**MECHANISM 8-11** Olefin Metathesis

\[
\begin{align*}
&M=\overset{\bullet}{C} = R \\
&\overset{\bullet}{C} = R^1 H \quad \longleftrightarrow \quad \overset{\bullet}{C} = R \quad \longleftrightarrow \quad \overset{\bullet}{C} = R^1 \quad H
\\
&\overset{\bullet}{C} = R^2 H
\end{align*}
\]

**PROBLEM 8-43**
Propose a mechanism for the triolefin process using a metal alkylidene as the catalyst.

\[
\begin{align*}
&\overset{\bullet}{C} = CH_3 \quad [M] \\
&\overset{\bullet}{C} = CH_3
\end{align*}
\]

2 propylene \quad (cis + trans) \quad 2-butene \quad ethylene

**PROBLEM 8-44**
Show what reagents would be needed to synthesize the pheromone of the omnivorous leafroller (OLR) using olefin metathesis to assemble the molecule at the double bond.

\[
\begin{align*}
&\overset{\bullet}{C} = C \quad CH_3
\end{align*}
\]

OLR pheromone (cis + trans)

**PROBLEM-SOLVING STRATEGY**

**ORGANIC SYNTHESIS**

Alkyl halides and alkenes are readily made from other compounds, and they are easily converted to other functional groups. This flexibility makes them useful as reagents and intermediates for organic synthesis. Alkenes are particularly important for industrial syntheses because they are inexpensive and available in large quantities from cracking and dehydrogenation of petroleum fractions.

**Organic synthesis** is the preparation of desired compounds from readily available materials. Synthesis is one of the major areas of organic chemistry, and nearly every chapter of this book involves organic synthesis in some way. A synthesis may be a simple one-step reaction, or it may involve many steps and incorporate a subtle strategy for assembling the correct carbon skeleton with all the functional groups in the right positions.

Many of the problems in this book are synthesis problems. In some synthesis problems, you are asked to show how to convert a given starting material to the desired product. There are obvious one-step answers to some of these problems, but others may require several steps and there may be many correct answers. In solving multistep synthetic problems, it is often helpful to analyze the problem backward: Begin with the desired product (called the target compound) and see how it might be mentally changed or broken down to give the starting materials. This backward approach to synthesis is called a *retrosynthetic analysis*.

Some problems allow you to begin with any compounds that meet a certain restriction. For example, you might be allowed to use any alcohols containing no more than four carbon atoms. A retrosynthetic analysis can be used to break down the target compound into fragments no larger than four carbon atoms; then those fragments could be formed from the appropriate alcohols by functional group chemistry.
The following suggestions should help you solve synthesis problems:

1. **Do not guess a starting material and try every possible reaction to convert it to the target compound.** Rather, begin with the target compound and use a retrosynthetic analysis to simplify it.

2. Use simple equations, with reagents written above and below the arrows, to show the reactions. The equations do not have to be balanced, but they should include all the reagents and conditions that are important to the success of the reaction.

   \[
   A \xrightarrow{\text{Br}_2, \text{light}} B \xrightarrow{\text{NaOH, alcohol}} \xrightarrow{\text{heat}} C \xrightarrow{\text{H}^+, \text{H}_2\text{O}} D
   \]

3. **Focus on the functional groups, since that is generally where reactions occur.** Do not use any reagents that react with a functional group that you don’t intend to modify.

In solving multistep synthesis problems, you will rarely be able to “see” the solution immediately. These problems are best approached systematically, working backward and considering alternative routes. To illustrate a systematic approach that can guide you in solving synthesis problems, we will work through the synthesis of a complex ether starting from alkenes. The problem-solving method described here will be extended in future chapters to multistep syntheses based on the reactions of additional functional groups.

A systematic retrosynthetic analysis begins with an examination of the structure of the product. We will consider the synthesis of the following compound from alkenes containing up to five carbon atoms.

\[
\begin{align*}
\text{OH} + \text{Br} & \rightarrow \text{OH} \\
\text{OH} + \text{Br} & \rightarrow \text{OH}
\end{align*}
\]

The first reaction is better because the S_N2 attack is on a primary alkyl halide, while the second is on a secondary halide. Also, in the second reaction the alkoxide might simply deprotonate the alcohol on the left and cause the reaction to fail.

4. **In general, reactive functional groups are best put into place toward the end of a synthesis.**

The target compound contains a reactive epoxide ring. Epoxides react with acids and bases, and the epoxide might not survive the crucial ether-forming reaction just shown. Perhaps the epoxide is best added after formation of the ether. That gives us the following final two steps in the synthesis:

\[
\begin{align*}
\text{OH} + \text{Br} & \rightarrow \text{OH} \\
\text{OH} & \rightarrow \text{OH}
\end{align*}
\]

(Continued)
5. Working backward through as many steps as necessary, compare methods for synthesizing the reactants needed for the final step. This process may require writing several possible reaction sequences and evaluating them, keeping in mind the specified starting materials.

Two reactants are needed to form the ether: an allylic halide and an alkoxide ion. Alkoxide ions are commonly formed by the reaction of an alcohol with sodium metal:

\[ R-OH + Na \rightarrow Na^+\cdot O\cdot R + \frac{1}{2}H_2 \uparrow \]

The alkoxide needed to make the ether is formed by adding sodium to a trans diol as shown below. Trans diols are formed by epoxidation and hydrolysis of alkenes (Section 8-13).

