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Organic Chemistry

Chapter 15

Organic Synthesis

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Chapter Outline

Objectives

- ✔ Understand the principles of retrosynthetic analysis and be able to apply these principles to an organic synthesis
- ✔ Learn the use of a protecting group in organic synthesis
- ✔ Know how a lithium dialkylcuprate reagent reacts

"It's a strange sort of memory that only works backwards," said the Queen.
—Lewis Carroll

Doing organic synthesis is the real test of your ability to use the reactions of organic chemistry. Chapters 7, 8, 12, 13, and 14 present many important organic reactions. Each chapter covers one mechanistic type. The chapter includes the rationale and scope of that particular bond-breaking and/or bond-forming reaction type, as well as several specific example reactions. Most examples are one-step reactions. With these one-step reactions, you can begin learning to do organic synthesis.

Organic synthesis involves the conversion of a substrate to the desired product molecule. To make the product molecule, most organic syntheses require the use of a series of one-step reactions. Determining which reactions to use follows a technique called **retrosynthetic analysis**. E. J. Corey developed retrosynthetic analysis, and for this technique, along with some related research, he was awarded the Nobel Prize in 1990.

Retrosynthetic analysis is working from the desired product back towards some readily available starting material.

Organic chemists use synthesis for a variety of purposes. Traditionally, a synthesis was the final proof of the structure of a natural product isolated from a plant or animal source. The necessity of using synthesis to prove the structure of a compound diminished after the advent of the instrumental methods of analysis, although chemists still commonly synthesize natural products. The synthesis of these natural products increases the available supply of the compounds for further study or use. Chemists also use synthesis to attempt to prepare previously unknown compounds that they predict to be useful either for testing chemical theories or for creating new products.

Organic synthesis impacts every aspect of your life. For example, organic chemists design and produce most new pharmaceuticals. Often they start by using sophisticated computer software to predict what molecules might be the most active against a particular disease. Then they synthesize those molecules. Next, biochemists and/or biologists screen them for their activity in living organisms, and eventually physicians administer trials to human subjects. Another example is the high-performance polymers that affect our lives in so many ways. Everything from automobile parts to most modern sporting gear had their origins in organic synthesis.

15.1 Synthesis Design and Strategy

A target molecule is the molecule that you wish to synthesize.

When designing the synthesis of a **target molecule**, you must consider the simplicity of the synthesis, the availability of potential starting materials, the product yield, the economics of the synthesis, and safety. In many respects the methods for designing a synthesis are similar to the methods used to solve puzzles. Both may have many possible pathways to follow in traveling from the starting point to the desired end. Some of these pathways are productive in reaching that end; others are not.

Exercise 15.1

The yields of the individual steps in a multistep synthesis are important in the overall yield of the synthesis. Assume that you are carrying out a three-step synthesis. Calculate the overall yield of the synthesis if the individual yields are 84%, 87%, and 79%. Calculate the overall yield if the individual yields are 91%, 44%, and 88%.

To develop a synthetic pathway for a particular compound, analyze the target molecule looking for a probable starting material. Because the concepts of mechanism and synthesis are inextricably blended in modern organic chemistry, follow much the same thought process that you use when trying to determine what mechanism a reaction follows. The more confident you feel about one, the better you will become at working with the other. The relationship between the probable substrate and the product involves two things: interconversion of the functional groups and changes in the carbon skeleton. These two factors also play an important part in the synthetic sequence that you use to prepare the product.

Most of the reactions discussed to this point are functional group interconversions. That is, the reaction converts from one functional group to another. Only a few change or expand the carbon skeleton.

To determine whether the reaction interconverts functional groups or changes the carbon skeleton, compare the number of carbons in both the target molecule and the potential starting material. If both molecules have the same number of carbon atoms, then it is likely that you can accomplish the synthesis by one or more functional group conversions. If they are of different sizes, then you must modify the skeleton. To modify the carbon skeleton, look for a substrate that allows you to add the simplest possible carbon-containing fragments to obtain the product. In most cases, expanding the number of carbons in the skeleton is easier than reducing the number of carbons.

After determining whether or not the carbon skeleton changes, decide what you need to do to obtain the functional groups of the target molecule. Almost all syntheses involve the interconversion of at least one functional group to another. You must incorporate these interconversions into your synthesis strategy. Remember that most bonds break or form at or near the functional groups. A functional group is the active or activating portion of the molecule and thus plays a key role in the synthesis design. The key to the design of most organic syntheses is the functional groups in the target molecule.

Exercise 15.2

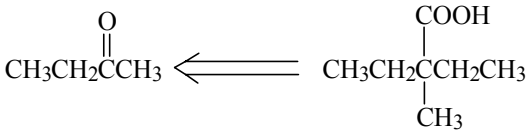
Review all the various chemical reactions presented in the book to this point. Review Reaction Summary I and look ahead to Reaction Summary II. Analyze each reaction and indicate whether it interconverts one functional group to another, modifies the carbon skeleton, or both.

Reaction Summary I begins on page 000.

Reaction Summary II begins on page 000.

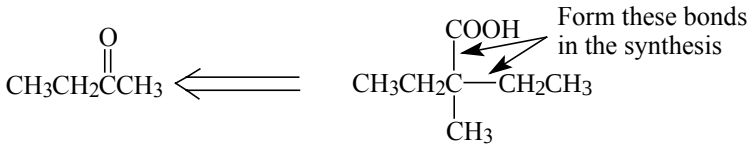
After determining what carbon skeleton and functional group changes are needed, you are ready to develop the synthetic sequence. If you need to change the size of the substrate, plan to sequentially add portions to a single starting material. You may need to alter or rearrange the structure of the starting material. You may even need to follow a pathway that requires two or more simultaneous syntheses to obtain the necessary fragments to join together for the target molecule.

Consider the development of the synthesis of 2-ethyl-2-methylbutanoic acid from 2-butanone following the above process.

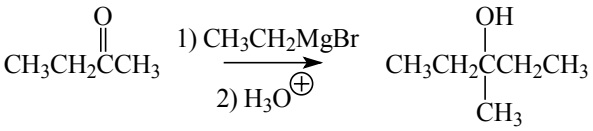


2-Butanone 2-Ethyl-2-methylbutanoic acid

Decide if the reaction requires any changes to the carbon skeleton. 2-Butanone has four carbons; 2-ethyl-2-methylbutanoic acid has seven. Therefore, the synthesis must add three carbons. The easiest way to do this is to add an ethyl group and a carboxylic acid group to the carbon skeleton of the starting material.

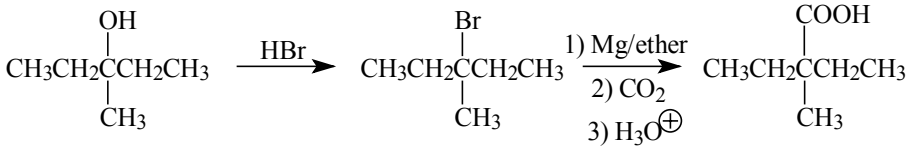


Of the various concepts you know at the present, the best synthetic method for this synthesis is the reaction of a Grignard reagent, or an organolithium compound, with a ketone.



This step accomplishes the synthesis of the carbon skeleton for the target molecule leaving you with one or more functional group conversions to complete the synthesis.

All the various synthetic methods you have seen for the formation of a carboxylic acid begin with an alkyl halide except for the chromate oxidation of an alcohol. An alcohol easily converts to a halide, so the remaining portion of the synthesis is alcohol ⟶ halide ⟶ carboxylic acid.



