In this chapter, and the next two, we will discuss two basic types of reactions: Nucleophilic, aliphatic substitution reactions of the basic form:

\[
\begin{align*}
R^+X & \quad + \quad Y^- \quad \rightarrow \quad R^+Y \\
R^- & \quad + \quad X^-
\end{align*}
\]

Elimination of reactions of the form:

\[
\begin{align*}
\overset{H}{R} & \quad \overset{R}{R} \quad \overset{R}{R} \quad + \quad B^- \quad \rightarrow \quad \overset{R}{R} \quad + \quad BH^+ \quad , \quad X^-
\end{align*}
\]

For each of the nucleophilic and elimination reactions there are two basic types: those that involve the formation of a carbocation intermediate and those that proceed smoothly in a concerted manner from the reactant to the product through a transition state without forming intermediates.

The material in this chapter builds upon our understanding of:
1. Acid-base chemistry and, in particular, the stability of conjugate bases;
2. Facile identification of primary, secondary, and tertiary carbons;
3. Basic electrostatic interaction between like and opposite charges and the role that solvents play in stabilizing charges;
4. Carbocations, their stability, and rearrangement chemistry;
5. Stereochemical implications of reaction mechanisms The chemistry of additions of HX to double bonds and
6. Basic rate equations (which will be covered in more depth).
Simple Kinetics

Watching the rate of disappearance of starting materials, or rate of appearance of products, can provide insight into the mechanism of a reaction.

For a simple reaction: A goes to B, the rate of disappearance of A equals rate of appearance of B

\[
A \rightarrow B
\]

\[-d[A]/dt = k[A]\]

where \(d[B]/dt\) is the rate of change of concentration of B with time, and \(k\) is the unimolecular rate constant characterizing how fast the reaction proceeds and is related to \(\Delta G^\ddagger\).
The Case of A + B Goes to C

In a reaction of A + B goes to C, the reaction may depend on the concentration of A, or B, or both, depending on the mechanism.

\[ A + B \rightarrow C \]

Case 1: If, in the rate-determining step, A and B must collide, then the probability of this event will be proportional to the product of their concentrations, and the rate expression for the reaction will be:

\[
\frac{d[C]}{dt} = k[A][B]
\]

Case 2: If, on the other hand, A does something in a slow step (the rate-determining step) to create an intermediate and then the intermediate rapidly reacts with B after the rate-determining step, the rate of formation of C (under normal conditions) will depend only upon the concentration of A and the rate expression for the reaction will be:

\[
\frac{d[C]}{dt} = k[A]
\]

Note: the order of a reaction (molecularity of a reaction) is the sum of the exponents to which the concentration of each of the reactants is raised in the rate expression. So for case 1, this is 1+1 =2. Hence this is called a second-order reaction (that is first order in each A and B). In contrast, the second reaction is a first-order reaction.

Thus, by following the rate of reaction, one can obtain information about the rate-determining step specifically the molecularity of that step.
Substitution-nucleophilic-bimolecular: $S_N^2$

Note: in the rate-determining step, the nucleophile $Y$ comes in from the backside and as it begins to form a $Y$-$C$ bond the $C$-$X$ bond begins to break. It is a *concerted* reaction not involving any intermediates.

Because both $Y^-$ and $R,RCH-X$ must collide in the rate determining step, $S_N^2$ reaction are second order; first order in both reactants. This is what the “2” stands for in $S_N^2$.

The back-side attack of $Y^-$ leads to a net inversion of configuration.
Notes for the $S_N2$ reaction

1. For this reaction to proceed efficiently there must be:
   - A good leaving group and a good nucleophile.
   - A nucleophile that is not well solvated so that it remains reactive.
   - A transition state that is relatively uncongested, such that the nucleophile can approach without being hindered by bulky groups. (Note that if the leaving group is large this is OK, since this bond is on the opposite side of the oncoming nucleophile and the bond is becoming longer and longer as we approach the transition state).
   - Specifically $1^\circ$ are less hindered than $2^\circ$, are less hindered than are $3^\circ$.

