

Lab 9A • 02/15/12

Let's start with one of the easier problems, one that's really just functional group transformation. It's going to be the easiest type of problem that you do get. The next level up from that is where we do start making carbon-carbon bonds; we'll do all of those problems afterwards. [mention of complication allowed by ozonolysis]

Doing that functional group problem first: we have butan-2-one that was being converted into but-2-yne. You might have guess that you could make that alkyne by going through [an] alkene intermediate, because you can start with an alkene, react it with Br₂ to make a vicinal dihalide, and then do a double elimination to make the alkyne. Of course, we need to get an alkene. Do we know of a reaction that can go direction from a ketone to an alkene? Do we know a reaction that goes directly from a ketone to an alkene without changing the number of carbons? No. If you said Wittig reaction, Wittig's going to add carbons to this, so it wouldn't give us the right answer. But, we could dehydrate an alcohol or convert an alcohol into a leaving group and eliminate it, so dehydration, elimination – either way, we can easily get to an alcohol. That's the sequence of steps – get to an alcohol first, make the alkene, and from there, go to the alkyne. To get to the alcohol, we're going to reduce. The number one small mistake is forgetting your 1s and 2s for reducing agents, which is going to be the same problem for Grignard reactions. You always have to separate the acid, because if you were to write it without the 1 and 2, what you're saying is both reagents react at the same time, which, in this case, they would, but only with each other; the acid would immediately destroy the sodium borohydride. You've got to put the 1/2 there. That'll get us the alcohol.

There are two ways we could then get to an alkene – acid and heat to dehydrate, or, turn it into a leaving group – for example, use tosyl chloride – and then do E2 elimination. Recall that if you use a big, bulky base, you make a less favorable alkene. I want to put a note here that something like t-butoxide would not be the right answer this time. Sodium hydroxide could potentially substitute, but higher temperatures favor elimination so we could assume we would get away with that reaction. It is technically true that we form both the cis and the trans isomers; in this particular problem, it doesn't matter, because once we get to the alkyne there is no stereochemistry, so we don't care, in this case, where we came from. To get to that alkyne, it is the two-step process: react with bromine – which that's bromine without light; bromine with light is free radical halogenation, a different reaction; this is making a vicinal dihalide, which happens in dark. Once we get there, two equivalents of sodium amide to eliminate and make the alkyne. That two equivalents is only necessary when you are doing that double elimination. If all you're trying to do is deprotonate an alkyne, you only need one molecule of sodium amide. There's a small variation to this: we could end up somehow with a diol and then get to the bromide and then get to the elimination. But could we make a hydrate out of this and then somehow end up with the alkyne by oxidizing. The answer is no, because if you were to dehydrate a hydrate, you'd just get the ketone back again, and we're not going to be able to overoxidize that secondary center, there's no way to get that other alcohol to the neighboring carbon instead – at least not through any reaction that you're learned yet. It turns out you could use the compound osmium tetroxide; it does let you make a vicinal diol from an alkene. Then, technically, you could use PBr₃ to make the vicinal dihalide and then do the double elimination. Notice that require another step compared to just reacting with bromine, so you could do it, but you wouldn't want to.

Let's so a similar one – taking a ketone and alkene and making a larger alkene. For any of the rest of these syntheses, there's two things that you've gotta do: evaluate which functional groups are there and where they're located, and then evaluate how many carbons we have. At the moment, we better be able to find some way to make the product have the same number of carbons as our reactants – the one exception to that is if we [use something twice] to create a larger reagent. This one's pretty direct: we have four carbons and four carbons. Where could we find those four carbon fragments? If you notice the first one, its four carbons with a functional group that's at position 2 on the molecule – not nomenclature-wise, just one in from the end. The product molecule also has a four-carbon fragment that, at the second carbon in, it's got a functional group. So, maybe that four-carbon fragment, one comes from the other. That of course means that the other four-carbon fragment would be the rest of the molecule. Notice that we have a functional group at the end of that fragment, and we start with an alkene. Remember that alkenes are one of those groups that bridges two carbons, so it'll allow us to make what looks like a functional group move from one position to another.

