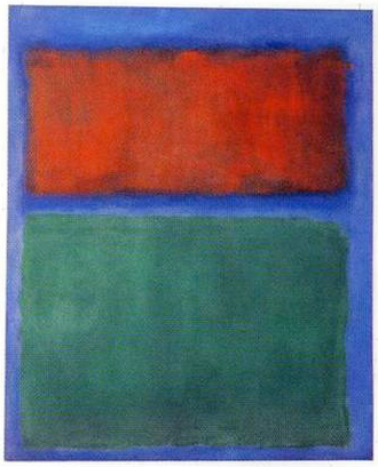
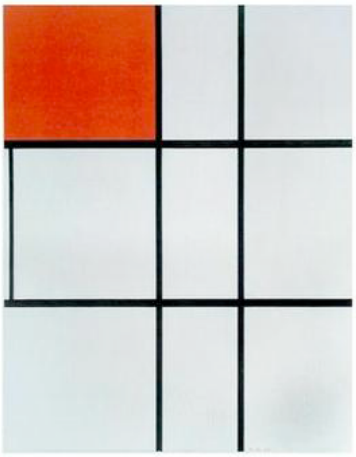




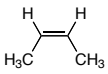
Chapter 9: Stereochemistry

three-dimensional arrangement of atoms (groups) in space

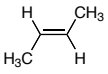
Stereoisomers: molecules with the same connectivity but different arrangement of atoms (groups) in space

cis-1,2-dimethylcyclopropane

trans-1,2-dimethylcyclopropane



cis-2-butene



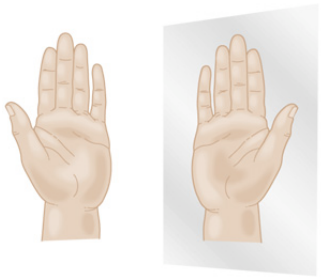
trans-2-butene

geometric isomers (diastereomers)

Enantiomers: non-superimposable mirror image isomers.
Enantiomers are related to each other much like a right hand is related to a left hand

Enantiomers have identical physical properties, i.e., bp, mp, etc.

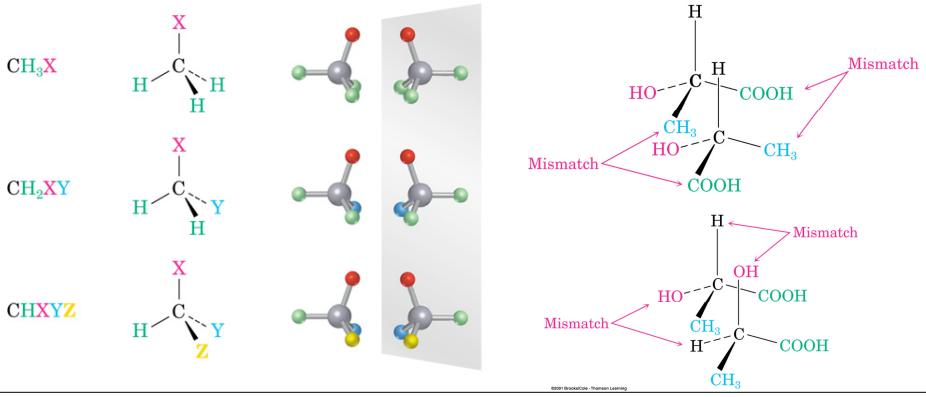
Chirality (from the Greek word for hand). Enantiomers are said to be *chiral*.