2. In an $S_N2$ reaction the nucleophile will displace the leaving group with inversion of configuration. Hence if you start with an optical active reactant, you will end up with an optically active product. Therefore the reaction is stereospecific.

3. Since the rate determining step involves a collision between the nucleophile and the starting material, the rate equation for the disappearance of starting material is:

   \[ \frac{d[\text{starting material}]}{dt} = -k[\text{starting material}][\text{nucleophile}] \]

   thus, there is a dependence of the rate on both reactants.
Examples of $S_N2$ Reactions

**Inter**molecular nucleophilic substitution reactions

1. $\text{N}_3^-$ azide
2. $\text{CN}^-$ cyanide
3. $\text{OCH}_3^-$ alkoxide
4. $\text{SCH}_3^-$ thiolate
5. $\text{N(CH}_3)_3$ amine
6. $\text{OH}^-$ hydroxide
7. $\text{Br}^-$ halide

- alkyl azide
- nitrile
- ether
- sulfide
- ammonium
- alcohol
- alkyl halide

**Intra**molecular nucleophilic substitution

\[
\text{NH}_2\text{Br} \quad \rightarrow \quad \text{NH}^+\text{H} \quad \rightarrow \quad \text{NH} \quad + \quad \text{BH}^+
\]
Effects of Solvent

1. Hydrogen bonding solvents that preferentially stabilize negative charge will often solvate the nucleophile and lower its energy relative to the transition state. Thus, solvents that stabilize negative charges will decelerate this reaction.

2. Solvents that stabilize positive charges will accelerate this reaction. Polar solvents will preferentially solvate the cation of a salt. If this occurs the anion and the cation will be well separated; thus, the interaction of the anion and the cation will be minimal. Accordingly, the anion will be destabilized and more reactive. As a result, polar aprotic solvents enhance the rate of $S_N2$ reactions. Thus, $S_N2$ reactions are run in polar aprotic solvents such as DMF or DMSO.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>CH$_3$OH</th>
<th>Water</th>
<th>DMSO</th>
<th>DMF</th>
<th>CH$_3$CN</th>
<th>HMPA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative Rate</td>
<td>1</td>
<td>7</td>
<td>1,300</td>
<td>2,800</td>
<td>5,000</td>
<td>200,000</td>
</tr>
</tbody>
</table>

Hexamethylphosphoramide (HMPA) is a very polar aprotic solvent that preferentially stabilizes cations (and is highly carcinogenic).
Steric Effects on $S_N2$ Reactions

$S_N2$ reactions are very sensitive to the steric congestion about the carbon bearing the leaving group. Thus, the more crowded the carbon atom the slower the rate. $1^\circ$ are faster than $2^\circ$, and $3^\circ$ will not react by $S_N2$ mechanism.
Relative Rate of Reaction of Different Alkyl Halides

<table>
<thead>
<tr>
<th></th>
<th>Neopentyl</th>
<th>Tertiary</th>
<th>Secondary</th>
<th>Primary</th>
<th>Methyl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rel rate:</td>
<td>3.3 x 10^{-7}</td>
<td>5.5 x 10^{-5}</td>
<td>8.4 x 10^{-4}</td>
<td>3.3 x 10^{-2}</td>
<td>1</td>
</tr>
</tbody>
</table>

Conclusions from this table are:

- The branching at the α carbon is very important. Methyl and primary halides undergo facile S\textsubscript{N}2 reactions under mild conditions. For nucleophiles attached to secondary carbons the reaction conditions used are forcing (i.e. high temperature) and S\textsubscript{N}2 reactions are not observed for tertiary alkyl halides.

- The branching at the β carbon is also very important, thus neopentylbromide is more than 10^4 less reactive than ethyl bromide. This is because it is impossible to have a backside approach to the carbon bearing the bromine without one of the methyl groups on the β carbon obstructing the approach.

- If there are branches further along the chain at the γ, δ, ... carbons these have much less of an effect on the rate.
Factors Effecting the Direction of a Nucleophilic Substitution Reaction

For the reaction

\[
\text{R}^\circ \text{X} + \text{Y} \rightarrow \text{R} \text{Y}^\circ \text{R} + \text{X} \circ
\]

it is fully possible that the reverse reaction can occur. That is, X can be the nucleophile and Y can be the leaving group.