![Diagram of ether synthesis]

6. Summarize the complete synthesis in the forward direction, including all steps and all reagents, and check it for errors and omissions.

This summary is left to you as a review of both the chemistry involved in the synthesis and the method used to develop multistep syntheses.

**PROBLEM:** Summarize the synthesis outlined in the problem-solving strategy. This summary should be in the synthetic (forward) direction, showing each step and all reagents.

Problem 8-45 requires devising several multistep syntheses. As practice in working such problems, we suggest that you proceed in order through the five steps just outlined.

**PROBLEM 8-45**

Show how you would synthesize each compound, starting with alkenes or cycloalkenes that contain no more than six carbon atoms. You may use any additional reagents you need.

(a) ![Compound A](attachment:imageA)

(b) ![Compound B](attachment:imageB)

(c) ![Compound C](attachment:imageC)

**SUMMARY**

Reactions of Alkenes

1. **Electrophilic Additions**
   a. Addition of hydrogen halides (Section 8-3)

\[
\begin{align*}
\text{C} &= \text{C}^+ \quad + \quad \text{H} - \text{X} & \rightarrow & \quad \text{C} \quad \text{C}^- \\
(\text{HX} = \text{HCl, HBr, or HI}) & & \text{Markovnikov orientation} \\
\quad & & \text{(anti-Markovnikov with HBr and peroxides)}
\end{align*}
\]

(Continued)
If the aldehyde is protected as an acetal, however, it is unreactive toward a Grignard reagent. The "masked" aldehyde is converted to the Grignard reagent, which is allowed to react with cyclohexanone. Dilute aqueous acid both protonates the alkoxyde to give the alcohol and hydrolyzes the acetal to give the deprotected aldehyde.

*Actual synthesis*

\[
\begin{align*}
\text{Br-CH}_2\text{CH}_2\text{CH}_2\text{CHO} & \quad \xrightarrow{\text{HOCH}_2\text{CH}_2\text{OH}} \quad \text{Br-CH}_2\text{CH}_2\text{CH}_2\text{C}=\text{H} \\
& \quad \quad \xrightarrow{\text{H}^+} \quad \text{"masked" aldehyde} \\
& \quad \quad \xrightarrow{\text{Mg, ether}} \quad \text{BrMg-CH}_2\text{CH}_2\text{CH}_2\text{C}=\text{H} \\
\text{O} & \quad + \quad \text{MgBr} \\
\text{CH}_3\text{CH}_2\text{C}=\text{H} & \quad \rightarrow \quad \text{CH}_3\text{CH}_2\text{C}=\text{H} \\
& \quad \quad \xrightarrow{\text{H}_2\text{O}^+} \quad \text{target compound}
\end{align*}
\]

**Selective Acetal Formation** Because aldehydes form acetals more readily than ketones, we can protect an aldehyde selectively in the presence of a ketone. This selective protection leaves the ketone available for modification under neutral or basic conditions without disturbing the more reactive aldehyde group. The following example shows the reduction of a ketone in the presence of a more reactive aldehyde:

\[
\begin{align*}
\text{C}=\text{H} & \quad \xrightarrow{\text{1 equiv OH, OH \quad H}^+} \quad \text{C}=\text{H} \\
& \quad \quad \xrightarrow{\text{NaBH}_4} \quad \text{C}=\text{H} \\
& \quad \quad \xrightarrow{\text{H}_2\text{O}^+} \quad \text{C}=\text{H}
\end{align*}
\]

**PROBLEM 18-34**

Show how you would accomplish the following syntheses. You may use whatever additional reagents you need.

(a)

(b)

(c)

(d)

(e)

(f)
MECHANISMS

$S_{N} 2$

\[
\begin{align*}
\text{CH}_3\text{C}^\cdot\text{CH}_2 & \rightarrow \text{CH}_3\text{C}^\cdot\text{CH}_2 - R \\
& + :\text{Cl}^-
\end{align*}
\]

NUCLEOPHILIC ADDITION

\[
\begin{align*}
\text{CH}_3-\text{C}^\cdot\text{CH}_2 + \text{CH}_3\text{C}^\cdot\text{CH}_3 & \rightarrow \text{CH}_3\text{C}^\cdot\text{CH}_2 - \overset{\cdot}{\text{C}} - \text{CH}_3 \\
\text{CH}_3\overset{\cdot}{\text{C}} - \text{CH}_2 - \overset{\cdot}{\text{C}} - \text{CH}_3 & \rightarrow \text{CH}_3\overset{\cdot}{\text{C}} - \text{CH}_2 - \overset{\cdot}{\text{C}} - \text{CH}_3
\end{align*}
\]

NUCLEOPHILIC ACYL SUBSTITUTION

\[
\begin{align*}
\text{CH}_3\text{C}^\cdot\text{CH}_2 & + \text{CH}_3\text{C}^\cdot\overset{\cdot}{\text{O}} - \text{CH}_3 \rightarrow \text{CH}_3\text{C}^\cdot\text{CH}_2 - \overset{\cdot}{\text{C}} - \overset{\cdot}{\text{O}} - \text{CH}_3 \\
\text{CH}_3\overset{\cdot}{\text{C}} - \text{CH}_2 - \overset{\cdot}{\text{C}} - \overset{\cdot}{\text{O}} - \text{CH}_3 & \rightarrow \text{CH}_3\overset{\cdot}{\text{C}} - \text{CH}_2 - \overset{\cdot}{\text{C}} - \text{CH}_3
\end{align*}
\]