8 Alkynes: An Introduction to Organic Synthesis

Organic KNOWLEDGE TOOLS

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An **alkyne** is a hydrocarbon that contains a carbon–carbon triple bond. Acetylene, H—C≡C—H, the simplest alkyne, was once widely used in industry as the starting material for the preparation of acetaldehyde, acetic acid, vinyl chloride, and other high-volume chemicals, but more efficient routes to these substances using ethylene as starting material are now available. Acetylene is still used in the preparation of acrylic polymers but is probably best known as the gas burned in high-temperature oxy–acetylene welding torches.

Much current research is centering on *polyynes*—linear carbon chains of *sp*-hybridized carbon atoms. Polyynes with up to eight triple bonds have been detected in interstellar space, and evidence has been presented for the existence of *carbyne*, an allotrope of carbon consisting of repeating triple bonds in long chains of indefinite length.

H—C≡C—C≡C—C≡C—C≡C—C≡C—C≡C—C≡C—H

A polyyne detected in interstellar space

WHY THIS CHAPTER?

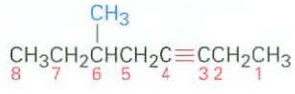
Alkynes are less common than alkenes, both in the laboratory and in living organisms, so we won't cover them in great detail. The real importance of this chapter is that we'll use alkyne chemistry as a vehicle to begin looking at some of the general strategies used in *organic synthesis*—the construction of complex molecules in the laboratory. Without the ability to design and synthesize new molecules in the laboratory, many of the medicines we take for granted would not exist and few new ones would be made.

8.1 Naming Alkynes

Alkyne nomenclature follows the general rules for hydrocarbons discussed in Sections 3.4 and 6.3. The suffix *-yne* is used, and the position of the triple bond is indicated by giving the number of the first alkyne carbon in the

Sean Duggan

chain. Numbering the main chain begins at the end nearer the triple bond so that the triple bond receives as low a number as possible.

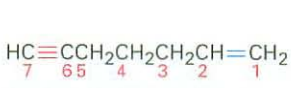


Begin numbering at the end nearer the triple bond.

6-Methyl-3-octyne

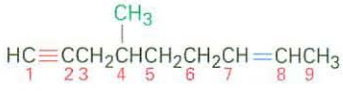
(New: 6-Methyloct-3-yne)

Compounds with more than one triple bond are called *diynes, triynes,* and so forth; compounds containing both double and triple bonds are called *enynes* (not *ynenes*). Numbering of an enyne chain starts from the end nearer the first multiple bond, whether double or triple. When there is a choice in numbering, double bonds receive lower numbers than triple bonds. For example:



1-Hepten-6-yne

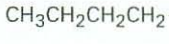
(New: Hept-1-en-6-yne)



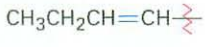
4-Methyl-7-nonen-1-yne

(New: 4-Methylnon-7-en-1-yne)

As with alkyl and alkenyl substituents derived from alkanes and alkenes, respectively, *alkynyl* groups are also possible.

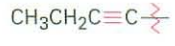


Butyl
(an alkyl group)



1-Butenyl
(a vinylic group)

(New: But-1-enyl)

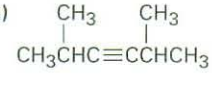


1-Butynyl
(an alkynyl group)

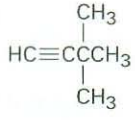
(New: But-1-ynyl)

Problem 8.1 Name the following compounds:

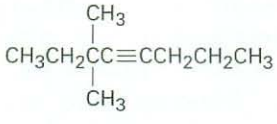
(a)



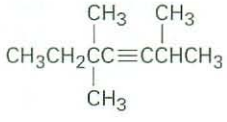
(b)



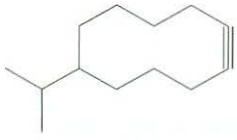
(c)



(d)



(e)



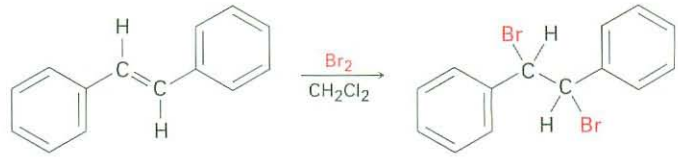
(f) $CH_3CH{=}CHCH{=}CHC{\equiv}CCH_3$

Problem 8.2 There are seven isomeric alkynes with the formula C_6H_{10}. Draw and name them.

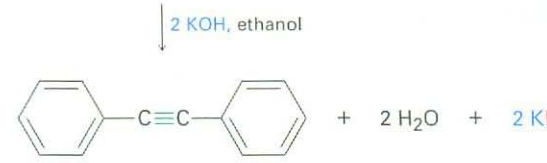
8.2 Preparation of Alkynes: Elimination Reactions of Dihalides

Alkynes can be prepared by the elimination of HX from alkyl halides in much the same manner as alkenes (Section 7.1). Treatment of a 1,2-dihaloalkane (a *vicinal* dihalide) with excess strong base such as KOH or $NaNH_2$ results in a twofold elimination of HX and formation of an alkyne. As with the elimination of HX to form an alkene, we'll defer a discussion of the mechanism until Chapter 11.

The necessary vicinal dihalides are themselves readily available by addition of Br_2 or Cl_2 to alkenes. Thus, the overall halogenation/dehydrohalogenation sequence makes it possible to go from an alkene to an alkyne. For example, diphenylethylene is converted into diphenylacetylene by reaction with Br_2 and subsequent base treatment.

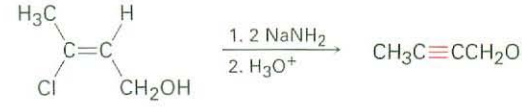


1,2-Diphenylethylene (stilbene) → **1,2-Dibromo-1,2-diphenylethane (a vicinal dibromide)**



Diphenylacetylene (85%)

The twofold dehydrohalogenation takes place through a vinylic halide intermediate, which suggests that vinylic halides themselves should give alkynes when treated with strong base. (*Recall:* A *vinylic* substituent is one that is attached to a double-bond carbon.) This is indeed the case. For example:



(*Z*)-3-Chloro-2-buten-1-ol → **2-Butyn-1-ol**

8.3 Reactions of Alkynes: Addition of HX and X_2

You might recall from Section 1.9 that a carbon–carbon triple bond results from the interaction of two *sp*-hybridized carbon atoms. The two *sp* hybrid orbitals of carbon lie at an angle of 180° to each other along an axis perpendicular to the axes of the two unhybridized $2p_y$ and $2p_z$ orbitals. When two *sp*-hybridized carbons approach each other, one *sp*–*sp* σ bond and two *p*–*p* π bonds are

formed. The two remaining *sp* orbitals form bonds to other atoms at an angle of 180° from the carbon–carbon bond. Thus, acetylene is a linear molecule with H–C≡C bond angles of 180° (Figure 8.1).

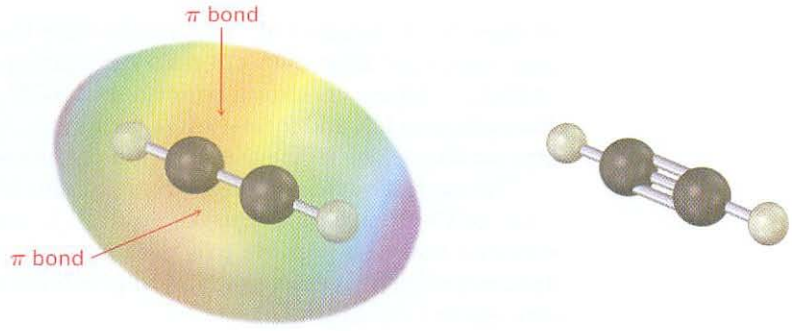


Figure 8.1 The structure of acetylene, H—C≡C—H. The H–C≡C bond angles are 180°, and the C≡C bond length is 120 pm. The electrostatic potential map shows that the π bonds create a negative (red) belt around the molecule.

The length of the carbon–carbon triple bond in acetylene is 120 pm, and the strength is approximately 835 kJ/mol (200 kcal/mol), making it the shortest and strongest known carbon–carbon bond. Measurements show that approximately 318 kJ/mol (76 kcal/mol) is needed to break a π bond in acetylene, a value some 50 kJ/mol larger than the 268 kJ/mol needed to break an alkene π bond.

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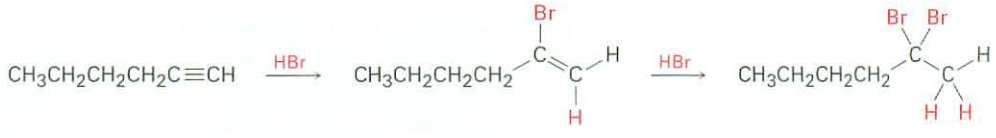
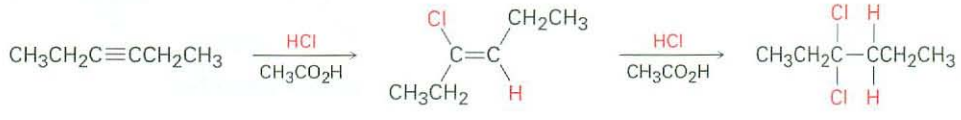
As a general rule, electrophiles undergo addition reactions with alkynes much as they do with alkenes. Take the reaction of alkynes with HX, for instance. The reaction often can be stopped after addition of 1 equivalent of HX, but reaction with an excess of HX leads to a dihalide product. For example, reaction of 1-hexyne with 2 equivalents of HBr yields 2,2-dibromohexane. As the following examples indicate, the regiochemistry of addition follows Markovnikov's rule: halogen adds to the more highly substituted side of the alkyne bond, and hydrogen adds to the less highly substituted side. Trans stereochemistry of H and X normally, although not always, results in the product.

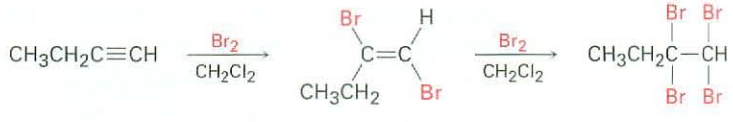


1-Hexyne **2-Bromo-1-hexene** **2,2-Dibromohexane**



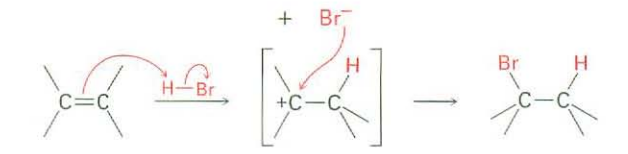
3-Hexyne **(*Z*)-3-Chloro-3-hexene** **3,3-Dichlorohexane**

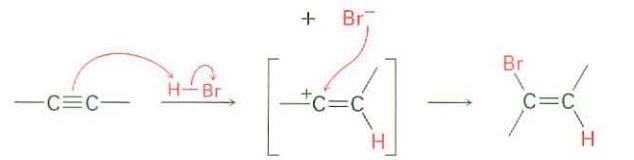
Bromine and chlorine also add to alkynes to give addition products, and trans stereochemistry again results.



