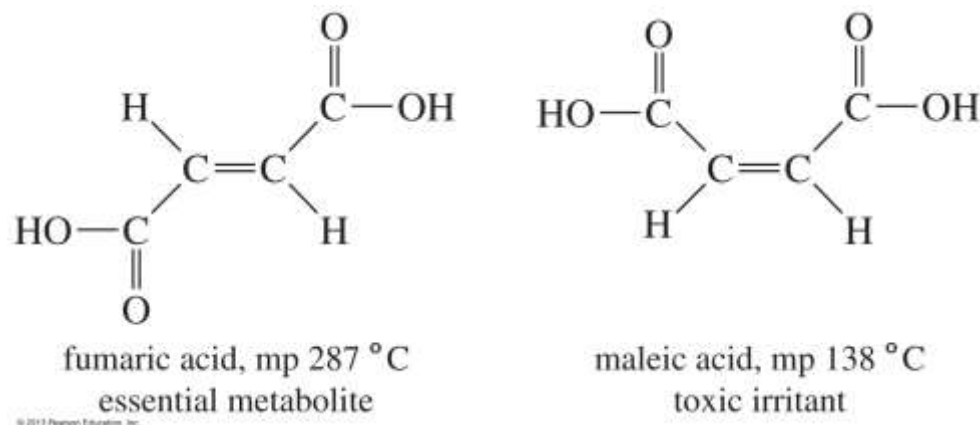# Stereochemistry

This is study of the 3 dimensional arrangement in space of molecules.

In organic chemistry, **subtle** differences in spatial arrangements can give rise to prominent effects.

E.g. the isomers of butenoic acid:

fumaric acid, mp 287 °C
essential metabolite

maleic acid, mp 138 °C
toxic irritant

The *cis* isomer (maleic acid) is toxic, whereas the *trans* isomer (fumaric acid) is an essential metabolite for plants and animals.

This chapter deals with the stereochemical concept of *chirality*.
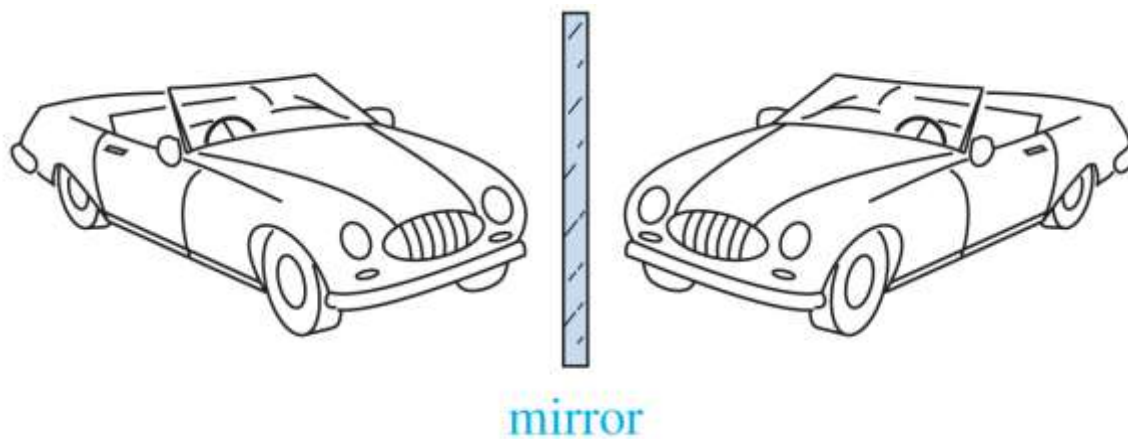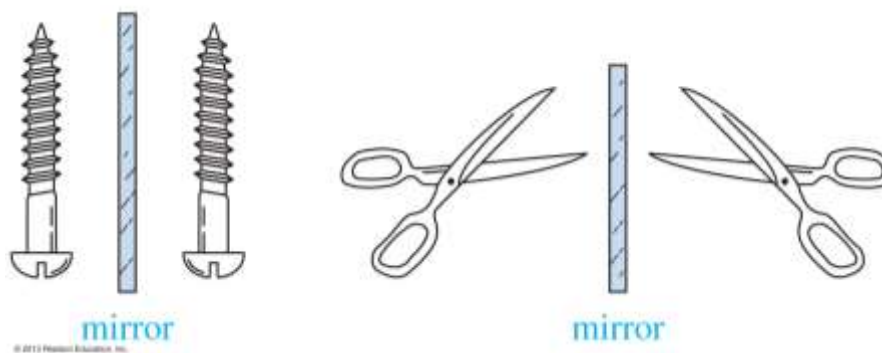
Chirality
Chirality means "handedness".

Every object has a mirror image, but if a molecule's mirror image is **different** from the molecule, it is said to be a *chiral* molecule.

Chiral objects include: hands, feet, gloves, screws, cork screws

Achiral objects have mirror images that are identical to the object.

achiral (not chiral)   chiral

right hand   left hand

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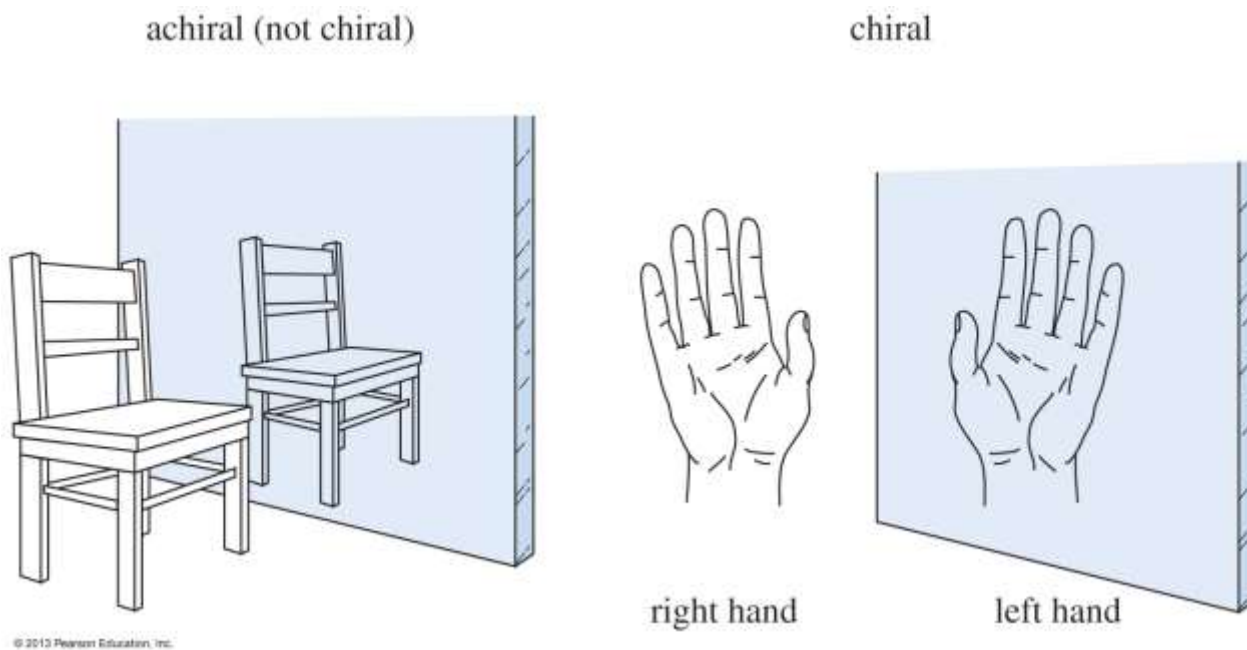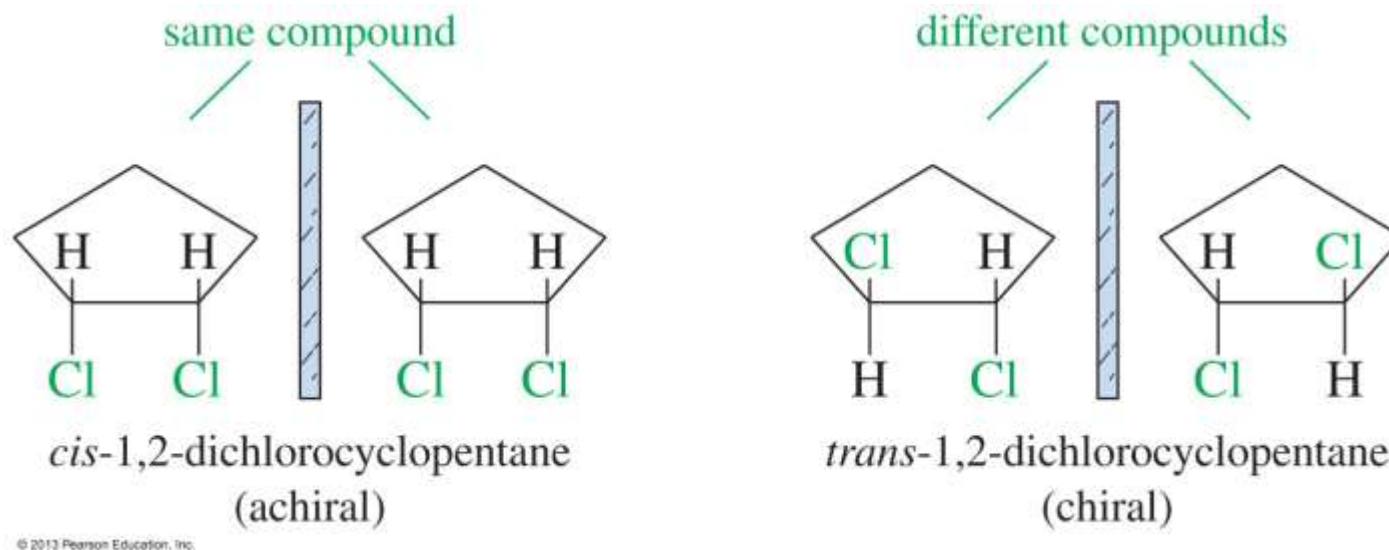
Common Chiral Objects

Chirality in Organic Molecules

If a **mirror image** of a molecule can be placed on top of the original, and the 3 dimensional arrangement of **every** atom is the same, then the two molecules are **superimposable**, and the molecule is <u>achiral</u>.

