

## Lecture 27B • 12/08/11

[Answers to exam 3]

Question 1 – We had four different mechanisms, and you were supposed to write out the mechanism. You were also given some products, and you were supposed to figure out which of those products was going to be the major product formed, and you were supposed to use your mechanism to justify which of those major products formed.

First reaction was of an alkene with tosic acid and water. By far the most common mistake for this problem was treating the tosic acid as if it was the molecule that was going to add in as the electrophile. Remember that tosic acid we had used in the past as a strong acid catalyst. It's exactly that compound that I had said was an organic-soluble solid; it's very easily manipulable, it's very inexpensive, it's a strong acid, and the conjugate that you get from that acid is not at all nucleophilic. The only reaction's that going to occur here with the alkene is that alkene is going to attack the H+ of that acid. The tosylate that's then formed as a by-product does not participate in the reaction, cause it's not a nucleophile. Instead, it is the water that surrounds that's going to end up being the nucleophile, so this is simple electrophilic addition using water. First step in the mechanism would be for the double bond to attack H+. If, instead, you had [the double bond] attacking the tosic acid, you need to show the attack on the hydrogen, and then you need to show that hydrogen dissociating from tosic acid, since, unless it's a borane-like compound, you can't have more than one bond to hydrogen at a time. If I abbreviate using -OTs for tosylate, then the first step of the reaction would look like this.

By far, the most likely intermediate is going to be the carbocation that I've shown here, which is in fact is the reason that the product that we're going to end up with is going to be an alcohol where the alcohol is at this most substituted position. This is Markovnikov addition, and that carbocation is the most stabilized by hyperconjugation. It's extraordinarily unlikely in this case that you're going to form the secondary carbocation; that's exactly what the point of Markovnikov addition is. This is going to be the likely intermediate, which now will be attacked by water. Since it is a planar intermediate, then you could have attack from both faces of that carbocation, so you are going to end up with an enantiomeric mixture. I will show one of the possible products.

After water does attack, you're going to end up with an oxonium ion; that'll deprotonate. We end up with the alcohol plus its enantiomer. The first of the two products listed was the most likely of the products, and this is simple electrophilic addition.

The second mechanism: here we had a mesylate – a mesylate that was on a tertiary carbon. It reacted with sodium hydroxide and heat. This is an elimination reaction because we have a strong base with heat with a good leaving group on a tertiary position. Since we have a strong base, what form of elimination is this going to be? E2, bimolecular elimination, which means the base is involved at the same time that the leaving group leaves. It would be incorrect to show the leaving group coming off as its own individual step and then showing a hydrogen being removed afterwards. You have to show the removal of that hydrogen and the leaving of that leaving group at the same time. This is an elimination reaction, so if you showed the nucleophile coming in to attack the leaving group directly, that would be more like a substitution reaction. But in elimination, it's not the [mesylate] that's going to be attacked, it's one of the hydrogens next door. The most likely one in this case to be attacked is the hydrogen that is at the other tertiary center. Why? Because once we eliminate that hydrogen, we're going to form the alkene that has the most substituents on it; the more substituents we have on an alkene, the more hyperconjugation we have to stabilize that alkene. We had talked about the possibility of causing exactly that opposite behavior by causing a kinetic effect, but that would be using a bulky base like potassium t-butoxide. Since we just have this small base of sodium hydroxide, we're going to get regular thermodynamic elimination. Hydroxide attacks the hydrogen; the pair of electrons that had been in that bond collapse towards the leaving group; the leaving group leaves; and we end up with the first of the products listed. That one, again, would be the most likely product; this one has the most substitution. It is a tertiary substrate because the carbon the mesylate is attached to has three other carbons on it. The neighbor where the hydrogen's located, since there's three other carbons attached to that position, it's also tertiary. If we did use that bulky ion t-butoxide instead, it would be from the primary position here that elimination would most likely occur; that would be the kinetic product.

The next mechanism: here we start with a plain alkane, react it with chlorine and light to produce this series of monohalogenated products. It does turn out that the four different products shown are four valid products. Let's see which one is going to be the most likely of the products, though, and let's review the mechanism of the reaction. This reaction had three distinct components to it: initiation, where the chlorine itself gets dissociated by light; then, the chlorine radical ends up in a two-step process adding to the alkane, that's the propagation step; then there's a termination step that follows it.