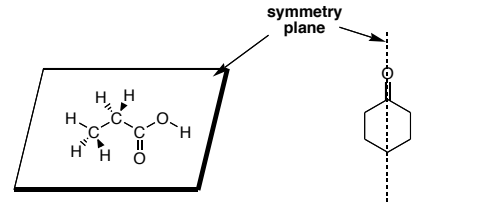


Left hand **Right hand**

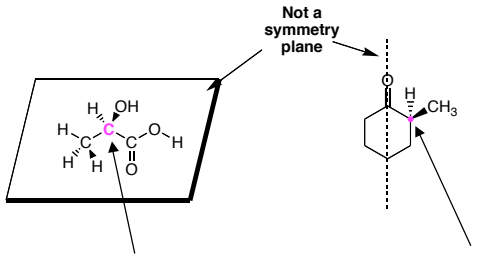
Molecules are <u>not</u> chiral if they contain a plane of symmetry: a plane that cuts a molecule in half so that one half is the mirror image of the other half. Molecules (or objects) that possess a mirror plane of symmetry <u>are</u> superimposable on their mirror image and are termed *achiral*.

A carbon with four different groups results in a chiral molecule and is refered to as a *chiral* or *asymmetric* or *stereogenic* center.





Achiral

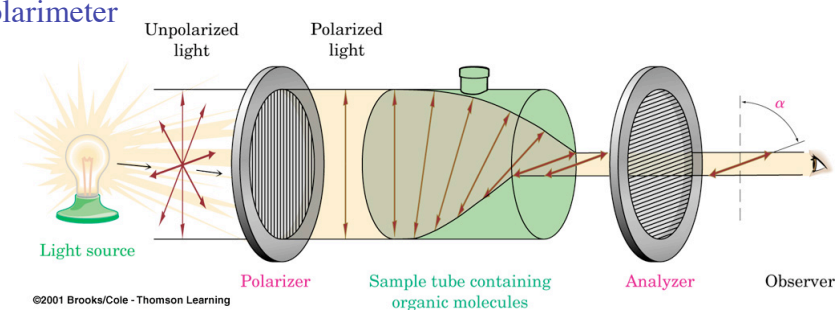


Chiral

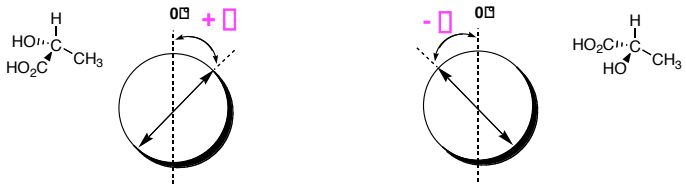
Chiral center (stereogenic, asymmetric)

Optical Rotation: molecules enriched in an enantiomer will rotate plane polarized light are are said to be optiically active. The optical rotation is dependent upon the substance, the concentration, the path length through the sample and the wavelength of light.

Polarimeter



Plane polarized light: light that oscillates in only one plane



dextrorotatory (*d*): rotates light to the right (clockwise)

levororotatory (*l*): rotates light to the left (counterclockwise)

α: angle (# of degrees) plane polarized light is rotated by an optically active sample. Expressed in degrees.

Enantiomers will rotate plane polarized light the same magnitude (α) but in opposite directions (+ or -)

90% (+) + 10% (-) will rotate light 80% of pure (+)
75% (+) + 25% (-) will rotate light 50% of pure (+)
50% (+) + 50% (-) will be optically inactive

50:50 mixture of enantiomers (+/-): racemate or racemic mixture
Each individual molecule is chiral, however the bulk property of the substance is achiral, if it is in an achiral environment.

Specific Rotation $[\alpha]_D$: a standardized value for the optical rotation

$$[\alpha]_{\lambda}^{T} = \frac{\alpha}{l \bullet c}$$

α= optical rotation in degrees
l = path length in dm
c = concentration of sample in g/mL
T = temperature in °C
λ= wavelength of light, usually D for the D-line of a sodium lamp (589 nm)

The specific rotation is a physical constant of a chiral molecule

The $[\alpha]_D$ may also depend upon solvent, therefore the solvent is usually specified.

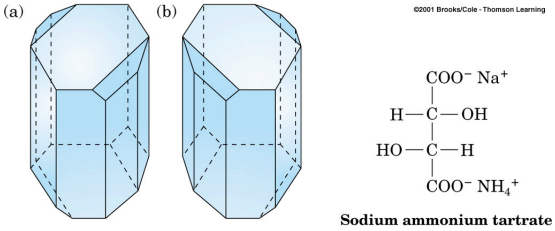
for alanine:

$[\alpha]_D^{20}$ = +14.5° (*c* 10, 6N HCl)

Discovery of chirality in chemistry
L. Pasteur (1949)

Crystallization of sodium ammonium tartrate. Crystals were mirror Images of each other and separated by tweezers under a microscope. Each crystal was a enantiomerically pure.

