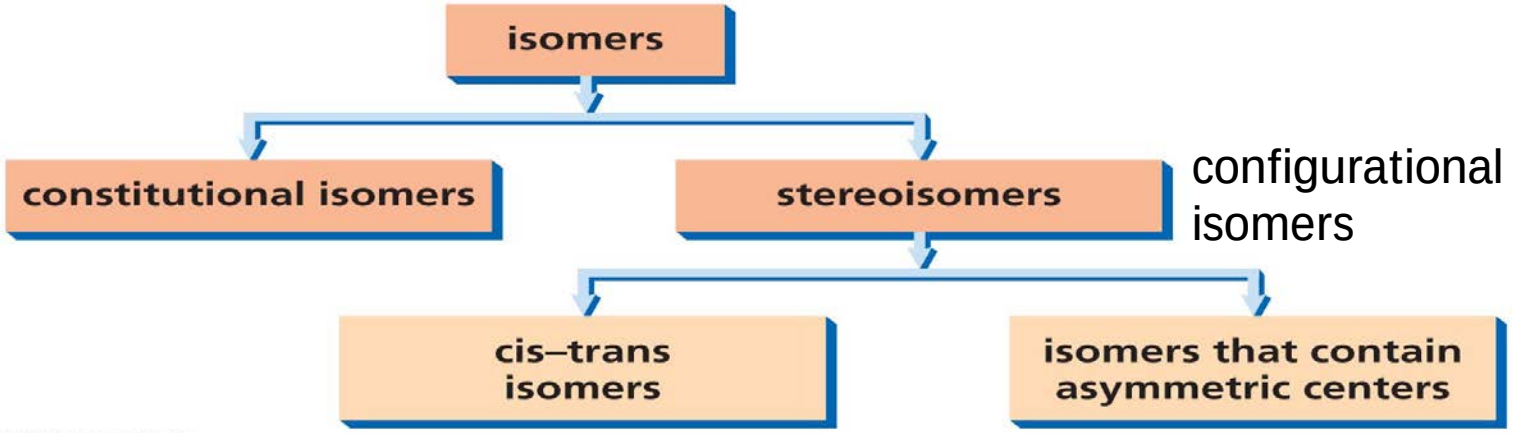
Chapter 5

Stereochemistry

Chirality and isomers

Stereoselectivity of reactions

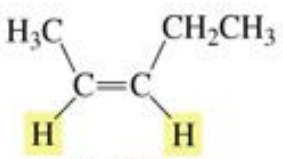
Isomers



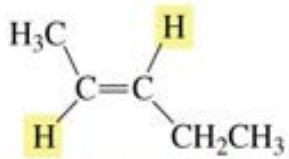
configurational isomers

geometric isomers

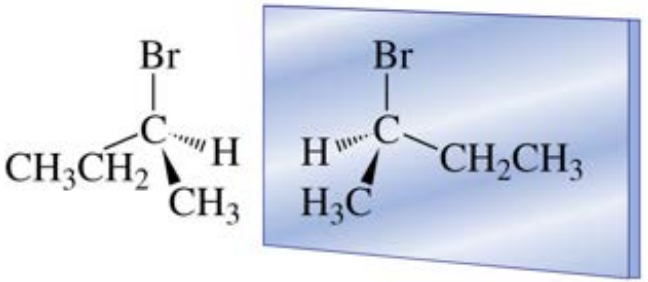
(optical isomers)

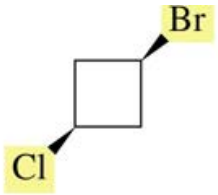


cis-2-pentene

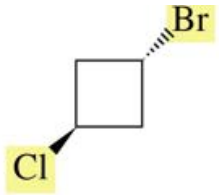


trans-2-pentene





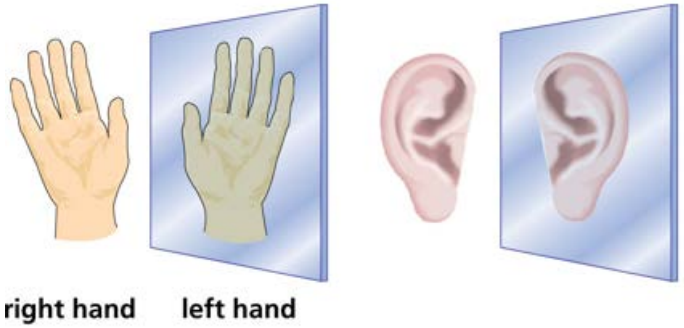
cis-1-bromo-3-chlorocyclobutane

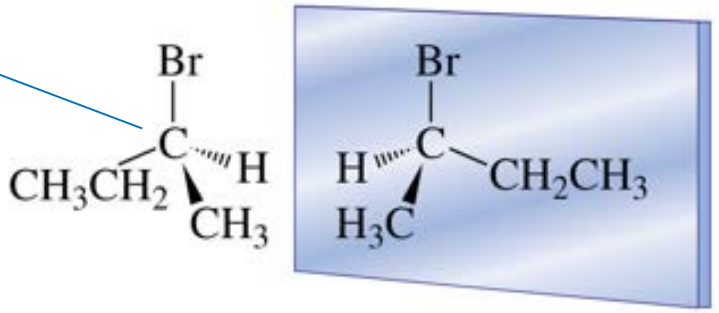


trans-1-bromo-3-chlorocyclobutane

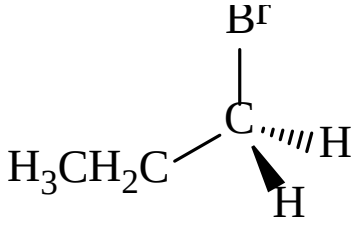
Chirality = handedness

- chiral object or molecule has
  - non-superimposable mirror image
  - asymmetric center

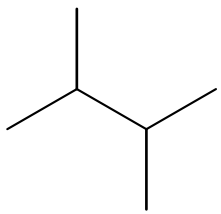


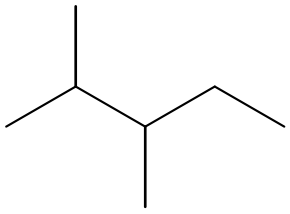


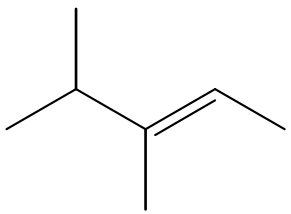
- achiral object or molecule has plane of symmetry

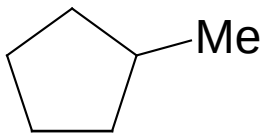


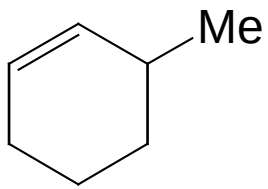
- chiral? achiral? Find
  - asymmetric center [= C with 4 different groups] → chiral
  - plane of symmetry → achiral ~ always true

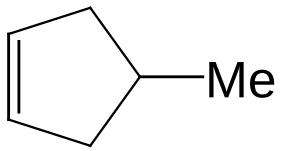


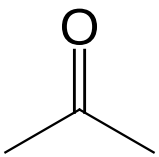


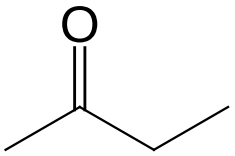


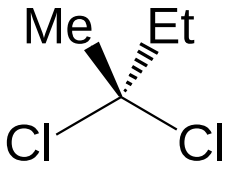


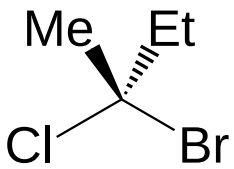




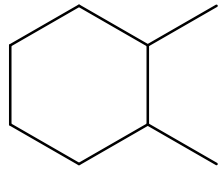








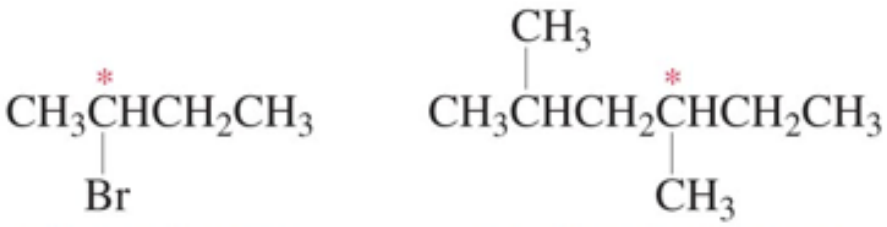
not always true



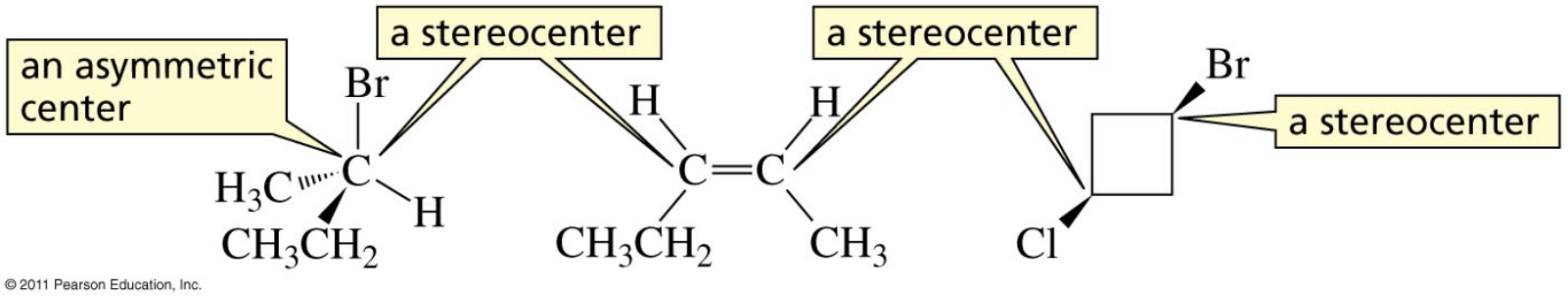
Asymmetric center

- atom bonded to 4 different groups

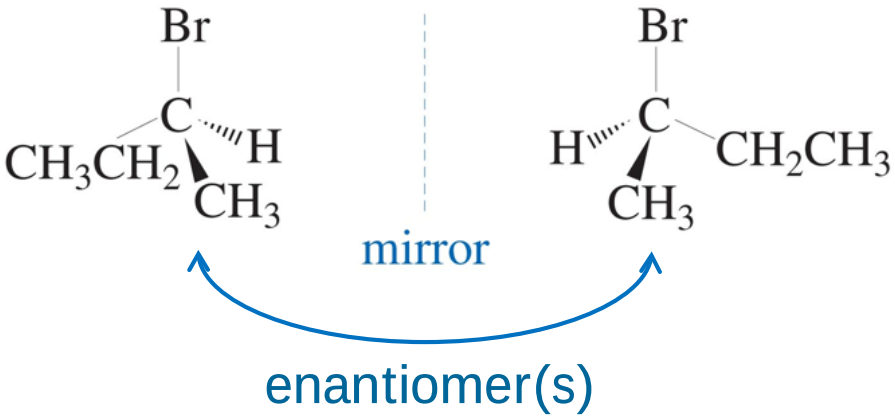
  = asymmetric carbon = chiral(ity) center = chiral carbon



