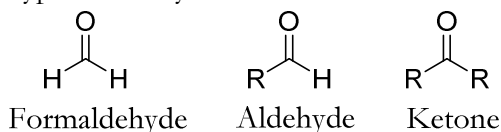


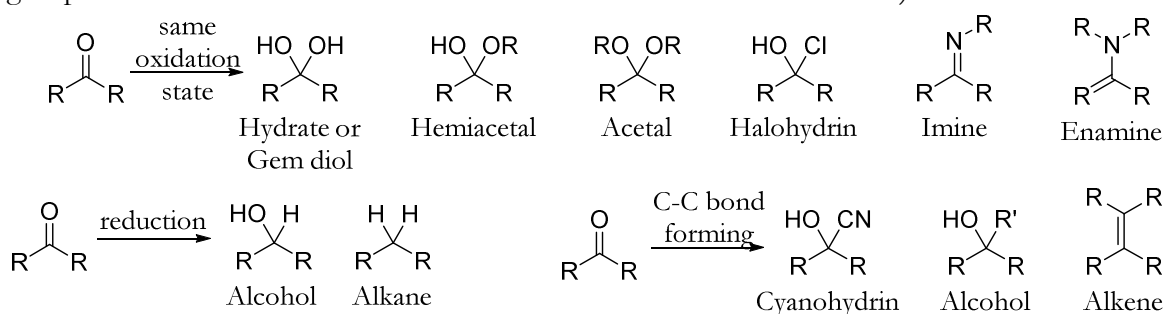
Loudon Chapter 19 Review: Aldehydes & Ketones

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Beginning with this chapter, we're looking at a very important functional group: the carbonyl. We've seen this as the product of reactions before, but we haven't used it as a starting point. The specific types of carbonyls in this chapter are the aldehyde and ketone. Formaldehyde is a specific type of aldehyde.



All of these are in the two-bonds-to-electronegative-atoms oxidation state, and they stay in that same state during many of the reactions in this chapter. We'll also see some reduction chemistry (the opposite of the oxidations we've done before), and some carbon-carbon bond forming reactions. (Technically enamines are in a different oxidation state, but they get grouped with imines because the mechanism to make them is so similar.)

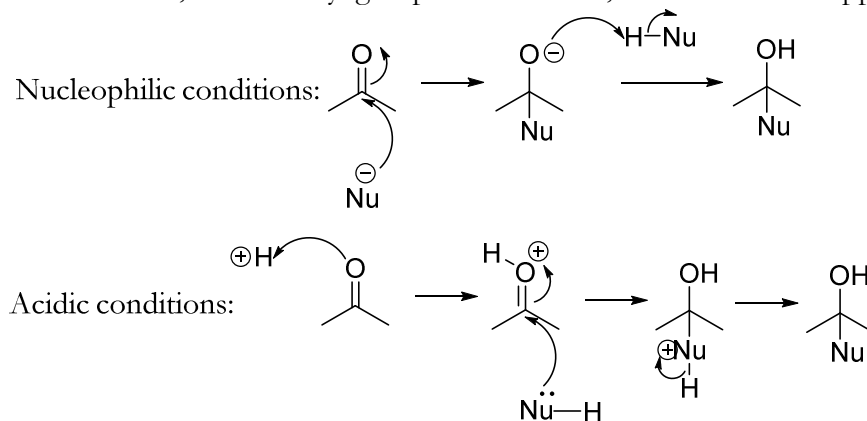


We won't cover the reactions in this order, but it helps to subdivide them based on what kinds of things they do during synthesis.

A key idea in this chapter has to do with charge distribution. The carbon at the base of the carbonyl is always partially positive, so all attacks are going to happen there.

Reversible additions

Depending on conditions, reactions here can fall into two categories: nucleophilic/basic conditions, and acidic conditions. (This should remind you of the options for attacking an epoxide. Just like for epoxides, acidic conditions will protonate the molecule first, before the attack happens.) Under nucleophilic additions, the nucleophile is strong enough to go straight in and attack on the carbonyl, which becomes negatively charged and picks up an H later. In acidic conditions, the carbonyl gets protonated first, then the attack happens.

