

Useful Definitions:

Mechanism – A scheme that illustrates all reaction intermediates, as well as the flow of electrons and movement of atoms during bond breaking and bond making processes. Remember that arrows are used only to indicate the movement of electrons. Movement of atoms is assumed, but not explicitly indicated, by the arrows.

Nucleophile – A molecule that contains an atom with a lone pair AND a full or partial negative charge.

Electrophile – A molecule that contains an atom with a full or partial positive charge AND can be attacked by a nucleophile without creating a non-viable species such as a pentavalent (five bonds) carbon.

Brønsted-Lowry Base – A molecule containing at least one atom with a lone pair that will accommodate binding to a proton during a proton transfer reaction.

Lewis Base – A molecule that can donate a lone pair in a bond-forming process.

Brønsted-Lowry Acid – A molecule that can donate a proton during a proton transfer reaction.

Lewis Acid – A molecule that can accept a lone pair in a bond-forming process.

Leaving group – A group that will be relatively stable when it departs, such as a small neutral species like H₂O or N₂, or a group such as a halide atom that departs as a relatively stable ion.

Stereochemistry – Refers to which of the possible stereoisomers predominate in a reaction. The details of the mechanism dictate whether a reaction will involve certain features such as *syn* addition, *anti* addition, require an antiperiplanar transition state geometry, involve stereochemical InVERSiON, etc.

Regiochemistry – Refers to which of the possible product constitutional isomers predominate in a reaction. The details of the mechanism dictate whether a reaction will predominately give products that are consistent with Markovnikov's rule, are exactly inconsistent with Markovnikov's rule (anti-Markovnikov), are consistent with Zaitsev's rule, give most reaction at the more substituted carbon, etc.

Key Recognition Element (KRE) – Characteristic functional groups in relation to a new carbon-carbon bond seen with many of the reactions encountered in second semester Organic Chemistry. Being able to identify the KRE's in product molecules for *each* reaction learned will greatly simplify the process of deciding which reactions to use in complex synthesis problems.

Intermediate – A species produced during a reaction mechanism that is less stable than the starting materials or products. It exists for a short time and knowing a key intermediate's structure can help predict stereochemistry and regiochemistry of a reaction (for example a carbocation intermediate or radical intermediate that predicts predominant products seen in many first semester reactions).

Transition State – A theoretical structure that represents the highest energy species encountered in moving between starting materials, intermediates or products during a reaction mechanism. Predicting the properties of a presumed transition state can sometime predict reaction stereochemistry or regiochemistry (for example an anti-periplanar transition state geometry required for an E2 reaction).

Mechanisms: The Basics

A) The Correct Use of Arrows to Indicate Electron Movement

The ability to write an organic reaction mechanism properly is key to success in organic chemistry classes. Organic chemists use a technique called **arrow pushing** to depict the flow or movement of electrons during chemical reactions. Arrow pushing helps chemists keep track of the way in which electrons and their associated atoms redistribute as bonds are made and broken. The first essential rule to keep in mind is the following:

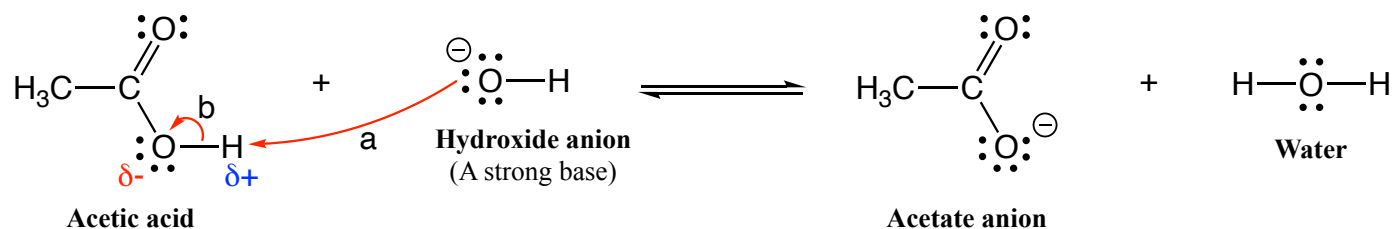
First rule: Arrows are used to indicate movement of *electrons*

A regular arrow (double-sided arrowhead) is used to indicate the movement of two electrons, while a line with a single-sided arrowhead (sometimes called a “fish hook arrow”) is used for single electron movement involved with radical reactions.



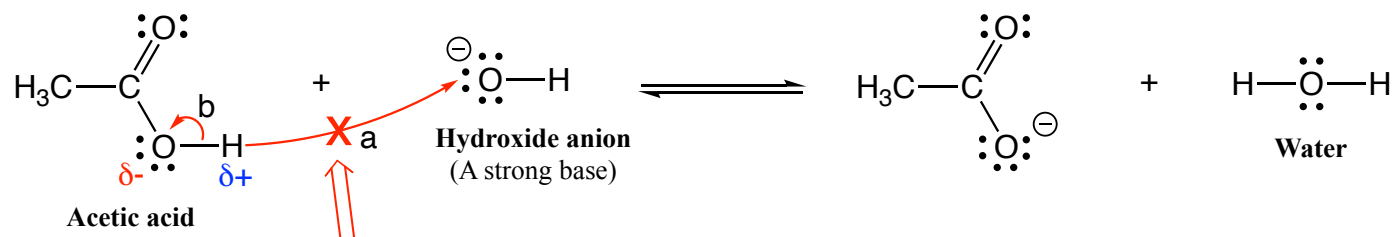
The great majority of reactions that will be discussed in this class involve movement of pairs of electrons, so they are represented by double-sided arrowheads.

Second Rule: Arrows are never used to indicate the movement of atoms directly. The arrows only show atom movement indirectly as a consequence of electron movement when covalent bonds are made and broken.



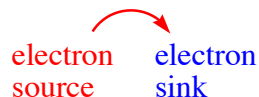
Correct use of arrows to indicate electron movement during reaction

A common mistake students can make is that they will erroneously write an arrow pointing *from* the H of the acetic acid *to* the O atom of the hydroxide anion (arrow a below). This is wrong, because such an arrow would be indicating the H *atom* movement directly, not *electron* movement!



Incorrect arrow because it is pointing in the wrong direction! Never use arrows to indicate atom movement directly

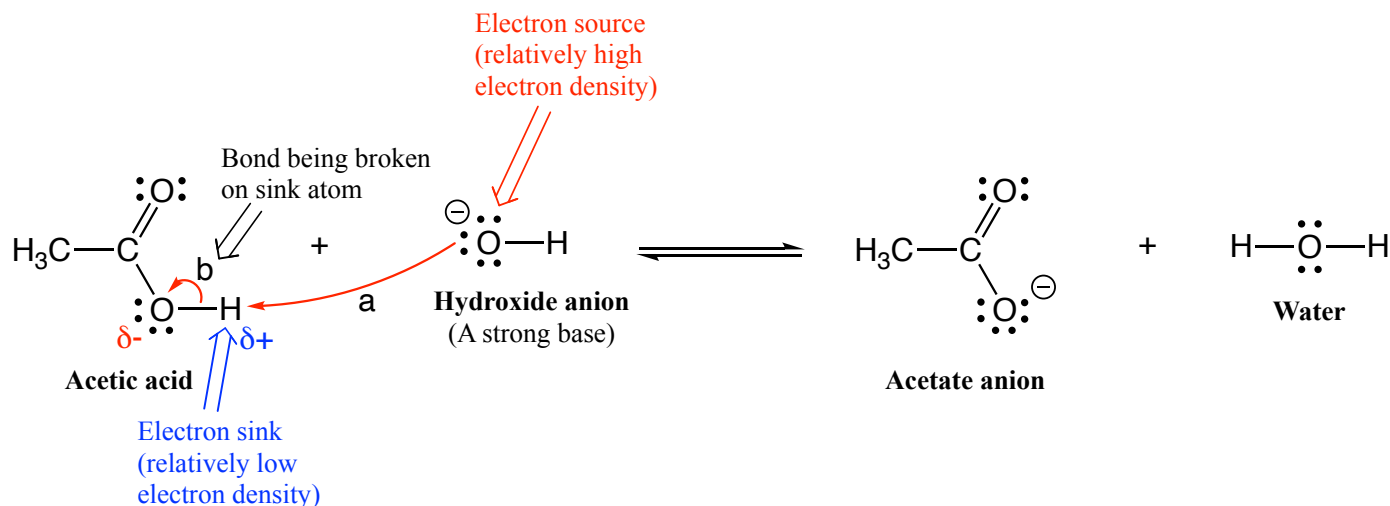
Third Rule: Arrows always start at an electron source and end at an electron sink.



An **electron source** is a bond or a lone pair of electrons. It is either a π bond or a lone pair on an atom of relatively high electron density in a molecule or ion, or a bond that must break during a reaction. An **electron sink** is an atom on a molecule or ion that can accept a new bond or lone pair of electrons.

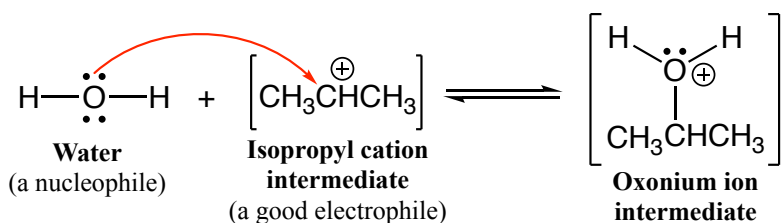
Fourth rule: Breaking a bond will occur to avoid overfilling valence (hypervalence) on an atom serving as an electron sink.

In these cases, the electron source for the arrow is the bond being broken, and the sink is an atom able to accommodate the electrons as a lone pair, generally an electronegative atom such as an O atom or a halogen. If an ion is created, that ion is often stabilized by resonance delocalization or other stabilizing interactions.

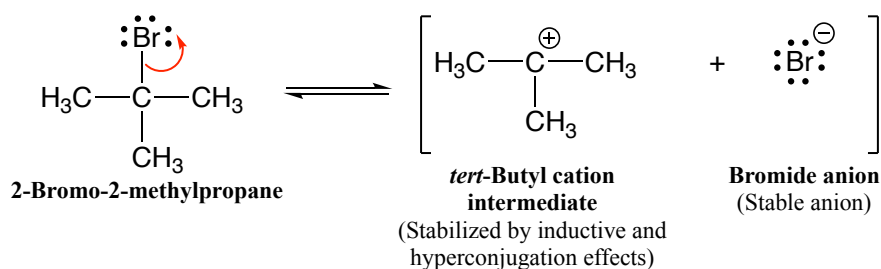


Polar Reaction Mechanisms: Polar reactions are most of what you will see in organic chemistry. There are only four different mechanistic elements that combine to make up the different steps of almost all the mechanisms you saw in CH320M/CH328M. Better yet, in CH320N the following four mechanistic elements are pretty much all you need to think about until we get to electrophilic aromatic substitution.

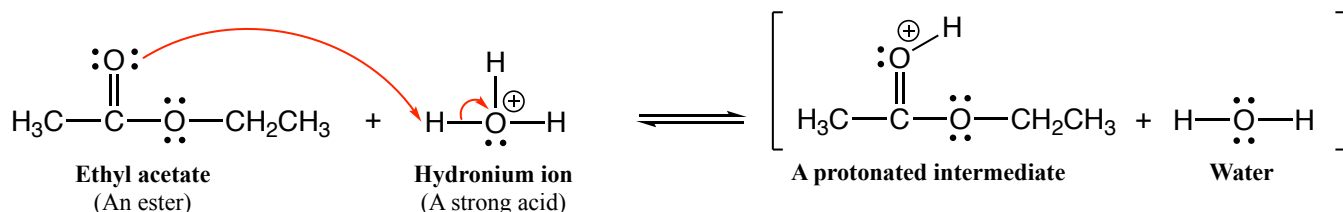
- 1. Make a new bond between a nucleophile (source for an arrow) and an electrophile (sink for an arrow).** Use this element when there is a nucleophile present in the solution as well as an electrophile suitable for reaction to occur.



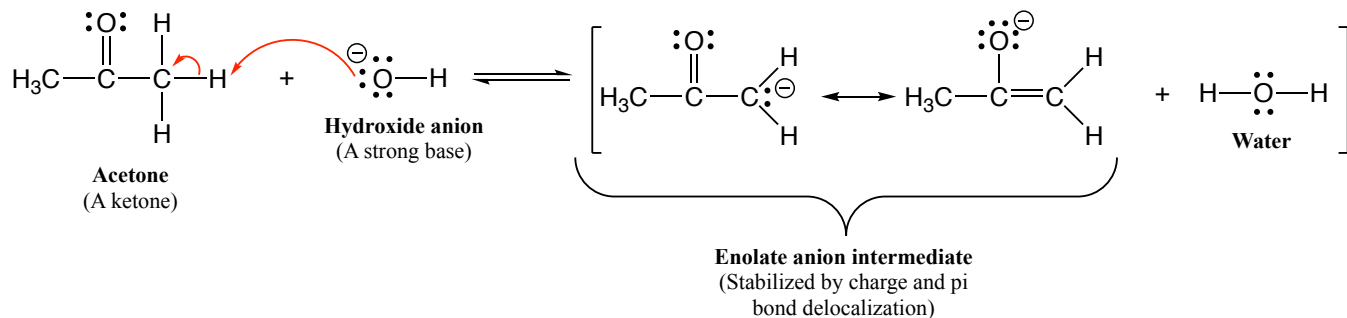
- 2. Break a bond so that relatively stable molecules or ions are created** Use this element when there is no suitable nucleophile-electrophile or proton transfer reaction, but breaking a bond can create neutral molecules or relatively stable ions, or both.



- 3. Add a proton** Use this element when there is no suitable nucleophile-electrophile reaction, but the molecule has a strongly basic functional group or there is a strong acid present.



- 4. Take a proton away** Use this element when there is no suitable nucleophile-electrophile reaction, but the molecule has a strongly acidic proton or there is a strong base present.



The situation is even simpler than you might expect because 1 and 2 are the functional reverse of each other, as are 3 and 4.

Mechanism Summary

The following questions and mechanistic elements are described from the point of view of the carbon-containing reagent, written in the form of a flowchart.

Is there a strong acid present or is the carbon-containing reagent a strong base?

YES
⇒

Add a proton

⇓
NO

Is there a strong base present or is the carbon-containing reagent a strong acid?

YES
⇒

Take a proton away

⇓
NO

Are there a nucleophile and electrophile present?

YES
⇒

Make a bond

⇓
NO

Can a bond be broken to create stable molecules or ions?

YES
⇒

Break a bond

⇓
NO

Think about alternative mechanistic elements (radical reaction, S_N2 , E2, etc.)