What determines the direction in which the reaction proceeds?

1. By analogy to acid base reactions the direction which gives the most stable leaving group will be favored. Thus if \( X = \text{I} \) and \( Y = \text{OH}^- \) the reaction will proceed to the right since \( \text{I}^- \) is much more stable than \( \text{OH}^- \). Remember their relative pKa

2. If \( \Delta G \) for the reaction was around 0 kcal/mol, then the conditions under which the reaction was run would have a significant effect on the course of the reaction. Using LeChatelier’s principal:

   • For example, if \( \text{OH} \) was used in large excess, the reaction would be driven towards the right.

   • If the case above \( \text{I}^- \) precipitated from the reaction mixture or if volatile leaving group could be removed from the mixture by distillation these processes could be used to drive the reaction towards the right.
Leaving Groups

The most important feature of the leaving group is that upon heterolytic cleavage of its bond to carbon, the species that is formed (be it neutral or anionic) is very stable. In general, that implies that it is a very weak base (Brønsted or Lewis).

Therefore, the conjugate acid of the leaving group should be a strong acid and thus have a relatively low pKa. If an acid has a pKa less than zero, then it is likely that the conjugate base will be a good leaving group. In general the weaker the base, the better the leaving group.

- Note that the \( \text{OH}_2^+ \) leaving group is formed by protonation of an alcohol. Thus, in order for this reaction to be favorable, the acid that protonates the alcohol must be at least as strong an acid as \( \text{H}_3\text{O}^+ \).
- Conversion of an alcohol to another group (such as a hydronium or a tosylate) prior to the nucleophilic substitution reaction is very common to “activate” the OH such that it is a much better leaving group.
- The reason for this is that \( \text{OH}^- \) is not a good leaving group. Remember the pKa of its conjugate acid (\( \text{H}_2\text{O} \)) is 15.5.
**Table of Leaving Group Trends Geared Toward S\textsubscript{N}2 Reactions**

This table is adapted from McMurray and is meant only as a rough guide. It is not universally applicable to all substitution reactions. There will be variation depending upon the mechanism of the reaction, the solvent, and the nucleophile.

<table>
<thead>
<tr>
<th>Conjugate Acid</th>
<th>Molecule with Leaving Group</th>
<th>Relative Rate</th>
<th>pKa</th>
</tr>
</thead>
<tbody>
<tr>
<td>HI</td>
<td><img src="image1" alt="HI molecule" /></td>
<td>30,000</td>
<td>-11</td>
</tr>
<tr>
<td>HBr</td>
<td><img src="image2" alt="HBr molecule" /></td>
<td>10,000</td>
<td>-8</td>
</tr>
<tr>
<td>HCl</td>
<td><img src="image3" alt="HCl molecule" /></td>
<td>200</td>
<td>-6</td>
</tr>
<tr>
<td>H\textsubscript{3}O\textsuperscript{+}</td>
<td><img src="image4" alt="H\textsubscript{3}O\textsuperscript{+} molecule" /></td>
<td>-</td>
<td>-2</td>
</tr>
<tr>
<td>HF</td>
<td><img src="image5" alt="HF molecule" /></td>
<td>1</td>
<td>3.18</td>
</tr>
<tr>
<td>\text{-SO\textsubscript{3}H}</td>
<td><img src="image6" alt="\text{-SO\textsubscript{3}H molecule}" /></td>
<td>60,000</td>
<td>-1</td>
</tr>
<tr>
<td>H\textsubscript{2}O, NH\textsubscript{3}, ROH</td>
<td><img src="image7" alt="H\textsubscript{2}O, NH\textsubscript{3}, ROH molecule" /></td>
<td>&lt;&lt;1 basicallly doesn’t occur</td>
<td>&lt;&lt;10</td>
</tr>
</tbody>
</table>
**Nucleophilicity**

The rate of an $S_{N}2$ reaction also depends on the nucleophile. A good nucleophile destabilizes the starting materials and therefore lowers the $\Delta G^\ddagger$.

