Understanding (as opposed to memorizing) mechanisms is critical to mastering organic chemistry. Although the mechanisms you encounter throughout the course may seem entirely different, they are actually related in fundamental ways. In fact, almost all of the organic reaction mechanisms you will learn are composed of only a few different individual elements (steps) that are put together in various combinations. Your job is to learn these individual mechanism elements, and then understand how to assemble them into the steps of the correct mechanism for the reactions you will see. The KEY idea is that each mechanism step should be thought of as a MULTIPLE CHOICE situation in which you evaluate the structures and reactivities of the molecules involved then rule out inappropriate elements on the way to deducing the appropriate element for each step of the mechanism.

Polar Reaction Mechanisms:
Polar reactions are most of what you will see in organic chemistry, amounting to greater than 95% of cases we will discuss. There are only a few different mechanistic elements that combine to make up the different steps of almost all the mechanisms you saw in CH320M. Better yet, in CH320N the following four mechanistic elements are pretty much all you need to think about until we get to electrophilic aromatic substitution near the end of the semester.

1. **Make a new bond between a nucleophile (source for an arrow) and an electrophile (sink for an arrow).** Use this element when there is a nucleophile present in the solution as well as an electrophile suitable for reaction to occur.

   ![Diagram of a nucleophile-electrophile reaction](image)

2. **Break a bond so that relatively stable molecules or ions are created** Use this element when there is no suitable nucleophile-electrophile or proton transfer reaction, but breaking a bond can create neutral molecules or relatively stable ions, or both.

   ![Diagram of a bond-breaking reaction](image)
3. **Add a proton**  Use this element when there is no suitable nucleophile-electrophile reaction, but the molecule has a strongly basic functional group or there is a strong acid present.

![Chemical reaction diagram](image)

- **Ethyl acetate** (a carboxylic ester)
- **Hydronium ion** (a strong acid)
- **Water**

4. **Take a proton away**  Use this element when there is no suitable nucleophile-electrophile reaction, but the molecule has a strongly acidic proton or there is a strong base present.

![Chemical reaction diagram](image)

- **Oxonium ion intermediate** (strongly acidic)
- **Water** (can act as a base)
- **2-Propanol**
- **Water**

The situation is even simpler than you might expect because 1. and 2. are the functional reverse of each other, as are 3. and 4. in many cases.

**Useful Definitions:**

- **Mechanism** – A scheme that illustrates all reaction intermediates, as well as the flow of electrons and movement of atoms during bond breaking and bond making processes. Remember that arrows are used only to indicate the movement of electrons. Movement of atoms is assumed, but not explicitly indicated, by the arrows.

- **Nucleophile** – An electron-rich species such as an atom with a lone pair or the pi bond of an alkene that reacts with an electrophile to make a new covalent bond. The nucleophile is the source for the arrow that indicates the new covalent bond being made.

- **Electrophile** – A molecule that is the sink for the arrow that indicates a new covalent bond. Electrophiles often have a full or partial positive charge as well as possessing a relatively weak bond that can be broken to accommodate the new covalent bond.

- **Bronsted-Lowry Base** – A molecule containing a lone pair (or pi bond) that will accommodate binding to a proton in a proton transfer reaction.

- **Bronsted-Lowry Acid** – A molecule that can donate a proton in a proton transfer reaction.

- **Leaving group** – A group that will be relatively stable when it departs, such as a small neutral species like H₂O or N₂, or a group such as a halide atom that departs as a relatively stable ion.
Putting it All Together:
The preceding discussion can be applied to all of the polar reaction mechanisms you will see in organic chemistry. For example, the following equation describes the conversion of a tertiary alcohol into a haloalkane under acidic conditions.

\[
\begin{align*}
\text{Br} & \quad \text{H} \\
\text{H}_3\text{C} & \quad \text{C} \quad \text{CH}_3 \\
\text{CH}_3 & + \quad \text{H} & \quad \text{Br} & \quad \text{O} & \quad \text{H} \\
\text{H}_3\text{C} & \quad \text{C} \quad \text{CH}_3 \\
\text{CH}_3 & + \quad \text{H} & \quad \text{O} & \quad \text{H}
\end{align*}
\]

3° Alcohol

Each step of the correct three-step mechanism for this process can be deduced by choosing the appropriate mechanistic element (1-7) based on the structures and reactivities of the molecules present.

