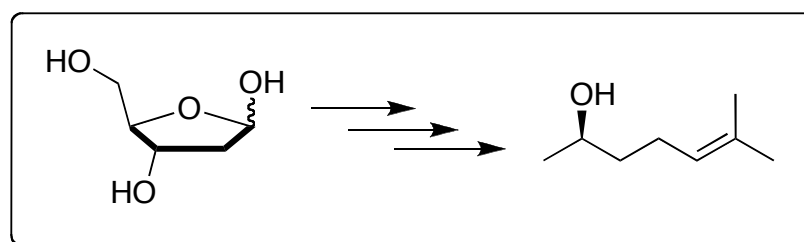
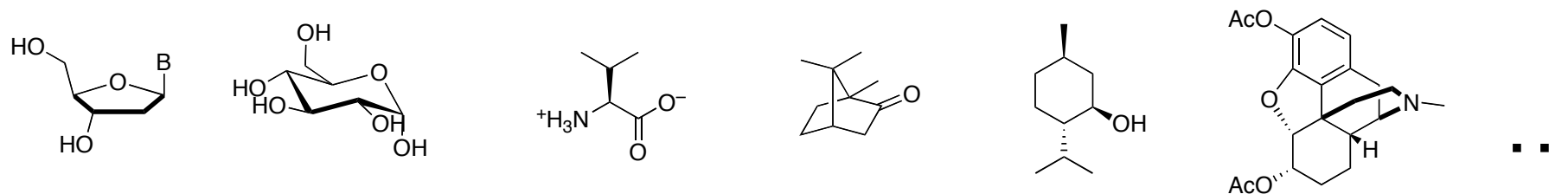


Chapter 45 — Asymmetric synthesis

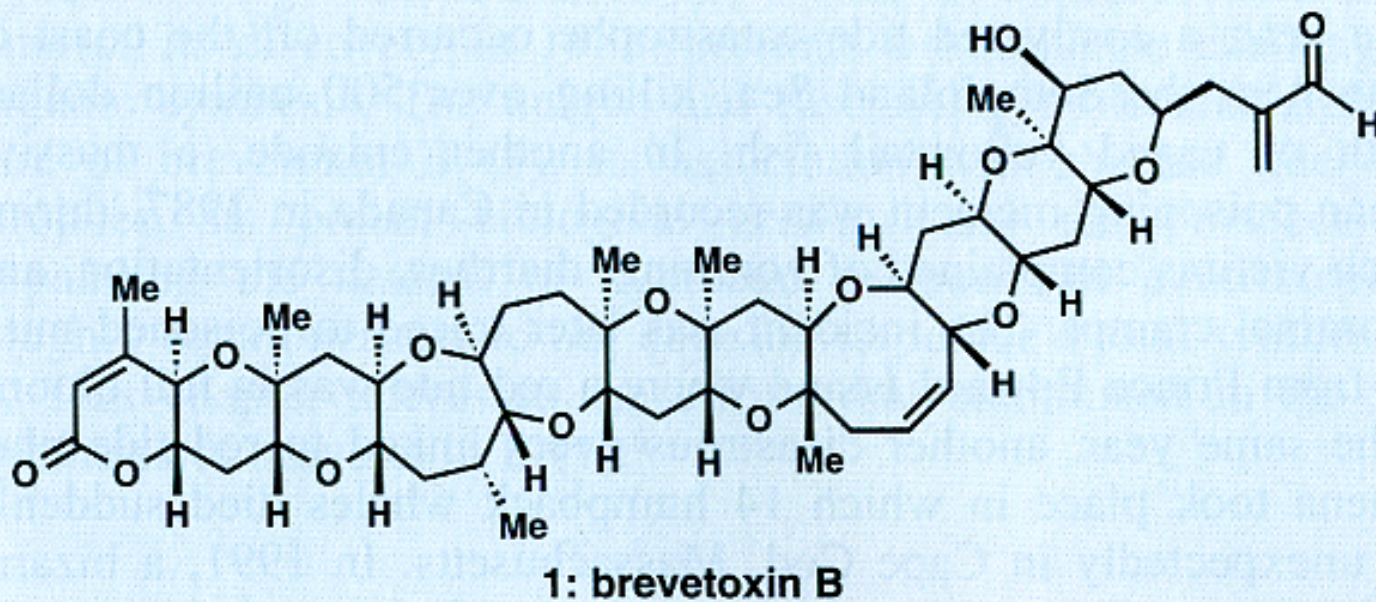
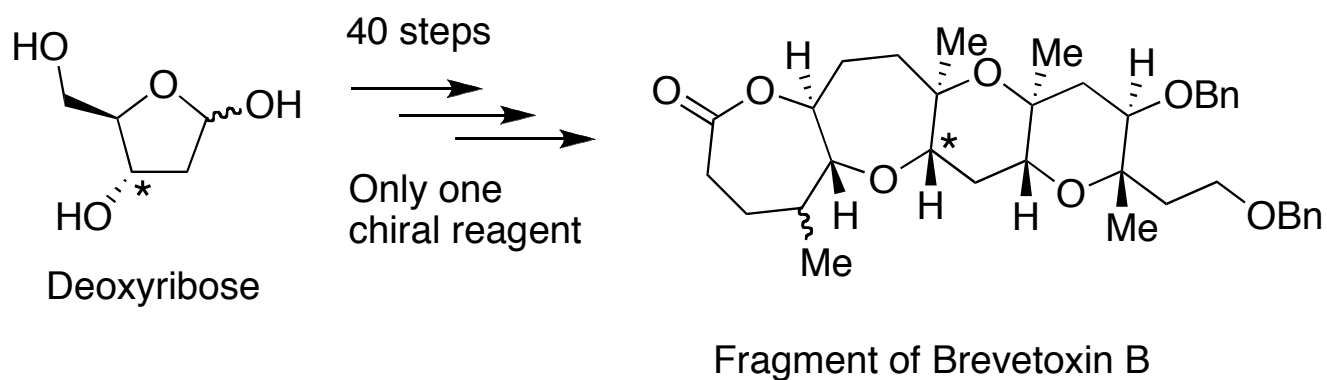
- Pure enantiomers from Nature: the chiral pool and chiral induction
- Asymmetric synthesis: chiral auxiliaries
 - Enolate alkylation
 - Aldol reaction
- Enantiomeric excess (ee)
- Asymmetric synthesis: chiral reagents and catalysts
 - CBS reagent for chiral reductions
 - Sharpless asymmetric epoxidation

