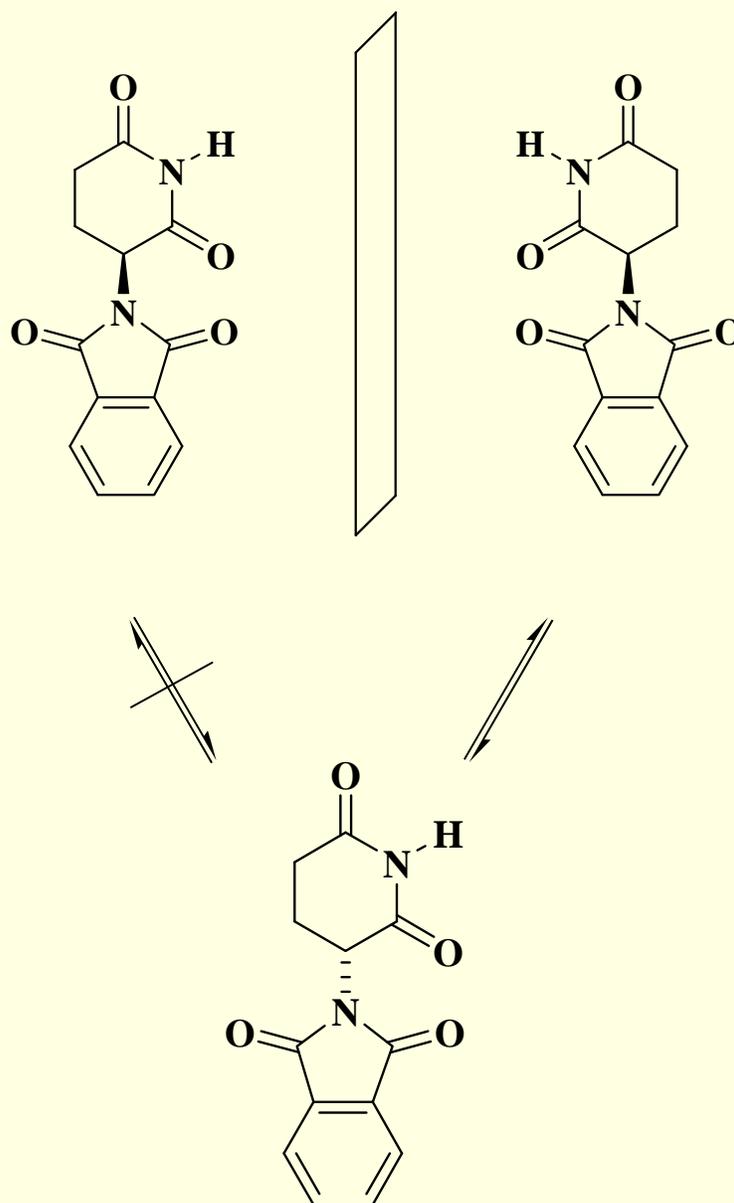


Chapter 9: Stereochemistry

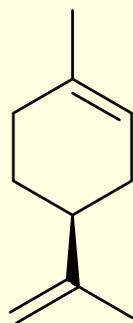
Two forms of Thalidomide

- One is a sedative used in 1960's
- One caused birth defects

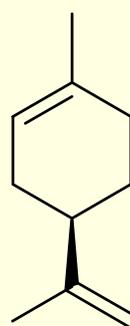


Chapter 9: Stereochemistry

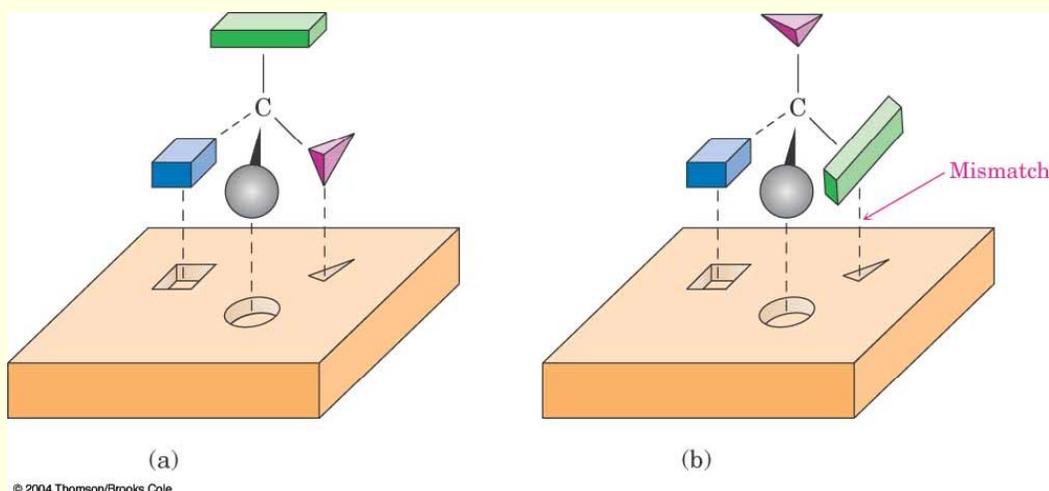
Stereoisomers of Limonene: Lemons vs Oranges



S-(-) Limonene
(lemons)



R-(+) Limonene
(oranges)



Stereochemistry Vocabulary

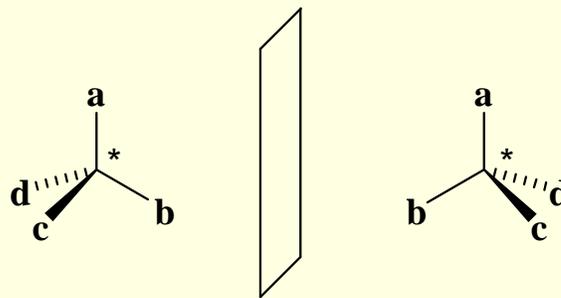
Enantiomers = non-superimposable mirror images (stereoisomers)

Chiral molecules = molecules that are not superimposable with mirror image (handedness)

Achiral molecules – molecules that are superimposable with mirror image (have some symmetry element)

Chiral Centers = tetrahedral C sp^3 bonded to four different groups (stereocenter)

Configurational Isomers = stereoisomers that differ in their configuration of a chiral center



How do we differentiate these two enantiomers?

