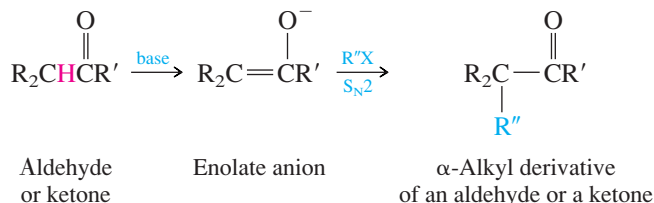


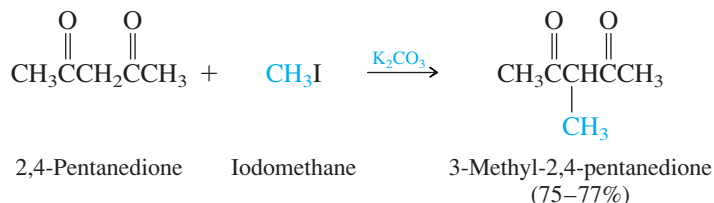
18.15 ALKYLATION OF ENOLATE ANIONS

Because enolate anions are sources of nucleophilic carbon, one potential use in organic synthesis is their reaction with alkyl halides to give α -alkyl derivatives of aldehydes and ketones:



Alkylation occurs by an $\text{S}_{\text{N}}2$ mechanism in which the enolate ion acts as a nucleophile toward the alkyl halide.

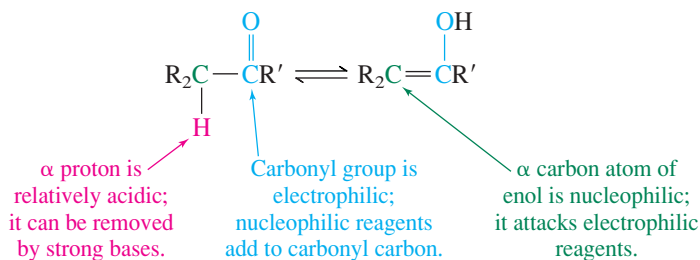
In practice, this reaction is difficult to carry out with simple aldehydes and ketones because aldol condensation competes with alkylation. Furthermore, it is not always possible to limit the reaction to the introduction of a single alkyl group. The most successful alkylation procedures use β -diketones as starting materials. Because they are relatively acidic, β -diketones can be converted quantitatively to their enolate ions by weak bases and do not self-condense. Ideally, the alkyl halide should be a methyl or primary alkyl halide.



18.16 SUMMARY

Section 18.1 Greek letters are commonly used to identify various carbons in aldehydes and ketones. Using the carbonyl group as a reference, the adjacent carbon is designated α , the next one β , and so on as one moves down the chain. Attached groups take the same Greek letter as the carbon to which they are connected.

Sections 18.2–18.15 Because aldehydes and ketones exist in equilibrium with their corresponding enol isomers, they can express a variety of different kinds of chemical reactivity.

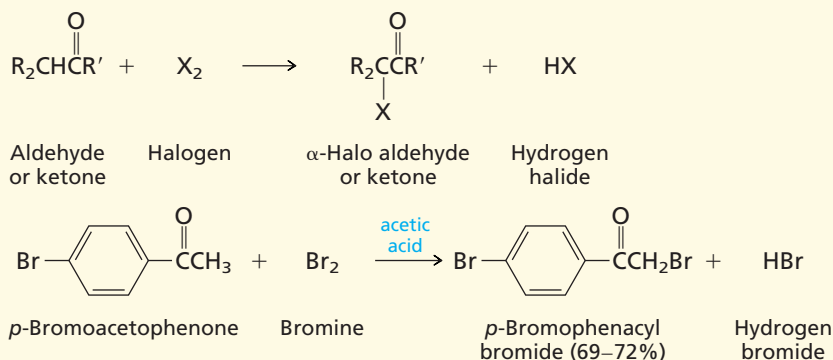


Reactions that proceed via enol or enolate intermediates are summarized in Table 18.1.

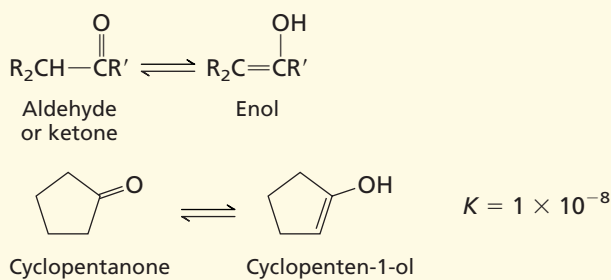
TABLE 18.1 Reactions of Aldehydes and Ketones That Involve Enol or Enolate Ion Intermediates

Reaction (section) and comments
General equation and typical example

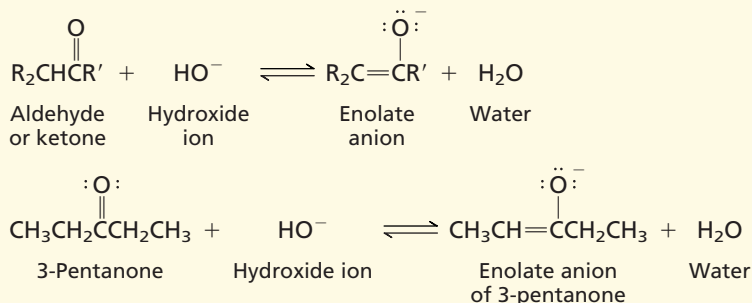
α Halogenation (Sections 18.2 and 18.3) Halogens react with aldehydes and ketones by substitution; an α hydrogen is replaced by a halogen. Reaction occurs by electrophilic attack of the halogen on the carbon-carbon double bond of the enol form of the aldehyde or ketone. An acid catalyst increases the rate of enolization, which is the rate-determining step.



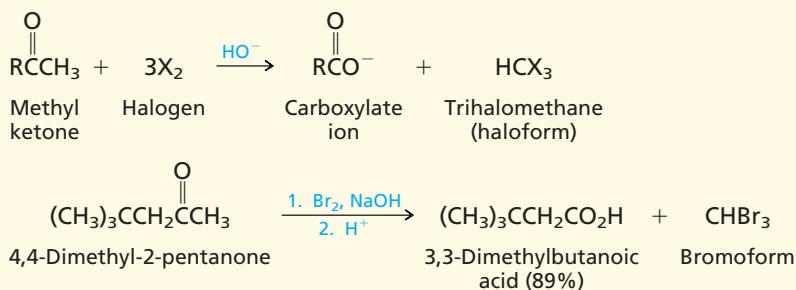
Enolization (Sections 18.4 through 18.6) Aldehydes and ketones having at least one α hydrogen exist in equilibrium with their enol forms. The rate at which equilibrium is achieved is increased by acidic or basic catalysts. The enol content of simple aldehydes and ketones is quite small; β -diketones, however, are extensively enolized.



Enolate ion formation (Section 18.6) An α hydrogen of an aldehyde or a ketone is more acidic than most other protons bound to carbon. Aldehydes and ketones are weak acids, with $\text{p}K_a$'s in the 16 to 20 range. Their enhanced acidity is due to the electron-withdrawing effect of the carbonyl group and the resonance stabilization of the enolate anion.



Haloform reaction (Section 18.7) Methyl ketones are cleaved on reaction with excess halogen in the presence of base. The products are a trihalomethane (haloform) and a carboxylate salt.



(Continued)

TABLE 18.1

Reactions of Aldehydes and Ketones That Involve Enol or Enolate Ion Intermediates (Continued)

Reaction (section) and comments	General equation and typical example
<p>Aldol condensation (Section 18.9) A reaction of great synthetic value for carbon–carbon bond formation. Nucleophilic addition of an enolate ion to a carbonyl group, followed by dehydration of the β-hydroxy aldehyde, yields an α,β-unsaturated aldehyde.</p>	$2\text{RCH}_2\overset{\text{O}}{\parallel}\text{CR}' \xrightarrow{\text{HO}^-} \text{RCH}_2\overset{\text{O}}{\parallel}\text{C}(\text{R}')\text{C}(\text{R})\text{CR}' + \text{H}_2\text{O}$ <p>Aldehyde α,β-Unsaturated aldehyde Water</p>
	$\text{CH}_3(\text{CH}_2)_6\overset{\text{O}}{\parallel}\text{CH} \xrightarrow[\text{CH}_3\text{CH}_2\text{OH}]{\text{NaOCH}_2\text{CH}_3} \text{CH}_3(\text{CH}_2)_6\text{CH}=\overset{\text{O}}{\parallel}\text{C}(\text{CH}_2)_5\text{CH}_3$ <p>Octanal 2-Hexyl-2-decenal (79%)</p>
<p>Claisen–Schmidt reaction (Section 18.10) A mixed aldol condensation in which an aromatic aldehyde reacts with an enolizable aldehyde or ketone.</p>	$\text{ArCH}=\overset{\text{O}}{\parallel} + \text{RCH}_2\overset{\text{O}}{\parallel}\text{CR}' \xrightarrow{\text{HO}^-} \text{ArCH}=\overset{\text{O}}{\parallel}\text{C}(\text{R}')\text{R} + \text{H}_2\text{O}$ <p>Aromatic aldehyde Aldehyde or ketone α,β-Unsaturated carbonyl compound Water</p>
	$\text{C}_6\text{H}_5\overset{\text{O}}{\parallel}\text{CH} + (\text{CH}_3)_2\text{C}=\overset{\text{O}}{\parallel}\text{CCH}_3 \xrightarrow[\text{water}]{\text{NaOH, ethanol}} \text{C}_6\text{H}_5\text{CH}=\overset{\text{O}}{\parallel}\text{C}(\text{CH}_3)_2$ <p>Benzaldehyde 3,3-Dimethyl-2-butanone 4,4-Dimethyl-1-phenyl-1-penten-3-one (88–93%)</p>
<p>Conjugate addition to α,β-unsaturated carbonyl compounds (Sections 18.11 through 18.14) The β-carbon atom of an α,β-unsaturated carbonyl compound is electrophilic; nucleophiles, especially weakly basic ones, yield the products of conjugate addition to α,β-unsaturated aldehydes and ketones.</p>	$\text{R}_2\text{C}=\text{CH}\overset{\text{O}}{\parallel}\text{CR}' + \text{HY} \longrightarrow \text{R}_2\overset{\text{O}}{\parallel}\text{C}(\text{Y})\text{CH}_2\text{CR}'$ <p>α,β-Unsaturated aldehyde or ketone Nucleophile Product of conjugate addition</p>
	$(\text{CH}_3)_2\text{C}=\text{CH}\overset{\text{O}}{\parallel}\text{CCH}_3 \xrightarrow[\text{H}_2\text{O}]{\text{NH}_3} (\text{CH}_3)_2\overset{\text{O}}{\parallel}\text{C}(\text{NH}_2)\text{CH}_2\text{CCH}_3$ <p>4-Methyl-3-penten-2-one (mesityl oxide) 4-Amino-4-methyl-2-pentanone (63–70%)</p>
<p>Robinson annulation (Section 18.13) A combination of conjugate addition of an enolate anion to an α,β-unsaturated ketone with subsequent intramolecular aldol condensation.</p>	$\text{2-Methylcyclohexanone} + \text{H}_2\text{C}=\overset{\text{O}}{\parallel}\text{CCH}_3 \xrightarrow[2. \text{ KOH, heat}]{1. \text{ NaOCH}_2\text{CH}_3, \text{ CH}_3\text{CH}_2\text{OH}} \text{6-Methylbicyclo[4.4.0]-1-decen-3-one (46\%)}$ <p>2-Methylcyclohexanone Methyl vinyl ketone 6-Methylbicyclo[4.4.0]-1-decen-3-one (46%)</p>

