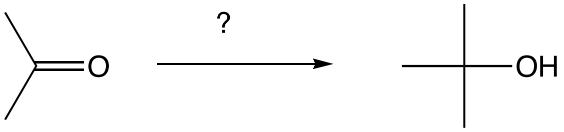
Strong Nucleophiles ($H:^-$ and $R:^-$) continued:

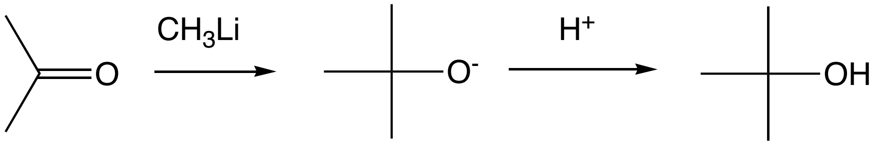
How to Accomplish:



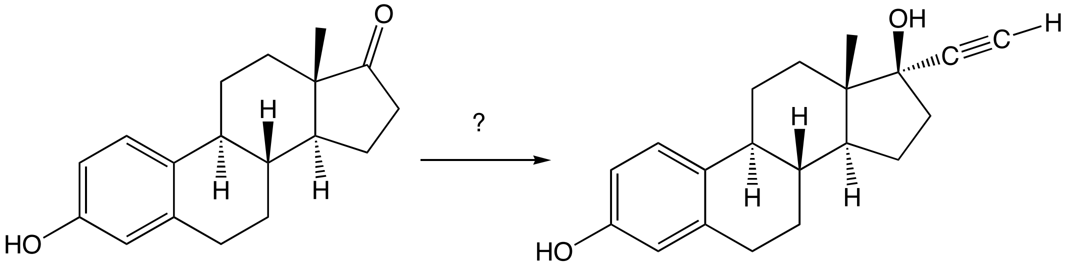
Needed: $H^{\oplus}$ $CH_3^{\ominus}$

$$CH_3I \xrightarrow{Li} CH_3Li + Li^+I^-$$

methyl lithium
behaves like CH_3^-

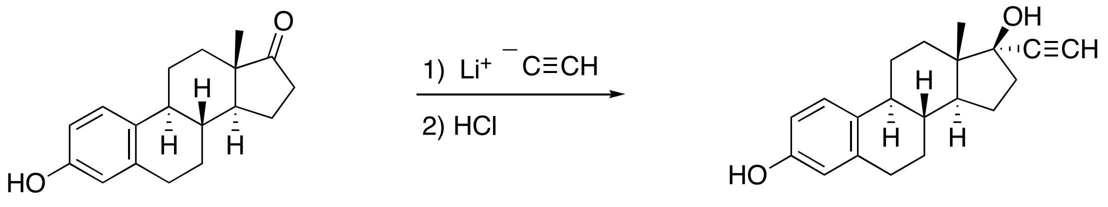


Determine the reagents needed for the following reaction:



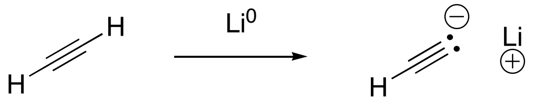
estrone

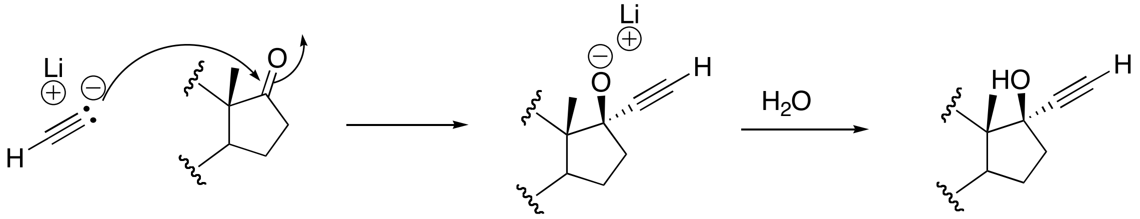
The addition of a lithium acetylide to estrone to yield ethinylestrone. Ethinylestrone is a major component in many birth control pills. This compound is very active in keeping the female body think it is pregnant.



