



CHEMISTRY 2500

Topic #7: Pi Bonds as Electrophiles
(*aka* Addition Reactions of Carbonyls and Similar Groups)

Spring 2020

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Carbonyls as Electrophiles

- Polar pi bonds are excellent electron pair acceptors (electrophiles).
- The most common example of a polar pi bond is the carbonyl:

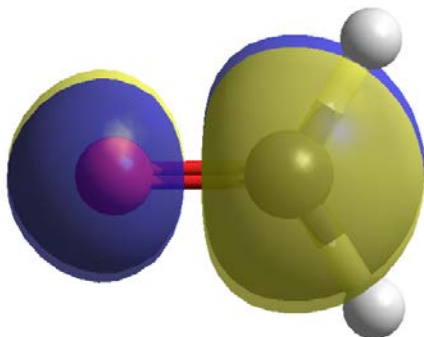
Other examples include nitriles, imines and thiocarbonyls:

- The common feature of all these groups is a carbon atom with a multiple bond to a more electronegative atom, giving that carbon atom a partial positive charge.

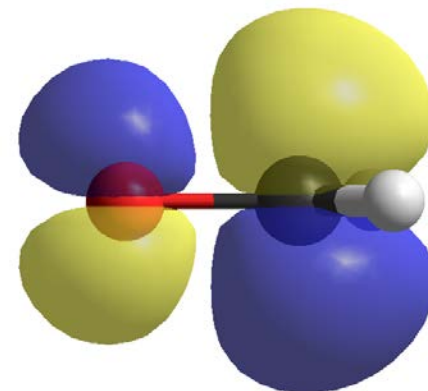
Carbonyls as Electrophiles

- Recall from CHEM 2000 that when a molecule accepts electrons, it reacts with its **LUMO** (**L**owest **U**noccupied **M**olecular **O**rbital).
- The LUMO for a simple carbonyl ($\text{O}=\text{CH}_2$) looks like this:

top view:



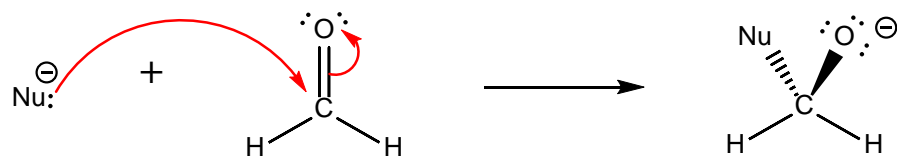
side view:



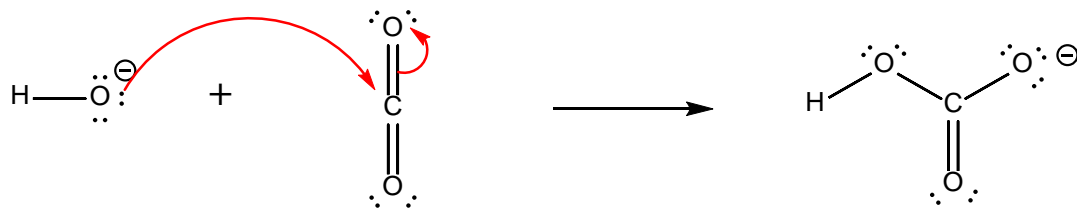
- Is this orbital bonding or antibonding?
- Is this orbital sigma symmetric or pi symmetric?
- Is this orbital polarized toward (larger on) carbon or oxygen?
- What does this LUMO tell us about what happens when this compound accepts electrons?

Carbonyls as Electrophiles

- So, looking at the LUMO has shown us that when a carbonyl group accepts a pair of electrons, they are accepted at the partially positive carbon atom and the pi bond is broken!
- This process can be shown using curved arrows:

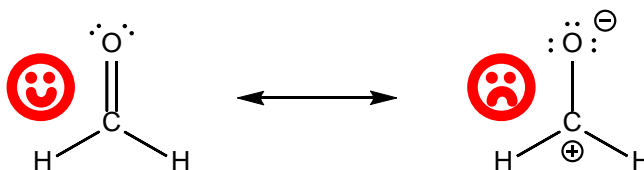


- This should look the same as the curved arrows we drew showing carbon dioxide acting as a Lewis acid in CHEM 1000:



Carbonyls as Electrophiles

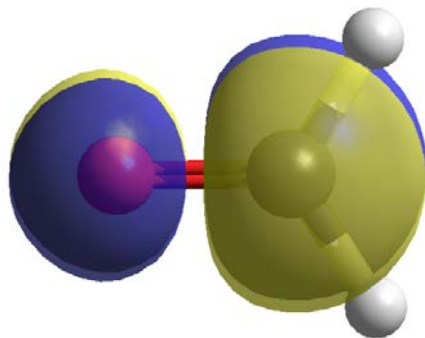
- It is important to note that BOTH PAIRS OF ELECTRONS MOVE AT THE SAME TIME!
- Some texts use the resonance structure below to rationalize attack at the C rather than the O, but it is NOT a significant contributor to the average structure and is an unnecessary crutch if you know how to “read” the LUMO. So, please don’t draw that resonance structure as part of any mechanism!



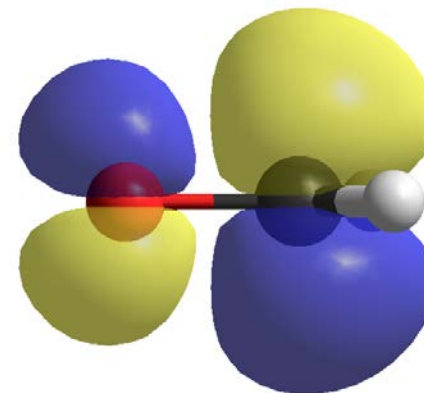
Other Polar Pi Bonds as Electrophiles

- The LUMO for a simple carbonyl ($\text{O}=\text{CH}_2$) looks like this:

top view:

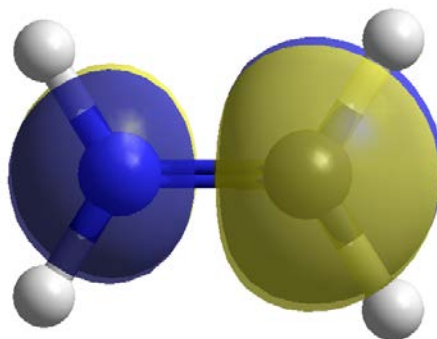


side view:

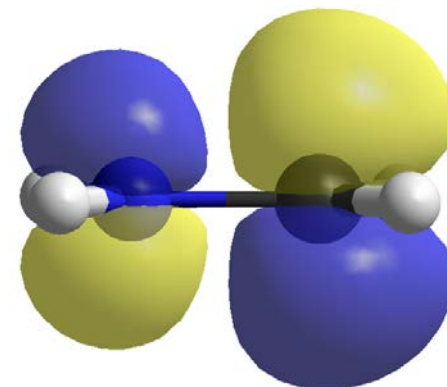


- The LUMO for a simple iminium ion ($\text{H}_2\text{N}^+=\text{CH}_2$) looks like this:

top view:



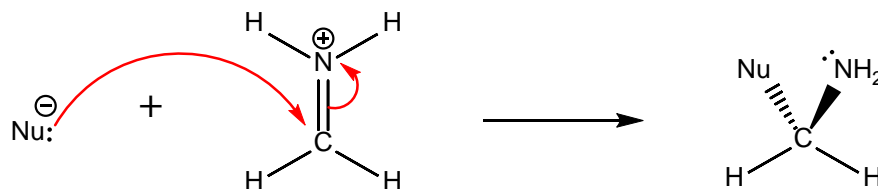
side view:



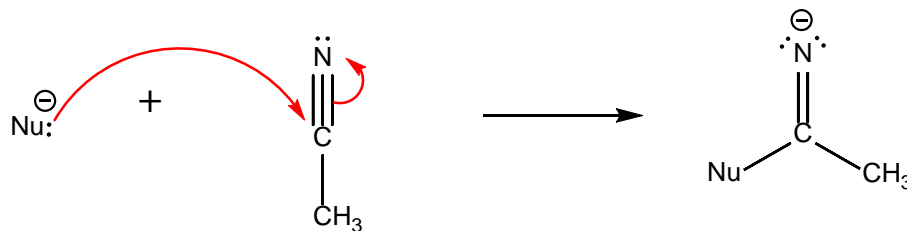
- They look exactly the same!

Other Polar Pi Bonds as Electrophiles

- So, the LUMO of an iminium ion shows us that it also accepts an electron pair at the partially positive carbon atom, breaking the pi bond:

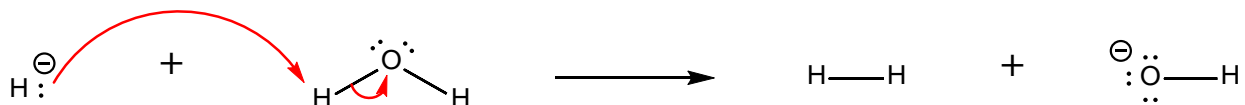


- The same is true for a nitrile:



Addition of Hydride to Polar Pi Bonds

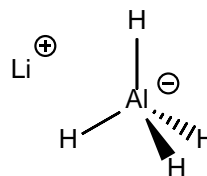
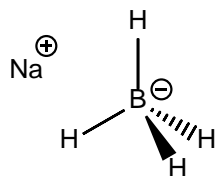
- One of the simplest nucleophiles we could imagine would be the hydride ion (H^-). You first encountered the hydride ion in CHEM 1000 and learned that it is an extremely strong base:



- Unfortunately, the hydride ion is too small to be a good nucleophile. So, if we want to do reactions in which " H^- " is the nucleophile, we have to use larger reagents containing one or more electron-rich hydrogen atoms...

Addition of Hydride to Polar Pi Bonds

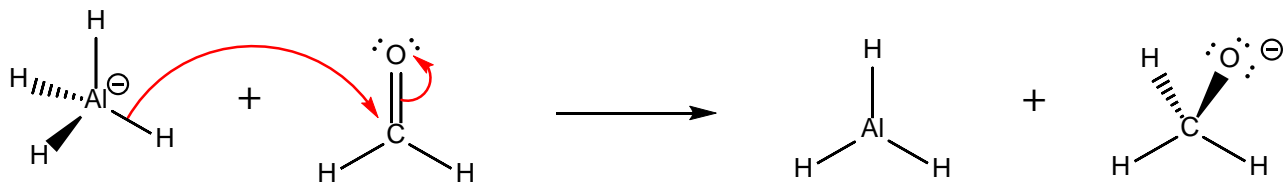
- How can we make an electron-rich nucleophilic hydrogen atom? Attach it to a less electronegative element! Boron and aluminium are the most common choices:



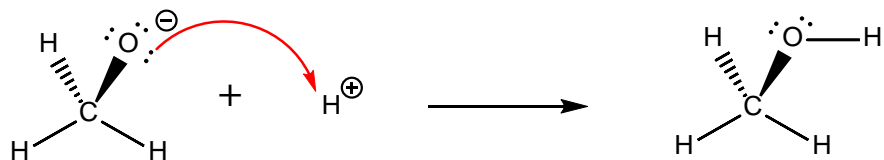
- LiAlH_4 is more reactive than NaBH_4 . Why do you think that is?

Addition of Hydride to Polar Pi Bonds

- When LiAlH_4 reacts with a carbonyl group, one of its hydrogen atoms forms a bond to the carbonyl carbon. We consider this a “hydride nucleophile” because LiAlH_4 is the source of electrons for the new C-H bond:

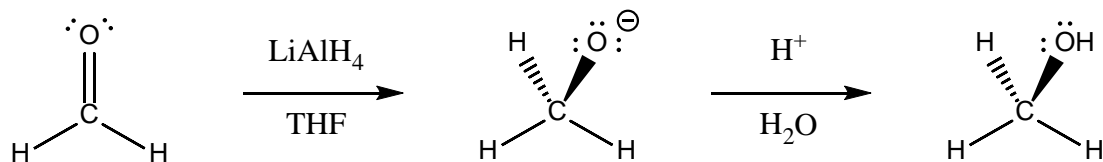


- Because LiAlH_4 is such a reactive electron pair donor (both as a nucleophile and as a base), there cannot be any acidic protons present while the reaction above is performed. AFTER that reaction has finished, it is typical to “work up” the reaction by adding aqueous acid (or water or some other aqueous solution) which protonates the organic product:

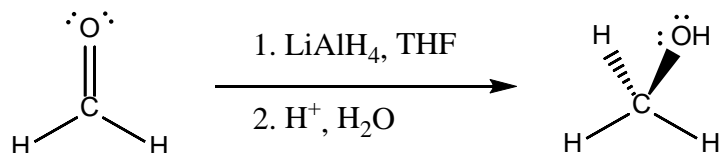


Addition of Hydride to Polar Pi Bonds

- A more compact way to write the reaction on the previous page would be to use “over-the-arrow” notation in which the reagents/catalysts/solvents added to the organic reactant are written either above or below the arrow (doesn't matter which):



- If a reaction has multiple steps that must be performed separately, they can be numbered instead of using separate arrows for each:

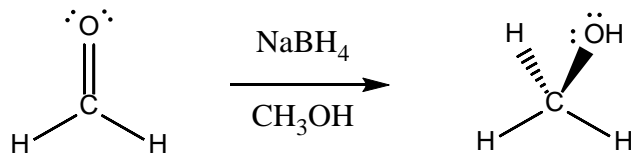


If you are asked to write a reaction equation, we want this!
If you are asked to write a mechanism, we want curved arrows!

Addition of Hydride to Polar Pi Bonds

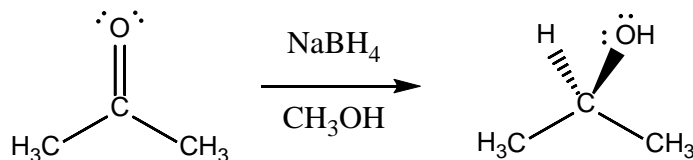
- LiAlH_4 is typically used in an ethereal solvent (THF or Et_2O) because they don't have acidic protons:

- NaBH_4 is typically used in an alcoholic solvent (CH_3OH or EtOH) because, for reasons we won't get into in this course, the alcohol increases the reactivity of the NaBH_4 . That means, however, that there is no need for a separate "add acid" step when performing the reaction:



Addition of Hydride to Polar Pi Bonds

- While the *reaction* of a ketone or aldehyde with NaBH_4 in an alcohol solvent can be done in one step, the *mechanism* still has two steps!
- Draw a mechanism for the following reaction:





Addition of Hydride to Polar Pi Bonds

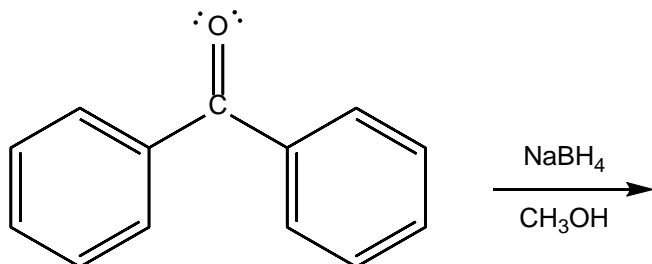
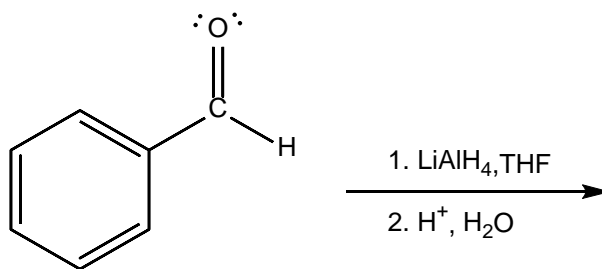
- Reactions which convert carbonyl groups to alcohols are classified as “reduction” reactions:

- Reactions which convert alcohols to carbonyl groups are classified as “oxidation” reactions:

- Some texts treat reductions and oxidations as separate classes of reactions, but it is more straightforward to learn about them with other reactions following the same mechanism.

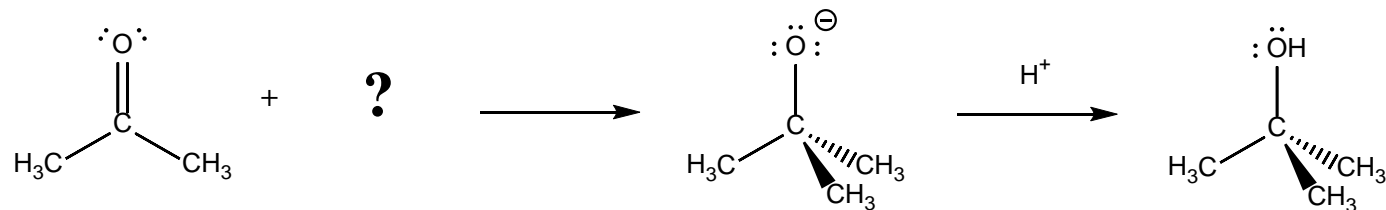
Addition of Hydride to Polar Pi Bonds

- Draw the organic product for each of the following reactions:



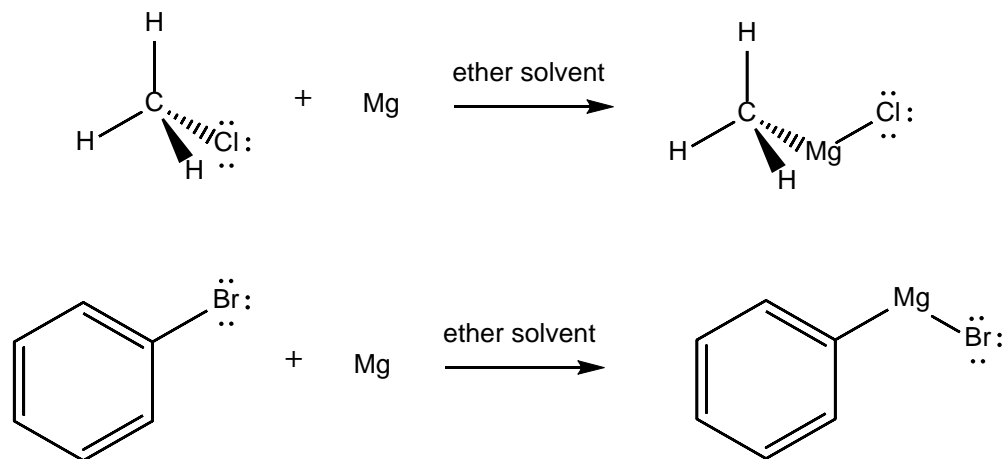
Addition of Carbanions to Polar Pi Bonds (Mg)

- Hydrides are just one class of nucleophile that can add to polar pi bonds. Another popular type of nucleophile is the carbanion.
- Imagine that you wanted to make *tert*-butanol via a nucleophilic addition to acetone. What nucleophile would you need?