Synthesizing pure enantiomers starting from Nature's chiral pool



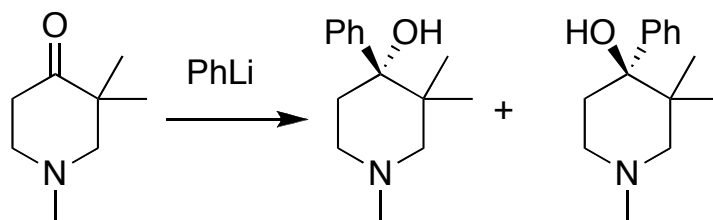
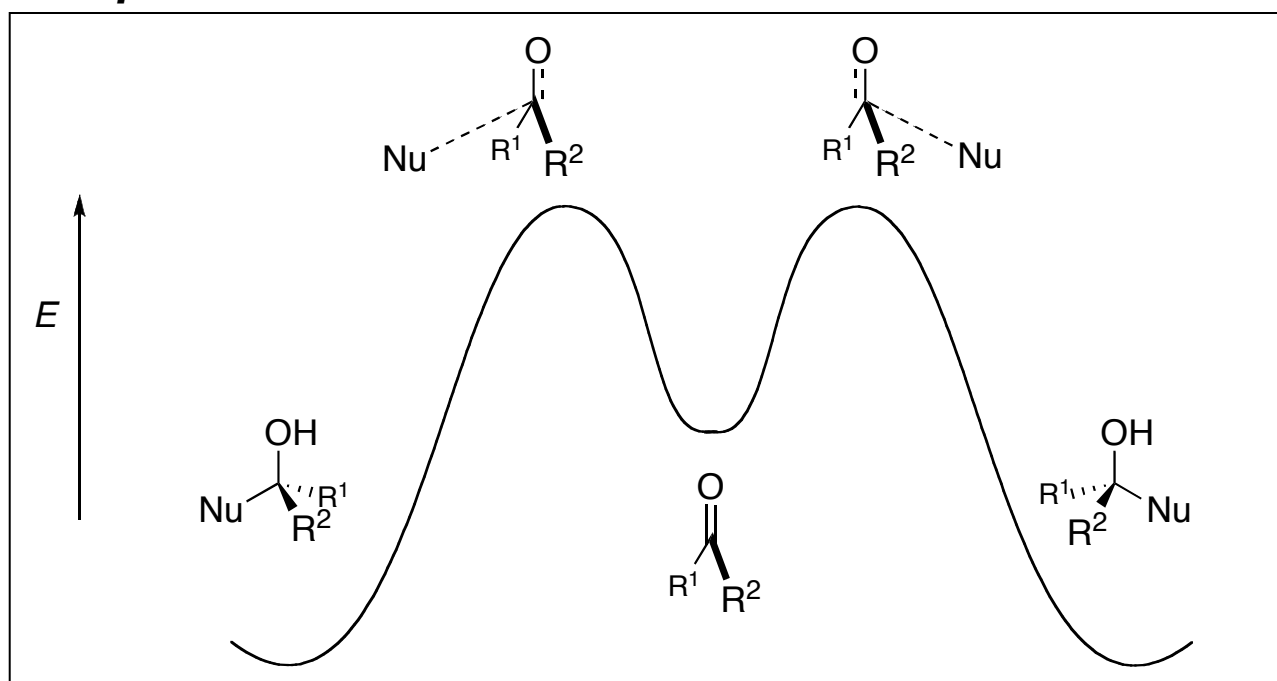
Sulcatol - insect pheromone

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

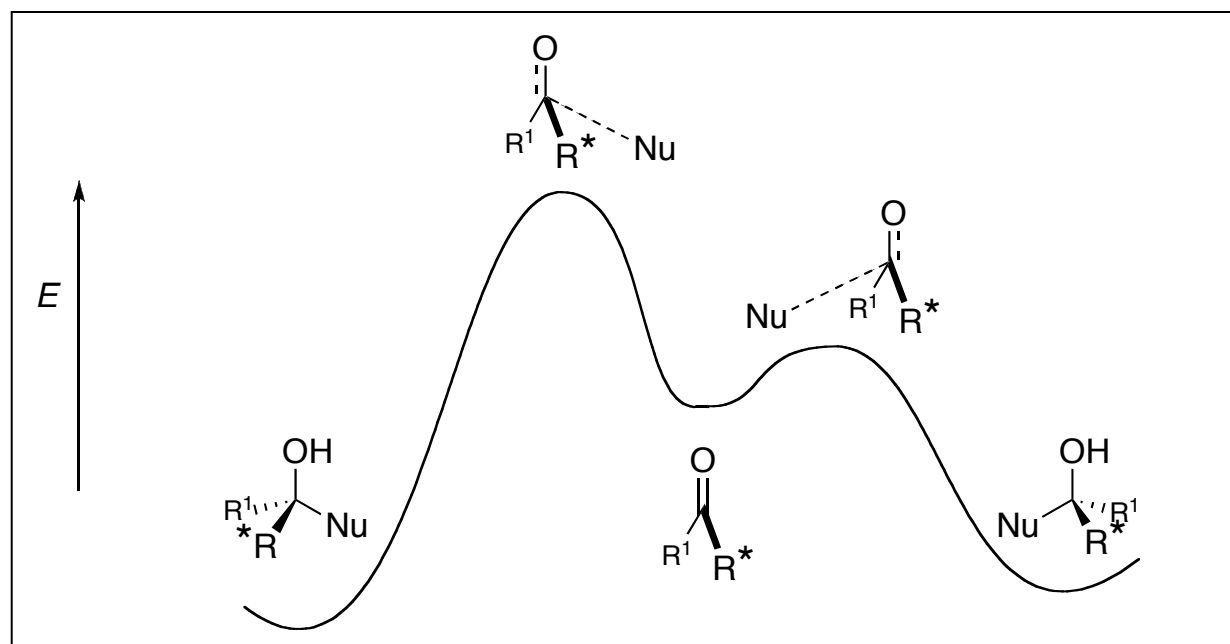


Asymmetric synthesis 1.

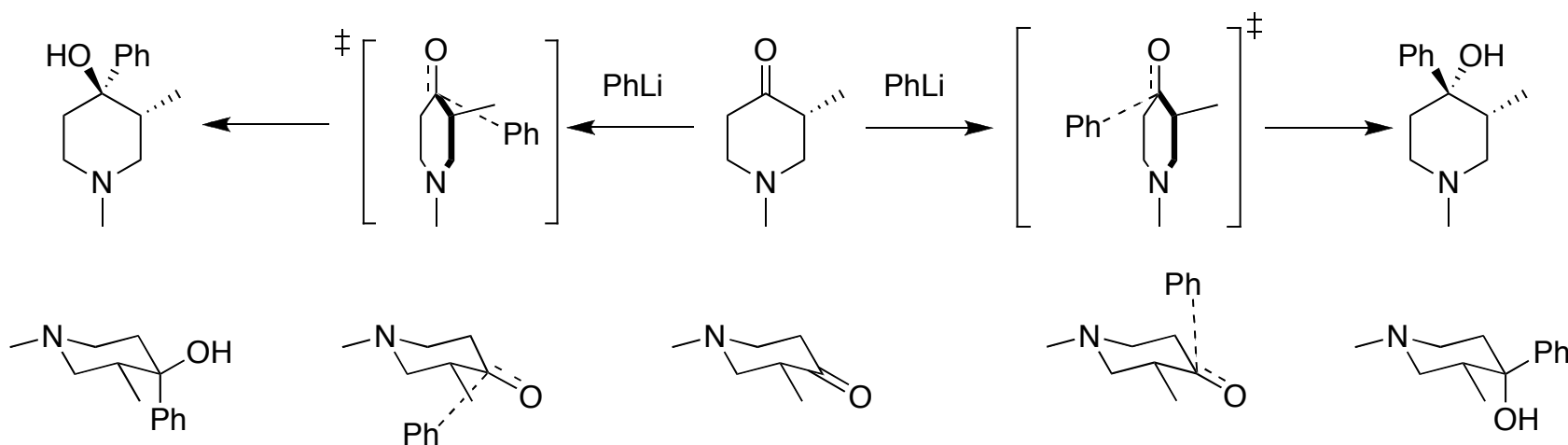
Producing a new stereogenic centre on an achiral molecule makes two enantiomeric transition states **of equal energy**... and therefore two enantiomeric products **in equal amounts**.



