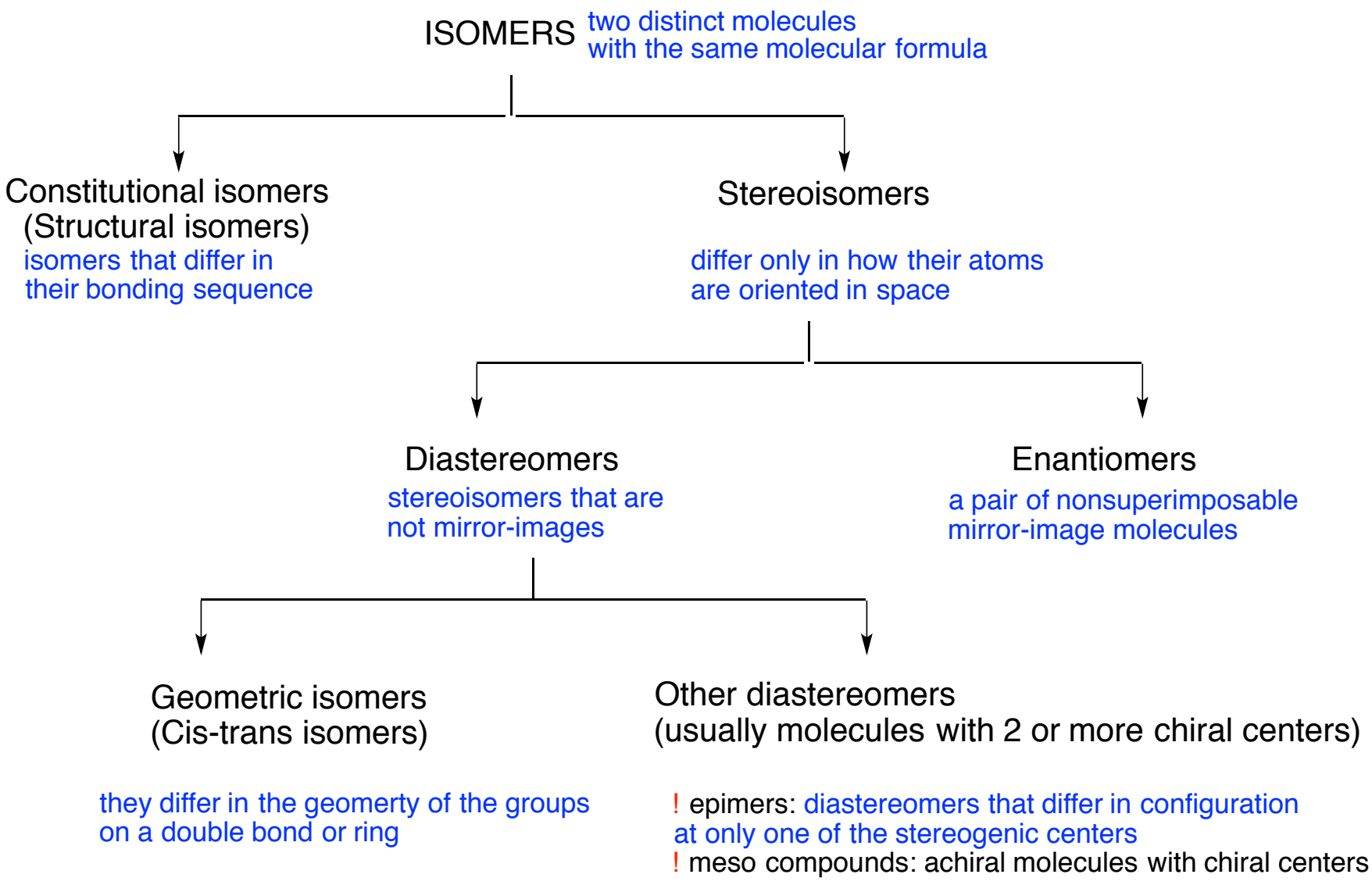
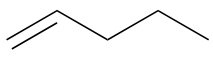


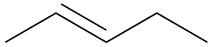
Confirmational isomers: are interconvertible by rotations about single bonds
Configuration: the relative position of the arrangement of atoms in space

Constitutional isomers

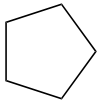
C_5H_{10}



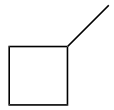
pent-1-ene



pent-2-ene

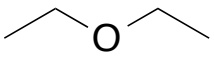


cyclopentene

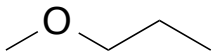


methylcyclobutane

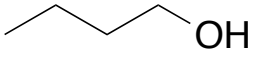
C_4H_9O



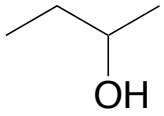
diethyl ether



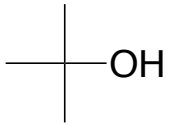
methyl propyl ether



butan-1-ol
1° alcohol

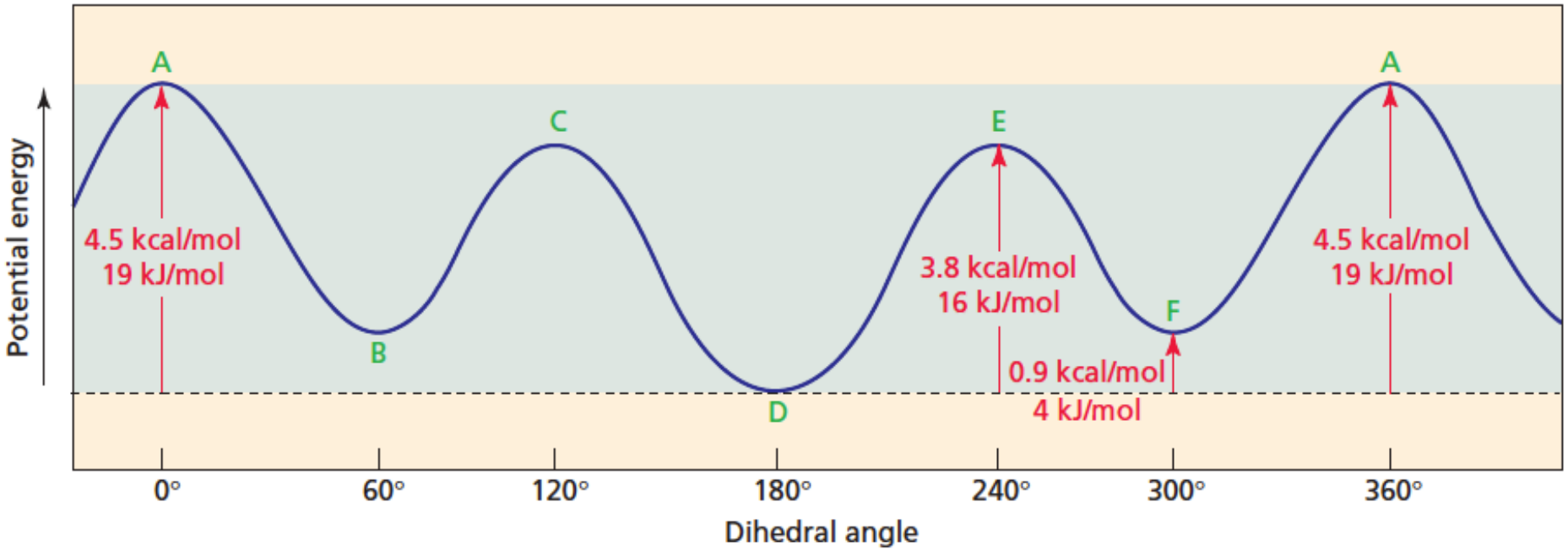


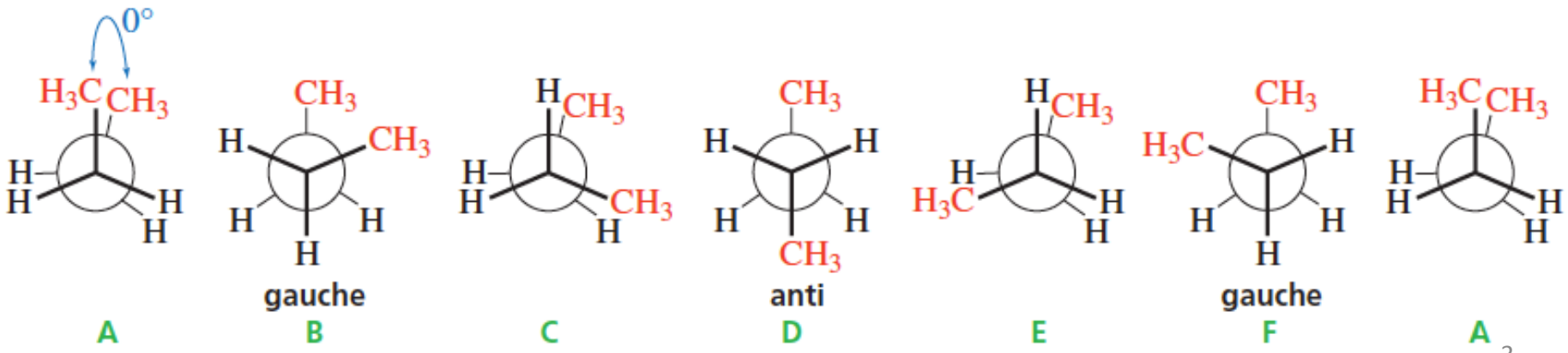
butan-2-ol
2° alcohol



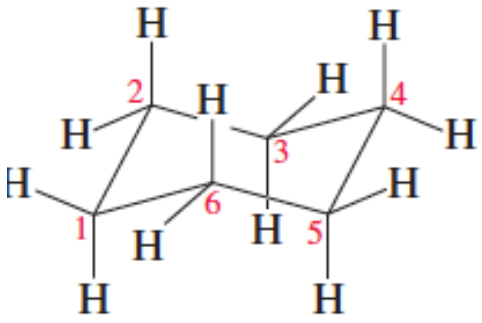
2-methylpropan-2-ol
3° alcohol

Conformations - Butane

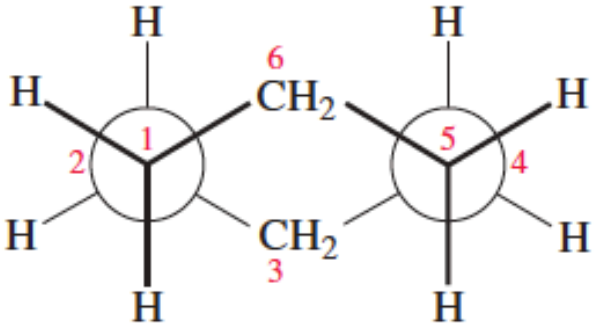




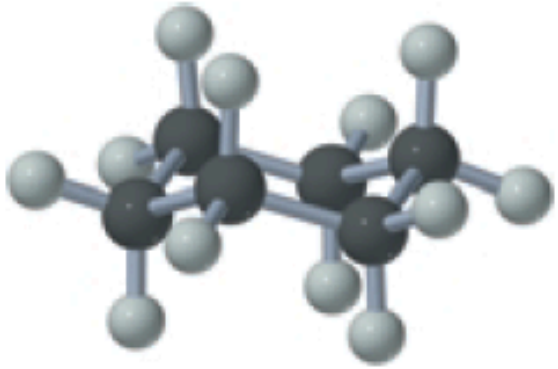
Conformations – Cyclohexane



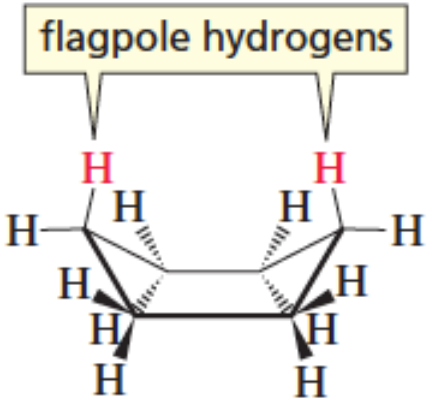
chair conformer of cyclohexane



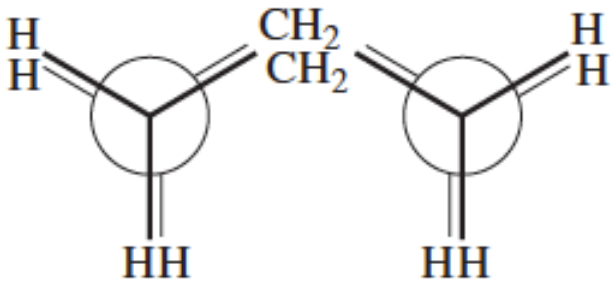
Newman projection of the chair conformer



