Lecture 4A • 04/18/12

[schedule for the quarter; quiz content]

What happens here? What functional group is this? An ester. What happens with the lithium aluminum hydride? [Hydride, H-, will attack the carbonyl] As a second step, we could have the collapse of that to reform a carbonyl, couldn't we? I'll write the hydrogen in to show it was added in. What's now likely to happen? It could reform the carbonyl, which will kick out ethoxide. It's not reversible; the original hydride is a much more basic reagent. This alkoxide that got kicked out is not nearly so basic, so this reaction only wants to go forward. But what's going to happen now? A second attack of the carbonyl. [In reductions of aldehydes and ketones], we ended up with something where we had an alkoxide, but we had nothing that could even remotely be a leaving group. We'll see that right here: here's an aldehyde that, if I reduce it, I'll push that carbonyl open, I'll make an alkoxide where if that alkoxide tried to reform a carbonyl, it would either have to kick a hydride out – which is far more basic, so it won't happen – or it has to kick an alkyl group out – which is far more basic so it won't happen. Last quarter, nothing happened after reduction, but starting with a carboxylic acid derivative that's going to have, in comparison to hydride, a leaving group, we get a double reaction. You would have a follow-up step here where you would add acid in order to release the alcohol. In other words, when you take an ester and reduce it, you go all the way down to an alcohol.

Having seen this mechanism, can we predict, then, what will happen when we react with a lactone? What is a lactone? A cyclic ester. Let's apply the exact same mechanism to this then. Hydride attacks the carbonyl. An alkoxide forms, which can reform a carbonyl, pushing the ring open – pushing the ring open. When we do this same thing again later with lactams and amides, we're going to see something else happen. When we reform the carbonyl, we've made an aldehyde; at that other end, we'll now have an alkoxide, which will sit around for now, since there's no acid source yet. The alkoxide will just flounder around a bit, but we still have lithium aluminum hydride that could react and again attack the carbonyl. We end up with a second alkoxide, which upon treatment with acid means we've generated a five-carbon diol. Reduction of lactone results in the opening of the lactone ring.

That's reduction. Shall we do a Grignard reaction? Why did I want to do both reductions and Grignard reactions at the same time? Because they have very, very similar mechanisms. Once you know for a particular functional group how reduction occurs, you know how a Grignard reaction occurs, because, if we had something like methyl magnesium bromide, then that methyl group's going to attack that carbonyl in exactly the same way that hydride would. Similarly, the base strength of a Gringard reagent is far greater than that of the alkoxide that would be formed at this point. Or that the difference between the fact that we're reacting with hydrogen versus a methyl group, the reaction is similar, so in a similar way the alkoxide can collapse to reform the carbonyl, which will make a ketone. As soon as you make a ketone, if there more Grignard reagent, it reacts, so that ketone's pushed open again. That means we've added a second R group, ending up with an alkoxide that cannot react further, so after a subsequent acid work-up, we end up with an alcohol. The point here is that two equivalents of a Grignard reagent will react with an ester. We do have a byproduct – the portion of the ester that was the alcohol portion. That gets recovered at the end as well; that's a good point if we're worried about synthesis problems.

Wouldn't it be useful, in certain situations, if we were able to take an ester and only reduce it once; it turns out, there is a reagent that can be used for that. There are two specialized reagents I'm going to introduce to you. Can [you] swap which reagent you use for which functional group? Yes, there are cases where these reagents can be swapped [, however this is not generally true.] It's abbreviated different ways; DIBALH is the common abbreviation for diisobutylaluminum hydride. There's some steric hinderance around that aluminum now; it prevents approach of that group as easily. It is used for more selective reductions, like the selective reduction of an ester. If you used this DIBALH under extremely cold conditions, -78 °C – which is not a random number, it's a temperature that can be achieved by the right proportion of dry ice and acetone, both of which are commonly available in more fully furnished research labs; a lot of places have their own dry ice generators. Throw dry ice and acetone together, and you can end up with this reproducible temperature. There's whole charts with lots of common solvents with dry ice if you want to make certain temperature. If you do that reduction, you're able to get the aldehyde. The extra alkyl groups lower the reactivity of the reducing agent, which matters, because not all reducing agents can reduce esters. For example, sodium borohydride will not work – not on any kind of appreciate time scale.

