Stereoselective Organic Synthesis

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

Prabhat Arya

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

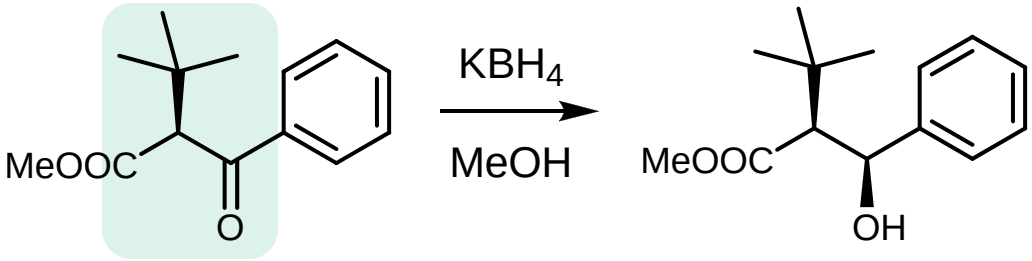
Day 4

Stereoselective Nucleophilic Addition to Carbonyl Group and Enantioselective Oxidation

Outline

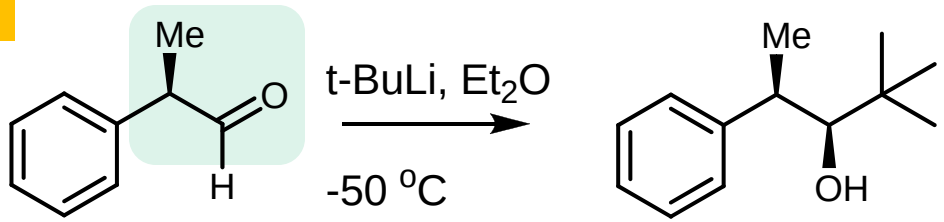
- Nucleophilic addition to carbonyl group
- Cram, Felkin-Anh, chelation and dipolar models
- 1,2 Asymmetric induction in carbonyl addition
- 1,3 Asymmetric induction in carbonyl addition
- enantieoselective carbonyl reduction (Masamune, Corey)
- Diastereoselective oxidation
- Enantioselective oxidation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

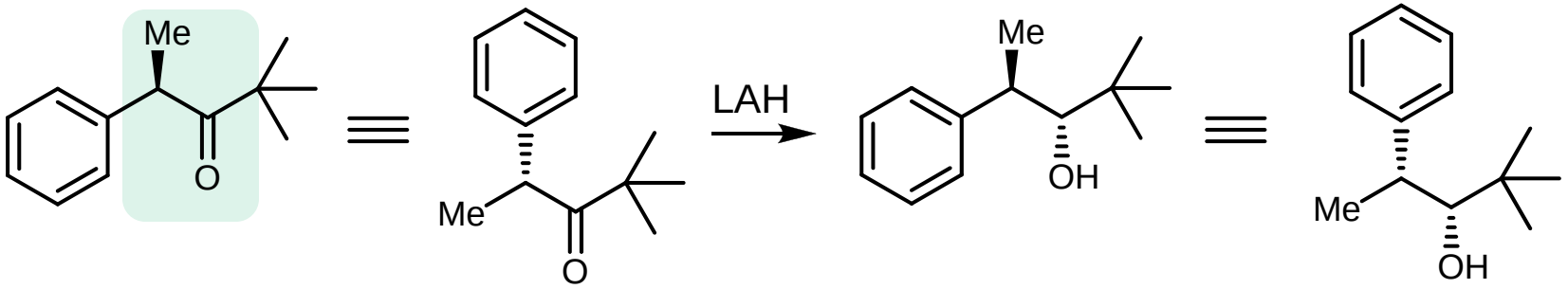
Examples of Stereoselective Nucleophilic Addition to Carbonyl Group



Use models here

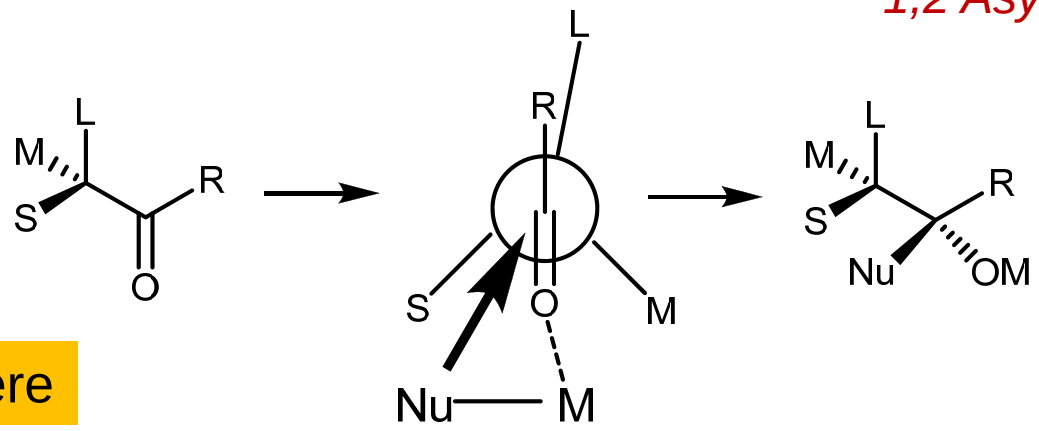
1,2 Asymmetric Induction





Cram's Rule

1,2 Asymmetric Induction



Use models here

Increase in stereoselectivity

large difference between S and M

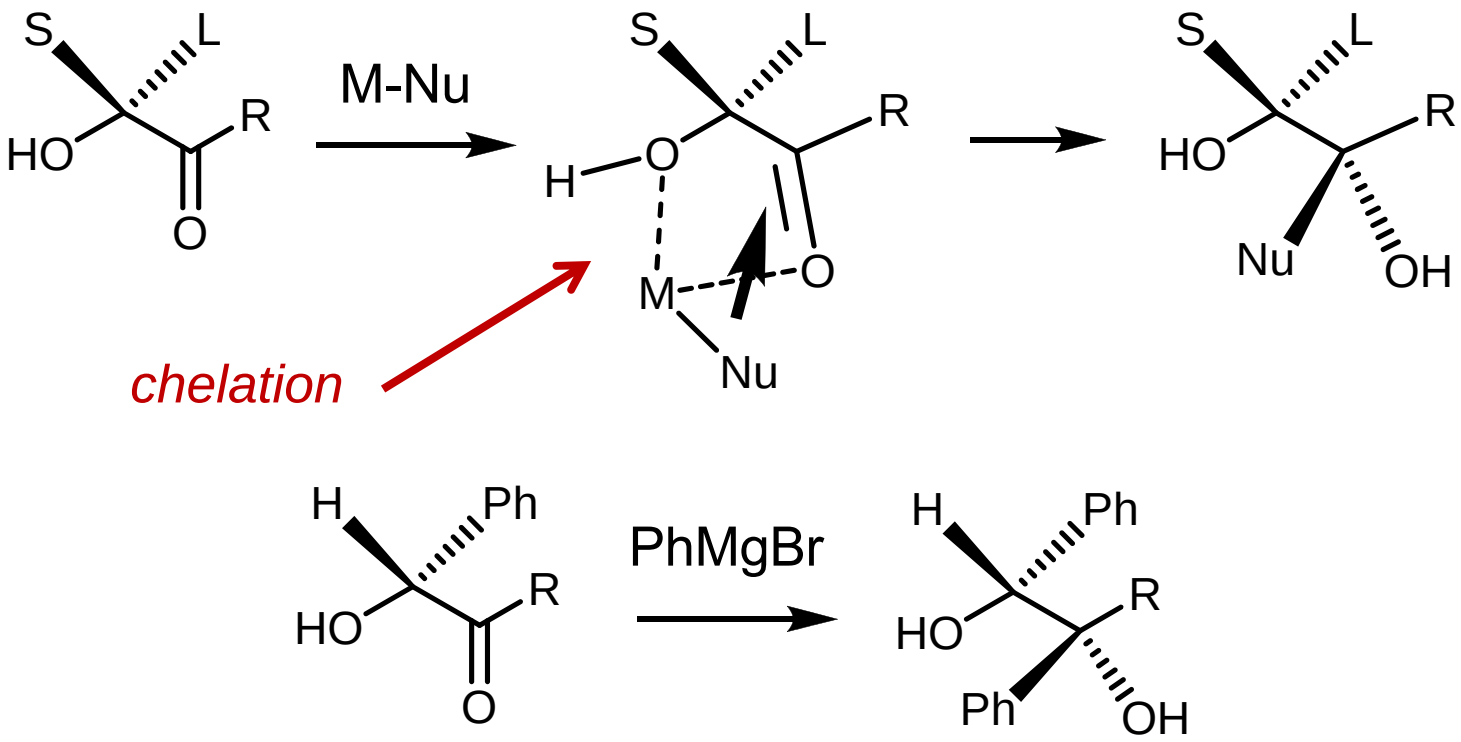
Decrease in stereoselectivity

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

Cram's Rule: *J Am Chem Soc* 5828 (1952)

The Cyclic Model for 1,2 Asymmetric Induction



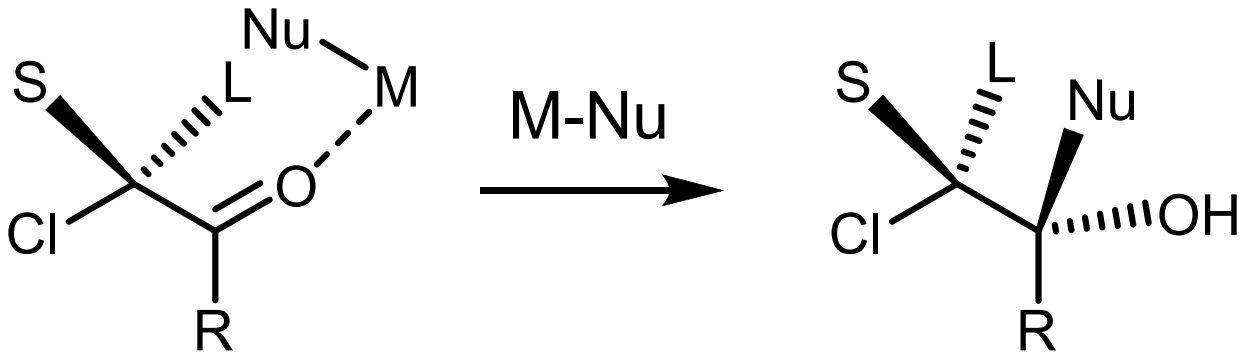
Use models here

1,2 Asymmetric Induction

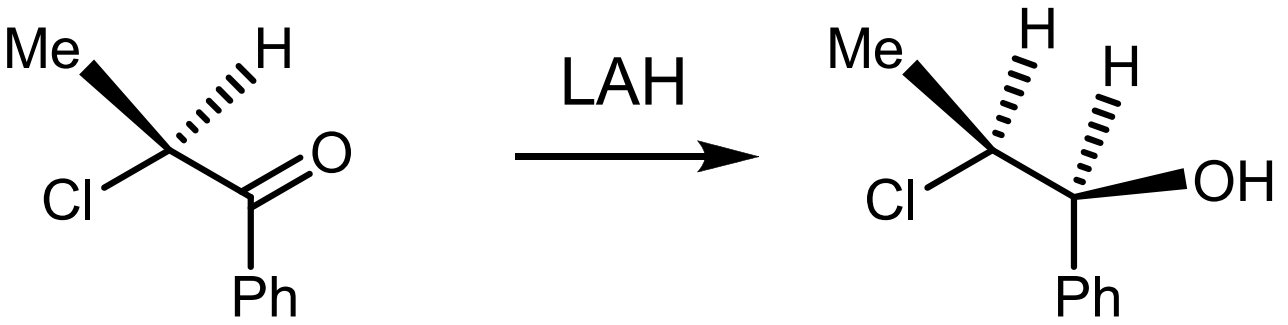
J Am Chem Soc, 2748 (1959)

The Dipolar Model (Cornforth's Model)

1,2 Asymmetric Induction

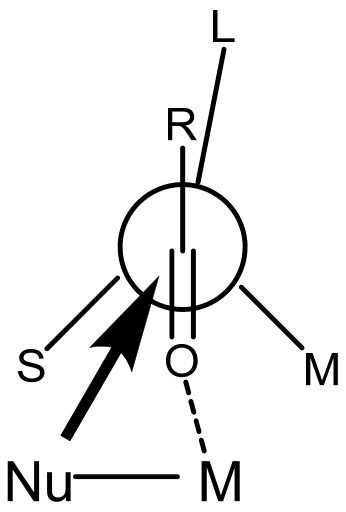


Use models here

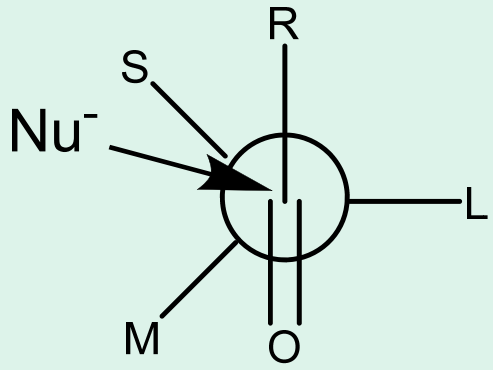


J Chem Soc, 112 (1959)

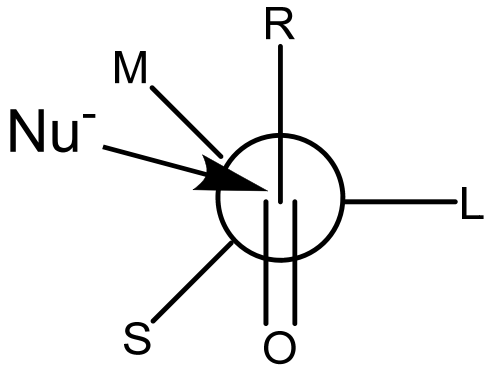
Cram Model



Felkin-Anh Model

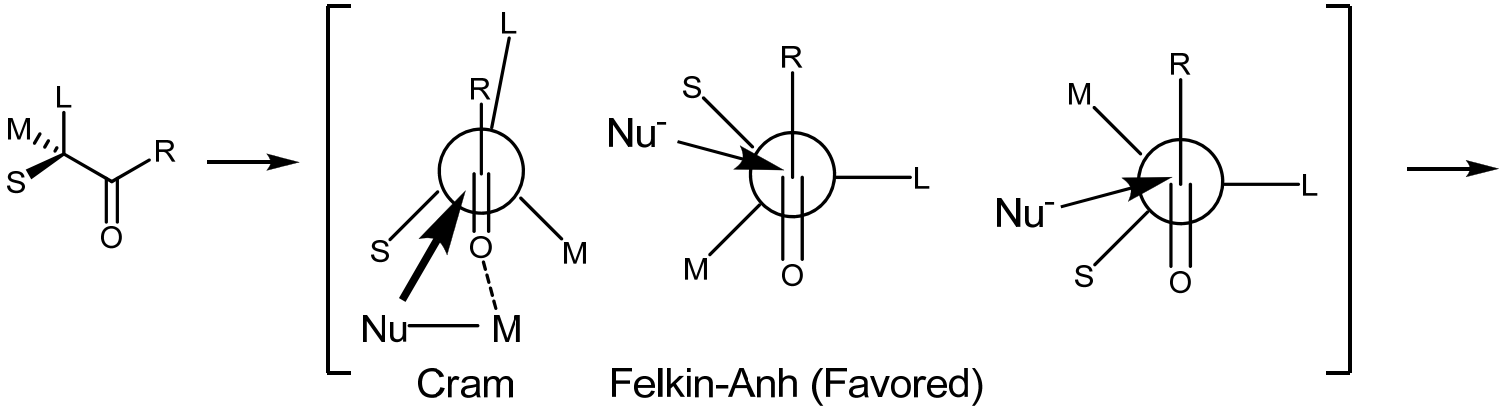


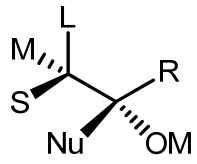
favored



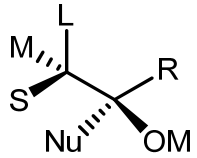
disfavored

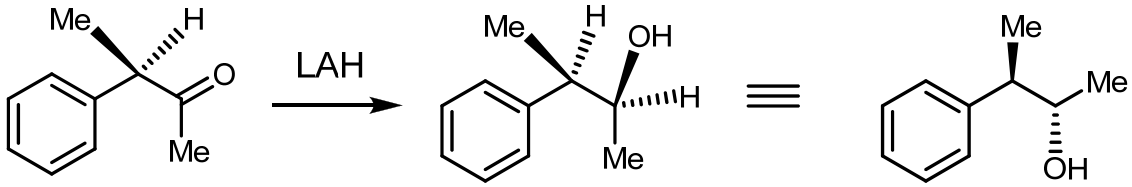
Use models here



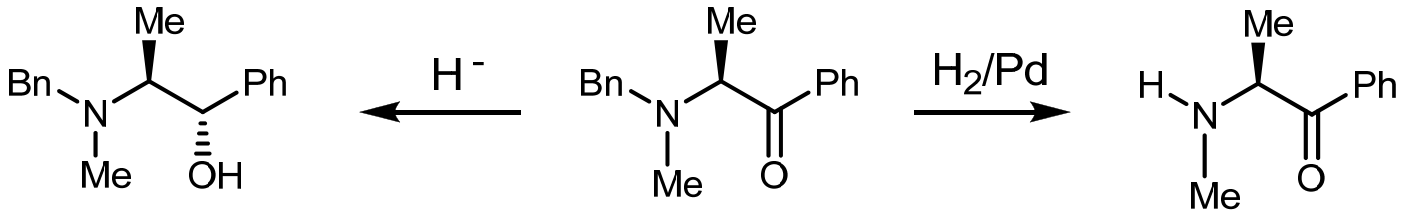


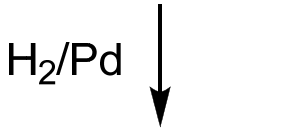
Cram/Felkin-Anh Product (Major) + anti Cram/anti Felkin-Anh Product (Minor)



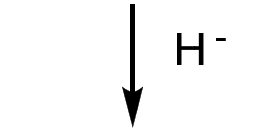


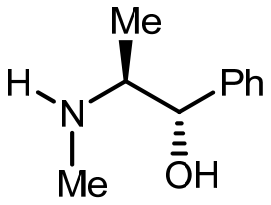
1,2 Asymmetric Induction

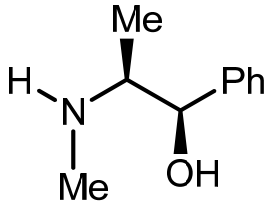




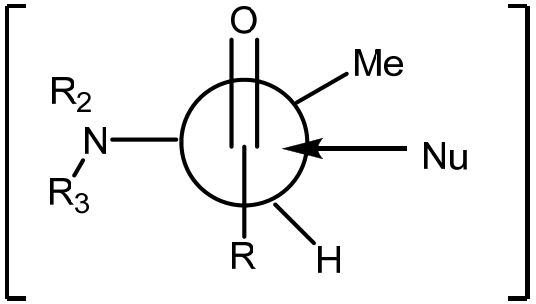
1,2 Asymmetric Induction

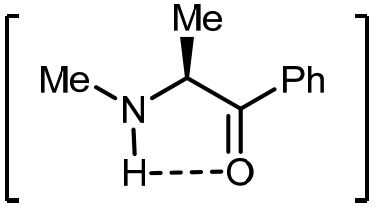






Felkin-Anh (favored)



