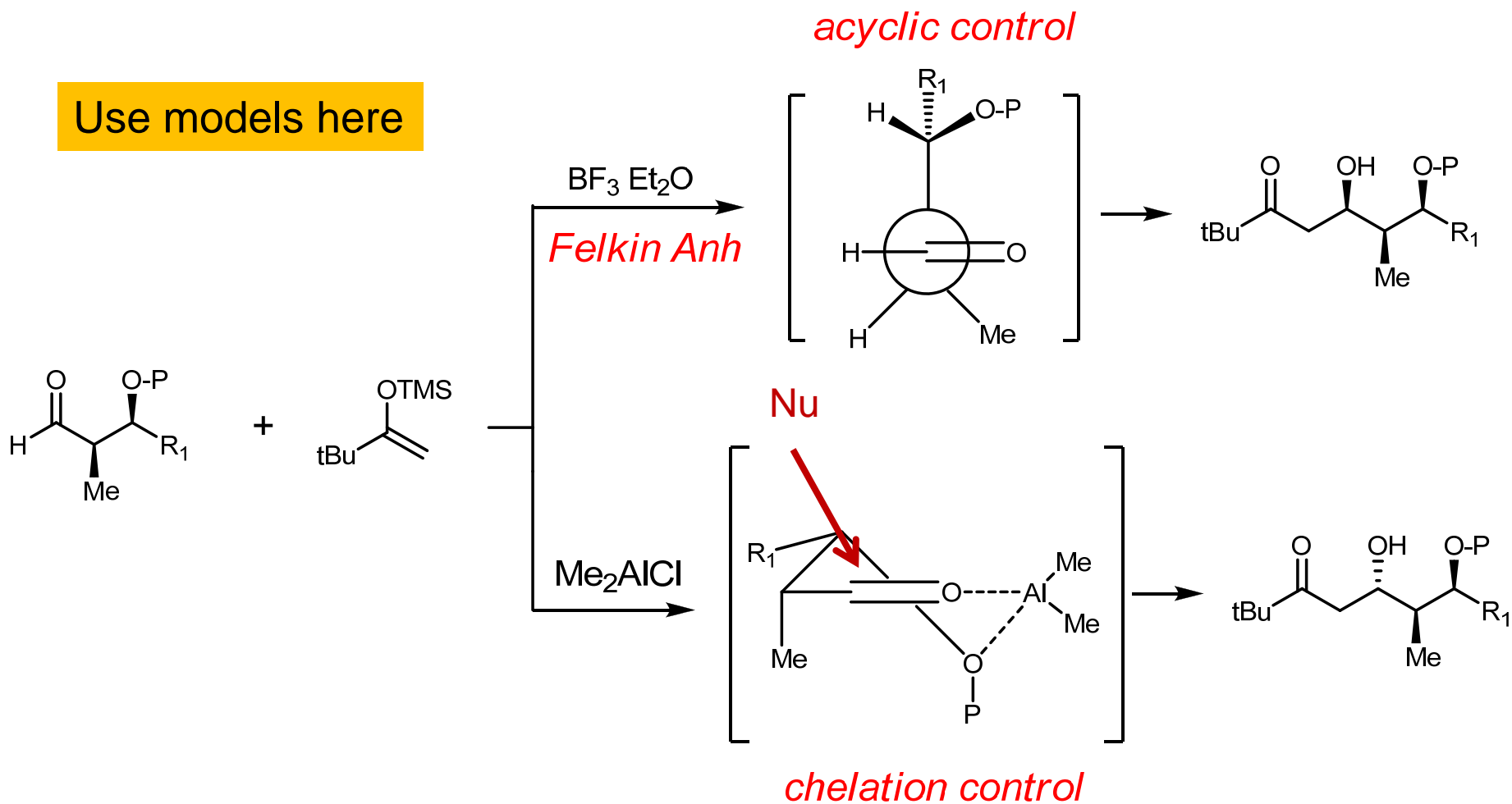
Use models here





Reagents-based Alteration in 1,3 Asymmetric Induction

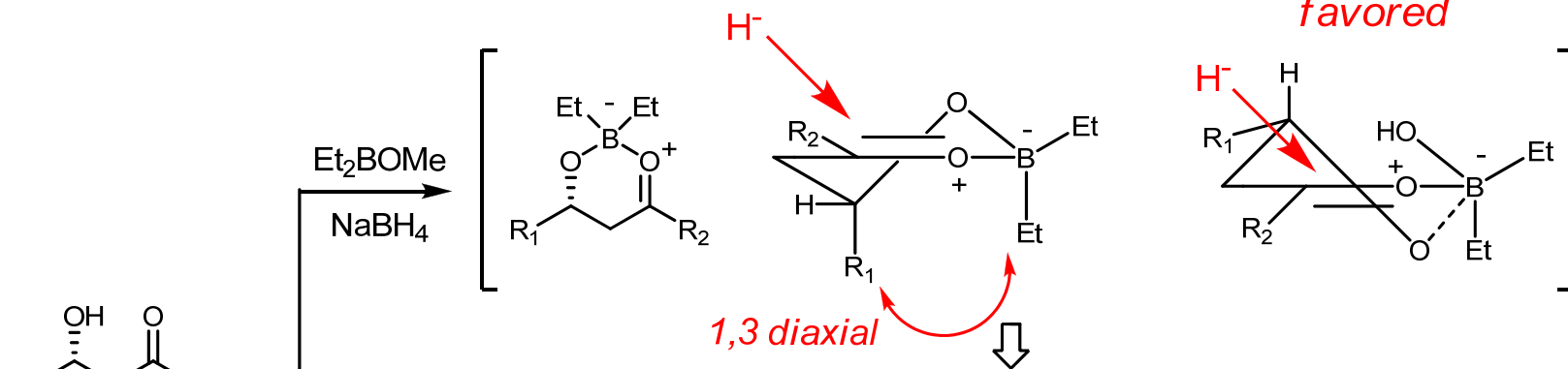
Use models here



Reagents-based Alteration in 1,3 Asymmetric Induction

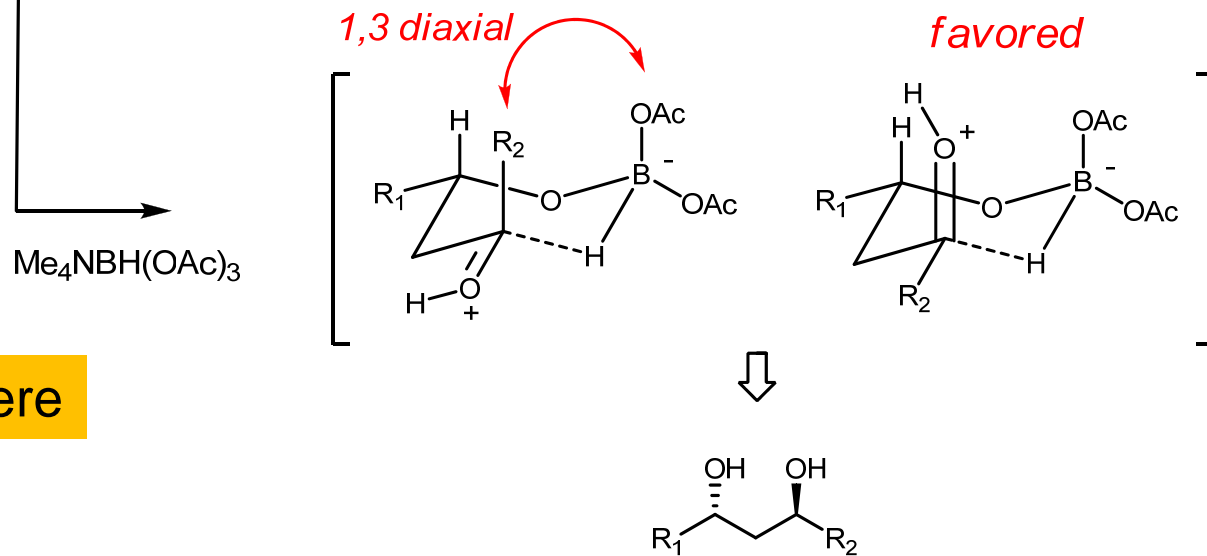
