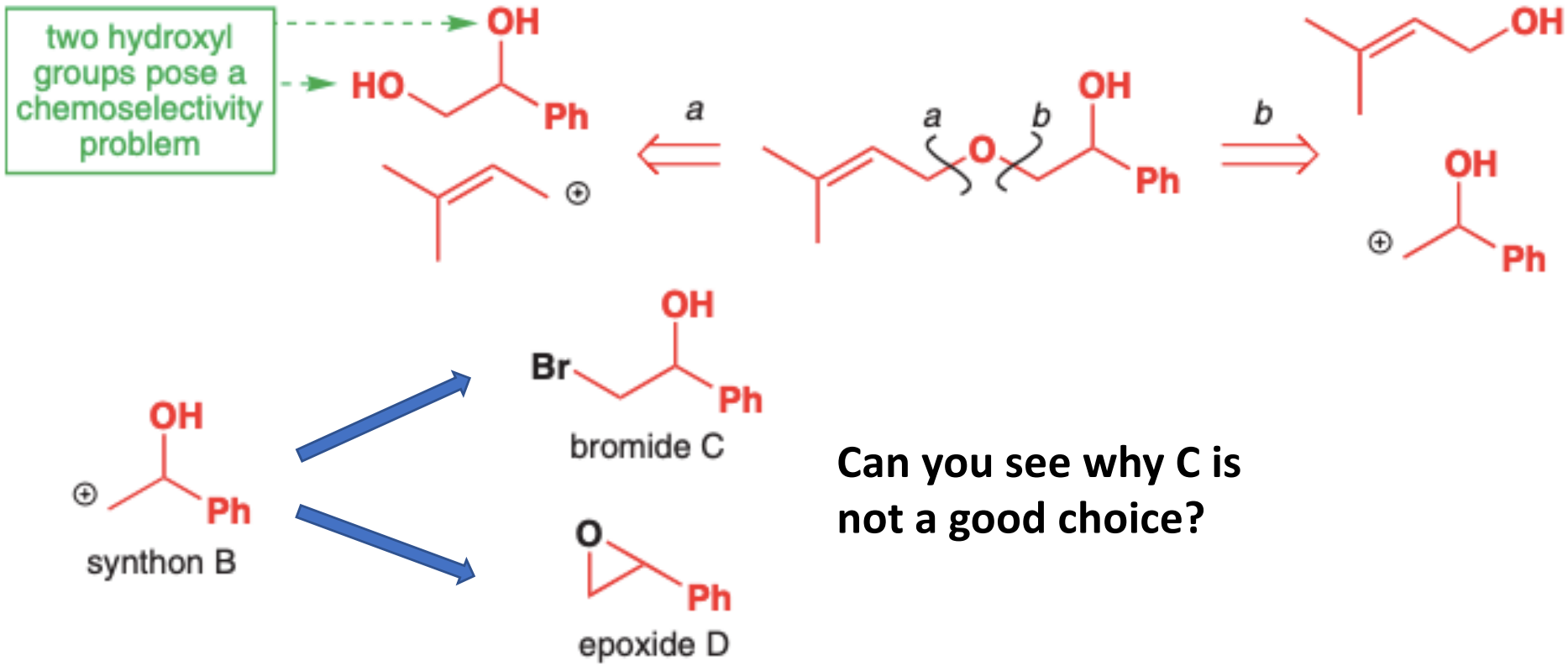
LS 2022

Lecture 3: 2022-12-14

From previous session

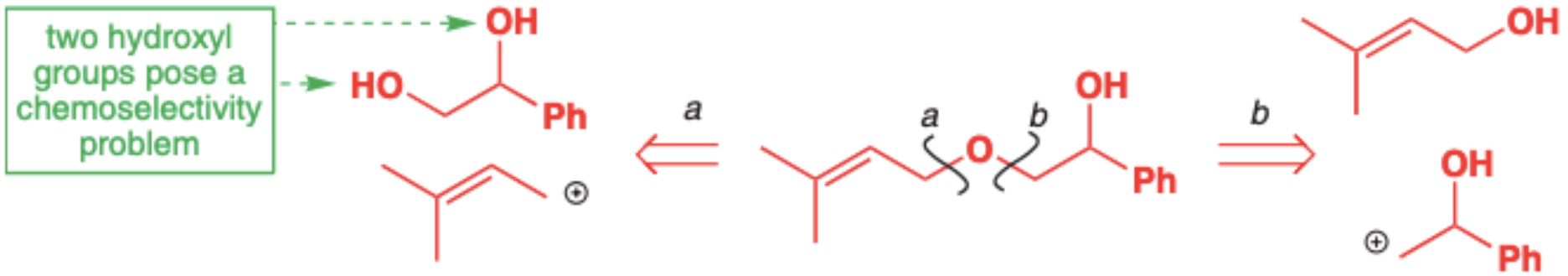
Two groups disconnection are better than one

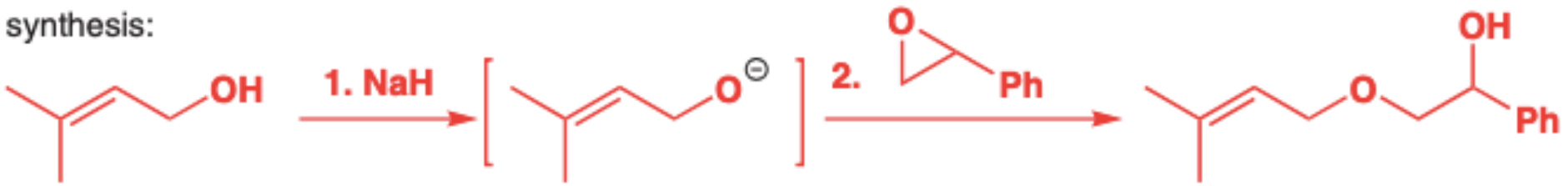


Can you see why C is not a good choice?

In using the epoxide we have gone one step beyond all the disconnections we have talked about so far because we have *used one functional group to help disconnect another*—in other words, we noticed the alcohol adjacent to the ether we wanted to disconnect and managed to involve them both in the disconnection. Such disconnections are known as two-group disconnections

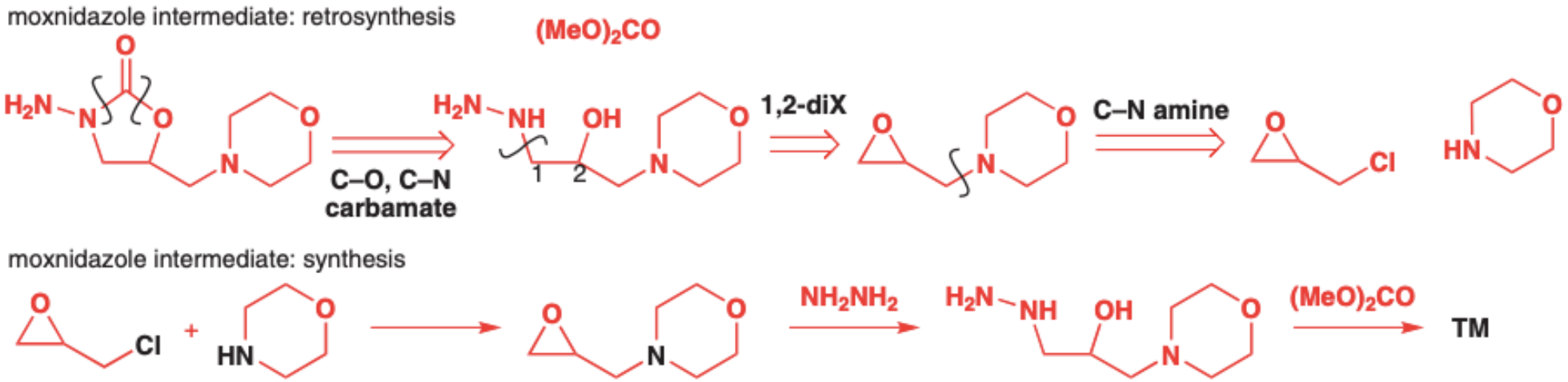
Two groups disconnection are better than one





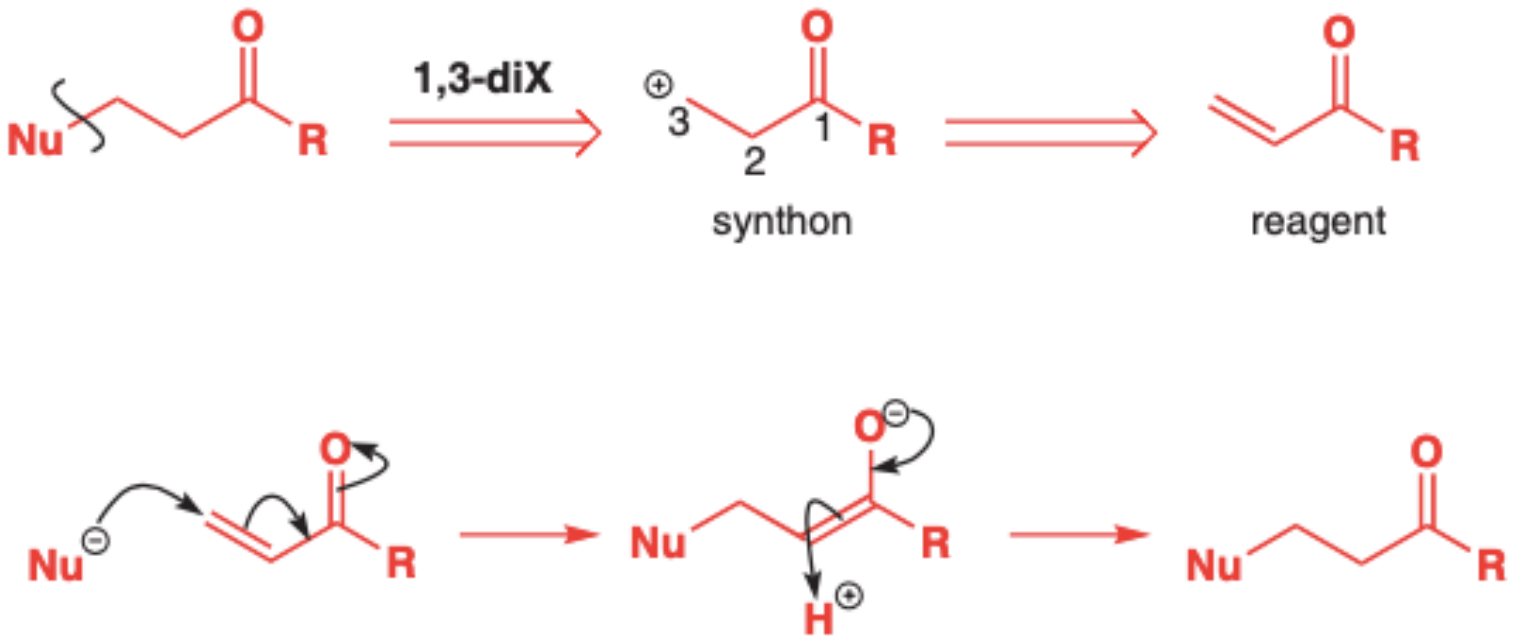
Two groups disconnection are better than one

Notice that we have written '1,2-diX' above the arrow to show that it's a two-group ('diX')



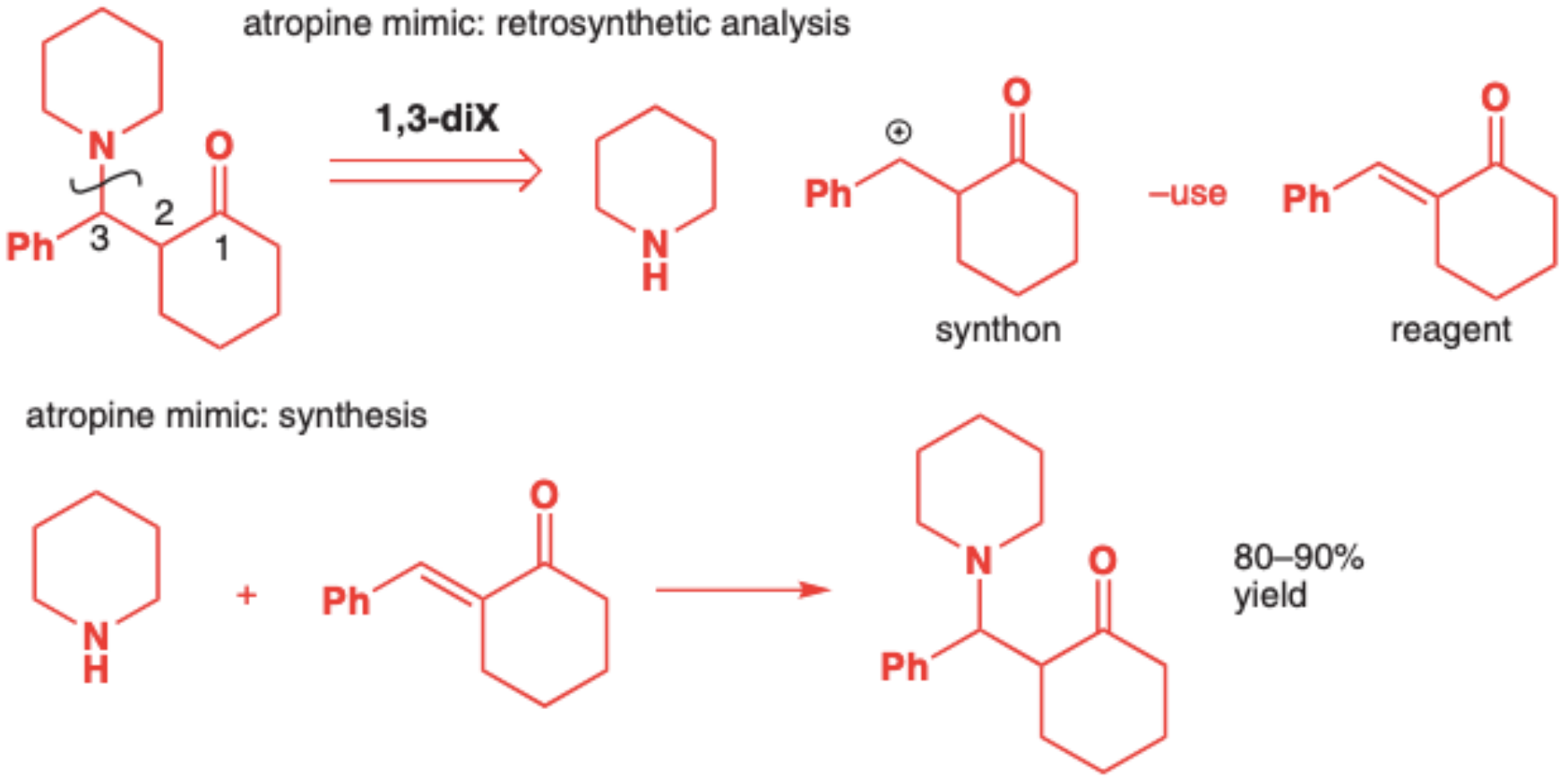
Moxnidazole is an antiparasitic drug, and our next target molecule is an important intermediate in its synthesis. The obvious first disconnection is of the carbamate group, revealing two 1,2-relationships. A 1,2-diX disconnection gives an epoxide that can be made by alkylation of morpholine with epichlorohydrin.

1,3-disconnections

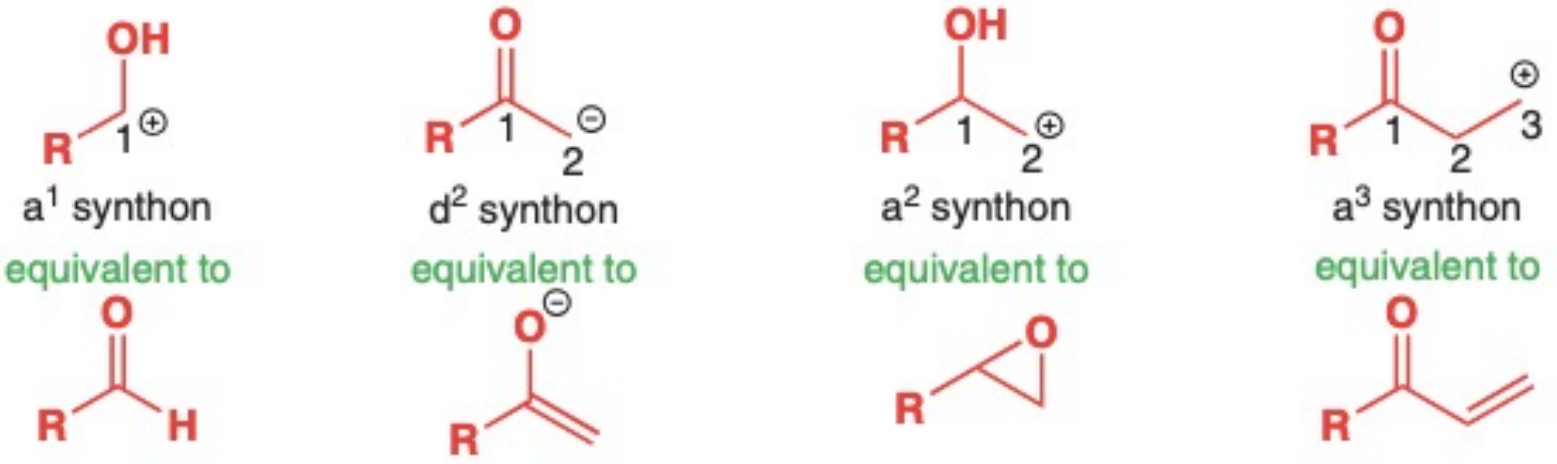


Remember that not all nucleophiles will successfully undergo Michael additions—you must bear this in mind when making a 1,3-disconnection of this type. Most reliable are those based on nitrogen, sulfur, and oxygen (enolates).

