Lab 1A • 01/09/12

The first word of warning that you need is that none of the exams this quarter will be multiple choice; everything is written out. Some students dislike it at first, because they're used to multiple choice exams, but eventually most people end up preferring it because I do, wherever I can, give as much partial credit as I can. If you get a chance to explain yourself, you might get points where you wouldn't have been able to on a multiple-guess exam. If English is not your native language, you are allowed to use electronic translators on your quizzes, exams, lab quizzes; it just needs to be something that is a dedicated translator and not an iPad or something like that that would have more than translator functionality.

There were three main classes of problems that we had last quarter. One of them was mechanism; there will be questions where you do nothing but write out the full mechanism. Another type of question, which is the one that we'll cover first, is what is know as the fill-in-the-blank problem. You might have a substrate, a reagent that acts on that substrate, and the product. One of the three of them will be left out, and you'll have to figure out what goes in the box. Another type of problem is just theoretical; for example, if you were learning about additions to alkenes, you've probably heard of Markovnikov addition, so a type of question I might ask is: what is Markovnikov addition? Why does addition occur that way? What's the underlying reason for that occurring? In that case, you would describe hyperconjugation being able to stabilize a carbocation at a particular position and then that's why additions to alkenes occur the way they do. Another common type of problem that shows up is nomenclature; not that I expect that you know every rule there is to nomenclature, but you need to be able to name common types of compounds.

A four type of problem that we didn't get yet, but that we're going to get a lot of this quarter, is a multistep synthesis problem, where you'll be given a particular starting material, you'll be shown the product, but it isn't just one reaction from the start to the end, it's a sequence of reactions that, part of the problem will be to figure out what is the sequence that will correctly perform that synthesis. That kind of problem they didn't get yet.

Let's start out with the fill-in-the-blank problem, which was the last problem on the final.

First of those, you start out an unknown substrate reacting with mercury acetate in methanol, followed by sodium borohydride and sodium hydroxide. It produced this methyl ether. In situations like this where you do have a 1 and a 2 listed for your sets of reagents, it does mean that everything listed after the 1 reacts first and then, separately from, everything listed with a 2 or a 3 and so forth. If there weren't 1s and 2s there, it explicitly means all of those reagents are reacting at one. Everywhere where you use reagents, you've got to be careful to use 1s and 2s where you should use them and not to use 1s and 2s where it's inappropriate. This two-step reaction is known as what? What does this set of reagents correspond to? Oxymercuration-demercuration. That's one where you make a cyclic mercury intermediate which then gets attacked, normally by water. Except in this case, I've replace the water with methanol; this is the reason that we end up with a methyl ether as a product and not an alcohol. Otherwise, it's just like oxymercuration-demercuration. What kind of substrate do you have to have for this kind of reaction? What kind of starting material do you have to have? What functional group? An alkene (or, conceivably, you could have an alkyne as well). In this case, since we only end up with the ether there, we're going to guess that it's an alkene. This is a cationic reaction, so it does occur by Markovnikov addition. It means that, when adding to an alkene, the nucleophile that adds in ends up in the most-substituted position. That's because the electrophile that adds in wants to go to the least substituted position, so it makes the best possible carbocation. We need an alkene as a starting material with the same number of carbons, and we need it in such a way where the most-substituted position is the one where the ether end up. The only possible solution for this reaction is 3-methylbut-1-ene. Why? Because the secondary carbon is the most substituted, so that's where the methanol is going to end up attacking. If we had the double bond here, between the tertiary and the secondary carbons, that would make the tertiary position the most substituted, so the ether would end up in that position [instead]. That's not what we want. This mercury reaction does have a cyclic intermediate, and because of that cyclic intermediate, it mean it does not have carbocation rearrangement, so it is perfectly fine having this terminal alkene and expect that we would get the right product. So that is the answer for this particular reaction.

