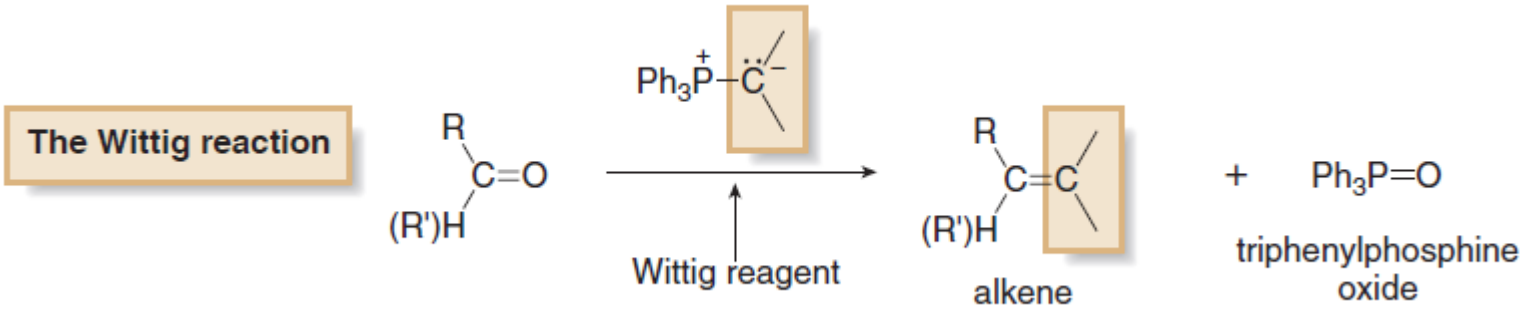
Aldehydes and Ketones 2

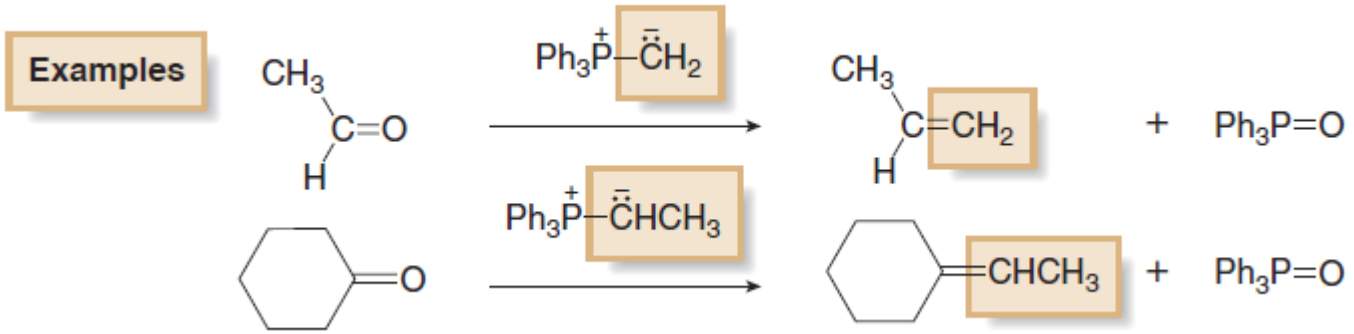
Based on Organic Chemistry, J. G. Smith 3rde.

The Wittig Reaction

Wittig reaction, named for German chemist Georg Wittig, who was awarded the Nobel Prize in Chemistry in 1979 for its discovery. The Wittig reaction uses a carbon nucleophile, the **Wittig reagent,** to form **alkenes.** When a carbonyl compound is treated with a Wittig reagent, the carbonyl oxygen atom is replaced by the negatively charged alkyl group bonded to the phosphorus—that is, **the C=O is converted to a C=C.**

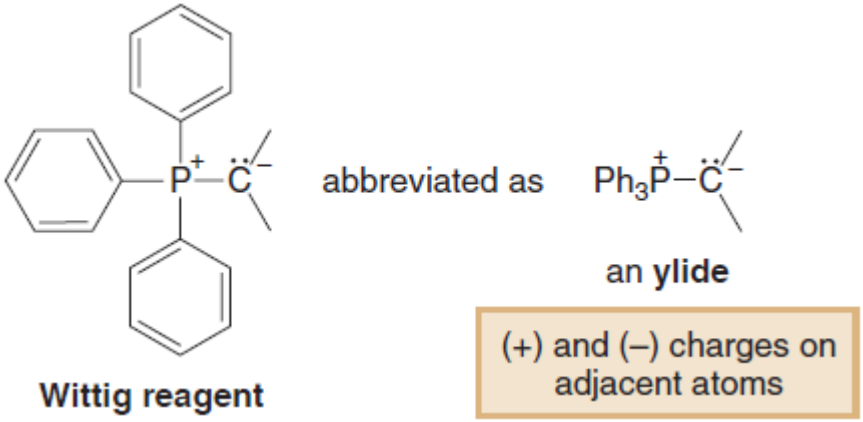


A Wittig reaction forms two new carbon–carbon bonds—one new σ bond and one new π bond—as well as a phosphorus by-product, $Ph_3P{=}O$ (triphenylphosphine oxide).

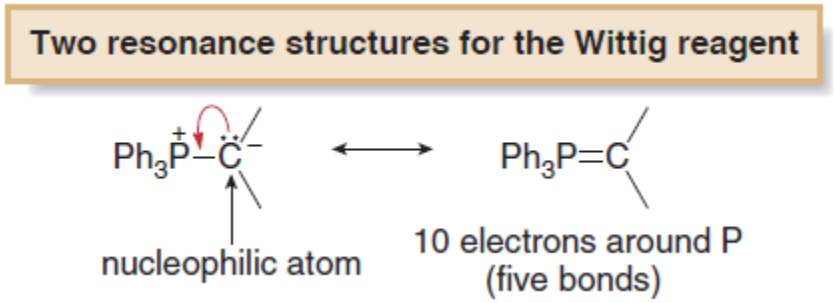


The Wittig Reagent:

A **Wittig reagent** is an **organophosphorus reagent**—a reagent that contains a carbon–phosphorus bond. A typical Wittig reagent has a phosphorus atom bonded to three phenyl groups, plus another alkyl group that bears a negative charge.

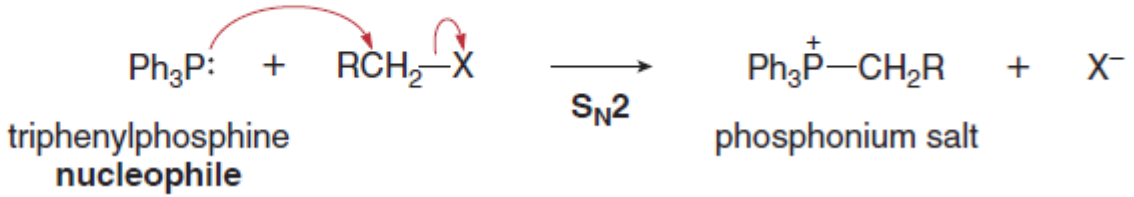


A Wittig reagent is an ***ylide,*** **a species that contains two oppositely charged atoms bonded to each other, and both atoms have octets.** In a Wittig reagent, a negatively charged carbon atom is bonded to a positively charged phosphorus atom.

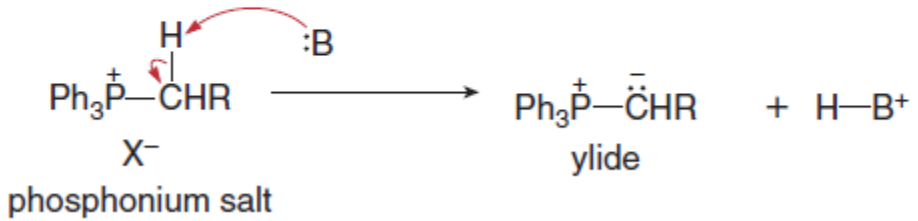


Wittig reagents are synthesized by a two-step procedure:

Step [1] S_N2 reaction of triphenylphosphine with an alkyl halide forms a phosphonium salt.



