

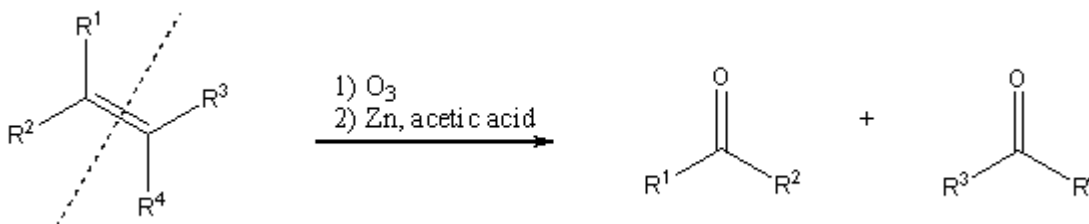
Average for the midterm is 102.5 / 150 (approx. 68%).

## Preparation of Aldehydes and Ketones

There are several methods to prepare aldehydes and ketones. We will only deal with a few different methods in this class. Most of these methods should be a review from Chem 161/263.

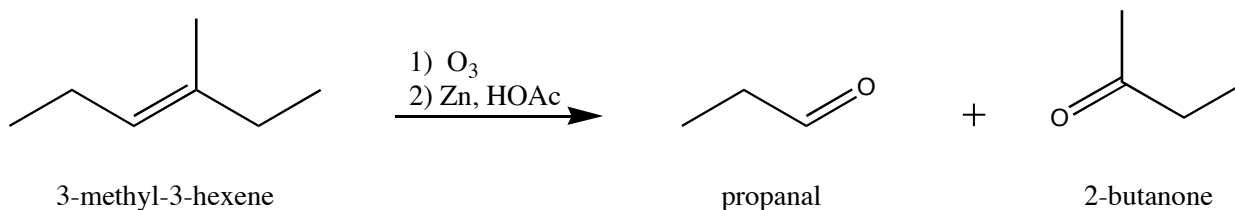
### 1. Ozonolysis

In ozonolysis, the double bond is cleaved and 2 new carbonyls are formed.



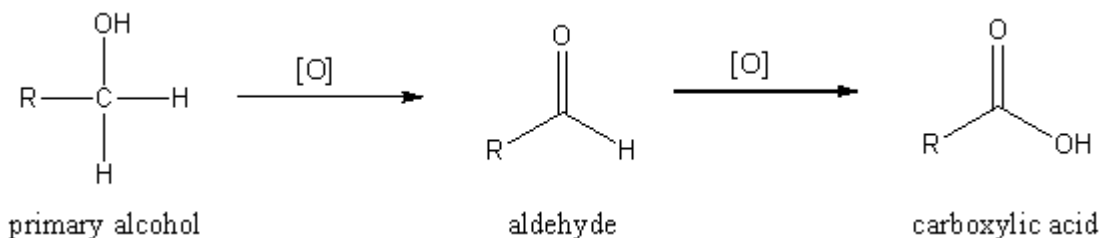
When R = H, an aldehyde is formed. Therefore, for ozonolysis, depending on the R groups of the starting alkene, the product can be aldehydes and/or ketones.

*Example:*



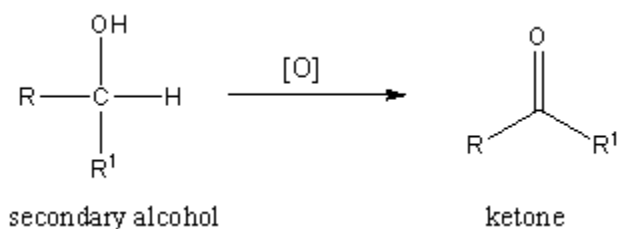
### 2. Oxidation of primary and secondary alcohols

Oxidation of a primary (1°) alcohol gives an aldehyde, but in aqueous conditions, subsequent oxidation of the aldehyde can also occur, yielding the carboxylic acid:



The oxidation of the aldehyde to the carboxylic acid is a faster reaction than the oxidation of the alcohol to the aldehyde. Thus, it is often difficult to oxidize just to the aldehyde when the oxidation is performed in aqueous conditions. For this reasons, special oxidizing agents are required.

