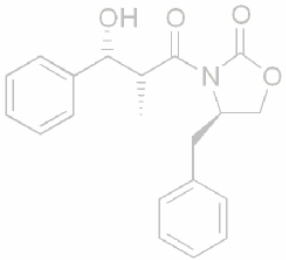
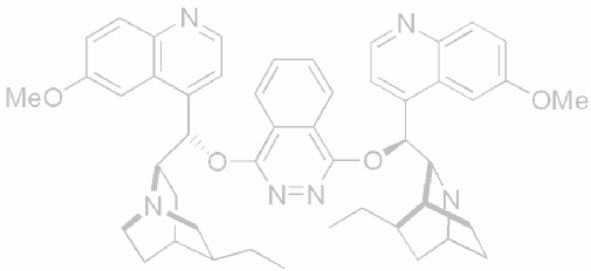
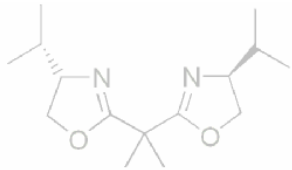
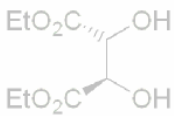
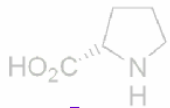
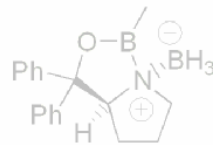
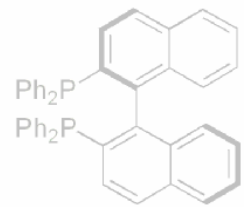
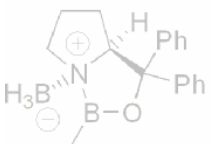
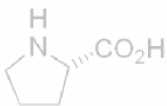
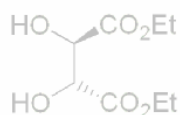
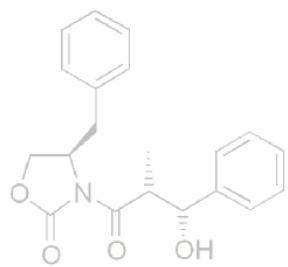
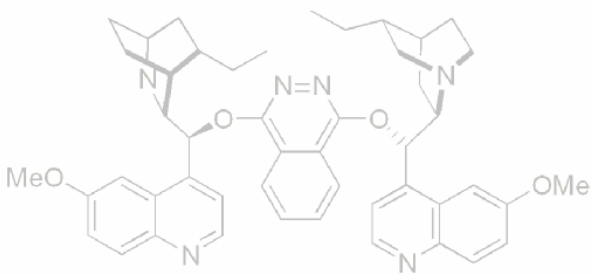
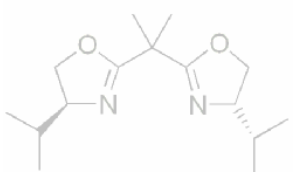







Asymmetric Synthesis

Dr. Paul A. Clarke

Room C170

Resources

‘Organic Chemistry’ by Clayden, Greeves, Warren and Wothers.

‘Asymmetric Synthesis’ by Gary Procter.

‘Stereoselectivity in Organic Synthesis’ by Gary Procter (Oxford primer)

http://www.york.ac.uk/res/pac/teaching/asymsyn.html

Scope of the Course

In the time available we will look at how synthetic chemists have developed methods for the synthesis of single enantiomers of chiral molecules. A brief introduction to the synthesis of single enantiomers and asymmetric synthesis will be given. This will be followed by an analysis of the several strategies for asymmetric synthesis. Particular emphasis will be placed on understanding the origins of the enantioselectivity of each transformation and on their use in the synthesis of single enantiomers of natural product targets.

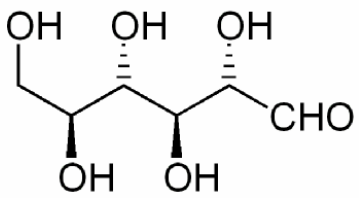
Learning Objectives

1) To gain an appreciation of the types of asymmetric reactions which may be employed in organic synthesis.

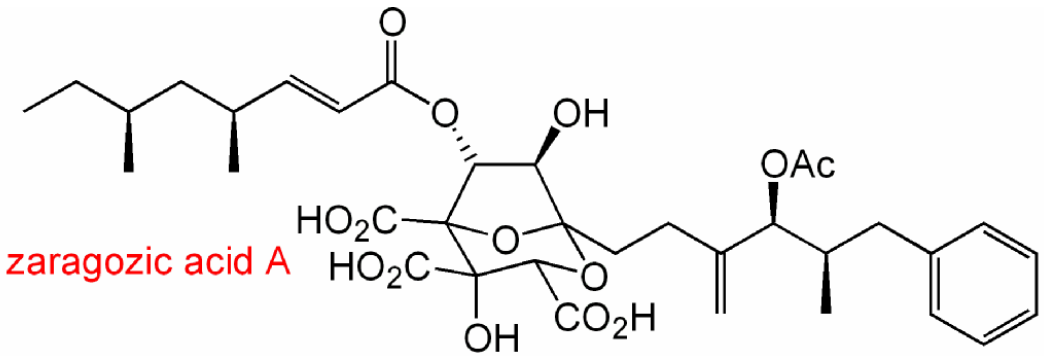
2) To an understand the origins of the enantioselectivities and the mechanisms of the reactions.

3) To be able to propose asymmetric syntheses of organic molecules of medium complexity.

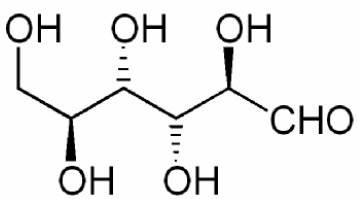
Examples of Natural Products Constructed by the use of Asymmetric Synthesis



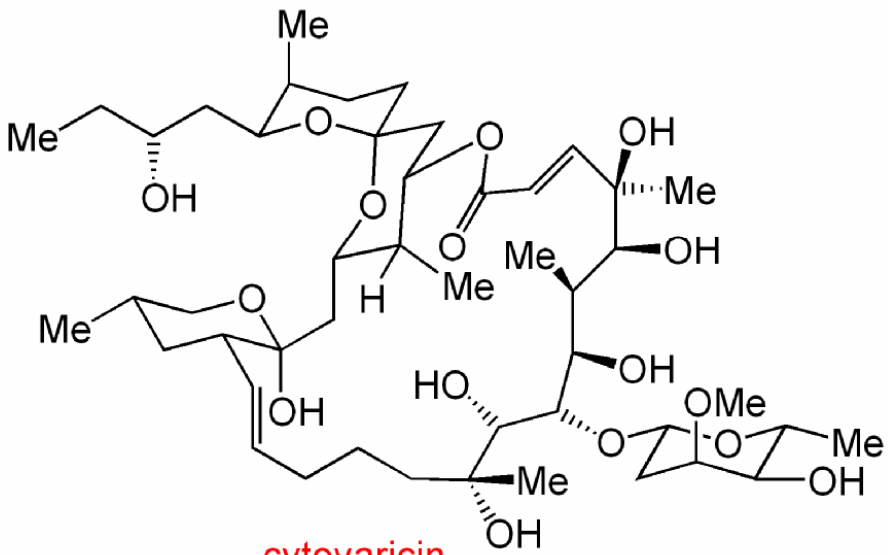
L- allose



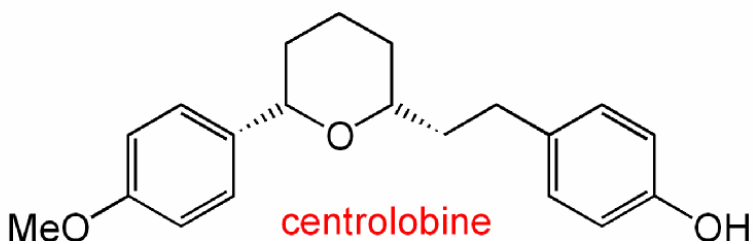
zaragozic acid A



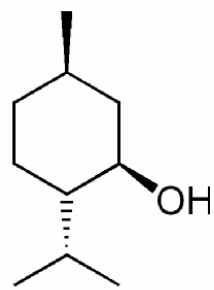
L- mannose



cytovaricin



centrolobine



(-)-menthol

Course Outline

Introduction to Asymmetric Synthesis.

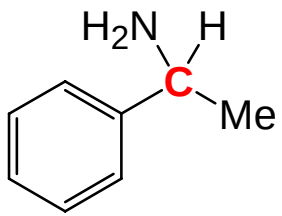
Use of Chiral Auxiliaries:
Evans's alkylation

Use of Chiral Reagents:
Hydroboration and Allylboranes

Use of Chiral Catalysts:
Reduction of Ketones
Hydrogenation of Olefins
Sharpless Epoxidation and Dihydroxylation
Organocatalysis

Introduction to Asymmetric Synthesis

Chirality: A molecule is chiral if it is non-superimposable on its mirror image. Any molecule which is chiral can exisit as two enantiomers. Two enantiomers have the same properties (*i.e*. NMR, solubility, melting point, etc., except in the presence of other chiral molecules or in their interaction with plan polarised light.



stereogenic carbon
as 4 different groups
molecule is chiral

optical rotation is **equal** and **opposite** for enantiomers

redraw

Enantiomers have **every** stereogenic centre with inverted stereochemistry as long as you draw the molecule in the same orientation.

Diastereoisomer (diastereomer): Is a stereoisomer of a chiral molecule which is **not** an enantiomer. Diastereomers have different properties (*i.e*: NMR, melting points, solubilities, etc.)

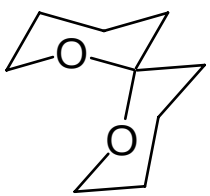
enantiomers: every stereogenic centre has been inverted.

diastereomers as only one stereogenic centre has been inverted.

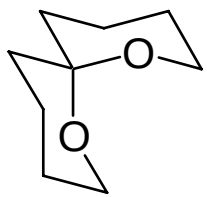
Asymmetric Synthesis:

The ability to synthesis single enantiomers of chiral molecules is important as different enantiomers can interact with biological receptors very differently. For example:

olive fly sex pheromones

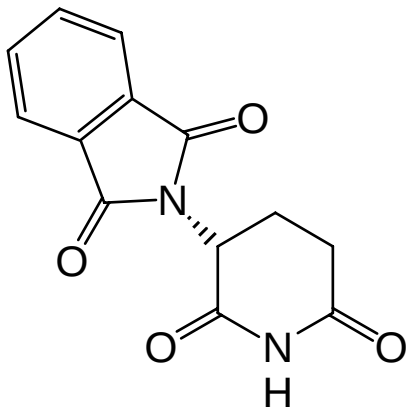


attracts Males

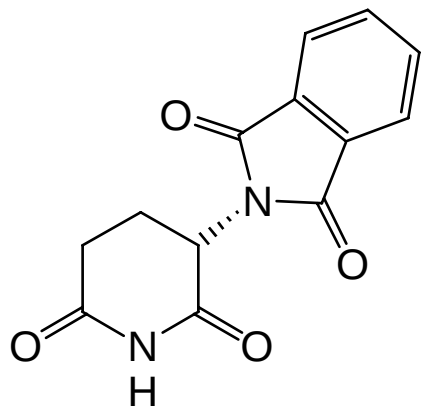


attracts Females

thalidomide



sedative for
morning sickness



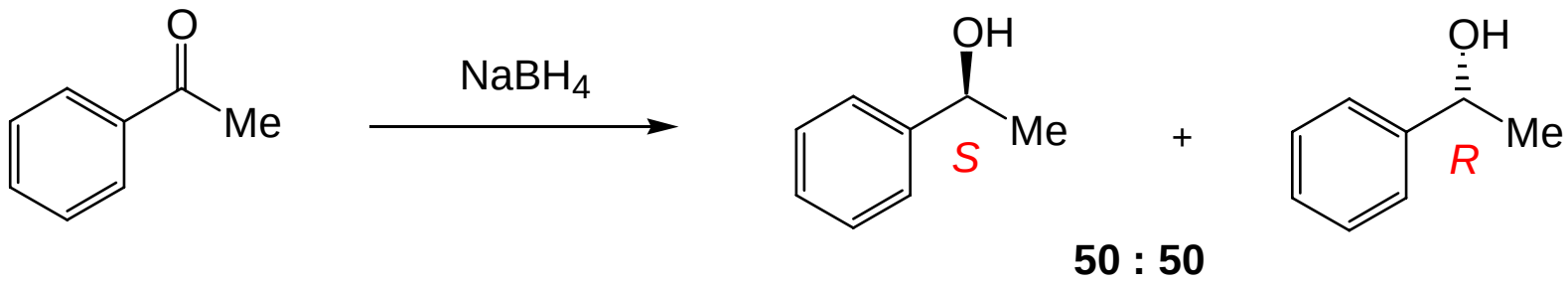
causes foetal defects

The efficiency of an enantioselective or diastereoselective reaction is given by either the enantiomeric excess (e.e.) or diastereomeric excess (d.e.) respectively.

The amounts of the major and minor diastereomers can be easily obtained from ^{1}H NMR spectra, HPLC or GC traces.

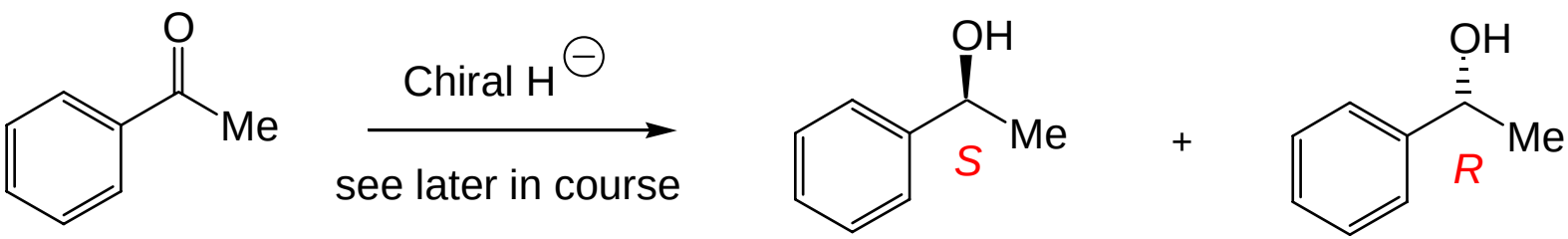
The amounts of the major or minor enantiomers are more difficult to determine as chiral NMR shift reagents, chiral HPLC or GC stationary phases must be used.

Racemic Reaction



50 : 50

Asymmetric Reaction



97.5 : 2.5

Prior to asymmetric synthesis there were two ‘classical’ ways of constructing molecules as single enantiomers.

Resolution:

This is usually achieved by formation of a diastereomeric mixture of salts by the reaction of the racemate with an enantiomerically pure acid or base. Followed by crystallisation of one of the diastereomeric salts. However, this is not very efficient as the maximum yield of the desired enantiomer after ‘cracking’ the salt is 50%.

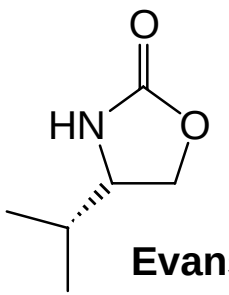
Chiral Pool:

However, these two strategies are beyond the scope of this lecture course. Although you should be familiar with them from earlier in the course and from additional reading.

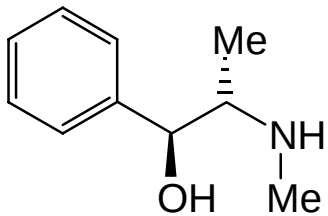
Chiral Auxiliaries: Evans Alkylation

Chiral Auxiliary: A chiral control element temporarily incorporated into the structure of the substrate in order to direct the stereochemistry at new stereogenic centre(s) formed in a reaction. The auxiliary is removed (either immediately during work up or in a separate subsequent step) and may be recovered for re-use. Some examples are given below.

