The Organic Chemistry Survival Guide

NeighborhoodGeeks

Table of Contents:

Chapter 0: Foreword from the Author……3

Chapter 1: General Chemistry Review……...4

Chapter 2: Acids and Bases……9

Chapter 3: Functional Group Cheat Sheet……..12

Chapter 4: Stereochemistry……22

Chapter 5: Basic Nomenclature……40

Chapter 6: Reactions of Alkenes and Alkynes…….50

Chapter 7: Aromaticity and Reactions of Conjugated Dienes…….87

Chapter 8: Reactions of Alkyl Halides…….120

Chapter 9: Using Alcohols in Synthesis ……..142

Chapter 10: Organometallic Chemistry……....163

Chapter 11: Reactions of Benzene and Benzene Derivatives……..173

Chapter 12: Introduction to Reactions of Carboxylic Acid Derivatives……..197

Chapter 13: Reactions of Ketones and Aldehydes + Advanced Reactions of…..216
Carboxylic Acid Derivatives

Chapter 14: Reactions at the Alpha Carbon……..255

Chapter 15: UV and IR Spectroscopy……...294

Chapter 16: NMR Spectroscopy……...305

Chapter 17: Radicals…….325

Chapter 18: Advanced Nomenclature (Carbonyls and beyond)……335

Chapter 19: A Bunch of Helpful Guidelines and Cheat Sheets…….351

Chapter 0: Foreword from the Author

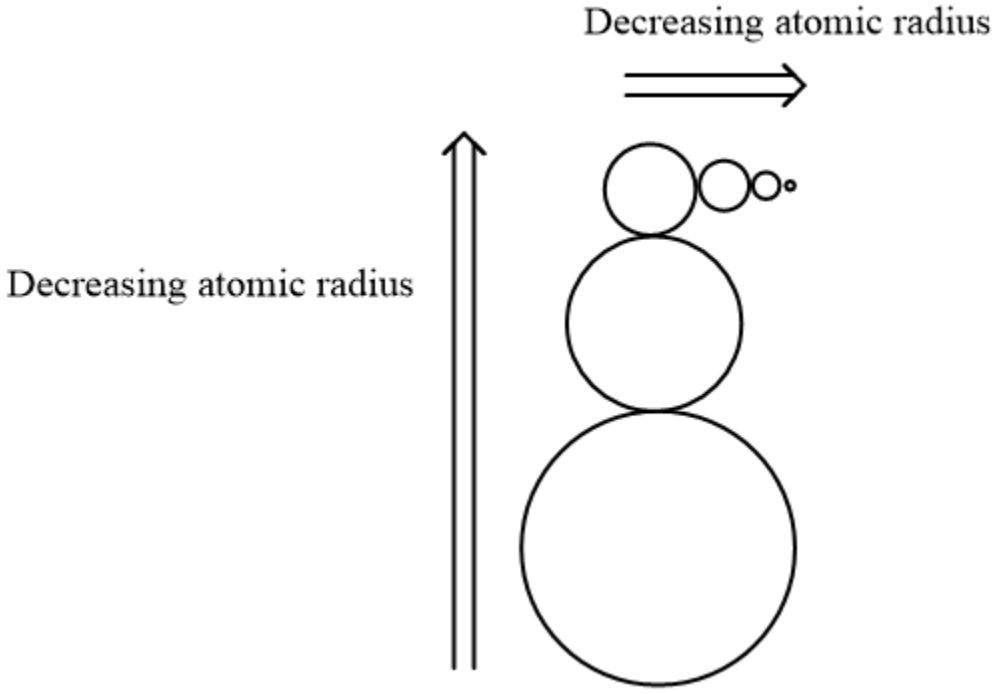
I know what you are probably thinking. Organic Chemistry?! That's such a hard subject! I heard that class eats premed kids for lunch! Well… here's something that you probably haven't heard. That's all a bunch of bologna. Anyone can do well in this class if they put in enough effort. That is why I am designing this textbook with the intent to teach from a student's perspective and highlight the things that I notice causes the most trouble when I tutor this course and what I personally found difficult when I took it. I will be using terminology that actual organic chemists use, but I will define them in simple terms, and explain this entire subject with a few key concepts that you absolutely most understand before you begin reading:

1. Acids react with bases
2. Minimize energy and charge
3. Strong bonds form
4. Opposite charges attract
5. Weak bonds break

Or AMSOW for short. These are what I refer to as the *Guiding Principles of Organic Chemistry*, and we will be referring back to it from time to time to explain why certain reactions happen the way they do. My goal in this textbook is not to teach you a bunch of reactions, unfortunately that is how many people are taught this course. Instead, my goal is to give you an 'Organic Chemistry sixth sense' so that you can make informed decisions on reactivity for situations you haven't seen before using AMSOW. Good luck and approach this course with an open mind and a positive attitude. That goes a long way, more than you would think.

Chapter 1: General Chemistry Review

The functional basis of organic molecules comes down to a few key concepts from General Chemistry, the first is periodic trends and the second is acid-base chemistry. The first of these two subjects will be covered here, while the second will be discussed in great detail in the next chapter. There are only two periodic trends that are relevant for this course, electronegativity and atomic radius. First, let us define what exactly electronegativity and atomic radius are. Electronegativity describes the tendency of an atom to suck electrons from a bond, the more electronegative you are, the more you will pull those electrons closer to you. The concept of electronegativity gives way to the idea of dipole moment, which is the property that determines how polar a compound is. Electronegativity increases the closer one is to fluorine (the top right), which is the most electronegative element on the periodic table. Atomic radius is the distance from the center of the nucleus to the outermost electron. The trend for atomic radius follows what I call the 'Snowman model' as shown:



This trend should make sense intuitively, from top to bottom, you are adding more and more electrons to higher principal energy levels, and therefore the atomic radius should increase. From the left to right, the outermost energy level electrons stay the same distance from the nucleus, but the amount of protons in the nucleus increase, therefore the effective nuclear charge increases and so the *opposite charges attract* and cause the radius to decrease. This same logic can be used to explain electronegativity trends, because fluorine is the smallest element that is not H and He,

it has the largest effective nuclear charge and therefore will have a greater pull on the electrons in the bonds it forms with other elements!

Practice questions:

1. What is more electronegative, O or S?
2. What is larger in atomic radius, O or S?
3. What is more electronegative, C or Al?
4. What has a larger atomic radius, Na or K?

Solutions:

1. Because oxygen is closer to fluorine than sulfur is, oxygen is more electronegative.
2. Because sulfur is beneath oxygen, it has one extra energy level and therefore is larger than oxygen.
3. Because aluminum is farther away from fluorine than carbon, carbon is more electronegative.
4. Because K is beneath Na it has a larger atomic radius for the same reason as 2.

These two trends help predict bond strength and the polarity of organic compounds. Smaller elements will form smaller bonds and smaller bonds are stronger bonds. Because smaller bonds are stronger bonds, typically these bonds are not the first to break (remember AMSO**W**). This can be clearly seen when looking at H-X bonds, where X is a halogen. This also explains why HF is not a strong acid.

Bond	Strength (kJ/mol)
H-F	569.7
H-Cl	431.4
H-Br	366.2
H-I	298.3

The trend above shows that as the atom attached to H increases in size, the bond strength decreases rapidly. Because the H-Cl bond strength is much less than H-F, HCl is a strong acid (it can donate its proton better) and HF is not. Before continuing on to electronegativity, it is often very useful to determine the hybridization of an element in organic chemistry. The hybridization of an atom can be determine very quickly through the following formula:

$$hybridization = sp^{3-n}$$

where n is the number of pi bonds the element has. Pi bonds are anything past the initial single bond, so double bonds would have 1 pi bond, triple bonds would have 2 pi bonds. Keep in mind that formula only works for second row elements because they cannot form expanded octets. This relationship holds because pi bonds are formed by overlapping p orbitals, that is why we

subtract away however many pi bonds we have from the number of p's in our hybridization, the max being 3.

There are geometries associated with each of the hybridizations:

sp^3 = tetrahedral

sp^2 = trigonal planar

sp = linear

These geometries also have preferred bond angles (degrees), these angles get decreased by the number of lone pairs (n) on the atom in question:

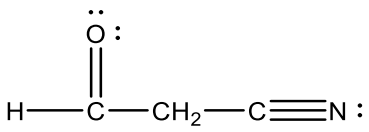
$sp^3 = 109.5 - 2.5(n)$

$sp^2 = 120$

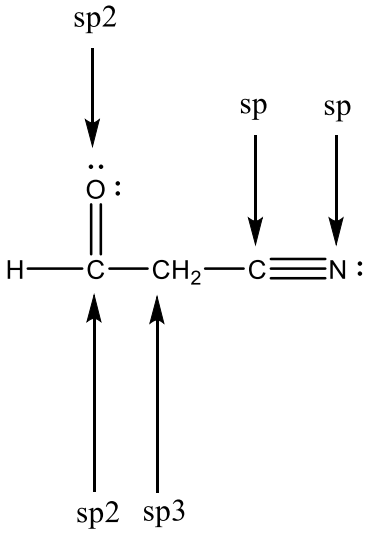
sp = 180

Practice question:

Assign the hybridization to all the second row elements in the compound shown below:



Solutions:



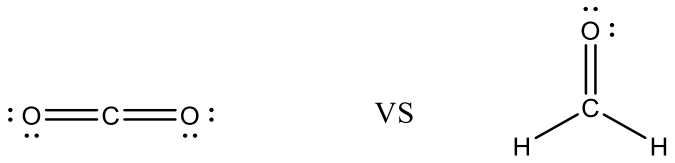
To determine the lengths of bonds, there is a quick tier list of importance in order:

1. Size of the atoms involved (smaller > bigger)

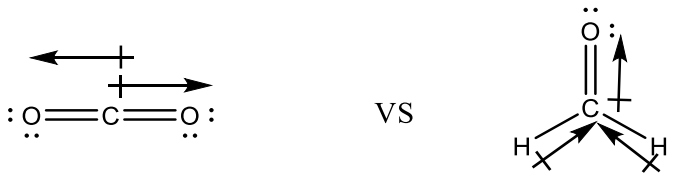
2. Bond order of the bond itself (triple > double > single)
3. Hybridization of the elements involved in the bond ($sp > sp^2 > sp^3$)

Therefore, the smallest bond in the above compound would have to be the C-H bond off the sp^2-hybridized carbon. Hydrogen is the smallest element, therefore those are going to be the smallest of all the bonds, and the carbon to which it is bonded is sp^2 hybridized, which form smaller bonds than sp^3 hybridized carbons.

Now that you can determine the bond length, we can discuss the role electronegativity plays in organic chemistry. The most important property that electronegativity brings to the table is dipole moment. To determine the dipole moment of a compound, you first have to draw the individual dipoles of all the bonds in the structure and see if they all point in one direction. If all the dipoles point in one direction, the molecule has a net dipole moment and is therefore polar. If all the dipoles cancel each other out, the molecule does not have a net dipole moment and therefore is nonpolar. Let us compare formaldehyde with carbon dioxide to see how geometry plays a role in determining dipole moment and polarity.



To draw the dipole moment of each bond, you must start your arrow from the less electronegative and draw it toward the more electronegative.



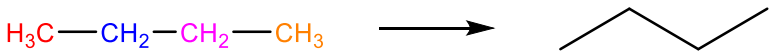
As you can see, the CO_2 molecule is nonpolar because the two dipoles cancel each other out (one points left and the other points right with the same magnitude), but the formaldehyde molecule is polar because all of the dipoles add together to point up. The larger the electronegativity difference is between two elements, the greater the bond dipole, and the more polar the molecule is if all else is equal.

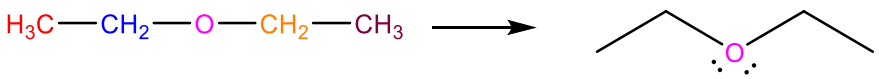
By now you have likely seen skeletal structures drawn on TV shows like Big Bang Theory or even in restaurants like Burgerology, now you are going to learn how to draw skeletal structures of your own and we are going to relate them to Lewis dot structures that you are familiar with from General Chemistry. First, let's discuss the preferred amount of bonds each second row element prefers to have (you just have to pay attention from B to F):

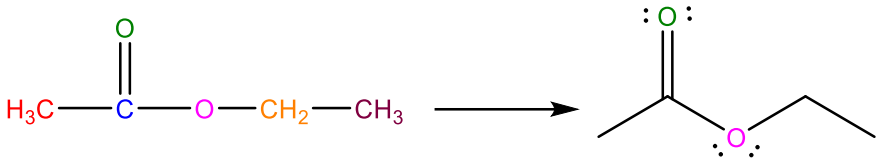
Li	Be	B	C	N	O	F
1	2	3	4	3	2	1

When drawing a skeletal structure, each kink in the chain represents a carbon with the right amount of hydrogens to make it have four bonds total, if there is a non-carbon element anywhere in the compound, simply draw a bond and write the element symbol where the kink would be.

Examples:







Chapter 2: Acids and Bases

Acid-base chemistry is foundational to the study of organic chemistry. Briefly, let's go over the two different types of acids that are commonly encountered in organic chemistry. The following is copied and pasted from my Inorganic Chemistry textbook:

Bronsted-Lowry Acids = **proton** *donor*, the typical acids that you were introduced to in General Chemistry. Acid strength is increased by the stability of the conjugate base, more stable conjugate base = stronger acid. For oxyacids the more oxygens present, the larger the acid strength ($HClO_4$ > $HClO_3$ > $HClO_2$ > HClO)

- Examples: HCl, HNO_3, H_2SO_4, $HClO_4$, Acetic acid, HF, H_2CO_3
- Problem: arrange the following chemicals in order of increasing Bronsted-Lowry Acid strength
    - HCl, HF, HI, HBr
- Answer:
    - HI > HBr > HCl > HF
        - Look at the stability of the conjugate bases (I^-, Br^-, Cl^-, and F^-), in iodide, the negative charge is distributed over a very large area (because I^- is the largest ion in the series) therefore it is more stable (remember A**M**SOW). This trend can also be explained through bond lengths as discussed in the previous chapter.

The second most important type of acid encountered in organic chemistry is *Lewis acids*, or *Electrophiles*. The opposite of *electrophiles* are *nucleophiles* and these are *Lewis bases*.

Lewis acids = **electron** *acceptors*, they are electron deficient species. Acid strength increases with increasing positive charge. Charge density is very important, generally, higher positive charge density = better Lewis acid. Charge density is the amount of charge divided by the volume of the ion.

$$\rho_{charge} = \frac{q_{ion}}{V_{ion}}$$

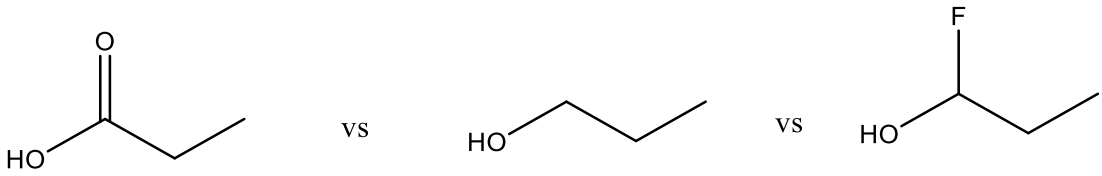
- Examples: any cationic metal species, carbonyl carbons, $AlCl_3$, BF_3, etc.

For the time being, we will focus our attention on Bronsted-Lowry Acids, since those follow a more rigorous hierarchy of strengths and the acid strengths help inform reactions of alkenes and alkynes. When determining which compound is more acidic, you first have to determine where the most acidic proton is by evaluating the *functional groups*. Some common sources of protons are alcohol groups (OH), carboxylic acid groups (COOH), and of course the strong acids from General Chemistry (HCl, HBr, HI, $HClO_4$, H_2SO_4, and HNO_3), all other functional groups are basic (NH_2 for example). If a functional group is protonated and positive charge, the acidity of that group will always increase, for example protonated alcohols are as acidic as strong acids like HCl. This is because the conjugate base is neutral and is therefore much more stable than the

parent compound because of charge minimization (remember A**M**SOW). In general, acidity increases from left to right on the periodic table and from top to bottom. Acidity generally increases from left to right because electronegativity increases in the same direction and when a compound gets deprotonated, a negative charge develops. This negative charge can be better stabilized with an electronegative atom such as F, rather than an electropositive atom like C or B. Acidity generally increases from top to bottom because the conjugate base (the deprotonated version of the compound) minimizes charge better if the atom holding the negative charge is larger, this is because the charge density is lower (again remember A**M**SOW).

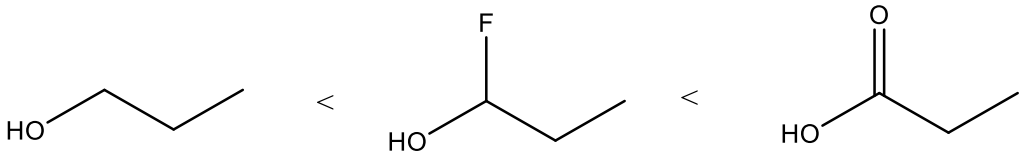
The acidity of an organic compound (such as an alcohol or carboxylic acid) can be affected by numerous factors. One such factor to consider when determining acid strength is inductive effects. Because the conjugate base of an acid generally is negative, we want to minimize that charge on the atom, and spread it across as many atoms as possible to decrease charge density (remember A**M**SOW). To do this, an electronegative atom such as a halogen can be added to the chain of the compound. This electronegative atom decreases the negative charge on the deprotonated portion of the molecule and therefore stabilizes the conjugate base, increasing the acid strength of the parent compound. Recall that strong acids give weak (stable) conjugate bases.

Example:



Rank the above compounds according to their acidity from weakest to strongest.

Answer:



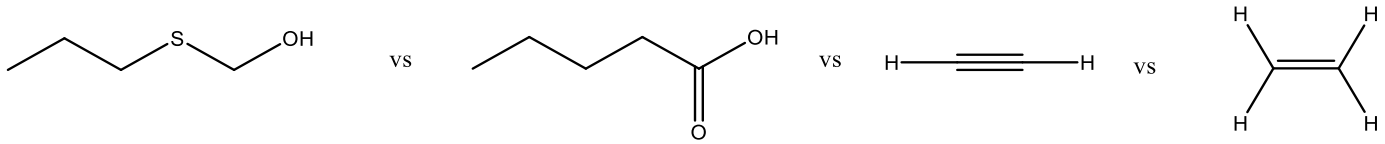
The first thing we evaluate is the functional groups present in the compounds, two of them are alcohols and the other is a carboxylic acid. Carboxylic acids are inherently more acidic than alcohols (hence the name), therefore that's the most acidic regardless of inductive effects. Then we compare the two alcohols, the one that has the fluorine is the most acidic because of the inductive electron withdrawing effect of the fluorine.

The effects of the halogen on the acidity is proportional to the electronegativity of the halogen, for example, F will increase acidity the most then Cl then Br then I. The effects of the halogen or

heteroatom (non-carbon atom) increase the closer it is to the acidic proton. For example, if there was another alcohol with a fluorine, but this compound had the fluorine farther away from the OH group, that would be a weaker acid than the one that is closer to the OH. This is because the electron withdrawing effects decrease rapidly with distance.

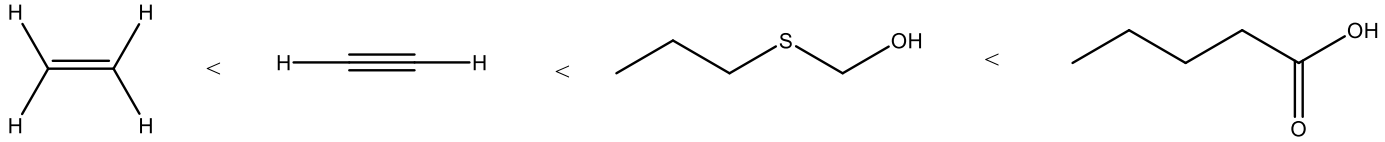
The least important factor to determine acid strength is the hybridization of the atom that is attached to the acidic proton. The less p-character the hybridization the atom has, the more acidic the proton is ($sp > sp^2 > sp^3$). This is only really relevant for the more basic functional groups, like C-H protons or N-H protons, in most cases the acid strength can be determined through functional groups and inductive effects.

Example:



Rank the above compounds in order of increasing acidity.

Answer:



The hierarchy of acidity is: hybridization < inductive effects < functional groups.

Chapter 3: Functional Group Cheat Sheet

Before I give you my functional group notecards, we should first go over some general characteristics of nucleophiles and electrophiles.

Nucleophiles generally have *AT LEAST* one of three characteristics:

1. A nonpolar pi bond
2. A lone pair
3. A negative charge

This should make sense, nucleophiles always do the attacking, and they attack with pi bonds and lone pairs since these are essentially extra electrons. The negative charge makes sense because nucleophiles fundamentally are *electron rich* species, therefore they generally have negative charges (recall electrons are negative).

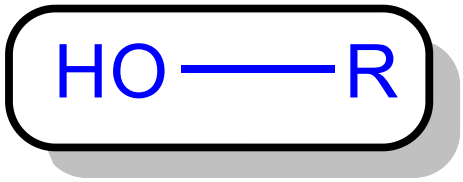
Electrophiles on the other hand have *AT LEAST* one of four characteristics:

1. A polar pi bond
2. A weak bond
3. A relatively large dipole
4. A positive charge

This should make sense, electrophiles are always the ones who get attacked. They get attacked because one or more of their bonds are weak or there is a partially positive (large dipole) or fully positive atom in the molecule. Remember, weak bonds break (AMSO**W**), so if we are going to attack anything, it will be to break the weakest bonds and form stronger bonds. The positive charge makes sense because at their core, electrophiles are *electron deficient* species.

With that in mind, I have consolidated all of the more common organic functional groups and put them on little flashcards with their important properties listed, they can be found below:

The Alcohol Group

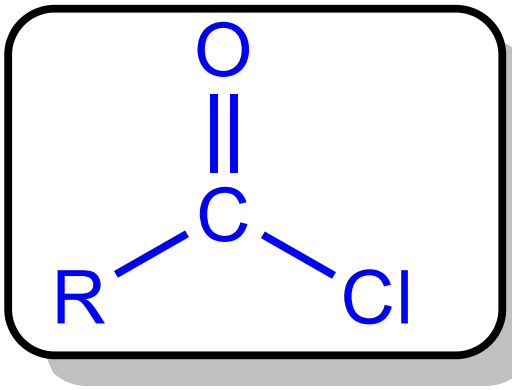


"Apathetic Alcohol"

Goes with the flow

Properties:
Nucleophile,
Bad leaving group,
Polar,
Hydrogen bond

The Acyl Chloride Group

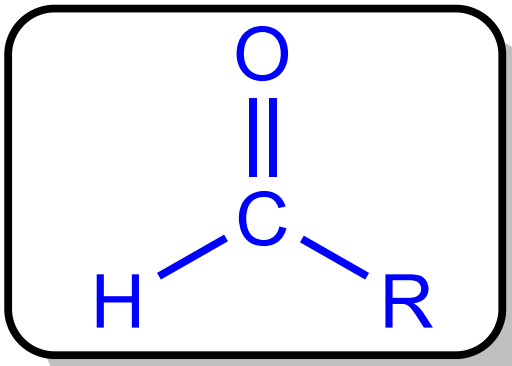


"CooCoo Chloride"

Handle with great care

Properties:
Electrophile,
Modestly Polar,
Dipole-Dipole

The Aldehyde Group

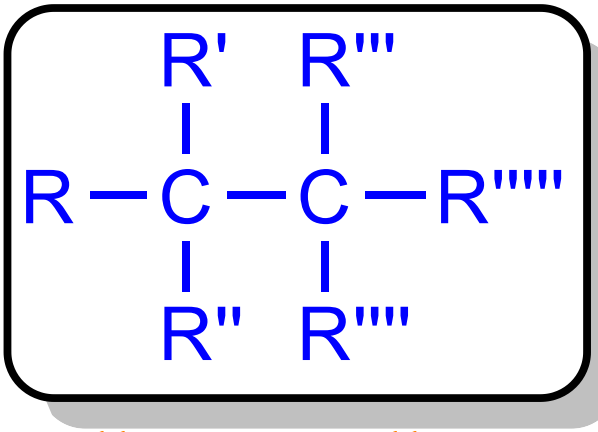


Properties:
Electrophile,
Modestly polar,
Dipole-Dipole

"Audible Aldehyde"

Smells so terrible you can hear it in your ear

The Alkane Group

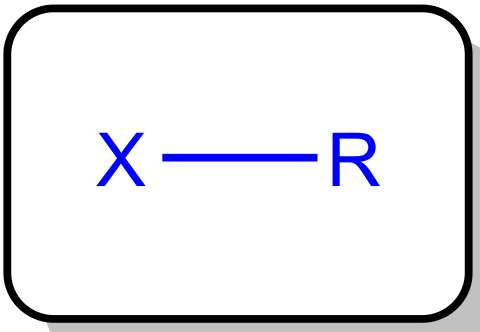


Properties:
Inert,
Nonpolar,
LDFs

"All-Over Alkanes"

Seriously, they're everywhere

The Alkyl Halide Group



Properties:
Electrophile,
Moderatly Polar,
Dipole-Dipole

"Asential Alkyl Halides"

They're super useful for substitution reactions

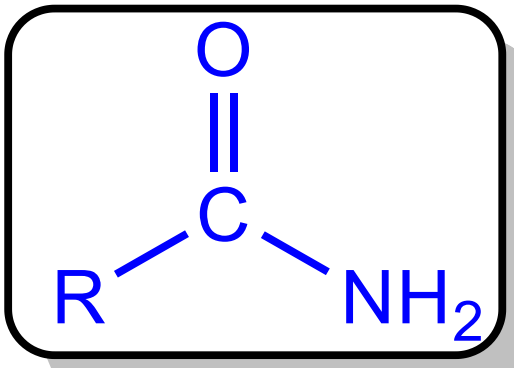
The Alkyne Group

Properties:
Nucleophile,
Nonpolar,
LDFs

"All-Purpose Alkyne"

Does Alkynes of reactions :)

The Amide Group

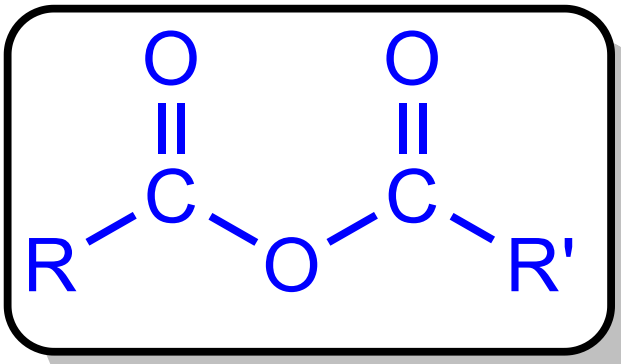


Properties:
Electrophile,
Polar,
Hydrogen bonding

"Amenable Amide"

Amino acids, peptides, and more

The Anhydride Group

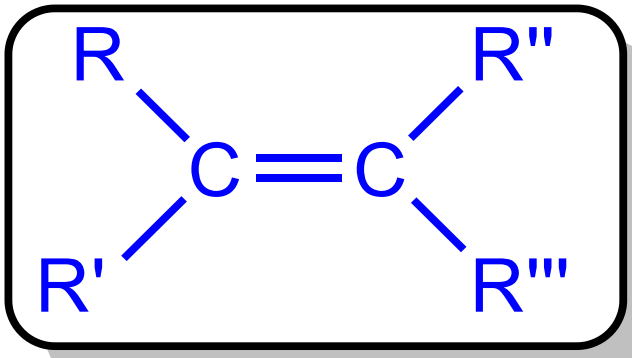


Properties:
Electrophile,
Moderatly Polar,
Dipole-Dipole

"Awesome Anhydride"

For all your protecting needs

The Alkene Group

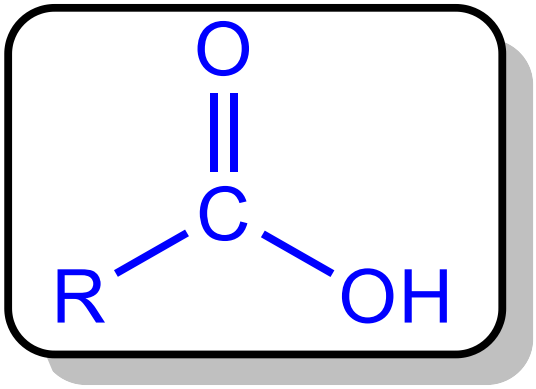


Properties:
Nucleophile,
Nonpolar,
LDFs

"Aggressive Alkene"

Like alkynes but cooler

The Carboxyl Group

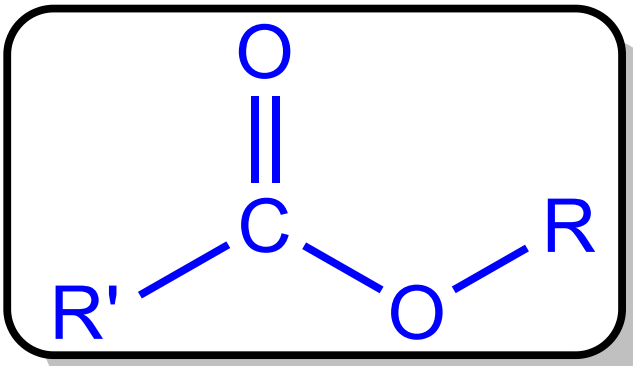


Properties:
Acidic,
Electrophile,
Polar,
Hydrogen bonding

"Crazy Carboxyl"

Pst... ya wanna proton?

The Ester Group

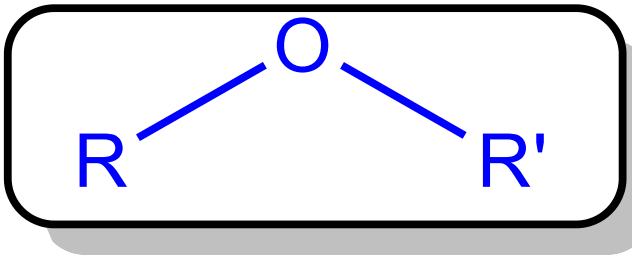


Properties:
Electrophile,
Modestly polar,
Dipole-Dipole

"Essential Esters"

Smell great

The Ether Group

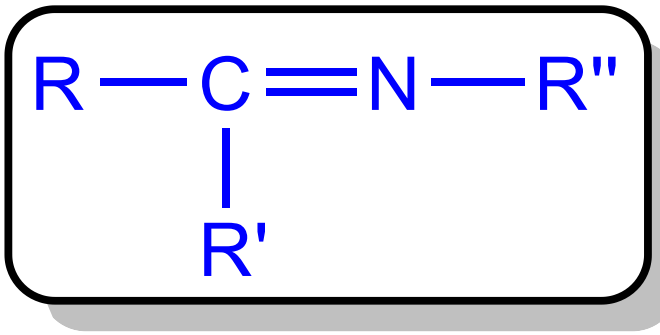


Properties:
Base,
Nucleophile,
Modestly polar,
Dipole-Dipole

"Exclusionary Ether"

Reacts with Acids Only

The Imine Group



Properties:
Electrophile,
Moderatly Polar,
Dipole-Dipole

"Immaculate Imine"

Its truly immazing

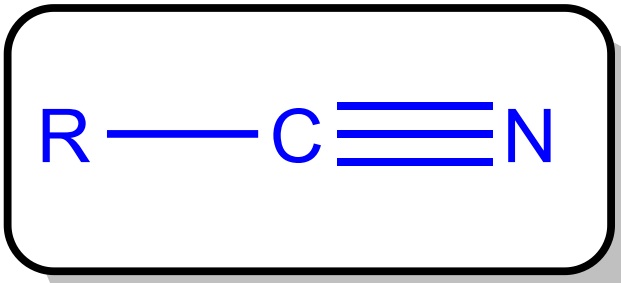
The Amino Group

"Angry Amino"

Easily provoked

Properties:
Base,
Nucleophile,
Bad leaving group,
Polar,
Hydrogen bond

The Nitrile Group

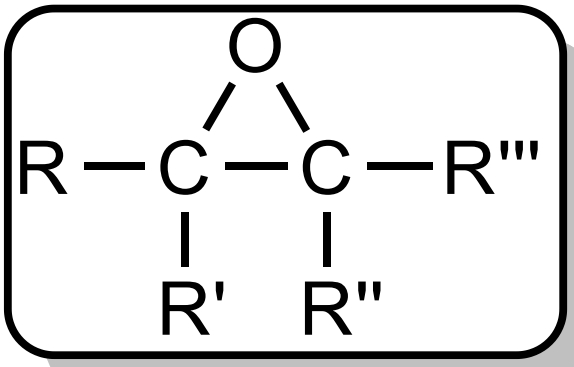


Properties:
Electrophile,
Moderatly Polar,
Dipole-Dipole

"No Time Nitrile"

Its like an imine, but triple bond

The Epoxide Group

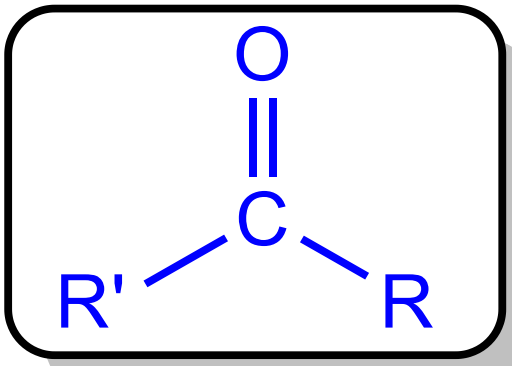


Properties:
Electrophile,
Modestly Polar,
Dipole-Dipole

"Explosive Epoxide"

Super strained

The Ketone Group



Properties:
Electrophile,
Modestly polar,
Dipole-Dipole

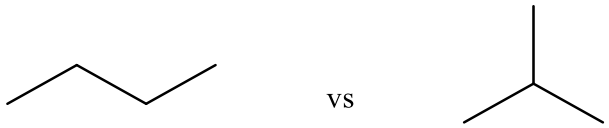
"Kourteous Ketone"

Willing to accept your nucleophile

Chapter 4: Stereochemistry

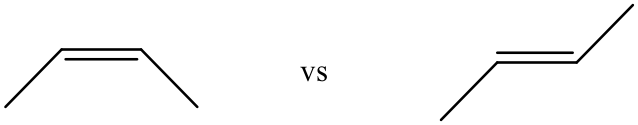
In general chemistry, there was a limited amount of compounds that were discussed, and none of them were chiral. However, in organic chemistry, the complex systems that can be developed with carbon cause there to be many different isomers for the same chemical formula. These isomers fall under a few different categories:

1. Structural isomers (or constitutional isomers) are those isomers that differ in their connectivity. An example of a structural isomer is shown below:

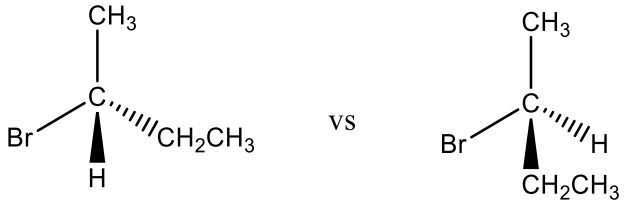


2. Stereoisomers are those isomers that differ not in connectivity, but in how the atoms are arranged in space. These isomers come in two different flavors.

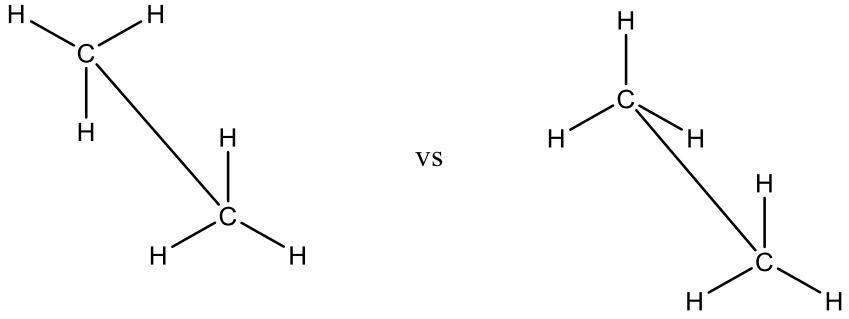
    a. Cis-trans isomers differ in how the groups are arranged around an sp^2 hybridized carbon, an example is shown below:



    b. R-S isomers differ in how the groups are arrange around an sp^3 hybridized carbon, an example is shown below:



3. Configurational isomers are those isomers that differ solely based off rotation of groups around a sigma bond, an example is shown below:



In order for stereoisomerism to exist, at least one of two conditions must be met:

1. There is an sp^3 hybridized carbon that has four distinct groups on it
2. There is a double bond that has sp^2 hybridized carbons that have distinct groups on them

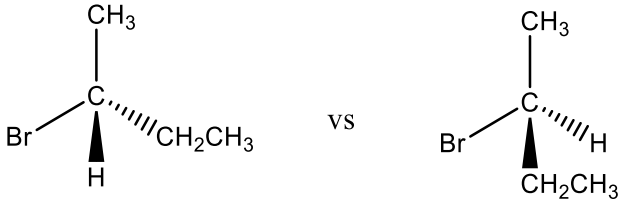
If neither of those two conditions are met, there is no stereoisomerism, and the only form of isomerism present is structural and configurational isomerism.

There is a reason why I referred to the sp^3 hybridized carbon case as R-S isomers, and that has to do with how we assign the chirality to the asymmetric carbons. Asymmetric carbons are the carbons in the molecule that have four distinct groups attached to them.

To assign chirality to an asymmetric carbon, you need to do the following things:

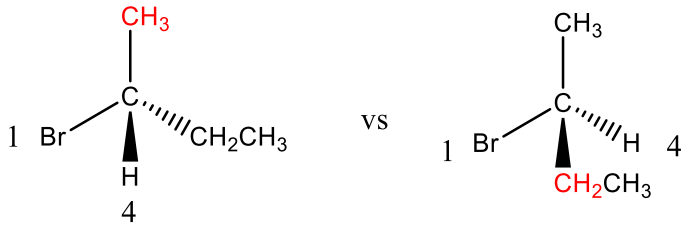
1. Identify all four of the distinct groups
2. Assign priority to the groups on the premise of molecular weight of the atom attached directly. Keep doing this and going down the chain until you get to the point of first difference. You must evaluate both the atom in question and also the atoms to which it is bonded to.
3. If the group has a double or triple bond, pretend that carbon is bonded to two or three of that element.
4. Number all groups 1-4
5. Move your finger from 1 to 2 to 3 to 4.
6. If the hydrogen is on a dashed line, a clockwise motion of the finger would mean an R configuration, a counterclockwise motion would mean an S configuration. If the hydrogen is on the wedged line, flip the configuration assignment.

As you can probably see from the guidelines above, the best way to do these evaluations is with examples, which we will do many of, starting with the one I put above.

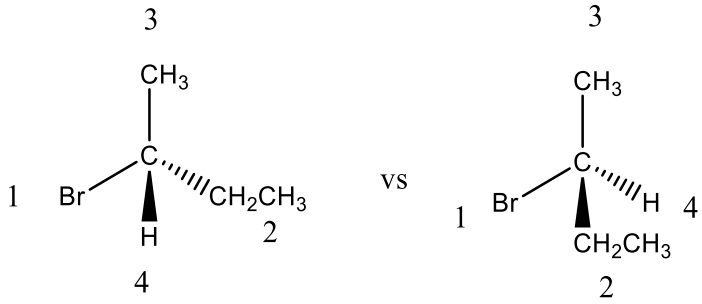


let's first try to assign priority to the groups attached to the asymmetric carbon:

first we look at the atoms directly attached to the asymmetric carbon and we evaluate their molecular weights, with the highest molecular weight getting highest priority. From this we know that Br is the highest priority group and H is the lowest priority group, but how do we distinguish between CH_3 and CH_2CH_3? We have to go another atom down in the chain and see which group has higher priority groups attached. So far we have this:



We now need to evaluate the groups attached to the carbons indicated in red. The CH_3 group has 3 H's attached, while the CH_2CH_3 group has 2 H's and a C attached, because C > H the CH_2CH_3 group gets higher priority. Therefore we have this for the priority of the groups:

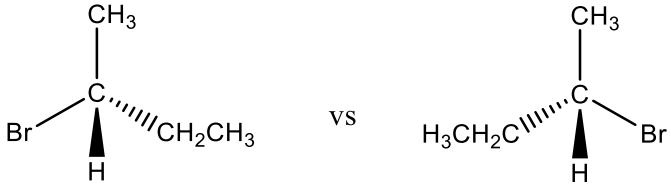


Now that we have the groups assigned proper priority, we simply need to move our finger from 1 to 2 to 3 to 4, if the direction of that rotation is clockwise and the lowest priority group is on a dashed line, the configuration is R and the configuration is S if the rotation is counterclockwise. Those assignments are *only if the lowest priority group (usually a H) is on a dashed line*, if it is on a bold-faced line you need to flip the assignment, if it is on a regular line, rotate the molecule so it is on either a bold-faced or dashed line.

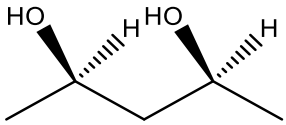
For the molecule on the left, going from 1-2-3-4 is a counterclockwise rotation, which ordinarily would mean an S configuration, BUT, the lowest priority group (H) is on a bold-faced line, therefore the configuration is the opposite. The chirality assignment for the molecule on the left is R.

For the molecule on the right, going from 1-2-3-4 is a counterclockwise rotation as well, because the lowest priority group is on a dashed line, the configuration assignment is normal and the molecule is S. This relationship is very important, *switching the dash and bold-faced lines will cause inversion of stereochemistry*.

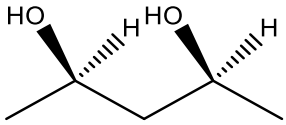
These two molecules (the one on the left and right) are referred to as *enantiomers*, and they are perfect mirror images of each other, meaning, it would also be valid to depict them like this:



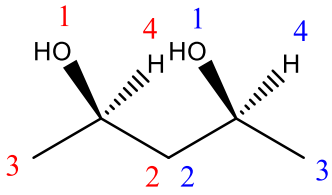
You can do the R and S assignment to prove that for yourself. Sometimes, there are special cases of R-S isomerism, these special cases occur when there are two (or more) chiral carbons (carbons that have four distinct groups), but these carbons have the exact same four distinct groups, these compounds are referred to as *Meso compounds*. An example of a meso compound is shown below:



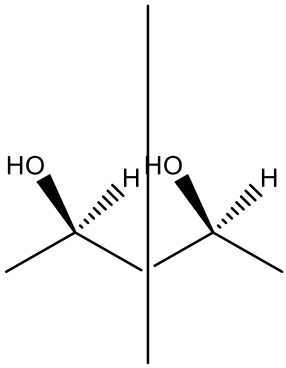
There are two chiral carbons here, namely the two carbons that have the OH groups, but these two chiral carbons share the same four distinct groups (OH, H, CH_3, $CH_2CHOHCH_3$). When this happens, you must look for planes of symmetry in each of the isomeric forms (RR, SS, RS, and SR), if there is a plane of symmetry then those two forms are equivalent to each other and are counted solely as one form of the molecule and that form is said to not be optically active. Let's tackle this issue of stereoisomerism with the above example by first assigning R and S configurations to both carbons.



By using our rules from before, it is clear to see that the OH group is the highest priority and the H is lowest priority. The two other groups have a carbon directly attached to the chiral center of interest, so they are tied, but the CH_3 group has its carbon only attached to H's, while the $CH_2CHOHCH_3$ group has its C attached to a C, therefore that is the second highest priority group. With this information, we can see that below is the correct assignment of priority for each group:



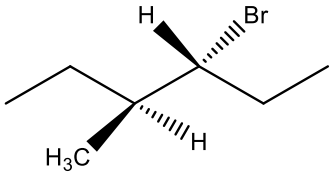
The red chiral carbon has the R configuration (the groups going from 1 to 2 to 3 go clockwise and the H is on the dashed line), and the blue chiral carbon has the S configuration (the groups going from 1 to 2 to 3 go counterclockwise and the H is on the dashed line). This isomer would be the RS isomer. The next question that we must ask ourselves is, is there a plane of symmetry in this molecule? The answer is clearly yes, as shown below:

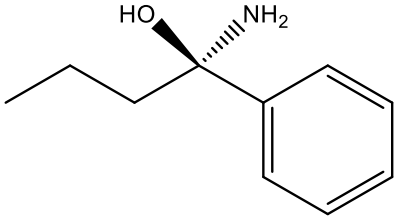


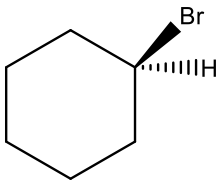
The molecule is clearly symmetrical along that line, therefore the RS and the SR enantiomers are equivalent, and the molecule has 3 stereoisomers, rather than the anticipated 4. The maximum number of stereoisomers is given by the following formula: $stereoisomer_{mx} = 2^n$ where n the number of chiral centers. Since there were two chiral centers here, we anticipated that there would be 4 stereoisomers (RR, SS, RS, and SR), but instead we found that there were only 3 because the RS and the SR are equivalent. Two enantiomers are the closest chemical cousins you can get without being the exact same compound, enantiomers exhibit the same physical properties and chemical properties in achiral environments. It is only when the compounds are exposed to plane-polarized light or are put in a chiral environment (such as enzyme active sites) do these compounds become distinct. When two enantiomers are exposed to polarized light, one enantiomer will bend the light upwards (+) and one will bend the light downwards (-). Keep in mind, (+) and (-) DO NOT tell you about R and S. Not all R is (+) and not all S is (-). All that we know is that if R is (+), S is (-), and vice versa. The angle measurement up or down is exactly reflected by the enantiomer. For example, if the R enantiomer bends light 10 degrees **downward**, the S enantiomer bends light 10 degrees **upward**. If you have an equal mixture of R and S enantiomers, that mixture is called a *racemic mixture*, and it will NOT bend polarized light (you can essentially view this as nobody won the tug of war). There are R-S isomers that are not enantiomers, *enantiomers are only those isomers that have the exact opposite chirality for each chiral center*. All other R-S isomers are considered to be *diastereomers*. For example, if we have two chiral centers and the compound is not meso, there are 4 possible stereoisomers (2^2) and they are RR, SS, RS, and SR. The ONLY enantiomer of RR is SS and the ONLY enantiomer of RS is SR, all other isomers are diastereomers. When you have determined the amount of stereoisomers, you can determine if they are optically active (will bend polarized light), by evaluating symmetry. If the isomer is symmetrical along some plane of symmetry, that isomer is NOT optically active irrespective of if it is a meso compound.

Practice Questions:

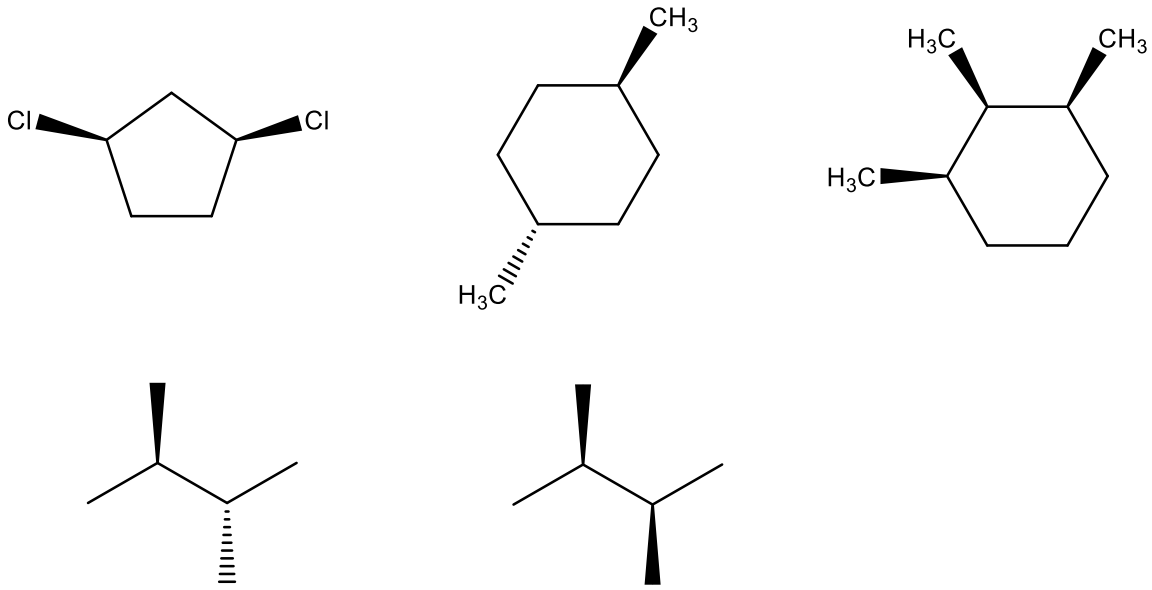
1. Determine the R and S configuration of the following compounds:



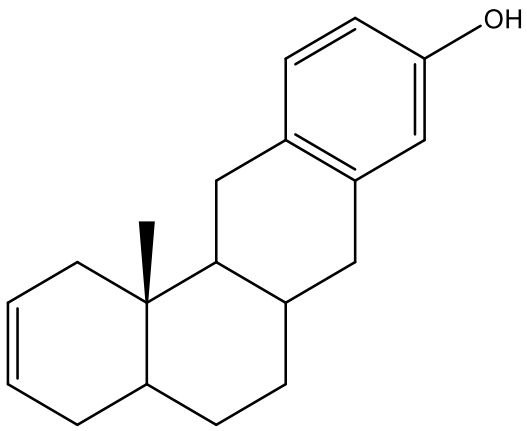




2. Determine if the following isomers are optically active:

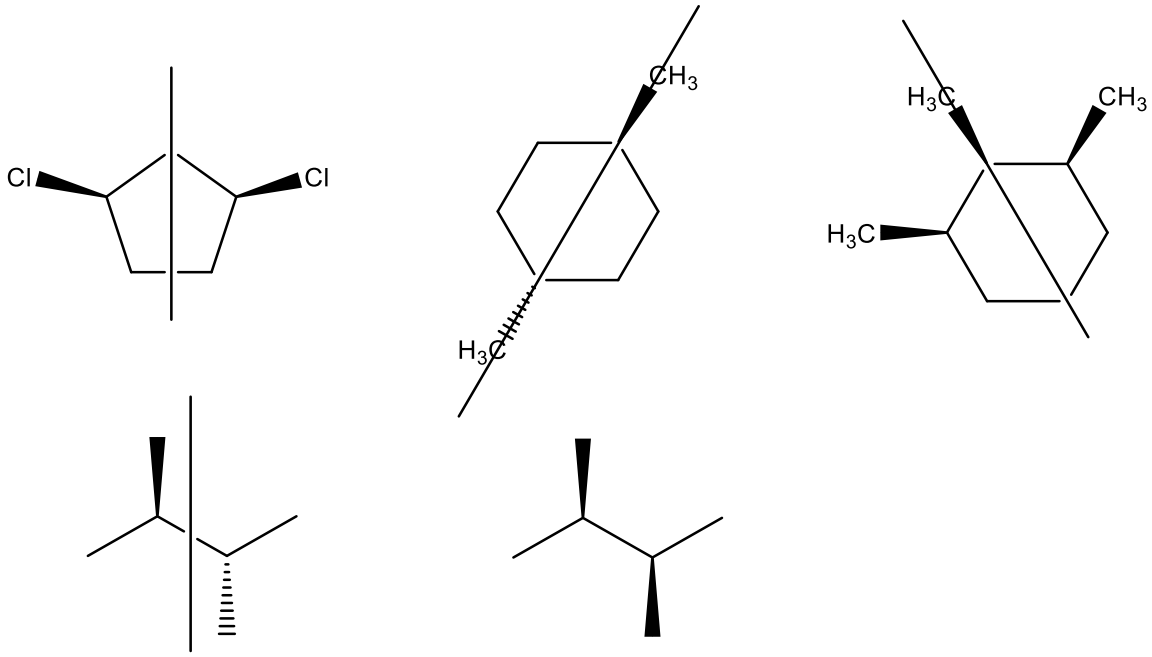


3. Determine how many asymmetric carbons there are in the below compound:

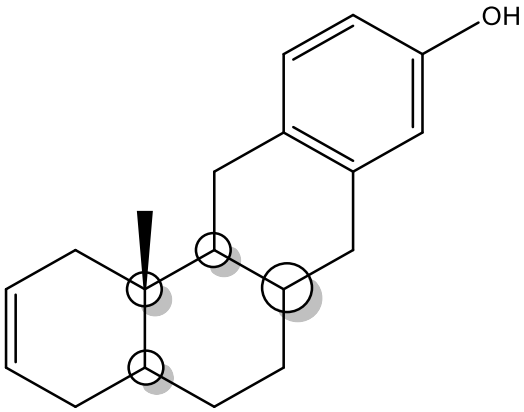


Answers:

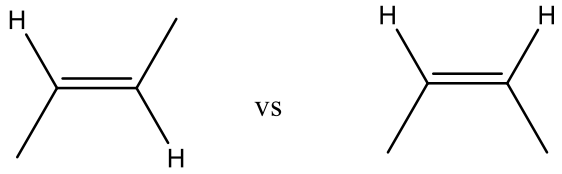
1. Reading from left to right for each compound: SR (flip second center because H is on bold line), R (rotate to make the lowest priority group on the dash line), Not chiral (has only 3 different groups).
2. Not active, not active, not active, not active, active (need to make the second dash or wedge face the same direction as the other then evaluate symmetry), planes of symmetry are shown below:



3. Asymmetric carbons are circled below:



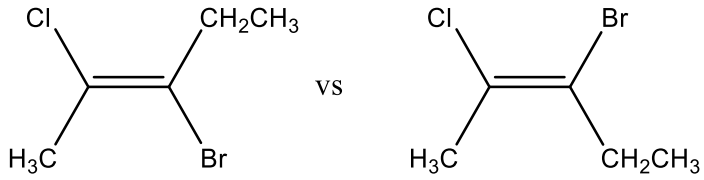
That was all for the sp^3 stereoisomers, but there are also sp^2 stereoisomers that exist for alkenes. For an alkene to be cis or trans, both of the sp^2 carbons in question must have a single hydrogen each. If the two hydrogens are facing the same direction, that double bond is said to be cis, cis = same. If the two hydrogens are facing opposite directions, that double bond is said to be trans, trans = opposite. Shown below are examples of cis-trans isomers:



Remember, cis-trans isomerism only happens if both sp^2 carbons have a hydrogen and another non-hydrogen group. For example, the following would NOT be an example of cis-trans isomerism:

This is not an example of cis-trans isomerism because the compound on the left is simply the compound on the right upside down. Generally speaking, the cis isomers are less stable than the trans isomers because the cis isomer puts the two bulkiest groups closest together. When two bulky nonpolar groups are close together, they are repelled because of steric repulsion. Essentially, all atoms are surrounded by electrons, and when two groups come together, those electrons repel each other and this destabilizes the compound (remember AMS**O**W). Nature always tends towards stability. Cis isomers also generally have higher boiling points and are slightly more polar because the slight dipole created with the double bond is canceled out in the trans isomer (the groups are facing opposite directions), but is not in the cis isomer.

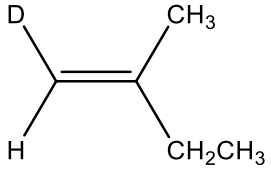
If the sp^2 carbons do not have one hydrogen each, but do have different groups, then cis and trans lose meaning, and we must use E-Z nomenclature. The E isomer is the isomer where the highest priority group on each of the sp^2 carbons are on OPPOSITE sides. The Z isomer is the isomer where the highest priority group on each sp^2 carbon are on the SAME side. Z = Zame side, E = Eppesite side. Luckily, we already know how to assign priority to the groups on each sp^2 carbon, this system follows the exact same rules from R-S isomers (hence why we introduced it first). Below is an example of an E-Z isomer pair:

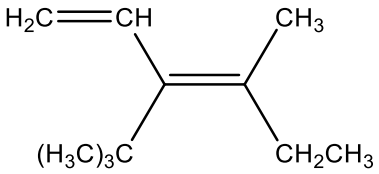


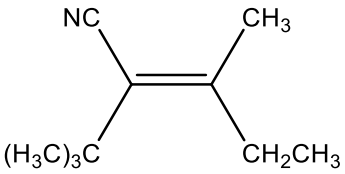
E isomer Z isomer

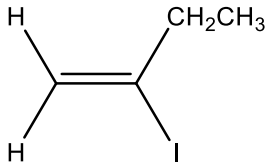
Practice questions:

1. Determine if the following alkenes are E or Z isomers:







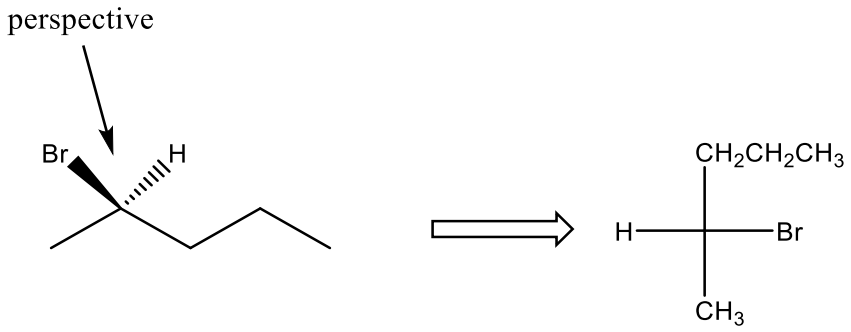


Answers:

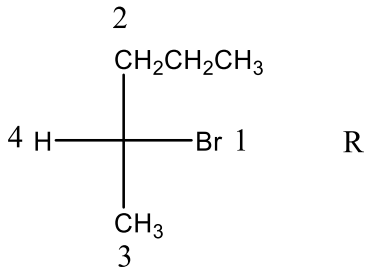
1. E, Z, E, neither

Now that we are well acquainted with looking at atoms in space, we can discuss different types of projections that you will often find useful for determining stereochemistry and stability. The two types of projections are the Fischer projection and the Newman projection for determining stereochemistry and stability respectively. The Fischer projection is essentially a bird's eye view of the molecule in space while the Newman projection is looking down a specific bond in the molecule. We will look at both of these in turn.

Fischer projections are frequently encountered in carbohydrate chemistry and are very useful in determining the stereochemistry of specific chiral centers. Fundamentally, the Fischer projection requires the chemist to view the molecule from above or below the dash and wedge lines for each chiral carbon. For example,

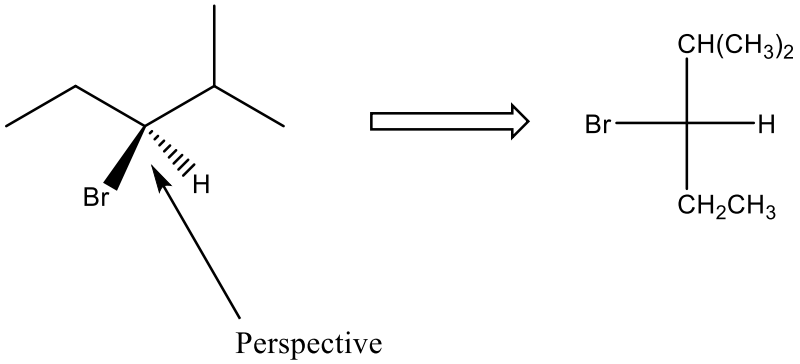


To do a proper Fischer projection, you effectively need to see in between the Br and H and view the molecule from above. If you do this, the H is to your left, the Br is to your right, the CH_3 is downward, and the rest of the chain is facing upward. To assign chirality to this carbon, you do the exact same procedure as normal (assign priorities and see if it turns clockwise or counterclockwise). If the H is on a horizontal line, you must flip whatever assignment you give it because if it is on a horizontal line, it is on a bold line from your perspective. Therefore for this example, the following would be your priority list and subsequent assignment:

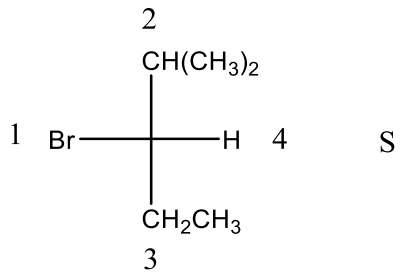


R

If you do it the traditional way, you will get the same result. This projection comes in handy particularly when you are faced with a situation where the lowest priority group is not on the bold or dashed line and is also very helpful when you are dealing with long chains of chiral carbons such as carbohydrates. You can also do this if the dash and wedge are facing downwards:

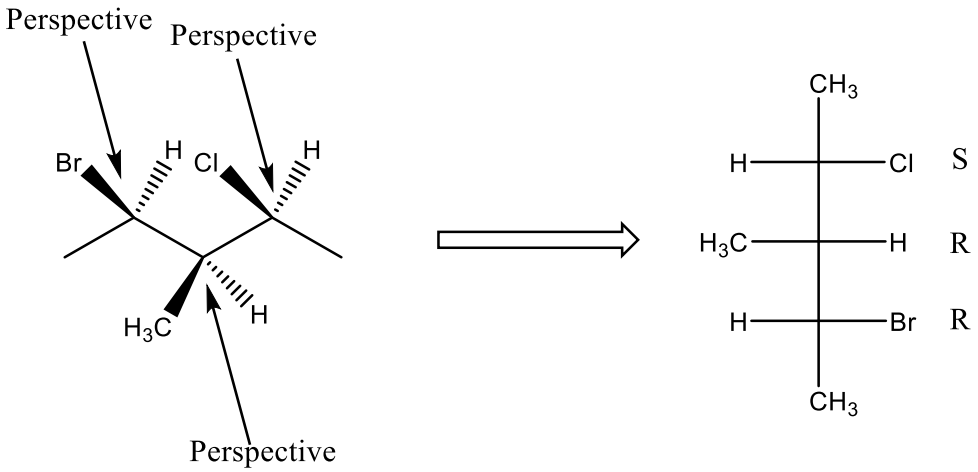


The configuration of that chiral center is S according to the Fischer and using the traditional way of solving chiral configurations. The Fischer way is shown below:



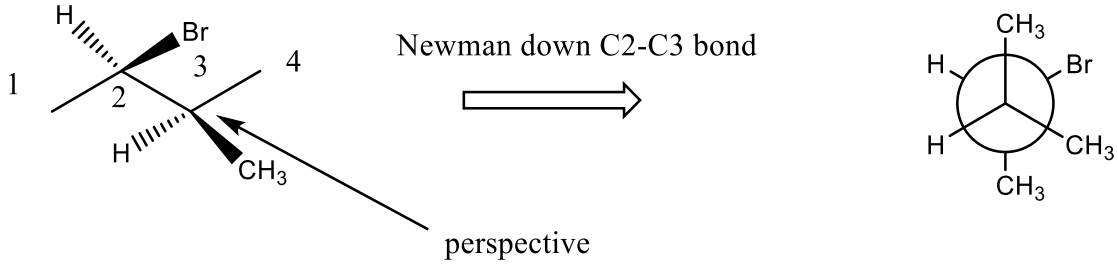
S

If there is a combination of several chiral centers in succession, you have to constantly adjust the perspective to accommodate the direction of the dash and bold lines. For example:

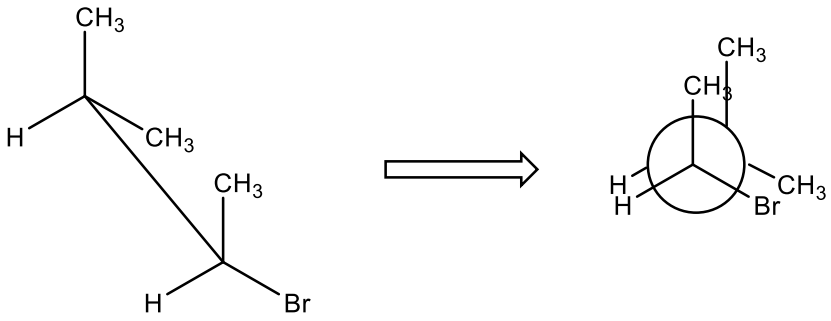


The chirality of the centers from top to bottom would be SRR according to the Fischer and traditional way. In the above Fischer projection, each of the intersection points represents a chiral carbon in the parent compound. In this way, we can make a single Fischer projection that gives the stereochemistry for the entire compound.

The second type of projection is referred to as the Newman projection, and this projection is used to determine the stability of conformational isomers. The Newman projection requires that you look down a C-C bond and determine the orientation of the groups on those carbons. For example,

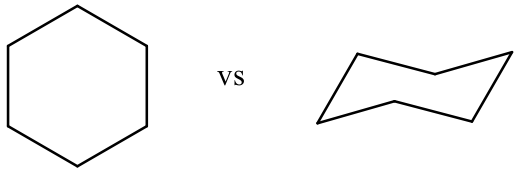


In the above example, C3 was the carbon in the front and C2 was the carbon in the back. The intersected dot in the front is C3. I like to think of Newman projections as the Mercedes Benz nobody wants, or a double Mercedes Benz. These projections can be used to determine stability by looking at what groups are closer to each other. In the conformation drawn above, there are a lot of unfavorable interactions at play. The goal whenever a Newman projection is drawn is to put the largest groups as far away from each other as possible (180 degrees in the Newman) to minimize steric hindrance and torsional strain. The most unfavorable position would be if the groups are eclipsed like below:



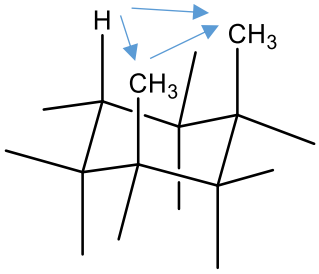
Gauche interactions also harm stability, gauche interactions are those interactions that occur when groups are not 180 degrees from each other, but not totally eclipsed, typically these are more pronounced the smaller the angle is between the groups. The goal to minimize energy is to minimize steric interactions by minimizing eclipsed groups and gauche interactions.

Conformations play a large role in determining cyclic compound stability. The most commonly occurring ring size in organic chemistry is the 6 membered ring followed by the 5 membered ring. The 6 membered ring, or cyclohexane ring, is the most stable ring size because it allows all carbons to be at 109.5 degree angles, the optimal angle for tetrahedral carbons. Ring sizes smaller than that cause the carbons to progressively decrease their bond angles and this causes ring strain, so small rings like cyclopropane (3 membered ring) and cyclobutane (4 membered ring) are extremely unstable. To allow all carbons to adopt a perfect 109.5 bond angle, cyclohexane takes on a unique structure, rather than being perfectly hexagonal like the planar structure would suggest, the actual structure is known as the chair conformation. These two structures are shown below:



Expectation Reality

In the cyclohexane molecule, there are two positions groups can be placed on: equatorial and axial. In the axial positions, the groups experience more unfavorable steric interactions as shown below with the blue arrows:

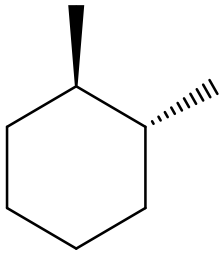
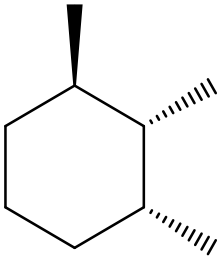
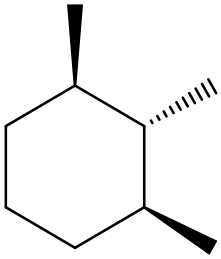
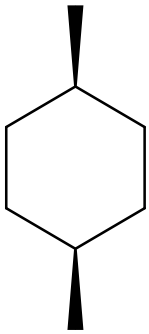


These unfavorable steric interactions are referred to as 1,3 diaxial interactions because they occur between carbons that have a carbon in between them. It is therefore preferable to place the

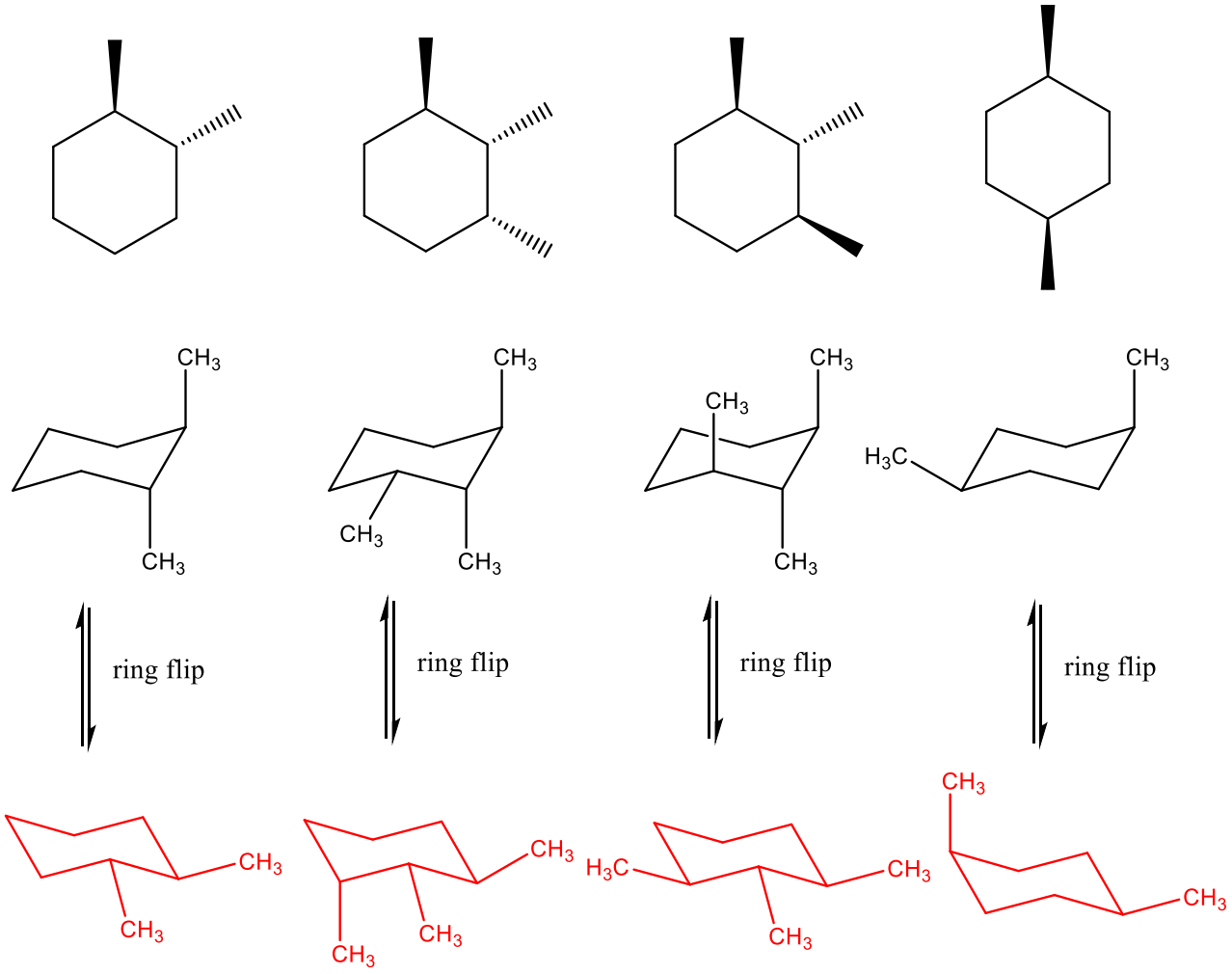
bulkiest groups on equatorial positions, rather than axial ones. Something important to note about the cyclohexane chair conformation is that the axial positions always alternate between facing up and facing down. This will help determine how the groups should be oriented depending on if the cyclic compound has them cis or trans in the planar skeletal form. When a group is placed on a position, whether axial or equatorial, that can be changed if the cyclohexane does a ring flip, as long as the groups on the ring are not sufficiently bulky ($C(CH_3)_3$ is one such example).

Practice questions:

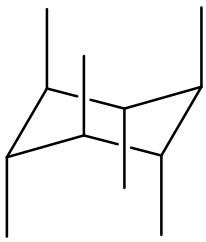
1. Draw the most stable conformation for the following cyclohexane rings:

Answers:

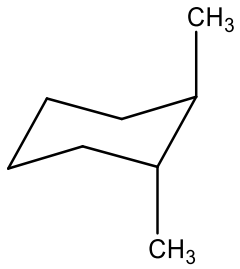


We will go through two examples step by step so that you understand the fundamental reason behind these responses. In the first ring, the two CH_3 groups were trans to each other, meaning they point in opposite directions. The easiest way to determine if two groups are trans to each other in the chair conformation is to draw them initially in the axial position. We know that the axial positions alternate between facing up and facing down, therefore we start off with the following chair conformation:

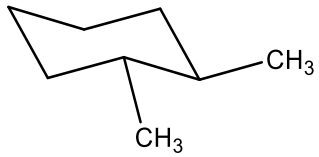


I always start with the carbon on the top right of the chair, but that choice is completely arbitrary. If we make that carbon 1, we need to add a CH_3 to that carbon and to the carbon next to it. We know those two CH_3 groups are trans to each other, therefore they must be facing opposite

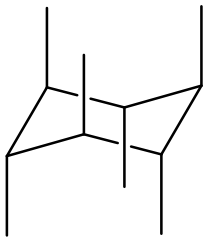
directions. If I put the first CH_3 group axial up, I must place the second CH_3 group axial down on the carbon over. Therefore, I am left with the following chair:



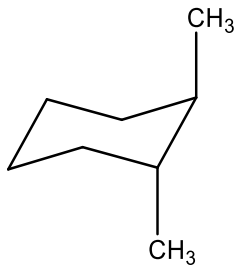
This, however, is not the most stable conformation because the two bulky groups (CH_3 groups in this case) are both occupying axial positions, and to minimize the energy we want to make the most amount of groups equatorial. To do this, we simply do a ring flip and that gets us our most stable conformation:



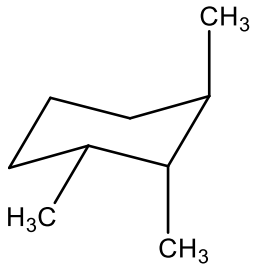
We can then apply the same process to the next example. We start off by drawing the cyclohexane chair with all the axial bonds shown like so:



We have three CH_3 groups on carbons 1,2, and 3. The CH_3 groups are trans relative to each other on carbons 1 and 2, but cis relative to each other on carbons 2 and 3. We start by drawing the CH_3 on the top right carbon in the axial up position. Because the CH_3 on carbon 1 is axial up, the CH_3 on carbon 2 must be axial down because they are trans with respect to each other, so we place the CH_3 on carbon 2 on the axial down position, this gives us the following cyclohexane chair:

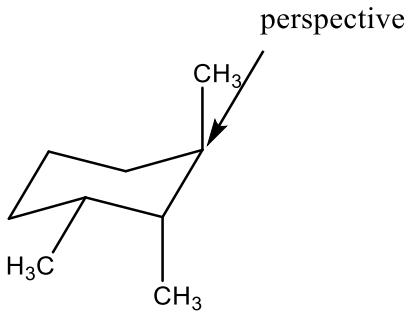


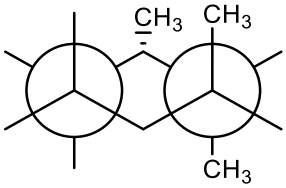
Now we have to place the CH_3 on carbon 3, but wait, the axial position on that carbon is pointing up, so we cannot place the final CH_3 on the axial position, instead we put it on the equatorial position since there are only two options and axial was eliminated. This gives us the following cyclohexane chair:

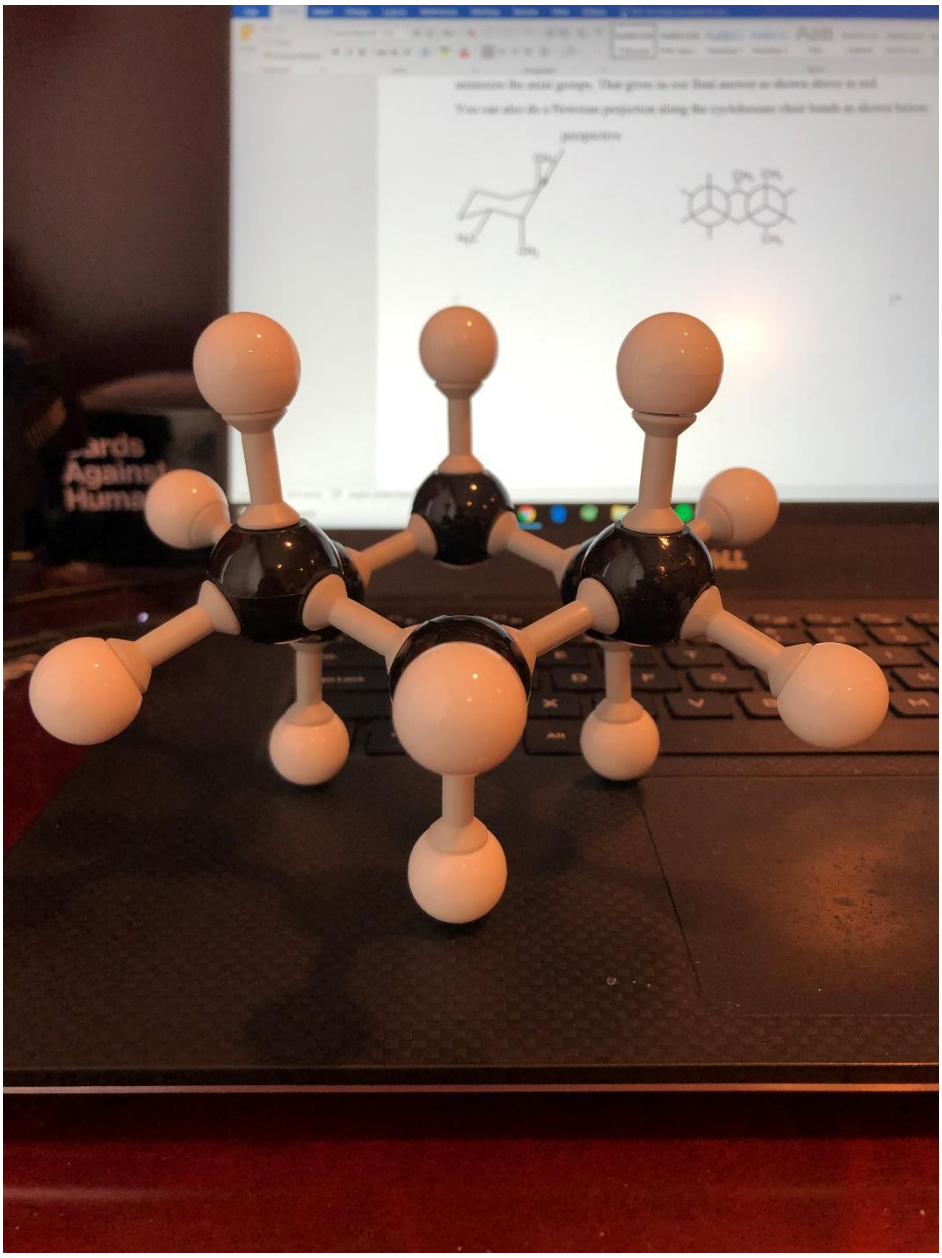


But there's still a problem here, that cyclohexane has 2 axial groups and 1 equatorial group, that would cause a lot of steric strain, therefore we ring flip to maximize the equatorial groups and minimize the axial groups. That gives us our final answer as shown above in red.

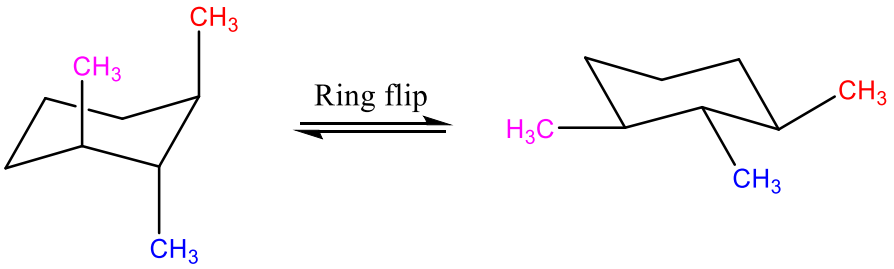
You can also do a Newman projection along the cyclohexane chair bonds as shown below:







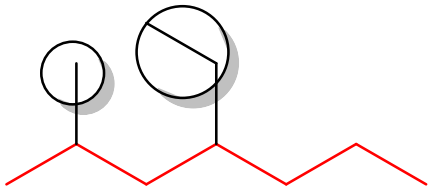
This is the perspective that you must take when you are doing Newman projections of cyclohexane's (excuse the clutter in the background). When doing ring flips, you make all the axial groups equatorial and all equatorial groups axial while moving the groups over in the clockwise direction.



Chapter 5: Basic Nomenclature

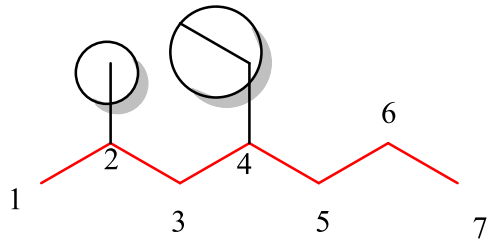
Before getting into the systematic nomenclature for complex organic molecules, it is worthwhile to discuss the common groups that you will see attached to the parent chain. A one carbon long group with three hydrogens (CH_3) is referred to as a methyl group, the prefix meth indicates one carbon, therefore methane is CH_4. A two carbon long group with five hydrogens (CH_2CH_3) is an ethyl group, the prefix eth indicates two carbons, and therefore ethane is C_2H_6. A three carbon long group with seven hydrogens ($CH_2CH_2CH_3$) is a propyl group, the prefix prop indicates three carbons, and therefore propane is C_3H_8. Finally, a four carbon long group with nine hydrogens ($CH_2CH_2CH_2CH_3$) is a butyl group, the prefix but indicates four carbons, and therefore butane is C_4H_{10}. All the other larger alkyl groups follow the traditional pent-, hex-, hept-, oct- nomenclature that you should be familiar with by this point from geometry. A good way to remember the alkyl groups shorter than five carbons long is with MEPB, methyl, ethyl, propyl, and butyl.

When naming an organic molecule, the first thing you must do is find the longest continuous chain of carbon atoms and count them. If the longest continuous chain is five carbons long then the end of the name will be pent-functional group, if it is fully saturated and has no double bonds or special groups, then the ending is –ane. If the chain contains an alcohol, the ending is –ol, if the chain contains a double bond then it is –ene, triple bond –yne, and finally if it contains an amine group it is –amine. Once the longest continuous chain is identified, circle the groups or substituents off the main chain and determine their names, for example:

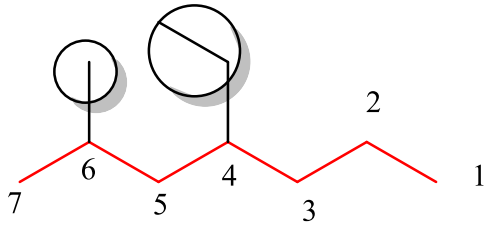


In this example, the longest chain is highlighted in red, and there are 7 carbons on the parent chain. Therefore, the name of this organic molecule will end in heptane because there is only alkane carbons in this molecule. Now we have to deal with the groups off the main chain, we have a methyl (group on the left) and an ethyl (group on the right). When numbering groups, we always want to give the numbering scheme that gives the lowest possible values to both groups. We can approach the methyl and the ethyl groups from either the left or right. Let's look at both scenarios below:

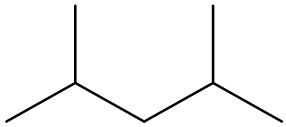
Approach from left to right



Approach from right to left



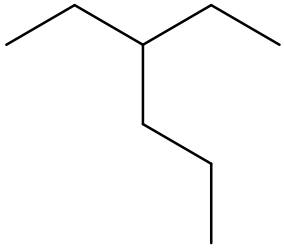
If we approached the groups from left to right, the methyl would be on the 2 carbon and the ethyl would be on the 4. If we approached it from right to left, however, the ethyl would be on the 4 and the methyl would be on the 6. Therefore, numbering the carbons from left to right would give the lowest numbering scheme and is the preferred method in this scenario. Now we know that the molecule will end in heptane and that it is 2-methyl and 4-ethyl, but how do we determine how to list the groups? The groups are always **listed in alphabetical order**, *regardless* of numbering for linear alkanes! Therefore, the name for this alkane would be 4-ethyl-2-methylheptane. Each number and group is separated by a – and the suffix is placed directly after the last group with no spaces. If there is more than one of the same group, use di- for two, tri- for three, tetra- for four, etc to indicate the number of groups. To indicate where they are indicate them with a comma, for example:

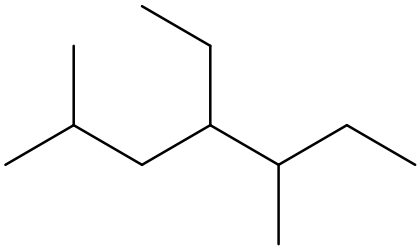


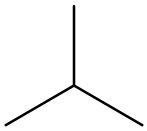
The parent chain is five carbons and there are methyl groups on the 2 and 4 carbons, therefore, the name for that molecule would be 2,4-dimethylpentane. These numerical prefixes *do not* affect the alphabetical order you essentially just ignore them.

Practice questions:

1. Name the following alkanes using IUPAC nomenclature

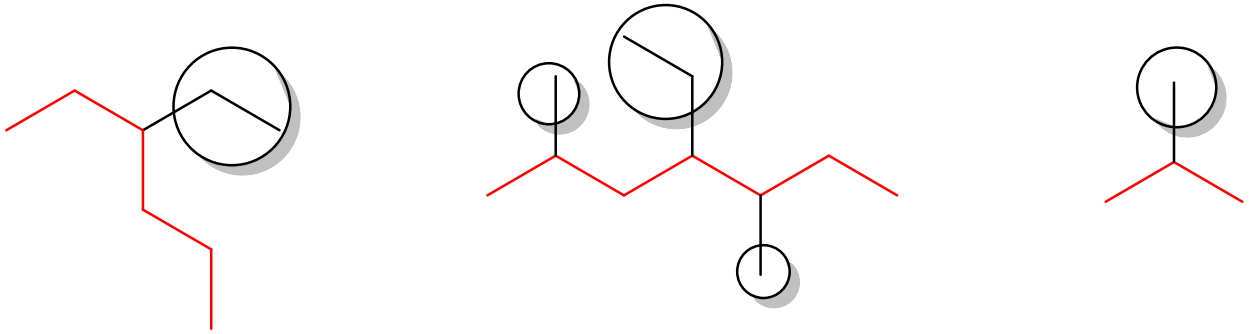




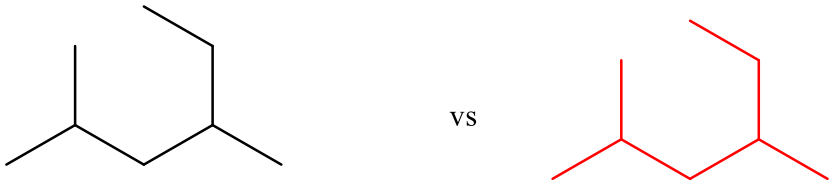


Answers:

1. 3-ethylhexane, 4-ethyl-2,5-dimethylheptane, 2-methylpropane



If there is a tie in the numbering scheme such that either group could get the other's number, the preferred numbering scheme is the one that gives the lowest number to the group listed first, for example:

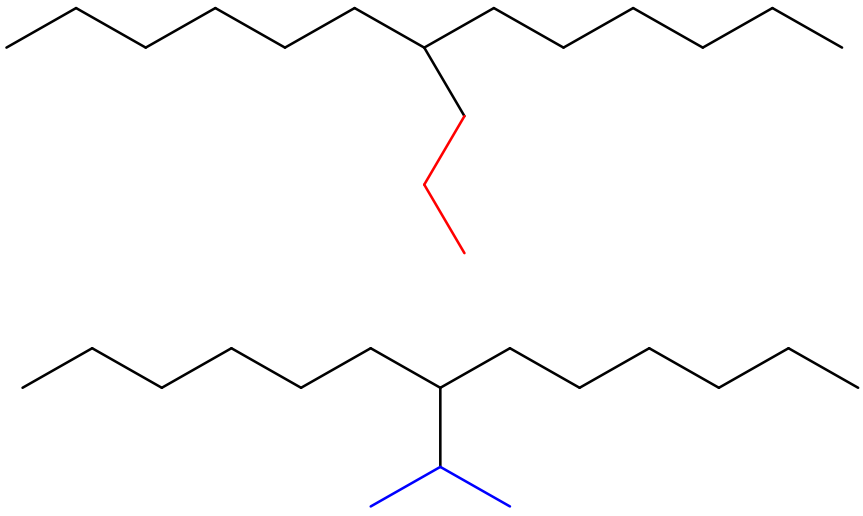


2-methyl-4-ethylpentane

vs

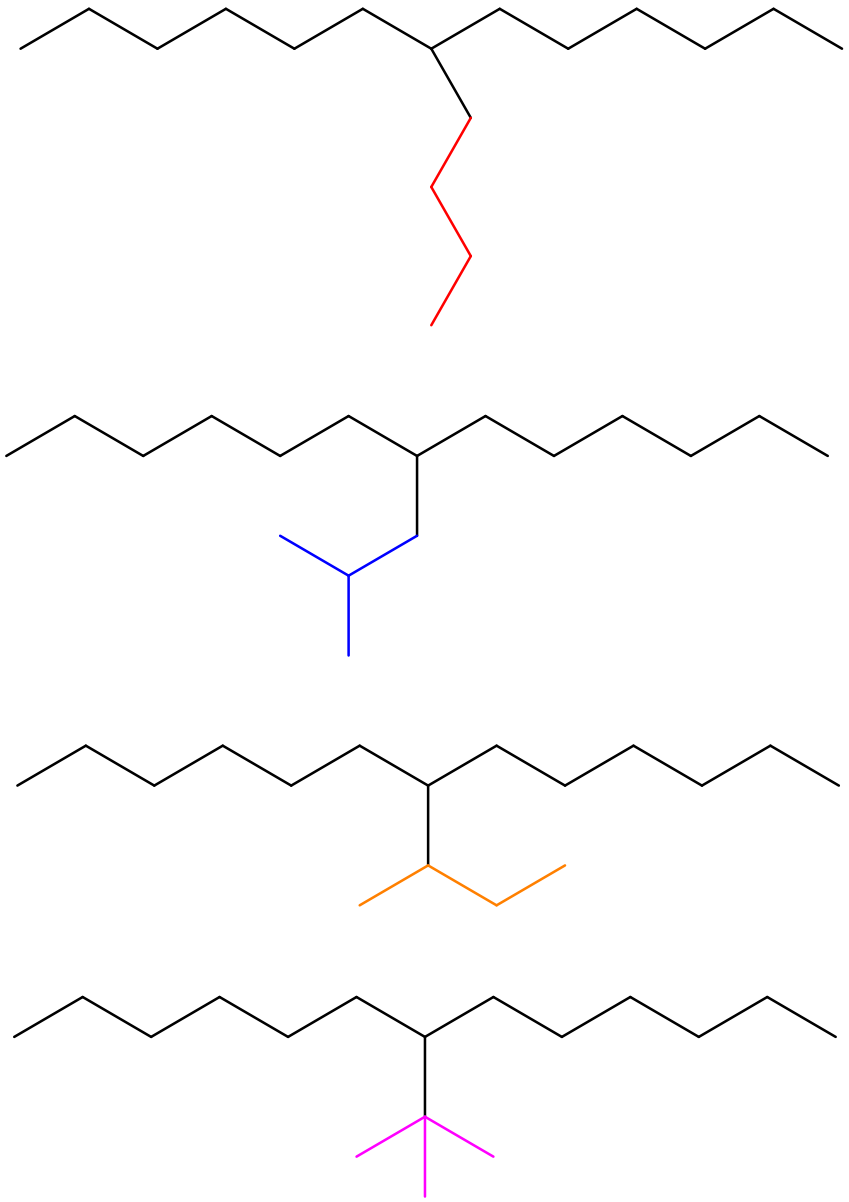
2-ethyl-4-methylpentane

There could also be groups that are branched off the main chain. In this case, there are special names that are given to these groups. The most common of these groups have common names that are also accepted for IUPAC nomenclature, we will discuss these now and then get into the more complex groups. A three-carbon chain can attach two ways to the main chain, for example:



The red three-carbon chain is a propyl group, while the blue three-carbon chain is an *isopropyl* group. The iso prefix in isopropyl IS counted towards the alphabetical order of the group, unlike the multiplier prefixes like di-, tri-, etc.

A four-carbon chain can attach to the main chain in four different ways as shown below:



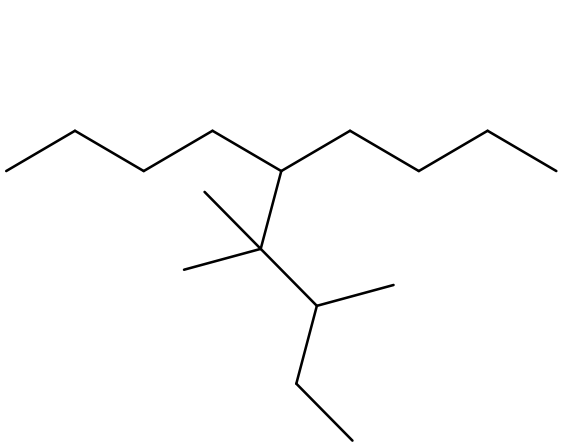
The red group is a butyl group, the blue group is an isobutyl group, the orange group is a sec-butyl group, and the pink group is a tert-butyl group. Unlike iso, sec and tert are NOT counted towards alphabetization because of the dash that separates the prefix and the group itself. All other groups that attach off the main chain are considered complex substituents and are therefore named in a different way.

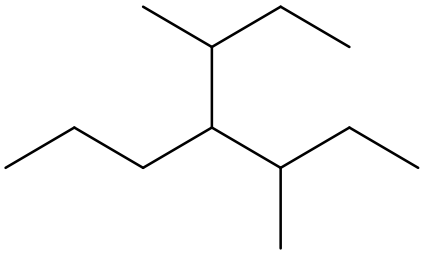
Naming complex substituents is essentially just doing a name within a name and surrounding it in parenthesis. The exact same naming procedures apply to naming complex substituents,

however, unlike regular substituents, complex ones do count di, tri, etc. in the alphabetization order. For example, a tert-butyl group would be named (1,1-dimethylethyl) if it were named using complex group nomenclature. Notice here that the ending of the group remains –yl and does not change to –ane like the parent chain does. The only thing that will have ending –ane is the parent chain! Be careful when you have complex groups, always make sure that the chain you pick is the longest possible chain. If two chains of the same length are possible, pick the one that has the most groups on it and name it accordingly.

Practice questions:

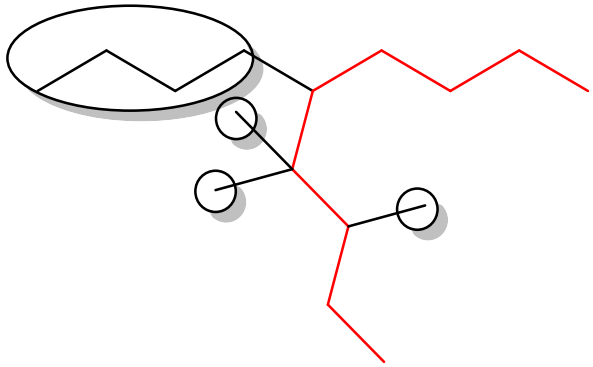
1. Name the following compounds using IUPAC nomenclature

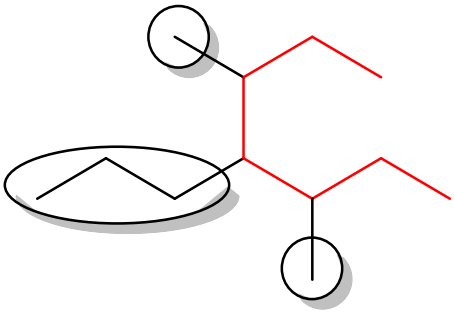




Answers:

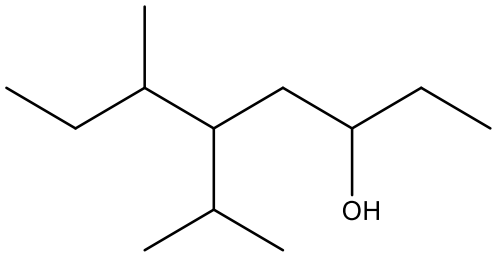
1. 5-butyl-3,4,4-trimethylnonane
2. 3,5-dimethyl-4-propylheptane



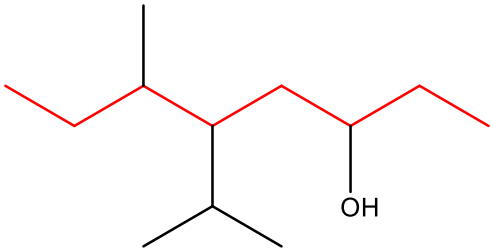


Now let's discuss non-carbon groups on the main chain. The most common non-carbon groups to add to a main chain are halogens, oxygen, and nitrogen. Halogens do not get priority and neither do ethers, but alcohols and amines do and of the two of them, alcohols get higher priority over amines. Priority simply means that you are no longer looking for the longest continuous

chain of carbons overall, but instead you are looking for **the longest continuous chain that contains the priority group**! The halogens are always listed as substituents, F = fluoro, Cl = chloro, Br = bromo, I = iodo and they follow the alphabetical ordering rule. When you have a priority group in the molecule, the placement of the priority group is specified by the number before the parent chain suffix. For example,



Would be named



5-isopropyl-6-methyl-3-octanol OR 5-isopropyl-6-methyloctan-3-ol

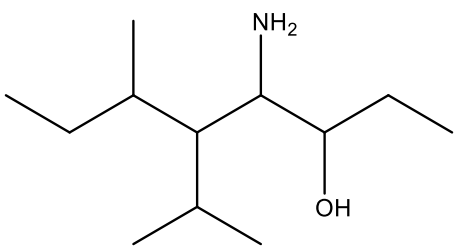
Because the alcohol is a priority group, it must also be on the lowest numbered carbon in the chain you select. The number that specifies the location of the alcohol group can be placed prior to octa, or at the very end. If there are two priority groups with different priority (OH vs NH_2 for instance), the lower priority group is given a substituent name. NH_2 is given the substituent name 'amino'. There are other priority groups that are not groups on the main chain, but are incorporated into the main chain itself, these groups are alkenes and alkynes. Alkenes and alkynes are of the same priority, but since groups listed after the main chain's numerical prefix such as octa- are listed in alphabetical order, the alkyne is listed last. If there is a tie between the alkene and alkyne for numbering purposes, the alkene takes priority. Otherwise, all naming procedures stay the same. If there are carbon groups added to the nitrogen, they are denoted with N-.

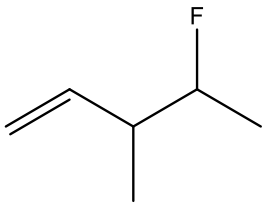
Table of Organic Functional Group Priority for IUPAC Nomenclature:

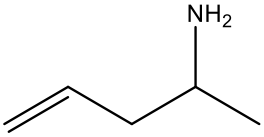
Group	Priority	Parent chain ending	When not top priority group name
OH	1	-ol	Hydroxy
NH_2	2	-amine	Amino
Alkene	3	-ene	-en
Alkyne	3	-yne	-yn
Ether	None	None	-oxy
Alkyl halide	None	None	Replace ine with o
Alkane	None	None	-yl

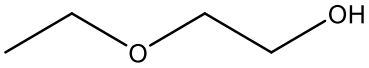
Practice questions:

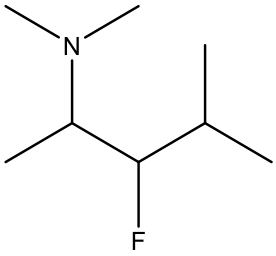
Name the following compounds according to IUPAC nomenclature:











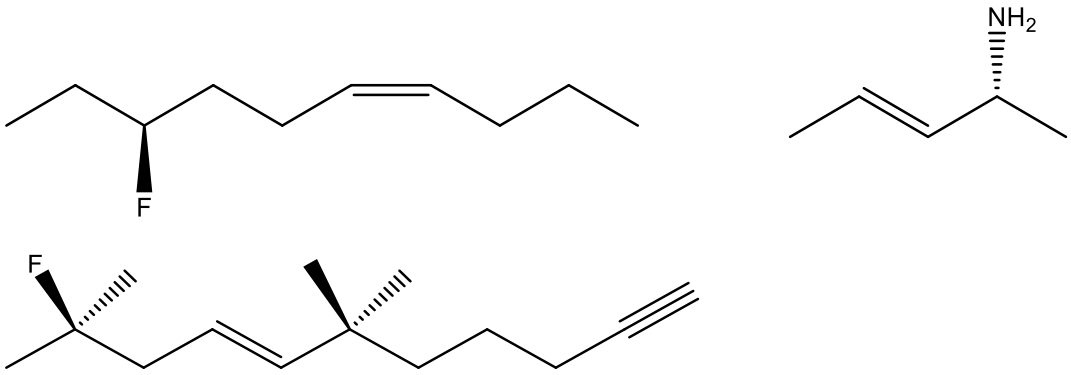
Answers:

1. 4-amino-5-isopropyl-6-methyloctan-3-ol OR 4-amino-5-isopropyl-6-methyl-3-octanol
2. 4-fluoro-3-methylpent-1-ene OR 4-fluoro-3-methyl-1-pentene
3. Pent-4-en-2-amine
4. 4-methoxybut-1-ene
5. 2-ethoxyethan-1-ol
6. 3-fluoro-N,N,4-trimethylpent-2-amine

If there is a chiral carbon in the molecule that you are naming, you must specify the stereochemistry with the chirality configuration in parenthesis before naming the rest of the molecule. If there are multiple chiral centers, you must specify all the R-S configurations and E-Z configurations of double bonds in parenthesis before the rest of the chain is named with each center separated by a comma.

Practice questions:

Name the following molecules according to IUPAC nomenclature



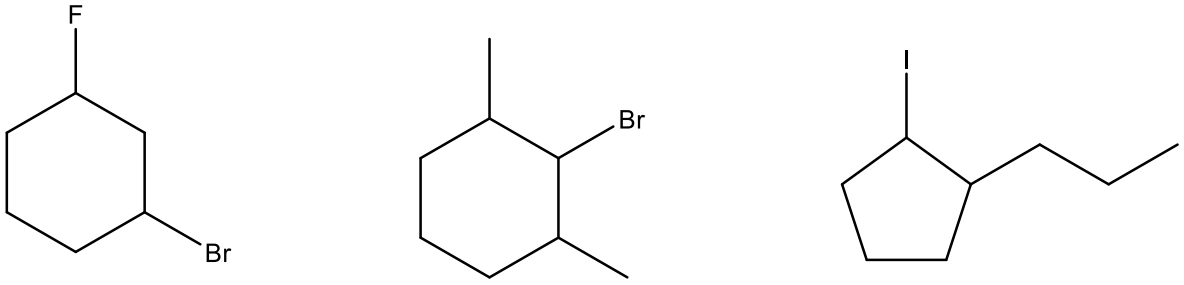
Answers:

1. (4Z, 8S)-7-fluorodec-4-ene
2. (2R, 3E)-pent-3-en-2-amine
3. (7E, 10R)-10-fluoro-6,6-dimethylundec-7-en-1-yne

Finally, we are going to discuss cyclic compounds. Cyclic compounds follow the same rules as linear compounds, except that the ending of the name is always cyclo followed by however many carbons are in the ring and that the numbering and alphabetization are one in the same if there are no priority groups.

Practice questions:

Name the following organic molecules using IUPAC nomenclature



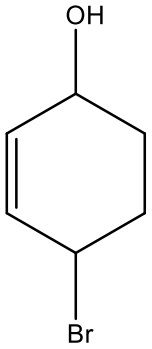
Answers:

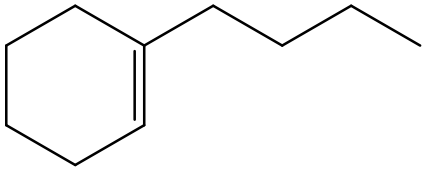
1. 1-bromo-3-fluorocyclohexane
2. 1-bromo-2,6-dimethylcyclohexane
3. 1-iodo-2-propylcyclopentane

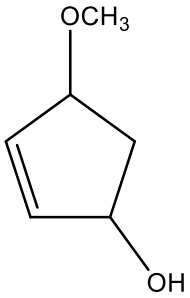
If there is a priority group, the carbon to which it is attached is assumed to be carbon 1. The numbering scheme then follows the same protocol from the linear case, in the case of a tie, number them alphabetically.

Practice questions:

Name the following organic molecules according to IUPAC nomenclature rules







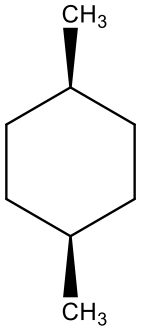
Answers:

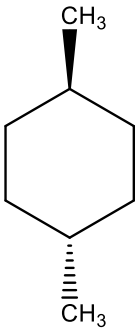
1. 4-bromocyclohex-2-en-1-ol
2. 1-butylcyclohex-1-ene
3. 4-methoxycyclopent-2-en-1-ol

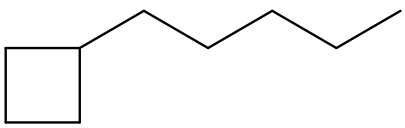
If two groups on the ring are facing the same direction, you must indicate that they are cis in the name, likewise if the two groups are facing opposite directions, you must indicate that they are trans in the name. The stereochemistry rules also apply to cyclic compounds, the alkenes are assumed to be Z alkenes because E alkenes produce too much ring strain for rings below 7 carbons large. If the group off the ring is larger than the ring itself, you must list the ring as a substituent off the main chain, if there are groups on the ring then you must name it using the complex group nomenclature. The cyclo prefix is counted when looking at alphabetical order because there is no dash.

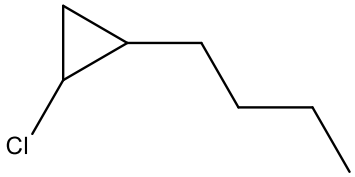
Practice questions:

Name the following organic molecules according to IUPAC nomenclature rules









Answers:

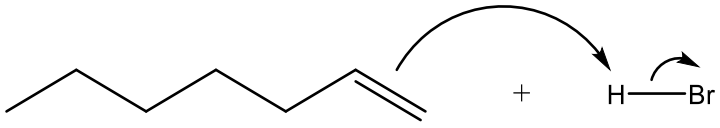
1. Cis-1,4-dimethylcyclohexane
2. Trans-1,4-dimethylcyclohexane
3. 1-cyclobutylpentane
4. 1-(chlorocyclopropyl)butane

Chapter 6: Reactions of Alkenes and Alkynes

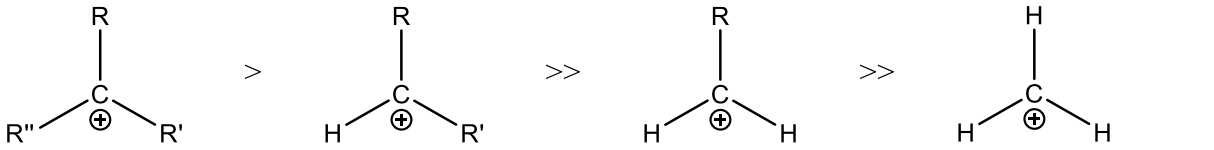
This is where the real fun begins… now we start reactions. Now before you get scared, I am going to explain each mechanism in depth and explain each step using AMSOW. I am not doing this to bore you, but rather to help develop your understanding of reactivity. I will be referring to the things we know about alkenes and alkynes throughout this chapter, so be sure to brush up on the functional group notecards that are included in chapter 3.

Fundamentally, alkenes and alkynes are nucleophiles. Therefore, they will react with electrophiles (**A**MSOW). Some of the most common electrophiles that we will discuss in this course are the inorganic strong acids (HCl, HBr, HI, H_2SO_4, and HNO_3). These species are all electrophilic because they have a very weak bond to hydrogen. That is what makes these chemicals such strong acids, they have a uniquely good ability to give away their proton. That being said, we will start our discussion on alkenes and then make alkynes. At the end of the chapter, I will provide a comparison chart between these two functional groups and will also provide a chart that gives the stereochemical consequences of using each of these reactions. Alkenes and alkynes are very similar in reactivity, this should make some sense, because the only difference between the two is an additional pi bond. That being said, let us begin by discussing the reaction of alkenes with the strong inorganic acids.

