

19.7: NUCLEOPHILIC ADDITION OF HYDRIDE AND GRIGNARD REAGENTS - ALCOHOL FORMATION

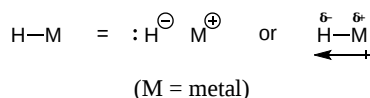
OBJECTIVES

After completing this section, you should be able to

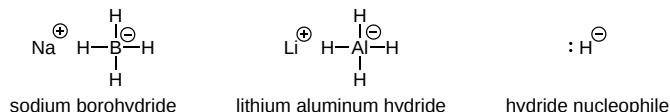
1. write the equation to describe the nucleophilic addition reaction between a Grignard reagent and a carbonyl group.
2. write the general mechanism of nucleophilic addition of the “hydride ion” in the reduction of a carbonyl group.

REDUCTION OF CARBONYLS TO ALCOHOLS USING METAL HYDRIDES

Like carbon, hydrogen can be used as a nucleophile if it is bonded to a metal in such a way that the electron density balance favors the hydrogen side. A hydrogen atom that carries a net negative charge and bears a pair of unshared electrons is called a **hydride ion**. How much negative charge density resides on hydrogen depends on the difference in electronegativity between hydrogen and the metal it's bonded to.

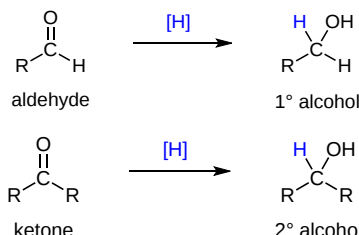


The most common sources of the hydride anion (:H^-) are **lithium aluminum hydride (LiAlH_4)** and **sodium borohydride (NaBH_4)**. Note! The hydride anion is not present during this reaction; rather, these reagents serve as a source of hydride due to the presence of a polar metal-hydrogen bond. Also, each are capable of delivering up to 4 hydride equivalents. The reaction equation of hydride reductions are not typically balanced (*i.e.* it does not specify the stoichiometry of the reagent). Because aluminum is less electronegative than boron, the Al-H bond in LiAlH_4 is more polar, thereby, making LiAlH_4 a stronger reducing agent.



GENERAL REACTION

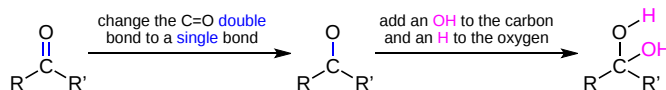
Nucleophilic addition of a hydride anion (:H^-) to an aldehyde or a ketone gives a tetrahedral alkoxide anion intermediate, which on protonation yields the corresponding alcohol. Aldehydes produce 1°-alcohols and ketones produce 2°-alcohols. Both LiAlH_4 and NaBH_4 are capable of reducing aldehydes and ketones to the corresponding alcohol.



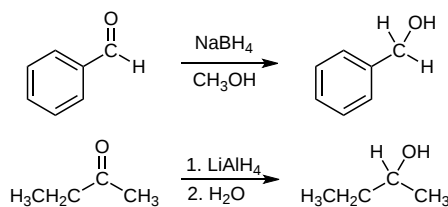
In metal hydrides reductions, the resulting alkoxide salts are insoluble and need to be hydrolyzed (with care) before the alcohol product can be isolated. In the sodium borohydride reduction the methanol solvent system achieves this hydrolysis automatically. In the lithium aluminum hydride reduction water is usually added in a second step. The lithium, sodium, boron and aluminum end up as soluble inorganic salts at the end of either reaction.

PREDICTING THE PRODUCT OF A HYDRIDE ADDITION TO A CARBONYL

During the reduction, the $\text{C}=\text{O}$ double bond in the reactant becomes a $\text{C}-\text{O}$ single bond in the product. The breaking of the $\text{C}=\text{O}$ double bond allows for the formation of two new single bonds in the product. One will be attached to the oxygen ($\text{O}-\text{H}$) and one to the carbon ($\text{C}-\text{H}$).



