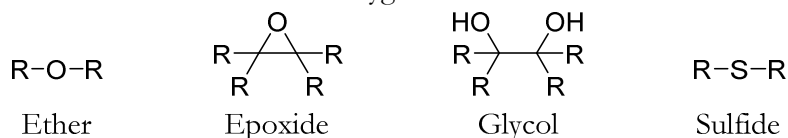


Loudon Chapter 11 Review: Ethers & Epoxides

Jacque Richardson, CU Boulder – Last updated 4/28/2016

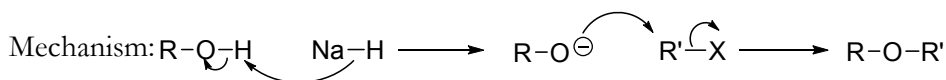
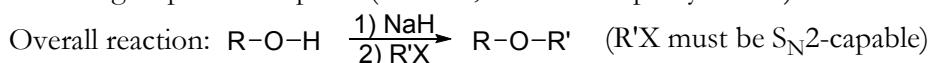
This chapter covers four different functional groups: ethers, epoxides, glycols, and sulfides. Ethers have a central oxygen with an R group to either side of it. Epoxides are a special kind of ether, where the R groups are linked together in a three-membered ring. Because they're strained, epoxides are a lot more reactive than regular ethers. Glycols, a.k.a. vicinal diols, are a type of alcohol that has two OH groups on adjacent carbons. Sulfides are similar to ethers, but they have a sulfur atom instead of an oxygen.



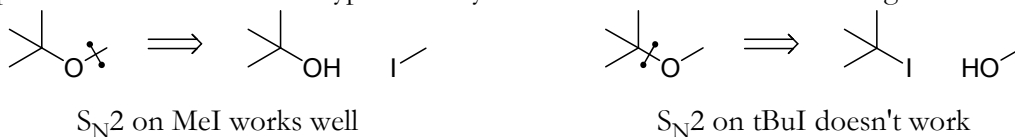
Synthesis of Ethers

Most of these methods are based on reactions we already know.

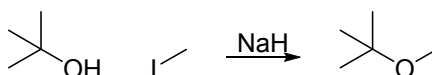
1. Williamson Ether Synthesis: this is based on getting the molecule set up for an S_N2 reaction, starting with an alcohol and an alkyl halide. You convert the alcohol into a strong base/good nucleophile first by deprotonating it with a stronger base, usually sodium hydride or just sodium metal. This is usually the best choice for making ethers, as long as one R group is S_N2 -capable (1° or 2° , with no neopentyl issues).



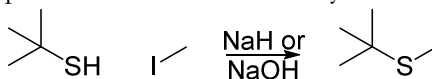
So, for example, if you want to make this molecule, there are two different potential options. The O atom could hypothetically start out on the left half or the right half.



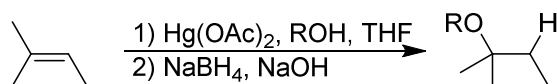
Overall reaction:



You can also use a similar reaction to make sulfides. You don't need such strong base to deprotonate the thiol group – NaOH will work – but you are still limited by S_N2 .



2. Alkoxymercuration-reduction: this is very similar to oxymercuration-reduction, only you bring in an alcohol instead of water.

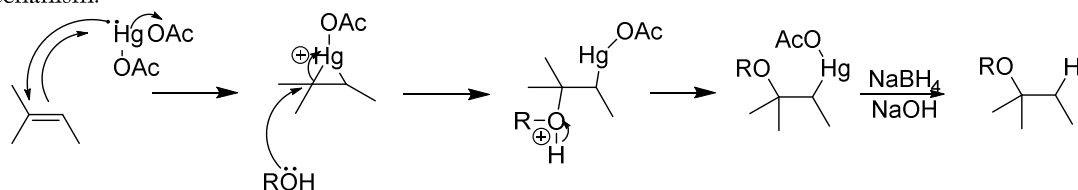


The mechanism is exactly what we saw for oxymercuration-reduction, only it uses ROH instead of H_2O .