**Step 1: Add a Proton** - There is no suitable nucleophile-electrophile reaction, the molecule has no good leaving groups, but there is a proton source present in the solution such as a strong acid. The alcohol oxygen atom lone pairs can accept the proton from a strong acid like HBr.

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{C} \quad \text{CH}_3 \\
\text{CH}_3 & \quad \text{Strong Acid} \\
\text{Br} & \quad \text{H} & \quad \text{O} & \quad \text{H} \\
\text{H}_3\text{C} & \quad \text{C} \quad \text{CH}_3 \\
\text{CH}_3 & + \quad \text{Br} & \quad \text{O} & \quad \text{H}
\end{align*}
\]

**Step 2: Break a bond so that relatively stable molecules or ions are created** – There is no suitable nucleophile-electrophile* or proton transfer reaction, but the molecule has a good leaving group attached.

*There is no suitable nucleophile-electrophile reaction despite the presence of a good leaving group and a good nucleophile (Br⁻) in the solution because of the steric hindrance caused by the three methyl groups around the tertiary carbon atom, preventing a backside attack required for an S_N2 reaction.

\[
\begin{align*}
\text{Br} & \quad \text{H} & \quad \text{O} & \quad \text{H} \\
\text{H}_3\text{C} & \quad \text{C} \quad \text{CH}_3 \\
\text{CH}_3 & \quad \text{Good Leaving Group} \\
\text{H}_3\text{C} & \quad \text{C} \quad \text{CH}_3 \\
\text{CH}_3 & + \quad \text{H} & \quad \text{O} & \quad \text{H}
\end{align*}
\]

These Methyl Groups Block Nucleophiles From Reacting
**Step 3: Make a new bond between a nucleophile and an electrophile** – There is a nucleophile present in the solution (water) and the molecule has an electrophilic atom (an atom with a positive charge). The nucleophile-electrophile reaction takes place because the electrophilic carbon atom is $sp^2$ hybridized (trigonal planar geometry), and the $Br^-$ can approach from either the top or bottom without interference from the methyl groups.

END OF MECHANISM

Note that steps 2 and 3 above correspond to an $S_N1$ mechanism, and that $E1$ was suppressed in this case because of the presence of the strong acid (never have a step involving base when the reaction is run in acid). Sometimes to save space, mechanisms are written in a more condensed format such as the following:
In second semester organic chemistry, the mechanisms get more complicated, but not the multiple choice type of analysis used to deduce appropriate mechanism elements for each mechanism step. For example, the following equation describes the acid-catalyzed hydrolysis of an acetal to give an aldehyde and two equivalents of alcohol.

\[
\text{Acetal} + \text{HCl} \rightarrow \text{HCHO} + 2 \text{H}_2\text{O}
\]

The following seven-step mechanism for acetal hydrolysis may look complicated, but it is actually a relatively straightforward sequence of mechanism elements 1-4 that can be deduced by analyzing each step according to the structures and reactivities of the molecules present.

**Step 1: Add a Proton** - There is no suitable nucleophile-electrophile reaction, the molecule has no good leaving groups, but there is a proton source present in the solution such as a strong acid.

**Step 2: Break a bond so that relatively stable molecules or ions are created** – There is no suitable nucleophile-electrophile or proton transfer reaction, but the molecule has a good leaving group attached.

**Good Leaving Group**

\[
\left[H_3C\text{C}H\left(\text{H}-\text{O}\text{H}+\text{H}^+\right)\right] += \left[H_3C\text{C}H\left(\text{H}_2\text{O}\right)\right] + \text{Cl}^-
\]

\[
\left[H_3C\text{C}H\right] += \left[H_3C\text{C}H\text{O}\right] + \text{H}_2\text{O}
\]

\[
\text{Resonance Delocalization Stabilization}
\]
Step 3: Make a new bond between a nucleophile and an electrophile – There is a nucleophile present in the solution (water) and the molecule has an electrophilic atom (an atom with a positive charge).

Step 4: Take a Proton Away – There is no suitable nucleophile-electrophile reaction, but the molecule has an acidic proton.

Note that the H₂O group is a good leaving group as well as being strongly acidic, but having it depart would simply reverse the previous step, so that is not a productive choice.

Step 5: Add a Proton - There is no suitable nucleophile-electrophile reaction, the molecule has no good leaving groups, but there is a proton source present in the solution such as a strong acid.

Hemiacetal Intermediate
**Step 6: Break a bond so that relatively stable molecules or ions are created** – There is no suitable nucleophile-electrophile or proton transfer reaction, but the molecule has a good leaving group attached.