estrone ethinyl estrone

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

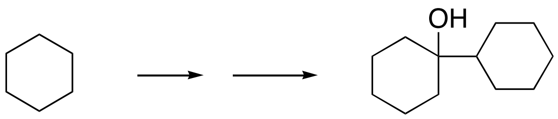


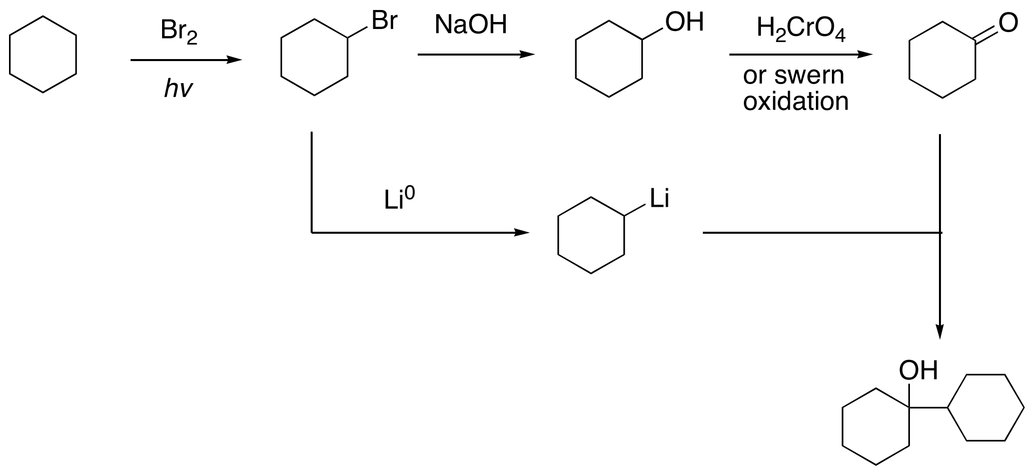


Q: Why does this reaction require two equivalents of lithium acetylide?
A: Since lithium acetylide is a strong base, the first equivalent of lithium acetylide is used to deprotonate the phenol.

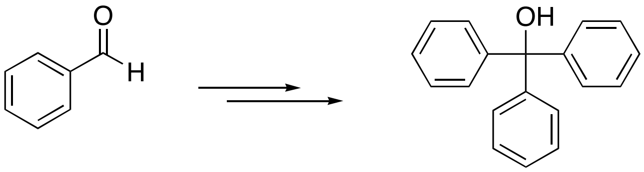
More examples:

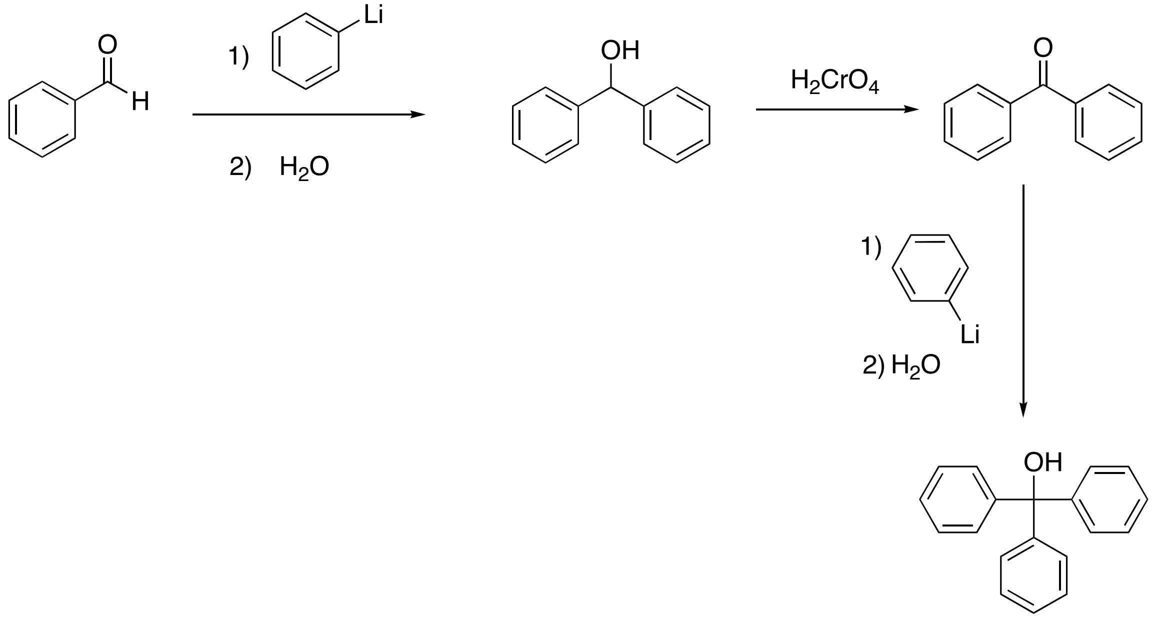
e.g.: Fill the reagents to finish the reactions (only inorganic reagents)