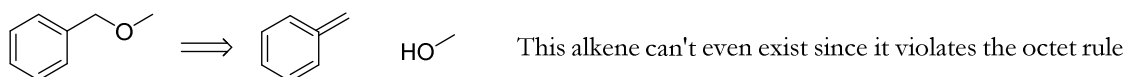
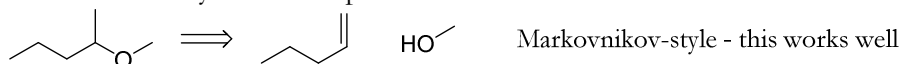
Loudon Chapter 11 Review: Ethers & Epoxides

Jacque Richardson, CU Boulder – Last updated 4/28/2016

Mechanism:

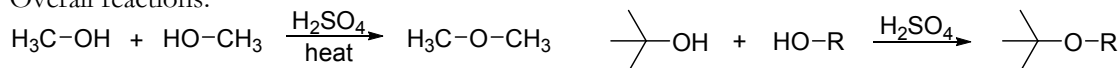


This reaction is limited by the fact that one side has to start out as an alkene that has Markovnikov-style addition performed on it.

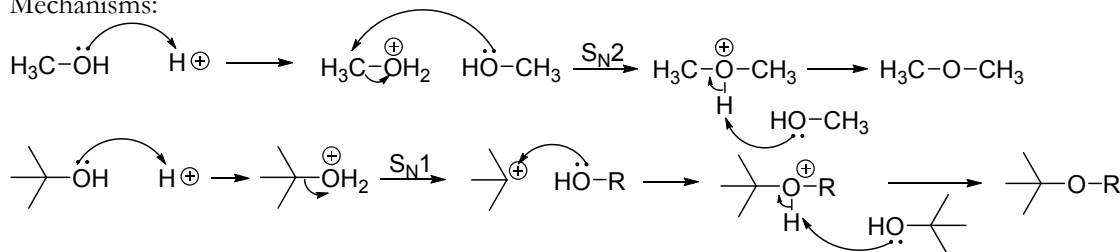


3. Alcohol Dehydration: this starts by protonating the alcohol, like in chapter 10, which allows another molecule of alcohol to do either S_N1 or S_N2 on it, depending on substrate. This works best for joining together two molecules of a primary alcohol (goes by S_N2), or a tertiary with any other kind of alcohol (goes by S_N1).

Overall reactions:

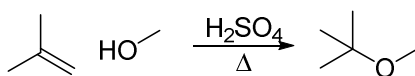


Mechanisms:



This reaction is limited by the need to avoid using alcohols that will rearrange if they form a carbocation. There also can't be any other acid-sensitive groups like alkenes attached to the molecule because they'll react as well.

Note that these conditions (ROH + acid) are the same conditions we used to perform dehydration of alcohols in Ch. 10. Again, we can take advantage of Le Chatelier's Principle by using a high concentration of alcohol, keeping the temperature relatively low and forcing the alkene to stay in the reaction mixture, rather than distilling it out. We could also just start with the alkene instead: (this looks like acid-catalyzed hydration of alkenes):



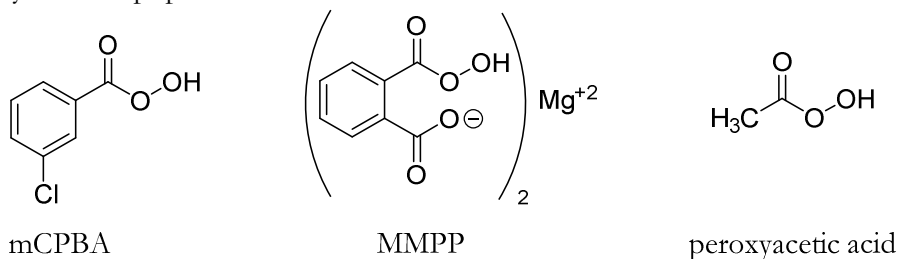
Synthesis of Epoxides

There are two ways to do this.

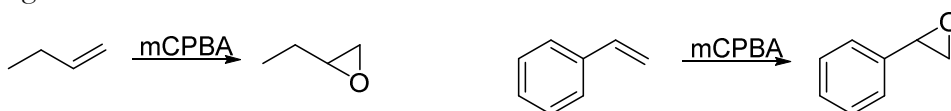
Loudon Chapter 11 Review: Ethers & Epoxides

Jacque Richardson, CU Boulder – Last updated 4/28/2016

- With peroxyacids. Usually it'll be either mCPBA or MMPP, but peroxyacetic acid is an older reagent that also works. mCPBA and MMPP are both convenient, crystalline solids so they're more popular.

