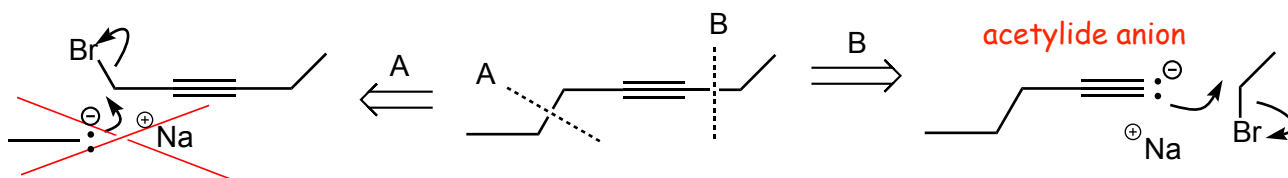
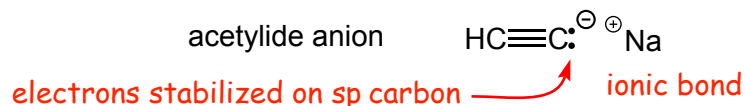


## 1 Carbon-Metal Bonds

We previously looked at the following two disconnections:

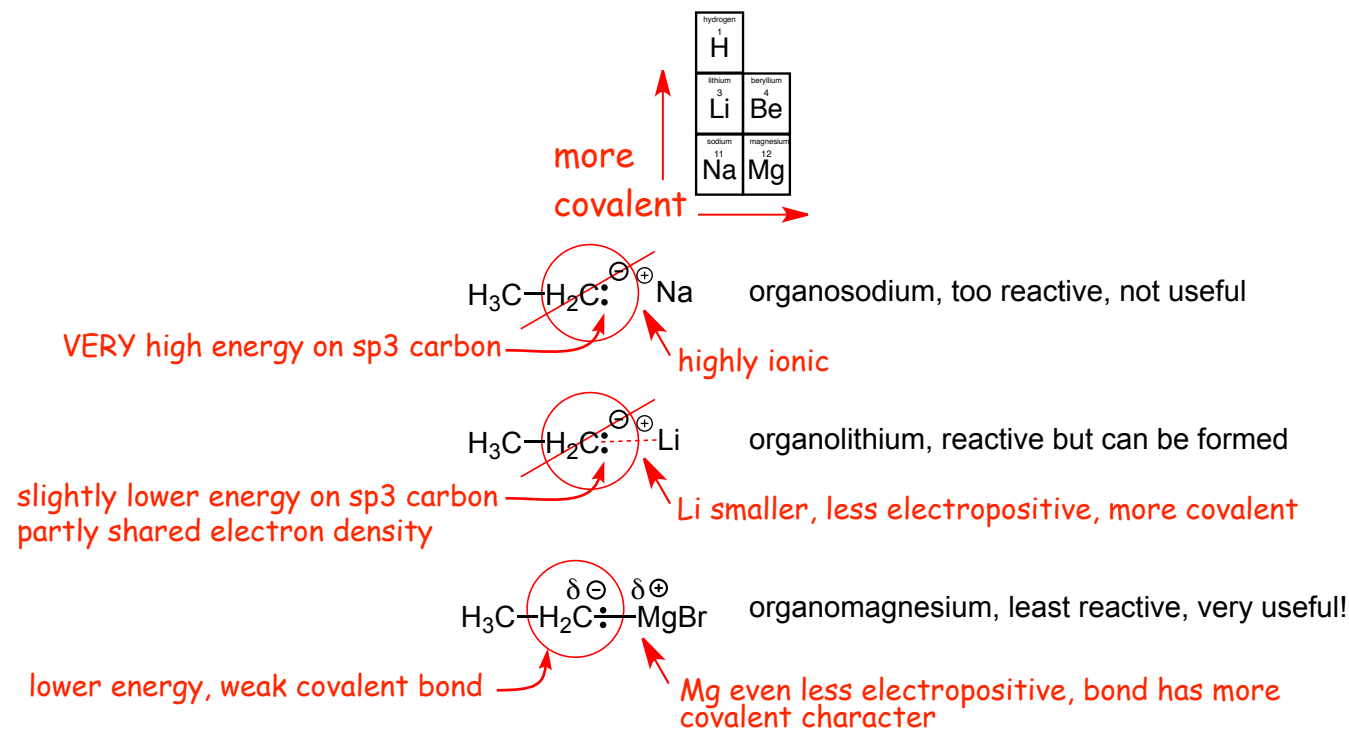


- Disconnection **B** is better since it generates a useful **acetylide** synthon/reagent.
- The acetylide anion is a simple organometallic reagent, i.e. an organic structure with a bond to a metal.
- In this case the carbon metal bond is essentially pure ionic:



- Suppose we **had** to do disconnection **A** above, how can we make a reasonable carbon synthon such as that in **A** if we don't have an sp A.O. to stabilize the electrons?
- An ionic bond to a sodium cation will not work if the hybridization has higher p character than sp.
- Instead, we must "temporarily" stabilize the non-bonding electrons on the carbon another way, we can put them into a weak bond to a metal atom

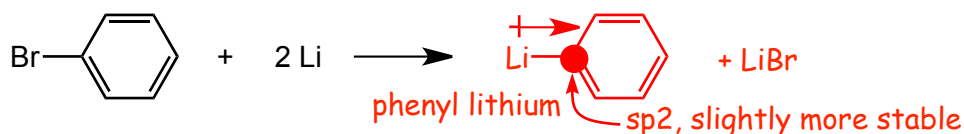
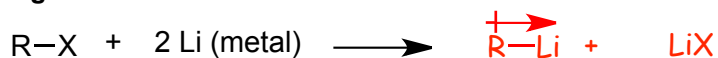
Compare bonding to different metals for  $\text{sp}^3$  hybridized carbon:



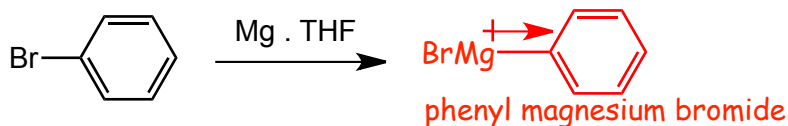
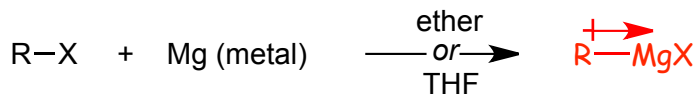
- Weak covalent bonds with a lot of ionic character mean that the electrons are still relatively high in energy and quite reactive.
- Both organolithiums (alkyl and aryl lithiums) and lithium compounds and organomagnesium compounds (Grignard reagents) can be made for carbons with **any** hybridization, including  $\text{sp}^3$  and are thus very useful.
- Alkyl and aryl lithiums are more ionic and tend to be very strongly basic, but they are still nucleophilic and can be used to make carbon-carbon bonds.
- Organomagnesium compounds in the form of Grignard reagents tend to be the most useful nucleophiles.

**Organometallic reagents are useful carbon anion synthons/reagents.**

## Organolithium reagents:



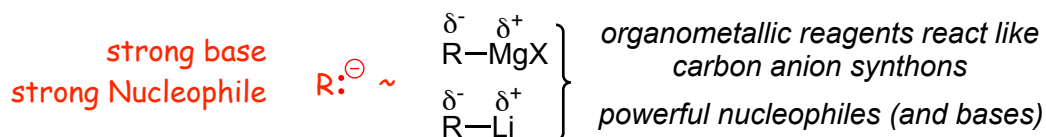
## Grignard reagents:



- The reaction is between an alkyl or aryl halide (often bromide) with metallic magnesium in an ether solvent.
- Solvents for Grignard reaction must be ethers, two are most commonly used:



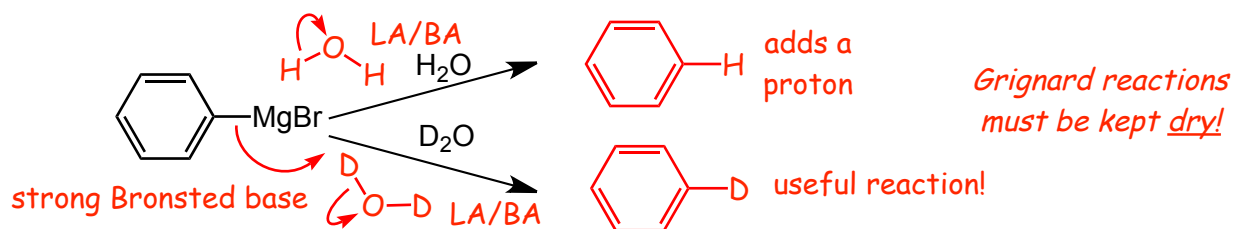
- As reagents.....



- The Grignard reagent is **less reactive, easier to handle**, although restricted to ether solvents.
- Organolithiums, more reactive, harder to handle, are **very strong Bronsted bases** (see later), can be used in different solvents.

