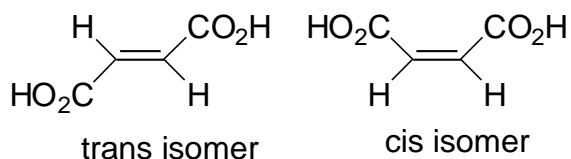


Stereochemistry

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. These effects can lead to profound differences in physiology and pharmacology.

E.g. the isomers of butenoic acid:



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

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.

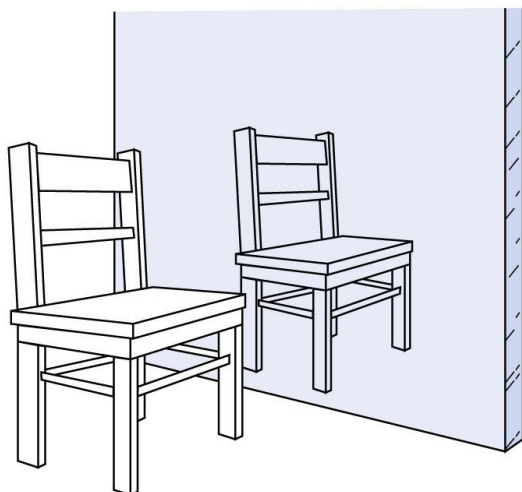
Chiral objects include: hands, feet, gloves, screws, cork screws, dice

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

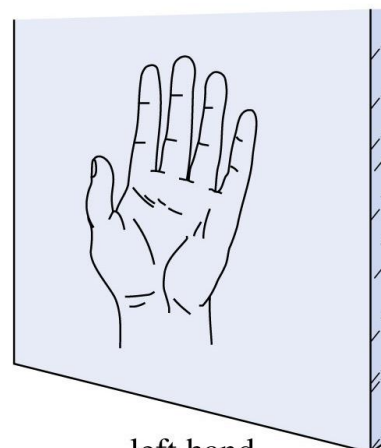
Chirality in Organic Molecules

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 achiral.

If a molecule has a **non superimposable** mirror image, it is chiral.

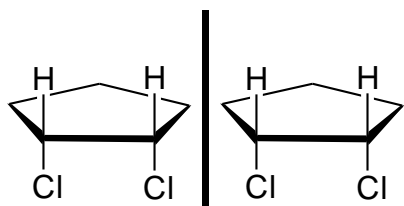


right hand

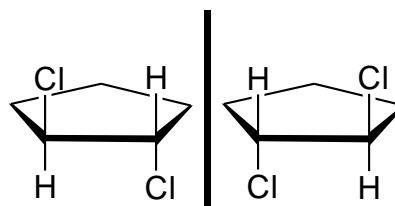


left hand

Consider stereoisomers of 1,2-dichlorocyclopentane:



cis isomer is achiral



trans isomer is chiral

The cis isomer has a superimposable mirror image – achiral.

The trans isomer is non-superimposable on its mirror image – chiral.

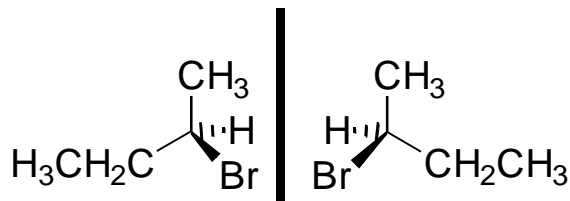
Such pairs of non superimposable mirror images are called **enantiomers**.

Every chiral compound has enantiomers.

Chiral compounds **do not** have enantiomers.

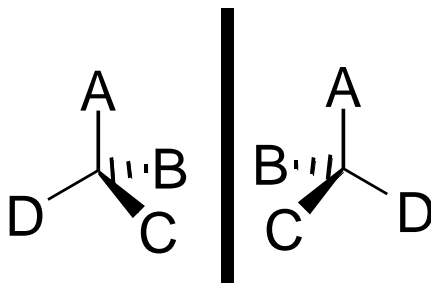
Chiral Carbon Atoms

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



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 center.



Such a carbon is called a chiral carbon atom (asymmetric carbon atom or stereocenter), and is usually denoted with an asterix (*).

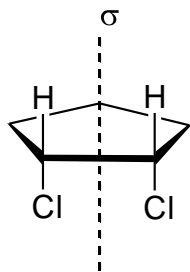
The **absolute** law is whether or not a molecule's mirror image is identical to the original, but a few quick rules are:

- 1) if the molecule has no chiral carbon, it is usually achiral
- 2) if the molecule has just one chiral carbon, it is usually chiral
- 3) if it has 2 or more chiral carbons, it may or may not be chiral.

(There are exceptions...)

Mirror Planes of Symmetry

If a molecule possesses an internal mirror plane of symmetry (σ), then it **cannot** be chiral.



(Note that the absence of a mirror plane does not imply chirality).

(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).

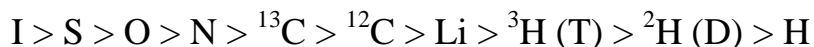
There are two steps to assigning (R) or (S) to an enantiomer:

- 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.



(b) In the case of the same atoms being bound directly to the chiral carbon, we go to the next atoms along the chain.



(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

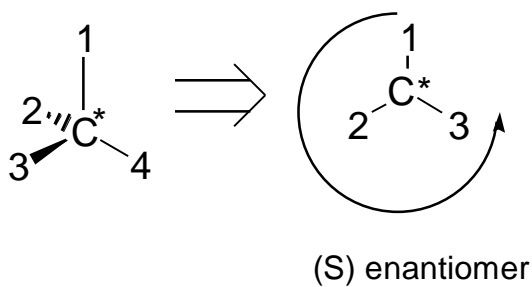
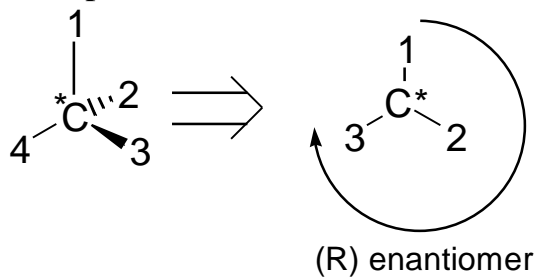
(a) The molecule is drawn in 3 dimensions, and arranged in such a way that the bond between the chiral carbon and the **lowest** priority group heads back into the paper.