Step [2] Deprotonation of the phosphonium salt with a strong base (:B) forms the ylide.

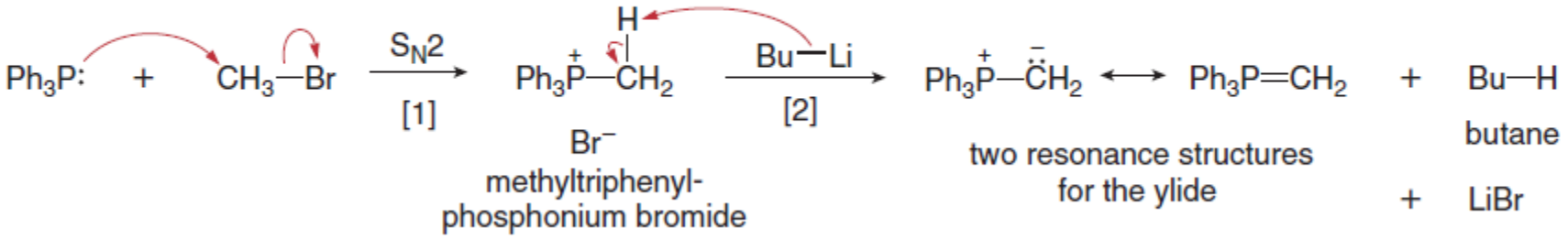


Typical strong base:

$CH_3CH_2CH_2CH_2$—Li

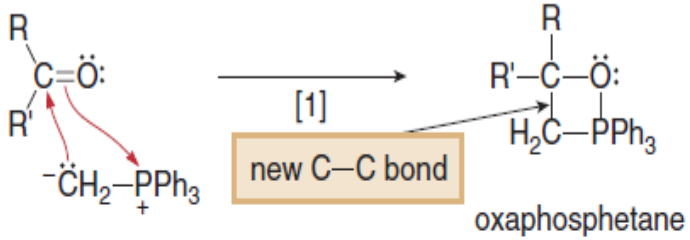
Bu—Li

To synthesize the Wittig reagent, $Ph_3P{=}CH_2$, use these two steps:



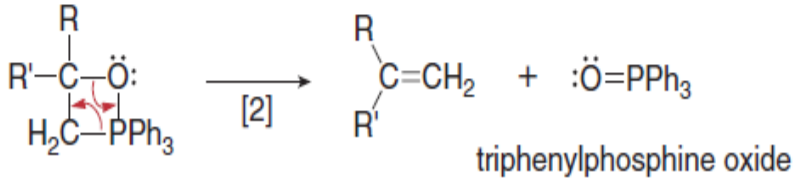
Mechanism of the Wittig Reaction

Step [1] Nucleophilic addition forms a four-membered ring.



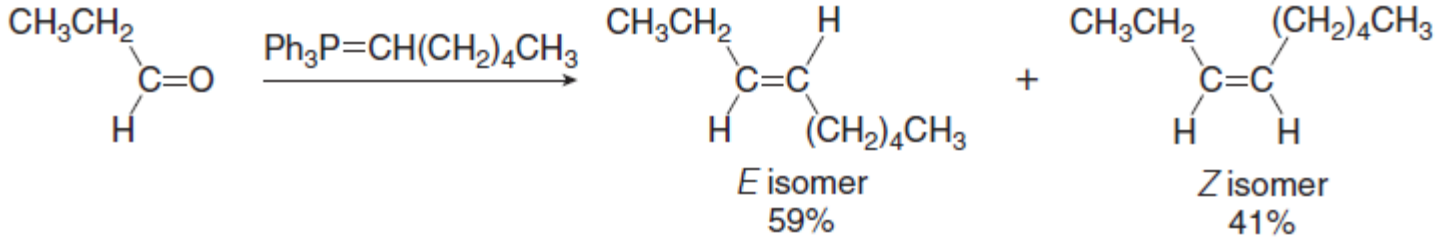
- Step [1] forms two bonds and generates a four-membered ring. The negatively charged carbon atom of the ylide attacks the carbonyl carbon to form a new carbon–carbon σ bond, while the carbonyl O atom attacks the positively charged P atom.
- This process generates an **oxaphosphetane,** a four-membered ring containing a strong P – O bond.

Step [2] Elimination of $Ph_3P=O$ forms the alkene.



- In Step [2], **$Ph_3P=O$ (triphenylphosphine oxide) is eliminated,** forming two new π bonds. The formation of the very strong P – O double bond provides the driving force for the Wittig reaction.

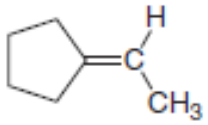
One limitation of the Wittig reaction is that a mixture of alkene stereoisomers sometimes forms.



Retrosynthetic Analysis

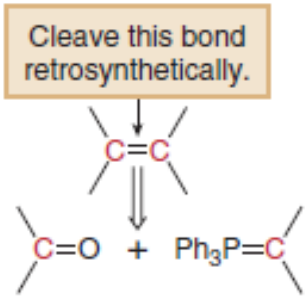
HOW TO Determine the Starting Materials for a Wittig Reaction Using Retrosynthetic Analysis

Example What starting materials are needed to synthesize alkene A by a Wittig reaction?



A

Step [1] Cleave the carbon–carbon double bond into two components.



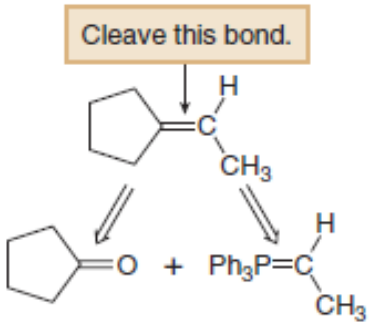
- Part of the molecule becomes the carbonyl component and the other part becomes the Wittig reagent.

—Continued

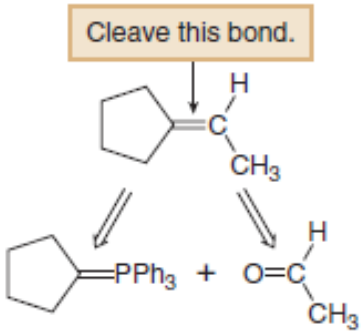
HOW TO, continued . . .

There are usually two routes to a given alkene using a Wittig reaction:

Possibility [1]



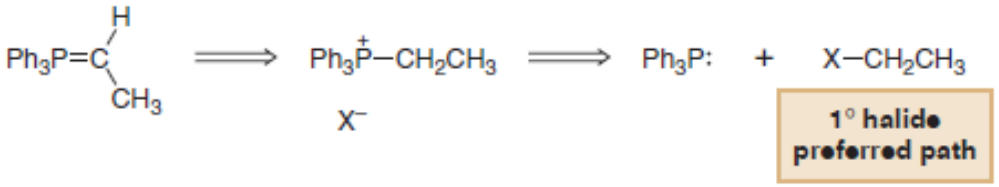
Possibility [2]



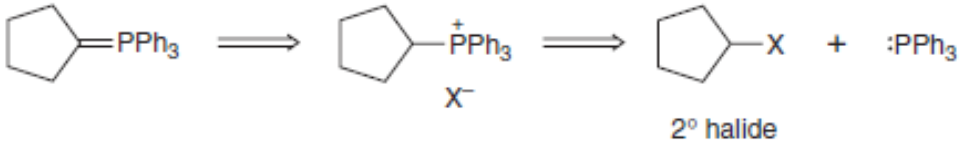
Step [2] **Compare the Wittig reagents. The preferred pathway uses a Wittig reagent derived from an unhindered alkyl halide—CH_3X or RCH_2X.**

Determine what alkyl halide is needed to prepare each Wittig reagent:

Possibility [1]



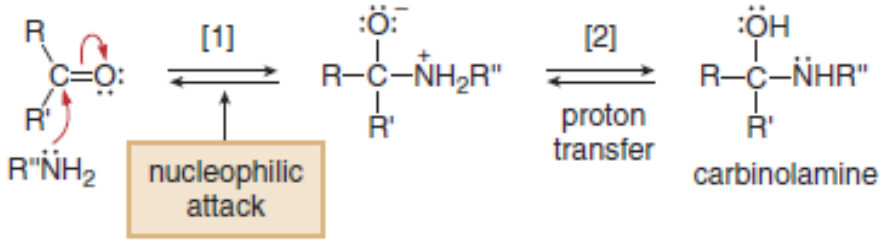
Possibility [2]



Because the synthesis of the Wittig reagent begins with an S_N2 reaction, **the preferred pathway begins with an unhindered methyl halide or 1° alkyl halide.** In this example, retrosynthetic analysis of both Wittig reagents indicates that only one of them ($Ph_3P{=}CHCH_3$) can be synthesized from a 1° alkyl halide, making Possibility [1] the preferred pathway.

