Introduction to Asymmetric Synthesis

(1) Chiral pool approach:

Pure enantiomers from Nature;

Tartrate, amino acids, carbohydrates, etc.

(2) Chiral auxiliaries:

Examples: Evans' enolate alkylation and aldol reactions, but still controlled by substrate;

Oxazolidinones, menthyl.

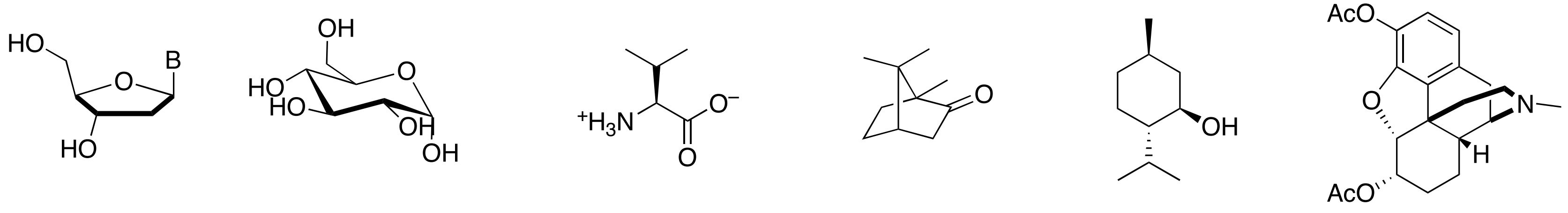
(3) Chiral reagents and catalysts:

Most flexible and efficient.

CBS reagent for chiral reductions

Sharpless asymmetric epoxidation

Synthesizing pure enantiomers starting from Nature's chiral pool



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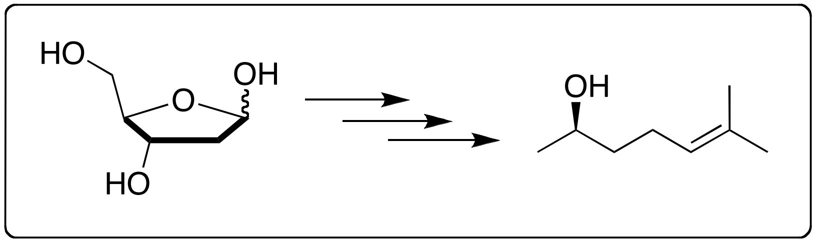
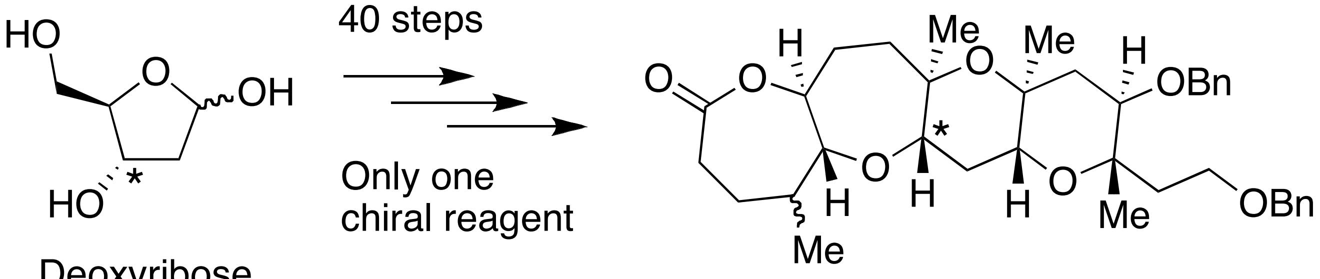


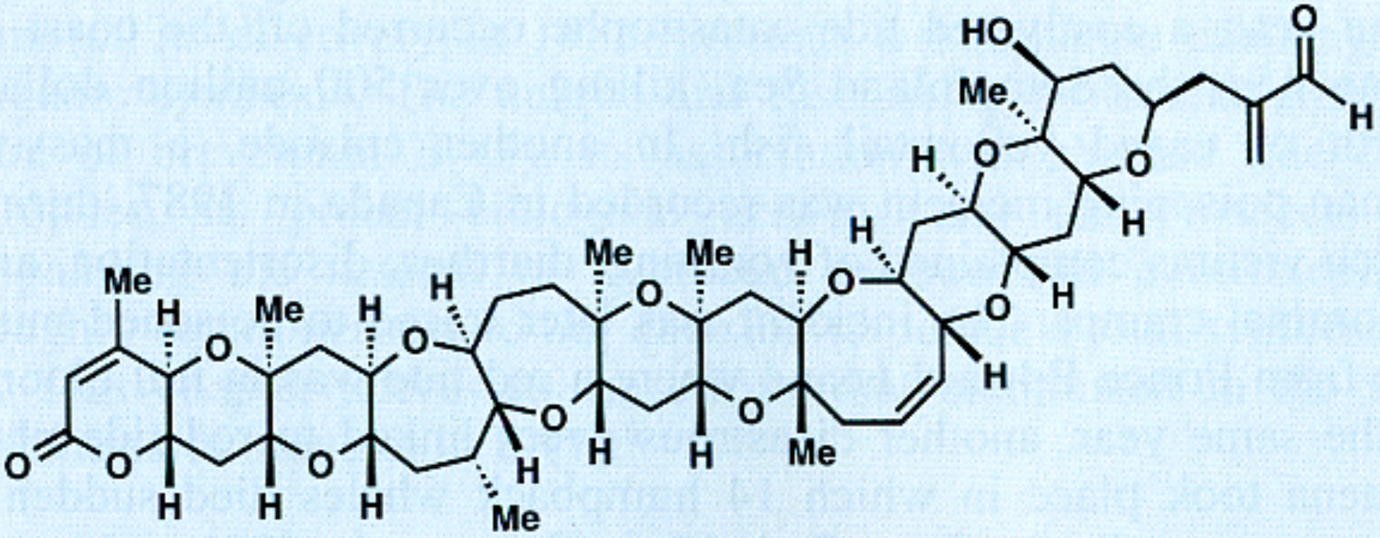
Sulcatol - insect pheremone

Synthesis from the chiral pool — chiral induction turns one stereocenter into many