Alkylation of enolates

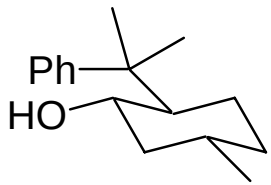


Evans



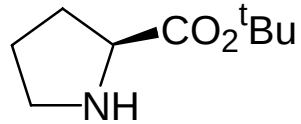
Myers

Diels-Alder

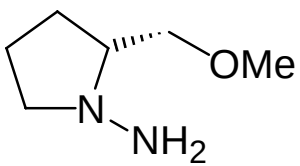


8-phenylmenthol

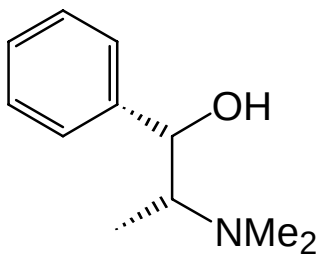
Enamine addition



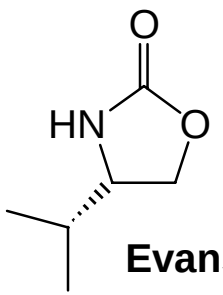
proline ester



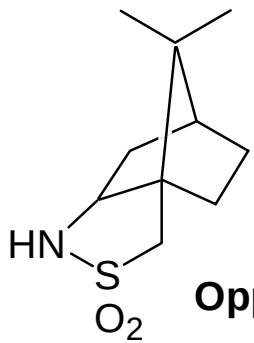
RAMP-hydrazine



Mukaiyama

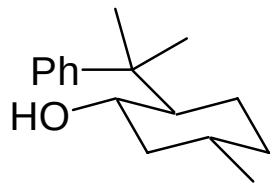


Evans



Oppolzer

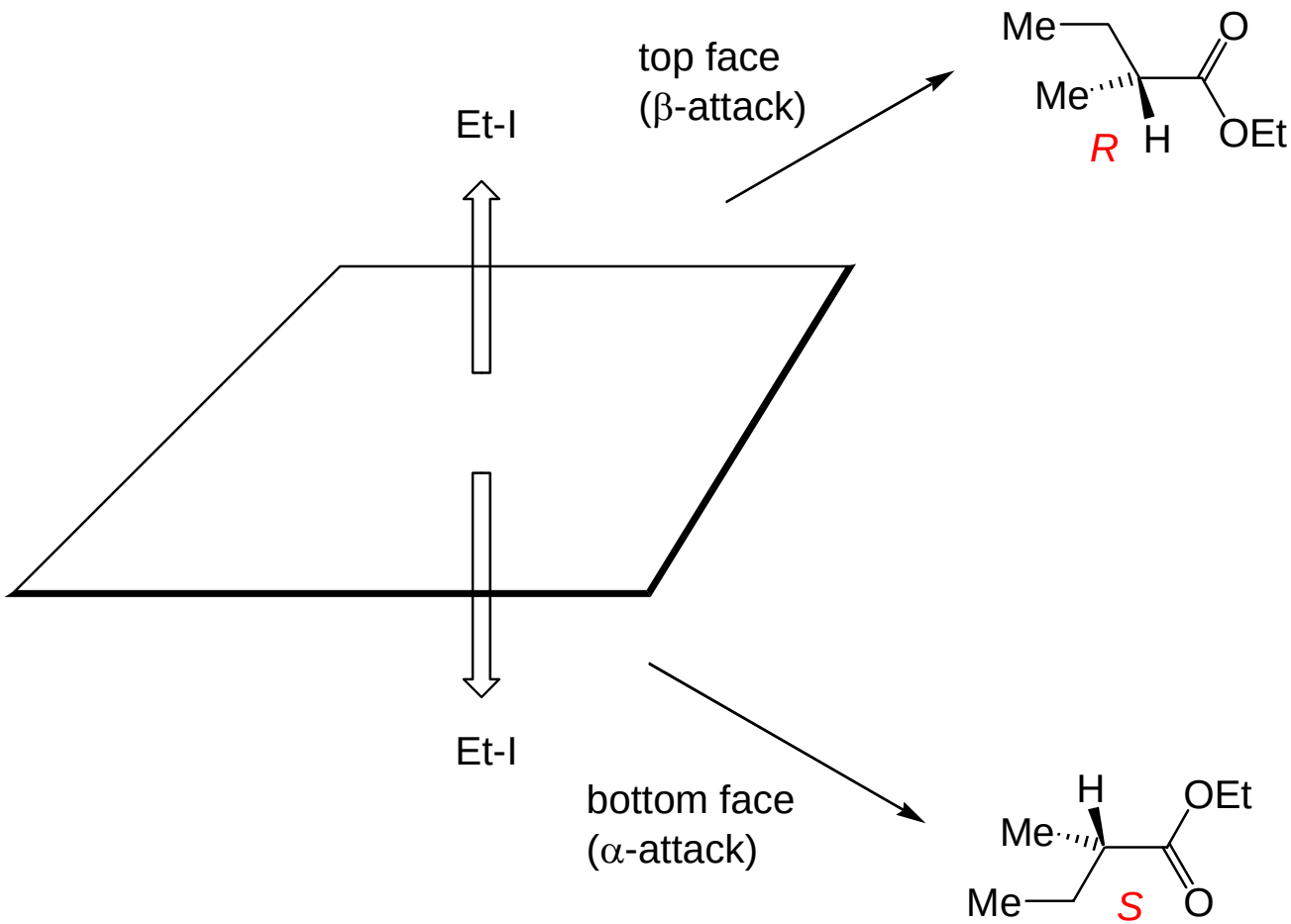
Ene reaction



8-phenylmenthol

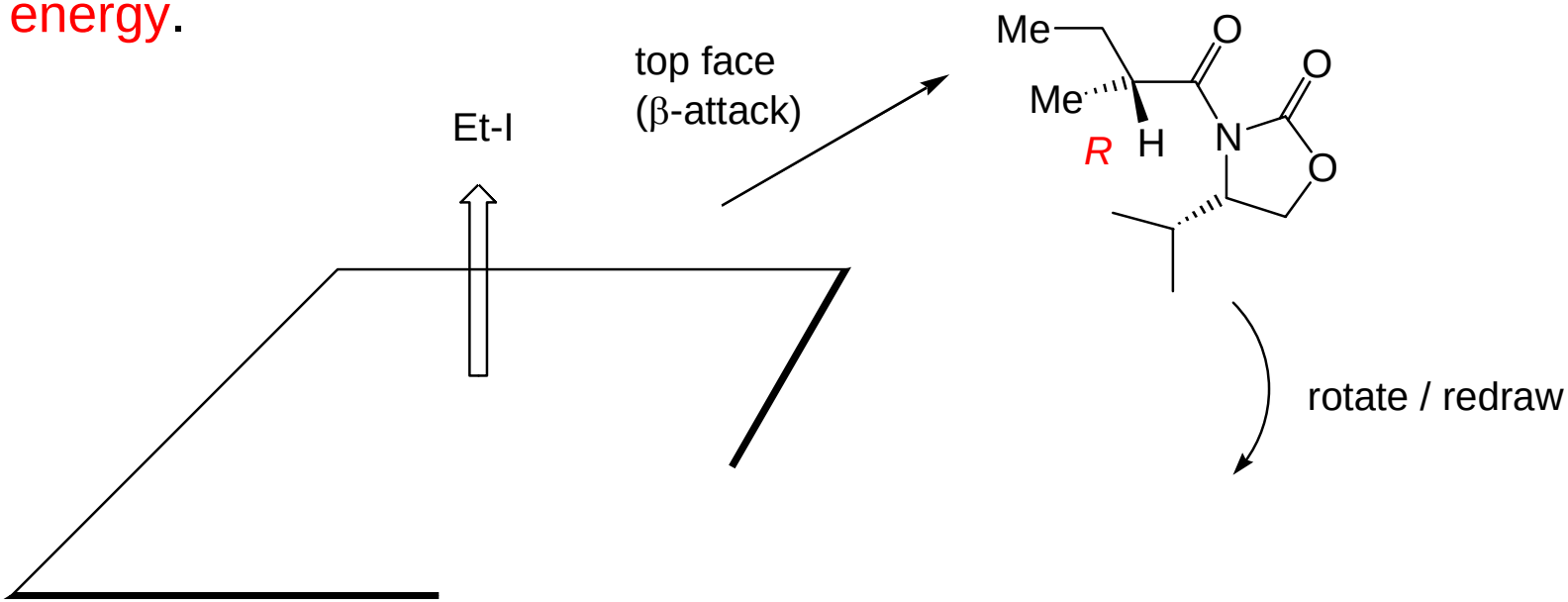
Evans's oxazolidinone for the asymmetric α-alkylation of enolates

Racemic alkylation – no chiral auxiliary present. Transition states for alkylation are enantiomeric and are therefore of the same energy.



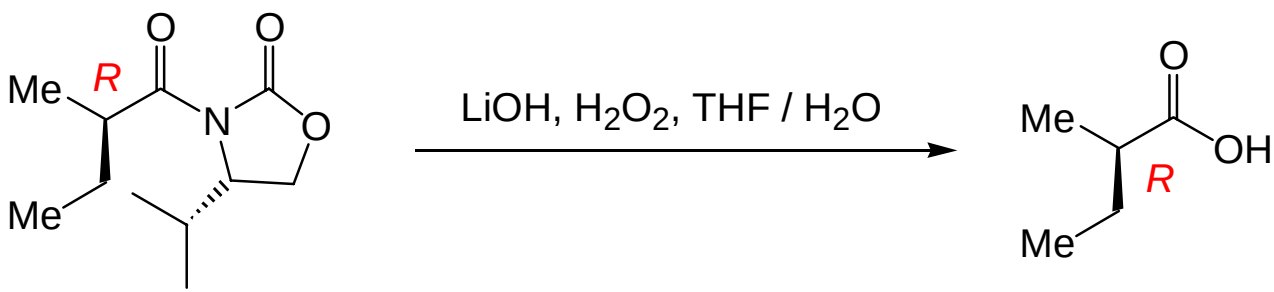
But, in the presence of the Evans oxazolidinone……

Transition states for alkylation are diastereomeric and are therefore **not** the same energy.

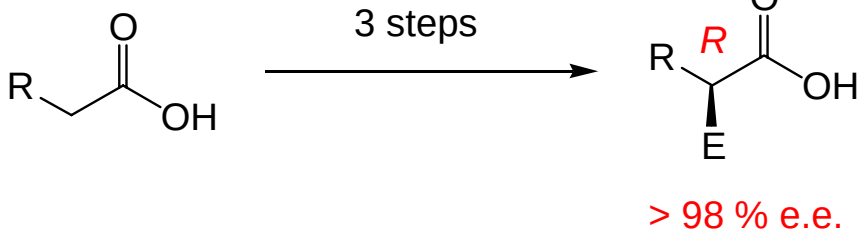


Bulky *iso*-propyl group blocks attack of the electrophile from the bottom face. Attack occurs from the top face.

Major product

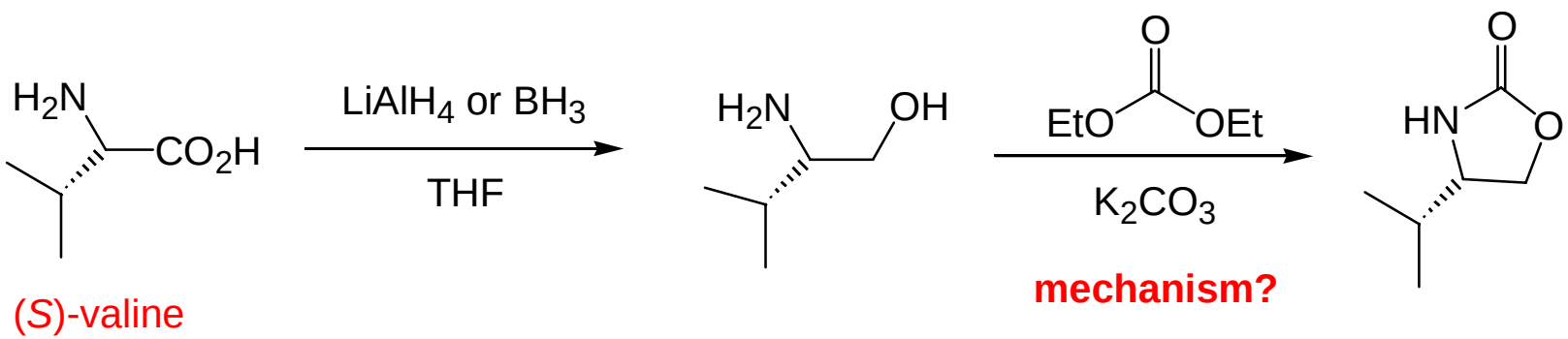


Evans's oxazolidinone approach to α-alkylation of carbonyl compounds was a cornerstone of modern asymmetric synthesis. Overall transformation:

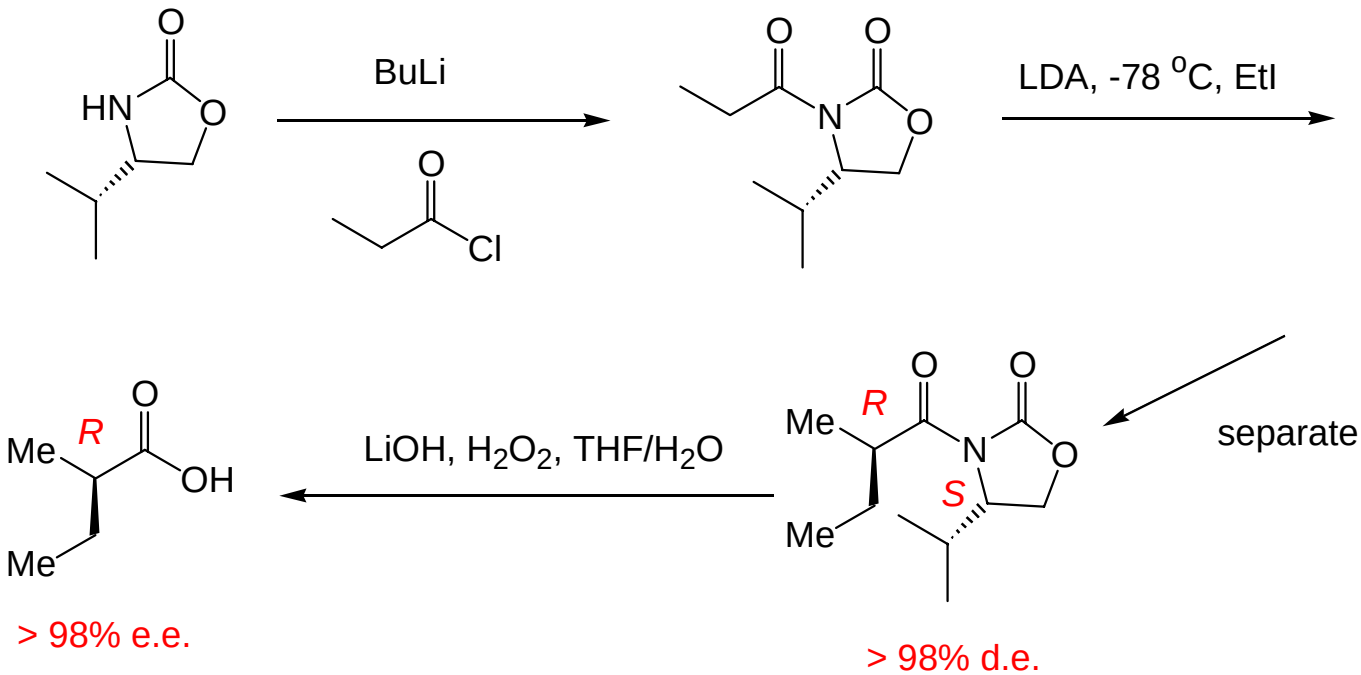


using or

Preparation of the chiral auxiliary.



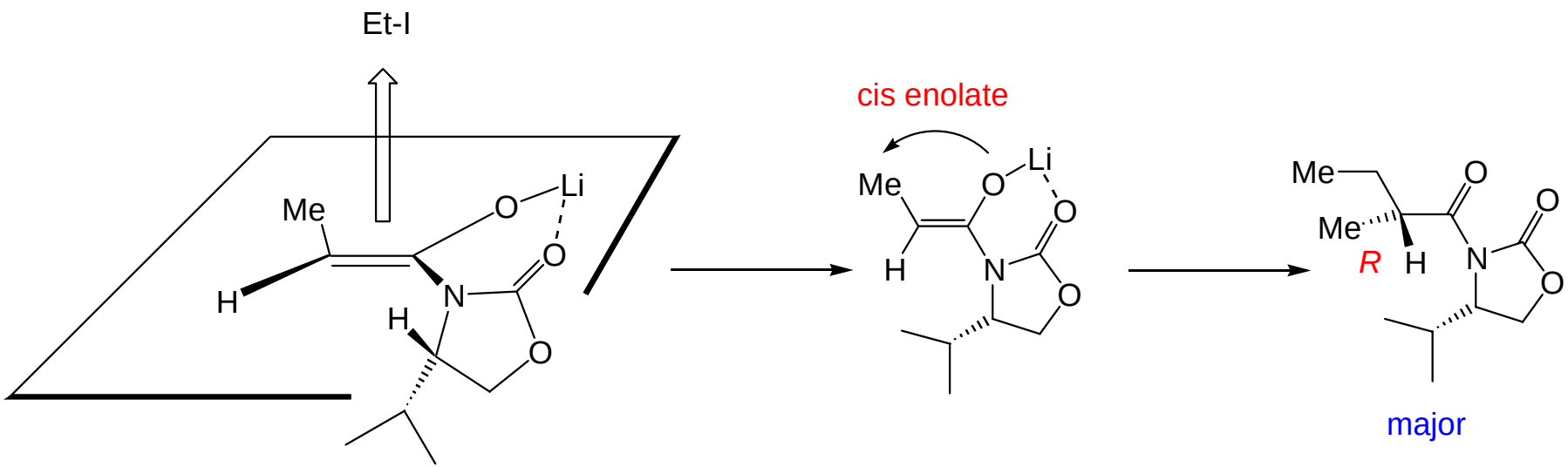
The Evans alkylation reaction in full:



88% d.e. for the (*R, S*) diastereomer. Ratio measured by i) HPLC, ii) GC or iii) ^{1}H NMR. Diastereomers can be separated by conventional methods (chromatography or crystallisation). This gives a single diastereomer, which when the chiral auxiliary is removed gives a single enantiomer. If the auxiliary was removed before separation then the product acid would only have a 88% e.e.

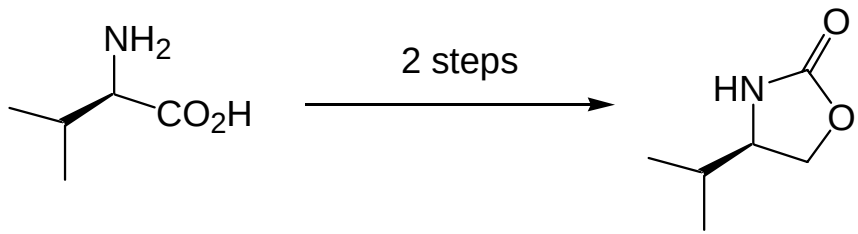
Origin of the high diastereoselectivity.

Only one enolate geometry formed (*cis*) due to **1)** chelation of Li to the carbonyl of the auxiliary and **2)** minimisation of steric interaction as H prefers to eclipse $^{i-}$Pr group instead of Me eclipsing $^{i-}$Pr group. Also the large $^{i-}$Pr group shields one face of the enolate.

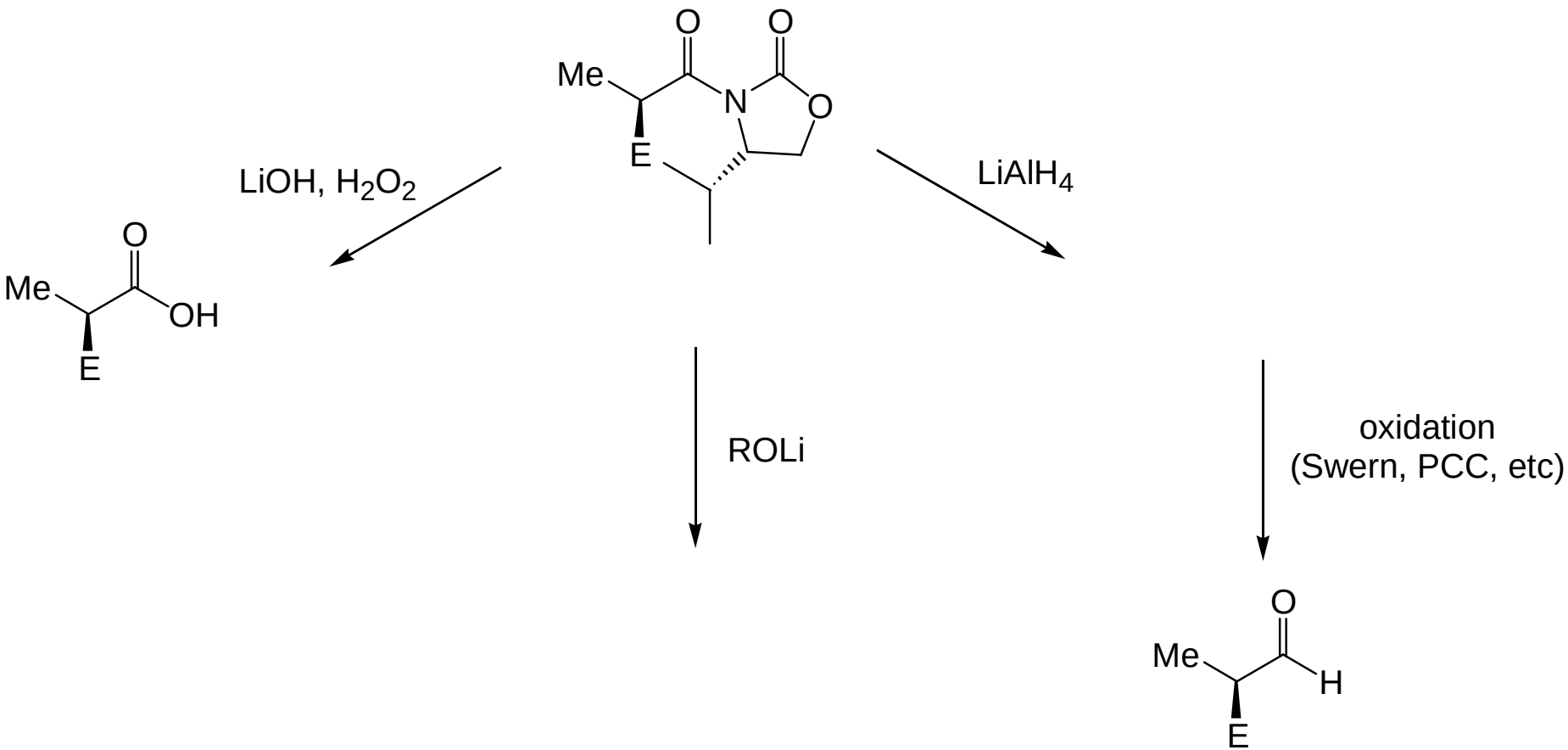


What about the synthesis of the other enantiomer?