Geminal
Dihaloalkanes

Vicinal
Tetrahaloalkanes

Alkynes

Aldehydes/Ketones

Vicinal
Dihaloalkanes

Vicinal
Diols

Alkenes

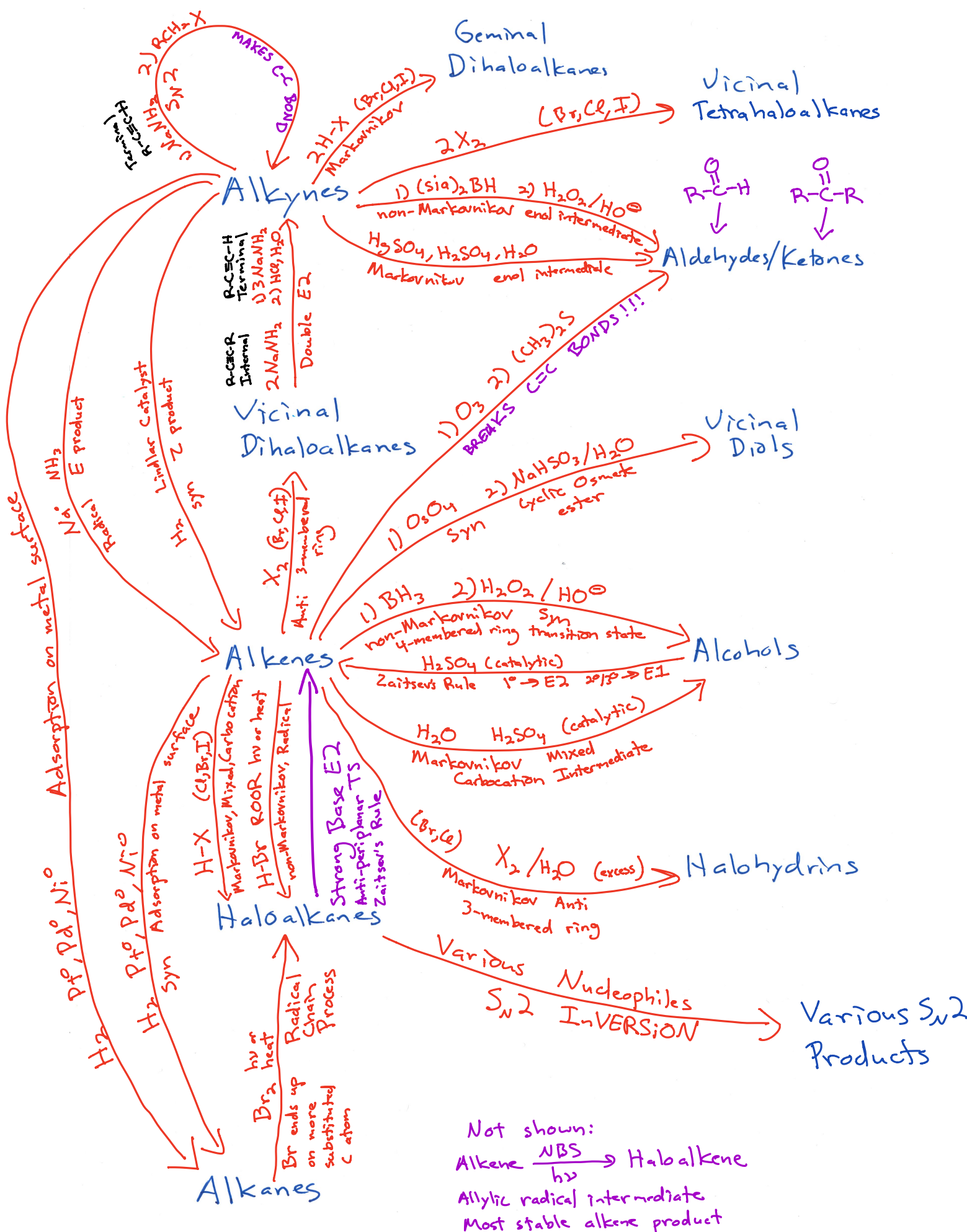
Alcohols

Haloalkanes

Halohydrins

Various S_N2
Products

Alkanes



Geminal
Dihaloalkanes

Vicinal
Tetrahaloalkanes

Alkynes (DFW)

Carboxylic
Acids



Aldehydes,
Ketones

Vicinal
Diols

Vicinal or Geminal
Dihaloalkanes (Waco)

Epoxides

Alkenes (Austin)

Alcohols

Halohydrins

Allylic
Halides

Haloalkanes (S.M., N.B.)

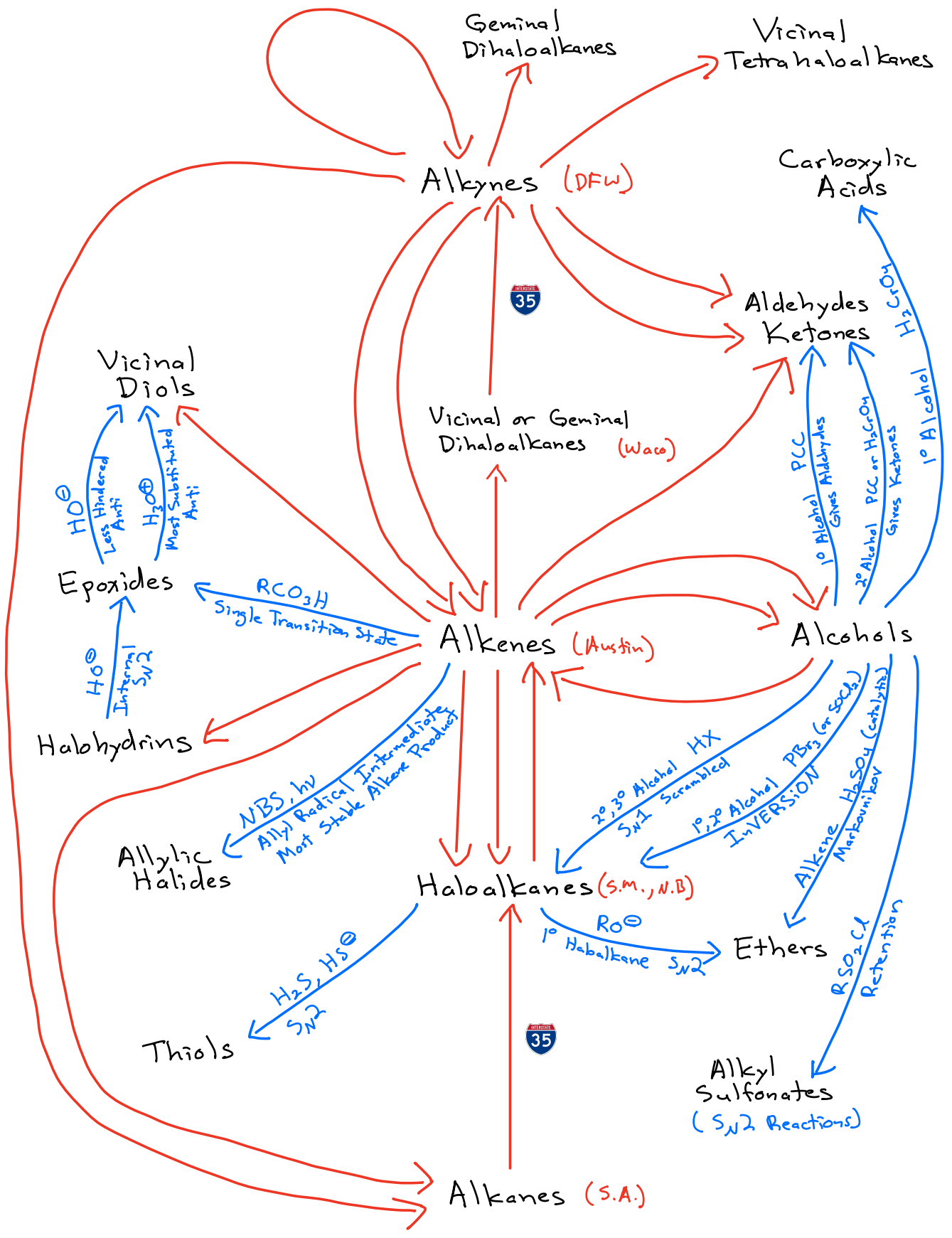
Ethers

Thiols

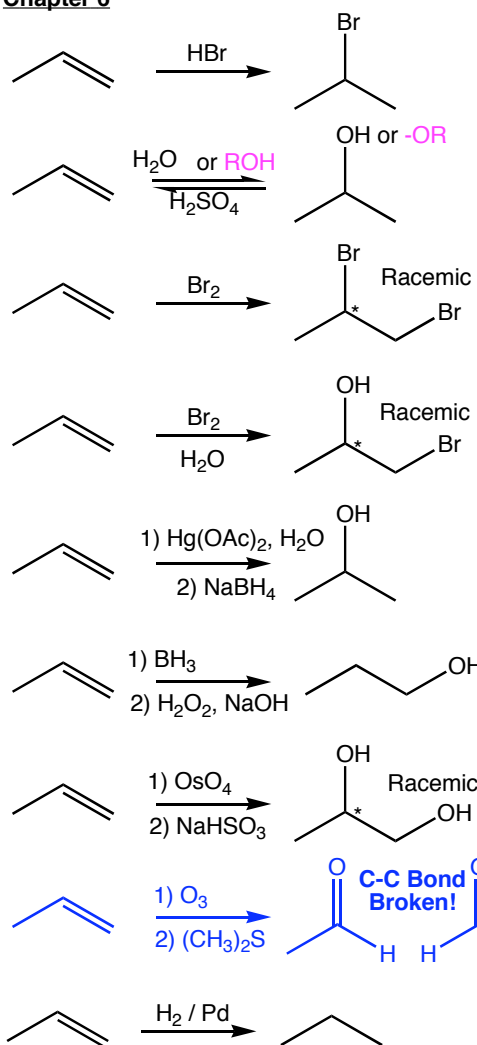


Alkyl
Sulfonates

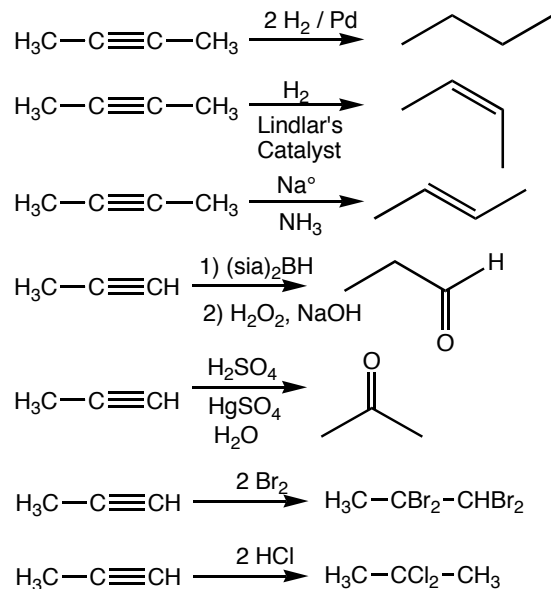
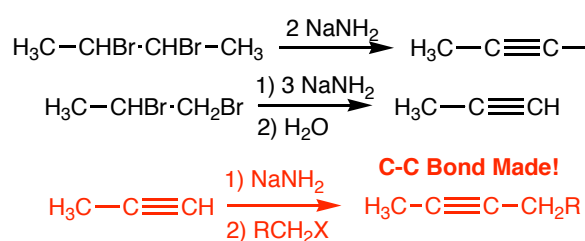
Alkanes (S.A.)



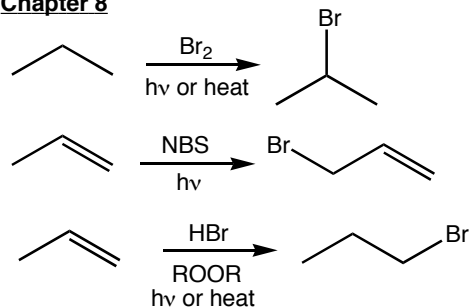
Chapter 6



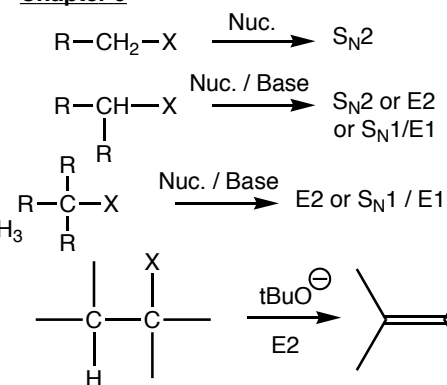
Chapter 7



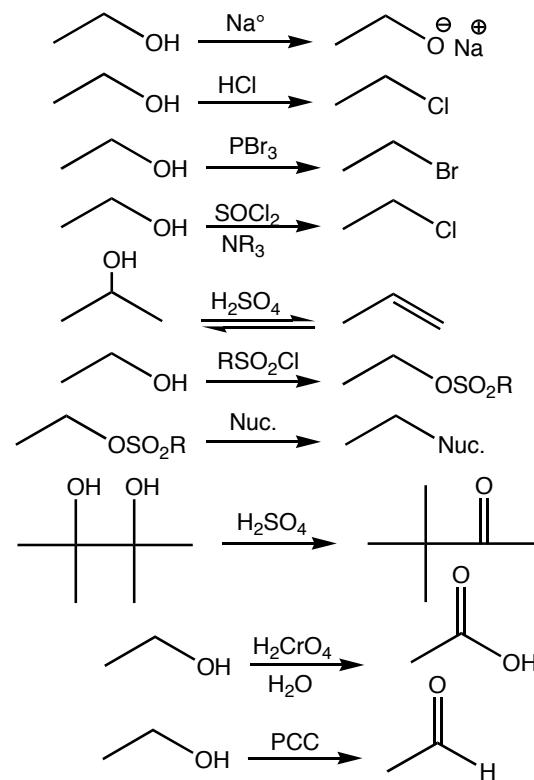
Chapter 8



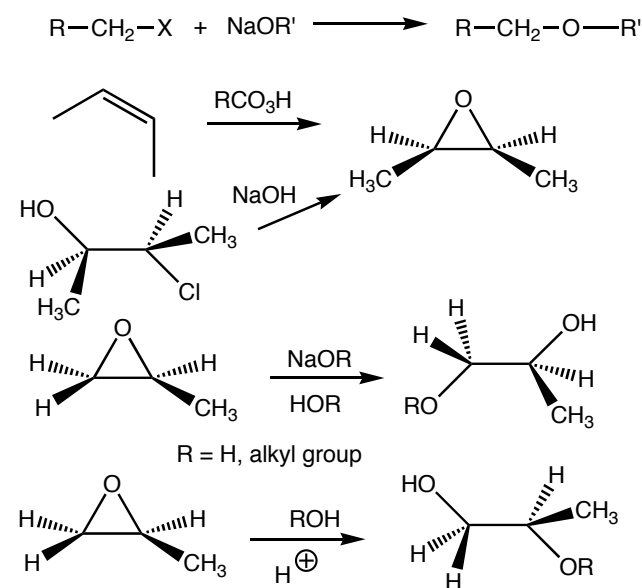
Chapter 9



Chapter 10



Chapter 11

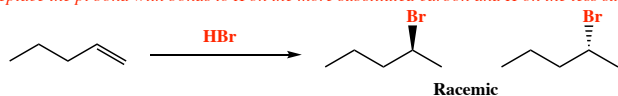


Chapter 6

1) Reaction of Alkenes with HX to Give Haloalkanes

Mechanism Keys: **Carbocation intermediate (rearrangement possible)**, add the proton to make the more stable carbocation **when there is a difference** Regiochemistry: **Markovnikov** Stereochemistry: **Mixed**

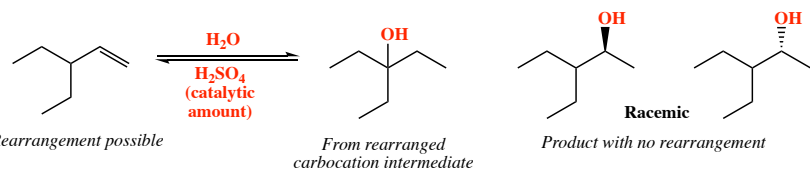
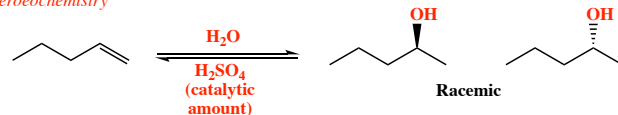
Replace the pi bond with bonds to X on the more substituted carbon and H on the less substituted carbon with mixed stereochemistry



2) Acid-Catalyzed Hydration of Alkenes to Give Alcohols

Mechanism Keys: **Carbocation intermediate (rearrangement possible)** add the proton to make the more stable carbocation **when there is a difference** Regiochemistry: **Markovnikov** Stereochemistry: **Mixed**

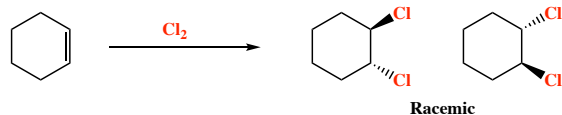
Replace the pi bond with bonds to OH on the more substituted carbon and H on the less substituted carbon with mixed stereochemistry



3) Halogenation of Alkenes to Give Vicinal Dihalalkanes

Mechanism Keys: **Three-membered ring halonium ion intermediate** Regiochemistry: **N/A** Stereochemistry: **Anti**

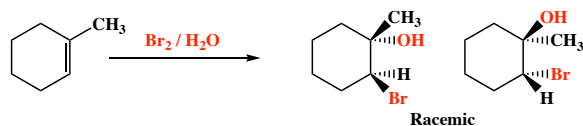
Replace the pi bond with bonds to X with anti stereochemistry only



4) Hydrohalogenation of Alkenes to Give Halohydrins

Mechanism Keys: **Three-membered ring halonium ion intermediate**, water will attack the more highly substituted carbon **because that has more positive charge** Regiochemistry: **Markovnikov** Stereochemistry: **Anti**

Replace the pi bond with bonds to OH on the more substituted carbon and X on the less substituted carbon with anti stereochemistry only

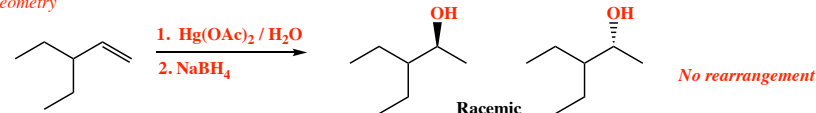


5) Oxymercuration-Reduction of Alkenes to Give Alcohols

Mechanism Keys: **Does not rearrange**, the OH ends up on the more highly substituted carbon Regiochemistry:

Markovnikov Stereochemistry: **Mixed**

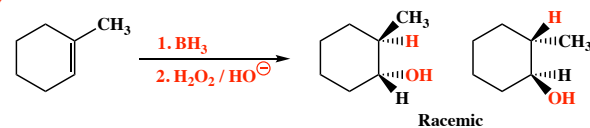
Replace the pi bond with bonds to OH on the more substituted carbon and H on the less substituted carbon with mixed geometry