Next one. Here the substrates are given, but not the reagents. The product in this case is difunctional: halogen right next to an alcohol group. What do we call this kind of functional group, where we have an alcohol and a halogen? A halohydrin. What are the conditions for synthesizing a halohydrin? Not the conditions, the reagents? Bromine and water (fror a bromide) – without light; this is an electron pair mechanism, not a single-electron mechanism, so you would not use light in this case. If you're not familiar with this set of reagents, Br_2 by itself makes an alkene into a dihalide, and it forms a cyclic intermediate in the process. If you have water instead of just bromine, water attacks that cyclic intermediate, and it does so sat the most substituent position. That matches what we have for this product, so a halohydrin from bromine and water.

Next one. An alkene reacting with meta-chloroperoxy benzoic acid (MCPBA). You might have instead learned about magnesium monoperoxyphthalate (MMPP). Peroxybenzoic acid looks just like benzoic acid, except it's got an extra oxygen. The MC, meta-chloro: meta is a position two positions away on the benzene ring, so that meta-chloroperoxybenzoic acid. You do need to know these acronyms. MCPBA makes what? Epoxides.

An epoxide is a cyclic ether, a three-membered ring, two carbons and one oxygen. Because this is a flat alkene, because this is sp2-hybridized, the MCPBA could react with either face of the double bond, which means you are going to generate a set of enantiomers in this case. The two products in this case would be the following (they would be unique because of that methyl group, they are not symmetric): one we could show with the epoxide ring pointed away from us, the other we could show it pointed towards us. This is a syn addition, meaning it does only occur on one face of the alkene: that's because, for a three-membered ring, it's not physically possible for one part of that ring to be a wedge and pointed out at us, while simultaneously the other side of the ring being pointed away from us; it just can't be done geometrically. So those are our two products.

Next one. Probably the one that's the most annoying when you see the correct answer. Something reacting with three equivalents of hydrogen and platinum to make this alkane. Hydrogen and platinum, that is hydrogenation. Notice that this is not Lindlar's catalyst, so this is not a form that has lead carbonate or quinoline or any of those poisoning reagents, so if you had either a double or triple bond, it would be reduced entirely down to a single bond. That's what the point of this question is. If you're told that three equivalents of hydrogen are used, that means there's three pi bonds in this molecule. But, the tricky bit of this is that you can't have a pi bond that goes to that central carbon. Why? Cause there's already four bonds there, so you can't make a double bond that goes to the center. So the only places for a double bond are on the left two carbons or the right two carbons, but somehow we have to fit three degrees of unsaturation in. That means the answer is to put a triple bond on one side and a double bond on the other. So the triple uses up two equivalents of hydrogen, the double bond uses up only one, put them together that's your three hydrogens, you three degrees of unsaturation. Again, the middle one can't have a double bond because it already has four bonds.

Next problem. Starting with an alkyne and reacting with something to make an alkene. Alkyne to alkene – that is partial hydrogenation, which can be accomplished using Lindlar's catalyst, which is a variation of a platinum or palladium reagent which you do have some kind of poisoning or deactivating reagent, usually some form of lead like lead carbonate, usually some other bases that are thrown in like quinoline. Lindlar's itself is not the full reagent, it's just the catalyst. You need something to react with it. Since we end up putting deuterium on here, that means D2 is the reagent that goes with it. You had to specify both of those to get full credit.

Next problem. Probably the sneakiest. If you take an alkyne and try to react it with borane, it won't make this kind of product, because what kind of functional group is that starting material that I've shown you? What's the name of that type of molecule that has both and alkene and an alcohol – mainly it's used, that term, to talk about something where it's on the same carbon. Well, if you have an alk-ene and you have an alcoh-ol, these are called enols. Enols are thermodynamically unstable. Enols tautomerize, and in this case, since we have a secondary carbon where that enol is, we're going to end up with a ketone.

Last of the fill-in-the blank problems was the one multistep reaction that you did need to know last quarter. Something reacting with two sets of reagents to convert an alkene into an alkyne. This is the two-step process of first making a vicinal dihalide by reacting with just plain bromine, no light. That'll put one bromine on one carbon, one bromine on the other carbon. And then, doing a double elimination, using two equivalents of some strong base like sodium amide. Technically, you do need two separate molecules of the base so that you can do two different eliminations to get you to the alkyne.