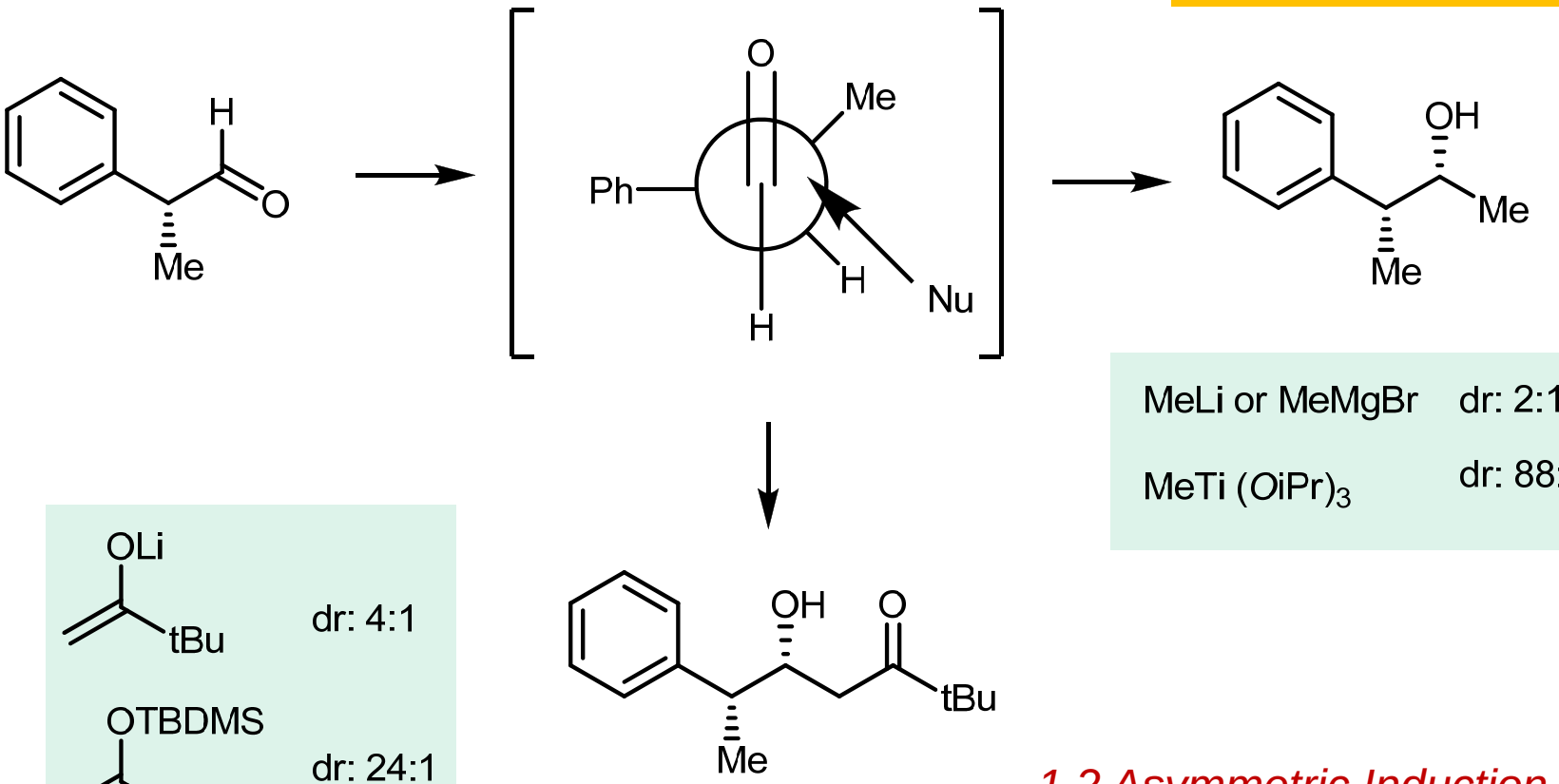


chelation

See: *Tetrahedron Letts* 2205 (1968);
J Am Chem Soc, 1124 (1969) and *Topics in Curr Chem*, 146 (1980)

Use models here

Felkin Anh Products



MeLi or MeMgBr	dr: 2:1
MeTi (OiPr)$_3$	dr: 88:12

dr: 4:1

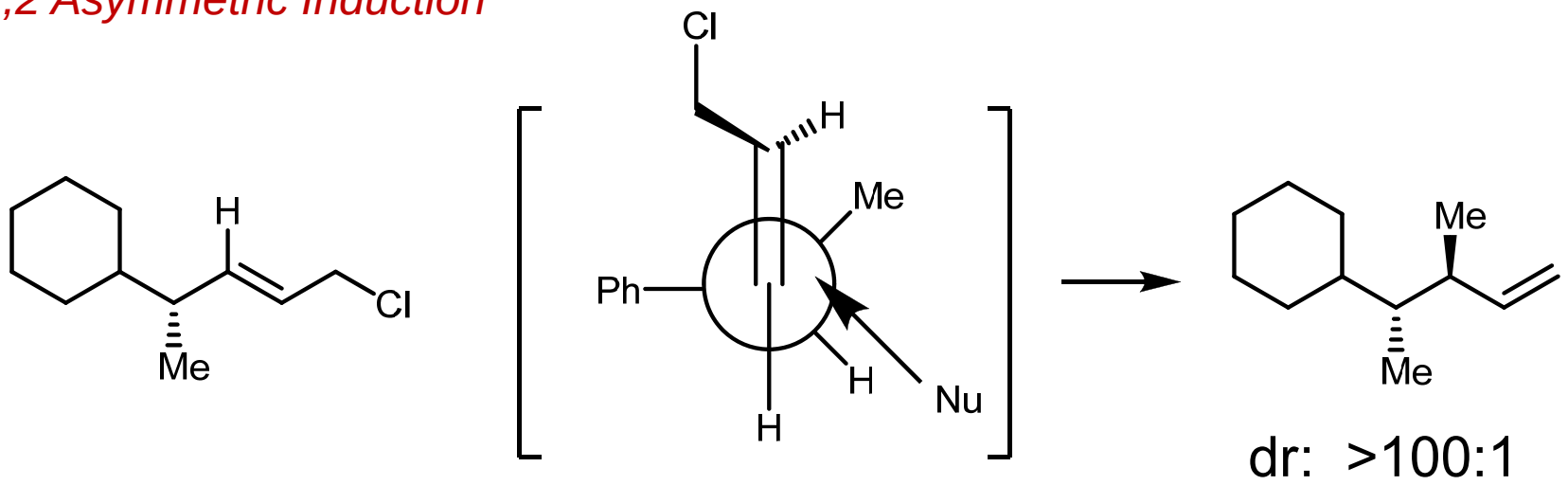
dr: 24:1

1,2 Asymmetric Induction

Taken from Book: *Classics in Stereoselective Synthesis*, Chapter 2

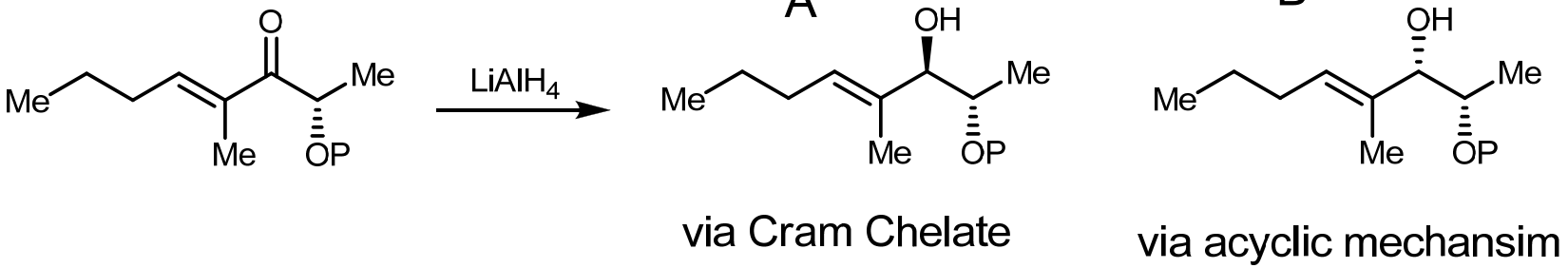
Felkin Anh Like

1,2 Asymmetric Induction



Use models here

Taken from Book: *Classics in Stereoselective Synthesis*, Chapter 2

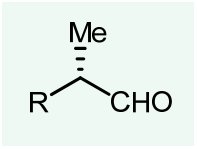


P	solvent	dr ratio A:B
Bn	Et_2O	98:2
TBDPS	THF	5:95
MOM	THF	70:30
MOM	Et_2O	98:2

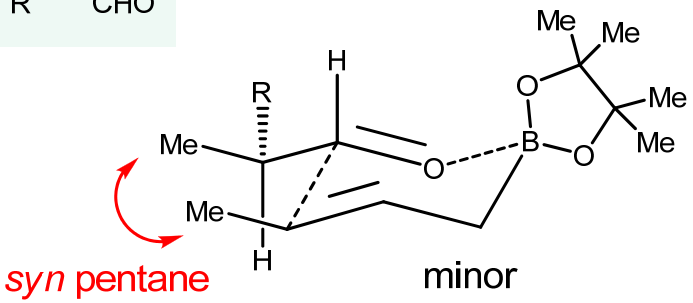
Taken from Book: *Classics in Stereoselective Synthesis*, Chapter 2

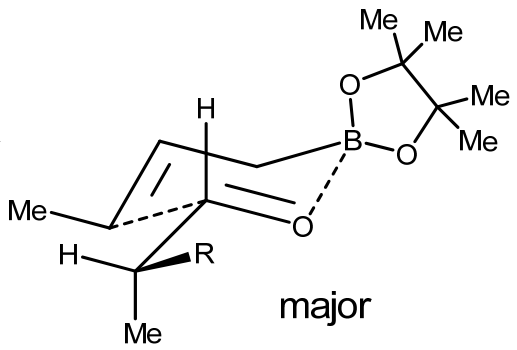
1,2 Asymmetric Induction: Diastereoselective Allylation with Chiral Boron Reagents

Use models here

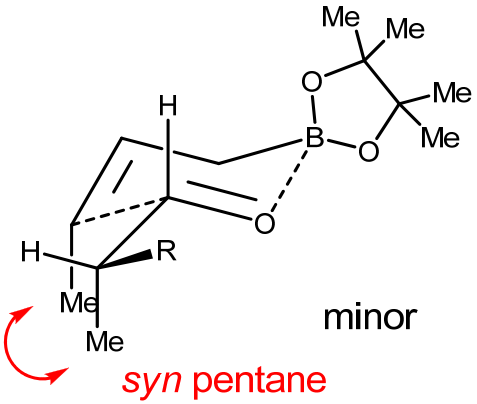


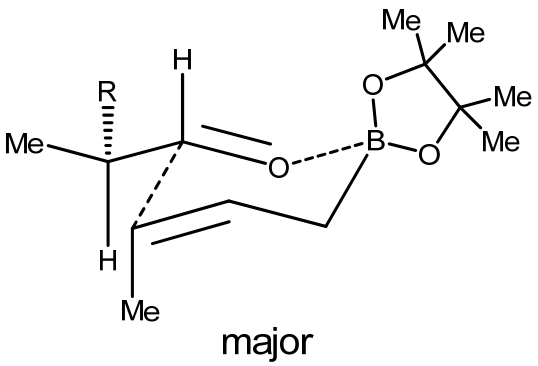
E-crotyl





Z-crotyl

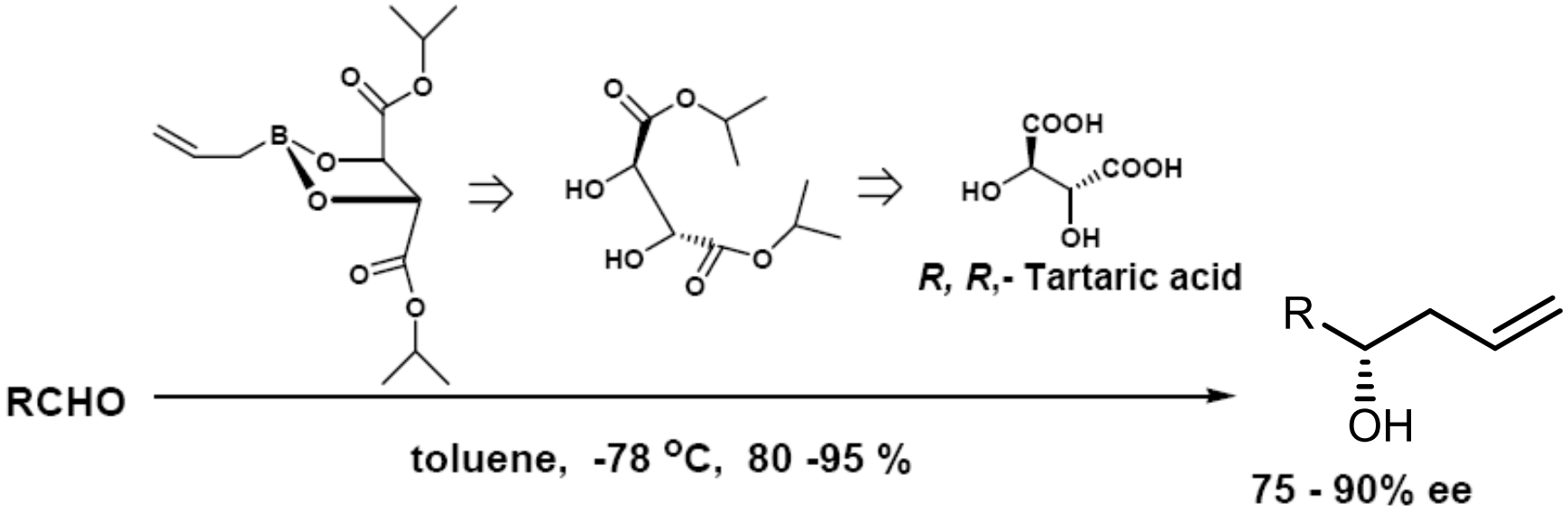




Taken from Book: *Classics in Stereoselective Synthesis*, Chapter 5

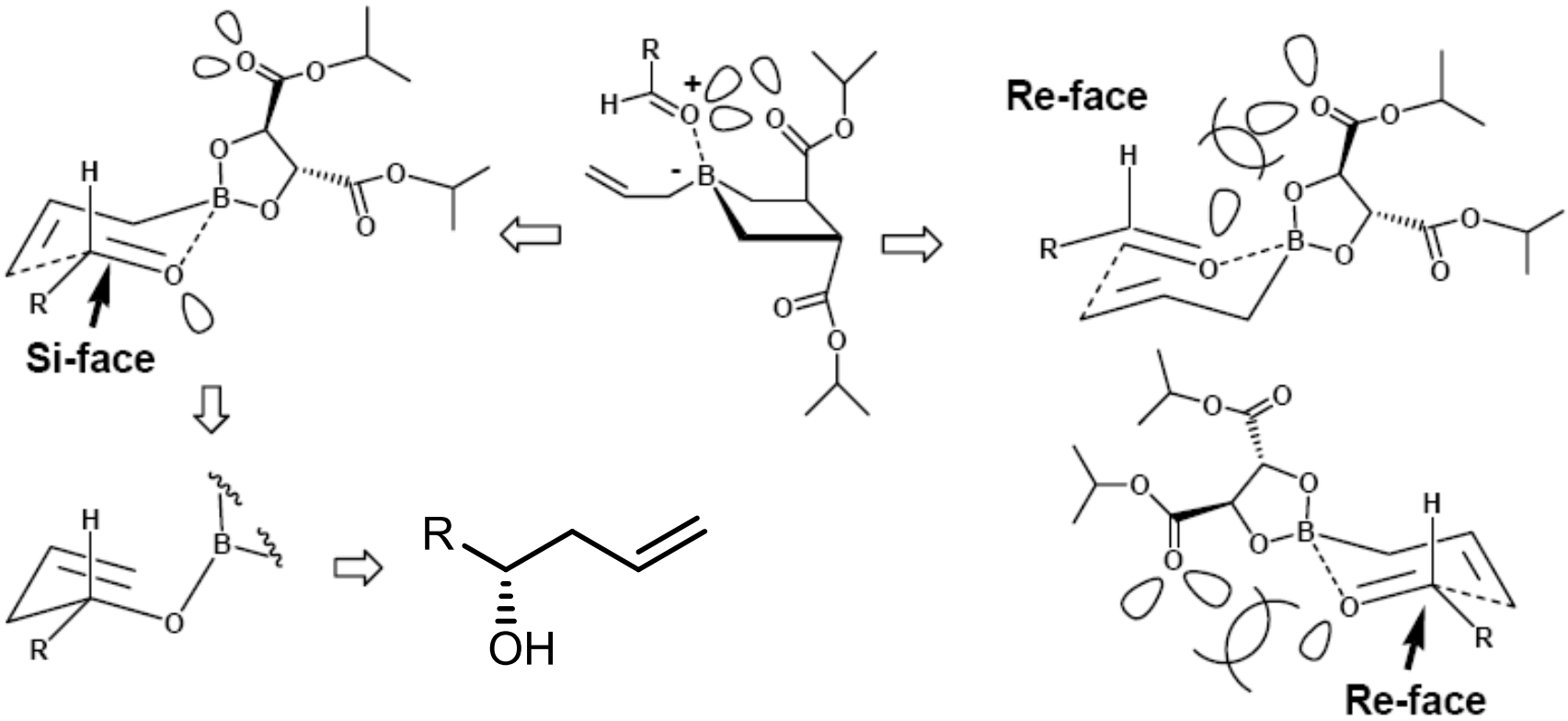
1,2 Asymmetric Induction: Diastereoselective Allylation with Chiral Boron Reagents

Enantioselective Organoborane Approach to Carbon-Carbon Bond Formation



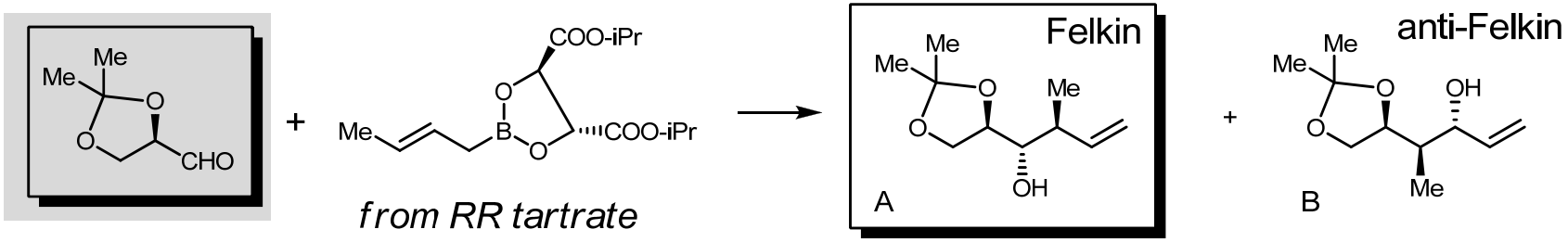
Roush et al, *J Am Chem Soc* 8186 (1985)

