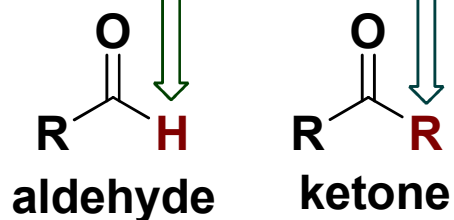


# **Chapter 8:**

# **Aldehydes and Ketones**

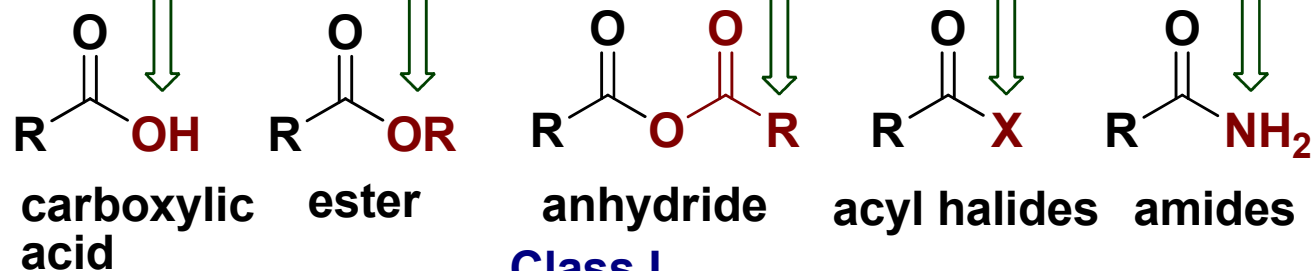
- **Carbonyl compounds are often classified as Class I or Class II depending if they have a group on the C=O that can be replaced by a nucleophile or not.**

cannot be replaced by a nucleophile



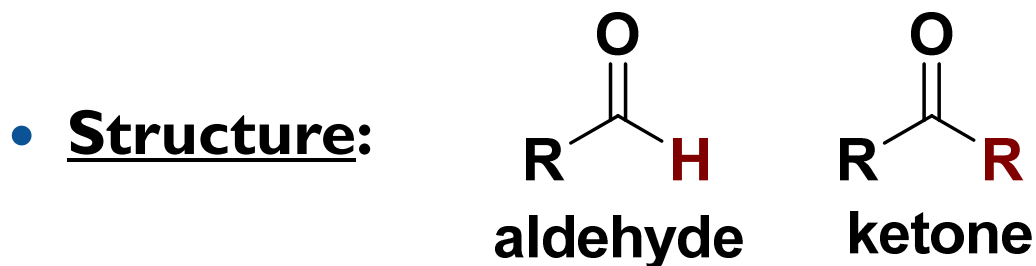
**Class II**

compounds with groups that can be replaced by a nucleophile



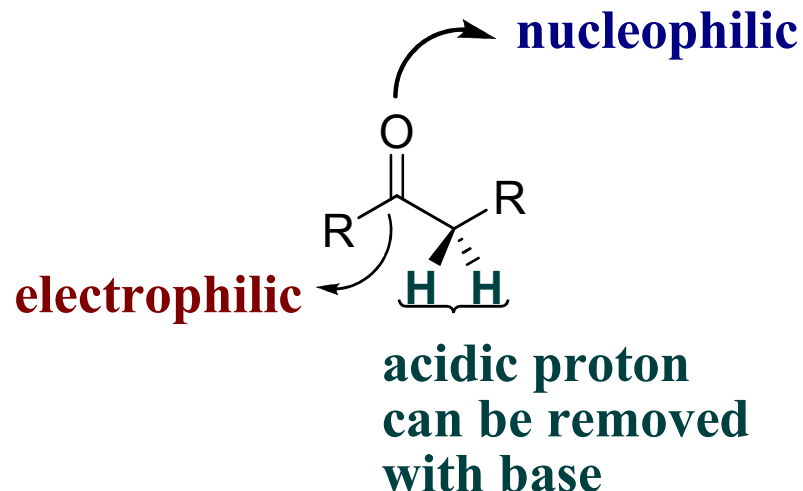
**Class I**

# Physical Properties

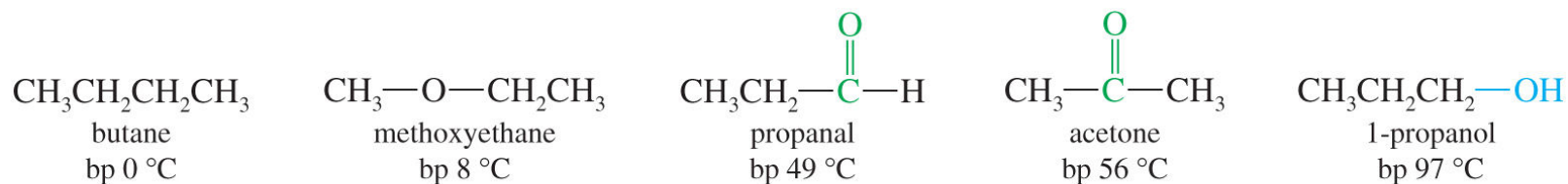


## Class II

- While most reaction of aldehydes and ketones are at the electrophilic site, there are two other reactive sites on the structure.

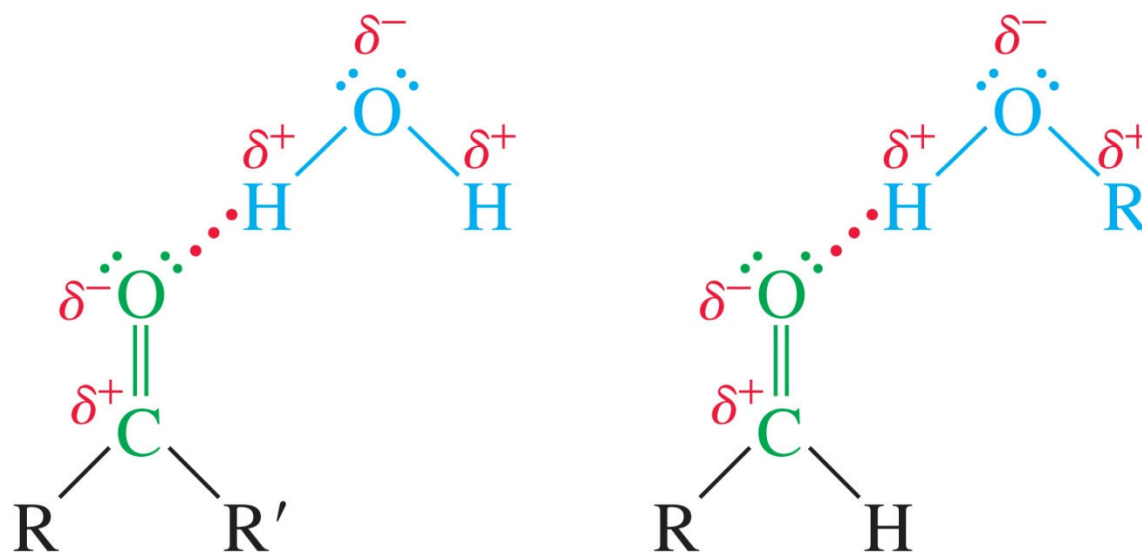


- **Boiling point**: since there are no hydrogen bonding in aldehydes or ketones, the boiling point will be lower than those of alcohols of similar molecular weights but higher than those non-polar molecules like alkanes, ethers, etc...because of the strong dipole.



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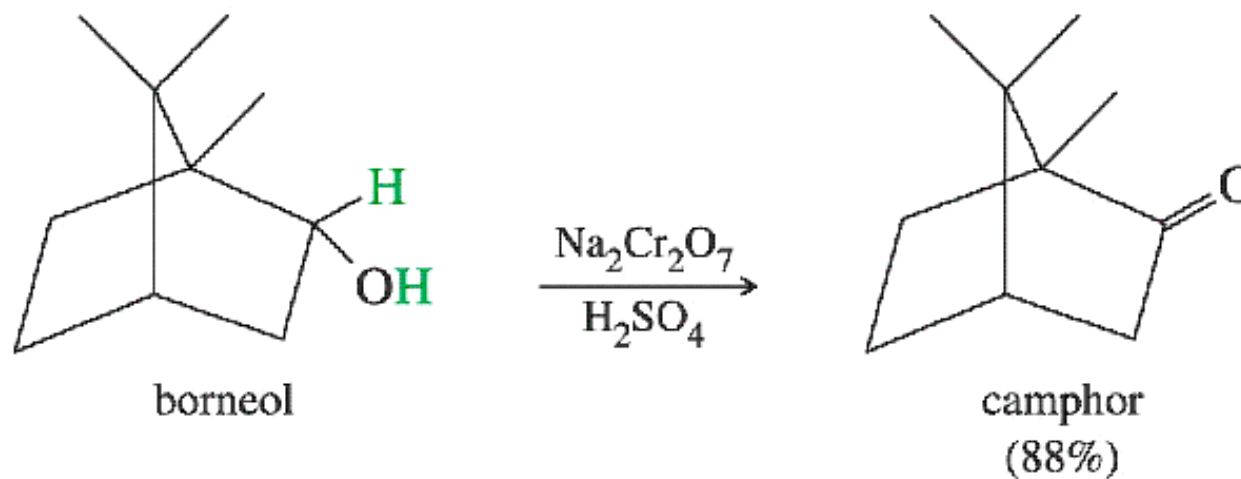
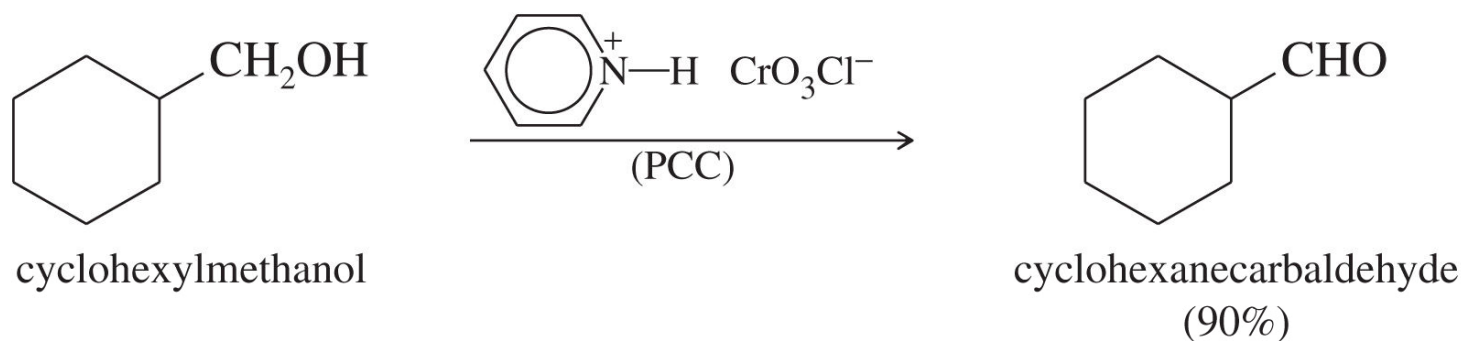
- **While aldehydes and ketones do not H-bond with themselves, they can hydrogen bond with other molecules bearing acidic hydrogen. They are therefore very good solvent for alcohols and amines.**



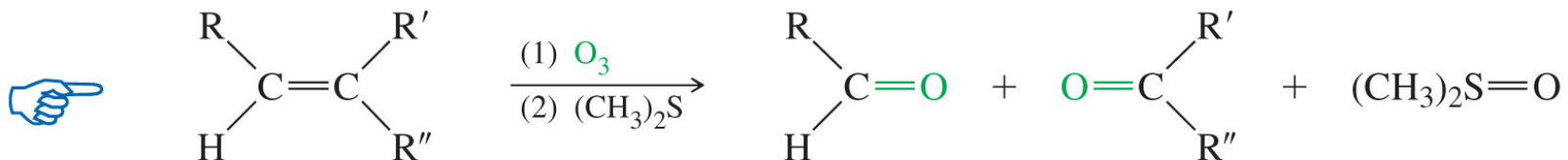
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# Synthesis of Aldehydes and Ketones (Review) 18.7