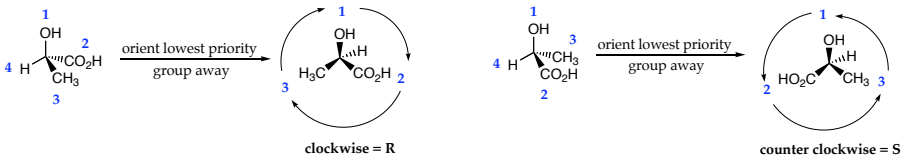
Resolution: The process of separating racemates into pure enantiomers. Crystallization is be a resolution process.



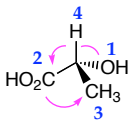
Assigning the Absolute Configuration

1. Use the Cahn-Ingold-Prelog priority rules (Chapter 6) to assign priority (one through four) to the four groups on the "chiral" atom.

2. Orient the molecule so that the lowest priority atom is in the back (away from you). Look at the remaining three groups of priority 1-3. If the remaining three groups are arranged so that the priorities 1-2-3 are in a *clockwise* fashion, then assign the chiral center as **R** ("rectus" or right). If the remaining three groups are arranged 1-2-3 in a *counterclockwise* manner, then assign the chiral center as **S** ("sinister" or left)

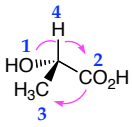


3. Or use the "Hand Rule." Orient the lowest priority group up. Point your thumb in the direction of the lowest priority group. If you need to use your *right hand* so that your fingers point in the direction of the group priorities in the order 1-2-3, then the stereogenic center is assigned **R** ("rectus" or *right*). If your *left hand* is required so that your fingers point in the direction of the group priorities 1-2-3, the the stereogenic center is assigned **S** ("sinister" or *left*).



(R)-(-)-Lactic acid
(Right Hand)

(S)-(+)-Lactic acid
(Left Hand)

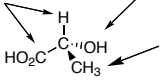


You must be able to draw tetrahedral carbons properly!!

In the plane of the paper and in the same plane as the tetrahedral carbon (adjacent position off the tetrahedral carbon)

Dash: projecting behind the plane of the paper away from you

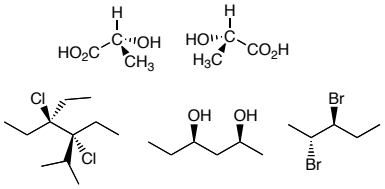
Dash and Wedge are on adjacent position off the tetrahedral carbon



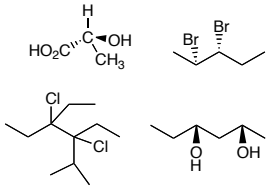
Wedge: projecting out of the plane of the paper toward you

LINEAR ALKANES: You should draw the backbone in the plane of the paper, and draw substituents either coming towards you (with wedges) or going away from you (with dashes). Note that each carbon should look like a tetrahedron.