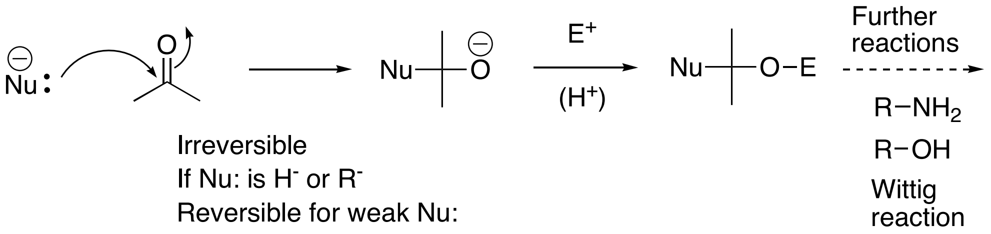
e.g. : Fill the reagents (any reagents you wish to use)





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).

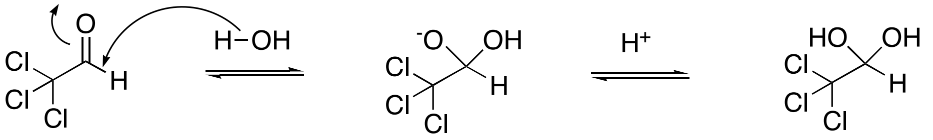


Weak nucleophiles

H_2O	$\ominus OH$	Hydrate Formation		
R–OH	$\ominus OR$	Hemiacetal Formation	→	Acetal Formation
HCN	$\ominus CN$	Cyanohydrin Formation		
$R-NH_2$	$R-\overset{\ominus}{N}H$	Aminal Formation	→	Imine Formation

Hydrate Formation

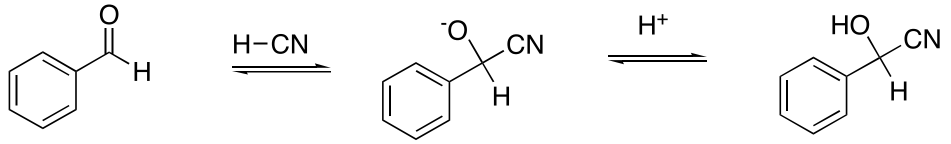
Aldehydes and ketones react with water in a reversible fashion to yield 1,1-diols, or geminal diols. The nucleophilic addition of water to ketones and aldehydes is slow in pure water but is catalyzed by acid. An example of hydrate formation is the reversible reaction of chloral (2,2,2-trichloroethanal) with water to form the hydrated species. Due to the inductive electron-withdrawing effect of chlorine, the equilibrium in water lies to the right (hydrated form).



chloral hydrate form

Cyanohydrin Formation

Aldehydes and ketones react with hydrogen cyanide (HCN) to yield cyanohydrins. Cyanohydrin formation works best with aldehydes but also works with certain ketones. An example of cyanohydrin formation is the addition of HCN to benzaldehyde to yield the cyanohydrin. Cyanide is strongly nucleophilic, and addition occurs by a typical nucleophilic addition pathway. Protonation of the anionic intermediate yields the cyanohydrin.



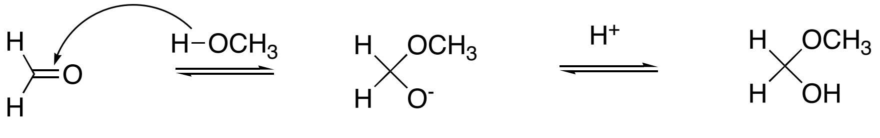
benzaldehyde cyanohydrin

Cyanohydrin formation is particularly interesting because of the further chemistry that can be done. For example, nitriles (RCN) can be reduced with LAH to yield primary amines (RCH_2NH_2) and can be hydrolyzed by aqueous acid to yield carboxylic acids.

