

# LS 2022

Lecture 1: 2022-12-12

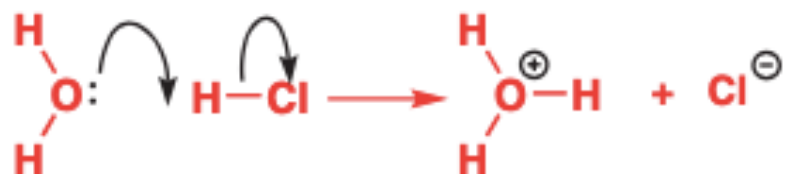
# Acidity, basicity, pKa

## Acidity

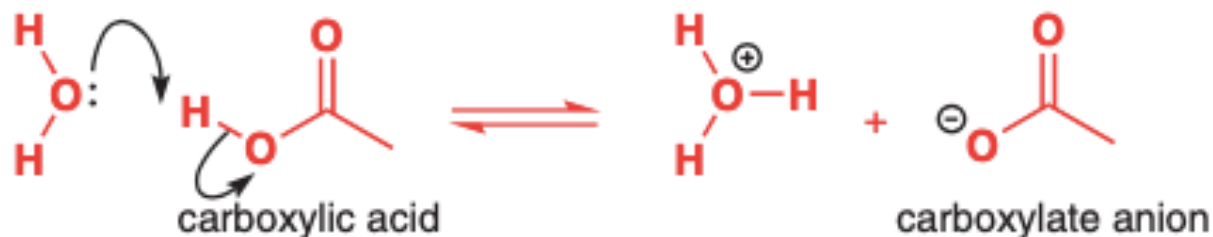
Let's start with two simple, and probably familiar, definitions:

- An acid is a species having a tendency to lose a proton.
- A base is a species having a tendency to accept a proton.

1



2



# Acidity, basicity, pKa

- For any acid and any base:



AH is an acid and A<sup>-</sup> is its conjugate base and B is a base and BH<sup>+</sup> is its conjugate acid. That is, *every acid has a conjugate base associated with it and every base has a conjugate acid associated with it.*



# Approximate $pK_a$ Values

**Table 2.1** Approximate  $pK_a$  Values

| $pK_a < 0$   | $pK_a \sim 5$   | $pK_a \sim 10$                          | $pK_a \sim 15$                |
|--|---|---|-------------------------------|
| $\text{ROH}_2^+$<br>protonated<br>alcohol  | $\begin{array}{c} \text{O} \\ \parallel \\ \text{R}-\text{C}-\text{OH} \end{array}$<br>carboxylic<br>acid | $\text{RNH}_3^+$<br>protonated<br>amine | $\text{ROH}$<br>alcohol       |
| $\begin{array}{c} \text{}^+\text{OH} \\ \parallel \\ \text{R}-\text{C}-\text{OH} \end{array}$<br>protonated<br>carboxylic acid |   |   | $\text{H}_2\text{O}$<br>water |
| $\text{H}_3\text{O}^+$<br>protonated<br>water  |   |   |                               |

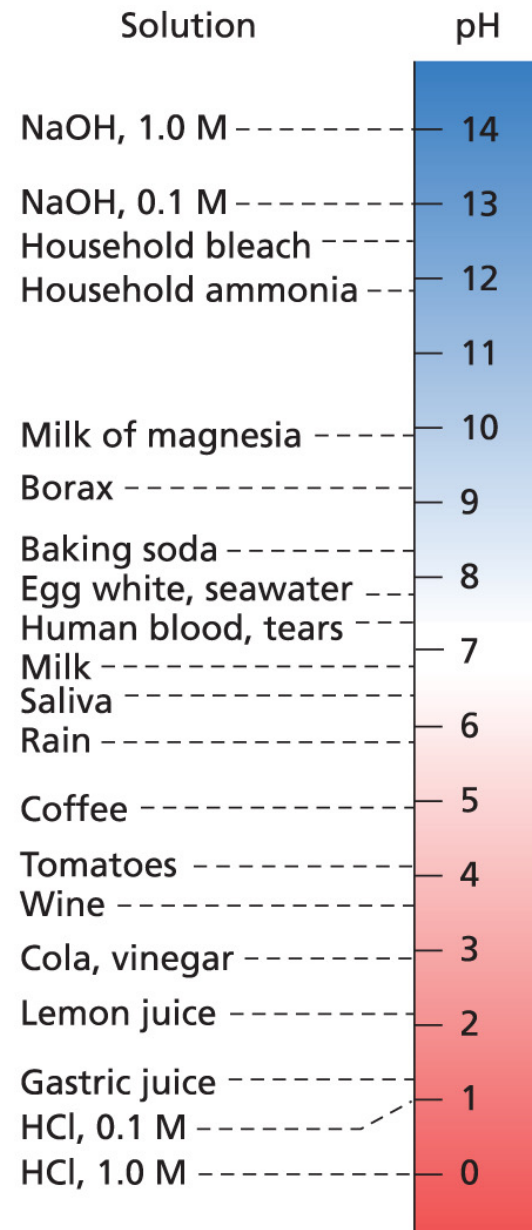
# pH

$$\text{pH} = -\log [\text{H}^+]$$

The pH indicates the concentration of protons in a solution.

The  $\text{p}K_a$  the tendency of a compound To lose its proton.

**They are not the same!!**



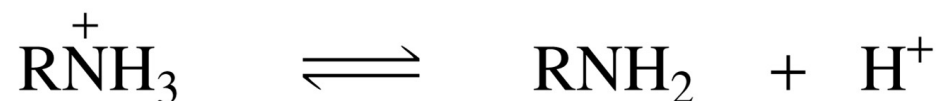
# The Henderson–Hasselbalch Equation

$$pK_a = \text{pH} + \log \frac{[\text{HA}]}{[\text{A}^-]}$$

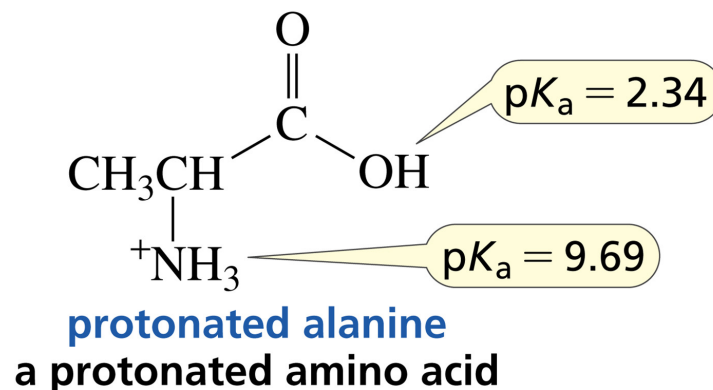
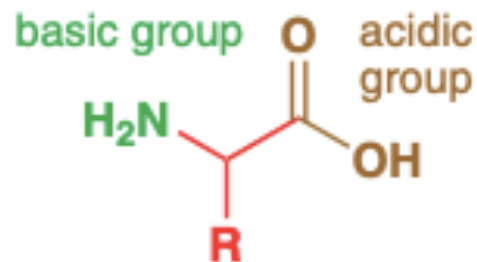
The Henderson–Hasselbalch equation tells us whether (at a given pH) a compound will be in its **acidic form** (with its proton) or in its **basic form** (without its proton).

**acidic form**

**basic form**

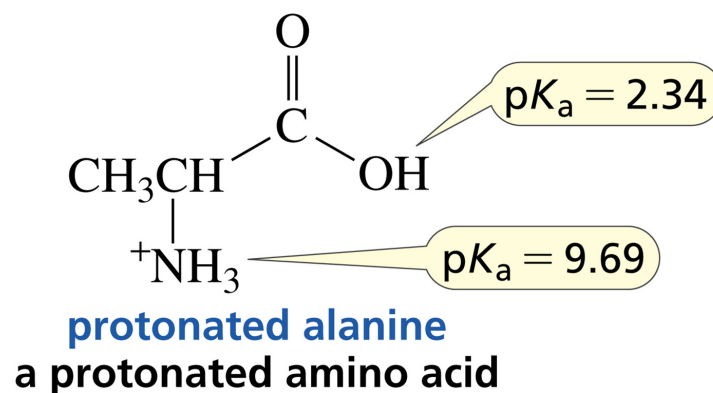
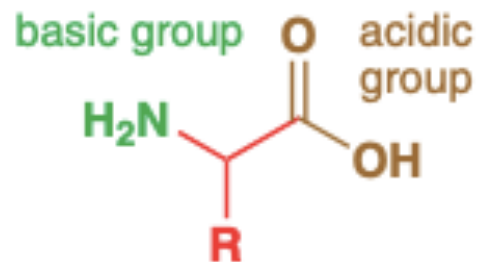


# Is a Compound Neutral or Charged?



**When we talk about pK<sub>a</sub> of amines, we refer to the protonated form, the conjugated acid.**

# Is a Compound Neutral or Charged?

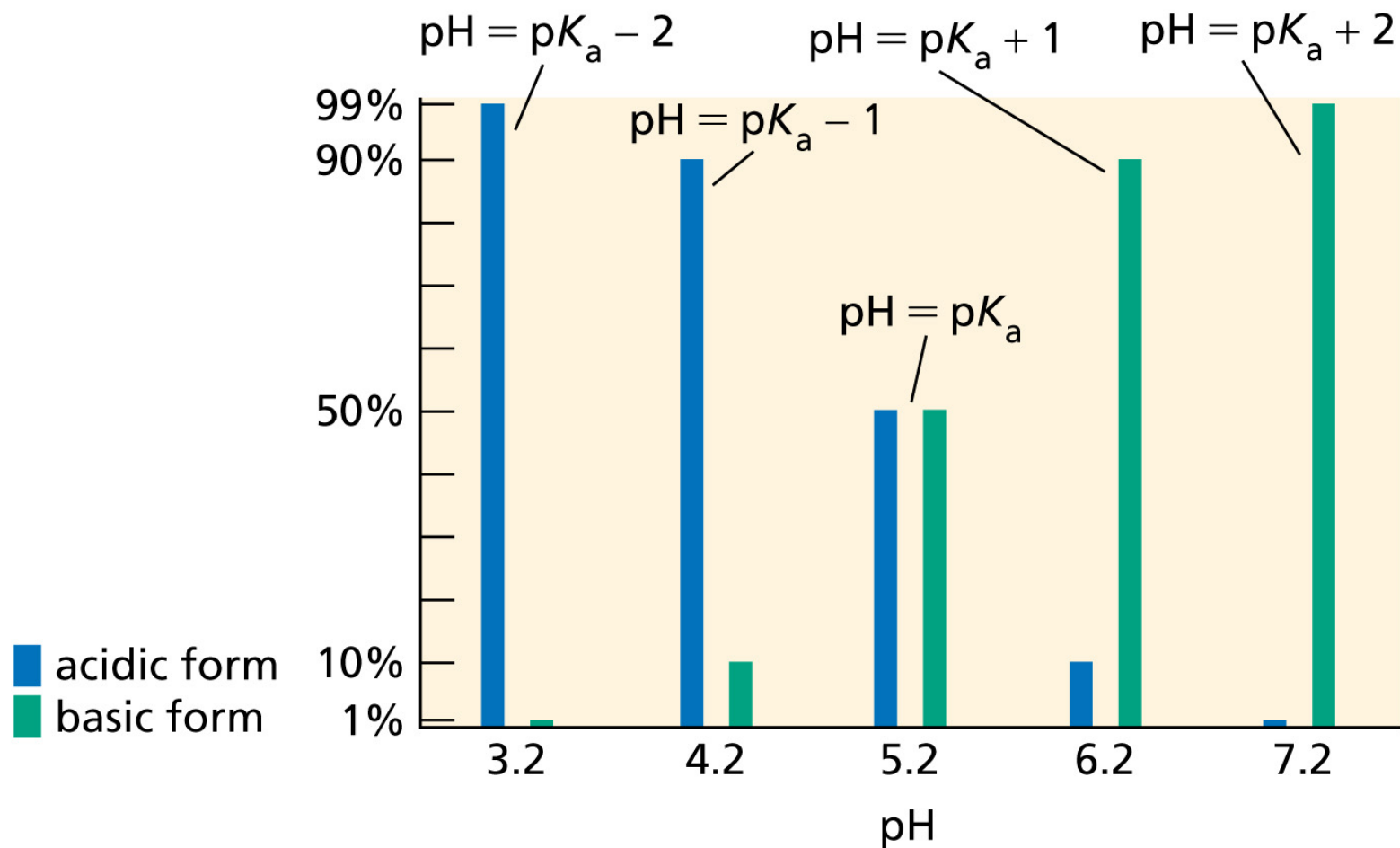


Will be the same structure at pH = 0 and pH = 7?

$$pK_a = \text{pH} + \log \frac{[\text{HA}]}{[\text{A}^-]}$$



# A Compound with a $pK_a = 5.2$

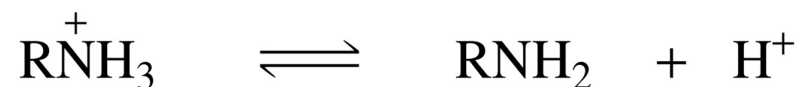


# Is a Compound Neutral or Charged?

$$pK_a = \text{pH} + \log \frac{[\text{HA}]}{[\text{A}^-]}$$

**acidic form**

**basic form**



A carboxylic acid is

neutral in its acidic form and charged in its basic form.

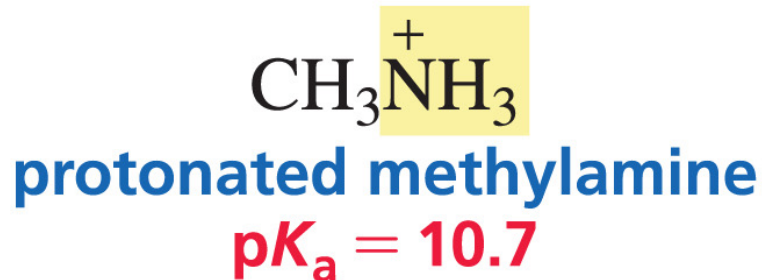
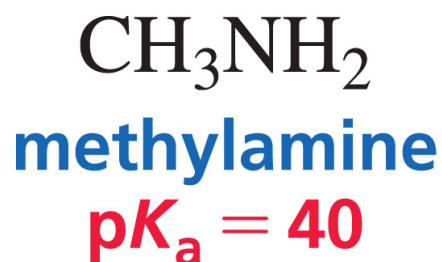
An alcohol is

neutral in its acidic form and charged in its basic form.

An amine is

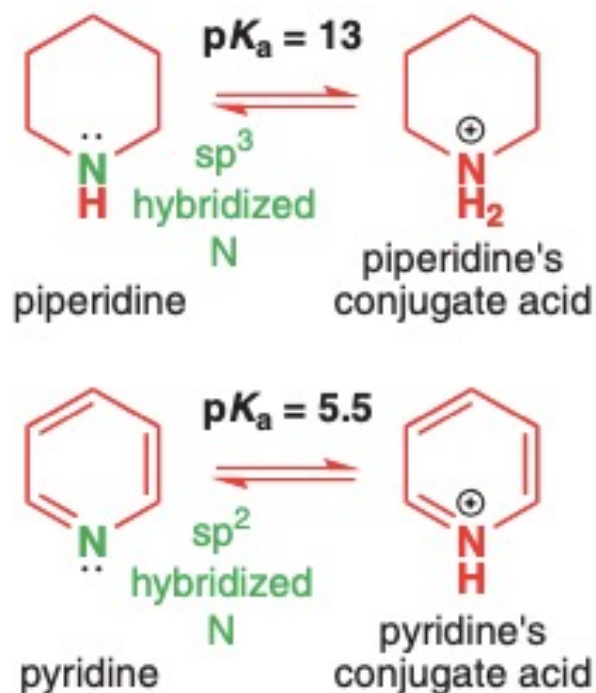
charged in its acidic form and neutral in its basic form.