Correct ☺



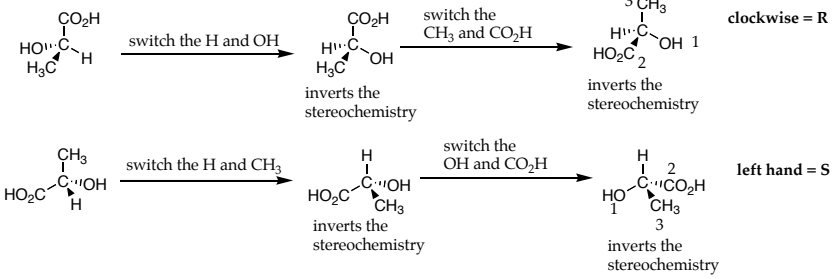
Incorrect ☹

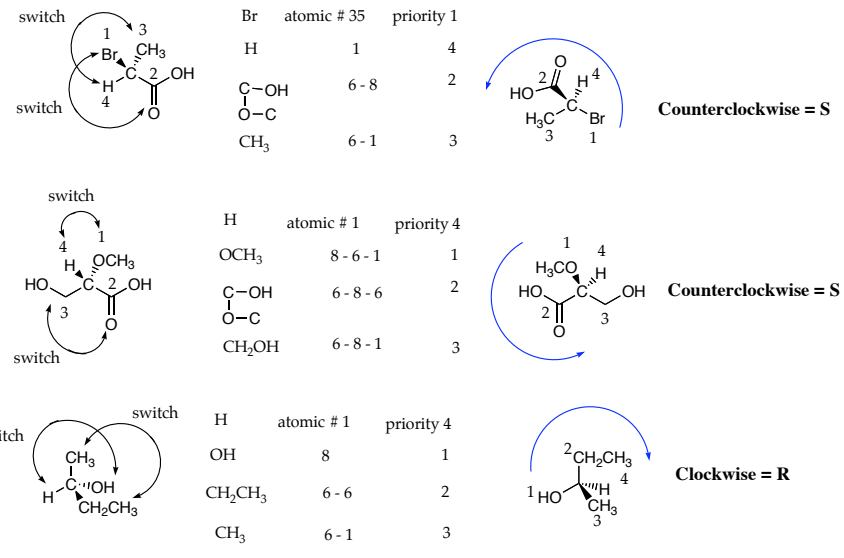


Do the Double-Switch Trick!!

In order to assign the stereochemistry you must be able to manipulate the structure on paper so that the lowest priority group is in the proper orientation (back for the steering wheel rule or up for the hand rule)

Interchanging any two groups inverts the stereochemistry. So switch the lowest priority group to the desired position. Then switch the other two groups. The "double-switch" does not change the stereochemistry.

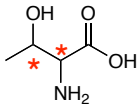




Note: assignment of R or S has **NO** relationship with the optical rotation (+) or (-).

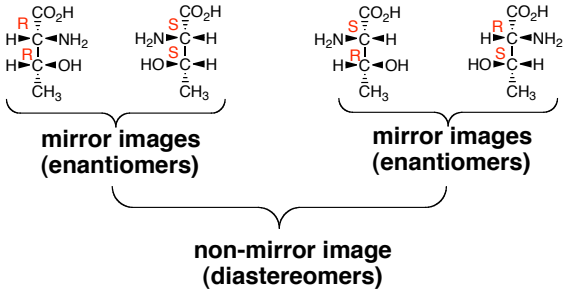
Diastereomers: non-mirror image stereoisomers. Occurs when more than one chiral centers are present in a molecule.

For a molecule with n chiral centers, there are 2^n number of stereoisomers possible, not including geometric stereoisomers of double bonds.



Threonine- two chiral centers

$2^2 = 4$ possible stereoisomer



Natural threonine possesses the 2R, 3S stereochemistry

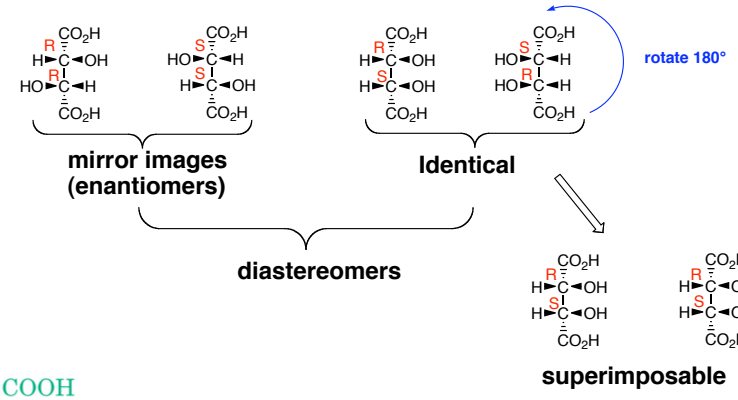
Enantiomers must have the opposite configuration at **all** chiral centers.

