Lecture 24B • 03/20/12

[Exam 2]

[Functional groups: hydrazone, oxime, cyanohydrin, carbinolamine]

Ketones and formation of enamines versus imines

You're told that an imine can be formed by reacting cyclohexanone with a primary amine and an enamine can be formed if you used a secondary amine. However, imines cannot be formed from secondary amines, and enamines, if they're formed from primaries, end up decomposing. The first part of that question was to write a mechanism for the formation of an imine from cyclohexanone and any primary amine of your choosing. I'll just use ethanamine; nice, small, simple molecule. This is a mechanism that has an exception to the POAD pattern that we had seen for carbonyl reactions. Many of these reactions that have an acid catalyst, you protonate the carbonyl, then attack it. But, because nitrogen is somewhat basic, it's allowable to write the attack of nitrogen on the carbonyl first. That is not true for neutral oxygen, so in other problems like in producing the hydrate, it would be wrong to have water push the carbonyl open, cause water, even compare to this amine, is not basic. Other cationic, carbonyl reactions you do protonate first; this is the exception to that pattern.

Before we have any further kind of reaction, the nitrogen's going lose a hydrogen to become neutral; the oxygen's going to gain a hydrogen. It might be possible to have an intramolecular attack – I say might, it's more likely that you're going to get plain old dissociation. If you don't show intramolecular transfer of that hydrogen, then you have to show the protonation and deprotonation as two separate steps, because if it's not intramolecular, it's very unlikely that both protonation and deprotonation would occur exactly simultaneously. Which order you do it in isn't important, but the nitrogen needs to get deprotonated, and then the oxygen needs to get protonated. This is the halfway point, this is the carbinolamine, which is the nitrogen equivalent of a hemiacetal or a hemiketal. Normally, hemiacetals or [hemi]ketals are not isolatable. Neither is usually a carbinolamine, so the oxygen will get protonated again, and you form water as a leaving group.

Water comes off, and you can have the nitrogen attack through a resonance. You can combine the two steps, because resonance, that really isn't a reaction, that's just us pushing electrons around on paper. Resonance structures don't really exist. I can, if I want to write the mechanism in fewer steps, have the nitrogen being shown pushing the water out. That's acceptable because the lone pair on nitrogen moving, that's just resonance, effectively. We end up with nitrogen again positively-charged, so it loses a hydrogen to become an imine.

The second part was: using the mechanism that you just wrote, explain why imines cannot form from secondary amines. If you had two hydrogens on the nitrogen to begin with, notice that you lose one of them right after the first step, and you lose the second one in order to get rid of the positive charge at the end of the mechanism. If you had used a secondary amine, the first step can happen, but once you get to this point where you have the positively-charged nitrogen at the end, instead of an H, you'd have an R, which can't come off, so you could never stabilize that positive charge, you'd never get rid of that positive charge. That's why you can't make an imine from a secondary amine.

The third part of that question was write a mechanism for the tautomerization of an enamine that came from cyclohexanone and some form of primary amine. I could take something like this, which hopefully you recognize that as the tautomer of the molecule that we just saw a moment ago. You're asked to write the mechanism for tautomerization [not stated whether acidic or basic conditions]. [Under acidic conditions, the] double bond gets protonated. This time I'm writing it separately. We have a lone pair that we can show moving by resonance; then, deprotonation occurs to get to the imine.

Question three – mechanism problems. We start out with a hydrazone with sodium hydroxide - that is the Wolff-Kishner reduction. How does it work? Starts with the deprotonation of nitrogen, which we can then show electrons moving by resonance structure. Effectively, we're doing a tautomerization, cause we've exchange the effective position of a single and double bond, but in a situation that it wasn't just resonance, it was actually [a] change in the molecule that we have. You cannot say H+ because there's no H+ in solution; you have to say water instead, to show where the proton is coming from. Now we have a double bond on the nitrogen, which we're going to tautomerize again, at least attempt to, cause one we deprotonate the nitrogen one more time, then, if we were to push another pair of electrons between the nitrogens, that forces the carbon-nitrogen bond to break, which then will rapidly react with water, and water's around because we have hydroxide that did the deprotonation. It'll rapidly react with water to make an alkane.