# Amines and Protonated Amines



Chemists often say things like ‘the  $\text{p}K_{\text{a}}$  of triethylamine is about 10.’ (It’s actually 11.0 but 10 is a good number to remember for typical amines). This may surprise you as triethylamine has no acidic hydrogens. What they mean is of course this: ‘the  $\text{p}K_{\text{a}}$  of the conjugate acid of triethylamine is about 10.’

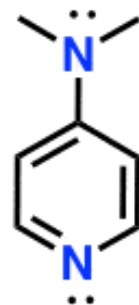
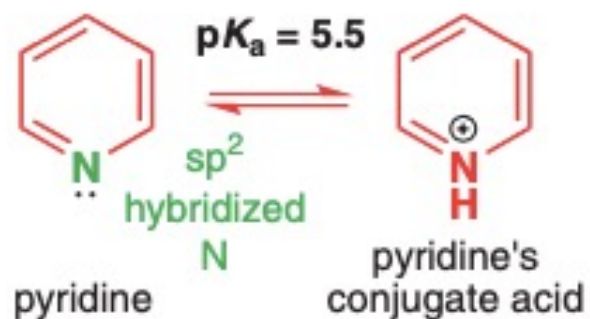
# Nitrogen compounds as Acids and Bases



The  $pK_a$  associated for protonation of piperidine, a typical secondary amine, is about 13. The equivalent  $pK_a$  for protonation of pyridine—a compound with a similar heterocyclic structure, but with its lone pair in an  $sp^2$  rather than an  $sp^3$  orbital, is only 5.5: pyridine is a weaker base than piperidine (its conjugate acid is a stronger acid).

Lone pairs with more p character ( $sp^3$  orbitals are 3/4 p, while  $sp$  orbitals are 1/2 p) are higher in energy—they spend more time further from the nucleus—and are therefore more basic.

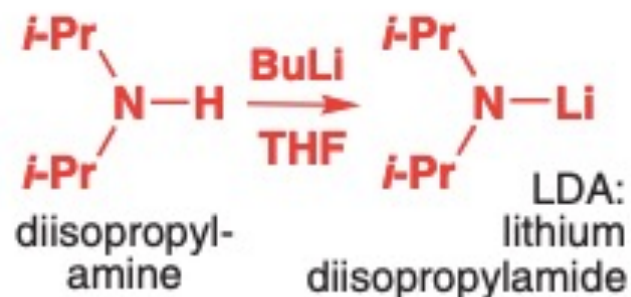
# Nitrogen compounds as Acids and Bases



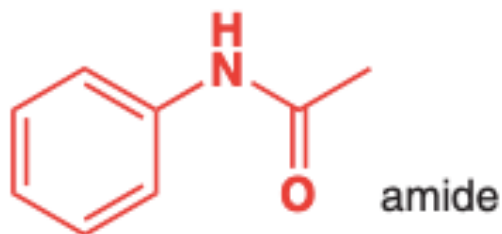
**4-dimethylamino pyridine  
(DMAP)**

pK<sub>a</sub>H = 9.2

# Nitrogen compounds as Acids and Bases

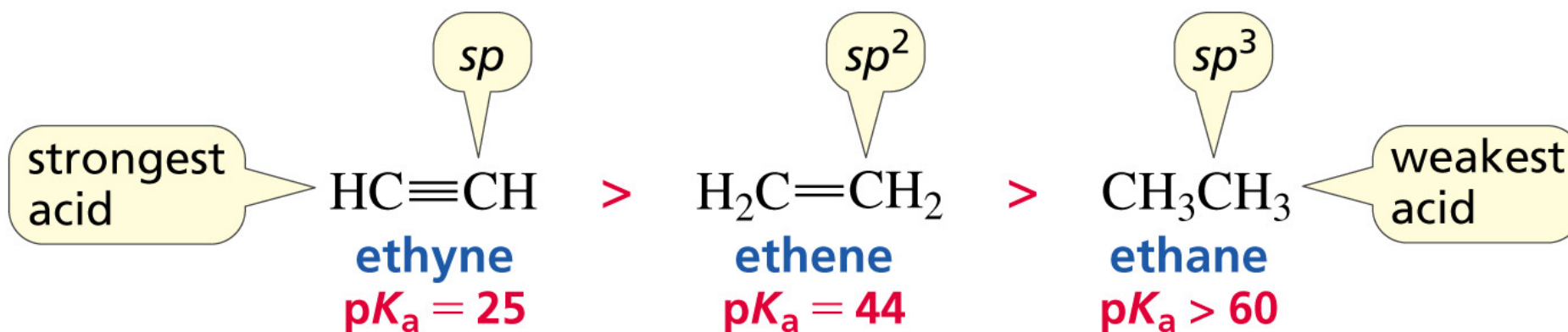
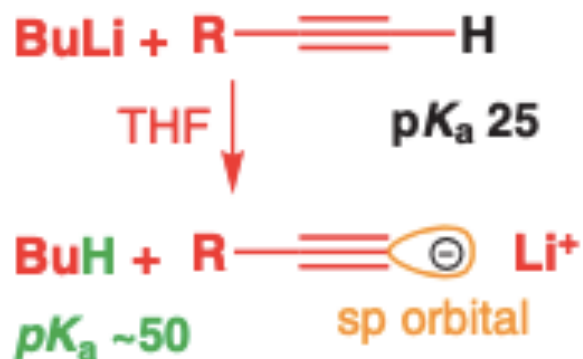


Removing a proton from an amine is very difficult as the anion (unfortunately called an 'amide' anion) is very unstable and very basic. The only way to succeed is to use a very strong base, usually an alkyllithium. The 'anion' then has a N-Li bond and is soluble in organic solvents. This example, known as LDA, is commonly used as a strong base in organic chemistry.



# Carbon Acids

■ If you don't see why this is, think about the shapes of an s and a p orbital: the nucleus sits in the node of a p orbital, but in an s orbital the nucleus is in a region of high electron density. The more s character a negative charge has, the closer the electron density is to the nucleus, and the more stable it is.



# Hybridization Affects Electronegativity

relative electronegativities

most  
electronegative

$sp$

$>$

$sp^2$

$>$

$sp^3$

least  
electronegative

strongest  
acid

$sp$

$\text{HC}\equiv\text{CH}$

ethyne

$\text{p}K_{\text{a}} = 25$

$>$

$sp^2$

$\text{H}_2\text{C}=\text{CH}_2$

ethene

$\text{p}K_{\text{a}} = 44$

$>$

$sp^3$

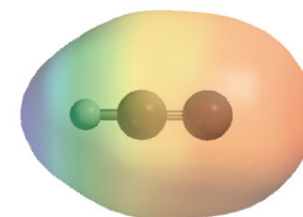
$\text{CH}_3\text{CH}_3$

ethane

$\text{p}K_{\text{a}} > 60$

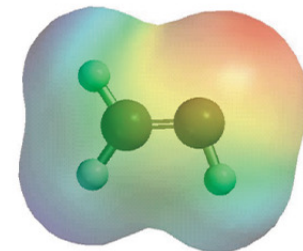
weakest  
acid

The **strongest acid** has the  
most stable (weakest) **conjugate base**.

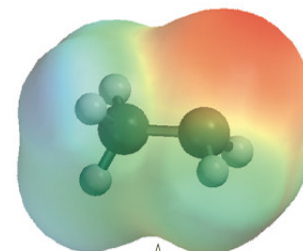


most stable

$\text{HC}\equiv\text{C}^-$



$\text{H}_2\text{C}=\text{C}^- \text{H}$

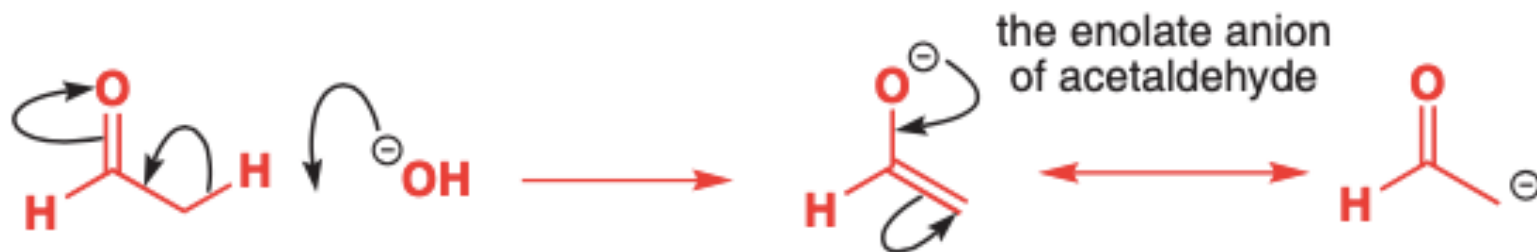


least stable

$\text{CH}_3\text{C}^- \text{H}_2$

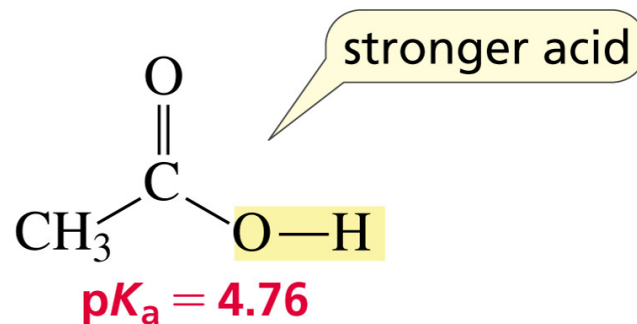
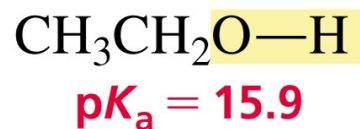


# Carbon Acids

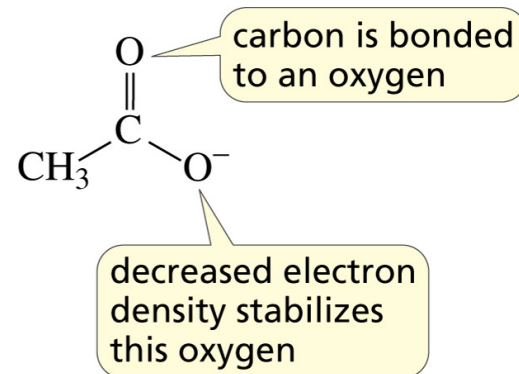
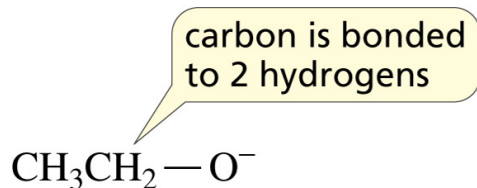


C-H bonds can be even more acidic than those of acetylene if stabilization of the resulting anion is possible by *conjugation*. Conjugation with a carbonyl group has a striking effect. One carbonyl group brings the  $\text{pK}_a$  down to 13.5 for acetaldehyde so that even hydroxide ion can produce the anion.

# Why is a Carboxylic Acid a Stronger Acid than an Alcohol?

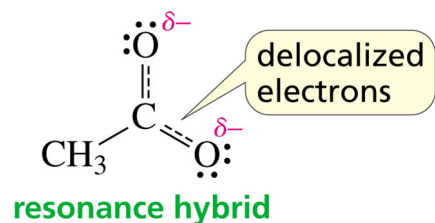
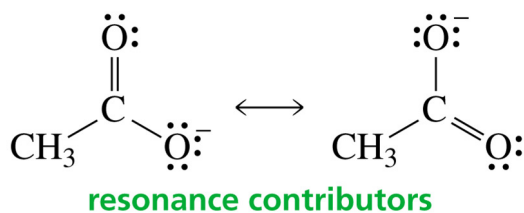
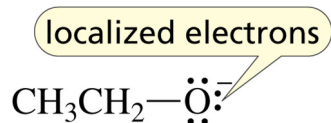


## 1. Inductive electron withdrawal

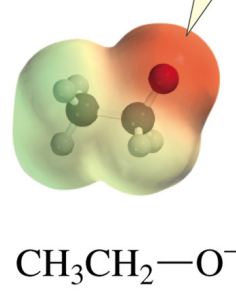


# Why is a Carboxylic Acid a Stronger Acid than an Alcohol?

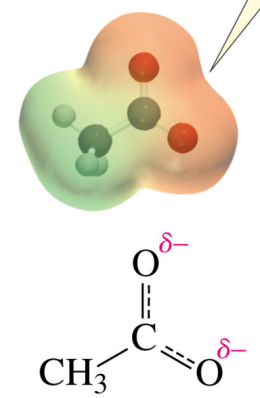
## 2. Delocalized electrons



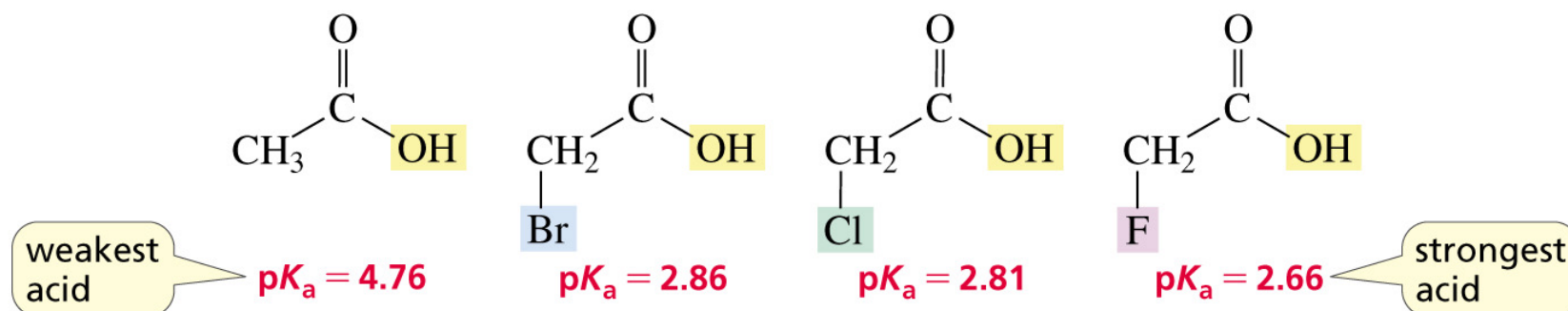
the negative charge is localized on 1 oxygen



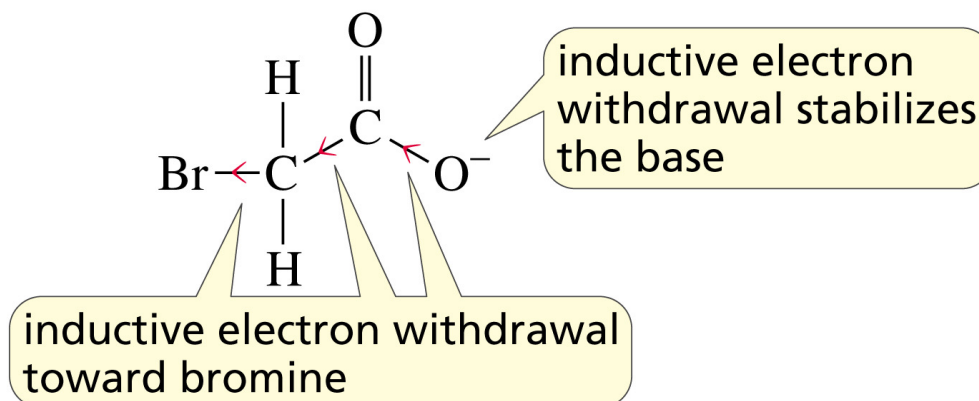
the negative charge is shared by 2 oxygens



