

Lecture 24A • 11/30/11

Let's go back to this oxymercuration-demercuration. Working with the same alkene that we had previously, which I chose this alkene only because we do end up with stereocenters at both the positions where the double bond had been once the reaction proceeds. We have this reagent mercury acetate. Just to save time in writing the structure, I'm going to continue using the Ac abbreviation for [acetyl], meaning carbonyl with a methyl group on it. The first reaction step, there's different ways to write it. The way that we ended up doing it was to show an alkene attacking mercury, a pair of electrons in response coming back to make a ring; at the same time, one of the acetate groups is kicked off. There are two intermediates that are formed. This ring compound: there's going to be two different forms that because the mercury can sit down on one face or the other of the double bond.

What's going to happen next? Because there are only two eventual products that end up forming in this reaction, and there's attack specifically at the tertiary center. That's going to be somewhat of an unusual step, cause at the same time, the ring opens. Let me turn that around: the ring does not open until the attack occurs, which is why there are only two products that form. If this ring were to open before the next attack could occur, then you could effectively end up with four different products, because we already have these two intermediates. If the ring was to open to form formally a carbocation, attack at that carbocation could again happen from two different sides, which means we have four products, much like we had with the first type of electrophilic addition. The whole point of this reaction is, because it maintains its ring form until the next attack occurs, that's why there's only two eventual products that form. In this reaction, the ring remains intact, until it is attacked by whatever nucleophile's present in solution. Because the ring remains intact, each intermediate will only produce one product.

In lab, we had this case: we had a cyclobromonium ion; same type of deal as we have with this cyclomercurinium ion. What can happen, though, in this case is the ring can open by itself. In this case, the ring can open independently only because the formation of a benzyl carbocation is favorable. Only in this case or ones like it, attack can occur from two different directions. Going back to our main focus, this mercury reaction, the next step that will occur is that water will come in and push open that ring. We'll get two products and only two products. In this very specific case [lab], we don't form four products, only because two of them are the same compound cause they're meso, but if this was not a symmetric compound, then yes, by having the benzene ring there, you would, in theory, form four products, versus the only two products that we're getting in this case. Now we'll, of course, have a deprotonation, so we'll end up with two products.

Notice that what did add in, the water, added in at the most substituted position, so this is a form of Markovnikov addition. The question is, though: why does it attack at this most substituted position? If we do have this concerted attack of water on that ring, and if both of those events are occurring simultaneously, it looks like it's an S_N2 -style reaction. S_N2 shouldn't be possible on tertiary substrates, so what's going on? This is a positively-charged three-membered ring, which is fairly unstable; it's going to want to react. Essentially what happens is one of the two bonds is weaker than the other in this case, because one of the bonds is to a tertiary carbon where, once the ring opens, if a carbocation forms, that would be the most favorable place to have the carbocation. That means that the bond to that position is a bit weaker, compared to the bond from mercury that had been there that had been to the secondary carbon, which ends up being stronger, because the secondary carbon doesn't want to have the carbocation, so it's not as favorable to break that bond, which means the bond is stronger. One bond is longer and weaker because the carbocation that could form would be favorable; the other bond is shorter and stronger because that carbocation is not favorable. The positive charge itself is what is allowing the ring to be pushed open, so sterics don't really have an influence here. Addition of water occurs at the most substituted position. This might seem strange, given that the mechanism of that step resembles an S_N2 reaction, and involves a tertiary substrate. Again, if we look at the intermediate, and let's say that I stylize it in this way: I simplify and just focus on the fact that I have a tertiary versus a secondary substrate. What's happening is the three-membered ring is strained to its small size and the positive charge. When the ring opens, it is more favorable to produce a tertiary versus secondary carbocation, so the bond to the tertiary carbon is weaker, and therefore breaks when water attacks.

There's one more step in this reaction; we're not to the end yet. This discussion started by [the fact that] we might want to make an alcohol out of a particular alkene, but what if that alkene is subject to carbocation rearrangement during the reaction. Here's this alternate method for making an alcohol. Notice we do have an -OH group on the products that we form, but we still have this mercury around. [next step without mechanism] Taking just one of the products, you'd simply be able to say sodium borohydride and base. What happens is we remove the mercury. It is thought that that reduction might actually be radical in nature; what ends up happening is the stereochemistry is therefore lost at that position. But, before that step had occurred, notice that the mercury, which was one of the things added in this reaction, and the -OH group, they are pointed opposite directions from each other; that's again because you had this ring that was maintained while water did the attack. The first step of the reaction occurred with syn addition, because the ring formed only on one side or the other of the double bond, but the overall mechanism is anti addition, because the two groups end up facing opposite ways.