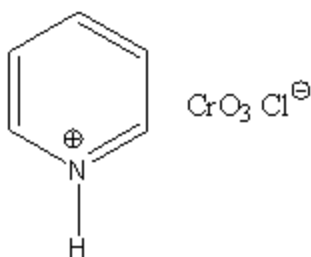
Oxidation of secondary ( $2^\circ$ ) alcohols gives ketones as products:



From the reaction schemes shown above, you will notice in the oxidation, there is a loss of hydrogen from the carbon bearing the hydroxyl group. Because of this, tertiary alcohols cannot be oxidized since there is no hydrogen on this carbon.

Shown below are three different reagents that can be used to perform the oxidation of either  $1^\circ$  or  $2^\circ$  alcohols to their corresponding aldehydes or ketones:

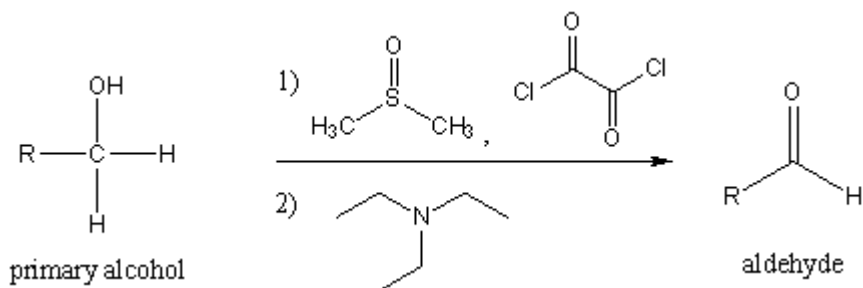
**a) PCC (pyridinium chlorochromate)**



This reagent is especially useful for the oxidation of primary alcohols to aldehydes. An aldehyde can be over-oxidized to the carboxylic acid if water is present in the reaction. Since PCC is soluble in organic solvents (such as dichloromethane,  $\text{CH}_2\text{Cl}_2$ ), the reaction can be kept away from water, and over-oxidation is prevented

PCC oxidizes **primary alcohols** to **aldehydes** and **secondary alcohols** to **ketones**.

## b) Swern Oxidation



This is a two step reaction. The first step requires dimethyl sulphoxide (DMSO) and oxalyl chloride. The second step requires the addition of a base, such as triethylamine (it has a lone pair on the nitrogen, therefore it is basic).

The Swern Oxidation is a nice alternative to the chromium based methods since it avoids the chromium (which is toxic), and can be carried out under very mild conditions. Swern oxidation selectively oxidizes **primary alcohols** to **aldehydes**. It also converts **secondary alcohols** to **ketones**.

## c) Jones Oxidation

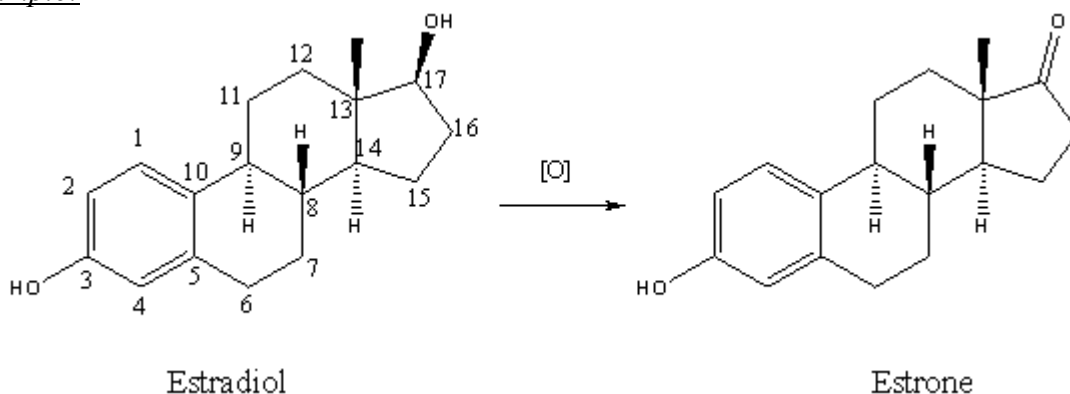
Jones Oxidation uses chromic acid (Jones Reagent) to carry out the oxidation. Jones reagent is prepared by adding CrO<sub>3</sub> (or Na<sub>2</sub>Cr<sub>2</sub>O<sub>7</sub>) to sulphuric acid (H<sub>2</sub>SO<sub>4</sub>). The oxidation is performed in aqueous acetone solutions.