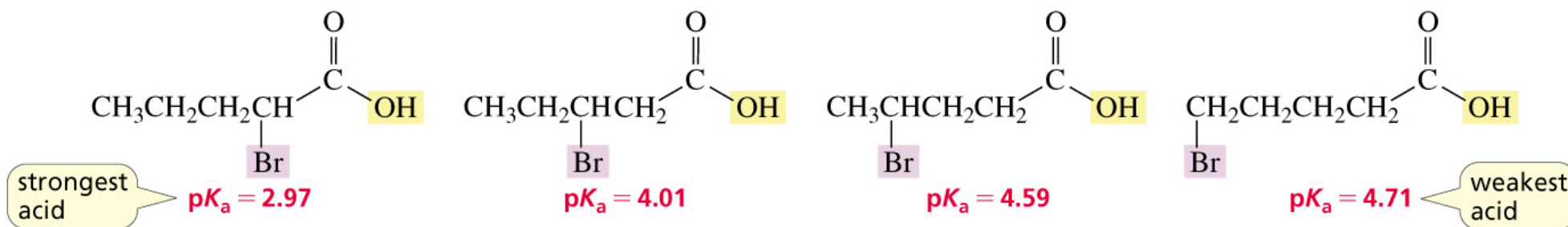
# Substituents Affect the Strength of an Acid



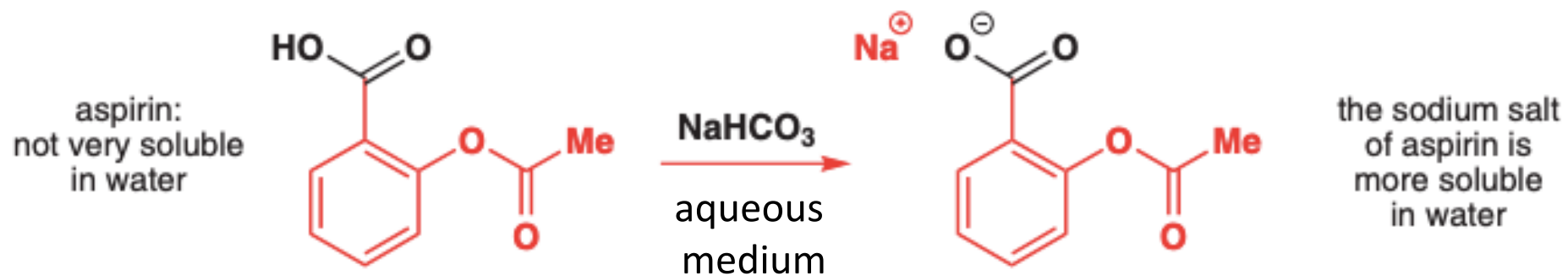
inductive electron withdrawal



# A Substituent's Effect on $pK_a$ Depends on Distance

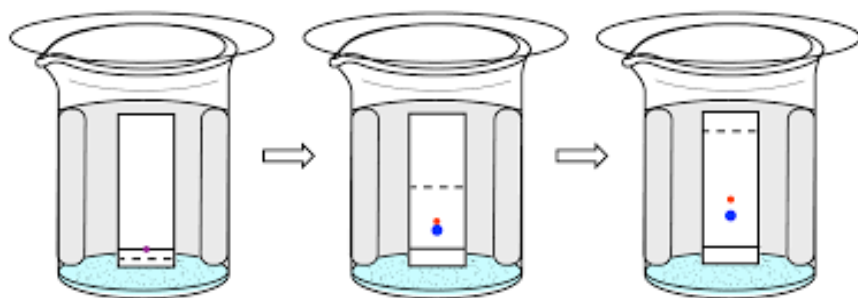


# Acidity, basicity, pKa

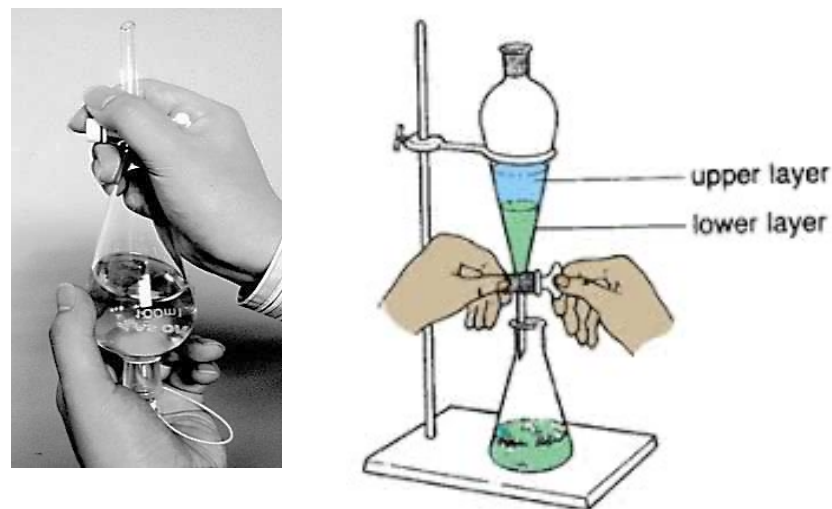


# Work up and isolation of a sample

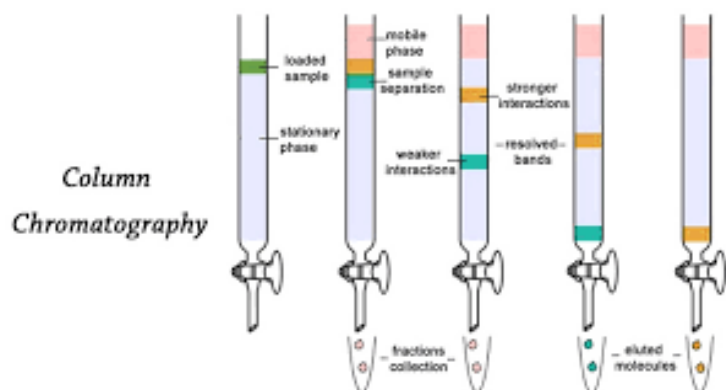
A) Thin layer chromatography (TLC)



B) Separation operation



C) Column chromatography



D) Structure determination

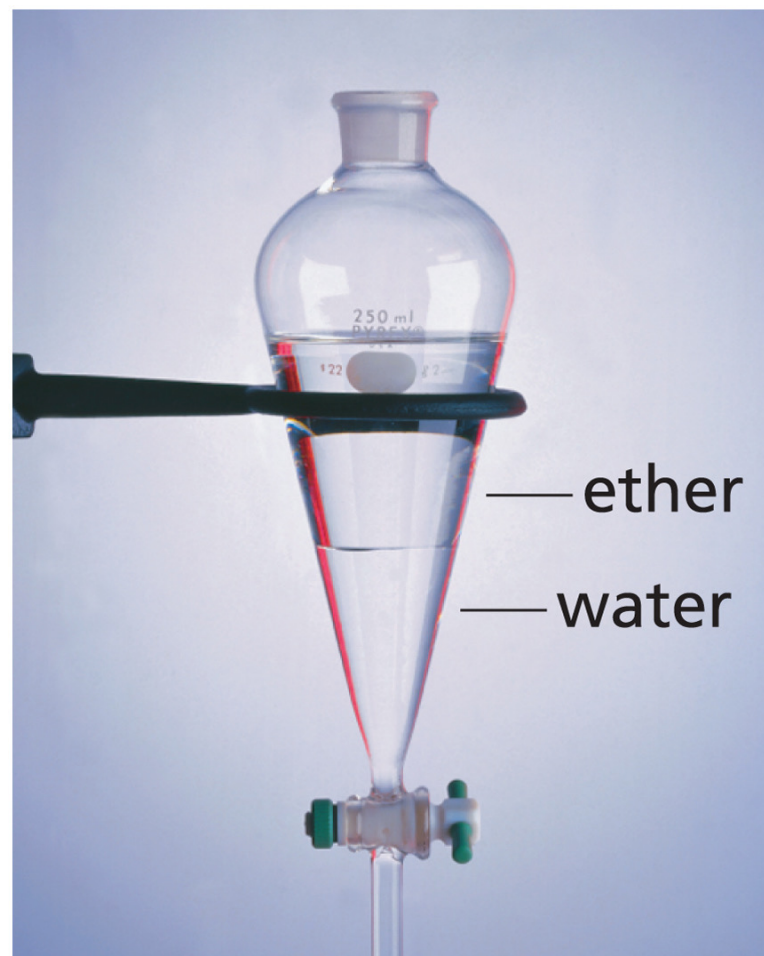
- Melting point
- IR
- MS
- NMR
- X-ray

# Water and Diethyl Ether Form Two Layers

Diethyl ether is less dense than water, so diethyl ether is on top.

Neutral compounds  
dissolve in diethyl ether.

Charged compounds  
dissolve in water.





# Extraction method

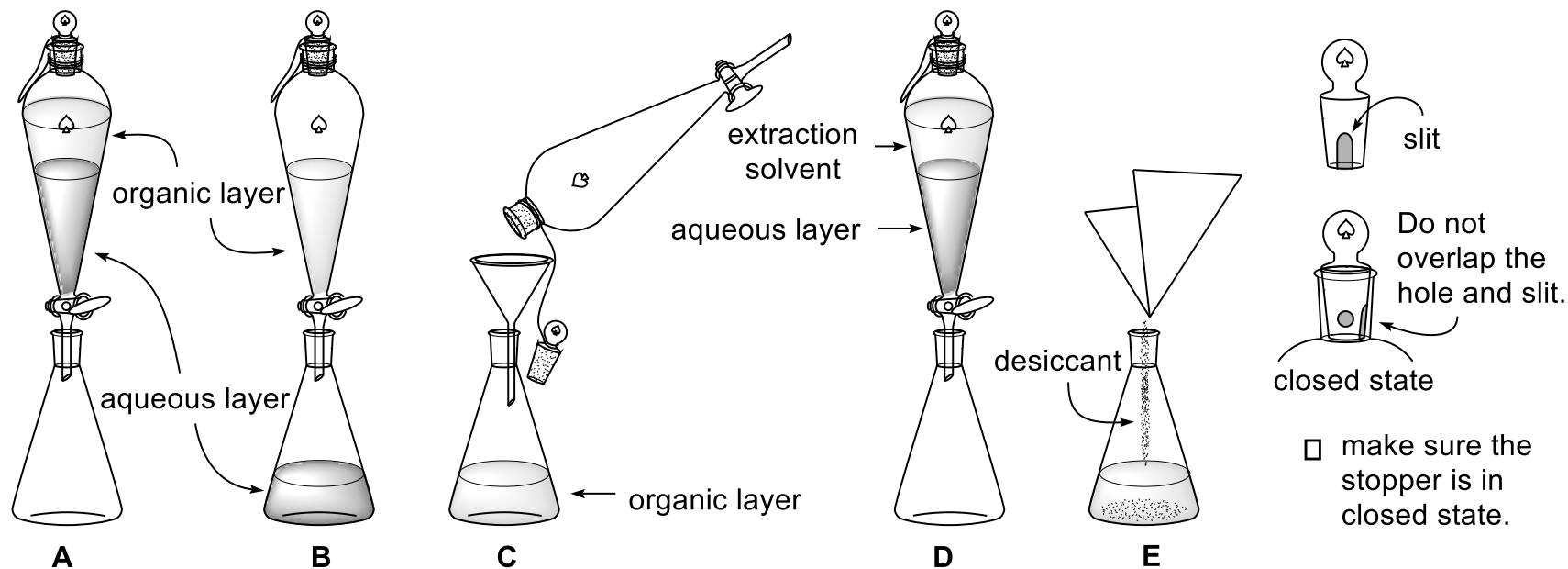
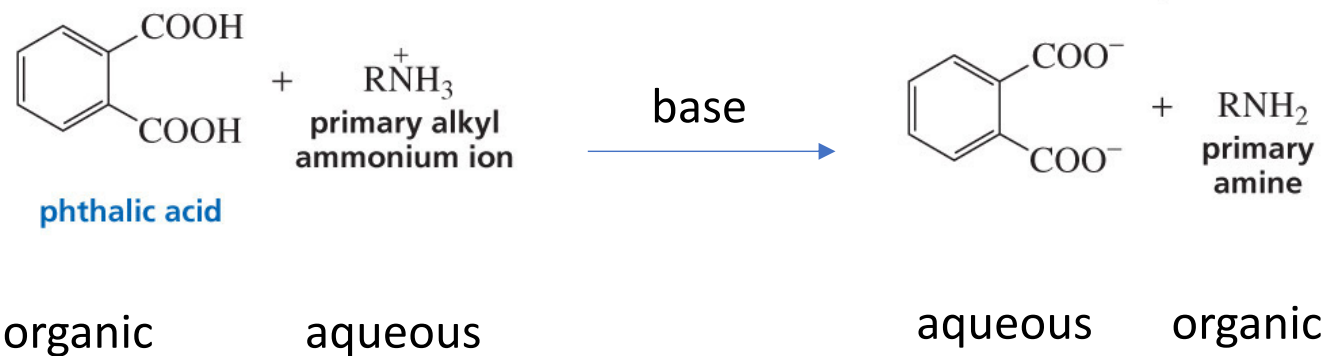


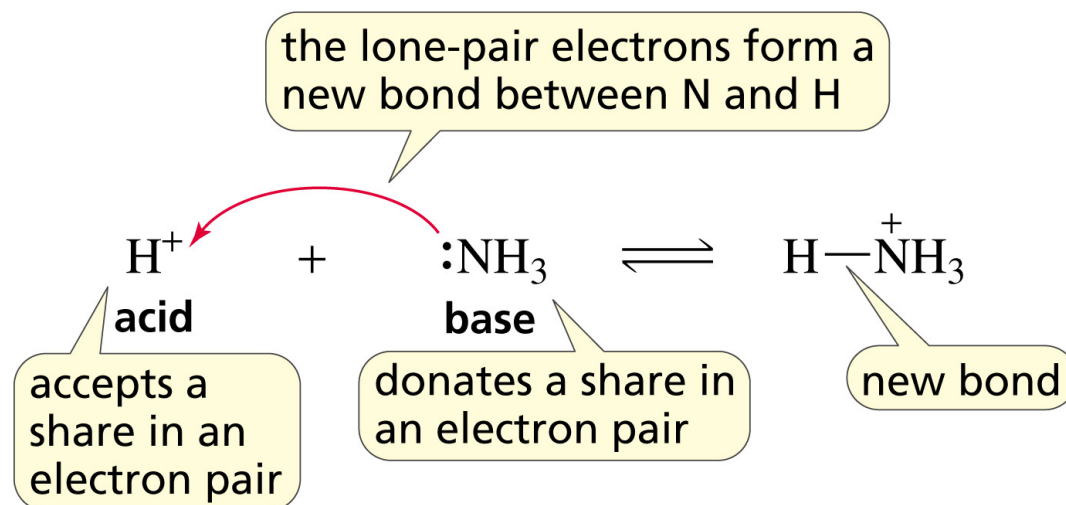
Fig 2 Separation operation



# Lewis Acids and Bases

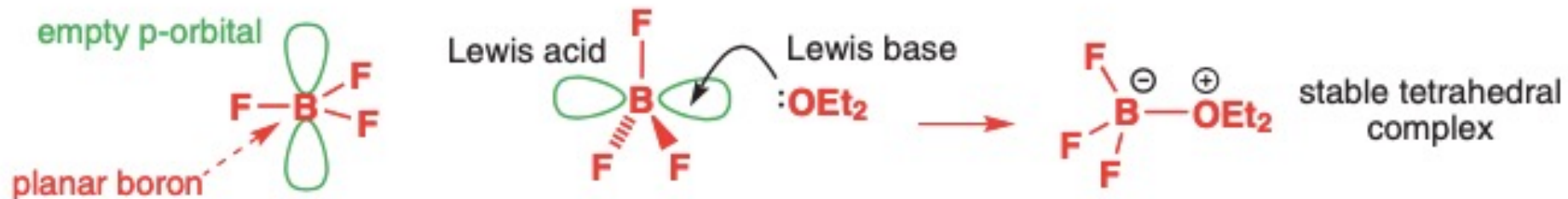
**Lewis acid:** a species that **accepts a share** in an electron pair

