# Stereochemistry at Tetrahedral Centers

# Chirality = “handedness”

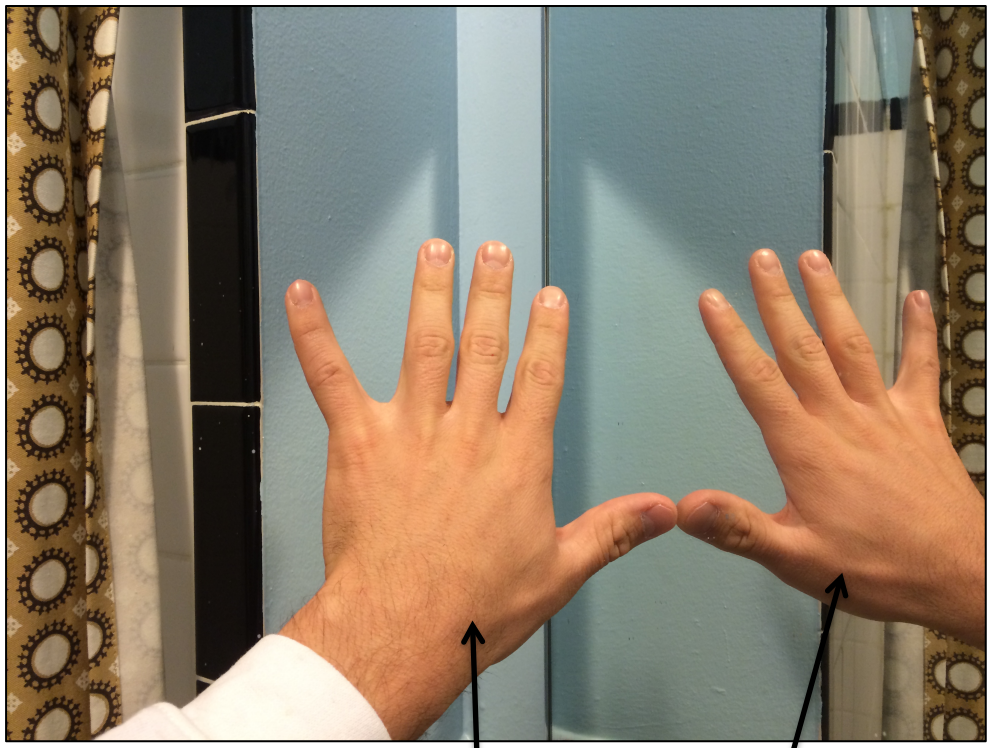
- ***Macroscale consequences:***

  - gloves, keys, screws, musical instruments, records, etc…

- ***Chemical consequences:***

  - 500+ pharmaceuticals, biological molecules (carbohydrates, amino acids, nucleic acids), smells/ flavoring agents, catalysts, plastics/polymers, etc…

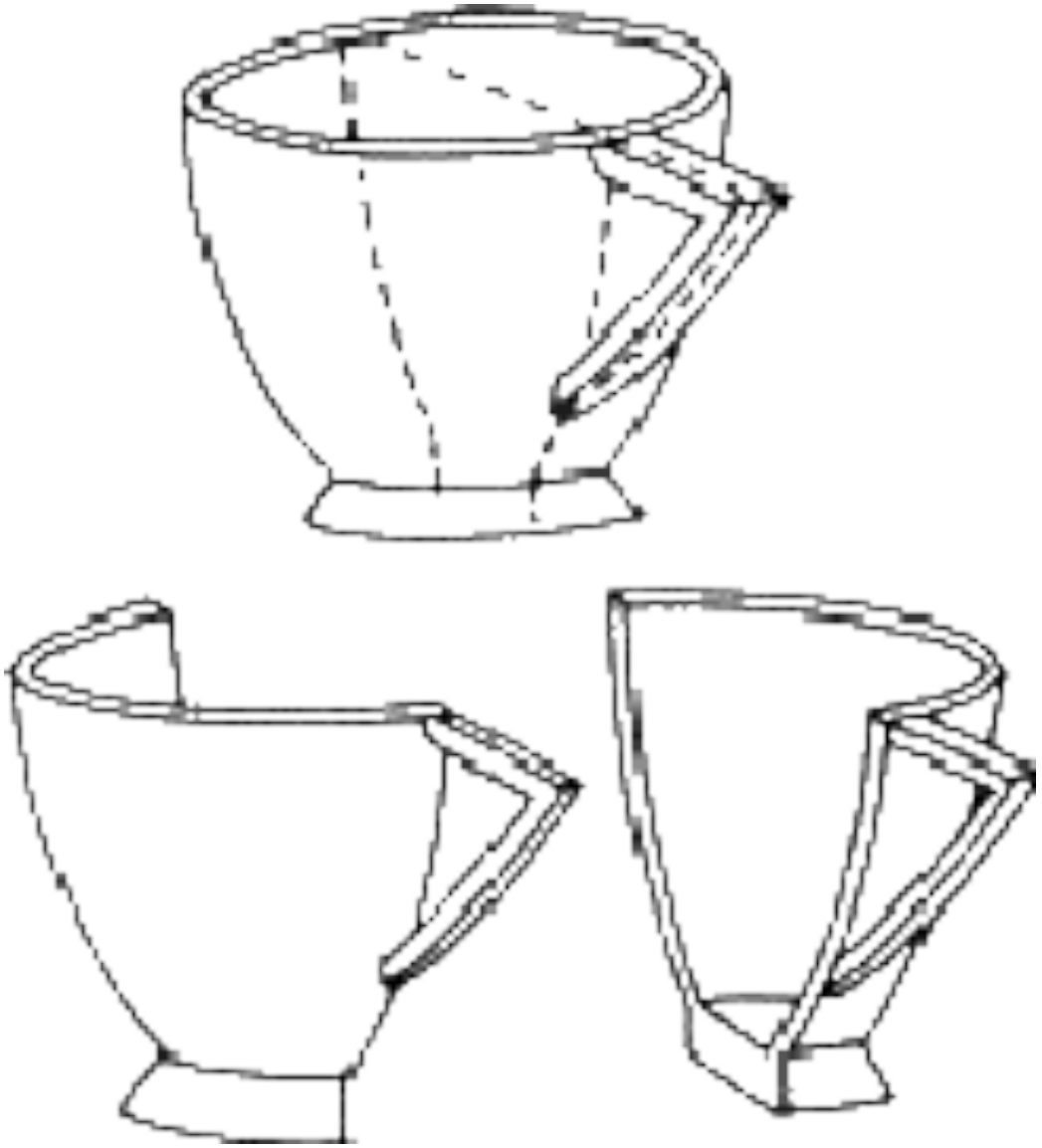
***Any non-superimposable mirror image that does not have a plane of symmetry has “chirality”***



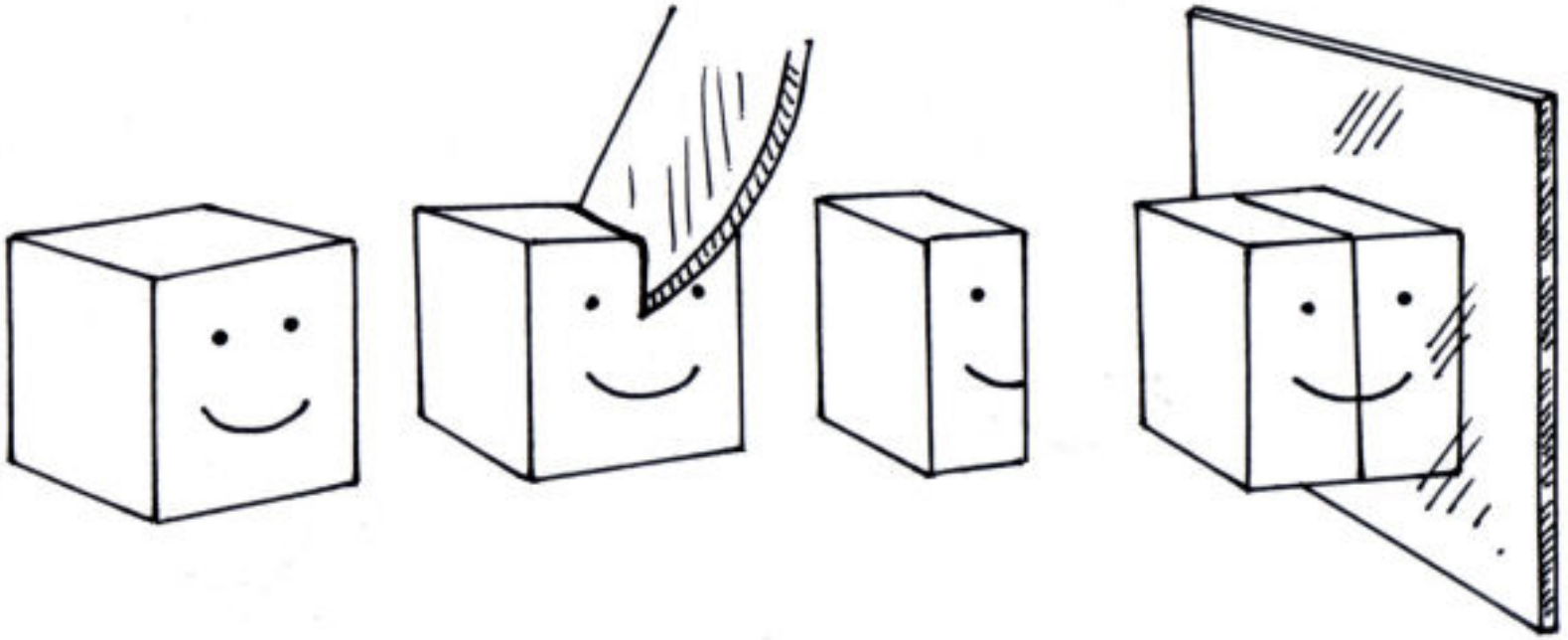
Left hand

Mirror image of left hand

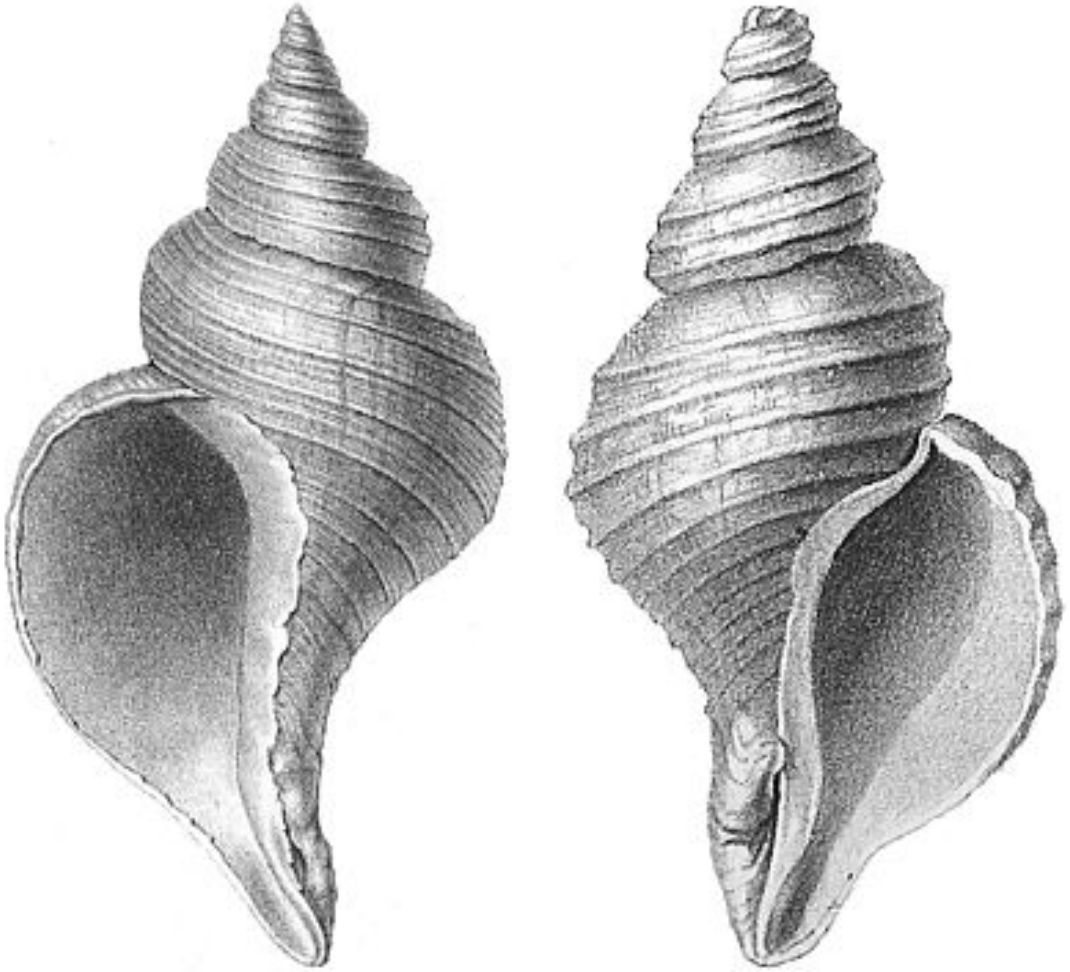
# Things that have a plane of symmetry are “achiral”