Jones oxidation will not selectively oxidize **primary alcohols** to aldehydes. Instead, it will over-oxidize to give **carboxylic acids**. **Secondary alcohols** will be oxidized to give **ketones**.

The nice thing about this reaction is that the reagents are fairly cheap and the reaction can be monitored by a colour change. Cr<sup>6+</sup> is orange, whereas Cr<sup>3+</sup> is green. During the reaction, chromium gets reduced and its oxidation state changes from Cr<sup>6+</sup> to Cr<sup>3+</sup>. This results in a colour change from orange to green that allows one to monitor the completion of the reaction.

*Note:* this reaction is carried out in harsh acidic condition. The starting material cannot be sensitive to acids, or else it can be decomposed by the acid.

Example:



You should be recognize that the above structures are steroids. You should also remember how to number the carbon skeleton, as well as differentiate alpha and beta substitutions (this is from last lecture).

For the above reaction, the beta hydroxyl group at C17 is converted to ketone. *What reagents do you use for this reaction?*

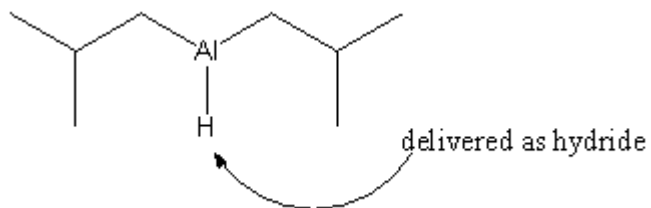
**Answer:** any of the above 3 reagents can be used since the OH is secondary. They all oxidize secondary alcohols to ketones.

### 3. Reduction of acid chlorides, esters, and nitrides – to make aldehydes

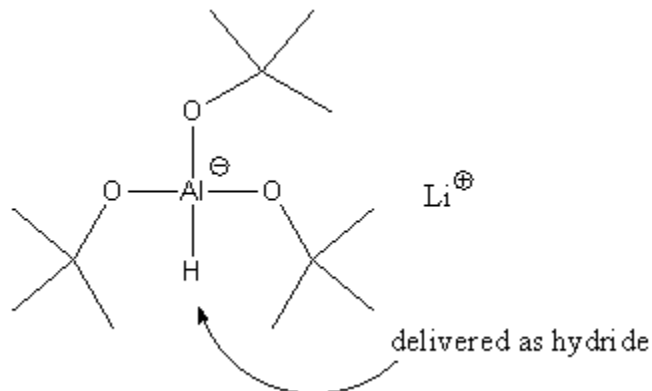
These reactions are carried out using a hydride ion ( $H^-$ ). Note the difference between a **proton** ( $H^+$ ) which is positively charged (acts as an electrophile), and **hydride** ( $H^-$ ) which is negatively charged with a pair of electron (acts as a nucleophile).

