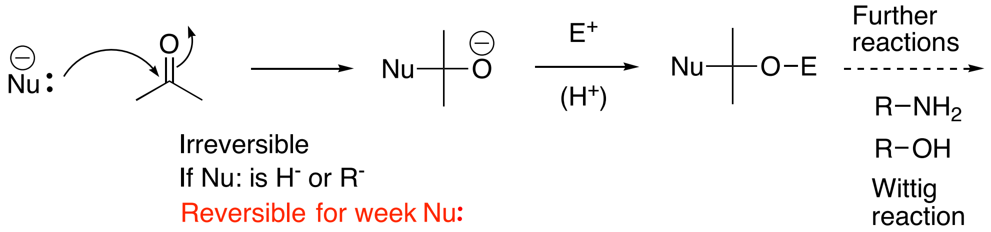
Weak Nucleophiles

Attack of 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.

Most such reactions are done under acidic conditions, in which case the mechanism involves initial protonation of the oxygen. Under basic conditions, many such reactions have an equilibrium that lies to the side of starting materials (i.e. ketone or aldehyde).

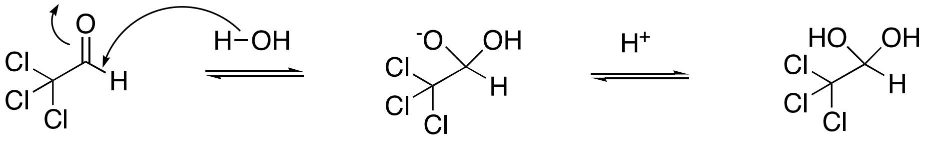


Weak nucleophiles

H_2O	OH^-	Hydrate Formation		
R−OH	OR^-	Hemiacetal Formation	⟶	Acetal Formation
HCN	CN^-	Cyanohydrin Formation		
$R-NH_2$	$R-NH^-$	Aminal Formation	⟶	Imine Formation

Hydrate Formation

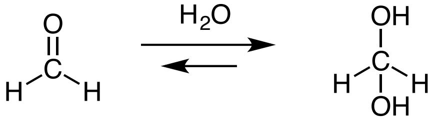
Aldehydes and ketones react with water in a reversible fashion to yield 1,1-diols, or geminal diols. The nucleophilic addition of water to ketones and aldehydes is slow in pure water but is catalyzed by acid. An example of hydrate formation is the reversible reaction of chloral (2,2,2-trichloroethanal) 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

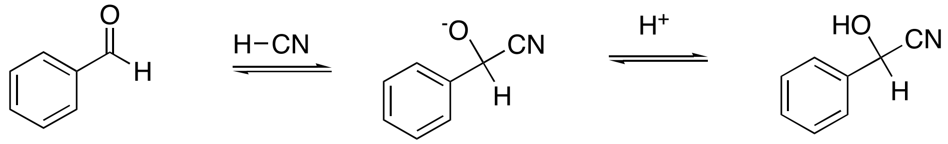
Another example:



formaldehyde
methanal

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 nucleophilic, and addition occurs by a typical nucleophilic addition pathway. Protonation of the anionic intermediate yields the cyanohydrin.



benzaldehyde

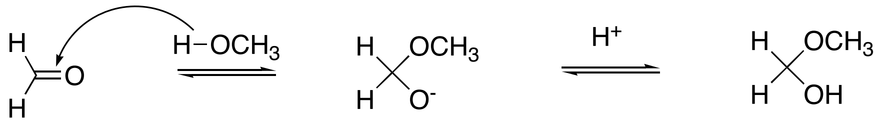
benzaldehyde cyanohydrin
a hydroxy nitrile

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).