If a molecule has a **non superimposable** mirror image, it is <u>chiral</u>.

Consider stereoisomers of 1,2-dichlorocyclopentane:

same compound

different compounds

H   H | H   H   Cl   H | H   Cl

Cl   Cl | Cl   Cl   H   Cl | Cl   H

cis-1,2-dichlorocyclopentane
(achiral)

trans-1,2-dichlorocyclopentane
(chiral)

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The *cis* isomer has a superimposable mirror image – achiral.
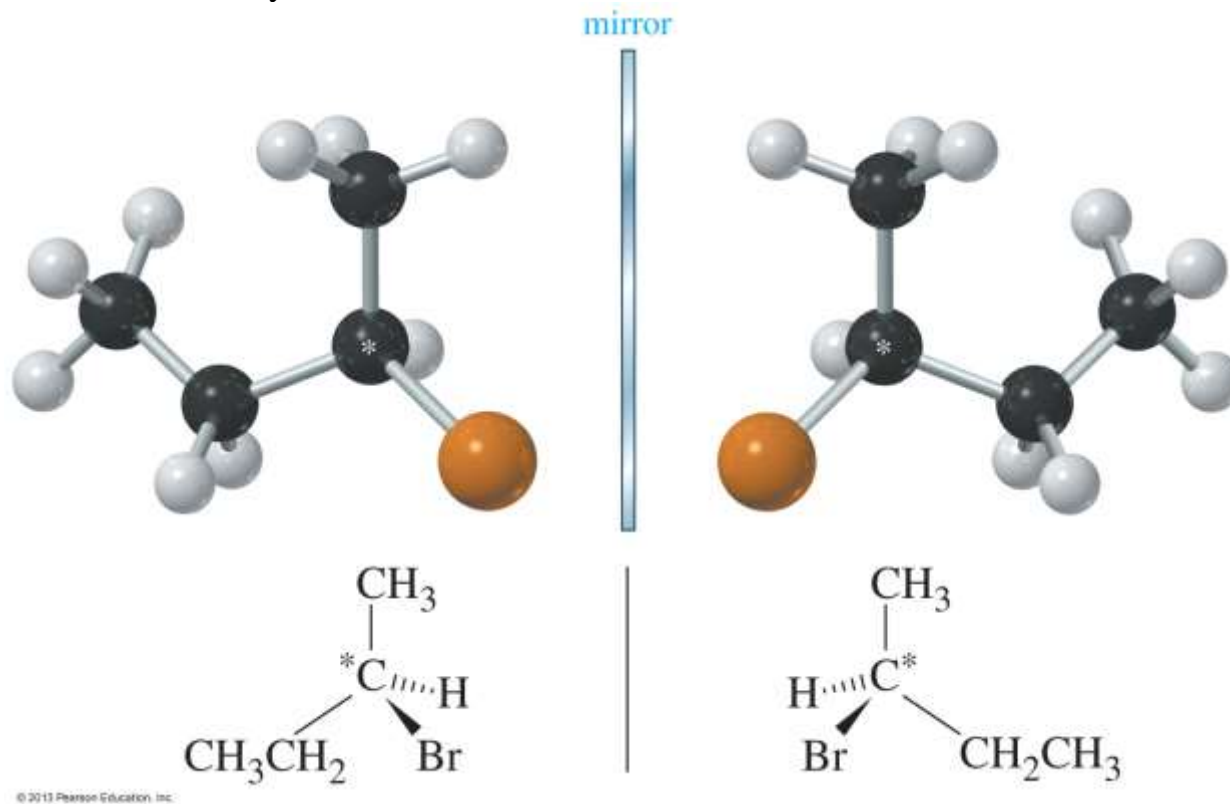The *trans* isomer is non-superimposable on its mirror image – chiral.

Such pairs of non superimposable mirror images are called **enantiomers**.

Every chiral compound has enantiomers.

Achiral compounds **do not** have enantiomers.

Chiral Carbon Atoms

Rings are not essential for chirality, consider 2-bromobutane:

mirror

$$CH_3$$
$$*C\text{''''}H$$
$$CH_3CH_2 \quad Br$$

$$CH_3$$
$$H\text{''''}C*$$
$$Br \quad CH_2CH_3$$

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2-Bromobutane cannot be superimposed on its mirror image – it is *chiral*, and it exists in two *enantiomeric* forms.

Any carbon bound to 4 different groups will be a chiral centre.

Any sp³ atom connected to 4 different groups is a chiral centre.
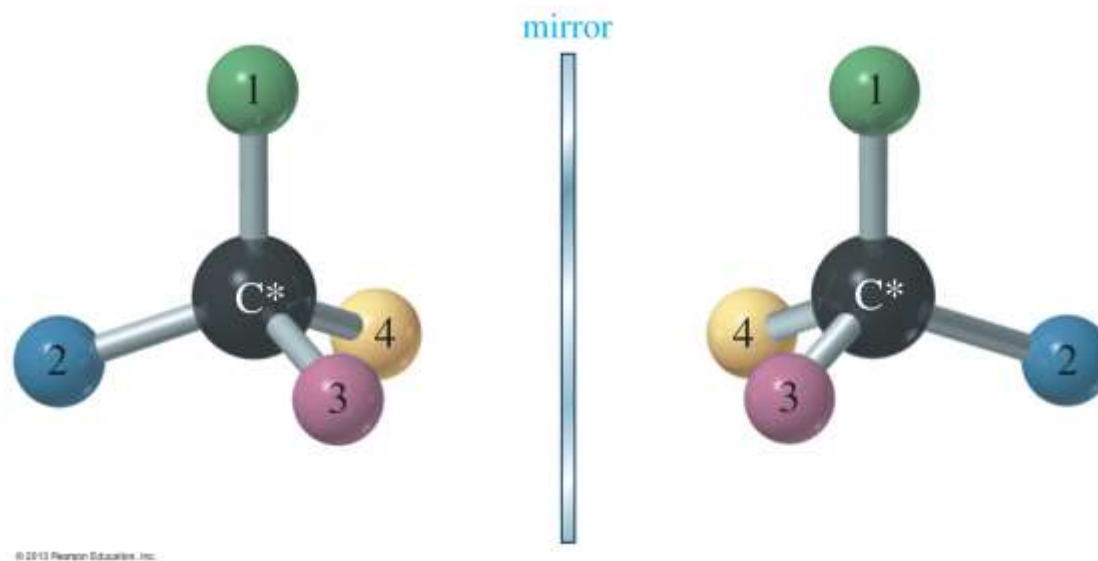
Such a carbon is called a chiral carbon atom (*asymmetric carbon* atom or *stereocenter*), and is usually denoted with an asterix (*).
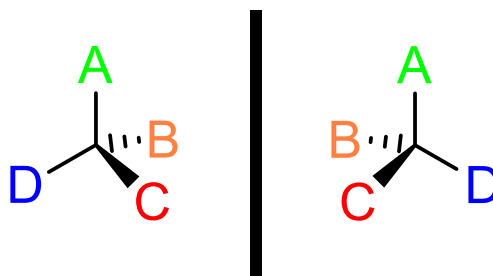
(R) and (S) Assignments
To distinguish between the two enantiomers, one is called the (S) enantiomer, and the other the (R) enantiomer.

The (R) and (S) assignments are designated via the Cahn-Ingold-Prelog Convention.

Each chiral center is designated either (R) or (S).

There are two steps to assigning (R) or (S) to an enantiomer:
    1) Assignment of "priority" to the groups **bound** to the asymmetric carbon
    2) Using the "priority" to decide on (R) or (S).

1) Assignment of Priority
We look at the atoms **directly** bound to chiral carbon.
(a) Atoms with higher atomic numbers receive higher priorities.

$$I > S > O > N > {}^{13}C > {}^{12}C > Li > {}^{3}H \ (T) > {}^{2}H \ (D) > H$$
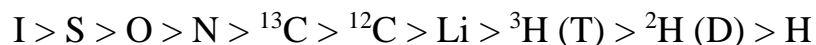
(b) In the case of the same atoms being bound directly to the chiral carbon, we go to the next atoms along the chain.

$$-CH_2Br > -CHCl_2 > -C(CH_3)_3 > -CH(CH_3)CH_2F > -CH(CH_3)_2 > -CH_2CH_3$$

(c) Double and triple bonds are treated as if each bond were to a separate atom. (Imagine that each π bond is broken and that the atoms at both ends were duplicated).

2) (R) and (S) Assignments

(a) The molecule is drawn in 3 dimensions, and arranged in such a way that the bond between the chiral carbon and the **lowest** priority group heads back into the paper.