- Oxidation of Alcohols

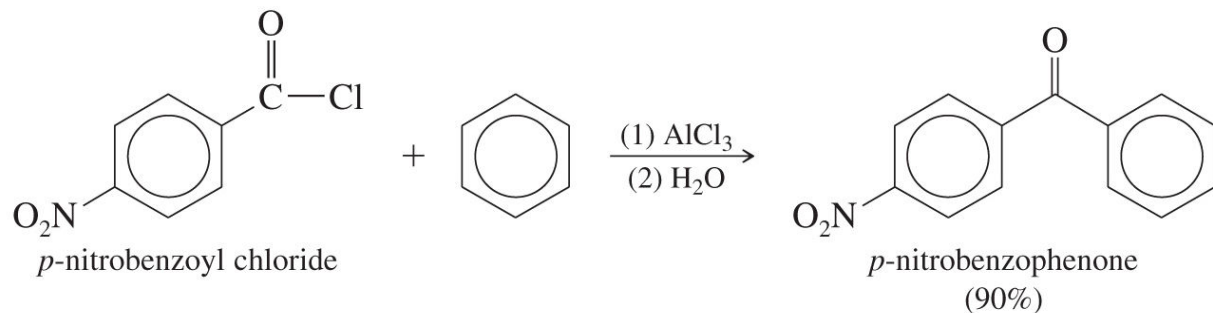
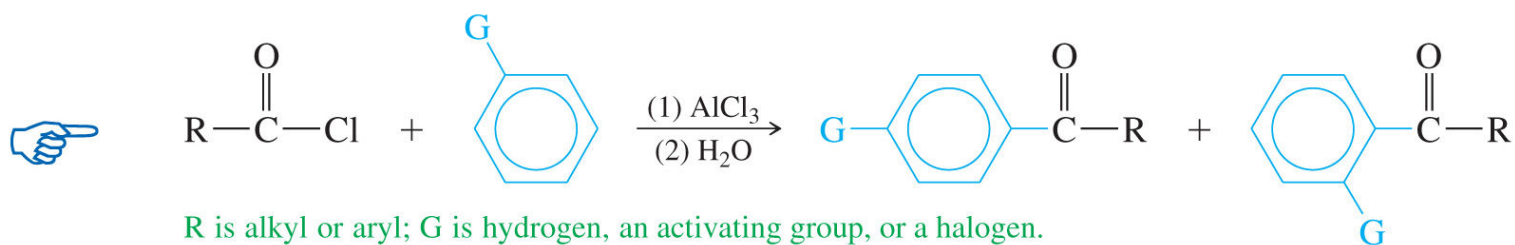


## • Ozonolysis of Alkenes



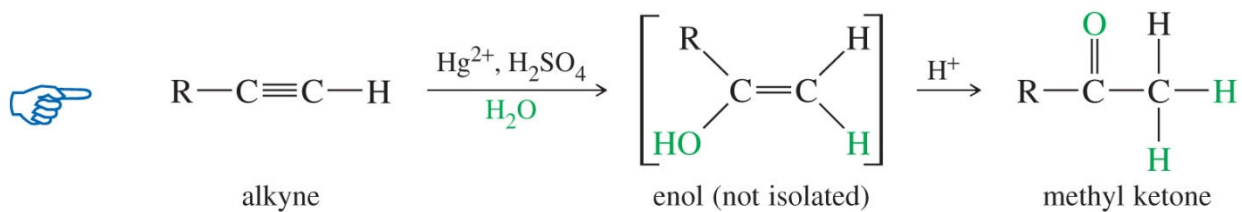
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## • Friedel-Crafts Acylation of Aromatics

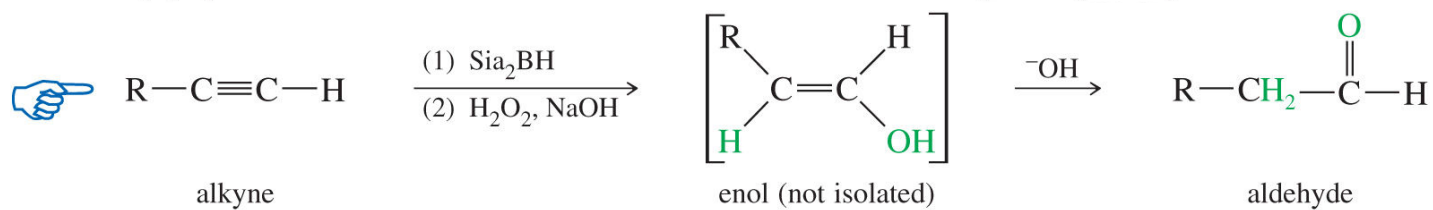
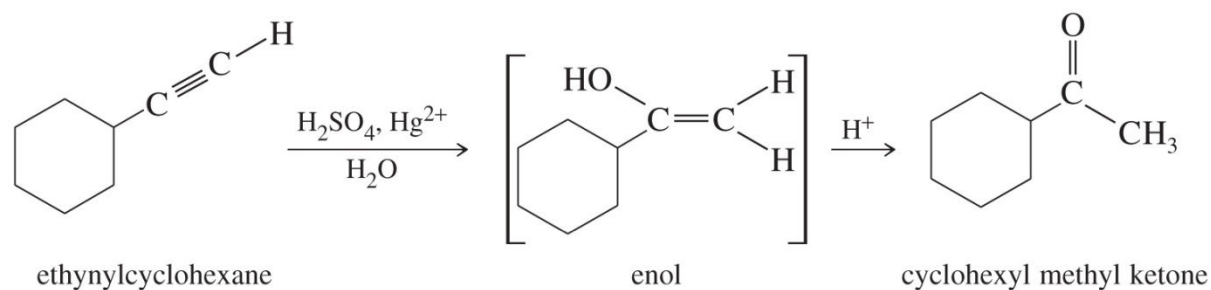


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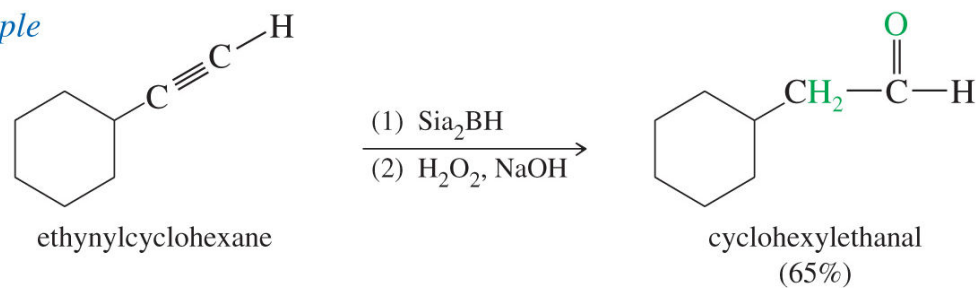
# • Hydration of Alkynes



*Example*



*Example*

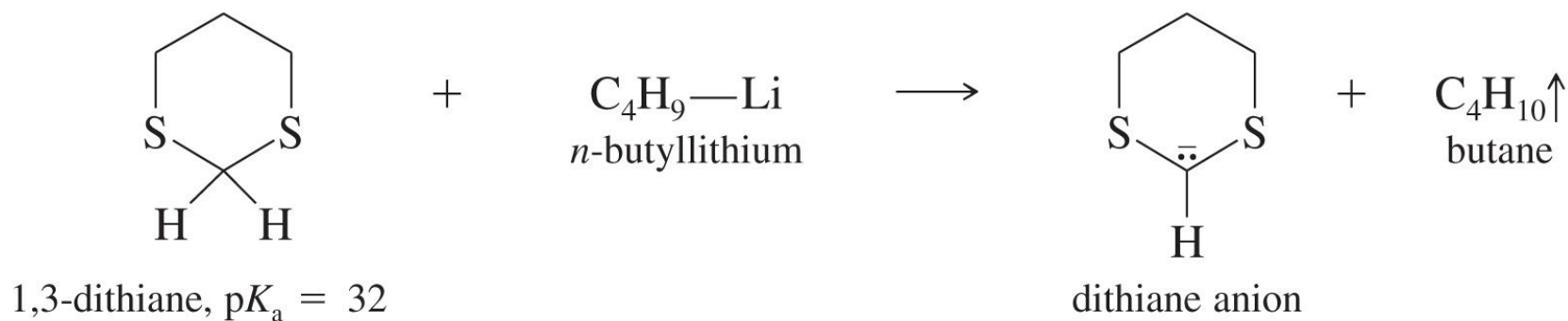




## New Synthesis of Aldehydes and Ketones

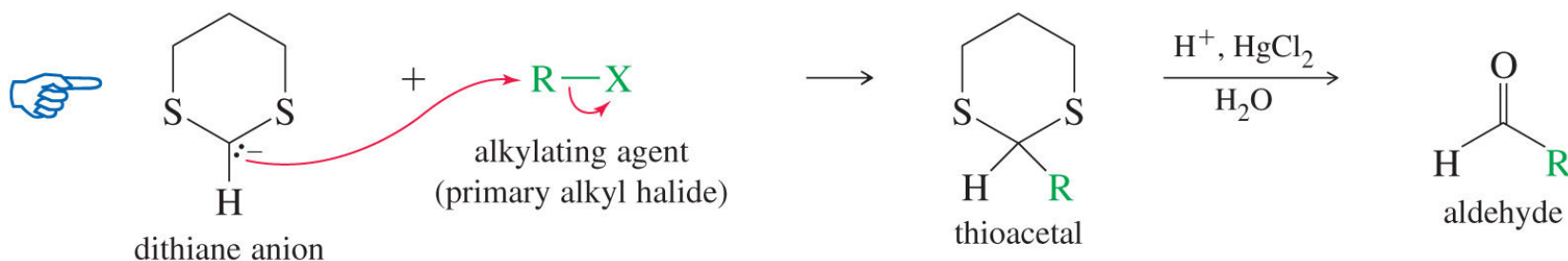
- From 1,3-dithiane (18-8)

1,3-dithiane has 2 weakly acidic protons that can be removed and alkylation of the carbon is possible. Once alkylated, the 1,3-dithiane becomes a “protected” carbonyl as it can be hydrolyzed to the corresponding carbonyl structure.



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# Mechanism of Dithiane Alkylation

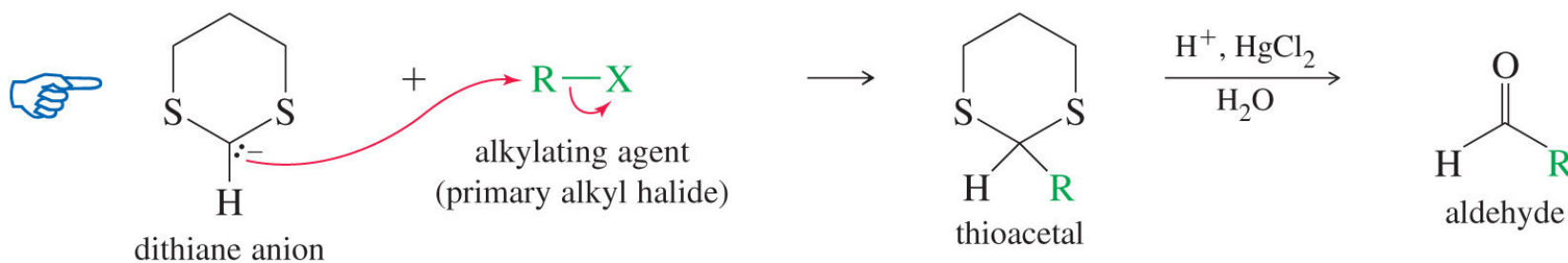


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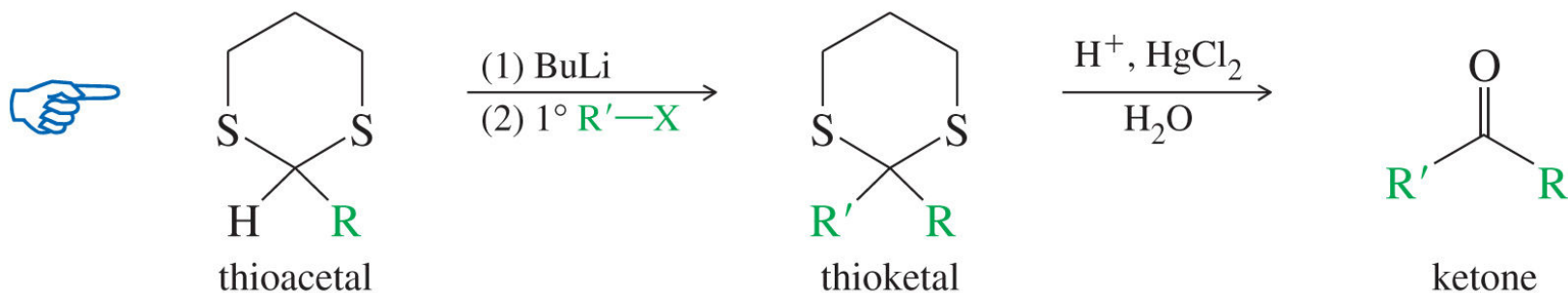
**Requires strong bases:  $RLi$ ,  $NaNH_2$**

**Works with primary halides only,  
Cl, Br, I**

- It is also possible to obtain ketones in this reaction simply by performing a second alkylation prior to the hydrolysis of the substituted dithiane.