Note that the CH₃OH group is strongly acidic as well as being a good leaving group, but taking a proton away would simply reverse the previous step, so that is not a productive choice.

**Step 7: Take a Proton Away** – There is no suitable nucleophile-electrophile reaction, the molecule has no good leaving groups, but it has an acidic proton.

**END OF MECHANISM**

Complex mechanisms such as this are often written in one of several condensed formats. Here is one such format in which the mechanism is drawn in a linear fashion:
Here is an alternative format that is similar to the one we will use in class:
Here are the keys to understanding mechanisms in 320N!!

1) There are basically four different mechanisms elements that make up the steps of carbonyl reactions.  
   A) Make a bond between a nucleophile and an electrophile  
   B) Break a bond to give stable molecules or ions  
   C) Add a proton  
   D) Take a proton away

2) These same four mechanism elements describe most of the other mechanisms you have/will learn!!! (Yes, organic chemistry really is this simple if you look at it this way!!)

There are basically four different mechanisms that describe the vast majority of carbonyl reactions, which are different combinations/ordering of the four mechanism elements listed above. In this class, I have termed them "Mechanism A", "Mechanism B", "Mechanism C", and "Mechanism D". They all involve a nucleophile attacking the partially positively charged carbon atom of the carbonyl to create a tetrahedral intermediate. Different reaction mechanisms are distinguished by the timing of protonation of the oxygen atom as well as the presence or absence of a leaving group attached to the carbonyl.

Four Mechanisms for the Reaction of Nucleophiles with Carbonyl Compounds

MECHANISM A: Reaction with a Strong Nucleophile

Step 1 Make a new bond between a nucleophile and electrophile

\[ \text{Nu}^- + R-C=Y \rightarrow \text{Tetrahedral Intermediate} \]

Step 2 Add a proton

\[ \text{Tetrahedral Intermediate} \rightarrow \text{Nu}^- + R-C=Y + A^+ \]

Here H-A is a weak acid such as water

MECHANISM B: Reaction with a Strong Nucleophile When "Y" is a Good Leaving Group (-OR, -Cl, etc.).

Step 1 Make a new bond between a nucleophile and electrophile

\[ \text{Nu}^- + R-C=Y \rightarrow \text{Tetrahedral Intermediate} \]

Step 2 Break a bond to give stable molecules or ions

\[ \text{Tetrahedral Intermediate} \rightarrow \text{Nu}^- + R-C=Y + Y^+ \]

MECHANISM C: Reaction with a Weak Nucleophile

Step 1 Make a new bond between a nucleophile and electrophile

\[ \text{H-Nu}^- + R-C=Y \rightarrow \text{Tetrahedral Intermediate} \]

Step 2 Add a proton and Take a proton away

\[ \text{Tetrahedral Intermediate} \rightarrow \text{Nu}^- + R-C=Y + Y^+ \]

Note: this proton transfer can actually take place in two steps, i.e. Add a proton then Take a proton away or vice versa.
MECHANISM D: Reaction with a Weak Nucleophile in the Presence of Acid (H-A)

Step 1 Add a proton

\[
\begin{align*}
\text{R}^+\text{C}^-\text{Y} & \quad \text{H}^+ \quad \text{A}^- \\
\text{R}^-\text{C}^-\text{Y} & \quad \text{R}^-\text{C}^-\text{Y} + \text{A}^- \\
\end{align*}
\]

Step 2 Make a new bond between a nucleophile and electrophile

\[
\begin{align*}
\text{R}^+\text{C}^-\text{Y} & \quad \text{H}^- \quad \text{Nu}\_1 \quad \text{R}^-\text{C}^-\text{Y} \\
\text{R}^-\text{C}^-\text{Y} & \quad \text{R}^-\text{C}^-\text{Y} + \text{H}^- \quad \text{Nu}\_1 \\
\text{Tetrahedral Intermediate} & \quad \text{Tetrahedral Intermediate} \\
\end{align*}
\]

Step 3 Take a proton away

\[
\begin{align*}
\text{R}^+\text{C}^-\text{Y} & \quad \text{H}^- \quad \text{Nu}\_1 \quad \text{R}^-\text{C}^-\text{Y} + \text{H}-\text{A} \\
\text{R}^-\text{C}^-\text{Y} & \quad \text{R}^-\text{C}^-\text{Y} + \text{H}-\text{A} \\
\text{Tetrahedral Intermediate} & \quad \text{Tetrahedral Intermediate} \\
\end{align*}
\]