Why is it that sodium borohydride is so much less reactive than lithium aluminum hydride? The electronegativity difference between boron and hydrogen is not as large as the electronegativity difference between aluminum and hydrogen. That means that hydride coming off the aluminum, you could say, is more easily dissociable, which means it's more reactive. This means that if you have both a ketone and an ester, that if you wanted to reduce just the ketone, that is entire and easily possible. Lithium aluminum hydride, however, is quite reactive, so if you had a difunctional molecule – a ketone and an ester together – and you used lithium aluminum hydride, presuming there's excess, you will reduce both groups. Sodium borohydride is less reactive due to the small electronegativity difference of boron and hydrogen versus aluminum and hydrogen.

[summary for the quiz]

There is such a thing as aminolysis [of esters], but it's not that useful, usually, because esters are not so reactive.

Lithium aluminum hydride can certainly be used to reduce an aldehyde or ketone, but since it's a hassle to use, it's avoided when possible.

Let's do carboxylic acids next, because carboxylic acids, how they are different, kinda matches amides.

DIBALH is the one for an ester; an acyl halide also has its special reagent. Let's go back and pick up acyl halides real quick, because they match the reactivity of esters. With a Grignard reagent, two reactions would occur to put two R groups on – identical mechanism to esters. Grignard reagent attacks, pushes the carbonyl open; carbonyl collapses, kicks chlorine out; you've just made a ketone, so another Grignard reagent attacks; nothing further can happen until the acid work-up, in which case you end up with an alcohol. Similar story with reduction: identical to esters in form. If you reduce an acyl halide, you're going to make an alcohol. Similar to esters, though, wouldn't it be useful if we were able to stop the reduction. There is this thing – lithium trisisopropoxyaluminum hydride; it would look like this. It stops at the aldehyde. If you drew that structure out, it'd look like this. Presumedly, this works in two ways – oxygens, having those lone pairs that are delocalizeable ... even if they're not delocalizeable, oxygens, overall, provide electron density through their lone pairs, so it can attenuate the reactivity of the aluminum hydride. And, of course, we have the steric issue we would have had with DIBALH. There's our reagent for selective reduction [of acyl halides].

Now let's go to carboxylic acids. Carboxylic acids have an additional problem when we're doing reduction: you have to lithium aluminum hydride, because the very first thing that's going to happen with a reducing agent and carboxylic acid is what? Neutralize. You could have the lithium aluminum hydride; the first thing that happens is simple neutralization. After neutralization, we'll have aluminum hydride – not lithium aluminum hydride, just plain, neutral aluminum hydride. Aluminum hydride is electron deficient, so we could form this complex. This hydride kinda hop[s] over and push[es] open this carbonyl; that's a second reduction, but then there's something unusual that happens at this point: it turns out, with the aluminum attached, the oxygen now becomes a leaving group, [presumedly] because the lone pairs on that oxygen help satisfy the octet of aluminum. The alkoxide can kick that group out to make an aldehyde. Of course, once you have an aldehyde, a third hydride is going to come it [and] kick it open to make an alkoxide. Nothing further can happen, so there's a secondary acid workup to make an alcohol. So, a carboxylic acid reduces to make an alcohol. But, it does so through a slightly different mechanism. The fact that the aluminum ends up complexing is a key portion of that mechanism.

Let's look at the similarity with the amide mechanism. Notice that this hydrogen is not exactly an alpha hydrogen; it is in terms of position, but it's on a nitrogen instead. It turns out that that proton is actually easier to pull off than the alpha proton. [pKa of amide?] Like the carboxylic acid mechanism, the first step in the reduction of an amide is not the attack of the carbonyl; it is deprotonation of that amide. This looks stranger than the carboxylic acid because I'm going to combine the deprotonation with resonance – remember that resonance is just this fake thing that we do on paper. If you ever combine resonance with another step, that's always allowable, cause resonance doesn't count as a mechanism step. The reason I'm showing it this way is it helps to explain the complexation with the aluminum that happens, just like we had previously with the carboxylic acid. We make neutral aluminum hydride that, again, because aluminum is electron deficient [in compounds], we could continue and have this complexation.

