

Lecture 24B • 12/01/11

[I want to review simple electrophilic addition and addition through a cyclic intermediate] to compare the two reactions with one particular substrate. This substrate will demonstrate the difference between the two reactions. Why would you want to use one versus the other? Because if we did use an acid catalyst and water, we will get an alcohol from the first mechanism, but recall that in that simple electrophilic addition, we do have the formation of a carbocation, and because of that, carbocation migration is possible. The double bond would attack H^+ ; the carbocation initially forms at the secondary position, but then moves to the tertiary position before water attacks. Rearrangement occurs in this reaction, which, if you expect it to occur, if you wanted this product, then that's not a bad thing, but if you did want to place something specifically at the secondary position instead, that's why we have the oxymercuration-demercuration reaction.

In that oxymercuration-demercuration reaction, we do have the cyclic mercury intermediate that gets formed first. It's because it forms that intermediate, and when you don't have a carbocation, but instead have a mercurinium ion, you don't have rearrangement. In that cyclic structure that is formed, one of the two bonds is weaker than the other, and that ring opens according to which of the bonds is weak; that's the bond to the more substituted position. Water ends up attacking that intermediate at the secondary position. The follow-up reaction is to remove the mercury, using sodium borohydride. You can use an alcohol instead; that would put an ether at the position where the $-OH$ group is, so if you want specifically an alcohol, you do need to specify that water is present with that mercury reagent; otherwise, if you wanted to make an ether, then you have to show the appropriate alcohol.

There's a bromination reaction – not free radical halogenation, but Br_2 . I'll briefly review the mechanism here, because it matches, in fact, the mechanism for this oxymercuration-demercuration. Let's use the same starting alkene that I used the other day that is useful for illustrating stereochemistry. Let's say that I have bromine in some kind of non-reactive solvent, so it's the only reagent present. The first step of the reaction is similar to the mercury reaction, in that the bromine is going to bridge both of the carbons of the double bond. Just like that mercury reaction, there are different ways that you could write that process. The double bond attacks; you have a lone pair from the bromine that is attacked attacking back to make the ring at the same time that bromide is kicked off. You might recall that we had discussed that this reaction would want to occur because we end up reducing bromine in this way; you end up making Br^- . Of course, the double bond is flat, so the bromine can be attacked in front (from our perspective) of the double bond or behind, so we're going to get two different cyclic intermediates – very similar, again, to the mercury mechanism. I'll write the intermediates in the same way that I did for the mercury mechanism, where I'll show the main carbon chain in the plane of the paper, and therefore showing the bromine either coming out from or going into the plane of the paper; the other substituents are there[fore] pushed back or forward. This is a cyclobromonium ion; same type of terminology as that cyclomercurinium ion, just a fancy name for saying cyclic, positive-charged bromine.

In the same way, then, as the mercury reaction, we're not going to have carbocation rearrangement. The only time that that might happen, the only time that we might get other products, is specifically in a case like our lab that we performed. Here, because bromine's the only thing in solution, the ring is going to get kicked open by bromide itself, and, since this is a strained, charged intermediate, it's going to open in the same way, for the same reasons, that the mercury ion did – meaning that the bond between bromine and the tertiary position, the lefthand carbon, is weaker and longer than the bond to the righthand position, the secondary carbon, because were a positive charge to form on the carbon, it would be more favorable for it to do so on the tertiary, versus the secondary. Since it's more favorable to be on the tertiary, that means the bond breaks more easily, so, the ring is going to be kicked open at that position. Also, because the ring-opening is simultaneous, [we're] going to have inversion of stereochemistry at the position where the bromide attacks. So, bromide attacks, and we end up only with two products, which are enantiomers of each other.