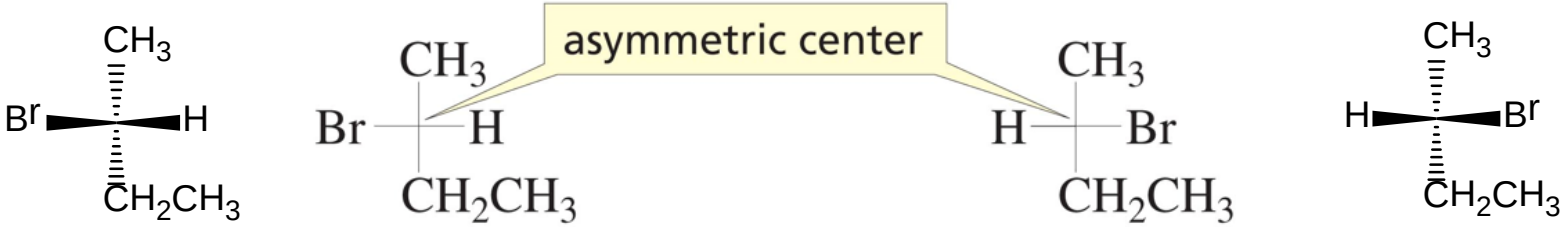
- stereocenter and asymmetric center



Enantiomer(s)



- Fischer projection
  - Horizontal bonds project above the paper; vertical bonds projects behind the paper.
    - Usually, C-C vertical, subs horizontal

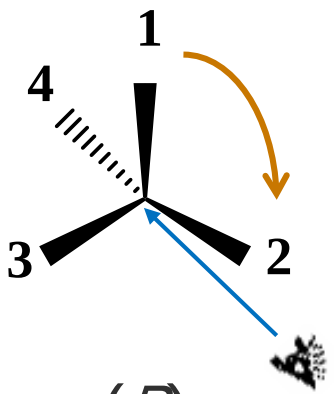


R,S designation of enantiomers

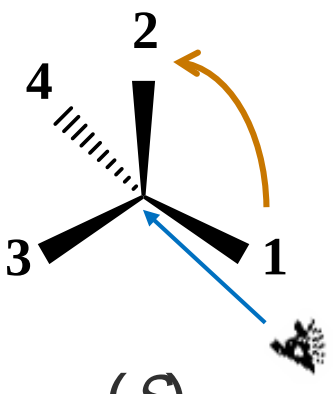
1. Find the asymmetric center.
2. Assign priority of the groups (1, 2 , 3, 4).
   - Using Cahn-Ingold-Prelog rules
3. View from asymmetric center to group 4.
4. Determine the direction from group 1 to 2.
   - Clockwise ~ (*R*)
   - Counterclockwise ~ (*S*)

R ~ rectus ['right']
S ~ sinister ['left']

'*R* for right-turn'

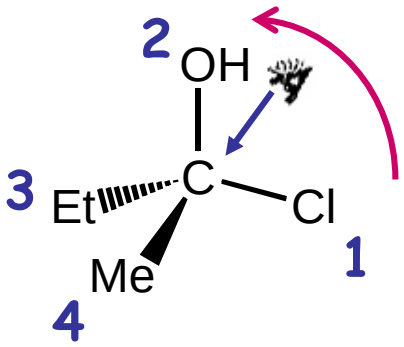


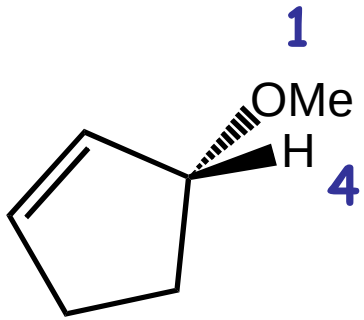
(*R*)

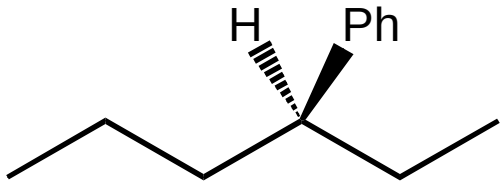


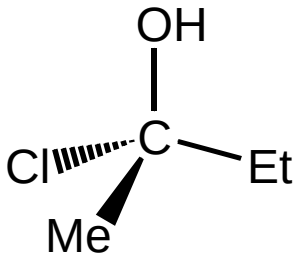
(*S*)

- Practice!

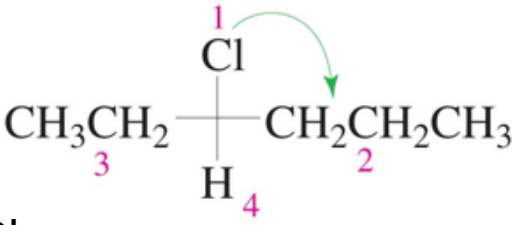


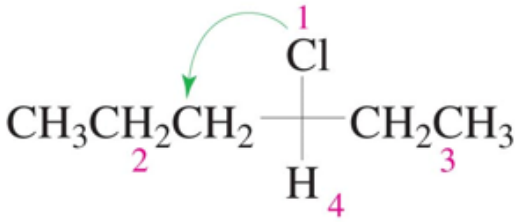


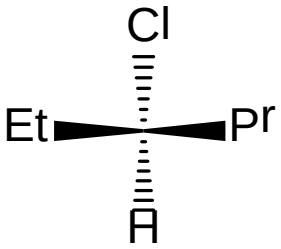


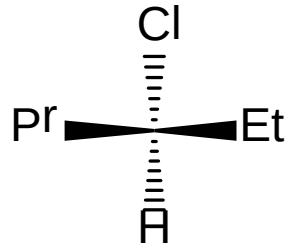


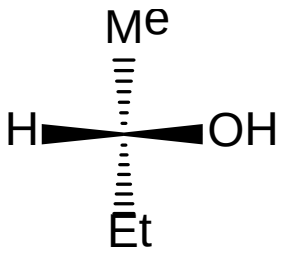
- *R*,*S* in Fischer projection

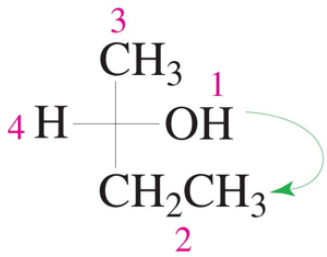


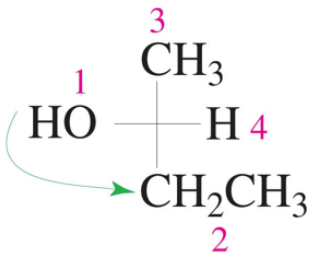


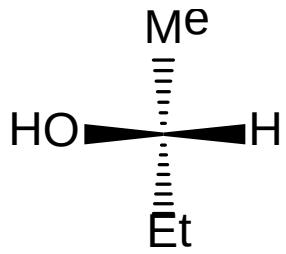












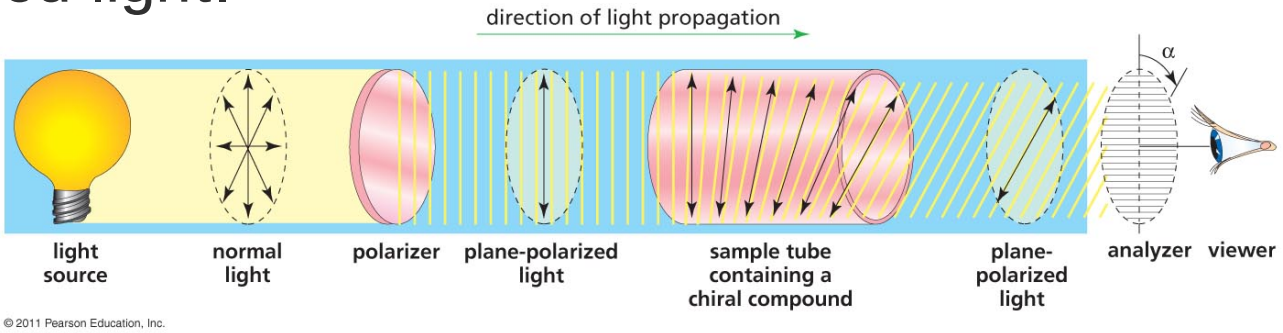
Properties of enantiomers

- For an enantiomeric pair:
  - properties that are not chiral are the same
    - properties observed in achiral environment
    - mp, bp, $\Delta H_{combustion}$,
    - solubility to achiral solvent, reactivity to achiral comp'd
  - properties that are chiral are different
    - properties observed in chiral environment
    - solubility to chiral solvent
    - reactivity with an enantiomer of a chiral comp'd
      - odor, drug [medicine]
    - optical rotation

hand
mitten
glove

Optical activity

- Chiral compounds are optically active, and rotate plane-polarized light.

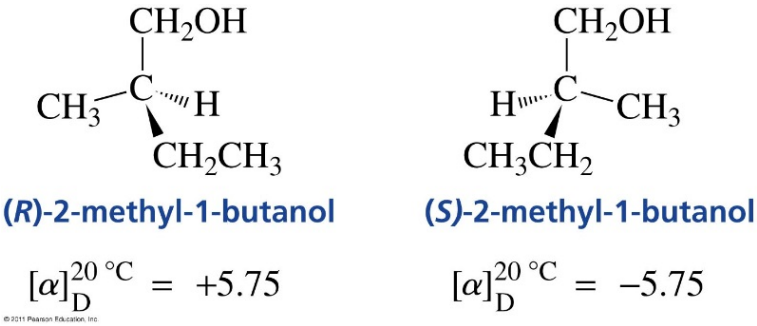


  - clockwise rotation ~ dextrorotatory ~ (+) or (*d*)
  - counterclockwise rotation ~ levorotatory ~ (–) or (*l*)
  - no rotation ~ not optically active [achiral] or racemic
    - racemate [racemic mixture] ~ 50/50 mixture of (+) and (–)
    - (±) or (*d,l*)

D/L ~ for carbohydrates

- relation between *R/S* and *+/–*? NO relation!
  - Observed rotation indicates only chirality and existence or excess of one enantiomer.