In this case, what we want to ask ourselves is: can we take an alkene and make it so that it has a functional group at the end of the molecule? The answer is yes – hydroboration-oxidation is an anti-Markovnikov addition to a double, puts an alcohol at the end of the molecule. Once we've figured that out, now we need to step back and say what kind of reaction appears to be going on here. This time, we are trying to assemble a larger molecule; we are trying to make a carbon-carbon bond – specifically, we're trying to make a carbon-carbon double bond. It seems like a Wittig reaction might be a good one to do in this case. For a Wittig reaction, you need a Wittig reagent and a ketone. We already have the ketone, so there's nothing we need to do to the first reagent; it's all about the second one. We could put a functional group in the right place if we react with borane and then oxidize it; makes a terminal alcohol. For a Wittig reagent, we need a leaving group – let's say I decide to make a chloride this time. Then, react with triphenylphosphine, which will make the alkytriphenylphosphonium salt. React that with butyllithium to make the Wittig, and finally throw in the initial ketone and that'll take us to the product.

Moving on to the third problem. [six carbons to six carbons, but mistake in problem] I left out one important functional group that make the problem a lot easier. What kind of starting material is this; what functional group is it? It's an acetal; why? Because we've got that carbon that's got two oxygens connected to it; there's a hydrogen at that same position. That means that there used to be a carbonyl right at that position – we could say a hidden carbonyl, once that opens back up, once we hydrolyze it. We have connected to that four carbons, so it's going to be a five-carbon chain once it opens. But here's the part [that was omitted]: at the end of that chain, you're going to have an alcohol present. So you're going to end up with a five-carbon aldehyde with an alcohol at the end. We get that just from hydrolysis – reaction with water and acid. You'll also get spit out of it methanol, because if you think about the mechanism, it's protonate-open-attack-deprotonate, protonate-open-attack-deprotonate. The first protonate is for the oxygen on the methoxide to get protonated and methanol leaves. That's the one carbon that we could use in, for example, a Grignard reaction. The only complication in this problem would have been that we would have needed to protect this alcohol before we did a Grignard. But if we did a Grignard, we'd add one carbon, oxidize back up, we could get straight to the product. It's actually a fairly quick synthesis. It requires that you recognize that: one, that's an acetal; [two,] you have to use protecting groups.

But the problem was worse than that, because I forgot about the alcohol, so somehow you have to be able to get rid of it. Think: do you know any ways that you could get rid of that alcohol? Convert the alcohol to a leaving group, eliminate it to make the alkene, and then hydrogenate it; you'll be left with an alkane. Here's another thought: what if you protect the carbonyl, make a Grignard reagent out of it, then on purpose destroy the Grignard reagent – react it with water. You'll end up with just a hydrogen at that position which is exactly what we want. Normally it's a waste, but it gets us what we want in this case. Otherwise, all we would do at this point is protect the alcohol; make a Grignard reagent out of methanol; have that Grignard reagent attack the aldehyde – that would add the last carbon we need. Afterwards, you would need to acidify the alkoxide, make an alcohol, and then oxidize the alcohol to get us back the carbonyl. [which protecting group can withstand oxidation?]

Let's do what I had originally put on paper. We're still going to have to do hydrolysis; we're still going to need that five-carbon platform to go somewhere with. But we need to get rid of the alcohol. Here's the three ways that we have now to do that. That last method I mentioned, let me draw it first. If we're going to try to make a Grignard reagent, no matter what our purpose, we have to protect the carbonyl because we don't want it to react. We now could make an alkyl halide, which we turn into a Grignard reagent, which we then destroy – use acid in water. At the same time that the Grignard reagent gets destroyed, if you have acid and water, you can undo the acetal, and we end up with the molecule that we want. Another way, the way that your classmate suggested: still convert it into a leaving group; just to be a little different, let's make it a chloride this time. Do elimination; this time it's fine to use a bulky base because there's only one product that can result. Dehydration would not be the best choice because dehydration forms a carbocation and carbocations shift; this will more guarantee us that we'll get the right alkene. If we then reduce it – hydrogen and palladium or platinum – turns out that carbonyls can survive standard reduction conditions. You can reduce or hydrogenate a ketone or aldehyde, but it takes a slightly different set of reagents. The carbonyl will survive, but the alkene will be hydrogenated, getting us the molecule that we want.