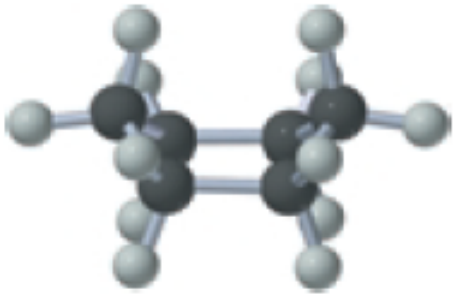
ball-and-stick model of the chair conformer of cyclohexane



boat conformer of cyclohexane

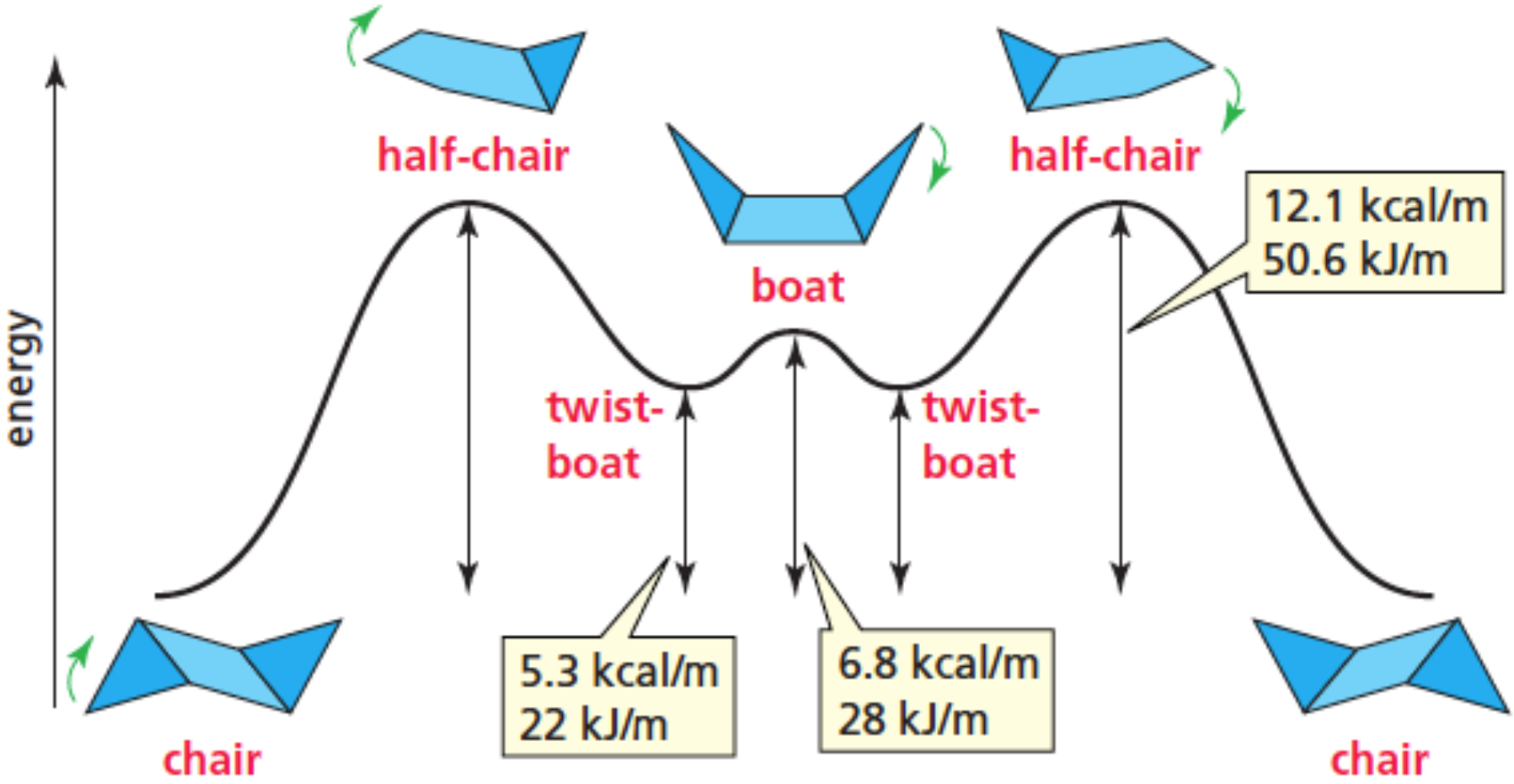


Newman projection of the boat conformer

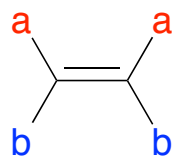


ball-and-stick model of the boat conformer of cyclohexane

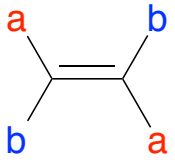
Conformations – Cyclohexane



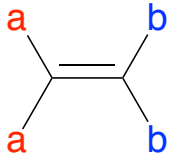
Geometric isomers



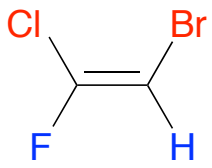
cis (*Z*)



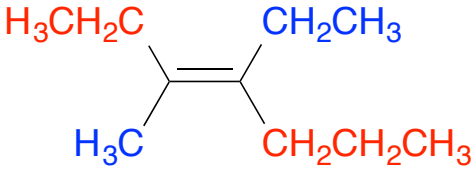
trans (*E*)



no geometric isomers

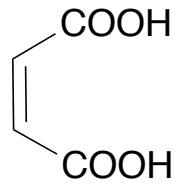


(*Z*)-2-bromo-1-fluoro-1-chloroethene

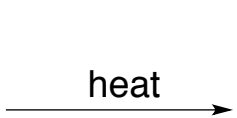


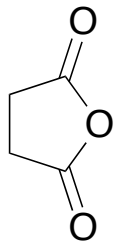
(*E*)-4-ethyl-3-methylhept-3-ene

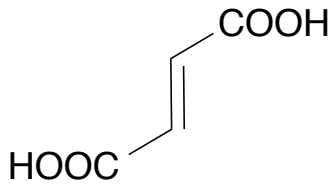
Difference in reactivity



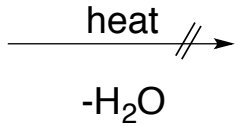
maleic acid
mp 138 °C
toxic, irritant



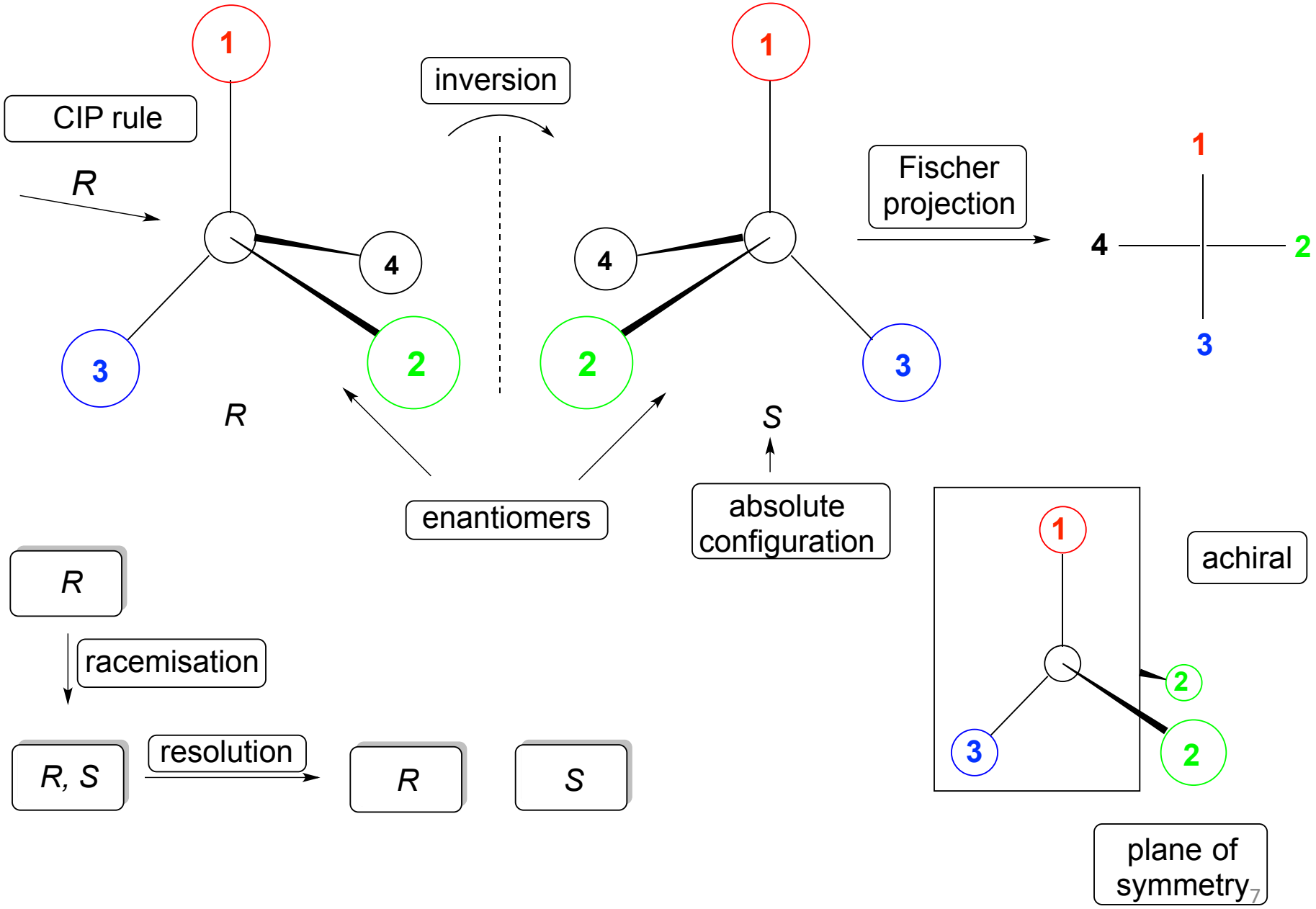




fumaric acid
mp 287 °C
essential metabolite

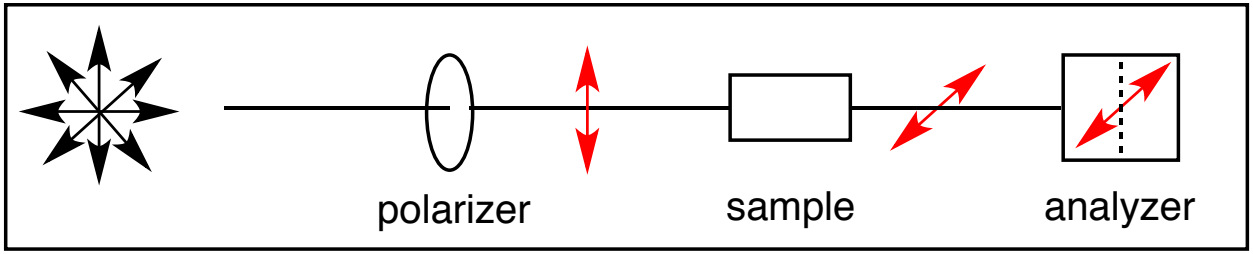


Chiral molecules / central chirality



Measurement of optical activity

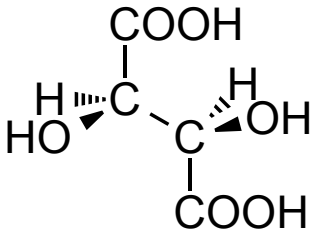
Polarimeter



Specific rotation

$\alpha_{measured} \times 100 = [\alpha] \times c \times l$ $\qquad [\alpha] = \frac{\alpha_m}{lc} \times 100$

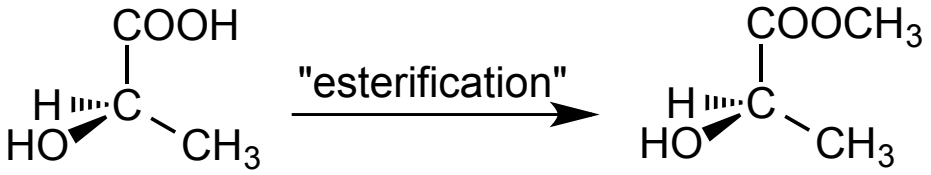
$[\alpha]$: specific rotation
l: 1 dm
c: concentration (g/100 ml)



(2R,3R)-tartaric acid

$[\alpha]_D^{20} = +12$ (c = 2, H_2O)

Specific rotation and absolute configuration

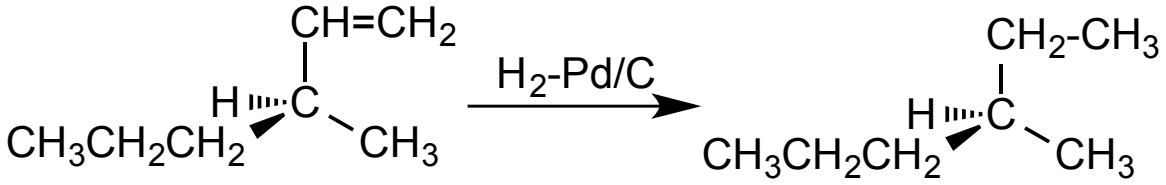


(*R*)-lactic acid

$[\alpha]_D^{20}$ = -3,3

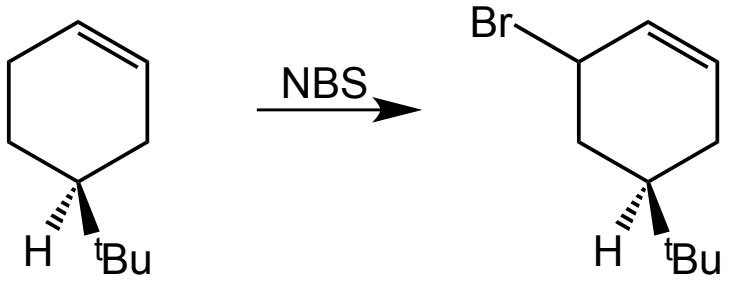
(*R*)-methyl lactate

$[\alpha]_D^{20}$ = +8,2



(*S*)-3-methylhex-1-ene

(*R*)-3-methylhexane



(*S*)-4-*tert*-butyl-cyclohexene

(*R*)-3-bromo-5-*tert*-butyl-cyclohexene

Enantiomeric excess (*ee*)

$$ee = \frac{[R] - [S]}{[R] + [S]} \times 100 = \%R - \%S$$

Determination of enantiomeric excess

chromatographic methods (chiral stationary phase)
NMR spectroscopy (chiral shift reagents)