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

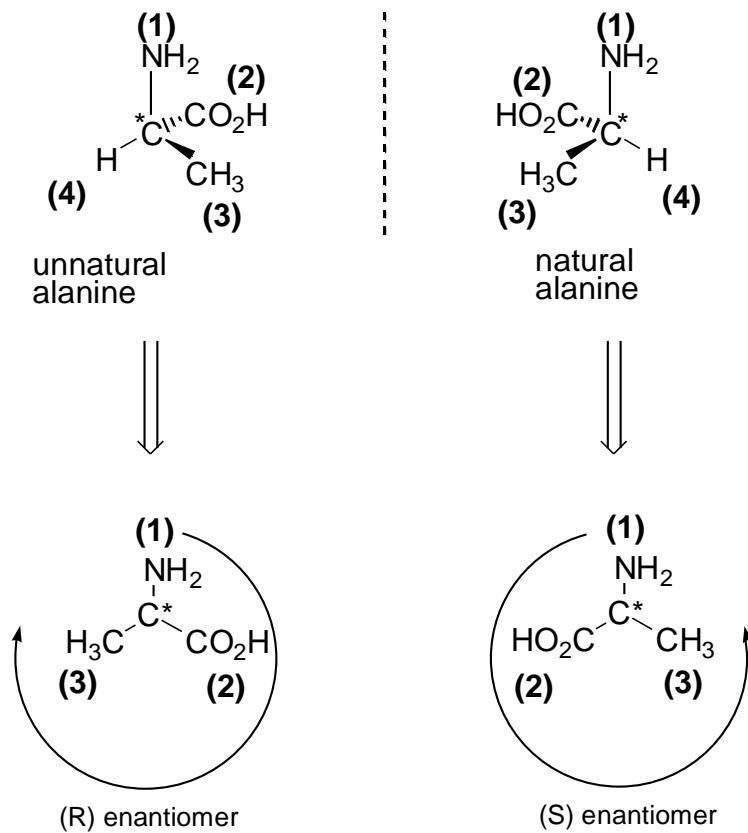
(c) If the arrow is clockwise, the chiral carbon is assigned (R).

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

Example:



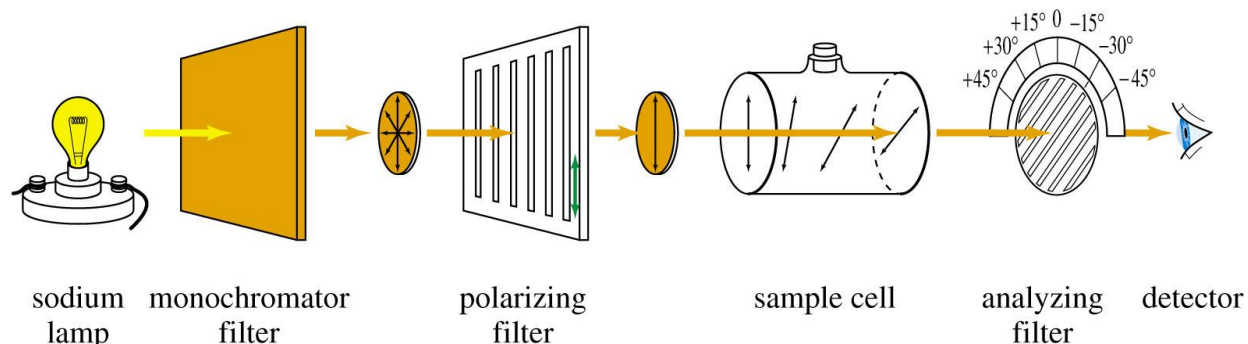
Consider the naturally occurring amino acid, alanine, and its enantiomer.



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.

Specific Rotation (α)

Specific rotation of an compound is measured on an instrument called a polarimeter.

$$[\alpha] = \alpha_{\text{obs}} / c.l$$

where α_{obs} = the observed rotation
 c = concentration (g/ml)
 l = sample path length (dm).

Rotation depends on the temperature and the wavelength of the light used. Standard conditions are at 25°C and using the D line of the sodium spectrum.

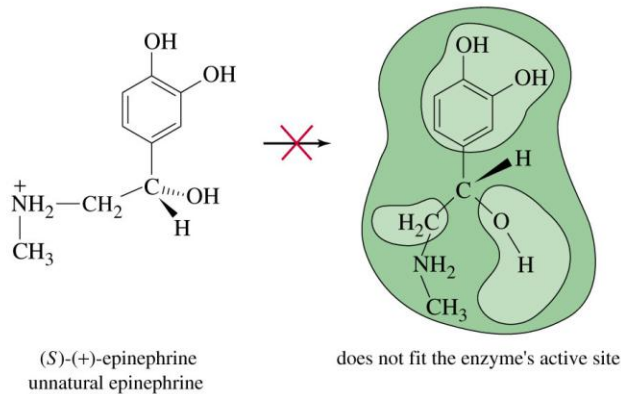
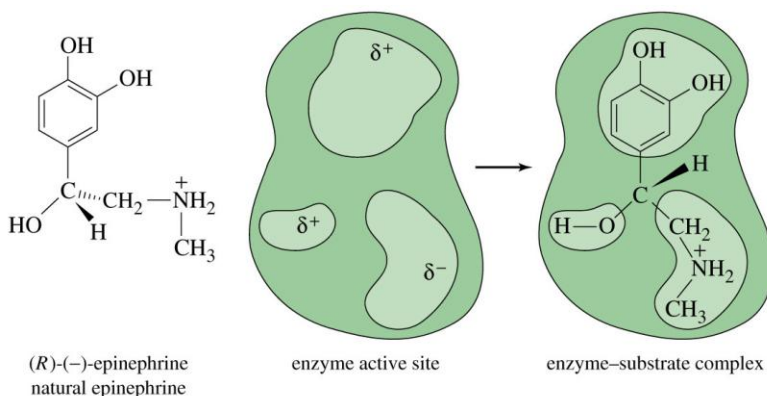
These are indicated thus: $[\alpha]^{25}_{\text{D}}$

