

## Lecture 9A • 02/08/12

First, when I approached this problem, I counted the carbons and tried to locate where this came from. I realized that even if you tried to attack this or that, it's going to give me a terminal one or end up at this position. First I thought it was just making this into an alcohol, but then it didn't really work, so I switched to a Grignard. There's a carbonyl that could be easily attacked that would give us the right number of carbons. But if you had taken that lefthand compound, made the Grignard reagent out of it, attacked the righthand one, the -OH group ends up at the wrong position. What did you do to get around that problem? Are you going to try to do an elimination to get an alkene? I want to try to make an alcohol and switch it over by dehydration. You could try to make a leaving group out of that alcohol and then eliminate, which it should give you an internal alkene; but then, if you try to make an alcohol out of it, you can have two different secondary positions; neither one is significantly different from the other. On paper this would work, but in real life the synthesis wouldn't quite work. But, you made the right observation at first, that if you had done the Grignard reaction the way it was set up, you would get the alcohol at the wrong position. What if you flipped which compound was the aldehyde and which one had the leaving group, the bromide.

Look at the starting materials. The problem with this is that if I leave the carbonyl on the two-carbon group, the alcohol ends up at the wrong position. But what if you could turn that into a Grignard reagent, and what if you take this starting compound, the first one, oxidize it, then you have the carbonyl in the correct position. [IQ force field] We want to make this aldehyde into a Grignard reagent. I'm reducing first with lithium aluminum hydride, and then remembering the follow-up step of protonation so you get an alcohol. Then we convert that into an alkyl halide; he's using PBr<sub>3</sub> to get the alkyl bromide. Then we react it with magnesium; he's remembering to put ether in, because you can't make a Grignard reagent unless you've got ether or what other solvent? THF. Acetone would react with a Grignard reagent. We're talking about the solvent that would complex with the Grignard reagent. Now he's going back to the other material which has the alcohol; what are you going to do with it? We're going to oxidize into an aldehyde, so we need PCC without water. Then we converge them. I've used these terms: divergent, which is where you start with one compound and go two different directions with it. But now he's doing convergent synthesis, where he's putting the two together. Then we add acid, gentle H<sup>+</sup> to do just a protonation.

We have an alkene. Now we use this one. Is there another way we could do this? Because you would not get carbocation migration, you could do hydration here. Now what we do on the other one is use bromination. We have a three-carbon fragment that's going to six. Can you explain a little bit what your logic is in this case. I converted an alkene to an alcohol. She's going to do a reaction to put the alcohol in the middle, because we do need one of the carbon fragments to have a functional group in the middle; if you look at the top part of that product, you see that the functional group is equivalently on the end, so she's making one of each kind. Then I convert the middle alcohol to a ketone, then I use the Wittig reaction to convert the ketone to an alkene. What are you trying to do there, oxidize? What reagent should we use for oxidation? Since it's a secondary alcohol, you could just use Jones' reagent, chromium trioxide in acidic water. PCC's fine. You've got the right idea, you wanted to make an alcohol at the end of the molecule. Let me see that part of it.

Start with the alkene, and we're going to go divergent here. This gives us a terminal alcohol. You need to make a Wittig reagent. Could you make a Wittig reagent from this? What is the first step in making a Wittig reagent? It's the alkyltriphenylphosphonium halide. What do you need for a Wittig reagent? An alkyl halide, correct? Can we make an alkyl halide out of that? Use PBr<sub>3</sub>. What would you do next? The alkyl halide, he's adding the triphenylphosphine, which is three benzene rings on a phosphorus. That phi is the abbreviation for phenyl for benzene. It's does an Sn<sub>2</sub>. You want to react it with a ketone, but there's one more step first. What is the next thing [needed]? n-Butyllithium, butane with a lithium at the end. If we did use n-butyllithium, that's going to act like an anion, it's going to pull a proton off; what you're going to end up with is the ylide. You put these two reagents together, and you directly get the answer. That's what a Wittig reaction does: it makes a carbon-carbon double bond.

Would you like to see an alternate version of this? Start out the same way, where you make an alcohol, turn it into a ketone. Instead of a Wittig reaction – Wittig is a good answer for this cause it does give you the double bond right away – but it would have been possible to do a Grignard reaction as well. Do the same process: hydroboration-oxidation to get you the anti-Markovnikov addition. If we're trying to make a Grignard reagent, then we make an alkyl halide out of it; this is very similar to the Wittig synthesis except for right here, we're going to use magnesium to make the Grignard reagent. Throw that Grignard reagent at acetone, followed by acid work-up, you'll get an alcohol that has the right number of carbons to it. If you turn that into a leaving group and then eliminate, the most stable alkene is the one that you want anyways. That would have been another possible approach.