Example

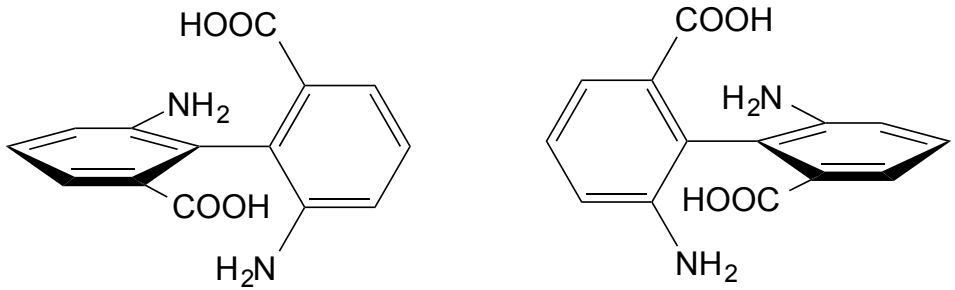
if R = 70%, S = 30%, then ee = 40%

The mixture contains: 40% R enantiomer, and
60% racemic mixture

Optical purity (OP)

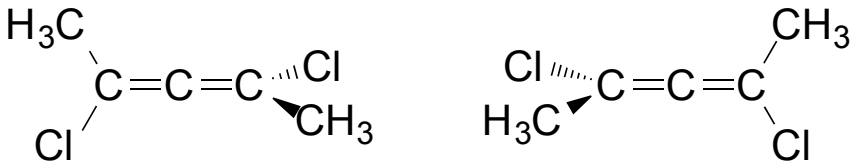
$$OP\% = \frac{[\alpha]_{measured}}{[\alpha]_{max}} \times 100$$

Optically active molecules without chiral center



atropisomerism

spiranes

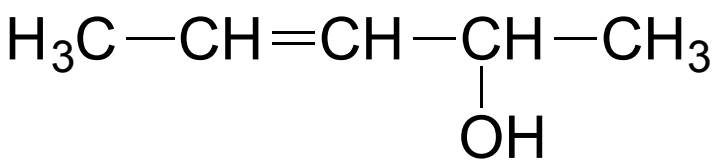


allenes

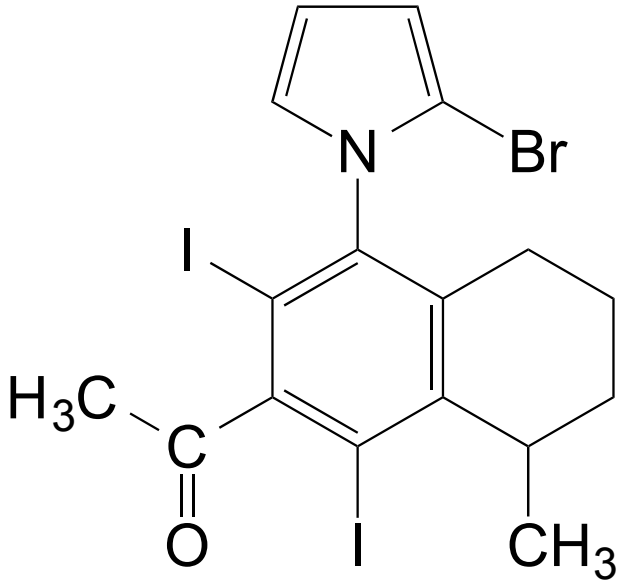
BUT!
odd number of cumulated bonds → *cis-trans* isomerism

Molecules with different symmetry elements

a) *cis-trans* isomerism and stereogenic center

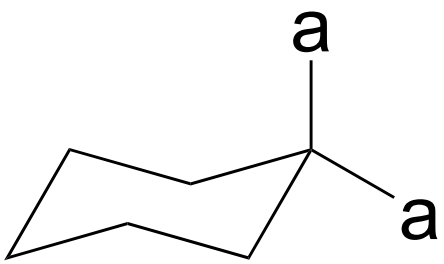


b) hindered rotation and stereogenic center

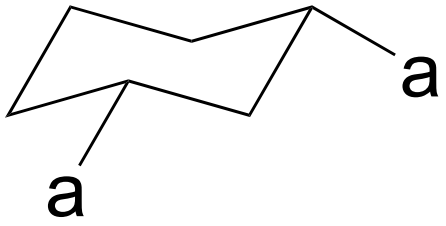


Stereoisomerism of 1,2-disubstituted cyclohexanes (conformational chirality)

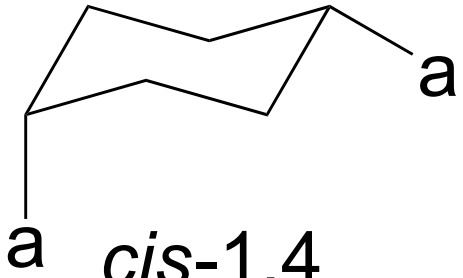
achiral derivatives (have inner mirror plane)



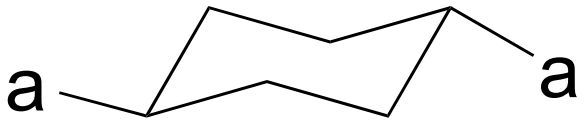
1,1



cis-1,3



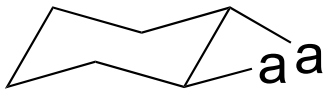
cis-1,4



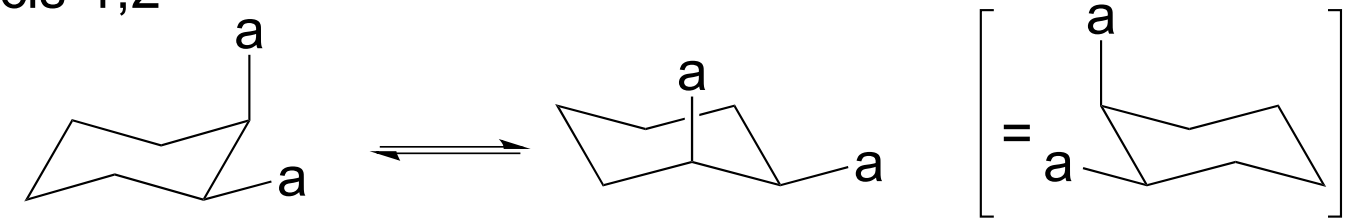
trans-1,4

chiral derivatives (no plane of symmetry)

trans-1,2

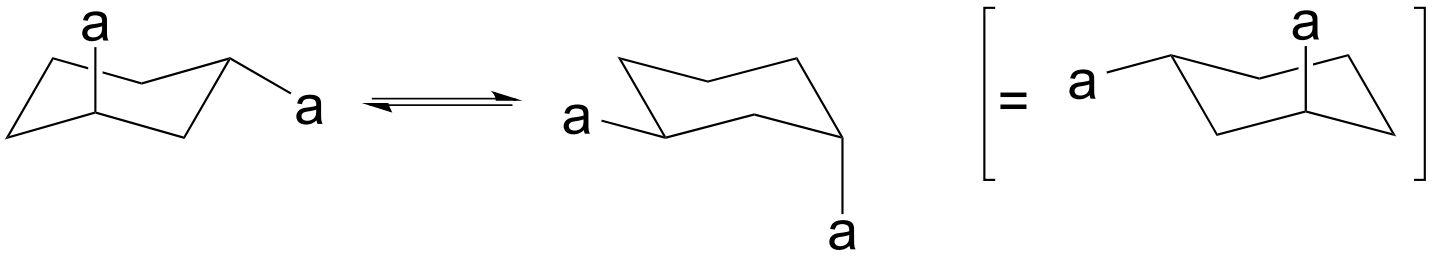


cis-1,2



not only conformers but also enantiomers

trans-1,3

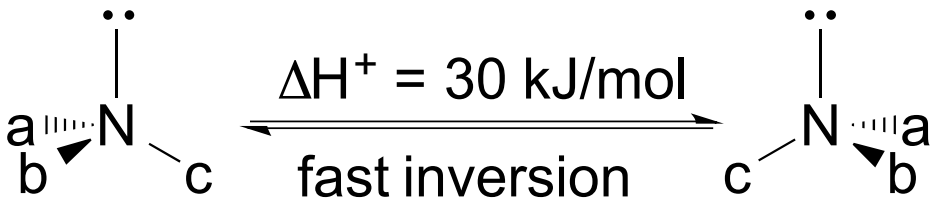


not only conformers but also enantiomers

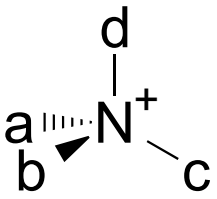
chiral molecules, but optilally inactive beacuse of the conformational equilibrium

Stereogenic centers (not carbon atoms)

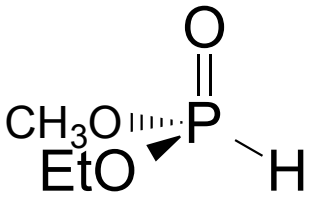
amines (not resolvable)



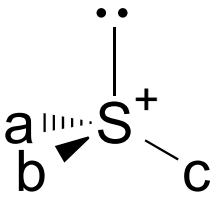
resolvable molecules



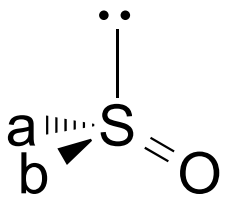
ammonium cation



phosphonic acid ester

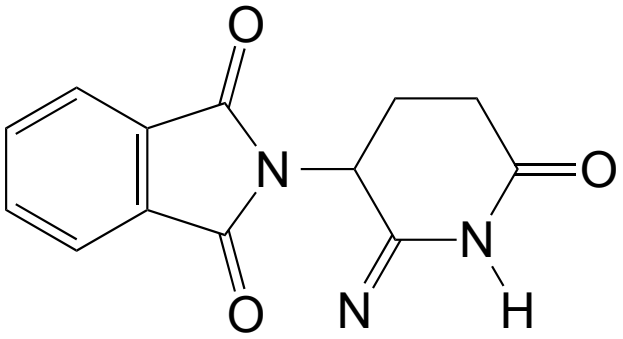


sulfonium cation

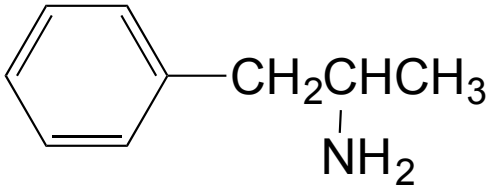


sulfoxide

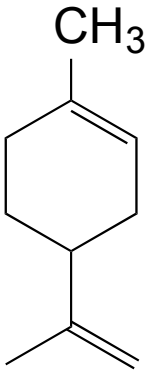
Different biological activity of the enantiomers



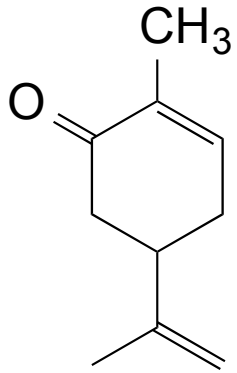
Contergane
- drug molecule
- teratogenic



Amphetamine
-stimulatory effect
-side effects



Limonene
- lemon smell
- orange smell



Carvone
- spearmint smell
- caraway smell

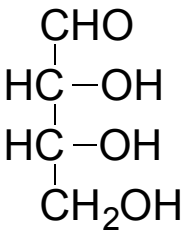
Two stereogenic centers with different ligands

enantiomers

enantiomers

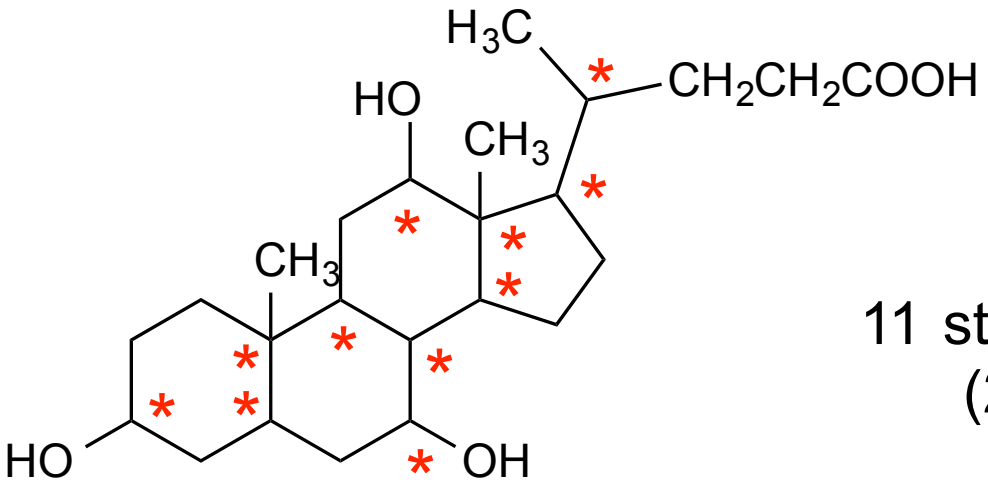
diastereomers

Erythrose, threose:



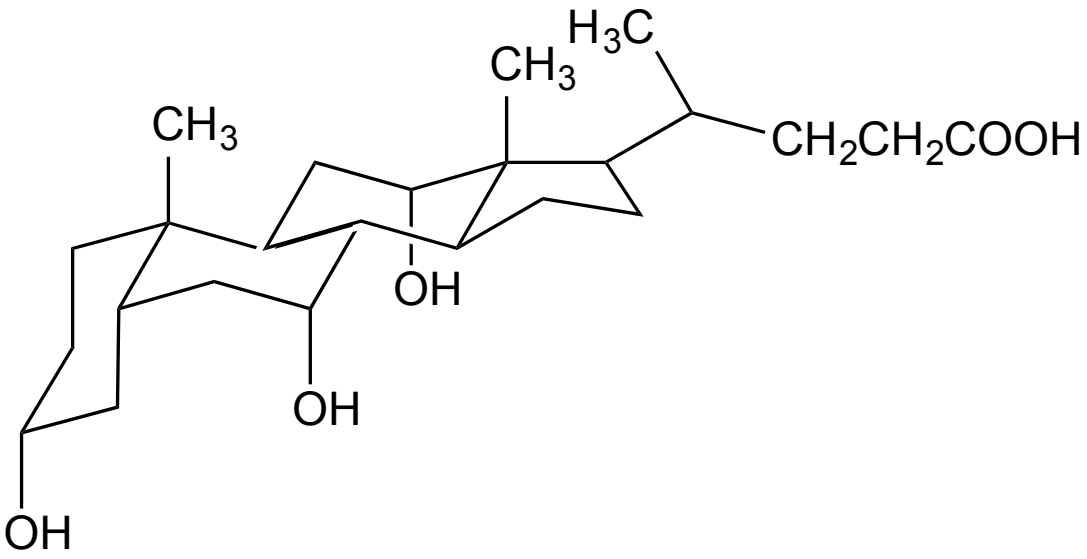
4 stereoisomers

n stereogenic center ⟶ 2^n stereoisomer

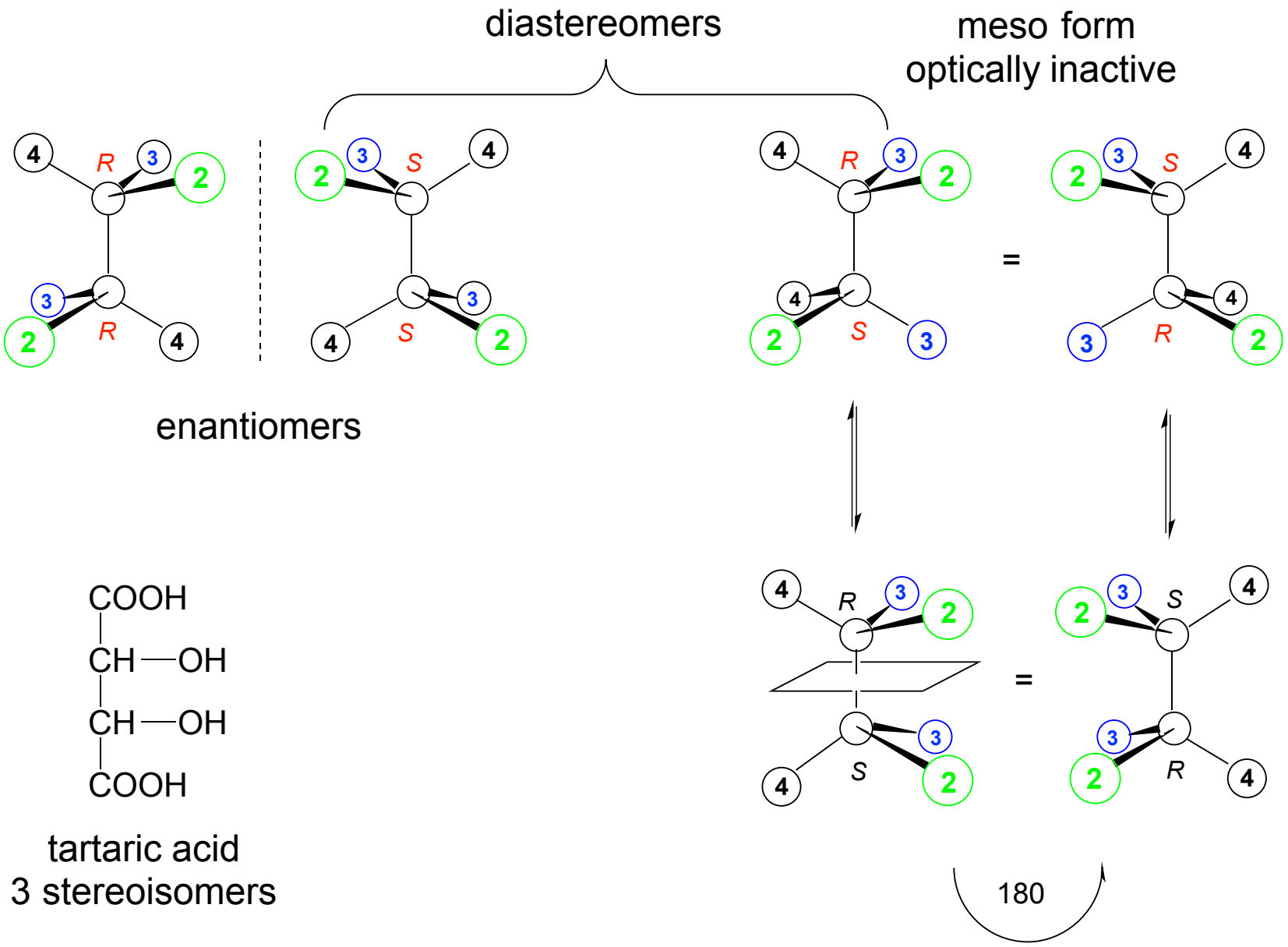


cholic acid

11 stereogenic carbon atoms
(2048 stereoisomers)



Two stereogenic centers with the same ligands / meso compounds

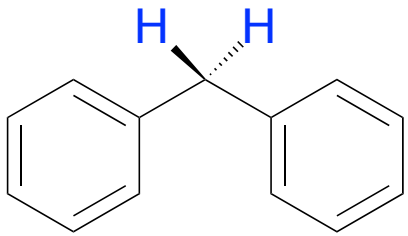


COOH
CH—OH
CH—OH
COOH

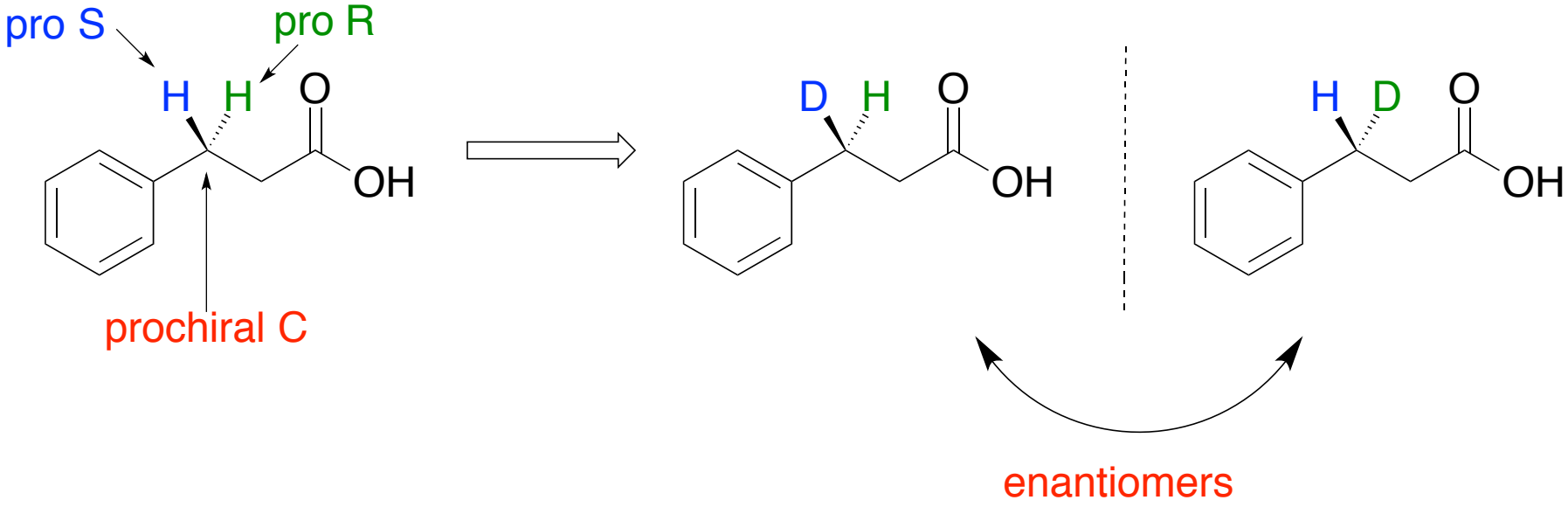
tartaric acid
3 stereoisomers

Concepts in stereochemistry (topism)

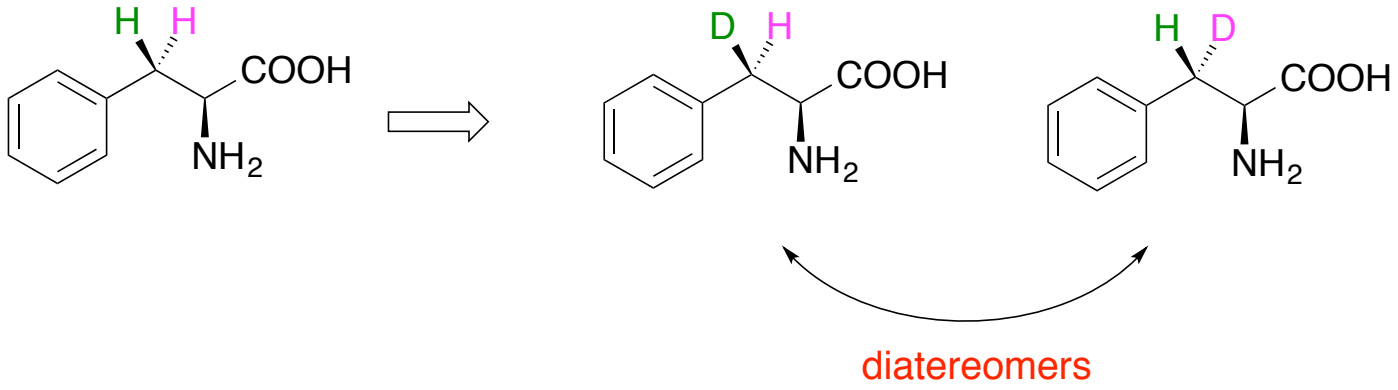
Homotopic = same



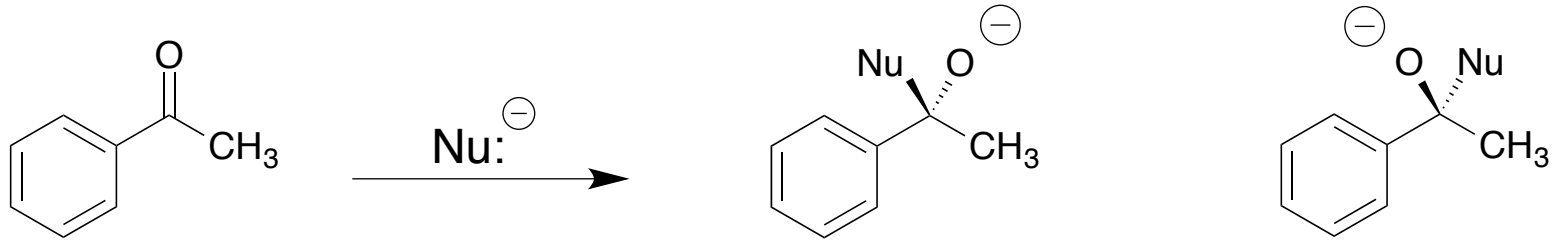
Enantiotopic: different; replacement of one or the other of them generates enantiomers

