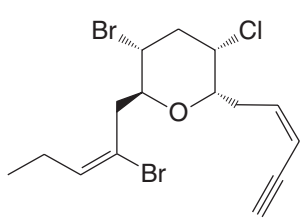
CHAPTER

8

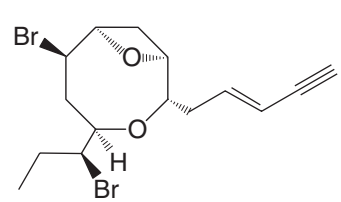
Alkenes and Alkynes II

ADDITION REACTIONS

In recent chapters we have discussed mechanisms that involve electron pairs in bond-forming and bond-breaking steps of substitution and elimination reactions. Nucleophiles and bases served as electron pair donors in these reactions. In this chapter we discuss reactions of **alkenes** and **alkynes** in which a double or triple bond acts as the electron pair donor for bond formation. These reactions are called **addition reactions**.



Dactylyne



(3*E*)-Laureatin

Alkenes and alkynes are very common in nature, both on land and in the sea. Examples from the sea include dactylyne and (3*E*)-laureatin, whose formulas are shown here. These compounds include halogens in their structures, as is the case for many other natural marine compounds. Certain marine organisms may produce compounds like these for the purpose of self-defense, since a number of them have cytotoxic properties. Interestingly, the halogens in these marine compounds are

incorporated by biological reactions similar to those we shall study in this chapter (Section 8.11). Not only, therefore, do compounds like dactylyne and (3*E*)-laureatin have intriguing structures and properties, and arise in the beautiful environment of the sea, but they also have fascinating chemistry behind them.

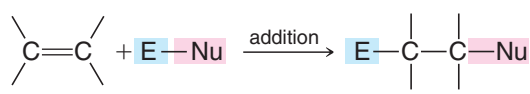
IN THIS CHAPTER WE WILL CONSIDER:

- the regio- and stereochemistry of addition reactions of alkenes
- processes that can add molecules of water, halogens, carbon, and other functionalities across alkenes
- events that cleave double bonds and provide more highly oxidized compounds
- alkyne reactions that are analogous to alkene reactions

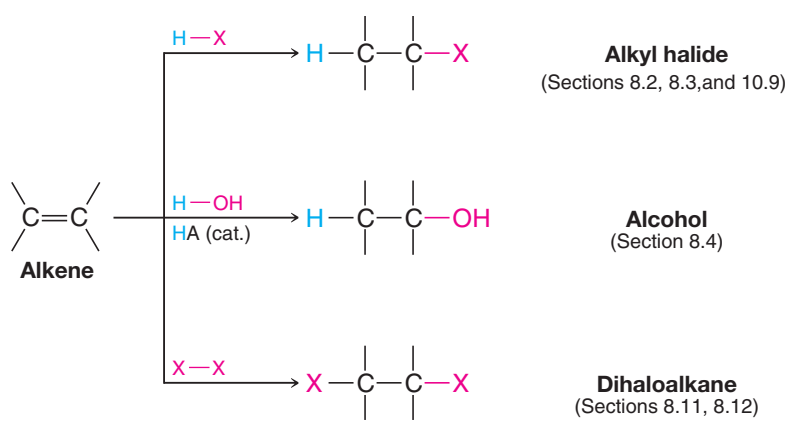
[WHY DO THESE TOPICS MATTER?] At the end of the chapter, we will show how, in nature, a special class of alkenes is involved in the creation of tens of thousands of bioactive molecules, all through processes that mirror the core reactions discussed in this chapter.

8.1 ADDITION REACTIONS OF ALKENES

We have already studied one addition reaction of alkenes—hydrogenation—in which a hydrogen atom is added at each end of a double (or triple) bond. In this chapter we shall study other alkene addition reactions that do not involve the same mechanism as hydrogenation. We can depict this type of reaction generally, using E for an electrophilic portion of a reagent and Nu for a nucleophilic portion, as follows.



Some specific reactions of this type that we shall study in this chapter include addition of hydrogen halides, sulfuric acid, water (in the presence of an acid catalyst), and halogens. Later we shall also study some specialized reagents that undergo addition reactions with alkenes.

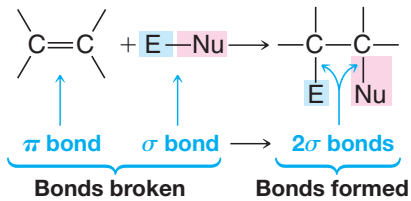


8.1A HOW TO Understand Additions to Alkenes

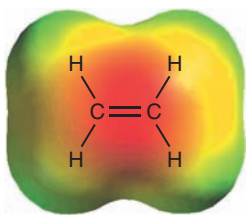
Two characteristics of the double bond help us understand why these addition reactions occur:

1. An addition reaction results in the conversion of one π bond and one σ bond (Sections 1.12 and 1.13) into two σ bonds. The result of this change is usually energetically favorable. The energy released in making two σ bonds exceeds that needed to break

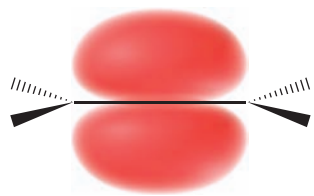
one σ bond and one π bond (because π bonds are weaker), and, therefore, addition reactions are usually exothermic:



2. The electrons of the π bond are exposed. Because the π bond results from overlapping p orbitals, the π electrons lie above and below the plane of the double bond:



An electrostatic potential map for ethene shows the higher density of negative charge in the region of the π bond.



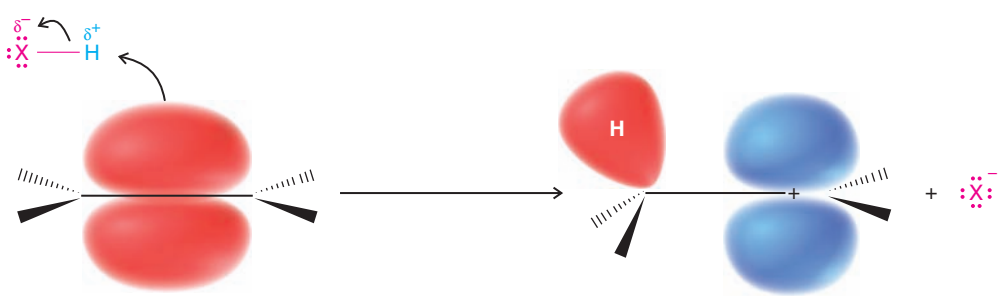
The electron pair of the π bond is distributed throughout both lobes of the π molecular orbital.

Electrophilic Addition

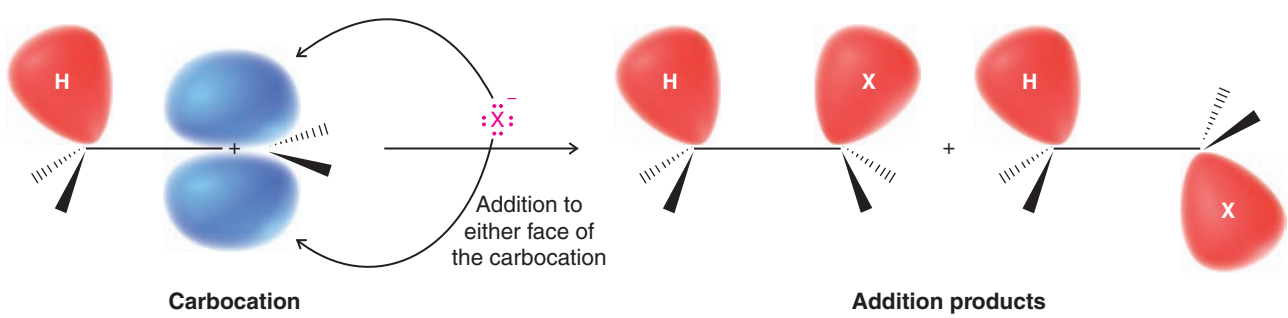
- Electrons in the π bond of alkenes react with electrophiles.
- **Electrophiles** are electron-seeking reagents. They have the property of being **electrophilic**.

Electrophiles include proton donors such as Brønsted–Lowry acids, neutral reagents such as bromine (because it can be polarized so that one end is positive), and Lewis acids such as BH_3, BF_3, and $AlCl_3$. Metal ions that contain vacant orbitals—the silver ion (Ag^+), the mercuric ion (Hg^{2+}), and the platinum ion (Pt^{2+}), for example—also act as electrophiles.

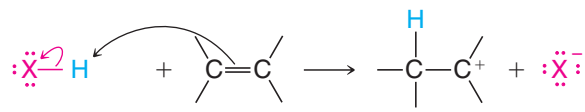
Hydrogen halides, for example, react with alkenes by accepting a pair of electrons from the π bond to form a σ bond between the hydrogen and one of the carbon atoms, with loss of the halide ion. This leaves a vacant p orbital and a + charge on the other carbon. The overall result is the formation of a carbocation and a halide ion from the alkene and HX:



Being highly reactive, the carbocation may then combine with the halide ion by accepting one of its electron pairs:

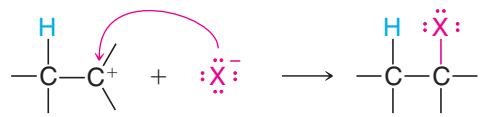


Electrophiles Are Lewis Acids Electrophiles are molecules or ions that can accept an electron pair. Nucleophiles are molecules or ions that can furnish an electron pair (i.e., Lewis bases). Any reaction of an electrophile also involves a nucleophile. In the protonation of an alkene the electrophile is the proton donated by an acid; the nucleophile is the alkene:



Electrophile **Nucleophile**

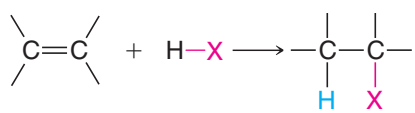
In the next step, the reaction of the carbocation with a halide ion, the carbocation is the electrophile and the halide ion is the nucleophile:



Electrophile **Nucleophile**

8.2 ELECTROPHILIC ADDITION OF HYDROGEN HALIDES TO ALKENES: MECHANISM AND MARKOVNIKOV'S RULE

Hydrogen halides (HI, HBr, HCl, and HF) add to the double bond of alkenes:



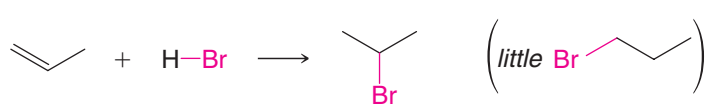
These additions are sometimes carried out by dissolving the hydrogen halide in a solvent, such as acetic acid or CH_2Cl_2, or by bubbling the gaseous hydrogen halide directly into the alkene and using the alkene itself as the solvent. HF is prepared as polyhydrogen fluoride in pyridine.

- The order of reactivity of the hydrogen halides in alkene addition is

$$HI > HBr > HCl > HF$$

Unless the alkene is highly substituted, HCl reacts so slowly that the reaction is not one that is useful as a preparative method. HBr adds readily, but as we shall learn in Section 10.9, unless precautions are taken, the reaction may follow an alternate course.

The addition of HX to an unsymmetrical alkene could conceivably occur in two ways. In practice, however, one product usually predominates. The addition of HBr to propene, for example, could conceivably lead to either 1-bromopropane or 2-bromopropane. The main product, however, is 2-bromopropane:



2-Bromopropane **1-Bromopropane**

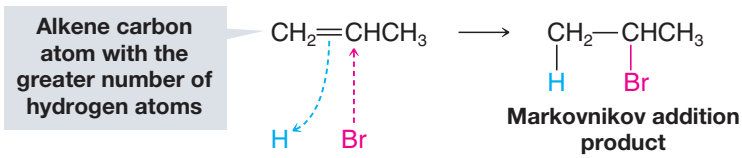
When 2-methylpropene reacts with HBr, the main product is 2-bromo-2-methylpropane, not 1-bromo-2-methylpropane:

2-Methylpropene **2-Bromo-2-methylpropane** **1-Bromo-2-methylpropane**

Consideration of many examples like this led the Russian chemist Vladimir Markovnikov in 1870 to formulate what is now known as Markovnikov's rule.

- One way to state **Markovnikov's rule** is to say that ***in the addition of*** HX ***to an alkene, the hydrogen atom adds to the carbon atom of the double bond that already has the greater number of hydrogen atoms.****

The addition of HBr to propene is an illustration:

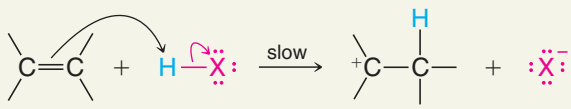


Reactions that illustrate Markovnikov's rule are said to be *Markovnikov additions*.

A mechanism for addition of a hydrogen halide to an alkene involves the following two steps:

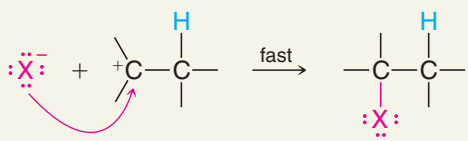
A MECHANISM FOR THE REACTION — Addition of a Hydrogen Halide to an Alkene

Step 1



The π electrons of the alkene form a bond with a proton from HX to form a carbocation and a halide ion.

Step 2

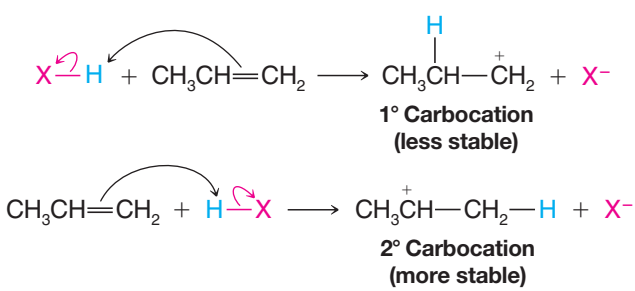


The halide ion reacts with the carbocation by donating an electron pair; the result is an alkyl halide.

The important step—because it is the **rate-determining step**—is step 1. In step 1 the alkene donates a pair of electrons to the proton of the hydrogen halide and forms a carbocation. This step (Fig. 8.1) is highly endergonic and has a high free energy of activation. Consequently, it takes place slowly. In step 2 the highly reactive carbocation stabilizes itself by combining with a halide ion. This exergonic step has a very low free energy of activation and takes place very rapidly.

8.2A Theoretical Explanation of Markovnikov's Rule

If the alkene that undergoes addition of a hydrogen halide is an unsymmetrical alkene such as propene, then step 1 could conceivably lead to two different carbocations:



*In his original publication, Markovnikov described the rule in terms of the point of attachment of the halogen atom, stating that "if an unsymmetrical alkene combines with a hydrogen halide, the halide ion adds to the carbon atom with the fewer hydrogen atoms."

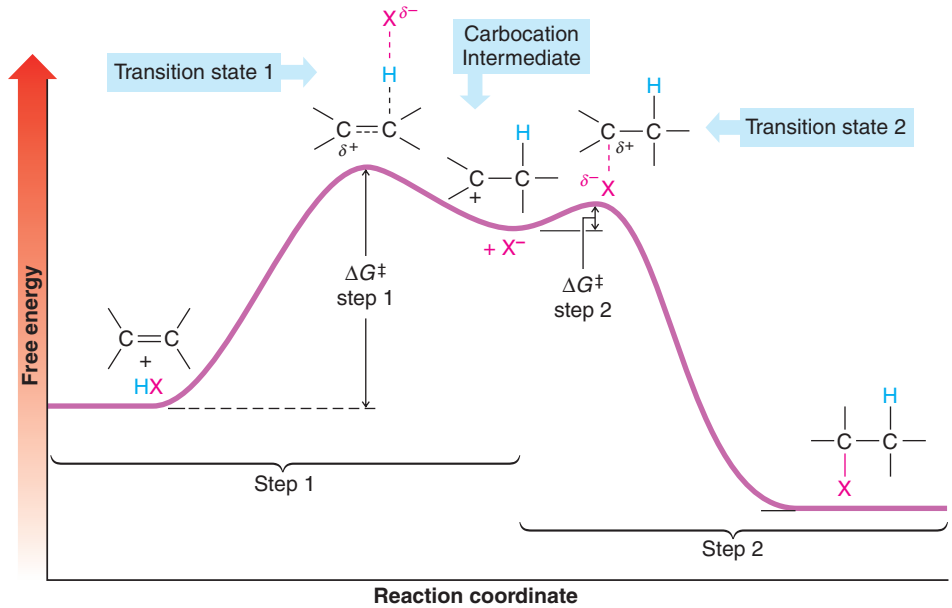
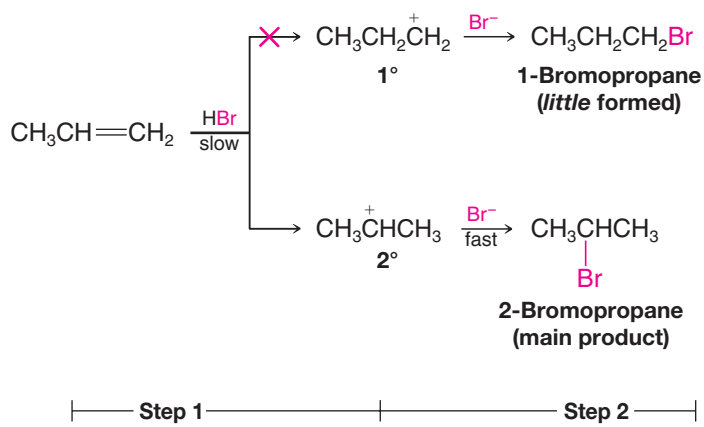


FIGURE 8.1 Free-energy diagram for the addition of HX to an alkene. The free energy of activation for step 1 is much larger than that for step 2.

These two carbocations are not of equal stability, however. The secondary carbocation is *more stable*, and it is the greater stability of the secondary carbocation that accounts for the correct prediction of the overall addition by Markovnikov's rule. In the addition of HBr to propene, for example, the reaction takes the following course:



The chief product of the reaction is 2-bromopropane because the more stable secondary carbocation is formed preferentially in the first step.

- The more stable carbocation predominates because it is formed faster.

We can understand why this is true if we examine the free-energy diagrams in Fig. 8.2.

- The reaction leading to the secondary carbocation (and ultimately to 2-bromopropane) has the lower free energy of activation. This is reasonable because its transition state resembles the more stable carbocation.
- The reaction leading to the primary carbocation (and ultimately to 1-bromopropane) has a higher free energy of activation because its transition state resembles a less stable primary carbocation. This second reaction is much slower and does not compete appreciably with the first reaction.

The reaction of HBr with 2-methylpropene produces only 2-bromo-2-methylpropane, for the same reason regarding carbocations stability. Here, in the first step (i.e., the attachment of the proton) the choice is even more pronounced—between a tertiary carbocation and a primary carbocation. Thus, 1-bromo-2-methylpropane is *not* obtained as a product of the reaction because its formation would require the formation of a primary

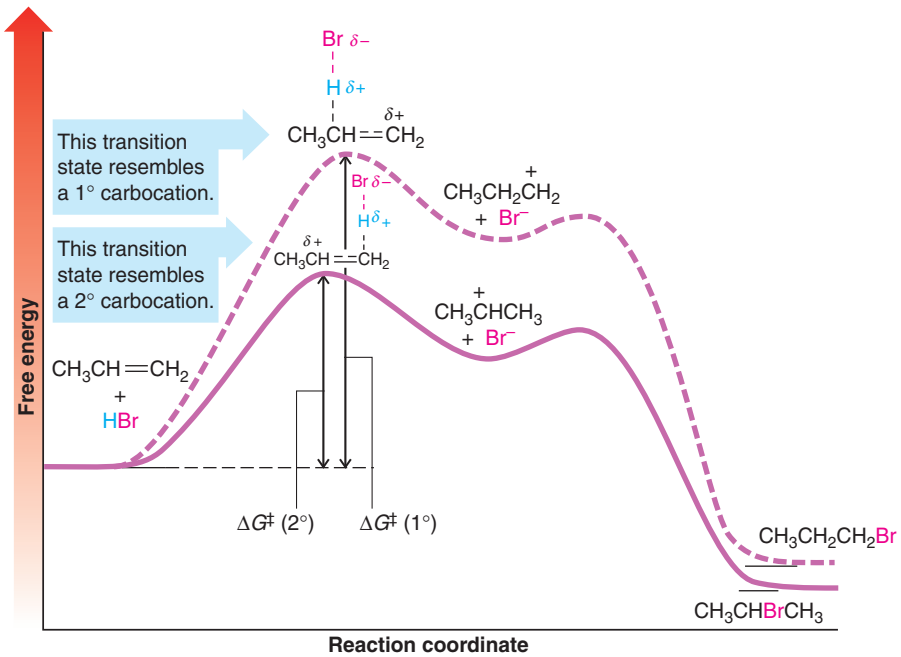


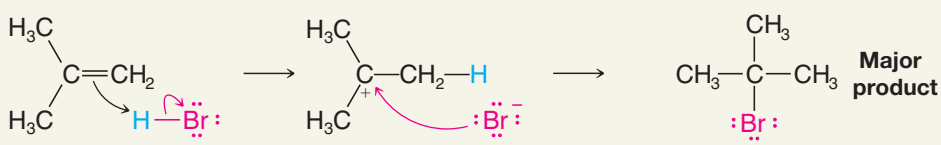
FIGURE 8.2 Free-energy diagrams for the addition of HBr to propene. $\Delta G^{\ddagger}$(2°) is less than $\Delta G^{\ddagger}$(1°).

carbocation. Such a reaction would have a much higher free energy of activation than that leading to a tertiary carbocation.

- Rearrangements invariably occur when the carbocation initially formed by addition of HX to an alkene can rearrange to a more stable one (see Section 7.8 and Practice Problem 8.3).

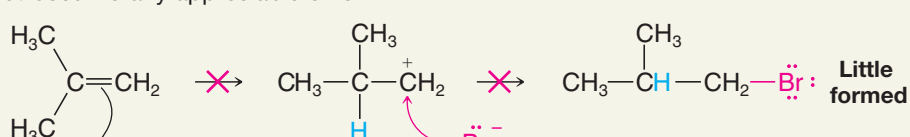
A MECHANISM FOR THE REACTION — Addition of HBr to 2-Methylpropene

This reaction takes place:



3° Carbocation (more stable carbocation) — 2-Bromo-2-methylpropane

This reaction *does not* occur to any appreciable extent:



1° Carbocation (less stable carbocation) — 1-Bromo-2-methylpropane

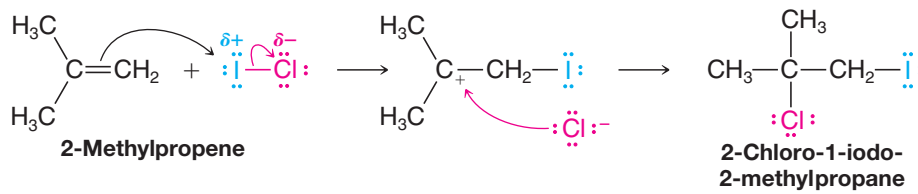
8.2B General Statement of Markovnikov's Rule

With this understanding of the mechanism for the ionic addition of hydrogen halides to alkenes, we can now generalize about how electrophiles add to alkenes.

- General statement of **Markovnikov's rule**: In the ionic addition of an unsymmetrical reagent to a double bond, the positive portion of the adding reagent attaches itself to a carbon atom of the double bond so as to yield the more stable carbocation as an intermediate.

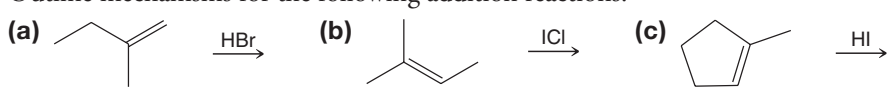
- Addition of the electrophile determines the overall orientation of the addition, because it occurs first (before the addition of the nucleophilic portion of the adding reagent).

Notice that this formulation of Markovnikov's rule allows us to predict the outcome of the addition of a reagent such as ICl. Because of the greater electronegativity of chlorine, the positive portion of this molecule is iodine. The addition of ICl to 2-methylpropene takes place in the following way and produces 2-chloro-1-iodo-2-methylpropane:

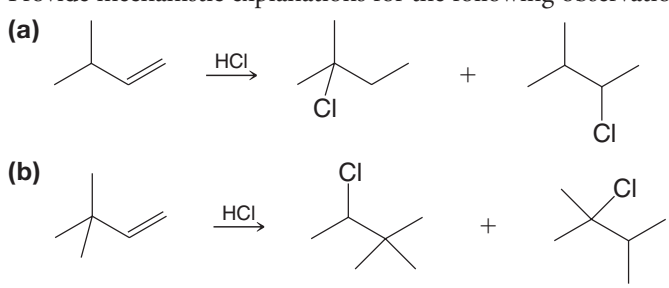


PRACTICE PROBLEM 8.1 Give the structure and name of the product that would be obtained from the ionic addition of IBr to propene.