**Lewis base:** a species that **donates a share** in an electron pair

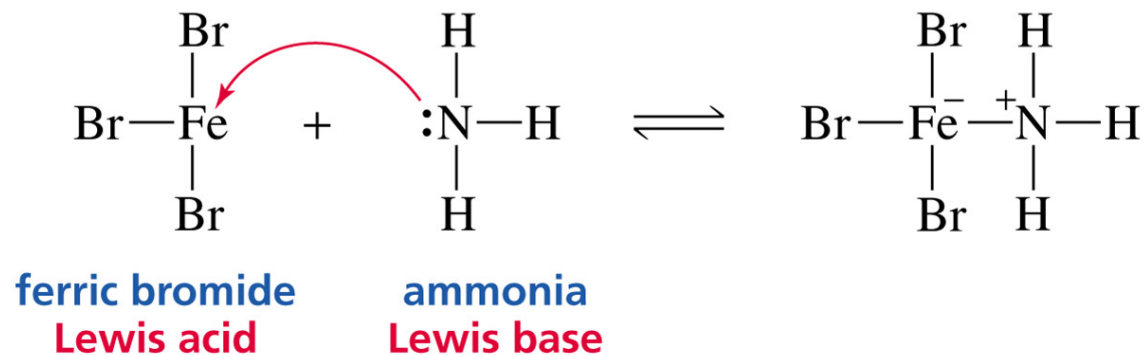
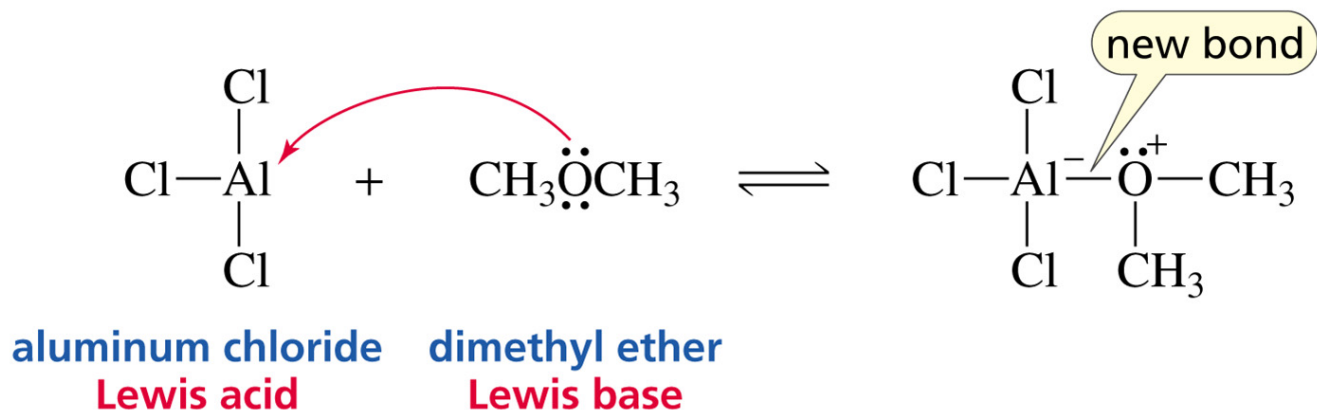


All **Brønsted acids** are **Lewis acids**.  
All **Brønsted bases** are **Lewis bases**.

# Lewis Acids and Bases



# Lewis Acids and Bases



# How Chemists Use the Terms

“acid” = a proton-donating acid

“Lewis acid” = a non-proton-donating acid

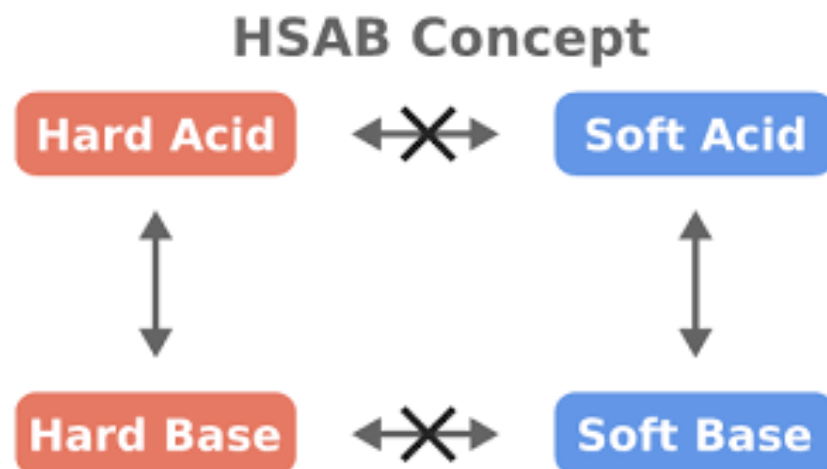
All bases are Lewis bases

because they have a pair of electrons they can share.

- Brønsted acids donate protons.
- Brønsted bases accept protons.

- Lewis acids accept electrons.
- Lewis bases donate electrons.

# HSAB



**Hard Lewis acids** are characterized by small ionic radii, high positive charge, strongly solvated, empty orbitals in the valence shell and with high energy LUMOs.

**Soft Lewis acids** are characterized by large ionic radii, low positive charge, completely filled atomic orbitals and with low energy LUMOs.

**Hard Lewis bases** are characterized by small ionic radii, strongly solvated, highly electronegative, weakly polarizable and with high energy HOMOs.

**Soft Lewis bases** are characterized by large ionic radii, intermediate electronegativity, highly polarizable and with low energy HOMOs.

***In short, Hard acids and bases are small and non-polarizable, whereas Soft acids and bases are larger and more polarizable.***

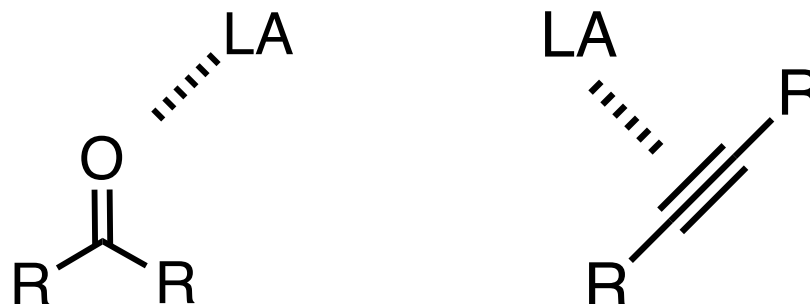
# HSAB

## HSAB Concept

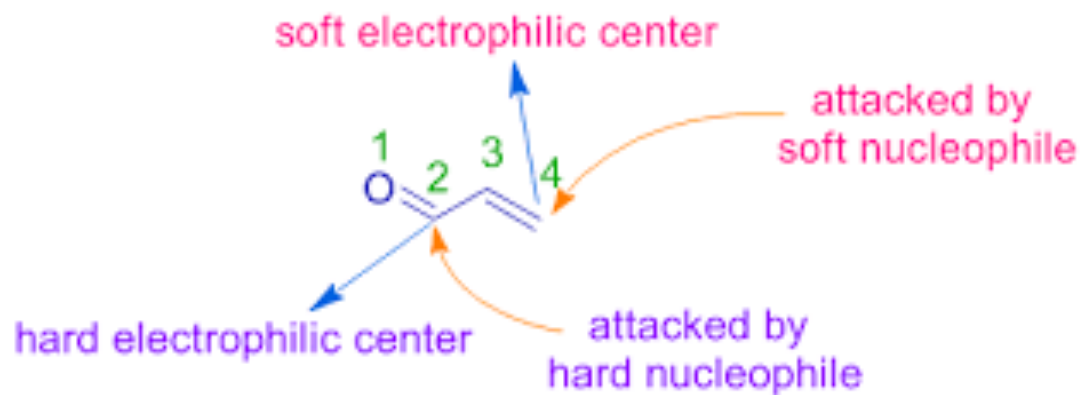


|            | Acids  | Bases   |
|------------|--|---|
| Hard       | $H^+$ , $Li^+$ , $Na^+$ , $K^+$ , $Be^{2+}$ , $Mg^{2+}$ , $Fe^{3+}$ , $Ca^{2+}$ , $Cr^{2+}$ ,<br>$Cr^{3+}$ , $Al^{3+}$ , $SO_3$ , $BF_3$ | $F^-$ , $OH^-$ , $H_2O$ , $NH_3$ , $CO_3^{2-}$ , $NO_3^-$ , $O^{2-}$ ,<br>$SO_4^{2-}$ , $PO_4^{3-}$ , $ClO_4^-$ |
| Borderline | $Fe^{2+}$ , $Co^{2+}$ , $Ni^{2+}$ , $Cu^{2+}$ , $Zn^{2+}$ , $Pb^{2+}$ , $SO_2$ , $BBr_3$   | $NO_2^-$ , $SO_3^{2-}$ , $Br^-$ , $N_3^-$ , $N_2$ , $C_6H_5N$ , $SCN^-$   |
| Soft       | $Cu^+$ , $Au^+$ , $Ag^+$ , $Tl^+$ , $Hg_2^{2+}$ , $Pd^{2+}$ , $Cd^{2+}$ , $Pt^{2+}$ ,<br>$Hg^{2+}$ , $BH_3$                              | $H^-$ , $R^-$ , $CN^-$ , $CO$ , $I^-$ , $SCN^-$ , $R_3P$ , $C_6H_5$ ,<br>$R_2S$                                 |

# HSAB



## Hard Soft Interactions

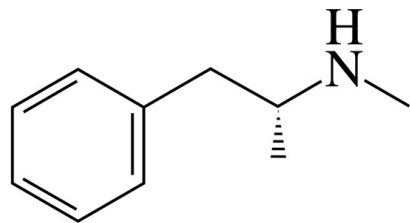




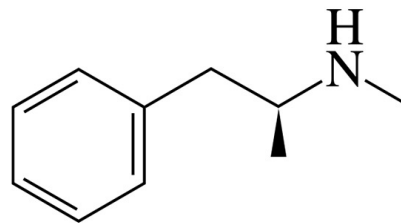


# Isomers

Enantiomers can have **very different** physiological properties.



the active ingredient  
in Vicks Vapor Inhaler®



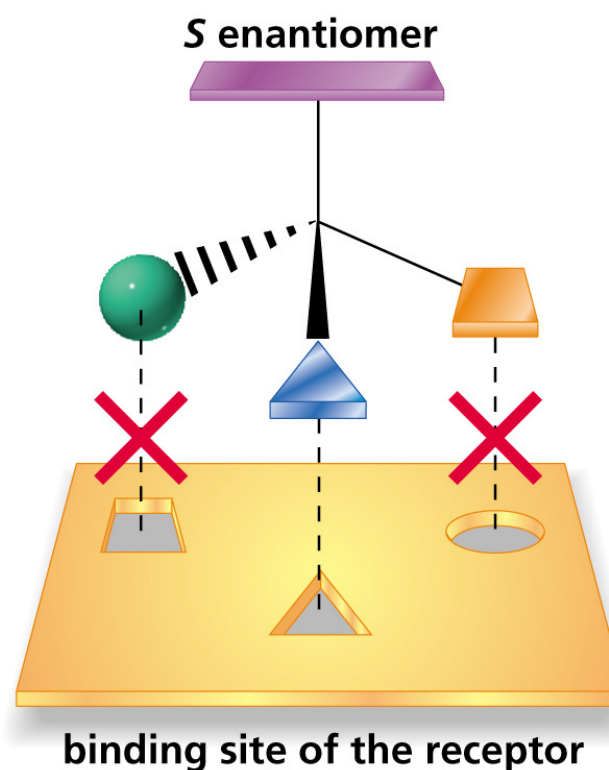
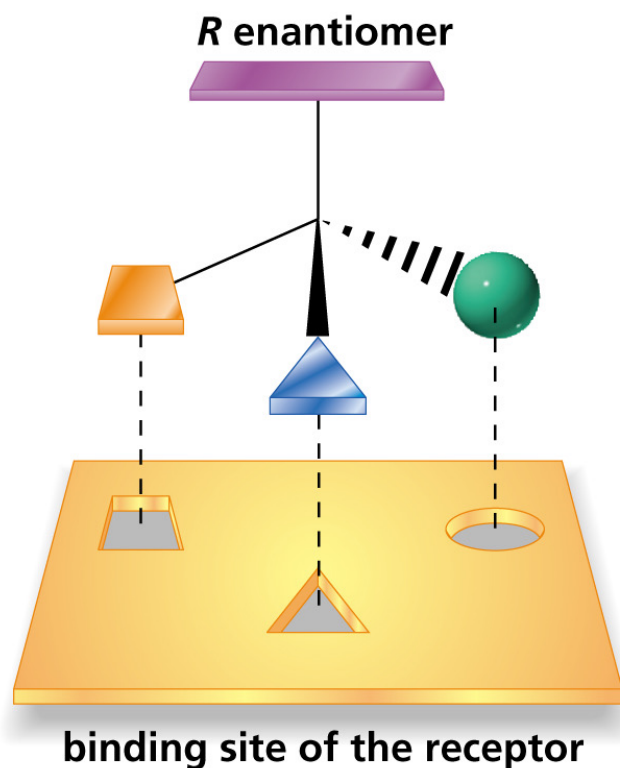
methamphetamine  
"meth"

# A Receptor is a Protein

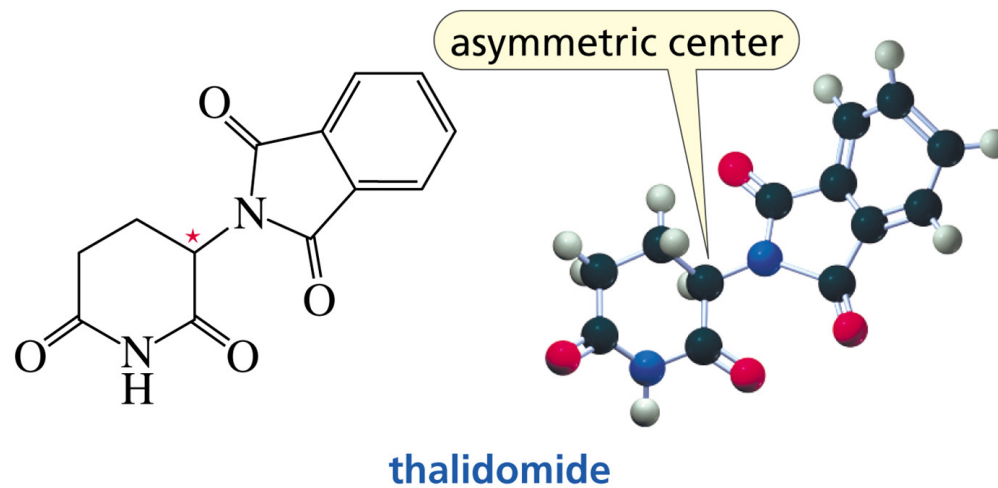
## Proteins are Chiral Molecules

Because a receptor is chiral, it binds **one enantiomer**.

A **right-handed glove** fits only a **right hand**.