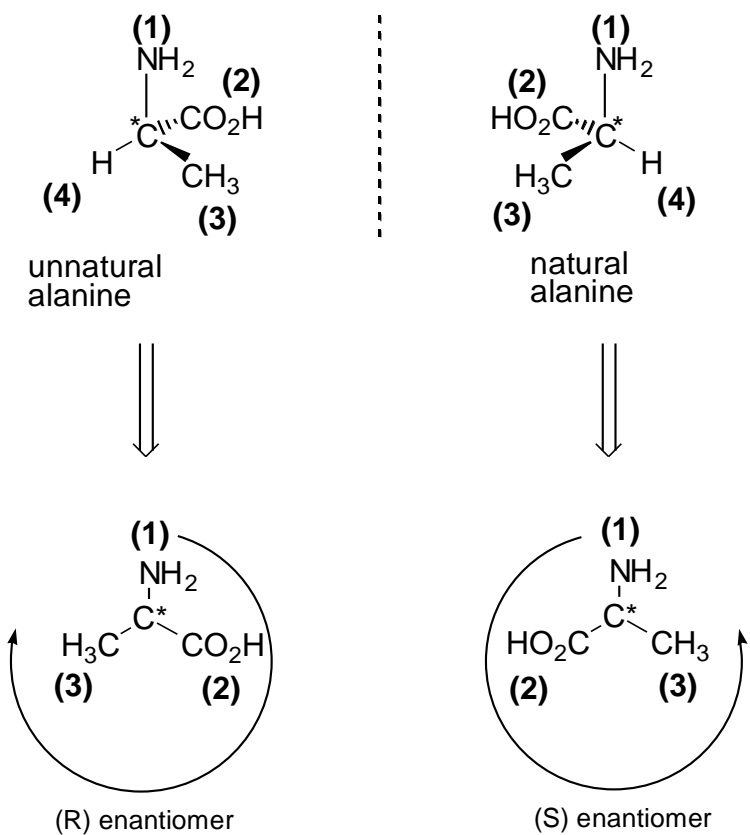(b) Draw an arrow from the group of highest priority, to the second, to the third priority group.

(c) If the arrow is clockwise, the chiral carbon is assigned (R).

If the arrow is counterclockwise, the chiral carbon is assigned (S).
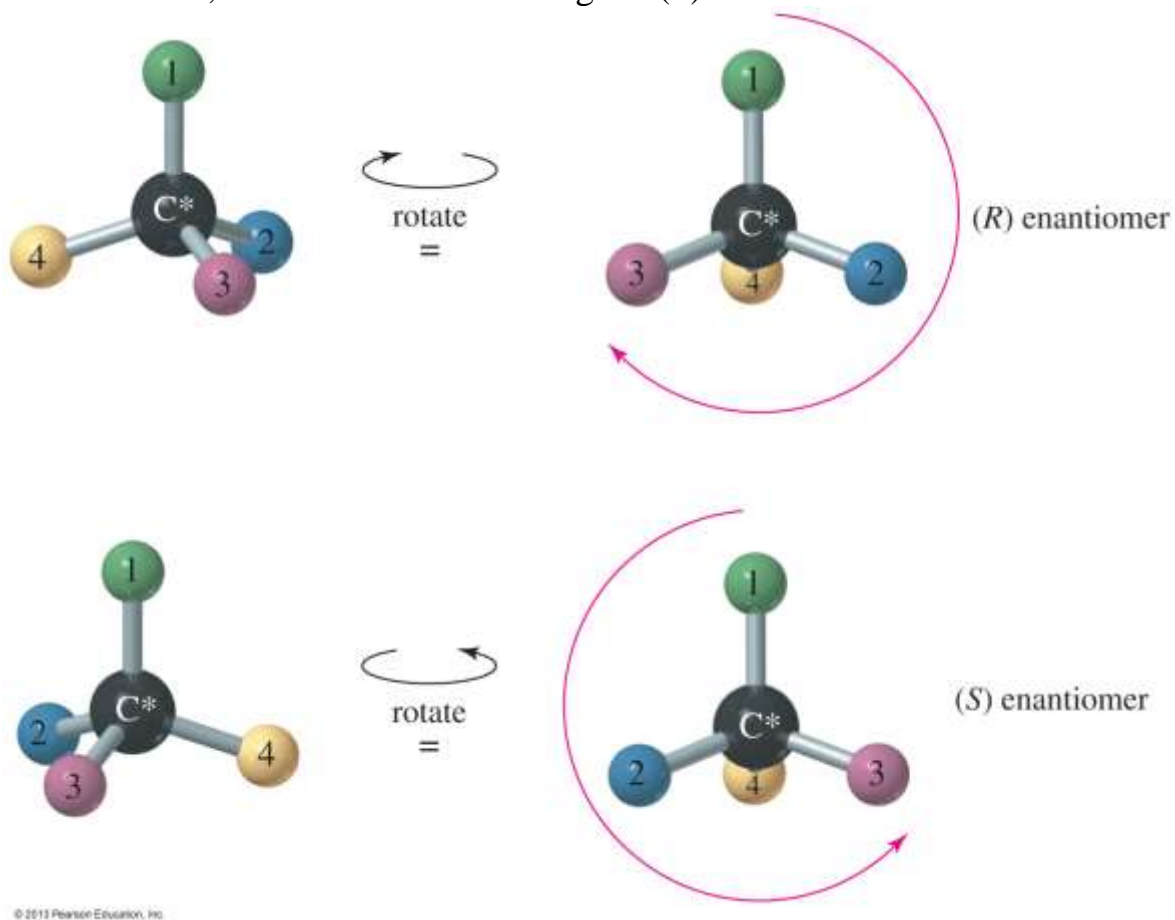
Example:

Consider the naturally occurring amino acid, alanine, and its enantiomer.

$$
\begin{array}{cc}
\textbf{(1)} & \textbf{(1)} \\
NH_2 & NH_2 \\
\textbf{(2)} & \textbf{(2)} \\
C\cdots CO_2H & HO_2C\cdots C \\
H \quad CH_3 & H_3C \quad H \\
\textbf{(4)} \quad \textbf{(3)} & \textbf{(3)} \quad \textbf{(4)} \\
\text{unnatural} & \text{natural} \\
\text{alanine} & \text{alanine}
\end{array}
$$

(1) NH_2

H_3C—C*—CO_2H

(3)   (2)

(R) enantiomer

(1) NH_2

HO_2C—C*—CH_3

(2)   (3)

(S) enantiomer

Optical Activity

Enantiomers have the same   Boiling points
                                          Melting points
                                          Density.

Almost all their physical properties are identical, but one exception is their effect on plane polarized light.

Enantiomeric compounds rotate the plane of polarized light in equal but opposite directions.

Chiral compounds are called **optically active** compounds.

Optically active compounds which rotate plane polarized light clockwise (dextrorotatory) are designated (+) or d.

Optically active compounds which rotate plane polarized light counterclockwise (levorotatory) are designated (-) or l.

Note: There is no relationship between (R) and (S) and the direction of the rotation of plane polarized light. (R) does not mean d and (+).

(R) and (S) are just names from the CIP convention. (+) and (-) are experimentally observed physical properties.
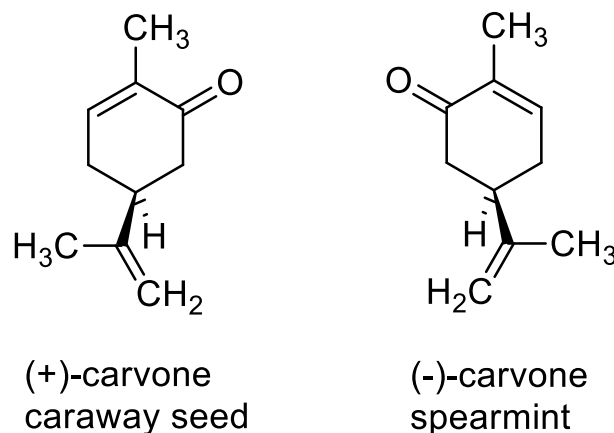
Chirality in Biological Systems

Chirality is very important in biological systems.

Enzyme active sites are capable of chiral discrimination.

Nature (enzymes) is still the best chemist for enantiomerically pure products.
The receptor sites for sense of smell can distinguish between enantiomers since:

(+)-carvone
caraway seed

(-)-carvone
spearmint

Absolute Configuration

The *absolute configuration* of a molecule is the detailed stereochemical picture including how the atoms are arranged in space.
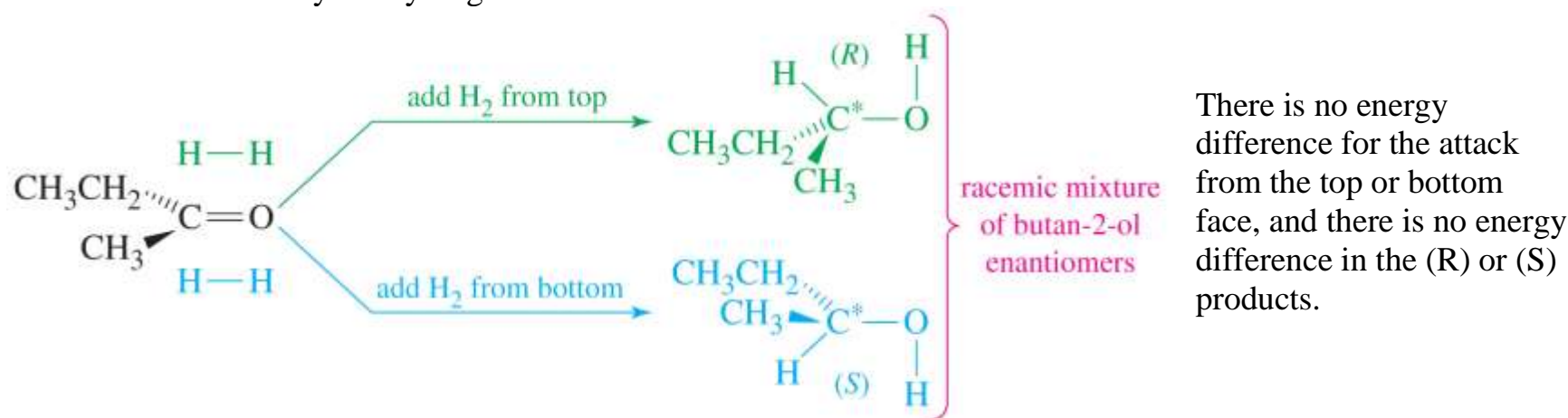
Racemic Mixture (racemate)

A mixture is said to be **racemic** when it contains exactly equal amounts of two enantiomers. Such a mixture is optically **inactive** (zero rotation of plane polarized light).