Deoxyribose

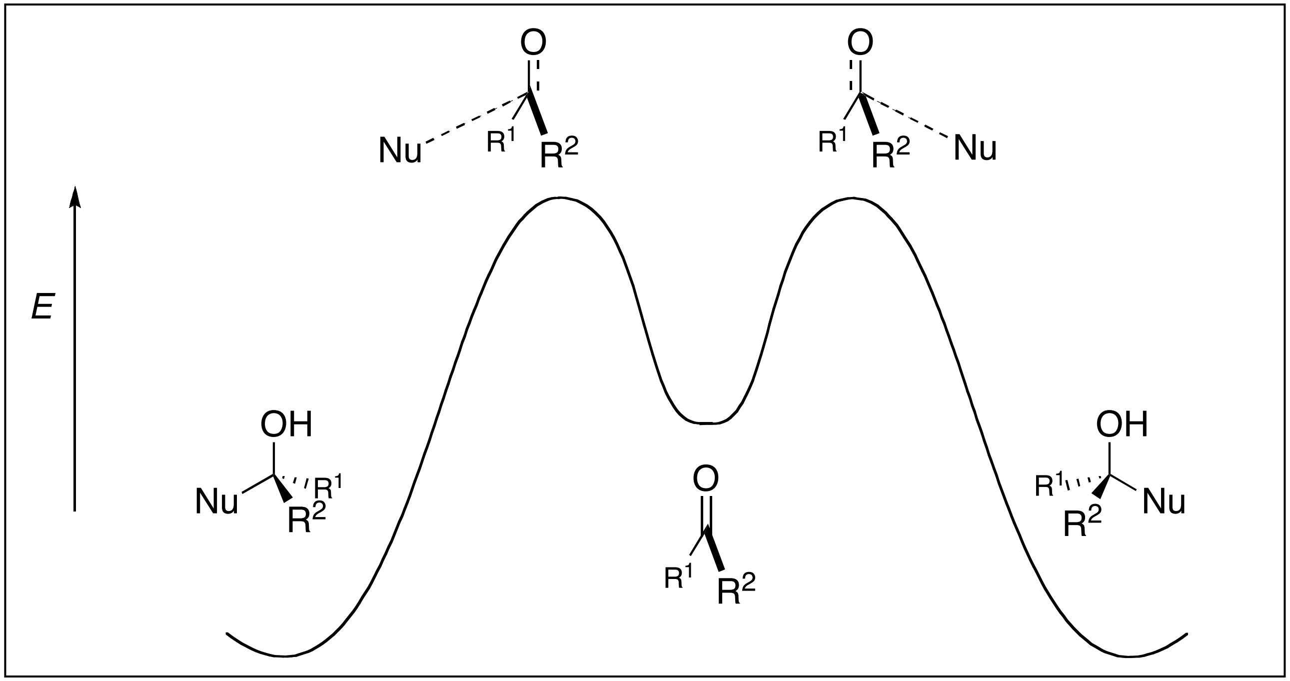
Fragment of Brevetoxin B

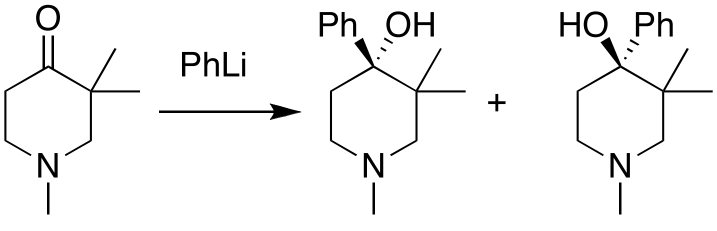


1: brevetoxin B

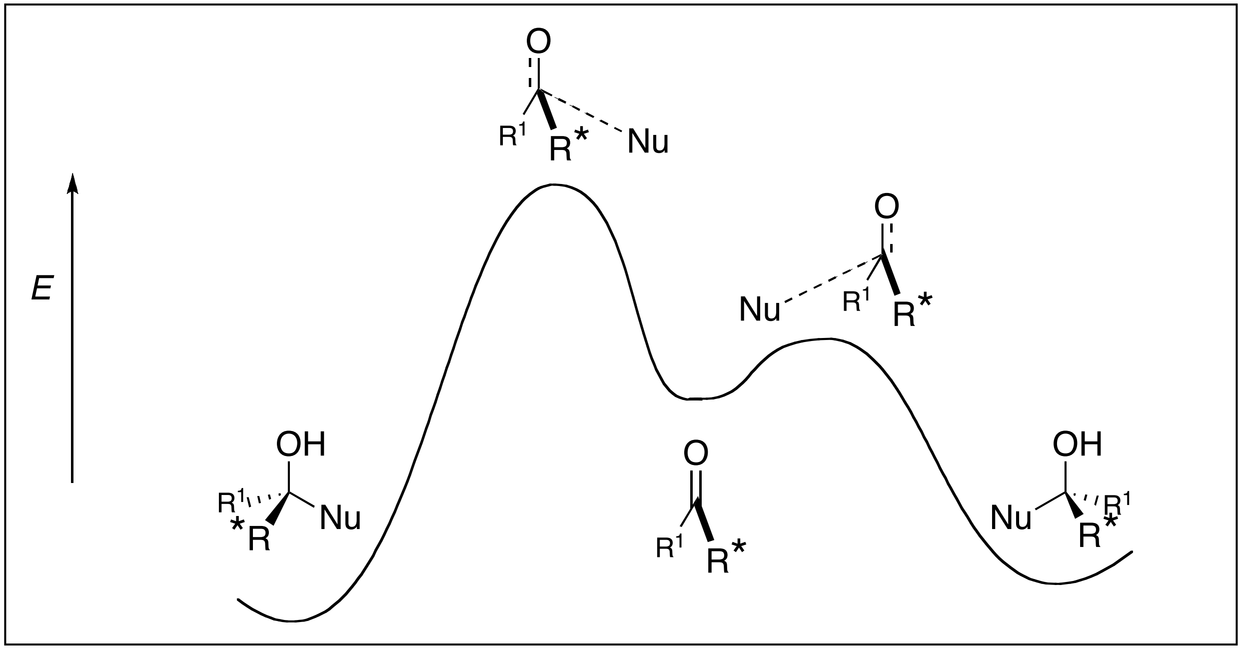
Asymmetric synthesis 1.

Producing a new stereogenic centre on an achiral molecule makes two enantiomeric transition states ***of equal energy***… and therefore two enantiomeric products ***in equal amounts***.