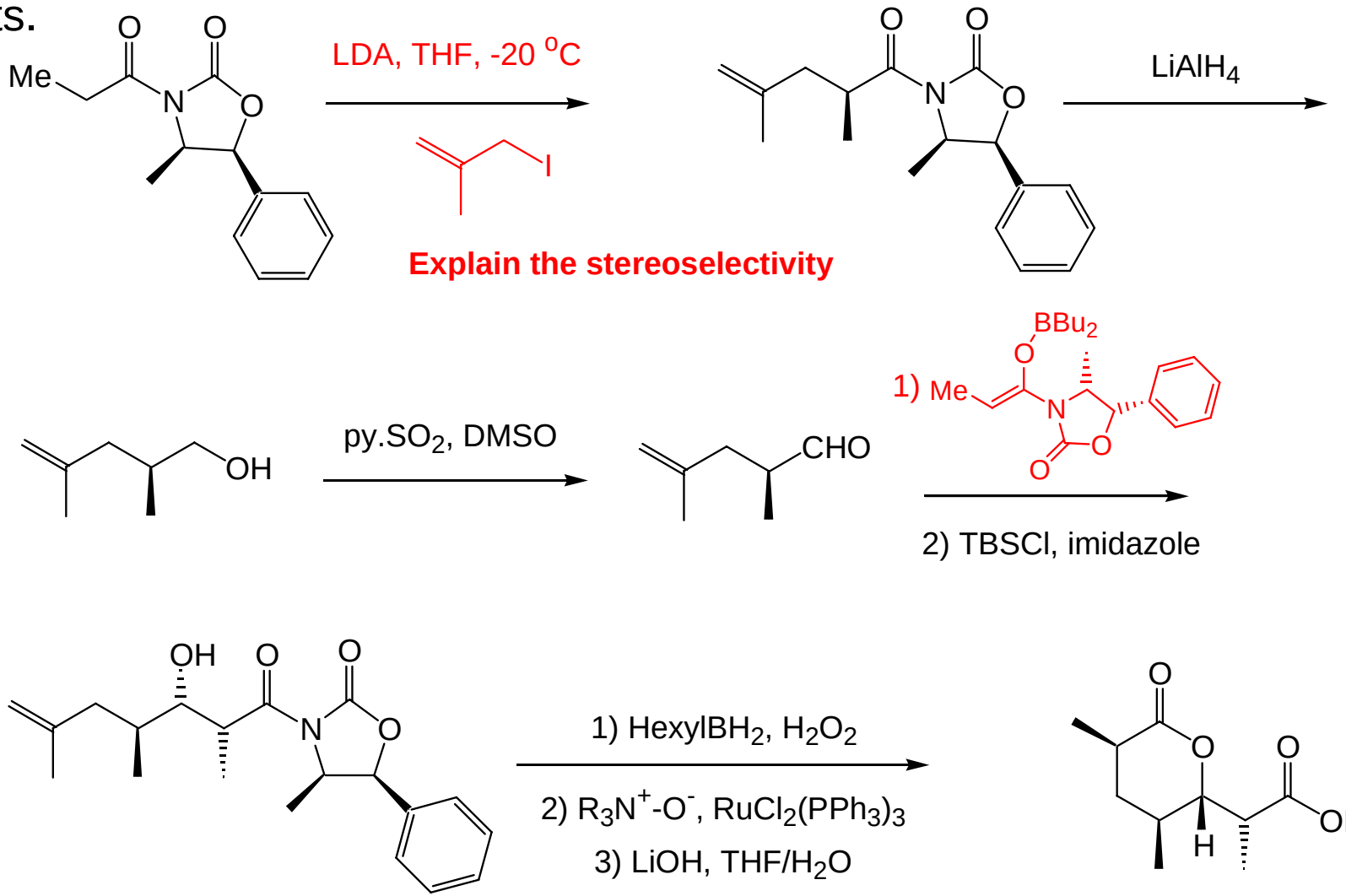
Use the other enantiomer (*R*)- valine



Other methods of cleaving the auxiliary:



Used in the synthesis of the Prelog-Djerassi lactonic acid which embodies the architectural features common in a range of macrolide antibiotic natural products.

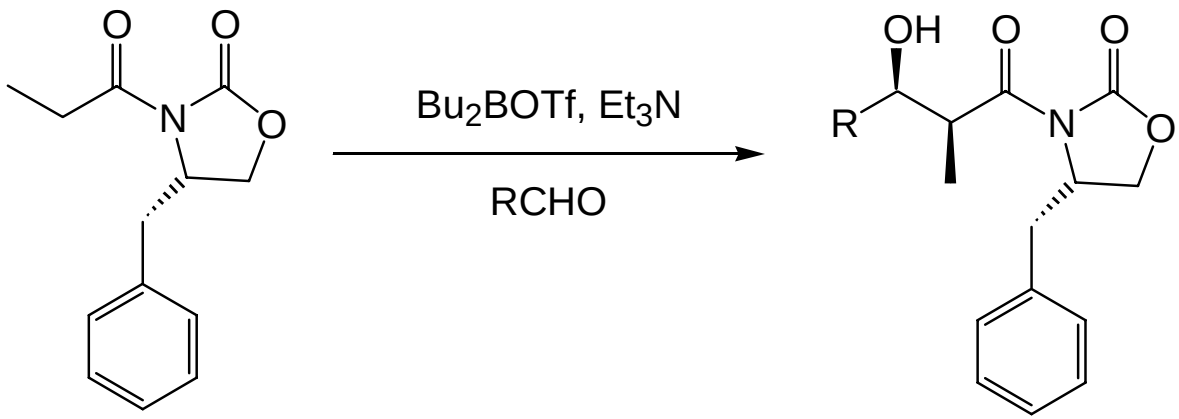


How was this product formed?

Reference: *Tetrahedron Lett.*, **1982**, *23*, 807

Additional Reading

Possibly the most useful asymmetric carbon-carbon bond forming reaction is the Evans Aldol reaction.

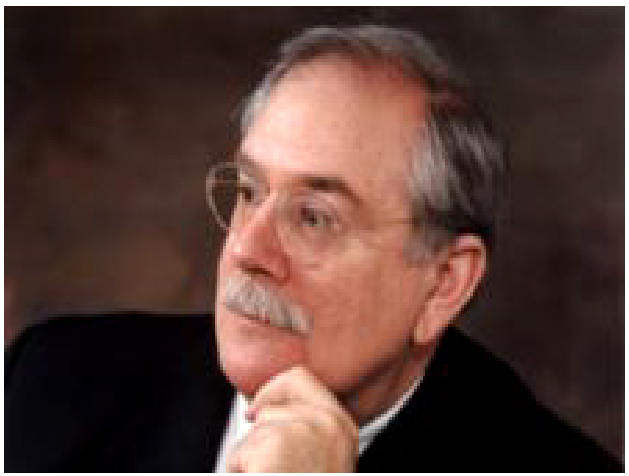


You should learn about this reaction during your own self-directed study. A good starting place is 'Stereoselectivity in Organic Synthesis' by Gary Procter (Oxford primer), Chapter 5 and 'Asymmetric Synthesis' by Gary Procter, Chapter 5. You will encounter this reaction in more detail in your final year studies.

Departmental Seminar

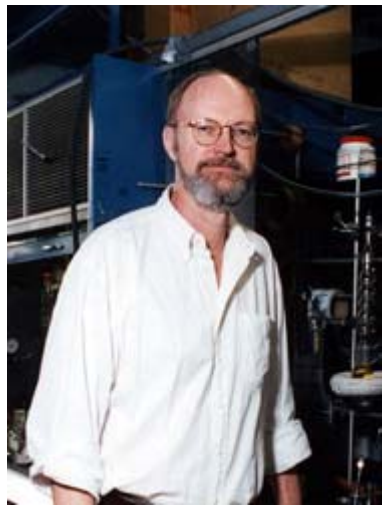
Wed 9th May 2007 at 2:00pm in A101.

Prof. Dave A. Evans
(Harvard University, USA)



"Studies in Natural Product Synthesis"

Prof. Bob Grubbs
(Caltech, USA)



2005 Nobel Prize in Chemistry

"Synthesis of Large and Small Molecules using Olefin Metathesis Catalysts"

Overview of chiral auxiliaries.

A good chiral auxiliary must be **1)** available in both enantiomeric forms, **2)** quick and easy to make, **3)** easy to put on, **4**) give good levels of asymmetric induction, **5)** easy to take off and **6)** recyclable.

Advantages:

Levels of diastereocontrol usually high.
Diastereomers can be separated by conventional methods (chromatography, crystallisation).
Auxiliary can be recycled.
Sense of asymmetric induction can be determined by X-ray crystalography.

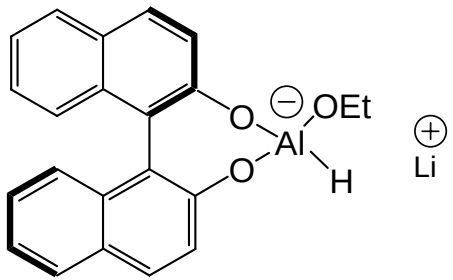
Disadvantages:

Both enantiomers of auxiliary not readily available.
Chiral auxiliaries need to be prepared.
Extra steps – instaltion and removal
Need stoichiometric amount of chirality

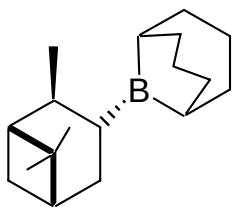
Chiral Reagents:
Brown's Hydroboration and Allylation

Chiral Reagent: A chiral control element is incorporated into the structure of the reagent (NOT the substrate) in order to direct the stereochemistry at new stereogenic centre(s) formed in a reaction. The reagent is used in stoichiometric quantities in the reaction and is not recovered for re-use. Some examples are given below.

Addition to carbonyls

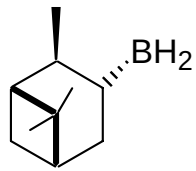


BINAL - H

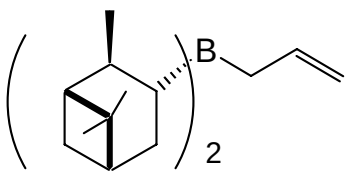


Alpine borane

Addition to olefins

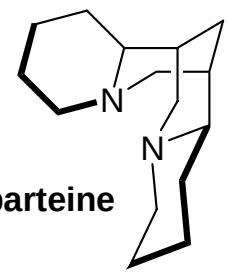


(-)-IpcBH$_2$

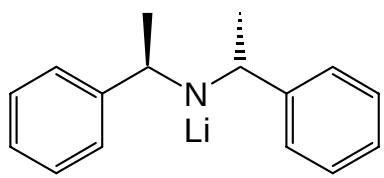


(-)-Ipc$_2$ allyl borane

Chiral Bases



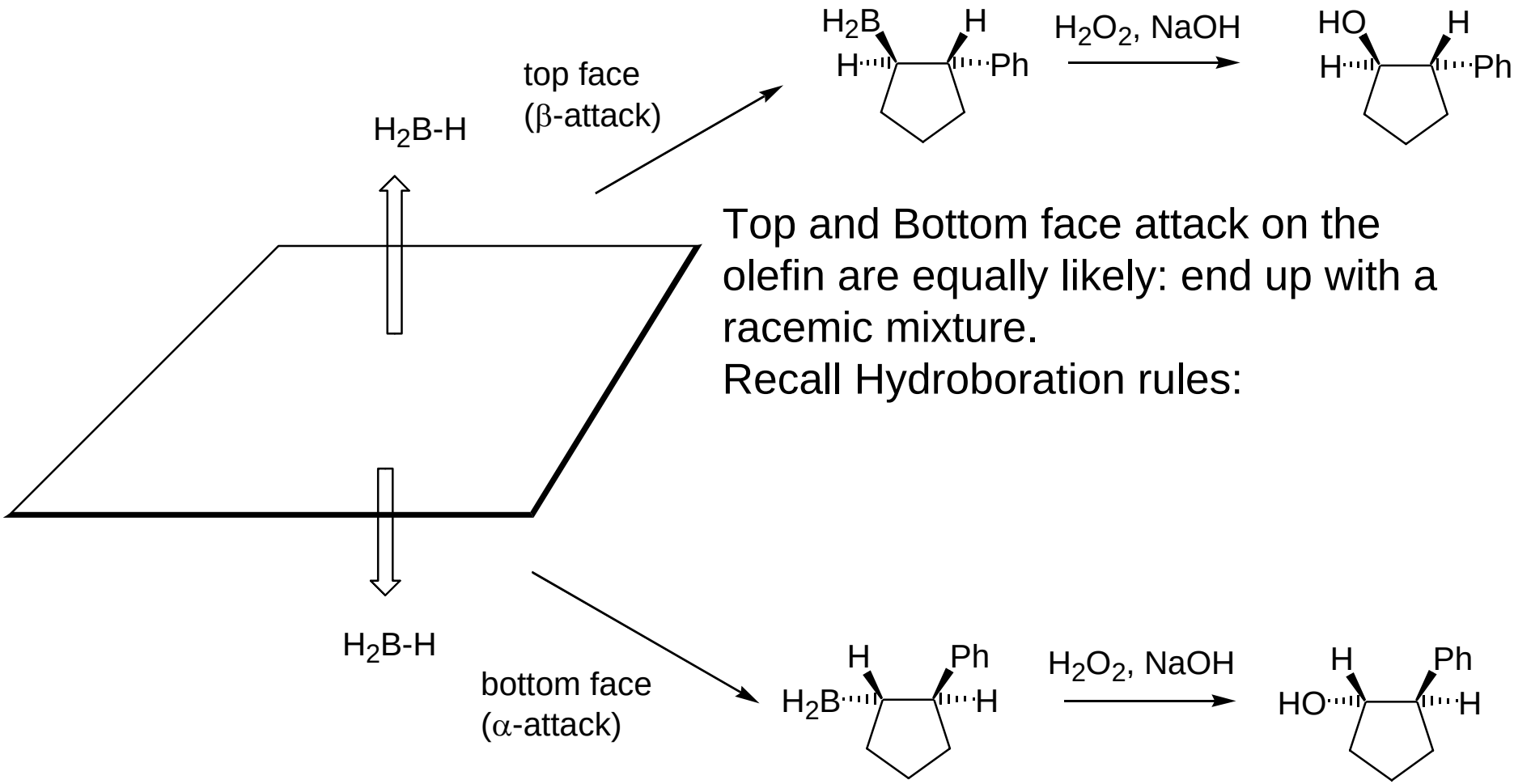
sparteine



Koga and Simpkins

Brown's asymmetric hydroboration

Racemic hydroboration – no source of chirality present. Transition states for hydroboration are enantiomeric and are therefore of the same energy.

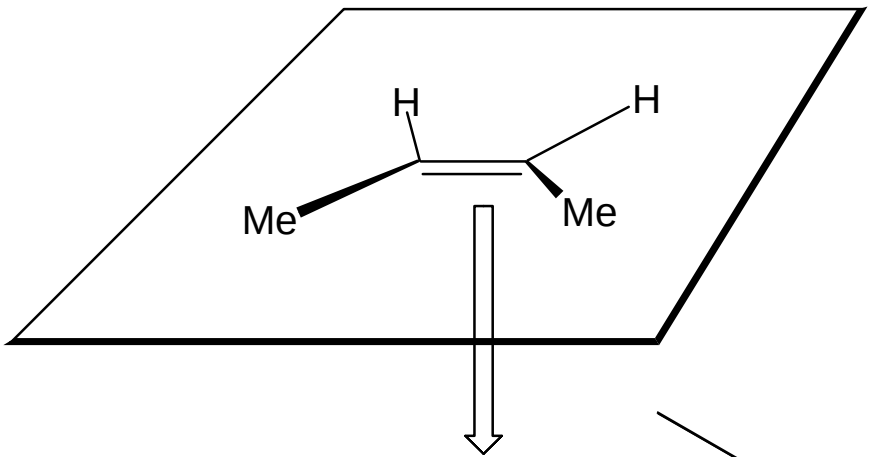


Top and Bottom face attack on the olefin are equally likely: end up with a racemic mixture.

Recall Hydroboration rules:

Brown's asymmetric hydroboration

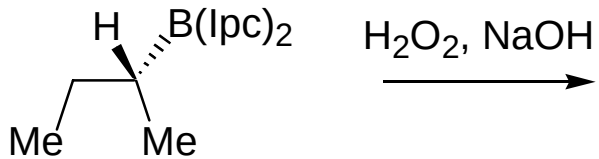
Asymmetric hydroboration – use a chiral BH_3 equivalent. Transition states for hydroboration are diastereomeric and are therefore **not** the same energy.



Ipc_2 borane from **(+)-α-pinene** adds to the double bond from the α-face (as drawn) to give the (*R*)-alcohol in 98% e.e.

Ipc_2 borane from **(-)-α-pinene** adds to the top face of the double bond to give the (*S*)-alcohol in 98% e.e.

bottom face
(α-attack)

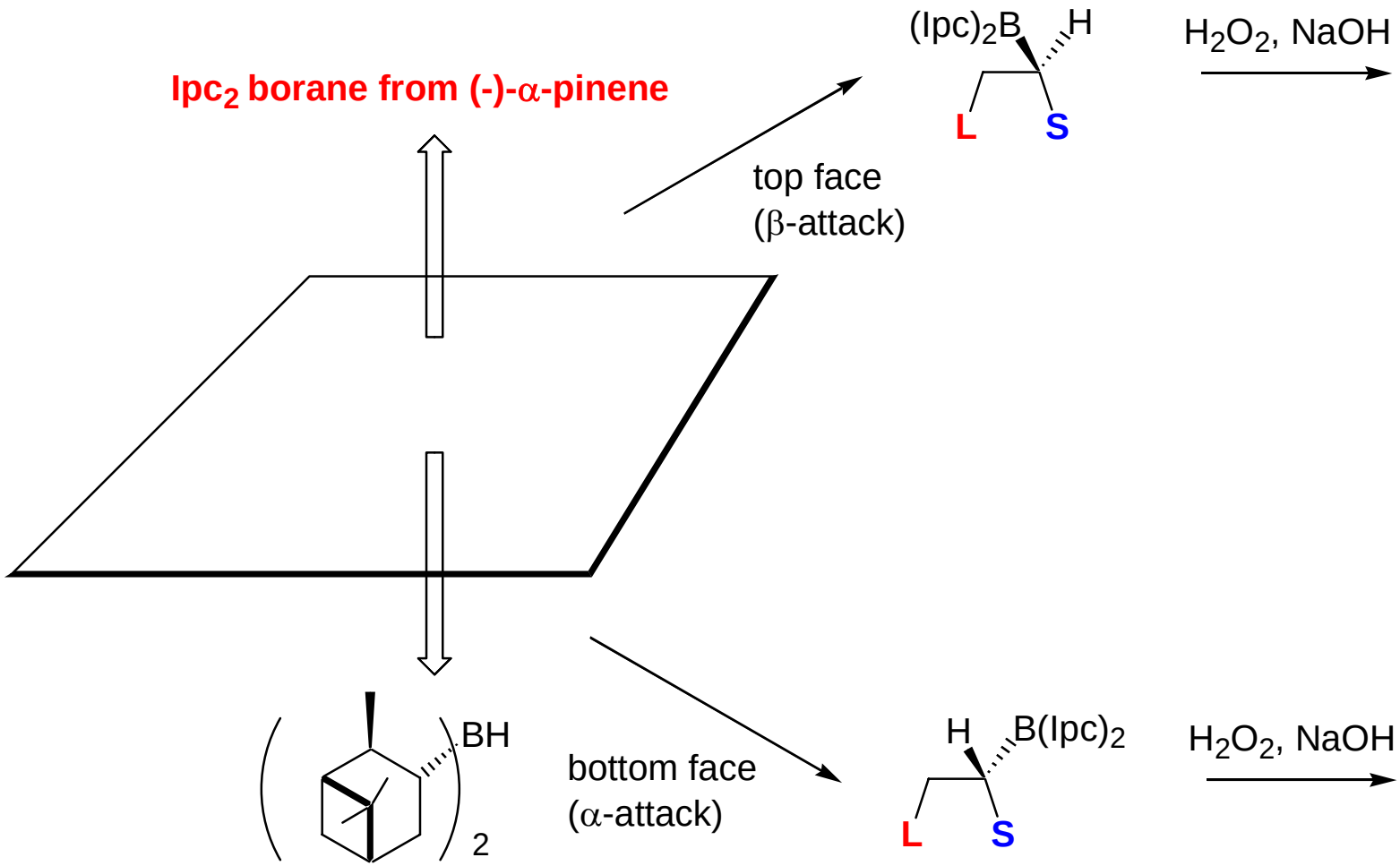


98% e.e.