There's one more way to do it, which is the sneaky way – which is to realize: when you first open the ring up from the starting material, you have a five-carbon chain with functional groups at either end. Our real goal is to get rid of the functional group at one end. But you're not locked into making the alcohol the one that has to disappear. What if you did this instead? Start with the aldehyde, react it with hydrazine, which makes what? Hydrazone. [competition with cyclization; nitrogen is more nucleophilic] Why is this good? Because it undergoes the Wolff-Kishner reduction, which means we get rid of the carbonyl; we're just left with the alcohol. We lose the carbonyl. We do want a carbonyl, so now at this point, we oxidize, and we get, yet again, to the material I want.

Regardless of which way that you approach this, we could take that material and react it with the methanol. I'm going to shorthand this. PBr_3 to make the alkyl halide; magnesium and ether to make the Grignard reagent. Combine the aldehyde and Grignard reagent; you initially have an alkoxide which you can acidify. Then, because it's secondary alcohol, we don't care about conditions, we just want to oxidize, so I can even use the Jones' reagent. I end up at the product. [pep talk]

Next one. Let's do the one with the bromoalcohol. We have an alcohol, an alkene that react to make a diol. Let's analyze it and see if we can pull it apart. We have a three-carbon fragment, a three-carbon fragment, and, fortunately, three plus three makes six; I have a six-carbon product. We should try to see where are these fragments, where are these starting materials buried in that product. I have a starting material that only has three carbons, has an alcohol at one end, and I have an alcohol at the end of my product. There would have to have been a new carbon-carbon bond that formed, and it could have formed right where that bromide is, which would likely mean that bromide became part of a Grignard reagent. That sounds pretty logical, so let's go ahead and circle that – three-carbon fragment here, three-carbon fragment here; alcohol – which means functional group – at one end, new carbon-carbon bond – which also means there was a functional group – at the other end. That seems to make sense.

Then we've got this other three-carbon fragment, but hey, here's the problem. We have three carbons, but we end up with an oxygen not where the new carbon-carbon bond formed. That's not a problem if you think about reagents that span two carbons, which include alkenes, alkynes, and epoxides.

If I converted this alkene to an epoxide, I'd attack the less substituted position if I made a Grignard reagent. That would push it open and put the alcohol exactly where I want it. That's the solution to this problem: I need to make a Grignard reagent, and I need to make an epoxide. The epoxide's easy: one-step, potentially, if I use MCPBA; two steps if I go the halohydrin route – first aqueous bromine to make the halohydrin, and then sodium hydride to do the intramolecular S_N2 . Now I need the Grignard reagent, but I can't make one directly, because if I tried to make it right now, as soon as it forms it would neutralize itself because we've got an alcohol. This is where we need an alcohol protecting group. We've learned two: silyl ethers and pyranyl ethers. [I'm going to use a silyl ether] The preferred reagent was tert-butyldimethylsilyl chloride; that will make the tert-butyldimethylsilyl ether, which is resistant to Grignard reagents. So we've got the two pieces we need.

We'll react that Grignard reagent with the epoxide. Initially we end up with an alkoxide; here's our new carbon-carbon bond. We still have the protecting group on there. Recall that we could, if we're careful, protonate the alkoxide without affecting the protecting group; but we want the protecting group knocked off and we want to turn the alkoxide back into an alcohol, so if we just use acid and not try to be careful – make it a more concentrated solution, heat it up – we'll simultaneously reprotonate and deprotect.

One more protecting group problem. Here we have a halogenated ketone that reacts with an aldehyde to form an oxoaldehyde, something that has a ketone and an aldehyde in it. Let's do the same analysis we did a moment ago. I have a four-carbon fragment, a one-carbon fragment, we end with five. Let's look at the four-carbon fragment – It's four carbons with a functional group at position two and a functional group at position four. What have we got in the product? A functional group at position two and a new carbon-carbon bond at position four. Seems like it's yet another Grignard reaction. We've added one carbon; our aldehyde has one carbon. We need an aldehyde in a Grignard reaction; why not make a Grignard reagent from the starting material, just attack the aldehyde, and we're almost there. That's the approach – the only complication is that we have to protect the ketone, because if we try to make the Grignard reagent, we would attack the ketone, again destroying it before you react it further.

