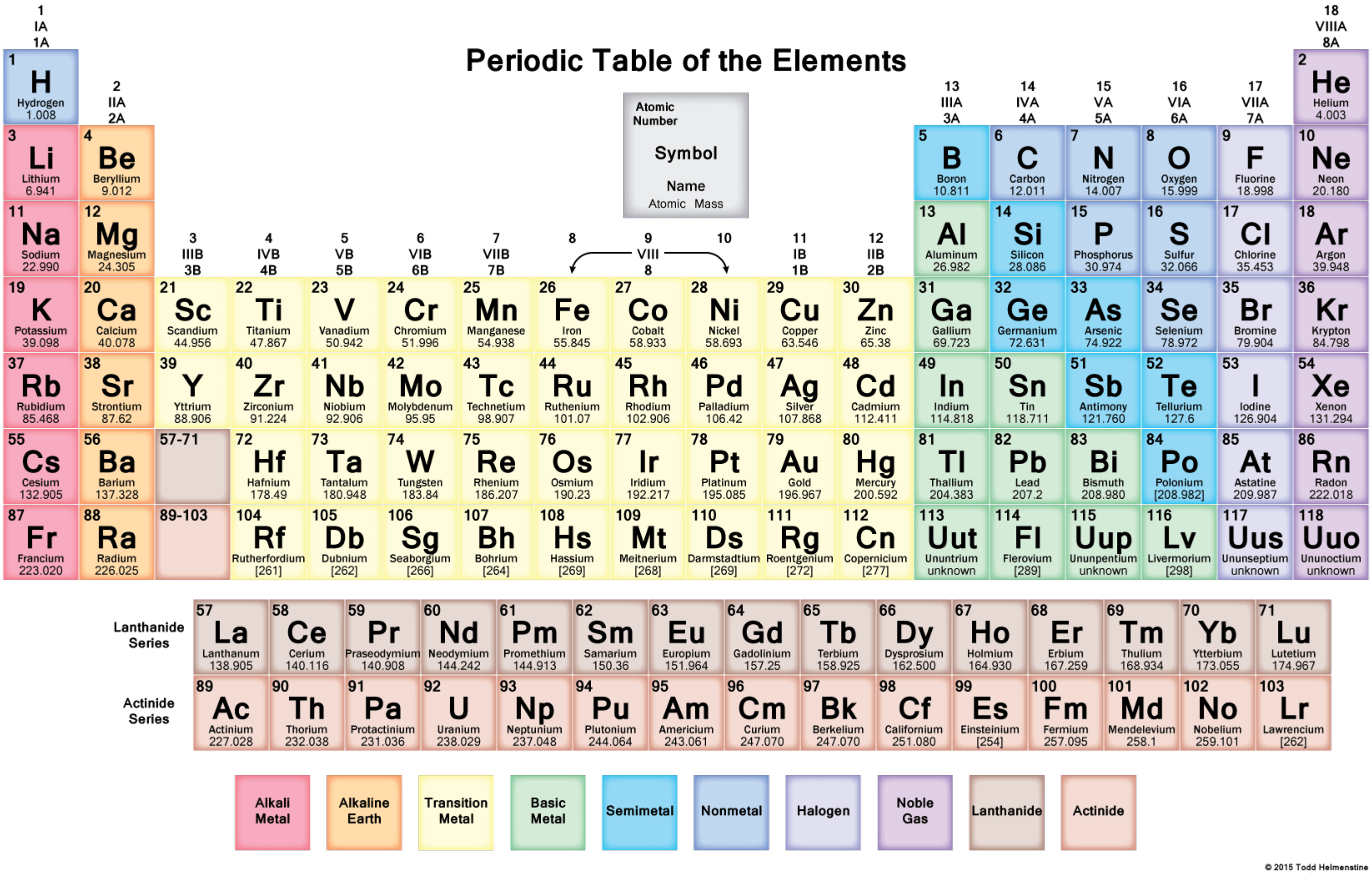
Medicinal Chemistry: An Overview

Course Outline

Lecture	Date	Topic
1	2015/12/17	General Aspects of Medicinal Chemistry
2	2016/01/07	General Biochemistry
3	2016/01/21	Principles of Chemical Synthesis
4	2016/02/04	Chemical Synthesis of Small and Complex Molecules
5	2016/02/18	Chemical Synthesis of Peptides
6	2016/03/03	Strategies for Discovery of Lead Compounds
7	2016/03/17	Structure Activity Relationship
8	2016/03/31	Spatial Organization, Receptor Mapping and Molecular Modeling
9	2016/04/14	Pharmacokinetic Properties
10	2016/04/28	Legal and Economic Aspects of Drug Development

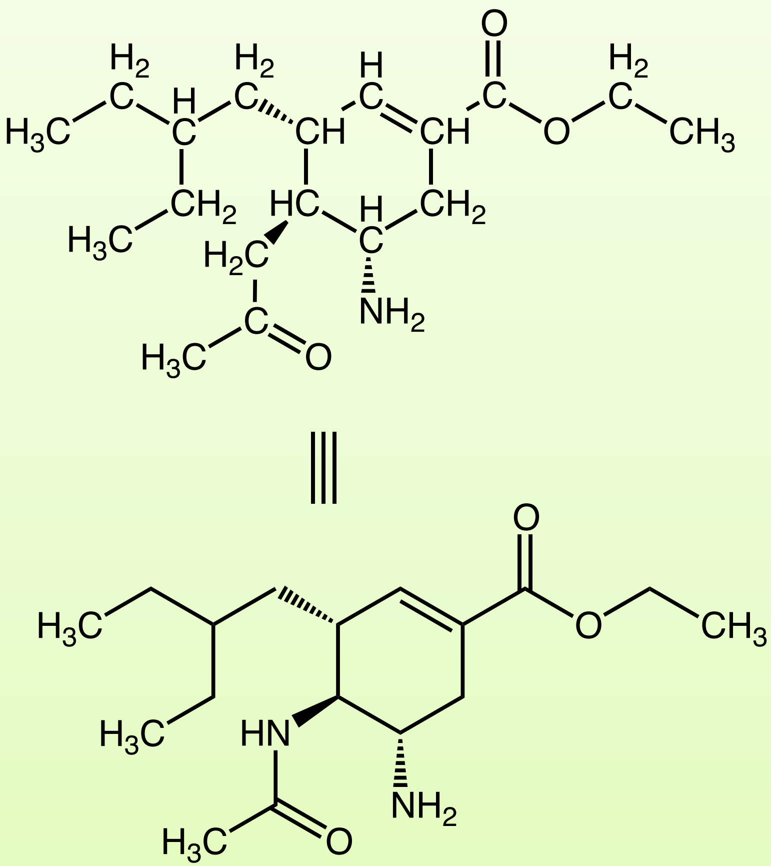
Periodic Table



Elements H, C, N, and O are usually found in drug molecules. Other elements that may be present in the drug substances include S, P, F, Cl, Br, and I. Metals such as Pt and Ru are also constituents of anti-cancer drugs.

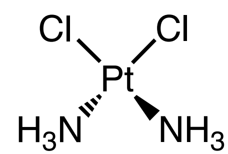
Chemical Synthesis

Organic Synthesis

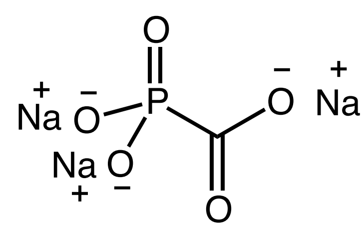


Oseltamivir (antiviral drug for treating influenza)

Inorganic Synthesis



Cisplatin (anticancer drug)



Foscavir (antiviral drug for treating herpes viruses)