PRACTICE PROBLEM 8.2 Outline mechanisms for the following addition reactions:



PRACTICE PROBLEM 8.3 Provide mechanistic explanations for the following observations:



8.2C Regioselective Reactions

Chemists describe reactions like the Markovnikov additions of hydrogen halides to alkenes as being **regioselective**. *Regio* comes from the Latin word *regionem* meaning direction.

- When a reaction that can potentially yield two or more constitutional isomers actually produces only one (or a predominance of one), the reaction is said to be a **regioselective reaction**.

The addition of HX to an unsymmetrical alkene such as propene could conceivably yield two constitutional isomers, for example. As we have seen, however, the reaction yields only one, and therefore it is regioselective.

8.2D An Exception to Markovnikov's Rule

In Section 10.9 we shall study an exception to Markovnikov's rule. This exception concerns the addition of HBr to alkenes ***when the addition is carried out in the presence of peroxides*** (i.e., compounds with the general formula ROOR).

- When alkenes are treated with HBr in the presence of peroxides, an **anti-Markovnikov addition** occurs in the sense that the hydrogen atom becomes attached to the carbon atom with the fewer hydrogen atoms.

With propene, for example, the addition takes place as follows:

$$CH_3CH{=}CH_2 + HBr \xrightarrow{ROOR} CH_3CH_2CH_2Br$$

In Section 10.10 we shall find that this addition occurs by *a radical mechanism*, and not by the ionic mechanism given at the beginning of Section 8.2.

- This anti-Markovnikov addition occurs ***only when*** HBr ***is used in the presence of peroxides*** and does not occur significantly with HF, HCl, and HI even when peroxides are present.

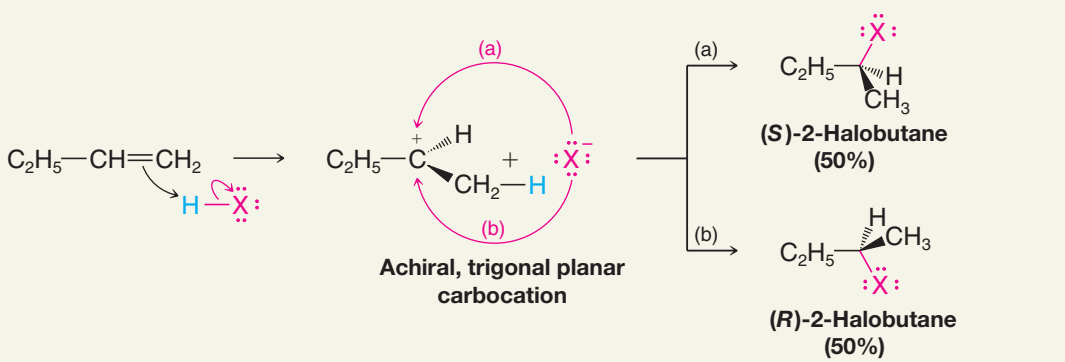
8.3 STEREOCHEMISTRY OF THE IONIC ADDITION TO AN ALKENE

Consider the following addition of HX to 1-butene and notice that the reaction leads to the formation of a 2-halobutane that contains a chirality center:

$$CH_3CH_2CH{=}CH_2 + HX \longrightarrow CH_3CH_2\overset{*}{C}HCH_3 \quad (X \text{ on } C)$$

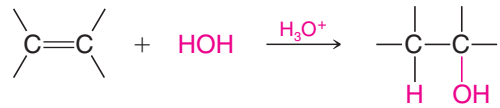
The product, therefore, can exist as a pair of enantiomers. The question now arises as to how these enantiomers are formed. Is one enantiomer formed in greater amount than the other? The answer is *no*; the carbocation that is formed in the first step of the addition (see the following scheme) is trigonal planar and is ***achiral*** (a model will show that it has a plane of symmetry). When the halide ion reacts with this achiral carbocation in the second step, ***reaction is equally likely at either face.*** The reactions leading to the two enantiomers occur at the same rate, and the enantiomers, therefore, are produced in equal amounts ***as a racemic mixture***.

THE STEREOCHEMISTRY OF THE REACTION... — Ionic Addition to an Alkene

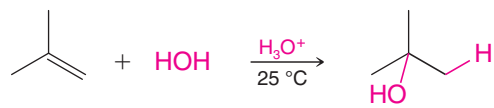


8.4 ADDITION OF WATER TO ALKENES: ACID-CATALYZED HYDRATION

The acid-catalyzed addition of water to the double bond of an alkene (**hydration** of an alkene) is a method for the preparation of low-molecular-weight alcohols. This reaction has its greatest utility in large-scale industrial processes. The acids most commonly used to catalyze the hydration of alkenes are dilute aqueous solutions of sulfuric acid and phosphoric acid. These reactions, too, are usually regioselective, and the addition of water to the double bond follows Markovnikov's rule. In general, the reaction takes the form that follows:

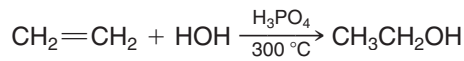


An example is the hydration of 2-methylpropene:



2-Methylpropene (isobutylene) **2-Methyl-2-propanol (*tert*-butyl alcohol)**

Because the reactions follow Markovnikov's rule, acid-catalyzed hydrations of alkenes do not yield primary alcohols except in the special case of the hydration of ethene:

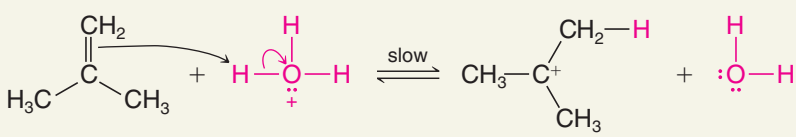


8.4A Mechanism

The mechanism for the hydration of an alkene is simply the reverse of the mechanism for the dehydration of an alcohol. We can illustrate this by giving the mechanism for the **hydration** of 2-methylpropene and by comparing it with the mechanism for the **dehydration** of 2-methyl-2-propanol given in Section 7.7A.

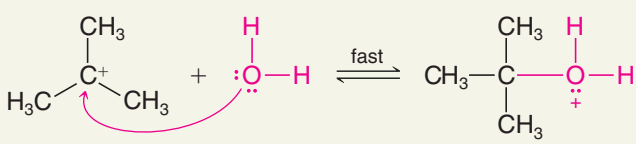
A MECHANISM FOR THE REACTION — Acid-Catalyzed Hydration of an Alkene

Step 1



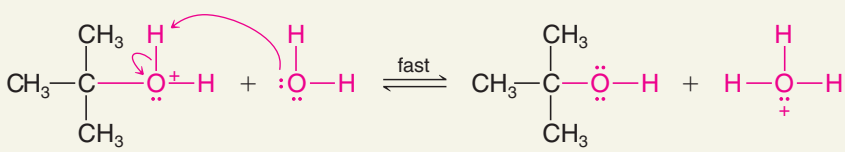
The alkene donates an electron pair to a proton to form the more stable 3° carbocation.

Step 2



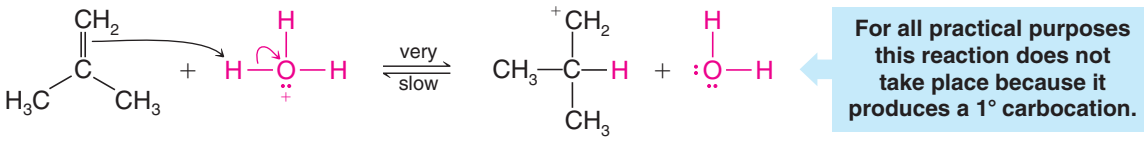
The carbocation reacts with a molecule of water to form a protonated alcohol.

Step 3



A transfer of a proton to a molecule of water leads to the product.

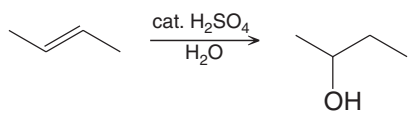
The rate-determining step in the *hydration* mechanism is step 1: the formation of the carbocation. It is this step, too, that accounts for the Markovnikov addition of water to the double bond. The reaction produces 2-methyl-2-propanol because step 1 leads to the formation of the more stable tertiary (3°) cation rather than the much less stable primary (1°) cation:



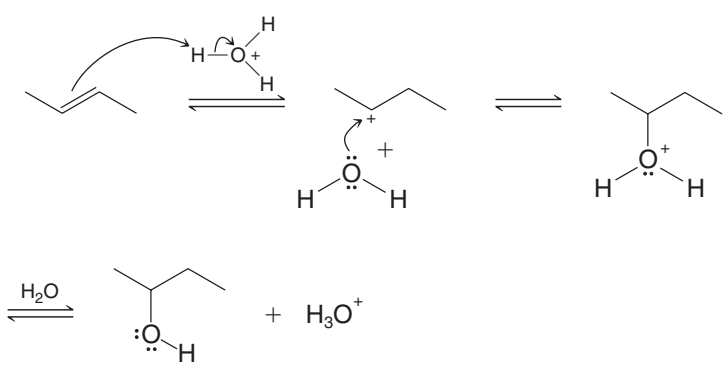
The reactions whereby *alkenes are hydrated or alcohols are dehydrated* are reactions in which the ultimate product is governed by the position of an equilibrium. Therefore, in the *dehydration of an alcohol* it is best to use a concentrated acid so that the concentration of water is low. (The water can be removed as it is formed, and it helps to use a high temperature.) In the *hydration of an alkene* it is best to use dilute acid so that the concentration of water is high. It also usually helps to use a lower temperature.

SOLVED PROBLEM 8.1

Write a mechanism that explains the following reaction.

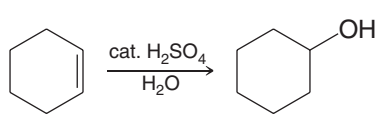


STRATEGY AND ANSWER: We know that a hydronium ion, formed from sulfuric acid and water, can donate a proton to an alkene to form a carbocation. The carbocation can then accept an electon pair from a molecule of water to form a protonated alcohol. The protonated alcohol can donate a proton to water to become an alcohol.



PRACTICE PROBLEM 8.4

(a) Write a mechanism for the following reaction.



(b) What general conditions would you use to ensure a good yield of the product?

(c) What general conditions would you use to carry out the reverse reaction, i.e., the dehydration of cyclohexanol to produce cyclohexene?

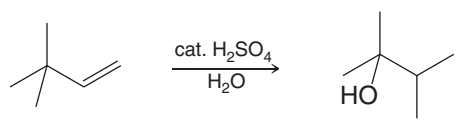
(d) What product would you expect to obtain from the acid-catalyzed hydration of 1-methylcyclohexene? Explain your answer.

PRACTICE PROBLEM 8.5 In one industrial synthesis of ethanol, ethene is first dissolved in 95% sulfuric acid. In a second step water is added and the mixture is heated. Outline the reactions involved.

8.4B Rearrangements

- One complication associated with alkene hydrations is the occurrence of **rearrangements**.

Because the reaction involves the formation of a carbocation in the first step, the carbocation formed initially invariably rearranges to a more stable one (or possibly to an isoenergetic one) if such a rearrangement is possible. An illustration is the formation of 2,3-dimethyl-2-butanol as the major product when 3,3-dimethyl-1-butene is hydrated:



3,3-Dimethyl-1-butene **2,3-Dimethyl-2-butanol (major product)**

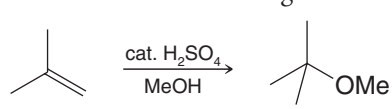
PRACTICE PROBLEM 8.6 Outline all steps in a mechanism showing how 2,3-dimethyl-2-butanol is formed in the acid-catalyzed hydration of 3,3-dimethyl-1-butene.

PRACTICE PROBLEM 8.7 The following order of reactivity is observed when the following alkenes are subjected to acid-catalyzed hydration:

$$(CH_3)_2C{=}CH_2 > CH_3CH{=}CH_2 > CH_2{=}CH_2$$

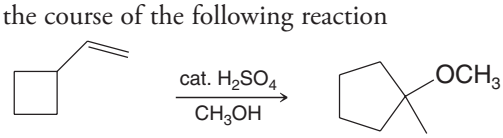
Explain this order of reactivity.

PRACTICE PROBLEM 8.8 Write a mechanism for the following reaction.

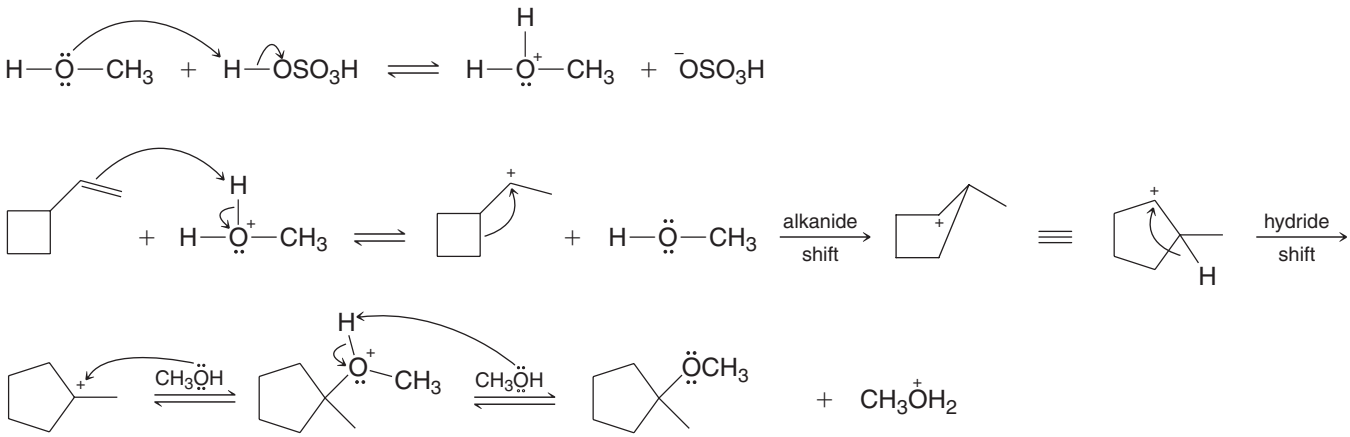


SOLVED PROBLEM 8.2

Write a mechanism that will explain the course of the following reaction



STRATEGY AND ANSWER: As we have learned, in a strongly acidic medium such as methanol containing catalytic sulfuric acid, an alkene can accept a proton to become a carbocation. In the reaction above, the 2° carbocation formed initially can undergo an alkanide shift and a hydride shift as shown below to become a 3° carbocation, which can then react with the solvent (methanol) to form an ether.

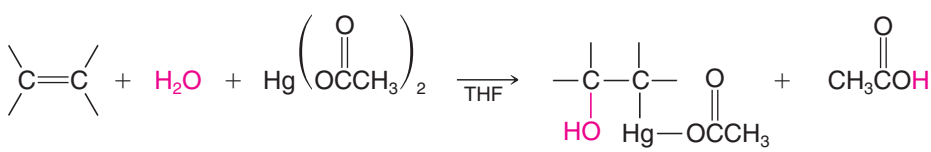


8.5 ALCOHOLS FROM ALKENES THROUGH OXYMERCURATION–DEMERCURATION: MARKOVNIKOV ADDITION

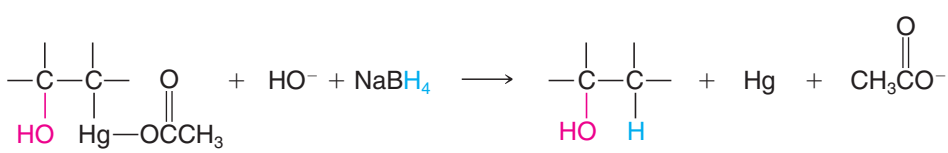
A useful laboratory procedure for synthesizing alcohols from alkenes that avoids rearrangement is a two-step method called **oxymercuration–demercuration**.

- Alkenes react with mercuric acetate in a mixture of tetrahydrofuran (THF) and water to produce (hydroxyalkyl)mercury compounds. These (hydroxyalkyl) mercury compounds can be reduced to alcohols with sodium borohydride.

Step 1: Oxymercuration



Step 2: Demercuration



- In the first step, **oxymercuration**, water and mercuric acetate add to the double bond.
- In the second step, **demercuration**, sodium borohydride reduces the acetoxymercury group and replaces it with hydrogen. (The acetate group is often abbreviated —OAc.)

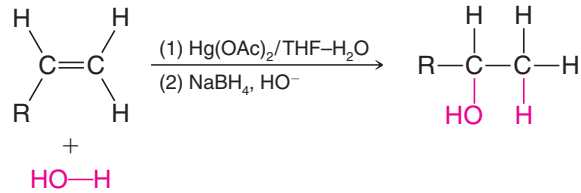
Both steps can be carried out in the same vessel, and both reactions take place very rapidly at room temperature or below. The first step—oxymercuration—usually goes to completion within a period of seconds to minutes. The second step—demercuration—normally requires less than an hour. The overall reaction gives alcohols in very high yields, usually greater than 90%.

Mercury compounds are extremely hazardous. Before you carry out a reaction involving mercury or its compounds, you should familiarize yourself with current procedures for its use and containment. There are no satisfactory methods for disposal of mercury.

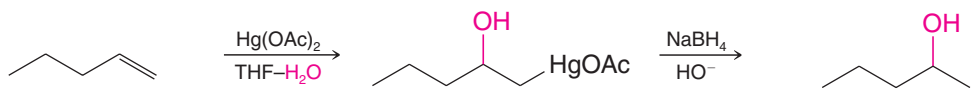
8.5A Regioselectivity of Oxymercuration–Demercuration

Oxymercuration–demercuration is also highly regioselective.

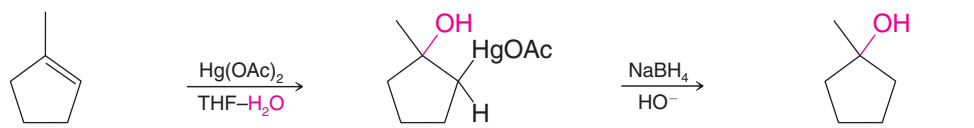
- In oxymercuration–demercuration, the net orientation of the addition of the elements of water, H— and —OH, ***is in accordance with Markovnikov's rule***. The H— becomes attached to the carbon atom of the double bond with the greater number of hydrogen atoms.



The following are specific examples:



1-Pentene **2-Pentanol (93%)**



1-Methylcyclopentene **1-Methylcyclopentanol**

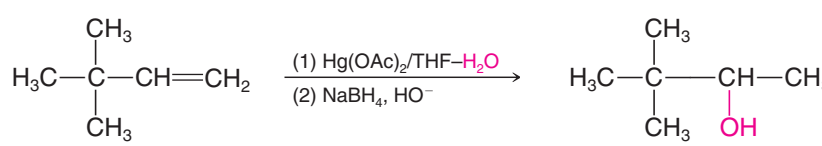
8.5B Rearrangements Seldom Occur in Oxymercuration–Demercuration

- Rearrangements of the carbon skeleton seldom occur in oxymercuration–demercuration.

Helpful Hint

Oxymercuration–demercuration is not prone to hydride or alkanide rearrangements.

The oxymercuration–demercuration of 3,3-dimethyl-1-butene is a striking example illustrating this feature. It is in direct contrast to the **hydration** of 3,3-dimethyl-1-butene we studied previously (Section 8.4B).



3,3-Dimethyl-1-butene **3,3-Dimethyl-2-butanol (94%)**

Analysis of the mixture of products by gas chromatography failed to reveal the presence of any 2,3-dimethyl-2-butanol. The acid-catalyzed hydration of 3,3-dimethyl-1-butene, by contrast, gives 2,3-dimethyl-2-butanol as the major product.

8.5C Mechanism of Oxymercuration

A mechanism that accounts for the orientation of addition in the oxymercuration stage, and one that also explains the general lack of accompanying rearrangements, is shown below.

- Central to this mechanism is an electrophilic attack by the mercury species, $\overset{+}{\text{H}}\text{gOAc}$, at the less substituted carbon of the double bond (i.e., at the carbon atom that bears the greater number of hydrogen atoms), and the formation of a bridged intermediate.

We illustrate the mechanism using 3,3-dimethyl-1-butene as the example:

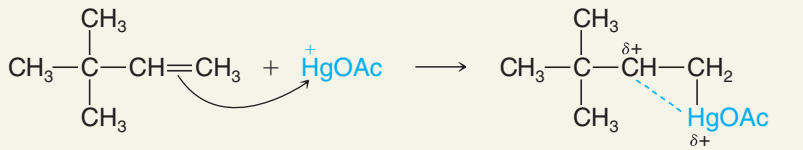
A MECHANISM FOR THE REACTION — Oxymercuration

Step 1

$$Hg(OAc)_2 \rightleftharpoons {}^{+}HgOAc + AcO^{-}$$

Mercuric acetate dissociates to form a $^{+}HgOAc$ cation and an acetate anion.

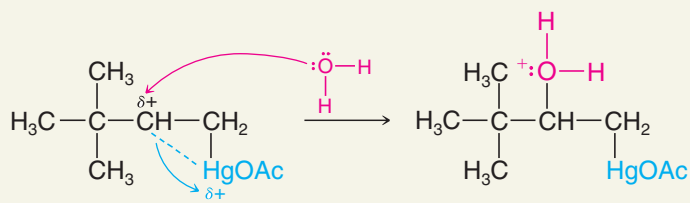
Step 2



3,3-Dimethyl-1-butene **Mercury-bridged carbocation**

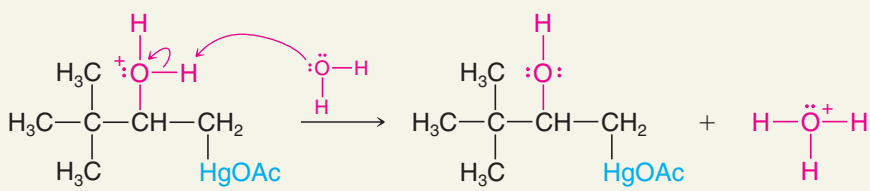
The alkene donates a pair of electrons to the electrophilic $^{+}HgOAc$ cation to form a mercury-bridged carbocation. In this carbocation, the positive charge is shared between the 2° (more substituted) carbon atom and the mercury atom. The charge on the carbon atom is large enough to account for the Markovnikov orientation of the addition, but not large enough for a rearrangement to occur.

Step 3



A water molecule attacks the carbon of the bridged mercurinium ion that is better able to bear the partial positive charge.

Step 4



(Hydroxyalkyl)mercury compound

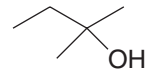
An acid–base reaction transfers a proton to another water molecule (or to an acetate ion). This step produces the (hydroxyalkyl)mercury compound.

Calculations indicate that mercury-bridged carbocations (termed mercurinium ions) such as those formed in this reaction retain much of the positive charge on the mercury moiety. Only a small portion of the positive charge resides on the more substituted carbon atom. The charge is large enough to account for the observed Markovnikov addition, but it is too small to allow the usual rapid carbon skeleton rearrangements that take place with more fully developed carbocations.

Although attack by water on the bridged mercurinium ion leads to anti addition of the hydroxyl and mercury groups, the reaction that replaces mercury with hydrogen is not stereocontrolled (it likely involves radicals; see Chapter 10). This step scrambles the overall stereochemistry.

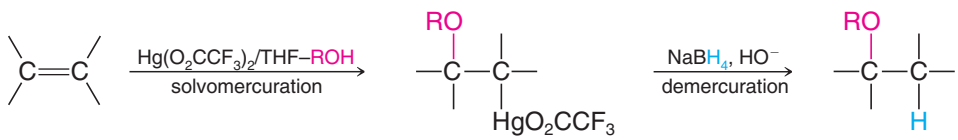
- The net result of oxymercuration–demercuration is a mixture of syn and anti addition of —H and —OH to the alkene.
- As already noted, oxymercuration–demercuration takes place with Markovnikov regiochemistry.

PRACTICE PROBLEM 8.9 Write the structure of the appropriate alkene and specify the reagents needed for synthesis of the following alcohols by oxymercuration–demercuration:

(a)  **(b)**  **(c)** 

When an alkene is treated with mercuric trifluoroacetate, $Hg(O_2CCF_3)_2$, in THF containing an alcohol, ROH, the product is an (alkoxyalkyl)mercury compound. Treating this product with $NaBH_4/HO^-$ results in the formation of an ether.

