

9. Stereochemistry

Based on McMurry's *Organic Chemistry*, 7th edition

Stereochemistry

- Some objects are not the same as their mirror images (technically, they have no plane of symmetry)
 - A right-hand glove is different than a left-hand glove. The property is commonly called “handedness”
- Organic molecules (including many drugs) have handedness that results from substitution patterns on sp^3 hybridized carbon



Left hand



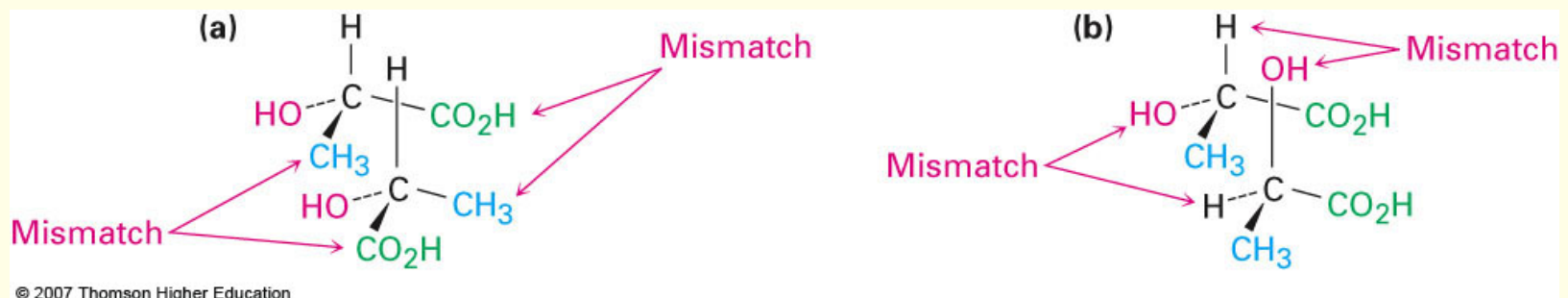
Right hand

Why this Chapter?

- Handedness is important in organic and biochemistry
- Molecular handedness makes possible specific interactions between enzymes and substrates

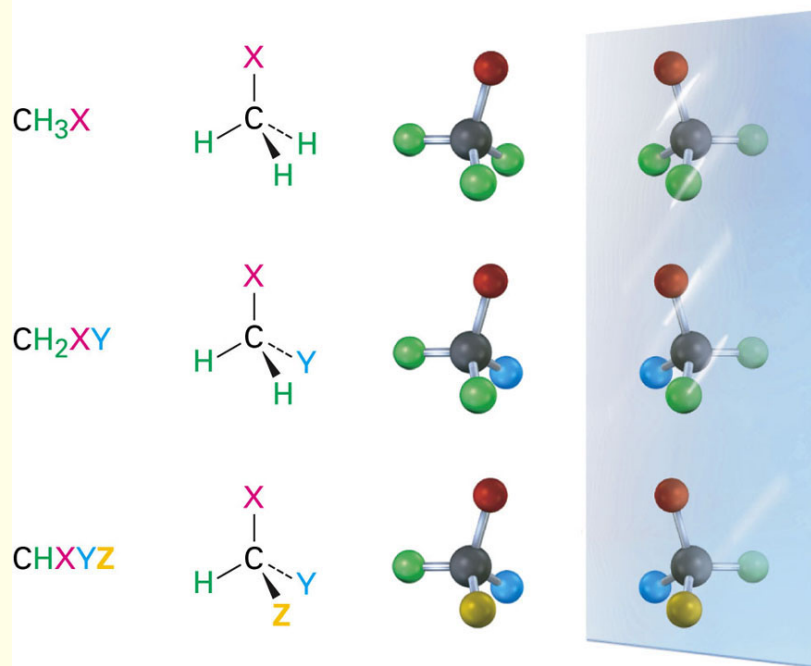
9.1 Enantiomers and the Tetrahedral Carbon

- **Enantiomers** are molecules that are not the same as their mirror image
- They are the “same” if the positions of the atoms can coincide on a one-to-one basis (we test if they are *superimposable*, which is imaginary)
- This is illustrated by enantiomers of lactic acid



Examples of Enantiomers

- Molecules that have one carbon with 4 different substituents have a nonsuperimposable mirror image – enantiomer
- Build molecular models to see this



9.2 The Reason for Handedness: Chirality

- Molecules that are not superimposable with their mirror images are **chiral** (have handedness)
- A **plane of symmetry** divides an entire molecule into two pieces that are exact mirror images
- A molecule with a plane of symmetry is the same as its mirror image and is said to be **achiral** (See Figure 9.4 for examples)

Chirality

- If an object has a plane of symmetry it is necessarily the same as its mirror image
- The lack of a plane of symmetry is called “handedness”, **chirality**
- Hands, gloves are prime examples of chiral object
 - They have a “left” and a “right” version

Plane of Symmetry

- The plane has the same thing on both sides for the flask
- There is no mirror plane for a hand

(a)



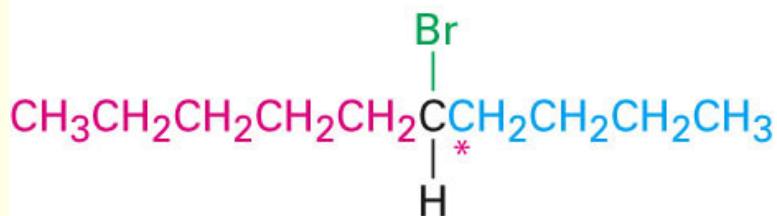
(b)



© 2007 Thomson Higher Education

Chirality Centers

- A point in a molecule where four different groups (or atoms) are attached to carbon is called a **chirality center**
- There are two nonsuperimposable ways that 4 different different groups (or atoms) can be attached to one carbon atom
 - If two groups are the same, then there is only one way
- A chiral molecule usually has at least one chirality center



5-Bromodecane (chiral)

Substituents on carbon 5

—H

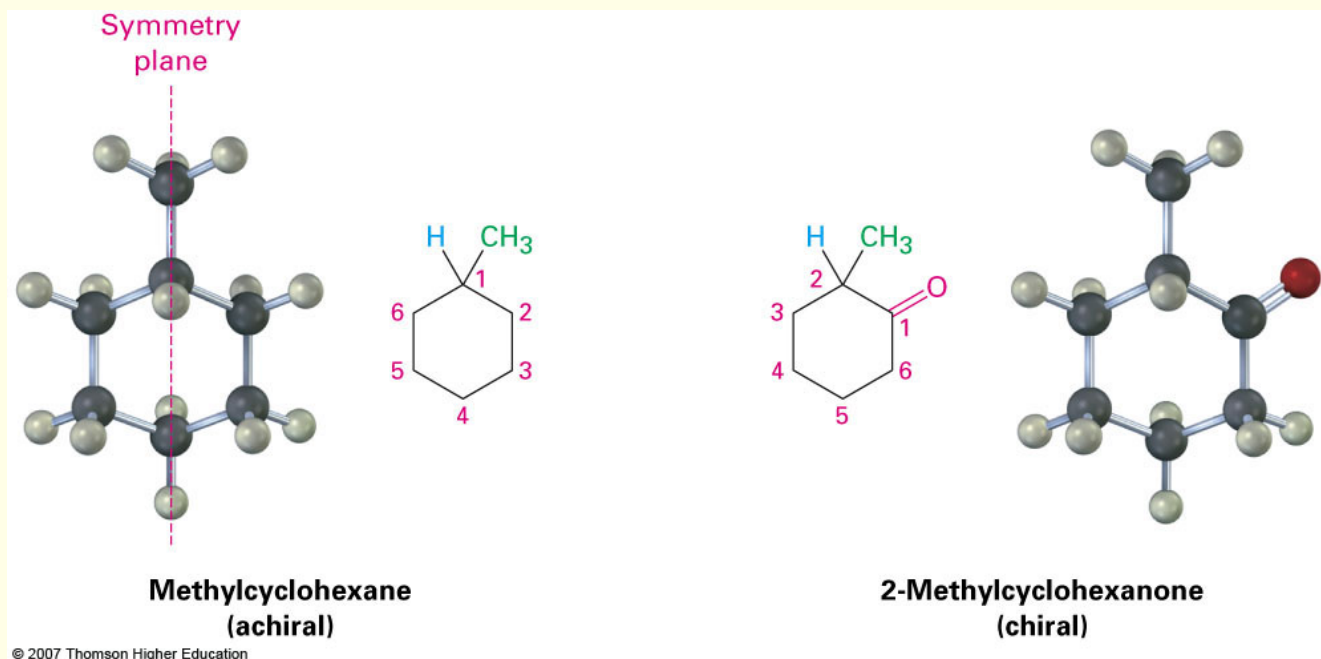
—Br

—CH₂CH₂CH₂CH₃ (butyl)