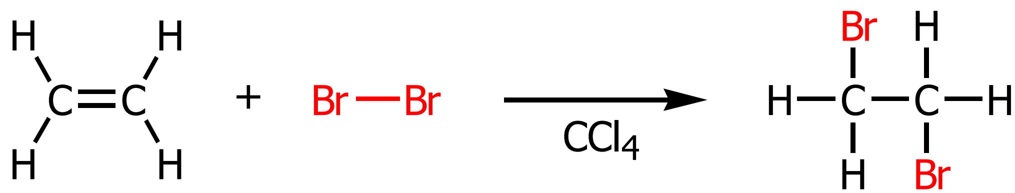
Types of Organic Reactions

❖ Almost all organic reactions fall into one of four categories

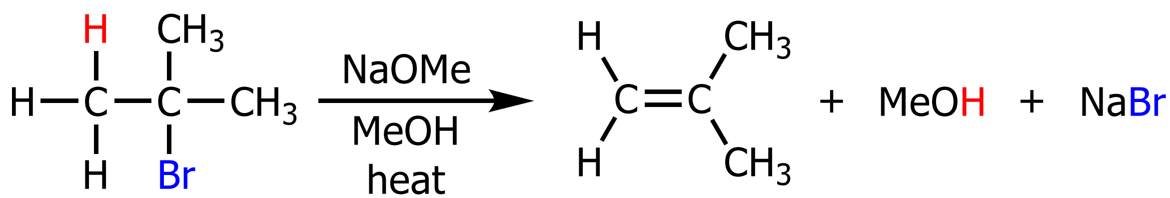
Substitutions

$$H_3C{-}Br + NaOMe \xrightarrow[MeOH]{} H_3C{-}OMe + NaBr$$

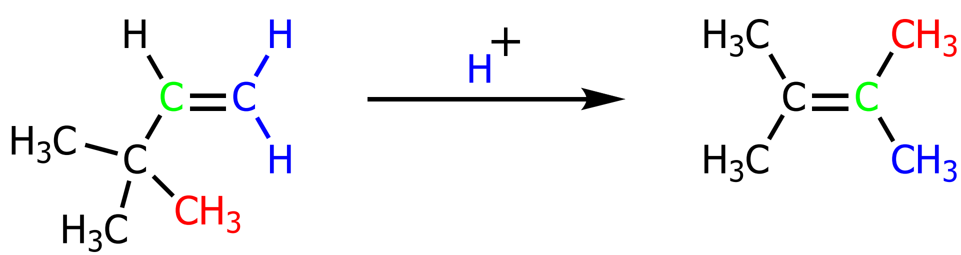
Additions



Eliminations

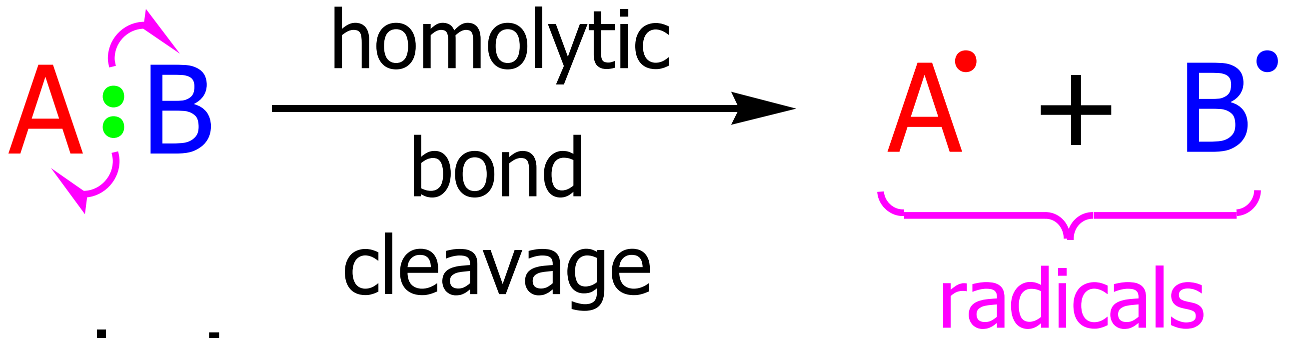


Rearrangements

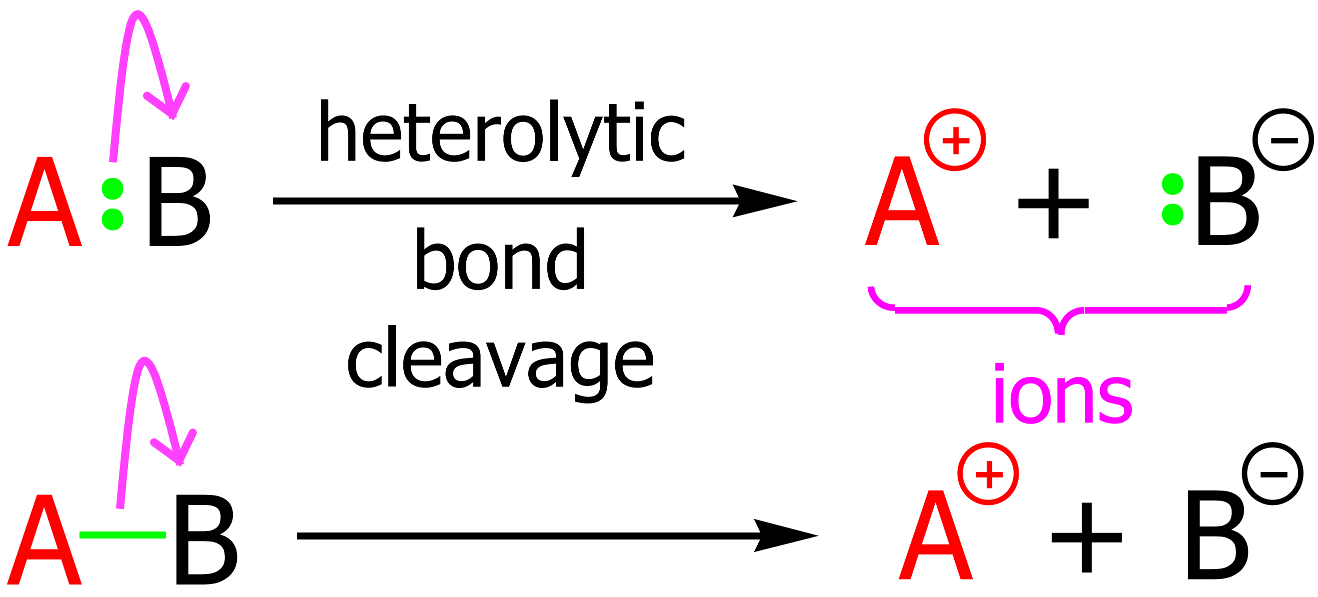


Types of Bond Cleavages

- Homolysis

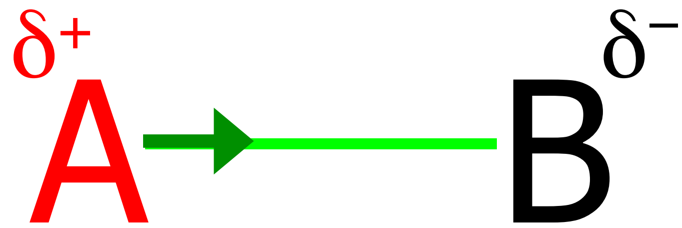


- Heterolysis

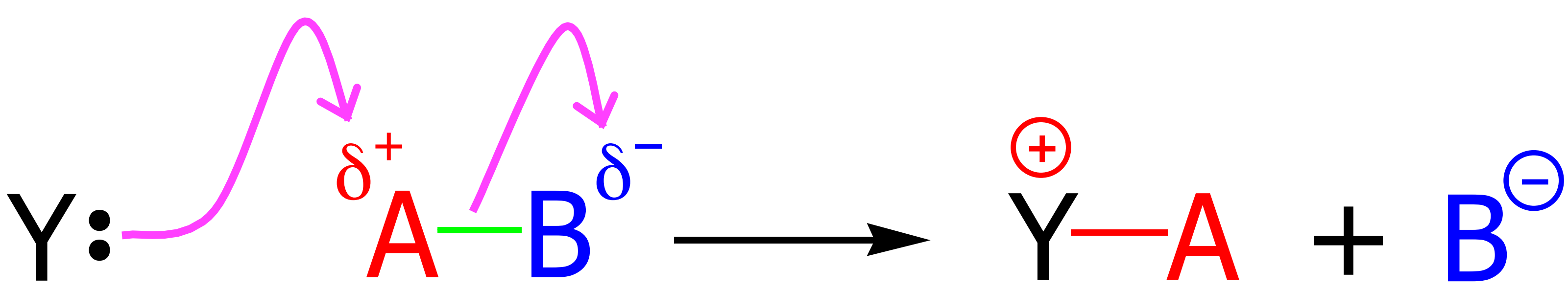


Heterolytic Bond Cleavage

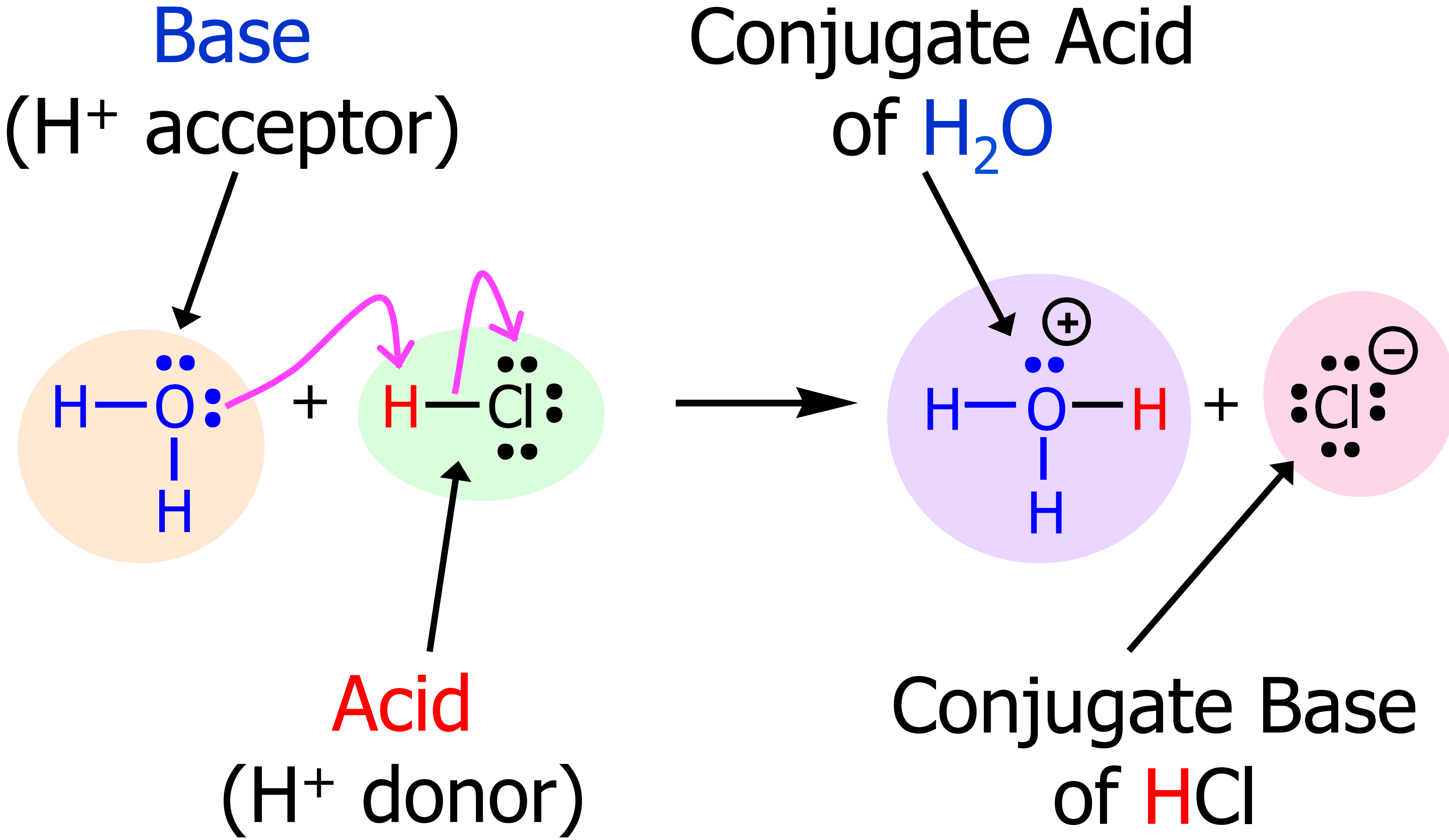
Normally requires the bond to be polarized



Usually occurs with assistance

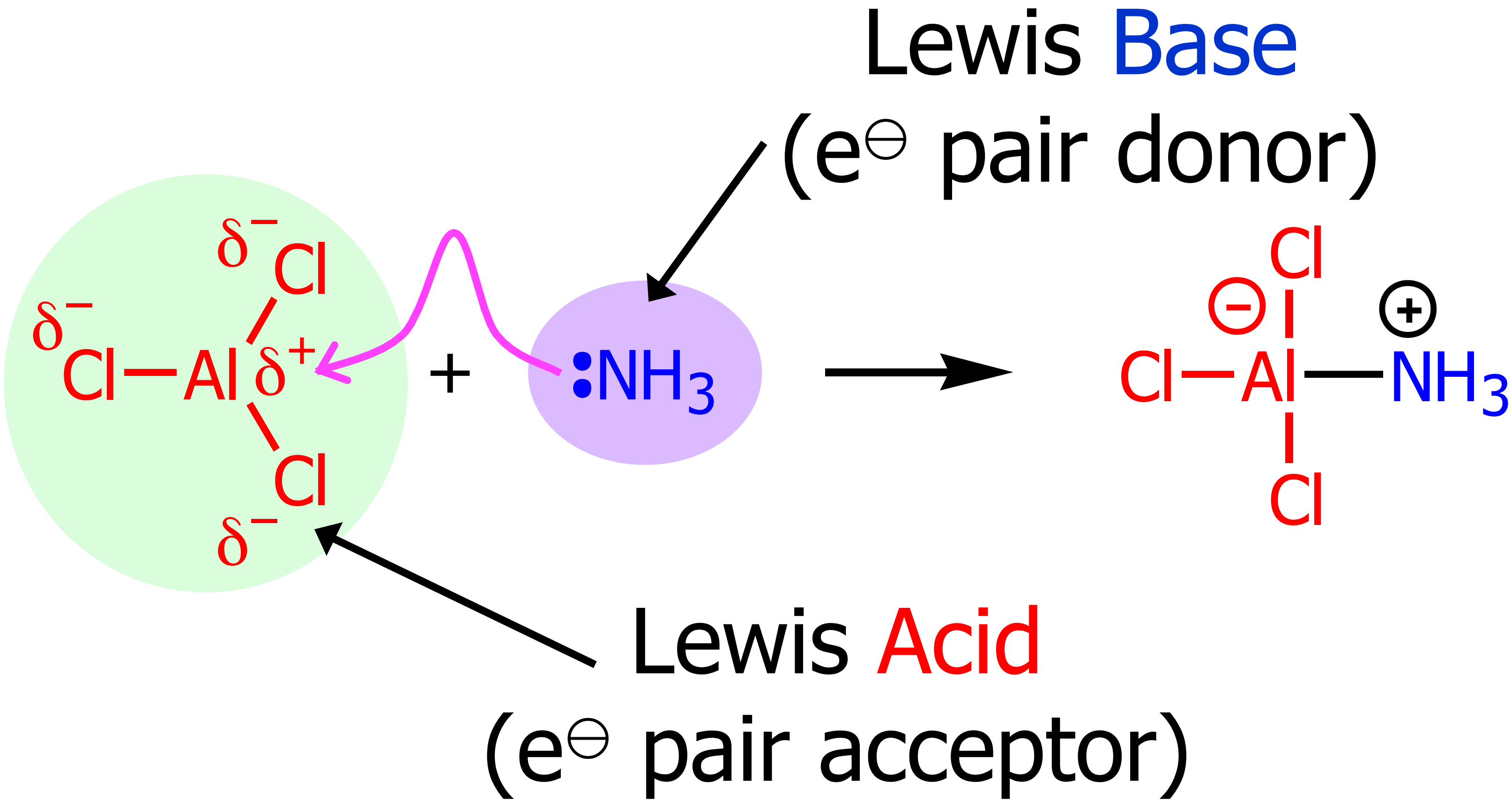


Brønsted-Lowry Acids and Bases



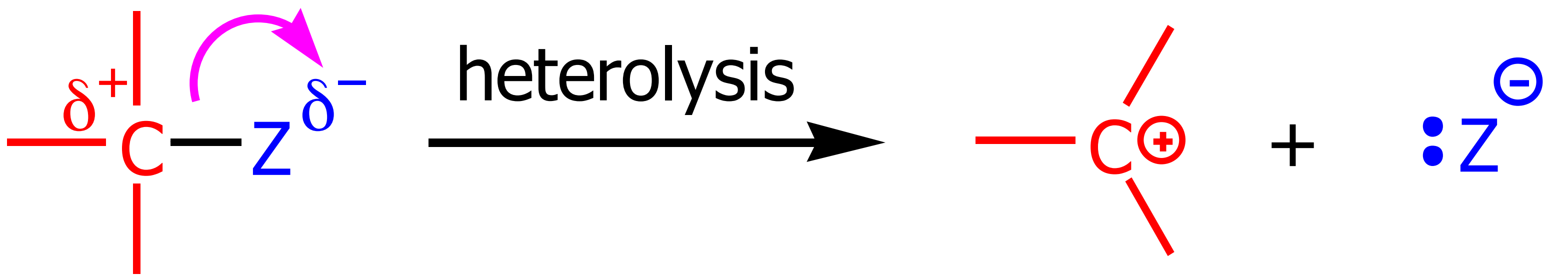
Lewis Acids and Bases

- Lewis Acids are electron pair acceptors.
- Lewis Bases are electron pair donors.

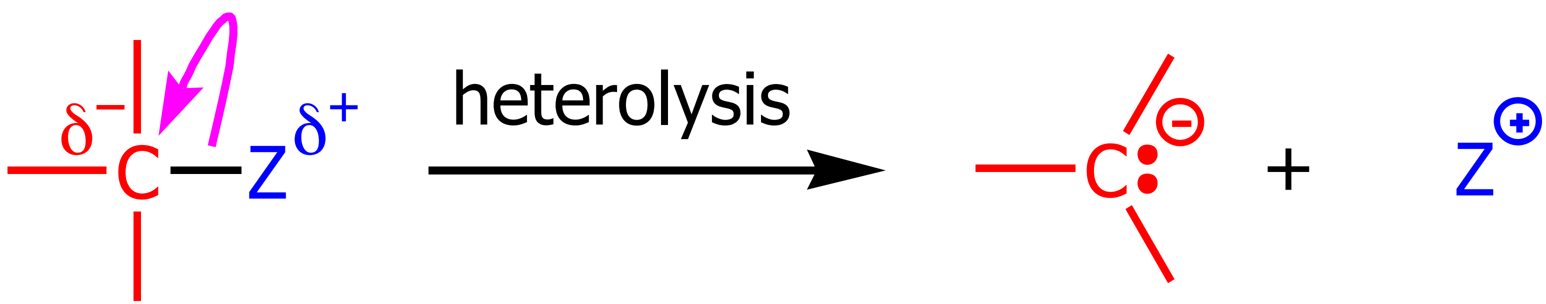


- In Lewis acid–base theory, the attraction of oppositely charged species is fundamental to reactivity.

Heterolysis of Bonds to Carbon: Carbocations and Carbanions



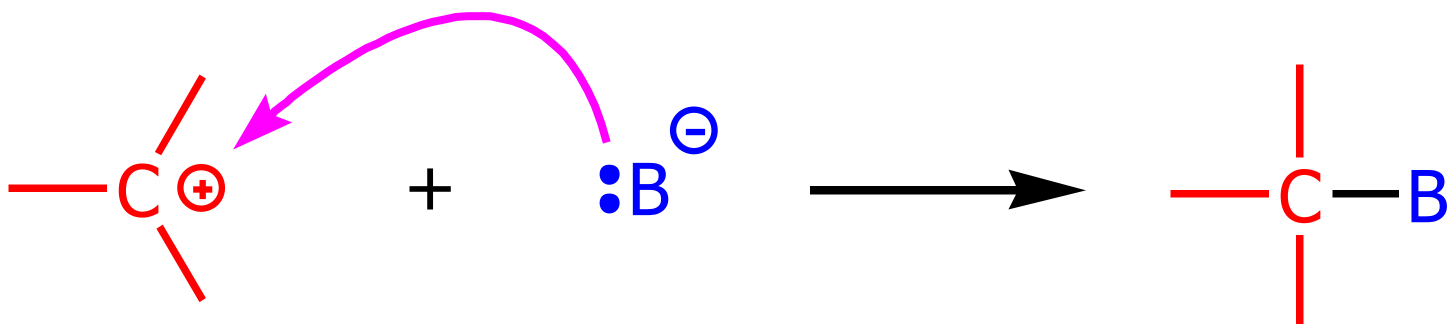
carbocation



carboanion

Electrophiles and Nucleophiles

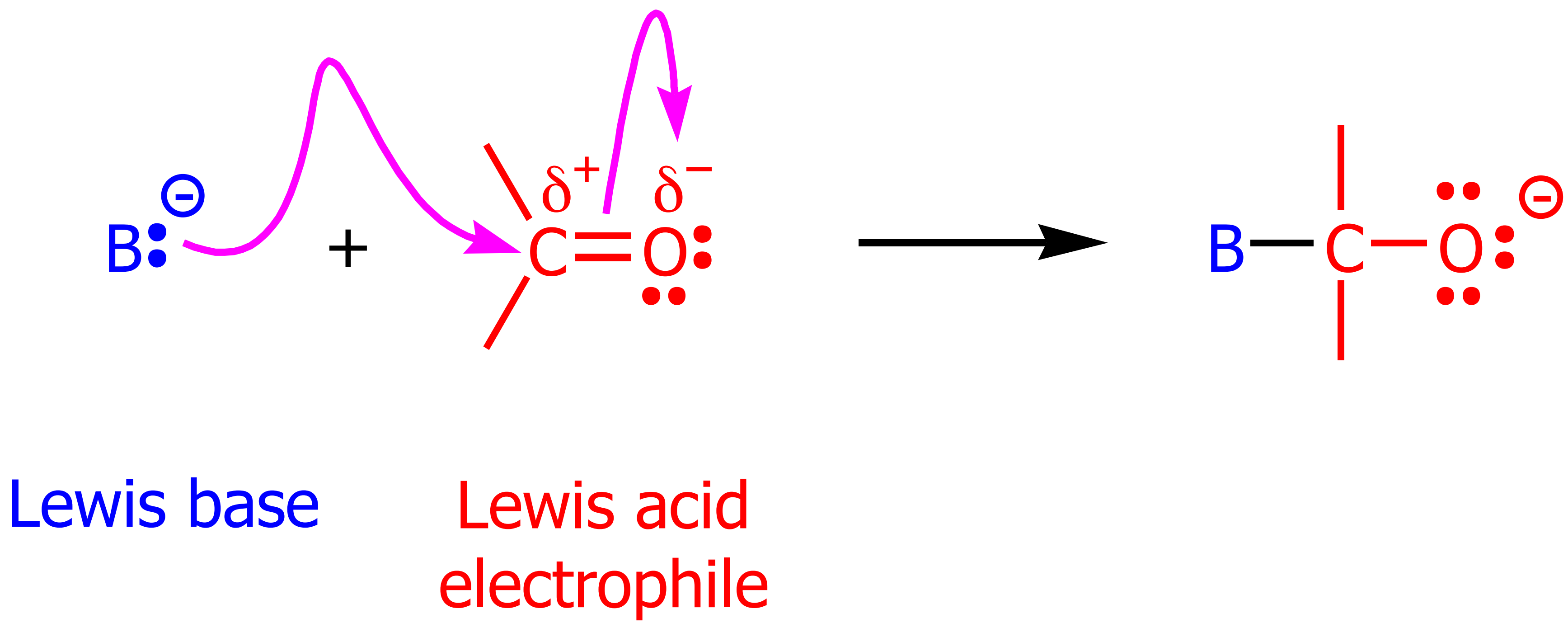
- *Because carbocations are electron-seeking reagents,* chemists call them **electrophiles.**