When an alkene is reacted with a strong acid, a carbocation forms. This *always* happens, so the first step in almost all alkene reactions is the pi bond attacks the proton of the strong acid and generates a carbocation. But wait, what is a carbocation? Great question, a carbocation is exactly what it sounds like, carbo = carbon, cation = positively charged. Therefore, a carbocation is a carbon that is positively charged. But why is it positively charged, that is because it lost a bond and therefore lost electrons. Take the reaction below as an example:



Note the direction of the arrows. *The arrows always show the movement of electrons***, NOT atoms**. Therefore, if you draw an arrow from anything other than a pi bond or a lone pair in this course, that arrow is WRONG. Let's discuss the chemical logic of the above reaction mechanism step and translate that drawing into words. First, we note that HBr is the electrophile in this reaction because it has a weak H-Br bond (recall electrophiles have weak bonds), therefore the alkene is the nucleophile because acids react with bases (**A**MSOW). The arrows say that the pi electrons from the double bond grab the proton from the HBr, therefore a bond between one of the sp^2 carbons and the hydrogen is forming with that arrow. But hydrogen can't have more than one bond, so the bond it has with Br HAS to break, and this makes sense because weak bonds break (AMSO**W**). Now we have a choice, do we put the hydrogen on the sp^2 carbon on the left or the right? This choice is dictated by whichever carbon forms the more stable carbocation and this is given by the diagram below:

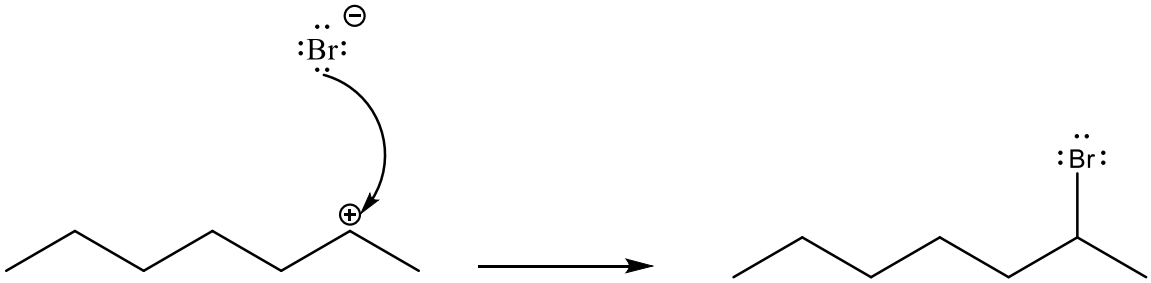


Tertiary Carbocation Secondary Carbocation Primary Carbocation Methyl Carbocation

Therefore, it can be said that the more carbons added to the carbocation, the more stable it is! This should make sense once we consider a phenomena called *hyperconjugation*. Hyperconjugation is the means by which carbon groups, or alkyl groups (R) donate electrons through space. Alkyl groups are said to be weakly inductively electron donating. We have already seen inductive effects before when we discussed acidity, but those were inductive electron-withdrawing effects. The electron donation from the carbon groups (R) help minimize the positive charge that is on the carbon and therefore increase stability (A**M**SOW). With that in mind, lets continue to discuss the reaction. Knowing that the sp^2 carbon with the most carbons attached will become the carbocation, we know that it is the sp^2 carbon on the left that will receive the positive charge, and therefore the other sp^2 carbon will receive the hydrogen. We are comparing the two carbocations below:

Secondary carbocation Primary carbocation

When we broke the bond between the H and the Br in the first step, the electrons that were in the sigma bond between those two elements had to go somewhere, therefore they went to the Br. This generated a bromide anion and we just established that we created a carbocation on the left-most sp^2 carbon. Therefore, using AMSOW, what do you think will happen next? Remember, acids react with bases and opposite charges attract (**A**MS**O**W)! If you said that the bromide anion would attack the carbocation, you would be correct. The arrow-pushing mechanism for that step is shown below:

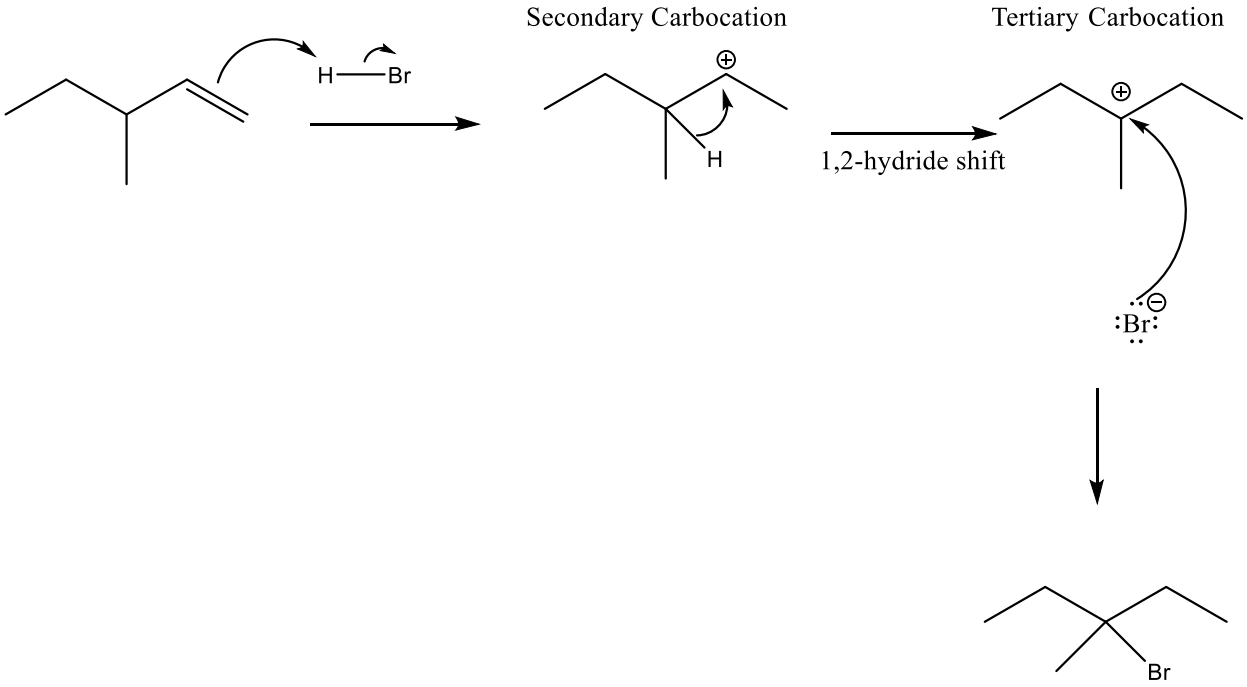


Secondary carbocation

Let's look at what the nucleophile and electrophile were in that step. The nucleophile was the bromide anion, this is clear to see for two key reasons, firstly, it has a negative charge, and secondly, it had an extra lone pair (that was why it was negatively charged in the first place). The

electrophile therefore has to be the carbocation, this also makes sense because we know that electrophiles are typically positively charged. Therefore, the bromide anion used its lone pairs to attack the carbocation. This accomplishes two things, firstly, it minimizes charge because now the Br and the C are both neutral (A**M**SOW) and secondly, it gave the carbon a full octet.

Carbocations are extremely unstable and this should make sense given what you know from general chemistry. All second row elements prefer to have a full octet, or 8 electrons in their valence shell. Carbocations are extremely unstable because initially, the carbon had 8 electrons (it had four bonds, two to the carbon to the right, one to the carbon on the left, and one to the hydrogen which isn't indicated in the skeletal structure), but when it loses the pi bond, the carbon has SIX electrons, NOT 8! This is why carbocations are extremely unstable and are even more unstable than most other positively charged atoms. It lost its octet. Because carbocations are so unstable, they are able to rearrange. The way they rearrange comes in two distinct flavors, either a 1,2-methyl shift or the more common 1,2-hydride shift. This only comes into play if you can get a more stable carbocation by rearrangement. For example,

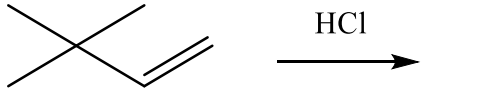


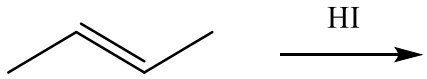
The 1,2-hydride and 1,2-methyl shifts may sound super scary, but they really aren't. They are just organic chemist speak for saying we are going to move a hydrogen or methyl group from an adjacent carbon to the original carbocation and in doing so, we are moving the positive charge over by one carbon. In the above example, the first step was the exact same as before, the alkene attacks the acidic proton off of HBr, because one of the sp^2 carbons lost a bond, it forms a carbocation. The secondary carbon supports the positive charge better so that is where the carbocation forms initially, however, the neighboring carbon is a tertiary carbon (it has three carbons bonded to it), therefore in an effort to minimize charge and stabilize the carbocation, the neighboring hydrogen moves over one carbon and the tertiary carbocation is formed (A**M**SOW). This tertiary carbocation is a strong electrophile and the bromide anion will be attracted to it

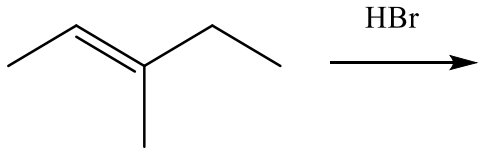
because opposite charges attract (AMS**O**W), as it approaches the carbocation, it attacks it with its lone pairs and forms the final product. This reaction works the exact same with all of the strong halogen acids (HCl, HBr, and HI).

Practice questions:

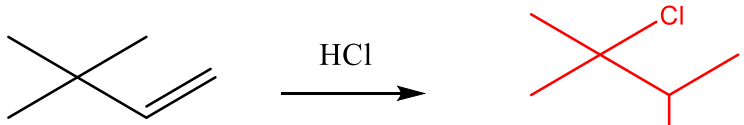
Predict the major organic products for each of the following reactions:

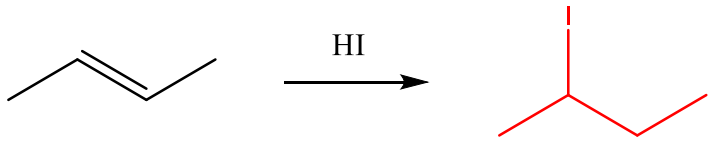


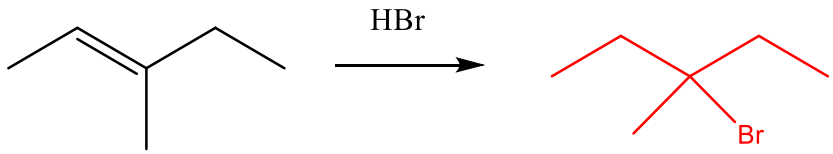




Answers:

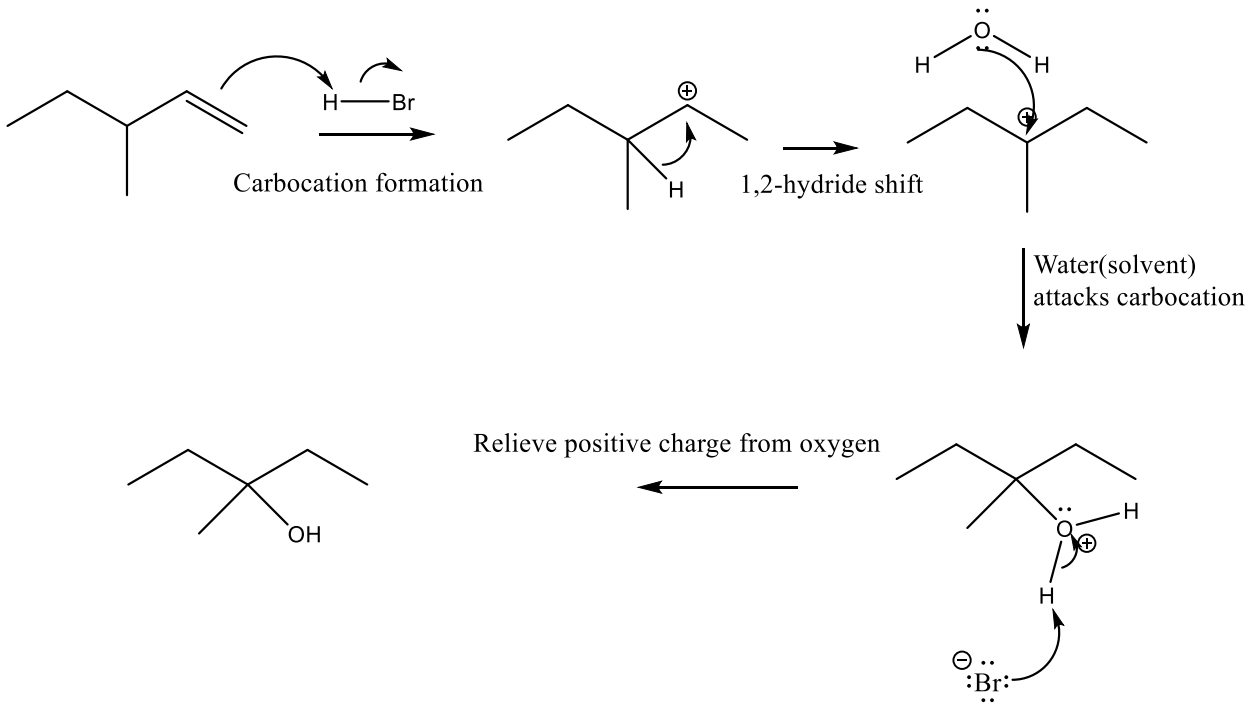






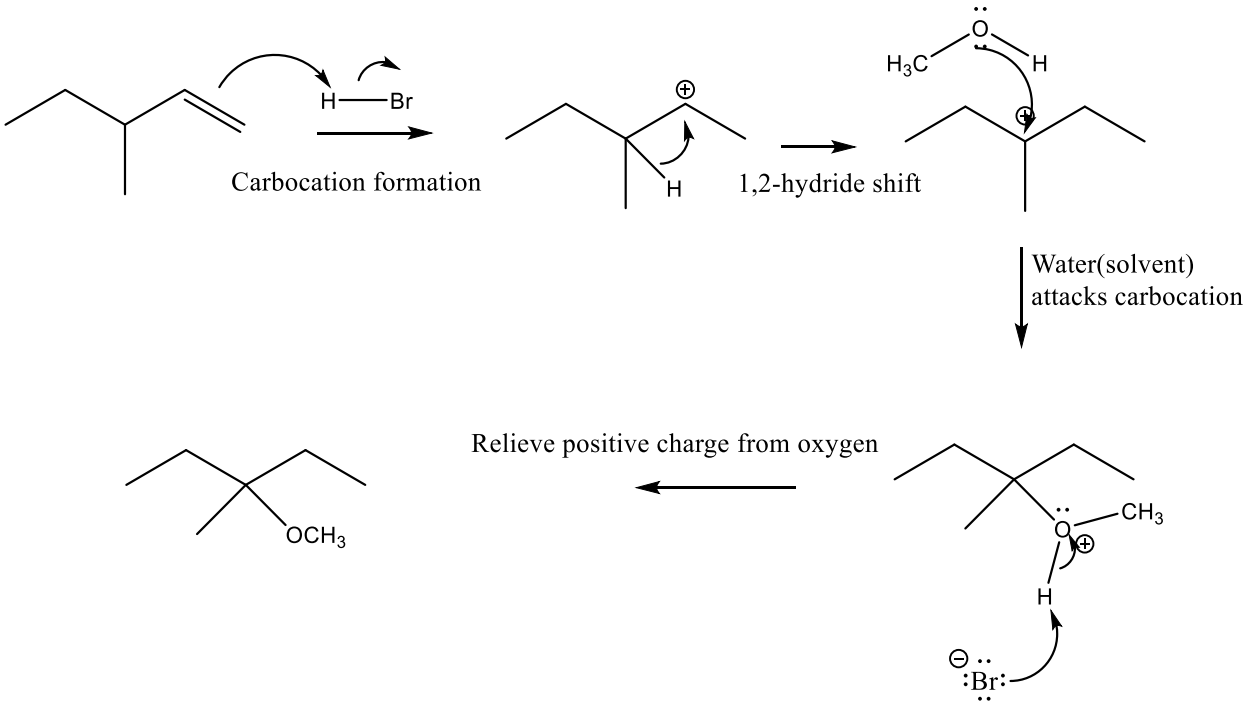
The first one goes through a 1,2-methyl shift to get to a tertiary carbocation, the second one could have the I on either carbon because they are both symmetrical, and the last one adds the bromine to the tertiary carbon because that forms the most stable carbocation.

This reaction can be altered slightly to add an OH or OR group instead. This is done by doing these reactions with dilute strong acid in a solvent of the form HOH or H_2O and HOR, where R could be any alkyl group to add an OH or OR group respectively. When these reactions are done in dilute acid, the acid's role changes from a reactant to a catalyst. The key difference is that a reactant is consumed in the course of the reaction, while a catalyst must be recycled. The mechanism is primarily the same, but instead of the halide anion attacking, the solvent molecule attacks instead. But wait, why would that happen? Wouldn't the halide be a stronger nucleophile because it has a negative charge while the solvent does not? While that may be true, if we are doing this in dilute acid, the solvent is the majority of the molecules interacting with our electrophile (carbocation), therefore it is more likely that the solvent attacks than our halide anion. It's like if I asked you to pick a marble from a mixture of red and black marbles. If 98 out of 100 marbles are black, it is more likely that you will pick up a black marble. While it is still possible that you get a red one, it is not the most likely outcome and therefore we can effectively ignore it. Let's consider a reaction in which we attack the carbocation with the solvent.



Let's go through this mechanism step by step. The first step is the same as all the other reactions we have done thus far, we form the carbocation at the sp^2 carbon that has the most amount of carbons attached, which in this case is a secondary carbocation. This secondary carbocation rearranges in the second step to become tertiary by moving the hydrogen from the carbon in the center to the original secondary carbocation in a 1,2-hydride shift. This forms our tertiary carbocation electrophile, now that our electrophile is prepared to get attacked, we attack with our water molecule. Water can act as a nucleophile in this case because the oxygen has a lone pair and because the carbocation is extremely unstable and willing to accept any electrons it can to minimize the positive charge on carbon (A**M**SOW). The water molecule uses its lone pairs on the oxygen to attack the carbocation and that forms our second intermediate. Because we did not

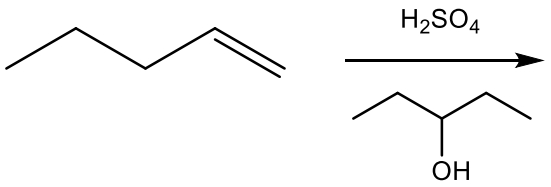
touch the hydrogens on the water, the oxygen still has those two bonds, therefore bonding to the carbocation gives it three bonds, one more than it wants. In doing this, the oxygen becomes positively charged (recall oxygen prefers to have two bonds). We need to fix this somehow because oxygen really hates being positively charged, recall that oxygen is extremely electronegative, therefore it really dislikes having a positive charge. To fix this situation, we need to remove one of the bonds oxygen has, therefore we use the bromide anion to take off one of its protons. This should make sense because we know that opposite charges attract (AMS**O**W) and by adding a bond to bromine and removing a bond from oxygen, both of them are now neutral, therefore we minimized our charges (A**M**SOW) and we recycled our HBr catalyst. This last step of protonating the bromide should also make sense considering the acidic nature of protonated alcohols that we discussed in chapter 2 (**A**MSOW). The mechanism for an HOR type solvent is exactly the same because all that is required for the reaction to proceed is one acidic proton, NOT two. This would be the mechanism for an HOR type solvent such as methanol:

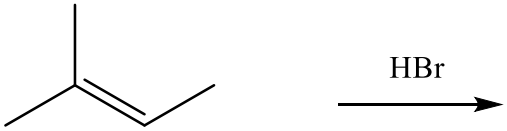


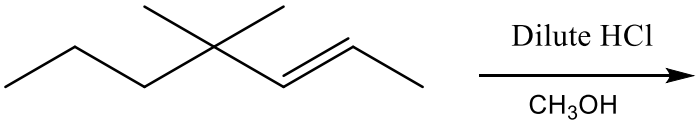
The addition of alcohols or ethers to double bonds is best performed using sulfuric acid, however, because the conjugate base of sulfuric acid is extremely weak and is a poorer nucleophile than the halides. The mechanism is essentially the exact same as above, except the conjugate base of sulfuric acid takes off the acidic proton in the last step to reform the sulfuric acid catalyst.

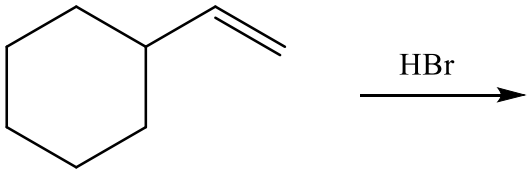
Practice questions:

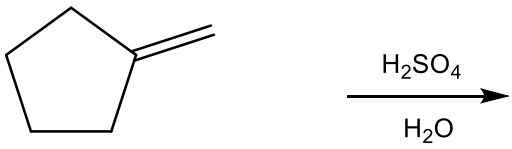
Predict the major organic products for each of the following reactions:



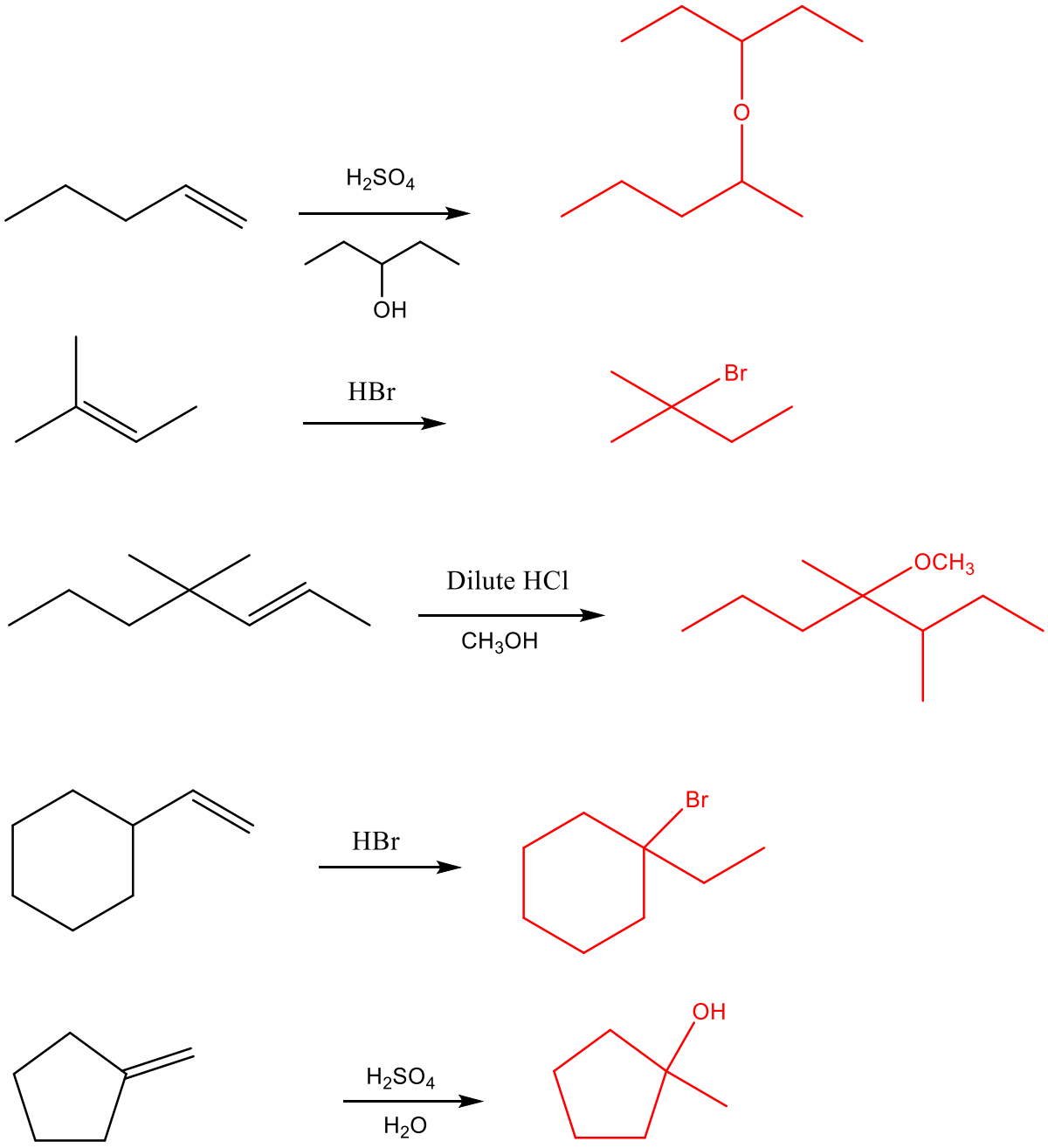




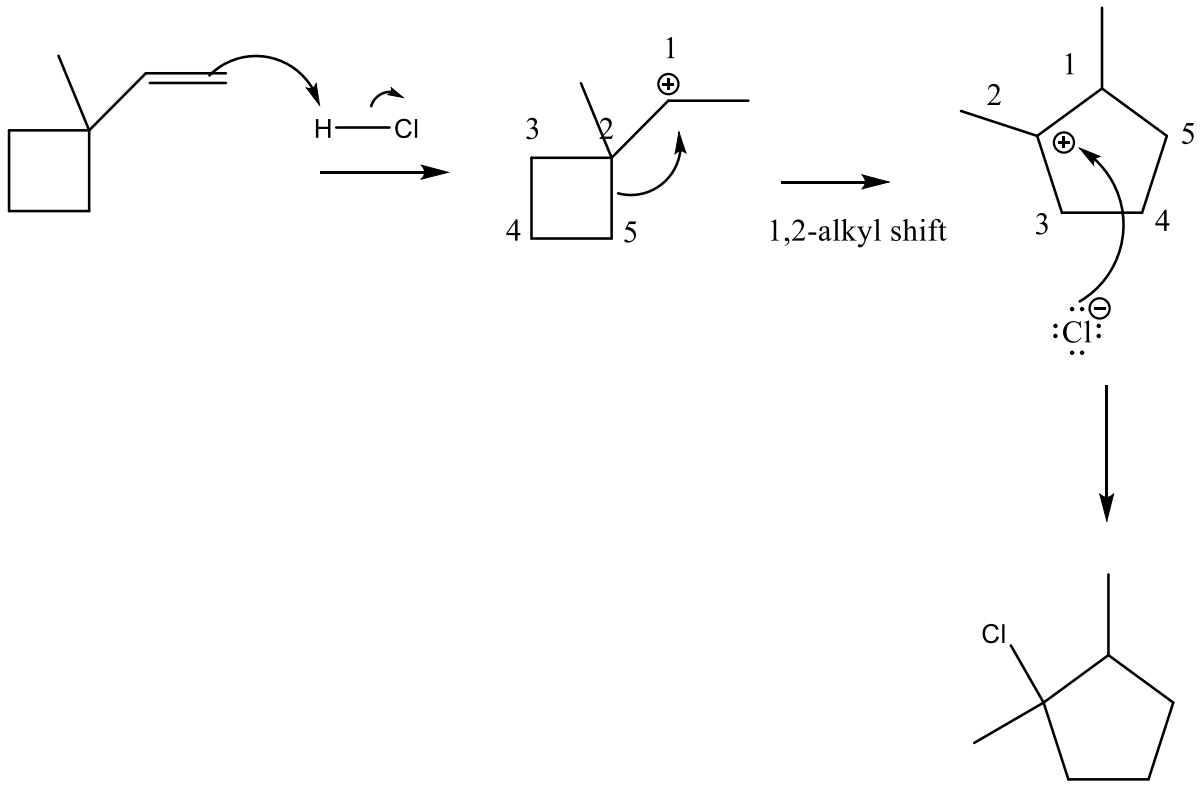




Answers:



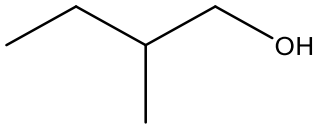
Carbocations are also so reactive that they can actually cause ring expansions if they are in rings smaller than 5 members. An example of this is shown below:



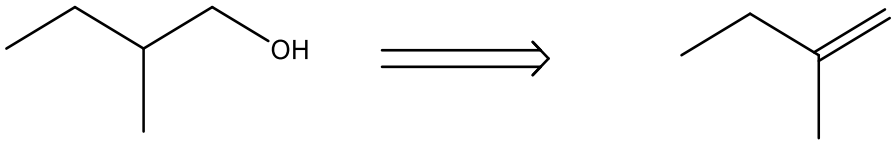
This reaction starts the same as before and forms a secondary carbocation. We know from our discussion in chapter 4 that rings smaller than 5 members are extremely unstable, therefore, by shifting over the bond between carbon 2 and 5 to the initial secondary carbocation that forms, two things are accomplished, reduction in ring strain by expanding the ring, and increase stability of the carbocation through charge minimization (A**M**SOW). Whenever we form or break up a ring, I always suggest numbering the carbons, this is a good way of keeping everything in order so that methyl groups aren't on the wrong carbons and the positive charge is located where it is supposed to be. I number the carbons the way I do because I know that the arrow that I drew in the second step will form a bond between carbons 1 and 5 because the electrons are moving over one carbon. The decision to make the carbon on the top of the cyclopentane be carbon 1 before putting the groups on the ring is completely arbitrary, but so long as you are consistent with placement you will get the right answer. This tertiary carbocation gets attacked by the chloride anion per normal and the final product is drawn.

Any reaction that goes through a carbocation, including the ones that we just did, result in a mixture of enantiomers if the carbon to which the group is added is asymmetrical. The carbocation is planar, and there is no preference for the incoming nucleophile (whether that be a halide anion or solvent molecule) to attack from on top or on bottom, because there is no preference, the product will be a racemic mixture of both enantiomers. Both the hydrogen and the group that is added to the carbocation could be added to the same side (syn addition) or opposite sides (anti addition), because there is no preference for one or the other, carbocation reactions such as those seen above are not *stereoselective*. Stereoselectivity means that a reaction or condition favors the formation of one stereoisomer over another.

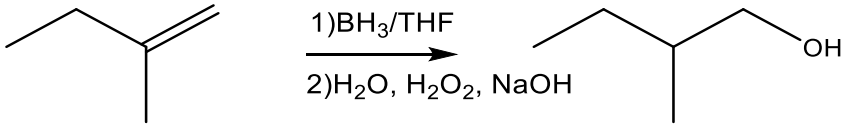
Alkenes can do more than just add alcohols, ethers, and halogens, though. Now we will discuss their reactivity with other electrophiles. First, I will pose a question, suppose we wanted to get the following alcohol, is there a way to do it with the reactions we currently know?



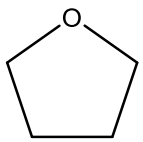
The answer you should have given is no because the alcohol is on the terminal carbon, and all of the reactions we know of currently go through carbocations and therefore add the group on the carbon that has the most number of carbons attached. If you were able to see where the alkene should be to get an alcohol at that position, you just did what we will refer to now as a *Retrosynthetic Analysis*, which is shown below:



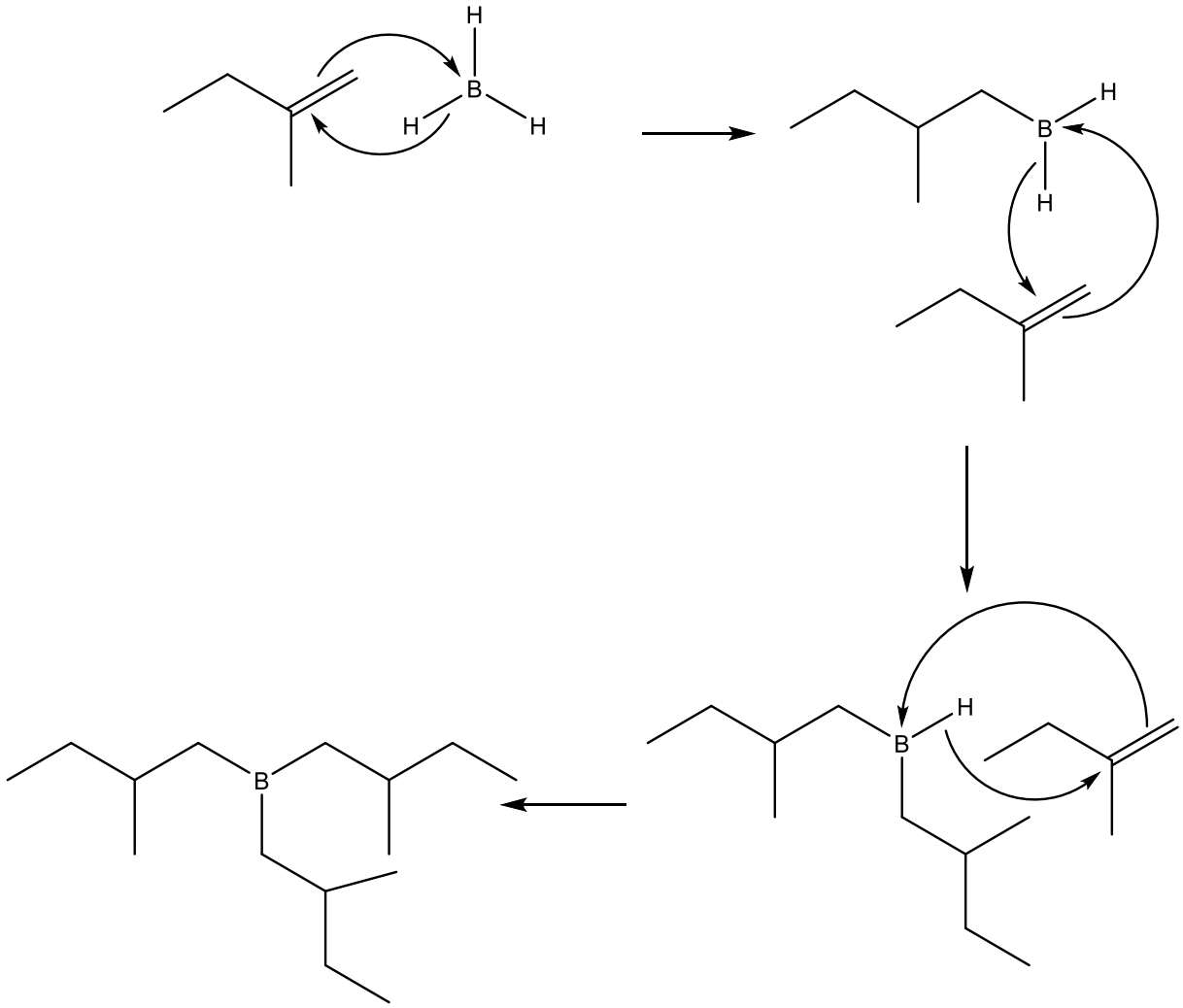
We are therefore limited in the *regioselectivity* of our products. Regioselectivity describes the ability of a reaction to prefer or select one constitutional isomer over another. Currently, we have a regioselective reaction that selects the more substituted carbon to get the group. These reactions are referred to as *Markovnikov* addition reactions. The product that we want to get would only be possible if we did an *Anti-Markovnikov* addition reaction. That is, a reaction that had the opposite regioselectivity. But enough of the organic chemistry jargon, how do we actually do this? Introducing hydroboration oxidation. This reaction functions similarly to sulfuric acid and water in that it adds an alcohol group to the alkene region, but it does so with opposite regioselectivity. This reaction works by adding the OH group to the LEAST substituted alkene carbon. Therefore, to get the product shown above, the following would be the reaction required:



The reaction mechanism you do not need to know explicitly, but we will show it here once and never again because it is rather long. If you don't want to see the mechanism, you can skip to page 61. The THF in the first step is simply an inert solvent, it looks like this:

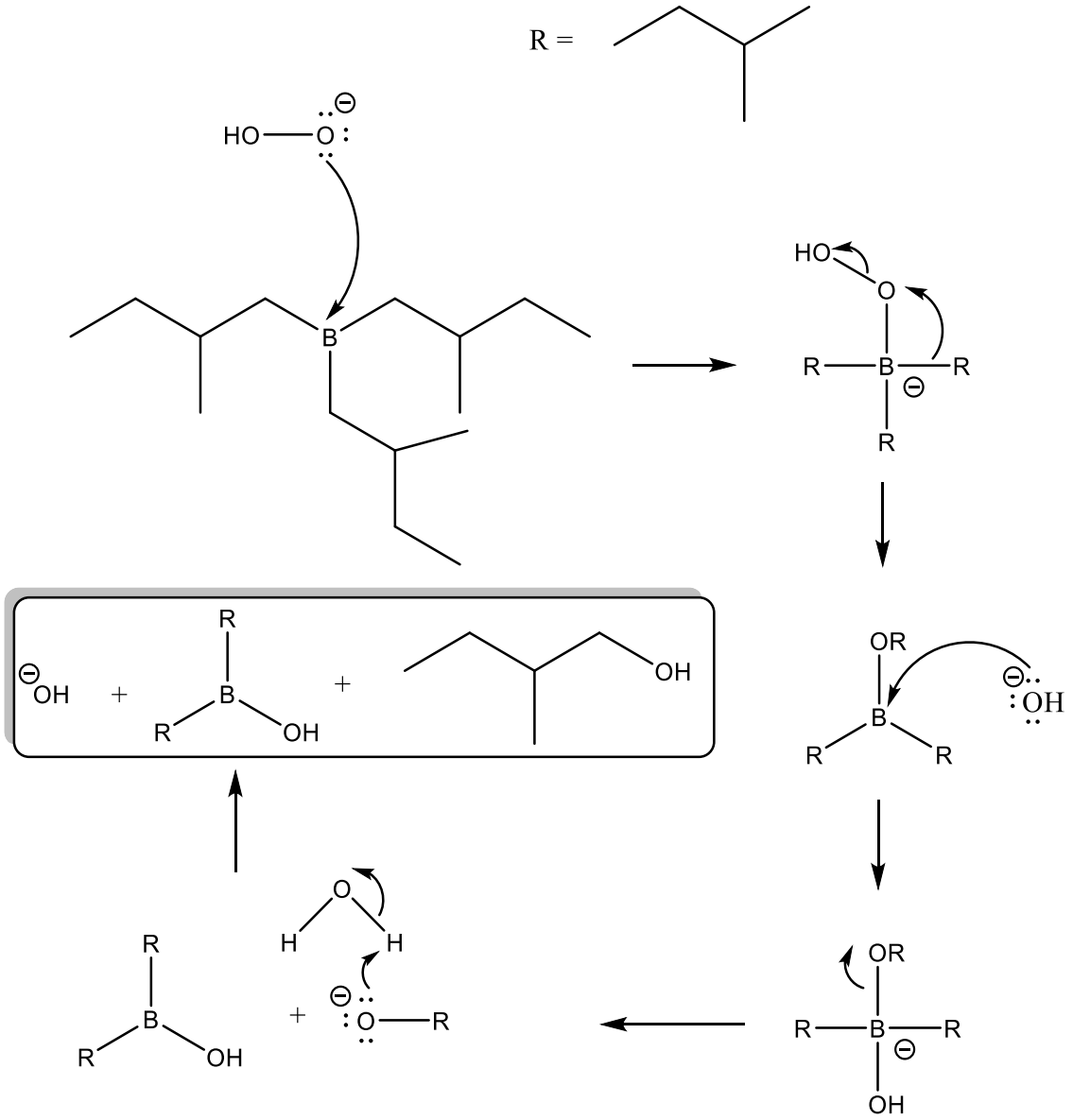


The hydroboration step is shown below (Reaction on the top of the arrow)



I know this is a lot, so let's break this down step by step. This mechanism is essentially the exact same thing happening over and over and over again (three times to be exact). We already know that alkenes are nucleophiles because they have excess electrons due to the pi bond, because of this they can react with electrophiles (**A**MSOW), but why is the boron an electrophile? Two reasons, firstly, hydrogen has a larger electronegativity than boron, so the boron is partially positive and secondly, the boron has an empty p orbital because it does not have a full octet. Because of these two traits, boron can get attacked by the alkene and act as a nucleophile. In doing so, it can donate its proton to the other sp^2 carbon that does not get the boron so that we can avoid generating a carbocation and a negatively charged boron (A**M**SOW). Something that we did not discuss before because it wasn't super important is that **electrophiles always add to the least substituted sp^2 carbon**, in the strong acid case the electrophile was the H, so we didn't see it. This cycle of boron getting attacked and donating its proton to reduce the double bond is repeated twice more, it is not done a fourth time because that would generate a carbocation (there is no more hydrogen to donate) and would cause the boron to get negatively charged (it is happy with three bonds) (A**M**SOW).

Oxidation step shown below:



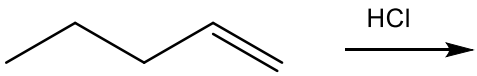
Like I said for the hydroboration step, I know this is a lot, but if we take it step by step we can use AMSOW to figure out the chemical logic. The first step has the deprotonated hydrogen peroxide anion attacking the boron. This is because the oxyanion is a strong nucleophile owing to its lone pairs and negative charge, this supercharged nucleophile was notably absent in the hydroboration step, which is why we didn't add the alkene four times and only did it three. Remember, acids (electrophiles) react with bases (nucleophiles), **A**MSOW. When this peroxide anion attacks the boron, that generates a negatively charged boron, which is extremely unhappy, this is remedied by moving one of the carbon chains to the oxygen, hence the arrow is drawn from R to the oxygen bonded to the B directly. However, O-O bonds are extremely weak, in fact they are one of the weakest bonds in nature (498 kJ/mol), this is very low considering what the B-O bond is (809 kJ/mol) and the O-C bond is (1076 kJ/mol), therefore the weakest bond breaks so that the oxygen that the carbon group attaches to does not become positively charged (A**M**SO**W**). We also have a second nucleophile in solution because of NaOH, this supercharged

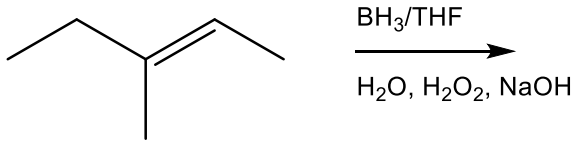
nucleophile, hydroxide, then attacks the boron and causes it to become negatively charged once more. However, there is no peroxide bond this time, so in order for the boron to minimize its charge and become neutral again, it has to kick off the OR group (A**M**SOW). After the OR group gets kicked off, it wants to minimize its charge as well, so it deprotonates a molecule of water and generates our alcohol product (**AM**SOW).

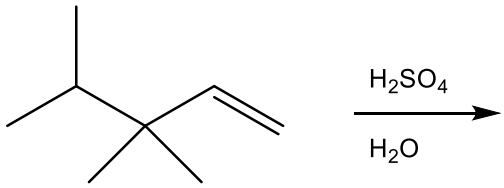
Unlike the strong acid reactions that we covered previously, the hydroboration oxidation reaction follows a strictly syn addition pattern, meaning that the hydrogen that is added and the OH are added to the same face, producing only one pair of enantiomers if the carbon to which the OH bonds is asymmetric.

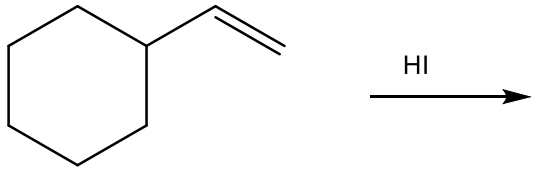
Practice questions:

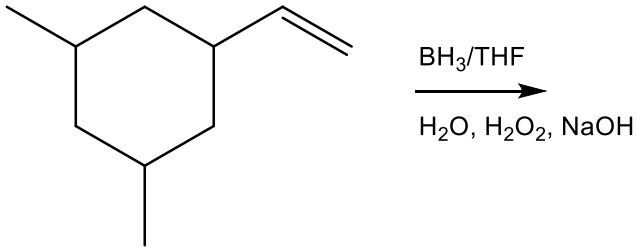
Predict the major organic products of the following reactions, be sure to include stereochemistry:

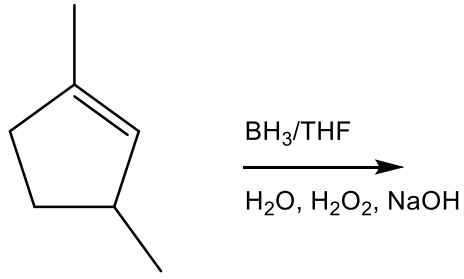

HCl


BH3/THF
H2O, H2O2, NaOH

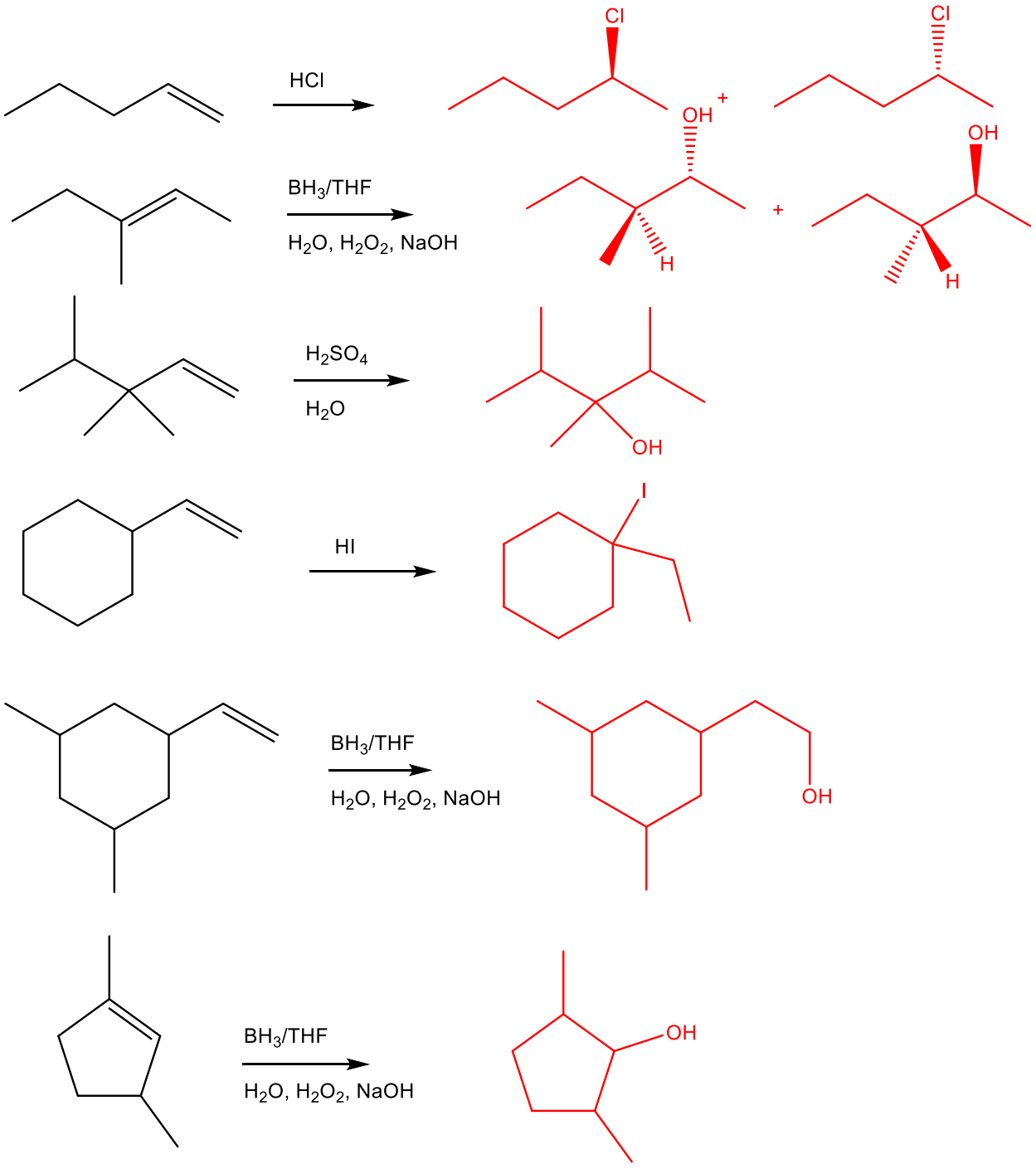

H2SO4
H2O


HI

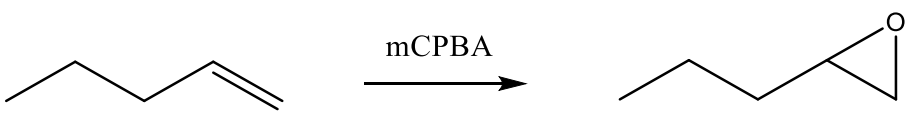

BH3/THF
H2O, H2O2, NaOH


BH3/THF
H2O, H2O2, NaOH

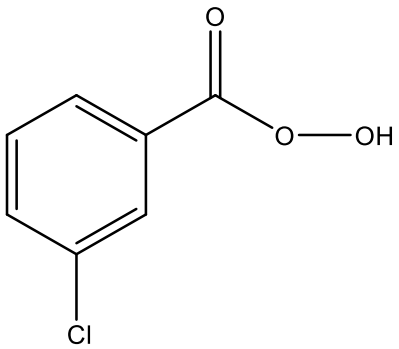
Answers:



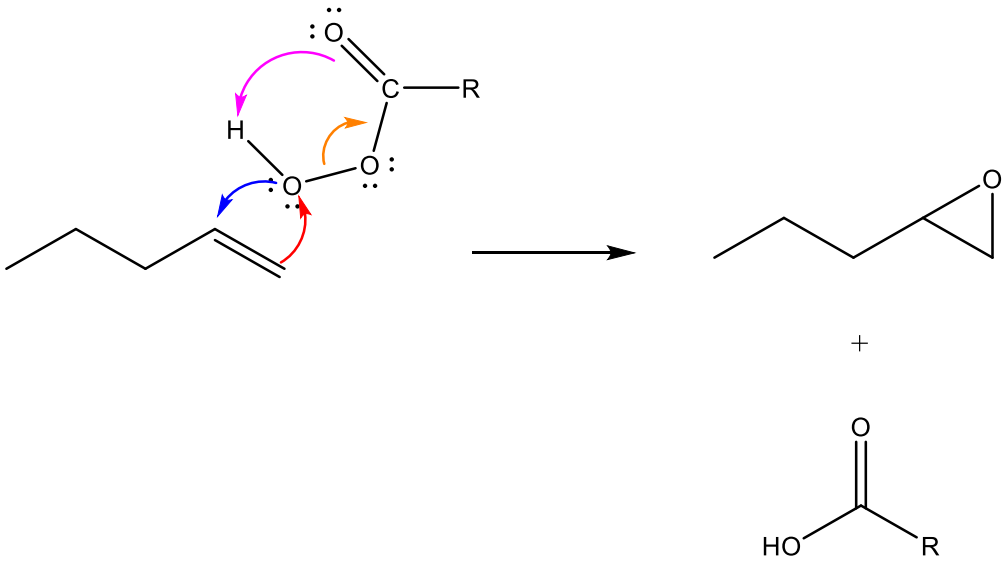
The next electrophile on our list are peroxy acids. Peroxy acids are like carboxylic acids, but with an extra oxygen. These acids are very electrophilic because of their weak peroxide linkage and because of their polar pi bond. Alkenes react with peroxy acids (such as mCPBA) to form epoxides in the reaction shown below.



The structure for mCPBA is shown below:



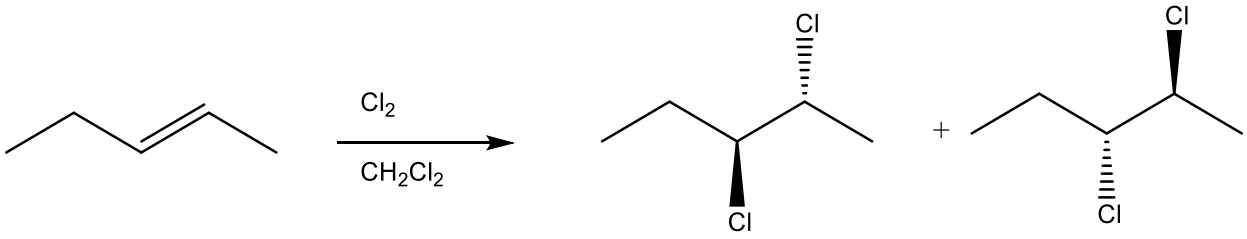
The reaction mechanism for the formation of epoxides by the reaction of alkenes and peroxy acids is shown below, however, just like the hydroboration oxidation mechanism, this too is optional. This reaction mechanism will be shown once and never again.



Let's start by addressing each arrow in turn, I colored them so that I can address them by color. The reaction starts by the nucleophilic attack of the alkene on the oxygen (red arrow). The nucleophile attacks this oxygen in specific because the peroxide linkage is very weak and weak bonds break (AMSO**W**). This forces the electrons in the peroxide linkage to move between the oxygen and the carbon to which it was bonded (orange arrow), this forces the pi bond to move (pink arrow) and pick up the extra hydrogen on the terminal oxygen. The pink arrow is forced to happen because carbon cannot have more than four bonds and a double bond is forming with the orange arrow between the oxygen and the carbon, therefore the pi bond attacks the acidic proton since acids react with bases (**A**MSOW). But now the oxygen that was initially attacked has only one bond, the hydrogen to its left got taken by the carbonyl pi bond attacking it and the oxygen to the right broke off since the peroxide bond is so weak, therefore the oxygen must attack the other sp^2 carbon in the alkene using its lone pairs (blue arrow). Doing this accomplishes two things, it prevents the oxygen from being negatively charged and it prevents the other sp^2 carbon from becoming a carbocation, therefore the blue arrow effectively minimizes charge (A**M**SOW).

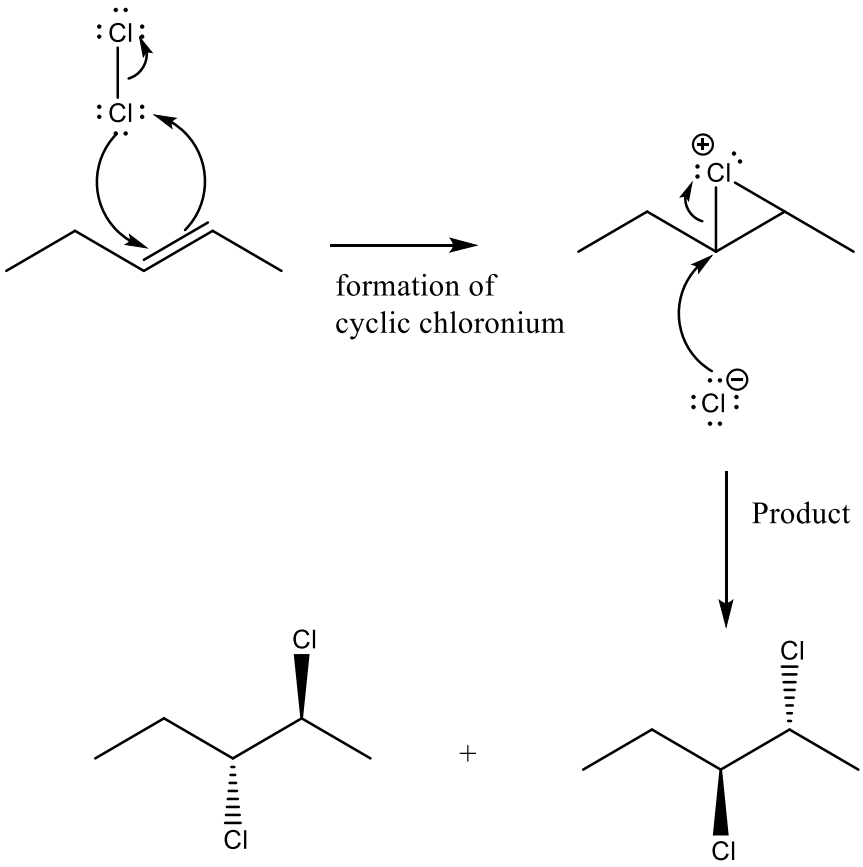
Like hydroboration oxidation, this reaction follows a syn addition mechanism, therefore both sp^2 carbons will connect to the oxygen bridge on the same side.

The next electrophile that alkenes can attack are the halogen gases Br_2 and Cl_2. These react with alkenes like so:



The solvent can also be written as DCM (dichloromethane).

The mechanism for this reaction you do need to know and we will go through it step-by-step per usual.

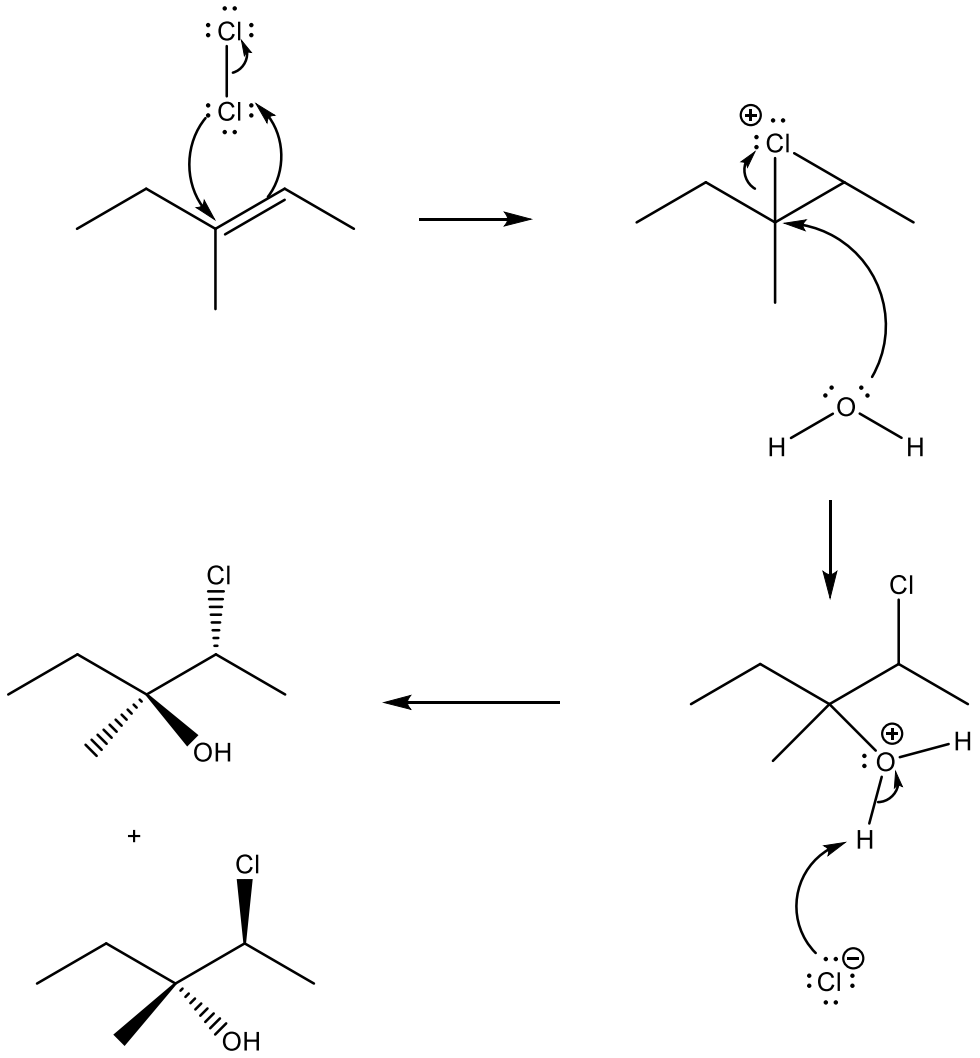


The first step in this reaction is the formation of the cyclic chloronium intermediate. This happens when the nucleophilic alkene attacks one of the chlorines in the chlorine gas molecule,

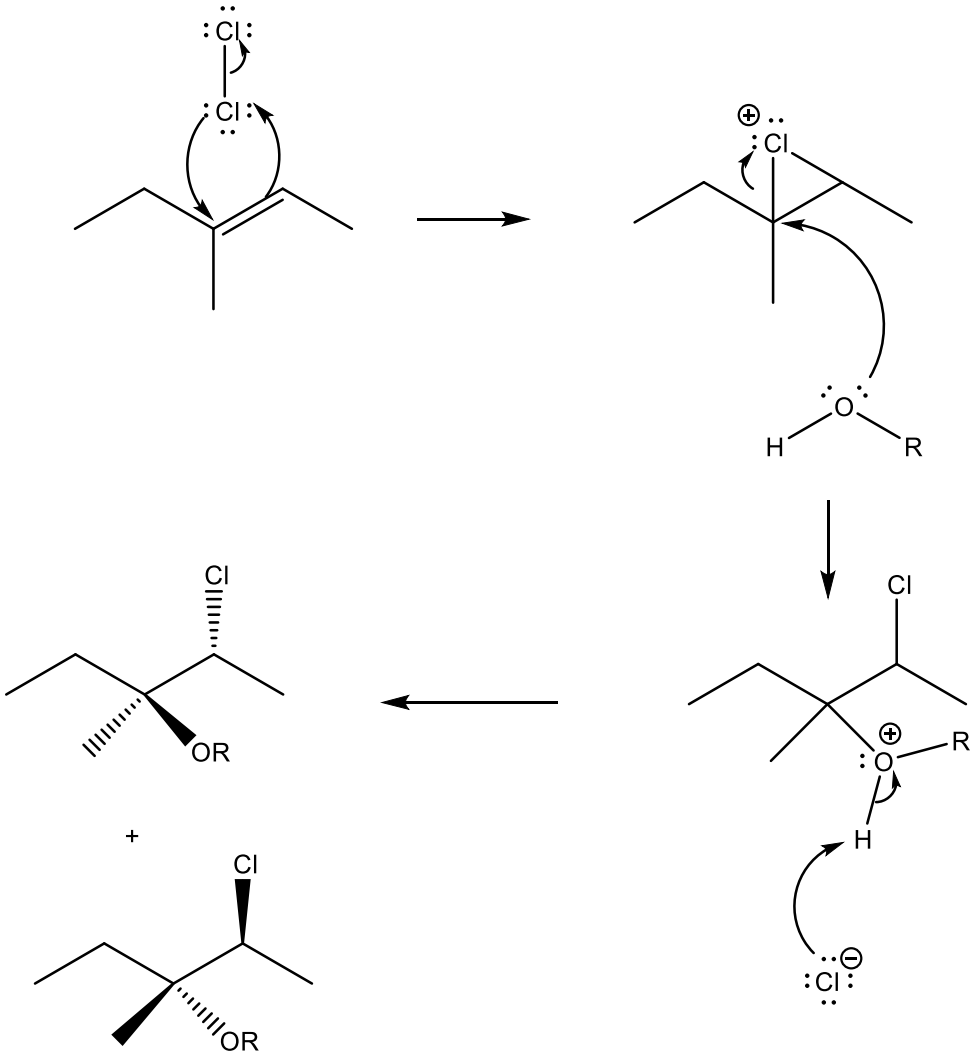
we have already established that alkenes are nucleophiles, but we should address why the chlorine or bromine gas is an electrophile. The key is that Cl-Cl and Br-Br bonds are extremely weak (436.3 kJ/mol and 193.9 kJ/mol respectively), therefore they can get attacked more easily because weak bonds break (AMSO**W**). Once the alkene attacks the first Cl, that causes the Cl-Cl bond to break, but in order for the Cl to maintain its octet, it must attack the other sp^2 carbon, this prevents the formation of a carbocation and allows the Cl to maintain its hold on 8 electrons (A**M**SOW). Chlorine is not happy being positively charged, however, and so because opposite charges attract, the chloride anion acts as a nucleophile and breaks open the chloronium intermediate. This minimizes the charge on both the chloride (goes from negative to neutral) and the chloronium (goes from positive to neutral), A**M**SOW. Initially, one would think that you may want to attack the chlorine, it is positively charged after all, but remember what that would do, chlorine likes to have 1 bond, its already unhappy with 2, so you can imagine how unhappy it would be with 3! Also recognize that the C-Cl bond without the chlorine being positively charged is relatively weak (394 kJ/mol), therefore with the chlorine being positively charged, that will make the bond be even weaker as the chlorine attempts to suck as many electrons away from carbon as possible to minimize its charge (A**M**SOW). This makes the carbon extremely electrophilic and therefore the chloride attacks there, this gives both chlorines their preferred number of bonds and everyone is happy (A**M**SO**W**).

Unlike the other reactions in this chapter, this reaction follows a strictly anti addition pattern. This should make sense, because it is easier for the chloride to attack from the opposite side that the chloronium is on. Remember, we want to avoid steric hindrance at all costs, therefore, the added bulk that the chloronium provides prevents the chloride from approaching the carbon from that face, therefore the two chlorines will face opposite directions in the product.

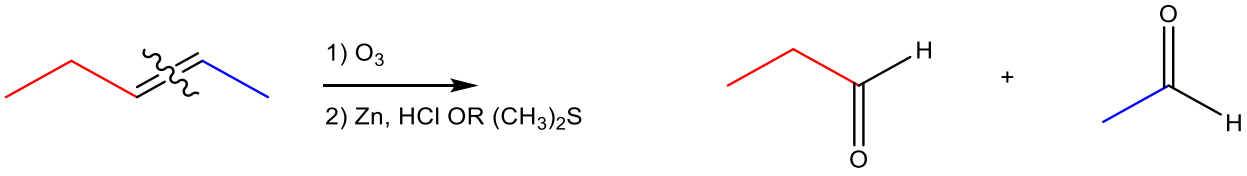
Just like how in the carbocation reactions we could add in a nucleophilic solvent, the same can be done here, we can add both HOH and HOR type solvents and they would give alcohols and ethers at the more substituted chloronium carbon. The mechanism is very similar to the one above, an example mechanism is shown below:



The chemical logic for both of these reactions is exactly the same as the above explanation for the first and second step and the same as the carbocation equivalent for the third step. This also works the same for HOR type solvents, the mechanism is shown below:



The second to last electrophile that we will react our alkenes with is ozone. The mechanism of this reaction we will not discuss in this course; the fundamental concepts going on here are beyond the scope of the typical introductory organic chemistry course, for which this textbook is written. Luckily, the reaction is not too difficult, it follows a very simple pattern shown below:

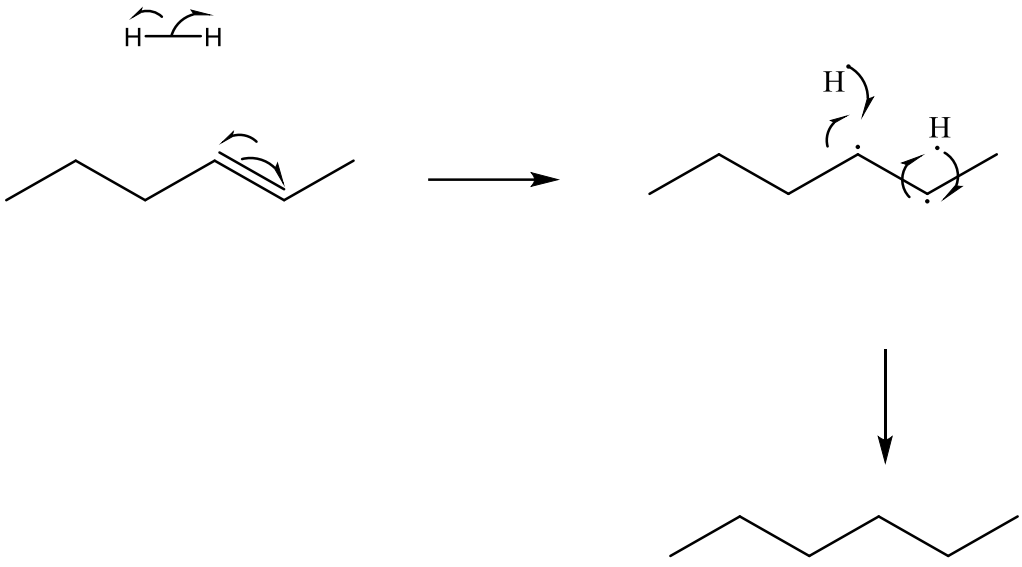


The first step allows the double bond to break apart, the second step causes the formation of aldehydes because the reagents shown on the second step are reducing agents. There is a second version of this reaction, which causes the formation of carboxylic acids; this is done by replacing Zn, HCl or the $(CH_3)_2S$ with $KMnO_4$. $KMnO_4$ is a very strong oxidizing agent and will oxidize the aldehydes to carboxylic acids. This brings use to a very important concept in organic

chemistry, the concept of oxidation and reduction. In organic chemistry, reduction is the loss of oxygen and/or the gain of hydrogens, oxidation is the gain of oxygens and/or the loss of hydrogens. This should make sense going back to general chemistry, we know oxygen always has a -2 oxidation state unless it is in a peroxide and we know hydrogen always has a +1 oxidation state, therefore we can assign oxidation states to the two most extreme states, CH_4 and CO_2. CH_4 is the most reduced form of carbon, while CO_2 is the most oxidized form. We know in both scenarios there is a net charge of 0, therefore for CH_4, it is $1(4) + x = 0$, $x = -4$, so the oxidation state of C in CH_4 is -4, let's see what it is in CO_2. Oxygen is always -2, there are two of them and the net charge is 0, therefore it is $-2(2) + x = 0$, $x = 4$. The oxidation state of carbon is +4 in CO_2. This goes to show that these rules for oxidation and reduction make sense what we know from general chemistry! The difference between aldehydes and carboxylic acids is one oxygen, therefore to make the aldehyde become a carboxylic acid, we must introduce an oxidizing agent ($KMnO_4$). Remember, adding oxygens is oxidation!

The last electrophile that we will discuss for alkene reactions is hydrogen gas. This reaction's mechanism is also not super important to know, but we will show it once for your reference. This reaction is called catalytic hydrogenation, and it is a reduction reaction because we are reducing the alkene to an alkane:

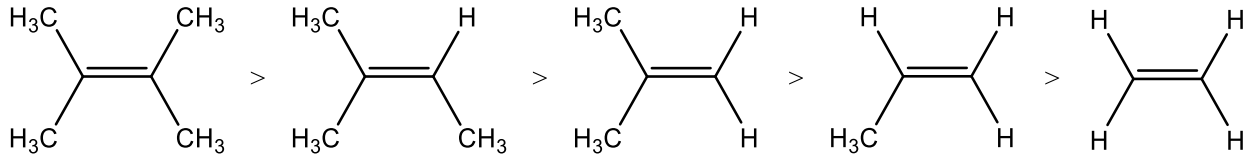
The metals on the bottom simply serve as a catalyst, specifically a surface catalyst that allows the reaction to take place at a faster rate. The mechanism for this reaction is shown below:



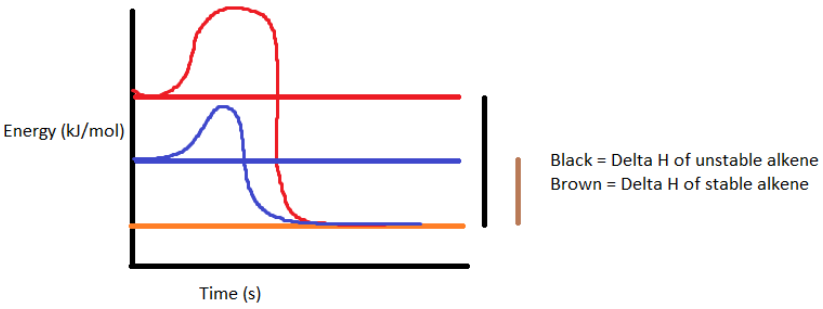
This reaction is different than the other reactions we have discussed so far because it involves radicals, when radicals are involved, we do not use a full arrow, but instead we use a half arrow to indicate the movement of only one electron, rather than the typical two. Two electrons are

required to form a sigma bond, therefore the two electrons from the hydrogen radical and the carbon radical come together to form a sigma bond between the hydrogen and the carbon. Otherwise, this reaction is not particularly noteworthy.

This reaction is a syn addition like most other reactions we have discussed so far, so both hydrogens get added to the same face. Because we are talking about hydrogenation, this is a good time to bring up how you can determine which alkene is more stable. The way you can determine if an alkene is more or less stable is by looking at how many carbon groups it has attached to it, for example



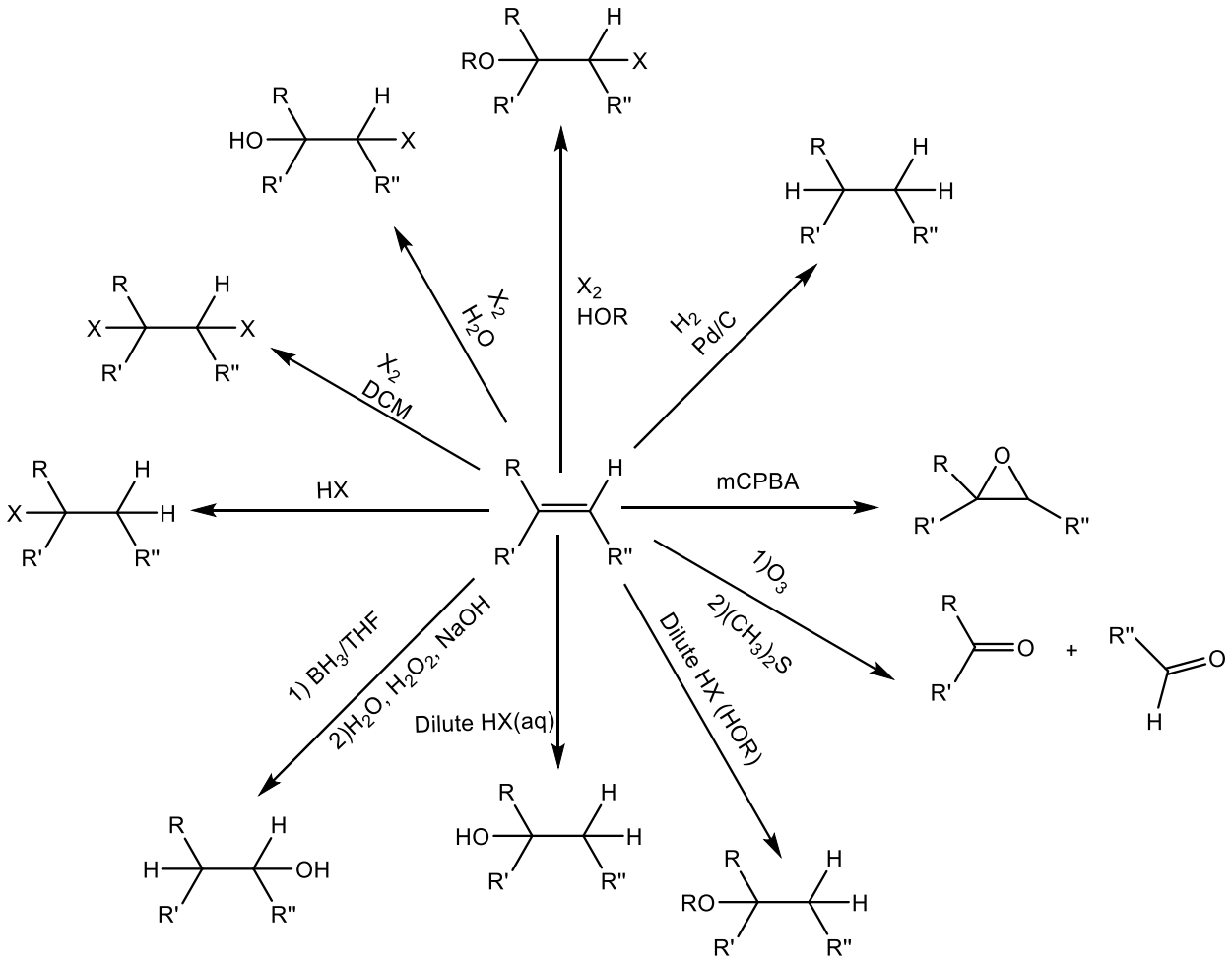
The more unstable the alkene, the higher its heat of hydrogenation if when hydrogenated the product is the same. This is because reducing an alkene is an exothermic process, meaning it always releases heat, and if the alkene you are starting with is higher in energy, there is a bigger difference between your initial and final energies, resulting in a larger heat of hydrogenation. This can be seen visually with the below figure:



As I promised, here is the table that summarizes the reactions we have discussed so far:

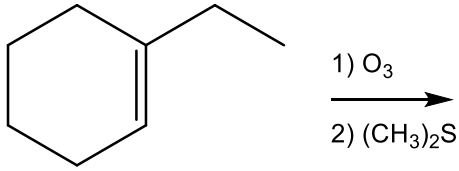
Nucleophile	Electrophile	Type of addition	Regiochemistry	Type of Product
Alkene	Strong acid	Syn or anti	Markovnikov	Alkyl halide in concentrated solution, Alcohol in dilute aqueous solution, Ether in dilute alcohol solution
Alkene	Peroxy acid	Syn	N/A	Epoxide (triangle oxygen)
Alkene	Halogen gas	Anti	Nucleophile approaches Markovnikov	Vicinal dihalide if DCM is the solvent, Halohydrin if HOH solvent used, Haloether if HOR solvent used
Alkene	Ozone	N/A	N/A	Ketone or aldehyde
Alkene	BH_3	Syn	Anti-Markovnikov	Alcohol
Alkene	Hydrogen gas	Syn	N/A	Alkane

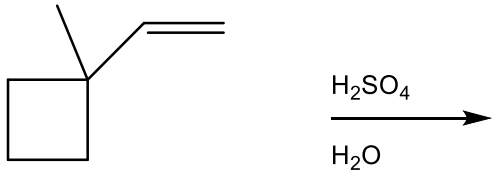
Graphically, these relationships are shown below:

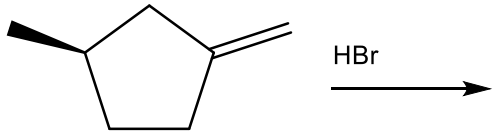


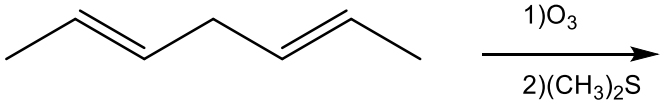
Practice Quiz:

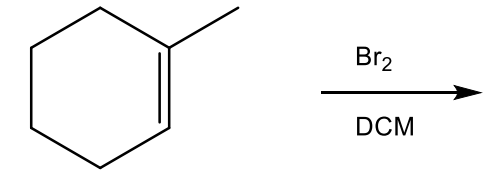
1. Predict the major product for the following reactions, be sure to include stereochemistry

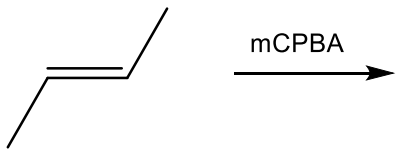

1) O_3
2) $(CH_3)_2S$

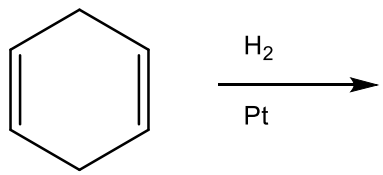

H_2SO_4
H_2O


HBr

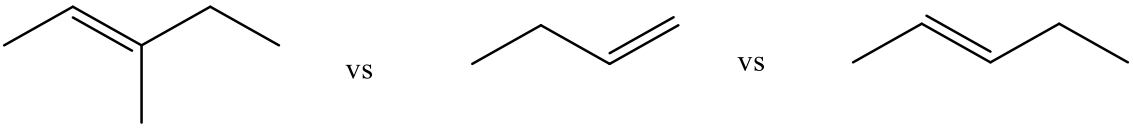

1)O_3
2)$(CH_3)_2S$


Br_2
DCM

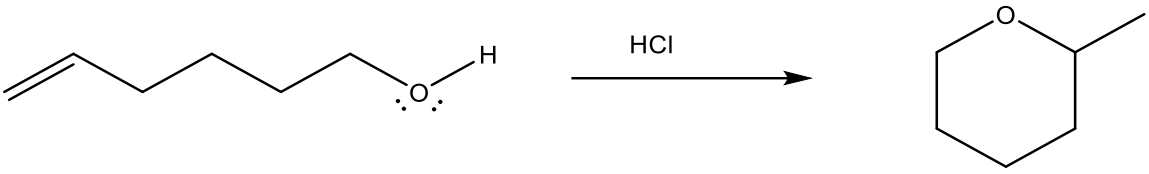

mCPBA


H_2
Pt

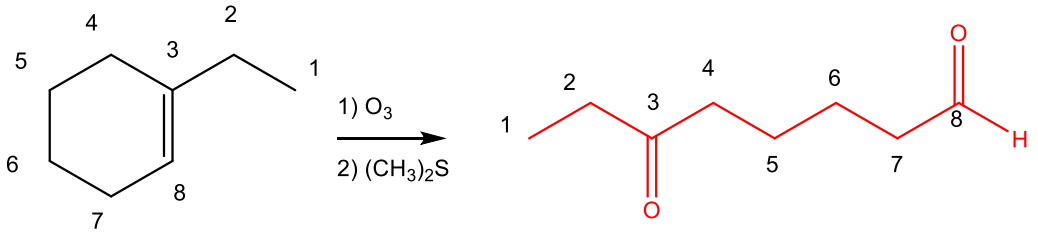
2. Which of the following alkenes would react fastest with HBr?

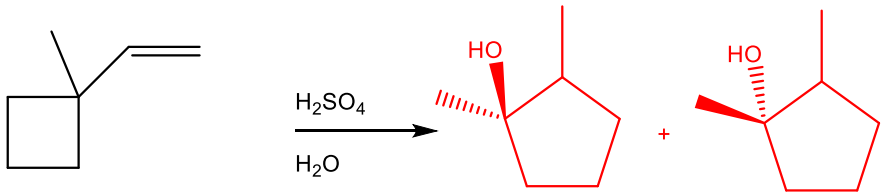


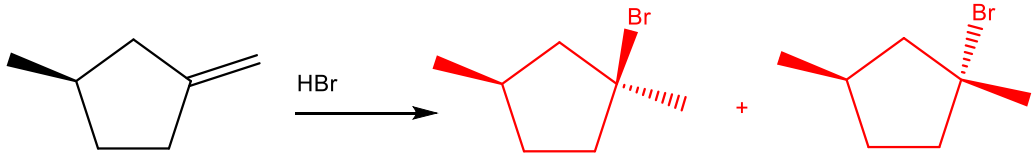
3. Propose a mechanism for the following reaction:

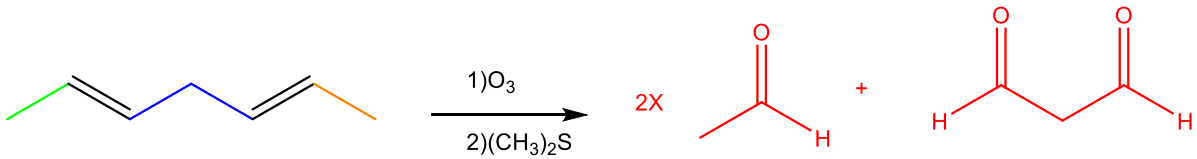


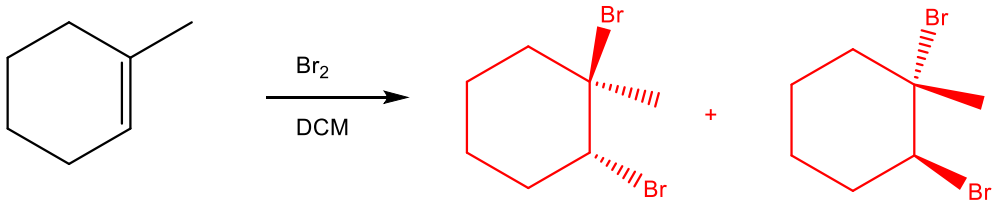
Answers:

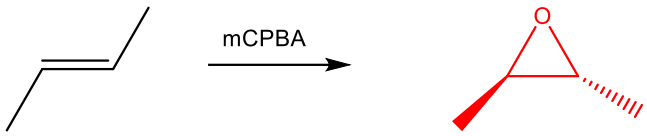

4
2
3
5
1
6
8
7
1) O_3
2) $(CH_3)_2S$
O
2
4
6
3
1
8
H
5
7
O

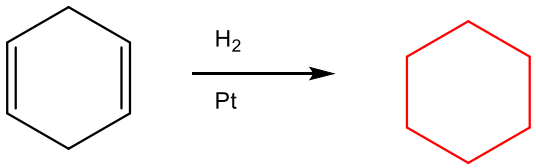

H_2SO_4
H_2O
HO
+
HO


HBr
Br
+
Br

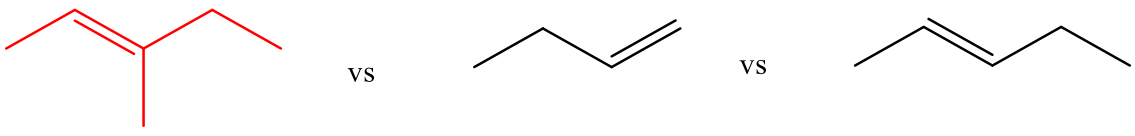

1)O_3
2)$(CH_3)_2S$
2X
O
H
+
O
O
H
H


Br_2
DCM
Br
Br
+
Br
Br

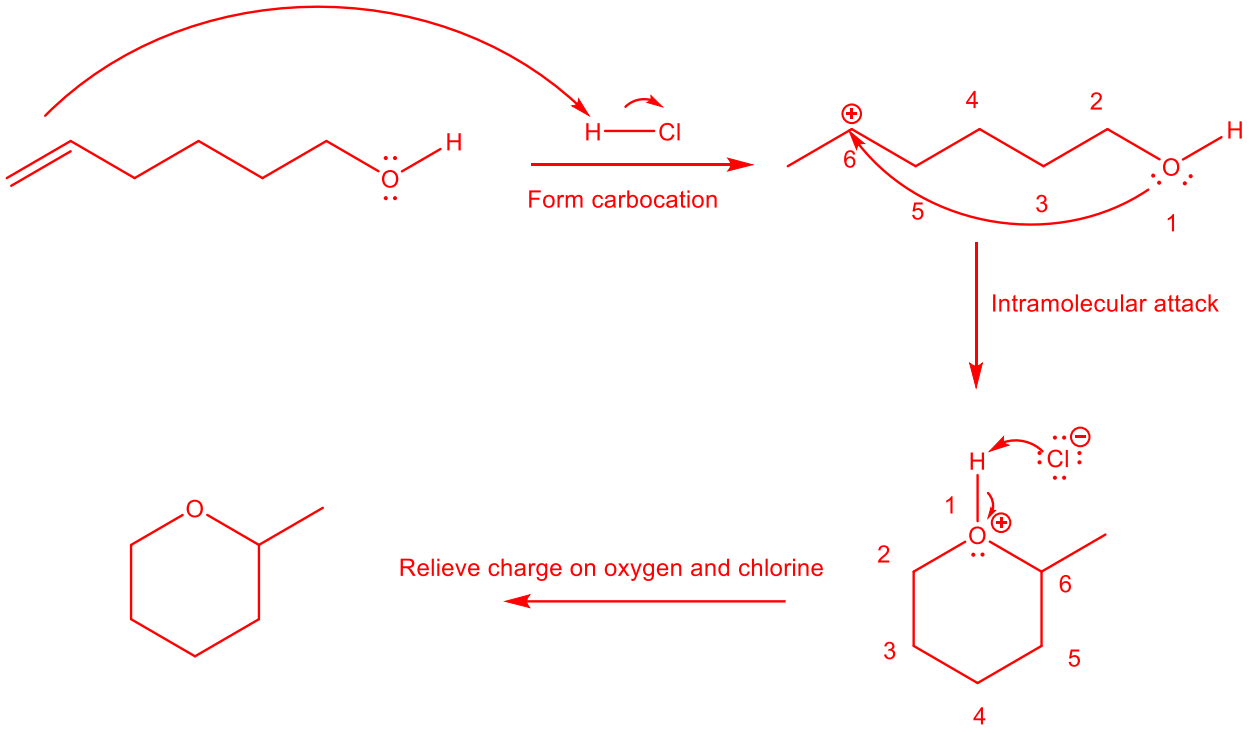

mCPBA
O


H_2
Pt

1.


vs
vs

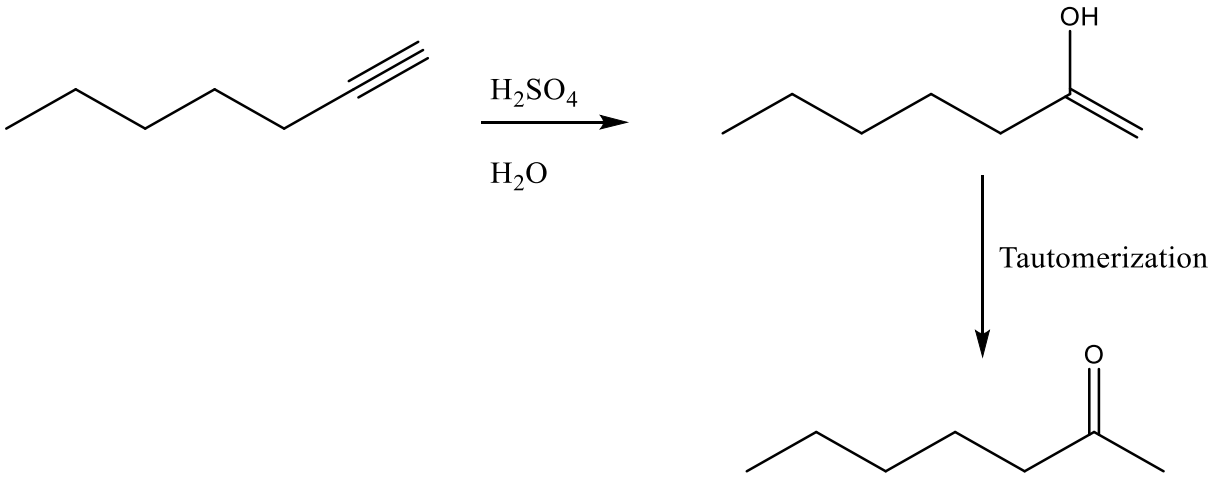
2.



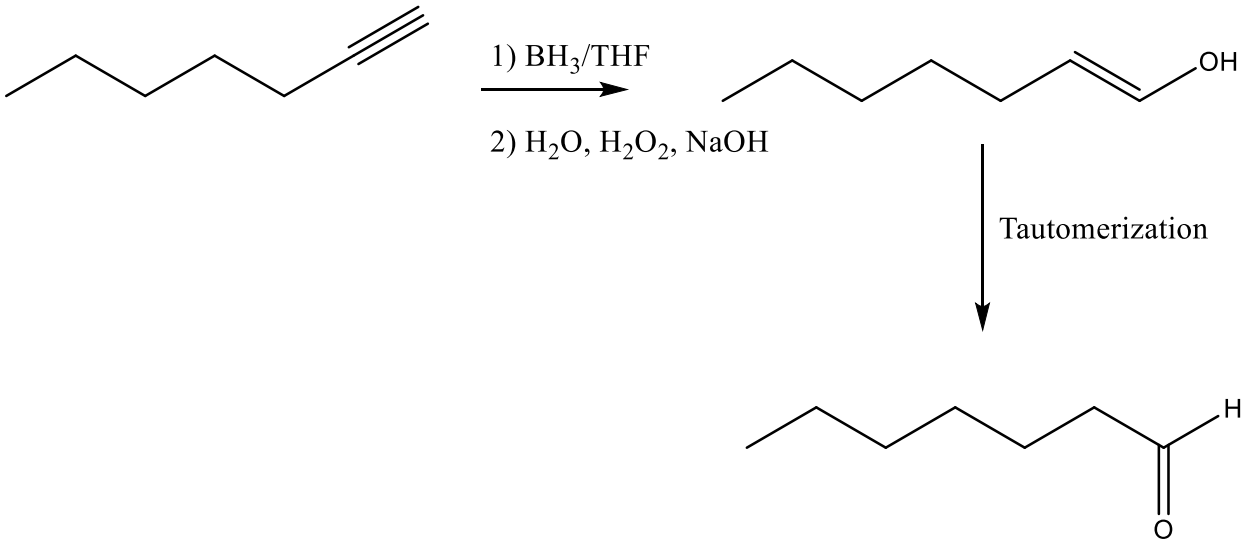
3.

Congratulations, you now know most all of the reactions for alkenes covered in an introductory organic chemistry course! There are a few more that we will sprinkle throughout the course, but for now, these are all the ones you are responsible for. Now that we have finished alkenes, let's discuss alkynes. This section will be rather fast, because alkyne reactions are typically just alkene reactions but twice, so if you have a good foundation in alkene reactions, alkyne reactions will be quite easy.

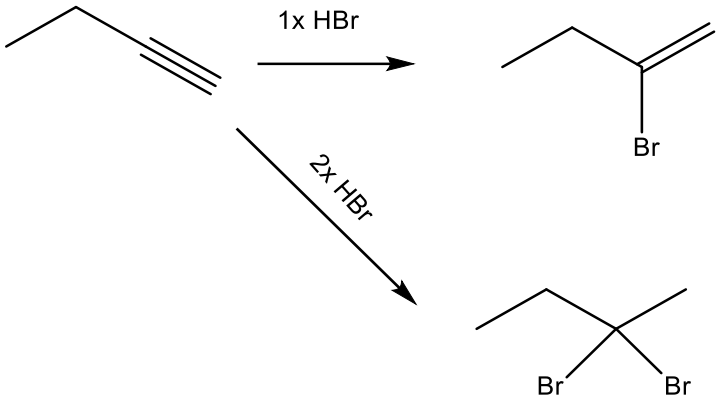
Just like with alkenes, alkynes also react with strong acids in much the same way as before, but there is a slight twist. When you add an alcohol to a triple bond, instead of creating a regular alcohol, you are instead creating an enol. Enols are inherently unstable and will rapidly *tautomerize* to the keto form like so:



Effectively what happens is that the carbon that has the OH from the alcohol addition will have a carbonyl on it. This happens regardless of regiochemical preference:



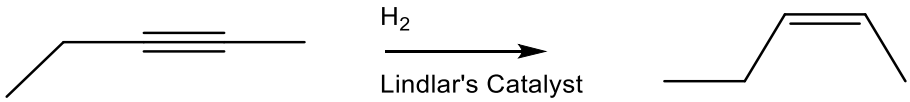
For the concentrated strong acid reactions, the addition still puts the halogen on the more stable carbocation/more substituted carbon, but now we have two pi bonds to work with, so if we have more than one equivalent of acid, we will add two halogens to the same carbon. This produces a *geminal dihalide*. An example is shown below:



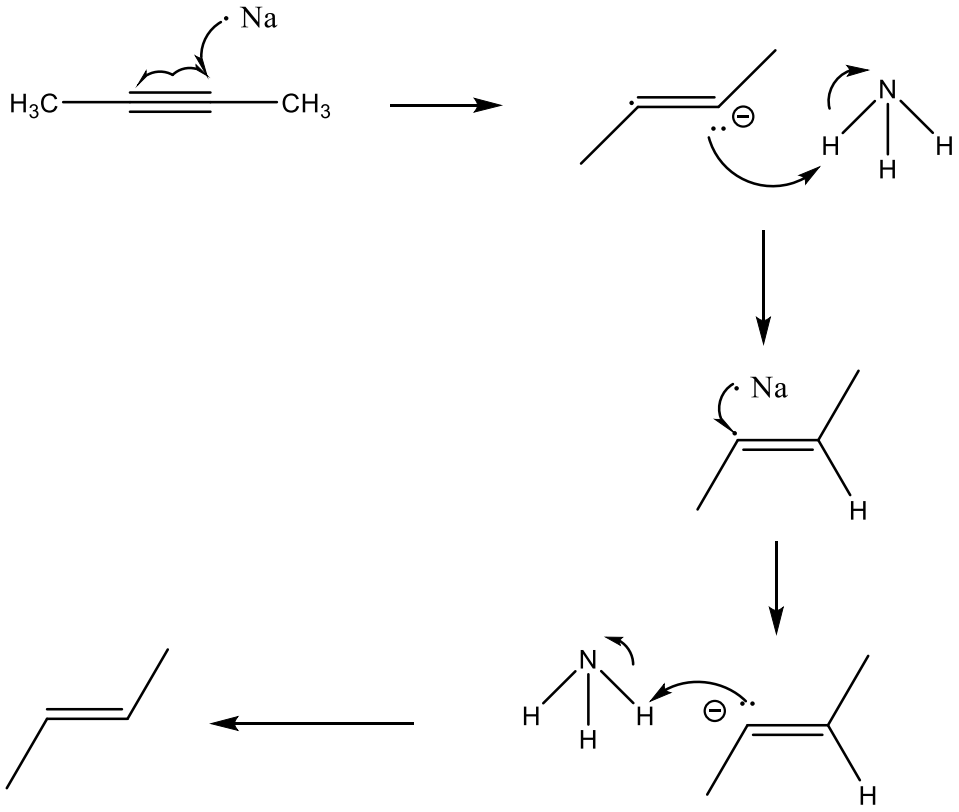
The chemical logic from before applies here as well, so I will not repeat myself, refer to the alkene portion of this chapter if you are still unsure why the bromine gets added to the secondary carbon.

Alkynes can also get reduced, but unlike alkenes where they can only get reduced to the corresponding alkane, here alkynes can be reduced to three different compounds: the cis alkene, the trans alkene, and the alkane. Let's tackle each of these in turn.

For making the cis alkene, you must use a *poisoned catalyst*, which is basically just a slightly deactivated catalyst that will help prevent over reduction of the alkyne. The poisoned catalyst of choice for the reduction of alkynes to cis alkenes is the Lindlar's catalyst, the mechanism for the Lindlar's catalyst reduction is the same as the one we saw for the regular Pt or Pd/C reduction of alkenes. Because the Lindlar's catalyst makes the cis alkene exclusively, the hydrogens add in a syn fashion just like the Pt or Pd/C case.

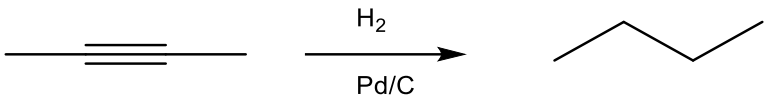


For making the trans alkene, you must use a special reaction called the liquid metal reduction reaction. In this reaction, you use sodium or lithium dissolved in liquid ammonia, the sodium or lithium acts as the electron source to get the hydrogens to add anti and make the trans alkene. The reaction mechanism is shown below:

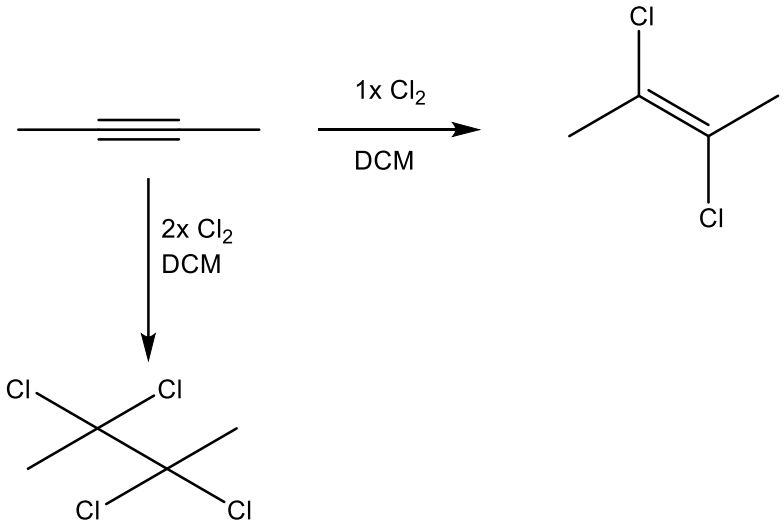


This reaction is also unique in that it involves a metal, something that we have not seen until this point, but don't worry about that, it is nothing we can't handle. Recall that Na is all the way to the left of the periodic table, therefore it holds on to its S electron extremely loosely, therefore it can give away its electron to potential acceptors. The alkyne can accept the electron to form a vinyl anion, this is favorable because the sodium now has a full octet, whereas before only the carbon had a full octet. In order for the sodium to donate its electron, though, the pi electrons in the pi bond need to scatter to both of the sp carbons, the one that got the electron from the sodium becomes an anion, and the remaining carbon becomes a radical. The anion is an extremely strong base and therefore will attack the proton of ammonia (the solvent) to give the hydrogen to one of the sp carbons, remember acids react with bases, and the carbanion is an extremely strong base if you recall from chapter 2. Basicity increases from right to left in the same row on the periodic table! The remaining sp carbon is a radical, and radicals are inherently unstable, and there is more sodium metal in the reaction container, therefore the sodium donates its electron to the radical, thereby becoming octet satisfied and getting rid of that pesky radical. Once the radical gets the extra electron from the sodium, it does an acid-base reaction with the solvent again to get the extra hydrogen (**A**MSOW).

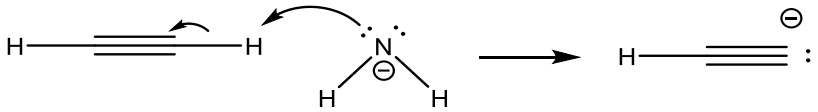
Lucky for you, you already know how to reduce the alkyne to an alkane, we had to poison the regular Pt or Pd/C catalyst to get it to an alkene, so if we DON'T poison it, it will go all the way to the alkane like so:



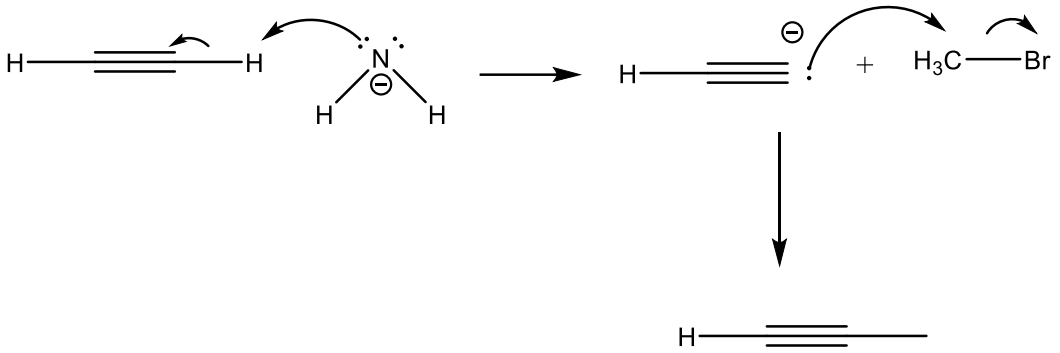
Alkynes can also react with halogen gases in the same way that alkenes do and just like the strong acid reactions, this too can vary depending on how much halogen gas you put in. One equivalent will produce the expected product, the vicinal dihalide and specifically the trans alkene because these reactions are still anti-additions. Two equivalents would put two halogens on each of the sp carbons like shown:



The only real way that alkynes differ from alkenes to any appreciable extent is their acidity. Recall from chapter 2 that the less p character the orbitals have, the more acidic their protons are, therefore, all else equal, alkynes are more acidic than alkenes. Because they are more acidic than alkenes, they can react with strong bases to give carbanions, which can be used to make ***carbon-carbon bonds***. This is a big deal, up until now, the chain that we started with was the only thing we could work with, we couldn't add carbons to it… until now! Hydroxide is too weak of a base to react with alkynes, therefore the preferred base is NH_2^- or amide anion. Alkynes react with amide like so



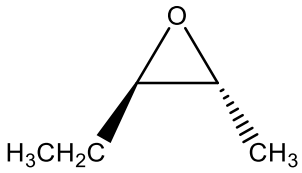
This reaction is exceptionally useful, because it allows for the formation of a carbon nucleophile. This anion that develops is a supercharged nucleophile that will react with most all electrophiles it finds, to extend the carbon chain, typically these carbanions are reacted with alkyl halides in a coupling reaction. The reaction mechanism is as follows:



This reaction can be done twice, because there is another alkyne proton on the left side, so you can make both symmetrical and asymmetrical alkynes. This mechanism follows AMSOW just like all the others. The first step is an acid-base reaction (**A**MSOW), the second step is relieving the negative charge on the carbon and is putting it on the bromine, who is much happier with the negative charge (A**M**SOW). But wait, let's first establish why alkyl halides are electrophiles in the first place. Alkyl halides are electrophiles for two key reasons, firstly, the halogens are more electronegative than carbon and therefore the carbon is partially positive and therefore electrophilic, secondly, the carbon-halogen bond is typically weaker than C-C bonds (318 kJ/mol for C-Br bond compared to 618.3 kJ/mol for C-C bond). It is therefore favorable to make the C-C bond and to break the C-Br bond (AM**S**O**W**) and this makes alkyl bromides electrophilic.

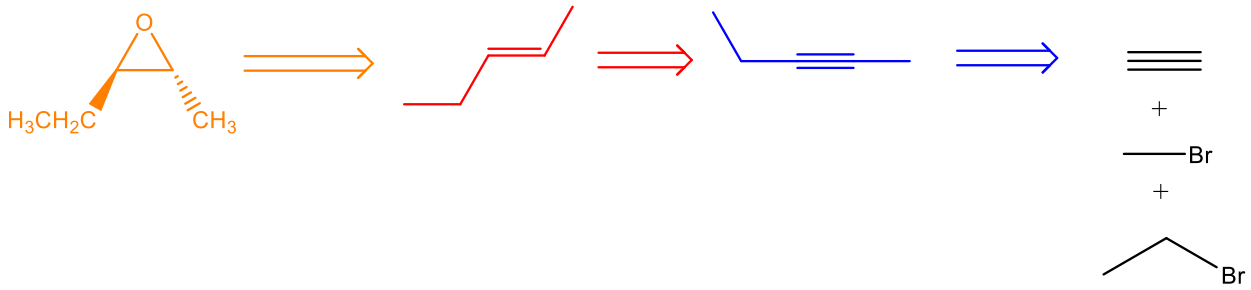
Now that you know how to add carbons to a main chain, we are going to discuss what will be using for synthesis questions for the remainder of the course, *retrosynthetic analysis*. We already saw this a bit before, but we should discuss it a bit more in the context of multistep synthesis.

Suppose that you wanted to make the following compound from ethyne:

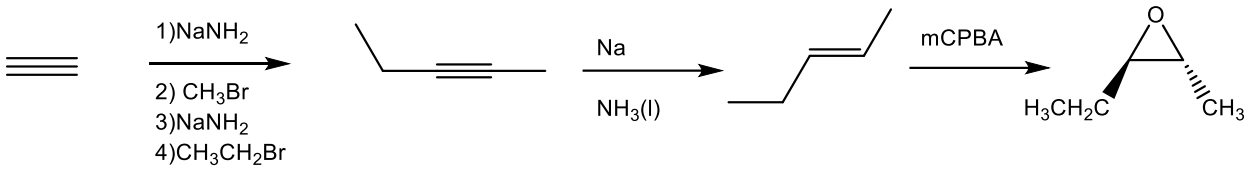


How would you start? Firstly, we should count our carbons and draw our starting reagent, ethyne has two carbons and the product has five, therefore we need to add carbons. For right now, we only know one reaction that allows us to do that, and we would need an alkyne for it. Luckily, ethyne is already an alkyne. Secondly, we should notice any functional groups that are present in our product that are not already present in our starting compound, in this case, we have an epoxide in our product but not in our starting compound. Thirdly, we should rack out brains to figure out what do we need to react to get an epoxide, immediately, we should think of an alkene and a peroxy acid. However, alkenes come in two different flavors, cis and trans, so we have to look at the orientation of the groups in the product, because the ethyl and methyl groups are trans in the product, they must have come from a trans alkene. Now we need to put these all together to form one cohesive story. First, we need to add two groups to ethyne, an ethyl group and a methyl group, that will get us our five carbons we need and it will get us in the right orientation, because we need to have the triple bond where the epoxide will ultimately form (blue structure

and arrow). Second, we need a trans alkene, but we are currently at an alkyne, therefore, we need to reduce the alkyne selectively to the trans isomer, we can do this with the sodium metal reduction reaction (red structure and arrow). Thirdly, we have the trans alkene, but we want the epoxide, to get the epoxide we react the alkene with MCPBA and we get our product (orange structure and arrow). This is shown graphically below:

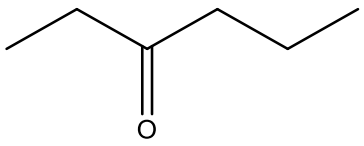


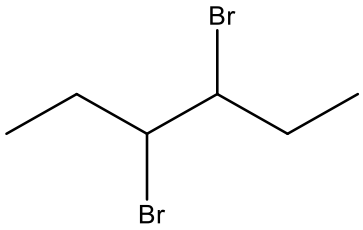
Therefore to get the product we want, we just have to go forward like so:

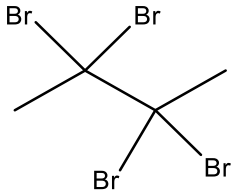


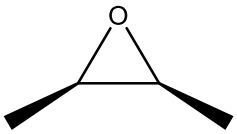
Practice questions:

1. Propose a synthesis of the following compounds from ethyne:

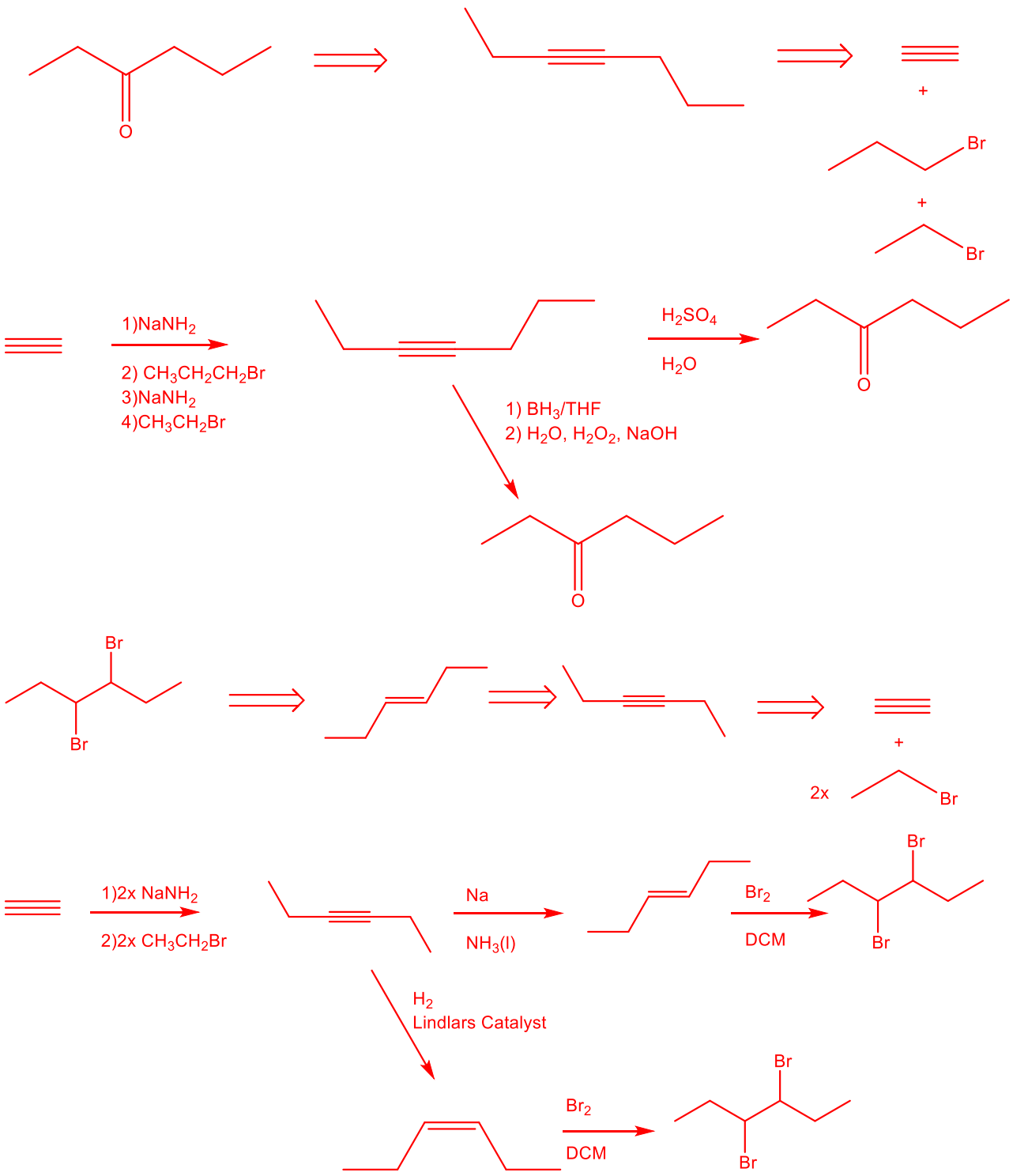


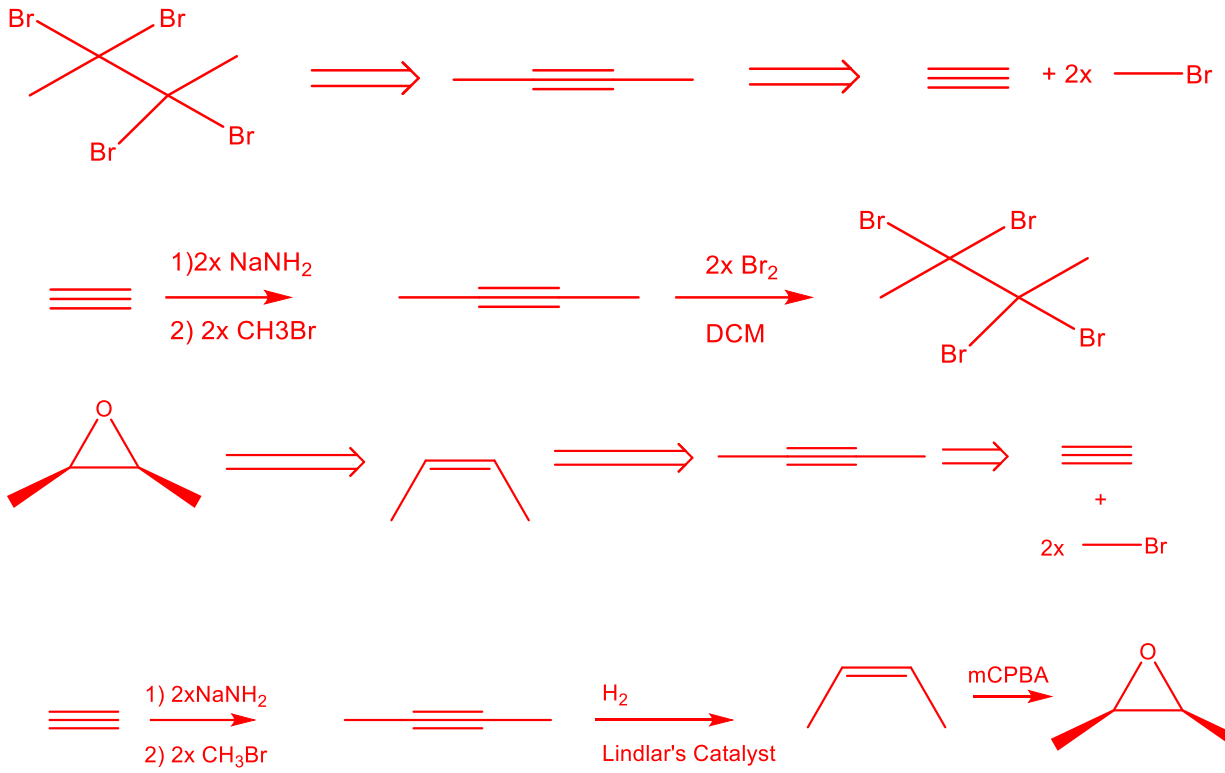






Answers:


O
+
Br
+
Br
1)NaNH2
2) CH3CH2CH2Br
3)NaNH2
4)CH3CH2Br
H2SO4
H2O
O
1) BH3/THF
2) H2O, H2O2, NaOH
O
Br
Br
+
2x
Br
1)2x NaNH2
2)2x CH3CH2Br
Na
NH3(l)
Br2
DCM
Br
Br
H2
Lindlars Catalyst
Br2
DCM
Br
Br

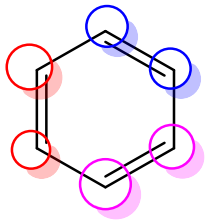

Br
Br
Br
Br
+ 2x
Br
1)2x NaNH2
2) 2x CH3Br
2x Br2
DCM
Br
Br
Br
Br
O
+
2x
Br
1) 2xNaNH2
2) 2x CH3Br
H2
Lindlar's Catalyst
mCPBA
O

Chapter 7: Aromaticity and Reactions of Conjugated Dienes

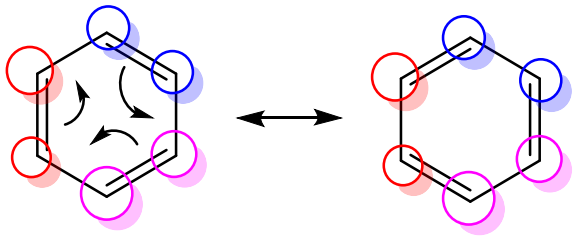
We started our discussion of acids and bases by discussing inductive effects, that halogens placed near the acidic proton will increase its acidity by stabilizing the conjugate base through charge minimization. But there are stronger effects that exist in organic chemistry, these effects are called *resonance effects* and these are caused by *conjugation*. There are four main scenarios where you encounter conjugation:

1. Double bond-single bond-double bond
2. Double bond-single bond-lone pair
3. Double bond-single bond-empty p orbital
4. Double bond-single bond-radical

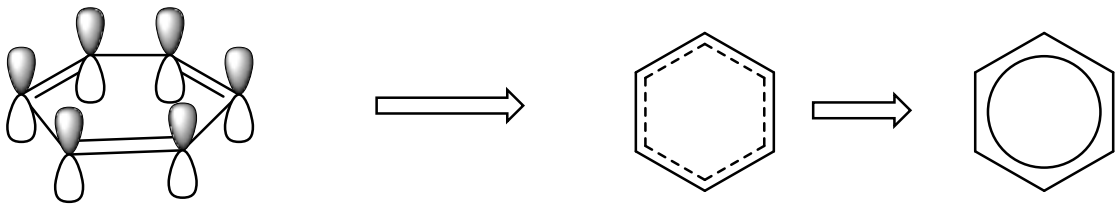
Let us use these criteria to explain why benzene is more stable than theoretical "cyclohexatriene" model without resonance stability:



Benzene is unique because it has conjugated double bonds, meaning that it follows criteria number 1, because it has a resonance form, I could also write benzene like this:



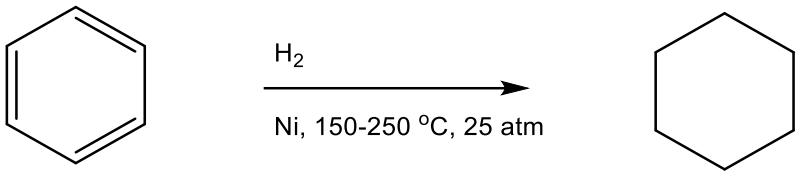
This conjugation is possible because there are consecutive occupied p orbitals around the ring like so, recall that all the carbons in the ring are sp^2 hybridized, therefore the extra p orbital is above and below the plane of the ring, which forms the pi bonds.