Again paralleling the mechanism we have with carboxylic acids, we could have a hydride transfer over again which attacks the imine-style bond that we have here. Of course, once that hydride attacks, we're going to end up with a negative charge on nitrogen; that's really basic. [Compare] the the carboxylic acid reduction that occurred: same point in that mechanism, there we did have a negatively-charged oxygen which is able to reform a carbonyl by kicking out this aluminum leaving group; same thing now happens here. Of course, once that's occurred, we formally have made an imine. Imines can be reduced just like aldehydes and ketones, so with the hydride that's around, you get one more reduction, which temporarily gets us this negatively charged ion that, upon acid work-up, we get an amine.

Let's compare – in both the carboxylic acid and amide mechanisms, the first step is deprotonation, and the second step is complexation of an anion with the leftover aluminum. There's now another, a second hydride that's transfered over, which, once that's occurred, then the aluminum group that's left over is eliminated, reforming, in the carboxylic acid case, a carbonyl – in the amide case, it makes an imine. Both the aldehyde and the imine are reduced one more time and then acidified to isolate an alcohol and an amine, respectively. I've made this big point about what happens when we cyclize, so now let's take a lactam and apply the same mechanism that we just saw for the amine.

The first step is still going to be the neutralization of the hydrogen that's on the nitrogen there. This is the mechanism for an amide that has a hydrogen available; later one, we'll worry about what if there's no hydrogen there. We have the aluminum with four hydrogens, so neutralization first, followed complexation of the oxygen with aluminum. We now have one more hydride that now transfers over, kicking open that carbon-nitrogen double bond, which forms a negatively-charged nitrogen, which now kicks that aluminum group out. But notice that at that point, you're not opening the ring up, you're kicking something off the ring during the reduction of lactams. The ring does not open.

That's because in the case of a lactone, we had an oxygen in the ring; it was the oxygen in the ring that was being kicked open. But now we have nitrogen. Nitrogen bears the negative charge, so it's not being kicked out of the ring; it, from the ring, kicks something else out. We make an imine – an intramolecular imine, but still just an imine. So, we have one more hydride that can attack, which means we're making a secondary amine, after it grabs a protons. Because we make this switch to acidic conditions, it is fine to show H+ here. It's four carbons all along. But a lactam doesn't have to have certain number of carbons.

[summary]

Nitriles

If we did not have a hydrogen on the nitrogen, if we had a hydrogen attached to the oxygen initially, oxygen negative is not anywhere near as basic as nitrogen negative. If the carbonyl somehow tried to reform and kick the ring open, the ring would kick right back and kick the carbonyl open, so it does have to do with basicity. Nitrogen negative is not going to get kicked out by oxygen negative. Even if you wrote a mechanism that got you to that situation, it won't happen. The overall reaction is irreversible, but if you ask which portions of it might or might not be reversible, we have to do a more careful review. The first step, neutralization, irreversible; hydride is so much more basic than even an amide's proton would be. Then, kicking off that leaving group's going to be irreversible, reducing that imine ... actually, the whole thing is pretty much irreversible.

It's understood that the bond being used, it's the hydride that's going to follow and not the aluminum; it's not specified that way with the notation, but a chemist reading that would undertand it's the hydride moving, just from experience. We did the same thing with Grignard reagents.

Recall that a nitrile can be made, if you're careful, using sodium cyanide and some kind of leaving group. These things are related to carboxylic acids because, under appropriate conditions, you can convert it to a carboxylic acid. Let's say that we had a concentrate solution of hydroxide and water. With enough heat and time, eventually the nitrile can be broken open, which if you have hydroxide and water around, then when we form the negative charge on nitrogen, water that may be around could be the source of the hydrogen for that to be protonated. We've now made an imine, which hydroxide is able to attack; that'll push the carbon-nitrogen bond open. It's not going to happen in one step, necessarily. Now what happens in tautomerization, because we've made the nitrogen equivalent of an enol, haven't we? So, hydroxide comes along and deprotonates. We have delocalization occurring, which means we just made a carbonyl and, after water gets involved again, we neutralize to make the amide. From the amide, we continue reacting and do saponification. Nitriles are less reactive than amides, so whatever reagent will react with a nitrile automatically will continue to react with the amide, so we eventually end up with a carboxylic acid – again, that's why nitriles are part of the carboxylic acid family.

_____

– Reduction of lactones results in the open of the lactone ring.
– 2 equivalents of a Grignard reagent with react with an ester.

