Chapter 3  
Reactions of Nucleophiles and Bases

1) Nucleophilic substitution
   (a) at sp³
   (b) at sp² centers
   (c) aromatic substitution

2) Eliminations
   (a) E2
   (b) Ei

3) Nucleophilic addition to carbonyl compounds
   (a) Organometallics
   (b) Aldol Condensation (Carbon nucs with carbonyls)
   (c) Michael Reaction and Other 1,4-Additions

4) Base promoted Rearrangements
   (a) Favorskii Rearrangement
   (b) Benzilic Acid Rearrangement
   (c) Others
There are MANY reactions that fit into this category.

MANY reactions, but only a **few** general mechanisms.

Usually organized into categories based on the reacting group, and the overall reaction. (E.g. Nucleophilic addition to a carbonyl group; nucleophilic acyl substitution, etc)

Our approach is to become familiar with a few general patterns, and use the general principles of Chapters 1+2 to be able to write correct mechanisms for these processes.
1) Nucleophilic substitution

(a) at sp³

The $S_N^2$ reaction is a concerted bimolecular nucleophilic substitution.

THIS IS THE MOST COMMON REACTION PROCESS IN ORGANIC CHEMISTRY.

It involves an Electrophile, Nucleophile and Leaving Group.

The leaving group (which usually has Electronegative atoms) polarizes its connected bond, making the electrophile partially positive.

The electron rich nucleophile attacks the electron poor center with 2 electrons.

A transition state with Nuc, substrate and LG all connected is reached.

Then the LG is expelled with two electrons.

$S_N^2$ reactions cannot occur at sp² or sp atoms.
(For C/N/O need sp³ hybridization)
Relative reactivities

For $S_{N2}$: $\text{CH}_3 > \text{primary} > \text{secondary} > \text{tertiary}$

**because of sterics**

Be aware that allylic, benzylic, etc. are especially reactive towards $S_{N2}$. 

\[ \text{PhCH}_2\text{-O-S-CF}_3 \rightarrow \text{PhCH}_2\text{-CN} \]
Leaving Groups

Leaving groups are better when size, inductive or resonance effects help stabilize negative charge.

Excellent

\[ \text{N}_2, \text{OSO}_2\text{CF}_3 \text{ (triflate), OSO}_2\text{NO}_2 \text{ (nosylate = Nos)}, \]
\[ \text{O-SO}_2\text{Br} \text{ (brosylate = Bs), O-SO}_2\text{CH}_3 \text{ (tosylate = Tos or Ts)}, \]
\[ \text{OSO}_2\text{CH}_3 \text{ (mesylate = Ms)} \]

Good

\[ \text{I}^-, \text{Br}^-, \text{Cl}^-, \text{SR}_2 \]

Fair

\[ \text{OH}_2, \text{NH}_3, \text{OCOCH}_3 \text{ (acetate = OAc)} \]

Poor

\[ \text{F}^-, \text{OH}, \text{OR} \]

Very Poor

\[ \text{NH}_2, \text{NHR}, \text{NR}_2, \text{R}^-, \text{H}^-, \text{Ar}^- \]

Solvent can influence relative leaving group ability.

E.g. negatively charged leaving groups will be stabilized by polar, protic solvents.
For the reaction of EtOH with HBr:
Stereochemistry

The $S_N2$ reaction always proceeds with 100% inversion of configuration at the electrophilic center.
Problem

Which of the two substitutions occurs first?
Problems (i)

Identify the nucleophile, electrophile & leaving group.
Then write the mechanism.

\[
\begin{align*}
\text{Ph} & \quad \text{CH}_3\text{CH}_2\text{Br} & \text{EtOH} & \rightarrow & \text{Ph-P}^+\text{Et} & \text{Br}^- \\
\text{Ph} & \quad \text{Ph} & \text{Ph} \\
\text{H}_3\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH} (\text{CH}_3) \text{Cl} & \text{CO}_3^{2-} & \rightarrow & \text{H}_2\text{N} & \text{Cl}^- \\
\end{align*}
\]
Problems (ii) (Nuc, E+, LG then Mech)
Neighboring Group Participation

Sometimes a molecule undergoing a nucleophilic substitution may contain a nucleophilic group somewhere in the molecule, which actually participates in the reaction.