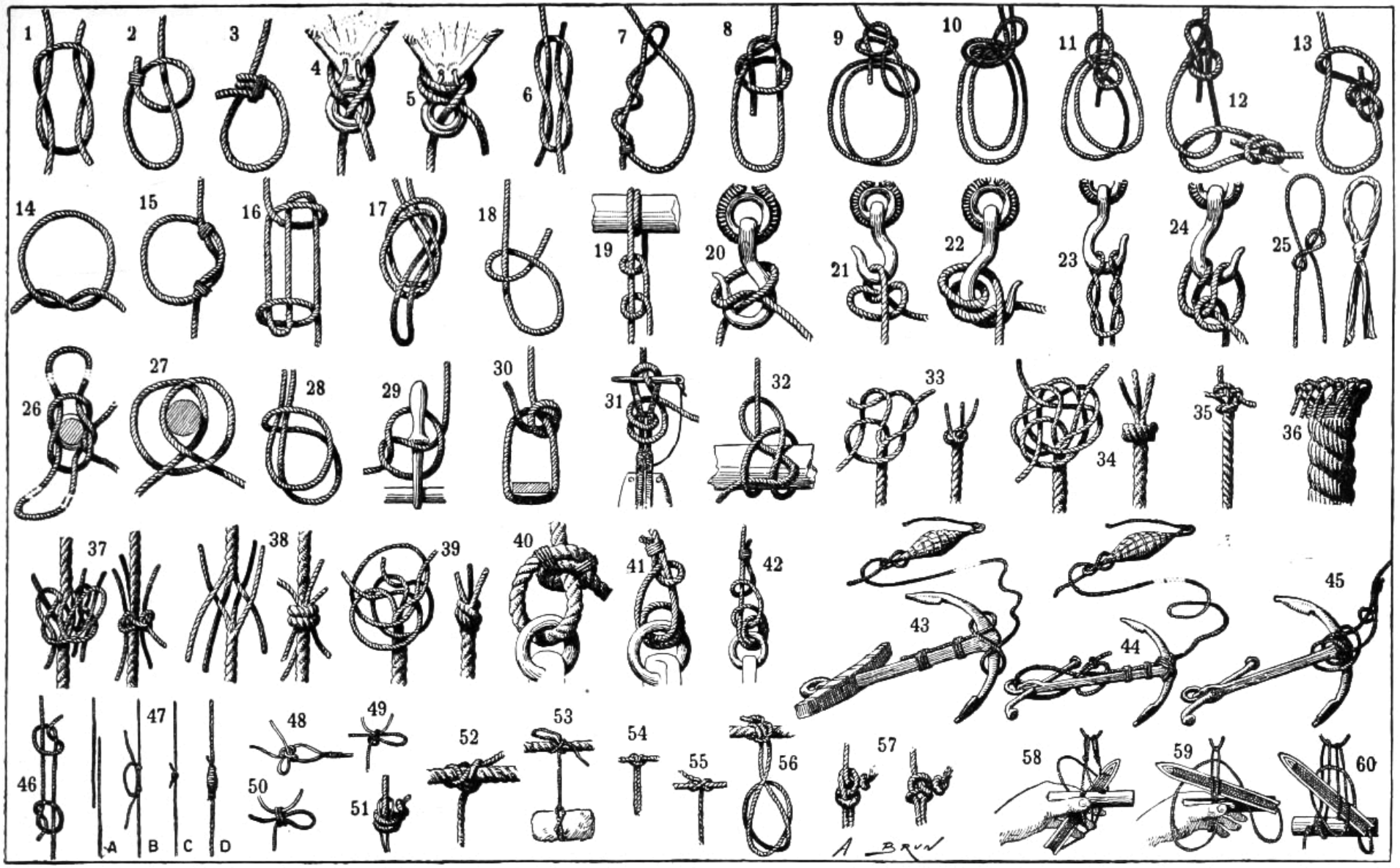
# This thing is achiral



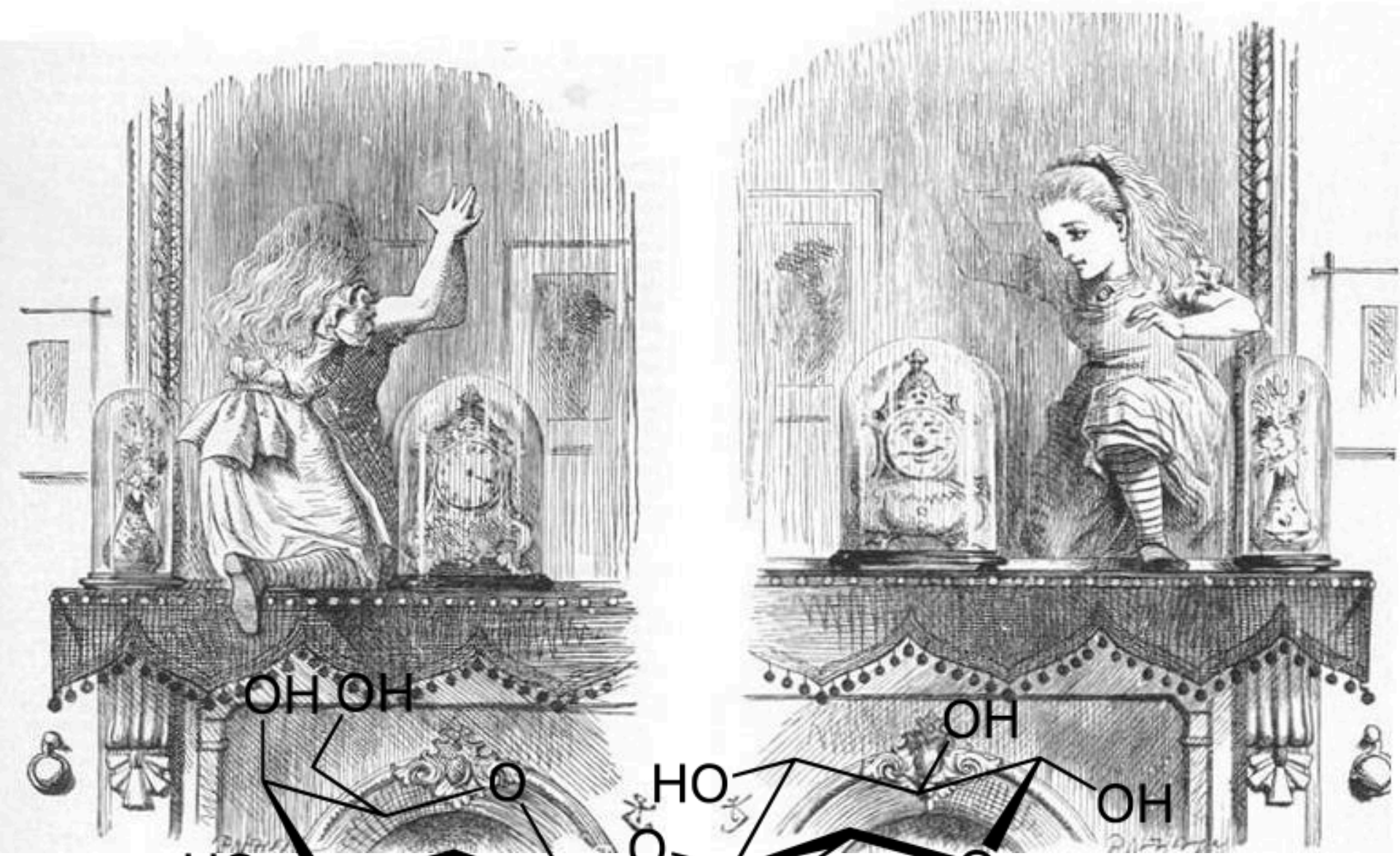
*"Perhaps it is trivial or obvious that life is chiral when looking at the nautilus, but this obvious chirality is a macroscopic feature which belies the fine arrangement of atoms which defines the chirality of biomolecules" The Astronomist (Jan 21, 2011)*



# Things that do not have a plane of symmetry are "asymmetric"



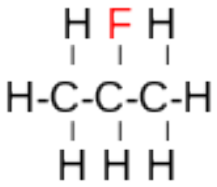
“Perhaps looking glass milk isn’t good to drink” – Alice (1871) *Through the Looking Glass*

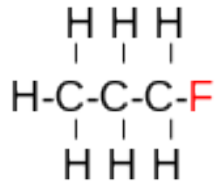



*D- lactose*

# Isomers

Constitutional (structural) isomers

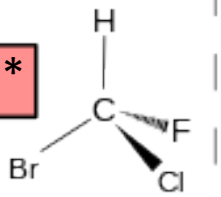


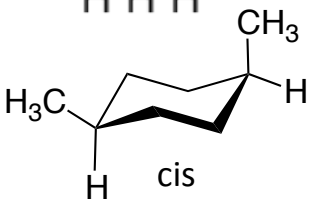


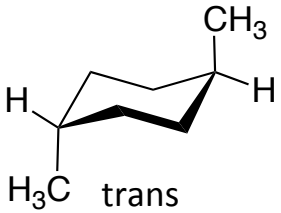
Stereoisomers (spatial isomers)

Diastereomers

Enantiomers *

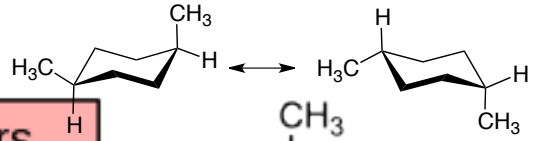




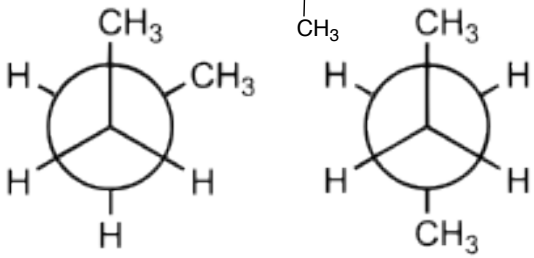



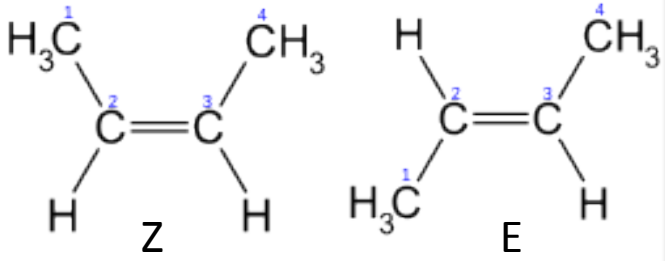

*cis/trans* isomers

***Chiral*** diastereomers **



Conformers






Rotamers

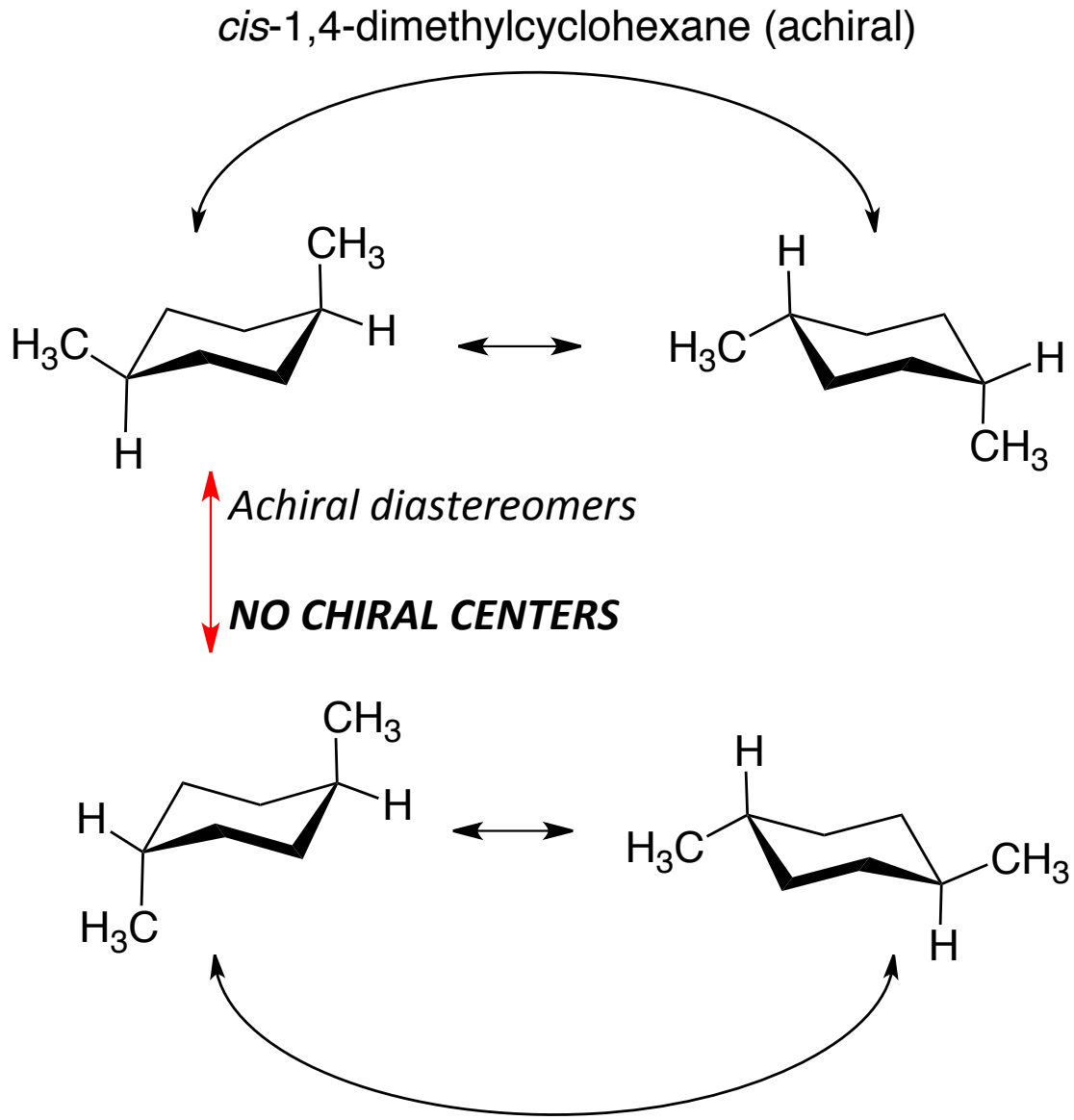
E/Z isomers

*Enantiomers *require least 1 chiral carbon atom* (a carbon bonded to 4 *different* substituents)