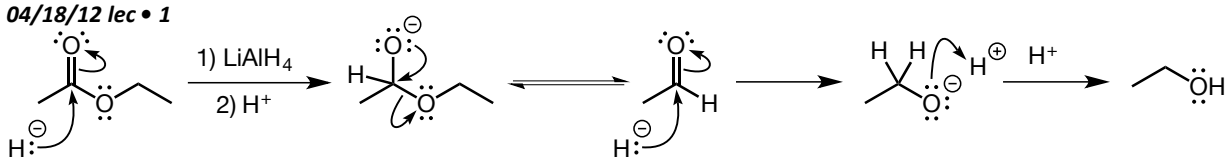
Sodium borohydride is less reactive due to the smaller electronegativity difference of B & H versus Al & H.

(Mechanism is identical to esters)

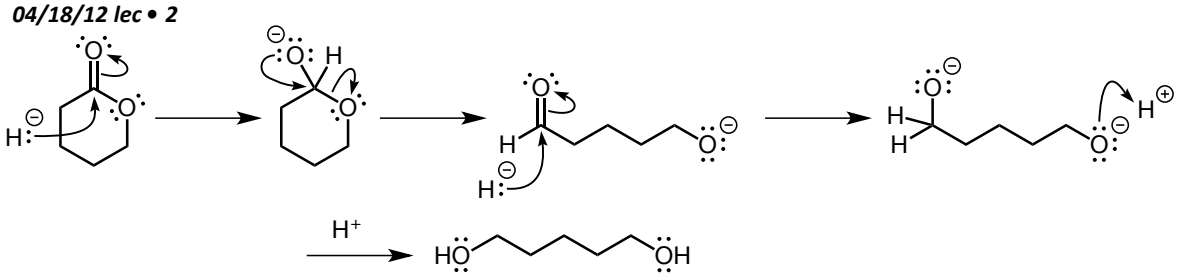
– During reduction of lactams, the ring does not open.

