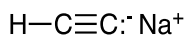
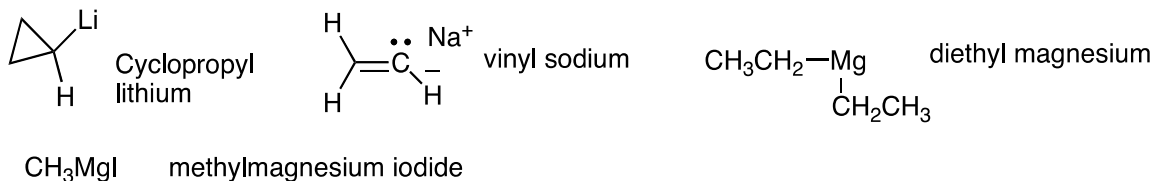


Chapter 15 Organometallic Chemistry

Organometallic compounds are those that have a carbon-metal bond such as sodium acetylide.

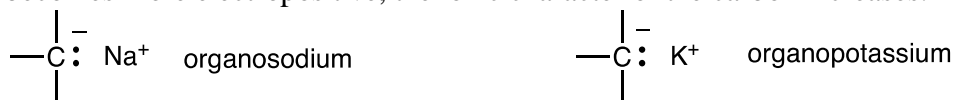


Nomenclature: name as a substituted derivative of a metal:



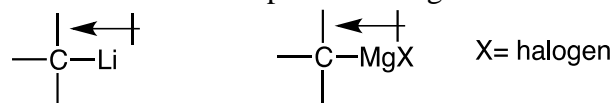
Carbon-Metal Bonds

Most metals are less electronegative than carbon and therefore the carbon will have a negative charge. A carbon with a negative charge is called a carbanion. Therefore the organometallic compounds that we will talk about have a carbanion character. As the metal becomes more electropositive, the ionic character of the carbon increases.



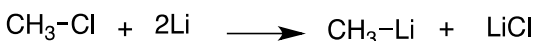
Organosodium and organopotassium compounds are essentially ionic. These compounds are sometimes very unstable and they are also not very soluble in common organic solvents and so are not very useful in organic synthesis.

Organolithium and organomagnesium compounds have a covalent bond between the carbon and the metal but the bond is highly polarized with the carbon having lots of negative charge and the metal lots of positive charge.

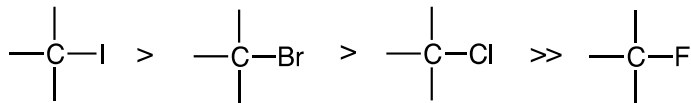


Preparation of Organolithium Compounds

We make organolithium compounds by reaction of alkyl or aryl or vinyl halides with lithium metal. This is an electron transfer process, not a substitution reaction. As we know, lithium is in the far left column of the periodic table and has an electronegativity (Pauling scale) of 0.98. It has one valence electron that it easily gives up to form Li^+ . Lithium metal is highly reactive and in fact is pyrophoric in air (i.e. it burns) and must be kept in an inert solvent at all times. We need two equivalents of the lithium to contribute the two electrons needed to form the C-X bond since each lithium atom has one valence electron and the halogen, X, ends up with a full negative charge.

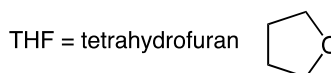
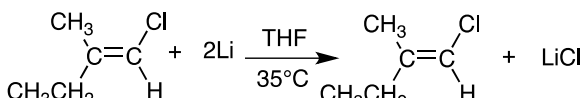
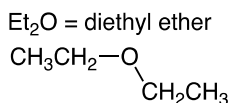
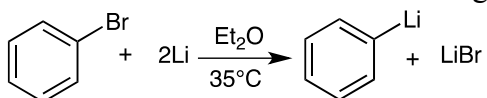


The alkyl halide may be primary, secondary or tertiary. Alkyl iodides are the most reactive, then alkyl bromides, then the chlorides. Alkyl fluorides are relatively unreactive.