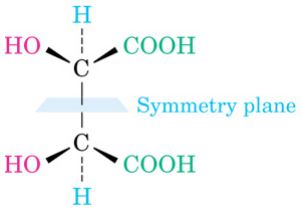
In general, enantiomers have identical physical properties except optical rotation (which is equal in magnitude but opposite in sign)

Diastereomers may have completely different physical properties

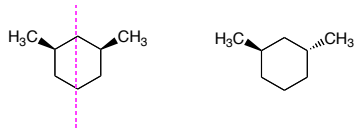
Meso Compounds: molecules that contain chiral atoms but are achiral because they also possess a plane of symmetry.

Tartaric acid:





meso tartaric acid: The groups on the top carbon reflect (through the symmetry plane)onto the groups on the bottom carbon



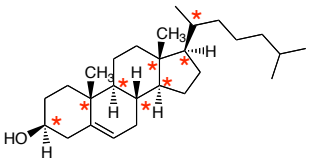
Molecules with more than two chiral centers:

molecules with n chiral centers:

maximum of 2^n stereoisomers

(excluding geometric isomers of double bonds)

maximum of $2^{(n-1)}$ pairs of enantiomers



Cholesterol: eight chiral centers

$2^8 = 256$ possible stereoisomers

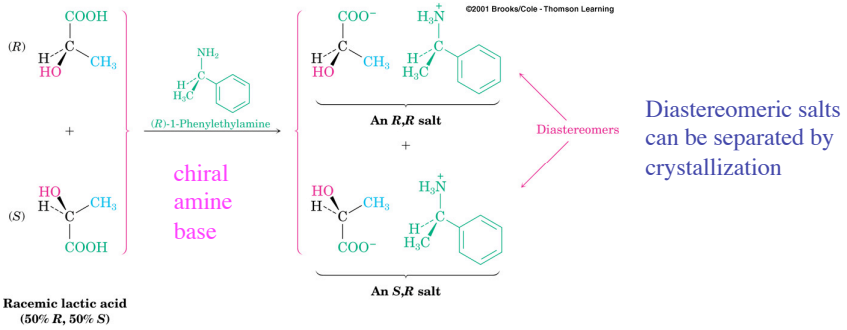
(only one of which is naturally occuring)

Resolution of Racemates:

50:50 mixture of enantiomers is a racemic mixture or racemate, denoted by (±) or (*d,l*)

Resolution: a process of separating a racemate into pure enantiomers. The enantiomers of the racemate must be converted into diastereomers.

Resolution of racemic acids by crystallization of their salts, using a chiral counter ion



Physical properties of Stereoisomers

Enantiomers have identical physical properties (such as mp, bp, solubility, density, etc.) except for optical rotation

Diastereomers may have completely different physical properties

Racemates act as if they were a single pure compound. Some physical properties of racemates may differ from those of the pure enantiomer

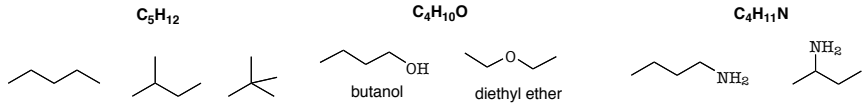
Table 9.3: Some physical properties of stereoisomers of tartaric acid

Stereoisomer	mp (°C)	$[\alpha]_D$	density (g/cm^3)	solibility (g/100mL H_2O)
+	168-170	+12	1.7598	139.0
-	168-170	-12	1.7598	139.0
meso	146-148	0	1.6660	125.0
±	206	0	1.7880	20.6

A Brief Review of Isomerism

Isomers: compounds with the same chemical formula, but different arrangement of atoms

Constitutional isomer: have different connectivities (not limited to alkanes)