—CH₂CH₂CH₂CH₂CH₃ (pentyl)

Chirality Centers in Chiral Molecules

- Groups are considered “different” if there is any structural variation (if the groups could not be superimposed if detached, they are different)
- In cyclic molecules, we compare by following in each direction in a ring



9.3 Optical Activity

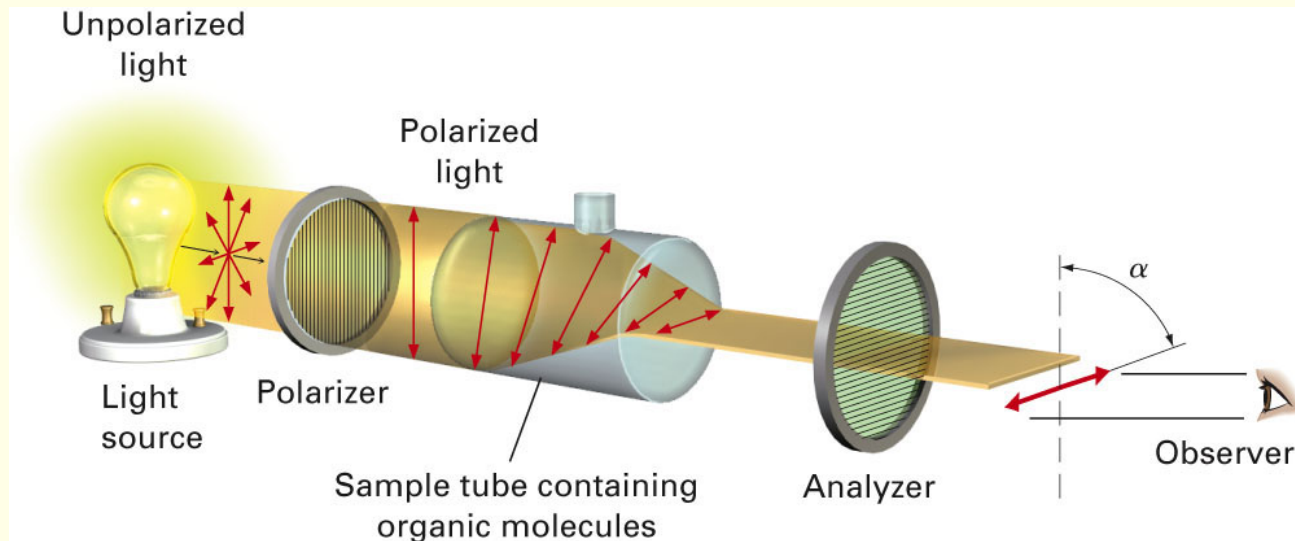
- Light restricted to pass through a plane is *plane-polarized*
- Plane-polarized light that passes through solutions of achiral compounds remains in that plane
- Solutions of chiral compounds rotate plane-polarized light and the molecules are said to be *optically active*
- Phenomenon discovered by Jean-Baptiste Biot in the early 19th century

Optical Activity

- Light passes through a plane polarizer
- Plane polarized light is rotated in solutions of optically active compounds
- Measured with polarimeter
- Rotation, in degrees, is $[\alpha]$
- Clockwise rotation is called **dextrorotatory**
- Anti-clockwise is **levorotatory**

Measurement of Optical Rotation

- A **polarimeter** measures the rotation of plane-polarized light that has passed through a solution
- The source passes through a **polarizer** and then is detected at a second polarizer
- The angle between the entrance and exit planes is the optical rotation.



Specific Rotation

- To have a basis for comparison, define **specific rotation**, $[\alpha]_D$ for an optically active compound
- $[\alpha]_D = \text{observed rotation}/(\text{pathlength} \times \text{concentration})$
 $= \alpha/(l \times C) = \text{degrees}/(\text{dm} \times \text{g/mL})$
- Specific rotation is that observed for 1 g/mL in solution in cell with a 10 cm path using light from sodium metal vapor (589 nm)

Specific Rotation and Molecules

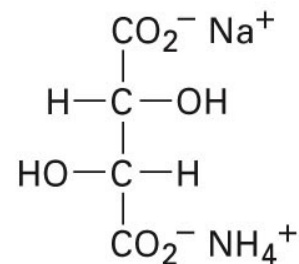
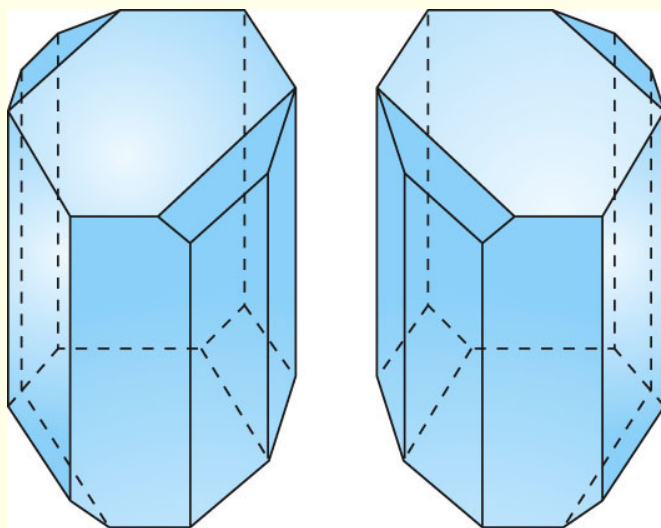
- Characteristic property of a compound that is optically active – the compound must be chiral
- The specific rotation of the enantiomer is equal in magnitude but opposite in sign

Table 9.1 | **Specific Rotation of Some Organic Molecules**

Compound	$[\alpha]_D$	Compound	$[\alpha]_D$
Penicillin V	+233	Cholesterol	-31.5
Sucrose	+66.47	Morphine	-132
Camphor	+44.26	Cocaine	-16
Chloroform	0	Acetic acid	0

9.4 Pasteur's Discovery of Enantiomers

- Louis Pasteur discovered that sodium ammonium salts of tartaric acid crystallize into right handed and left handed forms
- The optical rotations of equal concentrations of these forms have opposite optical rotations
- The solutions contain mirror image isomers, called **enantiomers** and they crystallized in distinctly different shapes – such an event is rare



Sodium ammonium tartrate

9.5 Sequence Rules for Specification of Configuration

- A general method applies to the configuration at each chirality center (instead of to the whole molecule)
- The configuration is specified by the relative positions of all the groups with respect to each other at the chirality center
- The groups are ranked in an established priority sequence and compared
- The relationship of the groups in priority order in space determines the label applied to the configuration, according to a rule