In order to avoid the dangers inherent in handling such a toxic gas as hydrogen cyanide (HCN), it is usually generated during the reaction by adding an acid (H_2SO_4) to a mixture of carbonyl compound and excess sodium cyanide (NaCN).

Hemi-Acetal Formation

Hemiacetal formation is similar to hydration but alcohols are used instead of water as the nucleophile. This reaction is reversible and is especially favored if you can form 5 or 6 membered rings as in sugars. An example of hemiacetal formation is the addition of methanol to formaldehyde to yield the hemiacetal.



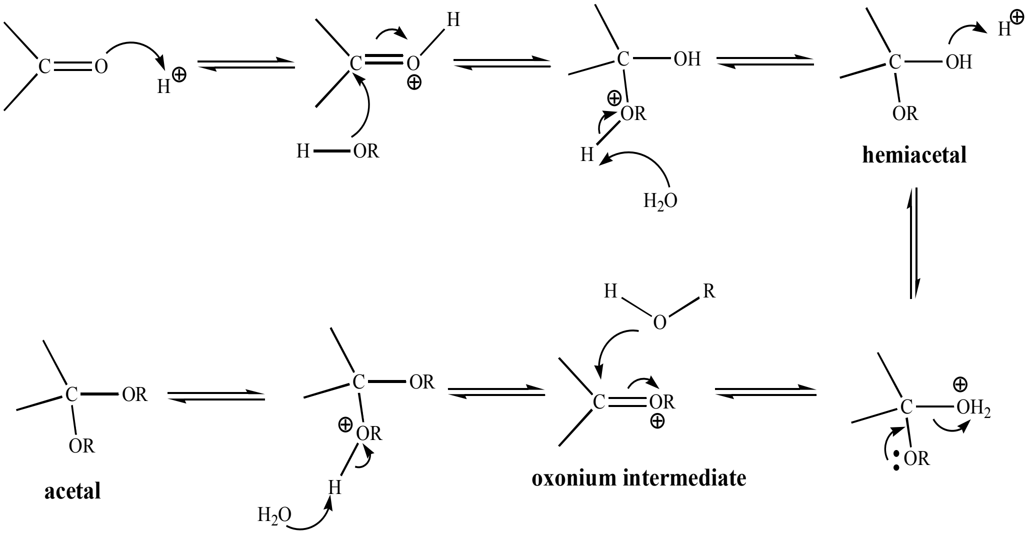
acetone hemi acetal

Acetal Formation

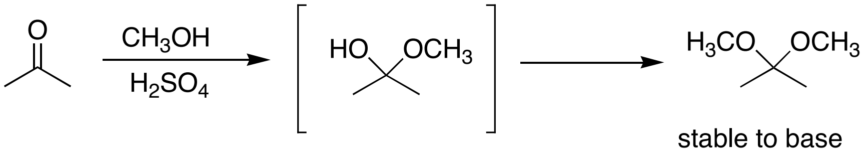
Hemiacetals can be converted to Acetals: two OR groups instead of one OR and OH

Addition then Elimination then 2nd Addition reaction

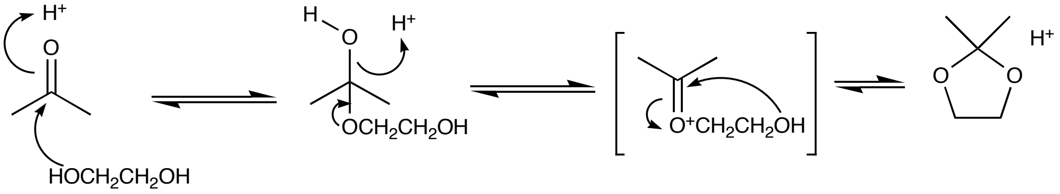
Mechanism:



Examples:



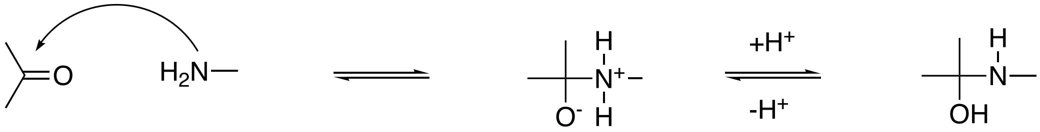
stable to base
protect ketone & RCHO



ethylene glycol

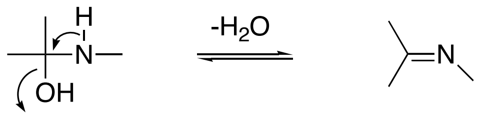
Aminal Formation

Aminal formation is similar to that of hydration except the nucleophile is an amine functionality. An example is the addition of methylamine to acetone to yield the aminal product in a reversible fashion.