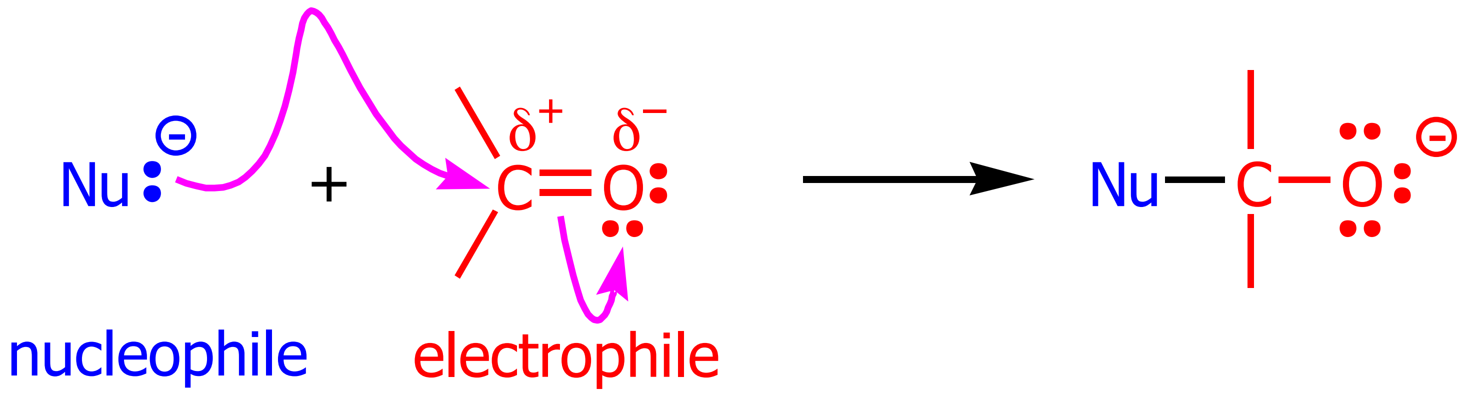
carbocation
(a Lewis acid
and electrophile)

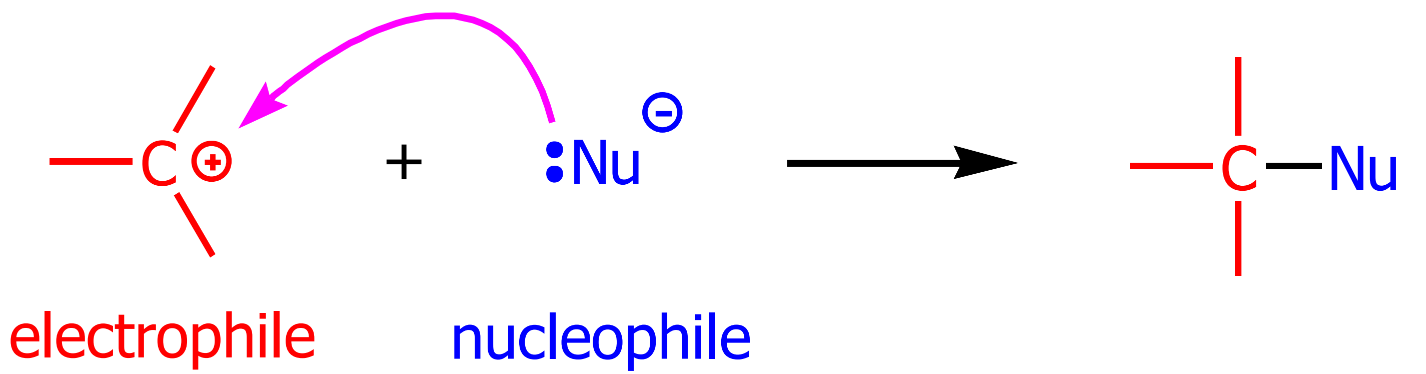
anion
(a Lewis base)

- Carbon atoms that are electron poor because of bond polarity, but are not carbocations, can also be electrophiles.



- Carbanions are Lewis bases
- A **nucleophile** is a Lewis base that seeks a positive center such as a positively charged carbon atom.

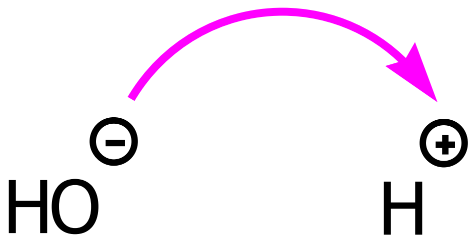




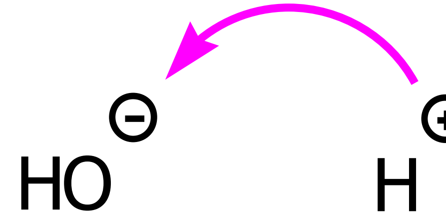
How to Use Curved Arrows in Illustrating Reactions

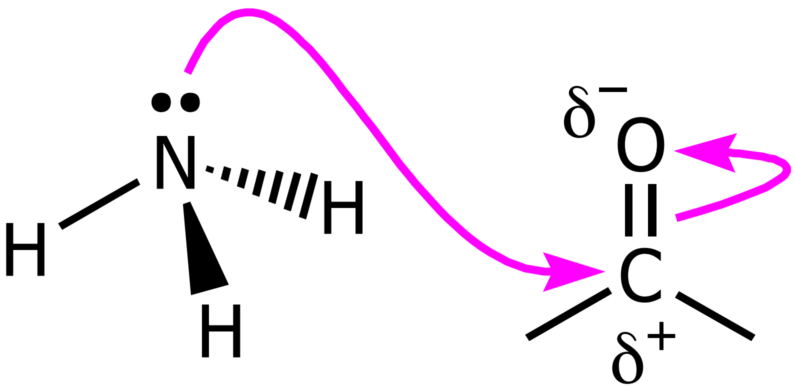
- Curved arrows
  - show the direction of electron flow in a reaction mechanism.
  - point from the source of an electron pair to the atom receiving the pair.
  - always show the flow of electrons from a site of higher electron density to a site of lower electron density.
  - never show the movement of atoms. Atoms are assumed to follow the flow of the electron.

Examples



NOT





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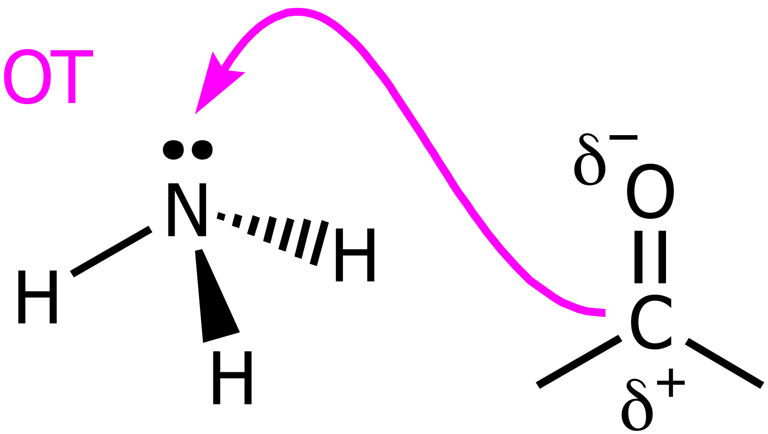
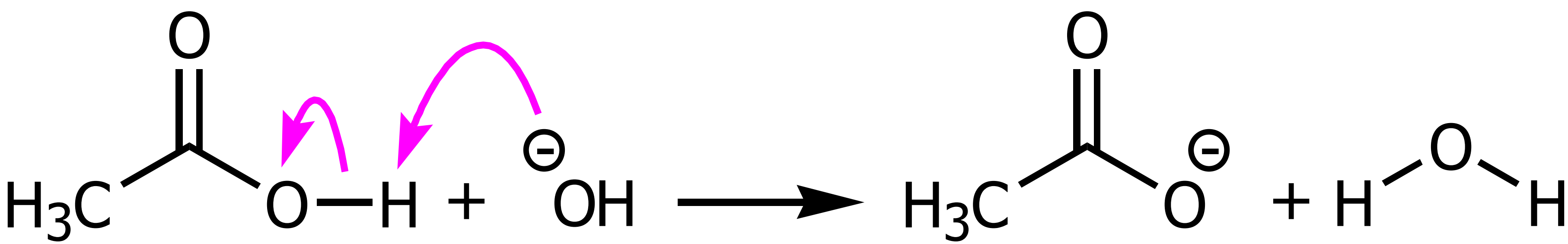




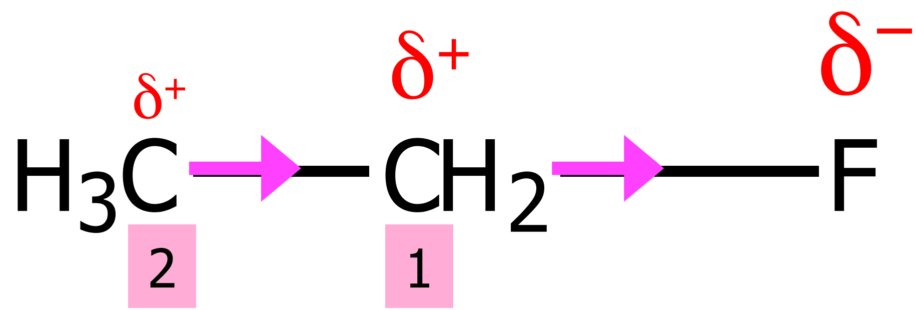
Inductive Effects

- Inductive effects are electronic effects transmitted through bonds.

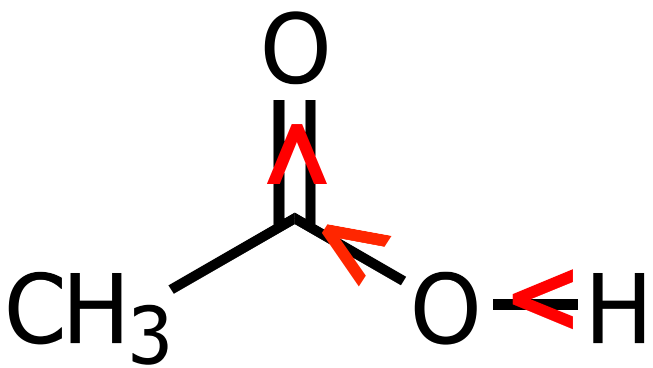
- The inductive effect of a group can be *electron donating* or *electron withdrawing*.

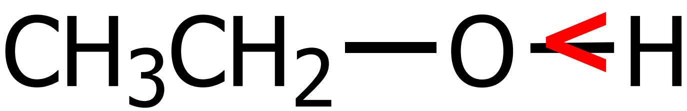
- Inductive effects weaken as the distance from the group increases.

Inductive Effects



- The positive charge that the fluorine imparts to C1 is greater than that imparted to C2 because the fluorine is closer to C1.





Acetic acid

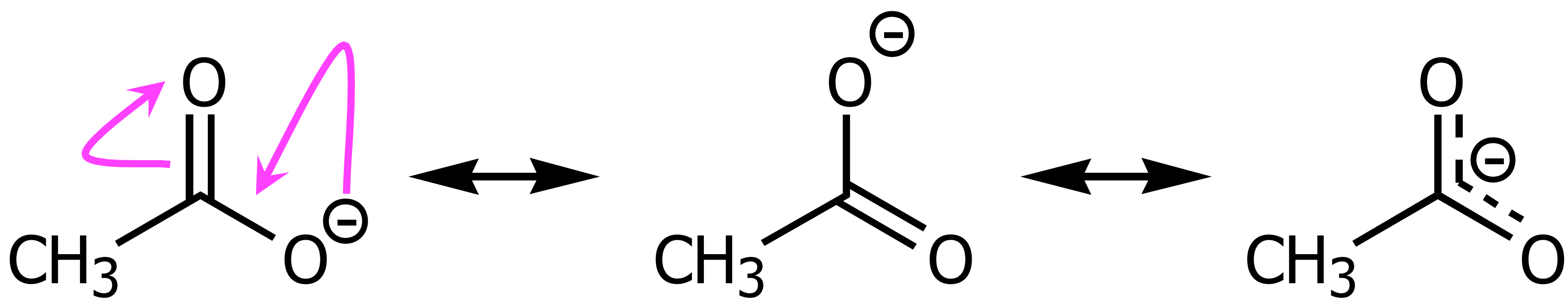
Stronger acid

Ethanol

Weaker acid

The Effect of Delocalization

- The conjugate base acetate is more stable (the anion is more delocalized) than ethoxide due to resonance stabilization.



- Thus, acetic acid is a stronger acid than ethanol.

Chirality & Stereochemistry

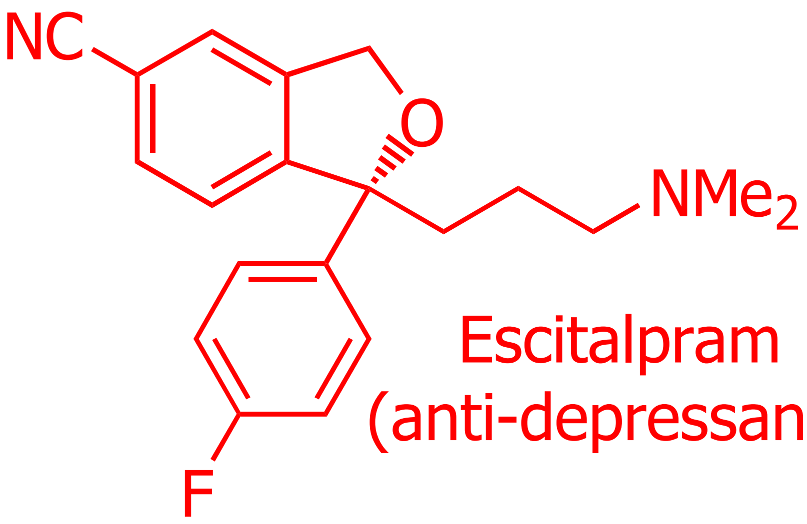
- An object is ***achiral*** (not chiral) if the object and its mirror image are identical.

- A ***chiral*** object is one that cannot be superposed on its mirror image.

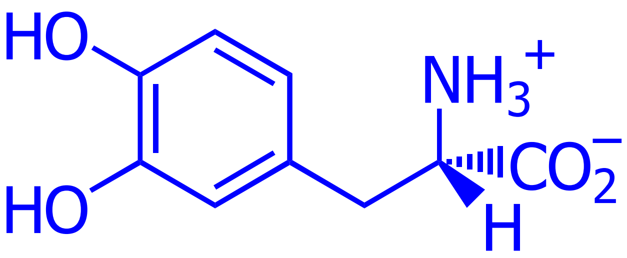
Chiral Drugs

- 66% of all drugs in development are chiral, 51% are being studied as a single enantiomer.

- Of the $475 billion in world-wide sales of formulated pharmaceutical products in 2008, $205 billion was attributable to single enantiomer drugs.

