Lecture 4A • 01/25/12

Continuing with epoxides and ethers

We learned how to synthesize epoxides. Hopefully everyone is now familiar with MCPBA as the main peroxyacid agent that can convert an alkene directly to an epoxide, then we have the 1/2 step of doing bromine in water and sodium hydride as a way of making first a halohydrin then doing an intramolecular Sn2 in order to form an epoxide. We saw two different sets of conditions for opening the epoxide. The behavior is opposite in those two cases. We had acidic conditions that cause the ring to open up one direction, and we had basic conditions that cause the ring to open up in the other direction. Let's review these two different cases. I'm going to simplify reality a little bit, since it turns out that if you have a primary position versus a secondary position on an epoxide, there can be some complicate behavior that occurs. I'm going simply and say let's just worry about primary versus [tertiary] positions.

Under acidic conditions, what thing or things [for synthesis] do I need to have? What are the reagents for cationic ring opening? You need an acid source; I'm going to use our common acid catalyst tosic acid. What else? Water, or an alcohol. If it was water, you're going to end up with a diol; if you use an alcohol, you're going to end up with an alcohol and an ether next to each other. What is the regiochemistry of this reaction going to be? Where is the –OH group going to end up? At the tertiary position or the primary position? Primary. Why is that? The intermediate in this reaction is an oxonium ion. You have two different bonds that can break. If this was an Sn1 style mechanism, what would happen next is one of the carbon-oxygen bonds would break, you'd form a carbocation. The carbocation could then be attacked. What is the evidence, then, that this is not the way the reaction occurs? It turns out you're going to have overall anti addition to the alkene; if you have an alkene, turn it into an epoxide, and then open the epoxide, you're going to end up with anti addition, which means that whatever attacked the ring was coming from the opposite direction from where the ring was. If this tertiary carbon ever did form a carbocation, then you would expect to have attack from both the top and the bottom, which is not what occurs. SInce that's not what occurs, that's the evidence that you do have a simultaneous attack on that ring. Why is it that it's that particular bond that opens, though; even if it's concerted, why is it that one? Because it's not a equal three-sided triangle like this drawing deceptively makes it out to be. That's because the bond to that tertiary center is weaker, because if it were to break, the positive charge that would form there would be more favorable. One way we could think about it is potential energy. There's a difference in potential energy of those two bonds. One can more easily break than the other, because the intermediate that you end up with is more stable for one than the other. If a carbocation formed, the carbocation could be attacked from two sides, potentially forming two products. Only product forms, so the ring does not open independent of the attack of the nucleophile. This is the cationic case. Notice that the ether is at the more substituted position.

Let's quickly review the anionic case. I want to show you an addition reagent that can undergo this anionic mechanism; [previously] we saw an alkoxide being used. How would I write the reagents that would be needed in an anionic reaction? Not an alcohol, because an alcohol is not a strong enough nucleophile. How could we make an alcohol stronger; what could we use instead? An alkoxide. So we use NaOR, so take an alcohol and deprotonate it. Notice I put a one there; why, what's the two? Acid. Instead of showing tosic acid, you could show H+. But, have to be careful in real life about what acids you use. For example, if you use something like nitric acid, nitric acid under the right conditions is an oxidizing agent. You might not want to oxidize the alcohol that results here. If you had hydrochloric acid, under the wrong conditions, hydrochloride can react with an alcohol to make an alkyl halide. H+, you could use hydrochloric or sulfuric acid if it's in really really dilute proportions, so you just barely neutralize the solution. If you have a super strong base, you could even through baking soda at it. Tosic acid could work but i wouldn't be the best choice in this case cause it is a bit pricey to be used as a neutralization agent. This isn't just a catalyst in this case, you're actually going to be quenching the reaction, so I would say not TsOH in this case. In this case, where's the ether going to end up, the more substituted or the less substituted position? Now the ether is going to end up at the less substituted position, which is because of sterics. That means that this really acts like an Sn2-style mechanism, which is a concerted mechanism.

[There are two other reagents that can open the epoxide ring.] One [is] lithium aluminum hydride. We're going to write the mechanism by just showing it attacking. The aluminum or boron in lithium aluminum hydride and sodium borohydride can complex with oxygen; that complexation can assist the attack of hydride. We can't use sodium hydride in these reductions because it doesn't work quite the same way. The hydride attacks the less substituted position, pushes the ring open. Notice that, synthetically, I wrote two steps, because [if] you use something super duper basic like sodium hydride or lithium aluminum hydride, you're going to end up with an alkoxide as a product; there is therefore a secondary step where protonation occurs. Notice that we effectively turned an epoxide into just an alcohol.

