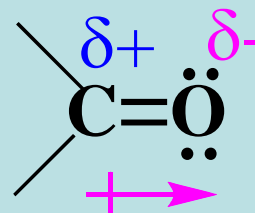


Nucleophilic Addition to the Carbon-Oxygen Double Bond

The reactivity of the carbon-oxygen double bond is determined by the **polarization**:

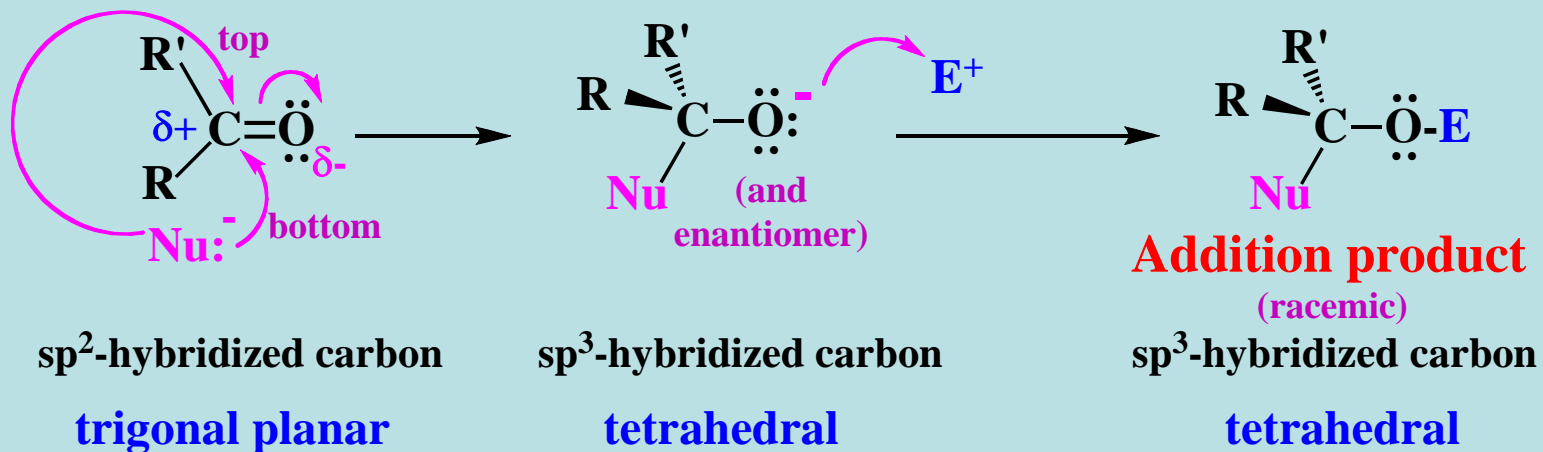


Because of the permanent dipole, nucleophiles add to the electropositive carbon and electrophiles add to the electronegative oxygen. These are **the most characteristic reactions of aldehydes and ketones**.

Two General Mechanisms for Nucleophilic Addition

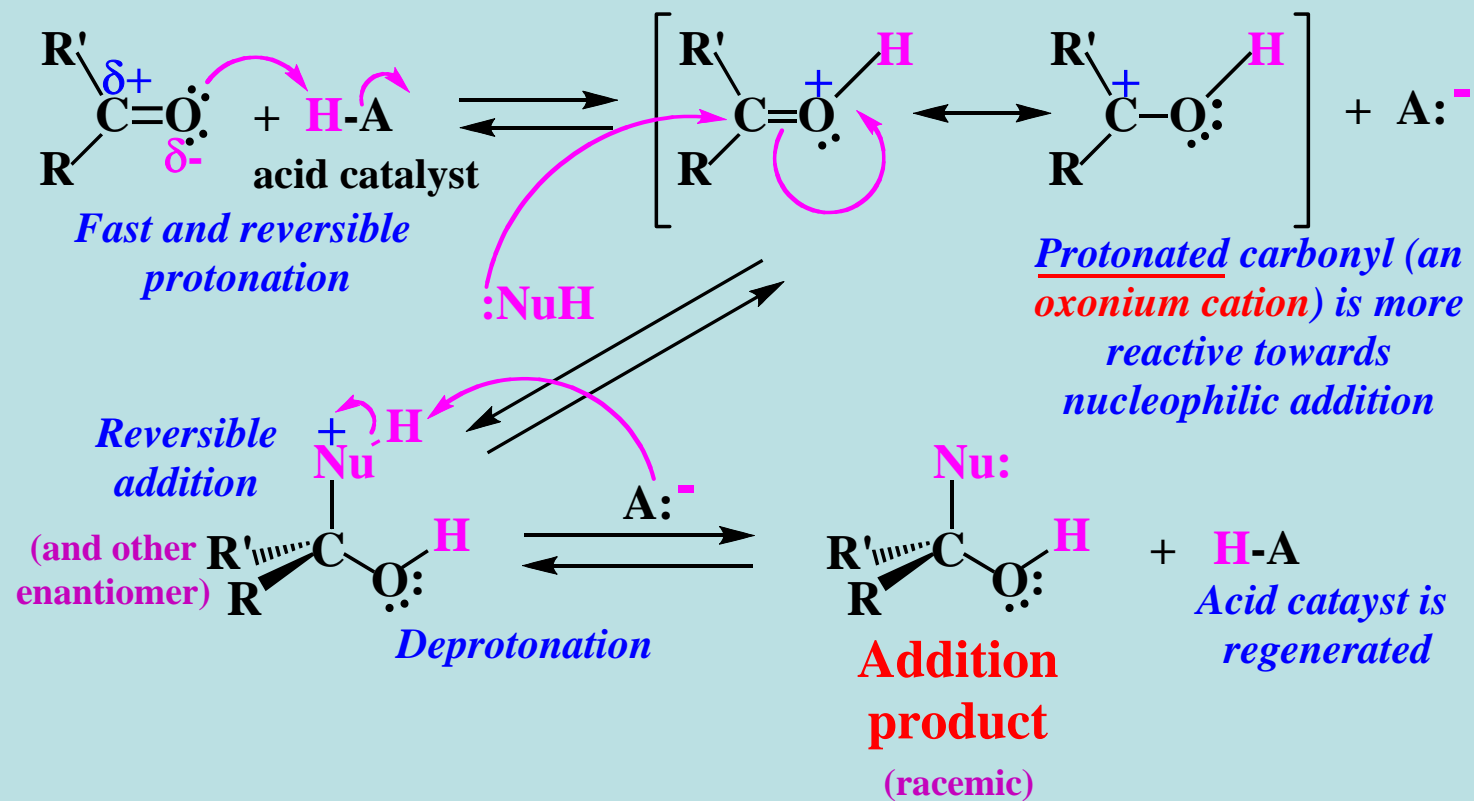
- (1) When the reagent is a **strong nucleophile** (Nu^-) such as an organometallic or metal hydride reagent, addition usually occurs first to the carbon center, forming an alkoxide ion. Electrophilic addition then occurs to the oxide.
- (2) A second general mechanism is **acid-catalyzed nucleophilic addition**. This involves a weaker nucleophile adding to the carbonyl group in the presence of catalytic amounts of acid, which protonates the carbonyl oxygen.