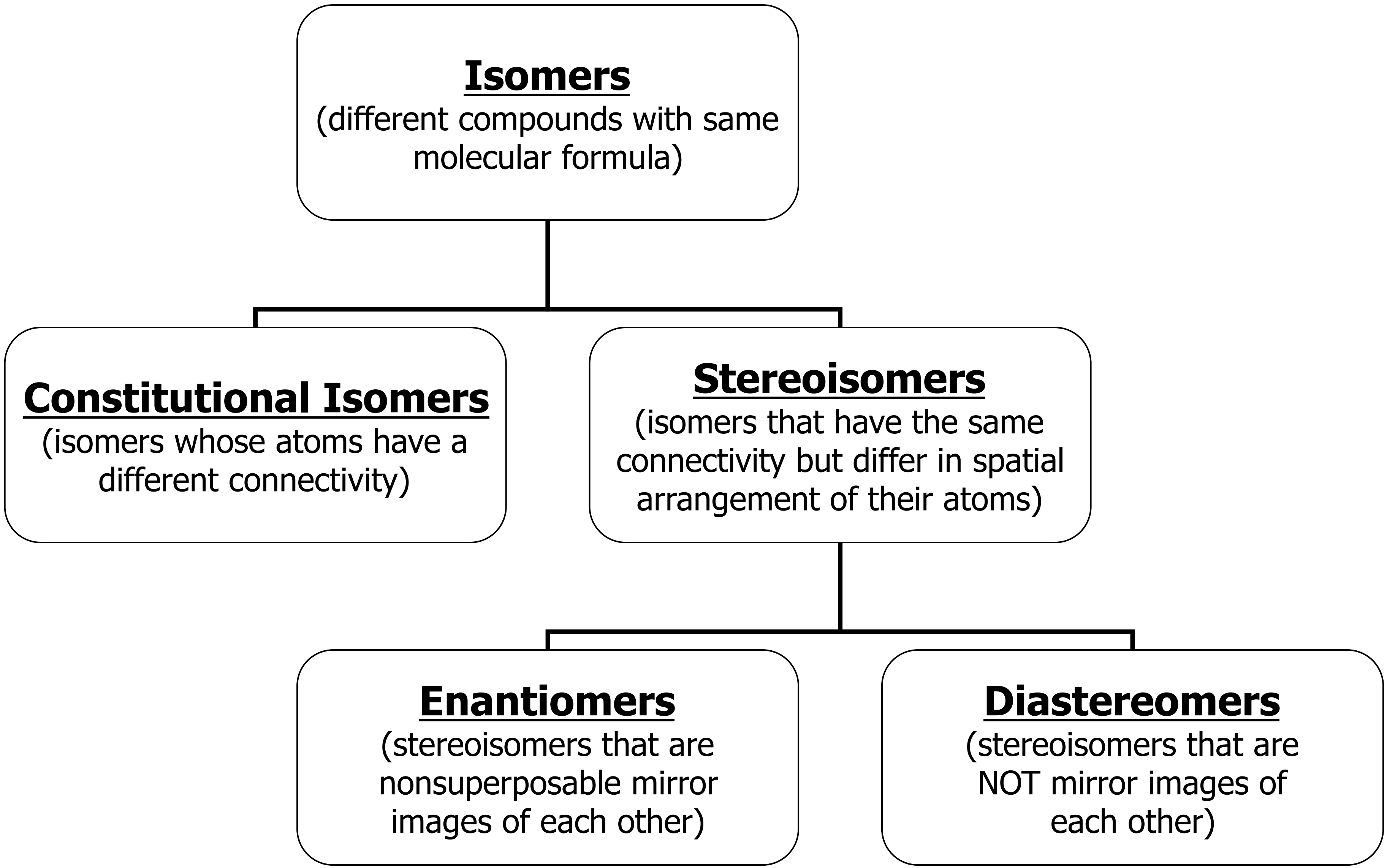


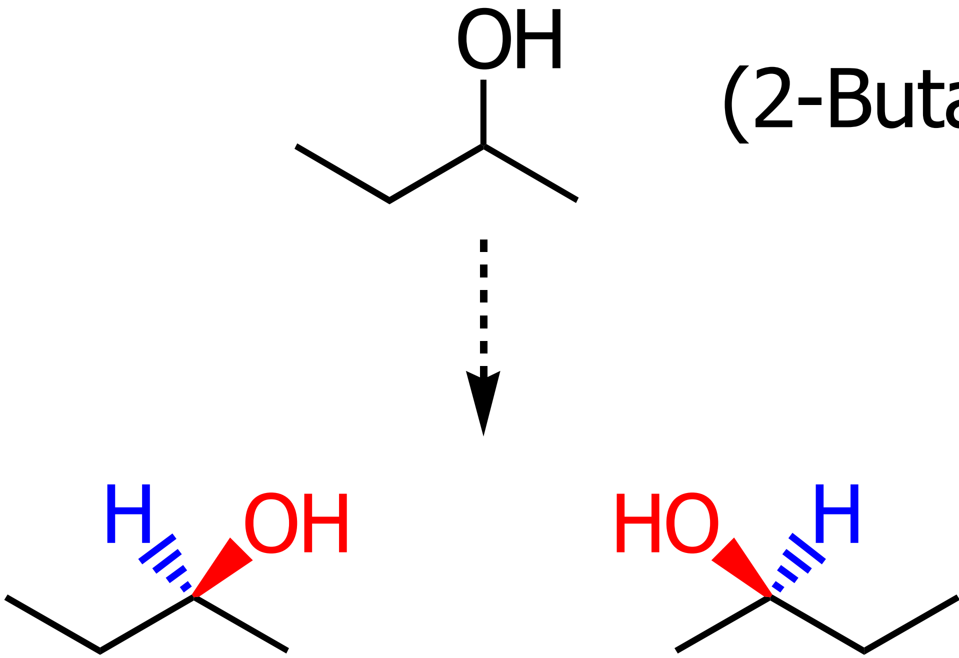
Escitalpram
(anti-depressant)



L-DOPA
(treatment for Parkinson's)

Isomerism

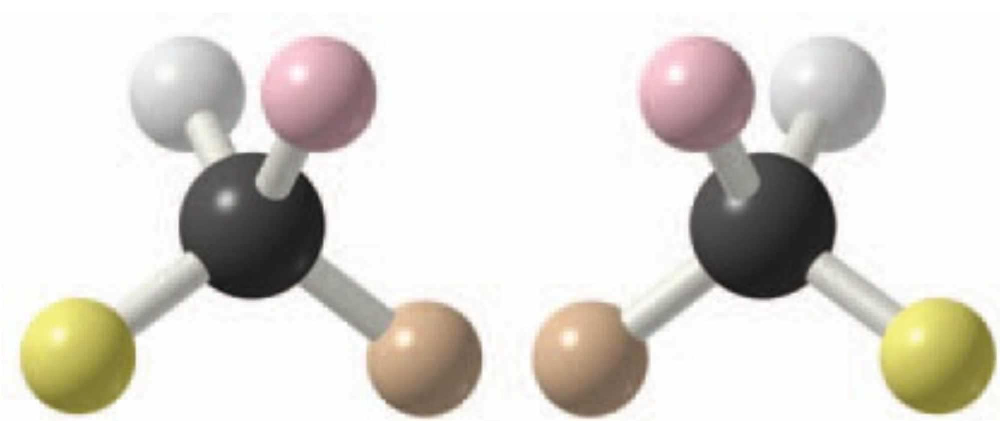

Isomers
(different compounds with same molecular formula)
Constitutional Isomers
(isomers whose atoms have a different connectivity)
Stereoisomers
(isomers that have the same connectivity but differ in spatial arrangement of their atoms)
Enantiomers
(stereoisomers that are nonsuperposable mirror images of each other)
Diastereomers
(stereoisomers that are NOT mirror images of each other)

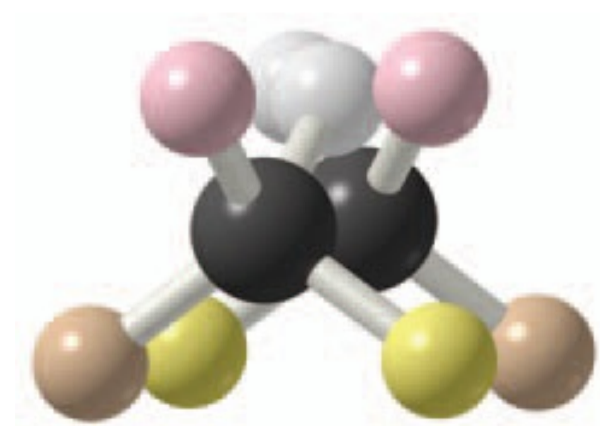


(2-Butanol)

(I) (II)

(I) and (II) are nonsuperposable mirror images of each other.

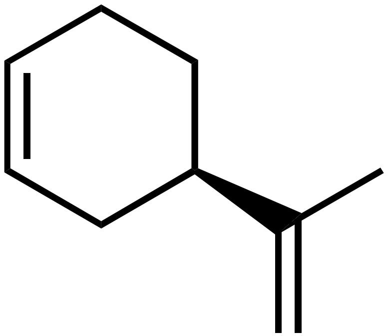




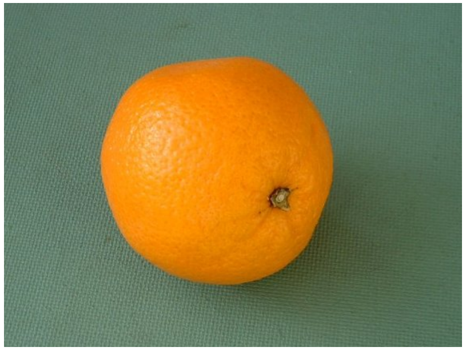
A Single Chirality Center Causes a Molecule to Be Chiral

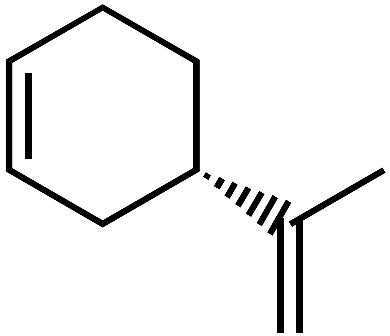
- The most common type of chiral compounds that we encounter are molecules that contain a carbon atom bonded to *four different groups*. Such a carbon atom is called an *asymmetric carbon* or a ***chiral center*** and is usually designated with an asterisk (*****).

More about the Biological Importance of Chirality



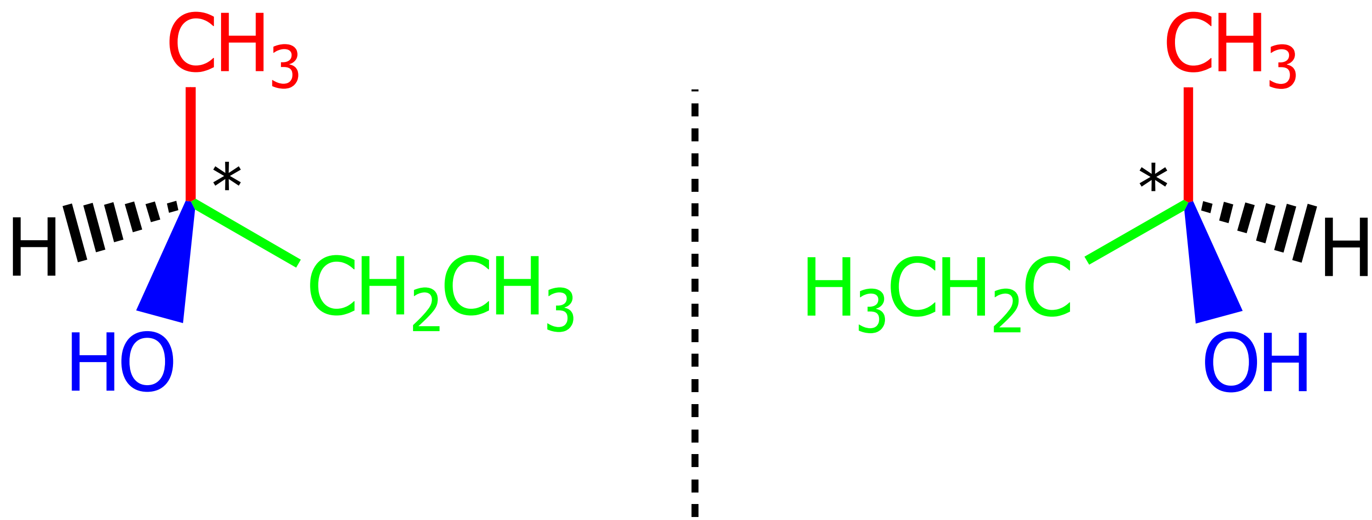
(+)-Limonene
(limonene enantiomer found in oranges)





(-)-Limonene
(limonene enantiomer found in lemons)

- Two enantiomers should have the same value of specific rotation, but the signs are opposite.



$[\alpha]_D^{25} = +\ 13.5^o$

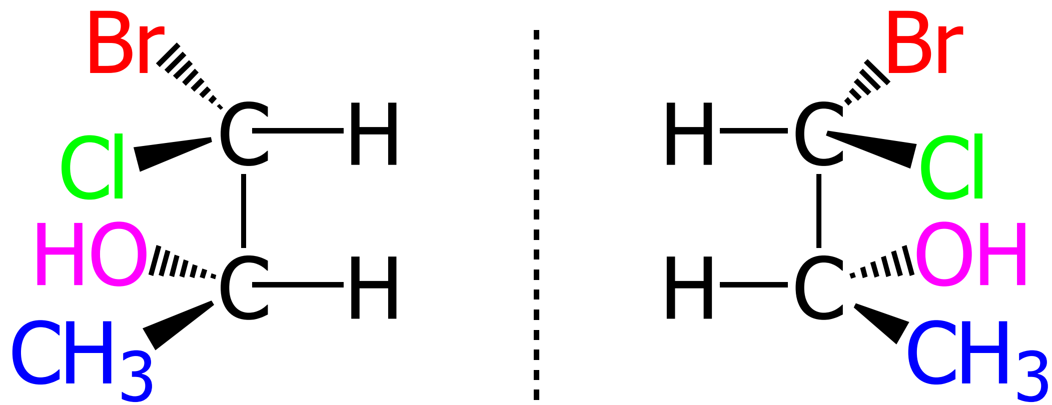
mirror

$[\alpha]_D^{25} = -\ 13.5^o$

Molecules with More than One Chirality Center

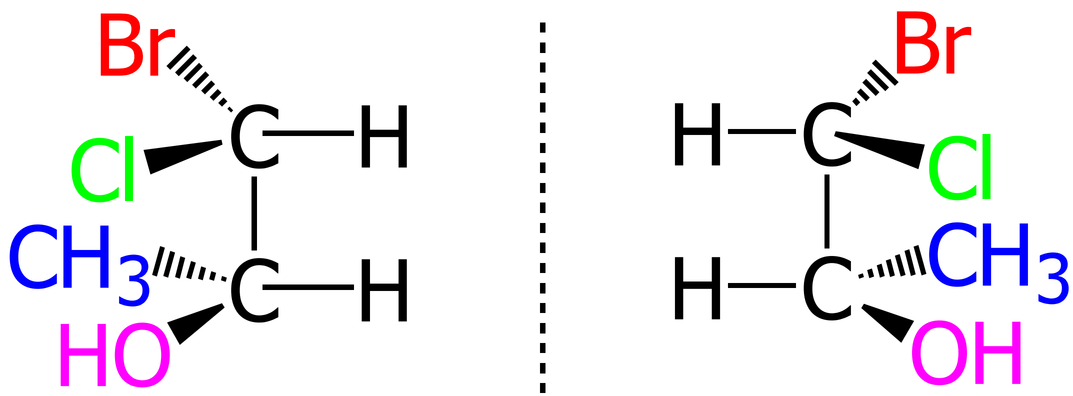
- Diastereomers
  - Stereoisomers that are not enantiomers.
  - Unlike enantiomers, diastereomers usually have substantially different chemical and physical properties.

(I)



(II)

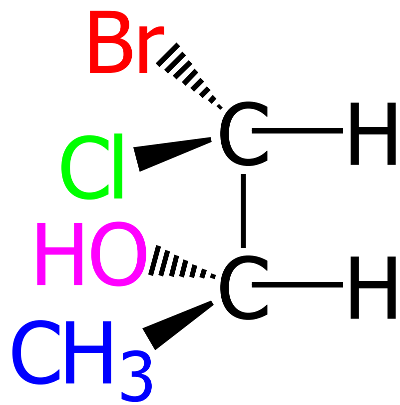
(III)



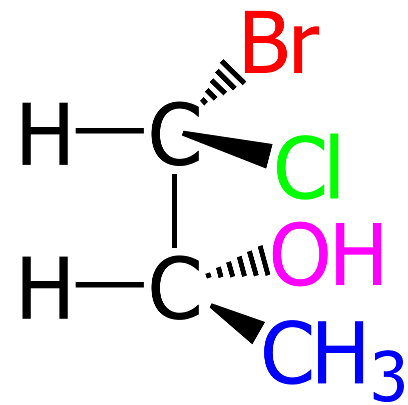
(IV)

- (I) & (II) are enantiomers to each other.
- (III) & (IV) are enantiomers to each other.