Chirality in Biological Systems

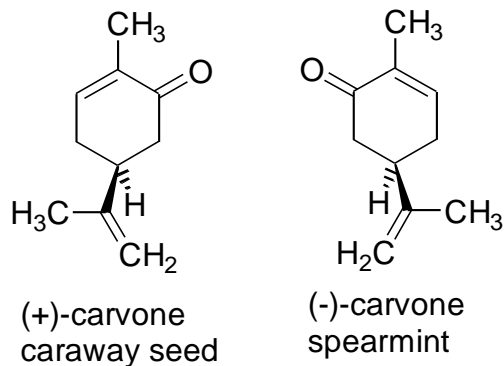
Chirality is very important in biological systems.

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:



Absolute Configuration

The absolute configuration of a molecule is the detailed stereochemical picture including how the atoms are arranged in space.

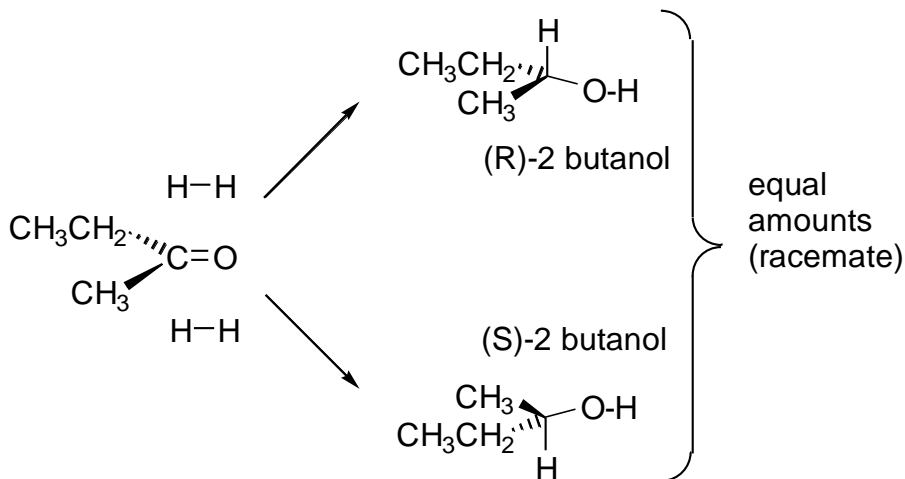
Racemic Mixture (racemate)

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 cannot 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.

Enantiomeric Excess (Optical Purity)

Sometimes there will be mixtures where there is more of one enantiomer than the other.

The optical purity is defined as the ratio of the observed optical rotation of the mixture to the rotation of a pure enantiomer. It is usually expressed as a percentage.

Example: (+) 2-butanol has a $+13.50^\circ$ specific rotation. A bottle on the shelf contains 2-butanol, which gives a specific rotation of $+9.54^\circ$.

$$\begin{aligned} \text{The optical purity } = \text{o.p.} &= \frac{\text{observed rotation}}{\text{Pure enantiomer rot.}} \times 100\% \\ &= \frac{9.54}{13.50} \times 100\% = 70.7\% \end{aligned}$$

Enantiomeric Excess (e.e.)

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.

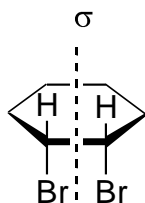
$$\text{e.e.} = \text{o.p.} = \frac{d - l}{d + l} \times 100\%$$

Notice that a 70 : 30 ratio of d to l is only a 40% e.e.

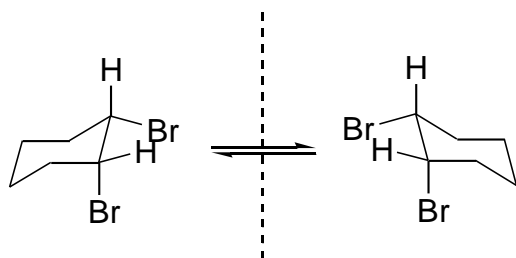
Chirality in Mobile Systems

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 cannot 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

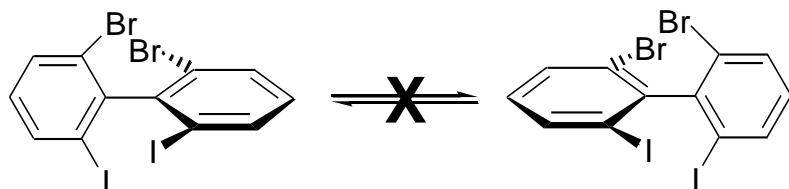
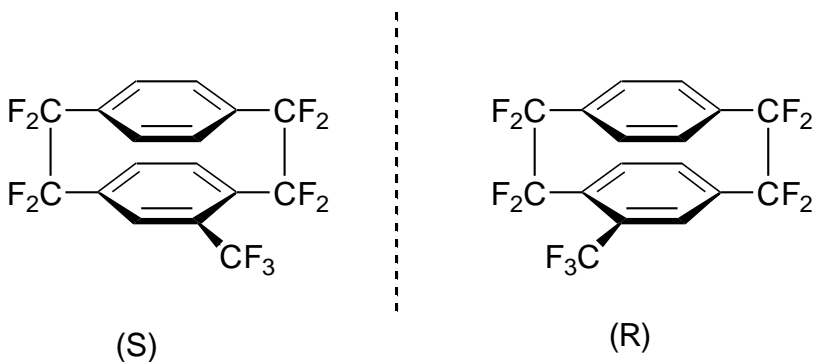
Most chiral compounds have at least one chiral (carbon) atom.