** Chiral diastereomers require at least 2 chiral carbon atoms

*** cis/trans isomers and E/Z isomers can be achiral

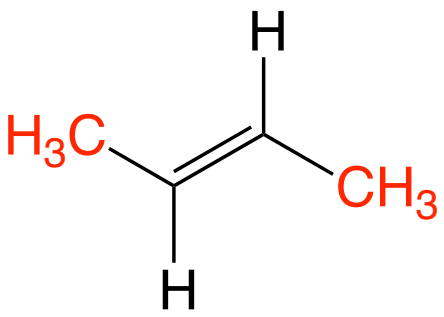
# Cis/Trans and E/Z Isomers: Achiral Diastereomers



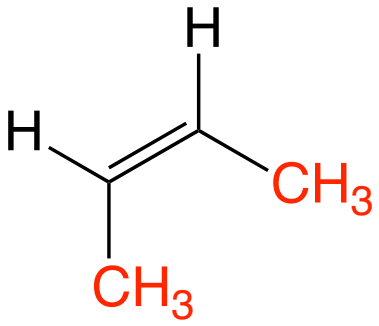
# Cis/Trans Isomers

- Priority is given to the longest alkyl chain with *cis-trans* nomenclature
- ***cis*** **= longest chains on same side of double bond**
- ***trans*** **= longest chains on opposite side of double bond**
- Best used for di-substituted alkenes
- Terminal alkenes cannot be cis-trans

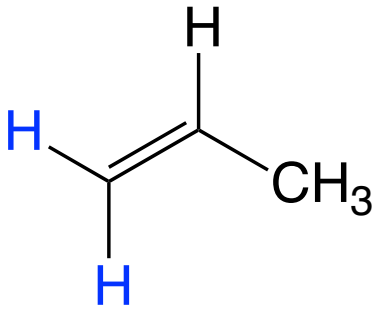
*Trans-2-butene*

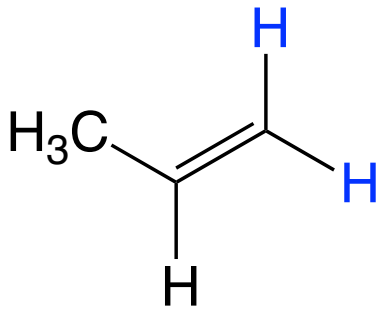



*Cis-2-butene*



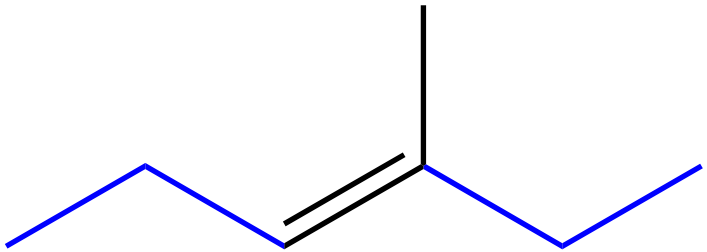

***cis/trans*** isomers
Di-substituted alkene



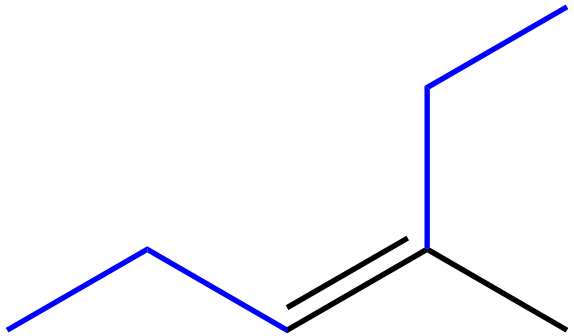




***not*** isomers
Mono-substituted alkene
Terminal alkene

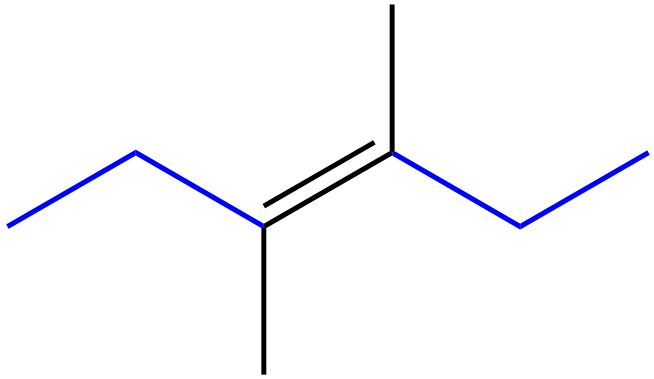
# *cis/trans* tri- and tetra- substituted alkenes



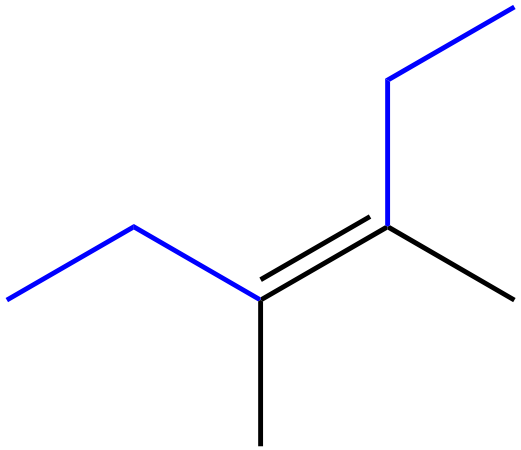
*trans*-3-methylhex-3-ene



*cis*-3-methylhex-3-ene

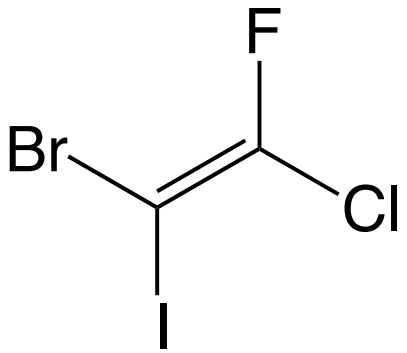


*trans*-3,4-dimethylhex-3-ene

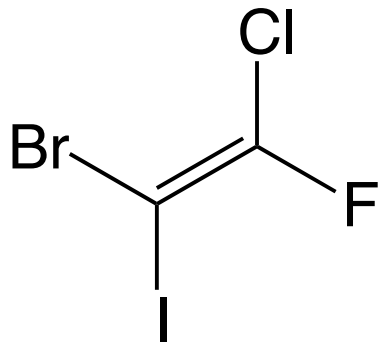


*cis*-3,4-dimethylhex-3-ene

# Sometimes the cis/trans system does not work…




1-bromo-2-chloro-
2-fluoro-1-iodoethene



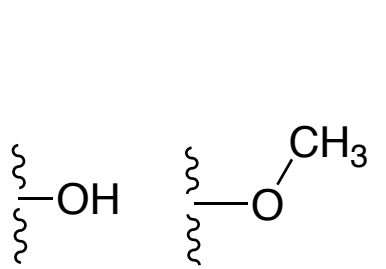

1-bromo-2-chloro-
2-fluoro-1-iodoethene

# Cahn-Ingold-Prelog Rules

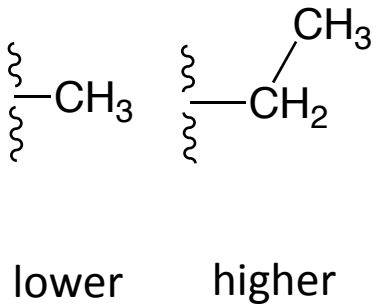
1. Rank the 4 atoms connected to chiral carbon:

| Atomic # | 35 | | 17 | | 16 | | 15 | | 8 | | 7 | | 6 | (2) | 1 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Higher ranking* | Br | > | Cl | > | S | > | P | > | O | > | N | > | C | $^{2}$H | $^{1}$H | *Lower ranking* |

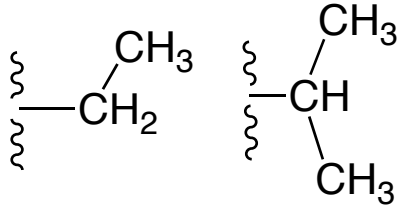
2. If a decision is not possible by 1st atom, look at 2nd, 3rd, 4th… until first difference is reached



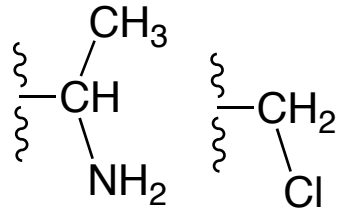

lower higher




lower higher



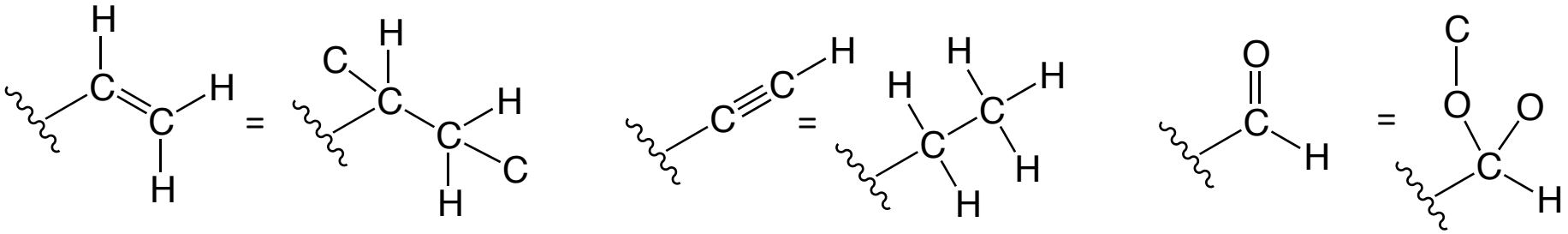

lower higher




lower higher

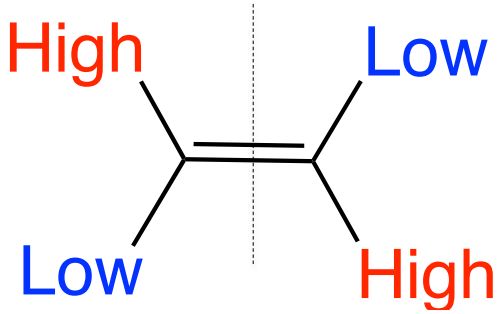
# Cahn-Ingold-Prelog Rules

3. Multiple bonds are equivalent to the same number of singly bonded atoms (i.e. split the multiple bond)



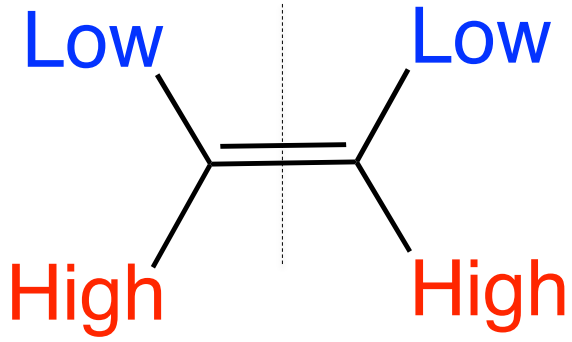
# Use the E/Z designation to describe achiral alkene diastereomers

- Works for all alkene systems
- Cahn-Ingold-Prelog rules apply for prioritizing substituents
- "Highest priority" substituent can be priority 1 and 2 or 1 and 3
- Highest priority substituents ***must*** be on separate $sp^2$ carbons




**E**

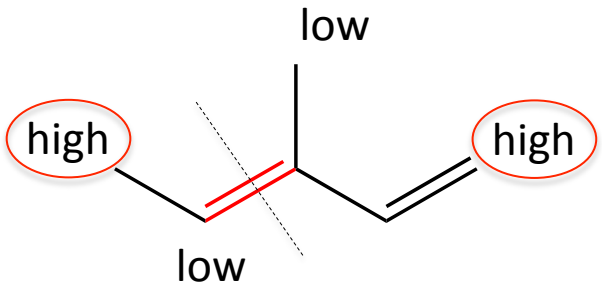
"*Entgegen*" German, ***opposite***
Highest ranking groups on *opposite* side of double bond
(and on different $sp^2$ cabon atoms)




**Z**

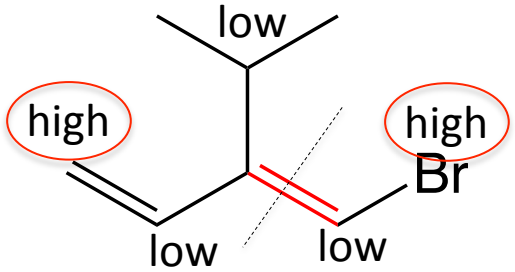
"*Zusammen*" German, ***same***
Highest ranking groups on *same* side of double bond
(and on different $sp^2$ cabon atoms)

# E/Z examples



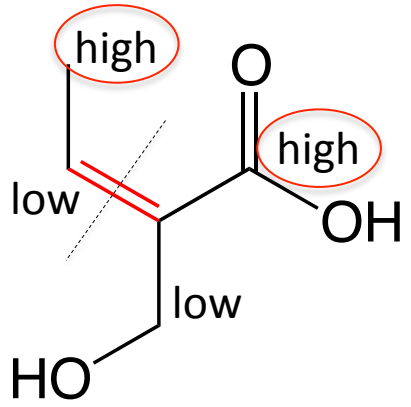

(*E*)-3-methyl-1,3-pentadiene

"High" are on opposite sides of double bond




(*E*)-1-bromo-2-isopropyl 1,3-butadiene

"High" are on opposite sides of double bond

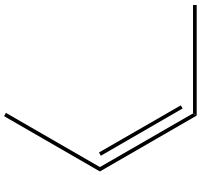



(*Z*)-2-hydroxymethyl 2-butenoic acid

"High" are on same side of double bond

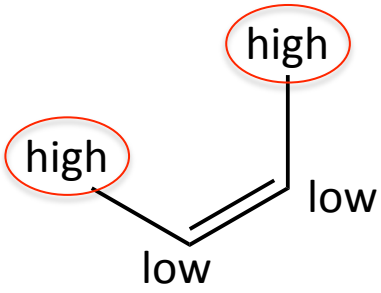
# There is no specific relationship between cis-trans and E/Z