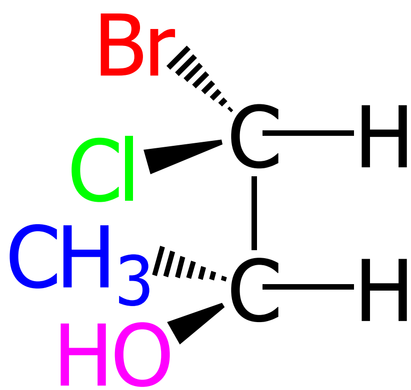
(I)



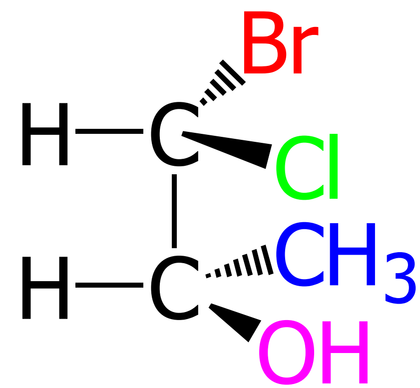
(II)



(III)

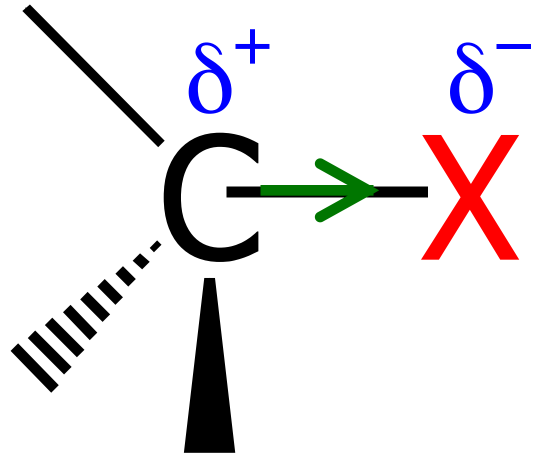


(IV)



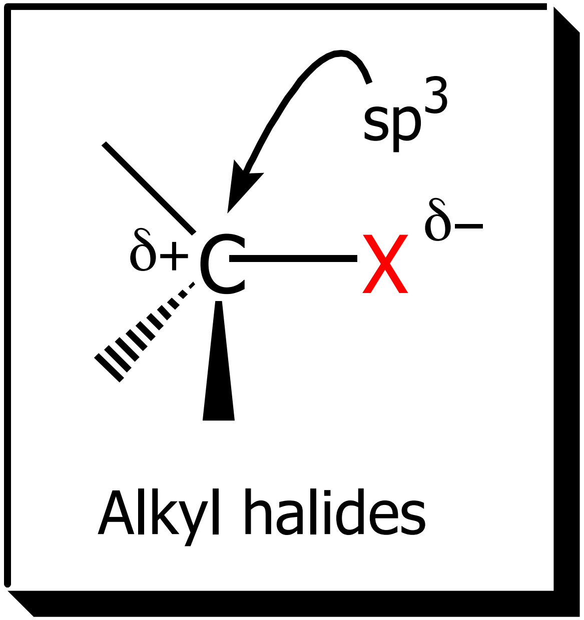
- Diastereomers to each other:
  - (I) & (III), (I) & (IV), (II) & (III), (II) & (IV).

Organic Halides

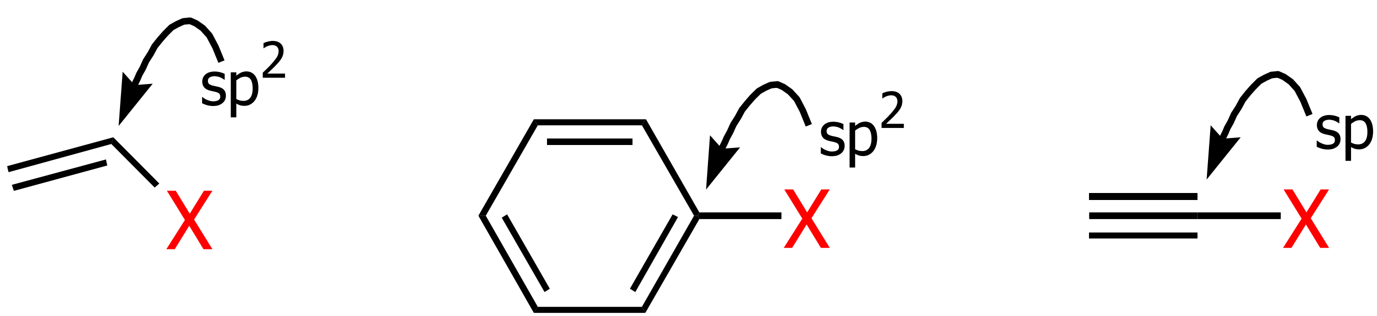


X = Cl, Br, I

- Halogens are more electronegative than carbon.

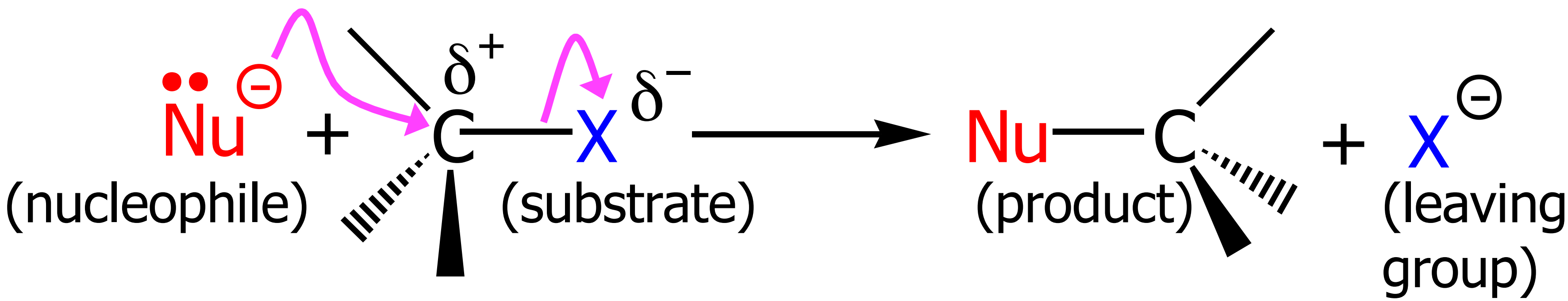


- Prone to undergo Nucleophilic Substitutions (S_N) and Elimination Reactions (E).



- Different reactivity than alkyl halides, and do not undergo S_N or E reactions.

Nucleophilic Substitution Reactions



The Nu$^{\ominus}$ donates an e$^{\ominus}$ pair to the substrate.

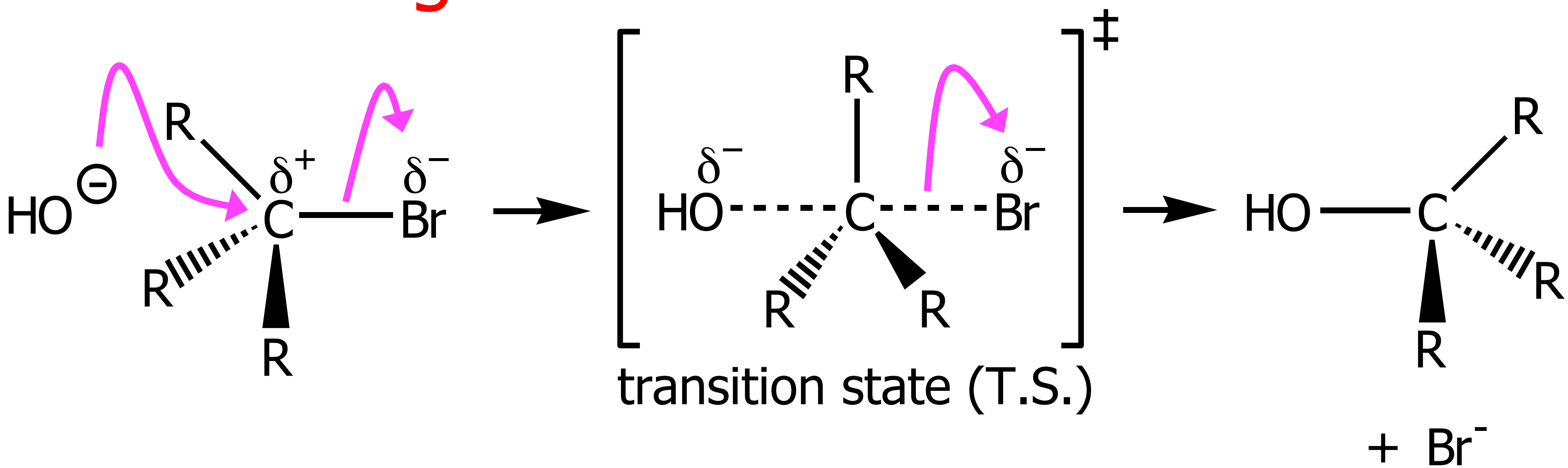
The bond between C and LG breaks, giving both e$^{\ominus}$ from the bond to LG.

The Nu$^{\ominus}$ uses its e$^{\ominus}$ pair to form a new covalent bond with C.

The LG gains the pair of e$^{\ominus}$ originally bonded in the substrate.

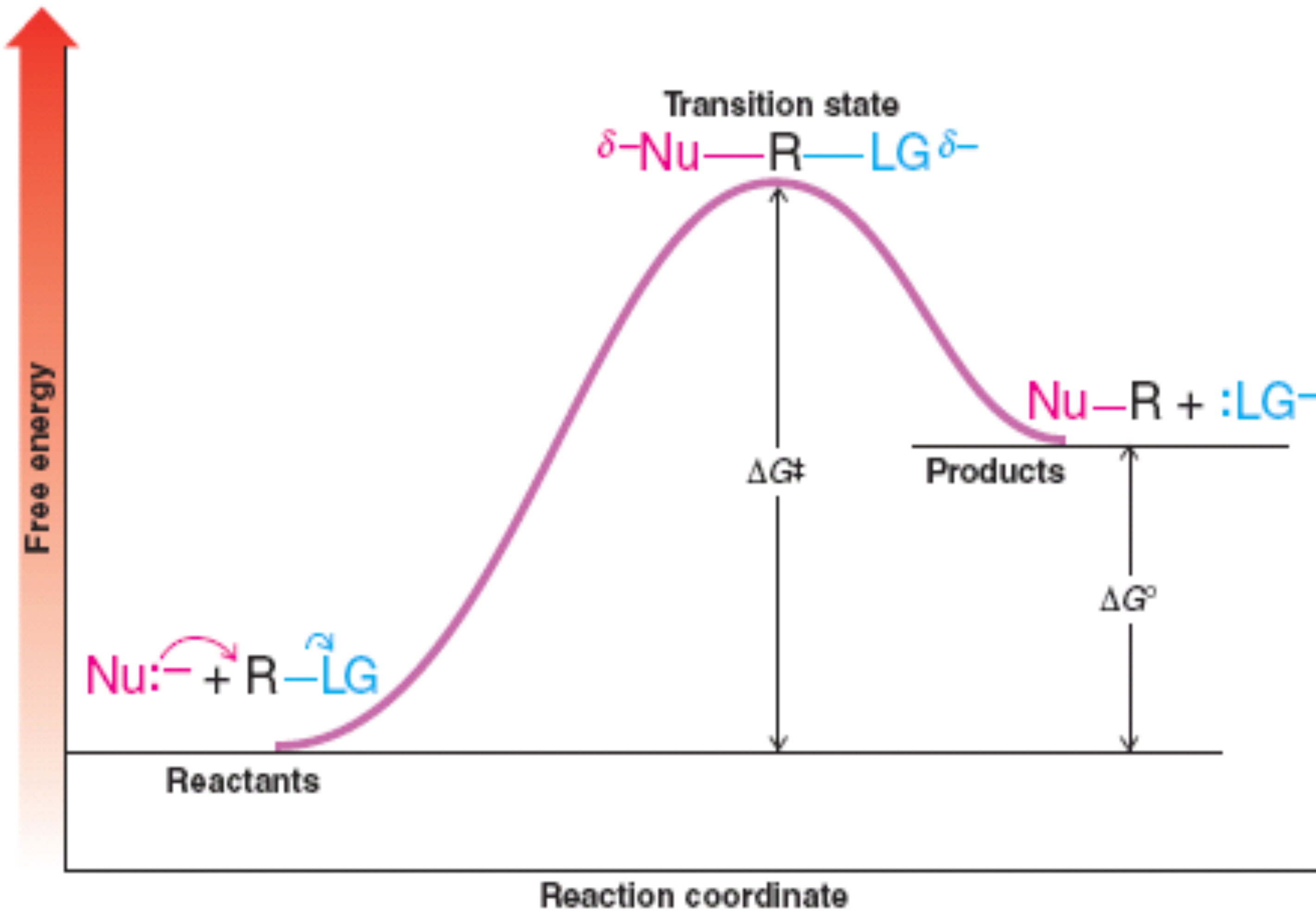
Timing of The Bond Breaking & Bond Making Process

- Two types of mechanisms
  - 1st type: S_N2 (concerted mechanism) include inversion of configuration



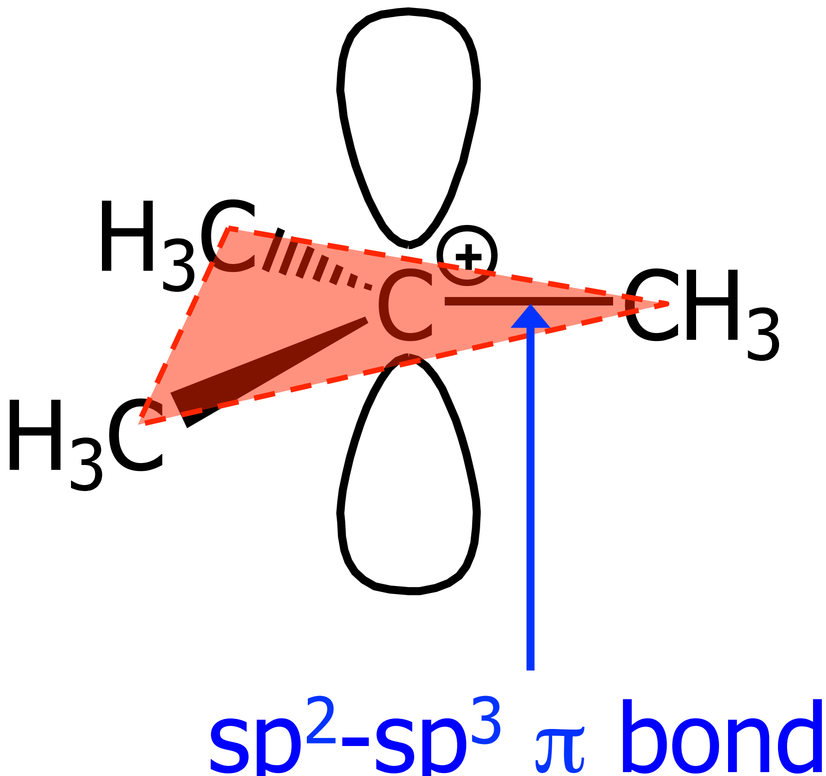
transition state (T.S.)