Let's write the six aspects of the reaction. The utility is to convert an alkene into a vicinal dihalide. We can use these vicinal dihalides to make alkynes. The reagent, bromine, or it turns out that chlorine can do this reaction as well. Conditions – to avoid free radical halogenation, the reaction should be conducted in the absence of light, because otherwise bromine itself could break apart, beginning the radical reaction. As far as mechanism, because the most important feature of this mechanism – the forming of a cation – because that controls both the stereochemistry and the regiochemistry of the reaction, I'm going to classify it as cationic. In terms of stereochemistry, it's more controlled than just plain electrophilic addition, because we have specifically anti addition. Notice that in either of the products, the two halogens added are pointed opposite ways of each other, so anti stereochemistry. We'll form, potentially, enantiomers, if you have a double bond such as this one that would have two carbons that would become asymmetric. In terms of regiochemistry, this occurs as a Markovnikov addition, meaning that whatever substitutes last in the reaction does end up at the most substituted position, and because we form that cyclic intermediate, it does not have rearrangement.

Let me show you a very related reaction. We're going to make a small switch in reagents. Let's say that I have a molecule like this, same that we started out the day with, and let's say that I have reaction with bromine, but specifying specifically that water is there as well.

The mechanism would start out the same way: bromine is attacked by the alkene, forms the cyclobromonium ion; gonna form enantiomers in this case, because the secondary position is a stereocenter. But now, because we have water as a reagent – and, in fact, you would ensure that water is there in large proportion – water would now be the molecule that could come in and attack. Once the ring opens, we lose the stereocenter at the primary position – in fact, it wasn't even one to begin with – and we end up with water attached with inversion of configuration. We'll have a deprotonation step, because we did start with neutral water, and we end up with this compound that has neighboring halogen and alcohol functionalities – this is something known as a halohydrin, hydrin like something that contains water, halo meaning halogen.

Why are halohydrins useful? There is a base, sodium hydride, which acts as a source of H minus, which, because it doesn't have as good of an orbital overlap, instead of being nucleophilic, it tends just to be basic. If you through H minus at this molecule, instead of it trying to attack the bromide, it will instead pull of the hydrogen from the alcohol. This particular alcohol would have a pKa probably roughly of 17, so it is less acidic than water; the hydride is significantly basic. If you were to deprotonate, we would end up with an alkoxide that has a leaving group right next door that, because there's a single bond joining the bonds between them, they would be able to achieve an antiperiplanar geometry. Even if those two were both stereocenters, because the overall addition of the first reaction is to make an anti-configured product, again, those products would be able to achieve an antiperiplanar configuration. As such, you could have an intramolecular Sn2 reaction. You end up forming a functional group known as an epoxide, which is nothing more than a small, cyclic ether, but [a] very useful functional group.

All the same characteristics of this reaction are the same as what we just saw for plain bromine, the only thing different being the reagent used, cause now there's water. That means instead of just making the dihalide, we make the halohydrin.

Let's move to the third main class of mechanism. The first was plain electrophilic addition. There's a few variations of that – we saw HBr, for example, a plain haloacid being used; we saw an acid catalyst with water (there's no reason you couldn't use an acid catalyst with an alcohol). The second type of mechanism was this bromination and the mercurization. Third mechanism addresses this synthetic goal: that what if we did have an alkene that we somehow wanted to be able to convert into an alcohol, but having that alcohol at the least-substituted position. There is a radical mechanism that would allow this, but, there's a much more direct mechanism that's often used, and it involves the compound borane. This is one way to draw the structure of borane; [it's a] perfectly isolatable molecule. [If] you were to analyze its Lewis dot structure, we'd see that it has no formal charges, but it's an incredibly reactive molecule. If you were to pour it out into open atmosphere, it would instantly catch on fire, instantly react. Why do you think that is? What is there about borane's structure that makes it so reactive? It doesn't have an octet. It's still a neutral molecule, but it doesn't have an octet, so it is quite reactive. Beyond that, [boron] forms very unusual structures with other atoms, because it's so small, partly because it has this unusual ability to be neutral, even without an octet. [Borane is] often found in the form of a dimer. The word dimer means to take two equal molecules and just stick them together into a new structure. If you were to take several molecules and put them together, we'd call that an oligomer. If we take a whole bunch of molecules, it turns into a polymer – that's a polymer is, it's the same molecule linked to itself an endless number of times. Dimer means sticking just two of them together. It's been extensively studied, because if you look at the way that I've drawn this, you can see that I've got hydrogen bridging two different atoms. How is it possible that the hydrogen here – which really [normally] can only form one bond, one true bond in that only two electrons can be involved, but this appears to make it look as if one electron each is somehow associated with each boron. That is the nature of its unusual reactivity.