- When a solvent molecule acts as the nucleophile in the oxymercuration step the overall process is called *solvomercuration–demercuration*:



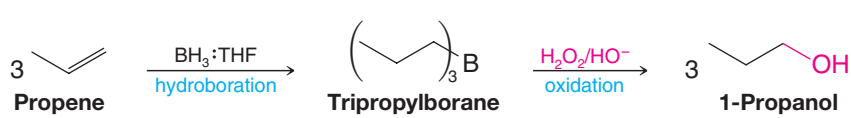
Alkene **(Alkoxyalkyl)mercuric trifluoroacetate** **Ether**

PRACTICE PROBLEM 8.10 **(a)** Outline a likely mechanism for the solvomercuration step of the ether synthesis just shown. **(b)** Show how you would use solvomercuration–demercuration to prepare *tert*-butyl methyl ether. **(c)** Why would one use $Hg(O_2CCF_3)_2$ instead of $Hg(OAc)_2$?

8.6 ALCOHOLS FROM ALKENES THROUGH HYDROBORATION–OXIDATION: ANTI-MARKOVNIKOV SYN HYDRATION

- **Anti-Markovnikov hydration** of a double bond can be achieved through the use of diborane (B_2H_6) or a solution of borane in tetrahydrofuran (BH_3:THF).

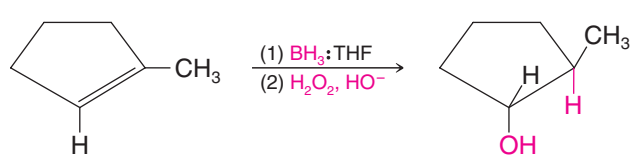
The addition of water is indirect in this process, and two reactions are involved. The first is the addition of a boron atom and hydrogen atom to the double bond, called **hydroboration**; the second is **oxidation** and hydrolysis of the alkylborane intermediate to an alcohol and boric acid. The anti-Markovnikov regiochemistry of the addition is illustrated by the hydroboration–oxidation of propene:



Propene **Tripropylborane** **1-Propanol**

- Hydroboration–oxidation takes place with **syn** stereochemistry, as well as anti-Markovnikov regiochemistry.

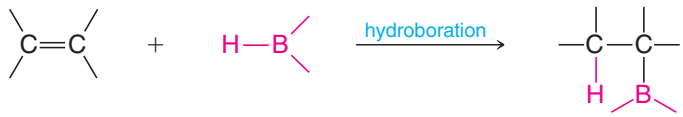
This can be seen in the following example with 1-methylcyclopentene:



In the following sections we shall consider details of the mechanism that lead to the anti-Markovnikov regiochemistry and syn stereochemistry of hydroboration–oxidation.

8.7 HYDROBORATION: SYNTHESIS OF ALKYLBORANES

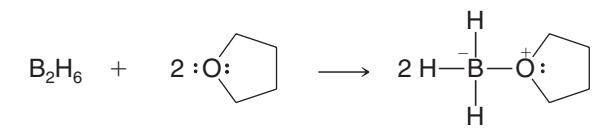
Hydroboration of an alkene is the starting point for a number of useful synthetic procedures, including the anti-Markovnikov syn **hydration** procedure we have just mentioned. Hydroboration was discovered by Herbert C. Brown (Purdue University), and it can be represented in its simplest terms as follows:



Alkene **Boron hydride** **Alkylborane**

Brown's discovery of hydroboration led to his being named a co-winner of the 1979 Nobel Prize in Chemistry.

Hydroboration can be accomplished with diborane (B_2H_6), which is a gaseous dimer of borane (BH_3), or more conveniently with a reagent prepared by dissolving diborane in THF. When diborane is introduced to THF, it reacts to form a Lewis acid–base complex of borane (the Lewis acid) and THF. The complex is represented as BH_3:THF.

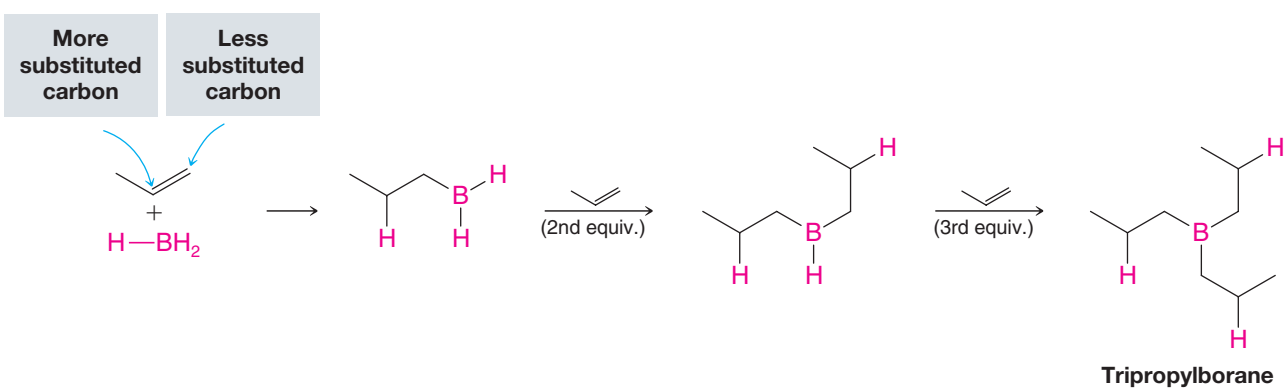


Diborane **THF (tetrahydrofuran)** **BH_3:THF**

Solutions containing the BH_3:THF complex can be obtained commercially. Hydroboration reactions are usually carried out in ethers: either in diethyl ether, $(CH_3CH_2)_2O$, or in some higher molecular weight ether such as "diglyme" [$(CH_3OCH_2CH_2)_2O$, *di*ethylene *gly*col di*me*thyl ether]. Great care must be used in handling diborane and alkylboranes because they ignite spontaneously in air (with a green flame). The solution of BH_3:THF must be used in an inert atmosphere (e.g., argon or nitrogen) and with care.

8.7A Mechanism of Hydroboration

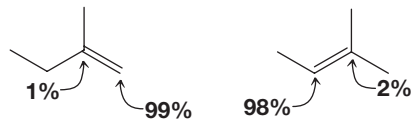
When a terminal alkene such as propene is treated with a solution containing BH_3:THF, the boron hydride adds successively to the double bonds of three molecules of the alkene to form a trialkylborane:



Tripropylborane

- In each addition step ***the boron atom becomes attached to the less substituted carbon atom of the double bond***, and a hydrogen atom is transferred from the boron atom to the other carbon atom of the double bond.
- Hydroboration is **regioselective** and it is **anti-Markovnikov** (the hydrogen atom becomes attached to the carbon atom with fewer hydrogen atoms).

Other examples that illustrate the tendency for the boron atom to become attached to the less substituted carbon atom are shown here. The percentages designate where the boron atom becomes attached.



These percentages, indicating where boron becomes attached in reactions using these starting materials, illustrate the tendency for boron to bond at the less substituted carbon of the double bond.

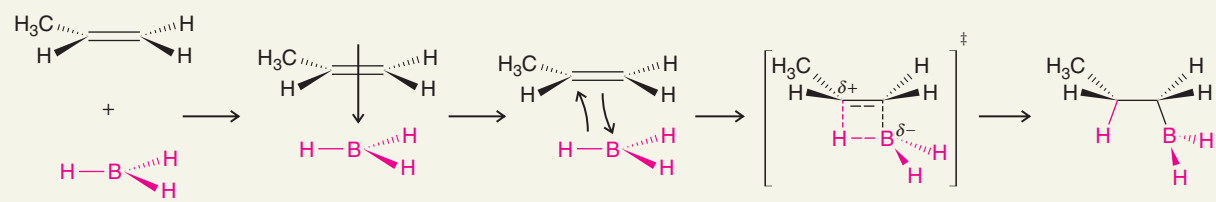
This observed attachment of boron to the less substituted carbon atom of the double bond seems to result in part from **steric factors**—the bulky boron-containing group can approach the less substituted carbon atom more easily.

In the mechanism proposed for hydroboration, addition of BH_3 to the double bond begins with a donation of π electrons from the double bond to the vacant *p* orbital of BH_3 (see the following mechanism). In the next step this complex becomes the addition product by passing through a four-atom transition state in which the boron atom is partially bonded to the less substituted carbon atom of the double bond and one hydrogen atom is partially bonded to the other carbon atom. As this transition state is approached, electrons shift in the direction of the boron atom and away from the more substituted carbon atom of the double bond. This makes the more substituted carbon atom develop a partial positive charge, *and because it bears an electron-releasing alkyl group, it is better able to accommodate this positive charge*. Thus, electronic factors also favor addition of boron at the least substituted carbon.

- Overall, both *electronic* and *steric factors* account for the anti-Markovnikov orientation of the addition.

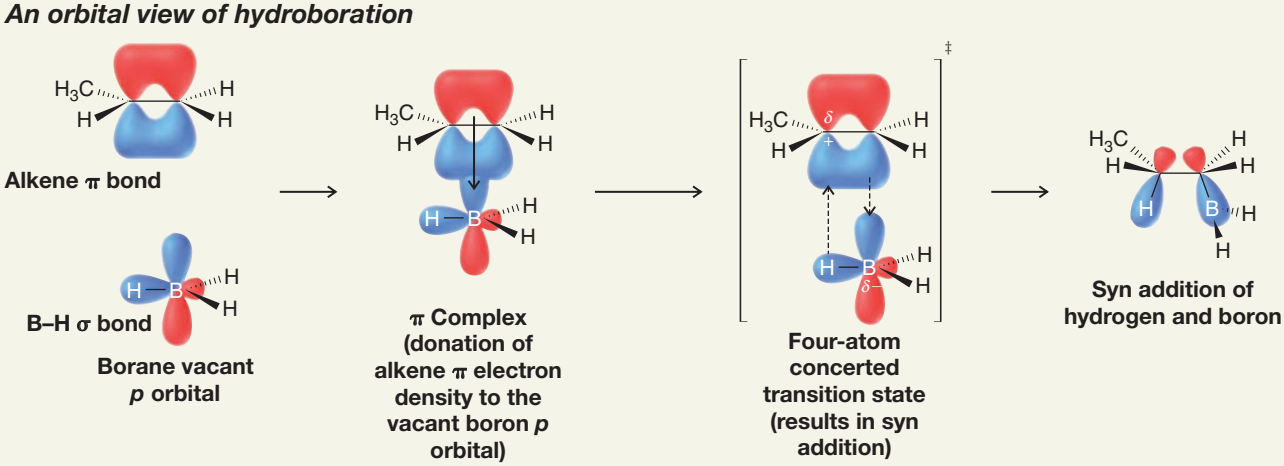
A MECHANISM FOR THE REACTION — Hydroboration

Hydroboration



Addition takes place through the initial formation of a π complex, which changes into a cyclic four-atom transition state with the boron adding to the less hindered carbon atom. The dashed bonds in the transition state represent bonds that are partially formed or partially broken. The transition state results in syn addition of the hydrogen and boron group, leading to an alkylborane. The other B–H bonds of the alkylborane can undergo similar additions, leading finally to a trialkylborane.

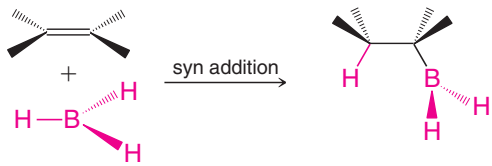
An orbital view of hydroboration



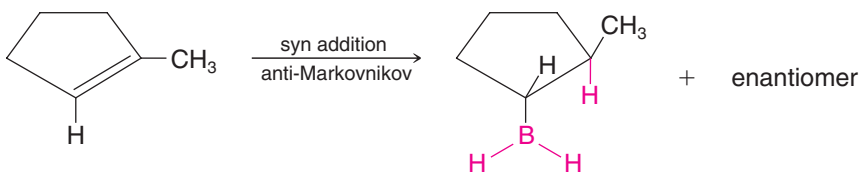
8.7B Stereochemistry of Hydroboration

- The transition state for hydroboration requires that the boron atom and the hydrogen atom add to the same face of the double bond:

Stereochemistry of Hydroboration



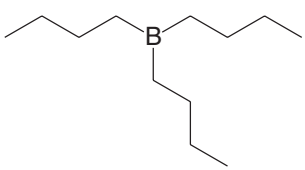
We can see the results of a syn addition in our example involving the hydroboration of 1-methylcyclopentene. Formation of the enantiomer, which is equally likely, results when the boron hydride adds to the top face of the 1-methylcyclopentene ring:



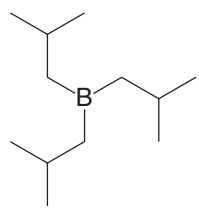
PRACTICE PROBLEM 8.11

Specify the alkene needed for synthesis of each of the following alkylboranes by hydroboration:

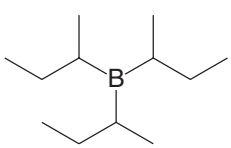
(a)



(b)



(c)



(d) Show the stereochemistry involved in the hydroboration of 1-methylcyclohexene.

PRACTICE PROBLEM 8.12

Treating a hindered alkene such as 2-methyl-2-butene with BH_3:THF leads to the formation of a dialkylborane instead of a trialkylborane. When 2 mol of 2-methyl-2-butene is added to 1 mol of BH_3, the product formed is bis(3-methyl-2-butyl)borane, nicknamed "disiamylborane." Write its structure. Bis(3-methyl-2-butyl)borane is a useful reagent in certain syntheses that require a sterically hindered borane. (The name "disiamyl" comes from "*dis*econdary-*i*so-*amyl*," a completely unsystematic and unacceptable name. The name "amyl" is an old common name for a five-carbon alkyl group.)

8.8 OXIDATION AND HYDROLYSIS OF ALKYLBORANES

The alkylboranes produced in the hydroboration step are usually not isolated. They are oxidized and hydrolyzed to alcohols in the same reaction vessel by the addition of hydrogen peroxide in an aqueous base:

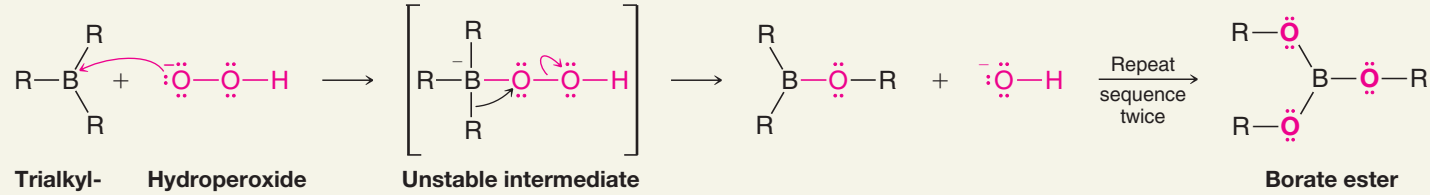
$$R_3B \xrightarrow[\text{Oxidation and hydrolysis}]{H_2O_2,\ \text{aq. NaOH},\ 25\ ^\circ C} 3R{-}OH + B(ONa)_3$$

- **The oxidation and hydrolysis steps take place with retention of configuration** at the carbon initially bearing boron and ultimately bearing the hydroxyl group.

We shall see how this occurs by considering the mechanisms of oxidation and hydrolysis.

Alkylborane oxidation begins with addition of a hydroperoxide anion (HOO^-) to the trivalent boron atom. An unstable intermediate is formed that has a formal negative charge on the boron. Migration of an alkyl group with a pair of electrons from the boron to the adjacent oxygen leads to neutralization of the charge on boron and displacement of a hydroxide anion. The alkyl migration takes place with retention of configuration at the migrating carbon. Repetition of the hydroperoxide anion addition and migration steps occurs twice more until all of the alkyl groups have become attached to oxygen atoms, resulting in a trialkyl borate ester, $B(OR)_3$. The borate ester then undergoes basic hydrolysis to produce three molecules of the alcohol and an inorganic borate anion.

A MECHANISM FOR THE REACTION — Oxidation of Trialkylboranes

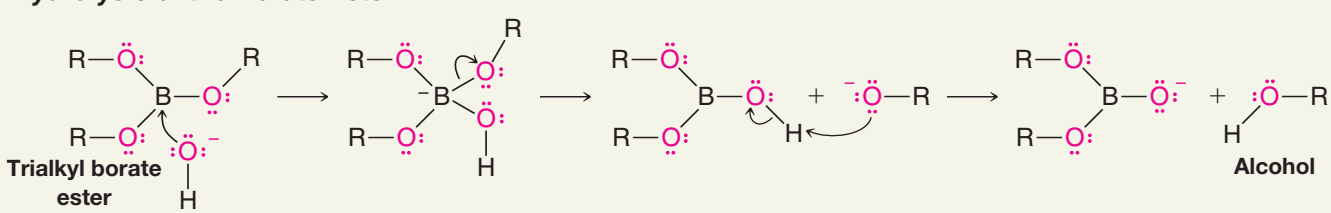


Trialkyl-borane | Hydroperoxide ion | Unstable intermediate | Borate ester

The boron atom accepts an electron pair from the hydroperoxide ion to form an unstable intermediate.

An alkyl group migrates from boron to the adjacent oxygen atom as a hydroxide ion departs. The configuration at the migrating carbon remains unchanged.

Hydrolysis of the Borate Ester



Trialkyl borate ester | Alcohol

Hydroxide anion attacks the boron atom of the borate ester.

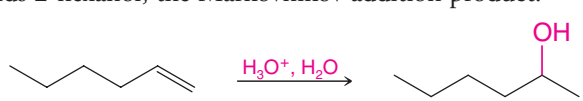
An alkoxide anion departs from the borate anion, reducing the formal change on boron to zero.

Proton transfer completes the formation of one alcohol molecule. The sequence repeats until all three alkoxy groups are released as alcohols and inorganic borate remains.

8.8A Regiochemistry and Stereochemistry of Alkylborane Oxidation and Hydrolysis

- Hydroboration–oxidation reactions are **regioselective**; the net result of hydroboration–oxidation is **anti-Markovnikov** addition of water to an alkene.
- As a consequence, hydroboration–oxidation gives us a method for the preparation of alcohols that cannot normally be obtained through the acid-catalyzed hydration of alkenes or by oxymercuration–demercuration.

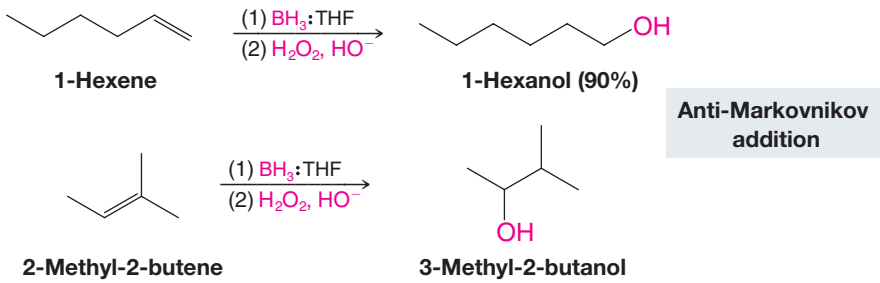
For example, the acid-catalyzed hydration (or oxymercuration–demercuration) of 1-hexene yields 2-hexanol, the Markovnikov addition product.



1-Hexene | 2-Hexanol

Markovnikov addition

In contrast, hydroboration–oxidation of 1-hexene yields 1-hexanol, the anti-Markovnikov product.



- Hydroboration–oxidation reactions are **stereospecific**; the net addition of —H and —OH is **syn**, and if chirality centers are formed, their configuration depends on the stereochemistry of the starting alkene.

Because the oxidation step in the hydroboration–oxidation synthesis of alcohols takes place with retention of configuration, **the hydroxyl group replaces the boron atom where it stands in the alkylboron compound**. The net result of the two steps (hydroboration and oxidation) is the syn addition of —H and —OH. We can review the anti-Markovnikov and syn aspects of hydroboration–oxidation by considering the hydration of 1-methylcyclopentene, as shown in Fig. 8.3.

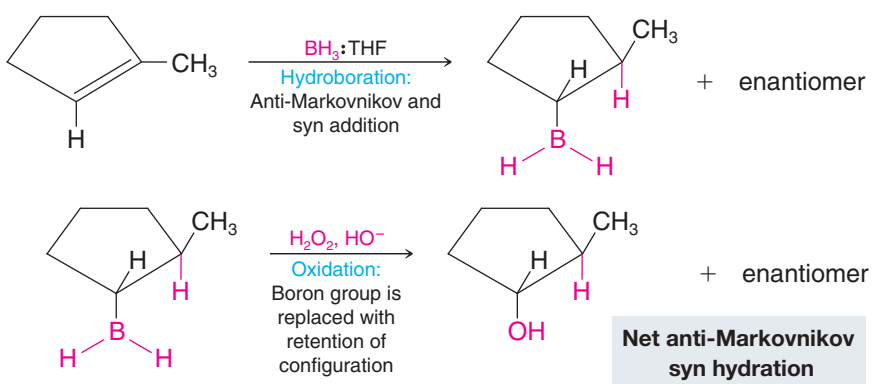
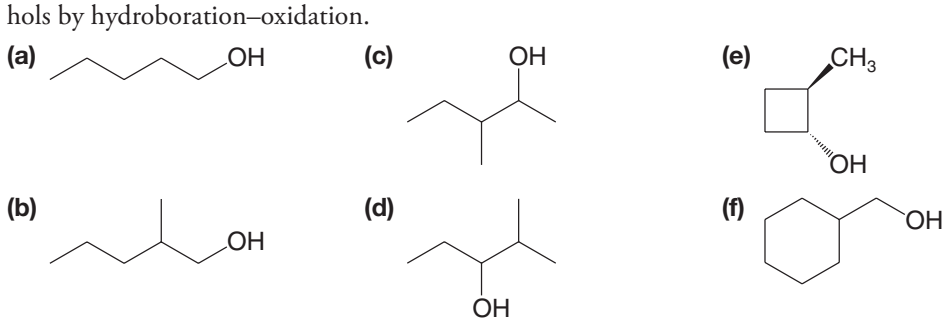


FIGURE 8.3 The hydroboration–oxidation of 1-methylcyclopentene. The first reaction is a syn addition of borane. In this illustration we have shown the boron and hydrogen entering from the bottom side of 1-methylcyclopentene. The reaction also takes place from the top side at an equal rate to produce the enantiomer. In the second reaction the boron atom is replaced by a hydroxyl group with retention of configuration. The product is *trans*-2-methylcyclopentanol, and the overall result is the syn addition of —H and —OH.

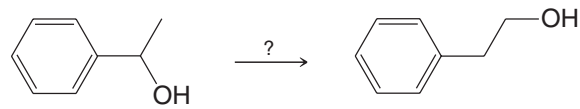
PRACTICE PROBLEM 8.13

Specify the appropriate alkene and reagents for synthesis of each of the following alcohols by hydroboration–oxidation.



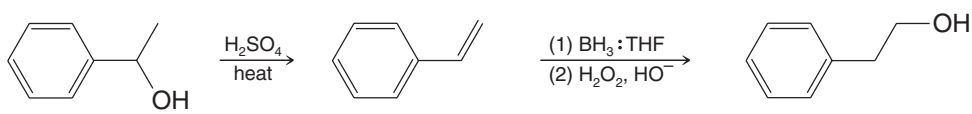
SOLVED PROBLEM 8.3

Outline a method for carrying out the following conversion.



1-Phenylethanol **2-Phenylethanol**

STRATEGY AND ANSWER: Working backward we realize we could synthesize 2-phenylethanol by hydroboration–oxidation of phenylethene (styrene), and that we could make phenylethene by dehydrating 1-phenylethanol.



Phenylethene

8.9 SUMMARY OF ALKENE HYDRATION METHODS

The three methods we have studied for alcohol synthesis by addition reactions to alkenes have different regiochemical and stereochemical characteristics.

1. **Acid-catalyzed hydration of alkenes** takes place with Markovnikov regiochemistry but may lead to a mixture of constitutional isomers if the carbocation intermediate in the reaction undergoes rearrangement to a more stable carbocation.
2. **Oxymercuration–demercuration** occurs with Markovnikov regiochemistry and results in hydration of alkenes without complication from carbocation rearrangement. It is often the preferred choice over acid-catalyzed hydration for Markovnikov addition. The overall stereochemistry of addition in acid-catalyzed hydration and oxymercuration–demercuration is not controlled—they both result in a mixture of cis and trans addition products.
3. **Hydroboration–oxidation** results in **anti-Markovnikov** and syn hydration of an alkene.