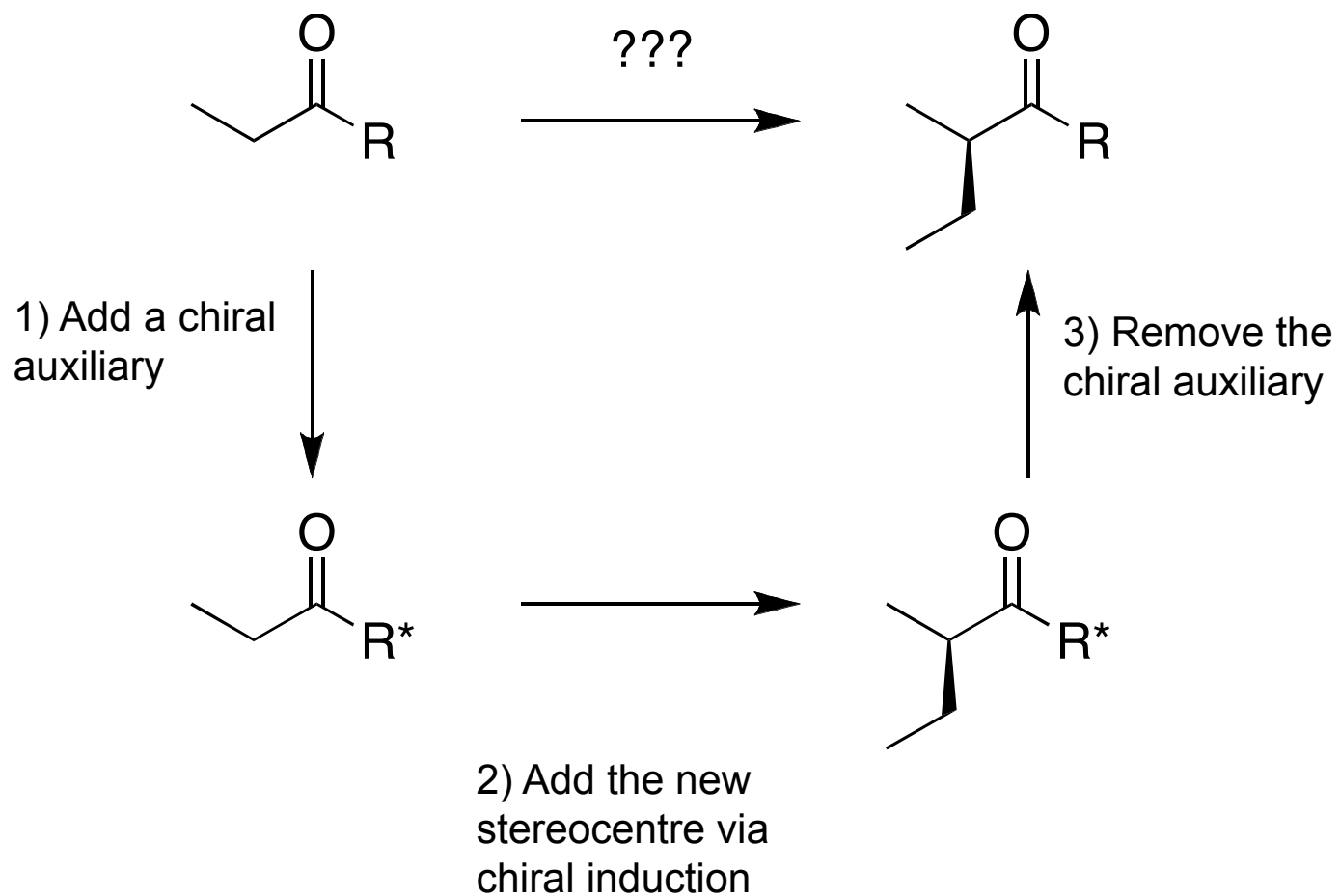
Asymmetric synthesis 2.



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**.