Ipc_2 borane from (+)-α-pinene

full name: di-*iso*pinocampheylborane

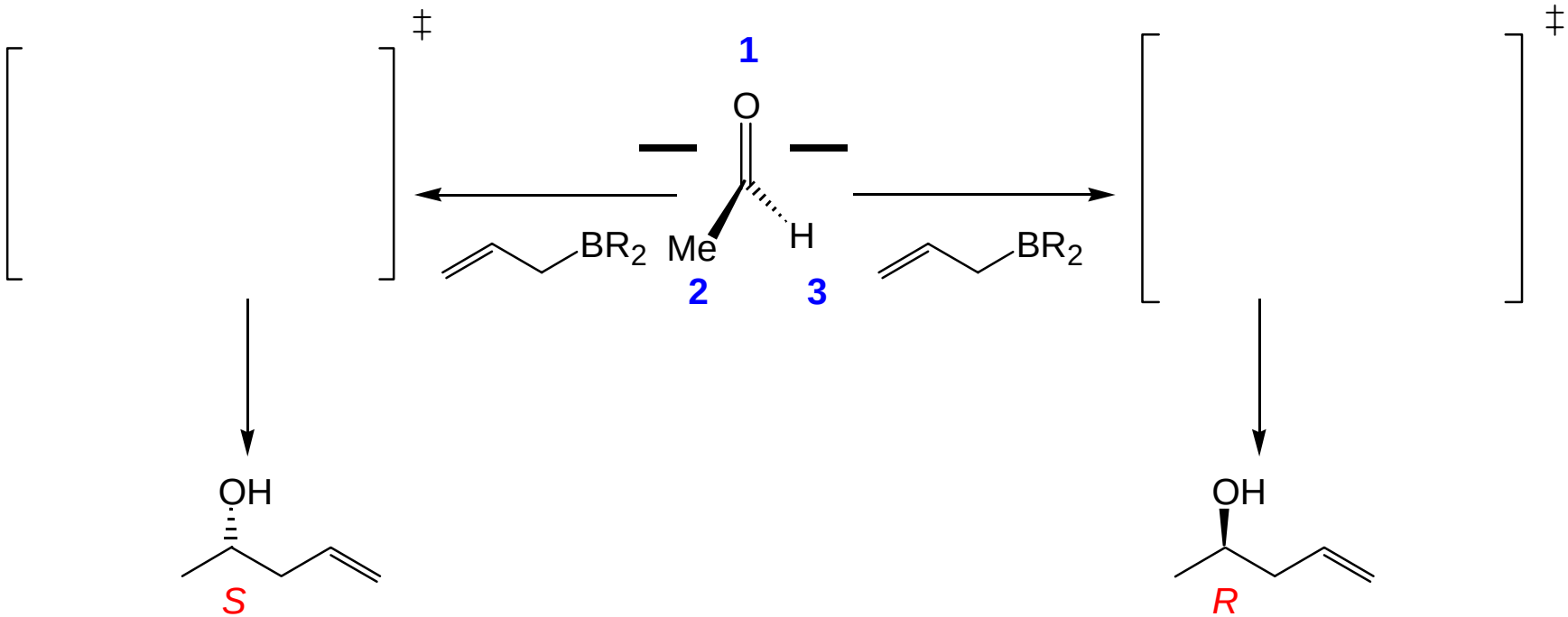
Brown's asymmetric hydroboration: Predictive model (Mnemonic)



Note: this only works well for (*Z*)- alkenes. Enantiomeric excesses tend to be substantially lower for (*E*)-alkenes

Brown's asymmetric allylation

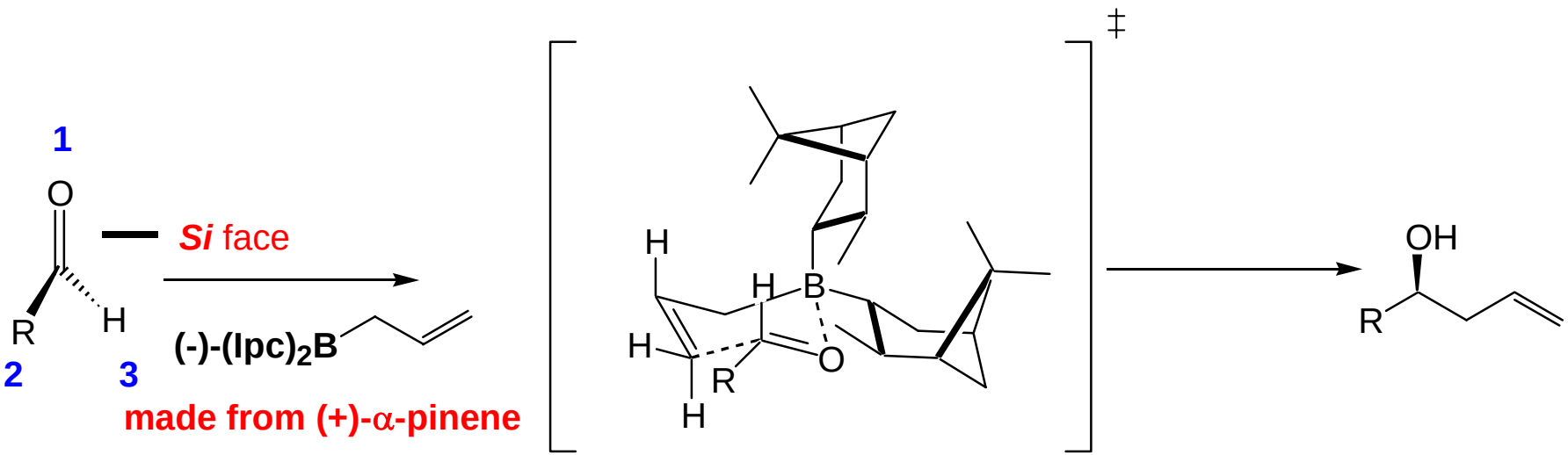
Racemic allylation – no source of chirality present. The 6-membered cyclic transition states shown below for allylation are enantiomeric and are therefore of the same energy. It therefore follows that a racemic product will result.



Re and Si faces: Using CIP rules if the substituents rank high priority to low priority clockwise then this is the *Re*-face. If they rank high priority to low priority anti-clockwise then this is the *Si*-face.

Brown's asymmetric allylation

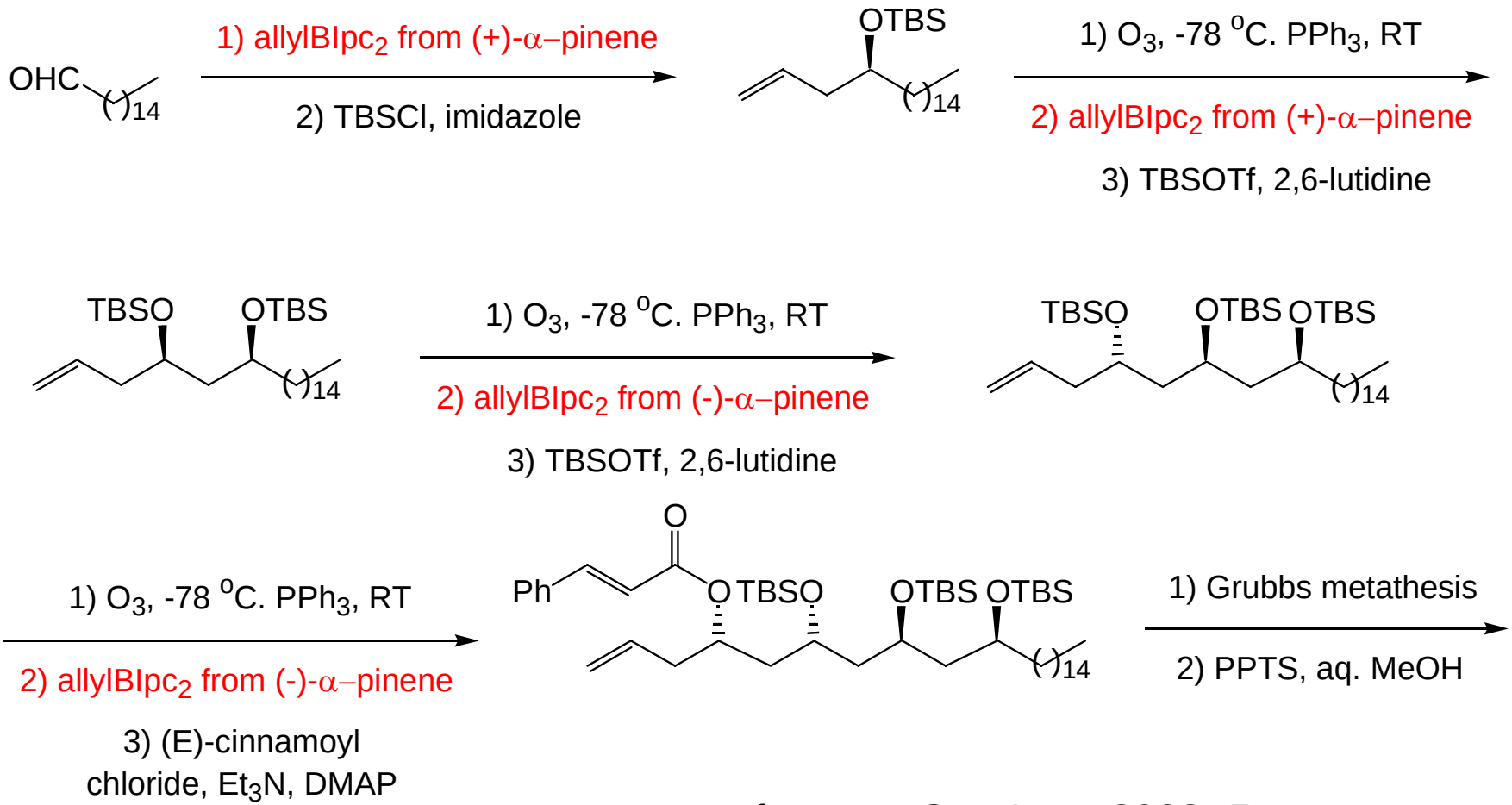
Asymmetric allylation – use a chiral allylborane equivalent.



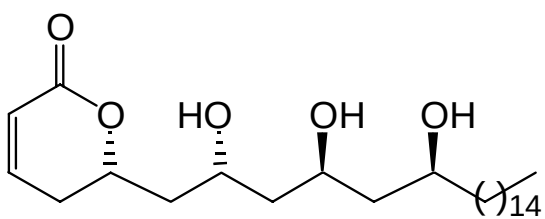
Allylation proceeds *via* a chair-lie TS‡ where R occupies an equatorial position. Facial selectivity (enantioselectivity) derives from minimisation of steric interactions between the *axial* Ipc-ligand and the allyl group.

Take home message: *iso*pinocampheyl allylboranes made from **(+)-α-pinene add to the *Si* face** of the aldehyde.

Brown's asymmetric allylation was used in synthetic work which disproved the published structure of passifloricin A.



Reference: *Org. Lett.,* **2003**, *5*, 1447



Not the published structure

Herbert C. Brown

19212 - 2004

In 1979, H. C. Brown was awarded the Nobel Prize for Chemistry his development of the use of boron- containing compounds, into important reagents in organic synthesis. (He shared the prize that year with Georg Wittig who was awarded it for his development of the use of phosphorous- containing reagents).

http://nobelprize.org/nobel_prizes/chemistry/laureates/1979/index.html

http://http://nobelprize.org/nobel_prizes/chemistry/laureates/1979/brown-lecture.pdf

Overview of chiral reagents.

Advantages:

Do not need to attach or remove chiral group (*c.f.* chiral auxiliaries).
Therefore, if the reagent is commercial, there are less synthetic steps.

Disadvantages:

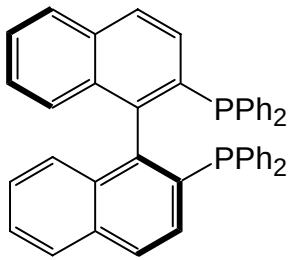
No opportunity to improve the % e.e. of the product by purification of the diastereomer (*c.f*. chiral auxiliaries).
Need stoichiometic amounts of reagent, and hence chirality (*i.e.* 1 mole of reagent for every 1 mole of substrate). Not very efficient in chirality.

And the answer is??.....

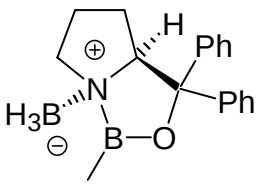
Chiral Catalysts:
CBS Reduction
Hydrogenation of Alkenes
Sharpless Oxidations and Organocatalysis

Chiral Catalyst:

Reduction

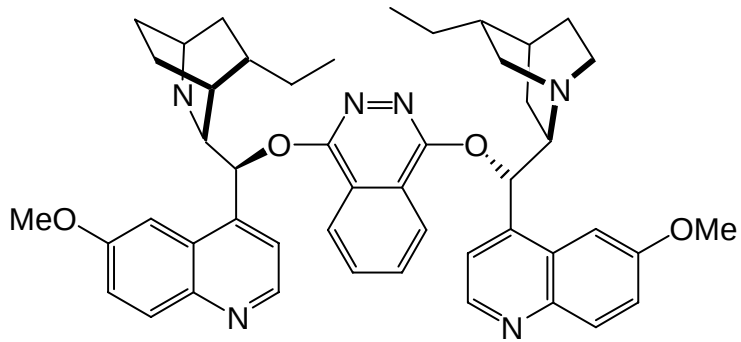


Binap



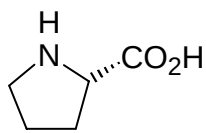
CBS

Oxidation

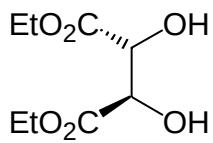


Sharpless's

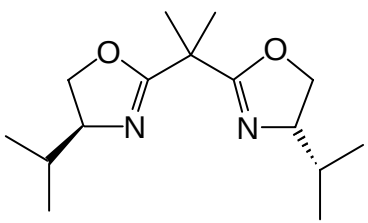
Aldol



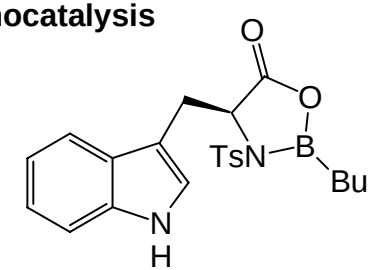
organocatalysis



Addition to double bonds



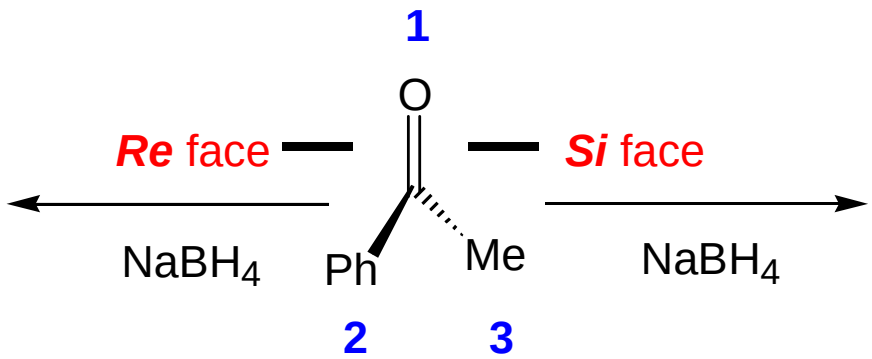
Evans's BOX ligands



Corey's Mukaiyama aldol catalyst

Corey-Bakshi-Shibata (CBS) asymmetric reduction of ketones

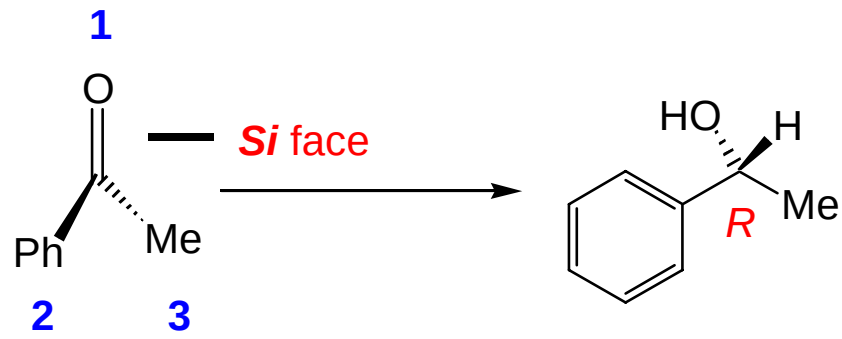
Racemic reduction – no source of chirality present. Addition of hydride occurs equally from both *Re*- and *Si*- faces and generates a racemate.



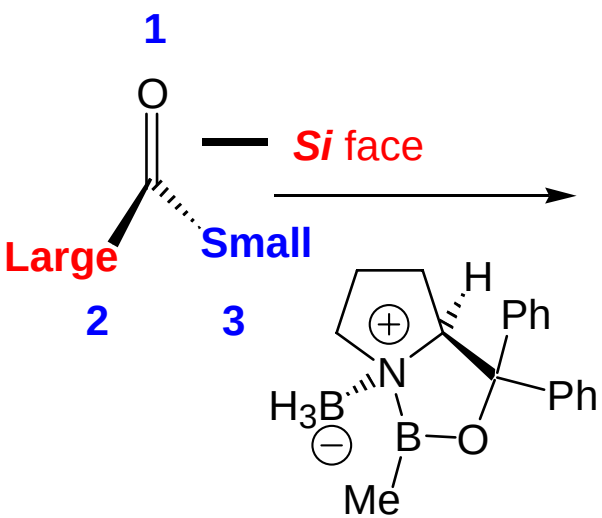
Re and Si faces: Using CIP rules if the substituents rank high priority to low priority clockwise then this is the *Re*-face. If they rank high priority to low priority anti-clockwise then this is the *Si*-face.

Corey-Bakshi-Shibata (CBS) asymmetric reduction of ketones

Asymmetric reduction – use a chiral borane (or hydride) equivalent. The energies of the diastereomeric transition states for reduction from either the *Re*- or *Si*-face are not equal. Therefore generates a product with an enantiomeric excess.