This is incredibly reactive. It's extraordinarily electrophilic – that's the point: it can be an electrophile in a reaction with an alkene. Plain borane itself, because it's so reactive and hazardous, is often shipped in some kind of solvent that complexes with borane. One of the most common solvents used for that purpose is THF, tetrahydrofuran. To understand where that term comes from, the five-ring compound with two double bonds and an oxygen is furan. If you add four hydrogens to it, you end up with a saturated structure that, with the four hydrogens – that where the word tetrahydro comes from. That will react with borane to form a complex. Notice that that ends up making boron negatively-charged, even though it has no lone pairs – again related to boron's unusual activity.

What is it that borane can do with alkenes? Part of the reason to show you the formation of this dimer and to show you some examples of borane's unusual reactivity is to set the groundwork for this unusual transition state that borane ends up forming. [Jones text] Let me show you that transition state, [then we'll discuss] why that's significant. The reaction that happens is that the alkene does attack boron, because boron is an electron. But at the same time, a hydrogen from the boron ends up attacking back onto the alkene. If both of those, then, are occurring simultaneously, then that means that this goes through an unusual four-centered transition state. Normally when you [write] mechanisms, you [don't] draw the transition state, but I'm drawing it in this case so we can discuss the regiochemistry that occurs. Look what's happen: the hydrogen, which in previous electrophilic reactions we've seen is now addition at the more-substituted position. Think about the very first electrophilic addition we did: we started out with HBr; hydrogen was attacked and ended up at the less substituted position, so that the carbocation ends up at the more-substituted position. How is it that, in this case, the hydrogen's adding to the more substituted position? It makes perfect sense if we take into account that boron is less electronegative than hydrogen. Hydrogen's got fairly low electronegativity, but boron, it turns out, is even lower. In this molecule borane, the delta negative lies on the hydrogen; the delta positive lies on the boron.

That would match previous reactions we've had, where the thing that's the electrophile, the thing that is more positive, does end up at the less-substituted position. Since hydrogen now is effectively a nucleophile in comparison, because it's got this delta negative on it, it's in fact going to induce a positive charge at the more substituted position, which is exactly what it would want to do. If we were to flip boron and hydrogen around, the hydrogen adding to the less-substituted position would effectively induce a partial positive charge on a carbon that doesn't, as much, want to have a positive charge.

Because boron is less electronegative than hydrogen, boron, not hydrogen, is the electrophile. Because of this, during this transition state, the hydrogen, which is effectively a nucleophile now, adds to the more substituted position, because the induced positive charge is more favorable at the more substituted position.

In some essence, this should be classified as Markovnikov addition, because that thing which is the more positive charge gets generated at the more substituted position. But, boron is what is going to be converted into the alcohol, so overall it has the appearance that the alcohol – the main structural component of this reaction – ends up at the less-substituted position, so overall this reaction is classified as anti-Markovnikov. The reason it's happening is the reactivity of hydrogen is reversed because it's attached to boron.