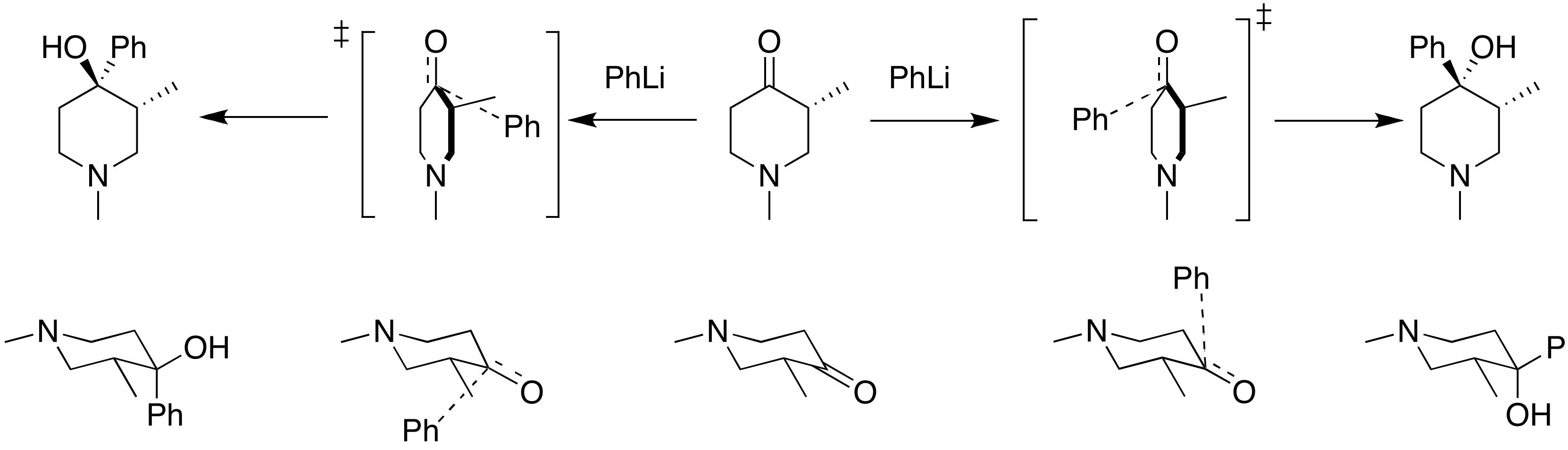




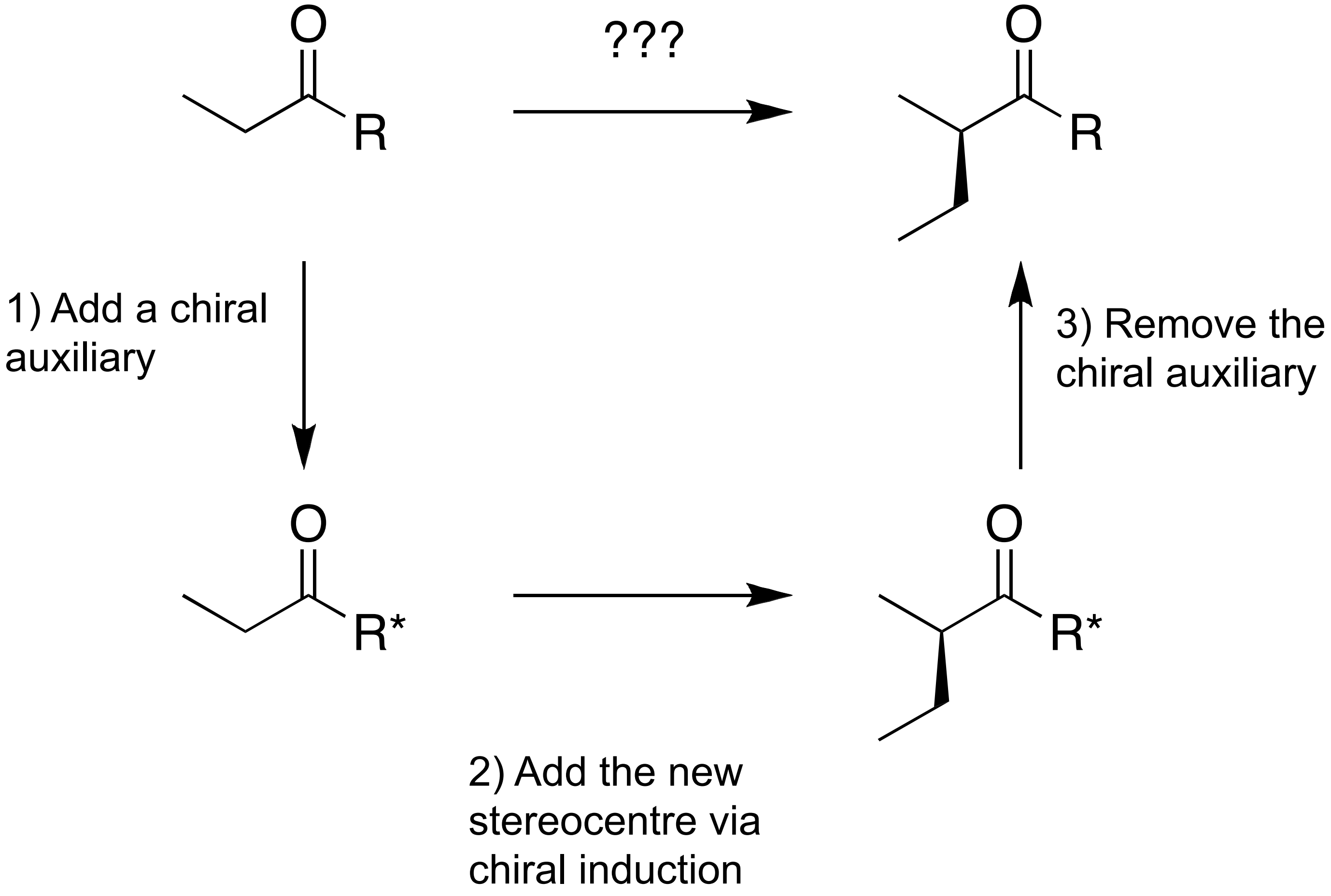
Asymmetric synthesis 2.



When there is an existing chiral centre, the two possible TS's are diastereomeric and can be ***of different energy***. Thus one isomer of the new stereogenic centre can be produced ***in a larger amount***.



A <u>removable</u> chiral centre… synthesis with chiral auxiliaries

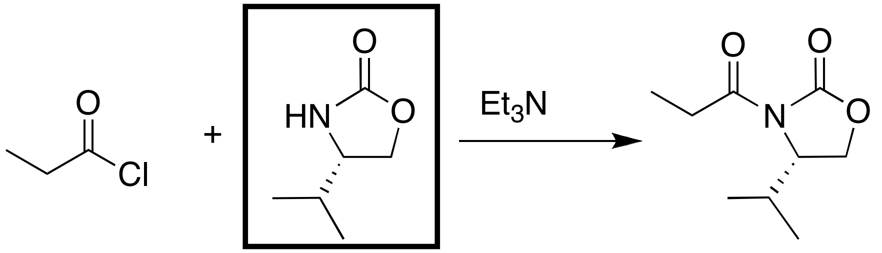


1) Add a chiral auxiliary

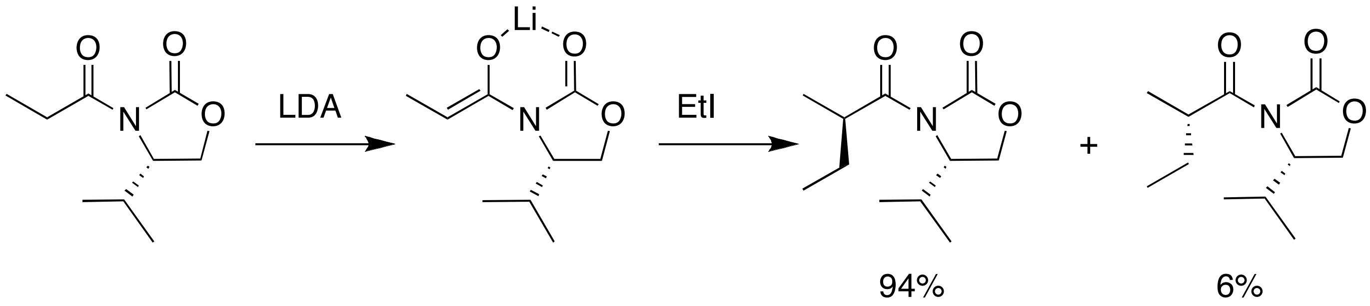
2) Add the new stereocentre via chiral induction