1. When comparing nucleophiles, if the nucleophile involve the same atom, effects that destabilize that atom (relative to the transition state) increase their nucleophilicity. Thus, for example, nucleophilicity increases with increasing basicity (destabilization of the nucleophile) and decreases with solvation of the nucleophile (stabilization of the nucleophile).

2. When comparing atoms that are of very different size the relationship between nucleophilicity and basicity holds in the gas phase and in aprotic solvents; however, as we will see the trend is reversed in protic solvents.

3. In general, anionic nucleophiles are more reactive than neutral ones.

4. A sense of the relative nucleophilicity of groups can be understood by considering the second order rate constants for an $S_{N}2$ reaction.
5. The nucleophilicity of a nucleophile is quite solvent dependent:

- Thus, in a protic solvent the most basic group will tend to be the least nucleophilic because they will form the strongest interaction with the hydrogen bonding solvent.

For methanol:

\[ F^- \ll Cl^- < Br^- < I^- \]

- Whereas in an aprotic polar solvent the most basic will be the most reactive.

For DMF:

\[ F^- > Cl^- > Br^- > I^- \]

Consider the reaction

\[
\text{Nu} + \text{I} \rightarrow \text{I}^- + \text{Nu}
\]

The free energy of activation will vary as a function of the strength of the nucleophile as described above and, in more detail, below. The rate will increase with decreasing free energy of activation.
To illustrate the how nucleophilicity is affected by solvent, the free energies of activation for different nucleophiles in a polar aprotic solvent (DMF) and a protic solvent (methanol) are given below.

<table>
<thead>
<tr>
<th>Nucleophile</th>
<th>DMF</th>
<th>Methanol</th>
<th>pKa</th>
</tr>
</thead>
<tbody>
<tr>
<td>CN⁻</td>
<td>14.0</td>
<td>21.8</td>
<td>9.3</td>
</tr>
<tr>
<td>CH₃COO⁻</td>
<td>15.7</td>
<td>25.1</td>
<td>4.75</td>
</tr>
<tr>
<td>NO₂</td>
<td>16.8</td>
<td>22.5</td>
<td></td>
</tr>
<tr>
<td>N₃⁻</td>
<td>16.8</td>
<td>23.0</td>
<td>4.74</td>
</tr>
<tr>
<td>Cl⁻</td>
<td>16.9</td>
<td>25.0</td>
<td>−5.7</td>
</tr>
<tr>
<td>Br⁻</td>
<td>17.3</td>
<td>23.0</td>
<td>−7.77</td>
</tr>
<tr>
<td>SCN⁻</td>
<td>19.0</td>
<td>22.0</td>
<td>−0.7</td>
</tr>
<tr>
<td>I⁻</td>
<td>20.9</td>
<td>18.0</td>
<td>−10.7</td>
</tr>
<tr>
<td>(CH₃)₂S</td>
<td>21.8</td>
<td>23.6</td>
<td>−5.3</td>
</tr>
</tbody>
</table>

*Note as mentioned earlier, protic solvents are NOT good solvents for S_N2 reactions*
Substitution-nucleophilic-unimolecular: $S_N 1$

If a tertiary halide is refluxed with a solvent that is weakly nucleophilic, in which no base or additional nucleophile has been added, both substitution and elimination discussed later can occur as shown below. The substitution reaction is called a solvolysis reaction.

Since the halide is tertiary, we know that the reaction is not $S_N 2$, as we will discuss later; in fact, another set of mechanisms are in place that involve an initial formation of a carbocation intermediate:

possibly rearranged products
Reaction Coordinate Diagram for $S_N1$ Reactions

Note that, by definition, in the rate determining step (slow step) of this type of reaction the C-X bond is simply broken heterolytically. Afterwards, in a relatively rapid step, the nucleophile comes in and adds (from either face of the carbocation intermediate) to the carbocation to give the substitution product. This reaction mechanism is called $S_N1$.

Alternatively, a proton can be lost from the $\beta$ carbon of the intermediate to give the elimination product by an E1 mechanism and can be seen in the mechanism.