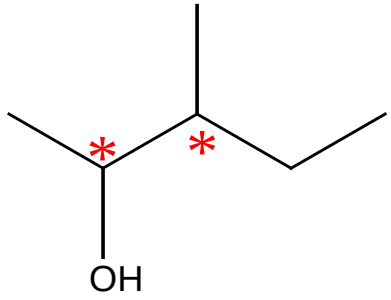
- specific rotation $$[\alpha]_{\lambda}^{T} = \frac{\alpha}{l \times c}$$
  - T ~ temperature (°C)
  - λ ~ wavelength (usually, D ~ sodium D-line, 589 nm)
  - α ~ observed raotation (degree)
  - l ~ length of sample tube (dm = 10 cm)
  - c ~ concentration (g/mL)
  - specific rotation for one enantiomer
    - not for racemate



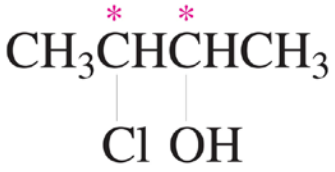
- enantiomeric excess [ee]
  - ee = observed [α] / [α] of pure enantiomer (%)
    - If [α] = 2.875 observed, ee = 50%. (50+25)% R + 25% S.

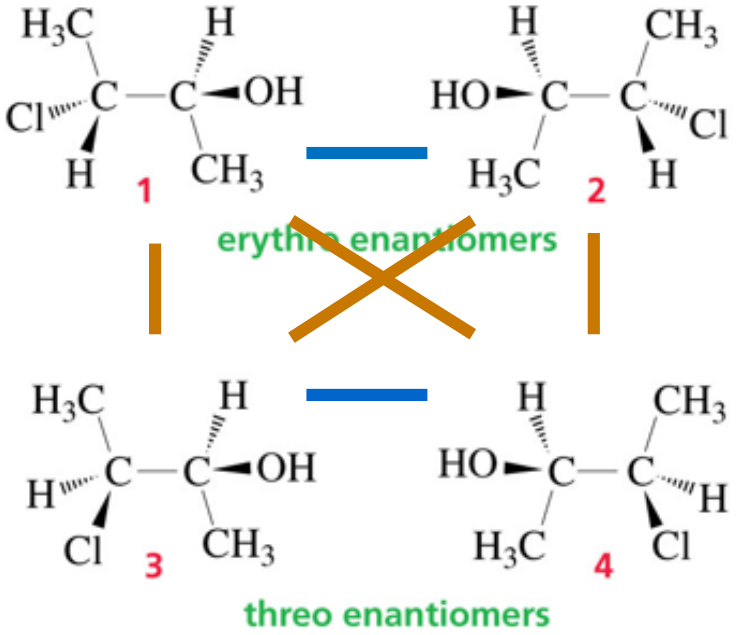
More than 1 asymmetric center

- # of stereoisomers
  - for molecules with *n* asymmetric centers [C*]
  - maximum number of stereoisomers = 2^n
- with 2 C*'s
  - 4 stereoisomers

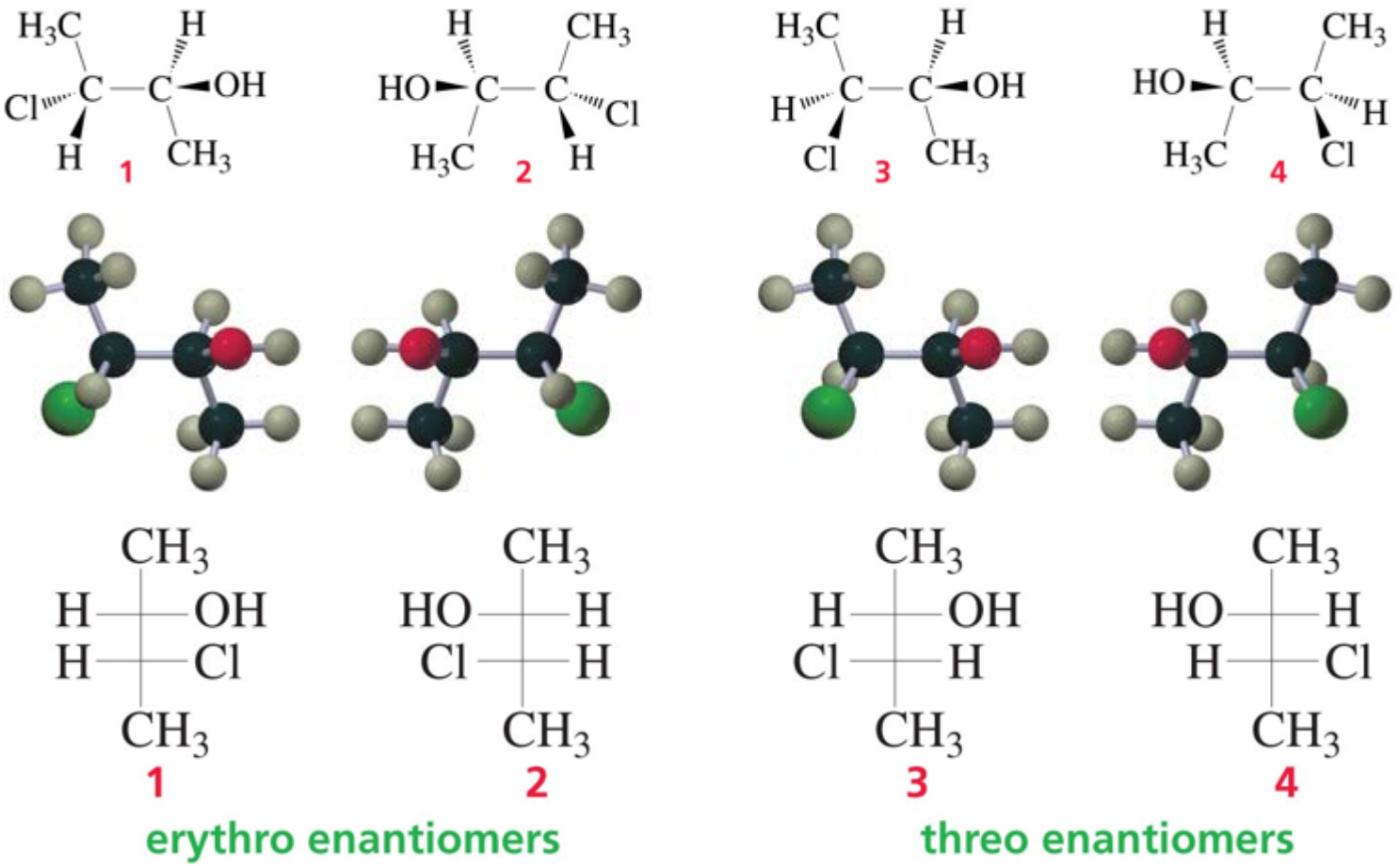


    - 2 enantiomers + 2 diastereomers
    - for 1 isomer, 1 enantiomer + 2 diastereomers
  - with *n* C*'s
    - for 1 isomer, 1 enantiomer and $2n - 2$ diastereomers

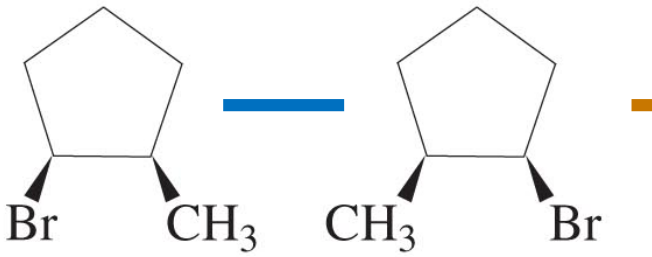




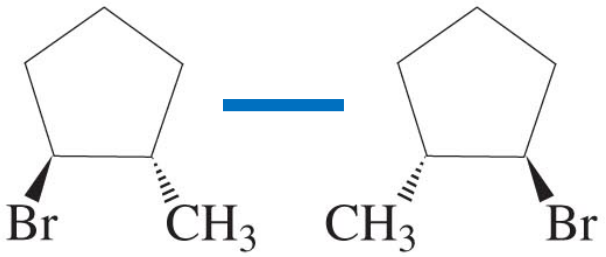
- Diastereomers are stereoisomers that are not enantiomers.
  - enantiomers ~ same achiral properties (mp, bp, ---)
    different chiral properties (+/– optical rotation)
  - diastereomers ~ different chiral and achiral properties
    - *Cis-trans* isomers are diastereomers.



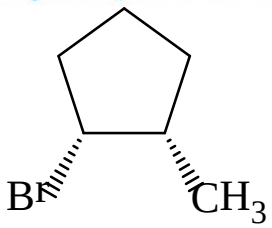
- erythro ~ similar group on the same side
- threo ~ on opposite sides in Fischer projection (eclipsed!)