Let's now step back and see the full mechanism. Alkene attacks boron; alkene shifts back over to the alkene. We form an alkyl borane. But, if the boron-hydrogen bond was so reactive in the first place, we've got two more boron-hydrogen bonds: couldn't those react as well? The answer is: yes, they do. A second alkene can attack this alkylborane; another hydride shifts over. In shorthand terms, I can now write the product in this way: notice the way I've written the parentheses through the bond. What that's showing then is there's two bonds to boron, on the other side of which is this alkyl group. We have a third hydrogen that can now react, so the initial product formed is what is known as a trialkylborane. That's only the first half of the reaction. The [full] name for this reaction is hydroboration/oxidation, because the whole point of taking advantage of this reverse behavior of boron is there is a way to convert boron into an alcohol – which is a bit sneaky. Let's see how that occurs.

The reagents used in the second step are sodium hydroxide and hydrogen peroxide. The pKa of hydrogen peroxide is significantly lower than water; what that means is that the conjugate base of water is able to deprotonate hydrogen peroxide to make the hydrogen peroxide ion. When you see those set of reagents listed, you have two, so that we can form that ion. That ion is going to attack borane. Recognize that since the trialkylborane was neutral to begin with, that's going to end up forming a negative charge on the boron. It is the next step of this reaction that is the key step, but also the most confusing. The oxygen-oxygen bond, the peroxide bond, is a very, very weak bond. An oxygen-carbon bond would be much stronger. Also, a carbon-boron bond is not as favorable as an oxygen boron bond. Notice that we started with a neutral boron that we've now made an anion; what if the alkyl group attached to boron were to move over and kick hydroxide off. You might think: wait, hydroxide, that can't be a leaving group. Normally, no, but because overall we're going to end up forming a boron-oxygen bond in the place of a boron-carbon bond, and at the same time make a carbon-oxygen bond instead of an oxygen-oxygen bond, thermodynamically this ends up being favorable. Mechanistically, you could compare it just to a hydride shift; in fact, it's just an alkyl shift, but it's a very unusual one [that occurs due to this unique situation] of having a peroxide connected to a boron connected to a carbon.

What that produces is an alkoxyborane, but since this is still in the solution with the hydrogen peroxide and sodium hydroxide, it happens a second time. To save time, I'm going to shorthand it and say, two more times. You must show a total of three times, because that is the way that boron reacts; to only show it reacting once is not matching the way that this reaction proceeds. Two more times; we're going to end up with a trialkoxyborane, which is not done reacting. Now we have hydroxide that's still around in solution. Yes, there may be more peroxide, but now what hydroxide were to attack? Of course, you might say: why didn't hydroxide attack before? It could, but then it wouldn't do anything useful reactivity-wise. Now it can attack. Notice I'm going to do another rewriting of the structure [with parentheses], where I'll show one of the alkoxy groups separate from the other two. The reason I want to show that separated out is because, by hydroxide attacking the boron, we now made it negatively-charged, because of boron's unusual ability to be neutral, even if it didn't have an octet, it's possible for the hydroxide to pop right back off. It can hop on and off and on and off and on and off. But, if a hydroxide could pop back off, why not an alkoxide, because they're very comparable basicities, so every once in a while the alkoxide pops off. If that happens, you instantly, then, have a neutralization reaction that can occur, because the boron-oxygen-hydrogen system produces an oxygen-hydrogen bond that's acidic, because boron loves electrons. Notice what that means that you make: you now have your final product – the alcohol that, from the perspective of the alkene, was formed with anti-Markovnikov regiochemistry. One could argue that the transition should be predicted by Markovnikov, because the electrophile ends up at the less-substituted position, but this is called anti-Markovnikov because the structural feature of the molecule, the alcohol that's added, that itself ends up at the less-substituted position.

Of course, we still have this intermediate left over in solution. This reacts two more times in exactly the same way: hydroxide attacks; alkoxide can come off; that alkoxide turns right back, neutralizes a hydrogen. What we end up with at the end is three equivalents – the term equivalent means if you start out with one mole of material, you're going to end up with one more; if you start with one mole and end up with three, that's three equivalents – per borane of the alcohol produced, plus, eventually, we end up with the borate ion.