Mechanism
Notes on S$_N$1 Reactions

1. Since you form a planar carbocation intermediate, if you start out with an optically active starting material, you end up with a racemic mixture of materials. (Simplification)

2. This type of nucleophilic substitution reaction will only occur when a stable carbocation can be formed. Therefore, you will never see this type of nucleophilic substitution reaction with primary carbocations.

3. Since the rate-determining step involves only a single species the rate equation for the disappearance of starting material is:

\[ \frac{d[\text{starting material}]}{dt} = -k[\text{starting material}] \]

There is no dependence of the rate on the nucleophile. This is true because the carbocation is very Lewis acidic and the Lewis basic solvent is present in extremely high concentration.

4. Polar protic solvents that stabilize both positive and negative charge will accelerate this reaction.

5. Rearrangements can occur:

\[ \text{Cl} \quad \rightarrow \quad \text{OH} \quad \rightarrow \quad \text{O} \]
Reactions of Alcohols

In this chapter, we will focus on substitution reactions of alcohols and related topics.

\[
\text{H}^+ + \text{ROH} \rightarrow \text{RO}^+ \text{H}^+ \quad \text{H}_3\text{PO}_4 \xrightarrow{\Delta} \text{alkene}
\]

- Note that the dehydration of the alcohol here is simply an E1 mechanism, but the OH\(^-\) is not a good leaving group. (Remember that the pKa of its conjugate base (H\(_2\)O) is 15.5). However, ROH\(_2^+\) is formed by protonation of the alcohol and the OH\(_2\) is a good leaving group. Thus in order for this reaction to be favorable, the acid that protonated the alcohol must be a stronger acid than ROH\(_2^+\) which is about the same as H\(_3\)O\(^+\).

- The reaction goes in the opposite direction of hydration reactions because it is run in the complete absence of water and, therefore, the equilibrium is driven in the direction of the alkene (Le Châtelier’s principle).

- Note that the mechanism here is exactly the reverse mechanism of the addition of water across a double bond catalyzed by acid.
Since the dehydration of alcohols involve carbocation intermediates, it follows from the Hammond postulate that the relative rates for dehydration will follow the order tertiary is faster than secondary, which is faster than primary. As you might expect, the dehydration of primary alcohols is not a synthetically useful reaction since a primary carbocation is so energetically unfavorable.
This is an E1 mechanism and a mixture of alkene products can be formed with the most stable alkenes favored as shown below:

![Reaction mechanism with alkene products and water formation.]

1. Since carbocations are involved, rearrangements are possible as shown below:

![Rearrangement of carbocation intermediates with minor and major product formation.]

...
Reactions of Alcohols with Hydrogen Halides

- Once the alcohol is protonated, we can simply consider its reactivity to be similar to any other S_N1 or S_N2 substrate toward nucleophiles with one key exception. Since the protonated alcohol is a strong acid (pKa ~−2 to −3), any basic nucleophile will simply deprotonate the species to regenerate the starting alcohol.

- However, nucleophiles that have very strong conjugate acids (comparable to the pKa of the protonated alcohol) can react by a nucleophilic displacement reaction to give the corresponding substitution product. This scenario is quite common when an alcohol is treated with HX, where X is Cl, Br, or I.

- One can use Le Châtelier’s principle to drive the reaction in the desired direction. The reaction will be pushed towards the product with an excess of HX, and if possible, the product alkyl halide will be removed from the reaction mixture. Often such reactions are run in aqueous solutions of strong acid since the halide that is formed is not soluble in water and separates from the reaction mixture.

- Whether the reaction proceeds by an S_N1 or S_N2 mechanism is simply governed by the parameters that we discussed in chapter 9. Thus, primary alcohols will react exclusively by an S_N2 mechanism, secondary can react by either an S_N1 or an S_N2 mechanism, and tertiary will react by a S_N1 mechanism.

- As in all S_N1 or S_N2 reactions, E1 and E2 processes can and will compete. Again, simply treat the protonated alcohol as you would any other substrate and look for features favoring elimination vs. substitution.