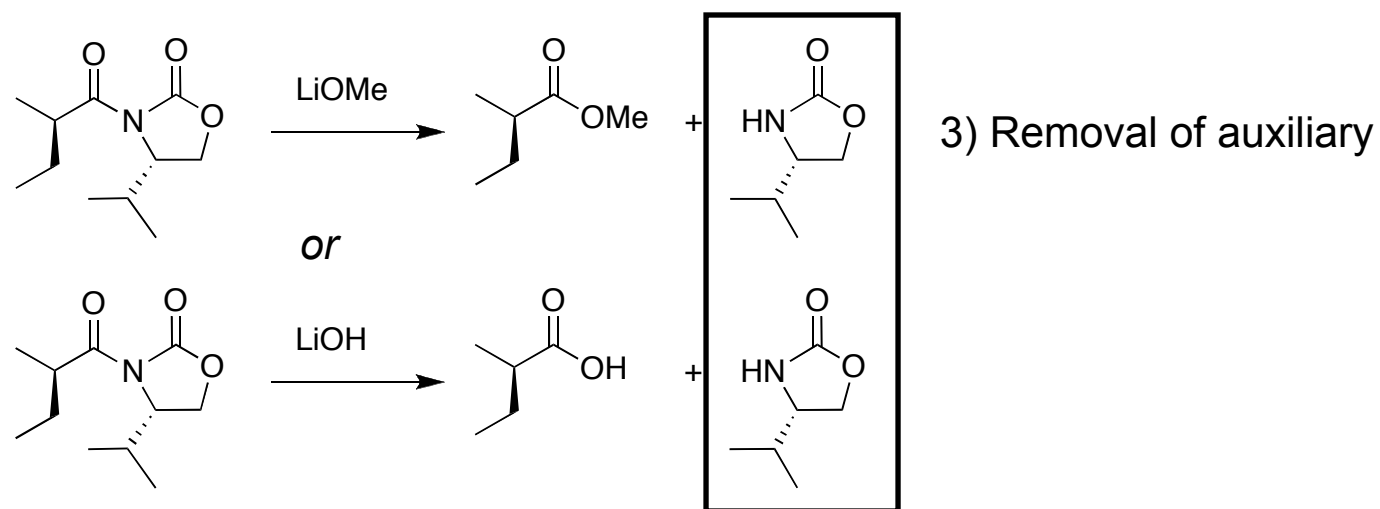
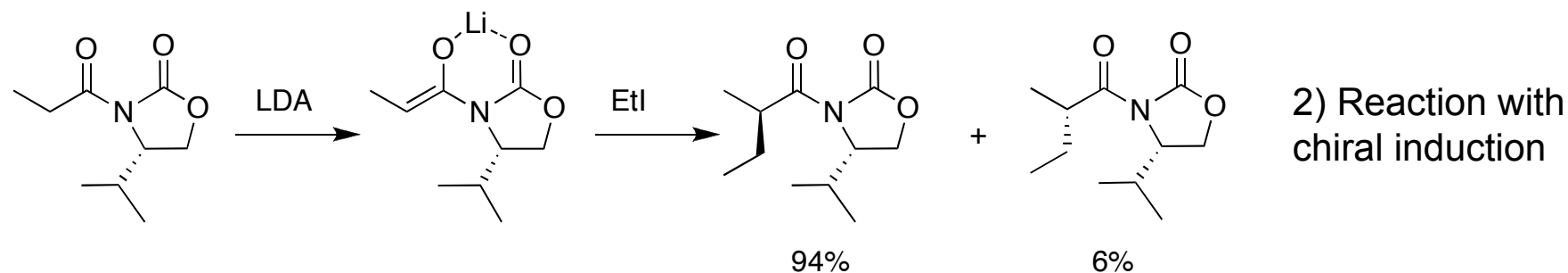
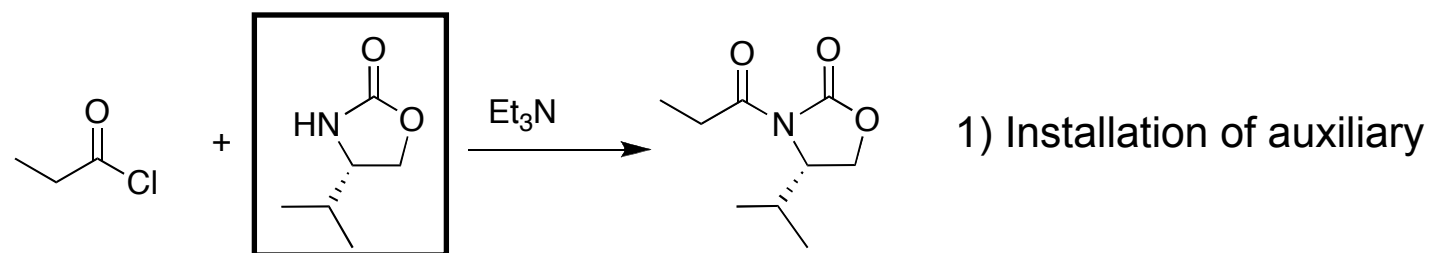


A removable chiral centre... synthesis with chiral auxiliaries



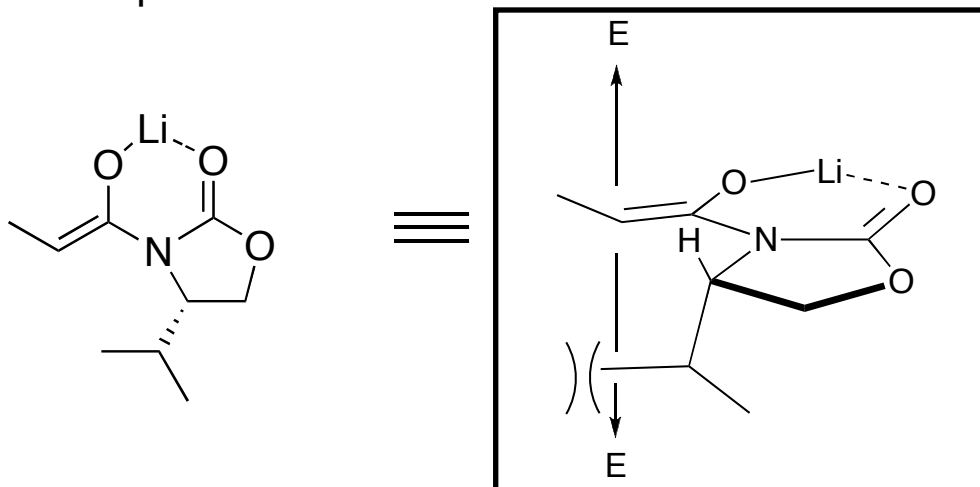
Enantiopure oxazolidinones as chiral auxiliaries