EXAMPLE

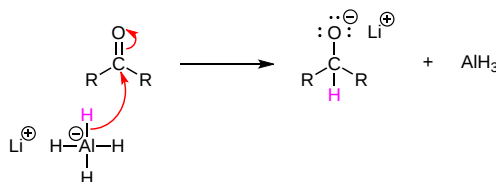


MECHANISM FOR THE REDUCTION OF CARBONYLS USING LIALH₄

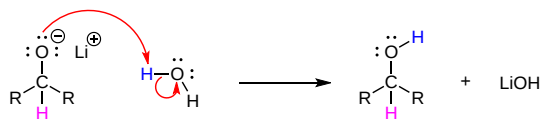
Both NaBH₄ and LiAlH₄ act as if they were a source of hydride. The hydride anion undergoes nucleophilic addition to the carbonyl carbon to form a C-H single bond and forming a tetrahedral alkoxide ion intermediate. The alkoxide ion is subsequently converted to an alcohol by reaction with a proton source (such as water). In the LiAlH₄ reduction, the resulting alkoxide salts are insoluble and need to be hydrolyzed (with care) before the alcohol product can be isolated. In the borohydride reduction the hydroxylic solvent system achieves this hydrolysis automatically. The lithium, sodium, boron and aluminum end up as soluble inorganic salts.

Note! The reaction and the corresponding mechanism of hydride reductions of carbonyls is fairly complicated. The following mechanism has been simplified for easier understanding.

Step 1: Nucleophilic attack to form a tetrahedral alkoxide intermediate



Step 2: Protonation to form an alcohol



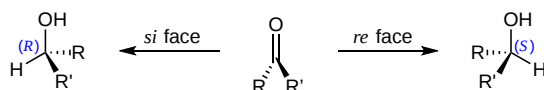
PROPERTIES OF HYDRIDE SOURCES

Two practical sources of hydride-like reactivity are the complex metal hydrides lithium aluminum hydride (LiAlH₄) and sodium borohydride (NaBH₄). These are both white (or near white) solids, which are prepared from lithium or sodium hydrides by reaction with aluminum or boron halides and esters. Lithium aluminum hydride is by far the most reactive of the two compounds, reacting violently with water, alcohols and other acidic groups with the evolution of hydrogen gas. The following table summarizes some important characteristics of these useful reagents.

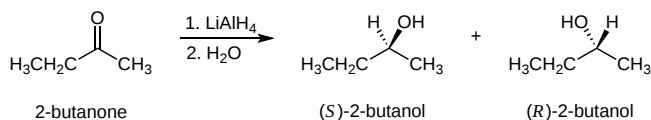
Reagent	Preferred Solvents	Functions Reduced	Reaction Work-up
Sodium Borohydride NaBH ₄	ethanol; aqueous ethanol 15% NaOH; diglyme avoid strong acids	aldehydes to 1°-alcohols ketones to 2°-alcohols inert to most other functional groups	1) simple neutralization 2) extraction of product
Lithium Aluminum Hydride LiAlH ₄	ether; THF avoid alcohols and amines avoid halogenated compounds avoid strong acids	aldehydes to 1°-alcohols ketones to 2°-alcohols carboxylic acids to 1°-alcohols esters to alcohols epoxides to alcohols nitriles & amides to amines halides & tosylates to alkanes most functional groups react	1) careful addition of water 2) remove aluminum salts 3) extraction of product

LIMITATIONS OF HYDRIDE REDUCTIONS

A hydride addition to an asymmetric ketone has the possibility of forming a chiral carbon that is not stereospecific. Attack by the hydride can occur from either the *re* or the *si* face of an asymmetrical carbonyl, leading to a mixture of the (*S*) and (*R*) alcohols. These reactions can be made to have stereochemical control by using several different methods including stereospecific reagents, sterics, and by the affect of an enzyme during a biological reduction.

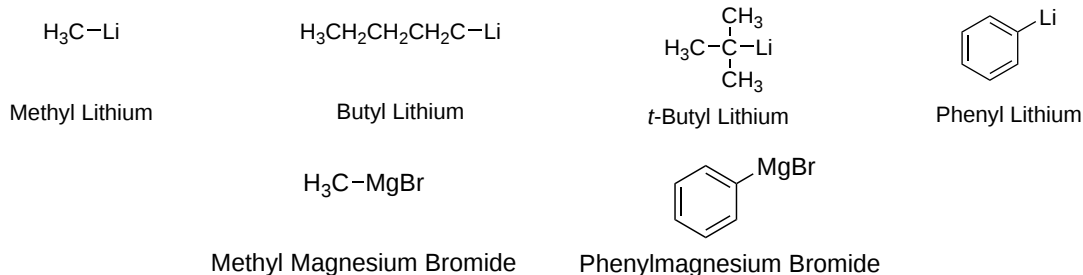


EXAMPLE



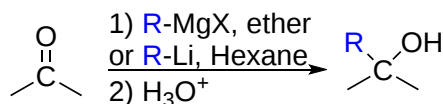
ORGANOMETALLIC REACTIONS

Lithium and magnesium metals reduce the carbon-halogen bonds of alkyl halides to form **organolithium reagents** and **Grignard reagents** respectively. In both cases, the carbon bonds to the metal and has characteristics similar to a **carbanion** (R^-) nucleophile. Some common organometallic reagents are shown below:

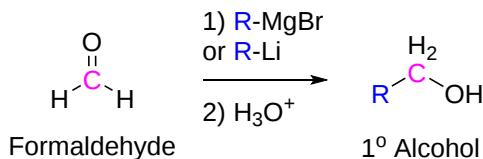


Because organometallic reagents react as their corresponding carbanion, they are excellent nucleophiles. Aldehydes and ketones will undergo nucleophilic addition with organolithium and Grignard reagent nucleophiles. The nucleophilic carbon in the organometallic reagents forms a C-C single bond with the electrophilic carbonyl carbon. An alkoxide ion intermediate is formed which becomes an alcohol with subsequent protonation with an acid. Both Grignard and organolithium reagents will perform these reactions.

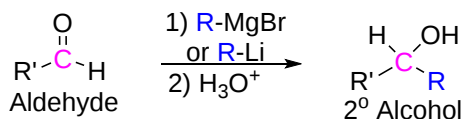
GENERAL REACTION



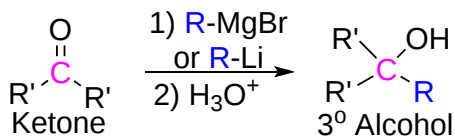
ADDITION TO FORMALDEHYDE GIVES 1° ALCOHOLS



ADDITION TO ALDEHYDES GIVES 2° ALCOHOLS



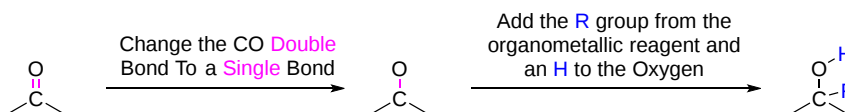
ADDITION TO KETONES GIVES 3° ALCOHOLS



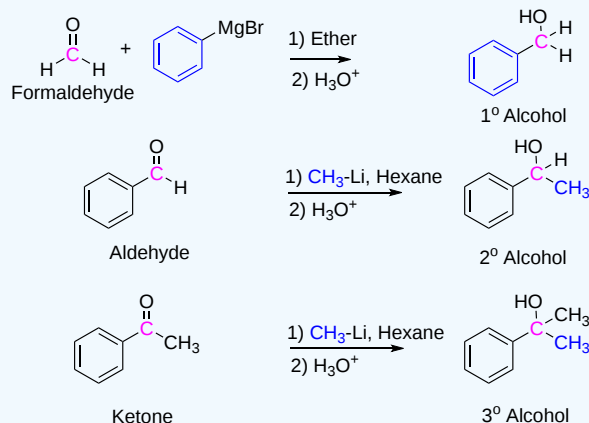
PREDICTING THE PRODUCT OF ADDITION OF ORGANOMETALLIC REAGENTS TO ALDEHYDES AND KETONES

During the reaction, the C=O double bond in the reactant forms a C-O single bond in the product. The breaking of the C=O double bond allows for the formation of two single bonds in the product. One will be attached to the oxygen and one to the carbon which was originally

in the carbonyl. The carbon will gain whatever R group was part of the organometallic reagent and the oxygen will gain a "H".



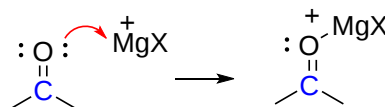
✓ EXAMPLE 19.7.2



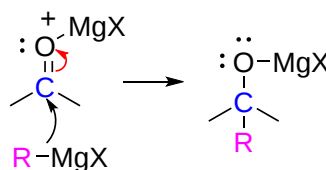
MECHANISM FOR THE ADDITION OF GRIGNARD REAGENTS TO CARBONYLS

The mechanism starts with the formation of an acid-base complex between ^+MgX and the carbonyl oxygen. The ^+MgBr of the Grignard reagent acts as a Lewis acid and accepts a lone pair of electrons from the carbonyl oxygen. This gives the oxygen a positive charge which correspondingly increases the partial positive charge on the carbonyl carbon increasing its susceptibility to nucleophilic attack. The carbanion nucleophile from the Grignard reagent adds to the electrophilic carbon of the acid-base complex forming a C-C bond. The two electrons of the C=O are pushed toward the carbonyl oxygen atom forming a tetrahedral magnesium alkoxide intermediate. The alkoxide intermediate is converted to an alcohol through addition of an acidic aqueous solution. The ^+MgX ion is also converted to $HOMgX$.