First General Mechanism



In these additions, E^+ is often a proton or metal ion.

Second General Mechanism

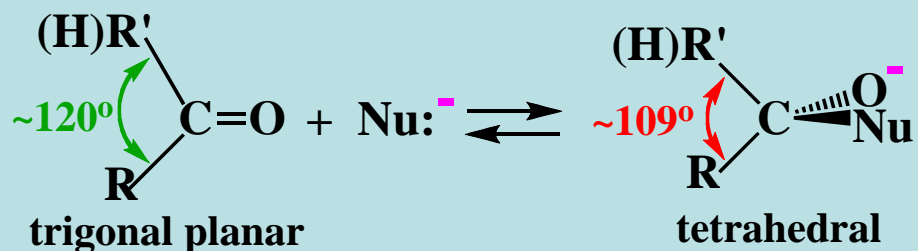


Relative Reactivity: Aldehydes versus Ketones

Generally, aldehydes are more reactive than ketones because of both steric and electronic factors.

Steric Factors

When a nucleophile adds to the carbonyl group, the reaction center changes from **trigonal planar** (sp^2) to **tetrahedral** (sp^3): there is a closing of the angle between R and R'(H) groups from $\sim 120^\circ$ to $\sim 109^\circ$.



With ketones, where R and R' are alkyl or aryl groups, there is more **buildup of steric strain** as the groups move closer together than there is with aldehydes, where at least one of the groups being squeezed together is the very small hydrogen atom.

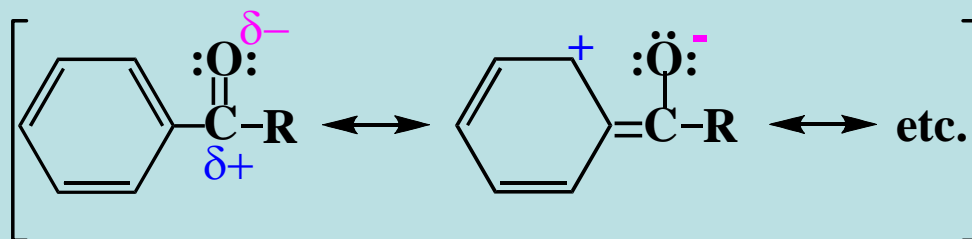
Electronic Factors

A ketone carbonyl is stabilized relative to that of an aldehyde by the presence of **two electron-releasing alkyl groups**.



This **diminishing of C=O carbon charge in ketones** contributes to their lower reactivity compared with that of aldehydes.

Alkyl ketones are generally **more reactive** than aryl ketones because of greater electronic stabilization of the starting state of the latter by π -electron delocalization.



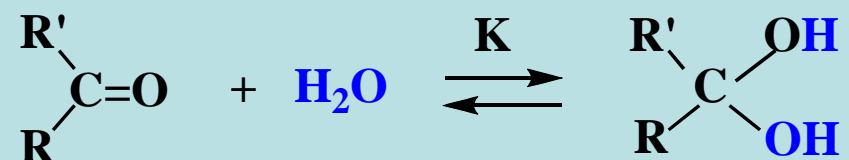
SUMMARY: Any reduction in the partial positive charge on the C=O carbon decreases its reactivity in nucleophilic addition. Any increase, e.g., by the presence of a strongly electron withdrawing group like $-\text{CF}_3$, increases reactivity.

Addition Reactions of Aldehydes and Ketones

Addition of Water and Alcohols: Hydrates and Acetals

Hydrates: *gem*-Diols

When aldehydes or ketones are dissolved in aqueous media, an equilibrium is established between the carbonyl compound and its **hydrate**. The hydrate is a **geminal diol** ("*gem*-diol").



The position of equilibrium depends on the size and electronic effects of the R groups. For most **ketones**, $K' = K[\text{H}_2\text{O}] = \ll 1$. Most ketones exist essentially 100% in the carbonyl form. Aldehydes hydrate somewhat more extensively.

Bulky and/or electron-donating R groups stabilize the carbonyl compound in the above equilibrium. Electron-withdrawing groups destabilize the carbonyl compound and promote formation of the hydrate. These factors are illustrated in the table that follows.

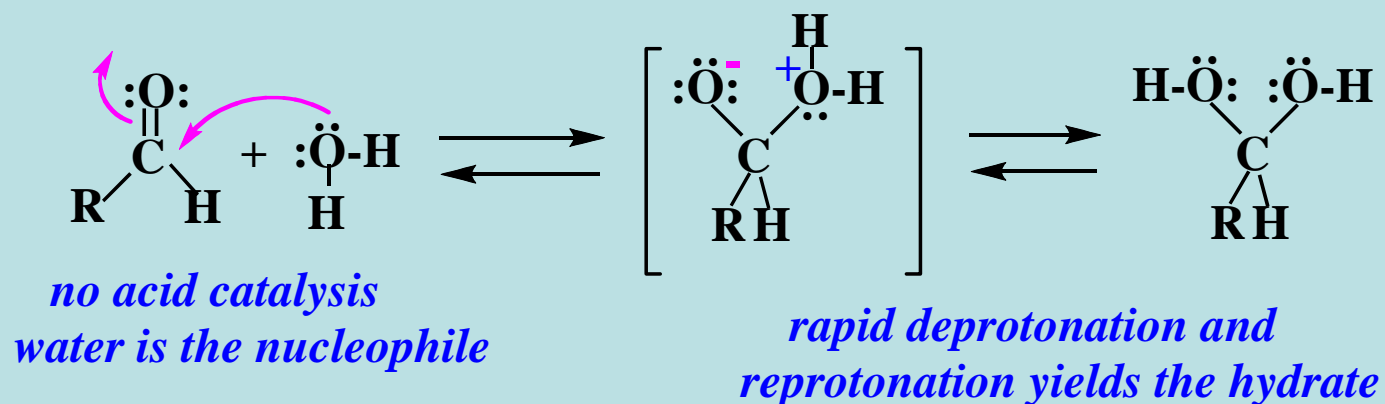
Equilibrium Constants at 25 °C for the Reaction



Carbonyl compound	$K' = K[\text{H}_2\text{O}] = \frac{[\text{RR}'\text{C}(\text{OH})_2]}{[\text{RR}'\text{C}=\text{O}]}$
-------------------	--