Of course, you can vary the details of each of these steps with any of the different reagents that you have studied earlier.

An important principle in laboratory organic synthesis is the same carbons that bear functional groups in the target compound often bear groups in the starting materials or intermediates in a synthesis. Numerous reactions remove a functional group from a carbon atom or exchange one functional group for another, but very few reactions introduce a functional group onto a carbon of a hydrocarbon. Often the location of a functional group in a starting material is more important than its actual structure. An existing functional group can usually be converted to the desired functional group.

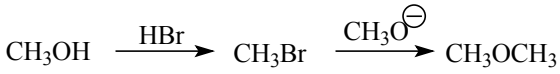
Exercise 15.3

Devise a synthesis for each of the following compounds from methanol as your only source of organic carbon and any required inorganic compounds.

a) Dimethyl ether b) Methyl acetate
c) 2-Bromopropane d) *N*-Methylacetamide

Sample solution

a)



15.2 Principles of Retrosynthetic Analysis

Section 15.1 introduces the process of determining a potential substrate and synthetic pathway that would allow the preparation of a particular target molecule. The process described in Section 15.1 works very well in syntheses involving two or three steps, but a longer synthesis requires you to use a different system. This section describes the process of analyzing the target molecule and working backward to find appropriate starting materials in a process called **retrosynthetic analysis**. When you determine the precursor for the first segment, this molecule then becomes your new target, and you analyze it to find a potential precursor for it. In turn, the new precursor becomes your new target, and you analyze it to find a precursor for it. This process of working backwards continues until you find a suitable substrate with which to begin the synthesis.

Retrosynthetic analysis involves dissecting the target molecule to determine a potential precursor for each part while working to keep all the parts fitting together.

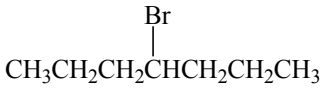
With experience, you will probably adopt a combination of both types of analyses. You might start with the retrosynthetic analysis and find precursors that require several steps to produce. Then you would work forward from those precursors planning the details of producing these intermediate molecules.

To plan a synthesis, you need a thorough knowledge of both the reactions and their mechanisms. You also need to know the types of starting materials that are available and where to get them. A number of major chemical companies stock and sell thousands of organic chemicals, but most of these chemicals are small molecules. As the size or complexity of the molecule increases, the variety of what the chemical companies stock decreases.

Major chemical companies stock most compounds containing up to five or six carbons with a single functional group. If the functional group is at or near the end of the chain, they also have available many straight chain compounds with up to ten carbons. Chemical companies commonly stock most five- or six-membered cyclic

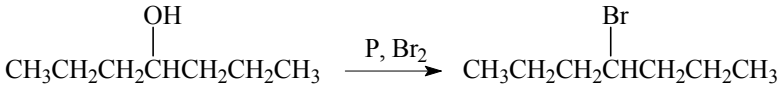
compounds with one functional group and possibly one additional alkyl substituent. Four-membered rings and rings larger than eight atoms are hard to find. Biochemical sources provide many complex biochemical molecules and many chiral molecules. In the syntheses of complex molecules, chemists usually start with molecules containing six carbons or less, as the more complex substrates are seldom readily available.

The following synthesis example of 4-bromoheptane uses only commercially available starting materials containing four or fewer carbons. This example also demonstrates retrosynthetic analysis to determine the synthetic pathway.



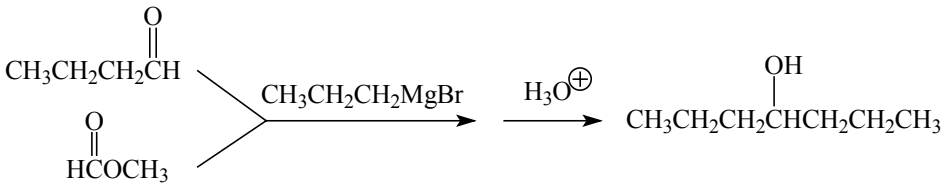
4-Bromoheptane

Many of the reactions discussed so far in this book that synthesize alkyl halides, begin with an alcohol. Therefore, this synthesis is really a synthesis of the corresponding alcohol, 4-heptanol.



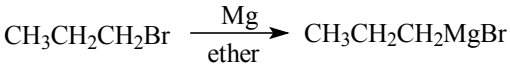
4-Heptanol

Sections 7.8 and 8.6 give two possible pathways for the synthesis of the alcohol. One pathway begins with butanal; the other begins with methyl formate. Both substrates react with propylmagnesium bromide, a Grignard reagent. Grignard reactions and alkyl lithium reactions involving a carbonyl group are the only methods presented so far that produce alcohols at the same time that they build the carbon skeleton. The following pathway also works with the propyllithium reagent:



Either pathway is a viable choice. The one you choose depends on the availability of reagents. You could easily synthesize the Grignard

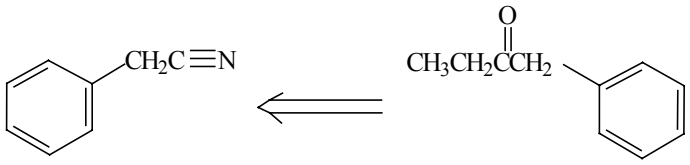
reagent from 1-bromopropane or possibly obtain it from a chemical supplier.



The technique of retrosynthesis allows you to propose an extended synthesis much more easily than proposing a synthesis from starting materials and working toward the product. Although working "backwards" in a synthesis may seem clumsy at first, chemists prefer this method for dealing with synthesis. Practice retrosynthesis with all the appropriate exercises in this, and subsequent, chapters.

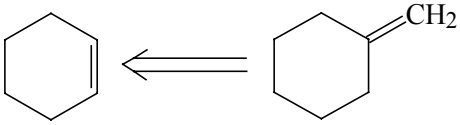
Exercise 15.4

Propose a synthesis of 1-phenyl-2-butanone from phenylacetonitrile. Show all the steps in your analysis of the synthetic sequence.



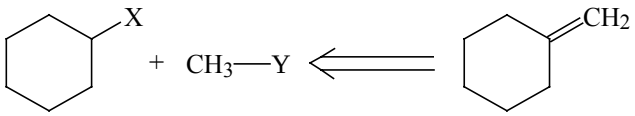
Phenylacetonitrile 1-Phenyl-2-butanone

The design of the synthesis of methylenecyclohexane from cyclohexene expands on the principles discussed above.



Methylenecyclohexane

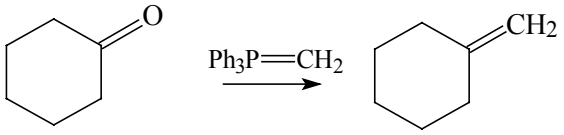
Begin the synthesis at the carbon skeleton. Rings are often best used as starting materials, so begin with a six-membered ring substrate. The proposed synthesis looks like this.



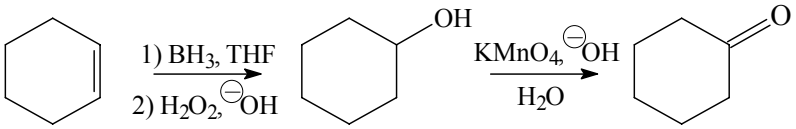
The above synthesis sketch represents the retrosynthetic analysis of the entire synthesis. Next comes the development of the steps of how

to do the actual synthesis. These steps break down into three smaller retrosynthetic analyses and the detailed synthetic steps of each.

You can easily produce the double bond by using the Wittig reaction on the cyclohexanone substrate.