1,3-disconnections



Donors and acceptors synthons

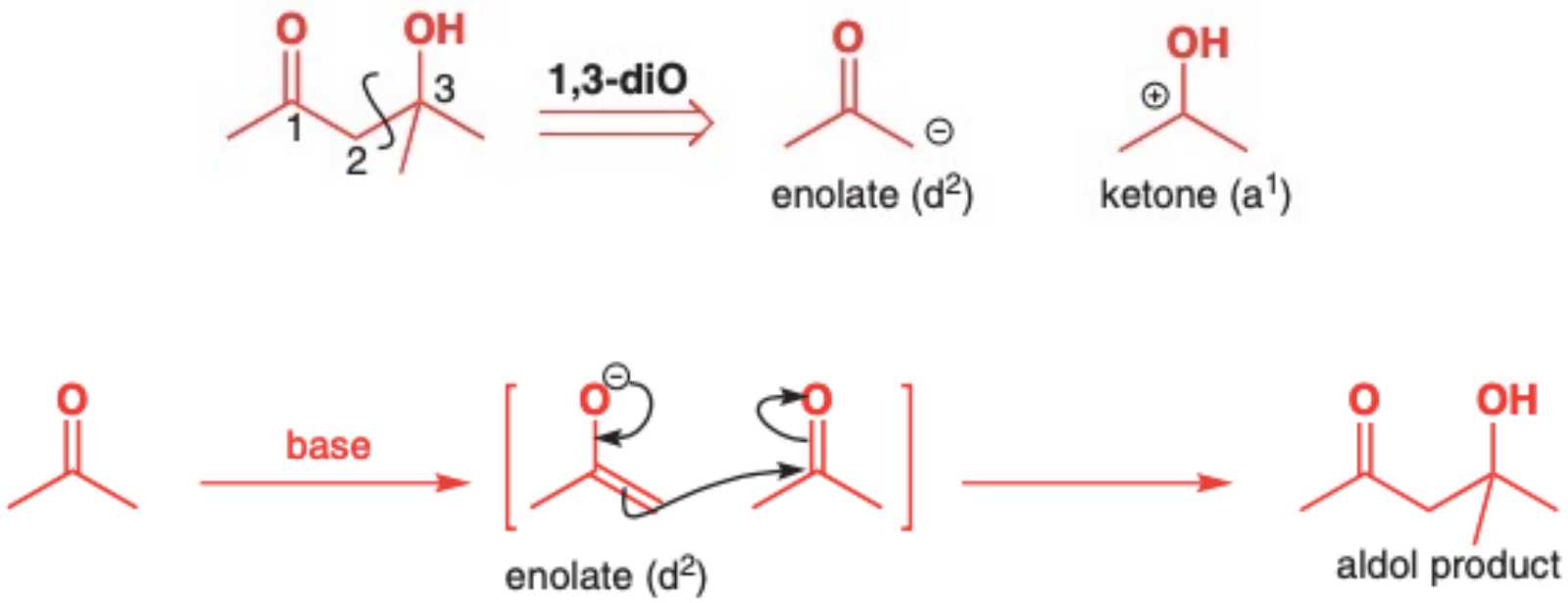


- **Synthons are classified as a (acceptor) or d (donor)**

  A number shows the position of the acceptor or donor site relative to a functional group.

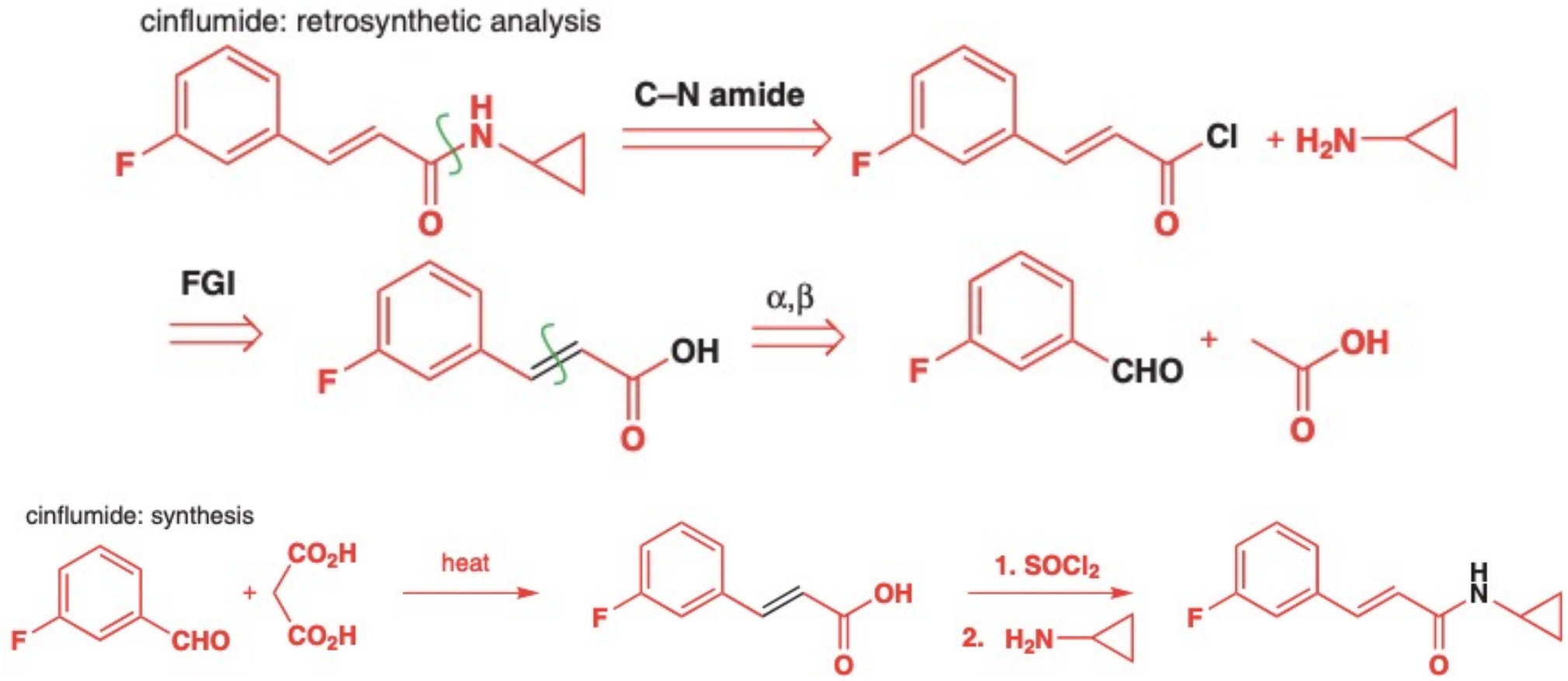
  An example of an a^1 synthon is a carbonyl compound and an example of a d^2 synthon is an enolate or an enolate equivalent.

Donors and acceptors synthons



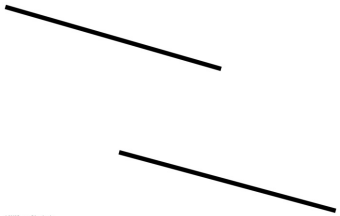
The aldol reaction is extremely important in organic synthesis because it makes compounds with two functional groups in a 1,3-relationship. Whenever you spot this 1,3-relationship in a target molecule—think aldol! In disconnection terms we can represent it like this.

Donors and acceptors synthons

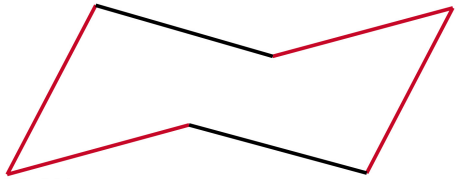


Drawing the Chair Conformer

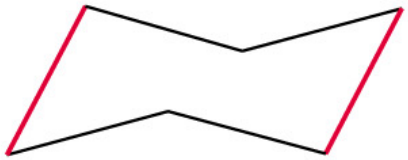
Draw 2 parallel lines.

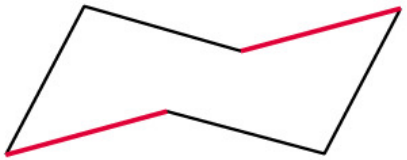


Connect ends with a V.

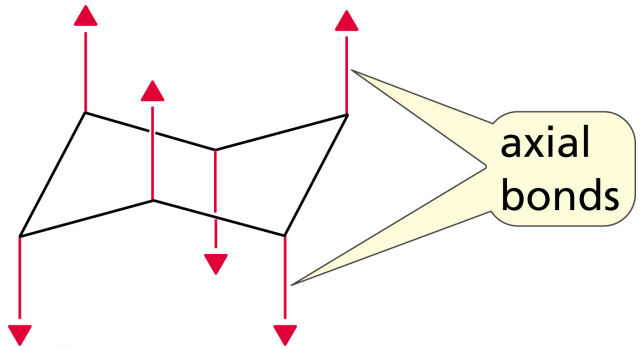


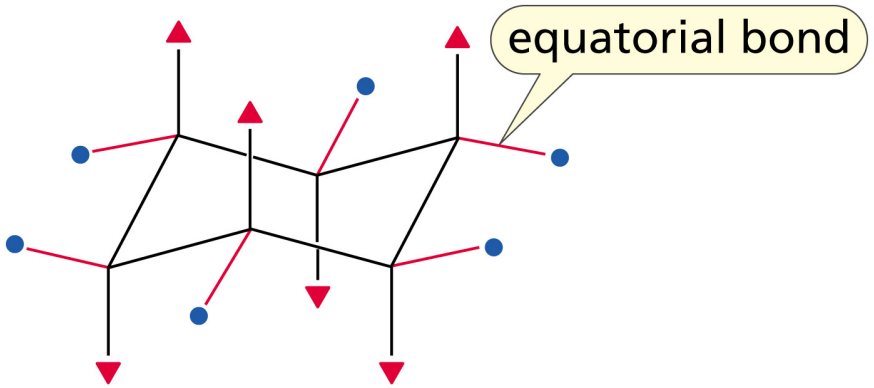
Notice that the chair has 3 sets of parallel lines.



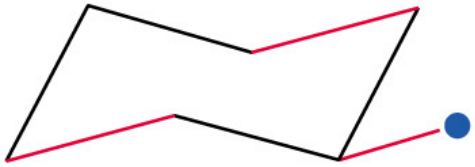


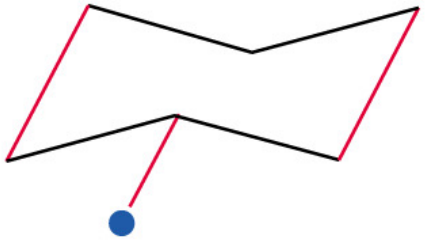
Axial and Equatorial Bonds



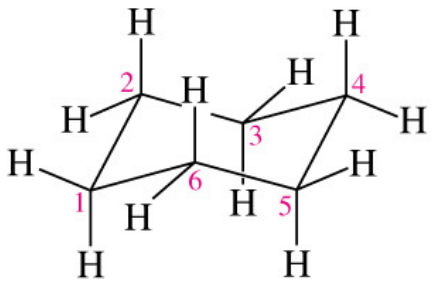


Notice that each equatorial bond is parallel to the two ring bonds one black bond away.

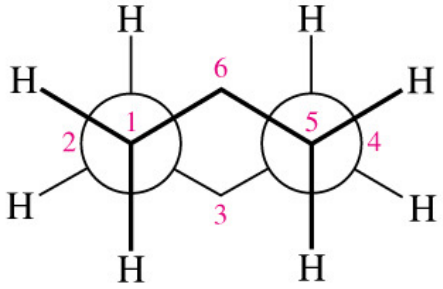




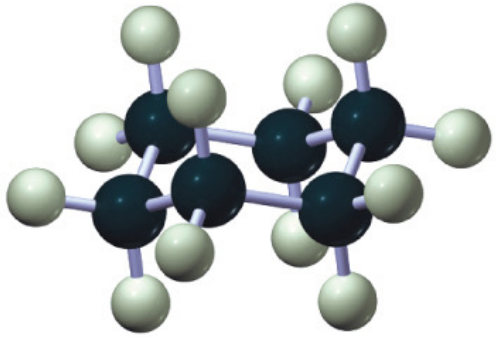
Chair Conformer of Cyclohexane



chair conformer of cyclohexane



Newman projection of the chair conformer looking down the C-1 — C-2 and C-5 — C-4 bonds



ball-and-stick model of the chair conformer

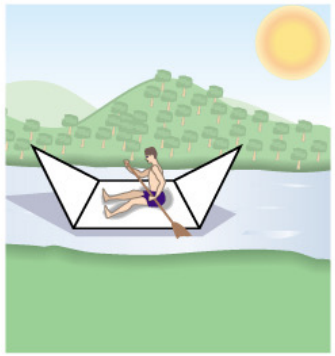
The chair conformer of cyclohexane is completely

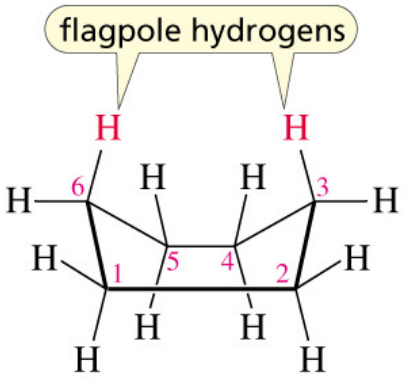
free of strain.

All bond angles are 111° and

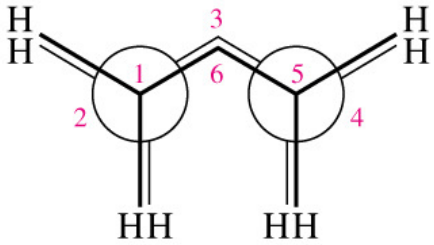
all adjacent bonds are staggered.