- If the protonated alcohol creates a secondary carbocation upon leaving, look for the possibility of the resultant carbocation to rearrange to a more stable tertiary carbocation, that will be trapped by the nucleophile (or possibly lose a proton and eliminate). Look for tertiary or quaternary carbon centers next to secondary carbocations and also look for the possibility of making resonance stabilized carbocations as well, by shifting a hydride, alkyl or aryl group.
The reaction shown in the image involves the reaction of a compound with HBr to yield a different compound. The reaction is represented by the following structural formulas:

Initial compound:  

Conversion steps:  

Final product:  

The reaction involves the substitution of a hydrogen atom with a bromine atom, indicating a substitution reaction.
Reactions of Alcohols

• Another way that alcohols can be converted to alkyl halides is by nucleophilic attack on Lewis acidic molecules that have halide leaving groups.

• The adduct of the alcohol and the Lewis acid creates a good leaving group and the halide that is created in the first step can displace this leaving group to make a halide.

• Primary and secondary alcohols react with PBr$_3$ by a nucleophilic substitution reaction at phosphorus to form an intermediate phosphite ester.

• With primary and secondary alcohols as starting materials, the Br$^-$ anion that is created attacks the carbon via an S$_N$2 mechanism and displaces the phosphite (a good leaving group). This yields an alkyl bromide with inversion of configuration.

• In a similar manner, primary and secondary alcohols react with SOCl$_2$ in polar solvents (e.g., pyridine) to form an intermediate sulfite ester.

• The sulfite ester undergoes S$_N$2 attack by chloride anion to yield an alkyl chloride with inversion of configuration.
Reaction of a primary or secondary alcohol with 4-toluenesulfonyl chloride (Tosyl-Cl) in pyridine (cold) converts the alcohol into an excellent leaving group for $S_N_2$ reaction, i.e. a tosylate (recall from the previous chapter the tosylate is one of the best leaving groups). Note here that there is retention of configuration. (For all the reactions discussed above, the first step goes with retention of configuration, but here there is no "second step").
Alkylating Reagents

• The tosylate can thus react cleanly with a variety of nucleophiles, both at primary and secondary carbons, to afford the desired nucleophilic substitution product.

• Because the tosylate is such a good leaving group, one can run nucleophilic substitution reactions under $S_{N}2$ conditions (i.e. polar, aprotic solvent, mild heating) and ensure that no carbocation intermediates are formed. Thus, the likelihood of side products resulting from rearrangements or elimination (if a good non-basic nucleophile is used) can be minimized.

![Chemical reaction diagram]

• Just as a strong acid is a reagent that will protonate an alkoxide (or alcohol for that matter), as shown below:

![Chemical reaction diagram]

an alkylating agent which is an alkyl group bound to an exceptional leaving group, can be used as a reagent to alkylate an alkoxide as shown below:

![Chemical reaction diagram]

• Alkylating agents such as dimethylsulfate are often potent carcinogens as they can alkylate DNA which can lead to mutations (not a good thing).
Synthesis of Ethers: Condensation of Alcohols

• Some ethers can be made by treatment of alcohols with strong acid. In this reaction, the acid protonates a hydroxyl group activating it for a nucleophilic substitution reaction and a second equivalent of alcohol can enter as a nucleophile:

\[
\begin{align*}
\text{products} & \quad \text{reaction} \\
\text{products} & \quad \text{products}
\end{align*}
\]

• In general, this is not a satisfactory method to prepare unsymmetrical ethers since both of the symmetrical ethers could be formed as well.

• There are exceptions to this guideline. In particular, if a tertiary alcohol is reacted with a primary alcohol acting as a solvent then this reaction proceeds relatively cleanly since the tertiary carbocation can be formed under mild conditions (by an \(S_N1\) solvolysis reaction).

\[
\begin{align*}
\text{products} & \quad \text{reaction} \\
\text{products} & \quad \text{products}
\end{align*}
\]

• Formation of the primary cation from protonation of the ethanol will not occur and the \(S_N2\) reaction will be kinetically much slower.
Synthesis of Ethers continued

- In a related manner, ethers can be prepared from some alkenes by treatment under alcoholic acidic conditions, (if rearrangements are not expected to occur).

\[
\text{HO}^+ + \text{H}^- \rightarrow \text{HO}^- + \text{H}_2\text{O}
\]
Reactions of Ethers

In general, ethers are relatively unreactive and are therefore used as solvents for a variety of reactions. In particular, they are quite inert to strong base.