Here H-A is a strong acid such as H-Cl
Grignard Reagent Reacting with an Epoxide

\[
\begin{align*}
\text{H}_3\text{C}&-\text{CH}_2\text{MgBr} + \\
\text{H}_3\text{C}
\end{align*}
\]

Chemist opens flask and adds acidic water

Key Recognition Element (KRE):

\[
\begin{align*}
\text{H}_3\text{C}&-\text{CH}_2\text{MgBr} + \\
\text{H}_3\text{C}
\end{align*}
\]

Products

\[
\begin{align*}
\text{H}_3\text{C}&-\text{CH}_2\text{MgBr} + \\
\text{H}_3\text{C}
\end{align*}
\]
Grignard Reagent Reacting with an Aldehyde or Ketone

Key Recognition Element (KRE):

1) CH₃CH₂MgBr
2) HCl / H₂O

O
H
H₃C
O
1) CH₃CH₂MgBr
2) HCl / H₂O

H₃C
O
H
H₃C
H
1) CH₃CH₂MgBr
2) HCl / H₂O

O
H
H₃C
O
1) CH₃CH₂MgBr
2) HCl / H₂O
Alkyne Anion Reacting with an Aldehyde or Ketone

\[
\text{H}_3\text{C} - \text{H} + \text{Na}^+ \text{NH}_2 \rightleftharpoons \text{H}_3\text{C}^{:\text{O}:} + \text{NH}_2^+ \text{Na}^+
\]

\[
\text{Tetrahedral Intermediate}
\]

Key Recognition Element (KRE):

\[
2) \text{H} - \text{Cl} : / \text{H}_2\text{O} \rightleftharpoons \text{Products}
\]
HCN Reacting with an Aldehyde or Ketone

H₃C

Key Recognition Element (KRE):

Tetrahedral Intermediate

Products
Wittig Reaction

Key Recognition Element (KRE):

Products

Phosphonium salt

n-Butyl lithium (n-BuLi)

Phosphonium ylide

Betaine intermediate

Oxaphosphetane intermediate
Acid Catalyzed Hemiacetal and Acetal Formation From an Aldehyde or Ketone

Key Recognition Element (KRE):

Products
Formation if an Imine (Schiff Base) From an Aldehyde or Ketone Reacting with an Amine

Key Recognition Element (KRE):

Note: this last step might actually occur as two steps in some cases.

* "Proton Transfer" refers to a situation in which a proton moves from one part of a molecule to another on the SAME MOLECULE. We do not draw arrows for proton transfer steps because that would be deceptive. In some cases, the same proton may move from one part of the molecule to the other directly, but in other cases, solvent molecules may be involved as indicated in the following scheme. To make things even more interesting, the following two steps might even be reversed in some cases. Because of all the ambiguity, we just write "Proton Transfer" and do not bother with arrows.
Wolff-Kishner Reduction of an Aldehyde or Ketone

Imine formation mechanism

Several steps

Resonance Stabilized Anion

Key Recognition Element (KRE):

Products
**Keto-Enol Equilibrium Catalyzed by Acid or Base**

**Acid**

\[ \text{Keto form} \quad \xrightarrow{\text{H--A}} \quad \text{Enol} \]

\[ \alpha\text{-hydrogen } pK_a = 18-20 \]

**Base**

\[ \text{Keto form} \quad \xrightarrow{\text{A--}} \quad \text{Resonance Stabilized Enolate Anion} \]

\[ \text{Enol} \]

For both aldehydes and ketones, the keto form predominates at equilibrium, because ____________ bonds are stronger than ________________ bonds.

Enols are significant, however, because they react like ________________, not carbonyls, and this is important in certain situations.
α-Halogenation of an Aldehyde or Ketone Catalyzed by Acid
Fischer Esterification
Reaction with Thionyl Chloride

Decarboxylation of a β-Keto Acid
The Haloform Reaction

\[
\begin{align*}
\ce{H3C\(\overset{\text{O}}{\text{C}}\text{H}\text{H}} & \xrightleftharpoons{\text{Resonance Stabilized Enolate Anion}} \xrightarrow{\text{Two more times}} \\
\ce{\overset{\text{O}}{\text{H}}} & \xrightarrow{\text{Acid-base reaction}} \text{Products}
\end{align*}
\]