The second mechanism was to react this hydroxyketone with DHP and tosic acid. One [common] mistake is using tosic acid as a nucleophile and ending up with tosylate in your product. Realize the only way you could ever end up with tosylate in your product is if you use have tosyl chloride that you reacted with an alcohol. Otherwise, the whole point of using that tosic acid is, once it dissociates, it doesn't want to react. That's why we use it. If your answer had tosylate in it at all, you've got to make sure – don't ever use tosylate as a nucleophile.

In fact, even if we had tosyl chloride, it's not a nucleophile, it's being attacked by the alcohol to make a tosylate. It is just providing the H+, which allows DHP to start its reaction. First, you have protonation. You form a carbocation that the hydroxy[ketone] can attack. After that attack, we have deprotonation, and at this point we've made the THP ether. There's a second step to the reaction, though, which was to react this with methylmagnesium bromide. The condensed way of showing this in mechanism is to just show that carbon-magnesium bond breaking and then simultaneously attacking the carbonyl. The other way I had shown it in the past was just to say CH3- and have that attack. [This is a] slightly more satisfactory way since you show what the true compound was, not just the reactive portion of it.

We end up with an alkoxide, which then is treated with sulfuric acid, water and heat. There was one particular product I was looking for, but I accepted multiple answers because you might have looked at the water and heat and thought: oh, he's trying to trick us, he's thinking yet another reaction's going to happen after this. Let's see what the real answer should have been, and what some of those possible side answers might have been. First thing's that going to happen is the negative charge is going to get protonated; that will happen before anything else occurs. Then, since we're in acid and water, you need to recognize that the THP ether is an acetal, so in acid and water, it can revert from an acetal back into an aldehyde. So, we can have protonate, open. Once it opens, you've made one of the two products, which is this diol. You also, though, have the leftovers of what was the THP ether. The directions did specify for you to show what happens to any byproducts. Water will attack next and deprotonate. We are at the hemiacetal stage, so one more round of POAD occurs. The other oxygen gets protonated; realistically, that ring will only open one direction, cause the way it does open allows a carbocation to form that is stabilized by resonance with the oxygen that's right next door. Here is that resonance. Rewriting the molecule to make it a little bit more traditional in its layout, we get this, and then we have a final deprotonation to give us 5-hydroxypentanal, the other byproduct.

Let's move right on into synthesis. First synthesis problem, we have a bromoketone reacting somehow with formaldehyde to make an alkenone – something that's got an alkene and a ketone combined. If we wanted to do our classic structure analysis, our carbon analysis, we can see that we have a three-carbon fragment that has functional groups in the middle and one end. We end up with a product that has part of the same functional group – it still has a ketone, it has a double bond at the other end but that means that somehow that position was involved. Another way to look at this is, we've made a new carbon-carbon double bond. The question gives you this big hint: it says no magnesium may be used in this synthesis. If it wasn't a magnesium-based reaction, which means a Grignard reaction, then you only had one other option: Wittig. We need to make a Wittig reagent out of the first molecule, it directly reacts with the second one to directly make the product. But, there's a problem with that: if you tried to make the Wittig reagent out of the first compound, it reacts with itself, cause it's already got a ketone on it, so you had to use a protecting group.

If I reacted it with methanol and acid, I still make a ketal, I just chose to make it out of two methoxys instead of connecting the ring. You can use any alcohol, in principle. But now we have protected it, which means we can make the Wittig reagent. First, triphenyl phosphine – technically, that compound should be a salt, so yes you need a positive charge on the phosphorus and you should also have a bromide accompanying it; you can't have a plus charge without a minus. This is then deprotonated using something like butyllithium. That makes the Wittig reagent, which can be written two different ways. I've written it in the octet-violation way. The other way to do it is the zwitterion. Now, it's ready to react. You throw the aldehyde at it, and it makes the carbon-carbon bond. Then, just a little acid and water undoes the ketal, and you get the product. What occurred here, with the acid and water? [What if that alkene reacts]? That is a possibility; however, if water and a very mild amount of acid is used, it's in theory possible to avoid hydration at this point. [showing other products]