The complementary regiochemical and stereochemical aspects of these methods provide useful alternatives when we desire to synthesize a specific alcohol by hydration of an alkene. We summarize them here in Table 8.1.

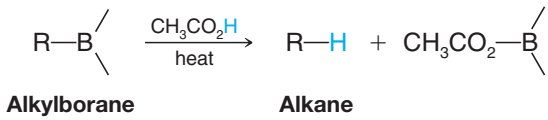
TABLE 8.1 SUMMARY OF METHODS FOR CONVERTING AN ALKENE TO AN ALCOHOL

Reaction	Conditions	Regiochemistry	Stereochemistry[a]	Occurrence of Rearrangements
Acid-catalyzed hydration	cat. HA, H_2O	Markovnikov addition	Not controlled	Frequent
Oxymercuration–demercuration	(1) $Hg(OAc)_2$, THF—H_2O (2) $NaBH_4$, HO^-	Markovnikov addition	Not controlled	Seldom
Hydroboration–oxidation	(1) BH_3:THF (2) H_2O_2, HO^-	Anti-Markovnikov addition	Stereospecific: syn addition of H— and —OH	Seldom

[a]All of these methods produce racemic mixtures in the absence of a chiral influence.

8.10 PROTONOLYSIS OF ALKYLBORANES

Heating an alkylborane with acetic acid causes cleavage of the carbon–boron bond and replacement with hydrogen:



Alkylborane **Alkane**

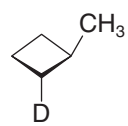
- Protonolysis of an alkylborane takes place with retention of configuration; hydrogen replaces boron **where it stands** in the alkylborane.
- The overall stereochemistry of hydroboration–protonolysis, therefore, is **syn** (like that of the oxidation of alkylboranes).

Hydroboration followed by protonolysis of the resulting alkylborane can be used as an alternative method for hydrogenation of alkenes, although catalytic hydrogenation (Section 7.12) is the more common procedure. Reaction of alkylboranes with deuterated or tritiated acetic acid also provides a very useful way to introduce these isotopes into a compound in a specific way.

PRACTICE PROBLEM 8.14

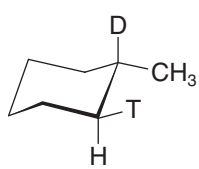
Starting with any needed alkene (or cycloalkene) and assuming you have deuterioacetic acid (CH_3CO_2D) available, outline syntheses of the following deuterium-labeled compounds.

(a) $(CH_3)_2CHCH_2CH_2D$ **(b)** $(CH_3)_2CHCHDCH_3$ **(c)**



(+ enantiomer)

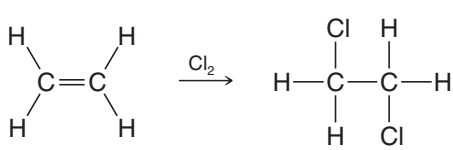
(d) Assuming you also have available BD_3:THF and CH_3CO_2T, can you suggest a synthesis of the following?



(+ enantiomer)

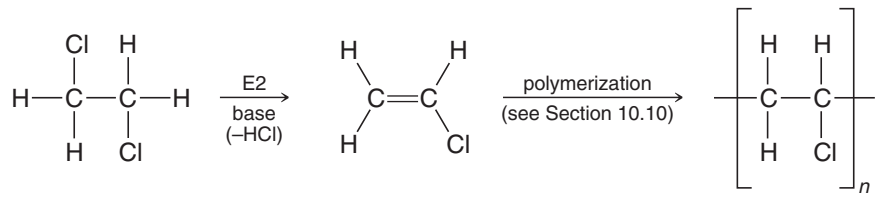
8.11 ELECTROPHILIC ADDITION OF BROMINE AND CHLORINE TO ALKENES

Alkenes react rapidly with bromine and chlorine in nonnucleophilic solvents to form **vicinal dihalides**. An example is the addition of chlorine to ethene.



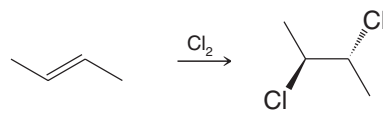
Ethene **1,2-Dichloroethane**

This addition is a useful industrial process because 1,2-dichloroethane can be used as a solvent and can be used to make vinyl chloride, the starting material for poly(vinyl chloride).

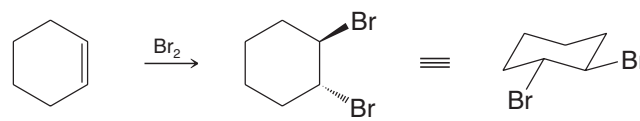


1,2-Dichloroethane **Vinyl chloride** **Poly(vinyl chloride)**

Other examples of the addition of halogens to a double bond are the following:



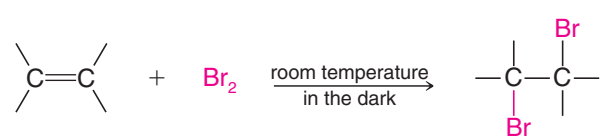
***trans*-2-Butene** ***meso*-1,2-Dichlorobutane**



Cyclohexene ***trans*-1,2-Dibromocyclohexane (racemic)**

These two examples show an aspect of these additions that we shall address later when we examine a mechanism for the reaction: **the addition of halogens is an anti addition to the double bond**.

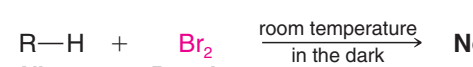
When bromine is used for this reaction, it can serve as a test for the presence of carbon–carbon multiple bonds. If we add bromine to an alkene (or alkyne, see Section 8.17), the red-brown color of the bromine disappears almost instantly as long as the alkene (or alkyne) is present in excess:



An alkene (colorless) **Bromine (red-brown)** ***vic*-Dibromide (a colorless compound)**

Rapid decolorization of Br_2 is a positive test for alkenes and alkynes.

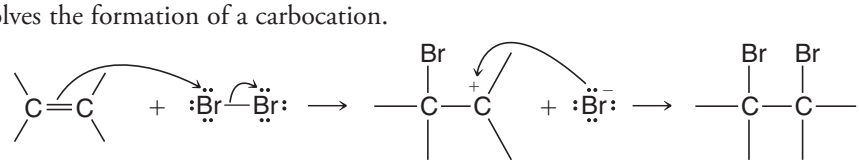
This behavior contrasts markedly with that of **alkanes**. Alkanes do not react appreciably with bromine or chlorine at room temperature and in the absence of light. When alkanes *do* react under those conditions, however, it is by substitution rather than addition and by a mechanism involving radicals that we shall discuss in Chapter 10:



Alkane (colorless) **Bromine (red-brown)** **No appreciable reaction**

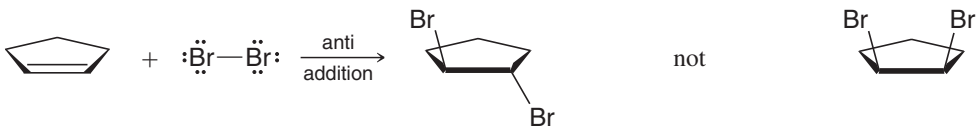
8.11A Mechanism of Halogen Addition

A possible mechanism for the addition of a bromine or chlorine to an alkene is one that involves the formation of a carbocation.



Although this mechanism is similar to ones we have studied earlier, such as the addition of H—X to an alkene, it does not explain an important fact. As we have just seen (in Section 8.11) the addition of bromine or chlorine to an alkene is an **anti addition**.

The addition of bromine to cyclopentene, for example, produces *trans*-1,2-dibromocyclopentane, not *cis*-1,2-dibromocyclopentane.



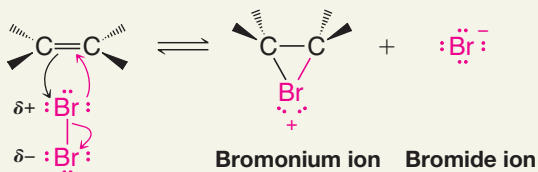
***trans*-1,2-Dibromocyclopentane (as a racemic mixture)** ***cis*-1,2-Dibromocyclohexane (a meso compound)**

A mechanism that explains anti addition is one in which a bromine molecule transfers a bromine atom to the alkene to form a cyclic **bromonium ion** and a bromide ion, as shown in step 1 of "A Mechanism for the Reaction" that follows. The cyclic bromonium ion causes net anti addition, as follows.

In step 2, a bromide ion attacks the back side of either carbon 1 or carbon 2 of the bromonium ion (an S_N2 process) to open the ring and produce the *trans*-1,2-dibromide. Attack occurs from the side **opposite the bromine of the bromonium ion** because attack from this direction is unhindered. Attack at the other carbon of the cyclic bromonium ion produces the enantiomer.

A MECHANISM FOR THE REACTION — Addition of Bromine to an Alkene

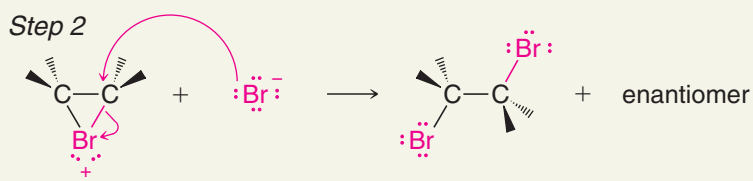
Step 1



Bromonium ion **Bromide ion**

As a bromine molecule approaches an alkene, the electron density of the alkene π bond repels electron density in the closer bromine, polarizing the bromine molecule and making the closer bromine atom electrophilic. The alkene donates a pair of electrons to the closer bromine, causing displacement of the distant bromine atom. As this occurs, the newly bonded bromine atom, due to its size and polarizability, donates an electron pair to the carbon that would otherwise be a carbocation, thereby stabilizing the positive charge by delocalization. The result is a bridged bromonium ion intermediate.

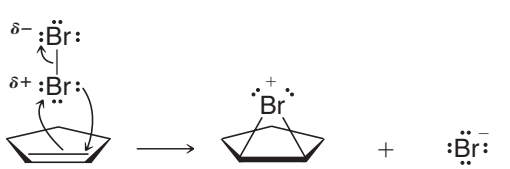
Step 2



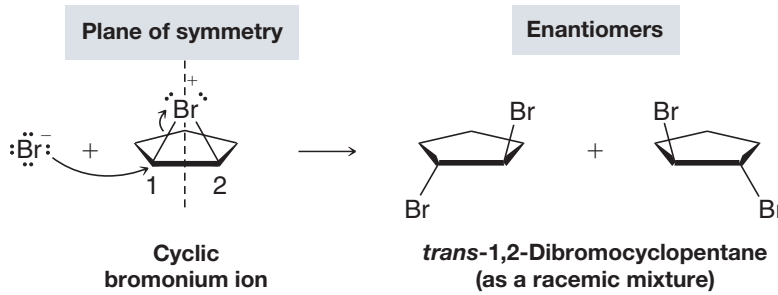
Bromonium ion **Bromide ion** ***vic*-Dibromide**

A bromide anion attacks at the back side of one carbon (or the other) of the bromonium ion in an S_N2 reaction, causing the ring to open and resulting in the formation of a *vic*-dibromide.

This process is shown for the addition of bromine to cyclopentene below.



Cyclic bromonium ion **Bromide ion**



Attack at either carbon of the cyclopentene bromonium ion is equally likely because the cyclic bromonium ion is symmetric. It has a vertical plane of symmetry passing through the bromine atom and halfway between carbons 1 and 2. The *trans*-dibromide, therefore, is formed as a racemic mixture.

THE CHEMISTRY OF... The Sea: A Treasury of Biologically Active Natural Products

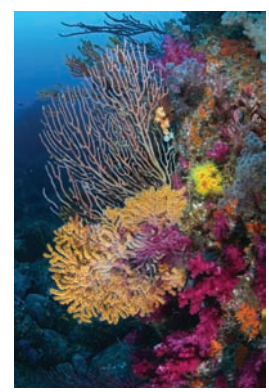
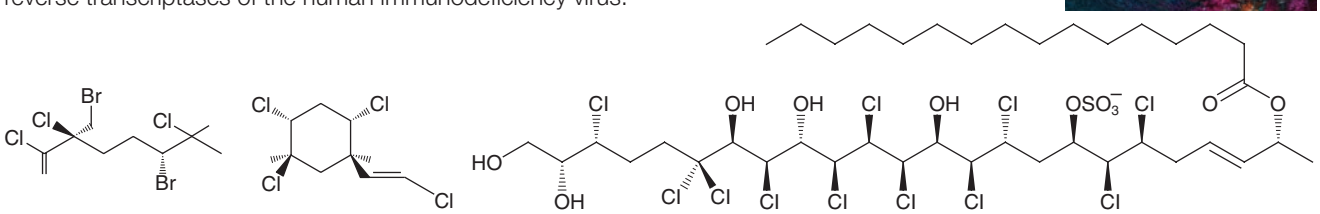
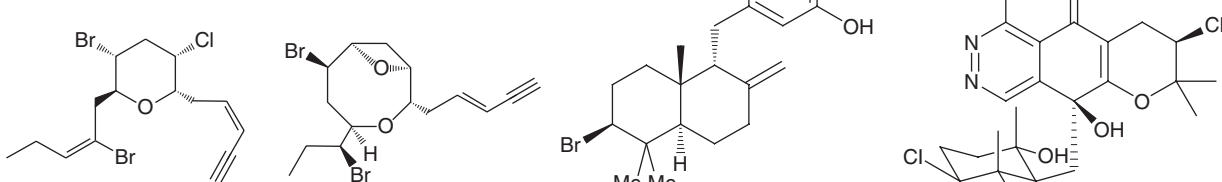


Image Source

The world's oceans are a vast storehouse of dissolved halide ions. The concentration of halides in the ocean is approximately 0.5 M in chloride, 1 mM in bromide, and 1 μM in iodide ions. Perhaps it is not surprising, then, that marine organisms have incorporated halogen atoms into the structures of many of their metabolites. Among these are such intriguing polyhalogenated compounds as halomon, dactylyne, tetrachloromertensene, (3*E*)-laureatin, peyssonol A, azamerone, and a structurally complex member of the polychlorinated sulfolipid family of natural products. Just the sheer number of halogen atoms in these metabolites is cause for wonder. For the organisms that make them, some of these molecules are part of defense mechanisms that serve to promote the species' survival by deterring predators or inhibiting the growth of competing organisms. For humans, the vast resource of marine natural products shows ever-greater potential as a source of new therapeutic agents. Halomon, for example, is in preclinical evaluation as a cytotoxic agent against certain tumor cell types, dactylyne is an inhibitor of pentobarbital metabolism, and peyssonol A is a modest allosteric inhibitor of the reverse transcriptases of the human immunodeficiency virus.



Halomon **Tetrachloromertensene** **A polychlorinated sulfolipid**



Dactylyne **(3*E*)-Laureatin** **Peyssonol A** **Azamerone**

The biosynthesis of certain halogenated marine natural products is intriguing. Some of their halogens appear to have been introduced as *electrophiles* rather than as Lewis bases or nucleophiles, which is their character when they are solutes in seawater. But how do marine organisms transform nucleophilic halide anions into *electrophilic* species for incorporation into their metabolites? It happens that many marine organisms have enzymes called haloperoxidases that convert nucleophilic iodide, bromide, or chloride anions into electrophilic species that react like I^+, Br^+, or Cl^+. In the biosynthetic schemes proposed for some halogenated natural products, positive halogen intermediates are attacked by electrons from the π bond of an alkene or alkyne in an addition reaction.

The final Learning Group Problem for this chapter asks you to propose a scheme for biosynthesis of the marine natural product kumepaloxane by electrophilic halogen addition. Kumepaloxane is a fish antifeedant synthesized by the Guam bubble snail *Haminoea cymbalum*, presumably as a defense mechanism for the snail. In later chapters we shall see other examples of truly remarkable marine natural products, such as brevetoxin B, associated with deadly "red tides," and eleutherobin, a promising anticancer agent.

The mechanisms for addition of Cl_2 and I_2 to alkenes are similar to that for Br_2, involving formation and ring opening of their respective **halonium ions**.

As with bridged mercurinium ions, the bromonium ion does not necessarily have symmetrical charge distribution at its two carbon atoms. If one carbon of the bromonium ion is more highly substituted than the other, and therefore able to stabilize positive charge better, it may bear a greater fraction of positive charge than the other carbon (i.e., the positively charged bromine draws electron density from the two carbon atoms of the ring, but not equally if they are of different substitution). Consequently, the more positively charged carbon may be attacked by the reaction nucleophile more often than the other carbon. However, in reactions with symmetrical reagents (e.g., Br_2, Cl_2, and I_2) there is no observed difference. We shall discuss this point further in Section 8.13, where we will study a reaction where we can discern regioselectivity of attack on a halonium ion by the nucleophile.

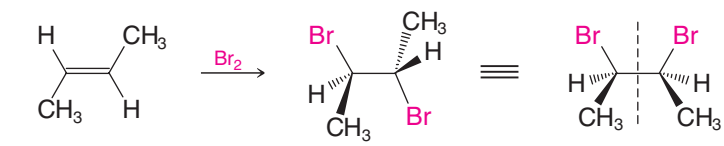
8.12 STEREOSPECIFIC REACTIONS

The anti addition of a halogen to an alkene provides us with an example of what is called a **stereospecific reaction**.

- A **stereospecific reaction** is one where a particular stereoisomer of the starting material yields a specific stereoisomeric form of the product.

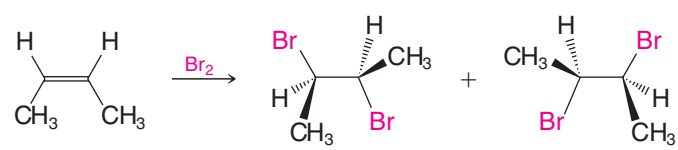
Consider the reactions of *cis*- and *trans*-2-butene with bromine shown below. When *trans*-2-butene adds bromine, the product is the meso compound, (2*R*,3*S*)-2,3-dibromobutane. When *cis*-2-butene adds bromine, the product is a *racemic mixture* of (2*R*,3*R*)-2,3-dibromobutane and (2*S*,3*S*)-2,3-dibromobutane:

Reaction 1



***trans*-2-Butene** **(2*R*,3*S*)-2,3-Dibromobutane (a meso compound)**

Reaction 2



***cis*-2-Butene** **(2*R*,3*R*)** **(2*S*,3*S*)**

(a pair of enantiomers)

The reactants *cis*-2-butene and *trans*-2-butene are stereoisomers; they are *diastereomers*. The product of reaction 1, (2*R*,3*S*)-2,3-dibromobutane, is a meso compound, and it is a stereoisomer of both of the products of reaction 2 (the enantiomeric 2,3-dibromobutanes). Thus, by definition, both reactions are stereospecific. One stereoisomeric form of the reactant (e.g., *trans*-2-butene) gives one product (the meso compound), whereas the other stereoisomeric form of the reactant (*cis*-2-butene) gives a stereoisomerically different product (the enantiomers).

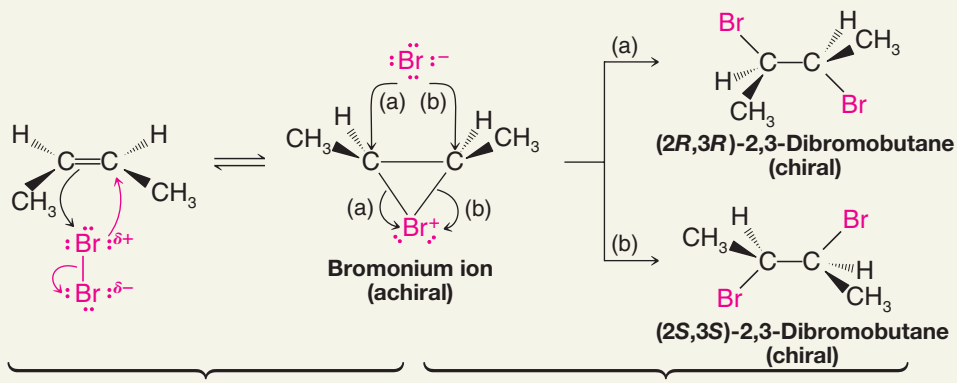
We can better understand the results of these two reactions if we examine their mechanisms. The first mechanism in the following box shows how *cis*-2-butene adds bromine to yield intermediate bromonium ions that are achiral. (The bromonium ion has a plane of symmetry.) These bromonium ions can then react with bromide ions by either path (a) or path (b). Reaction by path (a) yields one 2,3-dibromobutane enantiomer; reaction by

path (b) yields the other enantiomer. The reaction occurs at the same rate by either path; therefore, the two enantiomers are produced in equal amounts (as a racemic form).

The second mechanism in the box shows how *trans*-2-butene reacts at the bottom face to yield an intermediate bromonium ion that is chiral. (Reaction at the other face would produce the enantiomeric bromonium ion.) Reaction of this chiral bromonium ion (or its enantiomer) with a bromide ion either by path (a) or by path (b) yields the same achiral product, *meso*-2,3-dibromobutane.

THE STEREOCHEMISTRY OF THE REACTION... Addition of Bromine to *cis*- and *trans*-2-Butene

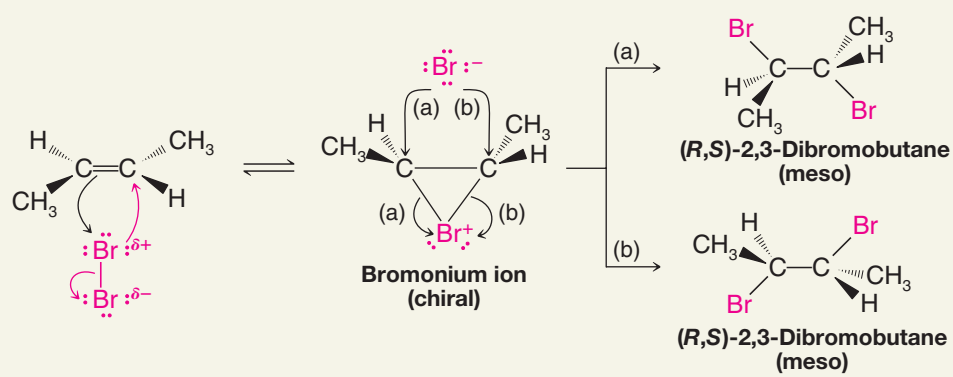
cis-2-Butene reacts with bromine to yield the enantiomeric 2,3-dibromobutanes by the following mechanism:



***cis*-2-Butene reacts with bromine to yield an achiral bromonium ion and a bromide ion. [Reaction at the other face of the alkene (top) would yield the same bromonium ion.]**

The bromonium ion reacts with the bromide ions at equal rates by paths (a) and (b) to yield the two enantiomers in equal amounts (i.e., as the racemic form).

trans-2-Butene reacts with bromine to yield *meso*-2,3-dibromobutane.



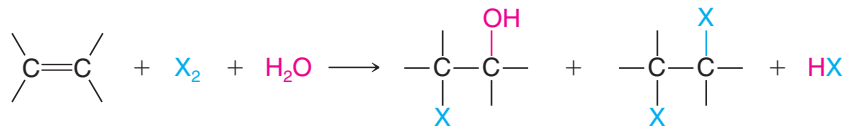
***trans*-2-Butene reacts with bromine to yield chiral bromonium ions and bromide ions. [Reaction at the other face (top) would yield the enantiomer of the bromonium ion as shown here.]**

When the bromonium ions react by either path (a) or path (b), they yield the *same* achiral meso compound. (Reaction of the enantiomer of the intermediate bromonium ion would produce the same result.)

8.13 HALOHYDRIN FORMATION

- When the halogenation of an alkene is carried out in aqueous solution, rather than in a non-nucleophilic solvent, the major product is a **halohydrin** (also called a halo alcohol) instead of a *vic*-dihalide.

Molecules of water react with the halonium ion intermediate as the predominant nucleophile because they are in high concentration (as the solvent). The result is formation of a halohydrin as the major product. If the halogen is bromine, it is called a **bromohydrin**, and if chlorine, a **chlorohydrin**.

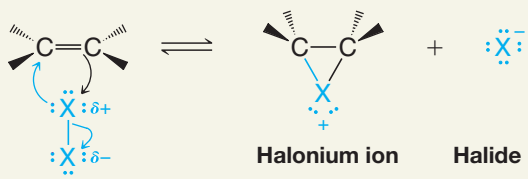


X = Cl or Br | Halohydrin (major) | *vic*-Dihalide (minor)

Halohydrin formation can be described by the following mechanism.