The Boat Conformer of Cyclohexane

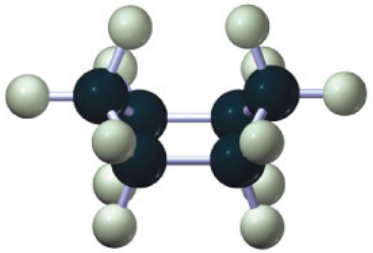




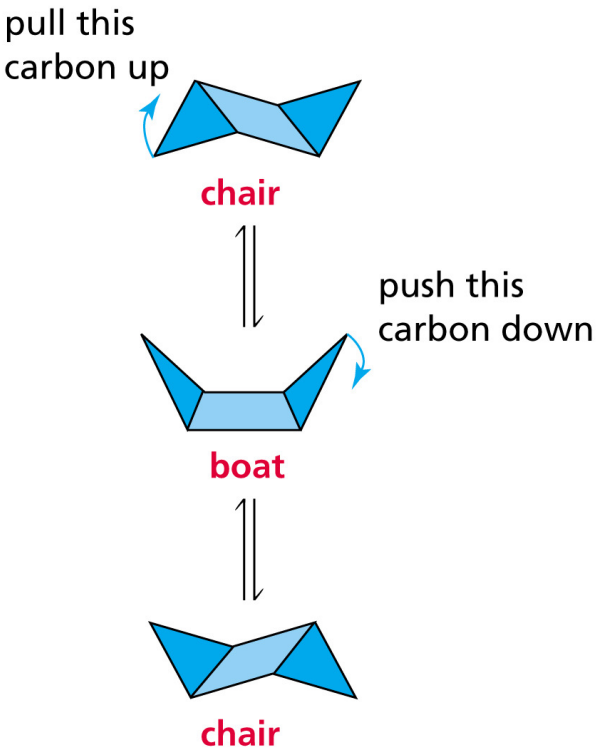
boat conformer of cyclohexane



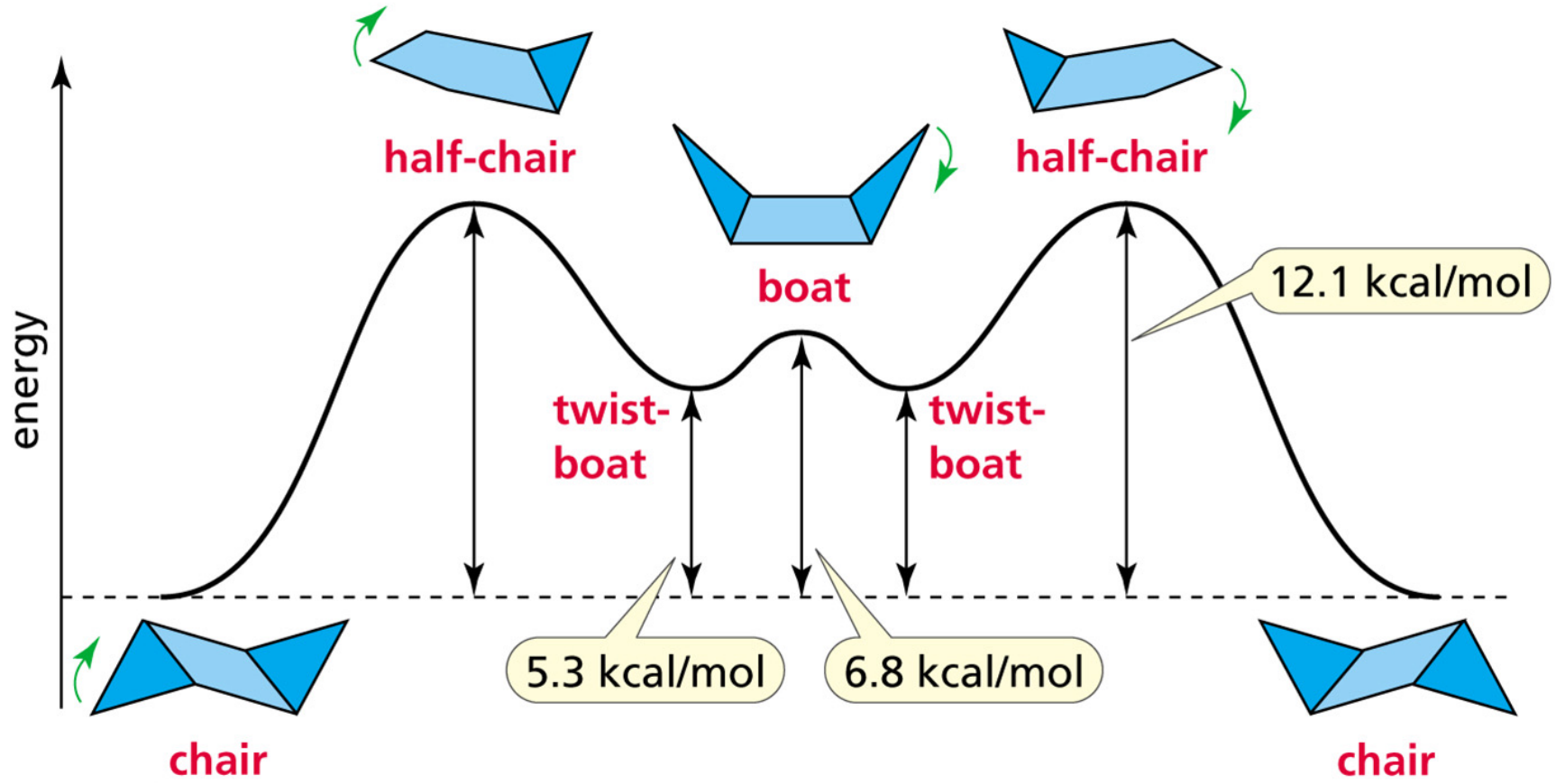
Newman projection of the boat conformer



ball-and-stick model of the boat conformer

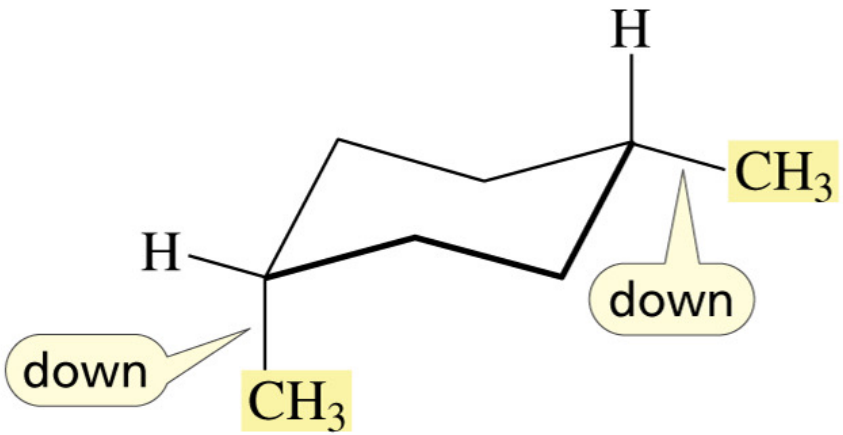


Conformers of Cyclohexane



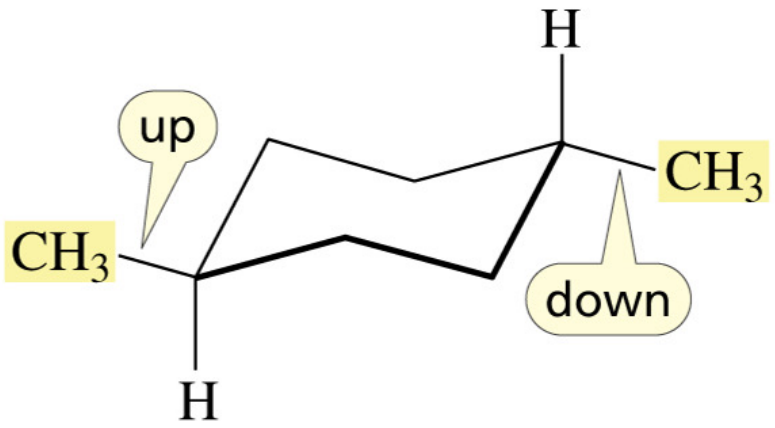
Cis and Trans Isomers

two methyl groups are on the same side of the ring



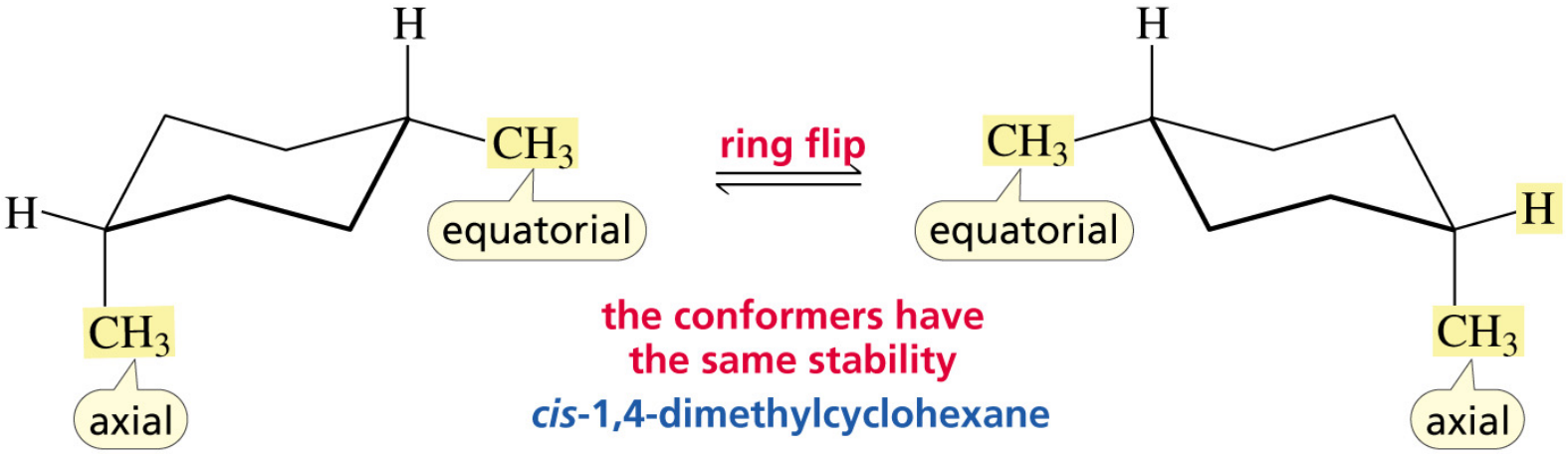
cis-1,4-dimethylcyclohexane

two methyl groups are on opposite sides of the ring



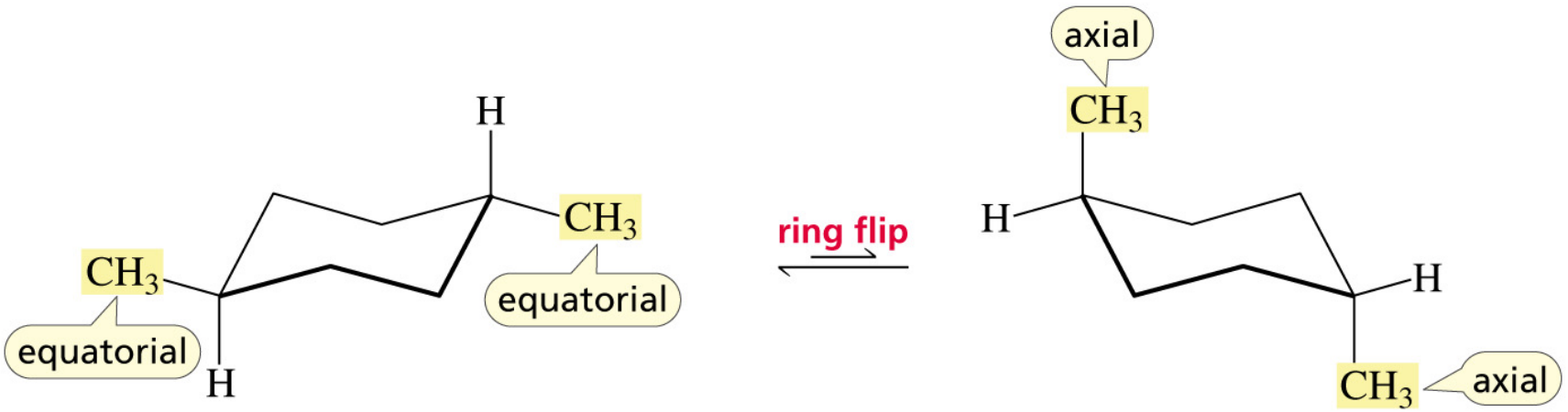
trans-1,4-dimethylcyclohexane

Each Isomer Has Two Chair Conformers



the conformers have
the same stability

cis-1,4-dimethylcyclohexane

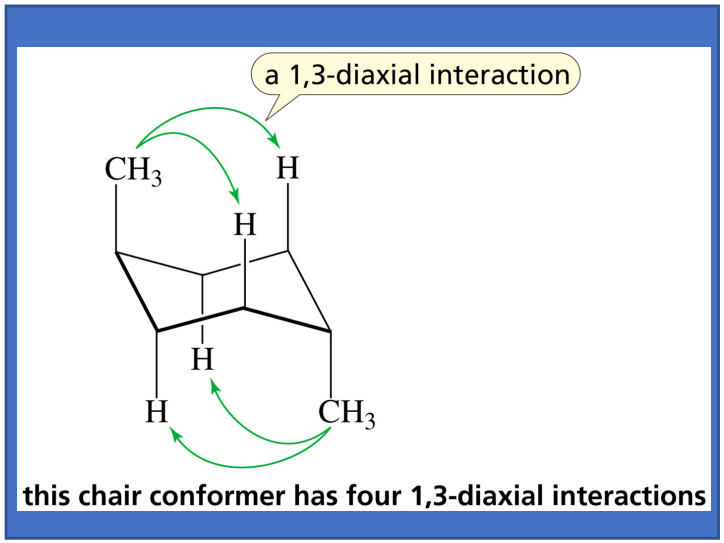


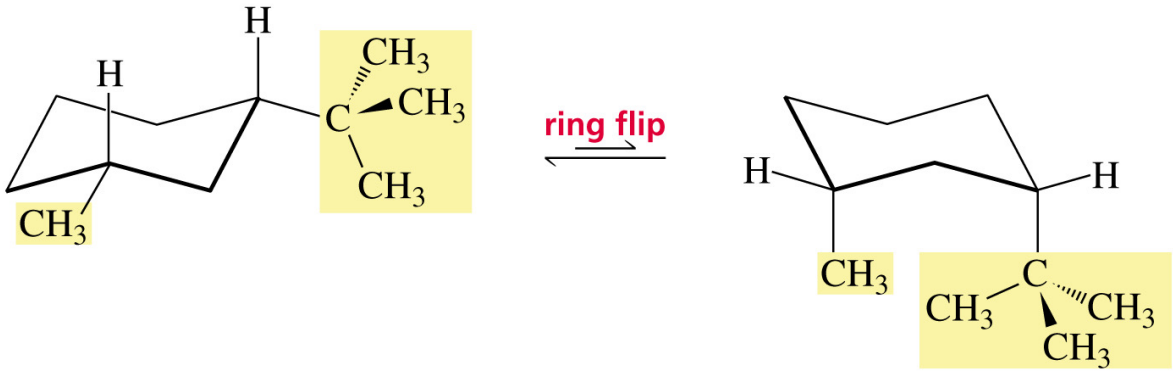
more stable

less stable

trans-1,4-dimethylcyclohexane

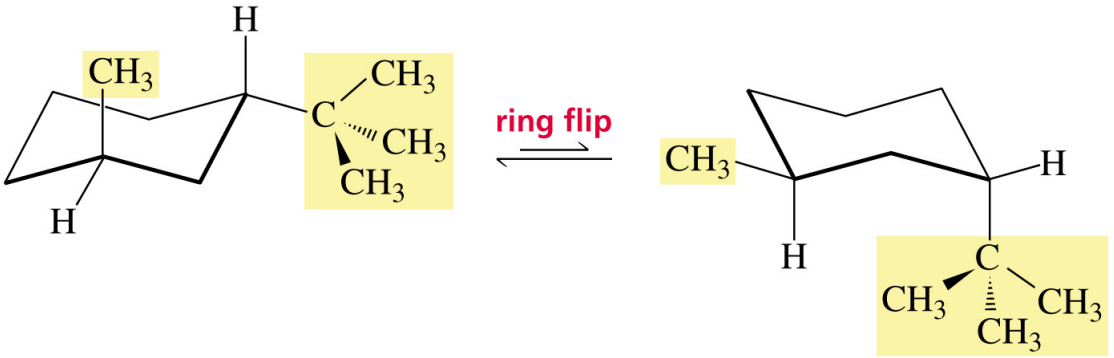
Each Axial Substituent has Two Diaxial Interactions





more stable — less stable

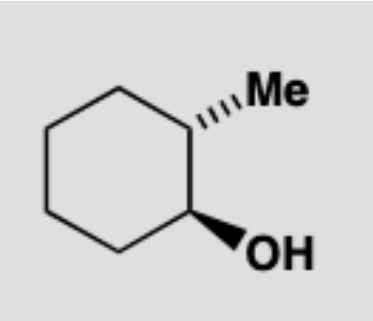
cis-1-*tert*-butyl-3-methylcyclohexane

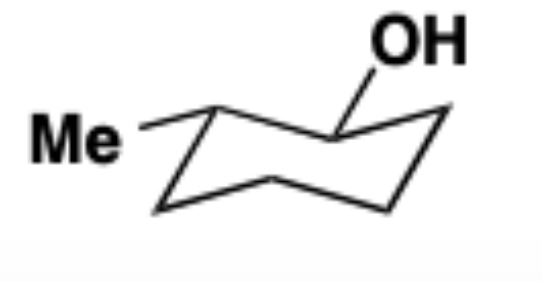


more stable — less stable

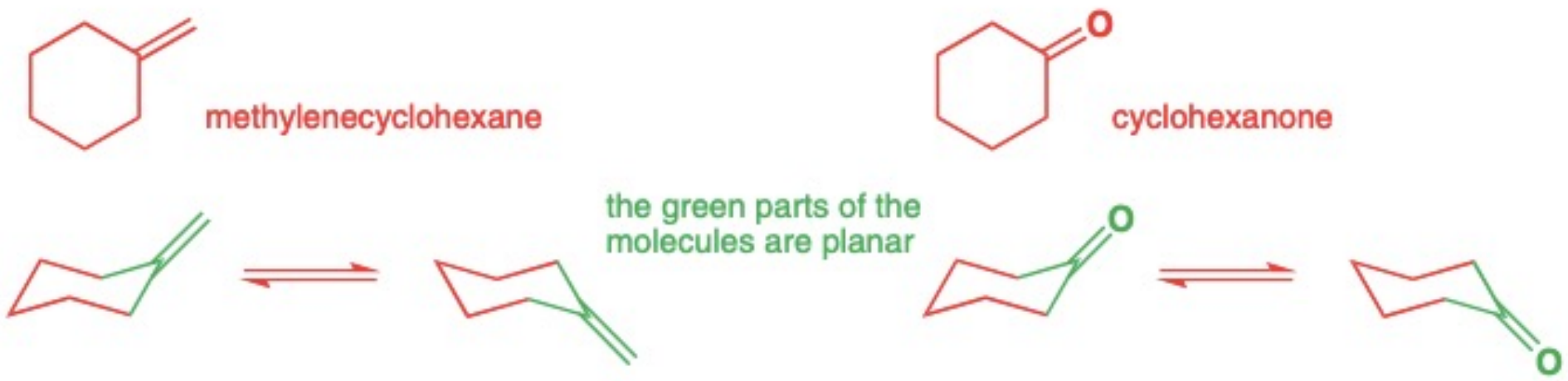
trans-1-*tert*-butyl-3-methylcyclohexane

Different representations



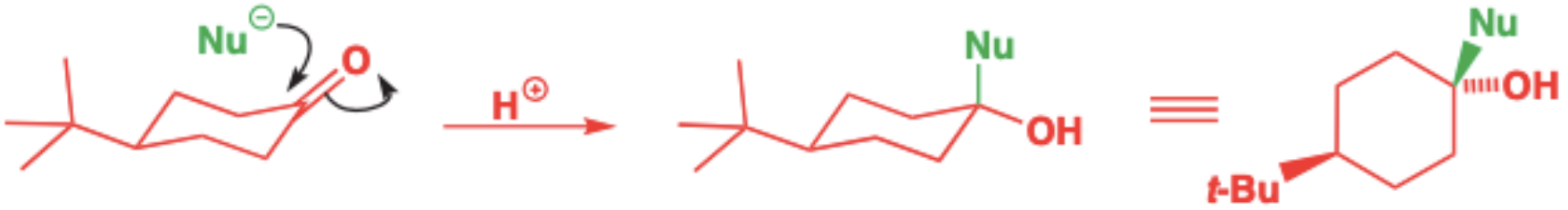


Six-membered ring with one C-sp^2 atom



Six-membered ring with one C-sp^2 atom

axial attack of the nucleophile

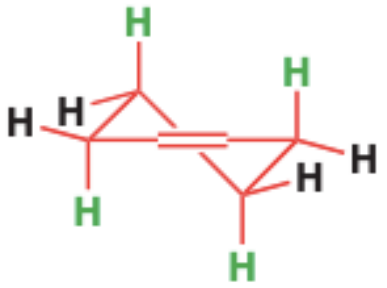


equatorial attack of the nucleophile

Now think of a nucleophile attacking 4-*t*-butylcyclohexanone. Since the *t*-butyl group locks the ring (*t*-Bu can never be axial), whether Nu is axial or equatorial will depend only on which face of the C=O group it attacks. Attack on the same face as the *t*-butyl group leaves the nucleophile axial and the hydroxyl group equatorial; attack on the opposite face leaves the nucleophile equatorial and the hydroxyl group axial.