Keto form

\(\alpha\)-hydrogen \(pK_a = 18-20\)
**Keto-Enol Tautomerization vs. Enolate Resonance**

**Keto-Enol Tautomerization**

\[
\begin{array}{c}
\text{Keto form} \\
\text{Enol}
\end{array}
\]

**Enolate Resonance**

\[
\begin{array}{c}
\text{Keto form} \\
\text{Resonance Stabilized Enolate Anion}
\end{array}
\]

\(\alpha\)-hydrogen \(pK_a = 18-20\)

**Diazomethane reaction**

\[
\begin{array}{c}
\text{Diazomethane contributing structures}
\end{array}
\]

**Amide Resonance \ VERY IMPORTANT!!!!!**

\[
\begin{array}{c}
\end{array}
\]
Interconversion of Carboxylic Acid Derivatives
Acid Catalyzed Anhydride Hydrolysis

Products
Acid Catalyzed Ester Hydrolysis

Products
Microscopic Reversibility: Acid Catalyzed Ester Hydrolysis-Fischer Esterification
Microscopic Reversibility: Acid Catalyzed Ester Hydrolysis-Fischer Esterification

Diagram showing the reaction mechanisms involving the conversion between ester and carboxylic acid structures, accompanied by the depiction of racemic molecules.
Microscopic Reversibility: Acid Catalyzed Ester Hydrolysis-Fischer Esterification

\[ \text{Racemic} \]

\[ \text{O} \]
Microscopic Reversibility: Acid Catalyzed Ester Hydrolysis-Fischer Esterification

1. Initial Ester Structure
2. Acid Catalyzed Hydrolysis
3. Fischer Esterification
4. Racemic Product
5. Isolated Reactant
Base-Promoted Ester Hydrolysis - Saponification

\[
\begin{align*}
\text{Products} & \\
\text{Base-Promoted Ester Hydrolysis} & \\
\text{2) } & \\
\end{align*}
\]
Acid Promoted Amide Hydrolysis

Products
Acid Promoted Nitrile Hydrolysis

tautomerization

several steps
(see amide hydrolysis mechanism)

Products
Acid Chlorides Reacting with Amines

\[ \text{H}_2\text{N} \rightleftharpoons \text{CH}_3 \]

Proton transfer

\[ \text{H}_2\text{N} \rightleftharpoons \text{CH}_3 \]

Products
Grignard Reacting with Esters

Chemist Opens Flask

Products
Grignard Reacting with Esters

[Diagrams of chemical reactions involving Grignard reagents reacting with esters, showing mechanisms A and B, with steps involving bond making and breaking, and the formation of products and Mg salts.]
Reduction of Esters with LiAlH₄

Chemist Opens Flask

2) 

Products
Reduction of Esters with LiAlH$_4$

Chemist Opens Flask

2) \[ \text{O} \]

\[ \text{O} \]

H

H

H

H

H

H

H

The second alcohol comes from this alkoxide that is also protonated in water

Products

Aluminum salts
Reduction of Amides with LiAlH₄

Note: In this reaction the chemist opens the flask and adds water in a second step that quenches any excess LiAlH₄. Therefore, you need a second step to add water when using this reaction in synthesis even though it is not shown in the mechanism above.
Interconversion of Carboxylic Acid Derivatives
Aldol Reaction

Products

Draw both enantiomers
Acid catalyzed dehydration

Aldol product

tautomerization

H

H

O

O

H

H

H

H

Products
Claisen Condensation

Initial Products

No chiral centers in this case

Draw both enantiomers

(Chemist opens flask and adds a mild acid)

2) Mild

Final Products
Enamine Formation

\[ \text{Enamine} \quad \text{Formation} \]

\[ \text{Product} \]

\[ \text{Proton} \quad \text{Transfer} \]

\[ \text{Slightly Acidic pH} \]

\[ \text{Products} \]
**Michael Reaction**

1. **Initial Products**

   - [Chemical structure of initial products]

   - [Text: 1 Equivalent (NaOEt)]

2. **Reaction**

   - [Chemical structure of intermediate products]

   - [Chemical structure of intermediate products]

   - [Text: tautomerization]

3. **Final Products**

   - [Chemical structure of final products]

   - [Text: (Chemist opens flask and adds a mild acid)]

4. **Finall Products**

   - [Chemical structure of final products]
β-Substituted aldehydes, nitriles, ketones, or esters