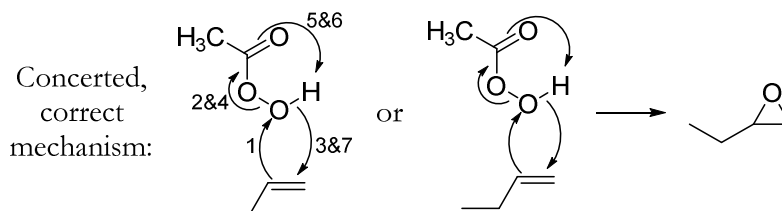
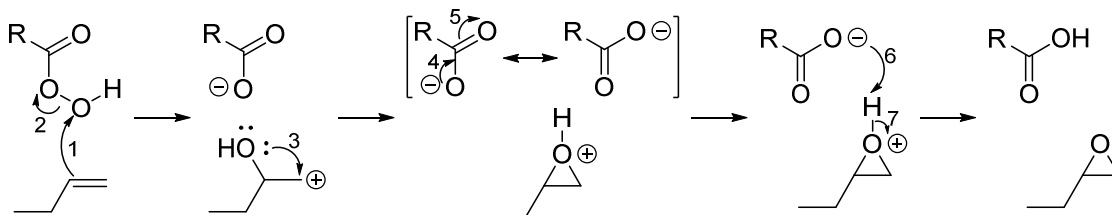


Whichever one you use, it's normally the only thing you need to write on the arrow. The starting material is an alkene.



The mechanism is concerted and happens as a single step, but to understand why things happen the way they do it's helpful to break it into hypothetical steps that look like things we've seen before. To begin with, the alkene attacks the oxygen with a leaving group on it (1), which then leaves (2). However, this would create a carbocation, so the lone pairs on oxygen back-attack to close the ring (3), just like in bromonium ring formation. Meanwhile, the leaving group has two different resonance forms, interconverted by arrows (4) and (5). The negative charge on one of these forms can pick off the extra proton on the epoxide by (6) and (7), creating the neutral product. Once you put all these steps together, you get a mechanism with four arrows. (Some arrows combine: if you have an arrow going to an atom, and another atom going away from it, you can combine them to a single arrow that hops over the atom so long as the steps are all concerted and happening at once.)

Individual parts of mechanism (THESE DON'T ACTUALLY HAPPEN)



Note: can be combined to

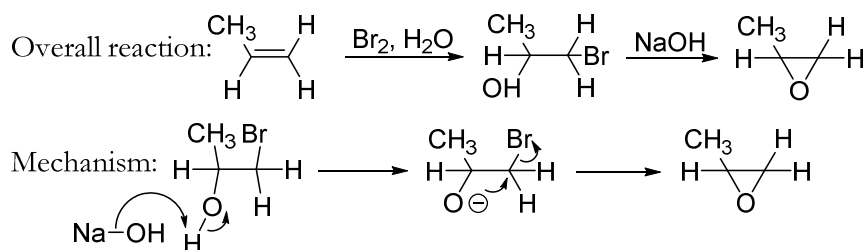
Loudon Chapter 11 Review: Ethers & Epoxides

Jacque Richardson, CU Boulder – Last updated 4/28/2016

We know this mechanism is concerted because no carbocation rearrangements are observed, and because it's always a syn addition. If it were stepwise, part of the molecule would have time to rotate around and scramble the stereochemistry.



2. From a halohydrin. We learned how to make halohydrins from alkenes in Ch.5, and now we can put them to use. The reaction goes by an intramolecular S_N2 , so it's a lot like Williamson but within the same molecule. Since the alkyl halide is right there and readily available, you can get away with using a weaker base such as NaOH, although NaH will still work too. This is due to the **proximity effect** – it's much easier for the alkoxide to react with the alkyl halide when they're already tethered together as part of the same molecule, because they're a lot more likely to run into each other than two separate molecules are.



Since this is S_N2 , we have the usual limitations – stereochemistry needs to be unhindered (no 3° or neopentyl) and backside attack needs to be possible. This means that in a cyclohexane ring, both the OH and the Br need to be axial for this to work.

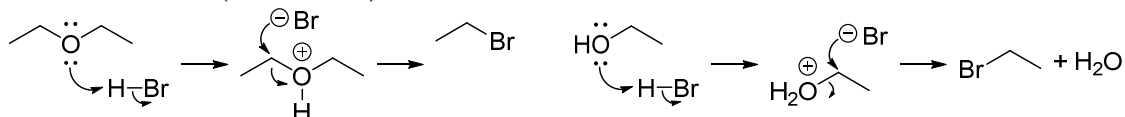


Reactions of ethers

Like the OH group of alcohols, OR is a bad leaving group. You need to turn it into a good leaving group, and the only way to do it is with protonation. So you need a strong acid of some kind.