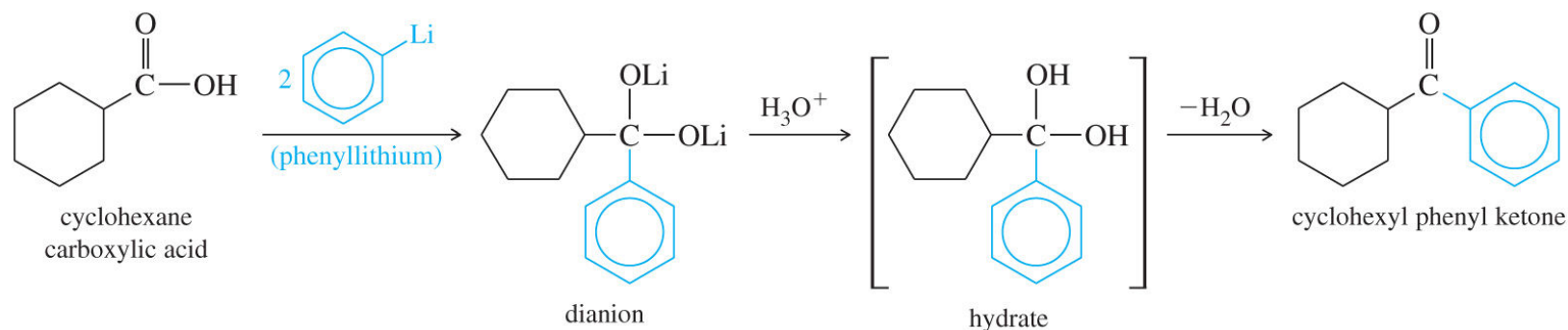
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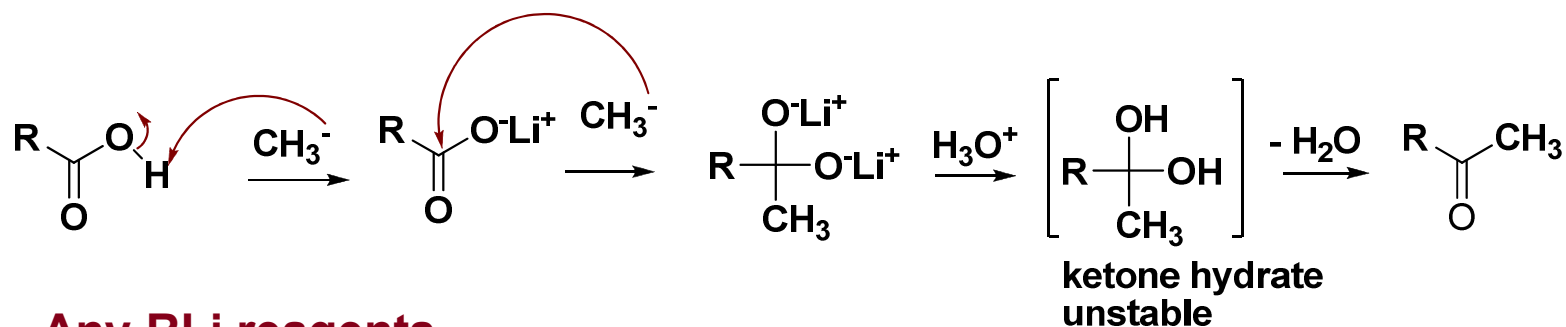
- Ketones from Carboxylic Acids (18-9)

**Deprotonation of a carboxylic acid give the normally unreactive carboxylate anion. However, with a very strong nucleophile (RLi), alkylation is possible leading to the ketone hydrate...hence the ketone.**

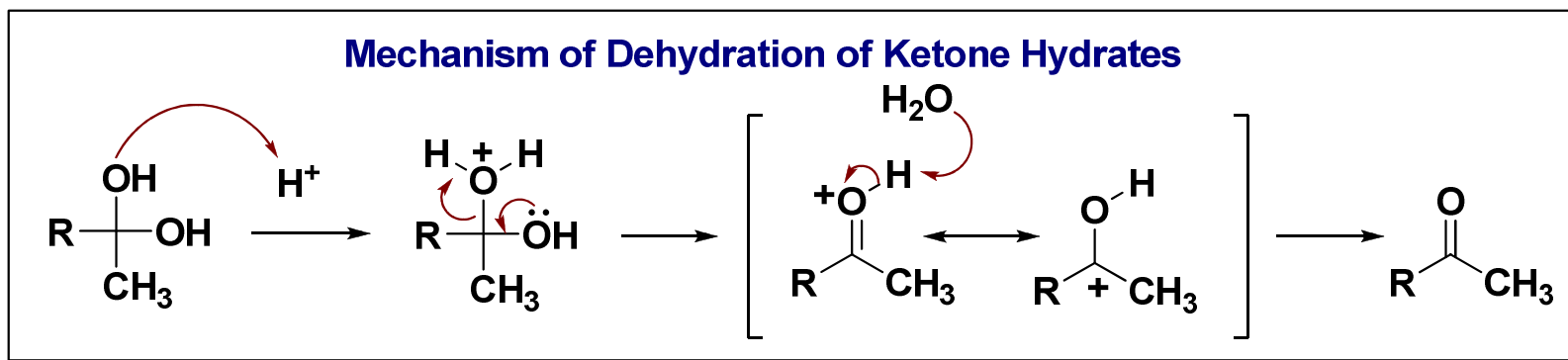


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# Mechanism of Formation of Ketones from Acids

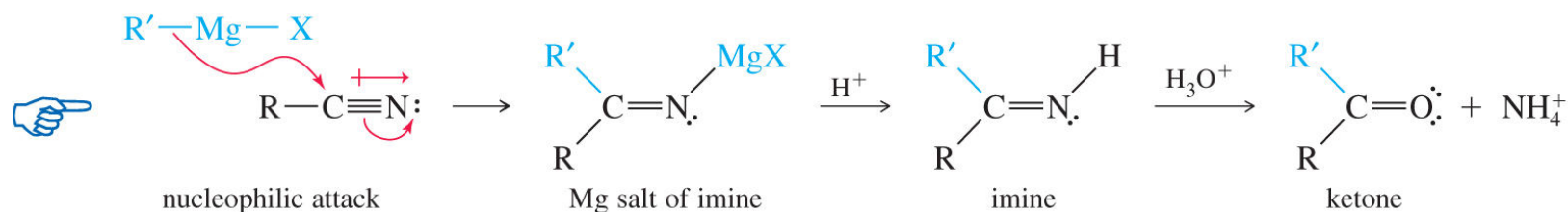


Any RLi reagents  
can be used



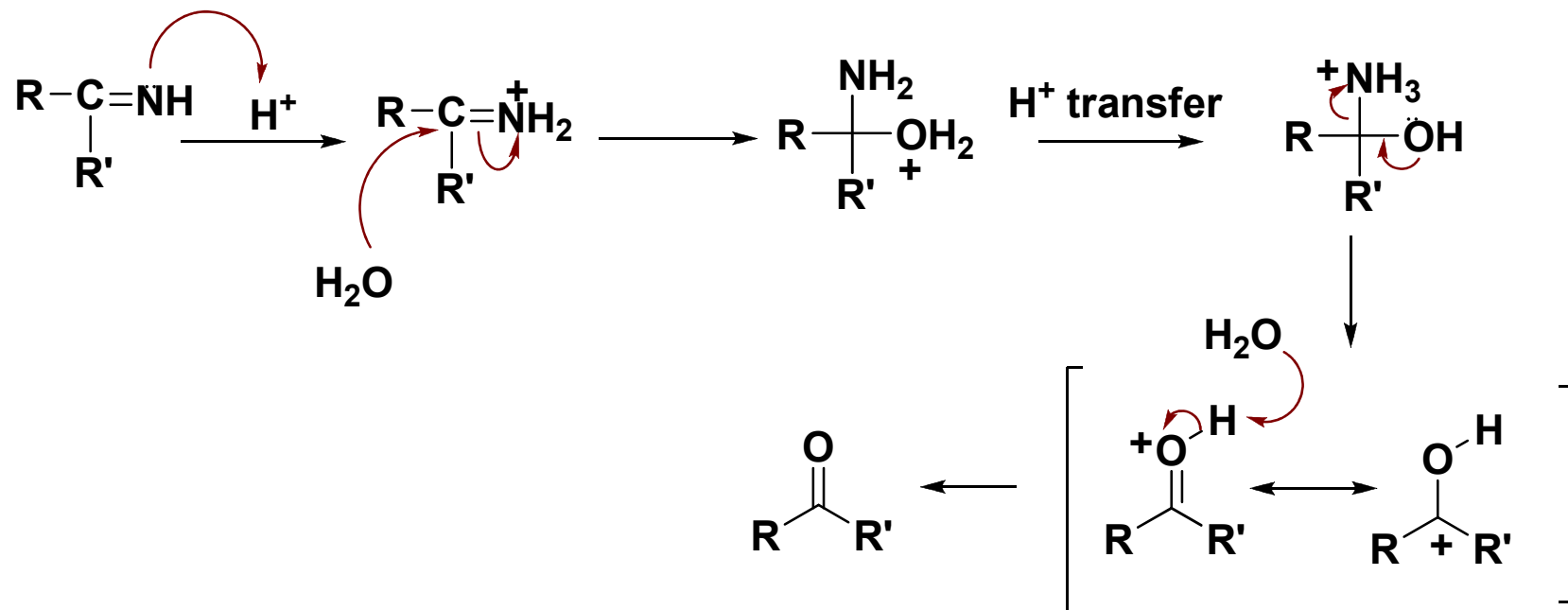
- Ketones from Nitriles (18-10)

**Nitriles have a structure similar to carbonyl, ie the C-N bond is strongly polarized and susceptible to nucleophilic attack. Nucleophiles such as Grignard reagents can add to the nitrile function and produce an imine which is hydrolyzed creating a ketone.**



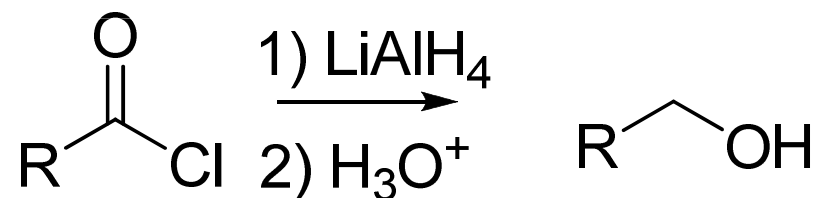
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# Mechanism of Imine Hydrolysis



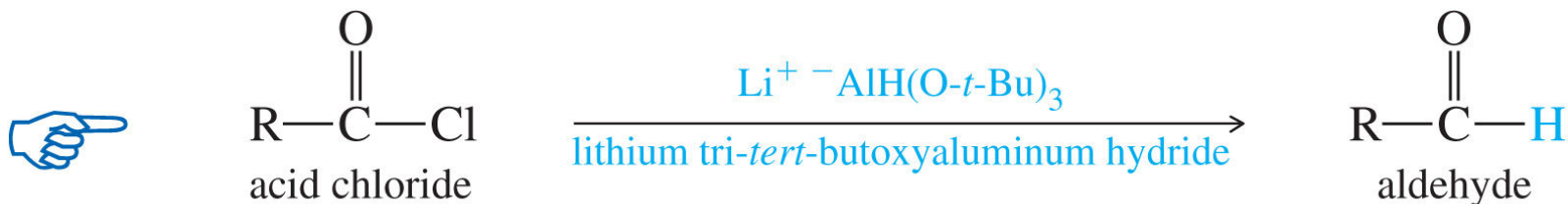
- Reduction of Acid Chlorides

**We have seen in section I (alcohols) that  $\text{LiAlH}_4$  reduces all carbonyl compounds to the corresponding alcohols. Acid chlorides are also reduced by this reagent to the 1° alcohols.**



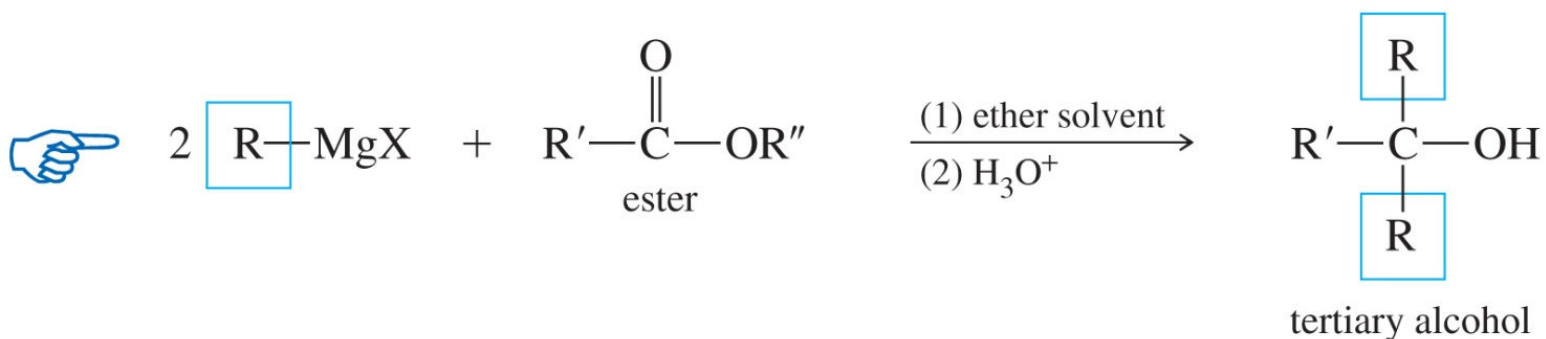
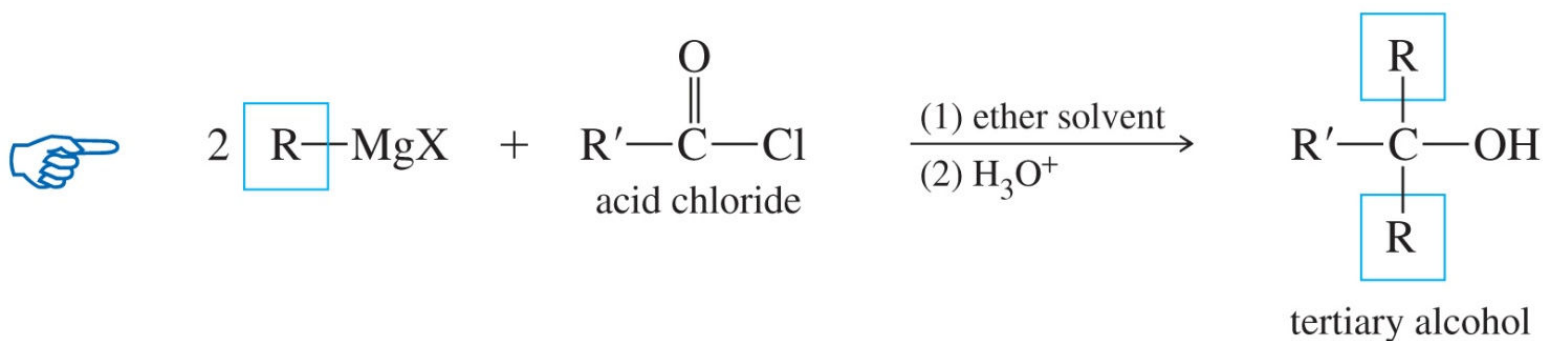


- However, it is possible to reduce the reactivity of the hydride reagent by replacing some hydrogen atoms by alkoxy groups. In such cases, the reagent is not active enough to reduce the intermediate, and the aldehyde is obtained.