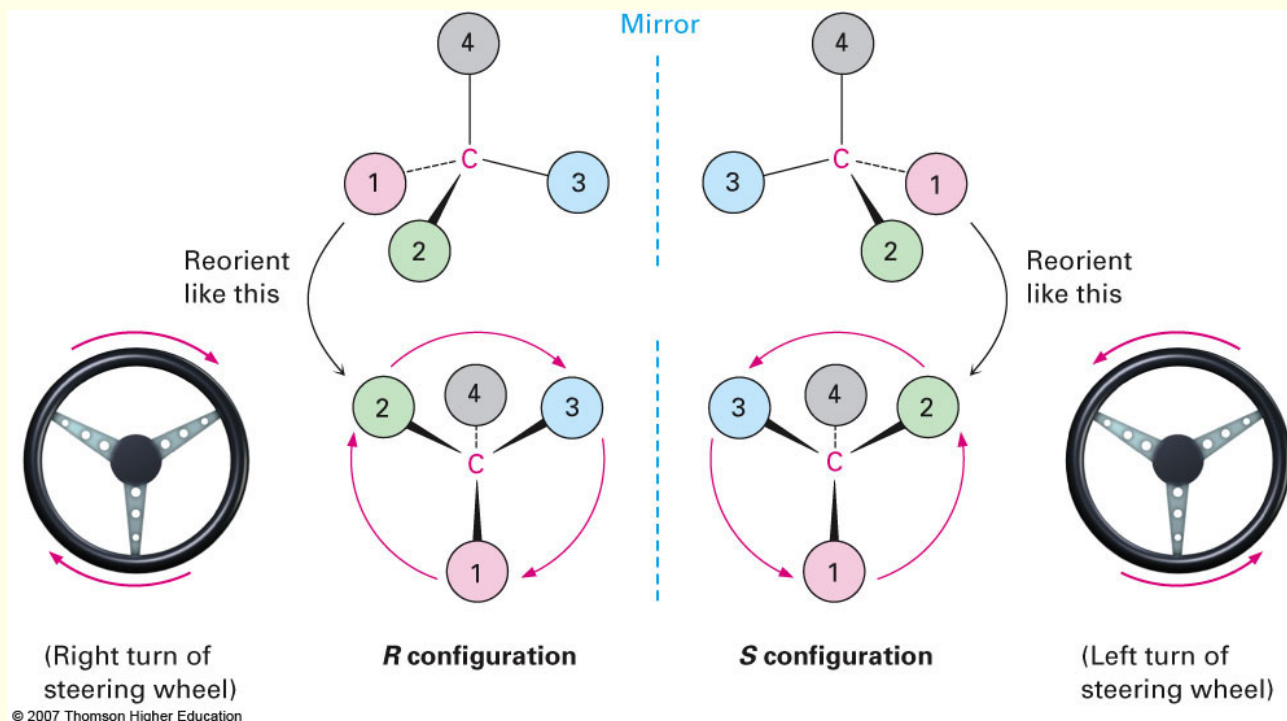
Sequence Rules (IUPAC)

Rule 1:

- Assign each group priority according to the Cahn Ingold-Prelog scheme
- With the lowest priority group pointing away, look at remaining 3 groups in a plane
- Clockwise is designated R (from Latin for “right”)
- Counterclockwise is designated S (from Latin word for “left”)

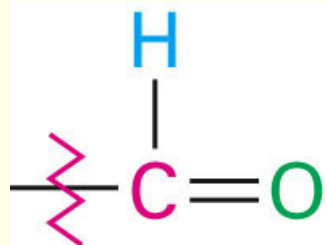
Rule 2:

- If decision can't be reached by ranking the first atoms in the substituents, look at the second, third, or fourth atoms until difference is found

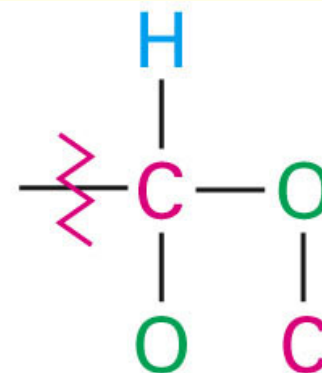


Rule 3:

- Multiple-bonded atoms are equivalent to the same number of single-bonded atoms



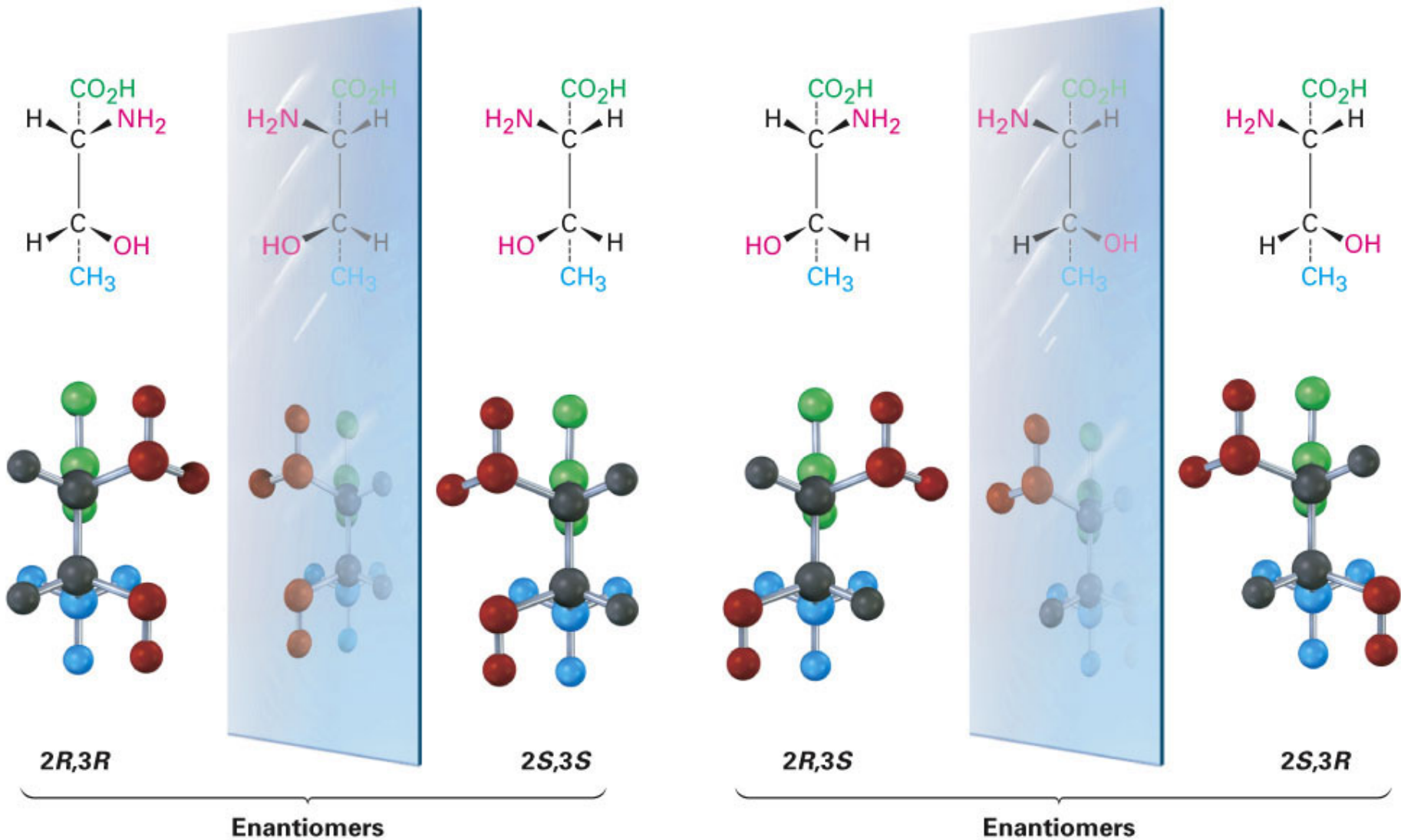
is equivalent to



9.6 Diastereomers

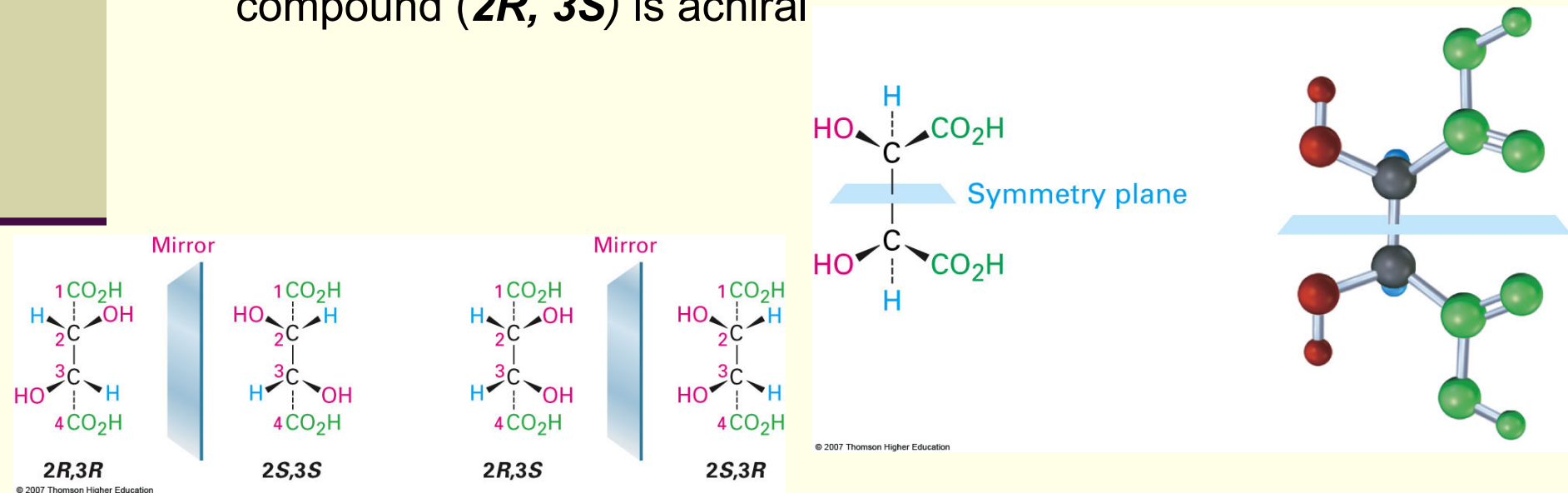
- Molecules with more than one chirality center have mirror image stereoisomers that are enantiomers

- In addition they can have stereoisomeric forms that are not mirror images, called **diastereomers**



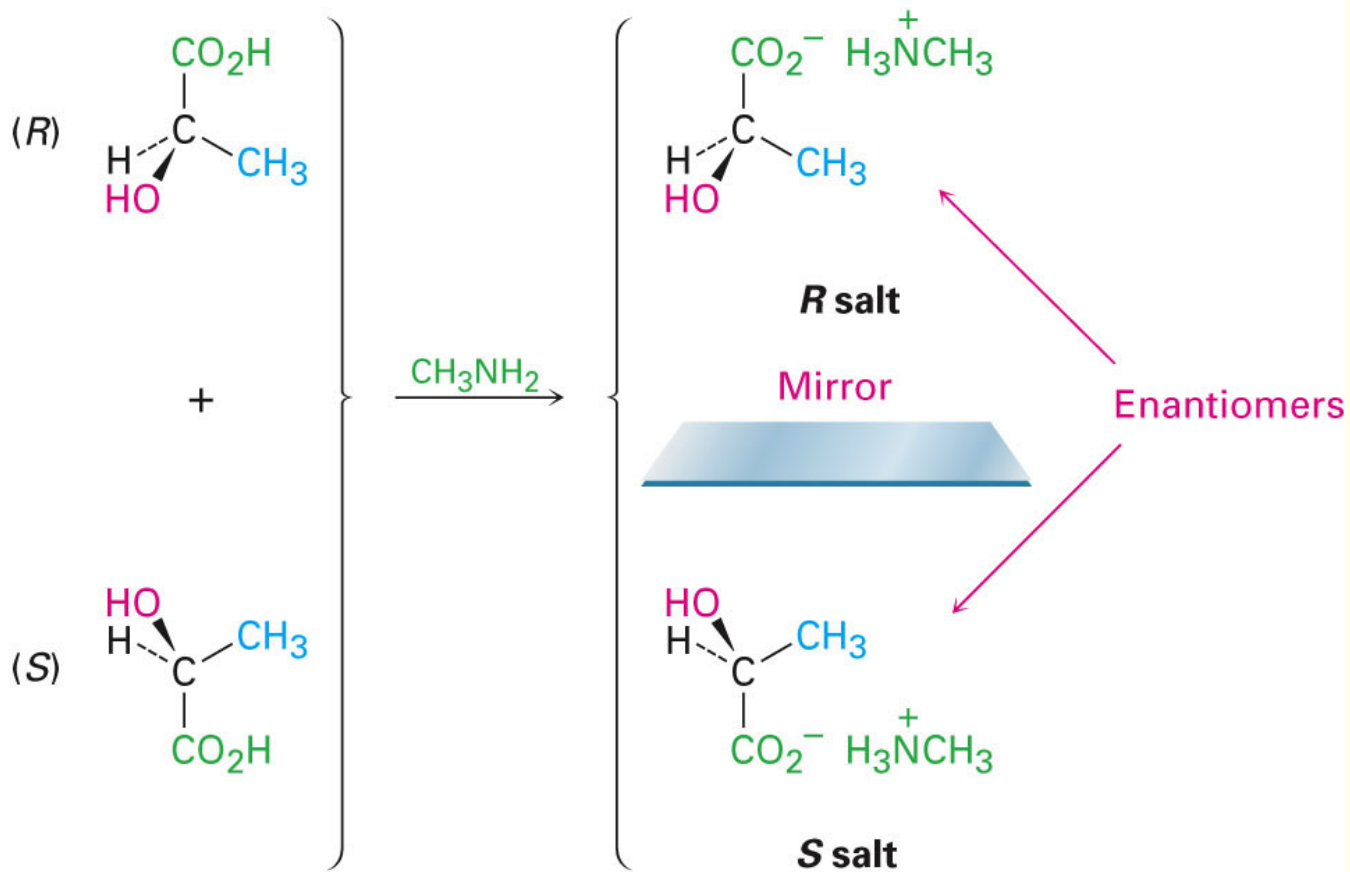
9.7 Meso Compounds

- Tartaric acid has two chirality centers and two diastereomeric forms
- One form is chiral and the other is achiral, but both have two chirality centers
- An achiral compound with chirality centers is called a *meso* compound – it has a plane of symmetry
- The two structures on the right in the figure are identical so the compound (**2R, 3S**) is achiral