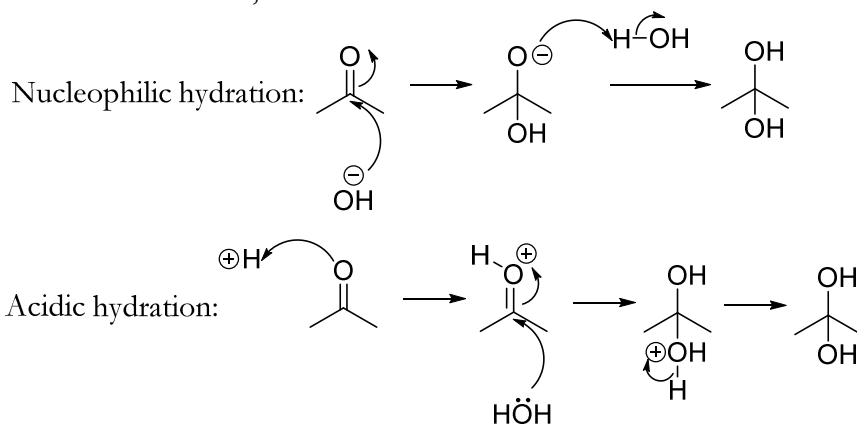


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The important thing to point out here is that protonating the carbonyl makes it much easier to attack, since the partial positive becomes bigger. So under acidic conditions, you can use a much weaker nucleophile (something neutral, instead of negative-charged) and still have the reaction work fine.

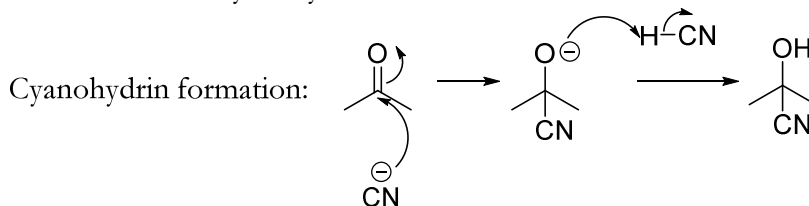
For specific details, there are two reactions in this category: hydration and cyanohydrin formation. Hydration can take place under nucleophilic or acidic conditions, depending on whether you use water and base, or water and acid.



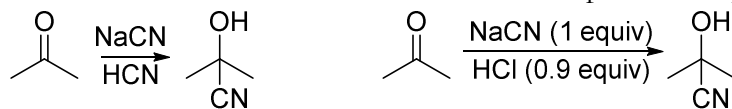
As a side note, these molecules are called either hydrates, geminal diols or gem-diols (from Gemini, the word for twins). The overall reaction is written as:



If we use cyanide as the nucleophile, we can create something with an OH and a CN on the central carbon. This is called a cyanohydrin.



This can only happen under conditions that are overall nucleophilic, not acidic. There has to be CN^- around, because HCN doesn't have any lone pairs on carbon. For the reaction setup, we need a source of acidic protons but we also need more CN^- than protons. There are several ways to show this in the overall reactions; here are a couple of examples.

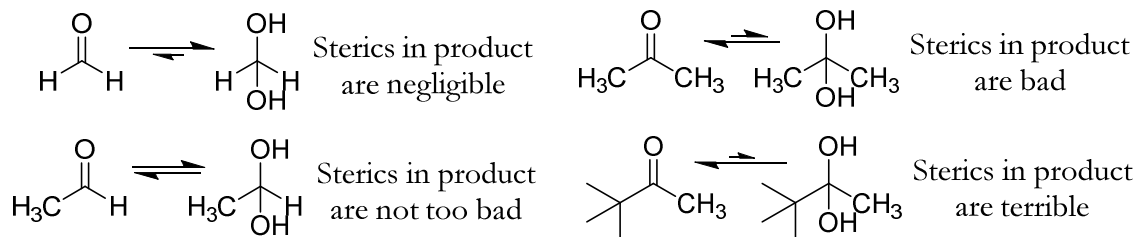


One other thing that is covered here is where the equilibrium lies, since these are both reversible reactions. There are two different factors which influence the stability of the starting material and product: sterics and electronics.

