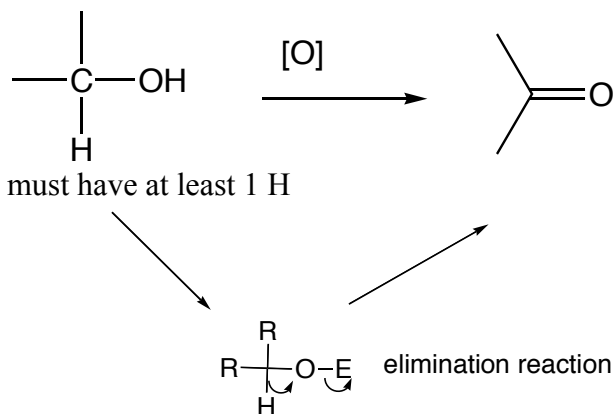


## Preparation of Ketones and Aldehydes from Alcohols

### Oxidation of Alcohols



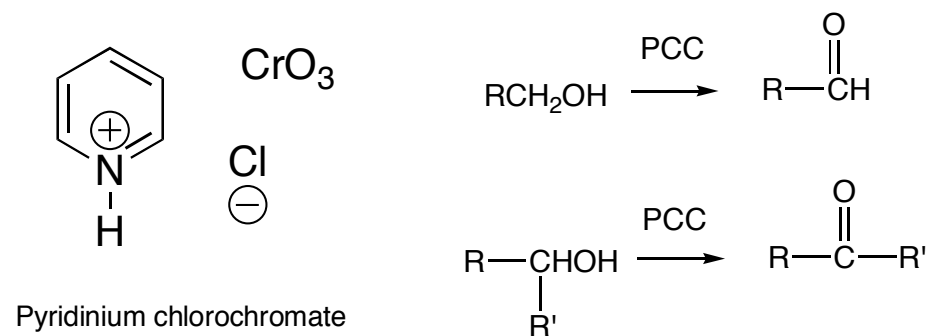
[O] = oxidation; removal of electrons

[H] = reduction; addition of electrons

There are many reagents that can be used for this reaction. Only three are given in this course:

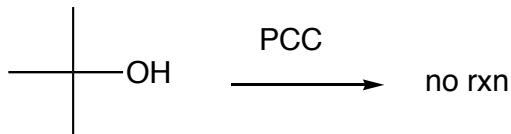
- 1) Pyridinium chlorochromate (PCC)
- 2) Chromic acid (Jones reagent) –  $\text{H}_2\text{CrO}_4$
- 3) Swern oxidation – oxalyl chloride, dimethyl sulfoxide (DMSO), base

#### 1. PCC:

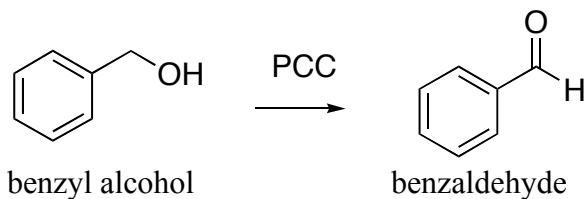
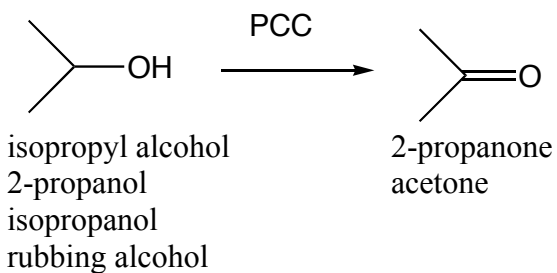


PCC needs an H to work (i.e., 1° or 2° alcohol but not 3° alcohols).