α,β-Unsaturated, nitriles, ketones, or esters

β-Keto esters

α,β-Unsaturated aldehydes

β-Keto esters

β-Hydroxy aldehydes

Acid Chlorides

Aldehydes

Ketones

Carboxylic esters

β-Ketoaldehyde

β-Diketone

Carboxylic acids

Substituted aldehyde

Substituted ketone

β-Diester
Enolate KRE’s. Identify the KRE’s and the new C-C bonds
H-X reacting with conjugated dienes

1,2 Addition

1,4 Addition - more stable, more highly substituted C=C

Products
Aromatic resonance stabilization of charged species

Phenoxide anion

Benzyl cation

Benzyl radical
Reagents

**HaloGenation** $X_2$, $FeX_3$

\[
\begin{array}{c}
\text{Fe} \quad X \quad : X \\
\text{Fe} \quad : X \\
: X \quad : X \\
\end{array} \quad \rightarrow \quad \left[ \begin{array}{c}
\text{Fe} \quad X \quad : X \\
\text{Fe} \quad : X \\
: X \quad : X \\
\end{array} \right] \quad \rightarrow \quad X^+ \quad FeX_4^– \\
\]

\(X = \text{Br, Cl}\)

**Nitration** $H_2SO_4/HNO_3$

\[
\begin{array}{c}
\text{H} \\
\text{O} \\
\text{S} \\
\text{O} \\
\text{O} \\
\text{H} \\
\end{array} \quad \rightarrow \quad \left[ \begin{array}{c}
\text{H} \\
\text{O} \\
\text{S} \\
\text{O} \\
\text{O} \\
\text{N} \\
\text{O} \\
\end{array} \right] \quad \rightarrow \quad \text{H} \quad \text{O} \\
\]

**Sulfonation** $H_2SO_4/SO_3$

\[
\begin{array}{c}
\text{H} \\
\text{O} \\
\text{S} \\
\text{O} \\
\text{O} \\
\text{H} \\
\end{array} \quad \rightarrow \quad \text{H} \quad \text{O} \\
\]

Fuming sulfuric acid contains both of the above reagents, the $SO_3$ is the important one.

Wicked strong electrophile

\[\text{E}^+\]

\[X^+\]
Reagents

**Friedel-Crafts Alkylation** $\text{R-X, AlX}_3$

$$
\begin{array}{c}
\text{Al} \\
\text{Cl} \\
\text{R} \\
\end{array}
\quad \text{E}^+ \\
\quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \ quad
Arenium ion \textit{stabilizing} interactions

A) \textbf{Pi donation}, a resonance effect for atoms with lone pairs attached to the ring

\begin{align*}
\text{Electrophile} & \leftrightarrow \text{Electrophile} \\
\end{align*}

B) \textbf{Hyperconjugation} for alkyl groups attached to the ring

\begin{align*}
\text{Electrophile} & \leftrightarrow \text{Electrophile} \\
\text{Side view} & \\
\end{align*}

Arenium ion \textit{destabilizing} interaction

A) \textbf{Inductive effect} of electronegative atoms or groups attached to the ring

\begin{align*}
\text{Electrophile} & \\
\end{align*}
ORTHO

META

PARA
ORTHO

META

PARA

Electrophile

Electrophile

Electrophile
Nucleophilic Aromatic Substitution

Products

Meisenheimer complex
Preparation of Diazoniums, The "Mr. Bill" Reaction

\[
\begin{align*}
Na^+ \Theta & \quad :\tilde{\cdots} \tilde{\cdots} \quad \tilde{\cdots} \\
H-\tilde{\cdots} & \\
\end{align*}
\]

\[
\begin{align*}
\text{The Mr. Bill reagent} & \\
\text{Several Steps} & \\
\end{align*}
\]

\[
\begin{align*}
\text{tautomerization} & \\
\text{Products} & \\
\end{align*}
\]
This can be another sugar!

Acetal product
(A glycosidic bond if this were a carbohydrate)

Cyclic hemiacetal
(a stable species)

Cyclic hemiacetal
(a stable species)

Cyclic hemiacetal
(a stable species)
Solid Phase Peptide Synthesis

Repeat as necessary then remove from resin. Can add up to 100 amino acids this way.
Solid Phase Synthesis of DNA

Mix then wash beads

Add I\(_2\) to oxidize P atom
Wash resin
Remove protecting group
Fig. 10  FDA approved HIV-1 protease inhibitors.