Even among conjugated compounds, benzene is special because it is *aromatic*, which means it is stabilized even further through *resonance stabilization energy*. For a compound to be aromatic, it must fulfill the following three criteria:

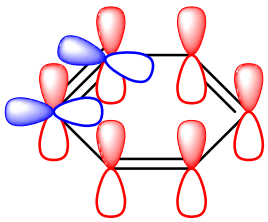
1. It must be cyclic
2. It must be planar
3. It must not have a multiple of four pi electrons around the ring (4n+2 rule)

If we look at benzene, it satisfies all three of those criteria. All of its carbons are sp^2 hybridized, which if you recall from chapters 1 and 2 means that they are all trigonal *planar* in geometry. This means benzene is planar, it is also obviously cyclic, the last criteria is the hardest one to determine here, but even that isn't too hard. Each double bond contributes two pi electrons to the party, there are three double bonds therefore there are six pi electrons. Because there are six pi electrons, the compound is aromatic and is substantially more stable than the theoretical cyclohexatriene model that neglects resonance and aromaticity. Because benzene is so stable, it does not react with many things, and it takes a tremendous amount of heat and pressure with harsh reduction catalysts to reduce benzene to cyclohexane:



Due to benzene's incredible stability, we will not discuss reactions of benzene until the end of the textbook. Benzene only reacts under very specific conditions and only with super charged nucleophiles and electrophiles.

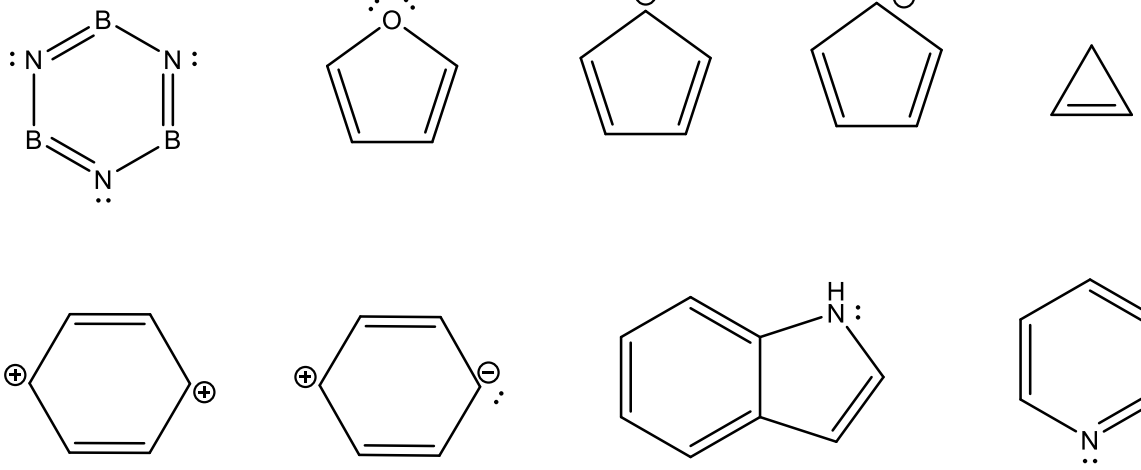
There are three types of cyclic compounds: aromatic, nonaromatic, and antiaromatic. Aromatic compounds satisfy all three of the criteria we set forth, nonaromatic fail either of the first two, and antiaromatic compounds fail only the third. But what if we have cyclic compounds that have noncarbon atoms in it? What do we do then? Or what about a triple bond? Luckily, there is a simple rule of thumb in place, if the noncarbon atom doesn't have a double bond already, count only one of its lone pairs, if it is a triple bond, only count one of its pi bonds. These rules work because aromaticity only cares about being able to circulate electrons above and below the plane of the ring and the extra lone pairs or pi bonds are located to the side of the ring,



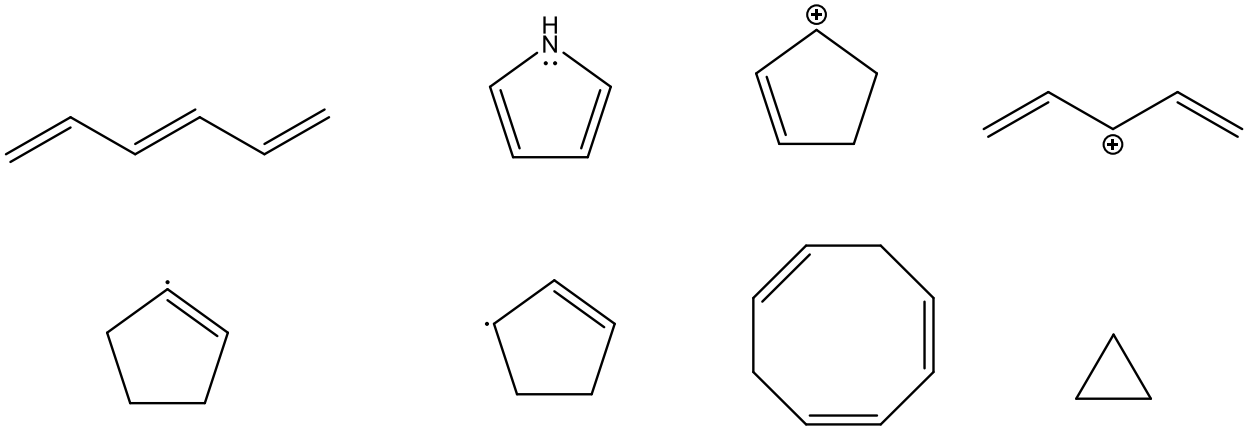
The p orbitals in blue don't contribute to the highway of electrons above and below the plane of the aromatic ring and therefore they do not count towards the electron count.

Practice questions:

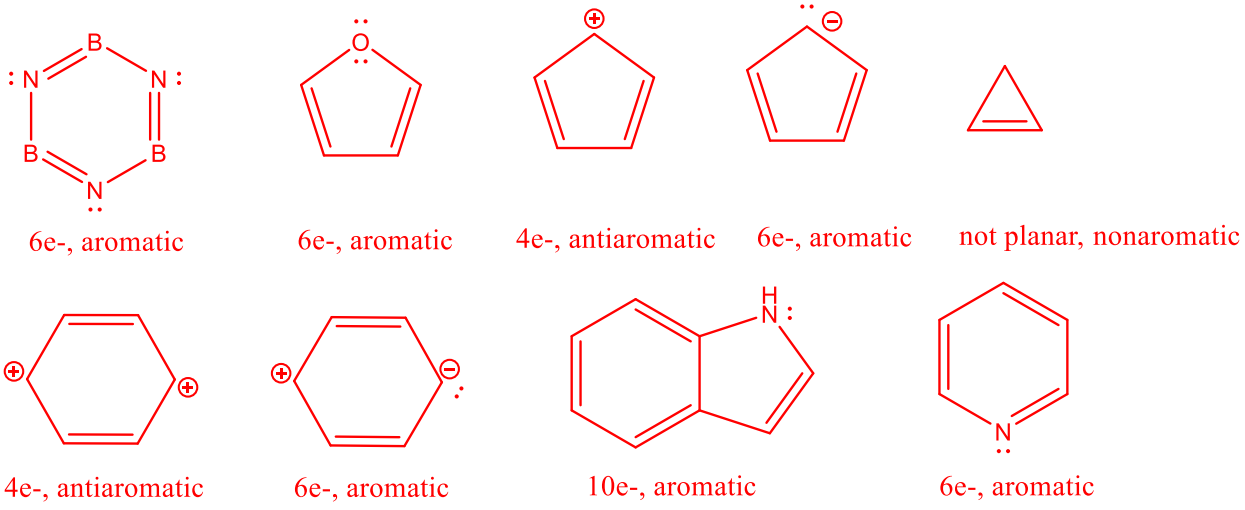
Determine if the following compounds are aromatic, nonaromatic, or antiaromatic

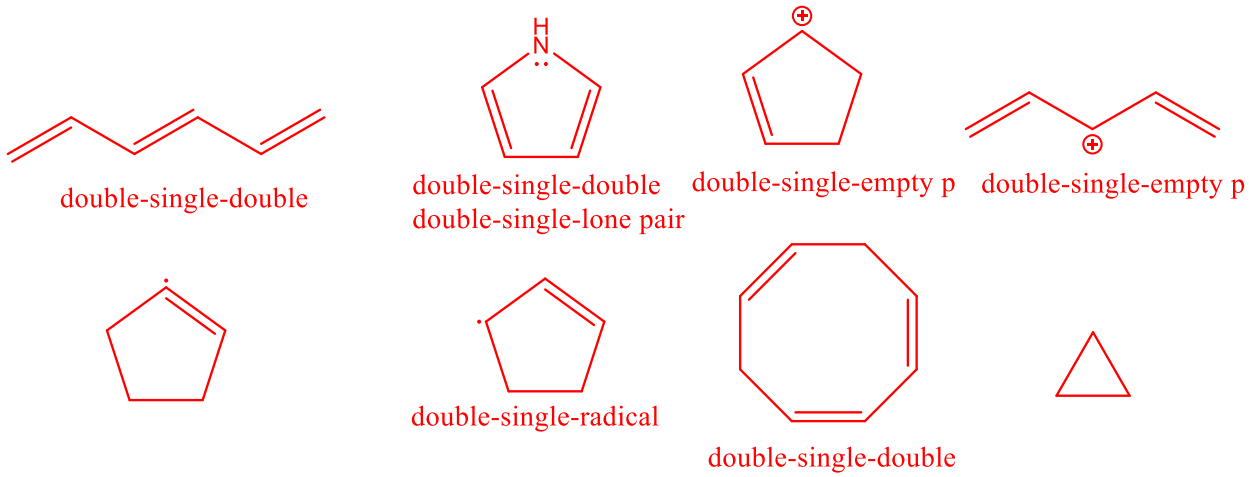


Determine which of the following compounds have a resonance form



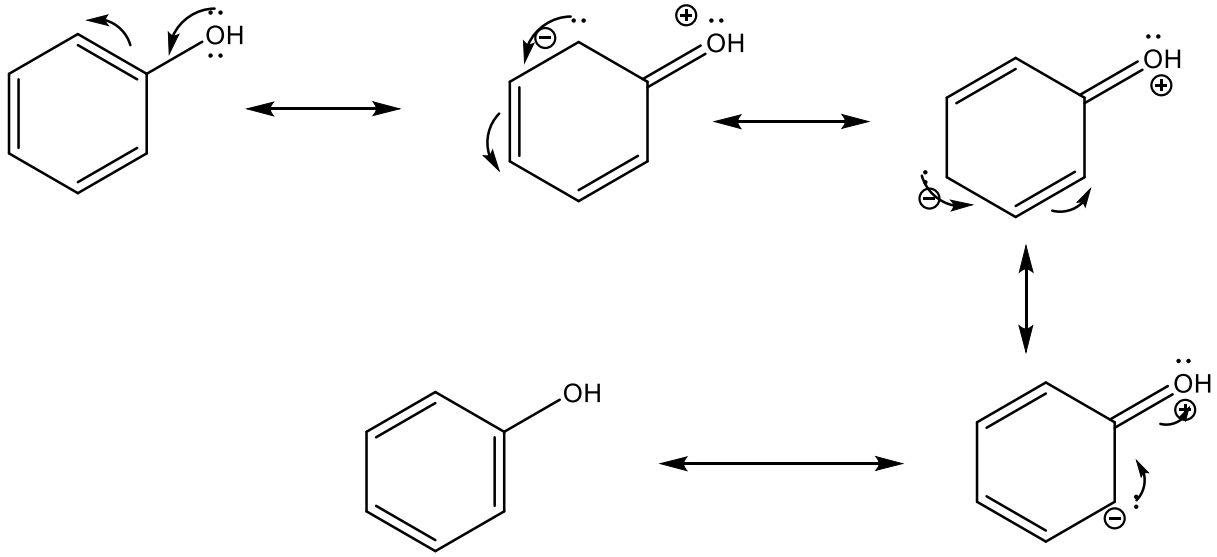
Answers:



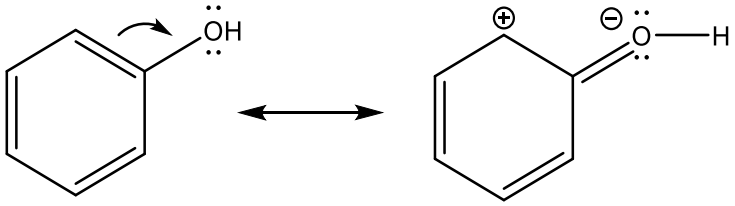


The two most common things to put in a ring that promote planarity are borons and carbocations. Both boron and carbocations have an empty p orbital, that is why they are both sp^2 hybridized, this should also make some sense because they are isoelectronic to each other (taking one electron from carbon makes it have the same electron configuration of boron). Therefore, carbocations and boron do not contribute to the electron count, they simply serve to preserve the planarity of the cyclic compound in question. If there are any sp^3 carbons in the cyclic compound, automatically that compounds is nonaromatic because sp^3 carbons are tetrahedral, NOT planar, therefore those compounds violate the planar criteria for aromaticity.

Resonance forms substantially impact many things, such as stability and acidity. To draw a resonance form, you start by moving either a pi bond or lone pair to an adjacent carbon or bond, if the arrow you draw is more than one carbon away, you drew the arrow incorrect. Keep in mind when drawing resonance forms the preferred number of bonds each element wants as well as the octet rule (if something has more than 8 electrons, one of their bonds need to move). For example, the following are the resonance forms for phenol (hydroxybenzene):



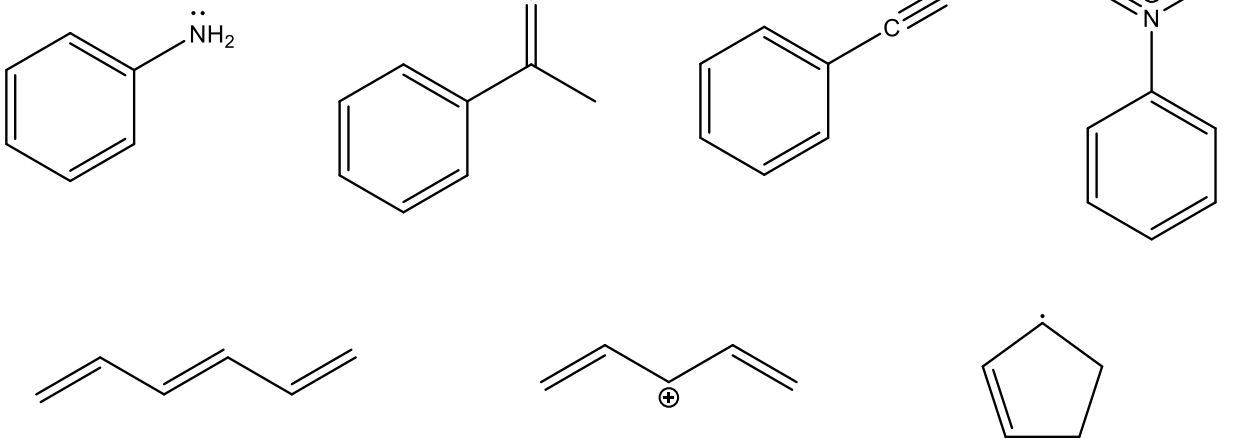
I know that is likely a lot to take in, so let's take it step by step. The first thing I recognize is that the lone pair of the alcohol group is in conjugation with the ring (double-single-lone pair), therefore there is a resonance form where I donate the lone pair into the ring. But wait, why do I know it has to donate, why can't it withdraw? Well the reason is because if I withdrew electrons from the ring (I drew the arrows in the opposite way), that would make oxygen have 2 lone pairs, a bond to a hydrogen and a double bond to carbon, meaning it has 10 electrons! That would make any chemistry teacher cringe.



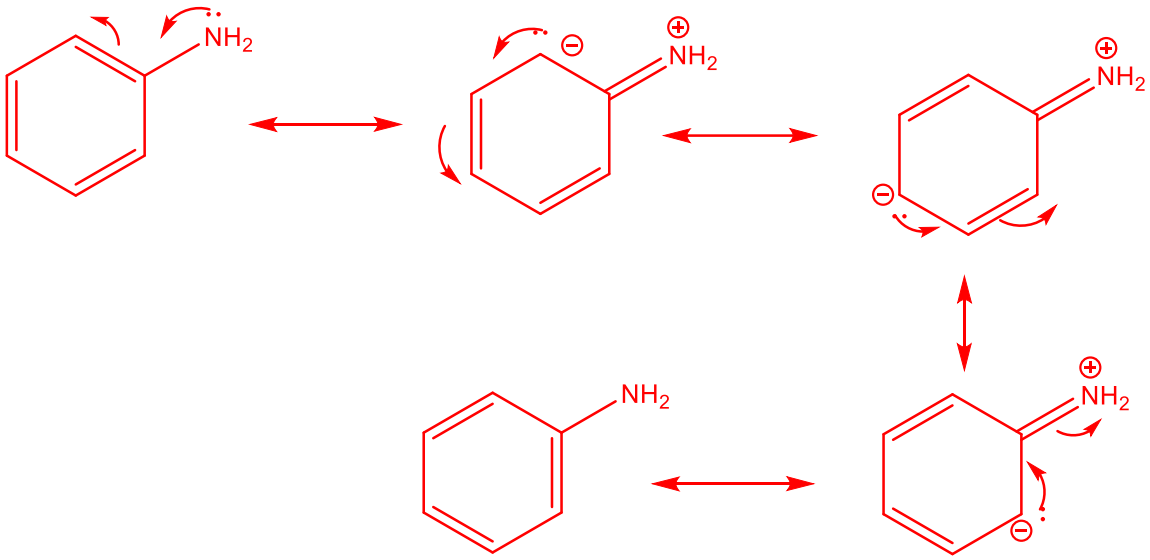
That is legit impossible because the oxygen doesn't have an empty d-orbital (it is a second row element), that structure violates the octet rule. It is therefore impossible for the alcohol group to withdraw electrons; therefore, OH is an *obligate electron-donating group*. Now that we understand the OH has to donate into the ring with its lone pairs, let's look at why the pi electrons in the benzene double bond have to go on the carbon atom itself in the second resonance form. Firstly, recognize that the oxygen of the OH group now has three bonds, therefore it must be positively charged. If the oxygen is positively charged and the original form we drew was neutral, there MUST be a negative charge to balance it out. This essentially forces the pi electrons to go onto the adjacent carbon since that makes the carbon negative, thus the resonance form overall is neutral. This negatively charged carbon has a lone pair, and therefore it is in conjugation with the double bond to the left of it (double-single-lone pair), therefore we push those electrons to form a pi bond. If we do that, though, the carbon in the center would have five bonds (two double bonds and a bond to hydrogen that isn't shown), because this can't happen the pi bond it has with the carbon further down is moved to shift the lone pairs onto that carbon. This negative charge keeps circulating throughout the ring until eventually it is on the carbon adjacent to the OH group again, but this time on the opposite side. Once we get to this resonance form, the lone pair has to go somewhere (recall carbon does not like to be charged) and the lone pair is in conjugation with the double bonded OH group (double-single-lone pair), therefore the lone pair on the negatively charged carbon push in to form the pi bond and that forces the double bond to the oxygen to break and this reforms the phenol. This last resonance form is just like the first one, except that the double bonds are shifted over by one.

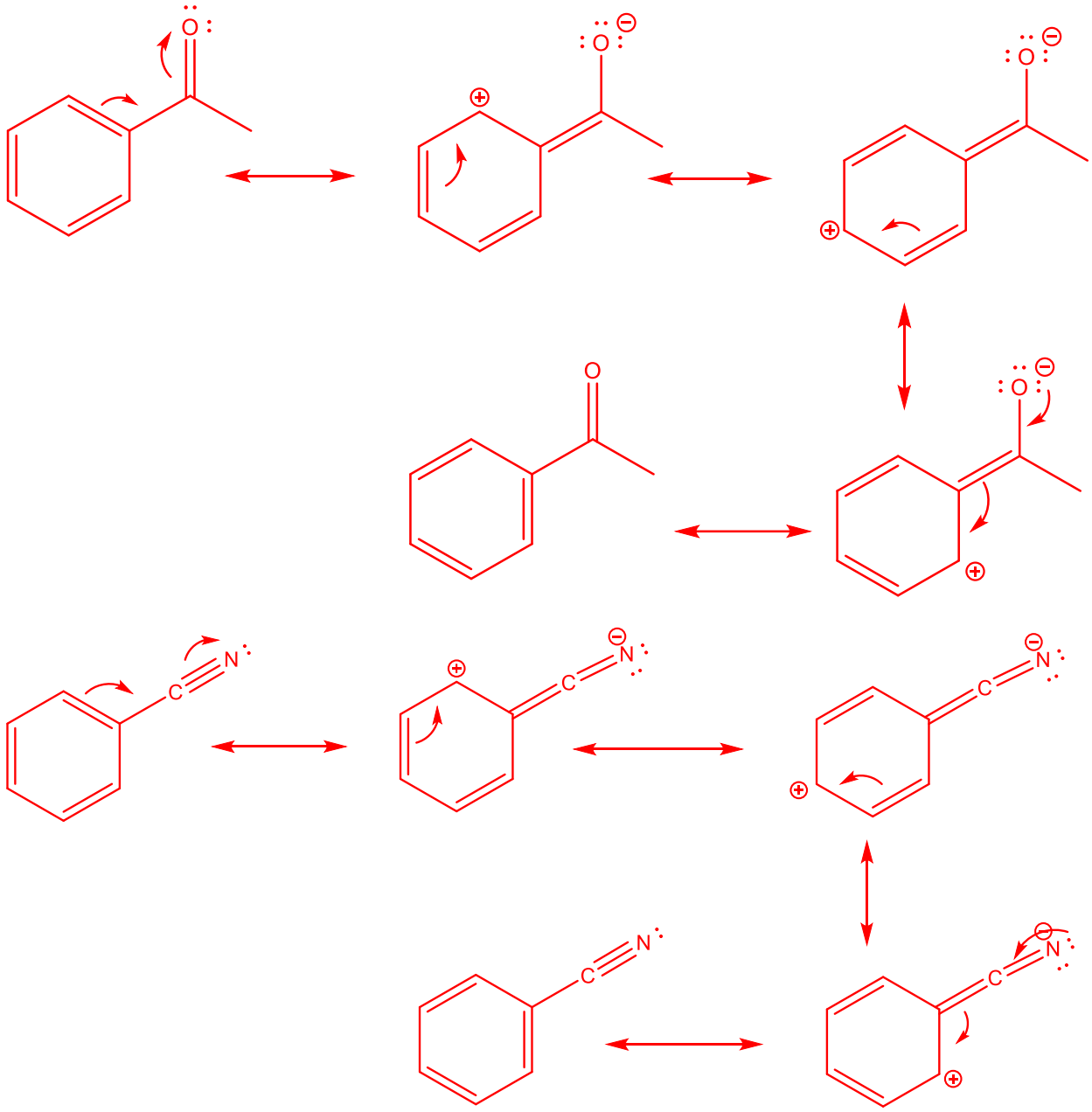
Practice questions:

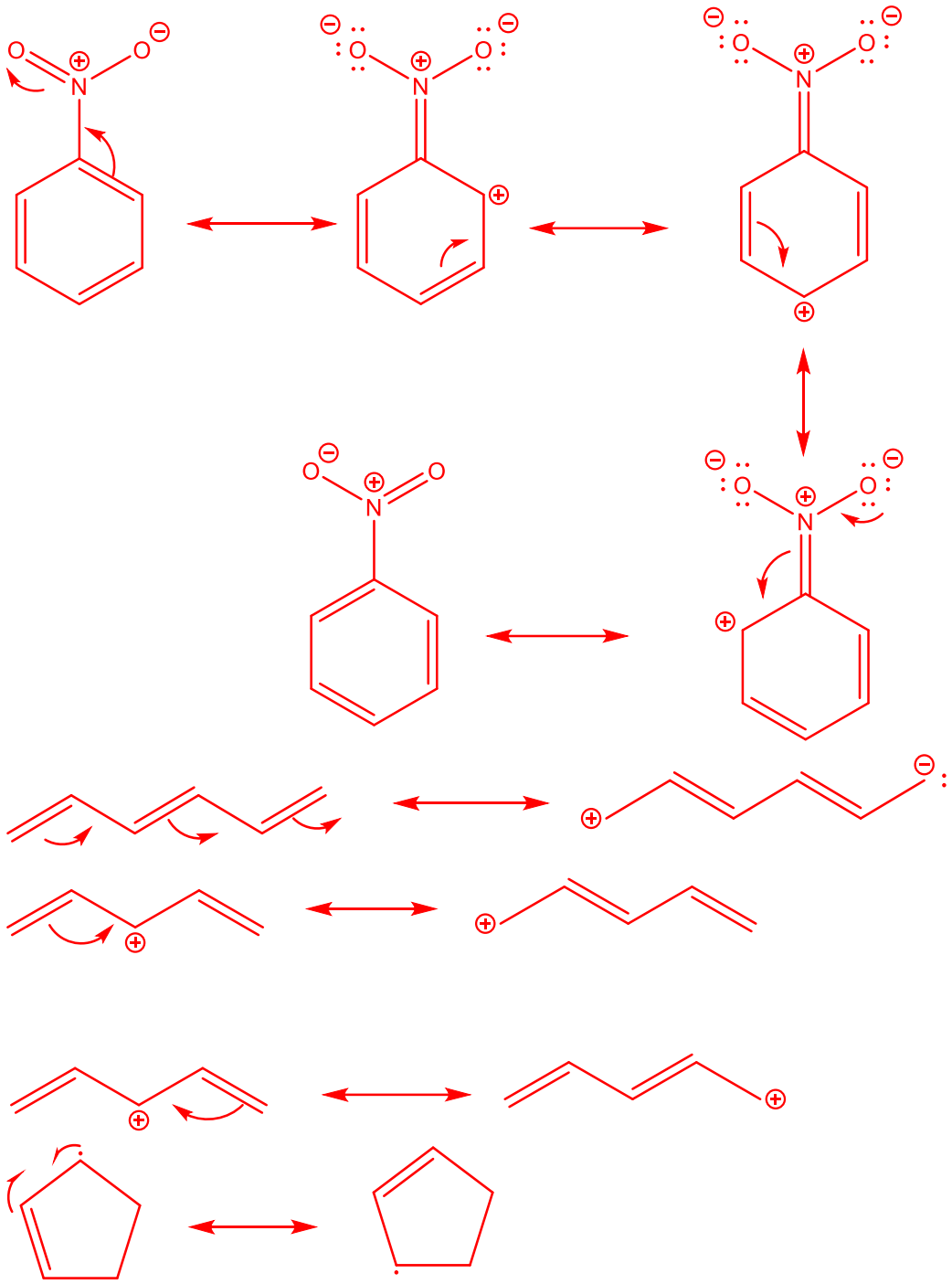
Draw the resonance forms for the following structures:



Answers:

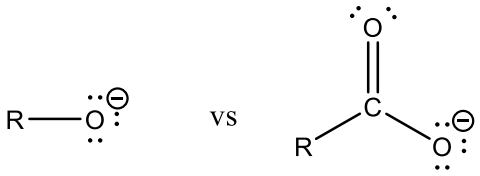



O
O
O
O
O
O
C
N
C
N
C
N
C
N

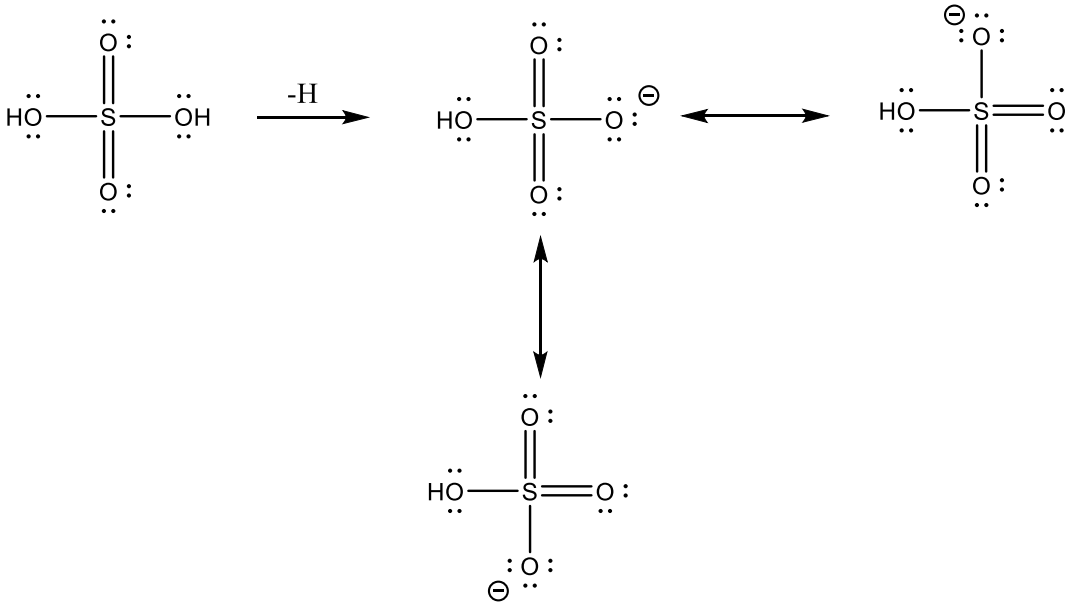


What do you notice about the groups that have lone pairs directly attached to the ring and the groups that have pi bonds in conjugation with the ring? **The groups that have lone pairs directly attached to the ring are electron-donating groups, while the groups that have pi bonds in conjugation with the ring are electron-withdrawing groups.**

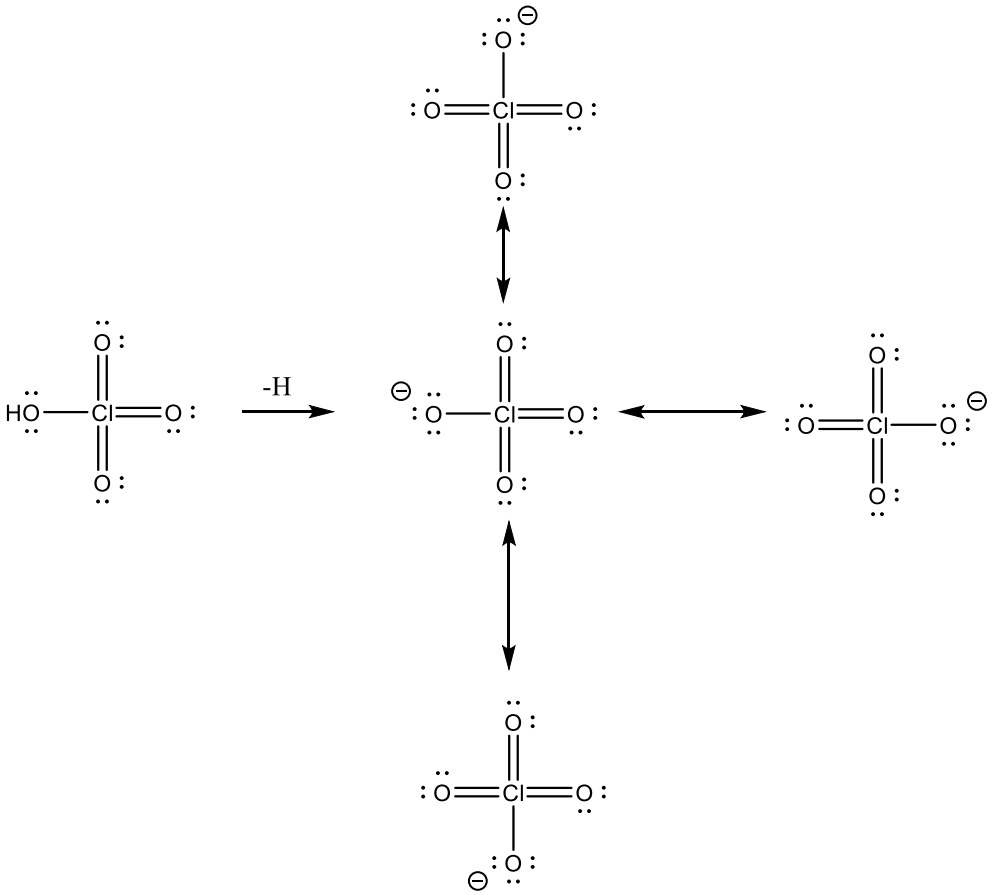
There is another pattern that you should notice for electron-withdrawing and electron-donating groups. They produce a positive and a negative charge ONLY on the carbons directly next to the group and the carbon directly across. These positions, as we will later discuss are the *ortho and para positions* of the benzene ring. These positions are also the *resonance positions* of the benzene ring, only these positions will be drastically impacted by resonance effects! That being said, how does resonance influence acidity? In a word, it strengths it. Let's compare alcohols and carboxylic acids, like many memers have mentioned in their posts, carboxylic acids are essentially just spicy alcohols. Let's compare the groups when they are in their deprotonated state and see if we can determine the cause of the carboxylic acid group's acidity:



The alcohol group has no possible resonance forms because there is nothing in conjugation with it, but look at the carboxylic acid group, that has a resonance form because it has the motif double-single-lone pair. Therefore, the carboxylic acid group has a resonance form and this increases the stability of the conjugate base! If we recall from chapter 2, strong acids give weak/stable conjugate bases, therefore, it is the conjugation that the carboxylate experiences that gives the carboxylic acid parent molecule its acidity. *The conjugate base for the carboxylic acid is resonance stabilized, while the conjugate base for the alcohol is not.* This can also be used to explain why sulfuric acid is a stronger acid than all organic acids, it simply has way more resonance forms:



The same goes for perchloric acid:



Because sulfuric and perchloric acid have more resonance forms, they have more stable conjugate bases and therefore are stronger acids (perchloric acid is stronger than sulfuric because it has more resonance forms as well). But fundamentally, why the heck does any of this matter, why are resonance forms so important? To answer that question, we can turn to our good pal AMSOW, resonance forms all for better charge minimization. If we take the alcohol and carboxylic acid example for instance, in the alcohol, the oxygen has a full negative charge. There is nowhere else the negative charge can go because there are no resonance forms. In the carboxylic acid example, though, that negative charge isn't only on one oxygen, it is spread across two of them. This essentially splits the charge burden in half, with each oxygen carrying ½ the negative charge. Therefore, to minimize the negative charge in one place, resonance forms stabilize the conjugate base and allow the parent compound to be more acidic.

In the context of aromatic acids such as phenol, you can accurately predict the effects resonance forms have on acidity by looking at the nature of its resonance effect. *Electron-withdrawing groups increase acidity by accepting excess negative charge. Electron-donating groups decrease acidity by increasing the concentration of negative charge on the proton donation site.* To help you in your studies, I have put together a list of all the common electron-withdrawing and electron-donating groups.

Guide to Electronic Effects on pKa

Electron-Withdrawing Groups:
Increase Acidity
Typically have double bonds in conjugation with the ring

In order of decreasing strength:
NO2
SO3H
Carbonyls
Nitriles
F
Cl
Br

Electron-Donating Groups:
Decrease Acidity
Typically have lone pairs in conjugation with ring

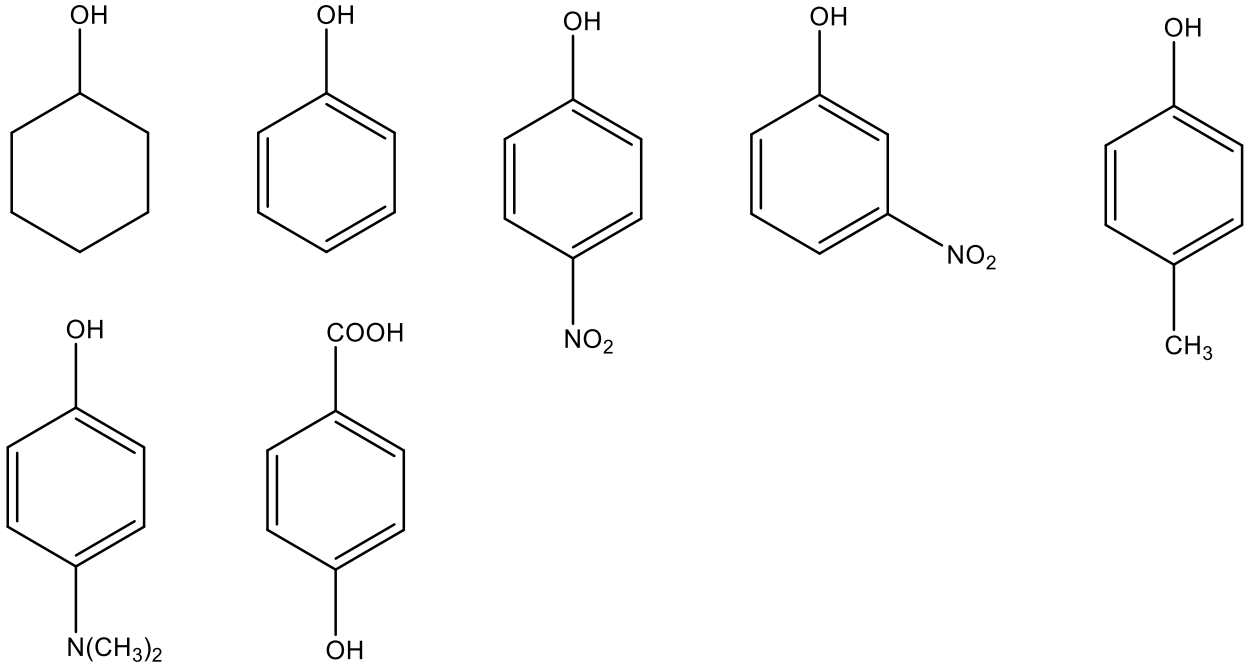
In order of decreasing strength:
NH2
OCH3
OH
CH3

Blue = Resonance contributing groups
Red = Inductive groups

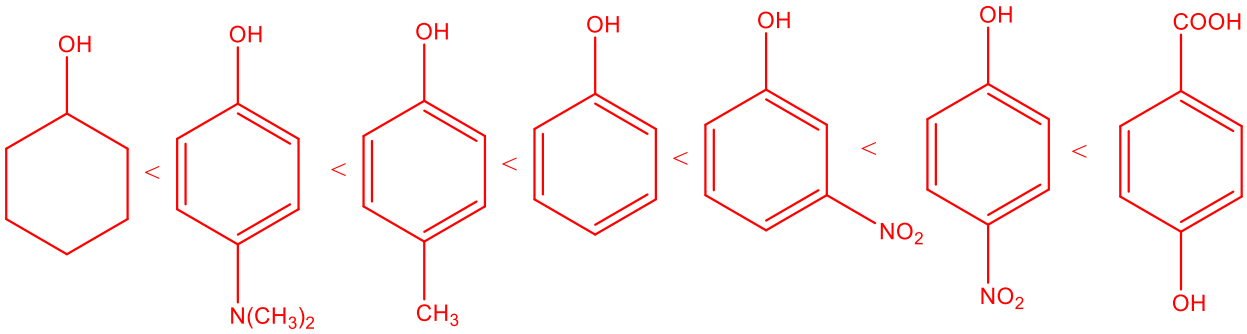
Nitriles are CN groups and carbonyls are any group that has a C=O. I have also arranged them in order of strength so that you can distinguish which are stronger or weaker groups.

Practice questions:

1. Order the following compounds in order of increasing acidity:



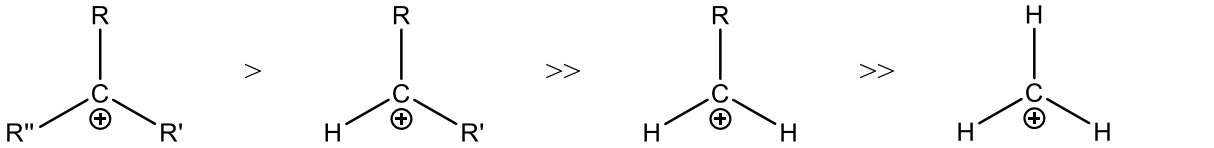
Answer:



Remember, the benzene ring itself is electron-withdrawing because it has a pi bond in conjugation with the acidic proton region, therefore cyclohexanol is by far the least acidic. Then you look at the chart, the $N(CH_3)_2$ group is functionally equivalent to the NH_2 group on the list, that is the strongest electron-donating group and therefore it will suppress acidity the best. The methyl group is only mildly electron-donating, therefore it only mildly suppresses acidity. The regular phenol is neutral in that it does not contain either group on the ring, but it is still aromatic and therefore it will be more acidic than cyclohexanol. The meta isomer of the nitro phenol is less acidic than the para isomer because the ortho and para positions are the resonance positions, the groups in the meta position are limited solely to inductive effects. The last compound has a completely different acidic region, instead of it being an alcohol, it is a carboxylic acid, therefore it is the most acidic by default, despite it having a strong electron-donating group in the para position (OH).

The revised priority list for acidity is: hybridization < inductive effects < resonance effects < functional group or HIRF.

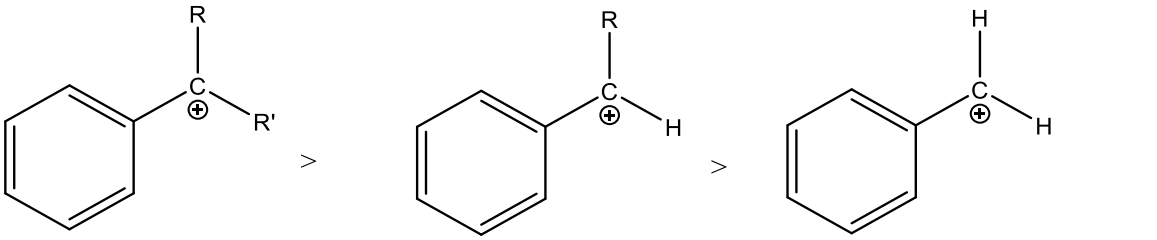
Now that we understand the drastic effects resonance has on stability and acidity of chemicals, we will now discuss the effects it has on carbocation stability. Initially, our tier list of stability for carbocations went like this:



Tertiary Carbocation Secondary Carbocation Primary Carbocation Methyl Carbocation

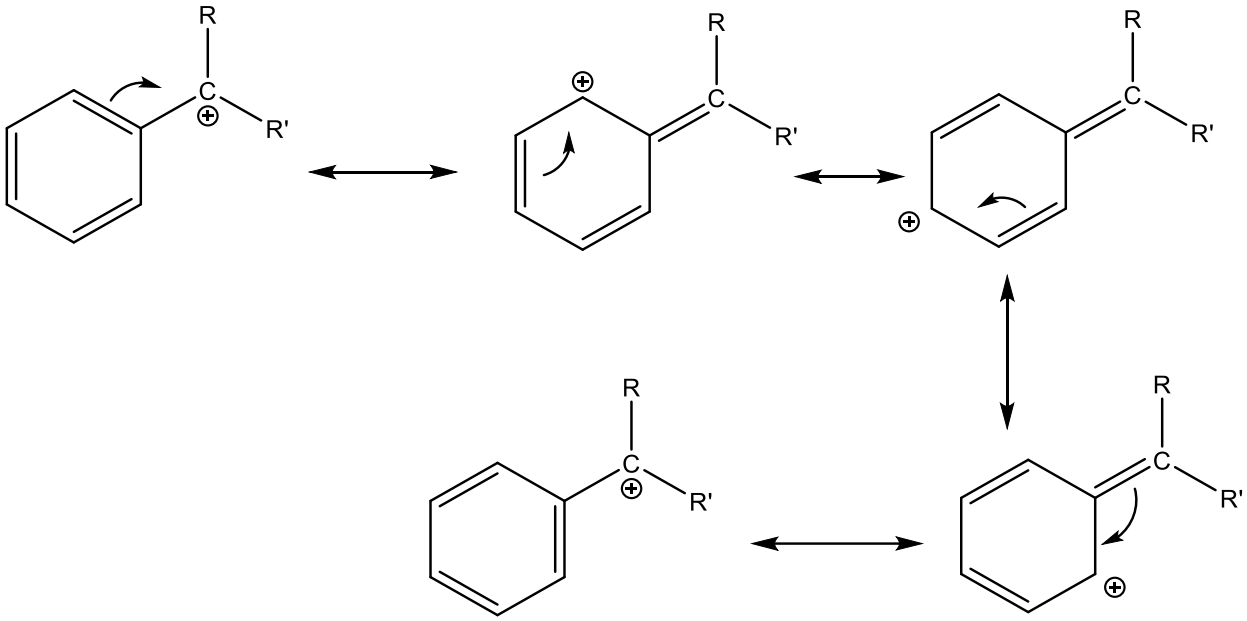
But that was when we were limiting ourselves to purely inductive effects and the reason for that order was because carbon groups are weakly electron-donating through hyperconjugation (look at the guide to acidity). However, in the same way that resonance effects are more impactful for acidity, they are also more important when discussing carbocation stability, therefore we will introduce two more types of carbocations, benzylic and allylic carbocations.

Benzylic carbocations are those carbocations that are directly off the benzene ring like so:



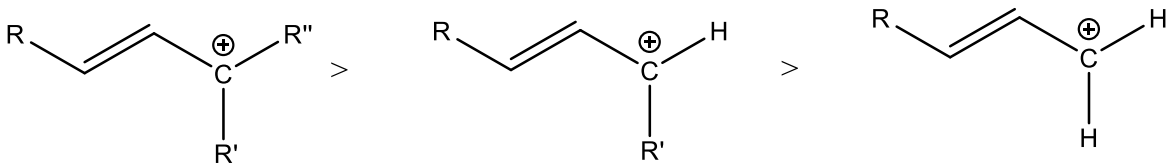
Tertiary benzylic carbocation Secondary benzylic carbocation Primary benzylic carbocation

These carbocations are inherently more stable than traditional carbocations that we discussed in previous chapters because they are resonance stabilized (double-single-empty p) like shown:



Like before, resonance stabilization occurs because the positive charge on the initial carbocation is being minimized (A**M**SOW). Instead of the carbon having a full plus 1 charge, it now only has a fraction of that charge since it is being shared with the ortho and para positions in the ring.

Allylic carbocations are similar to benzylic, but instead of a benzene ring being in conjugation with the positive charge, a linear double bond is instead:



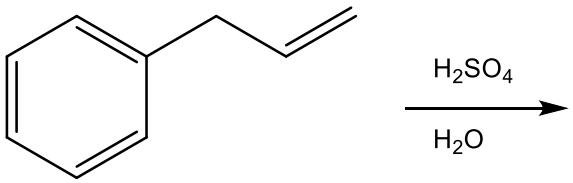
Tertiary allylic carbocation Secondary allylic carbocation Primary allylic carbocation

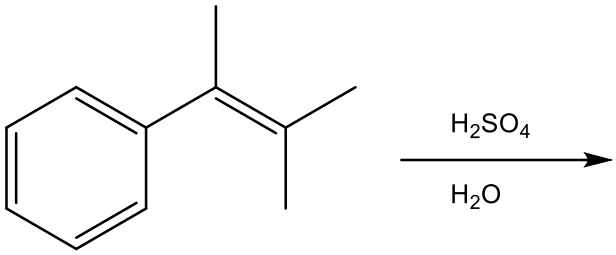
Both allylic and benzylic carbocations are inherently more stable than the traditional carbocations that we discussed in the alkene chapter, therefore the new tier list of stability is as follows:

Benzylic ~ allylic > tertiary > secondary > primary carbocations.

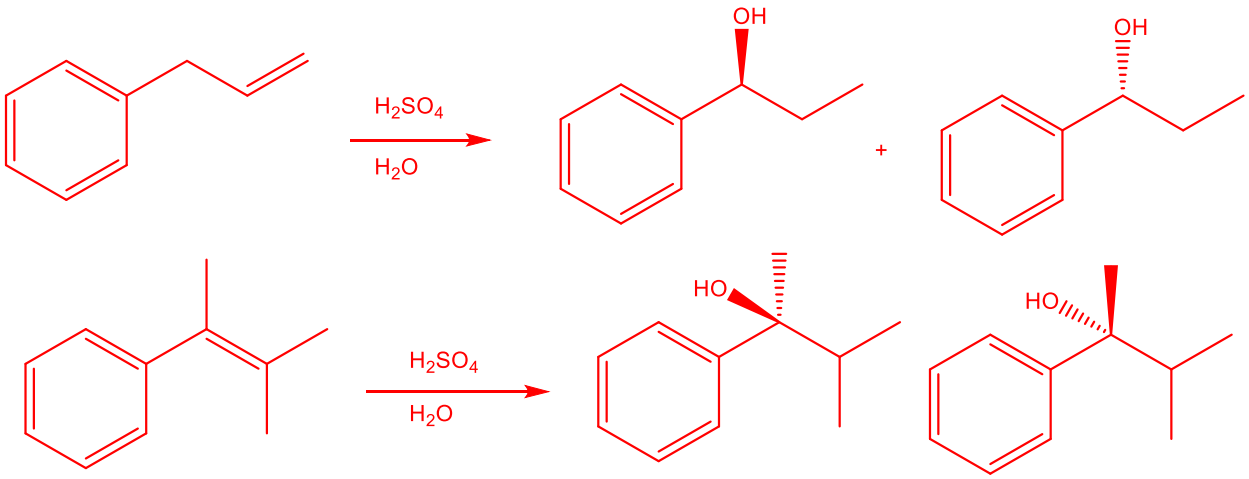
Practice questions:

Predict the major product of the following reactions:



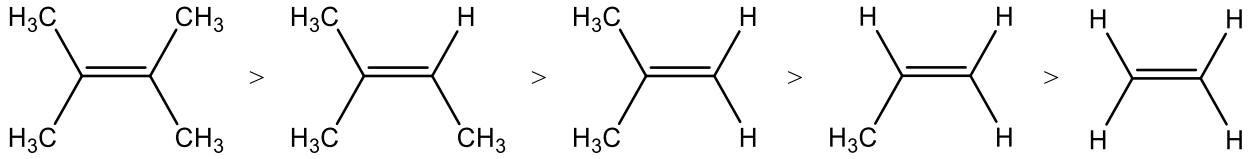


Answer:

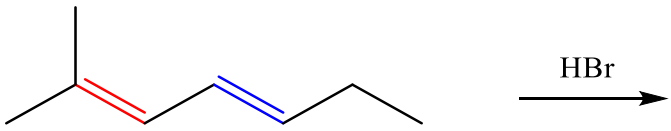


Now let's discuss the reactions of conjugated dienes. There will be two different products that you can get, they are called the 1,2 or 1,4 products. Although that is the more common name for

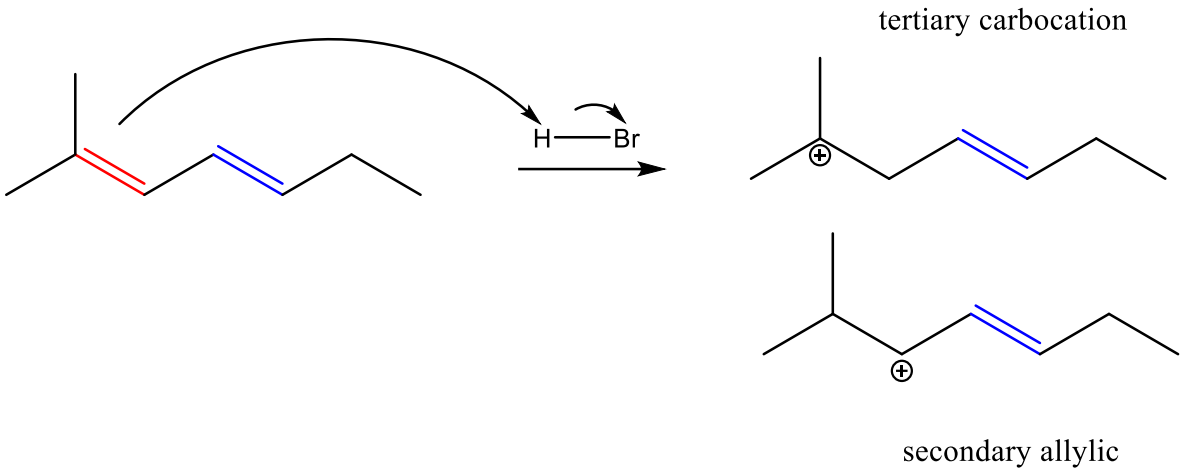
them, I prefer the names direct and conjugate addition products because they tell you more about how you get the product itself. The *direct* addition product will be the product you get when you attack the initial carbocation *directly*. The *conjugate* addition product will be the product you get when you attack the carbocation that results because of the *conjugation* that *conjugated* dienes have. But wait, how do you determine which alkene to use to form the carbocation? You can probably surmise how to do this. Although it is a pain, you have to look at both carbocations that would form with either alkene, there will generally be a more stable 1,2 carbocation, however, if there is a tie, draw the resonance form and evaluate the stability of the 1,4 carbocation. Whichever one is more stable chose that alkene and go from there with the standard reaction mechanism we already discussed with the reactions of alkene chapter. This method of choosing an alkene should make sense, ultimately carbocations are super unstable and the driving force in this method is to minimize the charge on the carbocation (A**M**SOW). When you do a reaction with a conjugated alkene (diene, triene, etc), there will always be a kinetic and thermodynamic product. The kinetic product will ALWAYS be the 1,2 product, or the direct addition product. This should make sense, it will take time for you to switch from the 1,2 carbocation to the 1,4 carbocation, therefore kinetically it is easier to get the unrearranged carbocation. The thermodynamic product has to do with how stable of an ALKENE you form as your PRODUCT. Just as a refresher for alkene stability, here is the tier list, it follows the pattern that the more substituted the alkene the more stable it is:



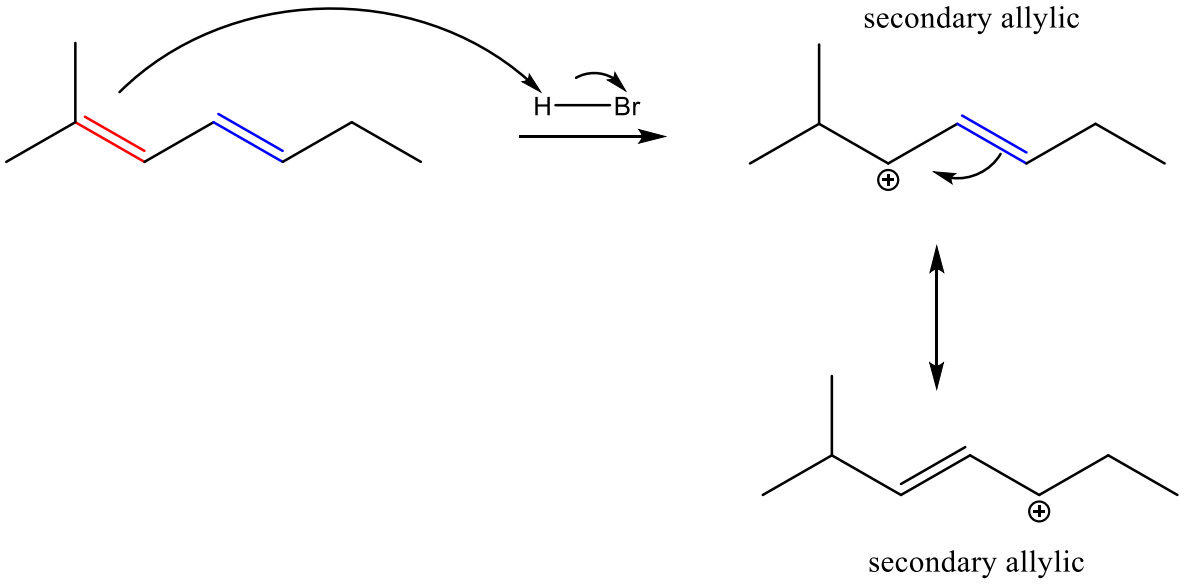
For example, let's look at the reaction of the following conjugated diene and go step by step:



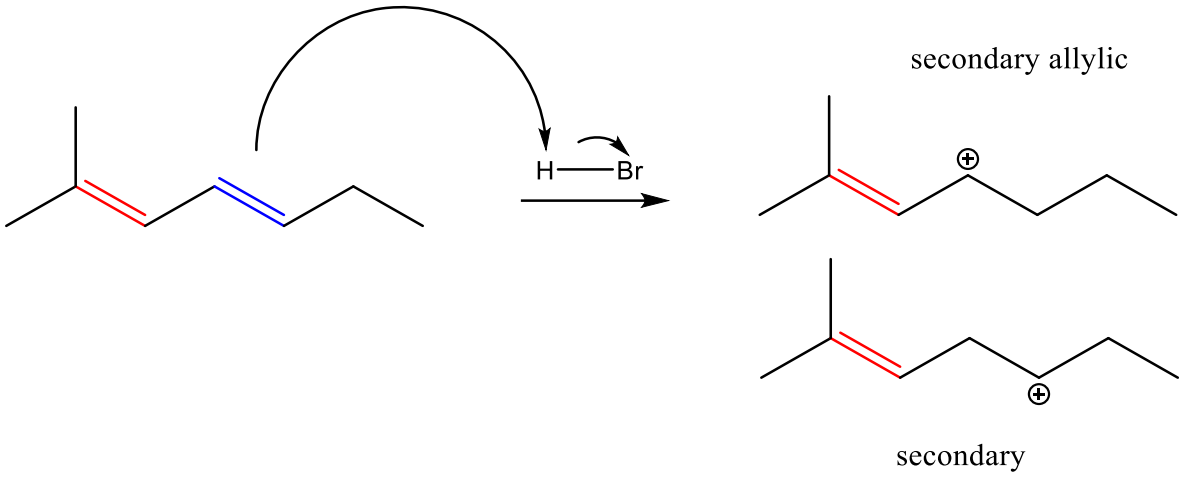
Now in the above reaction, we have a choice, we have to determine which alkene (red or blue) to use to attack the proton of the HBr. To do this, we should look at each case in turn, let's first look at the case where we attack with the red alkene:



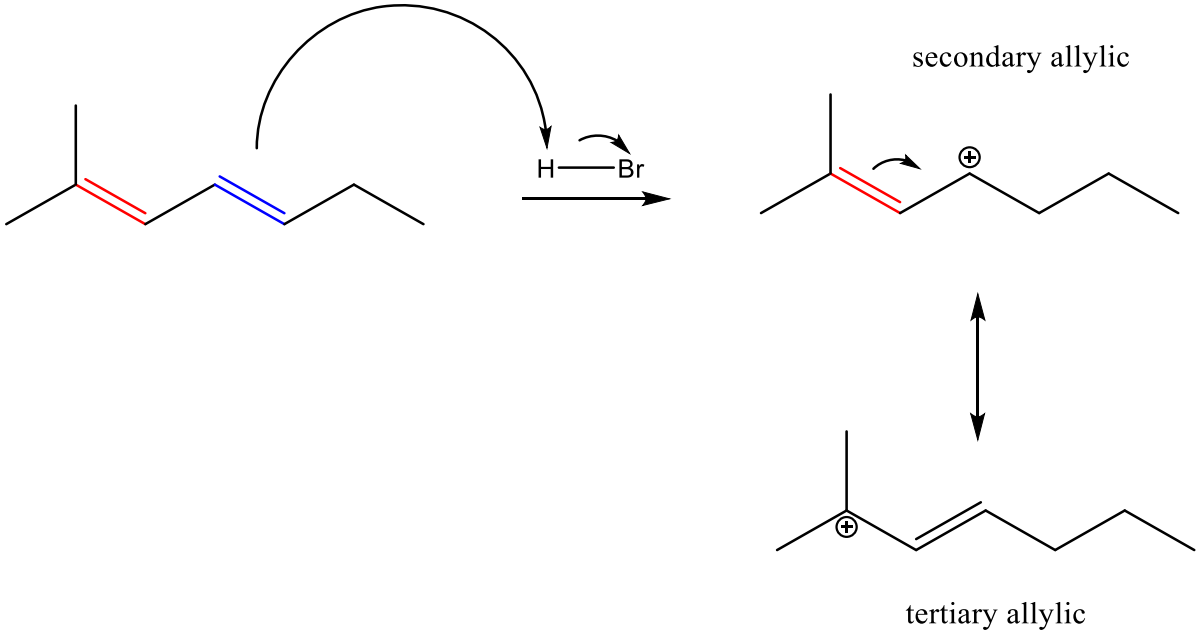
If I attacked with the red alkene, I could produce those two 1,2 carbocations. However, the secondary allylic carbocation is much more stable, therefore I will choose that to look at the 1,4 form:



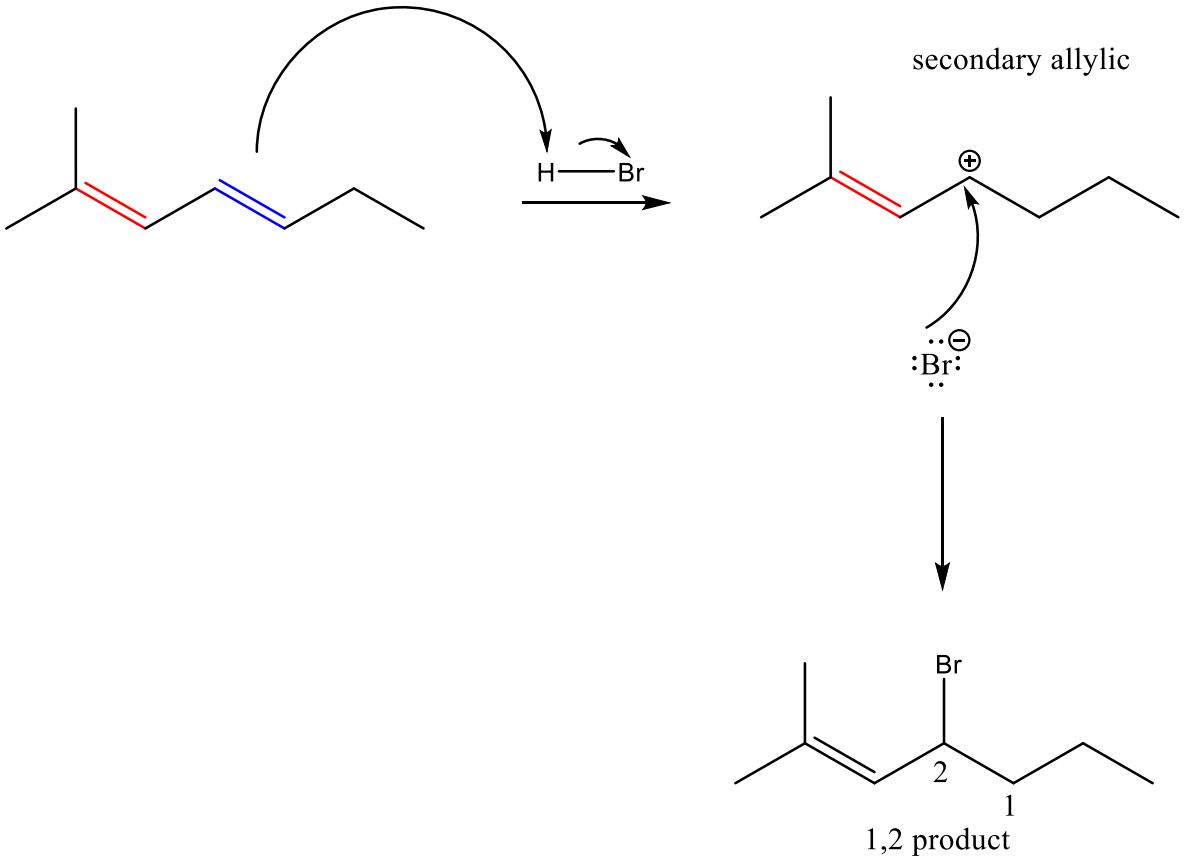
Therefore, if I chose to make the red alkene be the one I attack with, I have two secondary allylic carbocations to attack. Let's see if we can improve upon that if we use the blue alkene:



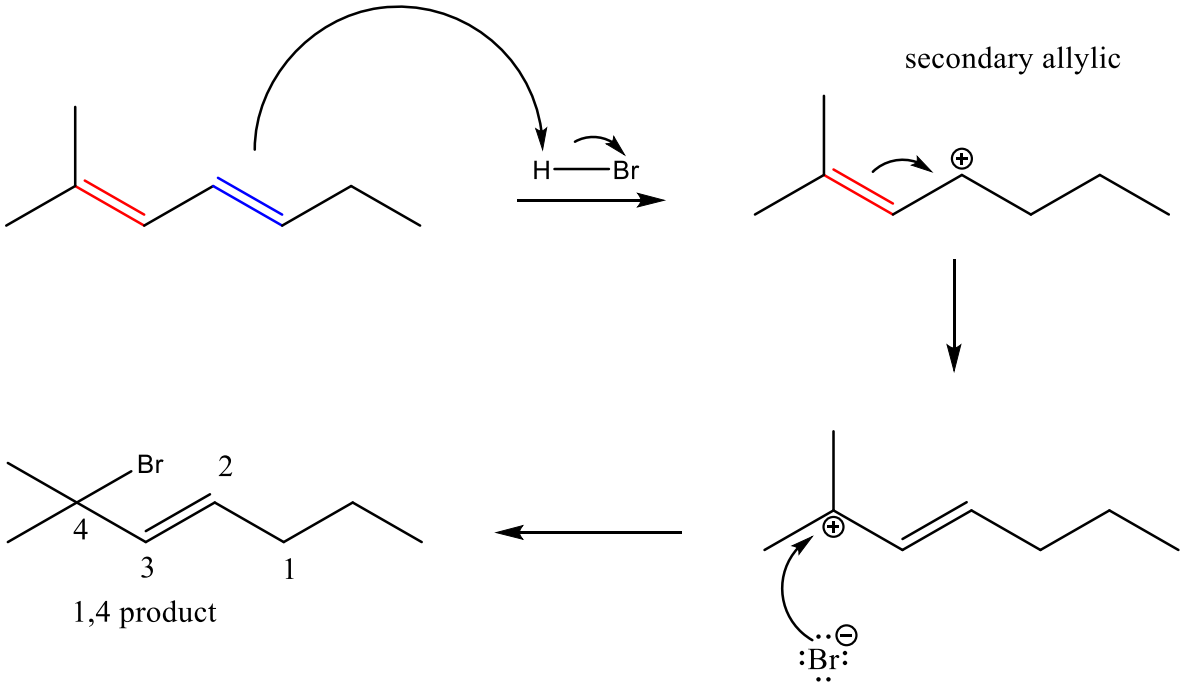
If we attack with the blue alkene, we have two 1,2 carbocations like before, but this time we have a secondary allylic and a regular secondary carbocation. Because the secondary allylic is more stable, we can ignore the secondary one and we will consider the resonance form of the secondary allylic carbocation:



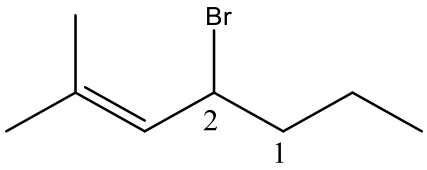
When the secondary allylic carbocation rearranges, we get a tertiary allylic carbocation. Because that is the most stable carbocation we can get, we must attack with the blue alkene. This example demonstrates a rule of thumb, *when in doubt, pick the less substituted alkene to attack with in the first step.* The rest of the mechanism follows exactly how we described it in the alkene reaction chapter:



The 1,4 product we can get by attacking the rearranged carbocation:

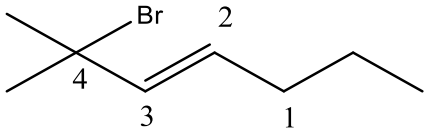


Now that we have both products we need to determine which is the thermodynamic and kinetic product. We have to compare the following two alkenes:



1,2 product

vs

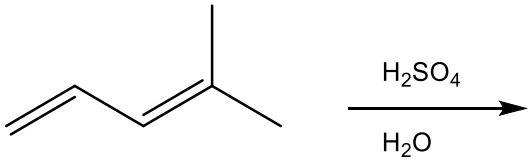


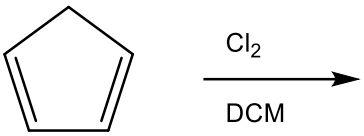
1,4 product

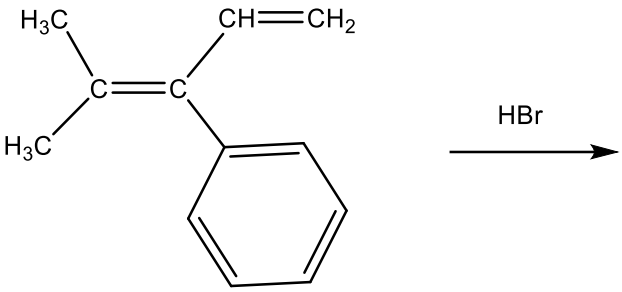
Well the kinetic product is super easy, its always the 1,2 product or direct addition product. The thermodynamic product is a bit more nuanced, we have to evaluate the stability of the alkene products that we have. The more stable alkene of the two of them is also the 1,2 product or the direct addition product. This illustrates a critical feature of these conjugated diene reactions, one product may be *both thermodynamically and kinetically favored*. But wait a second, what exactly does it mean to say that a product is thermodynamically and/or kinetically favored? The kinetic product is the product that forms faster at lower temperature, while the thermodynamic product is the ideal product if there was sufficient thermal energy to promote its formation. In other words, the *kinetic product is seen mostly at low temperatures while the thermodynamic product is seen mostly at high temperatures*. In the reaction shown above, the major product is always the 1,2 product, regardless of temperature. That is not always the case, and in fact, it is usually not the case.

Practice questions:

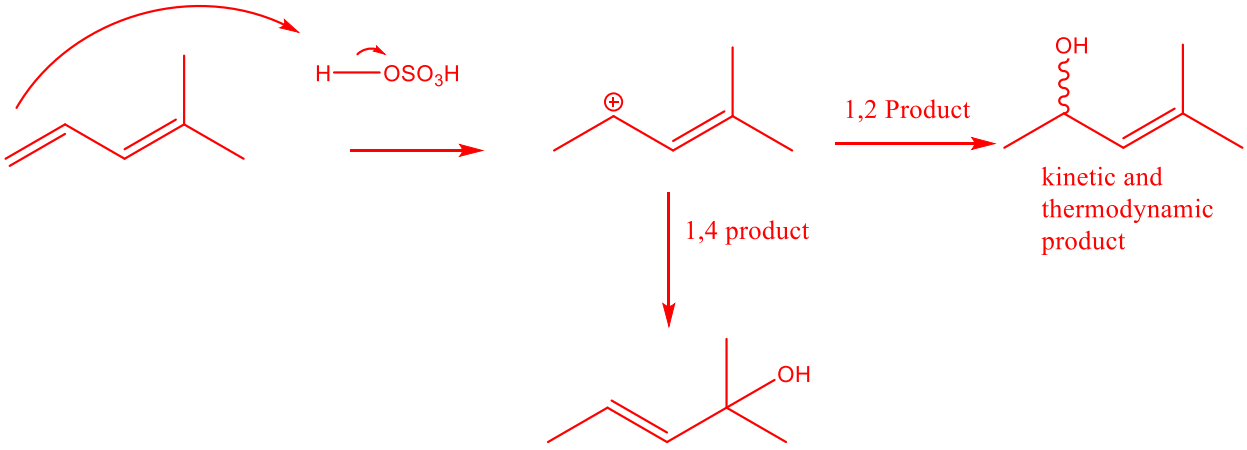
What is the thermodynamic and kinetic product for the following reactions:

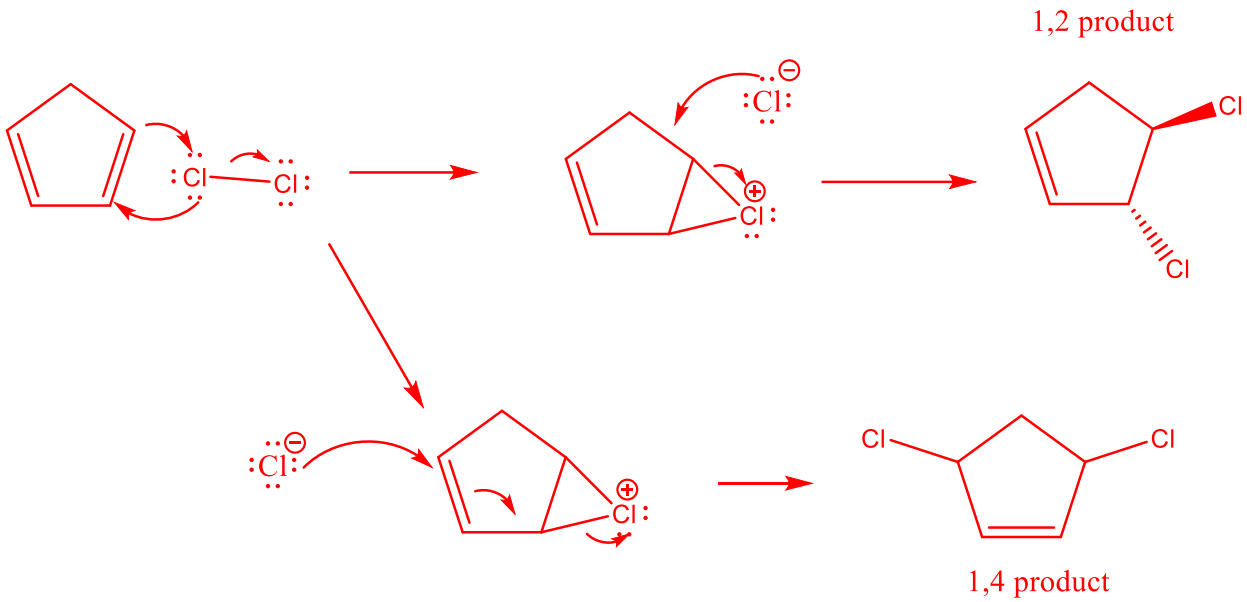

H_2SO_4
H_2O

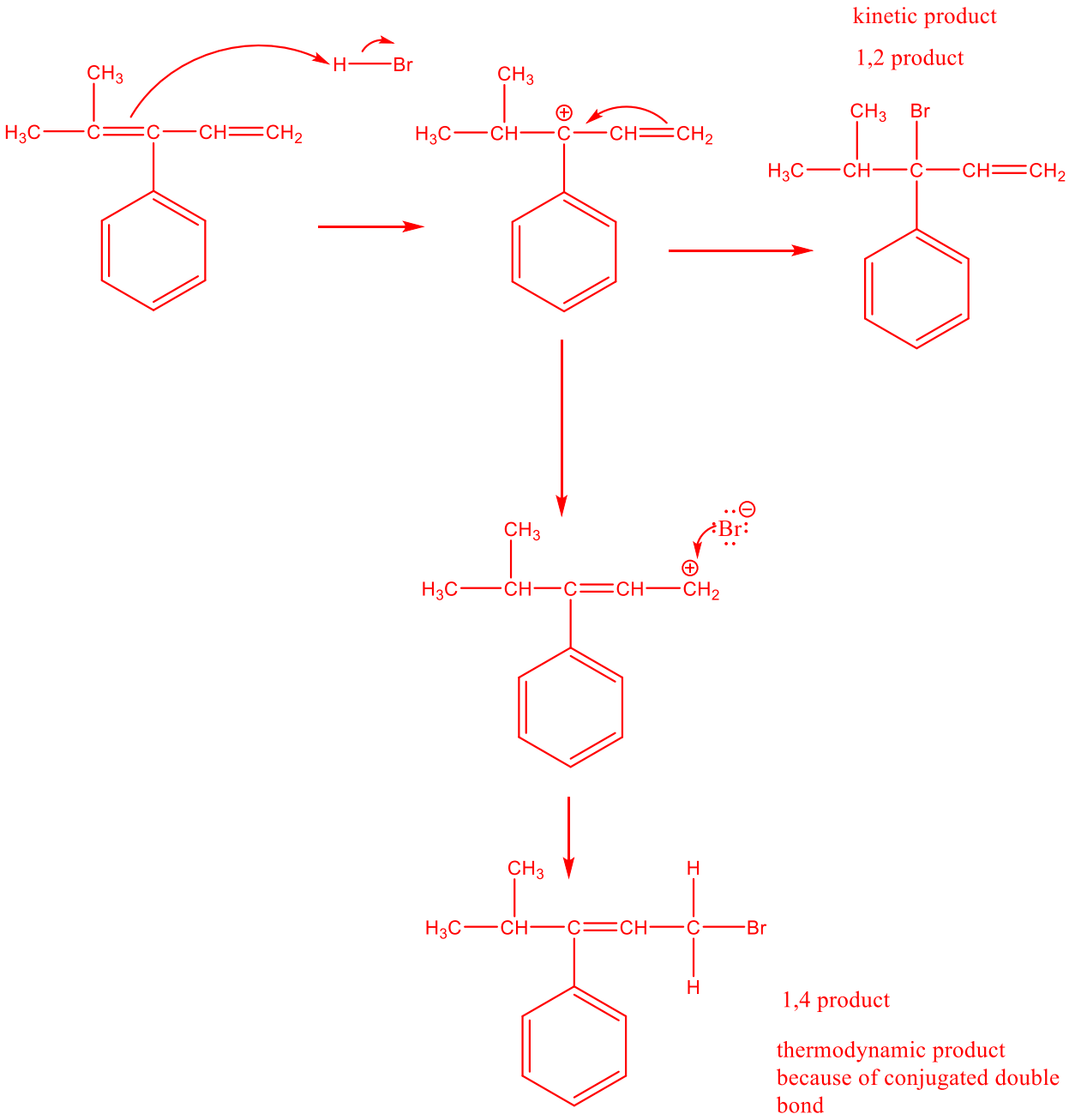

Cl_2
DCM


H_3C
$CH=CH_2$
C=C
H_3C
HBr

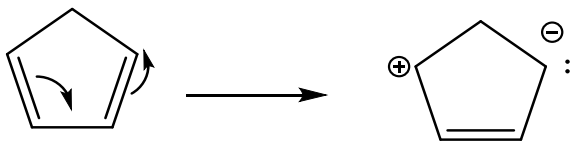
Answer:


H—OSO3H
1,2 Product
OH
kinetic and
thermodynamic
product
1,4 product
OH


1,2 product
Cl
Cl
Cl
Cl
Cl
Cl
Cl
Cl
1,4 product

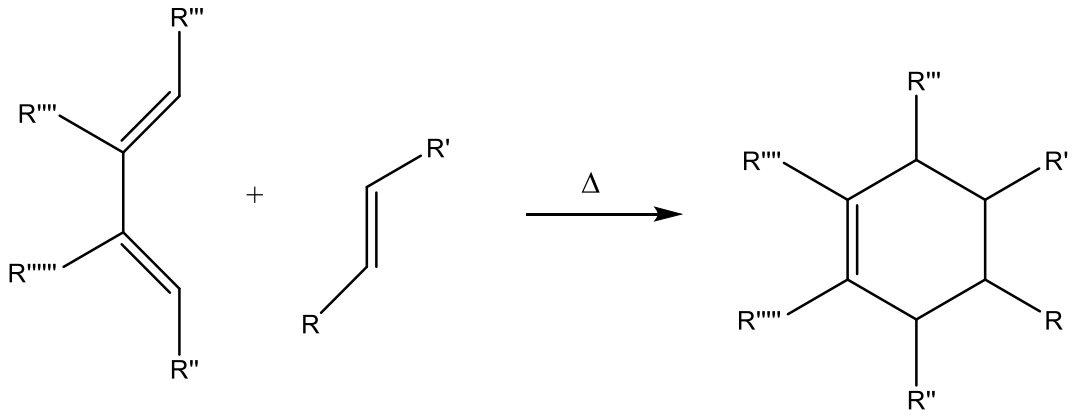


In the second example, it was a bit of a challenge to get both products. Ultimately, the reason why the second product arises is because of the following resonance form:

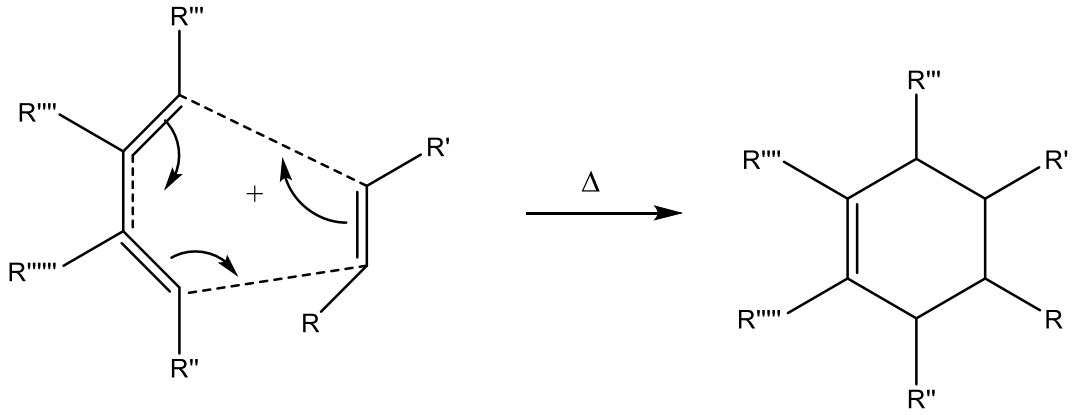


This makes the positively charged carbon more susceptible to nucleophilic attack and augments the nucleophilicity of the negatively charged carbon. The last question was also rather tricky and that's because in both products, they were equally substituted, however, the conjugation with the benzene ring makes the 1,4 alkene more stable and therefore it is the thermodynamic product.

Conjugated dienes can also undergo one of the most powerful reactions in organic chemistry. This reaction has two things going for it, firstly, it can form a ring and secondly, it can form carbon-carbon bonds. This reaction involves a conjugated diene and a chemical that 'loves a diene' or dienophile. This reaction of course is the Diels Alder reaction! Ready to see it? Here it is:



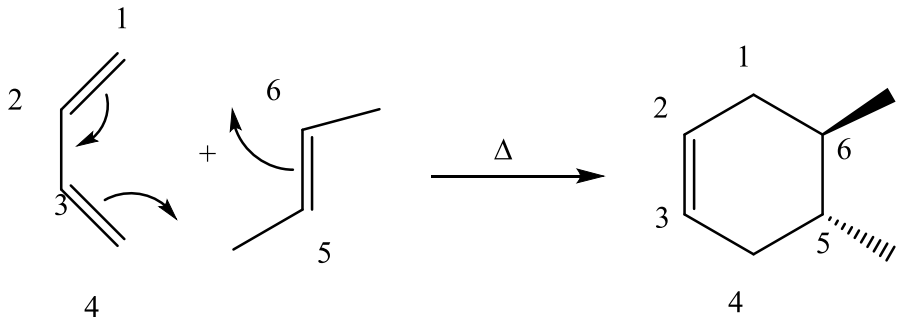
Not impressed? The true power of this reaction won't become clear until later, but this reaction was a SUPER big deal when it came out and it continues to find use in the pharmaceutical industry. The reaction mechanism must be super hard though right? Like how can this just happen like that without some voodoo magic? Well lucky for you, this reaction mechanism is super easy. However, I am going to draw the arrows in a nontraditional, but useful way to help illustrate how this reaction functions:

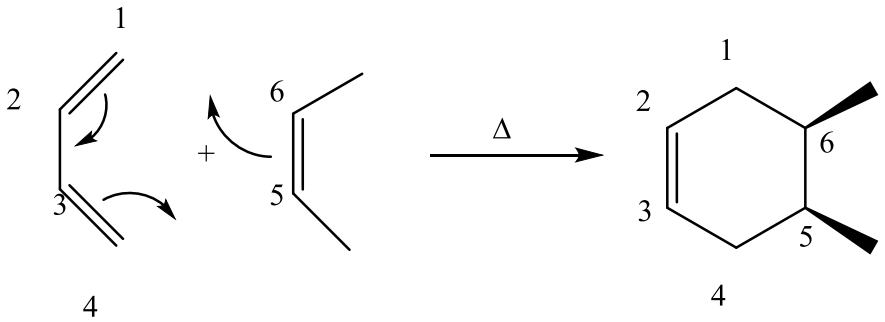


The order that you start your arrows DOES NOT matter, this is a pericyclic reaction, meaning that the transition state and the way you put your arrows are done in a circle. There is no start or end to a circle, therefore, it doesn't matter where you start your arrows. However, it useful to view the diene as the nucleophile and the dienophile as the electrophile. This is because this

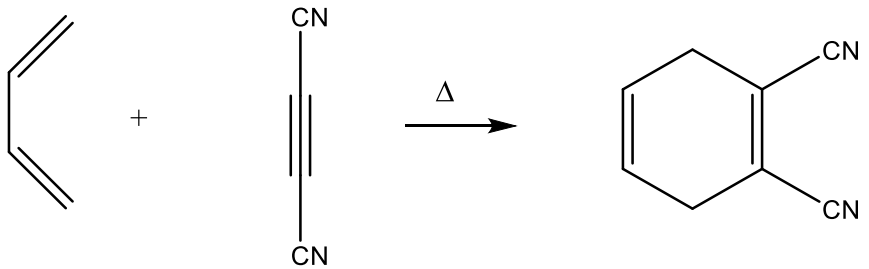
reaction is typically enhanced when electron-donating groups are added to the diene and electron-withdrawing groups are added to the dienophile. This should make some sense, nucleophiles have excess electrons and are always doing the attacking, therefore, the electron-donating groups are giving more ammo to attack the dienophile with. In a similar vein, electrophiles are electron-deficient and want to get attacked, this is enhanced if there are less electrons available for the dienophile.

This reaction is stereospecific, if you use the trans alkene as the dienophile, the groups on the dienophile side will continue to be trans in the product. Likewise, if the cis alkene is used, the groups will be cis in the product.

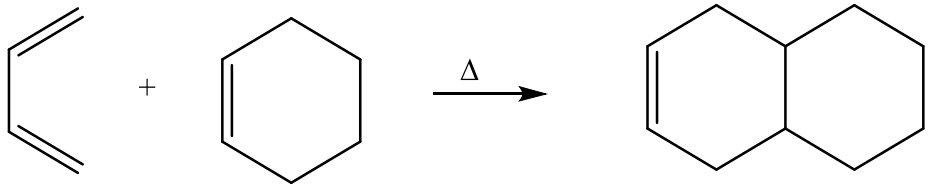




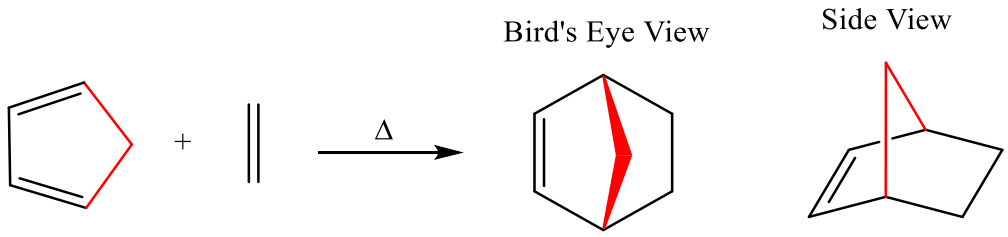
The Diels Alder reaction is extremely versatile for making cyclic molecules and can make use of alkynes as the dienophile as well, in this case, the dienophile still loses one pi bond so there is still a pi bond remaining in the product:



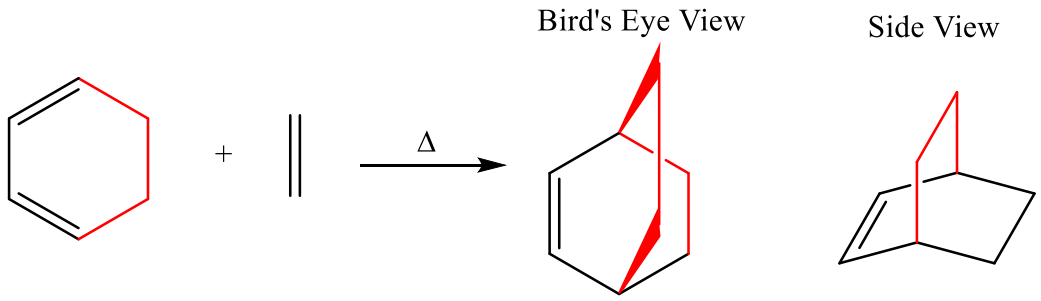
The Diels Alder reaction can also be used with cyclic dienophiles and cyclic dienes. That being said, cyclic dienes comes with a slight complication, but the cyclic dienophiles behave normally:



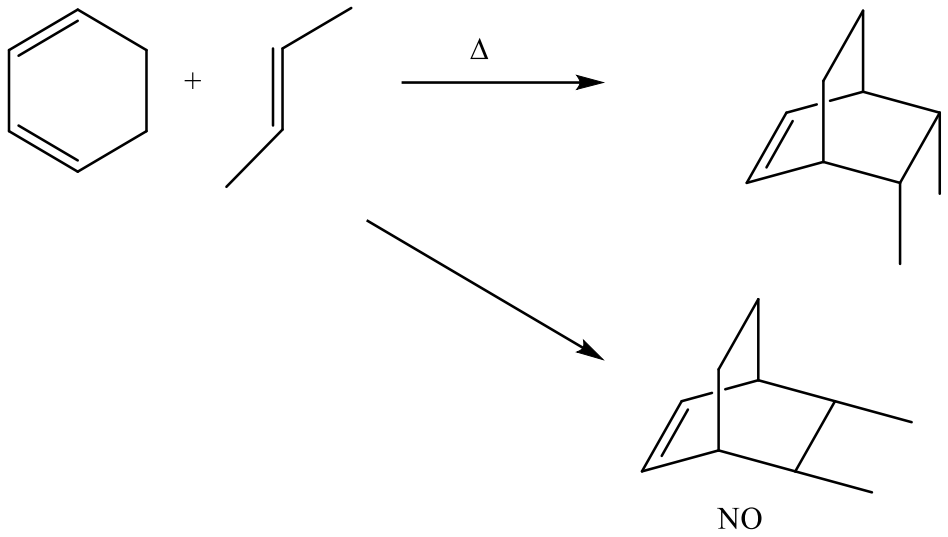
When the diene is cyclic, the pattern is still the same, but you have to push up the extra slack, for example:



The slack is highlighted in red, this pattern continues for cyclohexadiene:

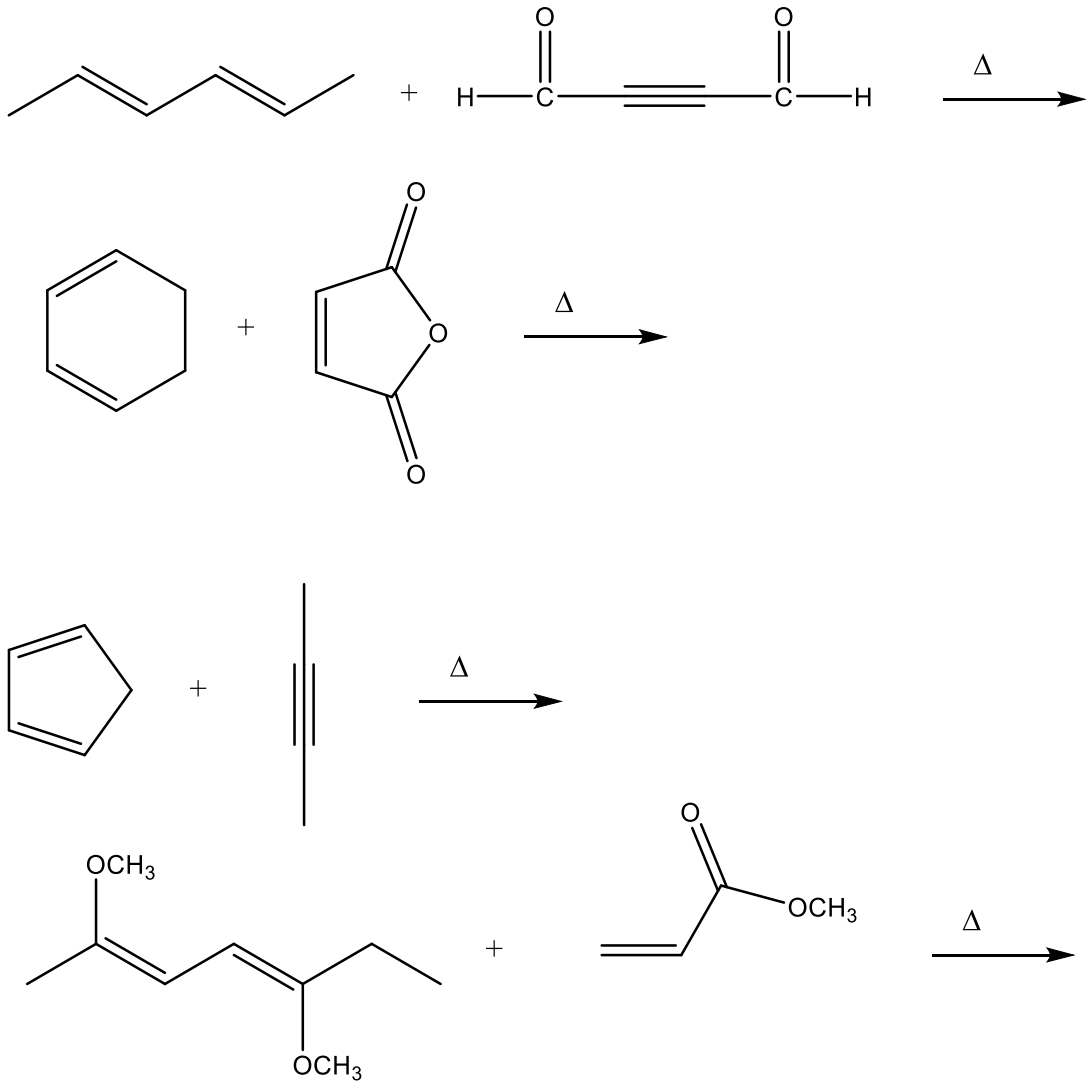


The pattern always persists, regardless of diene and dienophile identity, however, the side view of the bicyclic compounds shown above is the more accepted way of viewing the compound, that is why I included both. When a bicyclic compound is made, if there are any groups on the dienophile, they must be oriented in the endo configuration. This means that they must point towards the double bond that forms on the left hand side of the bicyclic compound:

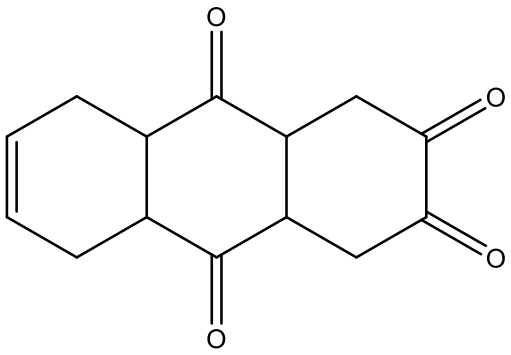


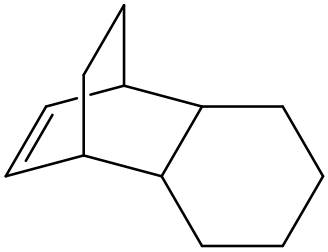
Practice Questions

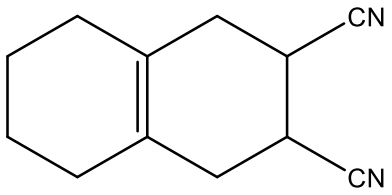
Predict the major products of the following reactions:



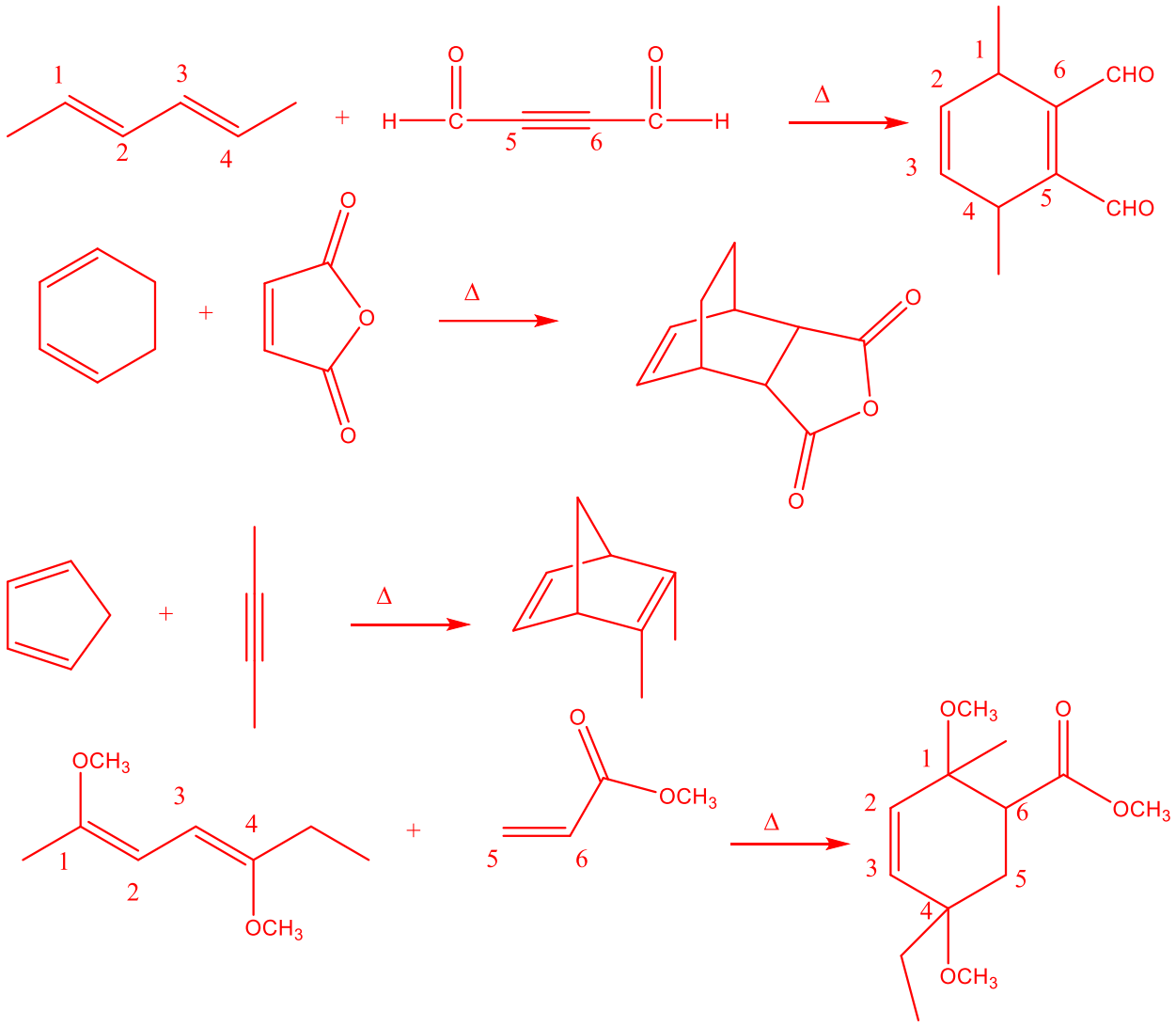
Identify the necessary diene and dienophile to make the following compounds:

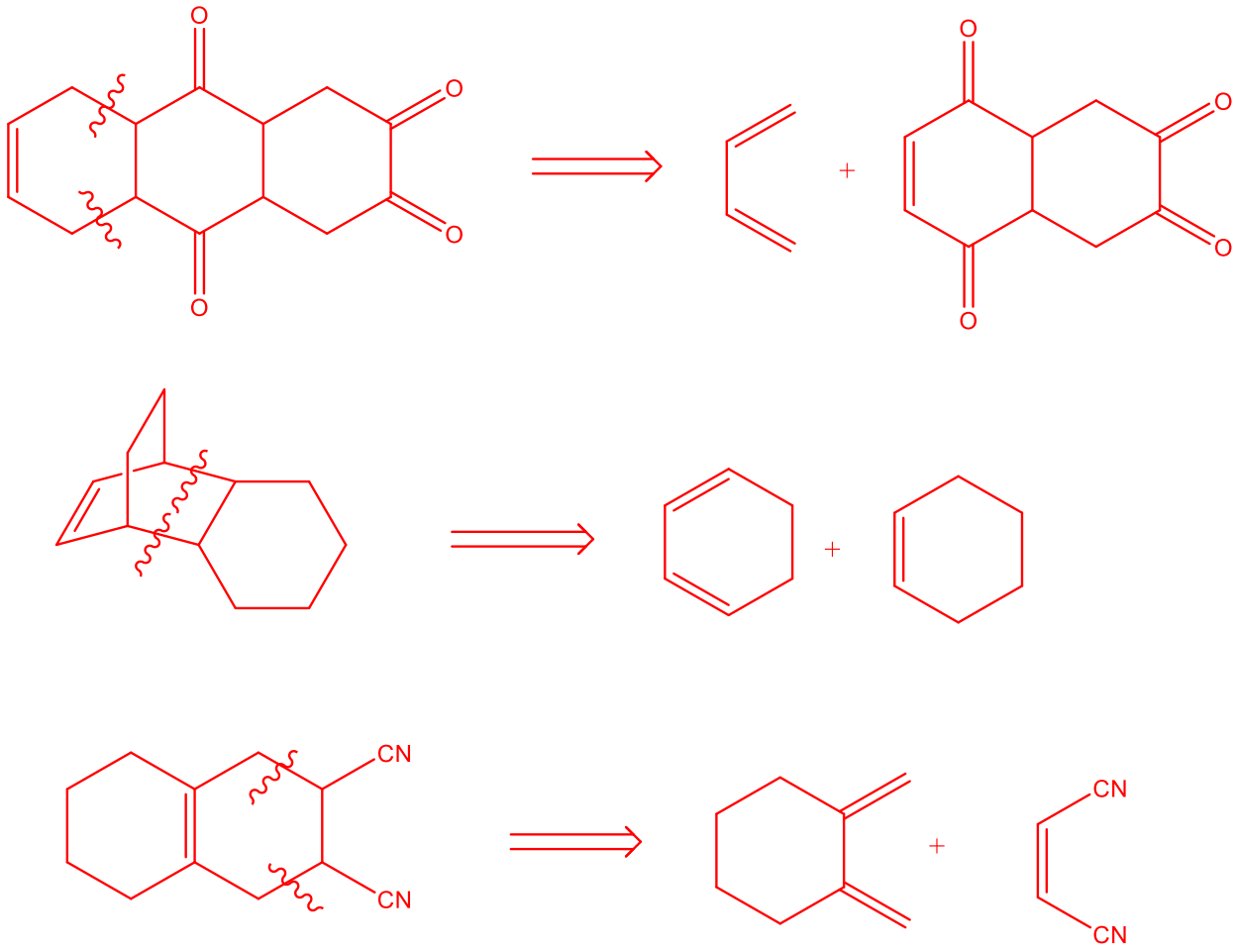






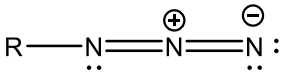
Answers:

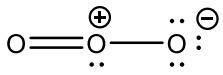

1
3
2
4
+
O
H
C
5
6
C
H
O
Δ
1
2
6
CHO
3
4
5
CHO
+
O
O
Δ
O
O
O
+
Δ
OCH3
3
4
1
2
OCH3
+
O
OCH3
5
6
Δ
OCH3
O
1
2
6
OCH3
3
5
4
OCH3

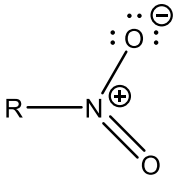


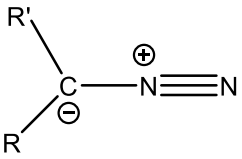
There is also a spin on the Diels-Alder reaction called the 1,3-dipolar cycloaddition reaction. These reactions occur when a compound has a negatively charged atom, positively charged atom, and double bond consecutively (the 1,3-dipolar compound) reacts with a dipolarophile (essentially a dieneophile from before, could be anything with a pi bond). These reactions, instead of making six-membered rings like before, will make five-membered rings, but the mechanism is the same. Common 1,3-dipolar compounds are shown below:

Common 1,3-dipolar functional groups

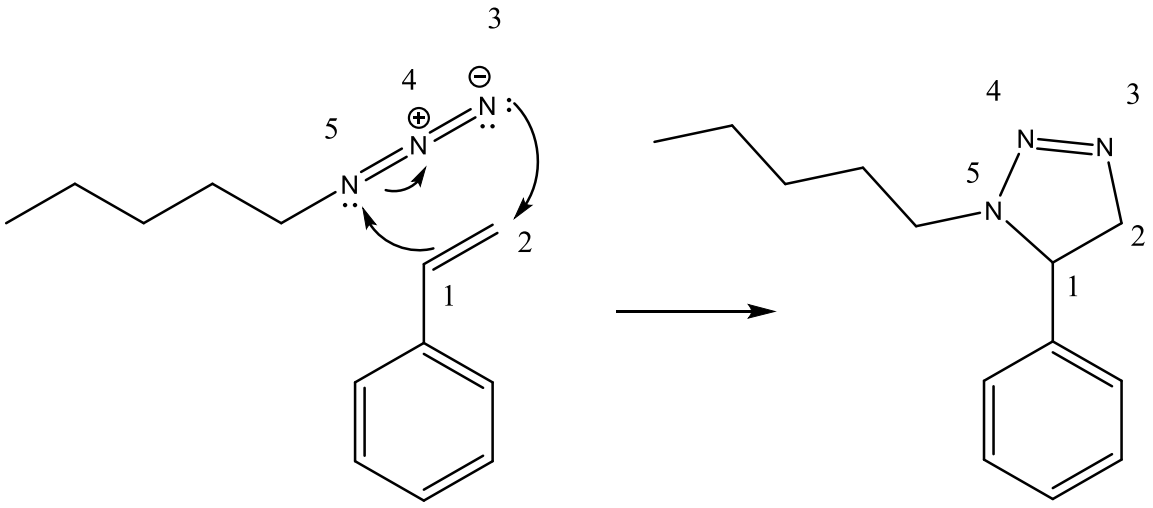
Azides  Can be made by reacting alkyl halides with NaN3

Ozone 

Nitros 

Diazos 

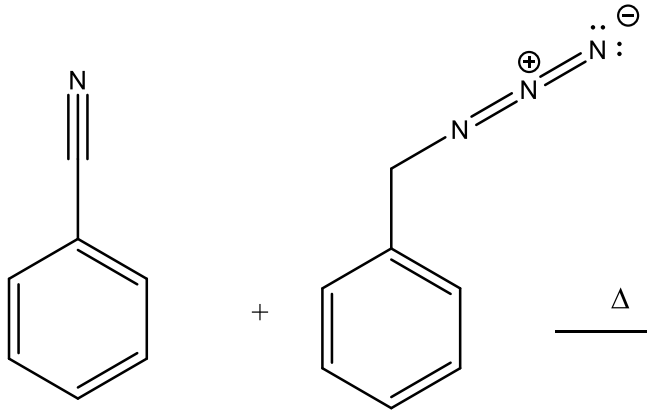
An example reaction is shown below:

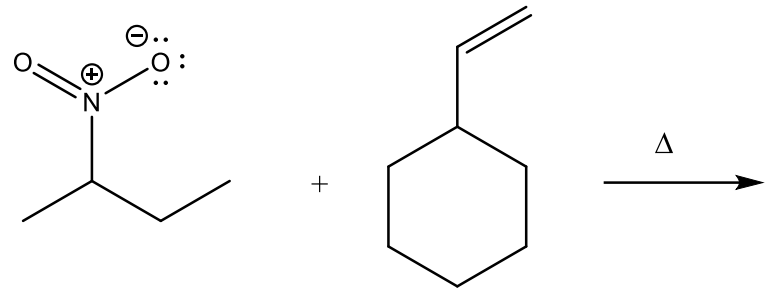


As you can see, it is almost the exact same mechanism, except it forms a five-membered ring as opposed to a six-membered ring.