Six features of the reaction. The utility is to convert an alkene into an alcohol, if you use water, or an ether, if you do the same reaction with an alcohol being present instead.

The reagents: first, it's mercury acetate and water, or an alcohol; two, it's followed up by the sodium borohydride and hydroxide. As far as conditions, there aren't going to be any special conditions that I show for this reaction. The mechanism, it is cationic and stepwise, overall. At the end here, yes, we did have a nucleophile come in to attack, but it's attacking that cyclomercurinium ion, and it's the formation of that cyclomercurinium ion that's the tough part of the reaction; that's why I'm still classifying this as cationic. In terms of stereochemistry, you'll form enantiomers, not diastereomers in this case. It's exactly because the ring stays closed that we don't make diastereomers. I say it forms enantiomers – there may be cases where you don't end up with stereocenters at all, but otherwise it can form enantiomers. Regiochemistry – the advantage of this reaction is that it is Markovnikov addition, no carbocation rearrangement, cause you don't ever form a carbocation. Items five and six are exactly the same for the bromination reaction.

If we had this initial example molecule – this is the one where I said a problem occurs if we tried to do simple electrophilic addition – if I want to show not the mechanism but just synthesis, then I could write it like this. The 1) and 2) are critical here. They mean: do everything with the first set of reagents entirely in the absence of the second set; then, once you've either isolated the intermediate or quenched the initial set of reagents, only then do you use the second set of reagents. This specifies the order of addition of reagents, and that they must be done as two separate steps. These numbers indicate the reagents must be used in a specific order as separate steps.

The bromine reaction, just to summarize. This is a somewhat poor example, because only one position ends up with a stereocenter, but this still would occur with the same kind of overall anti stereochemistry that we have. The utility is to convert to convert an alkene to a vicinal dihalide; vicinal means neighboring, so the two bromines on neighboring carbons. This is an important reaction, because as you're doing in lab today, you can then take a vicinal dihalide and, if it's the right kind of vicinal dihalide, make an alkyne out of it. The reagents – bromine, or it turns out chlorine can also undergo that reaction. The conditions – no light. Items five and six are exactly the same as for oxymercuration/demercuration.

Let me show you a slightly better example with bromination, and let me show you a variation. It's the formation of a compound called a halohydrin. I'll show you the full mechanism for this then. I'll use the same contrived alkene that we've had before. If I show you the reagents as being bromine, but not just bromine – bromine with water present as a [solvent?], water will far out-populate the bromine, which has the following effect. As the reaction goes on – start out with the bromine that gets attacked by the alkene; we make the two cyclic intermediates; now at this point, because you have so much water around, instead of bromide coming in to attack – which is the way we saw it happen in lab – water will be the one that comes in to attack. Because water attacked, we have a deprotonation step, so we'll end up with two products which are an alcohol that's right next to the bromine. Notice that, again, the bromine and the alcohol that result occur in overall anti addition. A halohydrin is a molecule that contains both an alcohol and a halide.

This is a particularly sneaky reaction. If I take one of these halohydrins and I throw a particular kind of base at it, sodium hydride – hydride tends to be basic without being as nucleophilic, so it can successfully deprotonate the alcohol. That means we now have an alkoxide. Look what we have right next door: a leaving group. Since this is a single bond between the two different carbons, that's free to rotate, and at some point the oxygen and bromine can end up antiperiplanar to each other, which if they do, you have an intramolecular S_N2 reaction. It forms a functional group called an epoxide. We're going to see another mechanism that will take us straight from an alkene to an epoxide.

We've seen one reaction of making an alcohol which is just to cook an alkene in water and acid. We've seen a second way of making an alcohol where it will have Markovnikov addition without carbocation rearrangement; that's oxymercuration/demercuration. But wouldn't it be great if there was some way to be able to take an alkene and have it undergo anti-Markovnikov addition, where something happens so that we could put the alcohol on the less-substituted position. This is called anti-Markovnikov addition because the substituent ends up on the less-substituted carbon. It turns out, there is such a reaction. You first use a compound called borane, BH_3 ; you follow that up with sodium hydroxide in hydrogen peroxide. This reaction is called hydroboration/oxidation. Let's see what this mechanism is, because it is unusual. It is your third type of alkene mechanism. Type one, plain electrophilic addition; type two, forming cyclic intermediates, which is what bromine and mercury do; type three, this is the only reaction in type three that we're going to learn, borane.