3) Remove the chiral auxiliary

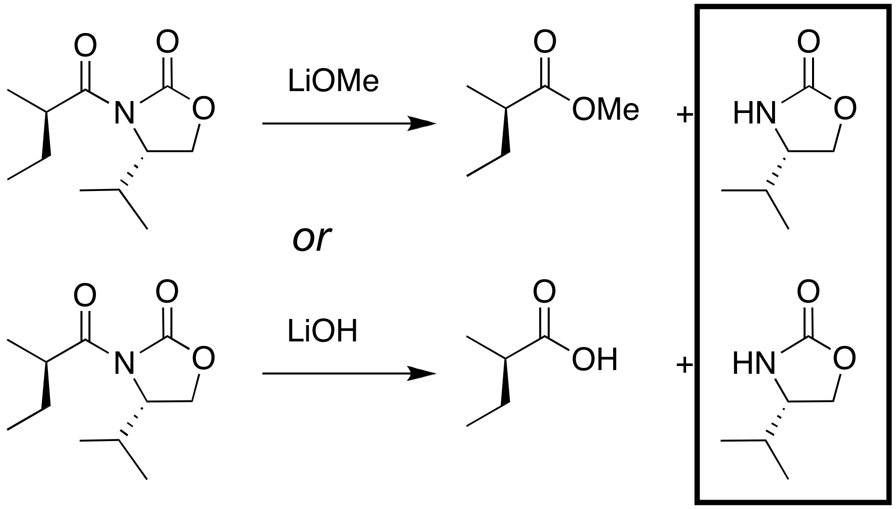
Enantiopure oxazolidinones as chiral auxiliaries
1. Enantioselective enolate alkylation



1) Installation of auxiliary



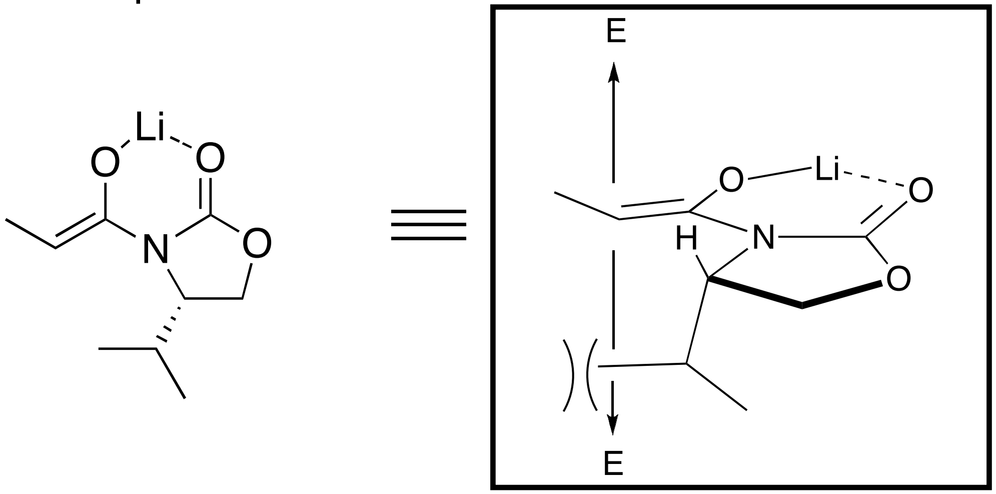
2) Reaction with chiral induction



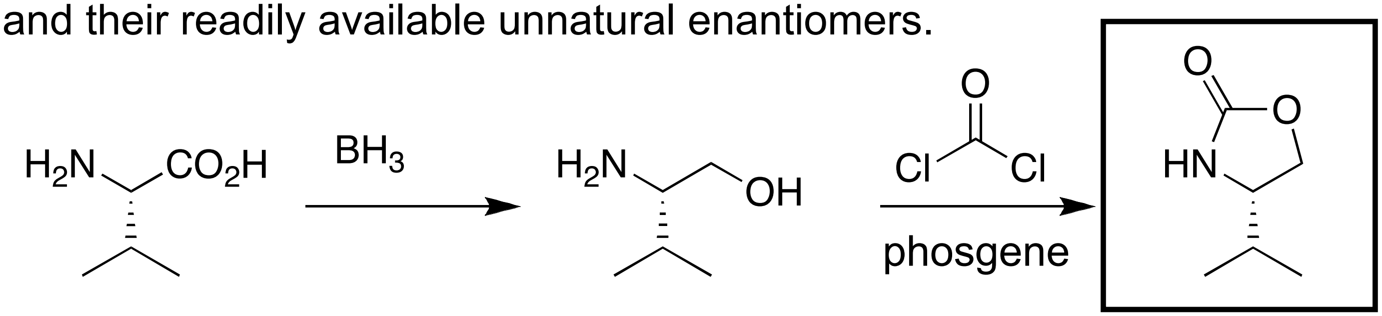
3) Removal of auxiliary

More on Evans' chiral oxazolidinones

A) A 3D model helps understand the observed chiral induction.



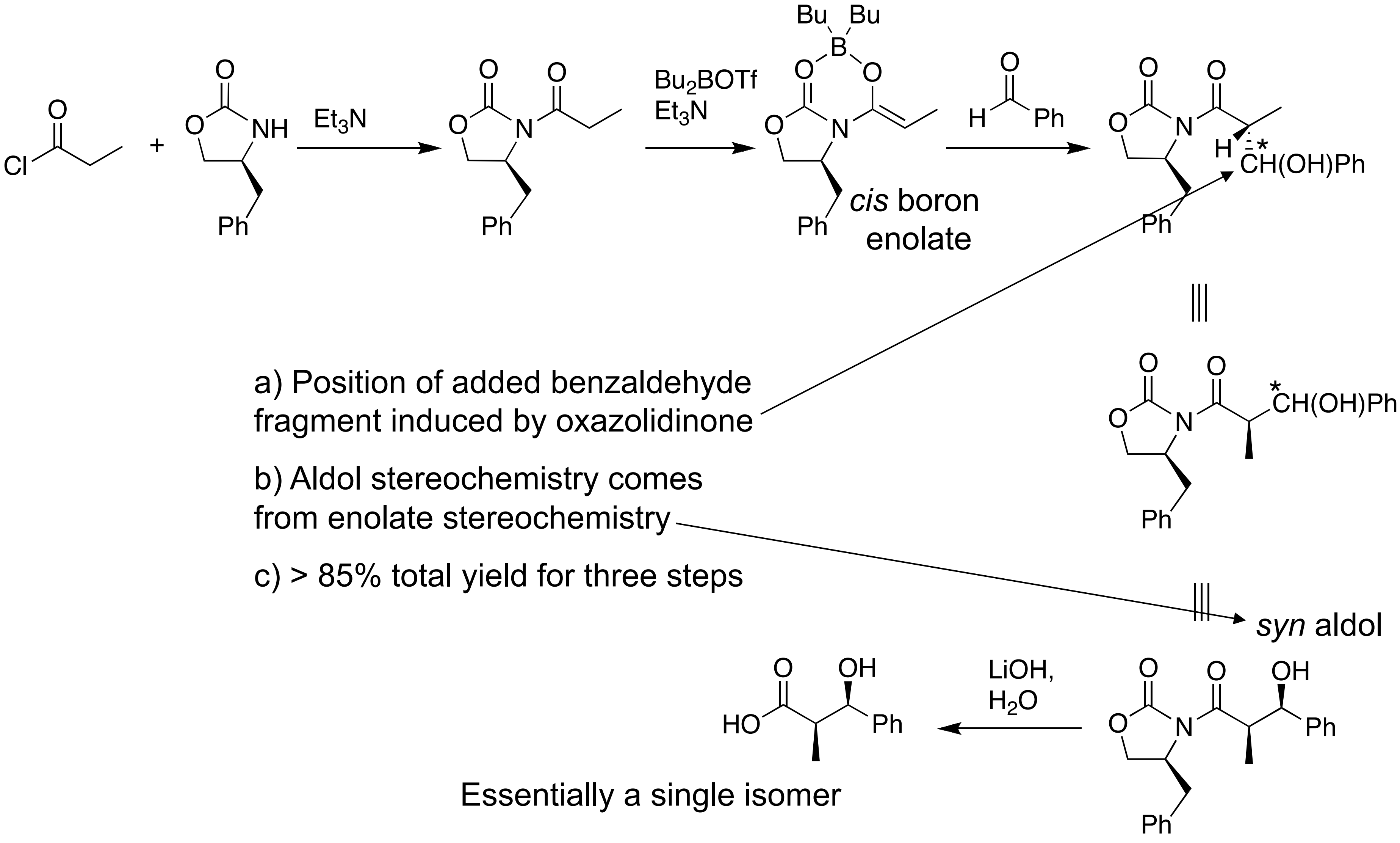
B) Many related chiral oxazolidinones are easily prepared from naturally occuring amino acids and their readily available unnatural enantiomers.