Then, depending on substrate, you can do either S_N1 or S_N2 with whatever halogen is the conjugate base. This temporarily makes an alkyl halide and an alcohol, but under these conditions, the alcohol will immediately turn into another alkyl halide. This example is showing S_N2 on both halves, but each half will choose S_N1 or S_N2 depending on its substitution level (1° , 2° , or 3°).



Normally this isn't a reaction you'd do on purpose; it just happens automatically if you put an ether in acid. This is about the only reaction that ethers do, which is why they're such popular solvents – they won't react under most conditions.

Loudon Chapter 11 Review: Ethers & Epoxides

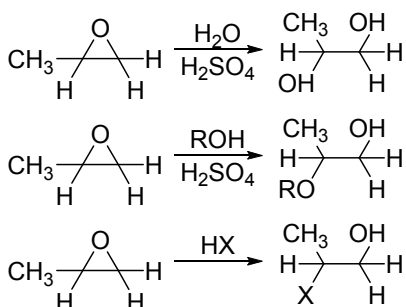
Jacque Richardson, CU Boulder – Last updated 4/28/2016

Reactions of epoxides

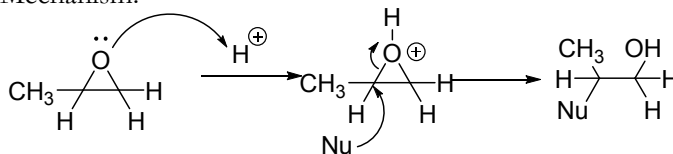
These can happen under acidic or basic conditions, or with organometallics like Grignards. In all cases, it acts like an S_N2 reaction in terms of geometry – it's a backside attack, which gives inversion of configuration.

- Under acidic conditions, the mechanism looks a lot like opening the bromonium ion opening from chapter 5. Just like in that case, the attack happens at the **more substituted carbon** due to charge density. But you have to protonate the oxygen first.

Overall reactions:

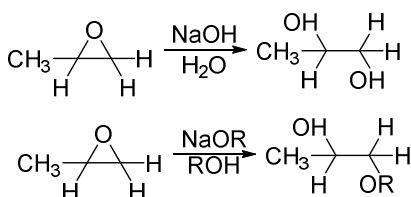


Mechanism:

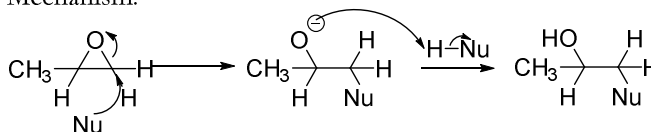


- Under basic conditions, the oxygen doesn't get protonated, but the nucleophile just goes straight in for the attack. The attack happens at the **less substituted carbon** now, since the only concern is sterics. There are only a couple of examples shown here, but most of the other nucleophile/bases we saw in chapter 9 can do this under the right conditions.

Overall reactions:

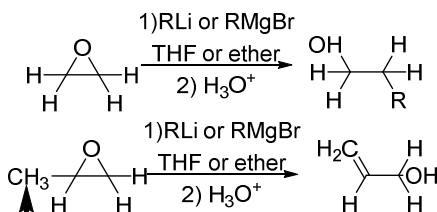


Mechanism:

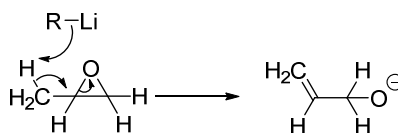


- With organometallics, the alkyl group attacks the **less substituted carbon** just like under regular basic conditions. Theoretically you could use a Grignard or organolithium to do the attack but there's a problem: these are such strong bases that they're more likely to pull off a β H if there's one available. So about the only time you can safely use these organometallics is if there are no other carbons attached to the epoxide ring.

Overall reaction:



Mechanism is same as above for first rxn. For second rxn, it's E2:



Problem!

To get around this problem, there's a new type of organometallics: cuprates. First, you need to know how to make them. You start with two molecules of an organolithium and react them with copper (I) chloride.