- They are based on fundamentally different naming rules

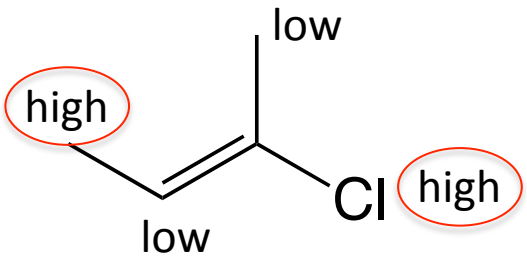


*cis*-but-2-ene
(*Z*)-but-2-ene

*trans*-but-2-ene
(*E*)-but-2-ene

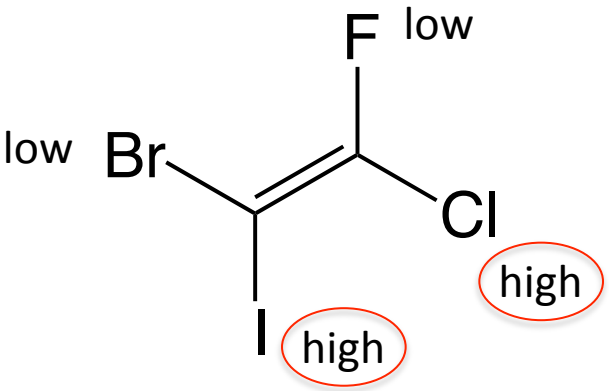



*cis*-2-but-2-ene
(Z)-2-but-2-ene

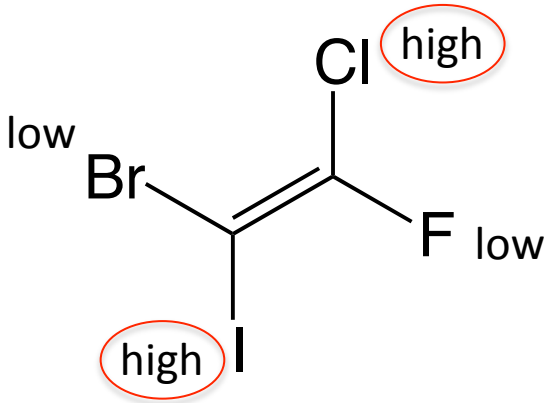



*cis*-2-chlorobut-2-ene
(E)-2-chlorobut-2-ene

# E/Z systems when it's impossible to name using *cis/trans*

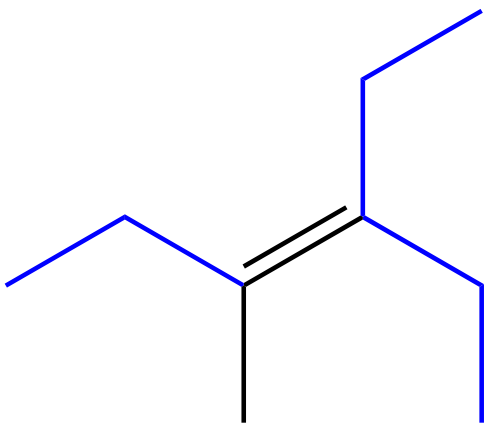



(*Z*)-1-bromo-2-chloro-2-fluoro-1-iodoethene

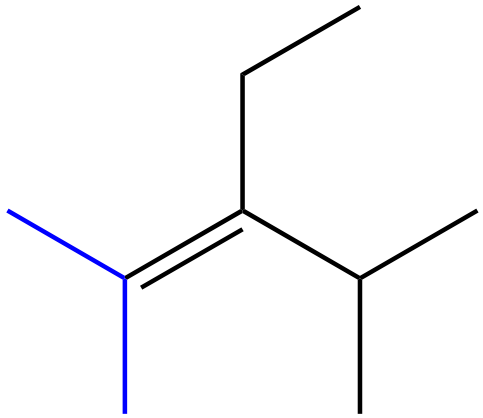



(*E*)-1-bromo-2-chloro-2-fluoro-1-iodoethene

# ***Non****-cis/trans,* ***non*** *E/Z* alkenes



3-ethyl-4-methylhex-3-ene



3-ethyl-2,4-dimethylpent-2-ene

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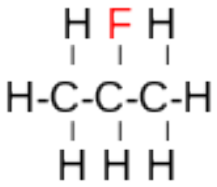

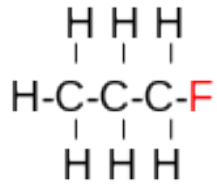

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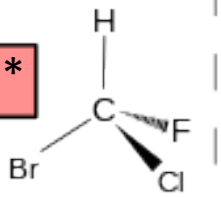
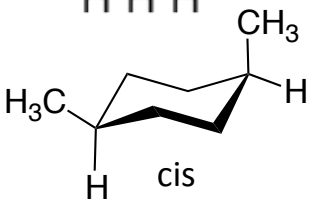
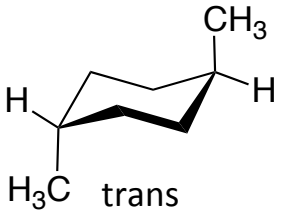
Enantiomers *

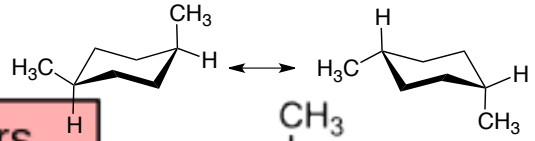




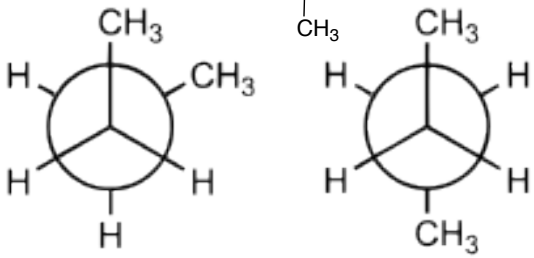



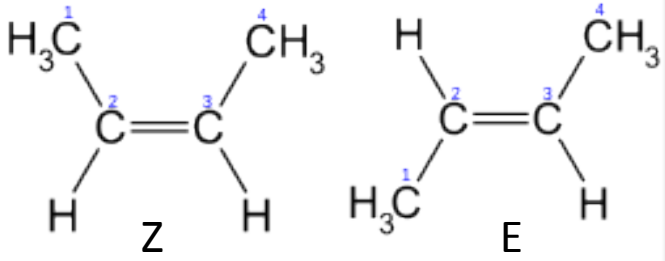

*cis/trans* isomers

***Chiral*** diastereomers **



Conformers






Rotamers

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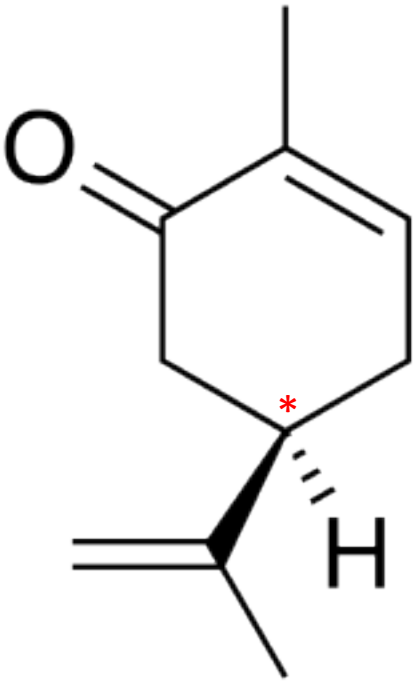
** Chiral diastereomers require at least 2 chiral carbon atoms

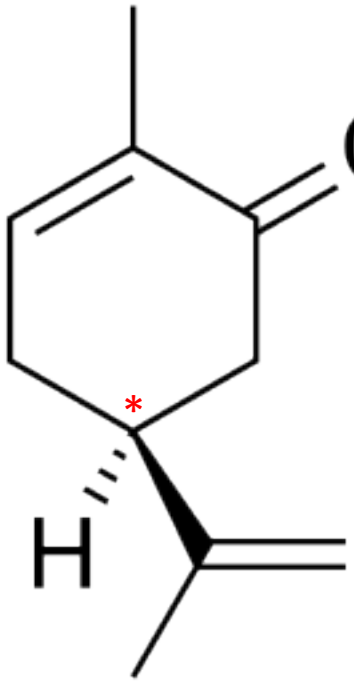
*** cis/trans isomers and E/Z isomers can be achiral

# Double your pleasure, double your fun


Spearmint leaves
(minty tasting)




***R*-enantiomer of carvone**



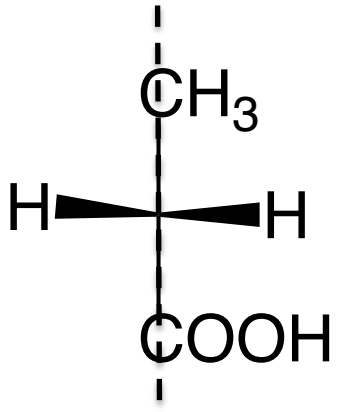

***S*-enantiomer of carvone**

Caraway seeds
(liquorice tasting)

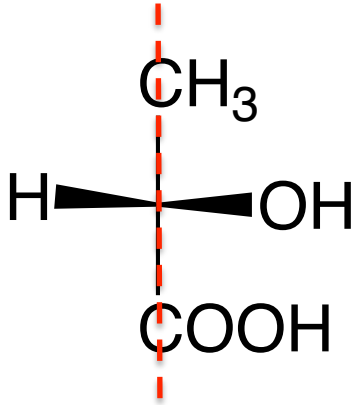
* = a chiral center or chiral carbon atom

# Chiral Carbon Atoms

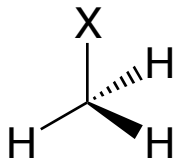
- Carbon atom must be bonded to 4 distinct atoms or functional groups
- Molecules with multiple chiral carbon atoms can be enantiomers or (chiral) diastereomers
- “chirality center” or “stereocenter”

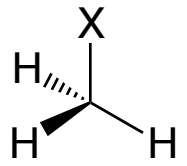



Propanoic acid
(achiral)

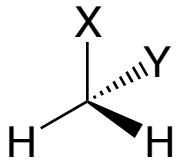


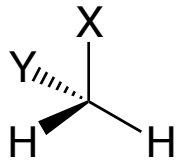

Lactic acid
(chiral)




NO

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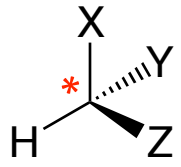
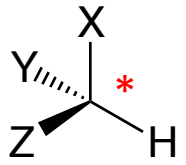
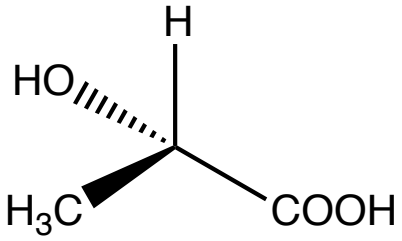


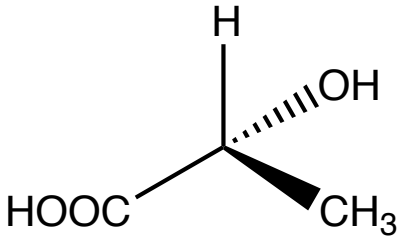

YES

# Enantiomers

- Molecules that are non-superimposable mirror images (optical isomers, like your hands)

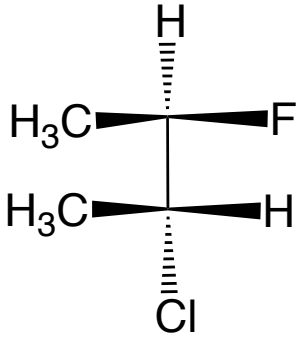



S lactic acid

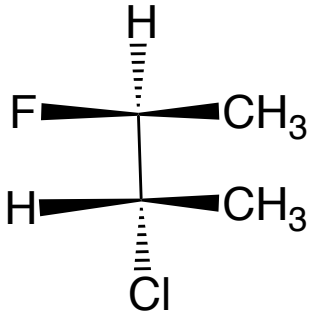



R lactic acid

- Enantiomers can have more than one chiral carbon atom




(2*R*,3*R*)-2-chloro-3-fluorobutane



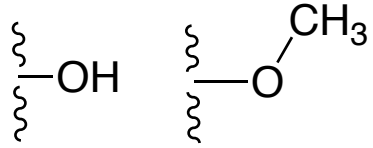

(2*S*,3*S*)-2-chloro-3-fluorobutane

# Cahn-Ingold-Prelog Rules

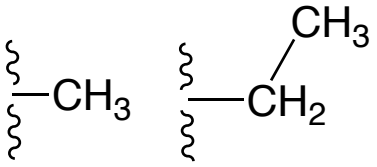
1. Rank the 4 atoms connected to chiral carbon:

| Atomic # | 35 | | 17 | | 16 | | 15 | | 8 | | 7 | | 6 | (2) | 1 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Higher ranking* | Br | > | Cl | > | S | > | P | > | O | > | N | > | C | $^{2}$H | $^{1}$H | *Lower ranking* |

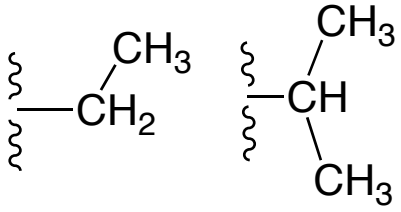
2. If a decision is not possible by 1st atom, look at 2nd, 3rd, 4th… until first difference is reached