## Reactions of Organometallics With Water:

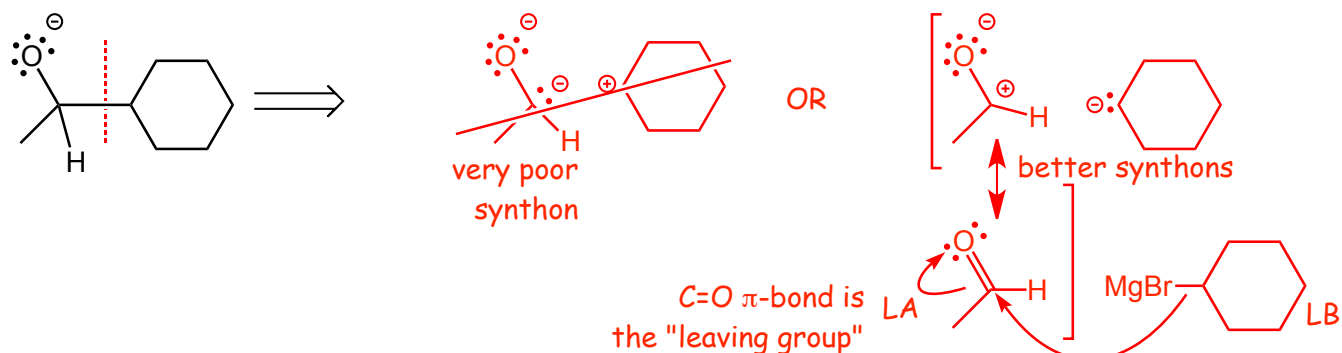
- This is not usually a useful reaction, but it is one that is important to know



- This is hydrolysis of a carbon-metal bond (breaking a carbon-metal bond, -lysis, with water), we have seen this before, and will see again (and again..)
- **This** is the reason that reactions of organometallic reagents have to be performed in the absence of **all** water (apparatus and solvents must be dried).

## 2 Nucleophilic Addition Reactions

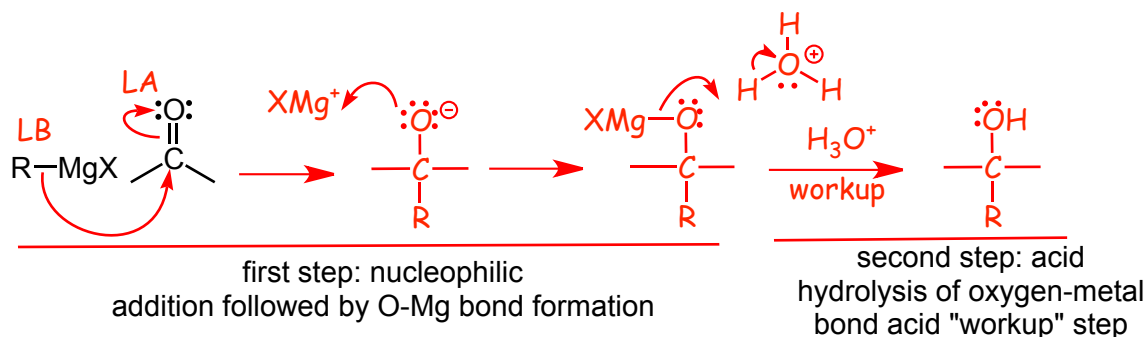
### Example Problem:



- The positive synthon (with the positive charge) is stabilized by simply generating a C=O bond, i.e. the positive synthon is simply an aldehyde, in this case the C-O  $\pi$ -bond is the "leaving group".
- The non-bonding electrons in the negative synthon are stabilized by putting them into a weak carbon-metal bond.
- We now have excellent synthetic equivalents (actual reactants), an aldehyde and a Grignard reagent.

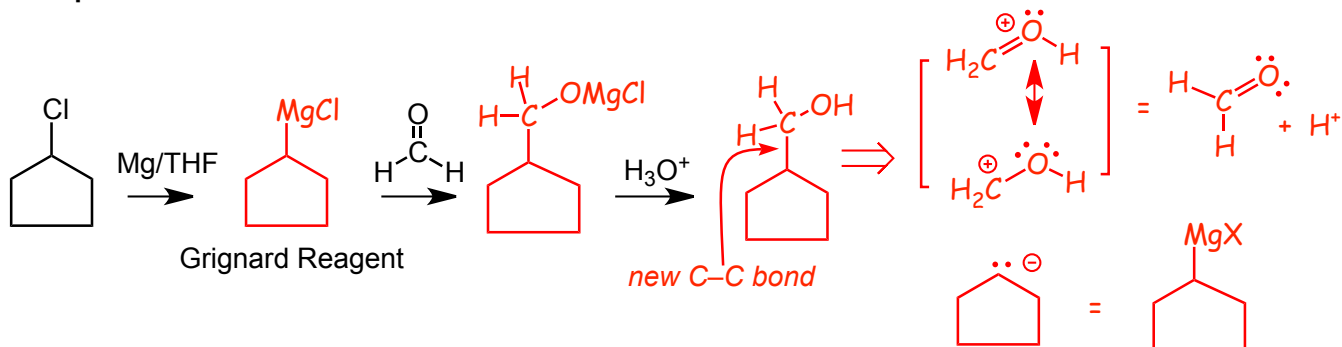
### Reactions With Aldehydes, Ketones and Epoxides:

- This reaction makes a new C-C bond (and an alcohol, similar to acetylides), **this is a very important reaction!**

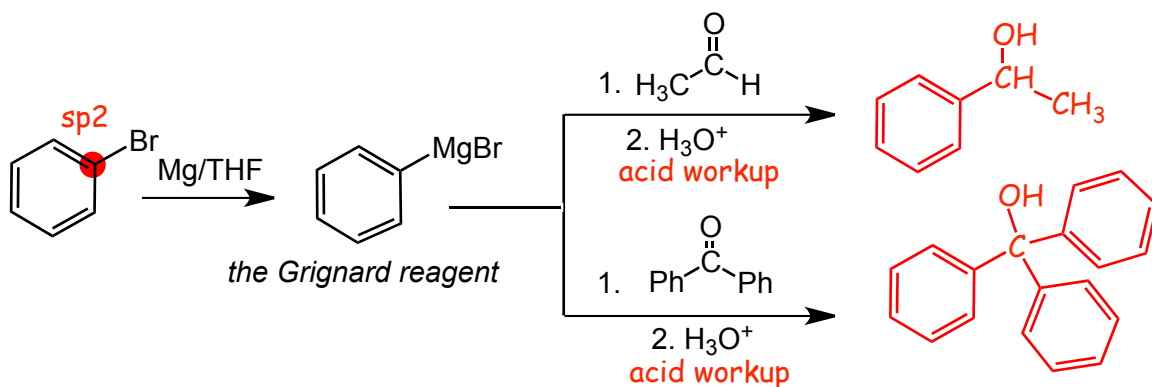


- This is a two-step reaction, the first is Grignard addition to the C=O bond (followed by addition of  $\text{XMg}^+$  to the oxygen)
- The second step is an "acid workup" step. This is very different from, for example, the acid catalyzed addition of water to an alkene, which requires a lot of acid, heat and time. Acid workup usually means using a fairly dilute acid solution for a short amount of time, the "reagent"  $\text{H}_3\text{O}^+$  can mean very different things in different contexts, in this case it means fairly dilute acid.
- This is important because unlike the acetylide reaction, the reagents can be prepared from a **halide**, and halides are much more readily available and generally useful than alkynes.

### Examples:

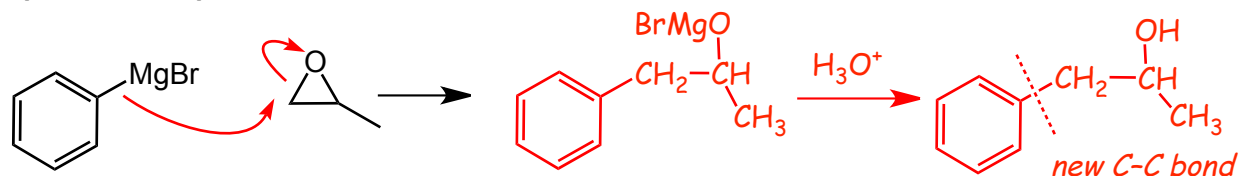


- Note: Retrosynthetic analysis in this case converts the positive synthon into a C=O structure **plus** a proton ( $\text{H}^+$ ), the proton is supplied in the second acid workup step in the form of  $\text{H}_3\text{O}^+$ .



Note: Grignard reagents can be made at  $sp^3$  and  $sp^2$  hybridized carbon atoms, they are very versatile!

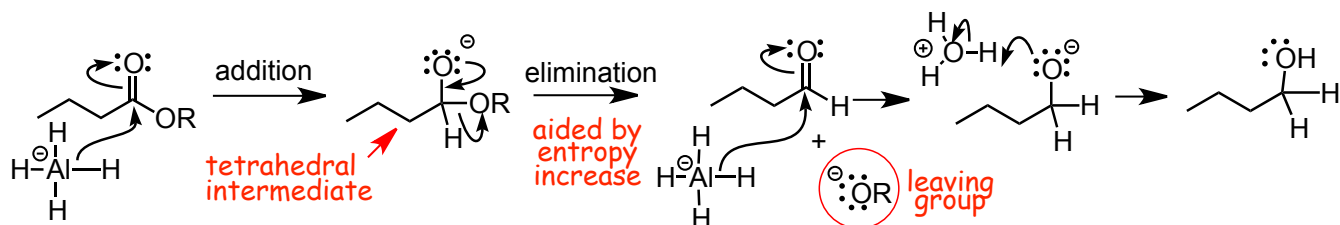
### Example With An Epoxide:



- The Grignard attacks the least-substituted side of the epoxide (seen before), for steric reasons.
- The oxygen on the carbon **adjacent** to that in the new C-C bond, characteristic of addition to an epoxide.