Six-membered ring with two or more C-sp^2 atoms

cyclohexene adopts a 'flattened chair' or 'half-chair' conformation

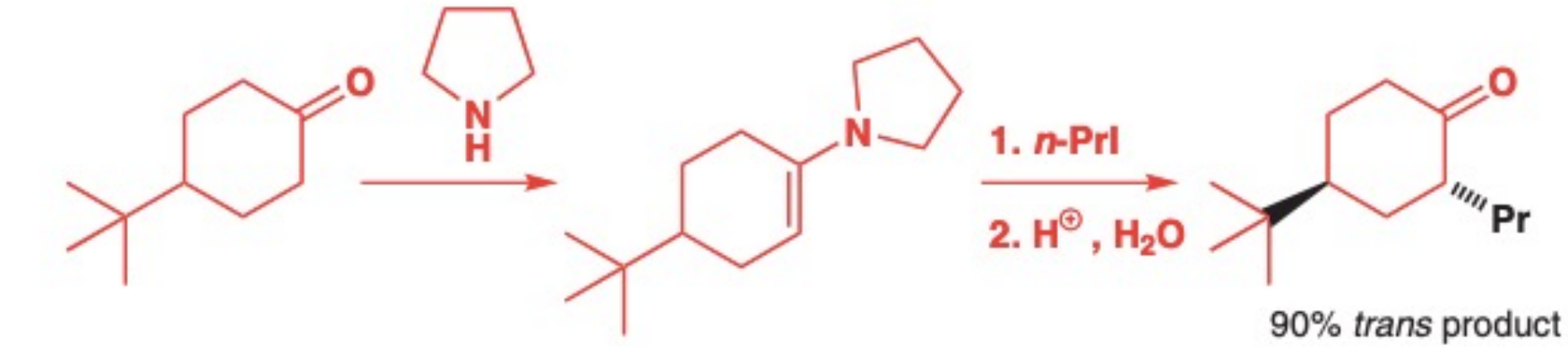


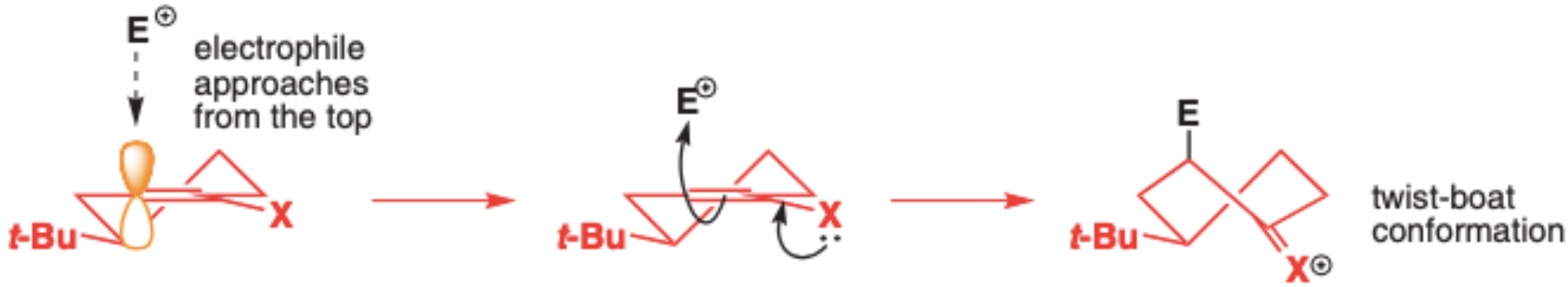
hydrogens adopt pseudoaxial or pseudoequatorial orientations

With more than two trigonal carbon atoms in the ring, a cyclohexene can no longer adopt a chair conformation. At least four of the atoms in the ring must now be in a plane, and the best way to represent this is in the diagrams shown below. The four atoms in the plane are nearest you, with the remaining two placed one above and one below that plane.

- **The number of trigonal carbon atoms in the ring decides which factors control stereoselectivity**
  - Six-membered rings with one trigonal (sp^2) carbon atom are already chairs and can undergo *axial or equatorial attack*.
  - Six-membered rings with two or more trigonal carbon atoms are not chairs and undergo *axial attack* in order to form chairs rather than boats. The final product may end up with axial or equatorial substitution, but this is not a consideration in the reaction itself.

Six-membered rings

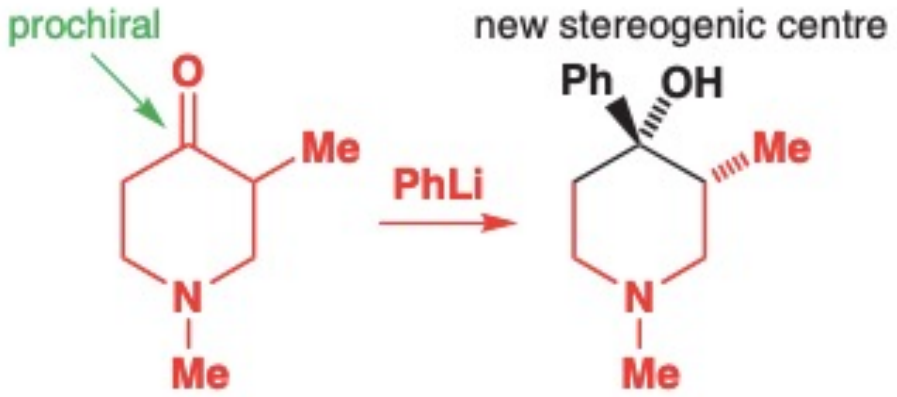




where X may be OH, O^-, $OSiMe_3$, NR_2, and so on. The double bond ($2 \times sp^2$

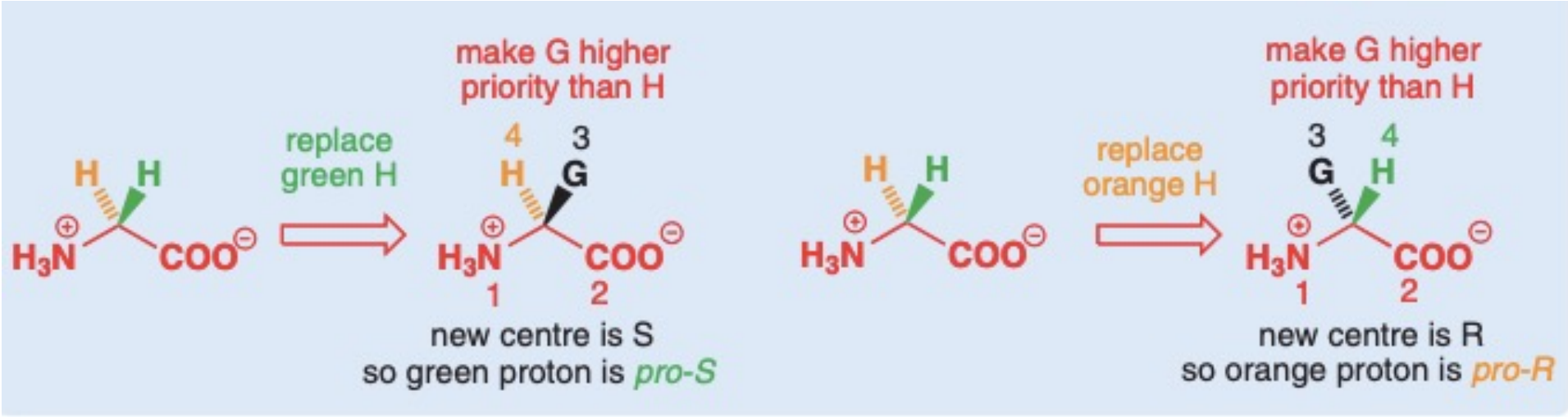
Diastereoselectivity

Prochiral

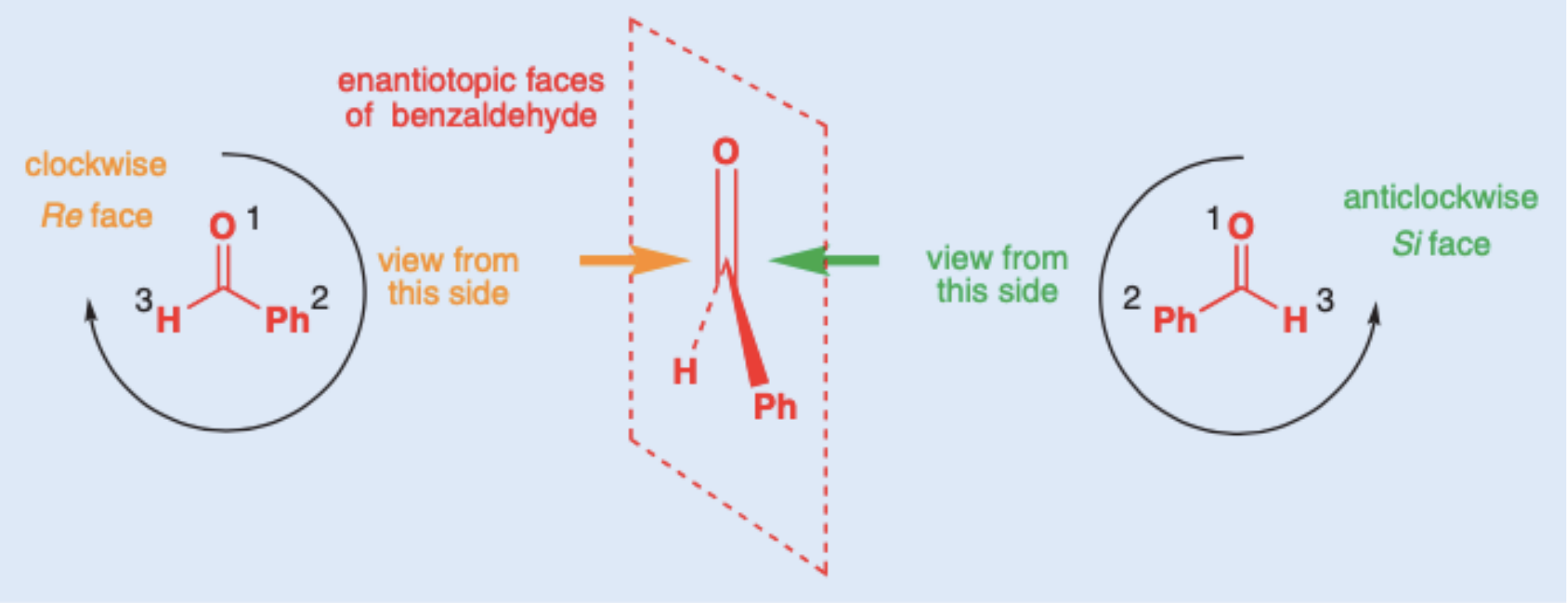


Trigonal carbons that aren't stereogenic (chiral) centers but can be made into them are called prochiral.

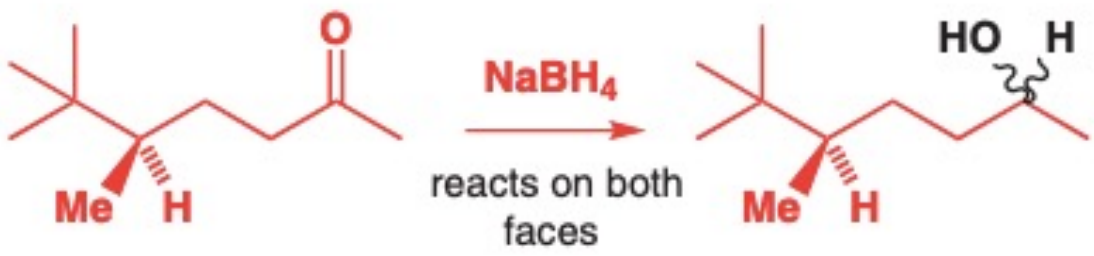
Prochiral

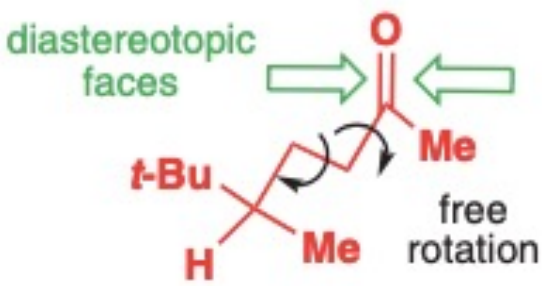

make G higher priority than H
replace green H
4
3
H
G
H
H
H3N
COO
1
2
new centre is S
so green proton is pro-S
make G higher priority than H
replace orange H
3
4
G
H
H
H
H3N
COO
1
2
new centre is R
so orange proton is pro-R

Prochiral

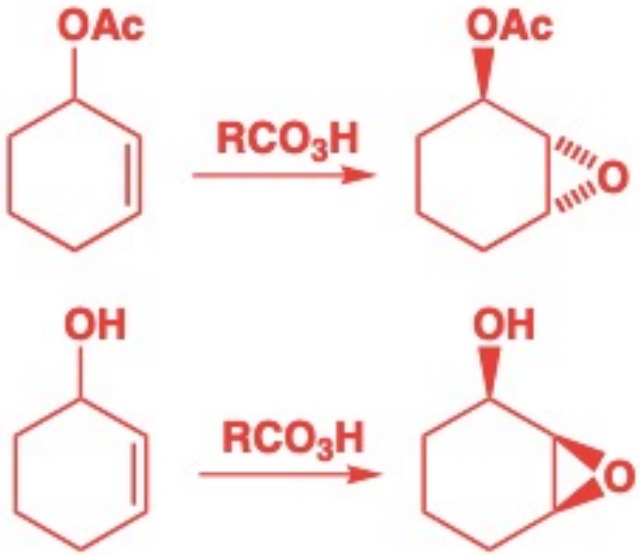

enantiotopic faces
of benzaldehyde
clockwise
Re face
O 1
3 H
Ph 2
view from
this side
O
H
Ph
view from
this side
anticlockwise
Si face
1 O
2 Ph
H 3

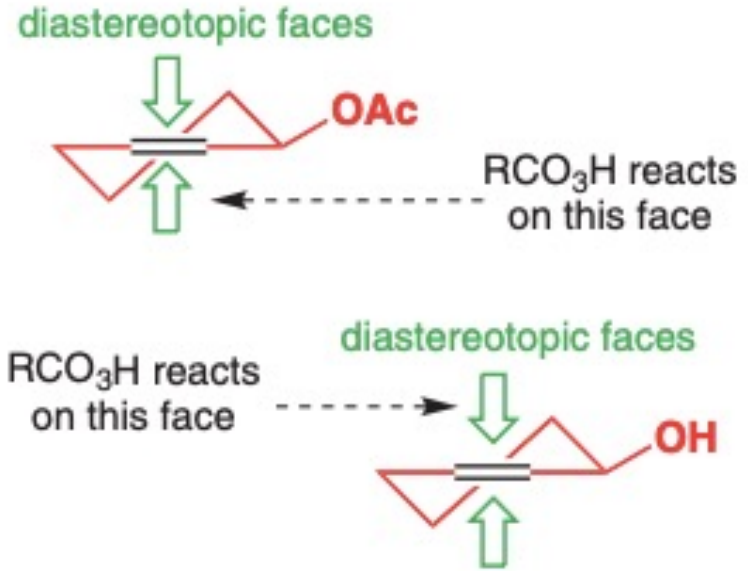
Prochiral


O
Me
H
NaBH4
reacts on both
faces
HO
H
Me
H

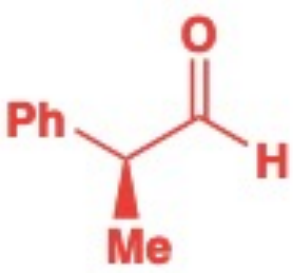

diastereotopic
faces
O
Me
t-Bu
H
Me
free
rotation

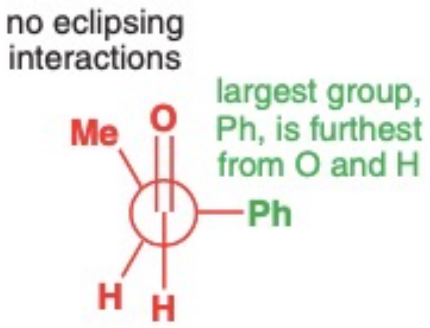
Diastereotopic face





Chiral aldehydes

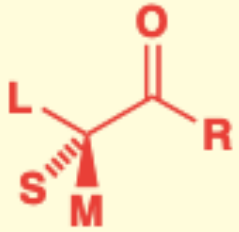




Newman projection of one possible conformation

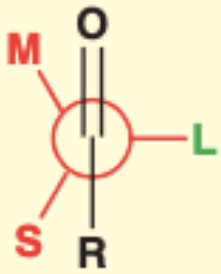
● Lowest-energy conformations of a carbonyl compound

The most important conformations of a carbonyl compound with a stereogenic centre adjacent to the carbonyl group are those that place the largest group perpendicular to the carbonyl group.