Let's step back one problem and go over the mechanisms. We had three different mechanisms. First one was a reaction with an alkyne. An alkyl first reacting with that strong base of sodium amide, followed by reaction with iodomethane, and then finally, sodium in ammonia. First step of the reaction is related to the acidity of alkynes. We talked last quarter about three main structural effects that can affect the acidity of a compound. One of them was hybridization, another one of those factors was inductive effects – you have a very electronegative element that can pull electron towards it, it makes a bond with whatever was there easier to break. And then, resonance – things like acetic acid are as acidic as they are because the ions they form once they lose a hydrogen are stabilized by resonance. In this case what happens is if that hydrogen were to come off and leave its lone pair behind, that lone pair would reside in an sp-hybridized orbital. An sp orbital, in a polyelectronic system like this, ends up being lower in energy than sp2, which is lower in energy than sp3. Putting that pair of electrons into an sp orbital is energetically more favorable than putting it into an sp2, than putting into an sp3. That means it's easier for the hydrogen to come off because the anion is easier to form for something that's sp versus sp2 versus sp3. Alkynes are much more acidic, with a pKa of about 25, than alkenes, which have a pKa of about 34, than alkanes, which have a pKa up in the 50s and 60s range.

So, first step of the reaction is that strong base, sodium amide, deprotonates the alkyne and makes a type of ion known as an acetylide ion. This acetylide ion is very basic, but it is also nucleophilic, and in fact, it's perfectly fine nucleophile as long as you have a primary substrate to react with. Secondaries and tertiaries, you'd have elimination. We have methyl iodide which is not even a primary, it's just a methyl substrate, one of the best targets for an Sn2 reaction you could possibly have, because it's got essentially no steric hindrance. So very rapid Sn2 reaction would then occur between the acetylide and the iodomethane. I'm fussy about lone pairs, because I want to make sure you know what oxidation state things are. The result here is adding another carbon to that alkyne, so we've converted from pro-1-yne to but-2-yne.

We still have one more step in the reaction, which is sodium in ammonia. That you need to recognize as the conditions for reduction to form a trans alkene. This is one of only two radical reactions we properly covered last quarter – one of them was this one, reduction, the other one is free-radical halogenation. Much of this mechanism occurs using the single-headed arrows, where only one electron at a time is moving around, unlike these double-headed arrows that you see [most frequently] where two electrons are involved. First step of the reaction is for the triple bond to be broken up by the addition of an electron. The electron is essentially just floating around in solution, and it comes from the sodium metal; sodium is a good reducing agent because it has a low ionization energy. An electron adds into the triple bond. In an alkyl, the three bonding orbitals between the two carbons are filled, that's how we get a triple bond. The only place, then, that an electron can go is into an antibond, which is why one of the three bonds then breaks. You end up with an intermediate known as a radical anion, and it doesn't actually matter which side you write the anion and which side you write the radical, because both sides are eventually going to react. The product that we just made is much more basic than the acetylide ion was, because we have an sp2-hybridized carbon instead of sp, which it's basic enough to be able to deprotonate ammonia. Ammonia itself is a base, but it becomes an acid in this situation. SInce this is a regular acid-base reaction, we're back to the double-headed arrows. We still have electrons floating around in solution, so the next step is for an electron from solution to add in to the radical that's present. This is the key part of the reaction, because when it was just a radical, that carbon was sp-hybridized. Remember that single electrons do not have the repulsive force of pairs of electrons, so they don't affect geometry, so they're not counted in VSEPR theory, and since hybridization is done to match geometry, because that single electron doesn't count towards the geometry, it also does not count towards hybridization. So, only one bond on either side of that carbon, that's why it's sp-hybridized. As soon as it gains that electron, it becomes sp2-hybridized, which is why the methyl group that's at that position now ends up being trans to the original methyl group, because that's thermodynamically favored – it avoids steric hinderance between the two methyl groups. We still have ammonia around, which will provide another hydrogen. So then our final product is trans-but-2-ene.