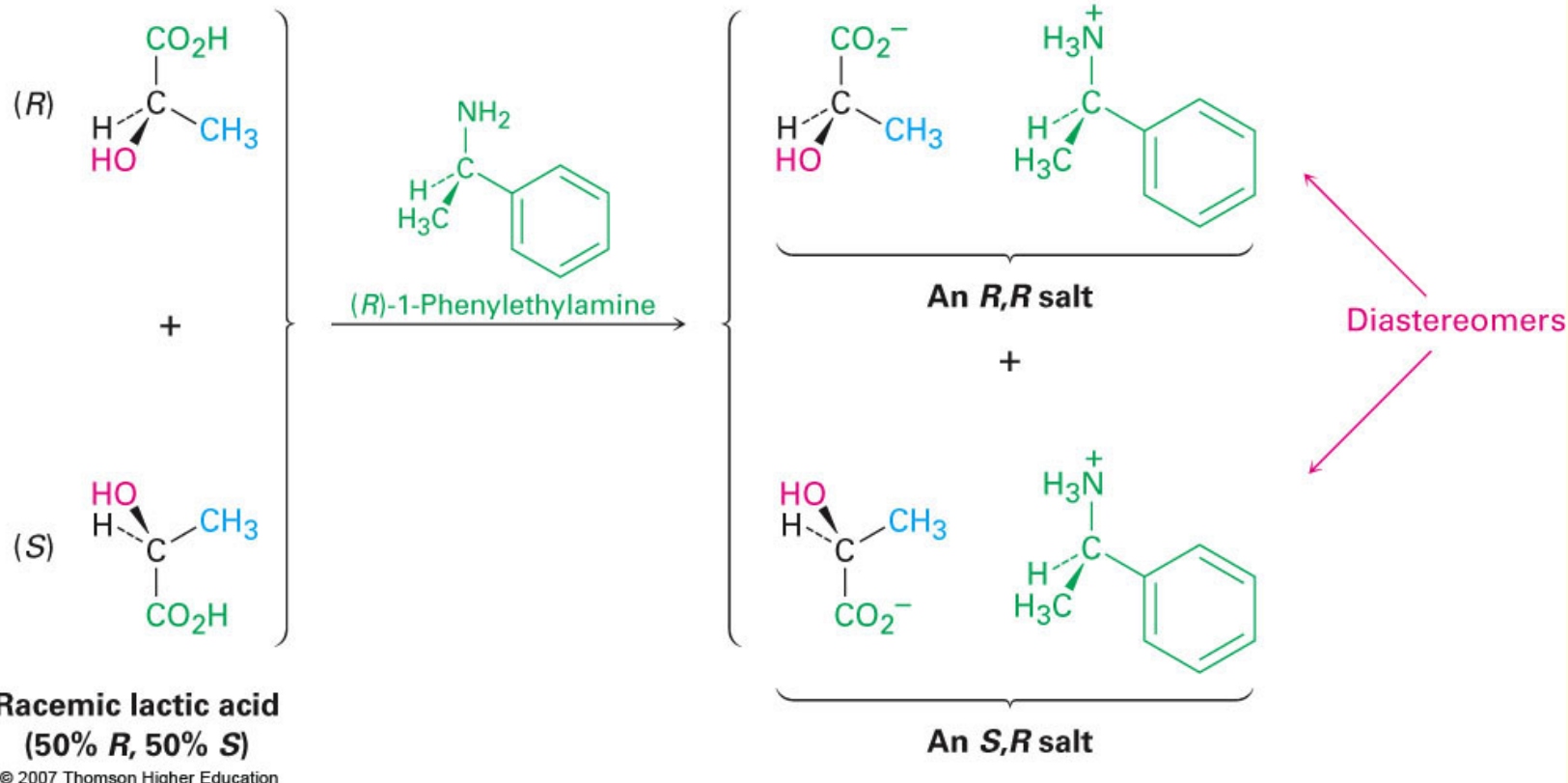
9.8 Racemic Mixtures and The Resolution of Enantiomers

- A 50:50 mixture of two chiral compounds that are mirror images does not rotate light – called a **racemic mixture** (named for “racemic acid” that was the double salt of (+) and (-) tartaric acid)
- The pure compounds need to be separated or **resolved** from the mixture (called a racemate)
- To separate components of a racemate (reversibly) we make a derivative of each with a chiral substance that is free of its enantiomer (resolving agent)
- This gives diastereomers that are separated by their differing solubility
- The resolving agent is then removed

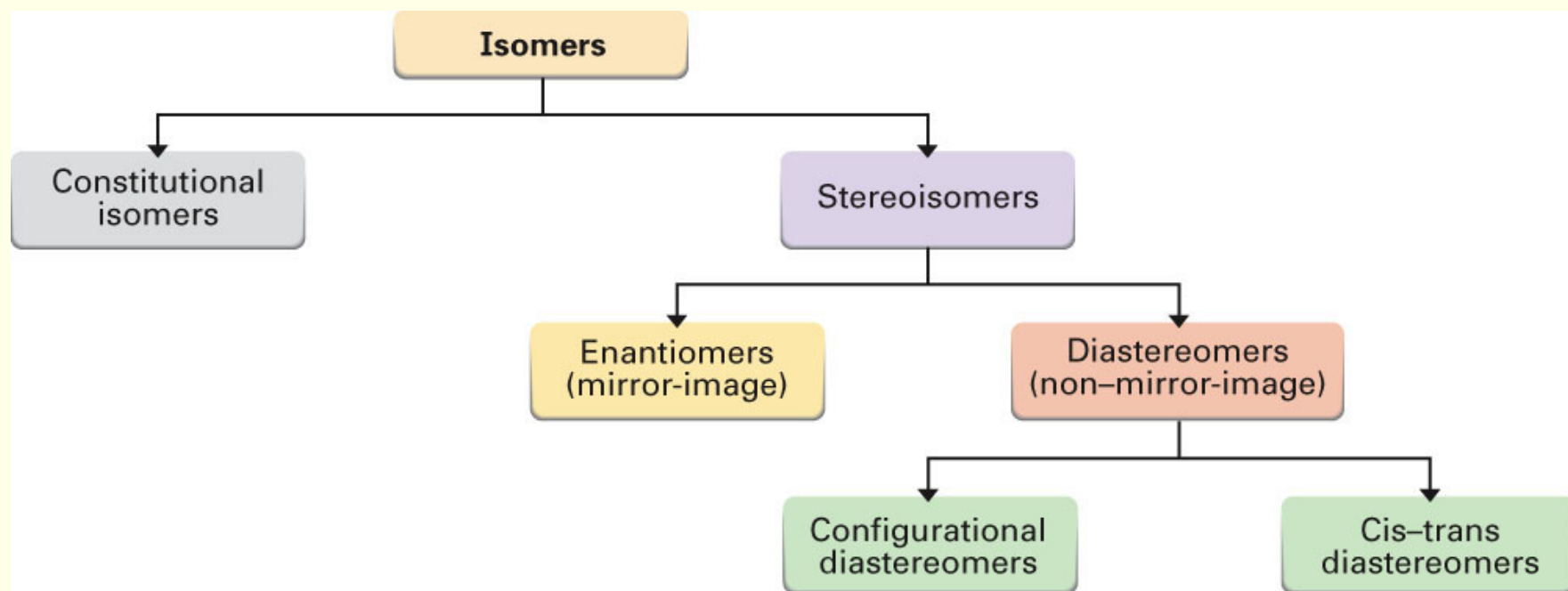


Racemic lactic acid
(50% *R*, 50% *S*)

Racemic ammonium salt
(50% *R*, 50% *S*)



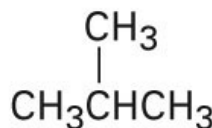
9.9 A Review of Isomerism



Constitutional Isomers

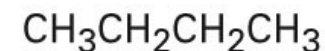
- Different order of connections gives different carbon backbone and/or different functional groups

Different carbon skeletons



2-Methylpropane

and



Butane

Different functional groups



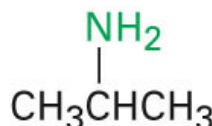
Ethyl alcohol

and



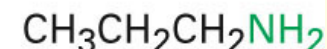
Dimethyl ether

Different position of functional groups



Isopropylamine

and



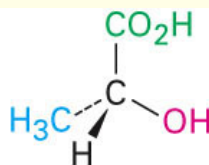
Propylamine

Stereoisomers

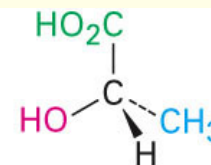
- Same connections, different spatial arrangement of atoms
 - Enantiomers (nonsuperimposable mirror images)
 - Diastereomers (all other stereoisomers)
 - Includes cis, trans and configurational

