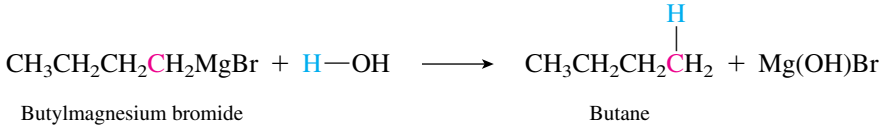
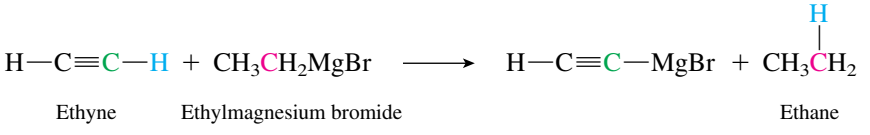
range of 45 to 50, all of these organometallic reagents behave as strong bases and react rapidly with even fairly weak acids, such as water and alcohols, as illustrated in the following equation. Therefore, the solvents that are used for their preparation must be scrupulously dried, and compounds containing OH or NH groups must be avoided.

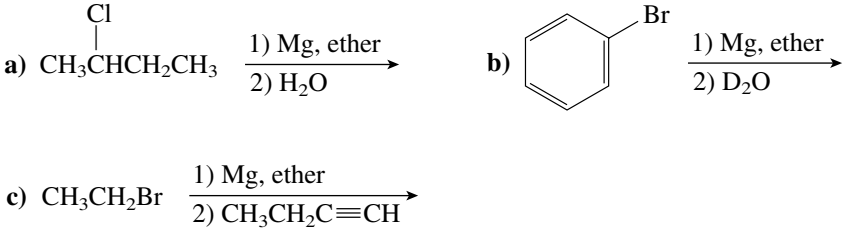


Even a 1-alkyne is acidic enough to react with a Grignard reagent. This reaction is the most common method of preparing Grignard reagents derived from these alkynes:



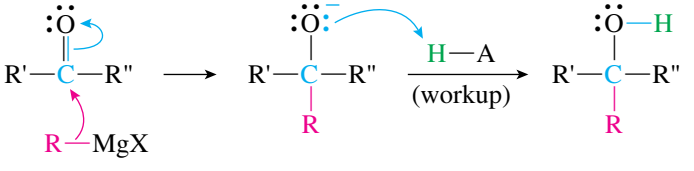
PROBLEM 18.8

Show the products of these reactions:



18.6 Addition of Organometallic Nucleophiles

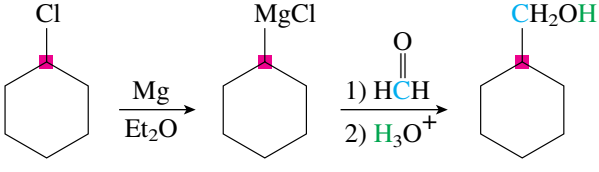
The reaction of Grignard reagents and organolithium compounds with aldehydes and ketones is perhaps the most useful method for the preparation of alcohols. The reaction is conducted under basic conditions and proceeds according to the following general mechanism:



Because these organometallic reagents are powerful nucleophiles, the reaction is irreversible. After the addition is complete, acid is added in the workup step to pro-

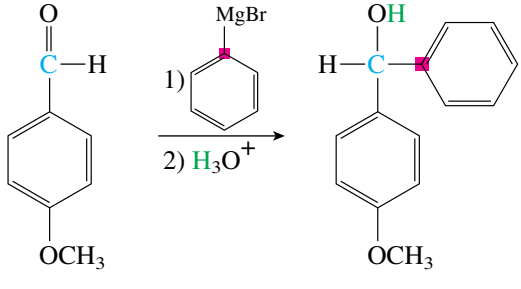
tonate the alkoxide ion and produce the alcohol. Reactions employing formaldehyde as the carbonyl component produce primary alcohols, those using other aldehydes produce secondary alcohols, and those using ketones produce tertiary alcohols. Solutions of hydrochloric or sulfuric acid are commonly used in the protonation step. However, to avoid alkene formation, the weaker acid, ammonium chloride ($pK_a = 9$) in aqueous solution, is used when the product is a tertiary or other alcohol that readily undergoes acid-catalyzed E1 elimination (Section 10.13). Of course, if the alkene is the desired product, the elimination can be accomplished during the workup without isolating the alcohol. A number of examples are provided in the following equations.

The reaction of an organometallic reagent with formaldehyde produces a primary alcohol:



(69%)

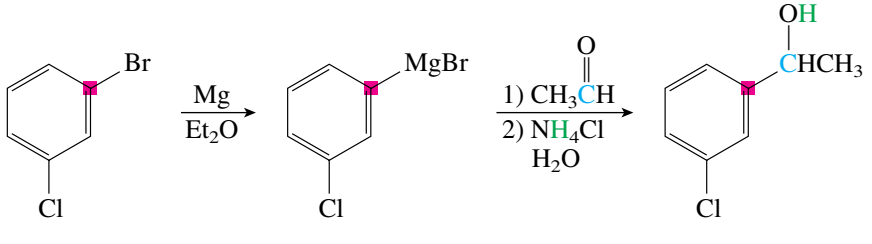
Reactions with other aldehydes produce secondary alcohols. Although the presence of most other functional groups (OH, NH, carbonyl groups, and so on) must be avoided because they react with Grignard or organolithium reagents, ether and alkene groups can be present:



(90%)

p-Methoxybenzaldehyde

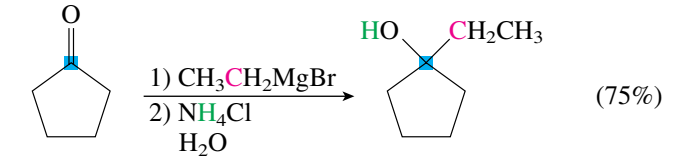
In the next example the bromine, being more reactive than chlorine, selectively reacts to form the Grignard reagent. The product alcohol is especially prone to E1 elimination (the carbocation would be stabilized by resonance), so the weak acid, ammonium chloride, is used in the workup step.



(88%)

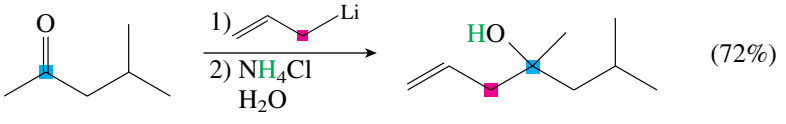
m-Bromochlorobenzene

Reactions with ketones give tertiary alcohols. These are very prone to E1 elimination, so weak acid is used in the workup.



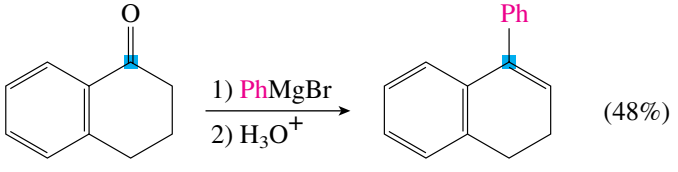
Cyclopentanone

Organolithium reagents work well in any of these reactions:



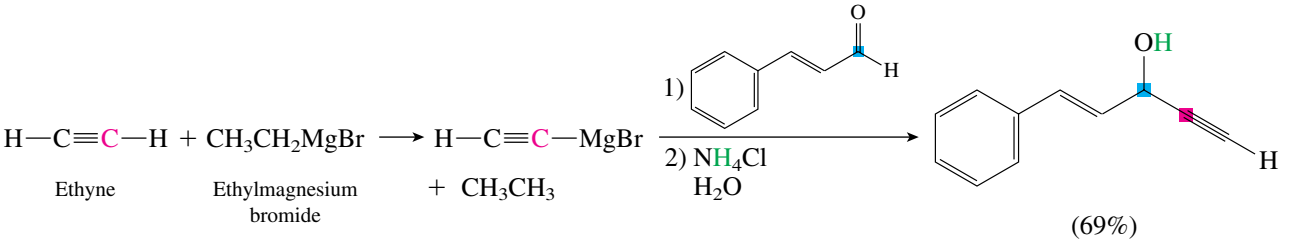
4-Methyl-2-pentanone

If the product resulting from elimination of water from the alcohol is desired, then the workup can be conducted by using a stronger acid so that the reaction proceeds directly to the alkene without the isolation of the alcohol.



α-Tetralone

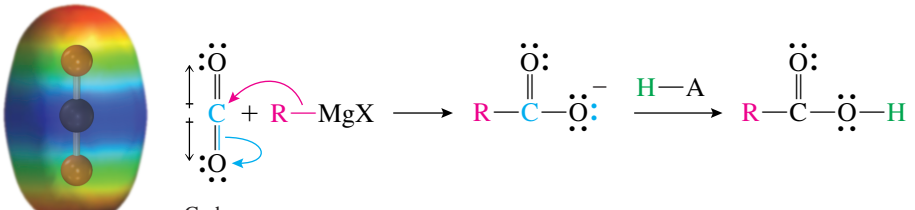
Acetylenic Grignard reagents are commonly prepared by reaction of the appropriate 1-alkyne with an alkyl Grignard reagent, such as ethylmagnesium bromide.



Ethyne

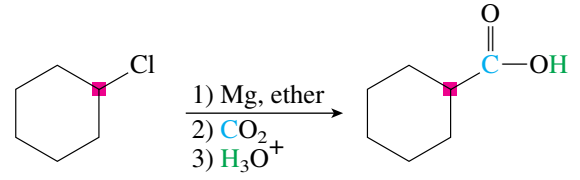
Ethylmagnesium bromide

The carbon of carbon dioxide is electrophilic, similar to a carbonyl carbon. Grignard reagents react with carbon dioxide to form salts of carboxylic acids:

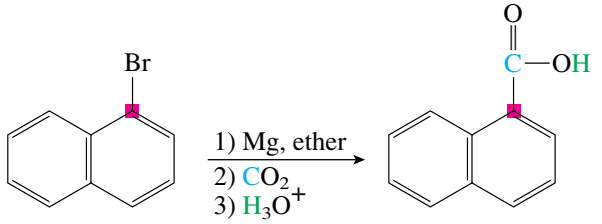


Carbon dioxide

Acidification of the reaction mixture produces a carboxylic acid. Examples are provided in the following equations:



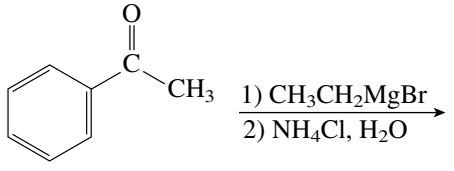
Chlorocyclohexane (85%)

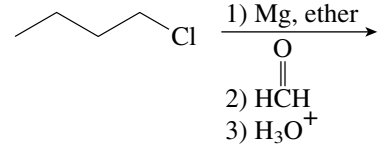


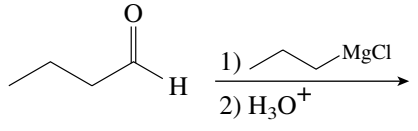
1-Bromonaphthalene (70%)

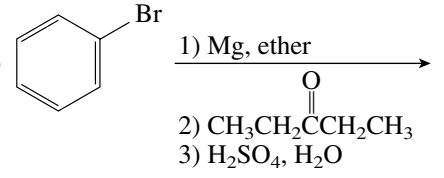
PROBLEM 18.9

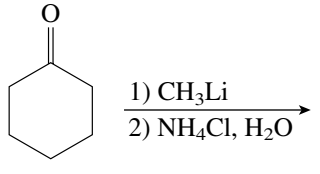
Show the products of these reactions:

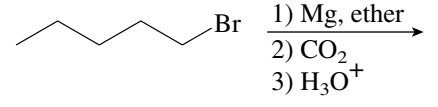
a) 

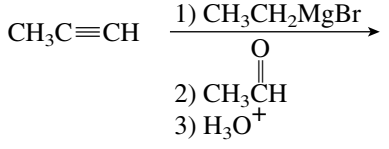
b) 

c) 

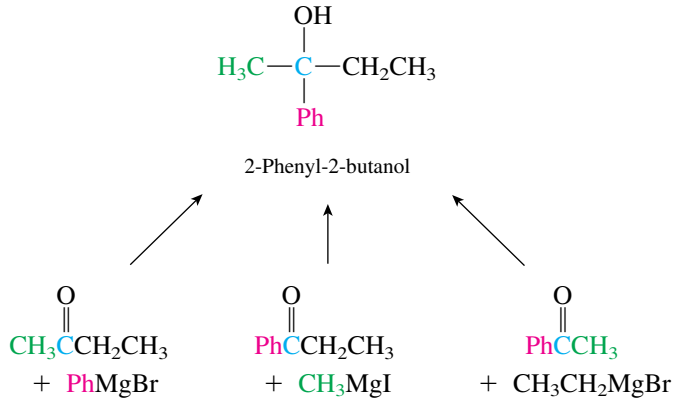
d) 

e) 

f) 

g) 

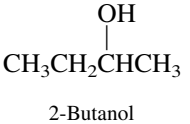
The Grignard reaction is an important and versatile way to prepare alcohols. Whenever an alcohol is encountered as a synthetic target, this reaction should be considered because it forms a carbon–carbon bond, building the alcohol from smaller compounds, and it often allows more than one route to the desired product. For example, suppose the target is 2-phenyl-2-butanol. This alcohol can be prepared by three different Grignard reactions:



Because the product is a tertiary alcohol, each of these reactions must be acidified with a weak acid (NH_4Cl/H_2O) to avoid elimination. Which of these pathways is the best depends on a number of factors, such as the availability of the ketone and the halide needed to prepare the Grignard reagent and the yield of the reaction.

PRACTICE PROBLEM 18.2

Show two ways to prepare 2-butanol using Grignard reagents.



2-Butanol

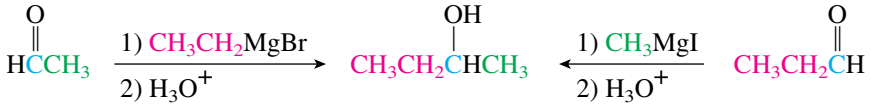
Strategy

When you encounter an alcohol as a synthetic target, consider using a Grignard reaction to synthesize it. The carbon bonded to the hydroxy group was the electrophilic carbon of the carbonyl group of the reactant. One of the alkyl groups bonded to this carbon was the nucleophilic carbon of the Grignard reagent or alkyllithium reagent. There are often several ways to accomplish the synthesis, depending on which alkyl group is added as the nucleophile. Remember to work up the reaction with the weak acid NH_4Cl if the product alcohol is prone to E1 elimination.

Solution

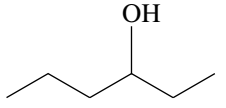
The carbon (blue) bonded to the hydroxy group in the alcohol comes from the carbonyl carbon electrophile of the starting material. This carbon is also bonded to a methyl group and an ethyl group. We can add the ethyl group, using the reaction of ethylmag-

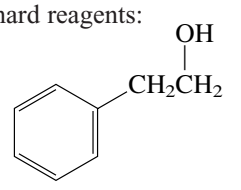
nesium bromide and ethanal, or we can add the methyl group, using methylmagnesium iodide and propanal.

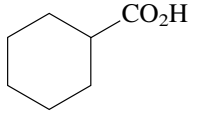


PROBLEM 18.10

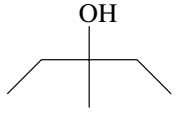
Suggest syntheses of these compounds using Grignard reagents:

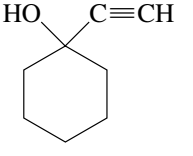
a)  (2 ways)

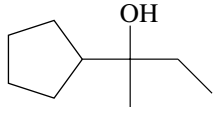
b) 

c) 

d) Ph_3COH

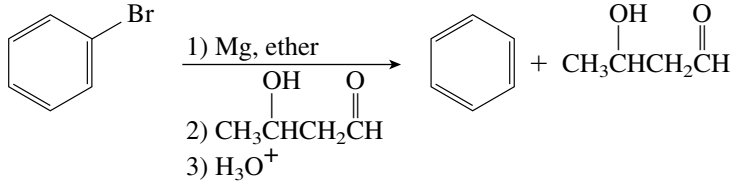
e)  (2 ways)

f) 

g)  (3 ways)

PROBLEM 18.11

When the Grignard reaction shown in this equation is attempted, the products are benzene and the starting hydroxyaldehyde. Explain this result.

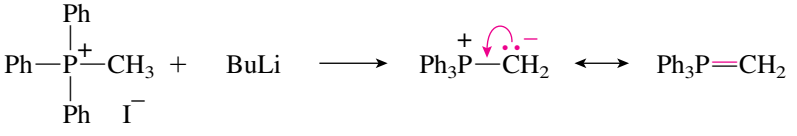


18.7 Addition of Phosphorus Ylides; The Wittig Reaction

In Chapters 9 and 10 the use of elimination reactions to prepare alkenes was described. The major problem with that method is that a mixture of alkenes is often produced, resulting in lower yields and separation problems. The Wittig reaction provides an alter-

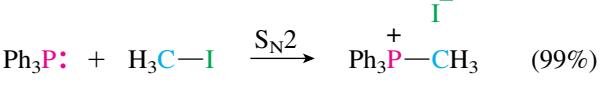
native method for the synthesis of alkenes. It is especially useful because it results in carbon–carbon bond formation and the position of the double bond is completely controlled. Georg Wittig shared the 1979 Nobel Prize in chemistry for developing this reaction. (He shared the award with H. C. Brown, who developed the hydroboration reaction; see Section 11.7.)

The nucleophile used in this reaction is called an **ylide.** It is a carbanion that is bonded to a positive phosphorus group that helps to stabilize it:



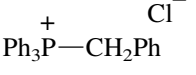
Phosphonium salt | Butyllithium | Ylide | Minor contributor

The ylide is prepared by deprotonating a triphenylalkylphosphonium salt with a strong base, commonly an organometallic base such as butyllithium or phenyllithium. The hydrogens on the carbon that is bonded to the phosphorus of the salt are somewhat acidic because the carbanion of the conjugate base (the ylide) is stabilized by the inductive effect of the positive phosphorus atom. In addition, a resonance structure with five bonds to phosphorus makes a minor contribution to the structure and provides some additional stabilization. The triphenylalkylphosphonium salt can be prepared by an S_N2 reaction of triphenylphosphine with the appropriate alkyl halide (see Section 10.9).

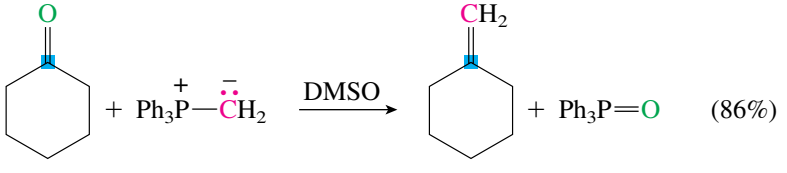


PROBLEM 18.12

Show a preparation of this phosphonium salt from an alkyl halide:

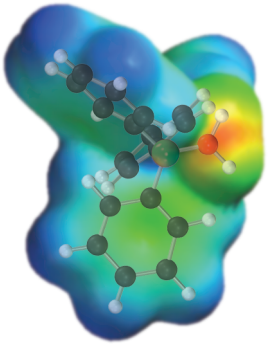


The reaction of the ylide with an aldehyde or ketone results in the formation of an alkene with the double bond connecting the carbonyl carbon of the reactant to the anionic carbon of the ylide, as shown in the following example:



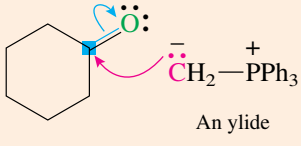
The by-product is triphenylphosphine oxide. The ylide is a strong nucleophile, so the equilibrium greatly favors the products and the reaction is irreversible.

The mechanism for this reaction is shown in Figure 18.2. The first part of the mechanism is similar to the others that have been presented so far: the nucleophile (the negative carbon of the ylide) attacks the carbonyl carbon. However, unlike the previous cases, this



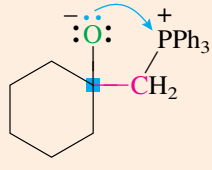
Electrostatic potential map of $Ph_3P—CH_2$

❶ This reaction begins in the same manner as other reactions that proceed by the mechanism for basic conditions. The nucleophile, the negative carbon of the ylide, attacks the carbonyl carbon.



Cyclohexanone

❶

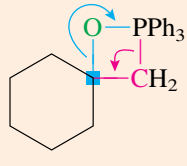


A betaine

However, the reaction does not stop at this intermediate, known as a **betaine.**

❷ Rather, the oxygen forms a bond to the phosphorus in a Lewis acid–base reaction, forming a four-membered ring. (The mechanism for this reaction is still being investigated, and it may be that these first two steps occur in a concerted manner.)

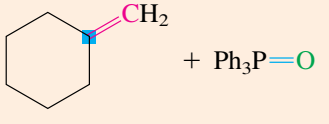
❷



An oxaphosphetane

The resulting four-membered ring, containing ing an oxygen and a phosphorus, is called an **oxaphosphetane.**

❸



Methylenecyclohexane

The reaction proceeds directly to the alkene. The intermediate betaine and oxaphosphetane are not isolated.

❸ Under the reaction conditions it spontaneously fragments to give the product alkene and triphenylphosphine oxide.

Active Figure 18.2 ORGANIC Chemistry Now™

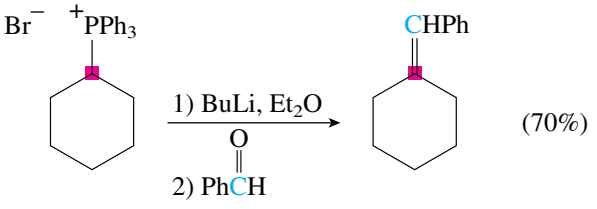
MECHANISM OF THE WITTIG REACTION. Test yourself on the concepts in this figure at **OrganicChemistryNow.**

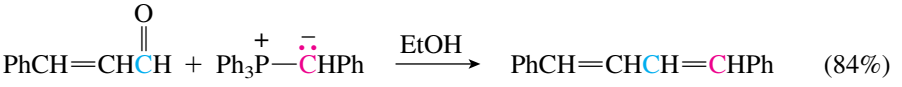
reaction proceeds beyond this step. The phosphorus, acting as a Lewis acid, bonds to the basic oxygen and ultimately leads to its removal from the product. The overall result is the formation of a double bond between the carbonyl carbon and the nucleophilic carbon of the ylide, while both of the carbon–oxygen bonds of the carbonyl group are broken.

Previous reactions in this chapter have involved only addition of the nucleophile and a hydrogen to the carbonyl group. In this reaction, addition is followed by elimination of the oxygen to form a double bond between the carbonyl carbon and the nucleophile. Such an **addition–elimination** reaction occurs when the nucleophile has or can generate (by the loss of a proton or a phosphorus group) a second pair of electrons that can be used to form a second bond to the electrophilic carbon. In the case of the Wittig reaction, the phosphorus and the oxygen are eliminated to form the alkene. The forma-

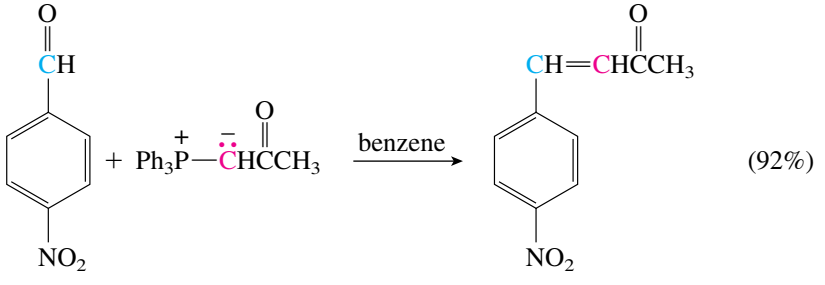
tion of the strong phosphorus–oxygen bond helps make this step of the reaction favorable. (Note that the previous reactions in this chapter, employing hydride, cyanide, and organometallic nucleophiles, did not have any way to form a second bond between the nucleophile and the electrophilic carbon, so only addition occurred.)

Because the location of the double bond in the product is well defined, the Wittig reaction provides probably the most useful general method for the preparation of alkenes. Some examples are provided in the following equations:



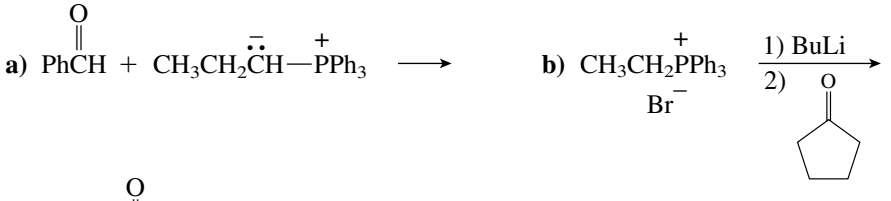


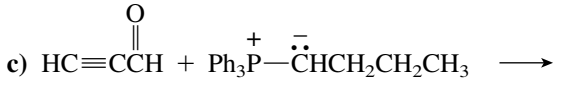
Because the electron pair of the carbanion of the ylide in the following example is stabilized by resonance delocalization with the carbonyl group, it is a weaker nucleophile. Such ylides react readily with aldehydes but do not react well with ketones.

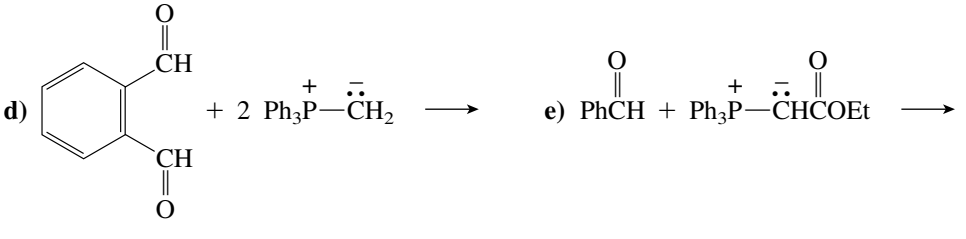


PROBLEM 18.13

Show the products of these reactions:

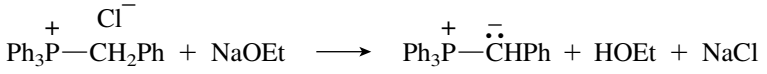






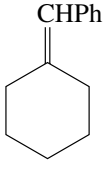
PROBLEM 18.14

Explain why the phosphonium salt shown in the following equation can be deprotonated by using sodium ethoxide, a much weaker base than the butyllithium that is usually needed to deprotonate other phosphonium salts.



PRACTICE PROBLEM 18.3

Show two ways to prepare this compound using a Wittig reaction.

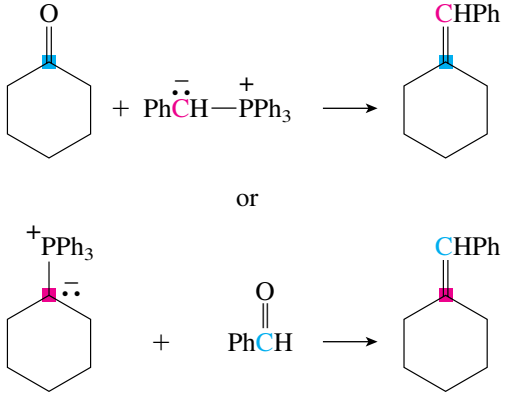


Strategy

When the synthetic target is an alkene, consider using a Wittig reaction, because the location of the double bond is completely controlled (unlike an E2 elimination, in which a mixture of products is often formed). One carbon of the alkene was the electrophilic carbonyl carbon of an aldehyde or ketone and the other carbon of the alkene was the nucleophilic carbon of the ylide. Because either carbon of the alkene could come from the nucleophile and the other from the electrophile, there are often two ways to accomplish the synthesis.

Solution

Break the double bond, making one carbon the nucleophile of an ylide and the other carbon part of a carbonyl group. The two possible ways to do this in this case are as follows:



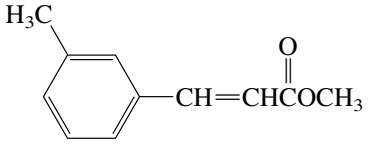
PROBLEM 18.15

Suggest syntheses of these compounds using the Wittig reaction:

a) $PhCH_2CH{=}CHCH_2CH_3$ (2 ways)

b) $CH_3CH_2CH{=}CHC(=O)CH_2CH_3$

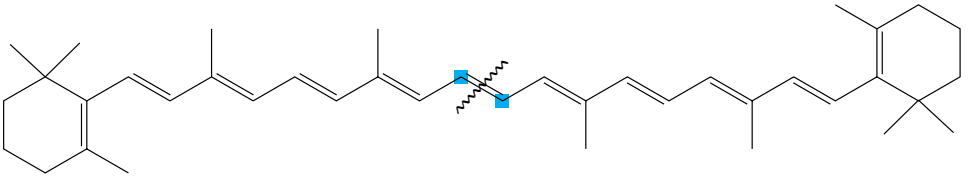
c)



Focus On

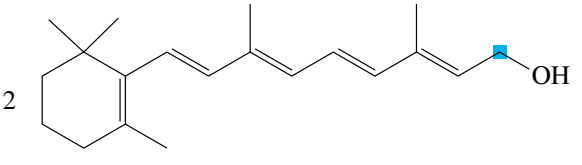
Synthesis of Vitamin A

Vitamin A, also known as retinol, is essential for vision in mammals (see the Focus On box on page 773) and is involved in a number of other important biological functions, such as bone growth and embryonic development. A deficiency in vitamin A leads to night blindness, in which the eye cannot see in dim light. Our bodies are capable of converting compounds such as β-carotene, an orange pigment that is present in many vegetables, to vitamin A. As its structure suggests, vitamin A is relatively nonpolar and therefore is not very soluble in water. It accumulates in fat deposits and is not readily excreted. For this reason, too much vitamin A is toxic.



β-Carotene

Oxidative cleavage



Vitamin A (retinol)

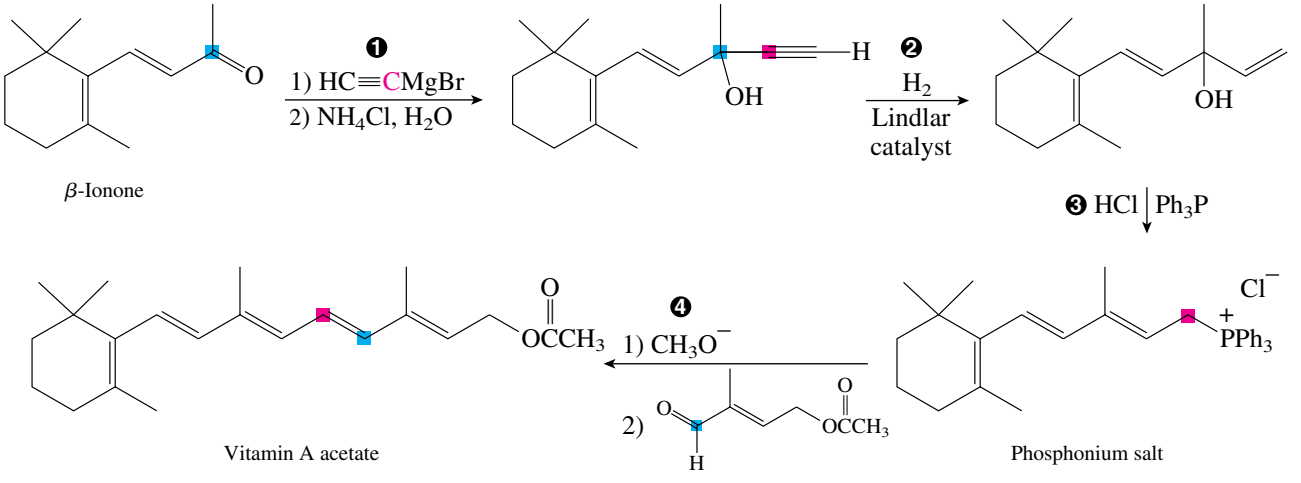
The Wittig reaction has proved to be especially useful in the synthesis of natural products, such as vitamin A, which contain a number of carbon–carbon double bonds. An industrial synthesis of vitamin A is outlined in the following equations:

Continued

❶ β-Ionone can be isolated from natural sources or synthesized in the laboratory. It is reacted with ethynyl magnesium bromide, or some other source of the anion derived from ethyne, to produce an alcohol (see Section 18.6).

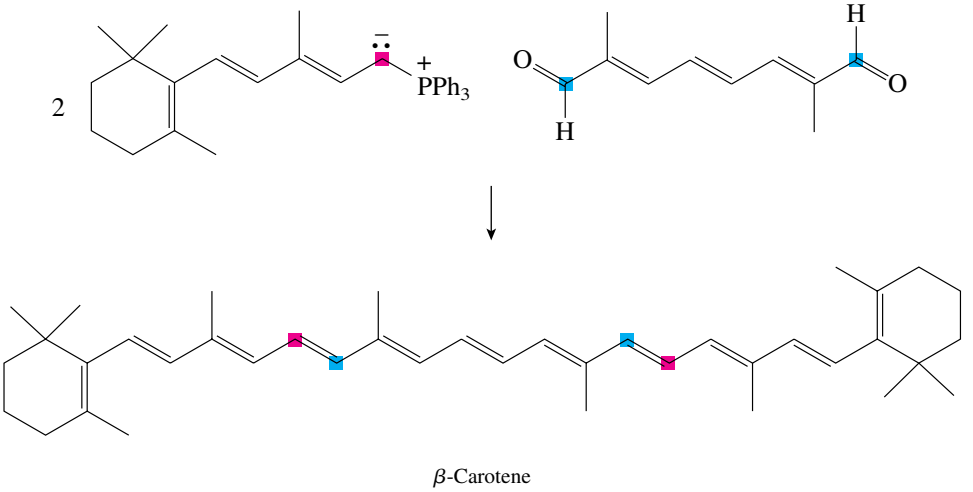
❷ The triple bond is reduced to a double bond using hydrogen and the Lindlar catalyst (see Section 11.12).

❸ Then, reaction of the alcohol with triphenylphosphine under acidic conditions produces the phosphonium salt by an S_N1 reaction. A resonance-stabilized carbocation is formed and reacts at the terminal position of the chain.

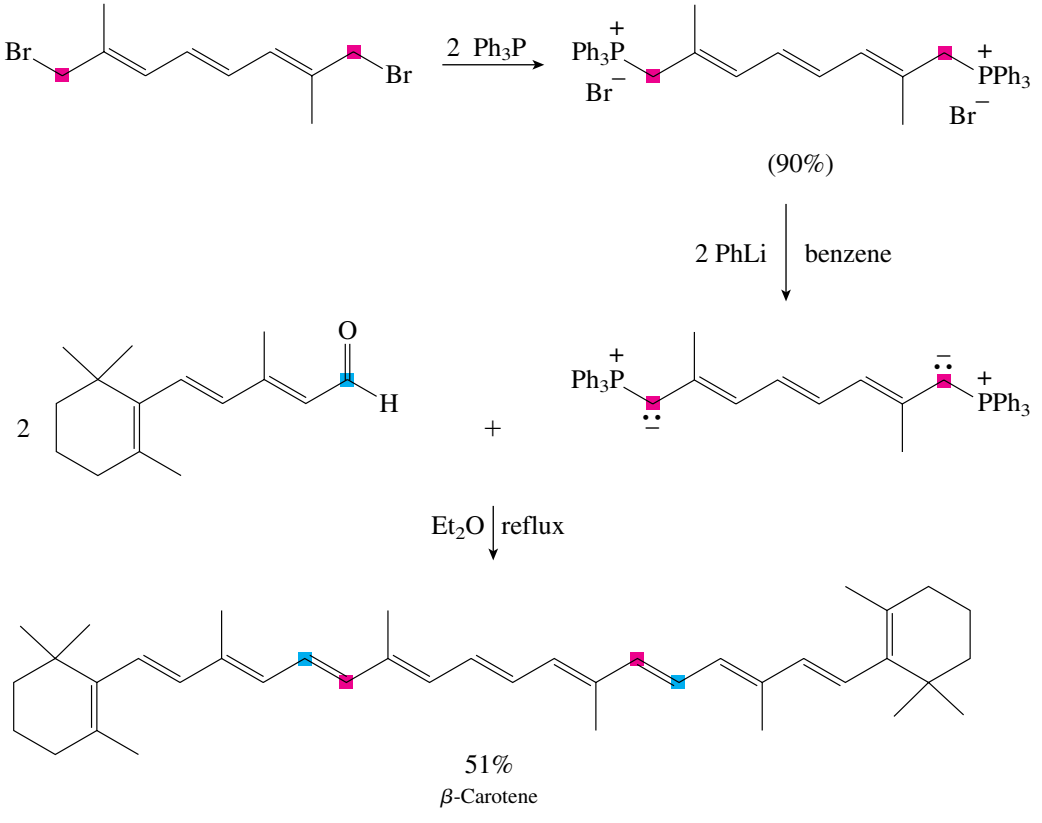


❹ The phosphonium salt is more acidic than usual because its conjugate base, the ylide, is stabilized by resonance involving the double bonds. Therefore, methoxide ion, a weaker base than usual, can be used to form the ylide. Reaction of the ylide with the aldehyde that has its hydroxy group protected as an ester produces vitamin A acetate. The acetate group can readily be removed to complete the synthesis of vitamin A (see Section 10.2).