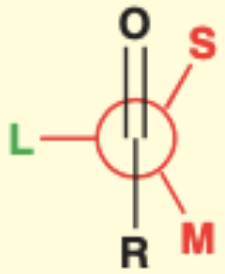


most important conformations are

L = large group, e.g. Ph
M = medium-sized group, e.g. Me
S = small group, e.g. H



and

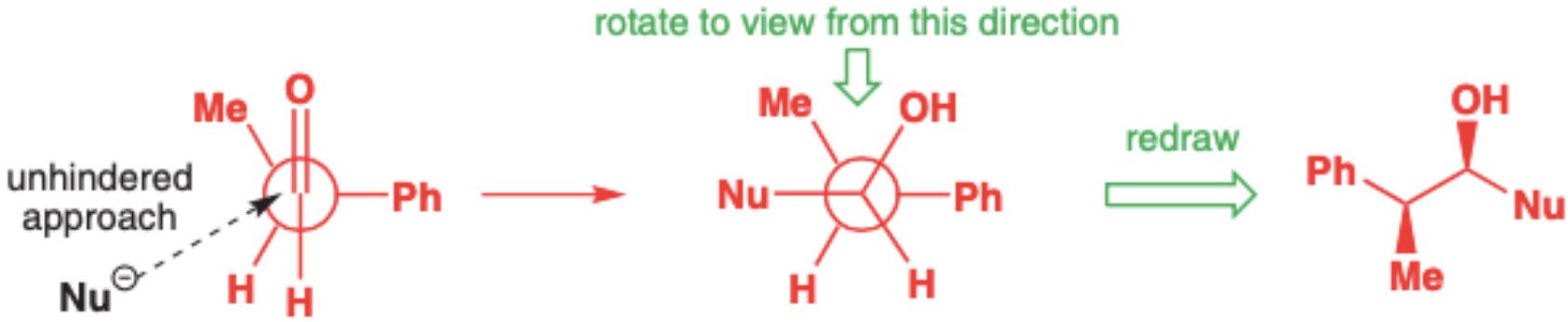


Burgi-Dunitz angle

the black flight path is the best

the three brown flight paths are hindered by Ph or Me

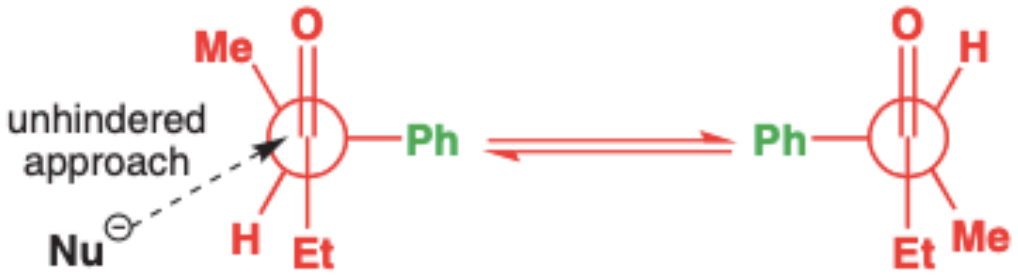
Felkin-Anh model

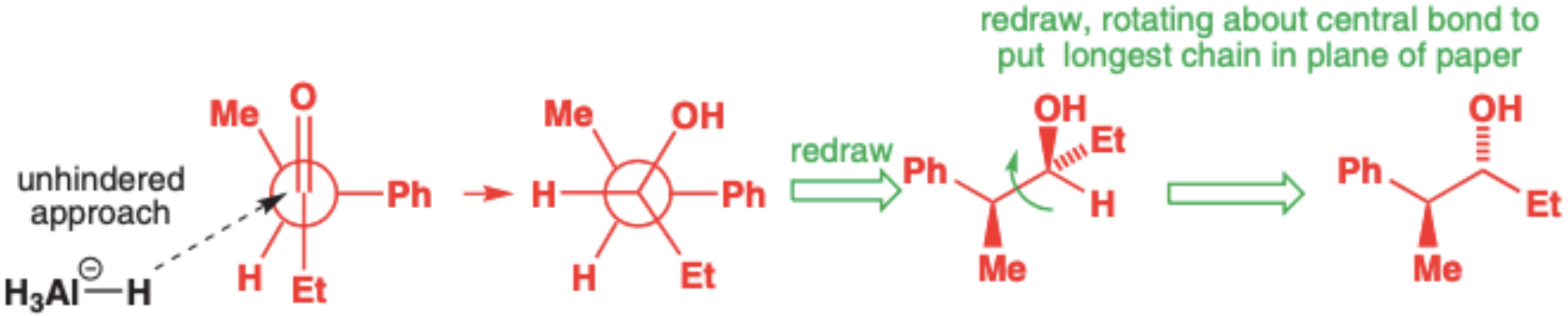


- **In order to avoid making mistakes, we suggest you:**
  - first draw the product in a conformation similar to that of the starting material
  - then redraw to put the longest chain in the plane of the paper.

Here, this just means drawing the view from the top of the Newman projection—there is no need to rotate any bonds in this case.

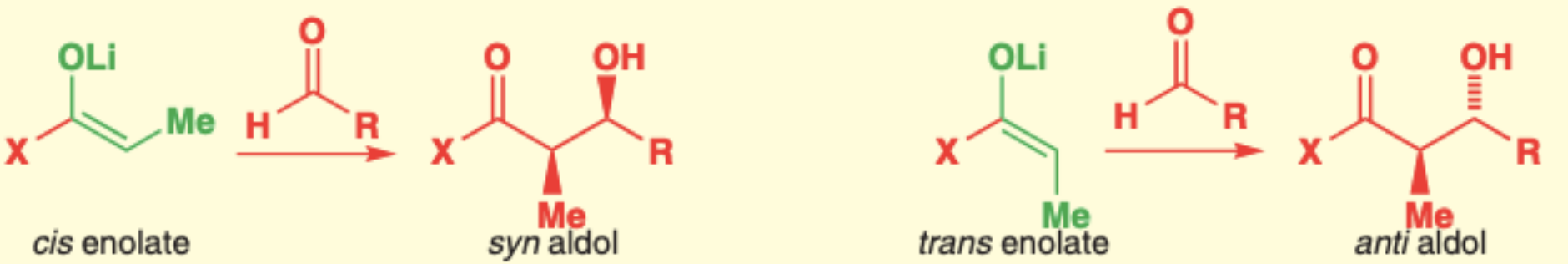
Felkin-Anh model





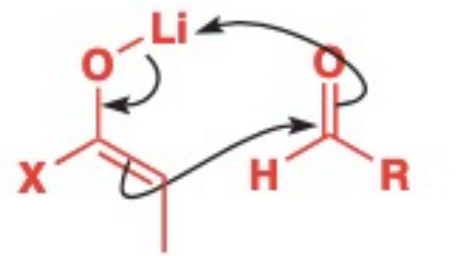
Diastereoselectivity in aldol reactions

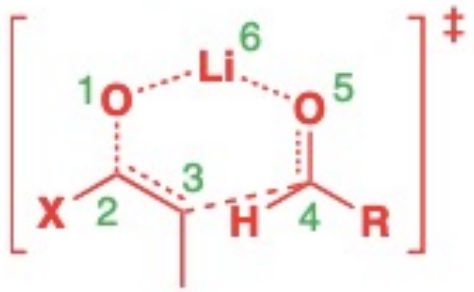
Generally (but certainly not always!) in aldol reactions:



The important point about substituted enolates is that they can exist as two geometrical isomers, *cis* or *trans*. Which enolate is formed is an important factor controlling the diastereoselectivity because it turns out that, in many examples of the aldol reaction, *cis* enolates give *syn* aldols preferentially and *trans* enolates give *anti* aldols preferentially.

Diastereoselectivity in aldol reactions



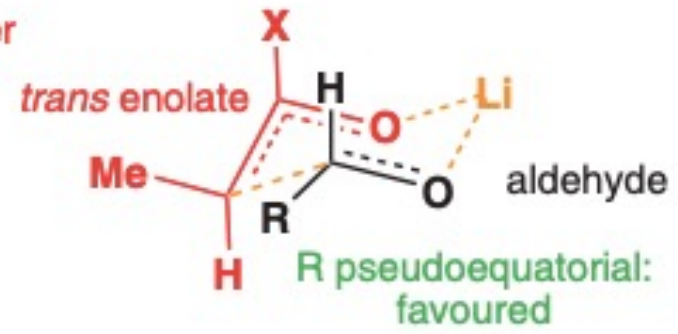


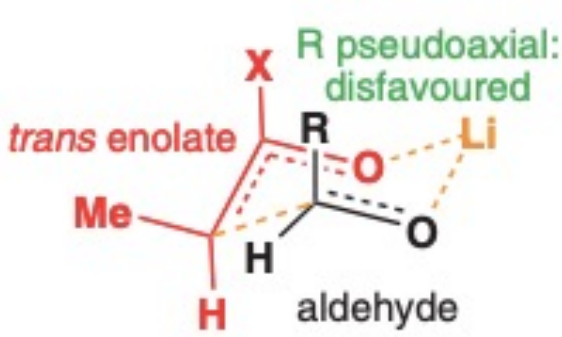
During the reaction, the lithium is transferred from the enolate oxygen to the oxygen of the carbonyl electrophile. This is represented in the margin both in curly arrow terms and as a transition state structure.

Diastereoselectivity in aldol reactions

enolate has no choice over orientation: Me must be pseudoequatorial

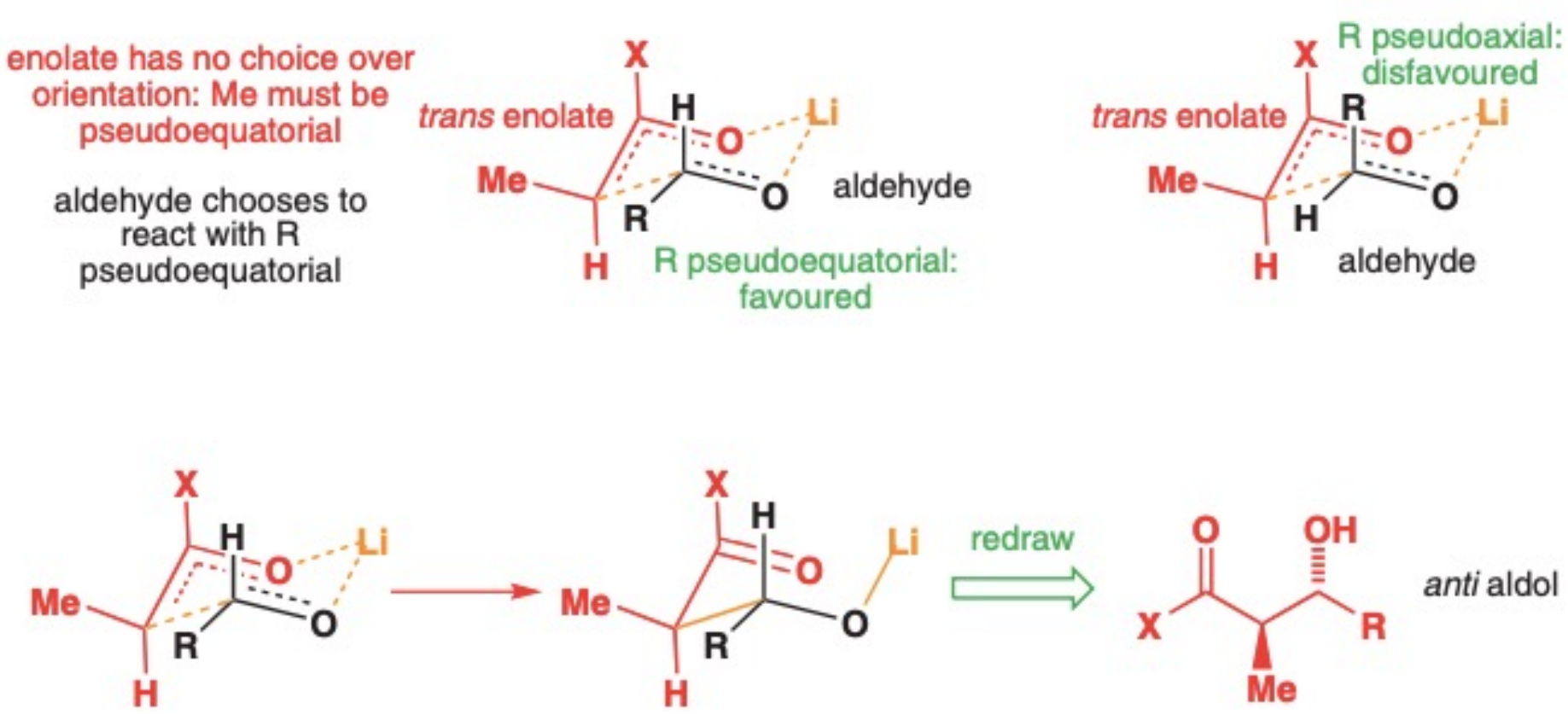
aldehyde chooses to react with R pseudoequatorial



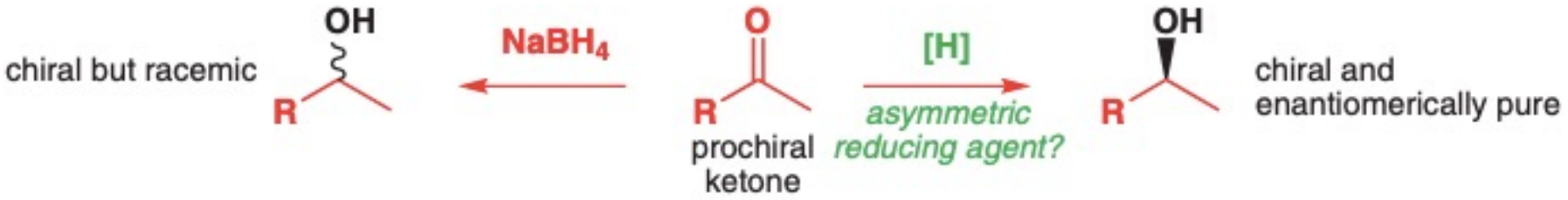


The six-membered ring transition state for the aldol reaction was proposed by Zimmerman and Traxler and is sometimes called the **Zimmerman–Traxler transition state**.

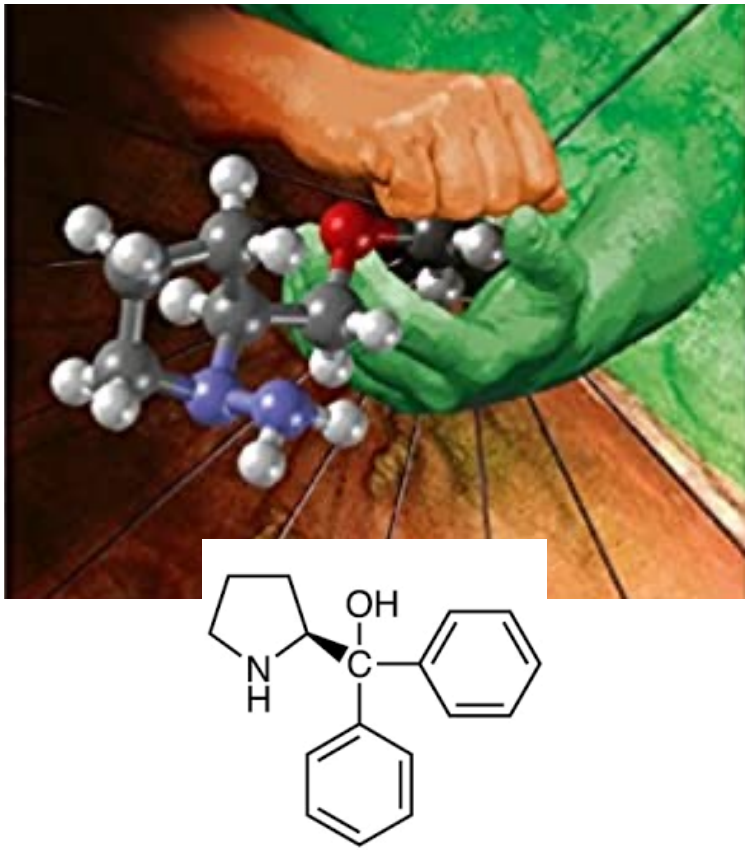
Diastereoselectivity in aldol reactions



Asymmetric synthesis



Metal catalyzed



Organocatalyst

Enzyme

Asymmetric synthesis

Asymmetric synthesis is a reaction or reaction sequence that *selectively* creates one configuration of one or more new *stereogenic elements* by the action of a chiral reagent or auxiliary, acting on *heterotopic* faces, atoms, or groups of a substrate. The stereoselectivity is primarily influenced by the chiral catalyst, reagent, or auxiliary, despite any stereogenic elements that may be present in the substrate.

Terminology

Key words

Chiral pool

Chiral catalyst

Chiral auxiliar

Heterotopic faces (enantio-diastereo)

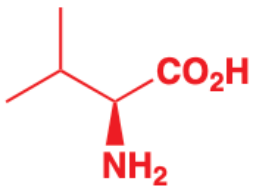
Chiral resolution

Enantiomeric excess (ee)

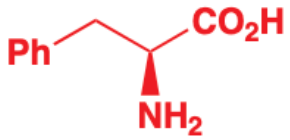
Chiral pool

The chiral pool: **Collection of natural, enantiomerically pure compounds. Amino acids, carbohydrates and their derivatives.**

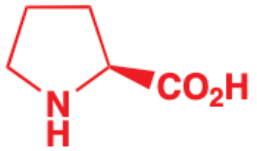
Available in nature



(*S*)-(+)-valine

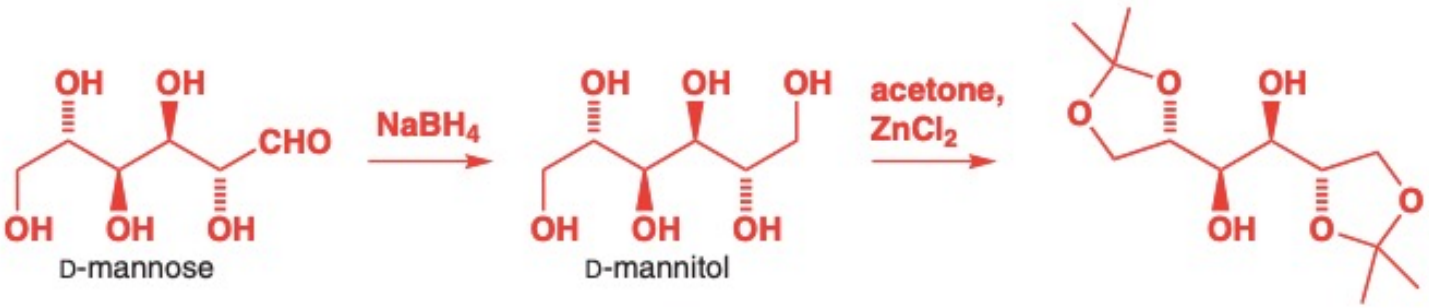


(*S*)-(–)-phenylalanine



(*S*)-(–)-proline

After simple transformations

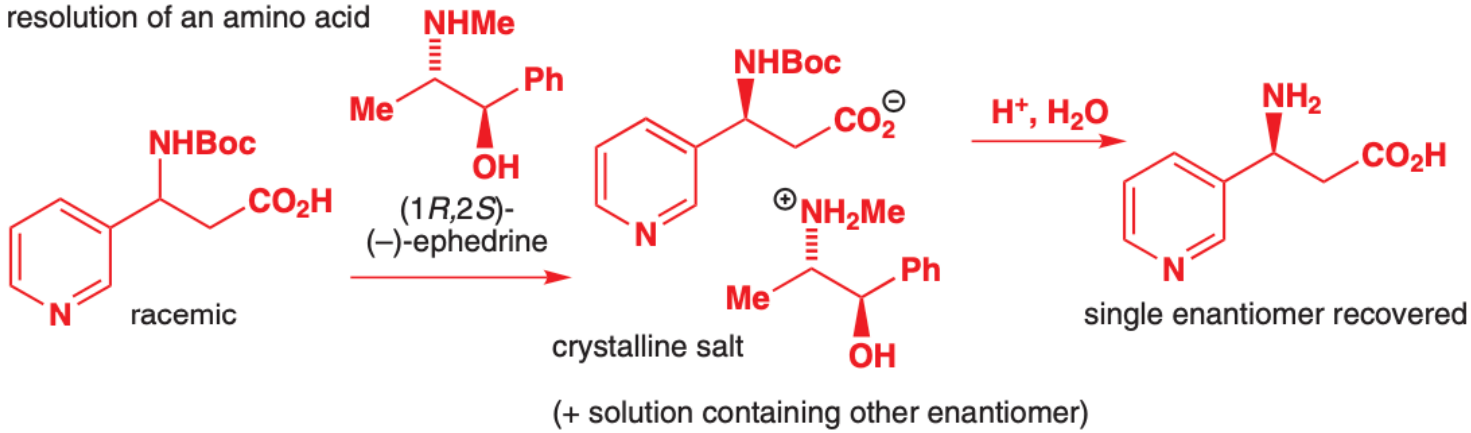


D-mannose D-mannitol

Chiral resolution

Resolution

requires an enantiomerically pure resolving agent, which must be a compound from the chiral pool or a simple derivative of that compound.