6) Hydroboration-Oxidation of Alkenes to Give Alcohols

Mechanism Keys: **Four-membered ring transition state as H and B atoms add simultaneously to same face of pi bond**, the H atom goes on the more substituted carbon atom Regiochemistry: **non-Markovnikov** Stereochemistry: **Syn**

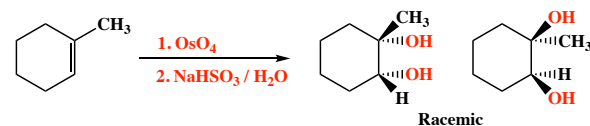
Replace the pi bond with bonds to H on the more substituted carbon and OH on the less substituted carbon with syn geometry only



7) Geminal Dihydroxylation of Alkenes to Give Vicinal Diols (the Oszy Osbourne reaction)

Mechanism Keys: **Cyclic osmate ester intermediate makes it so both OH groups are added to the same face of the double bond** Regiochemistry: **N/A** Stereochemistry: **Syn**

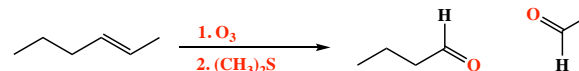
Replace the pi bond with bonds to OH with syn geometry only



8) Ozonolysis of Alkenes to Give Aldehydes and Ketones

Mechanism Keys: **Malozonide that then rearranges into an ozonide intermediate**, explaining why the carbon-carbon bond is broken Regiochemistry: **N/A** Stereochemistry: **N/A**

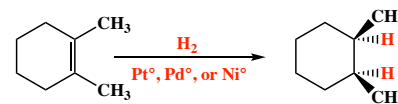
Replace the carbon-carbon double bond with two double bonds to an O atom (C=O) while **BREAKING THE C=C!**



9) Hydrogenation of an Alkene to Give Alkanes

Mechanism Keys: **Alkene and H2 adsorb on metal surface**, then new bonds form to both carbon atoms essentially **simultaneously** so the H atoms add to the same face Regiochemistry: **N/A** Stereochemistry: **syn**

Replace the pi bond with bonds to H with syn geometry only

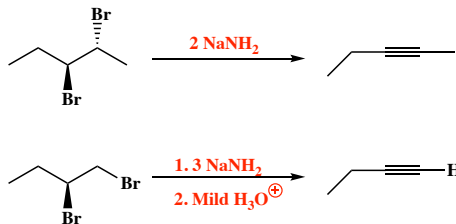


Chapter 7

10) Reaction of Vicinal Dihalides with Base to Give Alkynes

Mechanism Keys: **Double E2 reaction. For terminal alkynes, 3 equivalents of base are needed because the terminal H atom is also removed and must be replaced in mild acid** Regiochemistry: N/A Stereochemistry: N/A

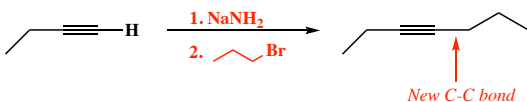
Replace the bonds to X with two pi bonds to give an alkyne



11) Reaction of Terminal Alkynes with Base then a Primary Haloalkane to Give an Alkyne with a New C-C Bond

Mechanism Keys: **S_N2 reaction. Haloalkane must be primary to avoid E2.** Regiochemistry: N/A Stereochemistry: N/A

Replace the terminal C-H bond with a new C-C bond to the carbon that had the C-X bond.

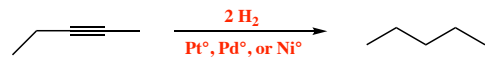


12) Hydrogenation of Alkynes to Give Alkanes

Mechanism Keys: **Alkyne and H₂ adsorb on metal surface, then new bonds form to both carbon atoms essentially simultaneously. Happens twice and cannot be stopped because alkenes produced as intermediates react faster than alkynes**

Regiochemistry: N/A Stereochemistry: N/A

Replace the two pi bonds with four bonds to H atoms

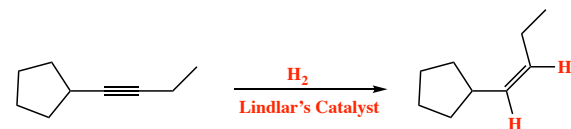


13) Reduction of Alkynes with H₂ and Lindlar's Catalyst to Give Z Alkenes

Mechanism Keys: **Alkene and H₂ adsorb on metal surface, then new bonds form to both carbon atoms essentially simultaneously. Pb and quinoline poison the catalyst so the reaction stops at a Z alken** Regiochemistry: N/A

Stereochemistry: Syn

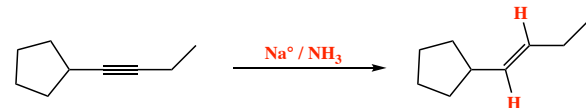
Replace one pi bond of an alkyne with bonds to H atoms to give only a Z product



14) Reduction of Alkynes with Na⁺ and NH₃ to Give E Alkenes

Mechanism Keys: **Radical mechanism, two one-electron transfers from Na⁺, followed by adding two protons from NH₃, the more stable trans alkene (less steric strain) predominates.** Regiochemistry: N/A Stereochemistry: Anti

Replace one pi bond of an alkyne with bonds to H atoms to give only an E product

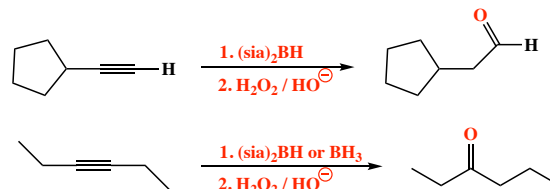


15) Hydroboration-Oxidation of Terminal Alkynes to Give Aldehydes (Using the "Antler" Reagent)

Mechanism Keys: **Four-membered ring transition state as H and B atoms add to same face of pi bond, enol intermediate followed by enol-keto tautomerization, "antlers" ensure regiochemical control so that H adds to more substituted carbon.**

Regiochemistry: **non-Markovnikov** Stereochemistry: N/A

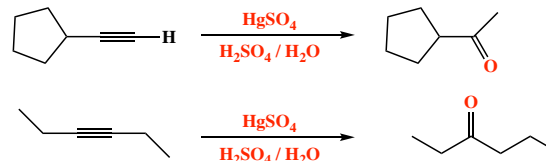
Replace the two pi bonds of a terminal alkyne with double bonds to an O atom to give an aldehyde. When the alkyne is not terminal, a ketone is the product.



16) Oxymercuration-Reduction of Alkynes to Ketones

Mechanism Keys: **Enol intermediate followed by enol-keto tautomerization. O atom ends up bonded to more substituted carbon** Regiochemistry: Markovnikov Stereochemistry: Mixed

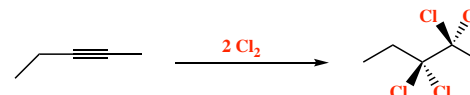
Replace the two pi bonds of an alkyne with double bonds to an O atom to give a ketone. When the alkyne is terminal the internal carbon ends up as the C=O



17) Reaction of Alkynes with X₂ to Give Tetrahaloalkanes

Mechanism Keys: **X₂ reacts with both pi bonds** Regiochemistry: N/A Stereochemistry: N/A

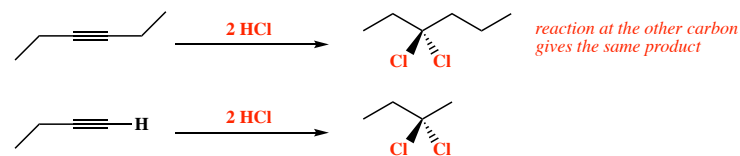
Replace both pi bonds with 2 bonds to X atoms for each carbon atom.



18) Reaction of Alkynes with HX to Give Geminal Dihalooalkanes

Mechanism Keys: **HX reacts with both pi bonds, and both X atoms always end up on the same carbon atom, which is the internal carbon of terminal alkynes** Regiochemistry: Markovnikov Stereochemistry: N/A

Replace both pi bonds on one carbon with 2 bonds to X atoms, and the other carbon with 2 bonds to H. For terminal alkynes, the internal carbon gets the two bonds to X and the terminal carbon gets the two bonds to H

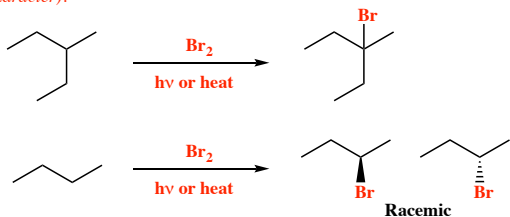


Chapter 8

19) Free Radical Halogenation of Alkanes to Give Haloalkanes

Mechanism Keys: **Free radical chain process, initiation when Br₂ is exposed to light (hv) or heat to give Br radicals that abstracts an H atom on the most substituted carbon during the propagation step** Regiochemistry: **Br ends up on most substituted C atom** Stereochemistry: **N/A**

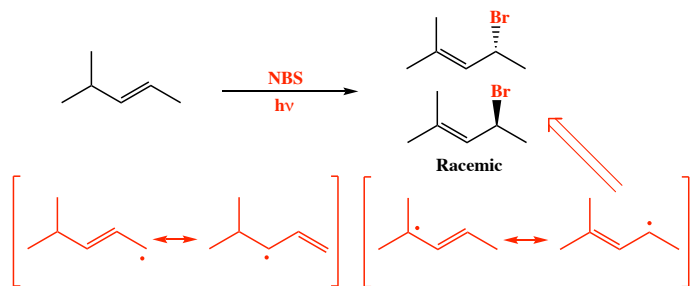
On the most substituted carbon with an H atom, replace one C-H bond with a C-Br bond. Use Br₂ because it is more selective than Cl₂ (Hammonds postulate: The Br₂ reaction has an endothermic first step so the transition state has more radical character).



20) Allylic Halogenation of Alkenes to Give Haloalkanes

Mechanism Keys: **Free radical chain process, initiation when NBS is exposed to light (hv) to give Br radicals that abstracts an H atom on the carbon adjacent to the C=C to create allylic radical intermediates that add a Br atom to make the most stable product (most highly substituted alkene)** Regiochemistry: **Br ends up on the carbon adjacent to the most stable possible alkene product** Stereochemistry: **N/A**

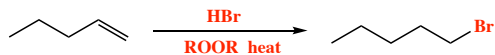
Analyze both of the contributing structures for both allyl radicals that are possible, consider adding a Br atom to the location of each carbon radical on each contributing structure, analyze each of these possible products and choose the most stable alkene (most substituted alkene) as the predominant product



21) Reaction of Alkenes with HBr in the Presence of H₂O₂ and Heat to Give Haloalkanes

Mechanism Keys: **Radical mechanism initiated by peroxide and hv or heat, product comes from most stable radical** Regiochemistry: **non-Markovnikov** Stereochemistry: **Mixed**

Replace the pi bond with bonds to Br on the less substituted carbon and H on the more substituted carbon with mixed geometry



Chapter 9

22) Substitution vs. Elimination of Haloalkanes to Give Various Substitution Products and Alkenes From Elimination

S_N2: Nucleophile attacks backside of carbon-leaving group bond as the leaving group departs

Regiochemistry: **N/A** Stereochemistry: **InVERSiON**

E2: Base removes H atom on carbon adjacent to leaving group as the leaving group departs. The H atom being removed and the leaving group must be in an antiperiplanar geometry for reaction to take place

Regiochemistry: **Zaitsev product (most highly substituted alkene)** Stereochemistry: **determined by antiperiplanar transition state requirement**

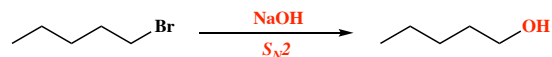
S_N1: Leaving group departs to give carbocation intermediate then nucleophile binds to carbocation

Regiochemistry: **N/A** Stereochemistry: **Scrambled (not quite racemic)**

E1: Leaving group departs to give carbocation intermediate that loses a proton on an adjacent carbon to give an alkene

Regiochemistry: **Zaitsev product (most highly substituted alkene)** Stereochemistry: **N/A**

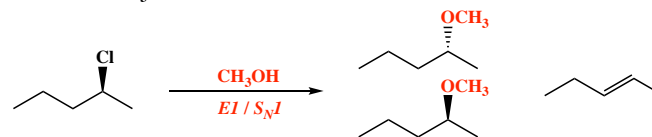
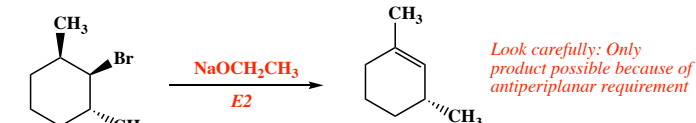
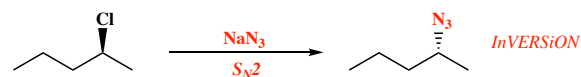
Primary haloalkane - S_N2 only (except when KOtBu is the base)



Secondary haloalkane - S_N2 when nucleophile is not strong or very weak base

E2 when nucleophile is a strong base

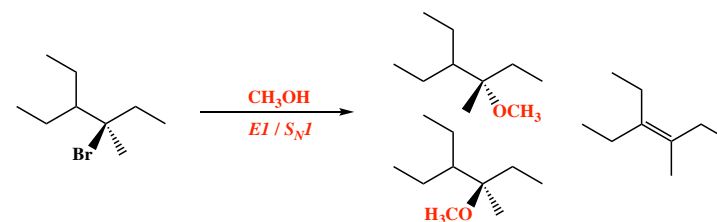
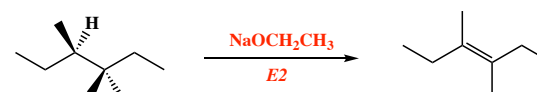
E1/S_N1 when nucleophile is a very weak base



Tertiary haloalkane - S_N2 never

E2 when nucleophile is anything but a very weak base

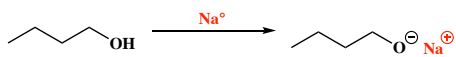
E1/S_N1 when nucleophile is a very weak base



Chapter 10

23) Reaction of Alcohols with Alkali Metals (Na^\ominus , Li^\ominus) to Give Alkoxides

Mechanism Keys: **Alkali metals react with alcohols to make alkoxides and H_2** Regiochemistry: N/A Stereochemistry: N/A
Replace the H atom of an OH group with a negative charge



24) Reaction of Alcohols with HX to Give Haloalkanes

Mechanism Keys: **Alcohols react with HX by protonating the OH group (thus creating a good leaving group), then the halide anion reacts via an $\text{S}_{\text{N}}2$ mechanism for primary alcohols and via an $\text{S}_{\text{N}}1$ mechanism for secondary/tertiary alcohols, to give a haloalkane** Regiochemistry: N/A Stereochemistry: InVERSION for $\text{S}_{\text{N}}2$ and scrambled for $\text{S}_{\text{N}}1$
Replace the alcohol OH group with X. This reaction must be used with tertiary alcohols as PBr_3 and SOCl_2 only work with primary and secondary alcohols.



25) Reaction of Alcohols with PBr_3 to Give Bromoalkanes

Mechanism Keys: **Primary and secondary alcohols react with PBr_3 to give an intermediate with an O-P bond (thus creating a good leaving group), that reacts with bromide anion via an $\text{S}_{\text{N}}2$ mechanism to give a haloalkane** Regiochemistry: N/A Stereochemistry: InVERSION
Replace the alcohol OH group with Br with InVERSION of any stereochemistry at the carbon that was bonded to the OH group of the original alcohol. Primary and secondary alcohols only because tertiary alcohols cannot react via $\text{S}_{\text{N}}2$.



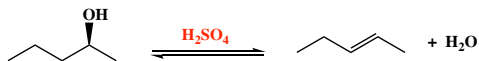
26) Reaction of Alcohols with SOCl_2 to Give Chloroalkanes

Mechanism Keys: **Primary and secondary alcohols react with SOCl_2 to give an intermediate with an O-S bond (thus creating a good leaving group), that reacts with chloride anion via an $\text{S}_{\text{N}}2$ mechanism to give a haloalkane** Regiochemistry: N/A Stereochemistry: InVERSION
Replace the alcohol OH group with Cl with InVERSION of any stereochemistry at the carbon that was bonded to the OH group of the original alcohol. Primary and secondary alcohols only because tertiary alcohols cannot react via $\text{S}_{\text{N}}2$.