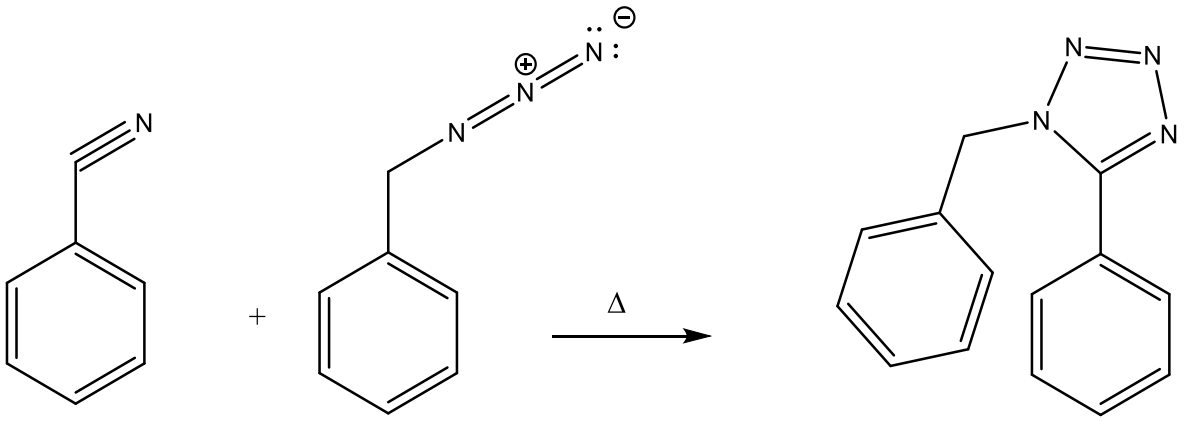
Practice questions:

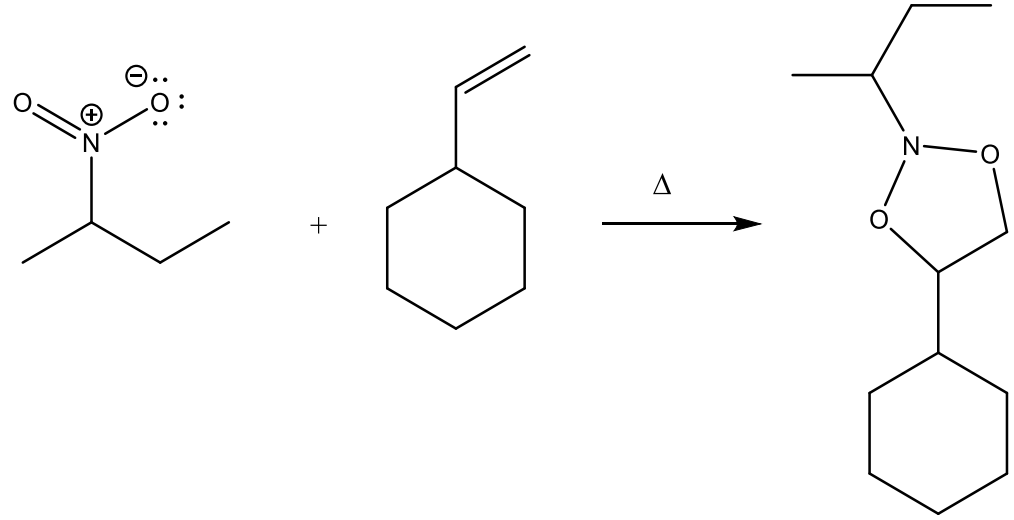
Predict the major organic products for the following reactions:





Answers:


N
N
N
N
+
Δ
N
N
N
N


O
N
O
+
Δ
N
O
O

Chapter 8: Reactions of Alkyl Halides

This chapter is fundamentally different than all the other chapters that we have covered so far. Instead of the carbon compound being the nucleophile like in the case of alkenes and alkynes, instead the carbon compound is the electrophile in that case of alkyl halides. However, what is it specifically that makes alkyl halides electrophilic? The answer to that question is twofold:

1. Halogens above iodine are more electronegative than carbon, therefore the carbon to which they are bonded is partially positive. Recall that electrophiles are either partially or completely positive, therefore alkyl halides have an electrophilic carbon attached to the halogen.
2. Halogens below fluorine are larger than carbon, therefore the bond between carbon and the halogen is extremely long, recall that bond strength decreases as bond length increases. Recall that electrophiles have weak bonds that can break, in this case it is the carbon halogen bond, or C-X bond that is the bond that breaks.

In all of the reactions in this chapter, the halogens are the ones who break off of the carbon chain and leave. The reason that this can happen can also be explained through leaving group strength, and this has a fairly reasonable trend that ties in with acid-base chemistry from chapter 2. Halogens are good leaving groups, meaning that when they leave, they are stable and don't react with anything. Can we make sense of this? Well, I don't think I would be asking that question if we couldn't. *Leaving group strength is inversely proportional to basicity*. In other words, *the stronger the base the worse the leaving group*. This should make sense, because if you are a weak base, then you are stable and unwilling to react with acids and therefore are happy the way you are, i.e. you won't object to leaving a carbon to form. If we are to compare the halogens and their halide basicity's, then the order that we would get is:

$I^- < Br^- < Cl^- < F^-$, and this is exactly the opposite order of the leaving group strength:

$I^- > Br^- > Cl^- > F^-$. This shows the direct relationship between basicity and leaving group strength and helps explain why the two reasons I gave above are important. I cannot stress this enough, you MUST understand leaving group strength for the rest of the course, it is imperative that you understand this NOW rather than later. This will build upon itself in this chapter, the next chapter, and every chapter after that. This trend should make more sense, if the group that you kick off is happy being negatively charged, then it should be easier to kick off, there is less resistance! Iodide is way more stable than fluoride because the charge density is much lower for iodide, they are both negatively charged and have a charge of -1, but that charge is distributed over a larger area for iodide, therefore that ion minimizes charge better and is therefore more stable (A**M**SOW).

There are four different types of reactions that we will cover in this chapter:

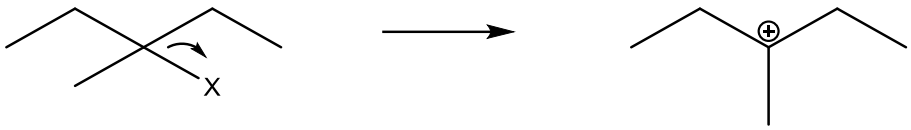
SN_1

SN_2

E_1

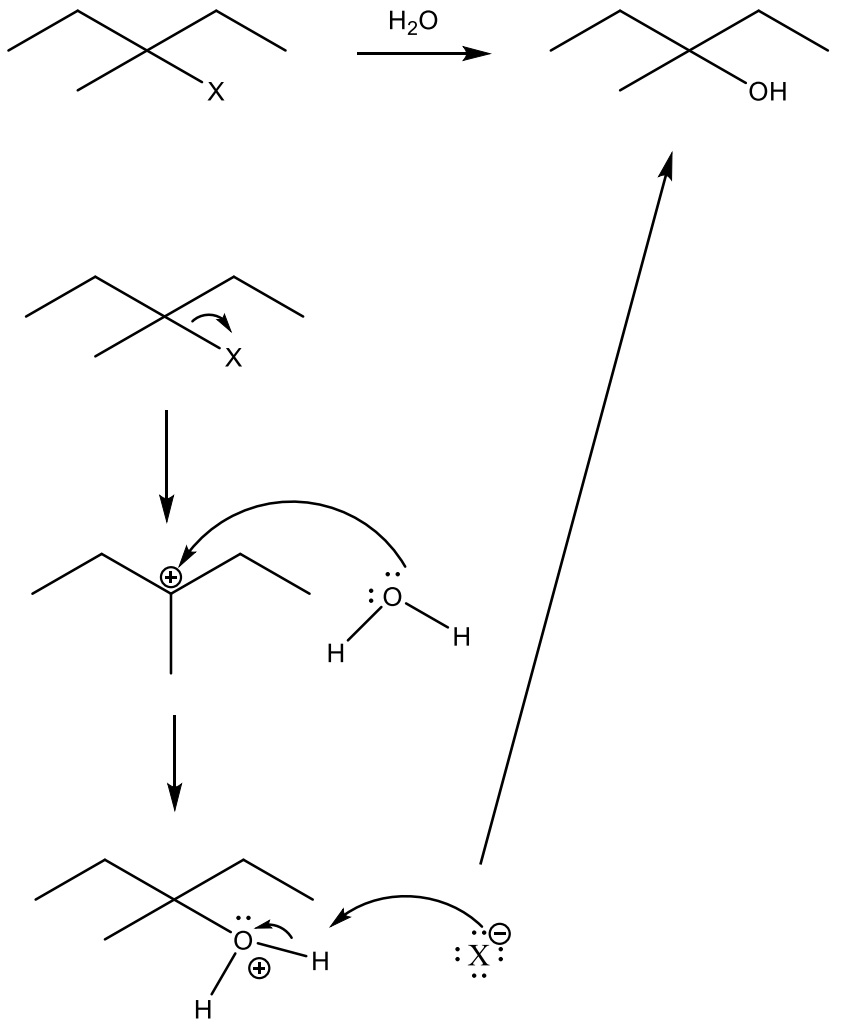
E_2

The 1's (SN_1 and E_1) go through carbocation intermediates, the first step in both of these mechanisms is the halogen leaves spontaneously:



The 2's (SN_2 and E_2) occur in a single step, they are *concerted* reactions, just like the Diels Alder reaction from the previous chapter. These reactions are also more stereospecific, making them more useful synthetically and are generally preferred over the 1's if possible.

Because the 1's go through a carbocation, they prefer to have more substituted alkyl halides. That should make some sense, the more substituted the alkyl halide, the more stable the carbocation is. Remember, CARBOCATIONS ARE HELLA UNSTABLE! Just like in the alkene, alkyne, and conjugated diene reactions, carbocations here can also rearranged, which makes them very difficult to control. Carbocations will ALWAYS rearrange to become more stable if they can, so you MUST check for possible hydride or methyl shifts and possible resonance forms if it is an allylic carbocation. For an SN1 reaction, you are replacing or SUBSTITUTING (hence the S in SN_1) the halogen for the NUCLEOPHILE (hence the N in SN_1). For example:



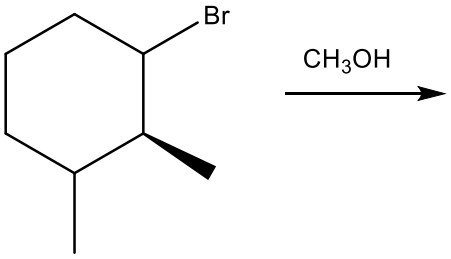
This reaction mechanism should look very similar to you, this is essentially the exact same reaction as dilute HX reaction with an alkene! If you don't believe me check out the chapter on alkene reactions again, it is almost the *exact same*. The chemical logic is very similar for the second and third steps as the alkene reaction, so I will only discuss the chemical logic for the first step. The first step is that the halogen leaves, this can happen because the C-X bond is extremely weak like we had previously discussed, that allows the carbocation to form. *This doesn't always happen, and it is very rare, so SN_1 reactions are limited by the extent to which the carbocation forms.* So if you are scratching your head asking yourself "I thought that we wanted to minimize charge and carbocations are hella unstable like you just mentioned, why is this happening?" The reason why these reactions are generally very slow and not preferable is because carbocations *are* unstable, therefore the *rate-limiting step* is the *formation of the carbocation*. Now we can discuss where the heck the 1 comes from in SN_1. Because the rate-limiting step involves the alkyl halide losing the halogen and nothing more, the rate law is *unimolecular*,

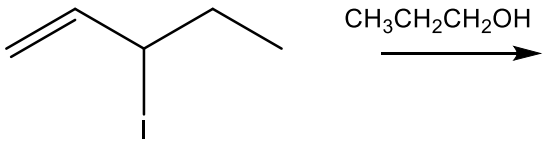
$$rate_{SN1} = k[AH]$$

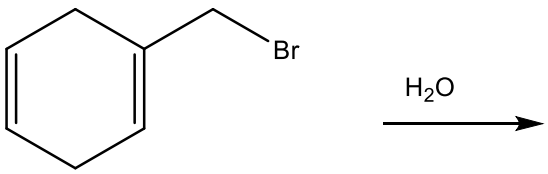
The rate is only related to the concentration of alkyl halide. This should make some sense, if there is more alkyl halide, there will inevitably be more carbocations forming and therefore the observed rate will be larger since that is the rate-limiting step. The other aspect of carbocations that is important when discussing the 1's is that carbocations are *planar*, meaning that the nucleophile can approach from the top OR the bottom. There is NO preference. Because of this, SN1 reactions are said to cause *racemization*, or to make equal parts of both enantiomers. But obviously, this is only relevant if the carbon to which you are adding your nucleophile is asymmetric or chiral. In the reaction I showed above, that was not the case because the carbon that the OH attached to had two ethyl groups on either side.

Practice questions:

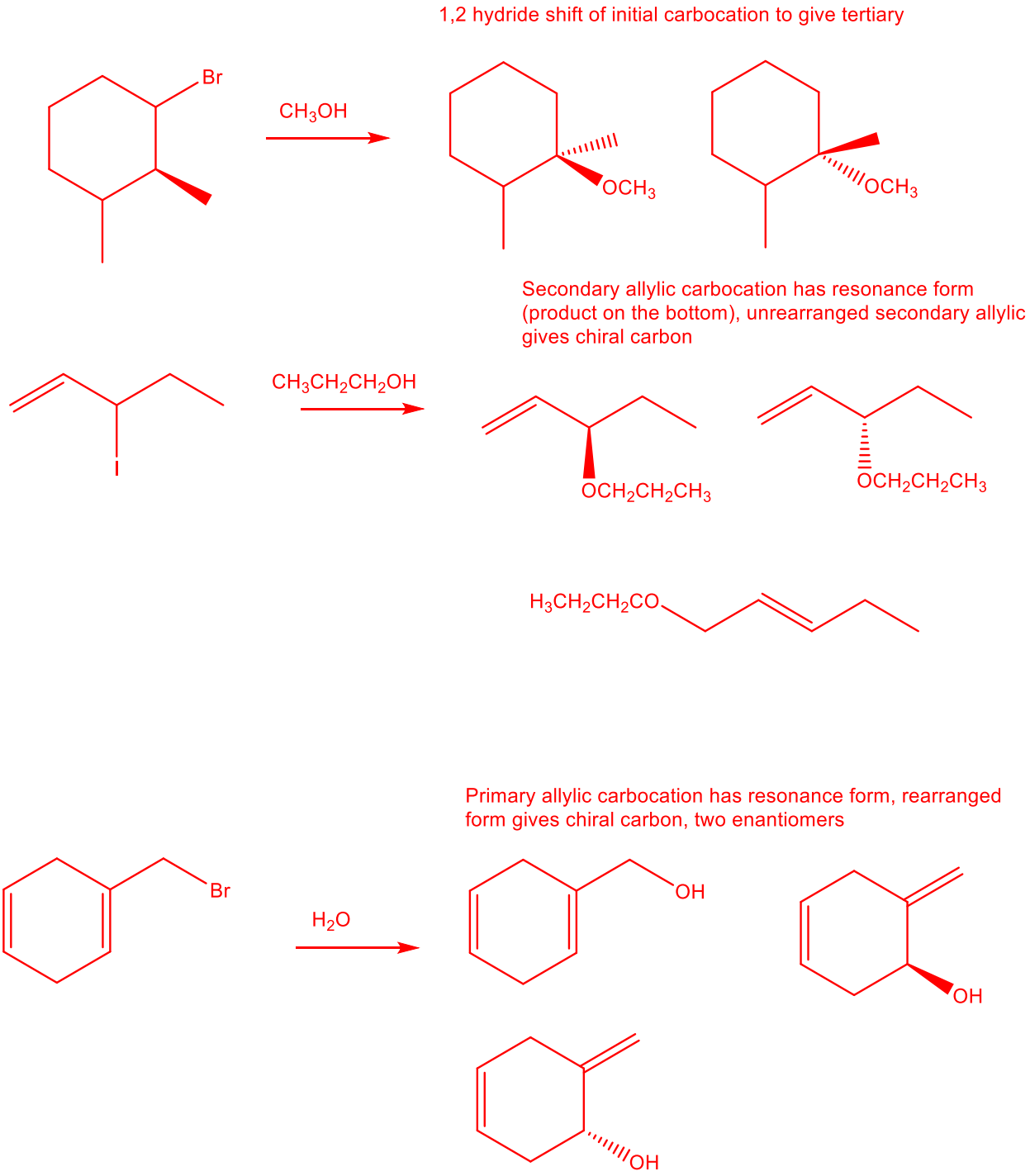
Predict the products of the following SN1 reactions:



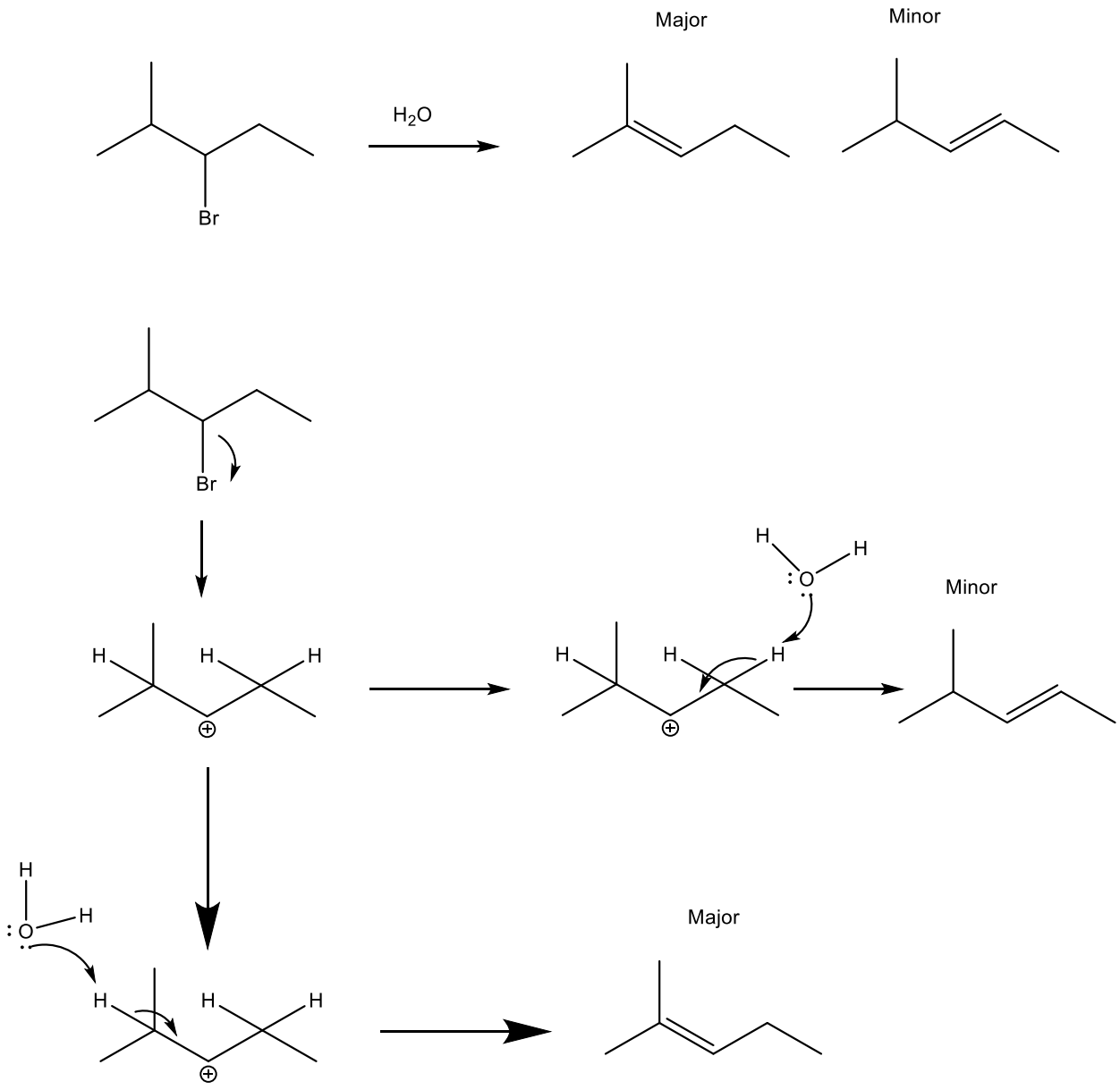




Answers:



That was all for the SN_1 reaction, but what about the E_1 reaction? The E_1 reaction starts the exact same as the SN_1 reaction with the halogen coming off and forming the carbocation, except instead of substituting the halogen with a nucleophile, you create a new *pi bond*. Let's see how that works with an example:

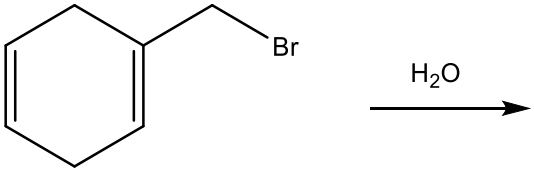


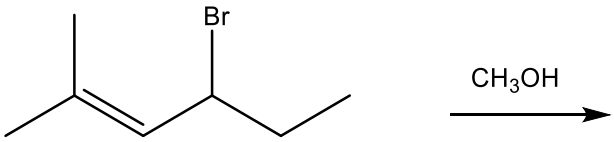
The first step, like before is the formation of the carbocation, and like the SN_1 reaction, this is also the rate-limiting step for the E_1 reaction, therefore the rate law for the E_1 reaction is the same as that for the SN_1 reaction. The second step is unlike anything that we have done before and therefore it is worth discussing the chemical logic. Once the carbocation is formed and we are doing an E_1 reaction, we have to look for neighboring protons, that is why I showed the protons on the carbon to the left and the ones on the carbon to the right of the carbocation. To relieve the positive charge on the carbon, we are going to use the solvent as a *base* and pluck off a neighboring proton. When the solvent, in this case water, acts as a base and attacks one of the neighboring protons, that allows those electrons to form a pi bond between the neighboring carbon and the carbocation. This gives the carbocation the extra bond it needs to become octet

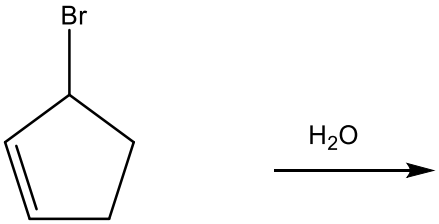
satisfied and have four bonds. This minimizes the charge on the carbon and makes it neutral and octet satisfied, rather than positive and not octet satisfied (A**M**SOW). There are two products that we can have here because each of the neighboring carbons have protons on them, to determine which one is more likely to give away its proton to the solvent, we have to look at the alkene that forms in each case. If we take the proton to the left of the carbocation, we generate a more stable alkene. The alkene is more stable because substituents = stability. This alkene product is referred to as the Zaitsev product and is the major product in 99% of cases. The exception to this rule will be discussed when the time arises. For now, know that the reaction will prefer to make the more substituted alkene because that is the more stable alkene. This should make some sense, both protons on the neighboring carbons are equally as acidic, they are both sp^3 hybridized carbons, they match each other in every other way, therefore, the only difference between the two of them is the stability of their alkene product. If we are going to commit ourselves to taking off a proton and making an alkene, we may as well make the more stable alkene, we want to minimize our energy (A**M**SOW). Like SN_1 and all other reactions with carbocations, *you must be vigilant to look for rearrangements and resonance forms.*

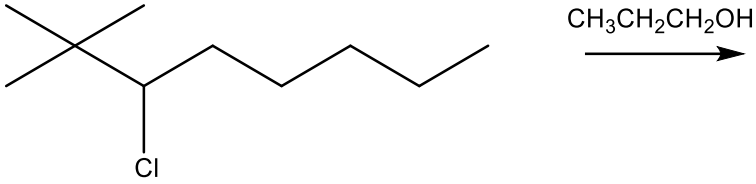
Practice questions:

Predict the products for the following E_1 reactions:

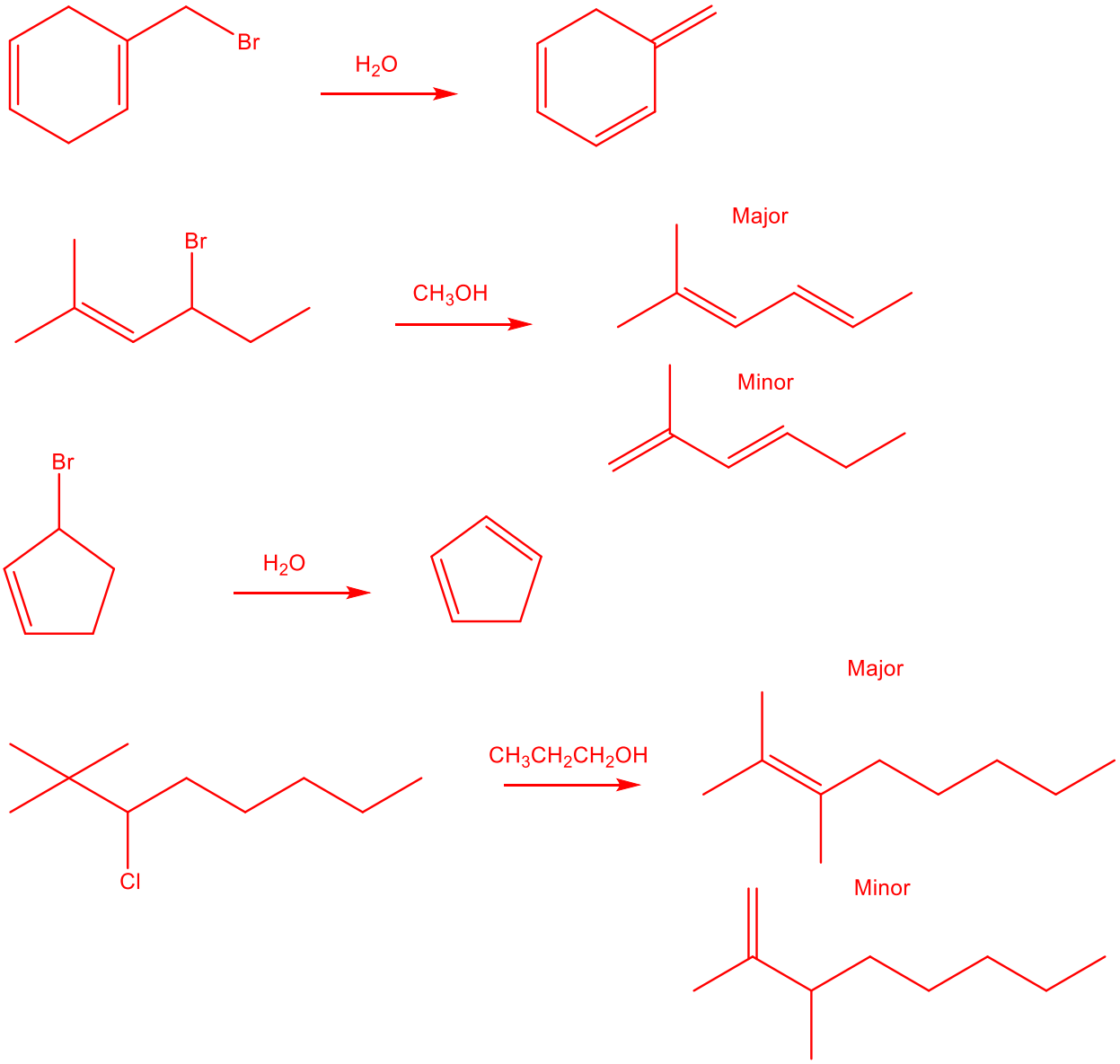








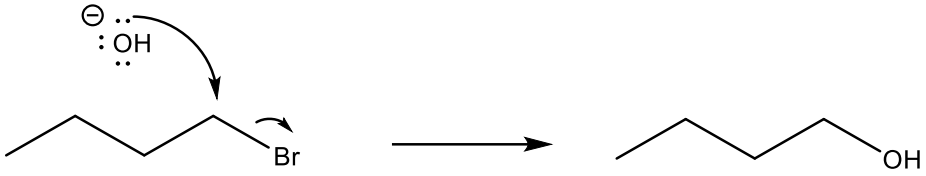
Answer:



Broadly, SN_1 has the solvent act as a *nucleophile*, while E_1 has the solvent act as a *base*. But what is the difference between a nucleophile and a base? Not much, a base is a chemical that attacks a *hydrogen* and a nucleophile is a chemical that attacks *any electron-deficient atom*. In the context of these reactions, if the solvent is big and bulky, that will prefer elimination over substitution. This should be relatively obvious, the nucleophile has to attack a very specific portion of the molecule and actually be able to get there, if the nucleophile is too sterically hindered, then it can't get into the nooks and crannies and attack the electrophile, instead it will take off an adjacent proton because that is much easier to accomplish. You can kind of think of it like putting a wide key (sterically hindered nucleophile) in a narrow keyhole (carbocation), you won't be able to get it into the keyhole effectively, but you will hit the door on the left and right side (adjacent protons). Because of that, *large and sterically hindered nucleophiles will preferentially act as bases*. Something else that you may have noticed with regards to SN_1 and E_1 reactions is that they occur in our ROH and HOH type solvents and nothing else, this is because

polar protic solvents are very good at stabilizing charge through hydrogen bonding interactions. This allows the carbocation to form, like we said before, carbocations are inherently unstable, so we need all the stabilization as possible to help cushion the carbocation and minimize its positive charge with solvent-carbocation interactions (A**M**SOW). A polar protic solvent are those solvents that have an acidic hydrogen and are able to do hydrogen bonding, these are almost always our ROH and HOH type solvents. All other solvents are *polar aprotic*, so things like THF, acetone, DCM, DMSO, and DMF are all polar aprotic, they do not have acidic hydrogens and they cannot do hydrogen bonding, therefore these will not stabilize the carbocation as well and therefore not promote SN_1 or E_1 reactions. We will get back to solvent effects later when we discuss SN_2 and E_2 reactions because the nucleophilicity and basicity of anions are HEAVILY dependent on solvent effects.

The SN_2 reaction is one of the most versatile reactions available to you as an organic chemist, it can be used to replace a halogen or other leaving groups with a wide variety of nucleophiles. The SN_2 reaction is also stereospecific in that it causes complete stereochemical inversion. Before we get into the practical applications of this reaction, however, let's first discuss the theoretical mechanism for how this reaction operates with an example:



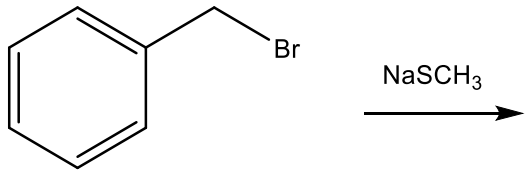
In the SN_2 mechanism, the nucleophile attacks AND the halogen leave in the SAME step, therefore BOTH concentrations are in its rate law:

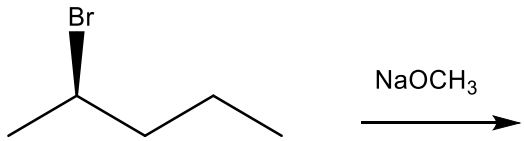
$$rate_{SN2} = k[AH][Nu]$$

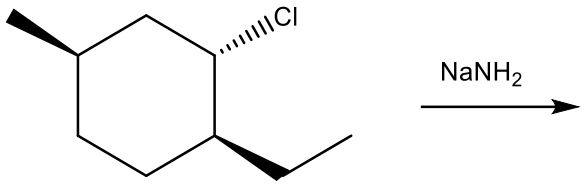
This reaction is concerted, meaning it happens all in one step. Something important to note about the SN_2 reaction is that it occurs through a backside attack, meaning that it attacks the alkyl halide from the opposite side that the halogen was facing. This means that the group that you are substituting for the halogen will always point in the opposite direction to what the halogen was pointing. This only comes into play of the carbon that you are attacking with the nucleophile is chiral, otherwise (like in the example above) you can just draw the bond normally. This mechanism is important to understand and can be rationalized through AMSOW. We know on a base level that the C-X bond is weak because of how long it is, recall bond strength is inversely proportional to bond length, therefore it is the C-X bond that will break during the course of the reaction (AMSO**W**). Because the nucleophile must approach from the backside, steric factors play a large role in determining if an SN_2 reaction will occur, the more substituted the alkyl halide, the less likely it is to go through an SN_2 reaction. SN_2 reactions will only occur on secondary, primary, or methyl halides. *Tertiary alkyl halides are too bulky for SN_2 reactions*.

Practice questions:

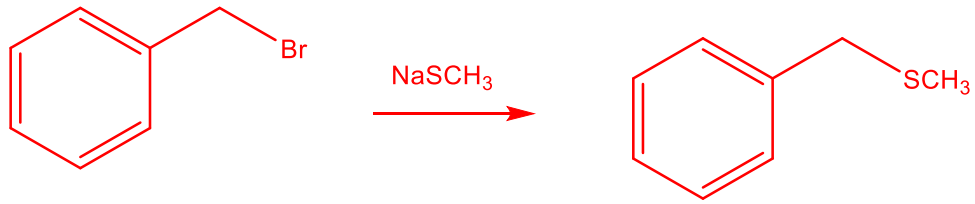
Predict the products for the following SN2 reactions:

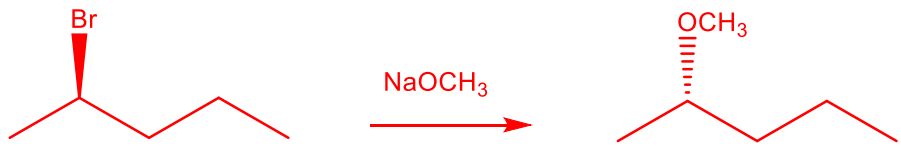


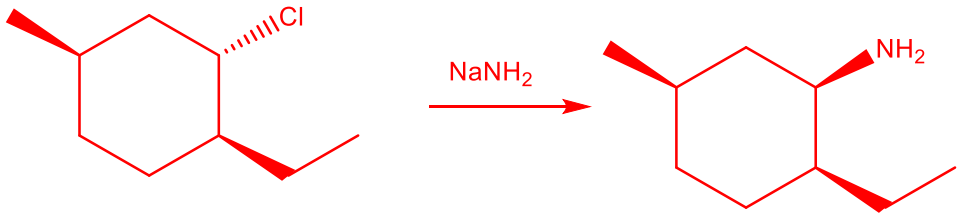




Answers:



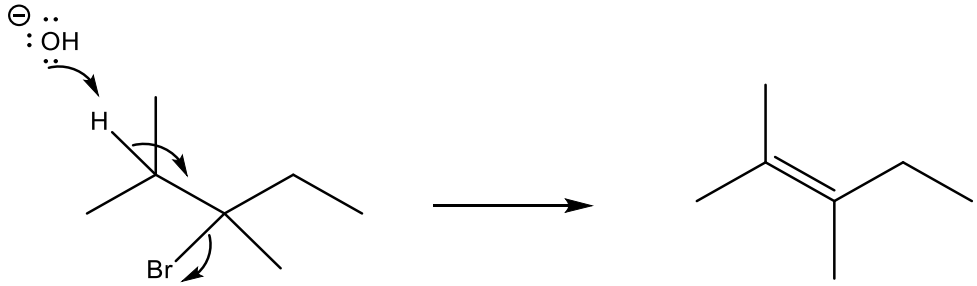




Something that we should notice immediately about SN_2 reactions is that they make use of negatively charged nucleophiles, rather than the neutral ones that we saw with SN_1. The reason for this is that *SN_2 reactions prefer negatively charged, strong nucleophiles*. SN_1 reactions are

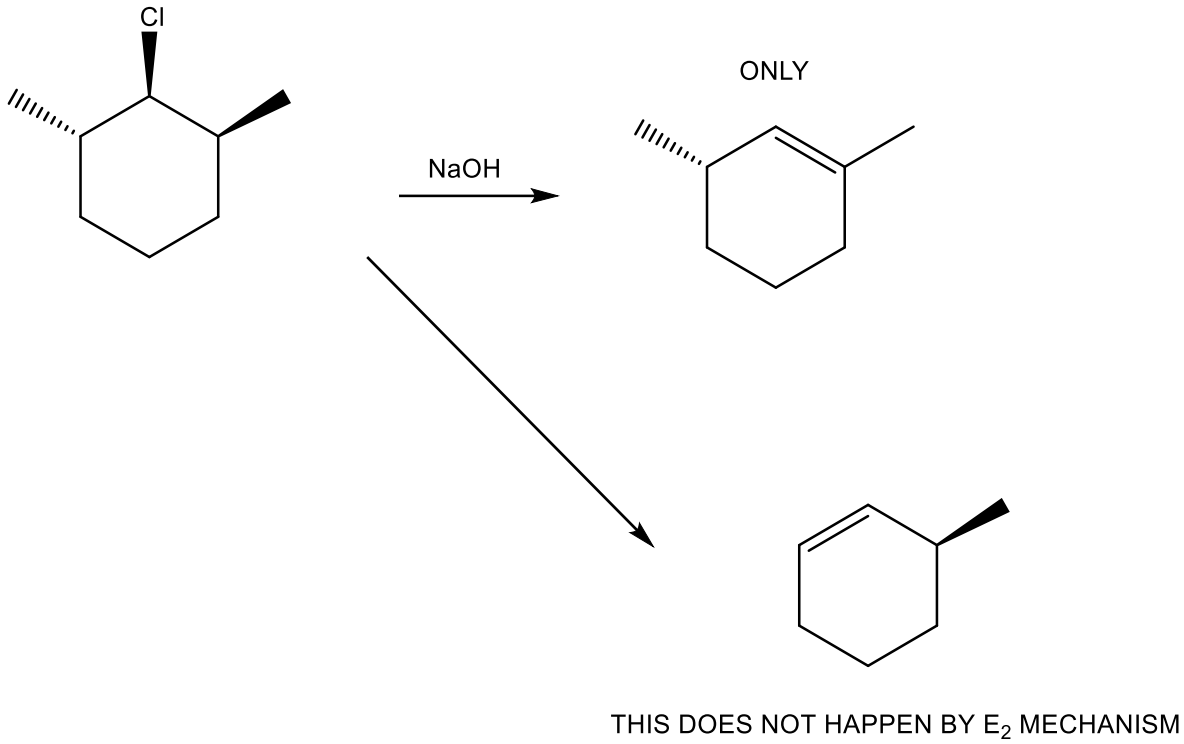
typically carried out when the solvent is the nucleophile, therefore it is also called a *solvolysis* reaction and does not necessarily need a strong nucleophile. *In short, SN_2 reactions prefer strong nucleophiles while SN_1 reactions prefer weak nucleophiles.* This preference can be rationalized by looking at the mechanism, in the SN_1 mechanism, the nucleophile could only attack and form the final product if there was a carbocation. Remember, carbocations are like EXTREME electrophiles, they are super duper electrophilic because carbon is positively charged AND is not octet satisfied. This makes it so that even poor nucleophiles like water and methanol can attack it so that we can minimize charge and minimize energy (A**M**SOW). That's why SN_1 reactions happen in 2 steps, you need the carbocation there before ANY substitution can occur. We need that electrophile, otherwise the alkyl halide is happy the way it is! In the SN_2 mechanism, everything happens in one step, so the nucleophile is essentially a wrecking ball. The nucleophile essentially says screw waiting, I want to attack NOW. But that can only happen if there is a strong enough desire for the nucleophile to minimize its charge and kick off the halogen (A**M**SOW). Its desire to attack something and minimize its charge is increased if it is negatively charged, attacking the alkyl halide would make it neutral which is inherently better than being charged (A**M**SOW). This desire to attack an alkyl halide and minimize its charge is amplified further if it is in a polar aprotic solvent. These solvents are worse at supporting charged ions and therefore will make the negatively charged nucleophiles MORE unstable. Therefore, these solvents will amplify the nucleophilicity of the anion by making it want to minimize its charge more and act as a nucleophile (A**M**SOW). Therefore in short, *SN_1 reactions prefer polar protic solvents while SN_2 reactions prefer polar aprotic solvents.*

The last reaction that we will cover in this chapter is the E_2 reaction. Like the SN_2 reaction, this too occurs in one step, and its rate law is exactly the same as the one for SN_2. Like the E_1 reaction, this reaction is used to make a pi bond between the carbon bearing the halogen and its neighbor. The mechanism for a typical E_2 reaction is as follows:

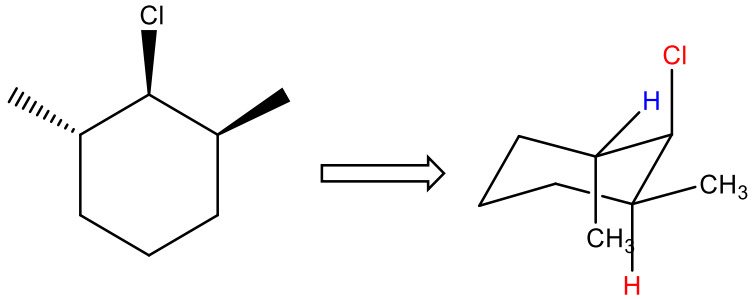


The E_2 reaction requires that the hydrogen and the halogen leaving group be at 180 degrees from each other. This requirement is otherwise known as being antiperiplanar, but let's be honest, who in the hell looks at that word and knows that it means that, so we won't really be using the term. I include it here solely so that if you read other textbooks or articles about this requirement, you know what they're saying and aren't totally confused. This requirement turns out to be essentially a nonissue for most cases for linear alkyl halides because they have free rotation about the C-C bonds, but it turns out to be a large deal for cyclohexanes because bulky groups like tert-butyl groups will prevent the ring from doing a ring flip and therefore prevent the

antiperiplanar relationship. For a cyclohexane ring to be able to go through an E_2 reaction, the halogen must be axial and there must be a neighboring axial hydrogen. For example:

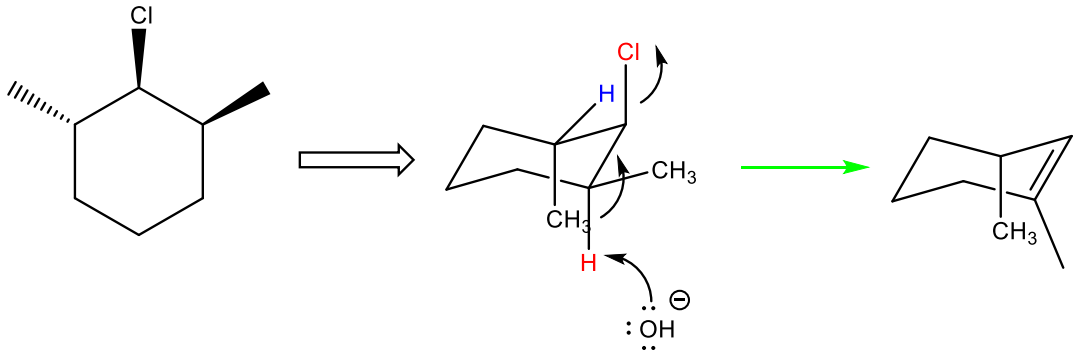


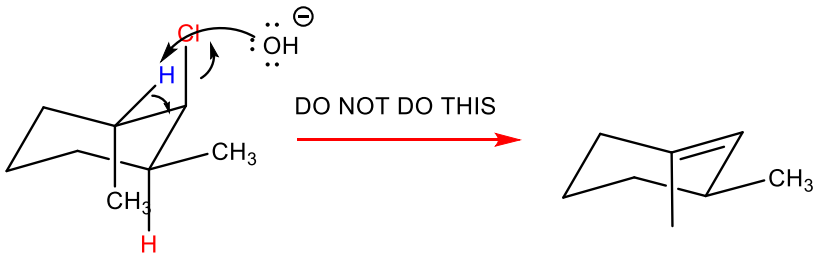
We can show that this is true by drawing the cyclohexane chair conformation:



We start by drawing our halogen on the top right carbon in the axial up position, then we draw all of our axial positions alternating between facing up and down. We know that one of the methyl groups is trans to the Cl, meaning that has to be axial down or equatorial down, because both of the methyl groups are adjacent to the halogen, the axial position on those carbons is axial down, therefore the trans methyl will be axial down. That means that the trans carbon will NOT have an antiperiplanar hydrogen. Instead, the hydrogen and the halogen would be at 90 degrees (blue hydrogen and red chlorine). The other methyl group is cis to the Cl, meaning that it CANNOT be on the axial position, otherwise that methyl would also be trans (the axial on that carbon faces down which is opposite of up). This allows the hydrogen on that carbon to me trans to the Cl and occupy the axial down position. This makes the red hydrogen and the red chlorine

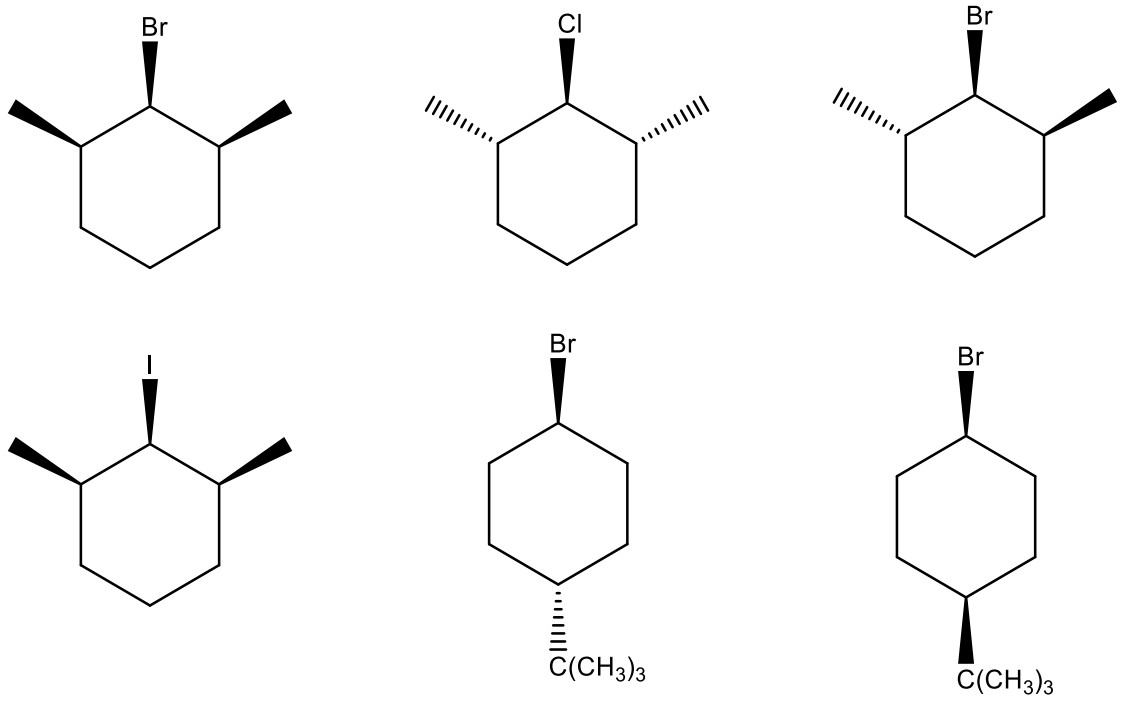
at the perfect angle for E_2 elimination (they are 180 degrees apart), therefore THAT is the hydrogen that gets taken in the E_2 reaction mechanism shown below:



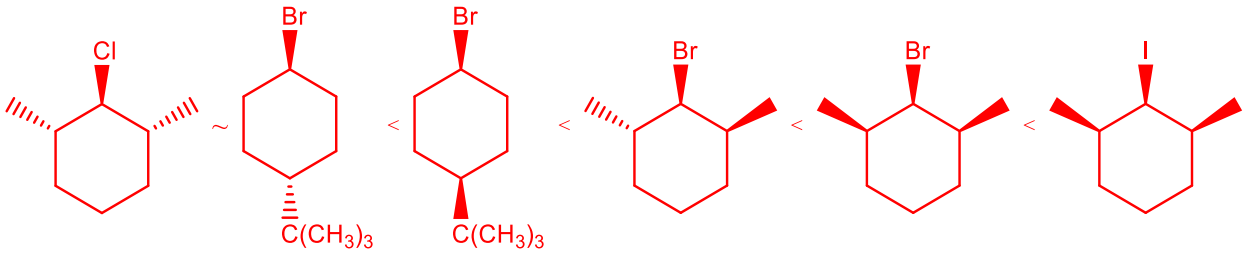


Practice questions:

Rank the following compounds with regard to reaction rate with NaOH:



Answer:



To answer any of the cyclohexane questions, you should always draw out the chair conformation and see if you have any antiperiplanar hydrogens (hydrogens that are 180 degrees from the leaving group). The tert-butyl group is forced to be equatorial because of how bulky it is, it CANNOT be axial because of 1,2-diaxial interactions (unfavorable steric interactions that were covered in chapter 4). E_2 prefers to have a strong base, that is why in all of our E_2 reactions we have used Na followed by some anion. Anions are stronger bases than neutral compounds!

Before, I said that the Zaitsev product was always the major product in 99% of circumstances, but what about the 1% that it isn't? There are two scenarios where this is the case:

1. There is a bad leaving group (F, NR_2, etc.)
2. You use a big bulky base

I know this is a lot of information, but I have consolidated this into a table:

Reaction type	Preferred alkyl halide	Preferred reactant	Preferred solvent	Preferred temperature	Stereochemistry/Preferred product	Special conditions
SN_1	More substituted	Weak nucleophile	ROH and HOH	Low/ RT	Racemic mixture	Carbocation rearrange
SN_2	Primary or methyl	Strong nucleophile	Polar aprotic	Low/ RT	Total inversion	None
E_1	More substituted	Weak base	ROH and HOH	High	Zaitsev (except for fluoroalkanes and bulky bases)	Carbocation rearrange
E_2	More substituted	Strong base	ROH and HOH	High	Zaitsev (except for fluoroalkanes and bulky bases)	Anti-periplanar H

Before you just take the table at face value, let's go through each preference in turn and explain why it is what it is. Both SN_1 and E_1 go through carbocations, therefore we want the most stable carbocation we can get, which would happen with more substituted alkyl halide. Substituents =

stability. SN_2 reactions occur through a backside attack, so the nucleophile has to get through all the steric garbage before it can attack the electrophilic alkyl halide carbon, therefore it prefers less sterically hindered substrates (primary or methyl). E_2 reactions form alkenes, the more stable alkenes will form faster, therefore E_2 reactions will prefer more substituted alkyl halides since these generally give more stable alkenes. Substituents = stability coming in again. Now that we understand the alkyl halide preference, let's discuss the solvent preference. Both SN_1 and E_1 go through carbocations, therefore, they will prefer the solvents that will stabilize that positive charge the most (A**M**SOW) which are the polar protic solvents (HOH and HOR type solvents). SN_2 does not go through a carbocation and prefers the nucleophile be as reactive as possible, therefore the solvent should not interact with the nucleophiles through hydrogen bonding, which would otherwise get in their way of attacking the electrophilic alkyl halide, it therefore would prefer polar aprotic solvents. E_2 reactions are always competing with SN_2 reactions because typically they use the same anions (OH^-, OCH_3^-, etc.), because SN_2 prefers polar aprotic for the reasons we just discussed, E_2 prefers polar protic solvents to prevent competing substitution.

Now that we have addressed the solvent effects, let's now discuss the preferred reactant. Both SN type reactions (SN_1 and SN_2) require that the reactant act like a nucleophile. The SN_1 reaction goes through a carbocation and therefore does not need a strong nucleophile to attack such an electrophilic species. If there is a strong enough nucleophile it would rather avoid making the carbocation (A**M**SOW) and would instead do SN_2 to avoid such an unstable intermediate. Therefore, to promote SN_1 reactions, we would want a weak nucleophile so that we HAVE to go through a carbocation to get a reaction to occur. SN_2 reactions have the wrecking ball that doesn't give a poop about carbocations and therefore they will react without going through that horribly unstable intermediate, hence they are promoted by strong nucleophiles. Both of the E reactions require that the reactant act as a base and take off one of their neighboring hydrogens. The same logic for why weak nucleophiles promote SN_1 can be given for E_1. We want to avoid carbocations at all costs, therefore, in order to force carbocations forming, we want to have as weak a base as possible so that that is our only recourse. E_2 reactions are generally preferred because they do not go through carbocations, therefore if there is a strong base it will always go through an E_2 over an E_1 (A**M**SOW).

The temperature preference has to do with attractive intermolecular forces. If you recall from general chemistry, gases behave most ideally under situations of high temperature, in these circumstances the attractive forces are minimized and the molecules can act on their own accord without reference to each other. As temperature is lowered, the attractive forces become more and more important and behavior deviates from ideal. This same logic can be used to explain the temperature preferences for SN and E reactions. SN reactions require that the reactant act as a nucleophile, but what guides the nucleophile to the electrophile? Opposite charges attract (AMS**O**W), therefore, to maximize the probability that the nucleophile finds the electrophile, the temperature needs to be lower or at room temperature so that the attractive forces allow the nucleophile to find the electrophile in the sea of solvent. Elimination reactions on the other hand are always competing with SN reactions, therefore, to minimize the impact these attractive forces have on the nucleophile and electrophile, the temperature should be raised to prevent the nucleophile from finding the electrophile and thereby being forced to act as a base. From a sheer

statistical sense, it is more likely that any given anion would act as a base than a nucleophile at high temperature because there are simply more neighboring hydrogens than there is electrophilic alkyl halide carbons. At a minimum the number is the same (in the case of only one neighboring proton), therefore higher temperatures favor elimination. These higher temperatures dissuade substitution and makes it so that the reaction is guided primarily by probability of proximity.

The stereochemistry for SN_1 reactions comes about because of its carbocation intermediate. Carbocations are planar, therefore the nucleophile could approach either from the top or from the bottom to produce two different enantiomers. Because these approaches are energetically equivalent, there is no preference for one versus the other, therefore, the SN_1 reaction causes racemization of your product. SN_2 reactions on the other hand, HAVE to go through a backside attack because the halogen leaves at the same time the nucleophile attacks. This forces the chirality to become inverted on that carbon, the SN_2 reactions cause complete inversion of configuration. Both E_1 and E_2 reactions prefer to have the Zaitsev product, or the most substituted alkene product, because this alkene is the most stable thermodynamically.

Before we finish up our discussion in substitution and elimination reactions, I would like to discuss the effects the solvent has on nucleophilicity. In a polar aprotic solvent, like DMSO for instance, the nucleophilicity is exactly the same as the basicity. In a polar protic solvent, like water, the nucleophilicity is also increased by how large the atom bearing the negative charge is. It increases going down the group. This can be rationalized because in a polar protic solvent, there are a lot more strong intermolecular forces that can screw up nucleophiles and prevent them from attacking their electrophiles. The bigger you are, the harder it is for effective solvation, so the greater the nucleophilicity is. Another way to put it is this, if you are playing a game of darts, would you rather have a microscopic dart to hit the bulls eye, or a dart the size of the gameboard itself (obviously the latter). However, because the size of atoms within the same row is more or less the same, the trend going from left to right is the same as it is in DMSO, namely that the nucleophilicity of the substance and the basicity are one and the same.

Practice question:

Rank the following in order of increasing nucleophilicity in DMSO:

A	B	C	D	E
CF_3COONa	CH_3COONa	$NaSCH_3$	$NaOCH_3$	H_2O

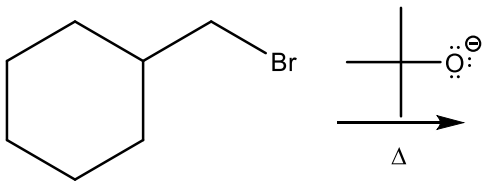
Answer:

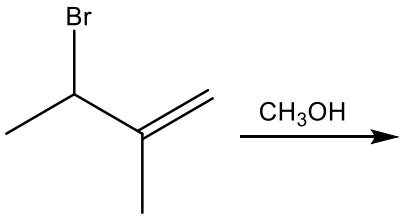
Remember, nucleophilicity in DMSO is the same as basicity, so really this question is asking you to rank basicity:

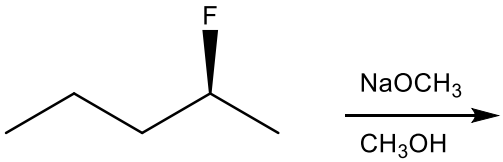
E < A < B < C < D

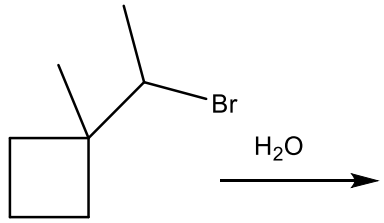
Finally, I wouldn't be a good orgo teacher if I didn't give a bunch of practice problems where I DON'T give you the exact reaction you need to do. Try these next few problems, they will likely be similar to ones you would see on your exams. Make sure you look at all possible angles and consider everything that you have learned so far.

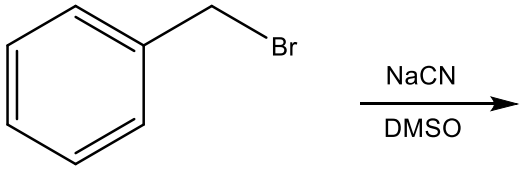
Predict the major products for the following reactions, be sure to include stereochemistry for all the products given:

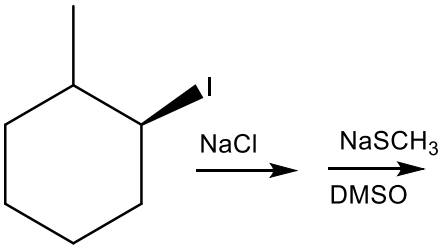

Br
O
Δ

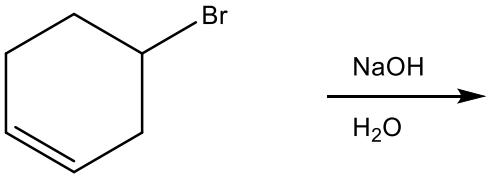

Br
CH3OH

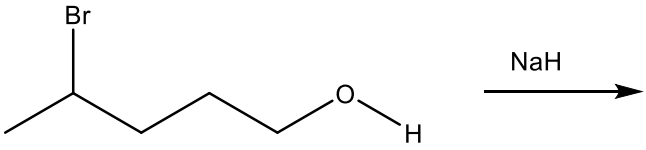

F
NaOCH3
CH3OH

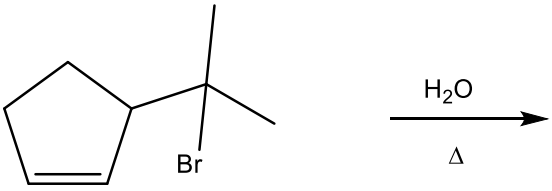

Br
H2O

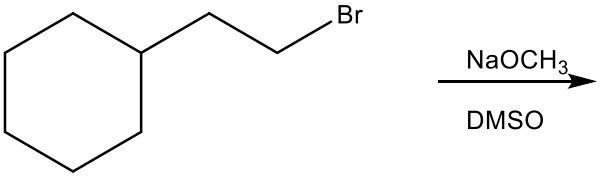

Br
NaCN
DMSO


I
NaCl
NaSCH3
DMSO

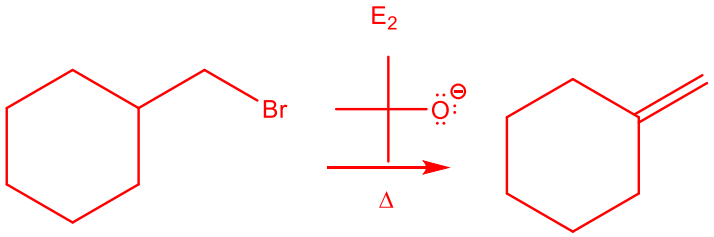

Br
NaOH
H2O

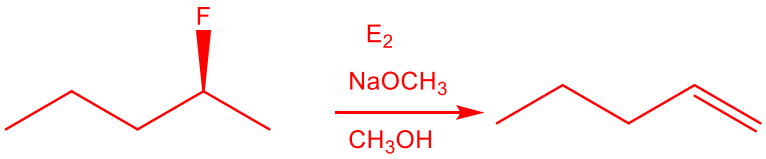

Br
O
H
NaH

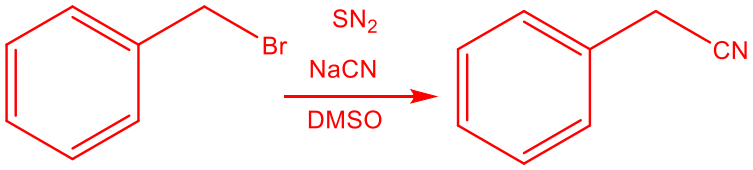

Br
H2O
Δ

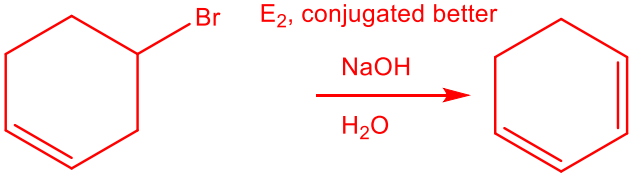

Br
NaOCH3
DMSO

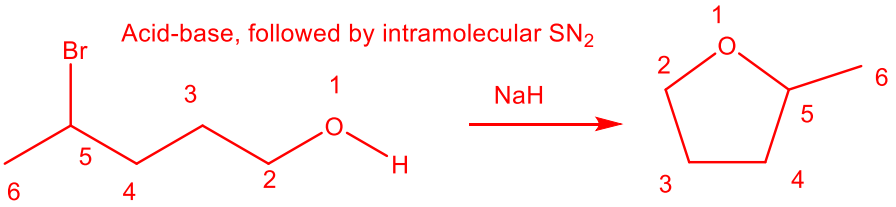
Answer:

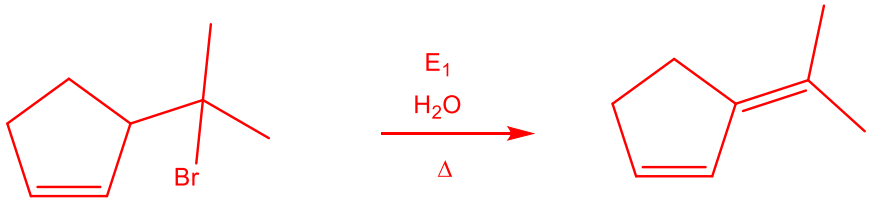

E2
Br
O
Δ

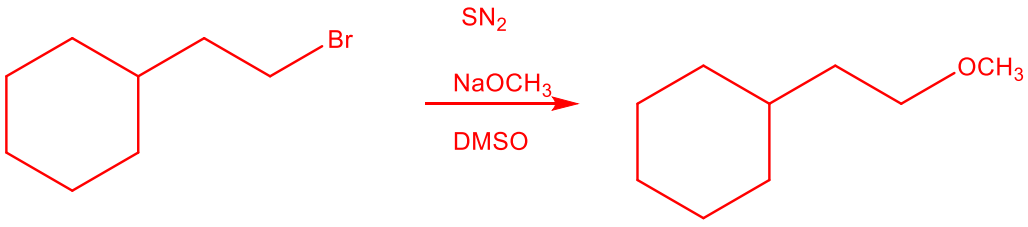

F
E2
NaOCH3
CH3OH

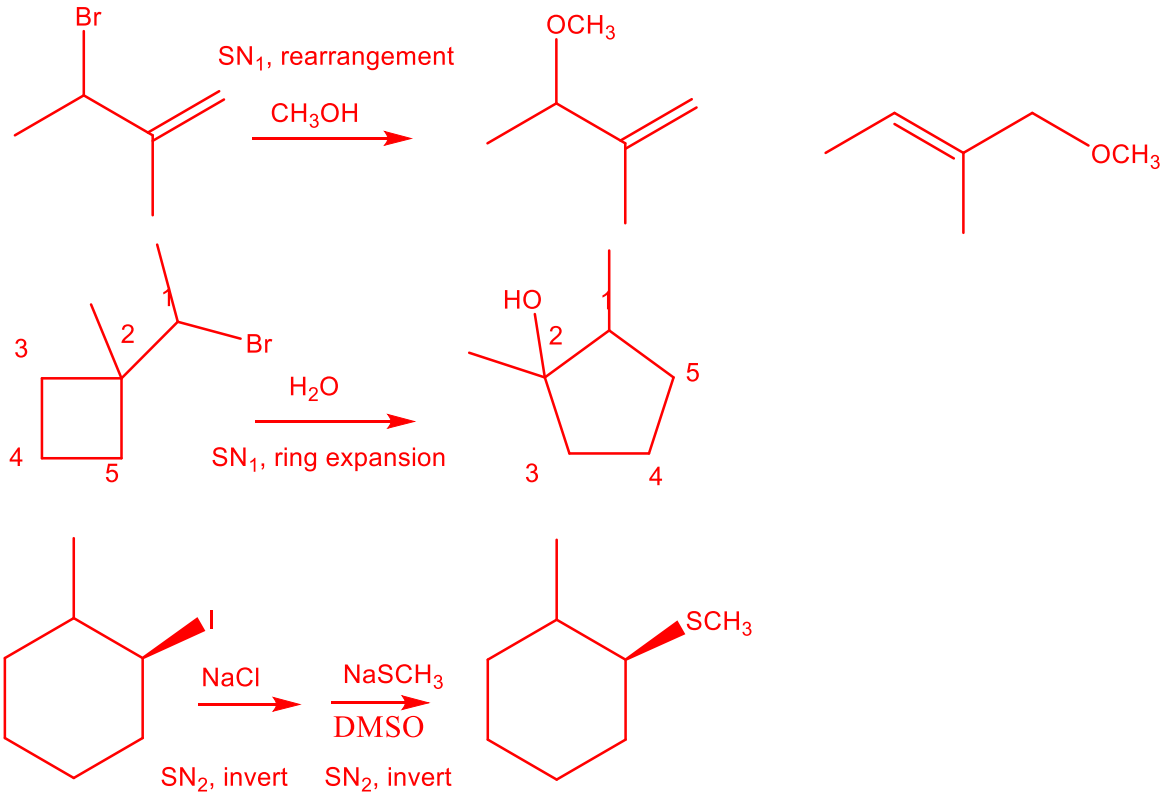

Br
SN2
NaCN
DMSO
CN


Br
E2, conjugated better
NaOH
H2O


Acid-base, followed by intramolecular SN2
Br
1
2
3
4
5
6
O
H
NaH
O
1
2
3
4
5
6


Br
E1
H2O
Δ


Br
SN2
NaOCH3
DMSO
OCH3

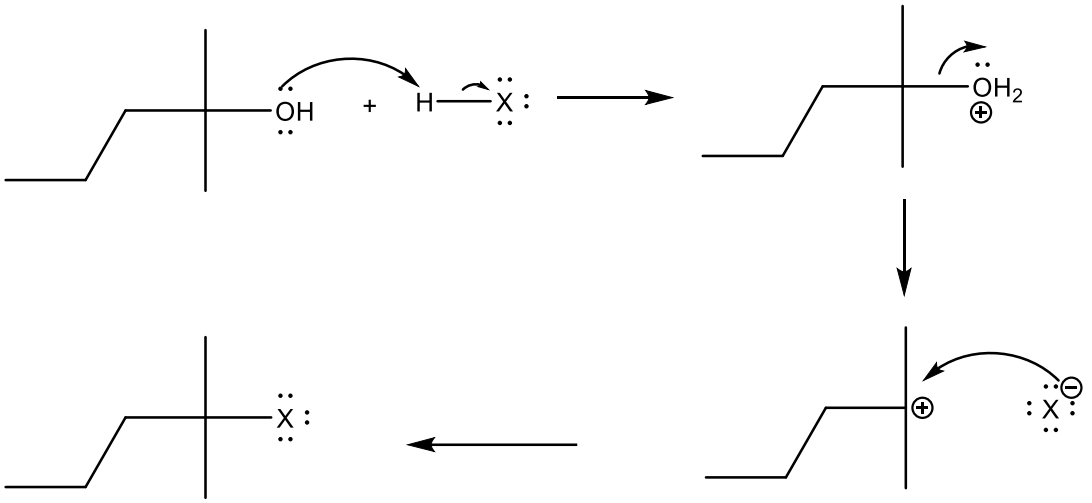

Br
SN1, rearrangement
CH3OH
OCH3
OCH3
1
2
3
4
5
Br
H2O
SN1, ring expansion
HO
1
2
3
4
5
I
NaCl
SN2, invert
NaSCH3
DMSO
SN2, invert
SCH3

Chapter 9: Using Alcohols in Synthesis

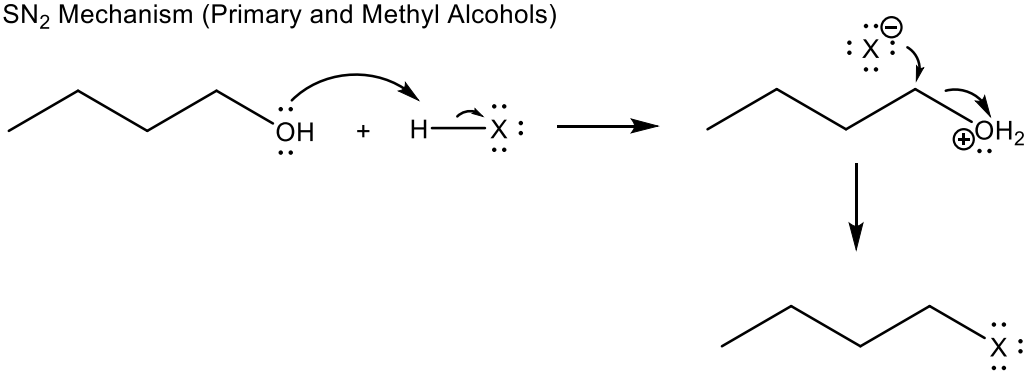
Until this point, you have only known how to make alcohols, but not why they are useful. In this chapter we will be discussing the functionality of alcohols and how we can activate the alcohol group to make useful things that we can then use SN_1, SN_2, E_1, and E_2 reactions with. First we need to discuss why alcohols by themselves are not super useful synthetically. To answer this question, we need to look at the leaving group strength of the OH group. Should the OH group leave, it would be OH^-, which is a strong base. *Because the leaving group is a strong base, it is a bad leaving group*. There are a few ways that this can be resolved, one of these is through protonation. By protonating the alcohol, the leaving group goes from OH^-, which is a strong base, to H_2O, which is not very basic at all. Because of this, acids can catalyze reactions where the OH group must leave.

One such example of this would be the halogenation reaction of alcohols. In these reactions, you would react a strong acid with alcohol. Typically these would be acids such as HCl, HBr, and HI. The mechanism by which a Cl, Br, and I are substituted depends upon the type of alcohol that we are dealing with. Methyl and primary alcohols proceed through an SN_2 type mechanism, while all other alcohols proceed through an SN_1 type mechanism. These are shown below:

SN_1 Mechanism (Tertiary and Secondary alcohols)



SN_2 Mechanism (Primary and Methyl Alcohols)

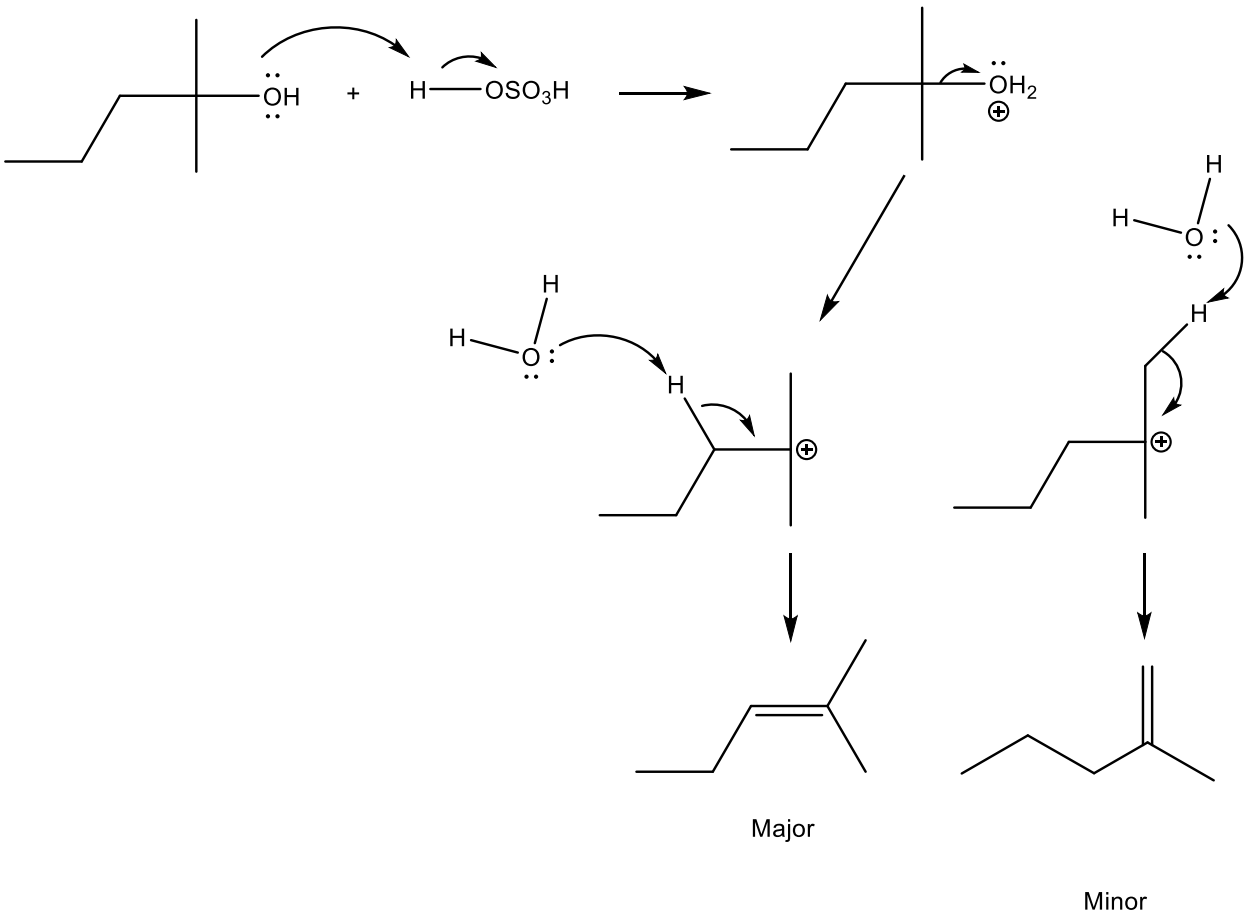


This preference for mechanism should come to no surprise. SN_1 reactions go through a carbocation and therefore would prefer more substituted alcohols, SN_2 reactions proceed through a backside attack and therefore would prefer if the alcohol was less sterically congested. Let's go through the chemical logic behind this reaction so that we have a better understanding of what is going on here. Let's start with the SN_1 mechanism. HX is a strong acid, therefore it will protonate the relatively basic alcohol group because acids react with bases (**A**MSOW). This creates the water leaving group, and the oxygen is positively charged, this is inherently unstable because the oxygen would prefer to be neutral, so it leaves to become neutral (A**M**SOW). Water is also a much better leaving group than the alcohol group because water is a weaker base than hydroxide. The three carbons to which the carbocation is bonded stabilize it, this helps minimize its positive charge (A**M**SOW), and the halogen is negatively charged and therefore is attracted to the carbocation (AMS**O**W). The halogen is a nucleophile and will donate its lone pairs to the carbocation so that the carbon and the halogen become neutral (A**M**SOW). The SN_2 reaction starts with the alcohol getting protonated by the strong acid because the alcohol group is sufficiently basic to take away the strong acid's proton (**A**MSOW). This causes the leaving group to become water rather than hydroxide, therefore the nucleophilic halogen can come in

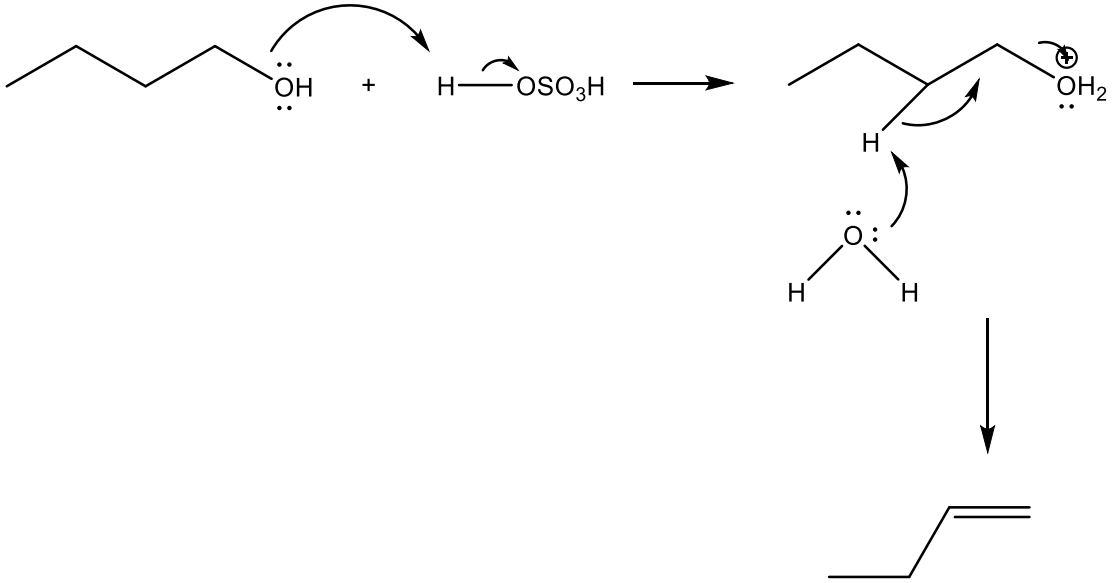
and attack the carbon that is bonded to the water. The carbon-water bond is extremely weak because the oxygen is positively charged, therefore to minimize the charge on oxygen and the halogen, the water group leaves and the alkyl halide forms (A**M**SOW).

Alcohols can also be used to make alkenes by using a non-nucleophilic strong acid such as sulfuric acid. This reaction is in equilibrium, however, because it is the opposite of the hydration of alkenes that we learned way back when. The mechanism is shown below, although this reaction is really awful and isn't of much use synthetically, like halogenation, dehydration also depends upon the type of alcohol reacting:

E1 Mechanism (Tertiary and Secondary alcohols)

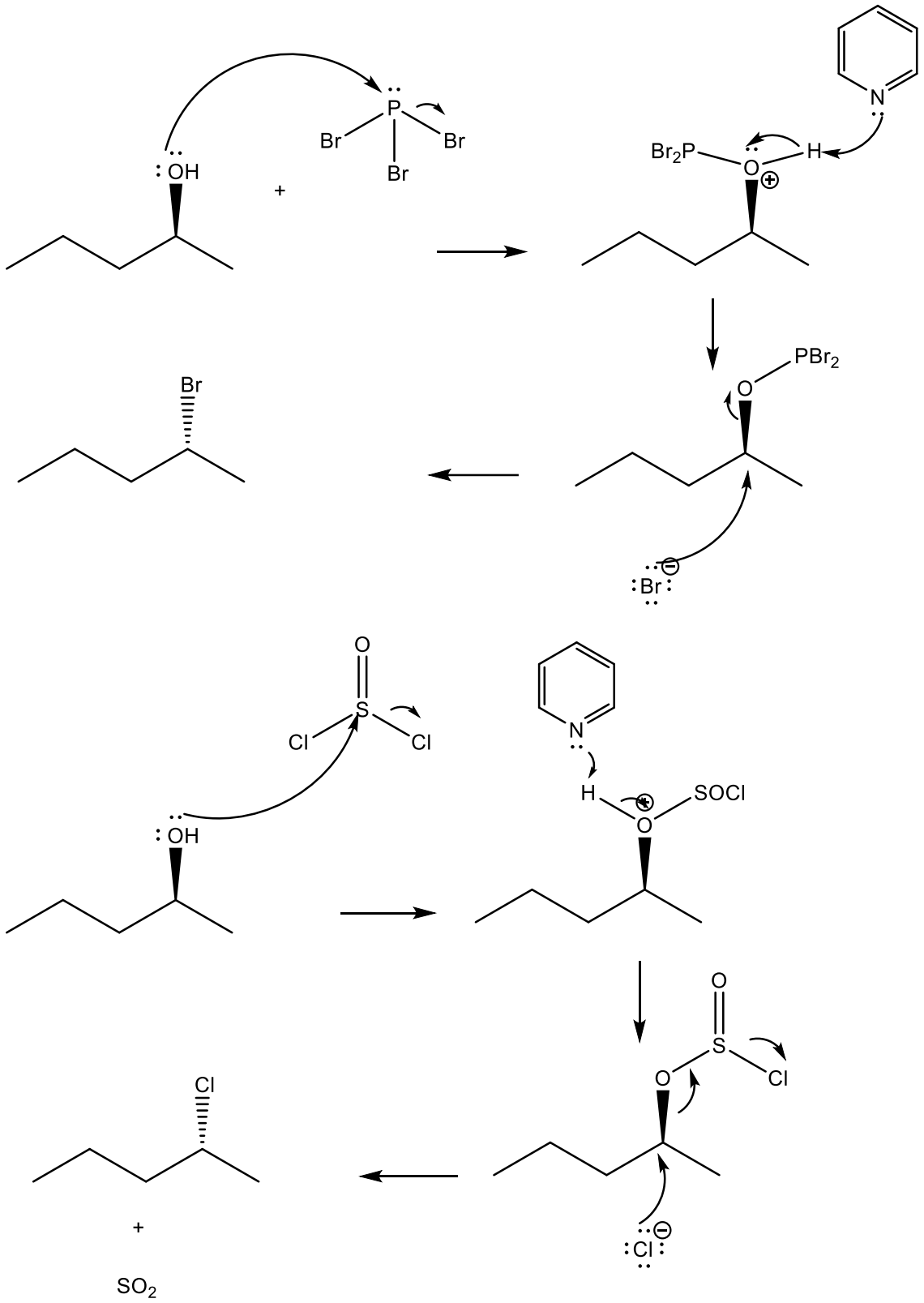


E2 Mechanism (Primary and Methyl Alcohols)

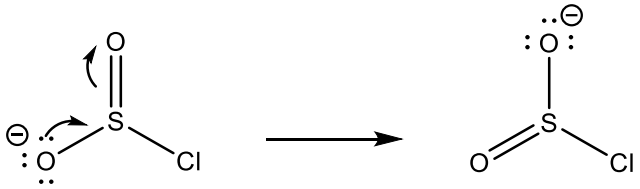


The Zatisev Rule still applies here because at the end of the day we are still going through an E_1 and/or E_2 reaction, so the major product will typically be the more substituted alkene because that is more stable. The mechanism for both of these reactions is essentially the exact same as previously discussed in the last chapter, so if you want a refresher on E_1 and E_2 reactions, you can go there. The first step is simply to increase the strength of the leaving group by protonating the alcohol, changing the leaving group from hydroxide to water.

We just discussed ways to activate the alcohol group to make it an alkyl halide, from there we can do the standard SN_1, SN_2, E_1, and E_2 reactions, but the method that we just described is typically low yielding and isn't great because of possible carbocation rearrangements. A way around that is by using a few specialty reagents that are designed specifically to make alkyl halides. To make alkyl chlorides, typically $SOCl_2$ is used and to make alkyl bromides, typically PBr_3 is used, both of these reactions are conducted in pyridine, a non-nucleophilic basic solvent. The mechanism for those reactions are shown below:

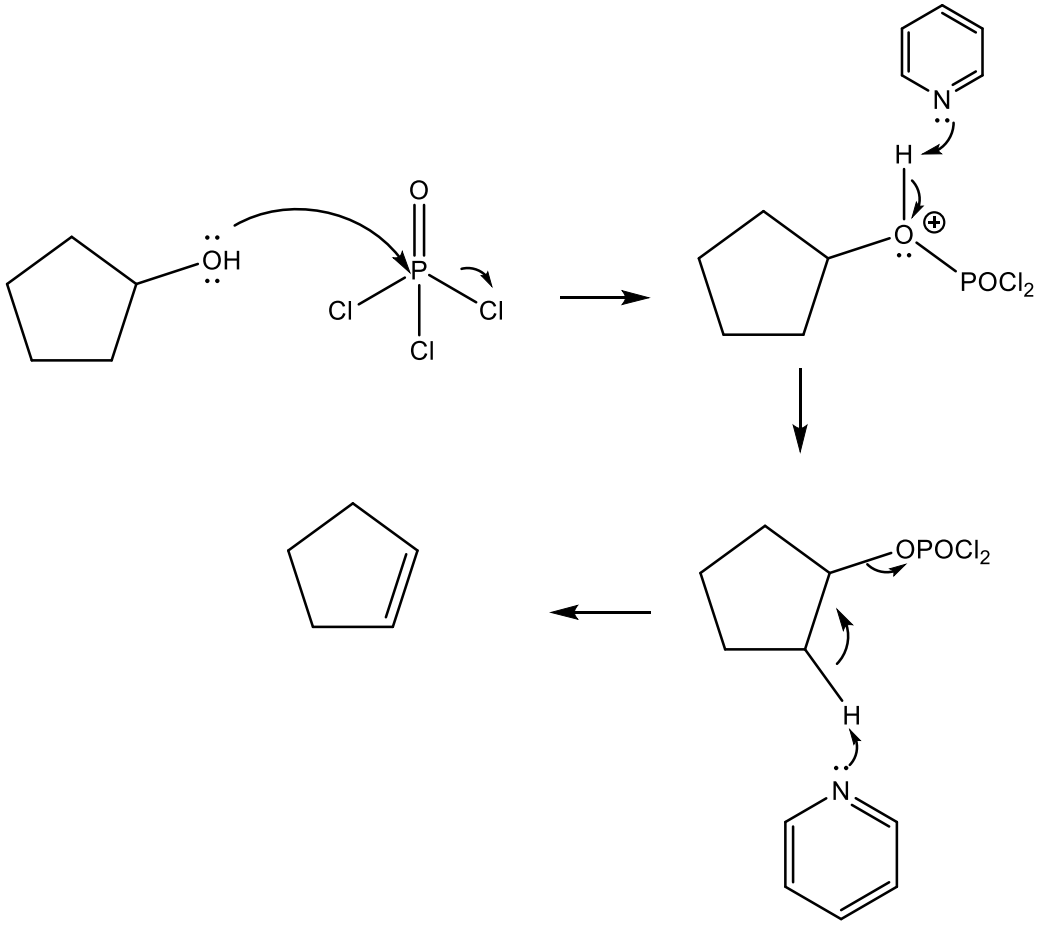

OH
P
Br
Br
Br
+
N
H
Br_2P
O
PBr_2
Br
:Br:
O
S
Cl
Cl
N
H
SOCl
O
OH
O
S
O
Cl
Cl
:Cl:
+
SO_2

Both the PBr_3 and $SOCl_2$ are good electrophiles because they have weak P-X and S-X bonds and because they are partially positive due to the electronegativity difference between P and Br and S and O and Cl. The mechanism for the above reactions are not super important to know. But what is important to know is that the reaction causes *inversion* of stereochemistry for the alcohol group because the last step is an SN2 reaction with the halide. Fundamentally, the leaving group strength is increased dramatically when the alcohol attacks both the PBr_3 and $SOCl_2$. This is because the basicity of the group is decreased, as opposed to a hydroxide leaving group, the leaving group becomes $OPBr_2^-$ and SO_2Cl^-. The SO_2Cl^- is resonance stabilized shown below:

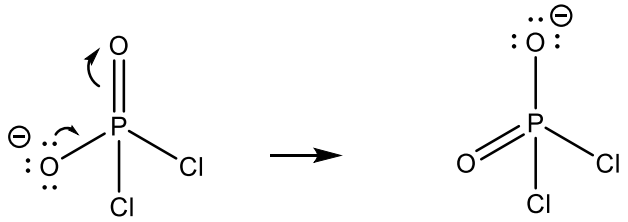


Additionally, the SO_2 molecule that escapes is exceptionally stable and is a gas, which causes an increase in entropy (remember your general chemistry), which drives the reaction forward (remember the universe goes towards a constant increase in entropy, that explains why my room is so messy). The $OPBr_2^-$ on the other hand has bromines which stabilize the negative charge through an inductive effect (remember acid base rules). These two reactions only work on methyl, primary, and secondary alcohols because they go through an SN_2 mechanism, and SN_2 reactions cannot occur on tertiary carbons (remember from last chapter).

There is also a better way to dehydrate alcohols to make them alkenes, and that is using $POCl_3$. This reaction converts the alcohol (OH) to a much better leaving group ($OPOCl_2$), which allows for the reaction to go through an E_2 mechanism, which avoids the carbocation and the rearrangements that causes. The reaction mechanism is shown below. Like the other reactions we have discussed so far, the mechanism is not super important to know, but we will go through it regardless:

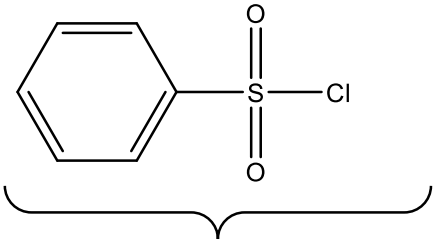


The first step in the mechanism is the alcohol uses its lone pairs to attack the electrophilic $POCl_3$. The $POCl_3$ is an exceptional electrophile because of its weak P-Cl bond and the large partial positive due to the electronegativity difference between the P and the other atoms in the molecule. When the nucleophilic OH group attacks the P, that causes the weakest bond to break, the P-Cl bond (AMSO**W**). The oxygen is now positively charged, to relieve that positive charge, the pyridine solvent acts as a base and the oxygen donates its proton because of its highly acidic nature (positively charged oxygens are exceptionally acidic) (**A**MSOW). This does two things, this minimizes the positive charge on oxygen and transfers it over to nitrogen, which is less electronegative and therefore more willing to be positively charged, thus minimizing charge (A**M**SOW). The alcohol group is now a much better leaving group because $PO_2Cl_2^-$ is a weaker base than OH^-, this can be seen through the resonance form that this molecule has:

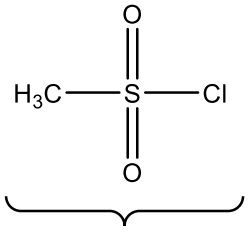


This resonance form stabilizes the leaving group and makes it less basic through charge minimization (A**M**SOW). Because the leaving group is so strong, the reaction can proceed through an E_2 elimination, rather than the E_1 elimination that we would have seen had we done the traditional dehydration reaction. To do the E_2 elimination, pyridine is used as the base and it deprotonates a neighboring carbon, this forms the pi bond between the neighboring carbon and the carbon bearing the good leaving group, which forces the leaving group to leave so that carbon does not have five bonds (which is illegal).

The reactions above are very useful, but they limit the stereochemistry in our product, in the above reactions with PBr_3 and $SOCl_2$, they caused stereochemical *inversion*, but what if we wanted retention while still activating the alcohol group? To do this, we would need to make the alcohol a *sulfonate ester*. To do this, we react an alcohol with a sulfonyl chloride, such as tosyl chloride (TsCl) or mesyl chloride (MsCl), the structure of these compounds are shown below:

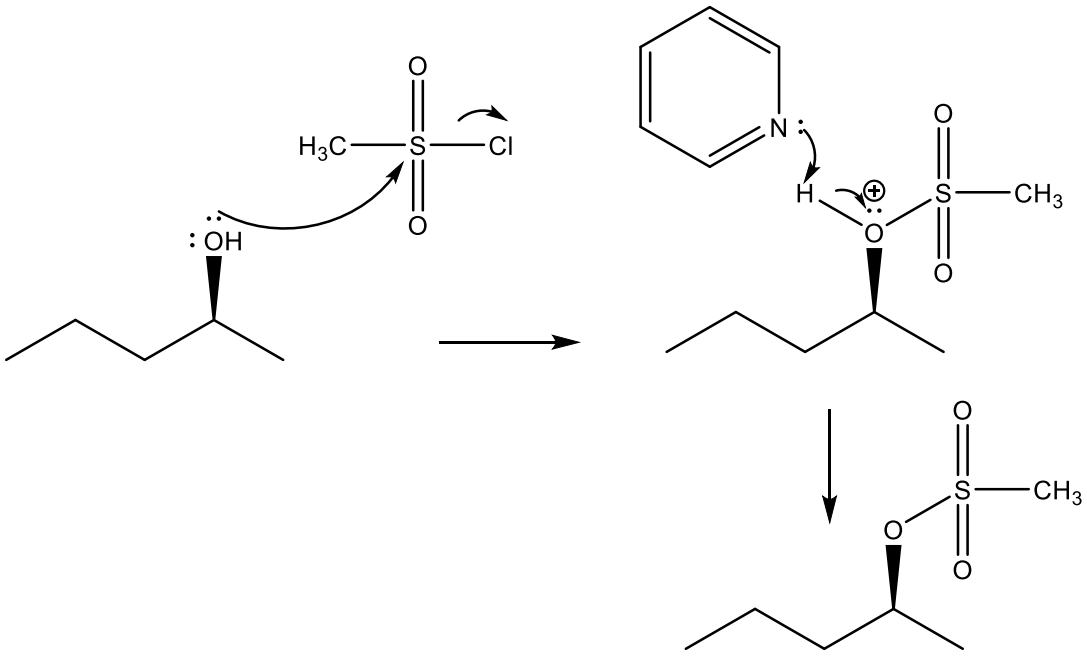


TsCl

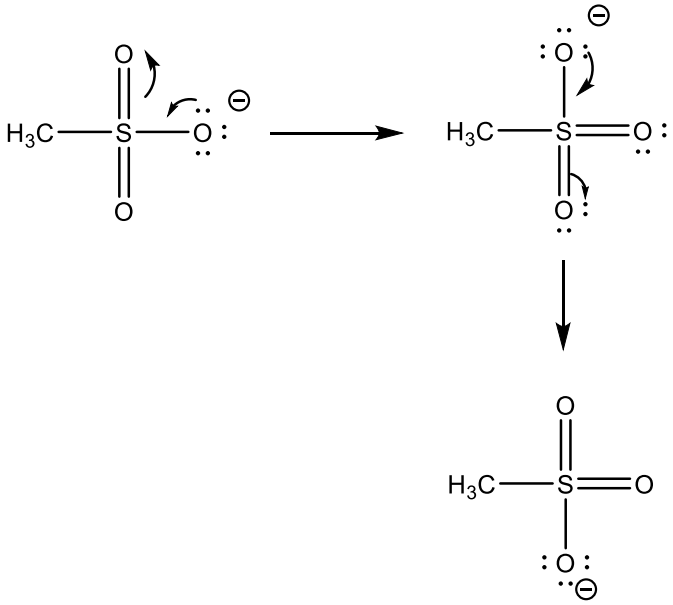


MsCl

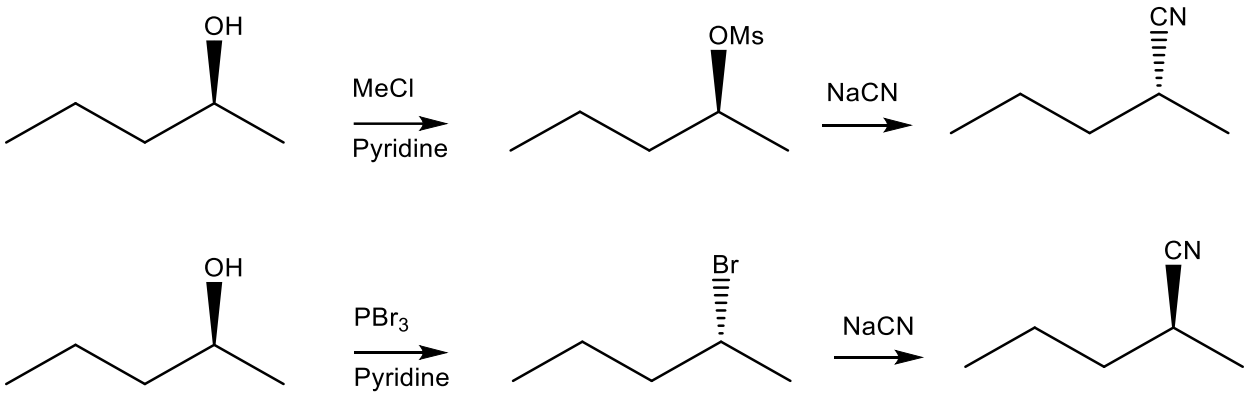
These reactions do not cause sterochemical inversion, because instead of making the halogen the leaving group that stays, the tosylate or the mesylate is the group that stays. There is no SN2 backside attack by the halogen here. The mechanism is shown below:



The first step in this reaction, like usual, is the alcohol attacks the electrophilic sulfur of the mesyl chloride molecule. The sulfur is electrophilic because of the weak S-Cl bond and because of the partial positive charge it holds due to the electronegativity difference between S and O and S and Cl. Once the nucleophilic alcohol attacks the electrophilic sulfur, the weakest bond breaks to prevent the sulfur from getting a negative charge, because the S-Cl bond is the weakest, that is the bond that breaks (A**M**SO**W**). This causes the oxygen to be positively charged after it gets its new bond with sulfur, so the basic pyridine solvent deprotonates the acidic oxygen, minimizing its charge and giving the nitrogen a positive charge, which it can support better due to its lower electronegativity (**AM**SOW). But why is the mesylate leaving group such a strong leaving group? The answer like before with $PO_2Cl_2^-$ is that the mesylate anion is stabilized tremendously through resonance as shown below:



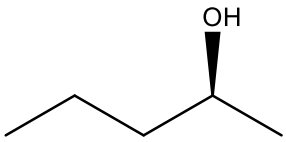
Because the leaving group is stabilized through resonance, it is a weaker base and therefore a stronger leaving group. *Remember, weaker bases are stronger leaving groups.* The key difference between this reaction and the ones with $SOCl_2$ and PBr_3 is that the halide does not come back to kick off the leaving group, it stays in solution as a counter ion to the protonated pyridine to make pyridinium chloride, the end result is that the following two reactions produce enantiomers of each other:



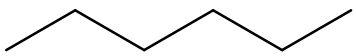
These reactions are exceptionally useful for multi-step synthesis questions:

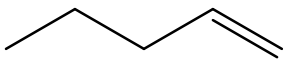
Practice your retrosynthetic analysis skills with these questions!

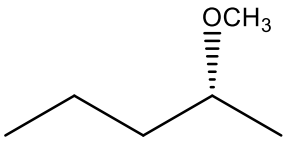
From the following compound, design a synthesis for these target molecules:



Target molecules:

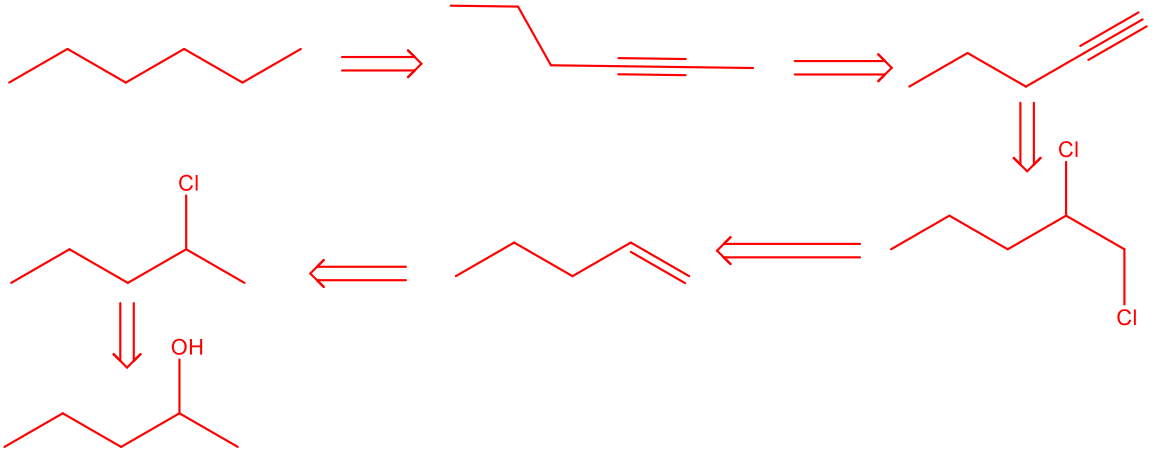


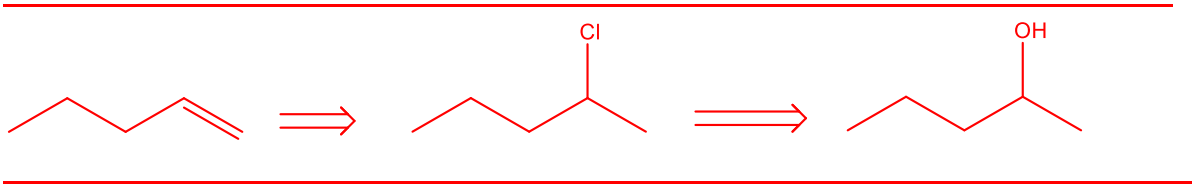


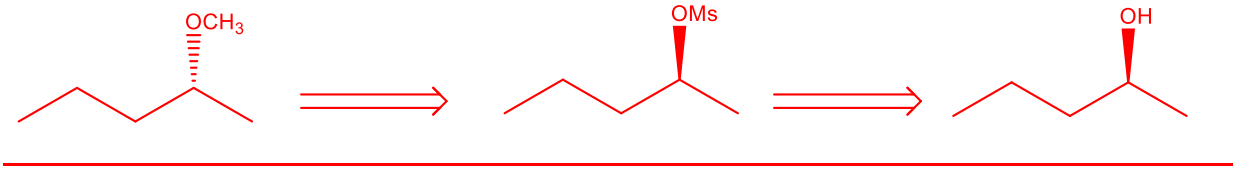


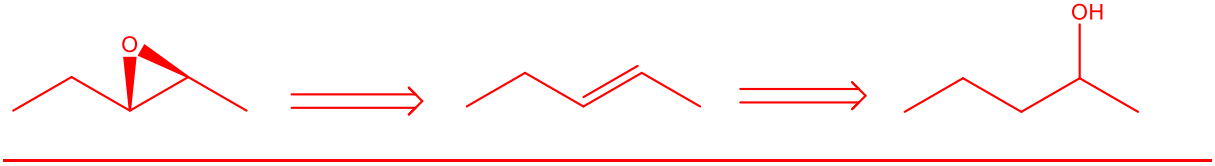
From the following compound, design a synthesis for these target molecules:

Target molecules:

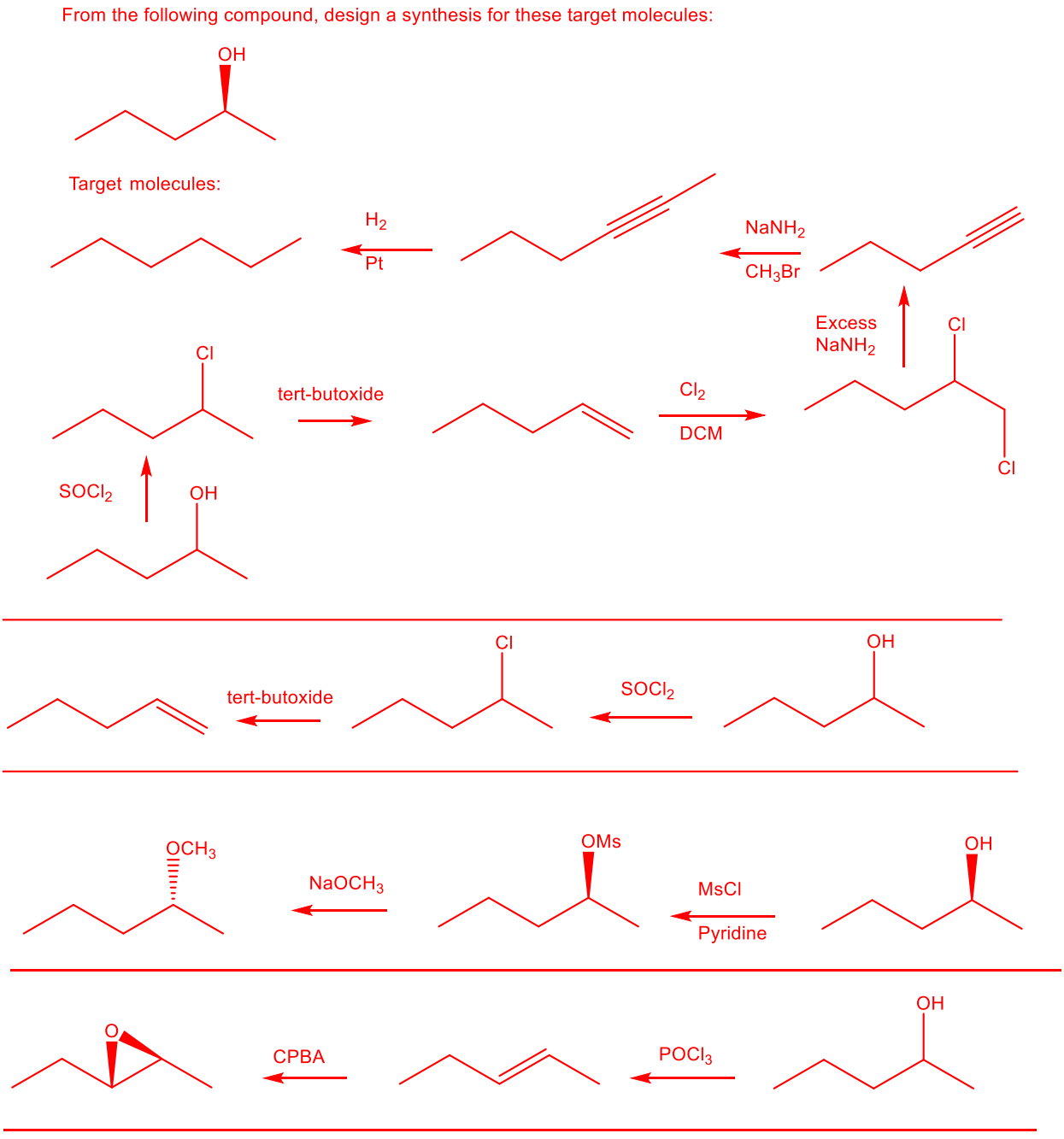








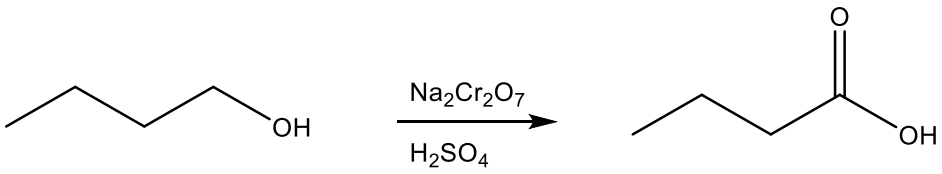
Putting in the forward direction:

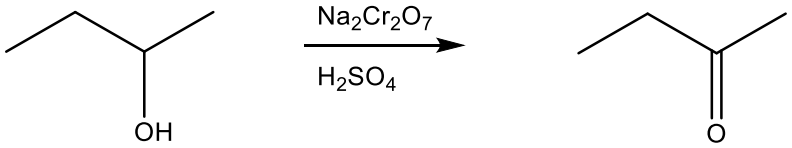


Now that we have discussed the activation of the alcohol group, we should discuss the oxidation of alcohols. Thus far, we have only discussed reduction reactions. The H_2 and Pt reaction was a reduction reaction because it resulted in the addition of hydrogen. *Reduction causes a reduction in the number of oxygens and an increase in the number of hydrogens while oxidation causes an increase in the number of oxygens and a decrease in the number of hydrogens*. Therefore, oxidation of alcohols can result in three different kinds of compounds depending upon the type of alcohol and how harsh an oxidizing agent you use. Secondary alcohols will *always* oxidize to ketones, it is the primary alcohols that are different. Primary alcohols with harsh oxidizing agents

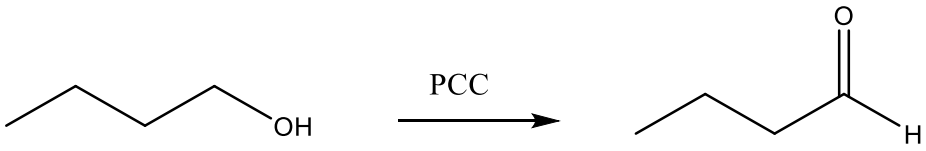
such as chromic acid will oxidize all the way to carboxylic acids, while primary alcohols treated with mild oxidizing agents such as PCC will oxidize only to aldehydes. Like many things in this course, there are a plethora of ways to get a desired product. There are many oxidizing agents for alcohols, I will give an example of each type (harsh and mild) and then list the others you may see in your coursework after each example.