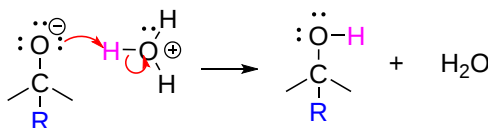
STEP 1: LEWIS ACID-BASE FORMATION



STEP 2: NUCLEOPHILIC ATTACK

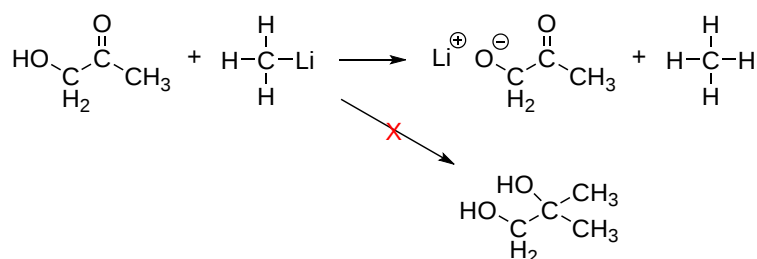


STEP 3: PROTONATION



LIMITATION OF ORGANOMETALLIC REAGENTS

As discussed above, Grignard and organolithium reagents are powerful bases. Because of this they cannot be used as nucleophiles on compounds which contain acidic hydrogens. If they are used they will act as a base and deprotonate the acidic hydrogen rather than act as a nucleophile and attack the carbonyl. A partial list of functional groups which cannot be used with organometallic reagents includes: alcohols, amides, 1° amines, 2° amines, carboxylic acids, and terminal alkynes.

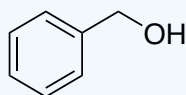


PLANNING AN ALCOHOL SYNTHESIS USING A GRIGNARD REACTION

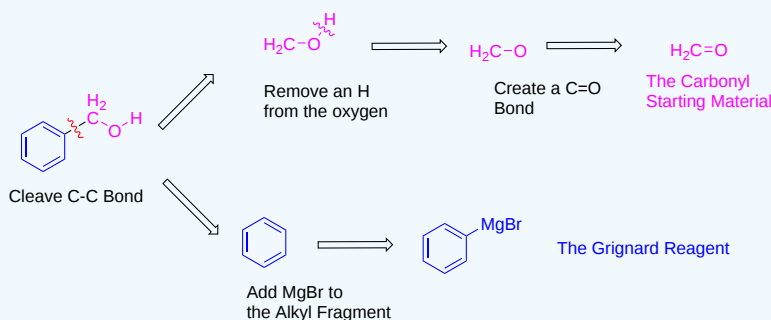
The nucleophilic addition of a Grignard reagent to a carbonyl is a powerful tool in organic synthesis because it forms a C-C bond. Also, there is often more than one way to make a given target molecule. Primary alcohols have one C-C bond which can be retrosynthetically cleaved. Secondary alcohols have two and tertiary alcohols have three.

✓ EXAMPLE 19.7.2

What reagents are required to make the following molecule using a Grignard Reaction?

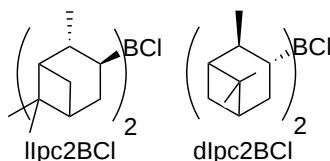


Solution



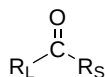
SOMETHING EXTRA

As previously mentioned, a hydride reduction using LiAlH_4 or NaBH_4 has the possibility of forming R or S stereoisomers of a chiral carbon in the product. An important area of organic synthesis is developing stereoselective methods which yield only one of the possible R and S stereocenters. Stereoselective hydride reductions can be accomplished by using the reagent **Diisopinocampheylchloroborane (Ipc_2BCl)**. The two versions of this reagent, (+)- Ipc_2BCl & (-)- Ipc_2BCl , allow for either an R or S stereocenter to be created during the hydride reduction. Ipc_2BCl was first reported in 1961 by Zweifel and Brown and is considered a pioneering work in stereoselective synthesis using boranes. Herbert Charles Brown (1912-2004) was an American chemist who received the Nobel Prize in Chemistry in 1979 for his work with organoboranes.