Stereoelectronic Effect



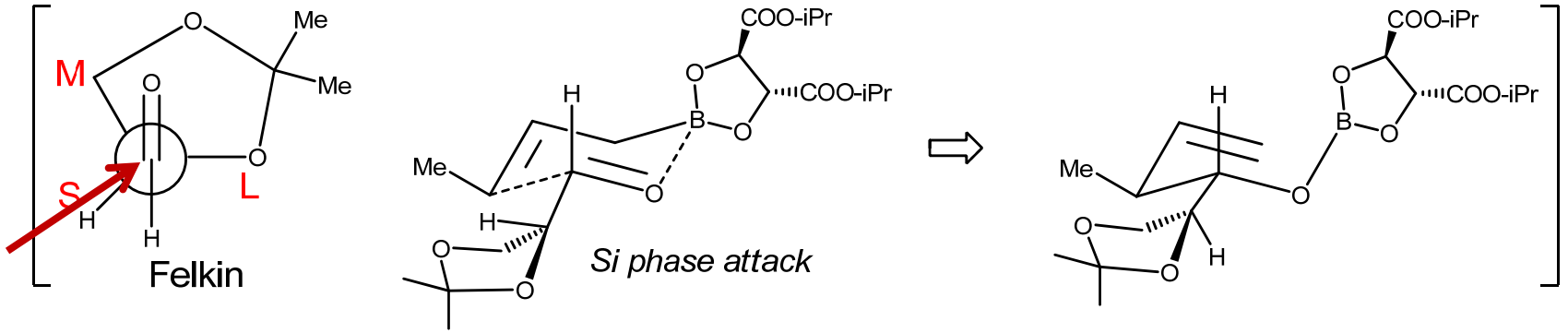
Use models here

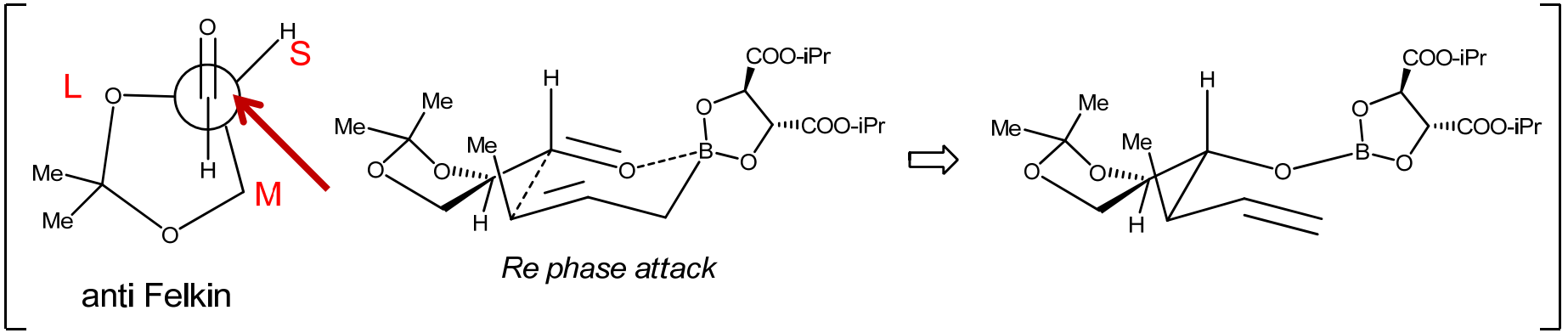
Roush et al, *J Am Chem Soc* 8186 (1985)



Use models here

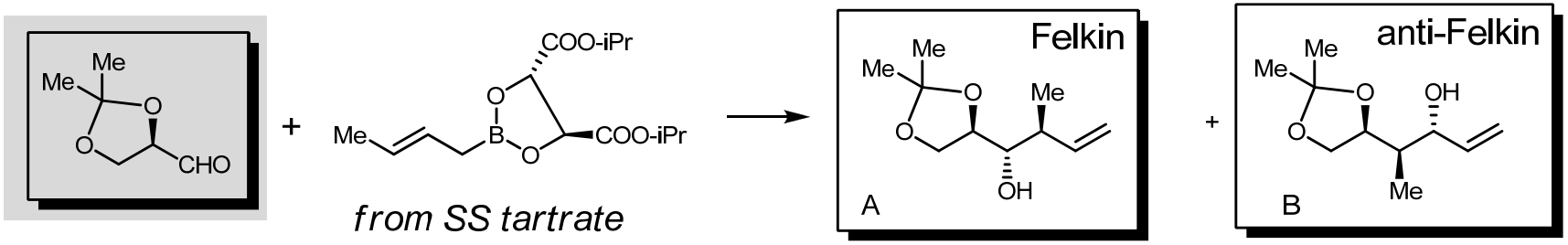
matched case (with RR tartrate), dr (A+B) = 91 : 9



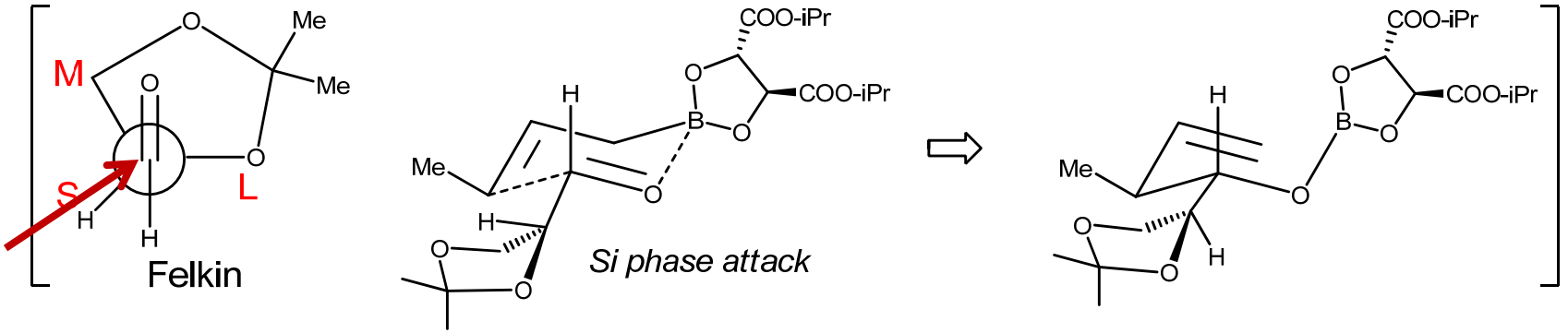


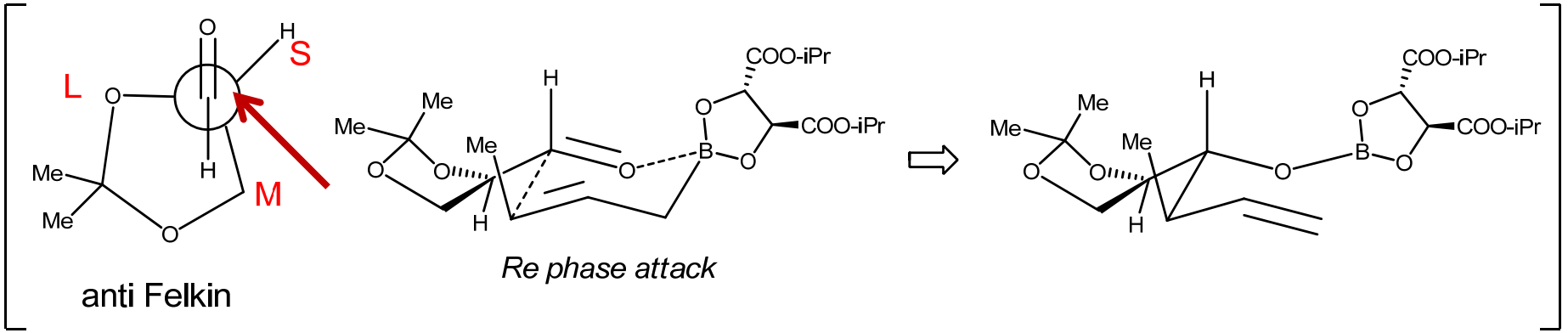
Taken from Book: *Classics in Stereoselective Synthesis*, Chapter 5

Use models here

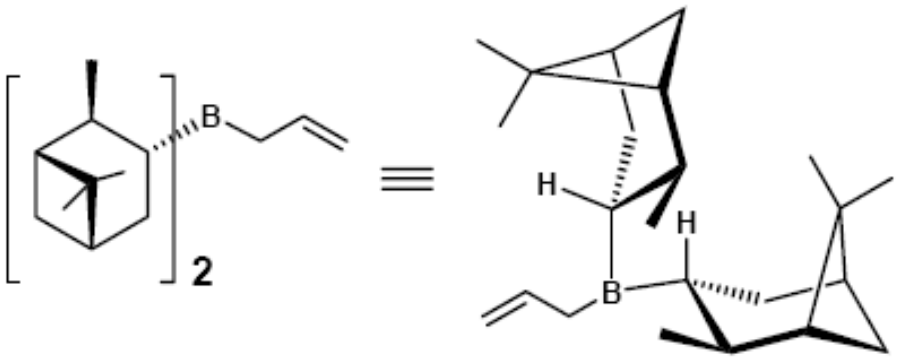


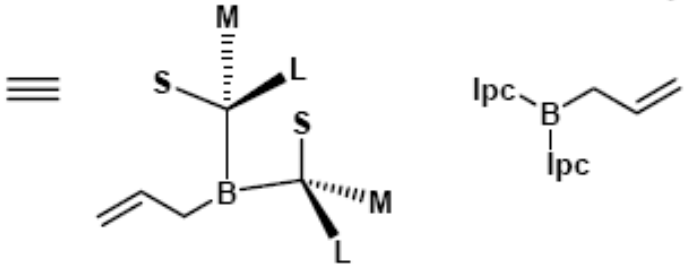
mismatched case (with SS tartrate), dr (A+B) = 2 : 98

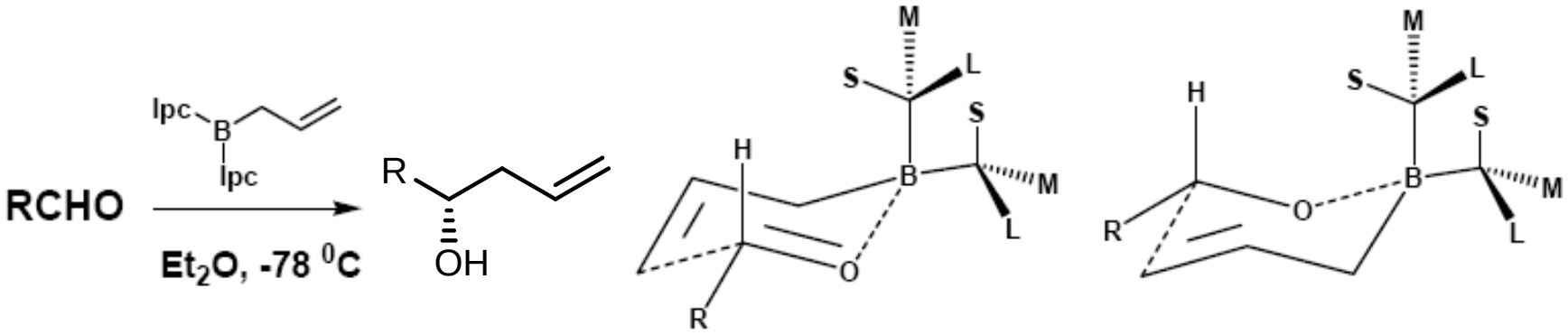




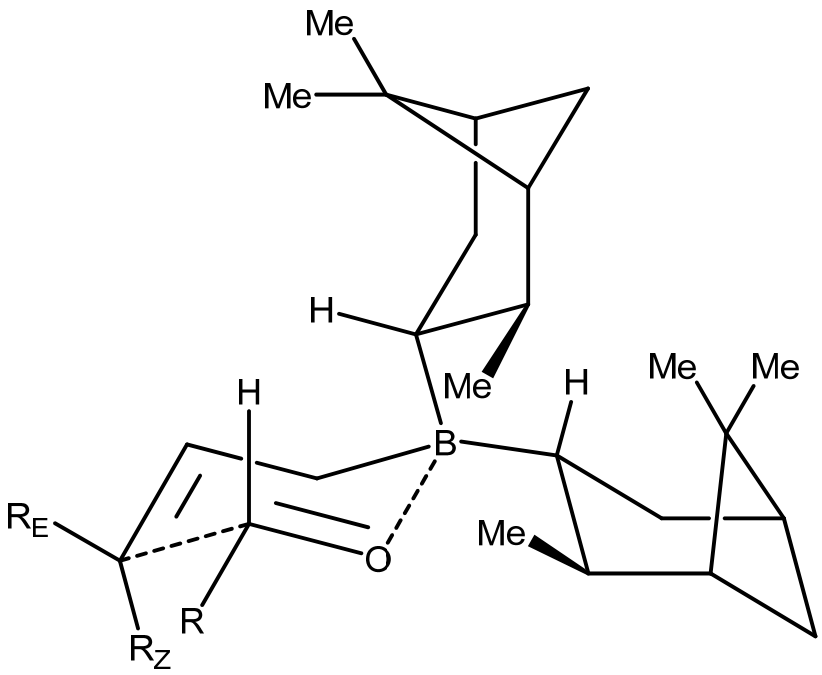
Taken from Book: *Classics in Stereoselective Synthesis*, Chapter 5