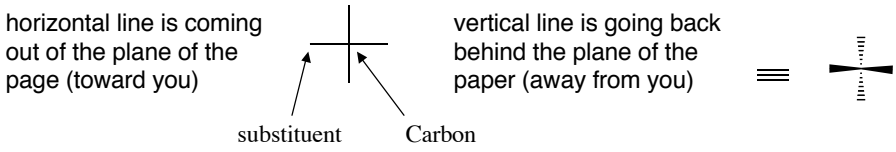
different carbon skeleton | different functional group | different position of FG

Stereoisomers: Atoms connected in the same way, but different three-dimensional arrangement of atoms or groups (topology)

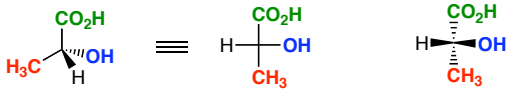
enantiomers: non-superimposable mirror image isomers
diastereomers: non-superimposable, non-mirror image isomer (more than one chiral center.
geometric isomers (diastereomers): E / Z alkene isomers

Fischer Projections: representation of a three-dimensional molecule as a flat structure

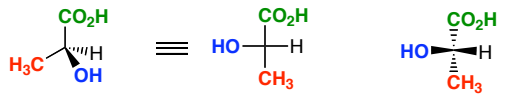
Tetrahedral carbon represented by two crossed lines:



(*R*)-lactic acid

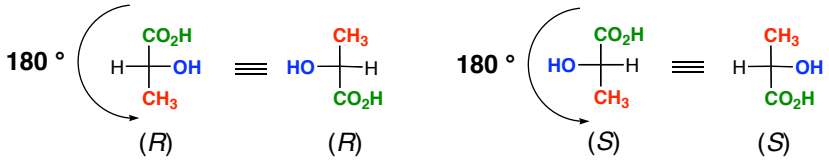


(*S*)-lactic acid

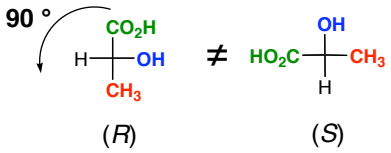


Manipulation of Fischer Projections

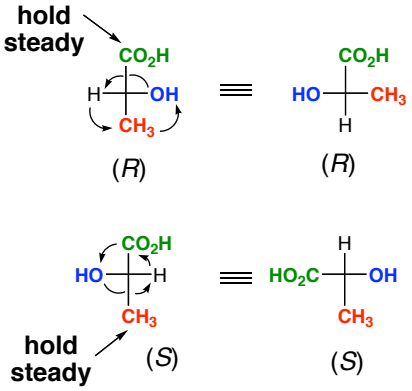
1. Fischer projections can be rotate by 180° only!



a 90° rotation inverts the stereochemistry and is illegal!

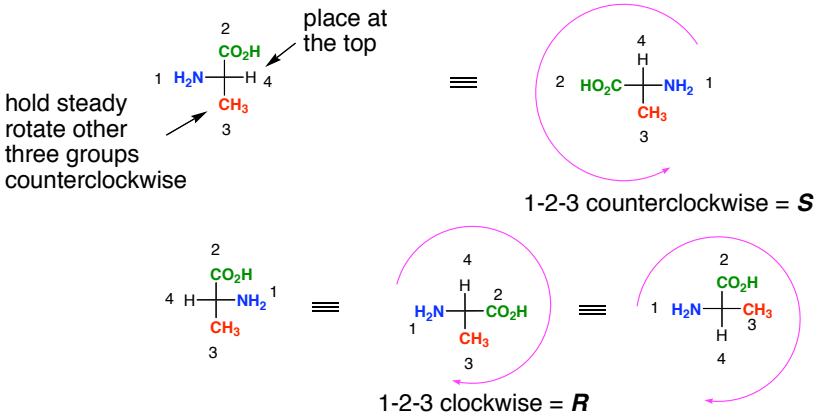


2. If one group of a Fischer projection is held steady, the other three groups can be rotated clockwise or counterclockwise.