Examples:



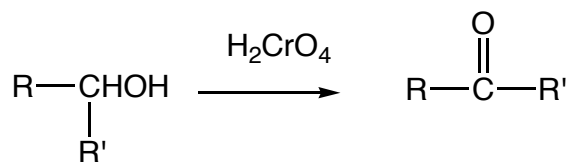
(no H)  
*tert*-butyl alcohol  
2-methyl-2-propanol



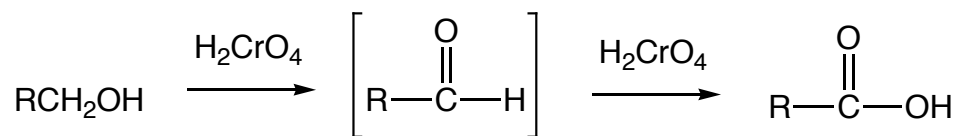
## 2. H<sub>2</sub>CrO<sub>4</sub> aka chromic acid, Jones reagent

This reagent is orange, and as it reacts it becomes green. It turns secondary alcohols into ketones, and primary alcohols into carboxylic acids. Primary alcohols first form aldehydes, but the reagent quickly reacts with the aldehyde to form the carboxylic acid. Tertiary alcohols are unreactive.

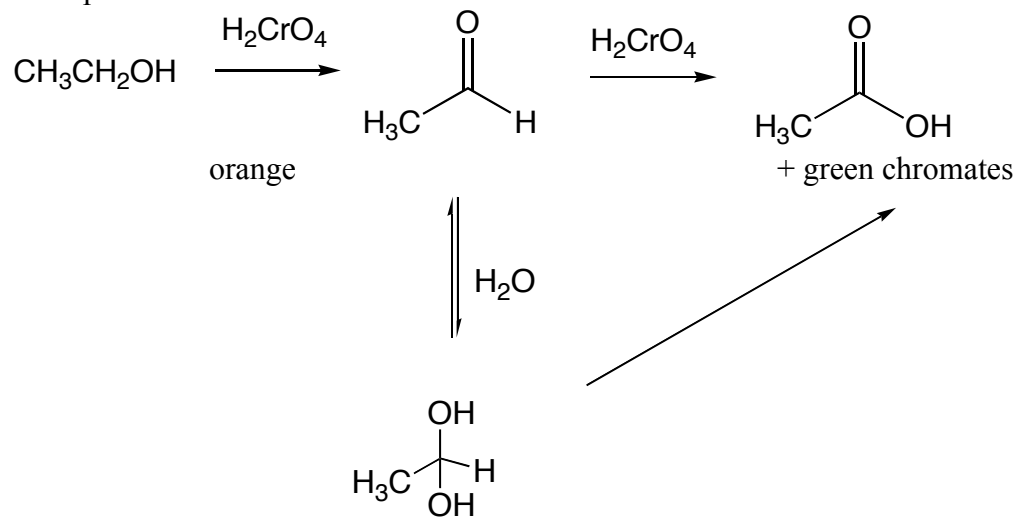
Secondary Alcohol:



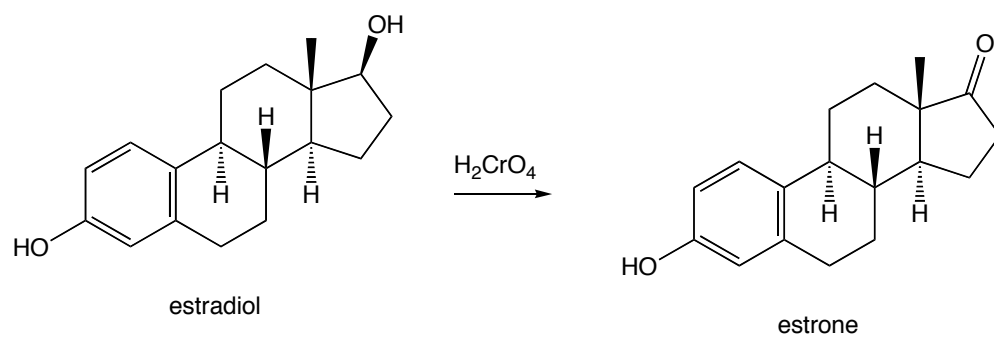
Primary Alcohol:



Example:



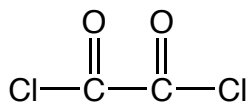
Another secondary alcohol:



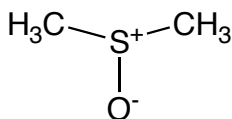
R. B. Woodward

### 3. Swern Oxidation

Swern reagents:



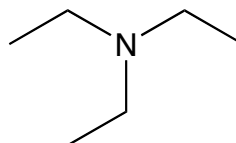
oxalyl chloride



DMSO

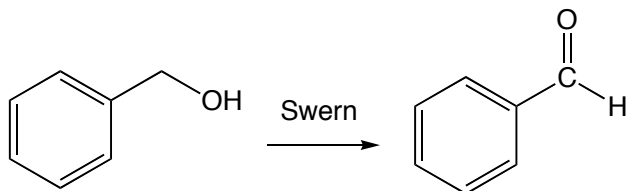
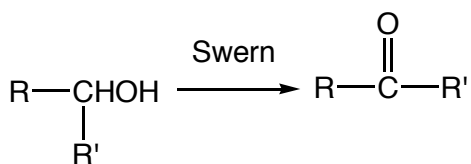
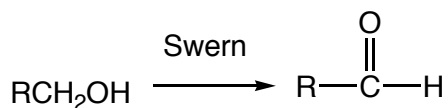
dimethyl sulfoxide

Organic Base  
eg Triethylamine  
 $\text{Et}_3\text{N}$



The Swern Oxidation is fairly mild and will oxidize primary alcohols to aldehydes and secondary alcohols to ketones.

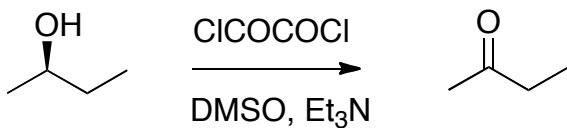
The mechanism will be described in a later lecture.



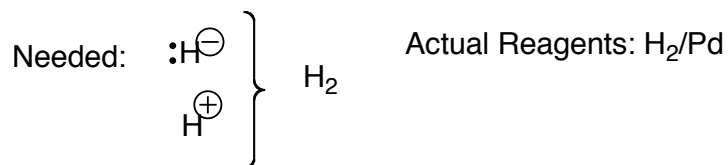
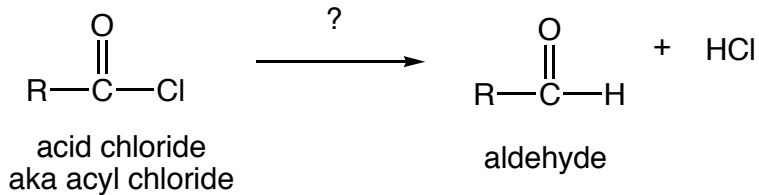
Benzyl alcohol

Benzaldehyde

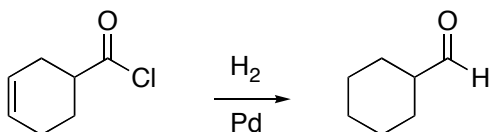
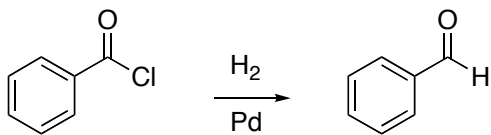
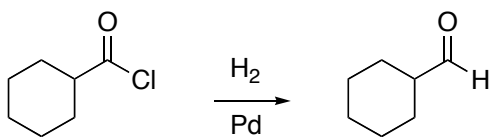
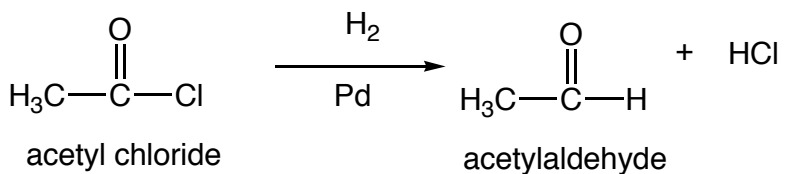
If benzyl alcohol were treated with Jones reagent, the resulting product would be benzoic acid, a structure you've seen before.



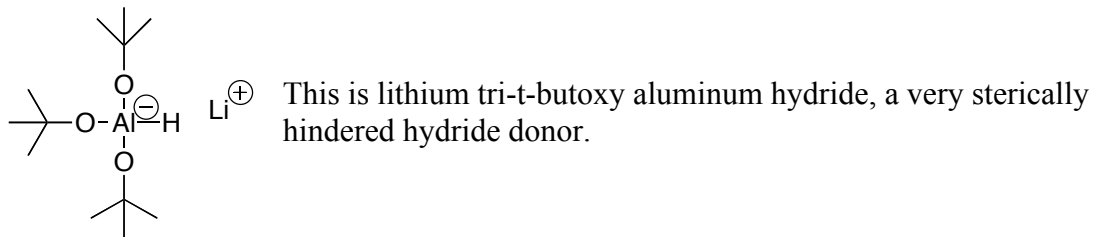
## Preparation of Aldehydes from Acid Halides