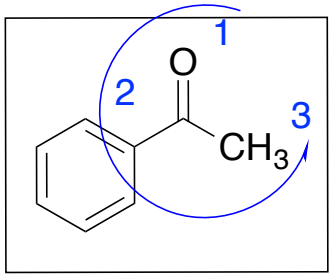


Diastereotopic: different; replacement of one or the other generates diastereomers

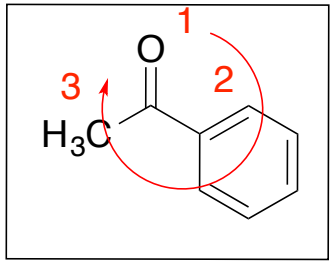


Prochiral C



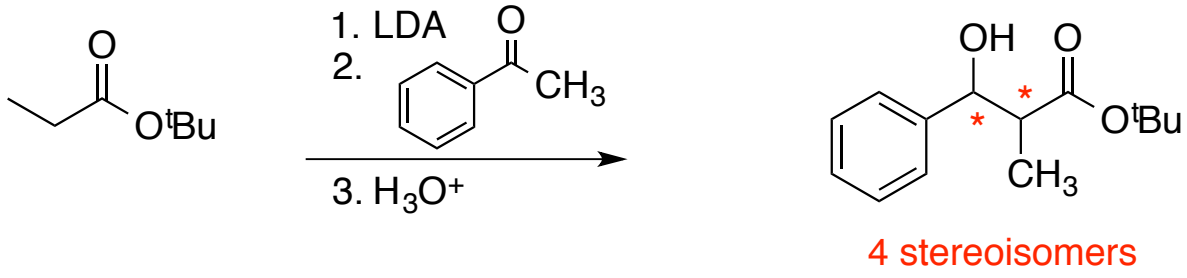


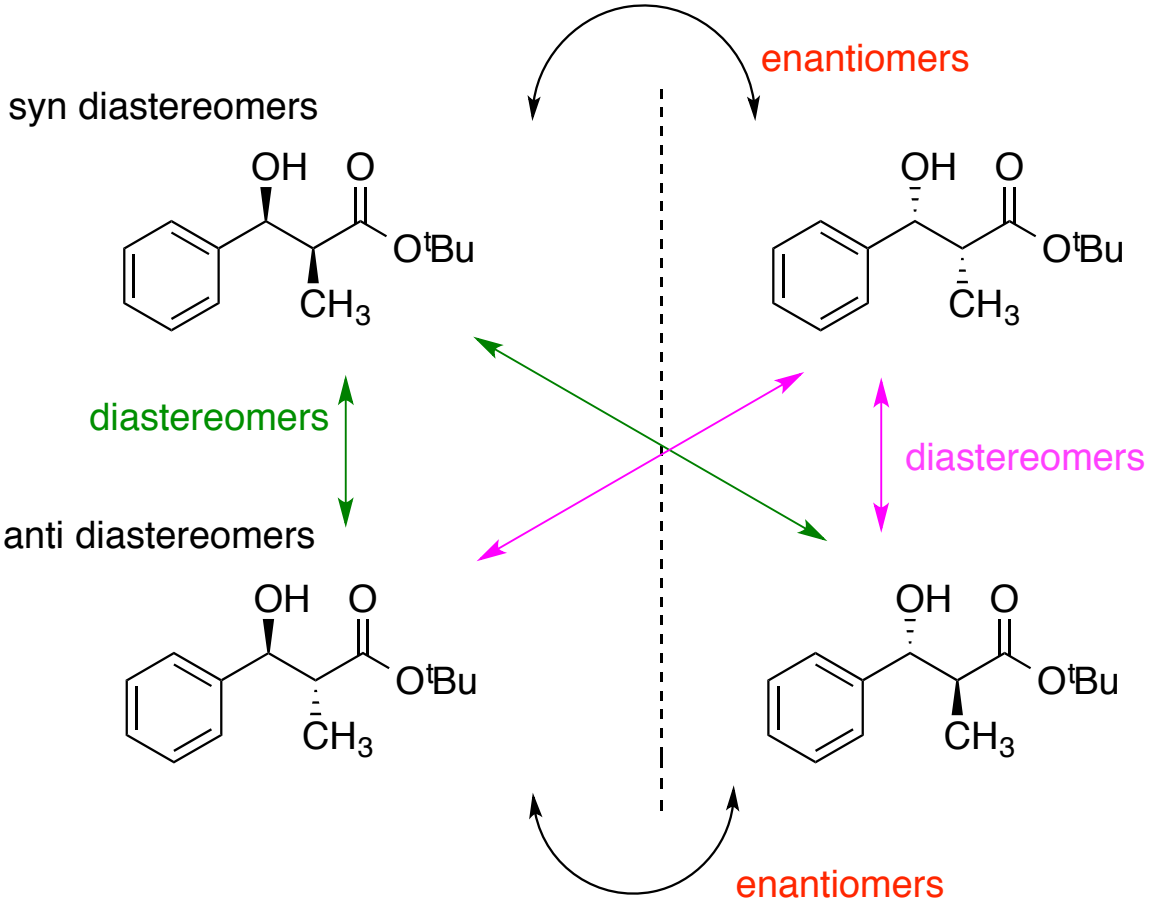
si face (counterclockwise)



re face (clockwise)

Example


1. LDA
2.
3. H_3O^+
OH
O
O^tBu
CH_3
4 stereoisomers

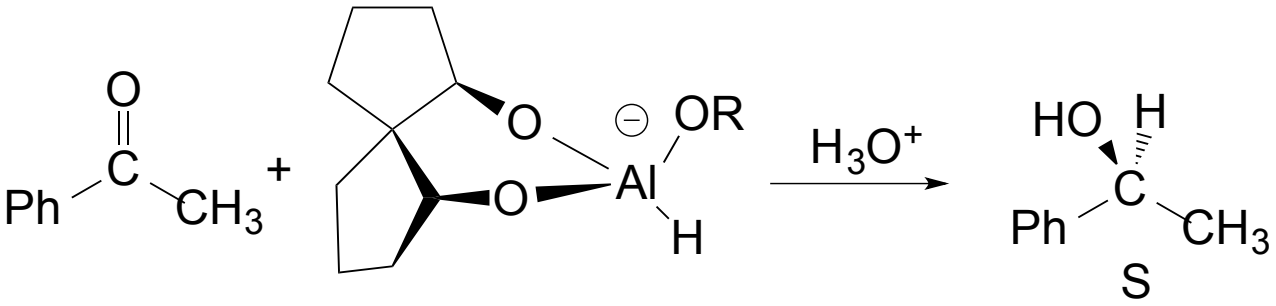

enantiomers
syn diastereomers
diastereomers
diastereomers
anti diastereomers
enantiomers

Synthesis of enantiomers

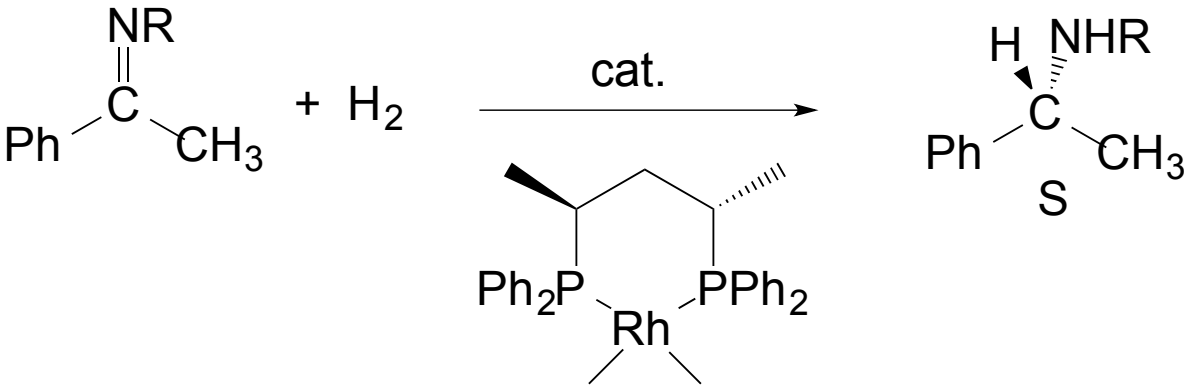
1) Isolation of chiral compounds and/or transform
e.g. morphine, and morphine derivatives