27) Reaction of Alcohols with Sulfuric Acid to Give Alkenes

Mechanism Keys: **Alcohols react with H_2SO_4 to give alkenes via a carbocation intermediate, in a mechanism that is the exact reverse of hydration of an alkene, this is a reversible equilibrium process (Le Chatlier)** Regiochemistry: Zaitsev Stereochemistry: N/A
Replace the alcohol OH group with a new pi bond chosen to make the Zaitsev product (most substituted alkene)



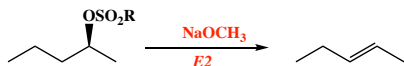
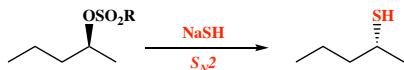
28) Reaction of Alcohols with Sulfonyl Chlorides to Give Sulfonyl Esters

Mechanism Keys: **Alcohols react as nucleophiles with sulfonyl chlorides to give sulfonyl esters, a good leaving group** Regiochemistry: N/A Stereochemistry: Retention (not InVERSION)
Replace the alcohol OH group with a new sulfonyl ester, without changing the stereochemistry



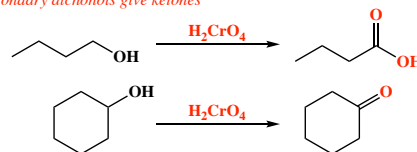
29) Reaction of Sulfonyl Esters with Nucleophiles to Give Various Substitution and Elimination Products

Mechanism Keys: **Sulfonyl esters react with nucleophiles and bases analogous to haloalkanes** Regiochemistry: E2 and E1 give Zaitsev product alkene Stereochemistry: $\text{S}_{\text{N}}2$ gives InVERSION, $\text{S}_{\text{N}}1$ scrambled, E2 gives product based on antiperiplanar transition state
Replace the sulfonyl ester with a nucleophile with InVERSION or carry out an elimination to give the Zaitsev alkene (most substituted) based on the same rules used with haloalkanes



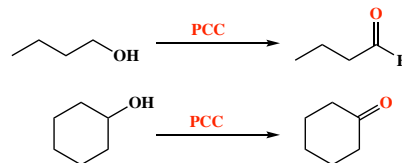
30) Reaction of Alcohols with Chromic Acid (Jones Reagent) to Give Carboxylic Acids and Ketones

Mechanism Keys: **The mechanism with primary alcohols involves a chromate ester intermediate then loss of an H atom on the carbon of the original alcohol to give an aldehyde, that adds water then reacts again. Secondary alcohols react once to give a ketone** Regiochemistry: N/A Stereochemistry: N/A
Replace every H atom on the carbon attached to the OH group with bonds to O atoms. Primary alcohols give carboxylic acids, secondary alcohols give ketones



31) Reaction of Alcohols with PCC (Pyridinium Chlorochromate) to Give Aldehydes and Ketones

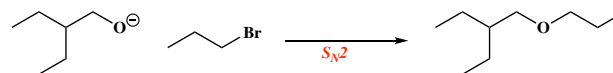
Mechanism Keys: **The mechanism with primary alcohols involves a chromate ester intermediate then loss of an H atom on the carbon of the original alcohol to give an aldehyde, and because there is no water it stops there. Secondary alcohols react once to give a ketone** Regiochemistry: N/A Stereochemistry: N/A
Replace an H atom on the carbon attached to the OH group with a pi bond to an O atom. Primary alcohols give aldehydes, secondary alcohols give ketones



Chapter 10

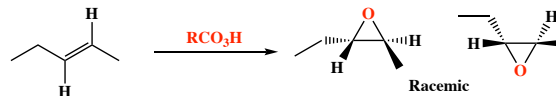
32) Reaction of Alkoxides with Primary Haloalkanes to Give Ethers (Williamson Ether Synthesis)

Mechanism Keys: **Alkoxides and primary haloalkanes react via an $\text{S}_{\text{N}}2$ mechanism. The haloalkane must be primary to avoid E2.** Regiochemistry: N/A Stereochemistry: N/A
Choose the alkoxide and haloalkane so the haloalkane is primary



32) Reaction of Alkenes with Peroxides to Give Epoxides

Mechanism Keys: **Alkenes react with peroxides in a single concerted step to give the epoxide and a carboxylic acid** Regiochemistry: N/A Stereochemistry: N/A
Create the epoxide from the alkene, making sure to keep the groups consistent (groups that are cis on the alkene stay cis in the epoxide) and add the O atom to both the top and bottom faces of the alkene



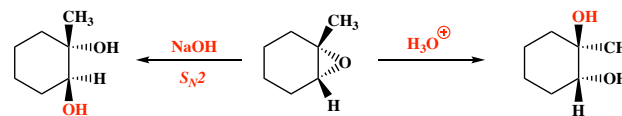
33) Reaction of Halohydrins with Base to Give Epoxides

Mechanism Keys: **Halohydrins react with base to deprotonate the OH group and give an alkoxide intermediate, which attacks the backside of the C-X bond in a single step to give the epoxide** Regiochemistry: N/A Stereochemistry: N/A
Create the epoxide from the halohydrin by lining up the OH group to be antiperiplanar to the X before making the new bond from O to the carbon of the original C-X bond

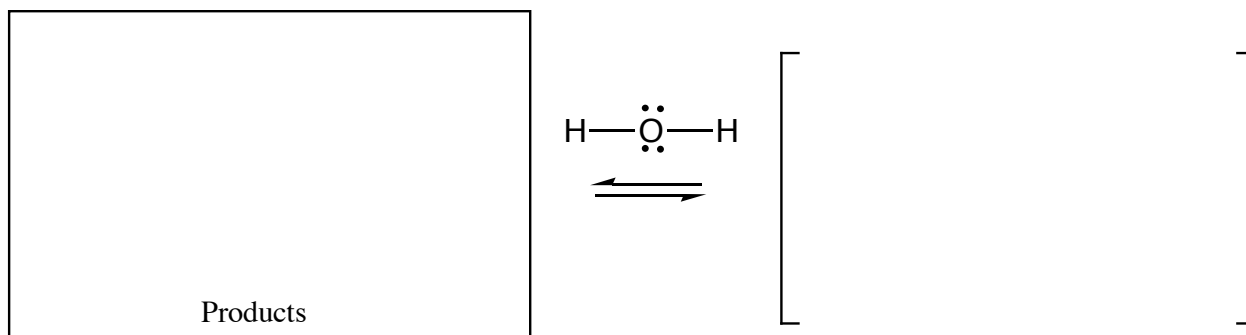
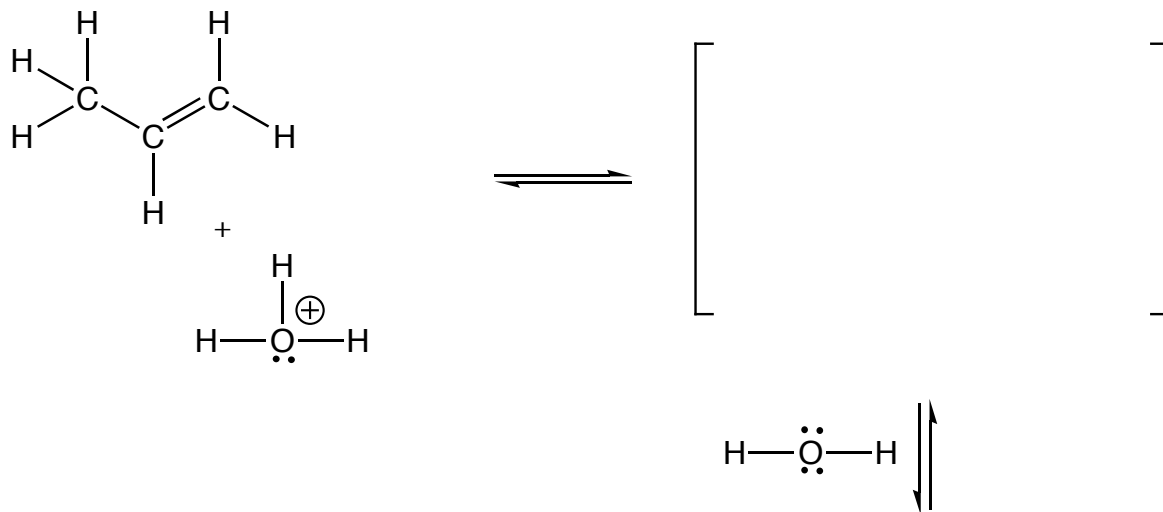
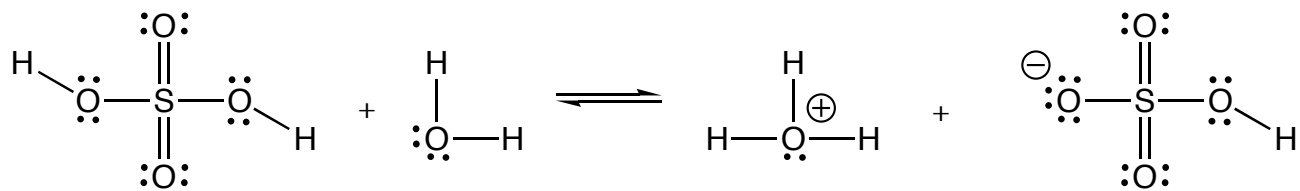


34) Reaction of Epoxides in Acid or Base to Give Vicinal Diols

Mechanism Keys: **Epoxides react with hydroxide from the backside of the C-O bond via an $\text{S}_{\text{N}}2$ mechanism at the less-hindered carbon, and in acid epoxides are protonated to give a positively-charged intermediate analogous to the halonium ion intermediate, so water attacks the more substituted carbon** Regiochemistry: In base, OH adds to less-hindered carbon atom, in acid OH adds to the more substituted carbon atom Stereochemistry: Anti (backside attack on epoxide C-O bond)
Create the vicinal dihalide by adding the OH from the less-hindered side in base and more hindered side in acid, inverting the chiral center at the carbon of the attack and retaining stereochemistry at the carbon that keeps the O atom of the original epoxide, always giving trans product in both cases



Acid-catalyzed Hydration of an Alkene

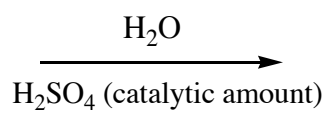
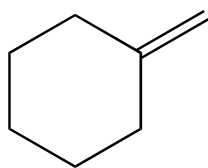


Summary:

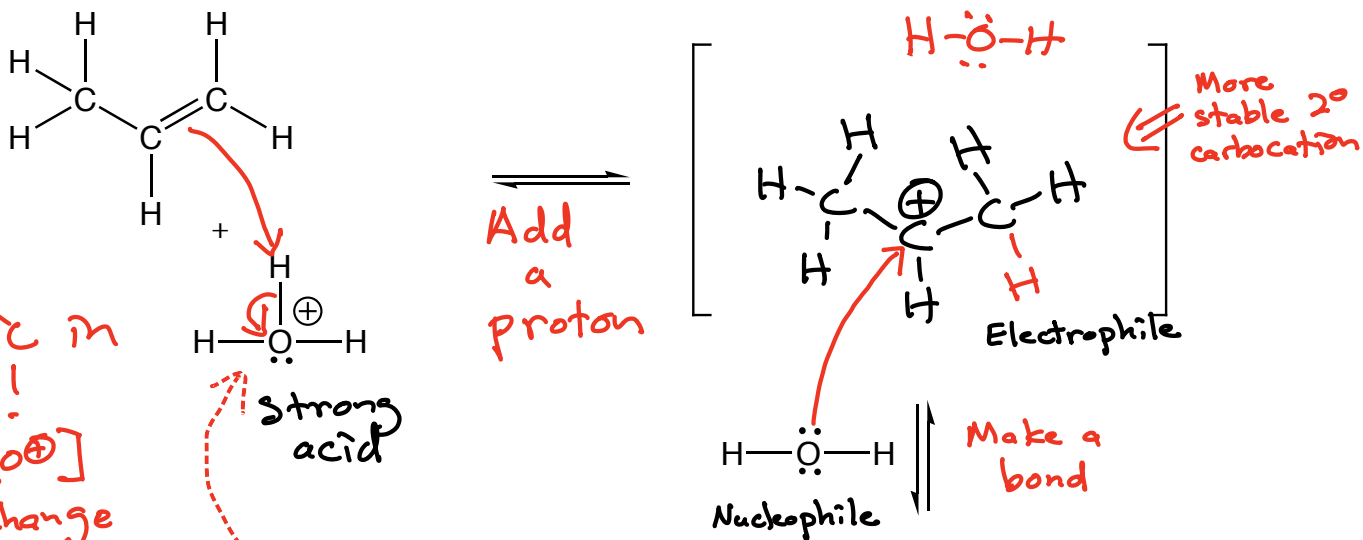
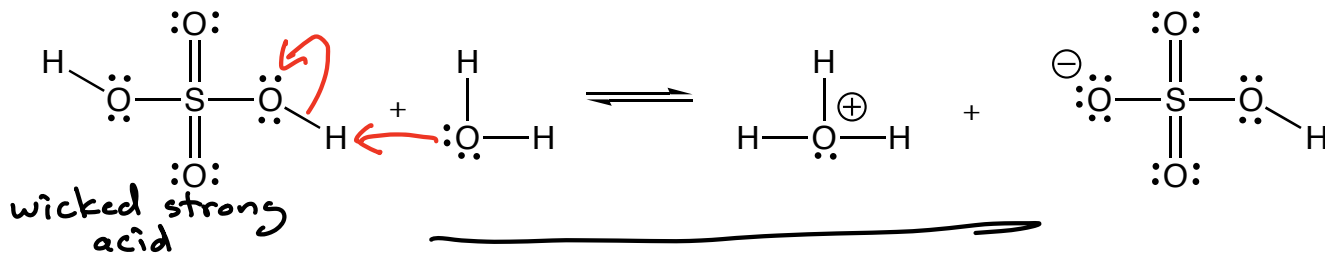
Regiochemistry:

Stereochemistry:

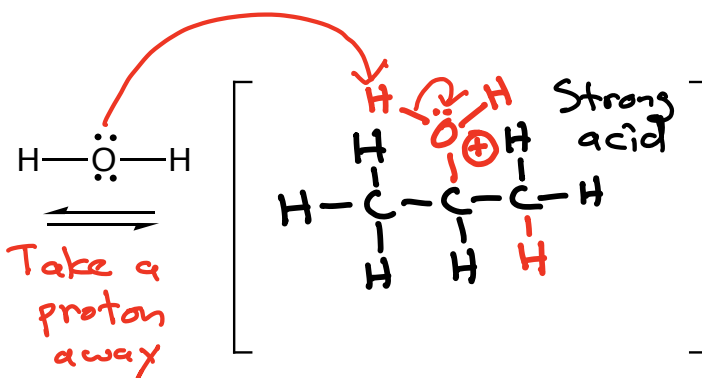
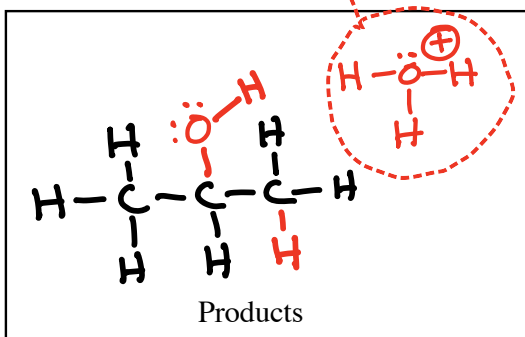
Example:



Acid-catalyzed Hydration of an Alkene



Catalytic in Acid!
 ⇒ The $[\text{H}_3\text{O}^+]$ does not change during the reaction

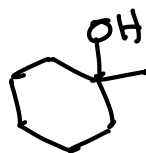
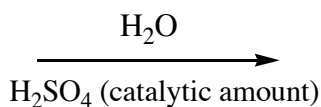
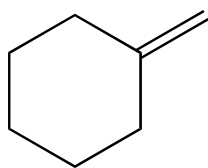


Summary: Proton adds to make a carbocation intermediate, water attacks to make a new bond, take a proton away to make the product alcohol. Catalytic in H_3O^+