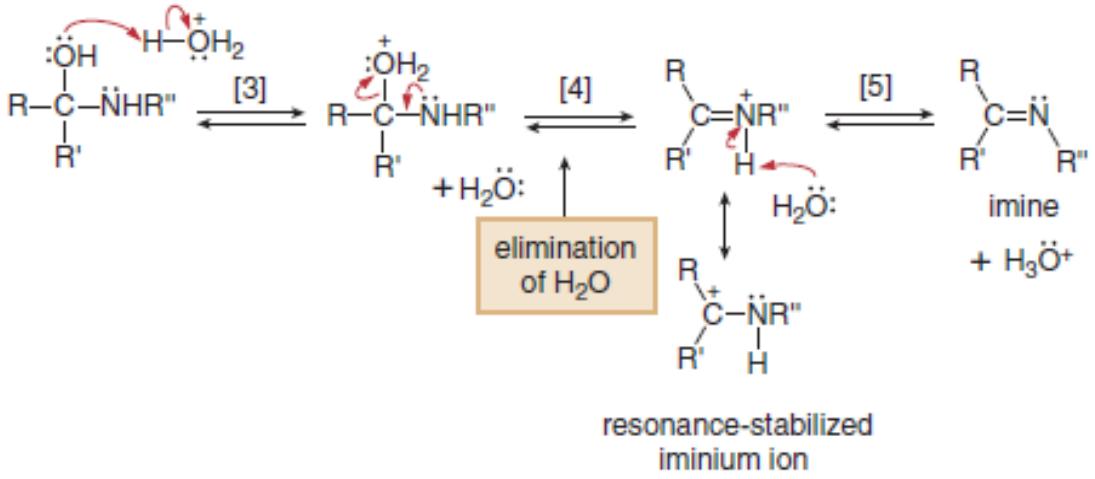
Addition of 1° Amines (Formation of Imines)

Part [1] Nucleophilic addition forms a carbinolamine.



- **Nucleophilic attack** of the amine followed by proton transfer forms the unstable carbinolamine (Steps [1]–[2]). These steps result in the addition of H and NHR" to the carbonyl group.

Part [2] Elimination of H_2O forms an imine.

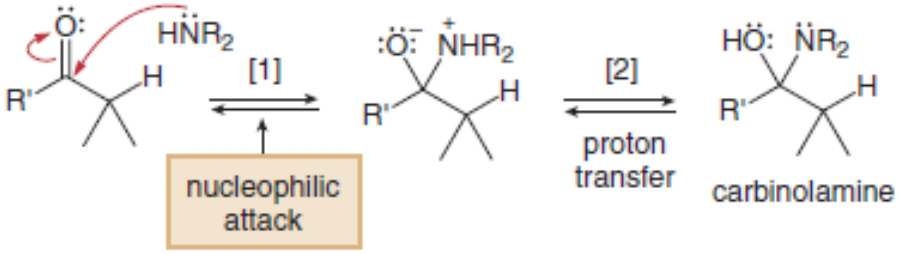


- Elimination of H_2O forms the imine in three steps. Protonation of the OH group in Step [3] forms a good leaving group, leading to **loss of water** in Step [4], giving a resonance-stabilized **iminium ion.** Loss of a proton forms the imine in Step [5].
- Except for Steps [1] (nucleophilic addition) and [4] (H_2O elimination), all other steps in the mechanism are acid–base reactions—that is, moving a proton from one atom to another.

Imine formation is most rapid at pH 4–5. Mild acid is needed for protonation of the hydroxy group in Step [3] to form a **good leaving group.** Under strongly acidic conditions, the reaction rate decreases because the amine nucleophile is protonated. With no free electron pair, it is no longer a nucleophile, and so nucleophilic addition cannot occur.

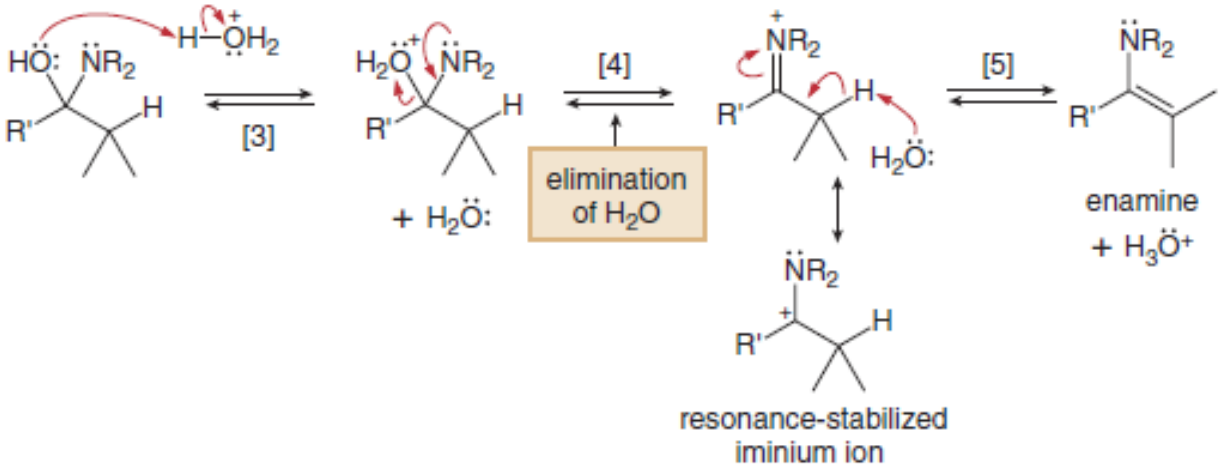
Addition of 2° Amines (Formation of Enamines)

Part [1] Nucleophilic addition forms a carbinolamine.



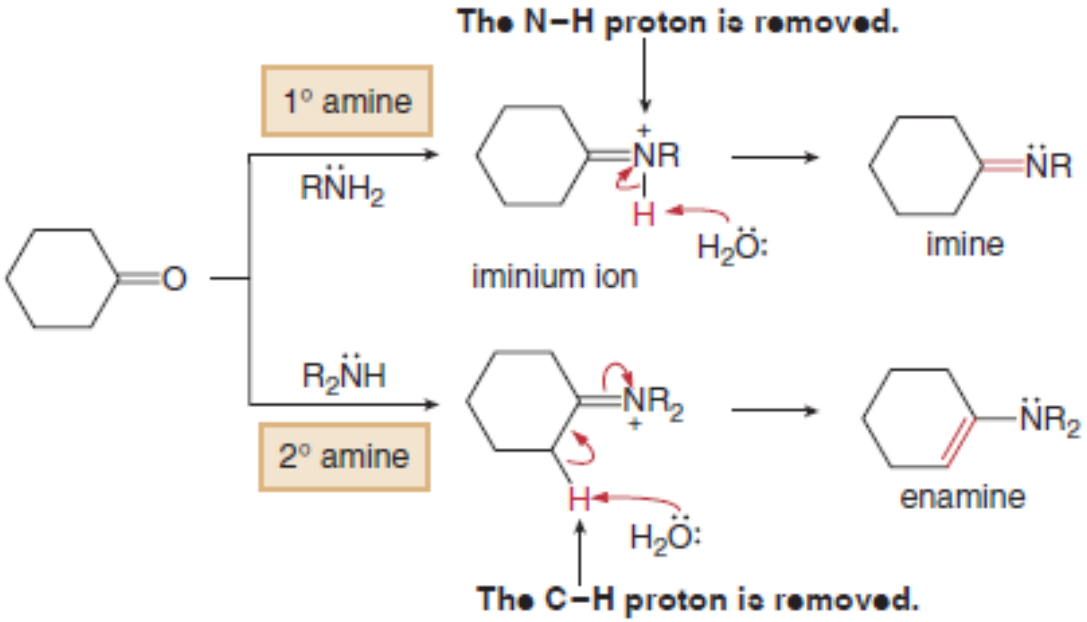
- **Nucleophilic attack** of the amine followed by proton transfer forms the unstable carbinolamine (Steps [1]–[2]).