- By name?
- Chemically? Enantiomers have same physical properties (mp, bp, etc)

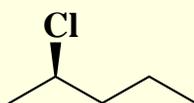
Configurations of Chiral Centers

IUPAC sequence rules for R and S Configuration

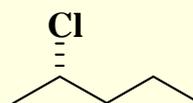
1. Assign priority letters to the four groups (A-D) using same rules we used for E & Z alkenes (based on atomic number of atoms connected to chiral center, if same find first point of difference; multiple bonds count multiple times).
2. View molecule so group D points away from you.
3. Trace from group A to B to C:

Clockwise = R

Counterclockwise = S

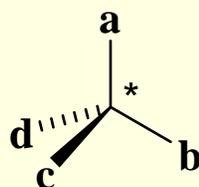


(2R) – 2-chloropentane



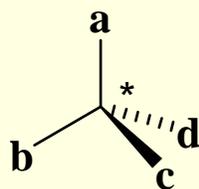
(2S) – 2-chloropentane

R



- easy when group D already points away from you

S

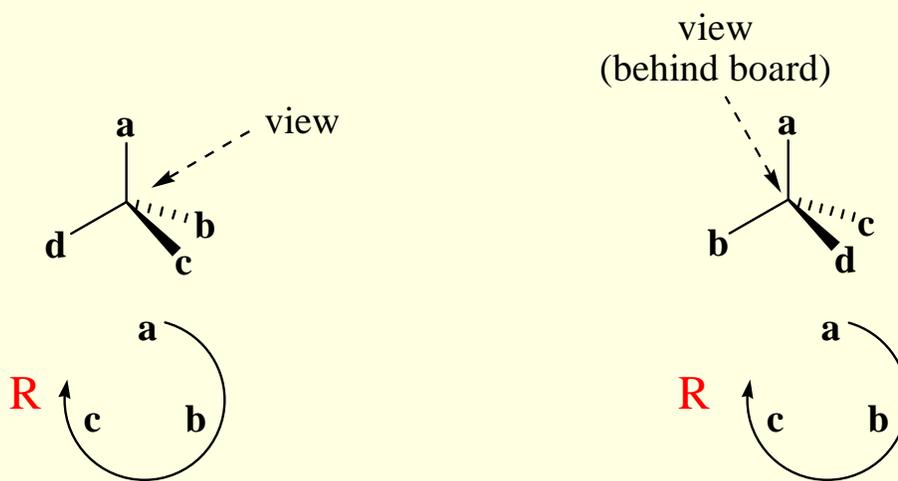


- note the wedge and dash are always next to each other

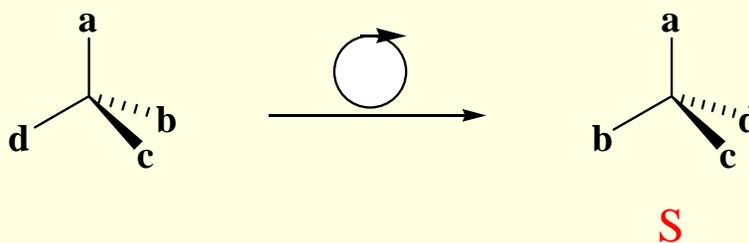
Configurations of Chiral Centers

What do you do when group D does not point away from you?

1. View from a different perspective:



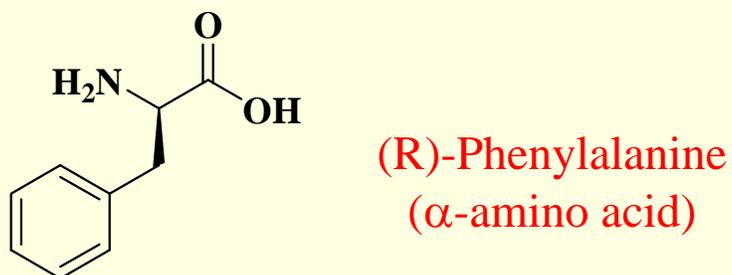
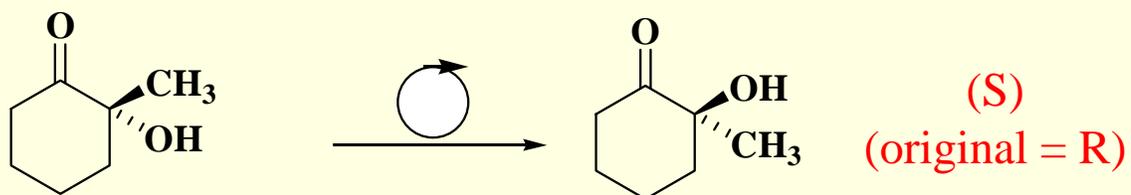
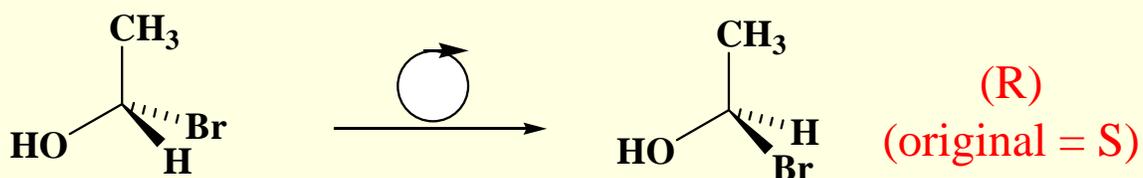
2. Shortcut – if you switch two groups (on paper) you invert stereocenter (go from R to S and vice versa)