L-Valine

L-Valinol

Enantiopure oxazolidinones as chiral auxiliaries
2. Enantioselective aldol reactions



a) Position of added benzaldehyde fragment induced by oxazolidinone

b) Aldol stereochemistry comes from enolate stereochemistry

c) > 85% total yield for three steps

Essentially a single isomer

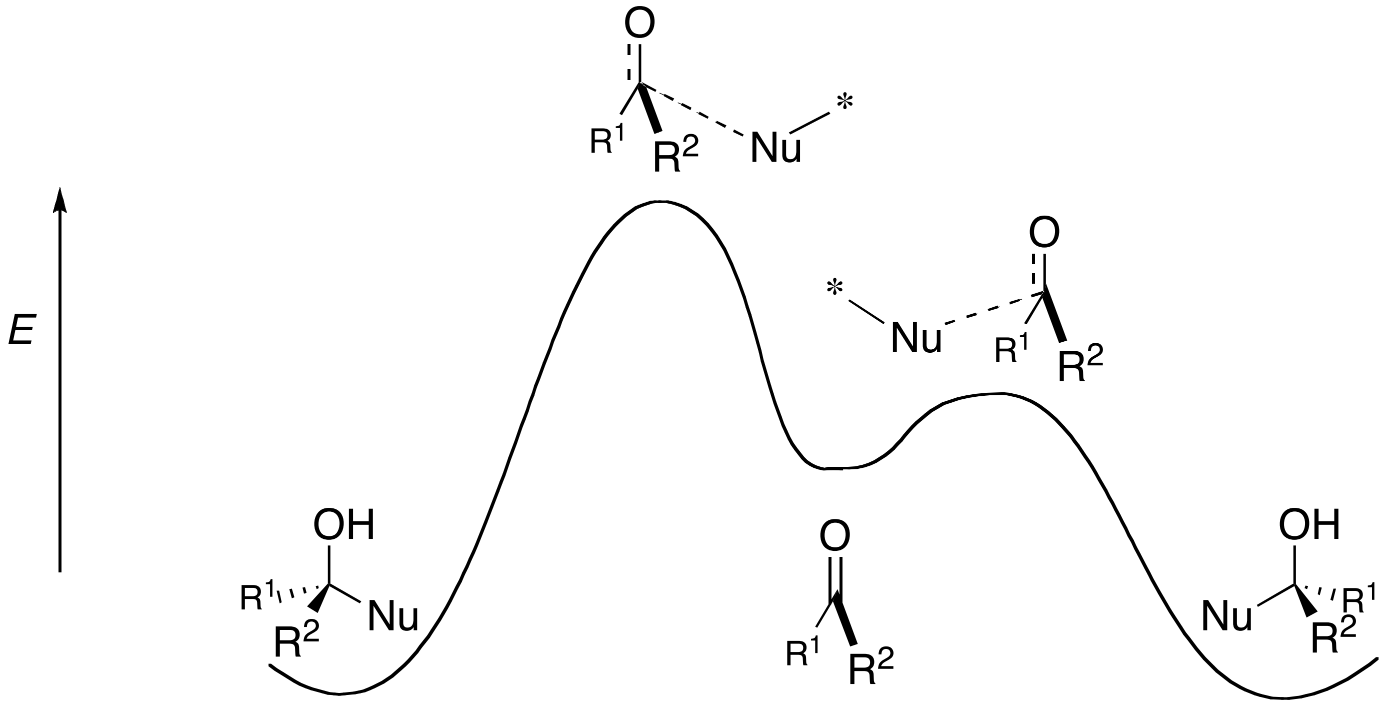
A quick word on enantiomeric excess (ee)

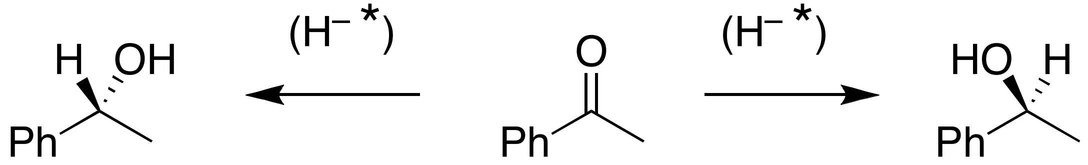
Enantiomeric excess is the most common way to report the level of enantioselectivity observed for a reaction.

The ee is the amount (in %) of one enantiomer present subtracted from the amount of the other, thus…

50:50	0% ee
75:25	50% ee
90:10	80% ee
99:1	98% ee
99.5:0.5	99% ee

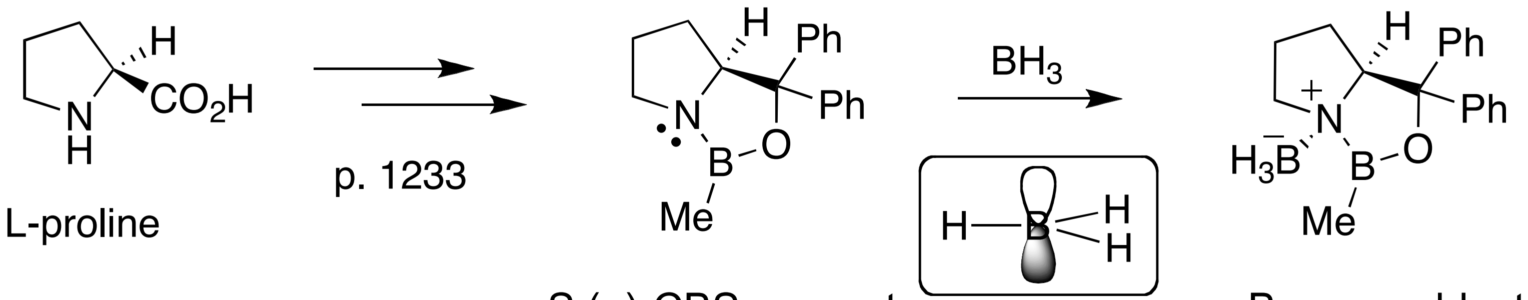
Asymmetric synthesis: chiral catalysts and reagents





Chiral reagents can form energetically different TS's when approaching *prochiral* faces or groups on a molecule, and thus perform enantioselective reactions DIRECTLY on an achiral starting material.