β-Carotene is also prepared industrially by a Wittig reaction. A dialdehyde is reacted with two equivalents of the same ylide used in the vitamin A synthesis, as shown in the following equation:

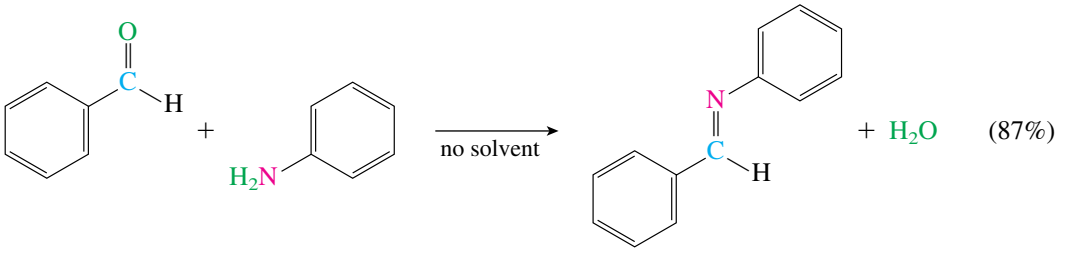


It is interesting to note that an alkene can be prepared by two different Wittig pathways, depending on which of the doubly bonded carbons was originally the carbon of the carbonyl group and which was the carbon of the ylide. Thus, the synthesis of β-carotene has also been accomplished by using the reaction of a diylide with two equivalents of an aldehyde, as illustrated in the following equations:



18.8 Addition of Nitrogen Nucleophiles

Amines add to the carbonyl groups of aldehydes or ketones to produce compounds containing CN double bonds and water. These nitrogen analogs of aldehydes and ketones are called **imines.**

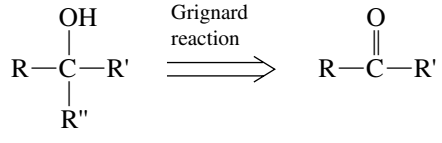


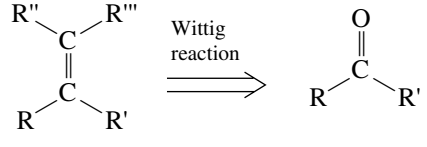
Benzaldehyde Aniline An imine

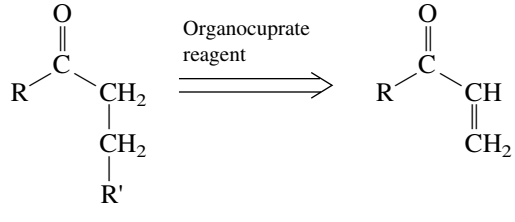
18.11 SYNTHESIS

By now, you should be fairly comfortable using retrosynthetic analysis to design the synthesis of a target molecule. Remember that carbon–carbon bond forming reactions are especially important in synthesis. Several extremely useful reactions that result in the formation of carbon–carbon bonds have been introduced in this chapter. These are the Grignard reaction to prepare alcohols, the Wittig reaction to prepare alkenes, and the conjugate addition of organocuprate reagents to α,β-unsaturated carbonyl compounds.

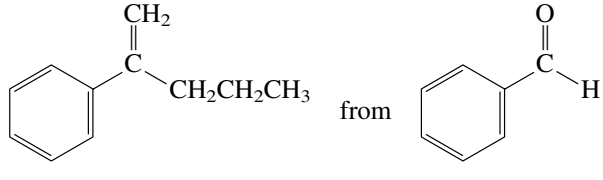
When you are designing a synthesis, the presence of certain structural features in the target suggests that the use of certain reactions be considered. Whenever an alcohol is the synthetic target, you should consider using a Grignard reaction to make it. The presence of an alkene suggests the use of the Wittig reaction, and the presence of a carbonyl compound with a substituent on the β-carbon suggests the use of a conjugate addition reaction. You do not have to use these reactions, but you should consider using them. Using retrosynthetic notation, these possibilities are summarized as follows:





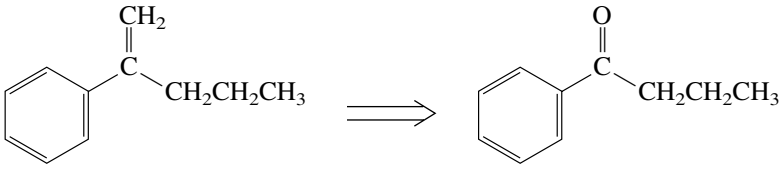


Let's try some syntheses. Suppose we need to prepare 2-phenyl-l-pentene, starting from benzaldehyde:

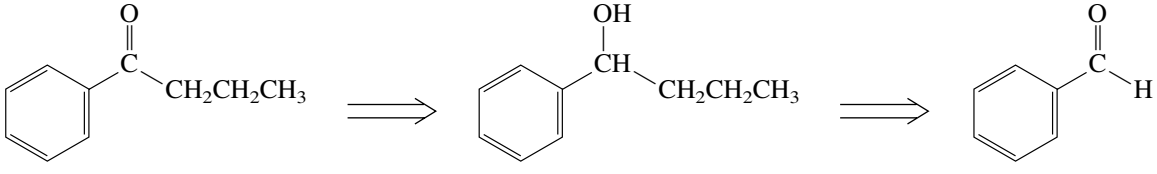


2-Phenyl-1-pentene Benzaldehyde

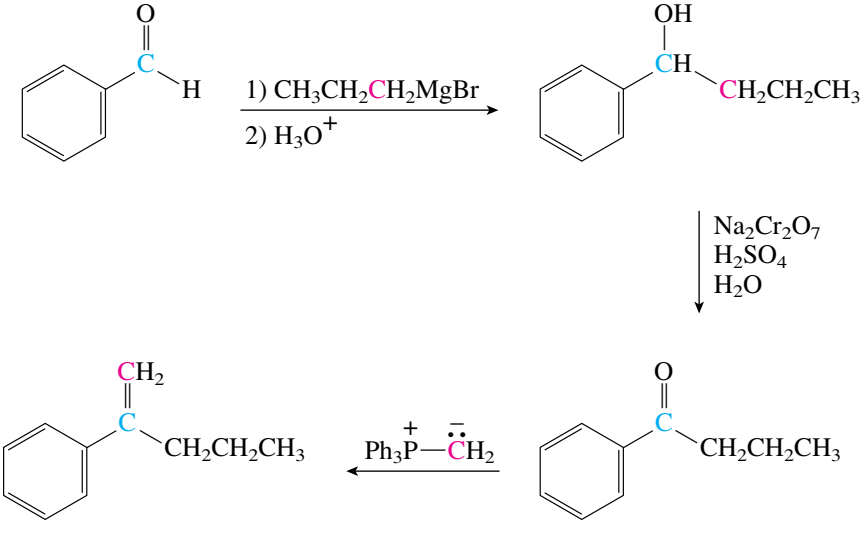
Applying retrosynthetic analysis, the presence of the alkene group in the target suggests using a Wittig reaction in its preparation.