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

Conformational Enantiomerism

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).

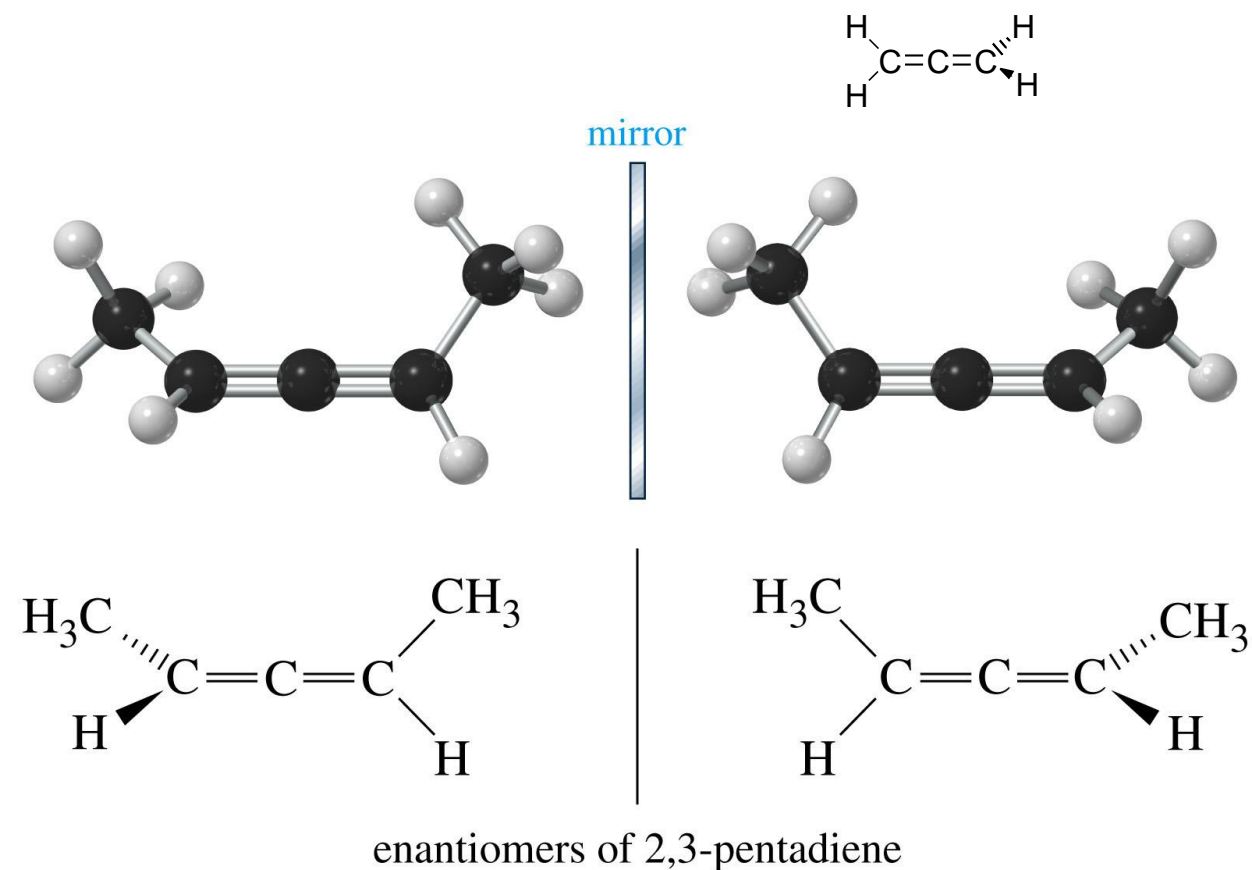
Molecules can become ‘locked’ or stuck in one conformation which **cannot** equilibrate.



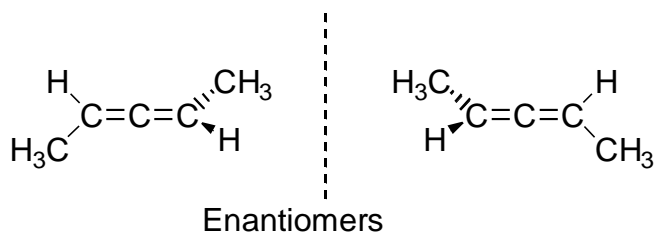
This is more common for strained ring systems and /or bulky substituents.

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.



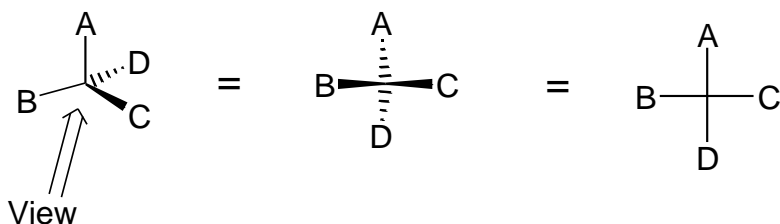
2,3-Pentadiene is chiral even though there are no chiral atoms.

Fischer projections

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



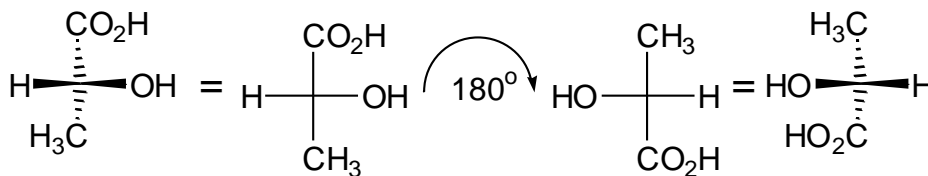
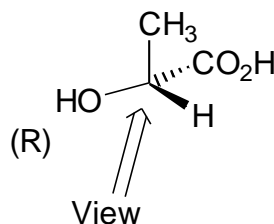
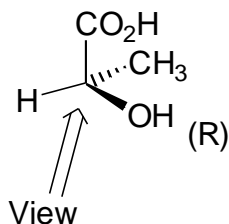
Fischer projections are drawn with a cross, with the chiral atom at the center of the cross.