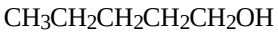
Cyclohexanone becomes the new target. The synthesis for cyclohexanone is an oxidation of cyclohexanol. Either oxymercuration or hydroboration of cyclohexene accomplishes the synthesis of cyclohexanol.



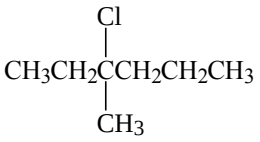
Exercise 15.5

Propose a synthesis for each of the following compounds starting from monofunctional organic compounds of three or fewer carbons as well as monofunctional rings of up to six carbons.

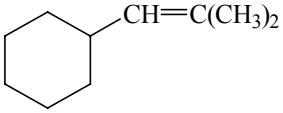
a)



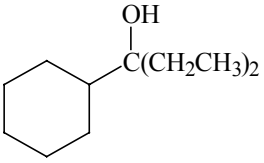
b)



c)

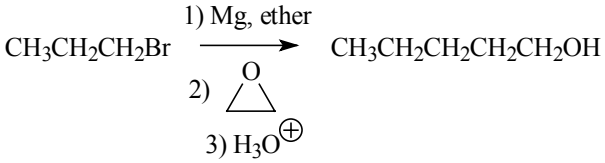


d)



Sample solution

a) This product is readily made from the reaction of a Grignard reagent with ethylene oxide.

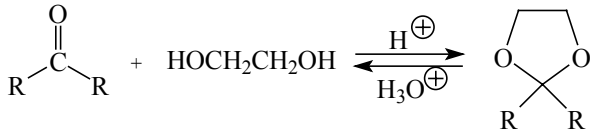


15.3 Protecting groups

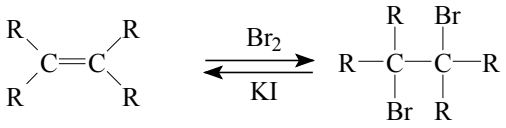
A protecting group temporarily transforms one reactive functional group to another functional group that is unreactive with a particular set of reaction conditions.

Many times a particular compound appropriate to use as the substrate in a reaction has more than one reaction site, but the chemist wants the reaction to occur at only one of the reaction sites. To *protect* the site that should not react, another reaction is used to form a **protecting group** at that site. Using a protecting group, the chemist temporarily transforms one functional group, the one that should not react, to another functional group that does not react or that reacts slowly. The chemist does this by choosing a reagent that reacts with the group to be protected and doesn't react, or reacts slowly, with the desired group in the primary reaction. When this group is protected, the chemist runs the reaction on the unprotected functional group, then regenerates the original functional group from the protected group. Protecting a group allows a reaction only at the desired site of the substrate.

Two previously discussed reactions that chemists routinely use to synthesize and remove protecting groups are the formation/hydrolysis of an acetal (Section 7.5) and the addition of bromine to a double bond (Section 14.6) and its elimination (Section 13.8)



Acetal formation/hydrolysis

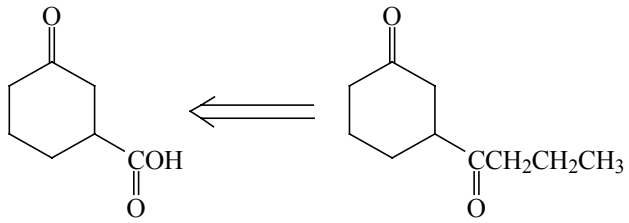


Bromination/elimination of a double bond

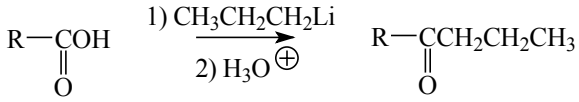
Both reactions qualify as protecting reactions because both change the functional group, an aldehyde or ketone in the first reaction and a double bond in the second, to a different functional group with a different reactivity. In both cases, the original functional group is

readily regenerated after you no longer need the protecting group. This ease of regeneration is very important as it allows you to return the protecting group back to the original functional group.

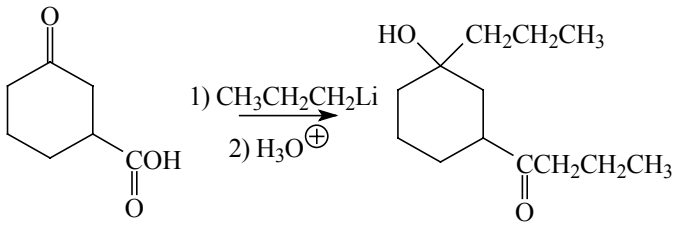
The following example shows the use of a protecting group in the reaction of a keto acid to form a diketone.



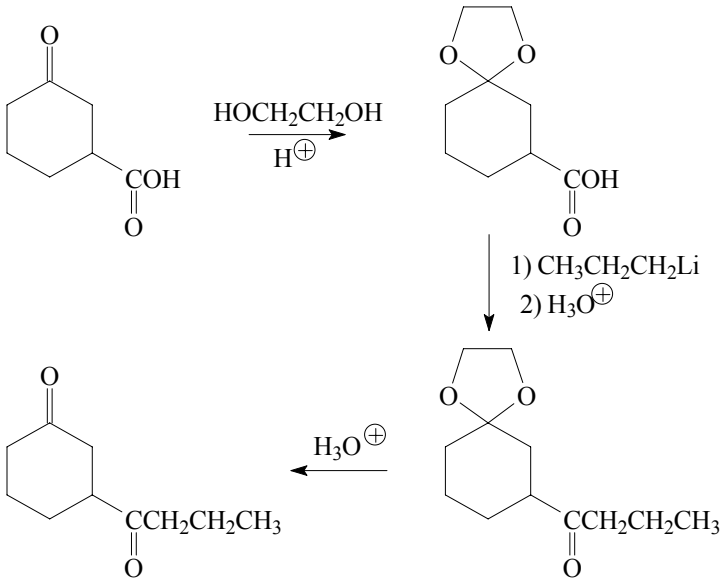
Reacting the carboxylic acid functional group with propyl lithium easily transforms it to the ketone.



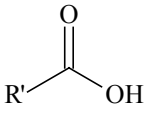
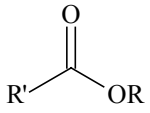
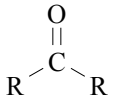
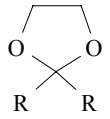
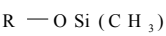
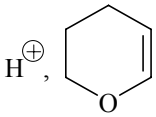
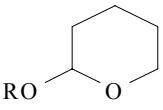
However, the propyllithium would also react with the ketone to form an alcohol. Thus, instead of a diketone, you would get the following product.



The plan is to protect the ketone functional group, by reacting it with ethylene glycol to form the acetal group, then to react the carboxylic acid with propyllithium, and finally to add acid to regenerate the ketone. The following illustration shows the complete synthetic scheme.



Organic chemists have many, many protecting groups that they use. Table 15.1 lists five common ones that relate to the reaction types that you have studied thus far. All protecting groups have two common properties: they decrease the reactivity of the substrate towards a particular reagent, and they regenerate the original functional group easily, after the completion of the desired reaction.