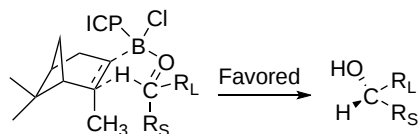


Ipc_2BCl allows for stereoselectivity by changing the mechanism of the hydride reduction and introducing sterics to the reaction. Asymmetric carbonyls which have a sterically large substituent (R_L) and a sterically small substituent (R_S) will have a preferred orientation during this reaction causing a particular stereoisomer to be formed.

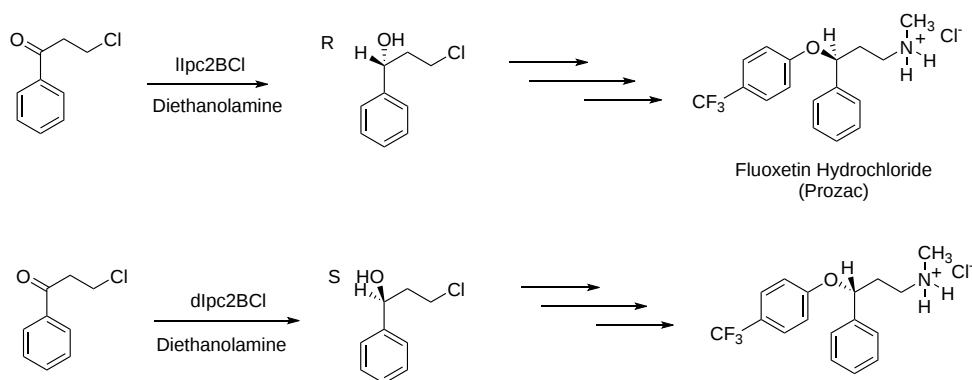
Asymmetric Carbonyl



RL = Sterically Large Substituent
RS = Sterically Small Substituent

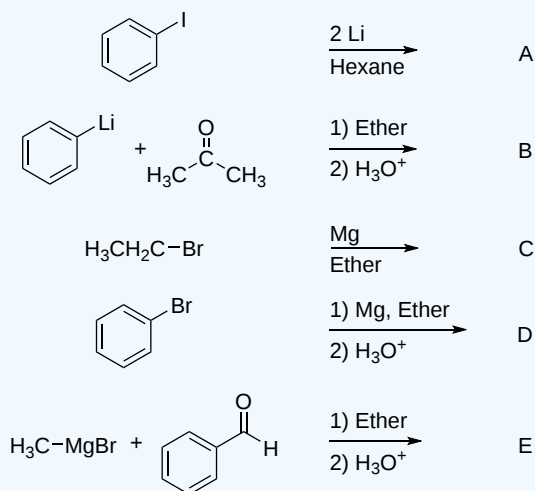


Stereochemical control during a synthesis is important because a particular stereoisomer is usually the target molecular. This is particularly true in the synthesis of pharmaceuticals where one stereoisomer often has different biological properties and another. An example of this is the drug Fluoxetine (Prozac) which was shown to have superior biological properties when the R isomer of its single chiral carbon was tested. Fluoxetine is an antidepressant given FDA approval in 1987. In 2010, over 24.4 million prescriptions for fluoxetine were filled in the United States alone. Currently, there are many different synthesis pathways to Fluoxetine. A fragment of one pathway is shown below which uses the two Ipc₂BCl versions to synthesize both the R and S enantiomers of Fluoxetine.

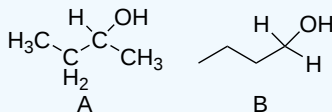


? EXERCISE 19.7.1

Please draw the products of the following reactions:

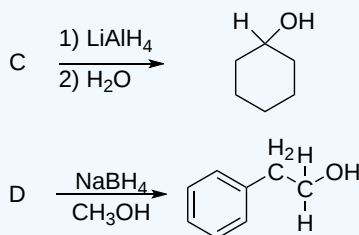


Answer

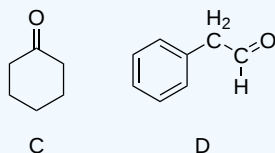


? EXERCISE 19.7.2

Draw the structure of the molecule which must be reacted to produce the product.