Regiochemistry: **Markovnikov's Rule**

Stereochemistry: **Mixed (time capsule)**

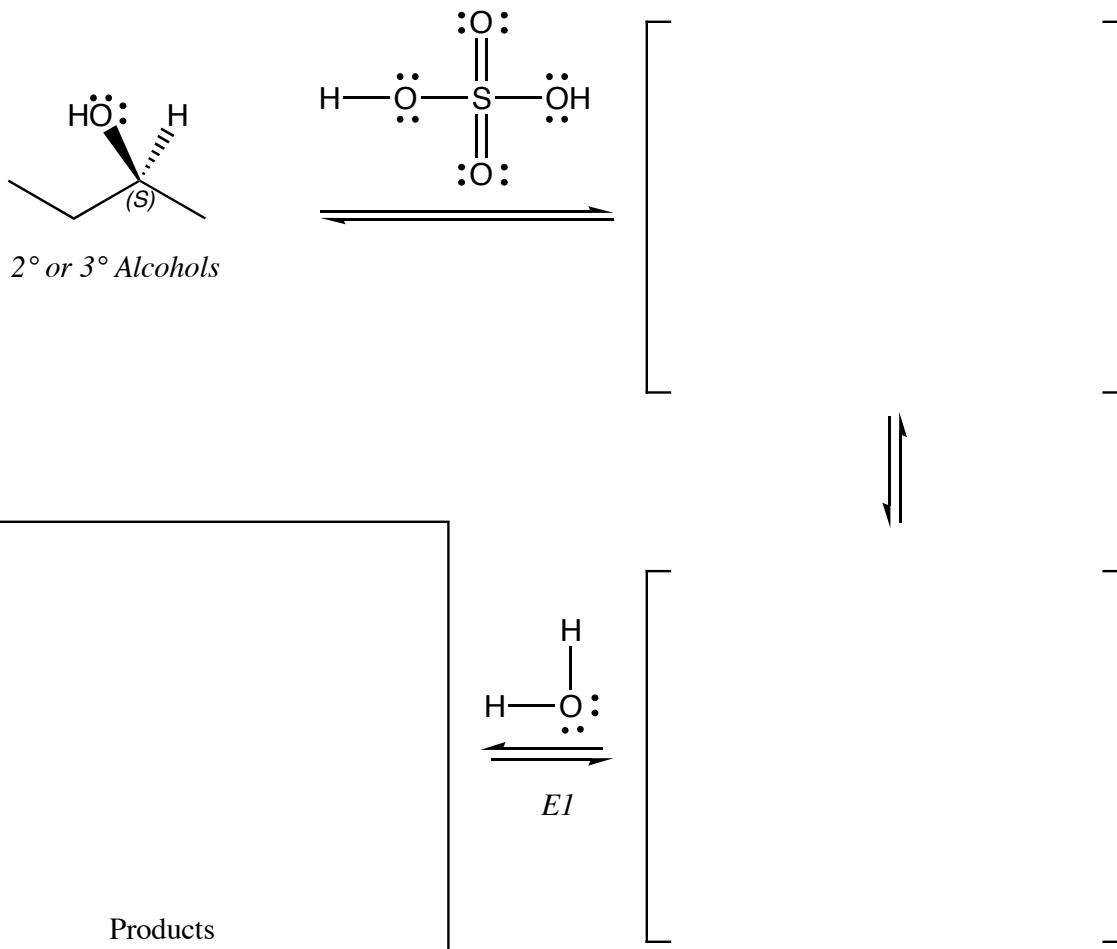
Example:



(Not chiral)

-OH on more substituted C atom ⇒ Markovnikov's Rule

2° or 3° Alcohol Dehydration

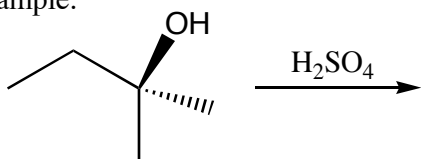


Summary:

Regiochemistry:

Stereochemistry:

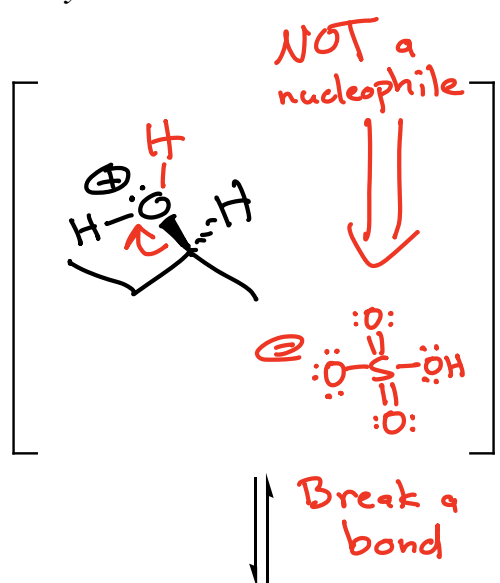
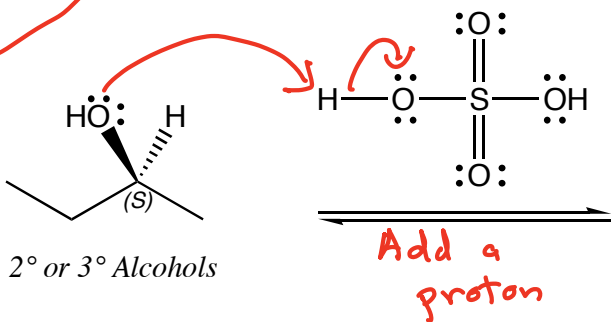
Example:



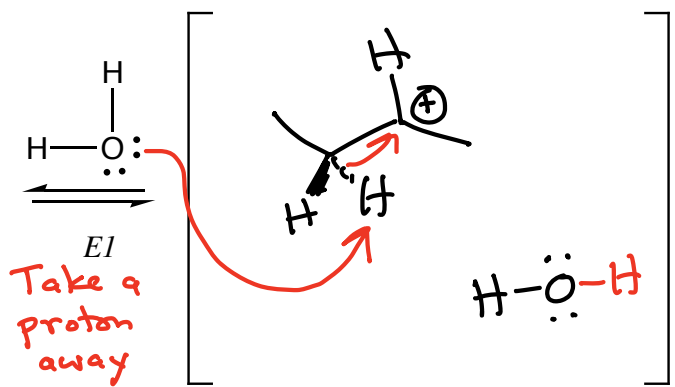
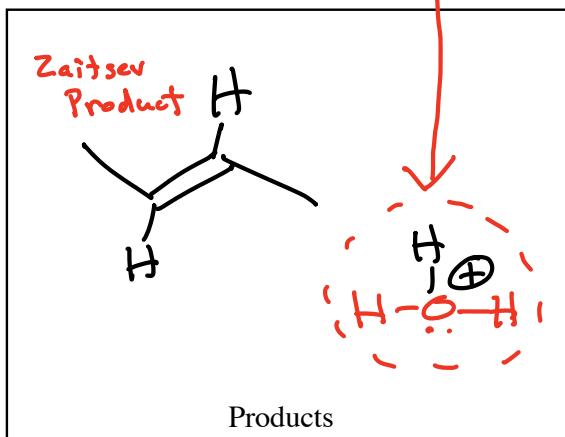
1° alcohols react via E2

2° or 3° Alcohol Dehydration

E1



Catalytic in acid

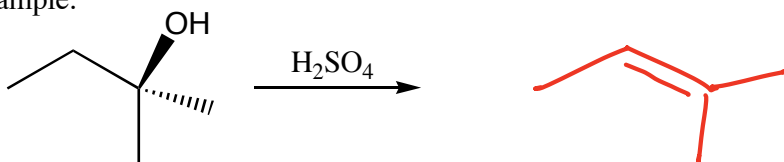


Summary: The OH group is protonated in strong acid to make a good leaving group, water, which breaks a bond to give a carbocation that has a proton taken away to give the product alkene

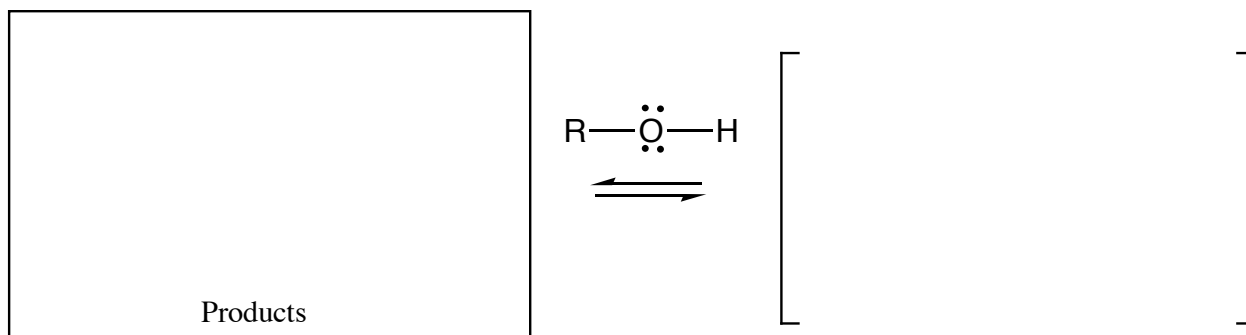
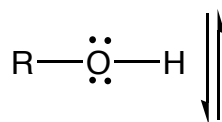
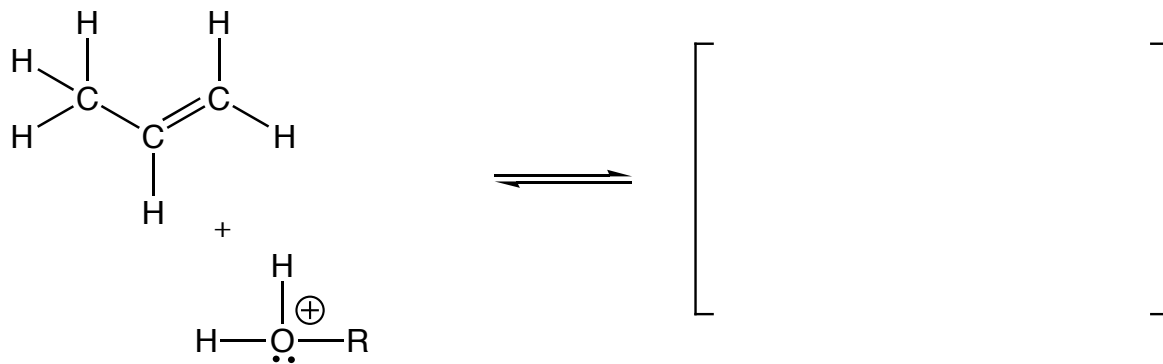
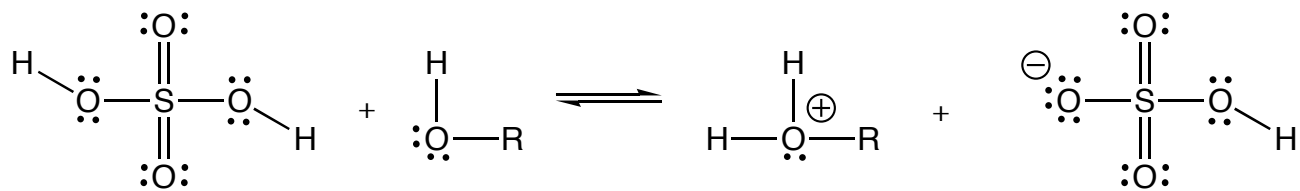
Regiochemistry: Zaitsev's Rule

Stereochemistry: N/A

Example:



Acid-catalyzed Reaction of an Alcohol with an Alkene

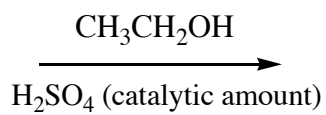
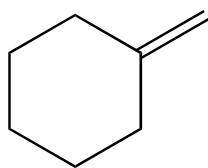


Summary:

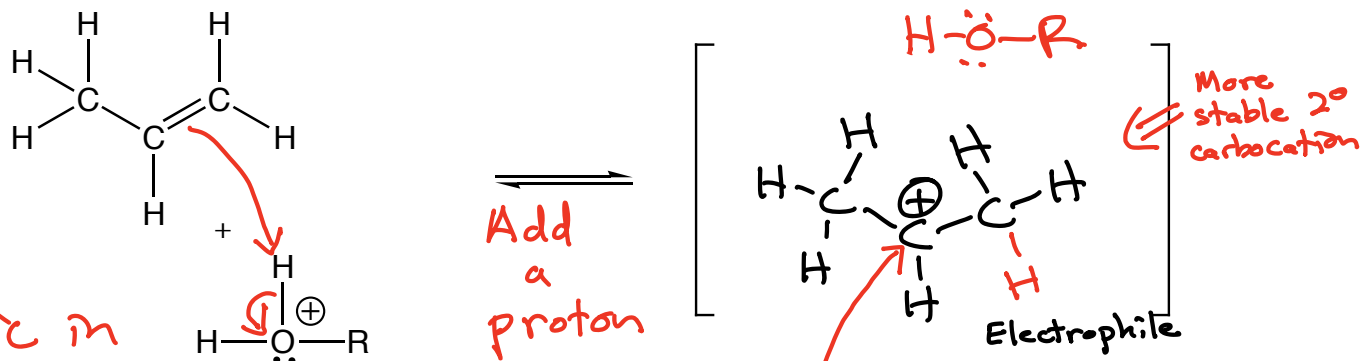
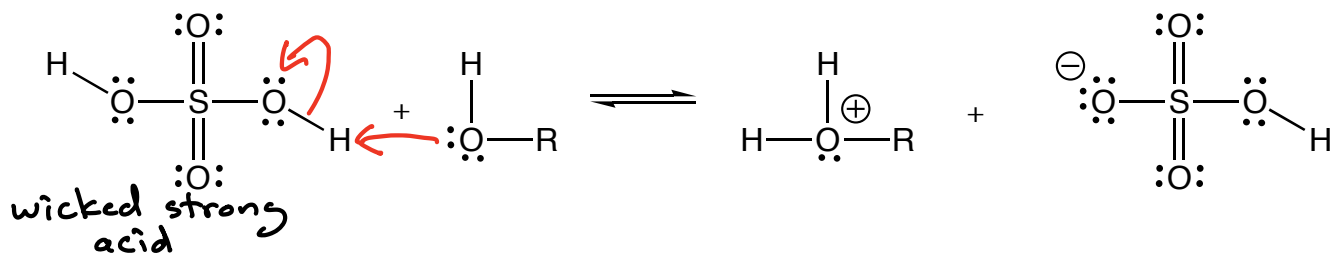
Regiochemistry:

Stereochemistry:

Example:

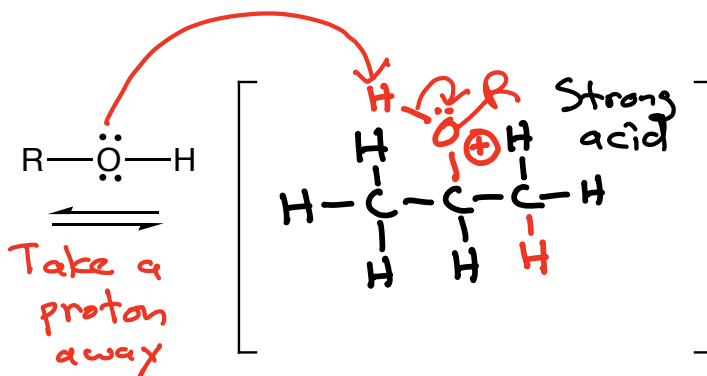
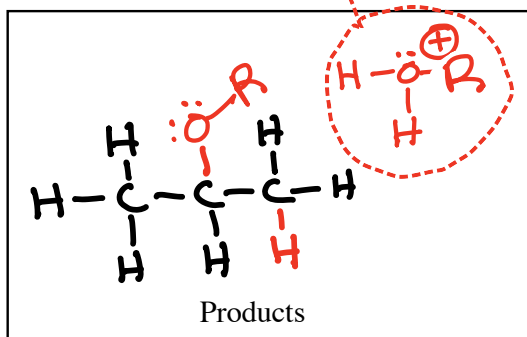
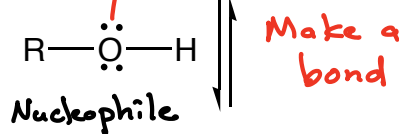


Acid-catalyzed Reaction of an Alcohol with an Alkene



Catalytic in Acid!
 ⇒ The $[\text{H}_3\text{O}^+]$ does not change during the reaction

strong acid

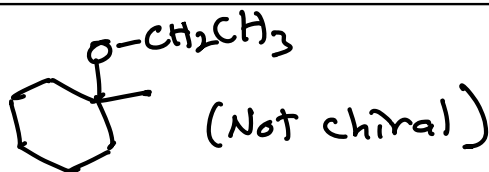
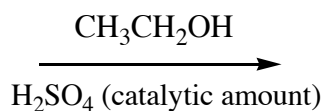
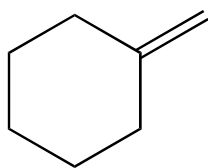


Summary: Proton adds to make a carbocation intermediate, alcohol attacks to make a new bond, take a proton away to make the product ether. Catalytic in H_3O^+