External hydride delivery

favored



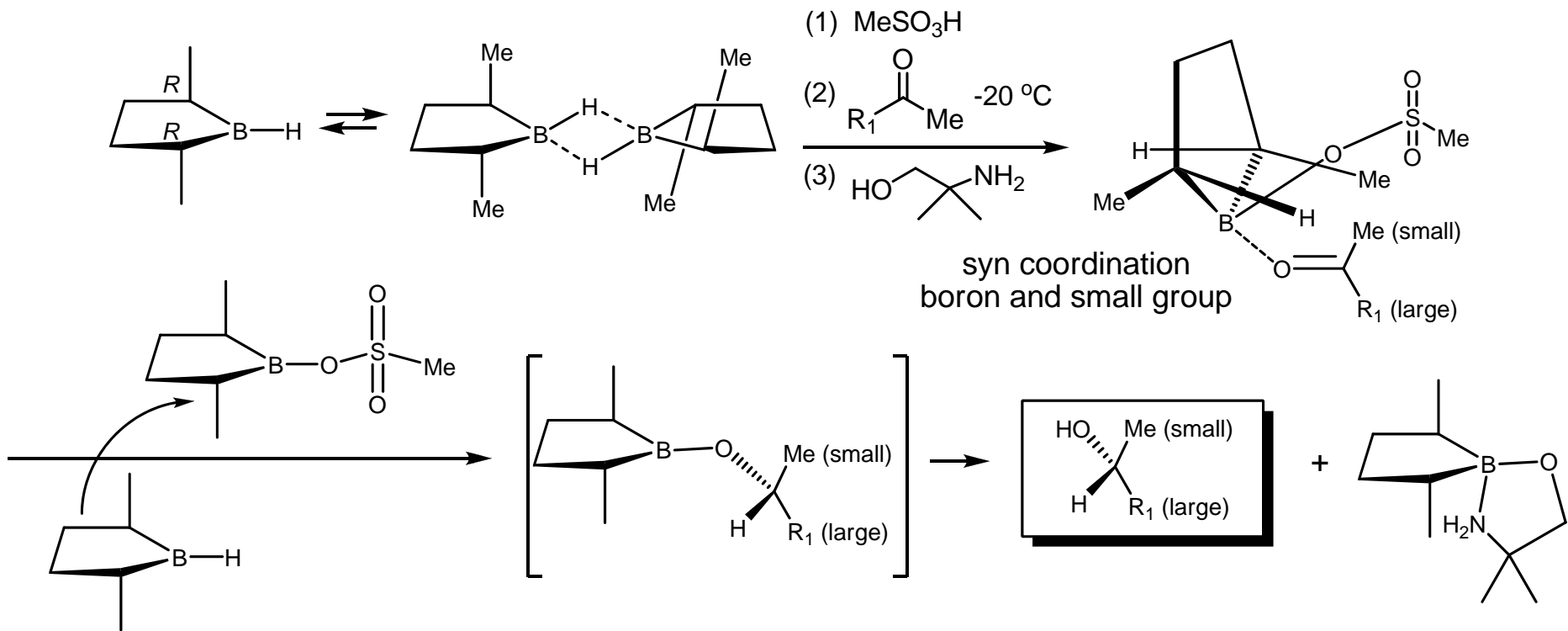
Internal hydride delivery

favored



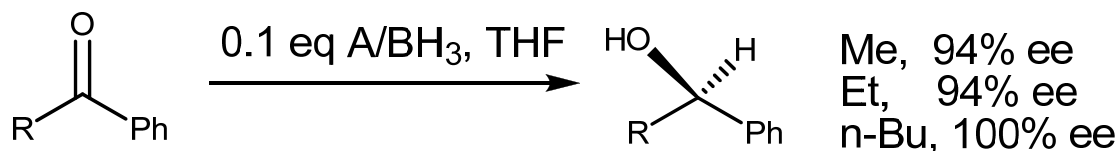
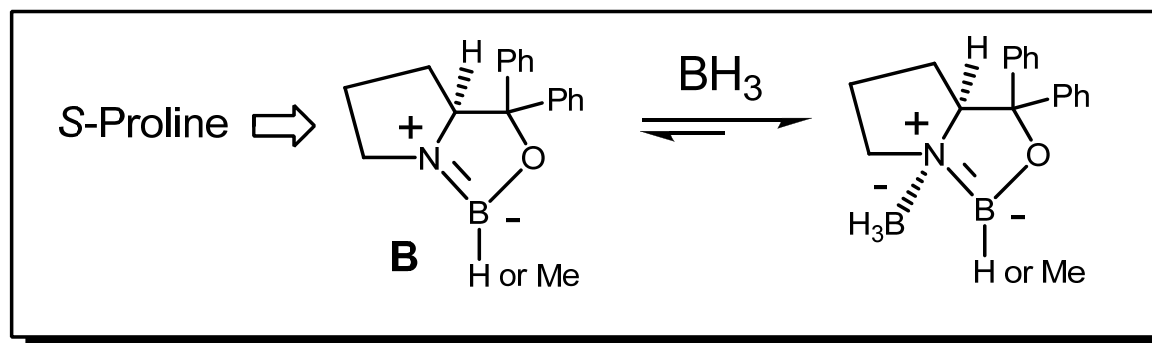
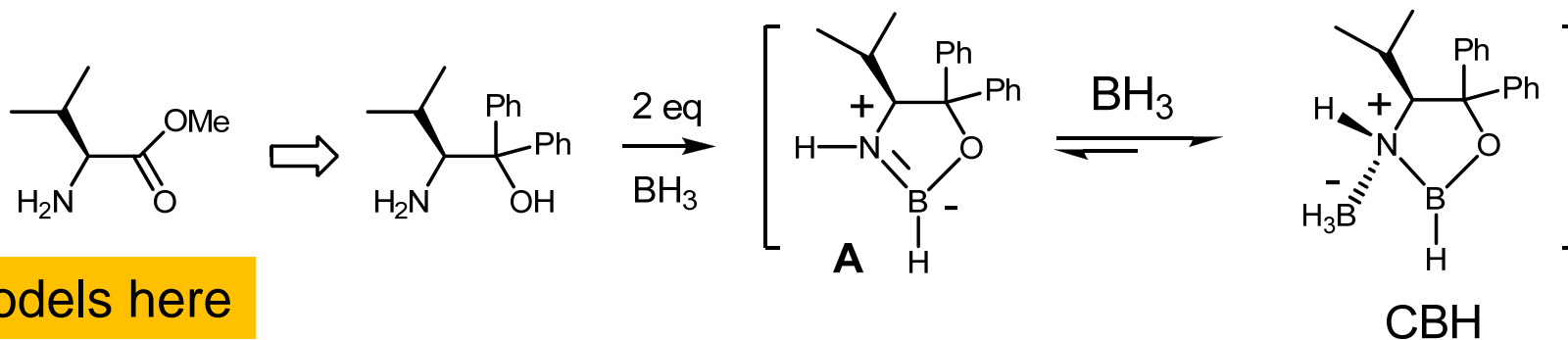
Use models here