A Free Energy Diagram for a Hypothetical Reaction with a Positive Free-Energy Change



Carbocations

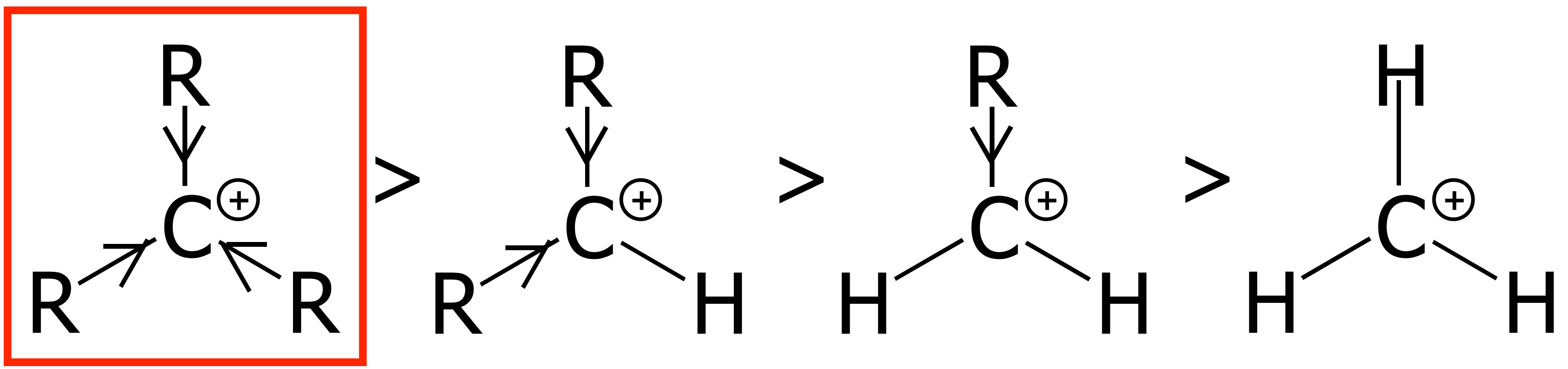
The Structure of Carbocations



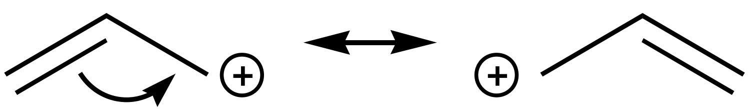
- Carbocations are trigonal planar
- The central carbon atom in a carbocation is electron deficient; it has only six $e^{\ominus}$ in its valence shell
- The *p* orbital of a carbocation contains no electrons, but it can accept an electron pair when the carbocation undergoes further reaction

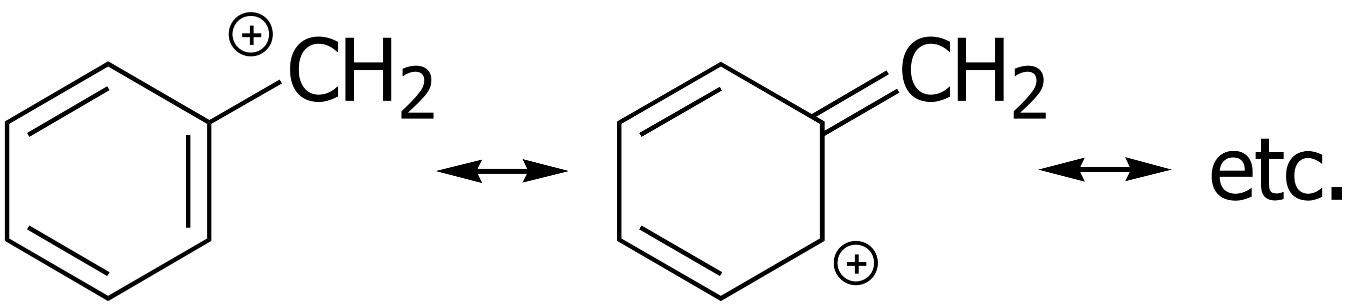
- Stability of cations

most stable (positive inductive effect)

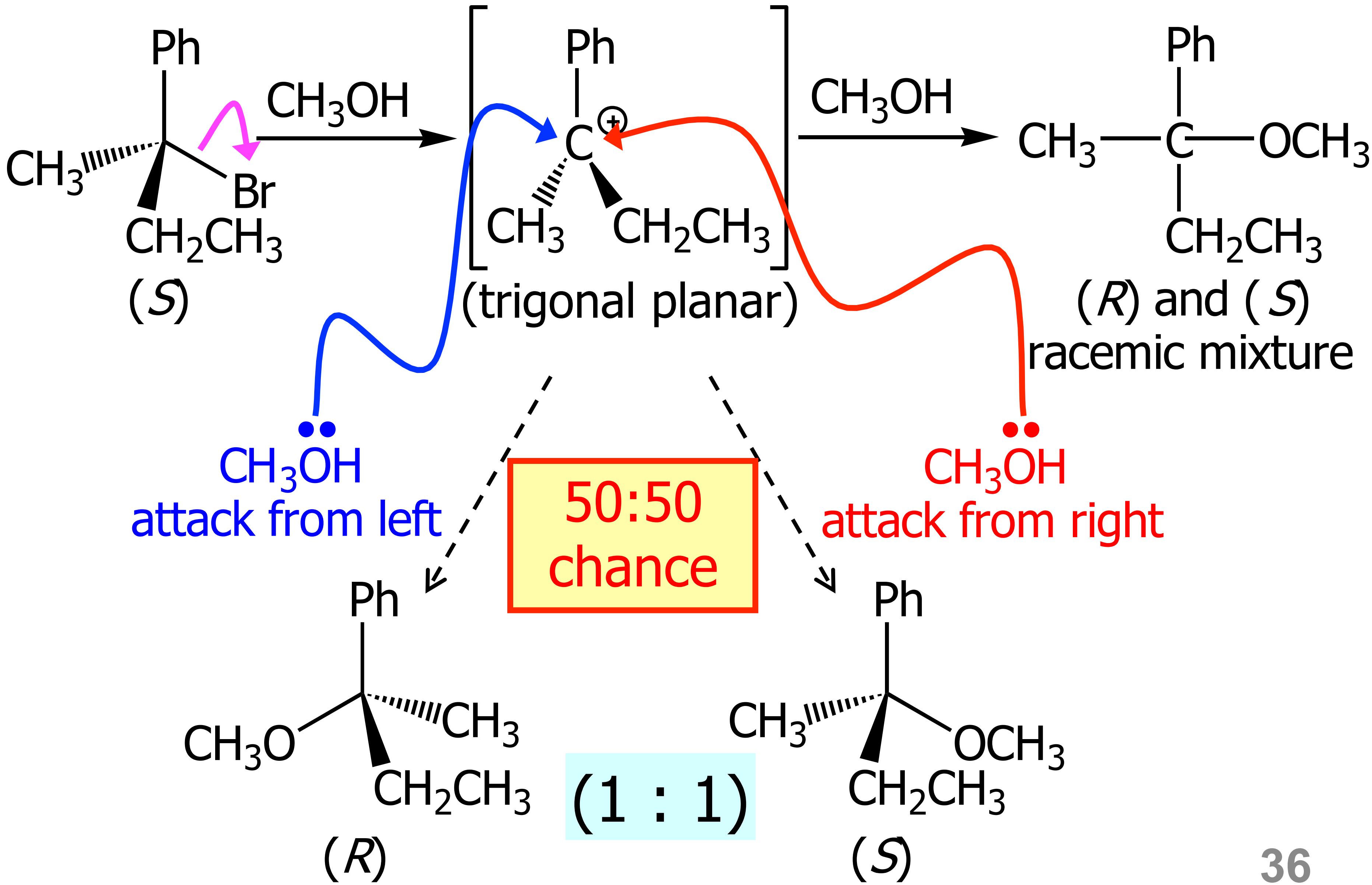


- Resonance stabilization of allylic and benzylic cations





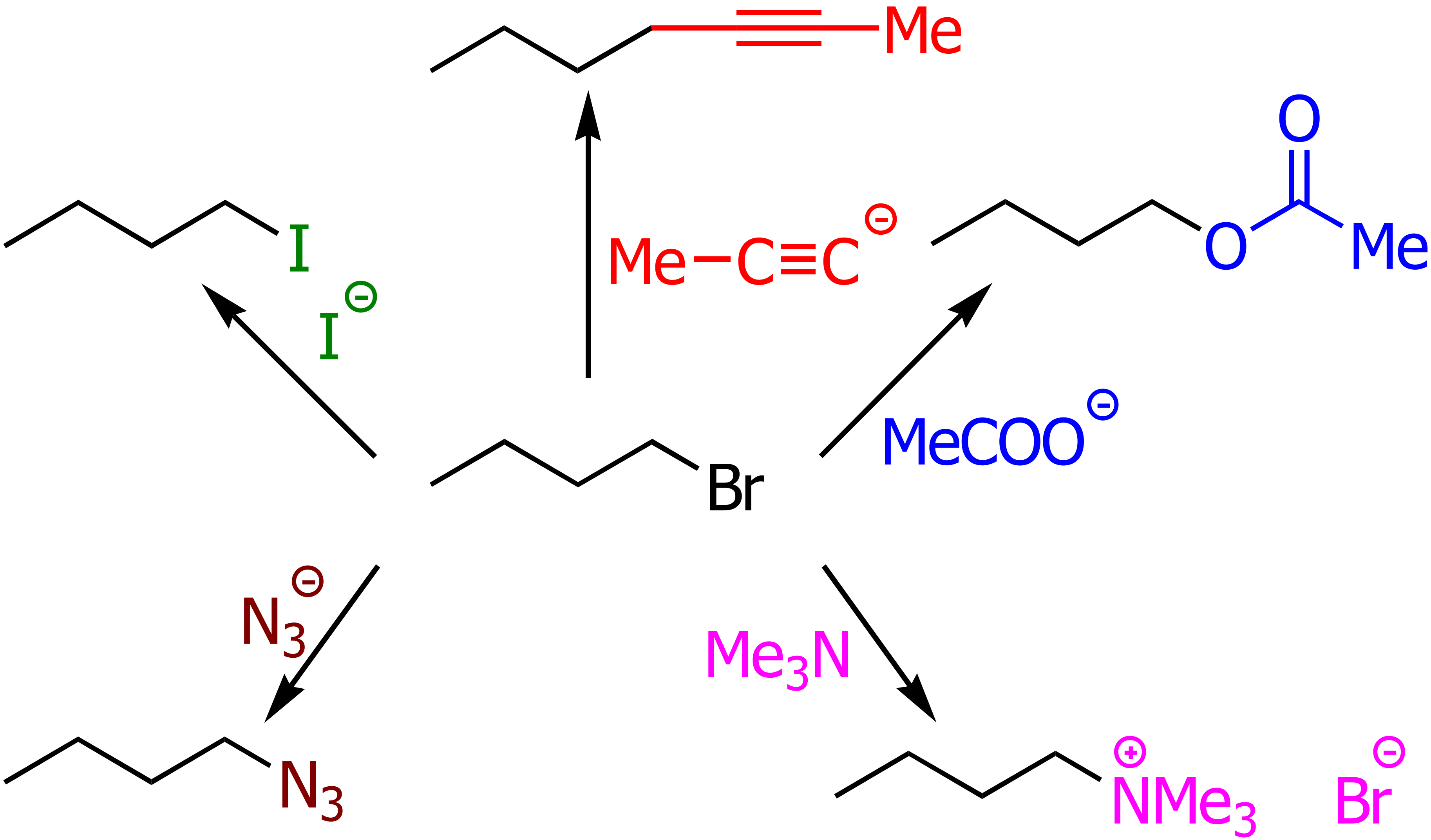
The Stereochemistry of S_N1 Reactions



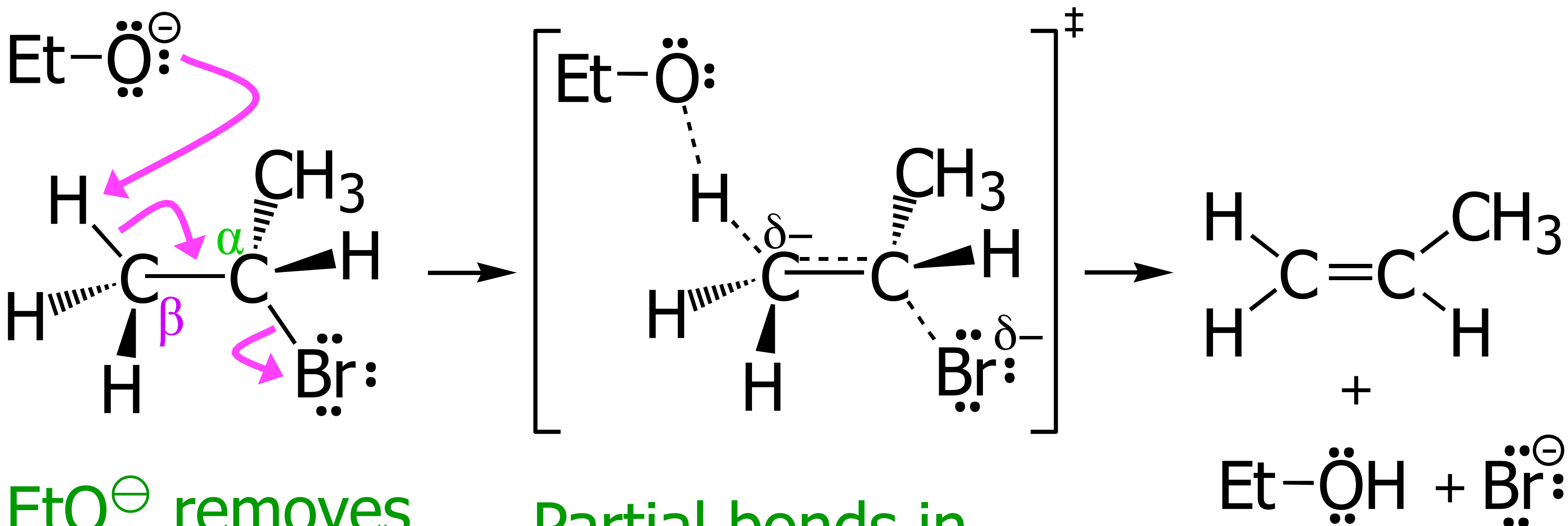
Factors Affecting the Rates of S_N1 and S_N2 Reactions

- The structure of the substrate
- The concentration and reactivity of the nucleophile (for S_N2 reactions only)
- The effect of the solvent
- The nature of the leaving group

Organic Synthesis: Functional Group Transformation Using S_N2 Reactions



Mechanism for an E2 Reaction

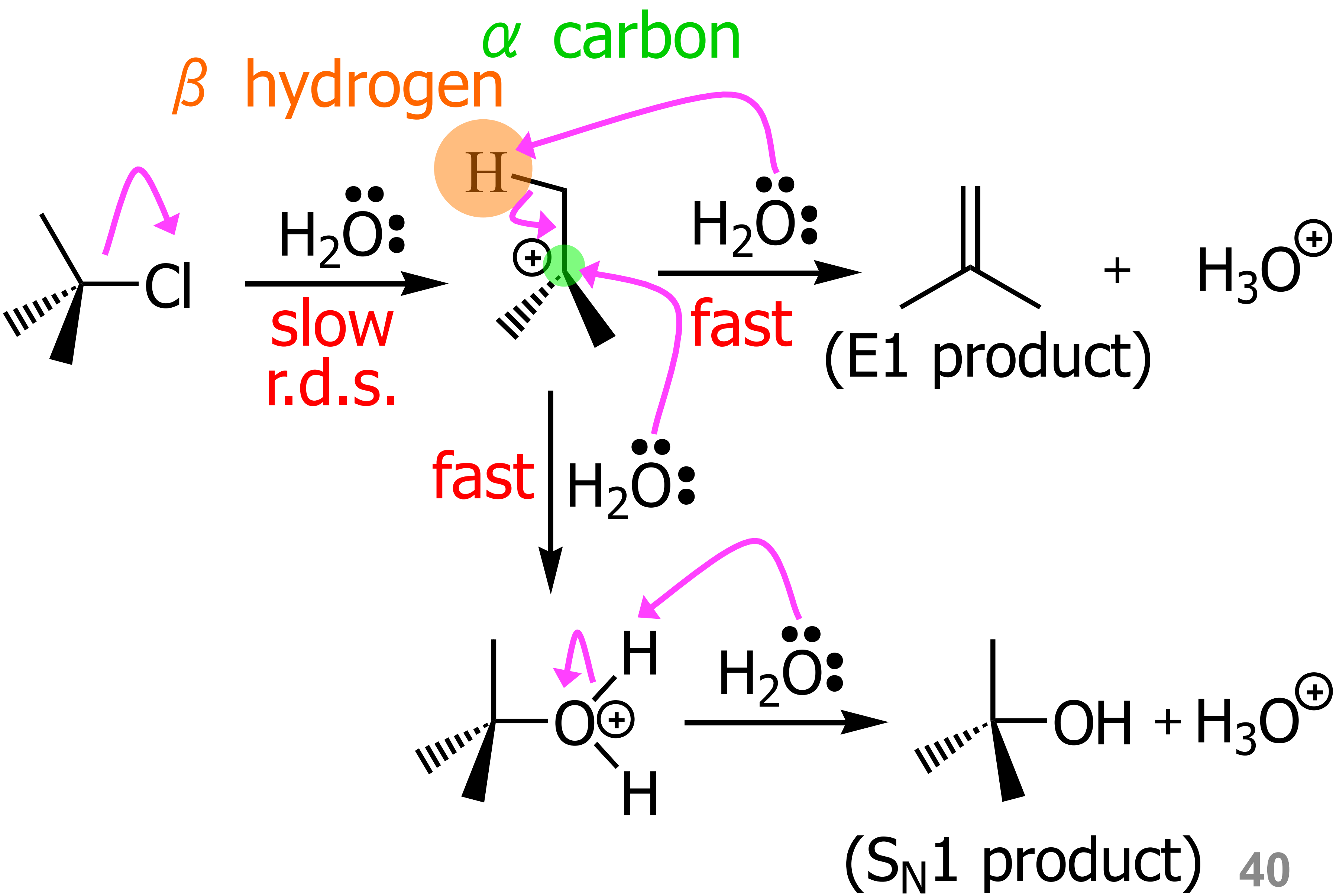


EtO$^{\ominus}$ removes a β proton; C–H breaks; new π bond forms and Br begins to depart.