Chiral reductions with Corey-Bakshi-Shibata (CBS) reagent



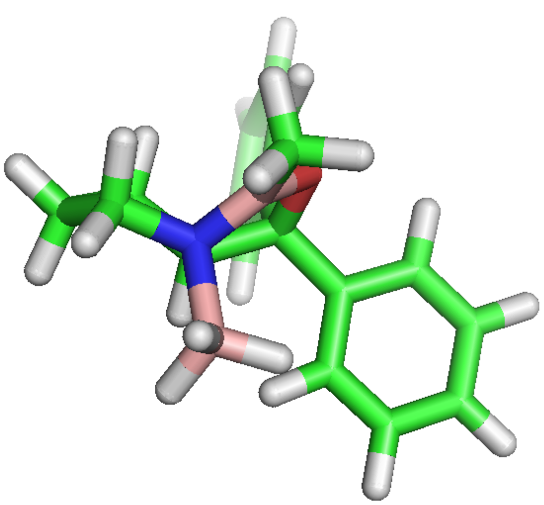
L-proline

S-(–)-CBS reagent

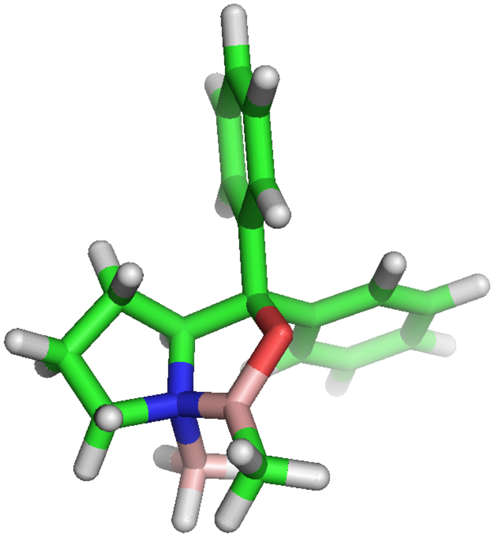
Borane adduct

Elias J. Corey

Nobel prize (1990) for retrosynthetic analysis



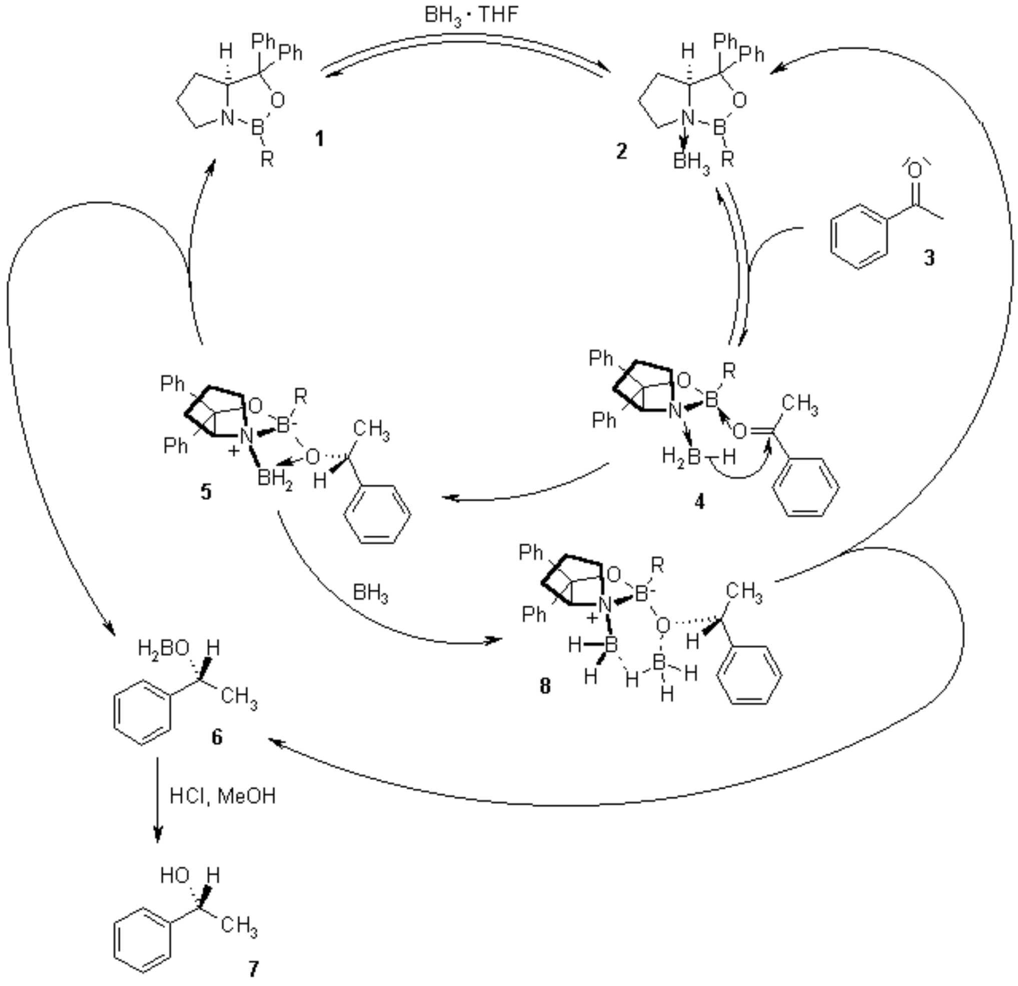
Borane adduct - side view



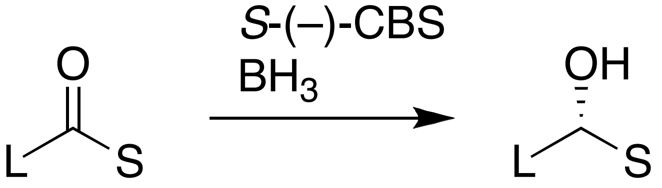
Borane adduct - top view

Predicting the stereochemistry of CBS reductions

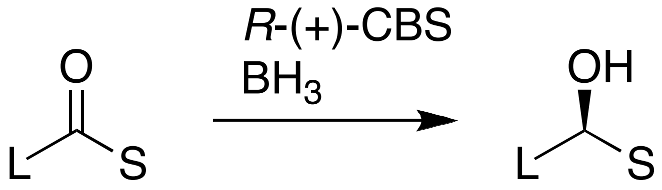
Hard way…



Easy way…

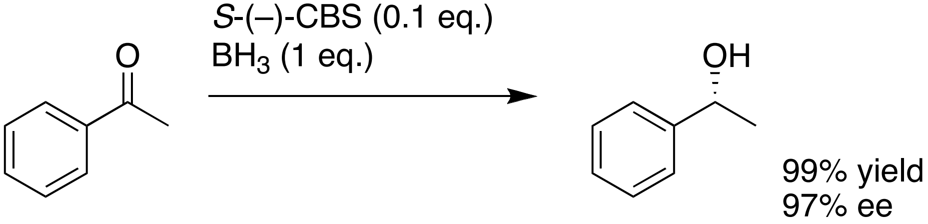


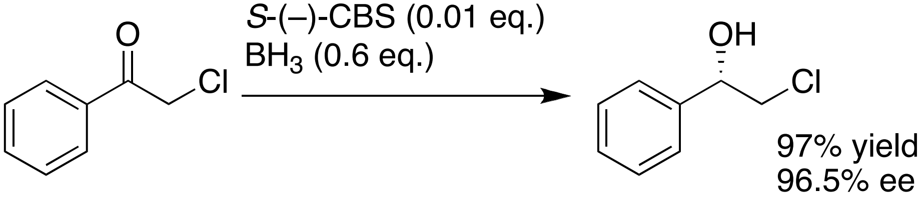
S-(–)-CBS
BH_3



R-(+)-CBS
BH_3

CBS/BH_3 reduction examples…

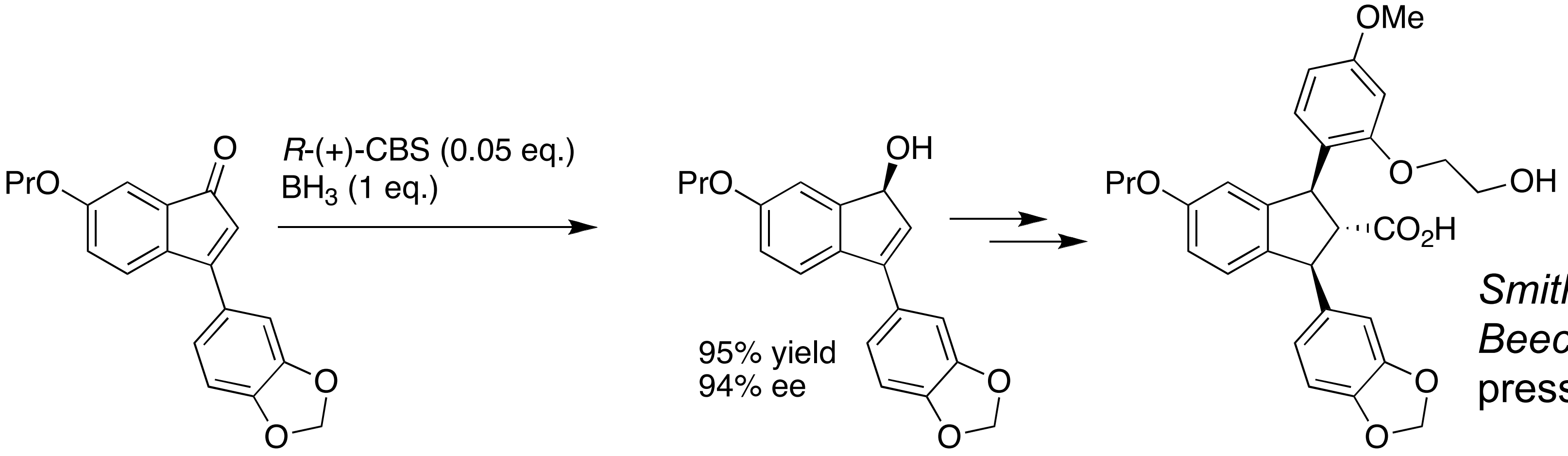




Remember that BH_3 is usually unable to reduce ketones, but it can reduce amides and carboxylic acids because they activate it by first engaging it's empty p-orbital.