A little story about borane. It is one heck of a reactive chemical. [It] is perfectly synthesizable, but if you squirt it out into open atmosphere, it instantly would catch on fire. Why? Cause it so violently reacts with water that's in the air. Why would that happen? Why would this be such a hot compound? It doesn't have an octet; but, if you were to do formal charges, this molecule is neutral. It just happens to be boron, because it can just be trivalent, it doesn't have to follow the octet rule, but that means that boron is going to be particularly reactive in molecules that only have three connections, as we have here. THF, that stands for tetrahydrofuran. Furan is this molecule; it's a cyclic molecule that has two double bonds in it, and it has quite unusual reactivity. Put four hydrogens on there, though, get rid of the double bonds, and that's how you get tetrahydrofuran, THF. You can see that it's structurally effectively just the cyclic cousin of diethyl ether, your common lab solvent; you take the two carbon chains on either side and join them together in a ring, that is THF. Why is THF mentioned in this reaction? Because THF will form a complex with borane; it won't react, per se, because it doesn't make a product that can do anything further, but it helps to satisfy boron's intense need for electrons, and it makes the compound easier to ship.

Because borane is so electron-deficient, you often don't buy it just as itself, you buy it as the complex. This complex is still amazingly reactive, so it's not that you can throw it around, it just does make it more handleable.

What does borane do? Something quite unusual. Bor[on] forms all these very complicated structures because it is one of the few cases in which hydrogen can be shared between more than one atom. In fact, borane is normally found as the borane dimer, which looks like the following. This shouldn't be able to exist, in some senses, because hydrogen really should only be able to have one bond. Really, if you get into the technical analysis of this, this is one bond that's shared between two atoms, so quite an unusual structure. In the same way that it's able to make these structures that are quite unusual, it's got an unusual transition state it goes through.

Here's how the mechanism starts. [The] hydrogen-boron bond reacts. At the same time, an alkene attacks boron. Why would the alkene attack boron? Because it's electron deficient. But at the same time that happens, the hydrogen goes back to attack the alkene. That means we're going to go through this four-centered transition state. Normally I don't ask you to write transition states [when writing mechanisms]; I'm only doing it in this case we can learn about what happens in the borane reaction. This is an unusual enough reaction that there are some presentation of this topic that may last ten or twenty pages. [story about Jones text] Without trying to get lost in twenty pages of arguments, let me tell you why this intermediate is significant. Notice that boron is ending up at the less-substituted position; the hydrogen, which in other additions we've seen the hydrogen usually ends up at the less-substituted position and whatever else is adding in ends up at the more-substituted position. This would appear to be anti-Markovnikov addition. But what's more electronegative: hydrogen or boron? Hydrogen. Boron is less electronegative, so as far as where the delta plus is on this molecule, it's on boron. Boron is the electrophile, so the electrophile ends up at the less substituted position. That actually follows what the other electrophilic additions do, but it looks backwards because it's putting hydrogen, which happens to be, in comparison, the nucleophile, at the more substituted position.

This reaction step appears to be anti-Markovnikov addition, since the hydrogen, which normally is the electrophile, ends up at the more-substituted position. However, hydrogen is more electronegative than boron, so boron is the electrophile. Looking at the four-center transition state, then, if boron is really the critter that's electron-deficient, then you could write a delta positive on the boron and a delta negative on the hydrogen. But if that's true, that means, effectively, you would be inducing or causing a delta positive on the more substituted carbon of what is becoming an alkane. A carbocation never forms, but the concentration of positive charge occurs at the most substituted position, which is exactly what wants to happen. So, it looks anti-Markovnikov, but that's because hydrogen happens to be the nucleophile in comparison in this reaction. Hydrogen is more electronegative than boron; boron is the electrophile; consequently, the boron adds to the less-substituted position, and the hydrogen ends up at the most substituted position. Because of this cyclic transition state, no carbocation forms, so no rearrangement occurs.