How would you write this out synthetically? I generally show this THF complex that usually borane is shipped in; you could write it $\text{BH}_3 \cdot \text{THF}$. Then, the second set of conditions is hydrogen peroxide and sodium hydroxide. The end product gives you anti-Markovnikov addition.

Let's go over the six aspects. The utility is to convert an alkene to an alcohol. The reagents: first, and separately, you have borane. Realize that if you tried to put borane and sodium hydroxide together at the start, all that would happen is borane would react with the hydroxide. Any time that you see 1s and 2s used when listing reagents, that explicitly means they must be used separately from each other, and that you must follow the order of addition shown by the numbers. If you don't have numbers, that explicitly means they are all reacting together. Whether you use the numbers or not is critical; every reaction you write, you must know whether you need to write the numbers or not. For simple electrophilic addition, even for bromination, everything occurred at the same time. For oxymercuration/demercuration and borane, these are the first two reactions you've seen that have the 1/2 in them. So, 1) borane \cdot THF; 2) hydrogen peroxide, hydroxide. Conditions: absolutely no water or other protic solvents whatsoever, cause borane would just simply react with them. Those solvents can have lone pairs; they'll complex with borane, just like THF, but that complex can't further react, and can further decompose; that's why borane still reacts shipped in THF.

As far as mechanism, this is a trickier one to classify, because we don't ever form even a carbocation; you go directly from the alkene to an alkyl borane. So how would I classify it? [dunno] As far as stereochemistry, that we need to do another reaction with, so let's go back one more time to our same asymmetric starting material. To simplify, I'll show the reaction only occurring once, and I won't write the mechanism. I'll just ask you to consider: would it be physically possible for a four-membered transition state, a square, to form in which one leg of that square is pointed the opposite way of another? No, physically you'd have to twist the square around in order to produce such a shape. The point of that, then, is that borane adds only to one face of the double bond or the other; it is physically impossible for it to add and have a hydrogen add on one side and boron, at the same time, flip around and attack from the other side. This occurs with syn addition. But, because the double bond is planar, we still have the possible formation of enantiomers. This stereochemistry is maintained during the rest of the reaction. If you look previously at the decomposition of the borane with hydrogen peroxide, the alkyl group simply shifts from boron to oxygen, but because it's just shifting, the stereocenter itself does not end up changing, so you have overall syn addition that occurs.

What about regiochemistry? Focusing on where the alcohol ended up, we therefore call this anti-Markovnikov. And, because we never even form a cation, we go straight from one set of reagents through the transition state to – not an intermediate, a compound that can be isolated; the trialkylborane, as long as you don't expose it to open atmosphere, can be bottled up, isolated. There are no rearrangements.

[preview of future reactions: hydrogenation, epoxides]

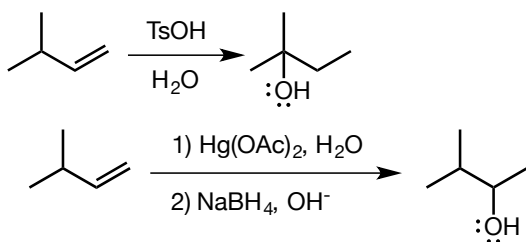
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- 1) utility: alkene \rightarrow vicinal dihalide
 - 2) reagents: Br_2 or Cl_2
 - 3) conditions: no light
 - 4) mechanism: cationic
 - 5) stereochemistry : anti additions; enantiomers
 - 6) regiochemistry : Markovnikov; no rearrangements

Because boron is less electronegative than hydrogen, boron (not H) is the electrophile. During the transition state, the hydrogen (which is effectively a nucleophile) adds to the more substituted position because the induced positive charge is more favorable @ the more substitute position.