_____

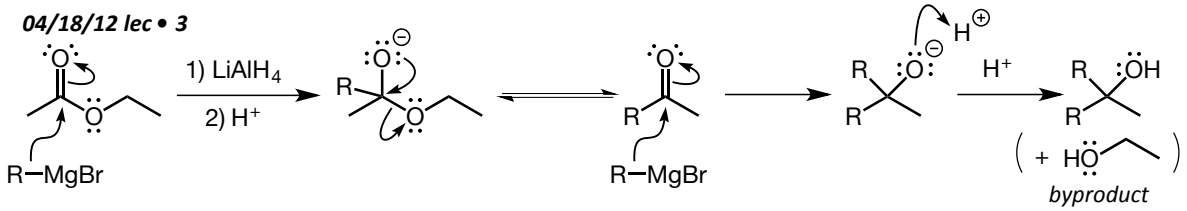
04/18/12 lec • 1



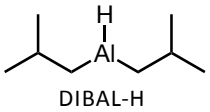
04/18/12 lec • 2



04/18/12 lec • 3

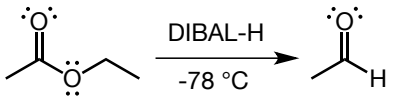


04/18/12 lec • 4

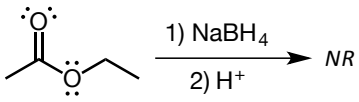


extra alkyl groups lower the reactivity of the reducing agent

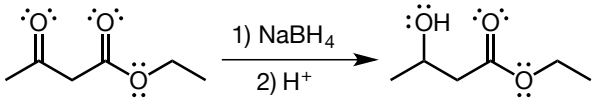
04/18/12 lec • 5



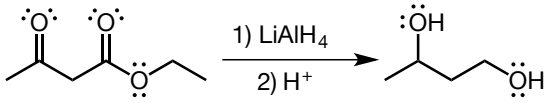
04/18/12 lec • 6



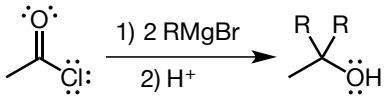
04/18/12 lec • 7



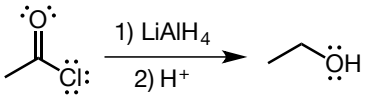
04/18/12 lec • 8



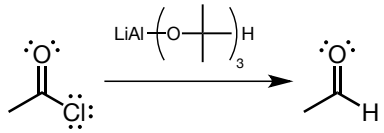
04/18/12 lec • 9



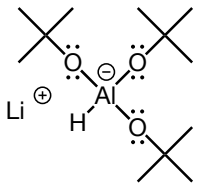
04/18/12 lec • 10



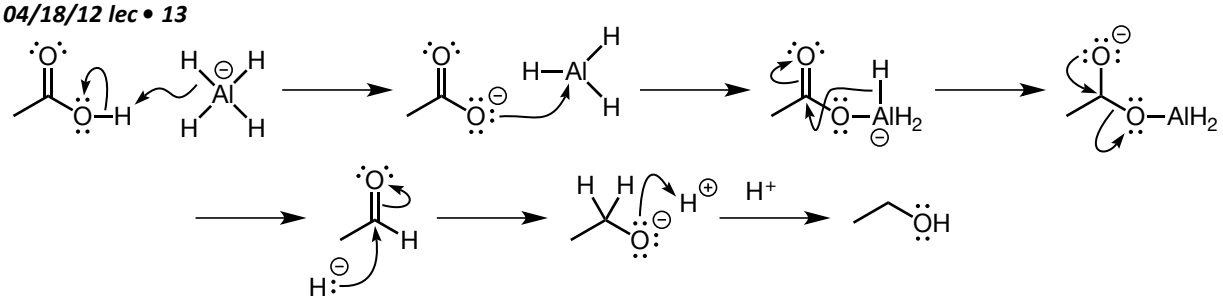
04/18/12 lec • 11



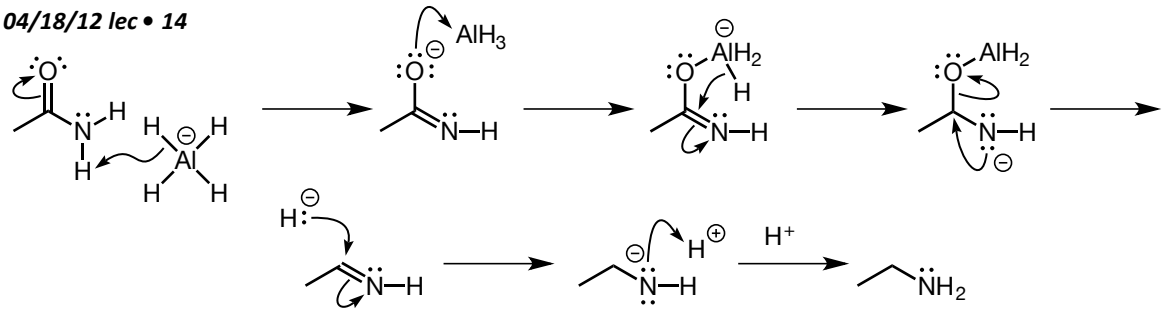
04/18/12 lec • 12



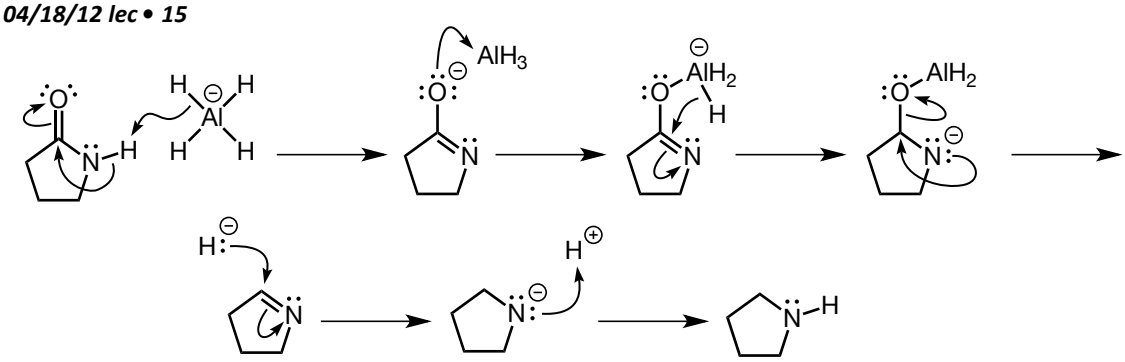
04/18/12 lec • 13



04/18/12 lec • 14



04/18/12 lec • 15



04/18/12 lec • 16