$\begin{array}{c} \text{H} \\ \\ \text{C}=\text{O} \\ \\ \text{H} \end{array}$	2×10^3	simplest aldehyde
$\begin{array}{c} \text{H} \\ \\ \text{C}=\text{O} \\ \\ \text{CH}_3 \end{array}$	1.3	
<div style="border: 1px solid black; padding: 5px; display: inline-block;"> $\begin{array}{c} \text{CH}_3 \\ \\ \text{C}=\text{O} \\ \\ \text{CH}_3 \end{array}$ <p>KETONE (Note all others are aldehydes.)</p> </div>	2×10^{-3}	← LOWEST VALUE
$\begin{array}{c} \text{H} \\ \\ \text{C}=\text{O} \\ \\ \text{CH}_3\text{CH}_2 \end{array}$	0.71	
$\begin{array}{c} \text{H} \\ \\ \text{C}=\text{O} \\ \\ (\text{CH}_3)_3\text{C} \end{array}$	0.24	
$\begin{array}{c} \text{H} \\ \\ \text{C}=\text{O} \\ \\ \text{Cl}_3\text{C} \end{array}$	2.8×10^4	electron-withdrawing CCl_3 group

Mechanism for Hydrate Formation

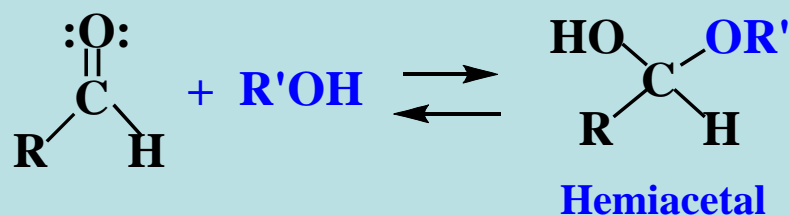


The **rate** of hydration is much faster under basic (higher pH) or acidic (lower pH) conditions than at pH 7.

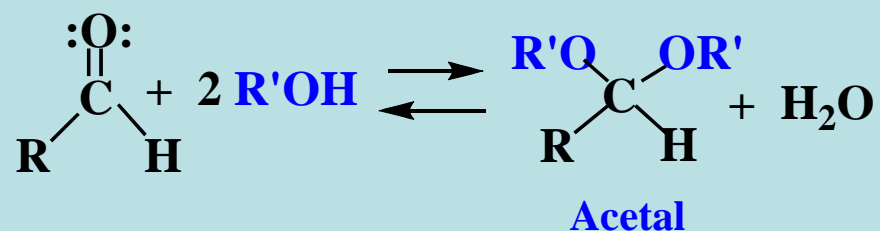
Additions of Alcohols: Hemiacetals and Acetals

Alcohols (R-OH) add to carbonyl compounds like water does. One important difference is that, overall, **two molecules of ROH** can react with one of an aldehyde or ketone.

A **hemiacetal** is formed from the addition of **one molecule of ROH**.



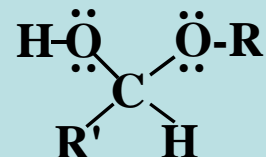
An **acetal** results from the addition of **two molecules of ROH**.



If the carbonyl compound is a ketone, the terms **hemiketal** and **ketal** are often but not always used in place of hemiacetal and acetal.

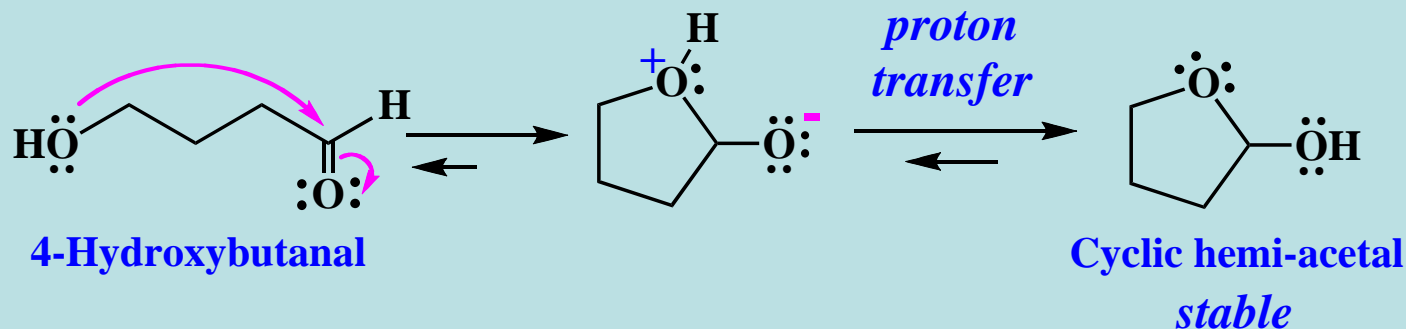
Hemiacetals

Most **acyclic hemiacetals** are **unstable** and cannot be isolated.



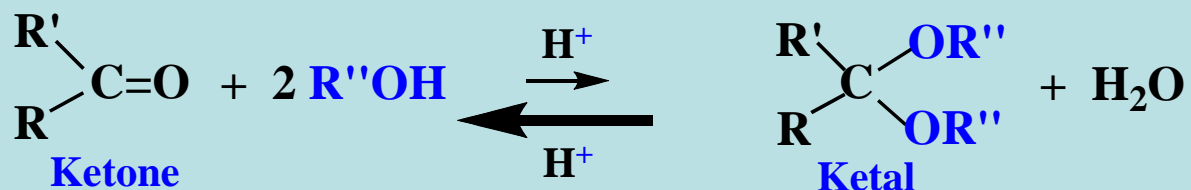
But **cyclic hemiacetals** with 5- and 6-membered rings are stable and are widely found in carbohydrates (sugars and polysaccharides like cellulose and starch).

Intramolecular hemiacetal formation:



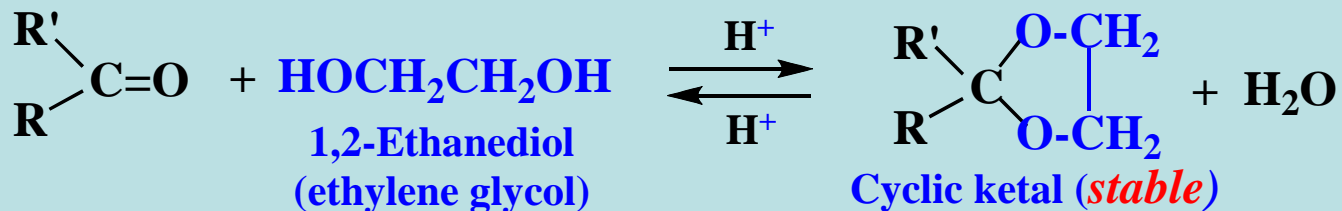
Ketals: Acetals of Ketones

Acetal (ketal) formation with ketones is generally not a favorable process:

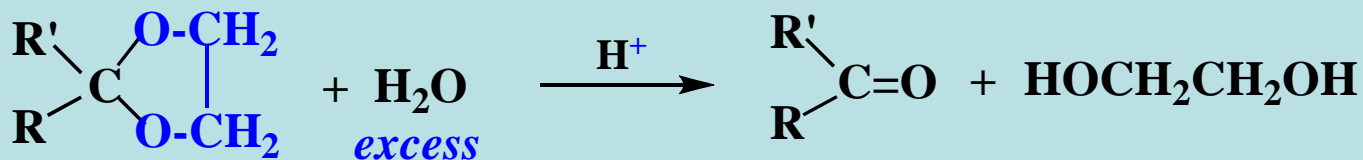


As in the hydration reaction, the equilibrium heavily favors the ketone.