Enantioselective Reducing Agents



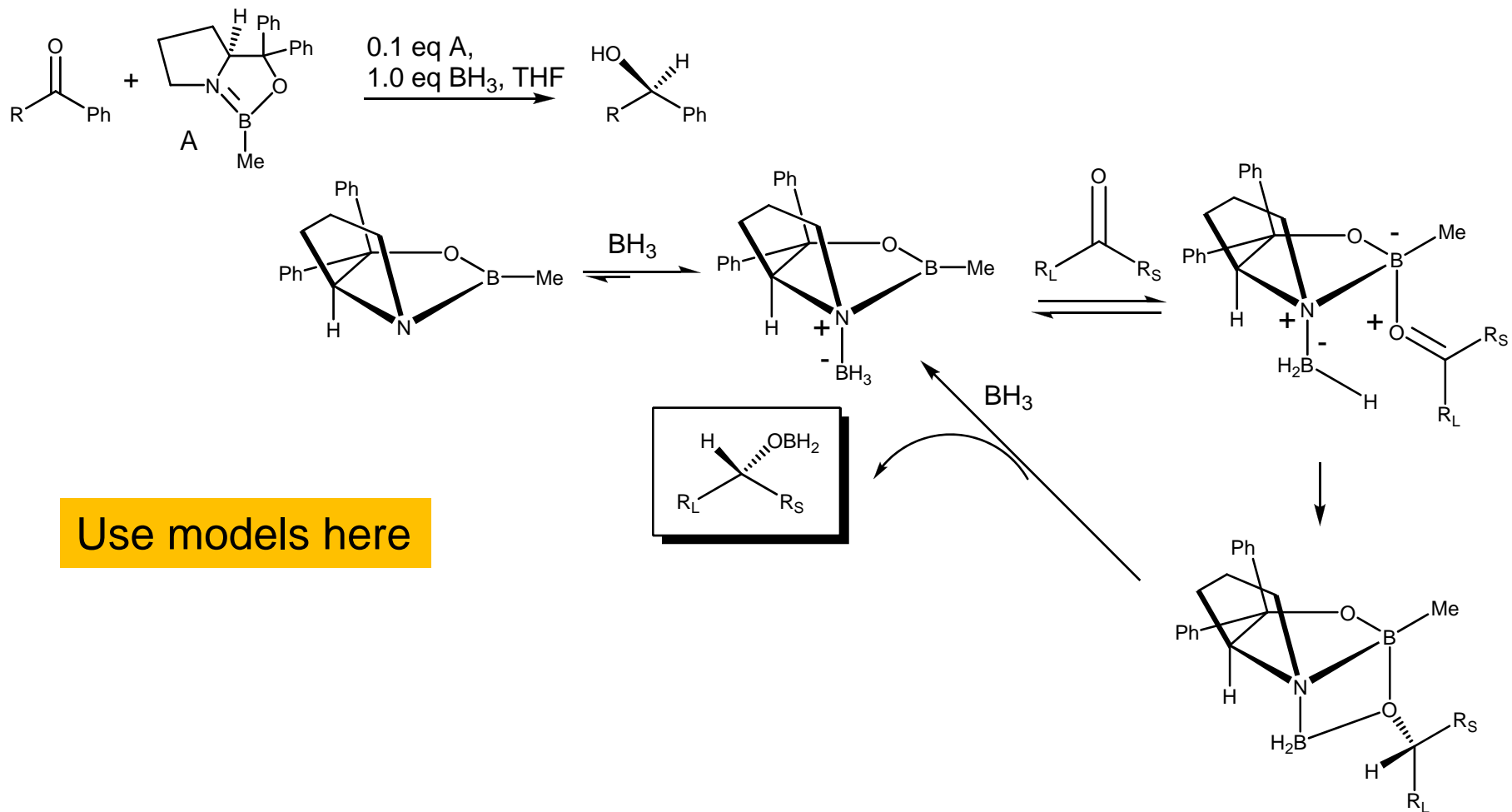
Use models here

Catalytic Chiral Reducing Agent



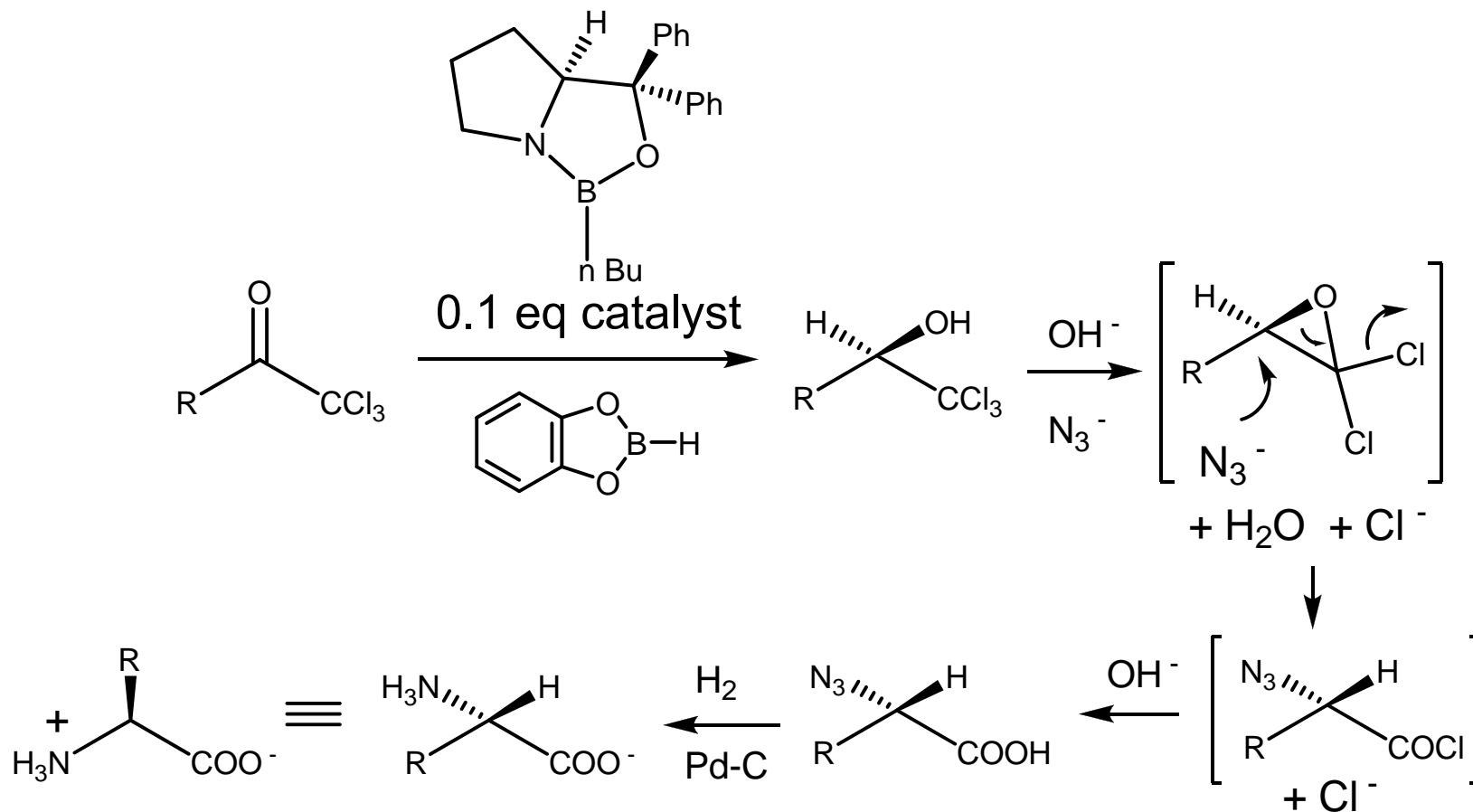
A and BH_3 are not reducing agents

The Proposed Catalytic Cycle



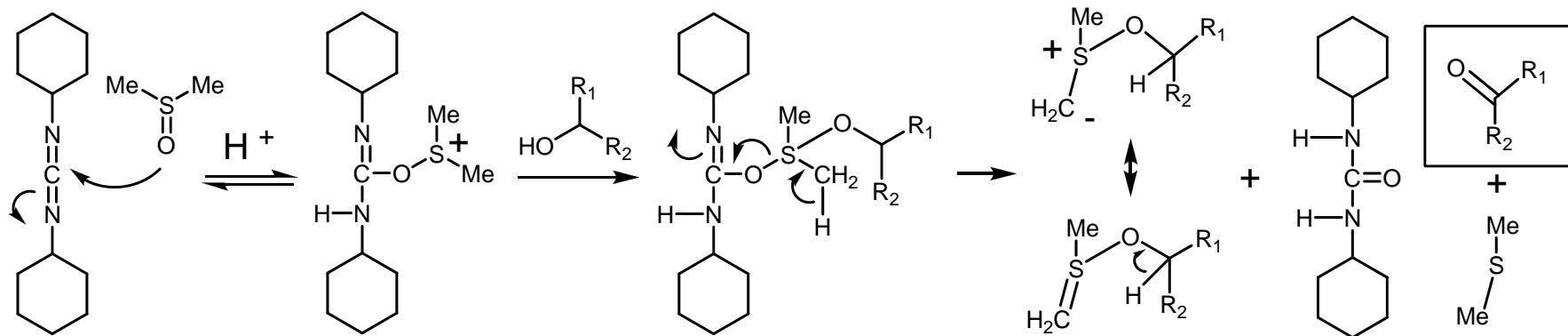
E J Corey et al *J Am Chem Soc*, 5551 (1987)
and covered in review article by David Evans et al in
Science, vol 240, 420 (1988)