This is called Neighboring Group Participation (or Anchimeric Assistance).

It results in enhanced rate of reaction.

E.g.

\[
\text{\begin{align*}
\text{S-Cl} & \quad \xrightarrow{\text{H}_2\text{O}} \\
\text{S-Cl} & \quad \xrightarrow{\text{H}_2\text{O}} \\
10,000 \times \text{faster than} \\
\text{O-Cl} & \quad \xrightarrow{\text{H}_2\text{O}} \\
\text{O-Cl} & \quad \xrightarrow{\text{H}_2\text{O}}
\end{align*}}
\]
So how do we explain this?

The rate enhancement occurs due to the formation of a cyclic sulfonium ion intermediate.

Other functionalities that exhibit this behavior include Thiols, Esters, Halogens and Phenyl.
Problem

Write mechanisms for:
1) Nucleophilic substitution (b) at sp² centers
These substitutions, like basic hydrolysis of esters, consist of two separate steps.

The overall process is Substitution, but the first step is nucleophilic addition and the second step is an elimination.

Notice that the carbonyl carbon goes sp² → sp³ → sp².
The below mechanism is **not** correct.

An alternative (ruled out by labelling)

\[
\begin{align*}
\text{CH}_3\text{C}=\text{O} & \quad \rightarrow \quad \text{CH}_3\text{C}=\text{O} \\
\text{OH} & \quad \text{CH}_2\text{OH}
\end{align*}
\]

Whilst this is not a ‘terrible’ mechanism (S$_{\text{N}2}$, reasonable LG), the mobility of the $\pi$ electrons make the carbonyl the best electrophilic center.

Rule: **cannot have S$_{\text{N}2}$ reactions at sp$^2$ carbons.**

If you *want* to write this in a mechanism, it probably is better written as two separate steps.
There are several reasons why direct substitutions do not occur at sp² centers:

a) the LG group is bound with an sp² hybrid orbital bond (= stronger than sp³)
b) the π bond is weakest, and hence the most mobile electron pair.
c) the planar atoms associated with sp² hybridization makes it hard for the nuc to backside attack the leaving group. The attack of nuc to the p orbital of the π bond is much preferred.
Problem

Why is this mechanism wrong?

Write the correct step.
Problems

Write mechanisms for:

1. \(\text{CH}_3\text{NH} - \text{CO}_2\text{Et}\) to \(\text{CH}_3\text{NH} - \text{N}\text{HNCO}_2\text{Et}\)
2. \(\text{CH}_3\text{C(\text{COEt})}_2\) to \(\text{CH}_3\text{N} - \text{N}\text{HNCO}_2\text{Et}\)
3. \(\text{R-CO}_{2}\text{Et} \text{Li}\) to \(\text{R-CO}_{2}\text{Et}\) (2 Equivs)
4. \(\text{R-CO}_{2}\text{Et}\) to \(\text{R-CO}_{2}\text{Et}\) (1 EQ)
1) Nucleophilic substitution (c) aromatic substitution

There are two flavors of nucleophilic aromatic substitutions.

These two processes consist of
i) addition – elimination
   or
ii) elimination – addition (Benzyne or Aryne mechanism)
i) Addition-elimination mechanism
This process dominates when there are electron withdrawing groups which help stabilize the negative charge generated in the ring.

Relative to the LG, ortho and para groups best stabilize the negative charge.

The first step is the RDS. *(why?)*

Thus leaving group ability is not so important.
Problem
Write a mechanism (and justifications) for this reaction:

Justify 1) Why this F
2) Why this N
ii) Elimination-Addition Mechanism

This mechanism dominates when stronger bases are used, and there are no EWG’s to stabilize negative sigma complexes.
Benzyne is still $6\pi$ aromatic.