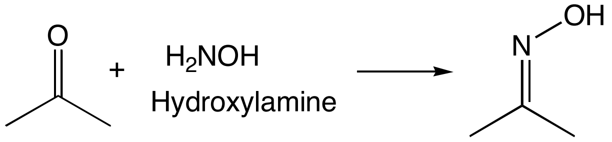
acetone methylamine aminal

Further reaction of the aminal can take place in which the elements of water (H_2O) are eliminated to yield an imine functionality as shown below. This elimination occurs with aminals, hemiacetals and the Wittig reagent.



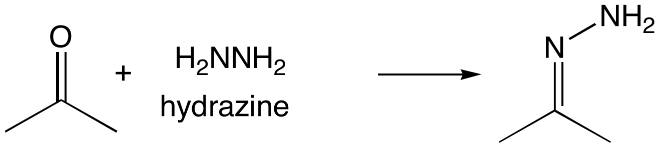
aminal imine

Examples:



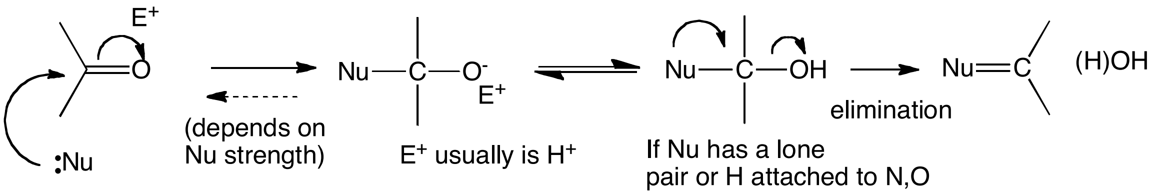
oxime

aka aldoximes or ketoximes
depending on whether they are derived
from an aldehyde or ketone