Part [2] Elimination of H_2O forms an enamine.



- Protonation of the OH group in Step [3] forms a good leaving group, leading to **loss of water** in Step [4], giving a resonance-stabilized **iminium ion.**
- Removal of a proton from the adjacent C – H bond forms the enamine in Step [5].

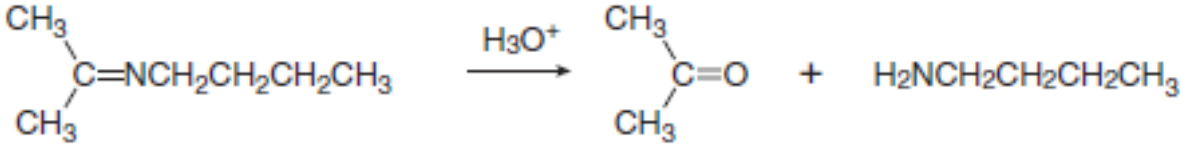
The formation of imines and enamines compared



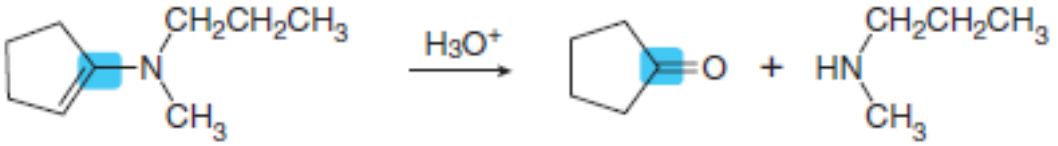
Imine and Enamine Hydrolysis

- Hydrolysis of imines and enamines forms aldehydes and ketones.

Imine hydrolysis



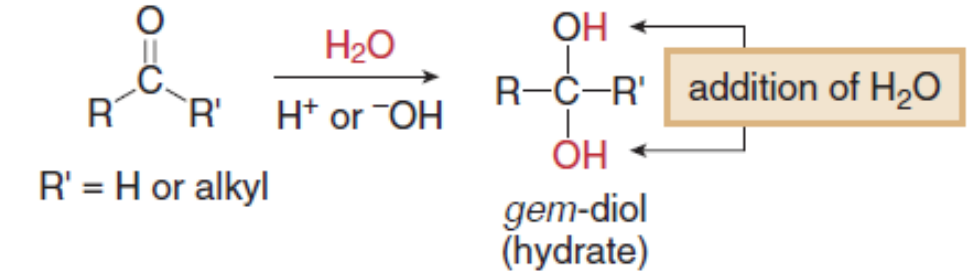
Enamine hydrolysis



Addition of H_2O—Hydration

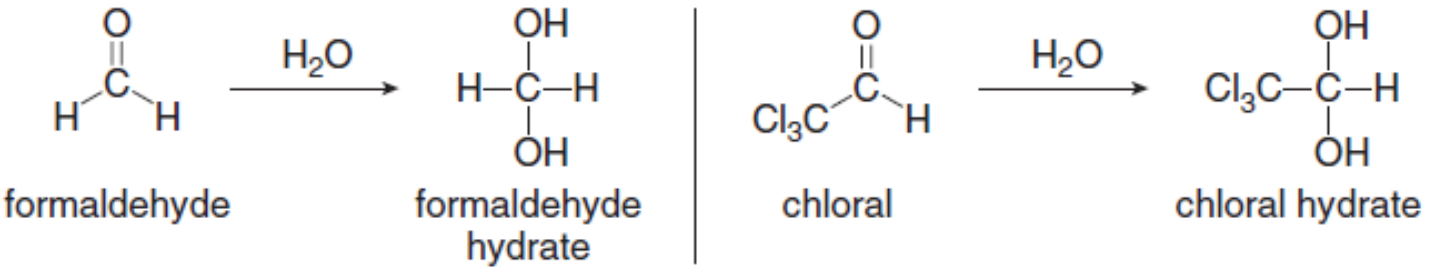
Treatment of a carbonyl compound with H_2O in the presence of an acid or base catalyst **adds the elements of H and OH across the carbon–oxygen o bond,** forming a ***gem*-diol** or **hydrate.**

Nucleophilic addition of H_2O



Hydration of a carbonyl group gives a good yield of *gem*-diol only with an unhindered aldehyde like formaldehyde, and with aldehydes containing nearby electron-withdrawing groups.

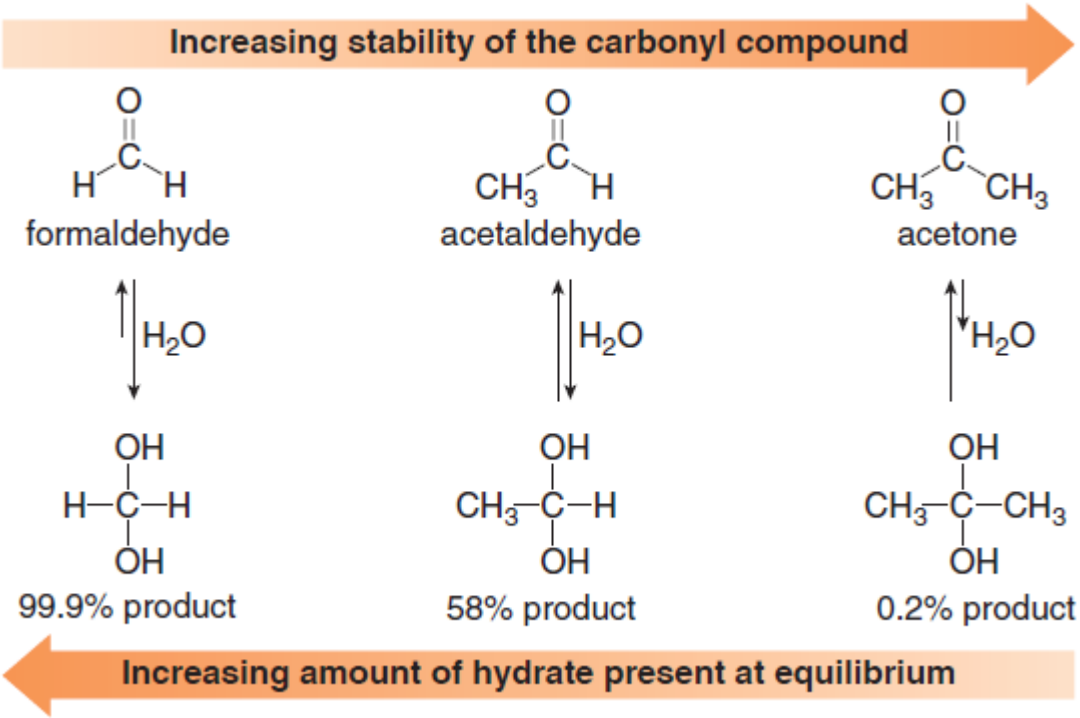
Examples



The Thermodynamics of Hydrate Formation

Whether addition of H_2O to a carbonyl group affords a good yield of the *gem*-diol depends on the relative energies of the starting material and the product. With less stable carbonyl starting materials, equilibrium favors the hydrate product, whereas with more stable carbonyl starting materials, equilibrium favors the carbonyl starting material.