B
2
H
H
B

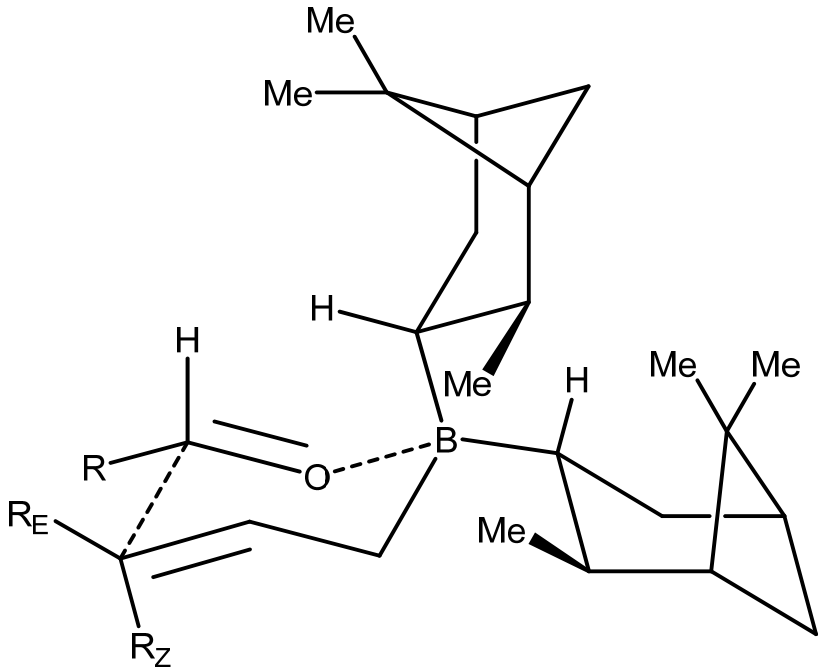

M
S
L
S
B
M
L
Ipc
B
Ipc


RCHO
Ipc
B
Ipc
Et2O, -78 0C
R
OH
M
S
L
H
S
B
M
L
O
R
M
S
L
H
S
B
M
L
R
O

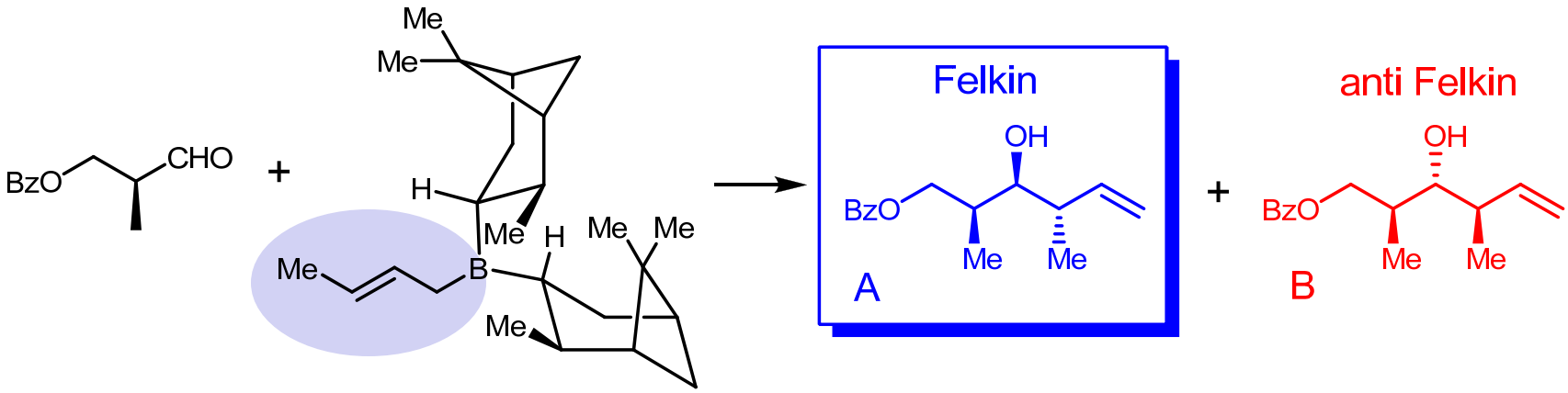
Favored Transition State



Disfavored Transition State



Derived from (+) pinene



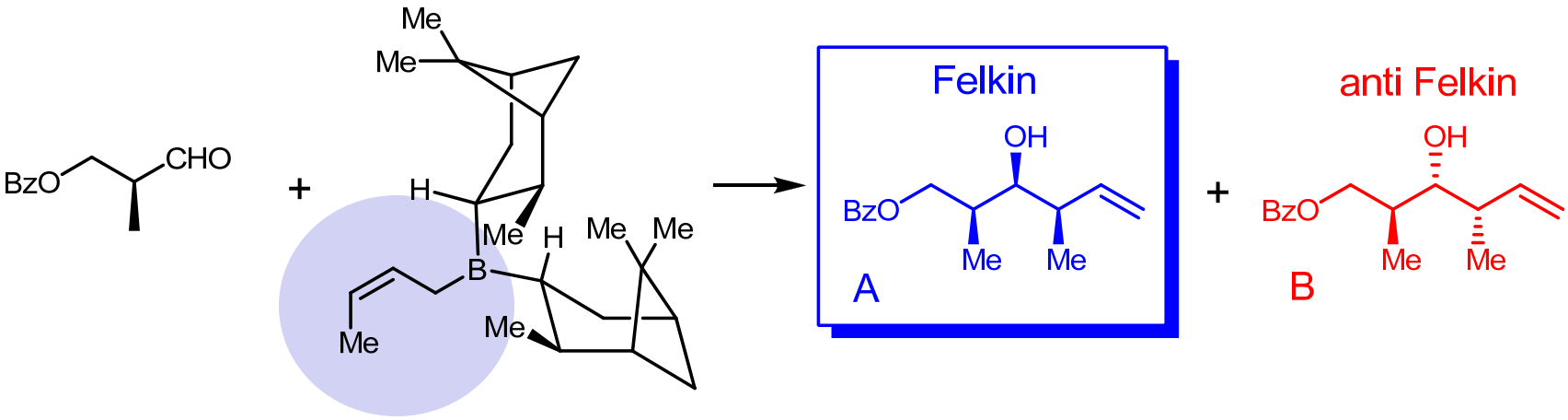
Use models here

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

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

Taken from Book: *Classics in Stereoselective Synthesis*, Chapter 5

Derived from (+) pinene



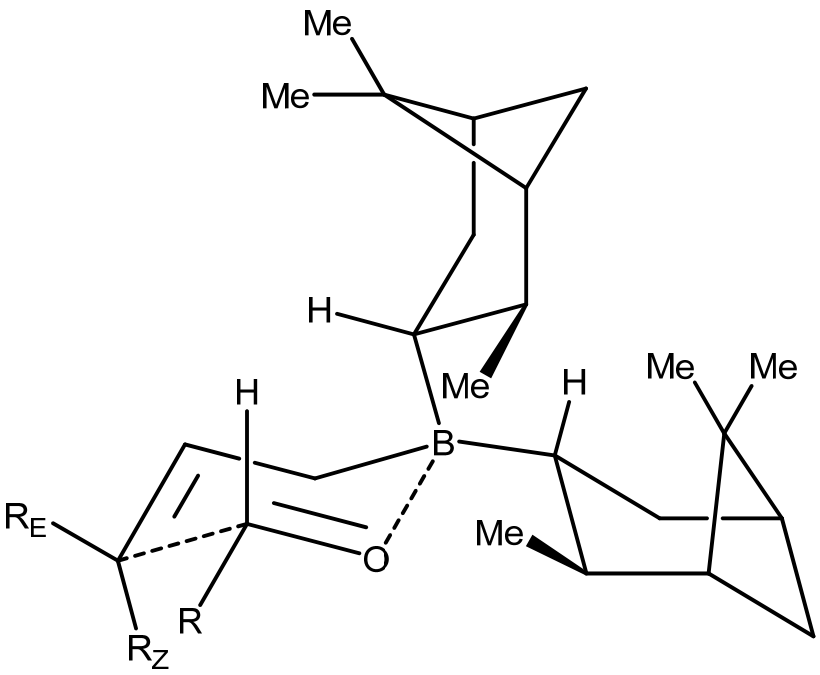
Use models here

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

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

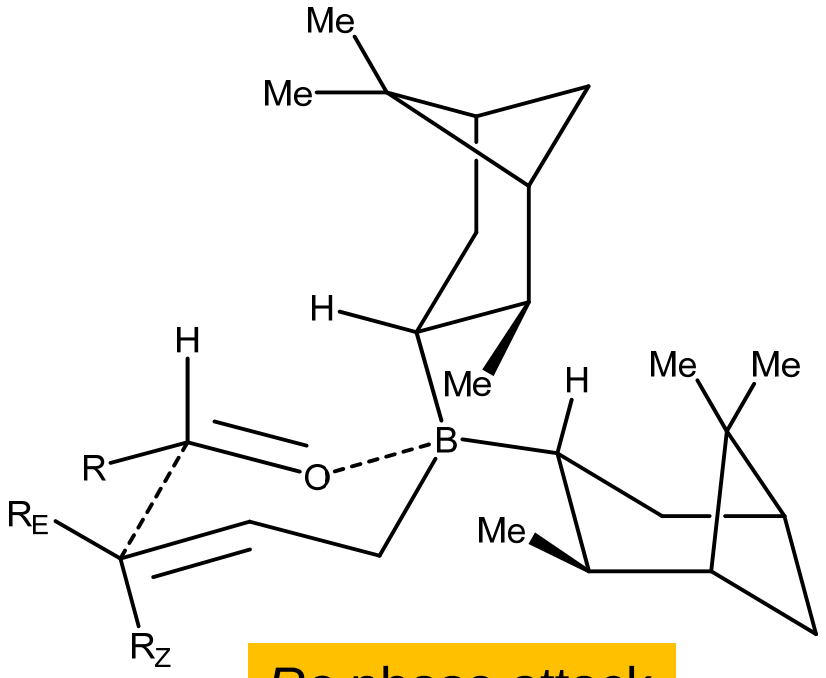
Taken from Book: *Classics in Stereoselective Synthesis*, Chapter 5

Favored Transition State



Si phase attack

Disfavored Transition State

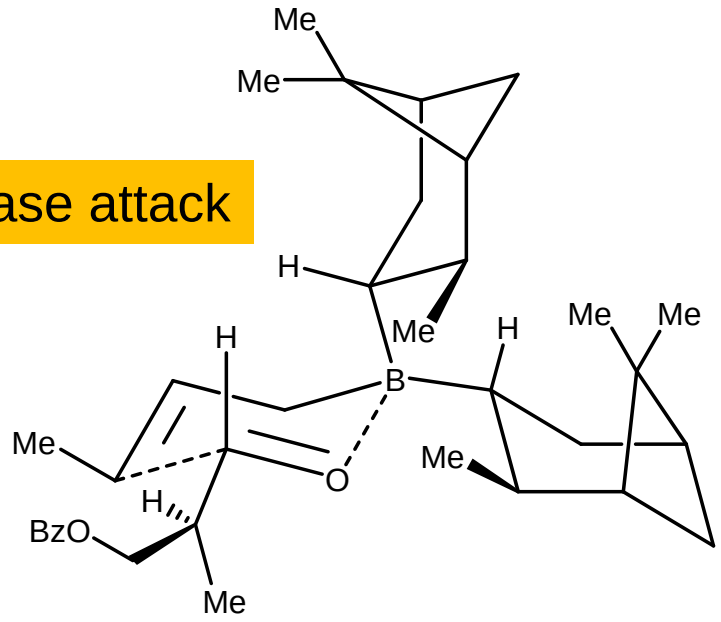


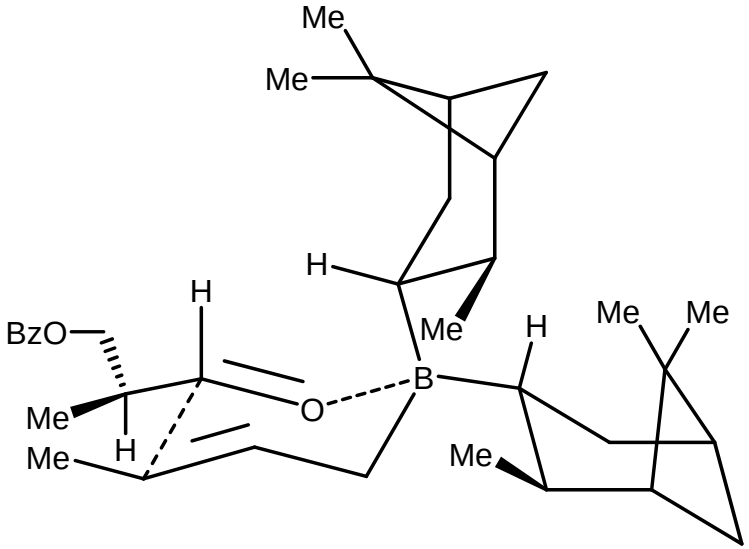
Re phase attack

Favored Transition State

Disfavored Transition State

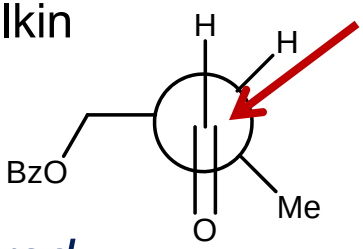
Si phase attack



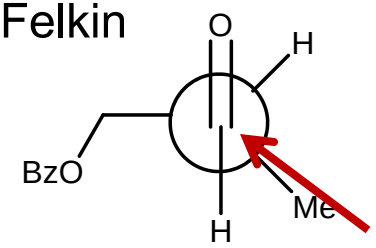


Re phase attack

Felkin

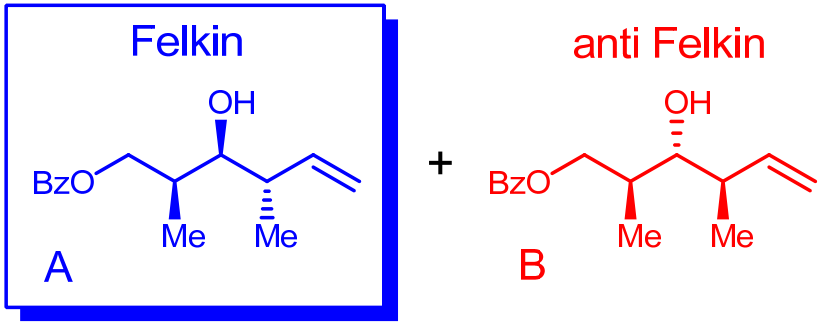


anti Felkin



favored

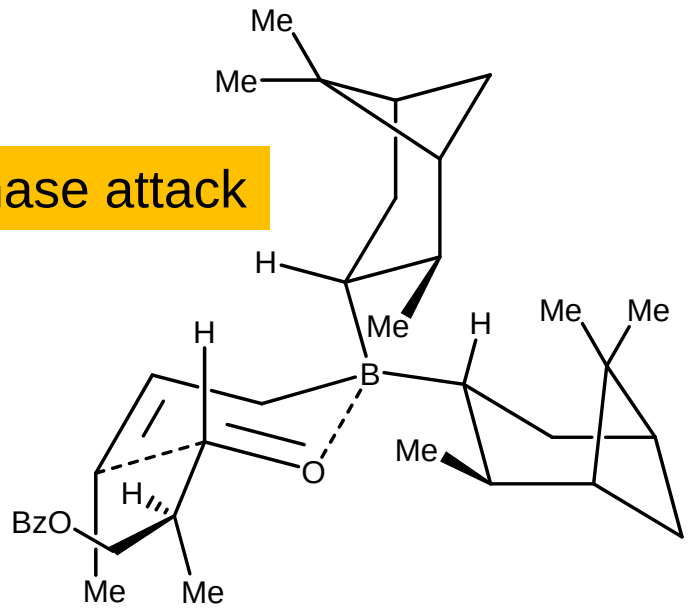
Use models here

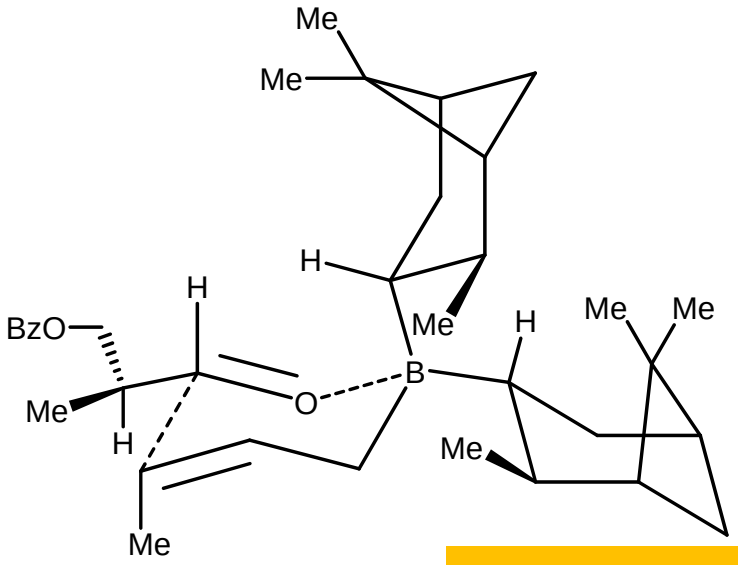


Disfavored Transition State

Favored Transition State

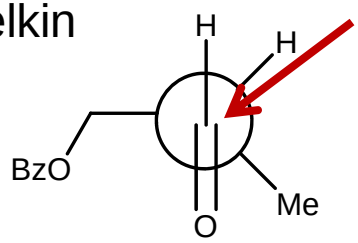
Si phase attack



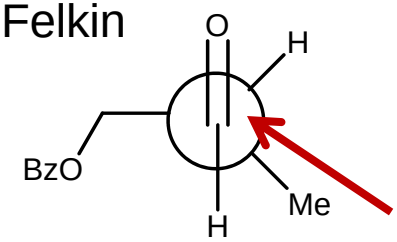


Re phase attack

Felkin

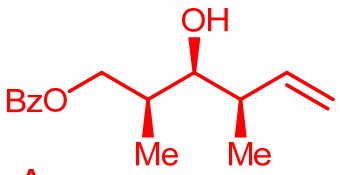


anti Felkin



Use models here

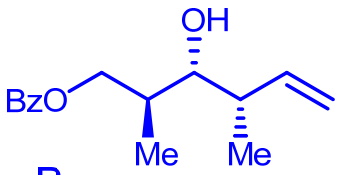
Felkin



A

+

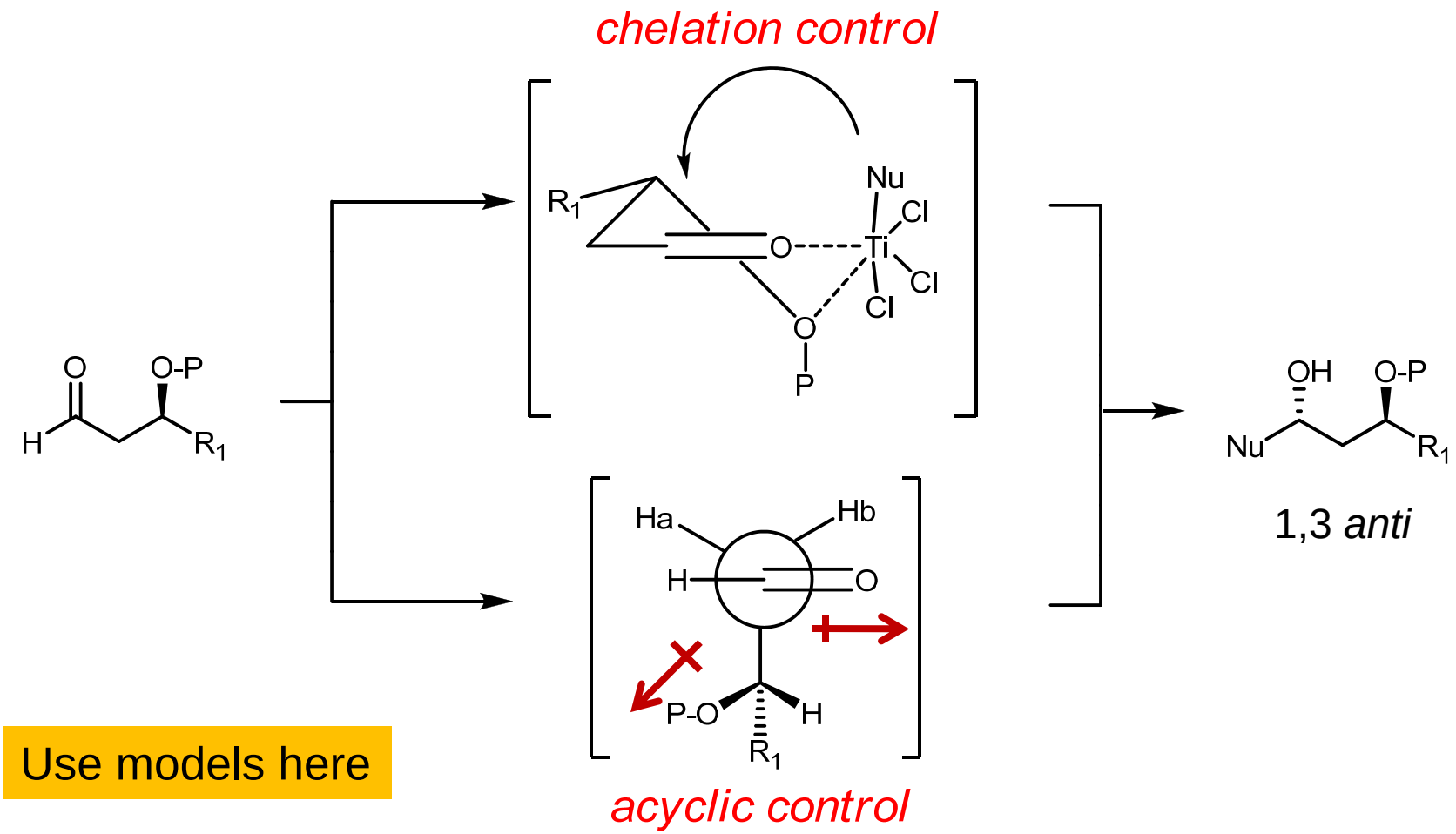
anti Felkin



B

favored

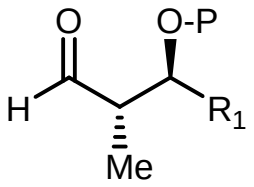
1,3 Asymmetric Induction: Stereogenic Centre β to the Carbonyl Group



