

Lecture 10A • 02/10/12

Protecting groups

I want to show you another common protecting group used for alcohols. It's the formation of what are known as silyl ethers. The version that your text has is the TMS ether. Don't get that confused with tetramethylsilane, which is our standard that we use in NMR; this is trimethylsilyl; this is very close in form. What it is – trimethylsilyl chloride is the reagent that's generally used. When you react it with an alcohol, the silicon-chlorine bond is active enough that you're able to do an Sn_2 -style reaction, even if you just have the neutral alcohol. You might notice that there's a whole bunch of alkyl groups on the silicon; how can you do an Sn_2 with something that's got that much steric hindrance? Silicon's larger enough that you don't have the same form of steric crowding, so this reaction is able to take place. We have the regular form of deprotonation step afterwards. If it weren't for the fact that we have a silicon there instead of a carbon, this would just be a regular old ether, but that's why this is called a silyl ether. That comes from the fact that SiH_4 is called silane. The -ane is actually used for other atoms besides carbon. You can have phosphane, silane – usually means add hydrogens to that particular element. Silicon can take four just like carbon because it's in the same column of the periodic table as carbon.

This particular protecting group is very widely used, but it has certain drawbacks, in that it very easily reacts in both acidic and basic media. A lot of care needs to be taken when using this protecting group. To show you what's often used instead, I want to do a slight variation. This is a trimethylsilyl ether; this can be abbreviated TMS, trimethylsilyl. The one that we're normally going to use in problems is TBDMS, which stands for tert-butyldimethylsilyl. We use TBDMS chloride, which looks like this. The greater steric hindrance slows down its decomposition, at least in acidic environments. That t-butyl group making it a little bit sterically more crowded around the silicon does make it less reactive enough it better survives acidic media – not very acidic, but makes it easier to handle in real life. The way that it's normally expressed is that it's less prone to hydrolysis, water breaking it up when you don't want it to. To form a TBDMS ether, it's the same type of process; you just throw an alcohol at it. If I wanted to write it out synthetically, I could write it like this. Since I've shown the structure of the reagent once, it is fine for you to abbreviate it afterwards.

How do we use this protecting group? Silyl ethers are usually stable in strong basic solutions, up to a certain extent. But even the more protected ones don't stand up that well to acidic conditions. But if we wanted to do a Grignard reaction, for example, is where a silyl ether is used: we could take a difunctional molecule – for example, a halogenated alcohol, one in which the halogen and the $-\text{OH}$ group are not necessarily right next door to each other. If we use TBDMS chloride, which we can abbreviate it TBDMSCl, we'll make the silyl ether, which means we've masked the fact that it's an alcohol – it's an ether, not an alcohol – so it's kinda like using the DHP, in that we end up with only ether-style functionality. Throw this into magnesium and ether, we'll make a Grignard reagent. We could then throw it at whatever substrate we wanted to; just to have shown another example of this, I'm going to throw it at an epoxide. Grignard reagents will attack at the less sterically-crowded position. Notice that I've got three carbons so I'm going to make sure that, if I'm attacking a three-carbon epoxide with a three-carbon Grignard reagent, that I've got six carbons total shown. Of course, we still have that silyl ether at the end of the molecule. If I were to use dilute H^+ – this is the advantage of TBDMS: the TMS group I showed first would be more likely to decompose even under these slightly acid conditions. TBDMS could withstand it, so that you could retain that functional group. Why would you want to do that in this case anyways? We currently have an alcohol and a protected alcohol on the same molecule. What if we wanted to be able to do something to this alcohol that's exposed? By keeping the protecting group on there, we keep that other alcohol still hidden, so you could do something on this now-formed alcohol without hurting the protected alcohol. In truly something that's a more sophisticated reaction, what if we used DHP to protect that new alcohol? There's a reagent that can be used to remove the TBDMS group without affecting a THP group – that is the molecule TBAF, tetrabutylammonium fluoride, which you might recognize as a quaternary ammonium salt. It's a way of removing that TBDMS group without affecting other protecting groups. The other way that you can get rid of the silyl ether is just to hydrolyze it, which means to put it in acid and water. So if you have a TMS group and just show H^+ and water, it'll make an alcohol.