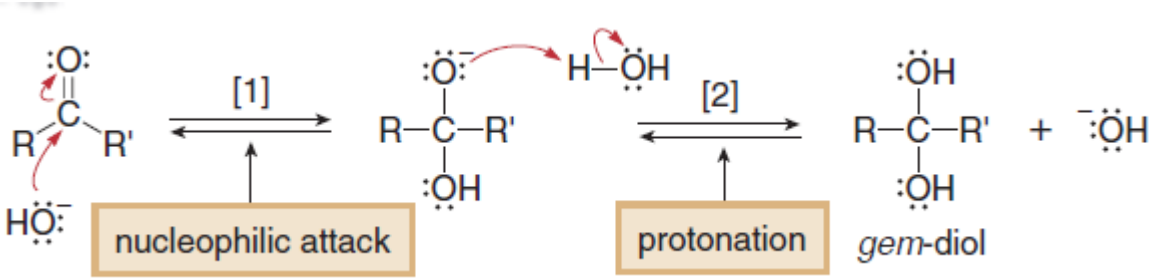
- Increasing the number of alkyl groups on the carbonyl carbon decreases the amount of hydrate at equilibrium.



- Electron-donating groups near the carbonyl carbon stabilize the carbonyl group, decreasing the amount of the hydrate at equilibrium.
- Electron-withdrawing groups near the carbonyl carbon destabilize the carbonyl group, increasing the amount of hydrate at equilibrium.

The Kinetics of Hydrate Formation

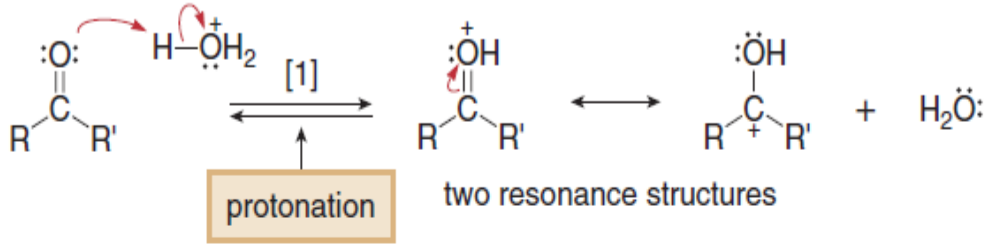
Base-Catalyzed Addition of H_2O to a Carbonyl Group



- In Step [1], **the nucleophile ($^-$OH) attacks the carbonyl group,** cleaving the π bond, and moving an electron pair onto oxygen.
- In Step [2], **protonation of the negatively charged O atom by H_2O** forms the *gem*-diol.

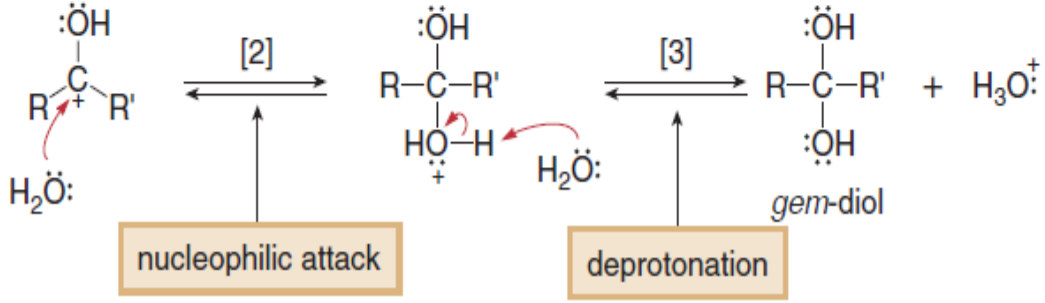
Acid-Catalyzed Addition of H_2O to a Carbonyl Group

Step [1] Protonation of the carbonyl group



- Protonation of the carbonyl oxygen forms a resonance-stabilized cation that bears a full positive charge.

Steps [2]–[3] Nucleophilic attack and deprotonation



- In Step [2], the nucleophile (H_2O) attacks, and then deprotonation forms the neutral addition product in Step [3].
- The overall result is the addition of H and OH to the carbonyl group and regeneration of the acid catalyst.

Acid and base increase the rate of reaction for different reasons.

- **Base converts H_2O into –OH, a *stronger nucleophile.***

- **Acid protonates the carbonyl group, making it *more electrophilic* towards nucleophilic attack.**

These catalysts increase the rate of the reaction, but they do not affect the equilibrium constant.

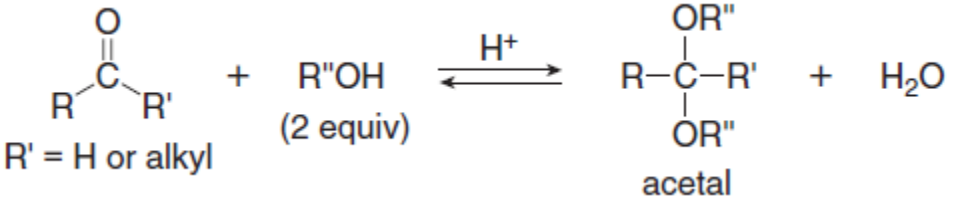
Starting materials that give a low yield of *gem*-diol do so whether or not a catalyst is present.

Because these reactions are reversible, the conversion of *gem*-diols to aldehydes and ketones is also catalyzed by acid and base, and the steps of the mechanism are reversed.

Addition of Alcohols—Acetal Formation

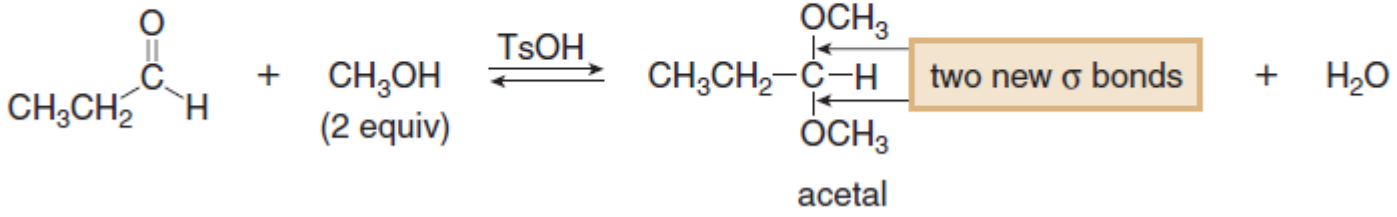
Aldehydes and ketones react with *two* equivalents of alcohol to form acetals. In an acetal, the carbonyl carbon from the aldehyde or ketone is now singly bonded to two OR" (alkoxy) groups.