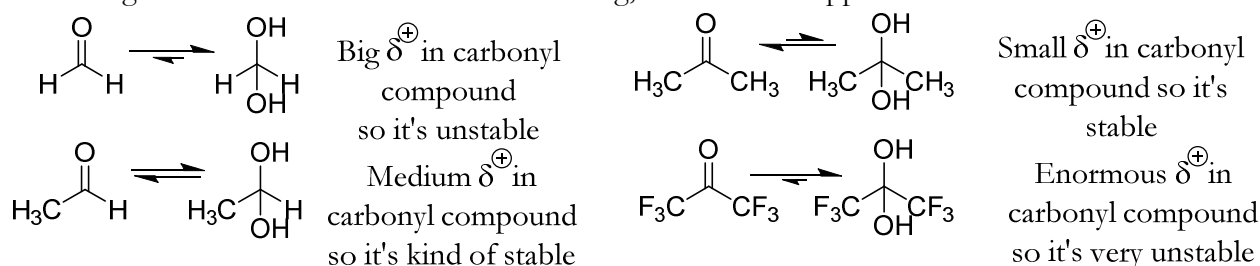
1. Sterics are mainly controlled by the fact that in the product, there are more groups that have to fit in around the central carbon, and they're closer together. The bigger or more numerous the R groups attached to the carbonyl are, the more crowded and unstable the product will be, and the less the reaction will favor products.

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2. Electronics are all about the partial positive on the carbon – in other words, how electrophilic the carbon is. The charge wants to be stabilized, and the more R groups there are the more stable the charge is and the less the starting material wants to react (just like in carbocations). Unlike for sterics, the size of the R group is not terribly important. But any R groups that are bad at stabilizing this charge – for example, things with halogens on them – are electron withdrawing, and have the opposite effect.



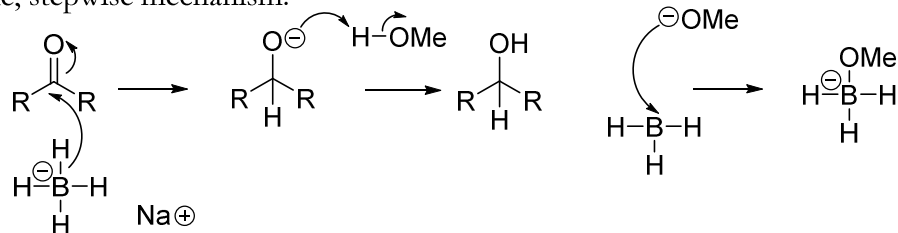
You'll notice that these two effects tend to reinforce one another – compounds that have a very unstable product usually also have a very stable carbonyl starting material, and vice versa. For these reactions the rate is generally proportional to the equilibrium constant.

Reduction to Alcohols

These reactions are kind of the opposite of oxidations that we've seen before. Rather than removing bonds to H and replacing them with bonds to O, we're doing the opposite. Since we're using a reducing agent, we'd expect it to be something with a lot of low-electronegativity atoms in it – for example, something with a large number of hydrogens. The two most commonly used are sodium borohydride (NaBH_4) and lithium aluminum hydride (LiAlH_4 or just LAH). Both of these act as a source of hydride ions (H^-), although this doesn't exist on its own during the reaction. LAH is the stronger of the two, so you have to use it in an inert solvent, usually THF or ether. NaBH_4 is weak enough to use in protic solvents like alcohols.

For NaBH_4 , the reaction happens concertedly since all the necessary reagents are there at the same time. But it helps to mentally break the mechanism down into separate steps. The BH_4^- gives up a hydride to the carbonyl, which breaks up. It then takes a proton from the solvent, which goes and sticks onto the boron.