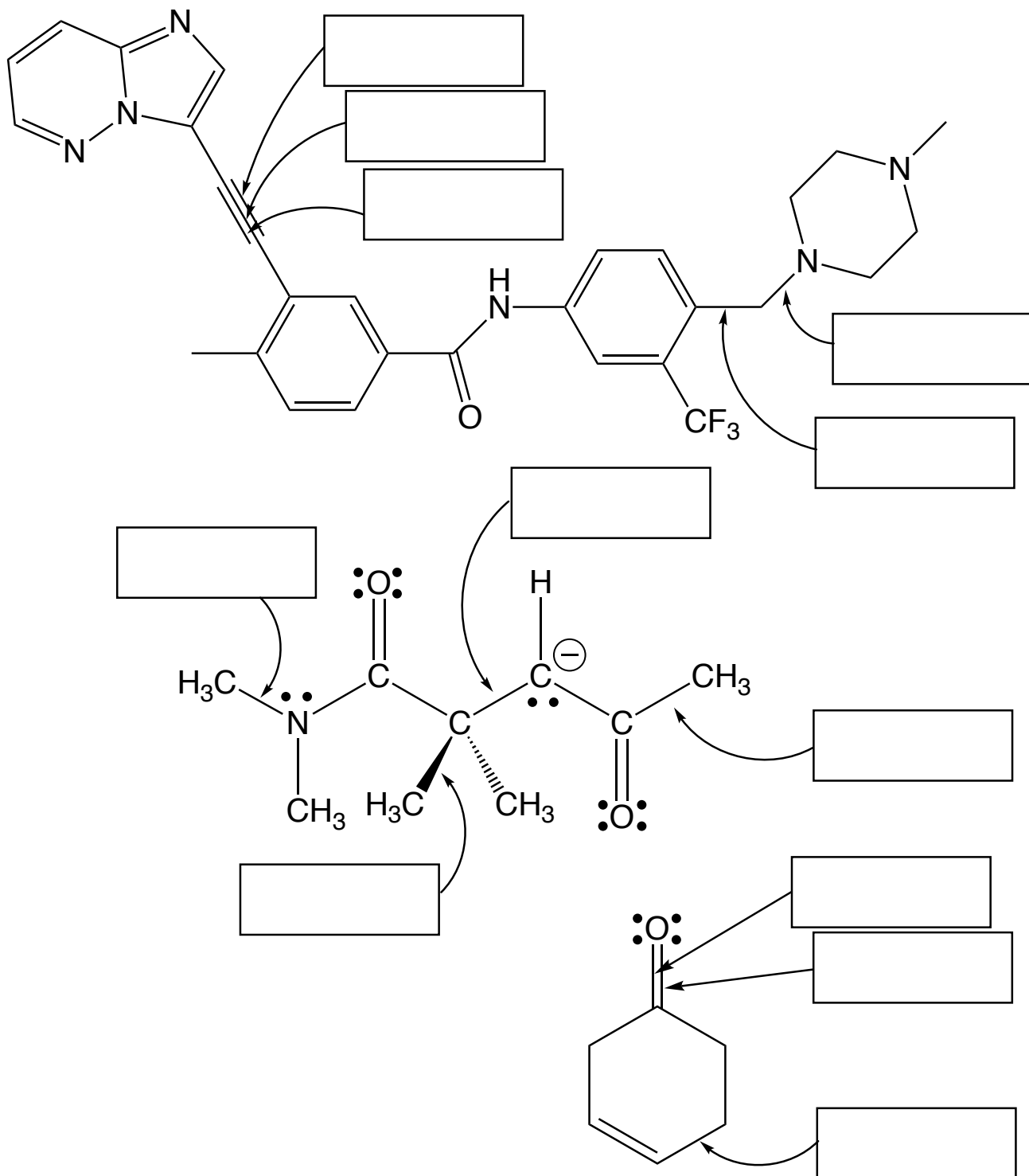
Regiochemistry: **Markovnikov's Rule**

Stereochemistry: **Mixed**

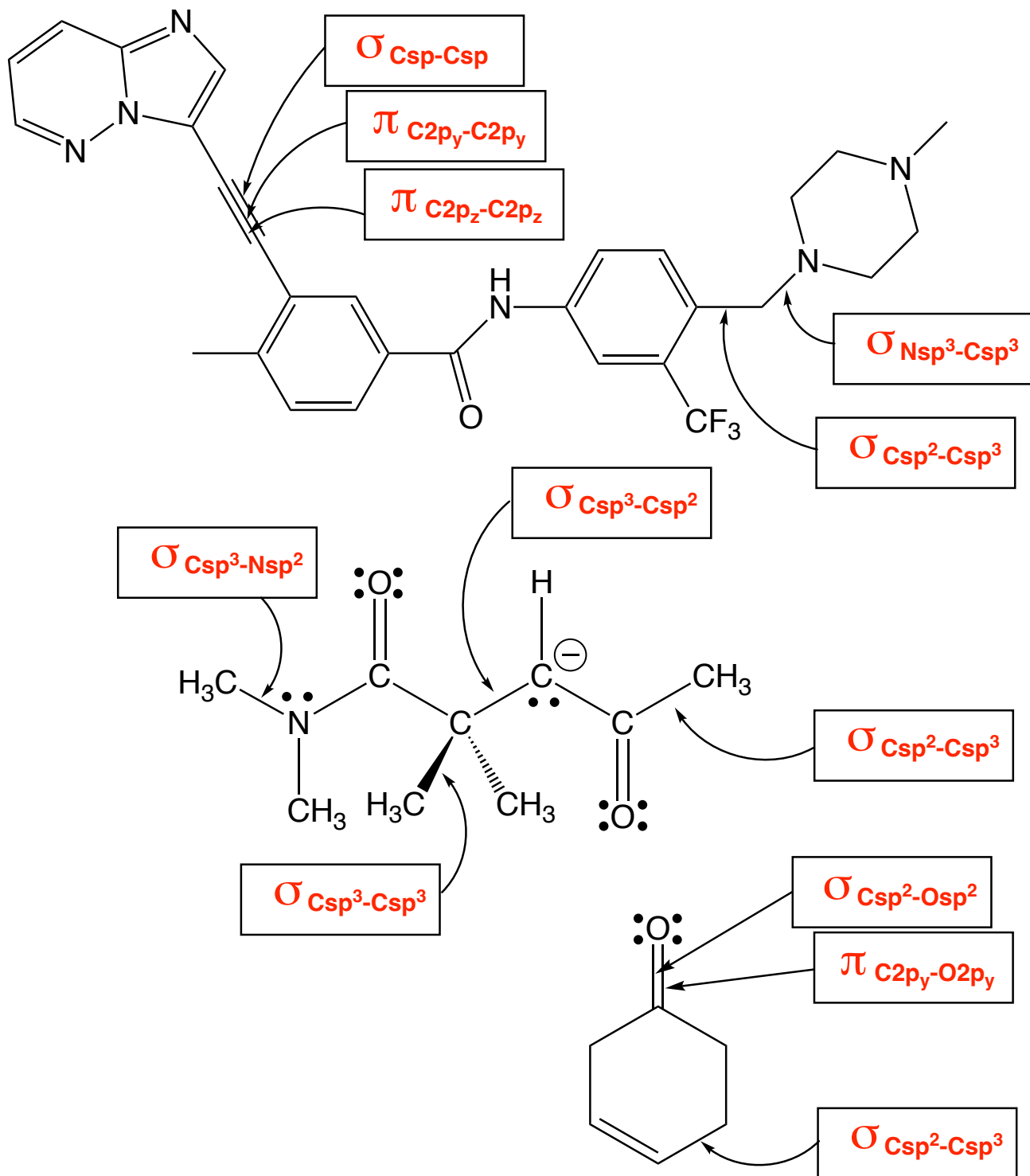
Example:



17. (2 pts each) Describe each bond indicated with an arrow as the overlap of hybridized orbitals. For example, an answer might be $\sigma \text{Csp}^3\text{-Csp}^3$

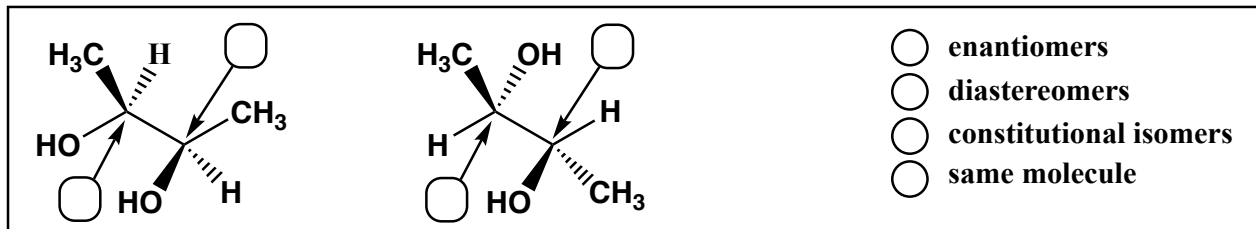
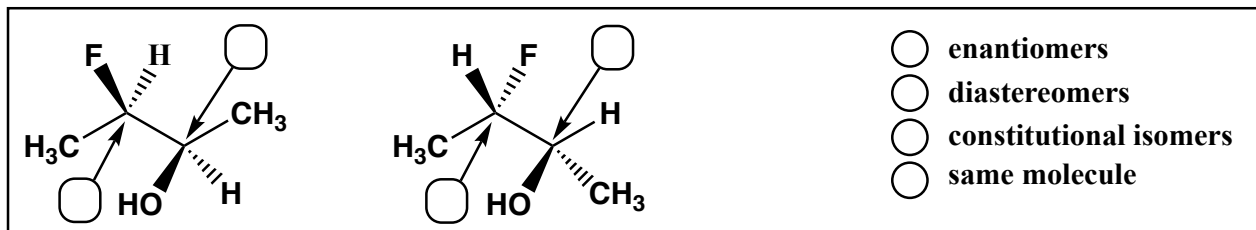
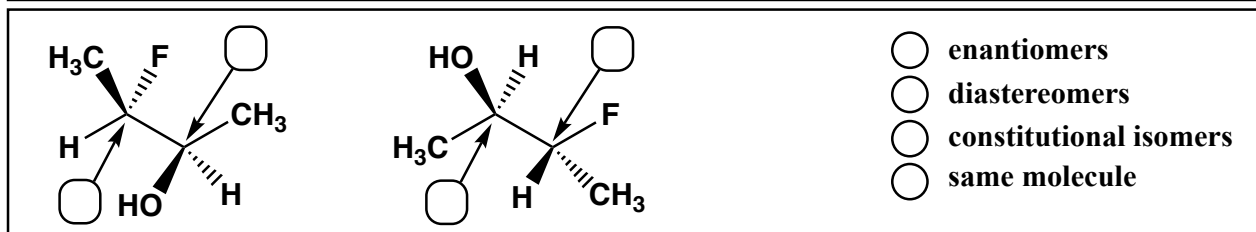
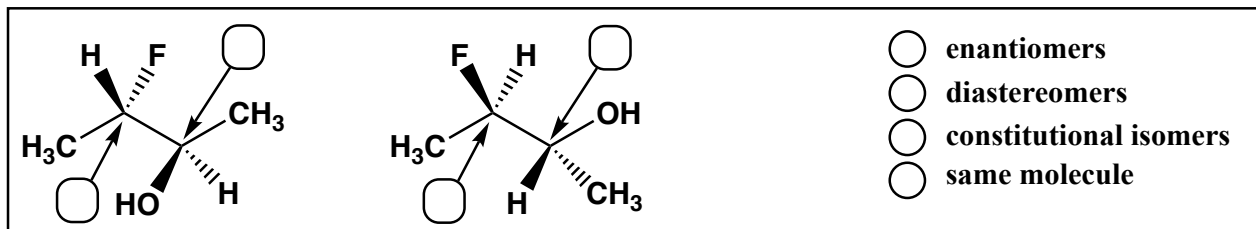


17. (2 pts each) Describe each bond indicated with an arrow as the overlap of orbitals. For example, an answer might be $\sigma_{\text{Csp}^3-\text{Csp}^3}$

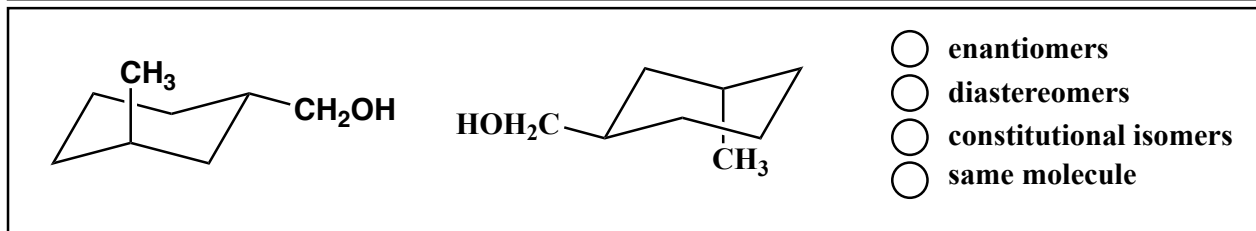
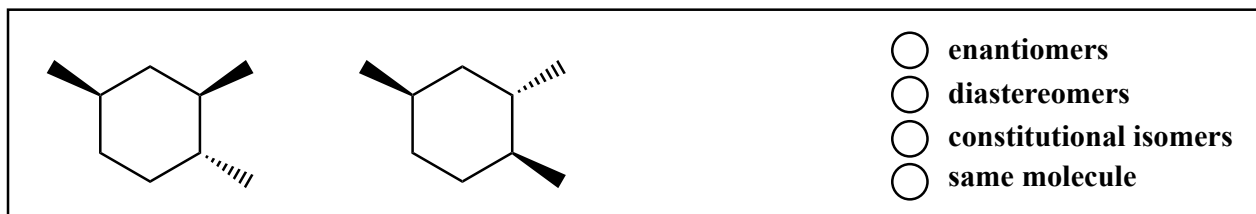


21. (38 pts) For each pair of molecules, on the line provided state the relationship between the two structures. Possible answers could be **enantiomers**, **diastereomers**, **constitutional isomers**, or **same molecule**. Fill in the circle to indicate the correct relationship between the molecules shown. In the boxes provided next to each chiral center, write "R" or "S" to indicate the absolute stereochemistry present.

Relationship:

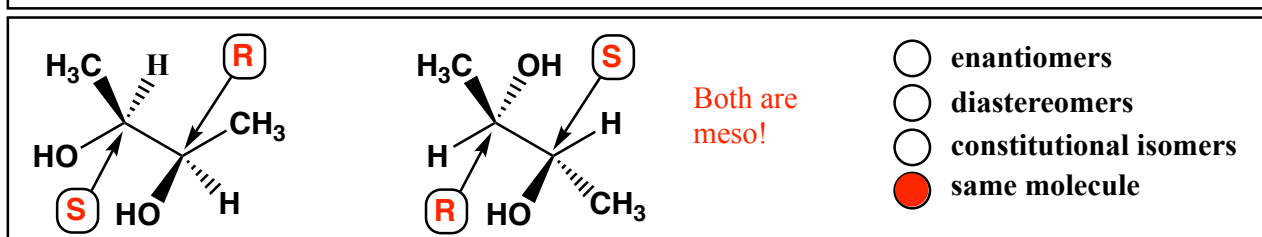
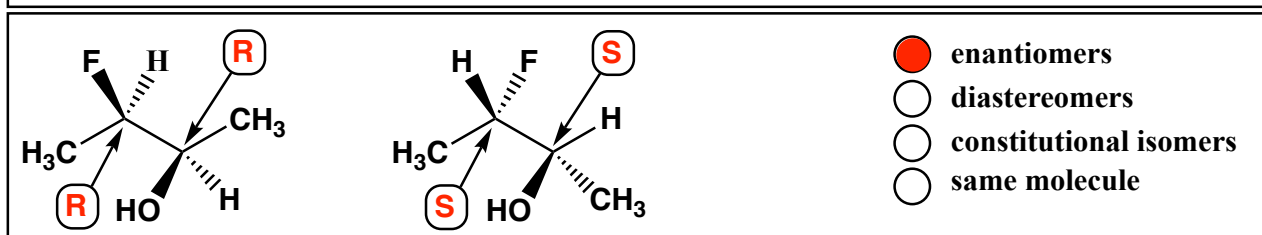
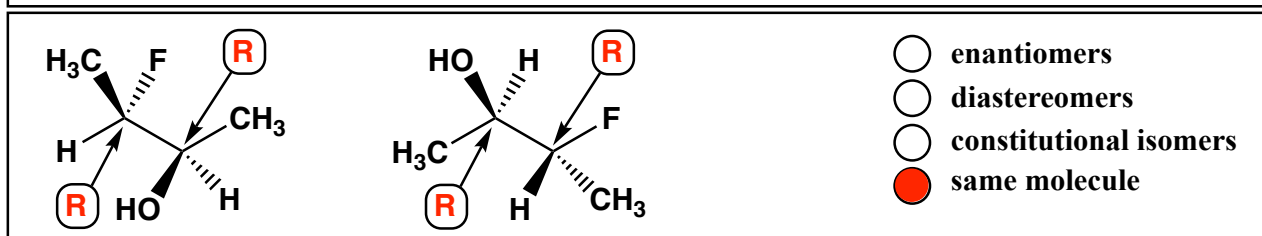
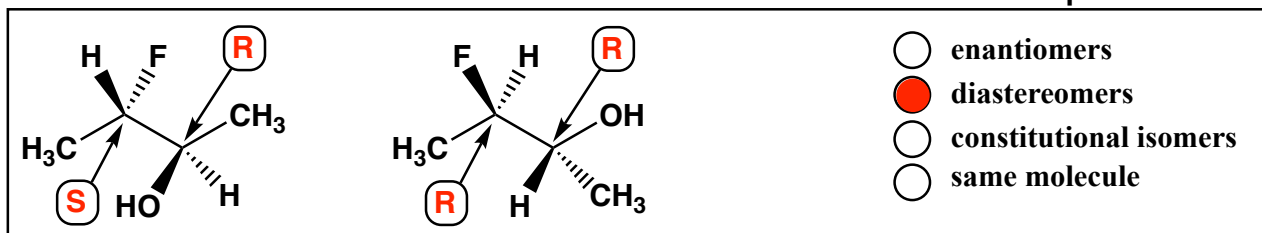


You do not need to label the chiral centers with "R" or "S" on these last two.