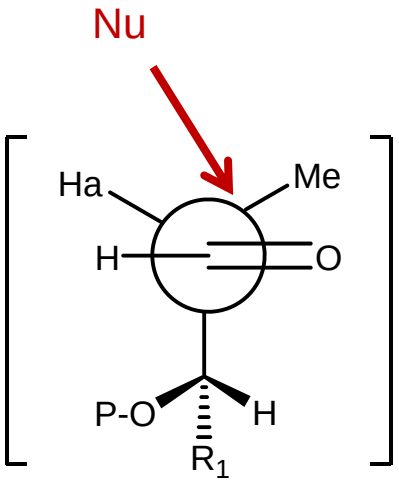
Use models here

Taken from Book: *Classics in Stereoselective Synthesis*, Chapter 2

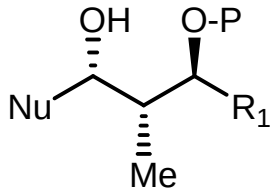
Use models here



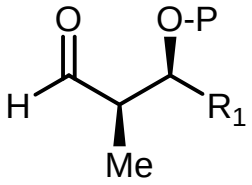
2,3 anti



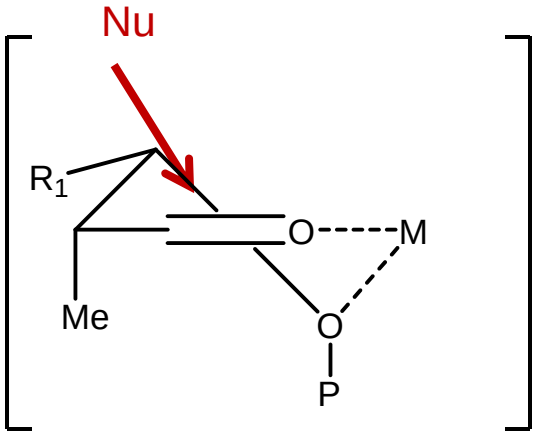
Felkin control



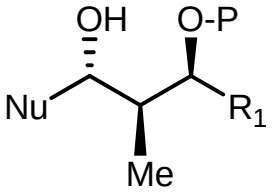
1,2 syn and 2,3 anti



2,3 syn

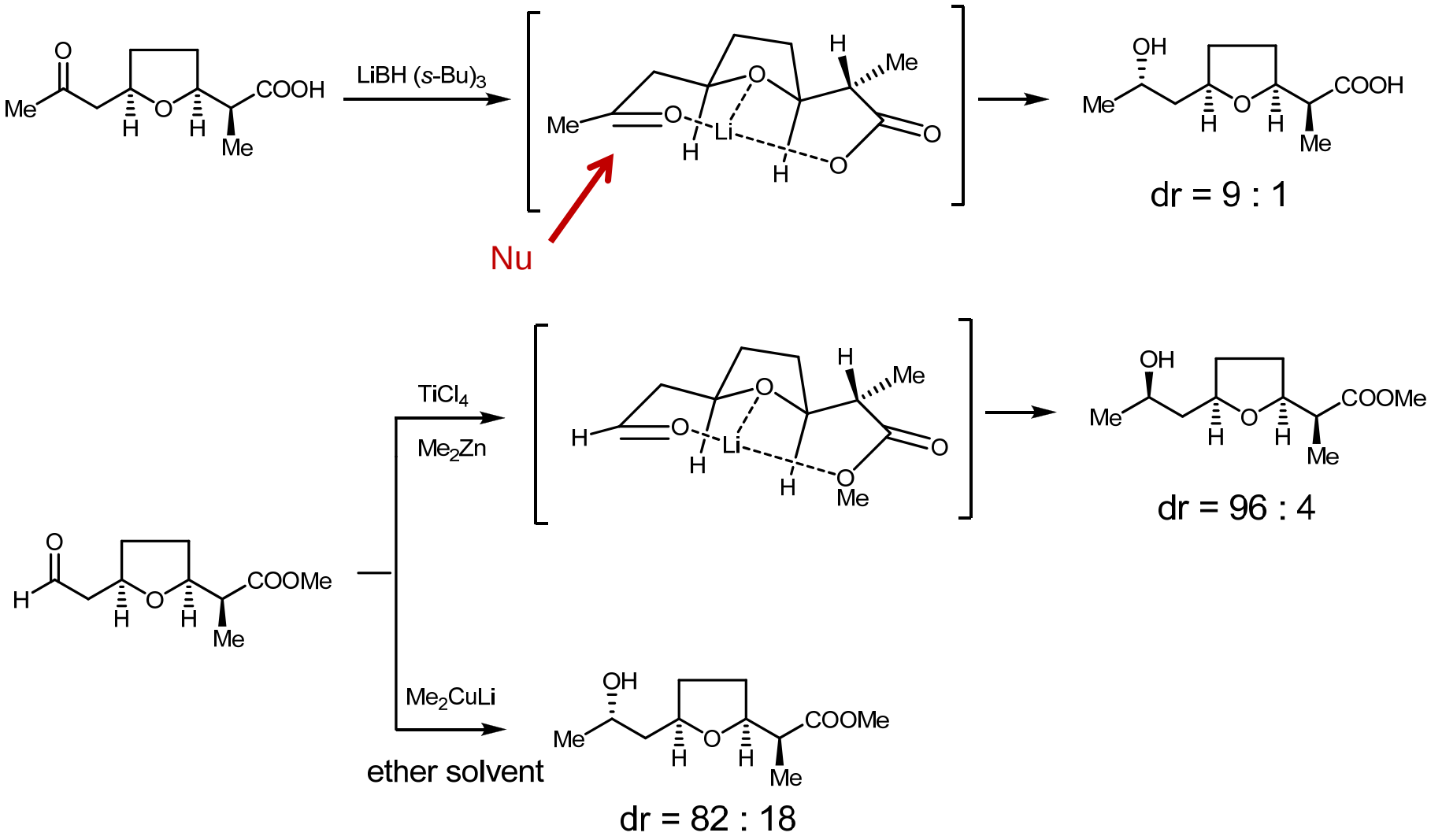


chelation control



1,2 anti and 2,3 syn

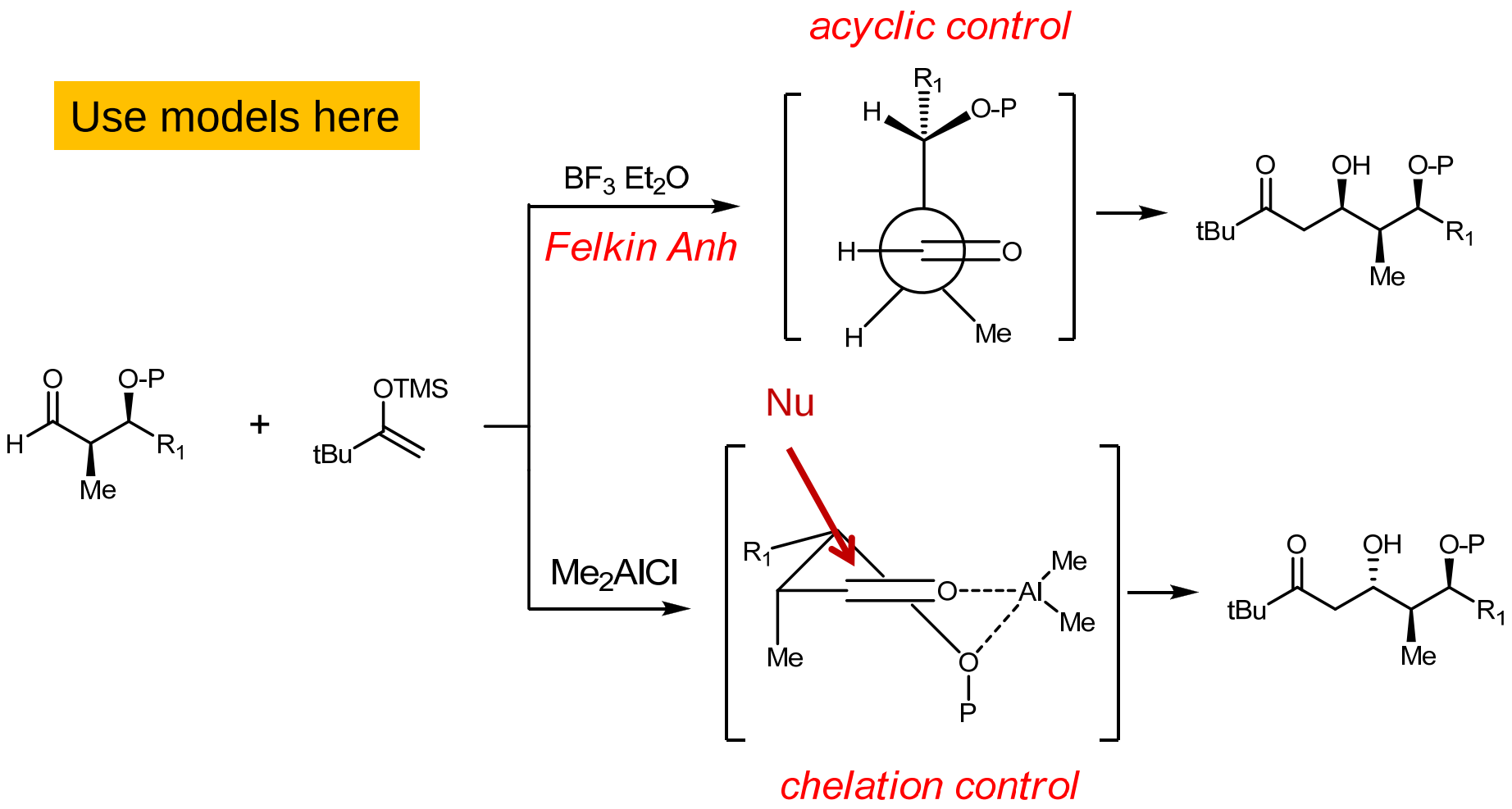
Taken from Book: *Classics in Stereoselective Synthesis*, Chapter 2



Taken from Book: *Classics in Stereoselective Synthesis*, Chapter 2

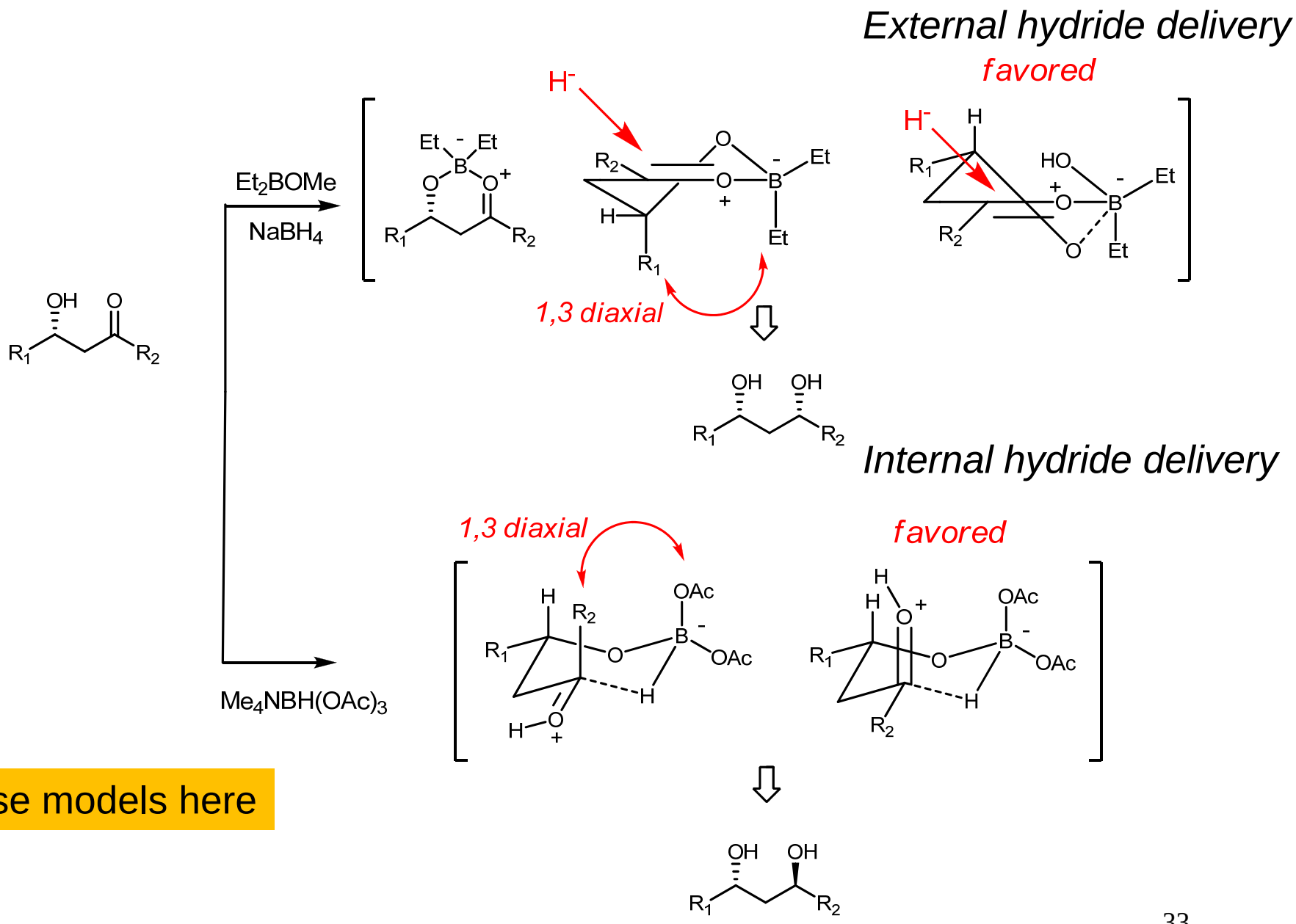
Regents-based Alteration in 1,3 Asymmetric Induction

Use models here



Taken from Book: *Classics in Stereoselective Synthesis*, Chapter 2

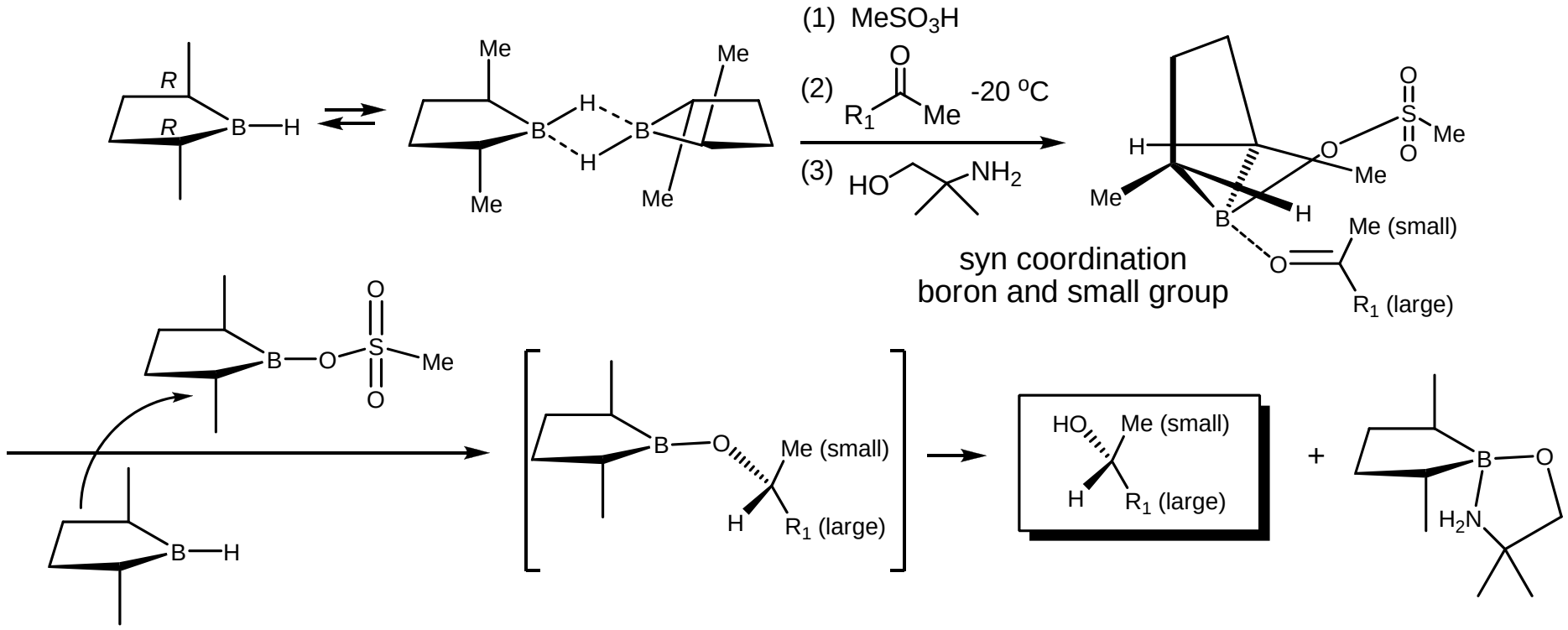
Regents-based Alteration in 1,3 Asymmetric Induction



Use models here

Taken from Book: *Classics in Stereoselective Synthesis*, Chapter 2

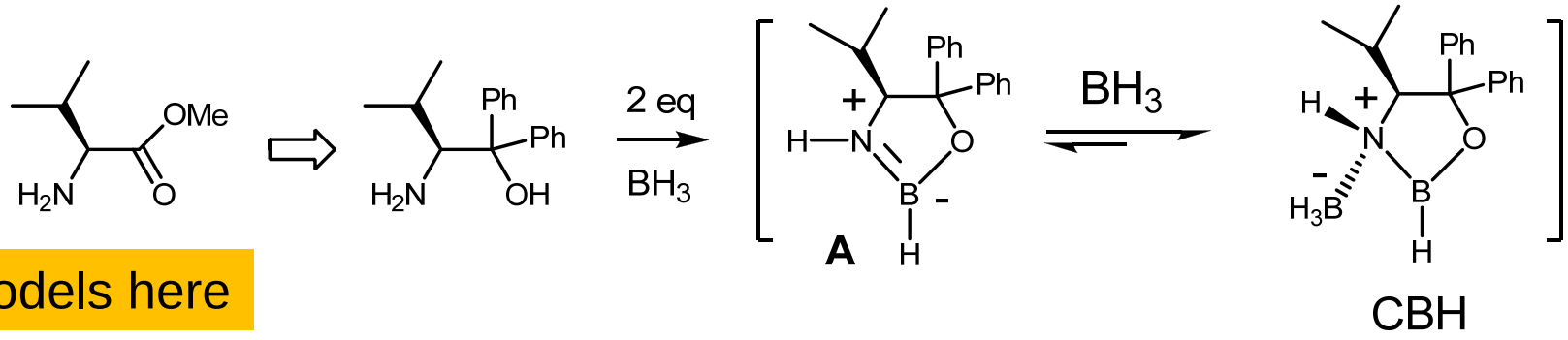
Enantioselective Reducing Agents



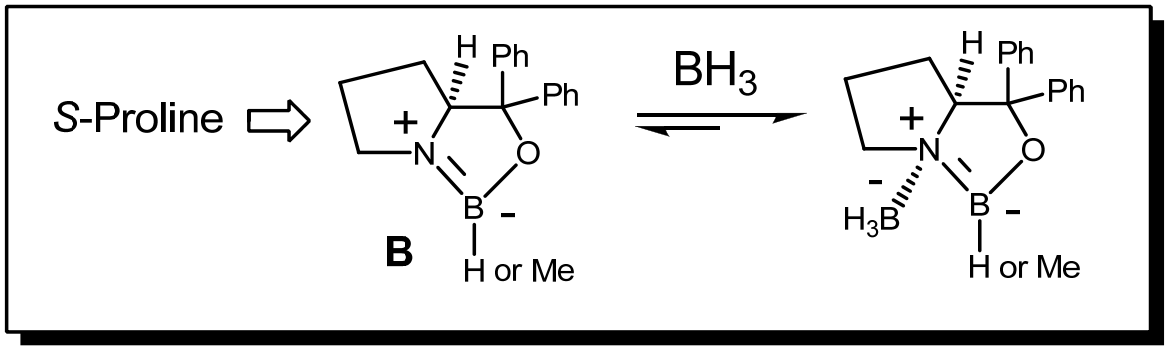
Use models here

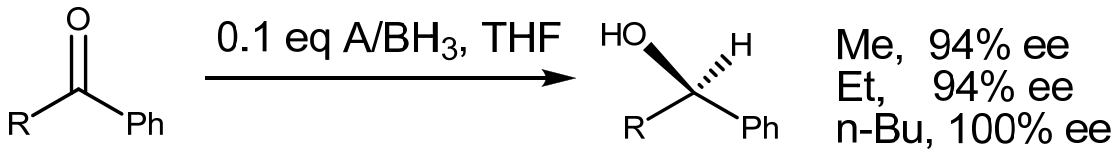
S Masmune, *J Am Chem Soc*, 4551 (1985) and 7402 (1986)