An Enantioselective Synthesis α Amino Acids

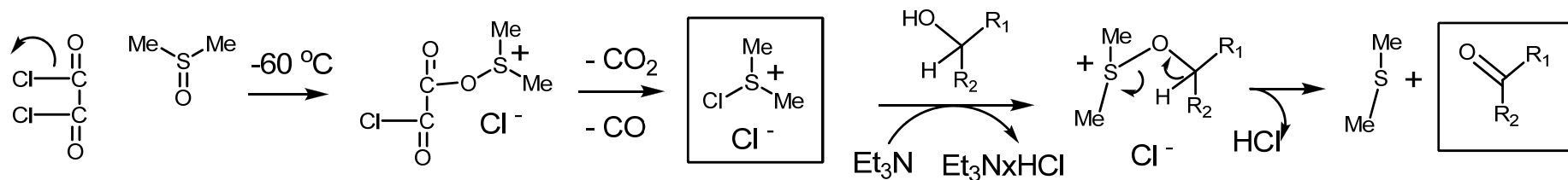


Enantioselective Oxidation

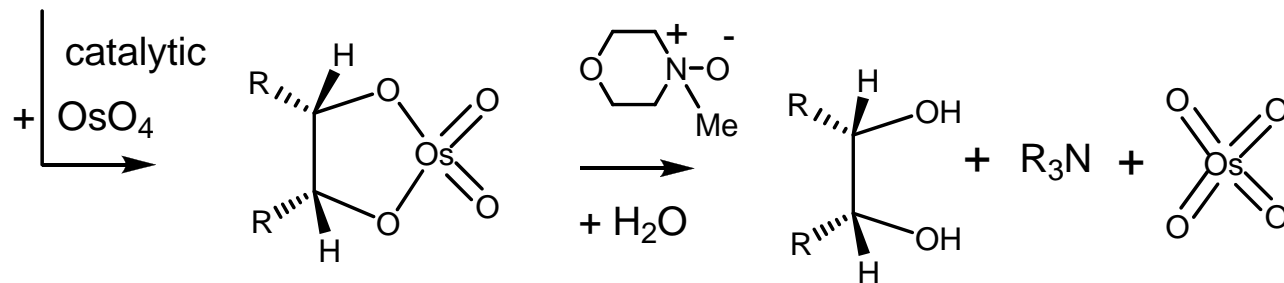
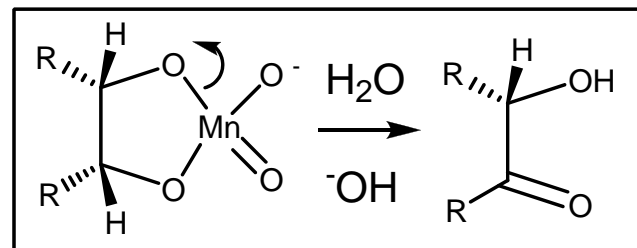
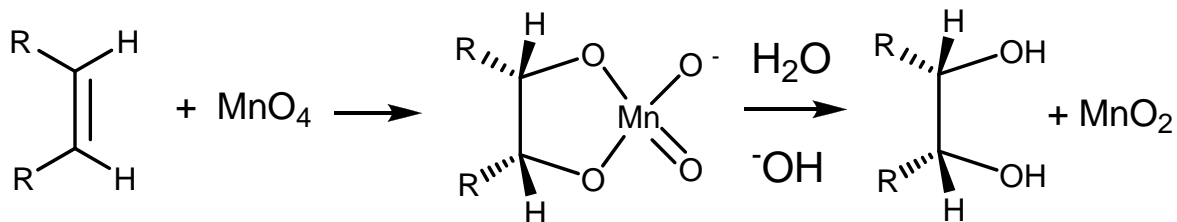
DMSO-DCC Oxidation

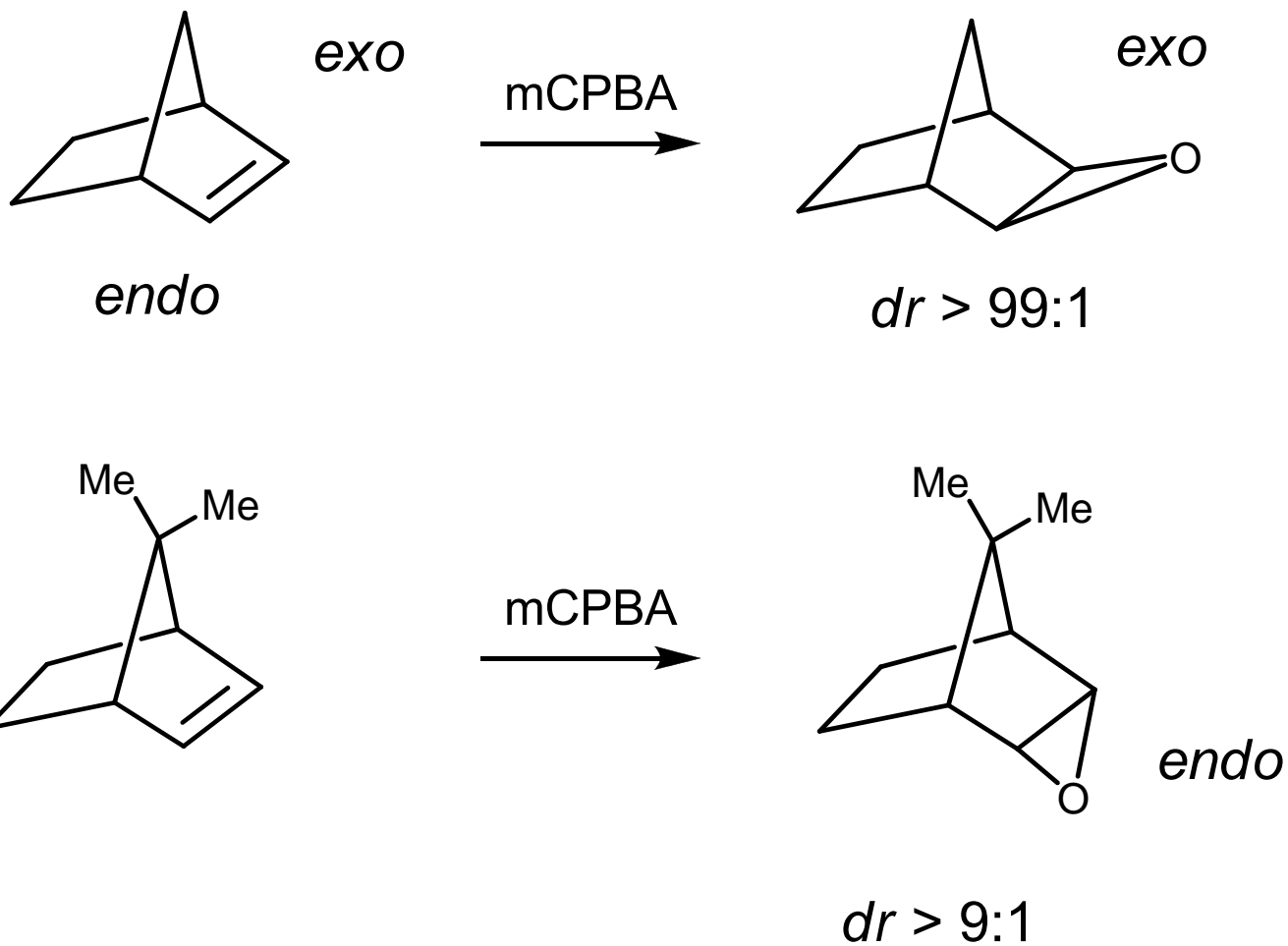


DMSO-Oxalyl Chloride Oxidation (Swern)