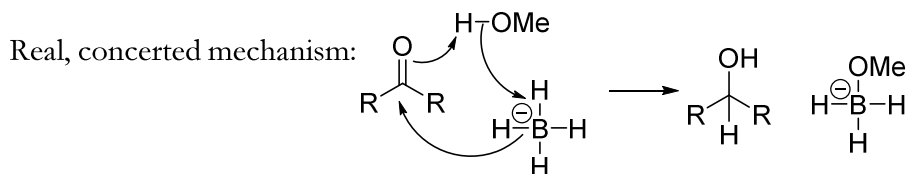
Fake, stepwise mechanism:



If you put this all together at once, you get:

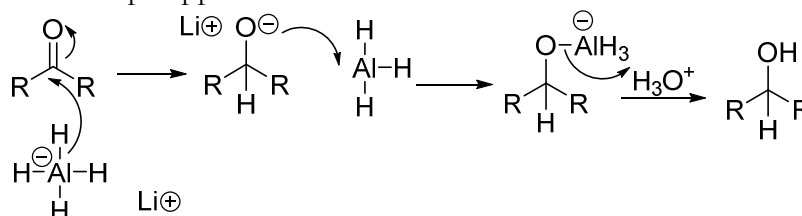
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It's not shown here but boron can do this reaction up to four separate times, once for each H that it has initially (similar to how BH_3 can react up to three times during hydroboration).

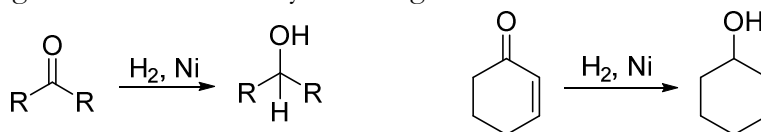
Since LAH is used in aprotic solvents like THF, the steps can't all happen at once. Instead you use an H_3O^+ workup to protonate the product. The alkoxide you make adds to the aluminum so again, you can do this reaction up to four times on the same molecule of LAH before the H_3O^+ workup happens.



The overall reactions are written as:

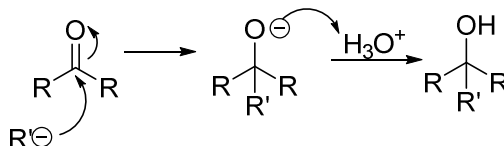


You can also use catalytic hydrogenation in $\text{C}=\text{O}$ double bonds, like you can for $\text{C}=\text{C}$ double bonds. It'll usually react with any alkenes on the molecule too, though, so it's generally not as good a choice as the hydride reagents above.

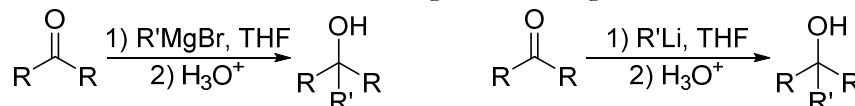


Reactions with Organometallics

Like always, Grignards and organolithiums act as if they have a negative charge on carbon. This lets them attack the carbon of the carbonyl. You need the usual organometallics solvents like THF or ether for this to work, but finish it up with an acid workup so the O^- gets protonated to an OH.



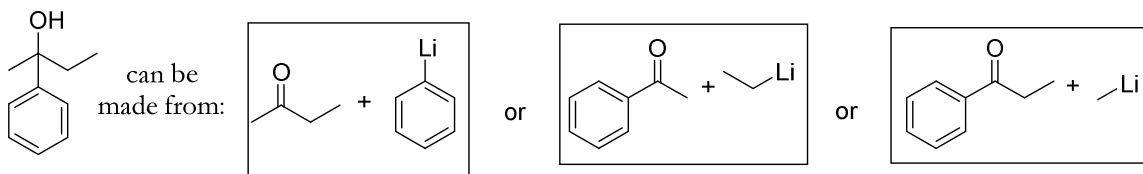
The overall reaction is about the same for Grignard and organolithiums.



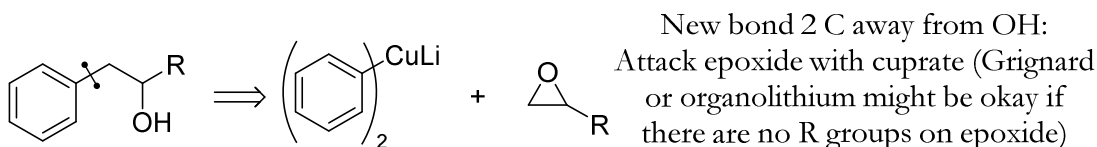
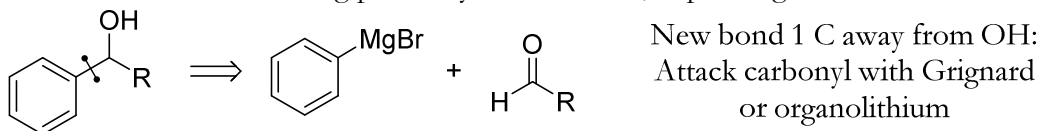
This reaction is extremely useful for synthesis. If you're trying to make a particular alcohol, you can do it by using one of three possible carbonyl/organometallics combinations.