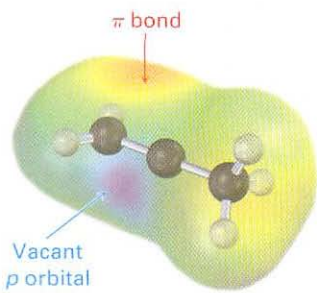
1-Butyne **(*E*)-1,2-Dibromo-1-butene** **1,1,2,2-Tetrabromobutane**

The mechanism of alkyne additions is similar but not identical to that of alkene additions. When an electrophile such as HBr adds to an *alkene* (Sections 6.7 and 6.8), the reaction takes place in two steps and involves an *alkyl* carbocation intermediate. If HBr were to add by the same mechanism to an *alkyne*, an analogous *vinylic* carbocation would be formed as the intermediate.





A vinylic carbocation has an *sp*-hybridized carbon and generally forms less readily than an alkyl carbocation (Figure 8.2). As a rule, a *secondary* vinylic carbocation forms about as readily as a *primary* alkyl carbocation, but a *primary* vinylic carbocation is so difficult to form that there is no clear evidence it even exists. Thus, many alkyne additions occur through more complex mechanistic pathways.



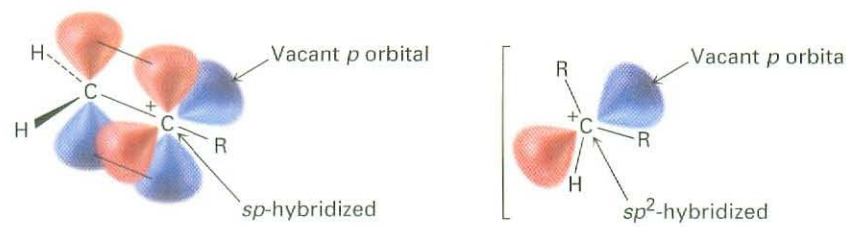
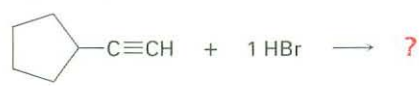


Figure 8.2 The structure of a secondary vinylic carbocation. The cationic carbon atom is *sp*-hybridized and has a vacant *p* orbital perpendicular to the plane of the π bond orbitals. Only one R group is attached to the positively charged carbon rather than two, as in a secondary alkyl carbocation. The electrostatic potential map shows that the most positive (blue) regions coincide with lobes of the vacant *p* orbital and are perpendicular to the most negative (red) regions associated with the π bond.

Problem 8.3 What products would you expect from the following reactions?

(a) $CH_3CH_2CH_2C{\equiv}CH + 2\ Cl_2 \longrightarrow$?

(b)  ?

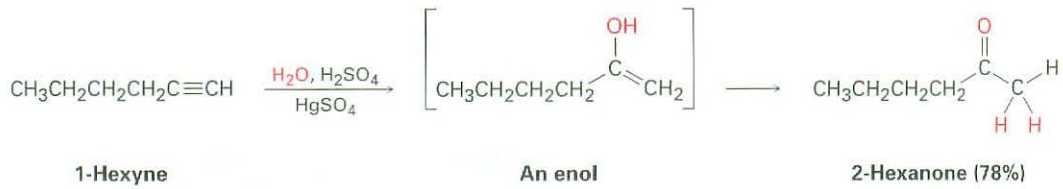
(c) $CH_3CH_2CH_2CH_2C{\equiv}CCH_3 + 1\ HBr \longrightarrow$?

8.4 Hydration of Alkynes

Like alkenes (Sections 7.4 and 7.5), alkynes can be hydrated by either of two methods. Direct addition of water catalyzed by mercury(II) ion yields the Markovnikov product, and indirect addition of water by a hydroboration/oxidation sequence yields the non-Markovnikov product.

Mercury(II)-Catalyzed Hydration of Alkynes

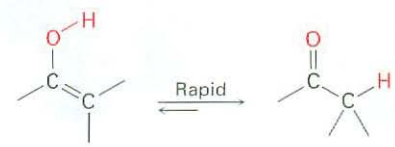
Alkynes don't react directly with aqueous acid but will undergo hydration readily in the presence of mercury(II) sulfate as a Lewis acid catalyst. The reaction occurs with Markovnikov regiochemistry: the −OH group adds to the more highly substituted carbon, and the −H attaches to the less highly substituted one.



1-Hexyne — An enol — 2-Hexanone (78%)

ThomsonNOW Click *Organic Interactive* to **learn to interconvert enol and carbonyl tautomers.**

Interestingly, the product actually isolated from alkyne hydration is not the vinylic alcohol, or **enol** (*ene* + *ol*), but is instead a *ketone*. Although the enol is an intermediate in the reaction, it immediately rearranges to a ketone by a process called *keto–enol tautomerism*. The individual keto and enol forms are said to be **tautomers**, a word used to describe constitutional isomers that interconvert rapidly. With few exceptions, the keto–enol tautomeric equilibrium lies on the side of the ketone; enols are almost never isolated. We'll look more closely at this equilibrium in Section 22.1.



Enol tautomer (less favored) — Keto tautomer (more favored)

As shown in Figure 8.3, the mechanism of the mercury(II)-catalyzed alkyne hydration reaction is analogous to the oxymercuration reaction of alkenes (Section 7.4). Electrophilic addition of mercury(II) ion to the alkyne gives a vinylic cation, which reacts with water and loses a proton to yield a mercury-containing enol intermediate. In contrast with alkene oxymercuration, however, no treatment with $NaBH_4$ is necessary to remove the mercury. The acidic reaction conditions alone are sufficient to effect replacement of mercury by hydrogen.

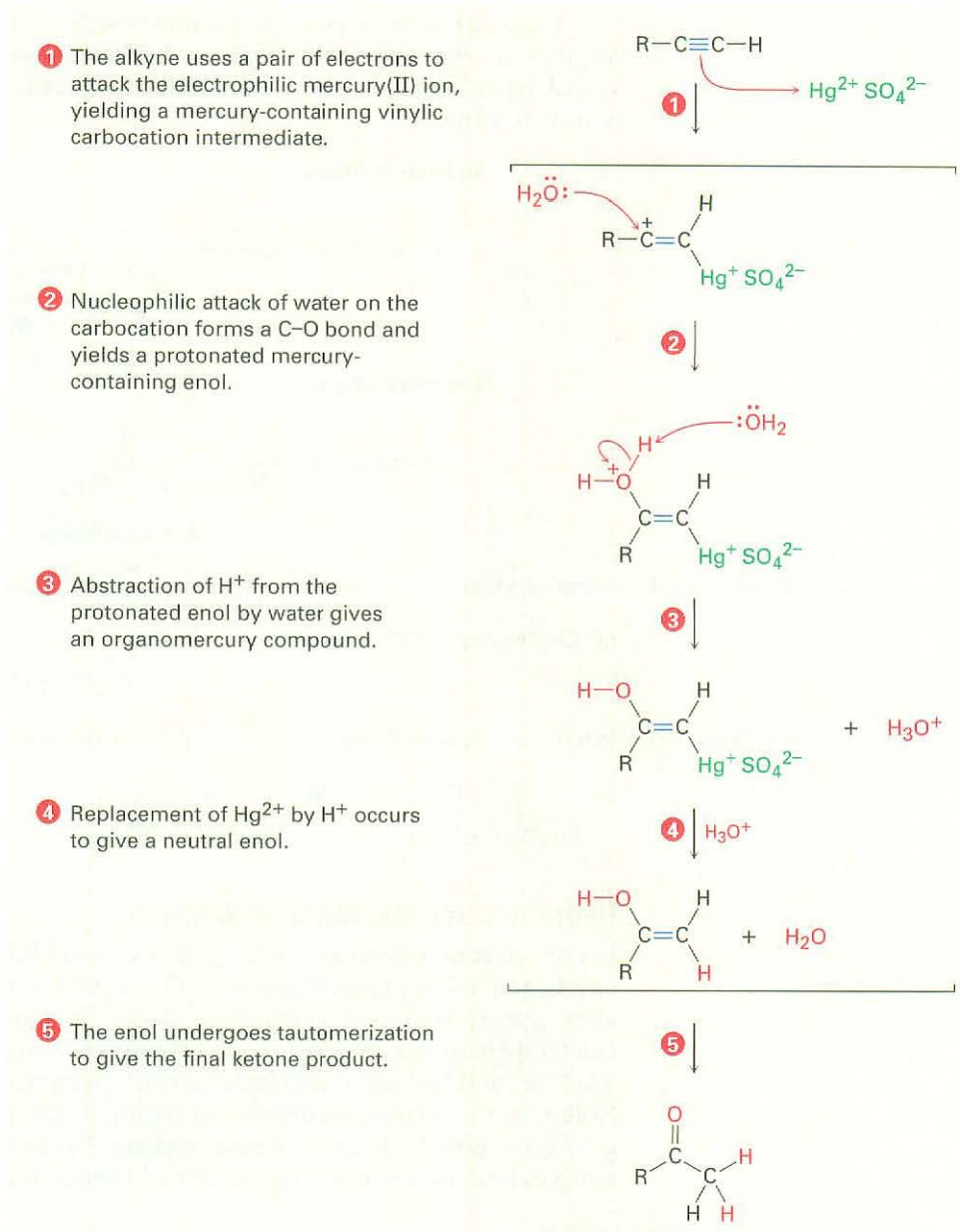
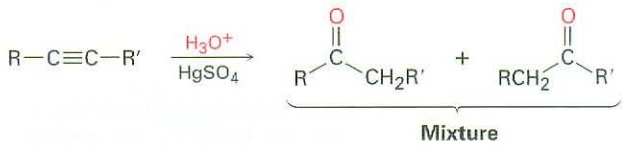


Figure 8.3 MECHANISM: Mechanism of the mercury(II)-catalyzed hydration of an alkyne to yield a ketone. The reaction occurs through initial formation of an intermediate enol, which rapidly tautomerizes to the ketone.

A mixture of both possible ketones results when an unsymmetrically substituted internal alkyne (RC≡CR′) is hydrated. The reaction is therefore most useful when applied to a terminal alkyne (RC≡CH) because only a methyl ketone is formed.

An internal alkyne



A terminal alkyne

A methyl ketone

Problem 8.4 What product would you obtain by hydration of the following alkynes?