A MECHANISM FOR THE REACTION — Halohydrin Formation from an Alkene

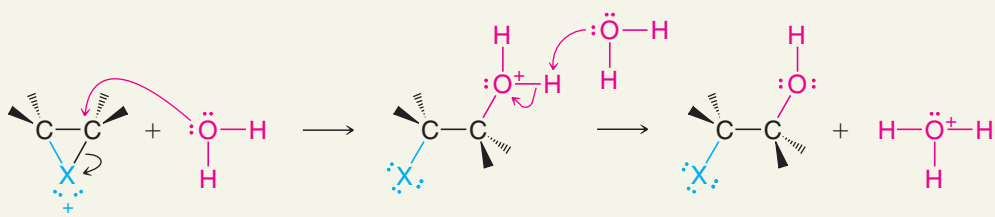
Step 1



Halonium ion | Halide ion

This step is the same as for halogen addition to an alkene (see Section 8.11A).

Steps 2 and 3



Halonium ion | Protonated halohydrin | Halohydrin

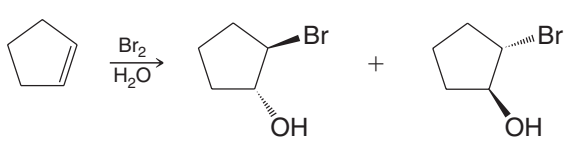
Here, however, a water molecule acts as the nucleophile and attacks a carbon of the ring, causing the formation of a protonated halohydrin.

The protonated halohydrin loses a proton (it is transferred to a molecule of water). This step produces the halohydrin and hydronium ion.

The first step is the same as that for halogen addition. In the second step, however, the two mechanisms differ. In halohydrin formation, water acts as the nucleophile and attacks one carbon atom of the halonium ion. The three-membered ring opens, and a protonated halohydrin is produced. Loss of a proton then leads to the formation of the halohydrin itself.

PRACTICE PROBLEM 8.15

Write a mechanism to explain the following reaction.

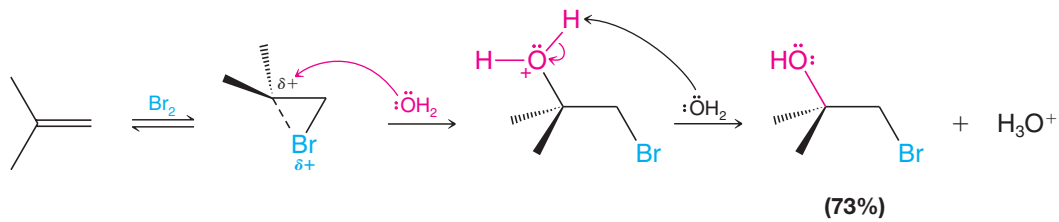


(as a racemic mixture)

- If the alkene is unsymmetrical, the halogen ends up on the carbon atom with the greater number of hydrogen atoms.

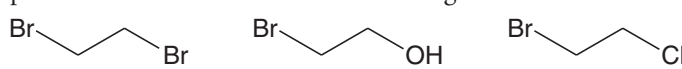
Bonding in the intermediate bromonium ion is *unsymmetrical*. The more highly substituted carbon atom bears the greater positive charge because it resembles the more stable carbocation. Consequently, water attacks this carbon atom preferentially. The greater positive charge on the tertiary carbon permits a pathway with a lower free energy of activation even though attack at the primary carbon atom is less hindered:

This bromonium ion is bridged asymmetrically because the 3° carbon can accommodate more positive charge than the 1° carbon.



(73%)

PRACTICE PROBLEM 8.16 When ethene gas is passed into an aqueous solution containing bromine and sodium chloride, the products of the reaction are the following:



Write mechanisms showing how each product is formed.

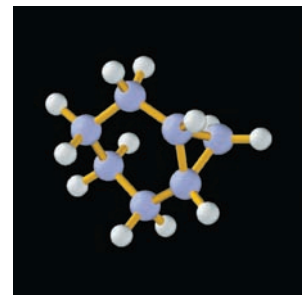
THE CHEMISTRY OF... Citrus-Flavored Soft Drinks

In Chapter 7 we discussed how double bonds within unsaturated fats could be hydrogenated to change their physical properties to convert materials like butter into margarine. It turns out that similar unsaturated fats can be used in the food industry in other ways, as well! For example, the properties of some unsaturated emulsifying agents can be enhanced if just a small percentage of their double bonds are brominated using Br_2, via the chemistry in this chapter. The increased density of these emulsifying agents, due to the bromine atoms, helps match the density of water more closely and creates a more stable, cloudy, colloidal-like mixture. The real value of this process, however, lies in what can now occur: other lipid-soluble molecules, such as many citrus flavors, can be used in aqueous foods due to the solubilizing action of these higher-density emulsifiers. The results are seen in beverages such as Mountain Dew, Squirt, or Fresca, soft drinks that all take advantage of this chemistry and that can be identified by the presence of "brominated vegetable oil" in the listing of ingredients.

8.14 DIVALENT CARBON COMPOUNDS: CARBENES

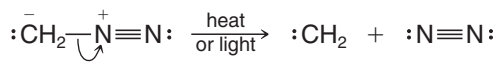
There are compounds in which a carbon has an unshared electron pair and only *two bonds*. These divalent carbon compounds are called **carbenes**. Carbenes are neutral and have no formal charge. Most carbenes are highly unstable compounds that have only a fleeting existence. Soon after carbenes are formed, they usually react with another molecule. The reactions of carbenes are especially interesting because, in many instances, the reactions show a remarkable degree of stereospecificity. The reactions of carbenes are also of great synthetic use in the preparation of compounds that have three-membered rings such as bicyclo[4.1.0]heptane, shown on the next page.

8.14A Structure and Reactions of Methylene



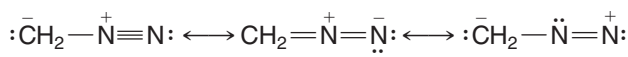
Bicyclo[4.1.0]heptane

The simplest carbene is the compound called **methylene** ($:CH_2$). Methylene can be prepared by the decomposition of diazomethane (CH_2N_2), a very poisonous yellow gas. This decomposition can be accomplished by heating diazomethane (thermolysis) or by irradiating it with light of a wavelength that it can absorb (photolysis):



Diazomethane **Methylene** **Nitrogen**

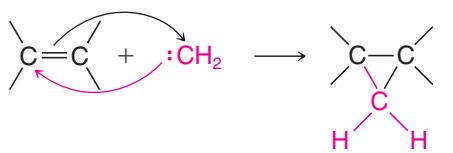
The structure of diazomethane is actually a resonance hybrid of three structures:



I **II** **III**

We have chosen resonance structure **I** to illustrate the decomposition of diazomethane because with **I** it is readily apparent that heterolytic cleavage of the carbon–nitrogen bond results in the formation of methylene and molecular nitrogen.

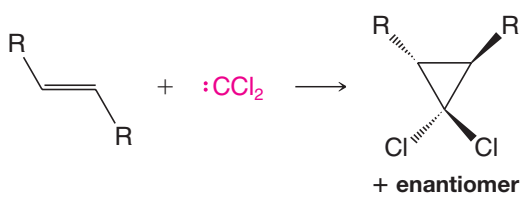
Methylene reacts with alkenes by adding to the double bond to form cyclopropanes:



Alkene **Methylene** **Cyclopropane**

8.14B Reactions of Other Carbenes: Dihalocarbenes

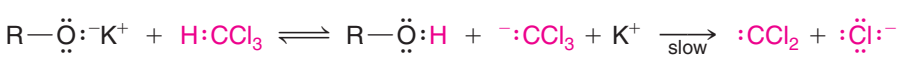
Dihalocarbenes are also frequently employed in the synthesis of cyclopropane derivatives from alkenes. Most reactions of dihalocarbenes are **stereospecific**:



+ enantiomer

The addition of $:CX_2$ is stereospecific. If the R groups of the alkene are trans, they will be trans in the product. (If the R groups were initially cis, they would be cis in the product.)

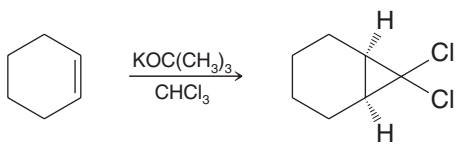
Dichlorocarbene can be synthesized by an ***α elimination*** of hydrogen chloride from chloroform. [The hydrogen of chloroform is mildly acidic ($pK_a \approx 24$) due to the inductive effect of the chlorine atoms.] This reaction resembles the β-elimination reactions by which alkenes are synthesized from alkyl halides (Section 6.15), except that the leaving group is on the same carbon as the proton that is removed.



Dichlorocarbene

Compounds *with a β hydrogen* react by β elimination preferentially. Compounds with no β hydrogen but with an α hydrogen (such as chloroform) react by α elimination.

A variety of cyclopropane derivatives have been prepared by generating dichlorocarbene in the presence of alkenes. Cyclohexene, for example, reacts with dichlorocarbene generated by treating chloroform with potassium *tert*-butoxide to give a bicyclic product:



7,7-Dichlorobicyclo[4.1.0]heptane (59%)

8.14C Carbenoids: The Simmons–Smith Cyclopropane Synthesis

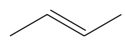
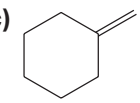
A useful cyclopropane synthesis was developed by H. E. Simmons and R. D. Smith of the DuPont Company. In this synthesis diiodomethane and a zinc–copper couple are stirred together with an alkene. The diiodomethane and zinc react to produce a carbene-like species called a **carbenoid**:

$$CH_2I_2 + Zn(Cu) \longrightarrow ICH_2ZnI$$

A carbenoid

The carbenoid then brings about the stereospecific addition of a CH_2 group directly to the double bond.

PRACTICE PROBLEM 8.17 What products would you expect from each of the following reactions?

(a)  $\xrightarrow[CHCl_3]{t\text{-BuOK}}$ **(b)**  $\xrightarrow[CHBr_3]{t\text{-BuOK}}$ **(c)**  $\xrightarrow[\text{diethyl ether}]{CH_2I_2/Zn(Cu)}$

PRACTICE PROBLEM 8.18 Starting with cyclohexene and using any other needed reagents, outline a synthesis of 7,7-dibromobicyclo[4.1.0]heptane.

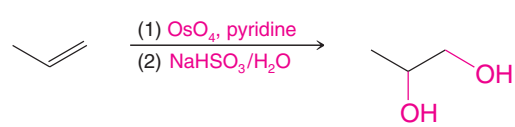
PRACTICE PROBLEM 8.19 Treating cyclohexene with 1,1-diiodoethane and a zinc–copper couple leads to two isomeric products. What are their structures?

8.15 OXIDATION OF ALKENES: SYN 1,2-DIHYDROXYLATION

Alkenes undergo a number of reactions in which the carbon–carbon double bond is oxidized.

- **1,2-Dihydroxylation** is an important oxidative addition reaction of alkenes.

Osmium tetroxide is widely used to synthesize **1,2-diols** (the products of 1,2-**dihydroxylation**, sometimes also called **glycols**). Potassium permanganate can also be used, although because it is a stronger oxidizing agent it is prone to cleave the diol through further oxidation (Section 8.15).



Propene — **1,2-Propanediol (propylene glycol)**

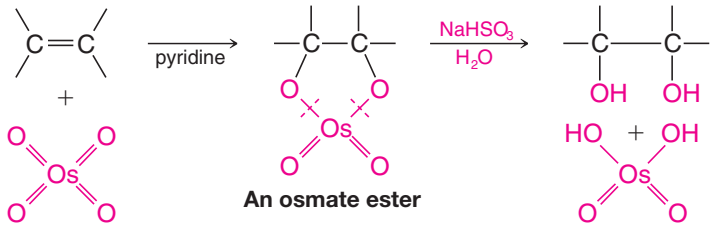
$$CH_2{=}CH_2 + KMnO_4 \xrightarrow[H_2O,\ \text{cold}]{HO^-} \text{HO}\!-\!\text{CH}_2\text{CH}_2\!-\!\text{OH}$$

Ethene — **1,2-Ethanediol (ethylene glycol)**

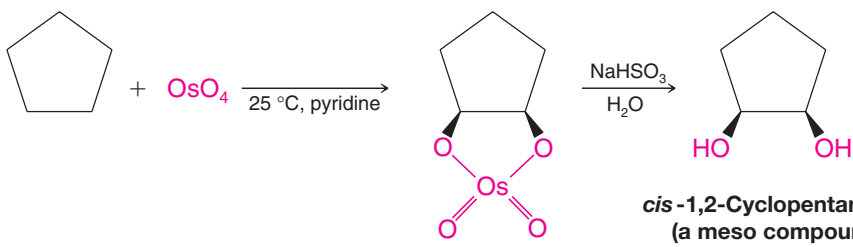
8.15A Mechanism for Syn Dihydroxylation of Alkenes

- The mechanism for the formation of a 1,2-diol by osmium tetroxide involves a cyclic intermediate that results in **syn addition** of the oxygen atoms (see below).

After formation of the cyclic intermediate with osmium, cleavage at the oxygen–metal bonds takes place without altering the stereochemistry of the two new C—O bonds.

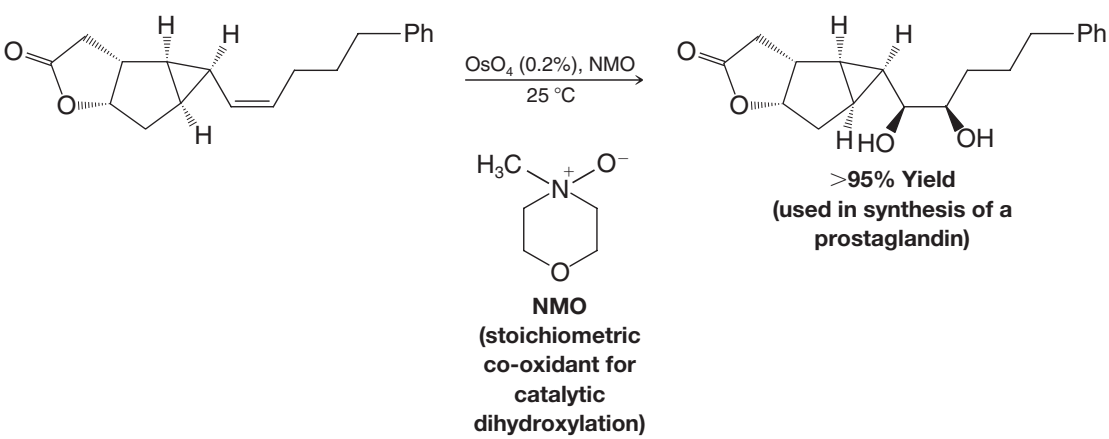


The syn stereochemistry of this dihydroxylation can readily be observed by the reaction of cyclopentene with osmium tetroxide. The product is *cis*-1,2-cyclopentanediol.



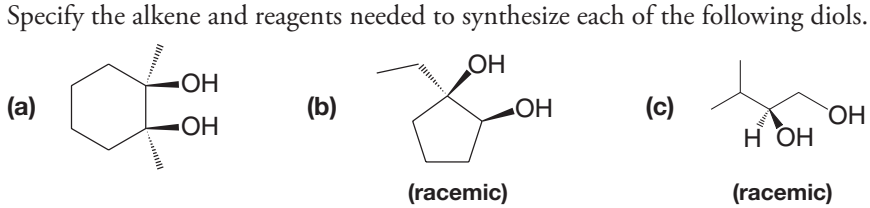
Osmium tetroxide is highly toxic, volatile, and very expensive. For these reasons, methods have been developed that permit OsO_4 to be used *catalytically* in conjunction with a co-oxidant.* A very small molar percentage of OsO_4 is placed in the reaction mixture to do the dihydroxylation step, while a stoichiometric amount of co-oxidant reoxidizes the OsO_4 as it is used in each cycle, allowing oxidation of the alkene to continue until all has been converted to the diol. *N*-Methylmorpholine *N*-oxide (NMO) is one of the most commonly used co-oxidants with catalytic OsO_4. The method was discovered at Upjohn Corporation in the context of reactions for synthesis of a prostaglandin† (Section 23.5):

Catalytic OsO_4 1,2-Dihydroxylation



PRACTICE PROBLEM 8.20

Specify the alkene and reagents needed to synthesize each of the following diols.



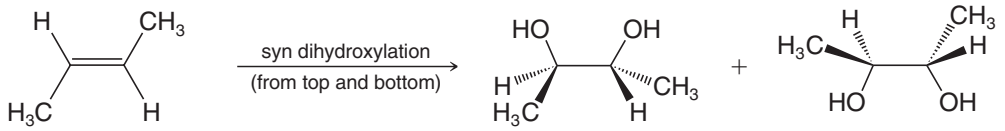
*See Nelson, D. W., et al., *J. Am. Chem. Soc.* **1997**, *119*, 1840–1858; and Corey, E. J., et al., *J. Am. Chem. Soc.* **1996**, *118*, 319–329.

†Van Rheenan, V., Kelley, R. C., and Cha, D. Y., *Tetrahedron Lett.* **1976**, *25*, 1973.

SOLVED PROBLEM 8.4

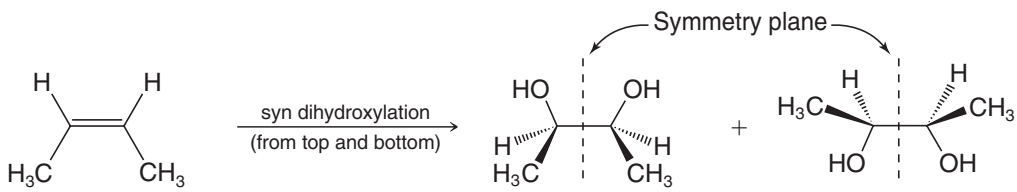
Explain the following facts: Treating (*Z*)-2-butene with OsO_4 in pyridine and then $NaHSO_3$ in water gives a diol that is optically inactive and cannot be resolved. Treating (*E*)-2-butene with the same reagents gives a diol that is optically inactive but can be resolved into enantiomers.

STRATEGY AND ANSWER: Recall that the reaction in either instance results in syn dihydroxylation of the double bond of each compound. Syn dihydroxylation of (*E*)-2-butene gives a pair of enantiomers, while syn dihydroxylation of (*Z*)-2-butene gives a single product that is a meso compound.



(*E*)-2-Butene

Enantiomers (separable and when separated, optically active)



(*Z*)-2-Butene

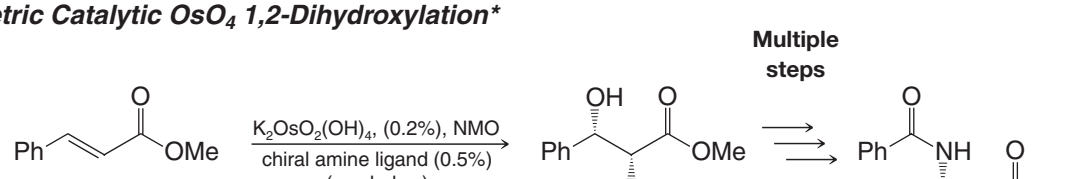
Identical (a meso compound)

THE CHEMISTRY OF... Catalytic Asymmetric Dihydroxylation

SHARPLESS shared the 2001 Nobel Prize in Chemistry for his development of asymmetric oxidation methods.

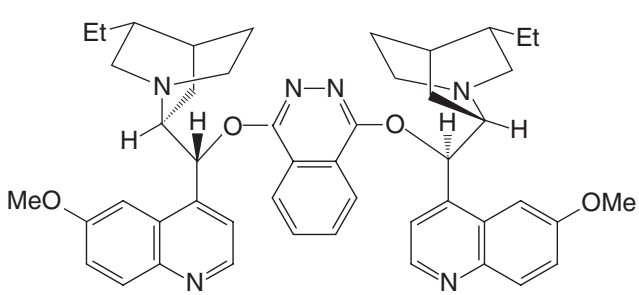
Methods for catalytic *asymmetric* **syn dihydroxylation** have been developed that significantly extend the synthetic utility of dihydroxylation. K. B. Sharpless (The Scripps Research Institute) and co-workers discovered that addition of a chiral amine to the oxidizing mixture leads to enantioselective catalytic syn dihydroxylation. Asymmetric dihydroxylation has become an important and widely used tool in the synthesis of complex organic molecules. In recognition of this and other advances in asymmetric oxidation procedures developed by his group (Section 11.13), Sharpless was awarded half of the 2001 Nobel Prize in Chemistry. (The other half of the 2001 prize was awarded to W. Knowles and R. Noyori for their development of catalytic asymmetric reduction reactions; see Section 7.13A.) The following reaction, involved in an enantioselective synthesis of the side chain of the anticancer drug paclitaxel (Taxol), serves to illustrate Sharpless's catalytic asymmetric dihydroxylation. The example utilizes a catalytic amount of $K_2OsO_2(OH)_4$, an OsO_4 equivalent, a chiral amine ligand to induce enantioselectivity, and NMO as the stoichiometric co-oxidant. The product is obtained in 99% enantiomeric excess (ee):

*Asymmetric Catalytic OsO_4 1,2-Dihydroxylation**

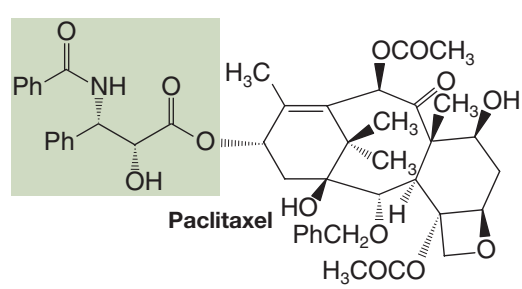


99% ee (72% yield)

Paclitaxel side chain



A chiral amine ligand used in catalytic asymmetric dihydroxylation



Paclitaxel

*(*Adapted with permission from Sharpless et al., The Journal of Organic Chemistry, Vol. 59, p. 5104, 1994. Copyright 1994 American Chemical Society.)*

8.16 OXIDATIVE CLEAVAGE OF ALKENES

Alkenes can be **oxidatively cleaved** using potassium permanganate or ozone (as well as by other reagents). Potassium permanganate ($KMnO_4$) is used when strong oxidation is needed. Ozone (O_3) is used when mild oxidation is desired. [Alkynes and aromatic rings are also oxidized by $KMnO_4$ and O_3 (Sections 8.19 and 15.13D).]

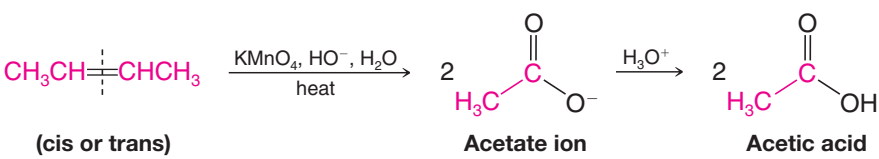
8.16A Cleavage with Hot Basic Potassium Permanganate

- Treatment with hot basic potassium permanganate oxidatively cleaves the double bond of an alkene.

Cleavage is believed to occur via a cyclic intermediate similar to the one formed with osmium tetroxide (Section 8.15A) and intermediate formation of a 1,2-diol.

- Alkenes with monosubstituted carbon atoms are oxidatively cleaved to salts of carboxylic acids.
- Disubstituted alkene carbons are oxidatively cleaved to ketones.
- Unsubstituted alkene carbons are oxidized to carbon dioxide.

The following examples illustrate the results of potassium permanganate cleavage of alkenes with different substitution patterns. In the case where the product is a carboxylate salt, an acidification step is required to obtain the carboxylic acid.



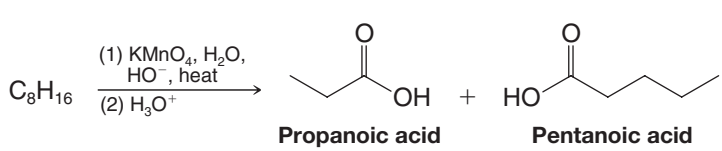
One of the uses of potassium permanganate, other than for oxidative cleavage, is as a **chemical test for unsaturation** in an unknown compound.

- If an alkene is present (or an alkyne, Section 8.19), the purple color of a potassium permanganate solution is discharged and a brown precipitate of manganese dioxide (MnO_2) forms as the oxidation takes place.

The oxidative cleavage of alkenes has also been used to establish the location of the double bond in an alkene chain or ring. The reasoning process requires us to think backward much as we do with retrosynthetic analysis. Here we are required to work backward from the products to the reactant that might have led to those products. We can see how this might be done with the following example.