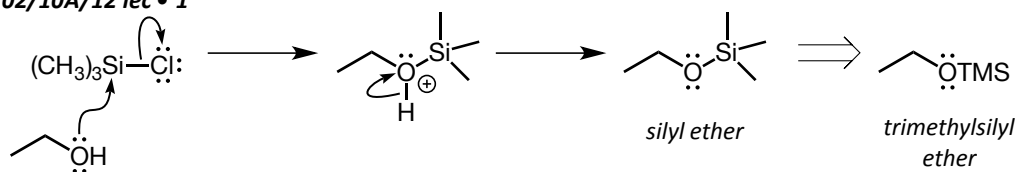
Synthetic utility – it's a protecting group for alcohols. It does the same purpose as DHP. In some cases, it's interchangeable which approach you might want to take. In real life, DHP is a lot cheaper. TBDMS chloride is a solid, it's easy to handle but it's expensive. TBDMSCl is expensive, while DHP is a much, much cheaper liquid. There will be applications where you couldn't use DHP where you might be able to get away with using TBDMS.

Cyanohydrins – Cyano-, coming from cyanide, the CN group; hydrin coming from water. There's an acidic version of this and a basic version of this. HCN – mechanism-wise, protonate, open, attack: ketone gets protonated; you could draw a resonance structure. Once the hydrogen from the hydrogen cyanide dissociates, it's an anion, so it's a small variation on the mechanism [no deprotonation occurs]. Then the basic version. Base version would be to use sodium cyanide, which initially gets us an alkoxide.

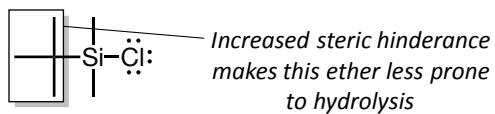
Silyl ethers – SiH_4 – silane – Silyl ethers are often resistant to bases (but not acids) – Cyanohydrin

Structures

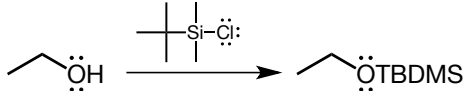
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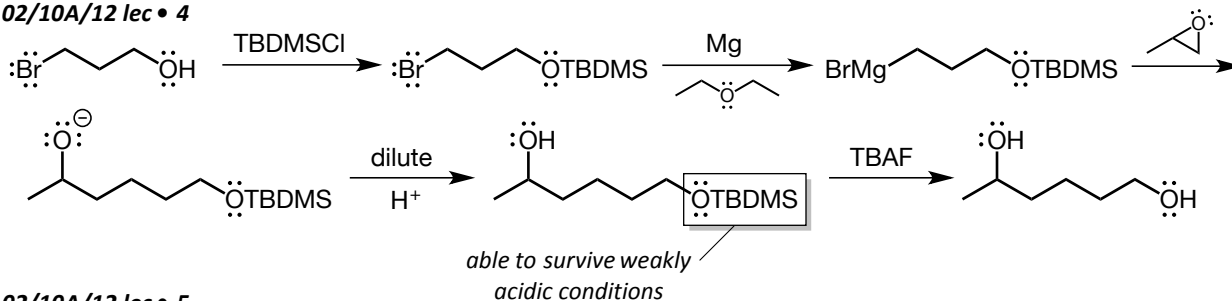
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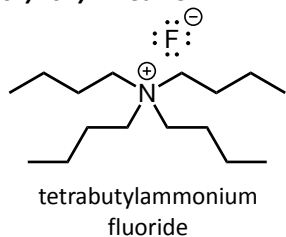
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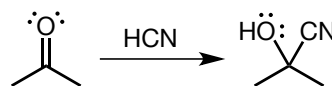
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