Racemic mixtures are very common. (The difficult part is to produce exclusively one enantiomer).

Any reaction that uses optically inactive reactants and catalysts <u>cannot</u> produce a mixture that is optically active. Any chiral products formed will be formed as a racemate.

This is demonstrated by the hydrogenation of 2-butanone:

There is no energy difference for the attack from the top or bottom face, and there is no energy difference in the (R) or (S) products.

Therefore although chiral products are produced, the products are formed in equal amounts – a racemic mixture.

<u>Enantiomeric Excess (ee)</u>
Sometimes there will be mixtures where there is more of one enantiomer than the other. This is a more common way of expressing how enriched a sample is in one enantiomer.

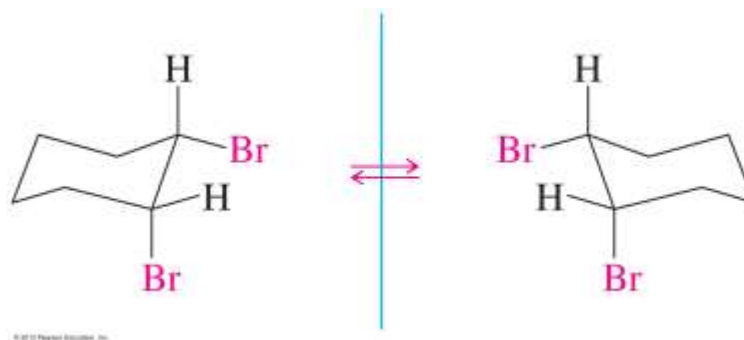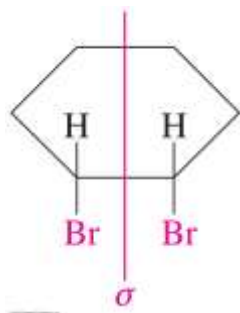The excess of the predominant enantiomer is calculated as a percentage of the entire mixture.

$$e.e. = \frac{R - S}{R + S} \times 100\%$$

Notice that a 70 : 30 ratio of R to S is only a 40% e.e.

Chirality in Mobile Systems

Consider cis-1,2-dibromocyclohexane.

If the ring was flat and planar, then an internal plane of symmetry would exist, and this molecule would therefore be achiral.

But the ring is not planar, it is puckered into a chair conformation, with one Br axial, and one equatorial.

These mirror images are non-superimposable.

BUT, this does not mean that cis-1,2-dibromocyclohexane is chiral:

A molecule <u>cannot</u> be optically active if its chiral conformations are in **equilibrium** with their mirror images.

Cis-1,2-dibromocyclohexane exists as a racemic mixture, but cannot be enriched to be optically active because the conformational equilibrium will racemise the mixture.

Other Chiral Compounds

Most chiral compound have at least one chiral (carbon) atom.

However some molecules are chiral **without** having any asymmetric (carbon) atoms – their chirality is due to their **shape**.

Conformational Enantiomerism occurs when certain molecules are so bulky or strained that they cannot easily convert from one chiral conformation to its mirror image conformation (the opposite of cis-1,2-dibromocyclohexane).
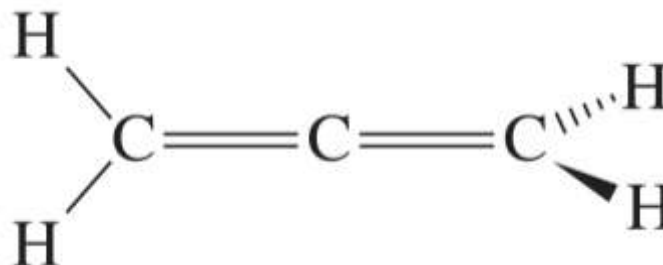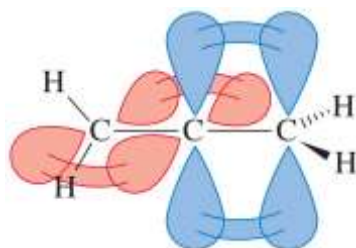
Molecules can become 'locked' or stuck in one conformation which **cannot** equilibrate.

(S)   (R)
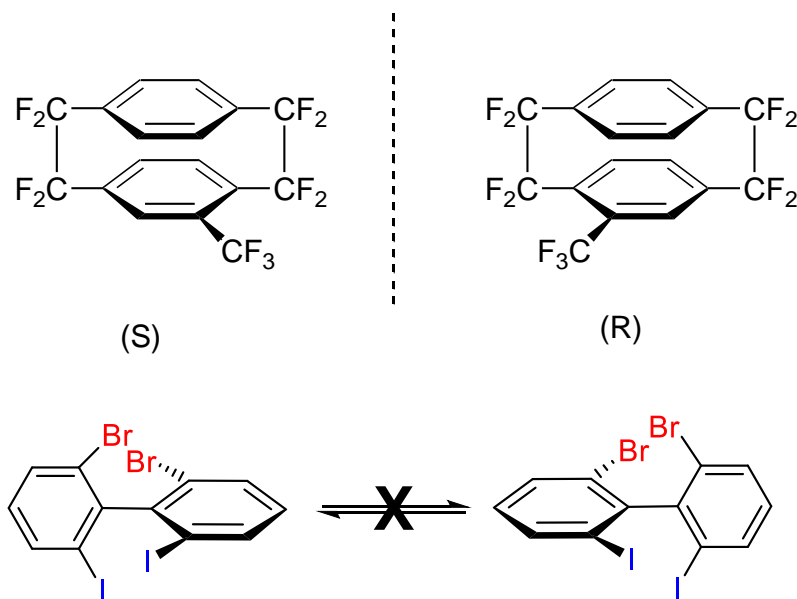
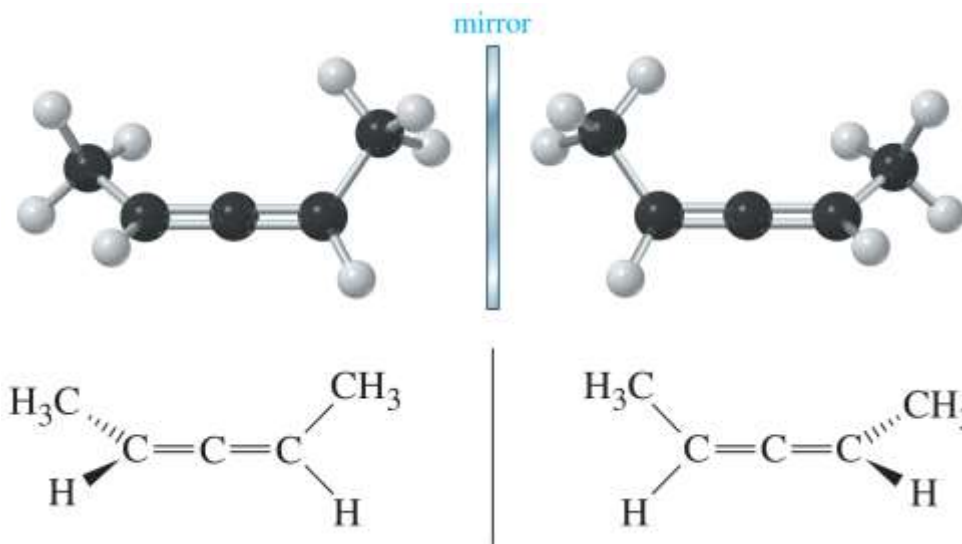This is more common for strained ring systems and / or bulky substituents.

Allenes

This is a class of compounds that contain a C=C=C bonding unit.

The middle C is sp, and the outer two C's are sp^2 hybridized.

The two contiguous π bonds must lie **perpendicular** to each other for p orbital overlap – thus the ends of an allene are perpendicular.


Penta-2,3-diene is chiral even though there are no chiral atoms.

We have already seen 3 dimensional representations using wedges, Sawhorse and Newman projections.

These become less convenient for molecules with many chiral carbon atoms, and we typically use Fischer Projections.