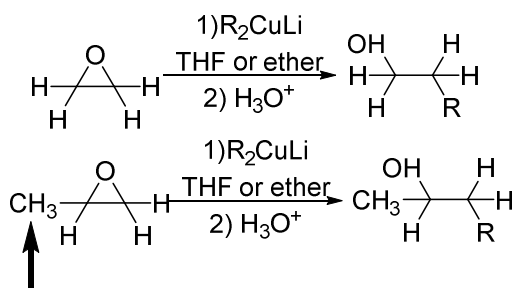
Loudon Chapter 11 Review: Ethers & Epoxides

Jacque Richardson, CU Boulder – Last updated 4/28/2016



These are weaker bases than Grignards or organolithiums, so they'll behave nicely and add an R group to the molecule without doing anything else.

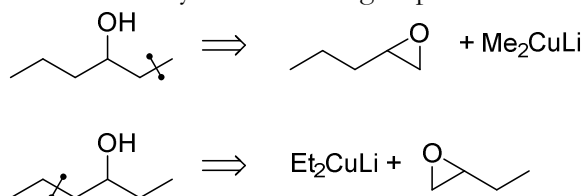
Overall reaction:



Mechanism is same as in basic conditions, for both rxns.

No problem!

This is an extremely useful reaction for making new carbon-carbon bonds, so long as we can break the bond two atoms away from an OH group:



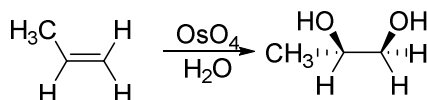
Synthesis of glycols

There are two different methods depending on what stereochemistry you want.

1. From an epoxide, like we saw above. Since this goes by backside attack, you'll always have one OH bold and one dashed. This is called an *anti* diol. It works in either acidic or basic conditions.



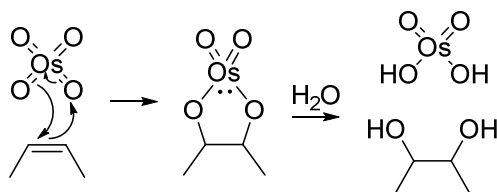
2. From an alkene. This is a new reaction that involves osmium tetroxide. Here, both oxygens add to the same face at the same time, so it gives a *syn* diol. Often, other reagents are included to recycle the osmium and allow it to be used in much smaller amounts, though they're not required. You also have the option of using KMnO_4 , although it can oxidize further and is not ideal.



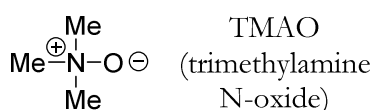
The mechanism for this involves oxidizing both carbons and reducing osmium. We won't cover the whole thing, but this is the general idea.

Loudon Chapter 11 Review: Ethers & Epoxides

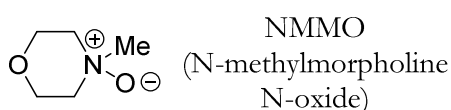
Jacque Richardson, CU Boulder – Last updated 4/28/2016



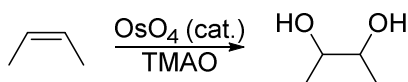
The old version of this reaction used 1 equivalent of OsO_4 , plus a reducing agent like NaHSO_3 that would safely reduce the OsO_4H_2 byproduct into even more-reduced forms that are easy to filter out of the reaction. Newer versions use only a catalytic amount of OsO_4 , plus an oxidizer to recycle OsO_4H_2 back to OsO_4 . Some examples are TMAO and NMAO.



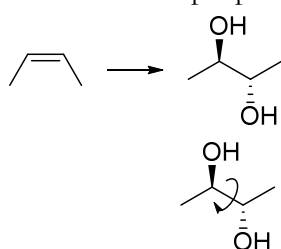
TMAO
(trimethylamine
N-oxide)



NMAO
(N-methylmorpholine
N-oxide)



Here's an example problem that involves choosing which of these methods to use.

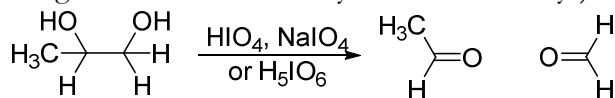


This looks like a trans-diol, so first guess is to use ring-opening of epoxides. However! Once we arrange groups to match layout in alkene, it becomes clear we need to use OsO_4 instead.

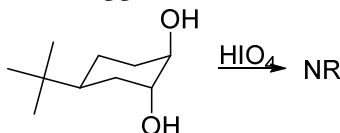


Reactions of Glycols

Glycols can do anything that regular alcohols can do, but there is one important, unique reaction. You can split them in half between the OH group using periodic acid (HIO_4) in some form. The end result of this looks a lot like ozonolysis on an alkene, only you start with a glycol (which you can get to from an alkene by two different ways).