So original must be R!

(Note that a second switch would give you the R enantiomer again)

Configurations of Chiral Centers



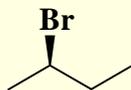
Optical Activity: Rotation of Plane Polarized Light

How do you physically tell the two enantiomers apart?

- Clockwise = dextrorotatory (+)
- Counterclockwise = levorotatory (-)
- Enantiomers rotate equally in opposite direction

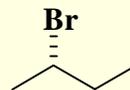
Specific Rotation $[\alpha]_D = \frac{\alpha}{c \times l}$

α = observed rotation ($^\circ$)
 c = concentration (g/mL)
 l = path length (dm)



(2R) – 2-bromobutane

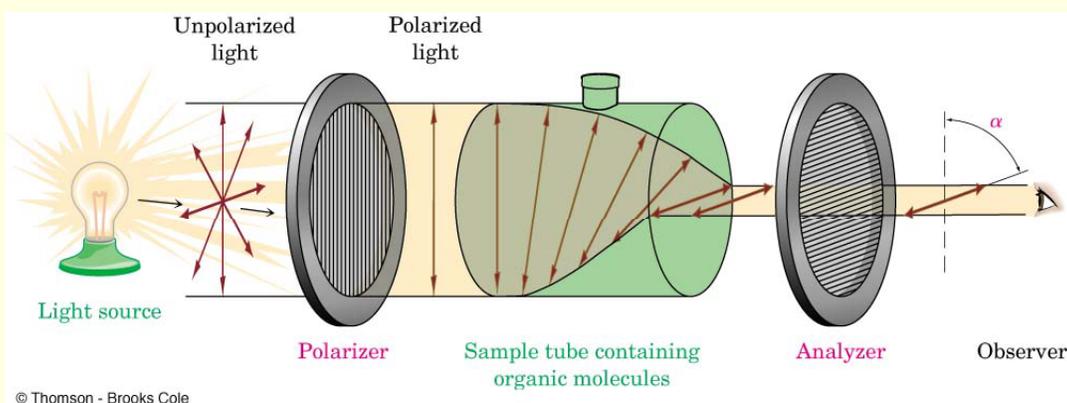
$$[\alpha]_D = -23.1^\circ$$



(2S) – 2-bromobutane

$$[\alpha]_D = +23.1^\circ$$

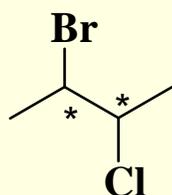
Note: No correlation between R & S with (+) and (-)



Compounds with Multiple Chiral Centers

Now how many stereoisomers are possible?

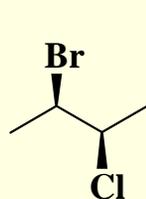
- For n chiral centers, 2^n possible stereoisomers



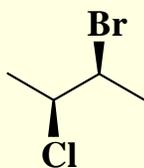
$2^2 = 4$ stereoisomers

2-bromo-3-chlorobutane

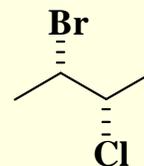
(2R, 3R) (2S, 3S)
(2R, 3S) (2S, 3R)



(2R, 3R)

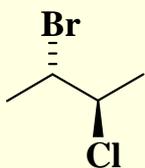


(2S, 3S)

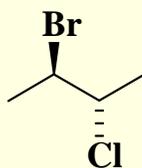


(2S, 3S)

- For enantiomers, configuration at every chiral center inverted



(2S, 3R)



(2R, 3S)

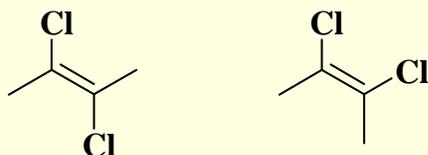
- How are these last two related to the first two?

Diastereomers

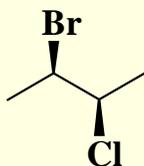
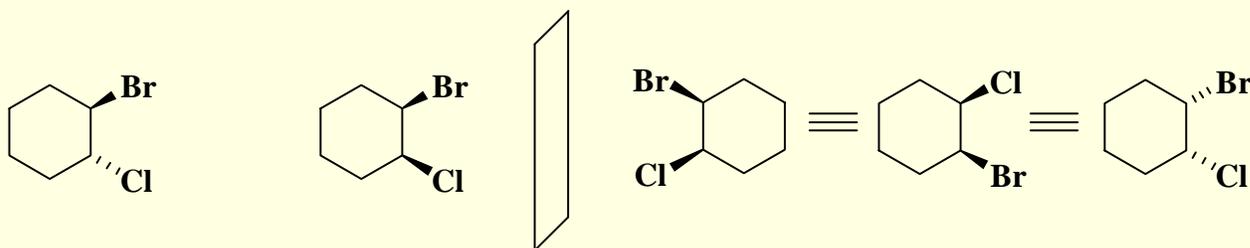
A new type of stereoisomers