Two common reagents used to deliver the hydride ion are:

a) **DIBAL-H: diisobutylaluminum hydride**  
( $AlH(i-Bu)_2$ )



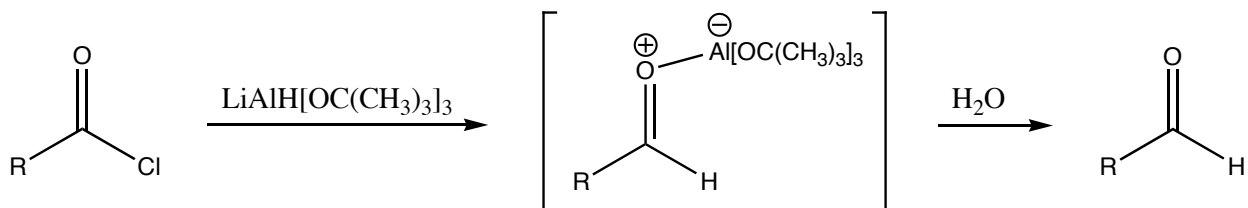
b) **Lithium tri-*tert*-butoxyaluminum hydride**  
( $LiAlH[OC(CH_3)_3]_3$ )



Use of stronger hydride donors (such as  $\text{LiAlH}_4$ ) leads to overreduction of the aldehyde or ketone, right down to the alcohol (aldehydes reduce  $1^\circ$  alcohol and ketones reduce to  $2^\circ$  alcohols). The two hydride donors shown above are not as reactive as  $\text{LiAlH}_4$  since they are sterically more bulky. This makes it harder for them to transfer the hydride ion to the carbonyl carbon.

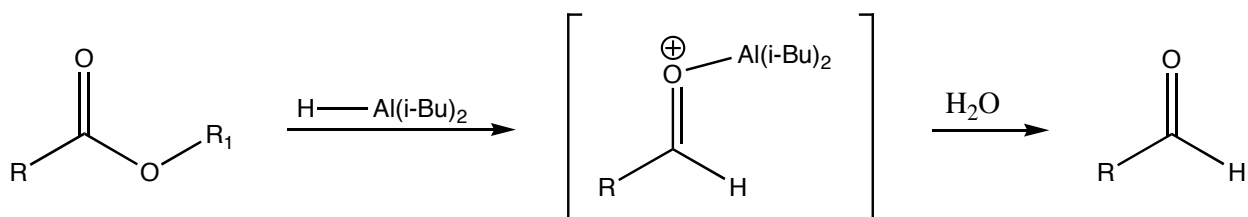
### Reduction of Acid Chlorides

To reduce an acid chloride, lithium tri-*tert*-butoxyaluminum hydride is used as the hydride donor. This reagent does not further reduce the aldehyde to the alcohol. The aqueous work-up (water) breaks the oxygen aluminum complex:



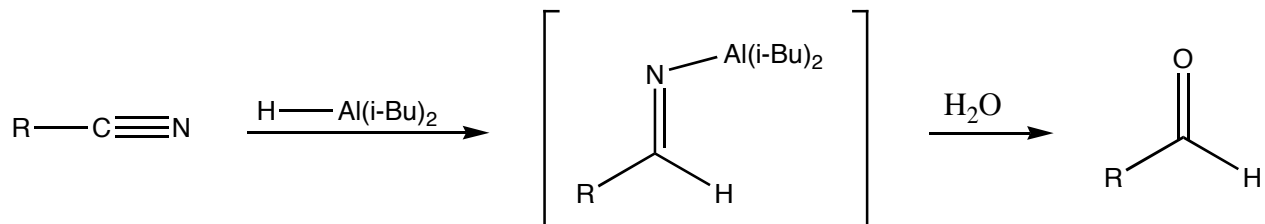
### Reduction of Esters

DIBAL-H can be used to reduce esters. Again, reduction stops at the aldehyde stage and water is added to hydrolyze the aluminum complex.