Partial bonds in the transition state: C–H and C–Br bonds break, new π C–C bond forms.

C=C is fully formed and the other products are EtOH and Br$^{\ominus}$.

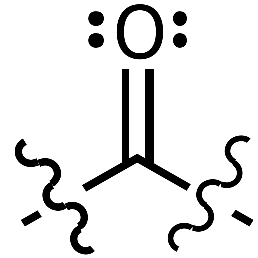
Mechanism of an E1 Reaction

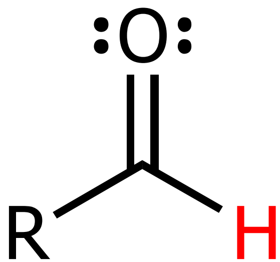


Overall Summary

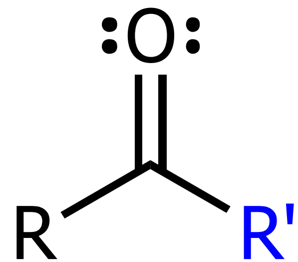
	S_N1	S_N2	E1	E2
CH_3X	—	Very fast	—	—
RCH_2X	—	Mostly	—	Hindered bases give mostly alkenes; e.g. with $^tBuO^\ominus$
$R'RCHX$	Very little; Solvolysis possible; e.g. with H_2O; MeOH	Mostly S_N2 with weak bases; e.g. with $CH_3COO^\ominus$	Very little	Strong bases promote E2; e.g. with $RO^\ominus$, $HO^\ominus$
$R'R''RCX$	Very favorable with weak bases; e.g. with H_2O; MeOH	—	Always competes with S_N1	Strong bases promote E2; e.g. with $RO^\ominus$, $HO^\ominus$

Structure of the Carbonyl Group

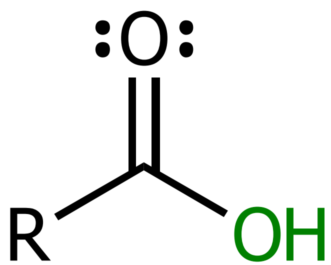
- Carbonyl compounds 



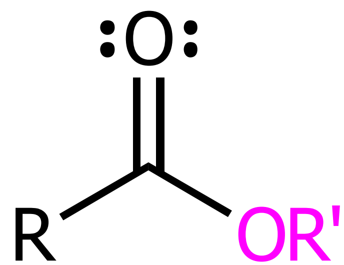
Aldehyde



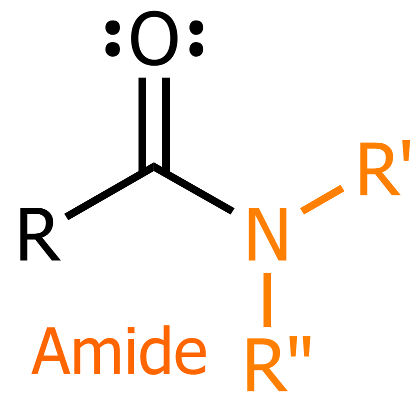
Ketone



Carboxylic acid

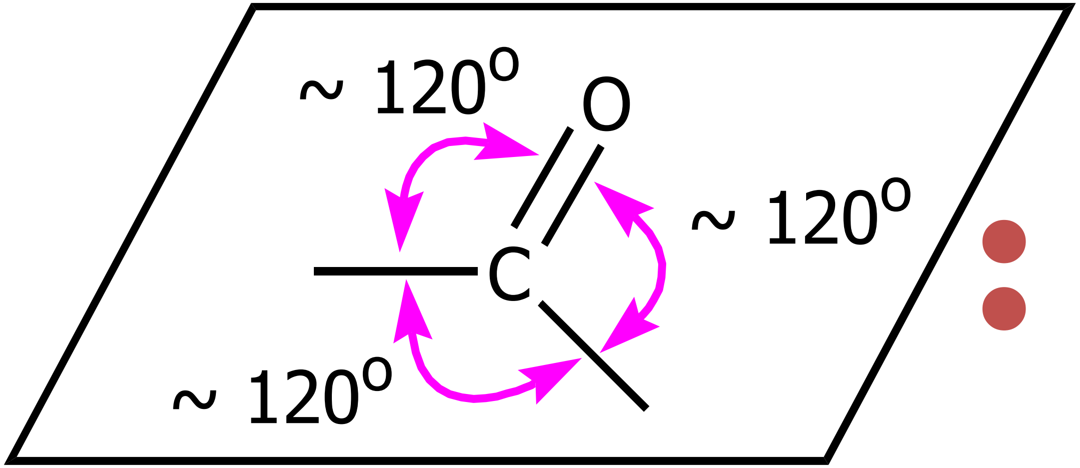


Ester



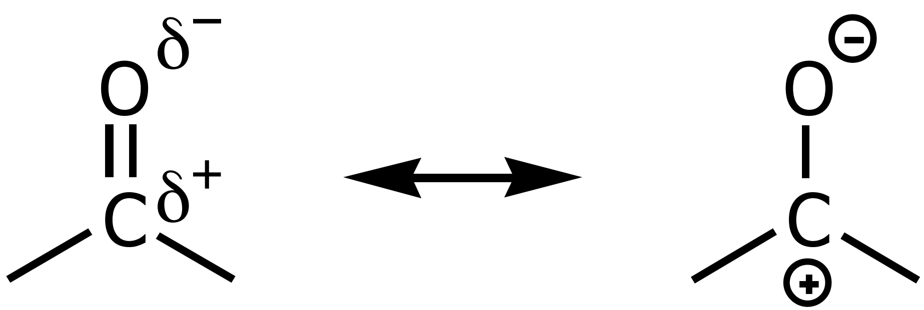
Amide

Structure of the Carbonyl Group



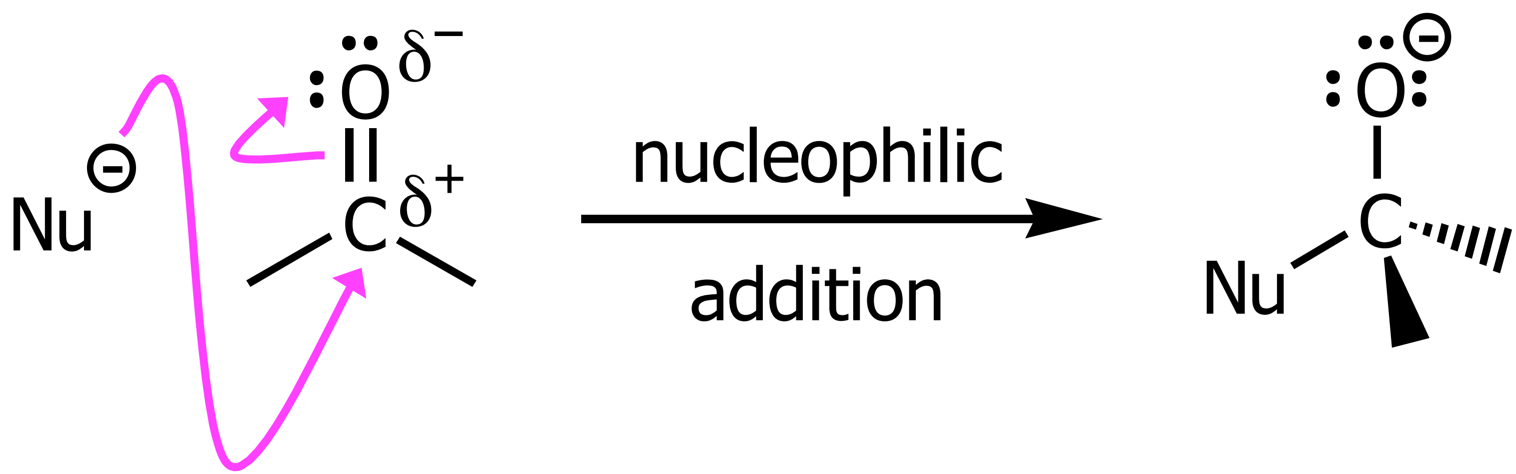
- Carbonyl carbon: sp^2 hybridized
- Planar structure

❖ Polarization and resonance structure



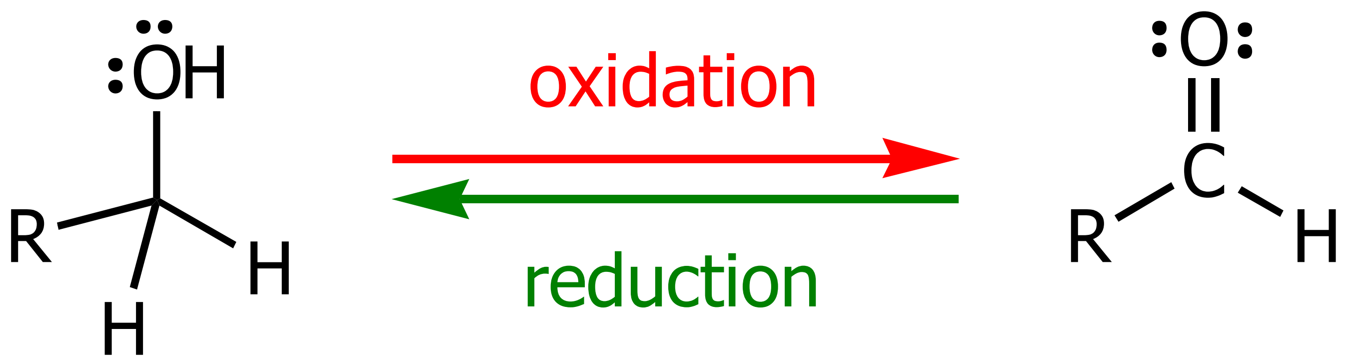
Reactions of Carbonyl Compounds with Nucleophiles

- One of the most important reactions of carbonyl compounds is nucleophilic addition to the carbonyl group



- Two important nucleophiles:
  - Hydride ions (from $NaBH_4$ and $LiAlH_4$)
  - Carbanions (from RLi and RMgX)

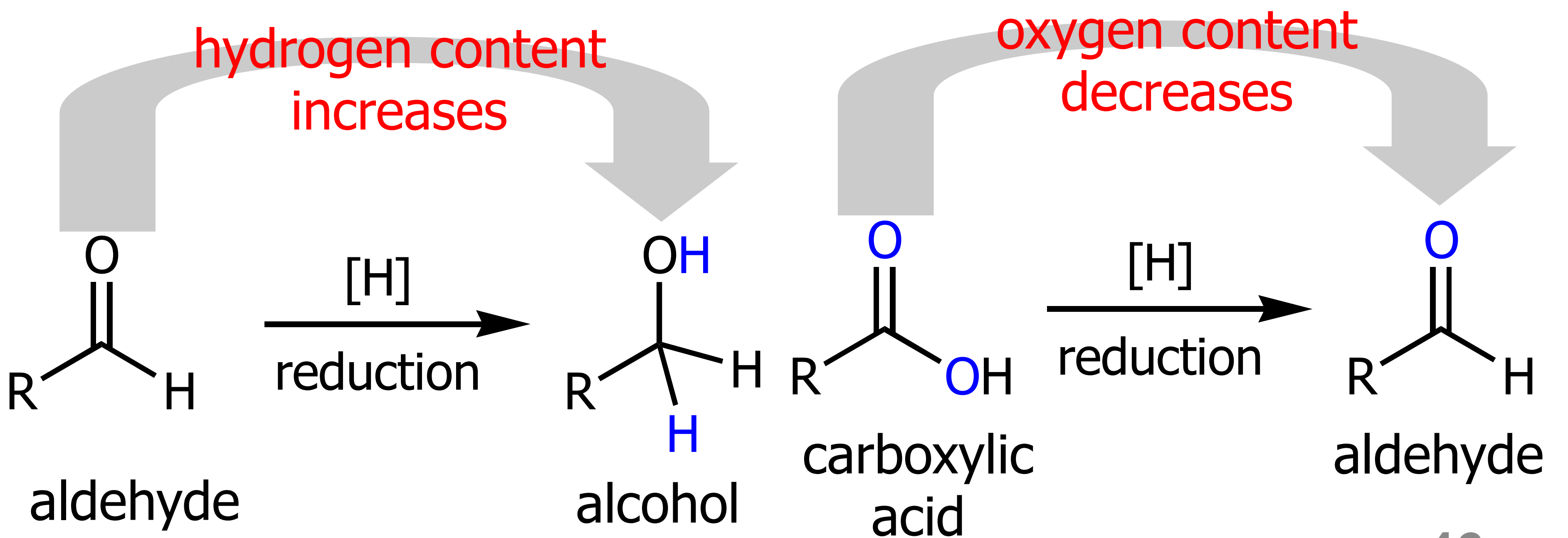
- Other important reactions:



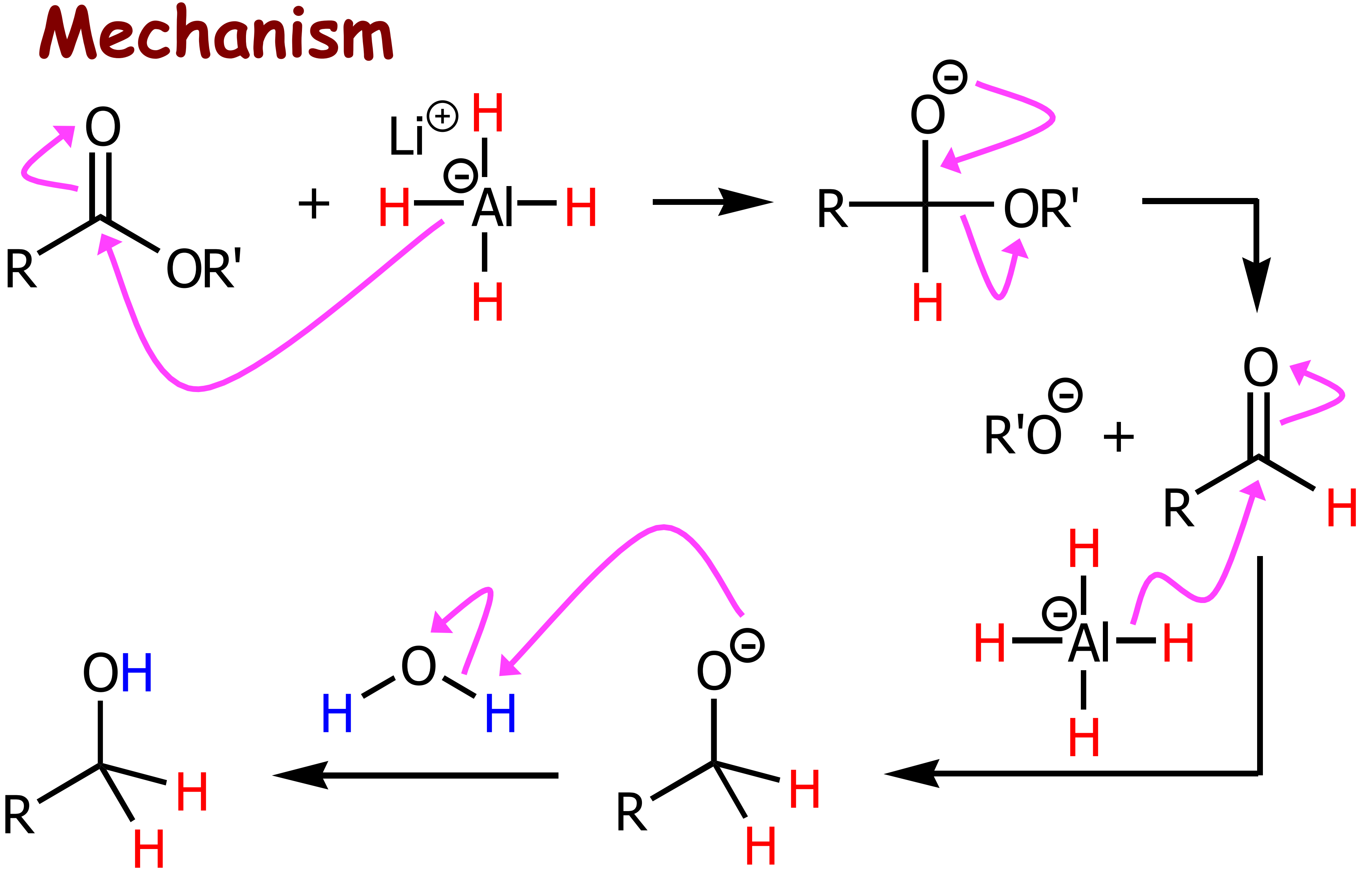
1^{o} alcohol aldehyde

Oxidation-Reduction Reactions in Organic Chemistry

- Reduction of an organic molecule usually corresponds to increasing its hydrogen content or decreasing its oxygen content