Fischer Projections

(S)-lactic acid
perspective drawing

(S)-lactic acid
Fischer projection
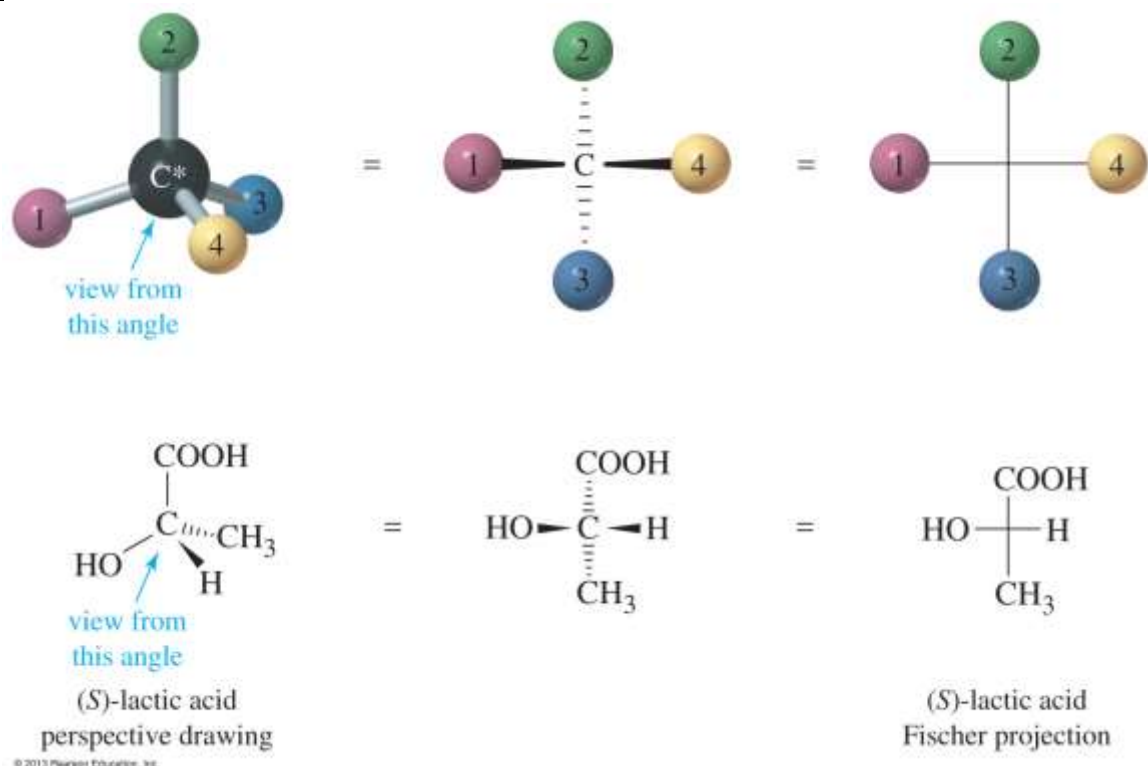
Fischer projections are drawn with a cross, with the chiral atom at the center of the cross.

The *horizontal* lines represent wedges (bonds) coming out of the plane of paper.
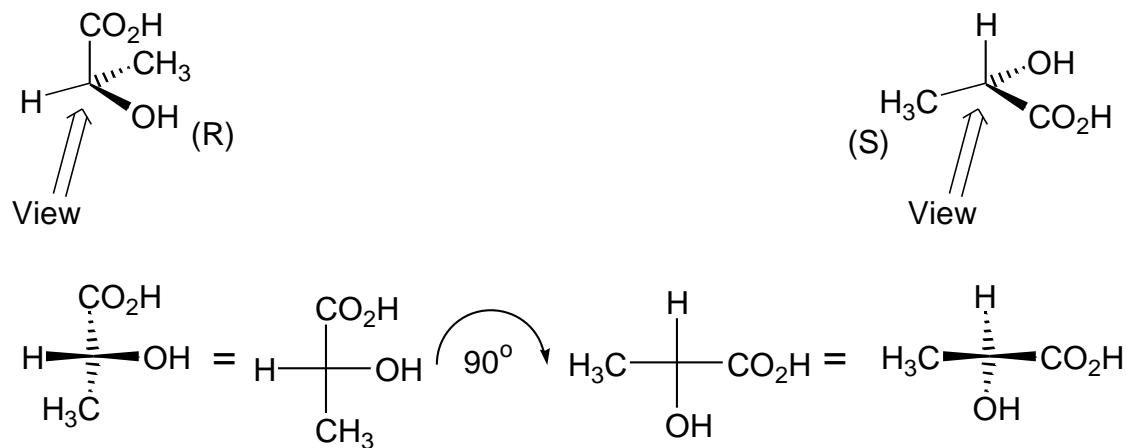The *vertical* lines represent dashed lines (bonds) going into the plane of the paper.   (*"Bow-tie" convention*).

Fischer projections that differ by a 180° rotation are the <u>same</u> enantiomer, since the vertical lines are still back, and the horizontal lines are still forward.
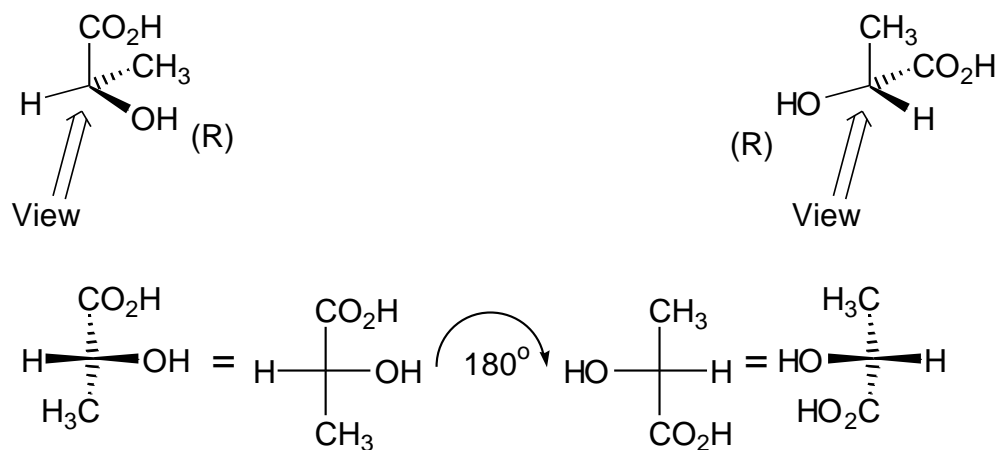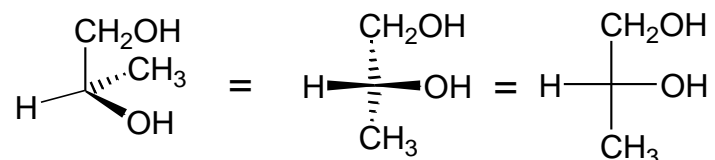

Fischer projections that differ by a 90° rotation are different enantiomers.

Fischer projections have another rule which helps with the above laws:
The carbon chain is drawn along the **vertical** line of the projection, with the most highly oxidized carbon substituent at the top.

(R)-1,2-propanediol

$$CH_2OH \quad \quad CH_2OH \quad \quad CH_2OH$$

H—C(''CH₃)(OH) = H——OH = H——OH

with CH₃ and CH₃ at the bottom

Drawing Mirror Images
To draw a mirror image of a Fischer projection, simply exchange the left and right positions, whilst keeping the top and bottom unchanged.

$$CO_2H \quad\quad\quad CO_2H$$

H——OH   HO——H

$$CH_3 \quad\quad\quad\quad CH_3$$

(R) lactic acid   (S) lactic acid
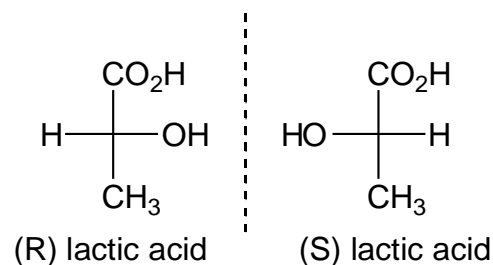
Fischer projections are very useful to determine if a compound is chiral or achiral.
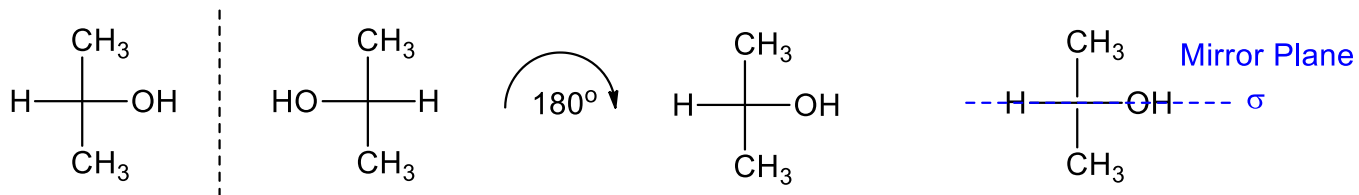(This assumes that the Fischer projections are correctly drawn).