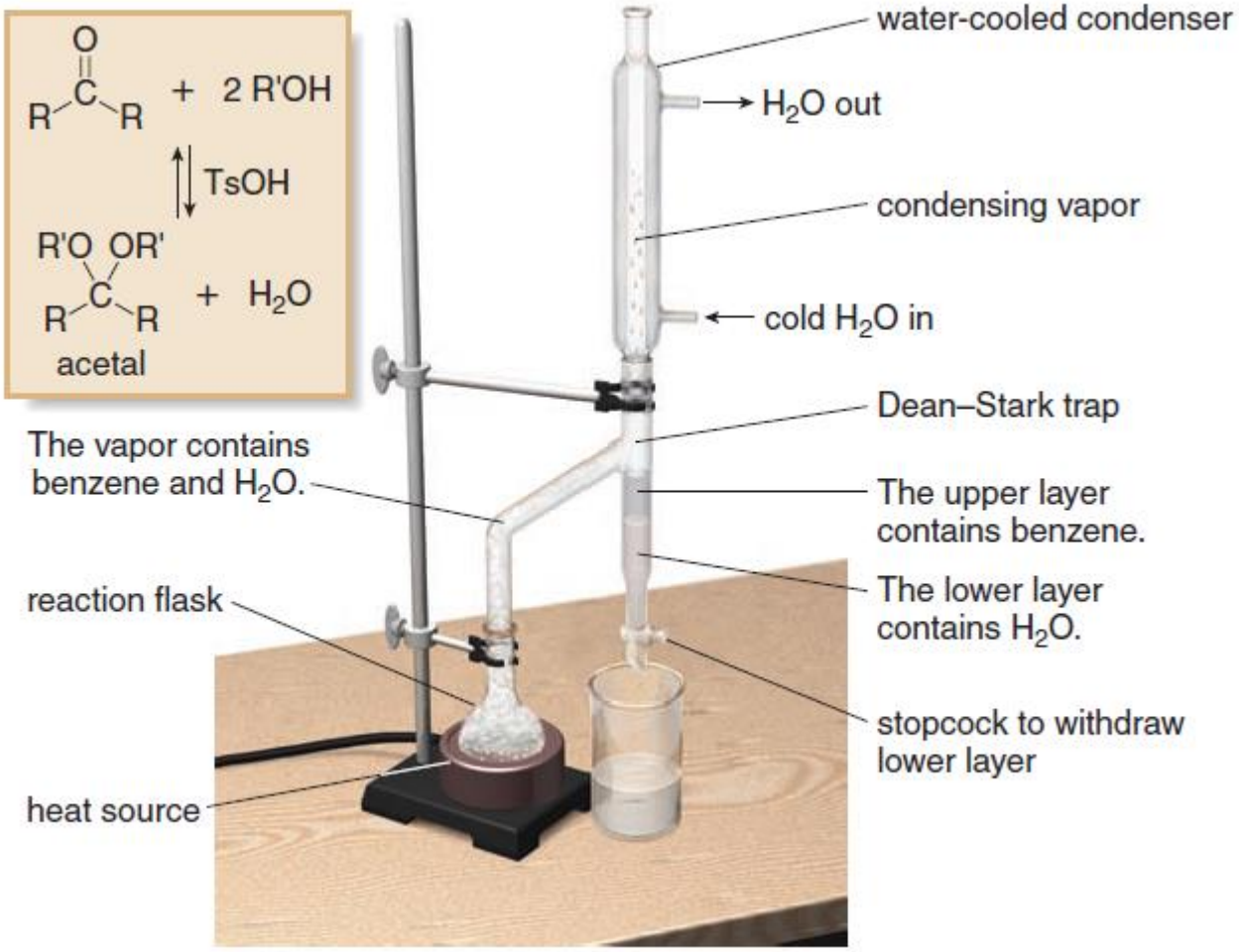
Acetal formation



This reaction differs from other additions we have seen thus far, because **two equivalents of alcohol are added to the carbonyl group,** and two new C – O σ bonds are formed. Acetal formation is catalyzed by acids, commonly *p*-toluenesulfonic acid (TsOH).

Example

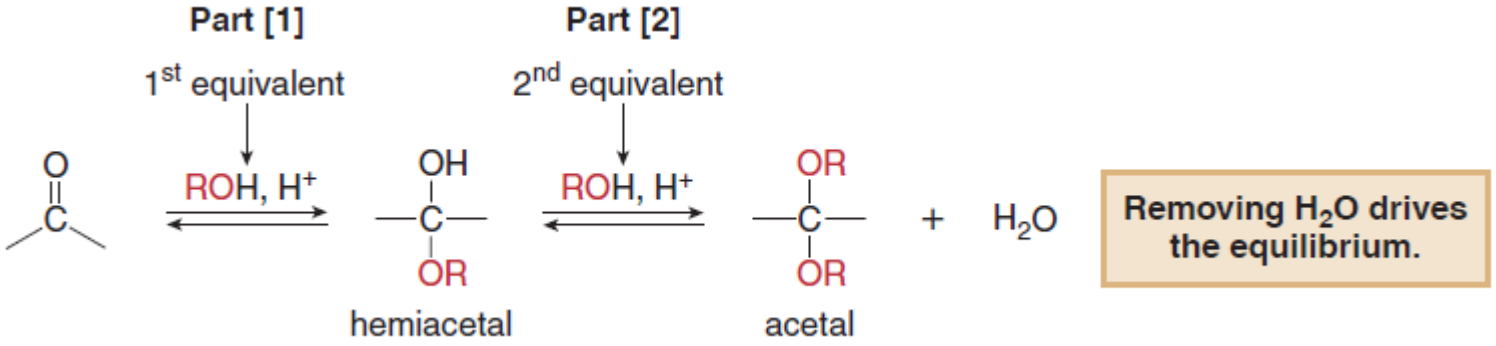




A Dean–Stark trap is an apparatus used for removing water from a reaction mixture. To use a Dean–Stark trap to convert a carbonyl compound to an acetal:

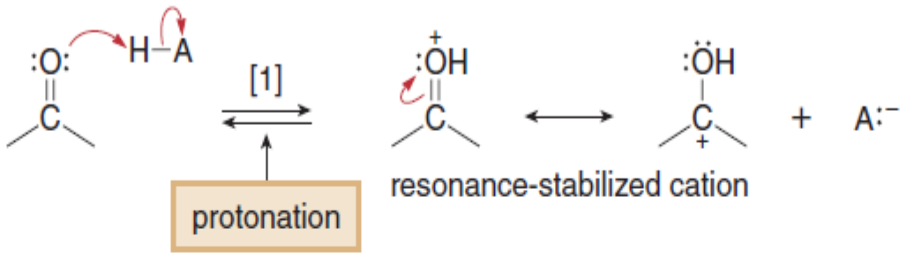
The carbonyl compound, an alcohol, and an acid are dissolved in benzene. As the mixture is heated, the carbonyl compound is converted to the acetal with water as a by-product. Benzene and water co-distill from the reaction mixture. When the hot vapors reach the cold condenser, they condense, forming a liquid that then collects in the glass tube below. Water, the more dense liquid, forms the lower layer, so that as it collects, it can be drained through the stopcock into a flask. In this way, water can be removed from a reaction mixture, driving the equilibrium.

The Mechanism



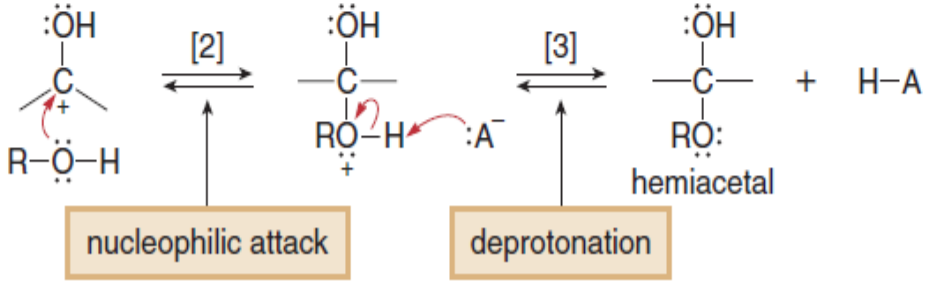
Acetal Formation—Part [1] Formation of a Hemiacetal

Step [1] Protonation of the carbonyl group



- **Protonation** of the carbonyl oxygen forms a resonance-stabilized cation that bears a full positive charge.