(a) $CH_3CH_2CH_2C{\equiv}CCH_2CH_2CH_3$ **(b)** $CH_3CHCH_2C{\equiv}CCH_2CH_2CH_3$ (with CH_3 on the CH)

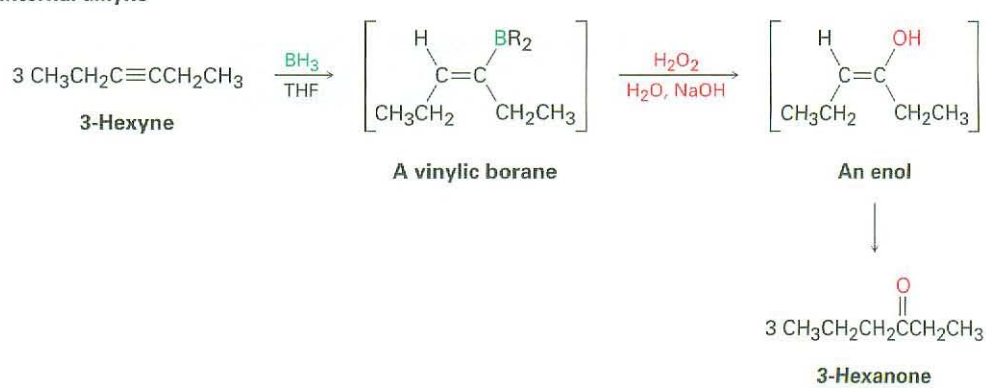
Problem 8.5 What alkynes would you start with to prepare the following ketones?

(a) $CH_3CH_2CH_2\overset{O}{\overset{\|}{C}}CH_3$ **(b)** $CH_3CH_2\overset{O}{\overset{\|}{C}}CH_2CH_3$

Hydroboration/Oxidation of Alkynes

Borane adds rapidly to an alkyne just as it does to an alkene, and the resulting vinylic borane can be oxidized by H_2O_2 to yield an enol. Tautomerization then gives either a ketone or an aldehyde, depending on the structure of the alkyne reactant. Hydroboration/oxidation of an internal alkyne such as 3-hexyne gives a ketone, and hydroboration/oxidation of a terminal alkyne gives an aldehyde. Note that the relatively unhindered terminal alkyne undergoes *two* additions, giving a doubly hydroborated intermediate. Oxidation with H_2O_2 at pH 8 then replaces both boron atoms by oxygen and generates the aldehyde.

An internal alkyne



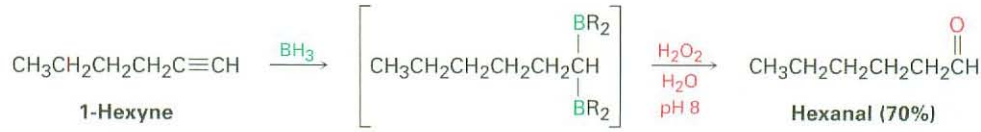
3-Hexyne

A vinylic borane

An enol

3-Hexanone

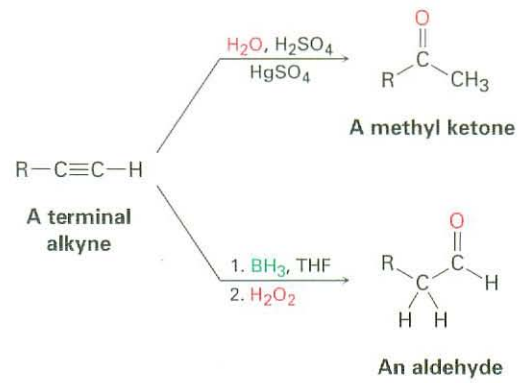
A terminal alkyne



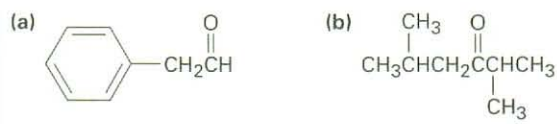
1-Hexyne

Hexanal (70%)

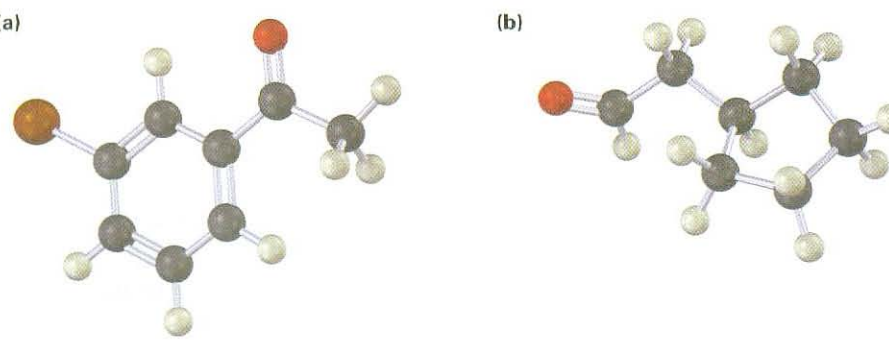
The hydroboration/oxidation sequence is complementary to the direct, mercury(II)-catalyzed hydration reaction of a terminal alkyne because different products result. Direct hydration with aqueous acid and mercury(II) sulfate leads to a methyl ketone, whereas hydroboration/oxidation of the same terminal alkyne leads to an aldehyde.



Problem 8.6 What alkyne would you start with to prepare each of the following compounds by a hydroboration/oxidation reaction?



Problem 8.7 How would you prepare the following carbonyl compounds starting from an alkyne (reddish brown = Br)?



8.5 Reduction of Alkynes

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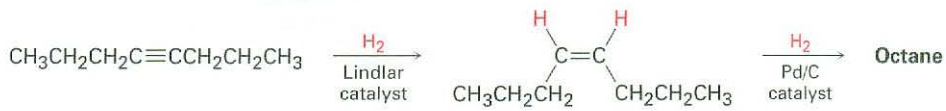
Alkynes are reduced to alkanes by addition of H_2 over a metal catalyst. The reaction occurs in steps through an alkene intermediate, and measurements indicate that the first step in the reaction is more exothermic than the second step.

$$HC{\equiv}CH \xrightarrow[\text{Catalyst}]{H_2} H_2C{=}CH_2 \qquad \Delta H^\circ_{\text{hydrog}} = -176 \text{ kJ/mol } (-42 \text{ kcal/mol})$$

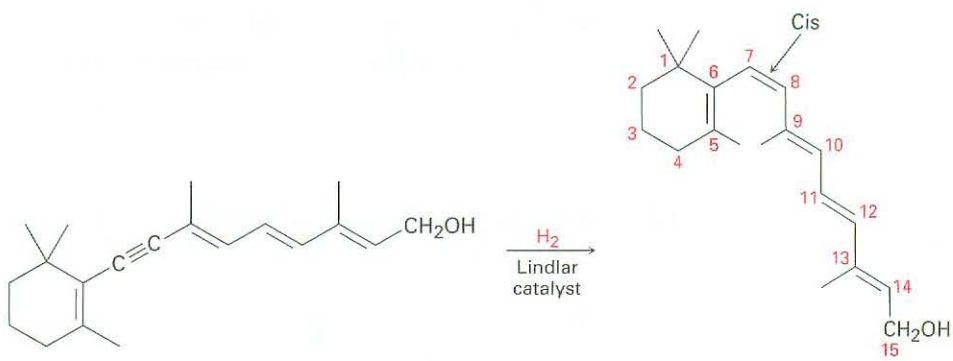
$$H_2C{=}CH_2 \xrightarrow[\text{Catalyst}]{H_2} CH_3{-}CH_3 \qquad \Delta H^\circ_{\text{hydrog}} = -137 \text{ kJ/mol } (-33 \text{ kcal/mol})$$

Complete reduction to the alkane occurs when palladium on carbon (Pd/C) is used as catalyst, but hydrogenation can be stopped at the alkene if the less active *Lindlar catalyst* is used. The Lindlar catalyst is a finely divided palladium metal that has been precipitated onto a calcium carbonate support and then deactivated by treatment with lead acetate and quinoline, an aromatic amine. The hydrogenation occurs with syn stereochemistry (Section 7.5), giving a cis alkene product.



4-Octyne **cis-4-Octene**

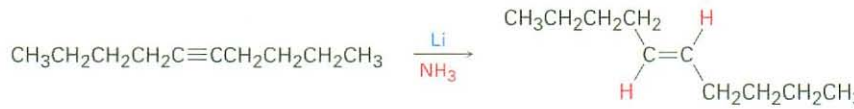
The alkyne hydrogenation reaction has been explored extensively by the Hoffmann–La Roche pharmaceutical company, where it is used in the commercial synthesis of vitamin A. The cis isomer of vitamin A produced on hydrogenation is converted to the trans isomer by heating.



7-*cis*-Retinol
(7-*cis*-vitamin A; vitamin A has a trans double bond at C7)

An alternative method for the conversion of an alkyne to an alkene uses sodium or lithium metal as the reducing agent in liquid ammonia as solvent. This method is complementary to the Lindlar reduction because it produces

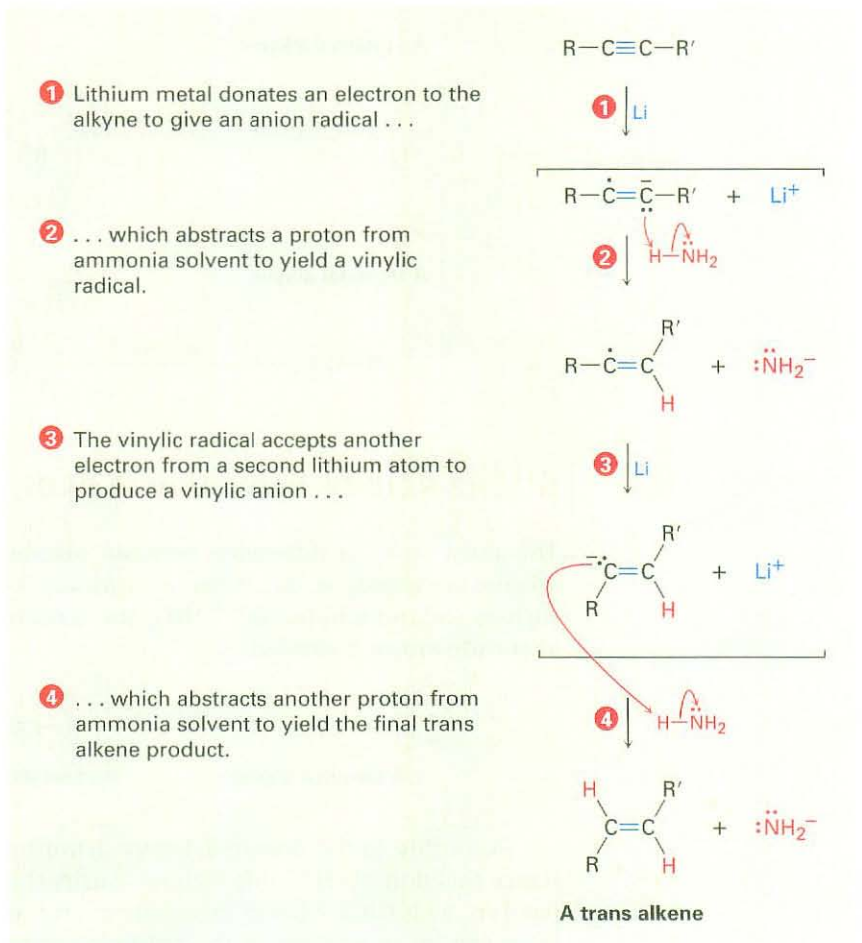
trans rather than cis alkenes. For example, 5-decyne gives *trans*-5-decene on treatment with lithium in liquid ammonia.