The horizontal lines represent wedges (bonds) coming out of the plane of paper.

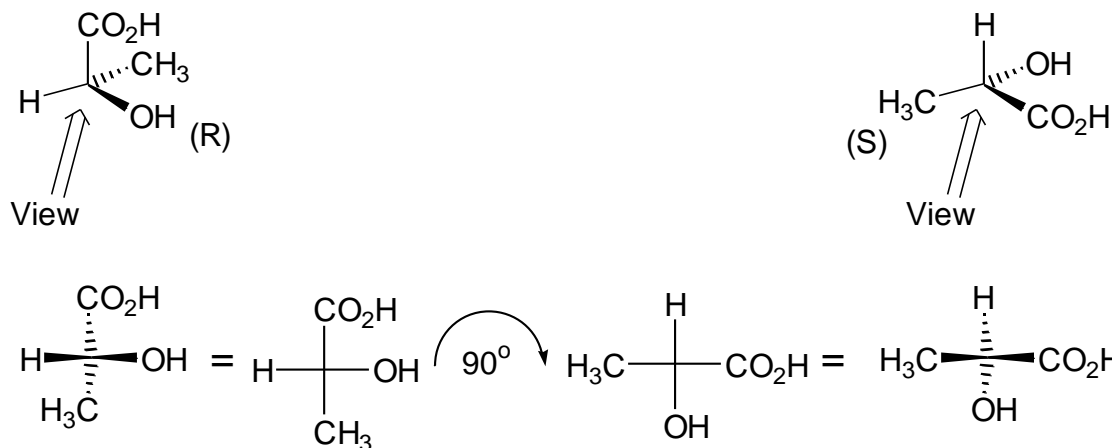
The vertical lines represent dashed lines (bonds) going into the plane of the paper.

(“Bow-tie” convention).

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

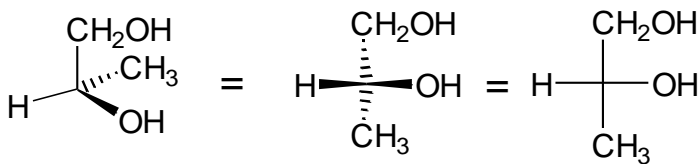


Fischer projections that differ by a 90° rotation are different enantiomers.



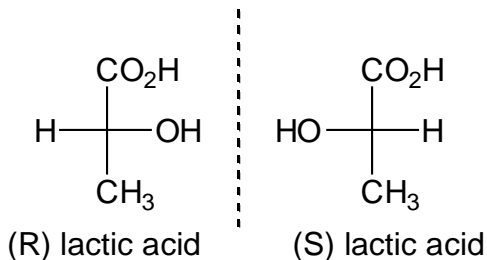
Fischer projections have another rule which helps with the above laws:
The carbon chain is drawn along the **vertical** line of the projection, with the most highly oxidized carbon substituent at the top.

(R)-1,2-propanediol



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.

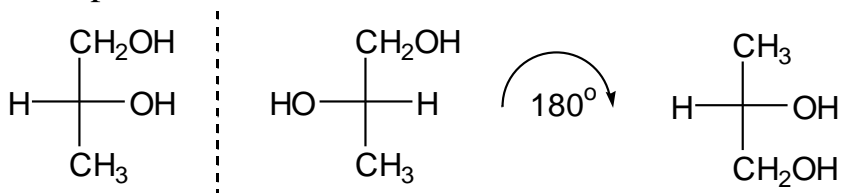


Fischer projections are very useful to determine if a compound is chiral or achiral.

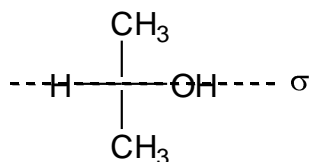
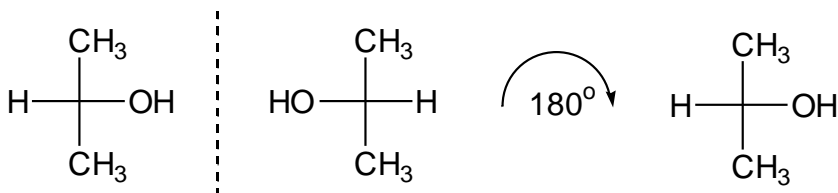
(This assumes that the Fischer projections are correctly drawn).

If the mirror image **cannot** be made to look like the original image by only rotating by 180° in the plane of the paper, then the images are enantiomers, and the original compound is therefore chiral.

Examples:

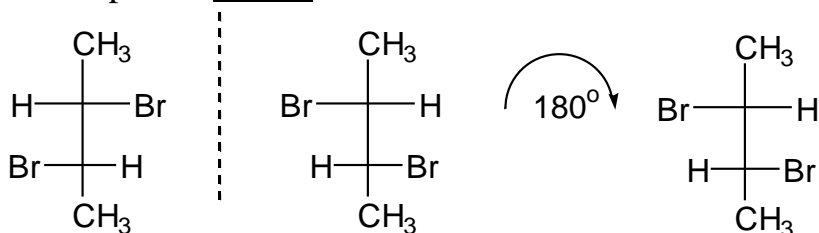


Mirror images are different, 1,2-propanediol is chiral.



Mirror images are the same, 2-propanol is achiral.

Mirror planes are easy to spot in Fischer projections, and molecules with mirror planes cannot 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.

(Normally we 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.