These $p$ orbitals overlap with each other but not the ring $\pi$ system.
Problem

Write a mechanism for:

\[ \text{IClNH}_2 \xrightarrow{\text{NH}_3 (\text{Li}_2)} \]

\[ \text{Cl} \rightarrow \text{CN} \]
2) Eliminations  (a) E2

The E2 reaction is a bimolecular elimination reaction.

It is a **concerted** process where the base bonds to the proton as the double bond forms as the leaving group is expelled.

The preferred stereochemistry between H and LG is **anti**, but can also be **syn**.
Leaving Groups

Leaving group ability is important.

  Good leaving groups lead to cation formation (discourages E2).
  Stable cations discourage E2.
Dehydration in Acidic Media
For the elimination step in an acid catalyzed Aldol type reaction, the mechanism is:
In acid, the following would **not** occur:

\[
\text{N} \quad \text{OT}
\]

\[
\overset{\text{OH}}{\text{H}} \quad \overset{\text{Acid}}{\text{Acid}} \quad \overset{\text{OH}}{\text{H}}
\]

In Basic media then the following *would* be acceptable.

\[
\overset{\text{CH}_2}{\text{Cl}} \quad \overset{\text{OH}}{\text{H}} \quad \overset{\text{KOH}}{\text{KOH}} \quad \overset{\text{OH}}{\text{H}} \quad \overset{\text{H}_2\text{O}}{\text{H}_2\text{O}} \quad \overset{\text{OH}}{\text{OH}}
\]

*In strong base, OH leaving is acceptable.*
2) Eliminations (b) Ei

Intramolecular elimination (Ei) occurs when the base is part of the same molecule as the proton removed.

Very common for sulfoxides and amine oxides, and also ester, xanthates, etc.

The large preference for syn stereochemistry provides high stereoselectivity from these intramolecular reactions.
The large preference for syn stereochemistry provides high stereoselectivity from these intramolecular reactions.
Write a mechanism for this elimination:
3) Nucleophilic addition to carbonyl compounds

These reactions are organized by type of nucleophile, and then by kind of carbonyl.

Addition reactions with organometallics are usually irreversible, but other nucleophilic additions are reversible, and are equilibrium controlled.
3) Nucleophilic addition to carbonyl compounds (a) Organometallics

Common organometallics include Grignards and organolithiums.

i) Additions to Aldehydes and Ketones

The electron pair of the carbon-magnesium bond is the nucleophile.

The carbonyl carbon is the electrophile.

In reality there is covalency between the Oxygen and magnesium.

Acidic workup furnishes the alcohol product.
Mechanism

Ph-MgBr → Ph-C-Ph

Ph-C-Ph + H⁺ → Ph-C=Ph + H₂O

Ph-C=Ph + MgBr → Ph-C-Ph + MgBr₂

Ph-C-Ph + H₂O → Ph-C=Ph + H⁺
Mechanism
Just about acceptable, but not really a true bimolecular process. (If any Mg is going to coordinate, it is from a separate Grignard reagent).
ii) Additions to Carboxylic Acid Derivatives

Hint: The stability of the intermediate formed by addition of the organometallic to a carboxylic acid derivative determines the product formed in subsequent steps.

Can have:
- organometallic with carboxylic acid → ketone (addn, then elimn = overall subn)
- organometallic with ester → tertiary alcohol (addn, elimn, addn)

Firstly, a Grignard addition to a Nitrile. (addn)
E.g. Alkyl lithium addition to a carboxylic acid.
This requires 2 molar equivalents of alkyl lithium per carboxylic acid.
E.g. Grignard reaction with an Ester.

