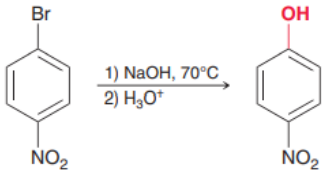
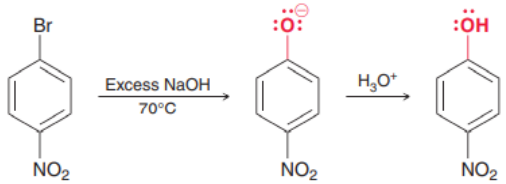
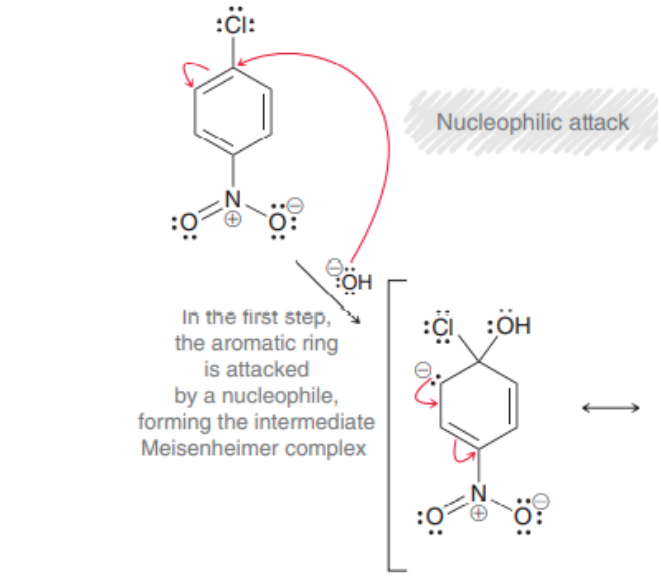
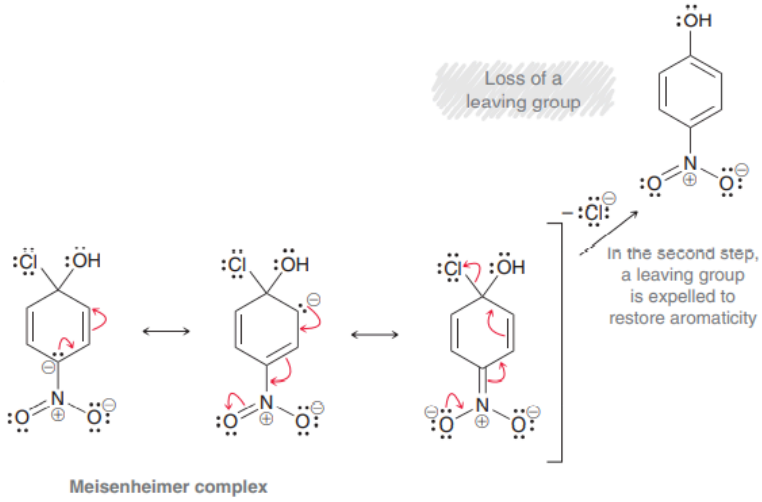
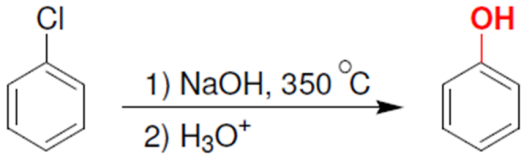
Reference Sheet 5: Organic Chemistry II Mechanisms Part III

Reaction(s) & Example(s)	Reagent(s)	Example Mechanism(s)
Nucleophilic Aromatic Substitution An aromatic compound is treated with a strong nucleophile (hydroxide), which displaces a leaving group (bromide):  **Notably, there are <u>three</u> criteria in order for this to occur:** **1. A ring must be electron poor; (a ring must be substituted with a <u>strong</u> electron withdrawing group, typically a nitro group).** **2. There must be a good leaving group (usually a halide).** **3. The leaving group must be positioned ORTHO or PARA to the withdrawing group. (If the leaving group is meta to the nitro group, the reaction is not observed).** **Also, consider that when hydroxide is used as the attacking nucleophile, the resulting product is a substituted phenol, which will be deprotonated by hydroxide to give a phenolate ion. Therefore, acid is required in a separate step to protonate the phenolate ion and obtain a neutral product:**  	1) NaOH, 70°C → 2) H_3O^+	  Note: Consider that the OH group on the substance made in the first step gets deprotonated. In the second step, the negatively charged oxygen gets protonated by H_3O^+. (See protonation mechanism in **Reference Sheet 3** for the second part of the mechanism).

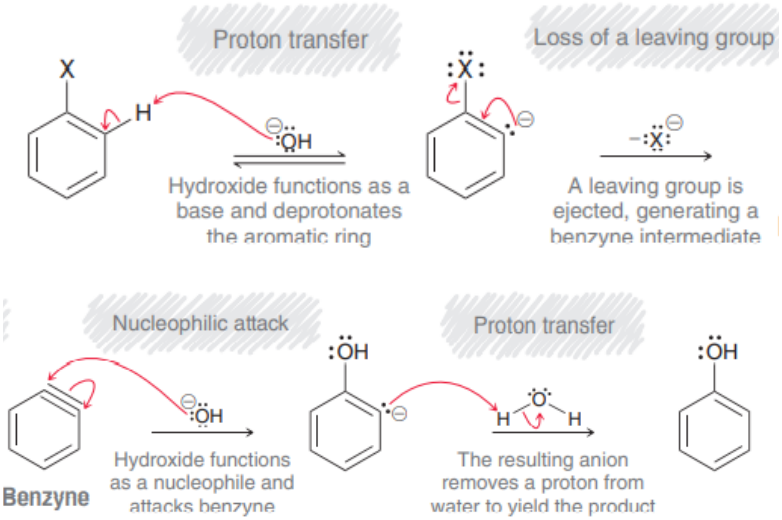
Elimination Addition: Adding a Hydroxyl Group

One could add an OH group to a halobenzene ring that doesn't contain a strong electron withdrawing group; (noting that significantly harsher conditions are required here):



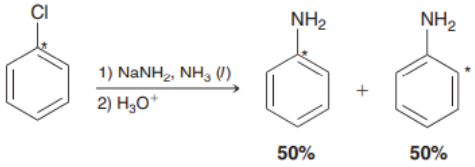
Addition of an OH:

1) NaOH, 350°C
→
2) H_3O^+

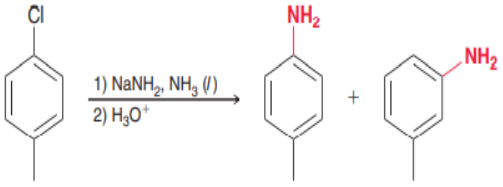


Elimination Addition of an Amino Group

Adding an NH_2 group to a halobenzene ring could occur much better here compared to the addition of a hydroxyl group; nevertheless, if there are any additional groups attached to the halobenzene ring, this causes multiple products to form:

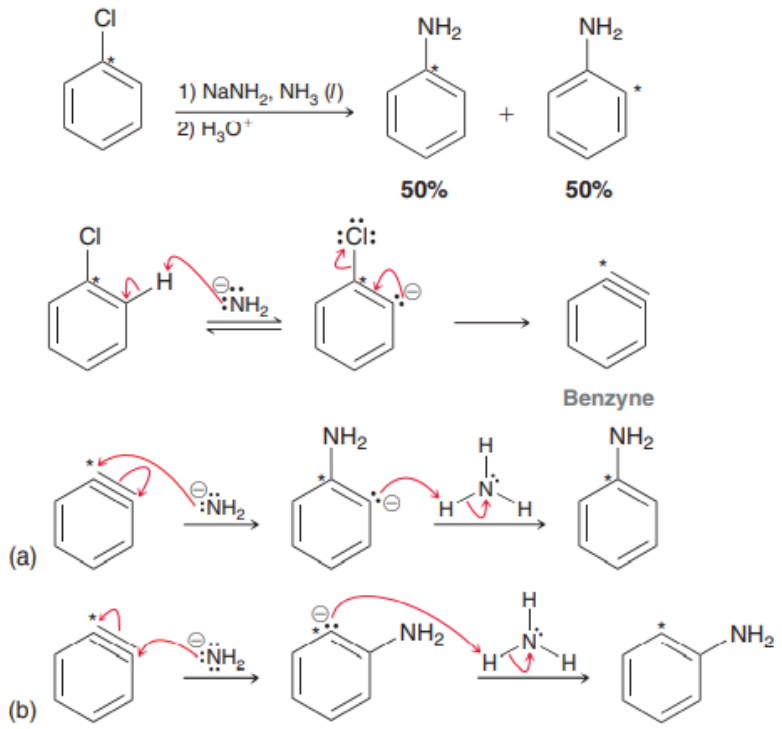


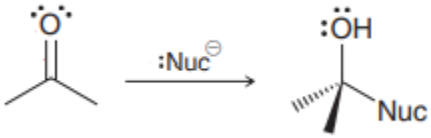
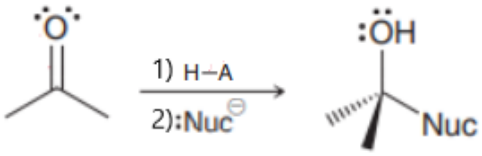
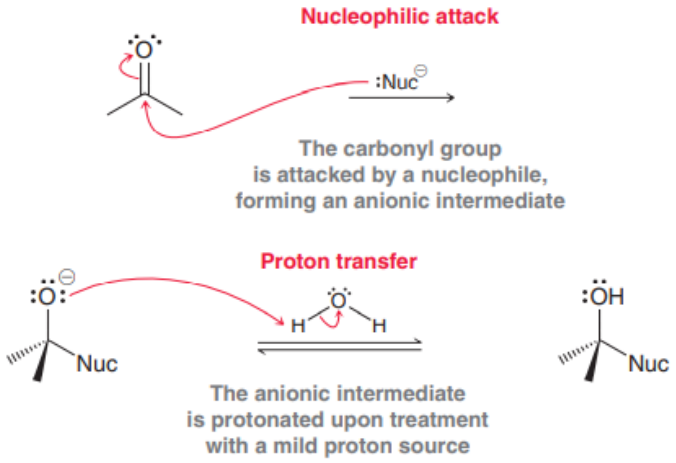
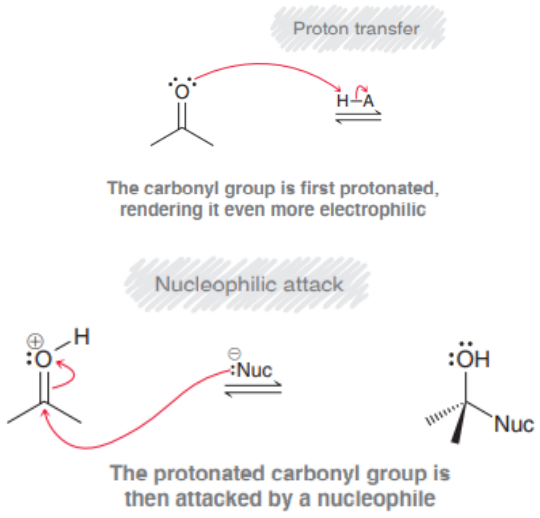
Notably, the products above are identical, but the mechanisms of each product differs (see mechanism example on the right).