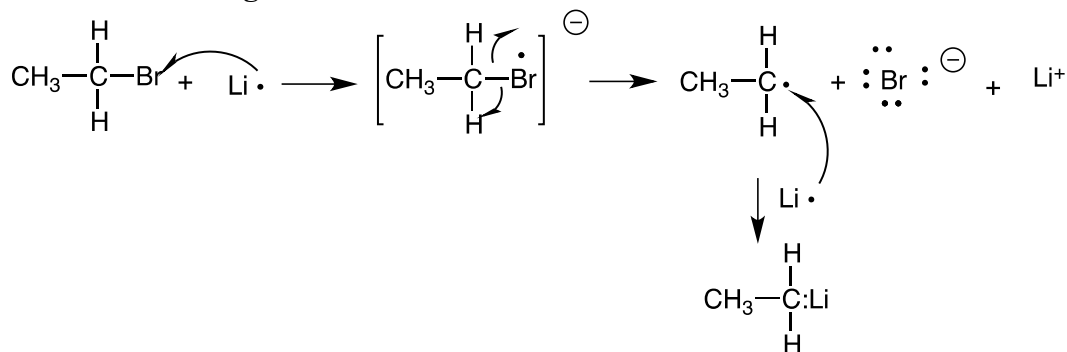
This correlates with the strength of the C-X bond.

As mentioned above, vinyl and aryl halides also react but do so more slowly than alkyl halides since the C-X bonds are stronger.



Two good solvents for these reactions are diethyl ether (Et₂O) and tetrahydrofuran (THF). Both of these are moderately polar due to the oxygen lone pair (for example, both are miscible with water) and they do not have acidic protons. Organolithium reagents are very strong bases and will react with compounds like alcohols that have relatively acidic protons (pK_a's ~16) and also with water. So it is very important that the solvents be anhydrous. Organolithium reagents react with alcohols and water to form insoluble lithium alkoxides and lithium hydroxide that coat the surface of the lithium and make it unreactive.

Mechanism of Organolithium formation:

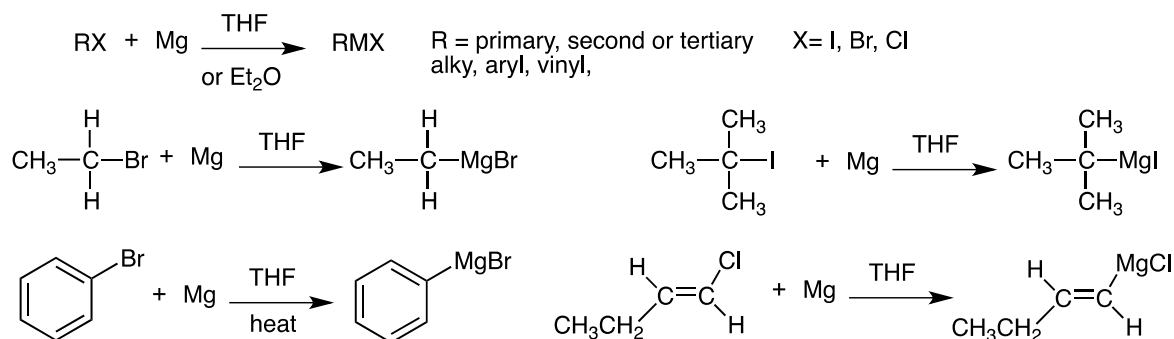


Preparation of Organomagnesium Compounds (Grignard Reagents)

Organomagnesium compounds are similar to organolithium compounds. Magnesium is in the second column on the far left of the periodic table and has an electronegativity of 1.31, about 25% more than for lithium so the carbon-magnesium bond is not quite as polarized as

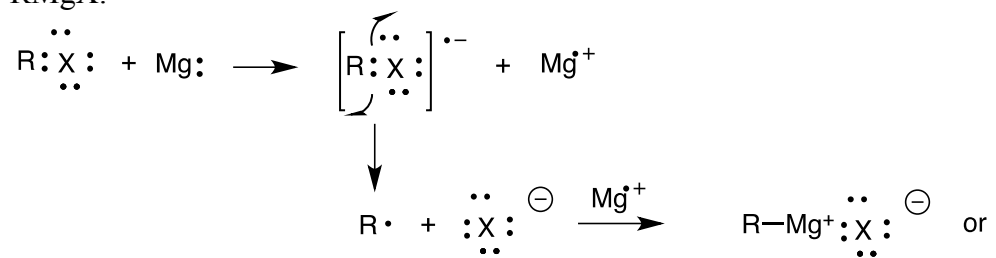
the C-Li bond but almost everything we said above about organolithium compounds also applies to the organomagnesium compounds. In some ways they are more useful than organolithium compounds because magnesium is less reactive than lithium and it can be safely handled in the air.

Organomagnesium reagents are usually called Grignard reagents after the French chemist, Victor Grignard, who developed their use and received the Nobel Prize in 1912.