[rewriting mechanism without transition state to show way to write it] Alkene attacks boron; hydrogen attacks back. You end up forming an alkylborane. But, if the hydrogen-bond was reactive once, why can't it be reactive twice, which is exactly what happens: another alkene will attack this same intermediate. Now we'll form a dialkylborane; I can abbreviate the structure this way. But if the first two bonds, won't the third one? Of course. Then you'll end up with a trialkylborane. This is only part of the reaction. [low on time, full mechanism shown] The trialkyl borane is not isolated; it's allowed to react with a mixture of sodium hydroxide and hydrogen peroxide. Hydrogen peroxide has a smaller pKa than water does, so that means hydroxide can deprotonate hydrogen peroxide, so the hydrogen peroxide ion attacks boron. When it does so, it does one of the single most unusual steps we're going to see [this quarter], because forming a boron-oxygen-carbon sequence of bonds is favorable enough that, to relieve the negative charge that ends up forming after the hydrogen peroxide attacks, the alkyl group will shift over and kick off hydroxide as a leaving group. It will kick off hydroxide, a base, as the leaving group. That's how favorable, though, this overall process is. It's kinda, sorta like a carbocation migration, except that we have anions involved instead.

What you now have is a dialkylmonoalkoxyborane; you've effectively added an oxygen in at that position. This happens two more times. After this happens three times, you'll end up with a trialkoxyborane. There's one more sequence of steps. It gets decomposed, and you end up with the alcohol. Overall, this is anti-Markovnikov addition. It's done in a sneaky way because we use borane, where the boron, being less electronegative, ends up at the less-substituted position, and we then convert it into an alcohol.

In this rxn, the ring remains intact until it is attacked by whatever nucleophile is present in sol'n. Because the ring remains intact, each intermediate will only produce one product.

In this case, the ring can open independently only because the formation of a benzyl carbocation is favorable. Only in this case, therefore, attack can occur from two different directions.

Addition of water occurred @ the most substituted position, so this is an example of Markovnikov addition. This might seem strange given that the mechanism of that step resembles an S_N2 rxn an involves a 3° substrate.

The 3-member ring is strained due to its small size and the + charge. When the ring opens, it is more favorable to produce a 3° vs 2° carbocation, so the bond to the 3° carbon is weaker and therefore breaks when water attacks.

The overall stereochemistry is anti addition, due to the cyclic intermediate.

1. utility: alkene \rightarrow alcohol (H_2O) or ether (ROH)
2. reagents: 1) $Hg(OAc)_2$ and H_2O or ROH ; 2) $NaBH_4$, $-OH$
3. conditions: _____
4. mechanism: cationic /stepwise
5. stereochemistry: forms enantiomers; overall anti addition
6. regiochemistry: Markovnikov; no carbocation rearrangement

These numbers indicate the reagents must be used in a specific order as separate steps.

1. utility: alkene \rightarrow vicinal dihalide
2. reagents: Br_2 or Cl_2
3. conditions: no light
- 5 + 6 \rightarrow same as oxymercuration-demercuration

Halohydrin – molecule that contains both an alcohol and a halide

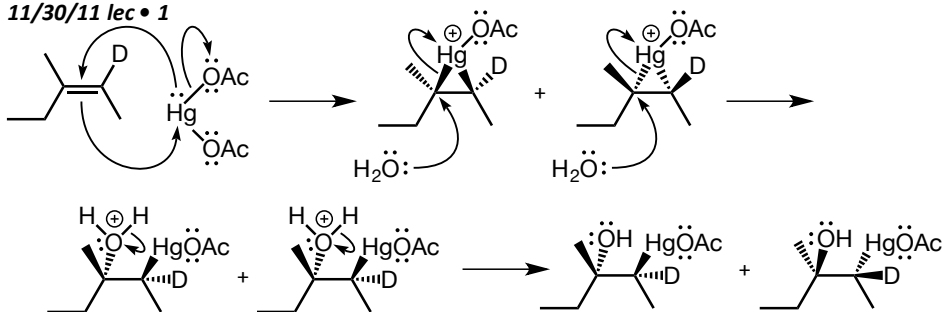
anti-Markovnikov add'n (substituent ends up on less substituted carbon)

hydroboration-oxidation

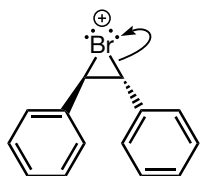
The rxn step appears to be anti-Markovnikov addition since the hydrogen (which normally is the electrophile) ends up at the more substituted position. However, hydrogen is more electronegative than boron, so boron is the electrophile, consequently, the boron ads to the less substituted position. Because of the cyclic transition state, no carbocation forms, so no rearrangement occurs.

Structures

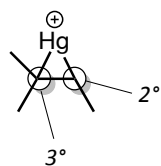
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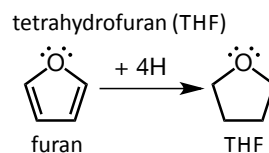
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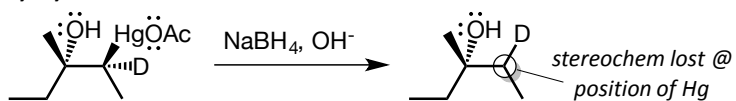
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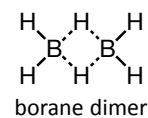
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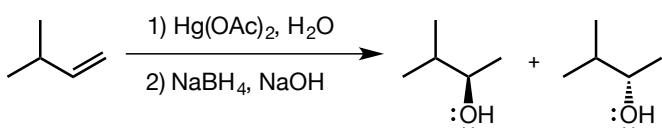
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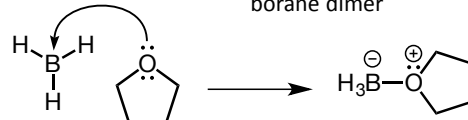
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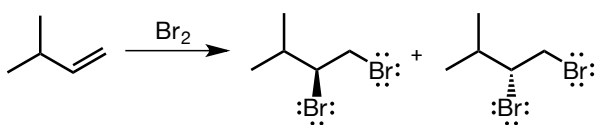
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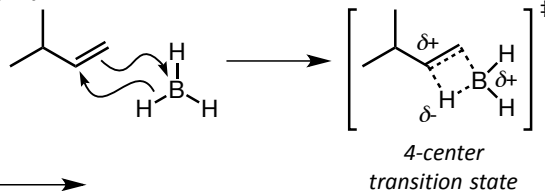
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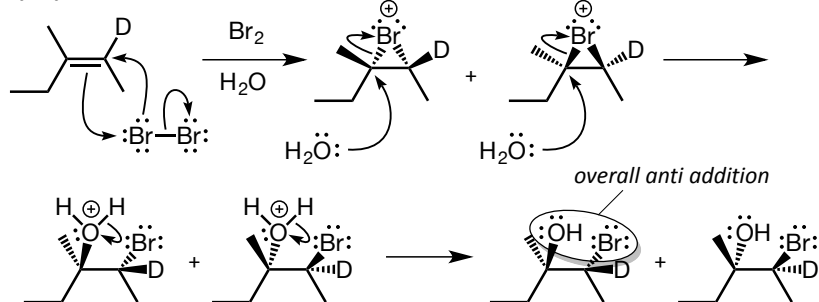
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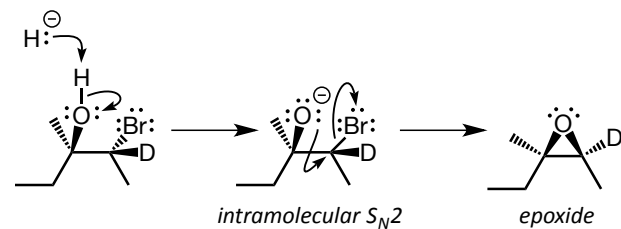
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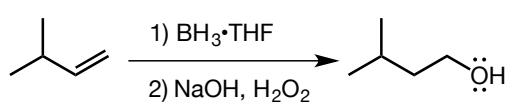
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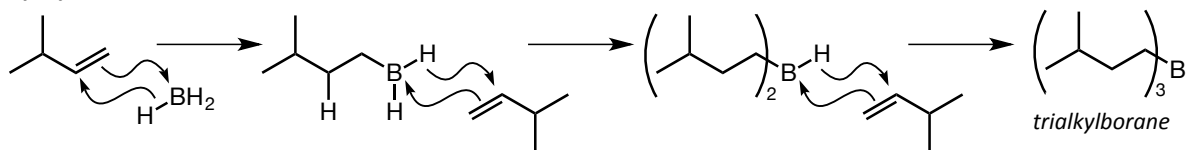
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