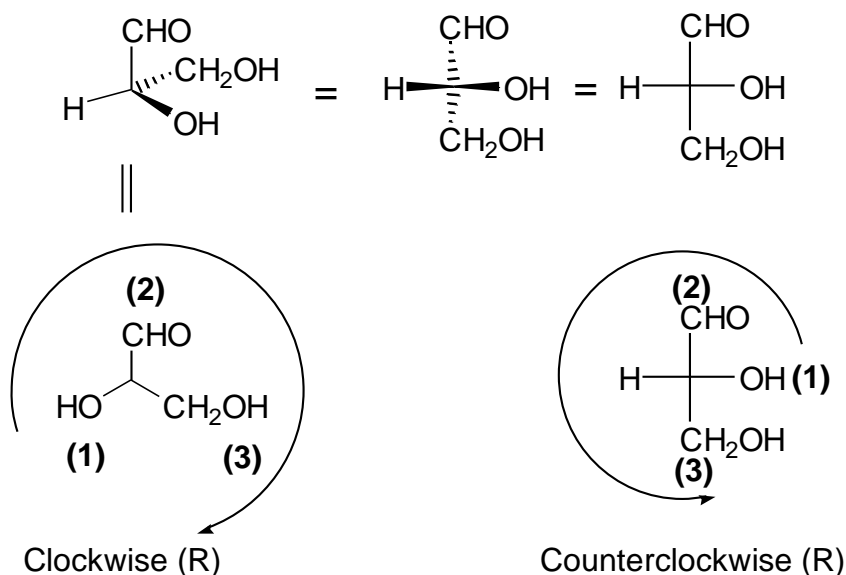
Recall that since the C chain is arranged vertically, the lowest priority group (usually H) will be on the horizontal axis (which means it is sticking out toward us).

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.



Diastereomers

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

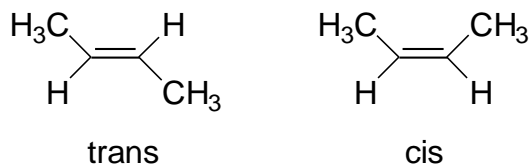
Enantiomers are mirror image isomers. All other stereoisomers are called diastereomers.

Alternatively, diastereomers are stereoisomers that are not mirror images.

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

Geometric Isomers

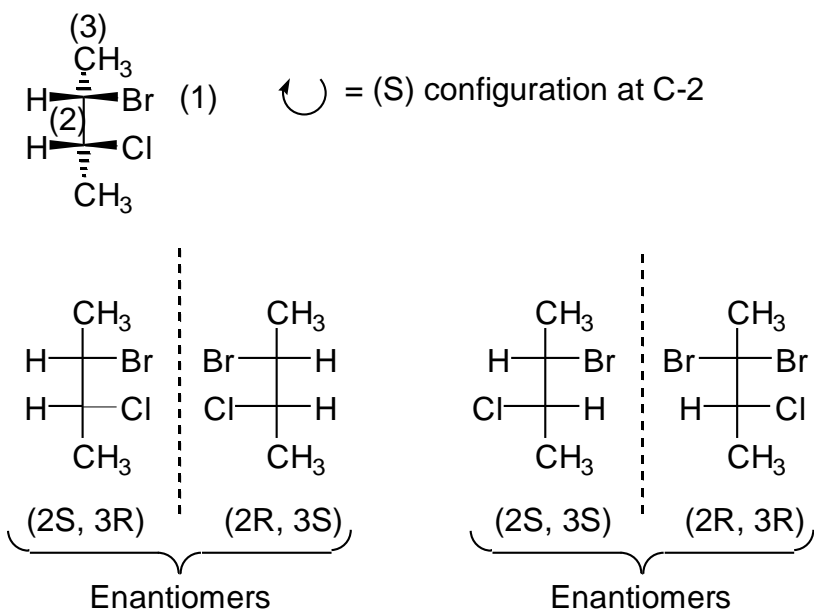
For example, 2-butene.



Seen these before. They are not mirror images of each other – not enantiomers.

Molecules with 2 or more Chiral Atoms

For example, 2-bromo-3-chlorobutane.



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).

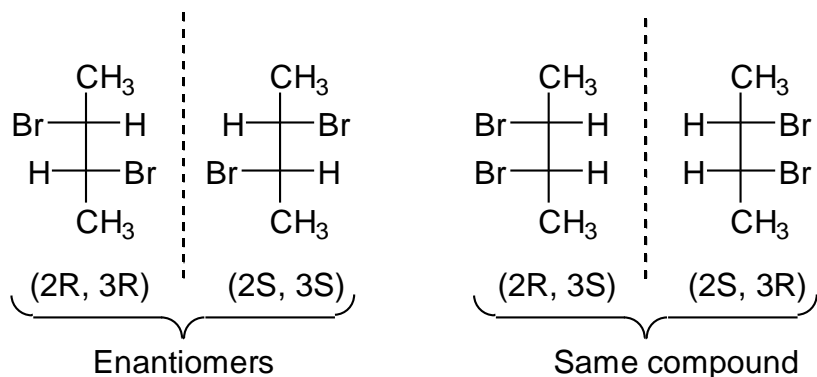
Meso Compounds

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 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 (\pm) diastereomer (or dl),
The 'same compound' pair are called the meso diastereomer.

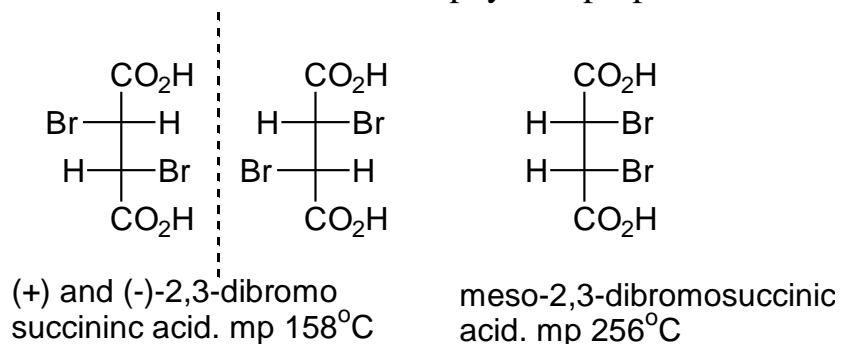
The meso diastereomer is achiral since it has a mirror plane of symmetry.