Addition of an amino group:

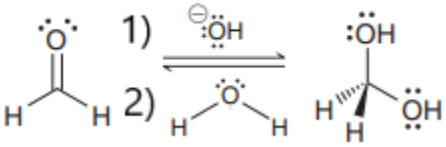
1) $NaNH_2$, NH_3 (liquid)
→
2) H_3O^+



<u>Benzyne Reaction</u> Benzyne is allowed to react with a diene via a Diels Alder Reaction:  	N/A	#(See mechanism in the "Reaction(s) and Example(s)").
<u>Nucleophilic Addition upon a Carbonyl</u> If the nucleophile is strong enough to attack and **NOT** a good leaving group, then the full addition will occur:  Notably, the reaction above will be under basic conditions. However, with a weak nucleophile, the presence of an acid makes the carbonyl more attractive to the nucleophile so the full addition occurs:  	<u>Basic Conditions w/ Carbonyl:</u> Strong Nucleophile → <u>Acidic Conditions w/ Carbonyl:</u> 1) Acid (A-H) → 2) Weak Nucleophile	<u>Nucleophilic Addition: Basic Conditions w/ Carbonyl:</u>  <u>Nucleophilic Addition: Acidic Conditions w/ Carbonyl:</u> 

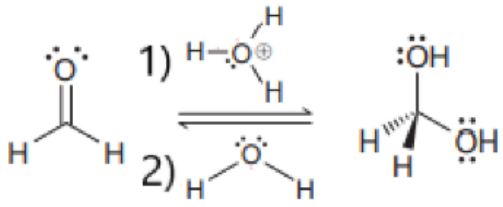
Hydrate Formation

When an aldehyde or ketone is treated with water, the carbonyl group can be converted into a hydrate. This could be effectively achieved via Base-Catalyzed Hydration:



Note: Under basic conditions, a mechanism will only be reasonable if it avoids the use or formation of strong acids (only weak acids can be employed).

This could also be achieved by Acid-Catalyzed Hydration:



Note: Under acidic conditions, a mechanism will only be reasonable if it avoids the use or formation of strong bases (only weak bases can be employed).

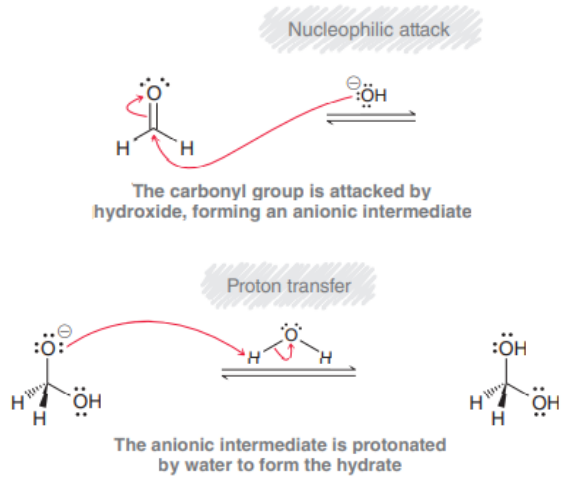
Base-Catalyzed Hydration:

1) NaOH
→
2) H_2O

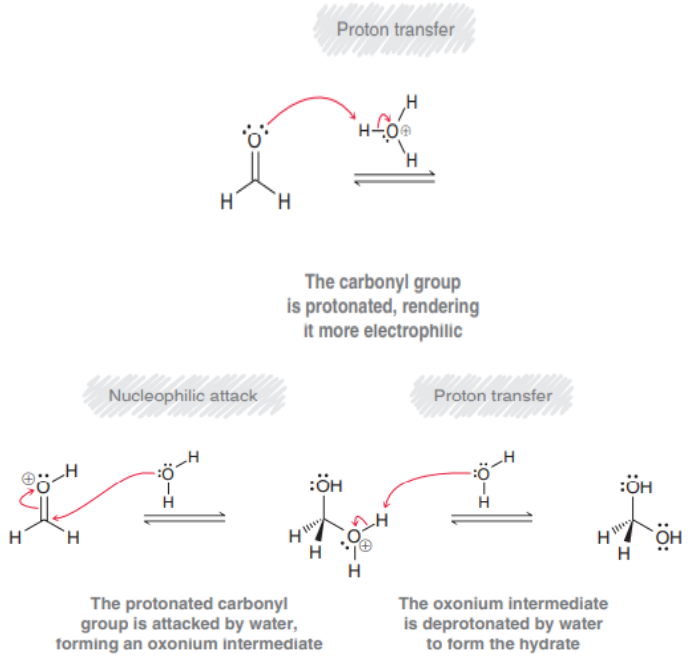
Acid-Catalyzed Hydration:

1) H_3O^+
→
2) H_2O

Base-Catalyzed Hydration:

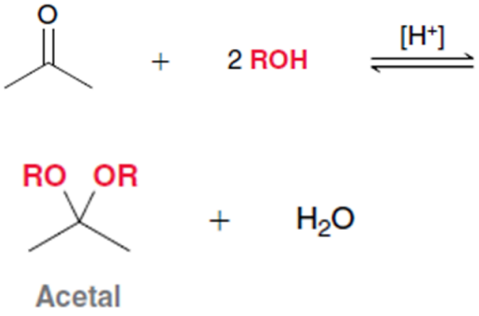


Acid-Catalyzed Hydration:



Acetal Formation

In acidic conditions, an aldehyde or ketone will react with two molecules of alcohol to form an acetal:



Note: One could use an acetal to selectively protect an aldehyde or ketone from reacting in the presence of other electrophiles.

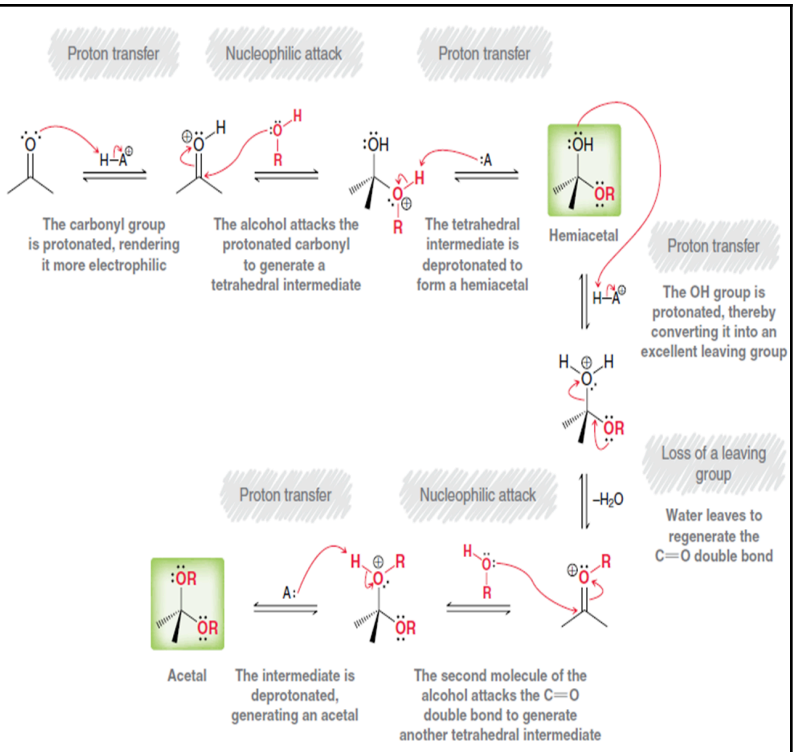
Ketone or Aldehyde w/ Alcohol:

$[H^+]$
→

*Note: $[H^+]$ is a Proton Source.

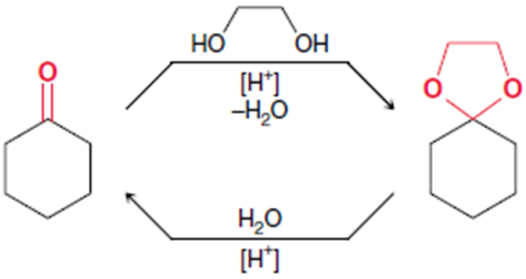
OR

H_3O^+
→



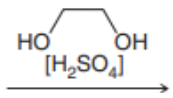
Cyclic Acetal Formation

Ethylene glycol can be used to convert an aldehyde or ketone into an acetal. The acetal group can be used to protect aldehydes and ketones. The acetal group is stable to basic conditions, but is removed when subjected to aqueous acidic conditions to regenerate the carbonyl group (AKA hydrolysis):



Note: This process is reversible!!! (Acetals act as protecting groups of ketones and aldehydes from reagents like LAH). :O

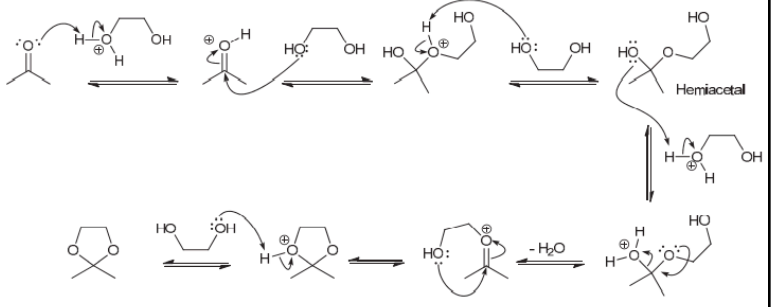
Typical Cyclic Acetal Formation:



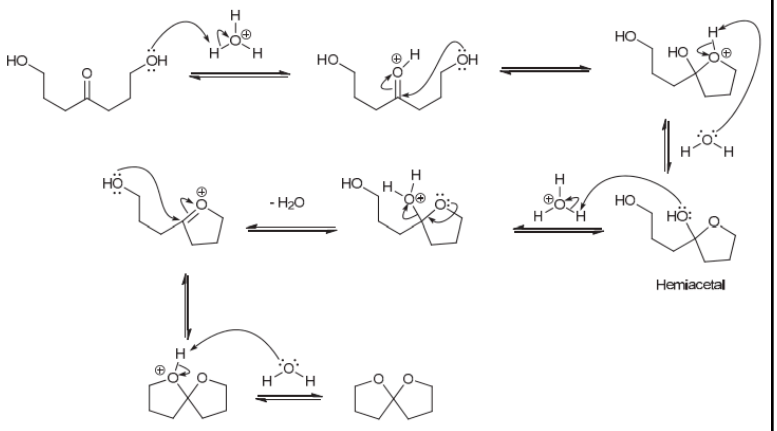
Intramolecular Cyclic Acetal Formation:

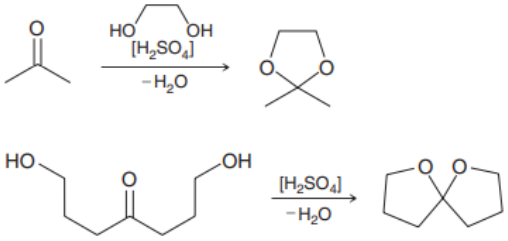
$[H_2SO_4]$
→

Typical Cyclic Acetal Formation:



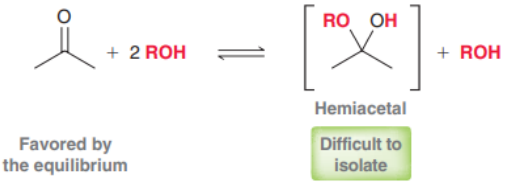
Intramolecular Cyclic Acetal Formation:

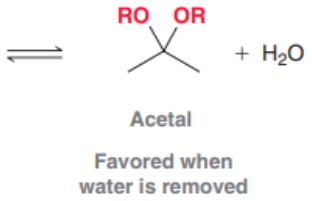




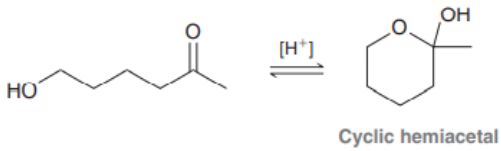
Formation of a Hemiacetal

As mentioned above, one could convert an aldehyde or ketone into an acetal. In most cases, it is very difficult to isolate the intermediate hemiacetal:

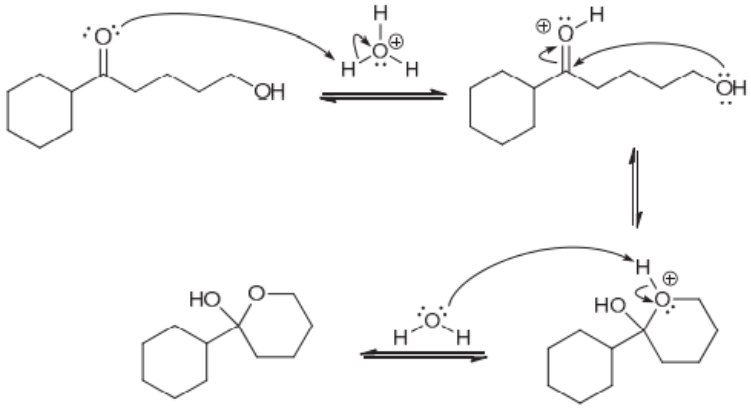




However, when a compound contains both a carbonyl group and a hydroxyl group, the resulting cyclic hemiacetal can often be isolated:

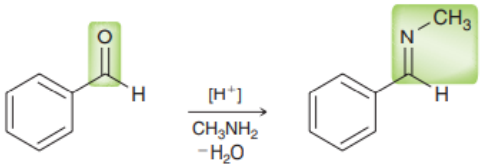


$[H_2SO_4]$
→



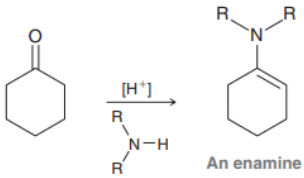
Formation of an Imine and an Enamine

In mildly acidic conditions, an aldehyde or ketone will react with a primary amine to form an imine (compounds that possess a C=N double bond):

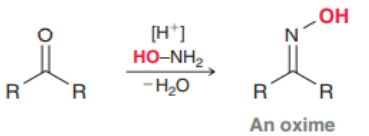


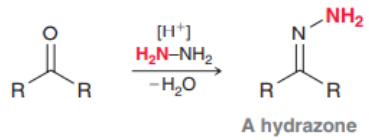
It is essential to note that one could also form an imine using a methyl amine (NH_3) as well.

However, if one were to utilize a secondary amine instead of a primary amine, one would form an enamine instead:



Many different compounds of the form RNH2 will react with aldehydes and ketones, including compounds in which R is not an alkyl group. In the following examples, the R group of the amine has been replaced with a group that has been highlighted in red:





Formation of an Imine:

#See reagents below*

[H^+] (**OR** [TsOH])
→
Primary Amine (**OR** Methyl Amine)

Formation of an Enamine:

#See reagents below*

[H^+] (**OR** [TsOH])
→
Secondary Amine

Formation of an Oxime:

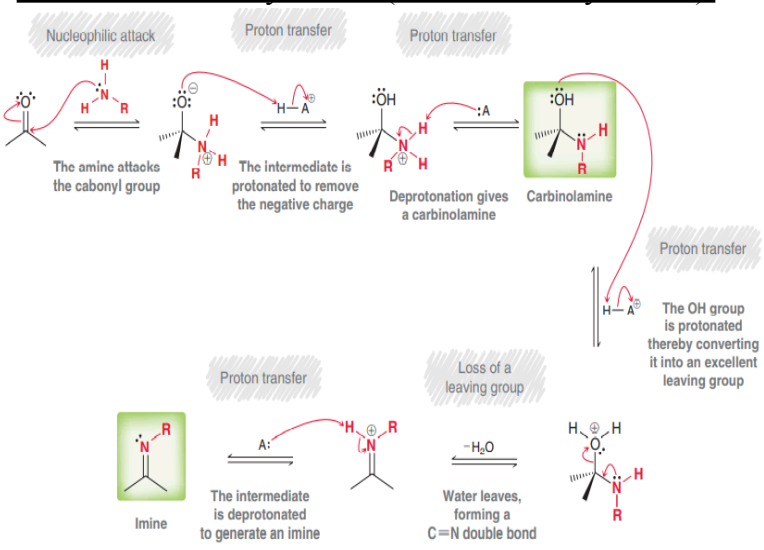
[H^+] (**OR** [TsOH])
→
OH-NH_2

Formation of a Hydrazone:

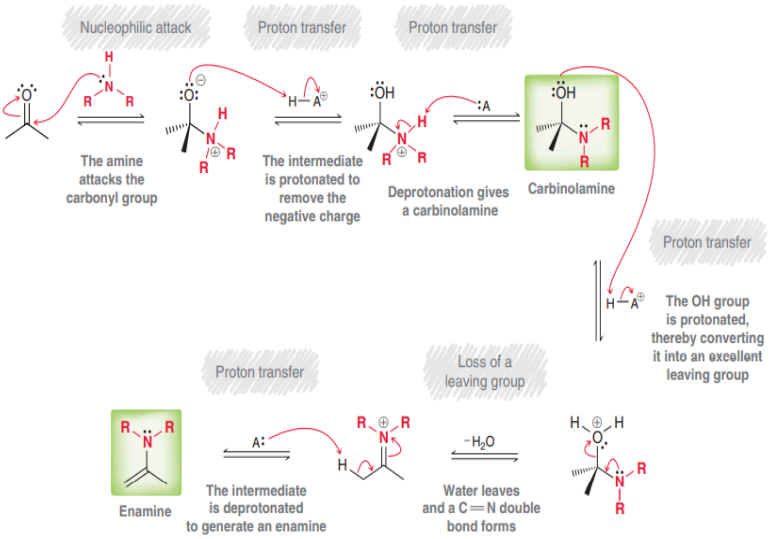
[H^+] (**OR** [TsOH])
→
H_2N-NH_2

#(Note: The mechanism requires an acid catalyst. Note that the optimal

Reaction w/ Primary Amine (or even a methyl amine):

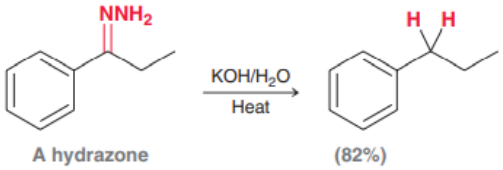
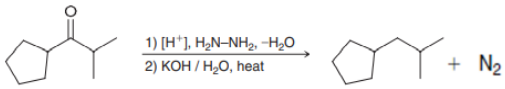
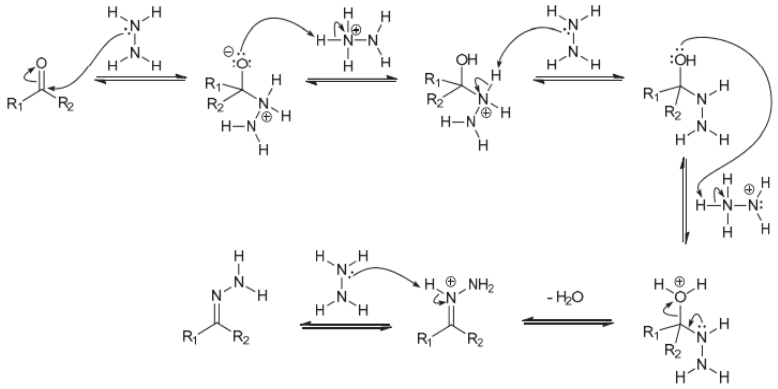
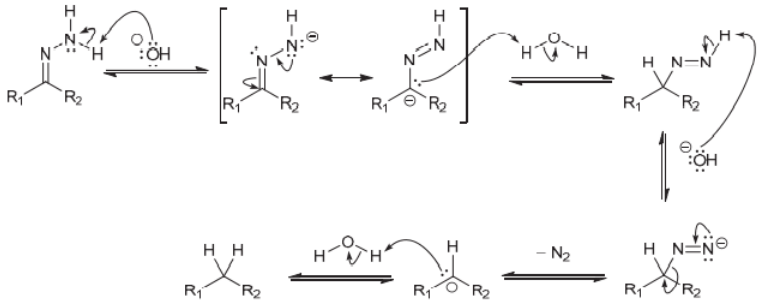


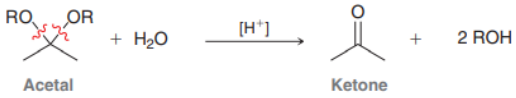
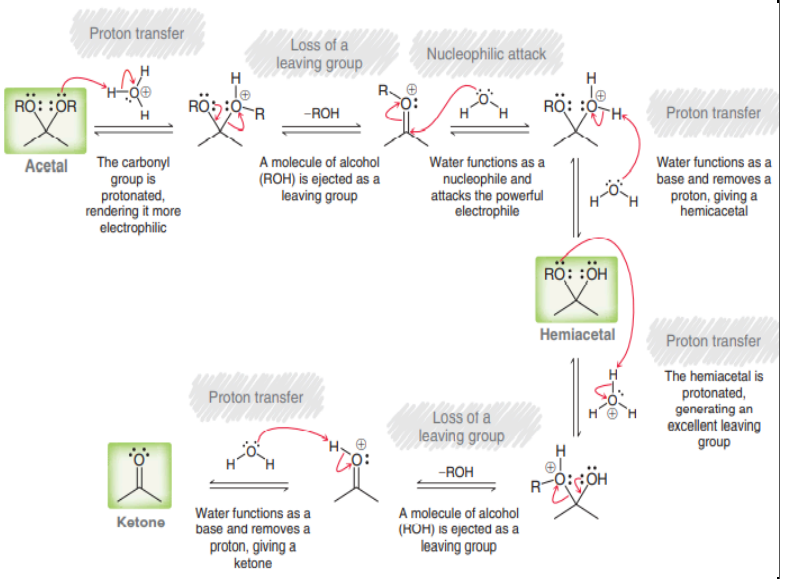
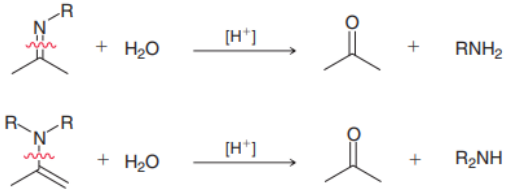
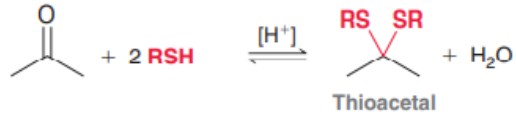
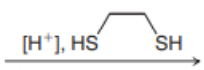
Reaction w/ Secondary Amine:

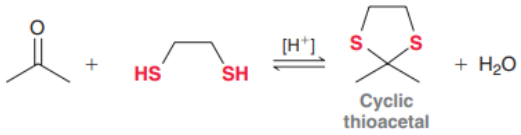
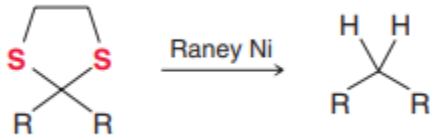
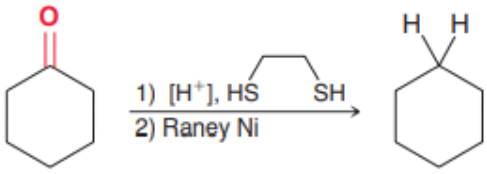
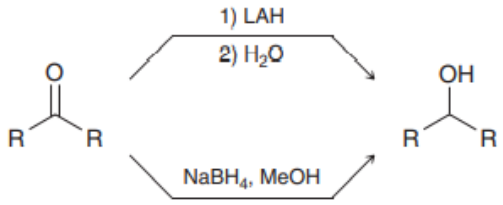
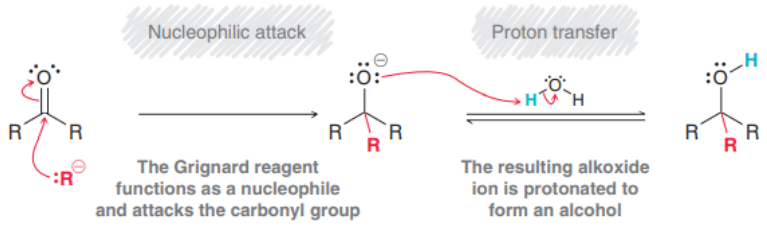