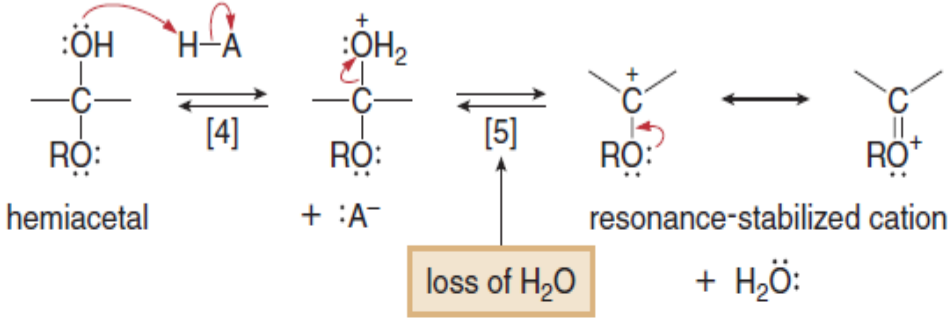
Steps [2]–[3] Nucleophilic attack and deprotonation



- In Step [2], the **nucleophile (ROH) attacks,** and then deprotonation forms the neutral addition product in Step [3].
- **The overall result is the addition of H and OR to the carbonyl group.**

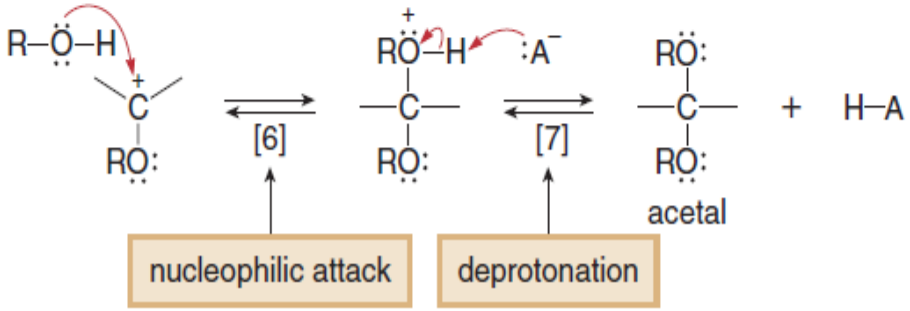
Acetal Formation—Part [2] Formation of the Acetal

Steps [4]–[5] Elimination of H_2O



- Protonation of the OH group in the hemiacetal in Step [4] forms a **good leaving group** (H_2O). Loss of H_2O in Step [5] forms a resonance-stabilized cation.

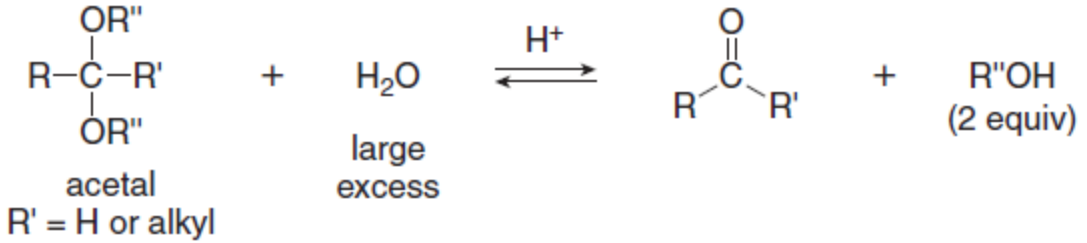
Steps [6]–[7] Nucleophilic attack and deprotonation



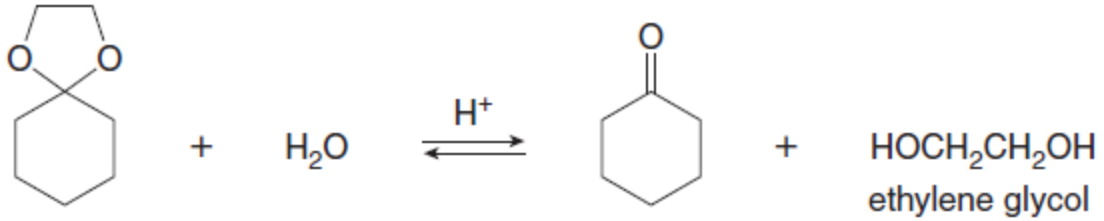
- Nucleophilic attack on the cation in Step [6] followed by loss of a proton forms the acetal.
- **The overall result of Steps [4]–[7] is the addition of a second OR group to the carbonyl group.**

Hydrolysis of Acetals

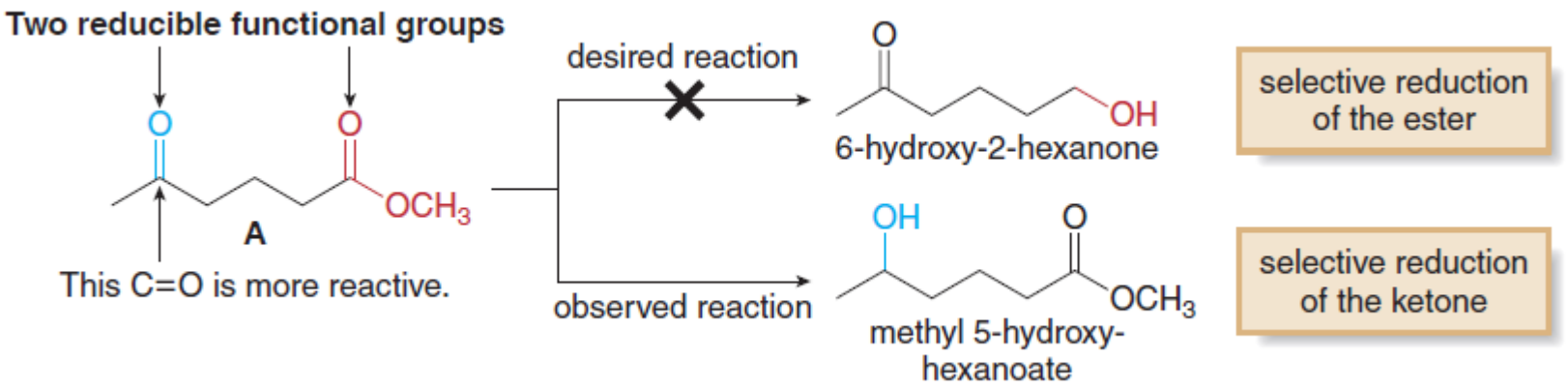
Acetal hydrolysis



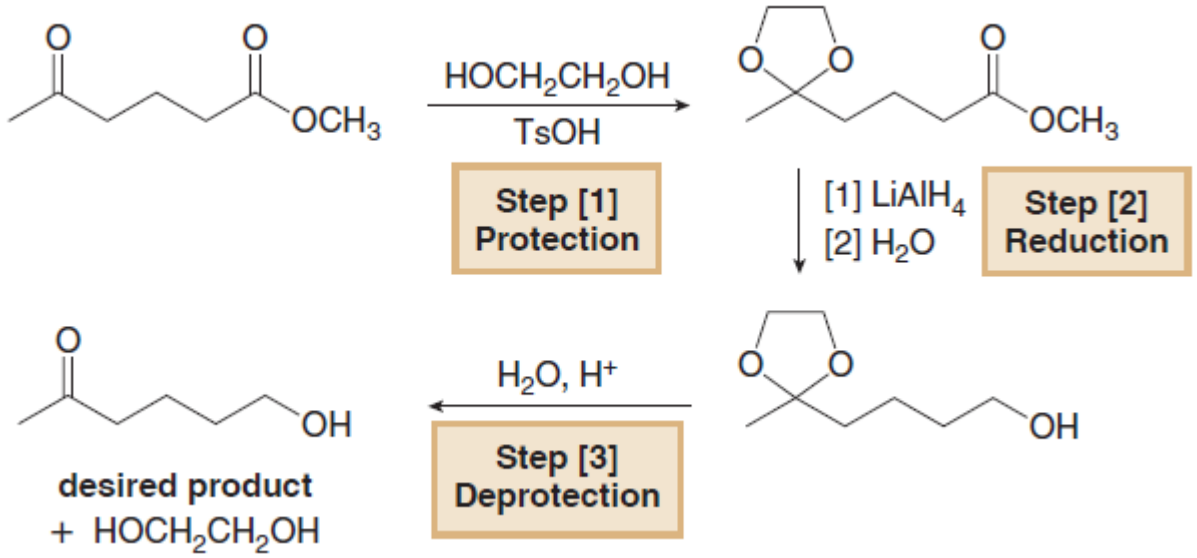
Example



Acetals as Protecting Groups



The following three-step sequence using a cyclic acetal leads to the desired product.