# The enantiomers of Thalidomide

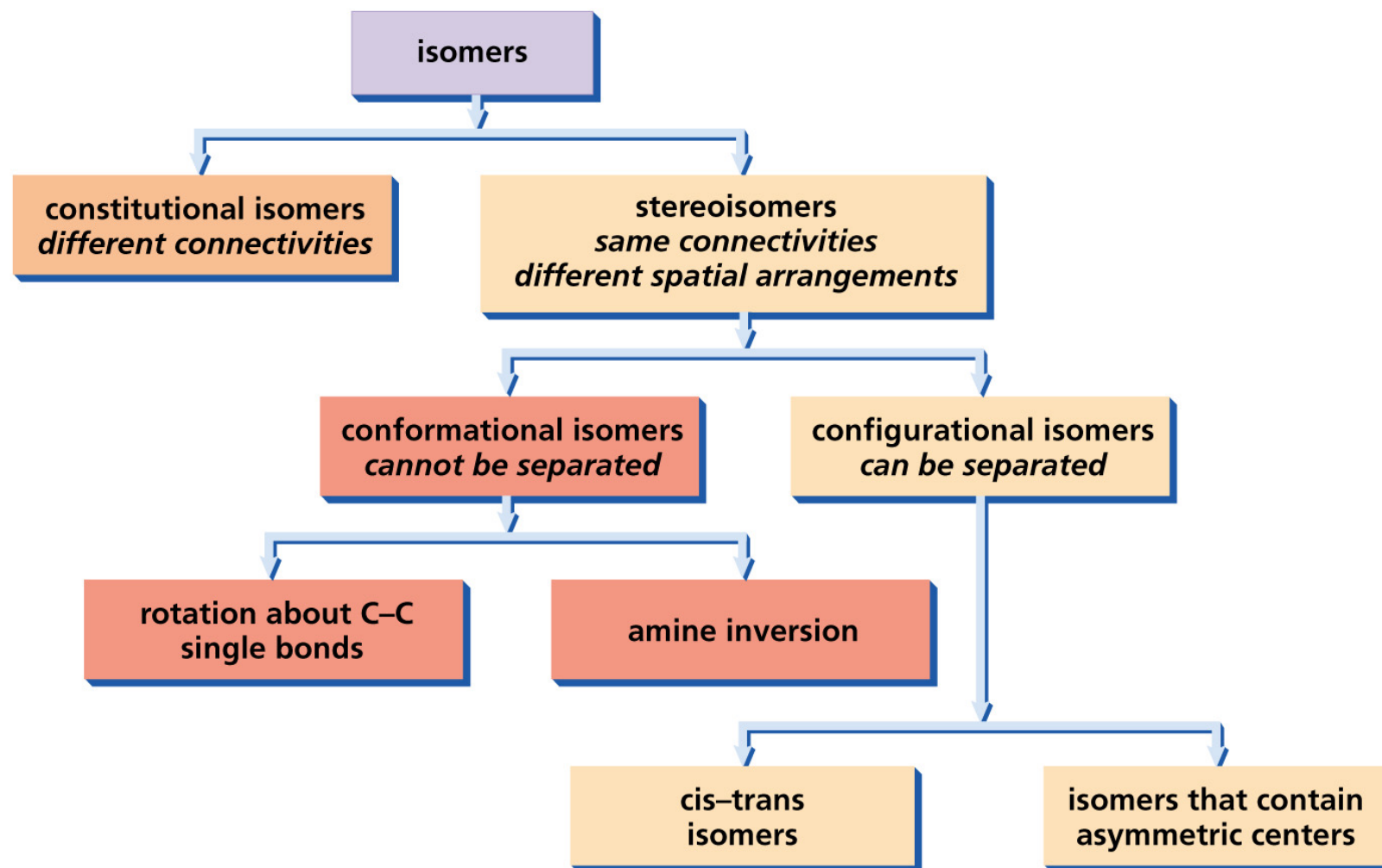


Thalidomide was developed in west Germany and was first marketed (as Contergan) in 1957 for insomnia, tension and morning sickness during pregnancy.

The (+) isomer has stronger sedative properties, but the commercial drug was racemic (contained 1:1 mixture of (+) and (-) isomers). At that time no one knew that the (-) isomer was a teratogen – a compound that causes congenital deformations -.

# Isomers

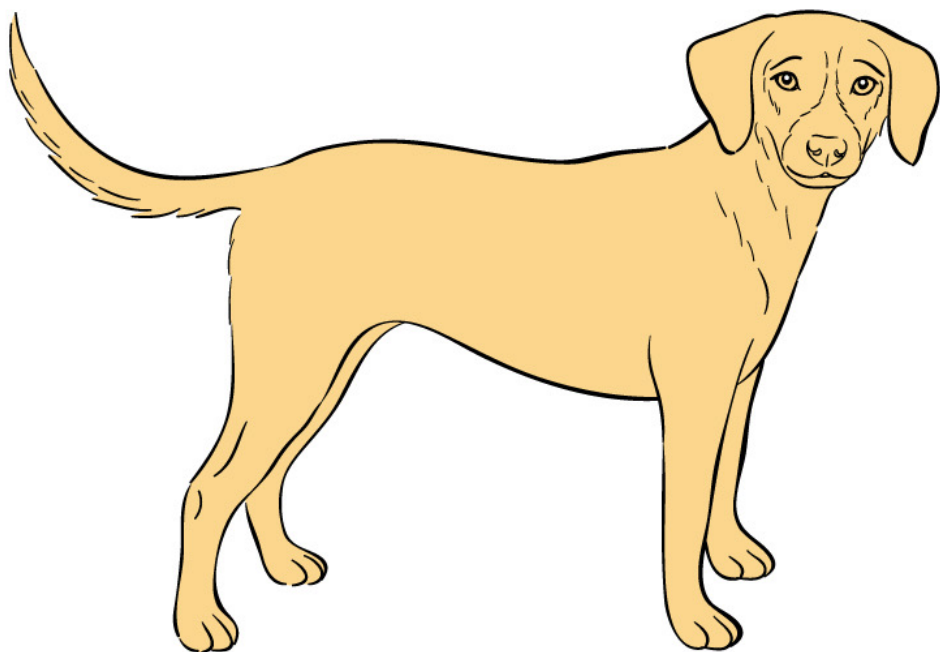
Isomers are compounds that have the same molecular formula but different structures.



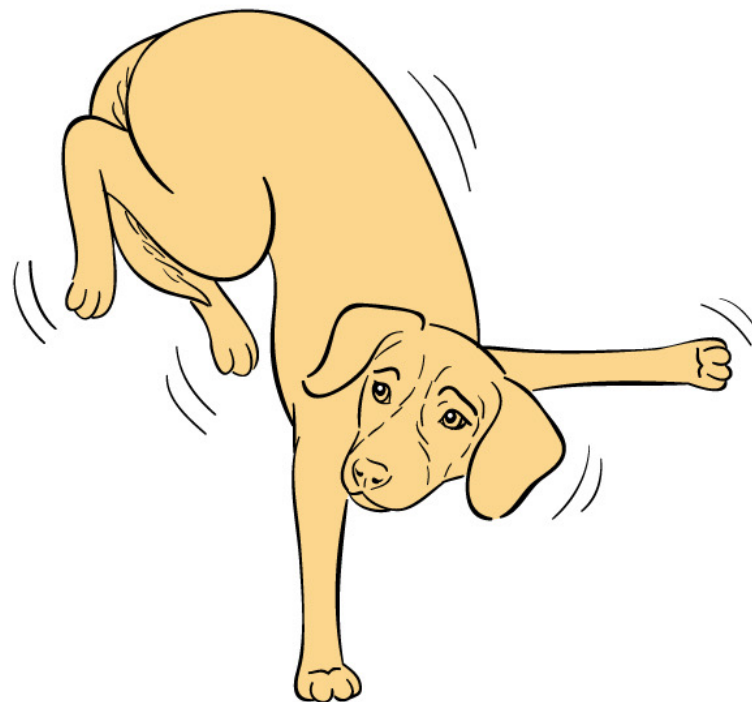
# Different Conformations

Different **conformations** (conformers) of a compound  
cannot be **separated**.

## Different Conformations



**Stable**

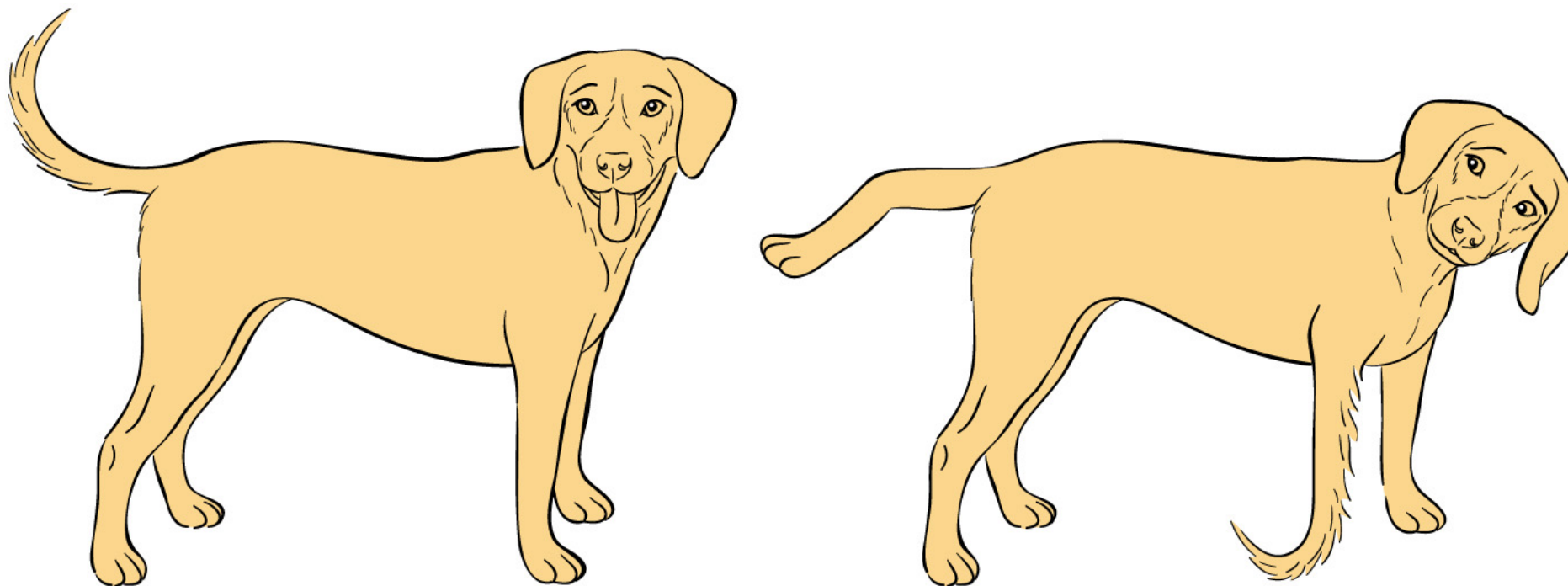


**Unstable**

# Different Configurations

Compounds with different configurations can be separated.

## Different Configurations

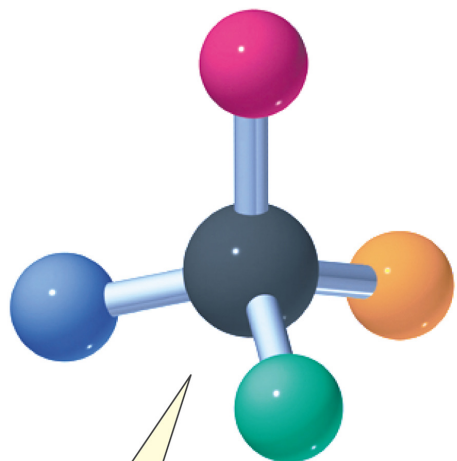


Cis–trans isomers have different configurations.

# Chiral Molecules

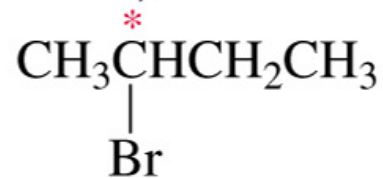
A chiral molecule has an **asymmetric center**.

An **asymmetric center** is an atom that is attached to **four different groups**.



an asymmetric center

C is bonded to H,  
Br, ethyl, methyl



2-bromobutane

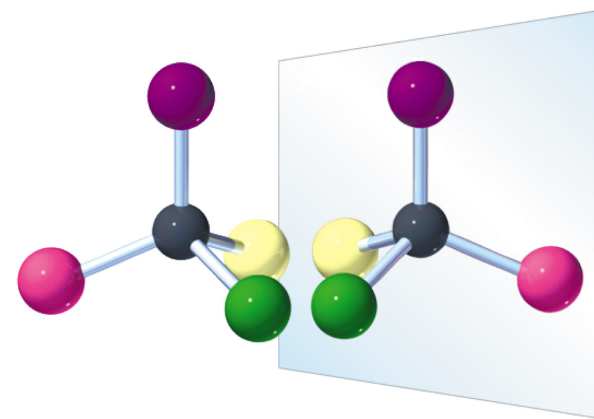


# Enantiomers

Definition: Molecules that are nonsuperimposable mirror images of each other are called enantiomers.



two stereoisomers of 2-bromobutane

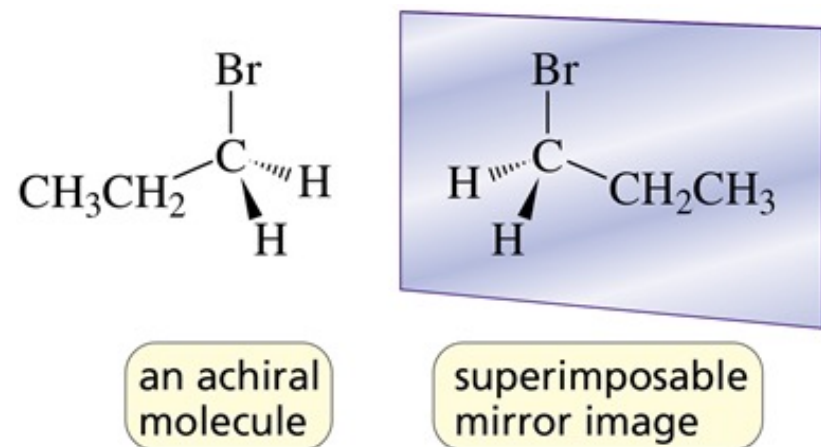
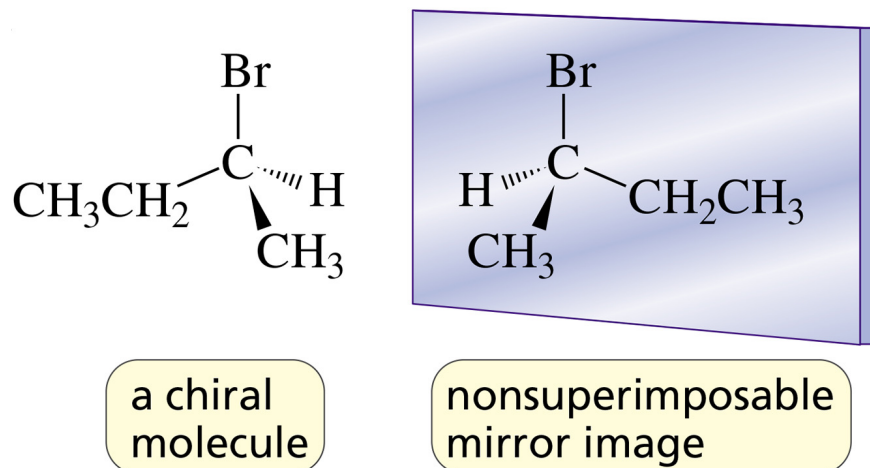


nonsuperimposable  
mirror images

The two stereoisomers are called **enantiomers**.

**Enantiomers** are different compounds: they **can be separated**.

# Chiral and Achiral Molecules



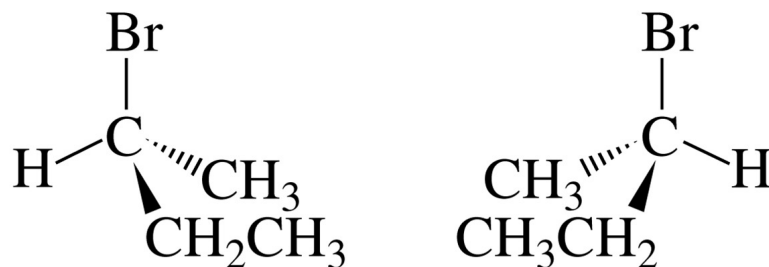
A **chiral** compound has a **nonsuperimposable** mirror image.

An **achiral** compound has a **superimposable** mirror image.

(it and its mirror image are identical molecules).