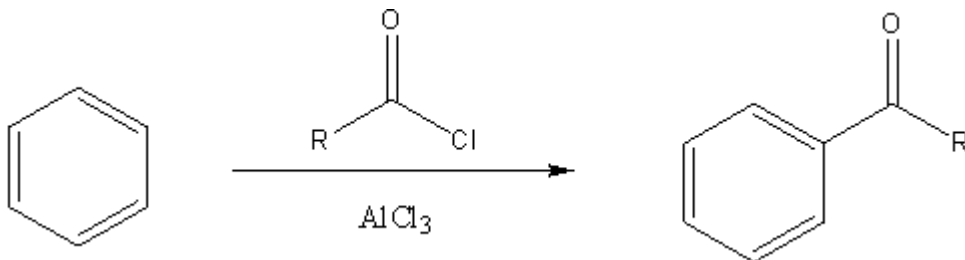
### Reduction of Nitriles

In this reaction, hydride attacks the carbon of the cyano group, resulting in the formation of an iminium-aluminum complex. The aqueous work-up breaks up the complex and hydrolyzes the imine to the carbonyl



#### 4. Friedel-Crafts Acylation – to make ketones

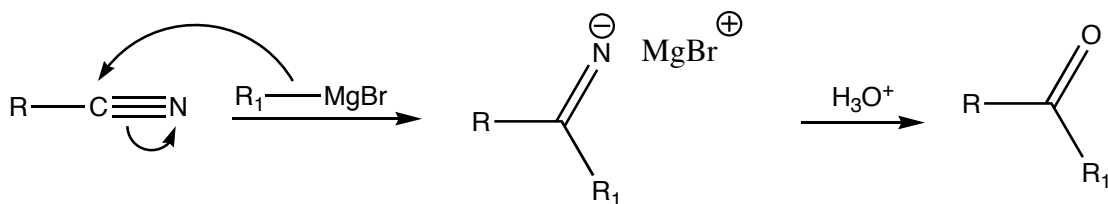
Treating an arene with an acid chloride or acid anhydride, in the presence of a Lewis acid, results in the formation of the ketone.



If the benzene ring is substituted, you must think about the directing effects of the substituent(s) in order to find out where the acylation will occur.

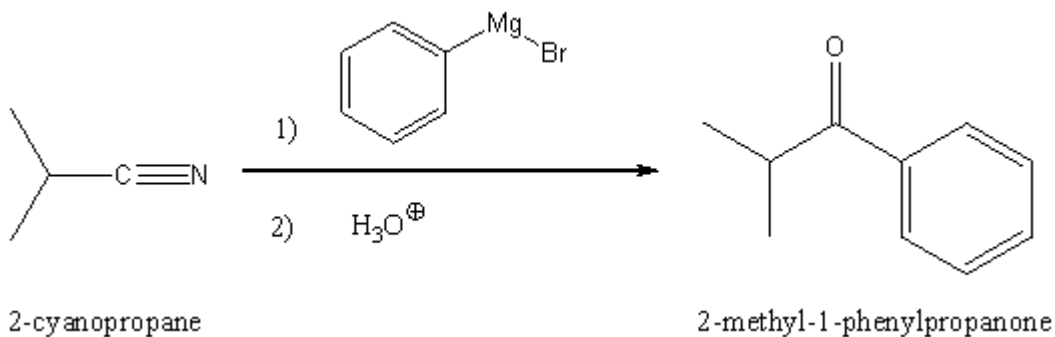
#### 5. Organometallic Reagent – to make ketones

##### a) Grignard reagent (R-MgBr)



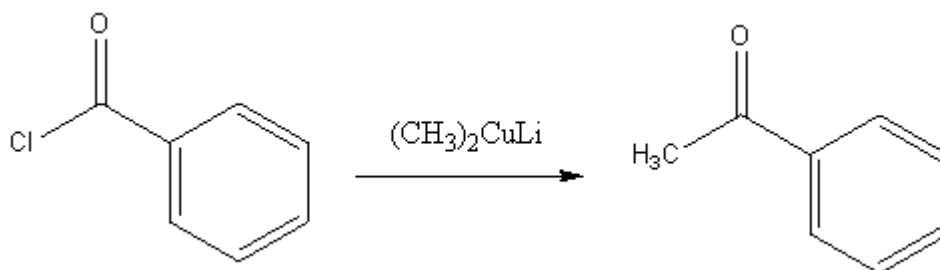
The alkyl group attacks the cyano carbon to give the iminium ion. Acidic workup yields the ketone.