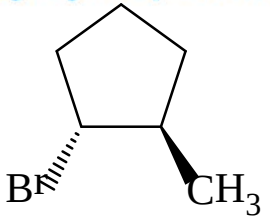


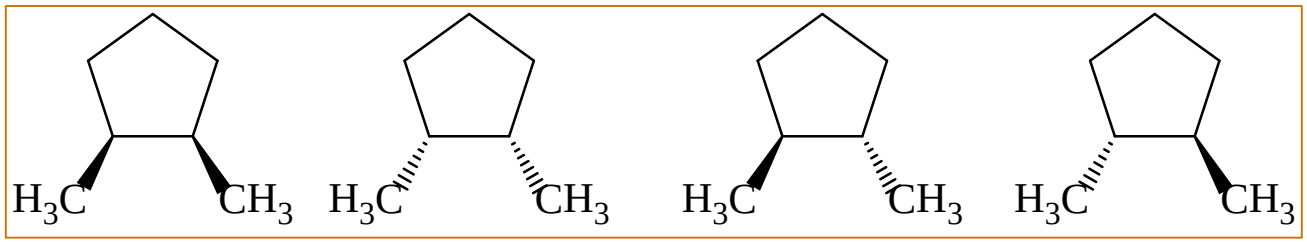
cis-1-bromo-2-methylcyclopentane



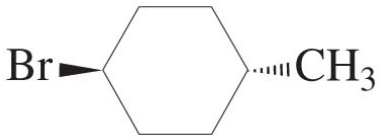
trans-1-bromo-2-methylcyclopentane







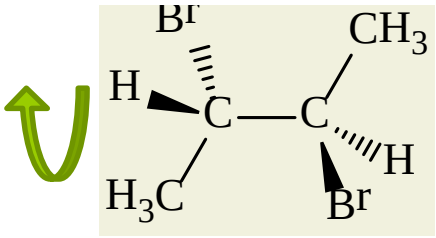
cis-1-bromo-4-methylcyclohexane

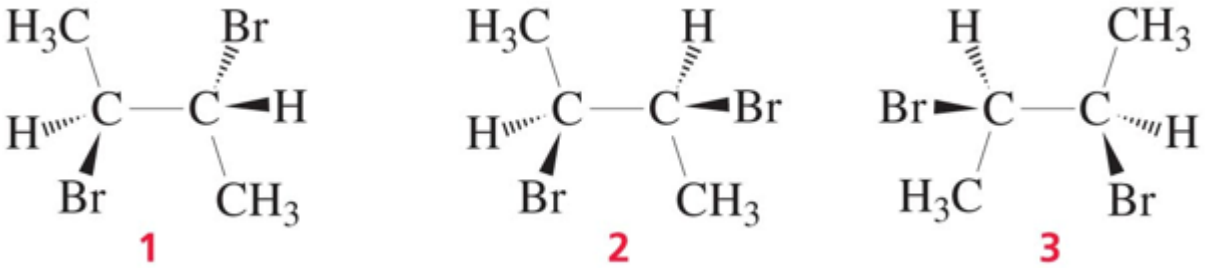


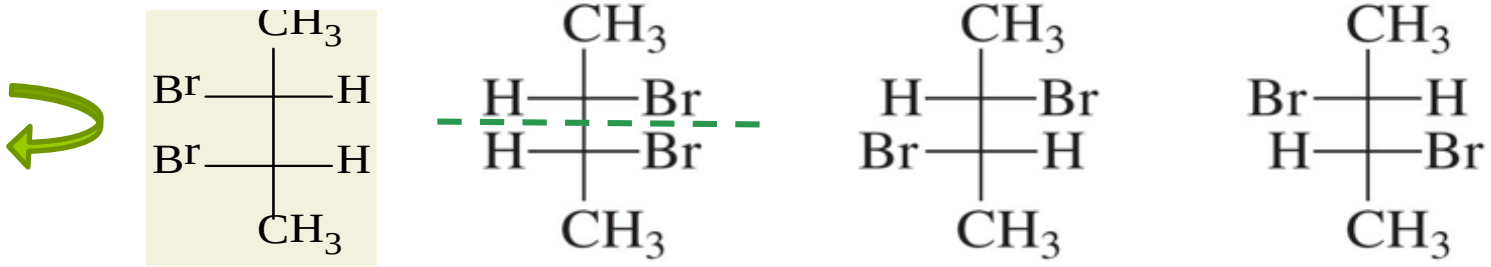
trans-1-bromo-4-methylcyclohexane

Meso compound

2 C*'s, only 3 stereoisomers
(1 meso and its 2 diastereomers)

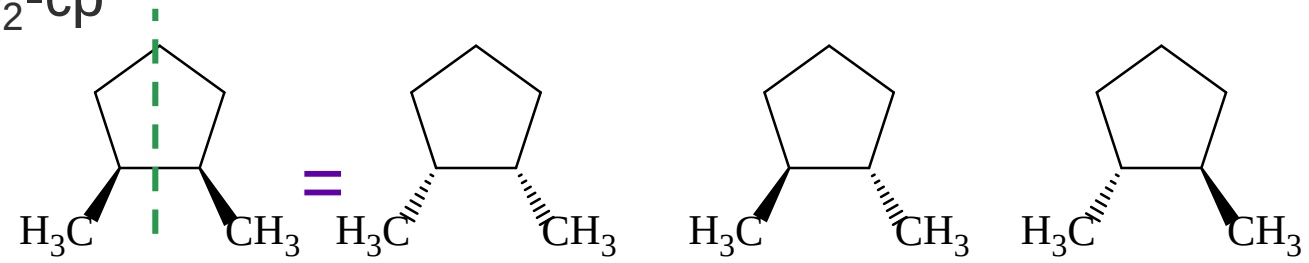




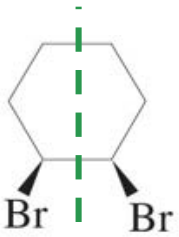


- meso compound [meso-stereoisomer]
  - superimposable mirror image ~ achiral
  - The 2 C*'s are bonded to the same 4 groups.

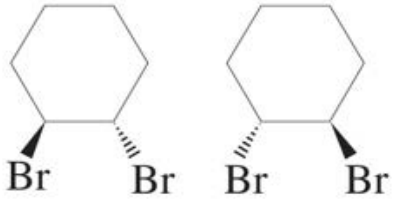
- Me_2-cp



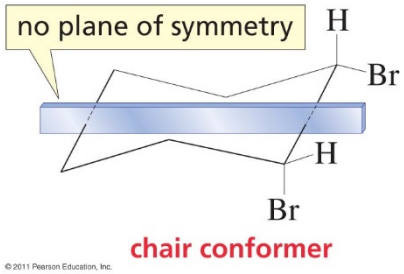
- Br_2-cx



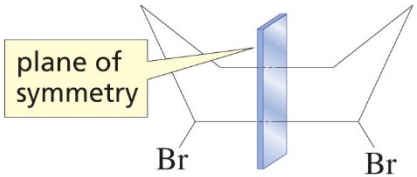
cis-1,2-dibromocyclohexane
a meso compound



trans-1,2-dibromocyclohexane
a pair of enantiomers

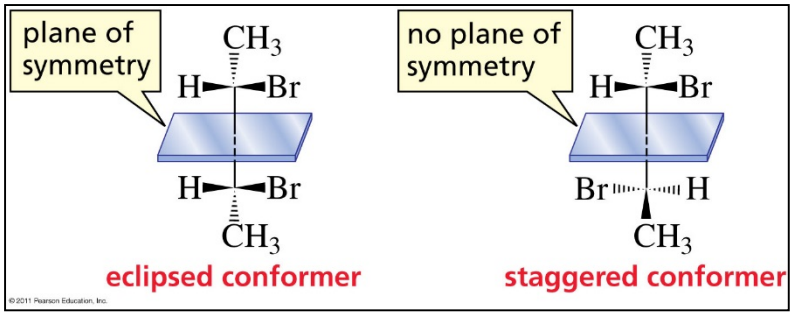


chair conformer



boat conformer

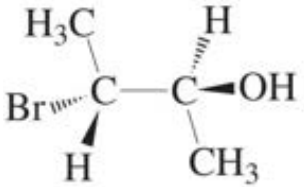
Still, achiral and meso



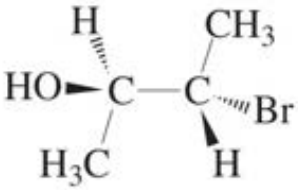
eclipsed conformer

staggered conformer

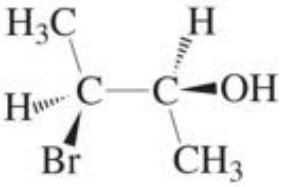
R,S for diastereomers



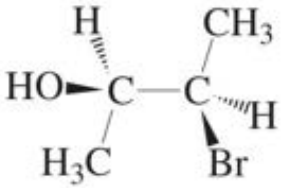
(2*S*,3*R*)-3-bromo-2-butanol



(2*R*,3*S*)-3-bromo-2-butanol

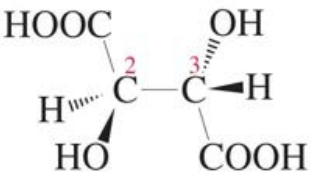


(2*S*,3*S*)-3-bromo-2-butanol

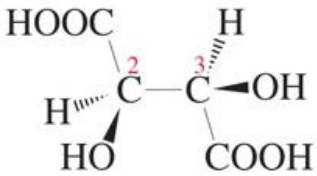


(2*R*,3*R*)-3-bromo-2-butanol

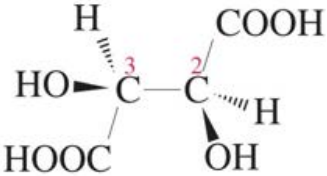
(2*S*,3*R*) =



(2*R*,3*S*)-tartaric acid
a meso compound



(2*R*,3*R*)-tartaric acid



(2*S*,3*S*)-tartaric acid

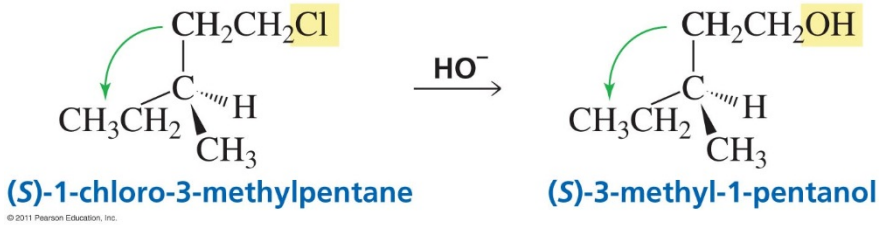
a pair of enantiomers

	Melting point, °C	Specific rotation	Solubility, g/100 g H_2O at 15 °C
(2*R*,3*R*)-(+)-Tartaric acid	171	+11.98	139
(2*S*,3*S*)-(−)-Tartaric acid	171	−11.98	139
(2*R*,3*S*)-Tartaric acid (meso)	146	0	125
(±)-Tartaric acid	206	0	139

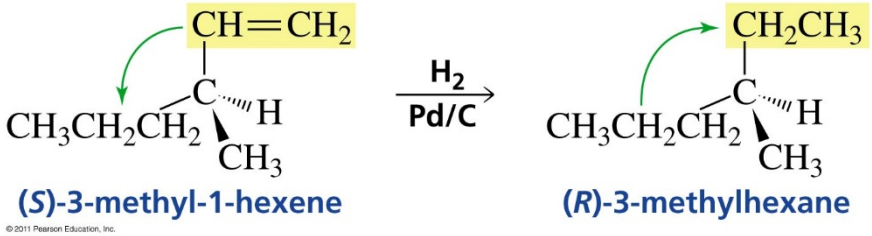
Absolute and relative configurations

- absolute config ~ *R* or *S*
- relative config ~ changed or not [the same or different]