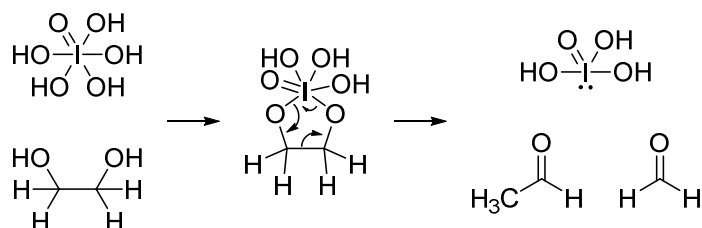
For this to work, the molecule has to be capable of getting its two OHs pointing in the same direction, whether it starts that way or whether it gets there by rotating around the bond between the two carbons. If this can't happen then there's no reaction.



This is because the mechanism involves getting both OH groups bonded onto the iodine atom at once. The actual reagent involved is H_5IO_6 , which results from periodic acid bonding with two molecules of water.

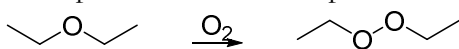
Loudon Chapter 11 Review: Ethers & Epoxides

Jacque Richardson, CU Boulder – Last updated 4/28/2016



Oxidation of Ethers

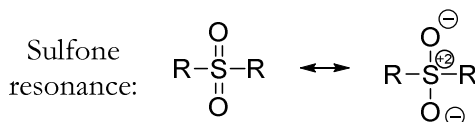
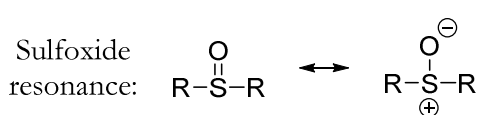
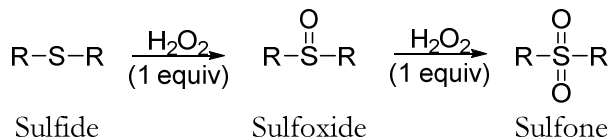
Ethers are generally unreactive – the one reaction we've seen them do is with an HX acid, to make alkyl halides. They also don't react with most oxidizers, even strong ones like Cr(VI)-based oxidizers. However, they do react with one oxidizer: oxygen from air. Over time, a bottle of ether left open to atmosphere will oxidize to peroxides.



This is dangerous, since peroxides can be shock-sensitive explosives. For this reason, if you ever pick up a bottle of ether (usually THF or diethyl ether are the most commonly used ones) and see white crystals in the bottle, immediately set it down gently and leave.

Oxidation of Sulfides

Just like thiols, oxidizing a sulfide involves adding more S-O bonds. Again, there are several different levels available – sulfides, sulfoxides and sulfones. You can increase the oxidation level by one if you react these with one equivalent of hydrogen peroxide, H₂O₂. As a side note, you can draw these molecules in two forms – one where the sulfur obeys the octet rule but has a charge, and one where it breaks the octet rule and is neutral.



More Synthesis

There are several fundamental types of operations we've covered in the past few chapters, but it's time to take a look at the big picture. The reactions we've seen can all be described in terms of what goal they're trying to accomplish during a synthesis.

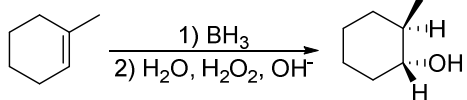
1. Functional group interconversions: This involves getting from one functional group to another. Most of the reactions we've seen so far fit into this category. Appendix V has a complete list.
2. Control of stereochemistry: This involves targeting a particular type of stereochemistry, like through *syn* vs. *anti* addition, or by backside attack for S_N2.
3. Control of regiochemistry: This involves targeting a particular location on a molecule. Some examples we've seen are Markovnikov-style vs. anti-Markovnikov-style addition, or Zaitsev vs. anti-Zaitsev elimination.
4. Formation of carbon-carbon bonds: this is a very important category because it lets us build up the carbon "skeleton" of the molecule. The only two examples we've seen so

Loudon Chapter 11 Review: Ethers & Epoxides

Jacque Richardson, CU Boulder – Last updated 4/28/2016

far are cyclopropane formation (Ch. 9) and cuprate on epoxides (Ch. 11). We'll see a lot more of these next semester.

An individual reaction can fall into several categories at once, like hydroboration-oxidation:



Functional group interconversion: alkene to alcohol
Control of stereochemistry: *syn* addition
Control of regiochemistry: anti-Markovnikov addition