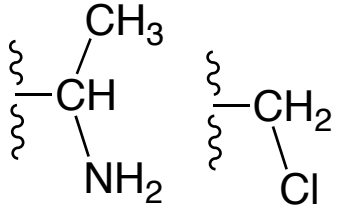

lower higher




lower higher



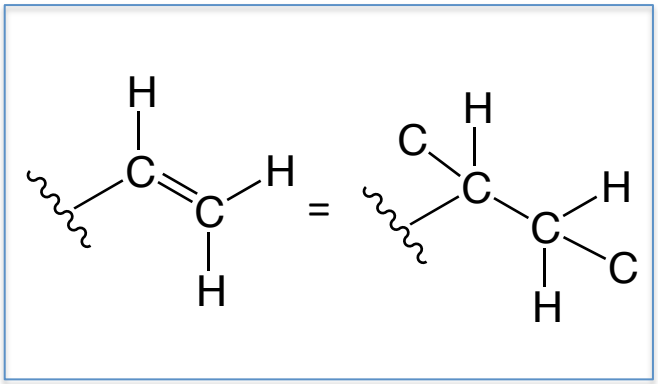

lower higher

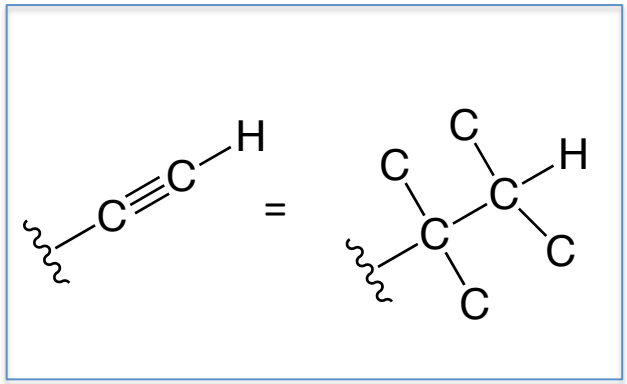


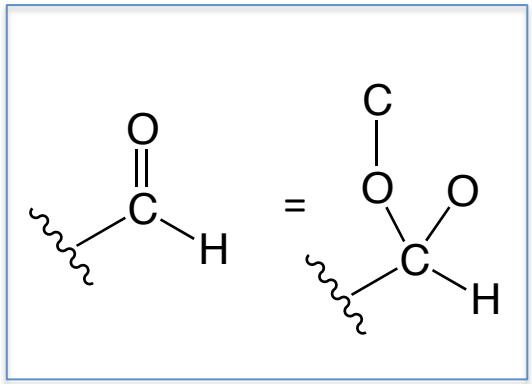

lower higher

# Cahn-Ingold-Prelog Rules

3. Multiple bonds are equivalent to the same number of singly bonded atoms (i.e. split the multiple bond)



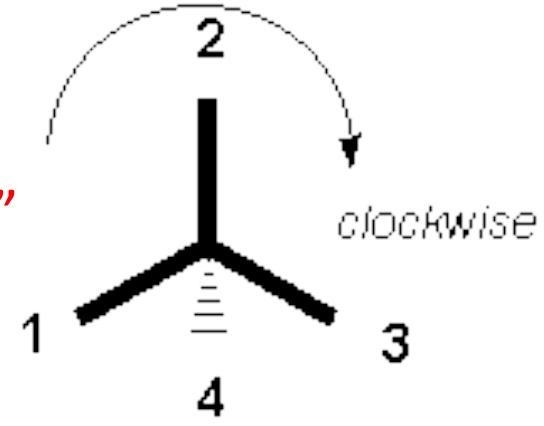
# Assigning *R* and *S* configurations at chiral centers using Cahn-Ingold-Prelog

1. Draw the chiral carbon and place the lowest ranking substituent (usually H) in the back

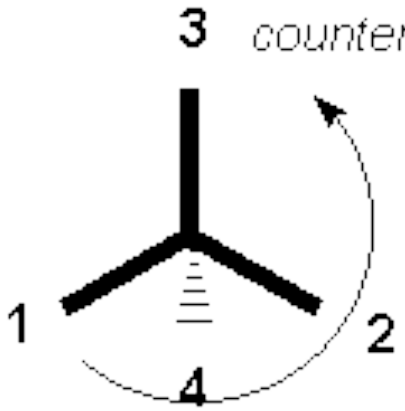
2. If 1, 2, 3 is clockwise it's and *R* configured carbon. If 1, 2, 3 is counter-clockwise it's and *S* configured carbon

3. If H cannot be easily placed in the back, flip the assignment

"Rectus"



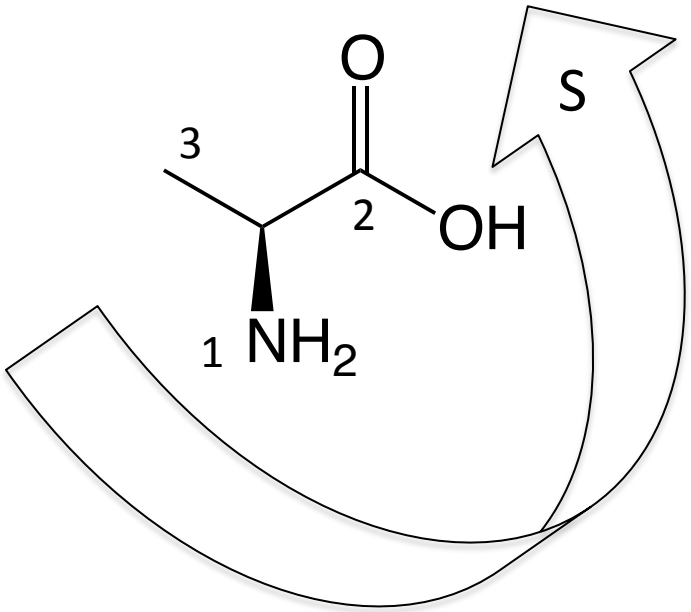

*R* configuration

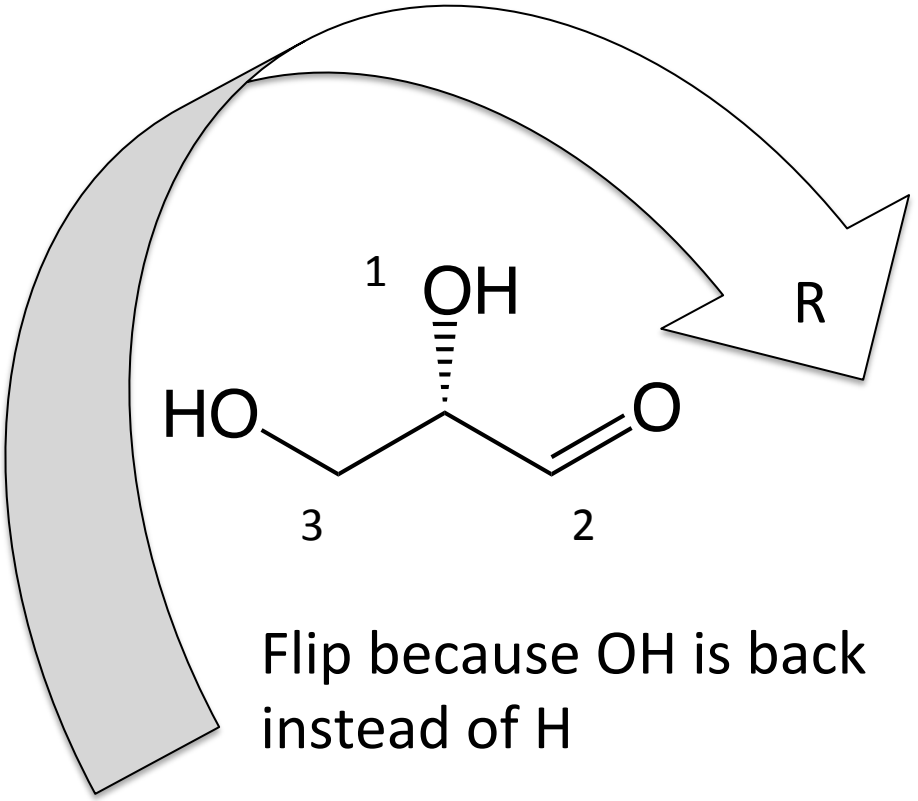



*S* configuration

"Sinister"

# Assigning *R* and *S* Configuration




Flip because OH is back instead of H

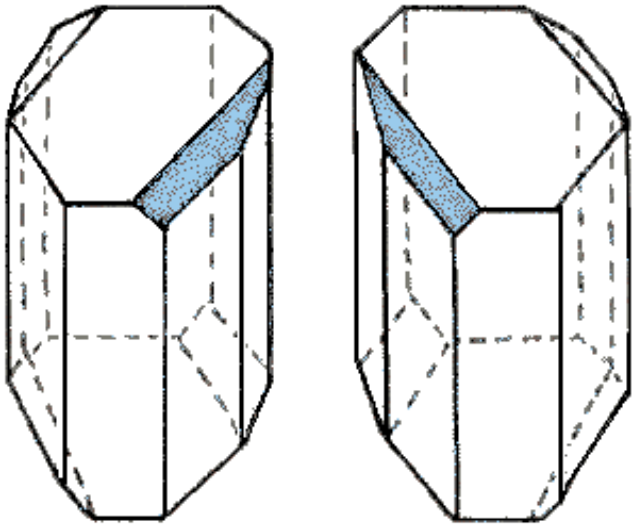
***So instead of R its S***

# Draw/model examples of achiral and chiral compounds (and enantiomers when appropriate) and assign R or S configuration to each enantiomer

- 5-bromodecane (chiral)
- methylcyclohexane (achiral)
- 1,2-dimethylcyclohexane (achiral)
- 1,1-ethylmethycyclopentane (chiral)
- 2-methylcyclohexanone (chiral)
- 2-butanol (chiral)

# Discovery of Enantiomers

- Tartaric acid crystals from wine by Louis Pasteur (1848)
- Separated mixture of enantiomers using tweezers!
- Enantiomers have identical physical properties (melting point, solubility, etc.)
- Melting point of mixture is elevated



*Crystals of + and – tartaric acid recreated from Pasteur's lab notebook*

| | Melting point, °C | $[\alpha]_D^{25\,°C}$ | Solubility, g/100 g $H_2O$ at 15 °C |
|---|---|---|---|
| (2*R*,3*R*)-(+)-Tartaric acid | 170 | +11.98° | 139 |
| (2*S*,3*S*)-(−)-Tartaric acid | 170 | −11.98° | 139 |
| (2*R*,3*S*)-Tartaric acid | 140 | 0° | 125 |
| (±)-Tartaric acid | 206 | 0° | 139 |

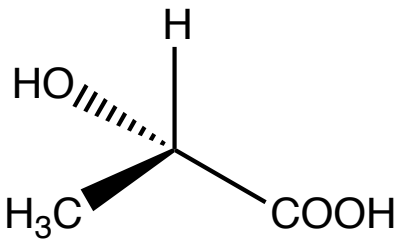
# Optical Activity of Enantiomers

- Enantiomers can rotate ***polarized light*** in opposite directions

  \+ (D) *or* – (L)

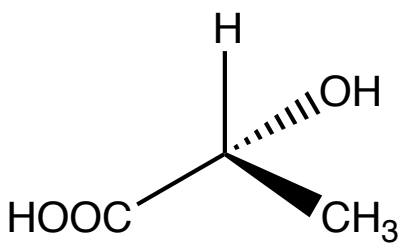
- *Racemic Mixtures* are 1:1 molar mixtures of enantiomers and give zero optical rotation of polarized light ($\alpha_D = 0$)

  ± *or* D/L




(+) lactic acid

$\alpha_D = + 3.82$




(-) lactic acid

$\alpha_D = - 3.82$

$\alpha_D = \alpha / l\, c$

*Where:* $\alpha_D$ = specific rotation of sample

$\alpha$ = observed rotation (degrees)

*l = path length (decimeters)*

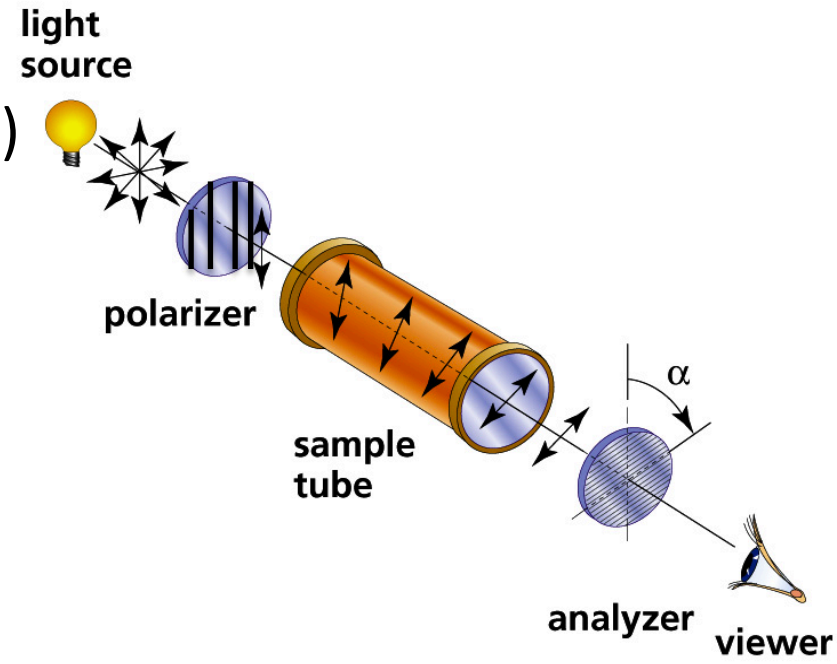
*c = concentration (g/cm$^3$)*

# Measuring Specific Rotation of a Sample

- Solutions of *some* organic molecules rotate plane polarized light (Biot, early 1800s)
- Angle and direction of rotation ($\alpha$) is measured in a *polarimeter.*
- Left (counter clockwise)

  = *levorotatory* (-)
- Right (clockwise

  = *dextrorotatory* (+)