A meso compound is an achiral compound which has chiral carbon 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.



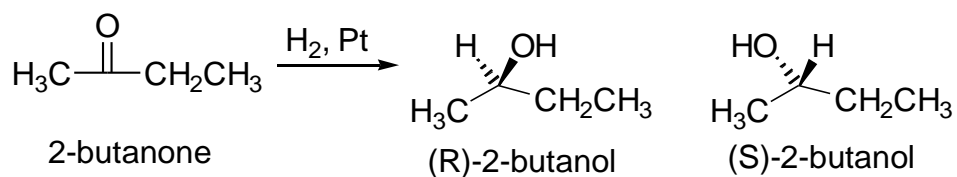
Since diastereomers have different physical properties, they are often easy to separate to by normal practical techniques (distillation, recrystallization, chromatography, etc).

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.



If we require just one enantiomer of 2-butanol, 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.

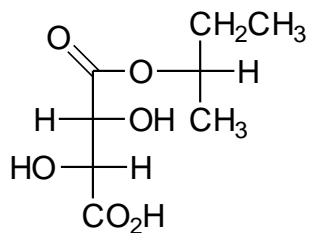
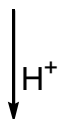
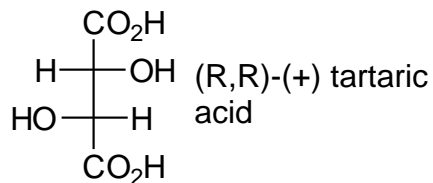
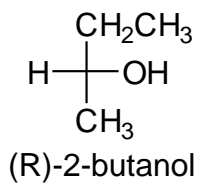
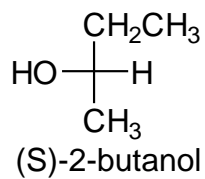
Chemical Resolution

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

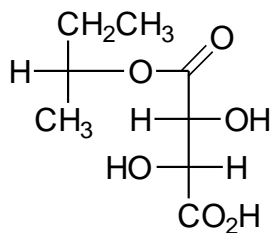
This gives rise to a pair of diastereomers – which have different physical properties and therefore can be separated.

The resolving agent is then cleaved off, leaving pure separated enantiomers.
Example: Resolution of 2-butanol.

(Need to know: carboxylic acid + alcohol \rightarrow ester + water)

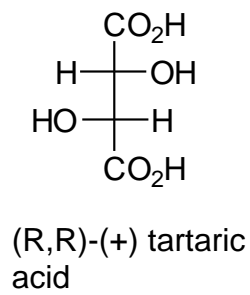
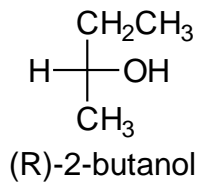
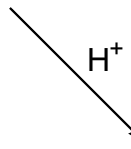
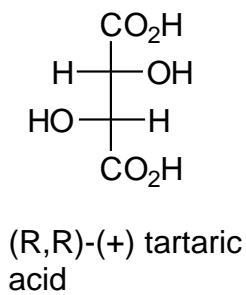
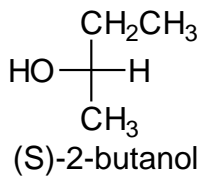
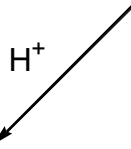


(S)-2-butyl-(R,R)-tartrate



(R)-2-butyl-(R,R)-tartrate

diastereomers (can be separated)



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 may be recycled. Typically enantiopure compounds are very expensive.

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

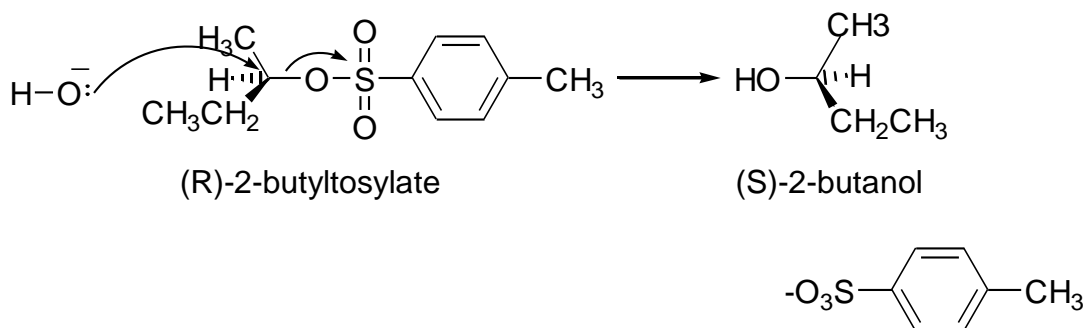
Reactions at a Chiral Atom

If a reaction occurs at a chiral atom, one of three things can happen.

- (a) Inversion of Configuration ($R \rightarrow S$)
- (b) Racemization of configuration ($R \rightarrow R + S$)
- (c) Retention of Configuration ($R \rightarrow R$)