2) Stereoselective synthesis

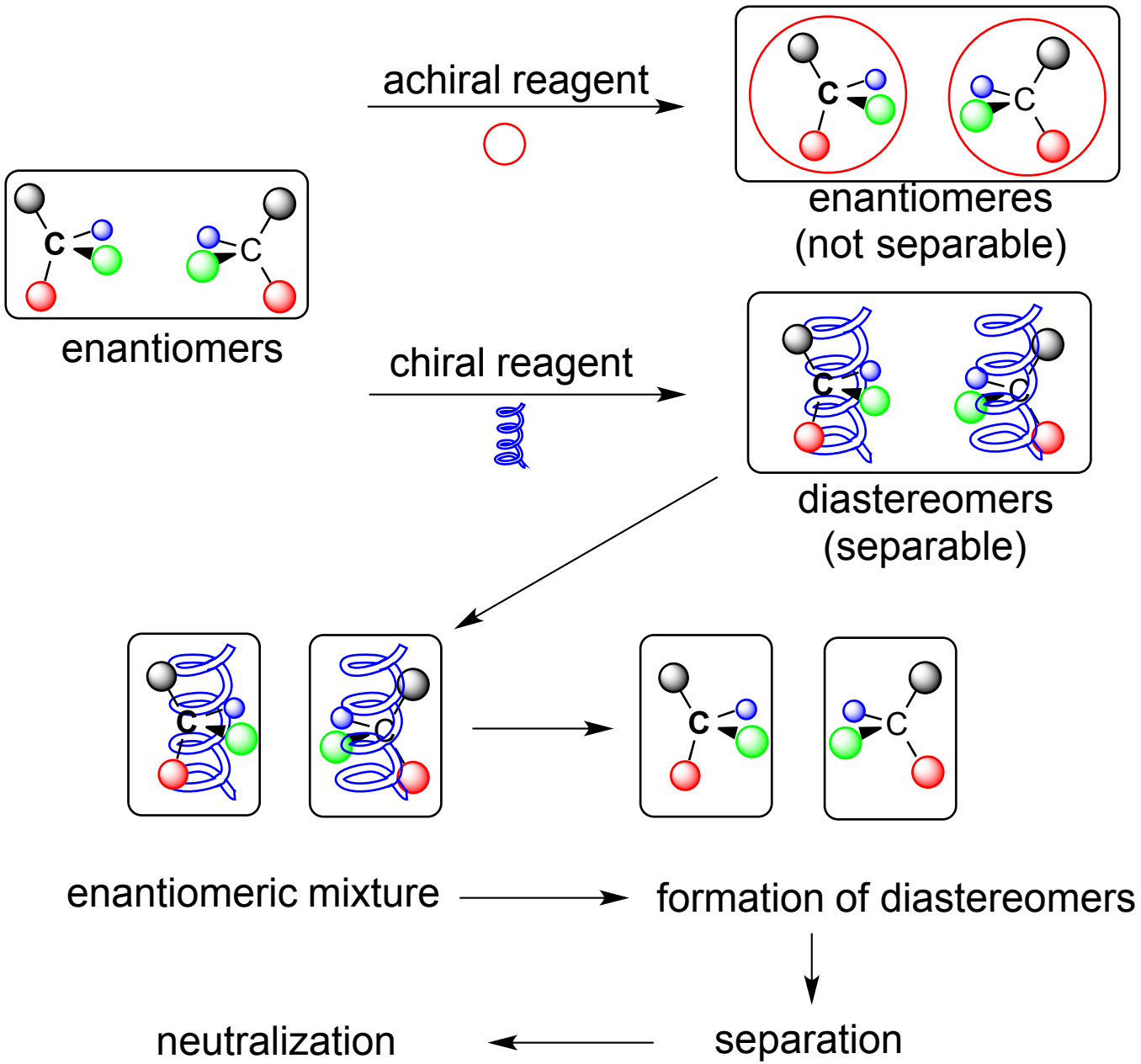
a) Utilization of chiral reagent



b) Utilization of chiral catalyst

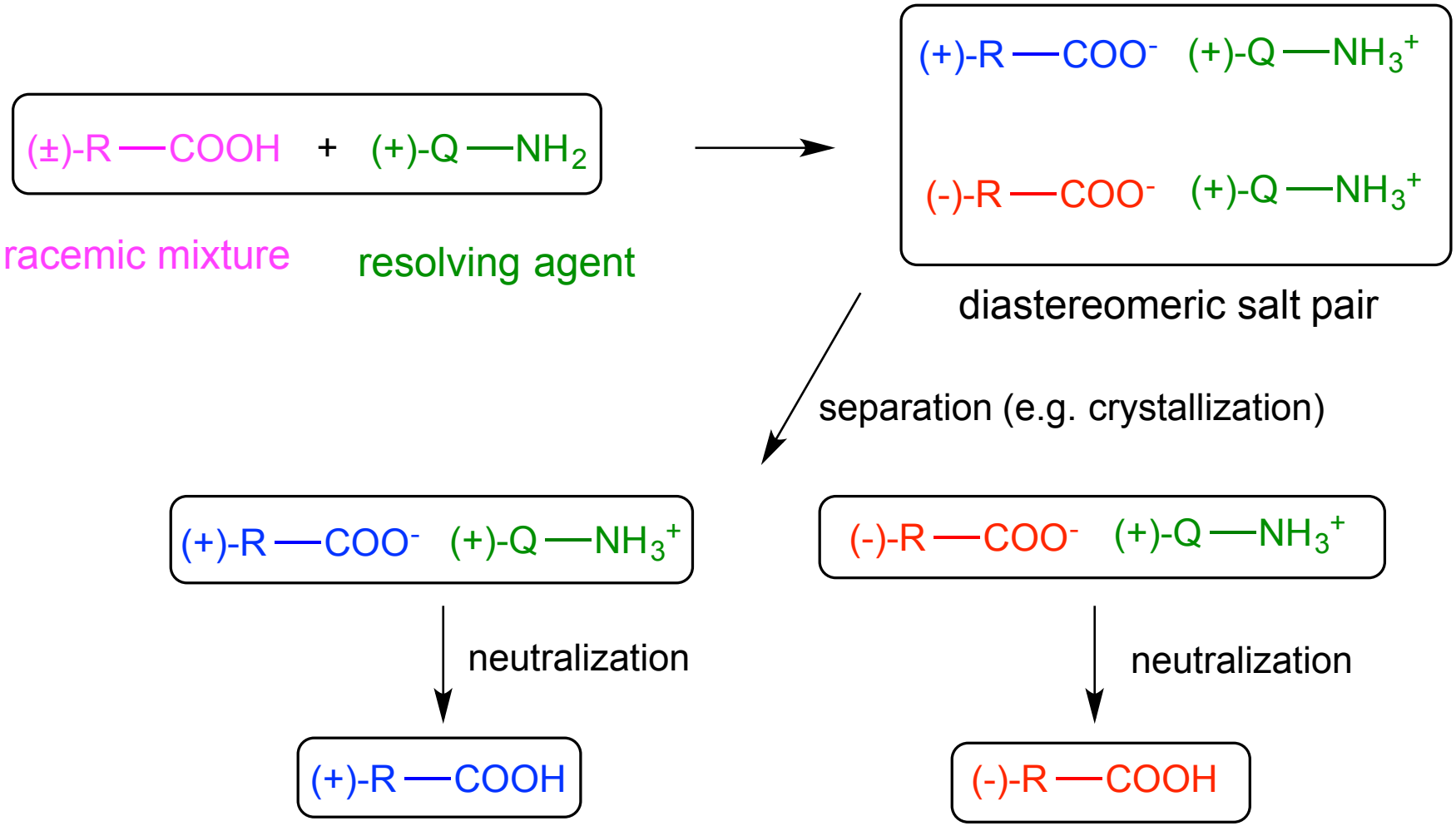


3) Optical resolution of racemic mixtures

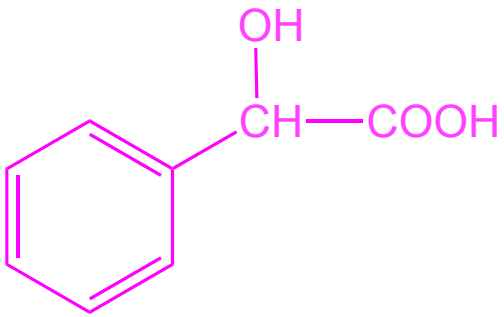


Formation of diastereomers with salt formation

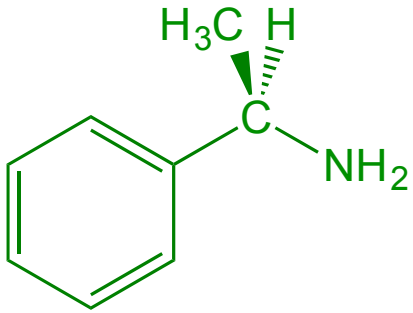
a) using one equivalent of resolving agent



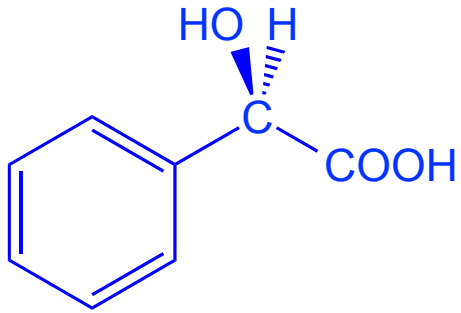
Example



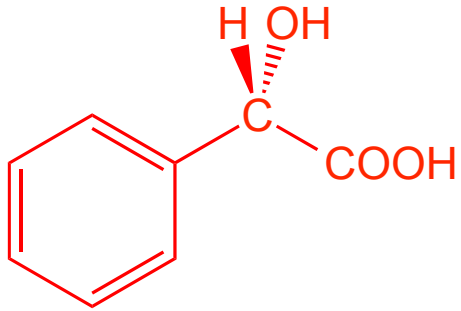
racemic mandelic acid



(*R*)-phenylethylamine

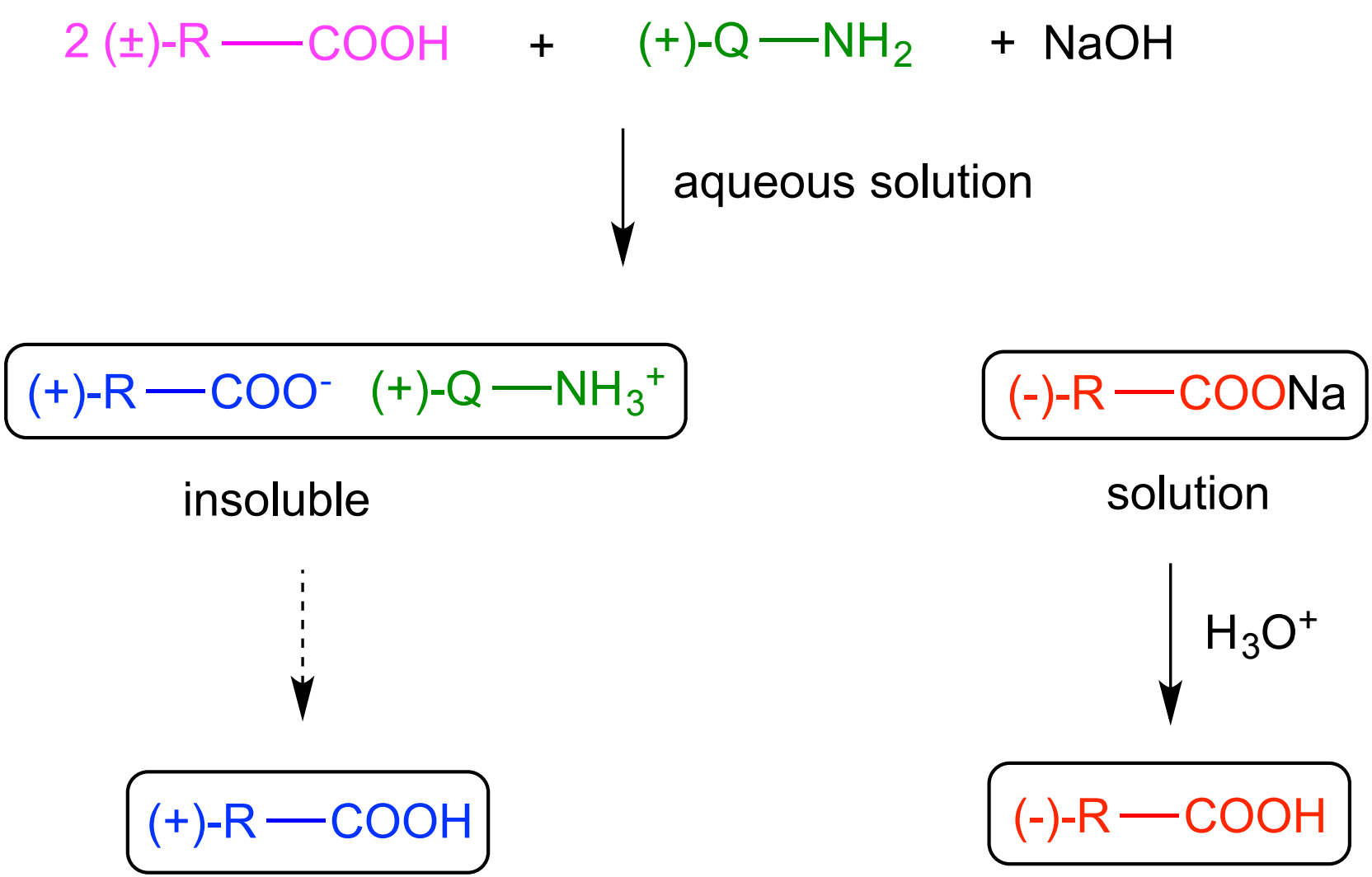


(*R*)-mandelic acid

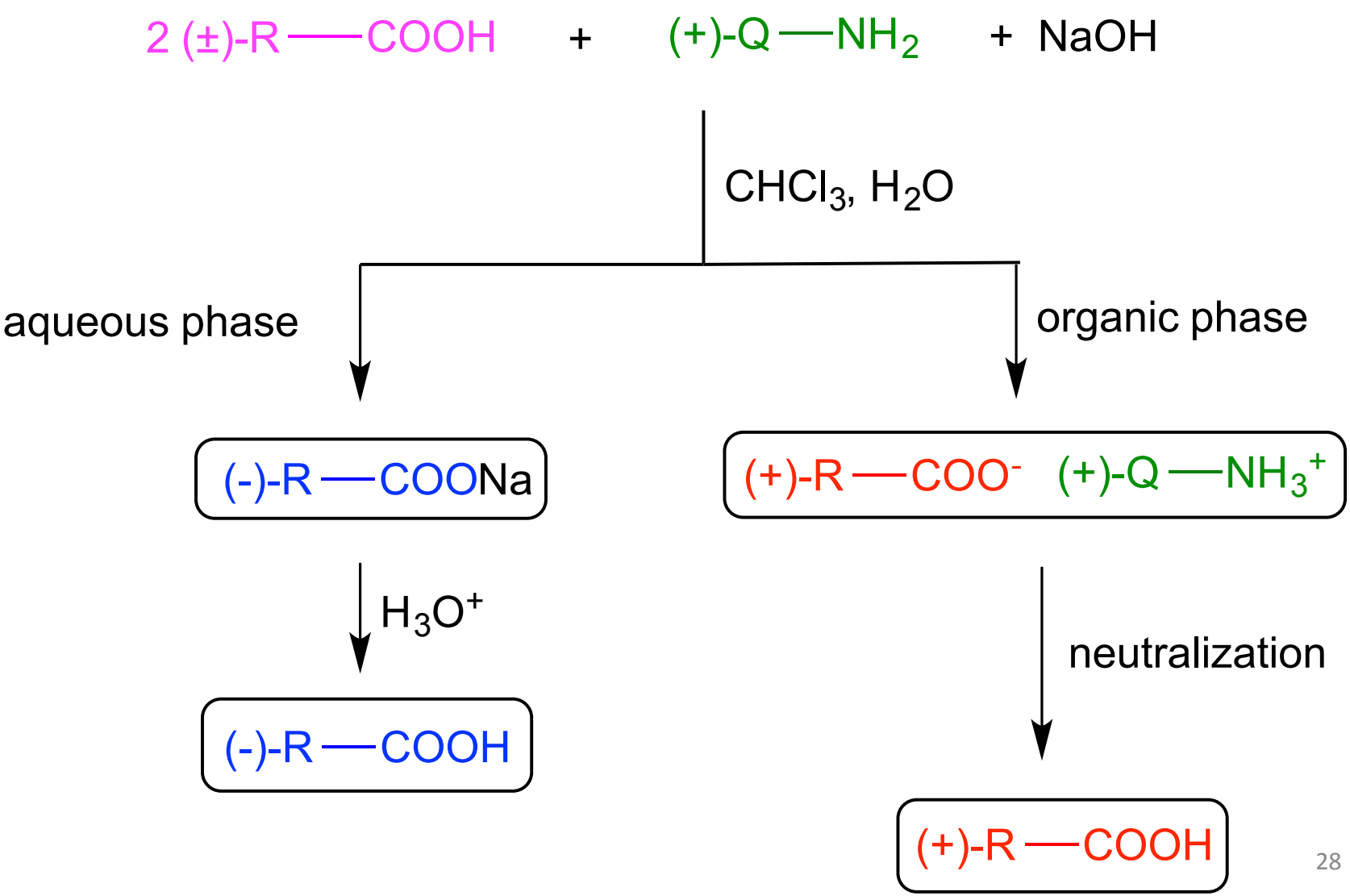


(*S*)-mandelic acid

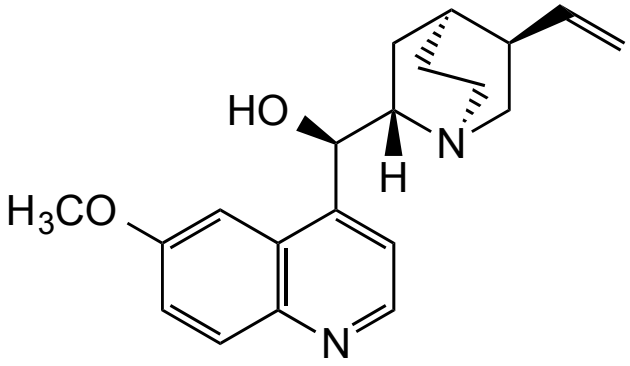
b) Using half equivalent resolving agent