Moving to the next one; much simpler reaction. An alkene reacting first with HBr, and then second, sodium methoxide. The first reaction, plain old simple electrophilic addition. Double bond attacks H+ first. This is Markovnikov addition because we end up with the hydrogen, the electrophile, at the less-substituted position, forming the more-substituted carbocation. Since there's bromide still floating around in solution, it attacks next to make only one product. Realize that since the ring is symmetric, there is no stereocenter there, but I am going to write it with wedges and dashes because of the next step that I want to show properly, but there is only one product being made at this point. The reason I'm showing this is because of the sodium methoxide. What kind of alkyl halide is this that I just produced: primary, secondary, or tertiary? What do primary, secondary, and tertiary mean? It's how many carbons are connected to that same position. You look where bromine is attached, there's the two directions of the ring and then the methyl group, so that means it is a tertiary alkyl halide. In terms of Sn1/Sn2/E1/E2, which reactions can tertiary substrates not do? A tertiary substrate cannot do Sn2; it can do E2 or Sn1/E1. But in order to do substitution, we need a non-basic weak nucleophile. What kind of nucleophile do we have here? It's a strong one. Why? Because it's anionic, and it's anionic on oxygen. Because it's oxygen, that means it's also basic. So, which type of reaction's going to happen? E2, because since it's a base, it won't wait around for a carbocation, so that's why Sn1 won't happen, and for similar reasons, since Sn1 and E1 have the same intermediate, E1 won't happen. Since this is E2, because we have a basic nucleophile and a tertiary substrate, what about regiochemistry? Is this base hindered or small? Is this as hindered as t-butoxide, for example? No, so for regiochemistry, it is possible to have what is called Hoffmann or anti-Zaitsev elimination, if you have a really hindered base. But we don't have a really hindered base, so that means that the more substituted alkene is going to be the one that's preferred, which means the hydrogen I wrote in on the ring there is the one that's going to get removed, so this is an E2 mechanism. Notice the stereochemistry of that hydrogen. It must be pointed the opposite way of bromine, because only if the hydrogen and the leaving group are antiperiplanar to each other is elimination possible from a cyclohexane ring. The both have to be able to be axial instead of equatorial. In terms of mechanism, methoxide pulls of hydrogen, the electron [pair] from the hydrogen collapses to kick bromine off, and so the one and only product that we get from the reaction is this. It's really a two-step process to move the double bond.

The last mechanism. Hydroboration-oxidation. This is a more interesting one that involves an alkyne. Since this is hydroboration-oxidation of an alkyne, it uses that special hindered reagent. If you're familiar with BH3 (borane), this has the same reactivity, except for two major differences. One, there's only one hydrogen on the boron, so only one hydrogen per boron will react. That reduces the formation of boron networks, a by-product that can interfere with the reaction of alkynes. It's also got all of this steric hinderance caused by the two alkyl groups on there, which again will help prevent the formation of a network product. After the reaction of that, it has the same work-up conditions of hydrogen peroxide and sodium hydroxide. This alkylating reaction you can abbreviate R2BH, because the alkyl group, you don't actually care about. It's just there to control the reactivity of borane. The alkyne is the main target, so you had to show what happened to it. Hydrogen is more electronegative than boron, so it's going to be boron that's going to end up on the less-substitute side, and hydrogen that ends up on the more substituted side, so I'm going to write out my mechanism like this, putting boron closer to where it is going to end up. To make it simpler to write, I am going to use R notation everywhere.

First step of the reaction is a concerted mechanism; four-centered transition state, where the alkene attacks the boron at the same time hydride slips onto the alkyne. You'll get syn addition to that double bond, because the four-centered transition state can only happen with syn geometry. Really, you only need to show this part of the mechanism once, because borane, this version of borane, only had one hydrogen on it.