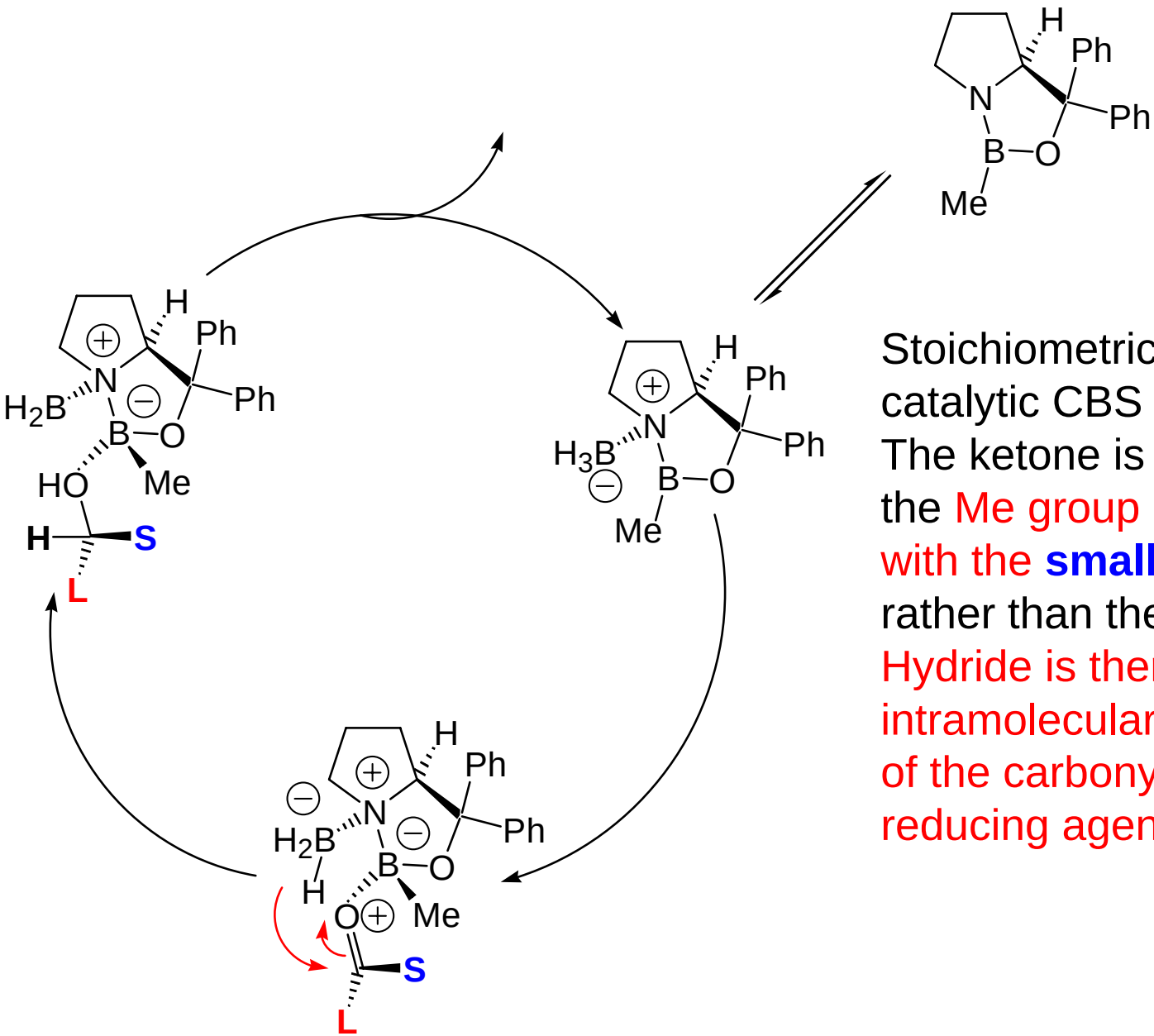
CBS catalyst from (S)-proline



CBS catalyst from (S)-proline

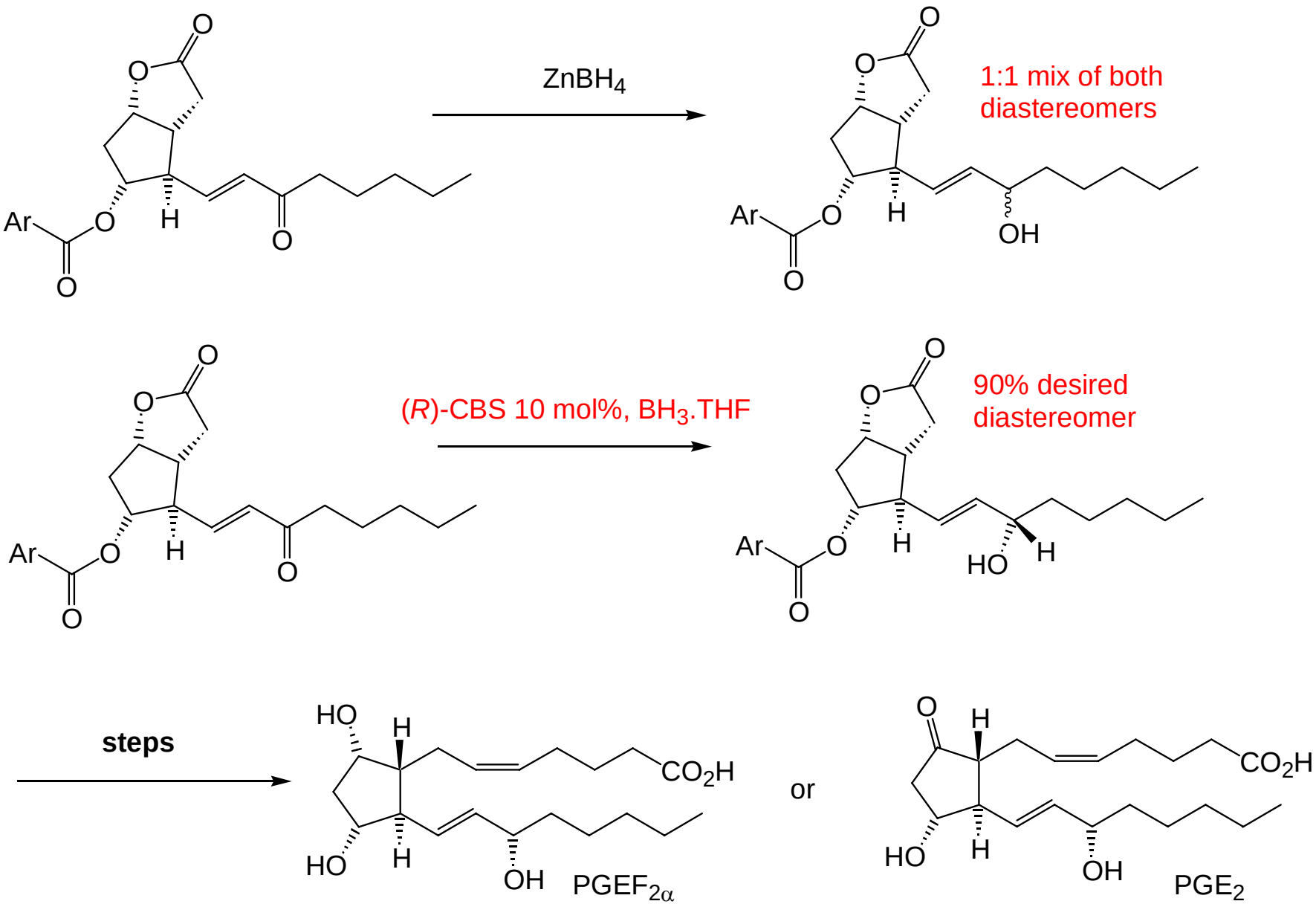
CBS Predictive model (Mnemonic)

CBS reagent: catalytic cycle and rationalisation of selectivity



Stoichiometric BH_3 and catalytic CBS reagent used. The ketone is oriented so that the Me group lies co-planar with the **smaller** substituent rather than the larger one. Hydride is therefore delivered intramolecularly to the π-face of the carbonyl facing the reducing agent.

CBS reduction in the synthesis of the prostaglandins $F_{2\alpha}$ and E_2.



Elias J. Corey

In 1990, Elias James Corey was awarded the Nobel Prize for Chemistry for his development of the theory and methodology of organic synthesis, particularly retrosynthetic analysis.

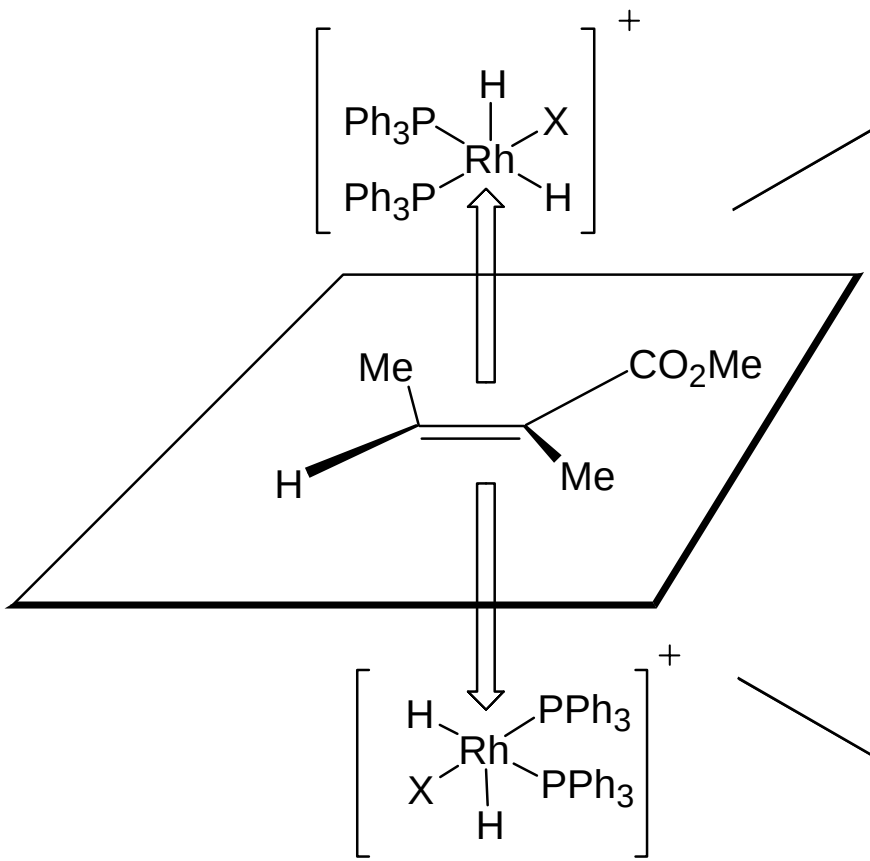
Born 1928

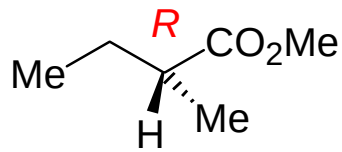
http://nobelprize.org/nobel_prizes/chemistry/laureates/1990/index.html

http://nobelprize.org/nobel_prizes/chemistry/laureates/1990/corey-lecture.pdf

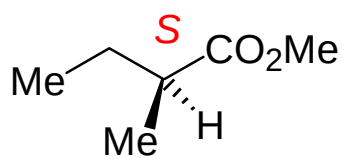
Asymmetric reduction of alkenes by Rh or Ru compelxes

Racemic reduction – no source of chirality present. Addition of hydride occurs equally from both *Re*- and *Si*- faces and generates a racemate.





Hydrogenation can be catalysed by Rh or Ru phosphine complexes such as $[RhCl(PPh_3)_3]$ which can react with H_2 to form the active species $[RhH_2X(PPh_3)_2]$, which co-ordinates with the π-bond of the alkene. (X = solvent)



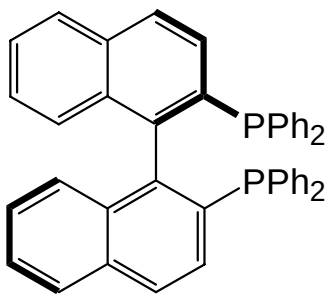
Asymmetric reduction of alkenes by Rh or Ru compelxes

Asymmetric reduction can occur when PPh_3 is replaced by chiral phosphines or diphosphines such as DIPAMP or BINAP.

DIPAMP is chiral at P.

(*R*, *R*)-DIPAMP

BINAP is chiral as it has no plane of symmetry due to restricted rotation about the biphenyl single bond. This specific type of chirality is called **Atropisomers.**



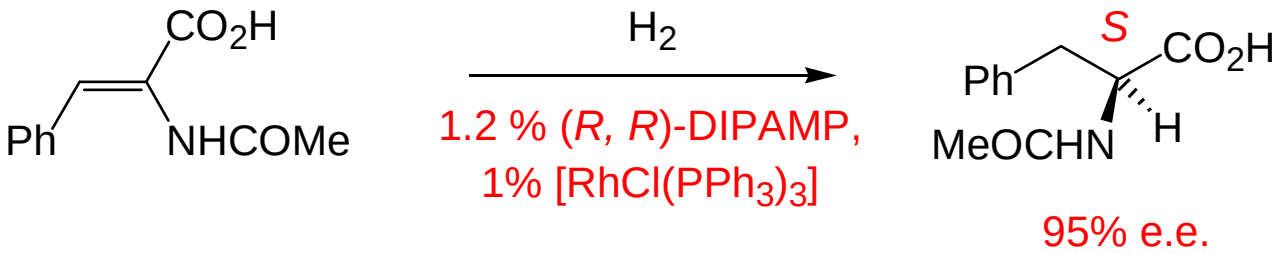
(*R*)-BINAP

(*S*)-BINAP

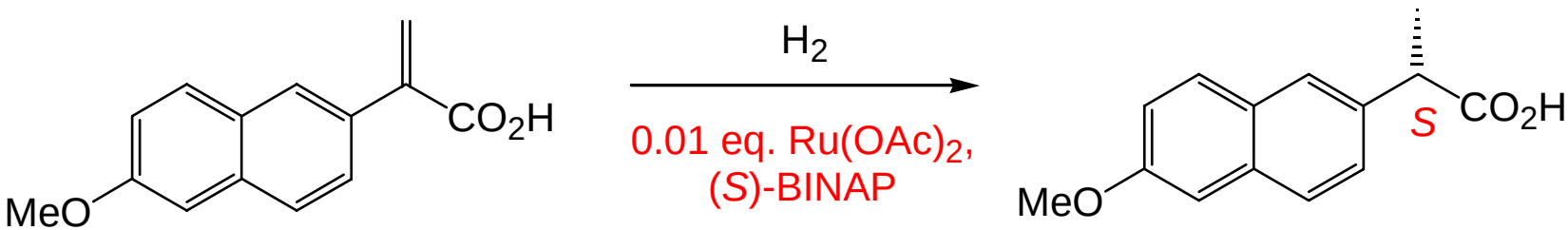
Mirror plane

(*R*)-BINAP

Examples



95% e.e.

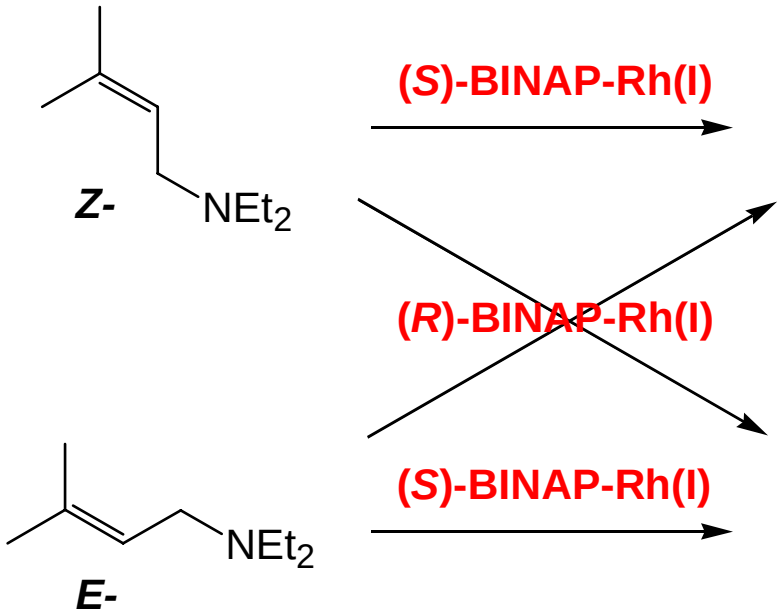


> 95% e.e.

Many more chiral phosphines have been used in the asymmetric reduction of double bonds.

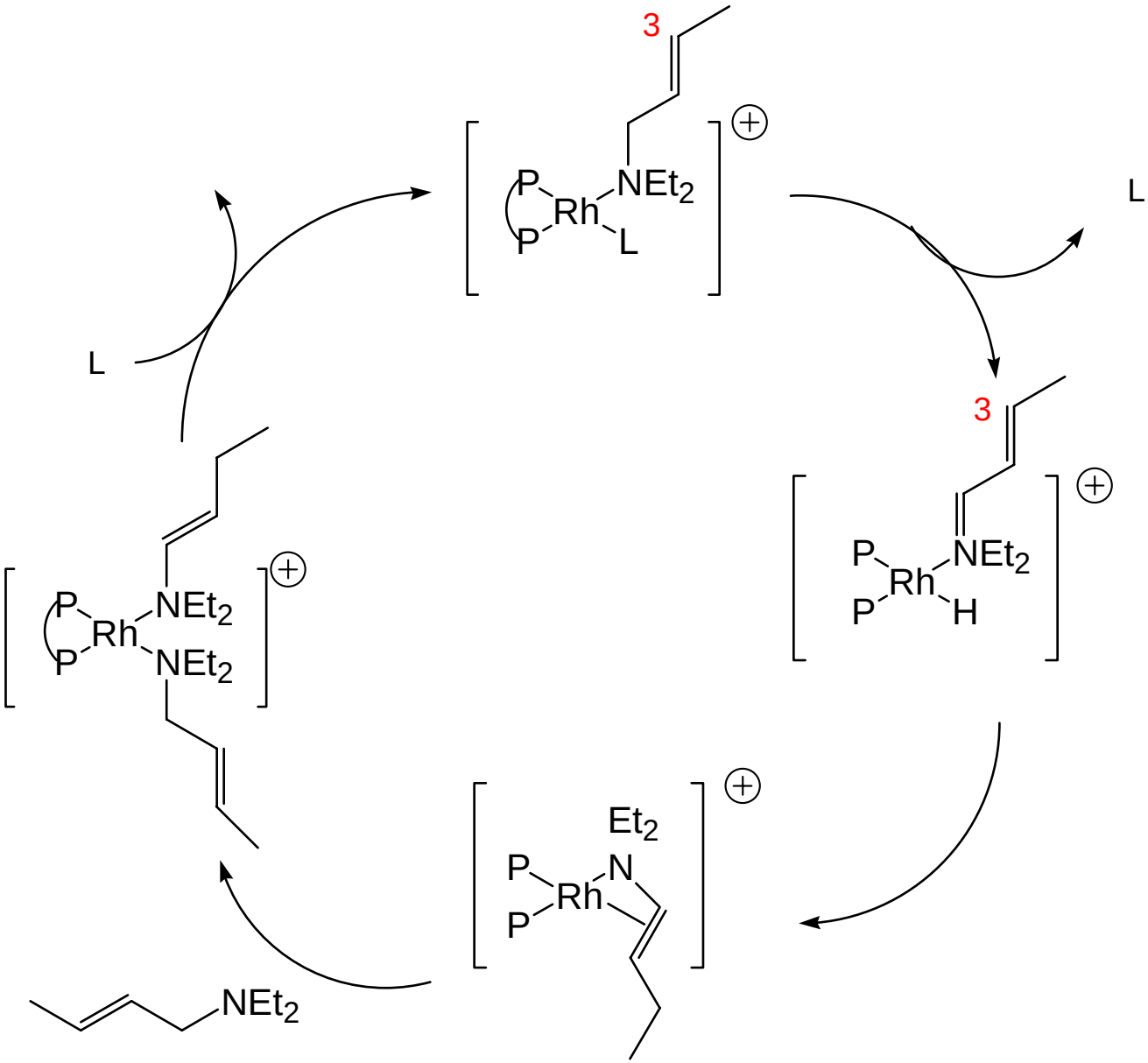
Literature work: find out the structures of the chiral phosphines DIOP, Chiraphos and DuPHOS and a reaction where they have each been used to successfully produce enatioenriched product.