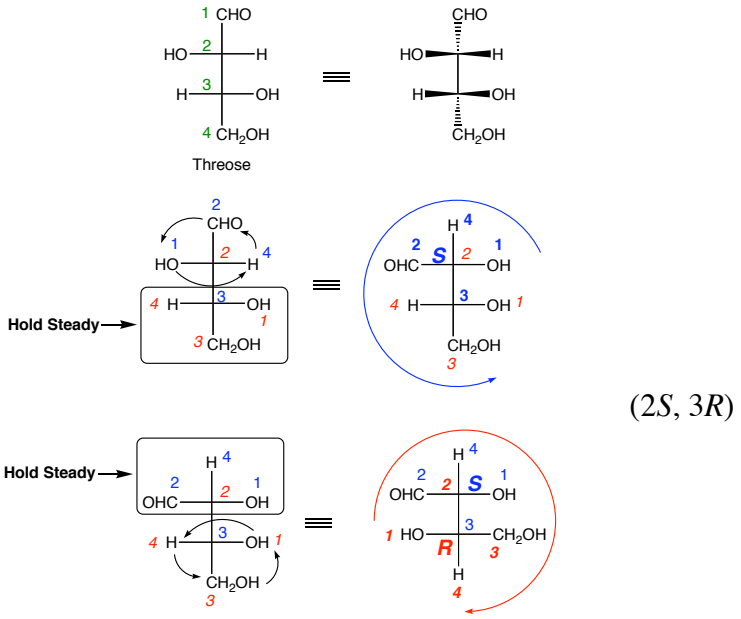


Assigning R and S Configuration to Fischer Projections

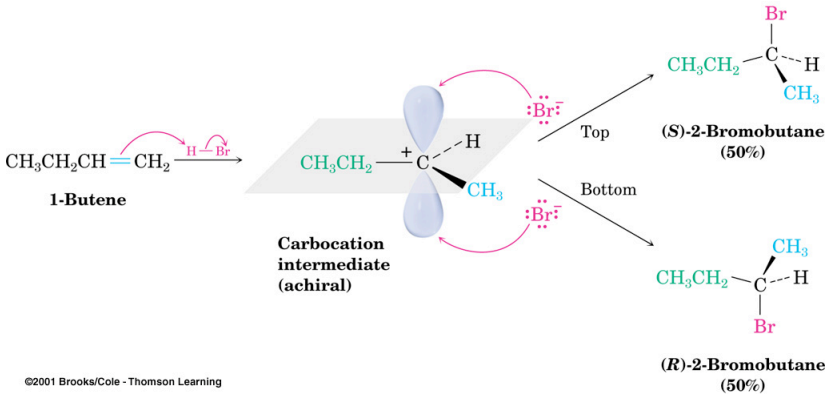
1. Assign priorities to the four substitutents according to the Cahn-Ingold-Prelog rules
2. Perform the two allowed manipulations of the Fischer projection to place the lowest priority group at the top (or bottom).
3. If the priority of the groups 1-2-3 are clockwise then assign the center as *R*, if 1-2-3 are counterclockwise then assign the center as *S*.



Fischer projections with more than one chiral center:



Stereochemistry of Reactions: reactions may generate chiral centers
addition of HBr to alkenes



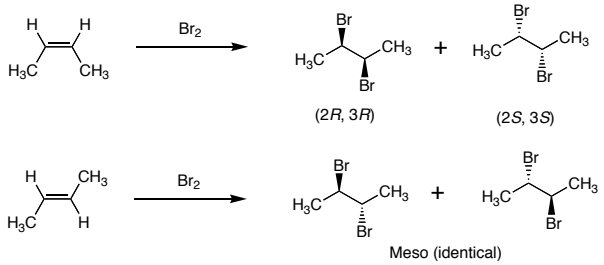
There is an equal chance for Br^- to add from the top face or the bottom face: 50:50 mixture.