Catalytic Chiral Reducing Agent



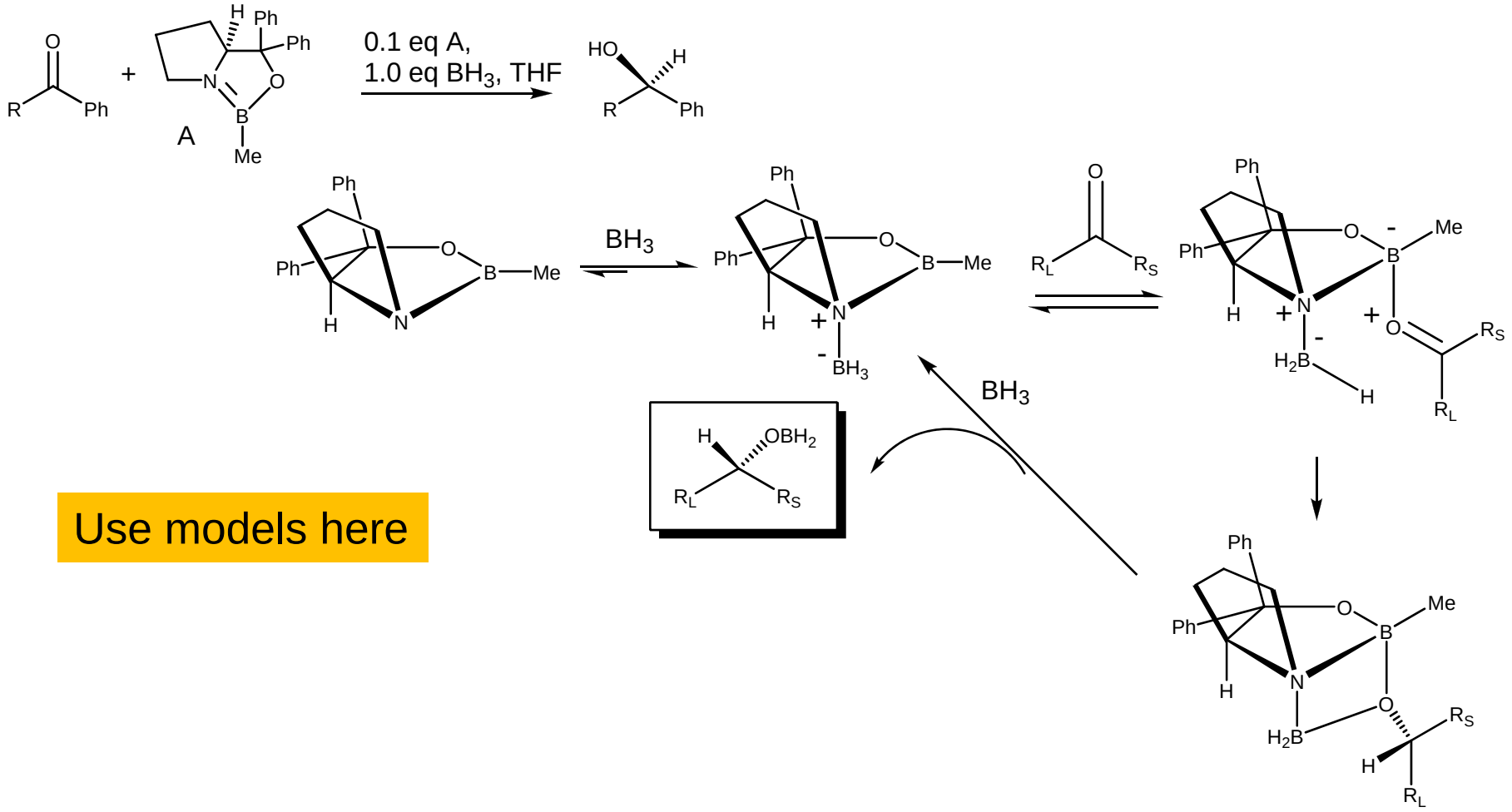
Use models here





A and BH_3 are not reducing agents

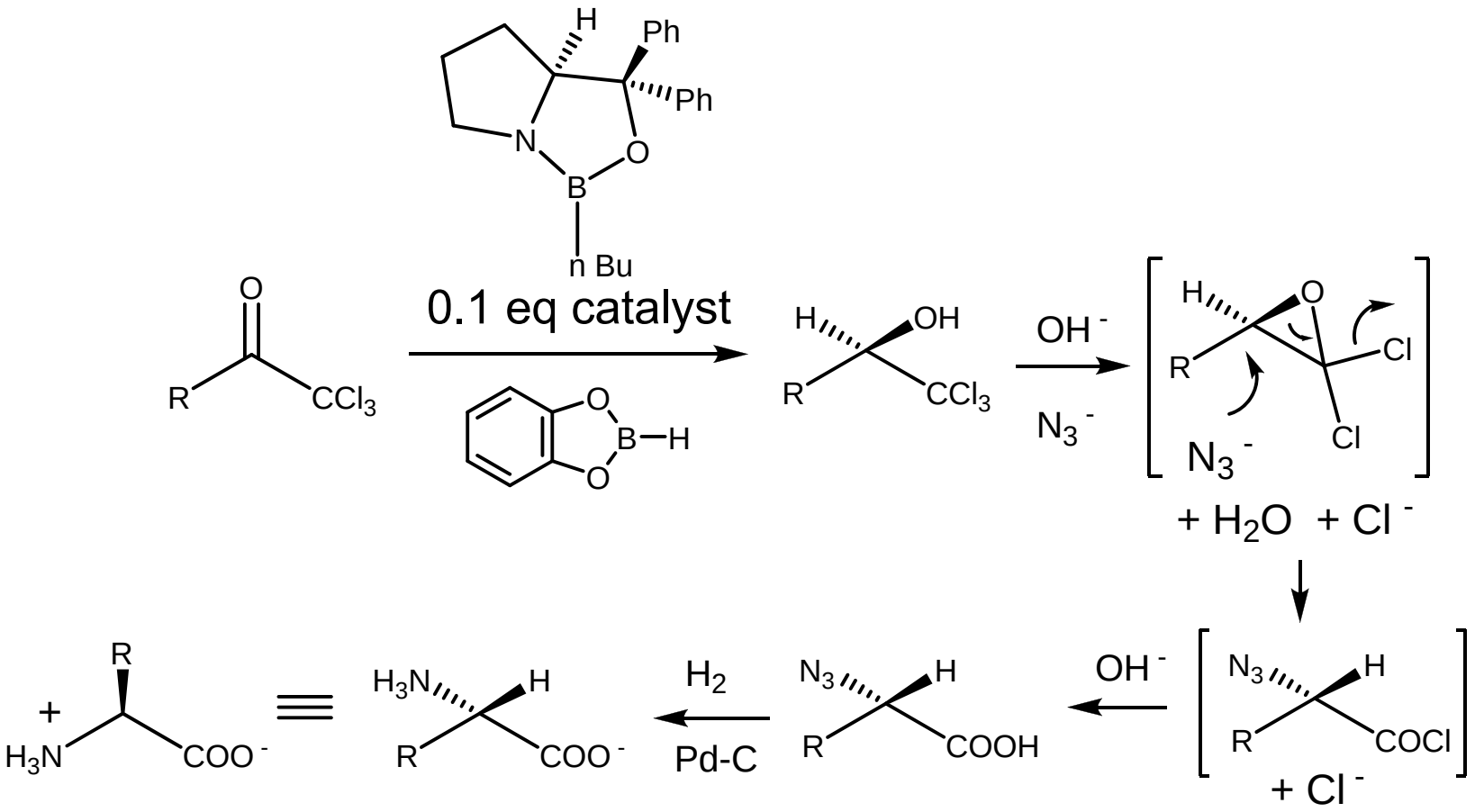
The Proposed Catalytic Cycle



Use models here

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

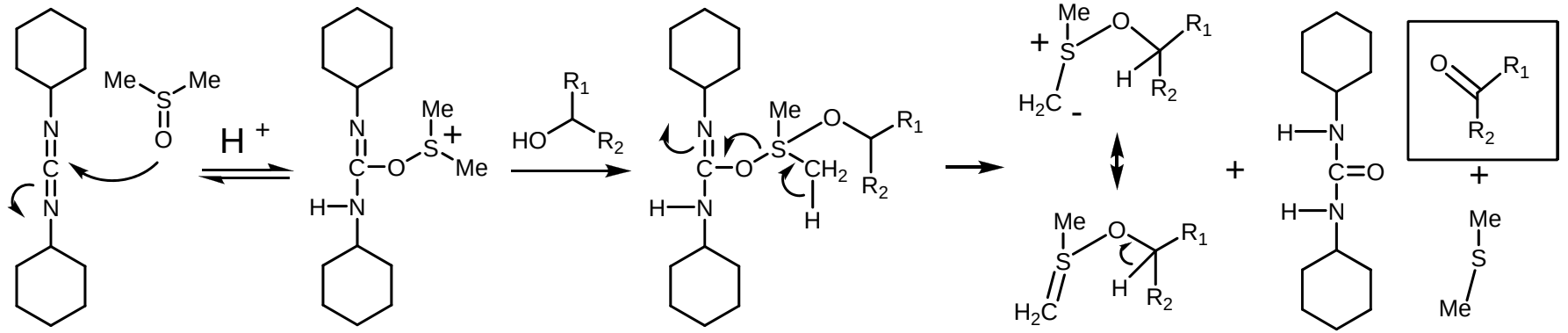


Corey et al, *J Am Chem Soc*, 1906 (1992)

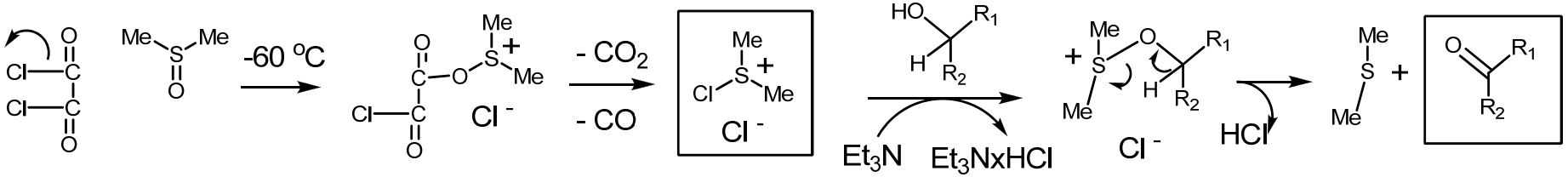
Enantioselective Oxidation

Simple Oxidizing Agents

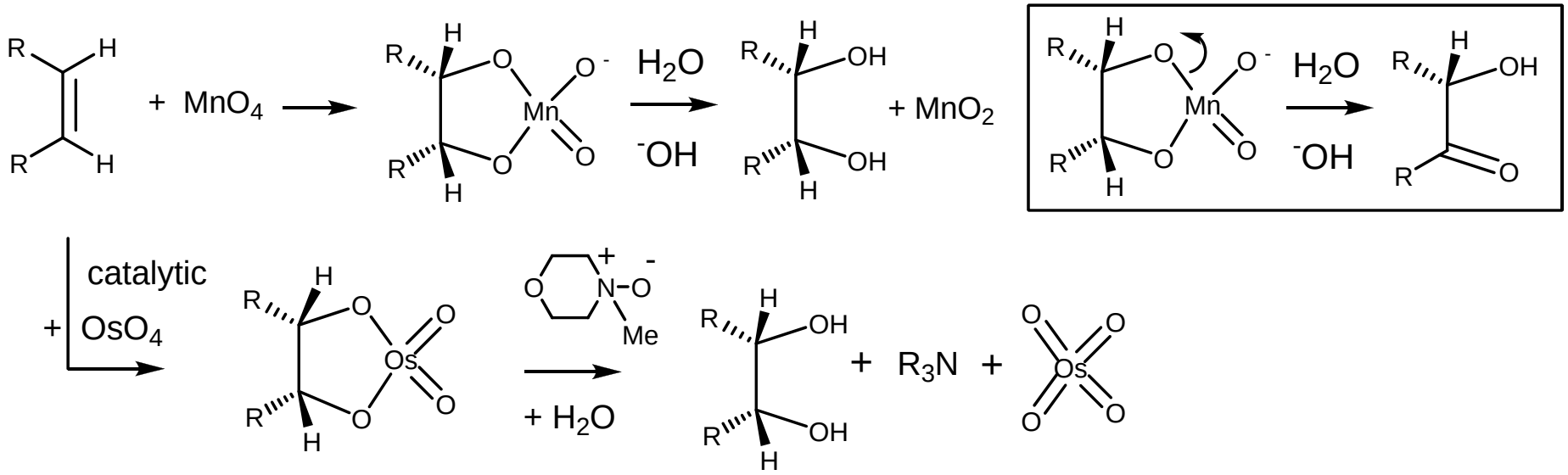
DMSO-DCC Oxidation

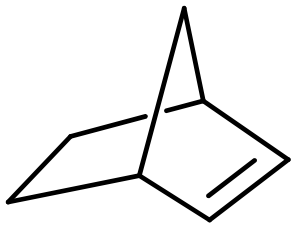


DMSO-Oxalyl Chloride Oxidation (Swern)



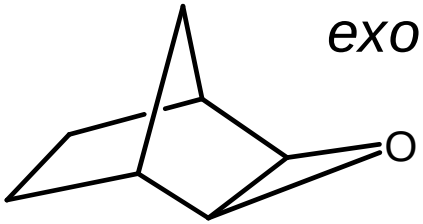
Oxidation of C=C Bond





exo

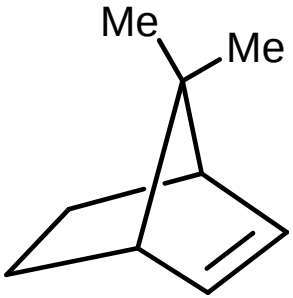
mCPBA



exo

endo

dr > 99:1



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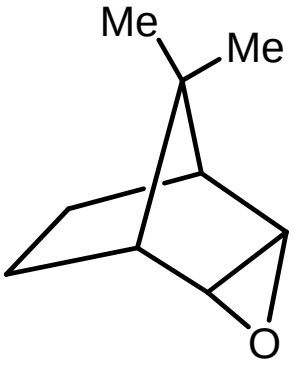
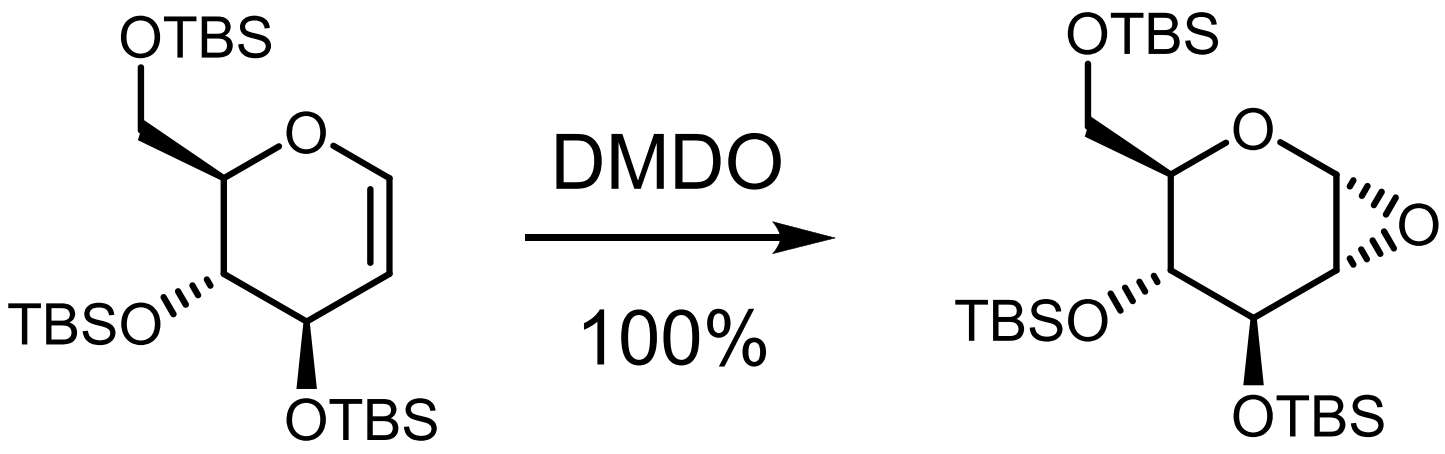


endo

dr > 9:1

Taken from Book: *Classics in Stereoselective Synthesis*, Chapter 9

Murray Approach



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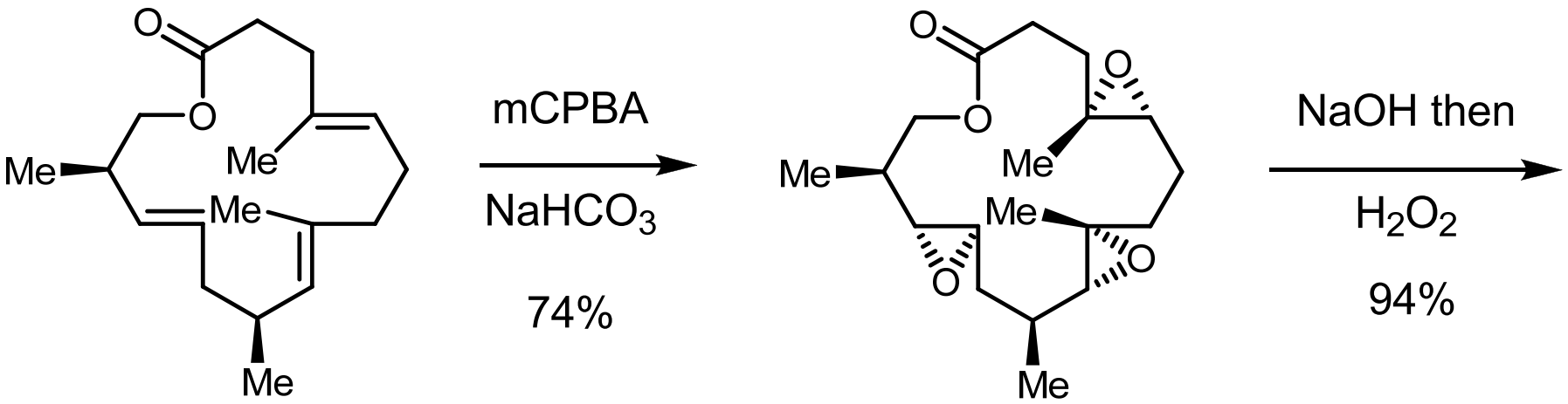
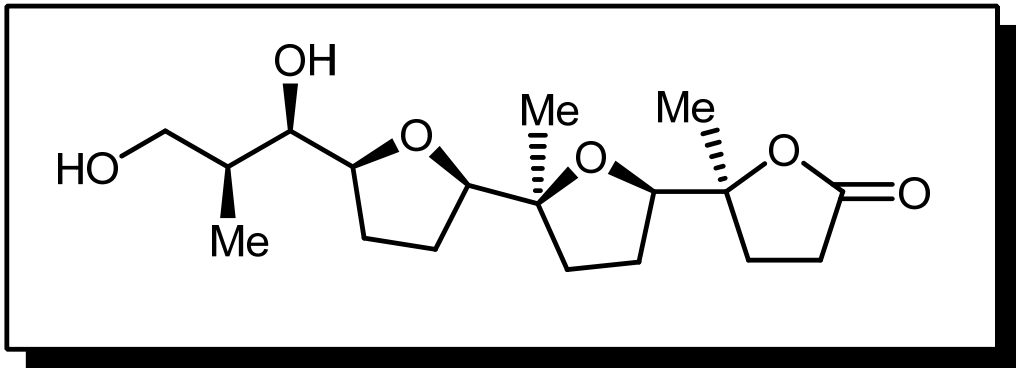
Taken from Book: *Classics in Stereoselective Synthesis*, Chapter 9