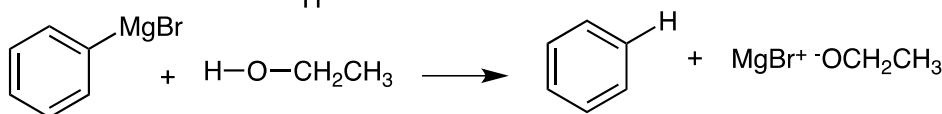
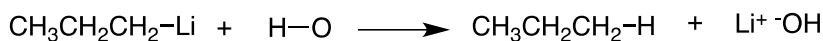
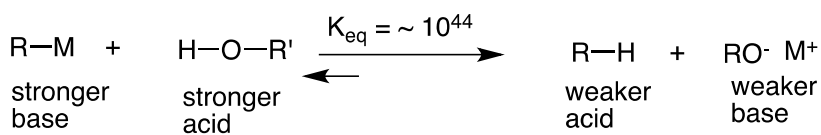
The halide reactivity order is the same as for the organolithium derivatives: $\text{I} > \text{Br} > \text{Cl} \gg \text{F}$. Alkyl halides are more reactive than aryl and vinyl halides. Aryl and vinyl halides do not form Grignard reagents in diethyl ether (b.p. $\sim 38^\circ\text{C}$). A higher boiling solvent such as THF is needed (b.p. 67°C). THF forms a more stable complex with the Grignard than does diethyl ether.

Magnesium has two valence electrons and so only one equivalent is needed to donate the two electrons to form the new C-Mg bond. The mechanism for formation is similar to that for the organolithium formation. The halogen has a negative charge and the magnesium has a plus charge so the organomagnesium compound is a salt but we usually just write it as RMgX .

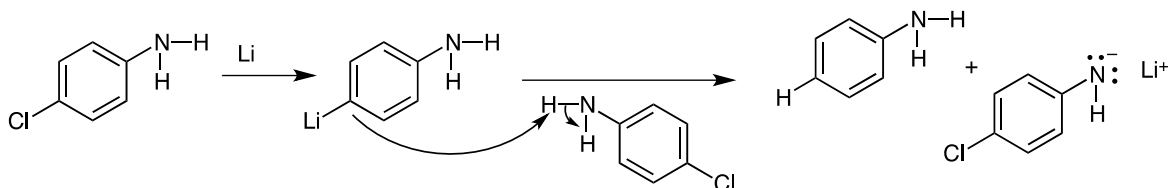
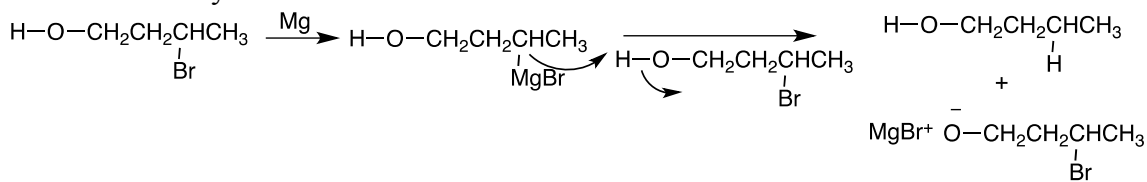


Organolithium and Organomagnesium Compounds as Bases

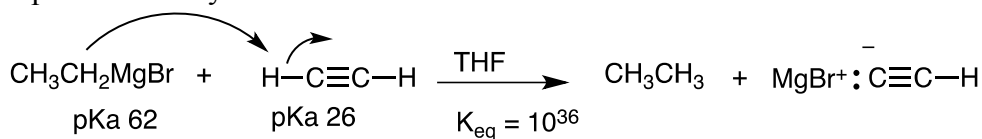
If we recall from chapter one in our discussion of acid-base chemistry, the strongest bases in chemistry are carbanions. They have pK_a 's in the 50-60 range and so are up to 10^{70} times stronger bases than say an iodine anion (I^-). Therefore, as we mentioned above organolithium and organomagnesium reagents will react rapidly with proton donors such as H_2O and HOR .



So we cannot prepare a Grignard or organolithium reagent from a compound that contains an acidic proton such as an O-H, N-H, or S-H bond. The organometallic reagent, once formed, would immediately react with itself.



Grignard and organolithium reagents can be used on purpose as strong bases to say deprotonate acetylene.