# How to Draw Enantiomers

## Perspective formulas



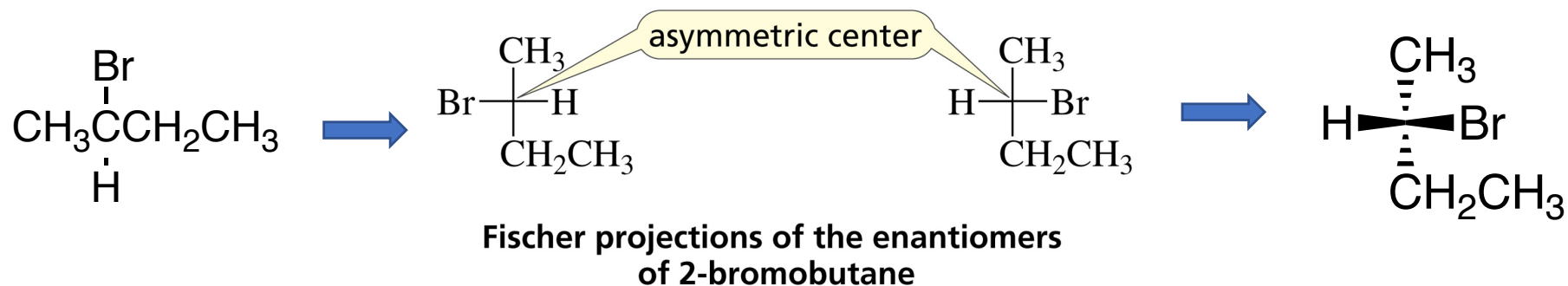
perspective formulas of the enantiomers  
of 2-bromobutane

- 1.- Two of the bonds center in the plane (adjacent to each other)
- 2.- One bond as a solid wedge protruding forward out of the paper
- 3.- The fourth bond as a hatched wedge extending behind the paper

!! The solid and hatched wedges must be adjacent to each other  
!! The solid wedge must be below the hatched wedge

# How to Draw Enantiomers

## Fischer projections



- 1.- Horizontal lines represent the bonds that project out of the plane toward the viewer
- 2.- Vertical lines represent the bonds that extend back from the plane away from the viewer
- 3.- The carbon chain is usually drawn vertically, with C-1 at the top

# Cahn-Ingold-Prelog



**Vladimir Prelog with R.S. Cahn and Sir Christopher Ingold, who proposed the CIP system for the unambiguous specification of stereoisomers. Shown at the 1966 Burgenstock Conference (l to r: Cahn, Ingold, Prelog).**

**Robert Sidney Cahn** (1899–1981), born in London, England, received an M.A. from Cambridge University and a doctorate in natural philosophy in France. He edited the Journal of the Chemical Society (London) from 1949 to 1963.

**Sir Christopher Ingold** (1893–1970), born in Ilford, England, was a professor of chemistry at Leeds University (1924–1930) and at University College, London (1930–1970). In 1958 he was knighted by Queen Elizabeth II.

**Vladimir Prelog** (1906–1998) was born in Sarajevo, Bosnia. In 1929 he received a Dr. Ing. degree from the Institute of Technology in Prague, Czechoslovakia. He taught at the University of Zagreb from 1935 until 1941, when he fled to Switzerland just ahead of the invading German army. He was a professor at the Swiss Federal Institute of Technology (ETH). For work that contributed to an understanding of how living organisms carry out chemical reactions, he shared the 1975 Nobel Prize in Chemistry with John Cornforth

# Naming Enantiomers

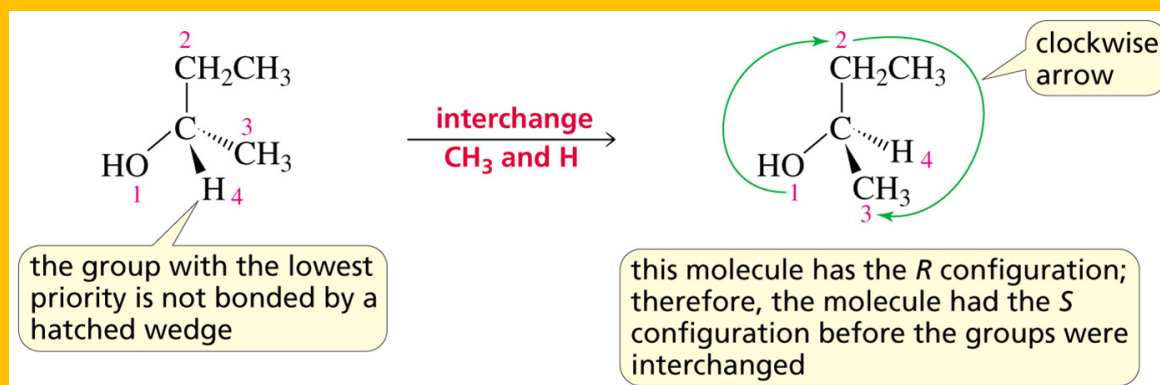
Assign **relative priorities** to the four groups  
**CIP** (Cahn-Ingold-Prelog) system.

1.- Rank the group (or atoms) bonded to the asymmetric center in order of priority (the higher the atomic number, the higher the priority).

2.- The group (or atom) with the lower priority (4) has to be bonded by a hatched wedge (pointing behind).

!! If the group (or atom) with priority (4) is not bonded by a hatched wedge:

- Interchange group (4) with the group that is bonded by a hatched wedge



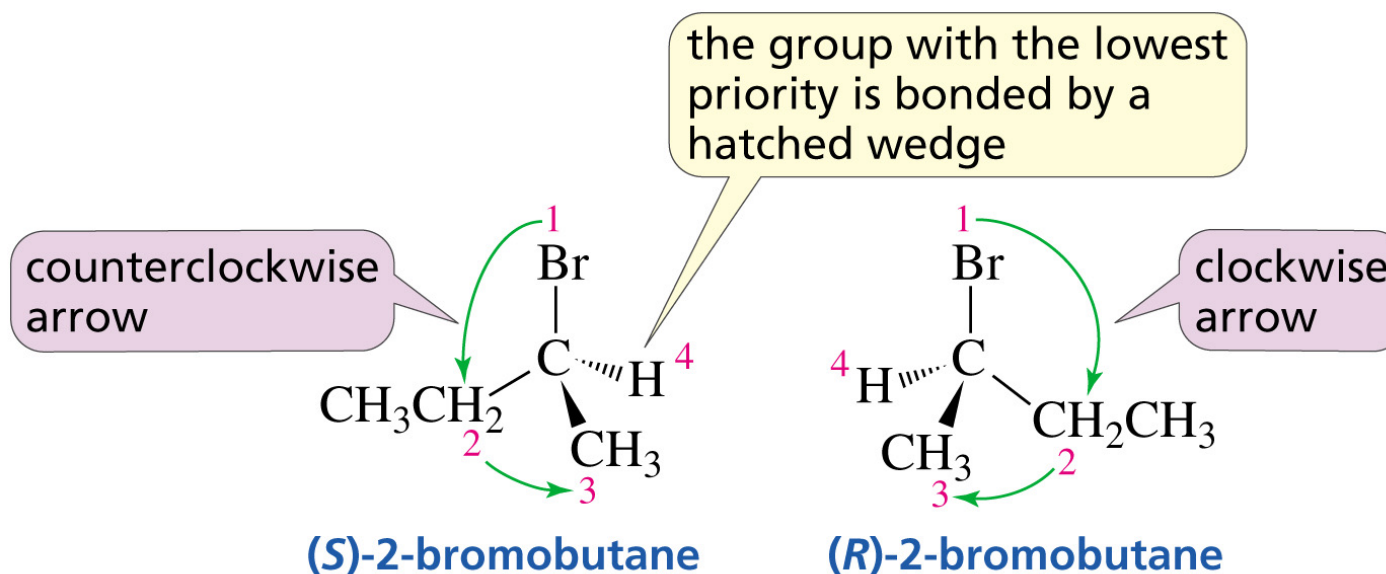
3.- Draw an arrow in order of decreasing priority,  $1 \rightarrow 2 \rightarrow 3$

!! Arrow pointing clockwise = (*R*), rectus (right)

Arrow pointing counterclockwise = (*S*), sinister (left)

# Naming Enantiomers

Draw an arrow from **1** to **2** to **3**.



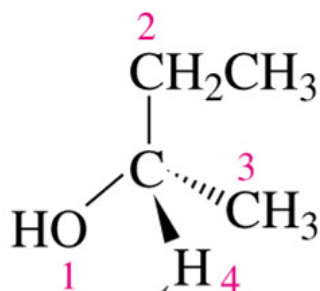
If the lowest priority group is on a hatched wedge, then

clockwise = *R*  
and  
counterclockwise = *S*

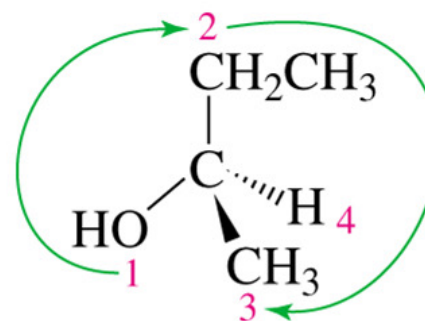
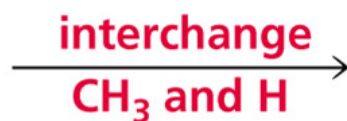
# Naming Enantiomers

If the lowest priority group is **not** on a hatched wedge, switch a pair so it is on a hatched wedge.

Then, name the new compound.



the group with the lowest priority is not bonded by a hatched wedge

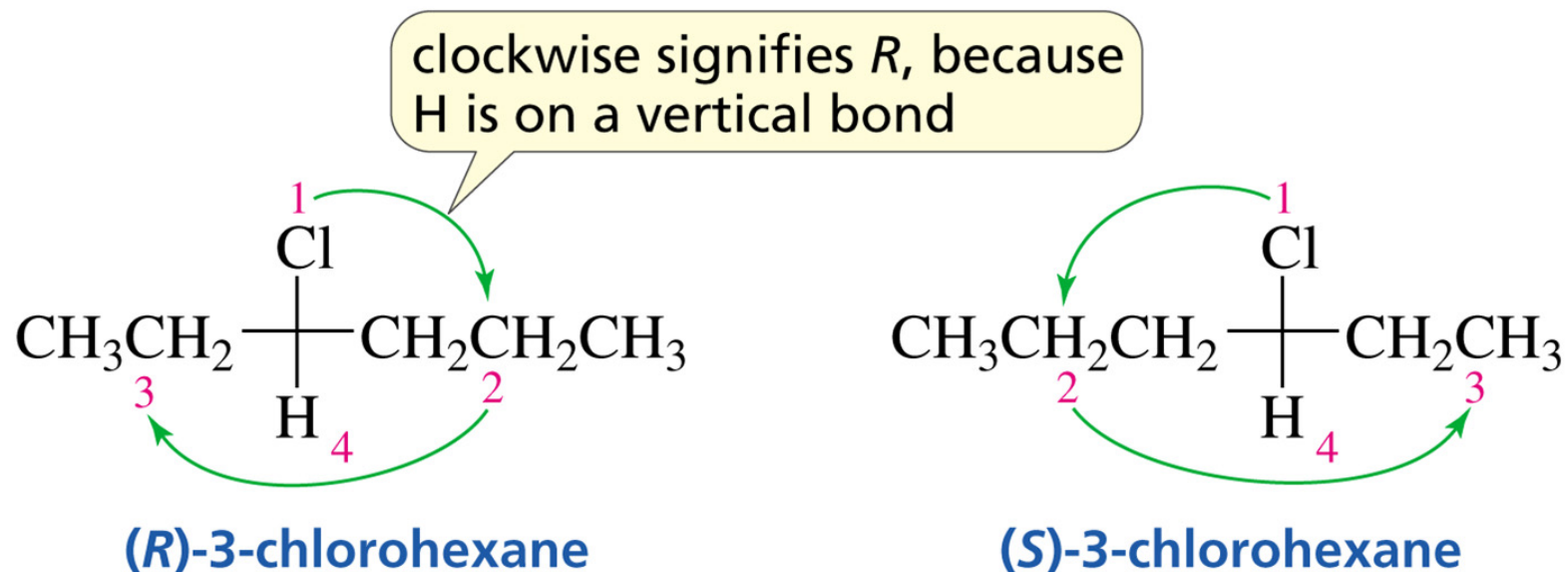


clockwise  
arrow

this molecule has the *R* configuration; therefore, the molecule had the *S* configuration before the groups were interchanged



# Naming Enantiomers

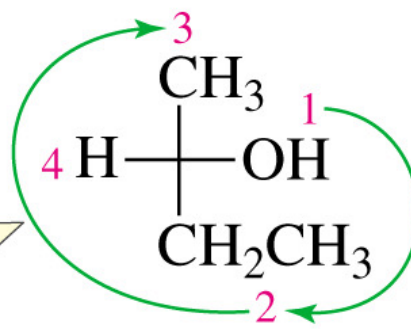


If the lowest priority group is on a **vertical bond**, then

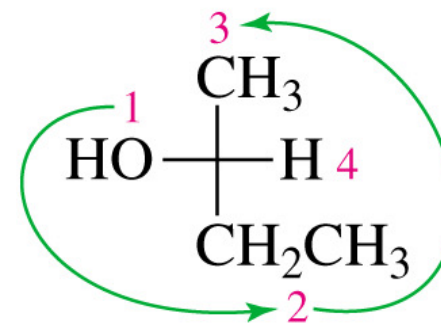
clockwise = *R*  
and  
counterclockwise = *S*

# Naming Enantiomers

clockwise signifies *S*,  
because H is on a horizontal bond



**(S)-2-butanol**



**(R)-2-butanol**

If the lowest priority group is on a **horizontal bond**, then

**counterclockwise = *R***

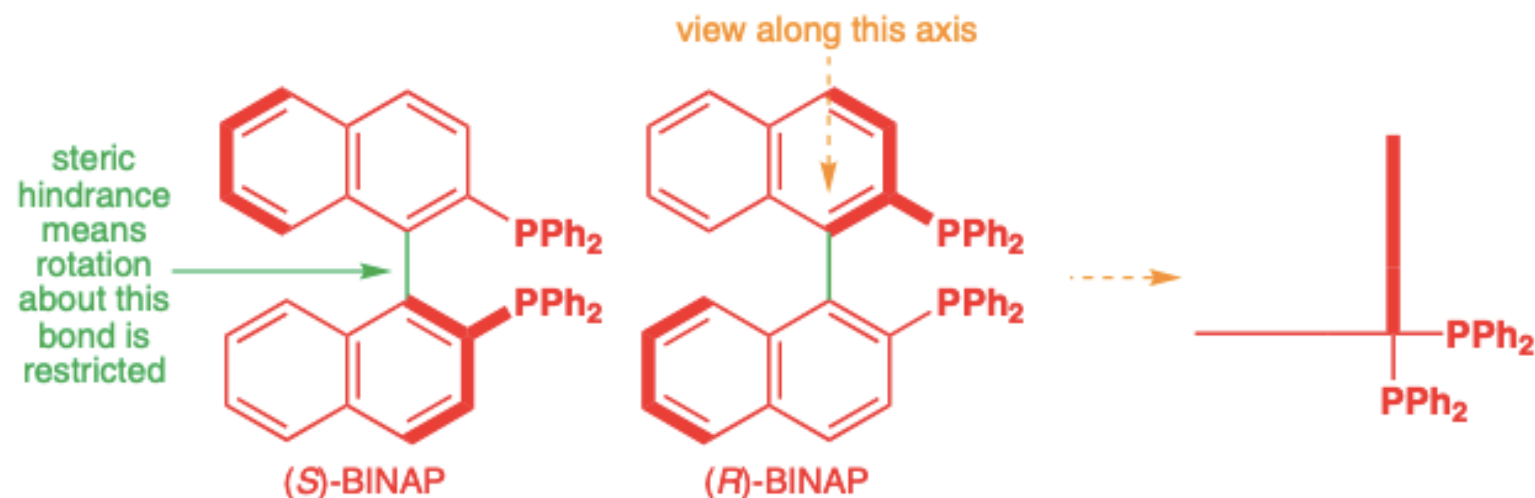
and

**clockwise = *S***

# Stereochemistry

## Chiral compounds with no stereogenic centres

some biaryl compounds, such as the important bisphosphine below, known as BINAP, exist as two separate enantiomers because rotation about the green bond is restricted.