Group to be protected.	Reagents	Protected group	Reagents for the removal of the protection.
	ROH and $H^{\oplus}$		$^{\ominus}OH$ and H_2O or $H_3O^{\oplus}$
	$HOCH_2CH_2OH$ and $H^{\oplus}$ (or BF_3)	 *Acetal*	$H_3O^{\oplus}$
	$(CH_3)_3SiCl$, pyridine	 *Trimethylsilyl ether*	$H_3O^{\oplus}$ or $F^{\ominus}$
		 *Tetrahydropyranyl ether (An acetal)*	$H_3O^{\oplus}$

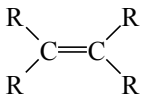
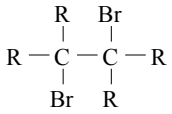
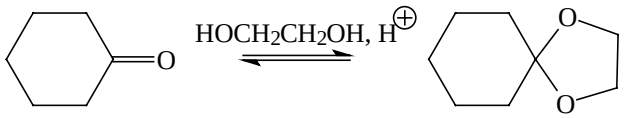
Group to be protected.	Reagents	Protected group	Reagents for the removal of the protection.
	Br_2	 *Vicinal dibromide*	KI

Table 15.1. Some common protecting groups.

Note that reactivity of the protected group determines the choice of what protecting group to use. For example an acetal is stable in alkaline reactions, but aqueous acid rapidly hydrolyzes the acetal. Or trimethylsilyl ethers are stable only under anhydrous conditions.

Synthesis of the Ethylene Glycol Acetal of Cyclohexanone



(80%)

Dissolve 5.9g (60 mmol) of cyclohexanone, 4.1 g (66 mmol) of ethylene glycol, and 0.05g of *p*-toluenesulfonic acid monohydrate in 25 mL of benzene. Place this solution in a 100 mL flask fitted with a Dean-Stark trap, a reflux condenser, and a drying tube filled with calcium chloride at the top of the condenser. Reflux the reaction until approximately 1.1 mL of water is collected in the Dean-Stark trap. Cool the reaction mixture and place it in a separatory funnel. Wash with 10 mL of 10% aqueous sodium hydroxide followed by five 5 mL portions of water. Dry over anhydrous potassium carbonate. Remove the drying agent by filtration. Remove the benzene solvent using the rotary evaporator. Distill the residue. The yield of product is 6.8g (80%), b.p. 73°C/13mm.

Discussion Questions

1. Why is the water removed from the reaction mixture as it forms?

Exercise 15.6

Chemists consider ethers to be chemically inert, but the tetrahydropyranyl ether that chemists use to protect the alcohol is quite easy to remove. Explain.

15.4 Lithium Dialkylcuprate Reagents

For the organometallic synthesis of alcohols and ketones see Sections 7.7, page 000, and 8.6, page 000.

A lithium dialkylcuprate reagent has the formula R_2CuLi.

Earlier discussions of the synthesis of alcohols and ketones presented numerous synthetic methods that use organometallic compounds. Another very versatile organometallic reagent to add to that list is the **lithium dialkylcuprate reagent**. The lithium dialkylcuprate reagent is called the Corey-House reagent in honor of its inventors, E. J. Corey (Harvard University) and Herbert O. House (Georgia Institute of Technology). The Corey-House reagent is synthesized by the reaction of one mole of copper(I) iodide (CuI) with two moles of an alkyl lithium compound (RLi). The empirical formula of the Corey-House reagent is R_2CuLi.

$$RLi \xrightarrow{CuI} R_2CuLi$$

The lithium dialkylcuprate reagent is widely used in reactions with alkyl halides to produce alkanes and with acyl halides to produce ketones.

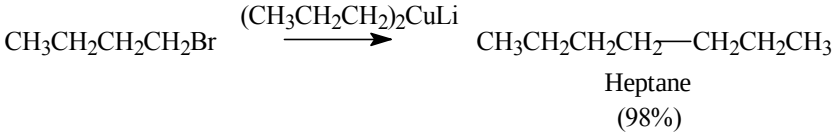
$$R'—X \xrightarrow{R_2CuLi} R'—R$$

$$R'—\overset{\overset{O}{\|}}{C}—X \xrightarrow{R_2CuLi} R'—\overset{\overset{O}{\|}}{C}—R$$

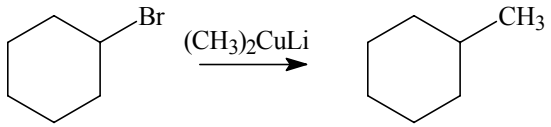
The general reaction takes place as if a carbanion ($R:^{\ominus}$) is present as the nucleophile in an S_N2 or nucleophilic carbonyl substitution reaction. However, the mechanism of reactions involving the lithium dialkylcuprate reagent is not well understood. A problem with the lithium dialkylcuprate reagent is that only one of the alkyl groups is used. The other becomes a copper(I) alkyl. Thus, when considering the use of an alkyl group with the cuprate reagent, you must think about the expense and difficulty of obtaining the cuprate reagent.

A coupling reaction is one where two reactants join together. This joining is usually via a C—C bond.

Coupling a lithium dialkylcuprate reagent with an alkyl halide normally produces excellent yields of alkanes. The alkyl groups of the halide can be methyl, primary, or secondary cycloalkyl halides, as would be expected from an S_N2 reaction. Acyclic secondary alkyl halides and all tertiary alkyl halides are too sterically crowded to react in an S_N2 reaction. The group in the lithium dialkylcuprate generally is methyl, primary, or secondary. Tertiary alkyl halides are too crowded for the lithium dialkylcuprate reagent to form. In the following examples, the lithium dialkylcuprate reagent acts as a source of $R:^{\ominus}$ nucleophile in an S_N2 reaction.

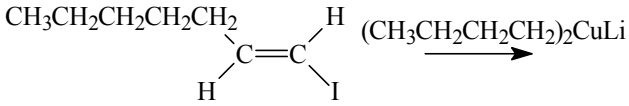


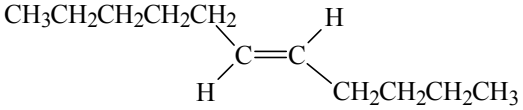
Heptane
(98%)



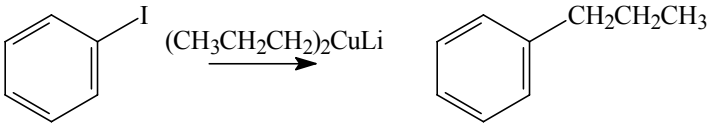
Methylcyclohexane
(77%)

Lithium dialkylcuprates also react with vinyl and phenyl halides, both of which are very unreactive to nucleophilic attack. These reactions do not occur with an S_N2 mechanism.



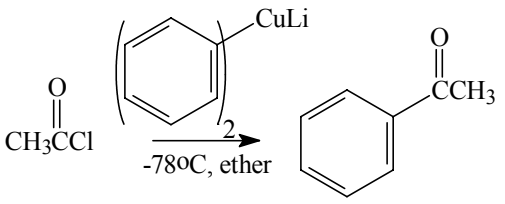


E-5-Undecene
(78%)

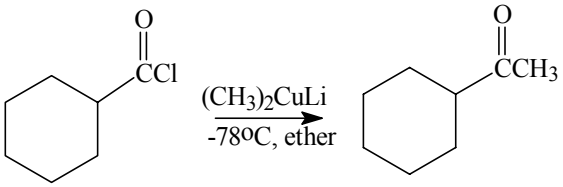


Propylbenzene
(78%)

The formation of ketones via reaction of the lithium dialkylcuprate with an acyl halide generally produces good yields of product. This reaction is limited to the use of methyl, primary alkyl, and aryl cuprates.