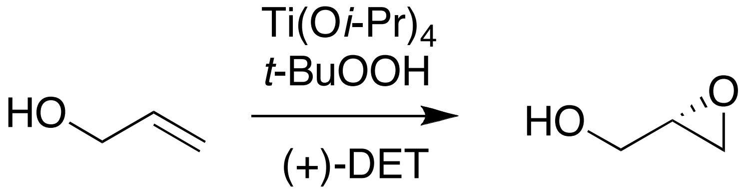
The CBS reagent's amine lone pair fills the borane p-orbital, and the resulting borane adduct is activated enough to make the reduction of ketones possible.

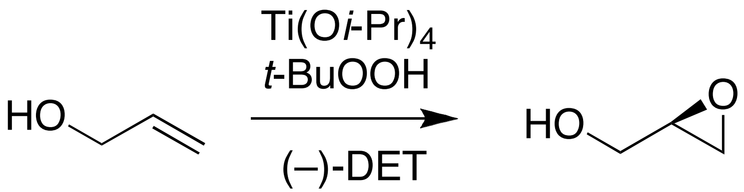
Only catalytic amounts of CBS are required!



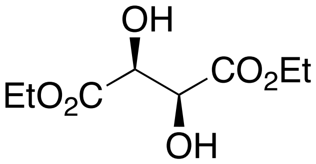
SmithKline Beecham blood pressure drug

Sharpless asymmetric epoxidation (S.A.E.)

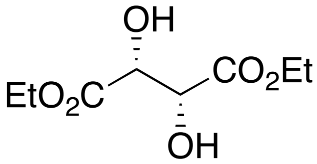




(+)-Diethyl tartrate (DET)



(–)-Diethyl tartrate (DET)



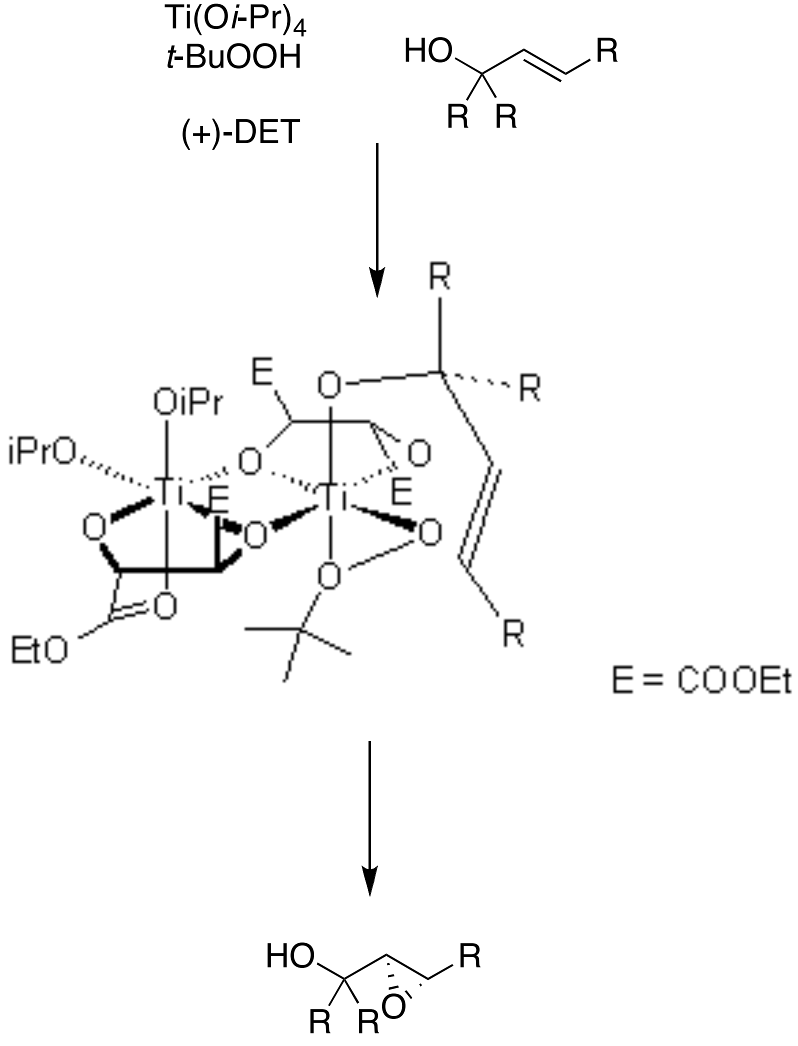
Ti(*i*-PrO)$_4$, the chiral DET, and *t*-BuOOH make a chiral aggregate that coordinates the allyl alcohol and delivers the epoxide selectively to one prochiral face of the alkene.