If the mirror image **cannot** be made to look like the original image by <u>only</u> rotating by 180° in the plane of the paper, then the images are enantiomers, and the original compound is therefore chiral.
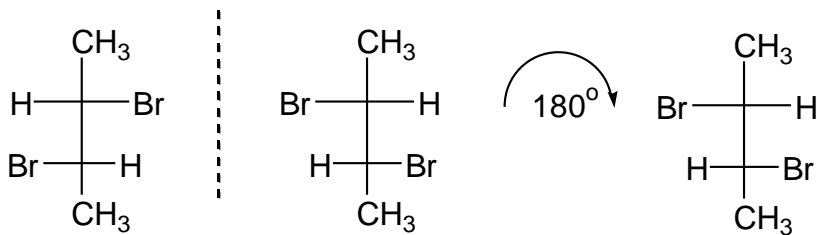
Examples:
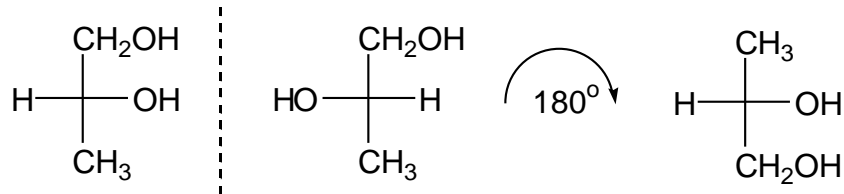
Mirror images are different, propan-1,2-diol is *chiral*.

Mirror images are the same, propan-2-ol is *achiral*.

(Mirror planes are easy to spot in Fischer projections, and molecules with mirror planes <u>cannot</u> be chiral).

Mirror image is different – molecule is *chiral*

Assignment of (R) and (S)
(R) and (S) are determined according to the Cahn-Ingold-Prelog convention.

Either translate the Fischer projection into wedges, shading and sticks, and proceed as previously.
(Rotate the molecule to view down the lowest priority bond, and then draw the highest to lowest priority arrow, and clockwise = R).

Alternatively, it can be determined **directly** from the Fischer projection.
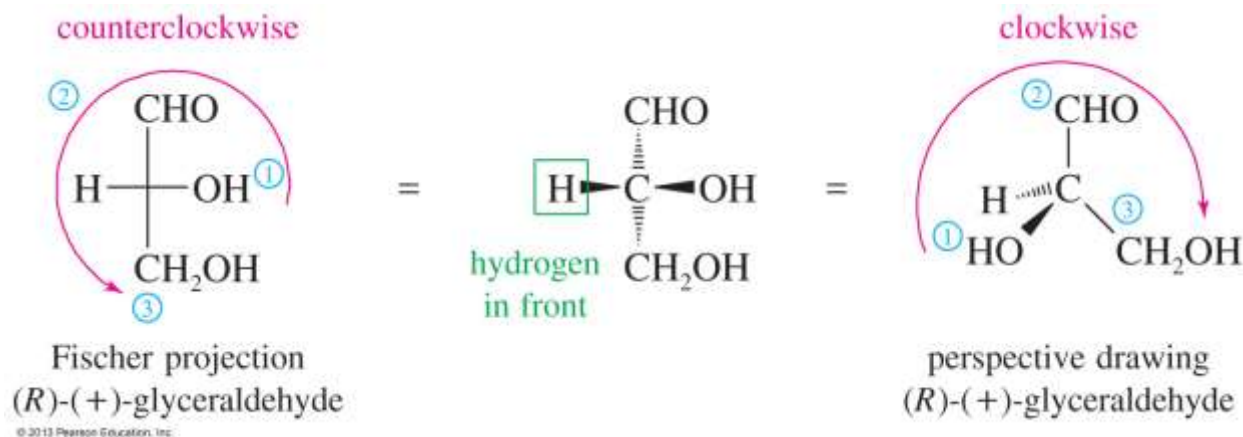
Recall that since the C chain is arranged vertically, the lowest priority group (usually H) will be on the horizontal axis (which means it is sticking out toward us).

To use the Fischer projection, ensure the Fischer projection is drawn correctly.
    Ignore the lowest priority group and label the other three.
    Draw the highest to lowest priority arrow.
    However, since the lowest priority bond is now sticking out (opposite to normal), a clockwise arrow means S
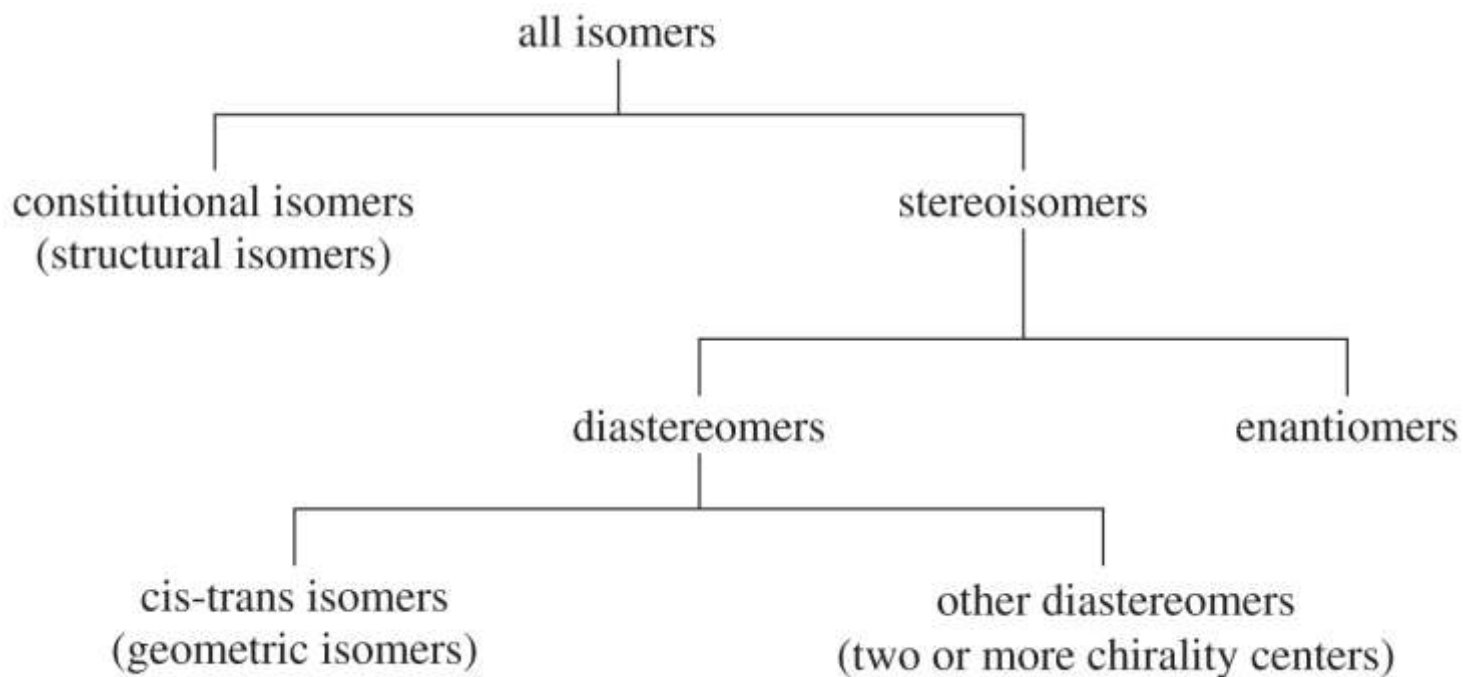   configuration.

counterclockwise

clockwise

Fischer projection
(R)-(+)-glyceraldehyde

hydrogen in front

perspective drawing
(R)-(+)-glyceraldehyde

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Diasteromers

Stereoisomers are molecules that have atoms bonded together in the **same** order, but **differ** in how the molecules are directed in space.

Enantiomers are mirror image isomers. All other stereoisomers are called diastereomers.
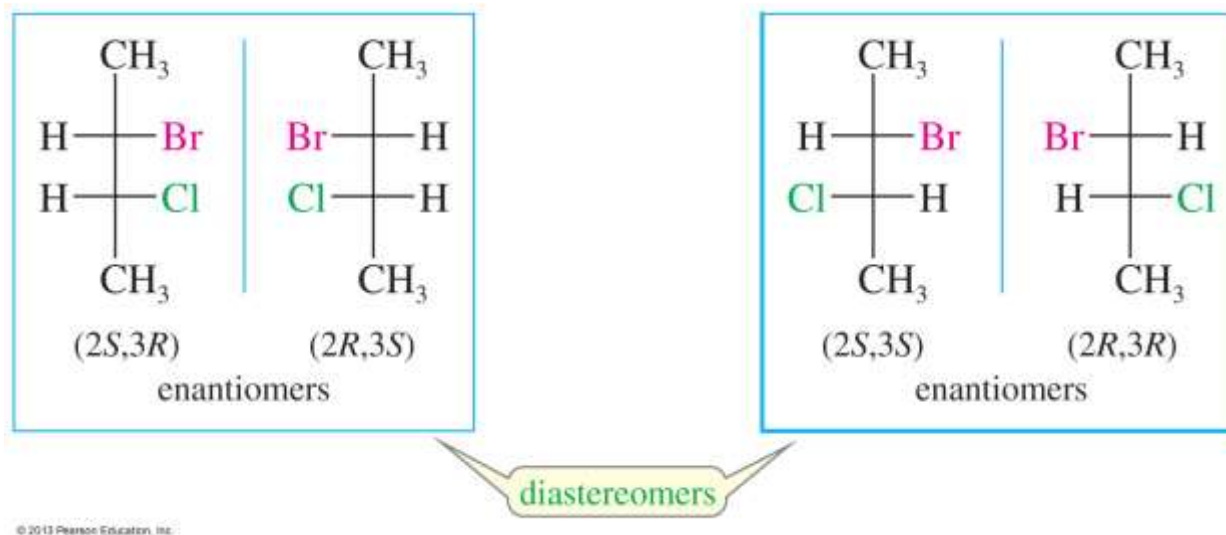Therefore, **diastereomers are stereoisomers that are not mirror images**.

Most diastereomers are either geometric isomers, or compounds with two or more chiral atoms.

```
                              all isomers
                                  |
              ┌───────────────────┴───────────────────┐
   constitutional isomers                        stereoisomers
   (structural isomers)                               |
                                   ┌──────────────────┴──────────────┐
                              diastereomers                      enantiomers
                                   |
                    ┌──────────────┴──────────────┐
           cis-trans isomers              other diastereomers
           (geometric isomers)         (two or more chirality centers)
```

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Molecules with 2 or more Chiral Atoms
For example, 2-bromo-3-chlorobutane.

$(2S,3R)$ $(2R,3S)$ $(2S,3S)$ $(2R,3R)$

enantiomers   enantiomers

diastereomers

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This can exist in 4 possible stereoisomers.
     (2S, 3R), (2R, 3S), (2S, 3S) and (2R, 3R).

          The (2S, 3R) and (2R, 3S) are enantiomers.

          The (2S, 3S) and (2R, 3R) are enantiomers.

We can also say (2S, 3R) is a diastereomer of (2S, 3S) and (2R, 3R), and
(2S, 3S) is a diastereomer of (2S, 3R) and (2R, 3S).

Meso Compounds

Previously we saw all the permutations (4) for a molecule with two chiral centers.

This follows a general rule that **n** *chiral centers give rise to 2^n possible stereoisomers*.

This gives the *maximum* possible number of stereoisomers that can exist – but often if the molecule is highly symmetrical, some of these stereoisomers are actually the same compound.

For example, 2,3-dibromobutane has two chiral carbons, but only 3 stereoisomers. (It has 4, but 2 are the same, giving 3 different).
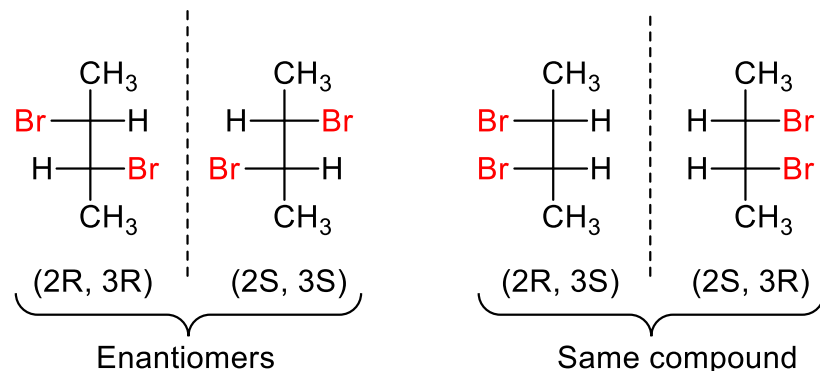
The enantiomer pair are termed the (±) diastereomer (or dl),
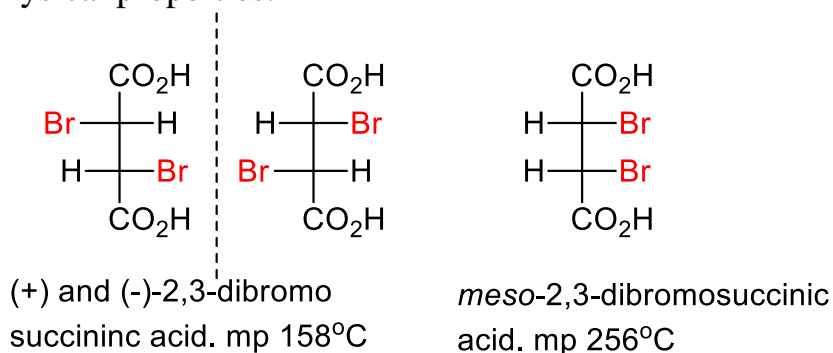The 'same compound' pair are called the *meso* diastereomer.

The meso diastereomer is *achiral* since it has a mirror plane of symmetry.

> A *meso* compound is an **achiral** compound which has **chiral** atoms.

Physical Properties of Diastereomers

Enantiomers have identical physical properties (b.p., m.p., density, etc) except for their rotation of plane polarized light.

Diastereomers have different physical properties.

$$\begin{array}{ccc}
CO_2H & CO_2H & CO_2H \\
Br{-}\!\!\!-\!\!\!-H & H{-}\!\!\!-\!\!\!-Br & H{-}\!\!\!-\!\!\!-Br \\
H{-}\!\!\!-\!\!\!-Br & Br{-}\!\!\!-\!\!\!-H & H{-}\!\!\!-\!\!\!-Br \\
CO_2H & CO_2H & CO_2H
\end{array}$$

(+) and (-)-2,3-dibromo   *meso*-2,3-dibromosuccinic
succininc acid. mp 158°C   acid. mp 256°C

Since diastereomers have different physical properties, they are often easy to separate by normal practical techniques (distillation, recrystallization, chromatography, etc).

Enantiomers are much more difficult to separate.

Separation of Enantiomers (resolution)

In nature, very often only one enantiomer is produced. Living organisms are one of the best sources of optically active compounds (plants, enzymes, cells, animals etc).

In a lab it is different.

In a lab it is different.

butan-2-one → H_2, Pt → (R)-butan-2-ol + (S)-butan-2-ol

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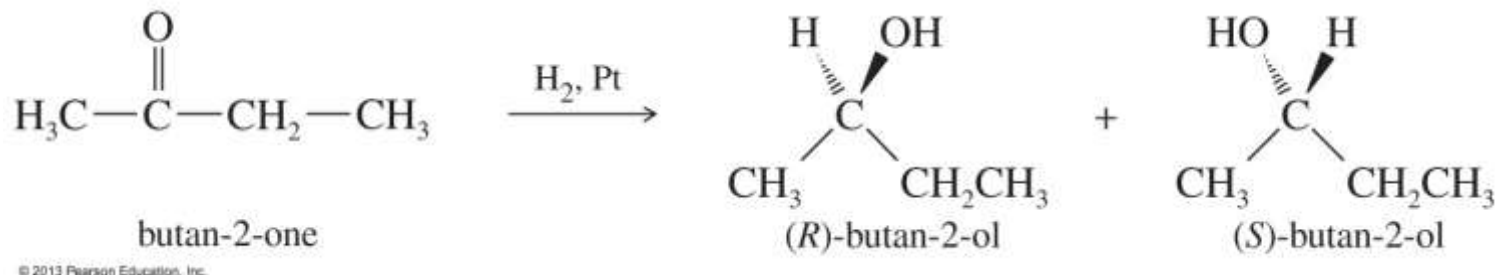
If we require just one enantiomer of butan-2-ol, we must separate it from the other enantiomer – this is called **resolution**.

Enantiomers have the same physical properties, but they differ in a chiral (or handedness) sense, so a chiral (or handed) probe must be used for such a separation.

Such a chiral apparatus or compound is termed a resolving agent.

Chemical Resolution
A typical procedure for the resolution of chiral compounds is to react the racemic mixture with an enantiomerically pure compound.

This gives rise to a pair of *diastereomers* – which have different physical properties and therefore can be separated.
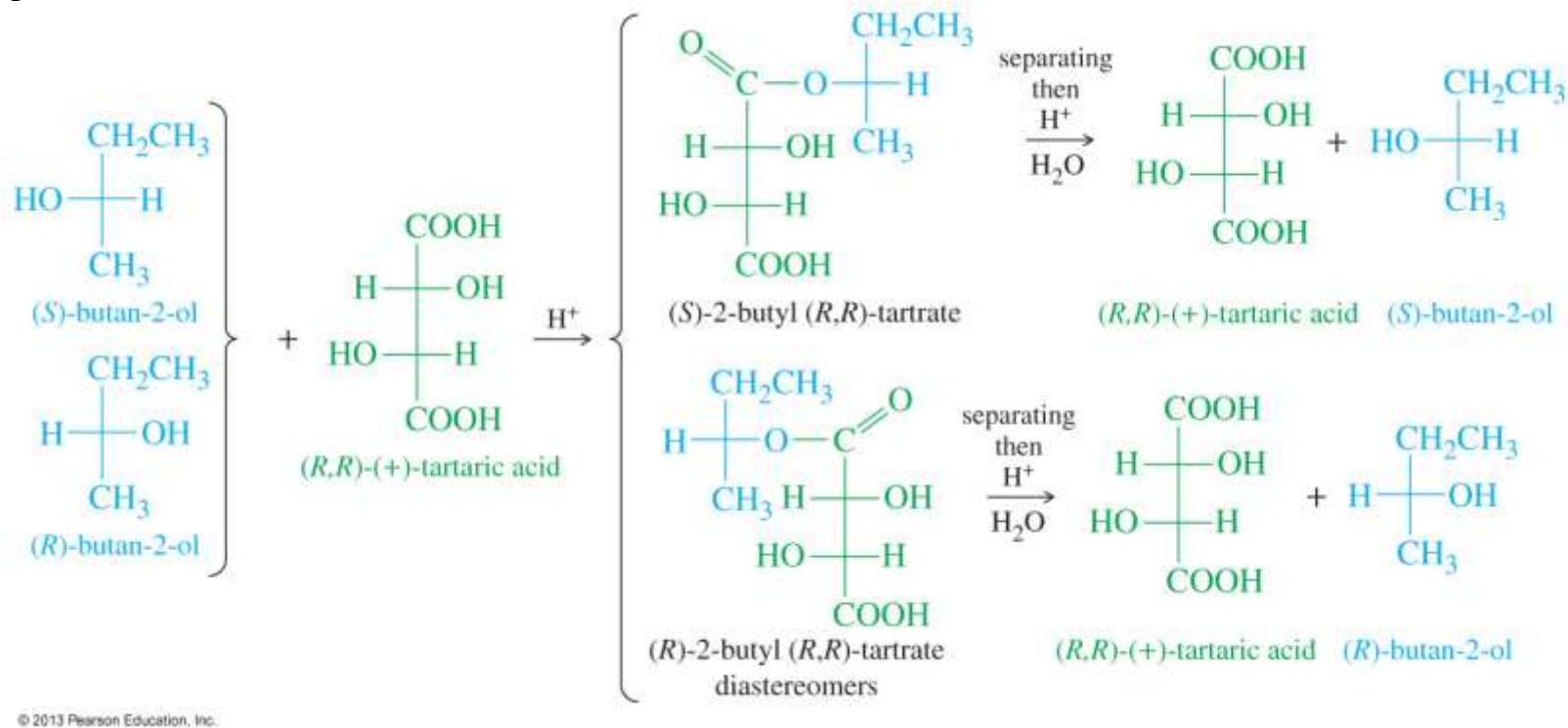
The resolving agent is then cleaved off, leaving pure separated enantiomers.