Still Approach

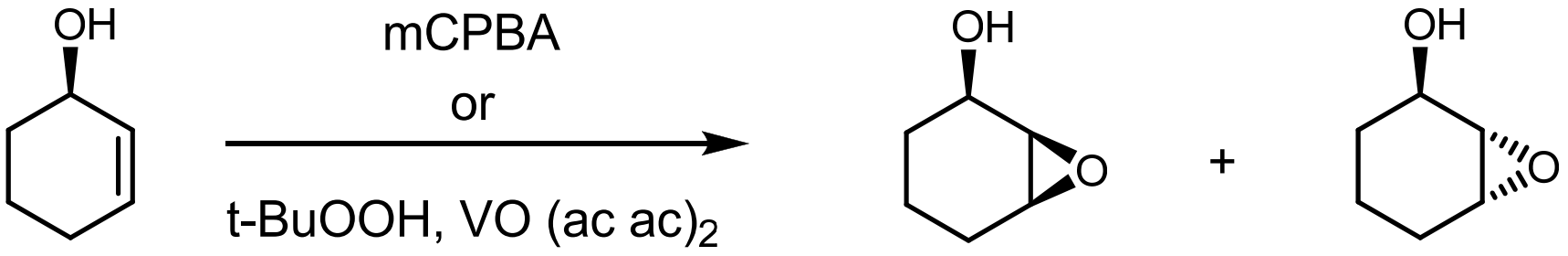


dr = 20:1:1



Taken from Book: *Classics in Stereoselective Synthesis*, Chapter 9

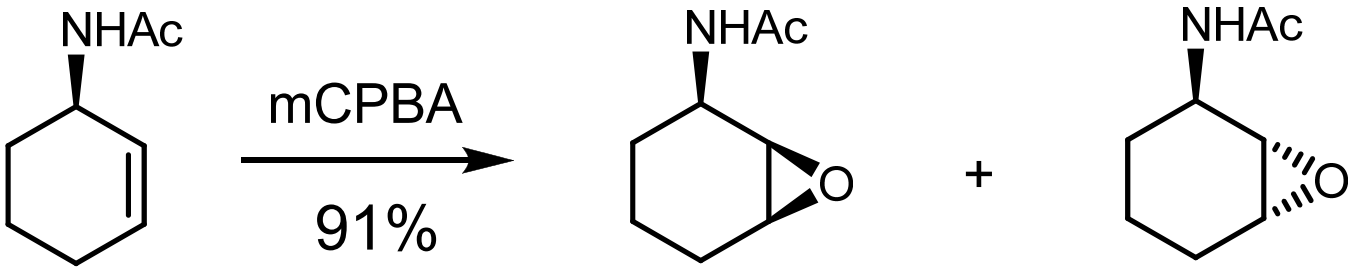
Directing Groups



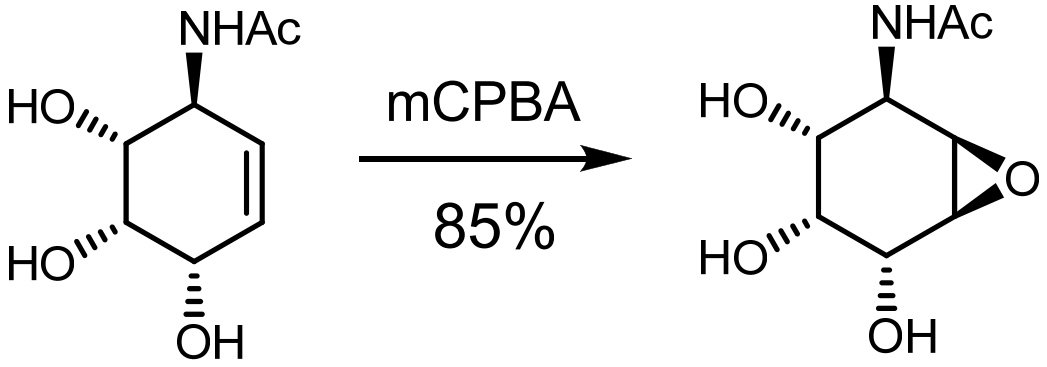
with t-BuOOH, VO (ac ac)$_2$ dr = 98:2

Taken from Book: *Classics in Stereoselective Synthesis*, Chapter 9

Directing Groups

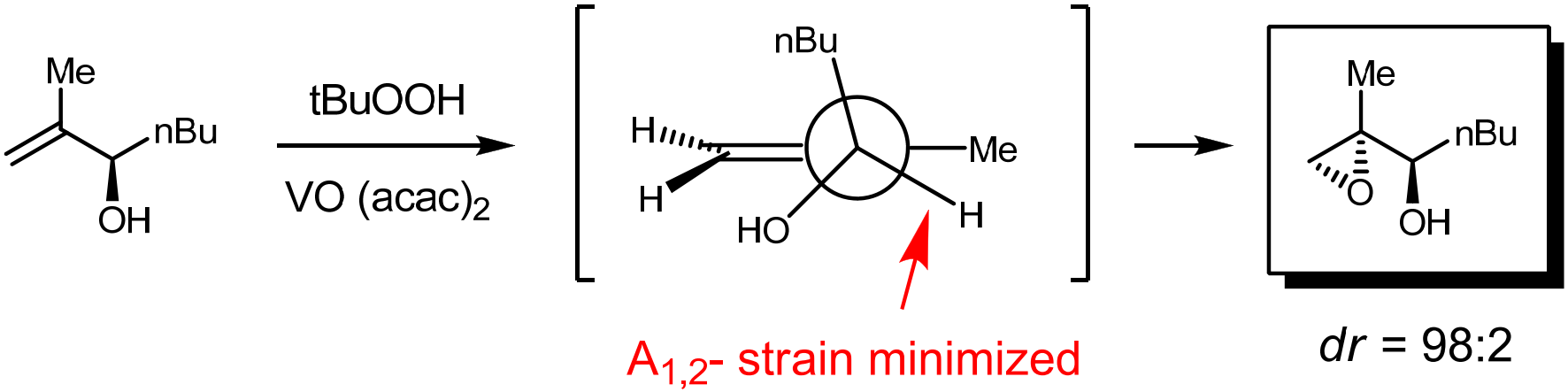


dr = > 99:1



Taken from Book: *Classics in Stereoselective Synthesis*, Chapter 9

Directing Groups

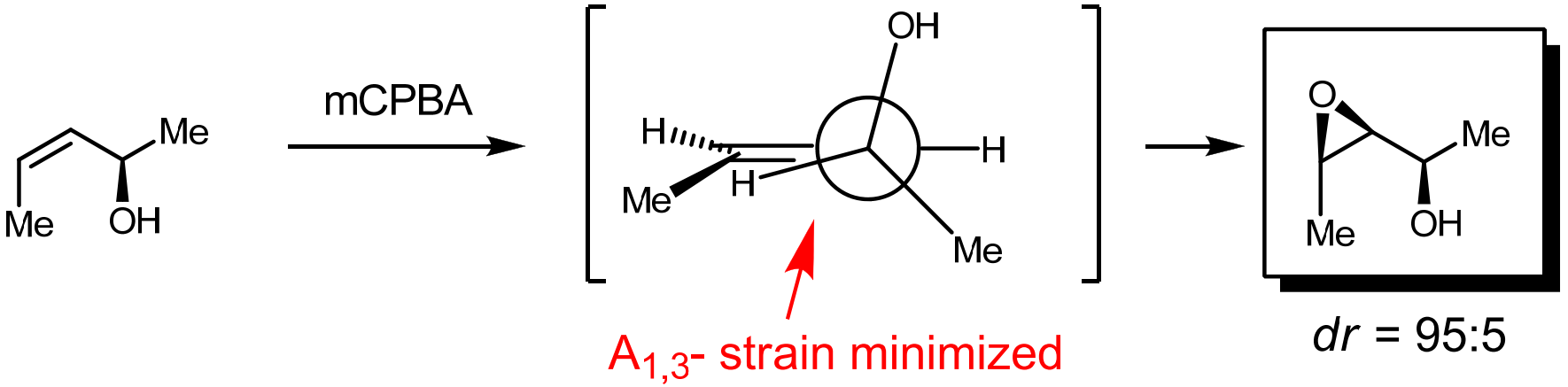


$A_{1,2}$- strain minimized

dr = 98:2

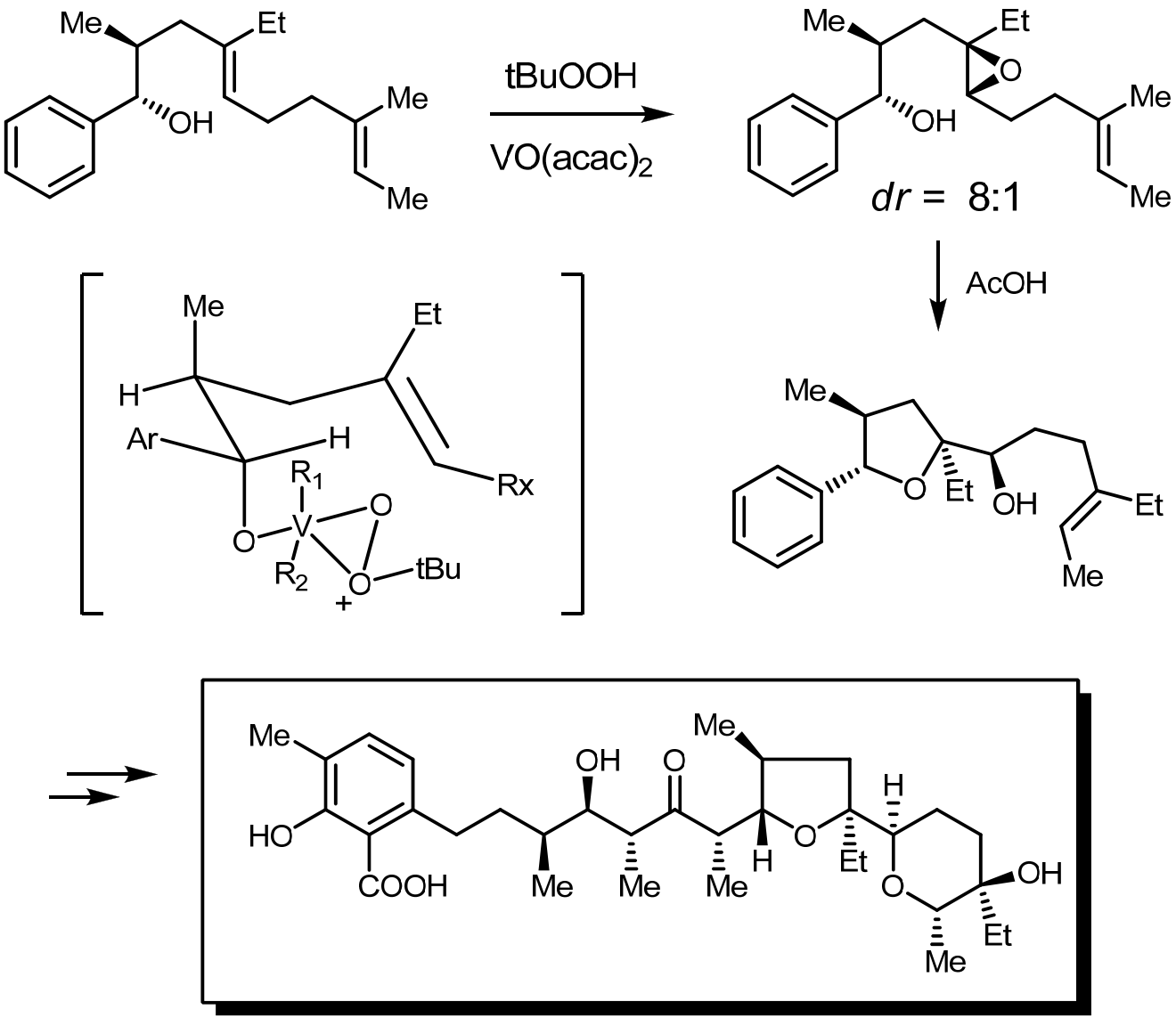
Taken from Book: *Classics in Stereoselective Synthesis*, Chapter 9

Directing Groups



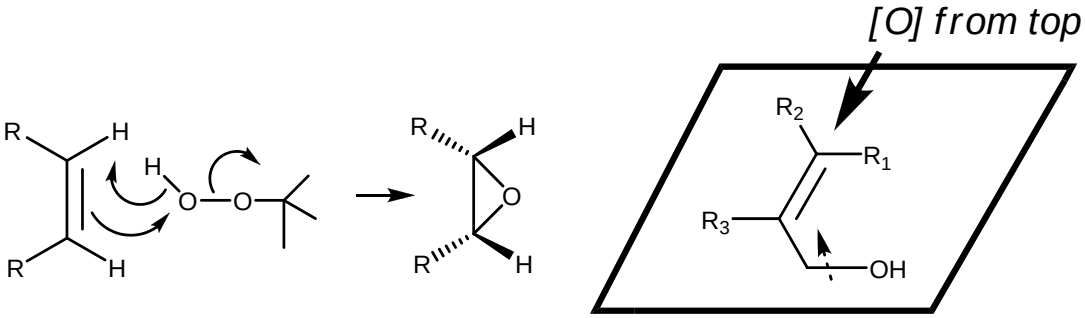
Taken from Book: *Classics in Stereoselective Synthesis*, Chapter 9

Application to Lasacolid Synthesis

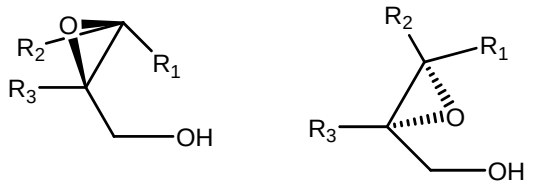


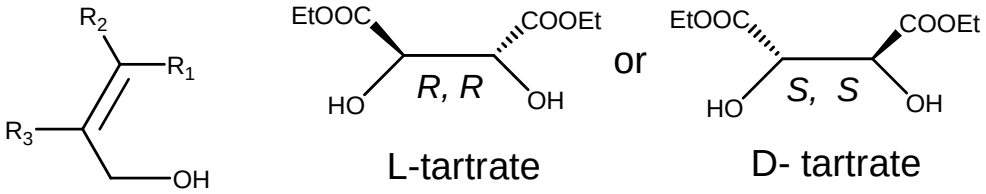
Taken from Book: *Classics in Stereoselective Synthesis*, Chapter 9

Enantioselective Sharpless Epoxidation

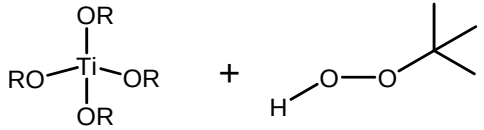


Use models here



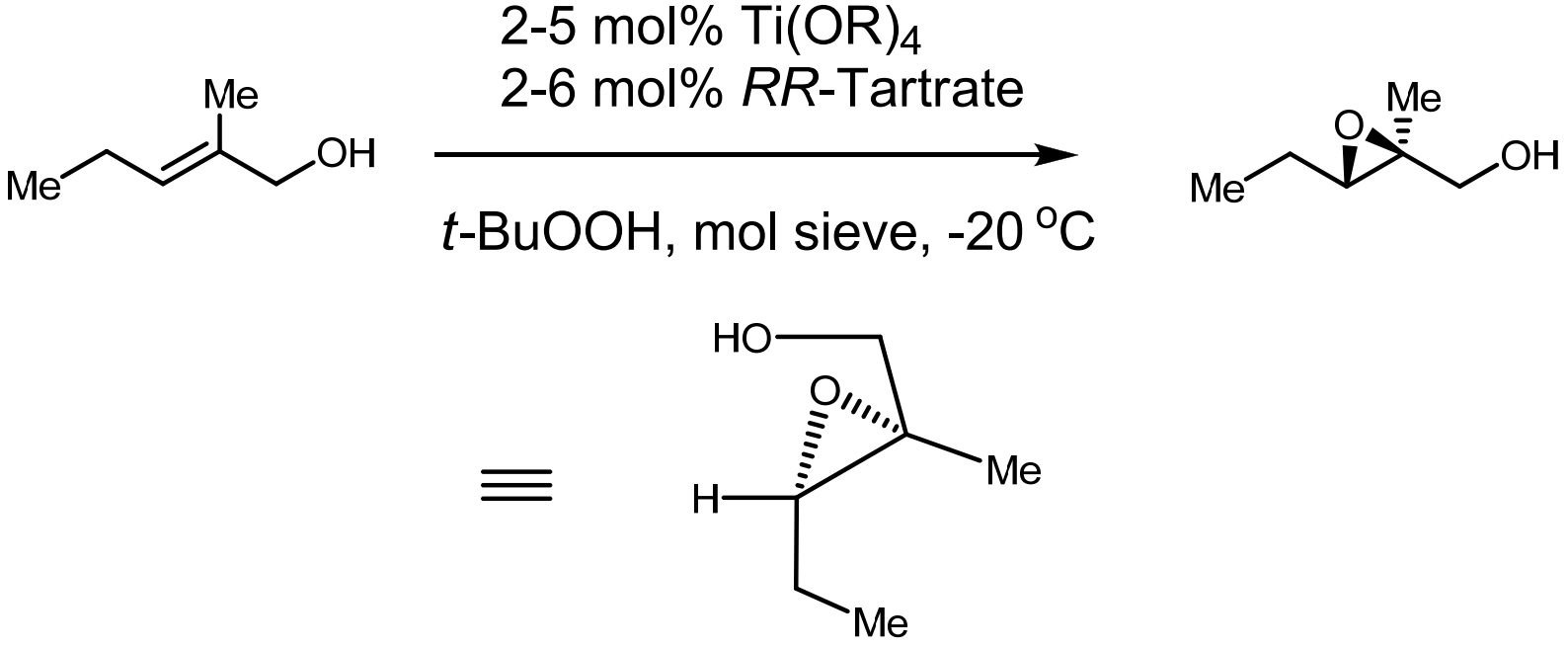


L-tartrate D- tartrate



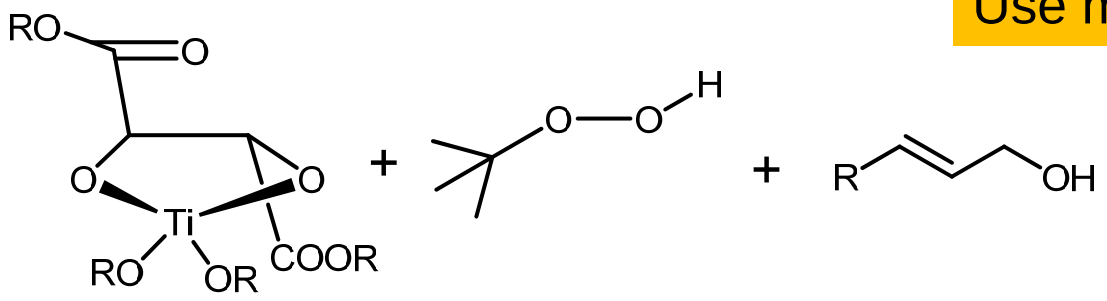
R : i-C_3H_7 CH_2Cl_2, -20 ^oC

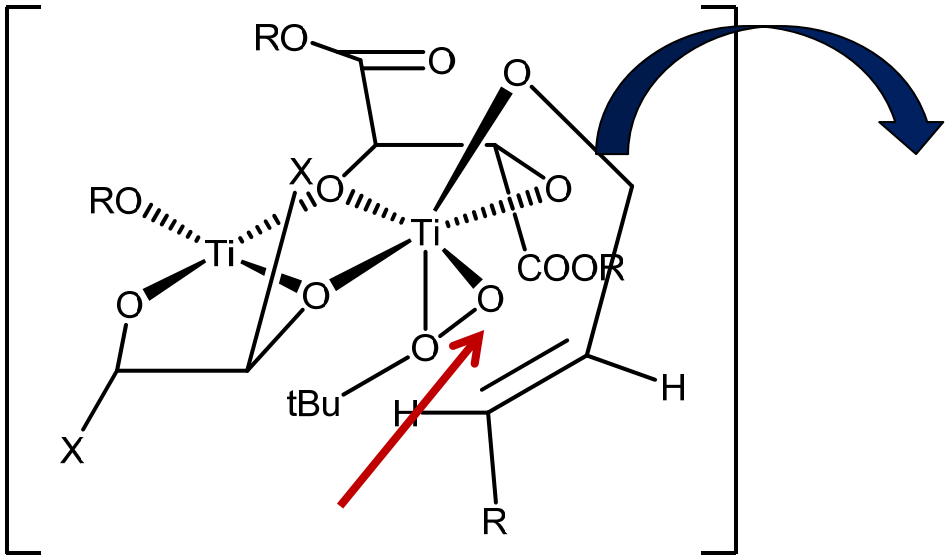
L-tartrate → attack from the bottom face
D-tartrate → attack from the top face