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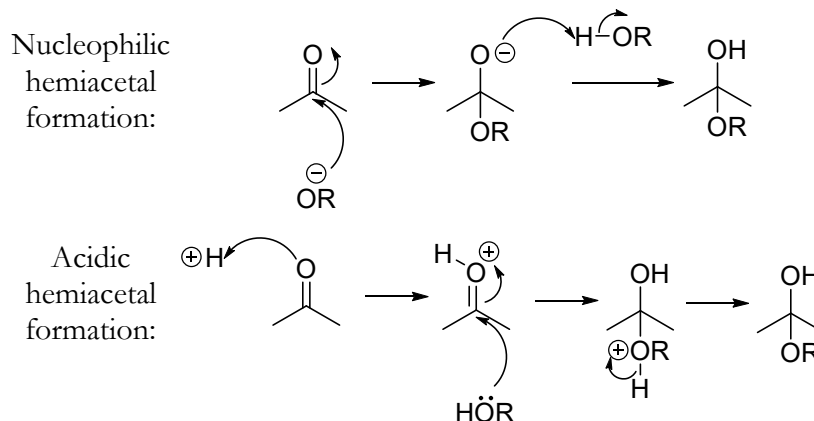


Now we have an interesting pair of synthetic routes, depending on where the OH is:

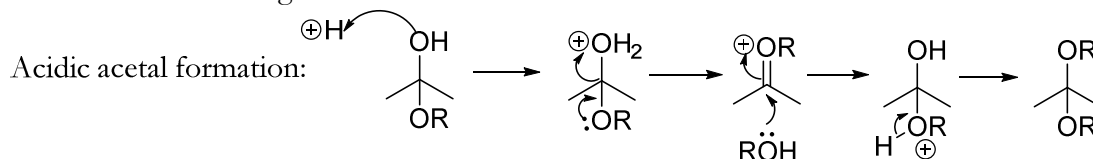


Acetals and Hemiacetals

We already saw what happens when you combine a carbonyl with water and either acid or base: you get the hydrate. A similar thing happens with alcohol and either acid or base, by the same mechanism. You end with a hemiacetal, which has an OH and an OR group coming off the same carbon.



Now, however, we can go one step further and get rid of the OH entirely. Like regular OH elimination, this happens only under acidic conditions. When it leaves, the OR kicks in some lone pairs to prevent the carbon from having to carry a positive charge. Then another molecule of alcohol can attack to give the acetal.



We can reverse all these steps and go back to the carbonyl by using water and acid. The overall reactions look like this.

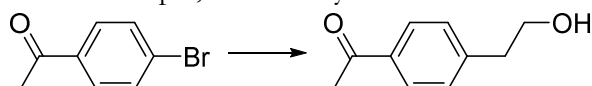
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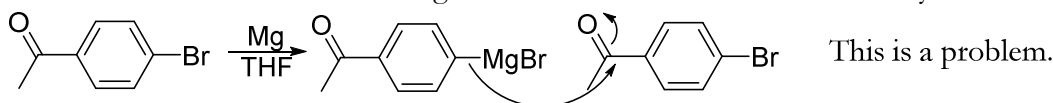


One thing that often shows up on the arrow for acetal formation is “4AMS”. This stands for 4-angstrom molecular sieves, which are a way to remove water from the reaction and drive it as far towards products as possible. You can also use heat to speed up the reaction in either direction.