K. Barry Sharpless

Nobel prize (2001) for catalytic asymmetric oxidations

Predicting the stereochemistry of Sharpless asymmetric epoxidations

Hard way…



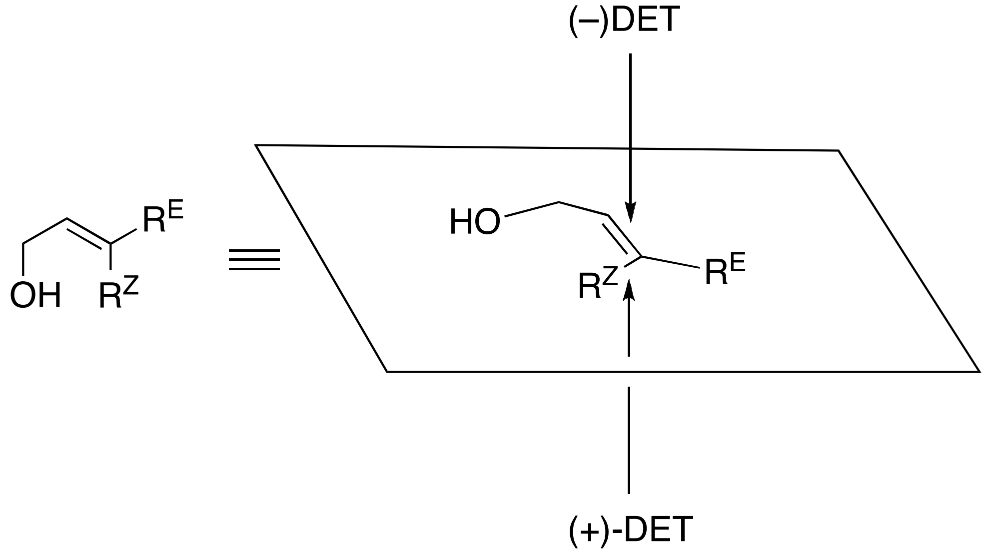
$Ti(O\textit{i}\text{-}Pr)_4$

t-BuOOH

(+)-DET

E = COOEt

Easy way…

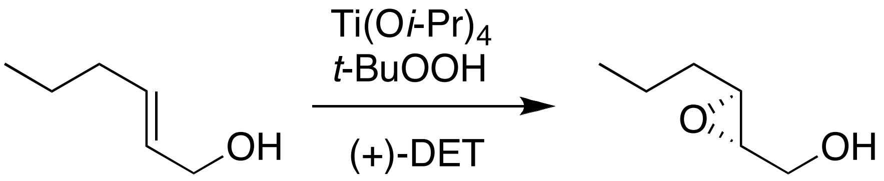


(–)DET

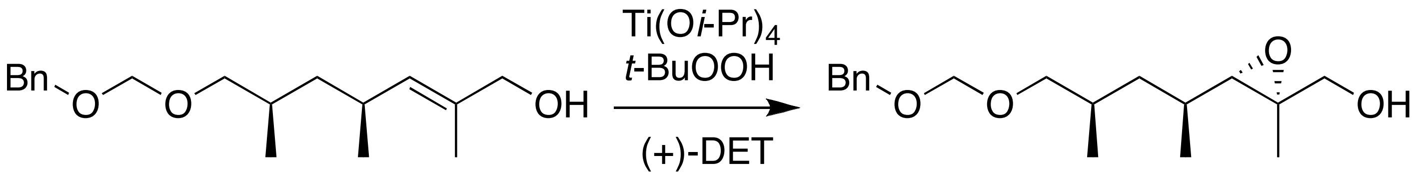
(+)-DET

Alcohol in the top left, (+)-DET delivers from the bottom, (–)-DET delivers from the top.

Sharpless asymmetric epoxidation examples



85% yield
94% ee



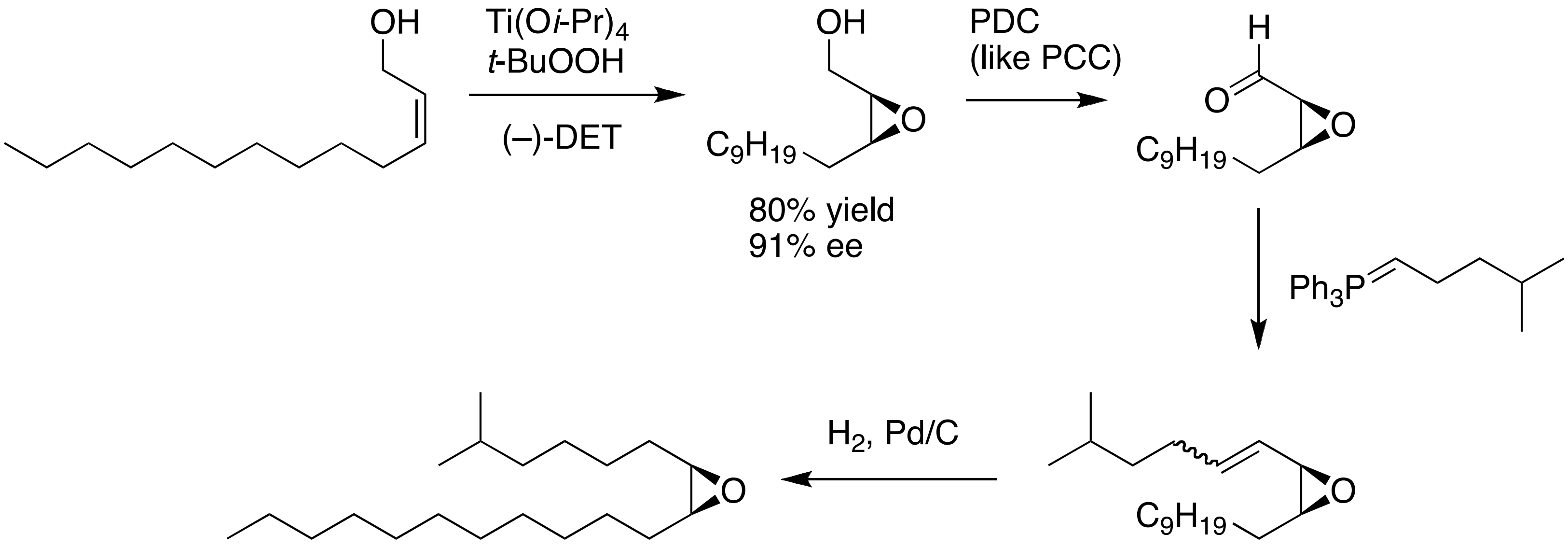
Ti(O*i*-Pr)$_4$ and DET are used catalytically (1–5%), but *t*-BuOOH, as the source of the epoxide oxygen atom, must be used stoichiometrically

Only allylic alcohols are epoxidized by these reagents

Synthesis of gypsy moth pheromone by S.A.E.

Enantiopure (+)-disparlure attracts male gypsy moths to their female mates

A racemic mixture of (±)-disparlure inhibits attraction



(+)-disparlure