Let's move to the second one. We had a haloalcohol reacting with an epoxide in order to form a diol. Here, there was a one-word hint: silicon. The only thing silicon you've learned other than TMS in NMR was trimethylsilyl, the protecting group, or TBDMS, t-butyldimethylsilyl. We need a protecting group; why? Let's analyze this carbon backbone. You've got a three-carbon compound and a six-carbon compound. Here, we can see where the three-carbon compound ended up, and so we can see that there is a new carbon-carbon bond. It's a carbon-carbon single bond, not a double bond, so that's one signal that this might not should be a Witting; instead, it should be a Grignard. That would make sense because Grignards attack epoxides; this is symmetric, so it's going to attack either side equally. But if we're going to make a Grignard reagent, we've got the same problem we did in the first synthesis problem, in which we need a protecting group, because otherwise as you try to make the Grignard reagent, it's just going to react with itself. We take the bromoalcohol and protect it. I'm going to use the TBDMS chloride. Once I protect it, I can make the Grignard using magnesium and ether, which now is ready to react directly with the epoxide. Then, if you used acid and water, if it were strong enough a solution, you could both protonate the alkoxide and simultaneously remove the protecting group. If you showed dilute acid, then you would have neutralized the alcohol, then you would have used TBAF in order to know off the protecting group.

Last problem on this exam was to take an imine, two equivalents of it, and turn it into an alkane. [One potentially creative answer is to take] the imine and react it with sodium hydroxide and heat in order to make the alkane. It can't work, because this is an imine, not a hydrazone. Hydrazones can undergo the Wolff-Kishner reduction, but not imines. What imines can do is be hydrolyzed to make [in this case] an aldehyde. I'll show you a couple of variations [of answers]. One way or another, you need to make a carbon-carbon bond, so you could do that doing a Wittig reaction. We already have the aldehyde, but we would need a Wittig reagent.

We could take that aldehyde, reduce it – problem the single most common mistake in any of these synthesis problems is not separating out the reduction from the acidification; you cannot show H+ and sodium borohydride without showing 1/2, because if you do it, that means react them both at the same time. That get's us an alcohol, which then we could turn into a leaving group. [Next, you react with triphenylphosphine and the base], which combined will make the Wittig reagent, which when you react with the original aldehyde, gets us a six-carbon compound, which then if we hydrogenate, we get the answer.

Another method is: let's say I pick up with the alkyl bromide; same initial steps to get there. I could go the Gringard route instead. You make the Grignard reagent, you react it with the aldehyde, followed by acid workup, and you get an alcohol. That alcohol you could turn into an alkane a few different ways. One is to oxidize and then do the Wolff-Kishner reaction. Another way is to take the alcohol and either dehydrate or turn it into a leaving group then eliminate. You'll get potentially a mixture of products but it doesn't matter, cause whatever alkene you get, you can then hydrogenate and you still end up with the alkane. The last way to do it was to turn it into a Grignard reagent and throw it at water, because water kills Grignard reagents. But we want that in this case because we want the alkane. Indirectly, by first turning it into a leaving group and then the Grignar reagent, it lets us get rid of the alcohol.

[review of pericyclic reactions]

Diels-Alder is actually a specific form of cycloaddition. Cycloaddition's called that because, if you look at the mechanism, it is cyclic in nature. It's specifically a four o-orbital and two o-orbital system participate. That combination of p orbitals always ends up occurring thermally. You could have a [2 + 2] addition, but, if you were to take the time to go over the molecular orbital description of that reaction, we would find out that it must occur by light. The reason this occurs thermally, the Diels-Alder, is we end up with this situation where we have the two end p orbitals of the diene that react on the same side of the alkene. In theory, you could have a cycloaddition where the ring is big enough that you could imagine somehow one side of that molecule reacting with one side of the alkene, where the other side is reacting with the other side of the alkene. Notice that both of these lobes are on the same face, both of these lobes are on the same face. Here, these are opposite faces that are reacting. When we have a situation in which the molecules are reacting face-to-face directly, that is called suprafacial. When you have opposite faces that react, that is called antarafacial. Antarafacial reactions are not possible for Diels-Alder reactions because you can't have four atoms and two atoms that, between them, one somehow wraps all alway around the other molecule and reacts underneath it. Imagine that I have a four-carbon chain, and i have the two carbons below. Antarafacial would mean one side reacts directly; the other side crawls around underneath and reacts – simply not enough atoms for something like that to occur. Antarafacial attack happens, but not in the Diels-Alder case.
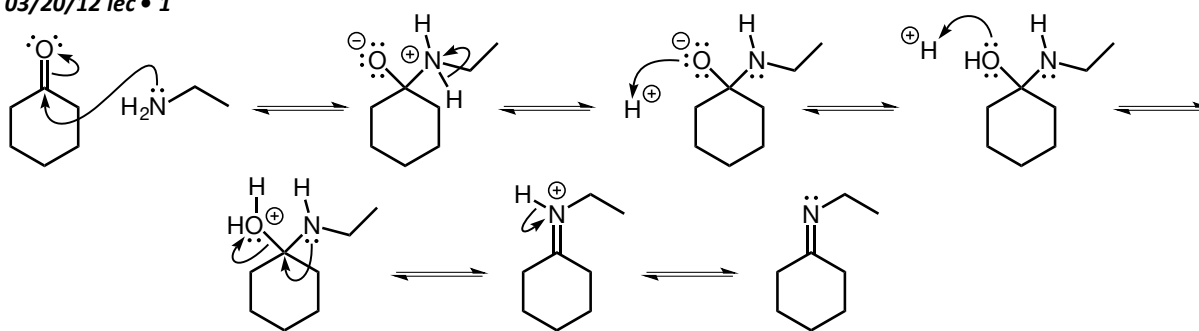
————