1. Enantioselective enolate alkylation

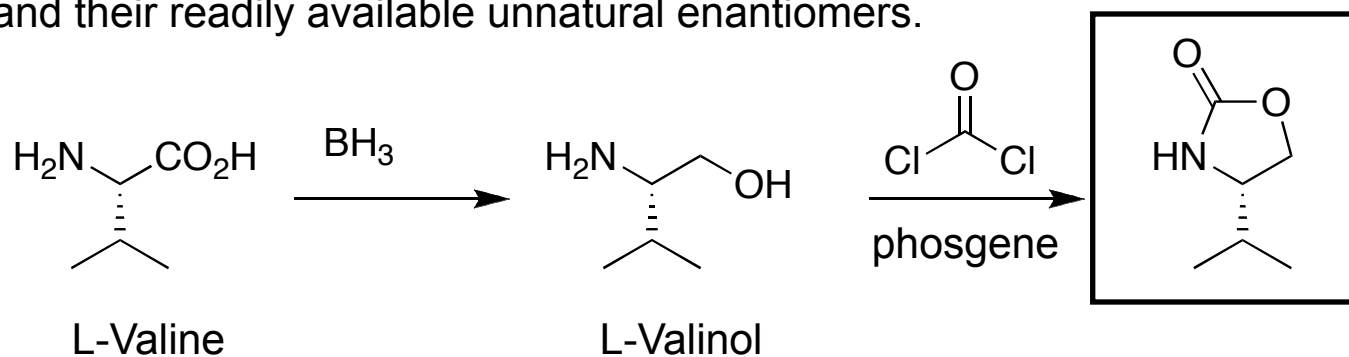


More on Evans' chiral oxazolidinones

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

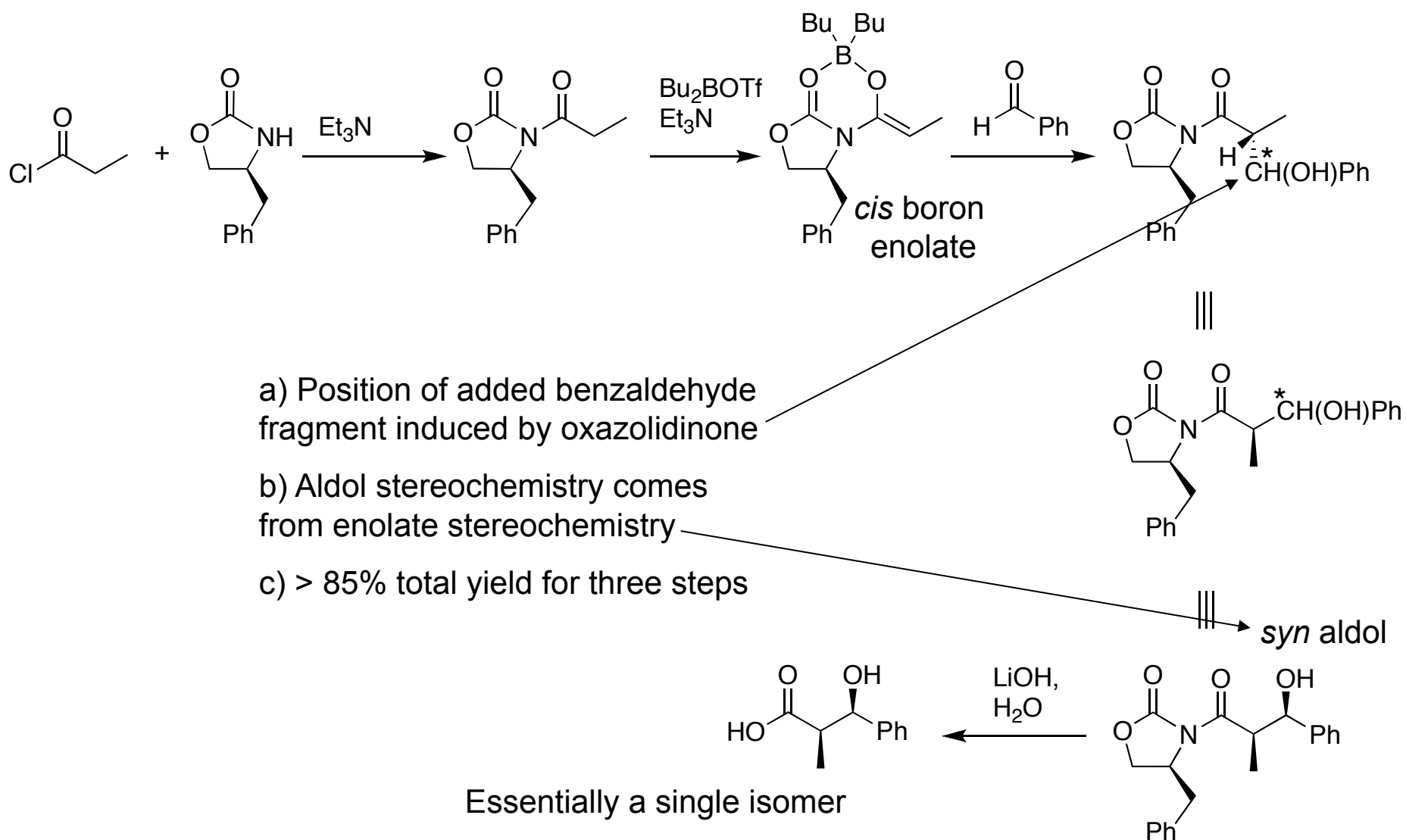


B) Many related chiral oxazolidinones are easily prepared from naturally occurring amino acids and their readily available unnatural enantiomers.



Enantiopure oxazolidinones as chiral auxiliaries

2. Enantioselective aldol reactions



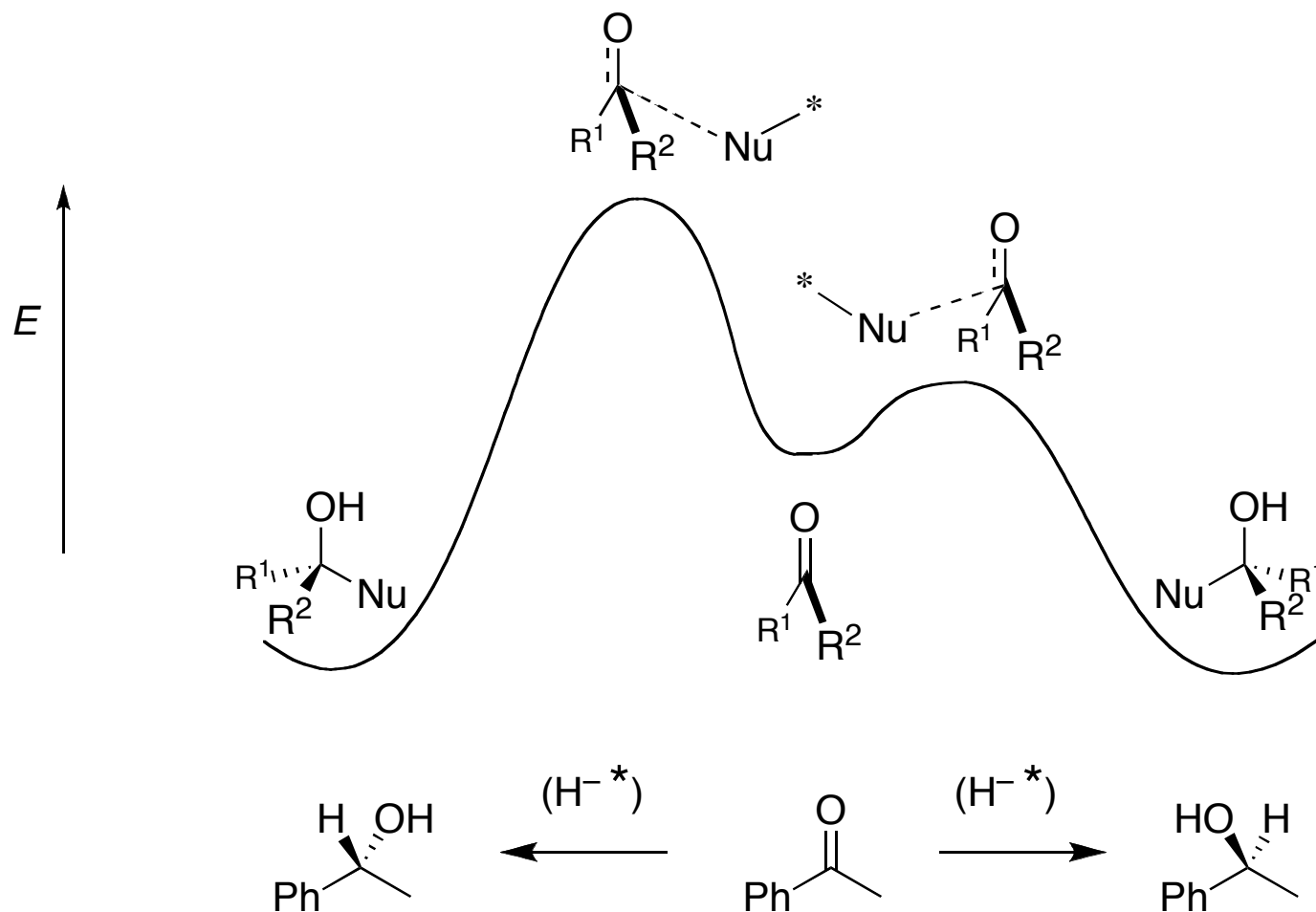
A quick word on enantiomeric excess (ee)

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...