Cyclic ketals, formed from 1,2- or 1,3-diols, are an exception:

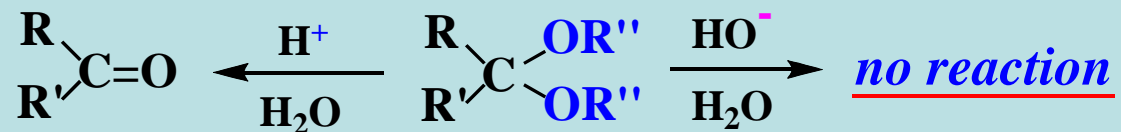


Cyclic acetals or ketals hydrolyze easily in aqueous acid solution:



Acetals as Protecting Groups

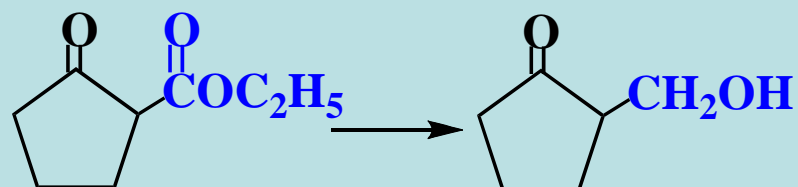
While acetals readily hydrolyze back to the carbonyl compound in the presence of acid as a catalyst, they are stable to bases, even strong bases.



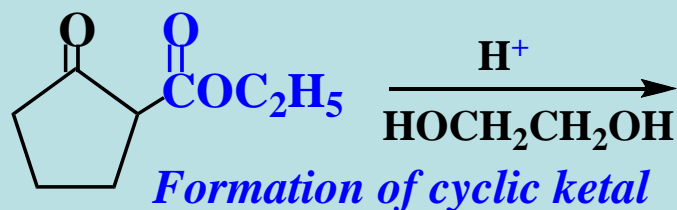
Acetals often are used to **protect** aldehyde and ketone functions from undesired reactions in the presence of strong bases during syntheses. The acetal function, a *geminal* (1,1) diether, is not reactive towards nucleophiles, and its hydrogens are very non-acidic.

An Example: The Selective Reduction of an Ester in the Presence of a Ketone

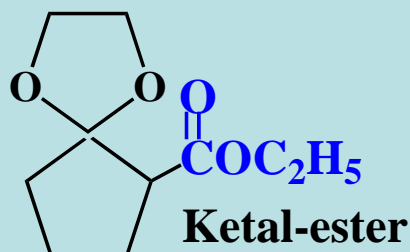
This is the desired conversion, but to **selectively** reduce the ester function it is necessary to protect (or mask) the ketone function.



Use of protecting group:



Formation of cyclic ketal protective group



Ketal-ester

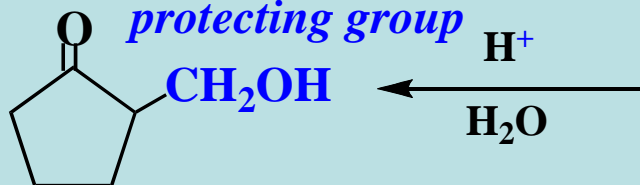
(1) LiAlH₄, ether

(2) H₂O

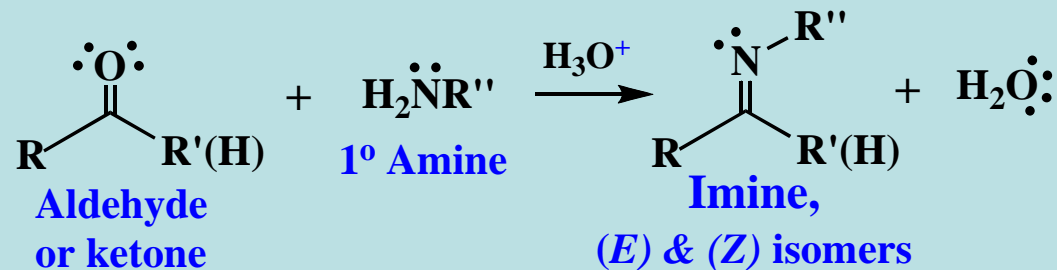
Ester reduction

(ketone C=O would, if not protected, have been reduced, also)