Ethers can react slowly with oxygen to create peroxides that are potentially explosive. This creates a safety hazard in the laboratory when cans of ether are left open for extended periods of time.

Ethers can also react with HI (or HBr) in the presence of water to give the corresponding alkyl iodide in a manner analogous to alcohols.

- This can occur by either an $S_N2$ mechanism in the case of when primary or secondary alcohols will be created (attack will be at the least hindered carbon if there is a choice):

\[
\begin{align*}
\text{O} & \quad \text{HI (or HBr)} \\
\text{O} & \quad \text{H} \\
\text{I} & \quad \text{H} \\
\text{O} & \quad \text{H} \\
\end{align*}
\]

OR

- By an $S_N1$ mechanism in the case when tertiary alcohols will be created, here E1 reactions are also possible:
Grignard and Lithium Reagents

The reaction of an alkyl, aryl or vinyl halide with magnesium metal in ether (note, when unspecified, “ether” refers to diethylether) creates organometallic, compounds commonly referred to as Grignard Reagents, after the chemist who studied them extensively.

\[
\begin{align*}
\text{H}_3\text{C}-\text{Br} + \text{Mg} & \quad \text{ether} \quad \text{H}_3\text{C}-\text{Mg}-\text{Br} \\
\text{R}-\text{Br} + \text{Mg} & \quad \text{ether} \quad \text{R}-\text{Mg}-\text{Br}
\end{align*}
\]

Grignard Reagent

In a similar vein, alkyl, aryl, and vinyl halides can react with lithium metal as shown below:

\[
\begin{align*}
\text{R}-\text{Br} + 2\text{Li} & \quad \text{ether} \quad \text{R}-\text{Li} \quad \text{LiBr}
\end{align*}
\]

The "R" groups in these complexes are very reactive nucleophiles. They behave as if they were carbanions stabilized by their association with the metal (i.e. Li, as in R-Li⁺).

Grignard and lithium reagents react with acidic (even weakly acidic) compounds (remember the pKa of hydrocarbons is about 45-50) so their conjugate bases (the carbanions) will deprotonate most compounds if given the chance.

\[
\begin{align*}
\text{R}-\text{Mg}-\text{Br} \quad \text{or} \quad \text{R}-\text{Li} + & \quad \begin{cases} 
\text{RNH}_2 \\
\text{ROH} \\
\text{H}_2\text{O}
\end{cases} \rightarrow \text{R-H} + \begin{cases} 
\text{RNHY} \\
\text{ROY} \\
\text{YOH}
\end{cases} \\
\text{where } Y = \text{either MgBr or Li}
\end{align*}
\]

On the opposite end of the spectrum, if one protonates water, alcohols, ethers, thiol and sulfides, then, as shown below, one creates strongly acidic groups.

\[
\begin{align*}
\text{H} & \quad \text{O}^+ \quad \text{H} \\
\text{H} & \quad \text{O}^+ \quad \text{H} \\
\text{H} & \quad \text{O}^+ \quad \text{H} \\
\text{S}^+ & \quad \text{H} \quad \text{S}^+ \\
\text{H} & \quad \text{S}^+ \\
\text{H} & \quad \text{S}^+
\end{align*}
\]

pKa \(-1.74\) \(-2\) to \(-3\) \(-5\) to \(-7\)
Other Organometallic Reagents via Transmetallation

7. If a lithium reagent or a Grignard reagent is reacted with a metal halide where the metal of the metal halide is *more* electronegative than lithium or magnesium, then the R group will be transferred to the more electronegative element. This is called transmetallation.

8. In such a case because the electronegativity difference between carbon and the new metal will be less, the new metal carbon bond will be more covalent.

