Chapter 5

Stereochemistry
Chiral Molecules

Created by
Professor William Tam & Dr. Phillis Chang

About The Authors

These Powerpoint Lecture Slides were created and prepared by Professor William Tam and his wife Dr. Phillis Chang.

Professor William Tam received his B.Sc. at the University of Hong Kong in 1990 and his Ph.D. at the University of Toronto (Canada) in 1995. He was an NSERC postdoctoral fellow at the Imperial College (UK) and at Harvard University (USA). He joined the Department of Chemistry at the University of Guelph (Ontario, Canada) in 1998 and is currently a Full Professor and Associate Chair in the department. Professor Tam has received several awards in research and teaching, and according to *Essential Science Indicators*, he is currently ranked as the Top 1% most cited Chemists worldwide. He has published four books and over 80 scientific papers in top international journals such as *J. Am. Chem. Soc., Angew. Chem., Org. Lett.,* and *J. Org. Chem.*

Dr. Phillis Chang received her B.Sc. at New York University (USA) in 1994, her M.Sc. and Ph.D. in 1997 and 2001 at the University of Guelph (Canada). She lives in Guelph with her husband, William, and their son, Matthew.

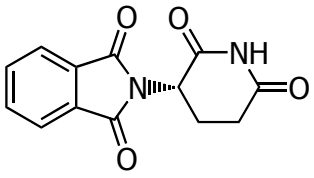
1. Chirality & Stereochemistry

- An object is ***achiral*** (not chiral) if the object and its mirror image are identical

- A ***chiral*** object is one that cannot be superposed on its mirror image

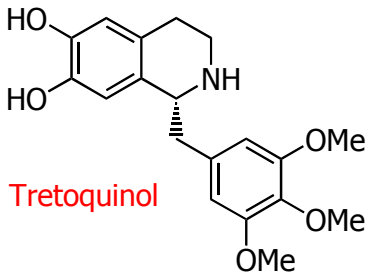
1A. The Biological Significance of Chirality

- Chiral molecules are molecules that cannot be superimposable with their mirror images



Thalidomide

- One enantiomer causes birth defects, the other cures morning sickness



Tretoquinol

- One enantiomer is a bronchodilator, the other inhibits platelet aggregation

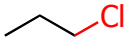
- 66% of all drugs in development are chiral, 51% are being studied as a single enantiomer
- Of the $475 billion in world-wide sales of formulated pharmaceutical products in 2008, $205 billion was attributable to single enantiomer drugs

2. Isomerisom: Constitutional Isomers & Stereoisomers

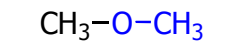
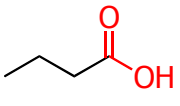
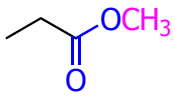
2A. Constitutional Isomers

- **Isomers**: different compounds that have the same molecular formula
  - **Constitutional isomers**: isomers that have the same molecular formula but different connectivity – their atoms are connected in a different order

- Examples

Molecular Formula	Constitutional Isomers
C_4H_{10}	 Butane and  2-Methylpropane
C_3H_7Cl	 1-Chloropropane and  2-Chloropropane

- Examples

Molecular Formula	Constitutional Isomers
C_2H_6O	 Ethanol and  Methoxymethane
$C_4H_8O_2$	 Butanoic acid and  Methyl propanoate

2B. Stereoisomers

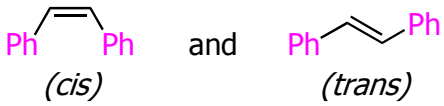
- Stereoisomers are **NOT** constitutional isomers
- **Stereoisomers** have their atoms connected in the same sequence but they differ in the arrangement of their atoms in space. The consideration of such spatial aspects of molecular structure is called ***stereochemistry***

2C. Enantiomers & Diastereomers

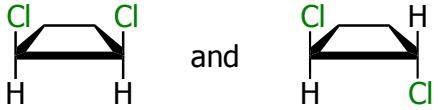
- Stereoisomers can be subdivided into two general categories: *enantiomers* & *diasteromers*
  - **Enantiomers** – stereoisomers whose molecules are nonsuperposable mirror images of each other
  - **Diastereomers** – stereoisomers whose molecules are not mirror images of each other

- Geometrical isomers (*cis* & *trans* isomers) are:
  - *Diastereomers*

e.g.

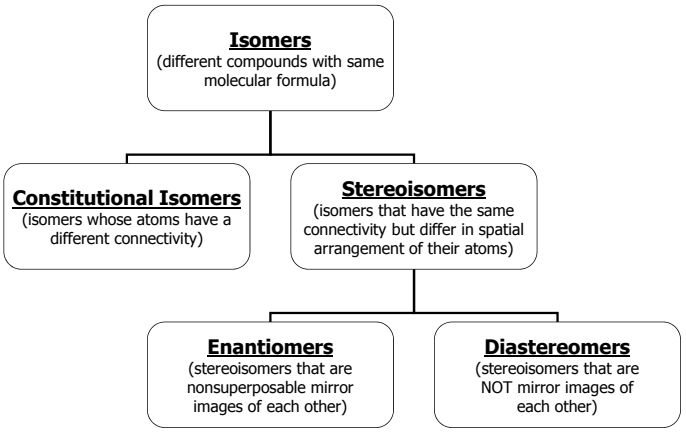


(cis) *(trans)*



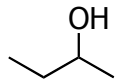
(cis) *(trans)*

Subdivision of Isomers



3. Enantiomers and Chiral Molecules

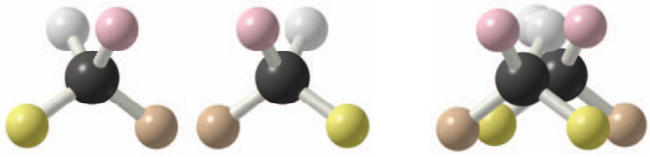
- Enantiomers occur only with compounds whose molecules are **chiral**
- A chiral molecule is one that is **NOT** superposable on its mirror image
- The relationship between a chiral molecule and its mirror image is one that is ***enantiomeric***. A chiral molecule and its mirror image are said to be enantiomers of each other



(2-Butanol)

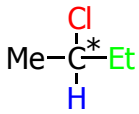
(I) (II)

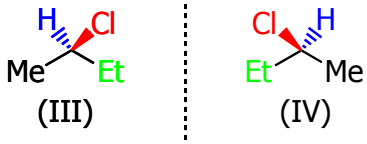
(I) and (II) are nonsuperposable mirror images of each other