Since this is a radical process, none of the arrows that you use should be the double-headed arrow that we use almost everywhere else; they should all be single-headed arrows. First step, is the dissociation of [the] chlorine-chlorine bond. After the formation of that chlorine radical, we're going to have a dissociation, and abstraction of a hydrogen.

Notice that there are three arrows in that part of the mechanism, because the chloride is going to attack the hydrogen, the hydrogen bond is going to break, but since this is a single-electron process, that one bond has two electrons, so you have to have two arrows coming from that one bond; there is also the electron coming from chlorine itself, so two of those arrows – one from the bond, one from chlorine – meet, and that ends up being the abstraction of hydrogen. The third arrow, that's falling back towards the alkane itself, so that's how you end up with the alkyl radical. That's the first of the two steps of the propagation.

Afterwards, the radical turns around and attacks another full molecule of chlorine. Yes, you could have an attack on a chloride radical, but that's not the propagation step; that's a termination step. The next step really, the one that happens more commonly, again involves three arrows, because the scission of that chlorine-chlorine and then the attack of the radical on one of those chlorines. That will give us one of the products. It'll regenerate the chlorine radical, [and then one of the forms of elimination will occur]. The simplest one, then, could just be for two chloride radicals to recombine.

This is, in fact, the most likely of the products, because although the tertiary center is more reactive, it does form the more substituted radical, the difference in reactivity between a primary, a secondary, a tertiary position is only 1:4:5. Since we only have one tertiary hydrogen, but we have two secondary hydrogens, the reactivity multiplied by the number of hydrogen means that this is going to be the more populous of the products. Tertiary, you would have had a relative population of five; the secondary has a relative population of 8; the one side where there's a primary, that would have a relative population of three; and then on the other side here, the two methyl groups are chemically equivalent, so that would be six, in terms of the number of hydrogens times 1 for the reactivity, so again, less populous than this product.

It's not unique necessarily to radical reactions, but it's one of the major features of this particular reaction. It's because, statistically, as that chlorine tries to react with a molecule, it's got all these different hydrogens to react with. Subtracting out that difference in reactivity, if you just think statistically, what's the likelihood that it's going to attack a certain position, it depends on how many hydrogens are attached to that position. So you take that number of hydrogens, then multiply it by its relative reactivity; combined, that tells you what product is more likely to form.

Let's go to the last of the mechanisms. This was cyclohexene reacting with bromine. A key difference between this reaction and what we saw previously was that light is not involved in this reaction. Unless light is specified, you cannot say that light is there. Since you just had plain bromine, that means you're going to have an electrophilic addition; specifically, this is going to be the formation of a vicinal dihalide. The first step of the reaction is attack on bromine. We're back to using regular double-headed arrows because this is an ionic or electron-pair mechanism. Because we again have a planar species that's getting attacked, we have the possibility of forming enantiomers. This is [a] cyclobromonium ion. This is the key part of the mechanism that explains what is the most likely product. You had two products that were shown: one where you had the bromines cis to each other on the ring, one where the product was trans. Only the trans one is going to form, because the ring does not open until it is attacked by the incoming bromine, so the attack only occurs from the opposite side, which means you're only going to get inversion of configuration. You'll also get its enantiomer. Because of that cyclic intermediate, that's why the stereochemistry of the reaction is controlled. It's also key that you show that opening of the ring is simultaneous with the attack of the bromide, because that's the whole thing that controls the stereochemistry of the reaction.

If you had it trans, you would have the ability for both substituents to be equatorial, so that would be lower in energy than having one of the substituents, so cis would actually be the less thermodynamically favored product – which you can't even form because the mechanism won't allow it.

Let's move to the set of eliminations. You had four molecules that you were shown, and you were told to explain why bimolecular elimination does not occur for these four different molecules. Let's look at the first one. In this particular case, on one of the carbons neighboring, there aren't any hydrogens to be able to be eliminated, so you're not going to get elimination in that direction. On the other neighbor, that's a bridgehead carbon – a carbon that's at the junction of multiple fused rings. He had discussed Bredt's rule, which says that because it is not possible to end up with planar geometry at that position, that's why elimination cannot occur to bridgehead carbons – unless the ring is sufficiently large in size.