Hemiacetal Formation

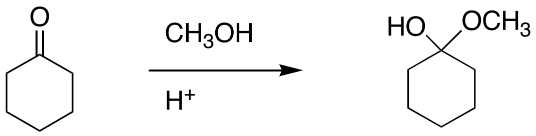
Hemiacetal formation is similar to hydration, but alcohols are used instead of water as the nucleophile. This reaction is reversible and is especially favored if you can form 5 or 6 membered rings as in sugars. An example of hemiacetal formation is the addition of methanol to formaldehyde to yield the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



acetone

hemiacetal

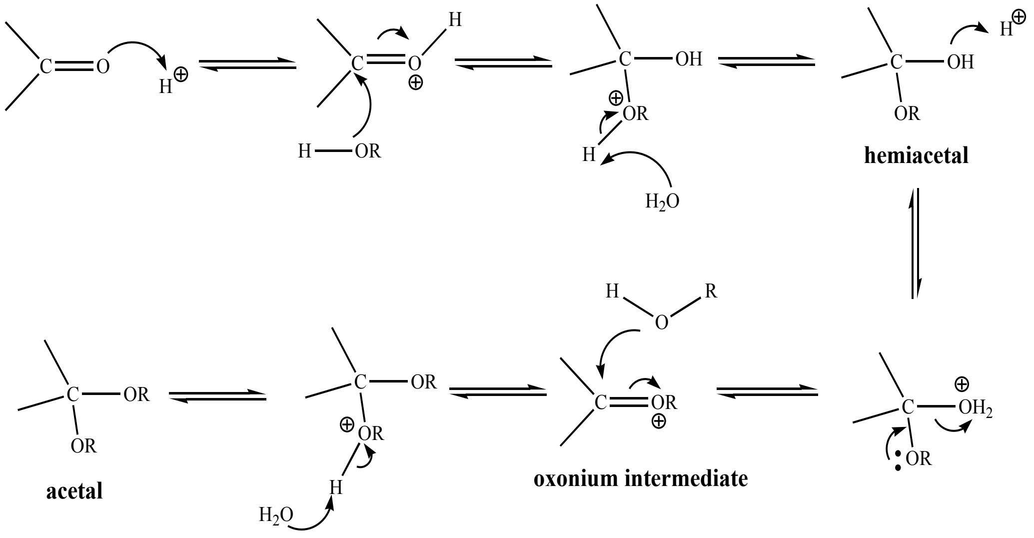
Another example:



Acetal Formation

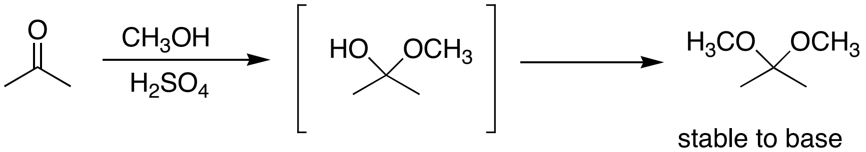
Hemiacetals can be converted to acetals - two OR groups instead of one OR and OH.
Addition, then elimination, then a second addition reaction

Mechanism:



Reactions are reversible
If excess alcohol is present, the reaction proceeds to the acetal

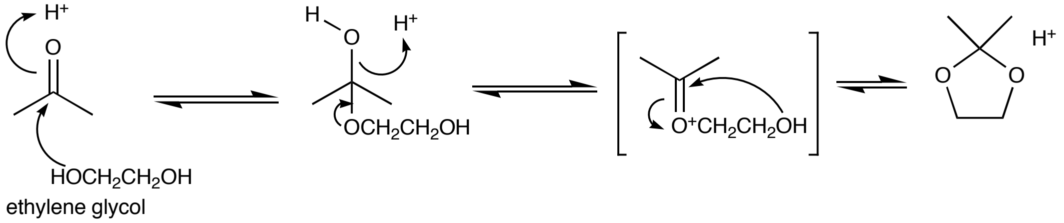
Examples:

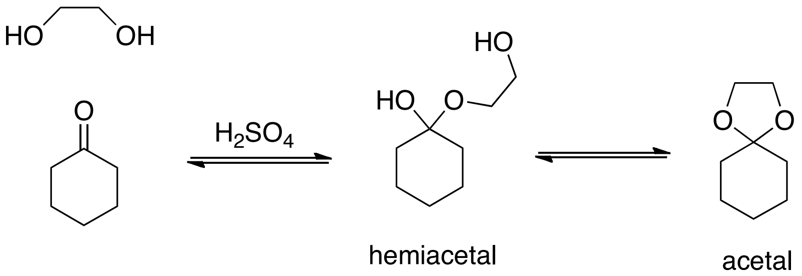


stable to base
protect ketone & RCHO

Cyclic acetals with diols

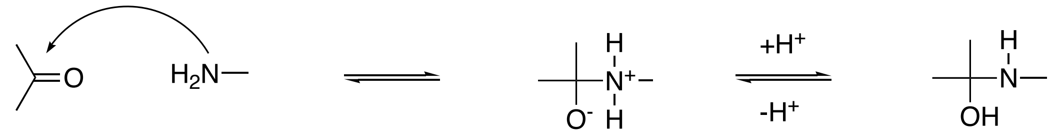
Cyclic acetals are much harder to hydrolyze because the hemiacetal produced can easily close back again to the acetal; this is because it is an **intramolecular** reaction.





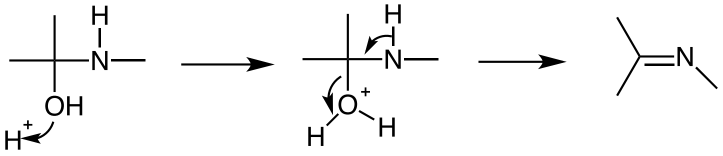
Aminal Formation

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



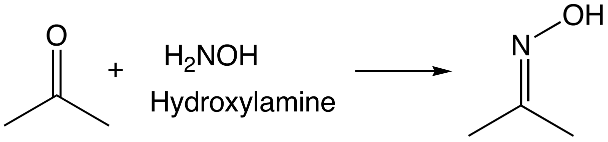
acetone methylamine aminal

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



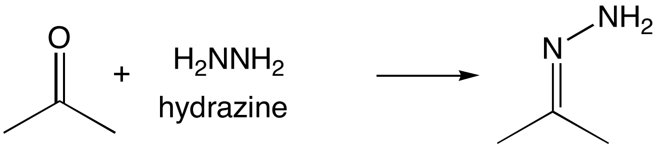
aminal imine

Imine Bond Formation – Addition, Elimination, Addition

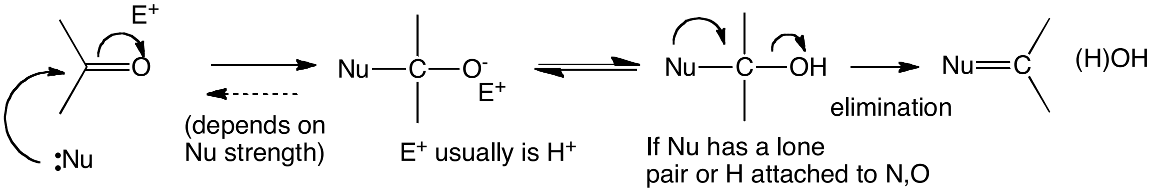


oxime

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



hydrazone

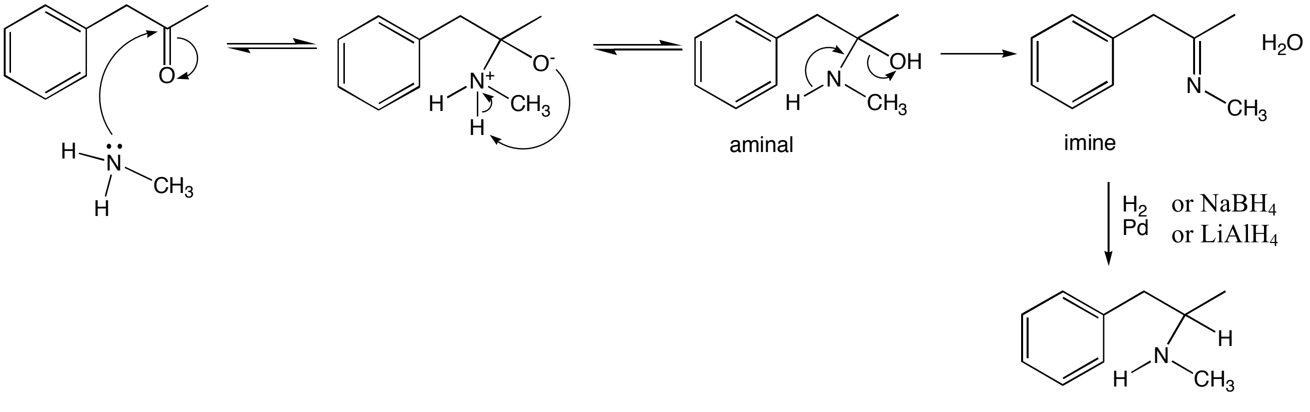


(depends on
Nu strength)