4. A Single Chirality Center Causes a Molecule to Be Chiral

- The most common type of chiral compounds that we encounter are molecules that contain a carbon atom bonded to *four different groups*. Such a carbon atom is called an *asymmetric carbon* or a ***chiral center*** and is usually designated with an asterisk (*)

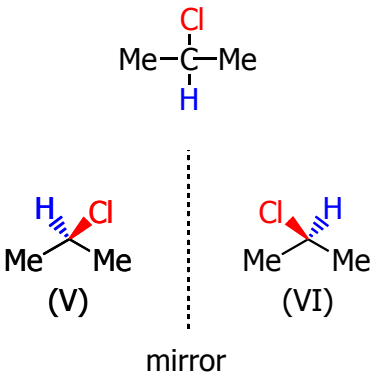




(III) (IV)

mirror

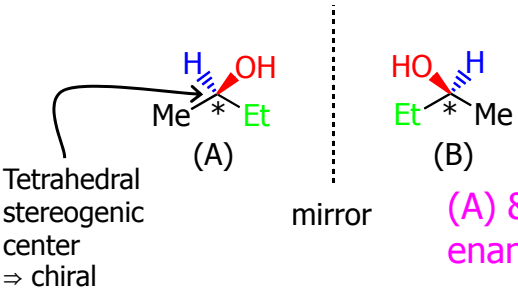
(III) and (IV) are nonsuperposable mirror images of each other



(V) and (VI) are superposable
⇒ not enantiomers ⇒ achiral

4A. Tetrahedral vs. Trigonal Stereogenic Centers

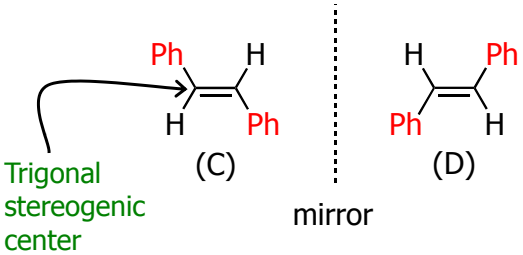
- Chirality centers are ***tetrahedral stereogenic*** centers



Tetrahedral stereogenic center ⇒ chiral

(A) & (B) are enantiomers

- *Cis* and *trans* alkene isomers contain trigonal stereogenic centers



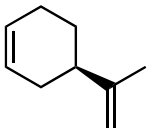
Trigonal stereogenic center ⇒ achiral

(C) & (D) are identical

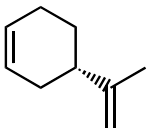
4A. Tetrahedral vs. Trigonal Stereogenic Centers

- Chirality centers are ***tetrahedral stereogenic*** centers
- *Cis* and *trans* alkene isomers contain trigonal stereogenic centers

5. More about the Biological Importance of Chirality



(+)-Limonene (limonene enantiomer found in oranges)

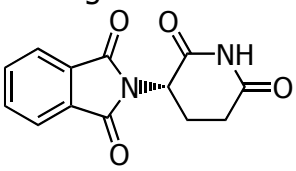


(-)-Limonene (limonene enantiomer found in lemons)

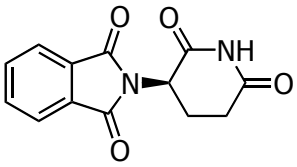
Thalidomide

- The activity of drugs containing chirality centers can vary between enantiomers, sometimes with serious or even tragic consequences
- For several years before 1963 thalidomide was used to alleviate the symptoms of morning sickness in pregnant women

- In 1963 it was discovered that thalidomide (sold as a mixture of both enantiomers) was the cause of horrible birth defects in many children born subsequent to the use of the drug



Thalidomide
(cures morning sickness)

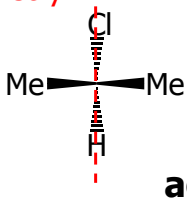


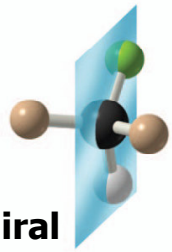
enantiomer of Thalidomide
(causes birth defects)

6. How to Test for Chirality: Planes of Symmetry

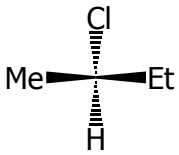
- A molecule will not be chiral if it possesses a plane of symmetry
- A plane of symmetry (mirror plane) is an imaginary plane that bisects a molecule such that the two halves of the molecule are mirror images of each other
- All molecules with a plane of symmetry in their most symmetric conformation are ***achiral***

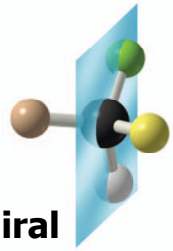
Plane of symmetry





achiral



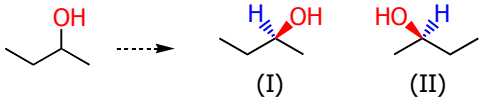


No plane of symmetry

chiral

7. Naming Enantiomers: *R,S*-System

Recall:



- Using only the IUPAC naming that we have learned so far, these two enantiomers will have the same name:
  - **2-Butanol**
- This is undesirable because each compound must have its own distinct name

7A. How to Assign (R) and (S) Configurations

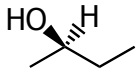
- Rule 1
  - Assign priorities to the four different groups on the stereocenter from highest to lowest (priority bases on atomic number, the higher the atomic number, the higher the priority)

- Rule 2
  - When a priority cannot be assigned on the basis of the atomic number of the atoms that are directly attached to the chirality center, then the next set of atoms in the unassigned groups is examined. This process is continued until a decision can be made.