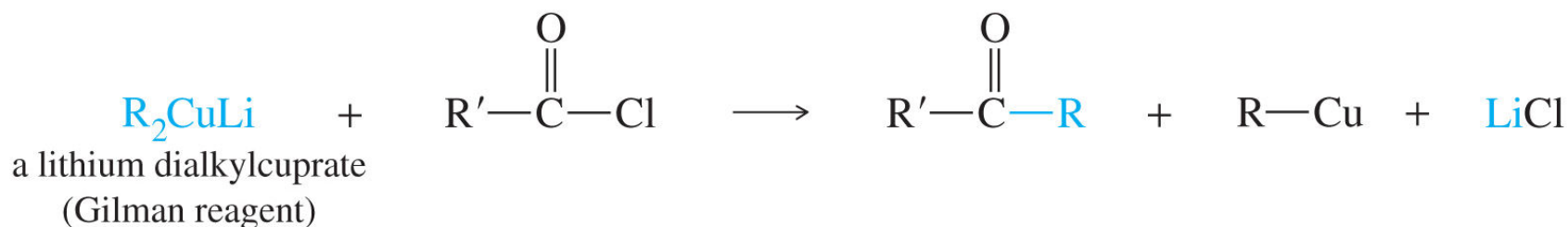
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- **Ketones can also be obtained from acid chlorides. We have seen that grignards add to acid chlorides to give the corresponding tertiary alcohols.**



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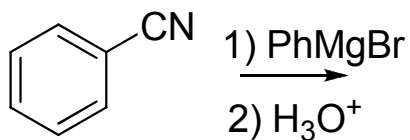
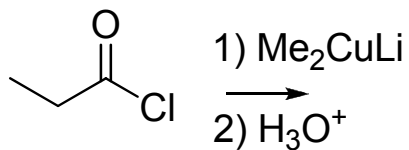
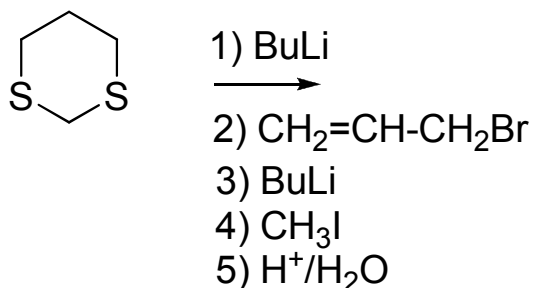
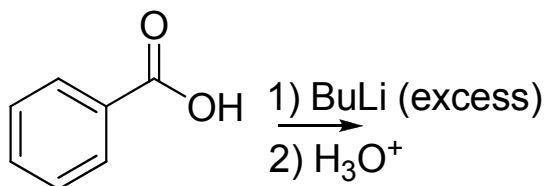
- **However using a weaker organometallic reagent allows the reaction to stop at the ketone stage. The Gilman reagent (an organocopper based nucleophile) is such a reagent.**



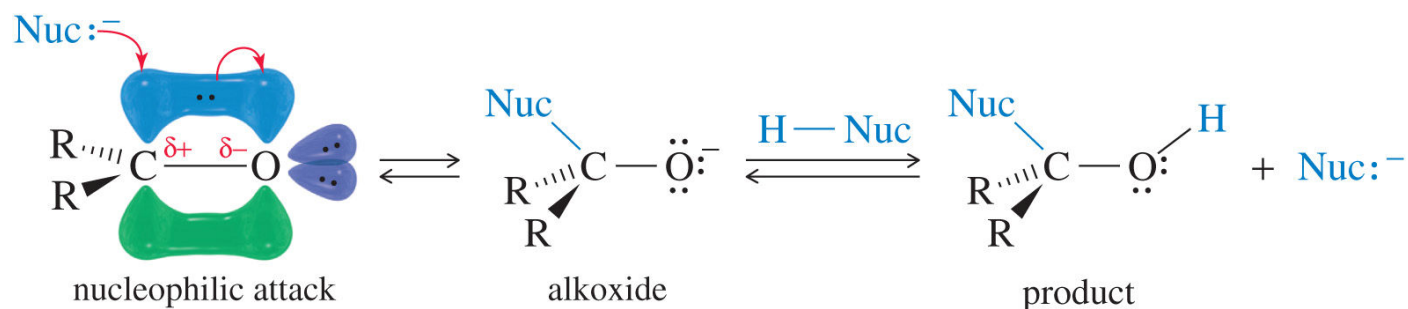
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# Practice Questions

- **Complete the following reactions. Draw the structure of the major organic product in each case.**



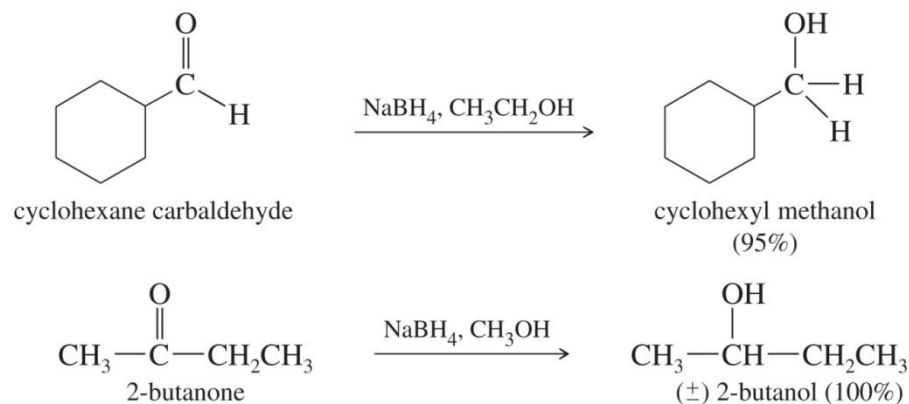
# Reactions of Aldehydes and Ketones: Nucleophilic Additions (Review) (18-12)



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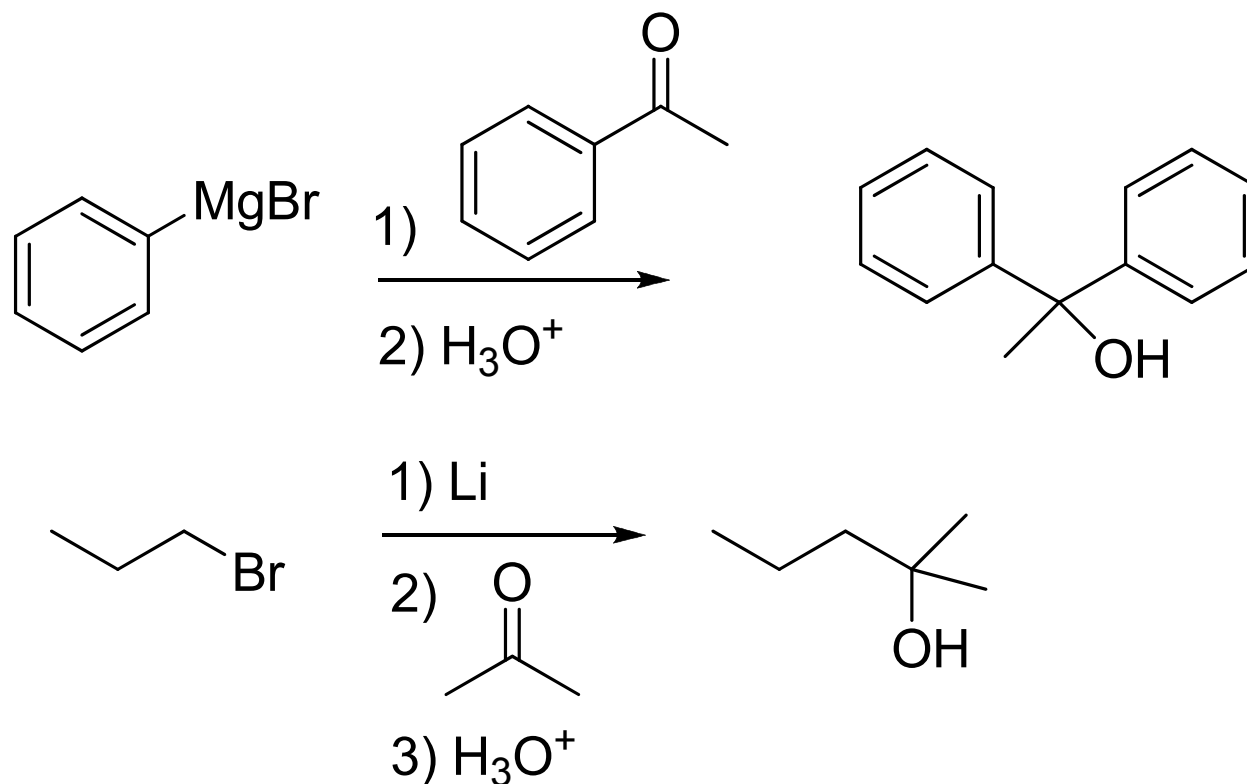
- Reduction**

**We have already seen that aldehydes and ketones can be reduced to the corresponding alcohols.  $\text{NaBH}_4$  or  $\text{LiAlH}_4$  can be used.**



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- **Similarly, aldehydes and ketones can add nucleophiles such as Grignard Reagent or alkyl lithium to produce alcohols**

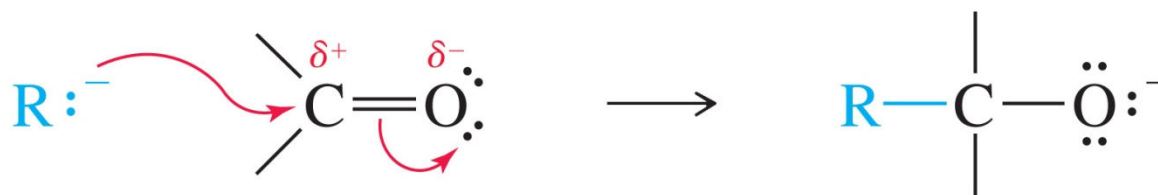


# New Reactions of Aldehydes and Ketones

- Nucleophilic Additions

**We have just reviewed the addition of Grignard reagents to carbonyl. In fact, this reaction is not limited to those reagents. Many other nucleophiles can add to aldehydes and ketones. These nucleophiles can be charged or not, and the nature of the nucleophile will dictate the mechanism involved in the reaction.**

- For charged nucleophile,  $\text{H}^-$ ,  $\text{R}^-$ ,  $\text{NC}^-$ , and others, the nucleophilic addition takes place directly on the carbonyl as shown below. We already have seen this mechanism for Grignard additions.