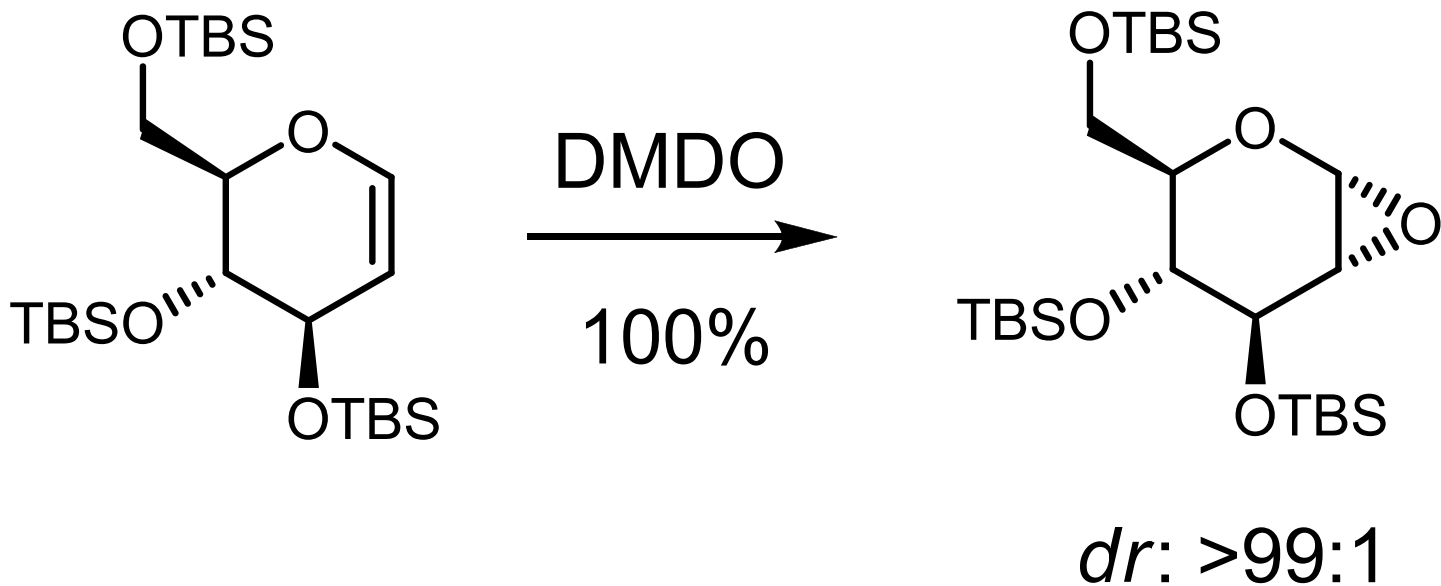


Oxidation of C=C Bond

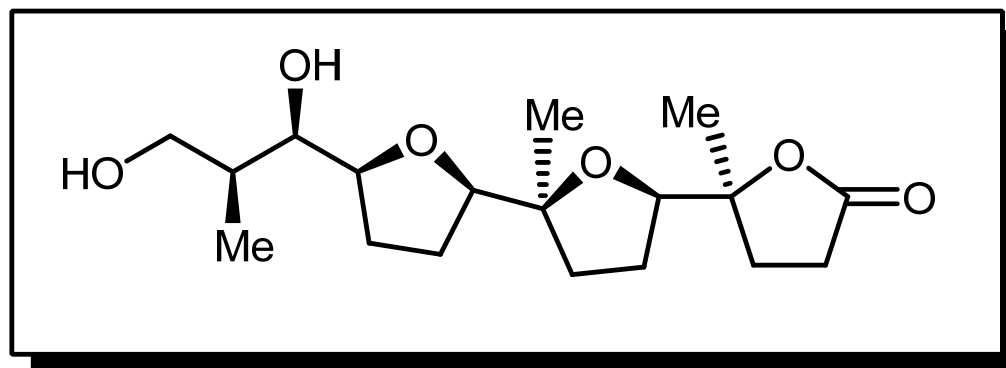
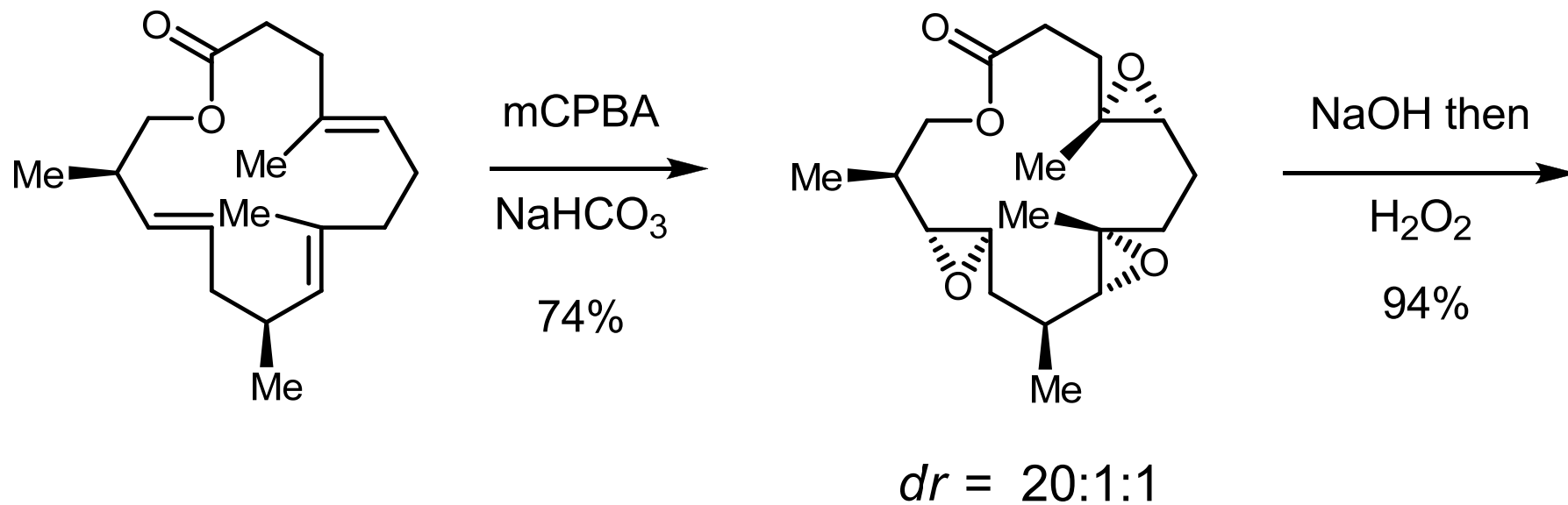




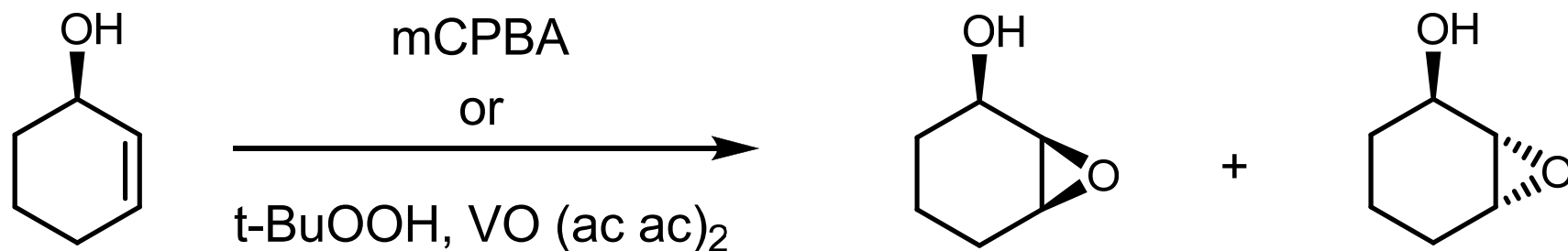
Murray Approach



Still Approach

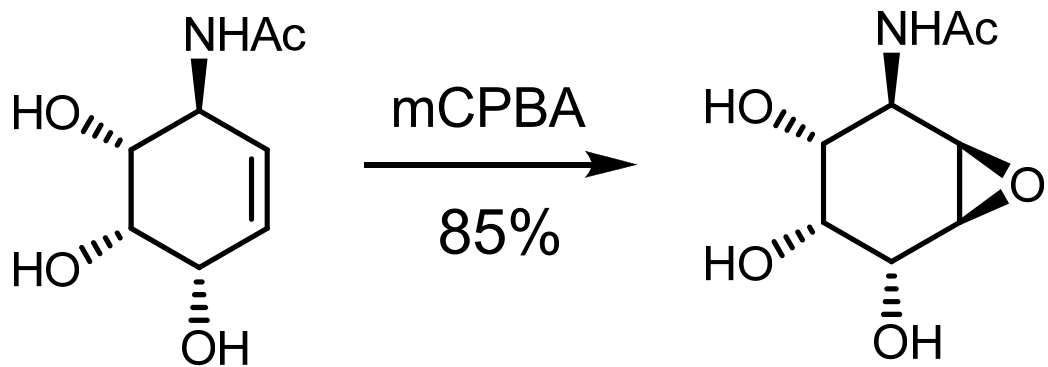
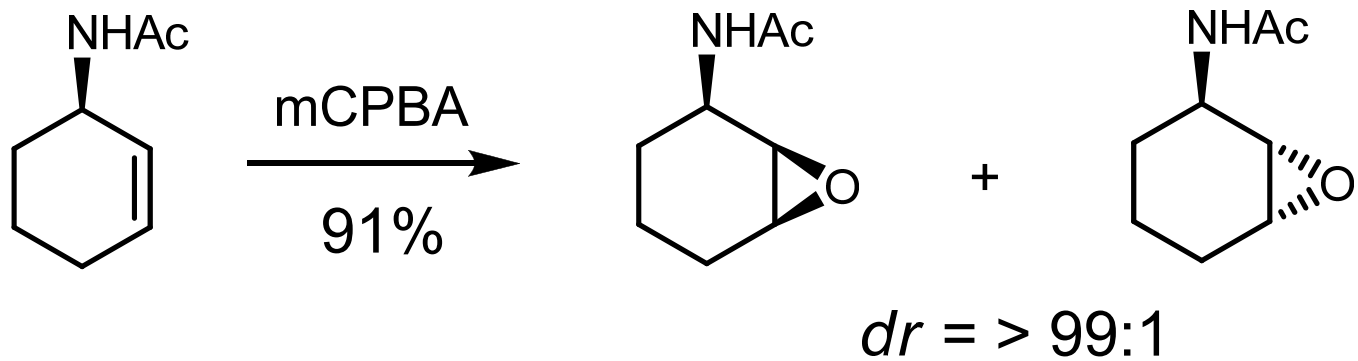