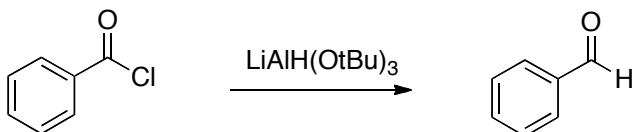
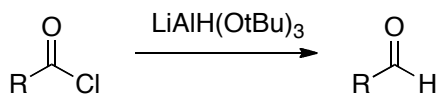
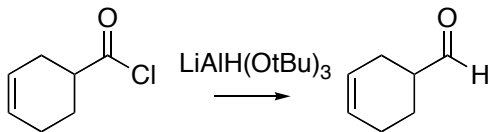
Examples:



A hydride donor may also be used for this transformation.

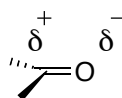


Examples:

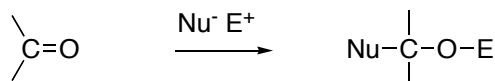


## Reactions of Aldehydes and Ketones

Aldehydes and ketones contain a carbonyl group, in which the carbon atom is doubly bonded to an oxygen atom. The carbonyl group is highly polarized, with a very electrophilic carbon atom.



Many reactions of aldehydes and ketones start with nucleophilic attack at the carbon atom of the carbonyl group by a nucleophile ( $\text{Nu}^-$ ). The nucleophile always has a pair of electrons available but may or may not bear a negative charge. The electrons of the carbon-oxygen double bond then become localized on the oxygen atom to form an alkoxide ion. This alkoxide ion then reacts with an electrophile ( $\text{E}^+$  which is usually a proton,  $\text{H}^+$ ) to quench the negative charge. Alternatively (especially with weak nucleophiles), the oxygen is protonated first and then the nucleophile adds. The net result is an addition reaction.

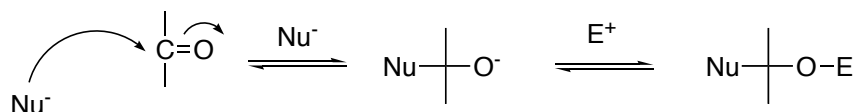


Many nucleophiles will react with the carbonyl group, and, depending on the reagents, reaction conditions, and nature of the intermediate formed, further reactions are possible before the final product is obtained. The most important step in all of these reactions is the bonding between a nucleophile and the carbon atom of the carbonyl group.

There are a variety of nucleophiles that react with aldehydes and ketones and can be classified as strong nucleophiles or weak nucleophiles. Strong nucleophilic attack onto ketones and aldehydes is an irreversible reaction whereas weak nucleophilic attack is reversible.

## Weak Nucleophiles

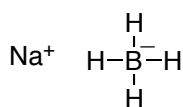
Attack by weak nucleophiles on ketones and aldehydes under basic conditions is shown below with the general mechanism. The first step involves the reversible attack of the nucleophile to form the alkoxide anion, which is then protonated. The reaction is usually acid catalyzed and always reversible. In fact, most such reactions are done under acidic conditions, in which case the mechanism involves initial protonation of the oxygen as discussed in the previous class. Under basic conditions, many such reactions have an equilibrium that lies to the side of starting materials (i.e. ketone or aldehyde).



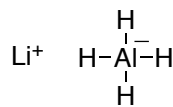
The weak nucleophiles include: hydroxide ion (<sup>-</sup>OH) or water (H<sub>2</sub>O), alkoxide anion (<sup>-</sup>O-R) or alcohols (H-O-R), cyanide ion (<sup>-</sup>CN) or hydrogen cyanide (HCN) and amines (H-NRR' where R and R' can be H or alkyl).