There's another reagent that works. An alkyne proton is more acidic than an alkene is more acidic than an alkane, due to the hybridization of the anion that results. This thing is still pretty darn basic, isn't it. The average pKa of an alkyne is 25; the average pKa of an alcohol is 16. If we had an acid that was pKa 25 versus an acid that was pKa 16, if we could have one or the other as a conjugate, what situation would we have? If we had an alcohol with an alkyne, the alkyne is going to be able to deprotonate the alcohol.

What I'm really getting at is that this thing is more basic than an alkoxide, and if it's more basic than an alkoxide, why can't it do the same reaction as above? Be careful drawing triple bonds. It is so frequent that people leave carbons out because of misinterpreting how to draw the triple bond. Either side of the triple bond is its own carbon. Notice that I had to draw a line to the triple bond to the position where the epoxide used to be attached, because if I didn't, that means I just lost a carbon. You would have weakly diluted H+ protonate that oxygen. This is called an acetylide ion. Whether you use an acetylide or lithium aluminum hydride or an alkoxide, they're all the same mechanism.

Imagine that you had the case of a double bond. If you had a double bond on the compound and you threw strong H+ on it, the double bond's going to react. If you want to make sure you put barely enough acid in to get that into an alcohol, that's a different procedure than if you want to make the double bond react.
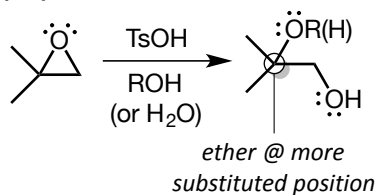
Let's say we had the following: propane. [mention of King of the Hill] Propane, is it a reactable molecule? No. But, [we did learn one reaction], radical halogenation, that could take that and, because bromine is so much more selective than chlorine, we could end up largely with this alkyl halide. Can I turn that alkyl halide into an alkyne? Not directly, but what functional group could be converted into an alkyne? We need a vicinal dihalide. Where can we get that from? An alkene. Where could we get an alkene from? By using t-butoxide; that gets us to the propene, which we can then react with bromine without water to get our vicinal dihalide, which we then react with two equivalents of sodium amide to make the alkyne. What if we did a divergent synthesis? We take the alkene from up above and, in a separate pot, react it with MCPBA, which will make an epoxide. We'll take the alkyne, use one more equivalent of sodium amide to deprotonate it to make an acetylide in. You can then throw both of these molecules together to make this alkoxide, with just a little H+ that we could turn into this molecule. Look at where we came from: propane; look at what we ended up with, an ynol.
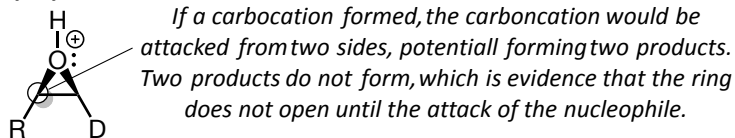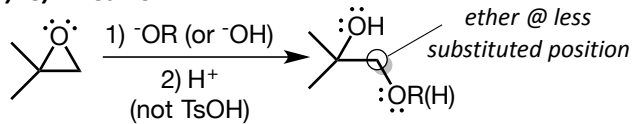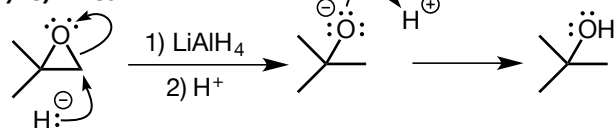
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Cationic

Anionic

————

Structures

01/25/12 lec • 1

TsOH
ROH
(or H₂O)

ether @ more
substituted position

01/25/12 lec • 2

If a carbocation formed, the carboncation would be attacked from two sides, potentiall forming two products. Two products do not form, which is evidence that the ring does not open until the attack of the nucleophile.

01/25/12 lec • 3

1) ⁻OR (or ⁻OH)
2) H⁺
(not TsOH)

ether @ less
substituted position

01/25/12 lec • 4

1) LiAlH₄
2) H⁺

01/25/12 lec • 5

acetylide

careful how
structures with triple
bonds are written

01/25/12 lec • 6

divergent synthesis

Br₂
hν

MCPBA

convergent synthesis

Br₂

2 NaNH₂

NaNH₂

H⁺
(dilute)

Lindlar's
H₂ (g)