Directing Groups

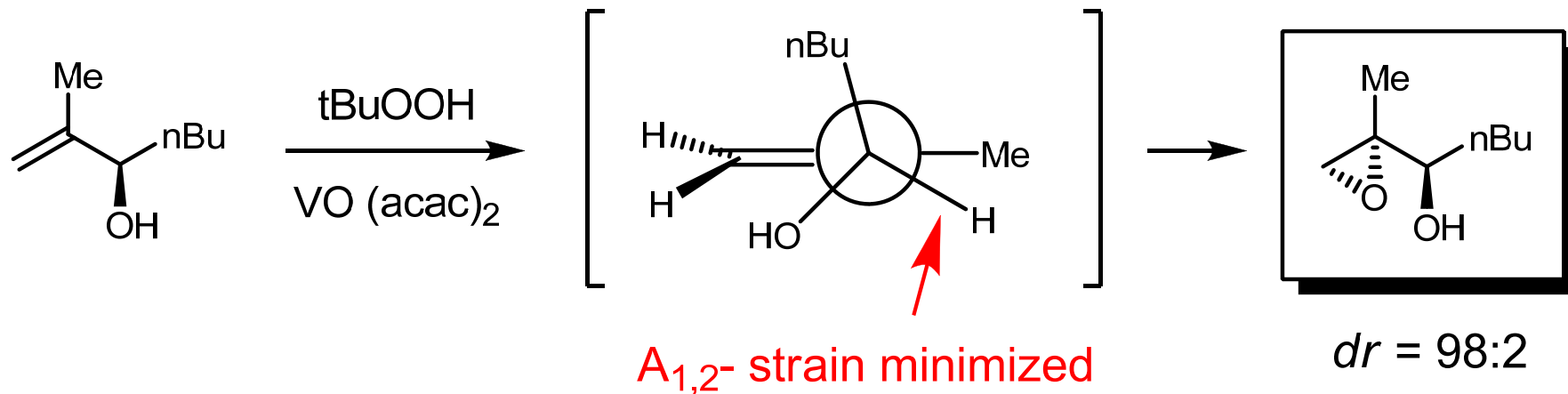


with t-BuOOH, VO (ac ac)₂ $dr = 98:2$

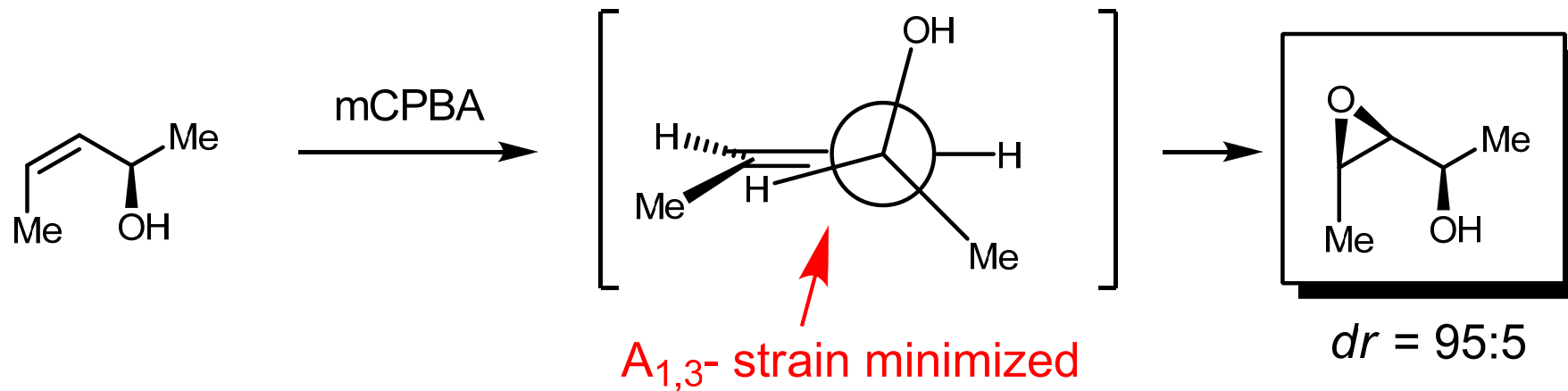
Directing Groups



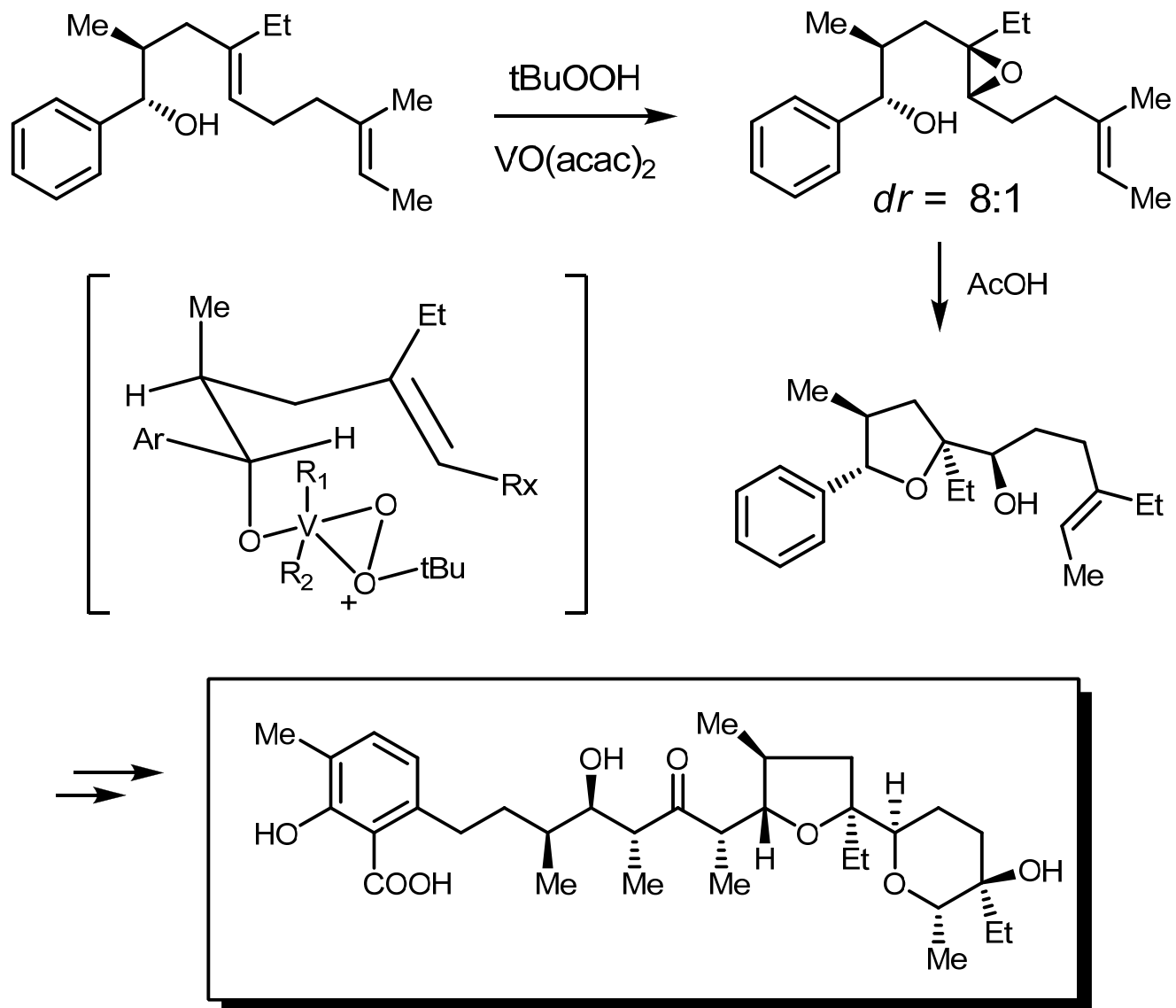
Directing Groups



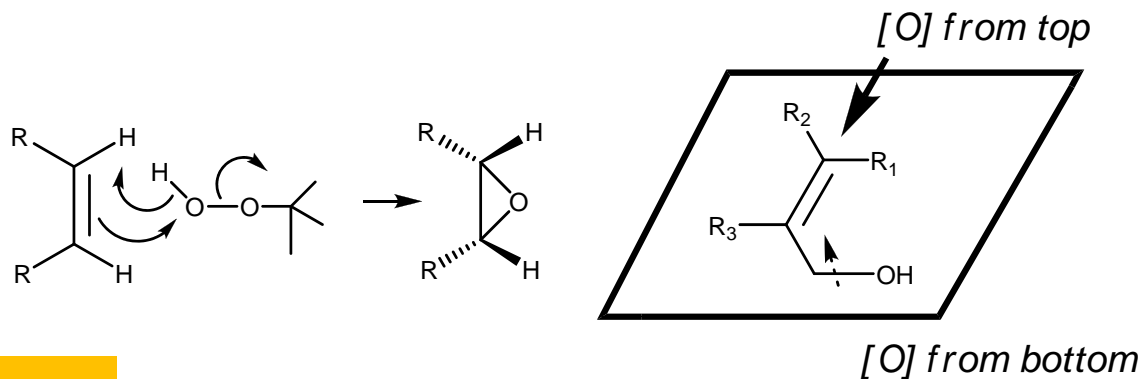
Directing Groups



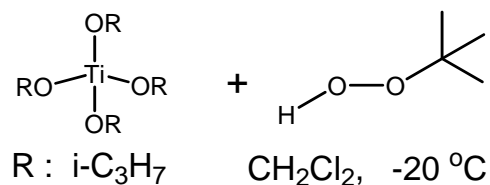
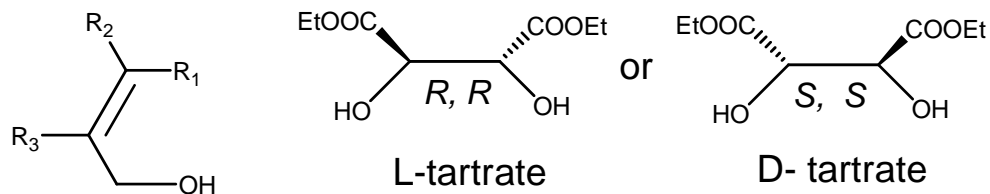
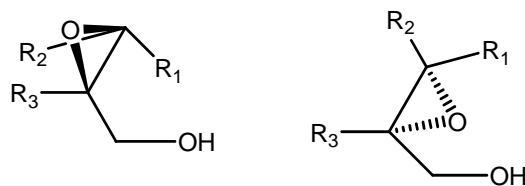
Application to Lasacolid Synthesis