Quiz 1

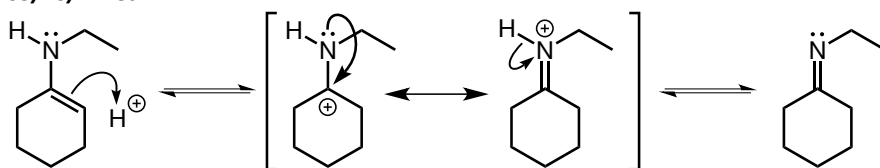Diels-Alder ≡ [4 + 2] cycloaddition

[2 + 2] addition:

Diels-Alder is a suprafacial rxn deacuse it is not possible for molecules of such small size (the pi systems) to reach around and react on both faces simultaneously.
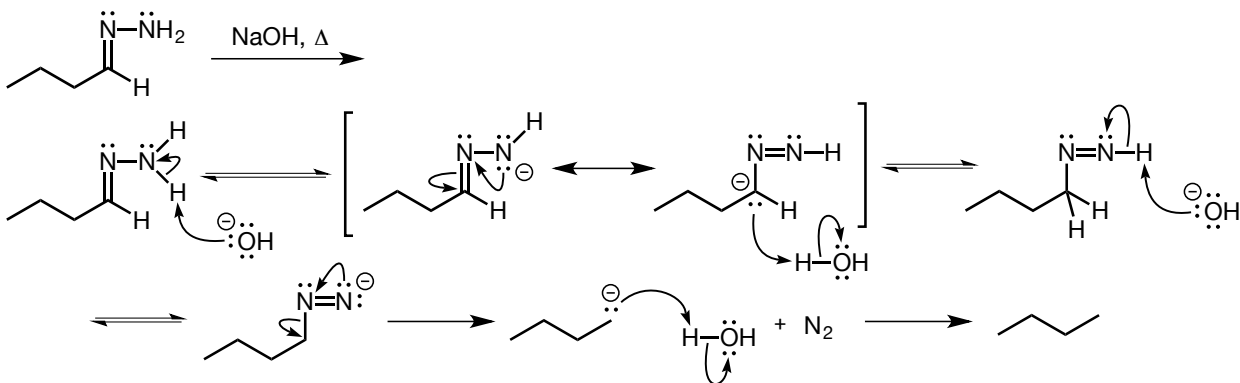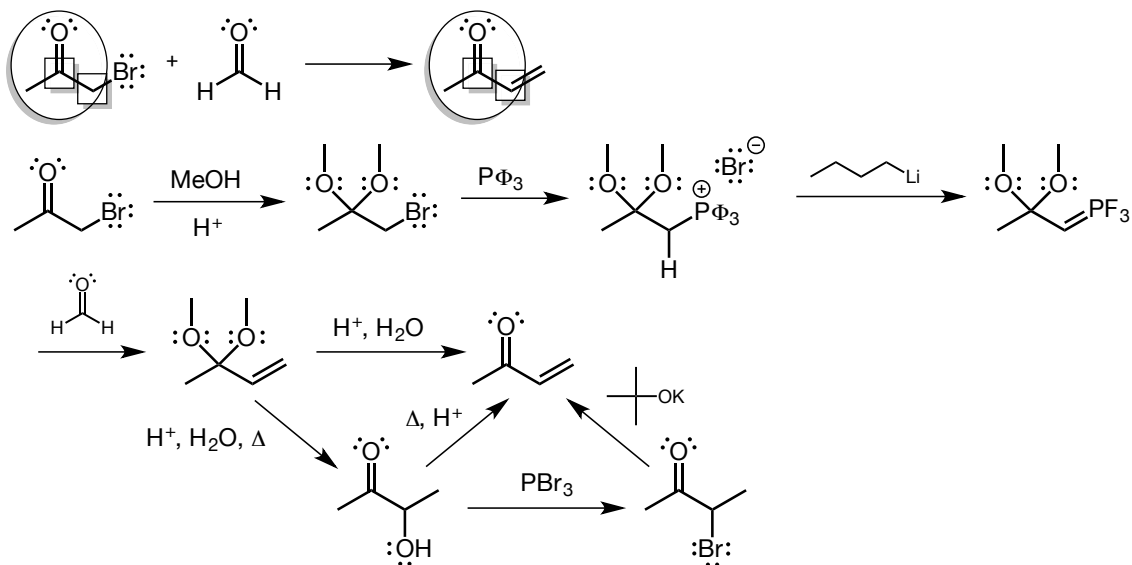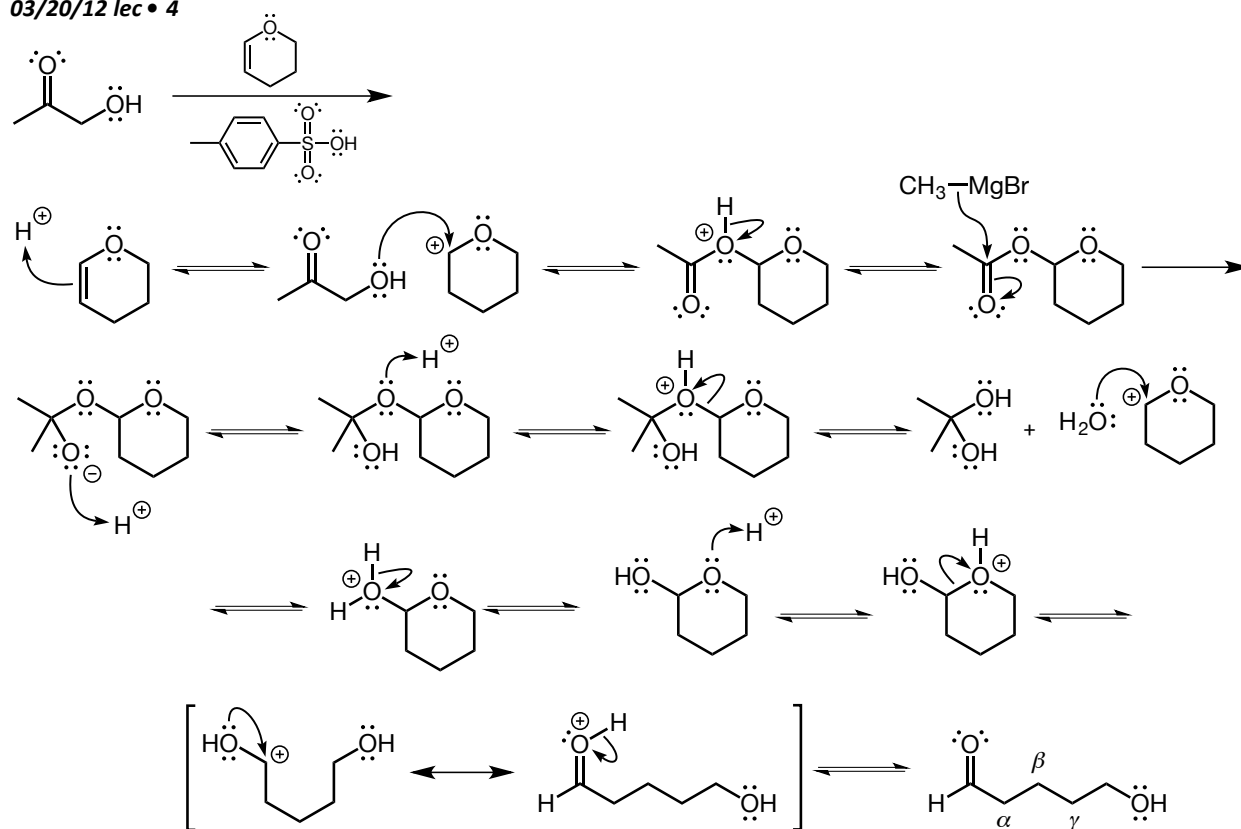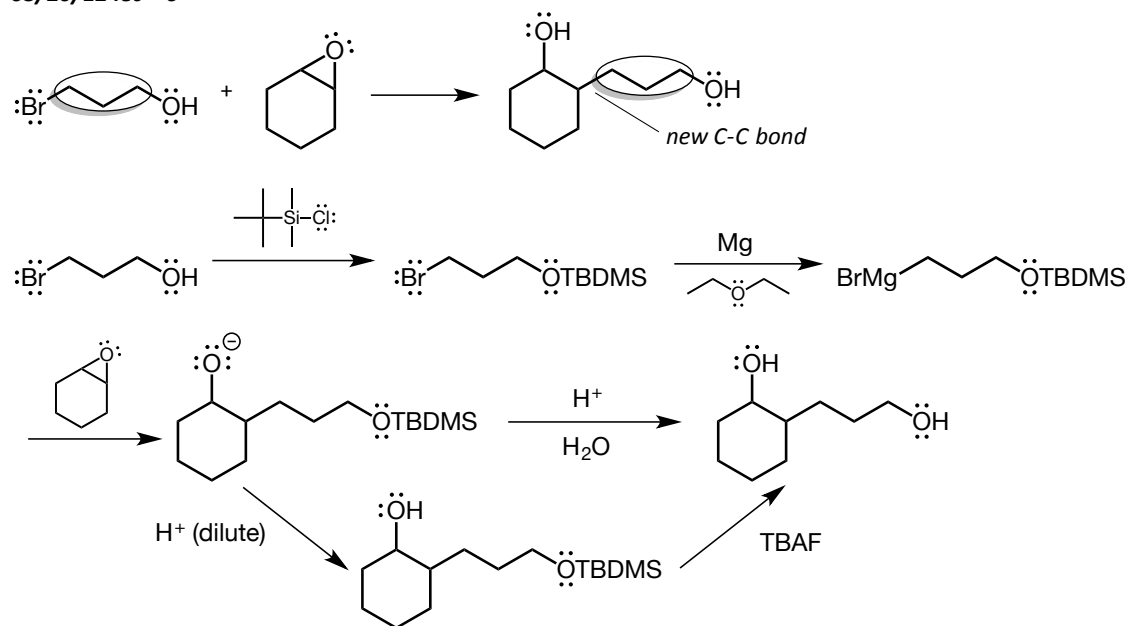
————

Structures

03/20/12 lec • 1

03/20/12 lec • 2

03/20/12 lec • 3

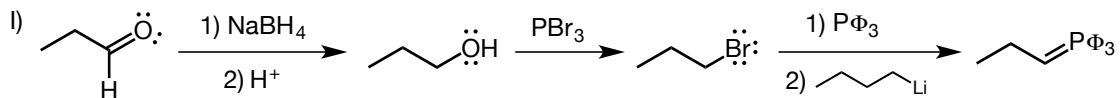NaOH, Δ

03/20/12 lec • 5

MeOH

H⁺

PΦ₃

Li

H⁺, H₂O

Δ, H⁺

OK

H⁺, H₂O, Δ

PBr₃

734

new C-C bond

I)

1) NaBH$_4$

2) H$^+$

PBr$_3$

1) PΦ_3

2) Li

H$_2$

Pd

II)

Mg

1)

2) H$^+$

a)

CrO$_3$

1) H$_2$N—NH$_2$

2) NaOH

b)

H$^+$, Δ

H$_2$

Pd

c)

PBr$_3$

Mg

MgBr

H$_2$O

D

PBr$_2$

H

R

R'

+

R'

Δ

R

R'

R

R'

R

R'