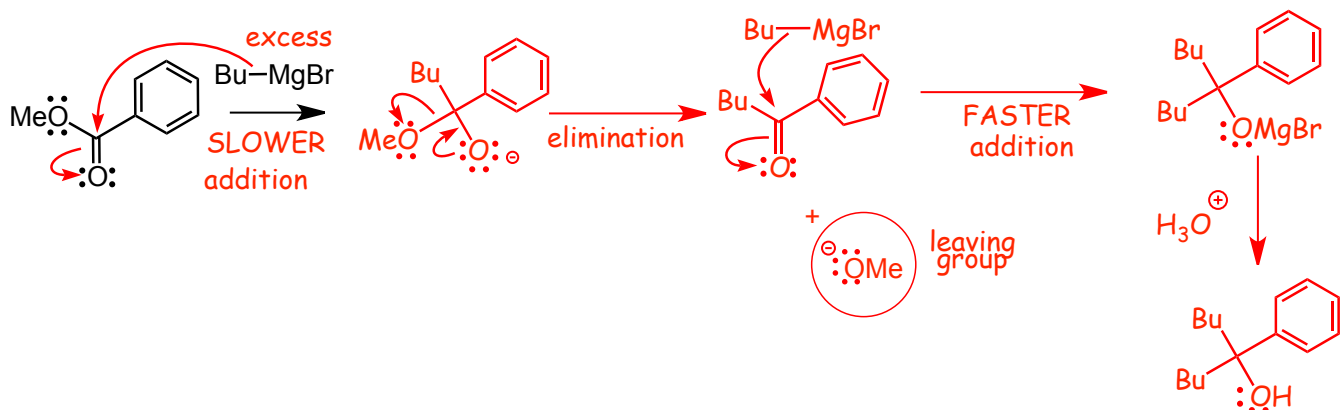
### Example With Esters: Addition/Elimination (again)

- Recall the Reaction of  $\text{LiAlH}_4$  with an ester:

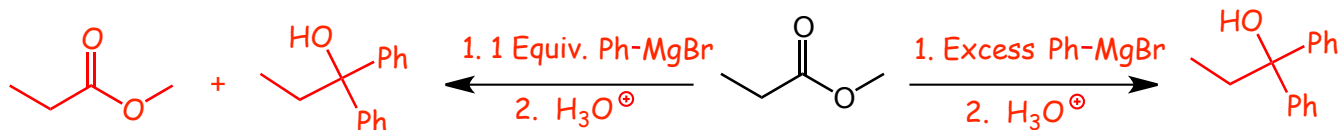


- Hydride addition to an ester, occurs **twice** in an **addition/elimination** mechanism followed by **addition**.
- $^-OR$  is the leaving group, and while not a particularly good one, **elimination is favored by entropy**, and, the intermediate also has a negative charge on oxygen, which isn't bad.
- $^-OR$  will only be a leaving group when the starting reactant has high chemical potential energy in the form of reactive electrons, usually as an **anion**,  $^-AlH_4$  in this case, **or**, as a Grignard reagent, see below.

### Similarly: Reaction of a Grignard Reagent with an ester:

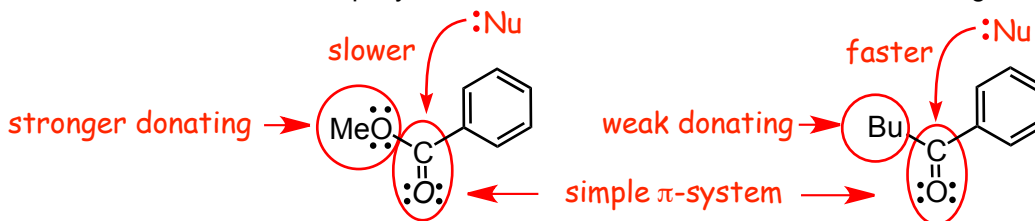


- The Grignard with an ester reaction occurs by **addition/elimination mechanism** followed by **addition**.
- $^-OR$  is the leaving group, and leaves for the reasons given above for hydride.
- The Grignard reacts **slower** with the ester than it does with the ketone.
- This turns out to be important, because the product of the Grignard reaction with the ester reacts **faster**, which means any attempt to use only 1 Equivalent of Grignard is doomed to fail, since as soon as the ketone is formed it will consume Grignard before it can react with the ester.