Formation of salts or complex with an enantiopure molecule

Non-covalent interaction

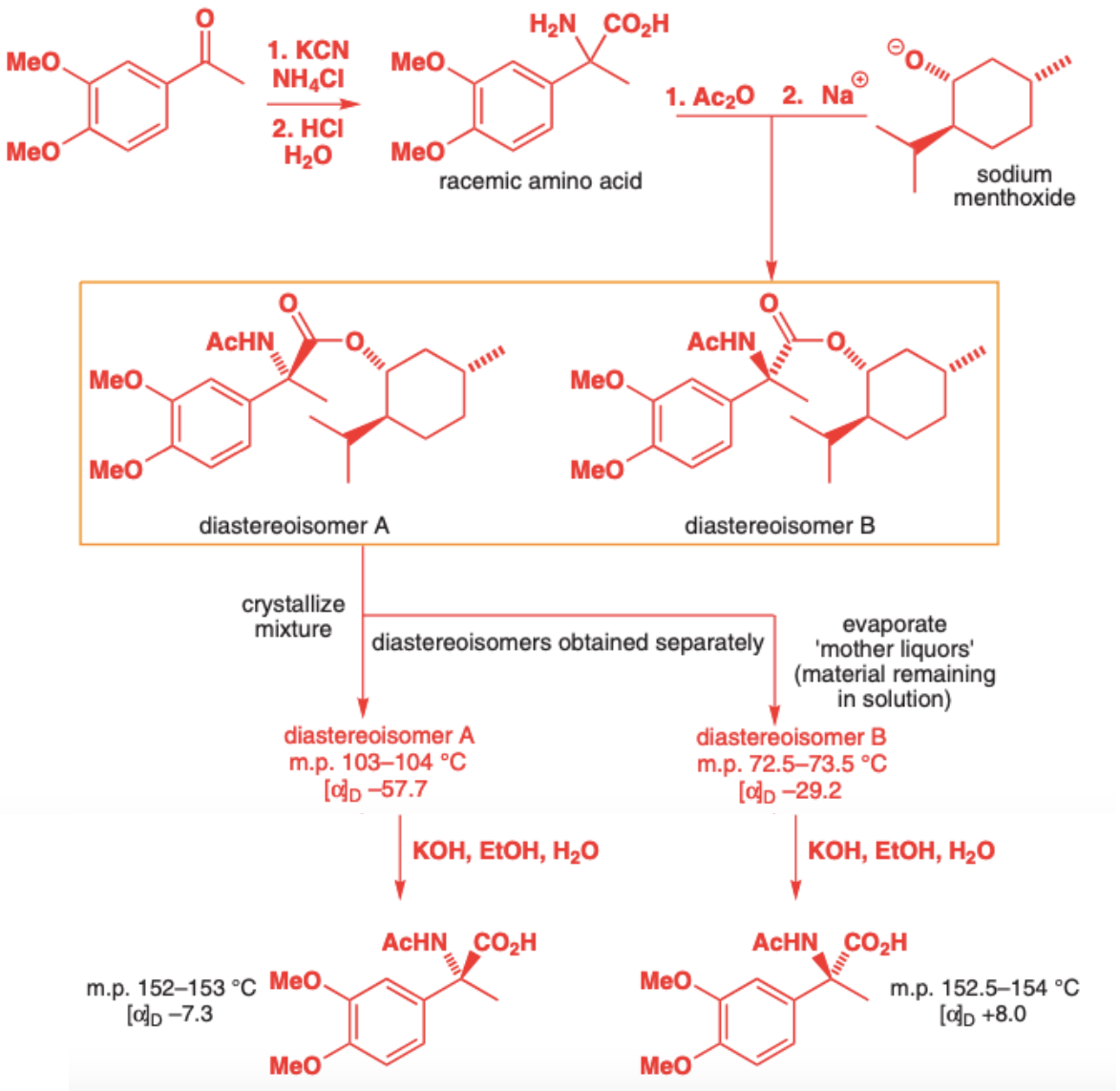
Disadvantage is that there is a maximum yield of 50% because if you only want one enantiomer, the other is wasted.

Chiral resolution

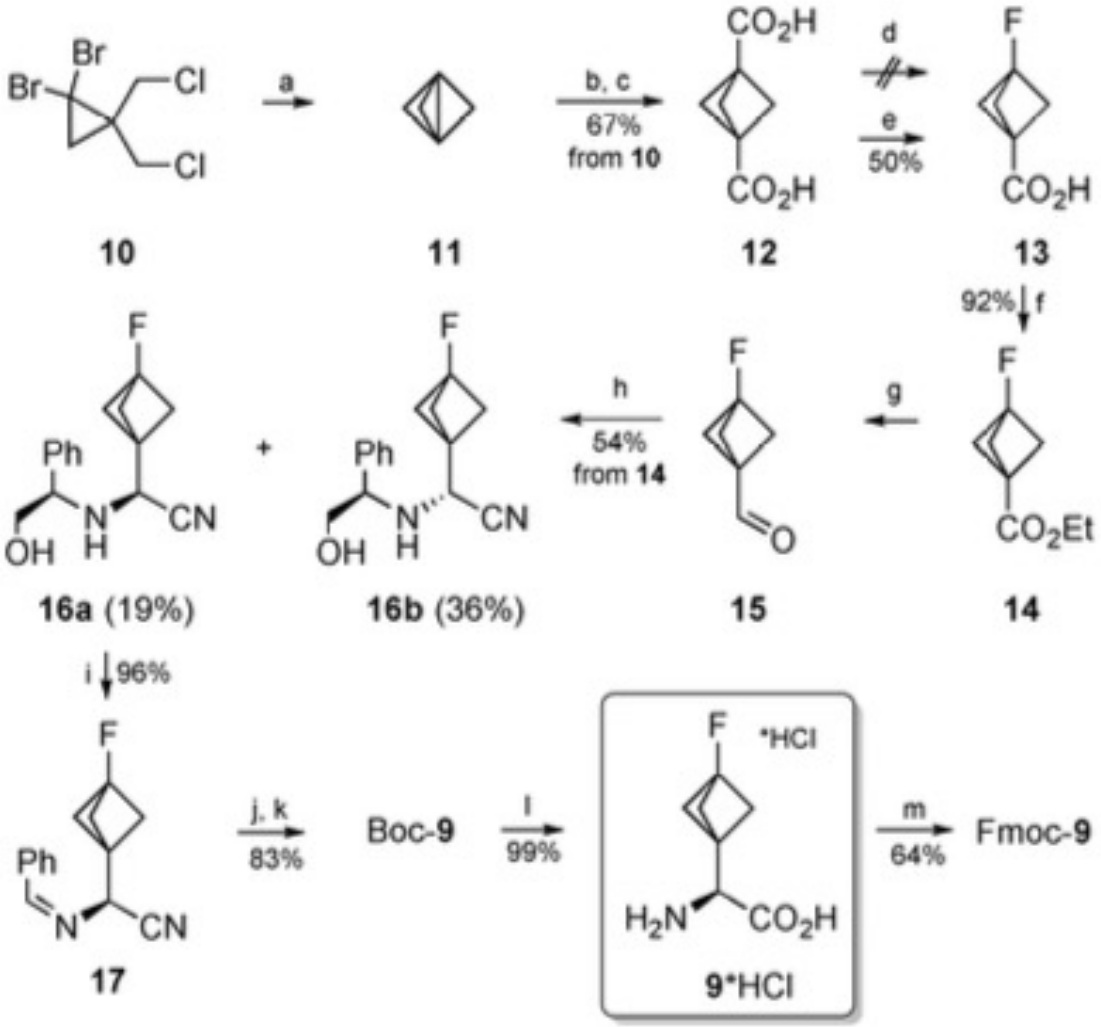
Resolution

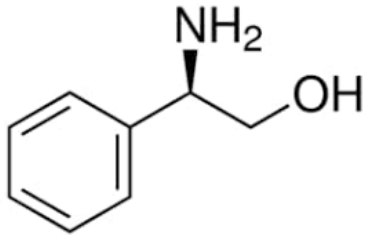
Formation of diastereomers with an enantiopure molecule

Covalent interaction



Synthesis of unnatural amino acids





(1.2 equiv), toluene, −78 °C, 2 h; h) (*R*)-2-phenylglycinol (1.2 equiv), Me_3SiCN (3.0 equiv), MeOH, 12 h; i) $Pb(OAc)_4$ (1.5 equiv), CH_2Cl_2/MeOH (1:1), 0 °C, 15 min; j) 6 N HCl, reflux, 24 h; k) Boc_2O

Chiral auxiliaries

Chiral auxiliaries

Chiral auxiliary: A chiral molecule that is covalently attached to a substrate so as to render enantiotopic faces or groups in the substrate diastereotopic. After the diastereoselective reaction, the auxiliary should be removable and recoverable intact.

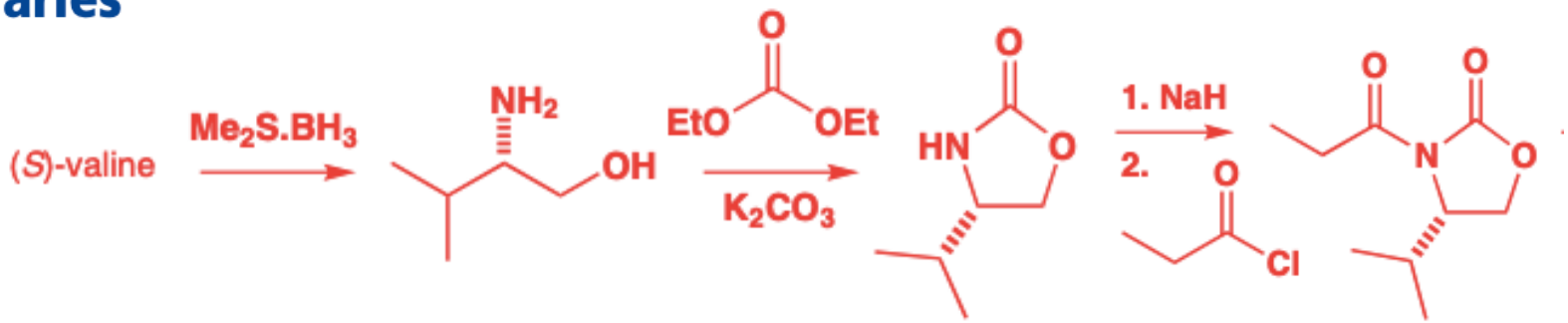
- **This is what we mean by a chiral auxiliary strategy**

1. **An enantiomerically pure compound (usually derived from a simple natural product like an amino acid), called a chiral auxiliary, is attached to the starting material.**
2. **A diastereoselective reaction is carried out, which, because of the enantiomeric purity of the chiral auxiliary, gives only one enantiomer of the product.**
3. **The chiral auxiliary is removed by, for example, hydrolysis, leaving the product of the reaction as a single enantiomer. The best chiral auxiliaries (of which the example above is one) can be recycled, so although stoichiometric quantities are needed, there is no waste.**

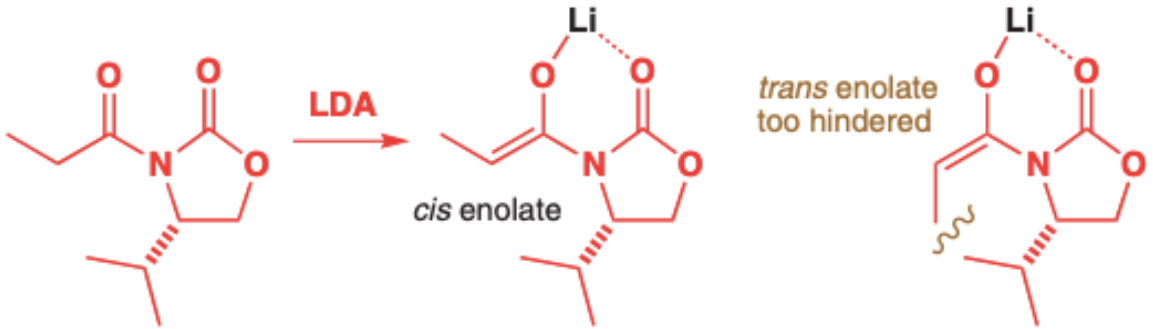
Chiral auxiliaries

Chiral auxiliaries

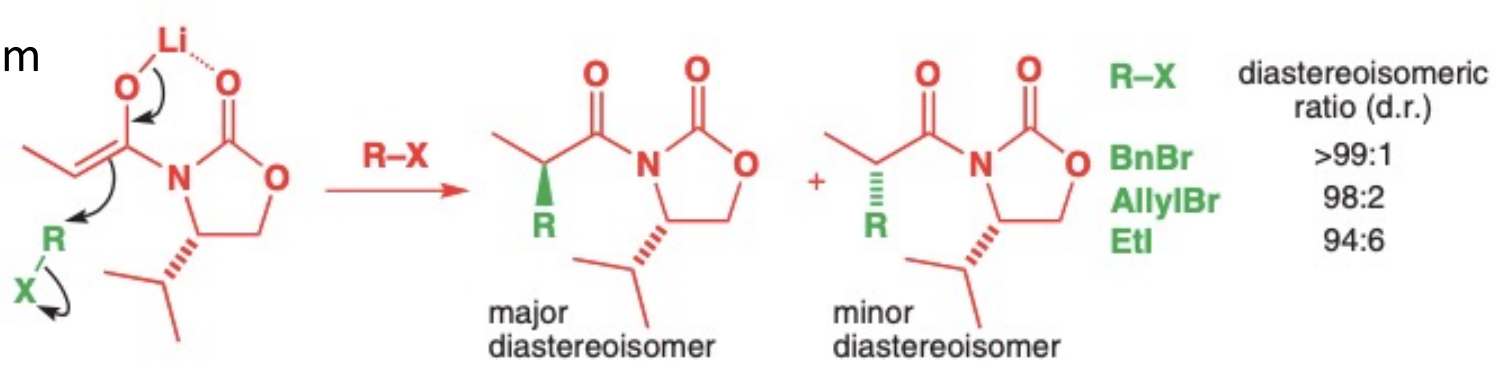
Synthesis from chiral pool



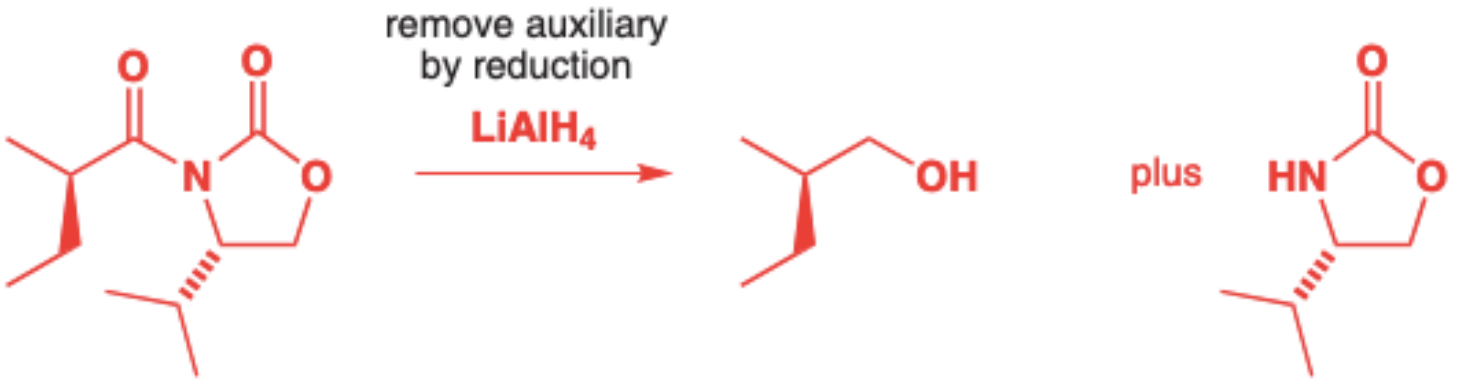
Application



Mechanism



Enantiomeric excess



94:6 mixture of diastereoisomers
94:6 d.r.