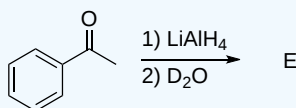


Answer

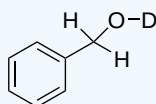


? EXERCISE 19.7.3

Deuterium oxide (D_2O) is a form of water where the hydrogens have been replaced by deuteriums. For the following LiAlH_4 reduction the water typically used has been replaced by deuterium oxide. Please draw the product of the reaction and place the deuterium in the proper location. Hint! Look at the mechanism of the reaction.

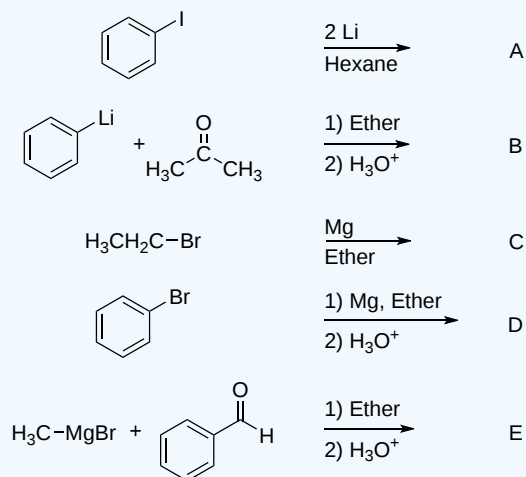


Answer

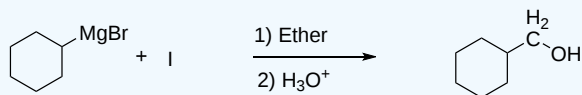
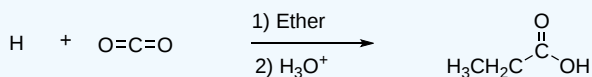
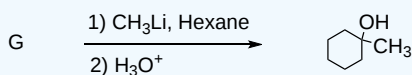



? EXERCISE 19.7.4

Please write the product of the following reactions.



Answer

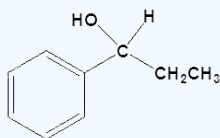
$$\text{F} \xrightarrow[2) \text{H}_3\text{O}^+]{1) \text{CH}_3\text{CH}_2\text{MgBr, Ether}} \begin{array}{c} \text{H} \\ | \\ \text{H}_3\text{C}-\text{C}-\text{H} \\ | \\ \text{CH}_2\text{CH}_3 \end{array}$$


$\text{H}_3\text{C}-\overset{\text{O}}{\parallel}\text{C}-\text{H}$  $\text{H}_3\text{CH}_2\text{C}-\text{MgBr}$ $\text{H}-\overset{\text{O}}{\parallel}\text{C}-\text{H}$
 F G H I

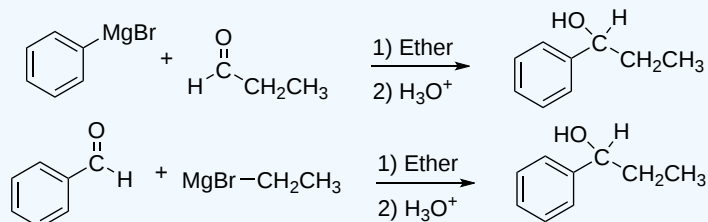
$$\text{H}_3\text{C}-\underset{\text{H}_2}{\text{C}}-\overset{\text{O}}{\parallel}{\text{C}}-\text{CH}_3 \xrightarrow[2) \text{H}^+]{1) \text{CH}_3\text{MgBr}}$$
$$\text{CH}_3\text{CH}_2\text{C}(=\text{O})\text{CH}_3 + \text{H}_3\text{C-MgX} \longrightarrow \text{CH}_3\text{CH}_2\text{C}(\text{O}^-)(\text{CH}_3)_2 [\text{MgBr}]^+$$
$$\text{CH}_3\text{CH}_2\text{C}(\text{CH}_3)_2\text{O}^- + \text{H}_3\text{O}^+ \longrightarrow \text{CH}_3\text{CH}_2\text{C}(\text{CH}_3)_2\text{OH} + \text{H}_2\text{O}$$

? EXERCISE 19.7.7

How two sets of reactants which could be used to synthesize the following molecule using a Grignard reaction.



Answer



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