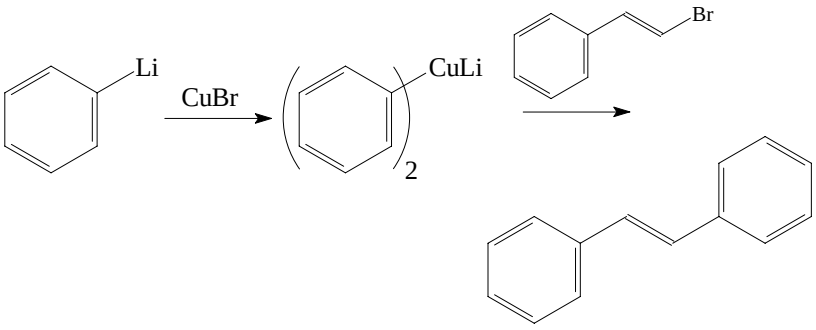


Acetophenone
(58%)



Cyclohexyl methyl ketone
(74%)

Synthesis of *trans*-Stilbene



trans-Stilbene
(90%)

Lithium diphenylcuprate

Place 728 mg (5.1 mmol) of CuBr in a dry 100 mL round-bottom flask. Add a stirbar and place a rubber septum on the flask. Attach a tube to a nitrogen source and another tube to a bubbler to monitor the flow of nitrogen. Place the flask in an ice bath. Flush the flask with nitrogen for 5-10 minutes while the flask and its contents are cooling. Stop the flow of nitrogen and add 15 mL of anhydrous ethyl ether to the flask. Rapidly stir the suspension of CuBr in the ether. Slowly add 5.5 mL (10 mmol) of ice-cold 1.8 M phenyllithium solution. After 10-15 minutes, most of the suspended solid should disappear and the slightly cloudy solution has become pale yellow or greenish yellow. Keep this solution cold and use as soon as possible.

trans-*Stilbene*

Dissolve 365 mg (2 mmol) of *trans*-β-bromostyrene in 8 mL of anhydrous ethyl ether. Add this solution to the lithium diphenylcuprate solution previously prepared. Remove the ice bath. Stir the reaction mixture under a nitrogen atmosphere for 4 hours at room temperature. During this time a yellow green precipitate slowly separates. Prepare 15 mL of a solution of saturated aqueous NH_4Cl adjusted to pH 9 by adding concentrated ammonia solution. Separate the layers formed. Extract the aqueous layer with two 5 mL portions of ether. Wash the combined ether solutions with 10 mL of saturated aqueous sodium chloride. Dry the ether layer with anhydrous sodium sulfate and evaporate the ether on a rotary evaporator. The residue is nearly pure *trans*-stilbene. The yield is 306 mg (90%), m.p. 119-123°C.

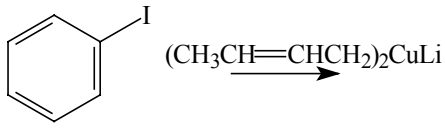
Discussion Questions

1. When making the lithium diphenylcuprate, why do you stop the nitrogen flow before adding the ether to the CuBr?
2. What is the yellow green precipitate that forms during the reaction? Look for the solubility of that compound in a chemical handbook. Is the compound soluble or insoluble in ether?

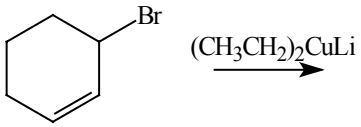
Exercise 15.7

Predict the major products for each of the following reactions.

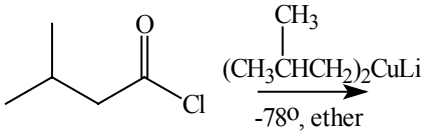
a)



b)

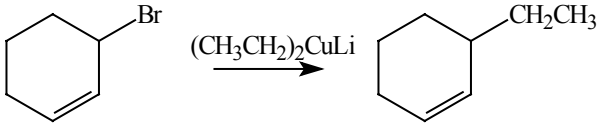


c)



Sample Solution

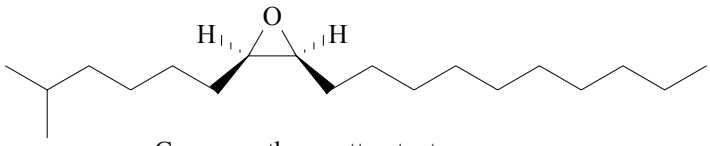
b)



15.5 A Synthetic Example

Pheromones are compounds that animals and insects use to communicate information to each other.

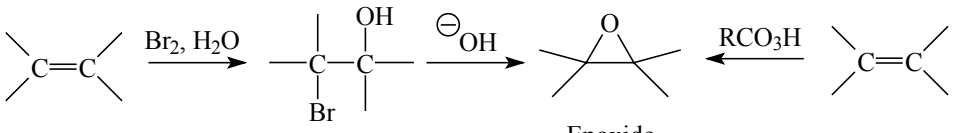
Chemists often deduce the structure of a naturally occurring product then use an organic synthesis to confirm that structure. A widely studied group of natural products is the **pheromones**. One of these pheromones, the gypsy-moth sex attractant, has the following structure.



Gypsy-moth sex attractant

The gypsy-moth sex attractant pheromone is readily synthesized using the principles and techniques presented to this point. The compound is monofunctional with an epoxide group. The two saturated alkyl chains attached to the ring are *cis* to one another. One of the alkyl groups contains one branch, a methyl group.

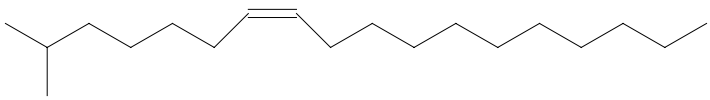
When planning the synthetic pathway, place the synthesis of the epoxide ring as the last step because the epoxide is quite reactive. Synthesizing the epoxide can follow either of two methods, both of which involve additions to a double bond. One method reacts bromine in water with the alkene. The resulting bromohydrin is reacted with a base. The other method is a peracid oxidation.



Epoxide

Both reactions retain the configuration of the alkene substrate. Either method works well for the formation of an epoxide. Generally, though, chemists choose the peracid oxidation, because it is simpler and usually gives a higher yield of product.

The next step backward in the retrosynthetic analysis is the synthesis of *cis*-2-methyl-7-octadecene.



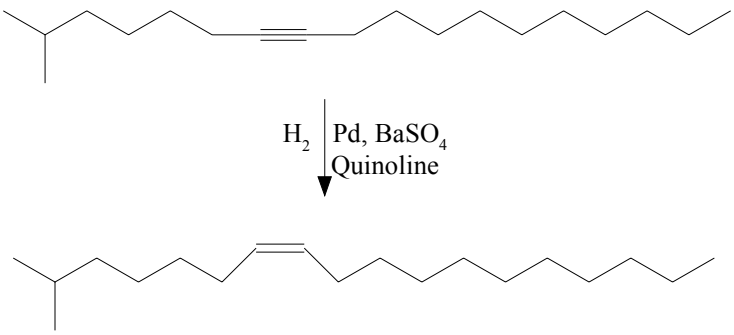
cis-2-Methyl-7-octadecene

Here again there are several methods available to consider for the synthesis of this compound. For example, you might dehydrate or

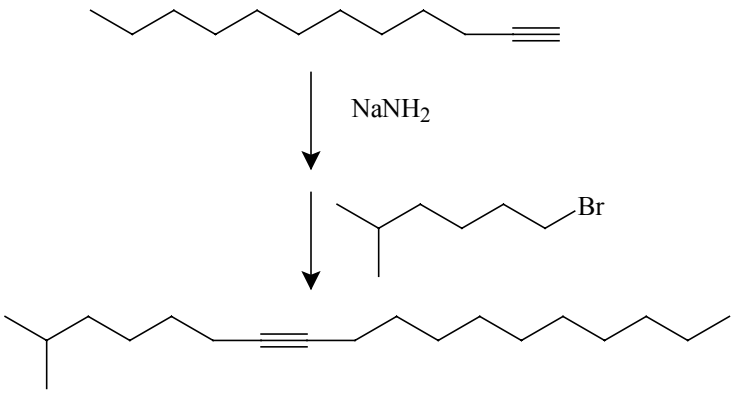
dehydrohalogenate the appropriate alcohol or alkyl halide. Unfortunately, neither method gives the double bond only in the desired position and neither one clearly gives only the *cis* double bond. In fact, either reaction usually gives a higher yield of the more stable *trans* double bond. This approach leads to a dead end.