Unreacted

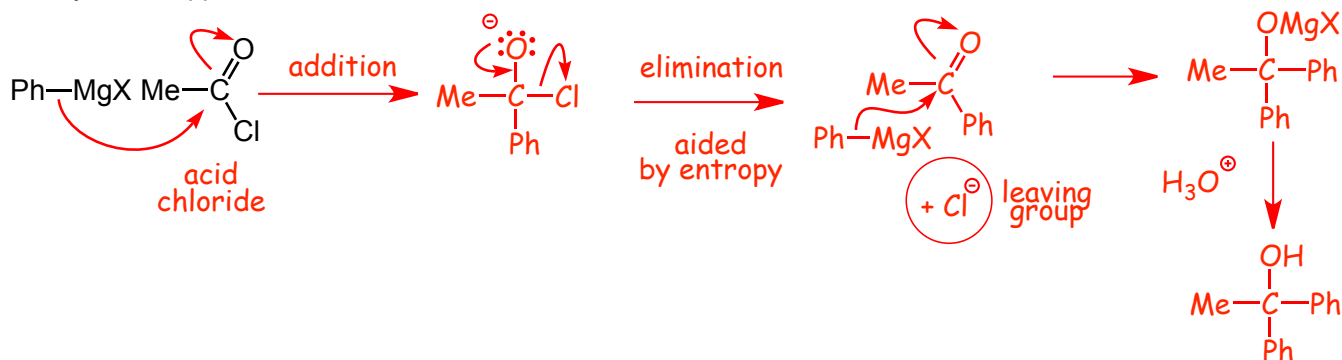
- Therefore, you must specify Excess (XS) Grignard in these reactions with esters.
- Recall, we previously learned that strong nucleophiles such as  $NaBH_4$  and  $LiAlH_4$  react slower with esters than they react with aldehydes and ketones, this is why you need the stronger nucleophile  $LiAlH_4$  to reduce an ester.
- This is because the  $C=O$  group in the ester is not as electrophilic as the  $C=O$  group in an aldehyde or ketone.
- We can consider the  $C=O$  to be a small  $\pi$ -system that has substituents with different donating abilities.



- The stronger donating  $^-OMe$  substituent decreases the reactivity of the ester with respect to the ketone.

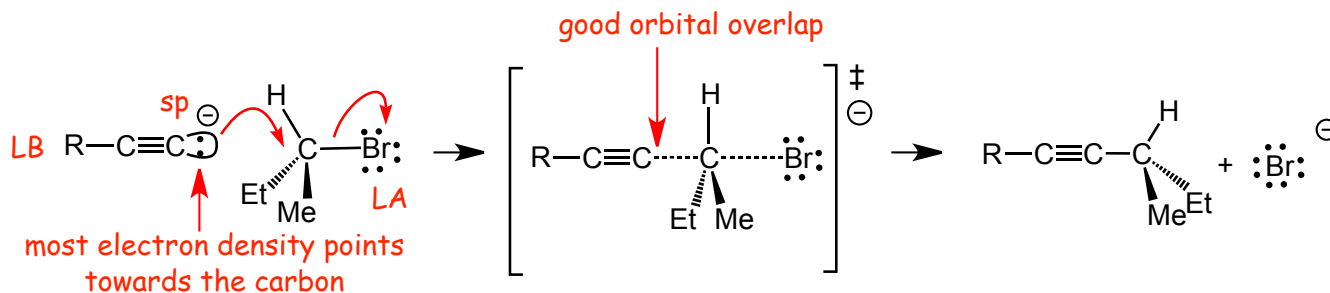
**Example With Acid Chlorides:** Addition/Elimination (again).

- Acid chlorides have an even better leaving group than esters, we expect addition/elimination also, and this is exactly what happens.



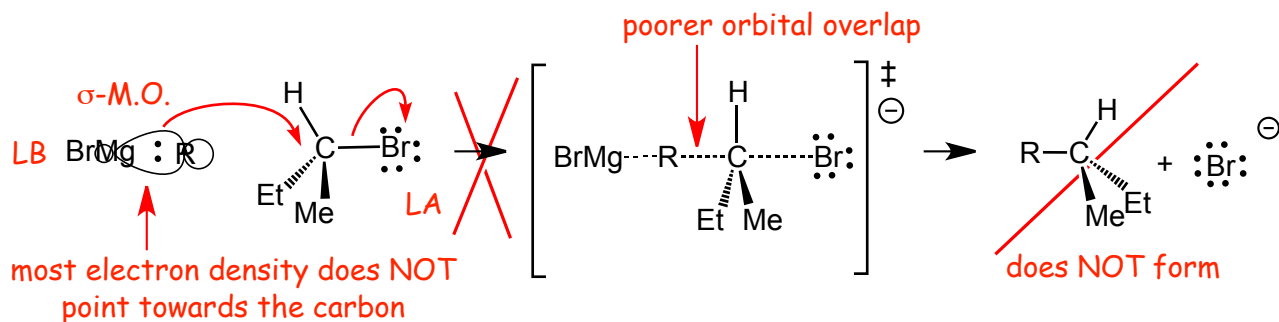
**Grignards do not do  $SN_2$  reactions with most alkyl halides:**

- Unlike the acetylide anion, Grignard reagents do not do  $SN_2$  reactions with most alkyl halides (allylic halides are an exception, as we will see later....)
- An acetylide  $SN_2$  reaction with a halide....