The thing that happens next is the hydrogen peroxide and hydroxide oxidize this compound. Hydrogen peroxide and hydroxide in solution will form the hydrogen peroxide ion, which can attack boron, because boron does not have a complete octet. That will make boron negatively charged. It is at this point where the strangest part of the reaction occurs. Currently there is a sequence of carbon-boron-oxygen-oxygen bonds. A carbon-boron bond is not as good as an oxygen-boron bond, and an oxygen-oxygen bond is weaker than that even and definitely worse than a carbon-oxygen bond. What occurs is an alkyl shift; it's rare, because it does end up making hydroxide a leaving group, but it happens because overall this is a thermodynamically-favored process. It's largely due to the fact that that oxygen-oxygen bond is relatively weak. That shift occurs, putting the oxygen between the carbon and the boron. At this point, the decomposition occurs: hydroxide attacks boron, which again makes a negatively-charged boron, which can relieve that negative charge if an oxygen turns right back around and disconnects. The hydroxide itself could be the thing that comes back off, but sometimes, this target alkyl group could be the thing that comes off, which if it does, it can stop reacting, because it can have a neutralization occur.

[This mechanism is not yet complete because the product is an enol,] and enols are thermodynamically unfavorable. So the last part of this mechanism is tautomerization. Hydroxide can pull a hydrogen back off of this molecule. This is a delocalized ion, so we could write a resonance structure, where we push the negative charge to carbon instead. Once we're at that point, water that would be floating around in solution because we had hydroxide could be the source of a hydrogen for that molecule to get protonated, and we end up with an aldehyde. Recognize we cannot use H+, it has to be water, because if you have basic conditions, there are no H+s around.

We only have time for one more problem today. [You were shown] pairs of Sn1 and Sn2 reactions, and you were asked to determine which of the pair of reactions is faster. First pair of reactions, we have the same substrate and same nucleophile – bromoethane reacting with sodium fluoride to make fluoroethane. Both of them have the same reagent, same substrate. But in one case, the reaction's conducted with methanol; in the other case, the reaction's conducted in this molecule, which you had to recognize that as DMF, N,N-dimethylformamide, very common lab solvent, very common Sn2 solvent. Why? Because good Sn2 solvents are polar aprotic solvents. Methanol's extremely protic, it's like water. DMF is aprotic, it does not have an easily-reactible hydrogen. DMF will not interfere with fluoride as much as methanol will, so that second reaction is the faster one, because it has an aprotic solvent.