Definition = stereoisomers NOT related as an object and its non-superimposable mirror image (not enantiomers)

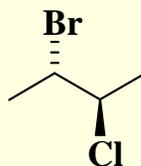
1. cis / trans diastereomers



2. configurational (R and S) diastereomers



(2R, 3R)



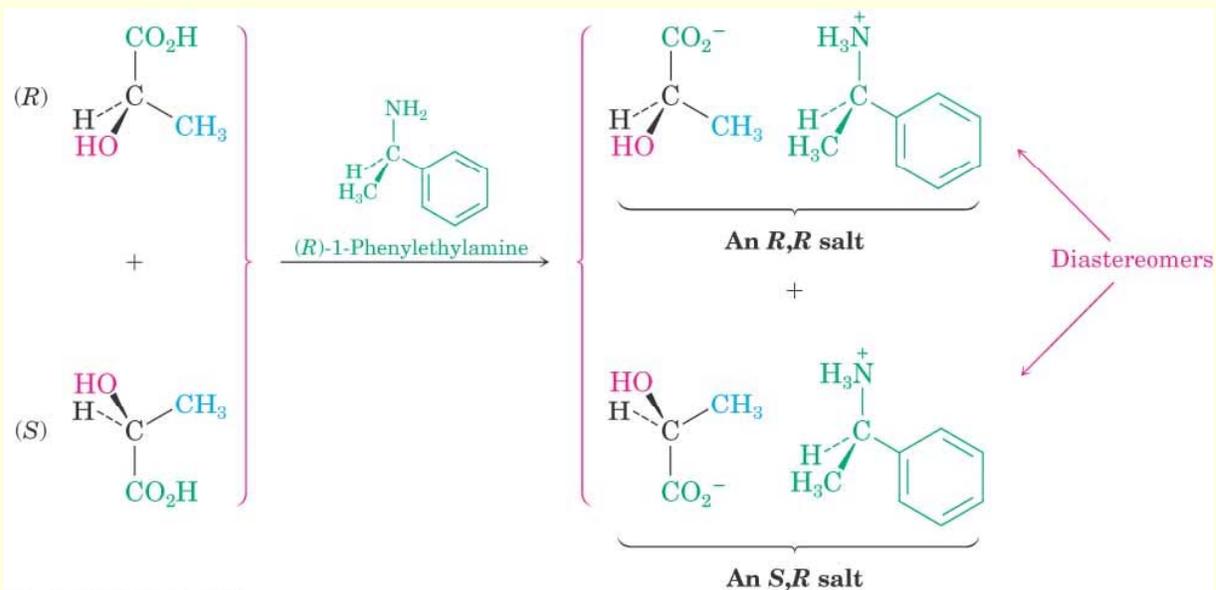
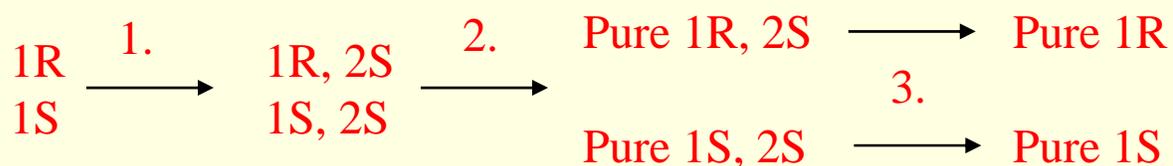
(2S, 3R)

- Do not have opposite configuration at every chiral center
- Unlike enantiomers, diastereomers have completely different physical properties (i.e. mp, bp, $[\alpha]$, etc)

Resolution

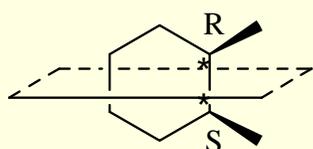
If enantiomers have the same properties, can you separate them?

1. Convert enantiomers into diastereomers
2. Separate diastereomers
3. Convert diastereomers back into pure enantiomers

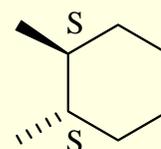
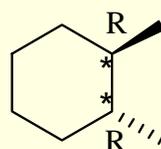


Meso Compounds

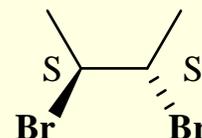
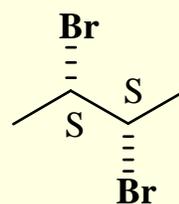
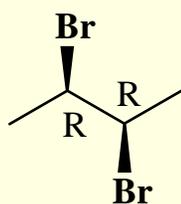
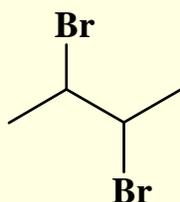
Molecules with chiral centers, but are achiral due to symmetry



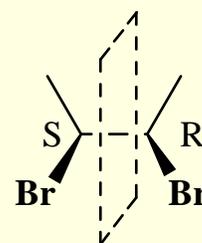
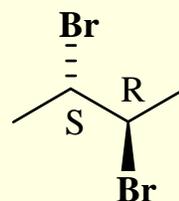
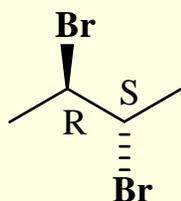
Plane of Symmetry
(Achiral)