- the same relative config ← not breaking bond to C*

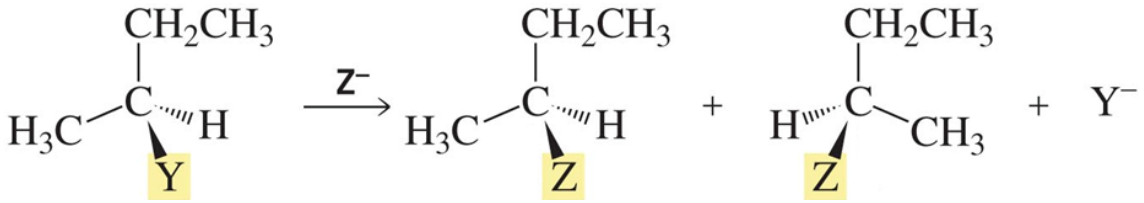


absolute config also the same



absolute config changed

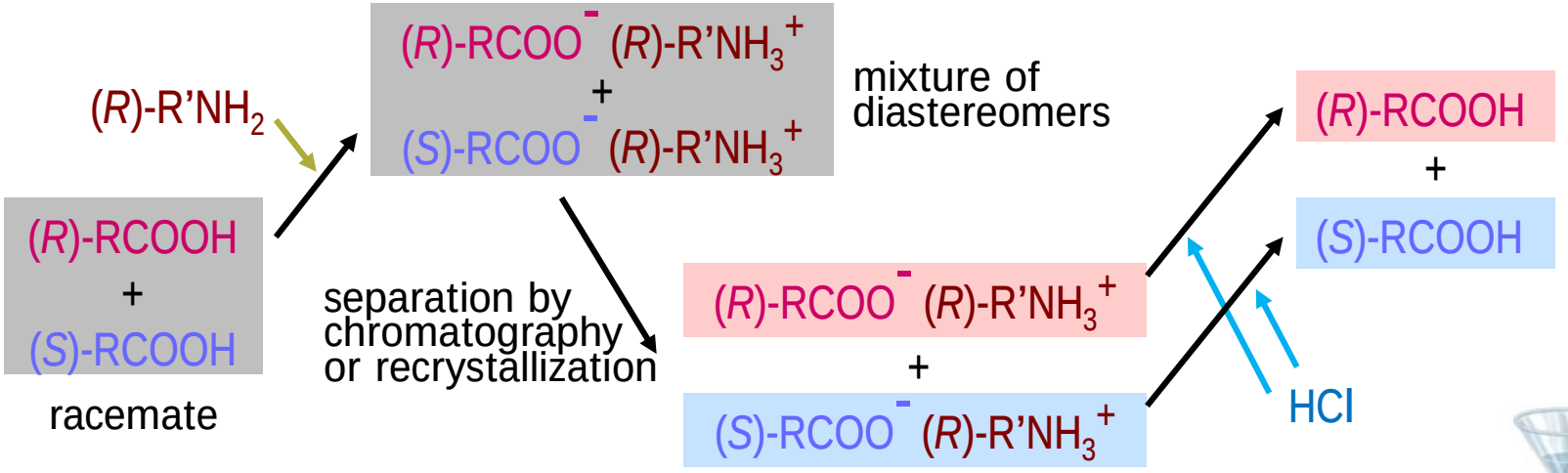
- relative config may change ← breaking bond to C*



Separation of enantiomers

- difficult, tedious, and costly

(1) converting to diastereomers

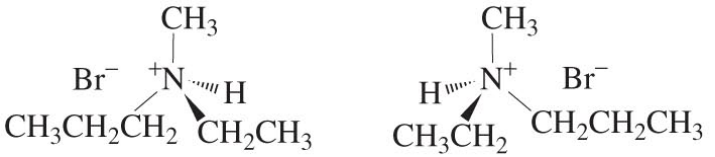


(2) selectively reacting one enantiomer with chiral reagent and/or chiral catalyst

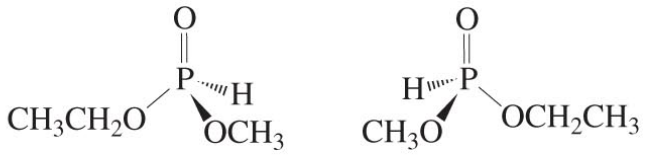
(3) chromatography with chiral stationary phase

Other chiral compounds

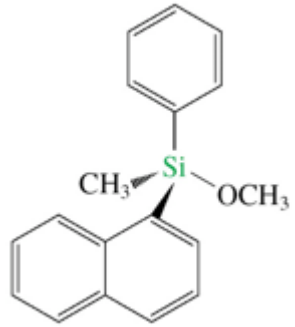
- other tetrahedral comp'ds



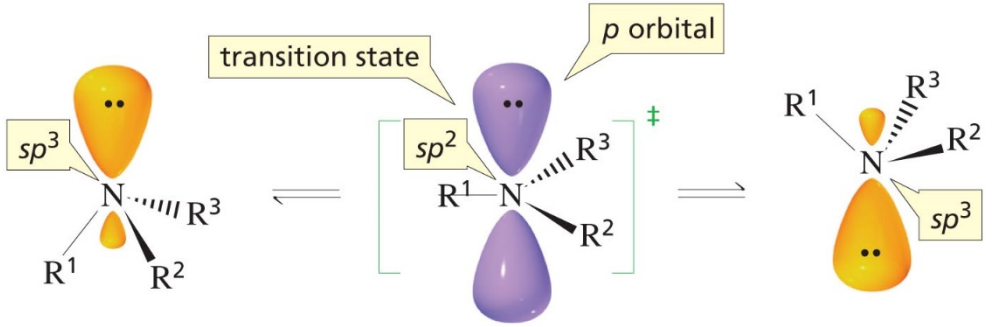
enantiomers



enantiomers

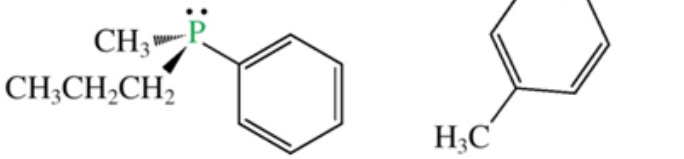


- pyramidal comp'ds
  - not separable

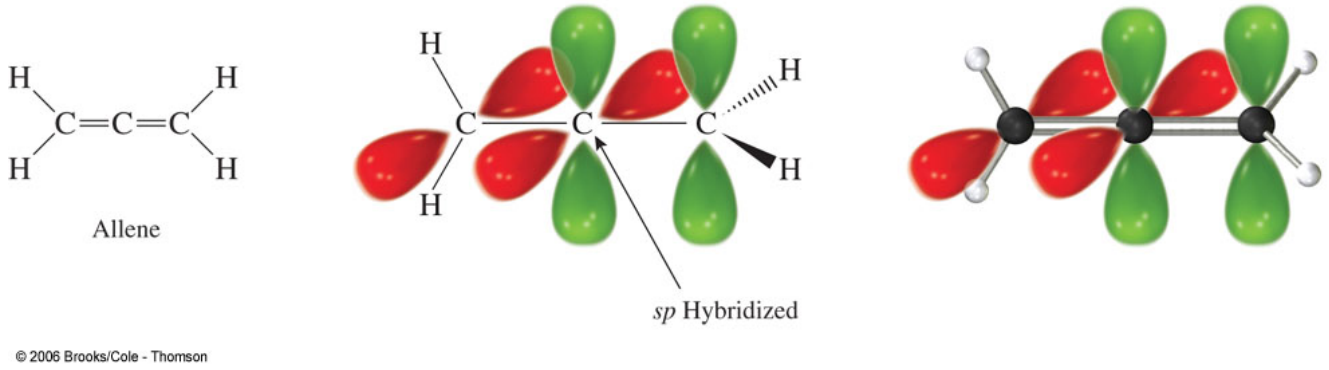


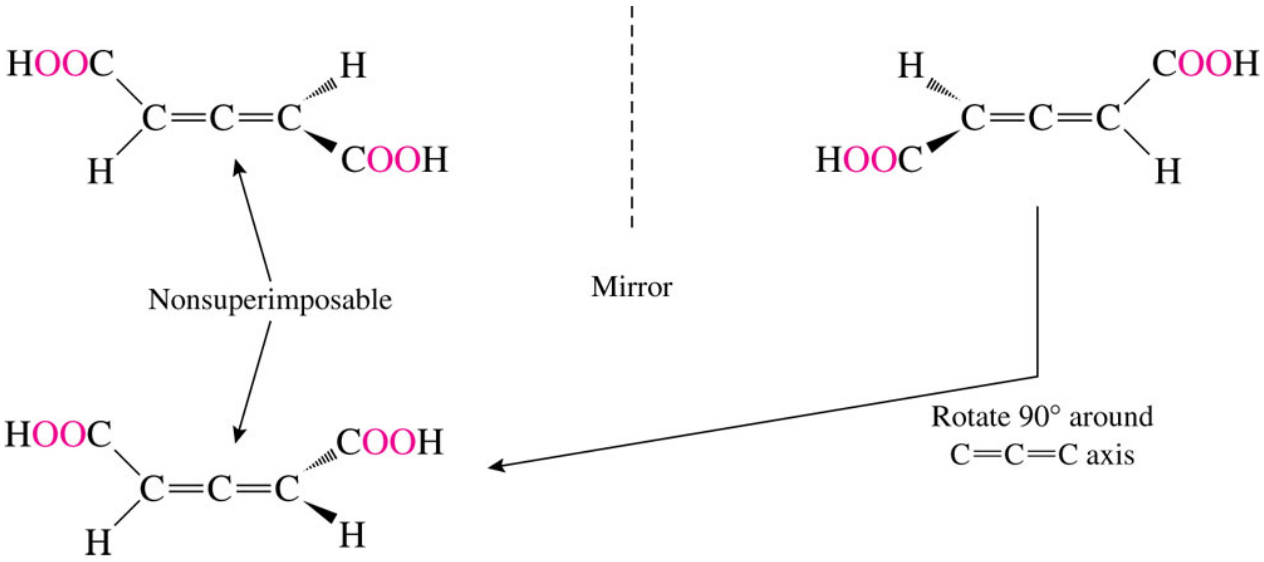
amine inversion

  - separable

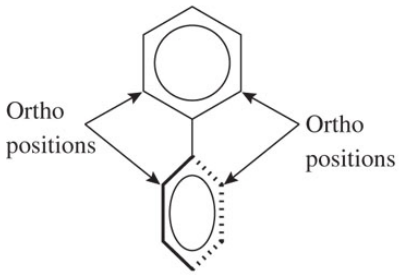


- substituted allenes

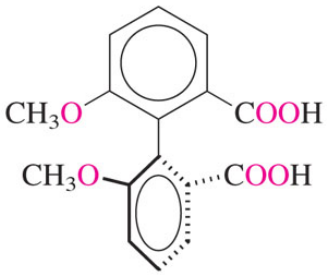


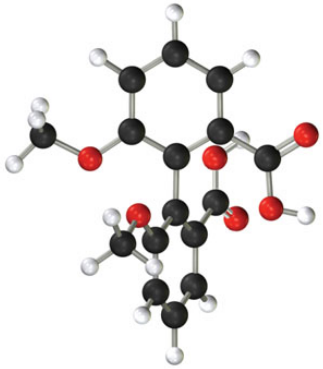


- substituted biphenyls



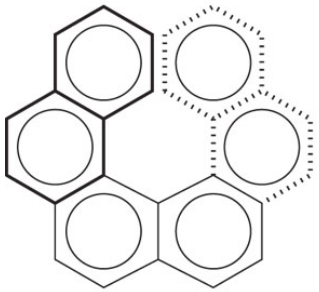
Biphenyl



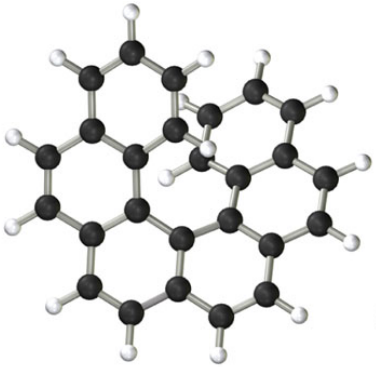


  - rings perpendicular ~ no plane of symmetry

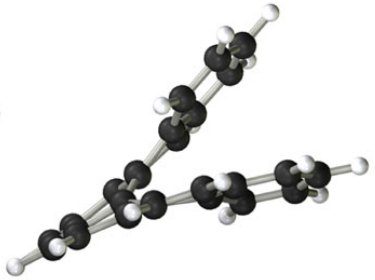
- helical molecules



Hexahelicene



Top view



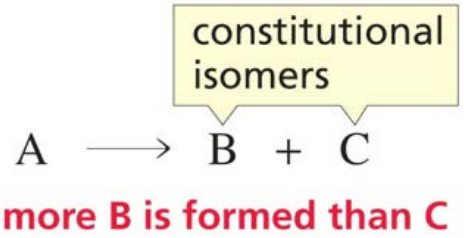
Side view

$[\alpha] = 3640$

  - right-handed and left-handed

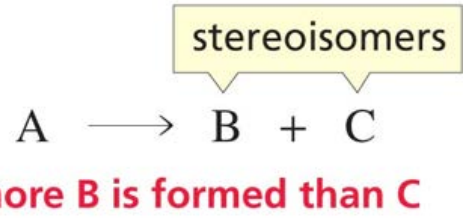
Stereochemistry of reactions

- regioselectivity



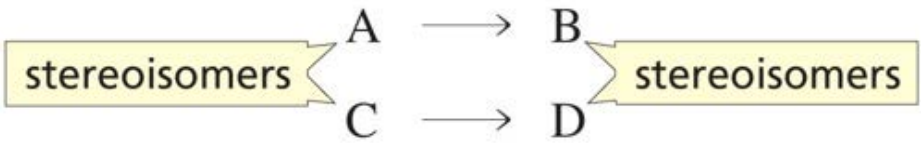
  - eg, Markovnikov addition
  - if completely regioselective ~ regiospecific