The next pair. This time you have the same reagent, but two different substrates. Fluoroethane reacting with sodium hydroxide to make ethanol, or bromoethane reacting with sodium hydroxide to make ethanol. [clarification of directions from the question; simply saying 'bromine is a better leaving group' not enough] Why is bromine a better leaving group? The underlying reason is that bromide is the conjugate base of a strong acid, which means bromide itself is not basic. Fluoride is the conjugate base of a weak acid, which means fluoride is basic, which is why it's a poor leaving group. It is true the second reaction is faster because bromine is a better leaving group since it is the conjugate base of a stronger acid.
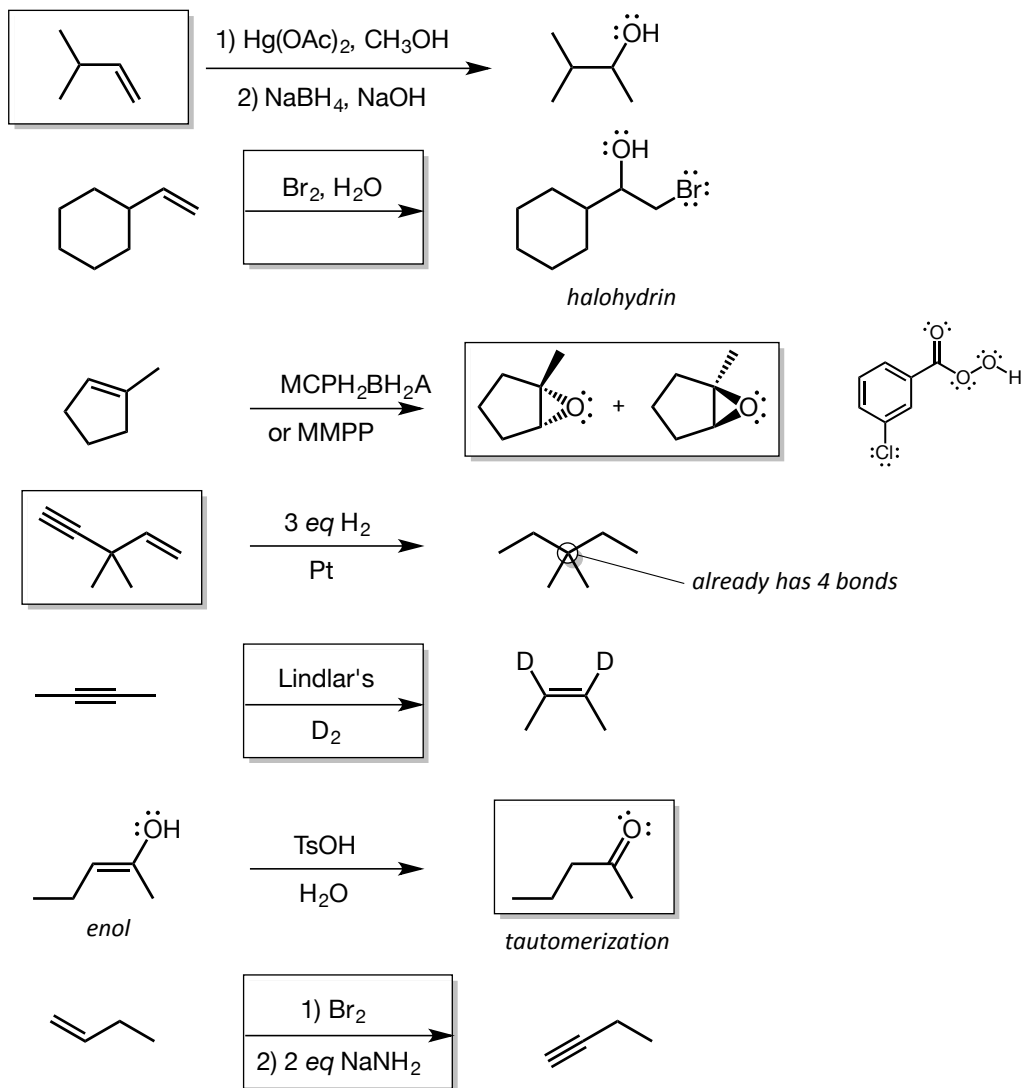
Next one. Same type of reaction, but two different substrates. In both cases, they involve an ionic nucleophile that has sulfur as the main attacking atom. Is this a strong nucleophile or a weak nucleophile being used? Strong. In fact, even though SH– is not as basic as hydroxide, it's far more nucleophilic due to the fact that sulfur's big and squishy – in other words, it is polarizable, so it begins the process of the bond formation more easily than oxygen. Strong nucleophile favors which type of reaction, Sn2 or Sn1? Sn2. Sn2 reaction favors what kind of substrate: primary or tertiary. Primary. Why? Less steric hindrance. So the faster reaction it's going to be the first one; it's Sn2, and there's less steric hindrance.