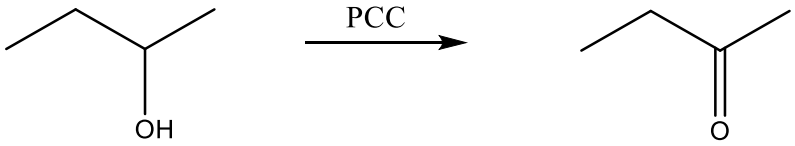
For harsh oxidation of alcohols, the standard choice is chromic acid, but chromic acid is so reactive that it needs to be made *in situ*, or made in the same reaction vessel just before the reaction starts. To make chromic acid, you have to dissolve sodium dichromate in sulfuric acid. This will oxidize primary alcohols to carboxylic acids and will oxidize secondary alcohols to ketones. Tertiary alcohols are NOT able to be oxidized, regardless of oxidizing agent. This is because the mechanism (which we will not get into) requires taking away the hydrogen on the alcohol carbon.





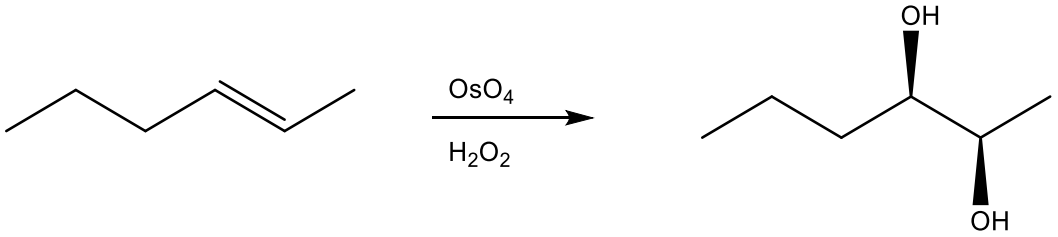
For mild oxidation of alcohols, the standard choice is PCC. Although there are many other reagents you may see, other common ones are sodium hypochlorite (NaOCl) in acetic acid at 0 C as well as the Swern oxidation, which makes use of DMSO. For mild oxidation, you will take primary alcohols to aldehydes and secondary alcohols, as always, to ketones. Just like before, tertiary alcohols CANNOT be oxidized.



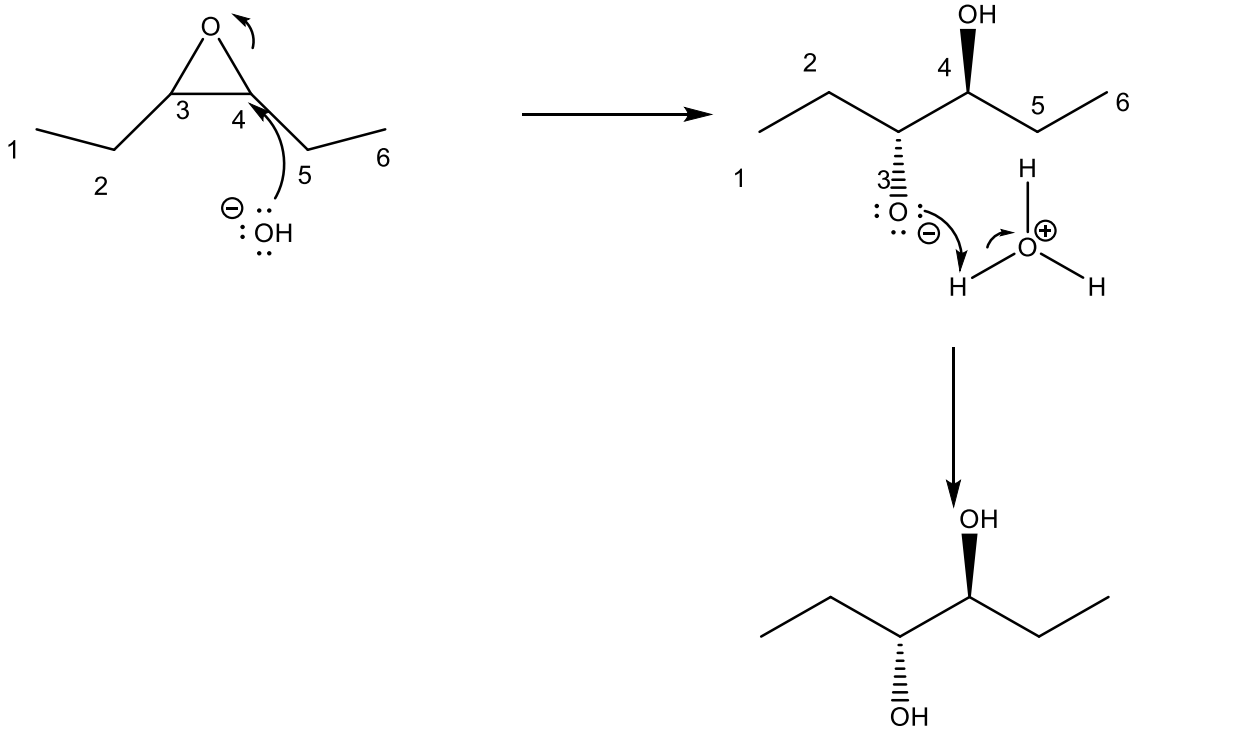


The only reason to use one over the other is simply due to safety concerns or other pragmatic reasons that unless you are doing the reaction in a lab, you don't need to concern yourself with.

Other functional groups can get oxidized, one of these is the alkene functional group. Though this is a niche reaction, it finds its uses in making cis diols. The reaction mechanism you do not need to concern yourself with, just know that OsO_4 followed by H_2O_2 can be used to oxidize alkenes to cis diols like so:

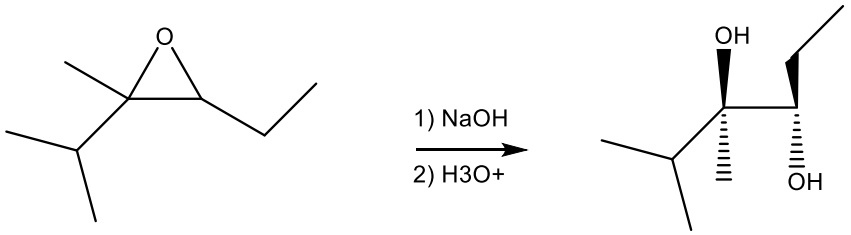


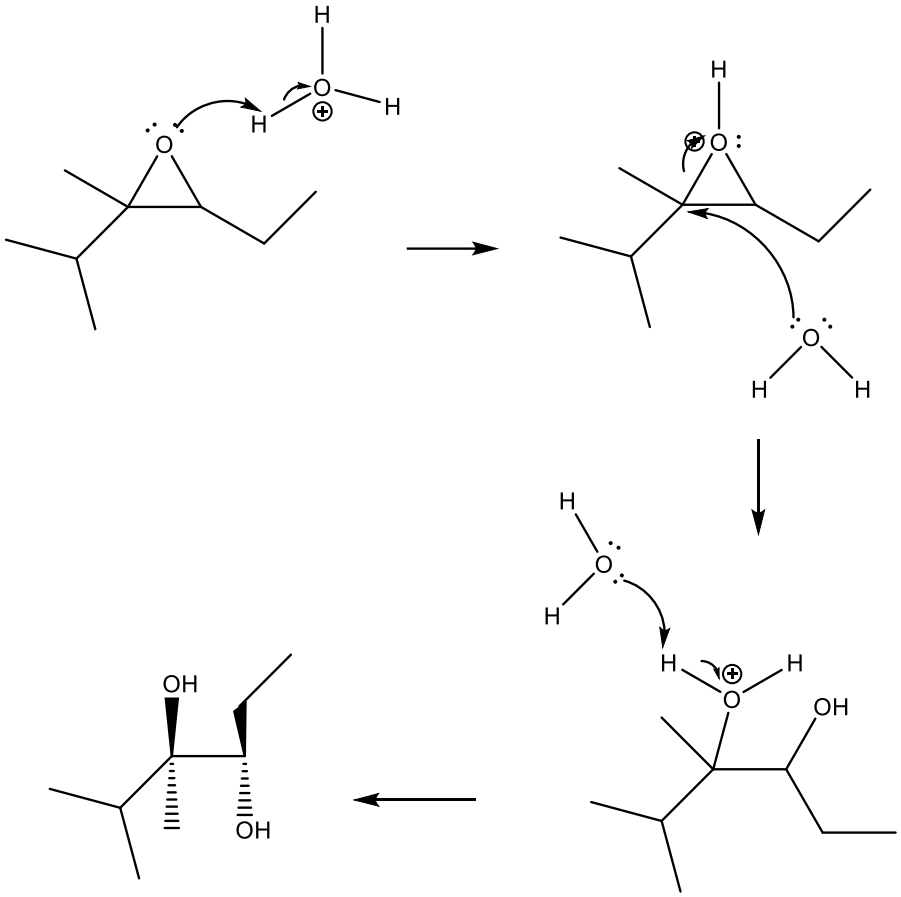
But what if we wanted to make a trans diol? How would we do that? You can break an epoxide. Remember those things? Epoxides are special ethers in that they are substantially more electrophilic. Epoxides are more electrophilic because of their tremendous amount of ring strain. Three membered rings are extremely unstable and therefore both epoxide carbons are electrophilic and susceptible to nucleophilic attack. Therefore, to make the trans diol, simply react the epoxide with NaOH. The mechanism for this reaction is as follows:



The first step starts with the nucleophilic hydroxide anion attacking one of the epoxide carbons. This can happen for the reason I mentioned above, the epoxide has tremendous ring strain and

that causes the carbons to form very weak bonds to oxygen. Therefore, when the hydroxide attacks one of the epoxide carbons that causes the epoxide bond to break (AMSO**W**). The negative charge on the oxygen is then minimized by deprotonating a neighboring hydronium molecule (this doesn't have to be hydronium, anything with an acidic proton could protonate this at this point), this makes both oxygens neutral and therefore minimizes charge (**AM**SOW). This forms the trans product because the hydroxide nucleophile is forced to attack from the opposite face that the epoxide was facing because of steric hindrance. In the case of an asymmetrical epoxide, the nucleophile will attack the less sterically hindered epoxide carbon. This preference for the less substituted epoxide carbon is reversed if the epoxide ring opening was done in acidic conditions. An example of an epoxide ring opening under both conditions is presented below and the differences between the two of them will be discussed and rationalized in the paragraphs that follow.



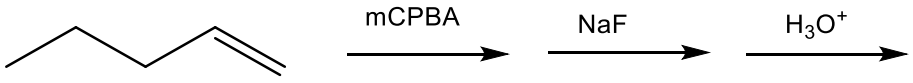


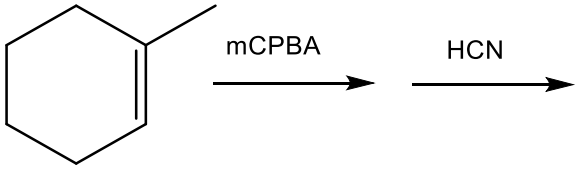
Under basic or nucleophilic conditions, the driving force for which carbon to attack is sterics, which carbon is less congested and can be more easily attacked by an incoming nucleophile. Under acidic conditions, however, the epoxide oxygen is protonated, making the bond between the carbon and the oxygen much weaker because the oxygen wants to break free even more. The driving force for which carbon to attack under acidic conditions is which carbon will support the positive charge better, because as the nucleophile approaches, the carbon-epoxide oxygen bond breaks, leaving that carbon with a partial positive. Therefore, the nucleophile will attack the *more substituted carbon* since that carbon will minimize the positive charge more (A**M**SOW).

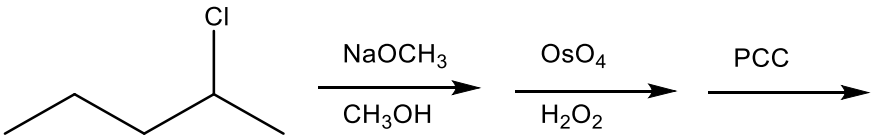
In short, epoxides will be attacked at the less sterically hindered carbon under basic or nucleophilic conditions, but will be attacked at the more sterically hindered carbon under acidic conditions.

Practice:

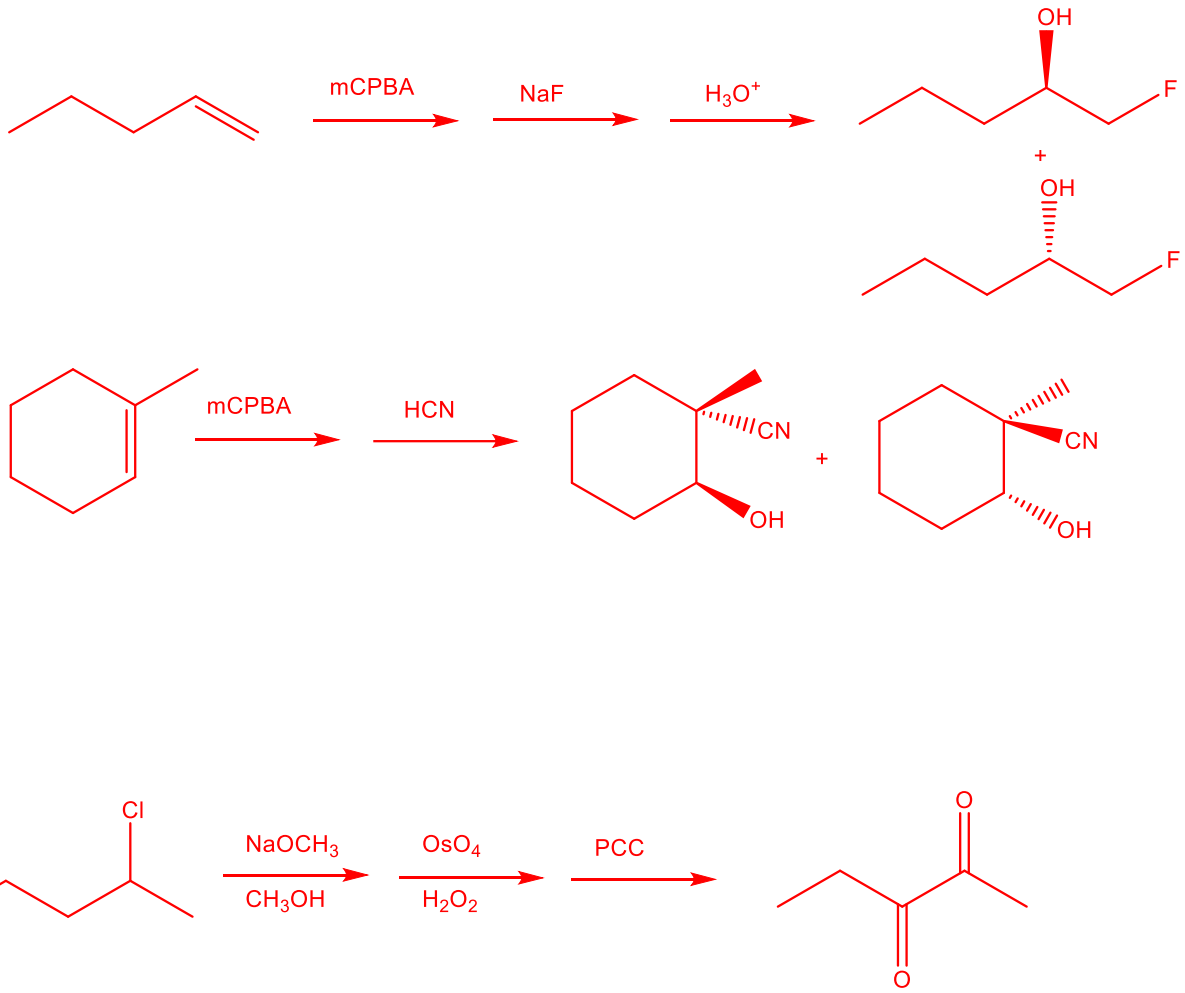
Predict the major product for the following reactions including stereochemistry:



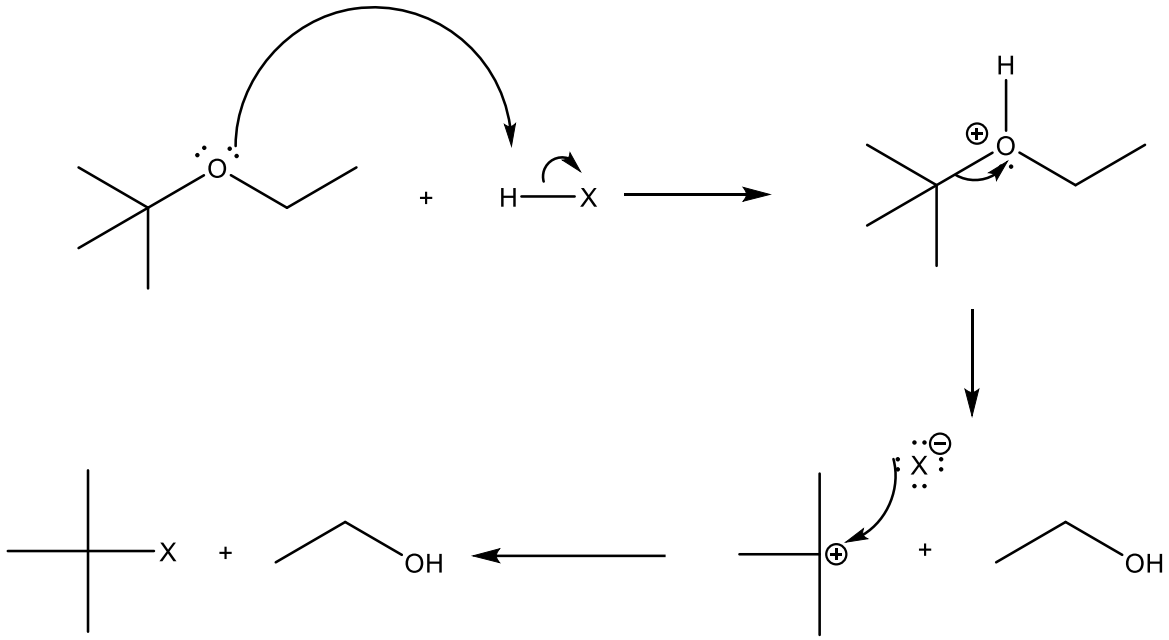




Answers:



Ethers are essentially less reactive epoxides, they earn their name exclusionary ethers because they will only really react with acids. The only reaction that is worth discussion with regard to ethers is the ether cleavage reaction. This reaction is caused by exposure of the ether to a strong acid and causes the ether to break in half with the more substituted half getting the nucleophilic attack by the solvent or anion from the acid. This reaction goes through a carbocation. Let's see how this works with an example:



This reaction is very very similar to the halogenation of alcohols reaction, it works the same way, first you protonate the oxygen with a strong acid because acids react with bases (**A**MSOW). The second step removes the leaving group and the carbocation is formed on the more stable side, in the example above, we have an option between a tertiary carbon and a primary carbon to put the positive charge on, to minimize charge the tertiary carbon is chosen (A**M**SOW). This carbocation is short lived and is attacked by the halide anion to give the tertiary alkyl halide in the last step.

In the last chapter, I mentioned that there were only 2 exceptions to the Zaitsev Rule, they were

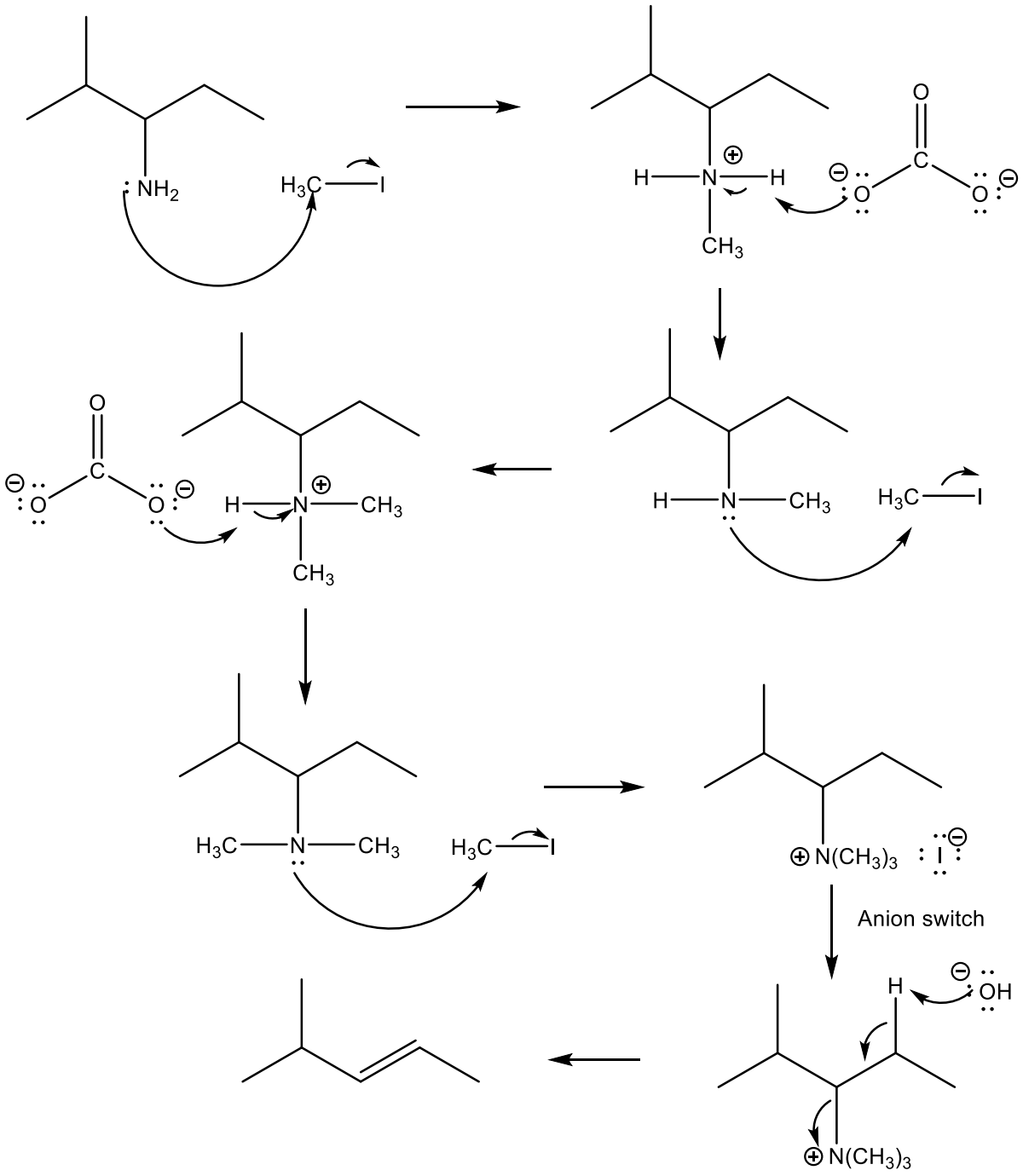
1. There is a bad leaving group (F, NR_2)
2. Bulky base

We never discussed the NR_2 example, this is a special reaction called the Hoffman elimination reaction. This reaction requires the use of an amine and makes the least stable alkene as the major product. This reaction occurs in 3 major steps:

1. Exhaustive methylation to make the leaving group better (just adding as many methyl groups to the amine as possible until it is a quaternary ammonium compound)
2. Anion exchange from I^- to OH^-
3. Elimination with OH^- to give Hoffman product

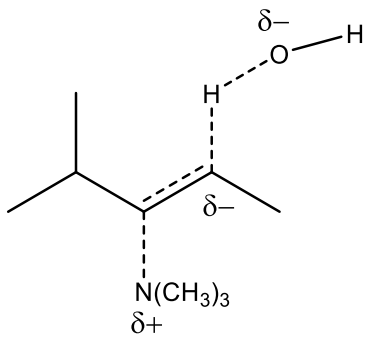
The reason why this reaction gives the least stable alkene is because it goes through a carbanion-like transition state, where the carbon that is getting deprotonated accumulates partial negative charge. This happens because the leaving group (NR_4^+) is reluctant to leave, so the electrons stay on the neighboring carbon, rather than force the ammonium group to leave. The trend for

carbanion stability is the exact opposite of carbocation stability for the same reason. The carbon has a negative charge and alkyl groups are mildly electron donating, therefore to minimize charge, it would prefer to be less substituted. An example of this reaction is shown below:

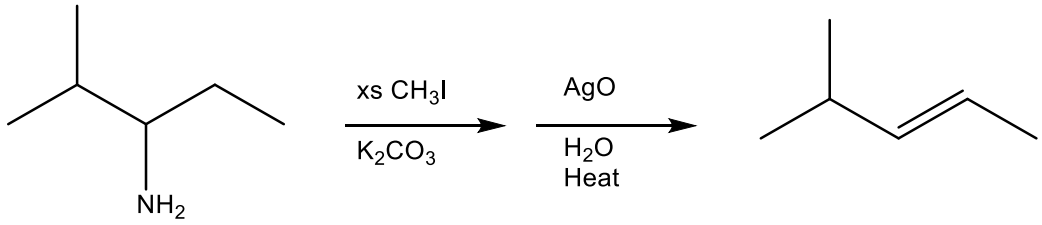


The anion switch is facilitated by AgO, and the carbonate (CO_3^{2-}) is provided by K_2CO_3. But wait a second, you guys don't know about transition states. Transition states are essentially the

process of the arrows that we draw when partial bonds form and partial bonds break in the above reaction, this is the transition state. Partial bonds are denoted with dashed bonds:



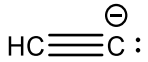
Transition states are so called because they represent the transition between steps. The hydroxide is forming partial bond with the hydrogen on the neighboring carbon, it is going from negative to neutral so it is partially negative, denoted with the lower case delta symbol. While the partial bond is forming between the hydroxide and the neighboring proton, the neighboring carbon is losing the bond between itself and the neighboring proton that is being grabbed by the hydroxide. The neighboring carbon is building up negative charge because the leaving group is still extremely bad, despite it being positively charged and therefore a weaker base, therefore it has a partial negative. While that is happening, the double bond between the neighboring carbon and the carbon with the quaternary ammonium leaving group is forming, and the leaving group is partially leaving hence the partial positive. The full reaction is written as follows:



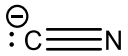
The heat is used to promote elimination.

Chapter 10: Organometallic Chemistry

Up until this point, there have only been two carbon nucleophiles that we have discussed. If you recall, it was the acetylide anion (deprotonated alkyne) and the cyanide anion. Both of these carbon nucleophiles were negatively charged and had a lone pair on the carbon, their structures are shown below:



Acetylide anion

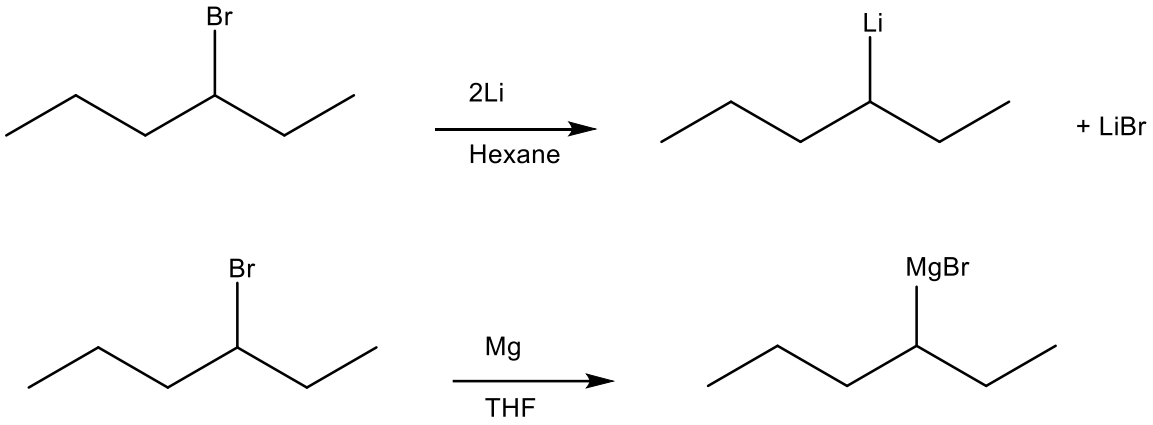


Cyanide anion

The common element among both of them is that they have triple bonds and they have carbons with a lone pair and a negative charge. The reason why carbon nucleophiles are exceptionally rare is because most elements in the p-block have either relatively the same electronegativity as carbon or higher electronegativity. The carbon is therefore never the element bearing the negative charge and instead we have seen a plethora of oxygen nucleophiles (OH^-, OCH_3^-, etc.) and nitrogen nucleophiles (NH_2^-, NH_3, etc.). This is not the case when we have metals bonded to carbon though, because if you recall from general chemistry, electronegativity decreases from right to left. This is the core principle behind organometallic chemistry, we want to make versatile carbon nucleophiles so that we can more easily make carbon-carbon bonds, the most important and useful bonds in organic chemistry. There are three main metals that are used in organometallic chemistry: Li, Mg, and Cu. There are others, no doubt, but the most common ones and the ones with the most versatility are those organometallic compounds. Some of the concepts that I refer to here will come from inorganic chemistry, so if you want a refresher on that I have a textbook posted on that as well on the website. If, however, you do not have a good foundation in inorganic chemistry, you don't necessarily need it for this chapter. I will be approaching this subject from an organic chemist's perspective. The only concepts that you have to understand from inorganic and general chemistry is electronegativity and dipole moment.

Organolithiums are organic compounds in which a carbon is bonded to a lithium. These compounds are prepared by making the corresponding the alkyl halide and reacting it with two equivalents of lithium metal. One of the lithiums will bond to the carbon and displace the halogen, while the other will act as the cation to the bromide that is ejected. These compounds, as you might suspect, are EXTREMELY reactive. Their extreme reactivity has to do with the large electronegativity difference between the carbon and lithium of 1.57. This effectively makes it so that the carbon has a full negative charge, in other words, the electrons between the carbon and lithium are essentially only on carbon. This makes the carbon act essentially as a carbanion just like the cyanide and acetylide anion cases. These carbon nucleophiles are also exceptionally strong bases, this should make sense, because the conjugate acid would be an alkane, and alkanes are not acidic AT ALL. These reagents are therefore extremely moisture sensitive, if they react with water, it will simply make the corresponding alkane. Organomagnesiums (Grignard's) react the exact same way and are formed the exact same way as organolithiums; however, because Mg is more electronegative than Li, these compounds are *less reactive*. This turns out to be extremely beneficial because organolithiums are sometimes TOO reactive and it is easier to work

with the corresponding Grignard. Unlike organolithiums, Grignard's are formed by the addition of one equivalent of Mg metal to the alkyl halide because Mg prefers to have two bonds, therefore it forms a bond with the C and the halogen, X.

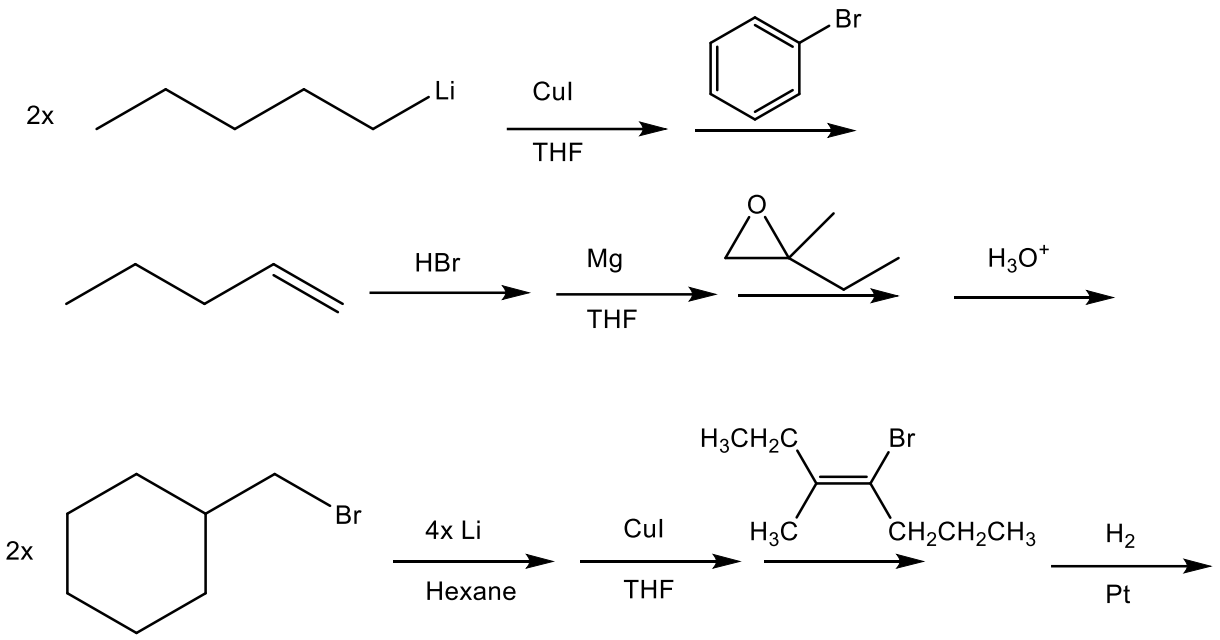


These organometallic compounds do reactions that no other reagent can do and they will be discussed in further depth in Chapter 12 and 13. *Surprisingly, Grignard's and organolithium compounds DO NOT react with alkyl halides to form carbon-carbon bonds.* This is because *Mg and Li are considered hard metals according to HSAB (look at inorganic textbook for more details) and therefore they like to react with electrophiles that have a larger positive charge on the carbon.* The C-X bond is moderately polar, but the carbonyl bond is more polar and therefore Grignard's react very well with carbonyls but not with alkyl halides. Grignard's and organolithium reagents will attack epoxides as well, also because the carbon-oxygen bond creates a larger dipole than carbon-halogen bonds. Both organolithiums and Grignard reagents function as if the carbon attached to the metal has lone pairs, so if it helps you draw the arrow pushing mechanisms for these reactions, just draw the carbon with lone pairs.

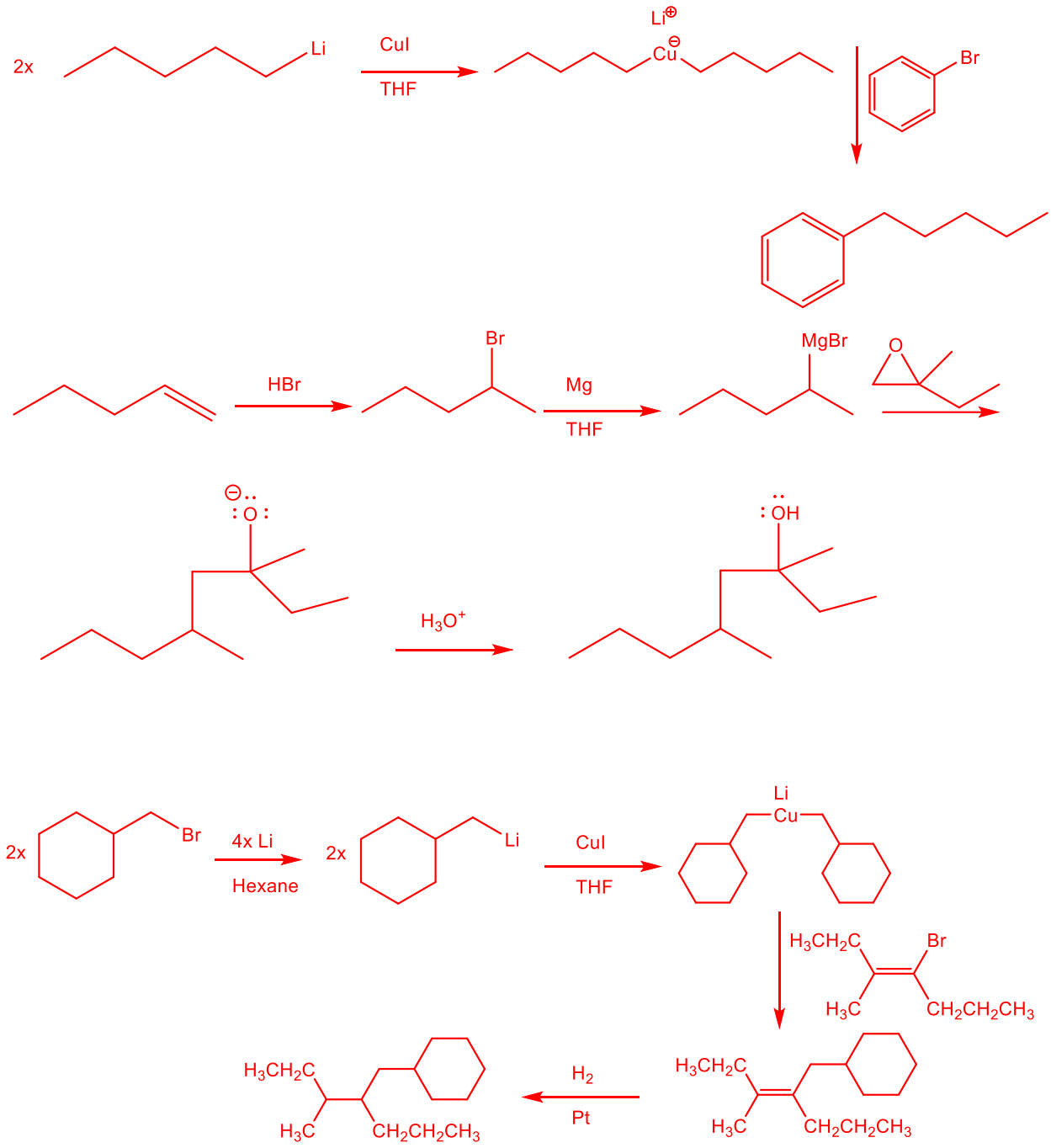
To react with alkyl halides, we need to use a softer metal, the metal that is typically used is Cu because of how cheap it is relative to other metals and because it is relatively common compared to most other soft metals like gold and silver. These organometallic compounds are referred to as *organocuprates or Gilman reagents*. Gilman reagents are prepared by reacting 2 equivalents of organolithium compounds with copper iodide. This is a *transmetallation* reaction and this works because the difference in electronegativity between C and Cu is less than C and Li, this allows for charge minimization and helps drive the reaction forward (A**M**SOW). Gilman reagents can be used to couple any carbon chain that is not secondary or tertiary to an alkyl halide. Gilman reagents essentially cover all the reactions that Grignard's and organolithiums don't, so they do react with alkyl halides and epoxides, but they do not react with carbonyl carbons. Gilman reagents are less reactive overall than the Grignard's and organolithiums because of the smaller electronegativity difference between C and Cu.

Practice questions:

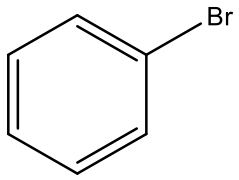
Predict the major product of the following reactions, include stereochemistry:



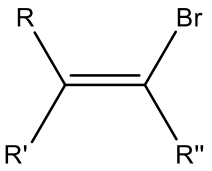
Answers:



The most important modern organometallic reactions are the Suzuki and Heck reactions. Both of these reactions require an aryl or vinyl halide, aryl halides are those alkyl halides that have a halogen on directly on the benzene ring. Vinyl halides are those alkyl halides that have a halogen directly on a double bond.



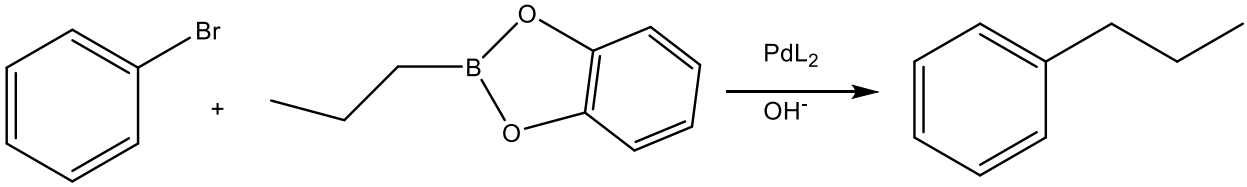
Aryl halide



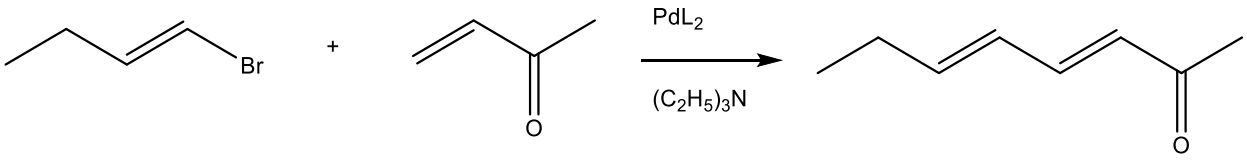
Vinyl halide

The Suzuki reaction uses an organoborane compound and the Heck reaction uses an alkene. These reactions both use a palladium catalyst to couple groups together to make carbon-carbon bonds and require a base to catalyze the reaction. The mechanism for both of these reactions is not necessary to understand for this course, so we will not include it.

The Suzuki reaction can couple an aryl or vinyl halide with any alkyl, alkenyl, or aryl group with stereochemistry preserved. An example of a Suzuki reaction is shown below using the most common organoboron compound:



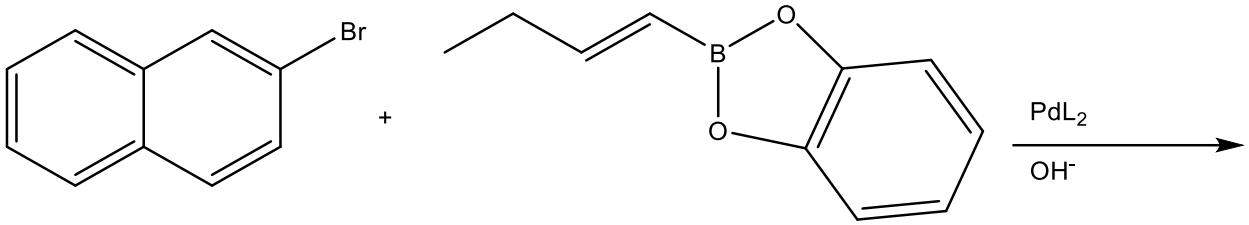
The Heck reaction can couple an aryl or vinyl halide with an alkene, typically these alkenes have electron withdrawing groups bonded directly do them to increase the selectivity for one alkene carbon over the other, otherwise a mixture of products will result. An example of a Heck reaction is shown below:

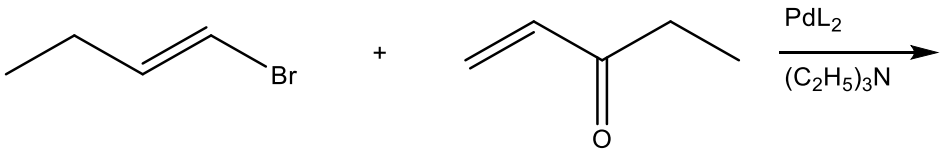


In both of these reactions, the Pd has two ligands (L) on it, or two attaching groups. Typically, these groups are acetate groups, but they can be anything.

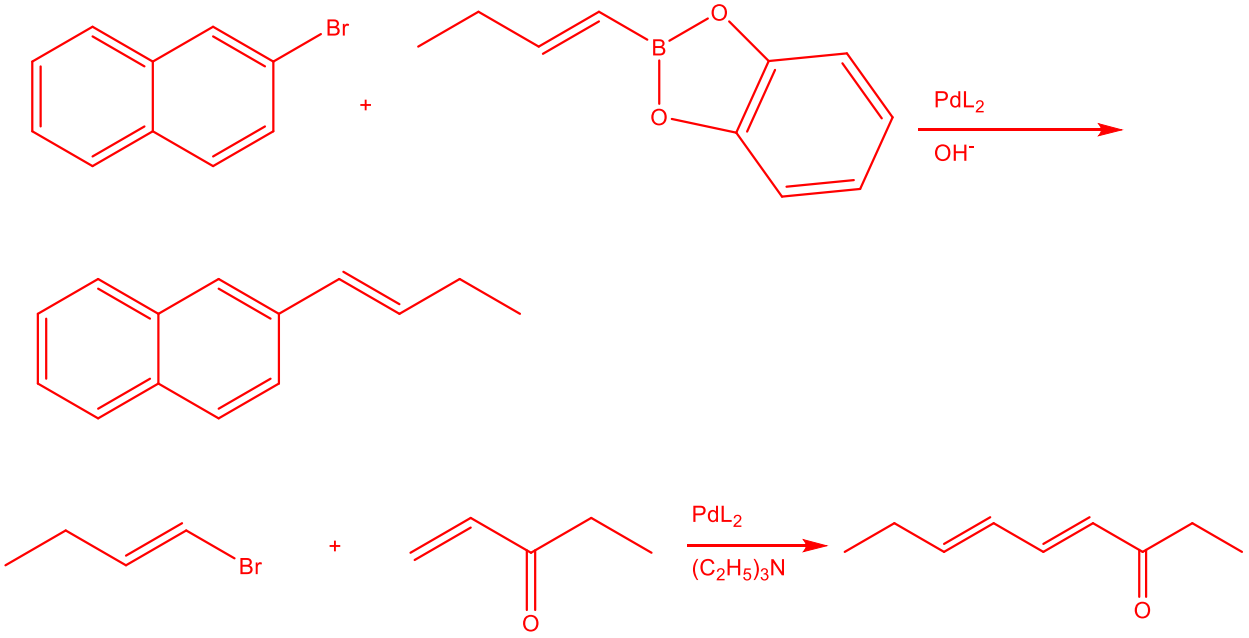
Practice Questions:

Predict the products for the following reactions:

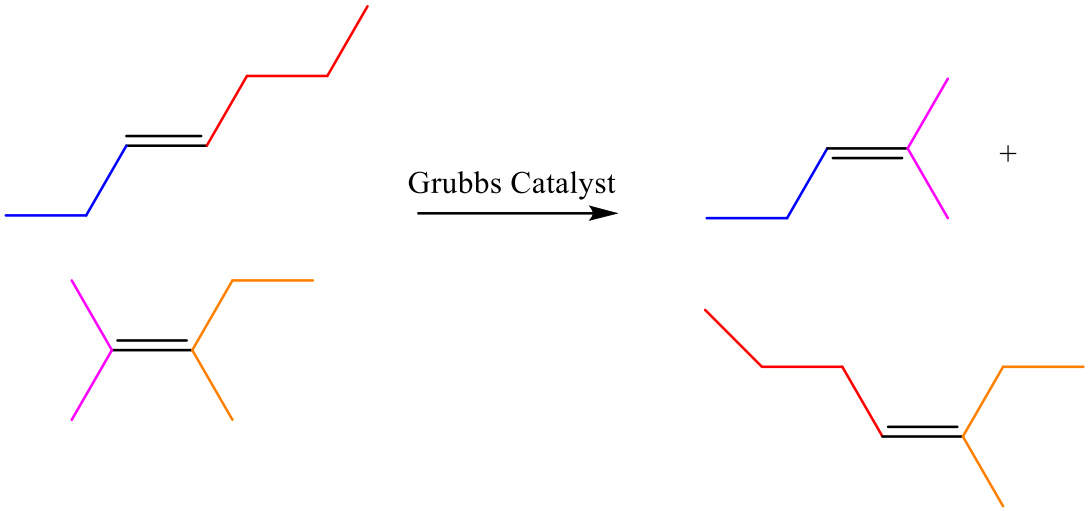




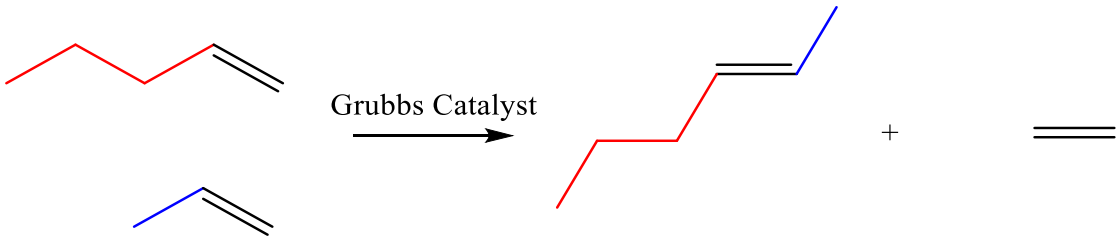
Answer:



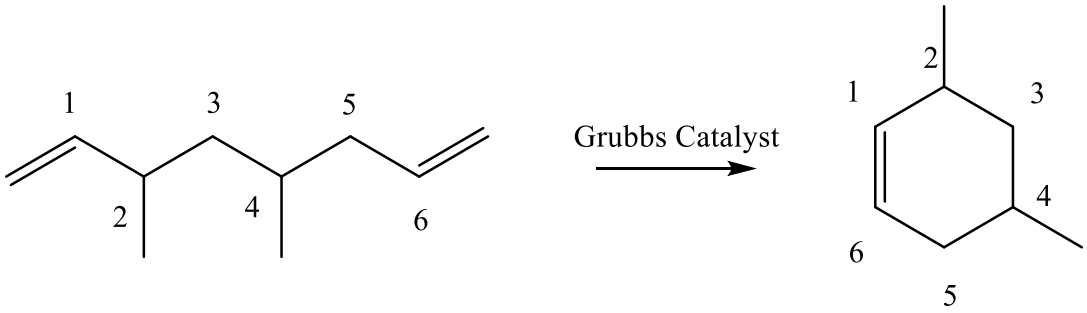
The very last organometallic reaction that we will learn is the metathesis reaction. This reaction comes in two flavors, alkene metathesis and alkyne metathesis. The alkene metathesis requires the use of the Grubbs catalyst and the alkyne metathesis requires the use of the Schrock catalyst. In both kinds of metathesis, two alkenes or alkynes, either in the same or different molecules come together to form new alkenes and alkynes. For example:



This reaction is not stereospecific, if the alkenes that are formed can have E/Z isomers, both will form. As you can see, each side of the alkene gets connected to the corresponding side of the other alkene (blue pairs with purple and red pairs with orange). This reaction is primarily used on terminal alkenes because typically only one alkene is the desired product, and the terminal alkenes will produce CH_2CH_2 gas which can be evaporated out of the reaction vessel to maximize yield and to give an easy clean up step. An example is given below:



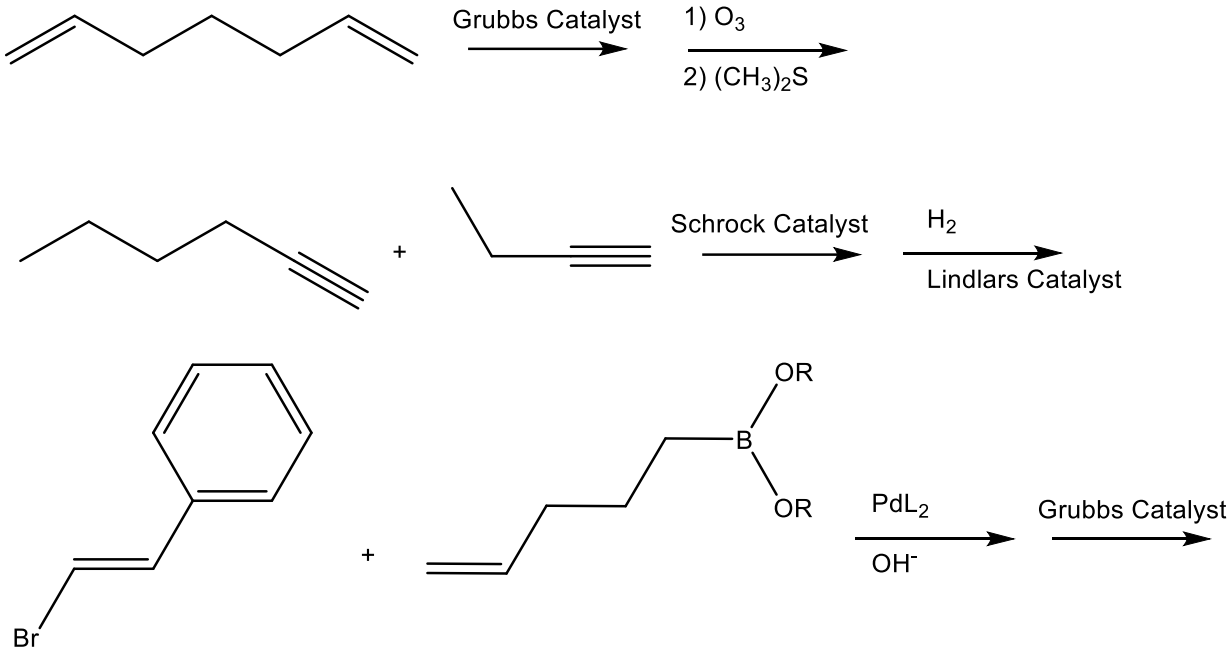
This catalyst can also work if the two alkenes are in the same molecule, and this is frequently used for ring closing metathesis reactions. Typically the two alkenes are again terminal alkenes to maximize the yield of the reaction, an example is shown below:



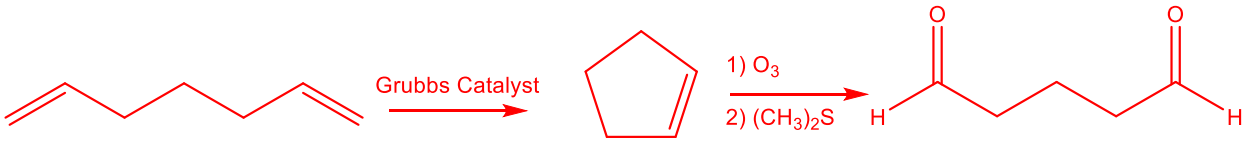
The alkyne analogue works the same way, it just uses the Schrock catalyst as opposed to the Grubbs catalyst. You do not need to know or understand the mechanisms for these reactions, they are beyond the scope of an introductory organic chemistry course for which this book is designed.

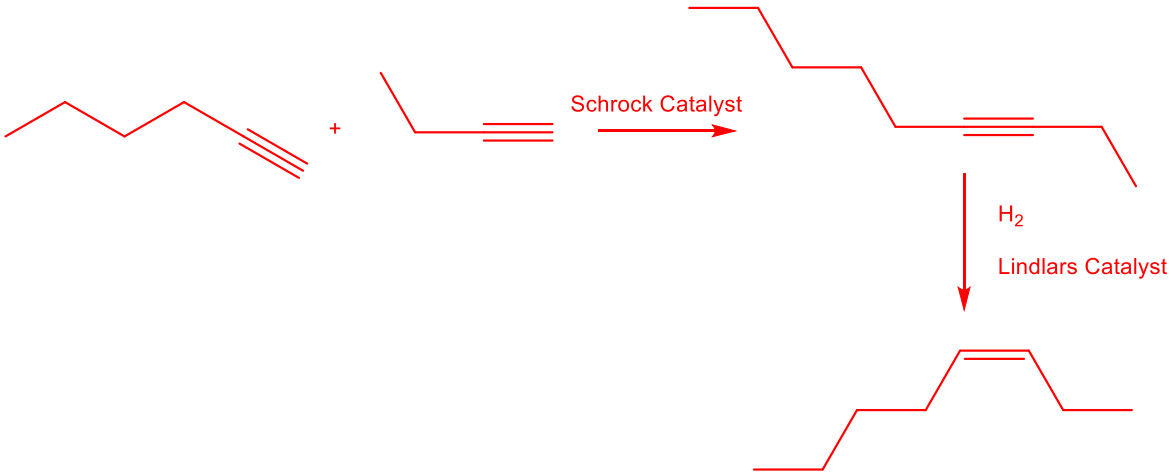
Practice questions:

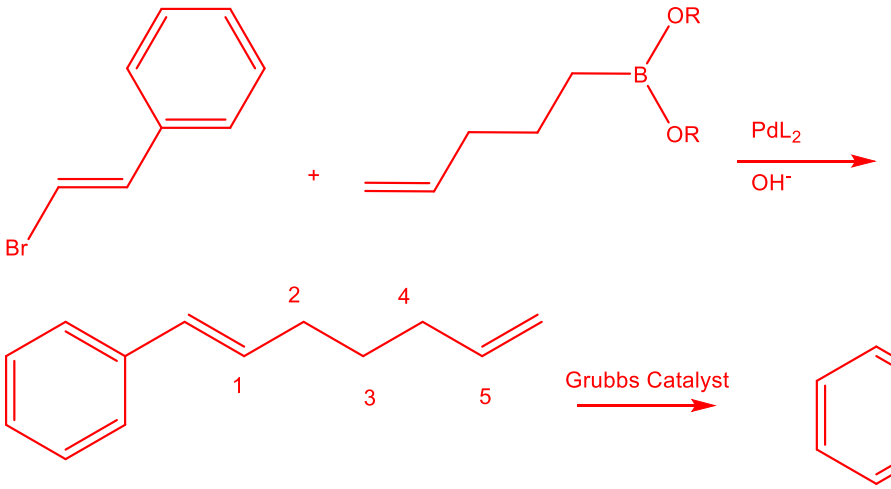
Predict the products for the following reactions:



Answer:


Grubbs Catalyst
1) O_3
2) $(CH_3)_2S$
O
O
H
H

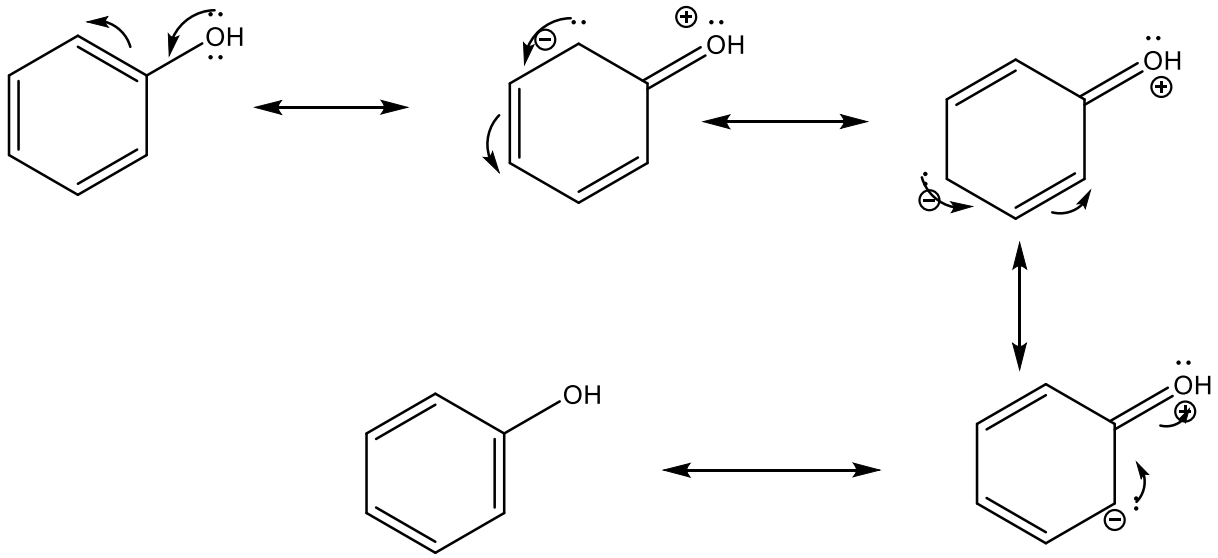

+
Schrock Catalyst
H_2
Lindlars Catalyst


Br
+
OR
B
OR
PdL_2
OH^-
2
4
1
3
5
Grubbs Catalyst
+

Chapter 11: Reactions of Benzene and Benzene Derivatives

Thus far, we have ignored the benzene ring and the reactions that it can undergo. This is because the benzene ring is exceptionally stable and would rather not react with anything, it is resonance stabilized. The only way we can get the benzene ring to react is if we alter its electronic properties with electron-withdrawing and/or electron-donating groups or if we react it with "super charged" nucleophiles/electrophiles. The benzene ring by itself, with no substituents on it, is slightly more nucleophilic than it is electrophilic. This should make some sense if we consider that it is an aromatic stabilized cyclohexane ring, therefore it shouldn't want to get attacked, and it has a full p-orbital highway of electrons above and below the plane of the ring, therefore it has ammunition to attack electrophiles with. Unlike other reactions, the reactions of benzene have numerous factors that play a role in how groups will add onto the ring. There are two main classes of reactions for benzene and its derivatives: EAS and NAS reactions. *EAS stands for electrophilic aromatic substitution* reaction and this reaction has the *benzene react with an electrophile*. The benzene ring in EAS reactions therefore acts as a nucleophile. *NAS stands for nucleophilic aromatic substitution* reaction and this reaction has *the benzene react with a nucleophile*. The benzene ring, consequently, acts as an electrophile in NAS reactions.

Electron-donating groups (EDG) promote EAS reactions; these groups will give more ammunition to the benzene ring to attack incoming electrophiles. We can also look at the directing preferences of EDG based off an example that we did in the aromaticity chapter. If you recall, the following are the resonance forms for hydroxybenzene (phenol):



The most nucleophilic carbons are those carbons that have the negative charge. The negative charge resides on the ortho and para positions relative to the hydroxyl group, therefore, electron-donating groups through resonance will direct ortho-para for EAS reactions because of the above

resonance forms. Just as a quick reminder, these are the common EDG and electron-withdrawing groups (EWG):

Guide to Electronic Effects on pKa

Electron-Withdrawing Groups:
Increase Acidity
Typically have double bonds in conjugation with the ring

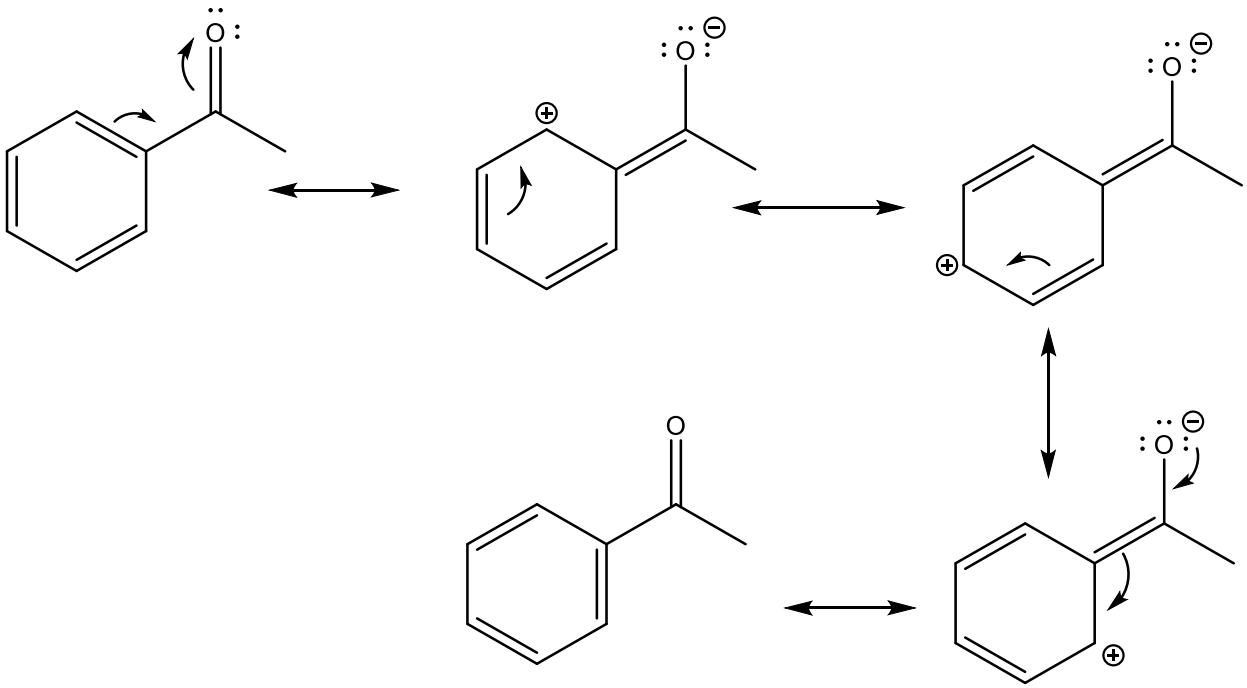
In order of decreasing strength:
NO2
SO3H
Carbonyls
Nitriles
F
Cl
Br

Electron-Donating Groups:
Decrease Acidity
Typically have lone pairs in conjugation with ring

In order of decreasing strength:
NH2
OCH3
OH
CH3

Blue = Resonance contributing groups
Red = Inductive groups

Electron-withdrawing groups will not direct to the ortho/para positions, but will instead direct to the meta position in EAS reactions because of the following resonance form:



Here, the ortho/para positions have positive charges, therefore they CANNOT act as nucleophiles (recall nucleophiles = negative charge). EWG direct towards the meta position because that position is relatively nucleophilic (neutral > positive for nucleophilicity).

This is an overall guide to directing effects for the benzene reactions:

Guide to Benzene Reaction Positions

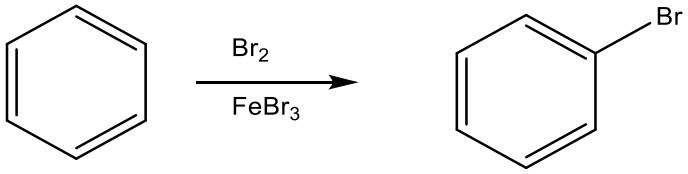
Meta Directors
Typically have a double bond or positive charge in conjugation with ring
In order of decreasing strength:
NO2
SO3H
Carbonyls
Nitriles
NH3+

Ortho/Para Directors
Typically have lone pairs in conjugation with ring
In order of decreasing strength:
NH2
OCH3
OH
N-Carbonyl
O-Carbonyl
CH3
Halogens

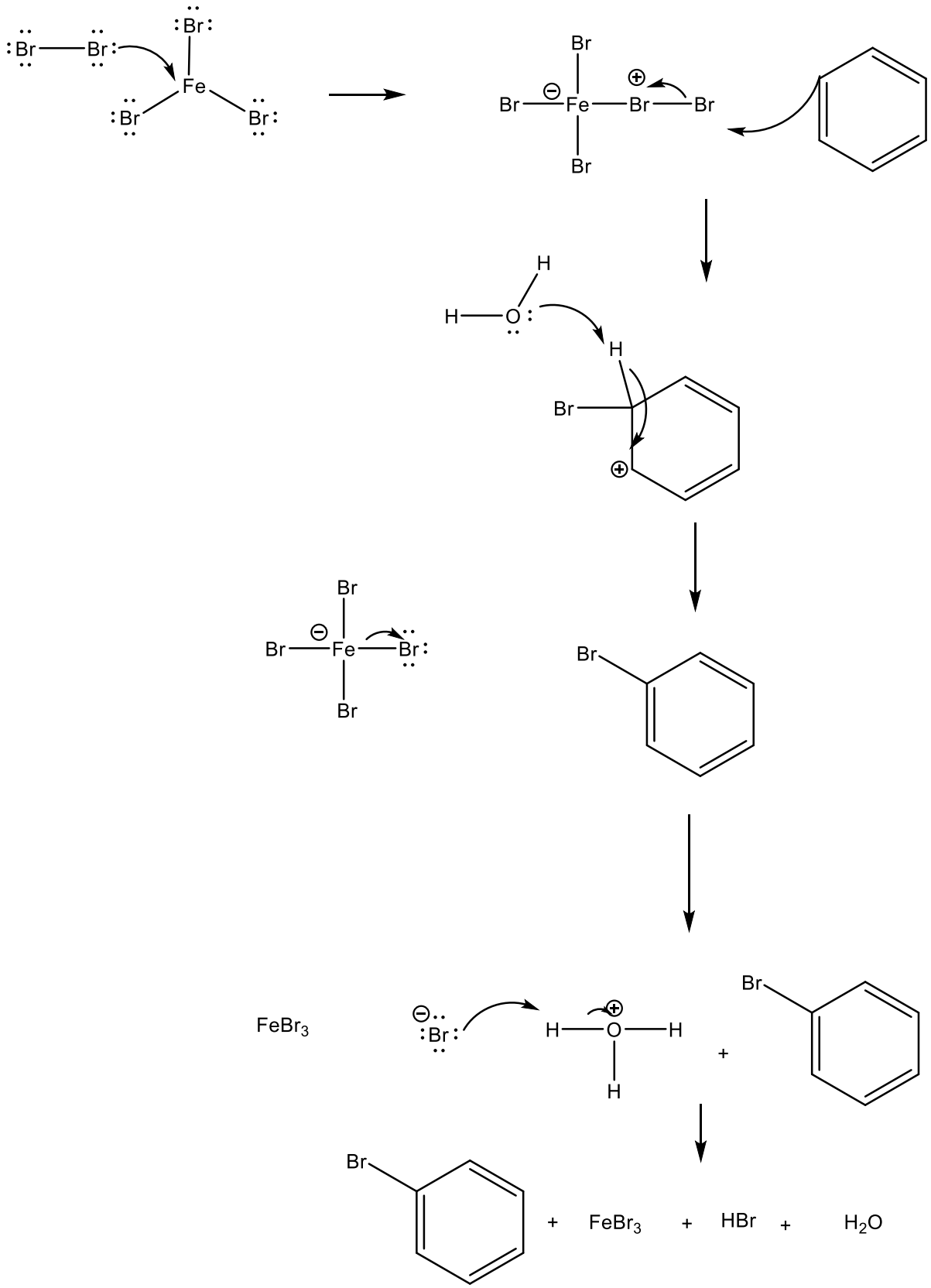
Blue = Resonance contributing groups
Red = Inductive groups

Now that we know the directing preferences for the groups that are on the benzene ring, let's discuss the benzene reactions themselves.

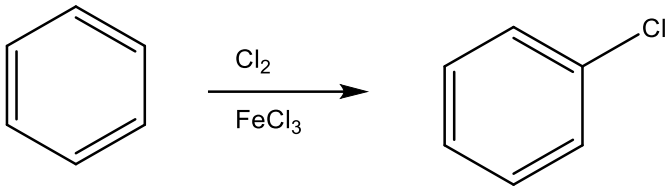
The first EAS reaction that we will discuss is halogenation, halogenation is the fastest EAS reaction and if there is a strong EDG on the ring, a catalyst may not be necessary and you run the risk of over-halogenation. The reaction is shown below:

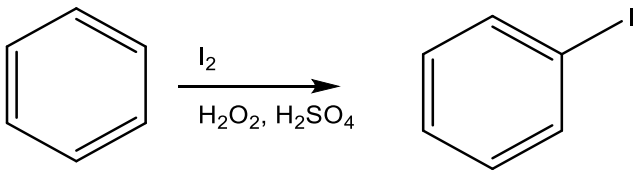


The reaction mechanism for this reaction, you do not need to know, but we can go over it briefly to develop our chemical logic skills and to discuss what the active electrophile is in this reaction.

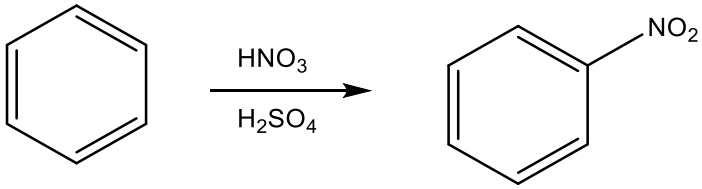

Br
Br
Br
Fe
Br
Br
Br
Br
Fe
Br
Br
Br
H
O
H
H
Br
Br
Fe
Br
Br
Br
FeBr3
Br
H
O
H
H
+
Br
Br
+
FeBr3
+
HBr
+
H2O

The first step of this reaction involves the bromine gas acting as a nucleophile and attacking the electrophilic $FeBr_3$ catalyst. The $FeBr_3$ is a good electrophile because of large electronegativity difference between Fe and Br in the compound, giving the Fe a large positive charge. When the bromine attacks the iron, that gives iron a negative charge and the bromine a positive charge, this causes the compound to be much more electrophilic because the Br-Br bond was substantially weakened. The bromine with a positive charge wants to have one bond and pull all the electrons between itself and the other bromine towards itself only, because of this, the benzene ring attacks the terminal bromine and that causes the positively charged bromine to get its extra electrons. This relieves the positive charge on the bromine and breaks a very weak Br-Br bond, therefore this step is favorable (A**M**SO**W**). Once the benzene ring attacks with its double bond, one of the carbons in the aromatic ring is positively charged, this is an inherently bad thing like we have been saying throughout the course, therefore to remedy this positive charge, a water molecule (or any other basic compound) deprotonates the neighboring carbon to relieve the carbon of its positive charge. This is essentially an E1 reaction at the end if you want to think of it that way. This reaction is favorable because it transfers the positive charged from a non-octet carbocation to an octet satisfied positive charge oxygen, thus it minimizes energy and charge (A**M**SOW). This step also restores the aromaticity of the ring and is driven by resonance stability of the final product as well. Because the $FeBr_3$ was a catalyst, it must be recycled at the end of the reaction, so the bromine that we added on to it in the first step gets ejected, this step makes sense following AMSOW because iron is less electronegative than bromine and therefore would rather be neutral. The bromide is a stable anion and therefore that step proceeds quickly following the production of bromobenzene (A**M**SOW). The bromide then reacts with the acidic water to give HBr and water back so that the next cycle of reaction can continue. This same reaction can be done with chlorine and iodine gas as well:

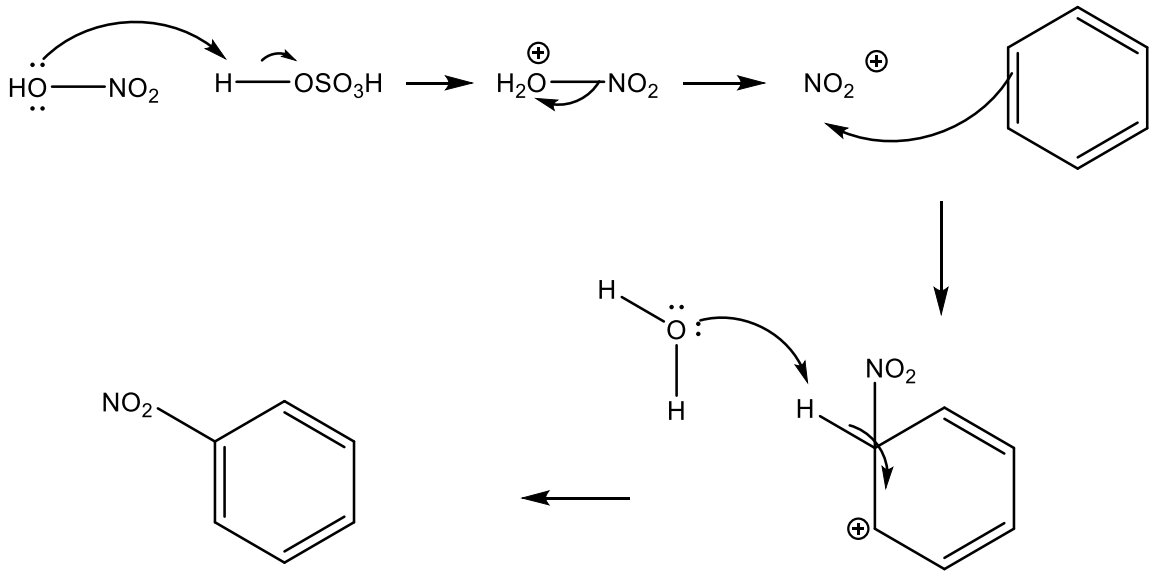




The next EAS reaction to consider is the nitration reaction. This reaction adds an NO_2 or nitro group to the benzene ring like so:

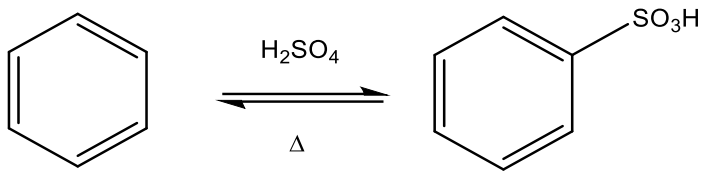


This reaction mechanism you are also not responsible for knowing, but we will discuss it anyway:

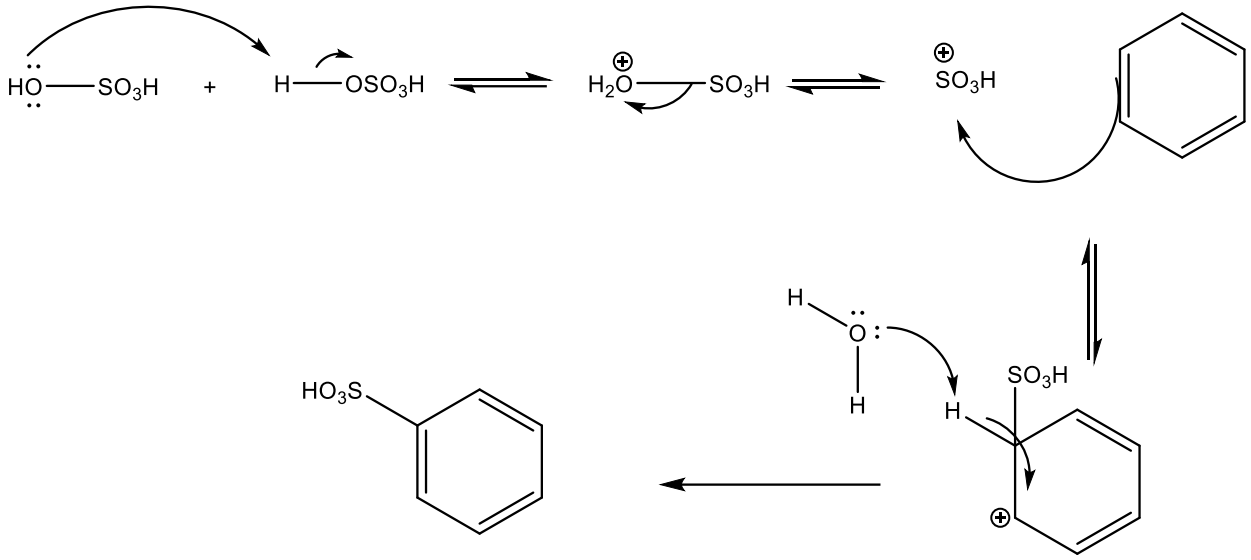


The first step is that the sulfuric acid protonates the nitric acid. This may seem weird to you, but it actually makes a lot of sense, nitric acid is the weakest of all strong acids that you learned in general chemistry, and sulfuric acid is the second strongest, being surpassed only by perchloric acid. Therefore, the first step is simply an acid base reaction (**A**MSOW). Once the nitric acid gets protonated by the sulfuric acid, the OH group goes from a bad leaving group (remember OH^- is a strong base and therefore a bad leaving group) to a good leaving group of H_2O. This leaving group leaves, this is favorable because the oxygen is more electronegative than nitrogen, therefore, of the two of them, nitrogen would prefer to be positively charged. This step effectively reduces charge and therefore is in accordance with A**M**SOW. This NO_2^+ ion is extremely electrophilic because of its positive charge and therefore the benzene ring attacks the nitrogen with its double bond. Steps that follow are the exact same as before, the solvent does an E1 elimination reaction and restores the aromaticity of the benzene ring and everyone is happy because the carbon is no longer positive and aromaticity is restored, energy and charge is effectively minimized (A**M**SOW).

The next EAS reaction is the sulfonation reaction, which will add an SO_3H group to the ring. This reaction has to be done in fuming, concentrated sulfuric acid and is a reversible process that is product favored if heated. The reaction is shown below and the mechanism, like before, is not super important, but we will discuss it regardless to get at the nuance of why it is an reversible reaction rather than a quantitative reaction like the others:



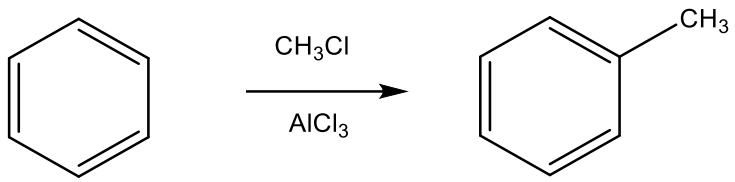
The mechanism is shown here:



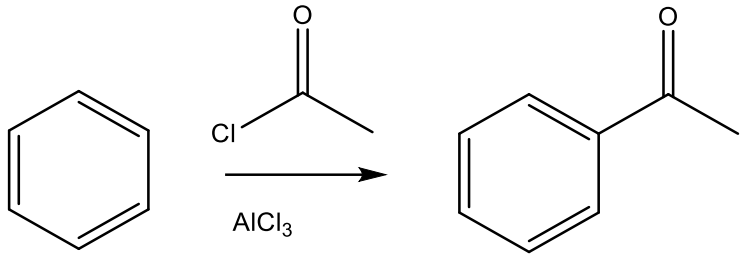
Like in the nitration reaction mechanism, we protonate one acid by deprotonating another. However, unlike in the nitration reaction, sulfuric acid is deprotonating itself, and while this may seem strange to you, this is essentially just the auto-ionization of sulfuric acid. Just like the auto-ionization of water, which produces H_3O^+ and OH^-, this is not a spontaneous process and is in equilibrium. That is the core reason why this reaction, unlike the nitration reaction is an equilibrium process. The issue here is that there is no difference in the pKa's of sulfuric acid and sulfuric acid, they are the same molecule, there WAS a difference in pKa's for the nitration reaction, therefore that reaction was NOT in equilibrium. The second step is just like the second step of the nitration reaction, the protonation happens so that the leaving group changes from the poor OH to the good H_2O leaving group, the leaving group does what it does best… leave and the active electrophile forms (SO_3H^+). This electrophile gets attacked by the benzene ring per the rest of the mechanisms from before and forms the carbocation in the benzene ring. This carbocation is resolved when a solvent molecule deprotonates a neighboring carbon to restore the aromaticity. The chemical logic for the last two steps is the exact same from before.

One of the coolest and most useful aromatic reactions are the Friedel-Crafts reactions. These reactions come in two flavors: alkylation and acylation. The alkylation reaction is shown below and results in adding a carbon chain to the ring. The acylation reaction results in adding an acyl group (carbonyl) to the ring.

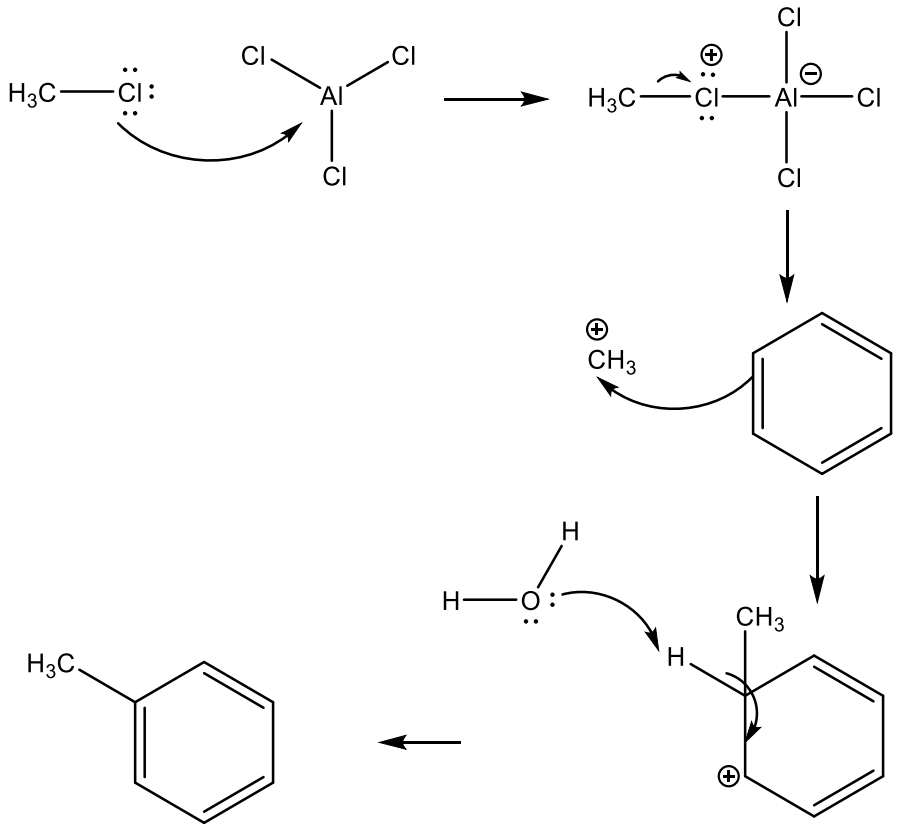
Friedel-Crafts Alkylation

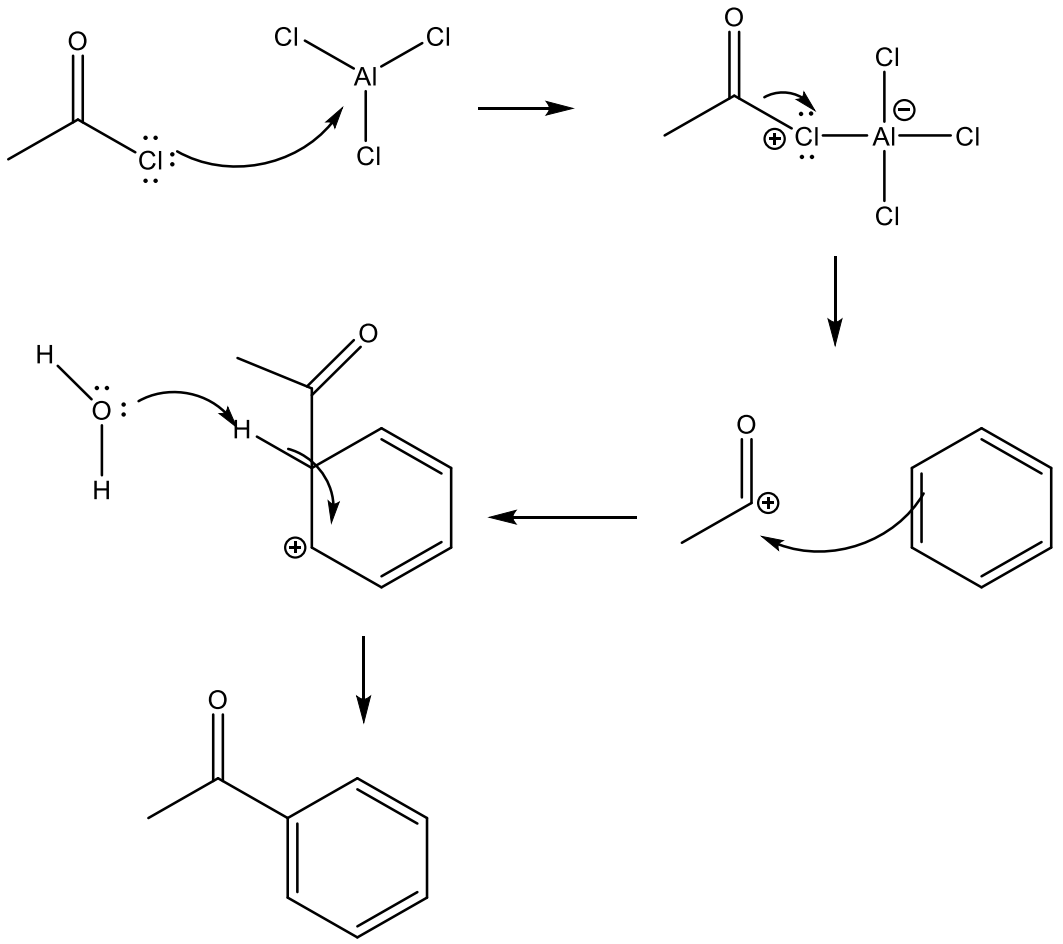


Friedel-Crafts Acylation



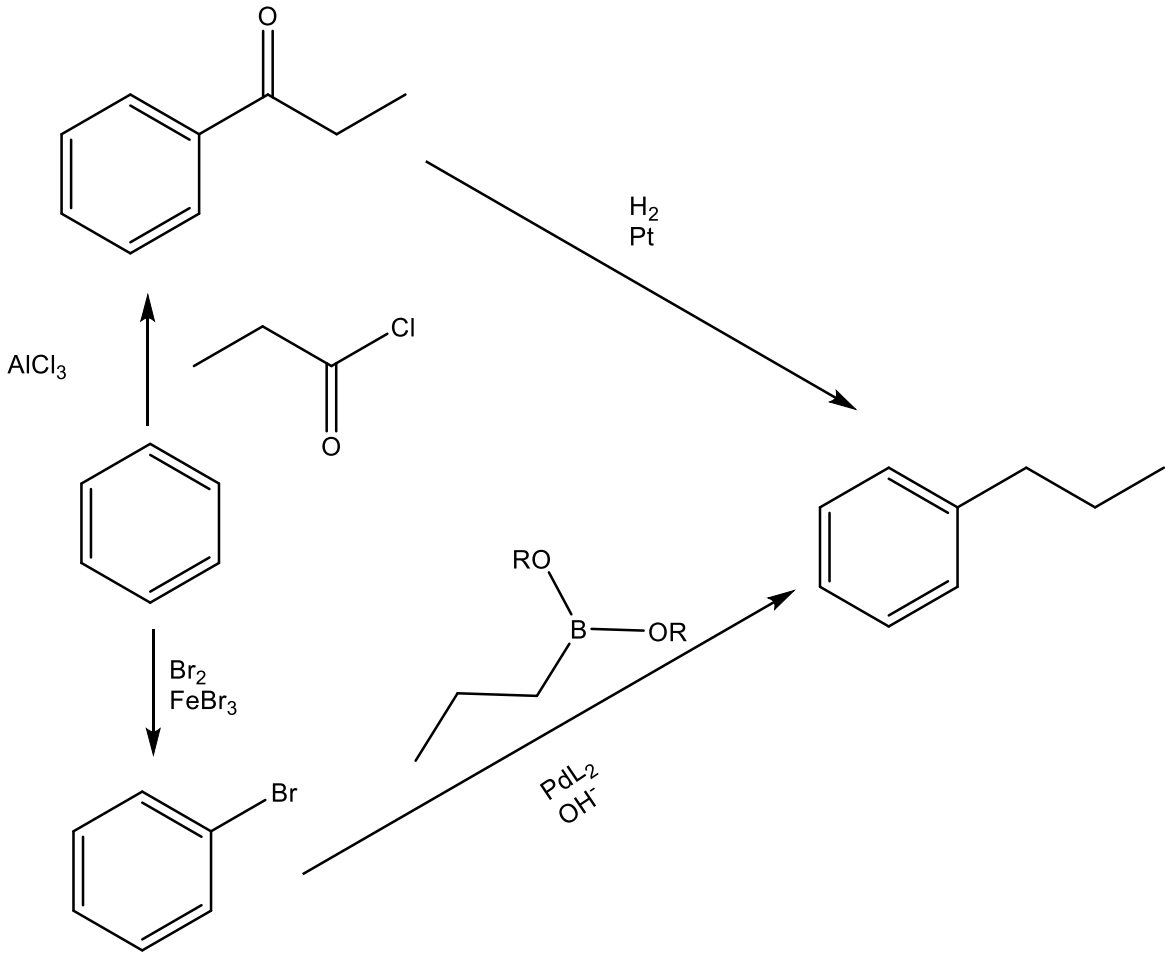
The big difference between the two of them is that they go through different active electrophiles. The alkylation reaction goes through a carbocation, which means that it can rearrange, thus it is typically not the best reaction to use for adding straight carbon chains to the ring, instead you could use Suzuki or Heck coupling reactions or Gilman reagents with bromobenzene. The mechanism for the above reactions is shown below, like before, the specifics are not super important to know, but it is a good exercise in employing AMSOW:


H3C
Cl
Cl
Al
Cl
Cl
H3C
Cl
Al
Cl
Cl
Cl
CH3
H
H
O
CH3
H
H3C

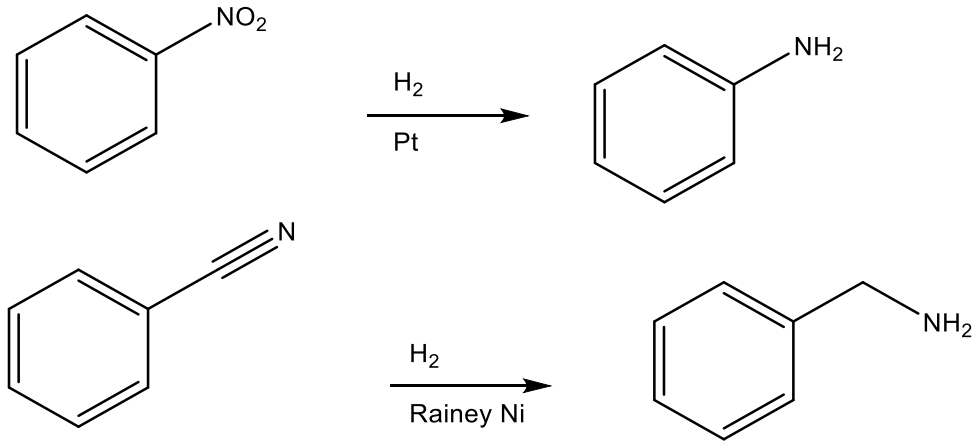


The first step in both of the reaction mechanisms, for both alkylation and acylation is the nucleophilic attack of the chlorine to the $AlCl_3$. The $AlCl_3$ is a good electrophile for the same reason that the $FeBr_3$ was, there is a large difference in electronegativity between Al and Cl such that the central Al is positively charged and therefore electrophilic. The chlorine is the most nucleophilic atom in both compounds (CH_3Cl and CH_3COCl) because it has lone pairs and has the lowest electronegativity between O and Cl which could act as nucleophiles. The second step for both reactions results in the chlorine leaving, this is favorable because the chlorine is relieved of its positive charge and the C-Cl bond is weak to begin with, the positive charge just makes it even weaker (A**M**SO**W**). The third step is where the two mechanisms differ slightly, the alkylation reaction results in the formation of the carbocation, like all carbocations this will rearrange to form a more stable carbocation in an attempt to minimize charge (A**M**SOW). The acylation reaction, on the other hand, results in an acylinium ion, which is unable to rearrange, but is still exceptionally electrophilic. Both of these intermediates get attacked by the benzene ring and the positive charge this generates in the ring gets relieved when a solvent molecule deprotonates the carbon to which the acyl or alkyl group attached, this restores the aromaticity and resolves all the charges (A**M**SOW).

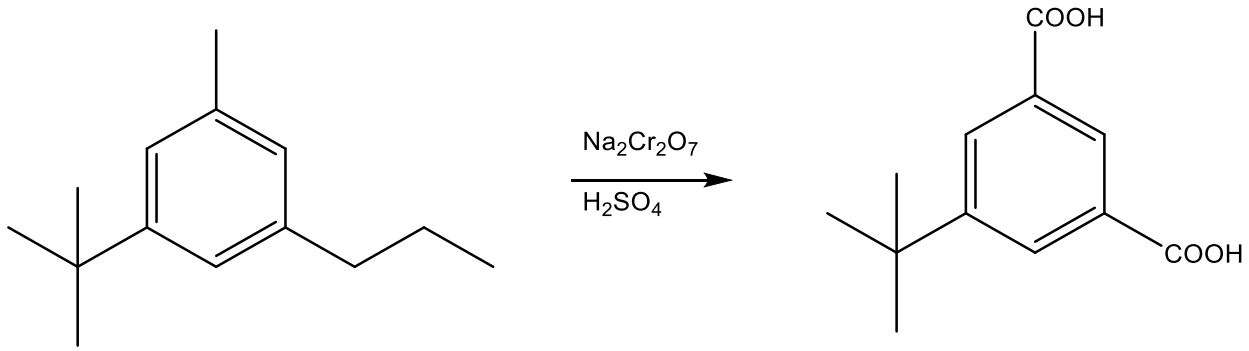
Because alkyl groups are weakly electron-donating, they activate the benzene ring towards EAS reactions, therefore the Friedel-Crafts alkylation reaction also suffers from the risk of overalkylation depending upon the amount of alkyl chloride added. Due to these issues, it is often better to use Suzuki or Heck reactions to add carbon chains to the benzene ring, but in the case where that is not possible, you can reduce the acyl group of Friedel-Crafts acylation using H_2 and Pt OR H_2NNH_2, KOH, and heat like so:



Another common reduction reaction that can be used, is the reduction of the NO_2 group to the NH_2 group using H_2 and Pt as well as the reduction of the CN group to a CH_2NH_2 group with a stronger reducing agent, Raney Ni like so:



Just as the carbon chains can be reduced, they can also be oxidized. If a primary or secondary alkyl group is added to the ring, of any size, and is treated with $Na_2Cr_2O_7$ in sulfuric acid, that alkyl group will become a carboxylic acid group like so:

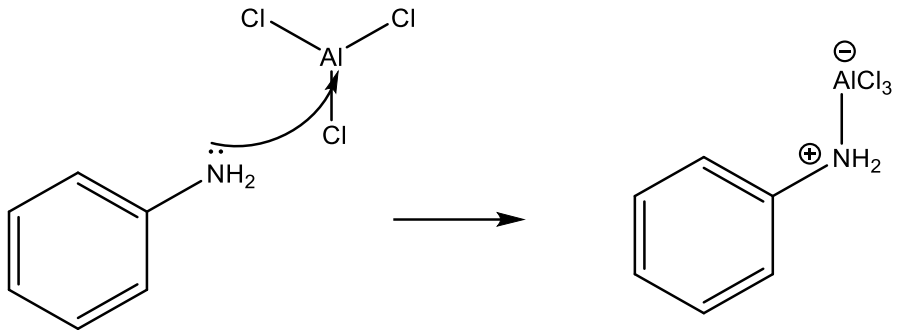


Just like the other redox reactions, the mechanism for this is not required of you to understand, just know that the first step requires taking off a benzylic hydrogen, therefore, because tertiary alkyl groups do not have that, they cannot get oxidized to carboxylic acids.

Once groups are on the ring, we have to look at their directing preferences. For ortho/para directors, or EDGs, the major product is typically the para product if the group you are adding is relatively large and the group already on the ring is relatively large. This should make sense, as the para position is farthest away from the group and therefore addition at this position would minimize steric interactions the best. For small groups that are adding to the ring (think halogens), the ortho positions are preferred because the guiding force is the random probability of adding to any one of the three positions, because there are two ortho positions, it is more likely to land on those by random chance.

There are also restrictions on what reactions you can do depending on what is already on the ring, Friedel-Crafts reactions are the slowest of all EAS reactions and therefore will not occur if

they have a meta-directing group on the ring. Friedel-Crafts reactions also cannot be done on amino-substituted benzene rings because the nitrogen can attack the $AlCl_3$ catalyst (recall NH_2 is a nucleophile and $AlCl_3$ is an electrophile) like shown below:

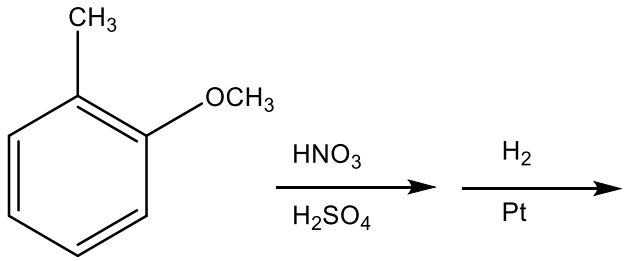


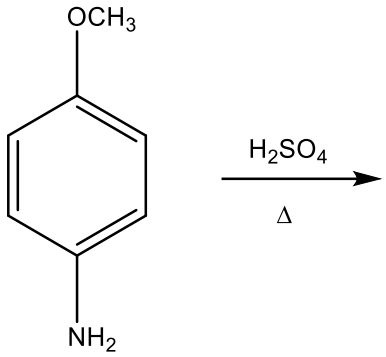
The fact that it attacks the $AlCl_3$ catalyst is problematic for two reasons: firstly, without the $AlCl_3$ catalyst the first step of the mechanism is not possible. Secondly, with the nitrogen losing its lone pair when it attacks the $AlCl_3$, it loses its ability to donate electrons into the ring and therefore it becomes a meta-directing group, which as we just discussed prevents Friedel-Crafts reactions.

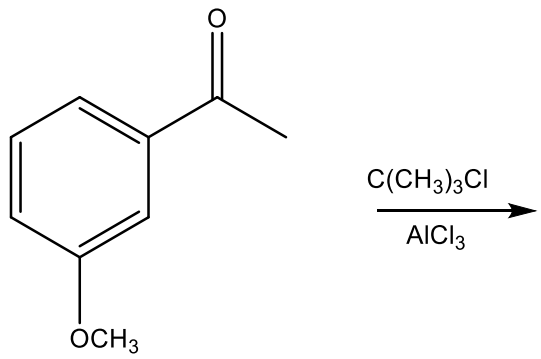
When more than one group is on the ring, the most powerful activating (ortho/para) group will have the dominant directing effect. Therefore, to determine how groups would attach to the ring, consult the chart I gave you, it will help make that determination.