Two equivalents of Grignard generate the salt of an alcohol.
Problem

Write mechanisms for:

(a) \( \text{CH}_3\text{C} = \text{C} = \text{O} - \text{CH}_3 + \text{EtMgBr} \xrightarrow{\text{after workup}} \)

\[
\begin{align*}
\text{(b1)} & & \text{(Ph)} & & \text{(Ph)} & & \text{(Ph)} & & \text{(Ph)} & & \text{N} = \text{O} & & \text{Ts} \\
\text{(Ph)} & & \text{(Ph)} & & \text{(Ph)} & & \text{(Ph)} & & \text{(Ph)} & & \text{PhMgBr} & & \text{PhMgBr} & & \text{Ph} & & \text{Ph} & & \text{Ph}
\end{align*}
\]
3) Nucleophilic addition to carbonyl compounds
(b) Aldol Condensation (Carbon nucs with carbonyls)

The Aldol Condensation involves an anion on carbon α to an aldehyde or ketone functionality, reacting with a carbonyl of another species.

Aldols can be intramolecular reactions, or mixed aldols.

These reactions are usually run in base (→ anion).

The product is usually an α,β unsaturated carbonyl compound.

Aldols involve a nucleophilic addition, followed by an elimination.
Aldol condensation
The base generates a resonance stabilized anion. (Enolate)
Be aware that typically $K_a$ for this deprotonation is low ~ $10^{-9}$

Then the nucleophilic carbon attacks the benzaldehyde carbonyl.
Protonation of the oxyanion, followed by dehydration gives the conjugated product.

So why does nucleophile go for the benzaldehyde carbonyl and not the acetophenone?
Problem

Write mechanisms for:

(a) $\text{H} \quad \text{CH}_3\text{COCH} \quad \text{OEt}$

\[
\begin{align*}
&\text{N}_2\text{OH} \\
&\text{MeOH} \\
&\Delta
\end{align*}
\]

(b) $\text{PhN}=\text{O}$

\[
\begin{align*}
&\text{NCCH}_2\text{CO}_2\text{Et} \\
&\text{EtOH} \\
&\text{K}_2\text{CO}_3
\end{align*}
\]
3) Nucleophilic addition to carbonyl compounds
   (c) Michael Reaction and Other 1,4-Additions

$\alpha,\beta$-Unsaturated carbonyl compounds are prone to nucleophilic attack at their $\beta$ position.

The final product is produced by protonation of the anion formed, and commonly the enol will tautomerize to the keto form.

Really this is a 1,4-addition, but tautomerization gives a product that looks like an overall 1,2-addition.

The **Michael Reaction** involves the addition of a carbon nucleophile to the $\beta$ position of an $\alpha,\beta$-unsaturated carbonyl (or its equivalent).
The Michael Reaction is a very, very common and useful reaction in organic synthesis since it makes carbon-carbon bonds. This Michael Reaction involves the addition of a fairly stable anion attacking an \( \alpha,\beta \)-unsaturated ketone.
Problem

Why is this wrong?

What should be written instead?
Problems

Write mechanisms for:

(a)

MeO₂C

OEt

LDA, Ph₃SPh

LDA, CH₂=CHNO₂

(b)

KCN

DMF/H₂O

CH₃

NH

CH₃

NH₂

CH₃

+ CO₂
4) Base promoted Rearrangements (a) Favorskii Rearrangement

A typical Favorskii rearrangement involves an α-halo ketone reacting with a base.

The product is a carboxylic acid or ester (depending if base = –OH or –OR). Often the rearrangement part is in the form of ring contraction/expansion.

Labeling studies show that the two α carbons become equivalent during this reaction.

This points to some type of symmetrical intermediate – most likely a cyclopropanone moiety.
Favorskii Mechanism:
4) Base promoted Rearrangements (b) Benzilic Acid Rearrangement

NOTICE THAT Benzilic ≠ Benzylic ≠ Benzoic Acid

This is a rearrangement of an $\alpha$-diketone in base yielding an $\alpha$-hydroxycarboxylic acid.