Addition of Carbanions to Polar Pi Bonds (Mg)

- Clearly, this nucleophile can't be made by deprotonating an alkane! So, how to make it?
- François Auguste Victor Grignard solved this problem (earning himself a Nobel Prize in 1912) by adding magnesium to organic compounds containing C-Cl, C-Br or C-I bonds. A magnesium atom inserts between the carbon and halogen atoms, making something that acts like it has a negatively charged carbon atom!

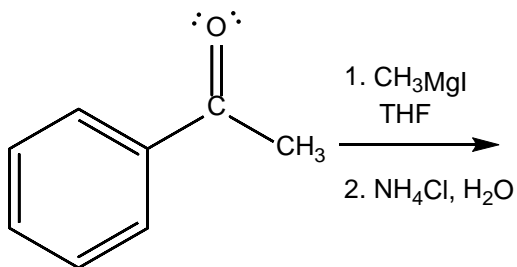
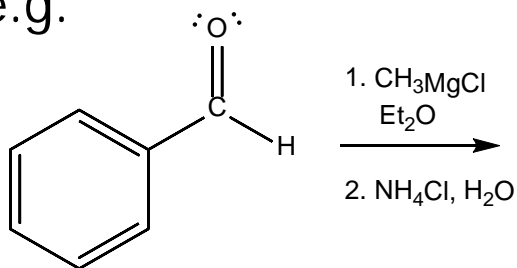


- This is how **Grignard reagents** are prepared. Grignard reagents are excellent nucleophiles (*as well as excellent bases*).

Addition of Carbanions to Polar Pi Bonds (Mg)

- Grignard reagents react readily with a variety of polar pi bonds.

e.g.



- What happens if water gets into step #1 of either reaction?

Addition of Carbanions to Polar Pi Bonds (Mg)

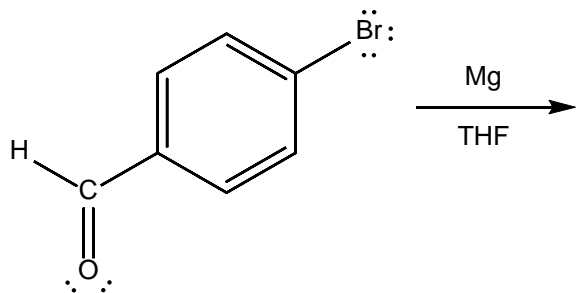
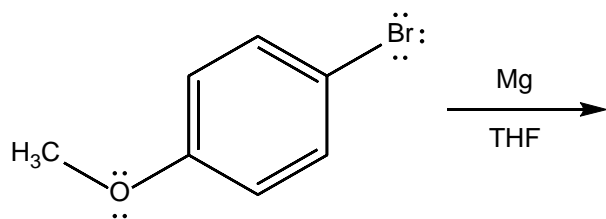
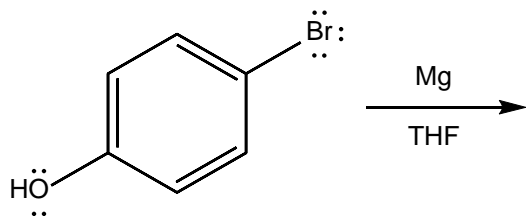
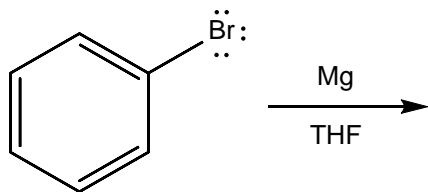
- Grignard reagents are exceptionally strong bases which will react with any hydrogens that are at all acidic.
- This can be taken advantage of to produce a Grignard reagent from a terminal alkyne:



- While very useful, the high reactivity of Grignard reagents limits which ones can be prepared.
 - It is **not** possible to prepare a Grignard reagent in the presence of any hydrogen atom that is at all acidic – including any hydrogen atom bonded to a heteroatom! (*No NH, OH, SH, etc. allowed.*)
 - It is **not** possible to prepare a Grignard reagent in the presence of any good electrophile. (*The Grignard reagent is always mixed with the electrophile after it's prepared.*)

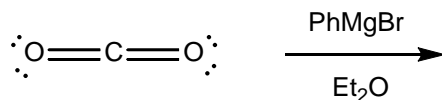
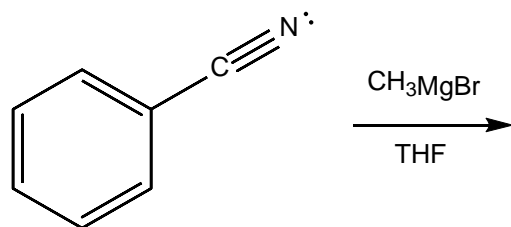
Addition of Carbanions to Polar Pi Bonds (Mg)

- Which of the following aromatic bromides can be converted into a Grignard reagent? For those that can, show the Grignard.



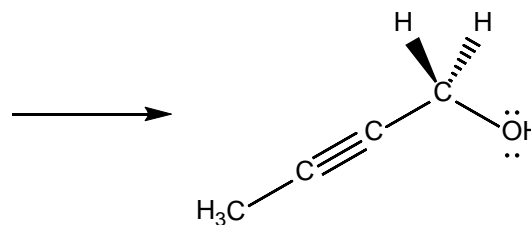
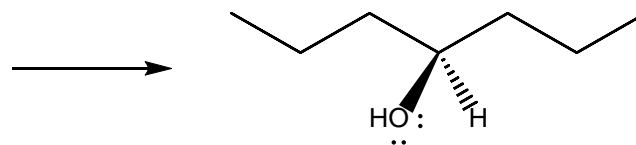
Addition of Carbanions to Polar Pi Bonds (Mg)

- Grignard reagents can add to a wide variety of different polar pi bonds – not just ketones and aldehydes!



Addition of Carbanions to Polar Pi Bonds (Mg)

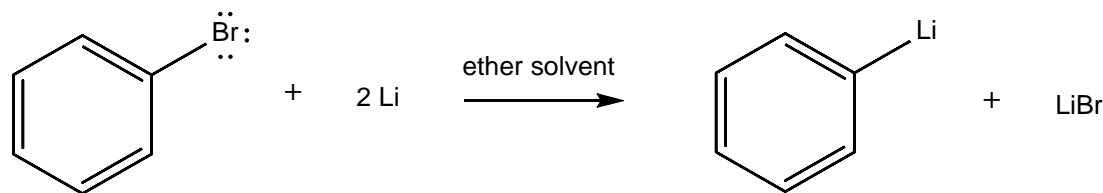
- How would you prepare each of the following alcohols from a carbonyl group and a Grignard reagent?