Practice questions:

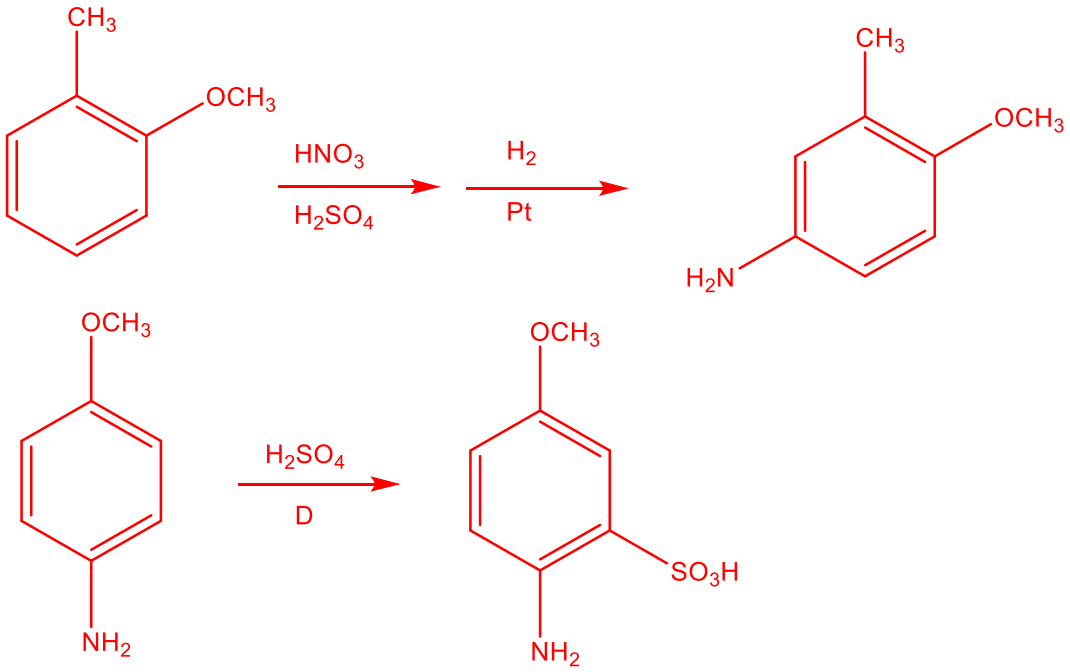
Predict the major organic product for the following reactions:

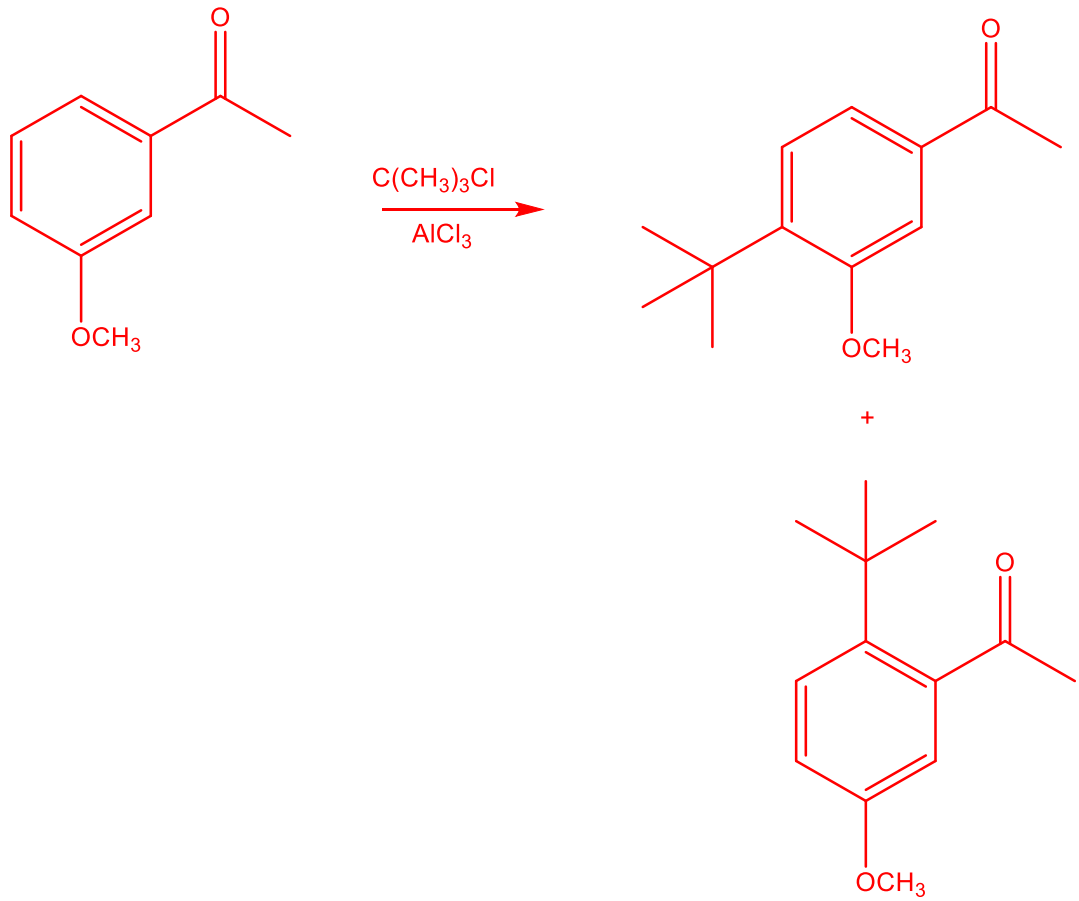

CH3
OCH3
HNO3
H2SO4
H2
Pt


OCH3
NH2
H2SO4
Δ

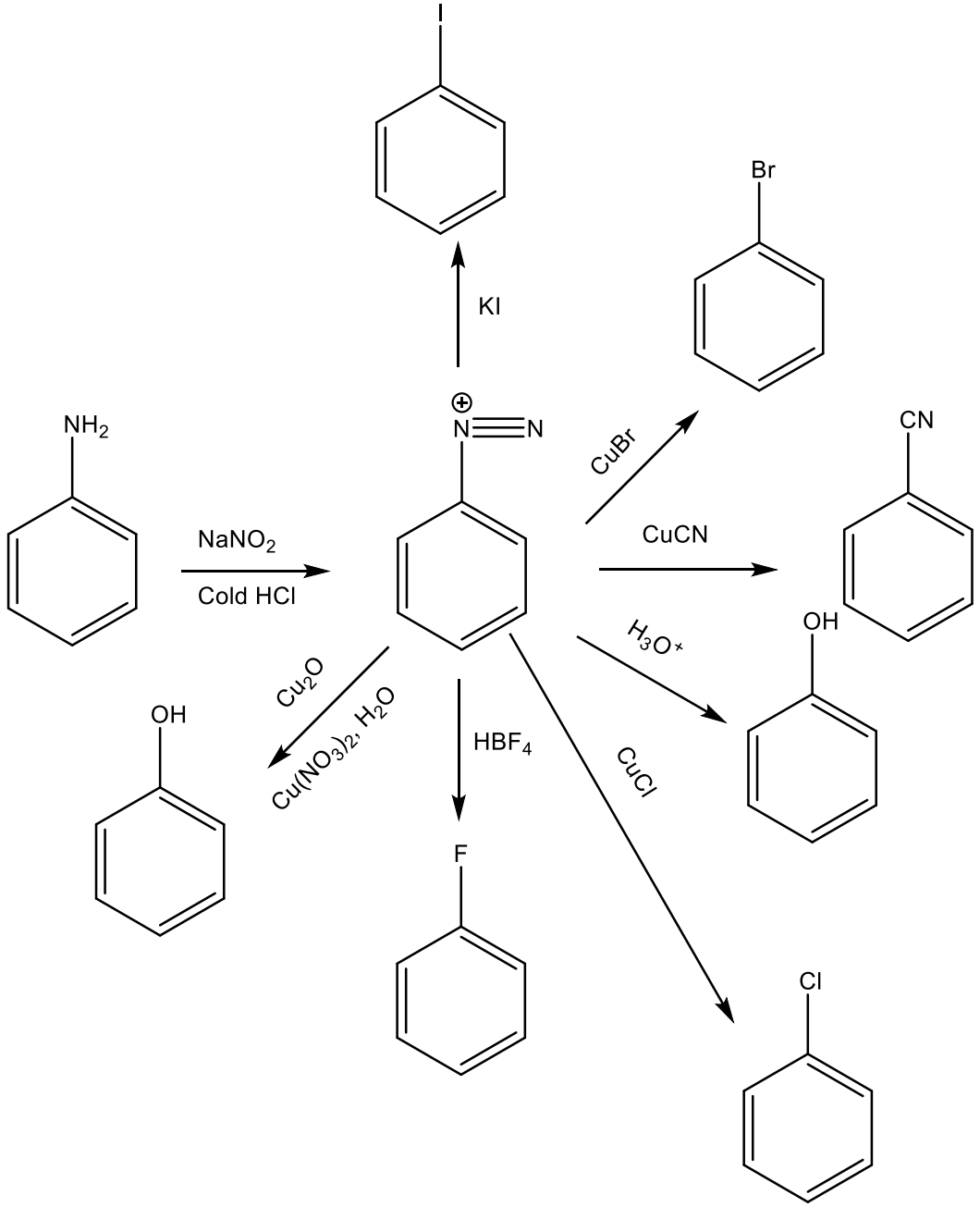

O
OCH3
C(CH3)3Cl
AlCl3

Answer:

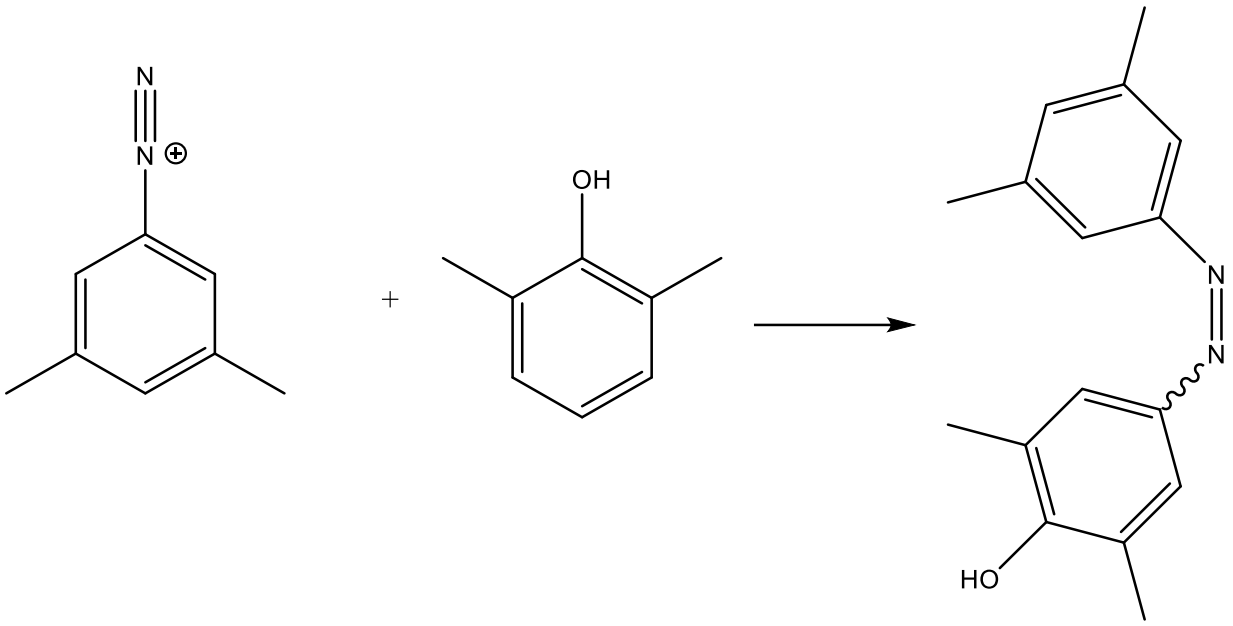

CH3
OCH3
HNO3
H2SO4
H2
Pt
CH3
OCH3
H2N
OCH3
NH2
H2SO4
D
OCH3
SO3H
NH2

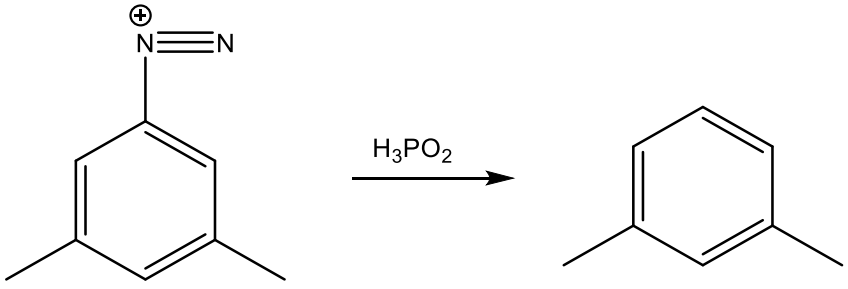

O
OCH3
C(CH3)3Cl
AlCl3
O
OCH3
+
O
OCH3

The last EAS reaction that we will discuss is the formation of the diazonium salt. Diazonium salts are incredibly useful compounds, they can be used to replace an NH2 group with a wide variety of groups, and these salts are electrophilic enough to act as reactants in EAS reactions with other activated benzenes. These reactions are shown below in a scheme and a good way to remember most of the reactions of the diazonium salt is that the N_2^+ group gets replaced by whatever is attached to the Cu. The mechanisms for these reactions are largely unknown at the time, the only mechanism that is known is the formation of the diazonium salt, however, this is not a super important reaction to discuss so we will skip the details in this text:

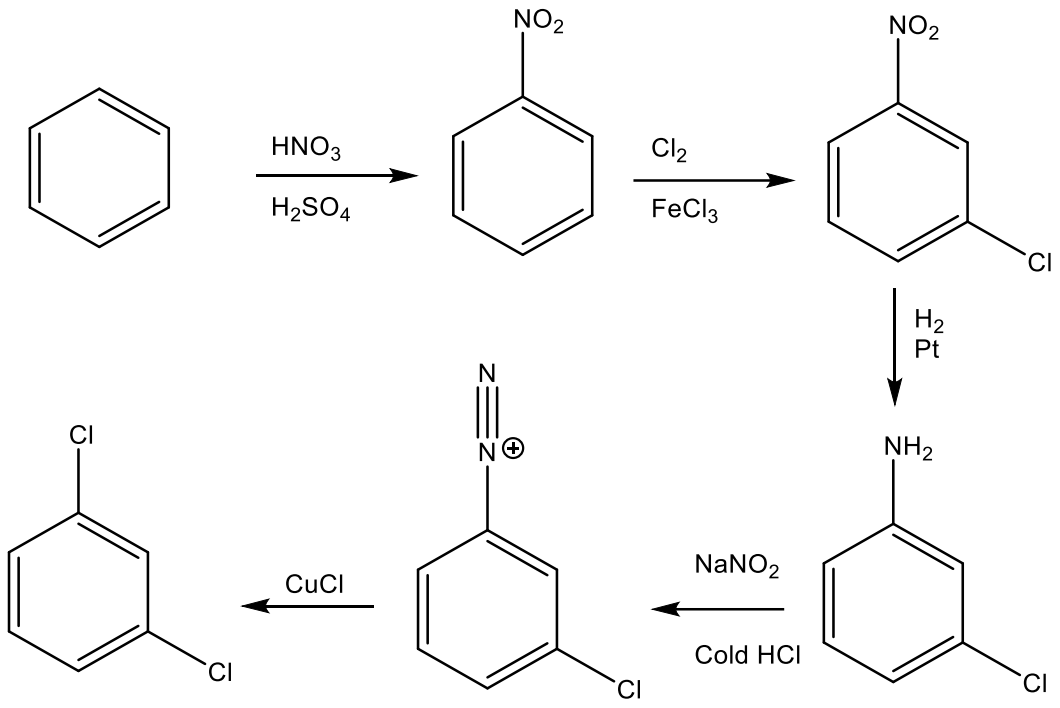


There are also two special reactions, one in which the diazonium acts as an electrophile in an EAS reaction with another benzene derivative, and one in which you can remove the diazonium group with H_3PO_2, these are shown below:



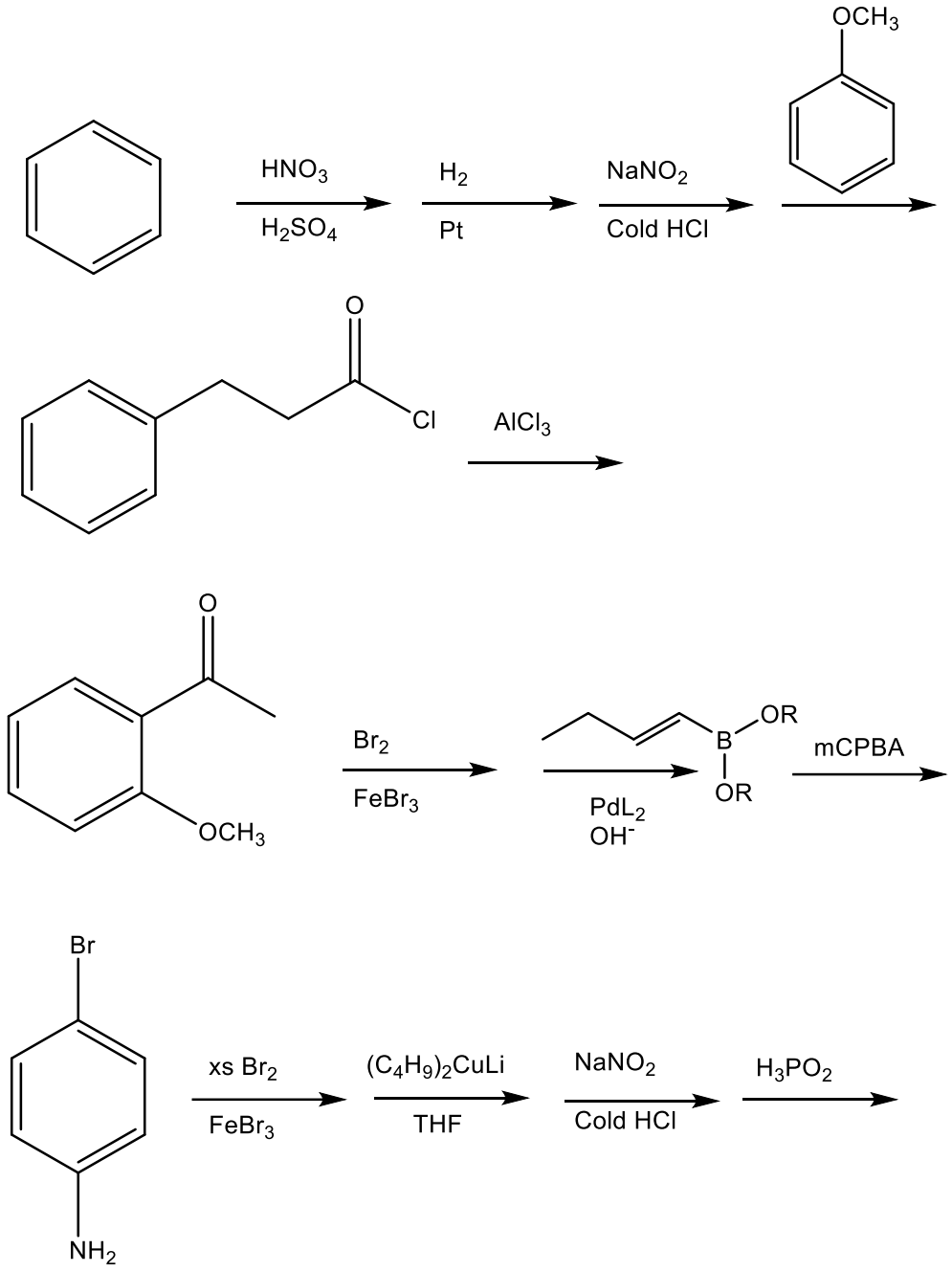


The reason why diazonium salts are useful is because they allow the synthesis of otherwise inaccessible molecules, such as meta dichlorobenzene. If you do it the traditional way, the chlorine gets added on first, but halogens are ortho/para directors, not meta directors, so getting the meta isomer is impossible. However, the synthesis of meta dichlorobenzene is possible with diazonium salts like so:

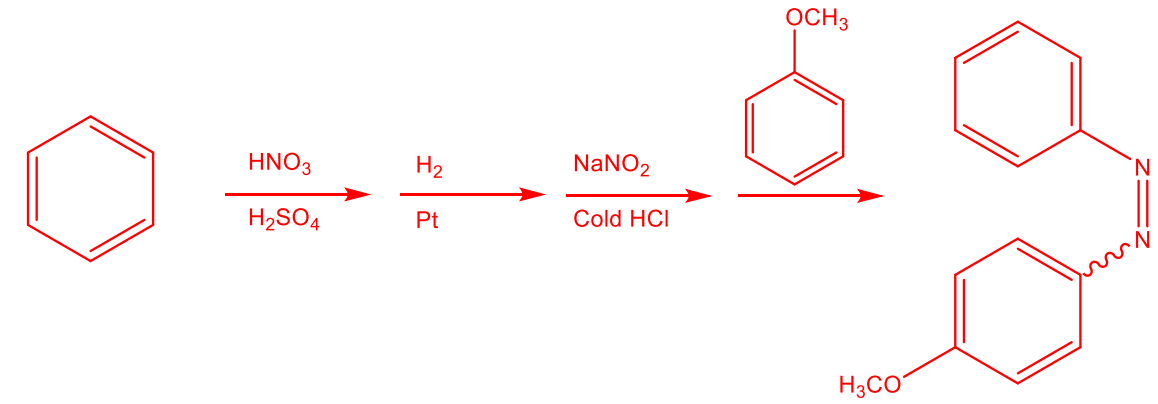


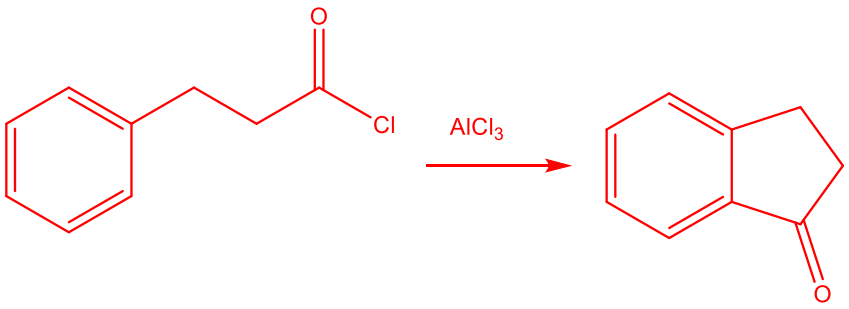
Practice questions:

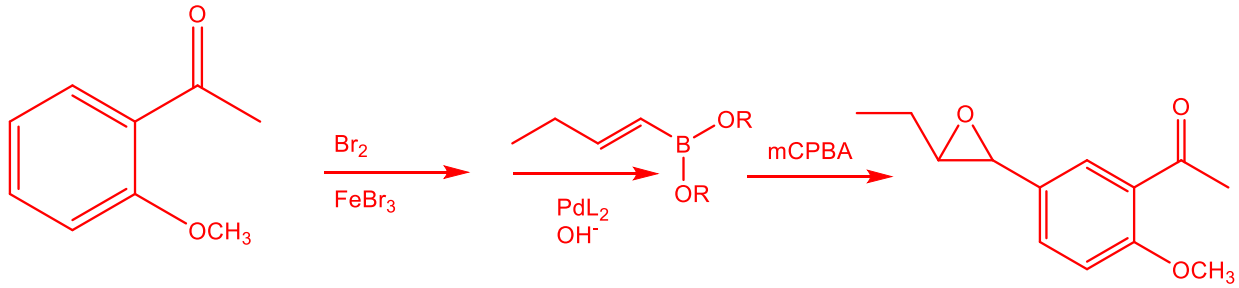
Predict the major organic products for the following reactions:

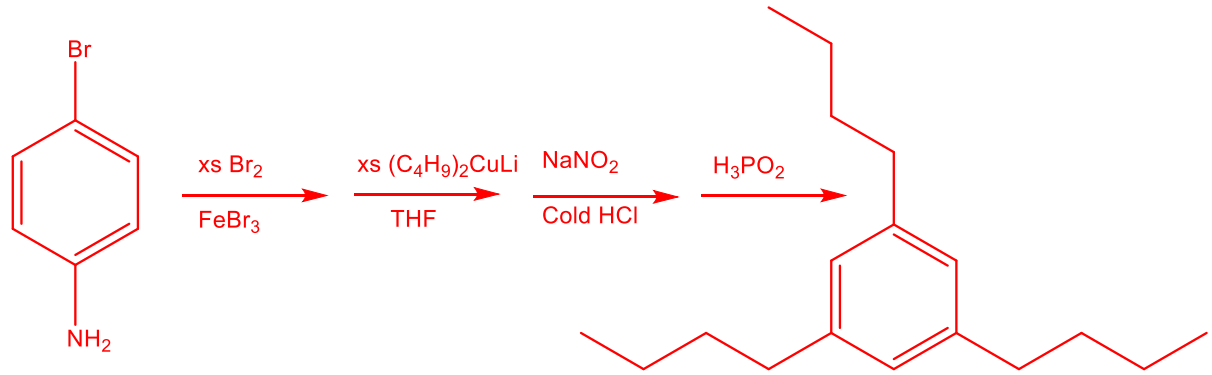

HNO3
H2SO4
H2
Pt
NaNO2
Cold HCl
OCH3
O
Cl
AlCl3
O
OCH3
Br2
FeBr3
OR
B
OR
PdL2
OH-
mCPBA
Br
NH2
xs Br2
FeBr3
(C4H9)2CuLi
THF
NaNO2
Cold HCl
H3PO2

Answers:

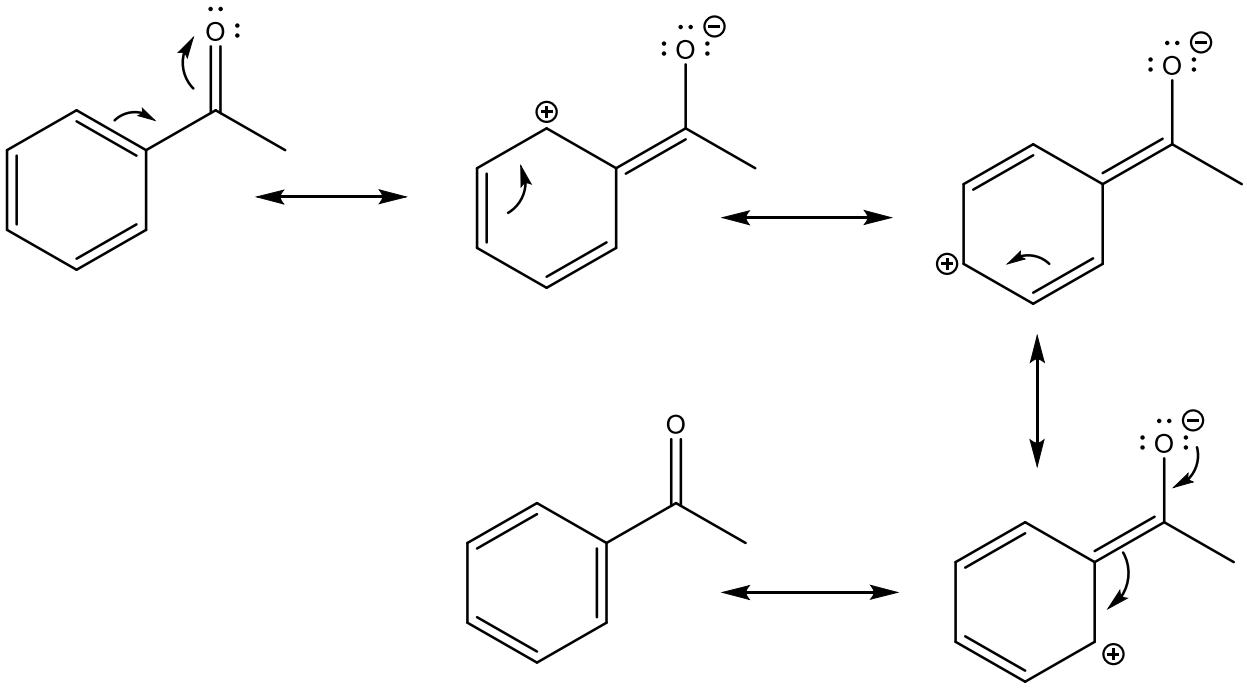

HNO3
H2SO4
H2
Pt
NaNO2
Cold HCl
OCH3
N
N
H3CO


O
Cl
AlCl3
O

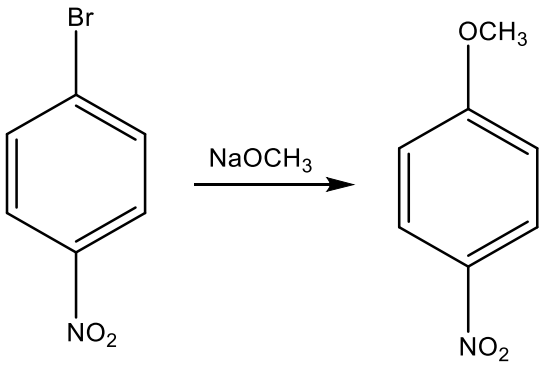

O
OCH3
Br2
FeBr3
B
OR
OR
PdL2
OH-
mCPBA
O
O
OCH3


Br
NH2
xs Br2
FeBr3
xs (C4H9)2CuLi
THF
NaNO2
Cold HCl
H3PO2

That about covers all of the EAS reactions that you are responsible for in a typical organic chemistry course. Now we will discuss the NAS reaction. The NAS reaction is not as commonly used as the EAS reaction because the ring needs to have at least ONE strong EWG on the ring, this is because the benzene ring would prefer to act as a nucleophile than an electrophile like it would in an NAS reaction. In NAS reactions, a hydrogen or halogen is replaced by a nucleophile. The reaction will proceed faster if there is a better leaving group and a stronger nucleophile if the benzene rings are equally deactivated. In NAS reactions, the directing preferences for the groups are inverted such that EWG direct ortho/para and EDG direct meta. This is because the most electrophilic carbons in the benzene ring when EWG are on the ring are the ortho and para positions, recall the resonance form for acetophenone:



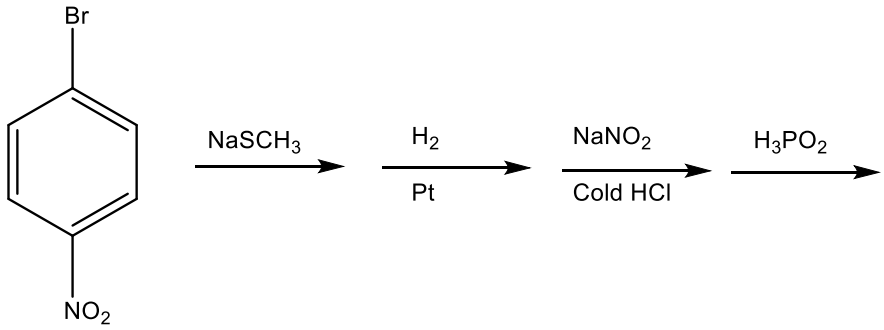
Remember, positive charge = electrophile. A typical NAS reaction is shown below:

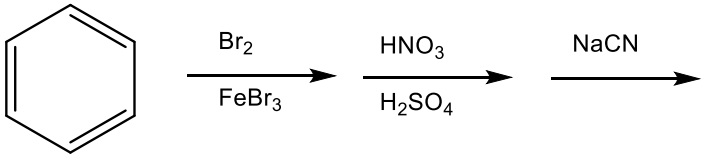


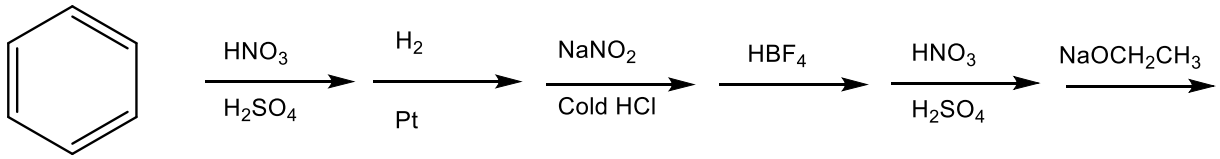
This reaction will proceed better with heat and if the incoming nucleophile is a stronger base than the halogen leaving group.

Practice questions:

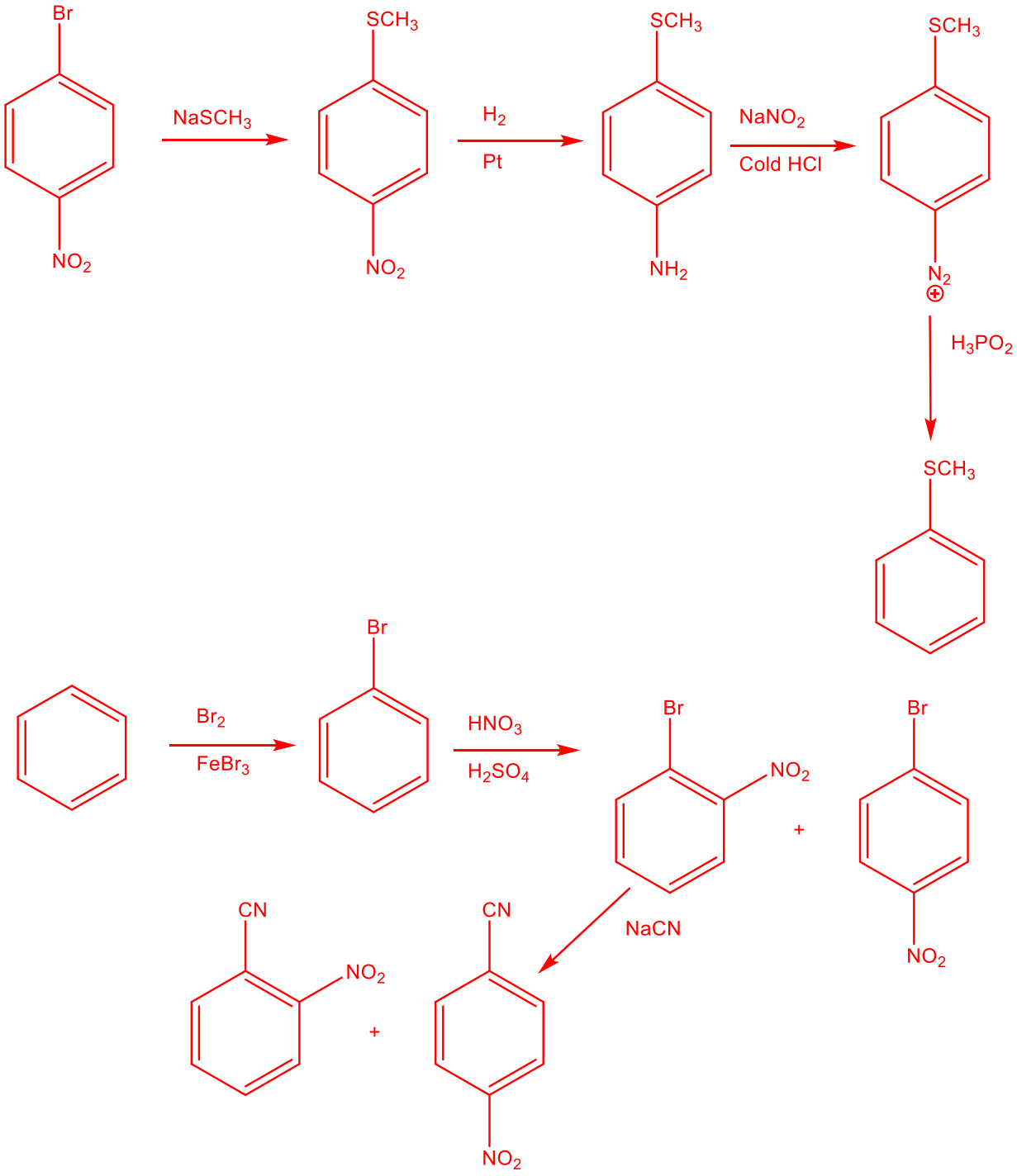
Predict the major organic products for the following reactions:

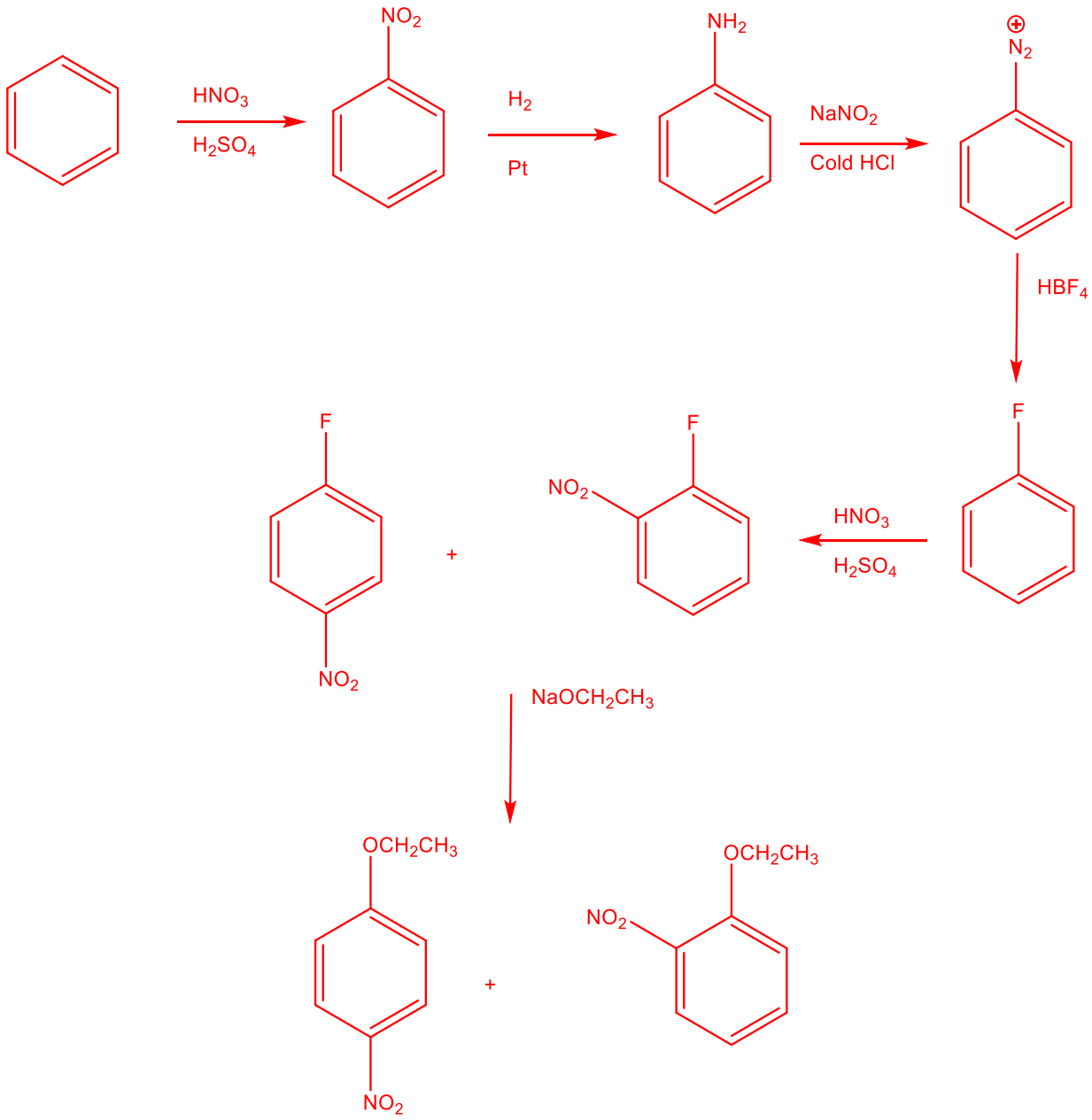






Answers:


Br
NO2
NaSCH3
SCH3
NO2
H2
Pt
SCH3
NH2
NaNO2
Cold HCl
SCH3
N2
H3PO2
SCH3
Br2
FeBr3
Br
HNO3
H2SO4
Br
NO2
+
Br
NO2
NaCN
CN
NO2
+
CN
NO2

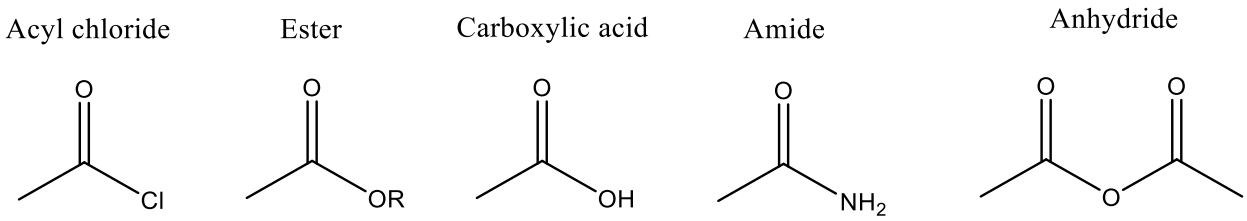

HNO3
H2SO4
NO2
H2
Pt
NH2
NaNO2
Cold HCl
N2
HBF4
F
HNO3
H2SO4
F
NO2
F
NO2
+
NaOCH2CH3
OCH2CH3
NO2
+
OCH2CH3
NO2

Chapter 12: Introduction to Reactions of Carboxylic Acid Derivatives

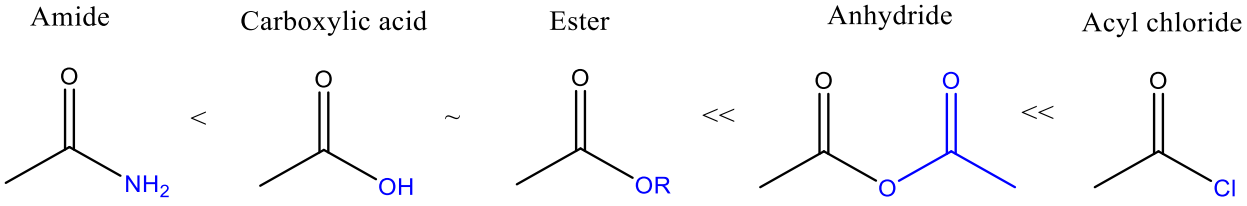
To start off, let's first discuss what exactly a carboxylic acid derivative is. Carboxylic acid derivatives are those carbonyl functional groups that are NOT ketones and aldehydes, they are carbonyl groups that have a heteroatom attached to the carbonyl carbon. These compounds all react very similarly, however, they differ in their reactivity. This reactivity trend can be explained through leaving group strength, the better the leaving group attached to the carbonyl carbon, the more reactive the carboxylic acid derivative is. These compounds always go through a reaction referred to as nucleophilic acyl substitution, in all of these reactions, a new carboxylic acid derivative is formed by substituting the original leaving group for a new one. Let's list all of the carboxylic acid derivatives and let's see if we can figure out their reactivity using what we know about leaving group strength:

Practice question:

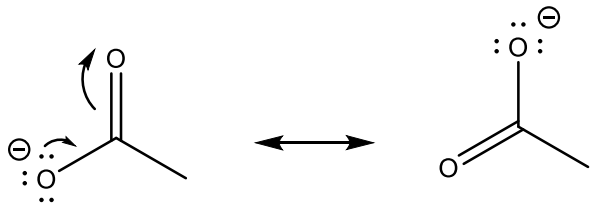
Rank the following carboxylic acid derivatives in order of increasing reactivity:



Answer:

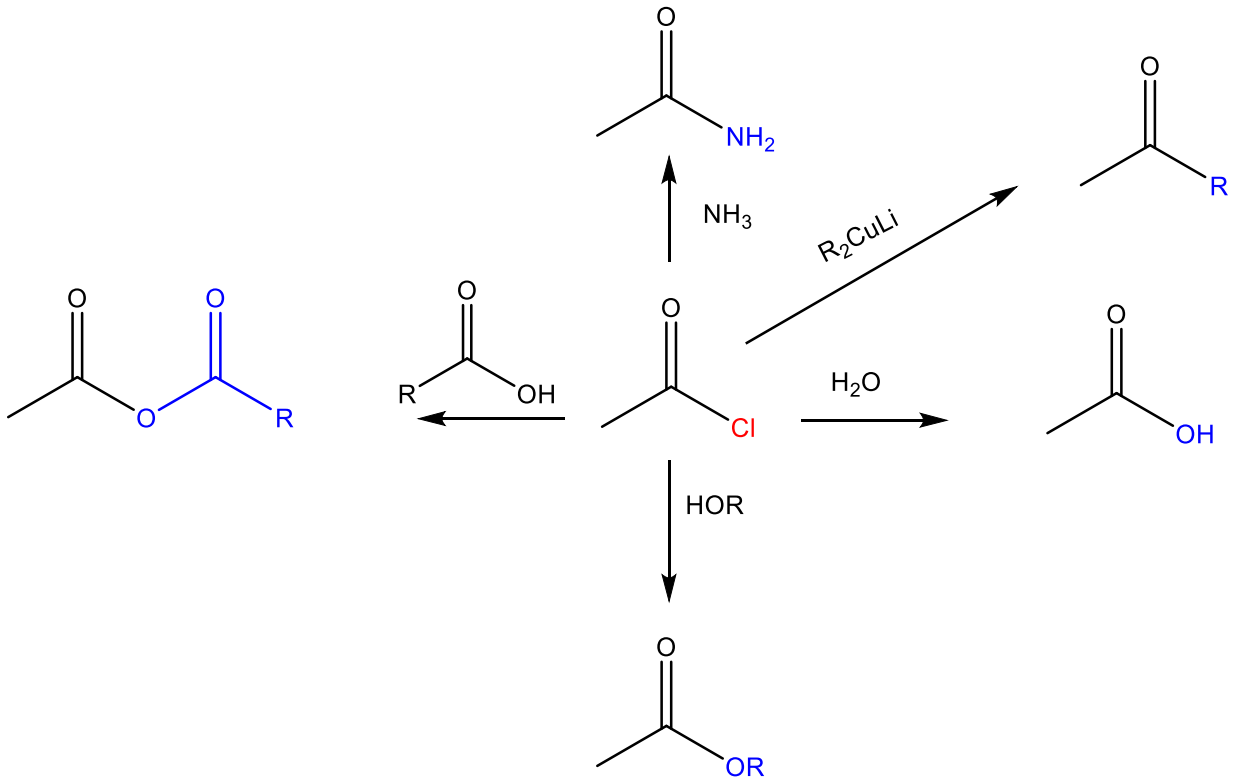


The groups highlighted in blue are the leaving groups for all of the carboxylic acid derivatives that we will discuss in this chapter. Recall that leaving group strength is opposite base strength, so the strongest base leaving group will be the weakest leaving group. We therefore order the leaving groups in order of decreasing basicity and that is our order of reactivity. The NH_2^- group is the strongest base and therefore the amide group is the least reactive carboxylic acid derivative. The OH^- and OR^- groups are roughly equal in base strength so they are essentially a tie. The acetate leaving group for the anhydride is resonance stabilized as shown below and we know that strong bases give weak conjugate acids, but carboxylic acids are stronger acids than alcohols (OR), water (OH), and ammonia (NH_2), therefore carboxylates are weaker bases.



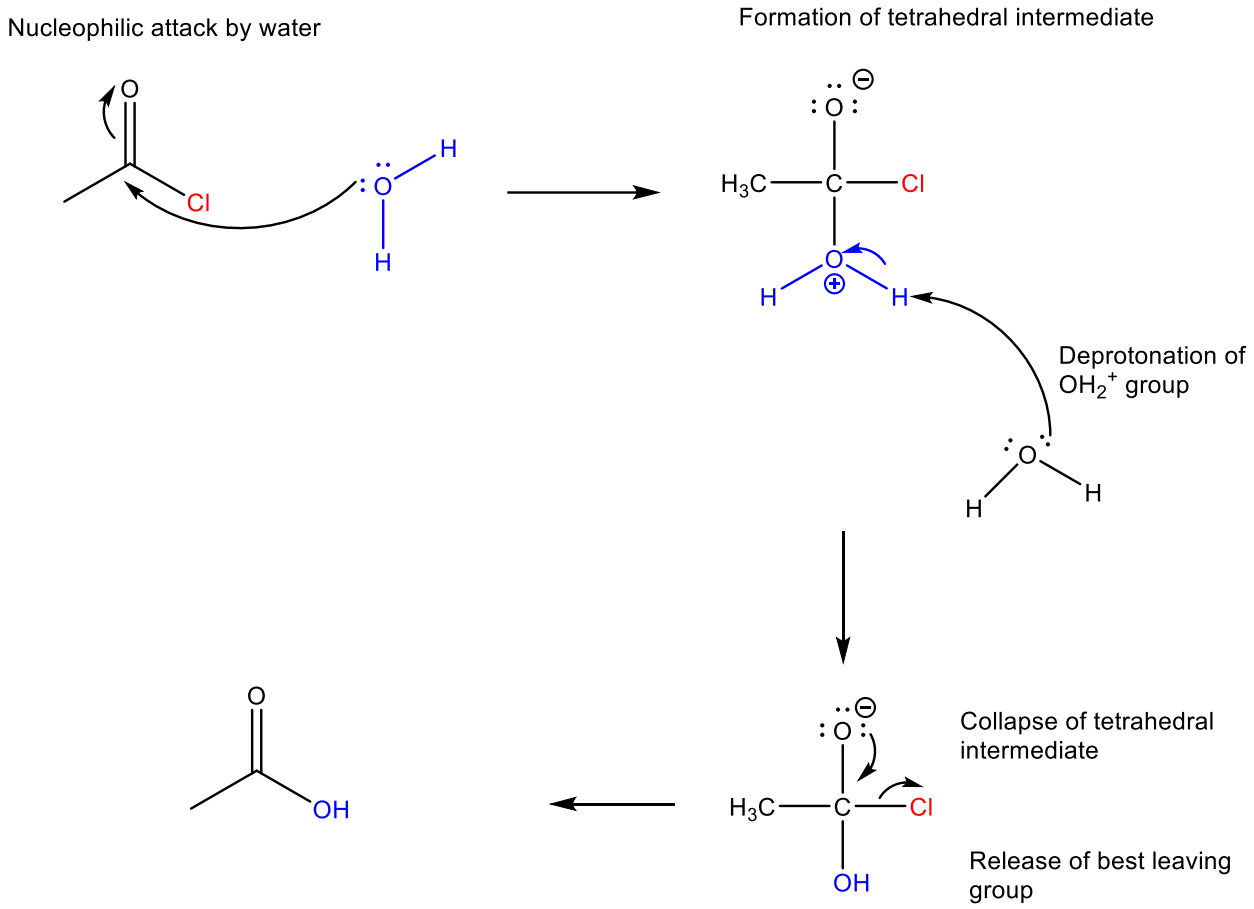
The last leaving group is Cl^-, the conjugate acid of which is HCl, which is a strong acid, therefore the acyl chloride group is the most reactive carboxylic acid derivative.

We will start our discussion of the reactions of carboxylic acid derivatives by going in order of decreasing reactivity. Therefore, we will start by discussing acyl chlorides. Acyl chlorides are incredibly reactive and extremely moisture sensitive. The acyl chloride functional group can be reacted with a plethora of compounds as shown below to create ALL the other carboxylic acid derivatives and ketones when they react with Gilman reagents:



On a fundamental level, carboxylic acid derivatives are electrophiles, and this should make sense given their structure. The carbonyl bond, C=O, is extremely polar because of the large electronegativity difference between C and O. Due to this extreme electronegativity difference and the moveable pi bond between the two elements, carbonyl compounds of all classes (carboxylic acid derivatives or not), are ELECTROPHILES. The carbonyl carbon is always very partially positive, making it electrophilic. While the above reaction scheme may seem very intimidating, all of these reactions occur through the same exact mechanism, except for the

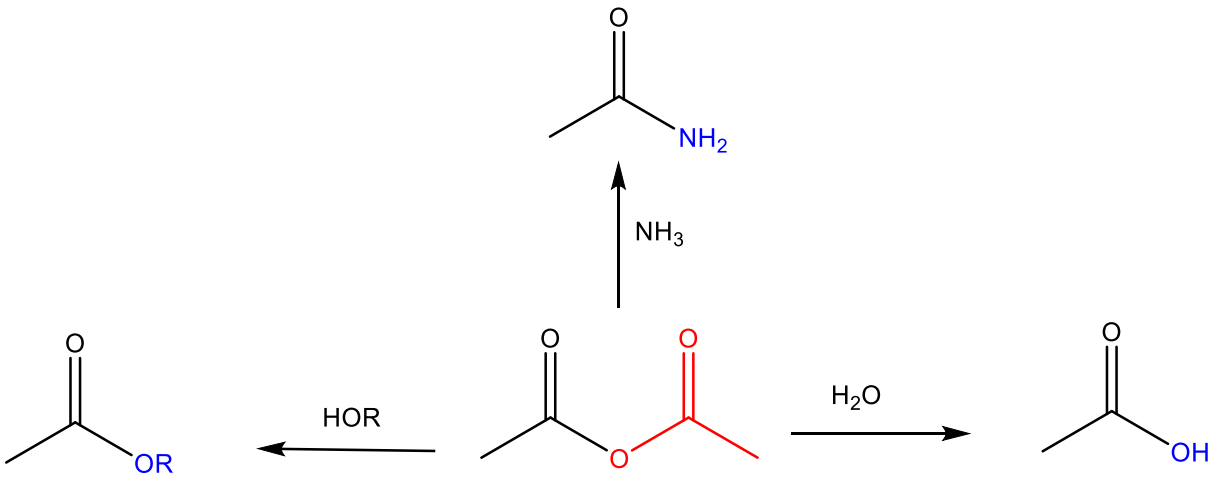
Gilman reagent, but we will not get into that, just view that as essentially the same as the coupling reactions to alkyl chlorides we discussed in the organometallics chapter. As an example case, we will discuss the reaction of the acyl chloride with water:



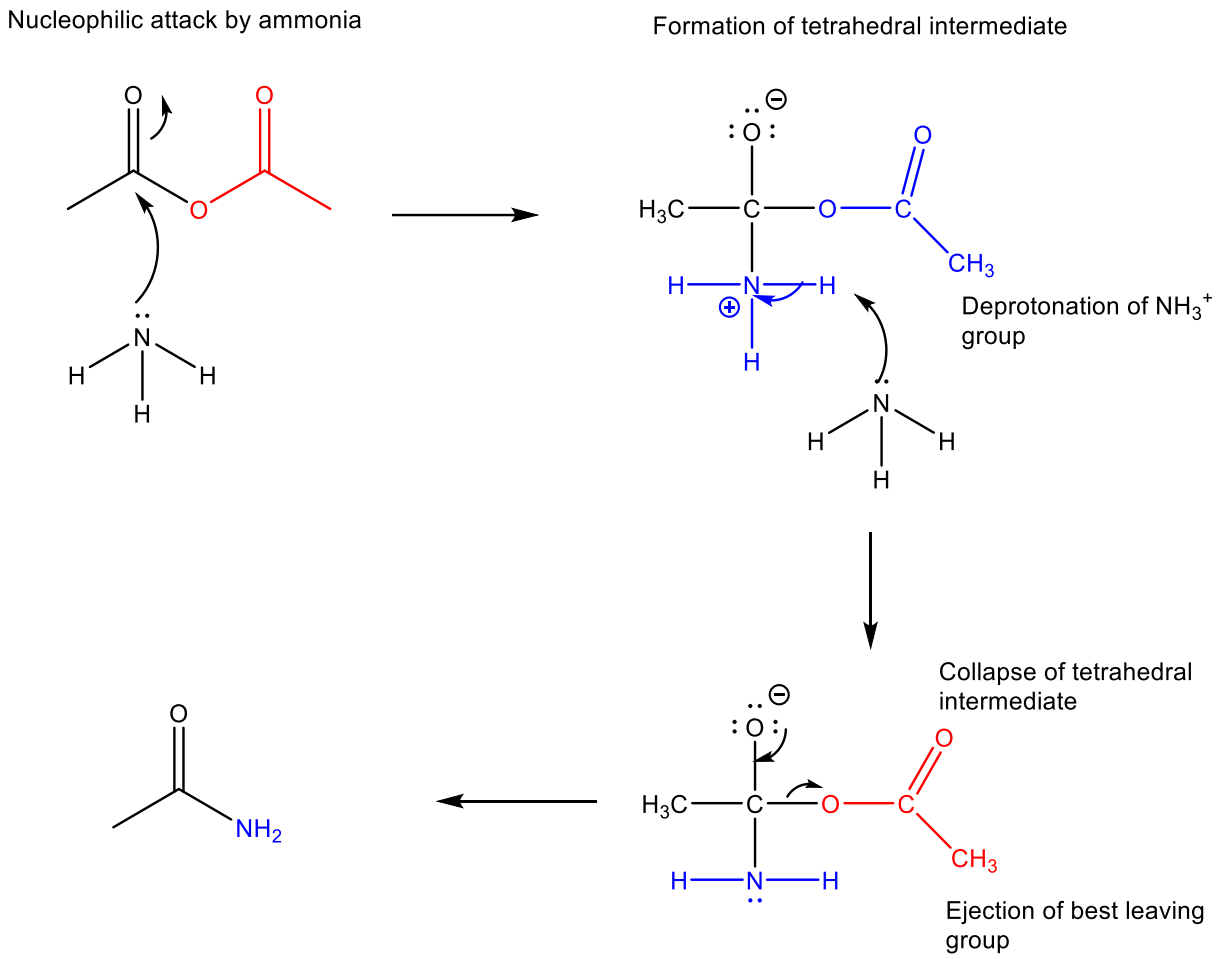
Since this reaction mechanism is the foundation for literally every single reaction mechanism in this chapter, let's dissect it so that we can make sense of it. The first thing that happens is the water attacks the carbonyl carbon, this is because the carbonyl carbon is an electrophile like we had previously discussed and the water molecule can act as a nucleophile because of its lone pairs. When the water molecule attacks the carbonyl carbon, the carbon is forced to break its weakest bond that is the pi bond between the carbon and the carbonyl oxygen (AMSO**W**), this forms the tetrahedral intermediate. In this new tetrahedral intermediate, there are effectively two leaving groups, the water that just attached and the chloride, so before the tetrahedral intermediate can close back up, the water leaving group needs to be weakened so that we don't run the risk of ejecting it and going back to square one. To do this, another water molecule will act as a base and deprotonate the water leaving group, this should make sense because protonated alcohols are exceptionally acidic and the oxygen on the top of the tetrahedral intermediate is inductively withdrawing electrons, making the protonated alcohol even more acidic (**A**MSOW). Once the water leaving group is deprotonated, the OH group is not going to want to get ejected

anymore, it is too strong a base and therefore too weak a leaving group. Then when the lone pairs of the oxygen come down to reform the carbonyl bond, the best leaving group gets ejected, in this case it is clearly the Cl group that is the best leaving group. The other options would be CH_3^- and OH^-, both of which are rip-your-hide off bases, so they are awful leaving groups. Once the chlorine gets kicked off, we get our product. The reason the carbonyl wants to reform if it can is because C=O bond is very strong compared to C-O bond (177 kcal/mol versus 85.5 kcal/mol), therefore strong bonds want to form and the chloride will get kicked off (AM**S**OW). The reactions of acyl chlorides are so vast because chloride is a good leaving group, as we will see soon, when the leaving group gets weaker, we need to use an acid catalyst and do extra steps to make the leaving group leave.

The next strongest carboxylic acid derivative, is the anhydride, and these compounds do the almost the exact same reactions as acyl chlorides and they proceed through exact same mechanism as acyl chlorides, the only thing that is not constant between them is that anhydrides do NOT react with Gilman reagents or carboxylic acids. The reaction web for anhydrides is shown below.

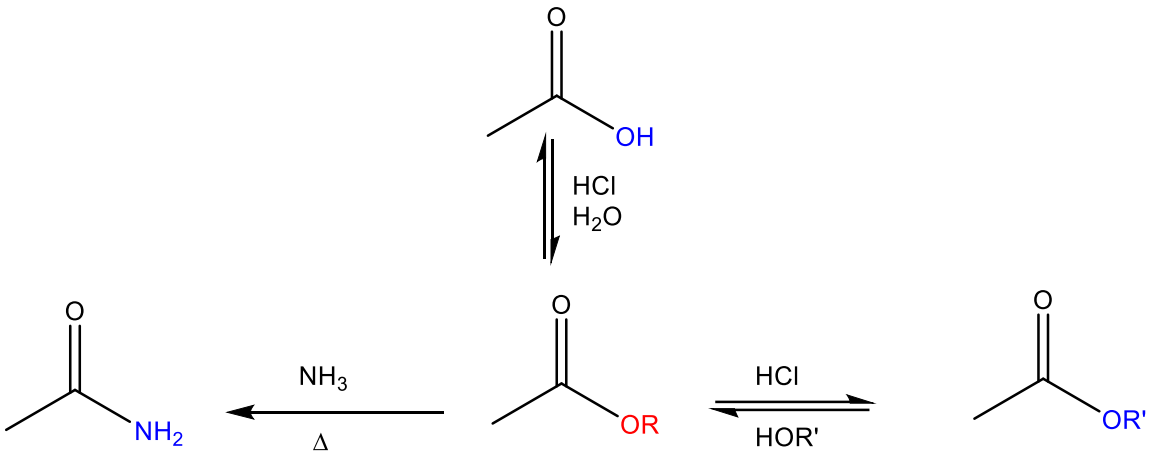


Remember, on a fundamental level, these reactions involve replacing a leaving group (red) with an incoming nucleophile (blue). In this way, they are similar to SN_1 and SN_2 reactions, except these reactions occur on carboxylic acid derivatives. But, why would you use anhydrides if they go through fewer reactions than acyl chlorides? The main reason is that unless you want to make a ketone, there is no real reason to use an acyl chloride because they are much too reactive and moisture sensitive, anhydrides are a good compromise between reactivity and stability. Let's go through the mechanism for the formation of an amide using an anhydride, and we can see how similar the reaction mechanism is to the one we just discussed:

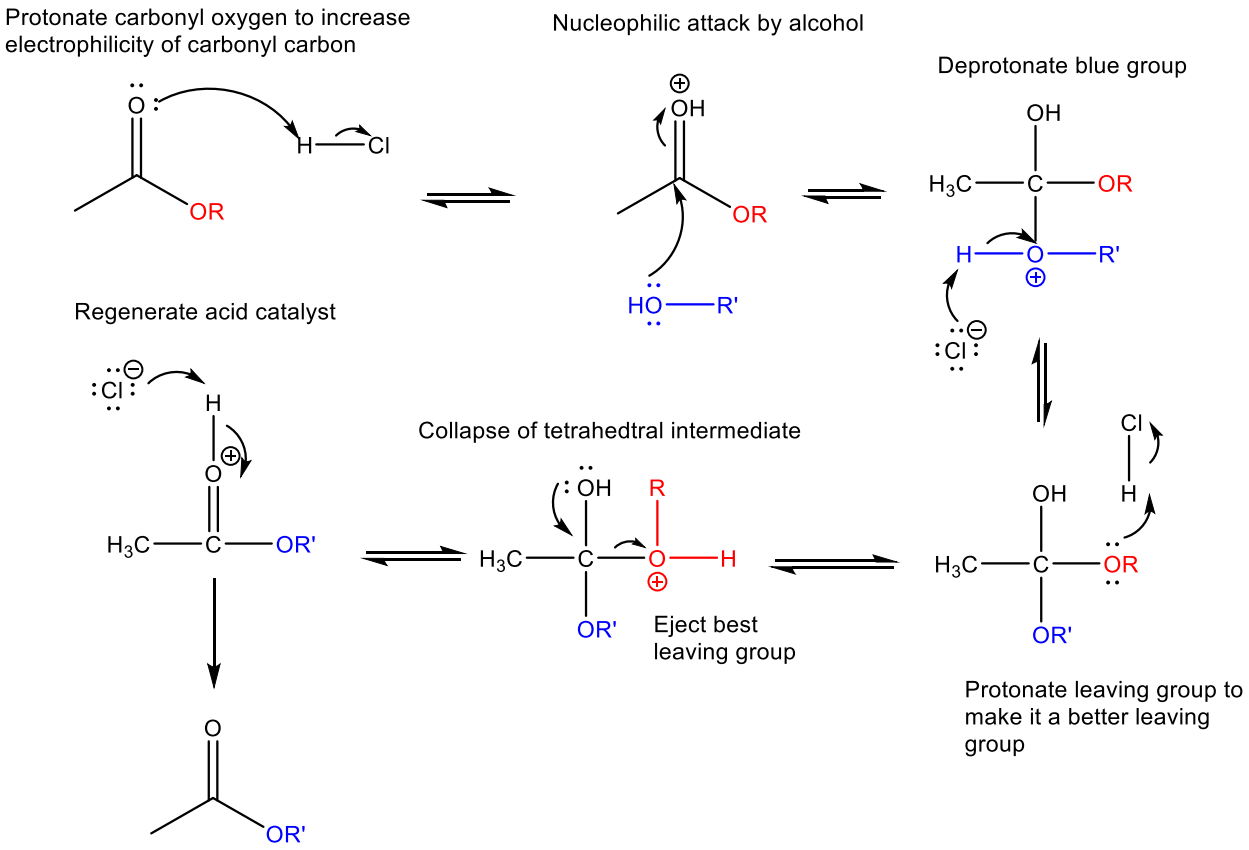


The chemical logic is the exact same as before, see if you can talk yourself through this reaction, if you want help, just look at the reaction of the acyl chloride for guidance.

After the anhydrides and acyl chlorides, the leaving group becomes sufficiently poor that the carbonyl compound needs to activated using an acid catalyst. *All carboxylic acid derivatives weaker than anhydrides will require the use of an acid catalyst*. Let's discuss the ester functional group. Esters are frequently found in perfume products because they typically smell very nice. The reaction web for esters is shown below:



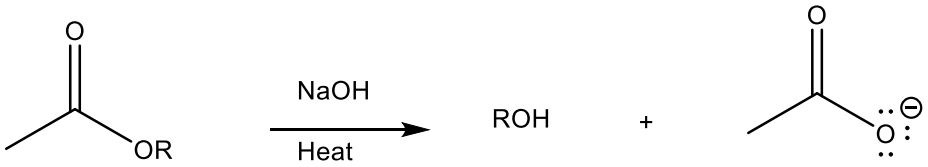
These mechanisms differ slightly in how they operate, we will do the mechanism for the transesterification reaction (reaction with HOR') as an example:



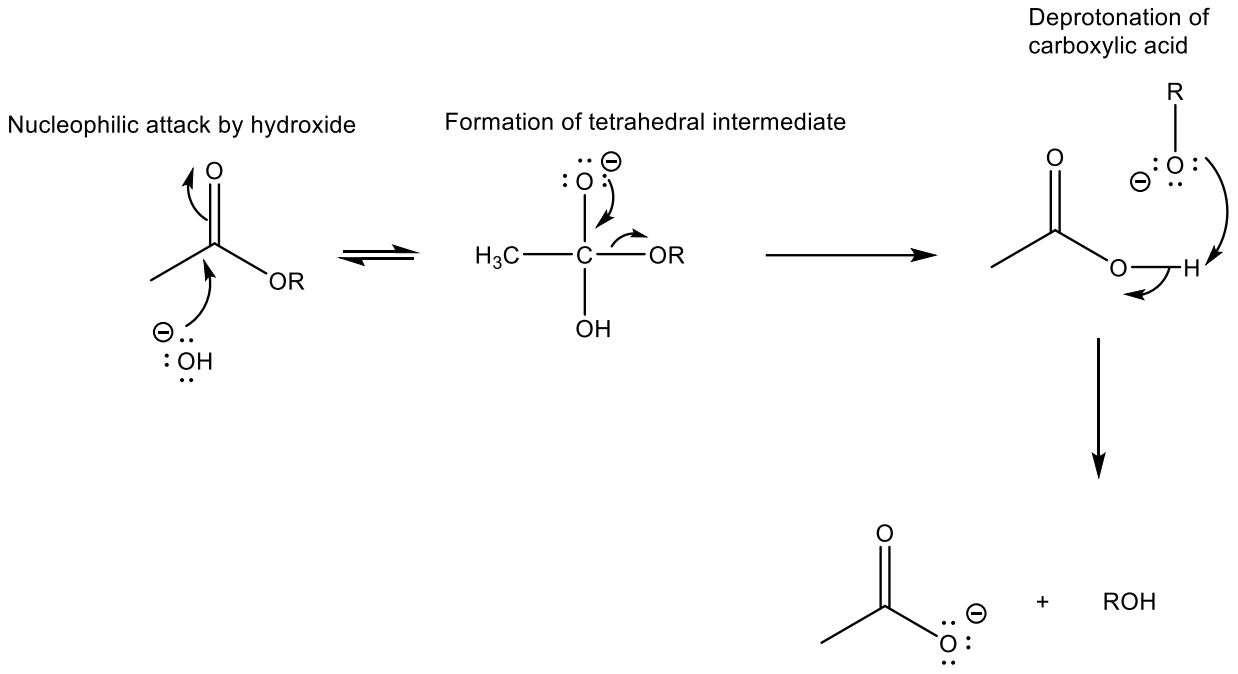
The first step is the carbonyl oxygen gets protonated by the acid, this is done so the carbonyl carbon is more electrophilic so the alcohol can attack it more easily. The reason why the acid catalyst increases the electrophilicity of the carbonyl carbon is because of the positive charge it

puts on the oxygen. The positive charge that is placed on the oxygen can be resolved if the carbonyl carbon is attacked, because then the carbonyl oxygen becomes just a regular alcohol. It therefore increases the electrophilicity of the carbonyl carbon by promoting nucleophilic attack to minimize the positive charge on oxygen (A**M**SOW). That is why the second step happens relatively quickly upon protonation, the alcohol uses its lone pairs to attack the carbonyl carbon and resolve the positive charge on the carbonyl oxygen (A**M**SOW). These are all equilibrium processes because HCl and the protonated carbonyl oxygen are roughly equal in acidity, therefore, there is no preference for one versus the other and the reaction is driven forward by an excess of HOR' (recall Le Chatelier's principle from general chemistry). When the nucleophilic alcohol attacks the carbonyl carbon, there is a positive charge on it. It is therefore the best leaving group, and if the tetrahedral intermediate collapses here, it would go back to the last step, that is why all of these steps are in equilibrium. The reverse reaction CAN and DOES occur, we just don't write our arrows like that because it doesn't give us interesting chemistry. Because we don't want our nucleophilic alcohol leaving, we deprotonate it with the Cl^- we generated in the first step when we protonated our carbonyl oxygen, this regenerates our acid catalyst so we can use it again and it prevents our new alcohol from leaving prematurely. Once the acid is regenerated, it can be used to protonate the alcohol leaving group, this makes it a weaker base and therefore a better leaving group. In the next step, the tetrahedral intermediate collapses and expels the best leaving group, which was the alcohol that got protonated (the one in red that was there initially). There is still an issue, firstly, the acid catalyst wasn't regenerated again, and catalysts must be regenerated at the end of the reaction, and secondly, the carbonyl oxygen is positively charged which is inherently bad and unstable. To resolve the positive charge on the oxygen and regenerate the acid catalyst, the Cl^- we generated when we protonated the red alcohol acts as a base and deprotonates the carbonyl oxygen, this gives us our desired product. I know this is a lot to take in, but if you continue to look at this, it will make sense with the explanation I just provided. The biggest issue that I personally had when learning this reaction is that I didn't understand why the arrows went the way they did and why it didn't go backwards, but that's the thing, it DOES go backwards, it is just not what we want to happen so we don't draw our arrows that way. The key thing to understand here is that all of these processes are in equilibrium, therefore they can and will go backwards, only maybe 25% of the molecules will take this route initially, the rest will go back and forth between steps. The way you get near quantitative results from these reactions is by doing them in an excess amount of alcohol so that the equilibrium is product-favored.

Esters can also be hydrolyzed in base, this process is called saponification, and it is the premise behind how soaps are made. The reaction is as follows:

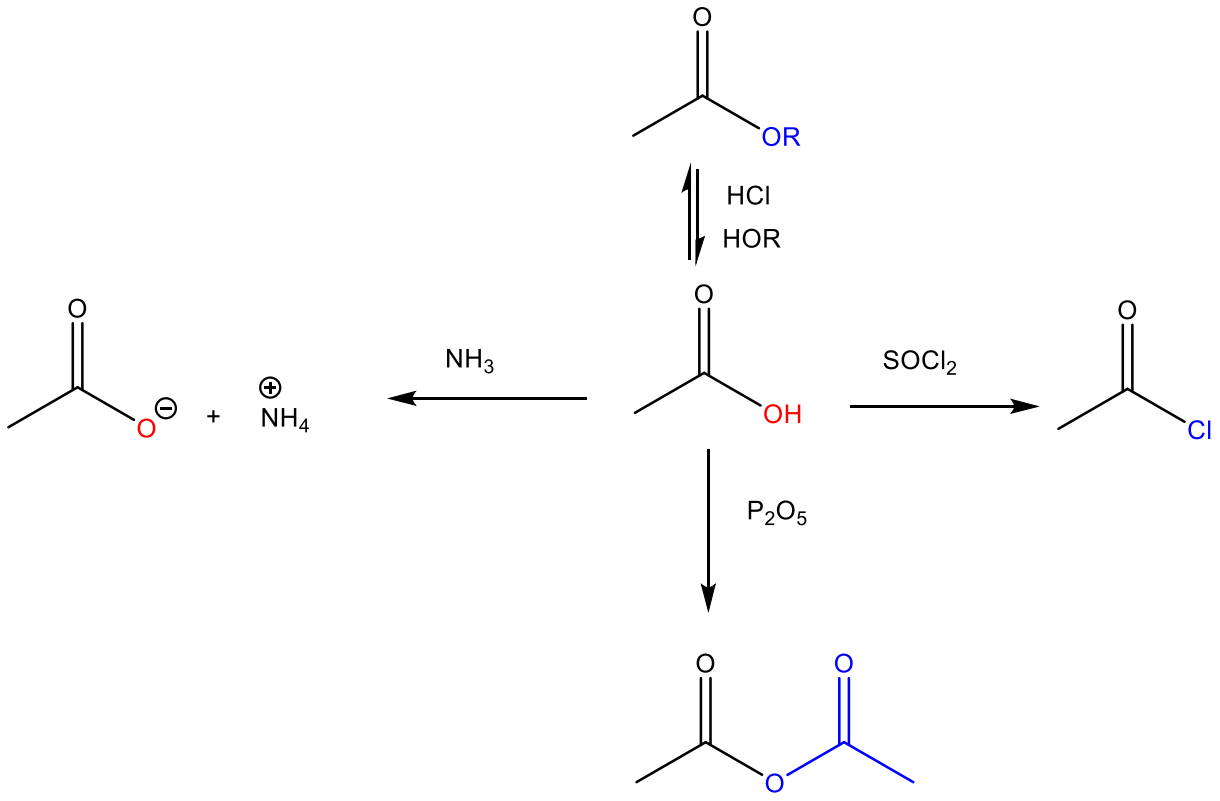


The mechanism for this reaction is shown below:



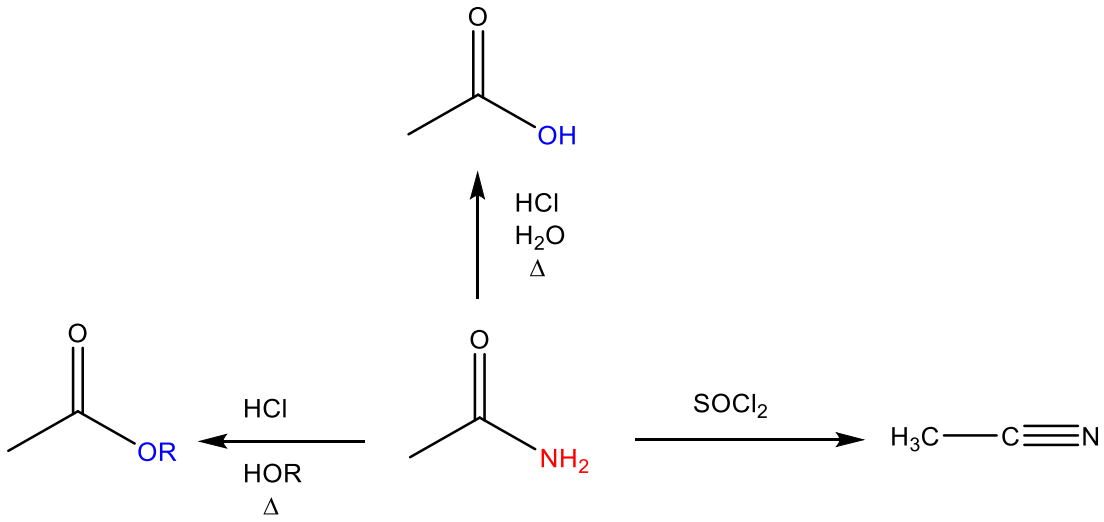
The first step involves the nucleophilic attack of the hydroxide anion to the carbonyl carbon. Because the two leaving groups OR and OH are both equally likely to get ejected in the second step, the first step is an equilibrium process. Once the OR group gets ejected, however, the OR^- strong base deprotonates the carboxylic acid that forms, this is a simple acid-base reaction (**A**MSOW).

Now we will discuss the reactions of carboxylic acids. Carboxylic acids by themselves are not very useful and can do all the reactions esters can do except for making amides. When carboxylic acids are reacted with amines, an acid-base reaction occurs instead because of the acidic nature of the COOH group. Because of this, it is oftentimes useful to activate the carboxylic acid and make it more reactive. In the same way that $SOCl_2$ could replace an alcohol with an alkyl chloride, it can also replace a carboxylic acid with an acyl chloride, which is much more useful and reactive. Alternatively you can use dehydrating agents such as P_2O_5 to make anhydrides from carboxylic acids. This can be done either intermolecularly or intramolecularly. The reactions of carboxylic acids are shown below:

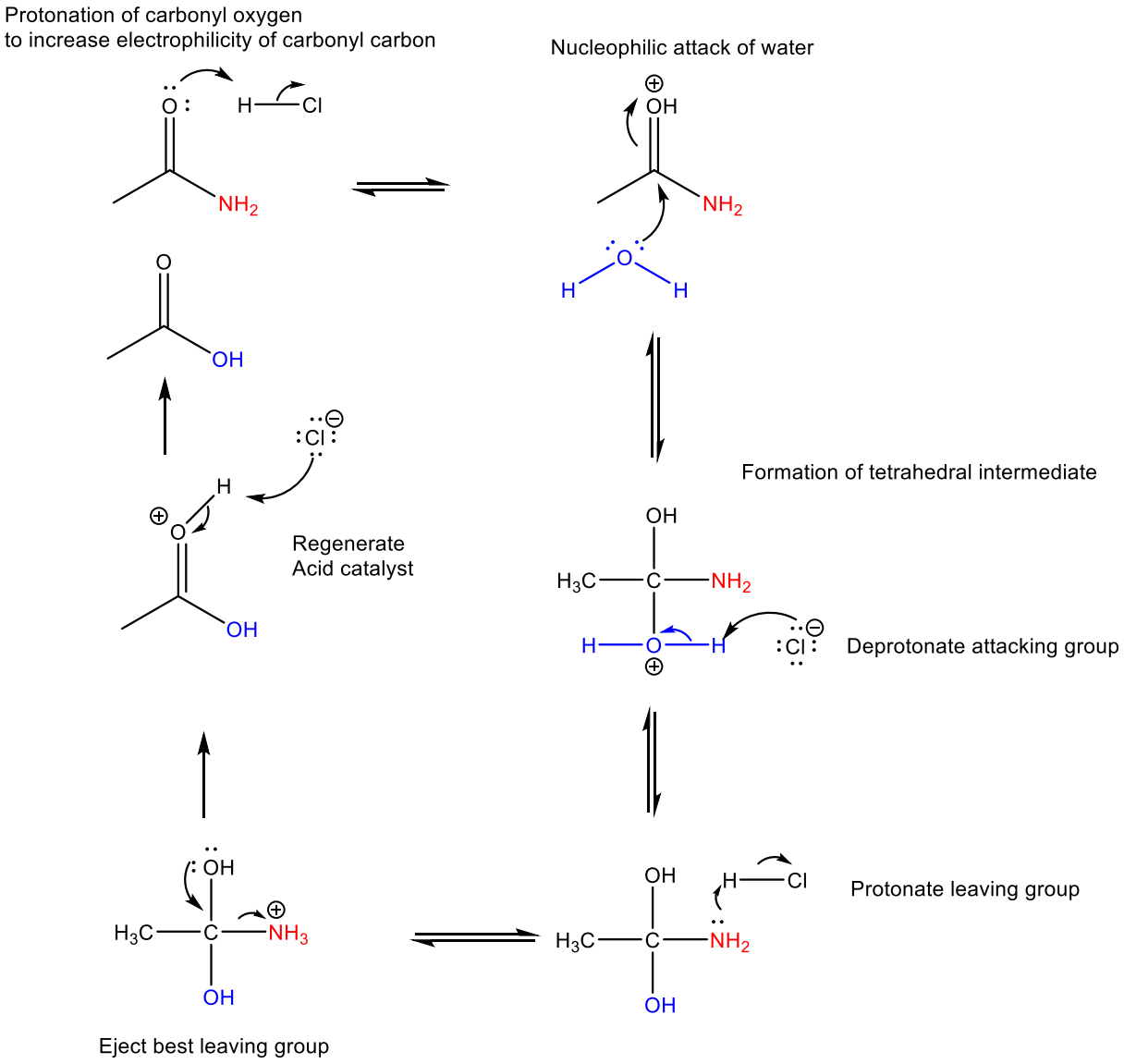


The only way to get an amide from a carboxylic acid is if you really heat up the reaction when you react it with an amine, this will cause a dehydration and give you the amide. The only reaction mechanism that you are responsible for is the reaction of the carboxylic acid with an alcohol to make an ester.

Lastly, we will discuss the reactions of amides and nitriles. Nitriles, while not a carboxylic acid derivative, can be made into a carboxylic acid by hydrolysis, and you can make a nitrile from an amide by reaction with $SOCl_2$, therefore their reactions will be discussed alongside amides. Because amides are the least reactive of the carboxylic acid derivatives, it is very difficult to make them react to form the derivatives that are more reactive. It is a good thing that amides are unreactive, however, because these are the linkages that form our proteins. If they were reactive, our proteins would be more susceptible to chemical attack and life as we know it would be very difficult to impossible. Therefore, reactions of amides cannot be catalyst with acid alone, they need to be heated up to high temperatures for them to react and move up the tierlist of reactivity. The reactions of amides are shown below:

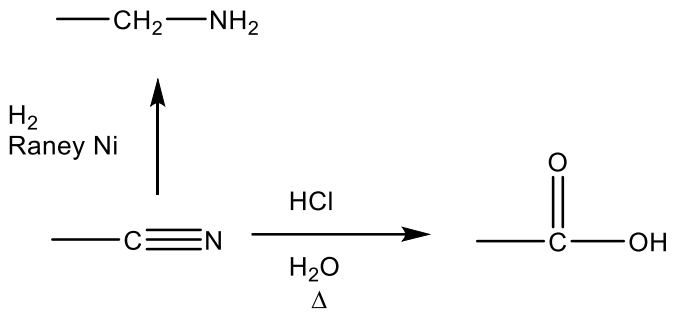


The conversion of an amide to a carboxylic acid goes through the same mechanism as the conversion of an amide to an ester, so we will go through the mechanism only once. Let's take the conversion of an amide to a carboxylic acid as our example mechanism, which is shown below:



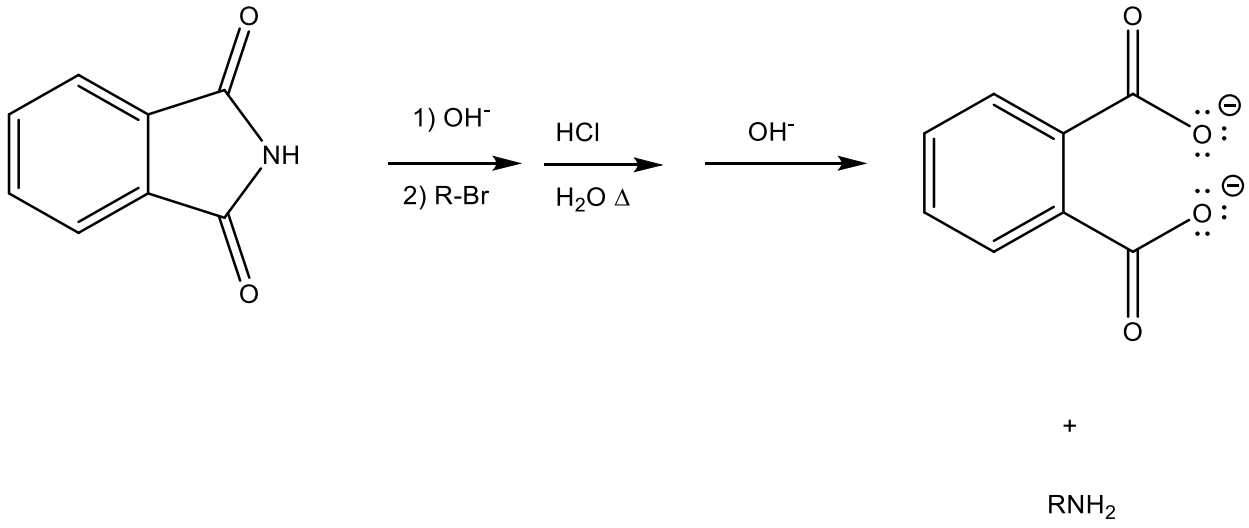
The chemical logic for this mechanism is the exact same as the others. All of these reactions have a standard pattern that you must recognize. *For those reactions that proceed without an acid catalyst, the pattern is always: attack, deprotonate, eject, product or **ADEP**. For the reactions with an acid catalyst, the pattern is always: protonate carbonyl oxygen, attack, deprotonate attacking group, protonate leaving group, eject, product **or PADPEP***. Whenever anything ever attacks a carbonyl carbon of a carboxylic acid derivative, there is always a tetrahedral intermediate. If you remember those pneumonics, you can answer essentially every carboxylic acid derivative question. Just remember, you deprotonate your attacking group and protonate your leaving group if you are in an acid catalyzed reaction. This is because you want to minimize the leaving group strength of your attacking group while at the same time maximize the leaving group strength of your leaving group.

The reactions of nitriles are shown below. Nitriles can be reduced to primary amines and can be hydrolyzed to give carboxylic acids as shown below:

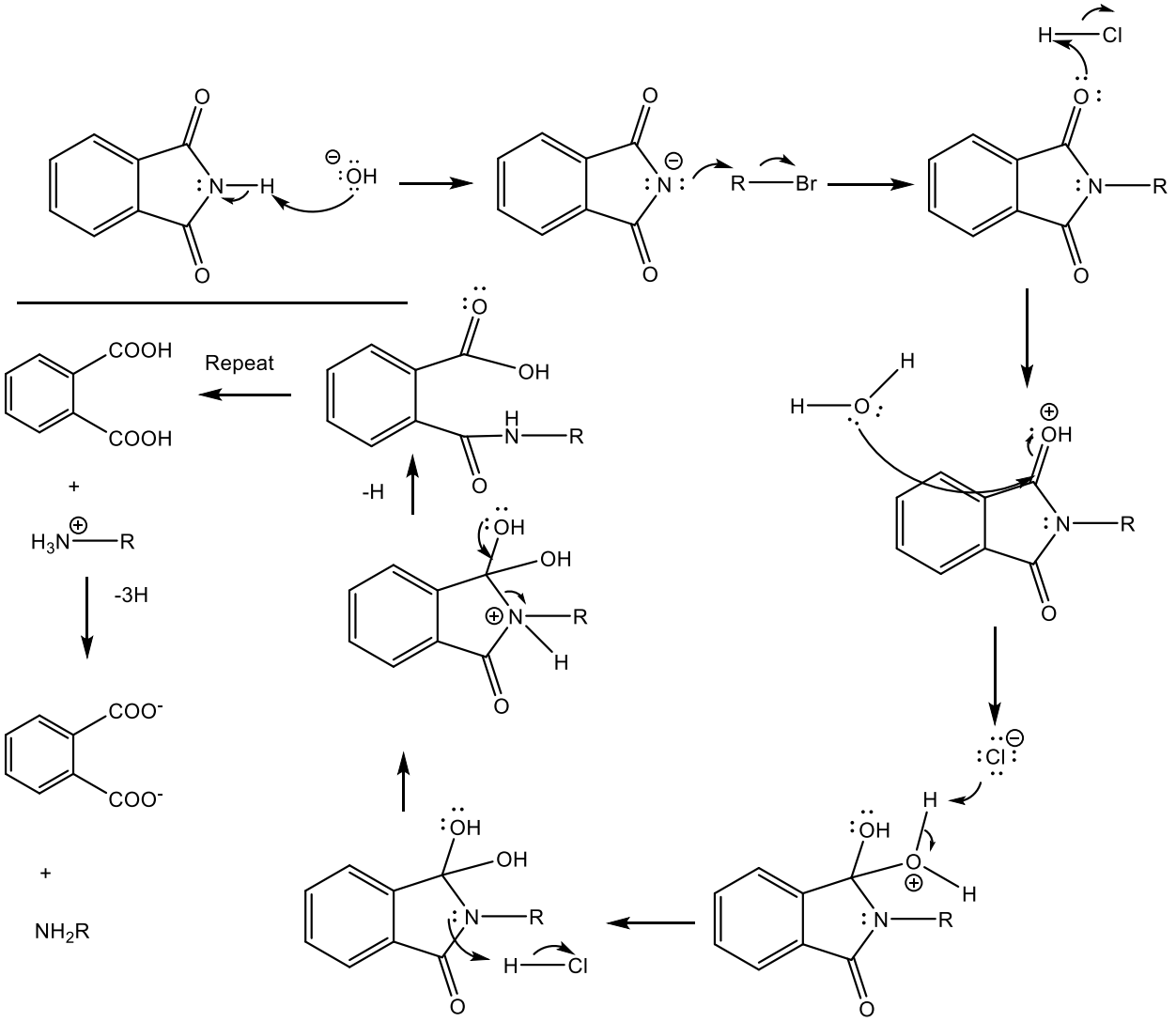


The mechanism for nitrile hydrolysis you do not need to know, but it is basically amide hydrolysis with a few extra steps. The nitrile group is also fairly resistant to hydrolysis and reduction, so harsh conditions for both reactions are necessary.

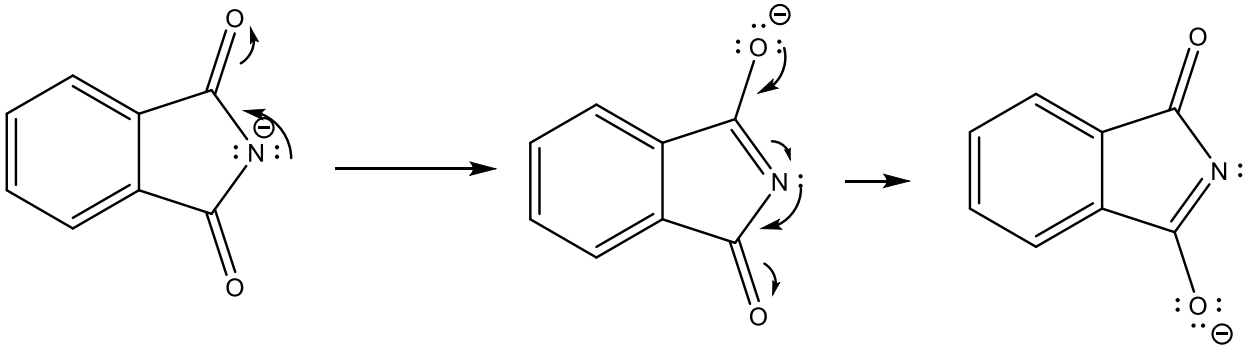
Another fairly common way to get primary amines is through the Gabriel Synthesis reaction. This is a named reaction that requires the use of phthalimide, base, and an alkyl bromide, followed by hydrolysis of the amide groups of phthalimide. The reaction is shown below with a mechanism following it:



The mechanism is:

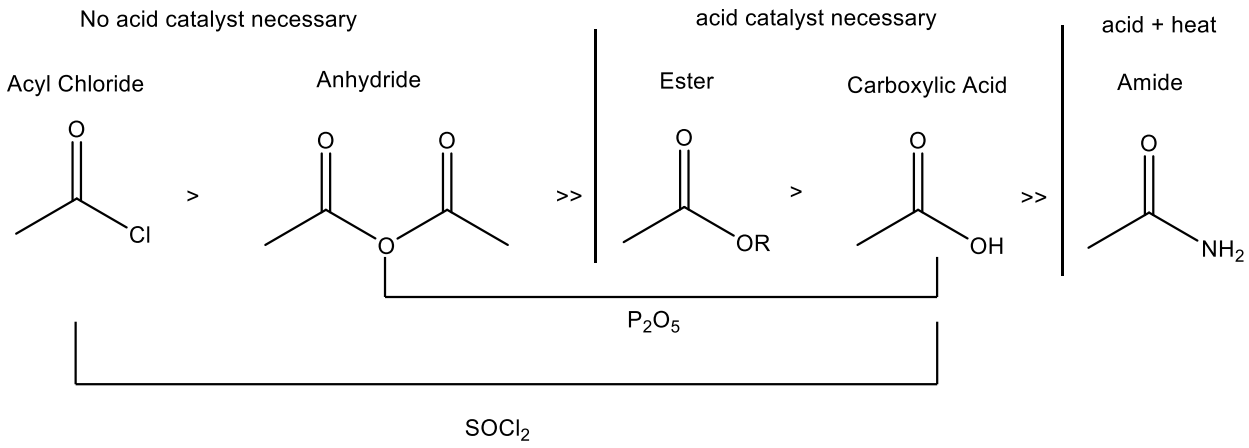


The first step of the mechanism is the deprotonation of the NH group on the phthalimide, this can occur because the negative charge that develops on the nitrogen is spread across the two carbonyl groups like so:



Therefore, because the conjugate base is heavily stabilized through resonance by the two flanking carbonyl groups, OH^- is a sufficiently strong base to fully deprotonate the nitrogen in the center. Because the nitrogen is negative, but not basic due to resonance stabilization by the flanking carbonyl groups, it is a good nucleophile and will easily attack a primary alkyl bromide via an SN2 reaction. All the steps after that are simply amide hydrolysis which we just covered, the mechanism and the chemical logic is the exact same.

Here is a comprehensive review of carboxylic acid derivative chemistry, covering reactivity trends and the pneumonics you can use to write out the mechanisms for these reactions:



Reaction with water gives a carboxylic acid

Reaction with amines gives an amide

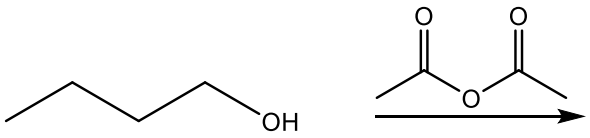
Reaction with alcohols gives an ester

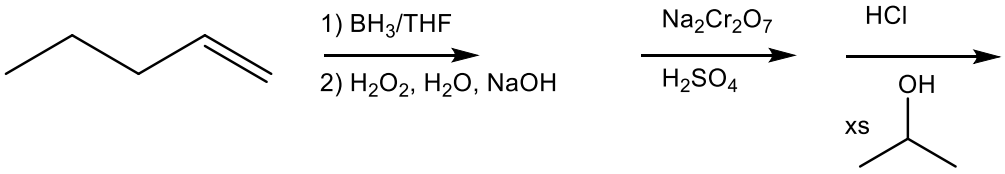
For reactions with an acid catalyst: the pattern is always: attack, deprotonate attacking group, eject, product or ADEP

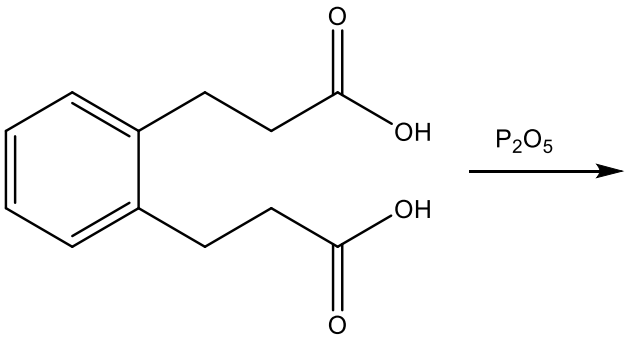
For reactions without an acid catalyst: the pattern is always: protonate carbonyl oxygen, attack, deprotonate attacking group, protonate leaving group, eject, product or PADPEP.

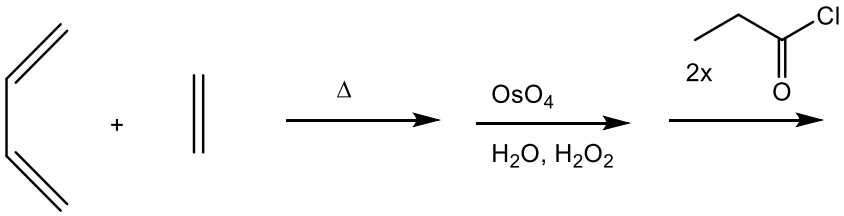
Practice questions:

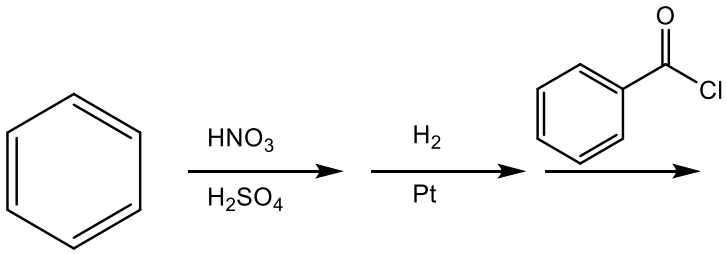
Predict the major organic products for the following reactions:

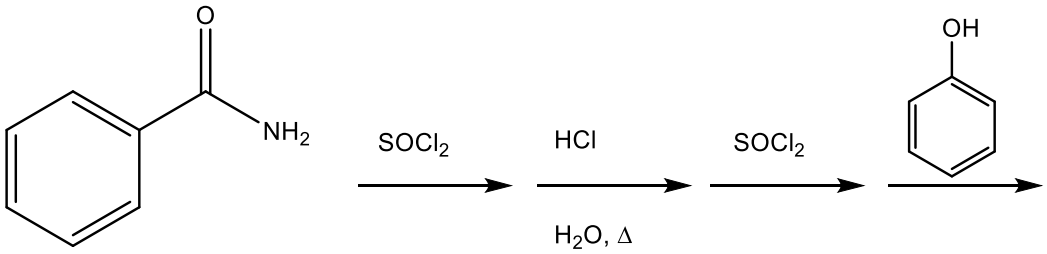

OH
O
O
O


1) BH3/THF
2) H2O2, H2O, NaOH
Na2Cr2O7
H2SO4
HCl
OH
xs

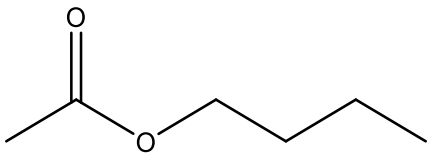

O
OH
OH
O
P2O5


+
Δ
OsO4
H2O, H2O2
2x
Cl
O

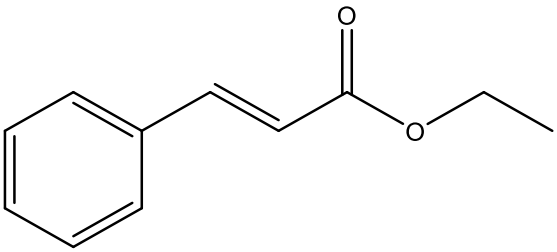

HNO3
H2SO4
H2
Pt
O
Cl


O
NH2
SOCl2
HCl
H2O, Δ
SOCl2
OH

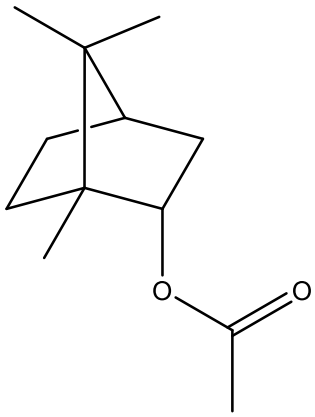
Ethyl butyrate shown below is responsible for the smell of bananas, pineapple, and strawberries, do a retrosynthetic analysis to determine the necessary building blocks for this compound:



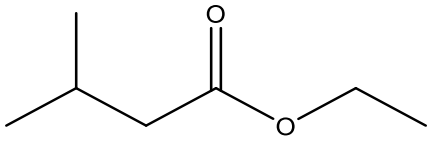
Ethyl cinnamate shown below is responsible for the smell of cinnamon, through retrosynthetic analysis, determine the requisite building blocks for this compound:



Bornyl acetate shown below is responsible for the smell of pine, determine the requisite building blocks for this compound (building blocks cannot be bicyclic for this question):

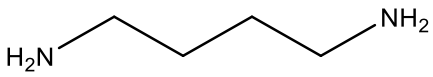


Ethyl isovalerate shown below is responsible for the smell of apples, determine the requisite building blocks for this compound:



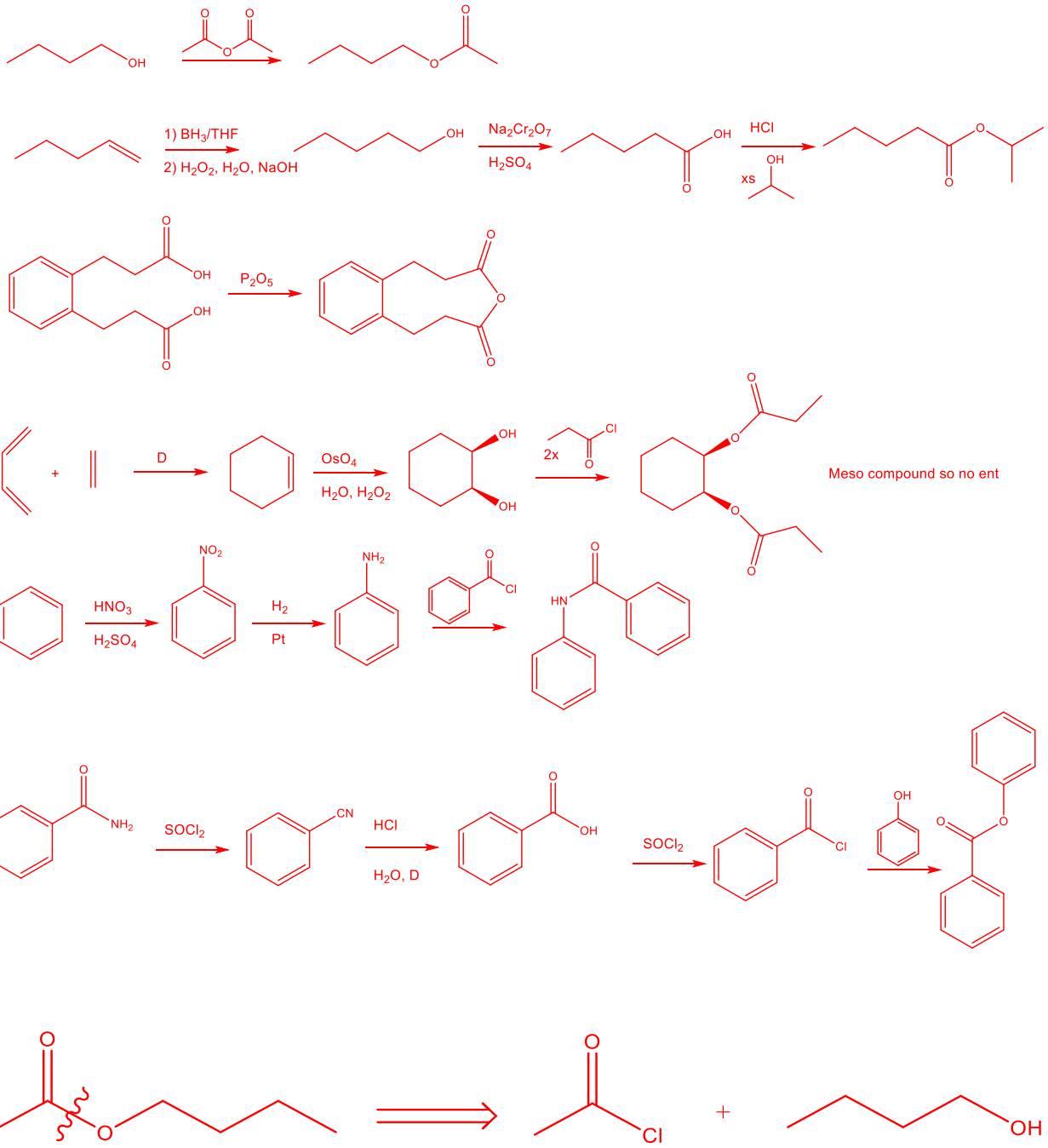
Putrescine is the compound responsible for the smell of decaying flesh, bad breath, and bacterial vaginosis, the structure is given below. Come up with a synthesis of putrescine from the giving starting material:

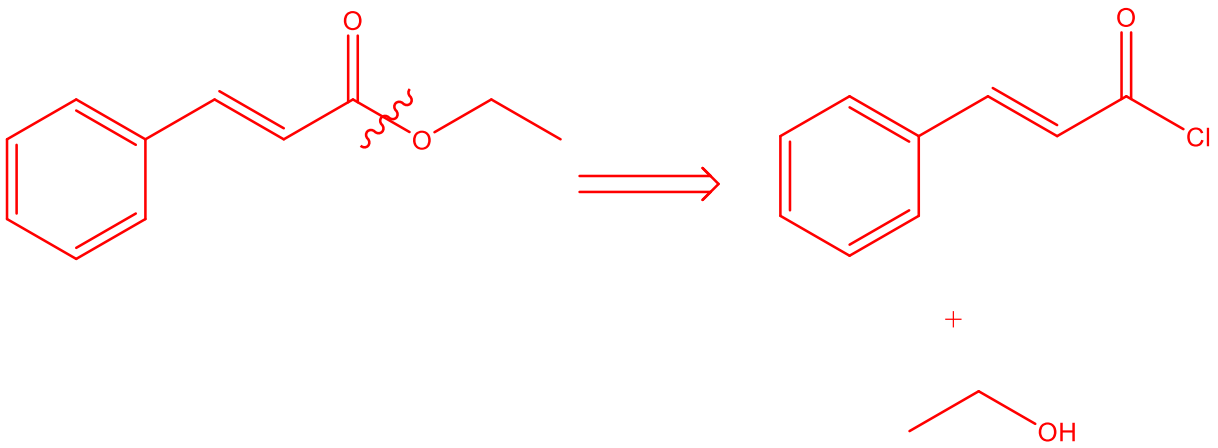
Target



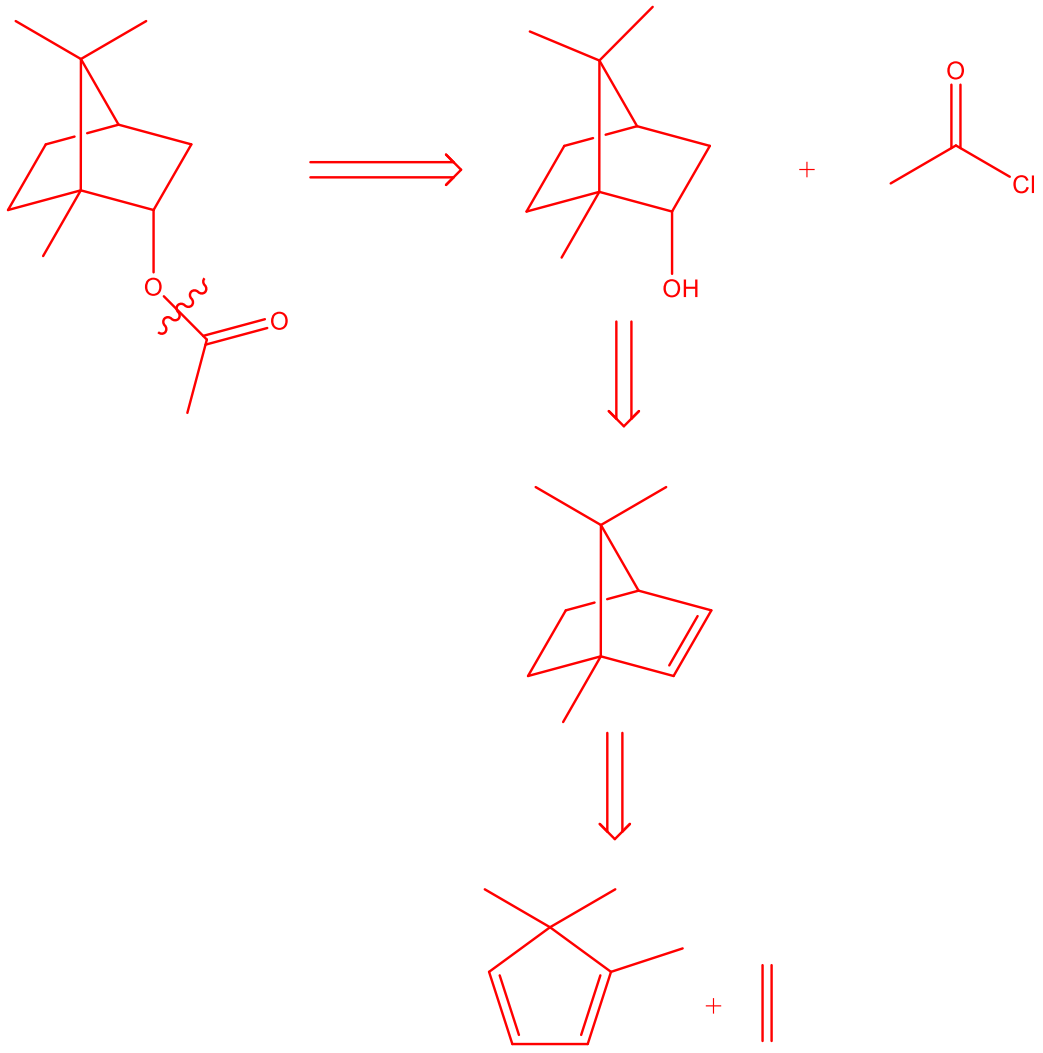
Starting material

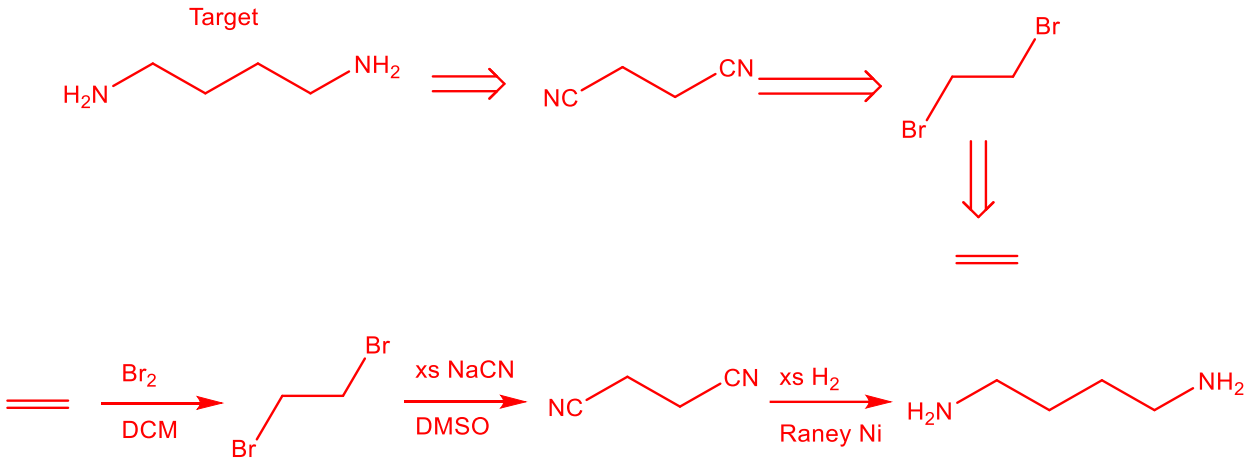
Answers:




O
O
O
Cl
+
OH

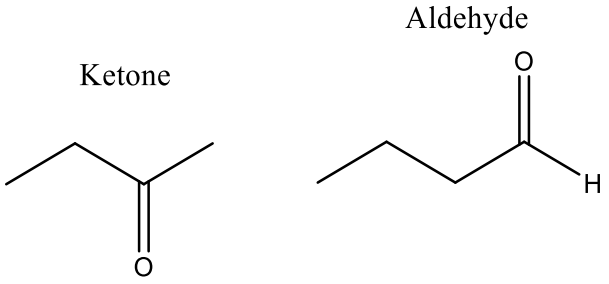
This strategy will not get 100% yield, there is very little regio and stereochemical control here



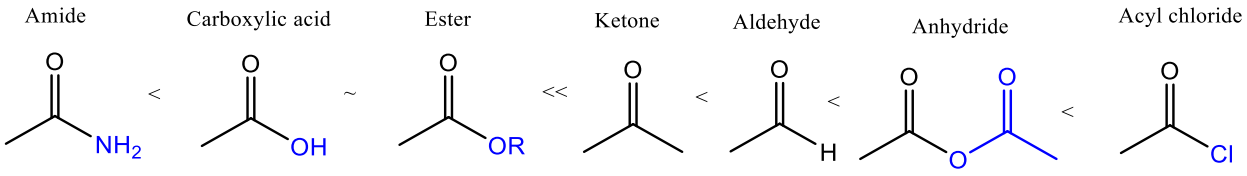


Chapter 13: Reactions of Ketones and Aldehydes + Advanced Reactions of Carboxylic Acid Derivatives

If we recall, leaving group strength is determined by basicity. In the case of ketones and aldehydes though, what is the leaving group? Just as a refresher, the following are structures of generic ketones and aldehydes:

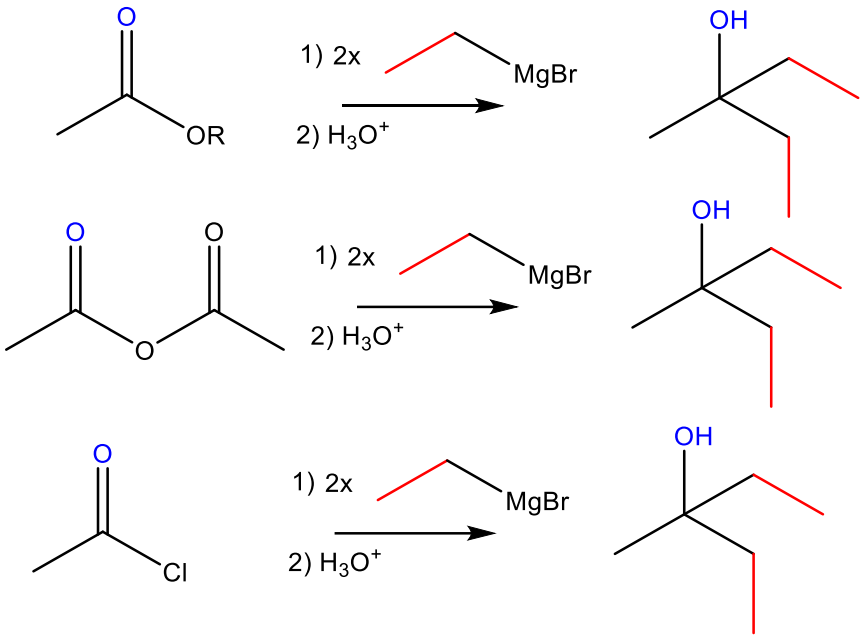


As you can see, ketones and aldehydes only have carbon and hydrogen leaving groups, but what do we know about CH_3^- and H^-, are those strong or weak bases? If you recall from chapter 2, strong bases give weak conjugate acids, the conjugate acid of CH_3^- and H^- is CH_4 and H_2. Since neither CH_4 nor H_2 are even remotely acidic (when have we EVER used them to donate a proton), we can conclude that CH_3^- and H^- are EXTREMELY strong bases. *Because both of these groups are super strong bases, they are AWFUL leaving groups*. This means that rather than substitution reactions, *ketones and aldehydes undergo addition reactions, no group leaves, we get stuck in a tetrahedral state and stay there.* This begs the question though, how do these functional groups compare in reactivity to the carboxylic acid derivatives that we just discussed? They undergo fundamentally different reactions because they do not reform the carbonyl bond, but instead get stuck in a tetrahedron. Without doing much analysis, we can conclude that aldehydes should, in general, be more reactive than ketones simply because aldehydes have substantially less steric hindrance. One side of the aldehyde needs to be a hydrogen, therefore, all else equal, aldehydes are more reactive than ketones. But where do aldehydes and ketones fit into the overall picture of carbonyl compounds? The answer is that they are not as reactive as acyl chlorides or anhydrides, but they are more reactive than esters, so the new tier list of reactivity is as follows:

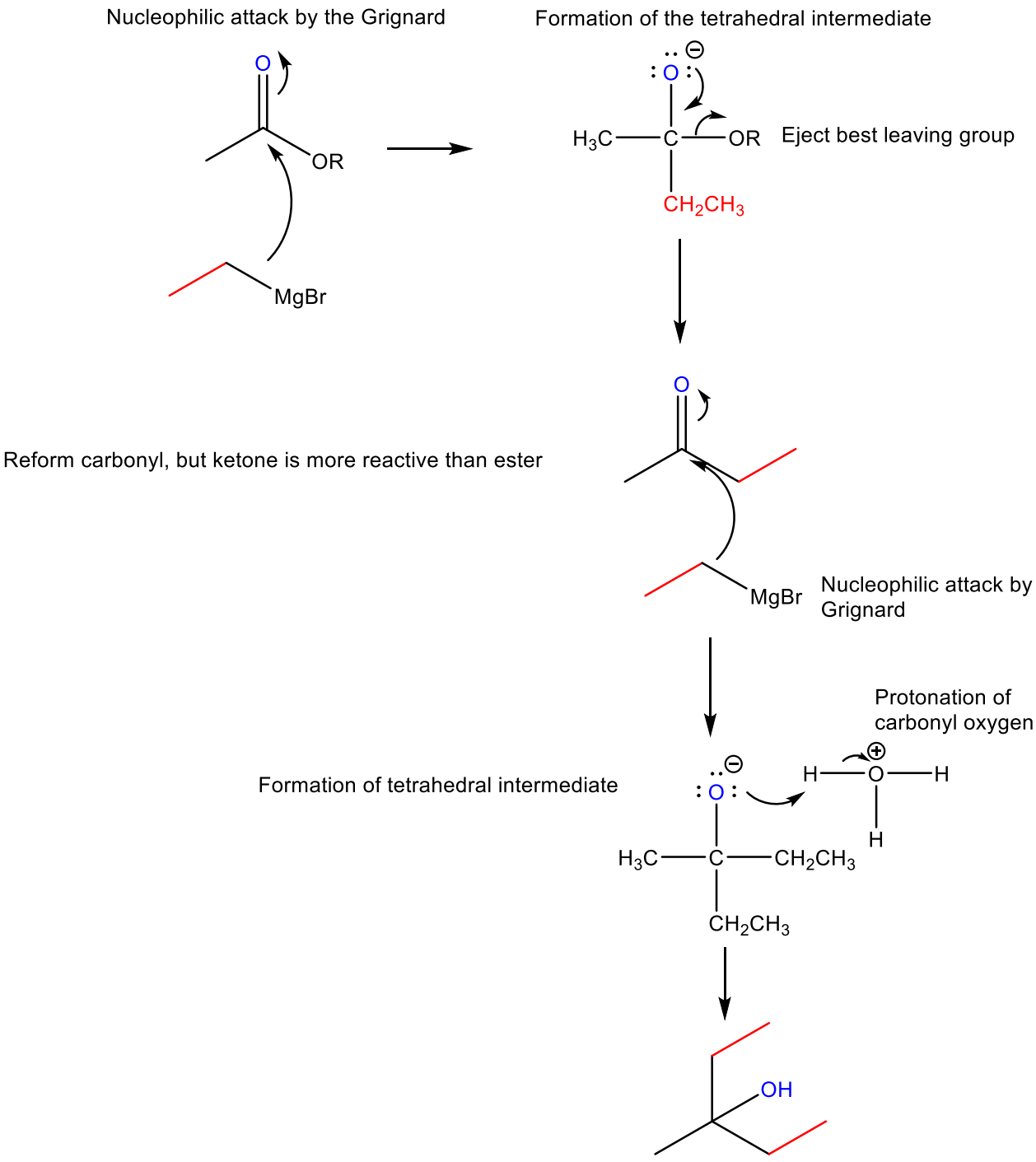


Now that we have discussed the relative reactivities of ketones and aldehydes, we will discuss the advanced reactions of carboxylic acid derivatives and then discuss the specific reactions of ketones and aldehydes.