❖ Rule 3

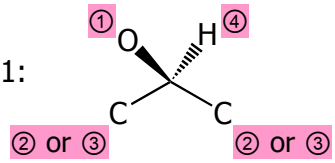
- Visualize the molecule so that the lowest priority group is directed away from you, then trace a path from highest to lowest priority. If the path is a clockwise motion, then the configuration at the asymmetric carbon is (*R*). If the path is a counter-clockwise motion, then the configuration is (*S*)

❖ Example

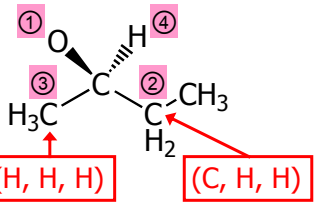


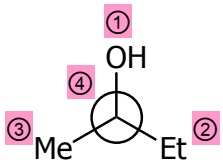
(2-Butanol)

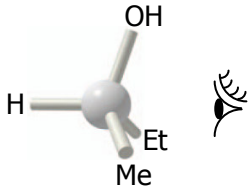
Step 1:

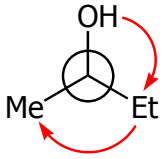


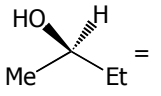
Step 2:











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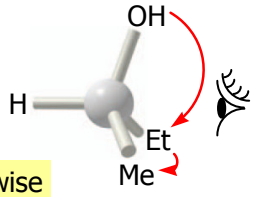
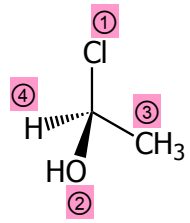


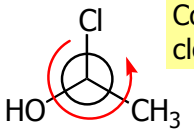
Arrows are clockwise

(*R*)-2-Butanol

❖ Other examples

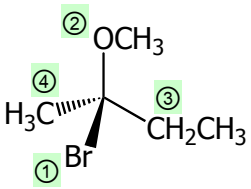


⇒



Counter-clockwise

(*S*)



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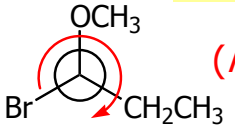
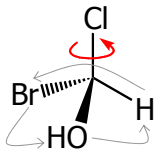


Clockwise

(*R*)

❖ Other examples

- Rotate C–Cl bond such that H is pointed to the back



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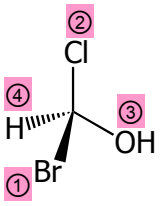

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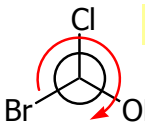
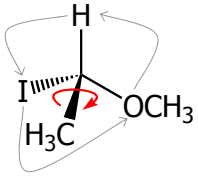


Clockwise

(*R*)

❖ Other examples

- Rotate C–CH_3 bond such that H is pointed to the back



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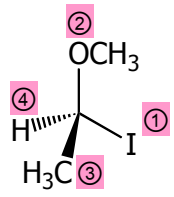
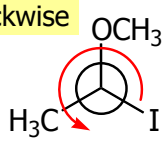


Counter-clockwise

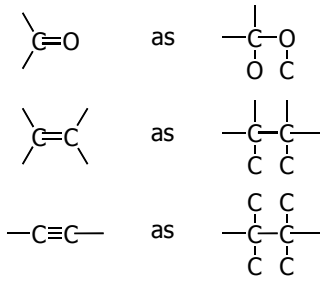
⇒



(*S*)

❖ Rule 4

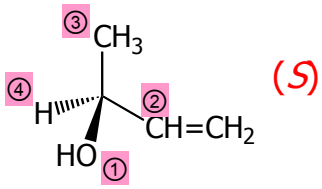
- For groups containing double or triple bonds, assign priorities as if both atoms were duplicated or triplicated

e.g.  as

 as

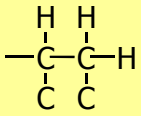
 as

❖ Example



(*S*)

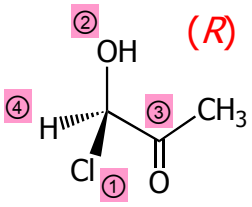
Compare —CH_3 & —$CH{=}CH_2$:

—$CH{=}CH_2$ equivalent to 

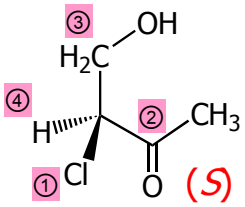
Thus, —CH_3 ⇒ (H, H, H)

—$CH{=}CH_2$ ⇒ (C, C, H)

❖ Other examples



(*R*)



(*S*)

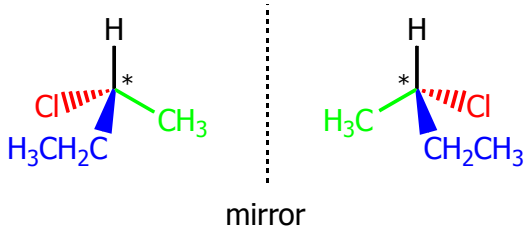
② C ⇒ (O, O, C)

③ C ⇒ (O, H, H)

8. Properties of Enantiomers: Optical Activity

❖ Enantiomers

- Mirror images that are not superposable



mirror

❖ Enantiomers have identical physical properties (e.g. melting point, boiling point, refractive index, solubility etc.)

Compound	bp (°C)	mp (°C)
(*R*)-2-Butanol	99.5	
(*S*)-2-Butanol	99.5	
(+)-(*R,R*)-Tartaric Acid		168 – 170
(–)-(*S,S*)-Tartaric Acid		168 – 170
(+/–)-Tartaric Acid		210 – 212

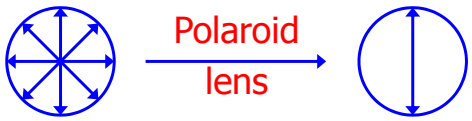
❖ Enantiomers

- Have the same chemical properties (except reaction/interactions with chiral substances)
- Show different behavior only when they interact with other chiral substances
- Turn plane-polarized light on opposite direction

- Optical activity
  - The property possessed by chiral substances of rotating the plane of polarization of plane-polarized light

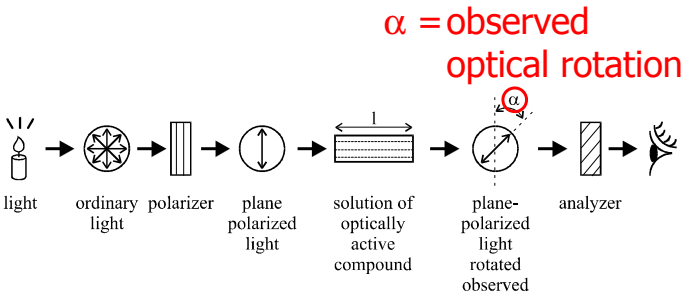
8A. Plane-Polarized Light

- The electric field (like the magnetic field) of light is oscillating in all possible planes
- When this light passes through a polarizer (Polaroid lens), we get plane-polarized light (oscillating in only one plane)