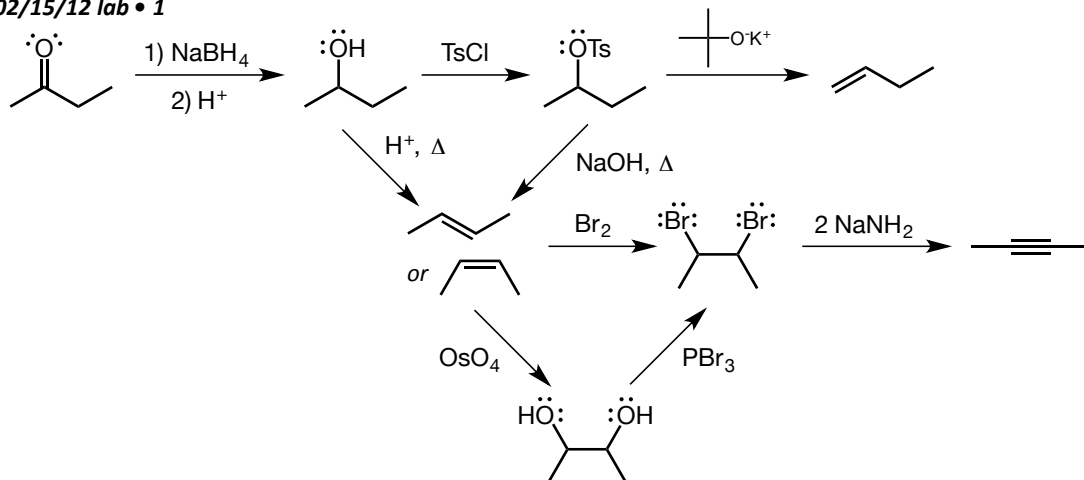
There are more than alcohol that would successfully make a ketal; I'm by default I'm going to use ethylene glycol because it forms one rather easily. Once we've protected it, make the Grignard reagent, which we're now ready to react with the aldehyde. We want to reprotonate the alkoxide, but we want to get rid of the protecting group, so why not do both at once. We almost have our product, except we need to turn the alcohol into an aldehyde, so last step, oxidize with PCC, and we've got our product.

The last synthesis. Start out with three carbons attached to a benzene, and ended with a product that has four carbons attached to the benzene. You might look at it and say: oh, I want to do some kind of Grignard reaction by making an aldehyde at the end here – but that won't work because you have an aldehyde and a ketone. One might be more reactive than the other, and maybe there's a way to make the aldehyde react instead of the ketone, but let's say we don't have those tricks, let's say there's not a difference in the reactivity that we could take advantage of in this case. We could do something very sneaky, because we could do a Grignard reaction, but unlike the one that seems to be implied, where we're going to take that methyl group and attack something here, what if we do it just like in the previous reaction: what if we attack methanol, turn it into an aldehyde first. Your response should be: hey, that's going to put the alcohol in the wrong place; well, we'll move it after the fact.

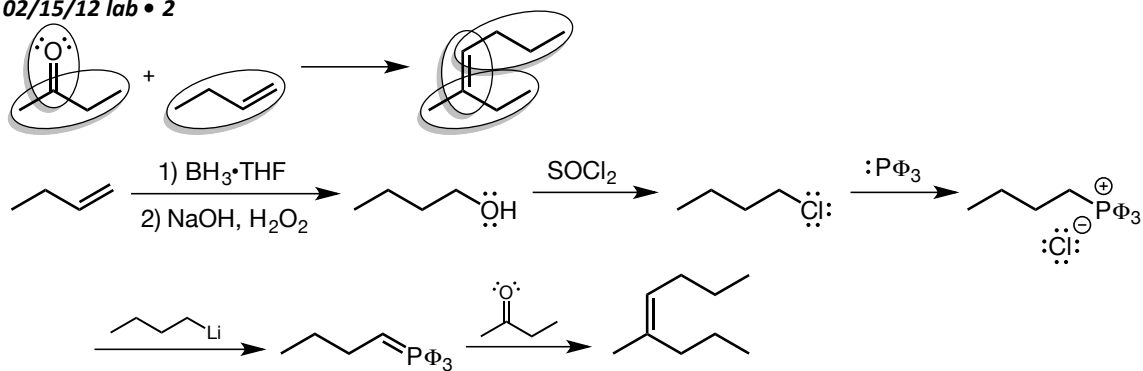
I'm going to do a Grignard reaction, but make this larger material the Grignard reagent. I've got to protect my ketone first. Now I can make my Grignard reagent. Separately, I'm going to take methanol, oxidize it in PCC and pyridine, put the two together, and acidify. This is much like one of the problems we already did; but, the alcohol's in the wrong place. So, we move it. React it with PBr_3 to make a leaving group; eliminate it, make an alkene. [watch out for extra carbons or missing carbons in synthesis problems] If I then do oxymercuration-demercuration to avoid carbocation migration, I'll put the alcohol exactly where I want it.