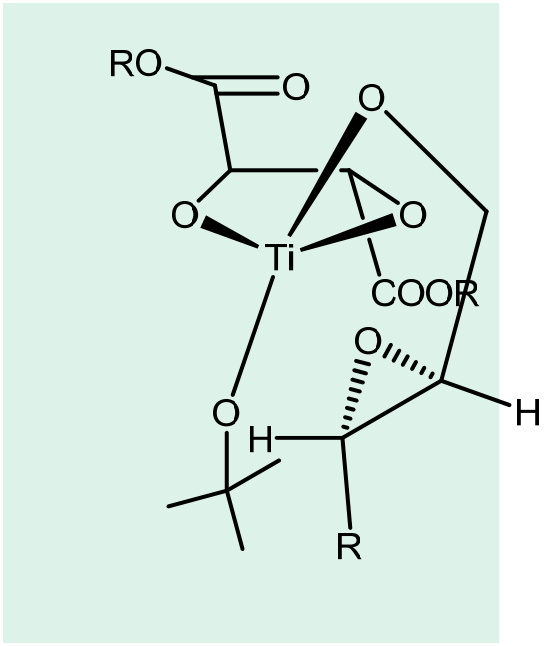

2-5 mol% Ti(OR)4
2-6 mol% RR-Tartrate
t-BuOOH, mol sieve, -20 °C
Me
OH
Me
Me
O
OH
HO
O
Me
H
Me

The Proposed Mechanism

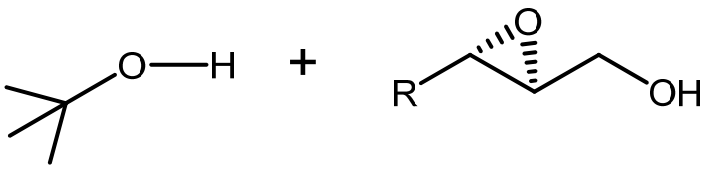
Use models here



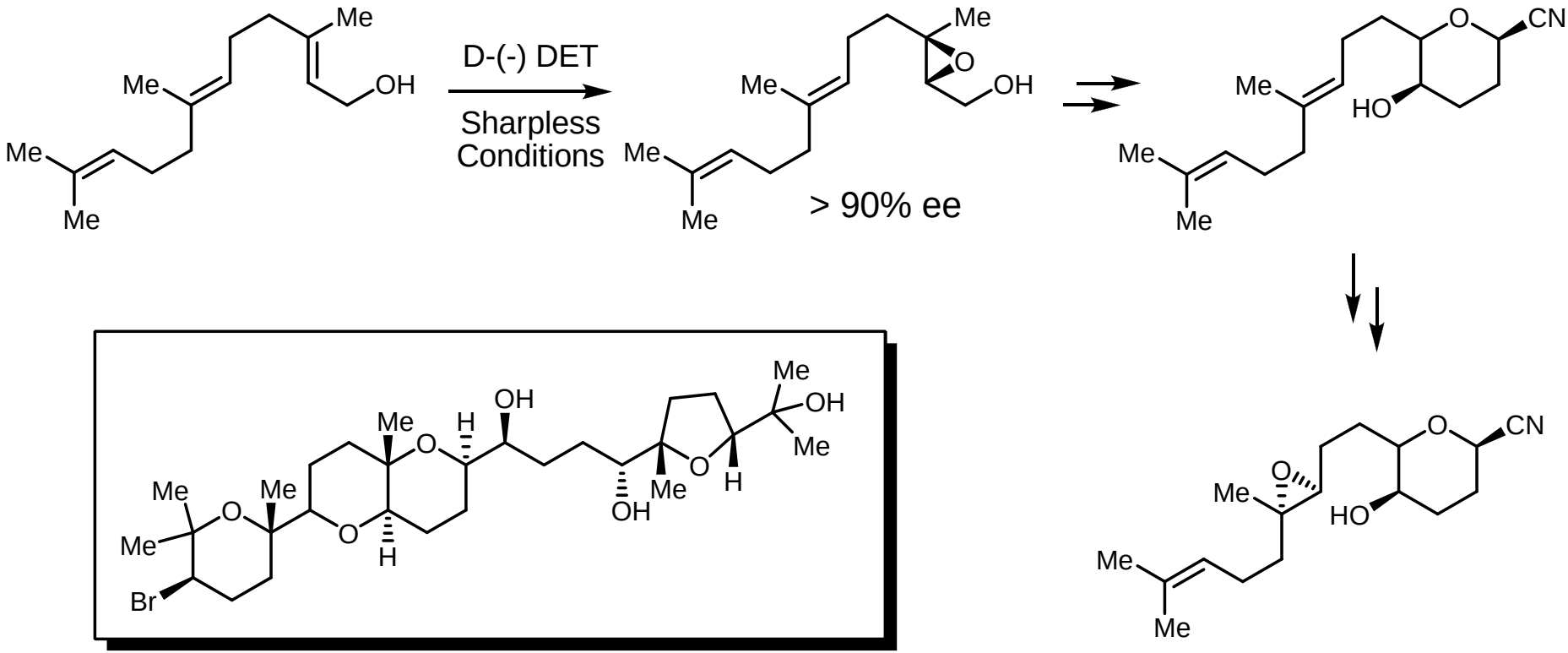




Approach from behind

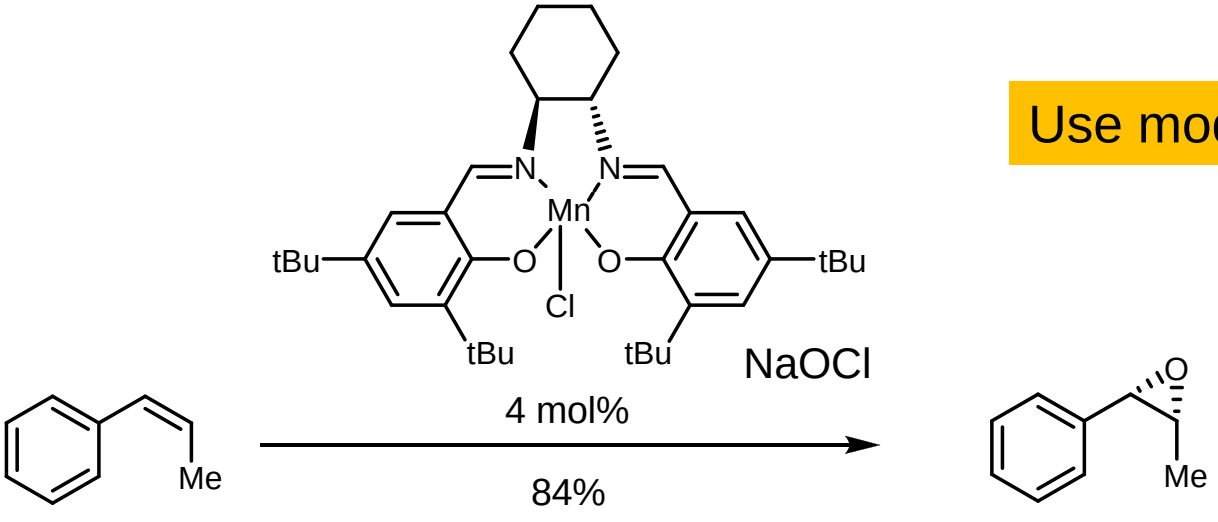


Application to Venustatriol Synthesis



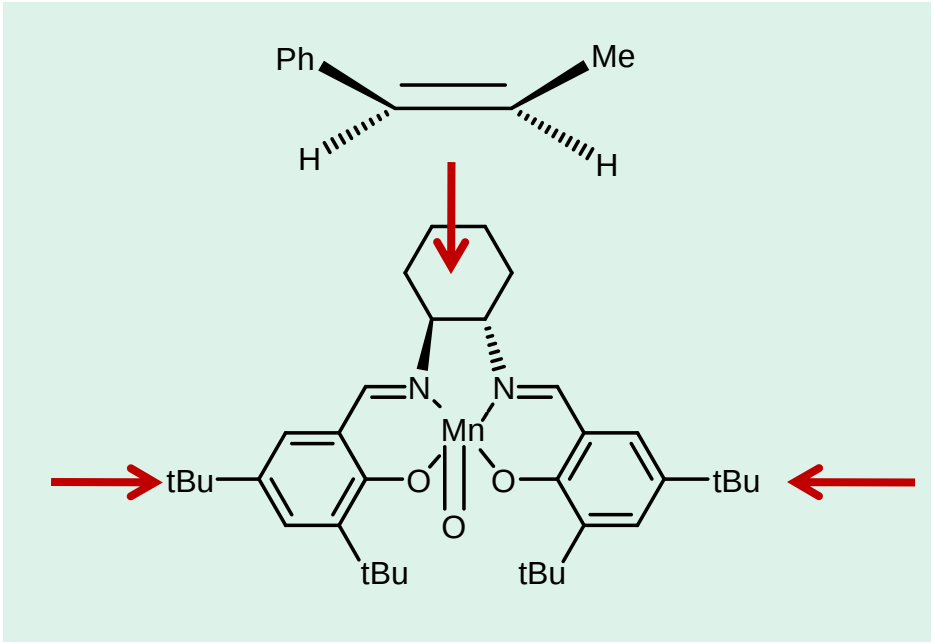
Taken from Book: *Classics in Stereoselective Synthesis*, Chapter 9

Jacobson Epoxidation



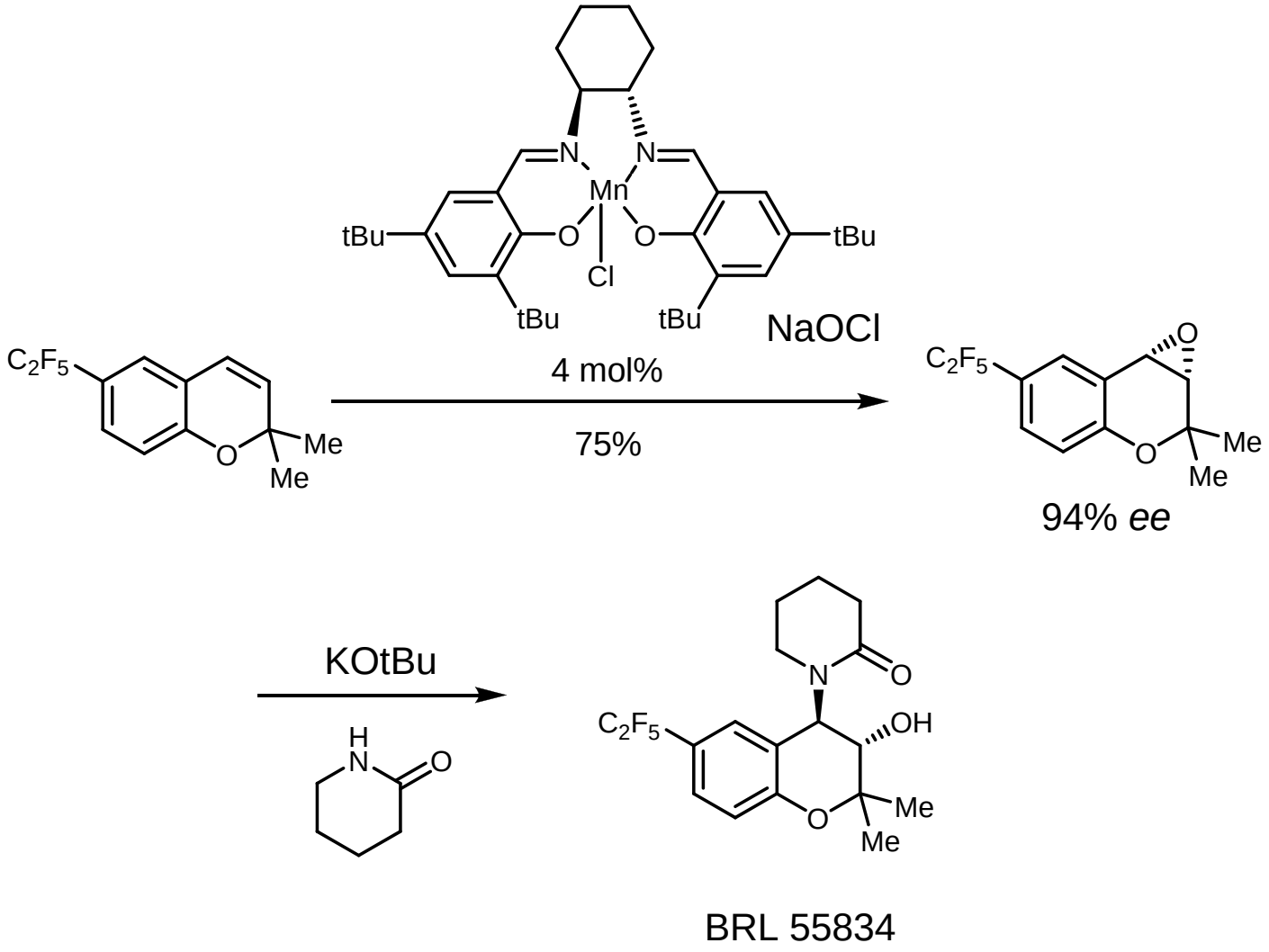
Use models here

92% *ee*



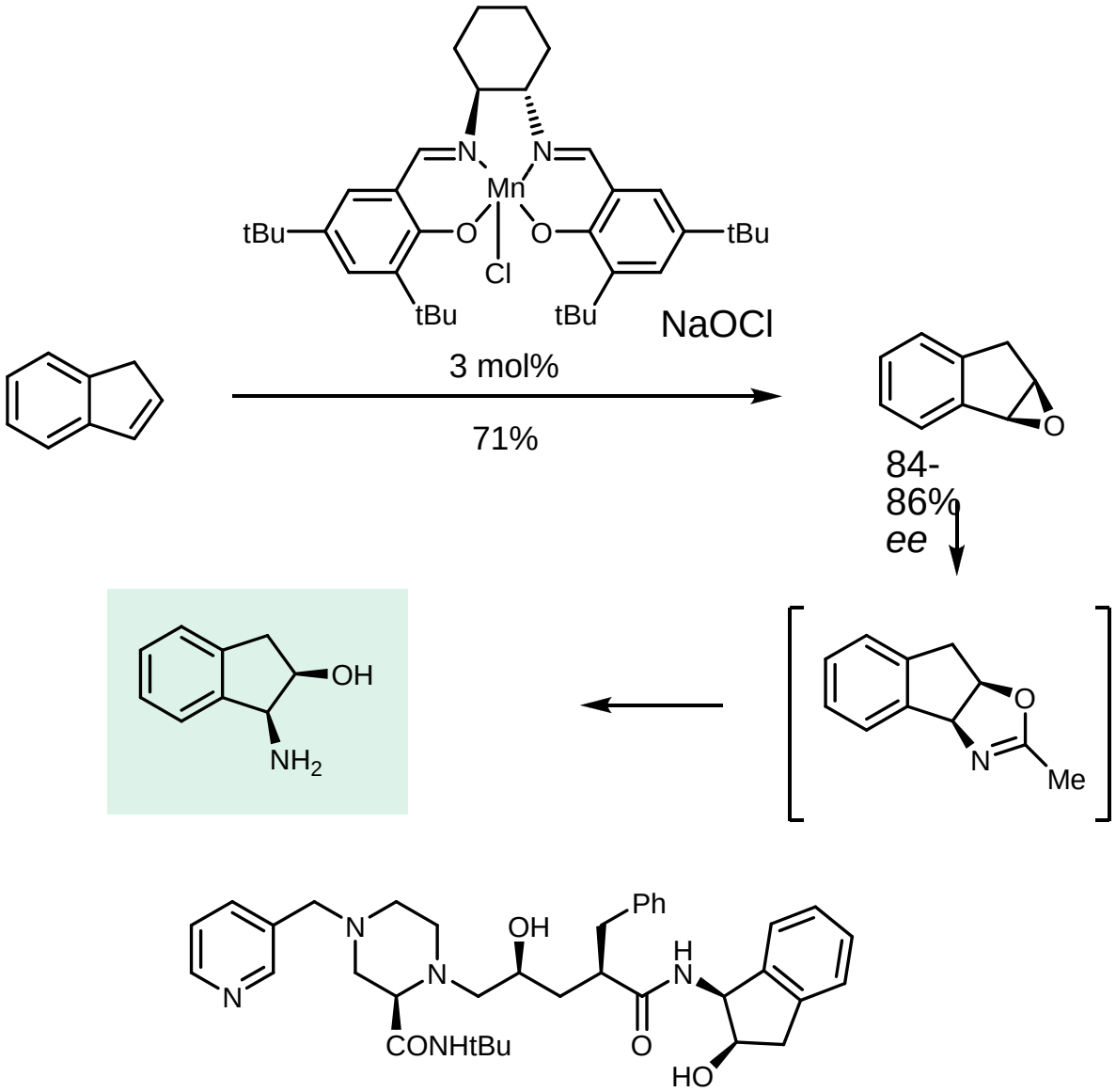
Taken from Book: *Classics in Stereoselective Synthesis*, Chapter 9

Enantioselective Synthesis of BRL 55834



Taken from Book: *Classics in Stereoselective Synthesis*, Chapter 9

Enantioselective Synthesis of Indinavir



Taken from Book: *Classics in Stereoselective Synthesis*, Chapter 9