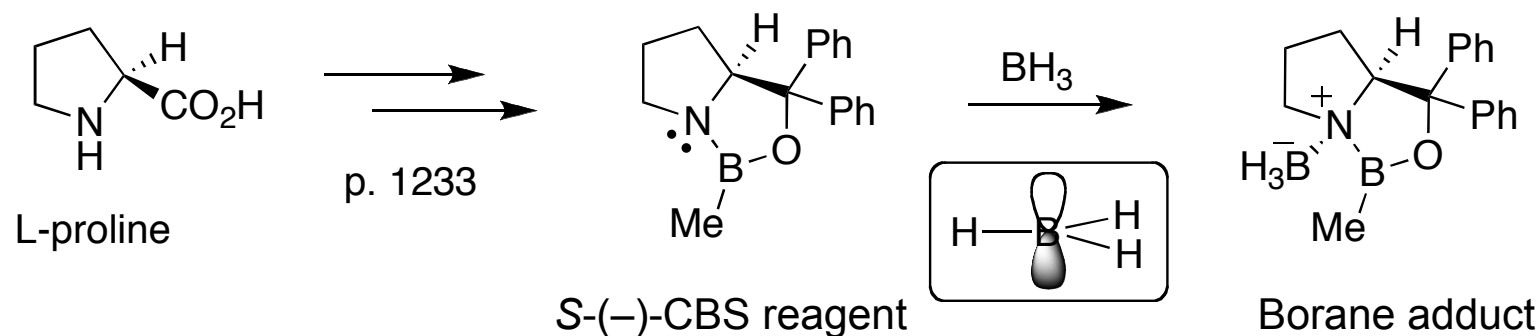
50:50	0% ee
75:25	50% ee
90:10	80% ee
99:1	98% ee
99.5:0.5	99% ee

Asymmetric synthesis: chiral catalysts and reagents

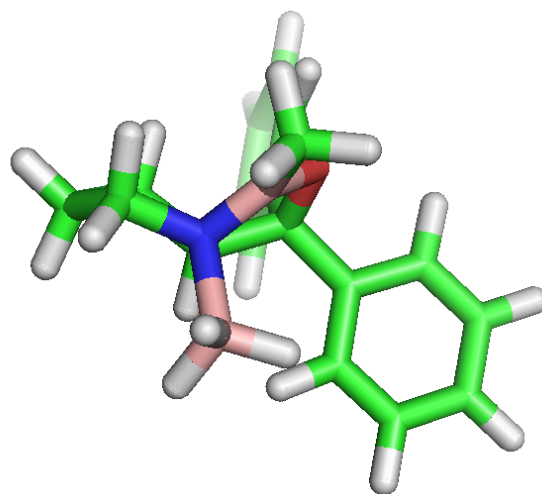


Chiral reagents can form energetically different TS's when approaching *prochiral* faces or groups on a molecule, and thus perform enantioselective reactions DIRECTLY on an achiral starting material.

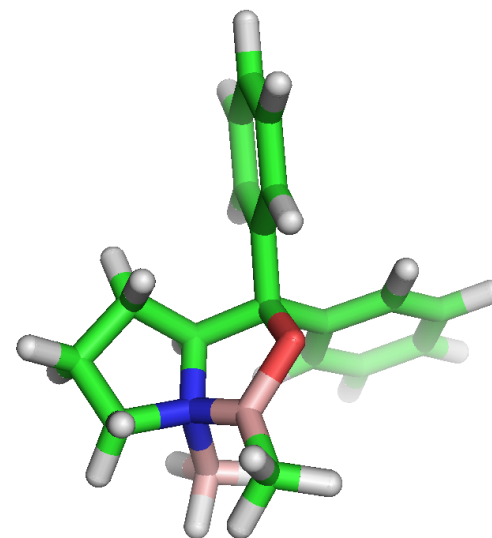
Chiral reductions with Corey-Bakshi-Shibata (CBS) reagent