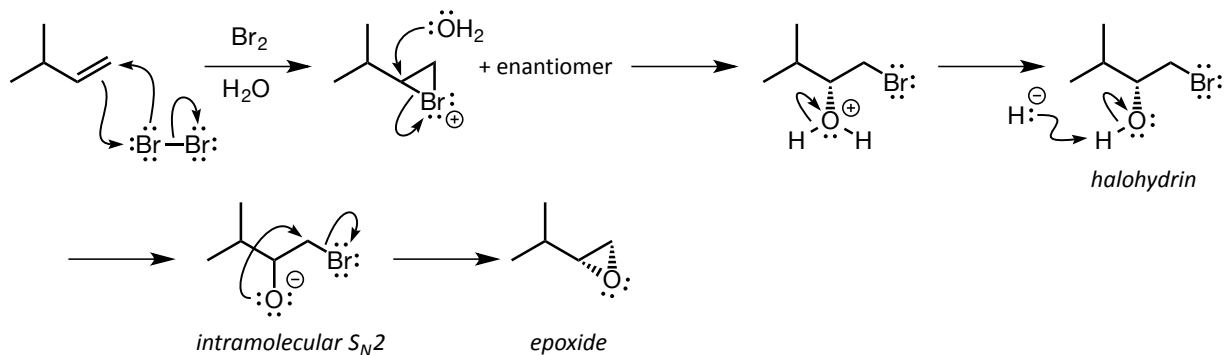
- 1) utility: alkene \rightarrow alcohol
- 2) reagents: 1) $\text{BH}_3 \cdot \text{THF}$ 2) H_2O_2 , OH^-
- 3) conditions: no H_2O !!!
- 4) mechanism: ?
- 5) stereochemistry: syn addition; enantiomers
- 6) regiochemistry: anti-Markovnikov; no rearrangements

Structures (remaining structures identical to lecture 24A and 25A)

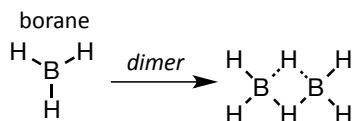
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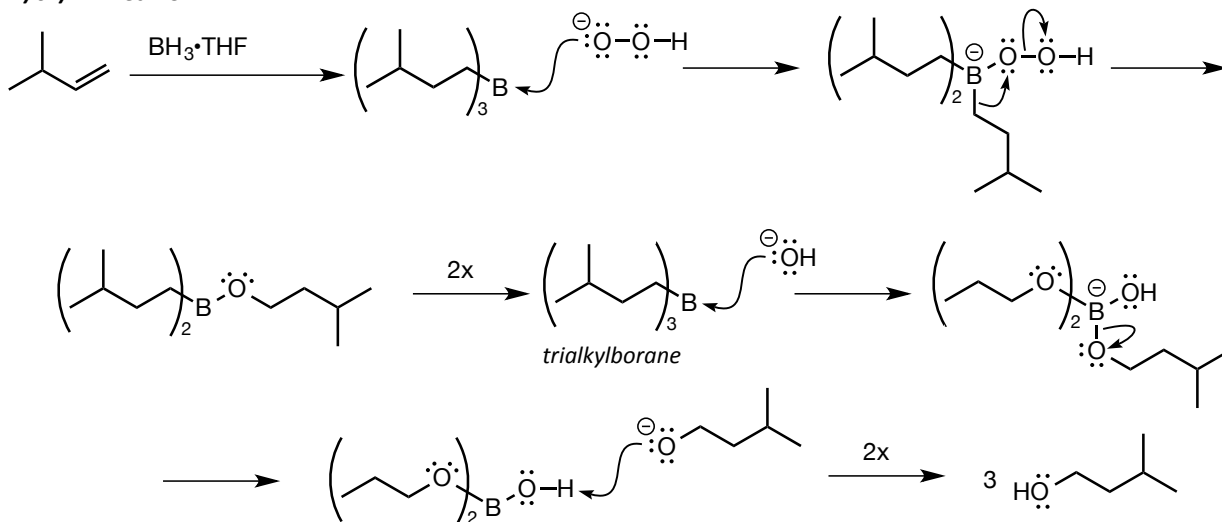
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