- This process of “thinking backwards” to choose reagents that will make a desired product is called **retrosynthesis**.

Addition of Carbanions to Polar Pi Bonds (Li)

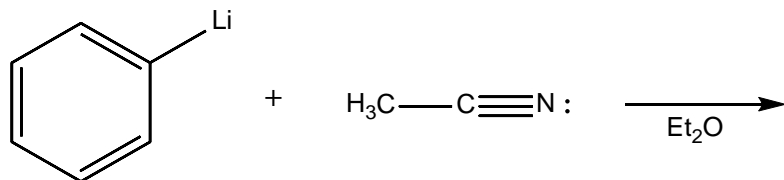
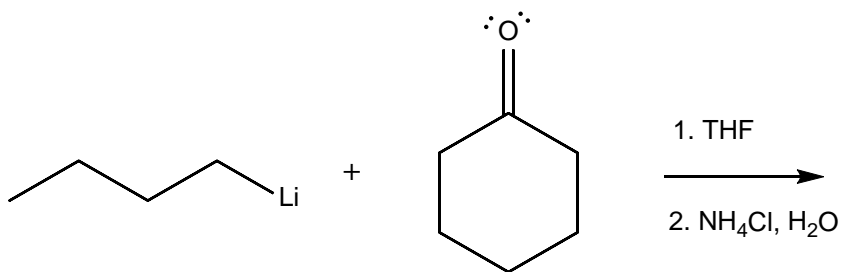
- Alkyl lithium reagents can be prepared just like Grignard reagents but using lithium instead of magnesium:



- Because lithium is even less electronegative than magnesium, alkyl lithium reagents are even more nucleophilic and even more basic than Grignard reagents.
- *n*-Butyllithium and *t*-butyllithium are often used to remove hydrogen atoms you really wouldn't consider to be particularly acidic – such as the hydrogen atoms on a benzene ring! Not all that surprising when you consider that the pK_a values for their conjugate acids (butane and 2-methylpropane) are $\sim 50!!!$

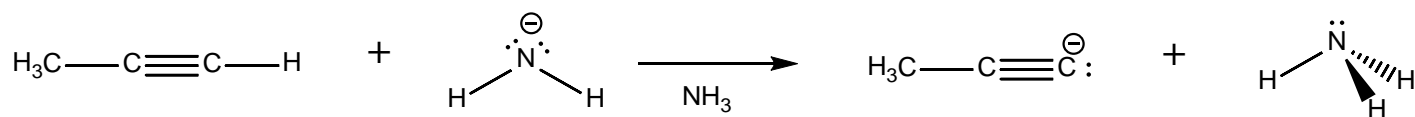
Addition of Carbanions to Polar Pi Bonds (Li)

- Alkyl lithium reagents react with polar pi bonds in the same way that Grignard reagents do.



Addition of Carbanions to Polar Pi Bonds ($\equiv\text{C}^-$)

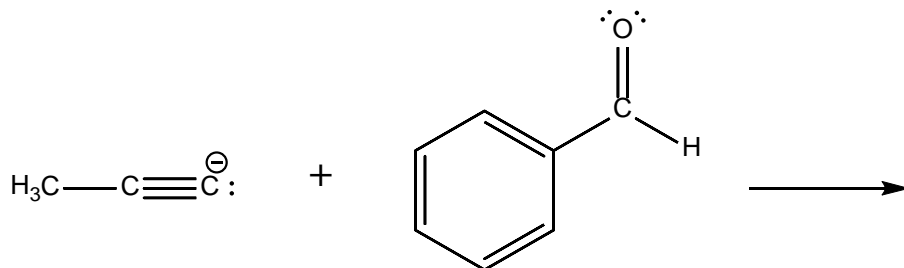
- While most carbanion reagents have to be made with the help of a metal, there is one type of hydrocarbon that is acidic enough to deprotonate with a strong base.
- Acetylide ions can be prepared by deprotonating a terminal alkyne:



- Use pKa values to justify why this reaction is favoured in the forward direction.

Addition of Carbanions to Polar Pi Bonds ($\equiv\text{C}^-$)

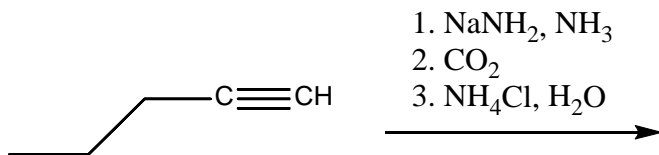
- Like the other carbanions we've seen so far, acetylide ions are good nucleophiles that react readily with polar pi bonds:



- It is essential that no water be added to this reaction until after the acetylide has reacted fully with the polar pi bond. Why?

Addition of Carbanions to Polar Pi Bonds ($\equiv\text{C}^-$)

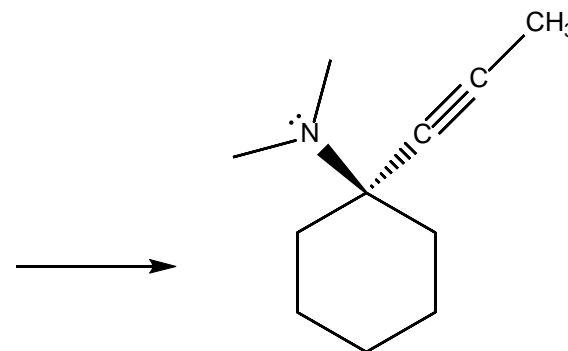
- Draw the product of each step in the following reaction sequence and use curved arrows to show the mechanism for each step.



Pay attention to charge! NH_4^+ and NH_2^- perform very different functions!

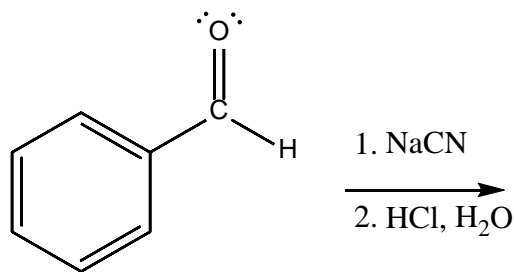
Addition of Carbanions to Polar Pi Bonds ($\equiv\text{C}^-$)

- How would you prepare the following amine from an acetylide?
(You do not have to show how to make the electrophile.)