5-Decyne **trans-5-Decene (78%)**

Alkali metals dissolve in liquid ammonia at −33 °C to produce a deep blue solution containing the metal cation and ammonia-solvated electrons. When an alkyne is then added to the solution, an electron adds to the triple bond to yield an intermediate *anion radical*—a species that is both an anion (has a negative charge) and a radical (has an odd number of electrons). This anion radical is a strong base, which removes H^+ from ammonia to give a vinylic radical. Addition of a second electron to the vinylic radical gives a vinylic anion, which abstracts a second H^+ from ammonia to give trans alkene product. The mechanism is shown in Figure 8.4.

Figure 8.4 MECHANISM: Mechanism of the lithium/ammonia reduction of an alkyne to produce a trans alkene.



Trans stereochemistry of the alkene product is established during the second reduction step when the less hindered trans vinylic anion is formed from the vinylic radical. Vinylic radicals undergo rapid cis–trans equilibration, but vinylic anions equilibrate much less rapidly. Thus, the more stable trans vinylic anion is formed rather than the less stable cis anion and is then protonated without equilibration.

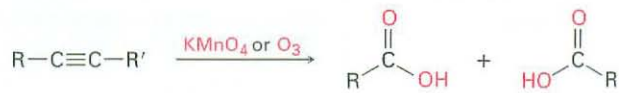
Problem 8.8 Using any alkyne needed, how would you prepare the following alkenes?
(a) *trans*-2-Octene (b) *cis*-3-Heptene (c) 3-Methyl-1-pentene

8.6 Oxidative Cleavage of Alkynes

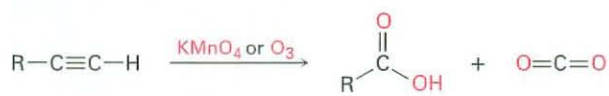
ThomsonNOW Click *Organic Interactive* to **use a web-based palette to predict products for the oxidative cleavage of alkynes.**

Alkynes, like alkenes, can be cleaved by reaction with powerful oxidizing agents such as ozone or $KMnO_4$, although the reaction is of little value and we mention it only for completeness. A triple bond is generally less reactive than a double bond and yields of cleavage products are sometimes low. The products obtained from cleavage of an internal alkyne are carboxylic acids; from a terminal alkyne, CO_2 is formed as one product.

An internal alkyne

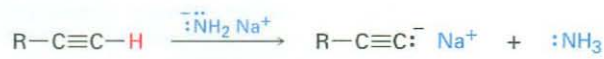


A terminal alkyne



8.7 Alkyne Acidity: Formation of Acetylide Anions

The most striking difference between alkenes and alkynes is that terminal alkynes are weakly acidic. When a terminal alkyne is treated with a strong base, such as sodium amide, $Na^+ {}^-NH_2$, the terminal hydrogen is removed and an **acetylide anion** is formed.



A terminal alkyne **An acetylide anion**

According to the Brønsted–Lowry definition (Section 2.7), an acid is a substance that donates H^+. Although we usually think of oxyacids (H_2SO_4, HNO_3) or halogen acids (HCl, HBr) in this context, any compound containing a hydrogen atom can be an acid under the right circumstances. By measuring dissociation

constants of different acids and expressing the results as pK_a values, an acidity order can be established. Recall from Section 2.8 that a low pK_a corresponds to a strong acid and a high pK_a corresponds to a weak acid.

Where do hydrocarbons lie on the acidity scale? As the data in Table 8.1 show, both methane ($pK_a \approx 60$) and ethylene ($pK_a = 44$) are very weak acids and thus do not react with any of the common bases. Acetylene, however, has $pK_a = 25$ and can be deprotonated by the conjugate base of any acid whose pK_a is greater than 25. Amide ion (NH_2^-), for example, the conjugate base of ammonia ($pK_a = 35$), is often used to deprotonate terminal alkynes.

Table 8.1 Acidity of Simple Hydrocarbons

Family	Example	K_a	pK_a	
Alkyne	HC≡CH	10^{-25}	25	Stronger acid
Alkene	$H_2C{=}CH_2$	10^{-44}	44	
Alkane	CH_4	10^{-60}	60	Weaker acid

Why are terminal alkynes more acidic than alkenes or alkanes? In other words, why are acetylide anions more stable than vinylic or alkyl anions? The simplest explanation involves the hybridization of the negatively charged carbon atom. An acetylide anion has an *sp*-hybridized carbon, so the negative charge resides in an orbital that has 50% "*s* character." A vinylic anion has an sp^2-hybridized carbon with 33% *s* character, and an alkyl anion (sp^3) has only 25% *s* character. Because *s* orbitals are nearer the positive nucleus and lower in energy than *p* orbitals, the negative charge is stabilized to a greater extent in an orbital with higher *s* character (Figure 8.5).

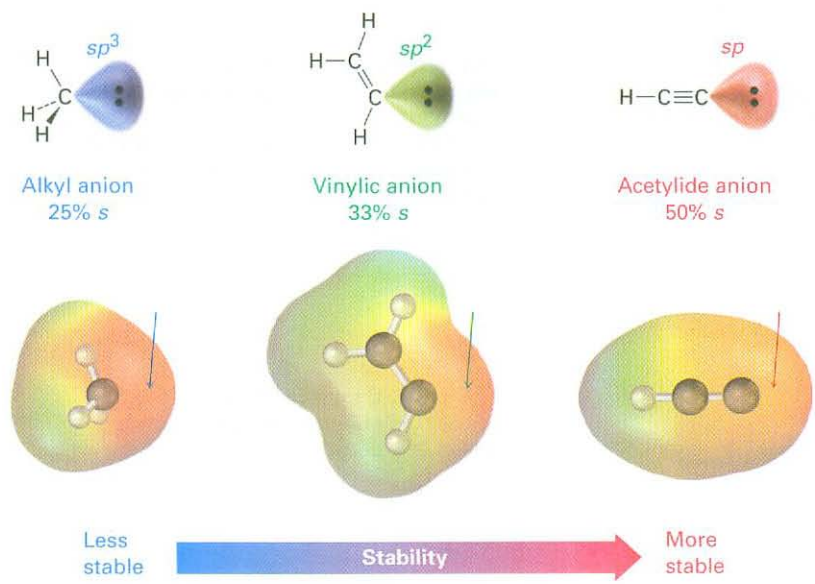


Figure 8.5 A comparison of alkyl, vinylic, and acetylide anions. The acetylide anion, with *sp* hybridization, has more *s* character and is more stable. Electrostatic potential maps show that placing the negative charge closer to the carbon nucleus makes carbon appear less negative (red).

The presence of a negative charge and an unshared electron pair on carbon makes acetylide anions strongly nucleophilic. As a result, they react with many different kinds of electrophiles.

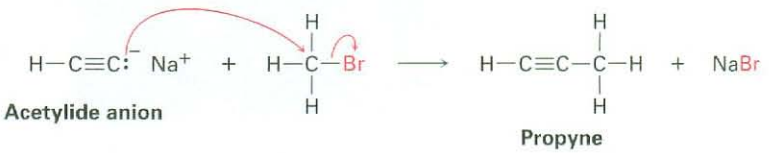
Problem 8.9 The pK_a of acetone, CH_3COCH_3, is 19.3. Which of the following bases is strong enough to deprotonate acetone?

(a) KOH (pK_a of H_2O = 15.7)
(b) $Na^+ {}^-C{\equiv}CH$ (pK_a of C_2H_2 = 25)
(c) $NaHCO_3$ (pK_a of H_2CO_3 = 6.4)
(d) $NaOCH_3$ (pK_a of CH_3OH = 15.6)

8.8 Alkylation of Acetylide Anions

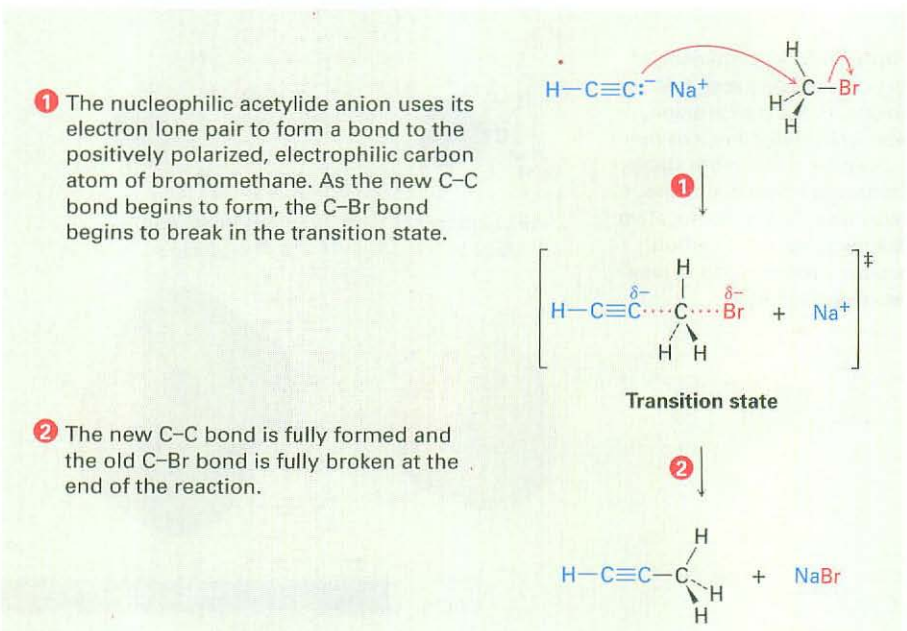
ThomsonNOW Click *Organic Interactive* to **use a web-based palette to predict products for alkyne alkylation reactions.**

The negative charge and unshared electron pair on carbon make an acetylide anion strongly nucleophilic. As a result, an acetylide anion can react with an alkyl halide such as bromomethane to substitute for the halogen and yield a new alkyne product.



We won't study the details of this substitution reaction until Chapter 11 but for now can picture it as happening by the pathway shown in Figure 8.6. The nucleophilic acetylide ion uses an electron pair to form a bond to the positively polarized, electrophilic carbon atom of bromomethane. As the new C–C bond forms, Br^- departs, taking with it the electron pair from the former C–Br bond and yielding propyne as product. We call such a reaction an **alkylation** because a new alkyl group has become attached to the starting alkyne.