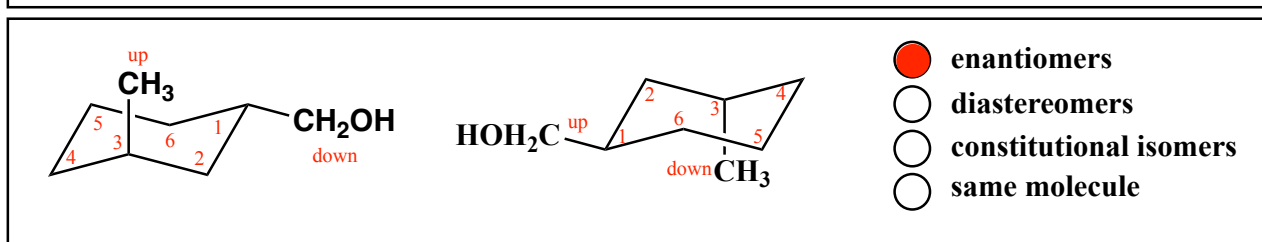
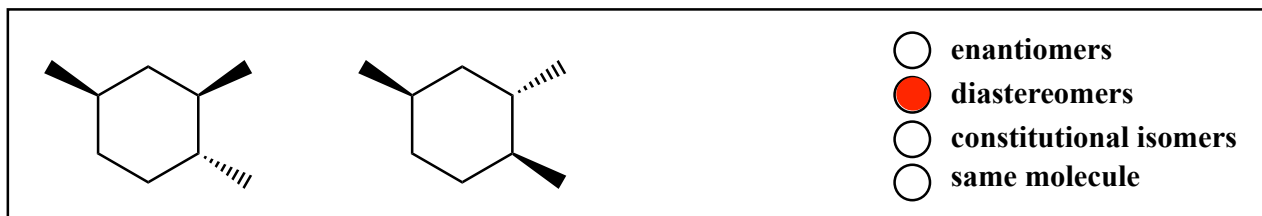


23. (38 pts) For each pair of molecules, on the line provided state the relationship between the two structures. Possible answers could be **enantiomers**, **diastereomers**, **constitutional isomers**, or **same molecule**. Fill in the circle to indicate the correct relationship between the molecules shown. In the boxes provided next to each chiral center, write "R" or "S" to indicate the absolute stereochemistry present.

Relationship:

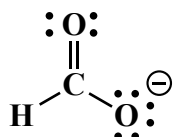


You do not need to label the chiral centers with "R" or "S" on these last three.

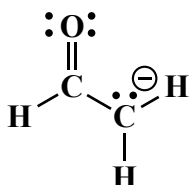


22. (22 points total). Here is an “apply what you know” problem in the form of an MCAT style passage.

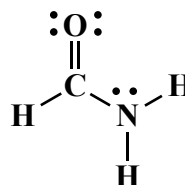
We have seen a number of molecules that contains a three-atom, delocalized pi bond (a “pi-way”). In particular, we have seen a carboxylate ion, enolate ion, and of course, amides. Each of the three atoms donates a 2p orbital that overlap.



Carboxylate Ion

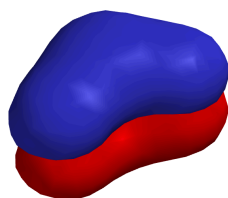


Enolate Ion

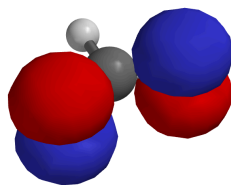


Amide

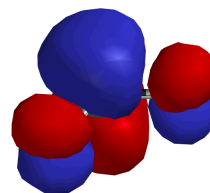
When the three 2p orbitals overlap, there are three pi molecular orbitals formed that extend over all three atoms. You have seen these before, and they are shown below:



Orbital A



Orbital B



Orbital C

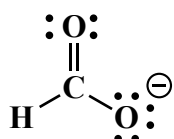
1. (4 pts) From the following choices, fill in the circle for the answer that accurately **lists the three molecular orbitals in order from lowest to highest energy**:

- Orbital A Orbital B Orbital C
 Orbital B Orbital C Orbital A
 Orbital A Orbital C Orbital B
 Orbital C Orbital B Orbital A

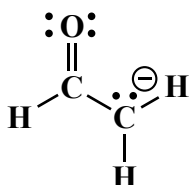
One of the more difficult parts of the analysis of delocalized pi bonding concerns how many electrons are involved in the pi molecular orbitals. Each of the ions shown above, the carboxylate ion, the enolate ion, and the amide, have the same number of pi electrons in the pi molecular orbitals.

22. (22 points total). Here is an “apply what you know” problem in the form of an MCAT style passage.

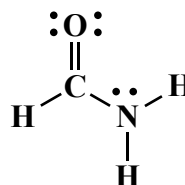
We have seen a number of molecules that contains a three-atom, delocalized pi bond (a “pi-way”). In particular, we have seen a carboxylate ion, enolate ion, and of course, amides. Each of the three atoms donates a 2p orbital that overlap.



Carboxylate Ion

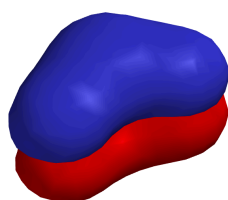


Enolate Ion

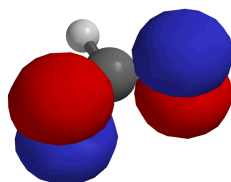


Amide

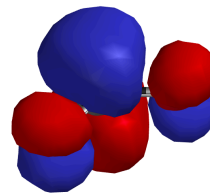
When the three 2p orbitals overlap, there are three pi molecular orbitals formed that extend over all three atoms. You have seen these before, and they are shown below:



Orbital A



Orbital B



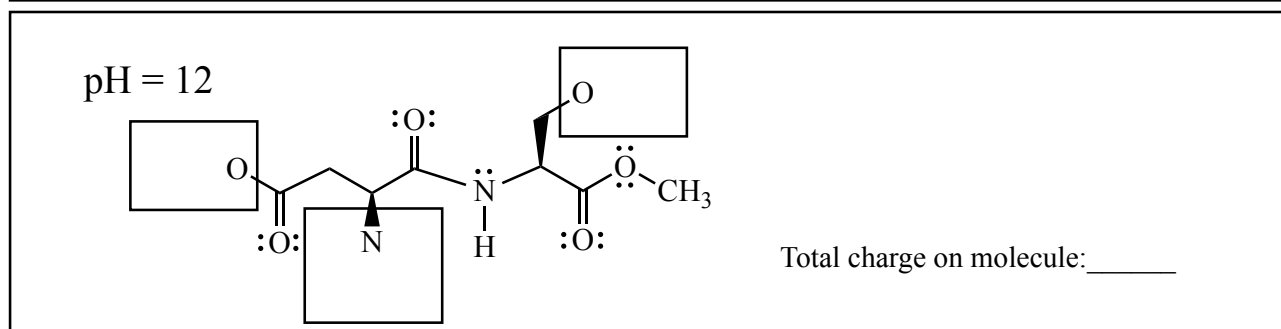
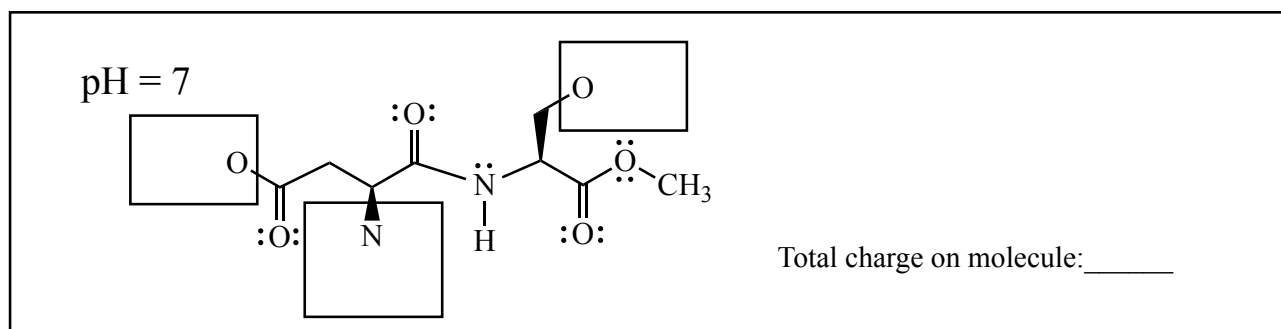
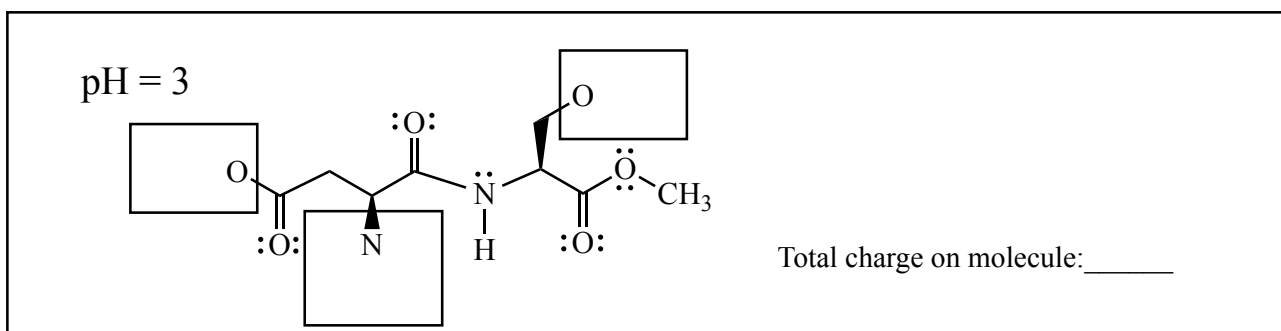
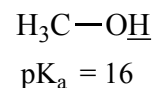
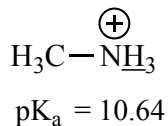
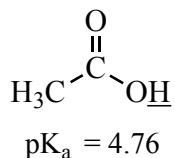
Orbital C

1. (4 pts) From the following choices, fill in the circle for the answer that accurately **lists the three molecular orbitals in order from lowest to highest energy**:

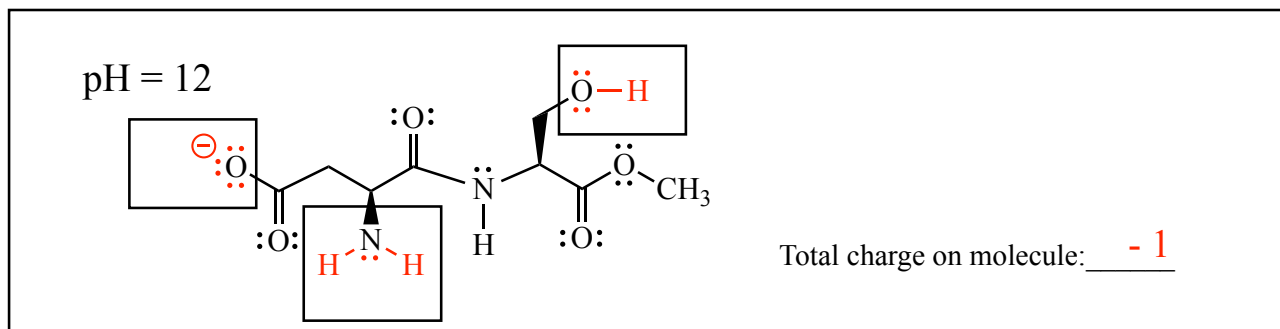
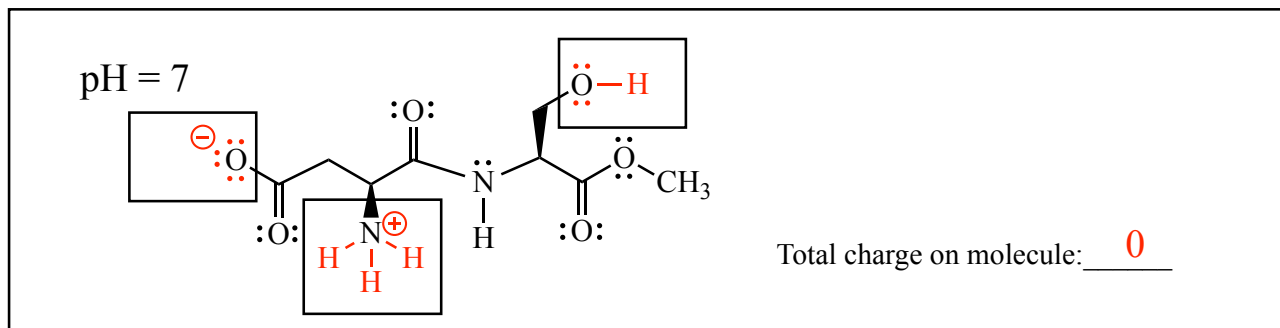
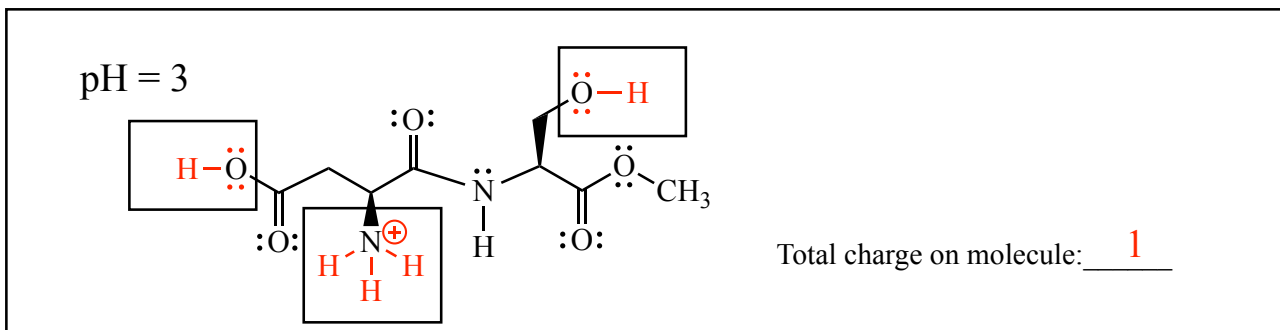
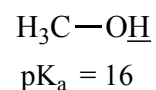
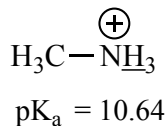
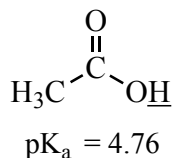
- Orbital A Orbital B Orbital C
 Orbital B Orbital C Orbital A
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One of the more difficult parts of the analysis of delocalized pi bonding concerns how many electrons are involved in the pi molecular orbitals. Each of the ions shown above, the carboxylate ion, the enolate ion, and the amide, have the same number of pi electrons in the pi molecular orbitals.