E^+ usually is H^+

If Nu has a lone
pair or H attached to N,O

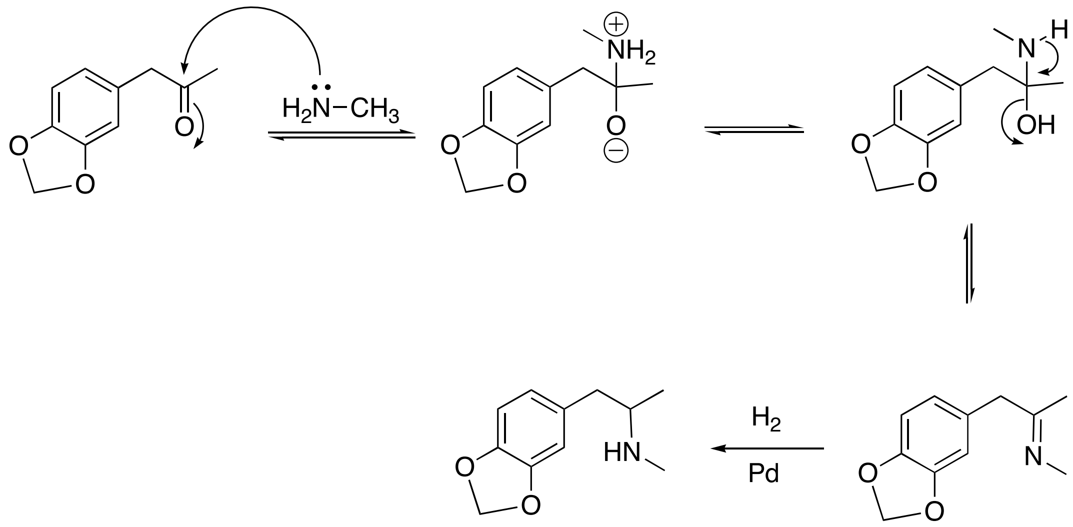
Example:



Methedrine aka
Methamphetamine

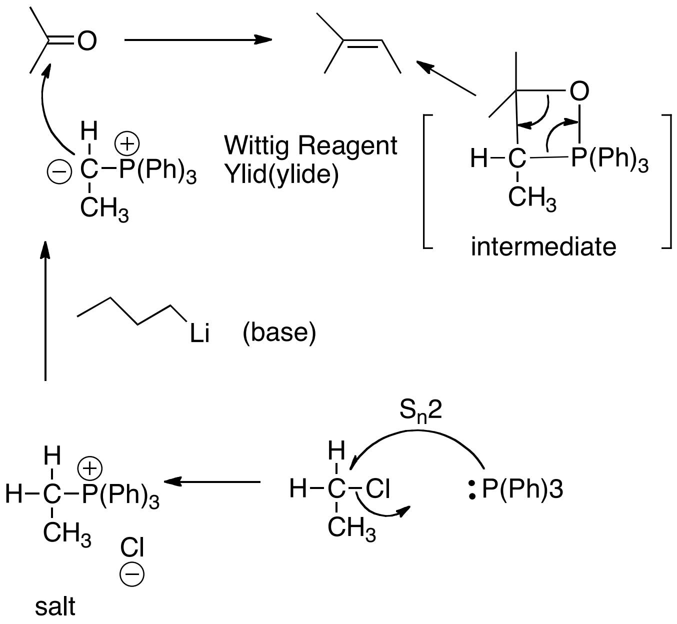
N-methylamphetamine, methedrine

Note: Imines can be reduced to amines



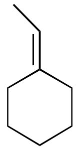
MDMA
Ecstasy

Wittig Reaction:

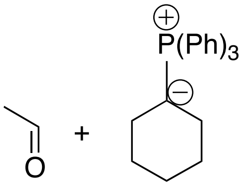


Example:

Consider how to make

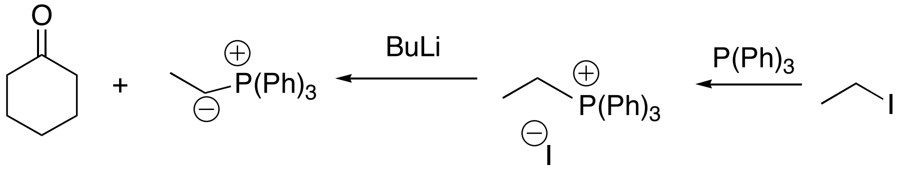


synthetic route A:



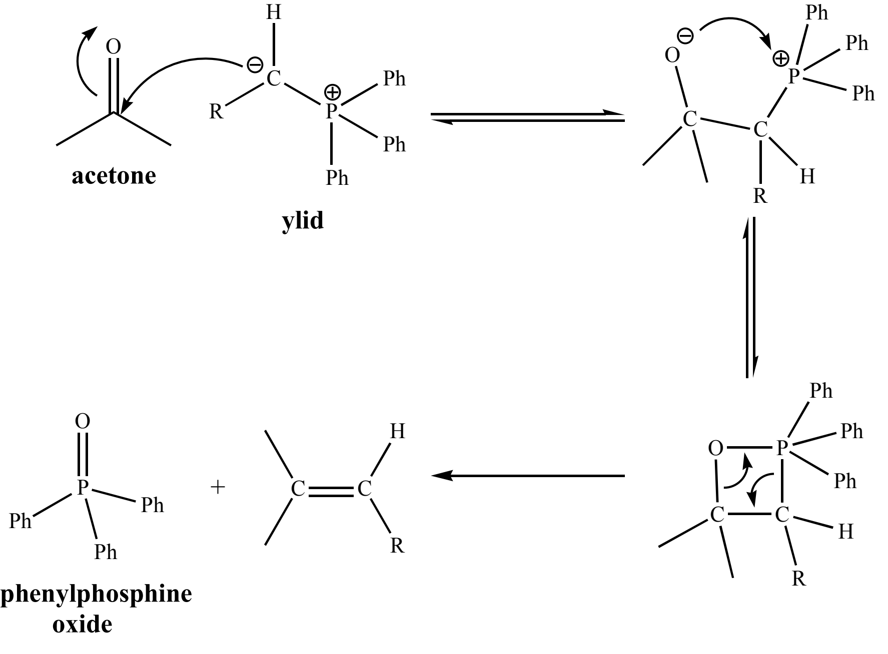
(but this wittig reagent is more hindered than the one in route B, so, route B is better)

synthetic route B:



As seen earlier, nucleophilic addition to a carbonyl can give an alcohol as the product. Elimination of water follows in the case of imine formation and is also part of the mechanism of acetal formation. The Wittig reaction is an example of a carbonyl addition followed by an elimination that produces an alkene. It involves a phosphorus ylide (ylid). An ylid is a substance that has both a negative charge and a positive charge (internal salt), generally on adjacent atoms.

General mechanism:

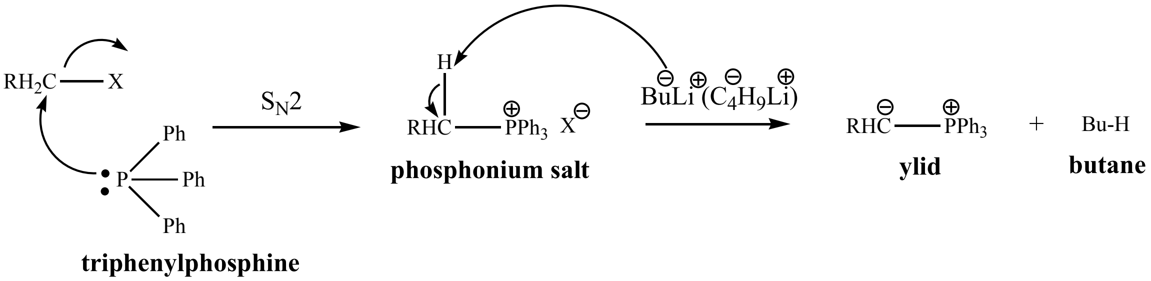


The Wittig reagent is an **ylid**, with adjacent positive and negative charges. The negatively charged carbon of the ylid is the nucleophile, and adds to the carbonyl carbon. The negatively charged oxygen generated from the first step attacks the positively charged phosphorus atom to form a four membered ring (intramolecular closure). This is possible because phosphorus can expand its valence shell to form 5 bonds. The four membered ring formed is quite strained, therefore it collapses to its constituent parts, triphenylphophine oxide and an alkene.