Inversion of Configuration

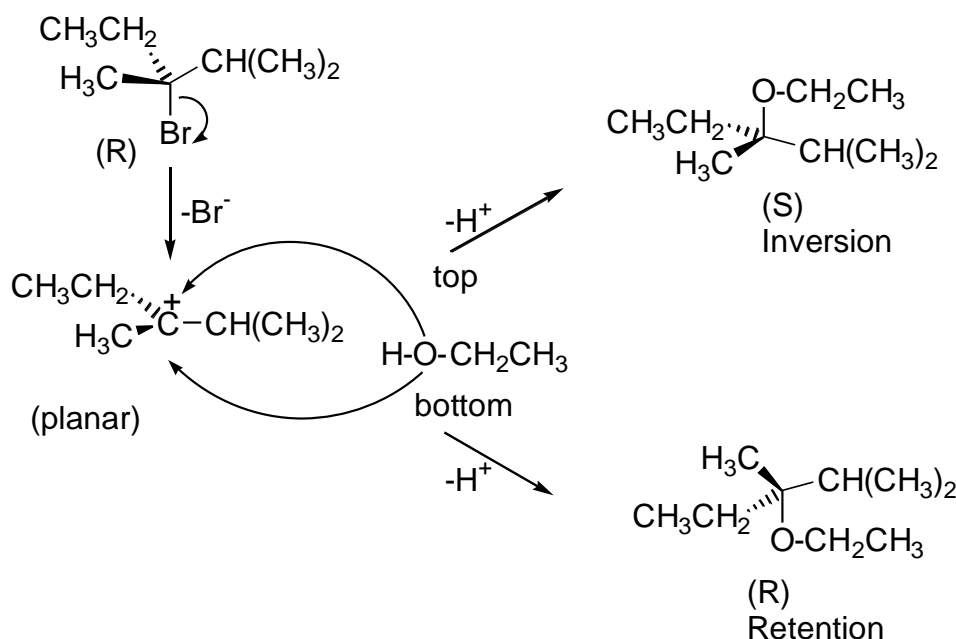
If a reaction takes place at a chiral center and the product has the opposite stereochemistry of the reactant, it has proceeded with inversion of configuration.



Racemization

Many reactions will display neither clean (total) inversion or clean retention of configuration. Such reactions are called **racemizations**.

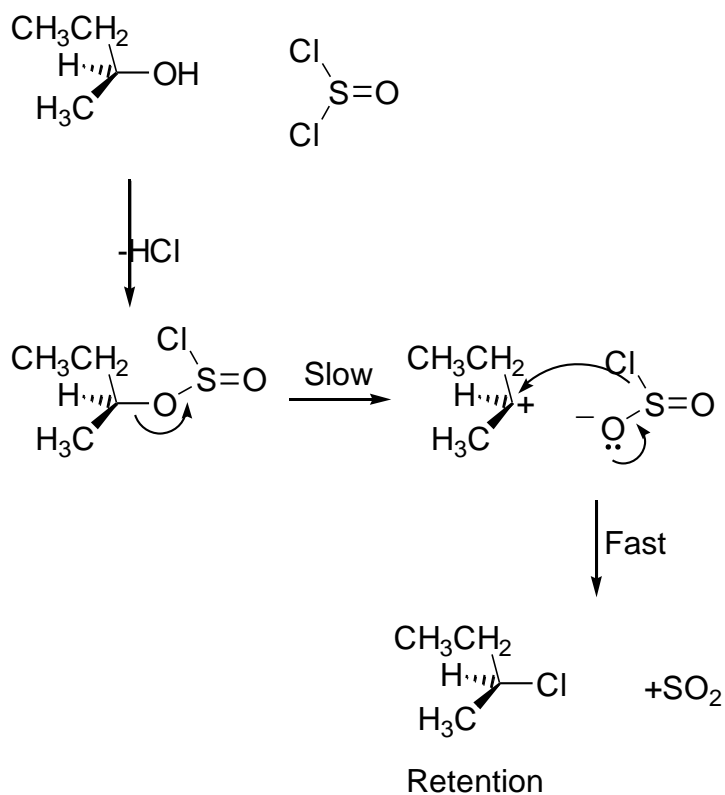
If all optical activity is lost it is a **complete** racemization, if some optical activity remains, it is a **partial** racemization.



The carbocation is planar, and therefore achiral. The attack of the nucleophile from the top and bottom faces are equally preferred – a **racemate** is produced.

Retention of Configuration

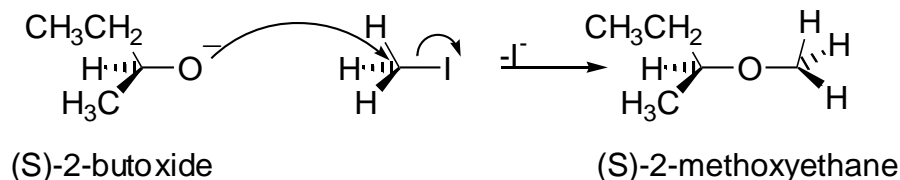
This is the least common type of reaction. When a product maintains the same configuration as the reactant, it proceeds with **retention** of configuration.



The product is not racemized since the slow C-O bond breaking and fast Cl attack do not allow the cation to achieve a planar (achiral) arrangement.

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.



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

Reactions that generate a new Chiral Center

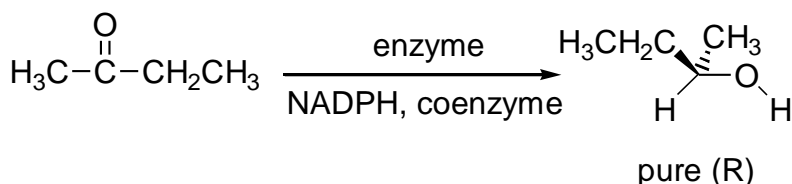
Lots of reactions form new chiral atoms, yet achiral reactants will always produce **racemic** mixtures, since there is no chiral control.

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.

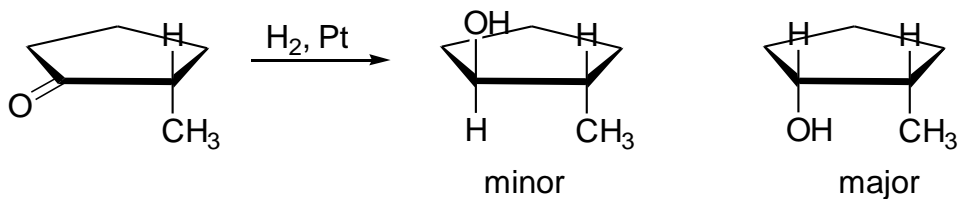


Similar results can be achieved in the lab using chiral catalysts or reagents (which are usually expensive).

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.