## Strong Nucleophiles (H: <sup>-</sup> and R: <sup>-</sup>)

Nucleophilic attack of the hydride ion (H: <sup>-</sup>) to the electrophilic carbon of the carbonyl group results in the reduction of aldehydes to primary alcohols and ketones to secondary alcohols. These reductions are done using sodium borohydride (NaBH<sub>4</sub>) or lithium aluminum hydride (LiAlH<sub>4</sub>) as shown below. Both of these reagents provide a source of the hydride ion, which is very basic and a powerful nucleophile.



sodium borohydride

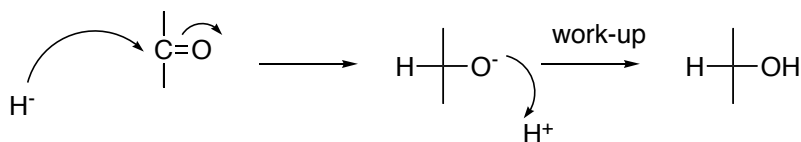


lithium aluminum hydride

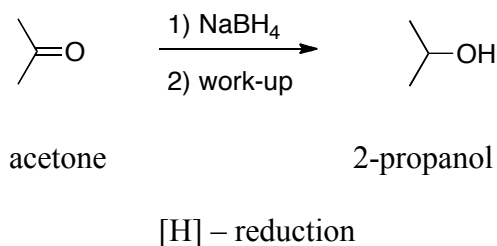
Lithium aluminum hydride (also known as LAH) reacts violently with water and alcohols to generate hydrogen gas (H<sub>2</sub>). Sodium borohydride reacts in a similar fashion, but is less reactive than LAH. Because sodium borohydride is less reactive than LAH, it is easier to handle and may be used with water or alcohol as the solvent. The reaction of sodium borohydride with carbonyl compounds is fast enough to compete successfully (i.e. reduce the carbonyl) with its decomposition reaction with water or alcohol.

## Hydride Addition

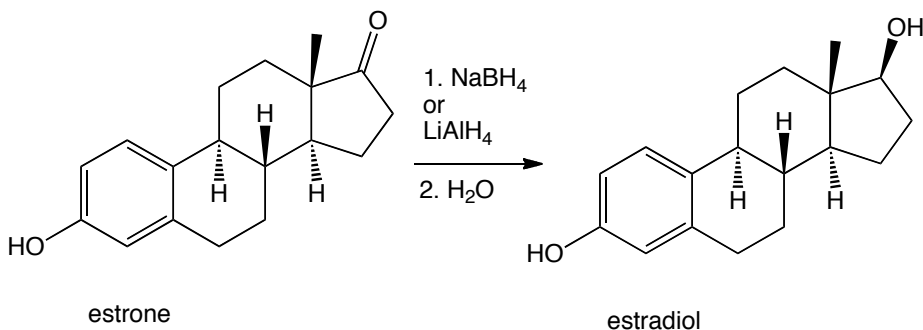
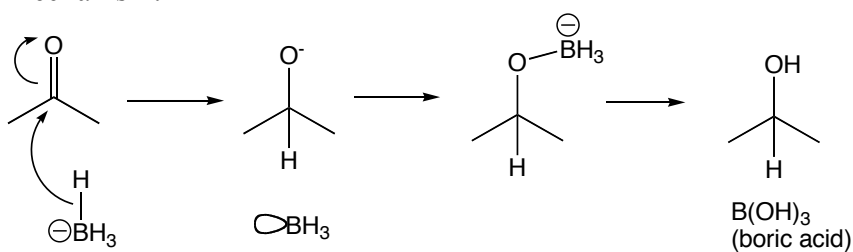
A general example of nucleophilic attack by hydride is shown below. The mechanism involves nucleophilic attack of the hydride to the electrophilic carbon atom of the carbonyl group. Rehybridization of the carbonyl carbon from  $sp^2$  to  $sp^3$  occurs, and a tetrahedral alkoxide ion intermediate is produced. The alkoxide ion that forms is then protonated in the work-up step, which usually involves the addition of water or an acid. The reaction is irreversible because the hydride species cannot stabilize the negative charge as well as the alkoxide.



An example is the reduction of acetone to 2-propanol with sodium borohydride followed by a work-up step.