Cyclic Hemiacetals

Although acyclic hemiacetals are generally unstable and therefore not present in appreciable amounts at equilibrium, **cyclic hemiacetals containing five- and six-membered rings are stable compounds** that are readily isolated

A hemiacetal—General structure

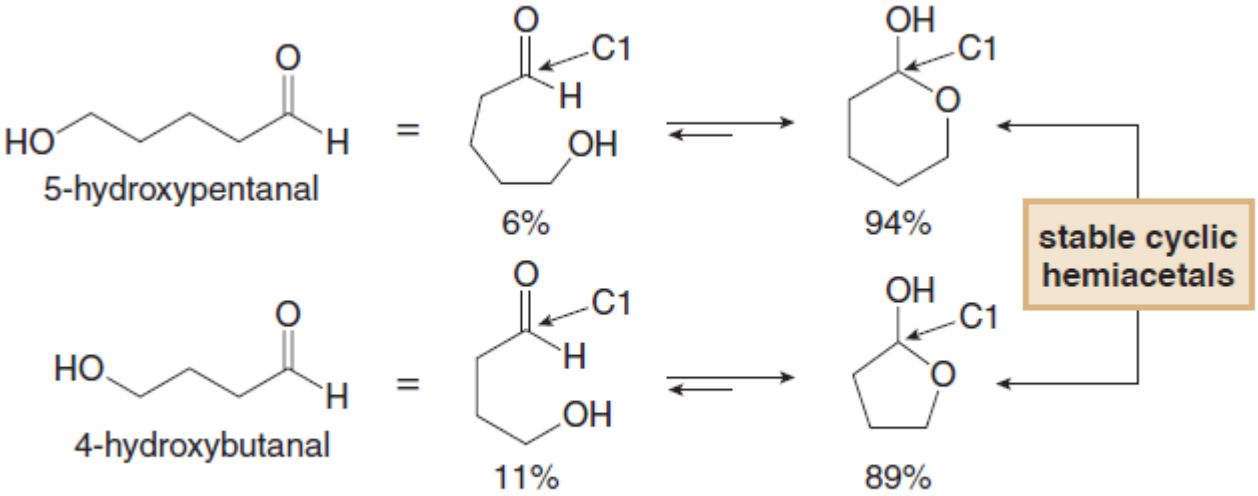
One C is bonded to:
- an OH group
- an OR group

Cyclic hemiacetals

Each indicated C is bonded to:
- an OH group
- an OR group that is part of a ring

Forming Cyclic Hemiacetals

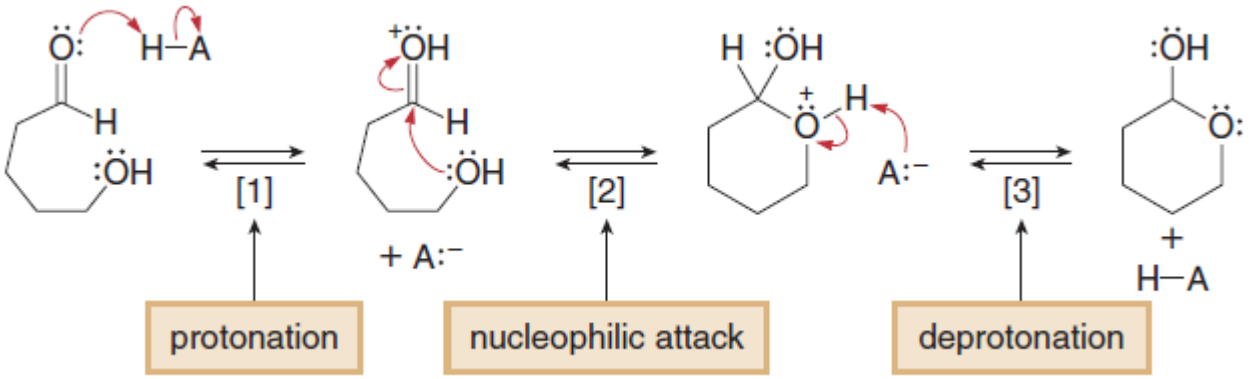
Cyclic hemiacetals are formed by **intramolecular cyclization of hydroxy aldehydes.**



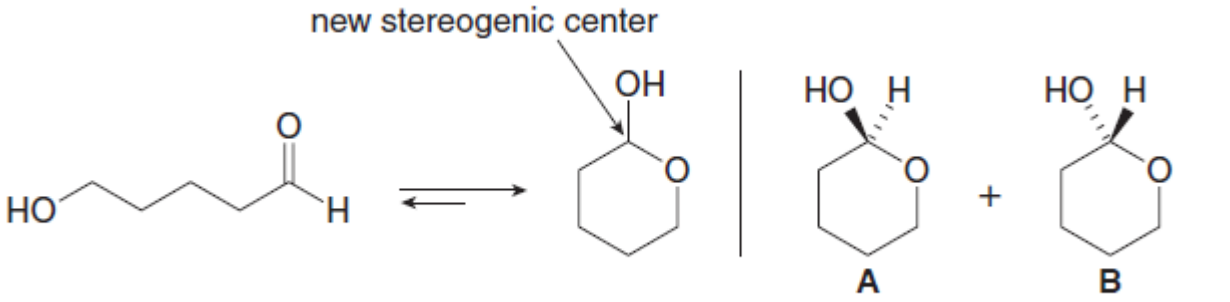
[Equilibrium proportions of each compound are given.]

Such **intramolecular** reactions to form five- and six-membered rings are faster than the corresponding **intermolecular** reactions. The two reacting functional groups, in this case OH and C=O, are held in close proximity, increasing the probability of reaction.

Acid-Catalyzed Cyclic Hemiacetal Formation

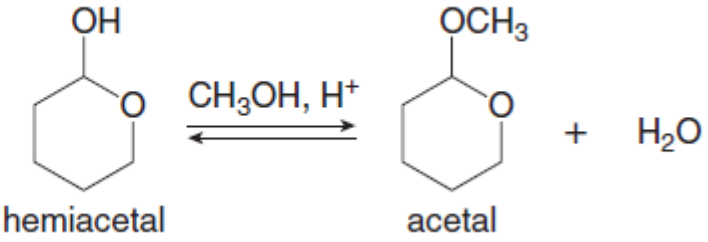


Intramolecular cyclization of a hydroxy aldehyde forms a **hemiacetal with a new stereogenic center, so that an equal amount of two enantiomers** results.

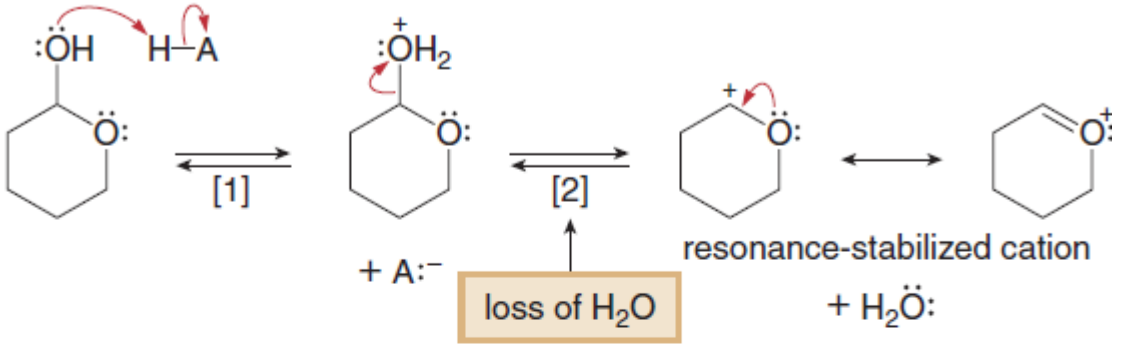


The Conversion of Hemiacetals to Acetals

Converting a hemiacetal to an acetal



Steps [1]–[2] Protonation and loss of the leaving group



Steps [3]–[4] Nucleophilic attack and deprotonation