Structures

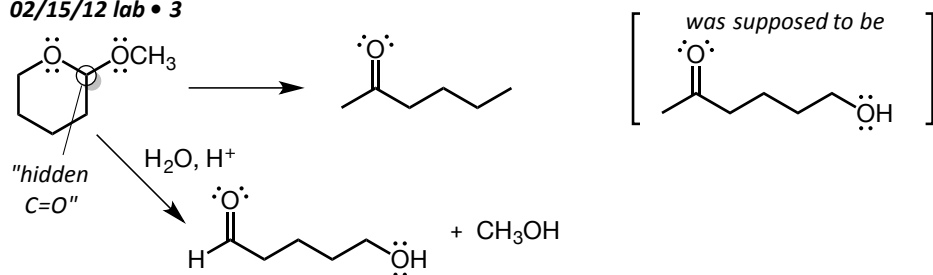
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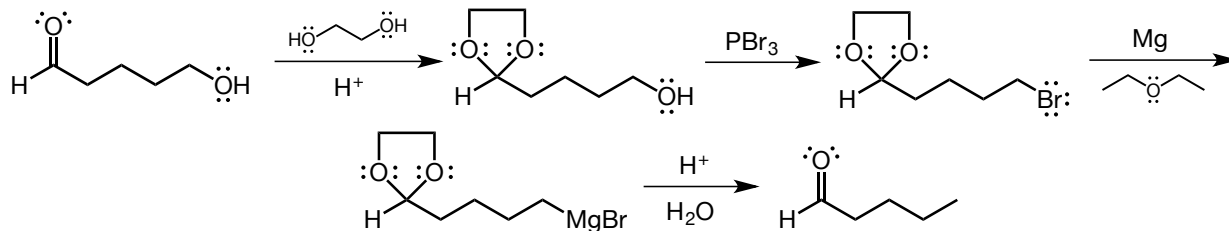


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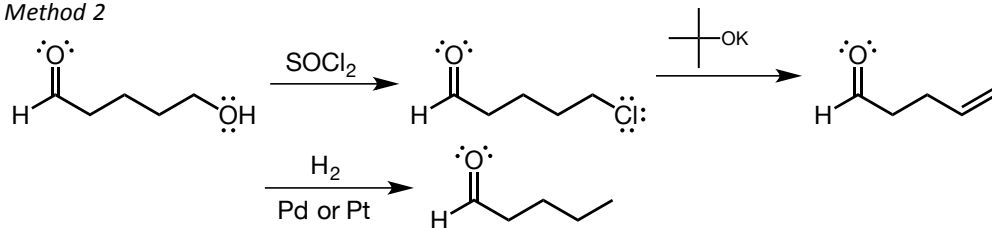
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Method 1