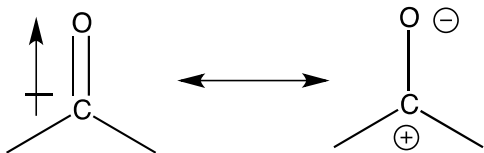
The sp carbon of the acetylene is much more electronegative than a normal sp³ carbon and this contributes to the acidity of the C-H bond. We have drawn the product as a salt with a full negative charge and lone pair on the carbon. We will see that this acetylide anion is an excellent nucleophile.

Synthesis of Alcohols Using Organolithium and Organomagnesium Compounds

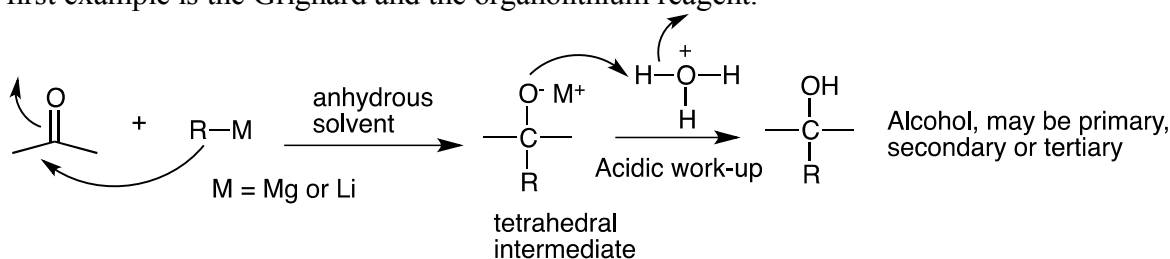
Both organolithium and organomagnesium reagents are excellent nucleophiles and will attack several kinds of electrophile as we will see. The most important of these is the carbonyl group. Grignards and organolithium reagents both attack the carbonyl group with

cleavage of the C=O bond to form alcohols with formation of a new C-C bond. This is a very, very important reaction.

First, look at the carbonyl group.

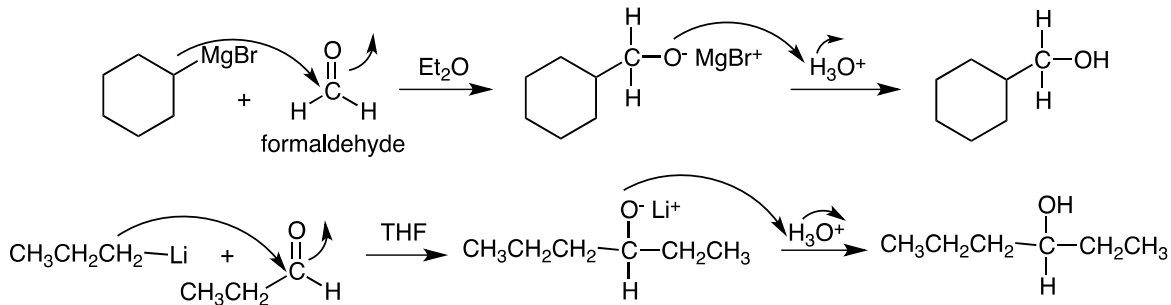


Oxygen (electronegativity 3.44) is more electronegative than carbon (electronegativity 2.55) and so the C=O bond is strongly polarized toward oxygen as shown by the resonance structure shown on the right. This means that nucleophiles will be attracted toward the carbonyl carbon. We will see a variety of nucleophiles that attack the carbonyl carbon. Our first example is the Grignard and the organolithium reagent.

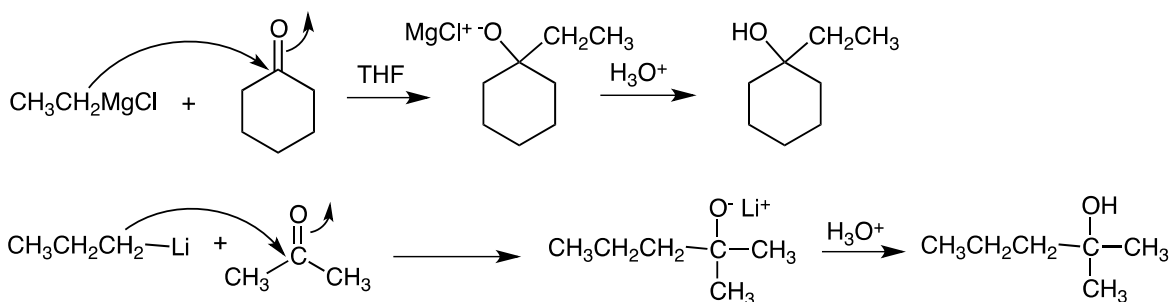


The organometallic reagent (M = Mg or Li) attacks the carbonyl carbon and the C=O bond breaks at the same time to give the tetrahedral intermediate with a negative charge on the oxygen. The organometallic reagent is often generated *in situ* (i.e. in place) and then the electrophilic carbonyl is then added usually at low temperature and with care taken that anhydrous conditions are maintained. Then, once the reaction has gone to completion, a solution of dilute acid is added so as to protonate the oxygen to make the neutral alcohol.