Active Figure 8.6
MECHANISM: A mechanism for the alkylation reaction of acetylide anion with bromomethane to give propyne. *Sign in at* **www.thomsonedu.com** *to see a simulation based on this figure and to take a short quiz.*



Alkyne alkylation is not limited to acetylene itself. *Any* terminal alkyne can be converted into its corresponding anion and then alkylated by treatment with an alkyl halide, yielding an internal alkyne. For example, conversion of 1-hexyne into its anion, followed by reaction with 1-bromobutane, yields 5-decyne.

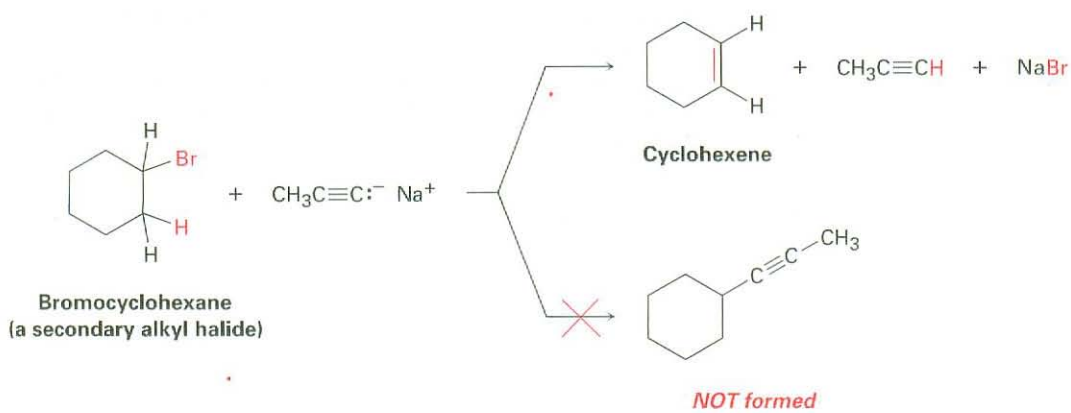
$$\underset{\textbf{1-Hexyne}}{CH_3CH_2CH_2CH_2C{\equiv}CH} \xrightarrow[2.\ CH_3CH_2CH_2CH_2Br]{1.\ NaNH_2,\ NH_3} \underset{\textbf{5-Decyne (76\%)}}{CH_3CH_2CH_2CH_2C{\equiv}CCH_2CH_2CH_2CH_3}$$

Because of its generality, acetylide alkylation is an excellent method for preparing substituted alkynes from simpler precursors. A terminal alkyne can be prepared by alkylation of acetylene itself, and an internal alkyne can be prepared by further alkylation of a terminal alkyne.

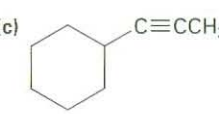
$$\underset{\textbf{Acetylene}}{H{-}C{\equiv}C{-}H} \xrightarrow{NaNH_2} \left[H{-}C{\equiv}C{:}^{-}\ Na^{+}\right] \xrightarrow{RCH_2Br} \underset{\textbf{A terminal alkyne}}{H{-}C{\equiv}C{-}CH_2R}$$

$$\underset{\textbf{A terminal alkyne}}{R{-}C{\equiv}C{-}H} \xrightarrow{NaNH_2} \left[R{-}C{\equiv}C{:}^{-}\ Na^{+}\right] \xrightarrow{R'CH_2Br} \underset{\textbf{An internal alkyne}}{R{-}C{\equiv}C{-}CH_2R'}$$

The alkylation reaction is limited to the use of primary alkyl bromides and alkyl iodides because acetylide ions are sufficiently strong bases to cause dehydrohalogenation instead of substitution when they react with secondary and tertiary alkyl halides. For example, reaction of bromocyclohexane with propyne anion yields the elimination product cyclohexene rather than the substitution product 1-propynylcyclohexane.



Problem 8.10 Show the terminal alkyne and alkyl halide from which the following products can be obtained. If two routes look feasible, list both.

(a) $CH_3CH_2CH_2C{\equiv}CCH_3$ (b) $(CH_3)_2CHC{\equiv}CCH_2CH_3$ (c) 

Problem 8.11 How would you prepare *cis*-2-butene starting from propyne, an alkyl halide, and any other reagents needed? This problem can't be worked in a single step. You'll have to carry out more than one reaction.

8.9 An Introduction to Organic Synthesis

There are many reasons for carrying out the laboratory synthesis of an organic compound. In the pharmaceutical industry, new organic molecules are designed and synthesized in the hope that some might be useful new drugs. In the chemical industry, syntheses are done to devise more economical routes to known compounds. In academic laboratories, the synthesis of complex molecules is sometimes done purely for the intellectual challenge involved in mastering so difficult a subject. The successful synthesis route is a highly creative work that is sometimes described by such subjective terms as *elegant* or *beautiful*.

In this book, too, we will often devise syntheses of molecules from simpler precursors. Our purpose, however, is pedagogical. The ability to plan a workable synthetic sequence requires knowledge of a variety of organic reactions. Furthermore, it requires the practical ability to fit together the steps in a sequence such that each reaction does only what is desired without causing changes elsewhere in the molecule. Working synthesis problems is an excellent way to learn organic chemistry.

Some of the syntheses we plan may seem trivial. Here's an example:

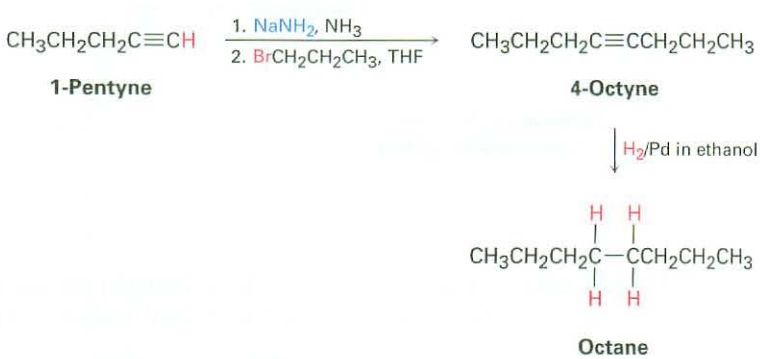
WORKED EXAMPLE 8.1 ***Devising a Synthesis Route***

Prepare octane from 1-pentyne.

1-Pentyne **Octane**

Strategy Compare the product with the starting material, and catalog the differences. In this case, we need to add three carbons to the chain and reduce the triple bond. Since the starting material is a terminal alkyne that can be alkylated, we might first prepare the acetylide anion of 1-pentyne, let it react with 1-bromopropane, and then reduce the product using catalytic hydrogenation.

Solution



1-Pentyne **4-Octyne** **Octane**

The synthesis route just presented will work perfectly well but has little practical value because you can simply *buy* octane from any of several dozen

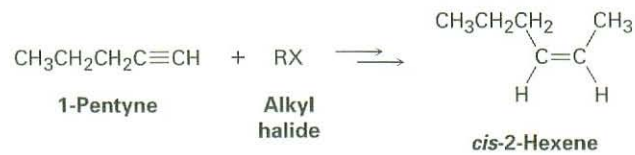
chemical suppliers. The value of working the problem is that it makes you approach a chemical problem in a logical way, draw on your knowledge of chemical reactions, and organize that knowledge into a workable plan—it helps you learn organic chemistry.

There's no secret to planning an organic synthesis: it takes a knowledge of the different reactions, some discipline, and a lot of practice. The only real trick is to work backward in what is often referred to as a **retrosynthetic** direction. Don't look at the starting material and ask yourself what reactions it might undergo. Instead, look at the final product and ask, "What was the immediate precursor of that product?" For example, if the final product is an alkyl halide, the immediate precursor might be an alkene (to which you could add HX). If the final product is a cis alkene, the immediate precursor might be an alkyne (which you could hydrogenate using the Lindlar catalyst). Having found an immediate precursor, work backward again, one step at a time, until you get back to the starting material. You have to keep the starting material in mind, of course, so that you can work back to it, but you don't want that starting material to be your main focus.

Let's work several more examples of increasing complexity.

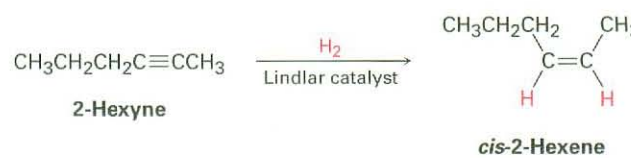
WORKED EXAMPLE 8.2 *Devising a Synthesis Route*

Synthesize *cis*-2-hexene from 1-pentyne and any alkyl halide needed. More than one step is required.



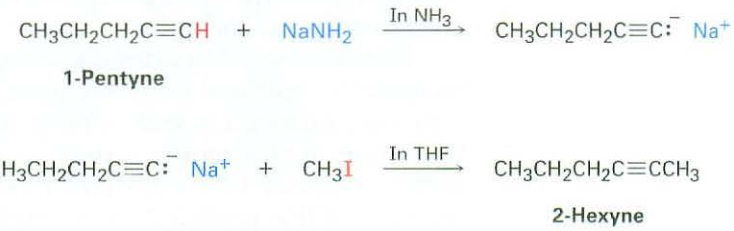
Strategy When undertaking any synthesis problem, you should look at the product, identify the functional groups it contains, and then ask yourself how those functional groups can be prepared. Always work in a retrosynthetic sense, one step at a time.

The product in this case is a cis-disubstituted alkene, so the first question is, "What is an immediate precursor of a cis-disubstituted alkene?" We know that an alkene can be prepared from an alkyne by reduction and that the right choice of experimental conditions will allow us to prepare either a trans-disubstituted alkene (using lithium in liquid ammonia) or a cis-disubstituted alkene (using catalytic hydrogenation over the Lindlar catalyst). Thus, reduction of 2-hexyne by catalytic hydrogenation using the Lindlar catalyst should yield *cis*-2-hexene.

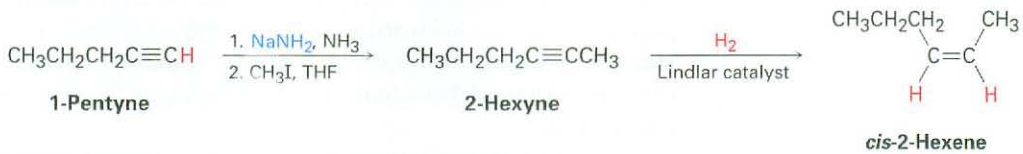


Next ask, "What is an immediate precursor of 2-hexyne?" We've seen that an internal alkyne can be prepared by alkylation of a terminal alkyne anion. In the present

instance, we're told to start with 1-pentyne and an alkyl halide. Thus, alkylation of the anion of 1-pentyne with iodomethane should yield 2-hexyne.