A second method for the formation of a double bond is the Wittig reaction. The reaction of the phosphorus ylide with a carbonyl group is regiospecific but gives a mixture of both *cis* and *trans* isomers. This is another dead end.

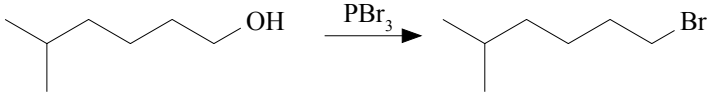
A third method for the formation of a double bond is the catalytic hydrogenation of an alkyne using a Lindlar catalyst. This reaction is both regiospecific and stereospecific. Thus, it gives the double bond in the correct position with only the *cis* isomer.



The alkyne is constructed from 1-dodecyne, which is commercially available, and 1-bromo-5-methylhexane, which is not readily available and will need to be synthesized.

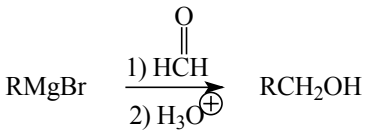


The synthesis is nearly complete. All that remains is to prepare 1-bromo-5-methylhexane. A halogen compound is generally prepared from an alcohol.

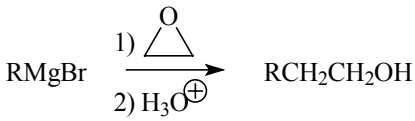


There are several ways to synthesize a primary alcohol. These include the reduction of an aldehyde, carboxylic acid, or ester; the addition of water by hydroboration or oxymercuration-demercuration; and a Grignard reaction with formaldehyde or an epoxide. The carbon skeleton has seven carbons making it unlikely that the required aldehyde, acid, ester, or alkene is readily commercially available. Thus, the Grignard reaction, which involves the construction of the skeleton from smaller fragments, is the best choice.

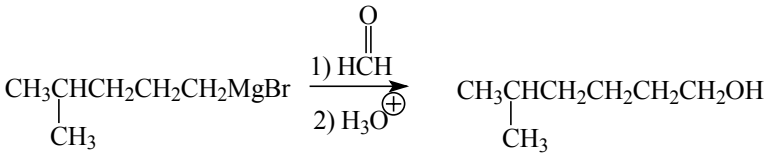
Recall from Chapter 7 that the reaction of a Grignard reagent with formaldehyde is a method that extends the length of a chain by one carbon.

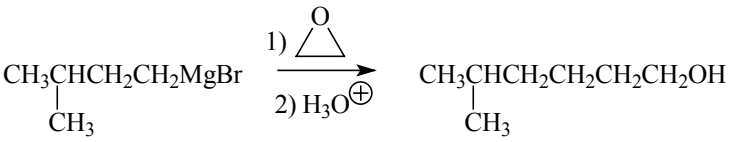


Recall from Chapter 12 that the reaction of a Grignard reagent with an epoxide extends the chain by two carbons.



The choice between these two Grignard reactions depends on the availability of the starting materials. Either reaction is a viable method. Usually you can get monofunctional molecules with either five or six carbons, so this gives you two alternate syntheses for 1-bromo-5-methylhexane.





Of these two syntheses, the second is preferred because the bromide for the Grignard reagent synthesis is more readily available.

Figure 15.1 shows the complete synthesis for the Gypsy-moth sex attractant.

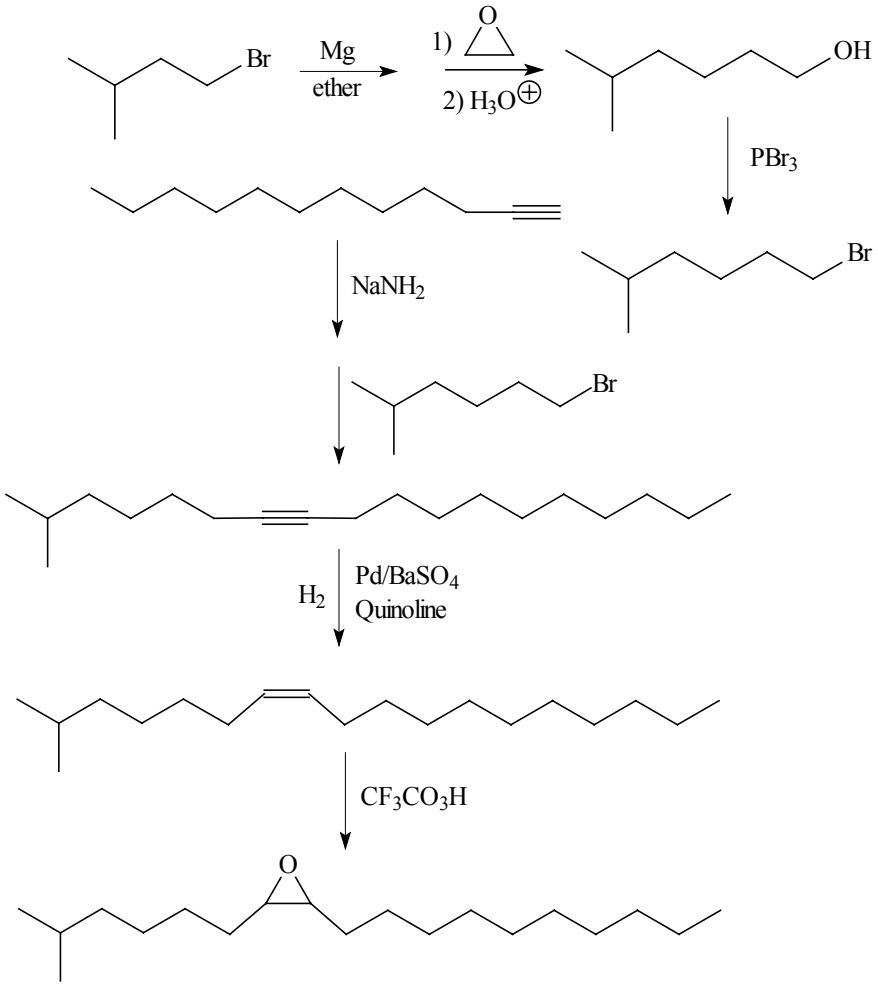
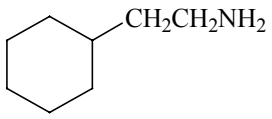


Figure 15.1. The complete synthesis for Gypsy-moth sex attractant.

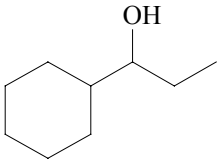
Exercise 15.8

Propose a synthesis for the following compounds starting with any monofunctional, unbranched organic molecules containing six or fewer carbons that are likely to be readily available. In addition, you may use any required inorganic reagents or specialized organic reagents necessary to complete the reaction.