- stereoselectivity



  - moderately, highly, completely

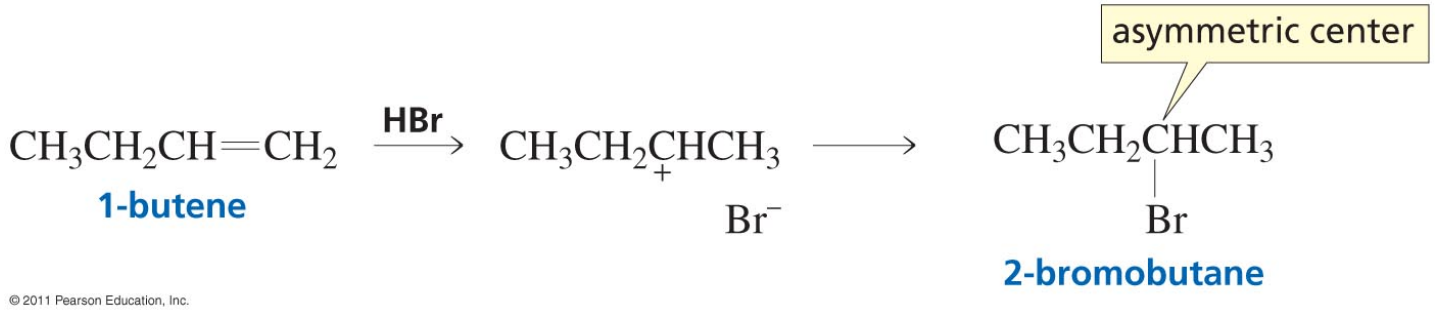
- stereospecificity



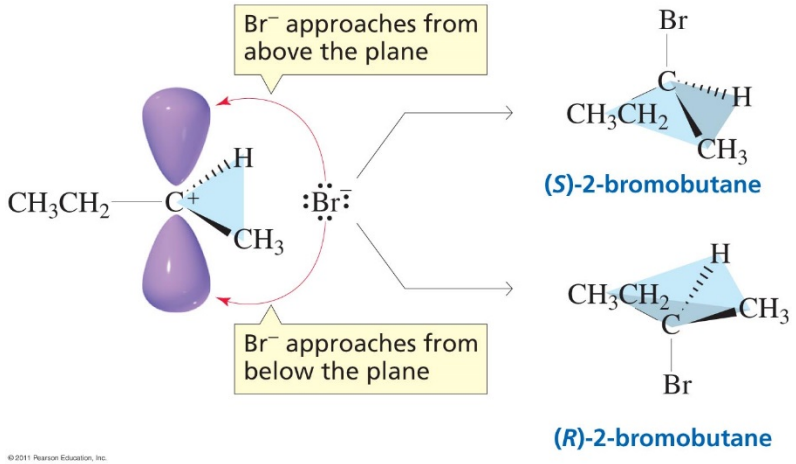
  - All stereospecific reactions are stereoselective. Not vice versa.

Addition rxn creating 1 C*

- reactant with no C*



- gives racemate

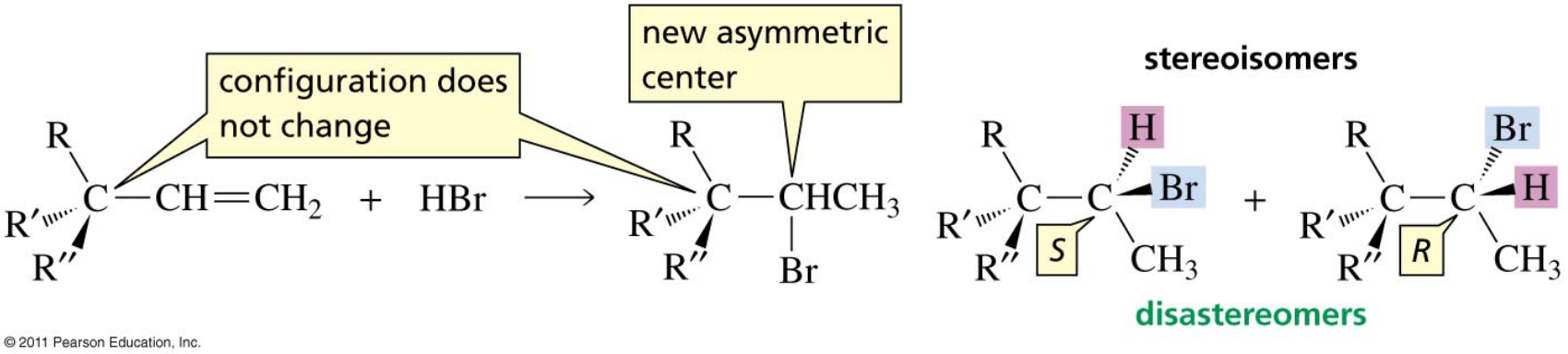


enantiomers

  - = not stereoselective

- not stereospecific ~ both cis- and trans- gives racemate

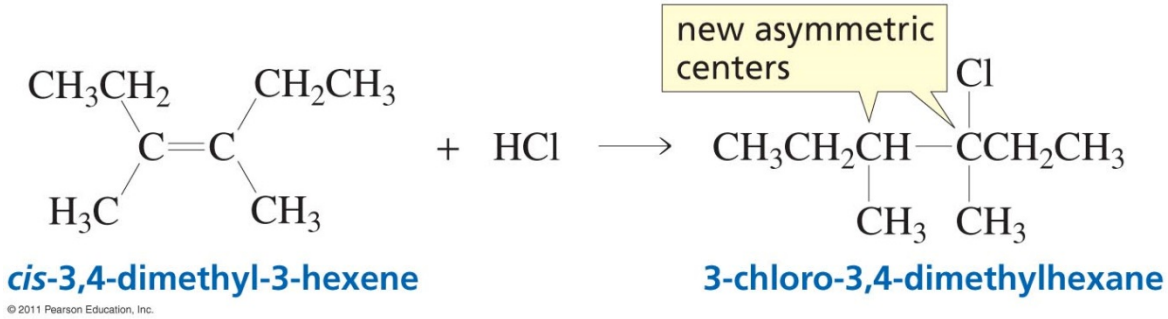
- reactant with C*



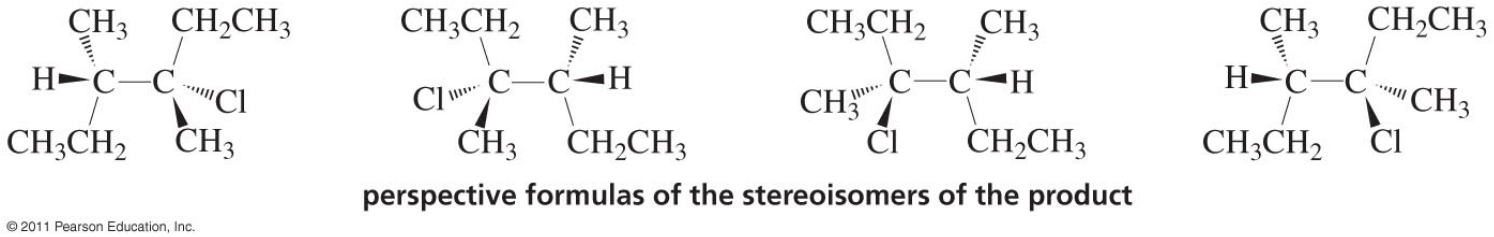
  - gives racemate?
    - *R* → *RS* + *RR*
  - stereoselective
    - diastereomers ~ *RS* > *RR* or *RS* < *RR*
  - stereospecific
    - *S* → *SR* + *SS*