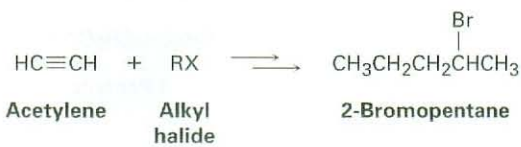


Solution *cis*-2-Hexene can be synthesized from the given starting materials in three steps.

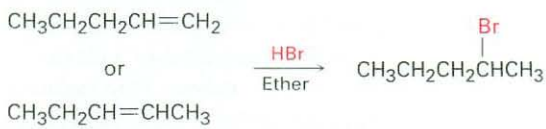


WORKED EXAMPLE 8.3 *Devising a Synthesis Route*

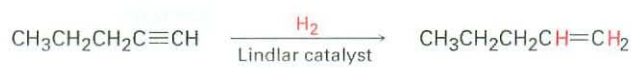
Synthesize 2-bromopentane from acetylene and any alkyl halide needed. More than one step is required.



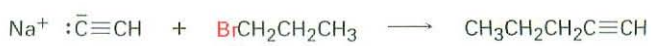
Strategy Identify the functional group in the product (an alkyl bromide) and work the problem retrosynthetically. "What is an immediate precursor of an alkyl bromide?" Perhaps an alkene plus HBr. Of the two possibilities, addition of HBr to 1-pentene looks like a better choice than addition to 2-pentene because the latter reaction would give a mixture of isomers.



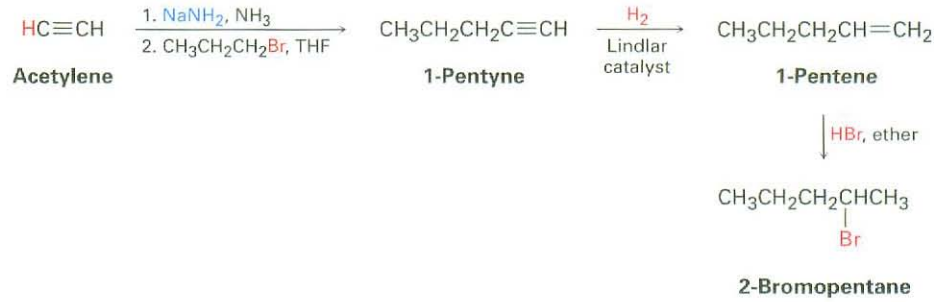
"What is an immediate precursor of an alkene?" Perhaps an alkyne, which could be reduced.



"What is an immediate precursor of a terminal alkyne?" Perhaps sodium acetylide and an alkyl halide.



Solution The desired product can be synthesized in four steps from acetylene and 1-bromopropane.



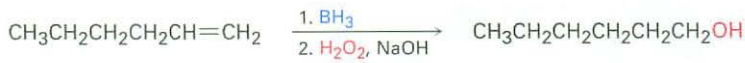
Acetylene **1-Pentyne** **1-Pentene** **2-Bromopentane**

WORKED EXAMPLE 8.4 *Devising a Synthesis Route*

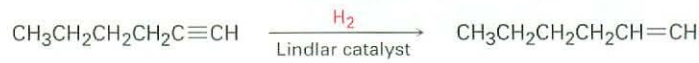
Synthesize 1-hexanol (1-hydroxyhexane) from acetylene and an alkyl halide.

Acetylene **Alkyl halide** **1-Hexanol**

Strategy "What is an immediate precursor of a primary alcohol?" Perhaps a terminal alkene, which could be hydrated with non-Markovnikov regiochemistry by reaction with borane followed by oxidation with H_2O_2.

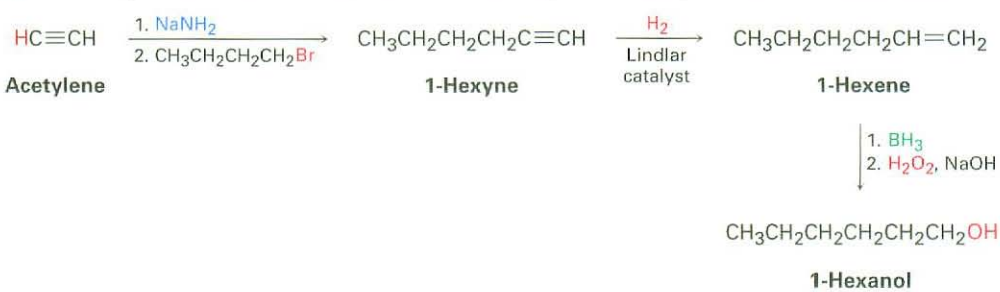


"What is an immediate precursor of a terminal alkene?" Perhaps a terminal alkyne, which could be reduced.



"What is an immediate precursor of 1-hexyne?" Perhaps acetylene and 1-bromobutane.

Solution The synthesis can be completed in four steps from acetylene and 1-bromobutane:



Acetylene **1-Hexyne** **1-Hexene** **1-Hexanol**

Problem 8.12 Beginning with 4-octyne as your only source of carbon, and using any inorganic reagents necessary, how would you synthesize the following compounds?

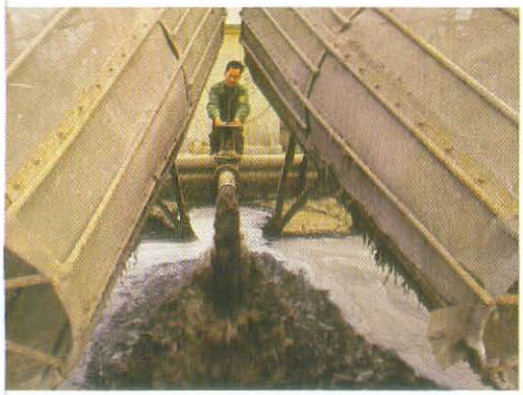
(a) *cis*-4-Octene (b) Butanal (c) 4-Bromooctane
(d) 4-Octanol (e) 4,5-Dichlorooctane (f) Butanoic acid

Problem 8.13 Beginning with acetylene and any alkyl halides needed, how would you synthesize the following compounds?

(a) Decane (b) 2,2-Dimethylhexane
(c) Hexanal (d) 2-Heptanone

Focus On . . .

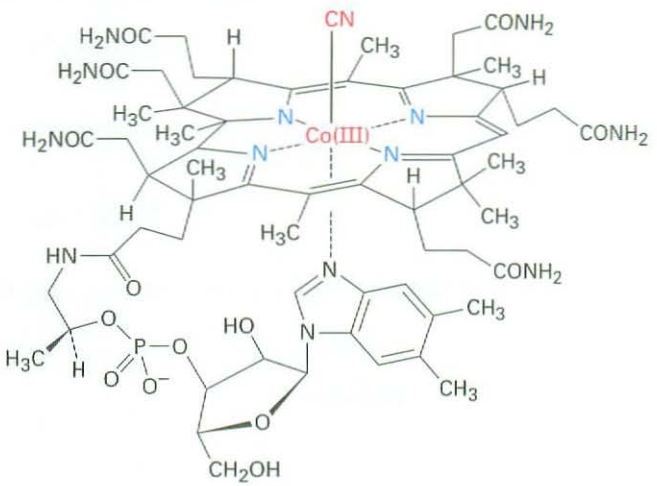
The Art of Organic Synthesis



© Bob Sacha/Corbis

Vitamin B_{12} has been synthesized from scratch in the laboratory, but bacteria growing on sludge from municipal sewage plants do a much better job.

If you think some of the synthesis problems at the end of this chapter are hard, try devising a synthesis of vitamin B_{12} starting only from simple substances you can buy in a chemical catalog. This extraordinary achievement was reported in 1973 as the culmination of a collaborative effort headed by Robert B. Woodward of Harvard University and Albert Eschenmoser of the Swiss Federal Institute of Technology in Zürich. More than 100 graduate students and postdoctoral associates contributed to the work, which took more than a decade.



Vitamin B_{12}

(continued)

Why put such extraordinary effort into the laboratory synthesis of a molecule so easily obtained from natural sources? There are many reasons. On a basic human level, a chemist might be motivated primarily by the challenge, much as a climber might be challenged by the ascent of a difficult peak. Beyond the pure challenge, the completion of a difficult synthesis is also valuable for the way in which it establishes new standards and raises the field to a new level. If vitamin B_{12} can be made, then why can't any molecule found in nature be made? Indeed, the three and a half decades that have passed since the work of Woodward and Eschenmoser have seen the laboratory synthesis of many enormously complex and valuable substances. Sometimes these substances—the anticancer compound Taxol, for instance—are not easily available in nature, so laboratory synthesis is the only method for obtaining larger quantities.

But perhaps the most important reason for undertaking a complex synthesis is that, in so doing, new reactions and new chemistry are discovered. It invariably happens in synthesis that a point is reached at which the planned route fails. At such a time, the only alternatives are to quit or to devise a way around the difficulty. New reactions and new principles come from such situations, and it is in this way that the science of organic chemistry grows richer. In the synthesis of vitamin B_{12}, for example, unexpected findings emerged that led to the understanding of an entire new class of reactions—the *pericyclic* reactions that are the subject of Chapter 30 in this book. From synthesizing vitamin B_{12} to understanding pericyclic reactions—no one could have possibly predicted such a link at the beginning of the synthesis, but that is the way of science.

SUMMARY AND KEY WORDS

acetylide anion, 270
alkylation, 272
alkyne (RC≡CR), 259
enol, 264
retrosynthetic, 275
tautomer, 264

An **alkyne** is a hydrocarbon that contains a carbon–carbon triple bond. Alkyne carbon atoms are *sp*-hybridized, and the triple bond consists of one *sp*–*sp* σ bond and two *p*–*p* π bonds. There are relatively few general methods of alkyne synthesis. Two good ones are the alkylation of an acetylide anion with a primary alkyl halide and the twofold elimination of HX from a vicinal dihalide.

The chemistry of alkynes is dominated by electrophilic addition reactions, similar to those of alkenes. Alkynes react with HBr and HCl to yield *vinylic* halides and with Br_2 and Cl_2 to yield 1,2-dihalides (*vicinal* dihalides). Alkynes can be hydrated by reaction with aqueous sulfuric acid in the presence of mercury(II) catalyst. The reaction leads to an intermediate **enol** that immediately isomerizes to yield a ketone **tautomer**. Since the addition reaction occurs with Markovnikov regiochemistry, a methyl ketone is produced from a terminal alkyne. Alternatively, hydroboration/oxidation of a terminal alkyne yields an aldehyde.