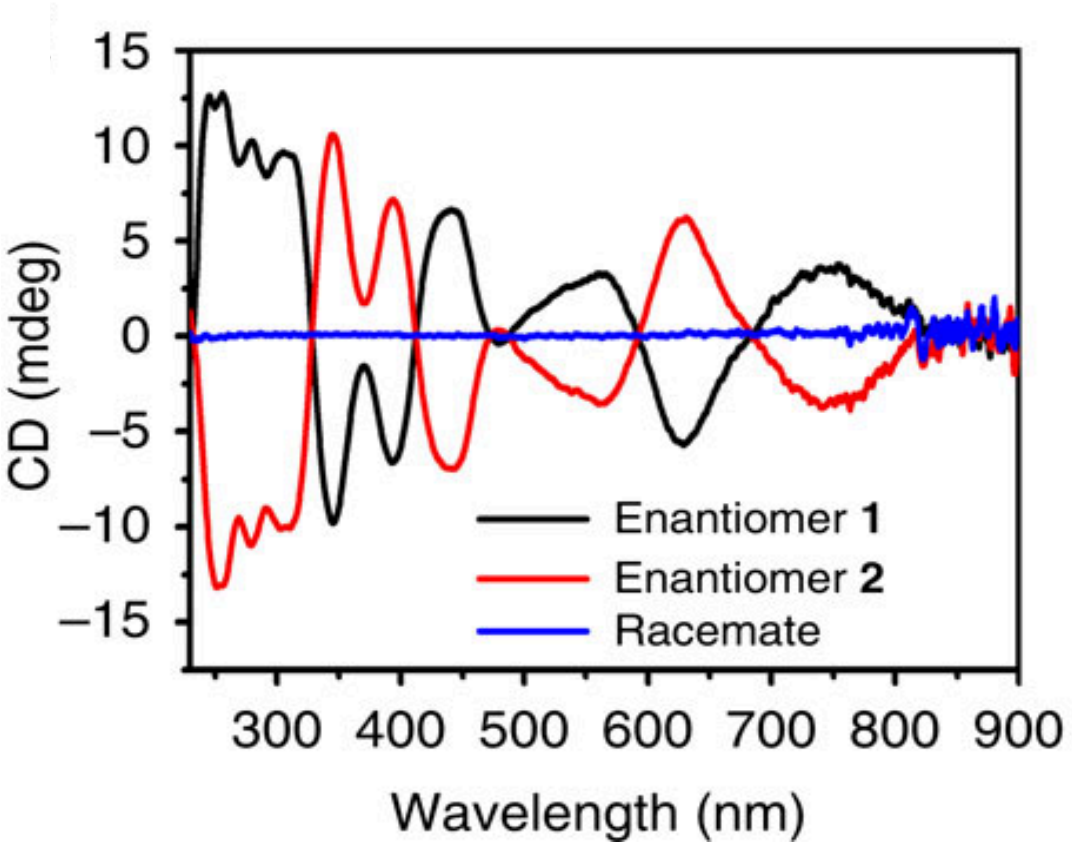



- Extent of rotation is dependent on path length (of sample tube) and concentration
- Specific rotation ($\alpha_D$) is measured at the "sodium D-line" (589.6 nm)

# Circular Dichroism (CD) Spectroscopy

- CD measures optical rotation through the full spectrum of wavelengths (not just 589.6 nm)
- Many sampling options (small molecules, DNA, proteins, etc.)
- Example = Gold nanoparticles with achiral thioether ligands $Au_{38}(SCH_2CH_2Ph)_{24}$
- However, the arrangement of the thioethers on the gold is chiral

These types of chiral metals are used in heterogeneous catalysis and modern optics

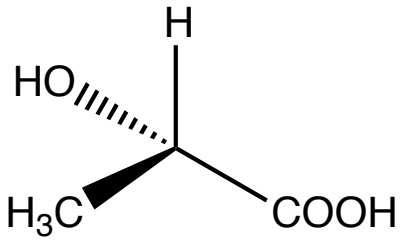



Dolamic et al, *Nat. Comm.* 3, 798, **2012**

# Calculations of Enantiomeric Excess (EE)

Specific rotation ($\alpha_D$) can be used to calculate reaction yields of enantiomeric ratios such as:

EE = [$\alpha_D$] observed / [$\alpha_D$] pure x 100




(+) lactic acid

$\alpha_D$ = + 3.82

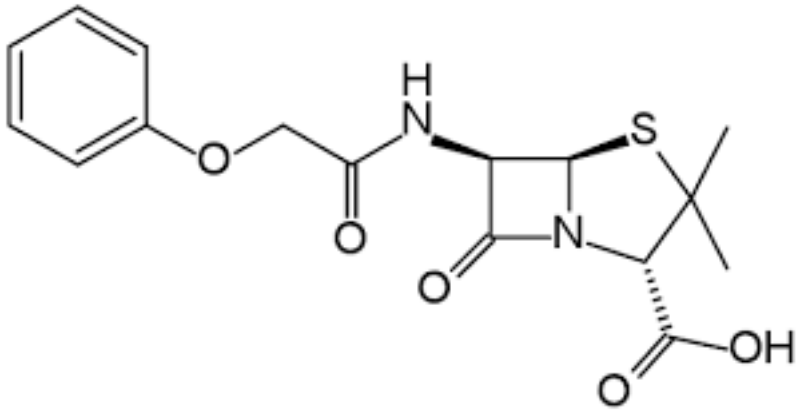
This is the $\alpha_D$ of the pure enantiomer

Data from polarimeter (observed) = $\alpha_D$ = + 1.42

*Therefore:*

EE = 1.42 / 3.82 x 100
= 37.2 %

# EE vs. Optical Purity




**Penicillin**

$\alpha_D$ = +233° for pure enatiomer

% optical purity = [$\alpha_D$] observed / [$\alpha_D$] pure x 100

[$\alpha_D$] observed for the sample is +93.2°
% optical purity for the sample is therefore 93.2°/233° x 100

***The remaining 60% of the sample is racemic mixture of enantiomers: 30% (+) and 30% (-)***

***Therefore, the calculated optical purity of (+) Penicillin in the sample is 70%***

# Non-linear effects of asymmetry

*Horeau Effect*: There is an observed non- equivalence between optical purity calculated from optical rotation data and the mass of each enantiomer after their resolution. Some enantiomers have different intramolecular interactions (i.e. internal H-bonds) which cause them to have different "shapes" and thus rotate light non-equally.

*Also*: When a chiral substance undergoes a reaction, the reaction rate and the product ratio will depend upon the enantiomeric excess present in the starting material.

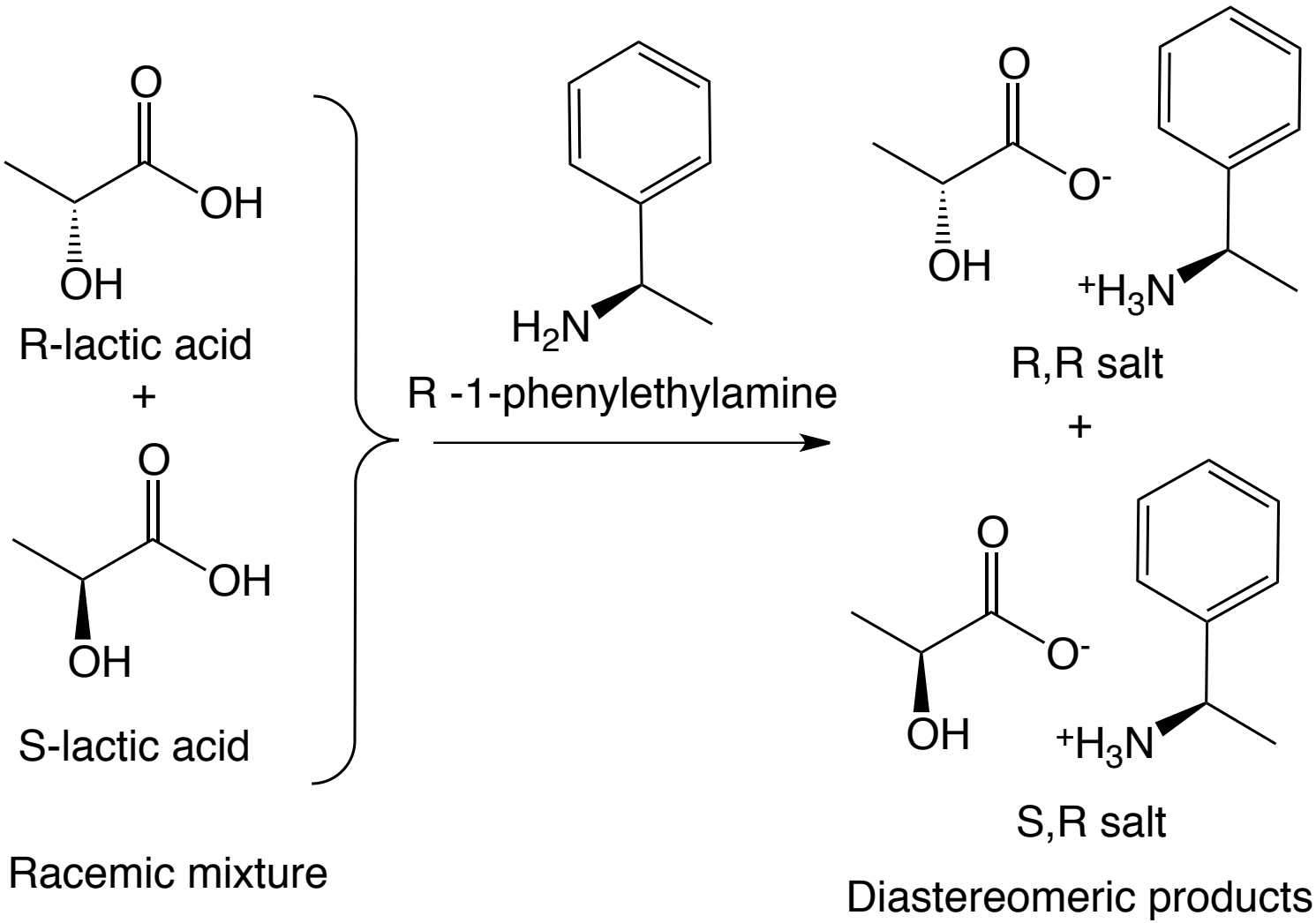
*Tetrahedron* **1973**, 29, 7, p 1055
*Angew Chem Int Ed* 1998, 37, 2922-2959

http://stoltz.caltech.edu/litmtg/mechclub/2008/JAELit06.pdf

# Resolution of Chiral Compounds

- Enantiomers have identical physical properties and as such cannot be separated from one another
- Reaction of a racemic mixture with a pure enantiomer (or another compound) allows diastereomers to form (which can be separated due to distinct physical properties – boiling point, melting point, polarity)

# Chiral Resolution: Creating Diastereomers from a Racemic Mixture of Enantiomers



# Relative and Absolute Configuration

- ***Relative configuration*** is determined for chiral carbons in relation their neighboring chiral carbons within the same molecule (this is usually a term used to describe chiral diastereomers)

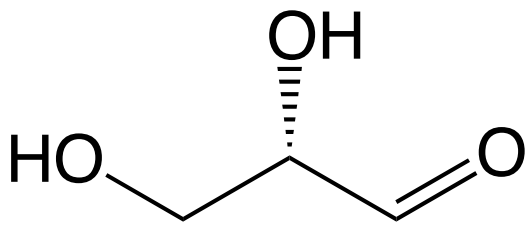
- ***There is no simple correlation between R, S configuration and the sign or magnitude of optical rotation (+ or -)***

- Why? light is absorbed differently by different functional groups, their relationship relative to one another determines sign/direction of optical rotation

- ***<u>This pairing</u>*** (for example + (R), - (S), + (R,S) - (S,R), etc…) is called the ***absolute configuration***

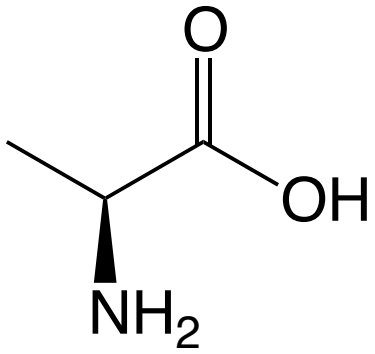
- Absolute Configuration is usually determined by x-ray diffraction comparison of individual enantiomers