For the second one, exactly the question of whether you can end up with antiperiplanar or synperiplanar geometry between the hydrogen being eliminated and the bromide. In this case, I've shown the methyl group being trans to bromine, which means, implicitly, the hydrogen is instead cis to the bromine. On the top of the ring, where the two methyl groups are, you again have a situation where you have no hydrogens. Here, the hydrogen can't be syn- or antiperiplanar, which is why no elimination can occur from that position.

The next problem: the one and only reason that elimination cannot occur is that there are no hydrogens in correct position. Bimolecular elimination [occurs when a strong base is present], so there's never a carbocation formed in E2 elimination, so you don't worry about the fact that the leaving group is as at a primary position; the only thing that you have to worry about is whether there are hydrogens available or not. Yes, there's two hydrogens on the same position as the bromine, but those are not the hydrogens that end up being removed in elimination; it is the hydrogens one position away that would be removed.

That's why elimination is not possible in this compound. Let me draw in those two hydrogens. These are geminal hydrogens, they're on the same carbon, and relative to the bromine, they're ipso, they're on the same position as the bromine. [carbene formation] If we're talking about elimination to form a double bond, we have to have a hydrogen that comes from the carbon next door to the position where the bromine is. By that hydrogen being removed, a pair of electrons then collapses to kick out that leaving group. Again, you have hydrogens here, but they won't be the ones that react in elimination. Over here where we do have a position that can eliminate, there aren't any hydrogens there.

The last molecule: hydroxide is not a leaving group. It is, in fact, the conjugate base of a weak acid; conjugates of weak acids are themselves basic, which would make it a terrible leaving group. There are ways to convert that alcohol, but there's no way to directly use it in E2.

#### Fill-in-the-blank problems

First one: starting with a blank, reacting with this nucleophile to form a sulfide. If you examine that product, we can see that this is a primary substrate; don't let the deuterium fool you, that's just a form of hydrogen. It's at a primary position, and you were told that all the reactions in this problem were possible. Backing up, if we look at the nucleophile, that is a strong nucleophile, because it is charged, it's not neutral, and you have sulfur as the focal point of the nucleophile instead of oxygen. Sulfur nucleophiles are much more nucleophilic than oxygen nucleophiles, due to polarizability. With a strong nucleophile on a primary position, what kind of reaction had to have happened? S<sub>N</sub>2. Again, that's because of the strong nucleophile and primary substrate. That means that the reaction had occurred with inversion, so if you're backing up to predict what the starting material had to be, one we're going to need a good leaving group, because in an S<sub>N</sub>2, S<sub>N</sub>1, E1, or E2 reaction, you need a leaving group. Aside from that you have to invert the stereochemistry at that position because the reaction itself had happened with inversion of stereochemistry. [I'm showing] bromide as the leaving group, with the deuterium shown with inversion of configuration. Whenever you have the deprotonated version [of a nucleophile], that makes it a strong nucleophile; whenever you have the neutral version, that makes it a weak nucleophile. On the basis of the fact that it was ionic, that's how you were expected to predict that it was strong.

Next one: here you had the substrate reacting with something in order to make a secondary alcohol. This was some form of hydration reaction, of which you have learned three: simple electrophilic addition, oxymercuration-demercuration, and hydroboration-oxidation. Hydroboration-oxidation is an anti-Markovnikov process; that would put the alcohol at the end of that ethyl group, which is not what we want. That means it has to be either regular hydration or it has to be oxymercuration-demercuration. It cannot be regular, simple electrophilic addition, because the carbocation that originally formed would be at a secondary position, which would then would have a hydride shift to the tertiary position, so this exactly why we have the oxymercuration-demercuration reaction because its mechanism does not allow for carbocation migration. The only correct answer here was first mercury acetate and water, followed by sodium borohydride. The reason that sodium hydroxide is used is because if you have a basic solution, it slows the decomposition of sodium borohydride. If you wanted to make the tertiary product, tosic acid and water [would be the appropriate set of reagents].

Next problem: you're given both the substrate and the reagents – that was MCPBA. That is a reagent used to form epoxides. Since you do have a stereocenter that's formed during epoxidation, you do need to show both of the products – that there are enantiomers formed.