*Example:*



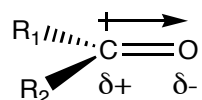
### b) Lithium dialkylcuprates ( $R_2CuLi$ )

When an acid chloride is treated with a lithium dialkylcuprate, a ketone is formed. One of the alkyl groups from the organometallic reagent is transferred to the carbonyl.

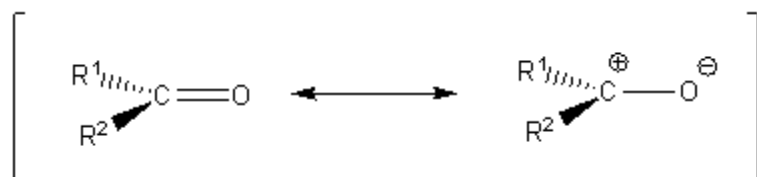


## Reactions of Aldehydes and Ketones

A carbonyl bond has some unique structural and electronic features that help to explain its reactivity. First of all, it is important to recognize that the carbonyl bond is polarized:



As a result, the carbonyl carbon bears a partial positive charge and the oxygen bears a partial negative charge. Because of this polarization, the carbonyl carbon is somewhat electron deficient, and hence electrophilic – it is therefore susceptible to nucleophilic attack. The electrophilicity of the carbonyl carbon is enhanced by acid catalysis. The electron deficient carbon can also be depicted by drawing resonance structures:

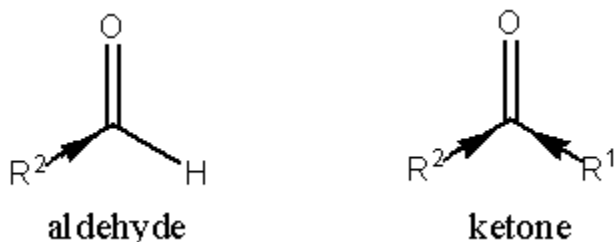


The geometry of the carbonyl group is trigonal planar, meaning that it is flat. This flat arrangement makes it easier for a nucleophile to access that carbonyl carbon. In addition, a nucleophile may approach from either face of the carbonyl.

In general, an aldehyde is more reactive than a ketone. This difference in reactivity can be explained by considering both *steric* and *electronic* factors:

1. **Sterics:** a hydrogen is a lot smaller than an alkyl group. It is easier for a nucleophile to attack. Also, the tetrahedral intermediate is less crowded and so, more stable.

2. **Electronics:** an alkyl group is electron donating/releasing. A ketone has two alkyl groups attached to the carbonyl carbon – this reduces the electrophilicity of the carbonyl carbon, compared to an aldehyde.



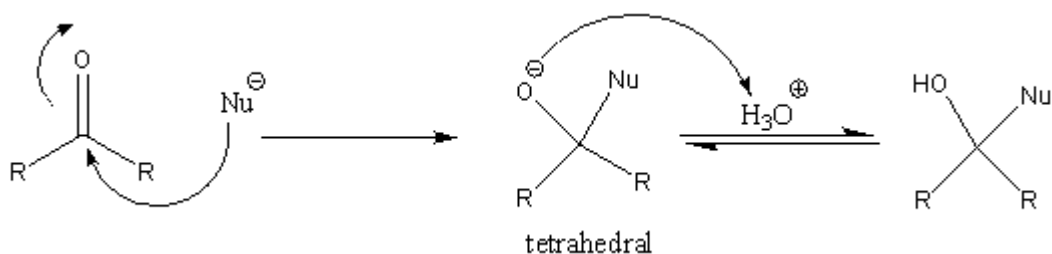
### Types of Reactions:

There are 4 types of reaction we will deal with:

1. nucleophilic attack at the carbonyl carbon
2. nucleophilic attack at the carbonyl carbon, follow by elimination
3. reactions at the alpha carbon
4. conjugate addition (for  $\alpha,\beta$  unsaturated carbonyl systems)