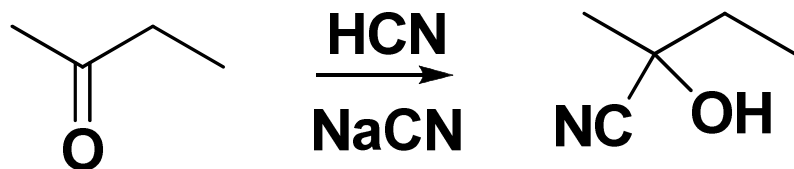
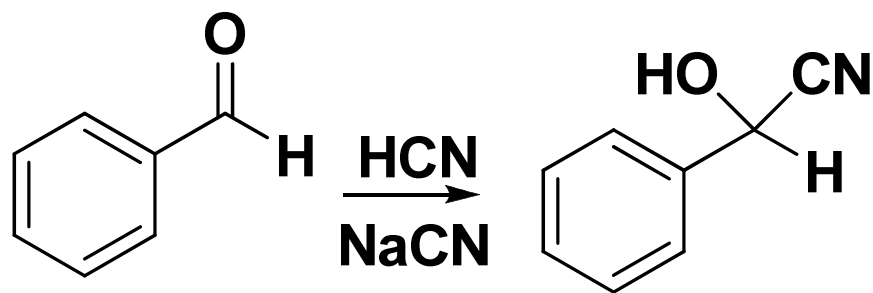


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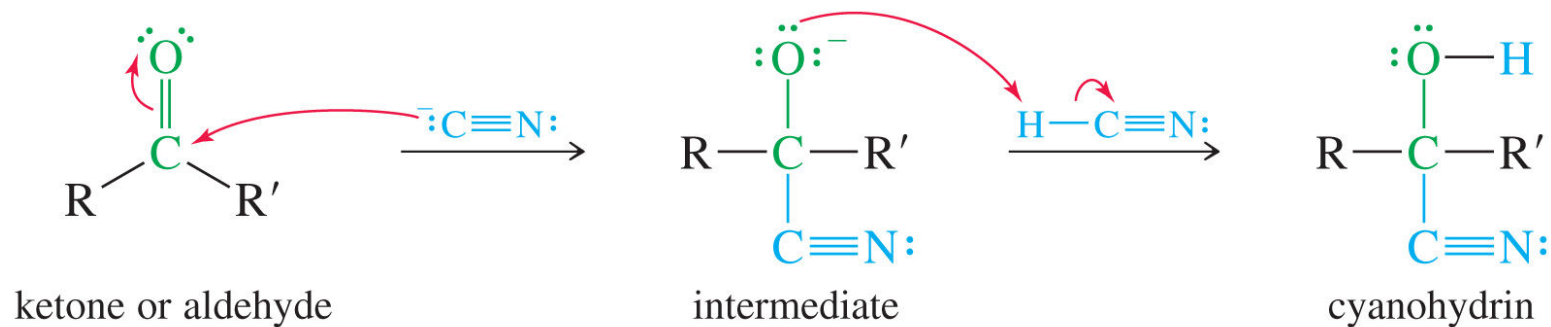


- Formation of Cyanohydrins (18-15)

**Cyanohydrins are important intermediates in organic synthesis since they can be hydrolyzed to the corresponding hydroxy-acids or reduced to the hydroxy-amines.**



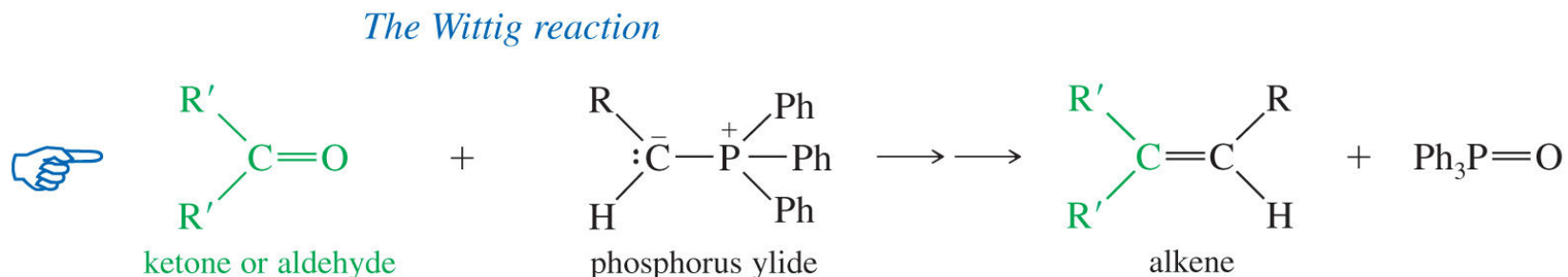
# Mechanism of Cyanohydrin Formation



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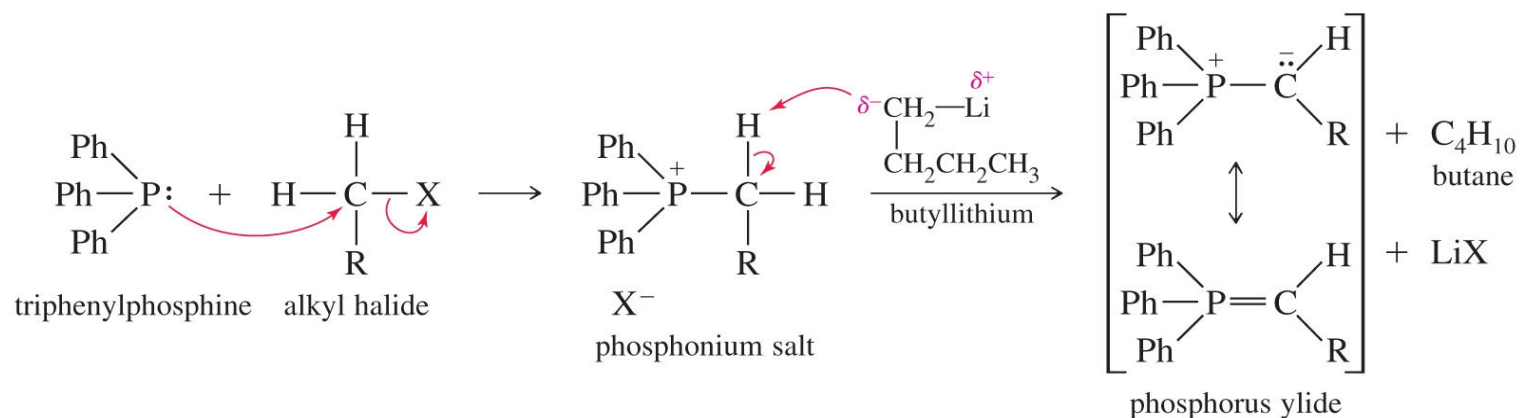
- Wittig Reaction (18.13)

The Wittig reaction is the addition of a phosphorus ylide to the carbonyl. The initial reaction is quickly followed by the rearrangement of the intermediate into the alkene and a phosphine oxide.

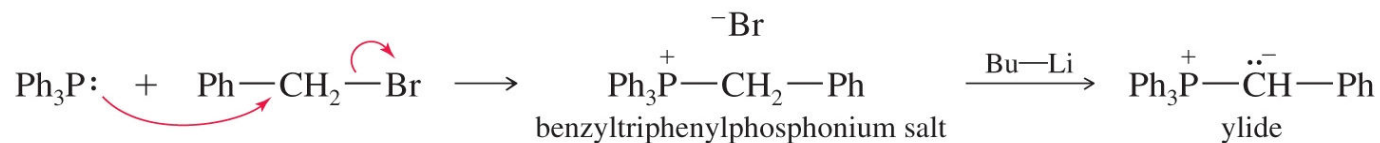
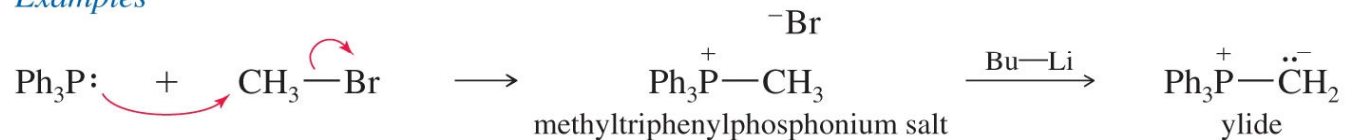


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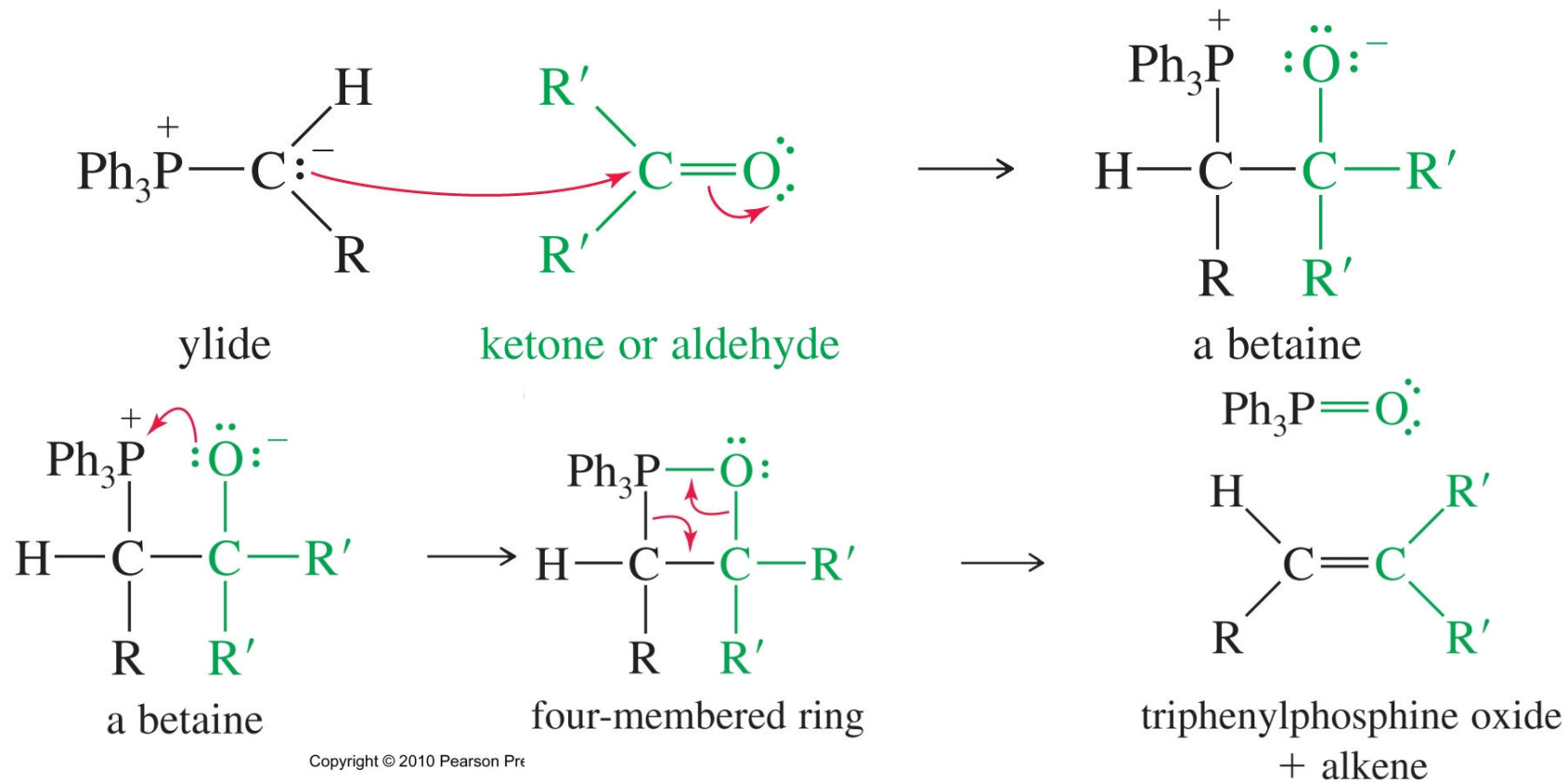
- The phosphonium ylide required for this reaction can be prepared by  $S_N2$  reaction of a phosphine and an alkyl halide, followed by deprotonation of the phosphonium salt with a strong base such as an alkyl lithium. Phosphorus ylides are stable due to resonance.



*Examples*



# Mechanism of the Wittig Reaction

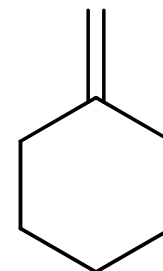


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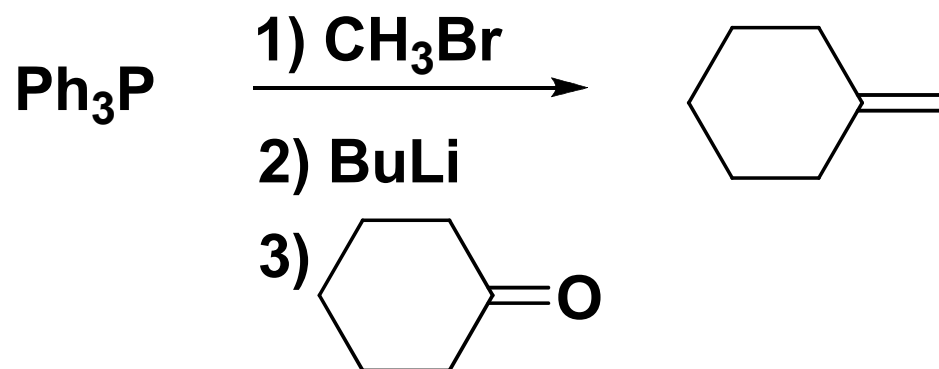
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- **The formation of the ylide follows the principles discussed for  $S_N2$  reaction (CHEM201 section 8). This means that if 2 choices are available, pick the one using the least sterically hindered alkyl halide.**

- The Wittig reaction is an **excellent method** to make alkenes since it is completely **regioselective** (know exactly where the double bond will be).
- How would you make this compound?  
How successful will you be?



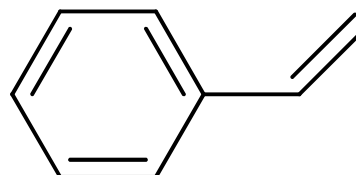
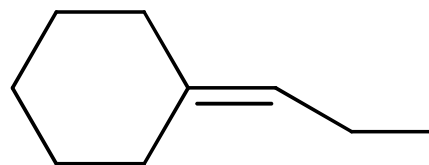
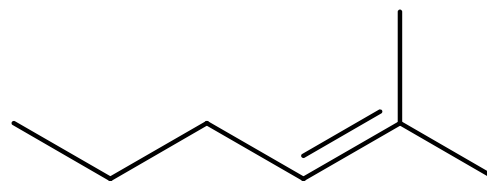
- But the **Wittig** reaction will give only the desired product since it is regioselective. The double bond is found at the same location that was previously occupied by the carbonyl **C=O**.