Next group of three: we're back to having an absent starting material. We do have potassium t-butoxide as a base; we see an alkene as a product, so we can predict that this is an E2 reaction. In this elimination reaction, it means we're going to have to have some kind of leaving group. There's a couple of different positions that we might posit it should be: two [of the most common answers are shown here]. Theoretically, both of them could end up giving the product indicated – except that this is a bulky base. The bulky base ends up favoring the less substituted alkene. That means that this second substrate, if I tried to react it under the same conditions, I'm going to get a terminal alkene instead. The correct answer was the first one I've drawn here; if you put the leaving group at that position, there is only one elimination possible. [should have shown appropriate stereochemistry] It causes it to be less likely to remove a tertiary versus secondary versus primary hydrogen, due to kinetic reasons, the steric factor. It's exactly because of the steric hinderance of the base itself that it has an easier time getting to a primary hydrogen versus tertiary. That's why you have reverse reactivity, particularly at low temperatures.

Moving into the next one: starting out with just an alkene to form an alkyl halide. There is only one reaction we have learned that can possibly do that: that's using bromine with UV light. HBr, there is no alkene for the hydrogen to be attacked by. Br<sub>2</sub> without light, again, there's no double bond to be able to react. The only thing that can force a plain alkane to react is some form of radical species. The only correct answer would have been bromine and light. Since there were no hydrogens other than the hydrogens on the methyl groups, there was only one monohalogenated product possible.

Next reaction: cis alkene reacting with D<sub>2</sub> and platinum. Remember that this is a syn addition because the alkene adds from one face down onto the metal, the platinum catalyst, where the deuterium's already been adsorbed, so the two deuteria, if you write the structure in this orientation, are either both going to be wedges, so they're both pointed towards you, or both going to be dashes, both pointed away from you. If you show dashes and wedges, you've gotta remember to put hydrogens in if they're really supposed to be hydrogens there, cause if you just write a wedge or a dash and you don't show anything else, that's a methyl group. The correct answers were these. If you wanted to show the hydrogens by showing the other dashes and wedges, you had to write the hydrogens in.

Last three reactions. Something reacting with borane•THF complex, followed by hydroden peroxide and sodium hydroxide to make a secondary alcohol. You need an alkene, because that's what borane reacts with. I'll throw two of the most common answers up: one in which the alkene is terminal, and one in which it's internal, connected to the ring. It is, in fact, that second structure that's correct, because hydroboration is going to put the alcohol at the less-substituted position. If we had used the first of the two starting materials I've shown, you'd end up with the alcohol at the end of the molecule, which is not what we want. So, I had to use the internal alkene in order to be able to get the alcohol to the less-substituted position.

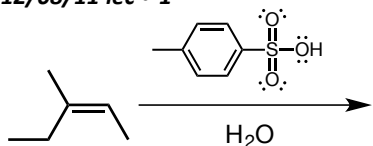
Two more. We have an allyl system, an allyl bromide that reacts with something to form an allyl ether. Since we have a tertiary substrate, where we don't form an alkene, that means S<sub>N</sub>1, cause no S<sub>N</sub>2 possible on a tertiary substrate. Since it's S<sub>N</sub>1, that means the reaction could only happen with a weak nucleophile. To get the right number of carbons, that means the only nucleophile possible was ethanol. You could not use and form of charged nucleophile, because that would have been basic and would have caused elimination instead.

Last reaction: some kind of alkene reacting with bromine and water. That is for the formation of a halohydrin. What you're going to end up with is bromine on the less substituted position, because it was originally the electrophile, and the alcohol on the more substituted position. In this case, you didn't need to show stereochemistry, cause there's no stereocenters. [No epoxide is formed because] there's no sodium hydride or any other base to cause the closure of the ring after the formation of the halohydrin.