Elias J. Corey
Nobel prize (1990)
for retrosynthetic
analysis



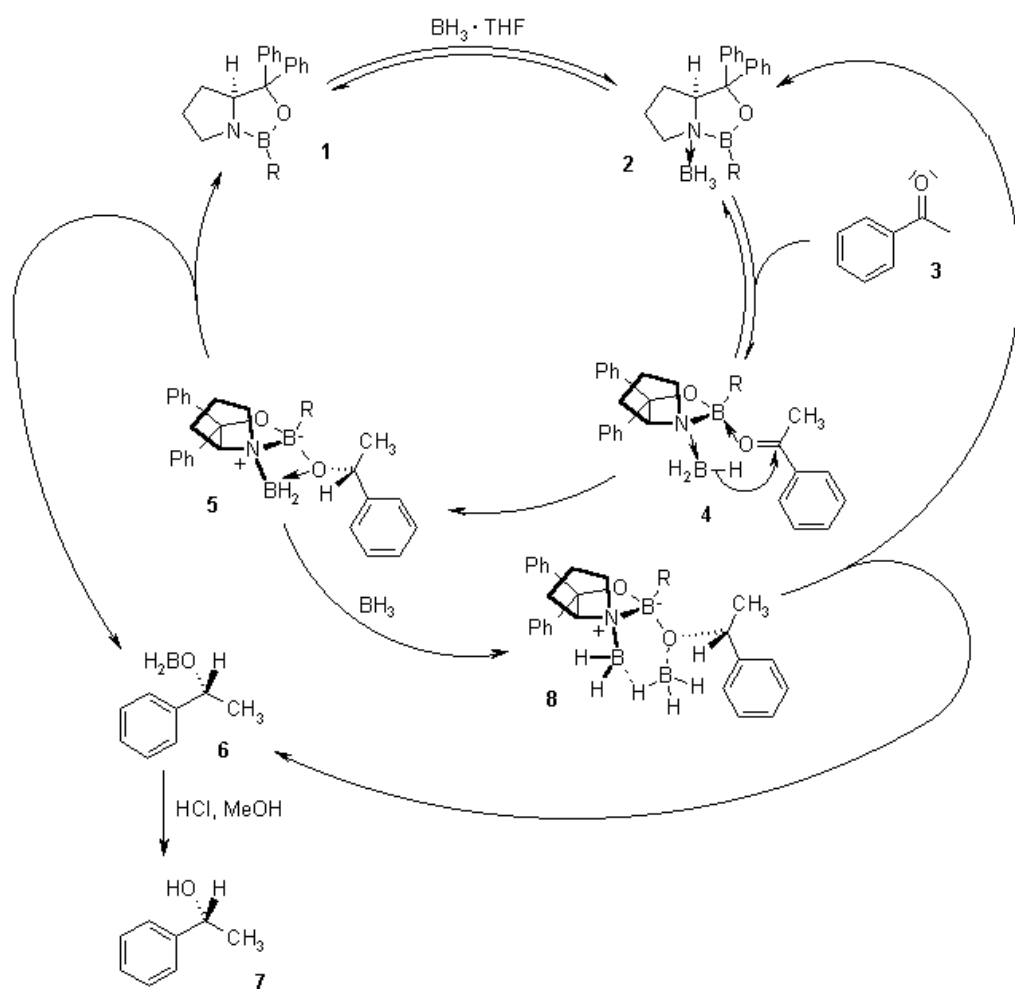
Borane adduct - side view



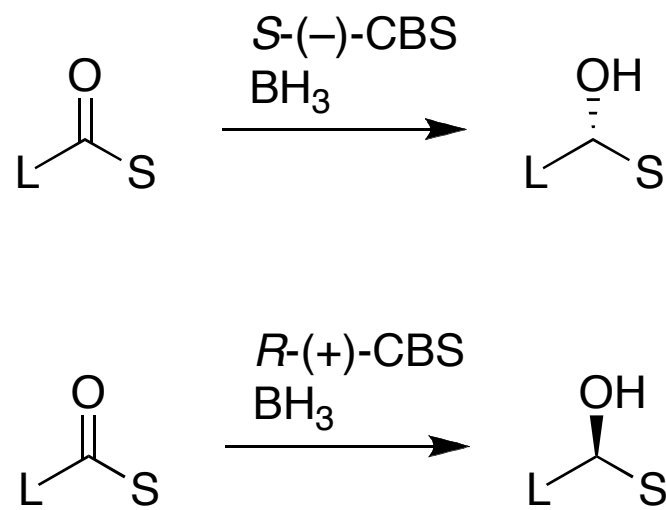
Borane adduct - top view

Predicting the stereochemistry of CBS reductions

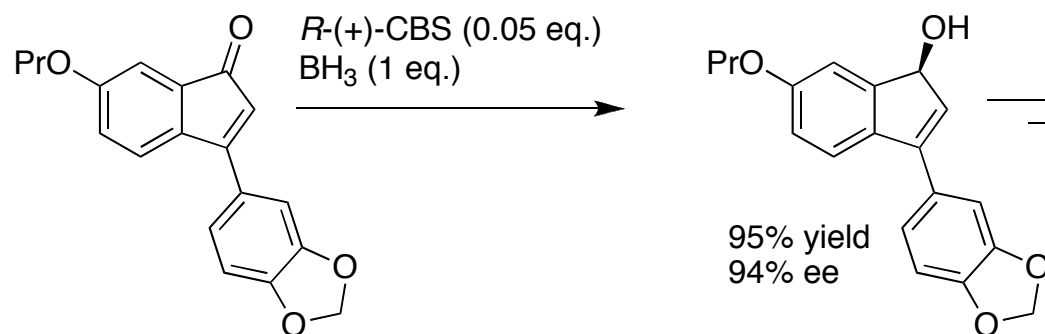
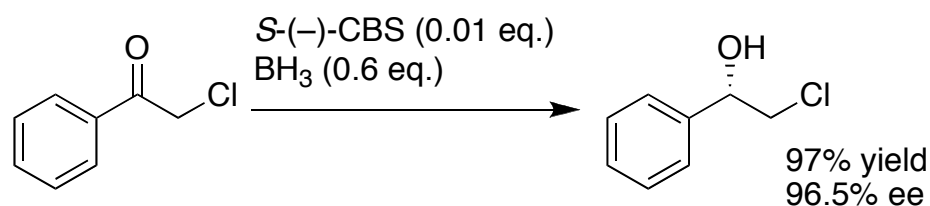
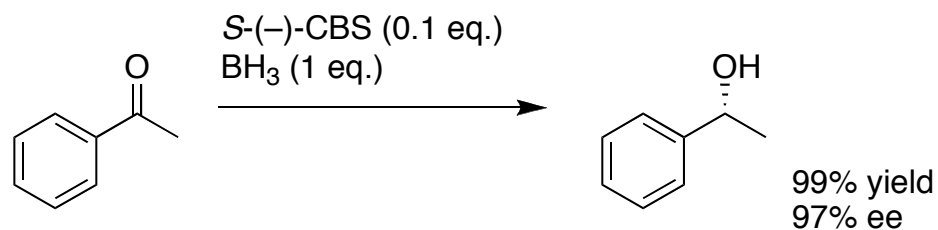
Hard way...



Easy way...



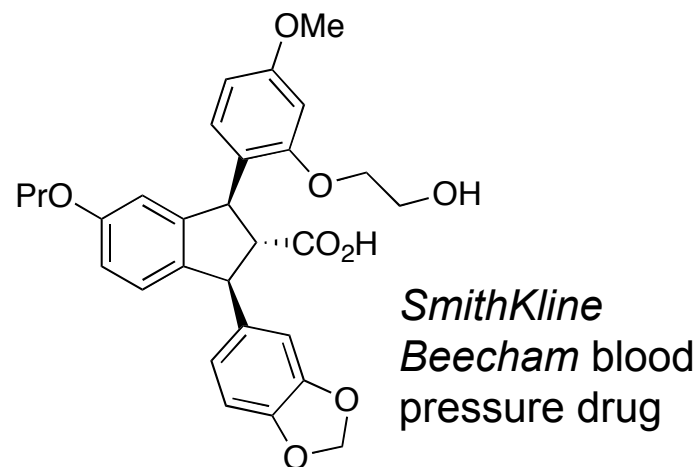
CBS/ BH_3 reduction examples...



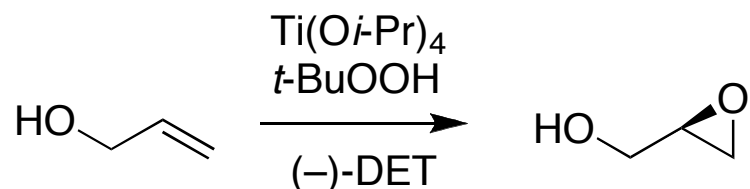
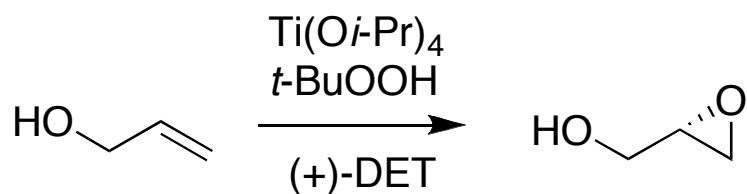
Remember that BH_3 is usually unable to reduce ketones, but it can reduce amides and carboxylic acids because they activate it by first engaging its empty p-orbital.

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.

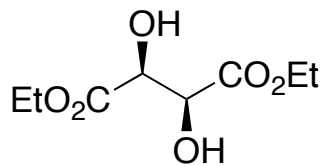
Only catalytic amounts of CBS are required!