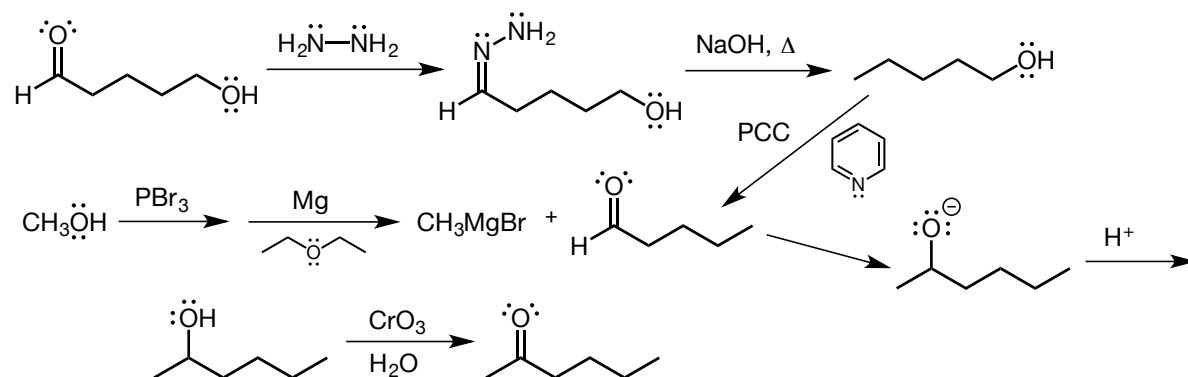
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Method 2

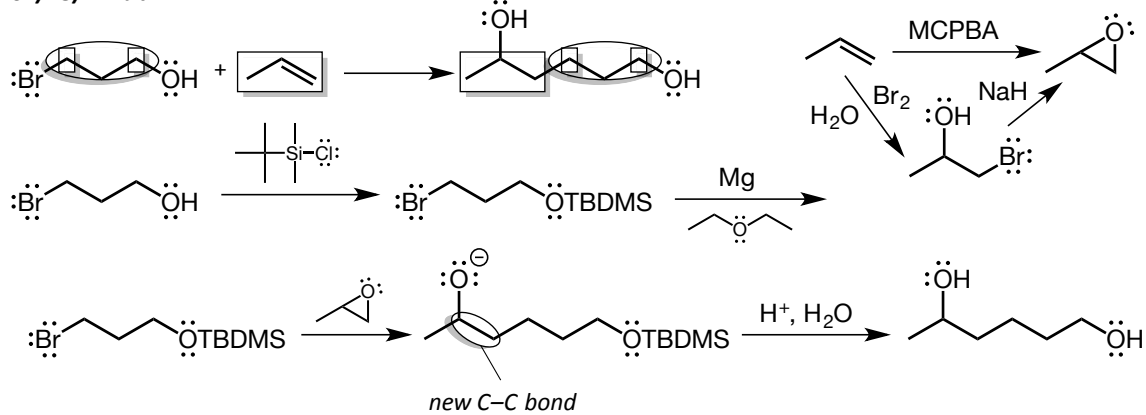


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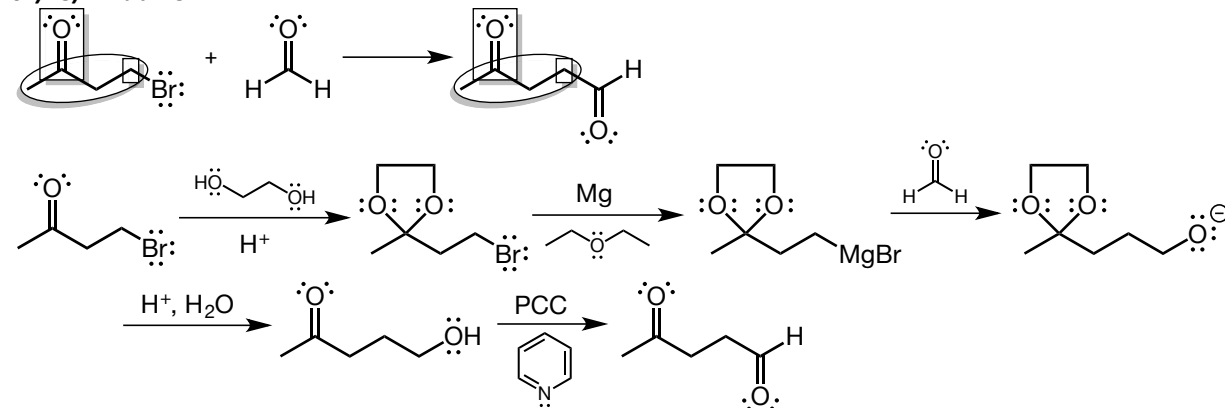
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