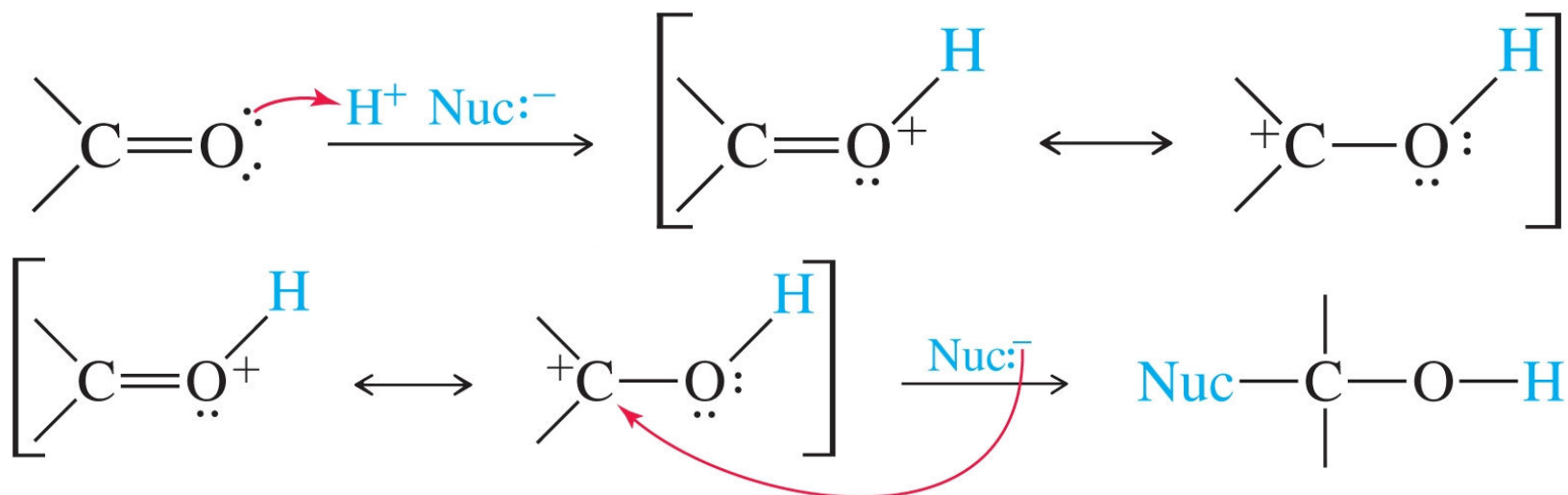


# Practice Question

- How would you prepare the following alkenes using a Wittig reaction?



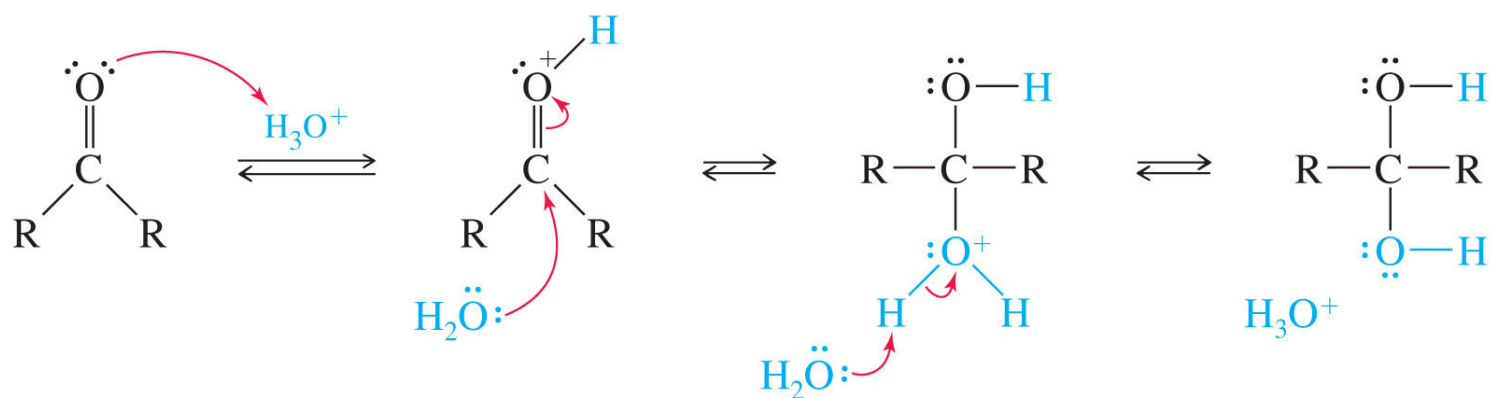
- For weak nucleophile,  $\text{H}_2\text{O}$ ,  $\text{ROH}$  and others, a strong acid is required to activate the carbonyl via the protonation of the oxygen. This is simply because the nucleophile is not strong enough to attack the electrophilic carbon. An example of this is the hydration of a ketone.



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- Hydration of Aldehydes and Ketones (18-14)

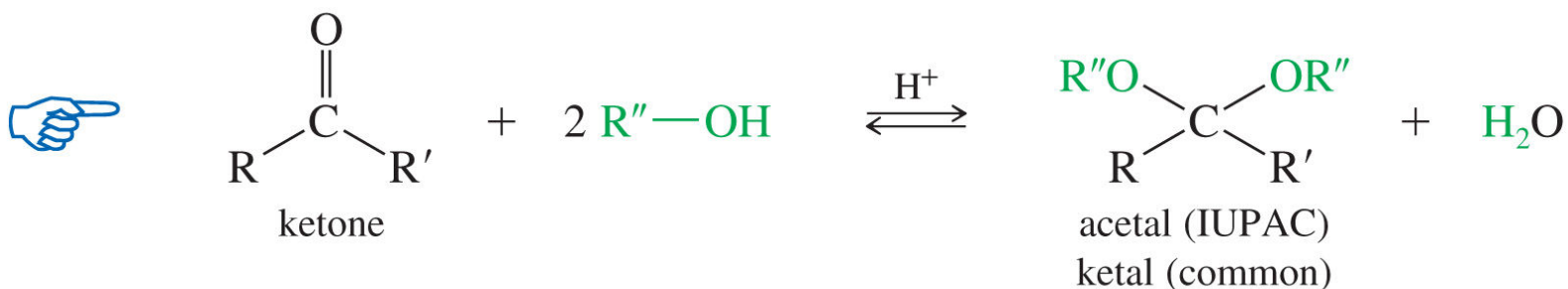
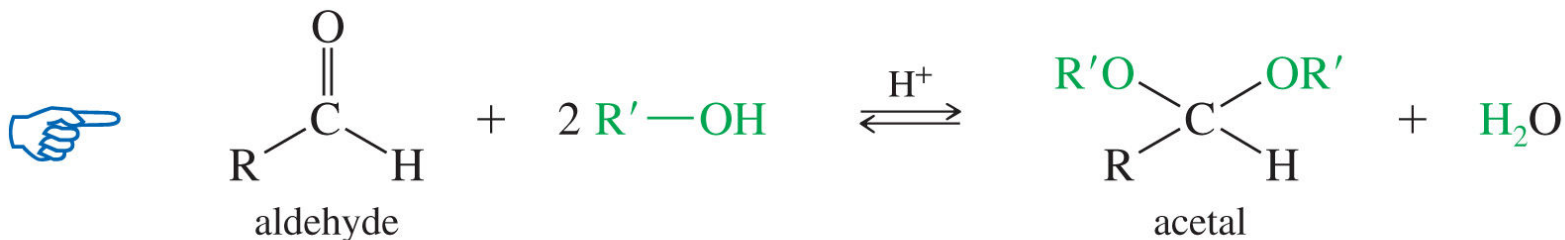
**Addition of water to the carbonyl is a good example illustrating the need to activate the carbonyl by protonation. This reaction is not a very useful reaction in the forward process since the carbonyl hydrate will rearrange to the carbonyl. However, when a carbonyl hydrate is formed during a reaction, the resulting product will be the ketone or aldehyde.**



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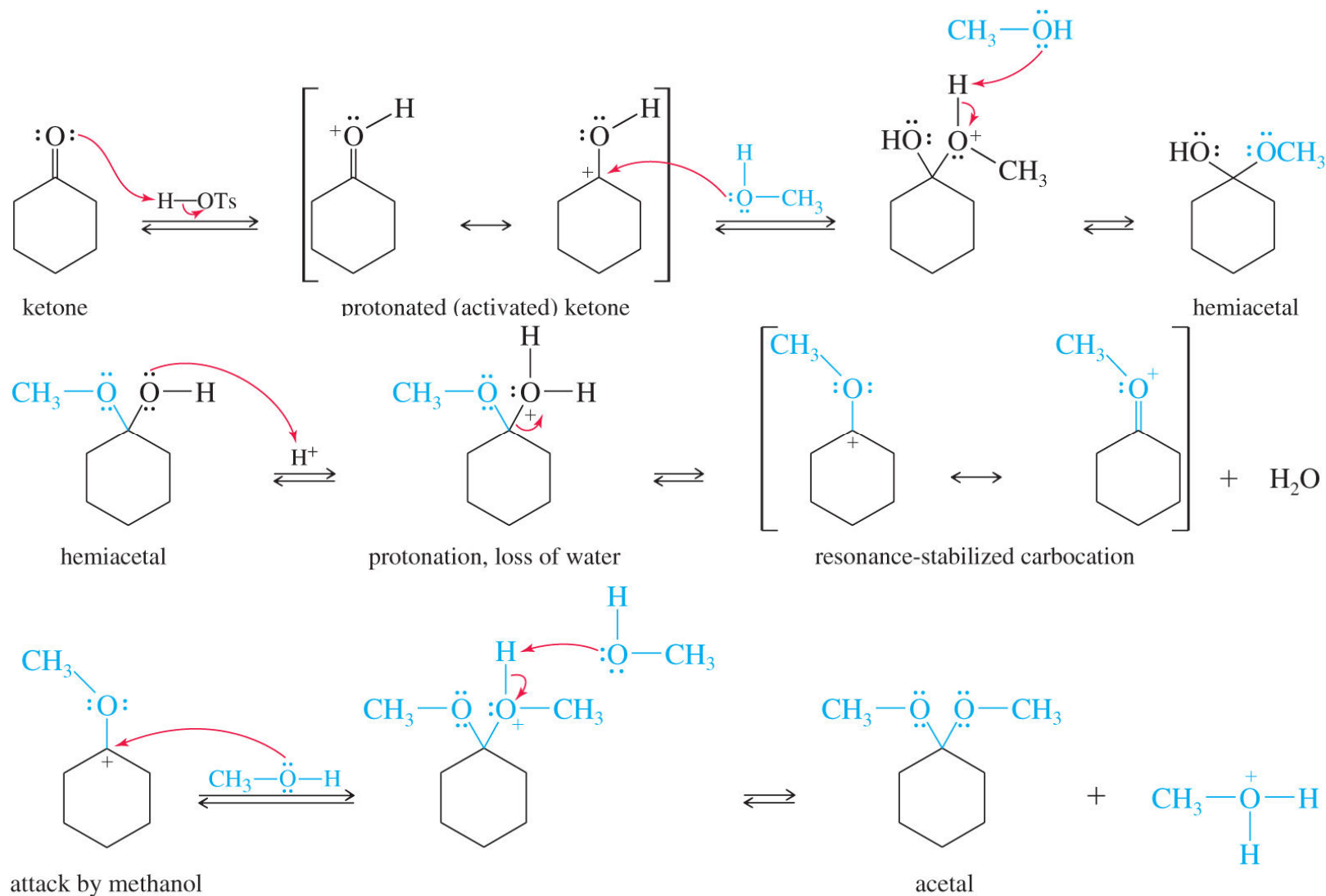
- Addition of Alcohols (Acetal Formation) (18.18)

**Addition of alcohols follows a similar mechanism. However, this reaction is very important in organic synthesis since it represent a good method to “protect” the carbonyl group.**



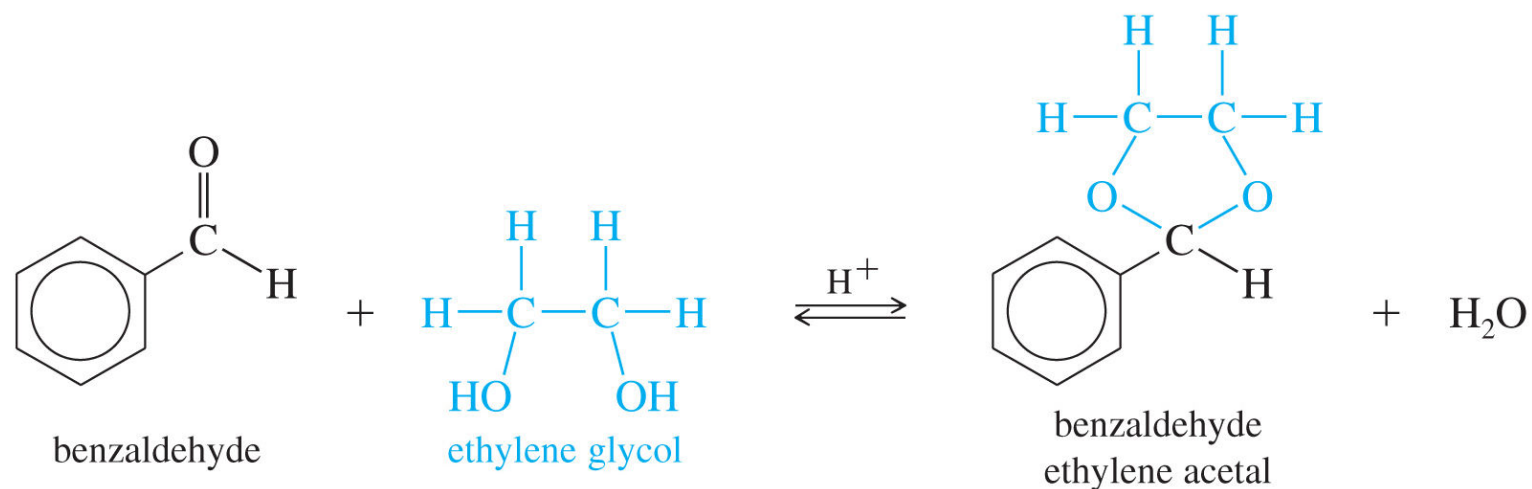
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# Mechanism of Acetal Formation