Mechanism

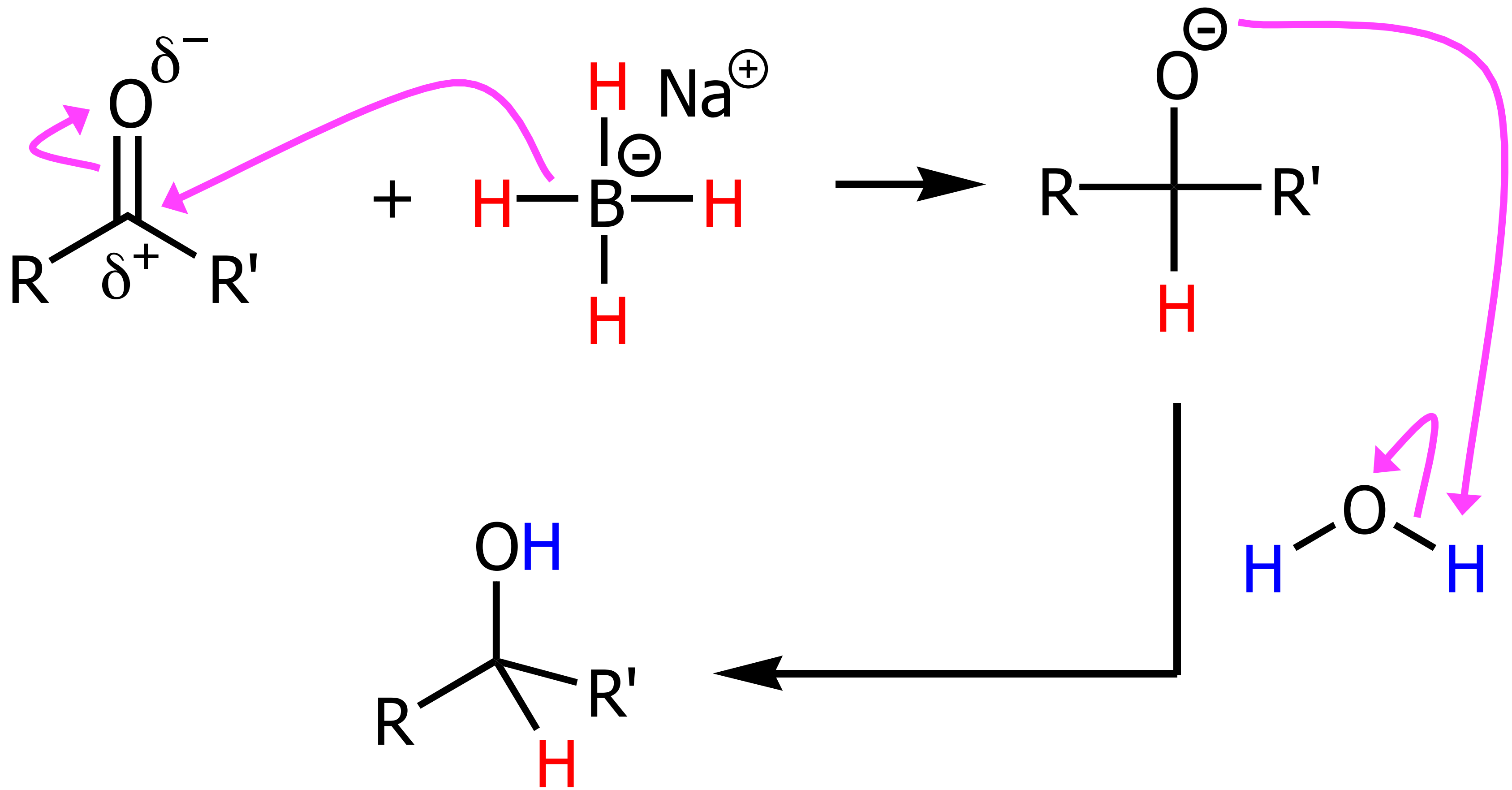


Esters are reduced to 1° alcohols

Sodium Borohydride

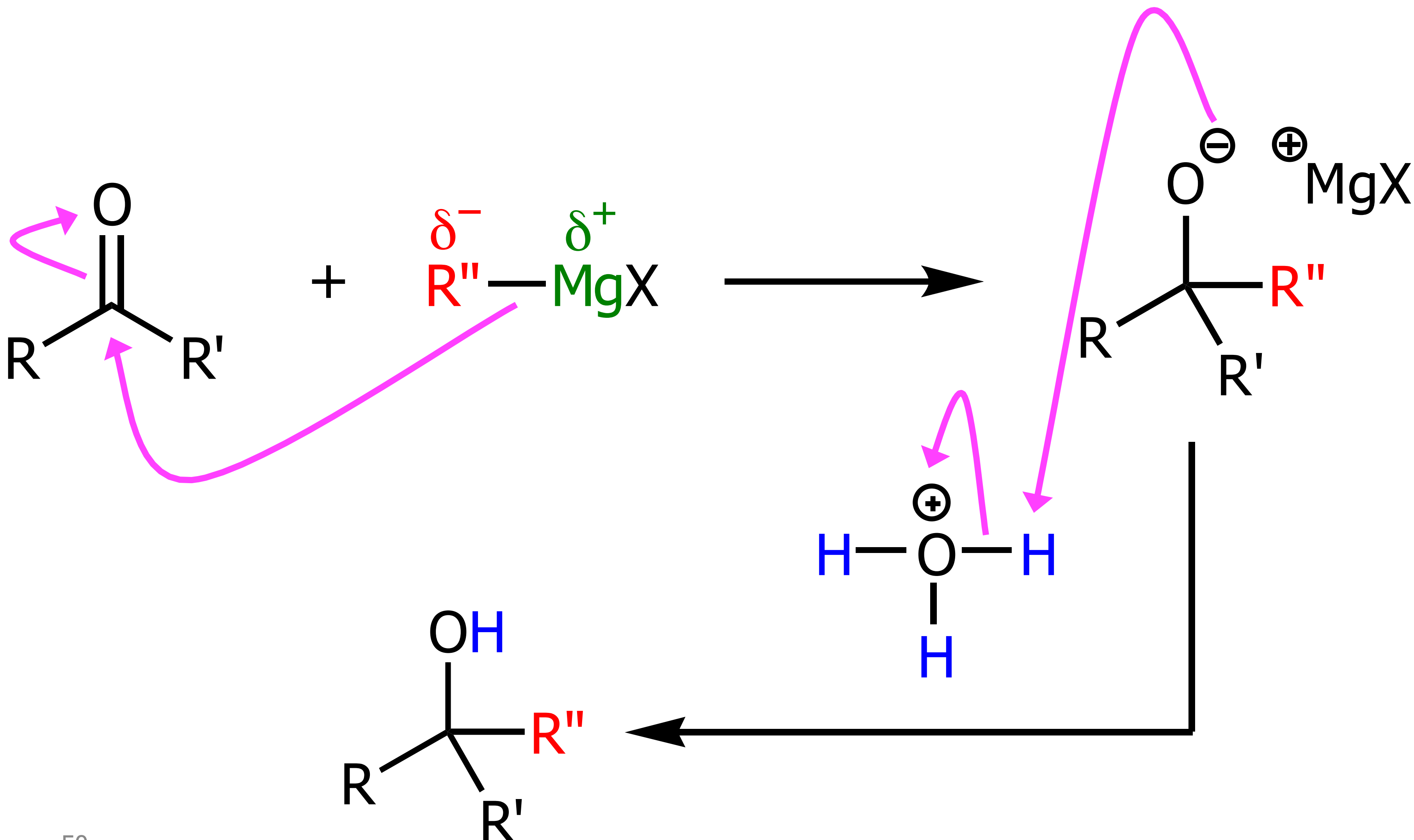
- $NaBH_4$
  - less reactive and less basic than $LiAlH_4$
  - can use protic solvent (e.g. ROH)
  - easily reduces more reactive carbonyl groups (i.e. aldehydes and ketones)

❖ Mechanism



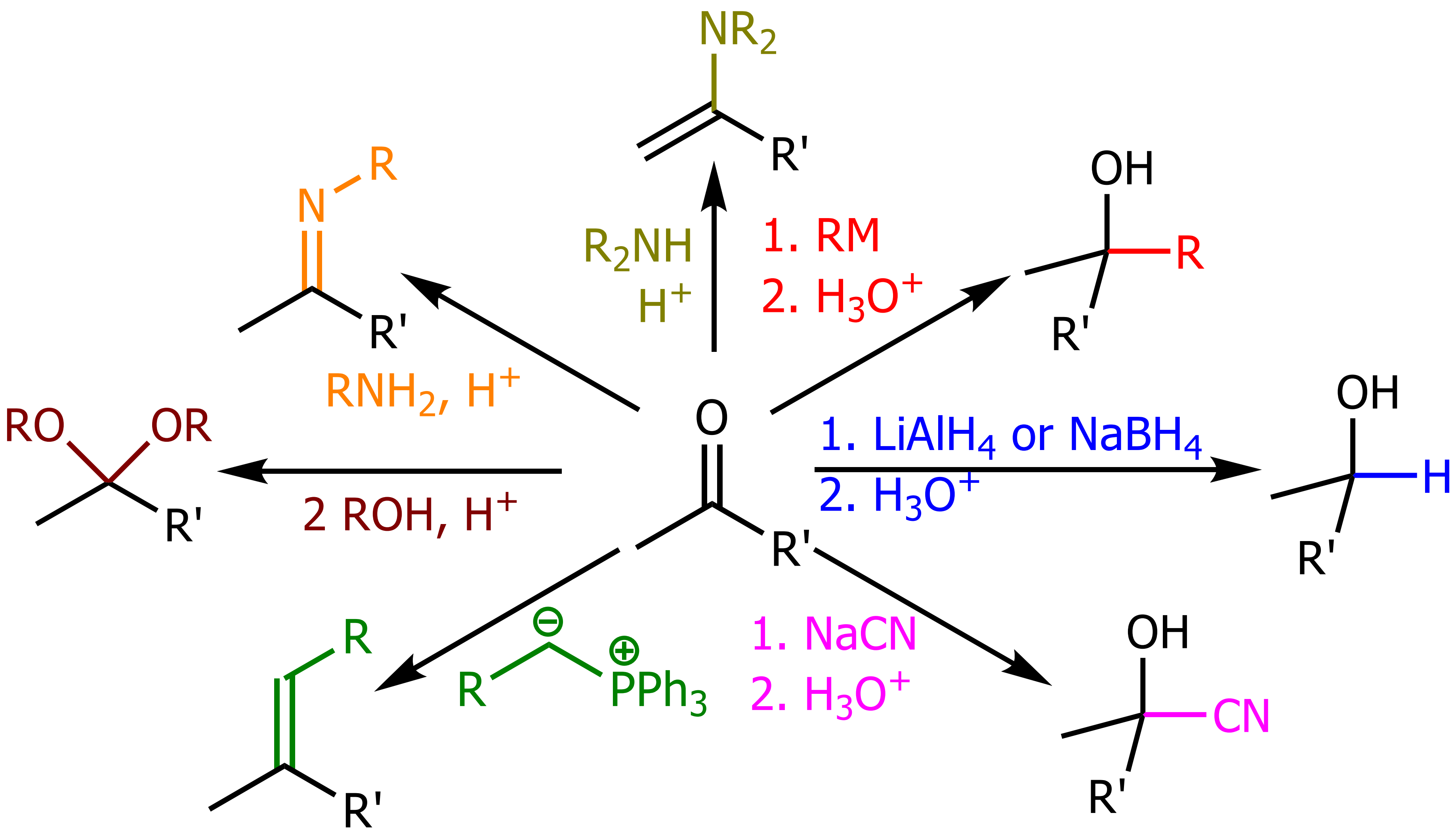
Aldehydes are reduced to 1° alcohols & ketones are reduced to 2° alcohols

Reactions of Grignard Reagents with Carbonyl Compounds



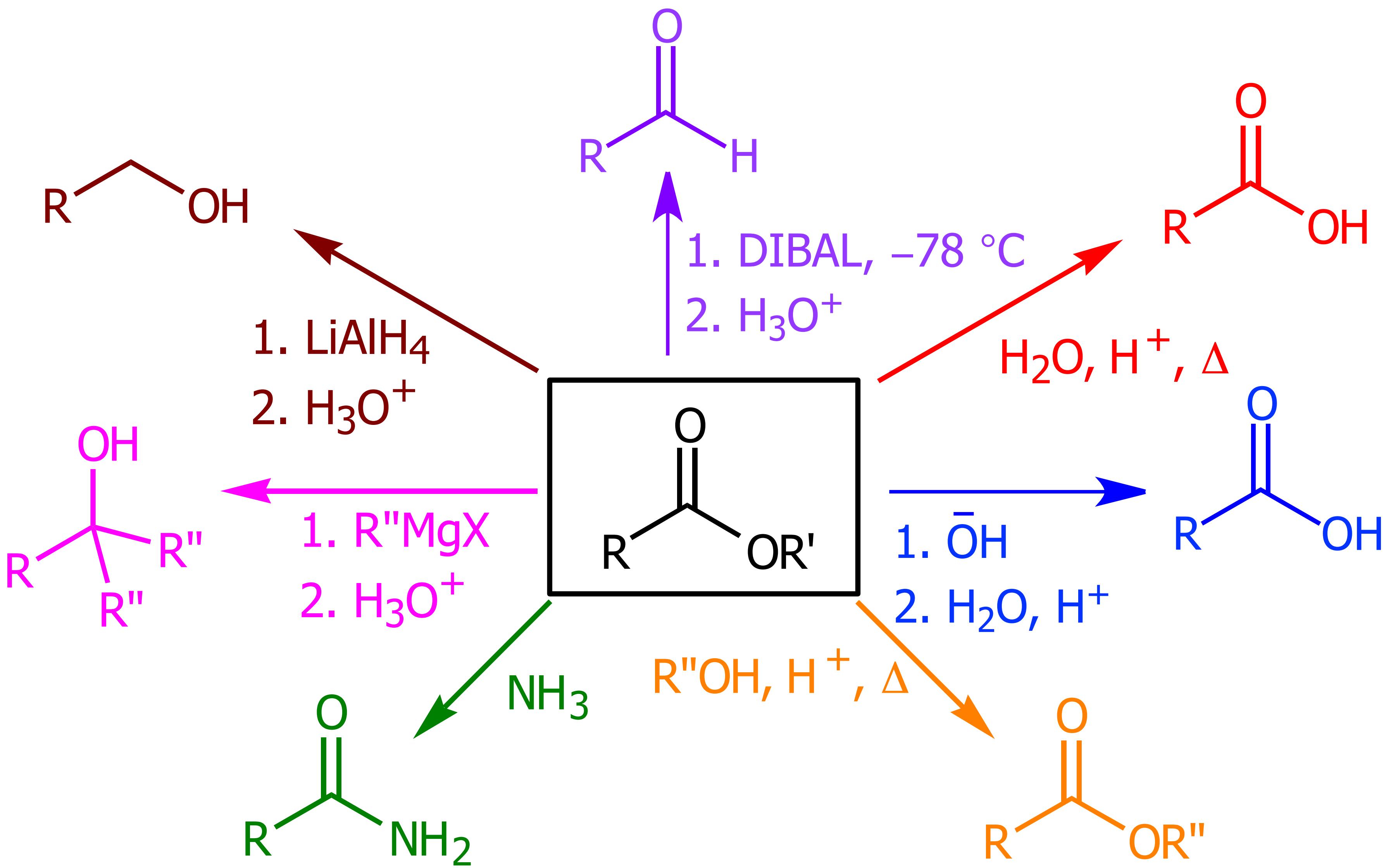
50

Summary of Addition Reactions to Ketones



51

Reactions of Esters



Summary

The synthesis of molecules is governed by few fundamental principles, notably, *the nucleophile will always attack the electrophile*.

Next Lecture, 2016/02/04

Chemical synthesis of small and complex molecules.