The two products are enantiomers. The two transitions states are enantiomeric and have identical activation energies

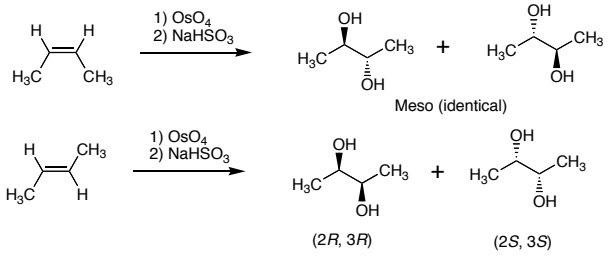
Any reaction between achiral reactants always leads to optically inactive products, either a racemate of meso.

Must consider the reactants and mechanism of the reaction

Addition of Br_2 to 2-butene (anti-addition)

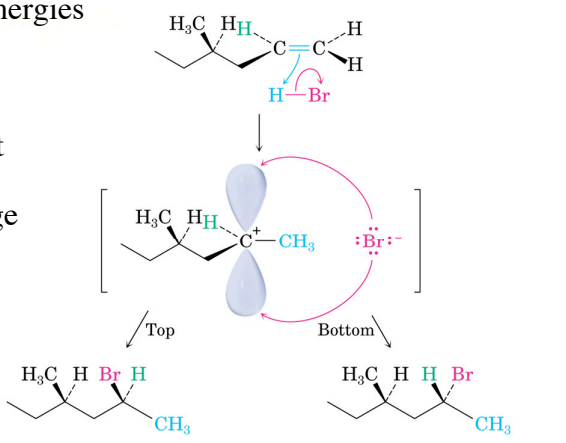


Reaction of OsO_4 with 2-butene (syn addition)

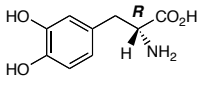


Addition of HBr to a chiral alkene: reactions of a chiral reactant with an achiral reagent gives diastereomeric products which may or may not be formed in equal amounts. The intermediate carbocation is asymmetric, therefore attack of Br^- from the top or bottom faces may not be equally probable. The two transition states are diastereomeric and therefore may have different activation energies

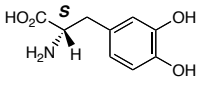
Chiral center of the reactant is not involved during the reaction and does not change



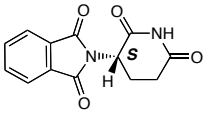
(2*S*,4*R*)-2-Bromo-4-methylhexane **(2*R*,4*R*)-2-Bromo-4-methylhexane**



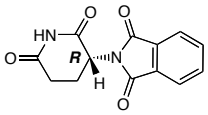
D-DOPA
no biological effect



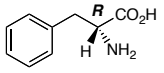
L-DOPA
used for the treatment of ParkinsonDisease



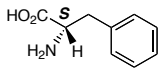
(S)-Thalidomide
teratogen



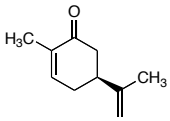
(R)-Thalidomide
sedative



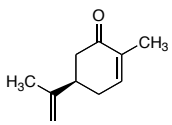
D-phenylalanine
(controlled substance)



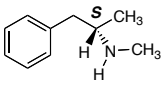
L-phenylalanine
naturally occuring amino acid



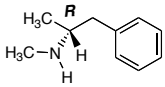
(S)-(+)-carvone
caraway seeds (rye)



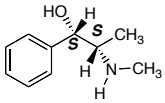
(R)-(-)-carvone
spearmint oil



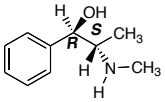
(S)-methampetamine



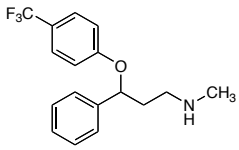
(R)-methamphetamine
no biological effect



Pseudoephedrine

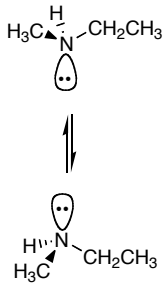


Ephedrine



(±) - prozac
(S)-Fluoxetine

Stereochemistry at atoms other than carbon: N, Si, P, S, and many other atoms have the potential to be chiral (stereogenic) centers



Barrier to inversion is very low

Inversion is a racemization process

You will learn more about stereochemistry and the stereochemistry of reactions next semester and in Chem 220c and 223