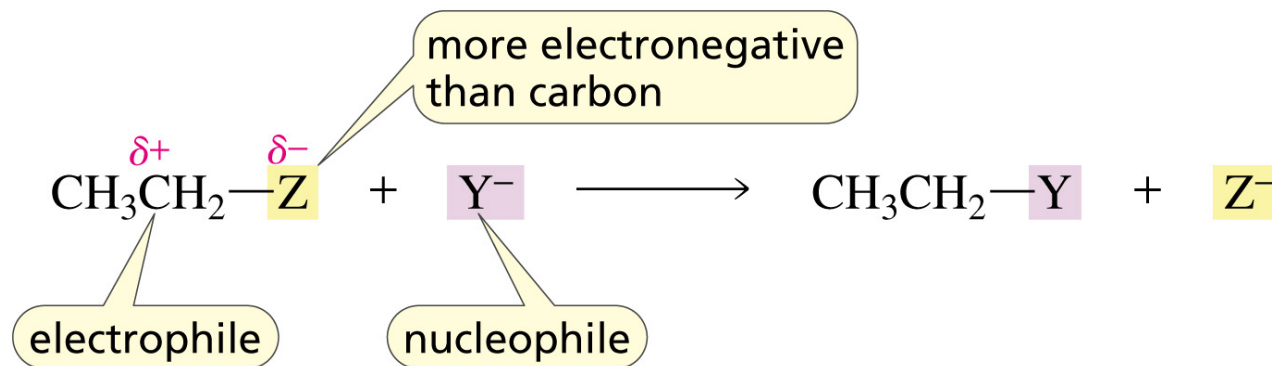


**Axial chirality**: an axis about which a set of substituents is held in a spatial arrangement that is not superposable on its mirror image.

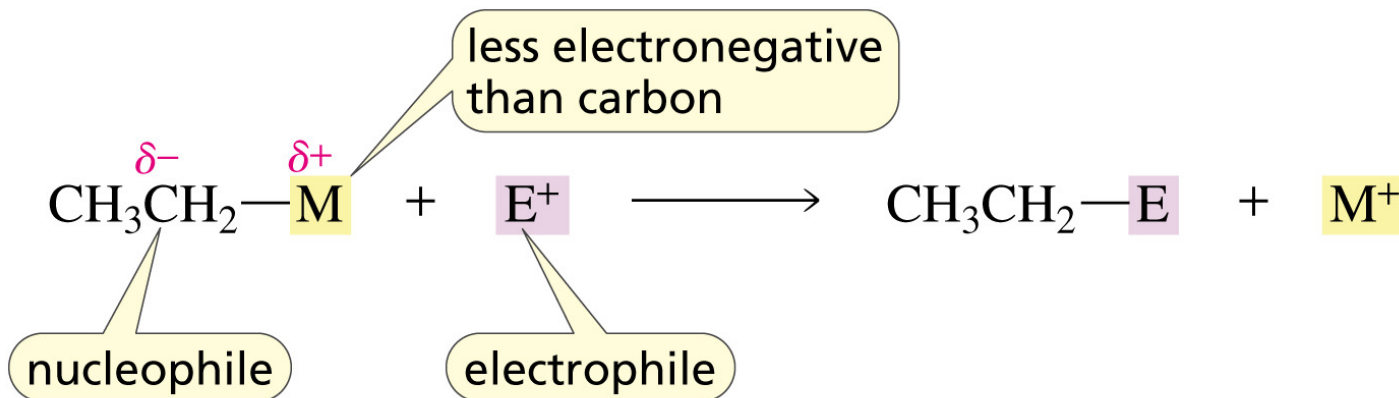


# **Organometallic Compounds**

# Carbon Can Be an Electrophile or a Nucleophile



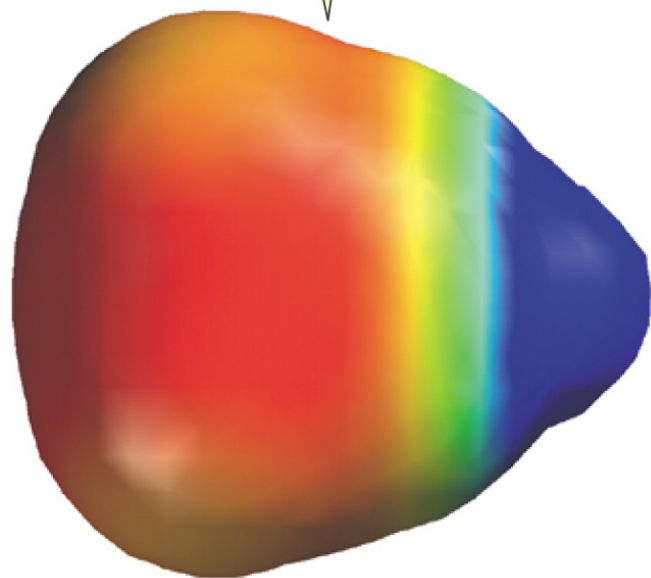
Carbon is an **electrophile** when it is attached to an **electron-withdrawing group**.



Carbon is a **nucleophile** when it is attached to a **metal**.

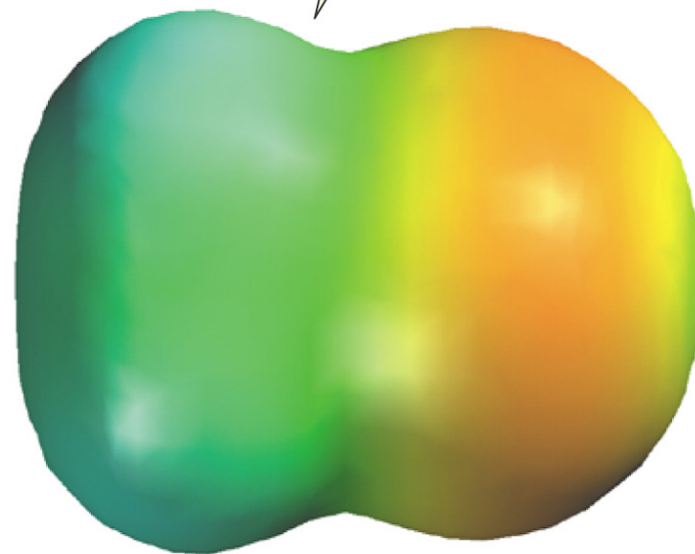
# Carbon Can Be an Electrophile or a Nucleophile

carbon is a  
nucleophile



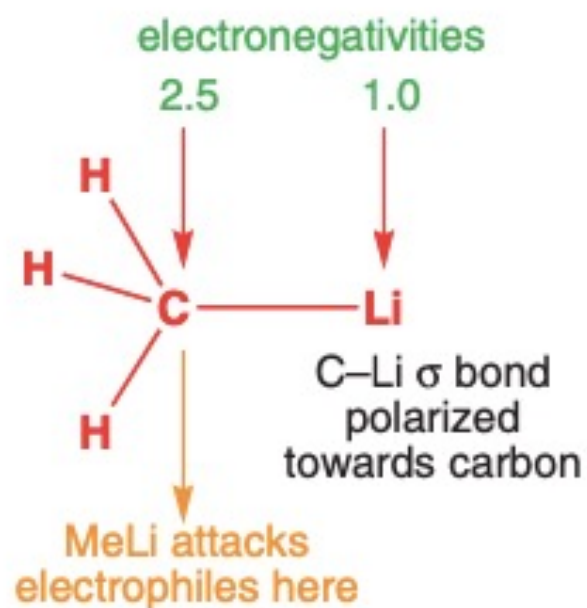
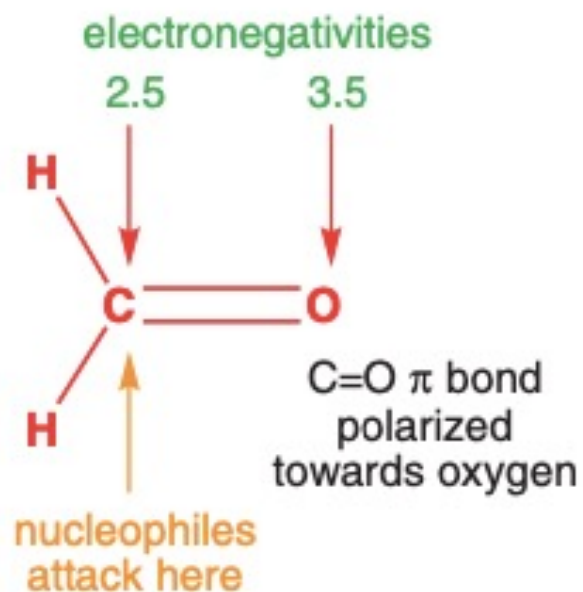
**CH<sub>3</sub>Li**  
organometallic compound

carbon is an  
electrophile



**CH<sub>3</sub>Cl**  
alkyl halide

# Carbon Can Be an Electrophile or a Nucleophile





# Electronegativities

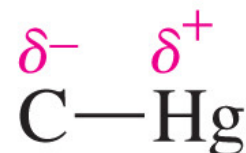
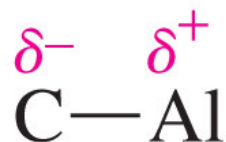
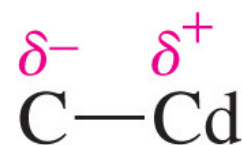
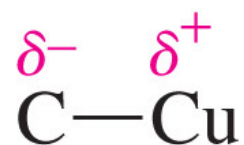
**Table 11.1** The Electronegativities of Some of the Elements<sup>a</sup>

| IA        | IIA       |           |           |           |           |           |           | IB | IIB | IIIA      | IVA       | VA       | VIA      | VIIA      |
|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|----|-----|-----------|-----------|----------|----------|-----------|
| H<br>2.1  |           |           |           |           |           |           |           |    |     |           |           |          |          |           |
| Li<br>1.0 | Be<br>1.5 |           |           |           |           |           |           |    |     | B<br>2.0  | C<br>2.5  | N<br>3.0 | O<br>3.5 | F<br>4.0  |
| Na<br>0.9 | Mg<br>1.2 |           |           |           |           |           |           |    |     | Al<br>1.5 | Si<br>1.8 | P<br>2.1 | S<br>2.5 | Cl<br>3.0 |
| K<br>0.8  | Ca<br>1.0 | Co<br>1.7 | Ni<br>1.7 | Cu<br>1.8 | Zn<br>1.7 | Ga<br>1.8 | Ge<br>2.0 |    |     |           |           |          |          | Br<br>2.8 |
|           |           | Rh<br>2.4 | Pd<br>2.4 | Ag<br>1.8 | Cd<br>1.5 |           | Sn<br>1.7 |    |     |           |           |          |          | I<br>2.5  |
|           |           |           |           |           |           | Hg<br>1.5 | Pb<br>1.6 |    |     |           |           |          |          |           |

<sup>a</sup>From the scale devised by Linus Pauling

# Many Metals Can Be Used to Make Organometallic Compounds

An organometallic compound contains a carbon–metal bond.



Organomagnesium and organolithium compounds are two of the most common organometallic compounds.

# Nomenclature

Name the **alkyl group**, then the **metal**.

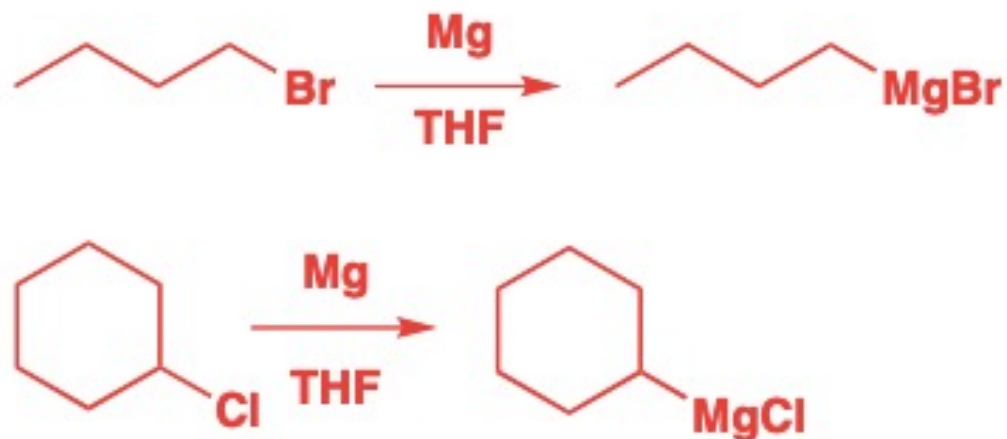
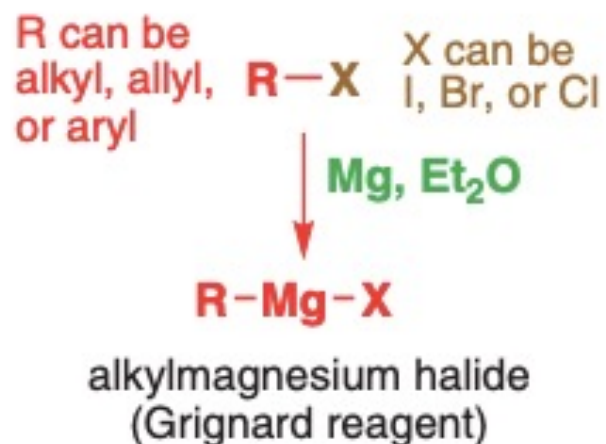
$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{Li}$   
**butyllithium**

$\text{CH}_3\text{CH}_2\text{MgBr}$   
**ethylmagnesium  
bromide**

$(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{Cd}$   
**dipropylcadmium**

$(\text{CH}_3\text{CH}_2)_4\text{Pb}$   
**tetraethyllead**

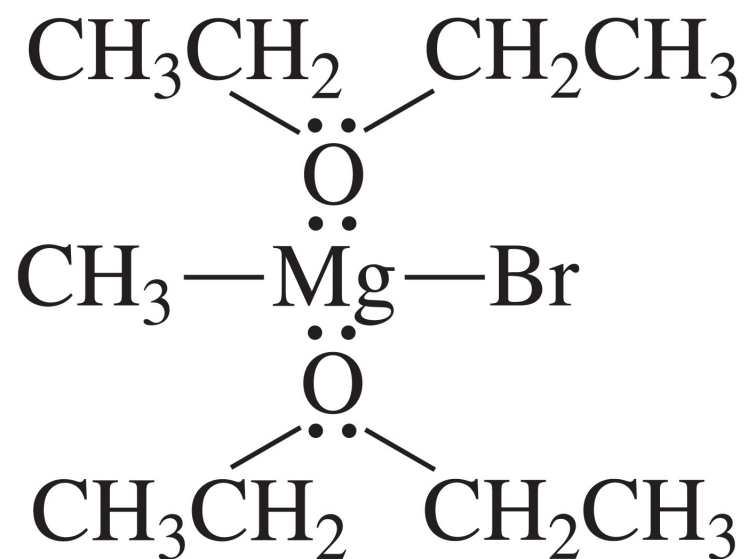
# Organomagnesium Compounds



## More on making Grignard reagents

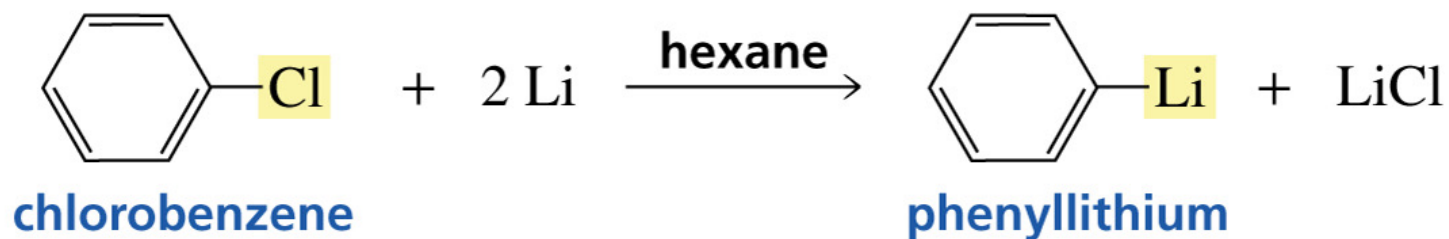
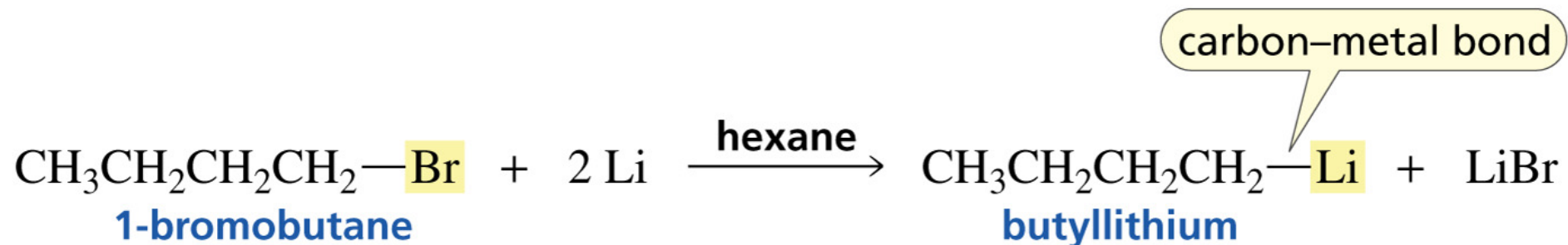
The reaction takes place not in solution but on the surface of the metal, and how easy it is to make a Grignard reagent can depend on the state of the surface—how finely divided the metal is, for example. Magnesium is usually covered by a thin coating of magnesium oxide, and Grignard formation generally requires 'initiation' to allow the metal to come into direct contact with the alkyl halide. Initiation usually means adding a small amount of iodine or 1,2-diiodoethane,