- The Lewis basic electrons in the acetylide anion are in a small  $sp$  hybrid A.O. that "points" directly towards the carbon of the alkyl halide, the partial bond in the transition state is strong, the reaction is fast
- The acetylide anion is a strong base **and** a very strong nucleophile (remember, the definition of nucleophilicity is based on reaction kinetics, how fast the reaction goes, not just on how strong a bond it can make)

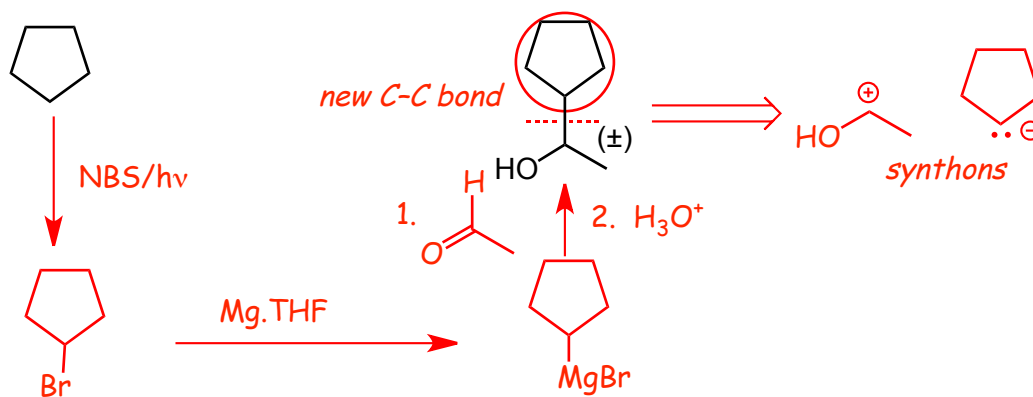
- A Grignard SN2 reaction with a halide....



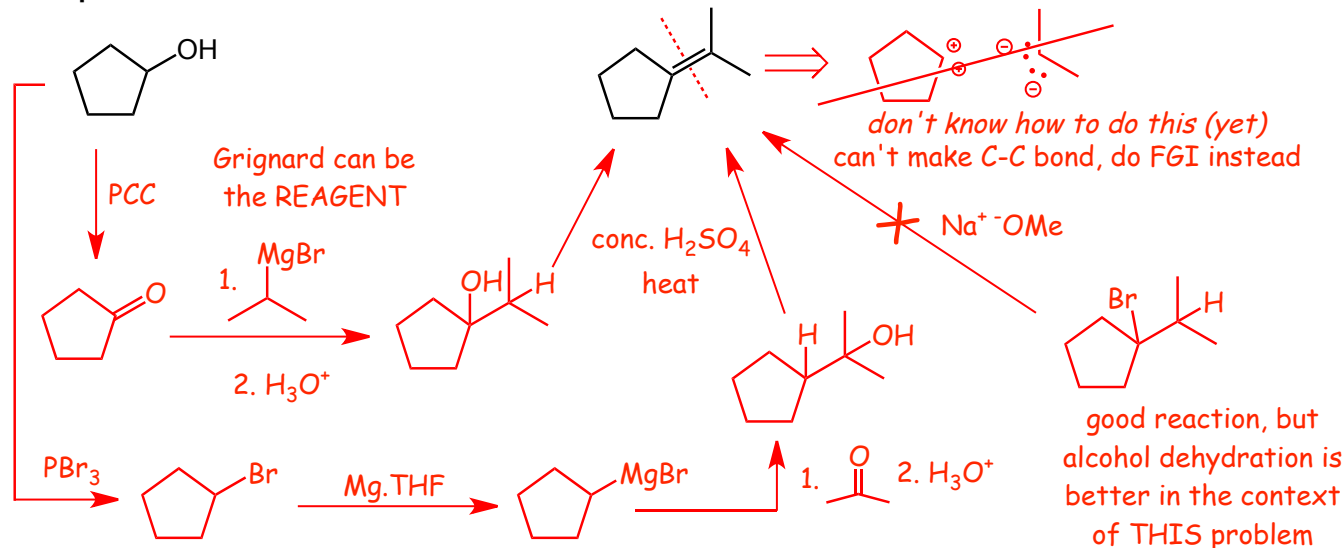
- The Lewis basic electrons in the Grignard reagent are in a larger  $\sigma$ -bonding M.O. and most of the electron density does **not** "point" directly towards the carbon of the alkyl halide, the partial bond in the transition state is weak, the reaction is slow.
- The Grignard reagent is a strong base **but** a weak nucleophile (remember, the definition of nucleophilicity is based on reaction kinetics, how fast the reaction goes, not just on how strong a bond it can make).
- We will find that Grignards **can** do SN2 reactions in special cases, specifically in the halide is allylic or benzylic due to stabilization of the transition state in that case (see later).
- In advanced organic chemistry classes you will also find that the reaction of Grignards with  $\text{C}=\text{O}$  bonds is actually a bit more complicated than we pretend it is here! But our model of these reactions is sufficient to explain everything we need for this course, and in organic chemistry we tend to use the simplest model that works.