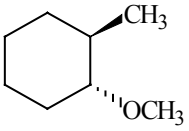
a)



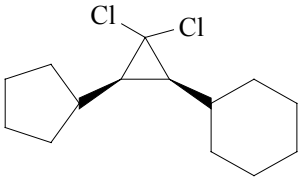
b)



c)

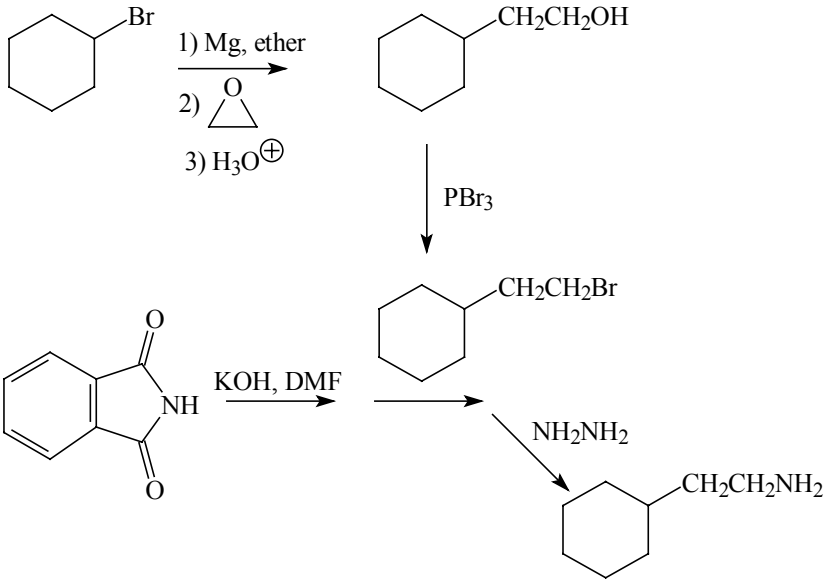


d)



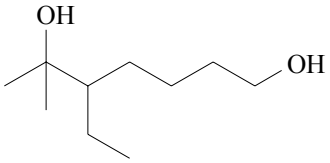
Sample solution

a)



15.6 Synthesis of Difunctional Compounds

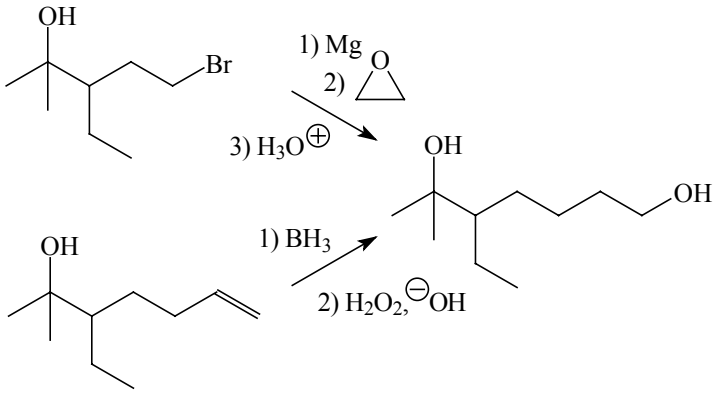
The types of organic syntheses that organic chemists most often perform are those that have more than one functional group in the target molecule. Synthesizing a molecule with multiple functional groups requires careful analysis of how a reaction at one functional group affects the other functional groups and how to control the reaction so that only the desired reaction takes place. The synthesis of 5-ethyl-6-methyl-1,6-heptanediol illustrates the retrosynthesis of a difunctional compound. Keep in mind that in this process you work backwards from the product to the substrate.



5-Ethyl-6-methyl-1,6-heptanediol

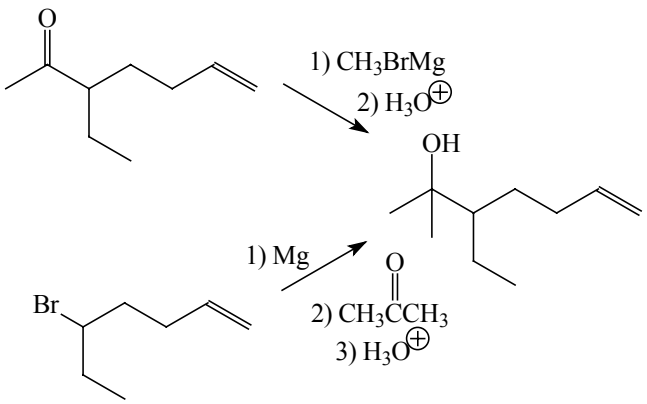
5-Ethyl-6-methyl-1,6-heptanediol contains two alcohol functional groups: one primary and the other tertiary. The carbon skeleton contains one methyl and one ethyl branch.

There are two basic methods for the synthesis of a primary alcohol: a Grignard synthesis and a hydroboration.

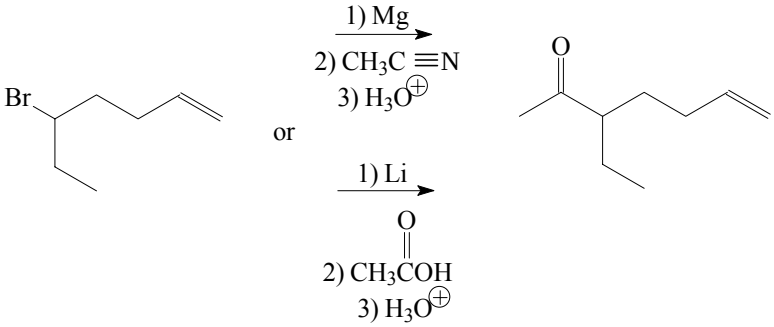


Because a Grignard reagent does not form in the presence of an acidic hydrogen, you must protect the tertiary alcohol when using a Grignard reaction. (Note: Trying to perform a Grignard reaction on one part of a molecule in the presence of an acidic functional group elsewhere in the molecule is a common error made by many beginning organic chemists.) The second reaction, hydroboration, can work in the presence of an alcohol. However, hydroboration requires an excess of reagent because the alcohol hydrogen reacts with the hydride from borane to produce hydrogen gas. But, borane is inexpensive enough to make protection of the alcohol unnecessary; thus, hydroboration is the preferred approach.

The synthesis of the tertiary alcohol has three possible approaches. Two are Grignard reactions, and the third is a solvolysis of an alkyl halide. The solvolysis reaction is not very practical because the alkyl halide substrate needed for the solvolysis reaction is most easily made from the alcohol you want to produce. Both Grignard reactions are viable possibilities, and both produce the tertiary alcohol in a good yield.



To use the first Grignard reaction, you must make the ketone. You know of two syntheses for ketone preparation. The first is a reaction of a Grignard reagent with a nitrile. The second is the reaction of an alkyllithium reagent with a carboxylic acid. Note, however, that both of those syntheses begin with 5-bromo-1-heptene, which is the same alkyl halide as the second Grignard pathway shown above. Therefore, it makes good sense to save a step in the synthesis and avoid the ketone altogether.



5-Bromo-1-heptene is not generally commercially available, but you can readily synthesize it from commonly available reagents. Use a Grignard reagent on an epoxide to produce an alcohol with the —OH group on the correct carbon. Then replace this —OH group with bromine by using PBr_3 as a reagent.