Enantiomers

(nonsuperimposable mirror-image stereoisomers)



(R)-Lactic acid

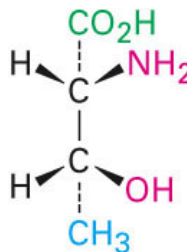


(S)-Lactic acid

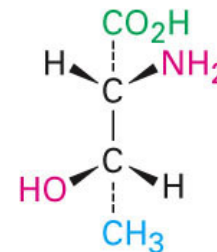
Diastereomers

(nonsuperimposable, non-mirror-image stereoisomers)

Configurational diastereomers



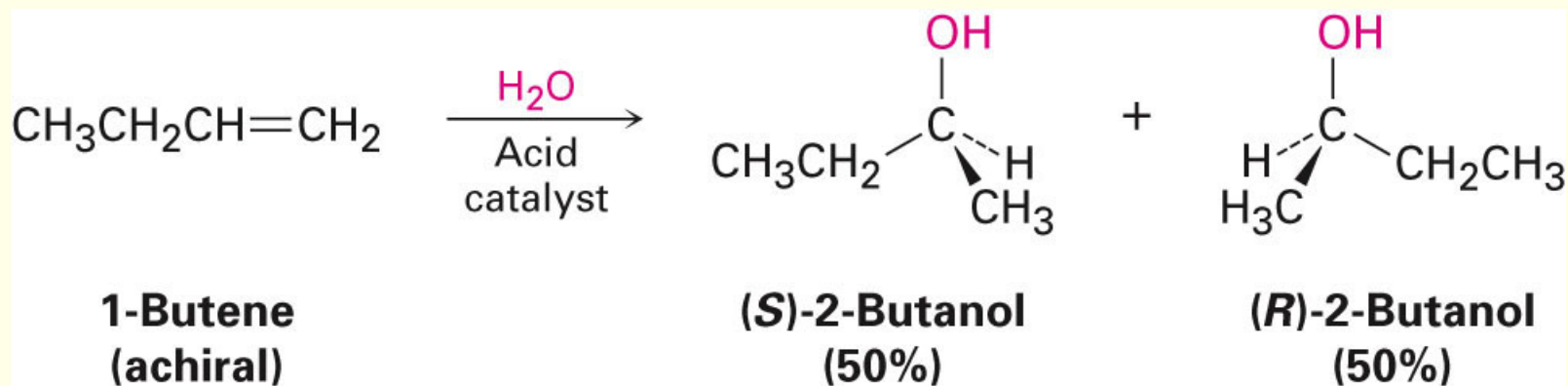
2R,3R-2-Amino-3-hydroxybutanoic acid



2R,3S-2-Amino-3-hydroxybutanoic acid

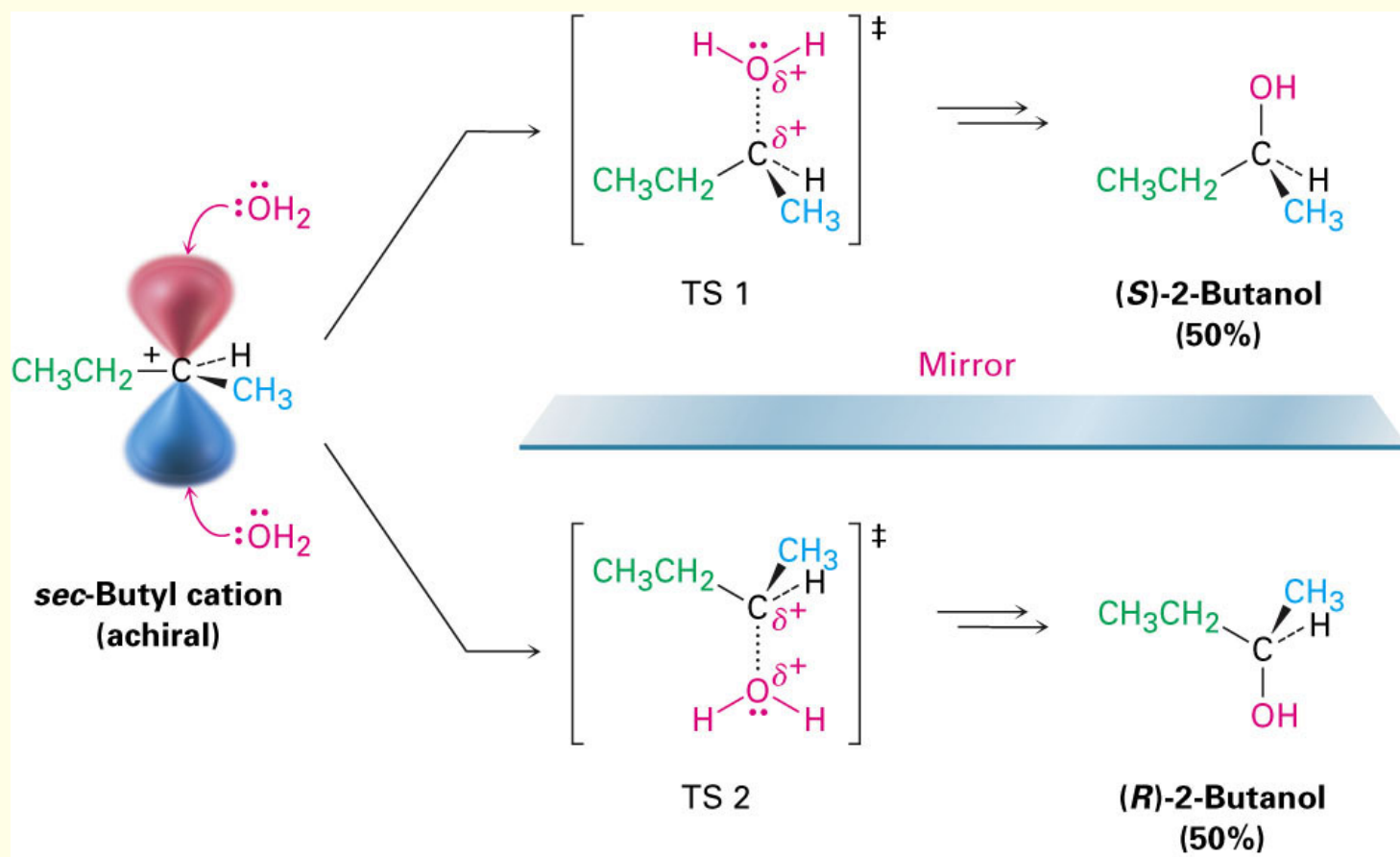
9.10 Stereochemistry of Reactions: Addition of H₂O to Alkenes

- Many reactions can produce new chirality centers from compounds without them
- What is the stereochemistry of the chiral product?
- What relative amounts of stereoisomers form?
- Example addition of H₂O to 1-butene



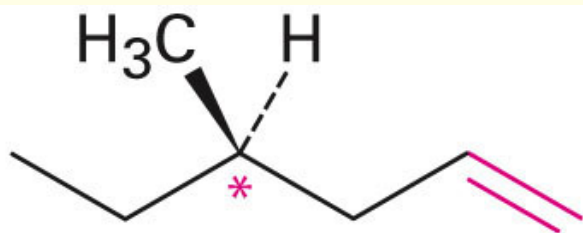
Achiral Intermediate Gives Racemic Product

- Addition via carbocation
- Top and bottom are equally accessible

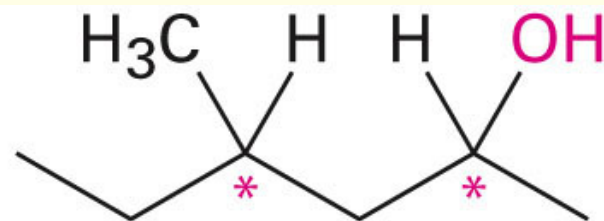
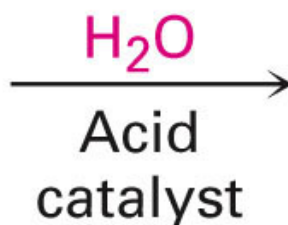


9.11 Stereochemistry of Reactions: Addition of H₂O to a Chiral Alkene

- What is the stereochemical result of the addition of H₂O to a chiral alkene R-4-methyl-1-hexene
- Product has 2 chiral centers



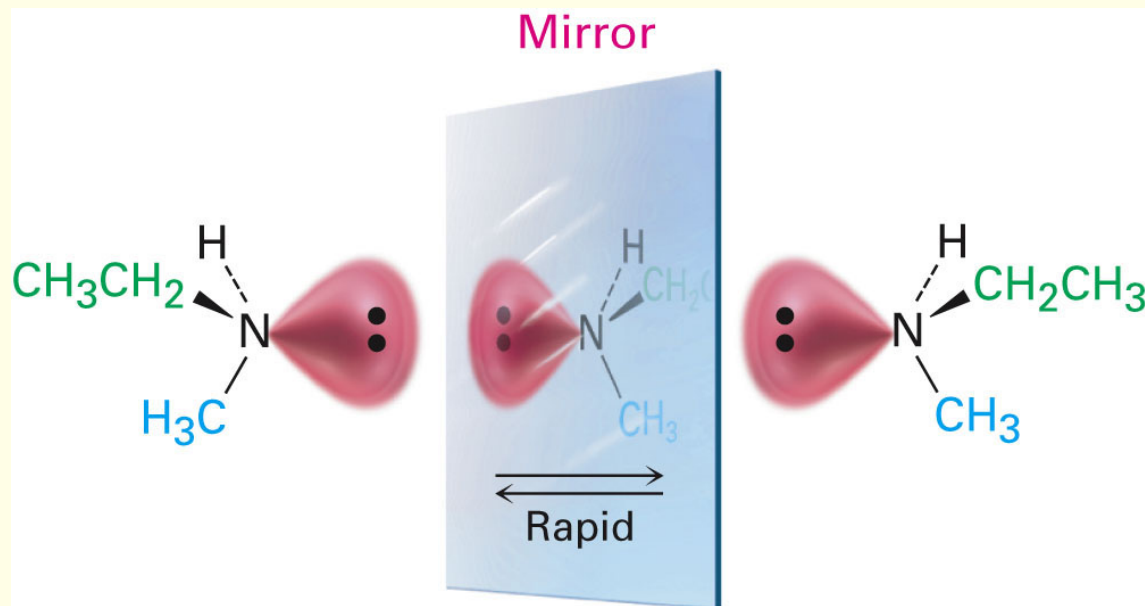
(R)-4-Methyl-1-hexene
(chiral)



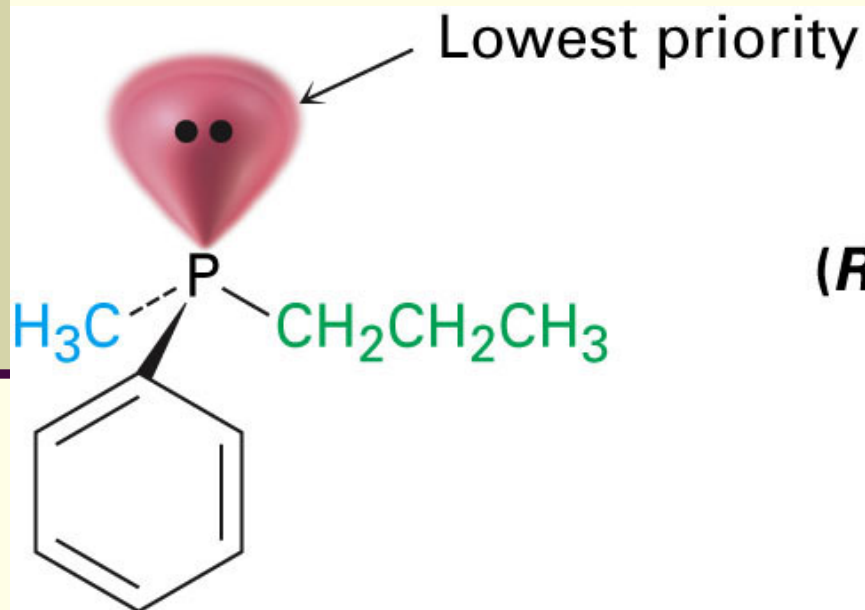
4-Methyl-2-hexanol
(chiral)

9.12 Chirality at Nitrogen, Phosphorus, and Sulfur

- N, P, S commonly found in organic compounds, and can have chirality centers
- Trivalent nitrogen is tetrahedral
- Does not form a chirality center since it rapidly flips
- Individual enantiomers cannot be isolated



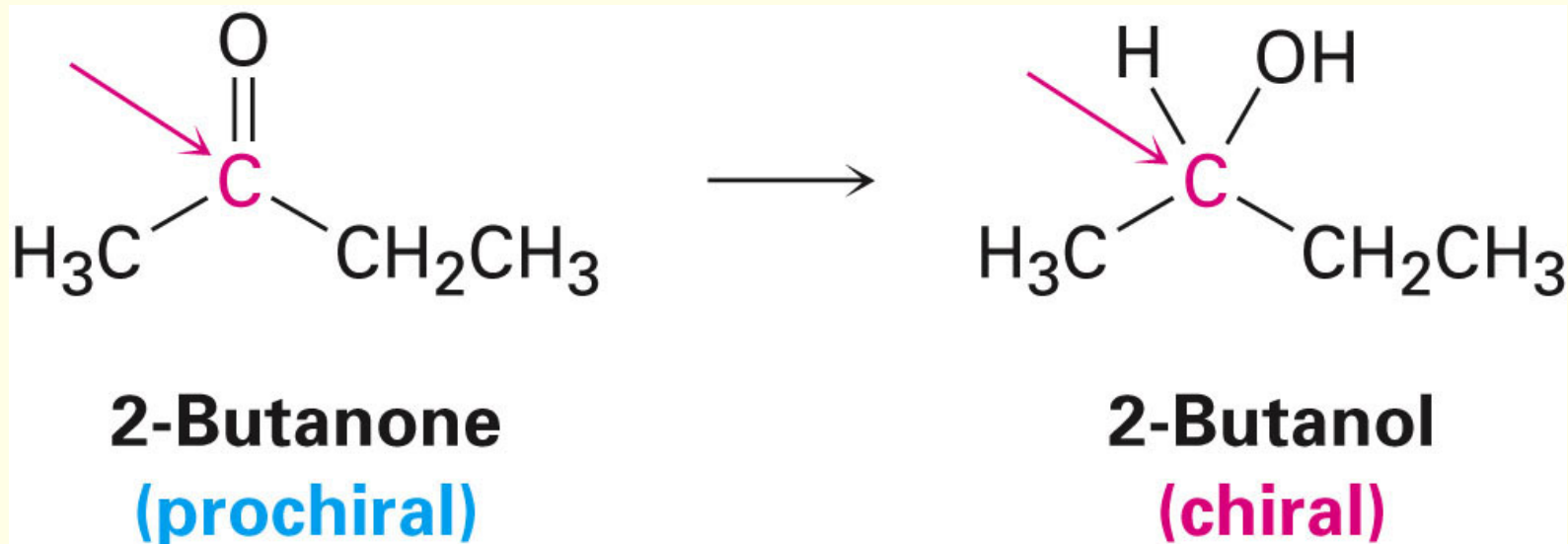
- Also applies to phosphorus but it flips more slowly