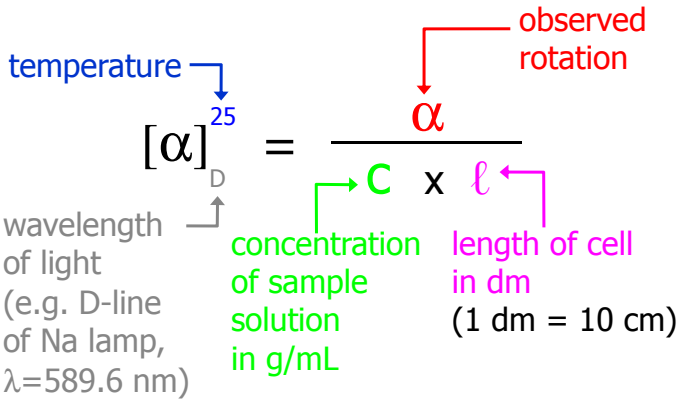


8B. The Polarimeter

- A device for measuring the optical activity of a chiral compound

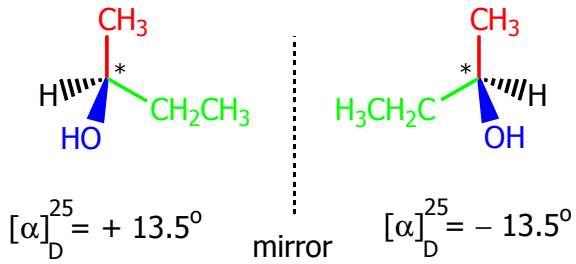


8C. Specific Rotation

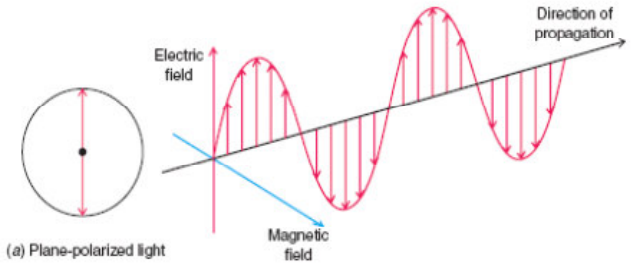


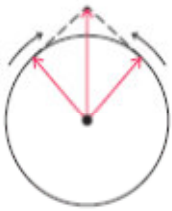
- The value of α depends on the particular experiment (since there are different concentrations with each run)
  - But specific rotation [α] should be the same regardless of the concentration

- Two enantiomers should have the same value of specific rotation, but the signs are opposite

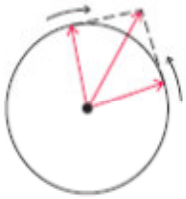


9. The Origin of Optical Activity





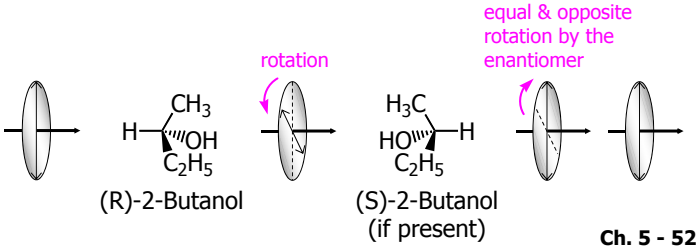
Two circularly-polarized beams counter-rotating at the same velocity (in phase), and their vector sum



Two circularly-polarized beams counter-rotating at different velocities, such as after interaction with a chiral molecule, and their vector sum

9A. Racemic Forms

- An equimolar mixture of two enantiomers is called a racemic mixture (or *racemate* or *racemic form*)
- A racemic mixture causes no net rotation of plane-polarized light



9B. Racemic Forms and Enantiomeric Excess

- A sample of an optically active substance that consists of a single enantiomer is said to be **enantiomerically pure** or to have an **enantiomeric excess** of 100%

- An enantiomerically pure sample of (*S*)-(+)-2-butanol shows a specific rotation of +13.52

$$[\alpha]_D^{25} = +13.52$$

- A sample of (S)-(+)-2-butanol that contains less than an equimolar amount of (*R*)-(–)-2-butanol will show a specific rotation that is less than 13.52 but greater than zero
- Such a sample is said to have an *enantiomeric excess* less than 100%

❖ Enantiomeric excess (ee)

- Also known as the optical purity

$$\%\ \text{enantiomeric excess} = \frac{\left(\begin{matrix}\text{mole of one}\\ \text{enantiomer}\end{matrix}\right) - \left(\begin{matrix}\text{moles of other}\\ \text{enantiomer}\end{matrix}\right)}{\text{total moles of both enantiomers}} \times 100$$

- Can be calculated from optical rotations

$$\%\ \text{enantiomeric excess *} = \frac{\text{observed specific rotation}}{\begin{matrix}\text{specific rotation of the}\\ \text{pure enantiomers}\end{matrix}} \times 100$$

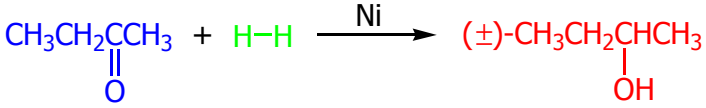
❖ Example

- A mixture of the 2-butanol enantiomers showed a specific rotation of +6.76. The enantiomeric excess of the (S)-(+)-2-butanol is 50%

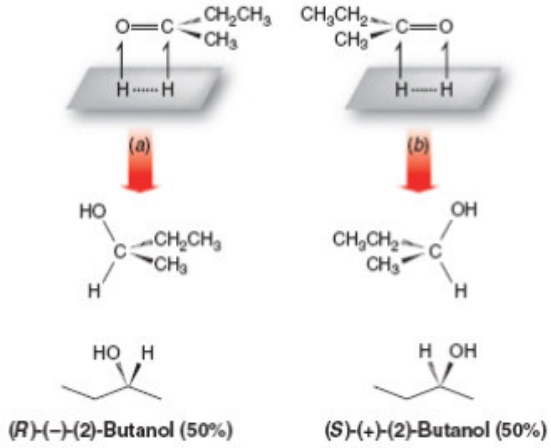
$$\%\ \text{enantiomeric excess *} = \frac{+6.76}{+13.52} \times 100 = 50\%$$