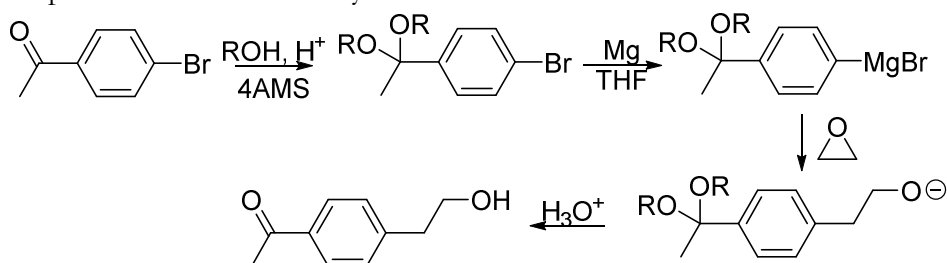
Acetals are extremely useful in synthesis. Basically, we now have a way to temporarily turn a carbonyl into some other group, and then easily turn it back to a carbonyl later. This means that we can “protect” the carbonyl as something else if we’re using conditions that would otherwise react with it. As an example, take this synthesis.



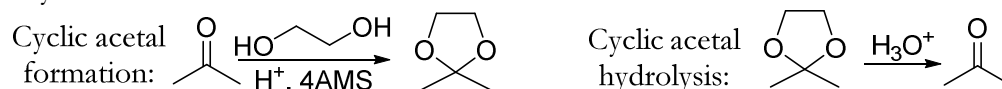
Your first thought might be to turn the bromide into a Grignard and attack an epoxide. But this molecule can’t exist as a stable Grignard because it attacks its own carbonyl.



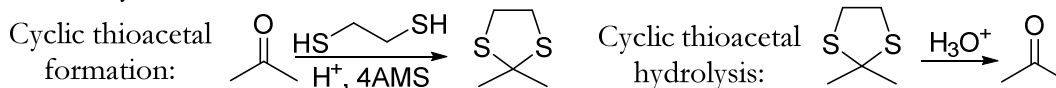
What you can do is temporarily protect the carbonyl as an acetal, do the chemistry you want, and then deprotect back to a carbonyl at the end.



This idea of protecting groups is very common in advanced synthesis. There are many different functional groups that can be turned into something else temporarily, and then turned back when it’s safe to do so. Acetals are not the most robust protecting group, and can accidentally deprotect. A way of increasing their stability is to set it up so that both alcohol groups are on the same molecule, instead of separate molecules of ROH, creating a ring. This is more stable because if one side of the ring breaks, it’s still tethered nearby and can easily add back on.



The mechanism for this is exactly the same as for regular acetal formation, just that both OH groups happen to be in the same molecule. A very similar reaction is the installation and removal of cyclic thioacetals, which use S instead of O:

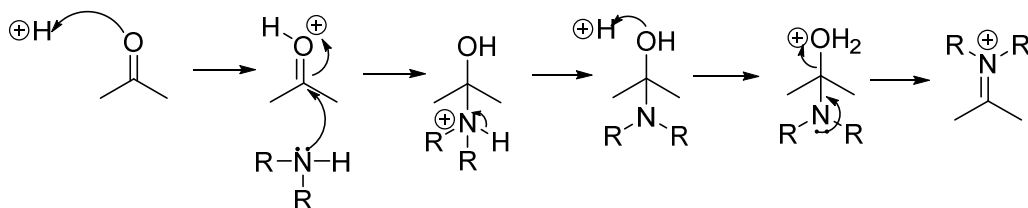


Reactions with Amines

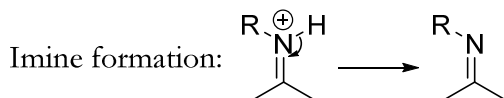
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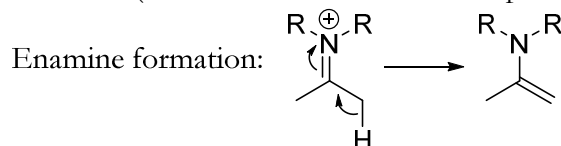
If you combine an aldehyde or ketone with an amine, you can start out going through steps that look a lot like acetal formation.



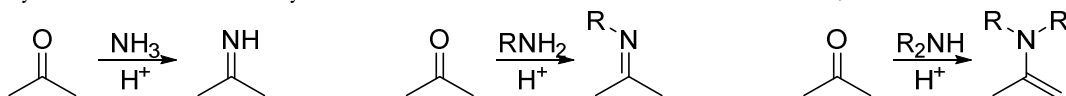
Once you get to this step, though, things are different. There are two possible outcomes, depending on what else is attached to the N. If at least one of the R groups on N is actually an H, then you can remove it and quench the charge that way. This gives you a C=N double bond in the product, known as an imine.