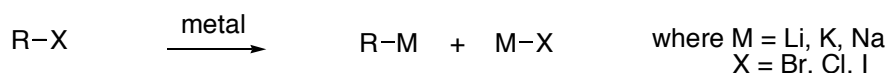
Mechanism:



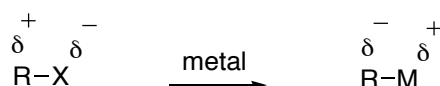


## Attack by organometallic reagents

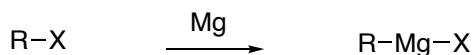
Nucleophilic attack of the alkyl anion ( $R^-$ ) to the electrophilic carbon of the carbonyl group results in the transformation of aldehydes to secondary alcohols and ketones to tertiary alcohols. These reductions are done using organometallic reagents. Organometallic reagents are prepared by the reaction of alkyl halides with metals such as lithium, sodium, potassium or magnesium. Alkyl, aryl, and vinyl halides will react with metals. The organometallic reagents ( $RMgX$ ) prepared from magnesium are named Grignard reagents, after Victor Grignard, a French chemist who discovered them at the beginning of the century.



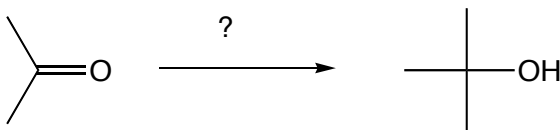
A carbon-halogen bond is polarized with partial positive charge on the carbon and partial negative charge on the halogen. When a metal is introduced, the partial charge on the carbon is now negative since these metals do not accept a negative charge.



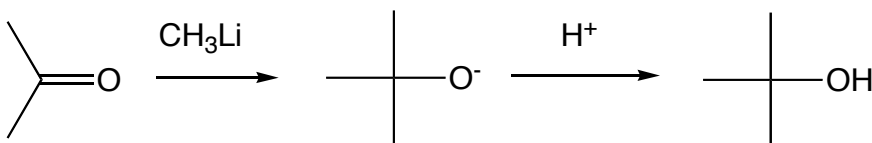
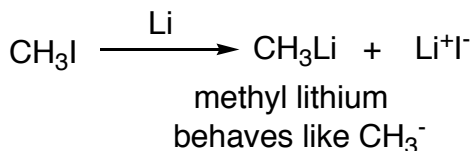
Metals such as lithium, sodium and potassium require two equivalents of metal to one equivalent of alkyl halide because these metals are monovalent. Magnesium on the other hand is divalent and only needs one equivalent.



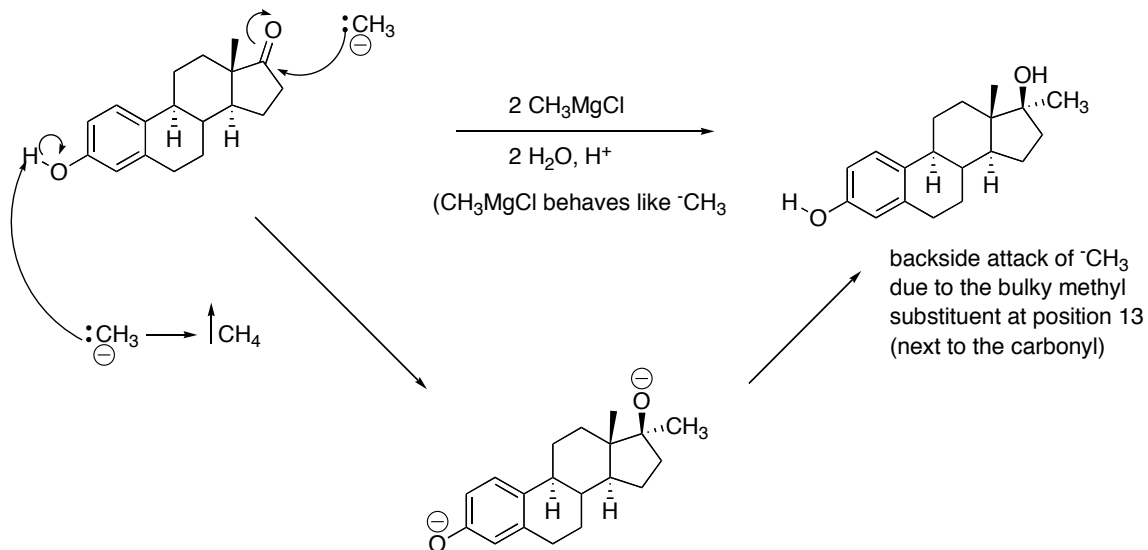
How to Accomplish:



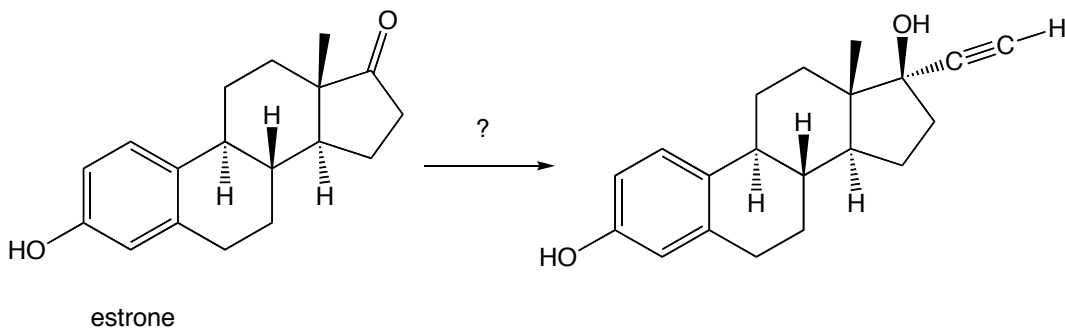
Needed:  $\text{H}^+$   $\text{CH}_3^-$



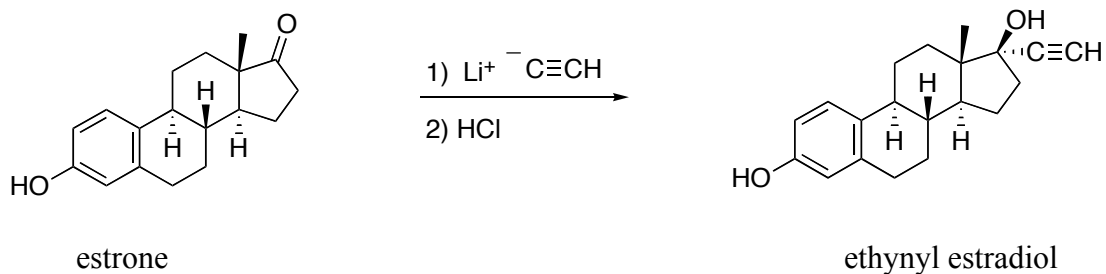
A more complicated example:



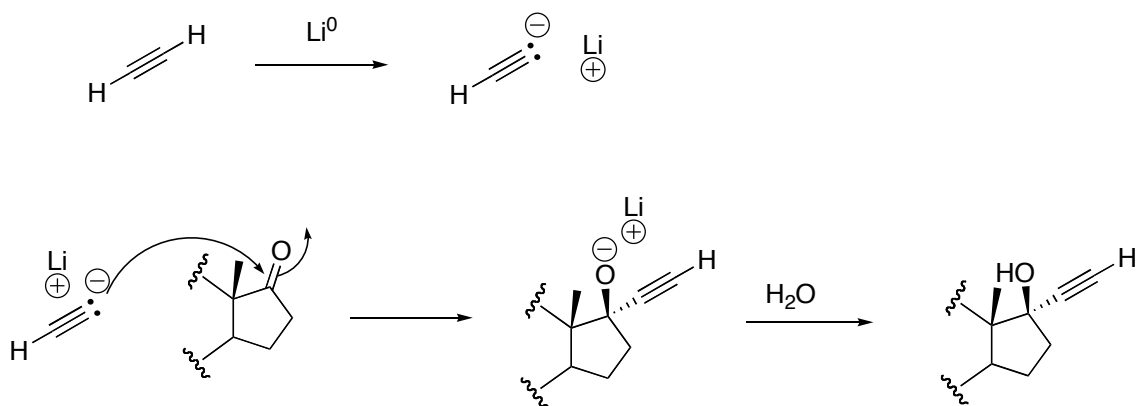
Determine the reagents needed for the following reaction:



The addition of a lithium acetylide to estrone yields ethynyl estradiol. Ethynyl estradiol is a major component in many birth control pills. This compound is very active in keeping the female body think it is pregnant.



Mechanism: the lithium acetylide can be generated by reacting acetylene with lithium metal and then acetylide acts as nucleophile to attack the carbonyl group.



Q: Why does this reaction require two equivalents of lithium acetylide?

A: Since lithium acetylide is a strong base, the first equivalent of lithium acetylide is used to deprotonate the phenol.