Asymmetric Isomerisation of Allylic Amines

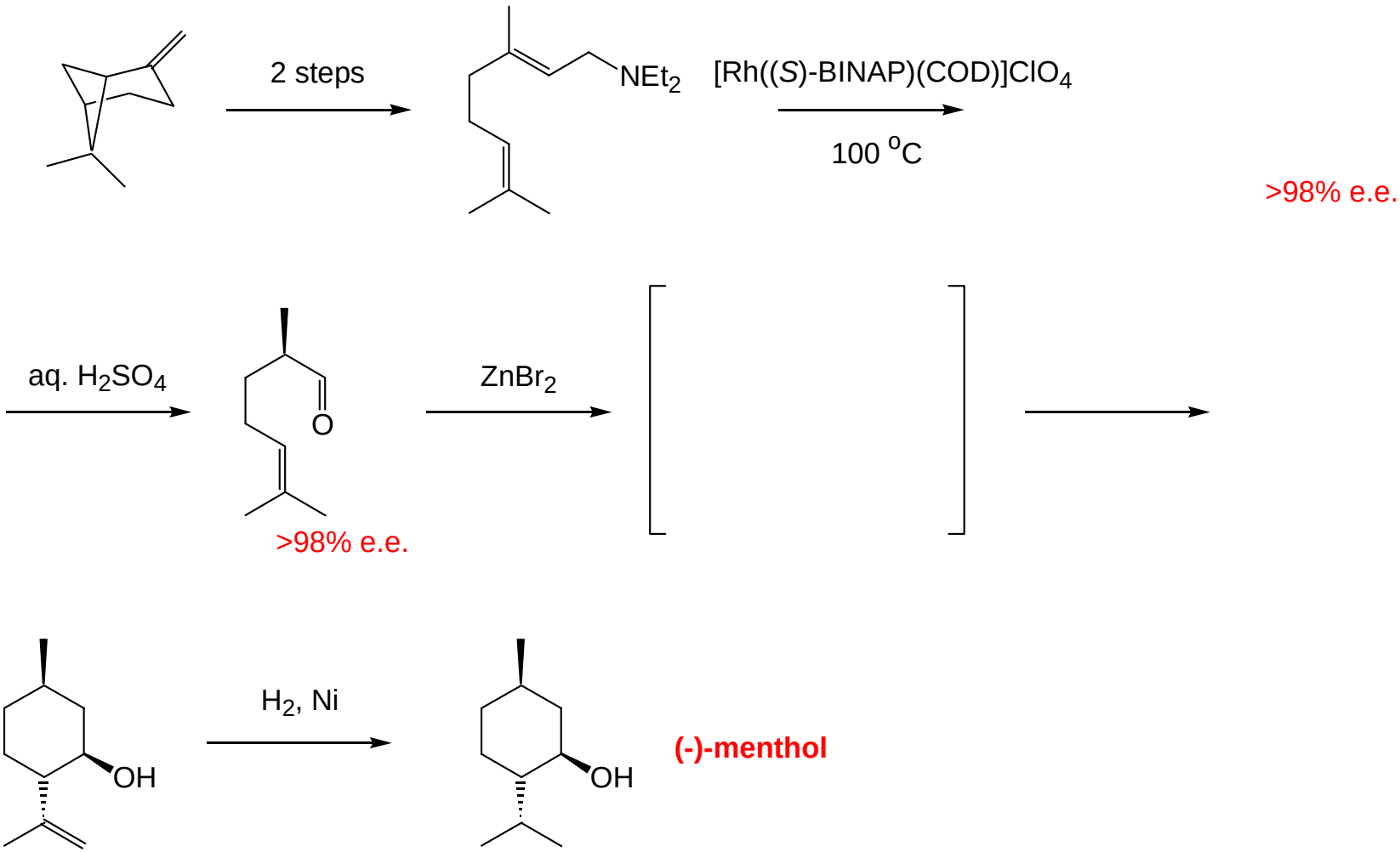


Stereochemically pure (*Z*)-allylic amine in the presence of (*S*)-BINAP-Rh(I) catalyst is smoothly isomerised to (*S, E*)-enamine, while stereochemically pure (*E*)-allylic amine in the presence of (*S*)-BINAP-Rh(I) catalyst is smoothly isomerised to (*R, E*)-enamine. So it is imperative that geometrically pure allylic amines are employed in this reaction.

Catalytic Cycle for the Isomerisation



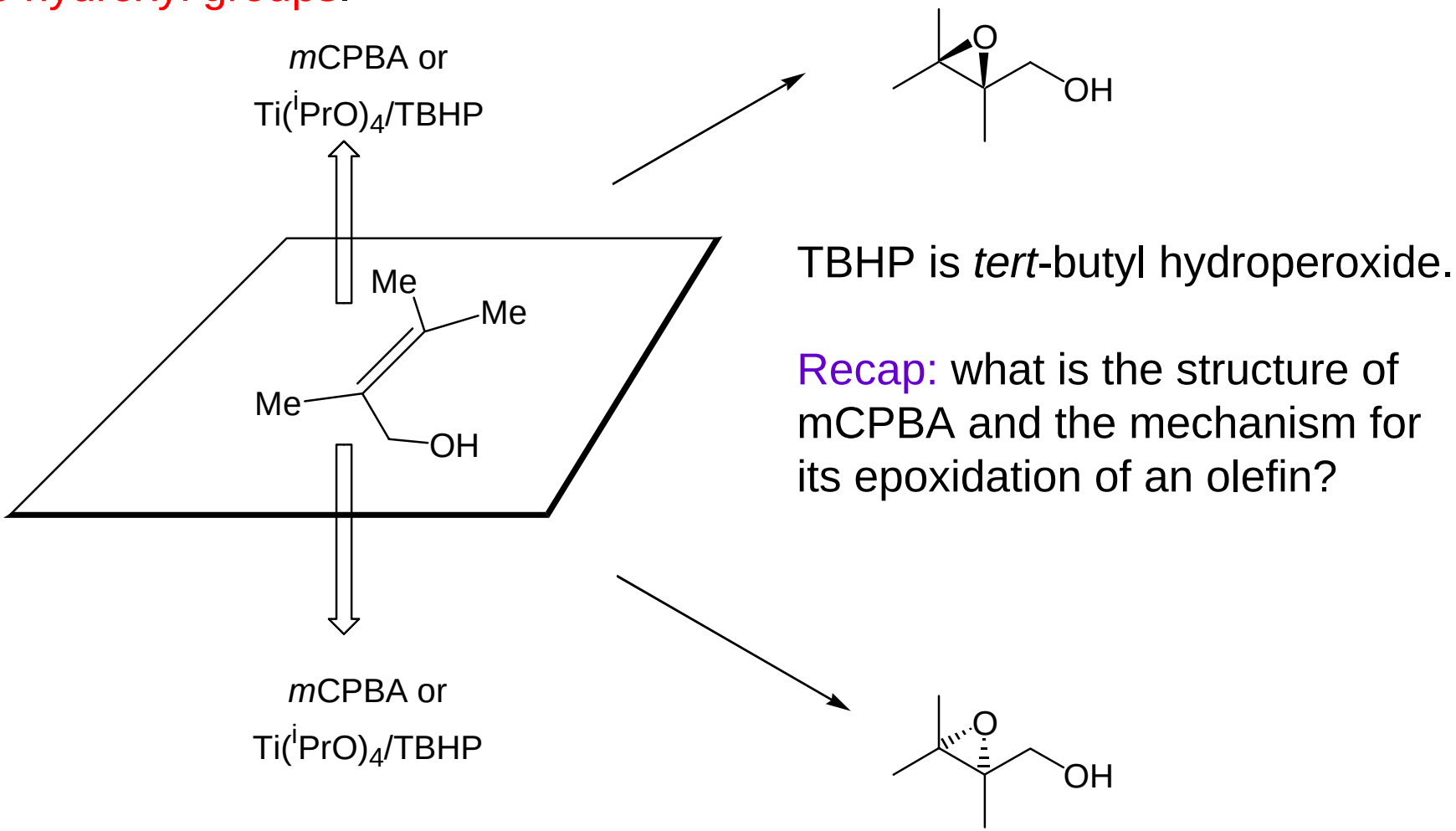
Takasago Process for the Industrial Synthesis of (-)- Menthol



The key steps are an asymmetric allylic amine-enamine isomerisation followed by a Lewis acid promoted carbonyl ene reaction

Sharpless Asymmetric Epoxidation (SAE) Reaction

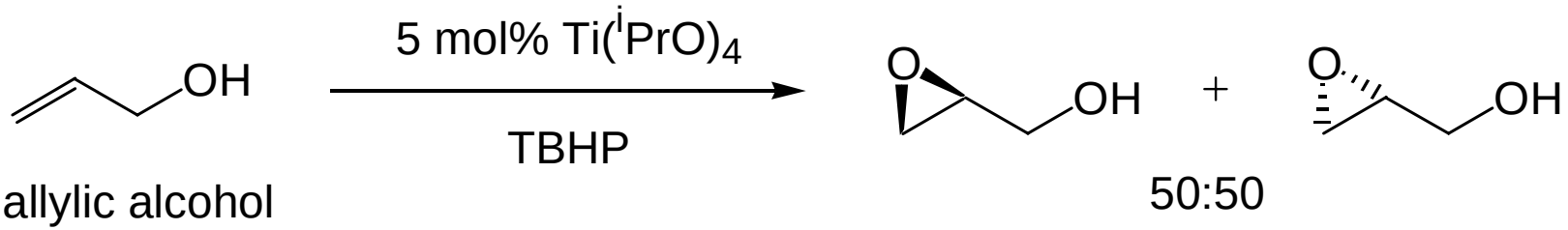
Racemic epoxidation – no source of chirality present so equal amounts of both enantiomers are produced. Can use oxidants like mCPBA or $Ti(^iPrO)_4$/alkyl hydroperoxides to epoxidise double bonds, although $Ti(^iPrO)_4$/alkyl hydroperoxide complexes only epoxidises double bonds next to hydroxyl groups.



TBHP is *tert*-butyl hydroperoxide.

Recap: what is the structure of mCPBA and the mechanism for its epoxidation of an olefin?

Mechanism of the racemic reaction

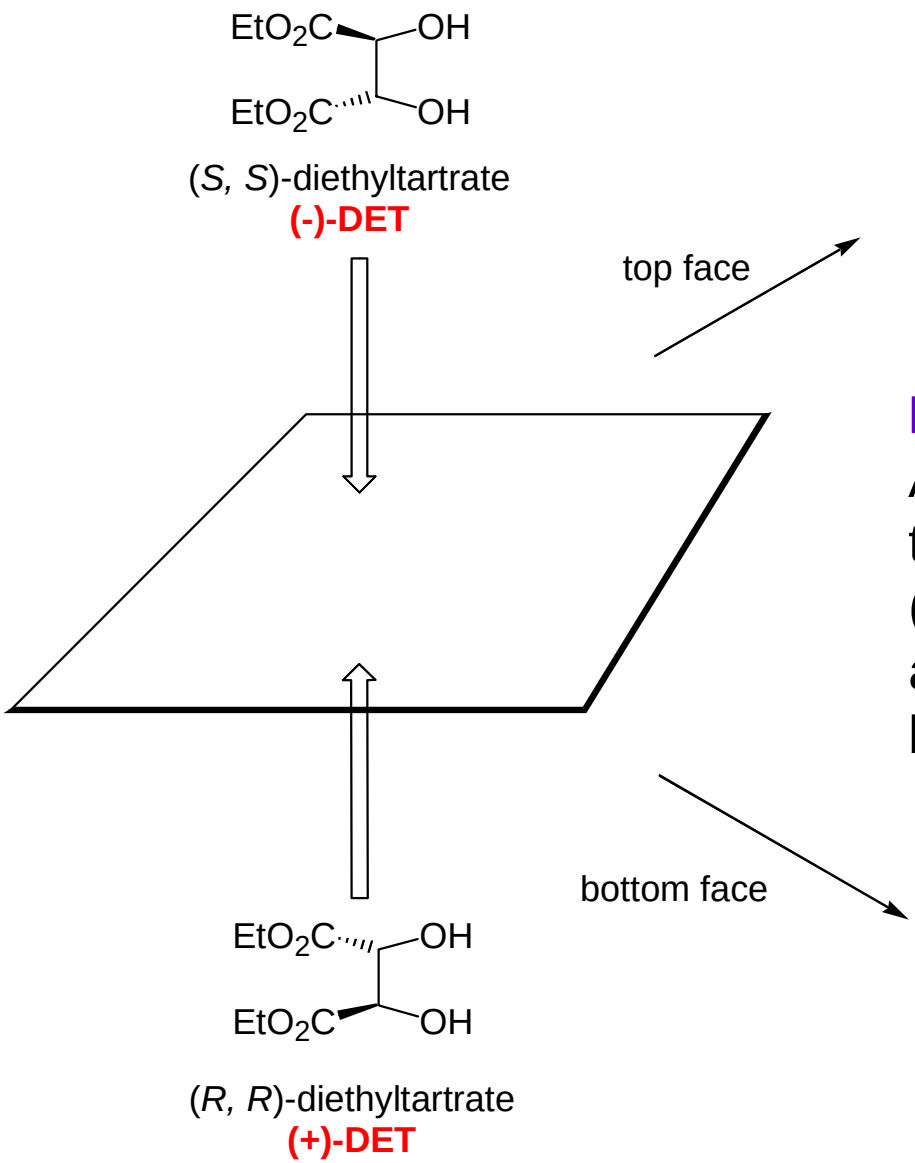


$Ti(O^iPr)_4$ works as a catalyst by bringing all the reagent together at the Ti centre. The alkyl peroxide is activated by bidentate cyclic co-ordination and nucleophilic attack by the alkene now takes place in the rate (and stereochemical) determining step.

Sharpless rationalised that if the ^{i}PrO ligands were replaced with a chiral alcohol then asymmetric induction may be achieved.

Sharpless Asymmetric Epoxidation (SAE) Reaction

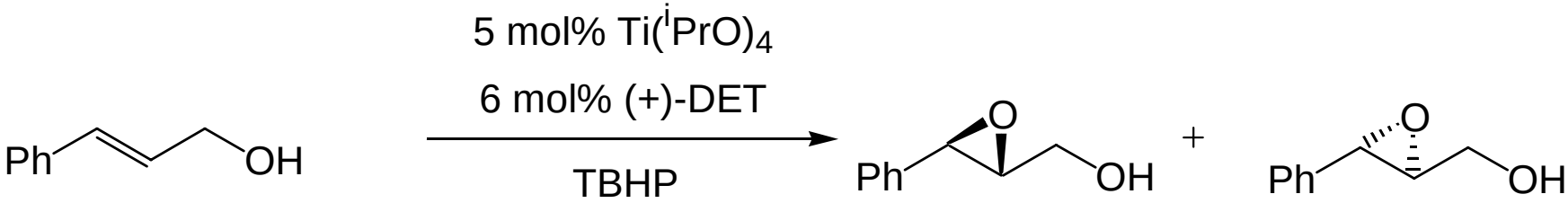
After much searching the optimum chiral alcohol was found to be diethyltartrate, which is readily available in either enantiomeric form.



Mnemonic:

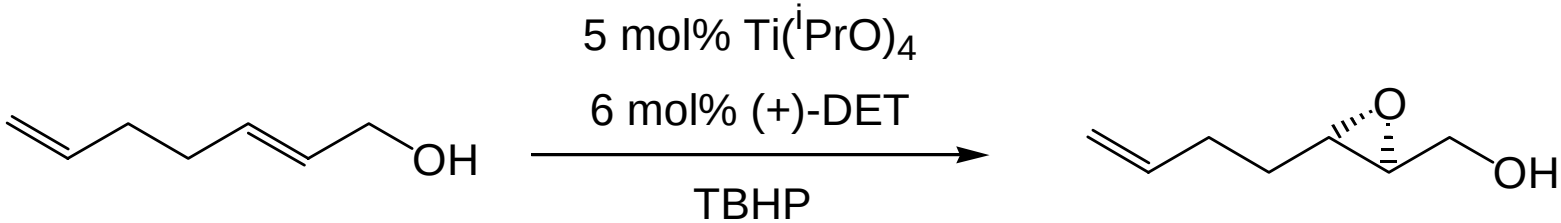
Alcohol function always goes in the front right (south east) corner. (-)-DET epoxidises the top face and (+)-DET epoxidises the bottom face.

Examples



3.5 : 96.5

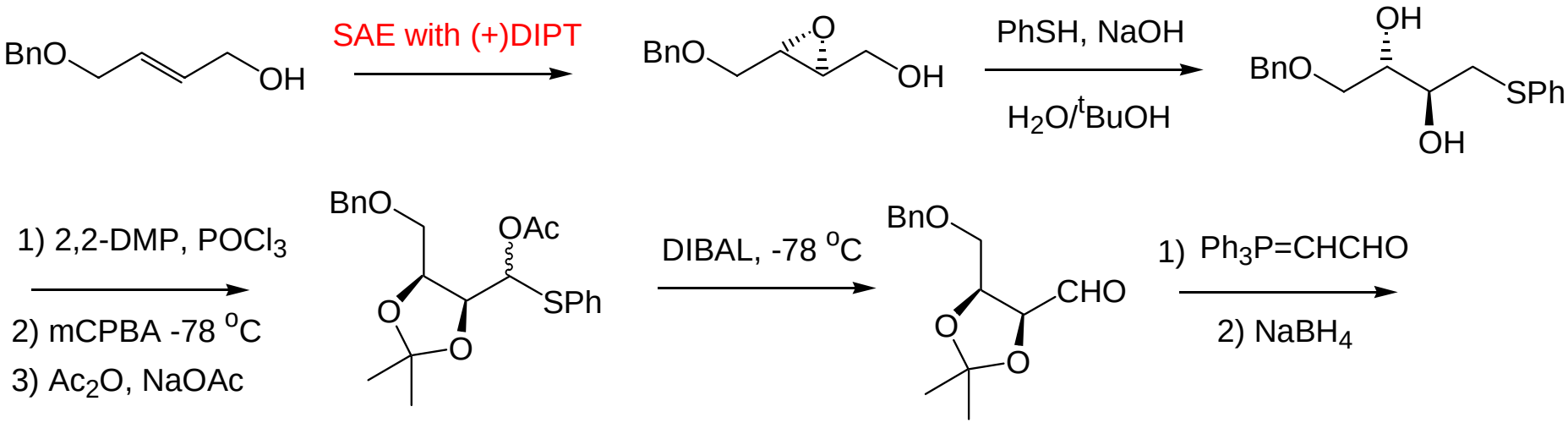
93% e.e.



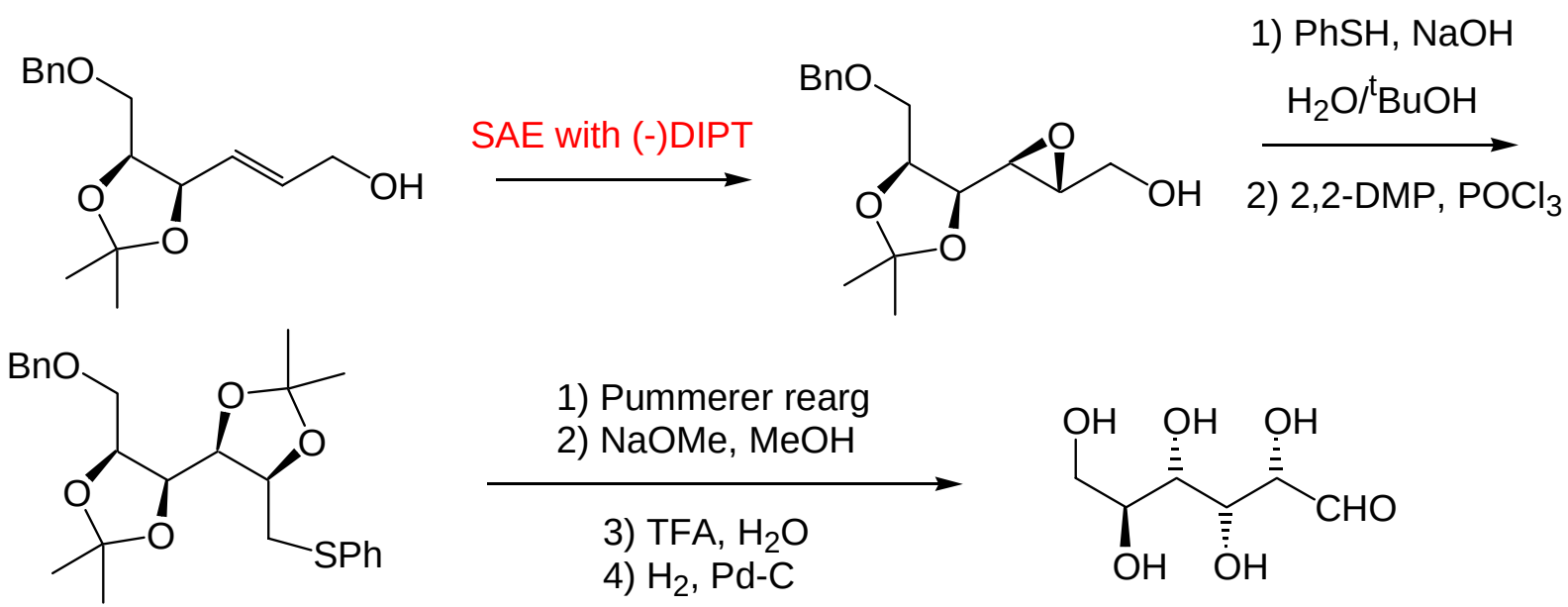
>95% e.e.