What were you thinking when saw that alcohol there? How are you going to get that alcohol in the right position, what kind of approaches were you think of? There's two more carbons in the product, so I want to make the two carbons first. She identified the problem – it's not just one Grignard reaction that would work, because you have a two-carbon fragment that's been added in, but I've only given you a one-carbon fragment. Can you take that one-carbon fragment and make a two-carbon one out of it? You're going to start with bromomethane, [and you're going to make the Grignard reagent]. What do Grignard reagents normally react with? Ketones, aldehydes, and epoxides. We need one of those three things to do what you want to do.

We need an aldehyde coming from that alkyl bromide. Can you think of a way we could do that? [Make an alcohol using sodium hydroxide. Where do we go next? We need to oxidize it; what reagent could we use to oxidize? CrO<sub>3</sub> has the problem of overoxidation, so if we wanted to oxidize, we would PCC. What would you get from that? An aldehyde.

What do you get when a Grignard reagent attacks an aldehyde? We get an alcohol, after we do protonation. Immediately after the Grignard reaction, what are we going to have? An alkoxide. You needed a two-carbon compound to do the Grignard reaction; can you make a Grignard reagent out of that? How? PBr<sub>3</sub> and then magnesium in ether. Because you already had a ketone as a starting material, you have the two-carbon fragment that you need, so I'll put 1) ethylmagnesium bromide; 2) H<sup>+</sup>.

A quick version of an alternate approach. If you took that original methyl bromide and you also took the Wittig approach of making the Wittig reagent and the deprotonating it, then react that with the ketone, you get an alkene, which if you then use MCPBA, you get an epoxide. If you take that same alkyl halide and you make a Grignard reagent out of it, put these two together, you push open that epoxide, you get the alkoxide, and then with H<sup>+</sup>, you get the answer.

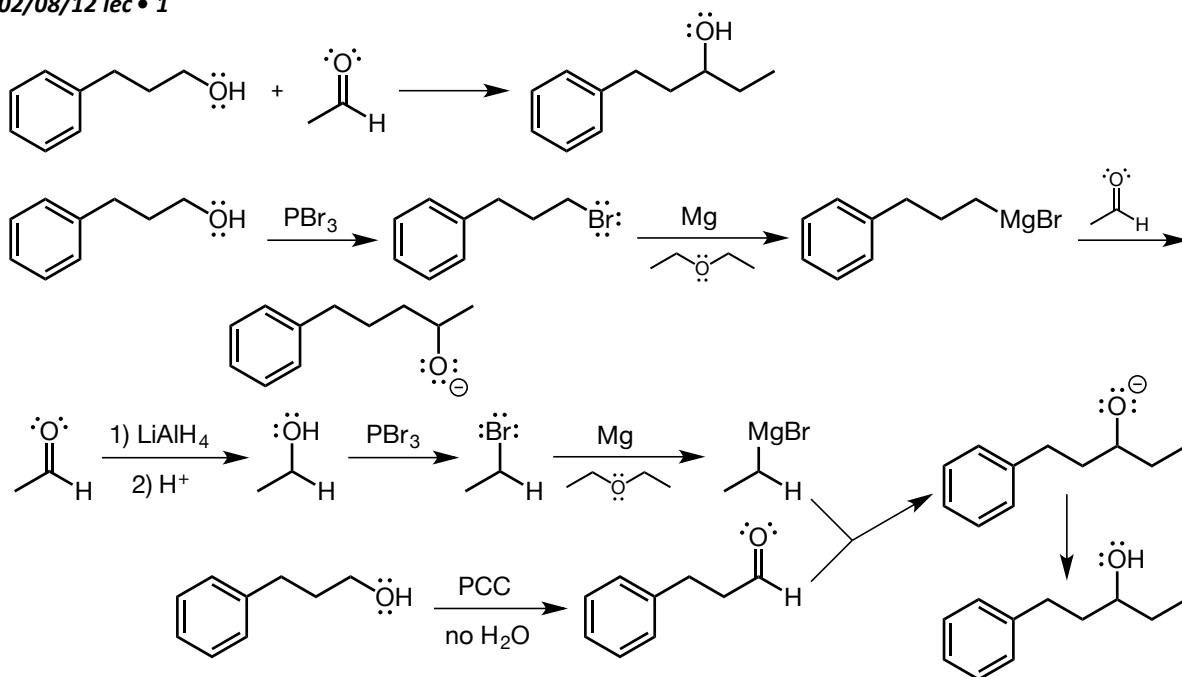
[quiz review]

[acetals, ketals, hemiacetals, hemiketals, hydrates, enamines, imines; POAD; Grignard reaction; Wittig]

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Structures

02/08/12 lec • 1



02/08/12 lec • 2