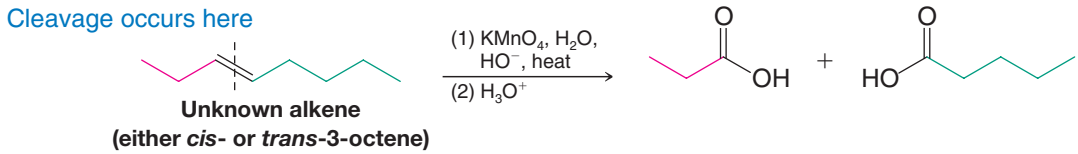
SOLVED PROBLEM 8.5

An unknown alkene with the formula C_8H_{16} was found, on oxidation with hot basic permanganate, to yield a three-carbon carboxylic acid (propanoic acid) and a five-carbon carboxylic acid (pentanoic acid). What was the structure of this alkene?



(continues on next page)

STRATEGY AND ANSWER: The carbonyl groups in the products are the key to seeing where the oxidative cleavage occurred. Therefore, oxidative cleavage must have occurred as follows, and the unknown alkene must have been *cis*- or *trans*-3-octene, which is consistent with the molecular formula given.

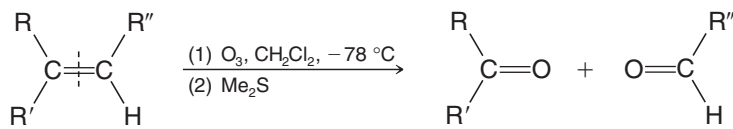


Unknown alkene
(either *cis*- or *trans*-3-octene)

8.16B Cleavage with Ozone

- The most useful method for cleaving alkenes is to use ozone (O_3).

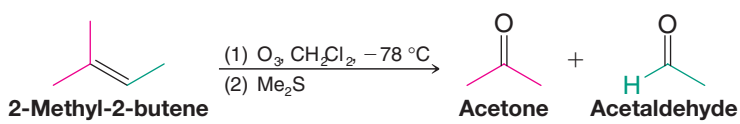
Ozonolysis consists of bubbling ozone into a very cold (−78°C) solution of the alkene in CH_2Cl_2, followed by treatment of the solution with dimethyl sulfide (or zinc and acetic acid). The overall result is as follows:



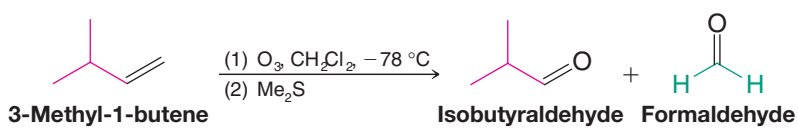
The reaction is useful as a synthetic tool, as well as a method for determining the location of a double bond in an alkene by reasoning backward from the structures of the products.

- The overall process (above) results in alkene cleavage at the double bond, with each carbon of the double bond becoming doubly bonded to an oxygen atom.

The following examples illustrate the results for each type of alkene carbon.



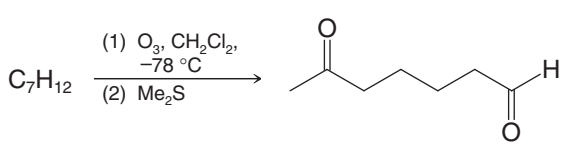
2-Methyl-2-butene **Acetone** **Acetaldehyde**



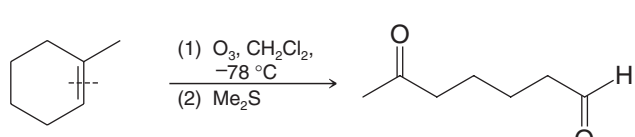
3-Methyl-1-butene **Isobutyraldehyde** **Formaldehyde**

SOLVED PROBLEM 8.6

Give the structure of an unknown alkene with the formula C_7H_{12} that undergoes ozonolysis to yield, after acidification, *only the following product*:



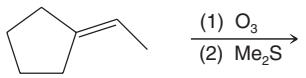
STRATEGY AND ANSWER: Since there is only a single product containing the same number of carbon atoms as the reactant, the only reasonable explanation is that the reactant has a double bond contained in a ring. Ozonolysis of the double bond opens the ring:

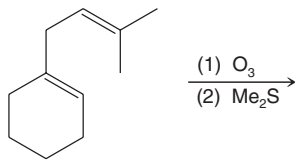


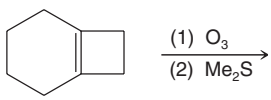
Unknown alkene
(1-methylcyclohexene)

PRACTICE PROBLEM 8.21

Predict the products of the following ozonolysis reactions.

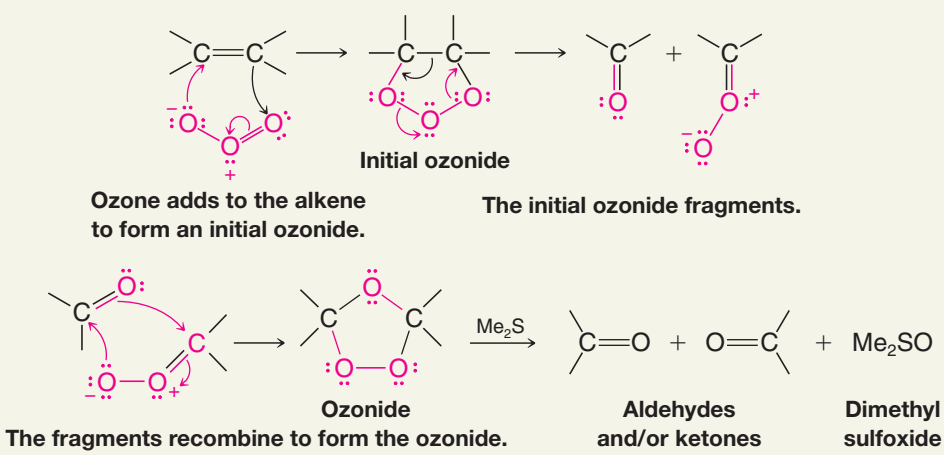
(a) 

(c) 

(b) 

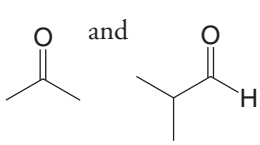
The mechanism of ozone addition to alkenes begins with formation of unstable compounds called *initial ozonides* (sometimes called molozonides). The process occurs vigorously and leads to spontaneous (and sometimes noisy) rearrangement to compounds known as **ozonides.** The rearrangement is believed to occur with dissociation of the initial ozonide into reactive fragments that recombine to yield the ozonide. Ozonides are very unstable compounds, and low-molecular-weight ozonides often explode violently.

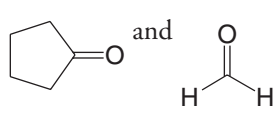
A MECHANISM FOR THE REACTION — Ozonolysis of an Alkene

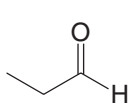


PRACTICE PROBLEM 8.22

Write the structures of the alkenes that would yield the following carbonyl compounds when treated with ozone and then with dimethyl sulfide.

(a)  and

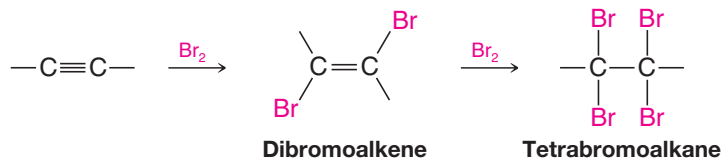
(c)  and

(b) 

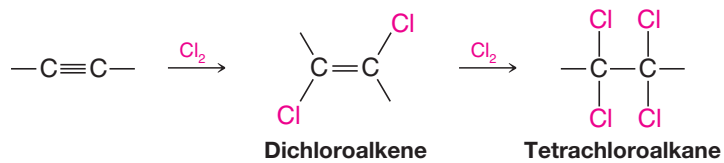
(2 mol is produced from 1 mol of alkene)

8.17 ELECTROPHILIC ADDITION OF BROMINE AND CHLORINE TO ALKYNES

- Alkynes show the same kind of addition reactions with chlorine and bromine that alkenes do.
- With alkynes **the addition may occur once or twice**, depending on the number of molar equivalents of halogen we employ:

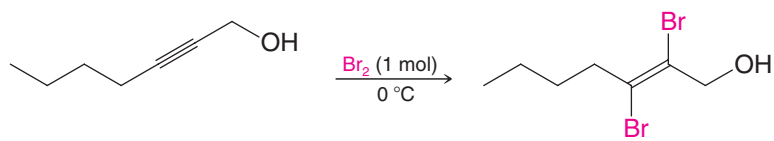


Dibromoalkene **Tetrabromoalkane**



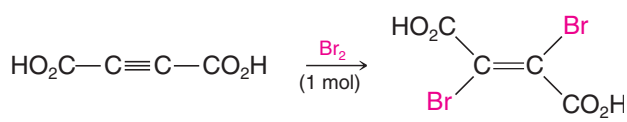
Dichloroalkene **Tetrachloroalkane**

It is usually possible to prepare a dihaloalkene by simply adding one molar equivalent of the halogen:



- Addition of one molar equivalent of chlorine or bromine to an alkyne generally results in anti addition and yields a *trans*-dihaloalkene.

Addition of bromine to acetylenedicarboxylic acid, for example, gives the trans isomer in 70% yield:

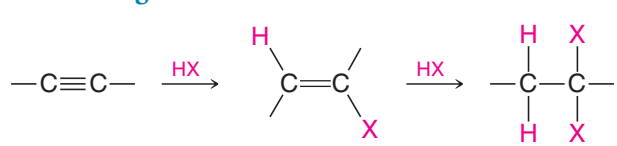


Acetylenedicarboxylic acid **(70%)**

PRACTICE PROBLEM 8.23 Alkenes are more reactive than alkynes toward addition of electrophilic reagents (i.e., Br_2, Cl_2, or HCl). Yet when alkynes are treated with one molar equivalent of these same electrophilic reagents, it is easy to stop the addition at the "alkene stage." This appears to be a paradox and yet it is not. Explain.

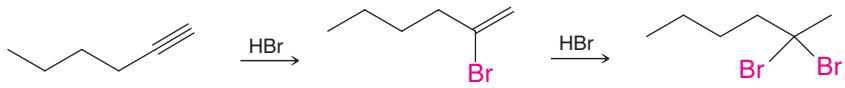
8.18 ADDITION OF HYDROGEN HALIDES TO ALKYNES

- Alkynes react with one molar equivalent of hydrogen chloride or hydrogen bromide to form haloalkenes, and with two molar equivalents to form geminal dihalides.
- Both additions are **regioselective** and follow **Markovnikov's rule**:



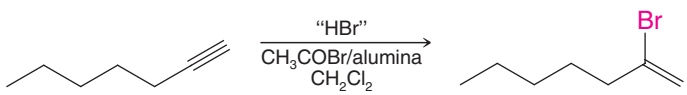
Haloalkene ***gem*-Dihalide**

The hydrogen atom of the hydrogen halide becomes attached to the carbon atom that has the greater number of hydrogen atoms. 1-Hexyne, for example, reacts slowly with one molar equivalent of hydrogen bromide to yield 2-bromo-1-hexene and with two molar equivalents to yield 2,2-dibromohexane:



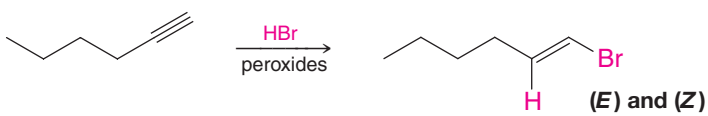
2-Bromo-1-hexene **2,2-Dibromohexane**

The addition of HBr to an alkyne can be facilitated by using acetyl bromide (CH_3COBr) and alumina instead of aqueous HBr. Acetyl bromide acts as an HBr precursor by reacting with the alumina to generate HBr. For example, 1-heptyne can be converted to 2-bromo-1-heptene in good yield using this method:



(82%)

Anti-Markovnikov addition of hydrogen bromide to alkynes occurs when peroxides are present in the reaction mixture. These reactions take place through a free-radical mechanism (Section 10.10):



(E)* and *(Z)

(74%)

8.19 OXIDATIVE CLEAVAGE OF ALKYNES

Treating alkynes with **ozone** followed by acetic acid, or with basic potassium permanganate followed by acid, leads to cleavage at the carbon–carbon triple bond. The products are carboxylic acids:

$$R{-}C{\equiv}C{-}R' \xrightarrow[(2)\ HOAc]{(1)\ O_3} RCO_2H + R'CO_2H$$

or

$$R{-}C{\equiv}C{-}R' \xrightarrow[(2)\ H_3O^+]{(1)\ KMnO_4,\ HO^-} RCO_2H + R'CO_2H$$

SOLVED PROBLEM 8.7

Three alkynes, **X**, **Y**, and **Z**, each have the formula C_6H_{10}. When allowed to react with excess hydrogen in the presence of a platinum catalyst each alkyne yields only hexane as a product.

(1) The IR spectrum of compound **X** shows, among others, a peak near 3320 cm^{-1}, several peaks in the 2800–3000-cm^{-1} region, and a peak near 2100 cm^{-1}. On oxidation with hot, basic potassium permanganate followed by acidification, **X** produces a five-carbon carboxylic acid and a gas.

(2) Compound **Y** has no IR peak in the 3300-cm^{-1} region and when oxidized with hot, basic $KMnO_4$ produces on acidification a three-carbon carboxylic acid only. Compound **Y** has peaks in the 2800–3000-cm^{-1} region, but no peak near 2100 cm^{-1}.

(3) On treatment with hot basic $KMnO_4$ followed by acid, **Z** produces a two-carbon carboxylic acid and a four-carbon one. In its IR spectrum, **Z** has peaks in the 2800–3000-cm^{-1} region and a peak near 2100 cm^{-1}, but no peaks near the 3300-cm^{-1} region. Consult Section 2.16A and propose structures for each alkyne.

(continues on next page)

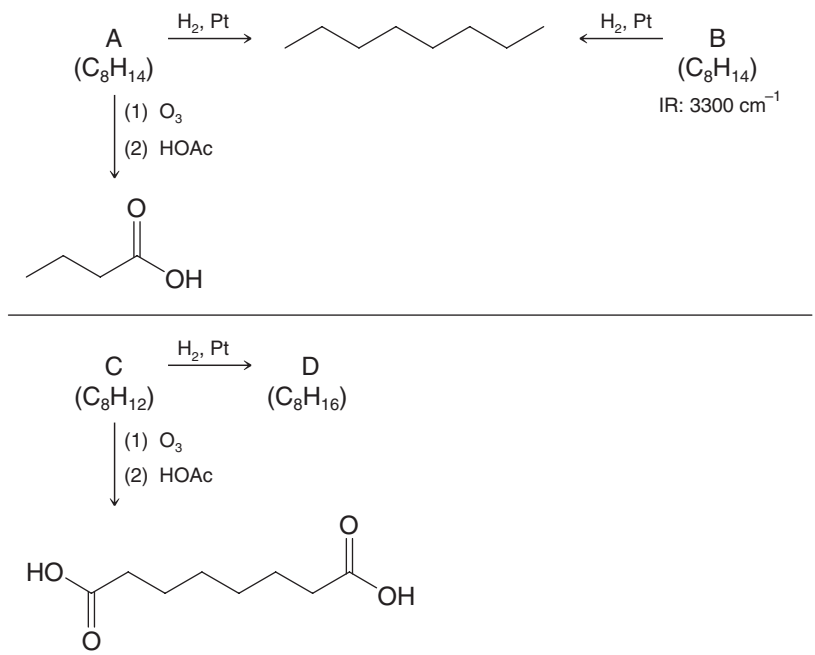
STRATEGY AND ANSWER: That all three alkynes yield hexane on catalytic hydrogenation shows that they are all unbranched hexynes.

(1) That compound **X** has a peak near 3200 cm^{-1} indicates that it has a terminal triple bond. The peak near 2100 cm^{-1} is also associated with that triple bond. These facts suggest that compound **X** is 1-hexyne, something that is confirmed by the results of its oxidation to a five-carbon carboxylic acid and carbon dioxide.

(2) That compound **Y**, on **oxidative cleavage**, yields only a three-carbon carboxylic acid strongly suggests that it is 3-hexyne; this is confirmed by the absence of a peak near 2100 cm^{-1}. (The triple bond of 3-hexyne is symmetrically substituted and, therefore, the absence of an IR peak in this region is consistent with there being no dipole moment change associated with its vibration.)

(3) That compound **Z** has a peak near 2100 cm^{-1} indicates the presence of an unsymmetrically substituted triple bond, and this is consistent with the formation of two different carboxylic acids (one with two carbons and one with four) when it is oxidized. **Z**, therefore, is 2-hexyne.

PRACTICE PROBLEM 8.24 **A**, **B**, and **C** are alkynes. Elucidate their structures and that of **D** using the following reaction roadmap.



8.20 HOW TO PLAN A SYNTHESIS: SOME APPROACHES AND EXAMPLES

In planning a synthesis we often have to consider four interrelated aspects:

1. construction of the carbon skeleton,
2. functional group interconversions,
3. control of regiochemistry, and
4. control of stereochemistry.

You have had some experience with certain aspects of synthetic strategies in earlier sections.

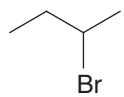
- In Section 7.15B you learned about *retrosynthetic analysis* and how this kind of thinking could be applied to the construction of carbon skeletons of alkanes and cycloalkanes.
- In Section 6.14 you learned the meaning of a *functional group interconversion* and how nucleophilic substitution reactions could be used for this purpose.

In other sections, perhaps without realizing it, you have begun adding to your basic store of methods for construction of carbon skeletons and for making functional group interconversions. This is the time to begin keeping a card file for all the reactions that you have learned, noting especially their applications to synthesis. This file will become your **Tool Kit for Organic Synthesis**. Now is also the time to look at some new examples and to see how we integrate all four aspects of synthesis into our planning.

8.20A Retrosynthetic Analysis

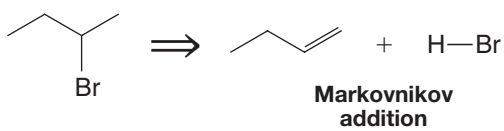
Consider a problem in which we are asked to outline a synthesis of 2-bromobutane from compounds of two carbon atoms or fewer. This synthesis, as we shall see, involves construction of the carbon skeleton, functional group interconversion, and control of regiochemistry.

HOW TO Apply Retrosynthetic Analysis to 2-Bromobutane

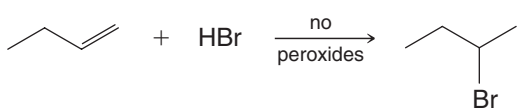


We begin by thinking backward. The final target, 2-bromobutane, can be made in one step from 1-butene by addition of hydrogen bromide. The regiochemistry of this functional group interconversion must be Markovnikov addition:

Retrosynthetic Analysis



Synthesis



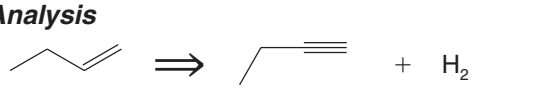
Remember: The open arrow is a symbol used to show a retrosynthetic process that relates the target molecule to its precursors:

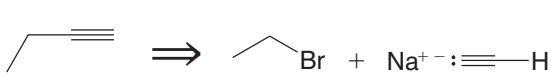
Target molecule ⟹ precursors

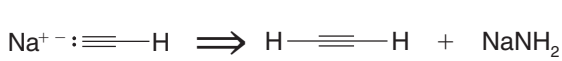
Continuing to work backward one hypothetical reaction at a time, we realize that a synthetic precursor of 1-butene is 1-butyne. Addition of 1 mol of hydrogen to 1-butyne would lead to 1-butene. With 1-butyne as our new target, and bearing in mind that we are told that we have to construct the carbon skeleton from compounds with two carbons or fewer, we realize that 1-butyne can be formed in one step from ethyl bromide and acetylene by an alkynide anion alkylation.

- The **key to retrosynthetic analysis** is to think of how to synthesize each target molecule in one reaction from an immediate precursor, considering first the ultimate target molecule and working backward.

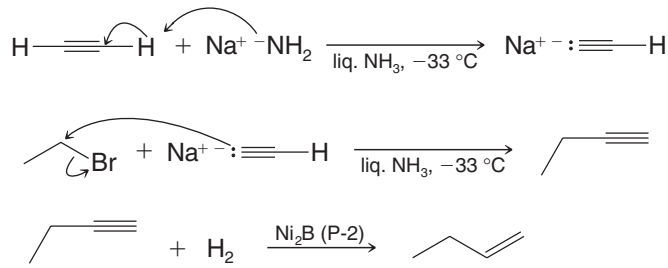
Retrosynthetic Analysis







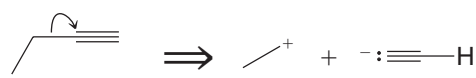
Synthesis



8.20B Disconnections, Synthons, and Synthetic Equivalents

- One approach to retrosynthetic analysis is to consider a retrosynthetic step as a "disconnection" of one of the bonds (Section 7.15).*

For example, an important step in the synthesis that we have just given is the one in which a new carbon–carbon bond is formed. Retrosynthetically, it can be shown in the following way:



The hypothetical fragments of this disconnection are an ethyl cation and an ethynide anion.

- In general, we call the fragments of a hypothetical retrosynthetic disconnection **synthons**.

Seeing the synthons above may help us to reason that we could, in theory, synthesize a molecule of 1-butyne by combining an ethyl cation with an ethynide anion. We know, however, that bottles of carbocations and carbanions are not to be found on our laboratory shelves and that even as a reaction intermediate, it is not reasonable to consider an ethyl carbocation. What we need are the **synthetic equivalents** of these synthons. The synthetic equivalent of an ethynide ion is sodium ethynide, because sodium ethynide contains an ethynide ion (and a sodium cation). The synthetic equivalent of an ethyl cation is ethyl bromide. To understand how this is true, we reason as follows: if ethyl bromide were to react by an S_N1 reaction, it would produce an ethyl cation and a bromide ion. However, we know that, being a primary halide, ethyl bromide is unlikely to react by an S_N1 reaction. Ethyl bromide, however, will react readily with a strong nucleophile such as sodium ethynide by an S_N2 reaction, and when it reacts, the product that is obtained is the same as the product that would have been obtained from the reaction of an ethyl cation with sodium ethynide. Thus, ethyl bromide, in this reaction, functions as the synthetic equivalent of an ethyl cation.

2-Bromobutane could also be synthesized from compounds of two carbons or fewer by a route in which (*E*)- or (*Z*)-2-butene is an intermediate. You may wish to work out the details of that synthesis for yourself.

8.20C Stereochemical Considerations

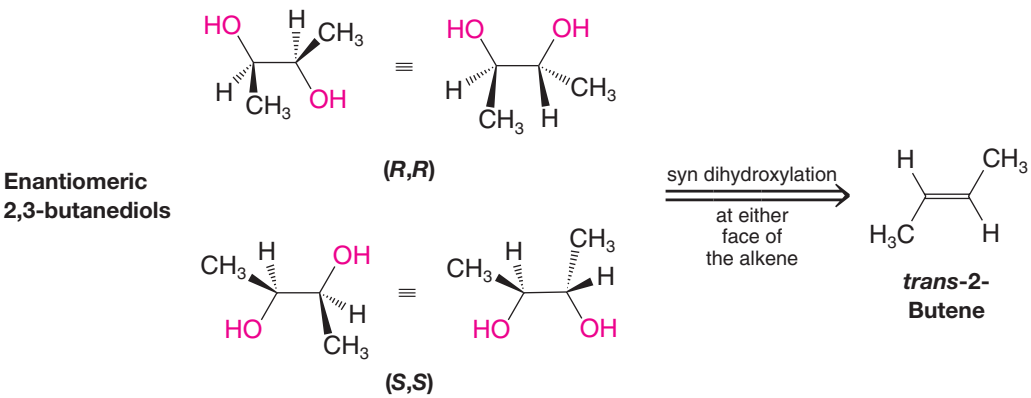
Consider another example, a synthesis that requires stereochemical control: the synthesis of the enantiomeric 2,3-butanediols, (2*R*,3*R*)-2,3-butanediol and (2*S*,3*S*)-2,3-butanediol, from compounds of two carbon atoms or fewer, and in a way that does not produce the meso stereoisomer.