Addition creating 2 C*'s

- through C^+ intermediate

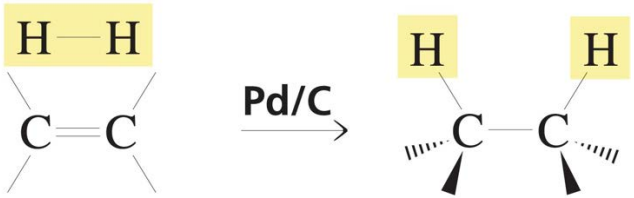


  - gives 4 stereoisomers

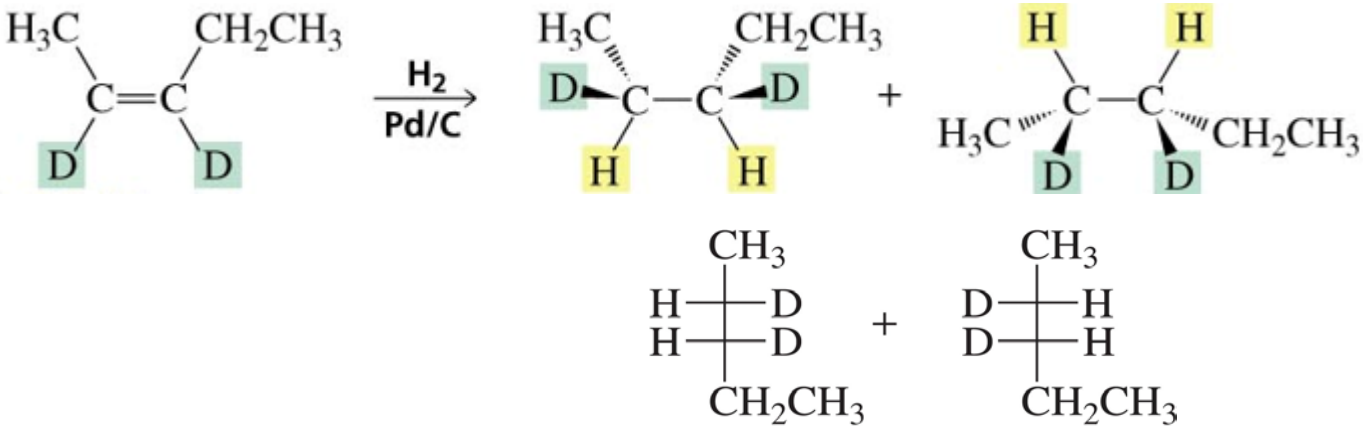


    - *RR, RS, SS, SR*
  - not stereoselective and not specific

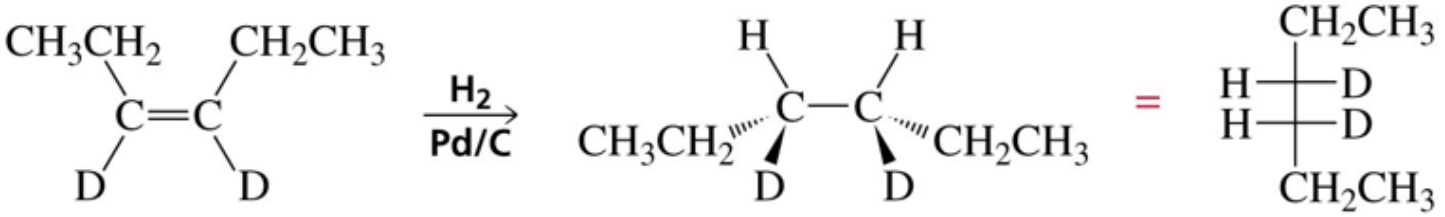
- catalytic addition
  - '**syn**' addition



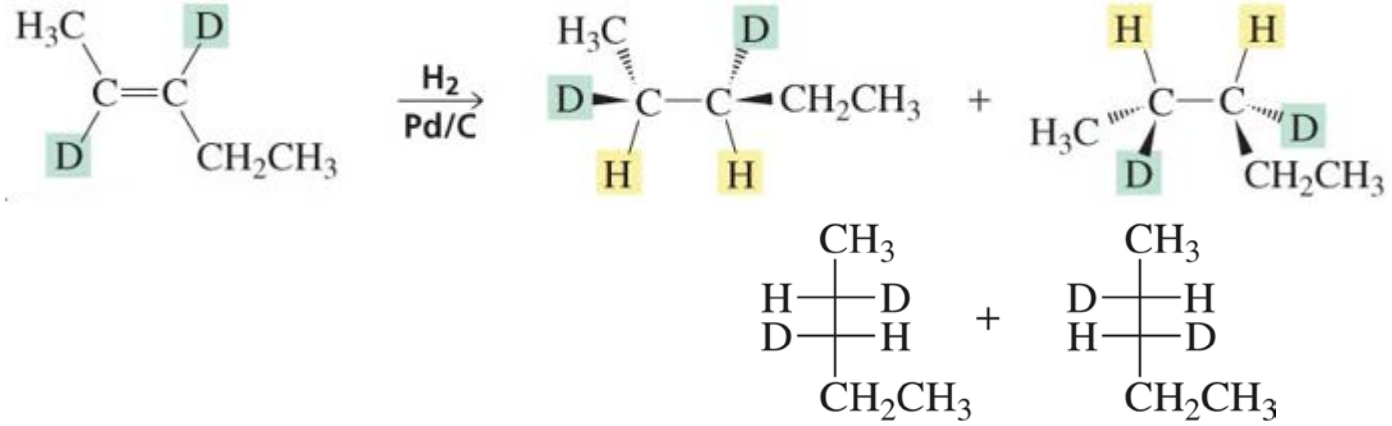
  - cis-isomer → erythro enantiomers



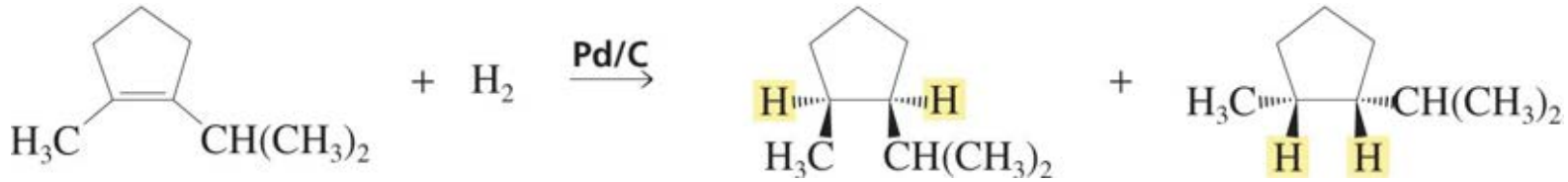
    - symmetric cis → meso compound

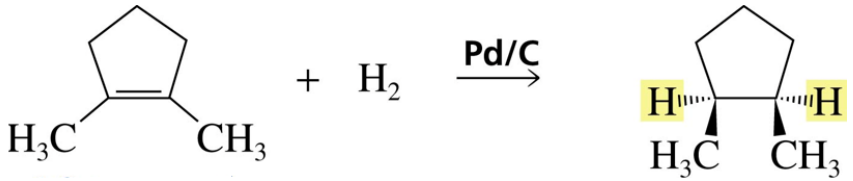


- trans-isomer → threo enantiomers

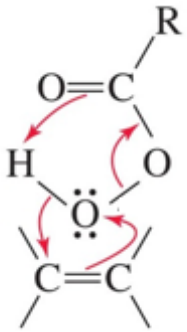


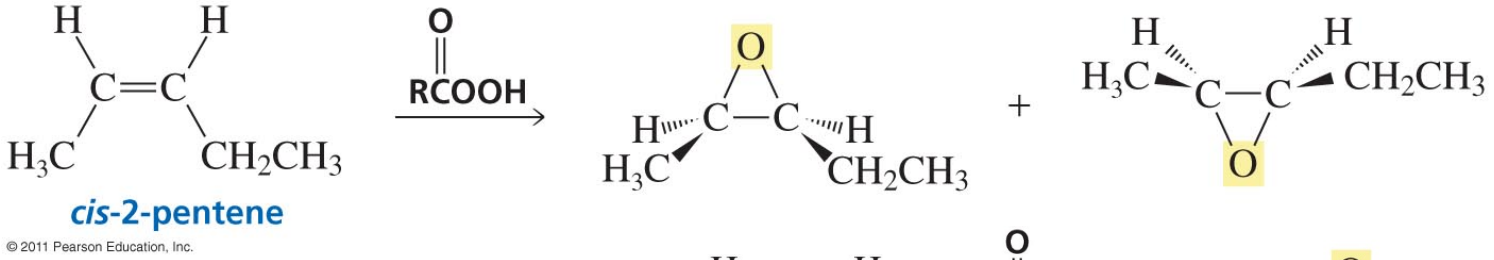
- cycloalkenes → cis or meso

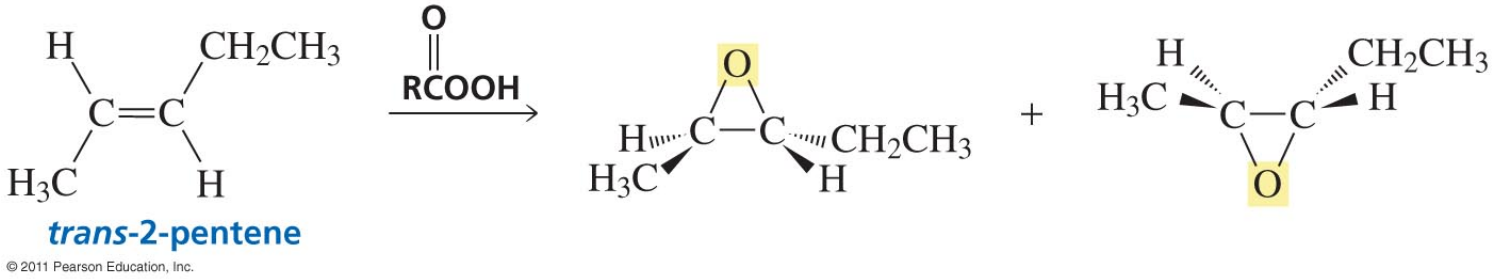




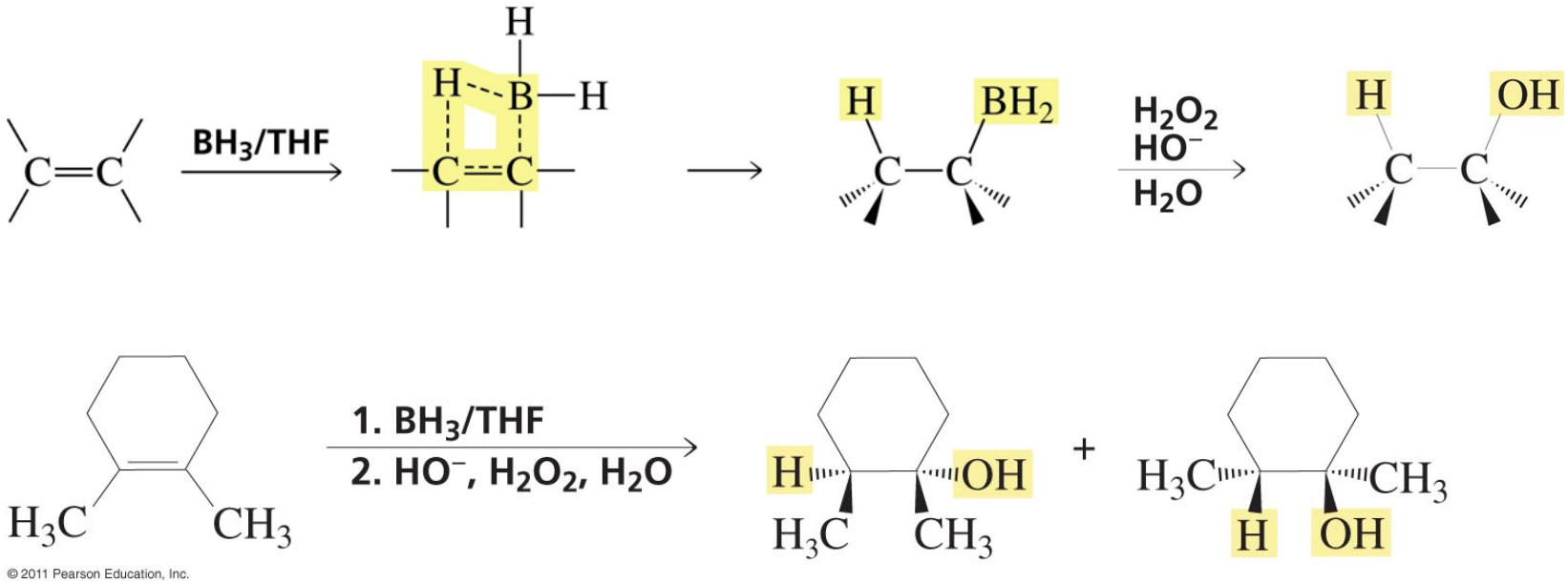
- peroxyacid addition
  - syn addition ← 'concerted'
  - cis to cis or meso
  - trans to trans