### 3 Organometallics in Retrosynthesis

#### Example 1:

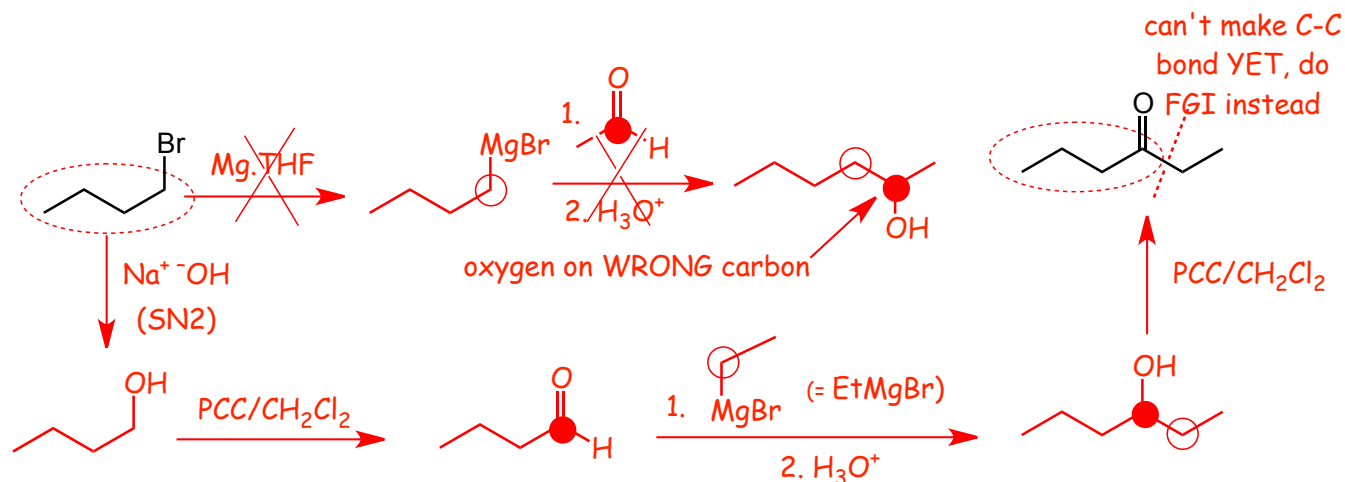


#### Example 2:



- The last reaction is **can't** be making the required C=C bond because we have not learned how to make a C=C bond yet, therefore the last reaction **has to be** making the alkene from another functional group, i.e. a functional group interconversion (FGI).
- We can make an alkene by E2 elimination of an alkyl bromide, **or**, by dehydration of an alcohol.
- Elimination of the bromide is a good reaction, but is less helpful in the context of this overall synthesis problem, because if we use an alcohol that will help us to solve the C-C bond making problem in the previous step. Since alcohols are often formed in Grignard reactions, therefore in this case dehydration of the alcohol is best.
- But there are **two** possible alcohols that can be dehydrated, which one to choose? It turns out that you can use either, in many multi-step synthesis problems there is **more than one** possible solution, this is one of those.

### Example 3:



- The last reaction is **can't** be making the required C-C bond because it is to an sp<sup>2</sup> hybridized carbon that is part of a ketone, we don't know how to do that, therefore the last step has to be making the ketone from another functional group, i.e. a functional group interconversion (FGI).
- We can make a ketone from an alcohol, which is a good idea because we know that we can make C-C bonds that have alcohols in the reaction products when using a Grignard reagent.
- Be **careful** when constructing Grignard reactions, make **sure** that you have the -MgBr and the C=O on the correct fragments to get the -OH on the correct carbon after the reaction is complete!

## 4 Organometallic Reagents : Summary of Reactions

**WARNING: Carbon-carbon bond forming reactions require lots of practice and occur in many more contexts than summarized here!**