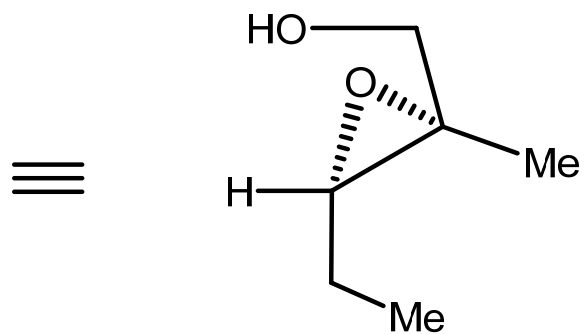
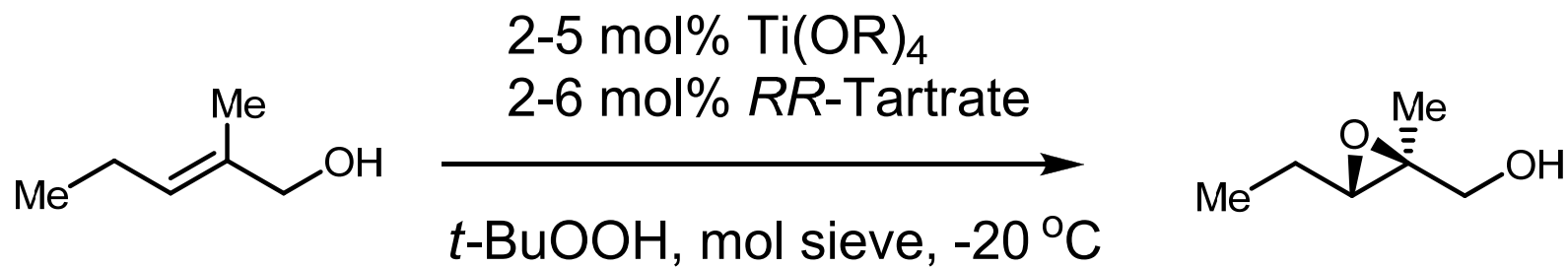
Enantioselective Sharpless Epoxidation



Use models here

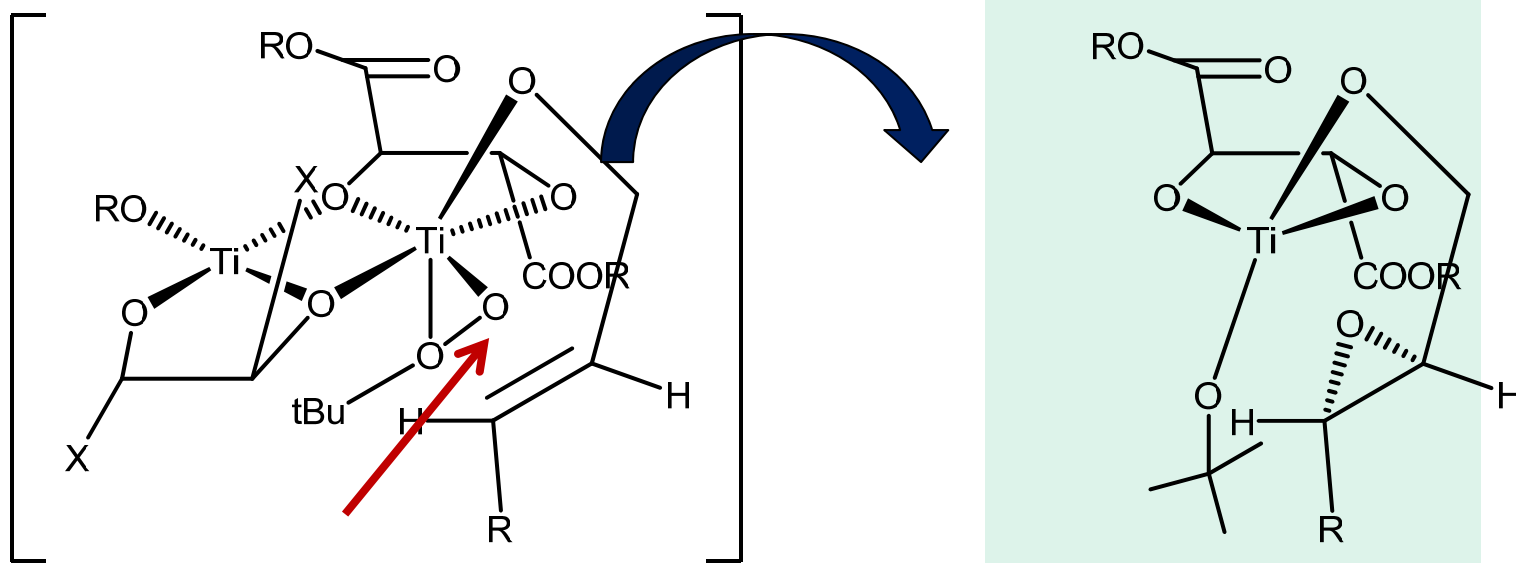
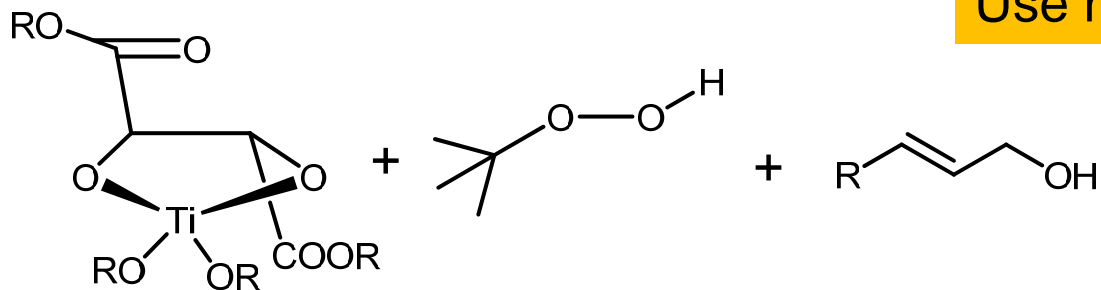


L-tartrate \longrightarrow attack from the bottom face
 D-tartrate \longrightarrow attack from the top face

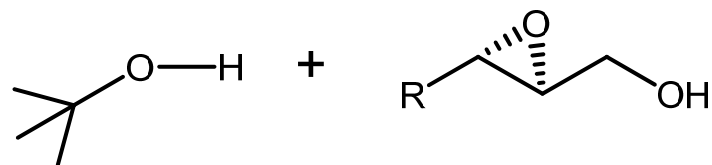


The Proposed Mechanism

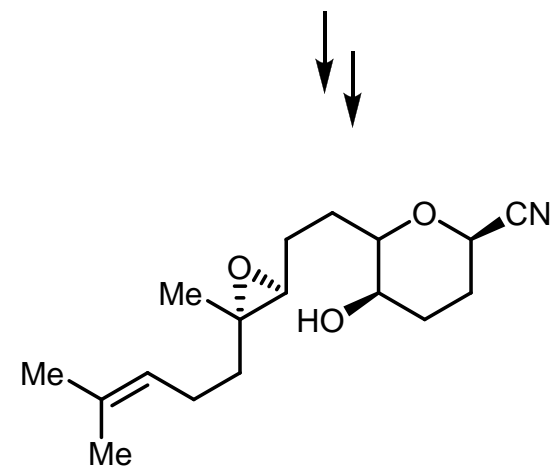
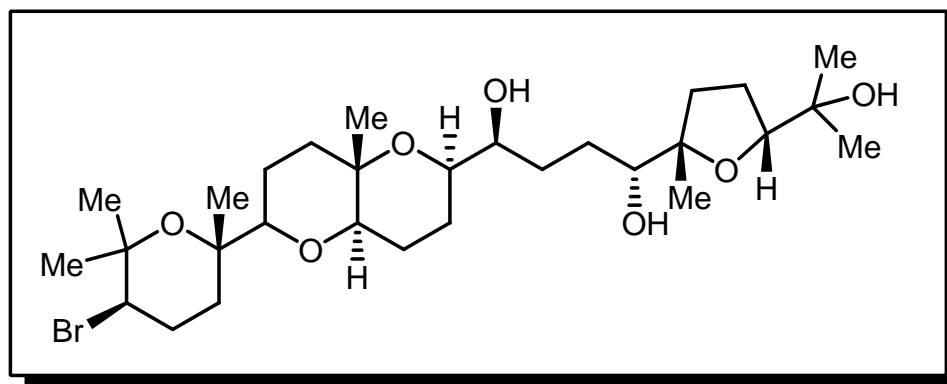
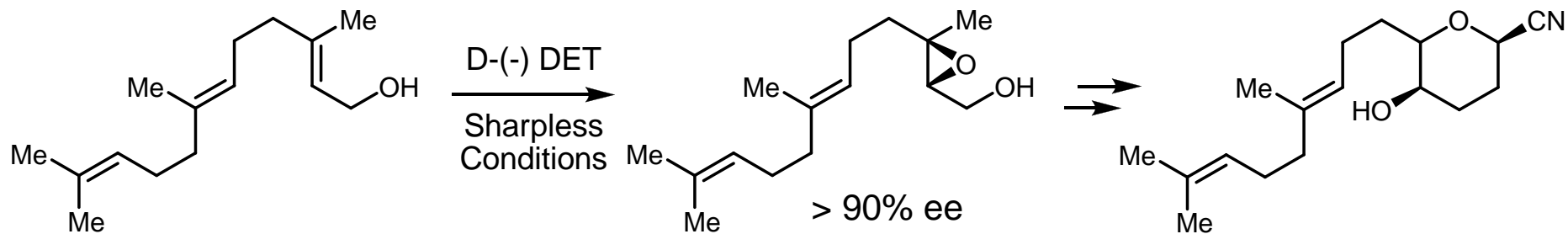
Use models here