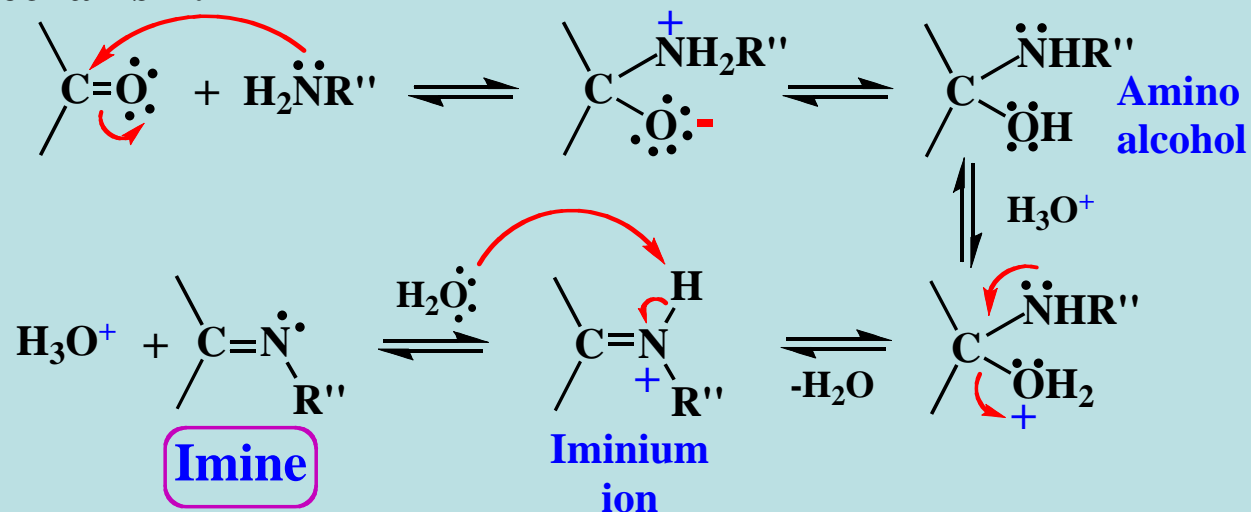
Hydrolysis: removal of protecting group



Imines: Addition of 1° Amines

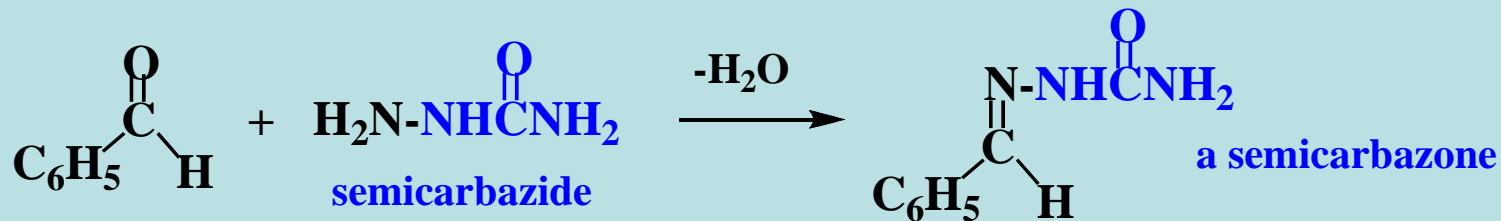
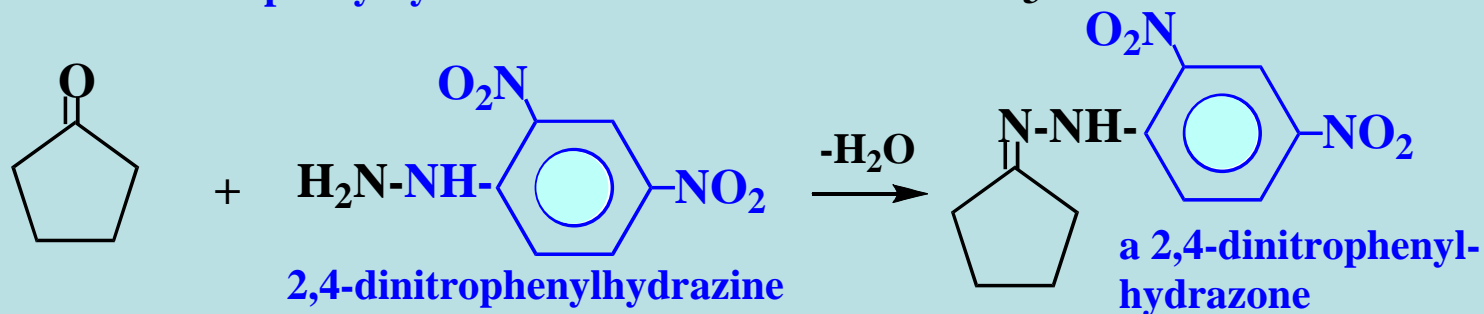
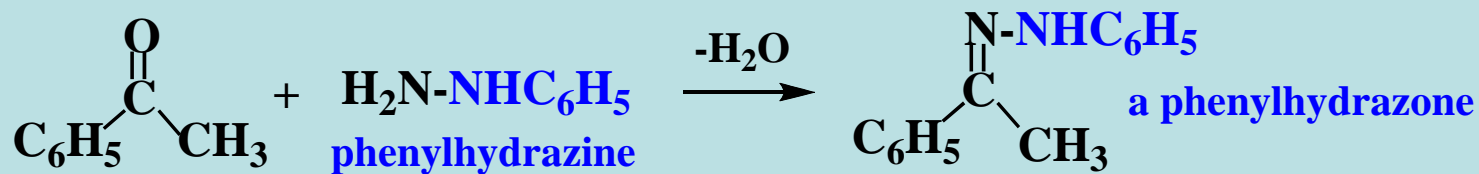
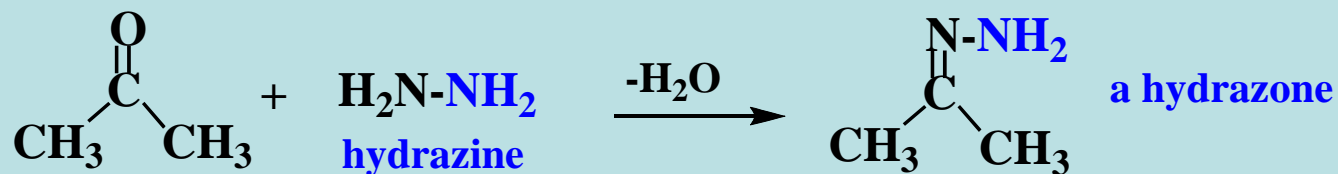
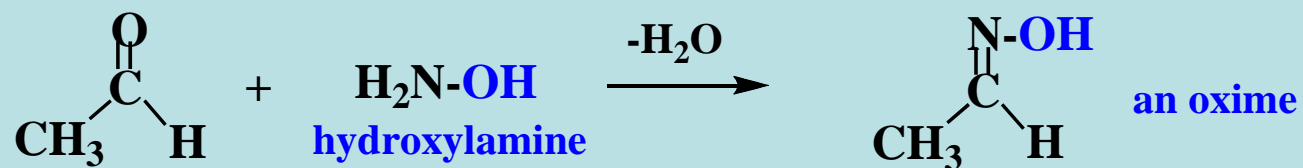


Mechanism:

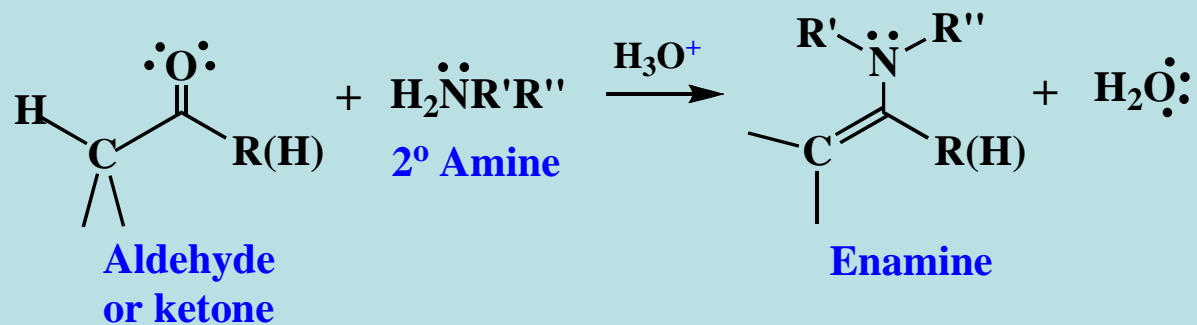


Note: All steps are **reversible**, so imines **hydrolyze** to carbonyl compounds in aqueous acid solution.