### 1) Nucleophilic Attack

The general mechanism is shown below:



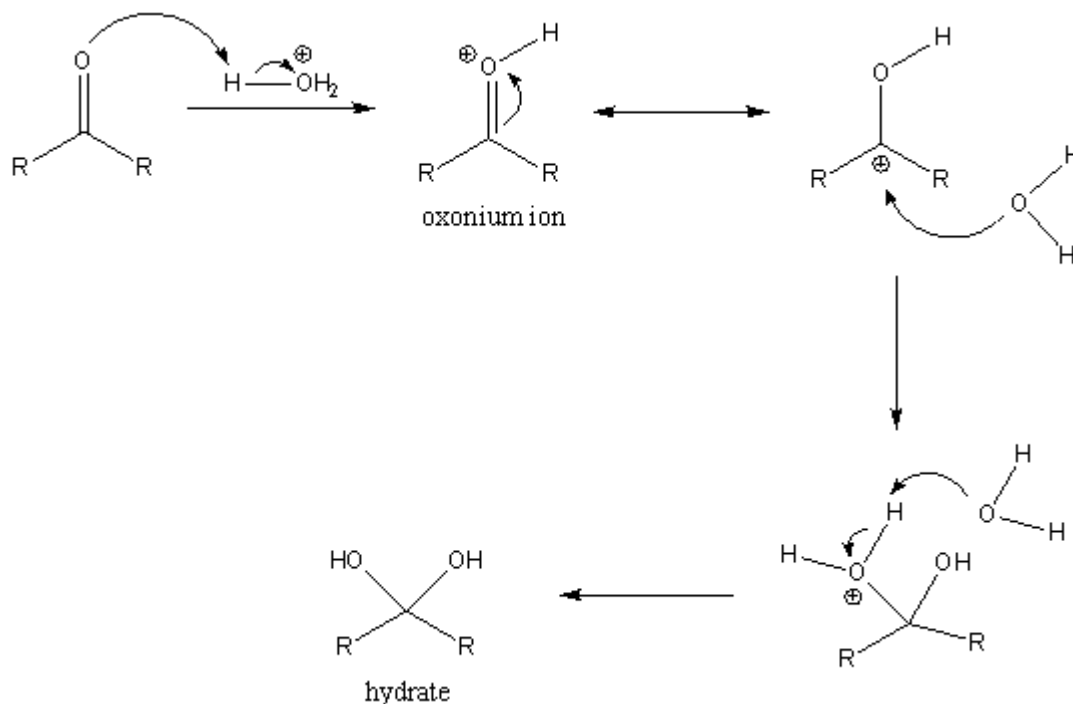
The  $\text{sp}^2$  carbonyl carbon becomes  $\text{sp}^3$  during the attack. The reversibility of the attack depends on the type of nucleophile. There are two types of nucleophiles - strong and weak

- **Strong Nucleophiles** – these react very fast and attack the carbonyl carbon irreversibly. Examples of strong nucleophiles are the hydride ion,  $\text{H}^-$  (from reagents like lithium aluminum hydride,  $\text{AlH}_4$ , and sodium borohydride,  $\text{NaBH}_4$ ) and alkyl anions,  $\text{R}^-$  (from Grignard reagents)
- **Weak Nucleophiles** – these attack the carbonyl carbon reversibly



a) **Hydrate formation:**

This is the addition of water to an aldehyde or ketone. The reaction proceeds under acidic or basic conditions. The general mechanism under acidic conditions is shown below:



Under acidic conditions, the oxygen of the carbonyl group is protonated, forming an oxonium species. This protonation enhances the reactivity of the carbonyl carbon and makes it more electrophilic – this can be understood by drawing resonance structures. The oxygen of a water molecule then attacks the carbonyl carbon. In the last step of the reaction, another water molecule removes a proton, regenerating the acid catalyst and yielding the hydrate.