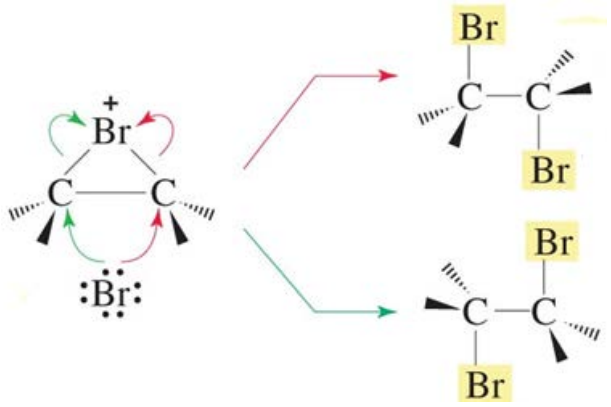


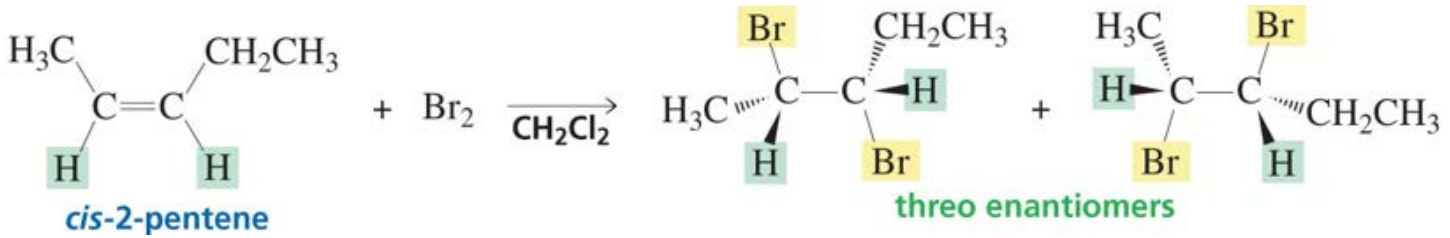


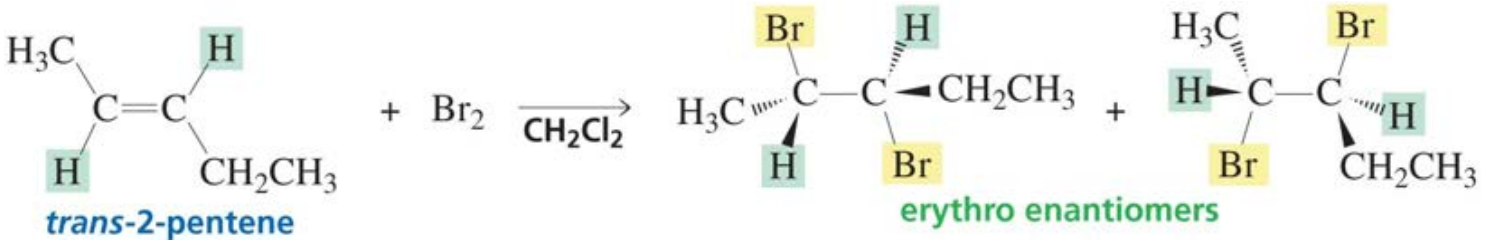
- Hydroboration-oxidation
  - syn addition ← 'concerted'
  - stereoselective
  - stereospecific



- halogenation, halohydrin formation
  - '**anti**' addition
    ← through cyclic intermediate
  - cis → threo
  - trans → erythro or meso







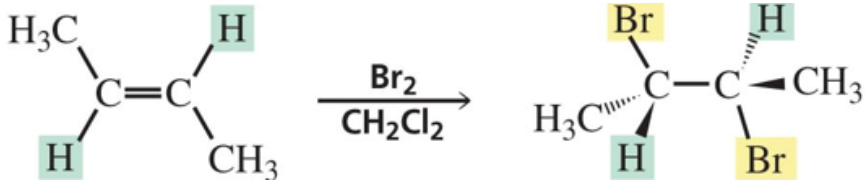


Table 5.3 Stereochemistry of Alkene Addition Reactions

Reaction	Type of addition	Stereoisomers formed
Addition reactions that create one asymmetric center in the product		1. If the reactant does not have an asymmetric center, a racemic mixture will be obtained.
		2. If the reactant has an asymmetric center, unequal amounts of a pair of diastereomers will be obtained.
Addition reactions that create two asymmetric centers in the product		
Addition of reagents that form a carbocation intermediate	syn and anti	Four stereoisomers will be obtained (the cis and trans isomers form the same products).
Addition of H_2	syn	cis ⟶ erythro or cis enantiomers*
Addition of borane		trans ⟶ threo or trans enantiomers
Addition of a peroxyacid		
Addition of Br_2, $Br_2 + H_2O$, $Br_2 + ROH$ (any reaction that forms a cyclic bromonium ion intermediate)	anti	cis ⟶ threo or trans enantiomers trans ⟶ erythro or cis enantiomers*

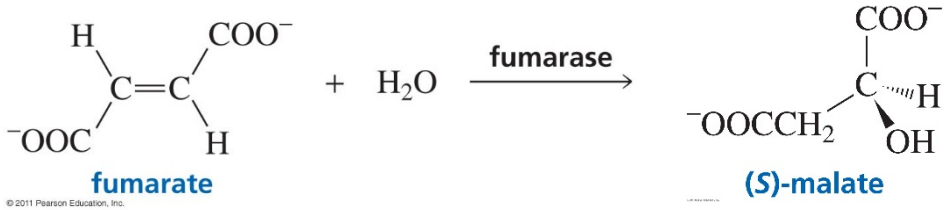
* If the two asymmetric centers have the same substituents, a meso compound will be obtained instead of the pair of erythro enantiomers.

Summary of addition reactions

- through C^+ interm
  - hydrohalogenation, hydration
  - regioselective to specific
  - not stereoselective or specific
- through 3-membered cyclic interm
  - halogenation, halohydrin, oxymercuration-reduction
  - regiospecific
  - stereoselective and specific (anti addition)
- concerted addition
  - epoxydation, hydroboration-reduction
  - regiospecific
  - stereoselective and specific (syn addition)
- catalytic hydrogenation
  - stereoselective and specific (syn addition)

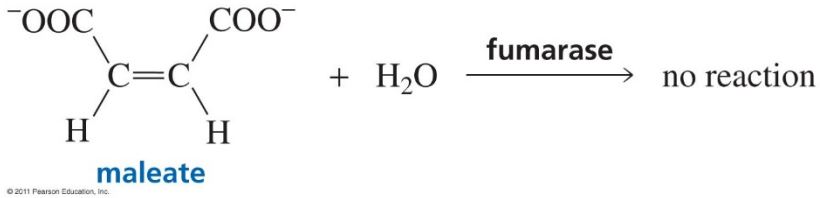
Chiral catalyst

- enzyme ~ protein catalyst for bio-reaction
  - (completely) stereoselective

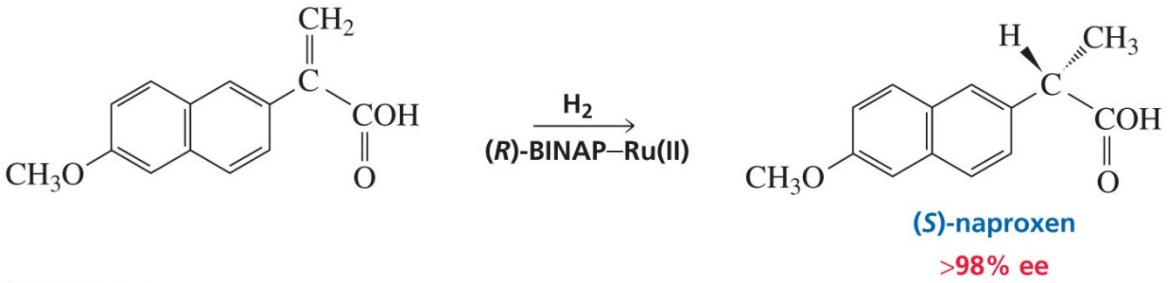


S only, no *R*

  - stereospecific

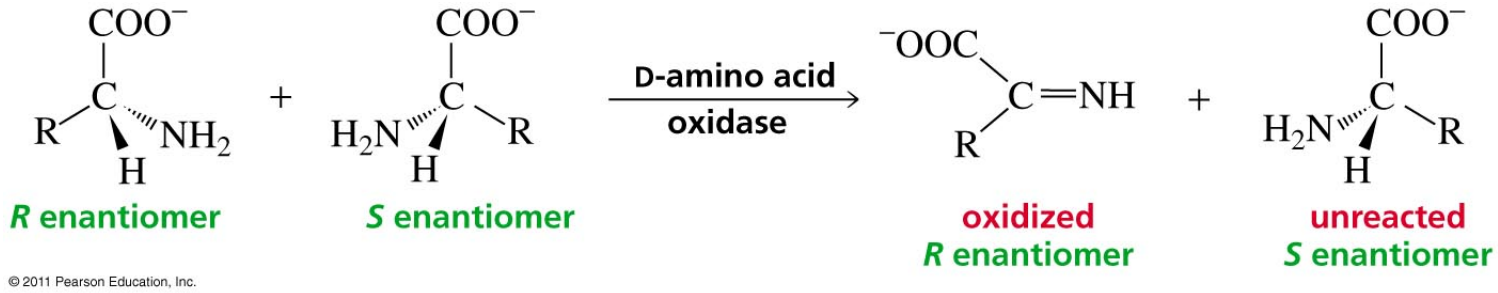


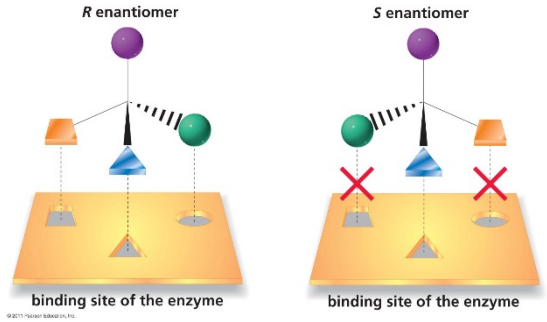
- other chiral catalyst



Chiral reagents

- enzyme





'lock-and-key'

- receptor
  - smells
  - drugs