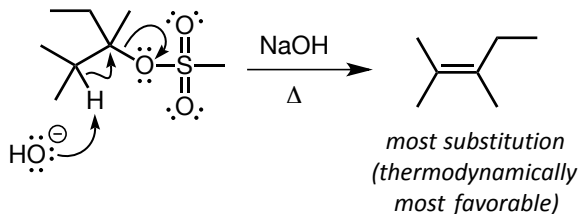
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Structures

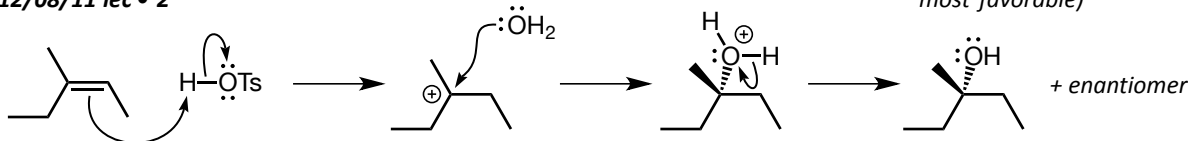
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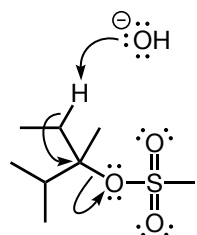
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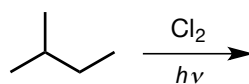
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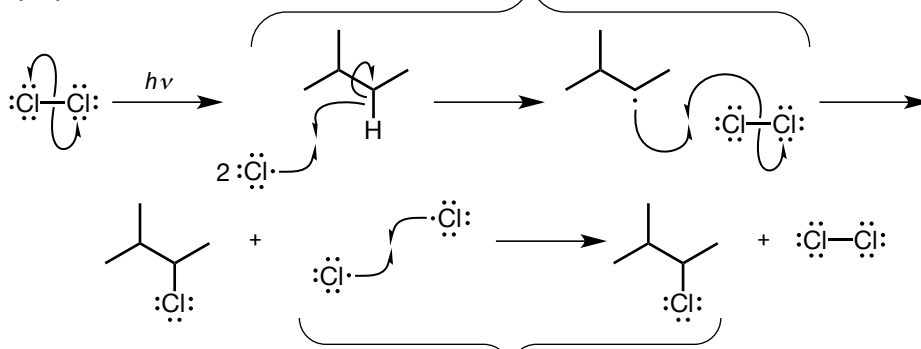
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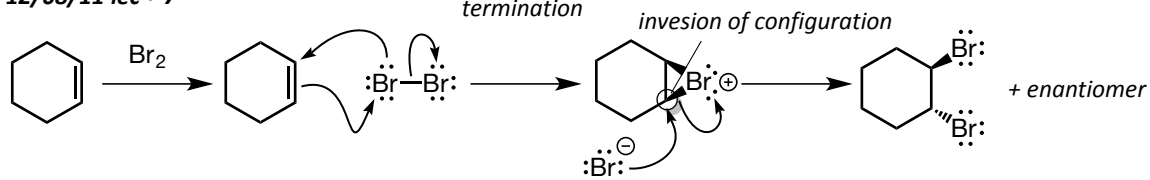
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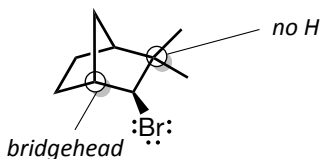
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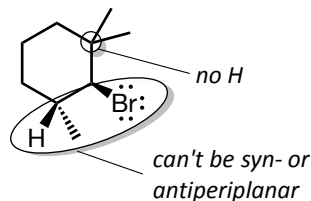
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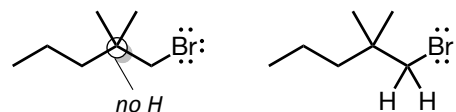
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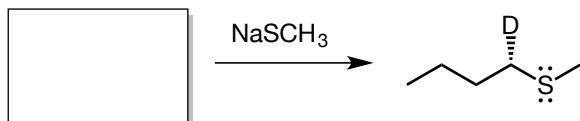
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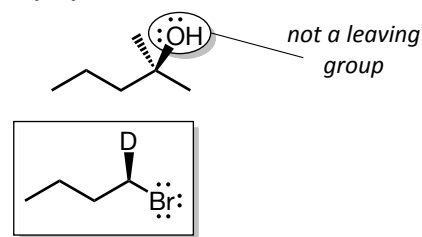
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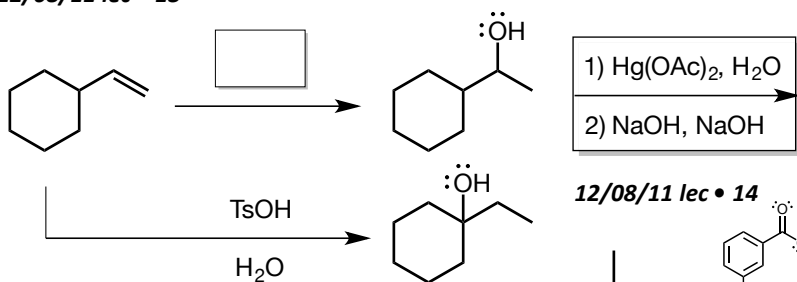