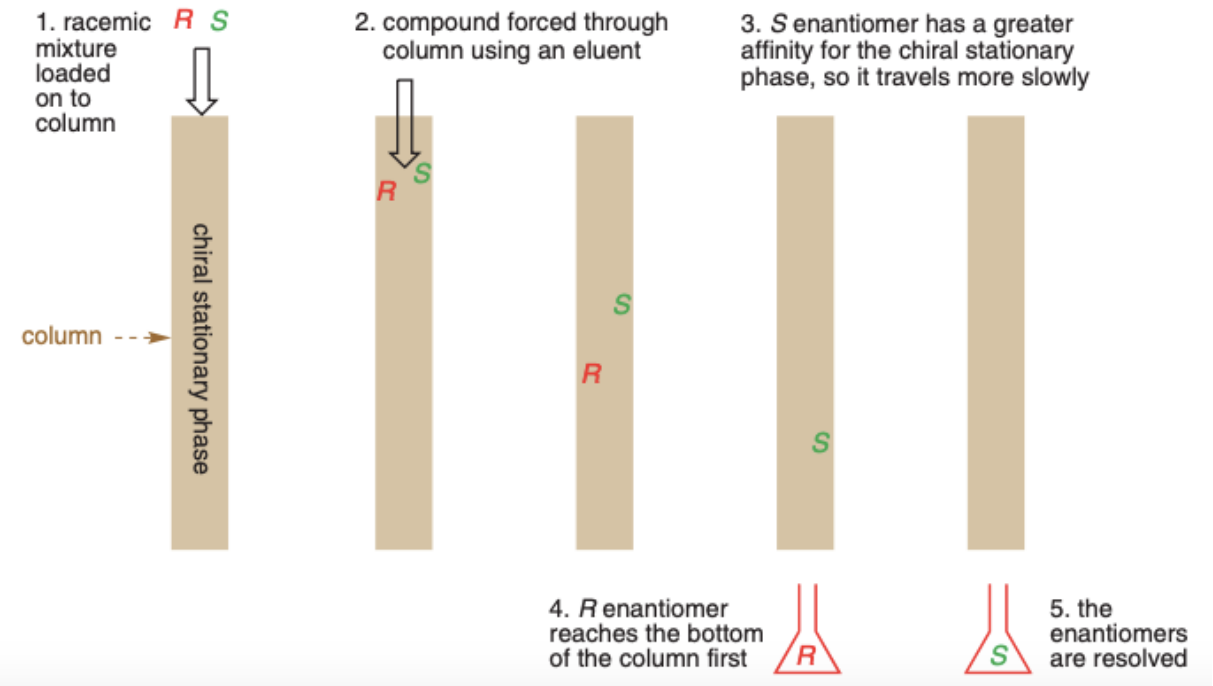
94:6 mixture of enantiomers
94:6 e.r. or 88% ee

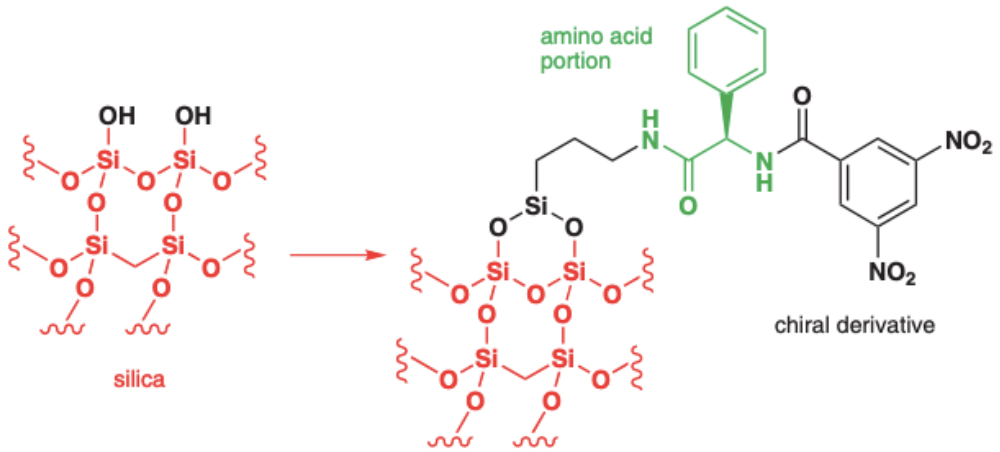
$$\% \text{ ee} = \frac{|E_1 - E_2|}{E_1 + E_2} \cdot 100 = |\%E_1 - \%E_2| \ ,$$

where E_1 and E_2 are the mole fractions of the two enantiomers. See *enantiomer purity*.

Enantiomeric excess

HPLC



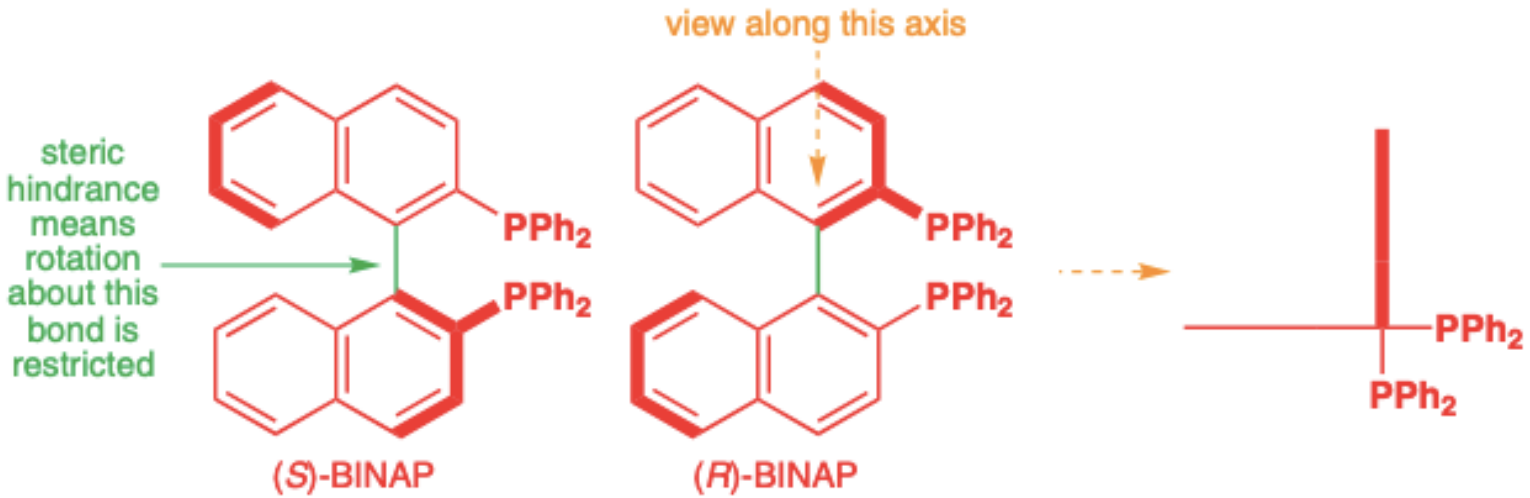


Chirality

Chirality

Chiral compounds with no stereogenic centres

some biaryl compounds, such as the important bisphosphine below, known as BINAP, exist as two separate enantiomers because rotation about the green bond is restricted.

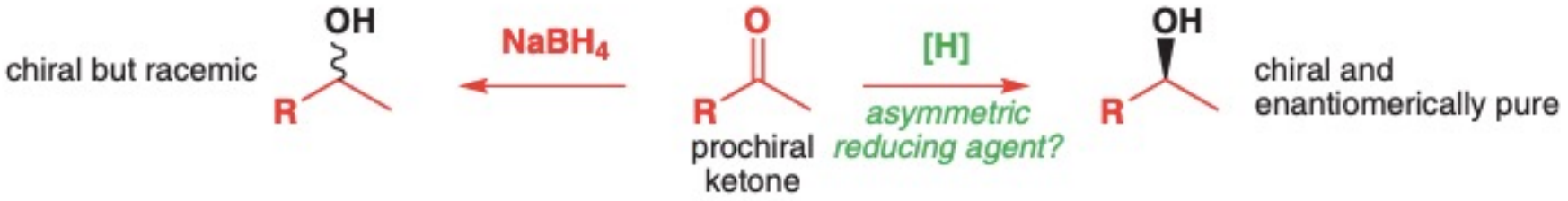


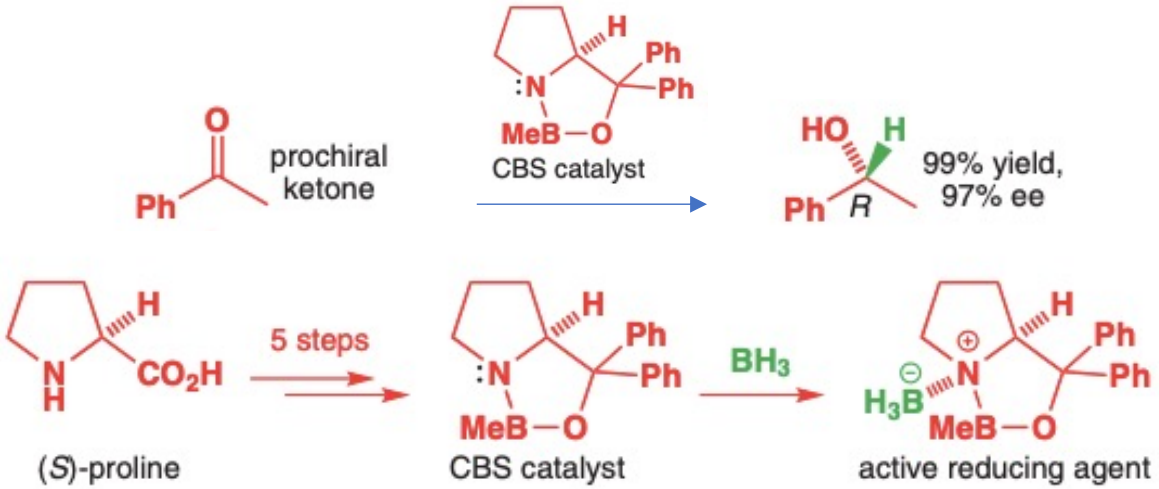
Axial chirality: an axis about which a set of substituents is held in a spatial arrangement that is not superposable on its mirror image.

Asymmetric catalysis

Asymmetric catalysis

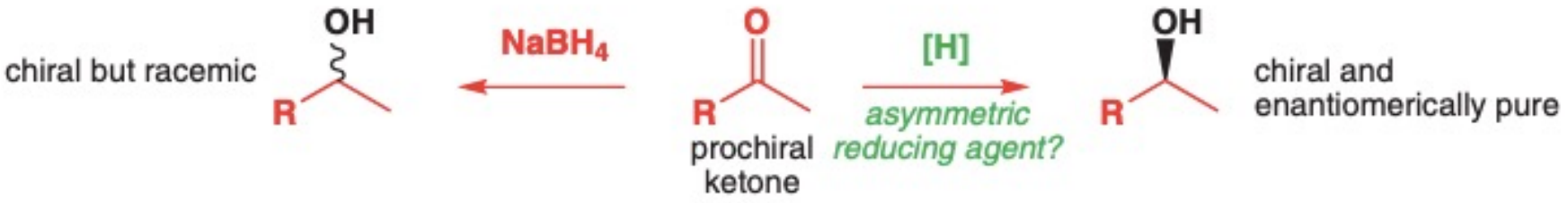
If we want to create a new chiral centre in a molecule, our starting material must have **pro-chirality**—the ability to become chiral in one simple transformation. The most common prochiral units that give rise to new chiral centres are the trigonal carbon atoms of alkenes and carbonyl groups, which become tetrahedral by addition reactions.

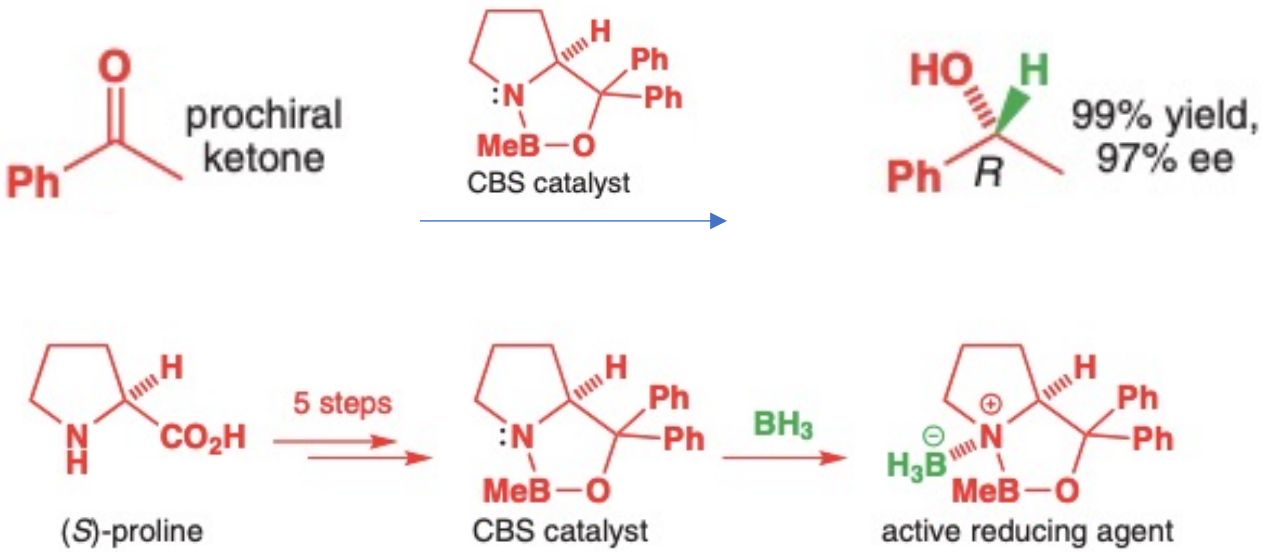




Yields up 100%, catalytic amount.

Asymmetric catalysis

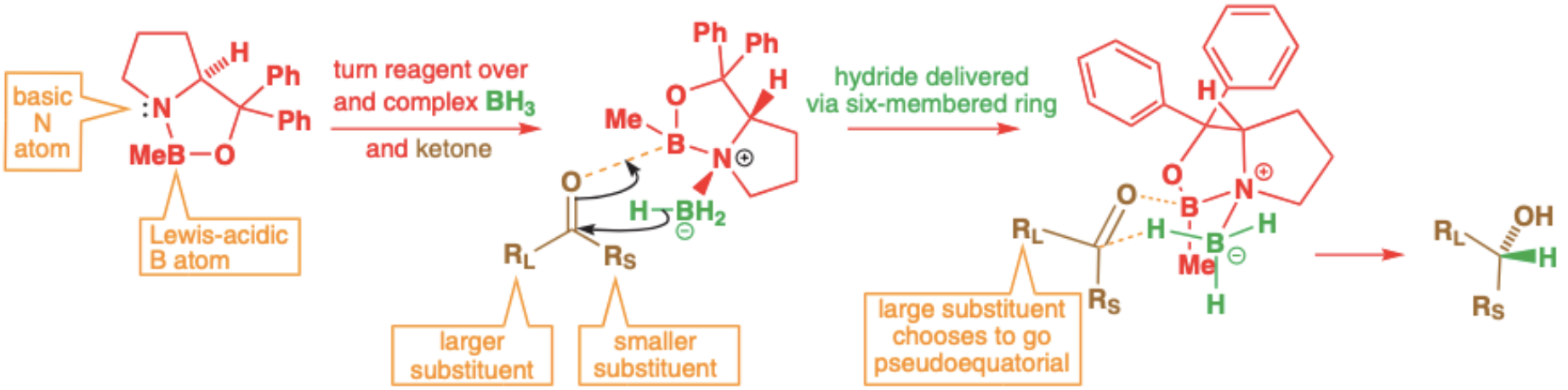




Yields up 100%, catalytic amount.

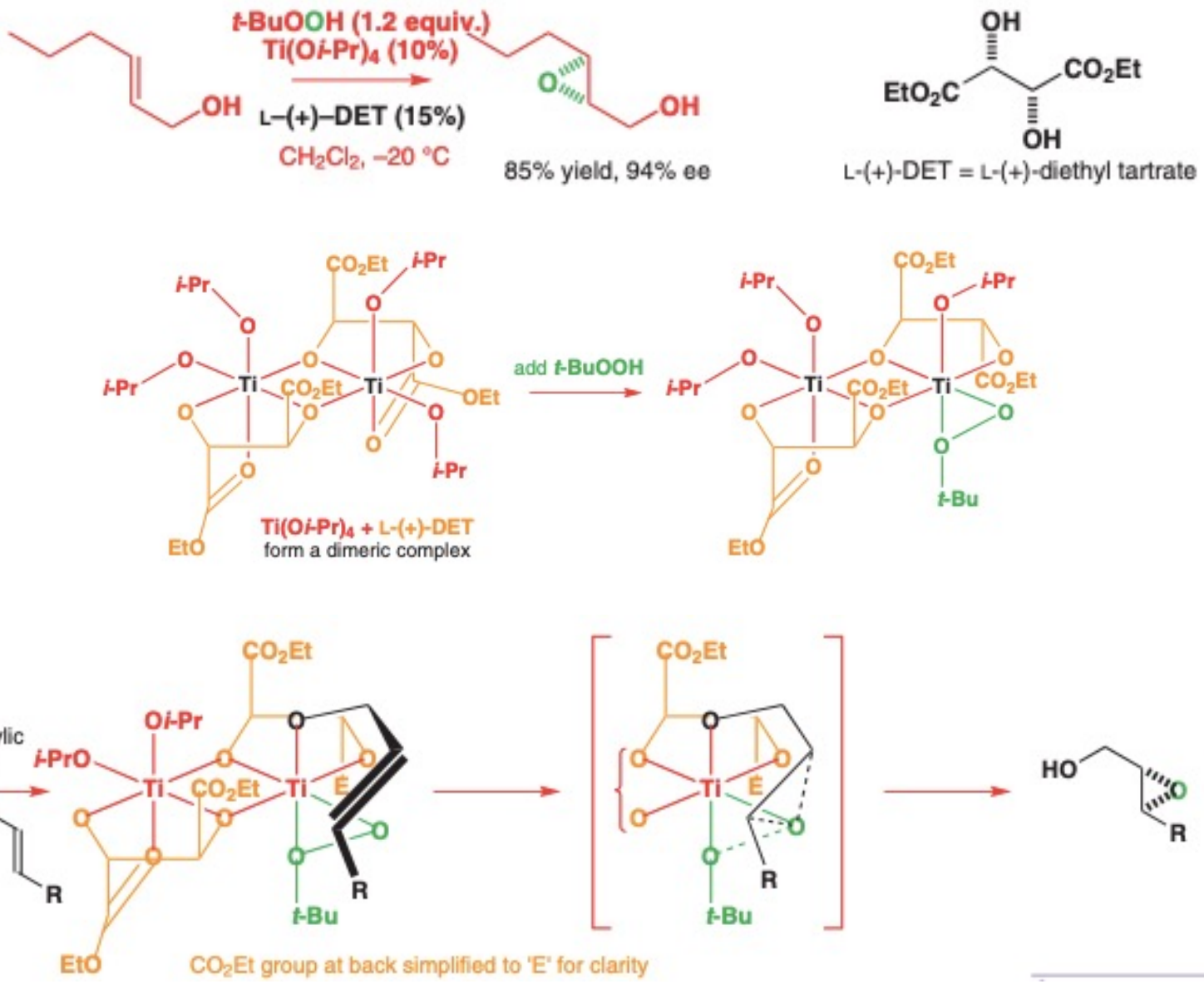
Asymmetric synthesis

Complexation activates both partners towards reaction: donating electron density to the borane is essential to persuade it to transfer hydride, and withdrawing electron density from the carbonyl group makes it electrophilic enough to react with a weak hydride source.