The last one: similar situation. Two substrates, same reagent. Bromoethane making ethanol, versus 2-bromo-2-methylpropane reacting to make t-butanol. We have water: is that a strong or a weak nucleophile? Weak, because it's neutral, it's non-ionic. Weak nucleophile favors Sn1 or Sn2? Sn1. Primary or tertiary substrate favors Sn1? Why tertiary? It makes the more stable carbocation. You almost can't make a primary carbocation. So it's Sn1 in this case, and it makes a more stable intermediate.
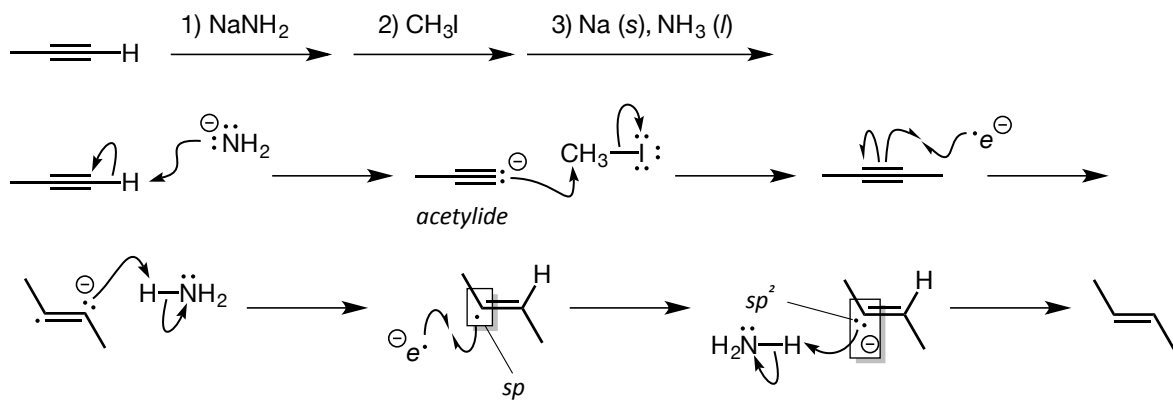
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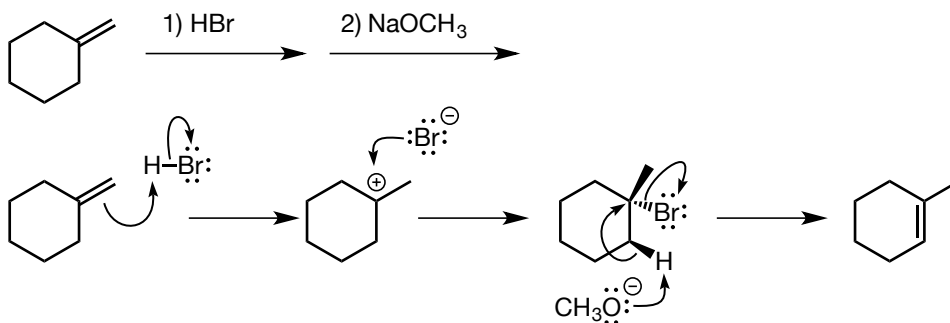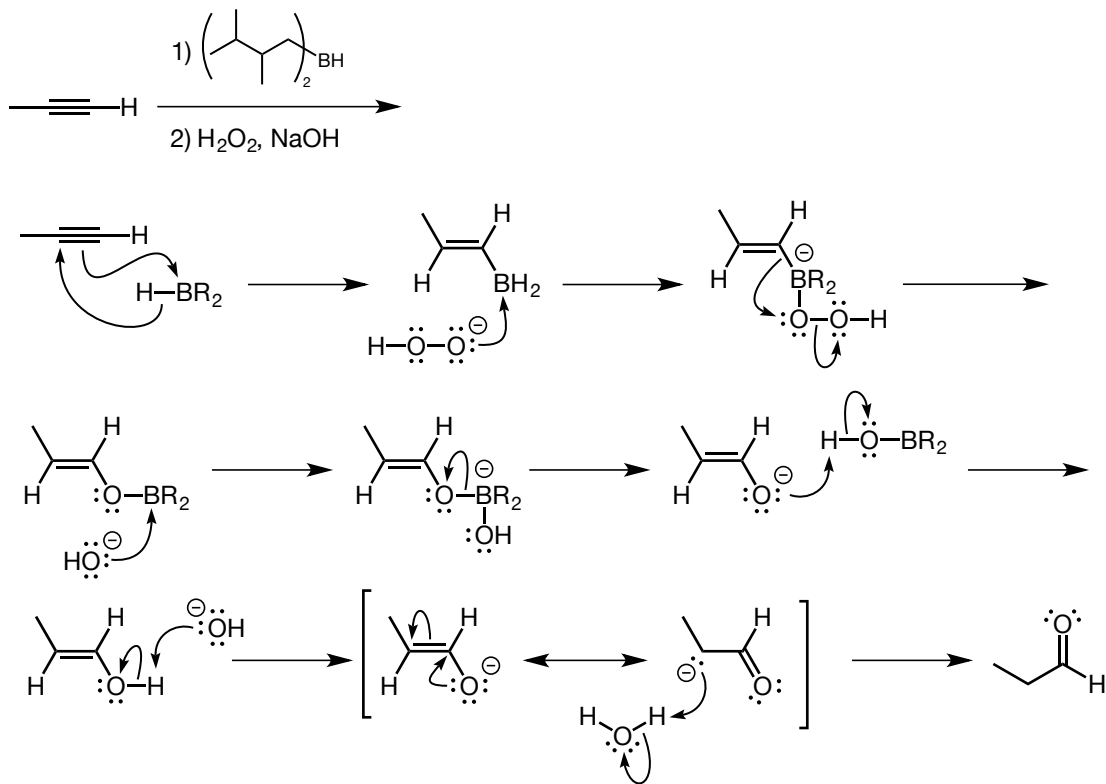**Structures**