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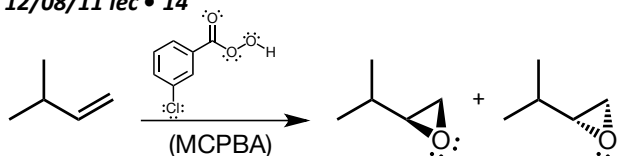


$S_N2 \rightarrow$  strong nucleophile (ionic, S),  $1^\circ$  substrate  $\rightarrow$  inversion

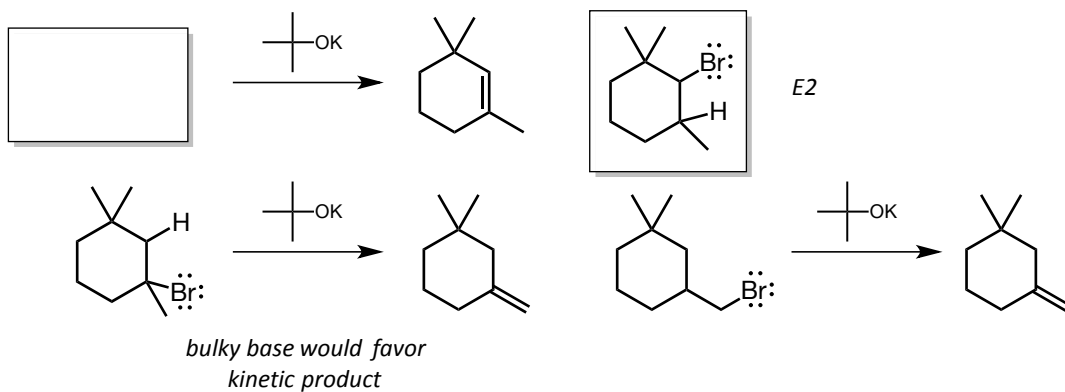
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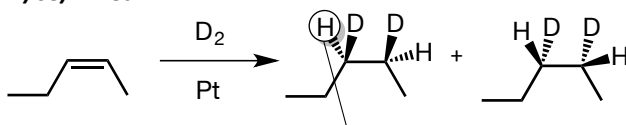
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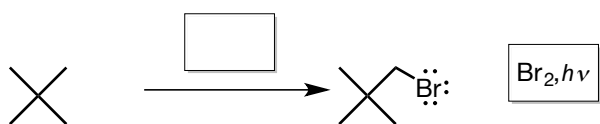


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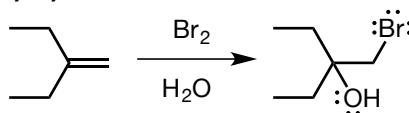


*must write H if using wedge or dash (otherwise it's a methyl)*

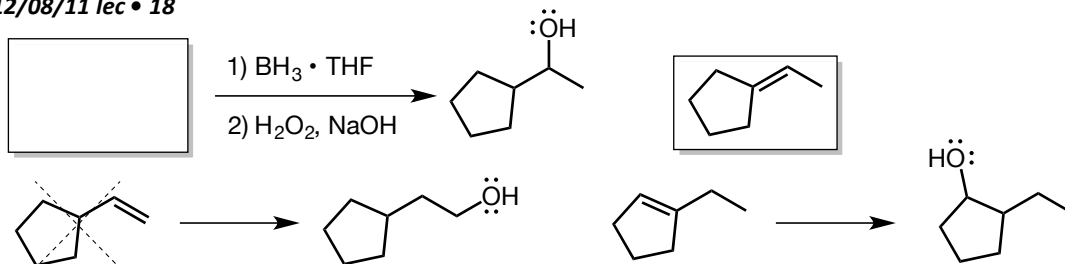
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