With Aldehydes: we form primary and secondary alcohols

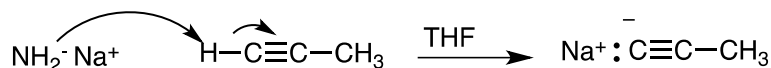
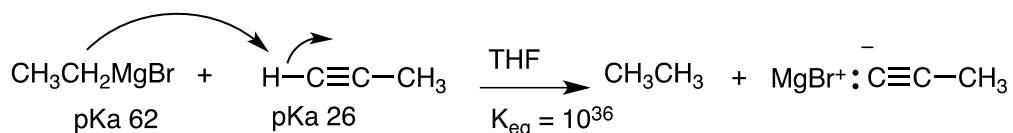


With Ketones: we form tertiary alcohols.

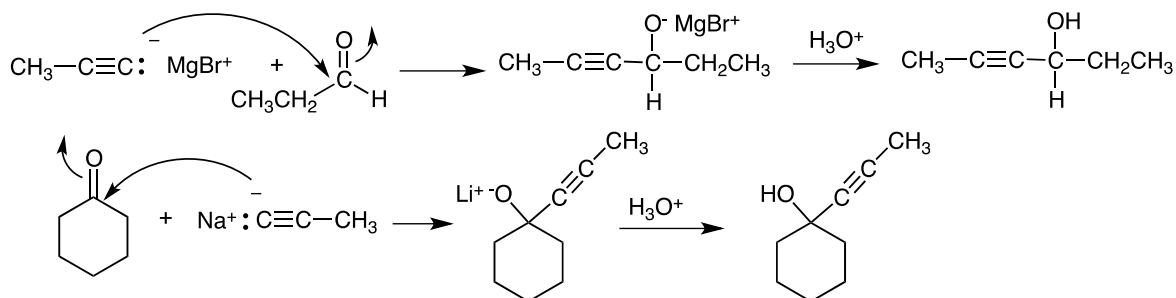


Acetylenic Alcohols

Anions of acetylene can be prepared using a strong base such as NaNH_2 or CH_3Li or CH_3MgBr .



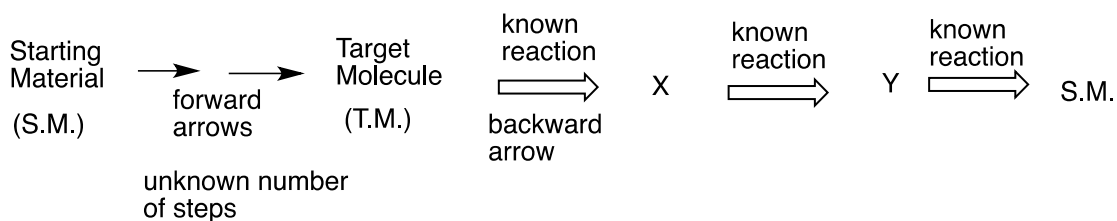
Both of these can attack carbonyls to make acetylenic alcohols.