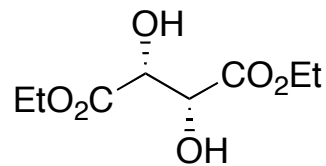
Sharpless asymmetric epoxidation (S.A.E.)



(+)-Diethyl tartrate (DET)



(-)-Diethyl tartrate (DET)



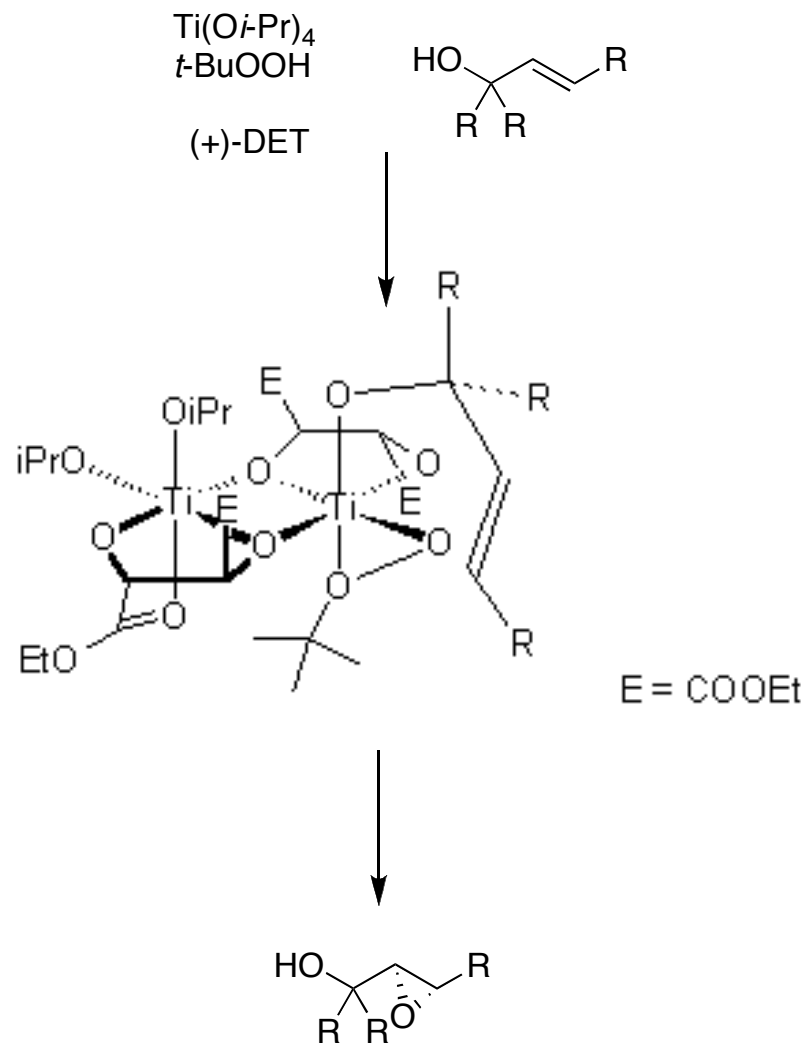
Ti(*i*-PrO)₄, the chiral DET, and *t*-BuOOH make a chiral aggregate that coordinates the allyl alcohol and delivers the epoxide selectively to one prochiral face of the alkene.

K. Barry Sharpless

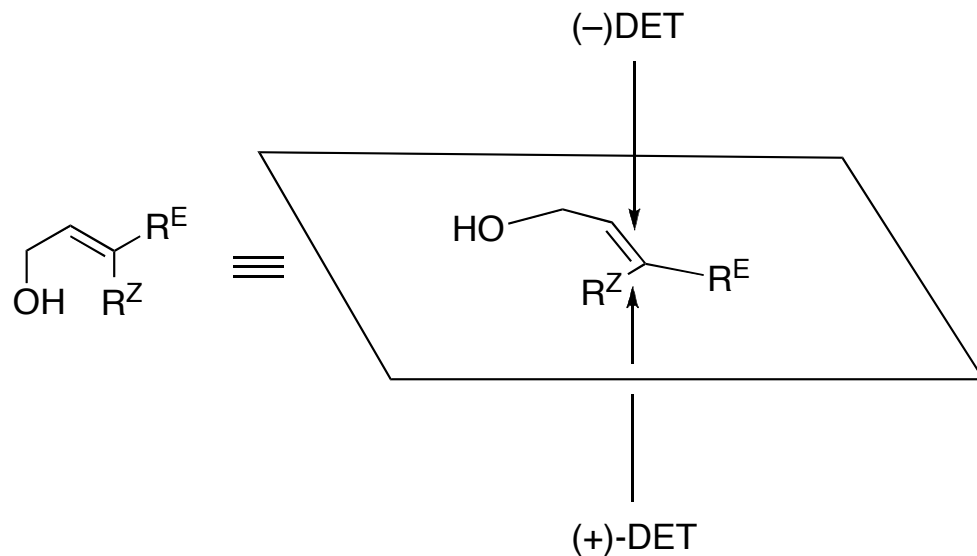
Nobel prize (2001) for
catalytic asymmetric
oxidations

Predicting the stereochemistry of Sharpless asymmetric epoxidations

Hard way...

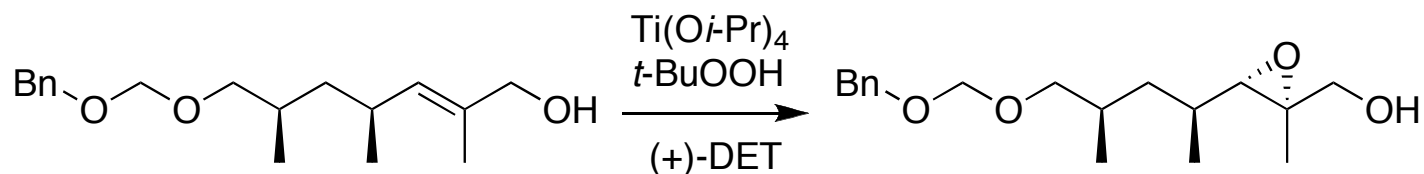
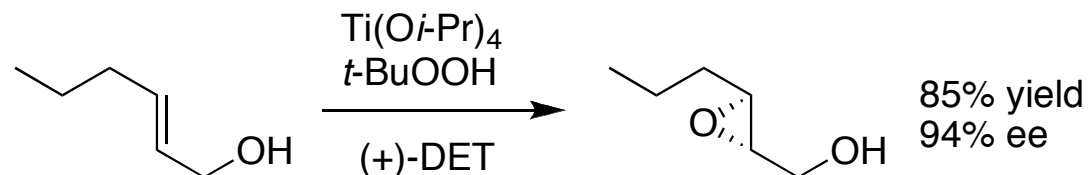


Easy way...



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

Sharpless asymmetric epoxidation examples



$\text{Ti}(\text{O}i\text{-Pr})_4$ and DET are used catalytically (1–5%), but $t\text{-BuOOH}$, 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 (\pm)-disparlure inhibits attraction