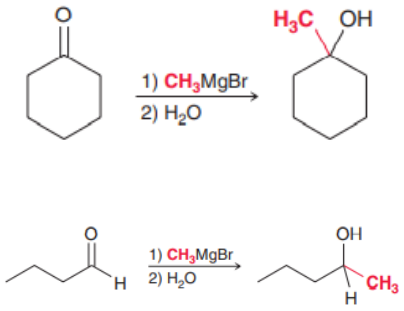
Formation of an Oxime: N/A

Formation of a Hydrazone: N/A

	pH to achieve a fast reaction is around 4 or 5).	
<u>Wolff-Kishner Reduction</u> Here, hydrazones are readily reduced under strongly basic conditions (converting a hydrazone to an alkane):  One could also use the Wolff-Kishner Reduction to assist in converting a ketone into an alkane:  	KOH → H_2O, heat	<u>Reducing a Ketone:</u> Part 1:  Part 2: ***Note that the second part of the mechanism (converting the hydrazone into an alkane) <u>is the Wolff-Kishner Reduction Mechanism</u>):** 

<u>Hydrolysis of Acetals</u> Reacting an acetal with aqueous acid results in the corresponding aldehyde or ketone:  	H_3O^+ →	
<u>Hydrolysis of Imines and Enamines</u> Imines and enamines also undergo hydrolysis when treated with aqueous acid, and the red wavy lines (below) indicate the bonds that undergo cleavage:  	H_3O^+ →	**^(See "<u>Hydrolysis of Acetals</u>" for mechanism example)^**
<u>Sulfur Nucleophiles</u> In acidic conditions, an aldehyde or ketone will react with two equivalents of a thiol to form a thioacetal:  The mechanism of this transformation is directly analogous to acetal formation, with sulfur atoms taking the place of oxygen atoms. If a compound with two SH groups is used, a cyclic thioacetal is formed:	Ketone or Aldehyde w/ Thiol: H_3O^+ → Typical Cyclic Thioacetal Formation:  	<u>Thioacetal Formation:</u> ***(See "<u>Acetal Formation</u>" for mechanism).*** <u>Cyclic Thioacetal Formation:</u> ***(See "<u>Cyclic Acetal Formation</u>" for mechanism).***

		
<u>Desulfurization</u> When any thioacetal is treated with Raney nickel, this results in an alkane:  One could utilize this reagent in the assistance of reducing a ketone into an alkane: 	Raney Ni →	**<u>Desulfurization & Second Step of Reducing a Ketone</u>: N/A!** <u>First Step of Reducing a Ketone:</u> ***See "<u>Wolff-Kishner Reduction</u>" mechanism (first part of reducing a ketone; <u>NOT</u> the second part)!***
<u>Hydrogen Nucleophiles</u> When treated with a hydride reducing agent, such as lithium aluminum hydride (LAH) or sodium borohydride (NaBH4), aldehydes and ketones are reduced to alcohols: 	$NaBH_4$ → EtOH, MeOH, or H_2O **OR** 1) LAH → 2) H_2O **(OR dilute HCl (aq))**	***(See "<u>Alcohol Prep via Reduction</u>" in Reference Sheet 4 Part I for mechanism)!***
<u>Grignard Reagents</u> When treated with a Grignard reagent, aldehydes and ketones are converted into alcohols, accompanied by the formation of a new C-C bond:	1) RMgBr → 2) H_2O	

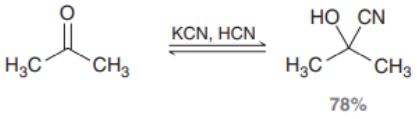


Cyanohydrin Formation

When treated with hydrogen cyanide (HCN), aldehydes and ketones are converted into cyanohydrins, which are characterized by the presence of a cyano group and a hydroxyl group connected to the same carbon atom:

A cyanohydrin

This process can be reversible:

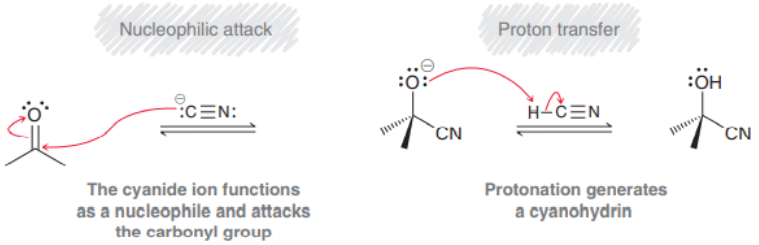


Formation of a Cyanohydrin:

KCN, HCN
→

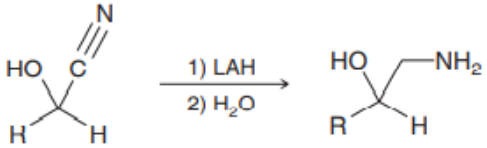
OR

KCN, HCl
→



Cyanohydrin Reaction

One could utilize a cyanohydrin in this way: one could reduce the cyano group to an amino group:



Formation of an Amine:

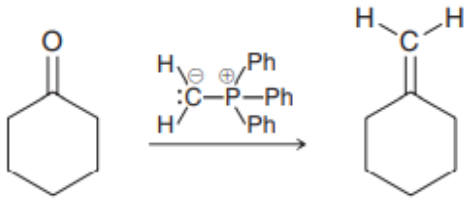
1) LAH
→
2) H_2O

Formation of an Amine:

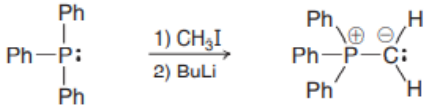
(See "Alcohol Prep via Reduction" in Reference Sheet 4 Part I for mechanism)!

Wittig Reaction

This reaction can be used to convert a ketone into an alkene by forming a new C-C bond at the location of the carbonyl group:



Notably, one could prepare a Wittig Reagent by treating triphenylphosphine with an alkyl halide followed by a strong base:

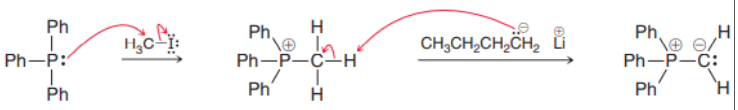


Triphenylphosphine — Wittig reagent

Wittig Reaction (given a ketone):

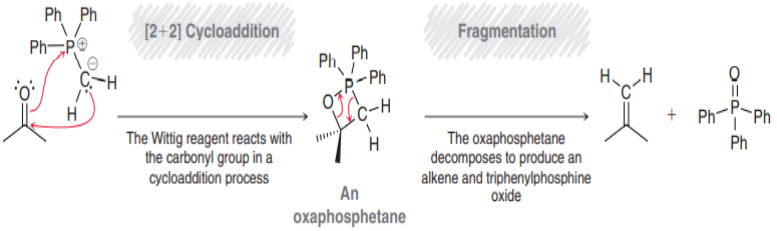
$RPPh_3$
→
Wittig Reagent (AKA a ylide):
1) CH_3I
→
2) BuLi

Formation of a Wittig Reagent:



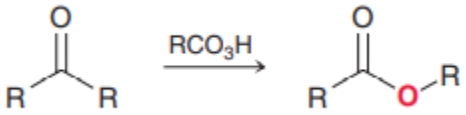
Triphenylphosphine

Wittig Reaction:

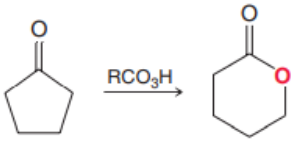


Baeyer-Villiger Oxidation of Aldehydes and Ketones

When treated with a peroxy acid, ketones can be converted into esters via the insertion of an oxygen atom:



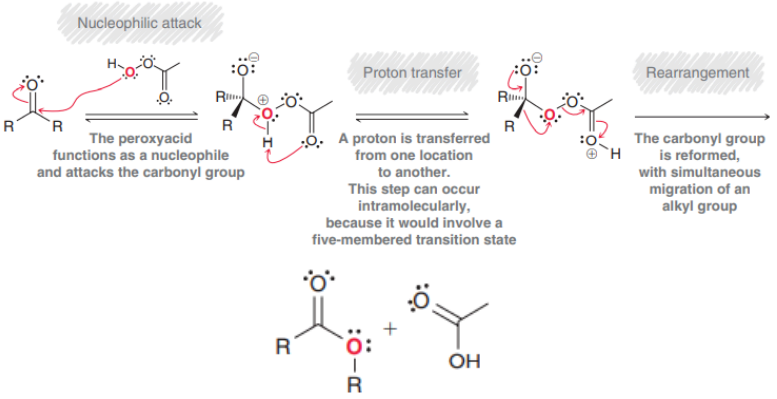
Additionally, treatment of a cyclic ketone with a peroxy acid yields a cyclic ester, or lactone.

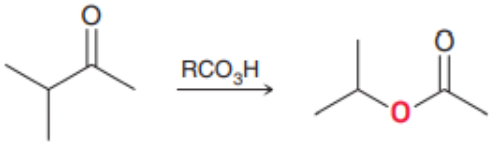
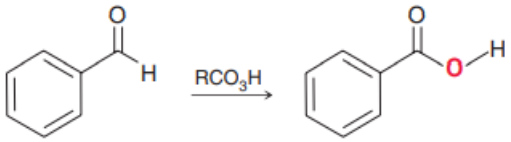
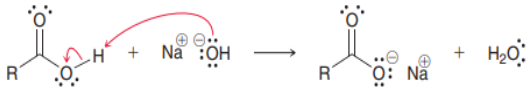
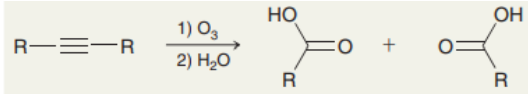
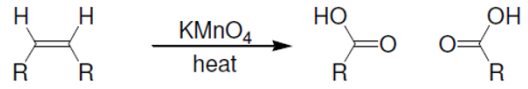


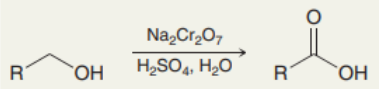
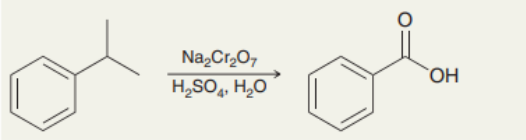
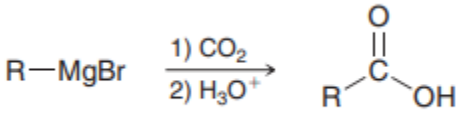
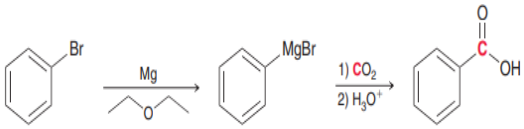
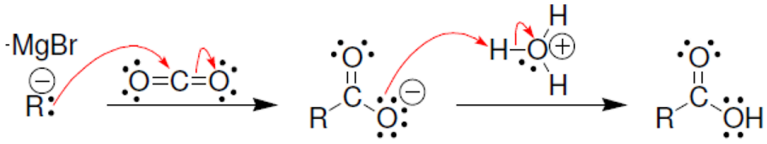
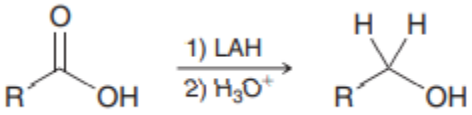
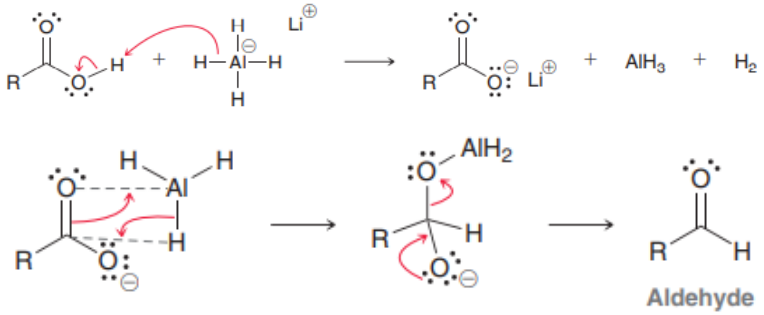
A lactone

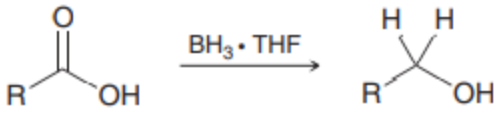
When an unsymmetrical ketone is treated with a peroxy acid, formation of the ester is regioselective:

RCO_3H

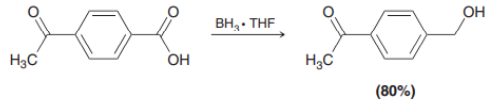


 Here, in this case, the oxygen atom is inserted on the left side of the carbonyl group, rather than the right side. This occurs because the isopropyl group migrates more rapidly than the methyl group during the rearrangement step of the mechanism. The migration rates of different groups, or migratory aptitude, can be summarized as follows: H > 3° > 2°, Ph > 1° > methyl 		
<u>Formation of a Carboxylate Salt</u> Treatment of a carboxylic acid with a strong base, such as sodium hydroxide, yields a carboxylate salt:  A carboxylate salt (Notably, in water, the equilibrium generally favors the acid).	NaOH →	***(See mechanism on the left)!***
<u>Formation of Carboxylic Acids</u> Oxidative cleavage will break a C≡C triple bond forming two carboxylic acids:   A variety of strong oxidizing agents (i.e.	1) O_3 → 2) H_2O **OR** 1) $KMnO_4$ → 2) heat **OR**	**N/A!**

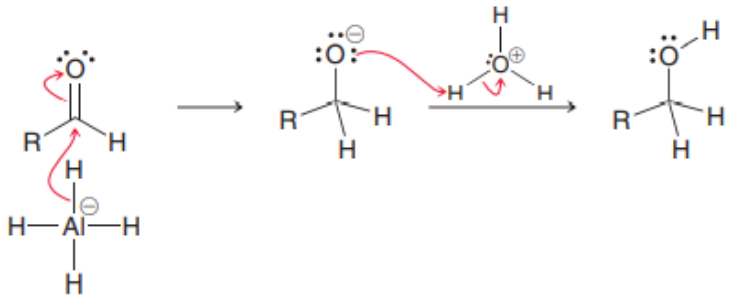
chromic acid) can be used to oxidize primary alcohols and produce carboxylic acids:  Any alkyl group on an aromatic ring will be completely oxidized to give benzoic acid, provided that the benzylic position has at least one hydrogen atom: 	$Na_2Cr_2O_7$ → H_2SO_4, H_2O **^This could also be written as:** **CrO_3** → **H_3O^+, acetone** **OR** **H_2CrO_4** → **acetone**	
<u>Carboxylation of Grignard Reagents</u> Carboxylation of a Grignard Reaction can be achieved using CO_2:  This gives a second method to convert an alkyl halide into a carboxylic acid: 	1) CO_2 → 2) H_3O^+	
<u>Reactions of Carboxylic Acids: Formation of an Alcohol</u> Carboxylic acids are reduced to alcohols upon treatment with lithium aluminum hydride:  An alternative method for reducing carboxylic acids involves the use of borane (BH_3):	1) LAH → 2) H_3O^+	<u>Carboxylic Acid w/ LAH:</u>  Aldehyde



(Note: Reduction with borane is often preferred over reduction with LAH, because borane reacts selectively with a carboxylic acid group in the presence of another carbonyl group. If the following reaction were performed with LAH instead of borane, both carbonyl groups would be reduced:



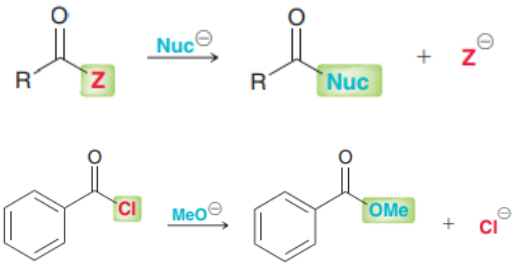
)



Carboxylic Acid w/ BH_3: **N/A!**

Nucleophilic Acyl Substitution

When a nucleophile attacks a carboxylic acid derivative (given that carboxylic acid derivatives possess a heteroatom that can function as a leaving group), a reaction can occur in which the nucleophile replaces the leaving group (Z):



Note that one **cannot** use an aldehyde or a ketone in this reaction!!!

*Also, see examples of basic, acidic, and neutral conditions of different Nucleophilic Acyl Substitution reactions.

#DO NOT draw S_N2 mechanisms for <u>any</u> of these reactions!!!

Given a Carboxylic Acid Derivative:

Strong Nucleophile (**See Reference Sheet 5 for a list of Strong Nucleophiles**).

→

OR

NaOH

→

OR

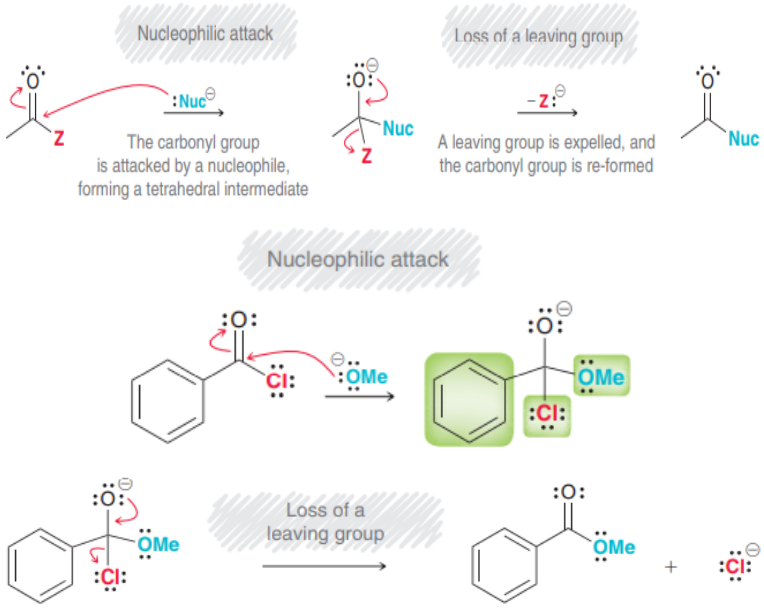
(Given H_2O, MeOH, EtOH, (etc)):

$[H^+]$

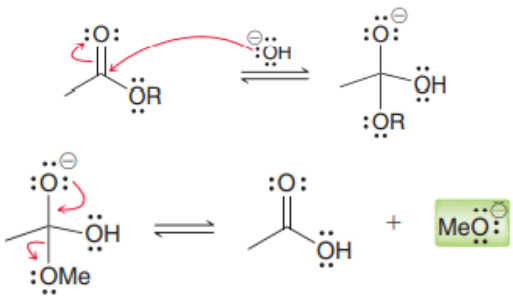
→

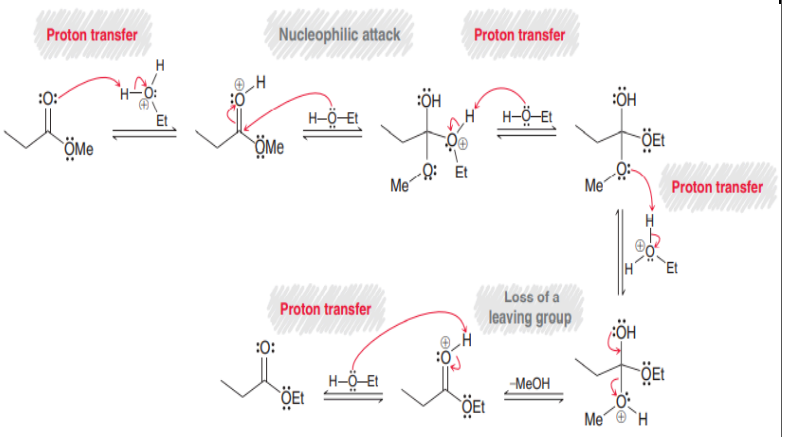
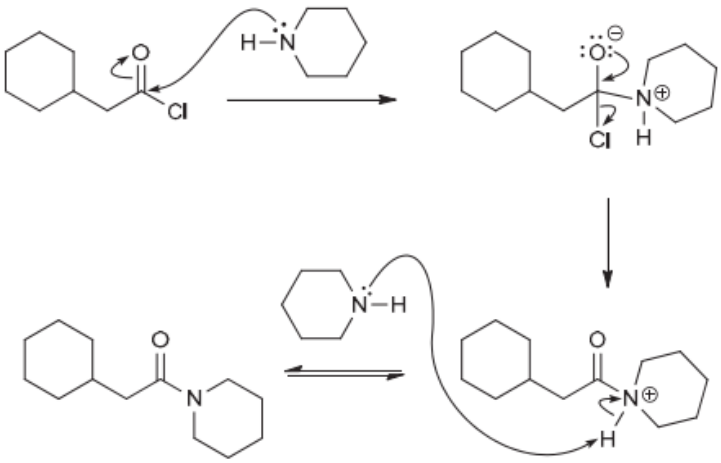
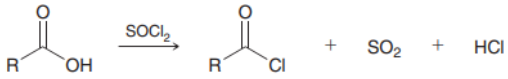
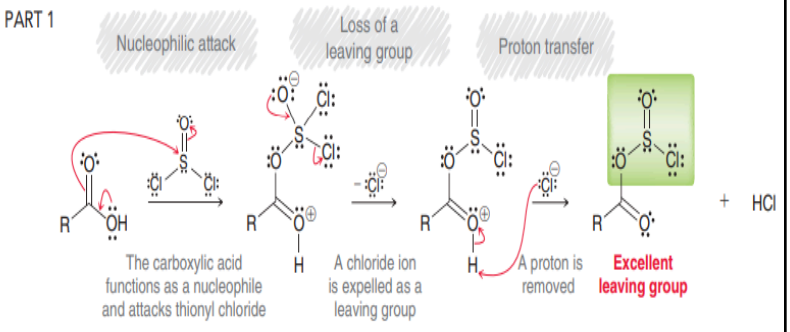
OR

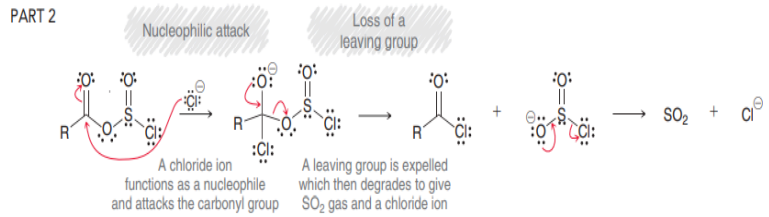
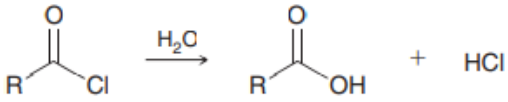
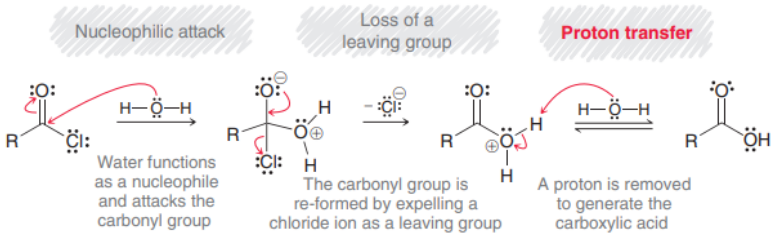
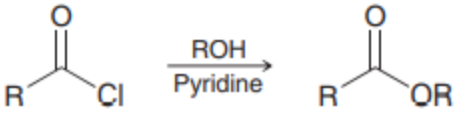
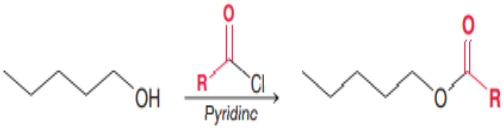
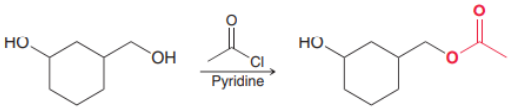
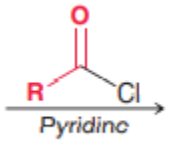
Typical Nucleophilic Acyl Substitution Reaction Mechanism Examples:

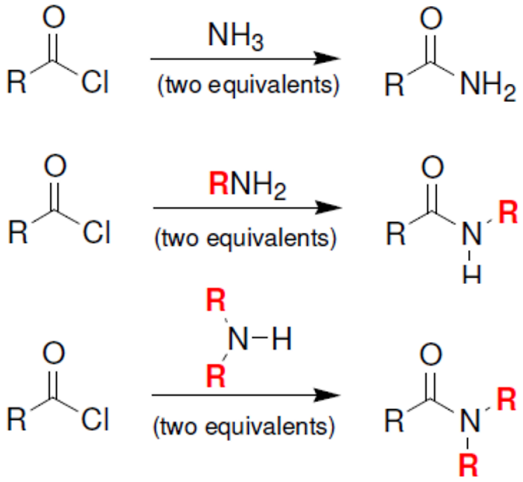
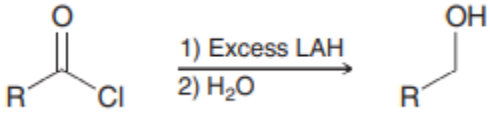
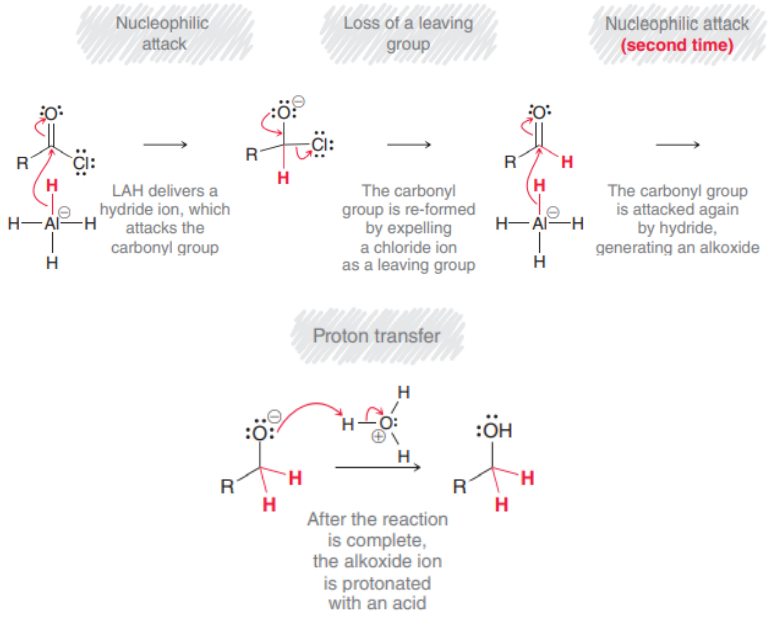


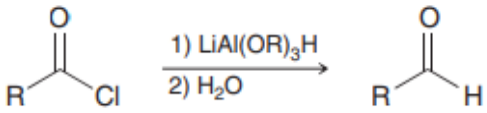
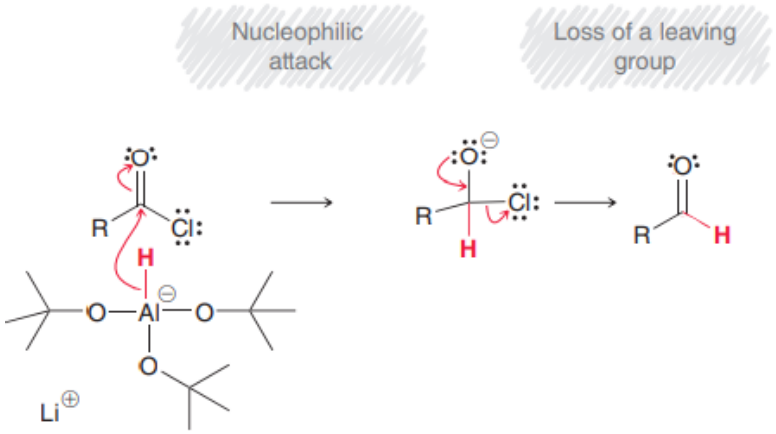
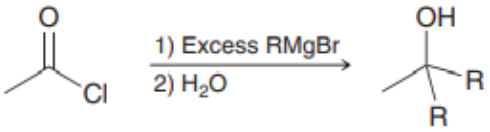
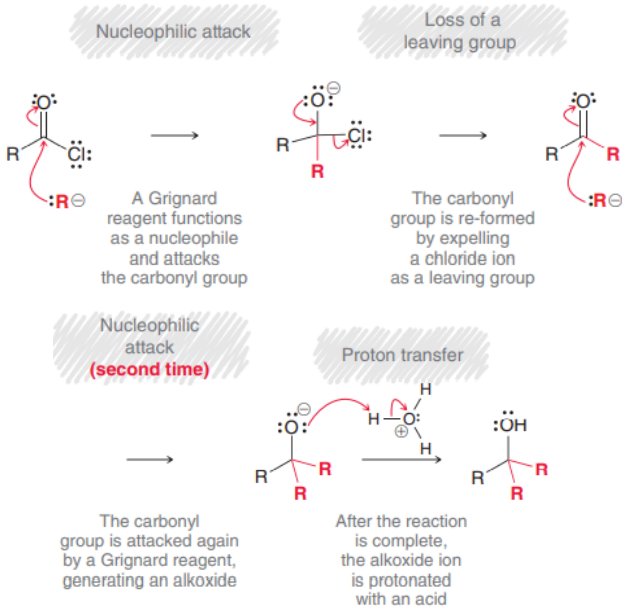
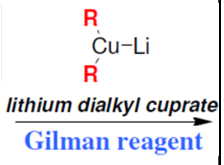
Under Basic Conditions:

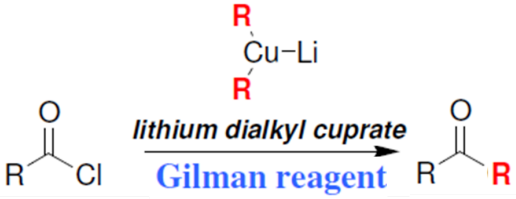
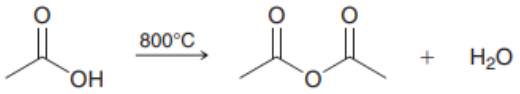
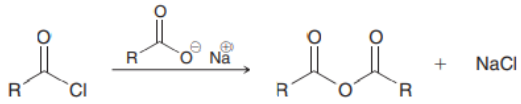
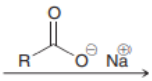
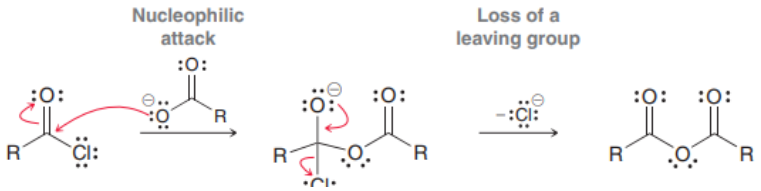
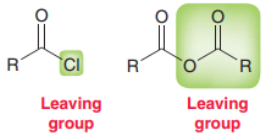


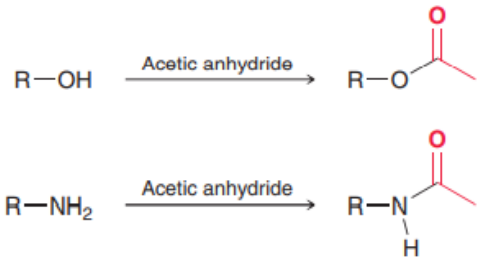
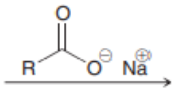
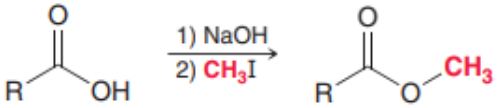
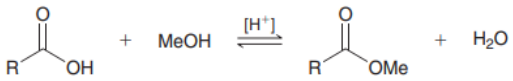
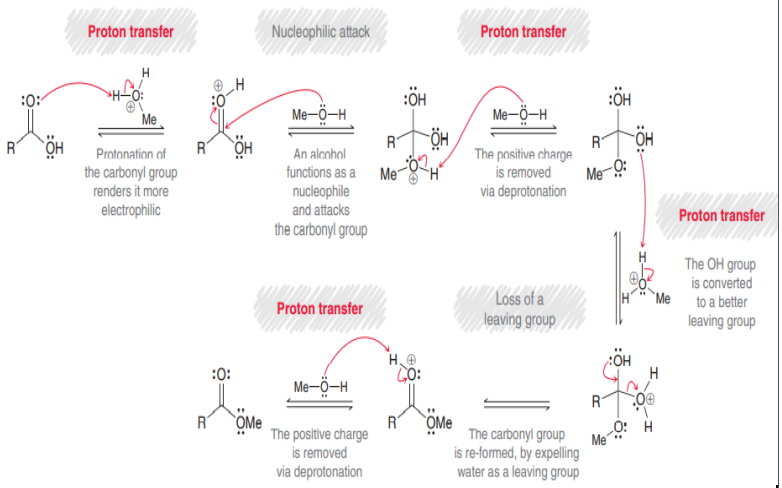
	Given H_2O, MeOH, EtOH, NH_3, or any neutral molecule →	<u>Under Acidic Conditions:</u>  <u>Under Neutral Conditions (notably, this process would take longer due to the formation of two charges):</u> 
<u>Preparation of Acid Chlorides</u> Acid chlorides can be formed by treating carboxylic acids with thionyl chloride ($SOCl_2$): 	$SOCl_2$ →	

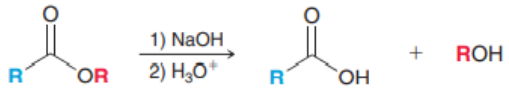
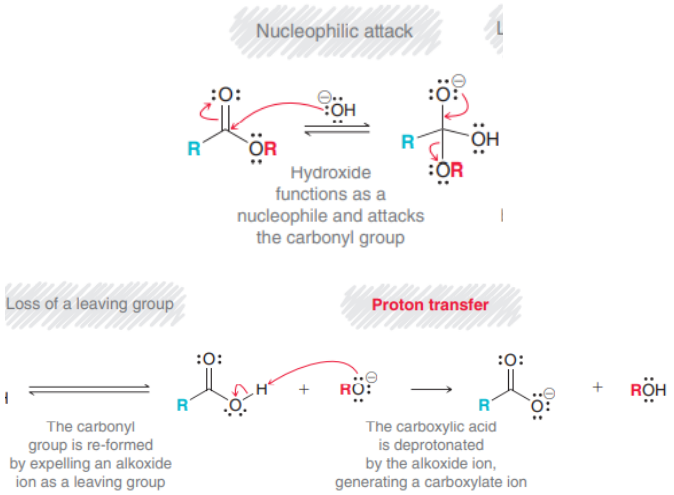
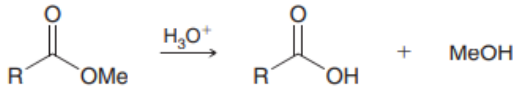
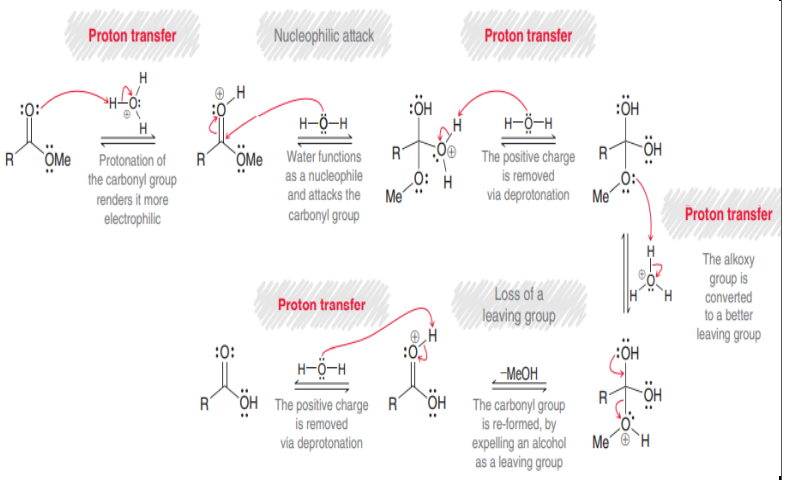
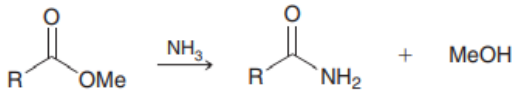
		
<u>Hydrolysis of Acid Chlorides</u> When treated with water, acid chlorides are hydrolyzed to give carboxylic acids: 	H_2O →	
<u>Alcoholysis of Acid Chlorides</u> When treated with an alcohol, acid chlorides are converted into esters:  This reaction is viewed from the perspective of the acid chloride, but the same reaction can be written from the perspective of the alcohol:  Note: This process is sensitive to steric effects, which can be exploited to selectively acylate a primary alcohol in the presence of a secondary (more hindered) alcohol: 	<u>Perspective of the Acid Chloride:</u> ROH → Pyridine (AKA Pyr) <u>Perspective of the Alcohol:</u> 	***(See similar mechanism demonstrated in "<u>Hydrolysis of Acid Chlorides</u>").*** **#Note that here, the pyridine is used as a base to neutralize the HCl as it is produced.** **In case of both the perspectives of the acid chloride and the alcohol, they both have the same mechanism occurring.**

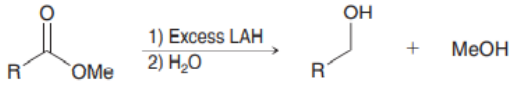
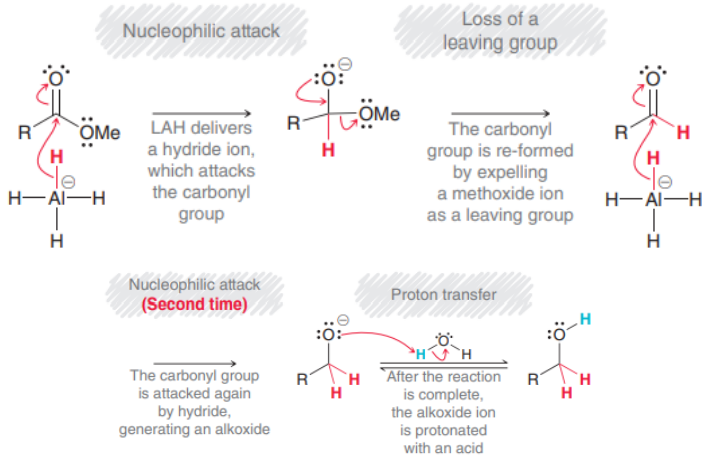
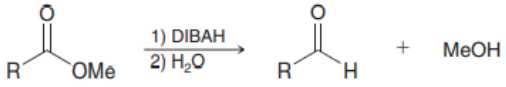
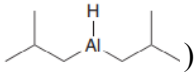
<u>Aminolysis of Acid Chlorides</u> When treated with ammonia, acid chlorides are converted into amides:  	Depending upon what product one desires to make given an acid chloride: NH_3 (methyl amine) → NRH_2 (primary amine) → NR_2H (secondary amine) →	***(See similar mechanism demonstrated in "<u>Hydrolysis of Acid Chlorides</u>").*** (Note: Pyridine is not used in this reaction, because ammonia itself is a sufficiently strong base to neutralize the HCl as it is produced. For this reaction, two equivalents of ammonia are necessary: one for the nucleophilic attack and the other to neutralize the HCl. This reaction also occurs with primary and secondary amines to produce N-substituted amides.)
<u>Typical Reduction of Acid Chlorides</u> When treated with lithium aluminum hydride, acid chlorides are reduced to give alcohols:  (The reaction between an acid chloride and LAH **<u>cannot</u>** be used to produce an aldehyde. Using one equivalent of LAH simply leads to a mess of products. Producing the aldehyde requires the use of a more selective hydride-reducing agent (i.e. lithium tri(t-butoxy) aluminum hydride)) that will react with acid chlorides more rapidly than aldehydes.)	1) xs LAH → 2) H_2O	

<u>Reduction of Acid Chlorides w/ $LiAl(OR)_3H$</u> Lithium tri(t-butoxy) aluminum hydride reacts with the acid chloride rapidly but will react with the aldehyde more slowly, allowing the aldehyde to be isolated. These conditions can be used to convert an acid chloride into an aldehyde:  	1) $LiAl(OR)_3H$ → 2) H_2O	
<u>Typical Reactions between Acid Chlorides and Organometallic Reagents</u> When treated with a Grignard reagent, acid chlorides are converted into alcohols, with the introduction of two alkyl groups:  #(Note that the reaction between an acid chloride and a Grignard reagent cannot be used to produce a ketone. Using one equivalent of the Grignard reagent simply leads to a mess of products. Producing the ketone requires the use of a more selective carbon nucleophile (i.e. lithium dialkyl cuprate, AKA a Gilman reagent) that will react with acid chlorides but not with ketones).	1) xs RMgBr → 2) H_2O	
<u>Reactions between Acid Chlorides and Organometallic Reagents (here, it's a Gilman Reagent)</u> The alkyl groups in this reagent are attached to copper rather than magnesium, and their carbanionic character is less pronounced (a C-Cu	 	***(See a similar mechanism presented in "<u>Typical Reactions between Acid Chlorides and Organometallic Reagents</u>" above)***

bond is less polarized than a C-Mg bond). This reagent can be used to convert acid chlorides into ketones with excellent yields: 		
<u>Preparation of Acid Anhydrides</u> Carboxylic acids can be converted into acid anhydrides with excessive heating:  **This method is only practical for acetic acid, as most other acids cannot survive the excessive heat. An alternative method for preparing acid anhydrides involves treating an acid chloride with a carboxylate ion, which functions as a nucleophile:** 	<u>Preparation of Acid Anhydrides w/ Heat:</u> 800°C → <u>Preparation of Acid Anhydrides w/ an Acid Chloride (with a Carboxylate Ion):</u> 	<u>Preparation of Acid Anhydrides w/ Heat: N/A</u> <u>Preparation of Acid Anhydrides w/ an Acid Chloride (with a Carboxylate Ion):</u> 
<u>Reactions of Acid Anhydrides</u>  **The reactions of anhydrides are directly analogous to the reactions of acid chlorides. The only difference is in the identity of the leaving group. With an acid chloride, the leaving group is a chloride ion, and the by-product of the reaction is therefore HCl. With an acid anhydride, the leaving group is a carboxylate ion,**	N/A	***(See similar mechanisms presented above concerning Acid Chlorides)***

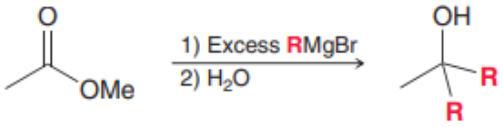
and the by-product is therefore a carboxylic acid. As a result, it is not necessary to use pyridine in reactions with acid anhydrides, because HCl is not produced.		
<u>Acetylation with Acetic Anhydride</u> Acetic anhydride is often used to acetylate an alcohol or an amine:  	 	***(Treat ROH and RNH_2 as nucleophiles, and draw out a mechanism similar to the one displayed in "<u>Preparation of Acid Anhydrides</u>").***
<u>Preparation of Esters via S_N2 Reactions</u> When treated with a strong base followed by an alkyl halide, carboxylic acids are converted into esters:  	1) NaOH → 2) Any Primary (or even Secondary) Halide (i.e. CH_3I)	**(The carboxylic acid is first deprotonated to yield a carboxylate ion, which then functions as a nucleophile and attacks the alkyl halide in an S_N2 process. The expected limitations of S_N2 processes therefore apply. Specifically, tertiary alkyl halides <u>cannot</u> be used.)** **#See Reference Sheet 3 under "<u>Proton Transfers</u>" for a sample mechanism of deprotonation (here, step one, AKA 1) NaOH). Also see Reference Sheet 5 for a sample S_N2 mechanism (referring to step two, AKA 2) Any Primary (or even Secondary) Halide).**
<u>Preparation of Esters via Fischer Esterification</u> Carboxylic acids are converted into esters when treated with an alcohol in the presence of an acid catalyst:  	ROH, $[H^+]$ →	

<u>Saponification</u> Esters can be converted into carboxylic acids by treatment with sodium hydroxide followed by an acid:  	1) NaOH → 2) H_2O	
<u>Acid-Catalyzed Hydrolysis of Esters</u> Esters can also be hydrolyzed under acidic conditions:  (This process is the reverse of a Fischer esterification. The mechanism is exactly what one would expect for a nucleophilic acyl substitution that takes place under acidic conditions.)	H_3O^+ →	
<u>Aminolysis of Esters</u> Esters react slowly with amines to yield amides:  #(This process has little practical utility, because preparation of amides is achieved more efficiently from the reaction between acid chlorides and ammonia or primary or secondary amines.)	NH_3 →	***(See "<u>Hydrolysis of Acid Chlorides</u>" for a similar mechanism).***

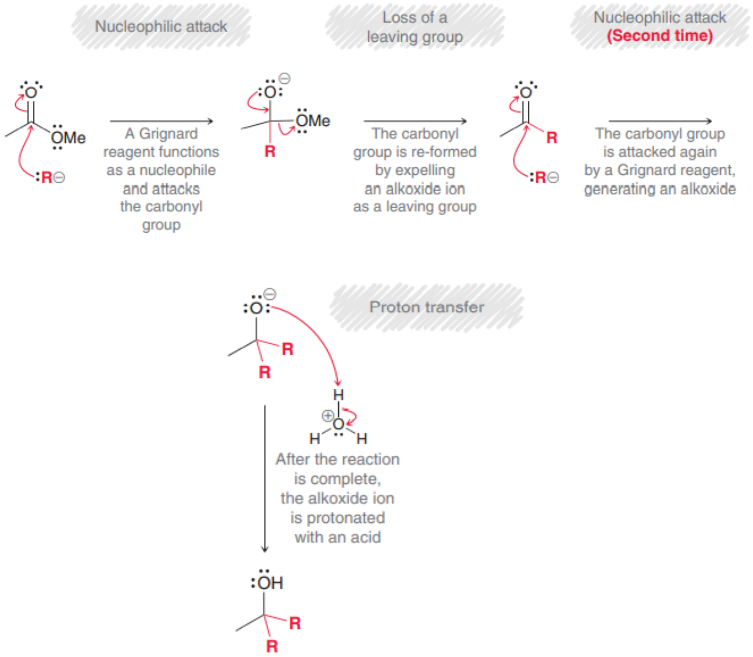
<u>Typical Reduction of Esters with Hydride-Reducing Agents</u> When treated with lithium aluminum hydride, esters are reduced to yield alcohols: 	1) xs LAH → 2) H_2O	
<u>Reduction of Esters with Hydride-Reducing Agents (in this case, DIBAH)</u> Treating an ester with only one equivalent of LAH is not an efficient method for preparing an aldehyde, because aldehydes are more reactive than esters and will react with LAH immediately after being formed. If the desired product is an aldehyde, then DIBAH can be used as a reducing agent instead of LAH. The reaction is performed at low temperature to prevent further reduction of the aldehyde: 	1) DIBAH (**AKA:** ) → 2) H_2O	***(See "<u>Typical Reduction of Esters with Hydride-Reducing Agents</u>" for a similar mechanism).***

Reactions between Esters and Grignard Reagents

When treated with a Grignard reagent, esters are reduced to yield alcohols with the introduction of two alkyl groups:

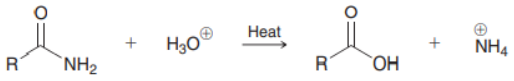


1) xs RMgBr
→
2) H_2O

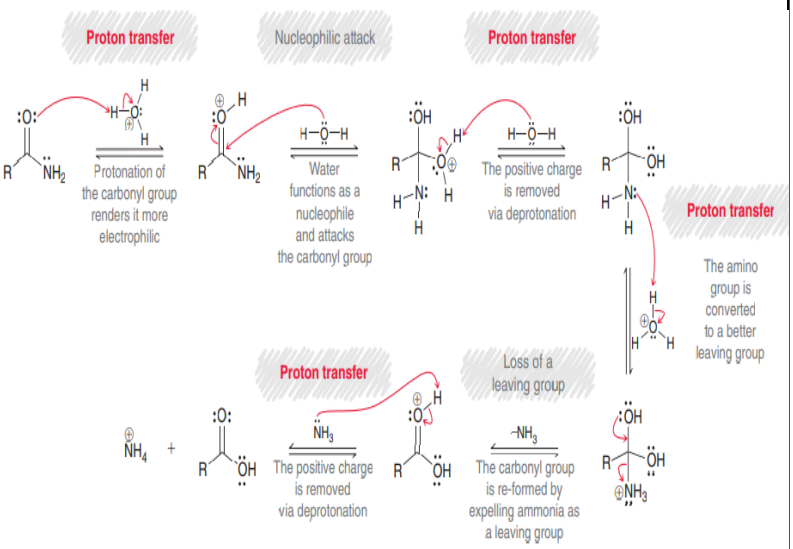


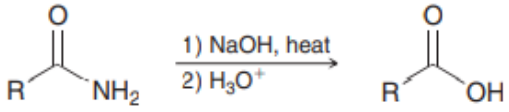
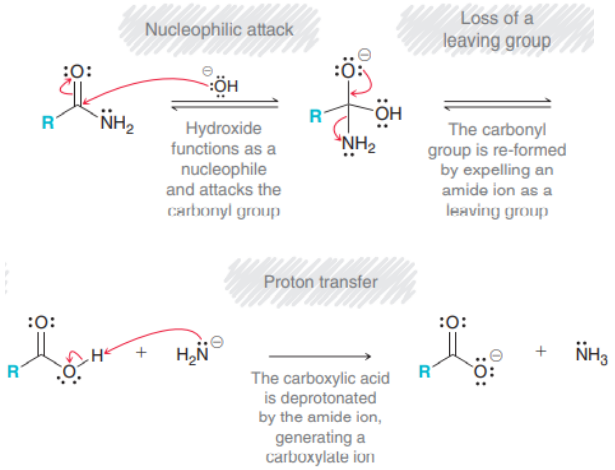
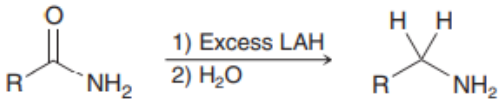
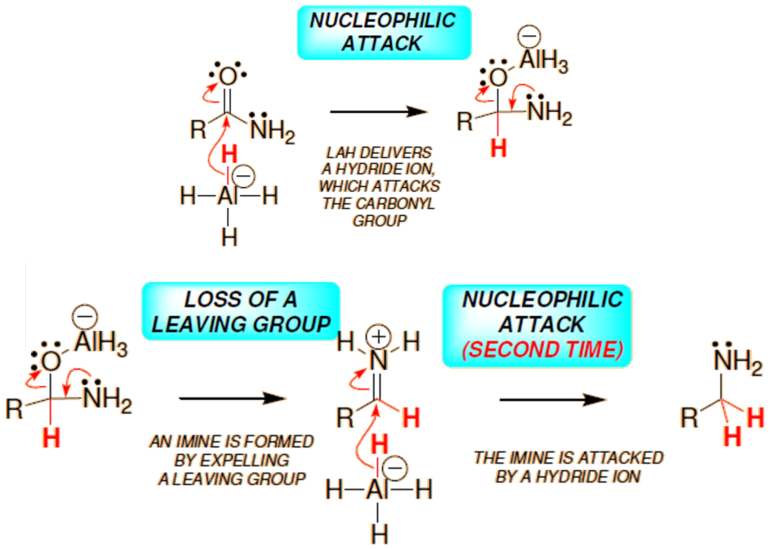
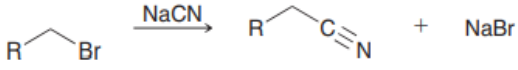
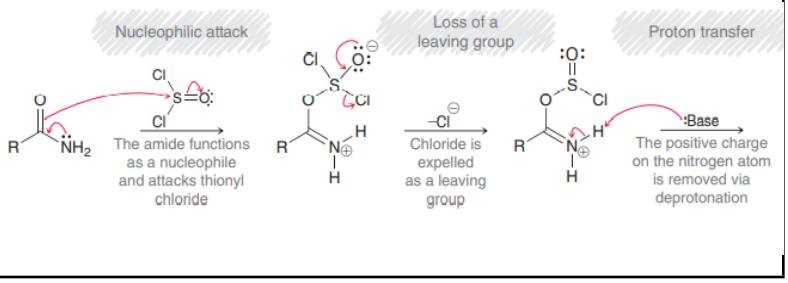
Acid-Catalyzed Hydrolysis of Amides

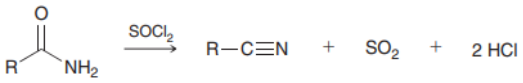
Amides can be hydrolyzed to give carboxylic acids in the presence of aqueous acid, but the process is slow and requires heating to occur at an appreciable rate:



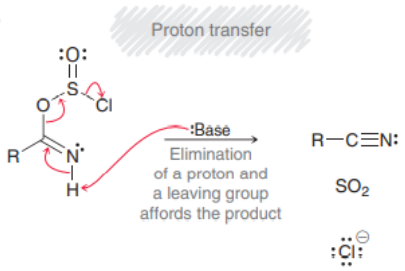
H_3O^+
→
heat



<u>Hydrolysis of Amides under Basic Conditions</u> Amides are also hydrolyzed when heated in basic aqueous solutions, although the process is very slow: 	1) NaOH, heat → 2) H_3O^+	
<u>Reduction of Amides</u> When treated with excess LAH, amides are converted into amines: 	1) xs LAH → 2) H_2O	
<u>Preparation of Nitriles via S_N2 Reactions</u> Nitriles can be prepared by treating an alkyl halide with a cyanide ion: 	NaCN →	***(See Reference Sheet 5 for a sample S_N2 mechanism).*** **#Notably, since this process proceeds via an S_N2 mechanism, so tertiary alkyl halides cannot be used.**
<u>Preparation of Nitriles from Amides</u> Nitriles can also be prepared via the dehydration of an amide. Many reagents can be used to accomplish the transformation (i.e. thionyl chloride ($SOCl_2$)):	$SOCl_2$ →	



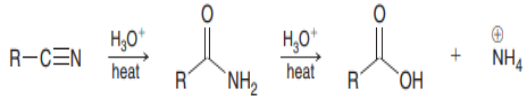
#It is crucial to note that this process is useful for preparing tertiary nitriles, which cannot be prepared via an S_N2 process.



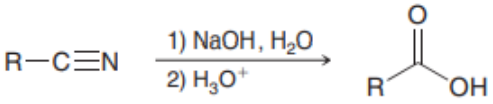
Hydrolysis of Nitriles

In aqueous acidic conditions, nitriles are hydrolyzed to afford amides, which are then further hydrolyzed to yield carboxylic acid.

Under Acidic Conditions:



Under Basic Conditions:



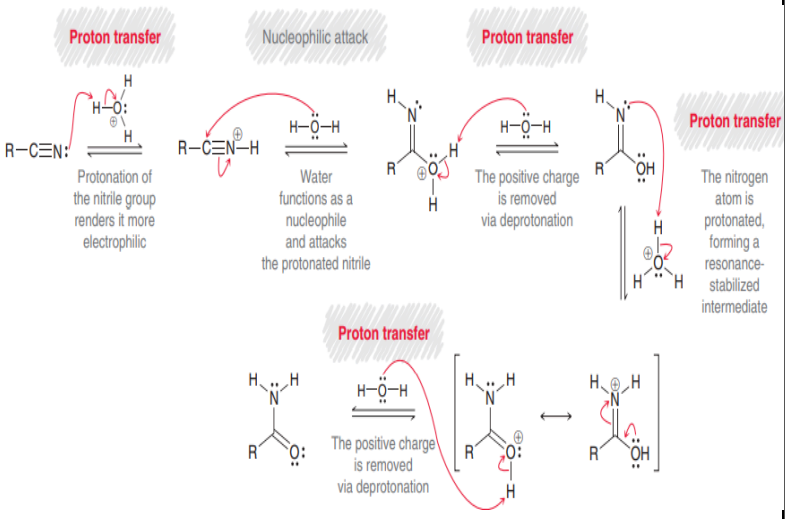
Under Acidic Conditions:

H_3O^+
→
Heat

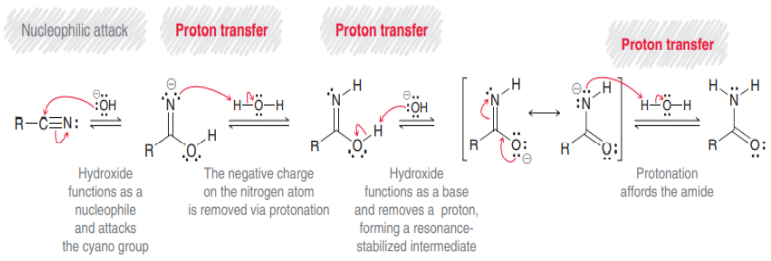
Under Basic Conditions:

1) NaOH, H_2O
→
2) H_3O^+

Under Acidic Conditions:

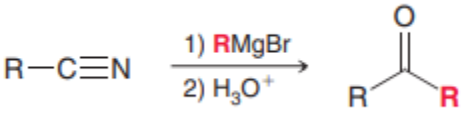


Under Basic Conditions:



Reactions between Nitriles and Grignard Reagents

A ketone is obtained when a nitrile is treated with a Grignard reagent, followed by aqueous acid:



1) RMgBr
→
2) H_3O^+