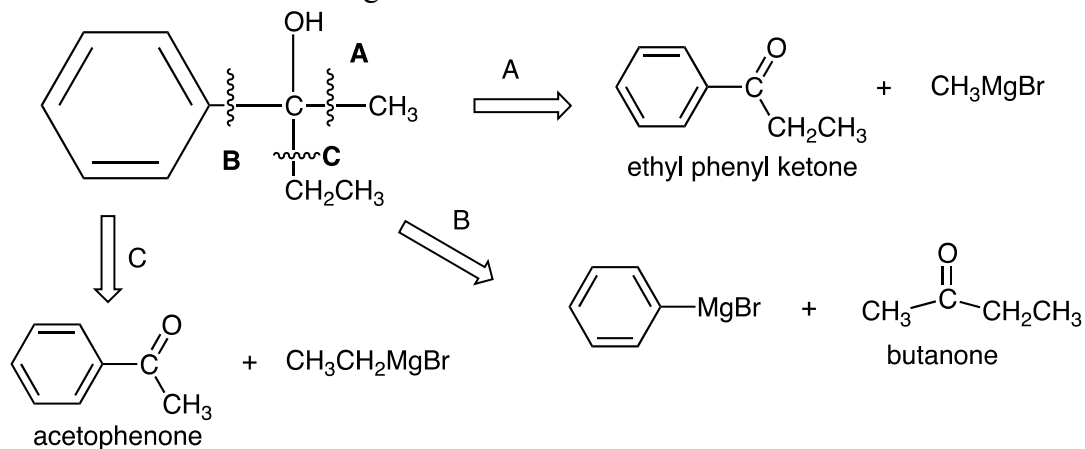
Retrosynthetic Analysis

This is a method of analysis that involves reasoning backward from the target molecule. Sometimes in a synthesis problem it is not obvious what the first step of the synthesis should be when looking at the starting material. The technique of retrosynthetic analysis is a way of helping find the best route to the target molecule (T.M.) from the starting material (S.M.).

What we do is look at the target molecule first and in our minds say if I had molecule X, then I could make the T.M. using a reaction that I know and that we have studied. Then we work one more step backward until we come to the starting material.

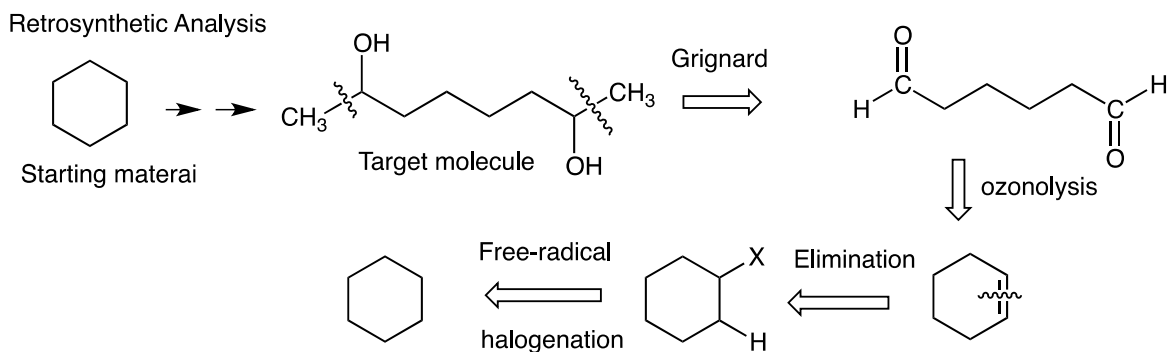


Here are some examples using the chemistry we have studied in this chapter. Our first step in this process is to imagine which bond we are going to form. In order to break this bond hypothetically in our minds, we must have a clear method for forming it in the forward direction. Breaking this bond is called a “disconnection” and we represent this typically by making a wavy line through the bond that we will break. Remember this is purely an imaginary exercise as we work backward step-by-step from the target molecule to the product. We do not have to do this and many times we can do it in our minds without actually writing it down but sometimes it is helpful, especially when the target molecule does not look similar to the starting material.