**(R)-Methylpropylphenylphosphine
(configurationally stable)**

9.13 Prochirality

- A molecule that is achiral but that can become chiral by a single alteration is a **prochiral** molecule

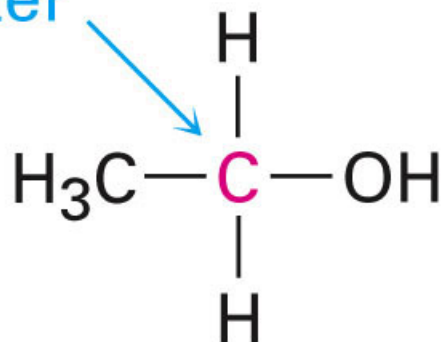


© 2007 Thomson Higher Education

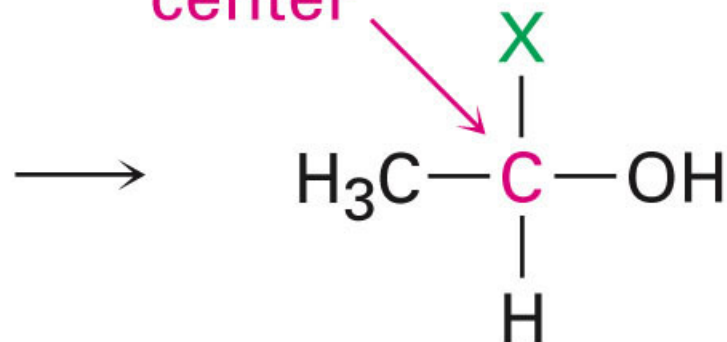
Prochiral Distinctions: Faces

- Planar faces that can become tetrahedral are different from the top or bottom
- A center at the planar face at a carbon atom is designated *re* if the three groups in priority sequence are clockwise, and *si* if they are counterclockwise

Prochirality
center



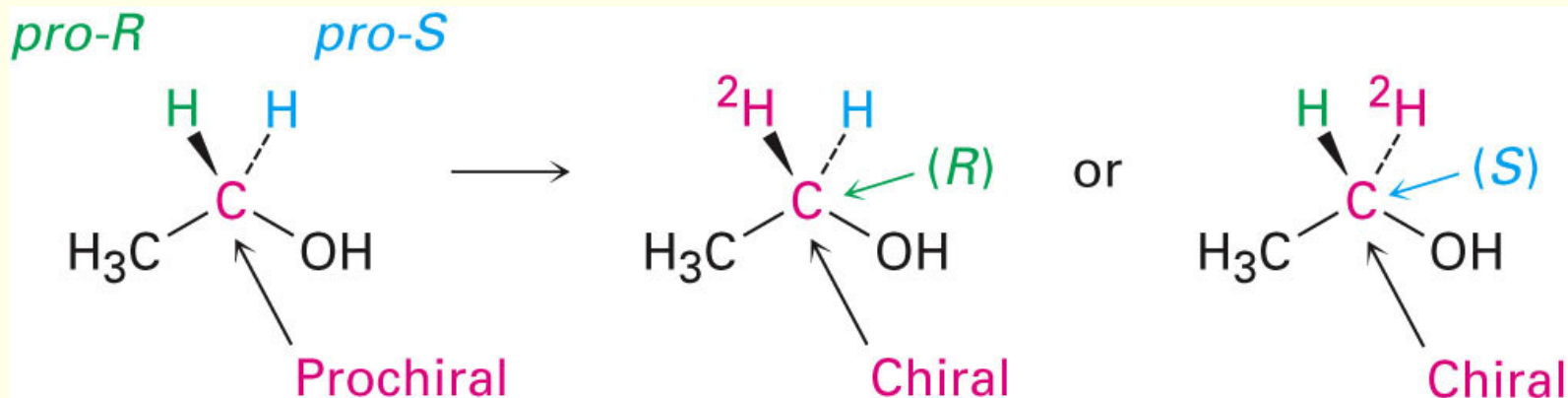
Chirality
center



Ethanol

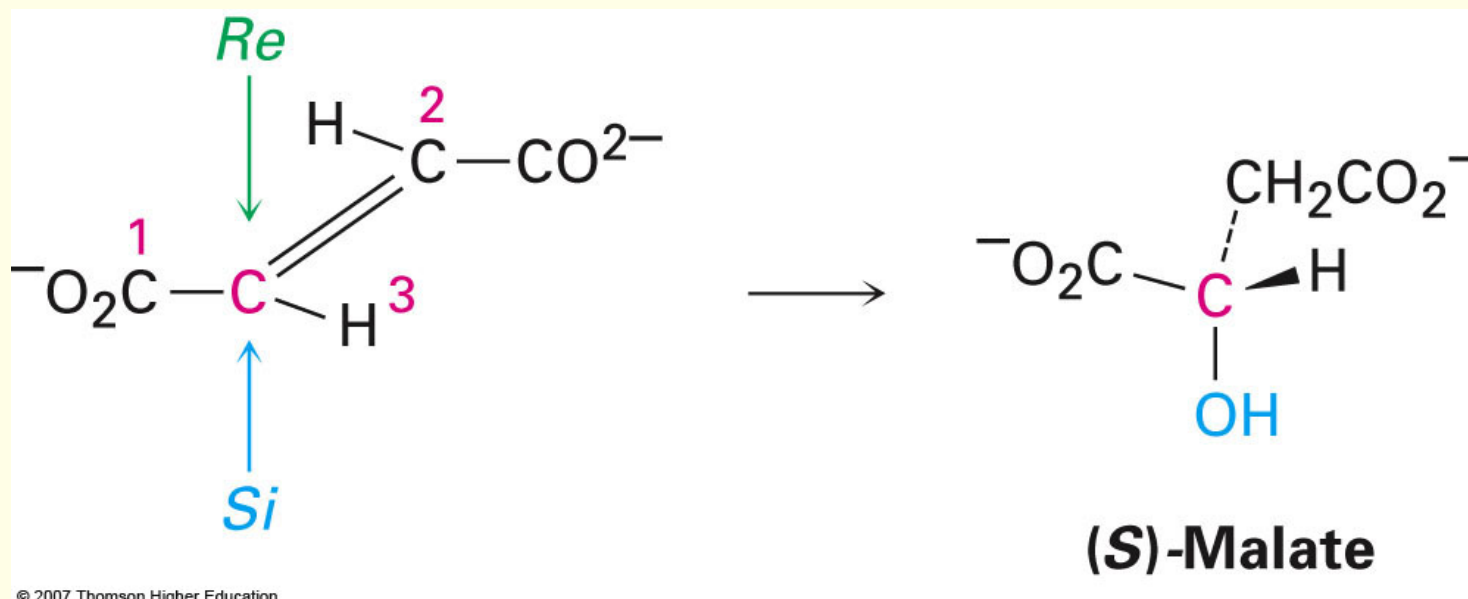
Prochiral distinctions, paired atoms or groups

- An sp^3 carbon with two groups that are the same is a **prochirality center**
- The two identical groups are distinguished by considering either and seeing if it was increased in priority in comparison with the other
- If the center becomes **R** the group is **pro-R** and **pro-S** if the center becomes **S**



Prochiral Distinctions in Nature

- Biological reactions often involve making distinctions between prochiral faces or groups
- Chiral entities (such as enzymes) can always make such a distinction
- Example: addition of water to fumarate



9.14 Chirality in Nature and Chiral Environments

- Stereoisomers are readily distinguished by chiral receptors in nature
- Properties of drugs depend on stereochemistry
- Think of biological recognition as equivalent to 3-point interaction
- See Figure 9-17