Example: Resolution of 2-butanol.

Need to know:
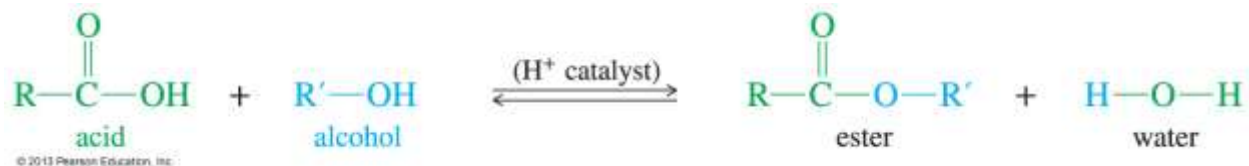
The process is:

-Alcohols react with the enantiomerically pure tartaric acid, to give two diastereomeric esters.
-These esters are separated.
-Acid hydrolysis cleaves each ester back to an optically active alcohol and carboxylic acid.

The resolving agent (tartaric acid) is recovered and often recycled. (Enantiopure compounds are often expensive).

More recently, chiral chromoatography has been developed for enantiomeric separation:
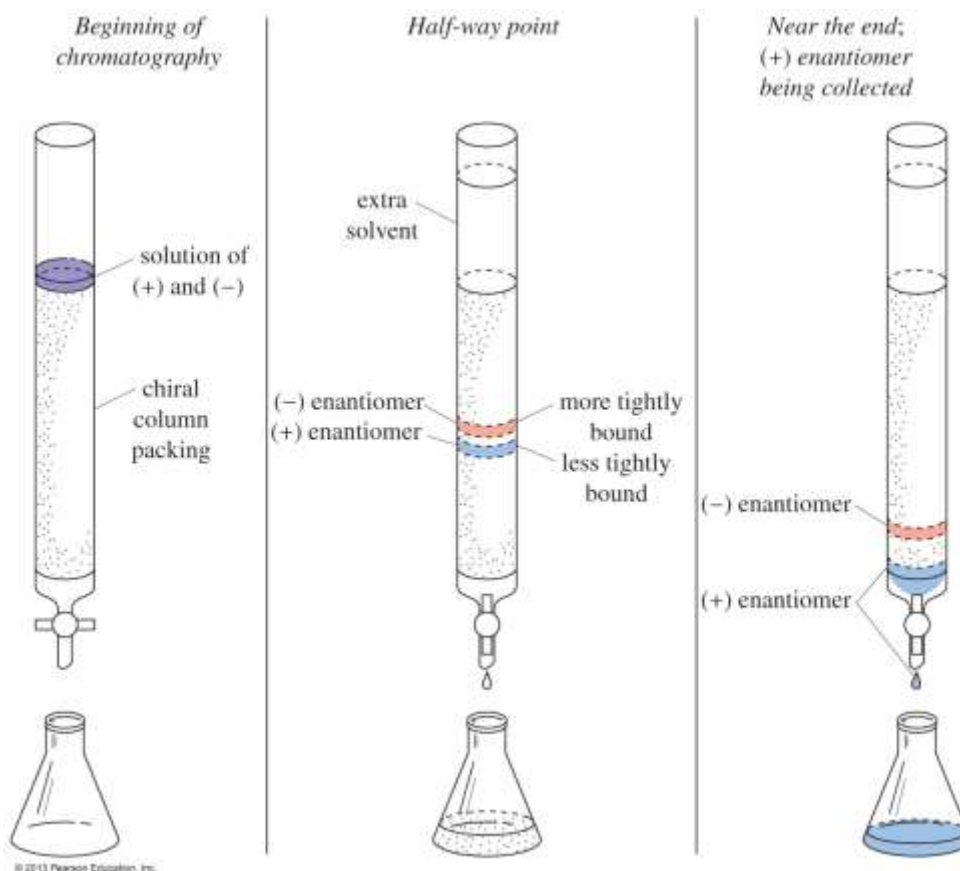
Stereochemistry of Reactions

This is the study of what happens when chiral compounds react. Studies with chiral compounds can reveal a vast amount of information about a reaction mechanism.

Three general types
1) Reactions that occur at the chiral atom
2) Reactions that do not involve the chiral atom
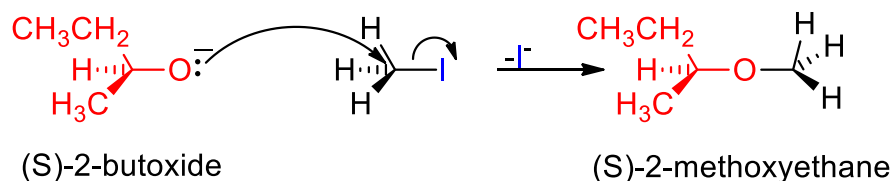3) Reactions that generate a new chiral atoms

1) Reactions at a Chiral Atom

If a reaction occurs at a chiral atom, one of three things can happen.
(a) Inversion of Configuration (R→S)
(b) Racemization of configuration (R→R + S)
(c) Retention of Configuration (R→R)
This depends on the *mechanism* of reaction.

2) Reactions that do not Involve the Chiral Atom

Typically, if bonds directly to the chiral atom are not broken or formed during the reaction, the configuration will remain unchanged.

(S)-2-butoxide   (S)-2-methoxyethane

The four bonds to the chiral C atom are unchanged, and the configuration is the same.

3) Reactions that generate a new Chiral Center
Lots of reactions form new chiral atoms, yet achiral reactants will always produce **racemic** mixtures, since there is no chiral control.

Asymmetric Induction
This is the use of an optically active reagent or catalyst to convert an *achiral* reactant into a *chiral* product.

Enzymes are especially useful for this type of transformation.
Hydrogen is selectively delivered from one face, to give only one enantiomer.
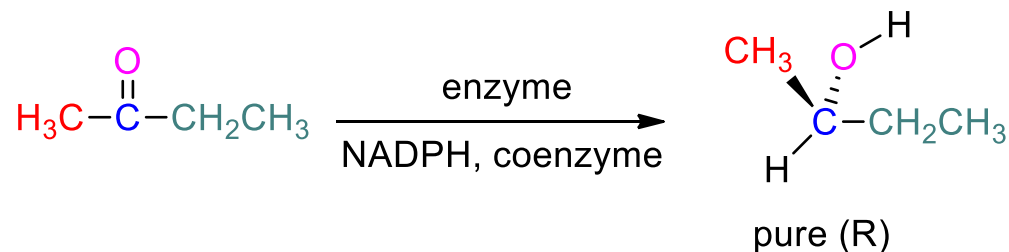

Similar results can be achieved in the lab using chiral catalysts or reagents (which are usually expensive).

Directing Effects of Chiral Carbons
If there is already a chiral atom in the molecule, it is possible that the stereochemistry around that atom can influence or direct a reagent to have a preferred direction of attack.

The platinum catalyzed hydrogenation of 2-methylcyclopentanone gives two products.
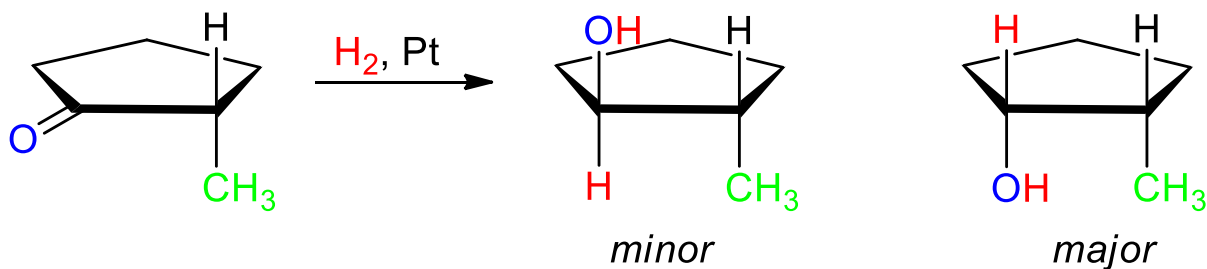
The **major** product is *cis*-2-methylcyclopentanol, the **minor** is the *trans* isomer.

The hydrogen attacks from the *least hindered* side.

The two faces of attack are not the same since the methyl group sterically hinders one face.
The chiral carbon atom *communicates* its chirality to the new center.