# Absolute Configurations: *S*-glyceraldehyde and *S*-alanine



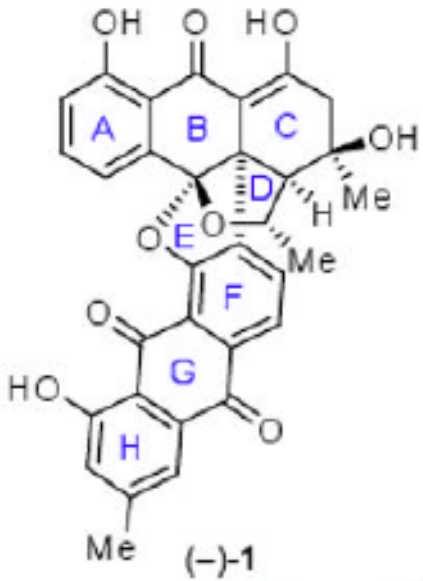

S (-) glyceraldehyde

$\alpha_D$ = - 8.7



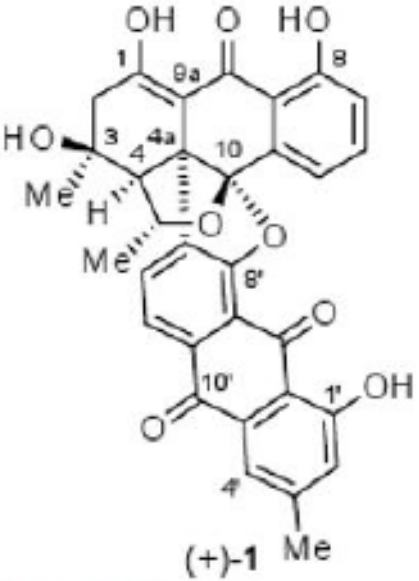

S (+) alanine

$\alpha_D$ = + 8.5

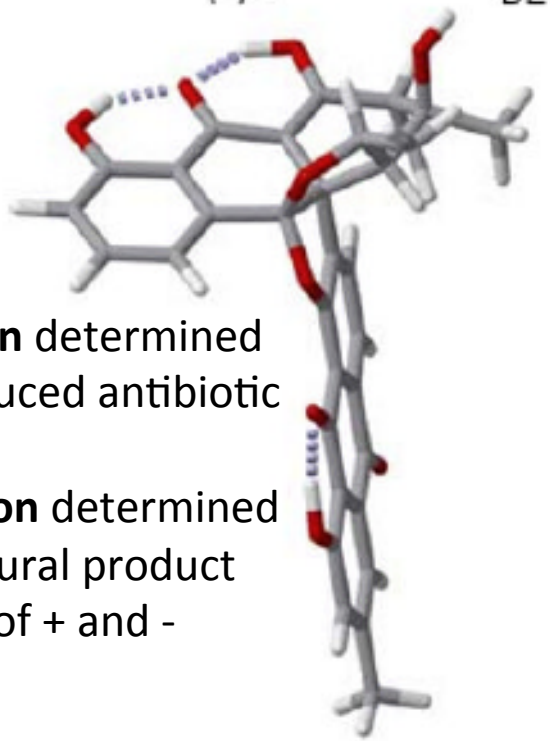


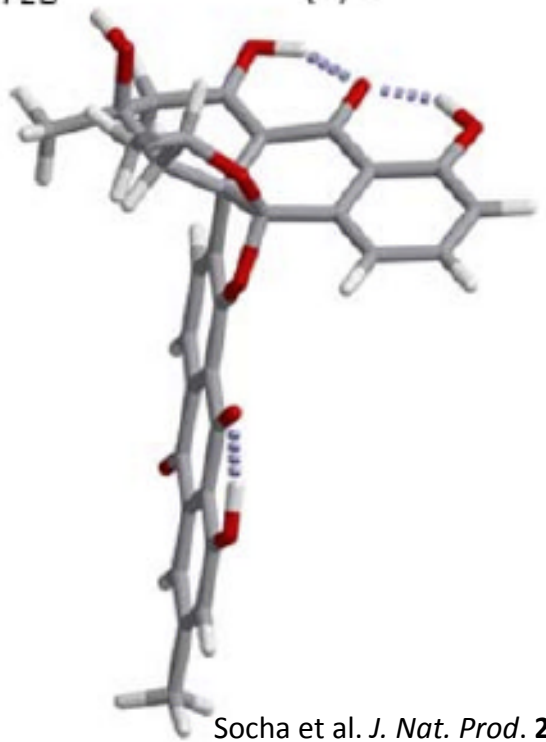

$\alpha_D^{22}$ = - 650

BE-43472B




$\alpha_D^{22}$ = + 650





**Relative Configuration** determined on the naturally produced antibiotic

**Absolute Configuration** determined by comparing the natural product to synthetic versions of + and -

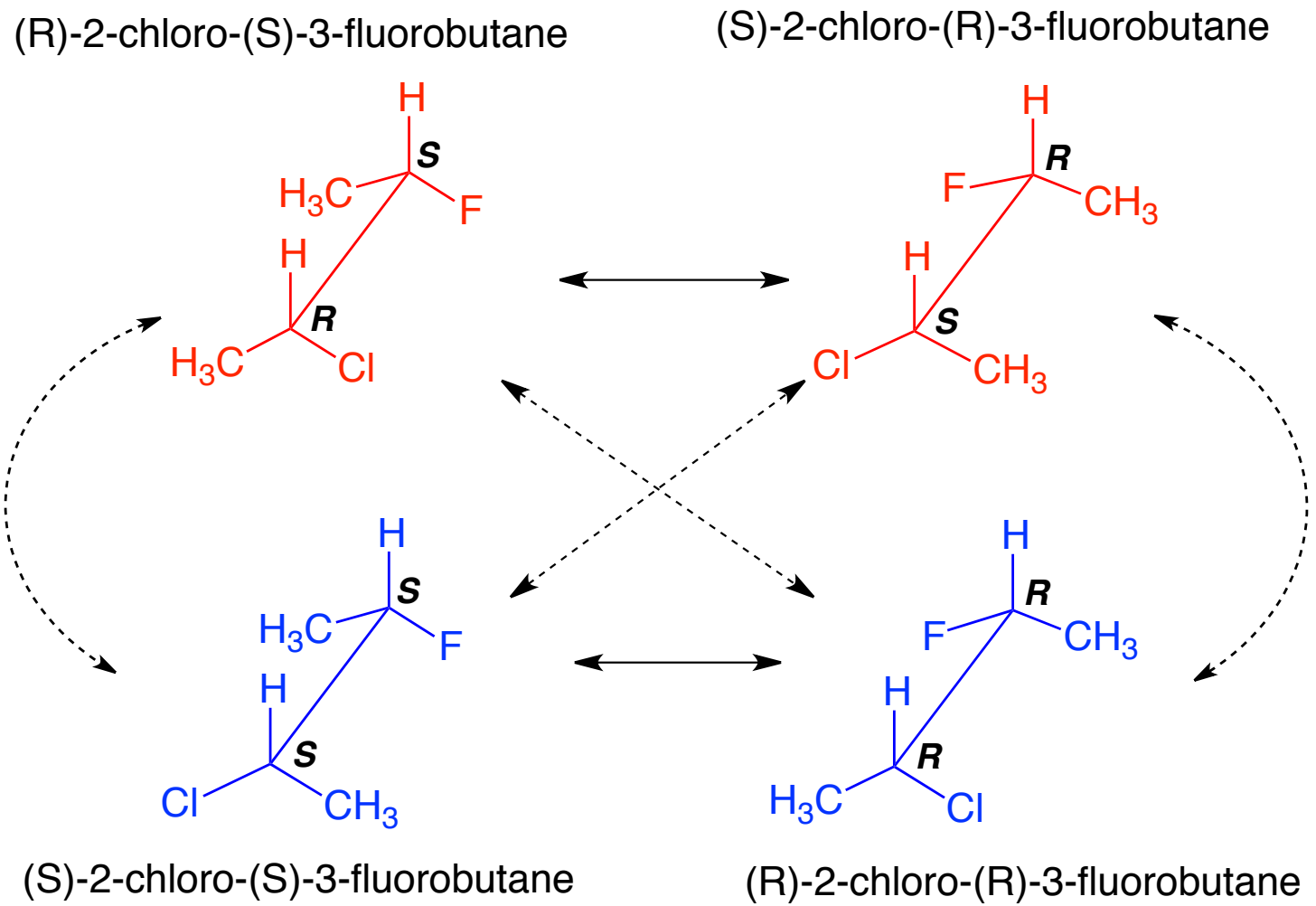
5 chiral centers =
$2^5$ (32) possible diastereomers!

Socha et al. *J. Nat. Prod*. **2006**, 69, 1070-1073
Nicolaou et al. *Angew Chem Int Ed Engl* . **2009** ; 48(19): 3444–3448

# Chiral Diastereomers

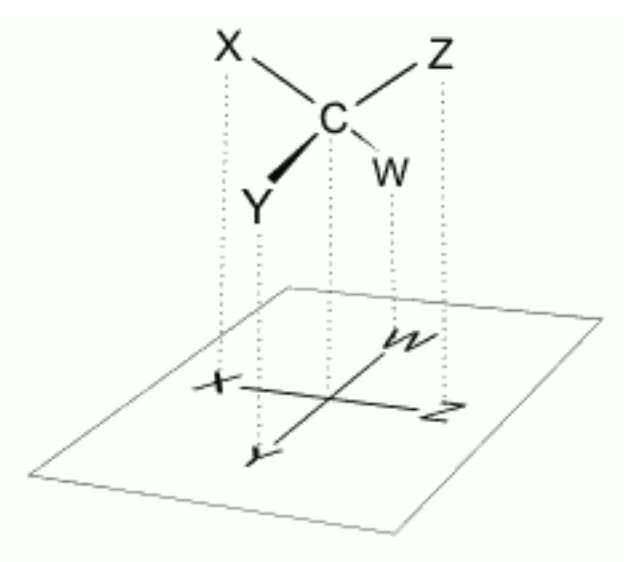
- Stereoisomers (spatial isomers) that are not enantiomers
- Contain 2 or more chiral carbons
  - In fact, all types of diastereomers (e.g. cis/trans isomers, E/Z isomers, rotamers, and conformers) ***can*** contain chiral carbons.
- $2^n$ diastereomers when $n$ = number of chiral carbons (e.g. 2 chiral centers = $2^2$ = 4 diastereomers, 3 chiral centers = $2^3$ = 8 diastereomers, etc…)
- *Epimers* are chiral diastereomers that differ at only one chiral center (thus they are ***not*** enantiomers)
- Chiral diastereomers have different physical properties

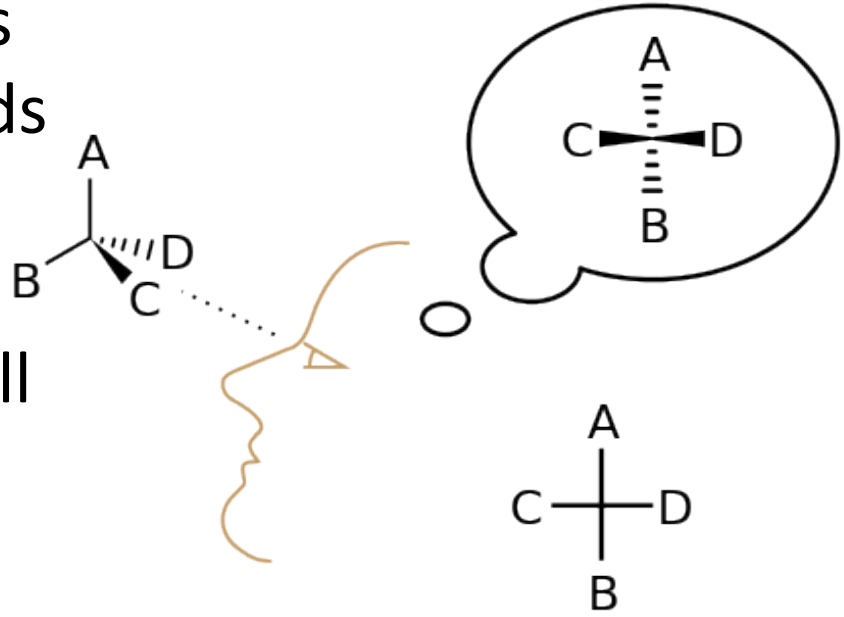
# Relationship between Enantiomers and Chiral Diastereomers

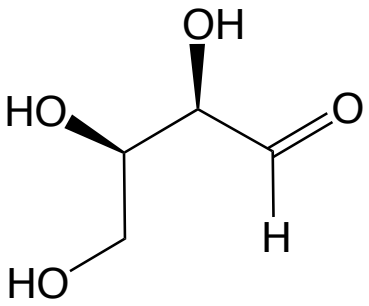


# Fisher Projections

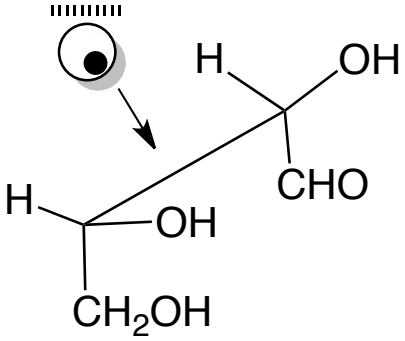
- Must convert 3D structure to 2D and visualize where atoms are spatially oriented
- Used to assign configurations to more complex diastereomers (i.e. carbohydrates, peptides) with several contiguous chiral centers
- Most useful for linear compounds for which sawhorse projections can be drawn
- Also useful for rapidly drawing all possible diastereomers of a compound





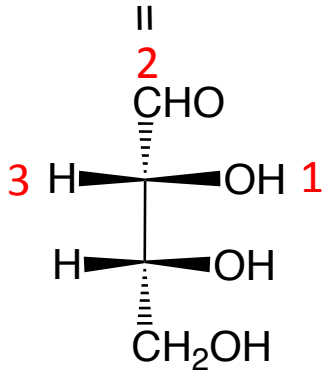

"threose" monosacchride
(carbohydrate/sugar)




Sawhorse projection

IUPAC:
(R,R) - 2,3,4-trihydroxybutanal

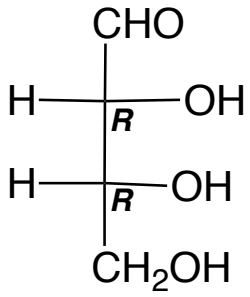
$2^n$ = 4 diasteromers




Counter clockwise
"S"

## *Assigning R and S using Fisher Projections*

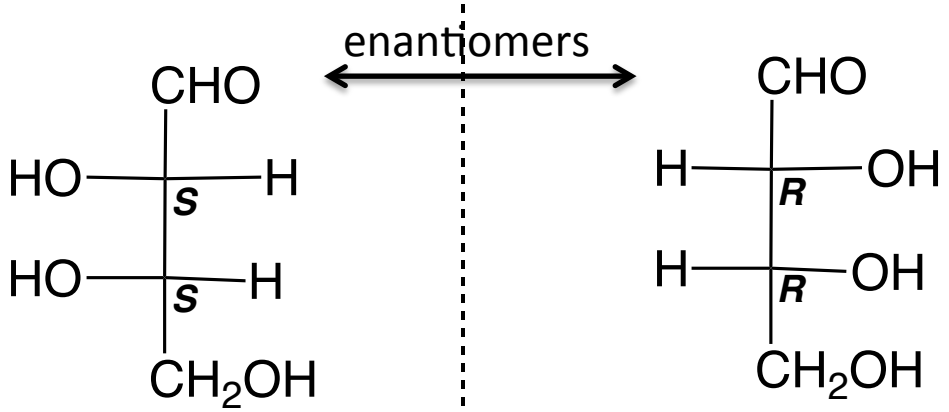
1. Draw a saw-horse projection
2. Put aldehyde on top (for sugars)
3. Looking down bond between chiral carbons
4. Use Cahn-Ingold-Prelog to assign priority and R or S to each center
5. If H is forward, reverse R and S