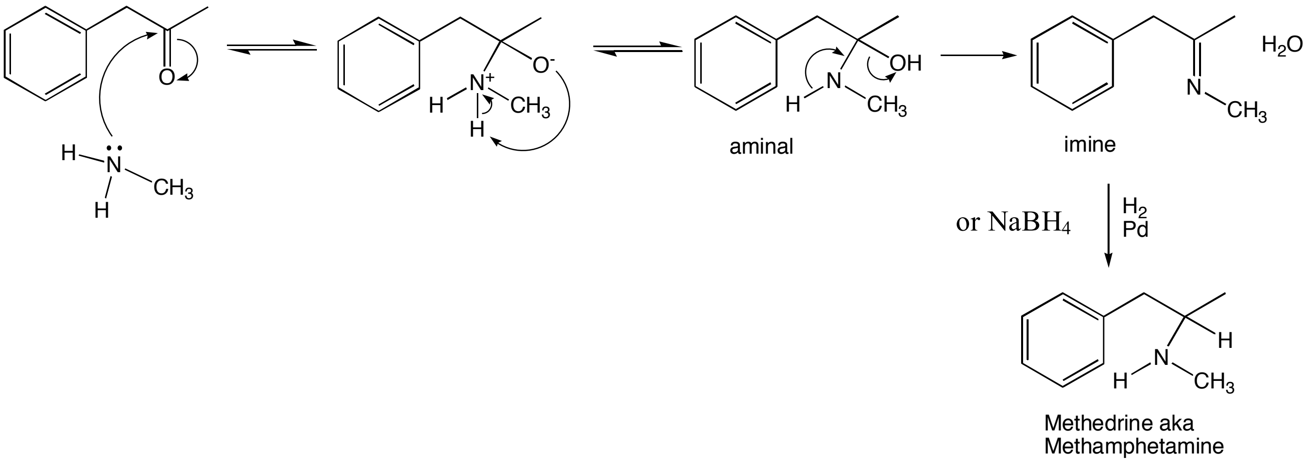


hydrazone

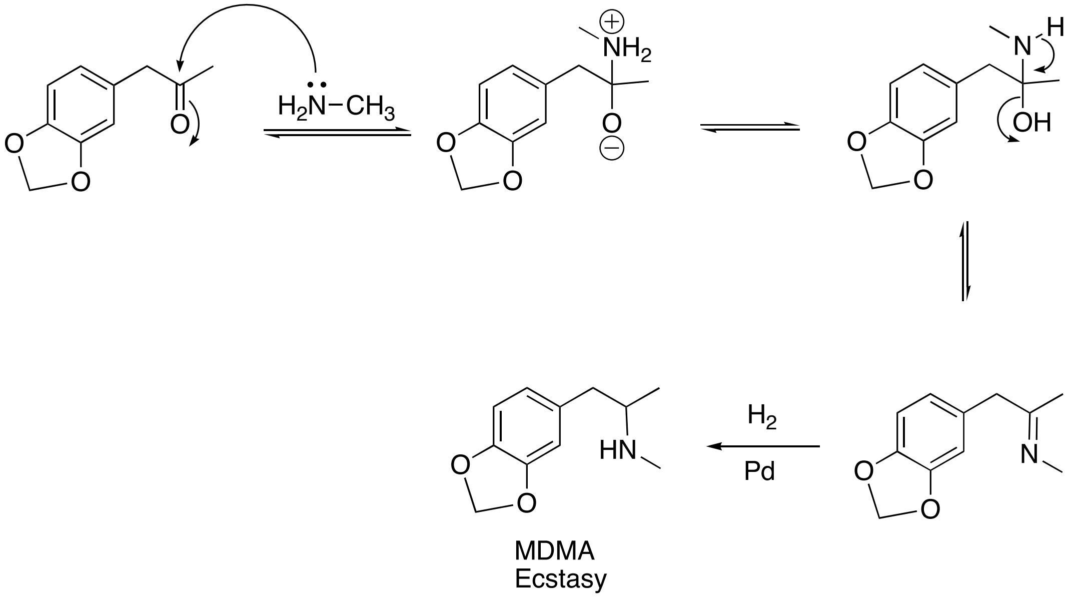
Imine Formation – addition then elimination



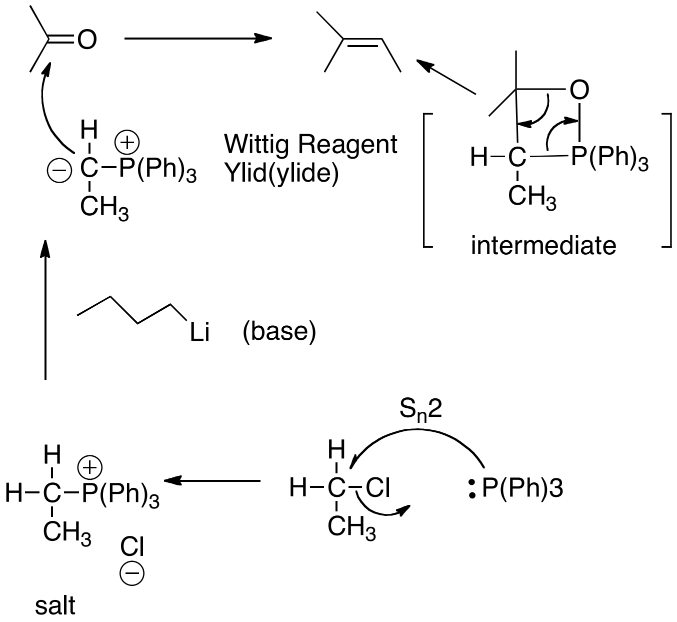
Example:



Note: Imines can be reduced to amines

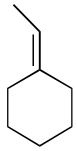


Wittig Reaction:

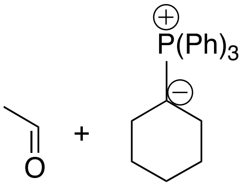


Example:

Consider how to make



synthetic route A:



(but this wittig reagent is more hindered than the one in route B, so, route B is better)

synthetic route B: