

In Summary α,β -Unsaturated aldehydes and ketones are more stable than their nonconjugated counterparts. Either base or acid catalyzes interconversion of the isomeric systems. Reactions typical of alkenes and carbonyl compounds are also characteristic of α,β -unsaturated aldehydes and ketones.

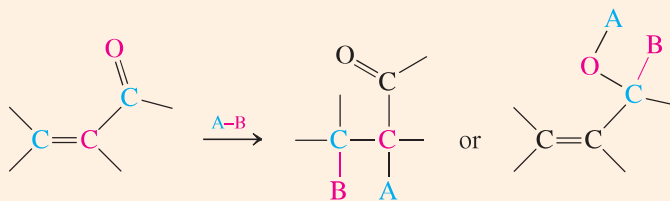
18-9 Conjugate Additions to α,β -Unsaturated Aldehydes and Ketones

We now show how the conjugated carbonyl group of α,β -unsaturated aldehydes and ketones can enter into reactions that involve the entire functional system. These reactions are 1,4-additions of the type encountered with conjugated dienes, such as 1,3-butadiene (Section 14-6). The reactions proceed by acid-catalyzed, radical, or nucleophilic addition mechanisms, depending on the reagents.

The entire conjugated system takes part in 1,4-additions

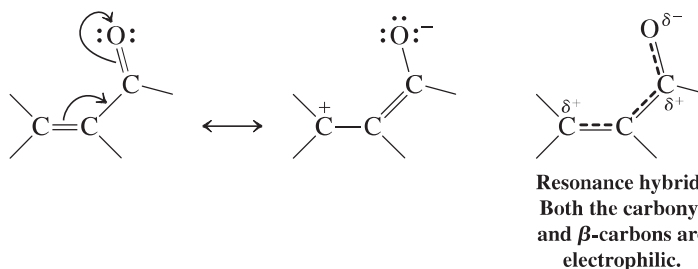
Addition reactions in which only one of the π bonds of a conjugated system takes part are classified as 1,2-additions (compare Section 14-6). Examples are the additions of Br_2 to the carbon-carbon double bond and NH_2OH to the carbon-oxygen double bond of α,β -unsaturated aldehydes and ketones (Section 18-8).

1,2-Addition of a Polar Reagent A-B to a Conjugated Enone



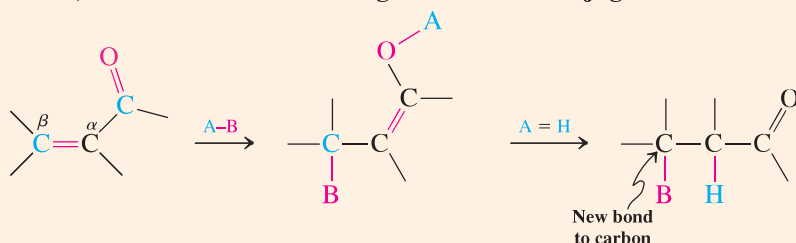
However, several reagents add to the conjugated π system in a 1,4-manner, a result also called **conjugate addition**. In these transformations, the nucleophilic part of a reagent attaches itself to the β -carbon, and the electrophilic part (most commonly, a proton) binds to the carbonyl oxygen. As the resonance forms and the resonance hybrid below illustrate, the β -carbon in an α,β -unsaturated carbonyl compound possesses a partial positive charge and is therefore a second electrophilic site in these molecules, in addition to the carbonyl carbon itself (recall Section 17-2). Addition of nucleophiles to the β -carbon is therefore not a surprising process.

Resonance Forms of α,β -Unsaturated Carbonyl Compounds



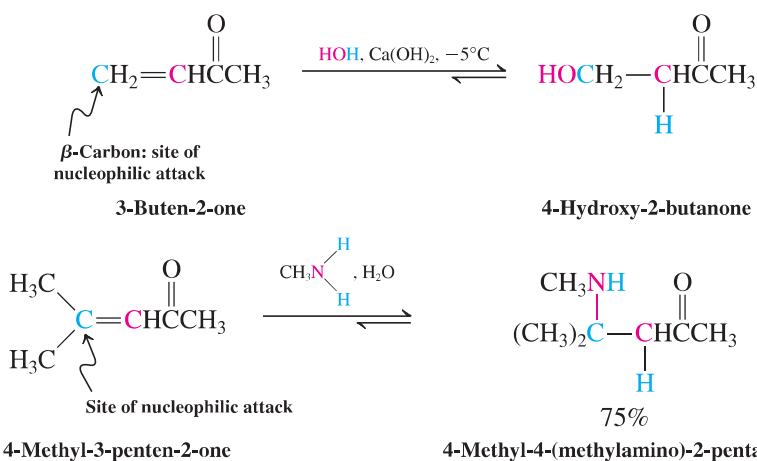
The initial product of conjugate addition to an α,β -unsaturated carbonyl compound is an enol, which subsequently rapidly tautomerizes to its keto form. Thus the end result *appears* to be that of 1,2-addition of Nu-H to the carbon-carbon double bond.

1,4-Addition of a Polar Reagent A-B to a Conjugated Enone



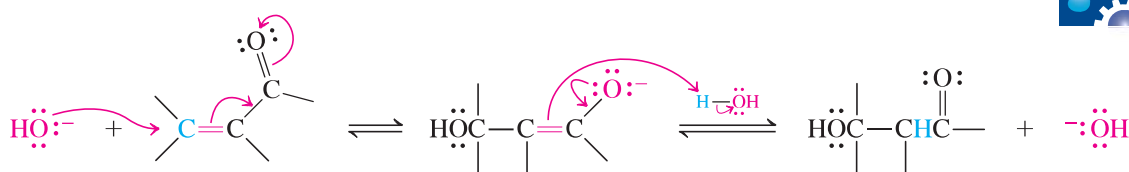
Oxygen and nitrogen nucleophiles undergo conjugate additions

Water, alcohols, amines, and similar nucleophiles undergo 1,4-additions, as the following examples (hydration and amination) show. Although these reactions can be catalyzed by acid or base, the products are usually formed faster and in higher yields with base. These processes are readily reversed at elevated temperatures.



What determines whether 1,2- or 1,4-additions will take place? With the nucleophiles shown, both processes are reversible. Usually the 1,4-products form because they are carbonyl compounds and are more stable than the species arising from 1,2-addition (hydrates, hemiacetals, and hemiaminals, Sections 17-6, 17-7, and 17-9). Exceptions include amine derivatives such as hydroxylamine, semicarbazide, or the hydrazines, for which 1,2-addition eventually leads to an imine product whose precipitation out of solution drives the equilibrium.

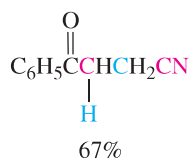
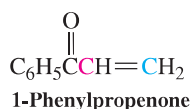
The mechanism of the base-catalyzed addition to conjugated aldehydes and ketones is direct nucleophilic attack at the β -carbon to give the enolate ion, which is subsequently protonated.

Mechanism of Base-Catalyzed Hydration of α,β -Unsaturated Aldehydes and Ketones

Exercise 18-24

Treatment of 3-chloro-2-cyclohexenone with sodium methoxide in methanol gives 3-methoxy-2-cyclohexenone. Write the mechanism of this reaction. (**Hint:** Start with a conjugate addition.)

The ability to form new bonds with nucleophiles at the β carbon makes α,β -unsaturated aldehydes and ketones extremely useful in synthesis. This ability extends to carbon nucleophiles, permitting the construction of new carbon-carbon bonds. The remainder of the chapter illustrates processes of this type.



4-Oxo-4-phenylbutanenitrile

Hydrogen cyanide also undergoes conjugate addition

Treatment of a conjugated aldehyde or ketone with cyanide in the presence of acid may result in attack by cyanide at the β -carbon, in contrast with cyanohydrin formation (Section 17-11). This transformation proceeds through a 1,4-addition pathway. The reaction includes protonation of the oxygen, then nucleophilic β -attack, and finally enol–keto tautomerization.

Exercise 18-25

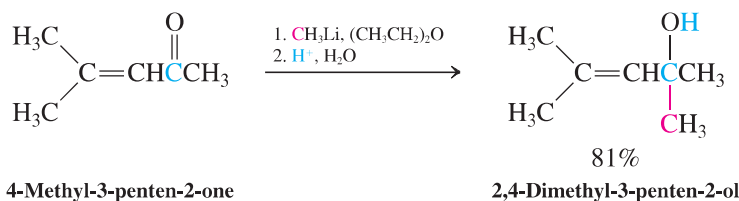
Formulate the mechanism of the acid-catalyzed 1,4-addition of cyanide to 1-phenylpropenone (see margin).

In Summary α,β -Unsaturated aldehydes and ketones are synthetically useful building blocks in organic synthesis because of their ability to undergo 1,4-additions. Hydrogen cyanide addition leads to β -cyano carbonyl compounds; oxygen and nitrogen nucleophiles also can add to the β -carbon.

18-10 1,2- and 1,4-Additions of Organometallic Reagents

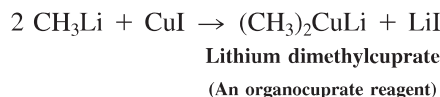
Organometallic reagents may add to the α,β -unsaturated carbonyl function in either 1,2- or 1,4-fashion. Organolithium reagents, for example, react almost exclusively by direct nucleophilic attack at the carbonyl carbon.

Exclusive 1,2-Addition of an Organolithium



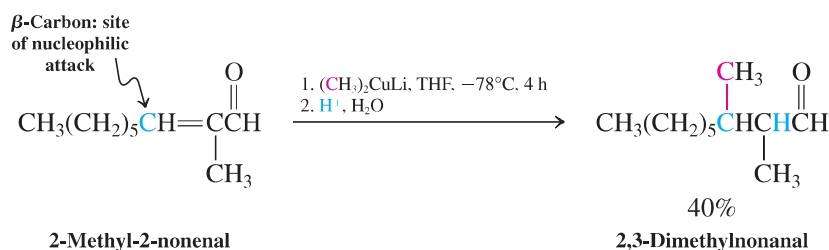
Reactions of Grignard reagents with α,β -unsaturated aldehydes and ketones are not generally very useful, because Grignards may give 1,2-addition, 1,4-addition, or both, depending on the structures of the reacting species and conditions. Fortunately, another type of organometallic reagent, an organocuprate, is very effective in giving rise only to products of conjugate addition. **Organocuprates** have the empirical formula R_2CuLi , and they may be prepared by adding two equivalents of an organolithium reagent to one of copper(I) iodide, CuI .

Example of Preparation of an Organocuprate



Organocuprates are highly selective in undergoing 1,4-addition reactions:

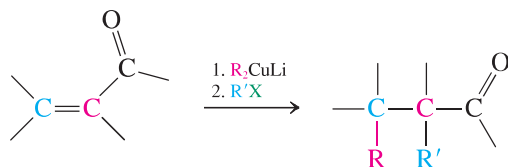
Exclusive 1,4-Addition of a Lithium Organocuprate



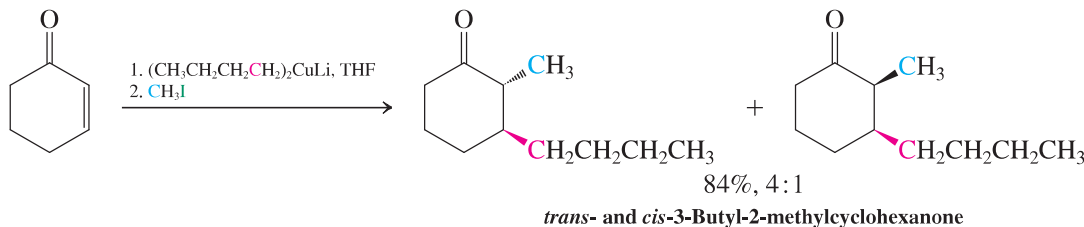
The copper-mediated 1,4-addition reactions are thought to proceed through complex electron-transfer mechanisms. The first isolable intermediate is an enolate ion, which can be

trapped by alkylating species, as shown in Section 18-4. Conjugate addition followed by alkylation constitutes a useful sequence for α,β -dialkylation of unsaturated aldehydes and ketones.

α,β -Dialkylation of Unsaturated Carbonyl Compounds

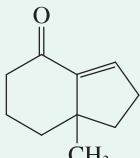


The following example illustrates this reaction.



Exercise 18-26

Working with the Concepts: Conjugate Addition in Synthesis

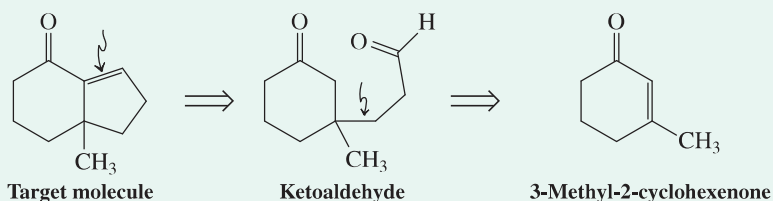
Show how you might synthesize  from 3-methyl-2-cyclohexenone.

Strategy

The fact that your starting material is an α,β -unsaturated ketone and your product has an additional bond to its β -carbon makes conjugate addition a reasonable place to start. However, for this problem, retrosynthetic analysis (working backward) is especially useful. The presence of an additional ring should suggest an intramolecular aldol condensation as a synthetic possibility. Analyze retrosynthetically first; then proceed in the forward direction.

Solution

- In the target molecule (below, left), consider the $C=C$ double bond of the α,β -unsaturated ketone (arrow) to be the result of an intramolecular aldol condensation between the α -carbon of a cyclohexanone and a side-chain aldehyde function (center structure).
- Consider the bond connecting this side chain to the β -carbon of the cyclohexanone (center, arrow) as deriving from a conjugate addition to 3-methyl-2-cyclohexenone, the specified starting material:



- Before translating this retrosynthetic analysis into a synthesis in the forward direction, notice that the side chain, which we intend to use as a nucleophile for 1,4-addition, will have to be introduced as an organocuprate reagent, which in turn has to come from a halide via an organolithium species. However, it also contains a carbonyl function, which will need to be protected, so that the organolithium reagent can be prepared successfully (recall Section 17-8):