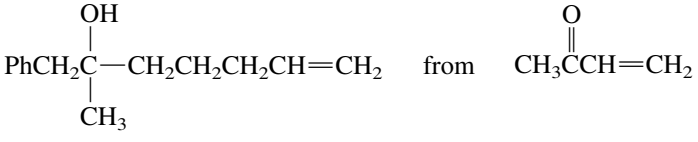
The new target is a ketone. We need to somehow add a propyl group to the carbonyl carbon of benzaldehyde to make this ketone. At this point we do not know of a reaction that will accomplish this transformation directly, but we recognize that a ketone can be prepared by oxidation of an alcohol. We can prepare the alcohol using the Grignard reaction. Our retrosynthetic analysis is as follows:



We are now ready to write the synthesis in the forward direction:



Let's try another example. This time our task is to prepare 2-methyl-1-phenylhept-6-en-2-ol from but-3-en-2-one.

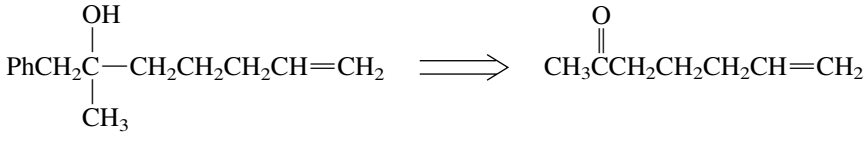


2-Methyl-1-phenylhept-6-en-2-ol

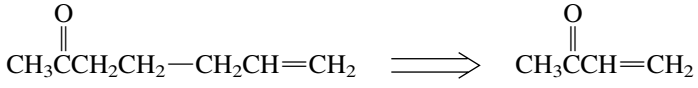
from

But-3-en-2-one

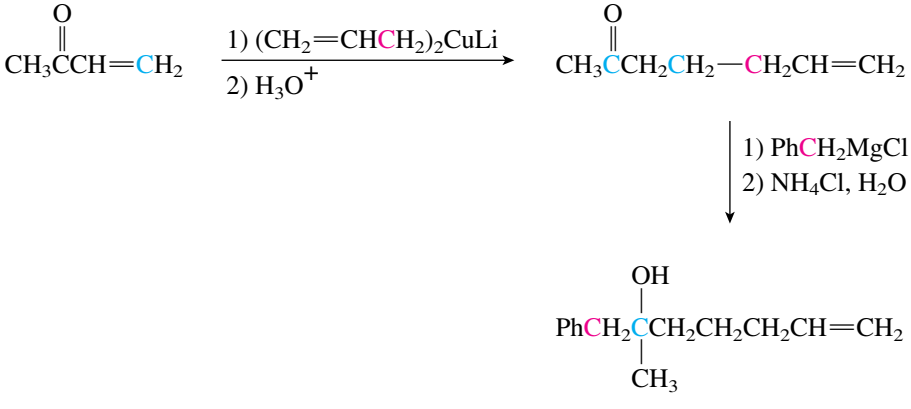
The target is an alcohol, so we should consider using a Grignard reaction. Any of the three groups attached to the carbon bonded to the hydroxy group could potentially be attached. Comparison of the target to but-3-en-2-one suggests that the benzyl group be added in the Grignard step. So the first step in our retrosynthetic analysis is as follows:



Our new target is a ketone that is related to but-3-en-2-one by the presence of an allyl group on the β-carbon. This suggests the use of a conjugate addition reaction:



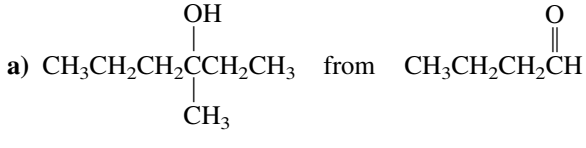
Written in the forward direction, the synthesis is as follows:

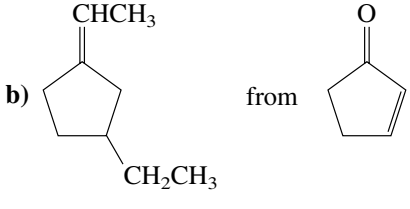


Remember that a synthesis can often be accomplished in more than one way. If your synthesis is not the same as the one shown in the answer, check to see that your steps are all correct. If all of the steps in your sequence appear reasonable, then your synthesis may be correct—and could even be better than the one in the answer.

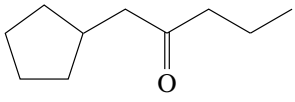
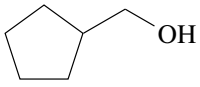
PROBLEM 18.26

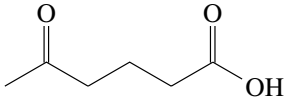
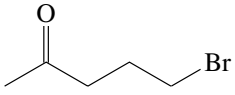
Show syntheses of these compounds from the indicated starting materials:





c) $CH_3\overset{\overset{CH_2}{\|}}{C}CH_2CH_2CH_2CH_3$ from $HC\overset{\overset{O}{\|}}{C}H{=}CH_2$

d)  from 

e)  from 

Review of Mastery Goals

After completing this chapter, you should be able to:

- Show the products resulting from the addition to aldehydes and ketones of all of the reagents discussed in this chapter. (Problems 18.27, 18.28, 18.32, 18.33, and 18.36)
- Show the products resulting from the addition of certain of these reagents to α,β-unsaturated compounds, noting whether 1,2- or 1,4-addition predominates. (Problems 18.29, 18.32, and 18.36)
- Show the mechanisms for any of these additions. (Problems 18.39, 18.41, 18.45, 18.47, 18.48, and 18.52)
- Predict the effect of the structure of the aldehyde or ketone on the position of the equilibrium for these reactions. (Problems 18.30, 18.31, 18.34, 18.35, 18.58, and 18.59)
- Use these reactions, in combination with the reactions from previous chapters, to synthesize compounds. (Problems 18.38, 18.42, and 18.43)
- Use acetals as protecting groups in syntheses. (Problem 18.43)

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Click *Mastery Goal Quiz* to test how well you have met these goals.

Visual Summary of Key Reactions

The reactions in this chapter begin with the addition of a nucleophile to the carbon of a carbonyl group and an electrophile, usually a proton, to the oxygen. Under basic conditions the nucleophile adds first, whereas the proton adds first under acidic conditions. Depending on the nature of the nucleophile, the reaction may stop at this stage or proceed further. Figure 18.7 summarizes the mechanisms followed by the various nucleophiles. Table 18.2 lists the nucleophiles and the products that result from their reactions with aldehydes and ketones.