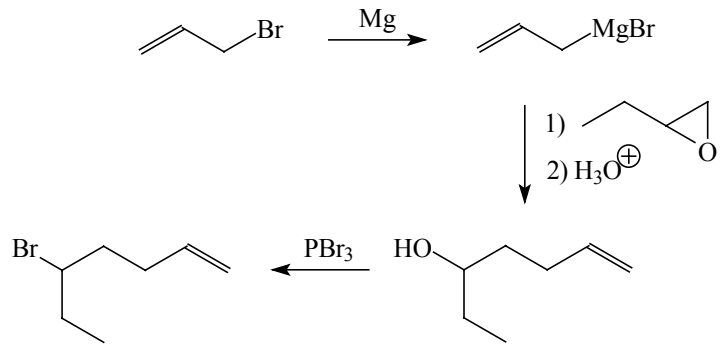


Figure 15.2 shows the complete synthesis for 5-ethyl-6-methyl-1,6-heptandiol.

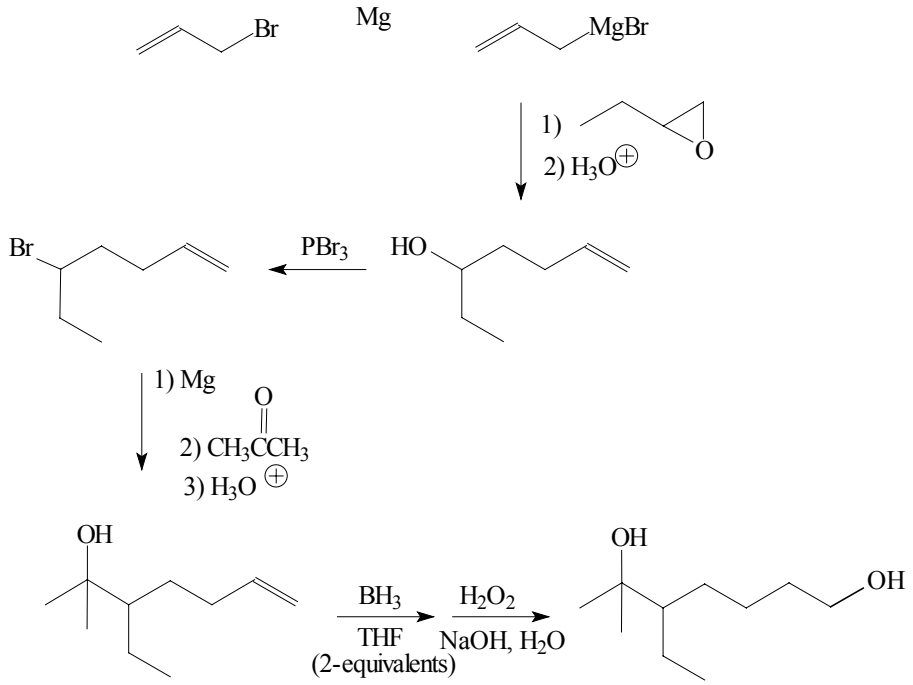
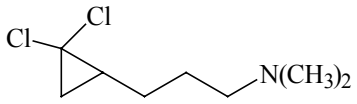


Figure 15.2. The complete synthesis for 5-ethyl-6-methyl-1,6-heptandiol.

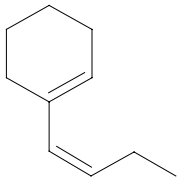
Exercise 15.9

Propose a synthesis for the following compounds starting with any monofunctional unbranched organic molecules likely to be readily available as well as any required inorganic reagents or specialized organic reagents.

a)

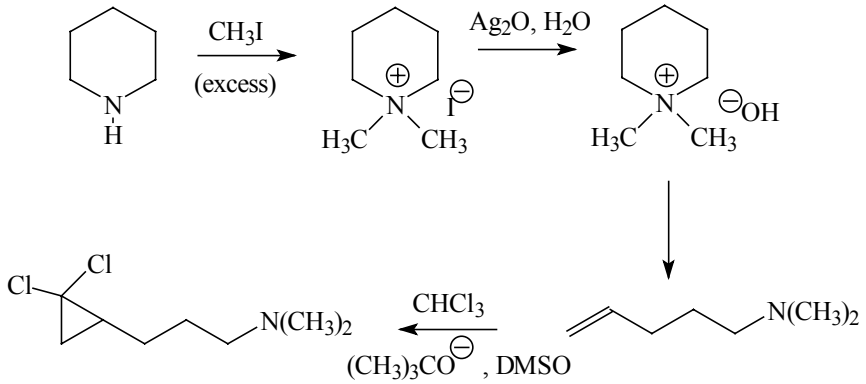


b)



Sample Solution

a)



Selectivity allows a reaction to proceed with one functional group in preference to another.

Recall from Section 15.3 that chemists deal with two functional groups either by turning one into a protecting group until they complete their reaction on the other functional group, or by controlling the reaction conditions. Another approach for using one functional group in a reaction but not the other is through **selectivity**. By applying the principles of selectivity you can make a change at one functional group but leave the other unchanged. Because of selectivity, one equivalent of reagent reacts almost completely with one functional group and very little with the other. Certain types of reactions provide selectivity, as do certain types of substrate structures. The following list summarizes how selectivity works in different types of related reactions.

1. The order of reactivity for carbonyl-containing functional groups toward a nucleophile is acyl halide > aldehyde > ketone > ester > nitrile > amide > carboxylate anion.
2. The reactivity difference between primary, secondary, and tertiary carbon atoms toward a nucleophilic substitution is sufficient to provide adequate selectivity.
3. Esterification of alcohols follows the sequence of primary > secondary >> tertiary. Tertiary alcohols are quite unreactive towards ordinary esterification techniques.
4. A reaction that forms a five- or six-membered ring is usually significantly faster than an intermolecular reaction. It also has a higher equilibrium constant.

5. Sodium borohydride reacts with acyl halides, aldehydes, and ketones. Lithium aluminum hydride reduces those substrates as well as the remaining members of the carboxylic acid family.
6. Carbon—carbon double bonds are not reactive towards nucleophiles unless conjugated with electron-withdrawing groups (more in Chapter 16).
7. The rate for catalytic hydrogenation is triple bond > double bond > carbonyl >> aromatic ring. A modified catalyst reduces a triple bond in the presence of a double bond.

Key Ideas from Chapter 15

- ❑ Organic synthesis uses a series of chemical reactions to convert a readily available substrate to a target molecule.

- ❑ The synthesis of a target molecule often seems to have many possible pathways. Some are productive, but some are dead ends.

- ❑ The choice of a particular pathway depends on the availability of the potential starting materials, the relative safety of the materials and procedures, the cost of the materials, the simplicity of the reaction, and the product yield. Each chemist approaching a particular synthetic problem will likely find a different pathway, particularly for a complex synthesis.

- ❑ A synthetic sequence may involve two types of chemical changes in the substrate: the interconversion of functional groups and changes in the carbon skeleton.

- ❑ Retrosynthetic analysis is a way of dissecting the target molecule to determine a potential precursor. This precursor in turn becomes a new target and is analyzed to find a potential precursor for this new target. This process of working backwards continues to locate a suitable starting material.

- ❑ Lithium dialkylcuprates couple with alkyl, aryl, vinyl, and acyl halides to produce alkanes, alkyl-substituted benzene rings, alkenes, and ketones.

- ❑ A protecting group allows the temporary transformation of one functional group to another less reactive functional group. The original functional group is readily regenerated from the protecting group. Protecting a group during a reaction prevents a reaction from occurring at that site as the reaction proceeds at another site.

- ❑ When doing a reaction on a substrate containing multiple functional groups, analyze the selectivity of the possible reactants. If a particular reactant will affect the functional groups other than the one where the reaction is to take place, use a protecting group or a different reagent.