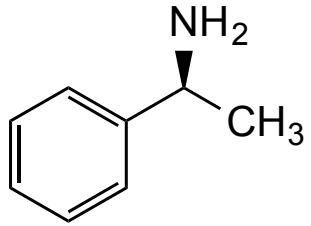
Optical resolution by extraction



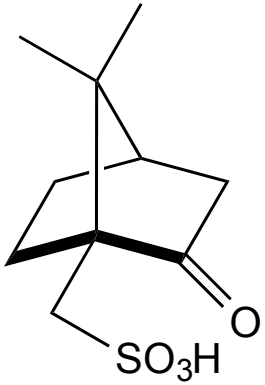
Resolving agents



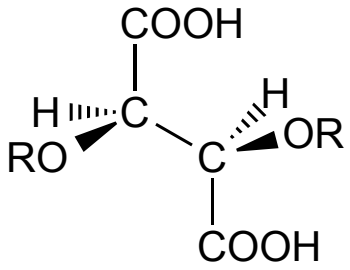
quinine



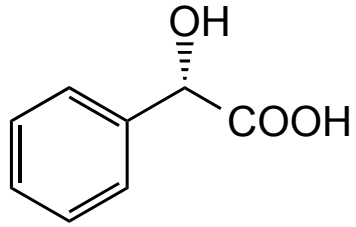
(*S*)-(-)-phenylethylamine



(*S*)-(+)-camphene-10-sulfonic acid

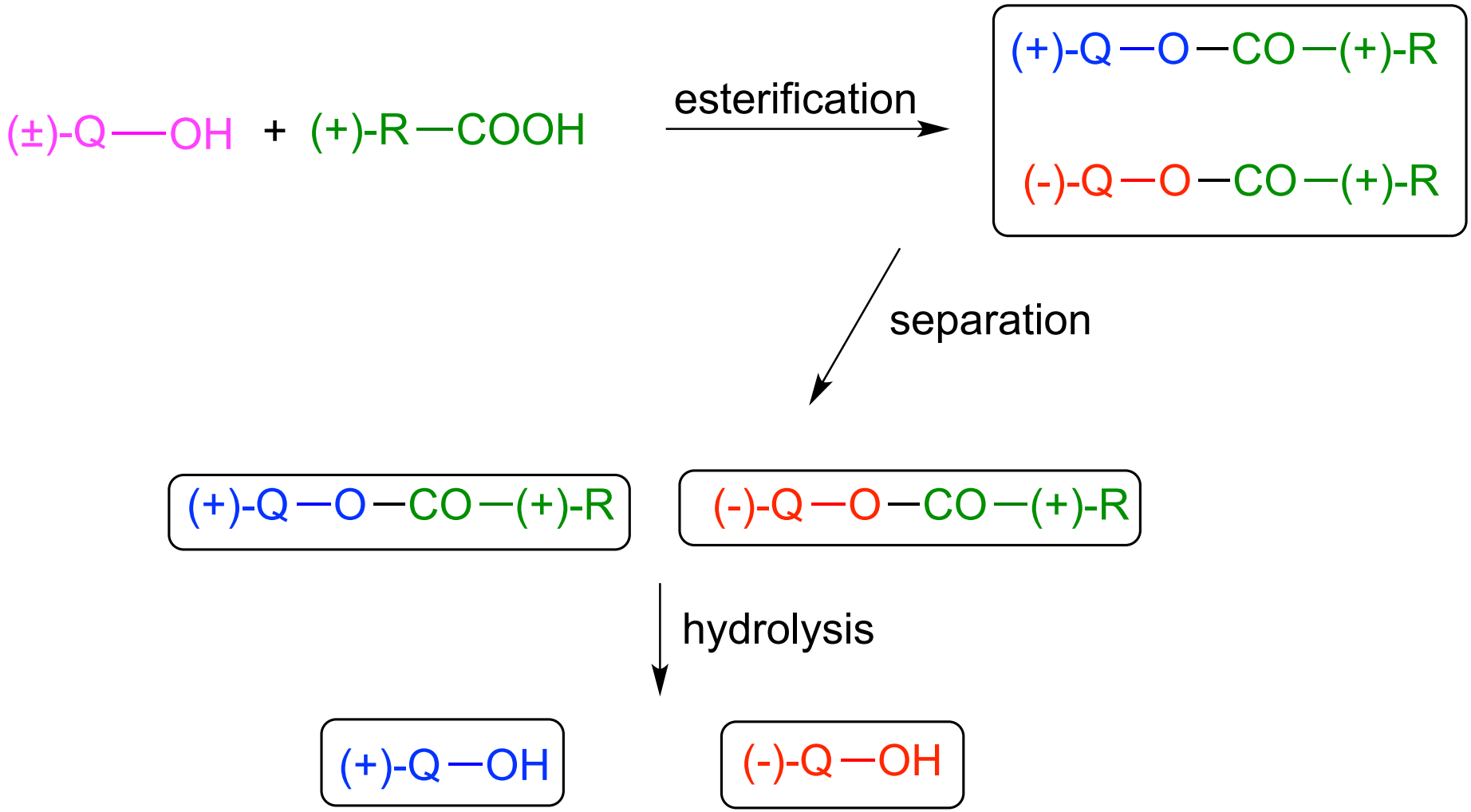


(R,R)-tartaric acid derivatives
pl. R = H, benzoyl, acethyl

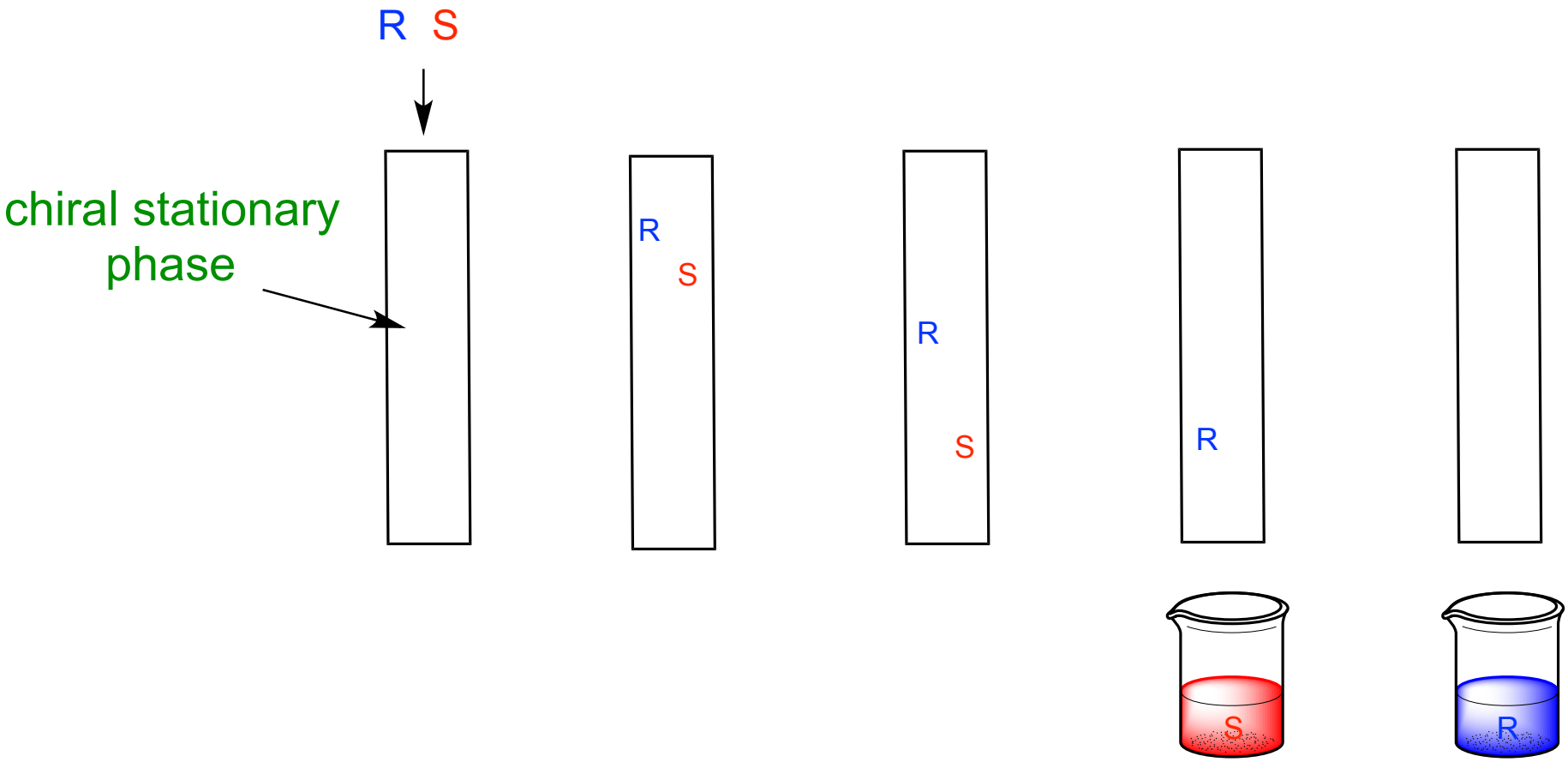


(*S*)-(+)-mandelic acid

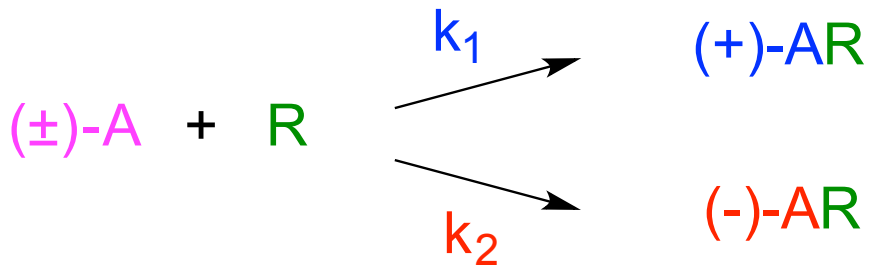
Optical resolution with derivatization



Optical resolution using chromatography

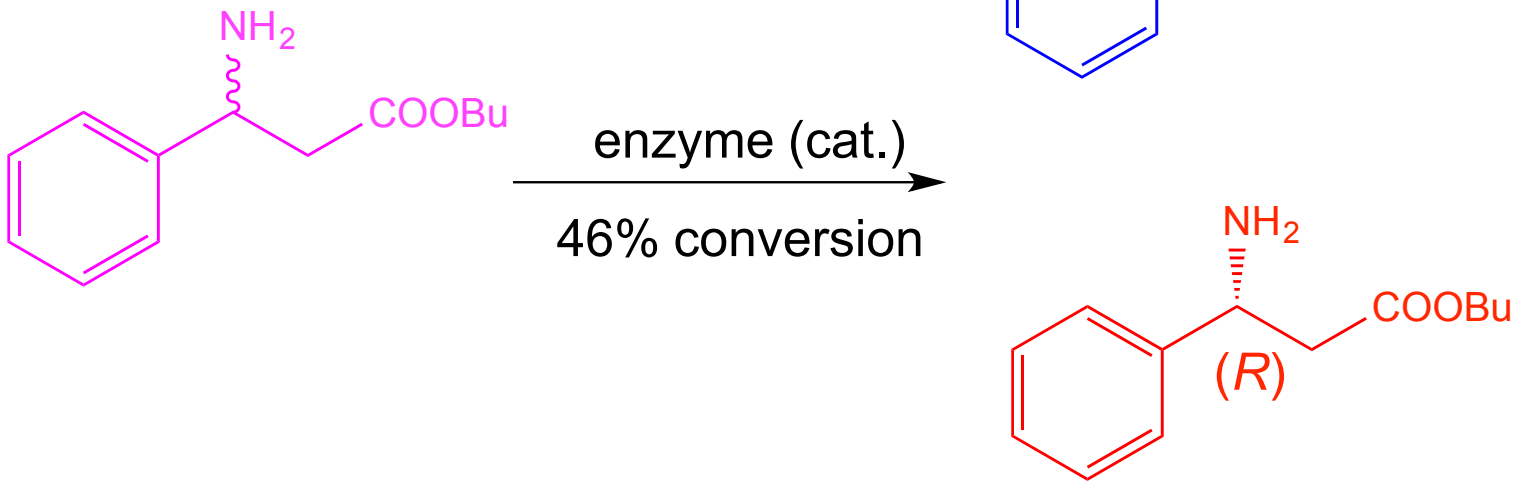


Kinetic resolution

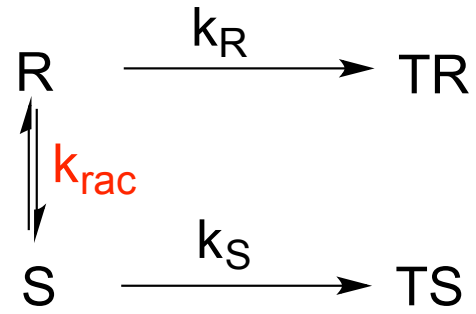


if $k_1 > k_2$, then end the reaction at a certain conversion gives [(+)-AR] > [(-)-AR]