If both groups on N are actually R groups, then you can't deprotonate to get rid of the charge. Instead, what you need to do is kind of like an E2 elimination. Pull an H from a carbon one away from the nitrogen to create a C=C double bond, and kick electrons up to the N. This gives you an enamine (named because it's an alkene plus an amine).

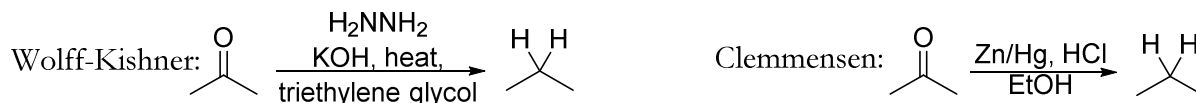


The only difference in whether you get an imine or an enamine is how many R groups are attached to the nitrogen. Ammonia or primary amines give you imines; secondary amines give you enamines. Tertiary amines don't do the reaction at all. Overall, it looks like this:



Reduction to Alkanes

We already looked at reducing carbonyl from the “two bonds to O” state to the “one bond to O” state by using LAH. Using different reagents, it's possible to go all the way to the “no bonds to O” state. There are two totally different reactions in this category: Wolff-Kishner, and Clemmensen.



We won't cover the mechanism for either of them, although both are similar to things we've seen before. The important thing to remember is that Wolff-Kishner uses basic conditions and Clemmensen uses acidic conditions, so if you have functional groups sensitive to one of these then you should use the other. For instance, if you had an alkene you would want to avoid acids, so you'd use Wolff-Kishner.

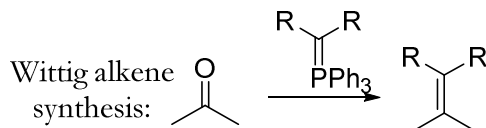
Wittig Alkene Synthesis

This is another extremely useful reaction, because it creates C=C bonds. Unlike organometallics, which create only single bonds (as shown above), this creates double bonds

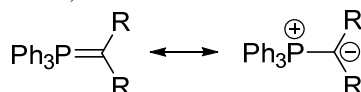
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at a very well-defined location: the place where the C=O used to be. The overall reaction is this.

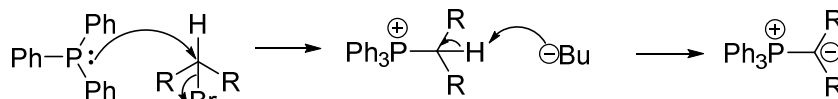


The phosphorous thing on the arrow is slightly unusual, because it has a resonance form with a plus and a minus charge on adjacent atoms. This is called an ylide.

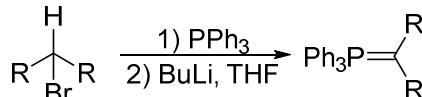


The way to make this ylide is based on getting each of these two charge one at a time. First, phosphorous does S_N2 on an alkyl halide, then you use a strong base like BuLi to deprotonate the same carbon that just got attacked.

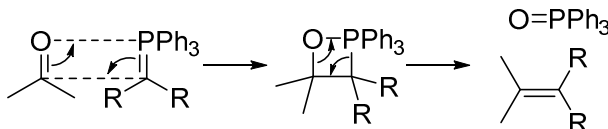
Ylide formation:



So the overall reaction for ylide formation looks like:



Going back and looking at the Wittig reaction itself, we can now explain why things happen the way they do. At the beginning, the partially negative carbon in the ylide attacks the partially positive carbon in the carbonyl. At the same time, the C=O bond breaks and attacks the partially positive phosphorous, creating a four-membered ring called an oxaphosphetane. (The book shows this occurring as two separate steps; there's an ongoing debate about whether it's more accurately shown as two steps or one, so either way you show it is fine.) This ring then collapses into C=C and P=O double bonds.