10. The Synthesis of Chiral Molecules

10A. Racemic Forms



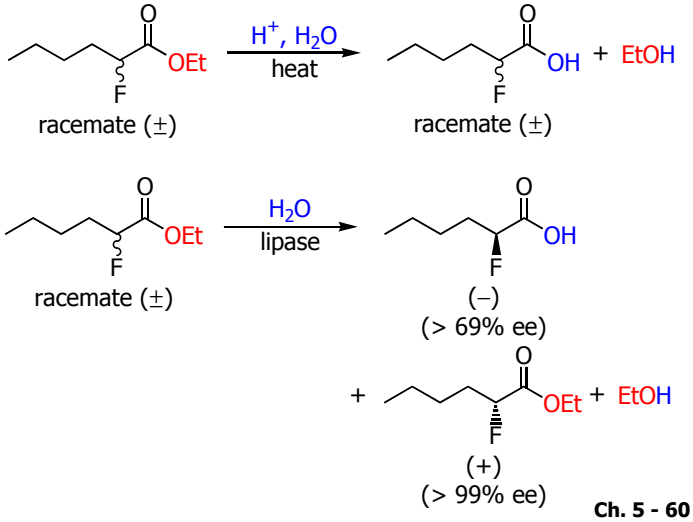
Butanone (achiral molecules) | Hydrogen (achiral molecules) | (±)-2-Butanol (chiral molecules; but 50:50 mixture (*R*) & (*S*))



10B. Stereoselective Syntheses

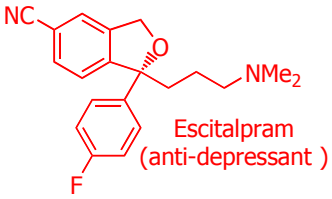
❖ **Stereoselective reactions** are reactions that lead to a preferential formation of one stereoisomer over other stereoisomers that could possibly be formed

- **enantioselective** – if a reaction produces preferentially one enantiomer over its mirror image
- **diastereoselective** – if a reaction leads preferentially to one diastereomer over others that are possible

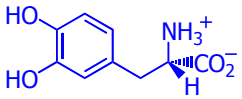


11. Chiral Drugs

- Of the $475 billion in world-wide sales of formulated pharmaceutical products in 2008, $205 billion was attributable to single enantiomer drugs

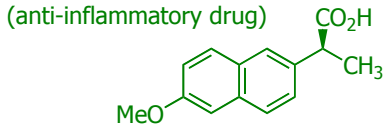


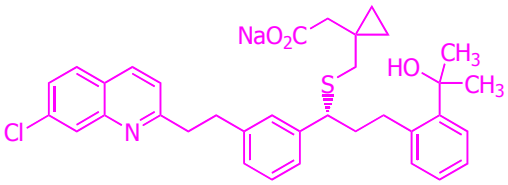
Escitalpram
(anti-depressant)



L-DOPA
(treatment for Parkinson's)

Naproxen
(anti-inflammatory drug)



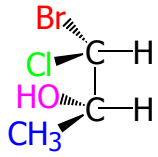


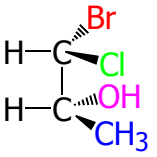
Singulair
(asthma and allergy treatment)

12. Molecules with More than One Chirality Center

- Diastereomers
  - Stereoisomers that are not enantiomers
  - Unlike enantiomers, diastereomers usually have substantially different chemical and physical properties

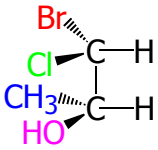
(I)

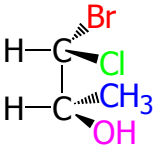




(II)

(III)

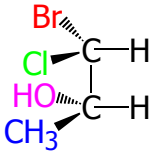


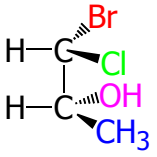


(IV)

Note: In compounds with *n* tetrahedral stereocenters, the maximum number of stereoisomers is 2^n.

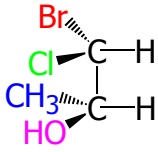
(I)

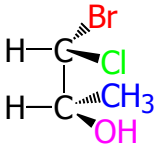




(II)

(III)

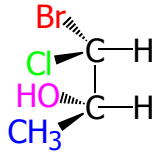


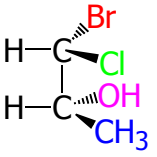


(IV)

- (I) & (II) are enantiomers to each other
- (III) & (IV) are enantiomers to each other

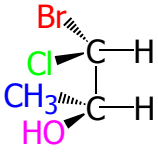
(I)

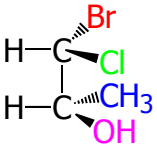




(II)

(III)



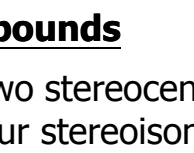
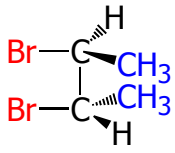


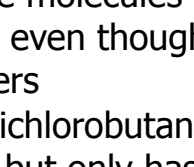
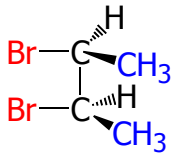
(IV)

- Diastereomers to each other:
  - (I) & (III), (I) & (IV), (II) & (III), (II) & (IV)

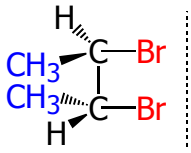
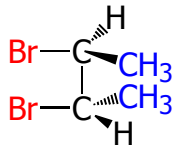
12A. Meso Compounds

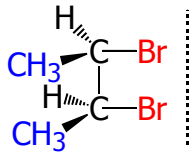
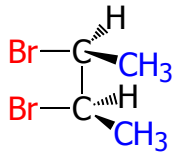
- Compounds with two stereocenters do not always have four stereoisomers ($2^2 = 4$) since some molecules are achiral (not chiral), even though they contain stereocenters
- For example, 2,3-dichlorobutane has two stereocenters, but only has 3 stereoisomers (not 4)

(I)  **(II)** 

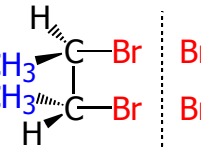
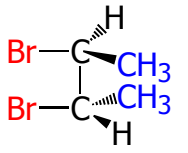
(III)  **(IV)** 

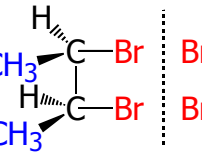
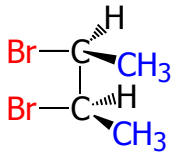
Note: (III) contains a plane of symmetry, is a meso compound, and is achiral ([α] = 0°).

(I)  **(II)** 

(III)  **(IV)** 

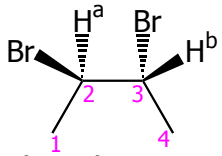
- (I) & (II) are enantiomers to each other and chiral
- (III) & (IV) are identical and achiral

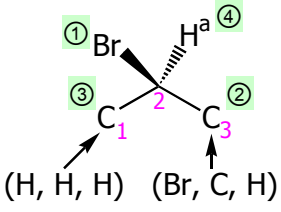
(I)  **(II)** 

(III)  **(IV)** 

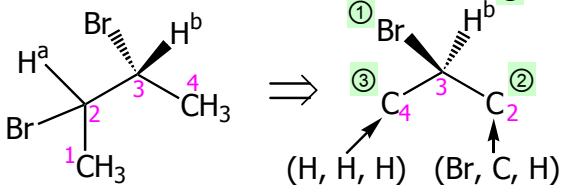
- (I) & (III), (II) & (III) are diastereomers
- Only 3 stereoisomers:
  - (I) & (II) {enantiomers}, (III) {meso}

12B. How to Name Compounds with More than One Chirality Center

- 2,3-Dibromobutane 
  - Look through C2–H^a bond

C2: *(R)* configuration 

- Look through C3–H^b bond

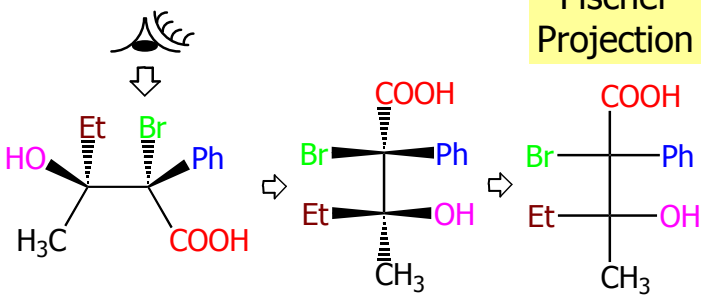


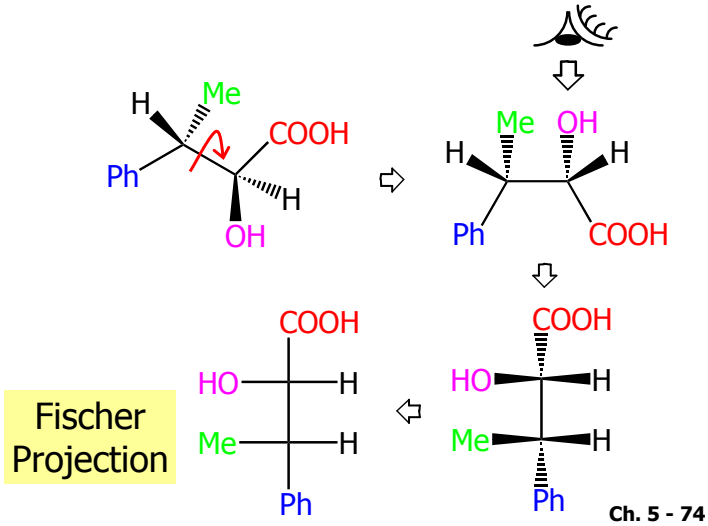
C3: *(R)* configuration

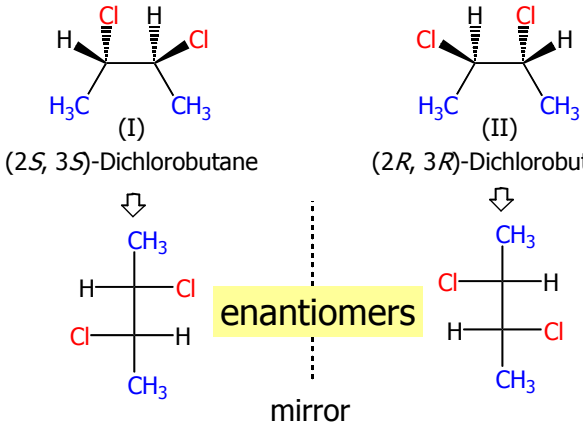
- Full name:
  - *(2R, 3R)*-2,3-Dibromobutane

13. Fischer Projection Formulas

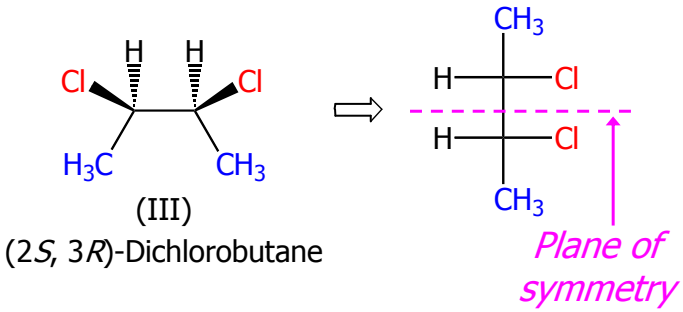
13A. How To Draw and Use Fischer Projections





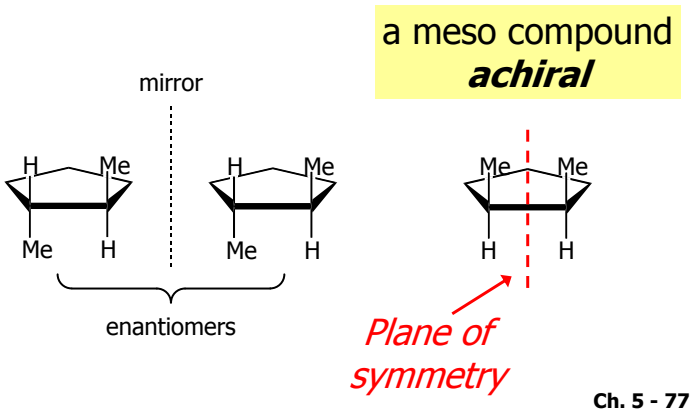


- (I) and (II) are both chiral and they are enantiomers with each other



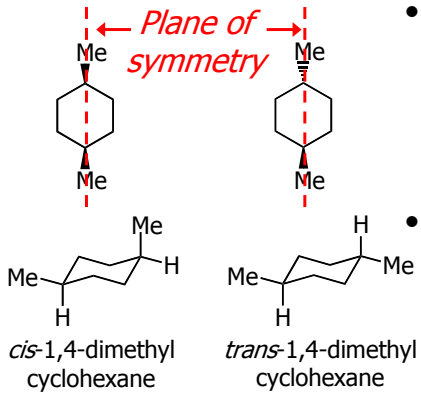
- (III) is achiral (a meso compound)
- (III) and (I) are diastereomers to each other

14. Stereoisomerism of Cyclic Compounds



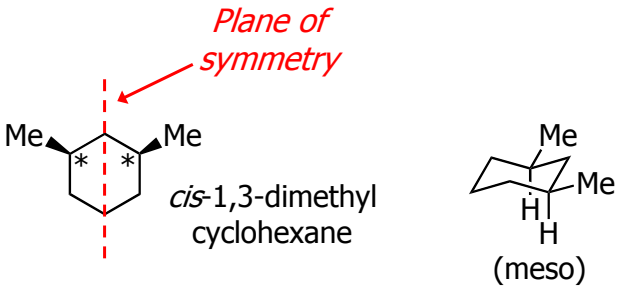
14A. Cyclohexane Derivatives

- 1,4-Dimethylcyclohexane



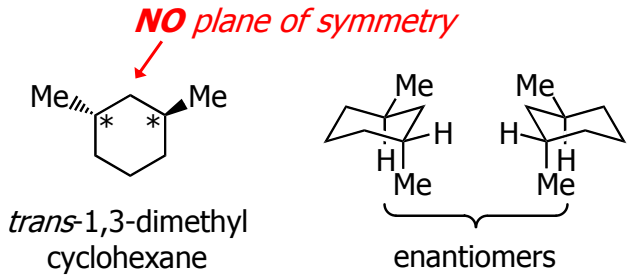
- Both *cis*- & *trans*-1,4-dimethylcyclohexanes are ***achiral*** and optically inactive
- The *cis* & *trans* forms are ***diastereomers***

❖ 1,3-Dimethylcyclohexane



- *cis*-1,3-Dimethylcyclohexane has a plane of symmetry and is a meso compound

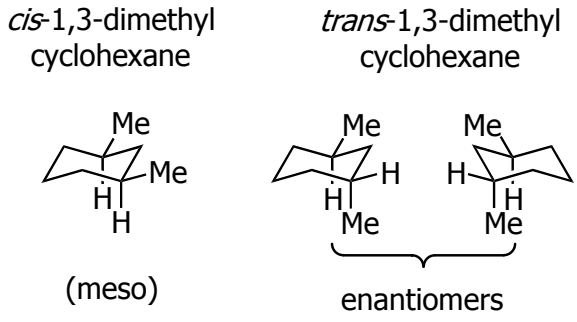
❖ 1,3-Dimethylcyclohexane



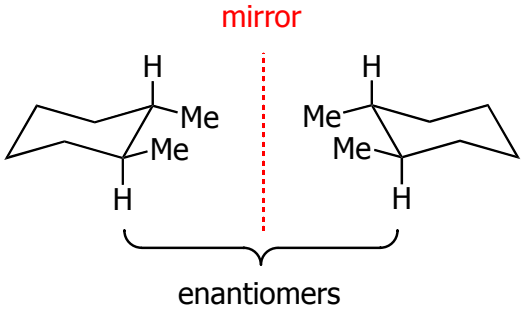
- *trans*-1,3-Dimethylcyclohexane exists as a pair of enantiomers

❖ 1,3-Dimethylcyclohexane

- Has two chirality centers but only ***three*** stereoisomers



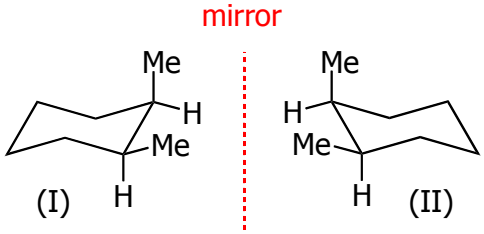
❖ 1,2-Dimethylcyclohexane



- *trans*-1,2-Dimethylcyclohexane exists as a pair of enantiomers

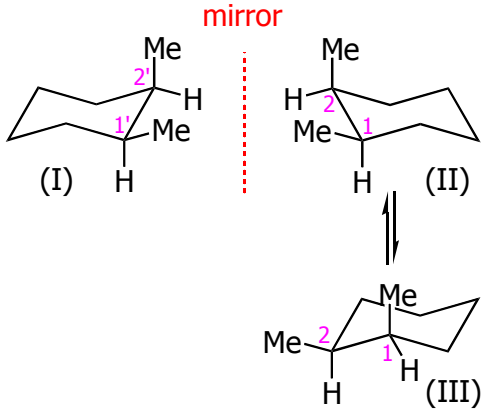
❖ 1,2-Dimethylcyclohexane

- With *cis*-1,2-dimethylcyclohexane the situation is quite complicated

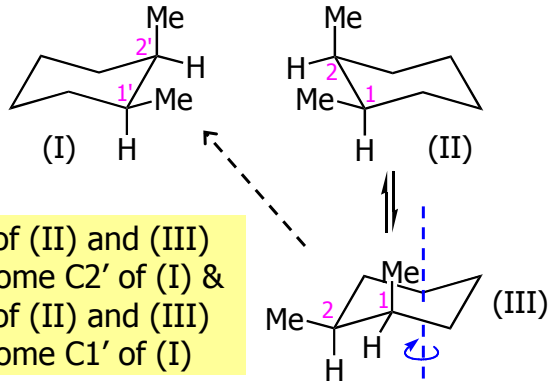


- (I) and (II) are enantiomers to each other

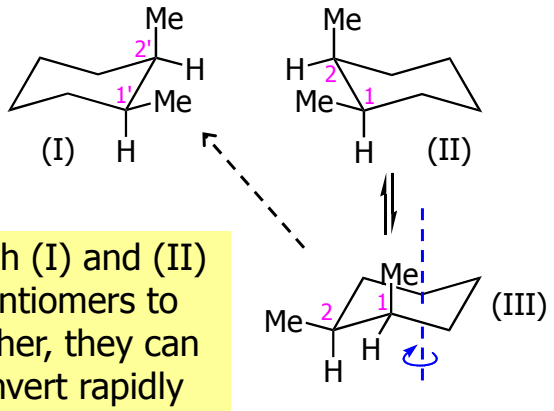
- However, (II) can rapidly be interconverted to (III) by a ring flip



- Rotation of (III) along the vertical axis gives (I)



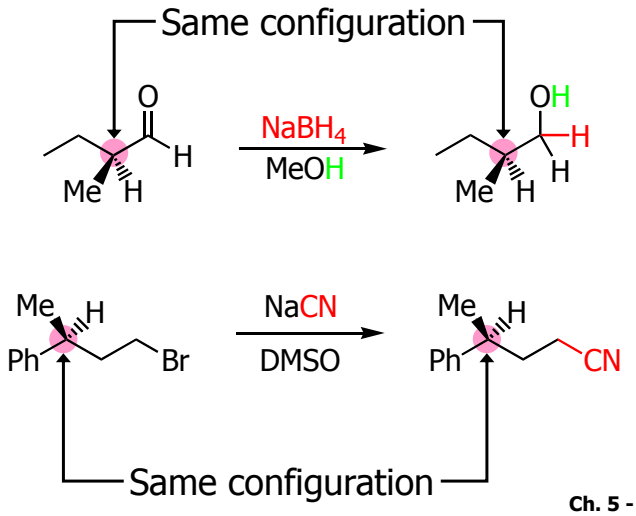
C1 of (II) and (III) become C2′ of (I) & C2 of (II) and (III) become C1′ of (I)



Although (I) and (II) are enantiomers to each other, they can interconvert rapidly ⇒ (I) and (II) are ***achiral***

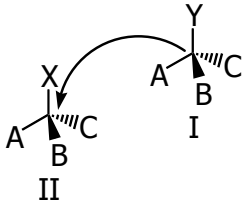
15. Relating Configurations through Reactions in Which No Bonds to the Chirality Center Are Broken

- **If a reaction takes place in a way so that no bonds to the chirality center are broken**, the product will of necessity have the same general configuration of groups around the chirality center as the reactant



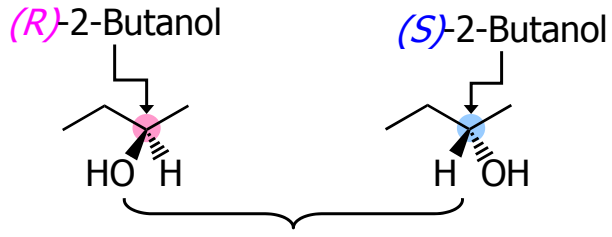
15A. Relative and Absolute Configurations

- Chirality centers in different molecules have the same **relative configuration** if they share three groups in common and if these groups **with** the central carbon can be superposed in a pyramidal arrangement



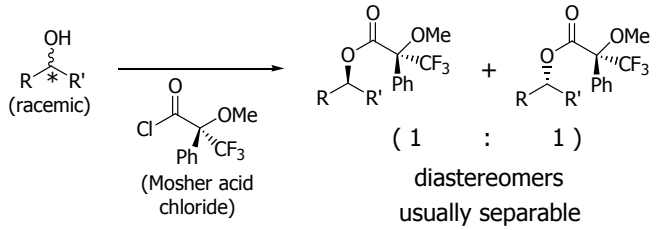
The chirality centers in I and II have the same relative configuration. Their common groups and central carbon can be superposed.

- The **absolute configuration** of a chirality center is its (*R*) or (*S*) designation, which can only be specified by knowledge of the actual arrangement of groups in space at the chirality center



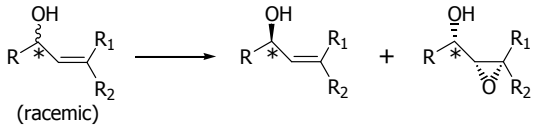
16. Separation of Enantiomers: Resolution

❖ Resolution – separation of two enantiomers

e.g. 

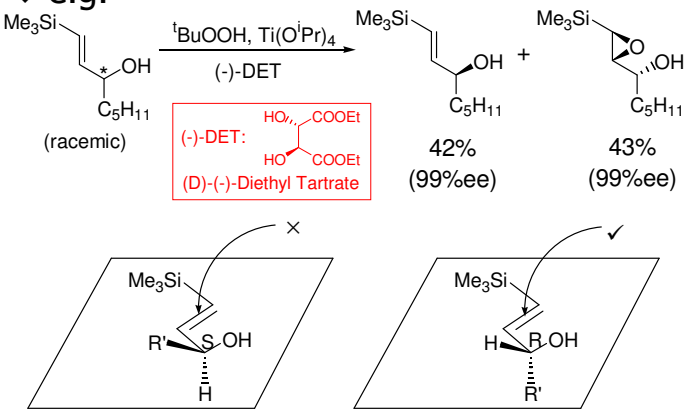
usually separable either by flash column chromatography or recrystallization etc.

❖ Kinetic Resolution



- One enantiomer reacts "fast" and another enantiomer reacts "slow"

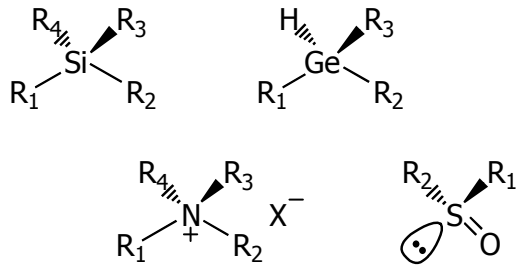
❖ e.g.



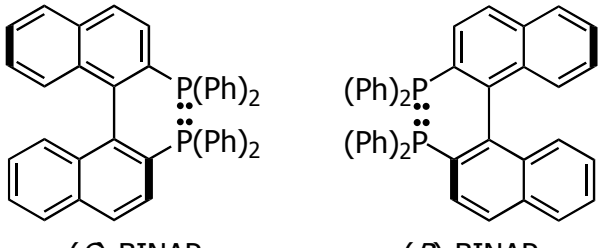
* stop reaction at ≤ 50%

* maximum yield = 50%

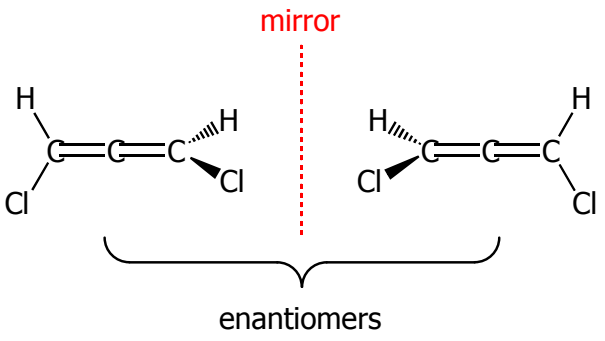
17. Compounds with Chirality Centers Other than Carbon



18. Chiral Molecules That Do Not Possess a Chirality Center



enantiomers



enantiomers

END OF CHAPTER 5