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<th>2</th>
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<th>13</th>
<th>14</th>
<th>15</th>
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<th>18</th>
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<td>O</td>
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</table>

In such cases the resulting organometallic reagent will be less reactive and in certain cases, can have greater selectivity. Examples of organometallic metal carbon bonds are shown below:

\[
\begin{align*}
\text{C—Mg} & \quad \delta^- \quad \delta^+ \\
\text{C—Li} & \quad \delta^- \quad \delta^+ \\
\text{C—Cu} & \quad \delta^- \quad \delta^+ \\
\text{C—Si} & \quad \delta^- \quad \delta^+ \\
\text{C—Zn} & \quad \delta^- \quad \delta^+ \\
\text{C—Al} & \quad \delta^- \quad \delta^+ \\
\text{C—Pb} & \quad \delta^- \quad \delta^+ \\
\text{C—Sn} & \quad \delta^- \quad \delta^+ 
\end{align*}
\]
Transmetallation Reactions and the Gilman Reagent

As noted previously, a transmetallation reaction will occur when RMgCl is reacted with CdCl₂ if the bond between the metal and the carbon becomes more covalent. (Why?)

\[ 2 \text{RMgCl} + \text{CdCl}_2 \rightarrow \text{R}_2\text{Cd} + 2 \text{MgCl}_2 \]

A particularly useful example of a transmetallation reaction is the formation of the Gilman Reagent:

\[ 2 \text{RLi} + \text{CuI} \rightarrow \text{R}_2\text{CuLi} + \text{Lil} \]

**Gilman Reagent**

Gilman reagents undergo carbon-carbon bond formation reactions with a wide variety of alkyl, alkenyl, alkynyl and aryl halides (except fluorides). One of the R groups on the Gilman reagent acts as a nucleophile, displacing the halide as shown below:

\[ \text{Br} + (\text{CH}_3)_2\text{CuLi} \rightarrow \text{CH}_2\text{CH}_2\text{Br} + (\text{CH}_3)\text{Cu} + \text{LiBr} \]

\[ \text{I} + (\text{CH}_3)_2\text{CuLi} \rightarrow \text{C}_6\text{H}_5\text{I} + (\text{CH}_3)\text{Cu} + \text{LiI} \]

Gilman reagents are sufficiently mild that they can be used in molecules where other reactive functional groups are present—more next term.

\[ \text{Br} + (\text{CH}_3)_2\text{CuLi} \rightarrow \text{CH}_2\text{CH}_2\text{O} + (\text{CH}_3)\text{Cu} + \text{LiBr} \]
**Crown Ethers**

Crown ethers are a class of cyclic polyethers. Shown below are 15-crown-5 and 18-crown-6. The first number is the total number of atoms in the ring and the second number is the number of oxygens.

![Crown Ethers](image)

Crown ethers were discovered by accident by a chemist at Dupont. He soon discovered that these molecules had a strong capacity to bind metal ions.

For example, a sodium ion fits very nicely into the center cavity (1.7 - 2.2 Å) of 15-crown-5. This sodium ion binds to each of the 5 oxygens. In a similar manner, the cavities of 18-crown-6 (2.6- 3.2 Å) and 12-crown-4 (1.2 - 1.5 Å) binds potassium and lithium ions, respectively.

9. Jean-Marie Lehn from Strasbourg developed a related class of molecules known a cryptands which also bind metal ions. In the molecular systems, the crown or cryptand is known as the host and the metal ion is known as the guest.

10. This type of selective binding is now known as "**host-guest chemistry**" which is a type of supramolecular chemistry. Its importance to chemistry and biology was recognized in 1987 by the award of a Nobel Prize.
11. One important role that crown ethers play is that they can aid in the dissolution of salts in relatively nonpolar solvents. They do so because the binding of the metal cation in the crown is so energetically favorable that having a naked anion can often be achieved.

12. In this way crown ethers and cryptands used in sub-stoichiometric amounts are said to be "phase transfer catalysts" because they provide a mechanism to transfer ions from one phase (solid or aqueous) to another (relatively nonpolar solution).

13. This feature makes crown ethers very useful for SN2 reactions since the naked anions are very destabilized and therefore highly reactive.

14. Because 18-crown-6 is so efficient at binding potassium can upset the balance of free potassium in the body, which in turn, can have some very unpleasant consequences on the nervous system.