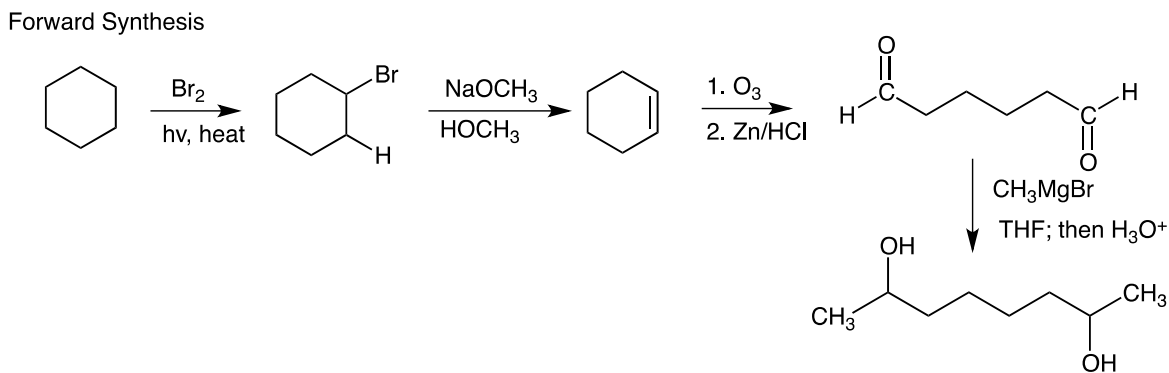


Here we are not given the starting material but the target molecule is a tertiary alcohol and we have just learned that we can make tertiary alcohols using Grignard reagents in reaction with ketones. So, looking at the formation of bond A (the backward disconnection represented by the wavy line) we know that we could form the target molecule if we had the methyl magnesium bromide and ethyl phenyl ketone. In this example we see that there are three possible disconnections that we could make and they are all about the same. Again, we do not have to perform the retrosynthetic analysis but sometimes in more complicated examples it is a useful technique, as we will see in later chapters.

Here is another example, using chemistry from Chem. 121.

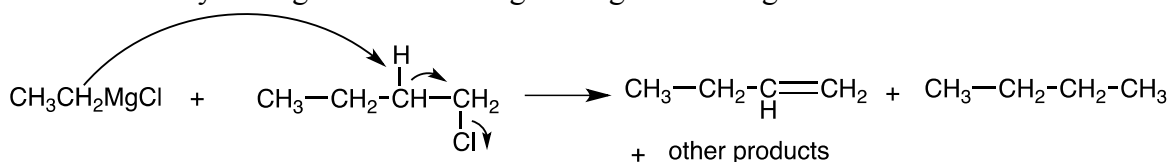


At first glance this looks impossible. How are we to break one of the unactivated C-C single bonds in cyclohexane to make a 1,6-diol with two extra carbons! So, rather than looking at the starting material, look at the target molecule and look at the first disconnection shown by the wavy line. If we had the dialdehyde (dihexanal) then we could do a Grignard reaction with methyl magnesium bromide and we could form our target molecule. But then the question in our minds is how do we make the six-carbon dialdehyde. Working backward one more step, we recall that we could form this using the ozonolysis reaction with a reductive work-up from cyclohexene. We also know that we can form alkenes by means of an E2 reaction using strong base if we have a good leaving group on the alkane. We need to add a halogen and we can do this using free-radical bromination of cyclohexane, another reaction we studied in Chem. 121. The forward synthesis is then simply the reverse of our backward analysis.



Organocopper Reagents for the formation of C-C Bonds

We cannot use Grignard or organolithium reagents for reaction with alkyl halides. The yields are low due to elimination reactions (E2 mechanism) and other reactions such as reduction of the C-X bond by the organolithium or organomagnesium reagent.



This reaction looks like it would work since the Grignard (or organolithium) is a good nucleophile and the primary alkyl halide is a good electrophile but it does not.

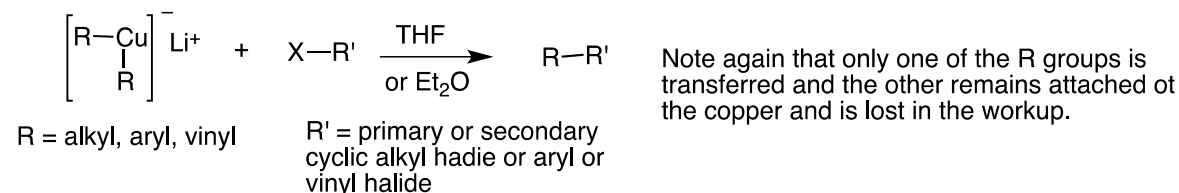
We can, however, do this coupling reaction by using an organocopper reagent. Without going into all of the details, we can see from the periodic table that copper (electronegativity 1.90) is much more electronegative than magnesium (1.31) or lithium (0.98) and the copper-carbon bond is less polarized and it is a less basic reagent. We see less elimination and less reduction of the alkyl halide and we get good yields of C-C bond formation with a variety of alkyl halides. The reaction has great scope. It also works well with vinyl and aryl halides and we can form the organocopper reagent from vinyl and aryl halides as well.

There are two major limitations, however:

(1) Steric hindrance is a major factor and so the alkyl halide must be primary or secondary cyclic.

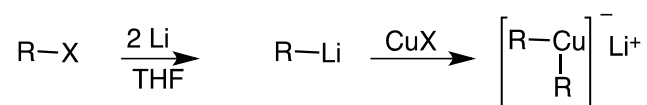
(2) One half of the original organic species from which the organocopper reagent is formed is lost. Only one of the organic groups attached to the copper is transferred in the reaction.