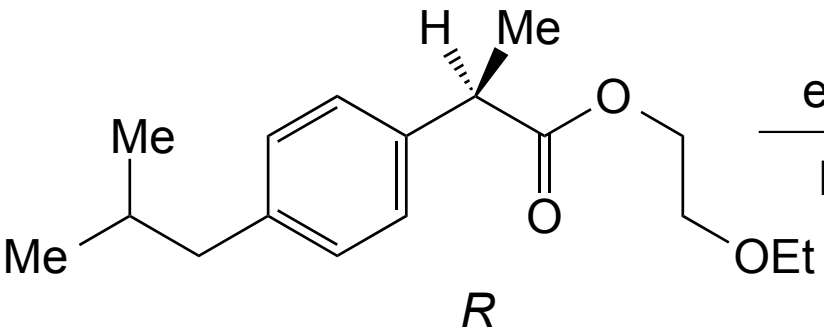
Example



Dynamic kinetic resolution



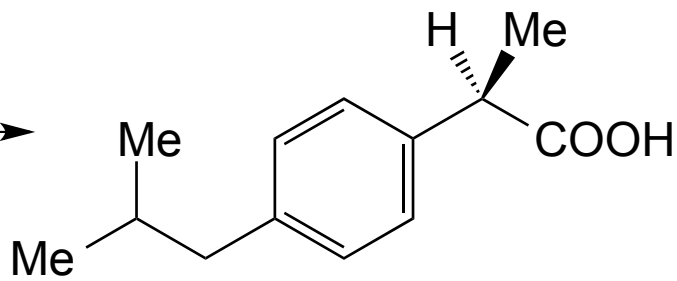
$k_{rac} > k_R > k_S$



R

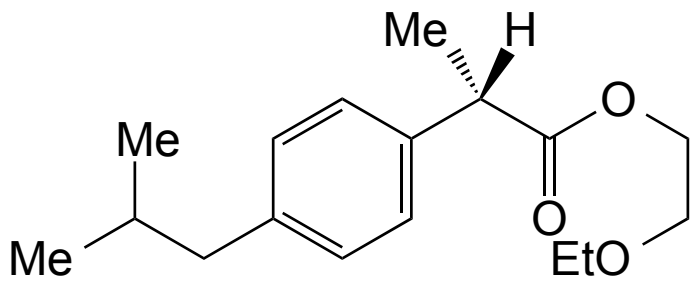
enzym

base



(*R*)-ibuprofen

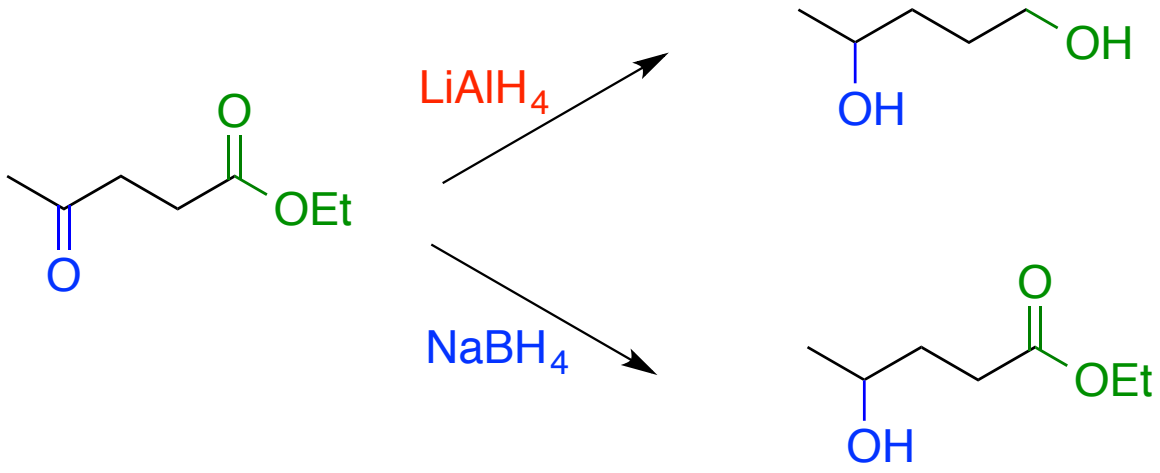
base



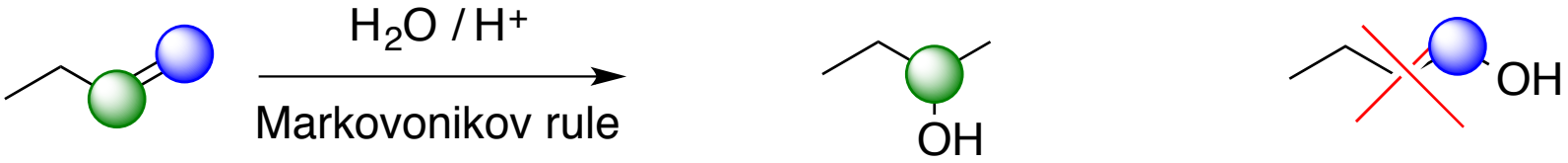
S

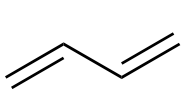
SELECTIVITY

Chemoselectivity

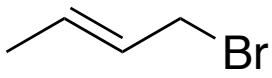


Regioselectivity

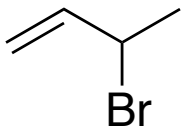




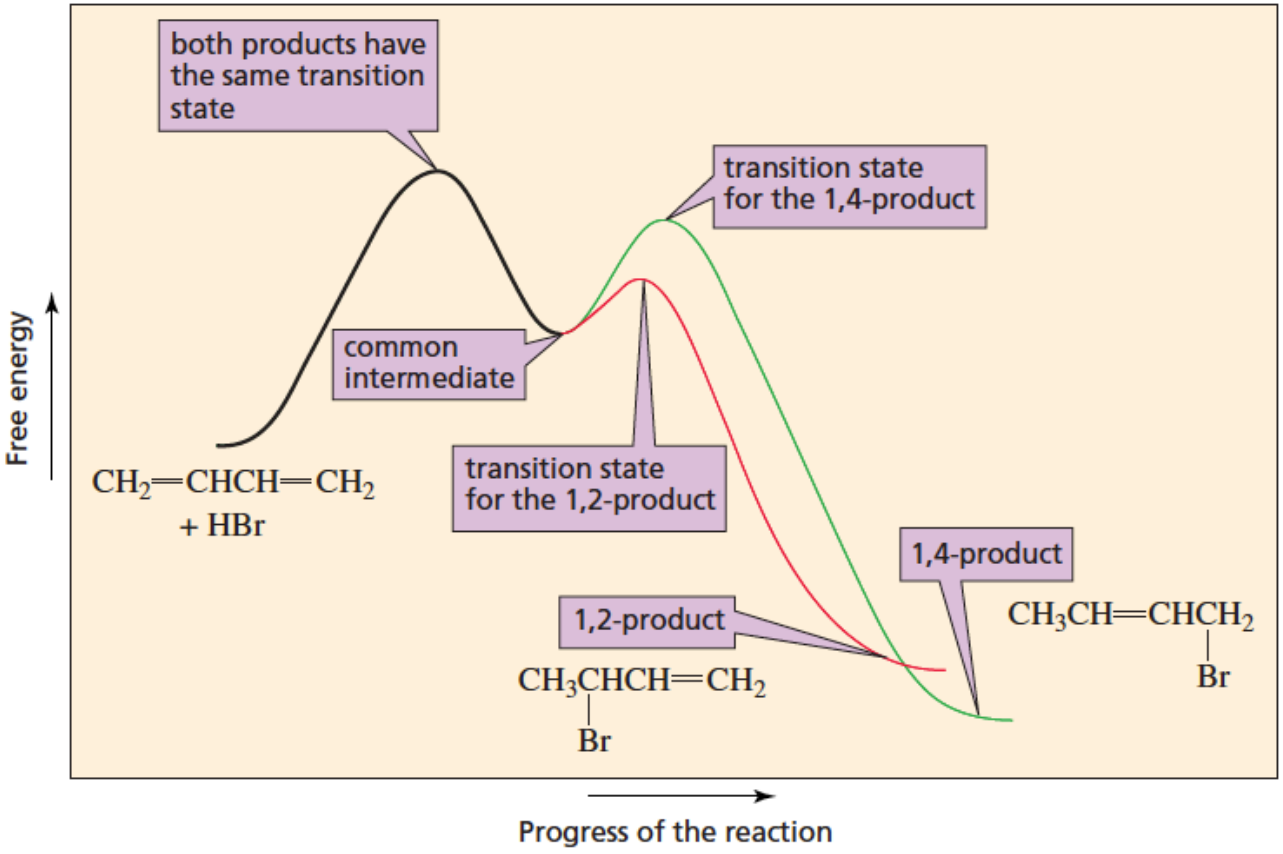
+ HBr



+

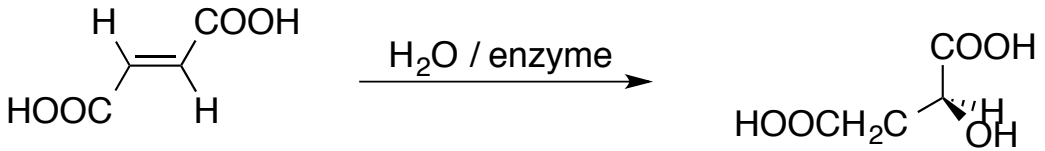


	thermodynamic control	kinetic control
40 °C	80 %	20 %
80 °C	20 %	80 %



Stereoselectivity

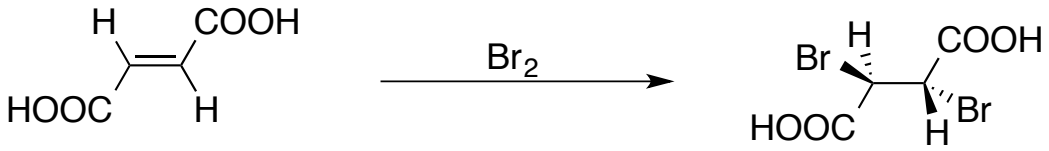
Describes reactions that have two mechanistically acceptable but stereochemically different pathways, so that the molecule may select the more favorable (e.g. the faster pathway - kinetic control; or the more stable product - thermodynamic control).



fumaric acid (*S*)-malic acid

Stereospecific reactions

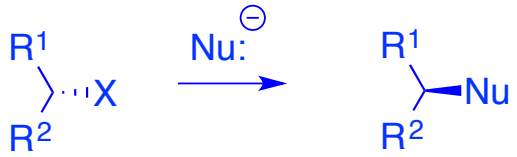
Gives specific and predictable stereochemical outcomes because the mechanism of the reaction demands this.



fumaric acid

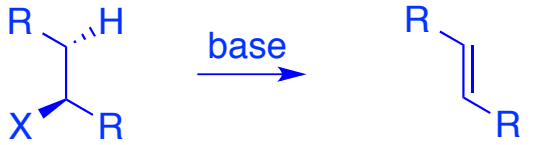
Stereospecific reactions

Substitution S_N2



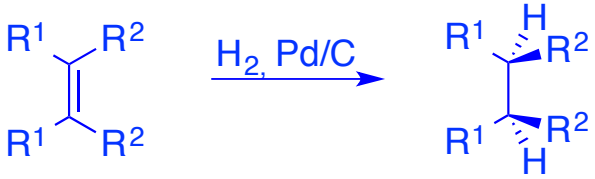
inversion

Elimination E2



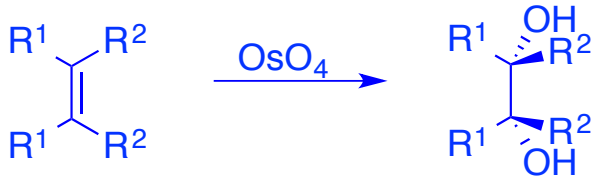
anti-periplanar X and H

Hydrogenation
of alkenes and alkynes



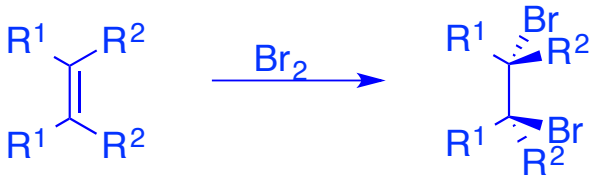
cis addition

Electrophilic addition
to alkenes



cis addition

Electrophilic addition
to alkenes



trans addition