Esters, anhydrides, and acyl chlorides will all react with Grignard reagents/organolithiums to give alcohols if two equivalents of Grignard reagent is provided. The reaction is shown below and the mechanism is shown after, which, as usual, we will go through step-by-step:



All of the above reactions go through the same mechanism, so we will discuss the ester reaction as our example, but all of these reactions work the same way:



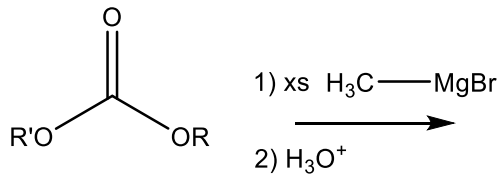
Recall that Grignard reagents can be viewed as a carbon with a lone pair where the MgBr is attached, so the first step in the reaction is the nucleophilic attack of the carbonyl carbon by the Grignard reagent. This, like always, gives a tetrahedral intermediate, however, unlike in the last chapter, there is a clear better leaving group, carbon and hydrogens will NOT leave, EVER. So the second step is the collapse of the first tetrahedral intermediate, this ejects the OR group since that is the weakest base and therefore the best leaving group. When this tetrahedral intermediate collapses, this forms a ketone, but ketones are more reactive than esters, so the Grignard reagent

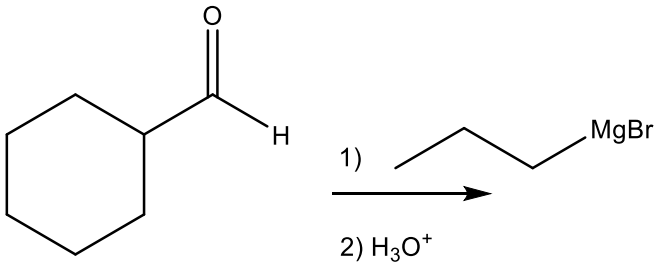
will preferentially attack the ketone, so the ketone is short-lived. When the Grignard reagent attacks the carbonyl carbon again, this forms another tetrahedral intermediate, but unlike the first one, there is NO leaving group, so the carbonyl oxygen just gets protonated by the acid in solution to give the alcohol.

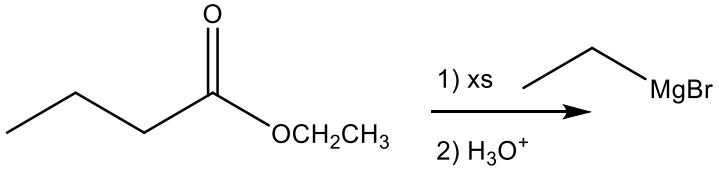
Within this mechanism, we just saw how ketones and, by extension, aldehydes, react with Grignard reagents, they form the tetrahedral intermediate and the carbonyl oxygen gets protonated to give an alcohol. The number of times the Grignard attacks the carbonyl carbon is given by a simple rule, the n+1 rule, where n is the number of non-carbon/hydrogen groups on the carbonyl carbon. These groups are also the "good" leaving groups. Given this information, see if you can answer the following practice questions:

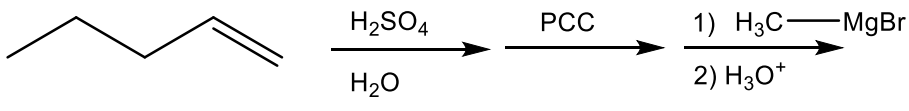
Practice questions:

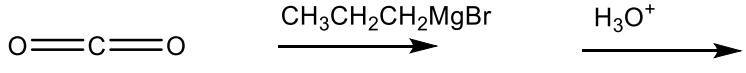
Predict the major organic product for the following reactions:



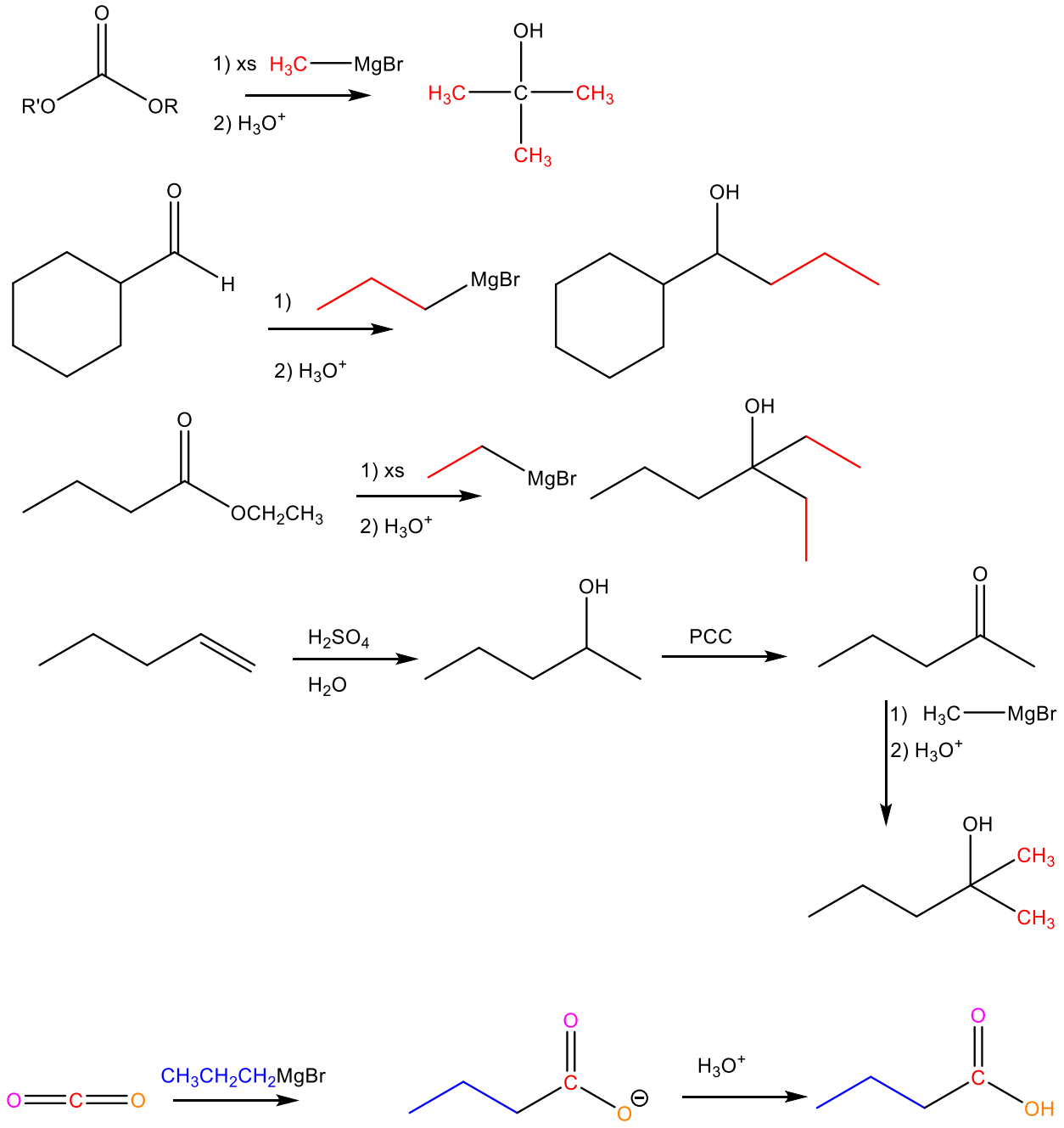




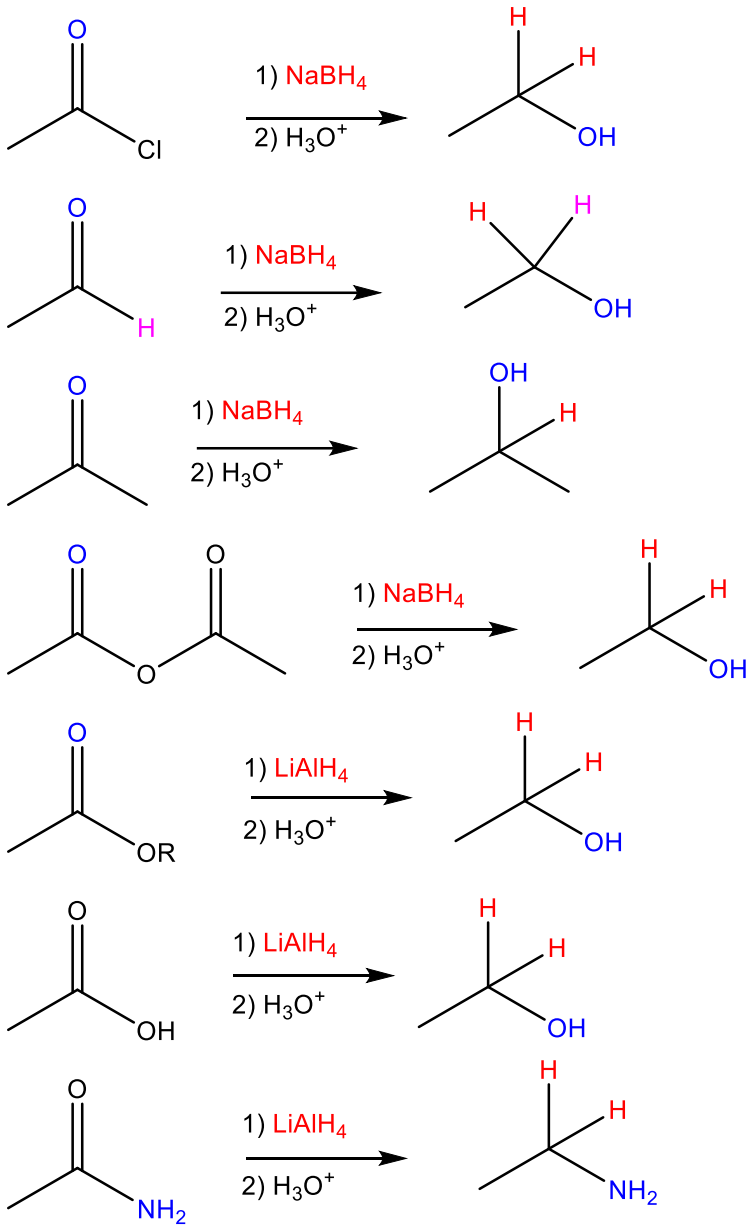




Answers:



Carboxylic acid derivatives, ketones and aldehydes can also get reduced using hydride, there are two reducing agents that are commonly used $NaBH_4$ and $LiAlH_4$. The $NaBH_4$ is used for carbonyl compounds that are more reactive than esters, the $LiAlH_4$ is used for esters and below. In all cases except for one, these reduction reactions result in an alcohol forming, these reactions are shown below:

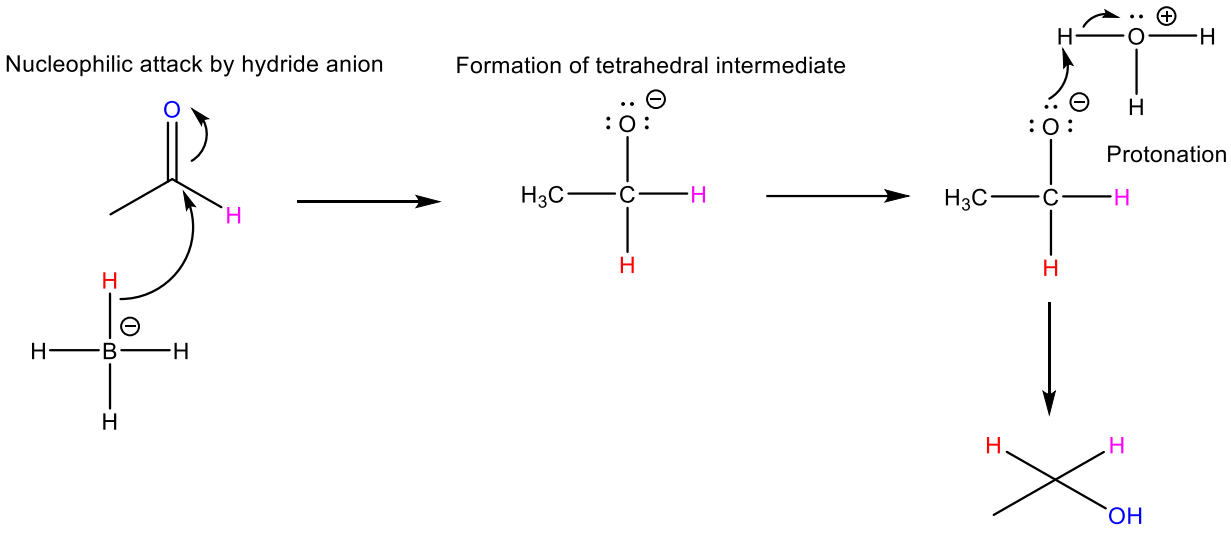


The reaction mechanism for this chemical transformation comes in three basic flavors, but they function mostly the same:

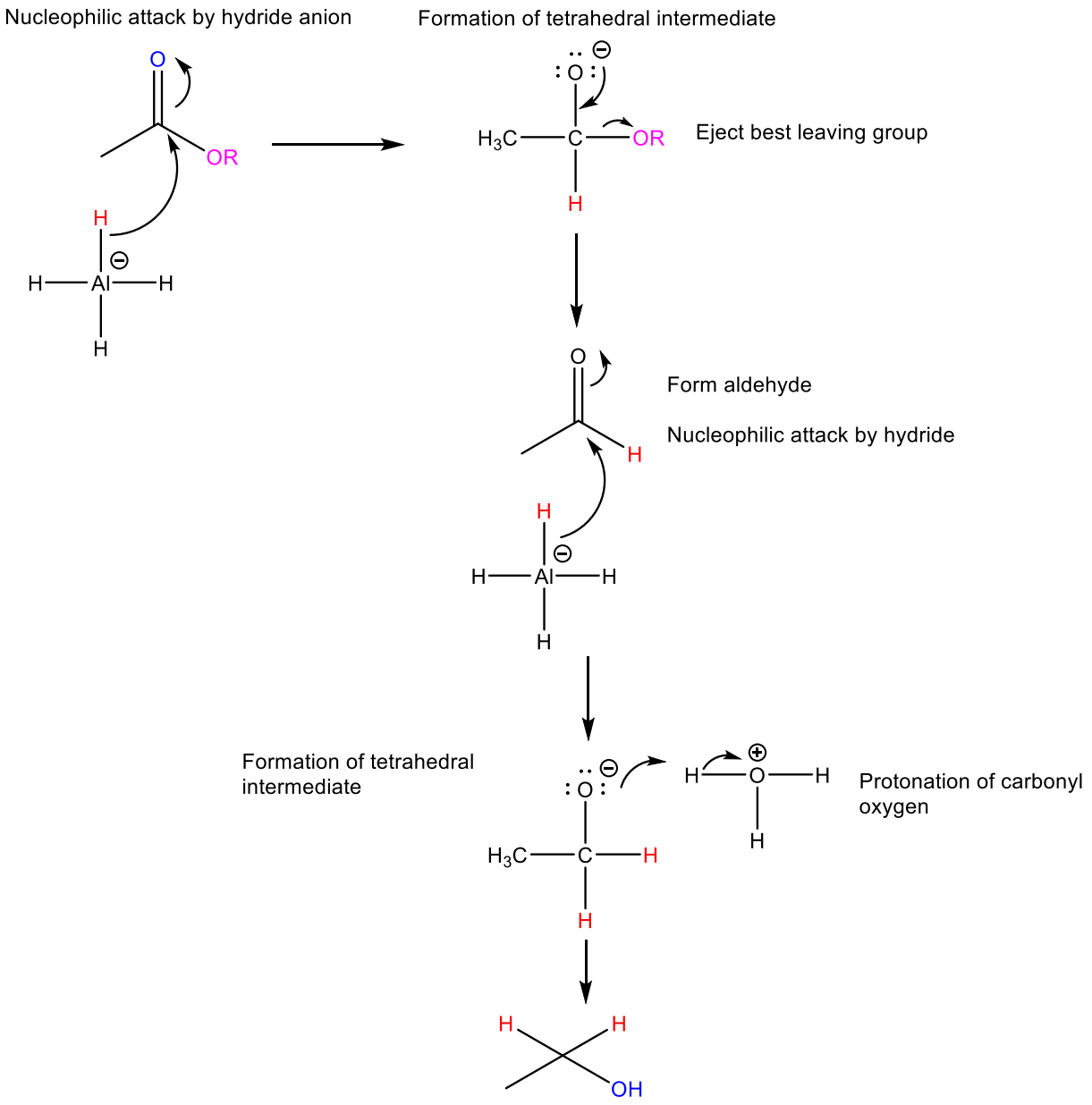
1. Reduction of carbonyls without a good leaving group
2. Reduction of carbonyls with a good leaving group
3. Reduction of carbonyls with acidic protons

As you may have noticed, for ketones and aldehydes, the reducing agent only added 1 hydrogen (red), while for the other carbonyl compounds the reducing agent added 2 hydrogens (red). The products for these reactions are mostly the same, except for the reduction of an amide, which resulted in an amine product.

We will go through each of these reaction mechanisms in turn and explain each step using AMSOW, for the carbonyl without a good leaving group, we will be using the aldehyde as our example but the ketone works the same way. For the carbonyl with a good leaving group, we will use an ester for our example, but the other carboxylic acid derivatives work the same way. And finally, we will address the odd ball of the bunch, the amide, since this is a special case.

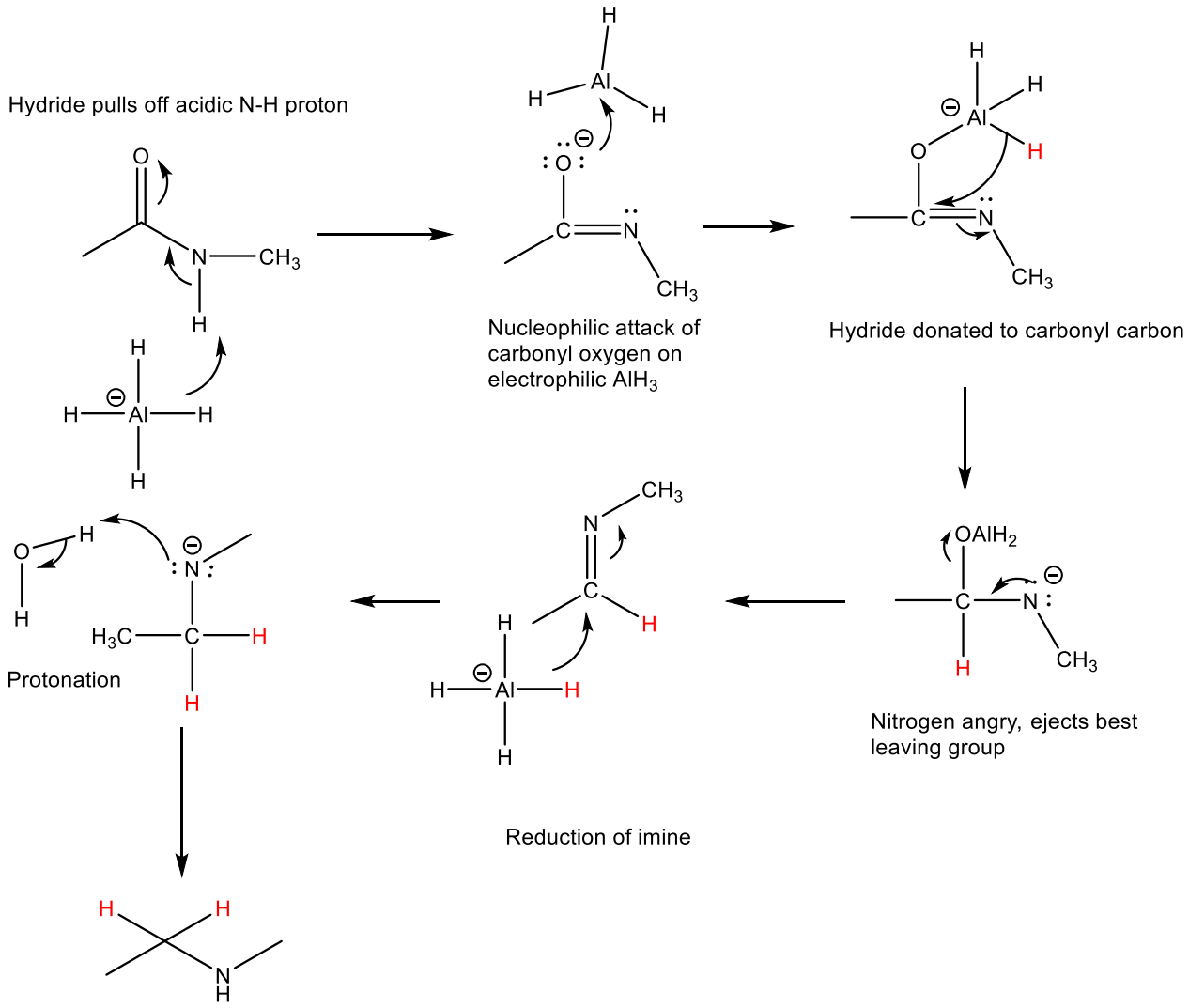


The first step is the BH_4^- donates one of its hydrides to the carbonyl carbon, this is done to minimize the charge on the boron (A**M**SOW). The boron is less electronegative than the oxygen who winds up with the negative charge, therefore, the charge is being transferred to an element that can stabilize that charge better due to its much higher electronegativity. This causes the formation of a tetrahedral intermediate like usual, this tetrahedral intermediate cannot eject a group because none of them are good leaving groups, therefore it is stuck until the H_3O^+ comes and protonates the carbonyl oxygen, this gives us our product. This is simply an acid-base reaction, and it resolves the negative charge on the carbonyl oxygen and the positive charge of the hydronium oxygen (**AM**SOW). As we will see, carbonyl compounds with a good leaving group will essentially do this mechanism twice:



Because the ester is not as reactive as the aldehydes and ketones, a stronger reducing agent must be used. The AlH_4^- is a stronger hydride donor because there is a larger incentive to resolve the negative charge on Al than B, remember that *Al is less electronegative than B* and therefore is comparatively more angry having a negative charge (A**M**SOW). When the hydride attacks the carbonyl carbon, this causes the formation of the tetrahedral intermediate, however, unlike before, we have a group we can kick off, because of this, the OR group gets ejected like before to reform the strong C=O bond (AM**S**OW). This causes the formation of an aldehyde, which is more reactive than the ester, so the AlH_4^- donates another hydride to the aldehyde and the reaction mechanism that we saw happens again to give the final product. *Essentially the reduction of carboxylic acid derivatives is the mechanism for aldehyde reduction but twice.*

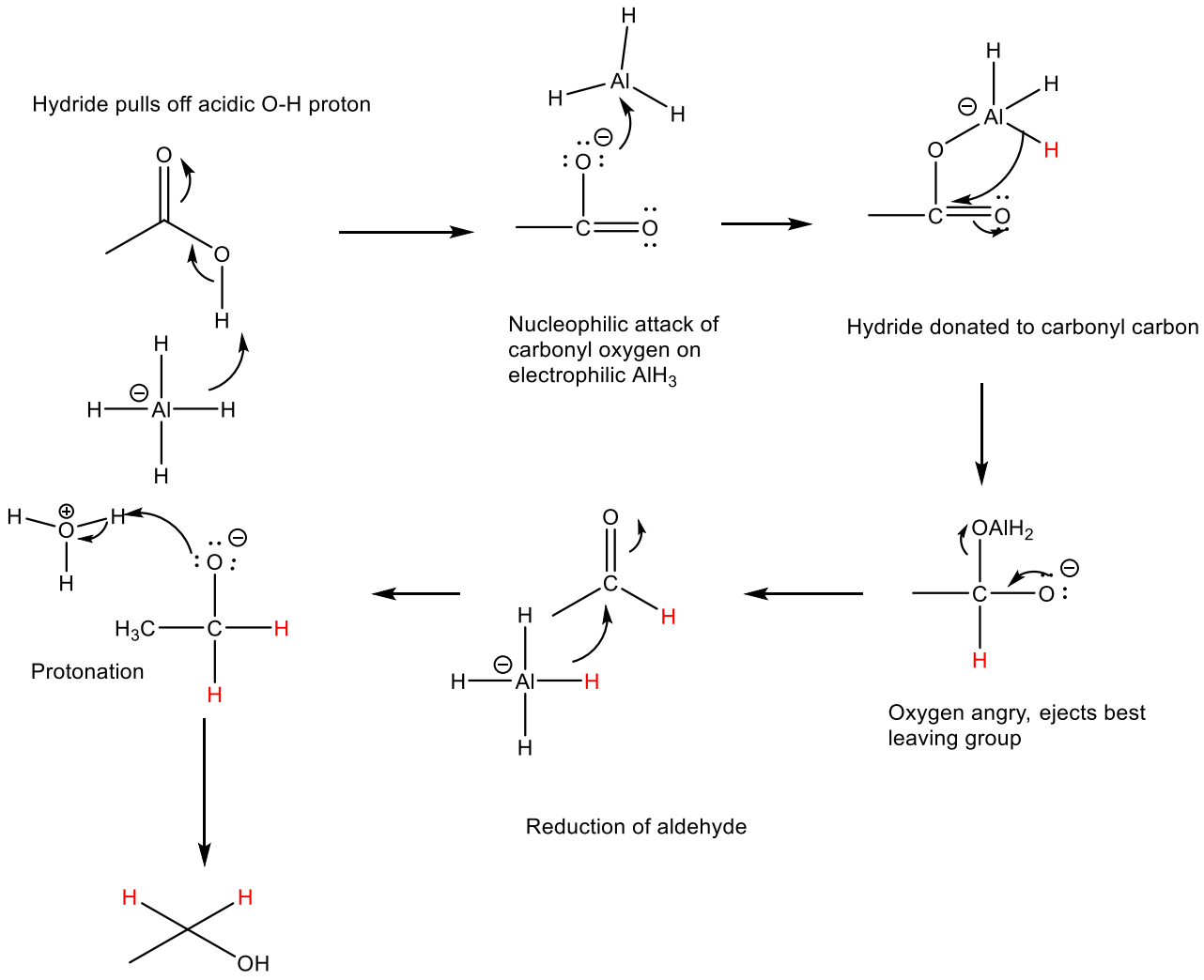
Finally, we get to the odd ball, the reduction reaction of amides and carboxylic acids. Unlike the other reactions, the reduction reaction of amides causes the formation of an amine, rather than an alcohol. While not completely obvious at first, the carboxylic acid reduction reaction is different than the other reduction reactions, despite giving the same product as the others. This is because hydride, H^- is a very strong base, and is a better base than a nucleophile (due to its small size). First, we will go through the amide reduction reaction and then we will go through the carboxylic acid reaction.



The first step in this reaction is simply an acid-base reaction, this occurs because hydride is a much better base than it is a nucleophile because of its small size (**A**MSOW). This reaction also resolves the negative charge on the Al and makes it so that the more electronegative element, O, has it instead, therefore it effectively minimizes charge (A**M**SOW). This step did not happen in any of the other reaction mechanisms because none of the other compounds had an acidic hydrogen to take off. Because the hydride deprotonated the nitrogen, those electrons go to

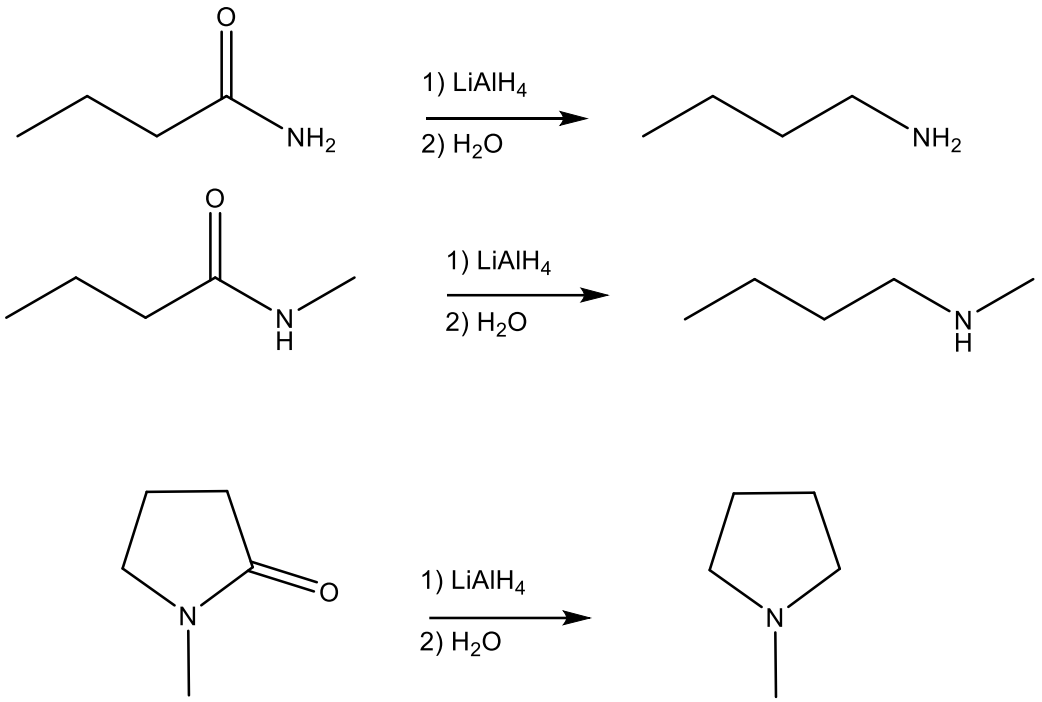
forming a double bond with the carbonyl carbon, this forces the pi bond between the C and O to break. Note that you could have draw the form where the nitrogen has a negative charge and two lone pairs, but the most stable resonance form would be where the oxygen has a negative charge because it can hold a negative charge better due to its higher electronegativity. This negatively charged oxygen is a strong nucleophile and will react with the electrophilic AlH_3, but this again makes the Al negative, which is inherently bad, so this step generates a new hydride donor. The negative Al donates a hydride again to resolve its negative charge, but this time, the hydride acts as a nucleophile to the center carbon, this is because there are no acidic hydrogens this time around (A**M**SOW). This hydride donation causes the weakest bond to carbon break, this would be the pi bond between the C and N, recall that pi bonds are always weaker than sigma bonds (AMSO**W**). When the pi electrons move onto the nitrogen, this gives it a negative charge and that makes nitrogen very unhappy, to resolve this negative charge, the lone pairs are pushed in again to reform the pi bond with carbon (A**M**SOW). This time, there is a good leaving group ($OAlH_2$) and this is ejected to shift the negative charge from N to O, which can support it better (A**M**SOW). This forms an imine, which as we know from our functional group notecards, is an electrophilic group, therefore the nucleophilic hydride will attack the imine carbon and cause the imine pi bond to break and give the nitrogen a negative charge, shifting the negative charge from Al to N, effectively minimizing energy and charge (A**M**SOW). The imine nitrogen is now negatively charged and angry, remember that negatively charged nitrogens are stronger bases than negatively charged oxygens, so any water being present in the solution will quickly get deprotonated in an acid-base reaction in an effort to minimize charge on nitrogen and shift the negative charge to the more electronegative oxygen of water (**AM**SOW). This gives us the amine product that we know to be the true product of this reaction.

We will now discuss the reaction mechanism of carboxylic acids with the $LiAlH_4$ reducing agent:



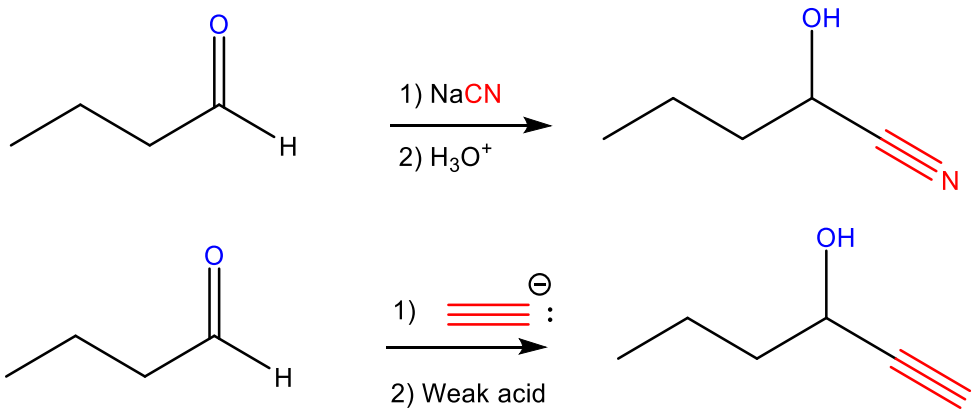
This reaction mechanism was so similar to the amide one that when I made this ChemDraw file, I just copied and pasted the amide mechanism and changed the amide nitrogen to an oxygen haha. The only difference between this mechanism and the amide one is that you have to use a stronger acid (H_3O^+) in the last protonation step because negatively charged oxygens are not as basic as negatively charged nitrogens. Everything else is the exact same, and so the chemical logic is also the same. See if you can explain this mechanism to yourself using AMSOW and using the amide reduction as a reference.

The reduction mechanism that was shown for the amide example will vary depending upon the substitution of the amide nitrogen, but the result will always be an amide:

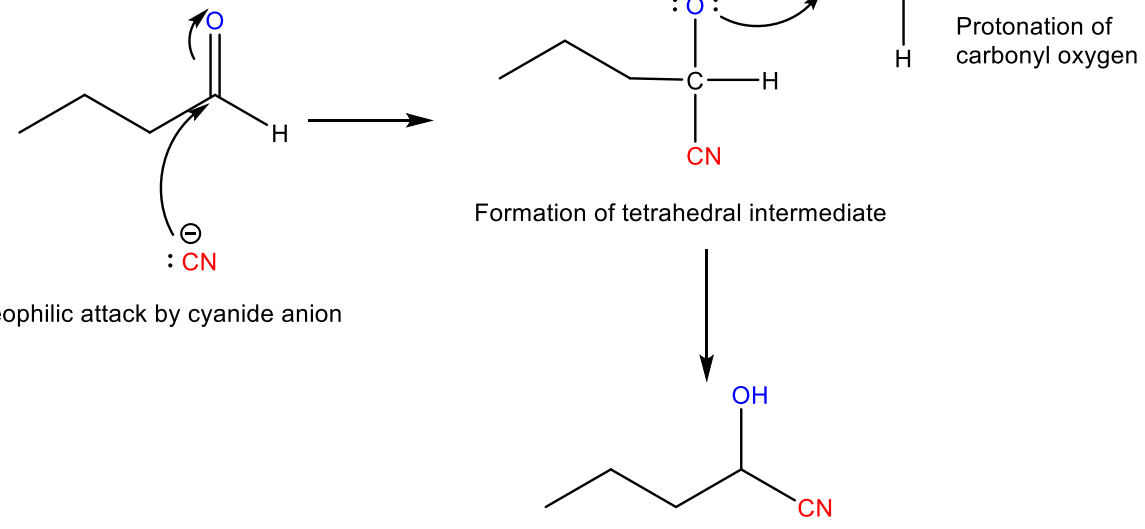


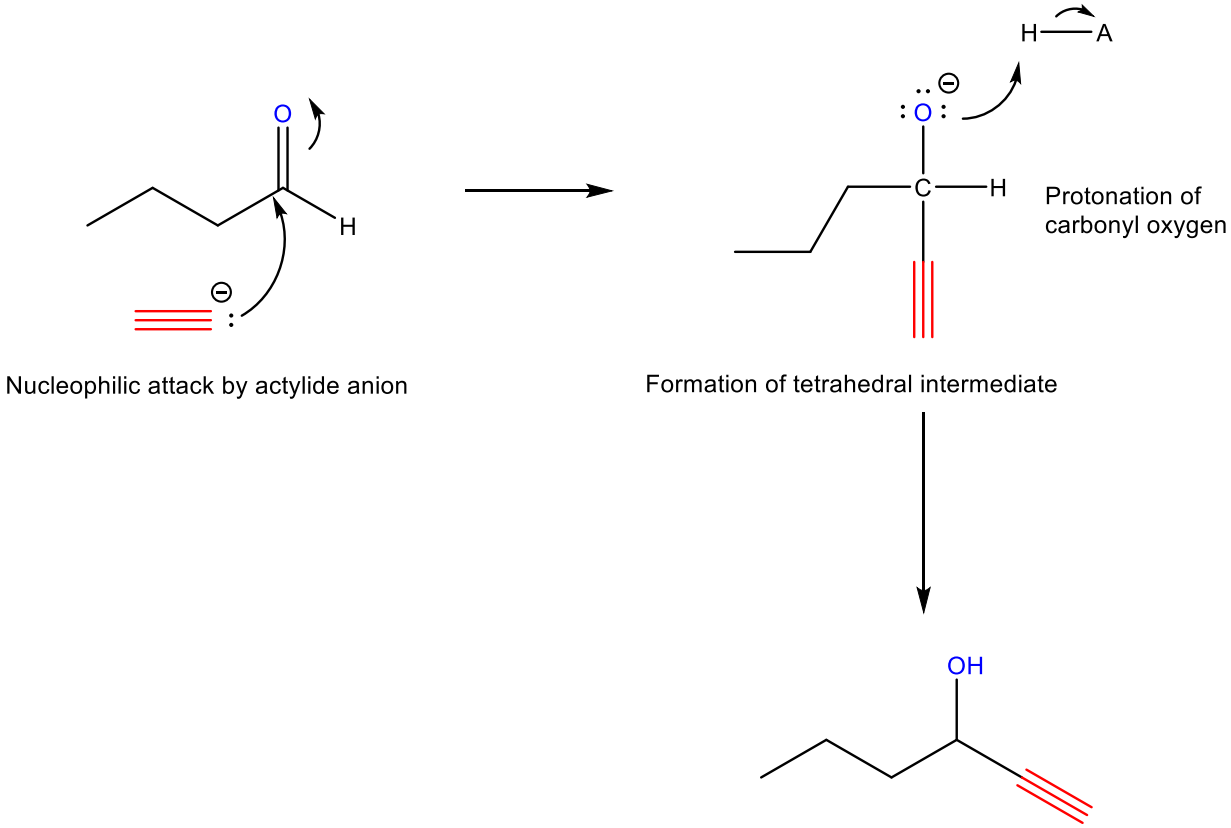
Sometimes, you want the reduction reaction for an ester to stop at the aldehyde, if you want to do that, you can use DIBALH, this is essentially a very bulky and deactivated hydride donor.

Let's now discuss specific reactions of ketones and aldehydes. These reactions are all characterized by ketones and aldehydes inability to kick off a group and being stuck in a tetrahedral intermediate before protonation occurs. We have already discussed the reaction of these compounds with Grignards, but there were two other carbon nucleophiles that we have seen so far in this course, CN^- and the actylide anion. These two nucleophiles, just like the Grignard will react with the ketones and aldehydes in the exact same way as Grignards:

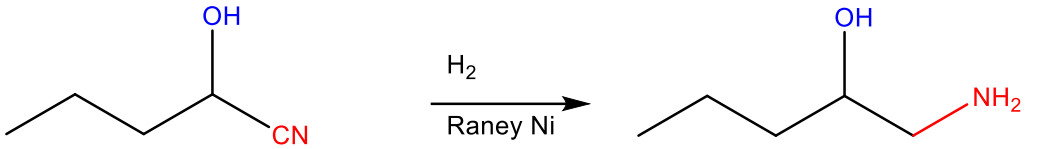


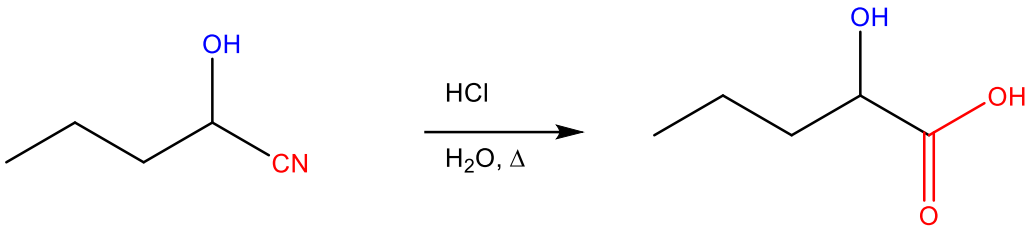
The reaction mechanism for these reactions are exactly the same as the Grignard reaction:





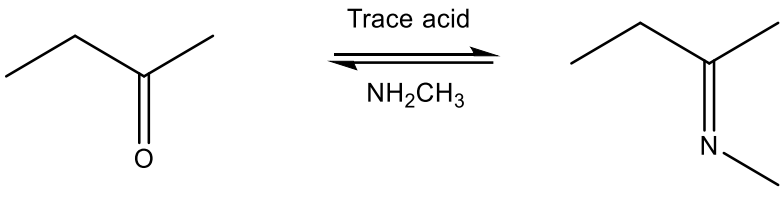
The actylide reaction requires the use of a weak acid to protonate the carbonyl oxygen because alkynes react with strong acids like we discussed in chapter 3. The reaction of aldehydes or ketones with cyanide results in compounds that are referred to as cyanohydrins. The cyano groups can be reduced or reacted with in the same ways we did in the last chapter:

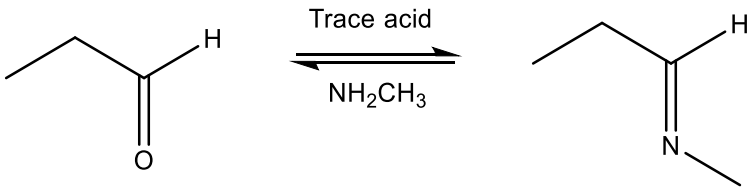




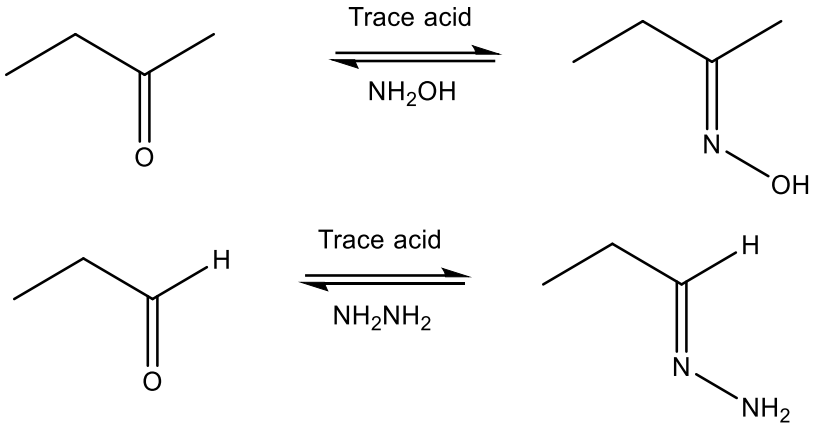
Ketones and aldehydes have important reactions with amines, alcohols, water, and thiols. We will discuss these reactions in that order since the reactions with amines is arguably the most important.

When ketones and aldehydes are reacted with a primary amine or ammonia in the presence of a small amount of acid, they create imines like so:

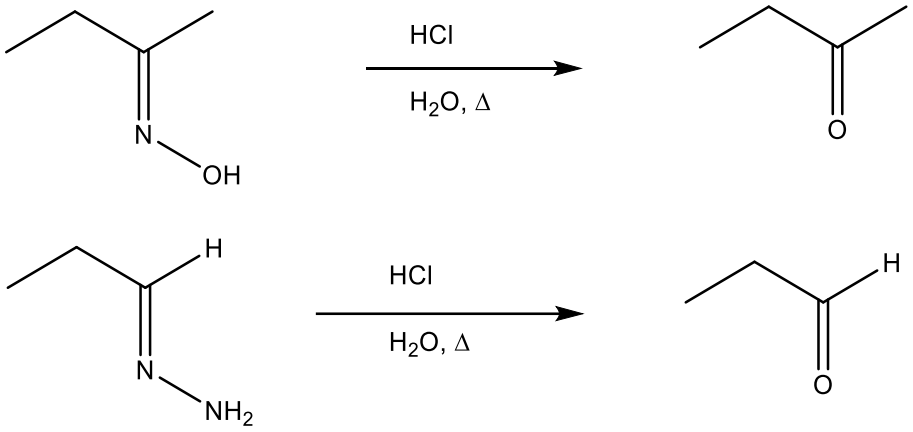




This reaction also works if the group on the nitrogen isn't a carbon group:

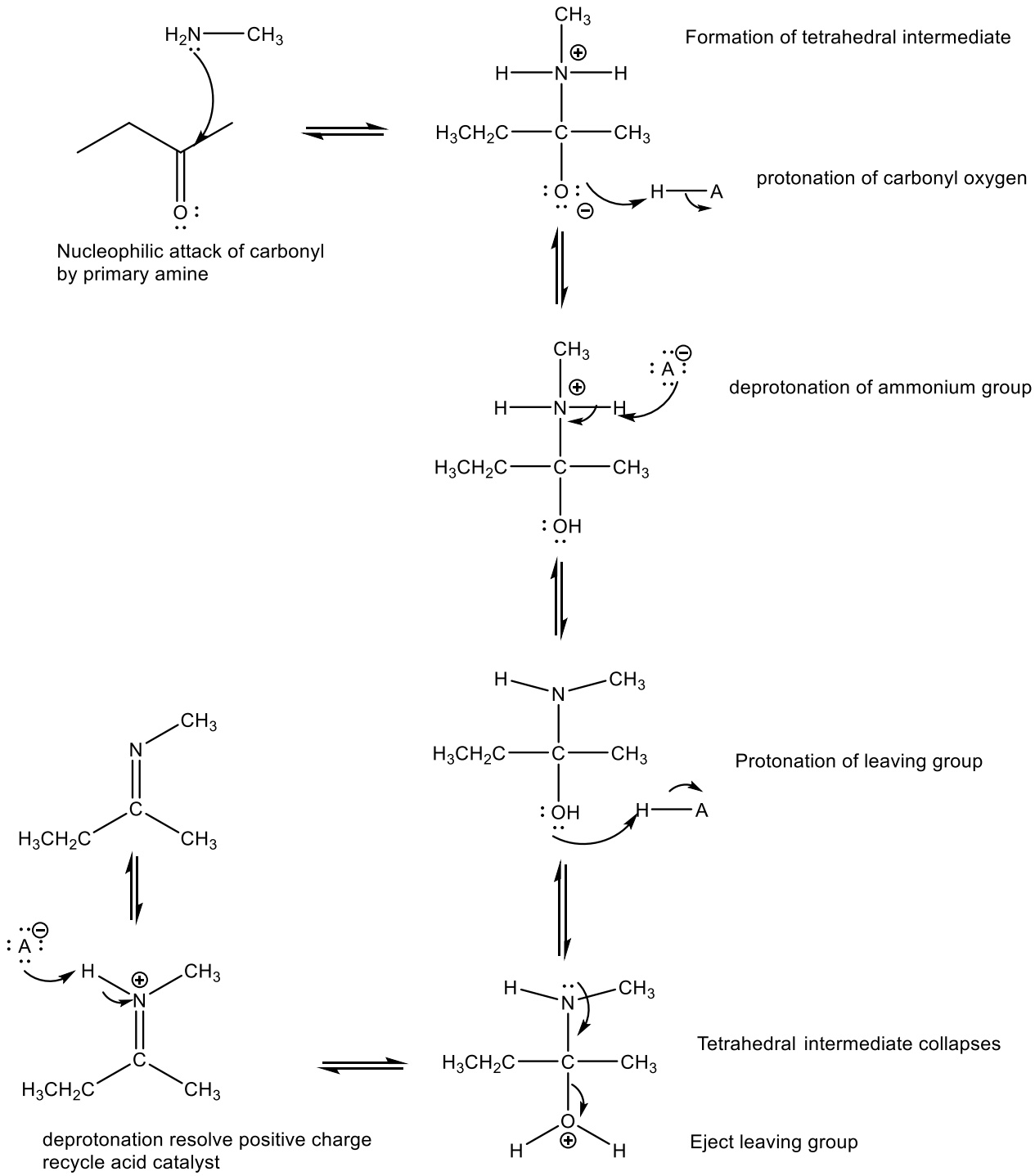


These groups and normal imines can be removed with HCl, H_2O and heat:



The mechanism for these reactions admittedly are not super important, but we will go through them:

Formation of an imine mechanism:

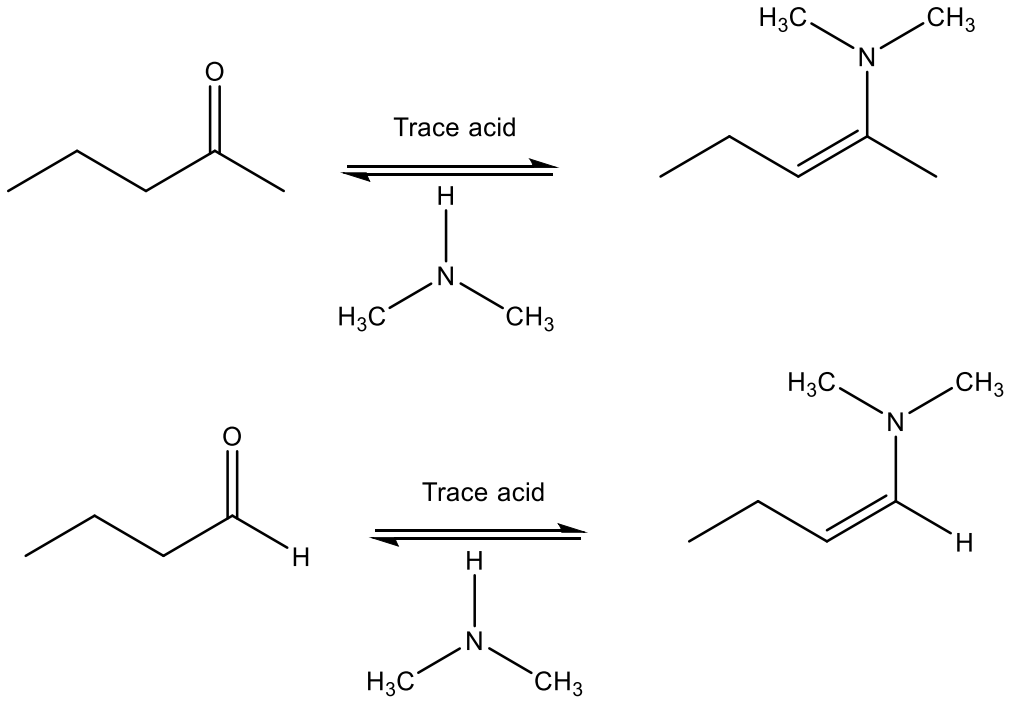


The first step of the reaction mechanism is that primary amine attacks the carbonyl carbon to give a tetrahedral intermediate. This step does not require any acid catalyst because the ketone is sufficiently electrophilic to be attacked without protonation by the acid catalyst. Once the primary amine attacks the carbonyl carbon, this causes the formation of a tetrahedral intermediate, the carbonyl oxygen needs to leave and get replaced with the nitrogen for this

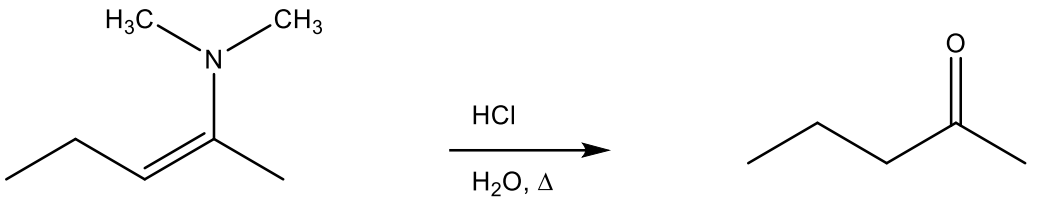
reaction to work so we need to make the carbonyl oxygen a better leaving group. To do this, we protonate it using the acid catalyst, this resolves the oxygens negative charge and makes it neutral (**AM**SOW). The conjugate base of the acid then deprotonates the ammonium group because that is the group that we want to keep in the compound and if it is positively charged it is a better leaving group than the OH group that we intend to eject. This step also resolves the positive charge on the nitrogen and regenerates the acid catalyst which we can use to further increase the leaving group strength of the OH group (A**M**SOW). The next step is, as one would expect, the protonation of the OH group, this forms water as the leaving group, which we have seen in our alcohol reaction chapter is a sufficiently good leaving group to get pushed off. The next step is the collapse of the tetrahedral intermediate by the nitrogen pushing its lone pairs into the carbonyl carbon and the H_2O group gets ejected, but the nitrogen is now positively charged, so the conjugate base of the acid catalyst deprotonates it in the last step to resolve its positive charge and give the imine product (**AM**SOW).

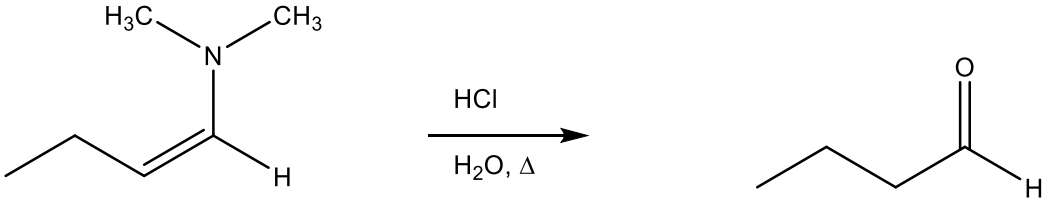
The mechanism for the hydrolysis of the imine will not be covered in this text, but it is essentially the reverse of the above mechanism.

If ketones or aldehydes are reacted with secondary amines in the presence of a small amount of acid, they form enamines like so:

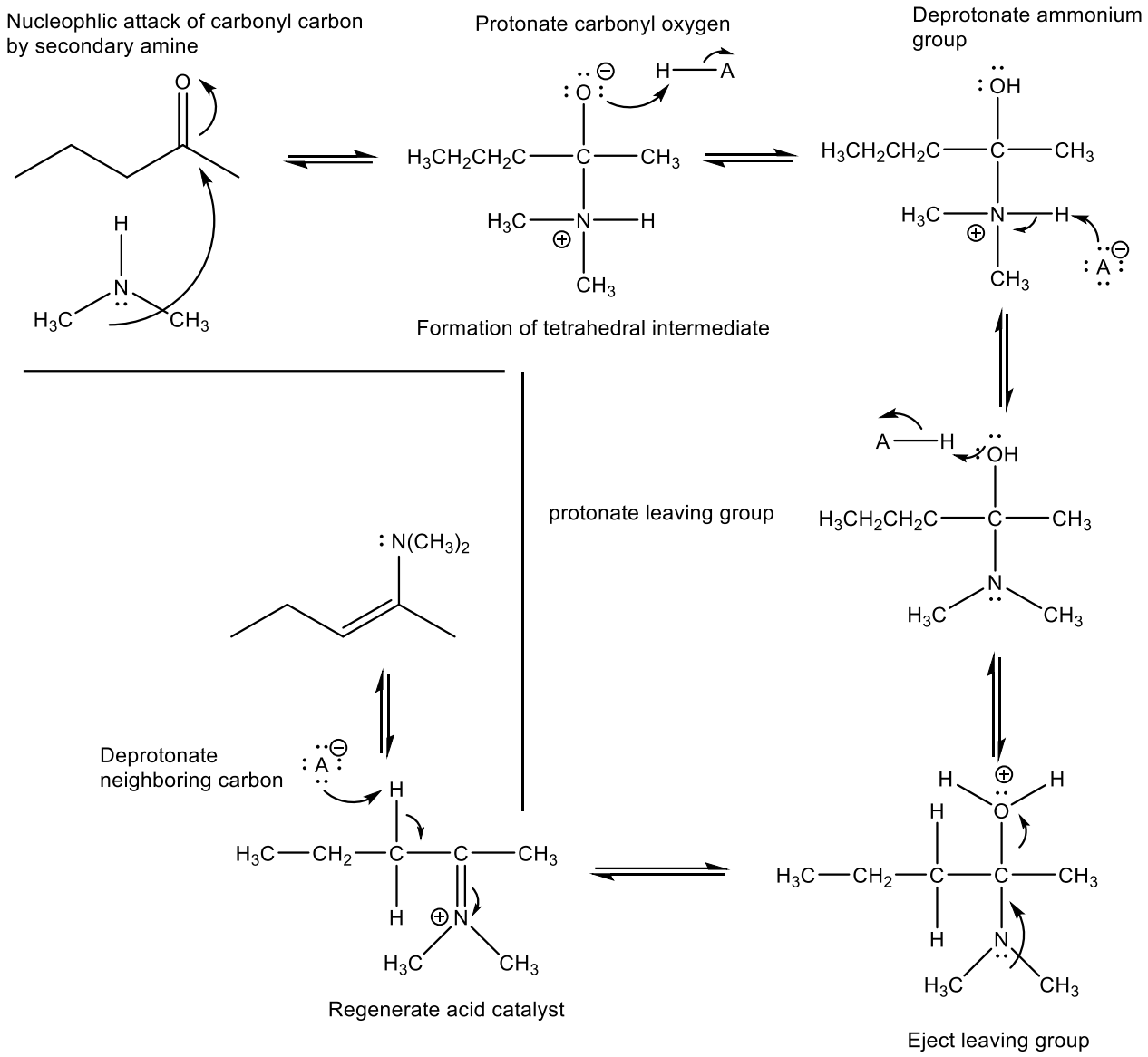


Enamines are good nucleophiles like we will see in the next chapter. Enamines, just like imines, can be hydrolyzed back to the corresponding ketone or aldehyde with HCl, H_2O, and heat like so:





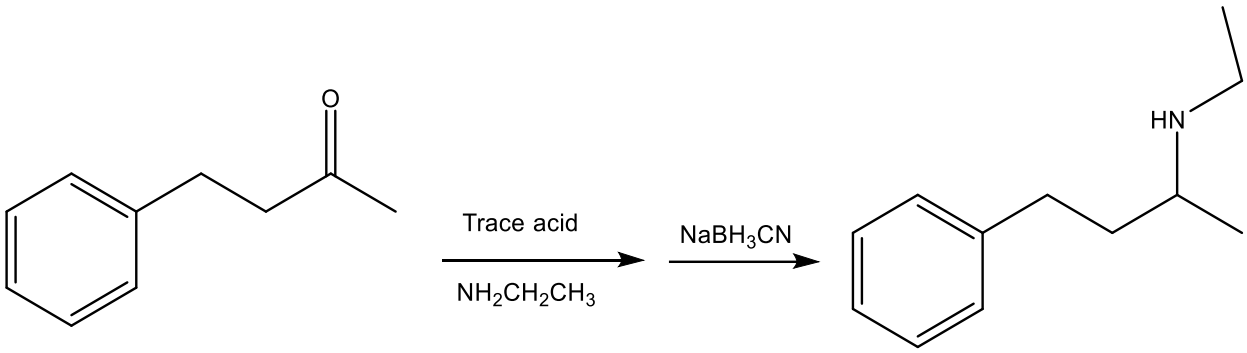
We will discuss the mechanism for enamine formation, but not the mechanism for hydrolysis as like the imine example, it is just the reverse of the formation reaction:



This mechanism is the almost the same as before. The only difference lays on the very last step, contrary to imine formation, which requires a primary amine that has two hydrogens; the enamine formation reaction requires a secondary amine that has only one hydrogen. The secondary amine does not have any protons to take off in the last step, so the only way to resolve the positive charge on the nitrogen is to deprotonate a neighboring carbon's hydrogen so that you can form a pi bond and move the C=N pi electrons onto the nitrogen directly. This is facilitated by the resonance stabilization of the enamine product, so this step effectively minimizes energy and charge (A**M**SOW).

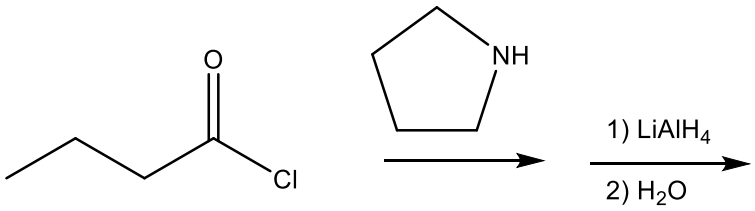
The utility of these reactions is best seen in the reductive amination reaction. Because these reactions are in equilibrium, to push them to be quantitative, you can siphon away the product by reacting it with a reducing agent, this allows for the formation of amines like we saw before

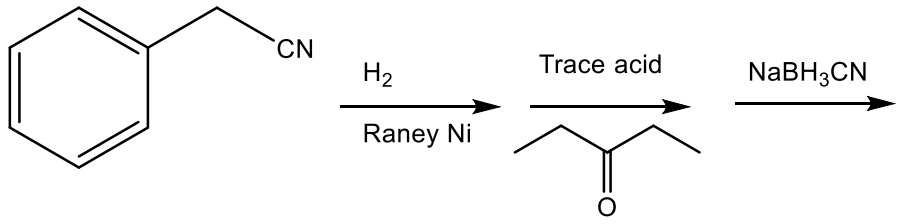
when we reduced amides. This reaction is extremely useful for making secondary and tertiary amines (those amines that have two carbons attached to the nitrogen and three carbons attached to the nitrogen respectively). An example of this reaction is shown below:

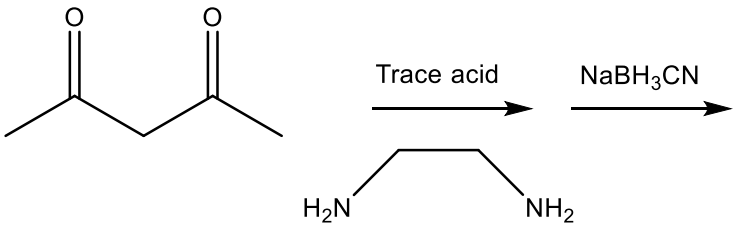


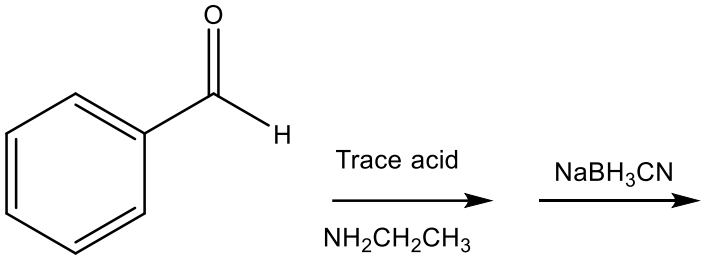
Practice questions:

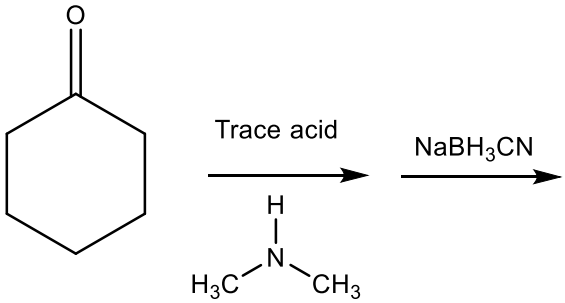
Predict the major organic products for the following reactions:


O
Cl
NH
1) LiAlH4
2) H2O

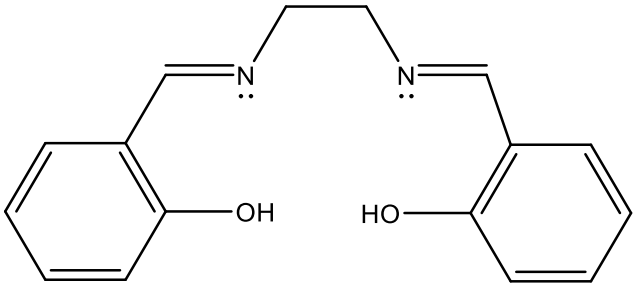

CN
H2
Raney Ni
Trace acid
NaBH3CN
O


O
O
Trace acid
NaBH3CN
H2N
NH2

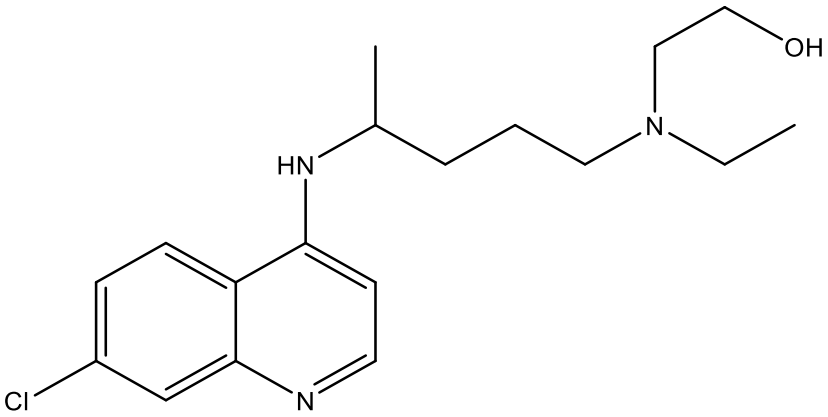

O
H
Trace acid
NaBH3CN
NH2CH2CH3


O
Trace acid
NaBH3CN
H
N
H3C
CH3

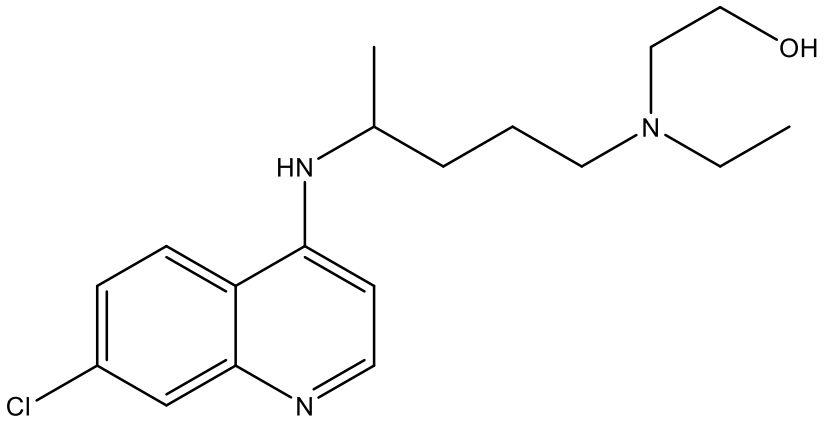
SALEN is a commonly used tetradentate ligand used in a wide variety of catalysts, it is shown below, determine the necessary organic compounds to make this tetradentate ligand:



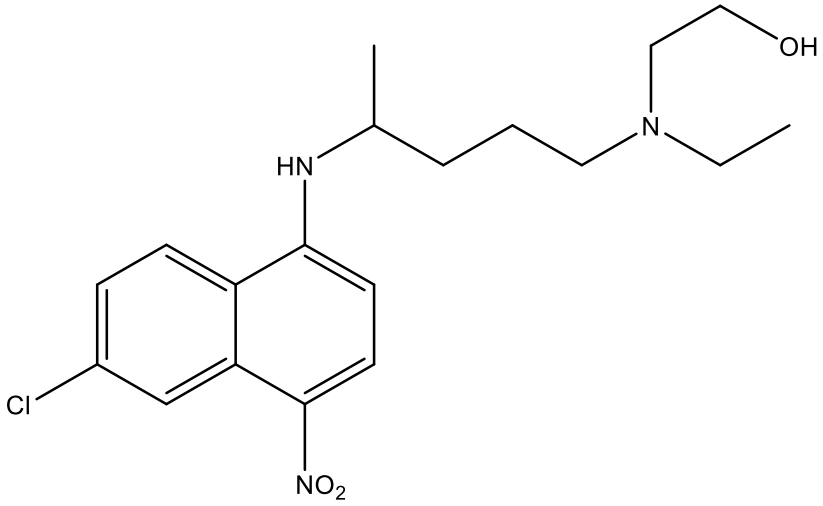
Hydroxychloroquine is a widely used antimalarial drug that was previously thought to treat COVID-19 patients during the 2020 global pandemic that at the time of this writing is ongoing. The structure of hydroxychloroquine is shown below, using retrosynthetic analysis, propose a synthesis for this compound:



You can treat the pyridine ring as a nitrobenzene in place of the nitrogen in the ring like so:

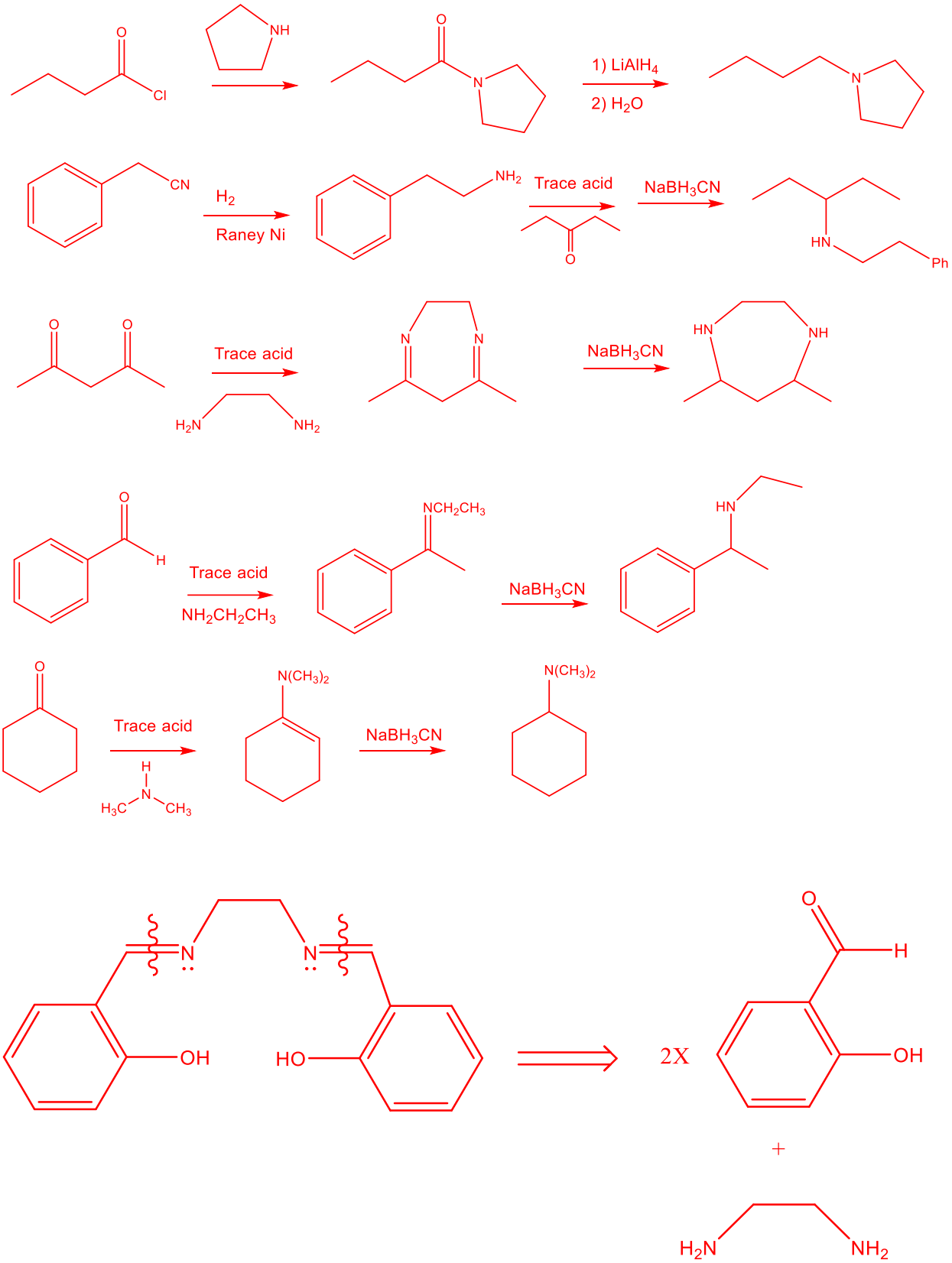


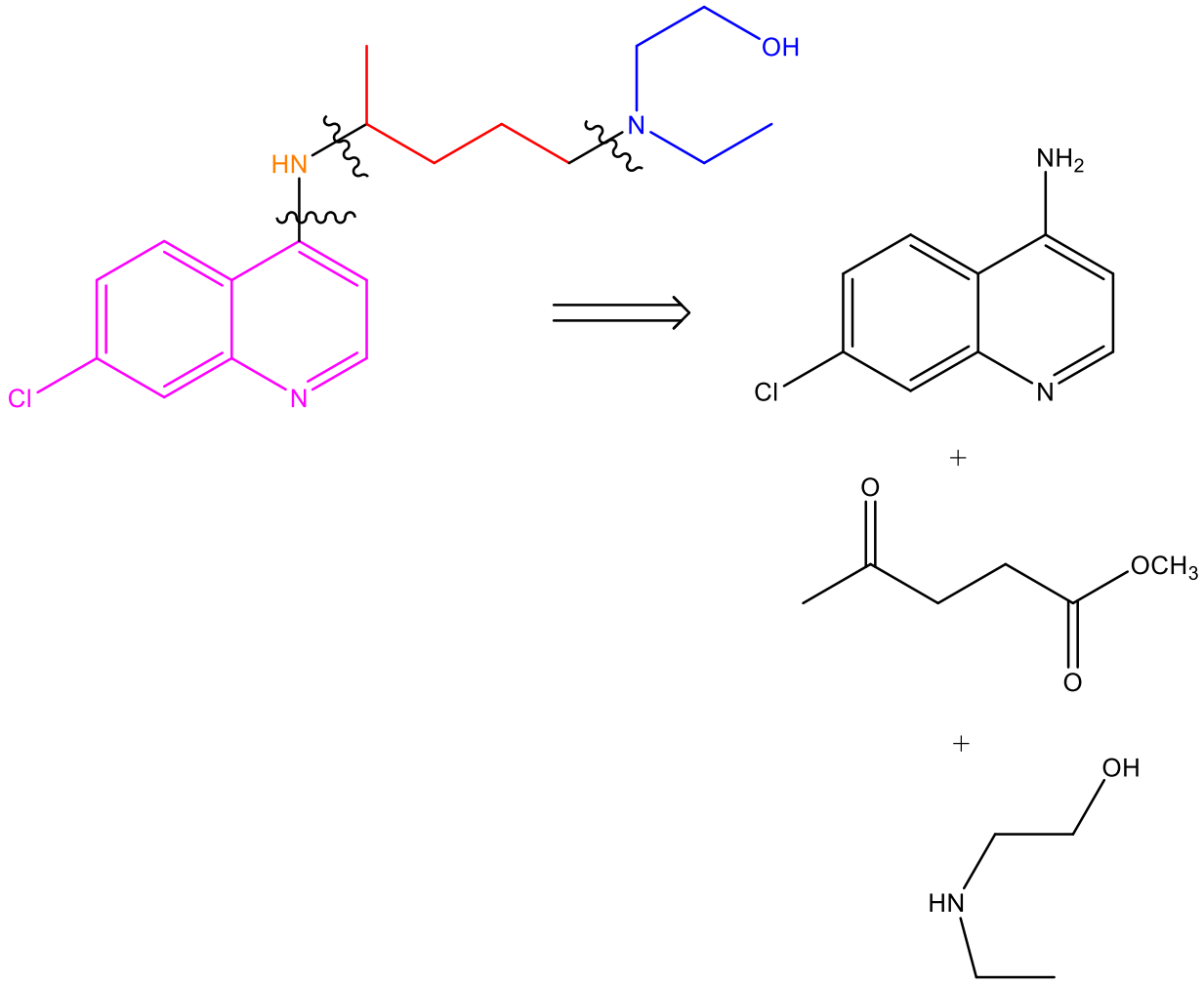
Can be treated like this:



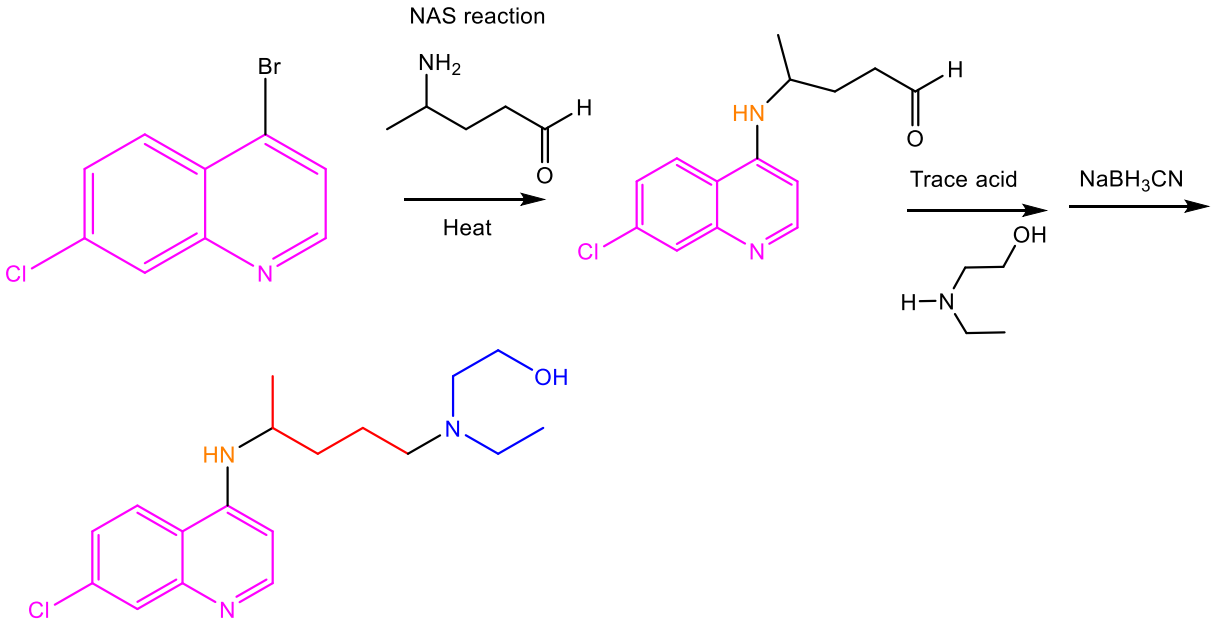
You can start your synthesis from any aromatic compound that is disubstituted with substituents that are NOT carbons (this is a hint).

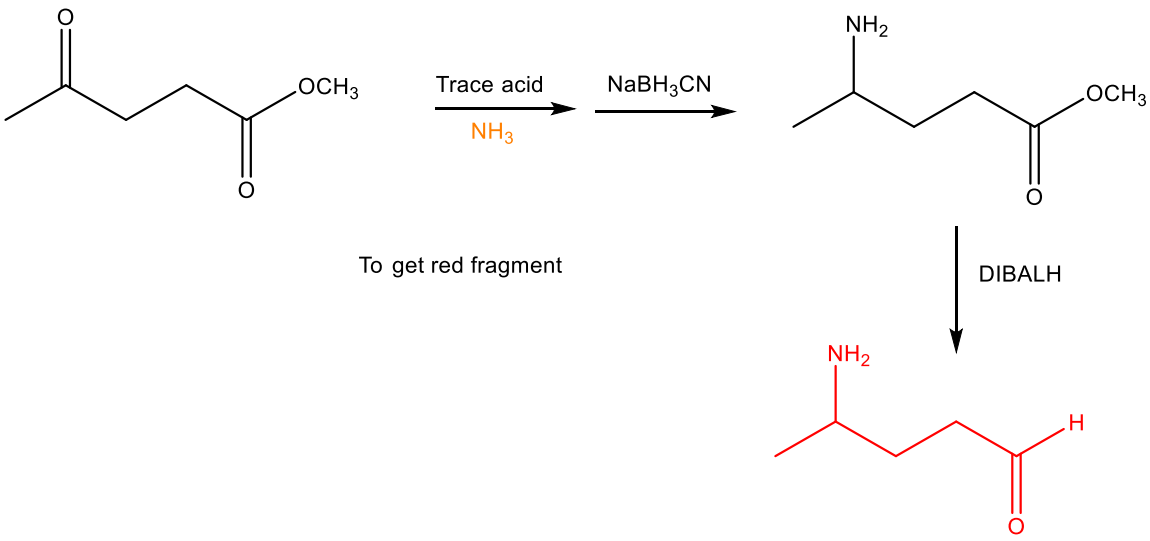
Answers:


1) LiAlH4
2) H2O
H2
Raney Ni
Trace acid
NaBH3CN
Trace acid
NaBH3CN
Trace acid
NH2CH2CH3
NaBH3CN
Trace acid
NaBH3CN
OH
HO
2X

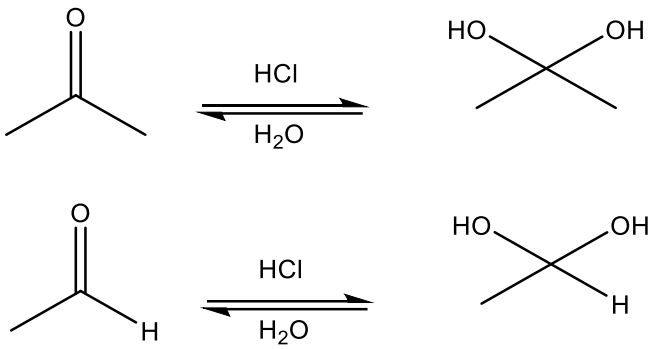


The full synthesis would be:

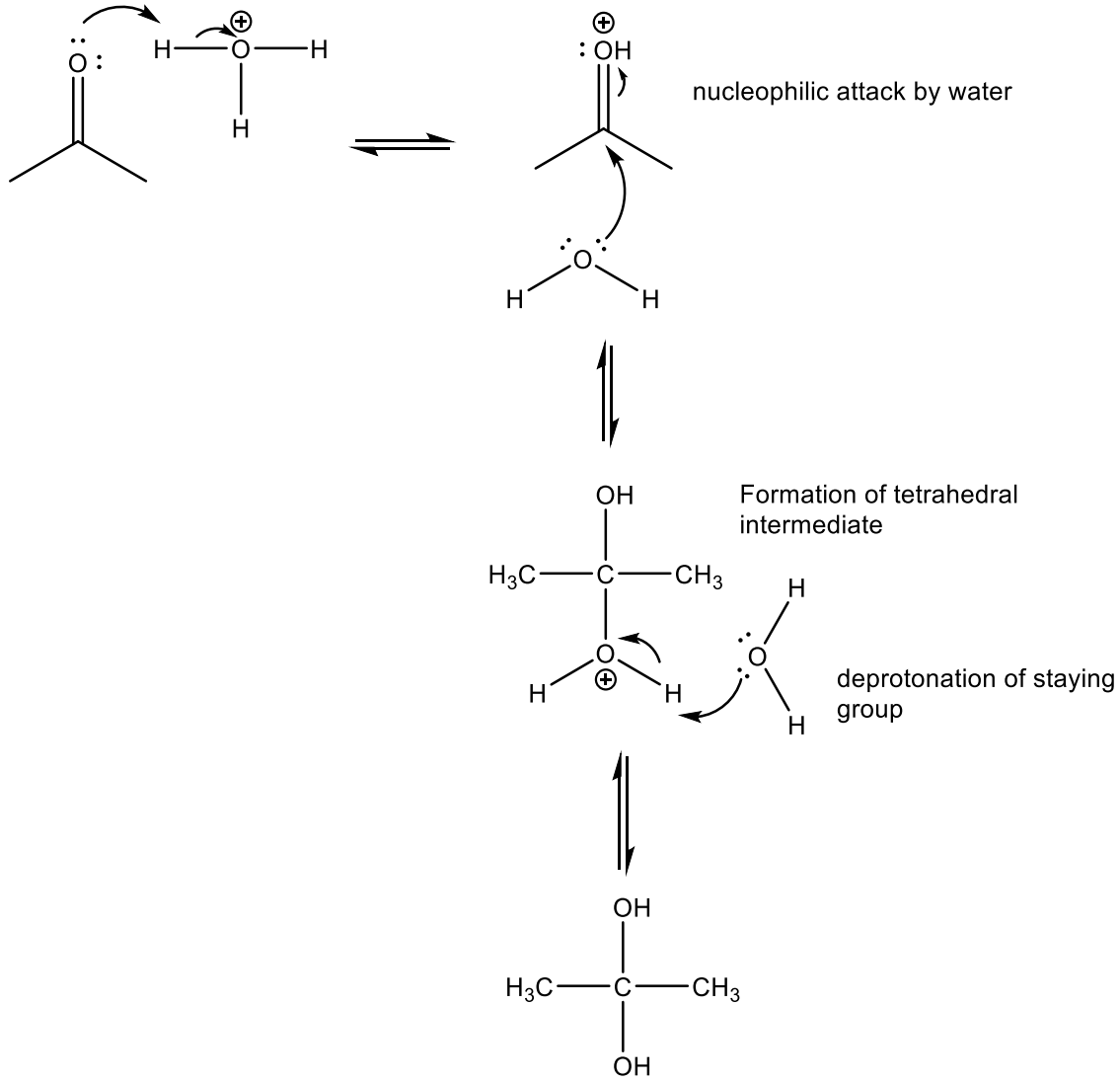

NAS reaction
Br
NH2
H
O
Heat
HN
H
O
Cl
N
Trace acid
NaBH3CN
OH
H–N
OH
HN
N
Cl
N


O
OCH3
O
Trace acid
NH3
NaBH3CN
NH2
OCH3
O
To get red fragment
DIBALH
NH2
H
O

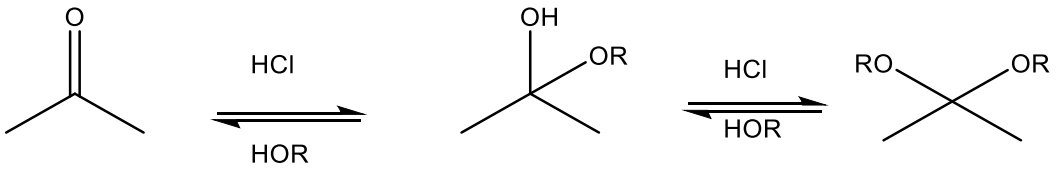
Ketones and aldehydes can also react with water to form geminal diols, or hydrates. The extent to which this happens largely has to do with how sterically hindered the ketone or aldehyde is, the more steric hindrance the less the water will attack and form the geminal diol. The reaction is shown below followed by the mechanism, truth be told, this is one of the least useful reactions so I'm not sure why people teach it, but I'm including it here for completeness sake:

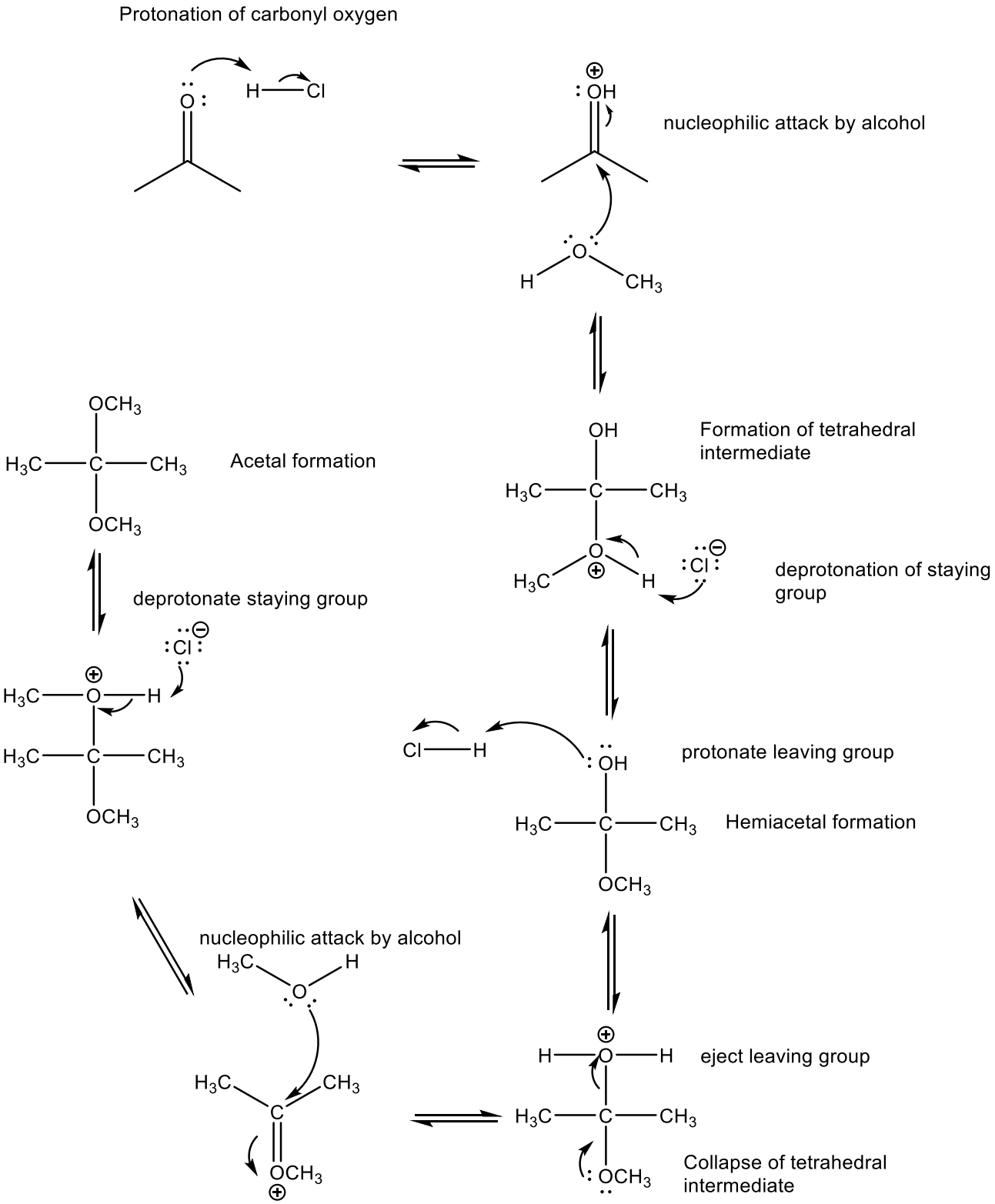


Protonation of carbonyl oxygen

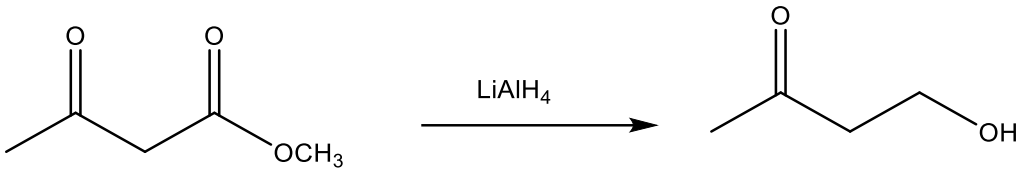


A similar reaction happens with alcohols; however, this reaction is useful as we will see later. In this reaction, the alcohol can add either once or twice. If the alcohol adds once then a hemiacetal forms, in the presence of excess alcohol, it adds twice and this product is called an acetal. The reaction is shown below followed by the mechanism:

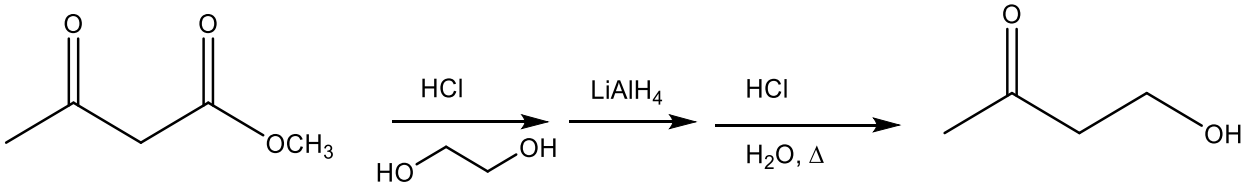



Protonation of carbonyl oxygen
nucleophilic attack by alcohol
Formation of tetrahedral intermediate
deprotonation of staying group
protonate leaving group
Hemiacetal formation
eject leaving group
Collapse of tetrahedral intermediate
nucleophilic attack by alcohol
deprotonate staying group
Acetal formation

This reaction is useful as a protecting group for carbonyl compounds. Protecting groups are those groups that prevent chemical reactions with more reactive functional groups within a molecule by temporarily masking them with a chemical shield. Acetals are fantastic chemical shields because acetals are comprised of ethers and ethers are "exclusionary", meaning they only react with acids and nothing else. Because of this, alcohols are used to protect reactive carbonyl groups like ketones and aldehydes through the acetal functional group. For example, if I wanted to make this reaction occur, it would not work as written:

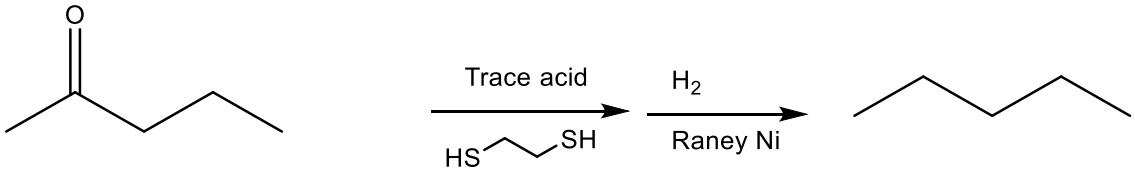


This is because the ketone functional group is more reactive than the ester one, therefore, if I reduce the ester with $LiAlH_4$ in the presence of the ketone, BOTH will get reduced. To do this reaction, I first need to PROTECT the ketone using an acetal. The most commonly used alcohol for making acetals is ethylene glycol because it packs the two alcohols into one molecule, preventing the need for two equivalents. The following would be the required synthetic route:

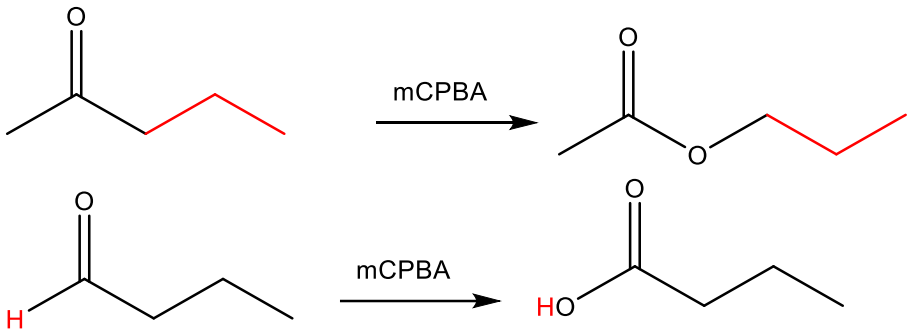


Just like imines, enamines, and hydrates, the acetal protecting group is removed with HCl, H_2O, and heat.

Because sulfur and oxygen are in the same group in the periodic table, it should come to no surprise that thiols work in the exact same way as alcohols. Instead of making acetals, they make thioacetals, which function the same way. The added benefit of the thioacetals is that they can be reduced to remove the carbonyl group if Raney Ni is used as the catalyst:



Those have been all of the reduction reactions that these compounds do, however, they can also get oxidized. These compounds can be converted to esters and carboxylic acids (for ketones and aldehydes respectively) if they are reacted with peroxy acids, such as mCPBA. An example of these reactions is shown below:

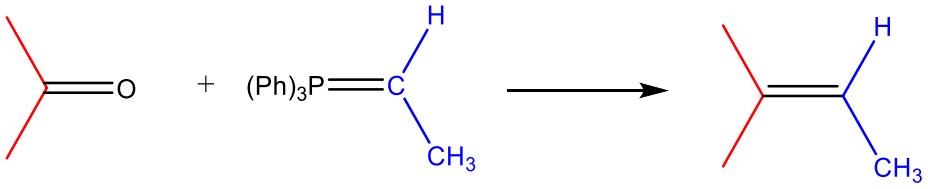


As you may have noticed, the oxygen did not go on both sides of the ketone, in other words, this reaction was *regioselective* in that it put the oxygen only on the more substituted side. This is always the case for ketones, the oxygen always gets put in between the carbonyl group and the more substituted side of the ketone. For aldehydes, they are always made into carboxylic acids because H has the largest tendency to get bonded with an oxygen. The tendencies to get an oxygen are shown below:

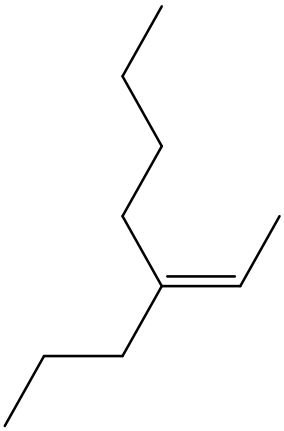
H > tertiary alkyl > secondary alkyl ~ phenyl > primary alkyl > methyl

A phenyl group, often denoted as Ph, simply refers to a benzene ring attached directly to the carbon.

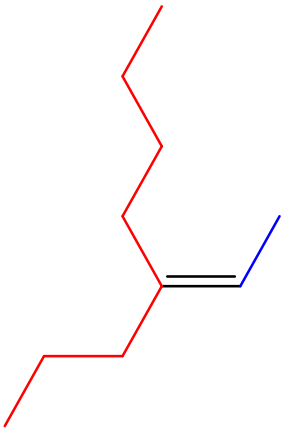
Ketones and aldehydes are also unique in that they can undergo the Wittig Reaction, which is a convienent way to make alkenes from ketones and aldehydes. The mechanism for the Wittig Reaction is not important to know and is likely beyond the scope of a typical introductory organic chemistry course, so we will not cover it here. A dead giveaway that a reaction is a Wittig Reaction is if there is a phosphonium ylide, no other reaction in the course has this reagent. A typical Wittig Reaction is shown below:



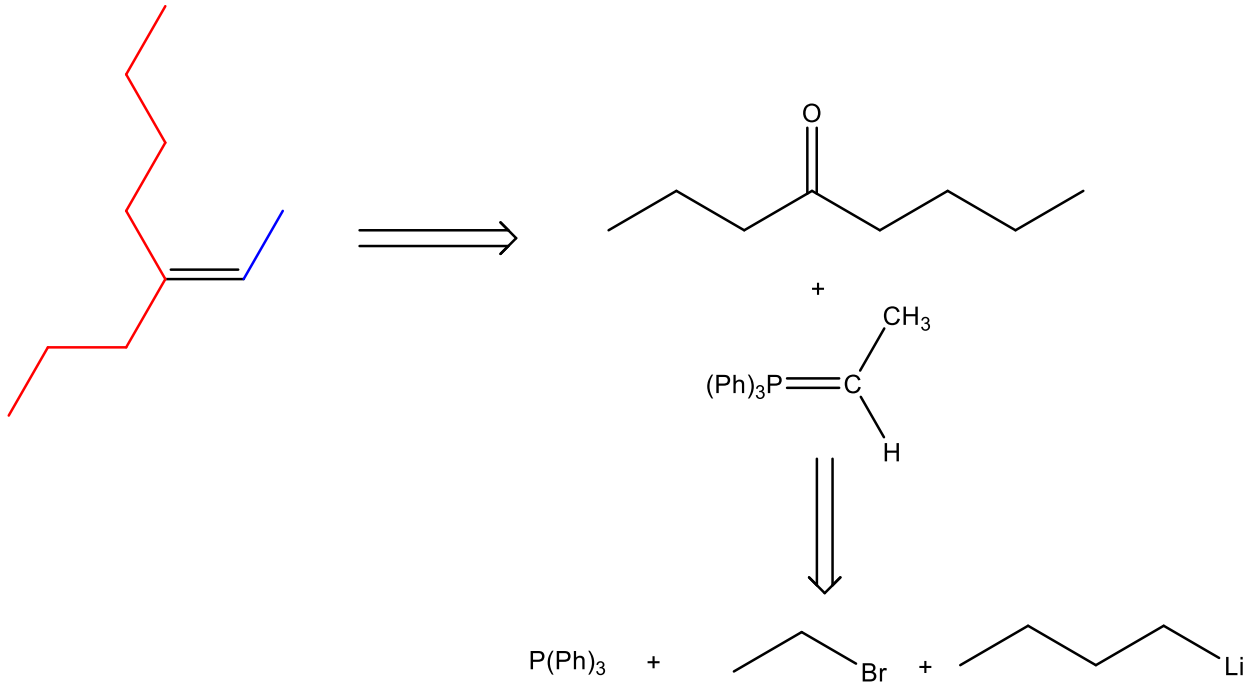
To make a phosphonium ylide, typically triphenyl phosphine is reacted with an alkyl halide in an SN2 reaction, and a strong base (typically n-butyl lithium) is used to generate the double bond. Because the preparation of the phosphonium ylide goes through an SN_2 reaction, it is preferential to use a primary or secondary alkyl halide. When looking at making any alkene through a Wittig reaction, always split the alkene in half and make the less substituted/less sterically hindered side be the side you use to make the ylide from. For example:



If that is your desired alkene, then you need to split the alkene in half like so:



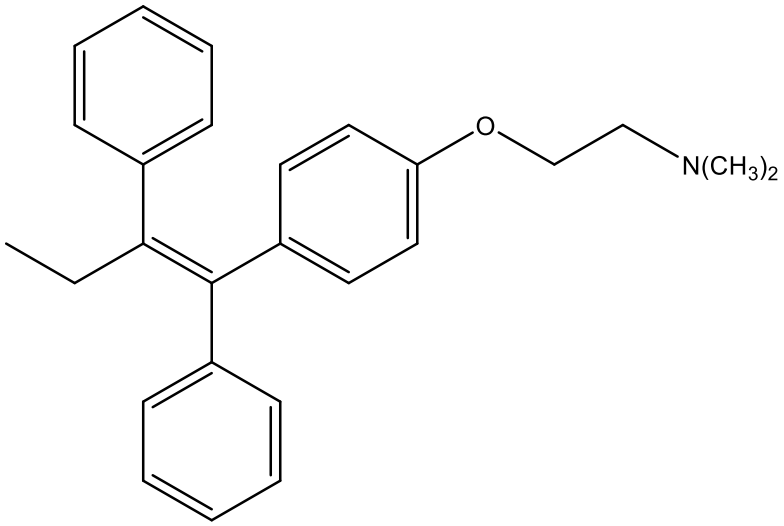
Clearly the less substituted side is the blue side, so I will make that my alkyl halide and the red side will have to be my carbonyl, so retrosynthetically, it would be:



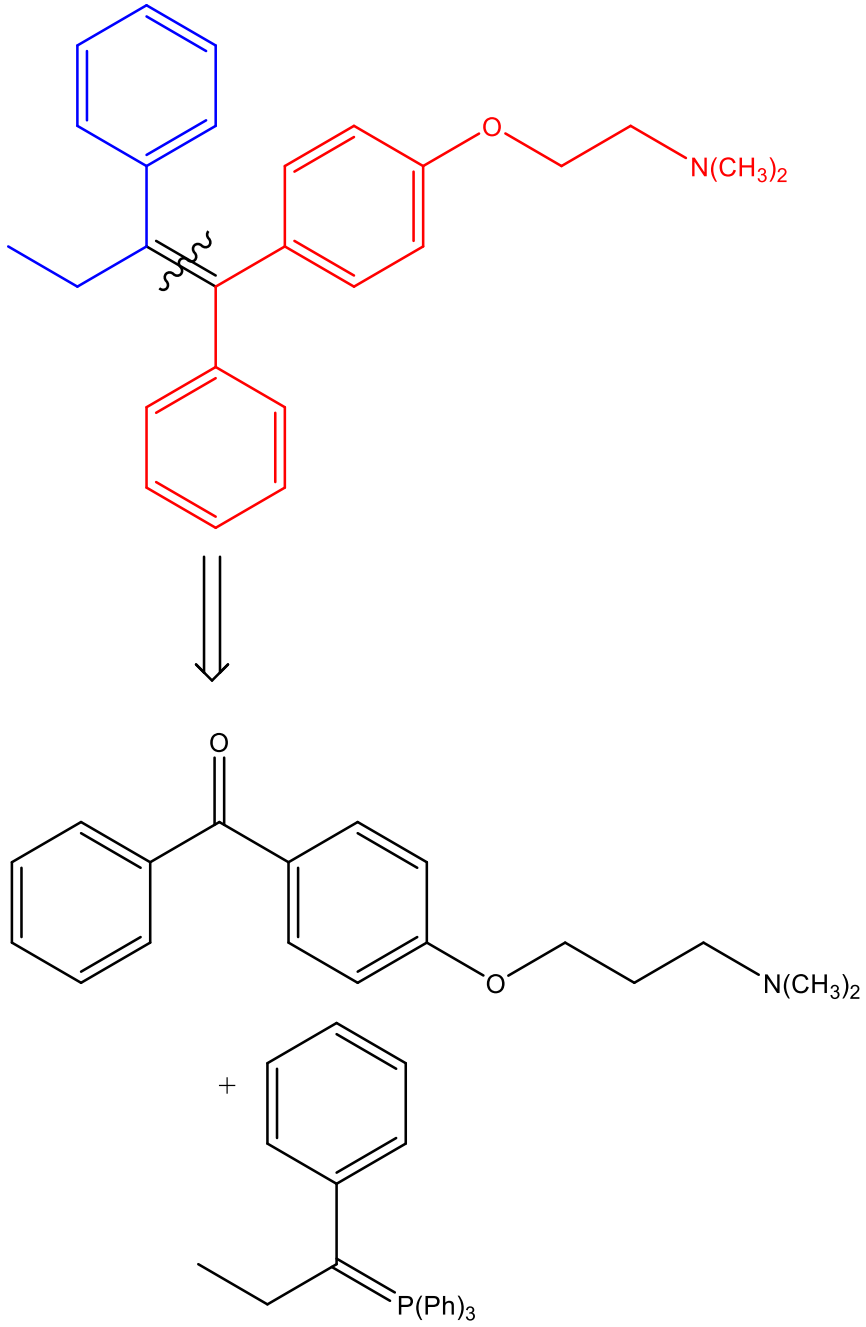
This reaction is not very stereoselective, so a mixture of E and Z products will result if you are aiming for an internal alkene.

Practice question:

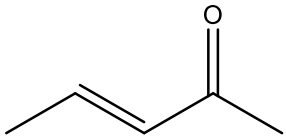
Tamoxifen is an anticancer drug that is used in the treatment of breast cancer, the structure is shown below. If you wanted to make this drug using a Wittig reaction, what organic compounds would you require?



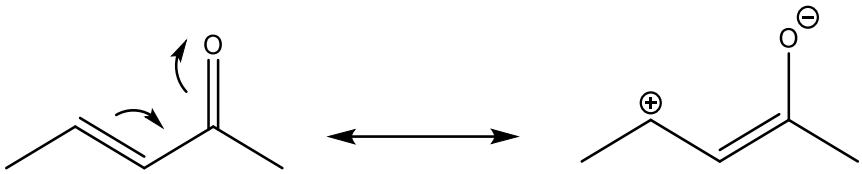
Answer:



The final reaction that we will cover in this chapter is the addition of nucleophiles to alpha-beta unsaturated carbonyl compounds. These come in three flavors: ketone, aldehyde, and carboxylic acid derivative. They all work functionally the same, so we will do the alpha-beta unsaturated ketone as an example. The structure of an alpha-beta unsaturated ketone is shown below:



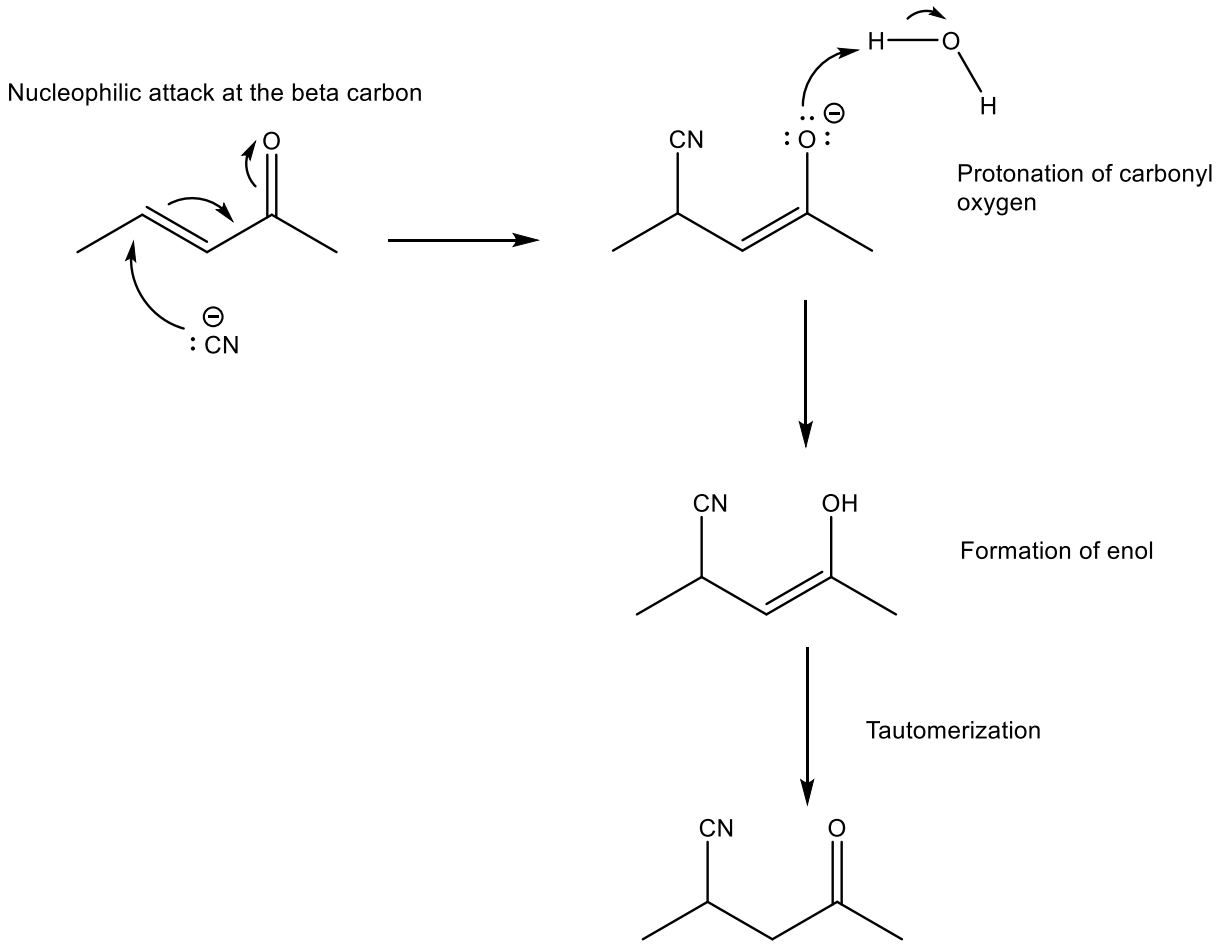
It is referred to as an alpha-beta unsaturated ketone because the alpha and beta carbons have a double bond connecting them. The alpha carbons, as we will discuss in the next chapter are the carbons that are directly adjacent to the carbonyl group. The reason these compounds are especially unique is because of their resonance form:



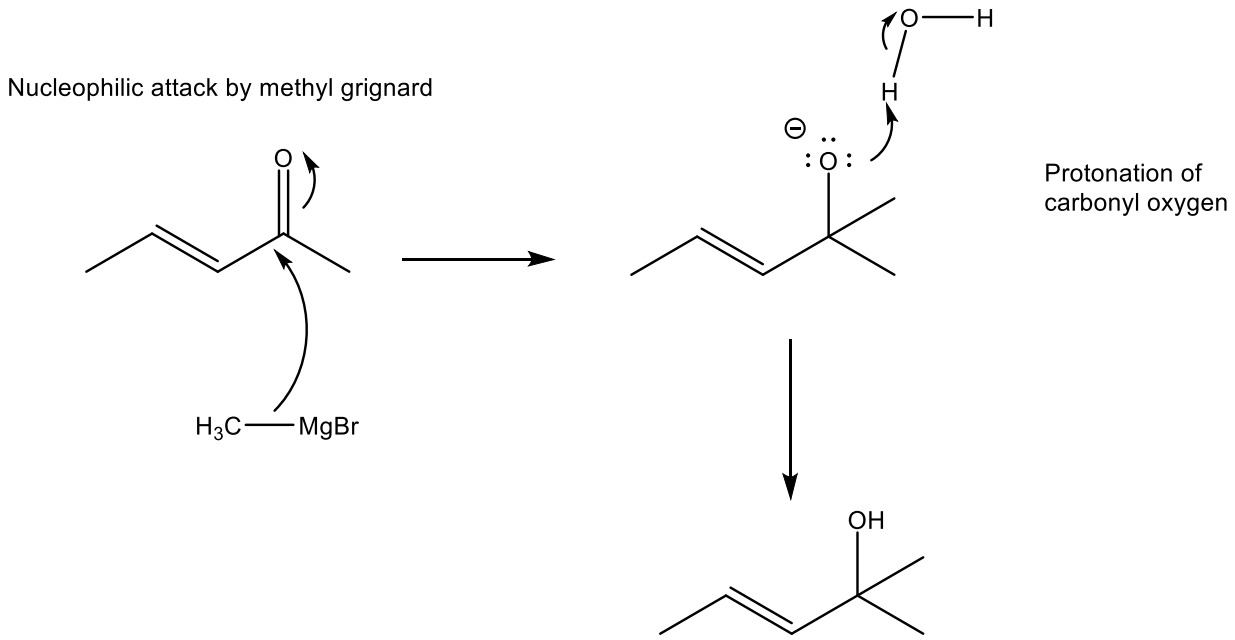
Now, as opposed to having one electrophilic carbon in our carbonyl compounds (the carbonyl carbon itself), we also have the beta carbon as a possible position of attack. Some nucleophiles will prefer to attack the beta carbon over the carbonyl carbon and vice versa. This preference comes down to base strength, *stronger bases prefer to attack the carbonyl carbon* as opposed to the beta carbon. *For most of the common bases that we see in this course, when in doubt, attack the beta carbon.* The only reagents that will attack the carbonyl carbon over the beta carbon are Grignards and organolithiums, and that is because their conjugate acids are alkanes which are the least acidic organic compound.