# The Synthesis of a Grignard Reagent is Carried Out in an Ether Solvent

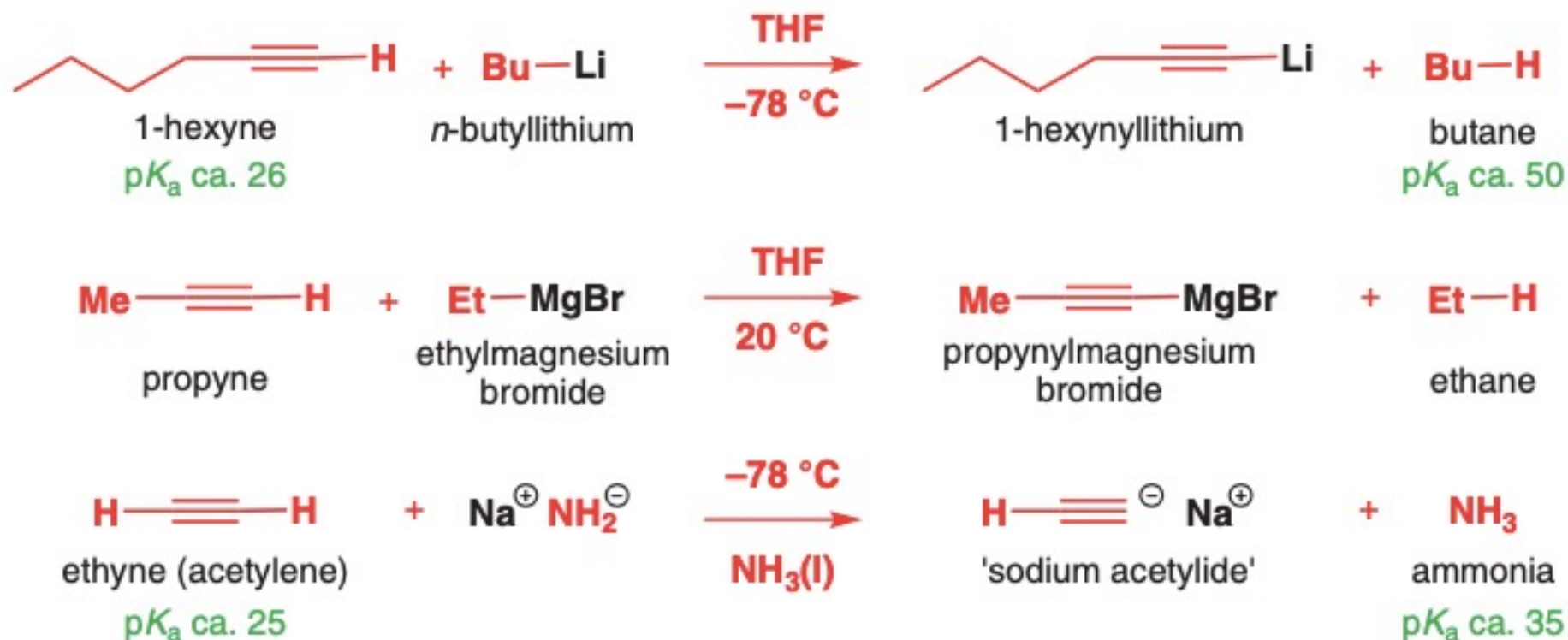


The solvent provides electrons so that magnesium can **complete its octet.**

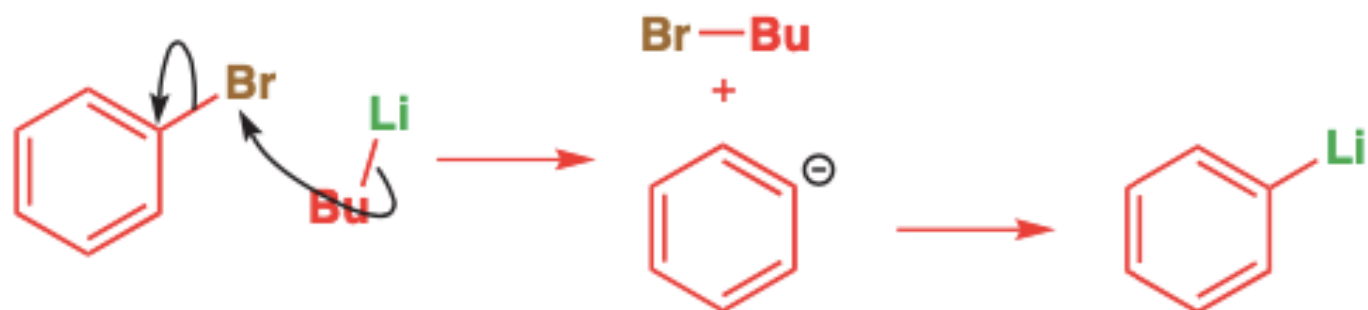
# Organolithium Compounds



# Deprotonation



# Halogen-metal exchange

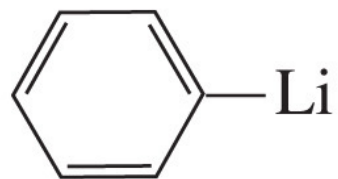




# Organomagnesium and Organolithium Compounds React as if They Were Carbanions

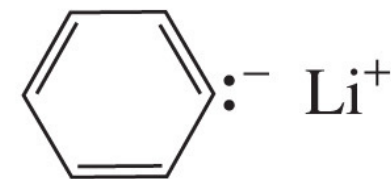
$\text{CH}_3\text{CH}_2\text{—MgBr}$   
**ethylmagnesium bromide**

reacts as if it were



**phenyllithium**

reacts as if it were

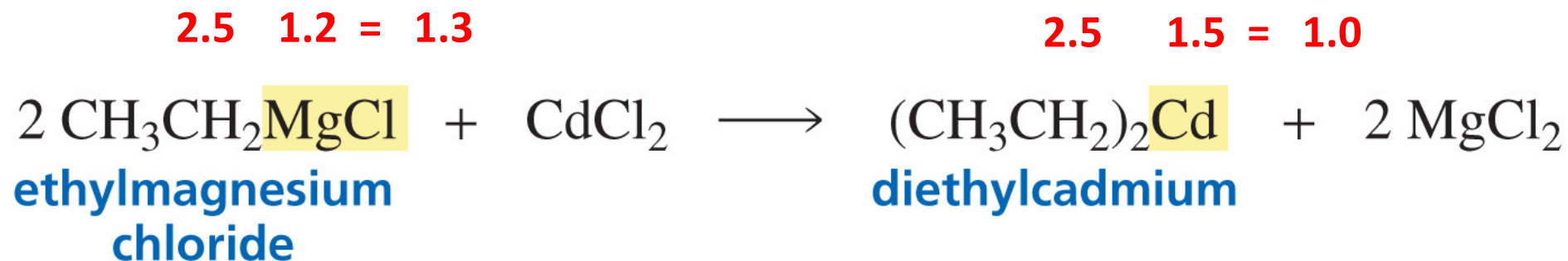


# Organomagnesium and Organolithium Compounds Will React with a Proton of an Acidic Group



When the **Grignard reagent** reacts with a **proton**, it forms an **alkane**.

# Transmetallation



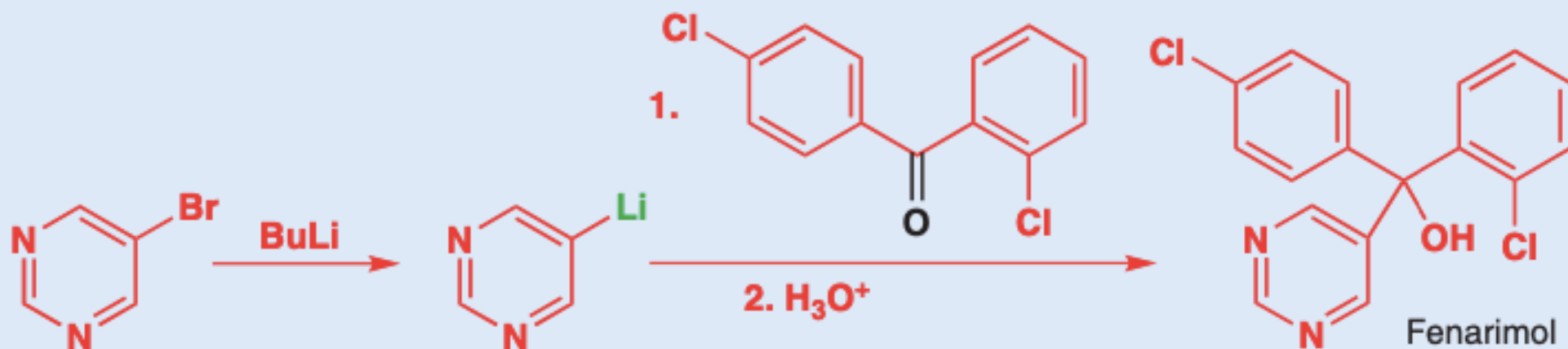
An organometallic compound will undergo **transmetallation** (metal exchange) if a **less polar** carbon–metal bond will be formed.

The **more polar** the carbon–metal bond, the **more reactive** the organometallic compound.

# Organometallics in action

## Fenarimol

Fenarimol is a fungicide that works by inhibiting the fungus's biosynthesis of important steroid molecules. It is made by reaction of a diarylketone with an organolithium derived by halogen-metal exchange.



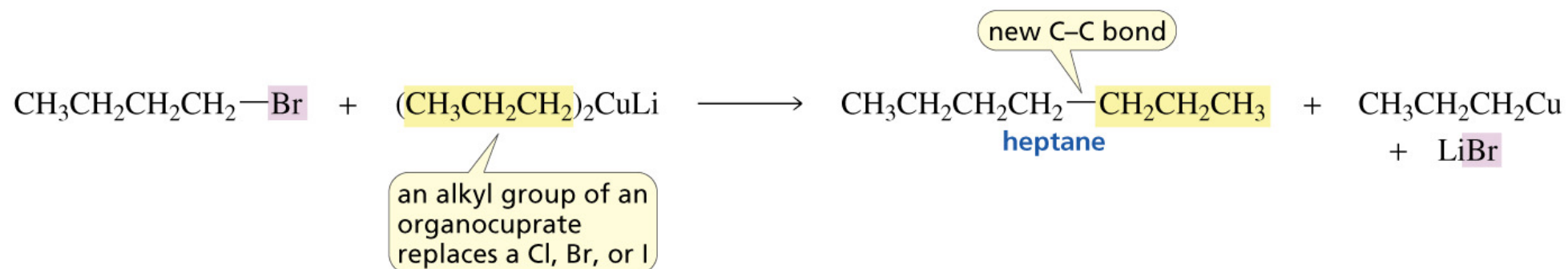
# Organocuprates



Organocuprates are also called **Gilman reagents**.

# The Alkyl Group of an Organocuprate Replaces a Halogen

## C-C bond forming reactions (coupling reactions)

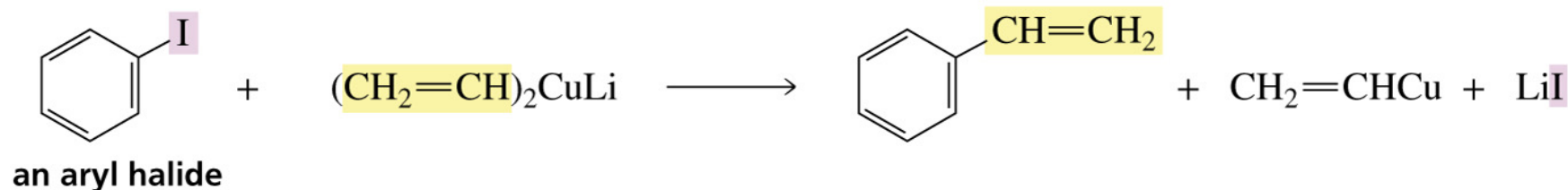
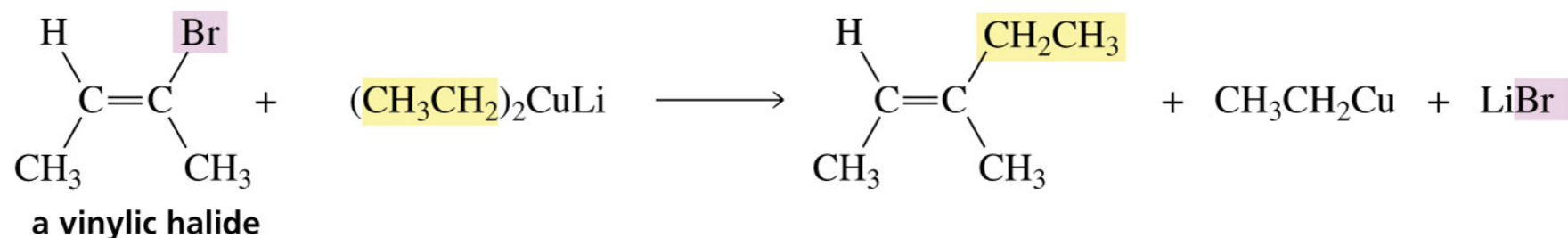


A **coupling reaction** joins two CH-containing groups.

# The Alkyl Group of an Organocuprate Replaces a Halogen

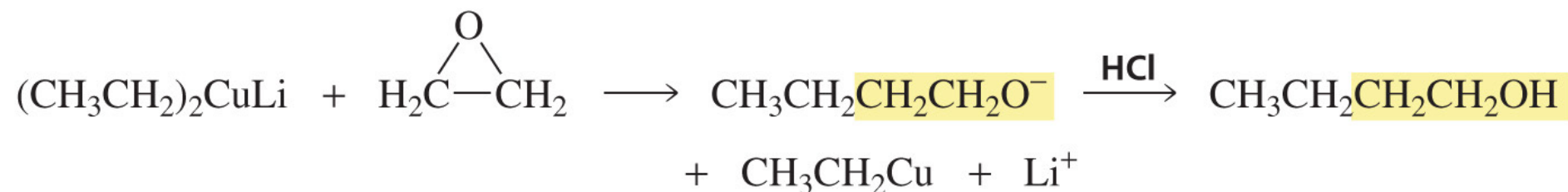
## C-C bond forming reactions (coupling reactions)

A **coupling reaction** joins two CH-containing groups.



# The Reaction of an Organocuprate with Ethylene Oxide

**An Organocuprate is a Nucleophile**



The **alcohol** has **two more carbons** than the **alkyl group** of the organocuprate.