H's are forward
thus "R"

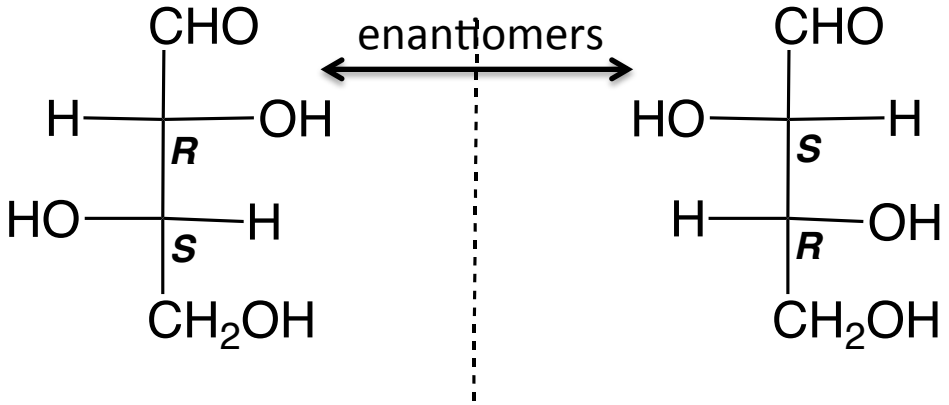
Fisher projection

# Using Fisher projections to draw all possible diasteromers of threose



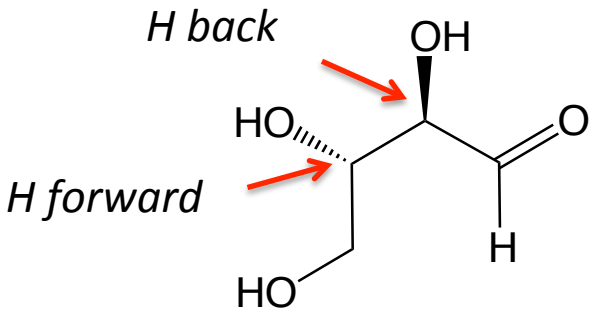

(2*S*,3*S*)-2,3,4-trihydroxybutanal

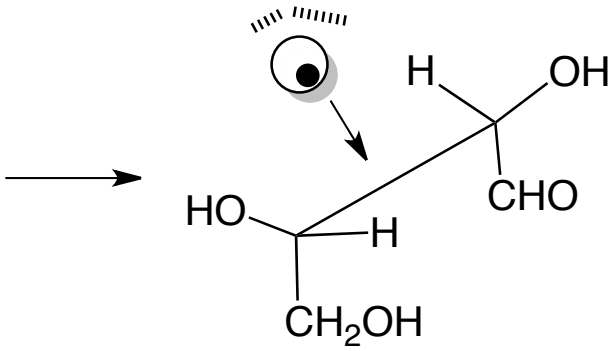
(2*R*,3*R*)-2,3,4-trihydroxybutanal




(2*R*,3*S*)-2,3,4-trihydroxybutanal

(2*S*,3*R*)-2,3,4-trihydroxybutanal



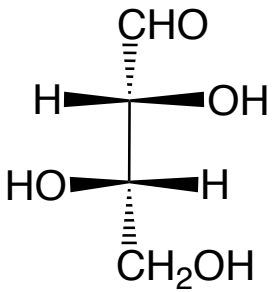

"threose" monosacchride
(carbohydrate/sugar)

Sawhorse projection

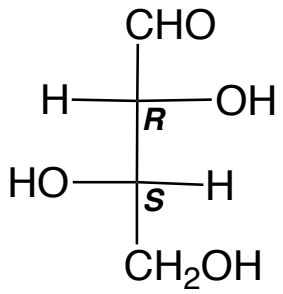
IUPAC:
(R,S) - 2,3,4-trihydroxybutanal

$2^n$ = 4 diasteromers

II




II




Fisher projection

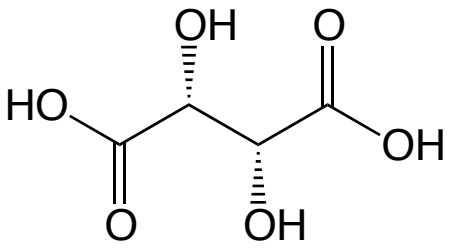
- Multiple chiral centers

*H atom in one is forward*
*H atom in one is back*

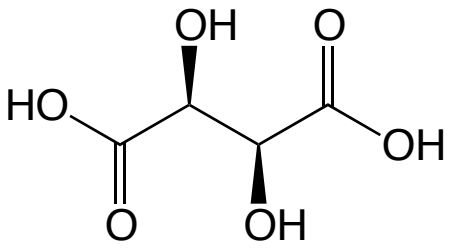
- Confuses R/S assignment using simple Cahn Ingold Prelog rules

# Meso compounds

- Have chiral centers but are achiral molecules
- Internal plane of symmetry
- Distinct physical properties from their other diastereomers
- Optically inactive
- Are identical to one another




enantiomers




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

***L (+) tartaric acid***

MP = 170°C

$\alpha_D$ = +11.98

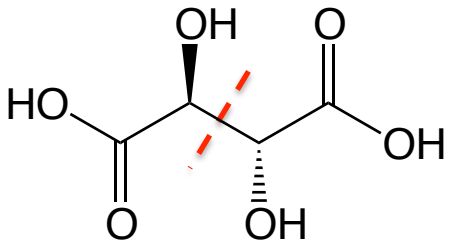
(2*S*,3*S*)-2,3-dihydroxysuccinic acid

***D (-) tartaric acid***

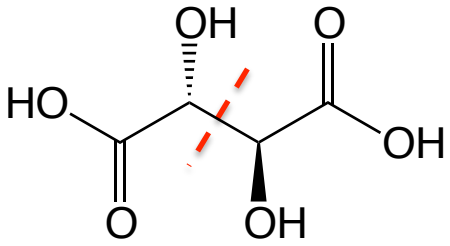
MP = 170°C

$\alpha_D$ = -11.98

diastereomers




meso




(2*R*,3*S*)-2,3-dihydroxysuccinic acid

***meso tartaric acid***

MP = 140°C

$\alpha_D$ = 0

# Spotting Meso Compounds

- *Look for:*

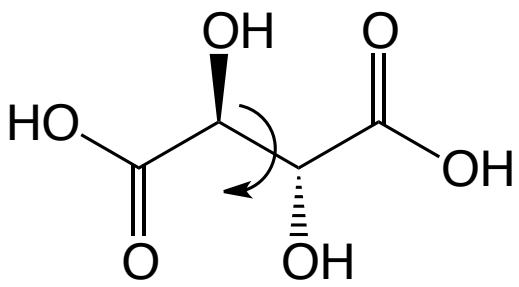
indistinguishable end groups (e.g. both sides of molecule have COOH functionality)

- *Rotate:*

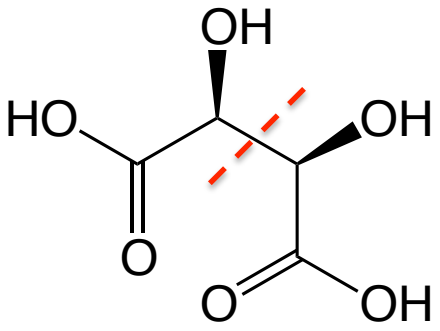
around same bond we eyed for Fisher Projections

- *Must have:*

Internal plane of symmetry (when in doubt, make a model)




(2*R*,3*S*)-2,3-dihydroxysuccinic acid

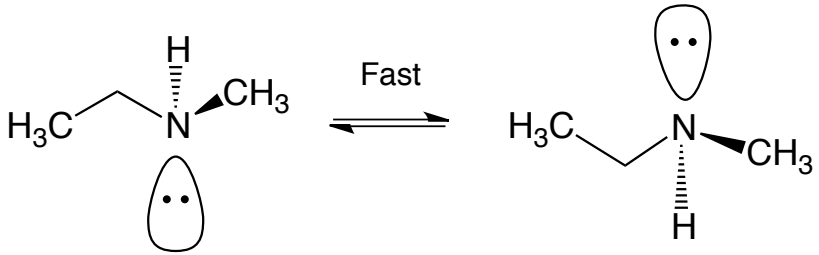


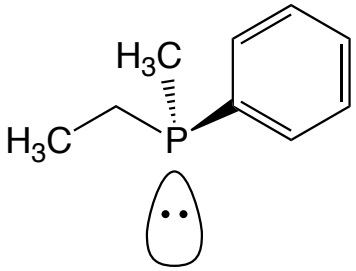

(2*R*,3*S*)-2,3-dihydroxysuccinic acid

***meso tartaric acid***

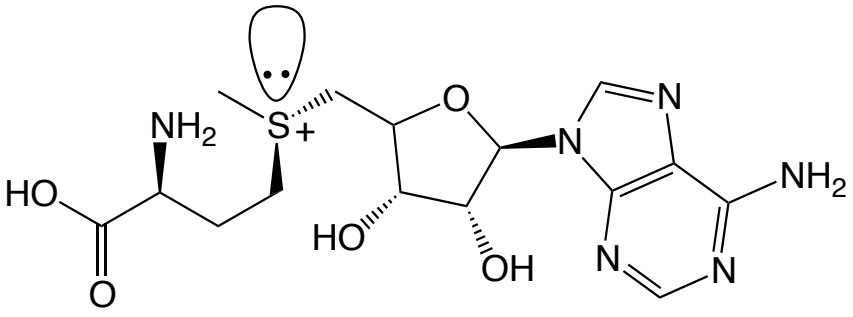
# Chirality at N, P, S

- Trivalent nitrogen is tetrahedral with its lone pair electrons acting as the fourth (lowest ranked) “substituent”
- As such, it is chiral in principal, but not in practice because it often interconverts too rapidly to isolate individual enantiomers
- Trivalent phosphorus (phosphines) has similar chirality, and interconvert slower – allowing for isolation of R and S enantiomers
- Divalent sulfur compounds (thiols, sulfides, disulfides) are achiral but trivalent sulfur compounds (sulfonium salts = $R_3S^+$) are chiral and interconvert slowly enough to be isolated.



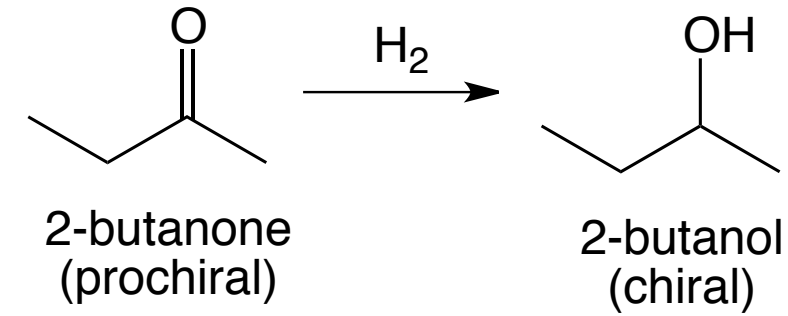

(*S*)-ethyl(methyl)(phenyl)phosphine

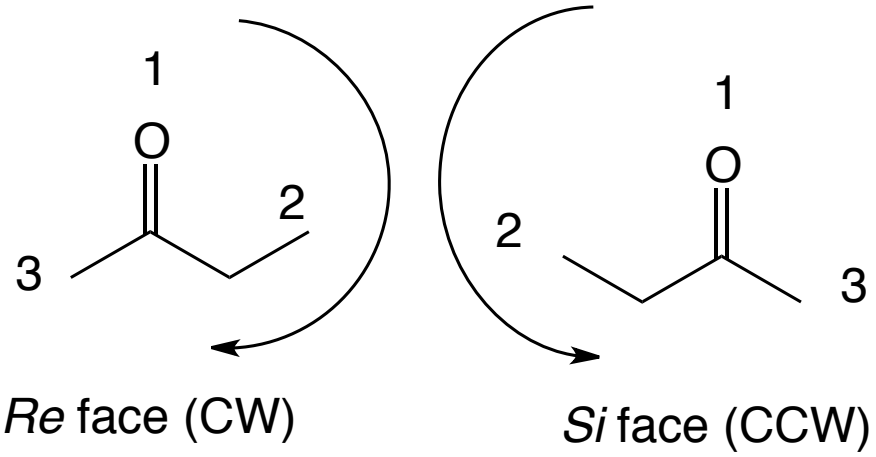


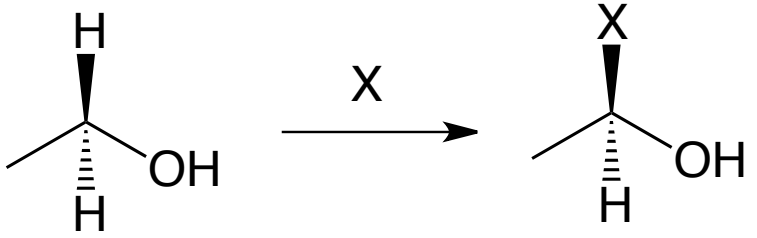

(*S*)-S-adenosylmethionine (SAM)

# Prochirality

- A molecule is *prochiral* if it can be converted from achiral to chiral in a single chemical step
- The enantiomer that is produced depends on the face of the planar carbonyl group that undergoes reaction (*Re* = CW and *Si* = CCW faces)
- *Prochirality centers* can also be $sp^3$ hybridized (*pro*-S substituent replacement leads to *R* chirality and *pro*-S substituent replacement leads to *S* chirality)



# Homework

*Watch Video on Stereochemistry:*

https://www.khanacademy.org/science/organic-chemistry/stereochemistry-topic/optical-activity/v/cahn-ingold-prelog-system-for-naming-enantiomers

Problems Chapter 5:

In text: 1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 13, 14, 16, 17, 20, 21, 22, 23

End of chapter: 31, 36, 37, 39, 40, 43, 52, ***54***, 68, 69, ***71***, 72, 75