Addition of Carbanions to Polar Pi Bonds (-CN)

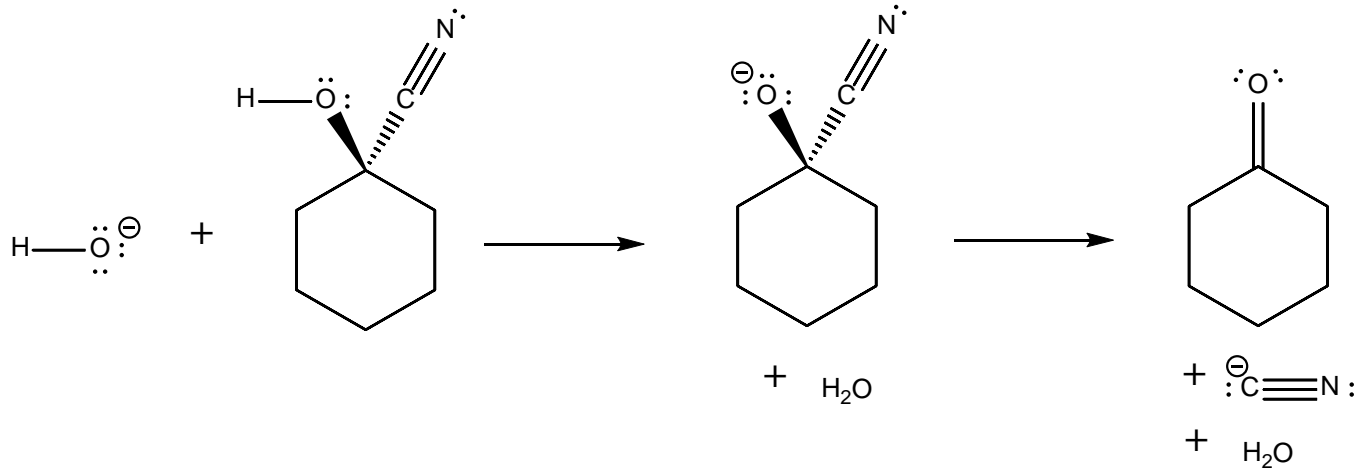
- Like acetylides, the cyanide anion is a good nucleophile and reacts readily with polar pi bonds. When a cyanide anion reacts with a ketone or aldehyde, the product is called a **cyanohydrin**.
- A small amount of acid is required to protonate the O⁻ generated when the cyanide attacks the carbonyl group:



- There cannot be too much acid present during the first step! Why not?

Elimination of Leaving Group Reforming C=O

- Cyanohydrin formation is reversible. If a strong base is added to the cyanohydrin, the carbonyl group will reform as the cyanide anion leaves.
- Use curved arrows to show the electron movement for this process:



- In this reaction, the cyanide is referred to as a **leaving group**.

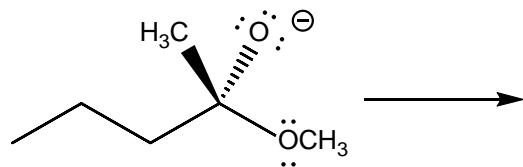
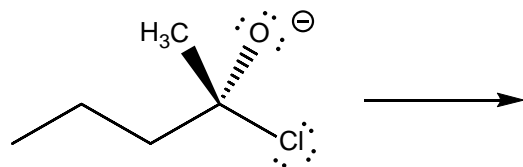


Elimination of Leaving Group Reforming C=O

- A leaving group takes a pair of electrons with it when it leaves, and a good leaving group is therefore a species with the capacity to do so. That usually means it's either a neutral molecule or a relatively stable anion.
- A convenient way to assess the quality of a leaving group is to look at the pK_a of its conjugate acid. Good leaving groups have strong conjugate acids. Why?
- A few examples of good leaving groups:
 - H_2O (conjugate acid is H_3O^+ which has a pK_a of 0)
 - Br^- (conjugate acid is HBr which has a pK_a of -9)
 - I^- (conjugate acid is HI which has a pK_a of -10)

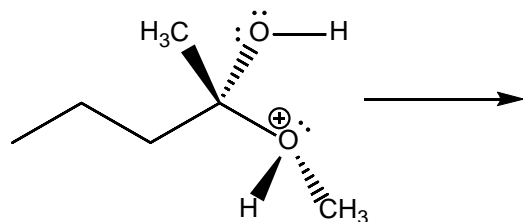
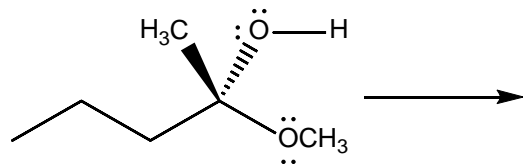
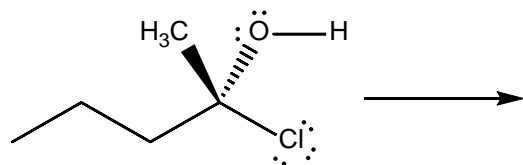
Elimination of Leaving Group Reforming C=O

- While they are certainly good electrophiles C=O bonds are actually quite stable. Molecules given the opportunity to form a carbonyl group, kicking out a leaving group, frequently do so. As such, if a carbon atom has both an O⁻ and a leaving group attached to it, it will collapse to give the corresponding carbonyl:



Elimination of Leaving Group Reforming C=O

- If the leaving group is good enough, a carbon atom with an OH and a leaving group attached will also collapse to a carbonyl. Two of the following three reactions proceed. Which two? Draw those products.