Substrate scope of SAE is limited to allylic alcohols, but this does mean that you can get chemoselective reactions, as this reagent set will only epoxidise alkenes next to alcohols. SAE works equally well for both *E*- and *Z*- alkene geometries.

The utility of the SAE was highlighted in a seminal piece of work: the asymmetric synthesis of all of the hexoses! We shall only look at *L*-glucose.

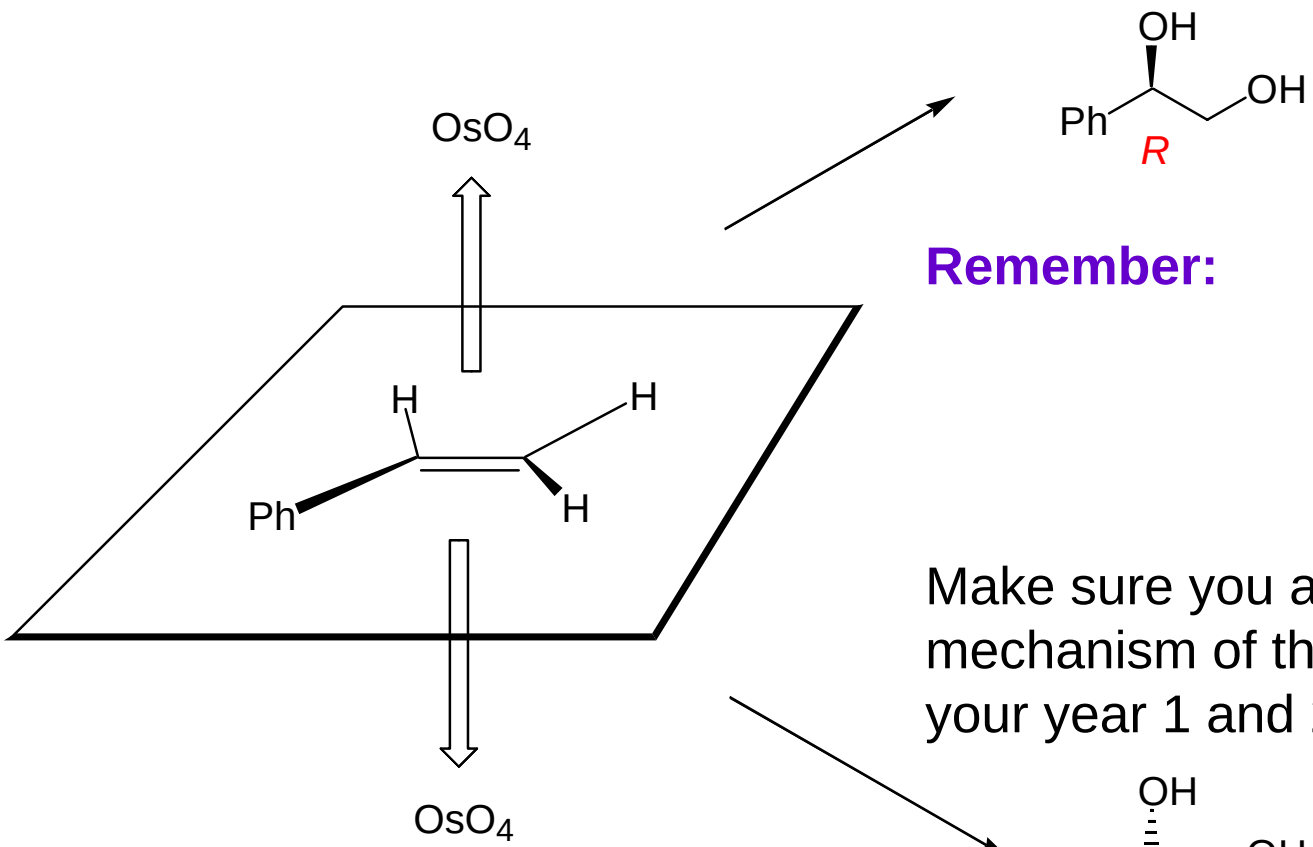


mechanism of Pummerer rearrangement?



Sharpless Asymmetric Dihydroxylation (ADH) Reaction

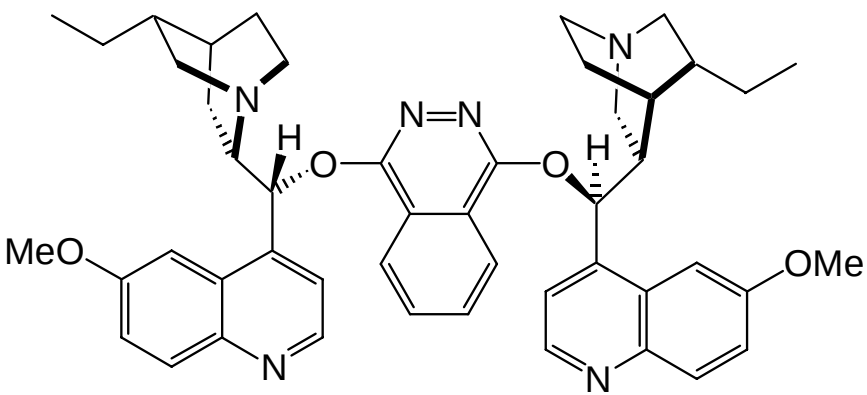
Racemic dihydroxylation using OsO_4 – no source of chirality present so equal amounts of both enantiomers are produced. If a stoichiometic oxidant (*i.e.* $K_3Fe(CN)_6$) is used then the osmium species can be re-oxidised and used in a catalytic amount. It was also know that the addition of amines to the reaction accelerated its rate.



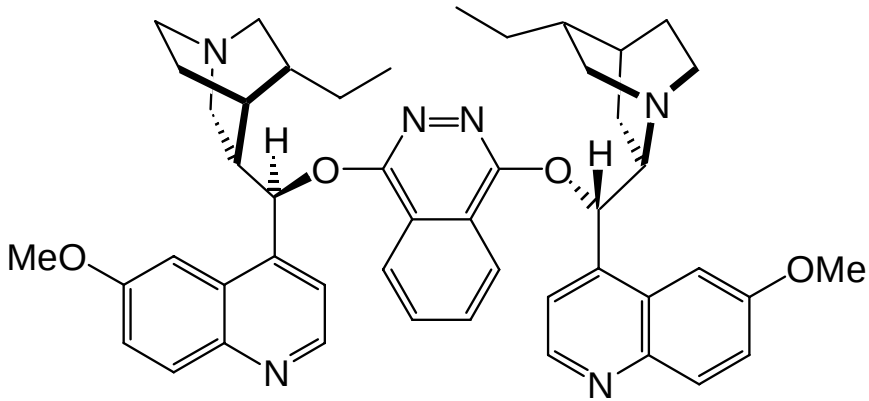
Remember:

Make sure you are familiar with the mechanism of this reaction from your year 1 and 2 notes.

Sharpless rationalised, that the use of chiral amines may result in an asymmetric ‘ligand accelerated’ reaction. After much investigation the optimum ligands were found to be:



$(DHQ)_2PHAL$
dihydroquinine

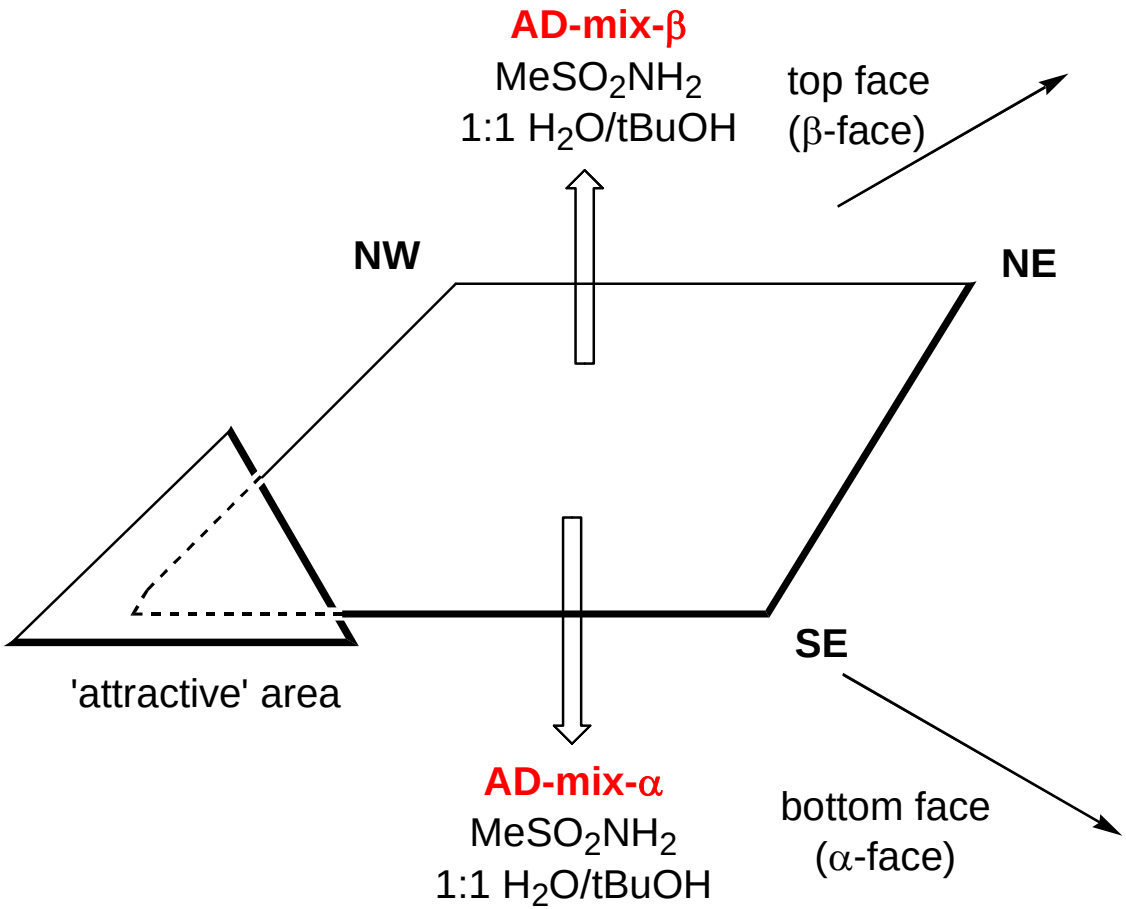


$(DHQD)_2PHAL$
dihydroquinidine

It was found that the catalytic ligand, catalytic OsO4, and the stoichiometic re-oxidant could be pre-mixed for ease of use. These pre-mixes are commercially available and are called AD-mix-α (contains $(DHQ)_2PHAL$) and AD-mix-β (contains $(DHQD)_2PHAL$).

Note: although dihydroquinine (DHQ) and dihydroquinidine (DHQD) are actually diastereomers they act like they are enantiomers of each other in the ADH reaction. For this reason they are termed pseudo-enantiomers.

Sharpless Asymmetric Dihydroxylation (ADH) Reaction: Mnemonic

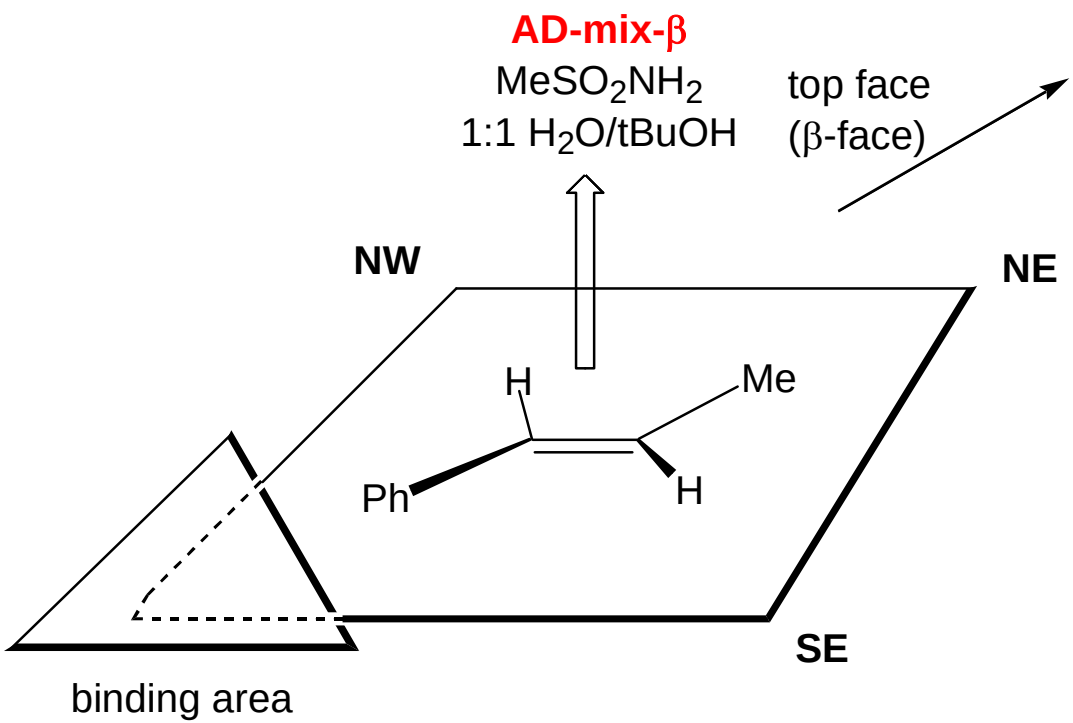


Must arrange the alkene in this way for the mnemonic to correctly predict which enantiomer is formed.

AD-mix-α: 3 eq. $K_3Fe(CN)_6$, 3 eq. K_2CO_3, 0.002 eq. $K_2OsO_2(OH)_2$, 0.01 eq. $(DHQ)_2PHAL$.

AD-mix-β: 3 eq. $K_3Fe(CN)_6$, 3 eq. K_2CO_3, 0.002 eq. $K_2OsO_2(OH)_2$, 0.01 eq. $(DHQD)_2PHAL$.

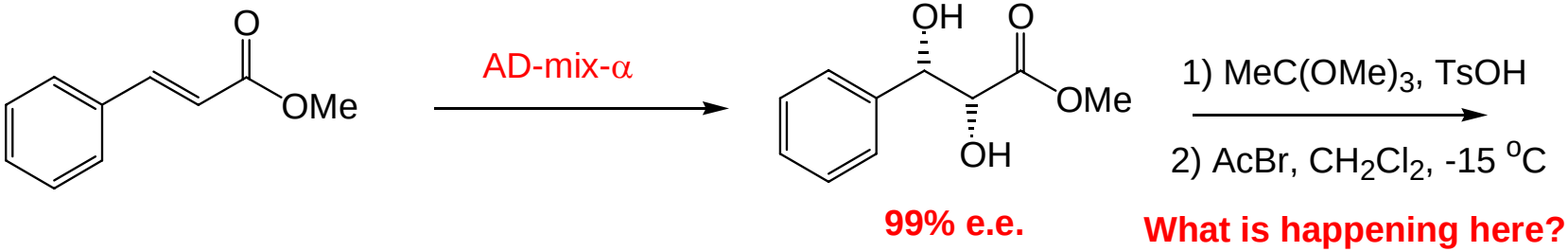
Example

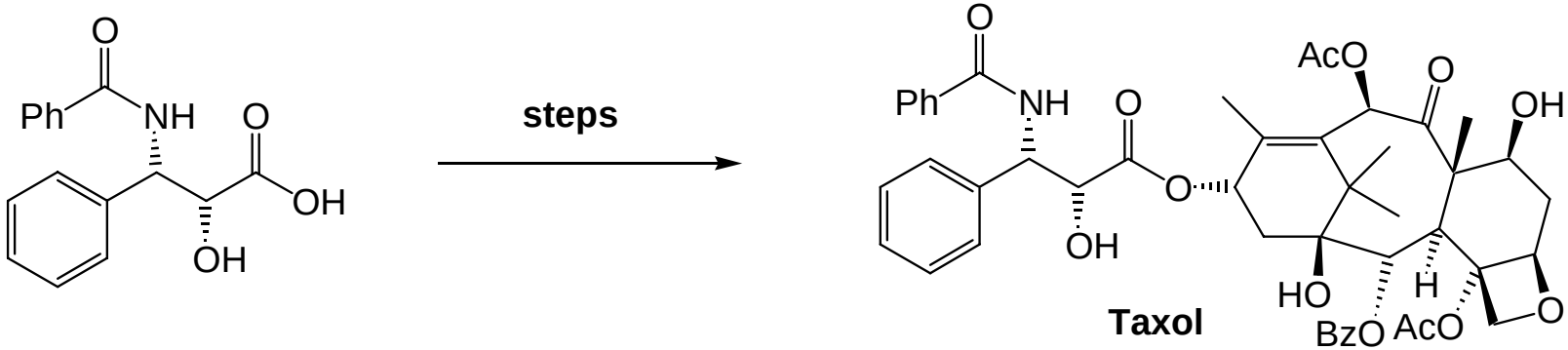


97% e.e.

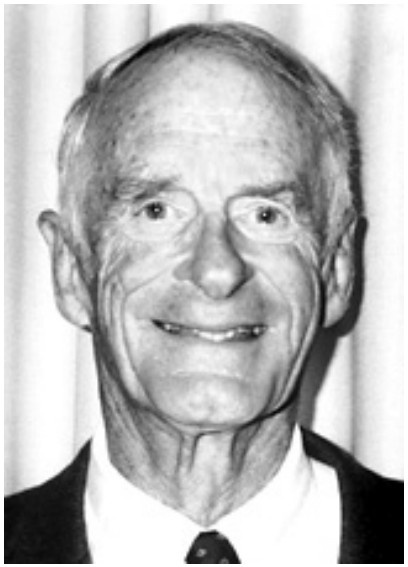
Note:

Synthesis of the Taxol side chain.