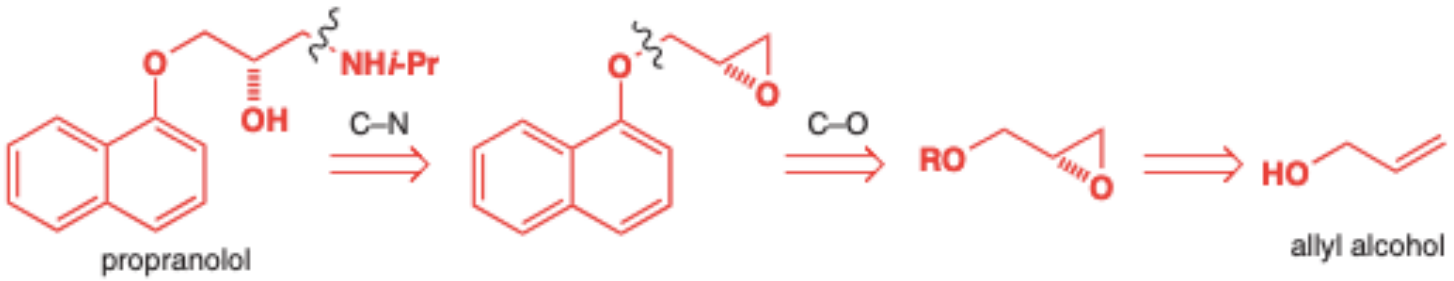


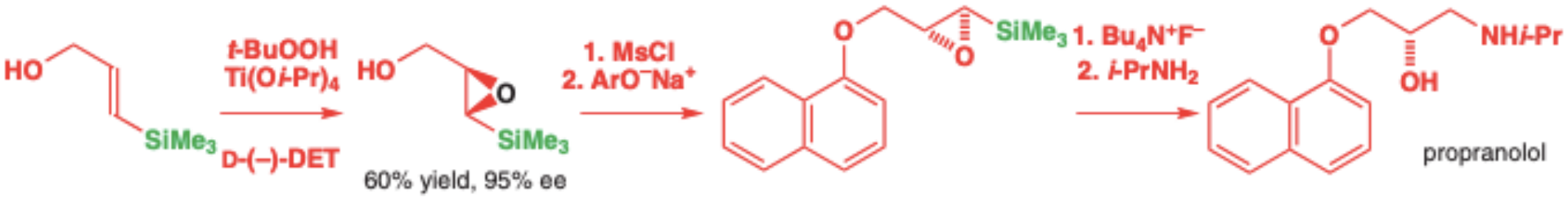
The hydride is delivered via a six-membered cyclic transition state, with the enantioselectivity arising from the preference of the larger of the ketone's two substituents (R_L) for the pseudoequatorial position on this ring.

Asymmetric synthesis

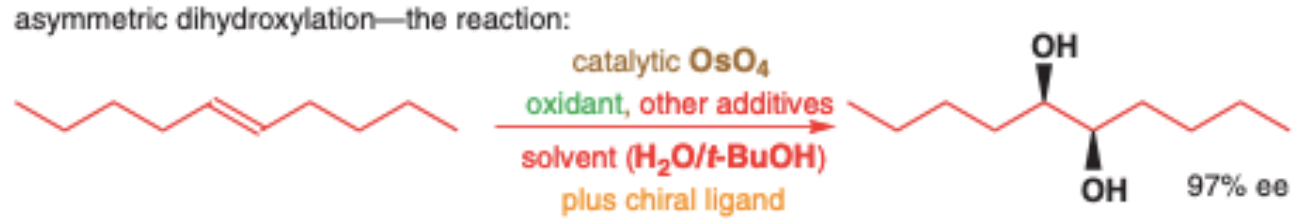


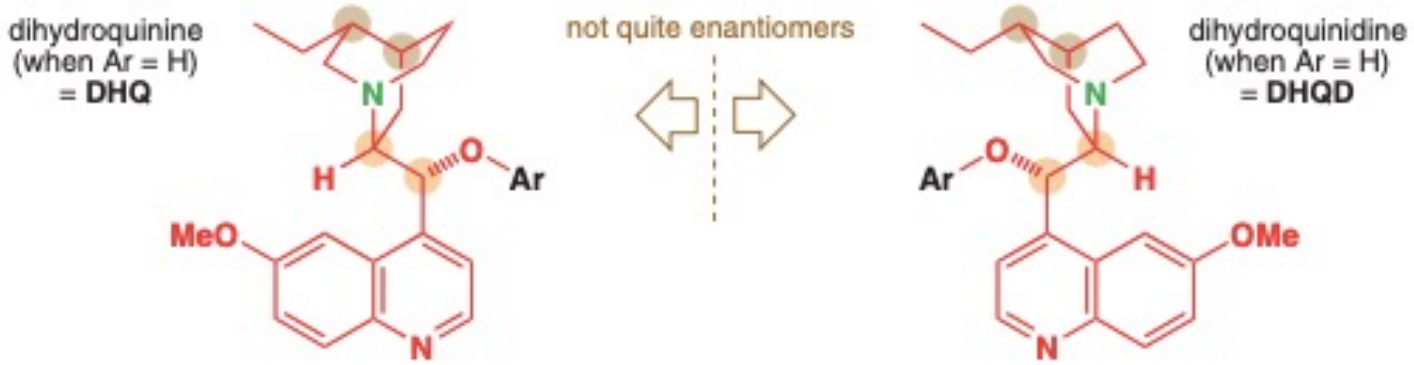
Asymmetric synthesis



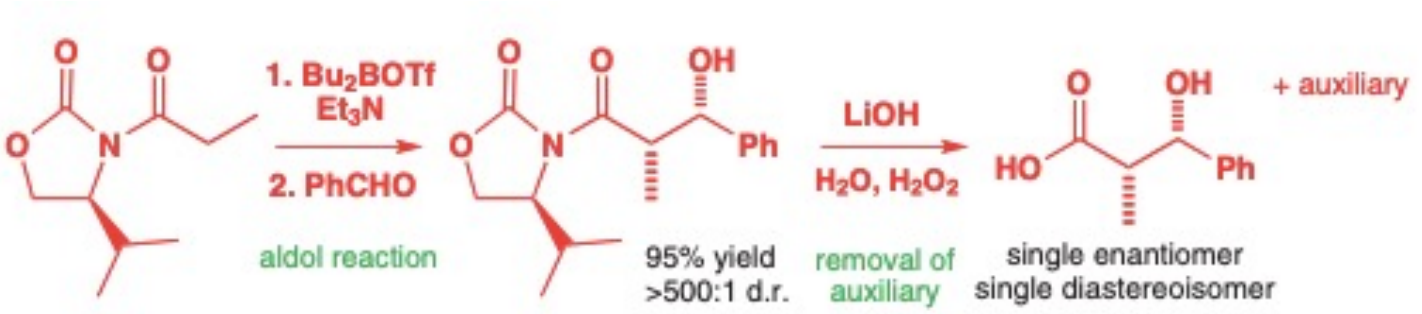


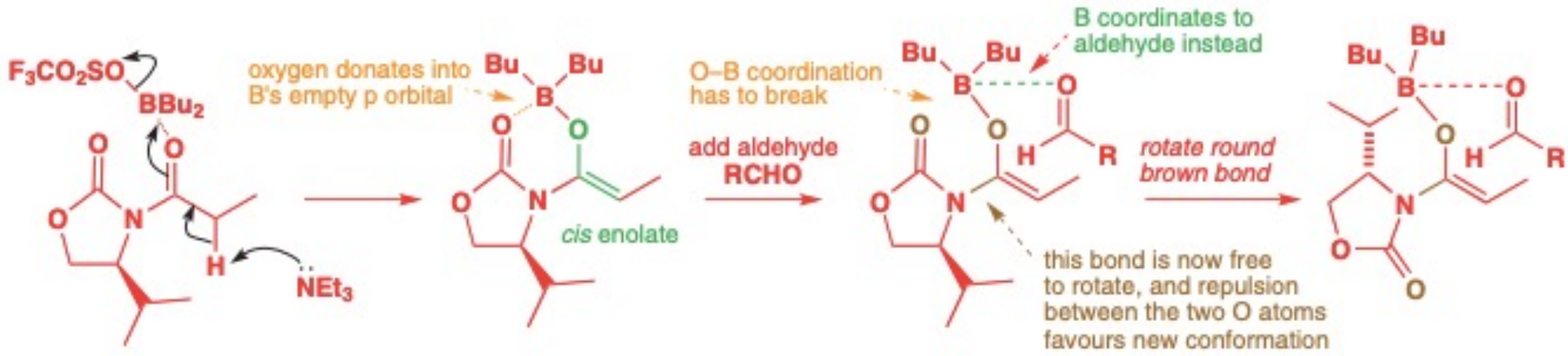
Asymmetric synthesis



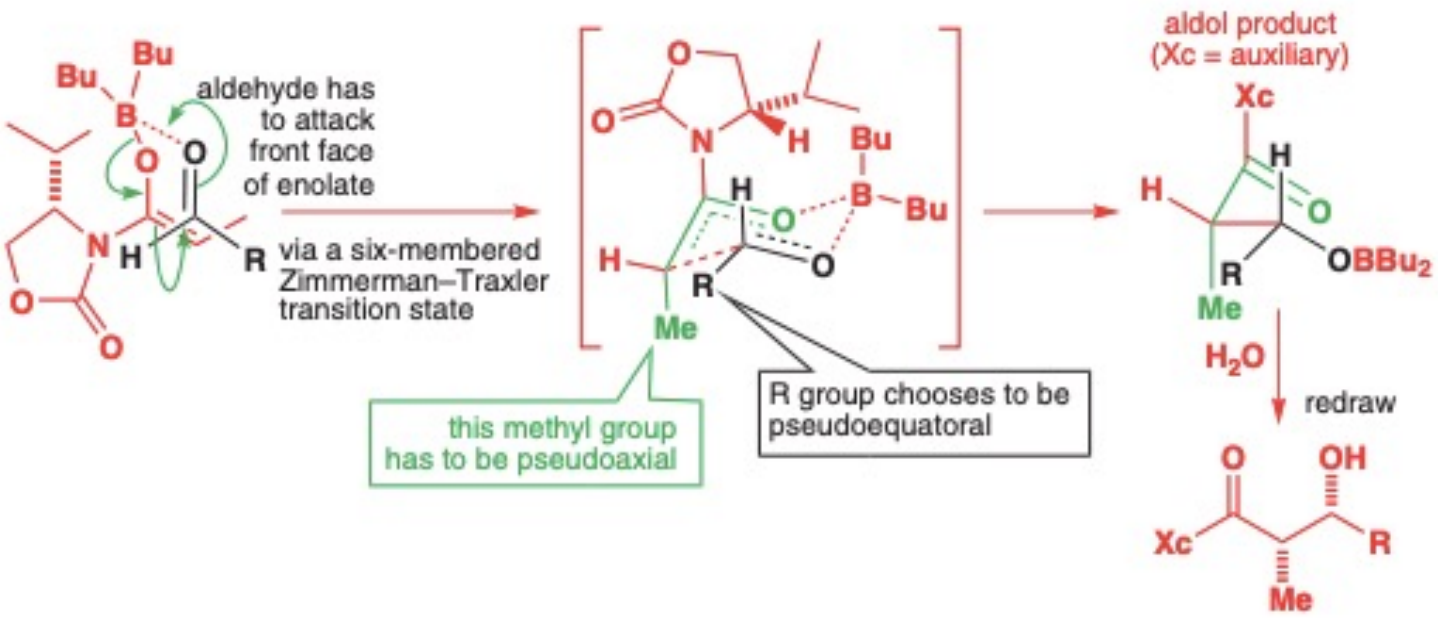


Asymmetric synthesis





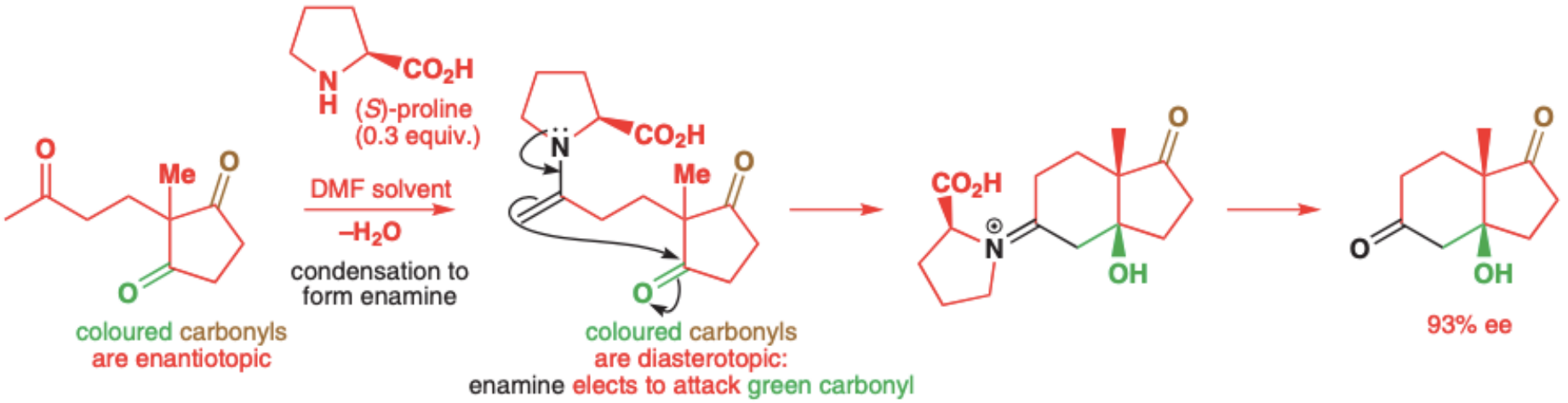
Asymmetric synthesis



Asymmetric synthesis

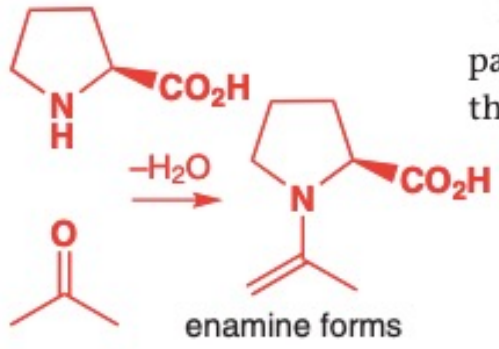
Organocatalysis

early years of the 21st century, several chemists around the world realized that it is not always necessary to use a metal to initiate high levels of enantioselectivity in catalytic reactions. Simple chiral and enantiomerically pure organic molecules, many of them amines, can also react reversibly with substrates, providing a chiral environment and simultaneously activating them towards enantioselective attack.

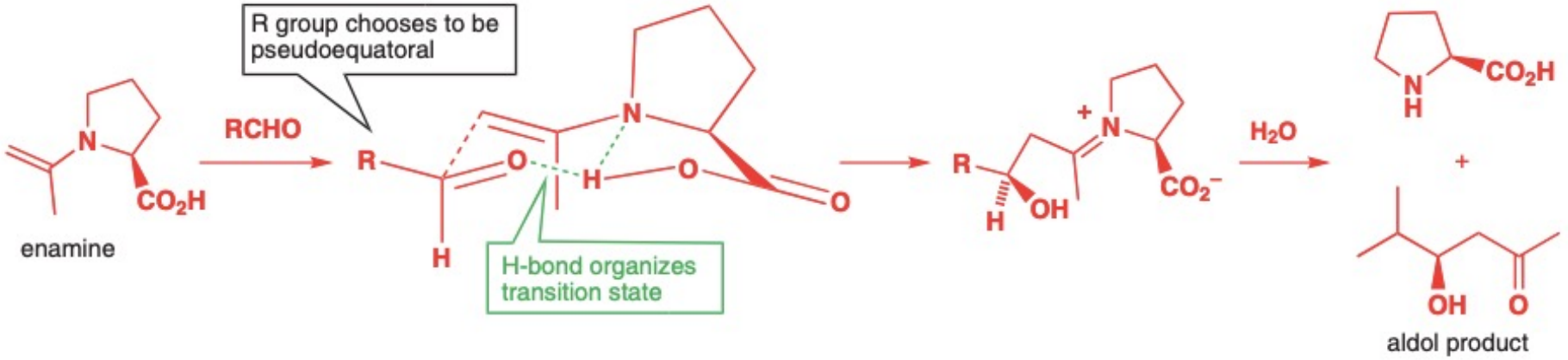


Asymmetric synthesis

Organocatalysis

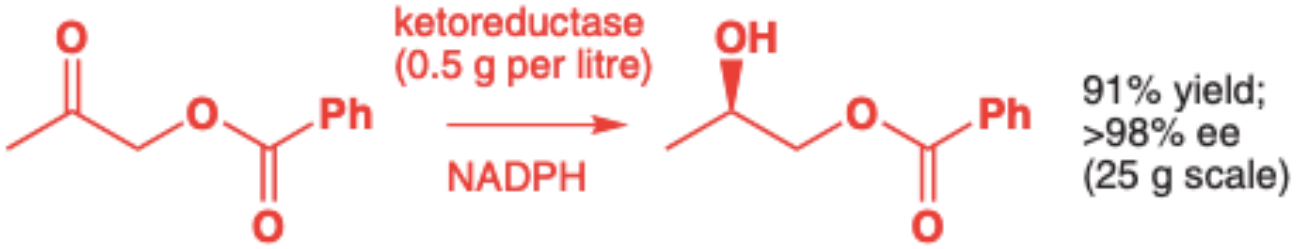


In the aldol reaction itself, proline's carboxyl group has a key role to play because it can participate in a hydrogen bond that organizes the six-membered transition state in such a way that only one of the possible enantiomeric products can form.



Asymmetric synthesis

Enzymes as catalysts



. This ketoreductase, isolated from yeast, may never have met this non-biological substrate—benzoyloxyacetone—before, but the reaction works.