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1) Hg(OAc)$_2$, CH$_3$OH

2) NaBH$_4$, NaOH

:ÖH

Br$_2$, H$_2$O

:ÖH

:Br:

halohydrin

MCPH$_2$BH$_2$A

or MMPP

+

3 eq H$_2$

Pt

— *already has 4 bonds*

Lindlar's

D$_2$

D   D

:ÖH

TsOH

H$_2$O

:Ö:

enol

tautomerization

1) Br$_2$

2) 2 eq NaNH$_2$

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1) NaNH$_2$ 2) CH$_3$I   3) Na (s), NH$_3$ (l)

H

:NH$_2$

H

:Ö:

CH$_3$—I:

•e$^{\ominus}$

acetylide

H—NH$_2$

H

•e$^{\ominus}$

sp

sp^2

H

H$_2$N—H

$^{\ominus}$

442

1) HBr   2) NaOCH₃

1) $\left(\begin{array}{c}\end{array}\right)_2 BH$

2) H_2O_2, NaOH

NaF / MeOH

NaF / DMF

aprotic solvent

NaOH

NaOH
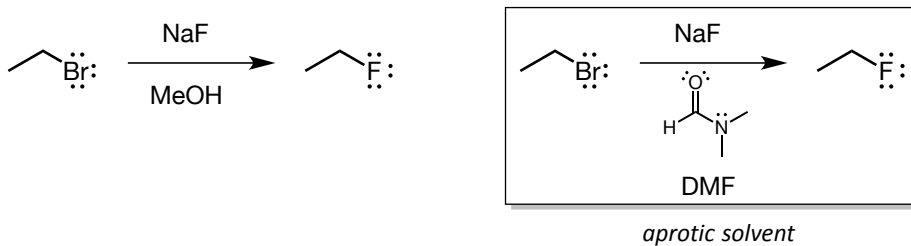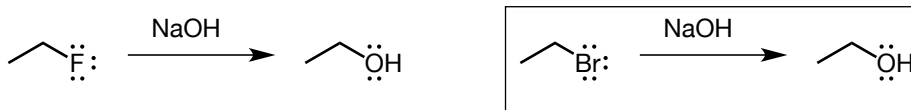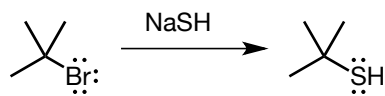
Br- better leaving group since it is the conj. base of a strong acid (HBr vs. HF)

NaSH

NaSH
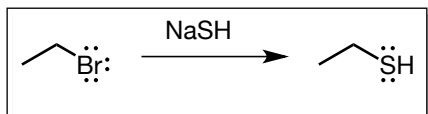
S_N2 - less steric hinderance

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H_2O

H_2O
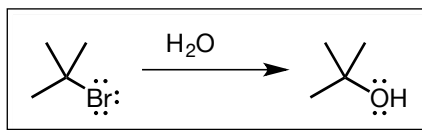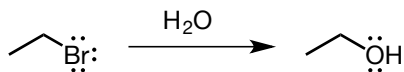
S_N1 - 3° cation much more favorable intermediate