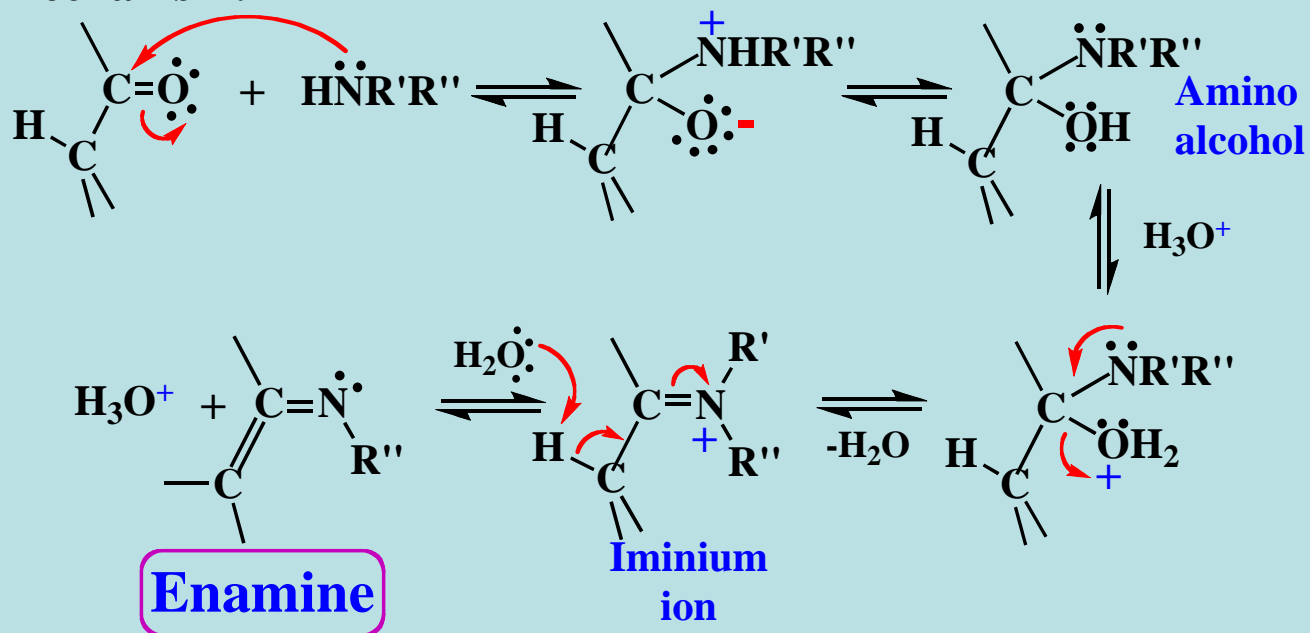
Imine-Type Carbonyl Derivatives



Enamines: Addition of 2° Amines

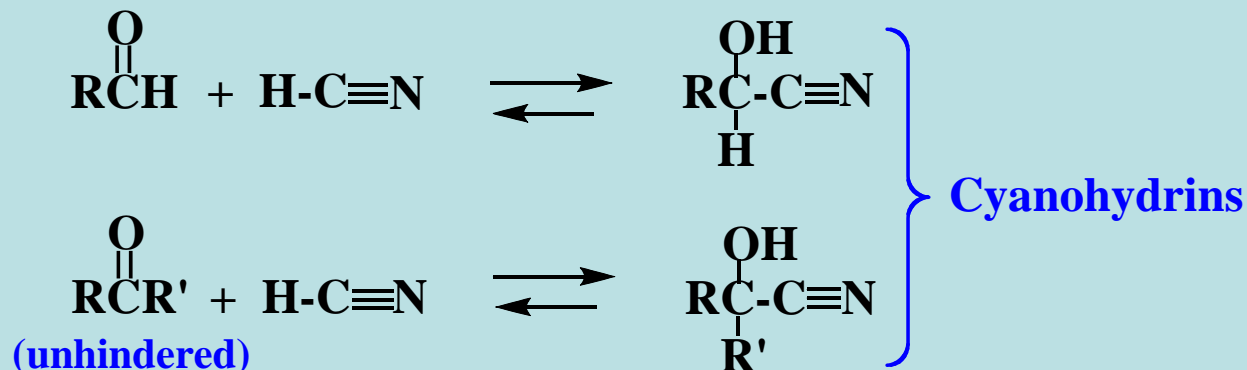


Mechanism:

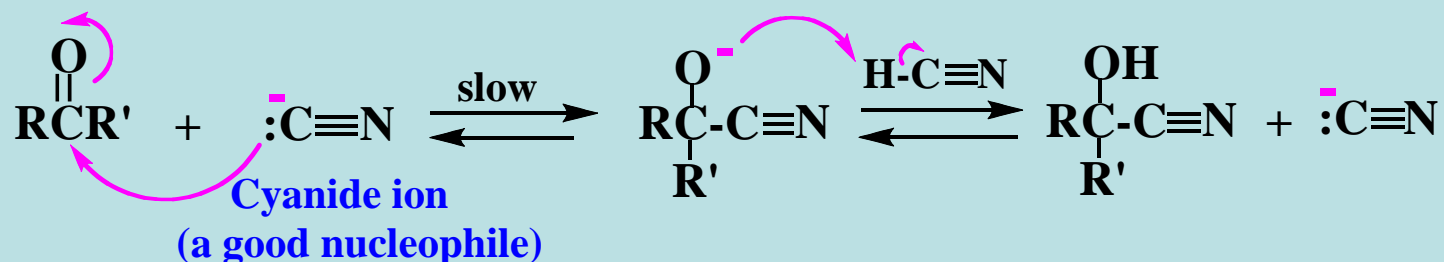


Addition of Hydrogen Cyanide: Cyanohydrins

Hydrogen cyanide (HCN) adds to aldehydes and unhindered ketones to produce **cyanohydrins**.

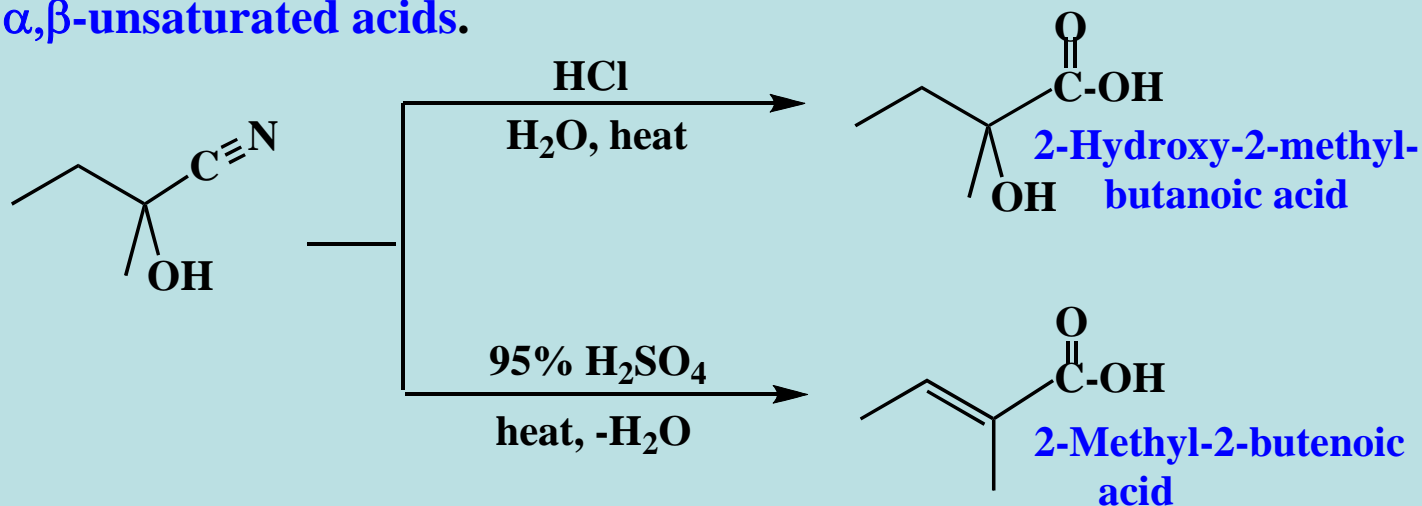


In the reaction, a mineral acid is added to a mixture of the carbonyl compound and sodium cyanide. Too much acid slows the reaction by tying up the nucleophilic cyanide ion as HCN. The following sequence describes the mechanism of cyanohydrin formation.