The overall reaction:

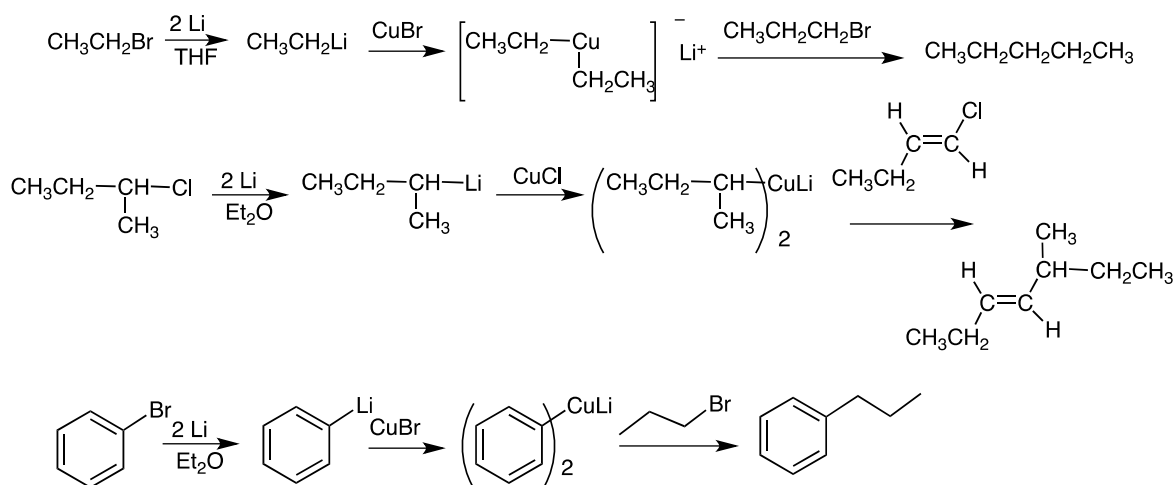


Note also that the organocopper reagent is still quite basic and requires strictly anhydrous conditions like the Grignard or organolithium reagents. It is destroyed by acidic protons so functional groups with S-H, O-H, N-H bonds cannot be present.

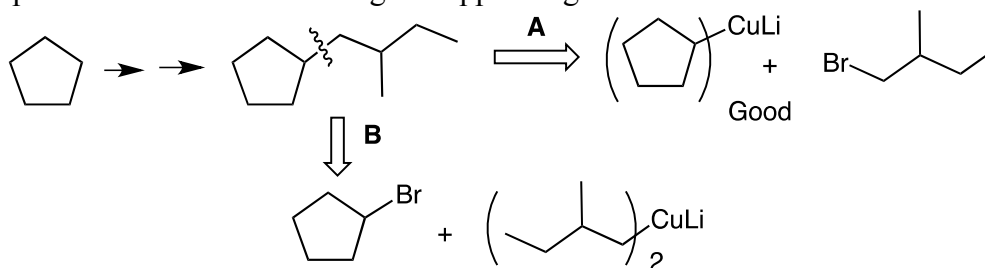
We form the organocopper reagent in two steps from an alkyl, aryl or vinyl halide, treating it first with two equivalents of lithium metal to form the organolithium reagent and then with a Cu(I) halide to form the organocopper reagent (or organocuprate). Two of the organic species are attached to one of the copper atoms and the molecule has a negative charge, balanced by the lithium cation. We can also form the organocuprate from organomagnesium compounds.



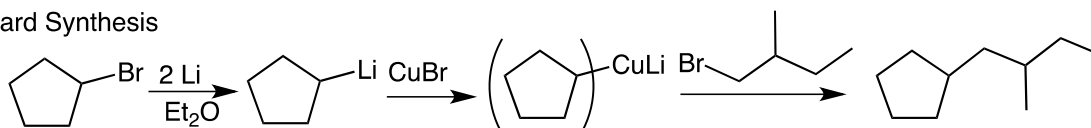
Examples:



Note in a synthesis, if the product does not contain oxygen, then the best route to the compound would be to use an organocopper reagent.



Forward Synthesis



Just as in the retrosynthetic analysis of the synthesis of alcohols, there is often more than one possible set of reagents that will give the target molecule. As we mentioned above, the organocopper coupling reaction is very sensitive to steric hindrance and the second group added must be primary or secondary cyclic. In this case both disconnections **A** and **B** above would work. **A** is probably better since the alkyl halide used is primary and less hindered.