Approach from behind

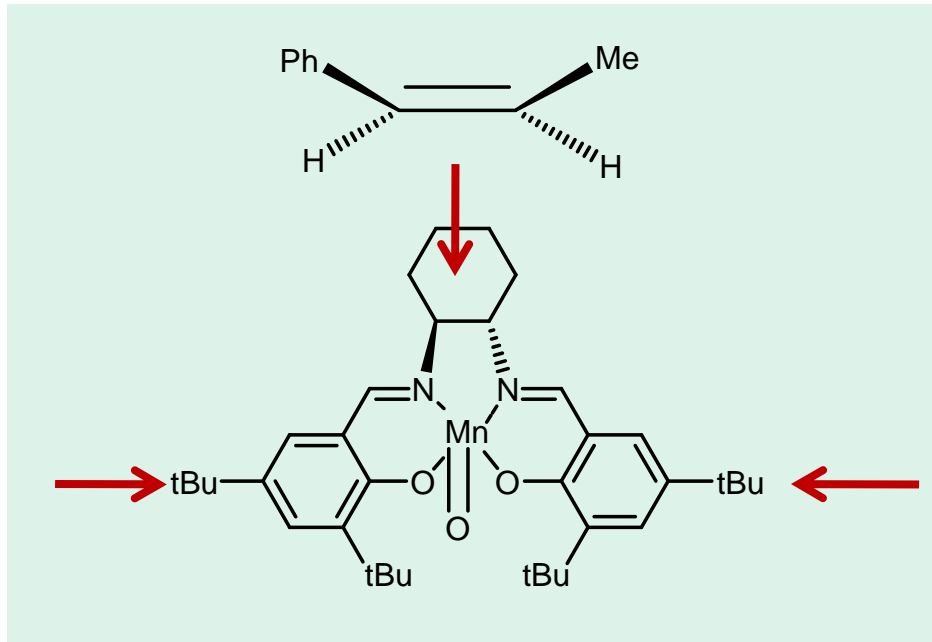
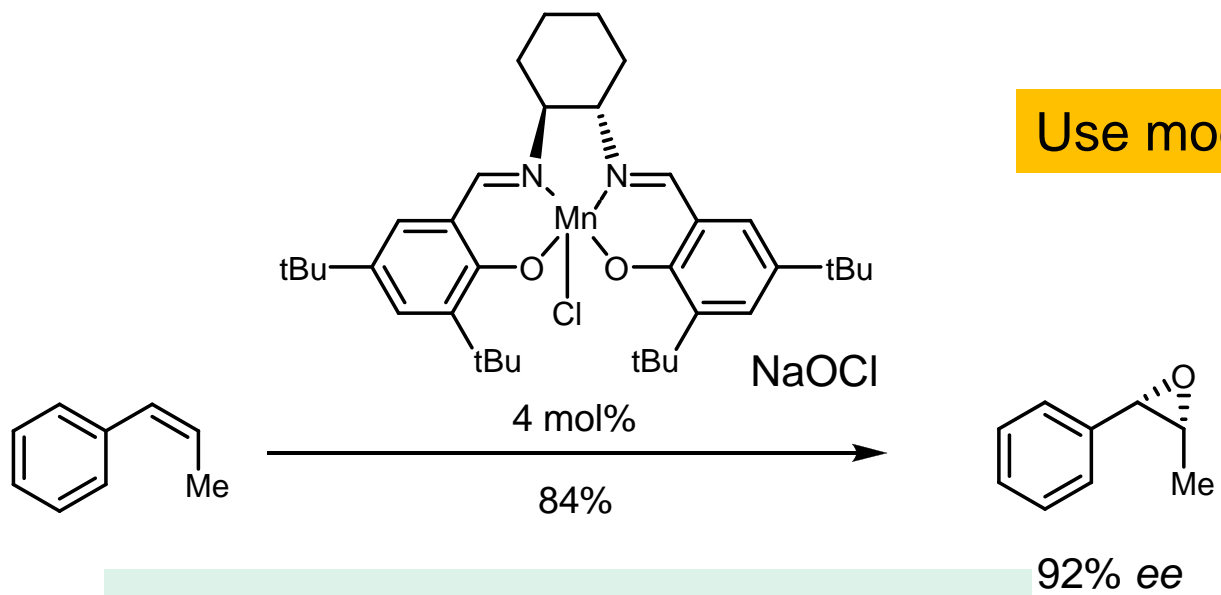


Application to Venustatriol Synthesis

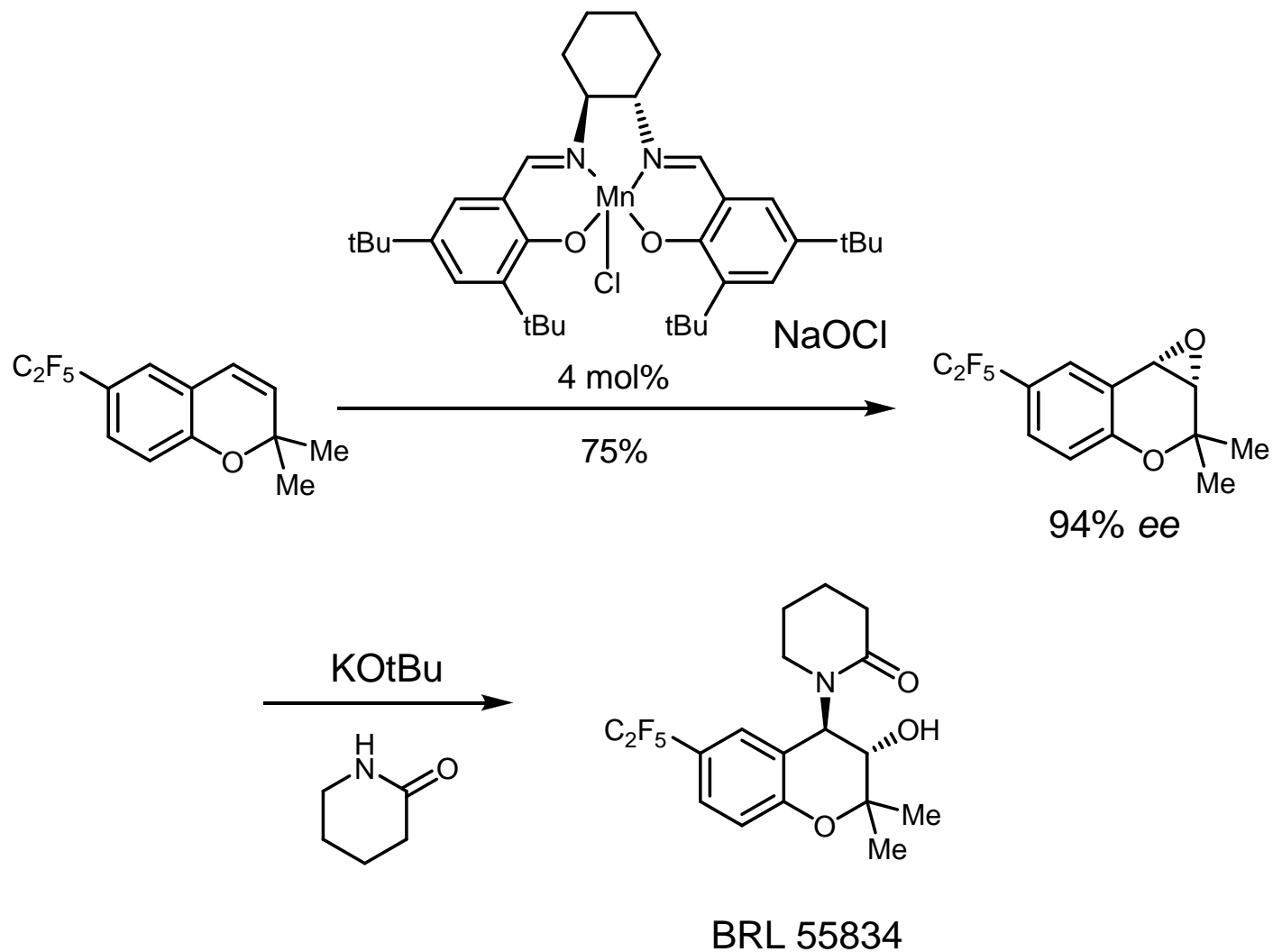


Jacobson Epoxidation

Use models here



Enantioselective Synthesis of BRL 55834



Enantioselective Synthesis of Indinavir