(Continued)

TABLE 18.1

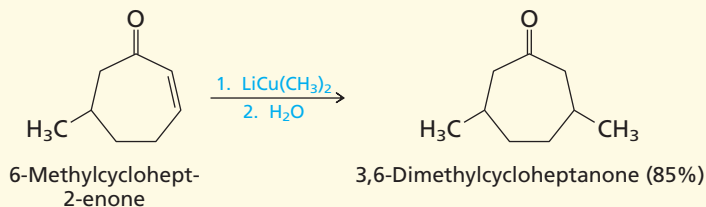
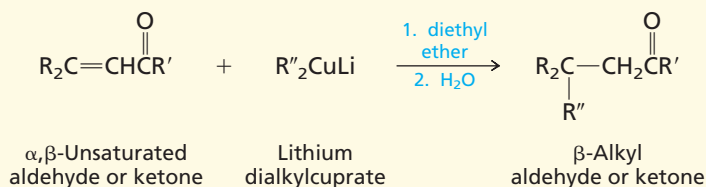
Reactions of Aldehydes and Ketones That Involve Enol or Enolate Ion Intermediates (Continued)

Reaction (section) and comments

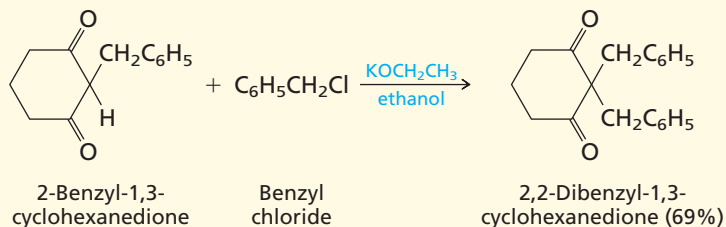
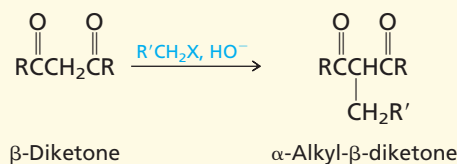
General equation and typical example

Conjugate addition of organocupper compounds (Section 18.14)

The principal synthetic application of lithium dialkylcuprate reagents is their reaction with α,β -unsaturated carbonyl compounds. Alkylation of the β carbon occurs.

 **α Alkylation of aldehydes and ketones (Section 18.15)**

Alkylation of simple aldehydes and ketones via their enolates is difficult. β -Diketones can be converted quantitatively to their enolate anions, which react efficiently with primary alkyl halides.



PROBLEMS



- 18.20** (a) Write structural formulas or build molecular models for all the noncyclic aldehydes and ketones of molecular formula $\text{C}_4\text{H}_6\text{O}$.
- (b) Are any of these compounds stereoisomeric?
- (c) Are any of these compounds chiral?
- (d) Which of these are α,β -unsaturated aldehydes or α,β -unsaturated ketones?
- (e) Which of these can be prepared by a simple (i.e., not mixed) aldol condensation?



18.21 The main flavor component of the hazelnut is (2*E*,5*S*)-5-methyl-2-hepten-4-one. Write a structural formula or build a molecular model showing its stereochemistry.

18.22 The simplest α,β -unsaturated aldehyde *acrolein* is prepared by heating glycerol with an acid catalyst. Suggest a mechanism for this reaction.