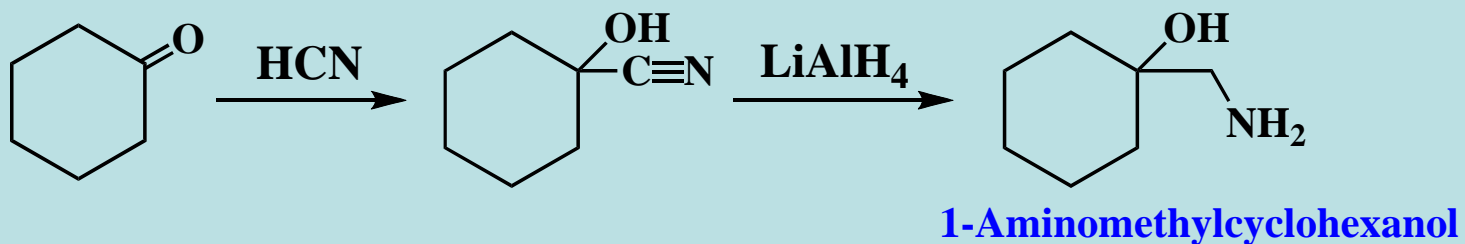


Synthetic Uses of Cyanohydrins

(1) Hydrolysis of the nitrile function gives α -hydroxyacids or α,β -unsaturated acids.



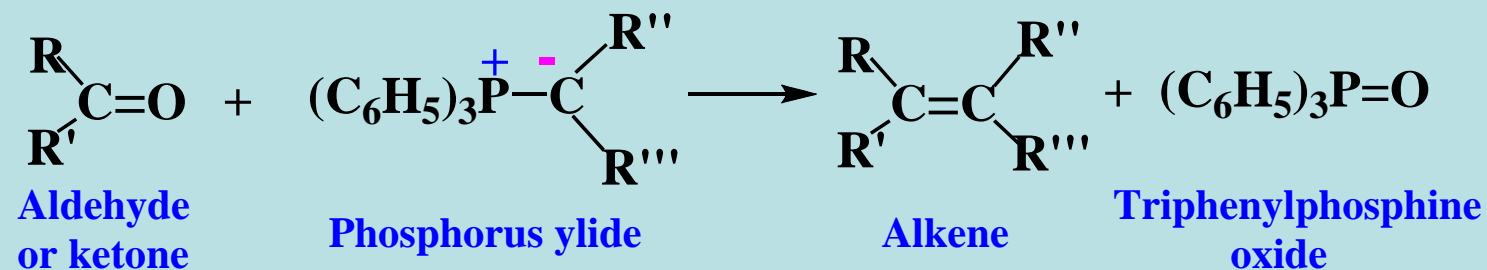
(2) Reduction with lithium aluminum hydride gives β -aminoalcohols.



The Addition of Ylides: The Wittig Reaction

One of the most useful and general synthetic reactions in organic chemistry is the **conversion of aldehydes and ketones into alkenes** by the **Wittig reaction**, discovered by Georg Wittig in 1954 (co-recipient of the Nobel Prize in Chemistry in 1979).

The classic reaction involves addition of a **phosphorus ylide** to the carbonyl compound. An ylide is a neutral compound with an **anionic carbon** bonded to a cationic heteroatom such as P or S.

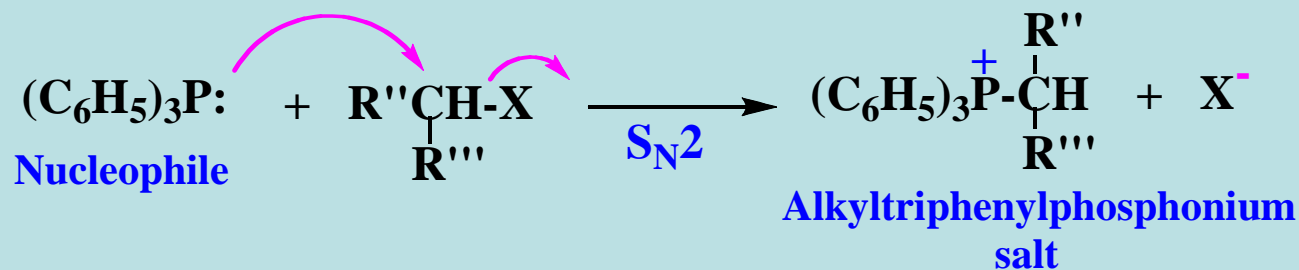


Synthesis of Ylides

The ylides required for the Wittig reaction may usually be made by a two-step synthesis beginning with triphenylphosphine.

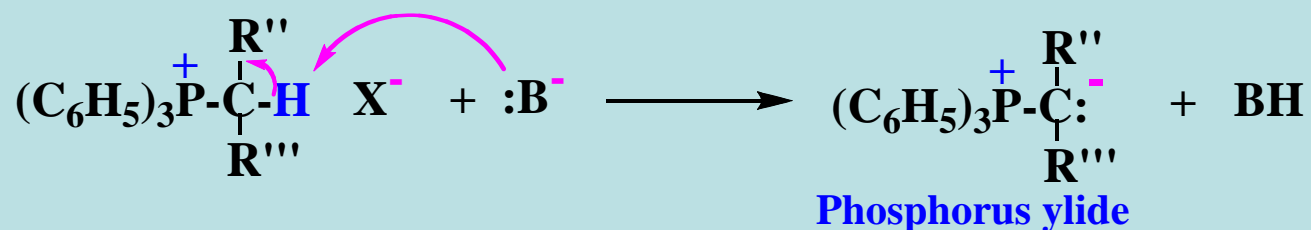
Step 1.

Triphenylphosphine reacts with **sterically unhindered** alkyl halides by an S_N2 mechanism yielding **alkyltriphenylphosphonium halides**, which are analogous to quaternary ammonium halide salts, $R_4N^+ X^-$.