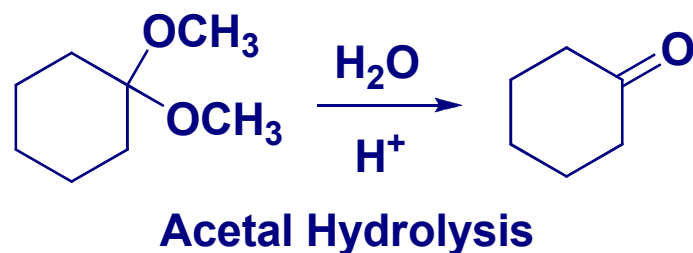
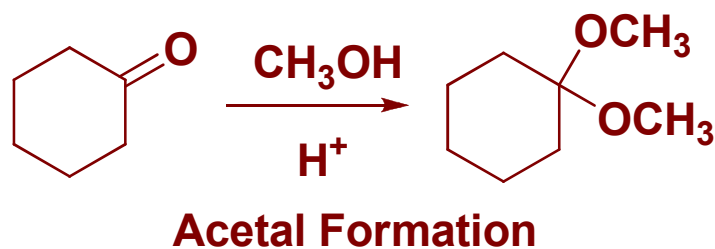
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- **Acetals can also be cyclic. In these cases, a diols is used to form the acetal.**



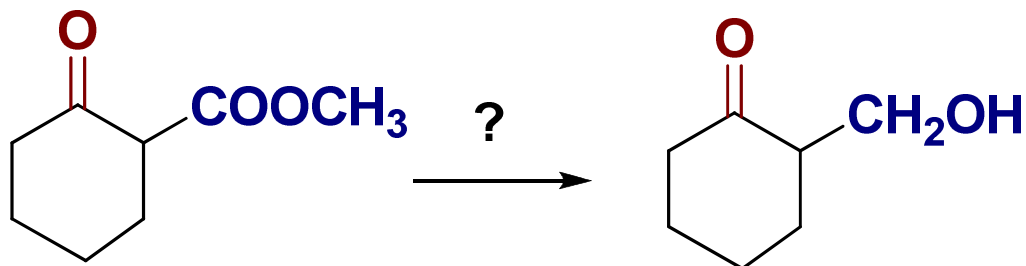
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- Use of Acetals as Protective Group (18-19)
- Because the reaction is reversible, acetals can be used to protect ketones/aldehydes from unwanted reactions, then the hydrolysis of the acetal regenerates the carbonyl compound.



## How do protecting group work?

- Suppose you want to carry out this reduction? Not easy, since the ketone is more reactive than the ester, and we have seen that to reduce an ester  $\text{LiAlH}_4$  is required (this will also reduce the ketone).



The **ketone** is more reactive than the **ester** and will be reduced first. However since the **ketone** is more reactive, it can be protected then hydrolysed back to the carbonyl once the **ester** has been reduced.



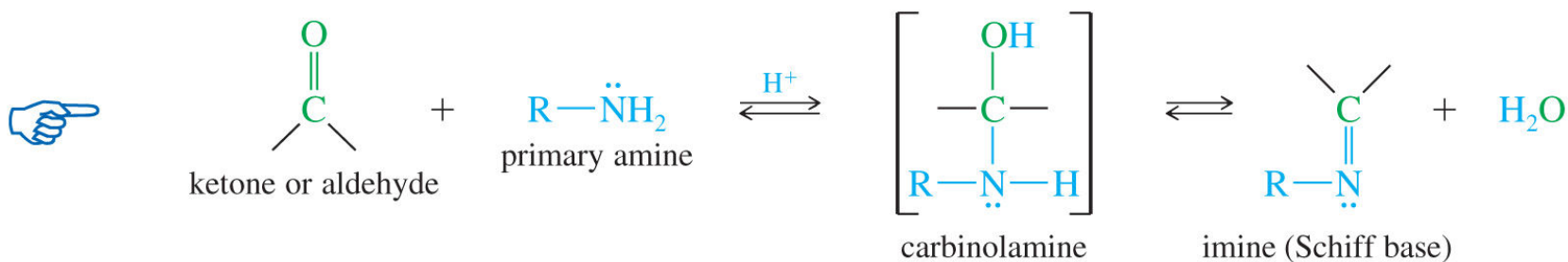
- The use of a **protecting group** can solve this problem.



aqueous acid protonates the alkoxide ion as well as hydrolyze the acetal to the corresponding ketone

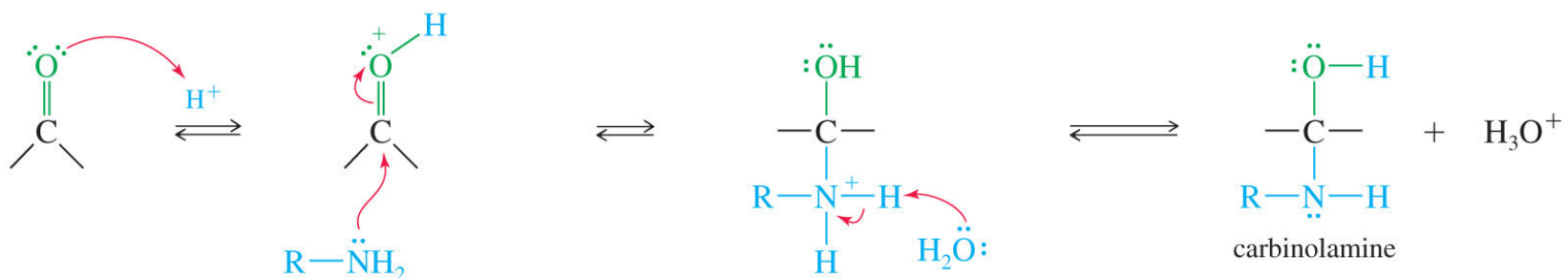
- Formation of Imines (18-16)

Aldehydes and Ketones react with 1° and 2° amines to give either imines or enamines. These products can be used as protective groups for the carbonyl and in the formation of amines or alkanes. We will see later that they are also useful in alkylation and condensation reactions.

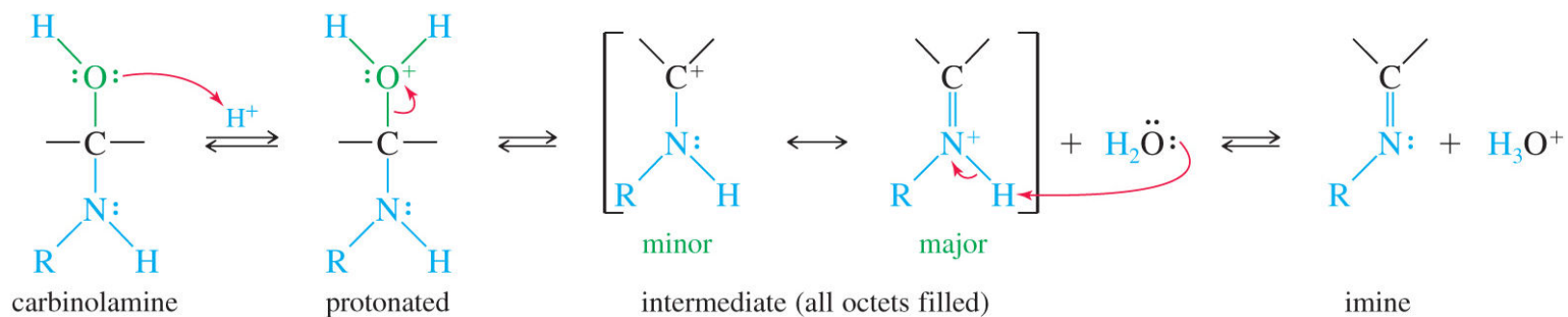


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# Mechanism of Imine Formation

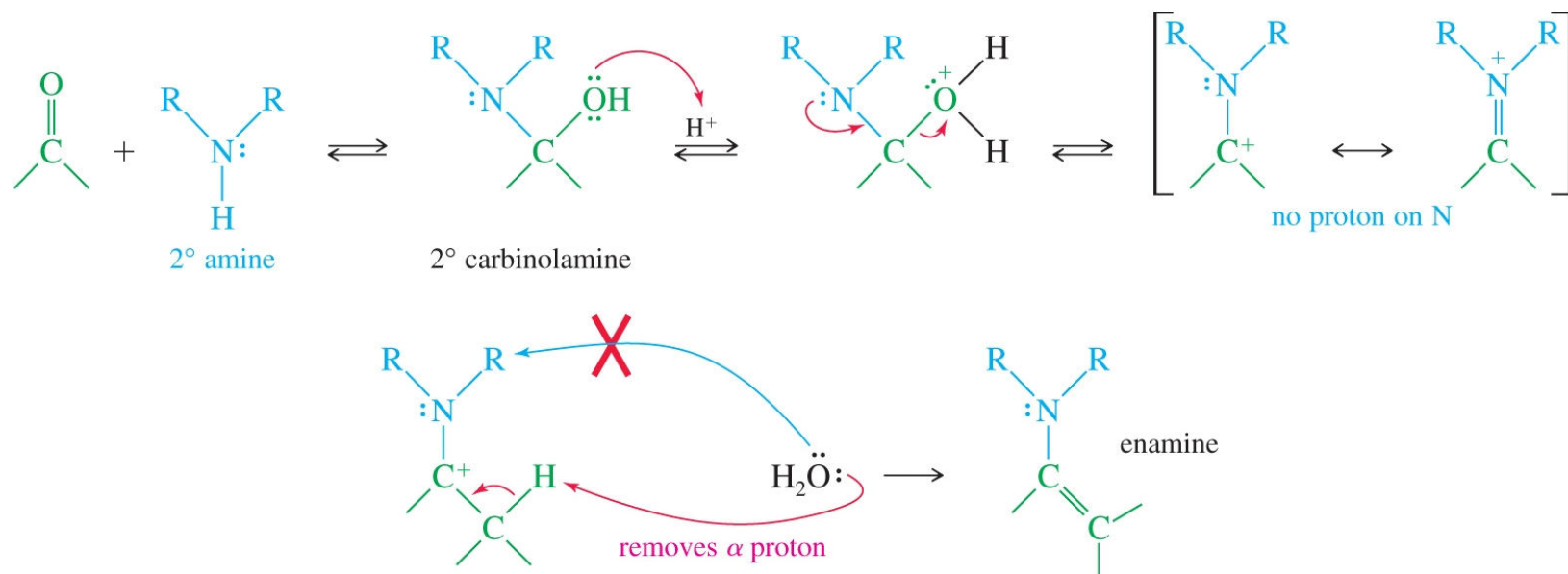


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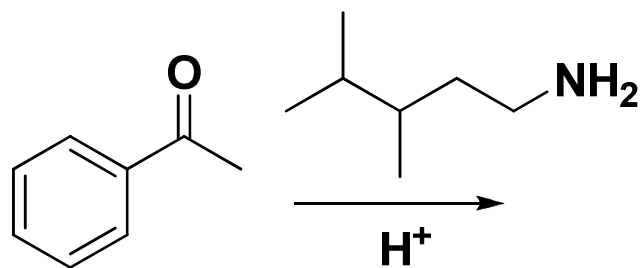
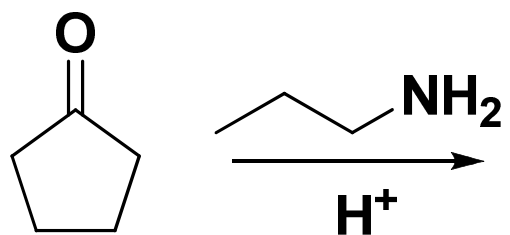
# Mechanism of Enamine Formation



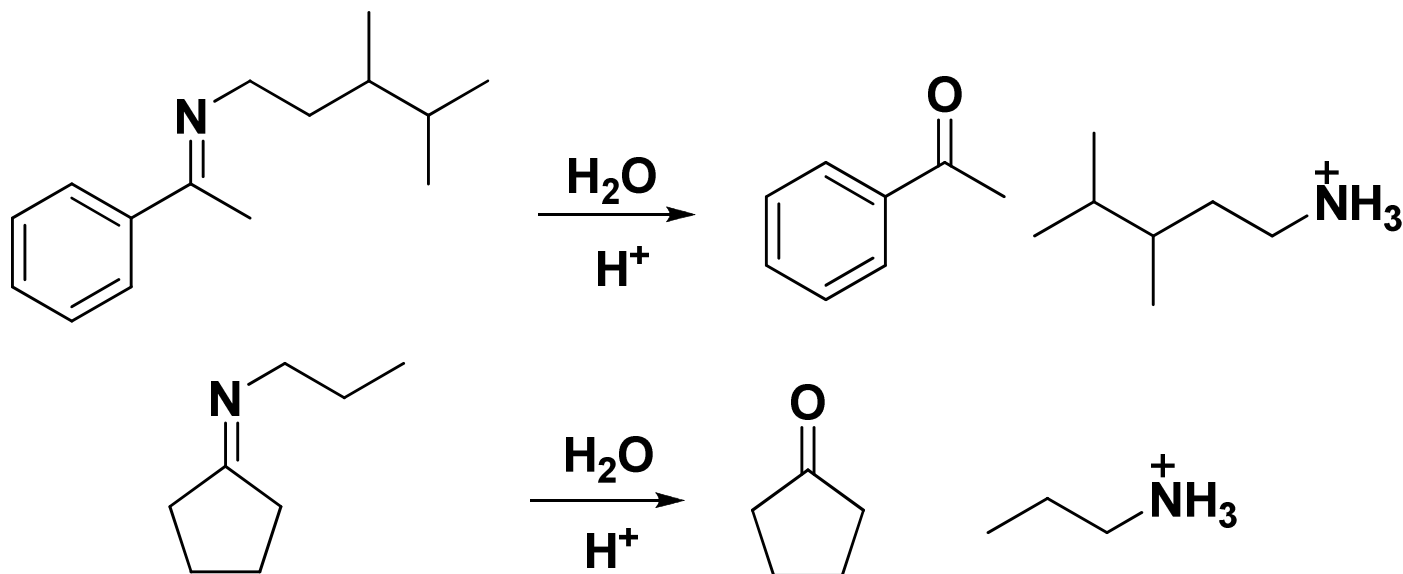
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# Practice Question

- What are the product of the following reactions?