12. (15 pts) Complete the following four structures by adding appropriate numbers of lone pair electrons, H atoms, and formal charges to the atoms in the boxes. You must adjust your answers to indicate the predominant species at each indicated pH value. (You do not have to add anything such as H atoms to atoms not drawn in the boxes.) This problem is testing your understanding of the relationship of protonation state to pH to pK_a values for certain functional groups we have discussed. Next, in the space provided, write the overall charge on each structure at the indicated pH. For your reference, here are the relevant pK_a values:



11. (15 pts) Complete the following four structures by adding appropriate numbers of lone pair electrons, H atoms, and formal charges to the atoms in the boxes. You must adjust your answers to indicate the predominant species at each indicated pH value. (You do not have to add anything such as H atoms to atoms not drawn in the boxes.) This problem is testing your understanding of the relationship of protonation state to pH to pKa values for certain functional groups we have discussed. Next, in the space provided, write the overall charge on each structure at the indicated pH. For your reference, here are the relevant pKa values:

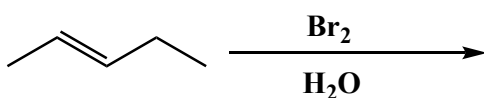


Signature _____

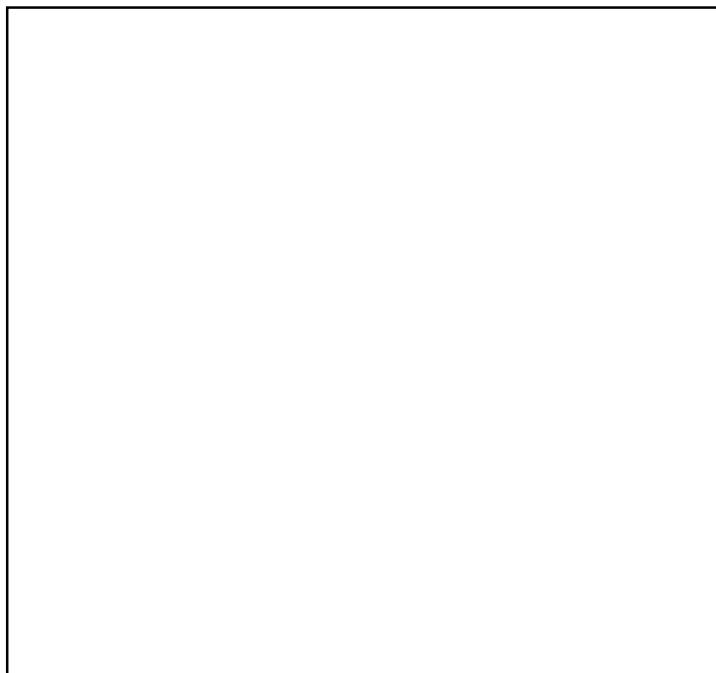
Pg 13 _____ (20)

14. (9 or 11 pts each) The following reactions all involve chemistry of alkenes. Fill in the box with the product(s) that are missing from the chemical reaction equations. Draw only the predominant regioisomer product or products if relevant and please remember that you must draw the structures of all the product stereoisomers using wedges and dashes to indicate stereochemistry as appropriate. When a racemic mixture is formed, you must write "racemic" under both structures EVEN THOUGH YOU DREW BOTH STRUCTURES.

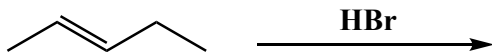
N.



(2 pts) Will the product mixture you drew to the right rotate the plane of plane polarized light?



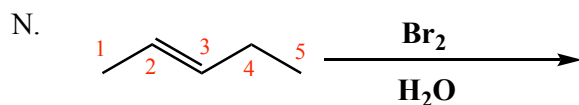
O.



(2 pts) Will the product mixture you drew to the right rotate the plane of plane polarized light?

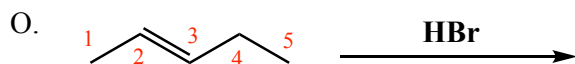
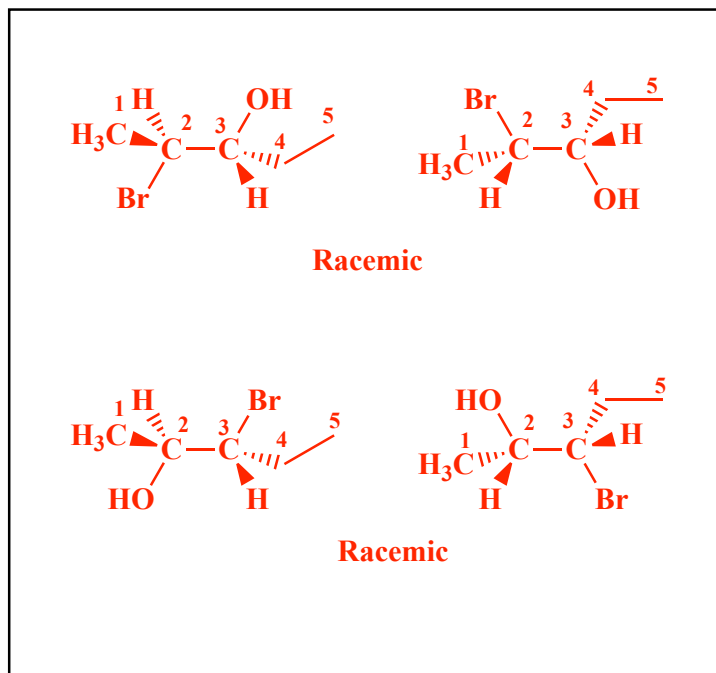


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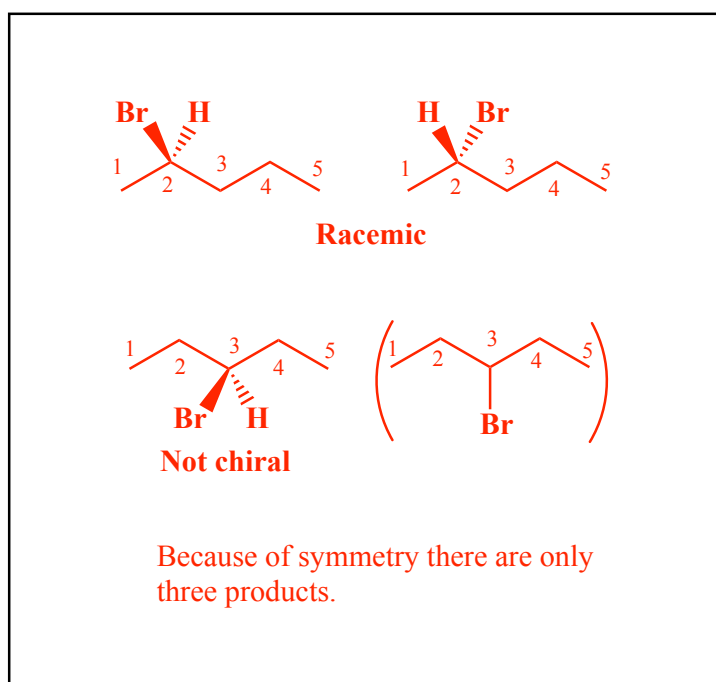
(2 pts) Will the product mixture you drew to the right rotate the plane of plane polarized light?

No



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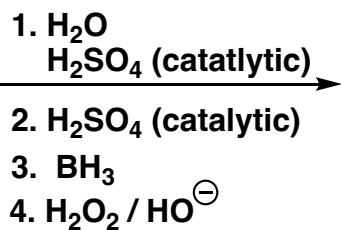
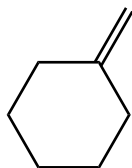
No



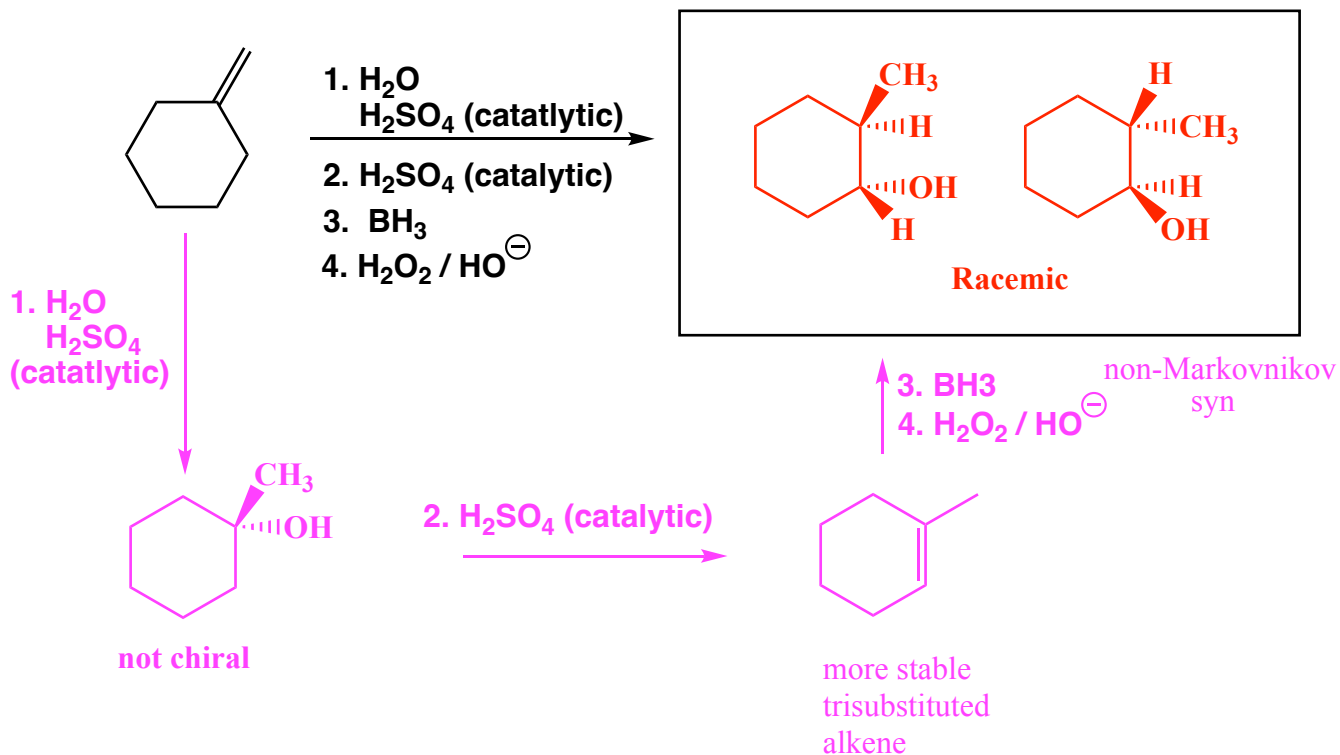
Signature _____

Pg 16 _____ (6)

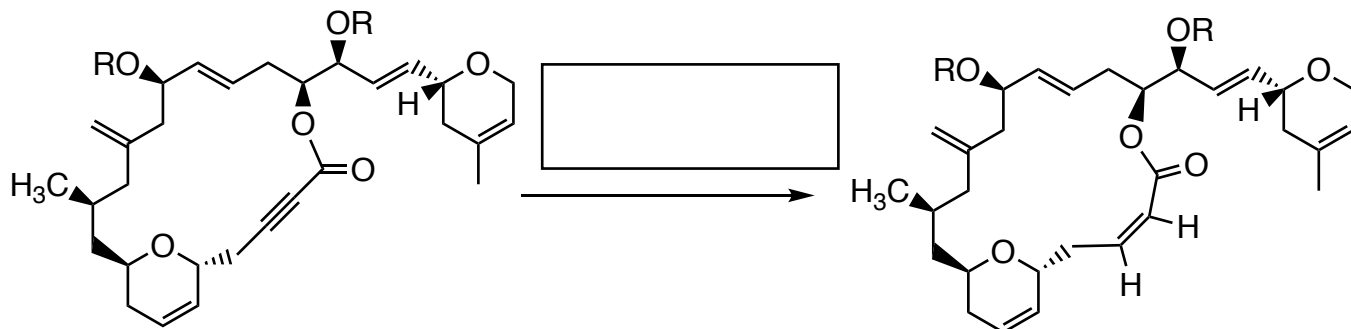
22. (8 pts) For the following sequence of reactions, **draw the final product(s)**. You only need to draw **the very last product(s) in the box provided**, although feel free to draw any other structures in the empty space provided. We will only grade the structure(s) in the box. As always, if a racemic mixture is created you need to draw both enantiomers using wedges and dashes and write "racemic".



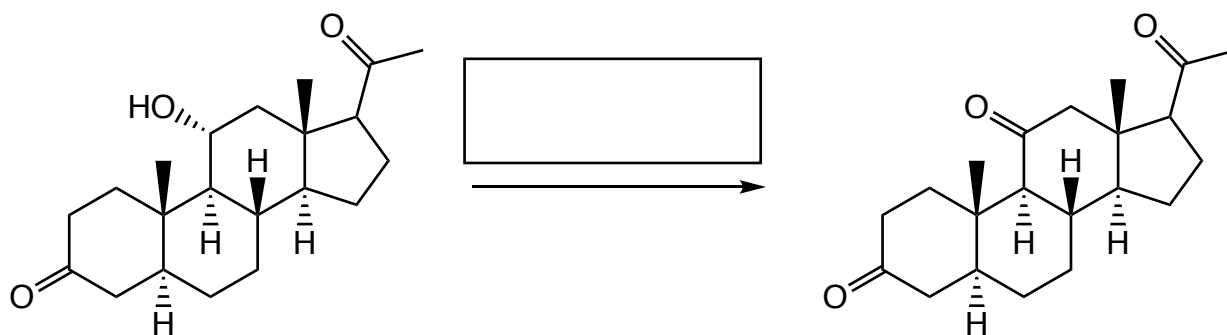
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19. (8 pts) The chemistry you have learned this semester is used in the synthesis of important pharmaceuticals. Here are two examples. Fill in the boxes with the reagent(s) required to carry out the transformation indicated.



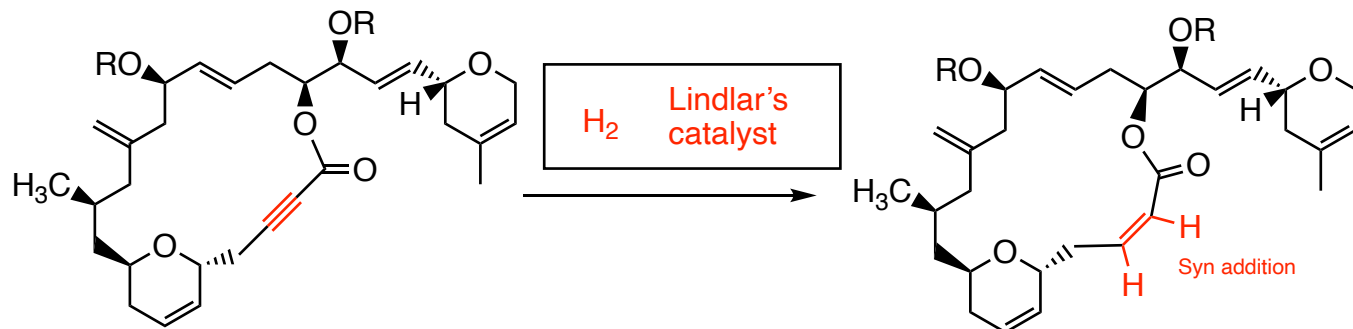
Swamy, *et al.*, Tetrahedron Letters, 2018, 59, 419-429



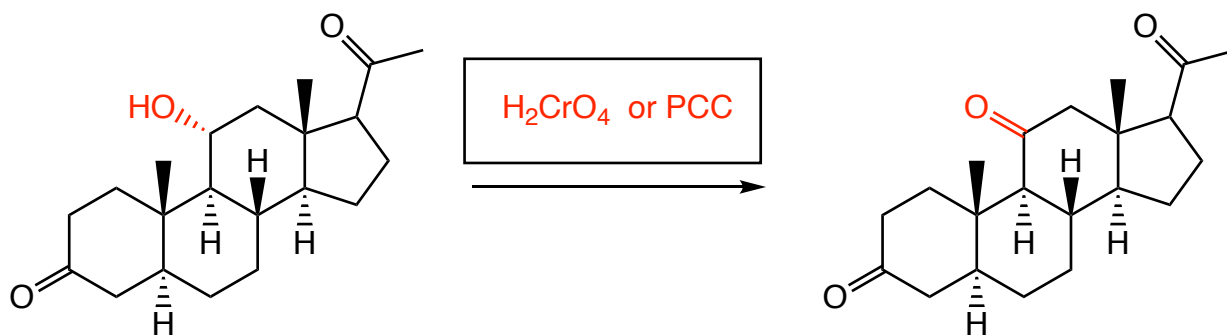
Have a great holiday break!!

...And remember to run every chance you get!

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Swamy, *et al.*, Tetrahedron Letters, 2018, 59, 419-429



Have a great holiday break!!

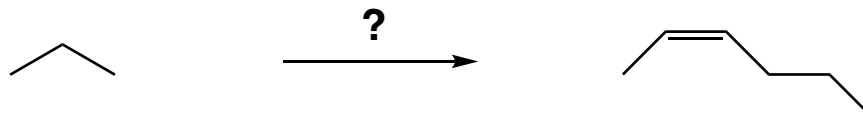
...And remember to run every chance you get!

Signature _____

Pg 21 _____ (22)

18. These are synthesis questions. You need to show how the starting material can be converted into the product(s) shown. You may use any reactions we have learned provided that the product(s) you draw for each step is/are the predominant one(s). Show all the reagents you need. Show each molecule synthesized along the way and be sure to pay attention to the regiochemistry and stereochemistry preferences for each reaction. You must draw all stereoisomers formed, and use wedges and dashes to indicate chirality at each chiral center. Write racemic when appropriate. **All the carbons of the product must come from carbons of the starting material.** OK, this is a long one. Work hard to Recognize that product and work backwards. You can do this!

E) (22 pts)



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