*For an excellent detailed treatment of this approach you may want to read the following: Warren, S., and Wyatt, P., *Organic Synthesis, The Disconnection Approach,* 2nd Ed. Wiley: New York, 2009; and Warren, S., and Wyatt, P., *Workbook for Organic Synthesis, The Disconnection Approach,* 2nd Ed. Wiley: New York, 2009.

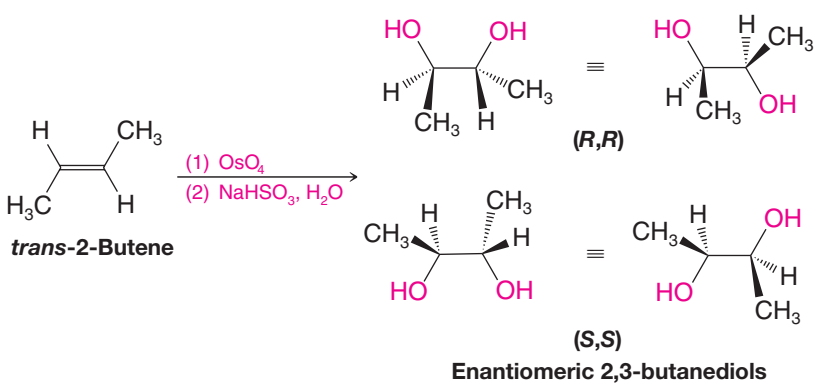
HOW TO Apply Stereochemical Considerations in Planning a Synthesis of 2,3-Butanediol Enantiomers

Here we see that a possible final step to the enantiomers is syn dihydroxylation of *trans*-2-butene. This reaction is stereospecific and produces the desired enantiomeric 2,3-butanediols as a racemic form. Here we have made the key choice **not** to use *cis*-2-butene. Had we chosen *cis*-2-butene, our product would have been the meso 2,3-butanediol stereoisomer.

Retrosynthetic Analysis

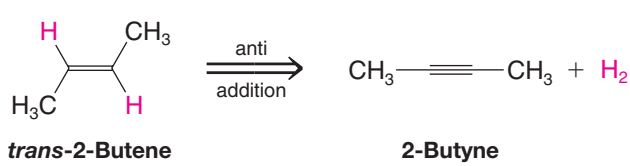


Synthesis

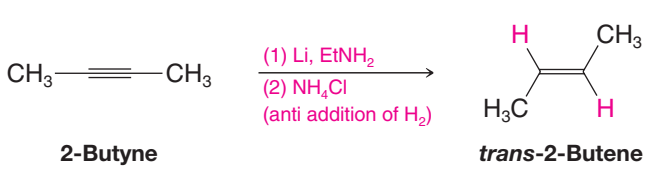


Synthesis of *trans*-2-butene can be accomplished by treating 2-butyne with lithium in liquid ammonia. The anti addition of hydrogen by this reaction gives us the trans product that we need.

Retrosynthetic Analysis



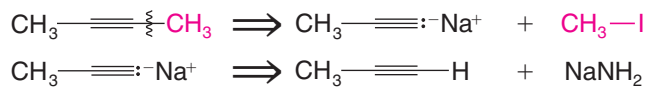
Synthesis



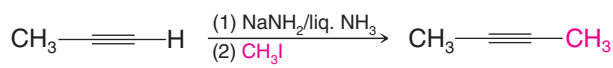
- The reaction above is an example of a **stereoselective reaction**. A **stereoselective reaction** is one in which the reactant is not necessarily chiral (as in the case of an alkyne) but in which the reaction produces predominantly or exclusively one stereoisomeric form of the product (or a certain subset of stereoisomers from among all those that are possible).
- Note the difference between stereoselective and stereospecific. A stereospecific reaction is one that produces predominantly or exclusively one stereoisomer of the product when a specific stereoisomeric form of the reactant is used. (All stereospecific reactions are stereoselective, but the reverse is not necessarily true.)

We can synthesize 2-butyne from propyne by first converting it to sodium propynide and then alkylating sodium propynide with methyl iodide:

Retrosynthetic Analysis

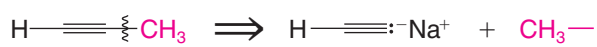


Synthesis

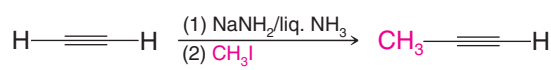


And to get propyne, we synthesize it from ethyne:

Retrosynthetic Analysis



Synthesis

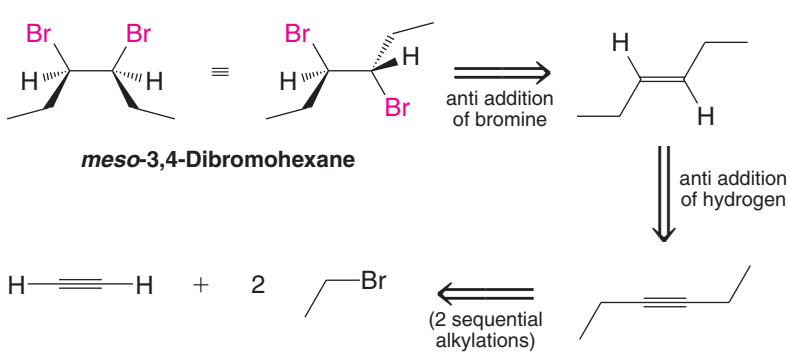


SOLVED PROBLEM 8.8

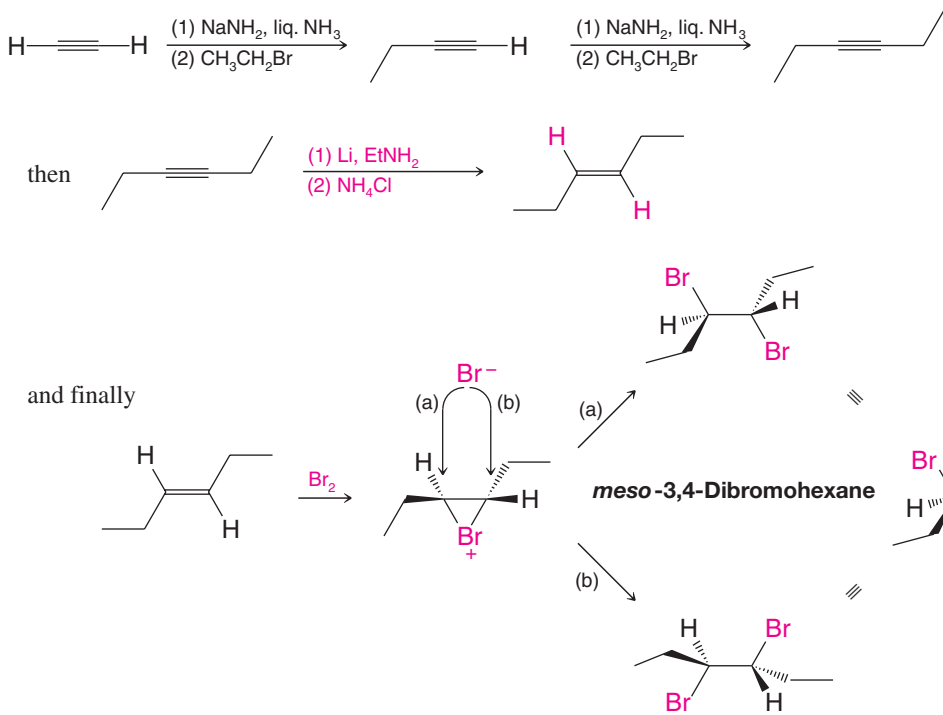
ILLUSTRATING A STEREOSPECIFIC MULTISTEP SYNTHESIS: Starting with compounds of two carbon atoms or fewer, outline a stereospecific synthesis of *meso*-3,4-dibromohexane.

STRATEGY AND ANSWER: We begin by working backward from the target molecule. Since the target molecule is a meso compound, it is convenient to start by drawing a formula that illustrates its internal plane of symmetry, as shown below. But since we also know that a vicinal dibromide can be formed by anti addition of bromine to an alkene, we redraw the target molecule formula in a conformation that shows the bromine atoms anti to each other, as they would be after addition to an alkene. Then, retaining the relative spatial relationship of the alkyl groups, we draw the alkene precursor to the 1,2-dibromide, and find that this compound is (*E*)-3-hexene. Knowing that an (*E*) alkene can be formed by anti addition of hydrogen to an alkyne using lithium in ethylamine or ammonia (Section 7.14B), we see that 3-hexyne is a suitable synthetic precursor to (*E*)-3-hexene. Last, because we know it is possible to alkylate terminal alkynes, we recognize that 3-hexyne could be synthesized from acetylene by two successive alkylations with an ethyl halide. The following is a retrosynthetic analysis.

Retrosynthetic Analysis



The synthesis could be written as follows:



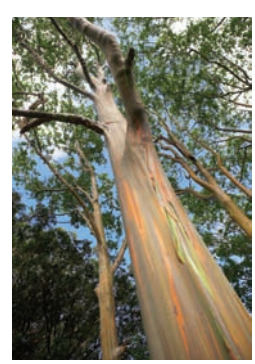
PRACTICE PROBLEM 8.25

How would you modify the procedure given in Solved Problem 8.8 so as to synthesize a racemic form of (3*R*,4*R*)- and (3*S*,4*S*)-3,4-dibromohexane?

[WHY Do These Topics Matter?

ALKENES IN NATURAL CHEMICAL SYNTHESES

As illustrated in Chapters 7 and 8, unsaturation within molecules provides numerous possibilities for the addition of functional groups and the creation of C—C bonds. Thus, it should probably come as no surprise that the synthesis of complex molecules in nature also involves sites of unsaturation. Alkenes, not alkynes, are the main players in such processes, often in the form of isoprene building blocks. The five-carbon isoprene unit is easily recognized as an unsaturated four carbon chain with a methyl branch. In nature, several isoprene units combine to make long carbon chains that terminate with a reactive pyrophosphate group, such as geranylgeranyl pyrophosphate (GGPP). Such compounds take part in highly controlled reaction processes that generate tens of thousands of distinct natural products—compounds that serve as critical hormones and signaling molecules, among a myriad of other functions.

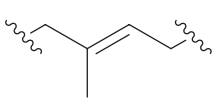


Corbis RF/Image Source

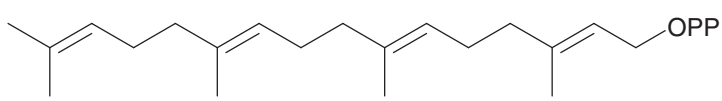
A eucalyptus tree, the source of eucalyptol.

© NHPA/Photoshot Holdings Ltd.

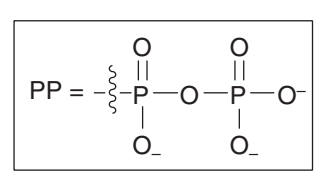
A Pacific yew tree, the source of Taxol.



Isoprene building block



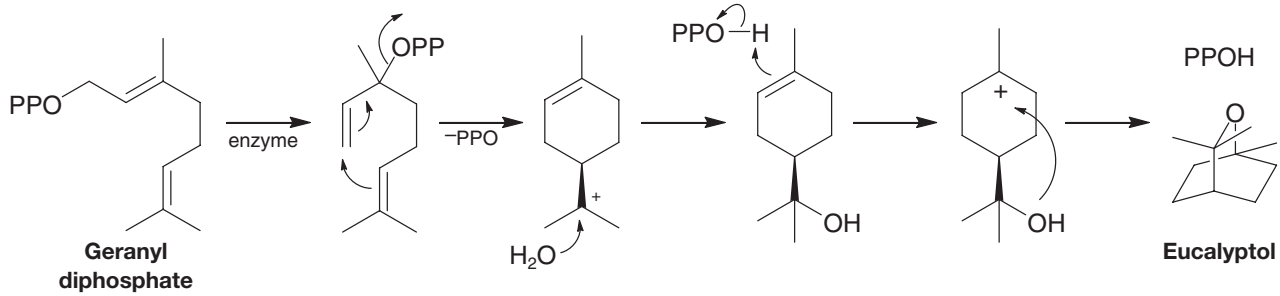
Geranylgeranyl pyrophosphate (GGPP)



This chemistry begins with an enzyme that folds the isoprene-containing building block into a distinct conformation, one meant to trigger specific C—C bond formations where the OPP group will serve as a departing group in S_N2 or S_N1 processes. In some

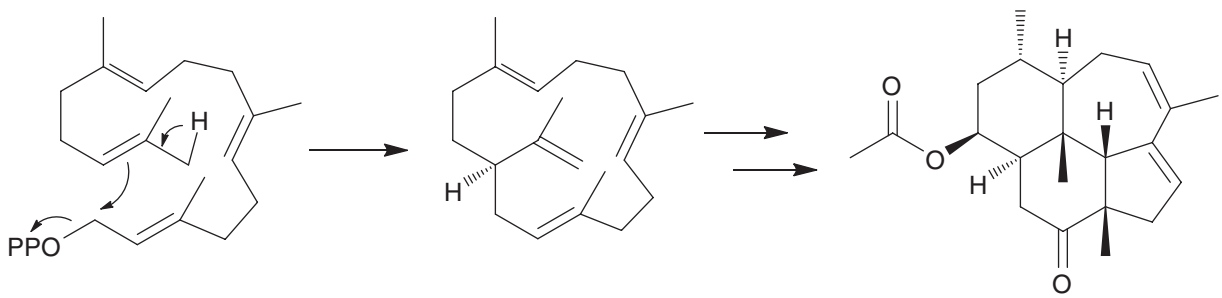
(continues on next page)

cases, the leaving group initially helps to reposition the site of C—C bond formation through chemistry such as that shown below for the synthesis of eucalyptol. After that key step, though, it is all chemistry of the type you have seen in this chapter where alkenes are attacking electrophilic species, with the OPP group serving to shuttle around protons (try filling in the missing proton transfer steps for yourself).



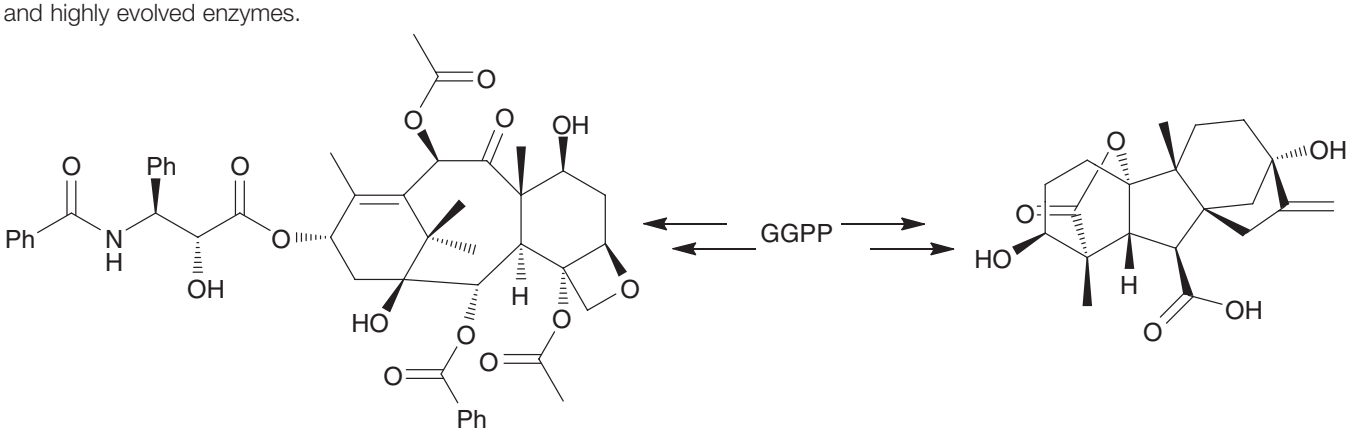
Geranyl diphosphate **Eucalyptol**

In other cases, the OPP group is replaced directly. For example, following enzymatic organization of GGPP as shown below, removal of the indicated proton by a base can cause the neighboring alkene to displace the OPP group, leading to a molecule known as cembrene A. Then, through a series of further alkene-based C—C bond formation reactions (using more of the standard principles of nucleophiles and electrophiles as we have discussed), and oxidations, and again controlled by specific enzymes, this carbon core can be converted into materials like kempene-2. For termites, this and related molecules serve as critical protective agents against invading species.



GGPP **Cembrene A** **Kempene-2**

What is amazing, however, is that other organisms can take the same starting piece and make completely different molecules through exactly the same processes (folding and oxidation). In the Pacific yew tree, for example, GGPP is converted into Taxol, a compound that is currently one of the world's leading cancer therapies. Several other plant species and fungi, by contrast, turn GGPP into a signaling molecule known as gibberellic acid 3. There is a lot of complex organic chemistry going on in these processes, but the key take-home message is both simple and elegant: from one single set of starting materials a large number of diverse compounds can be synthesized, all through the power of alkenes, one additional reactive group, and some very specialized and highly evolved enzymes.



Taxol **Gibberellic acid 3**

To learn more about these topics, see:

1. Fischbach, M. A.; Clardy, J. "One pathway, many products" in *Nature: Chem. Bio*. **2007**, *3*, 353–355.
2. Ishihara, Y.; Baran, P.S. "Two-Phase Terpene Total Synthesis: Historical Perspective and Application to the Taxol® Problem" in *Synlett* **2010**, *12*, 1733–1745.

SUMMARY AND REVIEW TOOLS

The study aids for this chapter include key terms and concepts (which are hyperlinked to the Glossary from the bold, blue terms in the *WileyPLUS* version of the book at wileyplus.com), a Mechanism Review of Alkene Addition Reactions, and a Synthetic Connections roadmap involving alkenes and alkynes.

PROBLEMS

Note to Instructors: Many of the homework problems are available for assignment via *WileyPLUS*, an online teaching and learning solution.

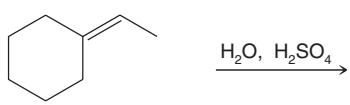
ALKENES AND ALKYNES REACTION TOOLKIT

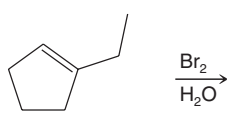
8.26 Write structural formulas for the products that form when 1-butene reacts with each of the following reagents:

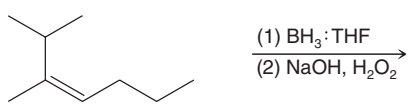
(a) HI
(b) H_2, Pt
(c) Dilute H_2SO_4, warm
(d) Cold concentrated H_2SO_4
(e) Cold concentrated H_2SO_4, then H_2O and heat
(f) HBr
(g) Br_2 in CCl_4
(h) Br_2 in H_2O
(i) HCl
(j) O_3, then Me_2S
(k) OsO_4, then $NaHSO_3/H_2O$
(l) $KMnO_4$, HO^-, heat, then H_3O^+
(m) $Hg(OAc)_2$ in THF and H_2O, then $NaBH_4$, HO^-
(n) BH_3:THF, then H_2O_2, HO^-

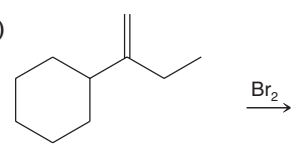
8.27 Repeat Exercise 8.26 using 1-methylcyclopentene instead of 1-butene.

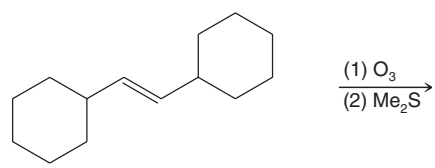
8.28 Write structures for the major organic products from the following reactions. Show stereoisomers where applicable.

(a) 

(b) 

(c) 

(d) 

(e) 

8.29 Give the structure of the products that you would expect from the reaction of 1-butyne with:

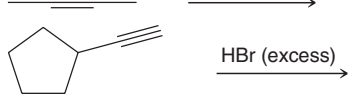
(a) One molar equivalent of Br_2
(b) One molar equivalent of HBr
(c) Two molar equivalents of HBr
(d) H_2 (in excess)/Pt
(e) H_2, Ni_2B (P-2)
(f) $NaNH_2$ in liquid NH_3, then CH_3I
(g) $NaNH_2$ in liquid NH_3, then $(CH_3)_3CBr$

8.30 Give the structure of the products you would expect from the reaction (if any) of 2-butyne with:

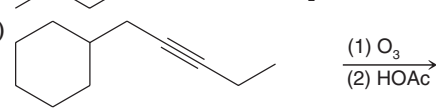
(a) One molar equivalent of HBr
(b) Two molar equivalents of HBr
(c) One molar equivalent of Br_2
(d) Two molar equivalents of Br_2
(e) H_2, Ni_2B (P-2)
(f) One molar equivalent of HCl
(g) Li/liquid NH_3
(h) H_2 (in excess), Pt
(i) Two molar equivalents of H_2, Pt
(j) Hot $KMnO_4$, HO^-, then H_3O^+
(k) O_3, then HOAc
(l) $NaNH_2$, liquid NH_3

8.31 Write structures for the major organic products from the following reactions. Show stereoisomers where applicable.

(a) 

(b) 

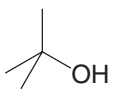
(c) 

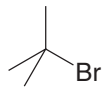
(d) 

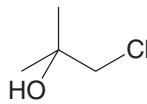
8.32 Show how 1-butyne could be synthesized from each of the following:

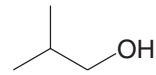
(a) 1-Butene **(b)** 1-Chlorobutane **(c)** 1-Chloro-1-butene **(d)** 1,1-Dichlorobutane **(e)** Ethyne and ethyl bromide

8.33 Starting with 2-methylpropene (isobutylene) and using any other needed reagents, outline a synthesis of each of the following:

(a) 

(b) 

(c) 

(d) 

MECHANISMS

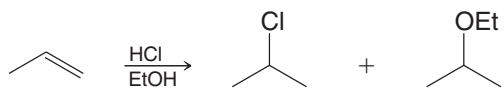
8.34 Write a three-dimensional formula for the product formed when 1-methylcyclohexene is treated with each of the following reagents. In each case, designate the location of deuterium or tritium atoms.

(a) (1) BH_3:THF, (2) CH_3CO_2T

(b) (1) BD_3:THF, (2) CH_3CO_2D

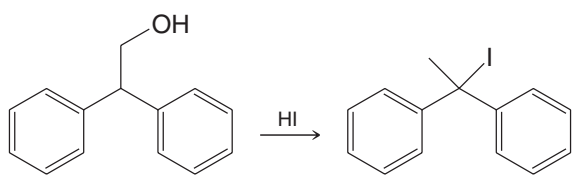
(c) (1) BD_3:THF, (2) NaOH, H_2O_2, H_2O

8.35 Write a mechanism that accounts for the formation of ethyl isopropyl ether in the following reaction.



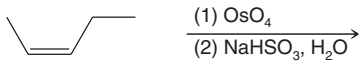
8.36 When, in separate reactions, 2-methylpropene, propene, and ethene are allowed to react with HI under the same conditions (i.e., identical concentration and temperature), 2-methylpropene is found to react fastest and ethene slowest. Provide an explanation for these relative rates.

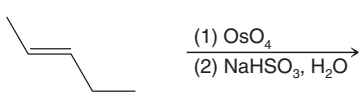
8.37 Propose a mechanism that accounts for the following reaction.

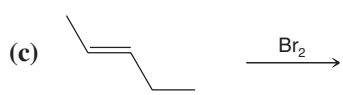


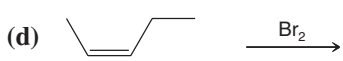
8.38 When 3,3-dimethyl-2-butanol is treated with concentrated HI, a rearrangement takes place. Which alkyl iodide would you expect from the reaction? (Show the mechanism by which it is formed.)

8.39 Write stereochemical formulas for all of the products that you would expect from each of the following reactions. (You may find models helpful.)

(a) 

(b) 

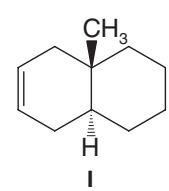
(c) 

(d) 

8.40 Give (*R, S*) designations for each different compound given as an answer to Problem 8.39.

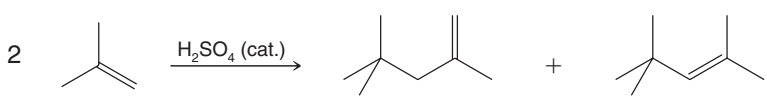
8.41 The double bond of tetrachloroethene is undetectable in the bromine test for unsaturation. Give a plausible explanation for this behavior.

8.42 The reaction of bromine with cyclohexene involves anti addition, which generates, initially, the diaxial conformation of the addition product that then undergoes a ring flip to the diequatorial conformation of *trans*-1,2-dibromocyclohexane. However, when the unsaturated bicyclic compound **I** is the alkene, instead of cyclohexene, the addition product is exclusively in a stable diaxial conformation. Account for this. (You may find it helpful to build handheld molecular models.)