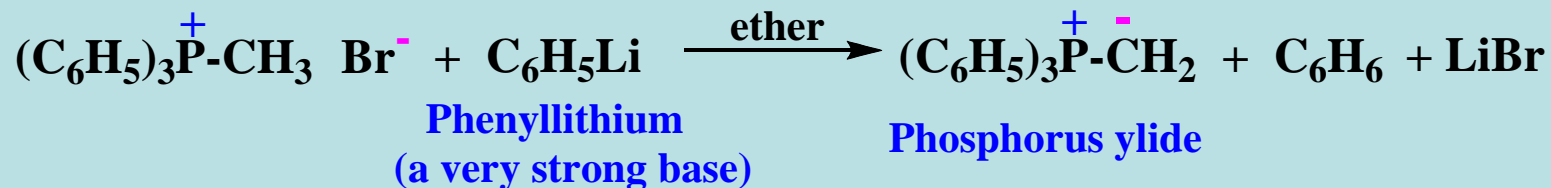
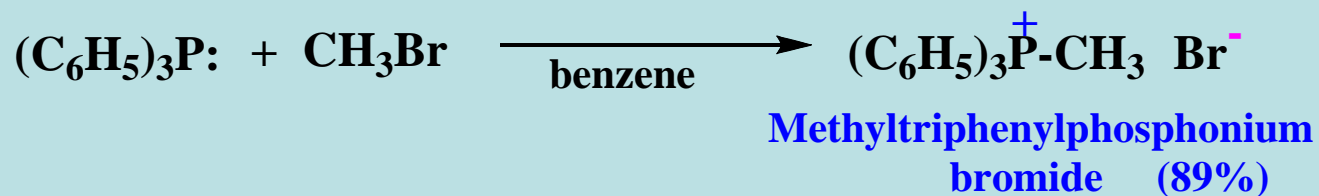


Step 2.

Because the phosphorus atom carries a full positive charge, protons on adjacent carbons (α -position) are **relatively acidic** and may be removed with an appropriate base, producing a **phosphorus ylide**.



Example:

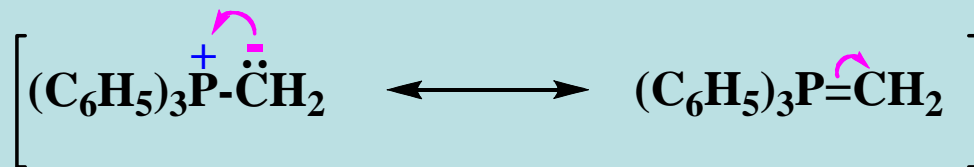


Choice of Base

The choice of base and solvent in the deprotonation of the phosphonium salt depends on the **acidity of the α -H**. When simple alkyl groups are deprotonated, very strong bases such as alkyl- and aryllithiums in ether solvents are used. When powerful electron-withdrawing groups are present, oxygen bases in alcohol solvents may be used to produce the ylide.

A Resonance Description of the Phosphorous Ylide

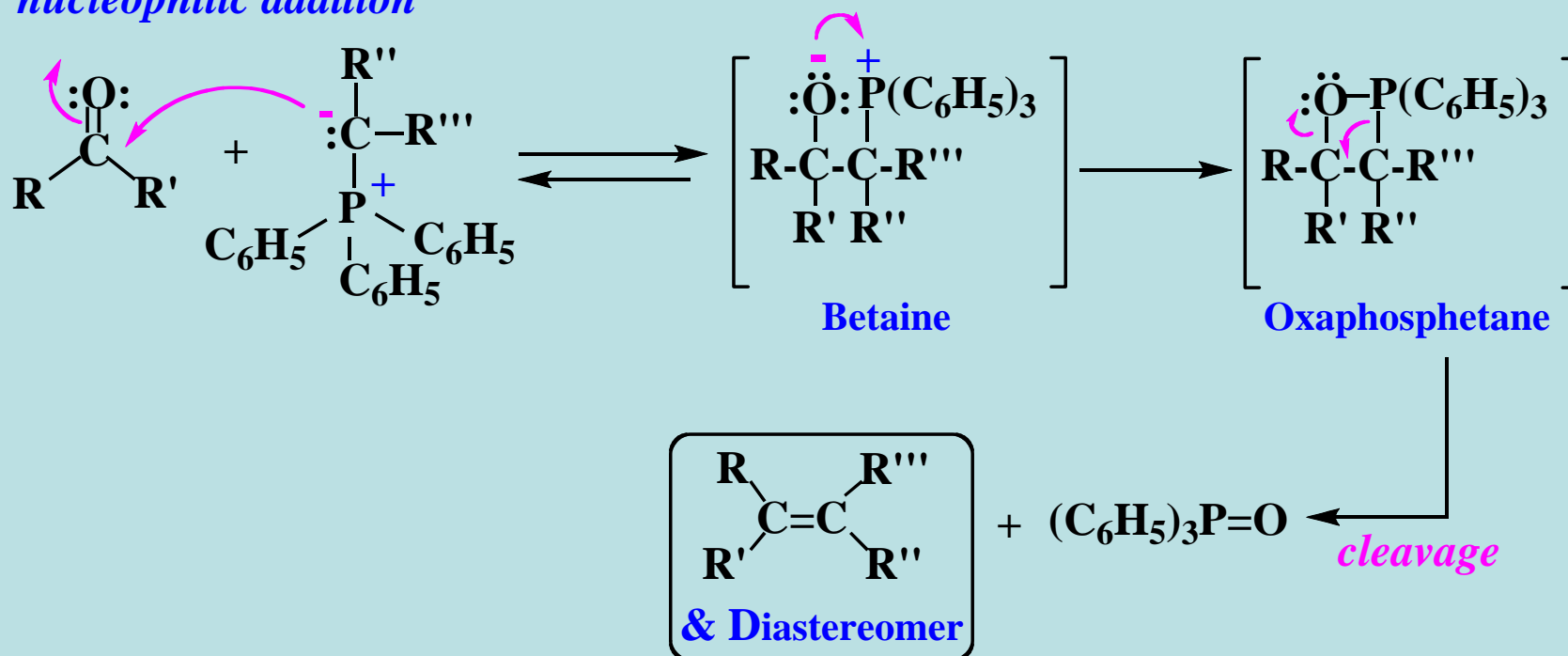
The phosphorus ylide is represented as a hybrid of the two resonance structures below. The octet rule restriction does not apply to phosphorus, a third-row element.



A Mechanism for the Wittig Reaction

The phosphorus ylide is **nucleophilic** via the α -carbanionic center. Its addition to aldehydes and ketones may be written as a nucleophilic addition producing a **betaine (zwitterion)** that proceeds through an **oxaphosphetane intermediate** to the final products.

nucleophilic addition



More recent studies suggest that the reaction is a **cycloaddition** that **directly produces the oxaphosphetane** that cleaves to the products.

Retrosynthetic Analysis Using the Wittig Reaction

To determine the reagents needed to synthesize an alkene using the Wittig reaction, **the alkene is cut in half**. One half of the alkene is supplied by the carbonyl compound, the other half is provided by the ylide.

TARGET ALKENE: 2-Phenylpropene