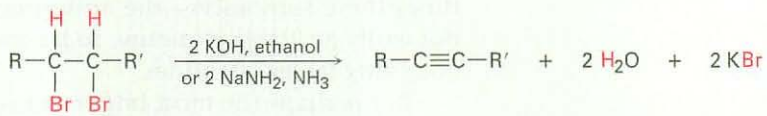
Alkynes can be reduced to yield alkenes and alkanes. Complete reduction of the triple bond over a palladium hydrogenation catalyst yields an alkane; partial reduction by catalytic hydrogenation over a *Lindlar catalyst* yields a cis alkene. Reduction of the alkyne with lithium in ammonia yields a trans alkene.

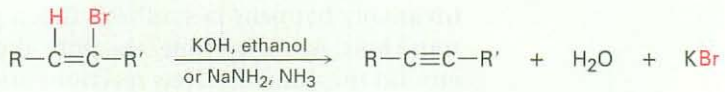
Terminal alkynes are weakly acidic. The alkyne hydrogen can be removed by a strong base such as $Na^+ \ ^-NH_2$ to yield an **acetylide anion**. An acetylide

anion acts as a nucleophile and can displace a halide ion from a primary alkyl halide in an **alkylation** reaction. Acetylide anions are more stable than either alkyl anions or vinylic anions because their negative charge is in a hybrid orbital with 50% *s* character, allowing the charge to be closer to the nucleus.

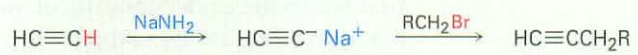
SUMMARY OF REACTIONS

1. Preparation of alkynes
   (a) Dehydrohalogenation of vicinal dihalides (Section 8.2)

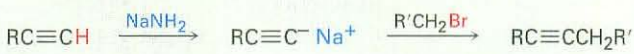




   (b) Alkylation of acetylide anions (Section 8.8)

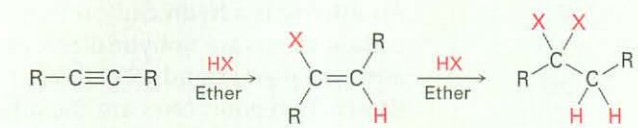


Acetylene — A terminal alkyne

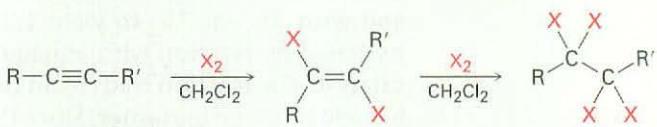


A terminal alkyne — An internal alkyne

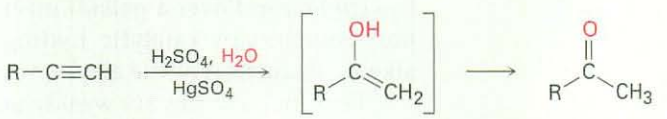
2. Reactions of alkynes
   (a) Addition of HCl and HBr (Section 8.3)



   (b) Addition of Cl_2 and Br_2 (Section 8.3)

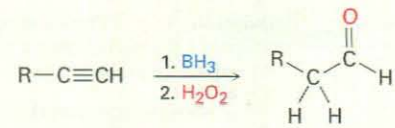


   (c) Hydration (Section 8.4)
      (1) Mercuric sulfate catalyzed



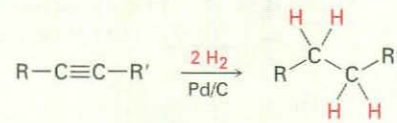
An enol — A methyl ketone

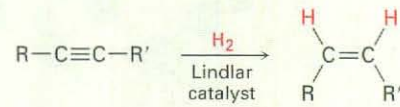
(2) Hydroboration/oxidation



An aldehyde

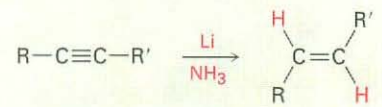
(d) Reduction (Section 8.5)
(1) Catalytic hydrogenation





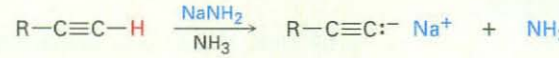
A cis alkene

(2) Lithium in liquid ammonia



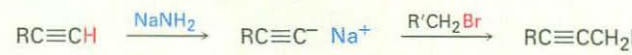
A trans alkene

(e) Conversion into acetylide anions (Section 8.7)



(f) Alkylation of acetylide anions (Section 8.8)

Acetylene **A terminal alkyne**



A terminal alkyne **An internal alkyne**

EXERCISES

Organic KNOWLEDGE TOOLS

ThomsonNOW Sign in at **www.thomsonedu.com** to assess your knowledge of this chapter's topics by taking a pre-test. The pre-test will link you to interactive organic chemistry resources based on your score in each concept area.

Online homework for this chapter may be assigned in Organic OWL.

■ indicates problems assignable in Organic OWL.

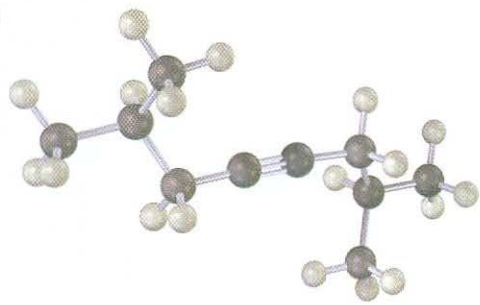
VISUALIZING CHEMISTRY

(Problems 8.1–8.13 appear within the chapter.)

8.14 ■ Name the following alkynes, and predict the products of their reaction with (i) H_2 in the presence of a Lindlar catalyst and (ii) H_3O^+ in the presence of $HgSO_4$:

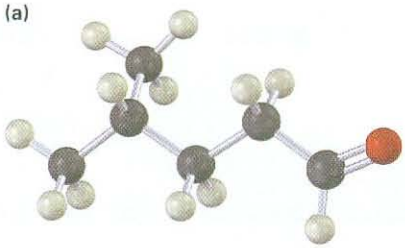
(a)

(b)

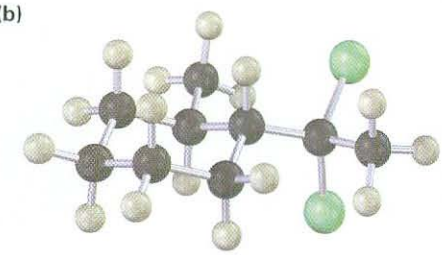


8.15 ■ From what alkyne might each of the following substances have been made? (Yellow-green = Cl.)

(a)

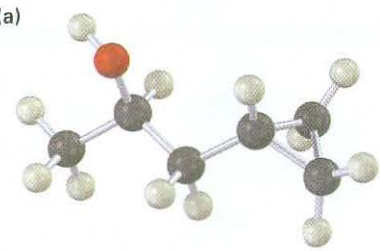


(b)

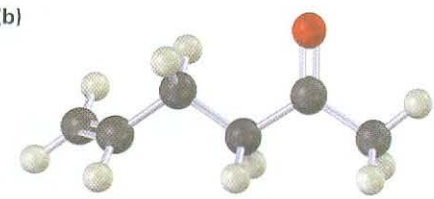


8.16 How would you prepare the following substances, starting from any compounds having four carbons or fewer?

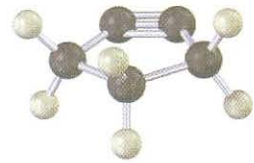
(a)



(b)

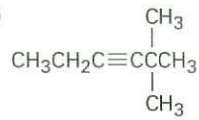


8.17 The following cycloalkyne is too unstable to exist. Explain.

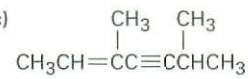


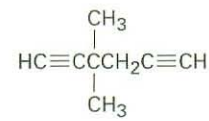
ADDITIONAL PROBLEMS

8.18 Give IUPAC names for the following compounds:

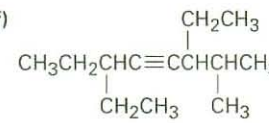
(a)


(b) $CH_3C{\equiv}CCH_2C{\equiv}CCH_2CH_3$

(c)


(d)


(e) $H_2C{=}CHCH{=}CHC{\equiv}CH$

(f)


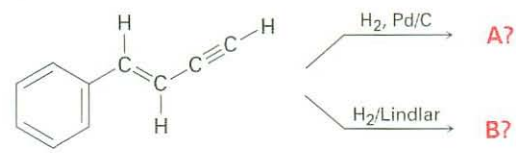
8.19 ■ Draw structures corresponding to the following names:

(a) 3,3-Dimethyl-4-octyne
(b) 3-Ethyl-5-methyl-1,6,8-decatriyne
(c) 2,2,5,5-Tetramethyl-3-hexyne
(d) 3,4-Dimethylcyclodecyne
(e) 3,5-Heptadien-1-yne
(f) 3-Chloro-4,4-dimethyl-1-nonen-6-yne
(g) 3-*sec*-Butyl-1-heptyne
(h) 5-*tert*-Butyl-2-methyl-3-octyne

8.20 The following two hydrocarbons have been isolated from various plants in the sunflower family. Name them according to IUPAC rules.

(a) $CH_3CH{=}CHC{\equiv}CC{\equiv}CCH{=}CHCH{=}CHCH{=}CH_2$ (all trans)
(b) $CH_3C{\equiv}CC{\equiv}CC{\equiv}CC{\equiv}CC{\equiv}CCH{=}CH_2$

8.21 ■ Predict the products of the following reactions:



8.22 ■ A hydrocarbon of unknown structure has the formula C_8H_{10}. On catalytic hydrogenation over the Lindlar catalyst, 1 equivalent of H_2 is absorbed. On hydrogenation over a palladium catalyst, 3 equivalents of H_2 are absorbed.

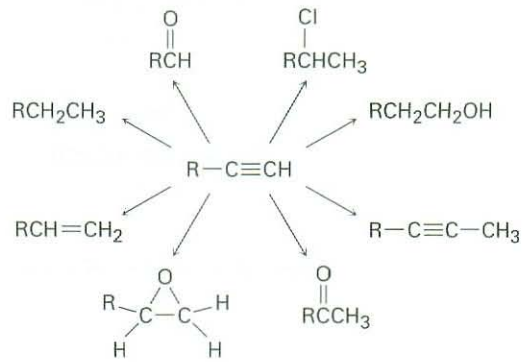
(a) How many degrees of unsaturation are present in the unknown?
(b) How many triple bonds are present?
(c) How many double bonds are present?
(d) How many rings are present?
(e) Draw a structure that fits the data.

8.23 ■ Predict the products from reaction of 1-hexyne with the following reagents:
(a) 1 equiv HBr (b) 1 equiv Cl_2
(c) H_2, Lindlar catalyst (d) $NaNH_2$ in NH_3, then CH_3Br
(e) H_2O, H_2SO_4, $HgSO_4$ (f) 2 equiv HCl

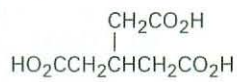
8.24 ■ Predict the products from reaction of 5-decyne with the following reagents:
(a) H_2, Lindlar catalyst (b) Li in NH_3
(c) 1 equiv Br_2 (d) BH_3 in THF, then H_2O_2, OH^-
(e) H_2O, H_2SO_4, $HgSO_4$ (f) Excess H_2, Pd/C catalyst

8.25 ■ Predict the products from reaction of 2-hexyne with the following reagents:
(a) 2 equiv Br_2 (b) 1 equiv HBr (c) Excess HBr
(d) Li in NH_3 (e) H_2O, H_2SO_4, $HgSO_4$

8.26 ■ How would you carry out the following conversions? More than one step may be needed in some instances.