**Imines can be hydrolyzed back to the corresponding carbonyl. Hence they can be used as protecting groups.**



- Condensations of Hydroxylamine and Hydrazines (18-17)

Many imine derivatives are available via the same reaction which gives the imine.

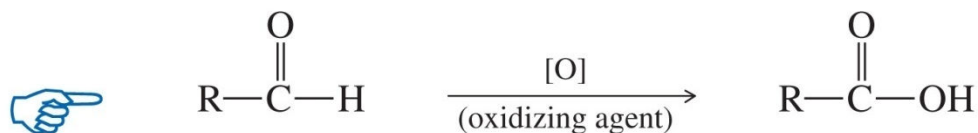


<i>Z in Z—NH<sub>2</sub></i>	<i>Reagent</i>	<i>Product</i>
—H	$\text{H}_2\ddot{\text{N}}-\text{H}$ ammonia	$\text{>C=}\ddot{\text{N}}-\text{H}$ an imine
—R	$\text{H}_2\ddot{\text{N}}-\text{R}$ primary amine	$\text{>C=}\ddot{\text{N}}-\text{R}$ an imine (Schiff base)
—OH	$\text{H}_2\ddot{\text{N}}-\text{OH}$ hydroxylamine	$\text{>C=}\ddot{\text{N}}-\text{OH}$ an oxime
—NH <sub>2</sub>	$\text{H}_2\ddot{\text{N}}-\text{NH}_2$ hydrazine	$\text{>C=}\ddot{\text{N}}-\text{NH}_2$ a hydrazone
—NHPh	$\text{H}_2\ddot{\text{N}}-\text{NHPh}$ phenylhydrazine	$\text{>C=}\ddot{\text{N}}-\text{NHPh}$ a phenylhydrazone
$\text{—NHC(=O)NH}_2$	$\text{H}_2\ddot{\text{N}}-\text{NH}-\text{C(=O)}-\text{NH}_2$ semicarbazide	$\text{>C=}\ddot{\text{N}}-\text{NH}-\text{C(=O)}-\text{NH}_2$ a semicarbazone

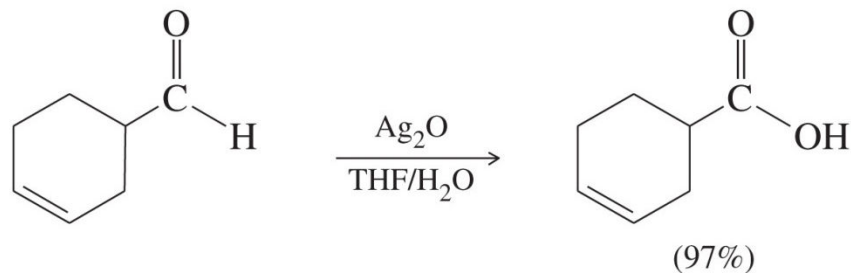
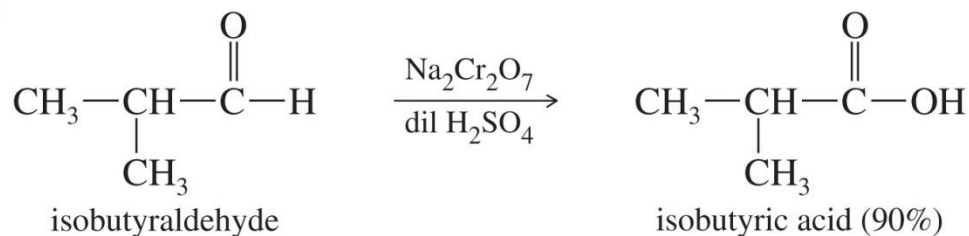
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- Oxidation of Aldehydes (18-20)

We have seen that alcohols can be oxidized to aldehyde with PCC (alcohols, section I), and that the aldehyde product could be further oxidized to the corresponding carboxylic acid with stronger oxidizing agents.

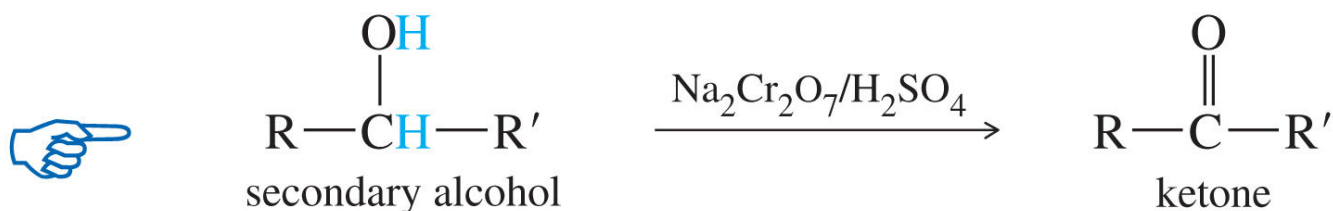


*Examples*

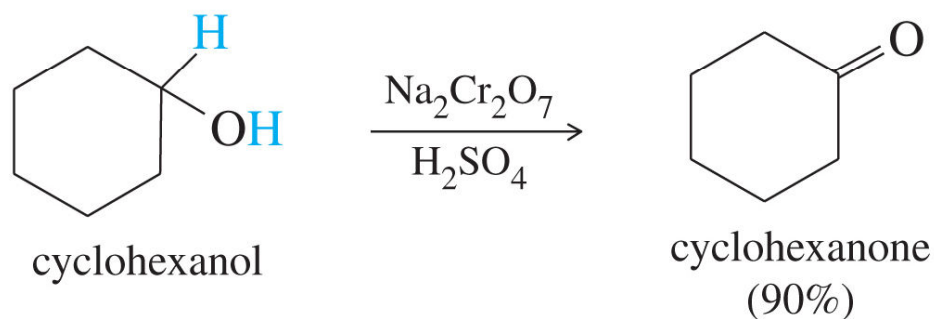




- **We have also established that ketones, because of their structures cannot be oxidized with conventional oxidizing agents.**



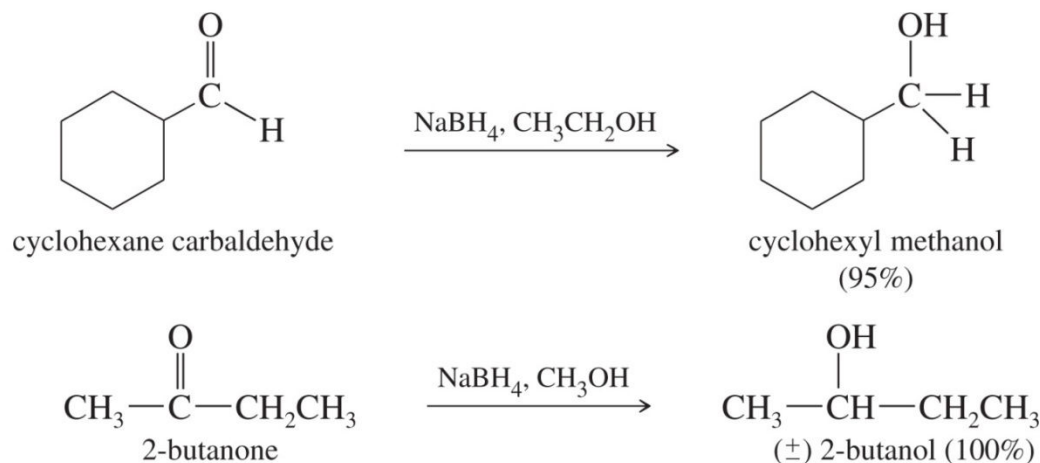
*Example*



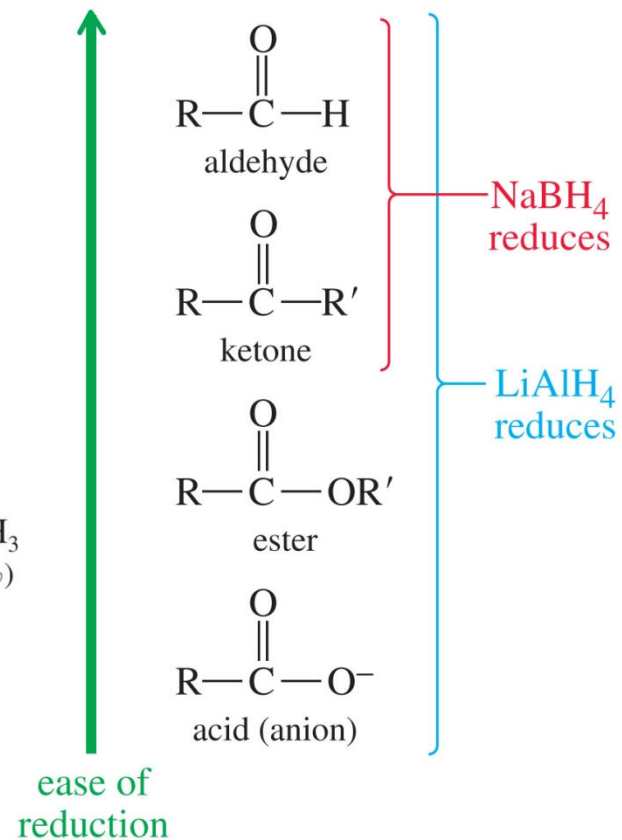
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- Reductions of Ketones and Aldehydes (18-21)

- We have already seen that it is possible to reduce aldehydes and ketones with two different reagents,  $\text{NaBH}_4$  and  $\text{LiAlH}_4$



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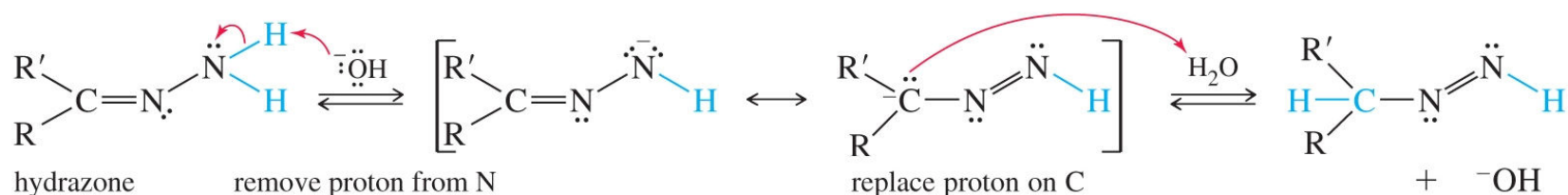
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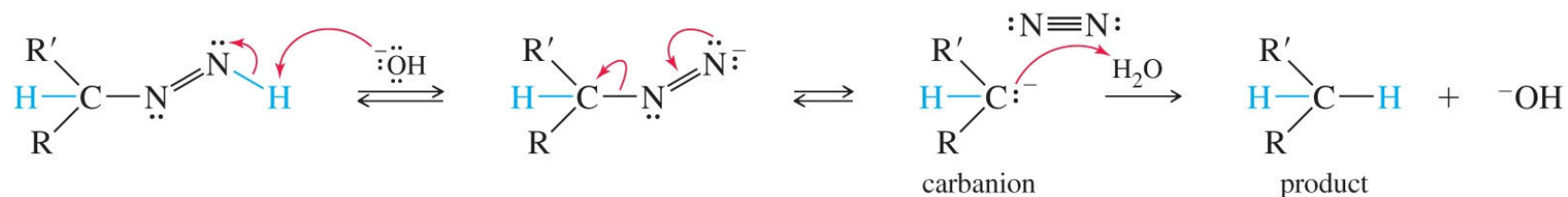


## Wolf-Kishner Reduction

The reaction goes through a **hydrazone intermediate** (imine derivative) followed by **hydrolysis with base**.



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