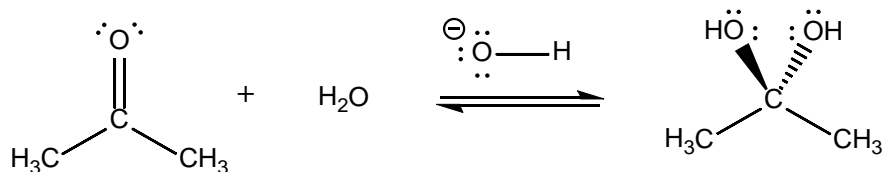


Activating Carbonyl Groups with Acid

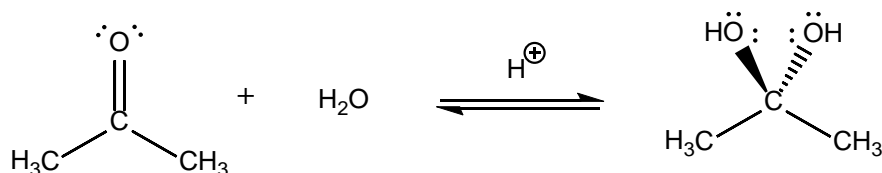
- Thus far, all of the reactions we've looked at have involved strong nucleophiles. If your nucleophile of choice is not strong, you need to compensate for that by activating at least one of the reactants.
- There are two main strategies for making a reluctant reaction proceed:
 - improve the nucleophile (make it more electron rich!)
 - improve the electrophile (make it more electron poor!)

Activating Carbonyl Groups with Acid

- So, if you want to add water (a weak nucleophile) to a ketone, you can choose to either:
 - Add hydroxide. It's a better nucleophile than neutral water:



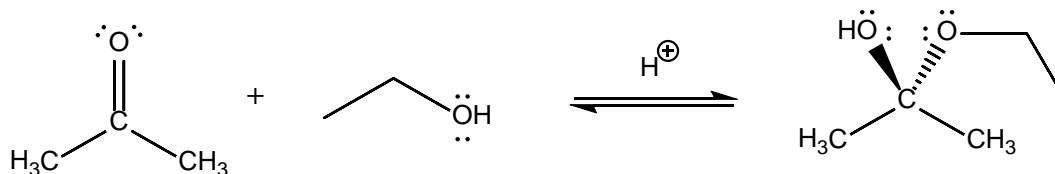
- Add acid to protonate the ketone. While the ketone was a good electrophile, a protonated ketone is a *better* electrophile:



- In either case, the product is called a **hydrate**. For most ketones and aldehydes, the carbonyl form is favoured in this equilibrium.

Activating Carbonyl Groups with Acid

- If you want to add an alcohol to a ketone or aldehyde, the usual approach is to use an acid catalyst to protonate the carbonyl.

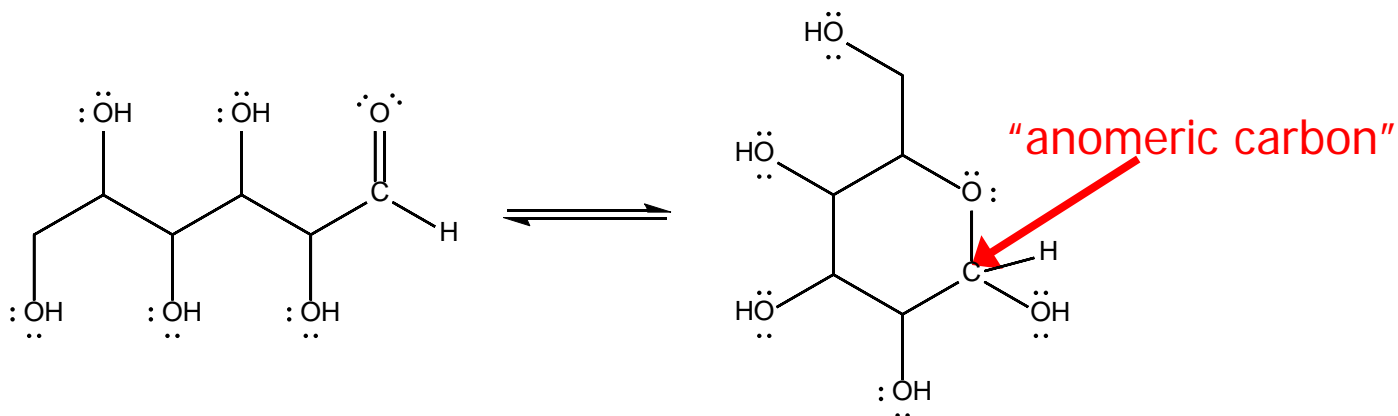


- The product of this kind of reaction is called a **hemiacetal**. This is also an equilibrium process. How would you favour the products side of the equilibrium?

Activating Carbonyl Groups with Acid

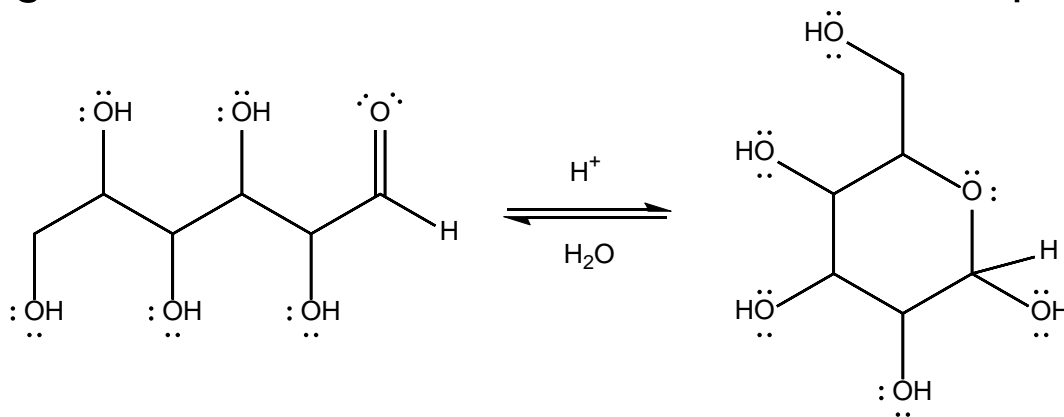
- The formation of a hemiacetal is particularly favourable if a molecule contains both a carbonyl group and one or more alcohol groups and if the reaction will result in formation of a 5- or 6-atom ring. Since this is the case for almost every sugar, hemiacetals are extremely important in biochemistry!

e.g. The polyhydroxyaldehyde below could be glucose (or galactose or any number of other sugars, depending on the stereochemistry). It exists primarily in the cyclic form shown (a **hemiacetal**, literally a “half acetal”).



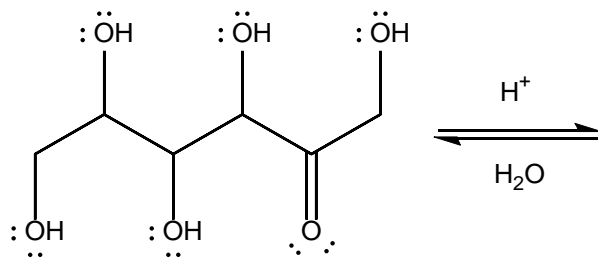
Activating Carbonyl Groups with Acid

- Propose a mechanism for the equilibrium reaction converting linear glucose to the hemiacetal form in dilute aqueous acid.