The name comes from Benzil being converted into Benzilic Acid.
Mechanism of the Benzilic Acid Rearrangement:

Nucleophilic addition of base, followed by a phenyl migration.
Problems

Write mechanisms for:

(a)  

\[ \text{KOH} \]  

(b)  

\[ \text{H}_2\text{O} \]  

(c)  

\[ \text{Ar-MgBr} \] after workup  

\[ \text{Ar} \]
Problem

Provide a mechanism for this transformation, and explain why the difference in stereochemistry in the two solvents:

\[
\begin{align*}
\text{CH}_3 & \quad \text{C} = \text{O} \\
\text{Cl} & \quad \text{H} \\
\text{CH}_3 & \\
\text{NaOMe} & \quad \text{CH}_3\text{OH} \\
\rightarrow & \\
\text{CH}_3 & \quad \text{CO}_2\text{CH}_3 \\
\text{H} & \\
\text{CH}_3 & \\
\text{NaOMe} & \quad \text{DME} = \text{CH}_3\text{OCH}_3
\end{align*}
\]

41% & 57%

94%
4) Base promoted Rearrangements (c) Others

   i) Nucleophilic Addition followed by rearrangement.

For this transformation, numbering the atoms reveals the rearrangement pattern.
The base removes a proton, which generates a three membered ring intermediate that ring opens differently to how it was formed (= a common way for rearrangements to proceed).
Methylation of the anion gives the product.
What about this interesting stereospecific transformation?

Let us approach this logically...

Cyanide in pyridine = a good nucleophile, which leads us to think about $S_{N2}$ displacement of Br (100% inversion).

True, but does not really get us closer to the product.
So what about cyanide attacking the carbonyl, leading to epoxide formation...

Notice that the oxygen nuc and LG **MUST** to be ANTI for epoxide formation.
But we are close...

What we need is a change in the stereochemistry....

(The authors of this reaction showed epimerization occurred under reaction conditions).
Problems (i)

Write mechanisms for the following:

(a) \[ \text{Ph}_2C\text{Cl} \xrightarrow{n\text{BuLi (excess)}} \text{Ph}_2C=\text{O} \]

(b) \[ \text{H}_3\text{C} \xrightarrow{\text{Et}_3\text{N}} \text{PhCON}_{\text{Et}} \]

(c) \[ \text{Ph} \xrightarrow{\text{NaNH}_2} \text{H}_3\text{C} + \text{CH}_3-\text{N}_2\text{Ph} \]
Problems (ii)

(c) \( \text{NH}_2-\text{NH}_2 \)
Problem

For this transformation:

\[
\begin{align*}
\text{Br} & \xrightarrow{\text{CH}_2\text{OCH}_3} \text{NO}_2\text{NH}_3
\end{align*}
\]

Both involve:

\[
\begin{align*}
\text{Ph} & \xrightarrow{\text{H}} \text{Ph} - \text{C} - \text{H} \xrightarrow{\text{NH}_3} \text{Ph} - \text{C} - \text{O}
\end{align*}
\]

Discuss the pros & cons of each mechanism, & decide which you like best.
Mech 2
Mitsunobu Problem

Write a mechanism for the MITSUNOBU REACTION, that always gives inversion of the alcohol group with a Nucleophile.

\[
\text{EtO}_3\text{C} \quad \text{N} = \text{N} \quad \text{CO}_2\text{Et} \quad + \quad \text{Ph}_3\text{P} \quad + \quad \text{PhCO}_2\text{H} \quad + \quad \text{H} \quad \text{C} - \text{OH} \quad \text{C}_6\text{H}_5
\]

\[
\text{EtO}_3\text{C} \quad \text{N} = \text{N} \quad \text{CO}_2\text{Et} \quad + \quad \text{Ph}_3\text{P}=\text{O} \quad + \quad \text{PhCO}_2\text{C} - \text{H} \quad \text{C}_6\text{H}_5
\]

HINTS:
1. Triphenyl Phosphine reacts with DEAD, followed by Protonation by RCO₂H
2. Alcohol attacks on from 0 (at $-\text{P}^+$)
3. Protonation of $\text{N}^-$
4. RCO₂⁻ does SN₂ giving INVERSION