While the nucleophilic attack of the ylid is reversible, the last step (the collapse to an alkene) is irreversible.

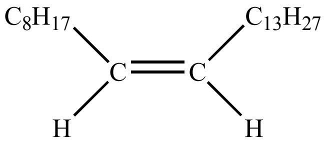
The geometry of the alkene formed is often predominantly *cis*.

Preparation of a Wittig reagent from a primary alkyl halide (S_N2 nucleophilic substitution, followed by treatment with a base)



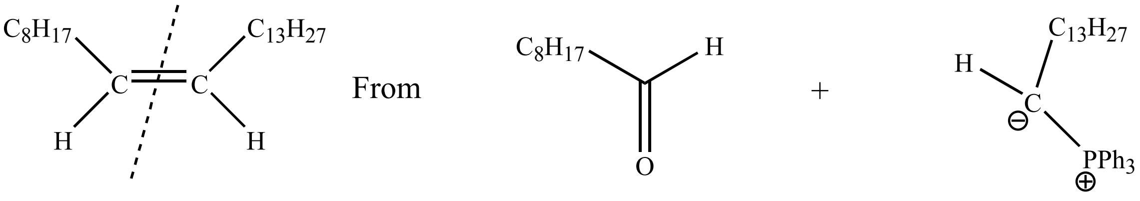
In this reaction, X is a halogen (Cl, Br, or I). Primary halides work the best for this substitution. Phosphorus is directly below nitrogen on the periodic table, and like nitrogen, it is a good nucleophile. It displaces halogen in an S_N2 reaction. The phosphonium salt has an acidic hydrogen on the carbon adjacent to phosphorus that can be removed by strong bases (usually butyllithium = BuLi). The product of the deprotonation is an ylid. BuLi can be made by reacting butyl iodide with lithium metal.

Synthesis of housefly pheromone



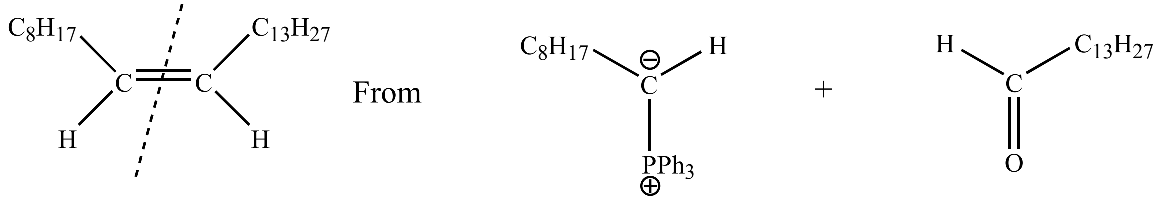
Looking at the structure, how do you make this pheromone using what you have just learned?

Answer: This pheromone can be made using the Wittig reaction.



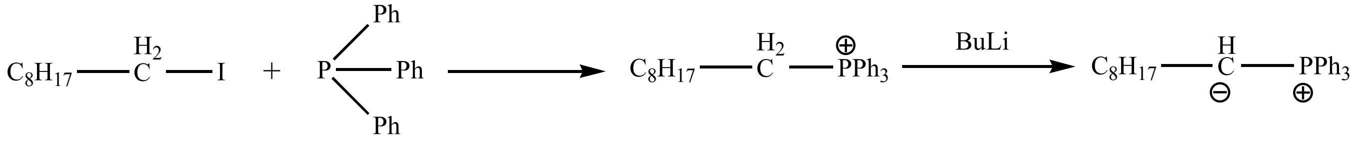
What other reagents can you use?

Answer: Just reverse the sense of the ylid and aldehyde.



How would you make the ylid shown above?

Answer: use triphenylphosphine and the corresponding halide, then treat with base (BuLi)



Note that the product of this Wittig reaction has a cis double bond.