Chiral
(no symmetry plane)



Enantiomers

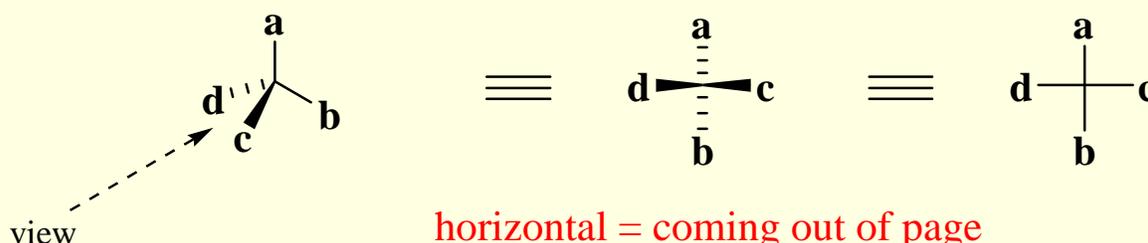


Meso (identical!)

2 identical chiral centers with opposite configuration

Fischer Projections

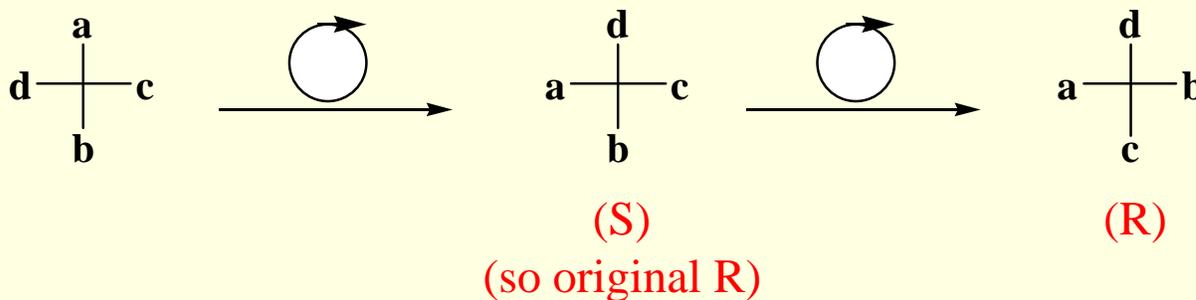
Alternative way to draw chiral centers



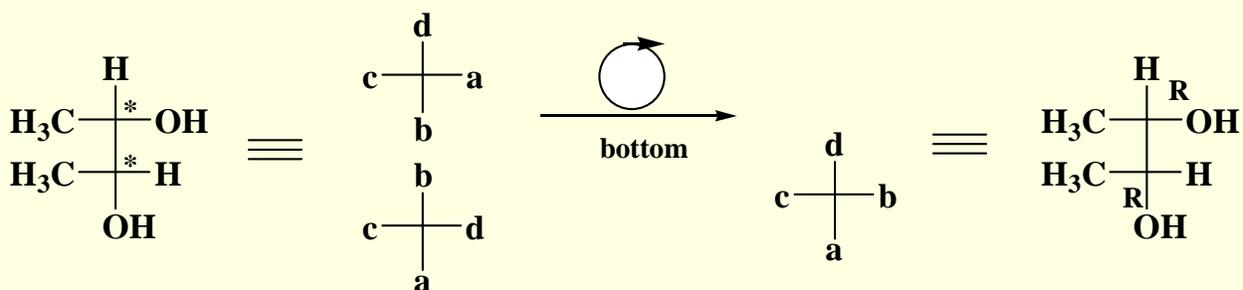
horizontal = coming out of page
vertical = going into page

To assign R/S configuration, place group “D” on top and trace from A to B to C

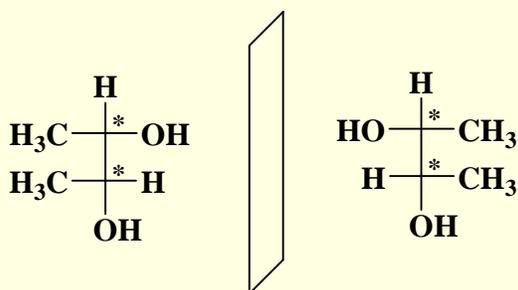
- Only certain ‘rotations’ allowed (180°)
- Easier to use method that switches groups



Fischer Projections: Multiple Chiral Centers



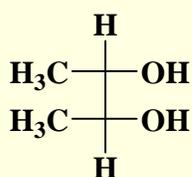
What does the enantiomer look like?



Confirm that this is the **S, S** stereoisomer

Any other stereoisomers possible?

Two chiral centers, $2^2 = 4$ possible (maximum)



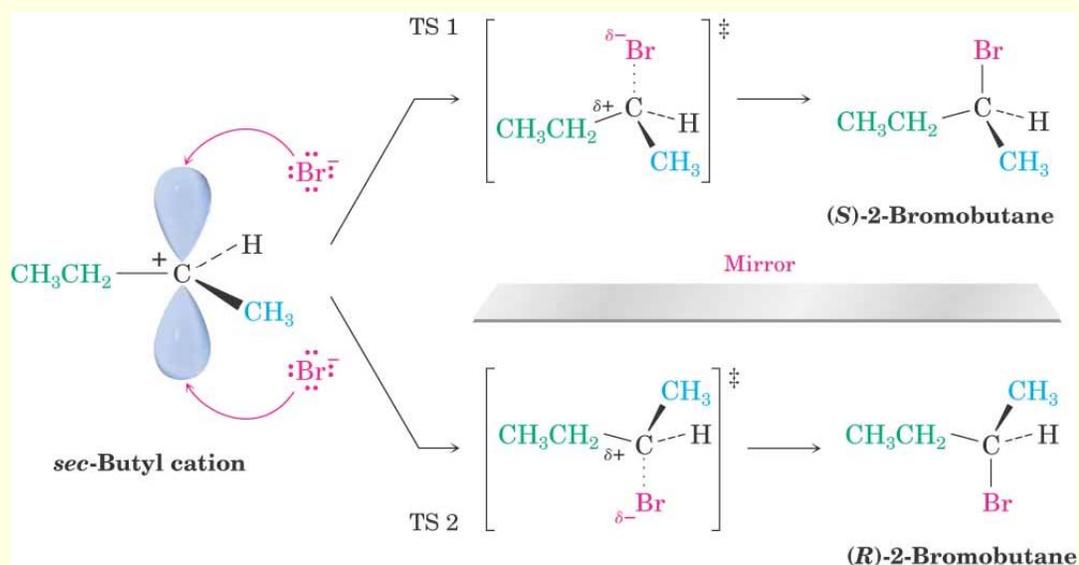
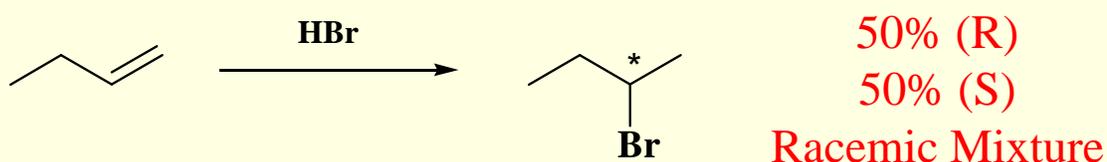
MESO! Only other stereoisomer possible
(total of three stereoisomers)
(R,S and S,R are identical)

Stereochemistry of Reactions

Part I: Reactions that make a chiral center

Achiral intermediates give achiral (racemic) products

- Carbocation intermediates
- Nuc can attack from 'top' or 'bottom'



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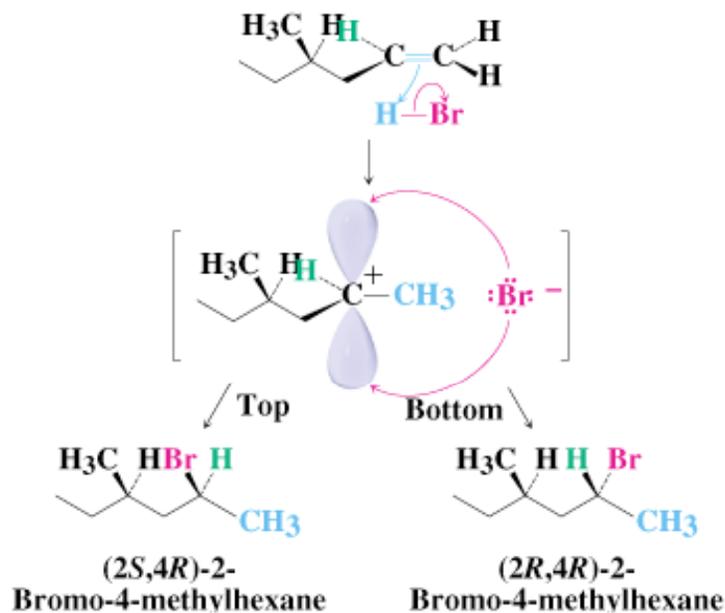
- The two transition states are enantiomeric, thus have equal energy so products form in equal amounts
- Achiral reagents lead to optically inactive products

Stereochemistry of Reactions

Part II: Chiral reactants that make new chiral centers

Chiral intermediates give chiral products

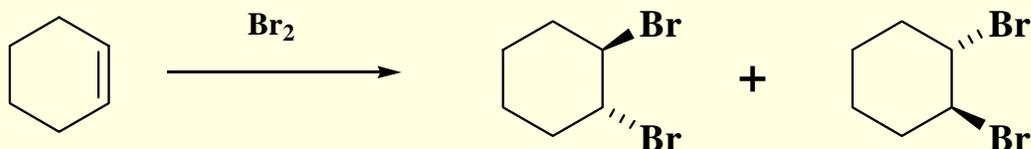
- form unequal mixtures of diastereomers
- transition states are now diastereotopic
(unequal energy so form in unequal amounts)



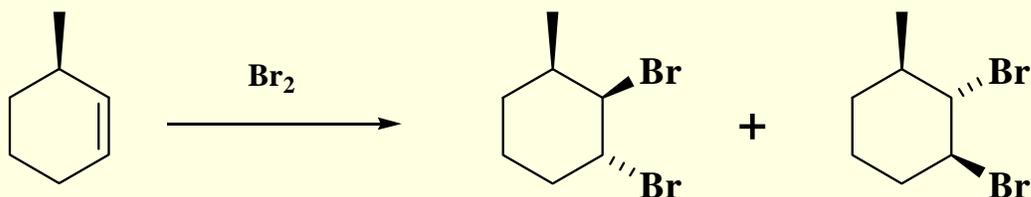
- Optically active reactants leads to optically active products

Stereochemistry of Reactions

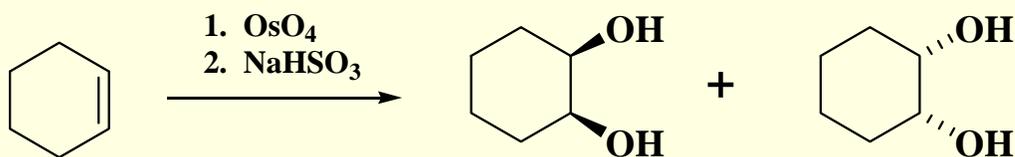
Examples



Equal amounts (racemate)
(optically inactive)



Unequal amounts (diastereomers)
(optically active)

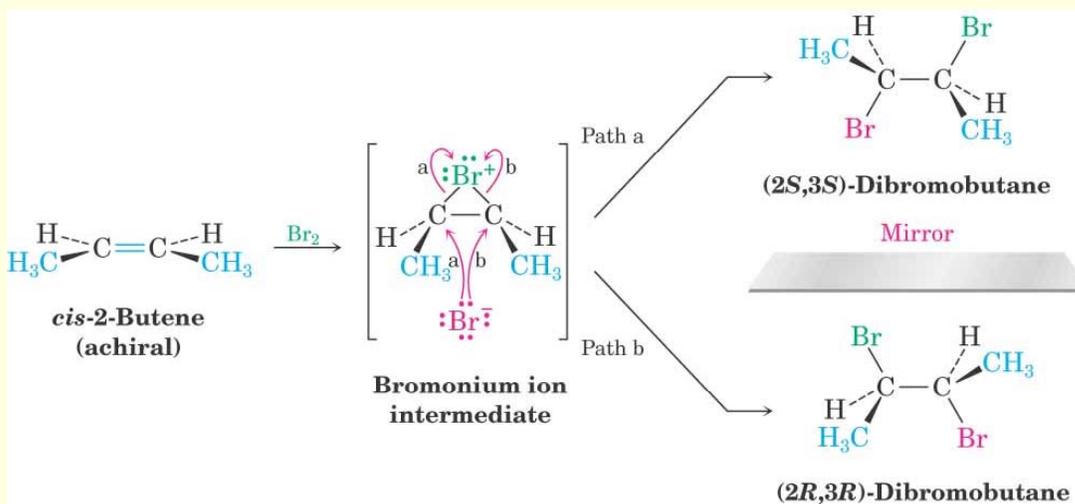


Meso – same product!
(optically inactive)

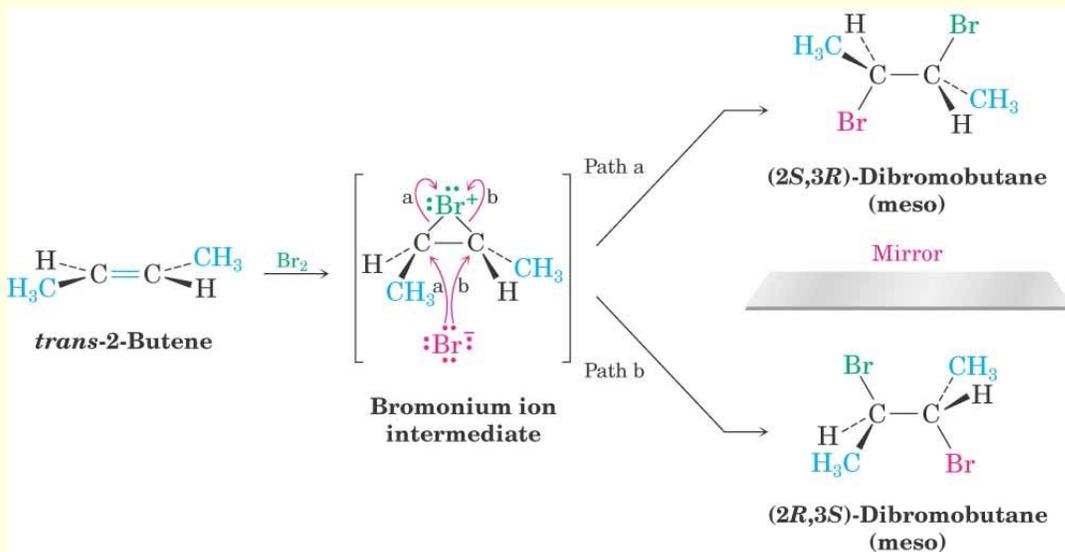
Stereochemistry of Reactions

Stereoselectivity - predominant formation of one of several possible stereoisomeric products

Cis and trans 2-butene produce different stereoisomeric products



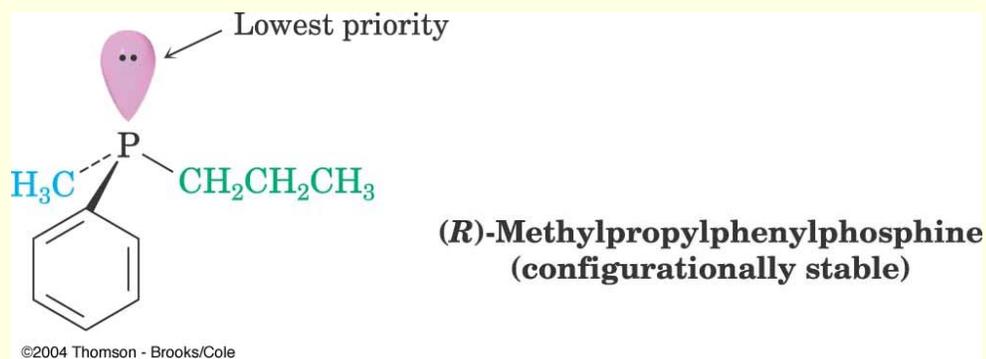
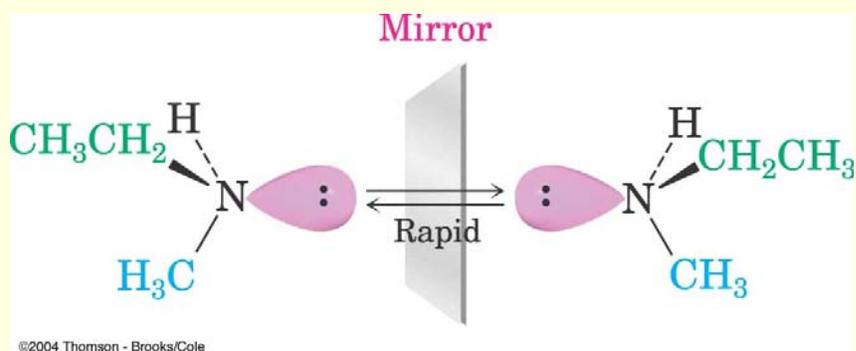
© 2004 Thomson/Brooks Cole



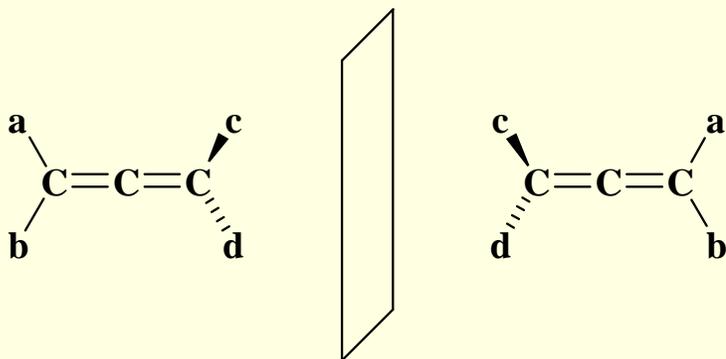
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Chirality at Atoms Other than Carbon

Requires tetrahedral atom with four unique groups



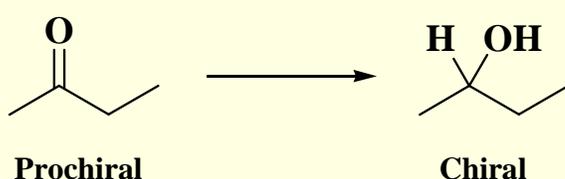
Chirality without chiral centers:



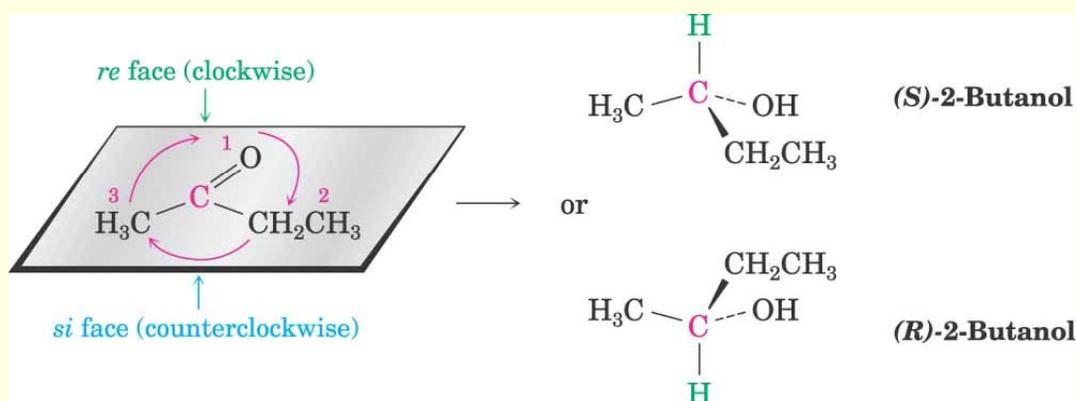
Prochirality

If an achiral molecule can be turned into a chiral molecule in a single chemical step it is "Prochiral"

sp² Prochiral Centers: Re and Si Faces



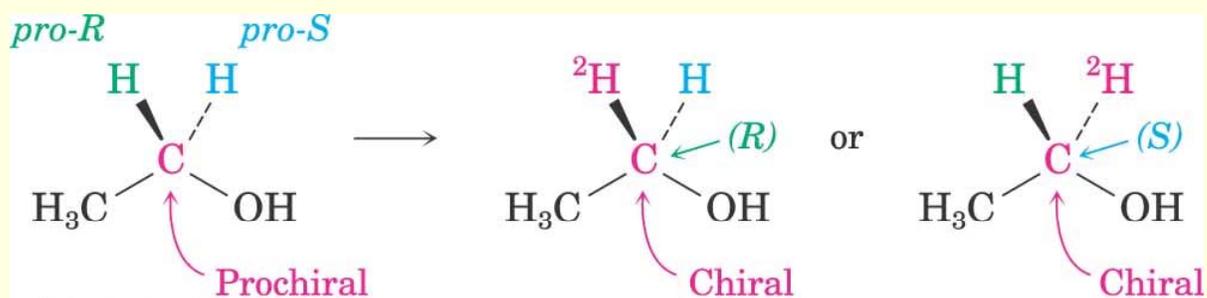
Produce a Racemic Mixture



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Note Re does not necessarily give (R) product!

sp³ Prochiral Centers: Pro-R and Pro-S



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