William S. Knowles, Ryoji Noyori and K. Barry Sharpless



b. 1917

b. 1938

b. 1941

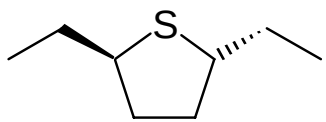
In 2001, Knowles, Noyori and Sharpless shared the Nobel Prize for Chemistry for their work on chirally catalysed hydrogenation reactions (Knowles and Noyori) and for his work on chirally catalysed oxidation reactions (Sharpless).

http://nobelprize.org/nobel_prizes/chemistry/laureates/2001/index.html

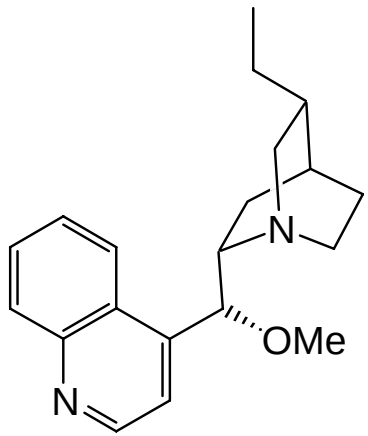
Asymmetric Organocatalysis

This is the use of small chiral organic molecules in the absence of any metals to promote asymmetric reactions. The first asymmetric organocatalytic reactions were reported in the early 20th century. Sporadic reports appeared over the years, but it took until the present day before the generality and scope of organocatalysis was fully realised. Simple chiral organic molecules are now used to catalyse a wide range of transformations with very high enantiomeric excesses. For example:

aldol,
mannich,
α-oxygenation,
α-amination

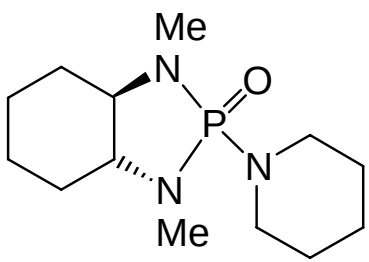


epoxidation

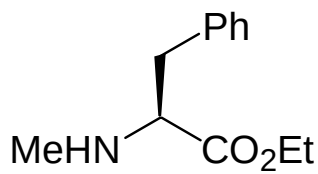


cyclopropanation

Diels-Alder,
Friedel-Crafts,
Michael



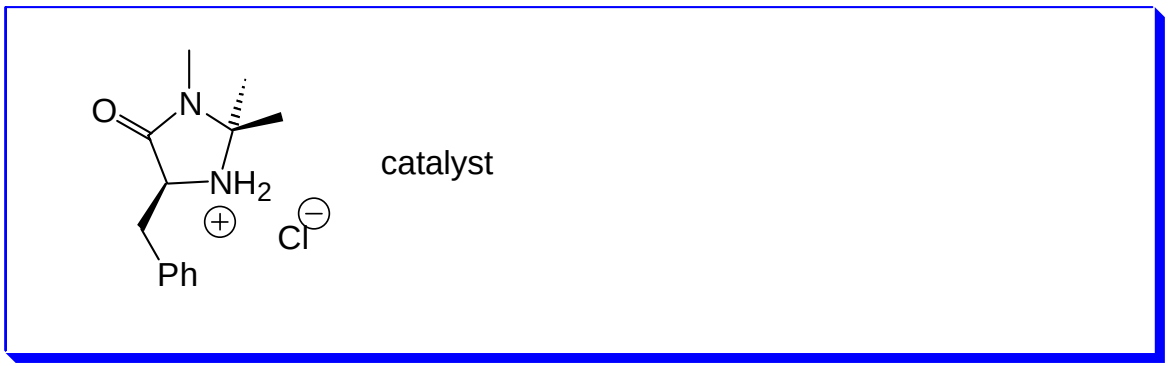
allylation

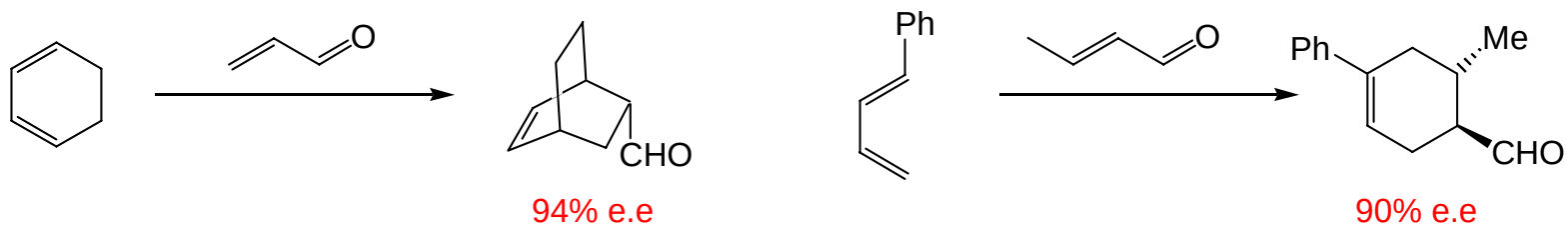


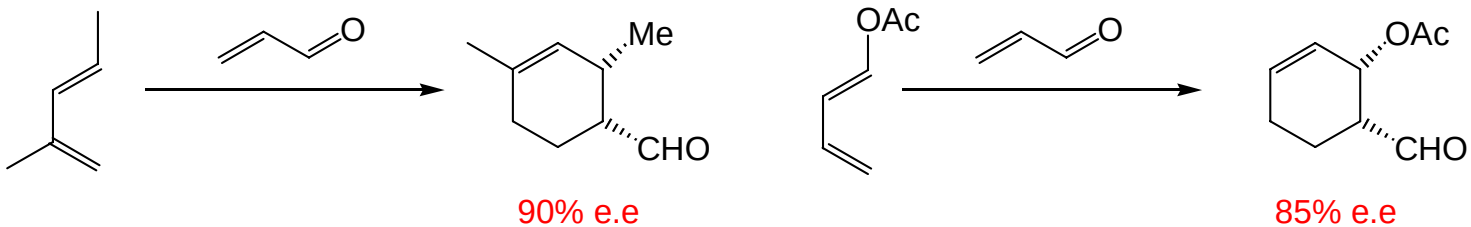
aqueous aldol

Iminium Catalysed Asymmetric Diels-Alder Reaction.

Formation of an iminium ion lowers the LUMO of the dieneophile in much the same way as co-ordination to a Lewis acid. As iminium ion formation is reversible it is possible to envisage catalytic cycle. This is exemplified by the work of MacMillan.

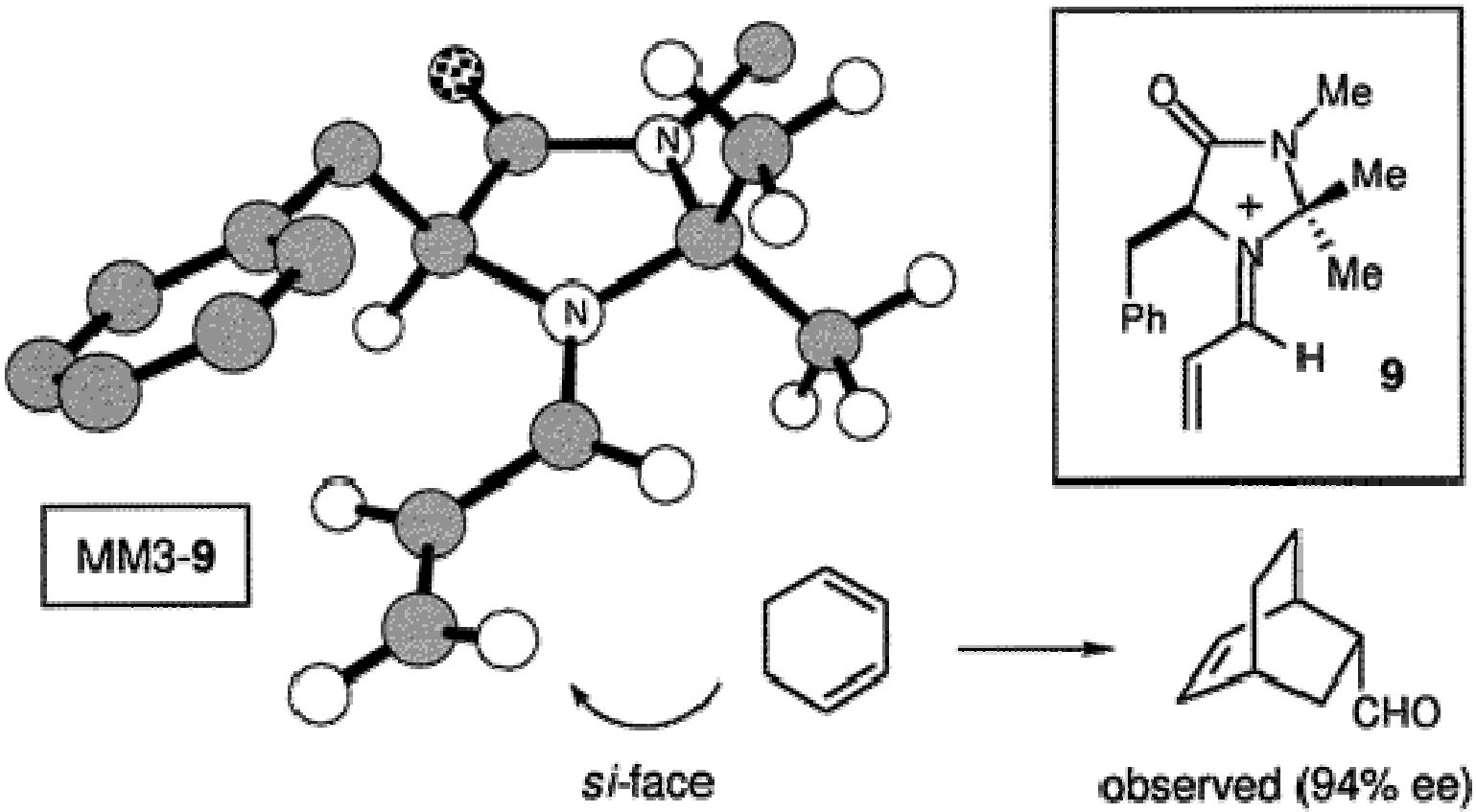






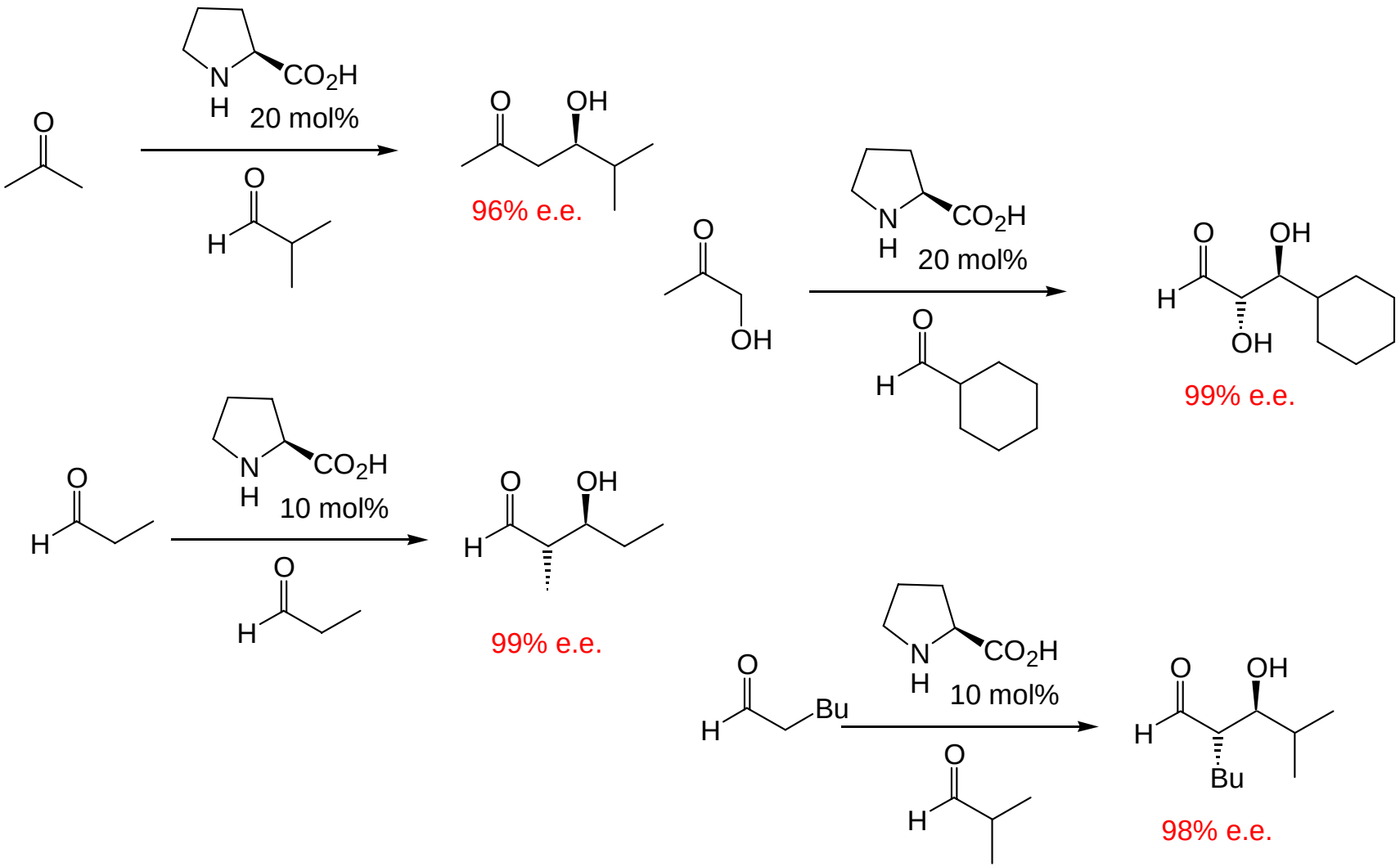
Explanation of the Selectivity

Steric clash between the dieneophile and the lower Me group on the catalyst coupled with π-stacking of the dieneophile double bond beneath the Ph-group of the catalyst orientates the dieneophile double bond as shown.



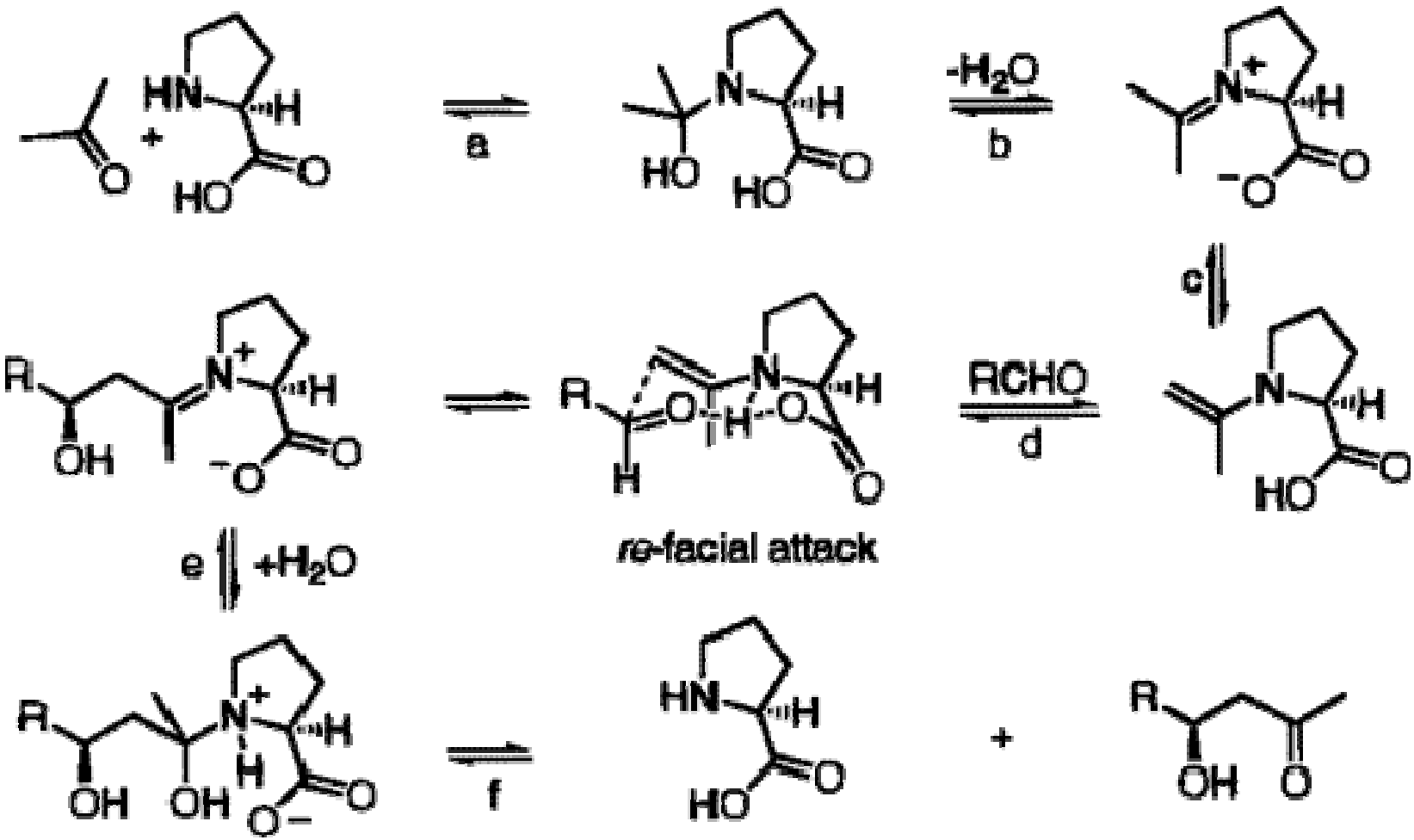
Proline Catalysed Aldol Reaction

The proline catalysed aldol reaction, developed independently by List, Barbas, MacMillan and Cordova, uses catalytic amounts (~20 mol%) of the amino acid proline.

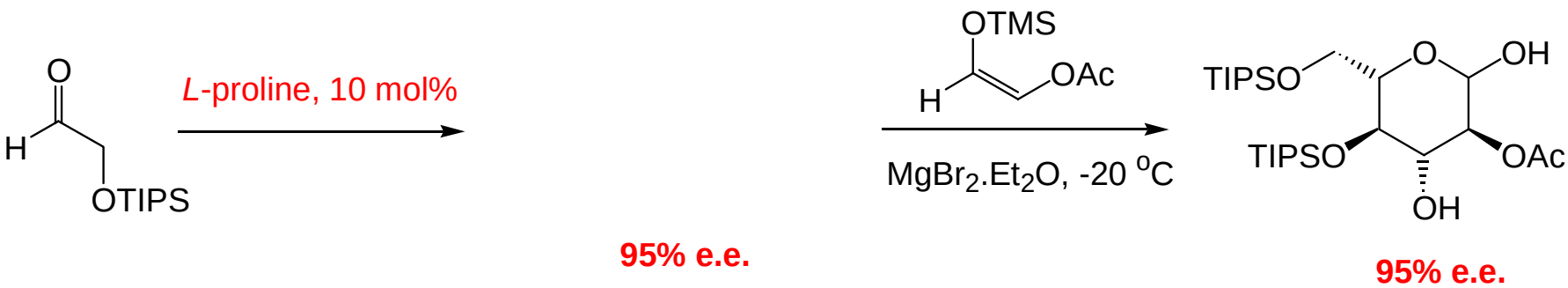


Rationalisation of the Enantioselectivity

Hydrogen bond formation between the carboxylic acid, enamine nitrogen and the aldehyde ensures that a 6-membered transition sate exists which, in the case of (*S*)-proline, means the enamine double bond attacks from the Re-face of the aldehyde's carbonyl group.



Organocatalytic synthesis of glucose.



Science **2004**, *305*, 1752

Compare this to the SAE synthesis of other hexoses discussed earlier!

End of the Course

You should have an appreciation of 1) the types of asymmetric reactions which may be employed in organic synthesis, 2) an understanding of the origins of the enantioselectivities and the mechanisms of the reactions and 3) the ability to propose asymmetric syntheses of organic molecules of medium complexity.