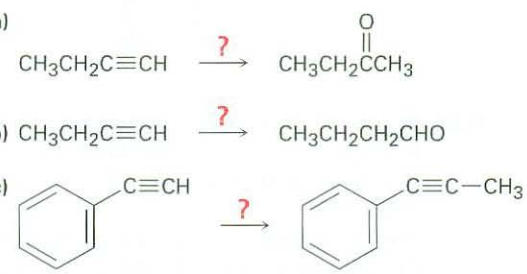


8.27 ■ Hydrocarbon A has the formula C_9H_{12} and absorbs 3 equivalents of H_2 to yield B, C_9H_{18}, when hydrogenated over a Pd/C catalyst. On treatment of A with aqueous H_2SO_4 in the presence of mercury(II), two isomeric ketones, C and D, are produced. Oxidation of A with $KMnO_4$ gives a mixture of acetic acid (CH_3CO_2H) and the tricarboxylic acid E. Propose structures for compounds A–D, and write the reactions.



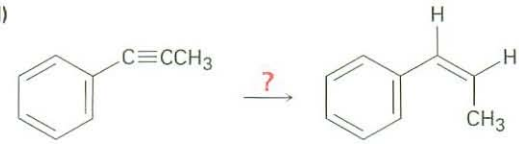
E

8.28 How would you carry out the following reactions?



■ Assignable in OWL

(d)



(e) $CH_3CH_2C{\equiv}CH \xrightarrow{?} CH_3CH_2CO_2H$

(f) $CH_3CH_2CH_2CH_2CH{=}CH_2 \xrightarrow[\text{(2 steps)}]{?} CH_3CH_2CH_2CH_2C{\equiv}CH$

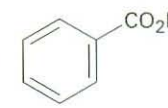
8.29 Occasionally, chemists need to *invert* the stereochemistry of an alkene—that is, to convert a cis alkene to a trans alkene, or vice versa. There is no one-step method for doing an alkene inversion, but the transformation can be carried out by combining several reactions in the proper sequence. How would you carry out the following reactions?

(a) *trans*-5-Decene $\xrightarrow{?}$ *cis*-5-Decene

(b) *cis*-5-Decene $\xrightarrow{?}$ *trans*-5-Decene

8.30 ■ Propose structures for hydrocarbons that give the following products on oxidative cleavage by $KMnO_4$ or O_3:

(a) $CO_2 + CH_3(CH_2)_5CO_2H$

(b) $CH_3CO_2H +$ 

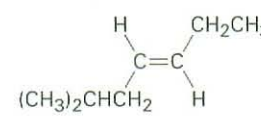
(c) $HO_2C(CH_2)_8CO_2H$

(d) $CH_3CHO + CH_3\overset{\overset{O}{\|}}{C}CH_2CH_2CO_2H + CO_2$

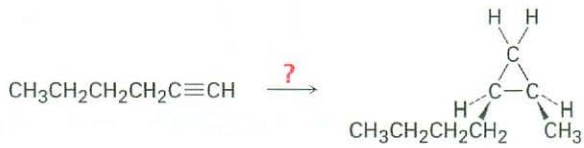
(e) $HC\overset{\overset{O}{\|}}{C}H_2CH_2CH_2CH_2\overset{\overset{O}{\|}}{C}CO_2H + CO_2$

8.31 ■ Each of the following syntheses requires more than one step. How would you carry them out?

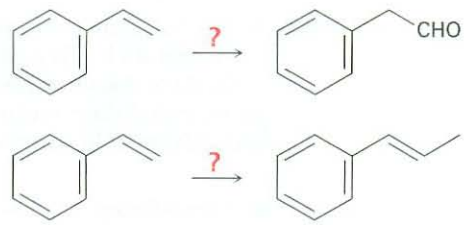
(a) $CH_3CH_2CH_2C{\equiv}CH \xrightarrow{?} CH_3CH_2CH_2CHO$

(b) $(CH_3)_2CHCH_2C{\equiv}CH \xrightarrow{?}$ 

8.32 How would you carry out the following transformation? More than one step is needed.



8.33 How would you carry out the following conversions? More than one step is needed in each case.



8.34 Synthesize the following compounds using 1-butyne as the only source of carbon, along with any inorganic reagents you need. More than one step may be needed.

(a) 1,1,2,2-Tetrachlorobutane **(b)** 1,1-Dichloro-2-ethylcyclopropane

8.35 ■ How would you synthesize the following compounds from acetylene and any alkyl halides with four or fewer carbons? More than one step may be required.

(a) $CH_3CH_2CH_2C{\equiv}CH$ **(b)** $CH_3CH_2C{\equiv}CCH_2CH_3$

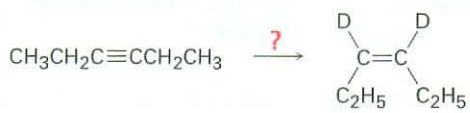
(c) $CH_3CHCH_2CH{=}CH_2$ (CH_3 on the second carbon)

(d) $CH_3CH_2CH_2\overset{\overset{O}{\|}}{C}CH_2CH_2CH_2CH_3$

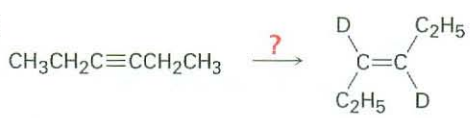
(e) $CH_3CH_2CH_2CH_2CH_2CHO$

8.36 How would you carry out the following reactions to introduce deuterium into organic molecules?

(a)

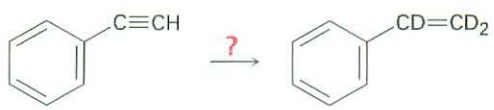


(b)



(c) $CH_3CH_2CH_2C{\equiv}CH \xrightarrow{?} CH_3CH_2CH_2C{\equiv}CD$

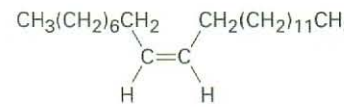
(d)



■ Assignable in OWL

8.37 How would you prepare cyclodecyne starting from acetylene and any alkyl halide needed?

8.38 The sex attractant given off by the common housefly is an alkene named *muscalure*. Propose a synthesis of muscalure starting from acetylene and any alkyl halides needed. What is the IUPAC name for muscalure?

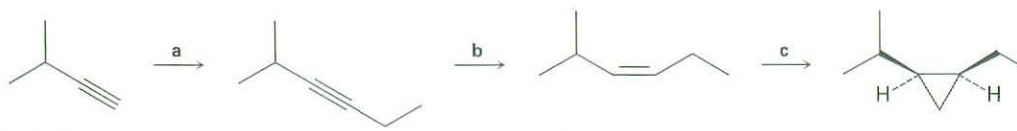


Muscalure

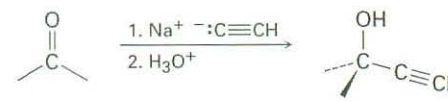
8.39 Compound A (C_9H_{12}) absorbed 3 equivalents of H_2 on catalytic reduction over a palladium catalyst to give B (C_9H_{18}). On ozonolysis, compound A gave, among other things, a ketone that was identified as cyclohexanone. On treatment with $NaNH_2$ in NH_3, followed by addition of iodomethane, compound A gave a new hydrocarbon, C ($C_{10}H_{14}$). What are the structures of A, B, and C?

8.40 Hydrocarbon A has the formula $C_{12}H_8$. It absorbs 8 equivalents of H_2 on catalytic reduction over a palladium catalyst. On ozonolysis, only two products are formed: oxalic acid (HO_2CCO_2H) and succinic acid ($HO_2CCH_2CH_2CO_2H$). Write the reactions, and propose a structure for A.

8.41 ■ Identify the reagents a–c in the following scheme:

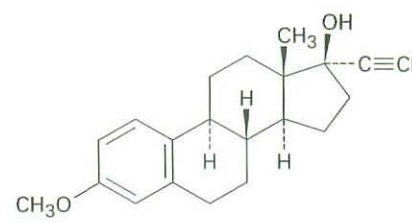


8.42 Organometallic reagents such as sodium acetylide undergo an addition reaction with ketones, giving alcohols:



How might you use this reaction to prepare 2-methyl-1,3-butadiene, the starting material used in the manufacture of synthetic rubber?

8.43 The oral contraceptive agent Mestranol is synthesized using a carbonyl addition reaction like that shown in Problem 8.42. Draw the structure of the ketone needed.

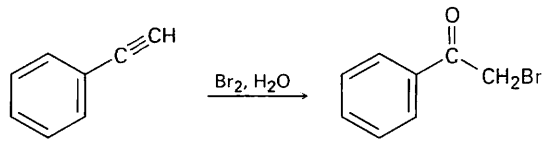


Mestranol

■ Assignable in OWL

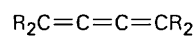
8.44 Erythrogenic acid, $C_{18}H_{26}O_2$, is an acetylenic fatty acid that turns a vivid red on exposure to light. On catalytic hydrogenation over a palladium catalyst, 5 equivalents of H_2 is absorbed, and stearic acid, $CH_3(CH_2)_{16}CO_2H$, is produced. Ozonolysis of erythrogenic acid gives four products: formaldehyde, CH_2O; oxalic acid, HO_2CCO_2H; azelaic acid, $HO_2C(CH_2)_7CO_2H$; and the aldehyde acid $OHC(CH_2)_4CO_2H$. Draw two possible structures for erythrogenic acid, and suggest a way to tell them apart by carrying out some simple reactions.

8.45 Terminal alkynes react with Br_2 and water to yield bromo ketones. For example:



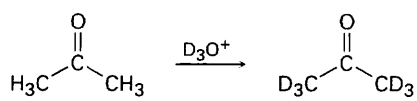
Propose a mechanism for the reaction. To what reaction of alkenes is the process analogous?

8.46 A *cumulene* is a compound with three adjacent double bonds. Draw an orbital picture of a cumulene. What kind of hybridization do the two central carbon atoms have? What is the geometric relationship of the substituents on one end to the substituents on the other end? What kind of isomerism is possible? Make a model to help see the answer.



A cumulene

8.47 Reaction of acetone with D_3O^+ yields hexadeuterioacetone. That is, all the hydrogens in acetone are exchanged for deuterium. Review the mechanism of mercuric ion–catalyzed alkyne hydration, and then propose a mechanism for this deuterium incorporation.



Acetone **Hexadeuterioacetone**