The byproduct, triphenylphosphine oxide, is discarded afterwards. However, it's very important for the reaction to occur. The phosphorous-oxygen double bond is extremely strong, and the ability to form this bond drives the thermodynamics of the reaction.

Oxidation to Acids

One final reaction involves oxidation chemistry that we've seen before. We already know that alcohols can be oxidized to carboxylic acids by strong oxidizers. You can do the same thing if you start with an aldehyde as well.

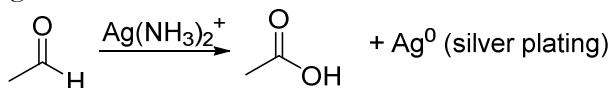


There's one other reaction that converts aldehydes to carboxylic acids – the **Tollens Test**. It's too expensive to be used as part of an actual synthesis, but it is very useful on a small scale to determine if a compound contains an aldehyde. If an aldehyde in the molecule is

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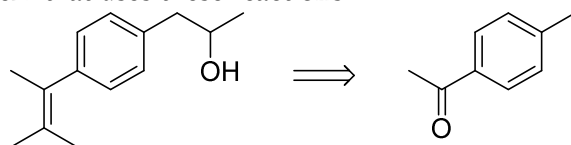
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oxidized by silver nitrate, then a coating of silver metal will form on the inside of the glassware as the silver gets reduced.

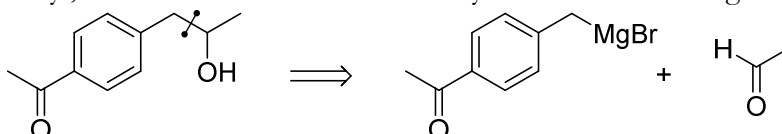


Ch. 19 Synthesis Practice

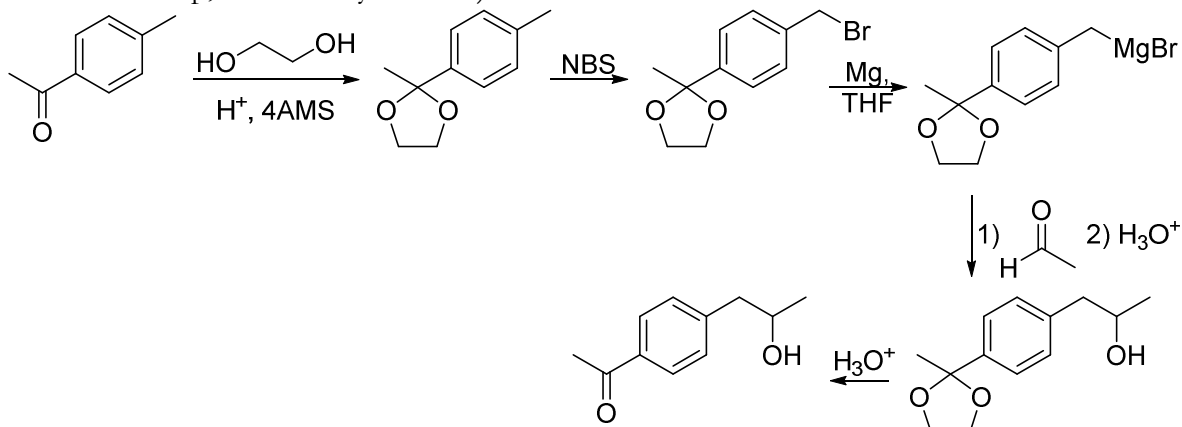
Here's a practice problem that uses these reactions.



The carbon-carbon bond forming that needs to happen on the right side looks like Grignard attacking a carbonyl, since the disconnect is one away from the new OH group.



But! This can't work with the carbonyl already on the left side of the molecule, since the Grignard will immediately attack another copy of itself. So we need to protect it. Then, to actually make the Grignard, we need to get a halogen onto the benzylic carbon. This sounds like a job for NBS. Putting together the protection, Grignard formation/attack, and deprotection, we get this sequence. (Note that the acidic workup for the step where the Grignard attacks the carbonyl isn't shown as deprotecting the acetal. This is because it usually takes at least some mild heat to deprotect, so you can show it as a separate step, or as a combined step, whichever you want.)



All we need to do now is change the carbonyl to an alkene, which looks like Wittig.