I

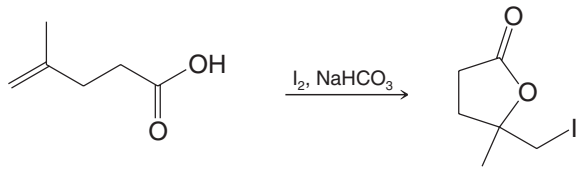
8.43 Propose a mechanism that explains formation of the products from the following reaction, including the distribution of the products as major and minor.



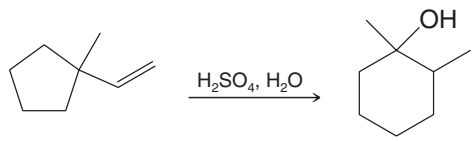
Major **Minor**

8.44 Internal alkynes can be isomerized to terminal alkynes on treatment with $NaNH_2$. The process is much less successful when NaOH is used. Why is there this difference?

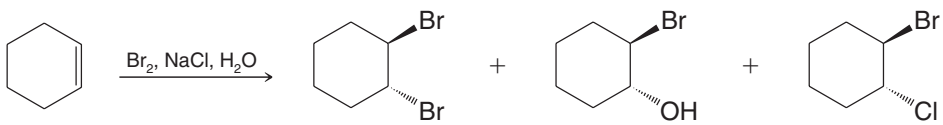
8.45 Write a mechanism that explains the following reaction.



8.46 Write a mechanism for the following reaction.



8.47 Write a mechanism that explains formation of the products shown in the following reaction.



STRUCTURE ELUCIDATION

8.48 Myrcene, a fragrant compound found in bayberry wax, has the formula $C_{10}H_{16}$ and is known not to contain any triple bonds.

(a) What is the index of hydrogen deficiency of myrcene? When treated with excess hydrogen and a platinum catalyst, myrcene is converted to a compound **(A)** with the formula $C_{10}H_{22}$.

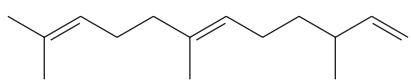
(b) How many rings does myrcene contain?

(c) How many double bonds? Compound **A** can be identified as 2,6-dimethyloctane. Ozonolysis of myrcene followed by treatment with dimethyl sulfide yields 2 mol of formaldehyde (HCHO), 1 mol of acetone (CH_3COCH_3), and a third compound **(B)** with the formula $C_5H_6O_3$.

(d) What is the structure of compound **B**?

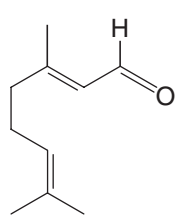
(e) What is the structure of myrcene?

8.49 Farnesene (below) is a compound found in the waxy coating of apples. (**a**) Give the structure and IUPAC name of the product formed when farnesene is allowed to react with excess hydrogen in the presence of a platinum catalyst. (**b**) How many stereoisomers of the product are possible?



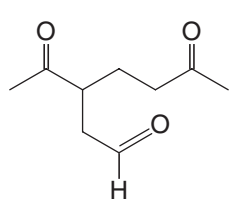
Farnesene

8.50 Write structural formulas for the products that would be formed when geranial, a component of lemongrass oil, is treated with ozone and then with dimethyl sulfide (Me_2S).

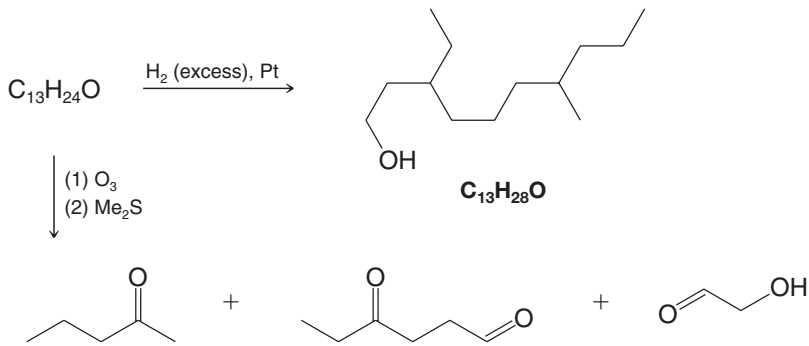


Geranial

8.51 Limonene is a compound found in orange oil and lemon oil. When limonene is treated with excess hydrogen and a platinum catalyst, the product of the reaction is 1-isopropyl-4-methylcyclohexane. When limonene is treated with ozone and then with dimethyl sulfide (Me_2S), the products of the reaction are formaldehyde (HCHO) and the following compound. Write a structural formula for limonene.

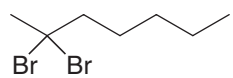


8.52 Pheromones (Section 4.7) are substances secreted by animals that produce a specific behavioral response in other members of the same species. Pheromones are effective at very low concentrations and include sex attractants, warning substances, and "aggregation" compounds. The sex attractant pheromone of the codling moth has the molecular formula $C_{13}H_{24}O$. Using information you can glean from the following reaction diagram, deduce the structure of the codling moth sex pheromone. The double bonds are known (on the basis of other evidence) to be (2*Z*,6*E*).

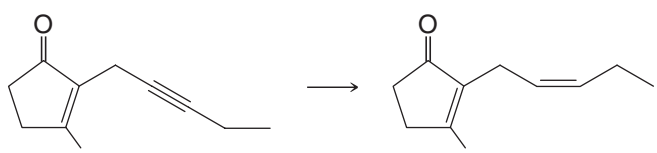


GENERAL PROBLEMS

8.53 Synthesize the following compound starting with ethyne and 1-bromopentane as your only organic reagents (except for solvents) and using any needed inorganic compounds.



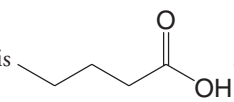
8.54 Shown below is the final step in a synthesis of an important perfume constituent, *cis*-jasmone. Which reagents would you choose to carry out this last step?

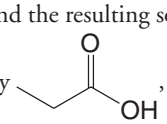


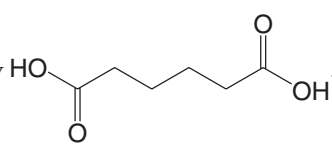
***cis*-Jasmone**

8.55 Predict features of their IR spectra that you could use to distinguish between the members of the following pairs of compounds. You may find the IR chart in the endpapers of the book and Table 2.1 useful.

(a) Pentane and 1-pentyne
(b) Pentane and 1-pentene
(c) 1-Pentene and 1-pentyne
(d) Pentane and 1-bromopentane
(e) 2-Pentyne and 1-pentyne
(f) 1-Pentene and 1-pentanol
(g) Pentane and 1-pentanol
(h) 1-Bromo-2-pentene and 1-bromopentane
(i) 1-Pentanol and 2-penten-1-ol

8.56 Deduce the structures of compounds **A**, **B**, and **C**, which all have the formula C_6H_{10}. As you read the information that follows, draw reaction flowcharts (roadmaps) like those in Problems 8.24 and 8.52. This approach will help you solve the problem. All three compounds rapidly decolorize bromine; all three are soluble in cold concentrated sulfuric acid. Compound **A** has an absorption in its IR spectrum at about 3300 cm^{-1}, but compounds **B** and **C** do not. Compounds **A** and **B** both yield hexane when they are treated with excess hydrogen in the presence of a platinum catalyst. Under these conditions **C** absorbs only one molar equivalent of hydrogen and gives a product with the formula C_6H_{12}. When **A** is oxidized with hot basic potassium permanganate and the resulting solution acidified, the only organic product that can be isolated is 

. Similar oxidation of **B** gives only 

, and similar treatment of **C** gives only 

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8.57 Ricinoleic acid, a compound that can be isolated from castor oil, has the structure $CH_3(CH_2)_5CHOHCH_2CH{=}CH(CH_2)_7CO_2H$.

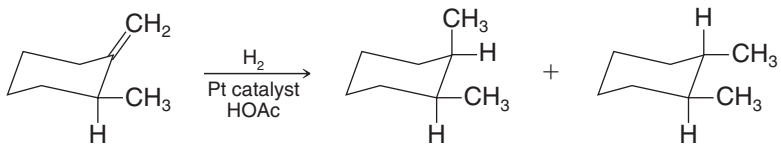
(a) How many stereoisomers of this structure are possible? **(b)** Write these structures.

8.58 There are two dicarboxylic acids with the general formula $HO_2CCH{=}CHCO_2H$. One dicarboxylic acid is called maleic acid; the other is called fumaric acid. When treated with OsO_4, followed by $NaHSO_3/H_2O$, maleic acid yields *meso*-tartaric acid and fumaric acid yields (±)-tartaric acid. Show how this information allows one to write stereochemical formulas for maleic acid and fumaric acid.

8.59 Use your answers to the preceding problem to predict the stereochemical outcome of the addition of bromine to maleic acid and to fumaric acid. **(a)** Which dicarboxylic acid would add bromine to yield a meso compound? **(b)** Which would yield a racemic form?

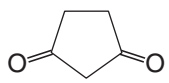
8.60 Alkyl halides add to alkenes in the presence of $AlCl_3$; yields are the highest when tertiary halides are used. Predict the outcome of the reaction of *tert*-pentyl chloride (1-chloro-2,2-dimethylpropane) with propene and specify the mechanistic steps.

8.61 Explain the stereochemical results observed in this catalytic hydrogenation. (You may find it helpful to build hand-held molecular models.)



I (70%) **II (30%)**

8.62 Make a reaction flowchart (roadmap diagram), as in previous problems, to organize the information provided to solve this problem. An optically active compound **A** (assume that it is dextrorotatory) has the molecular formula $C_7H_{11}Br$. **A** reacts with hydrogen bromide, in the absence of peroxides, to yield isomeric products, **B** and **C**, with the molecular formula $C_7H_{12}Br_2$. Compound **B** is optically active; **C** is not. Treating **B** with 1 mol of potassium *tert*-butoxide yields (+)-**A**. Treating **C** with 1 mol of potassium *tert*-butoxide yields (±)-**A**. Treating **A** with potassium *tert*-butoxide yields **D** (C_7H_{10}). Subjecting 1 mol of **D** to ozonolysis followed by treatment with dimethyl sulfide (Me_2S) yields 2 mol of formaldehyde and 1 mol of 1,3-cyclopentanedione. Propose stereochemical formulas for **A**, **B**, **C**, and **D** and outline the reactions involved in these transformations.



1,3-Cyclopentanedione

8.63 A naturally occurring antibiotic called mycomycin has the structure shown here. Mycomycin is optically active. Explain this by writing structures for the enantiomeric forms of mycomycin.

$$HC{\equiv}C{-}C{\equiv}C{-}CH{=}C{=}CH{-}(CH{=}CH)_2CH_2CO_2H$$

Mycomycin

8.64 An optically active compound **D** has the molecular formula C_6H_{10} and shows a peak at about 3300 cm^{-1} in its IR spectrum. On catalytic hydrogenation **D** yields **E** (C_6H_{14}). Compound **E** is optically inactive and cannot be resolved. Propose structures for **D** and **E**.

8.65 **(a)** Based on the following information, draw three-dimensional formulas for **A**, **B**, and **C**.

Reaction of cyclopentene with bromine in water gives **A**.

Reaction of **A** with aqueous NaOH (1 equivalent, cold) gives **B**, C_5H_8O (no 3590–3650-cm^{-1} infrared absorption). (See the squalene cyclization discussion in "The Chemistry of…Cholesterol Biosynthesis" in *WileyPLUS* for a hint.)

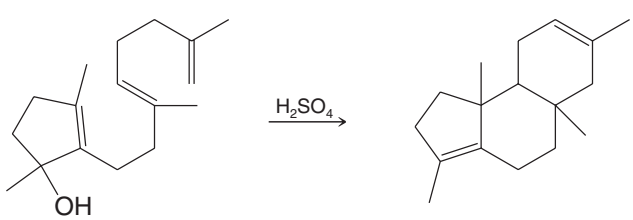
Heating of **B** in methanol containing a catalytic amount of strong acid gives **C**, $C_6H_{12}O_2$, which does show 3590–3650-cm^{-1} infrared absorption.

(b) Specify the (*R*) or (*S*) configuration of the chirality centers in your predicted structures for **C**. Would **C** be formed as a single stereoisomer or as a racemate?

(c) How could you experimentally confirm your predictions about the stereochemistry of **C**?

CHALLENGE PROBLEMS

8.66 Propose a mechanism that explains the following transformation. (Note its similarity to the cyclization of squalene oxide to lanosterol, as shown in "The Chemistry of…Cholesterol Biosynthesis." in *WileyPLUS*.)



8.67 Triethylamine, $(C_2H_5)_3N$, like all amines, has a nitrogen atom with an unshared pair of electrons. Dichlorocarbene also has an unshared pair of electrons. Both can be represented as shown below. Draw the structures of compounds **D**, **E**, and **F**.

$$(C_2H_5)_3N{:} + {:}CCl_2 \longrightarrow \mathbf{D} \qquad \text{(an unstable adduct)}$$

$$\mathbf{D} \longrightarrow \mathbf{E} + C_2H_4 \qquad \text{(by an intramolecular E2 reaction)}$$

$$\mathbf{E} \xrightarrow{H_2O} \mathbf{F} \qquad \text{(Water effects a replacement that is the reverse of that used to make } \textit{gem}\text{-dichlorides.)}$$

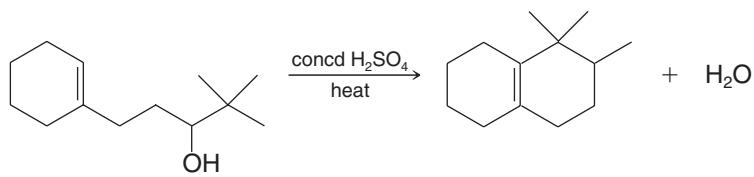
LEARNING GROUP PROBLEMS

1. **(a)** Synthesize (3*S*,4*R*)-3,4-dibromo-1-cyclohexylpentane (and its enantiomer, since a racemic mixture will be formed) from ethyne, 1-chloro-2-cyclohexylethane, bromomethane, and any other reagents necessary. (Use ethyne, 1-chloro-2-cyclohexylethane, and bromomethane as the sole sources of carbon atoms.) Start the problem by showing a retrosynthetic analysis. In the process, decide which atoms of the target molecule will come from which atoms of the starting reagents. Also, bear in mind how the stereospecificity of the reactions you employ can be used to achieve the required stereochemical form of the final product.

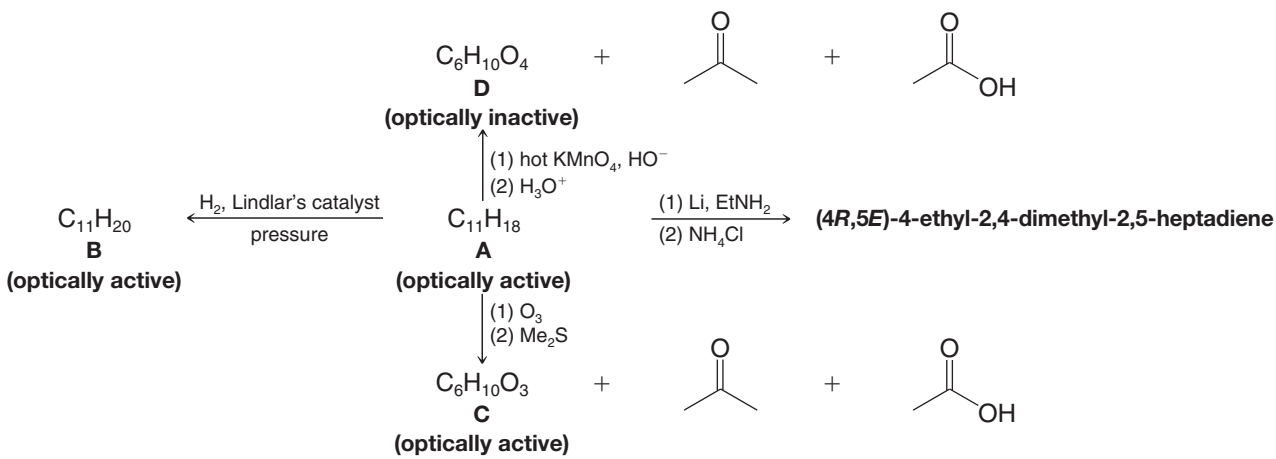
(b) Explain why a racemic mixture of products results from this synthesis.

(c) How could the synthesis be modified to produce a racemic mixture of the (3*R*,4*R*) and (3*S*,4*S*) isomers instead?

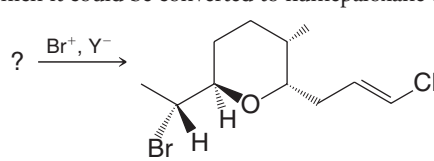
2. Write a reasonable and detailed mechanism for the following transformation:



3. Deduce the structures of compounds **A–D**. Draw structures that show stereochemistry where appropriate:

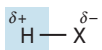
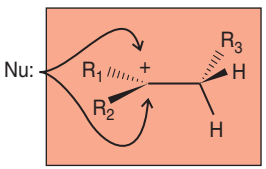
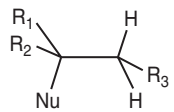
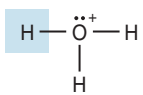
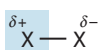
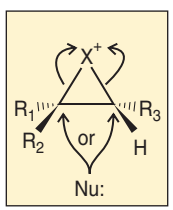
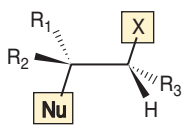
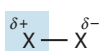
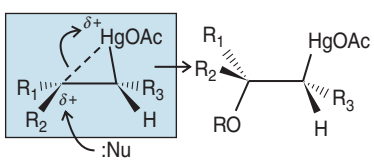
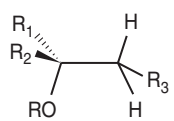
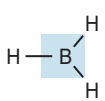
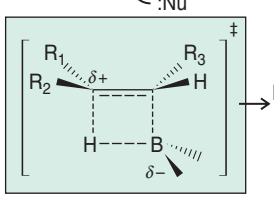
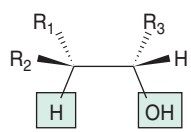
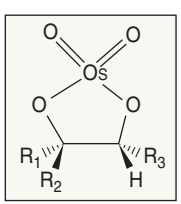
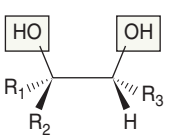


4. The Guam bubble snail (*Haminoea cymbalum*) contains kumepaloxane (shown below), a chemical signal agent discharged when this mollusk is disturbed by predatory carnivorous fish. The biosynthesis of bromoethers like kumepaloxane is thought to occur via the enzymatic intermediacy of a "Br^+" agent. Draw the structure of a possible biosynthetic precursor (*hint*: an alkene alcohol) to kumepaloxane and write a plausible and detailed mechanism by which it could be converted to kumepaloxane using Br^+ and some generic proton acceptor Y^-.



Kumepaloxane

Summary of Alkene Addition Reactions

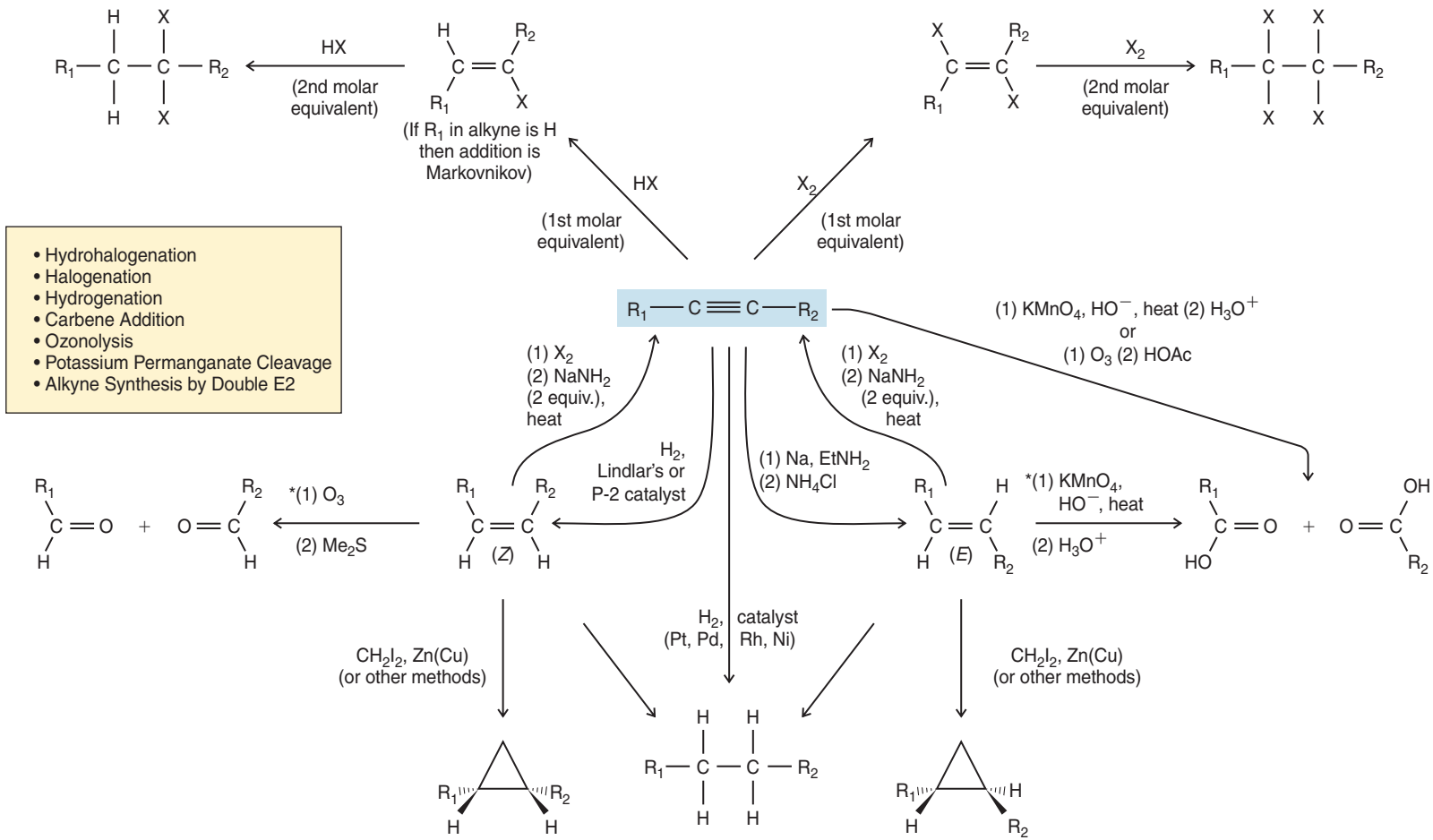
	Reaction Conditions	Electrophile	Nucleophile	Key Intermediates or Transition State	Regiochemistry	Stereochemistry of Addition	Product*
Hydrohalogenation	H — X				Markovnikov	Not controlled	 Nu = X or OH
Hydration (acid cat.)	Cat. HA, H_2O				Markovnikov	Not controlled	
Halogenation	X_2 (nonnucleophilic solvent)				Not applicable	Anti	 Nu = X or OR
Halohydrin Formation	X_2, ROH; R = H or C (nucleophilic solvent)				Markovnikov	Anti	
Oxymercuration–Demercuration	(1) $Hg(OAc)_2$, HOR: THF (R = H or C) (2) $NaBH_4$, HO^-				Markovnikov	Not controlled	
Hydroboration–Oxidation	(1) BH_3:THF (2) H_2O_2, HO^-				Net anti-Markovnikov	Syn	
1,2-Dihydroxylation	(1) OsO_4 (2) aq $NaHSO_3$					Syn	

*The generic alkene chosen has a substitution pattern that allows both regiochemistry and stereochemistry of the products to be discerned.

*The products are formed as a mixture of enantiomers in each case.

SUMMARY AND REVIEW TOOLS

Synthetic Connections of Alkynes and Alkenes: II



- Hydrohalogenation
- Halogenation
- Hydrogenation
- Carbene Addition
- Ozonolysis
- Potassium Permanganate Cleavage
- Alkyne Synthesis by Double E2

*If R_1 is H, then alkene ozonolysis generates formaldehyde and $KMnO_4$ generates CO_2.
If the alkene is disubstituted at one end, a ketone results from cleavage by either ozonolysis or $KMnO_4$.