Activating Carbonyl Groups with Acid

- Fructose occurs naturally as a mixture of two hemiacetals – one with a 5-atom ring (the “furanose” form) and one with a 6-atom ring (the “pyranose” form). The linear form of fructose is shown below – again, without the stereochemistry. Draw the structures of both hemiacetal forms of fructose.



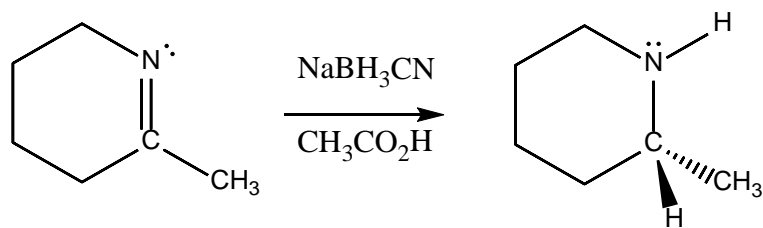


Activating Imines with Acid

- Carbonyl groups are not the only electrophiles that can be made more reactive by protonating them.
- We saw at the beginning of the topic that NaBH_4 was a weaker nucleophile than LiAlH_4 .
- Imines are also slightly less electrophilic than ketones and aldehydes. Why?
- So, the reduction of an imine with NaBH_4 is a sluggish reaction.

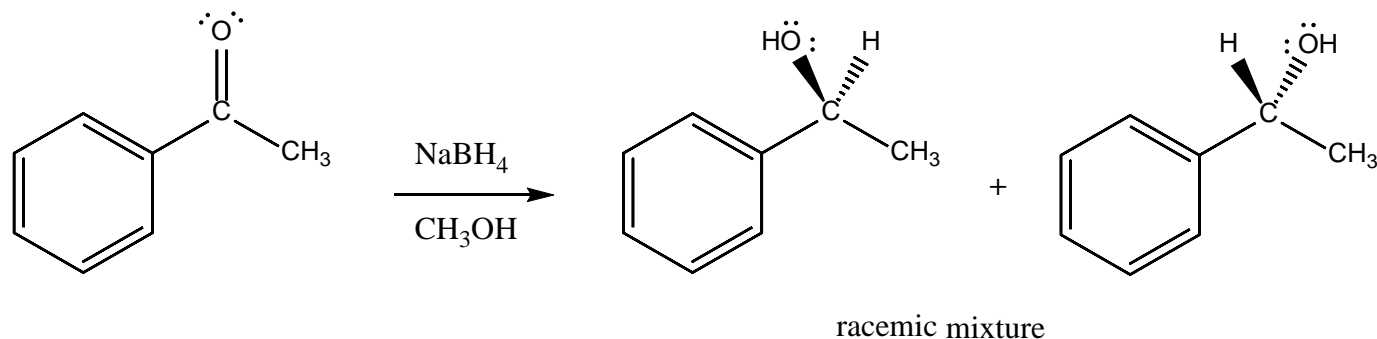
Activating Imines with Acid

- One solution would be to use LiAlH_4 instead (i.e. "use a better nucleophile") but another solution is to use NaBH_3CN in the presence of an acid like acetic acid:



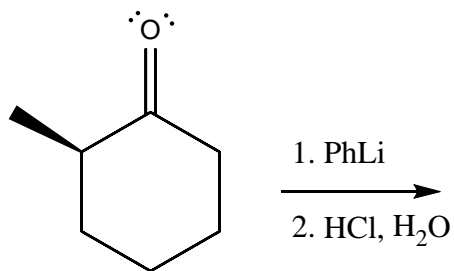
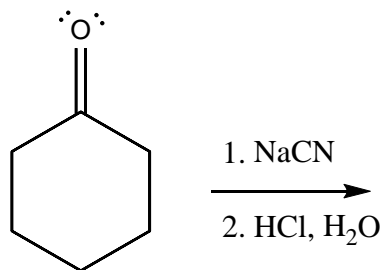
Stereochemistry of Additions to Polar Pi Bonds

- By definition, the electrophilic carbon atom in a polar pi bond is either linear or trigonal planar. After the addition reaction, one more group has been added so the geometry of the carbon atom changes.
- If the electrophilic carbon atom becomes tetrahedral, it is possible that the reaction creates a chirality center. In that case, the product(s) may form as a mixture of stereoisomers!

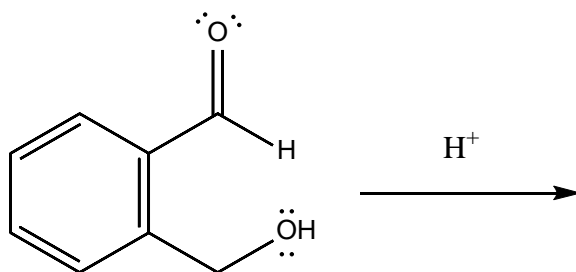
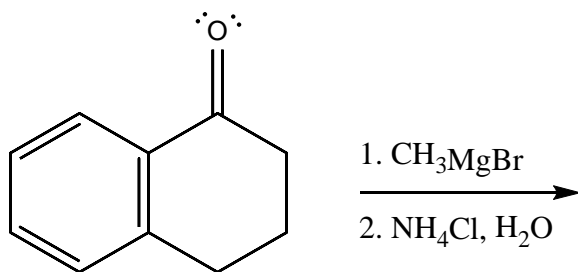


Stereochemistry of Additions to Polar Pi Bonds

- For each of the following reactions, draw all possible products. If more than one stereoisomer can form, indicate whether the products are enantiomers or diastereomers.



Stereochemistry of Additions to Polar Pi Bonds





Summary of Additions to Polar Pi Bonds

- **Every single reaction** in this chapter can be summarized as follows:
 - A nucleophile attacks a carbon atom that has a pi bond to a more electronegative atom; the pi bond breaks and those electrons are pushed onto the more electronegative atom as a lone pair.
 - Some acid-base chemistry may be needed to either make the carbon atom more electrophilic (by protonating the more electronegative atom) or to deprotonate the addition product.