For carboxylic acid derivatives, only esters and below on the reactivity chart will ever have attack at the beta carbon, that is because acyl chlorides are too reactive to have attacks at the beta carbon, the driving force in that cause is retention of the carbonyl group and expulsion of the chloride leaving group.

The following are the reaction mechanisms for when nucleophiles attack the beta carbon and carbonyl carbon:



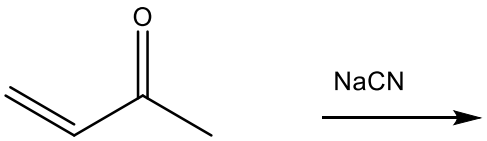
Cyanide anion is not a strong base, therefore it will attack the beta carbon as we had previously mentioned. Because it is attacking the beta carbon, the double bond has to move from the beta-alpha to the alpha-carbonyl position, which forces the carbonyl pi bond to break and creates a negatively charged oxygen. To resolve the negative charge on that oxygen, a solvent molecule is deprotonated, however, this forms an enol, and if you recall from the alkyne reactions chapter, enols rapidly tautomerize to the keto form, which has the carbonyl group on whichever carbon bore the OH in the enol form. This is favorable because it forms the strong C=O bond (AM**S**OW).

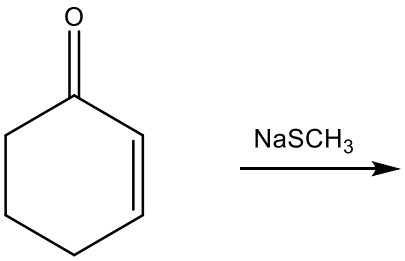


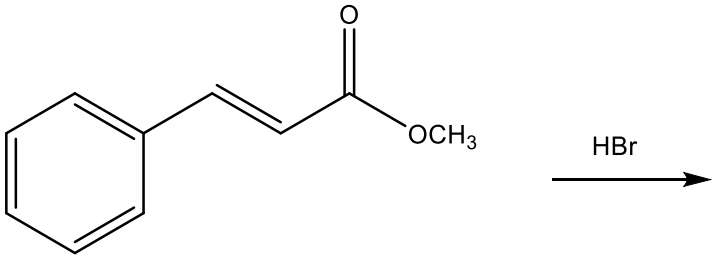
Methyl Grignard is a strong base, therefore it will preferentially attack the carbonyl carbon, when this happens, this forces the pi bond between the C and O to move onto the oxygen as lone pairs because carbon can only have four bonds. This creates a negatively charged oxygen, which needs to get protonated to resolve its charge, this happens in the second step (A**M**SOW) and our produt is formed.

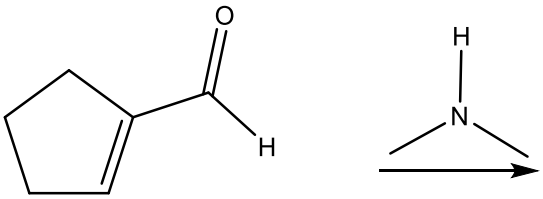
Practice questions:

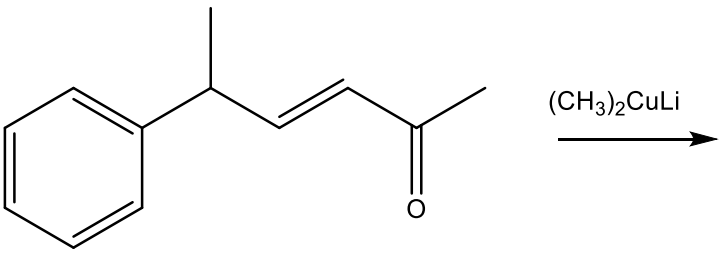
Predict the major organic products for the following reactions:

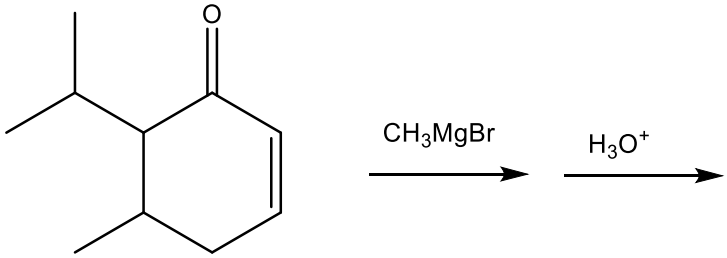

O
NaCN


O
NaSCH3


O
OCH3
HBr

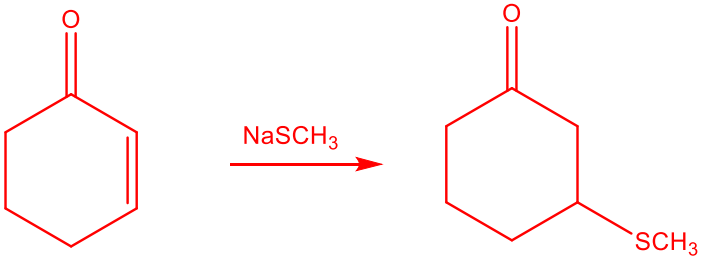

O
H
H
N

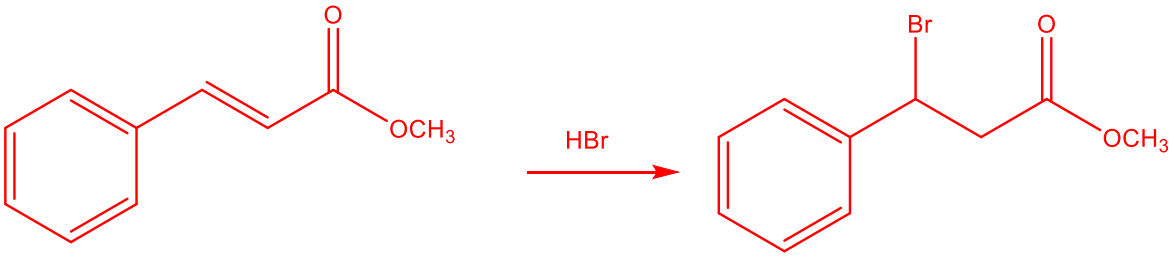

O
(CH3)2CuLi

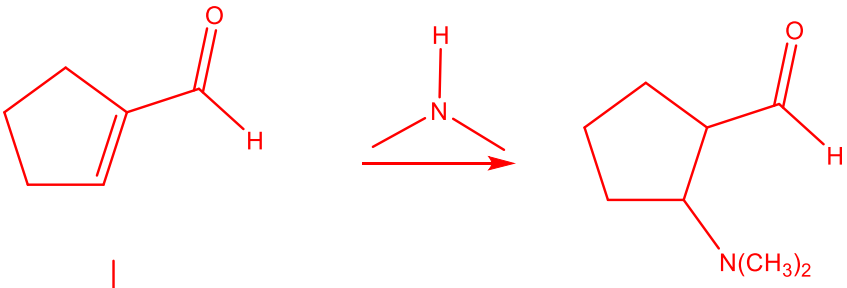

O
CH3MgBr
H3O+

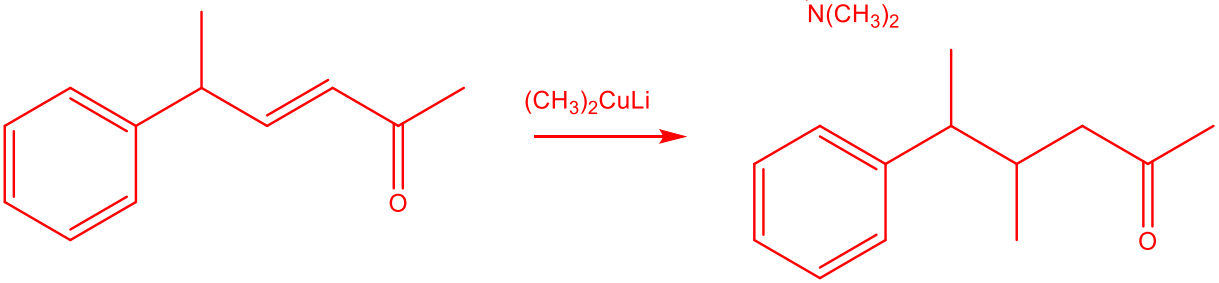
Answers:

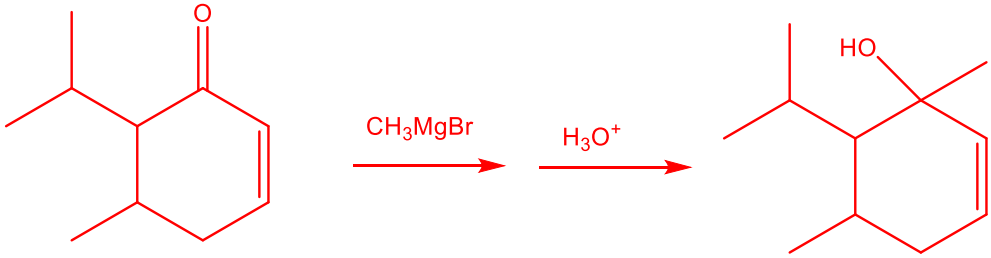

O
NaCN
O
NC


O
NaSCH3
O
SCH3


O
OCH3
HBr
Br
O
OCH3

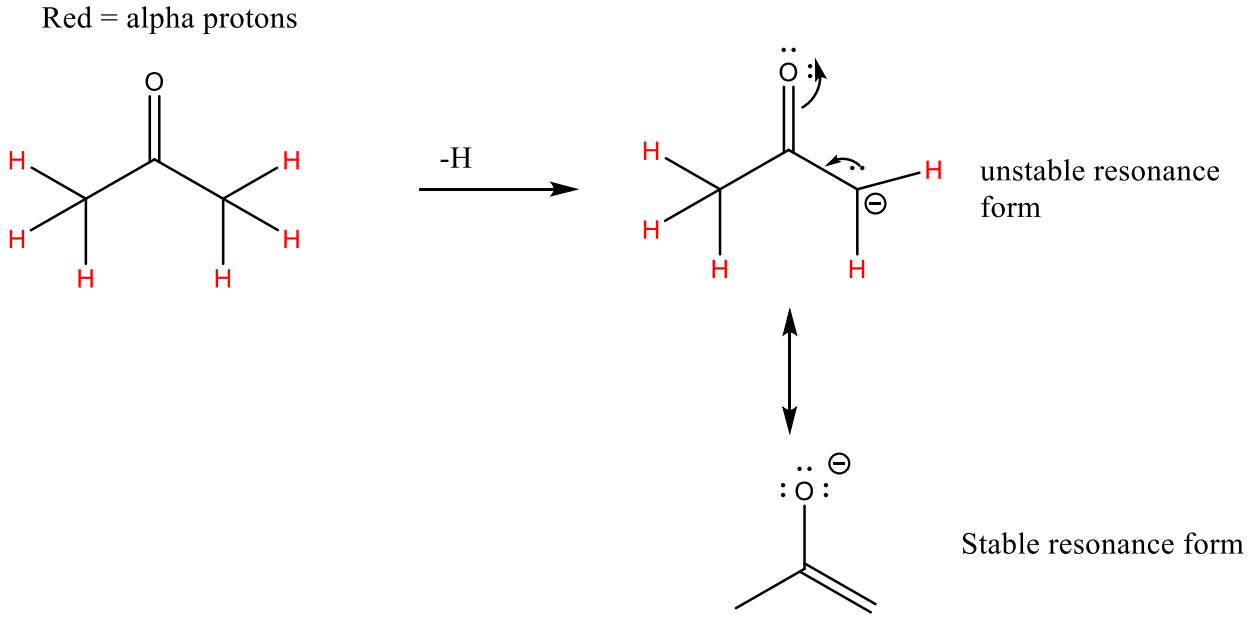

O
H
H
N
O
H
N(CH3)2


O
(CH3)2CuLi
O

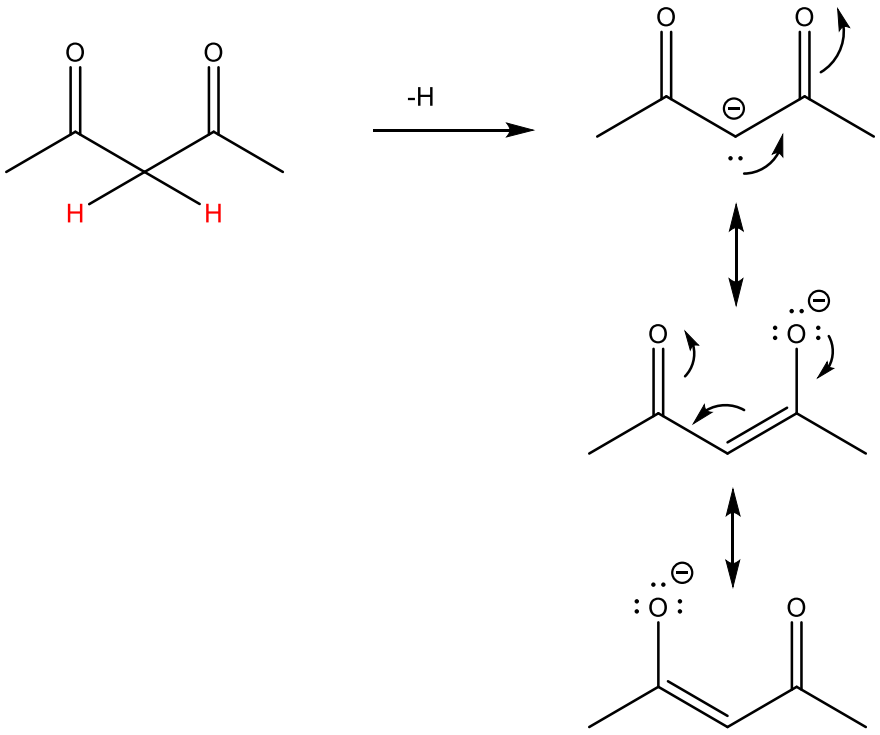

O
CH3MgBr
H3O+
HO

Chapter 14: Reactions at the Alpha Carbon

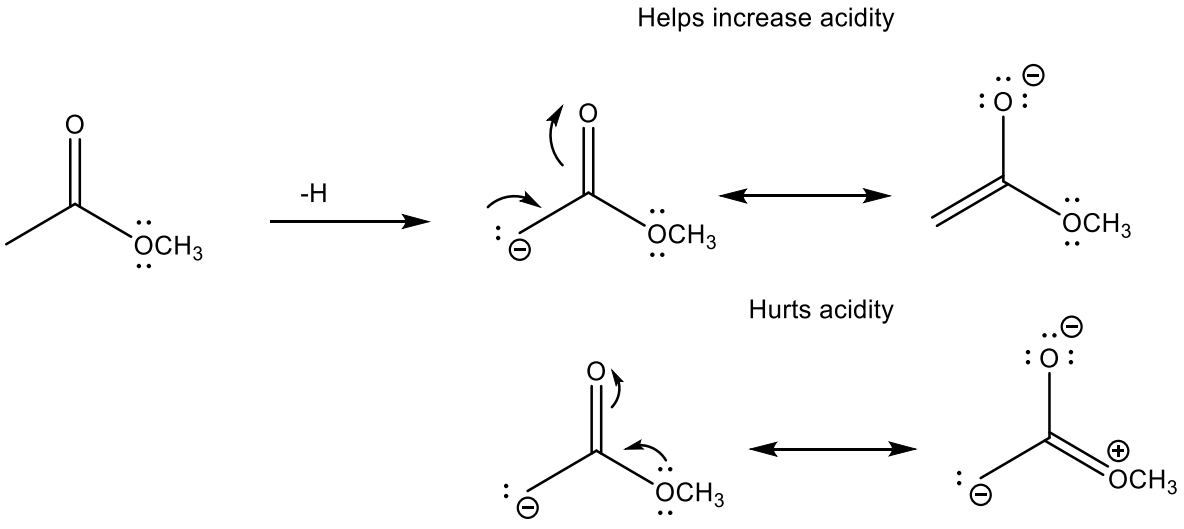
This entire chapter is dedicated to the reactions of the alpha carbon. We have already seen that the beta carbon of alpha-beta unsaturated carbonyl compounds is *electrophilic*, but the alpha carbon of regular carbonyl compounds has *acidic protons*. Whicka whutttttt? Yea, you read that correctly, *acidic protons*. Your gut reaction is probably something along the lines of "heh? I thought C-H bonds aren't acidic" and you are correct, C-H bonds in isolation are NOT acidic. The reason why alpha protons are acidic is because of, drum roll please, *resonance*. We can see that clearly with the following scenario. If we were to deprotonate an alpha carbon, that would generate a negative charge and give the alpha carbon lone pairs, well those lone pairs just so happen to be in conjugation with the carbonyl double bond, therefore the conjugate base is *resonance stabilized*.



This turns out to be a huge deal, because it means that *the alpha carbon can act as a nucleophile* when it is exposed to a strong enough base to deprotonate its alpha protons! *This gives us another carbon nucleophile* that we can use to make carbon-carbon bonds with. When an alpha proton is taken off and a negative charge is generated, these compounds are reffered to as enolates, its an enolate because its more stable resonance form (the one with the negative charge on the oxygen) is like an enol except it is deprotonated, hence the –ate ending. The form with the oxygen bearing the negative charge is the more stable form because oxygen is much more electronegative than carbon and can therefore support a negative charge better, this form minimizes energy (A**M**SOW). Because the alpha carbon can be nucleophilic, it is often used to attack other compounds. This resonance stabilization effect is even further enhanced when the alpha carbon is flanked by two carbonyl groups like so:



This further minimizes charge because now the negative charge is distributed over two oxygens and one carbon, as opposed to one oxygen and one carbon (A**M**SOW). The acidity of those alpha protons are therefore further increased because of more stable resonance forms. The acidity of the alpha protons can be decreased if there is competition by other lone pairs that are in resonance, think amides and esters. This competition is increased the more the heteroatom wants to give away its electrons, therefore, amides have the least acidic alpha protons because N is less electronegative and more willing to share its electrons than O. This competition is shown below:



Other electron-withdrawing groups have the same effect, just as a refresher, these are all the EWG that you should be familiar with:

Guide to Electronic Effects on pKa

Electron-Withdrawing Groups:
Increase Acidity
Typically have double bonds in conjugation with the ring

In order of decreasing strength:
NO2
SO3H
Carbonyls
Nitriles
F
Cl
Br

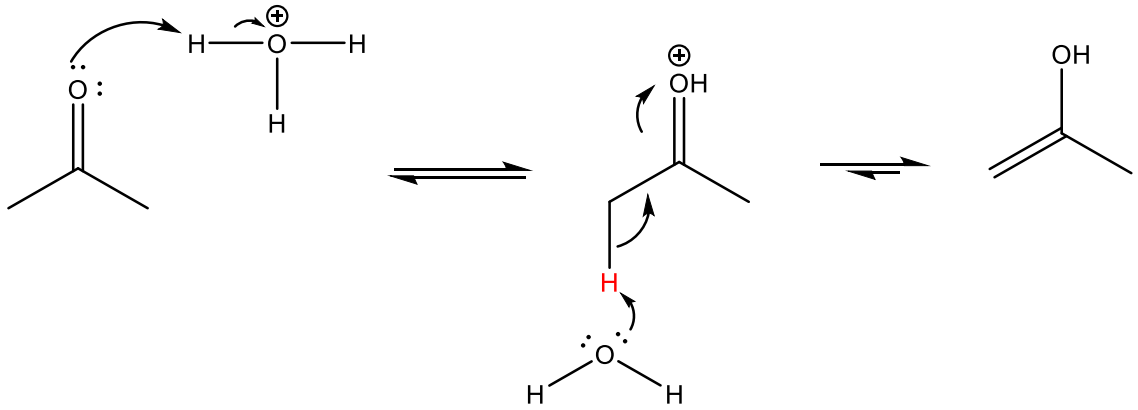
Electron-Donating Groups:
Decrease Acidity
Typically have lone pairs in conjugation with ring

In order of decreasing strength:
NH2
OCH3
OH
CH3

Blue = Resonance contributing groups
Red = Inductive groups

The alpha carbon can be turned nucleophilic in base and in acid, the key is that there needs to be either an enol or enolate for the alpha carbon to be nucleophilic. You have already seen the mechanism for how base makes the alpha carbon nucleophilic, but here is the mechanism for how it works in acid. Like you would expect, the alpha carbon is WAYYYY more nucleophilic in base than it is in acid, but some selective reactions will require the acidic conditions and therefore it is worth discussing the acidic enol formation mechanism:

Protonation of the alpha carbon

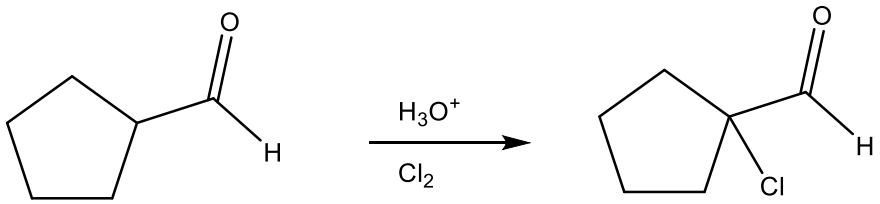


Regenerate acid catalyst

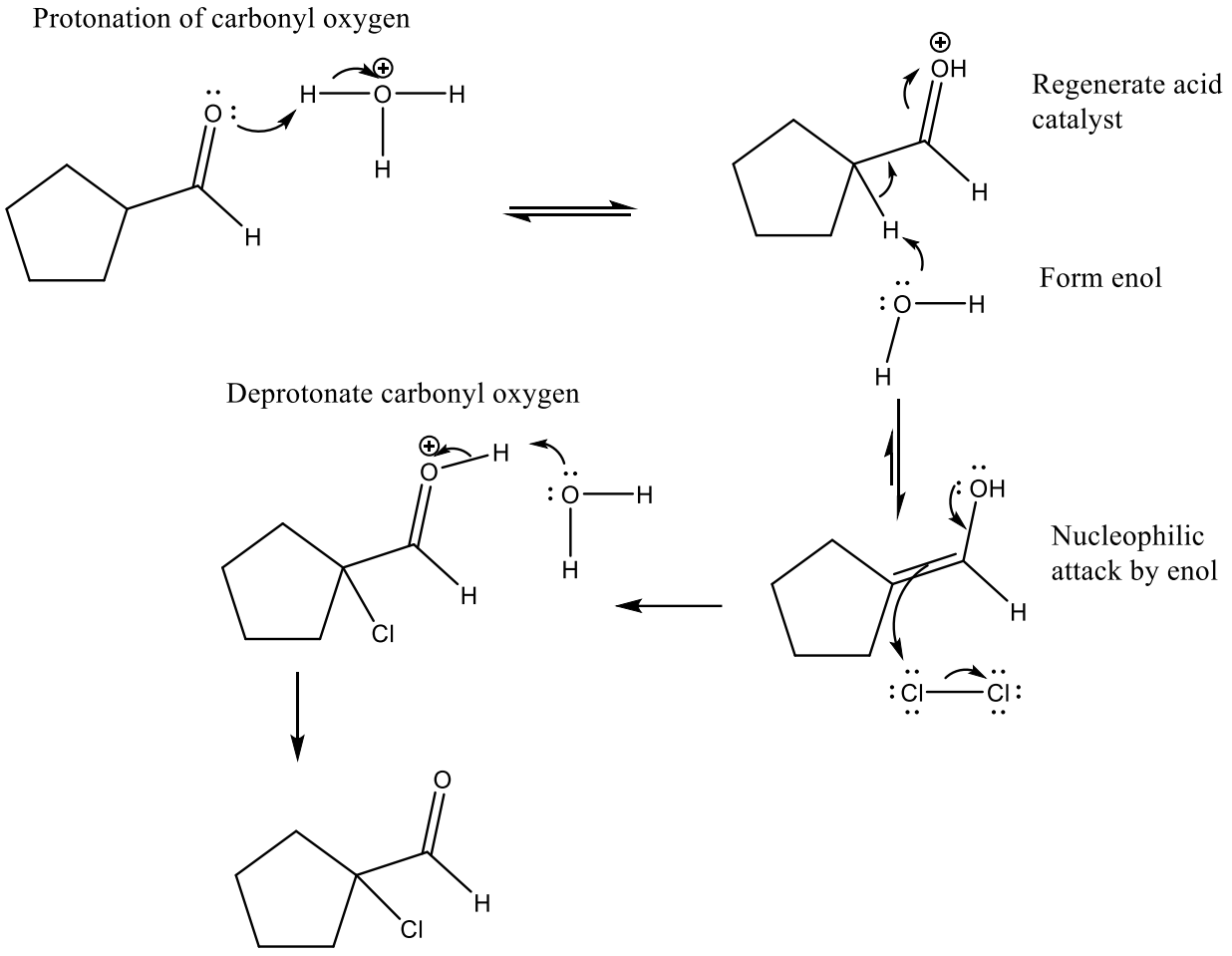
The mechanism starts off by protonating the carbonyl oxygen, this should come to no surprise as this has become a more standard starting step for a lot of the carbonyl reactions, it is also the

only atom in the carbonyl compound that can act as a base since it is the only one with lone pairs (**A**MSOW). This reaction is acid catalyzed, meaning that it needs to regenerate the acid catalyst at the end of the mechanism, so the water acts as a base and deprotonates the alpha carbon in an acid-base reaction, this forms the pi bond between the alpha carbon and the carbonyl carbon. This pushes the pi bond between the carbonyl carbon and oxygen onto the oxygen to resolve its charge (A**M**SOW).

The first reaction that we will discuss that uses acidic conditions to make the nucleophilic alpha carbon is acid catalyzed-halogenation. This reaction is selective and makes it so that the alpha carbon only gets a single halogen. The reaction is shown below and the mechanism is shown after:

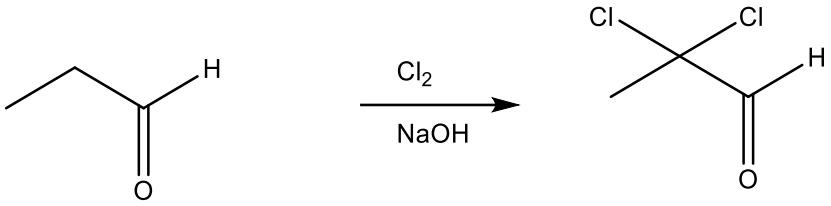


The mechanism:

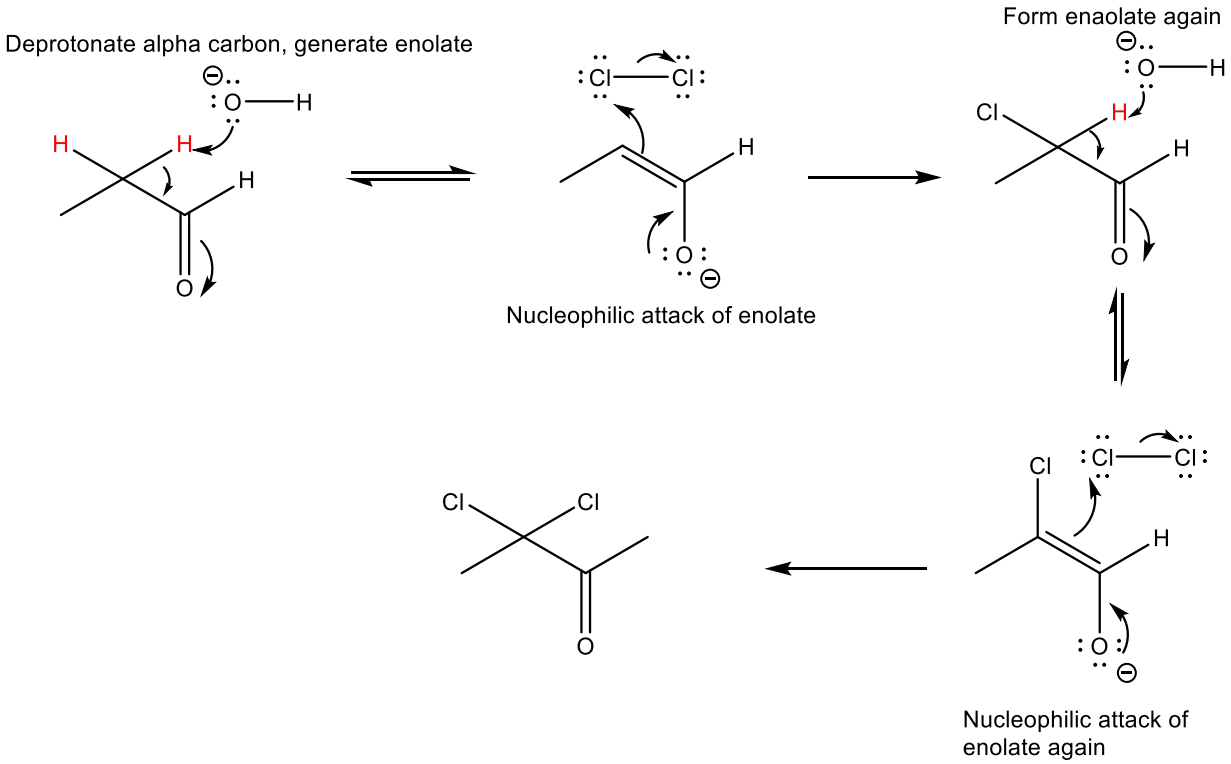


The first two steps of the mechanism is forming the nucleophilic enol. The reason why the enol is nucleophilic is twofold: firstly, it would prefer to reform the carbonyl C=O bond so there is an incentive to give up the pi electrons between the two carbons because C=O is a strong bond (AM**S**OW). Secondly, there is a nonpolar pi bond between the two carbons and we know from a base level that alkenes are nucleophilic. Once the enol forms and the halogen gas is exposed, the halogen gas gets attacked by the nucleophilic enol and the carbonyl bond is reformed with the halogen attaching to the alpha carbon, the driving force here being the reformation of the strong carbonyl bond (AM**S**OW). The carbonyl oxygen still has the hydrogen on it from the first step, so it needs to get removed for two reasons, firstly, oxygen hates having a positive charge and protonated carbonyls are some of the most acidic protons to exist in this course (A**M**SOW). Secondly, it must be done to regenerate the acid catalyst; this was a catalyzed reaction so H_3O^+ must be regenerated at the end. This reaction is selective for a single halogenation because once the halogen is on the alpha carbon, that decreases the nucleophilicity of the enol intermediate. Remember, nucleophiles are electron-rich and halogens suck electrons away through inductive electron-withdrawal. Enols are already not very stable to begin with, and the added halogen there effectively prevents a second attack by the enol. It makes the enol less electron-rich and therefore less nucleophilic.

This reaction can be done in base, but because enolates are much more nucleophilic than enols, this is for when you want to add several halogens to the alpha carbon. The reaction is shown below followed by the mechanism:

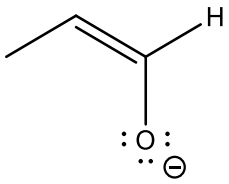


The mechanism:

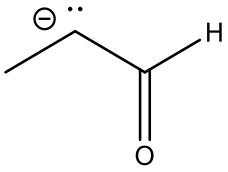


This reaction will continue to go until all of the alpha protons are taken and replaced with halogens. The key difference between this reaction and the previous is that this proceeds through the more nucleophilic enolate, because it is more nucleophilic, the inductive electron-withdrawing effects the halogens have become a nonissue and you can continue to halogenate continuously. The chemical logic for this reaction is similar to the previous one. Something important to note is that while the resonance form I drew in the mechanisms is the more stable form, it is often useful to draw the enolate in the other resonance form to make sure you know the carbon is going to attack, not the oxygen. This should make sense to you anyway though, which element wants to minimize its negative charge more, carbon or oxygen? Obviously carbon

because it is less electronegative and therefore it wants to be neutral way more than oxygen (A**M**SOW).



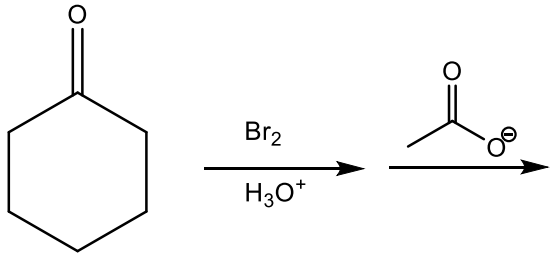
more usefully written as

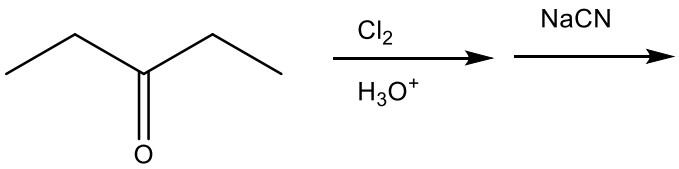


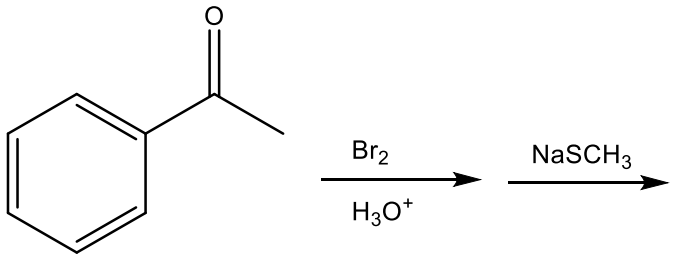
Halogenation is a useful reaction because these alkyl halides can still go through the same SN2 and E2 reactions that we discussed a while back.

Practice questions:

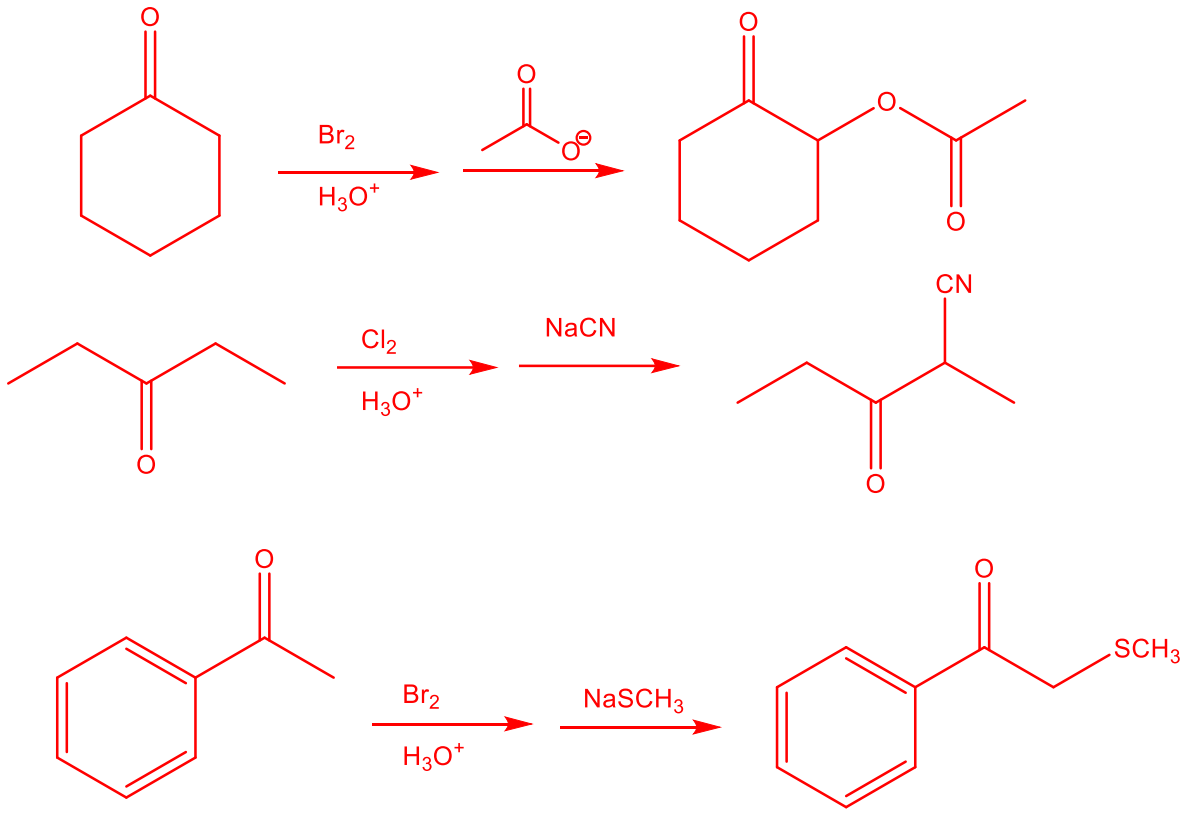
Predict the major organic products for the following reactions:



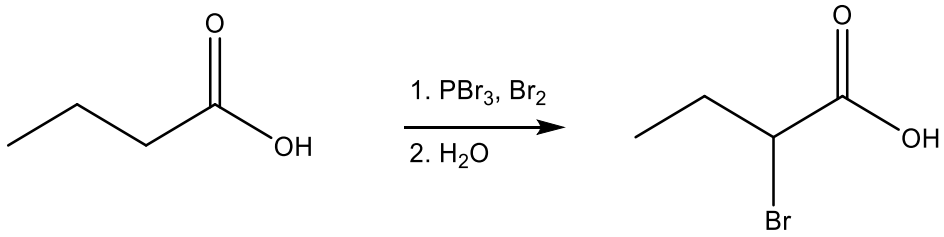




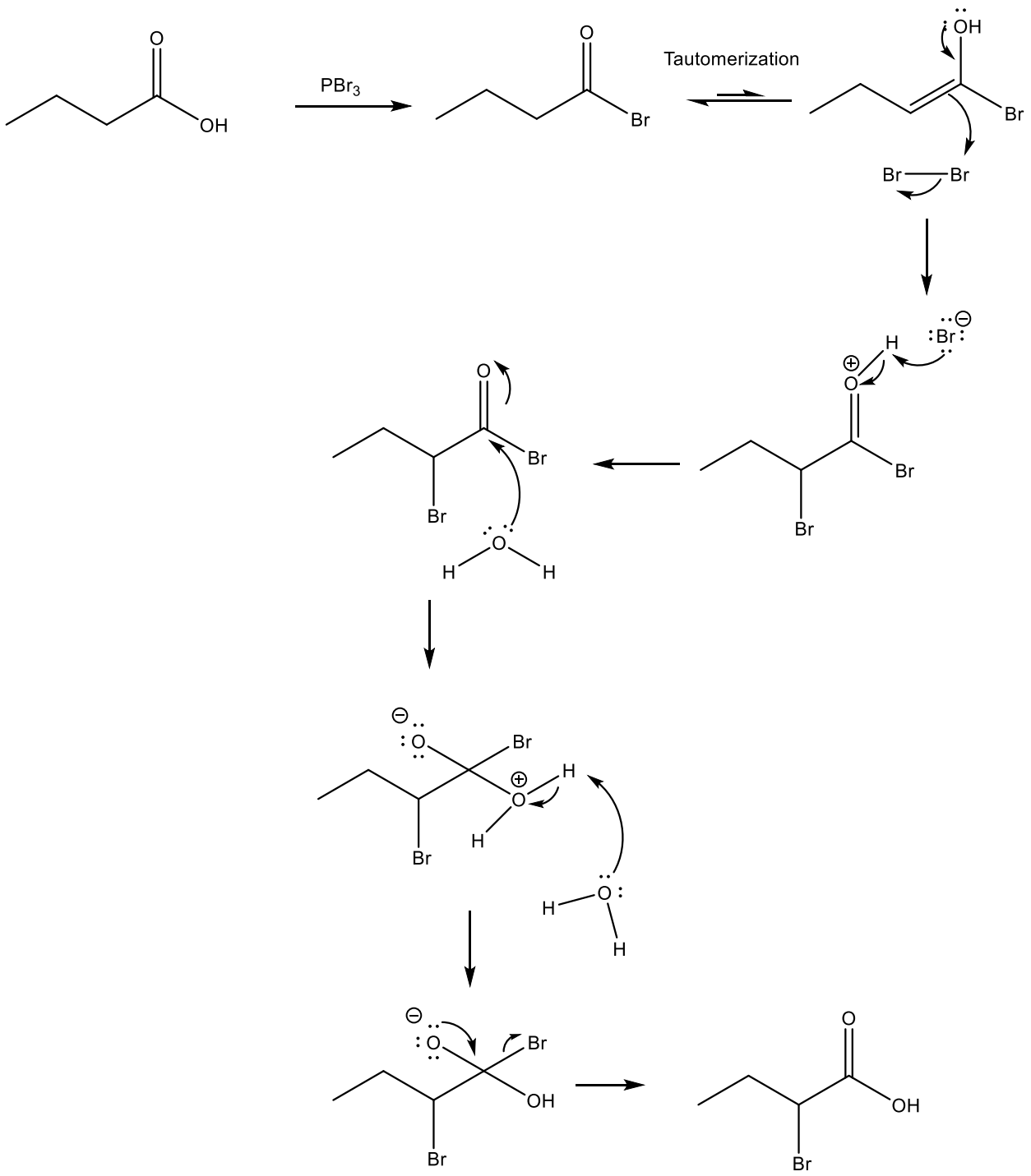
Answers:



You can also halogenate the alpha carbon of carboxylic acids using a special reaction called the Hell-Volhard-Zelinski reaction or HVZ reaction:



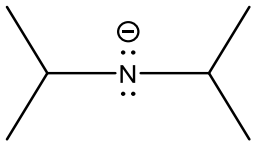
The reaction mechanism is shown below:



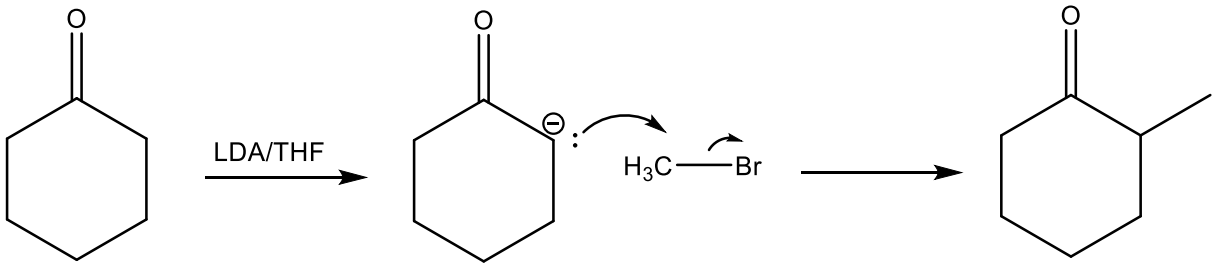
The first step replaces the OH group with a Br group, this uses the reagent that we used in the alcohol reactions chapter, the mechanism for it is not super important. The reason why this has to happen is so that we can get back the carboxylic acid at the end when we go through a hydrolysis reaction. We need a better leaving group. Once the acyl bromide is formed, it can tautomerize to the enol form, remember, this isn't great, the equilibrium is very reactant favored here, so this is not a great step. This enol form is nucleophilic as we have previously mentioned because it wants to reform the strong carbonyl bond and it has a nonpolar pi bond, so when the electrophilic

halogen gas is reacted with it, it gets attacked normally to reform the carbonyl bond and halogenate the alpha carbon (AM**S**OW). Once this happens, a base needs to deprotonate the carbonyl oxygen to resolve its charge (**AM**SOW). The last few steps is essentially the same as the reaction of an acyl chloride with water, it makes the carboxylic acid like we discussed two chapters ago.

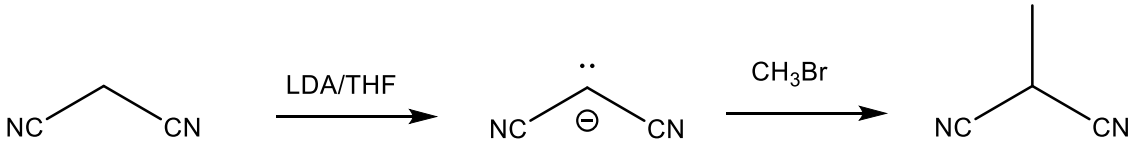
The enolate anion is a great nucleophile and it can go through SN2 reactions. The main issue with enolates is that the alpha protons are only *slightly* acidic, so strong bases are required to get good yields in this reaction and get all the alpha carbons ionized. The stereotypical strong base that is used is LDA, or lithium diisopropyl amide, the structure for which is shown below:



This is the preferred base because it is big and bulky, preventing it from acting as a nucleophile, because if we recall negatively charged nitrogens are very good bases and nucleophiles. The added steric hindrance provided by the isopropyl groups makes it a strong non-nucleophilic base. You can effectively alkylate the alpha carbon by reacting enolates with alkyl bromides like so:

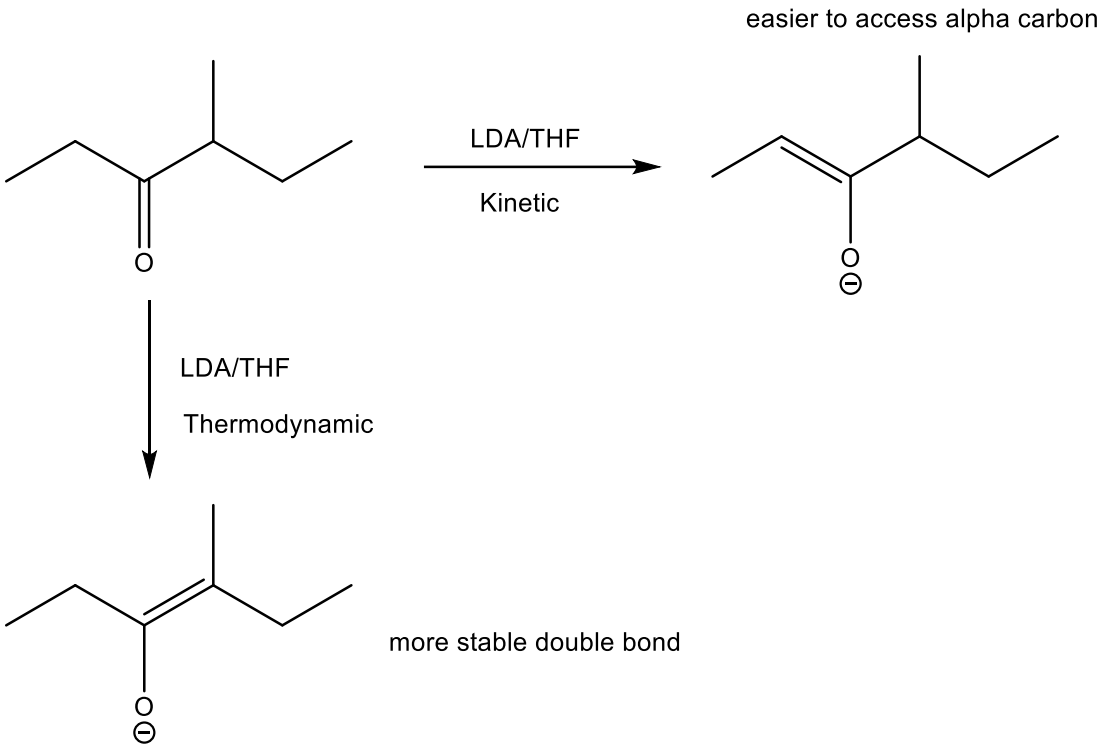


Other compounds can also do this reaction, such as nitriles and esters, this is again because the alpha protons are acidic in these compounds due to the electron-withdrawing effects of these groups:



In the case of asymmetrical ketones, the enolate that forms is controlled by the type of base and the temperature used. The kinetic enolate will occur on the carbon that is less sterically hindered, this should make sense because that is the carbon that is easiest to access and deprotonate. The

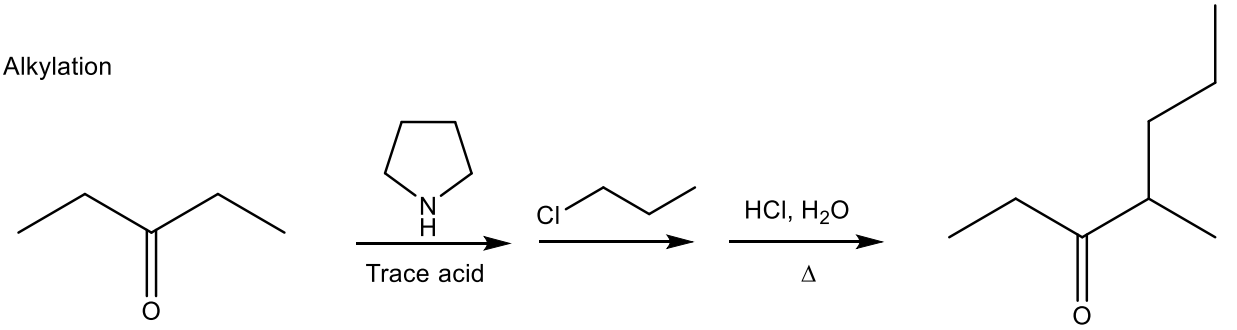
thermodynamic enolate will occur on the carbon that is more sterically hindered, this is the thermodynamic enolate because that forms the more stable double bond:



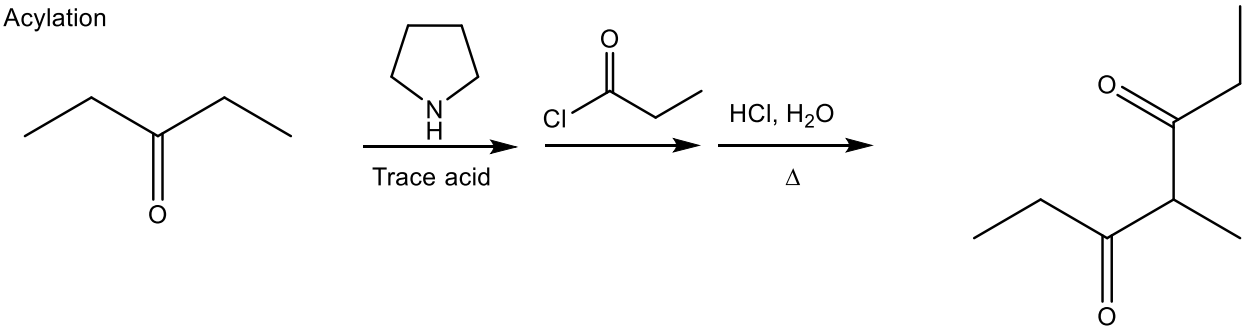
In general, the kinetic enolate is favored under low temperatures and bulky bases (LDA) and the thermodynamic enolate is favored under high temperatures and unhindered bases (NH_2^-, OH^-). Though the temperature is mainly the determining factor oftentimes.

If you do not want to go through an enolate, enamines are also capable of alkylating and acylating the alpha carbon. Recall from the last chatper that enamines are nucleophilic, therefore they will also react with alkyl halides (for alkylation) and acyl chlorides (for acylation), the only thing that needs to be done extra is removing the enamine group through hydrolysis:

Alkylation

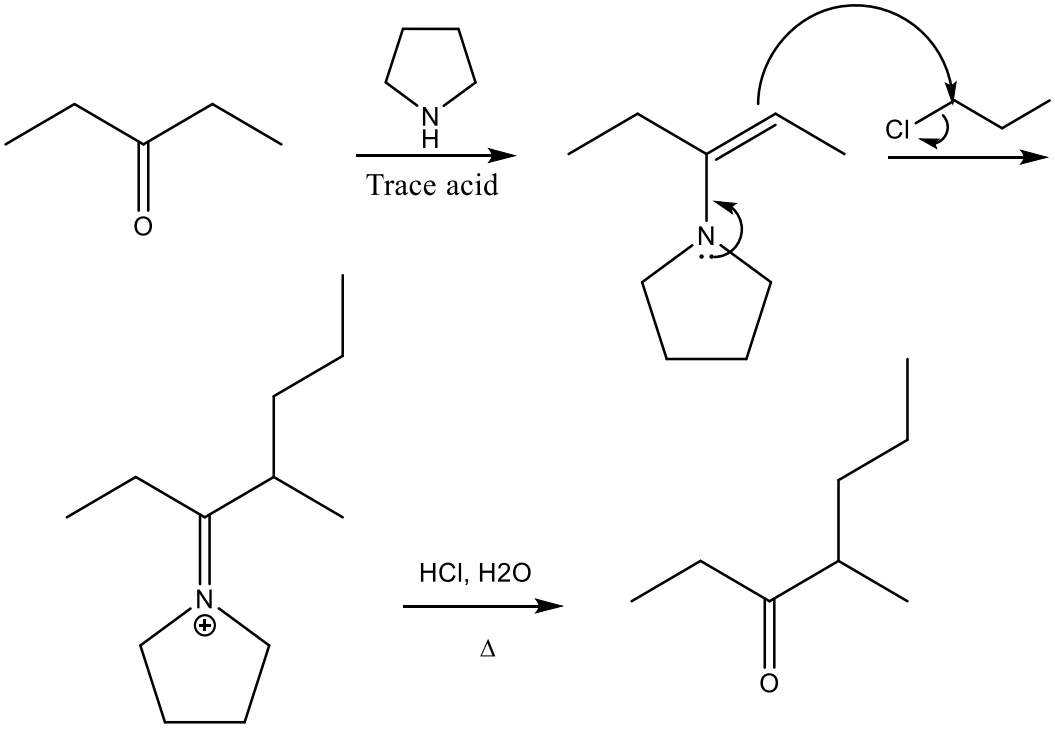


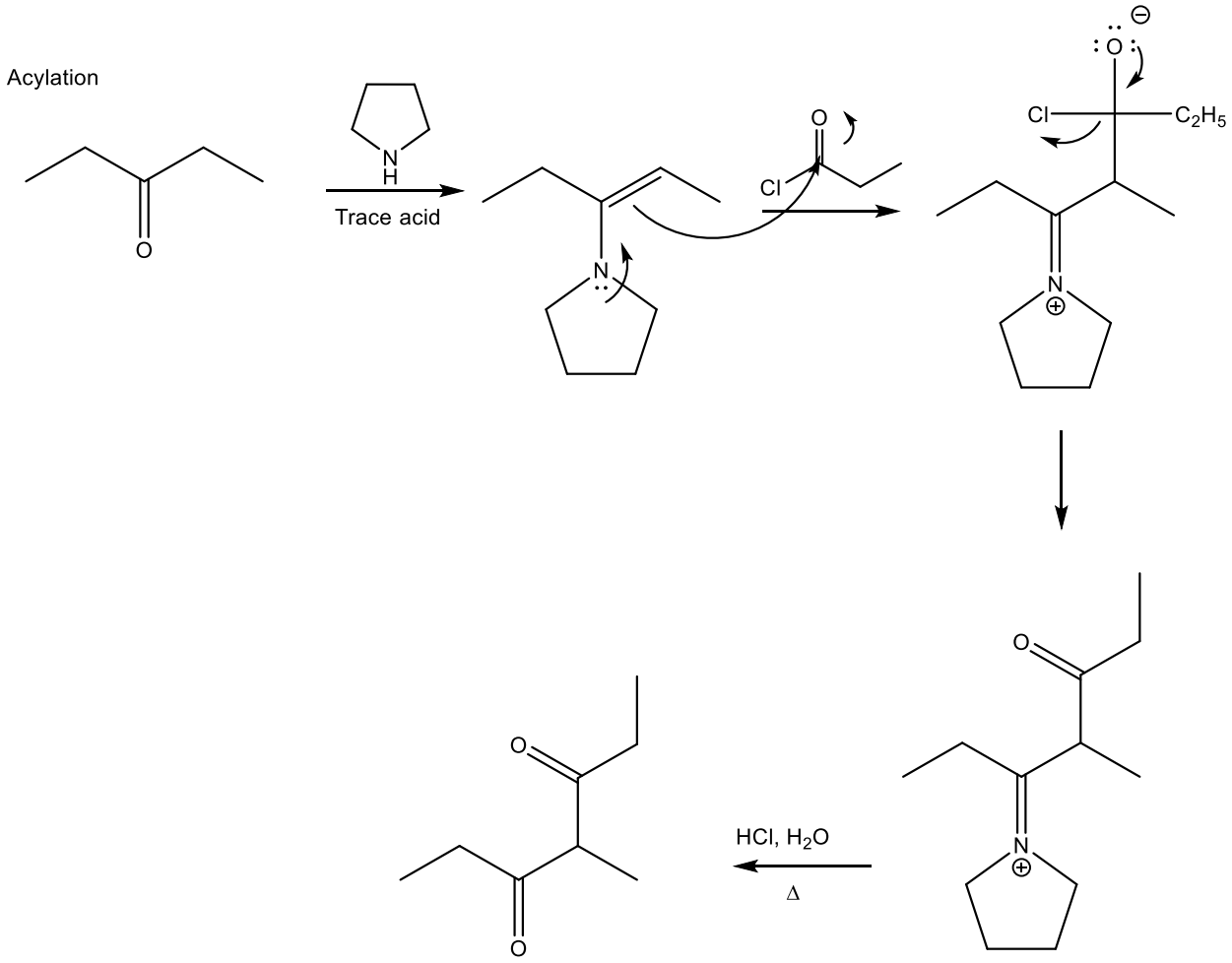
Acylation



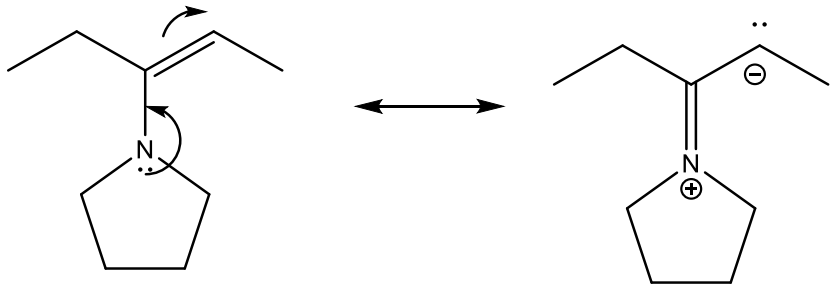
The mechanism for these reactions are shown below:

Alkylation

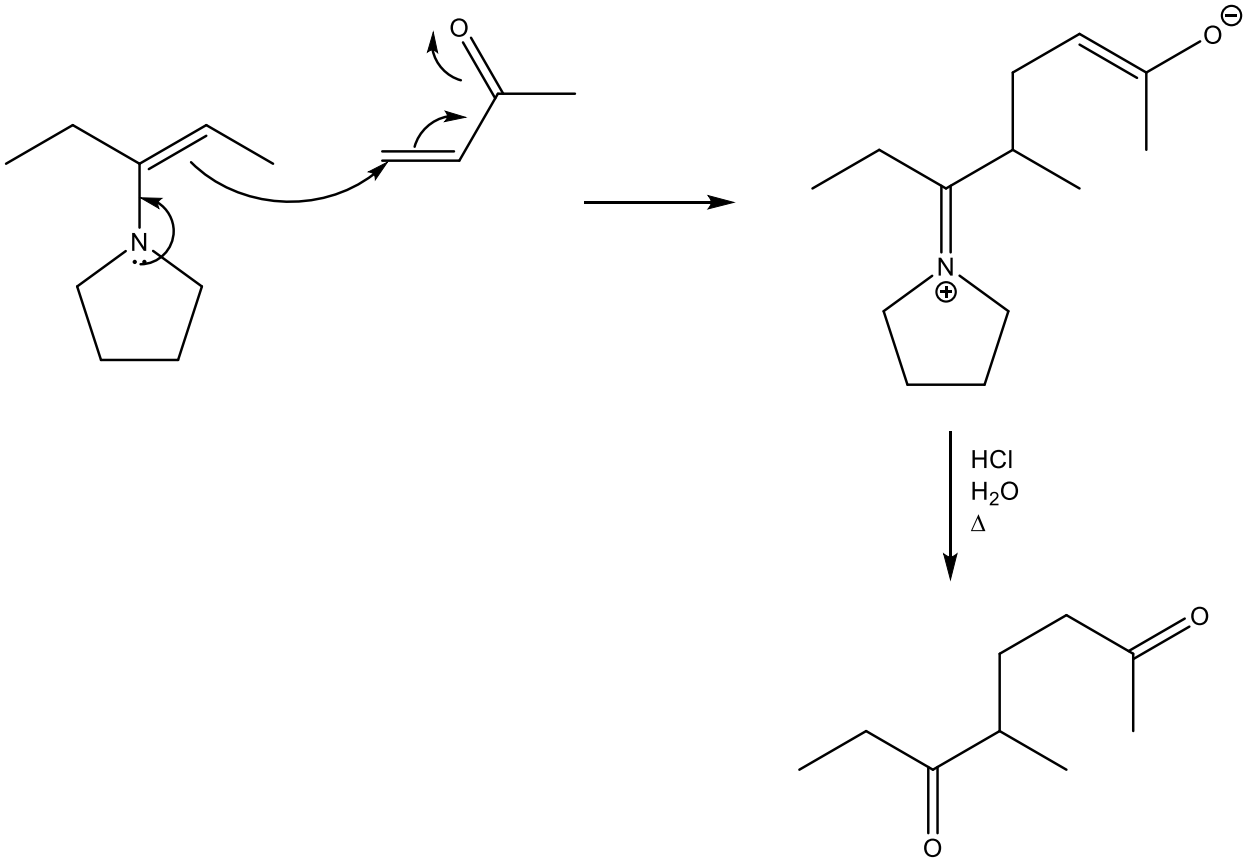




The alkylation reaction first has the carbonyl compound forming the enamine, its an enamine that forms because the amine is a secondary amine (N has two carbons bonded to it). The second step has the enamine attacking the electrophilic alkyl halide in an SN_2 reaction and the very last reaction has the removal of the enamine group. You're probably wondering why the enamine group is nucleophilic at all, because I did not adequately address that, I just sort of said it was without any explanation and I just now realized that. The enamine group is a nucleophilic group because of the nonpolar double bond and the ability of the nitrogen to donate its electrons, the resonance form for an enamine is this:



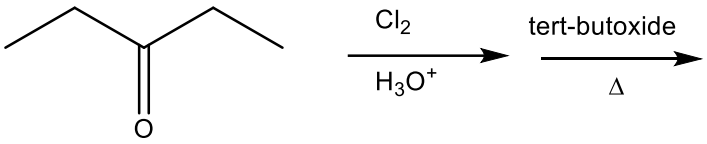
From that resonance form, it is clear to see that enamines are nucleophilic and will therefore react with electrophiles by attacking with the alpha carbon, which is the carbon that has the negative charge and lone pairs in the resonance form. *Enamines are therefore enolate equivalents.* Another electrophile that enamines could react with are alpha-beta unsaturated carbonyl compounds, like all the other nucleophiles except for Grignards and organolithiums, these also add to the beta carbon like so:

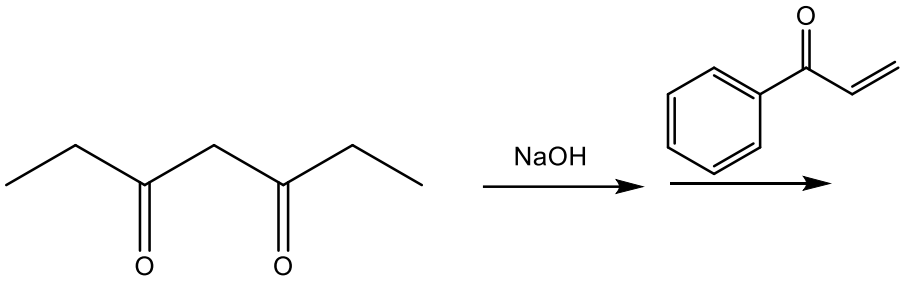


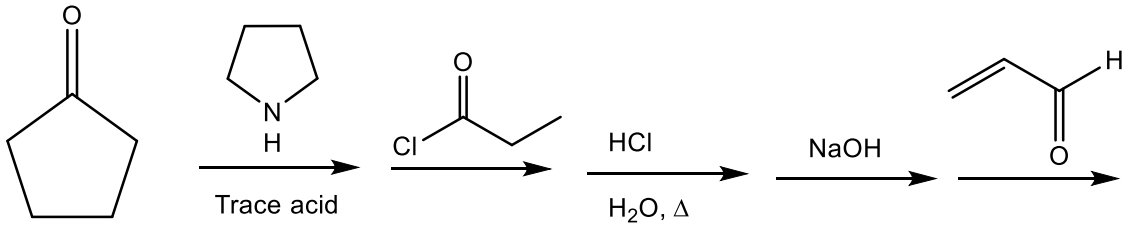
This, surprisingly works the exact same way with enolates. Remember, enamines are enolate equivalents. They react almost in the exact same way. If enamines can do it, so can enolates. When enolates attack the beta carbon of alpha-beta unsaturated carbonyl compounds, it is referred to as a Michael Reaction.

Practice questions:

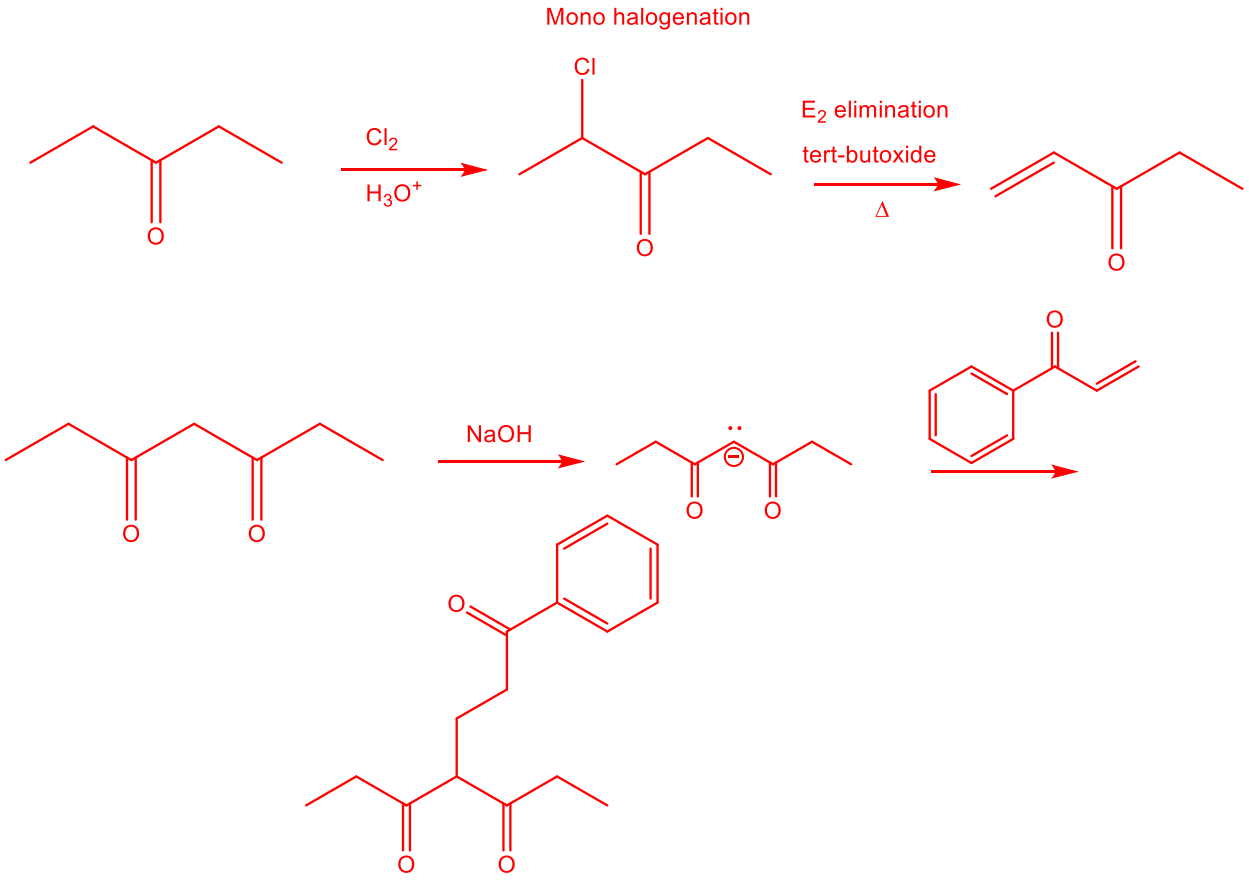
Predict the major organic products for the following reactions:

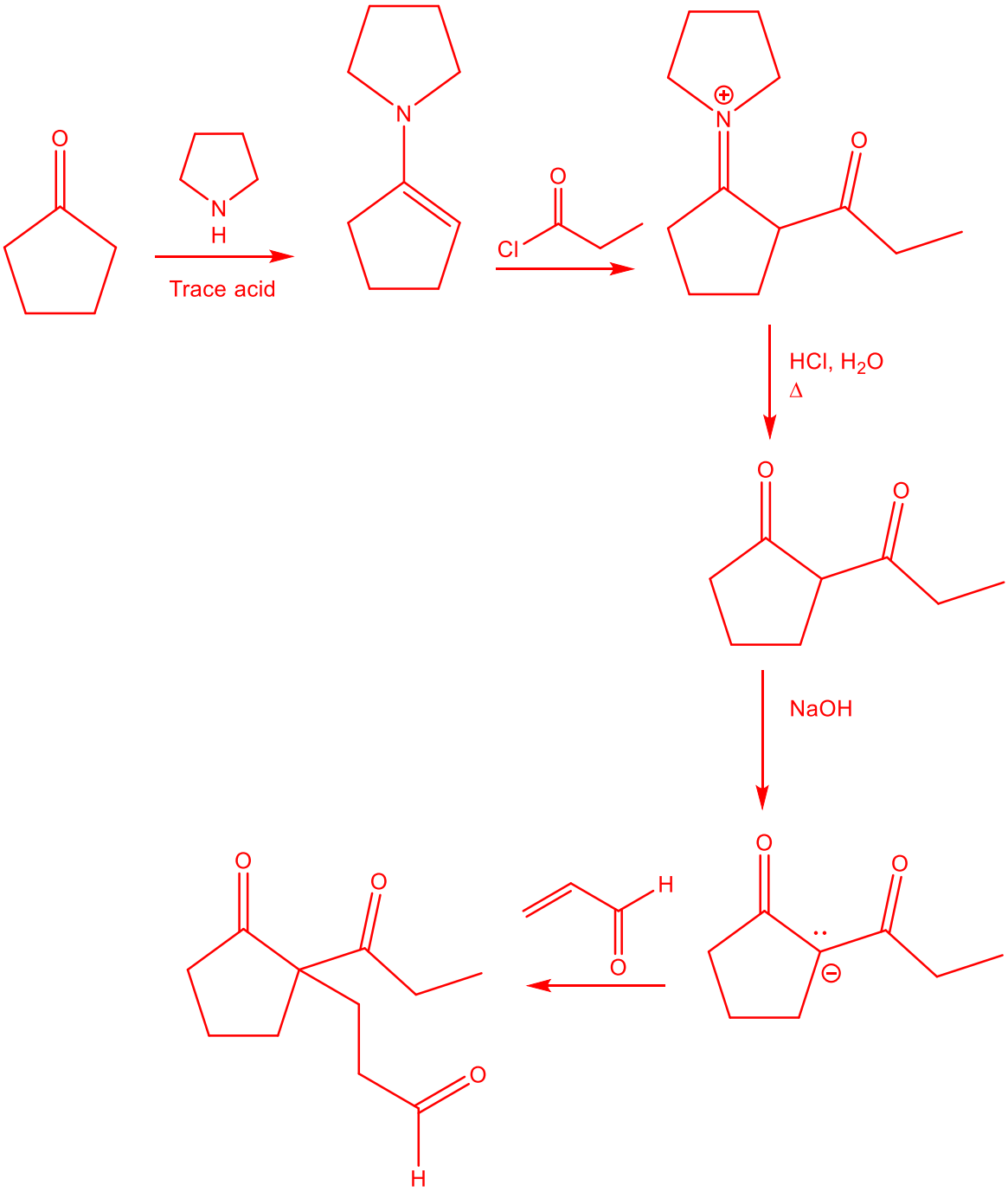

Cl2
H3O+
tert-butoxide
Δ
O


NaOH
O
O
O


O
N
H
Trace acid
O
Cl
HCl
H2O, Δ
NaOH
H
O

Answers:

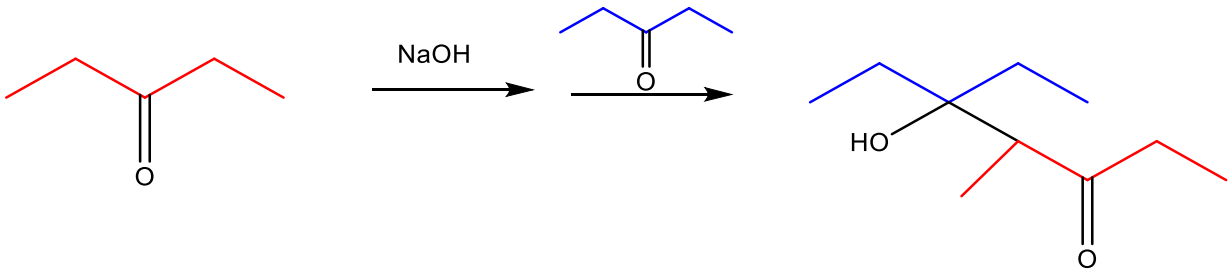

Mono halogenation
Cl
Cl_2
H_3O^+
E_2 elimination
tert-butoxide
Δ
O
NaOH



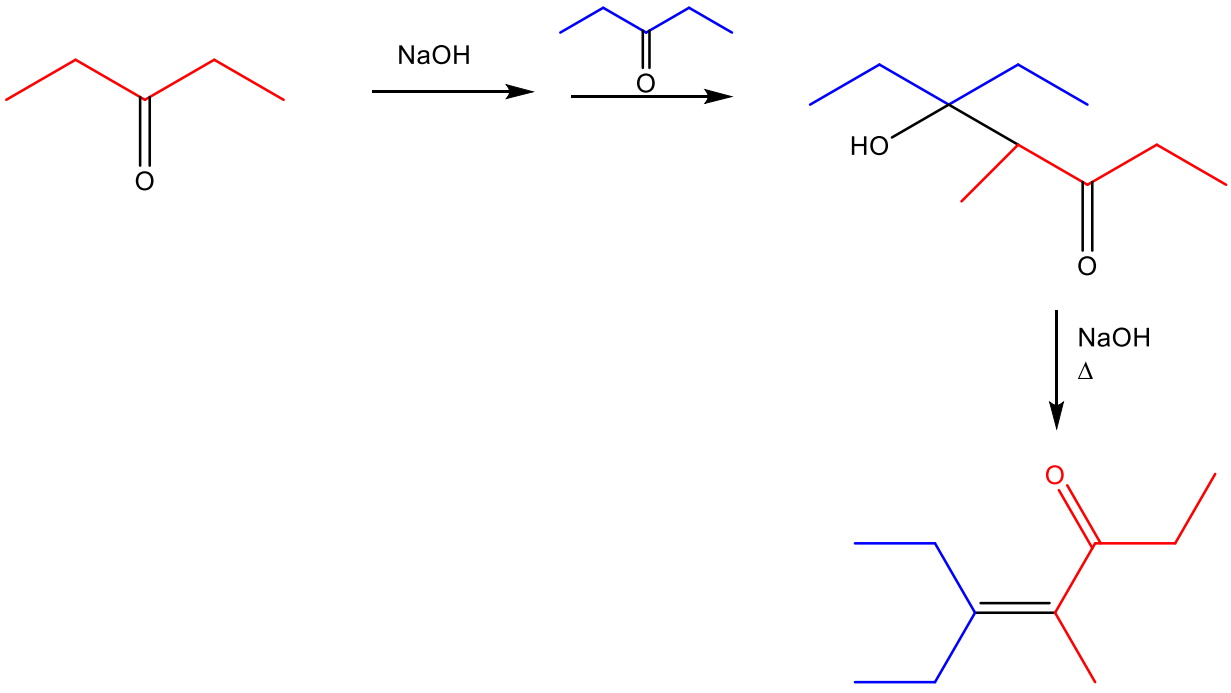
The next reaction we will discuss is an extremely useful reaction, the premise of which, will be used for different modifications. This reaction is the Aldol addition and condensation reactions. Recall that carbonyl compounds are electrophiles, therefore, enolates can attack them the same as any other electrophile that we have discussed so far (alpha-beta unsaturated carbonyl compounds and alkyl halides). The Aldol reaction is shown below and as previously stated, it comes in two flavors, addition and condensation. Addition reactions result in a hydroxyl (OH)

group located on the beta carbon relative to the carbonyl, the condensation results in an alpha-beta unsaturated carbonyl compound. The only difference is the condensation reaction has excess base and is heated to promote elimination of the OH group to form the double bond. But wait… isn't an OH group a bad leaving group? How can you just kick if off? The driving force is the conjugation that results in the reaction, the transition state is stabilized by resonance and that allows the OH group to leave. This elimination is referred to as an E1cb reaction and it only occurs if the product will be conjugated and the reaction is heated.

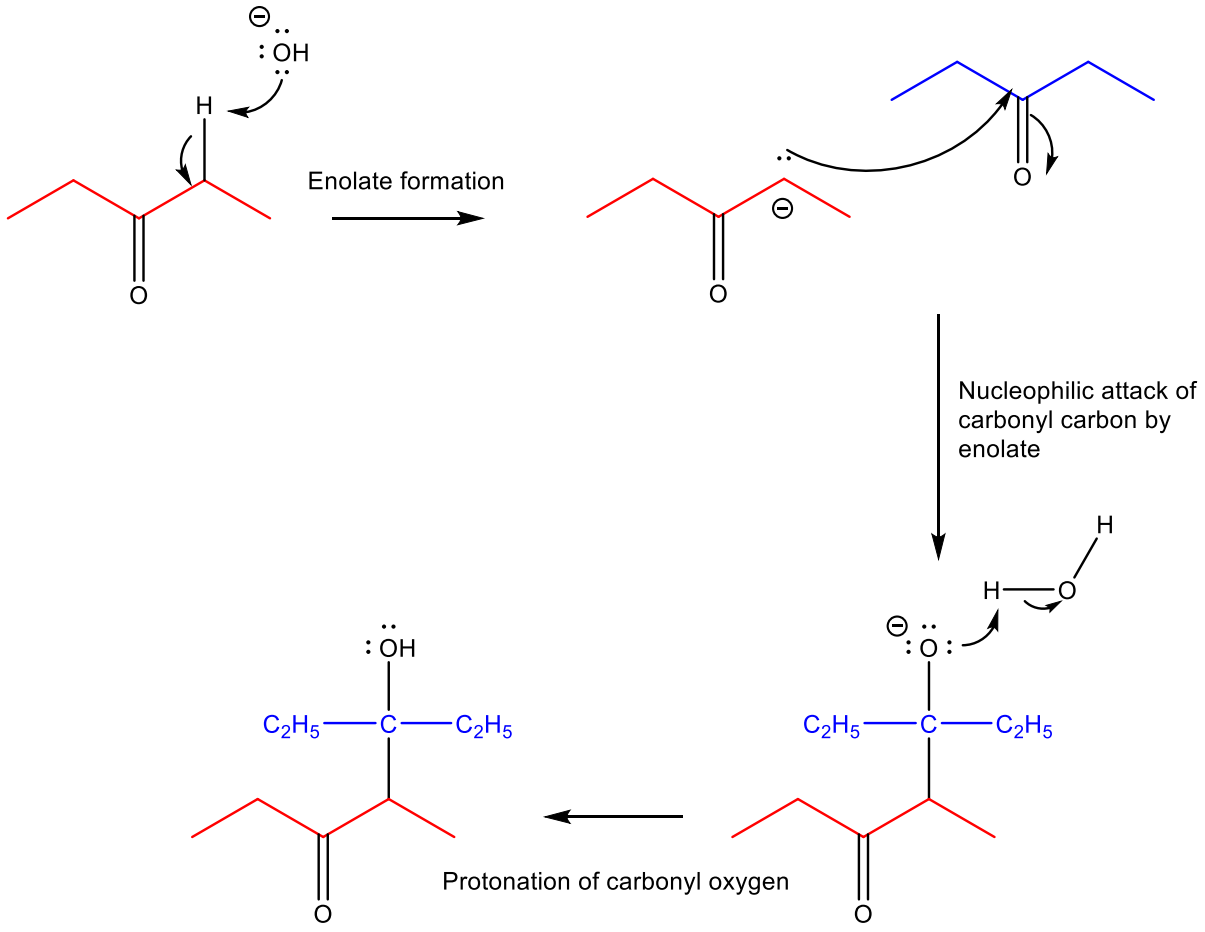
Aldol Addition reaction:



Aldol Condensation reaction:

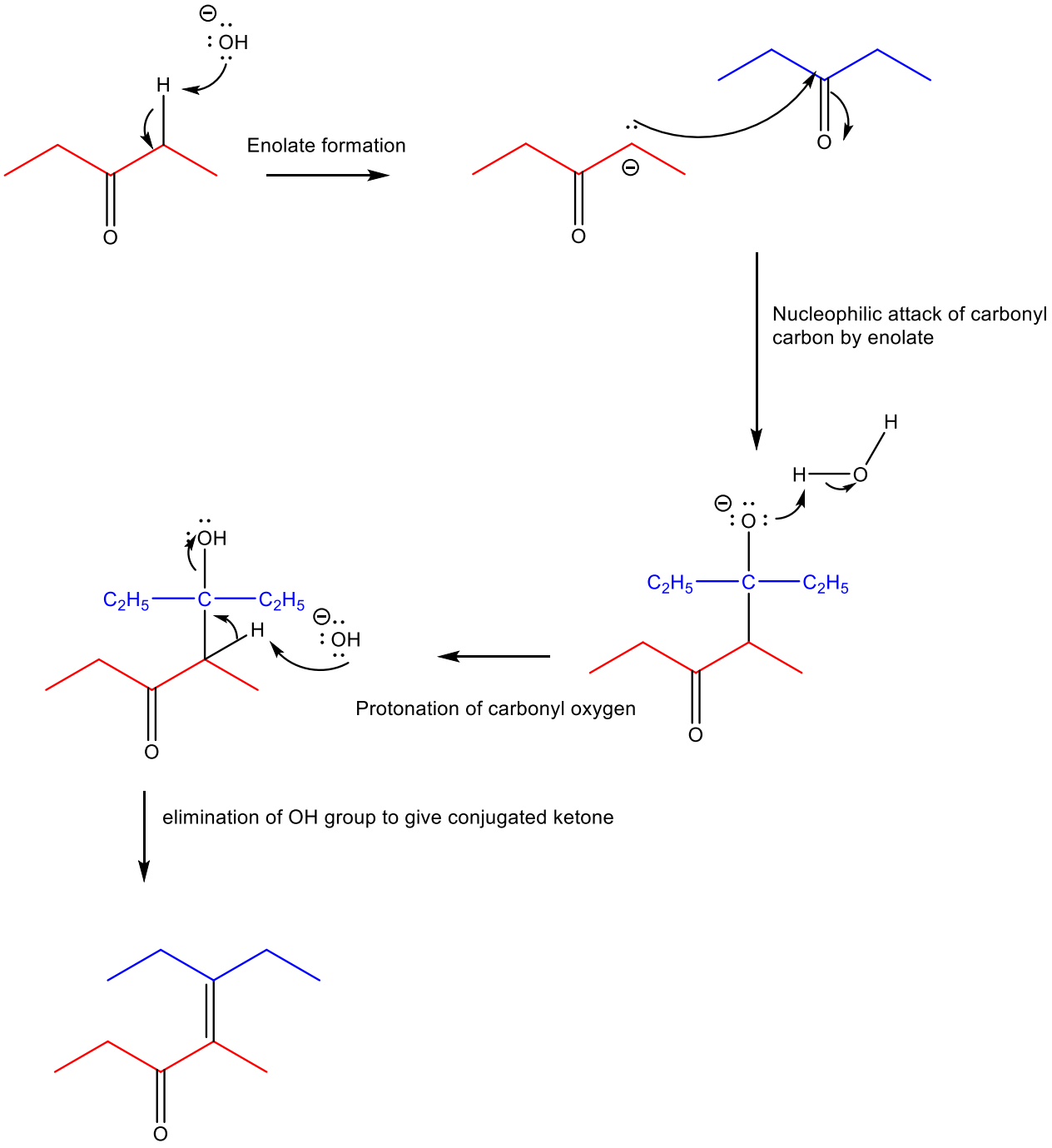


The reaction mechanism for the Aldol Addition reaction is shown below:

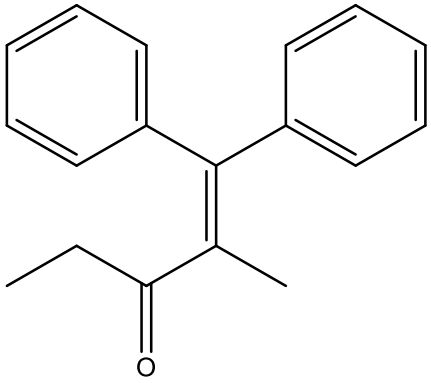


The first step in the reaction mechanism is making our active nucleophile, therefore we deprotonate the alpha carbon to generate our enolate using OH^- in an acid-base reaction (**A**MSOW). Then the enolate attacks the carbonyl carbon of the second equivalent of the 3-pentanone to give a tetrahedral intermediate just like it always does when we attack carbonyl carbons in every other context. This time, there is nothing to kick off, the only groups on the carbonyl carbon in blue are carbon groups which will not leave, therefore it goes through an acid-base reaction and minimizes its charge by deprotonating a solvent molecule (**AM**SOW). As you can probably suspect, there is a modification of this exact mechanism where the carbonyl carbon does have a good leaving group, but we will discuss that reaction once we finish the Aldol condensation reaction.

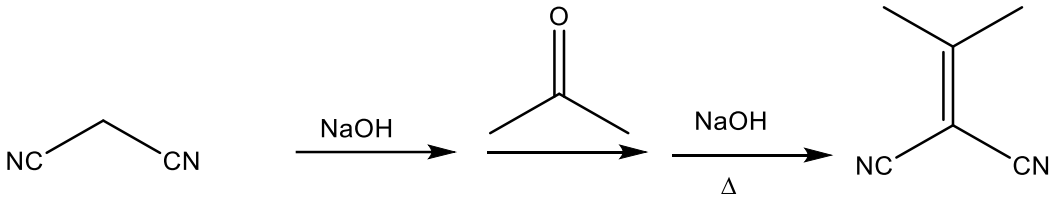
Aldol Condensation mechanism:



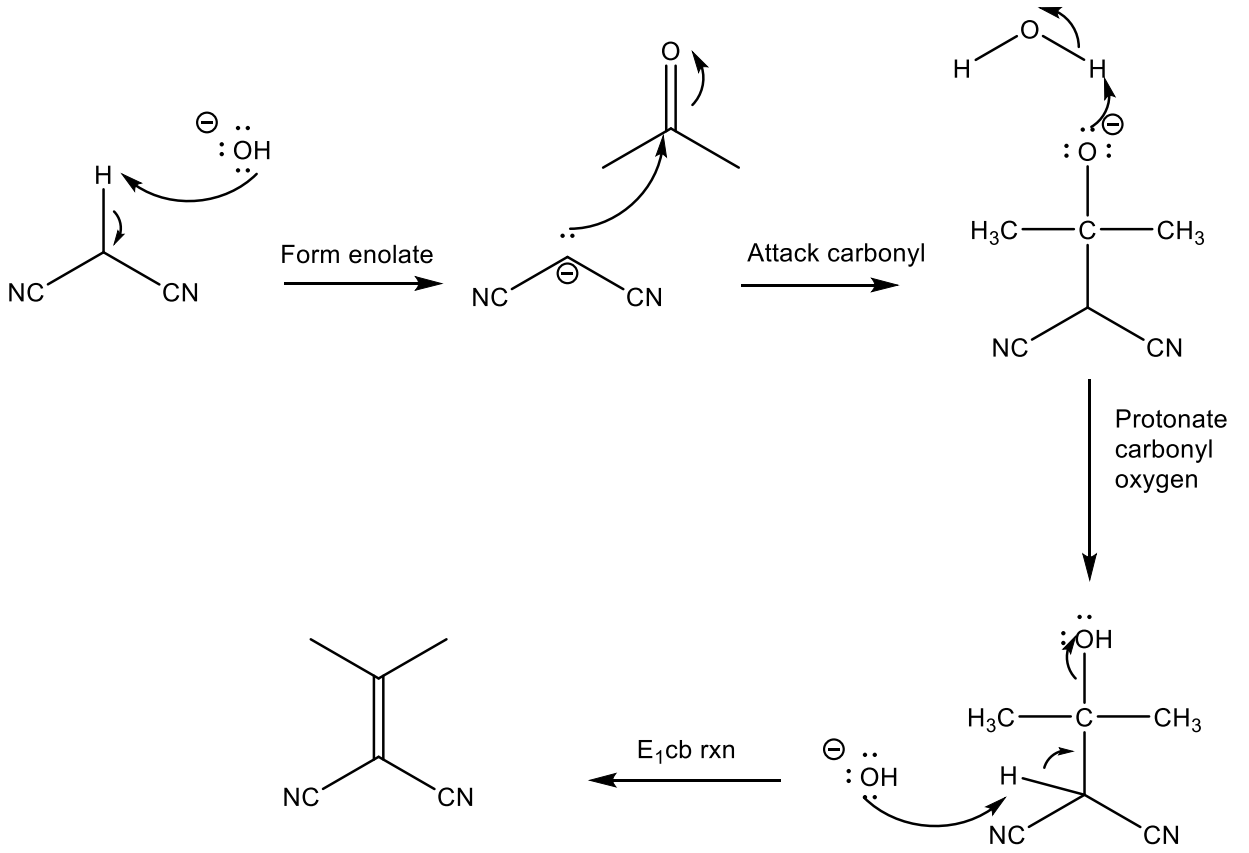
The mechanism is the exact same except there is an additional step which is the E1cb reaction where the OH group gets kicked out to form the conjugated ketone product. The more conjugated the product, the easier it is to get the elimination product and the less heat that is needed to be supplied, so the following alpha-beta unsaturated carbonyl would be easier to form:



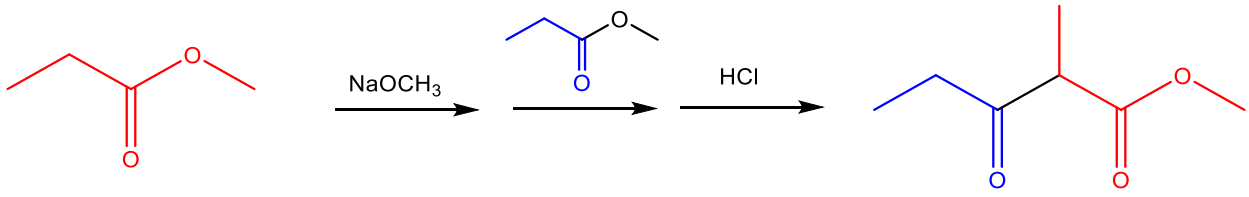
This product is much easier to form because the double bond is not only in conjugation with the carbonyl, but also two benzene rings, talk about stable! This same kind of logic can be used for other compounds that have alpha protons that are acidic, such as nitriles and esters. For nonaldehydes and ketones, these reactions go by different names, but they are essentially the exact same. For nitriles and nitro compounds, the reaction goes by the Knoevenagel condensation and for esters it is referred to as the Claisen condensation. Fundamentally, these reactions are practically the same, the only difference is what compound you are deprotonating and what you are attacking, but the underlying concepts are the same. Let's first discuss the Knoevenagel condensation:



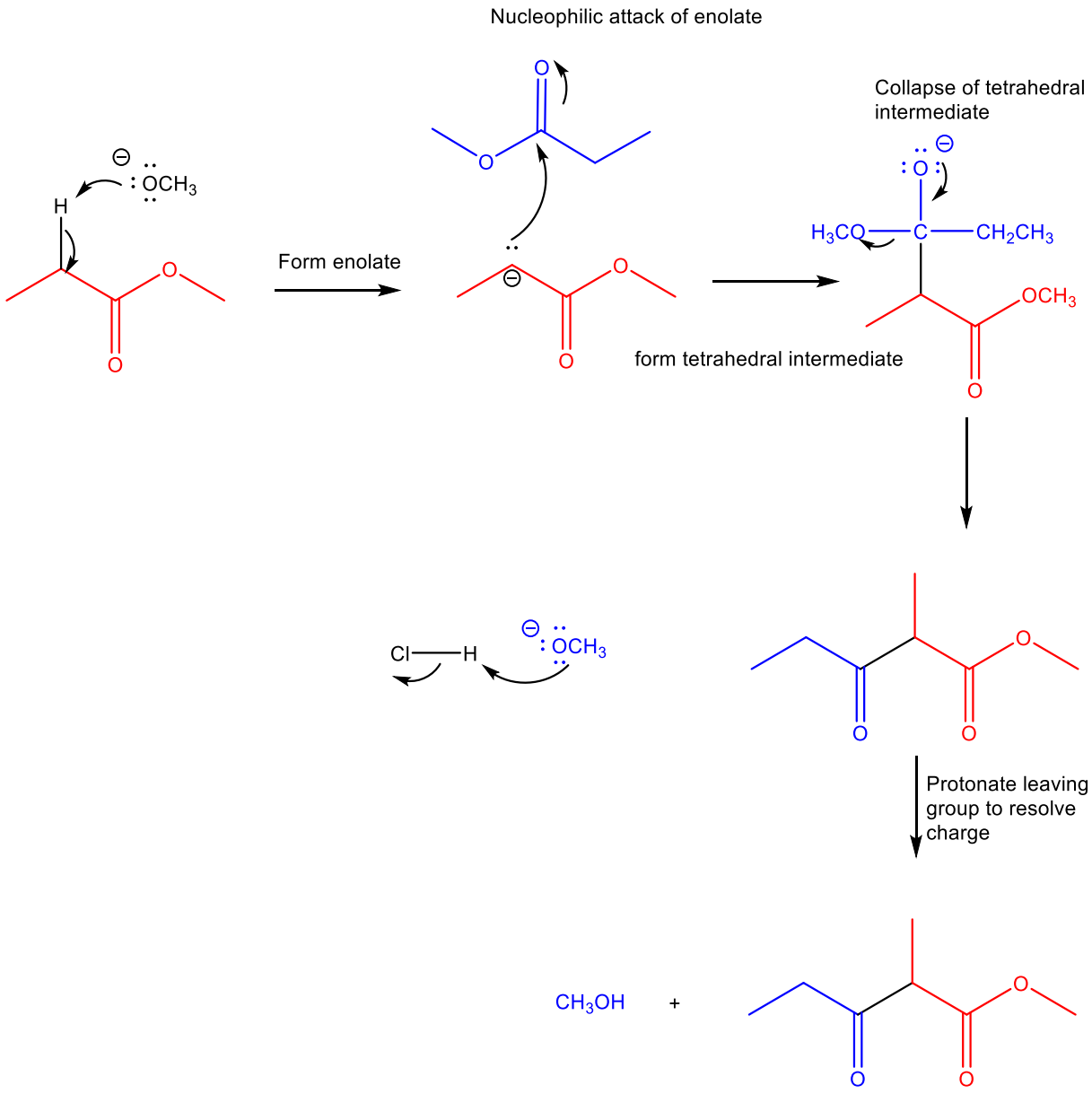
The mechanism is exactly what you'd expect:



The Claisen condensation is a reaction done with two equivalents of esters, the key difference between esters and ketones/aldehydes is that esters have a good leaving group (OR) and therefore when the tetrahedral intermediate forms, it can collapse, reform the carbonyl, and eject the OR group like so:



The mechanism is extremely similar to the previous one, except instead of protonating the carbonyl oxygen, we instead kick off the OCH_3 of the ester that we attacked with the enolate. When we do these reactions, it is important to use the conjugate base of the OR group to minimize transesterification reactions that may take place otherwise. For example, if we used $NaOCH_2CH_3$, then we would have competition between enolate formation and exchanging the OCH_3 of the ester with an OCH_2CH_3 and we would get a lower yield. Here is the mechanism:

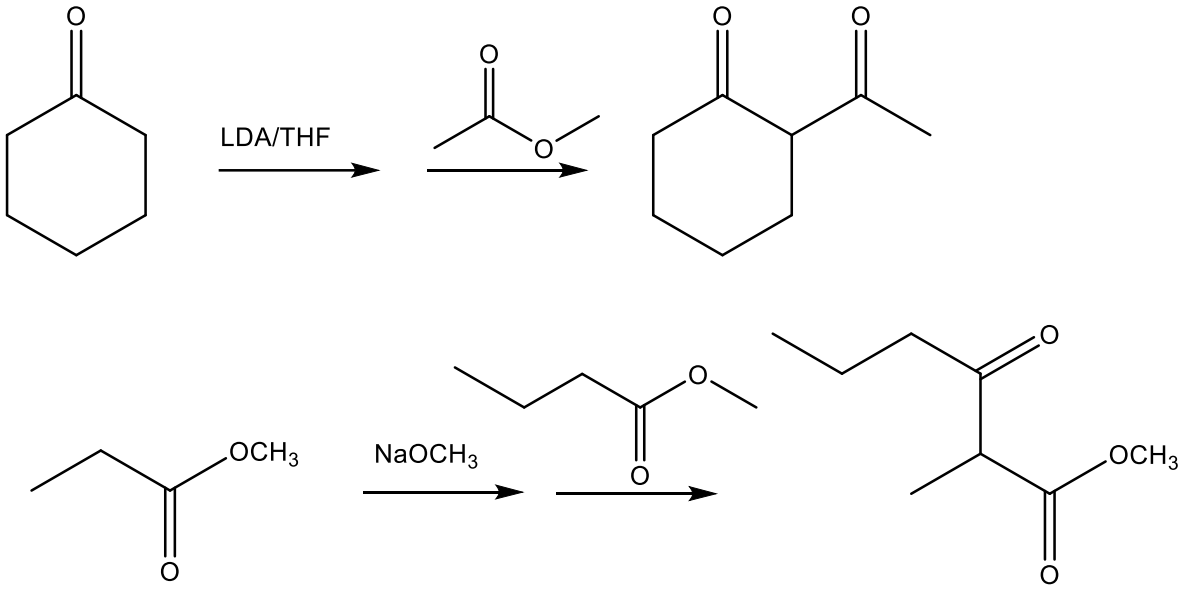


The chemical logic is the same as before for this mechanism, the ONLY key difference is that when the tetrahedral intermediate forms, it can eject a leaving group out and therefore it causes the reformation of the carbonyl bond and subsequent protonation of the leaving group to resolve the negative charge on the oxygen.

Ideally, the ester that you start with when doing the Claisen condensation will have two alpha protons because esters are less reactive than ketones and aldehydes and consequently their alpha protons are not as acidic. Because of this, this process is actually in equilibrium and the best way

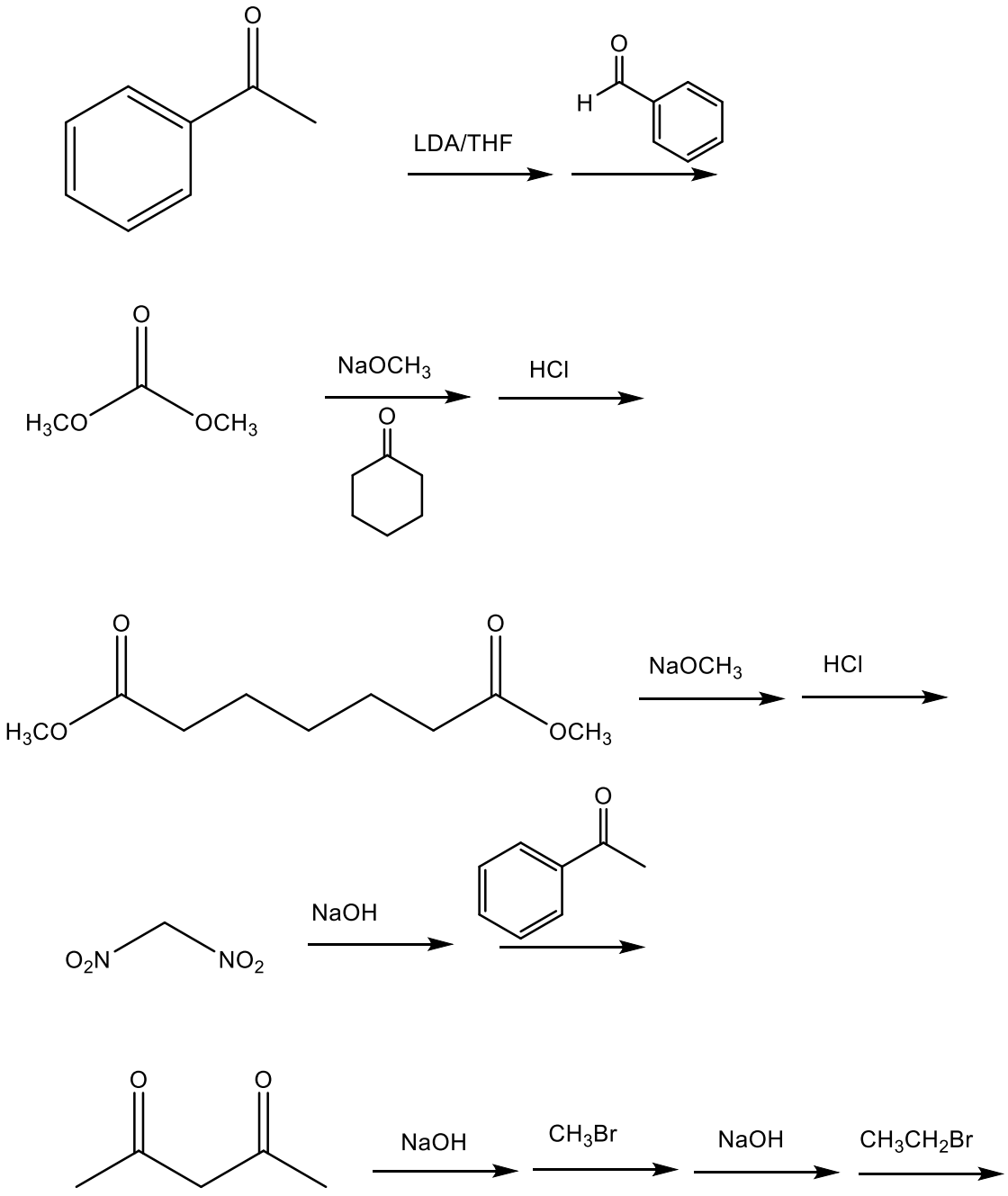
to push it to be quantitative is if you can deprotonate the end product, this in essence lowers the concentration of the product and drives the reaction forward.

These condensation reactions can also be done with other esters and ketones/aldehydes. These are called “Crossed” condensations because they occur between two different molecules, not two of the same like we have been seeing typically. The mechanism is the exact same and the chemical logic is the exact same. The only difference is that you typically want to deprotonate one compound first with LDA or an alkoxide (OR^-) anion and then introduce the second carbonyl compound you would like to react with. For example:

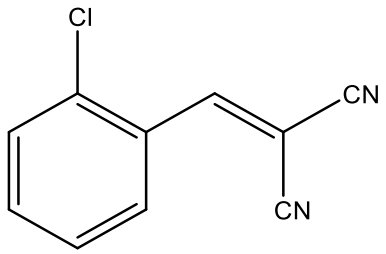


Practice problems:

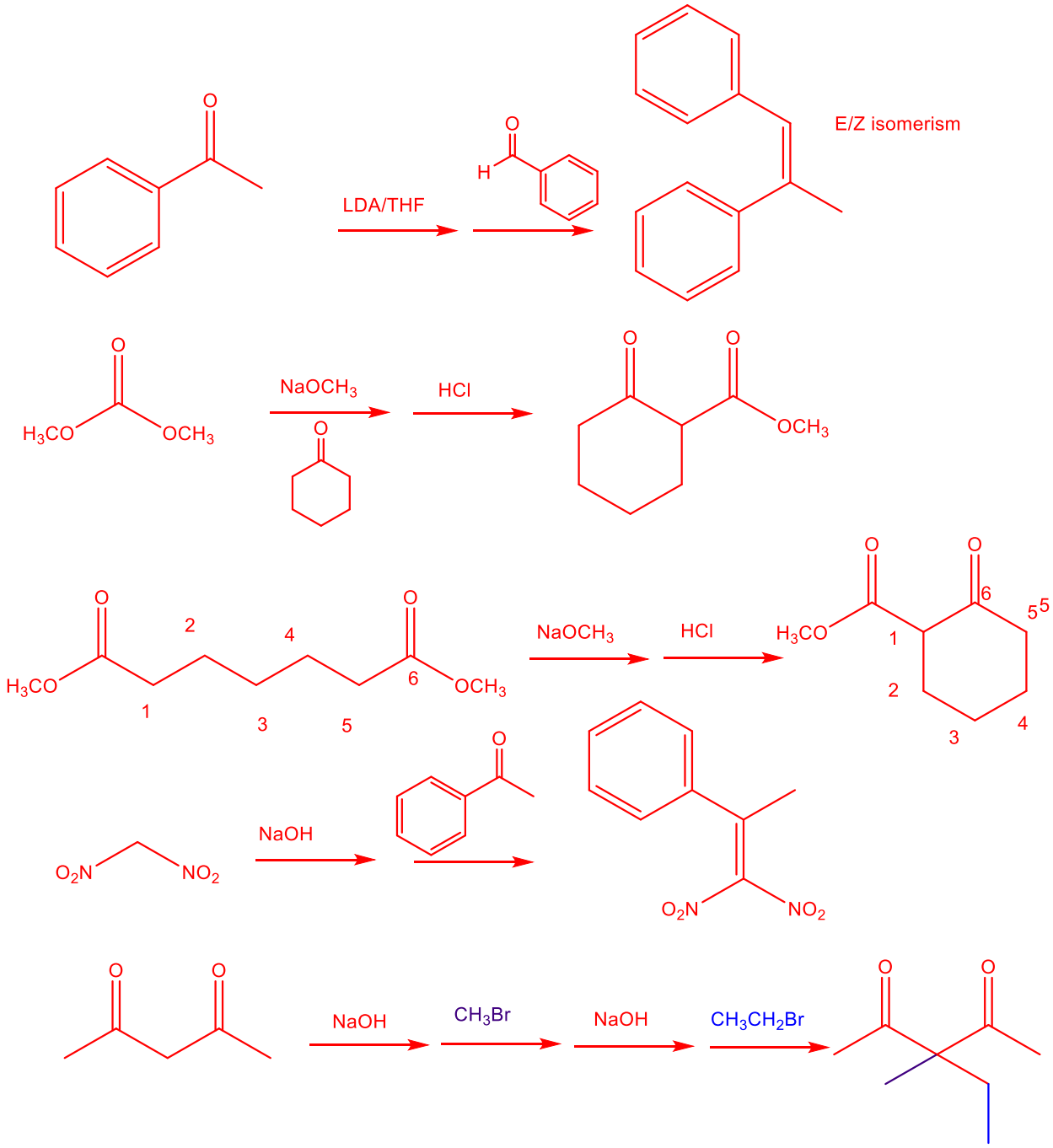
Predict the major products for the following reactions:

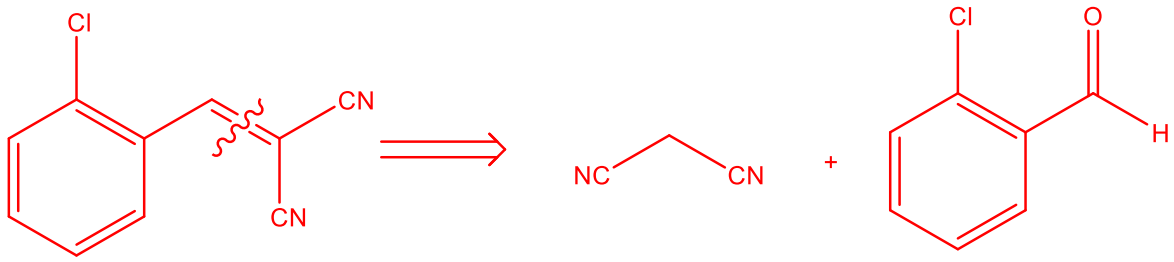


The most frequently used form of tear gas is referred to as CS gas, this compound's structure is shown below. Devise a synthesis for CS gas and show your retrosynthetic analysis steps:



Answers:

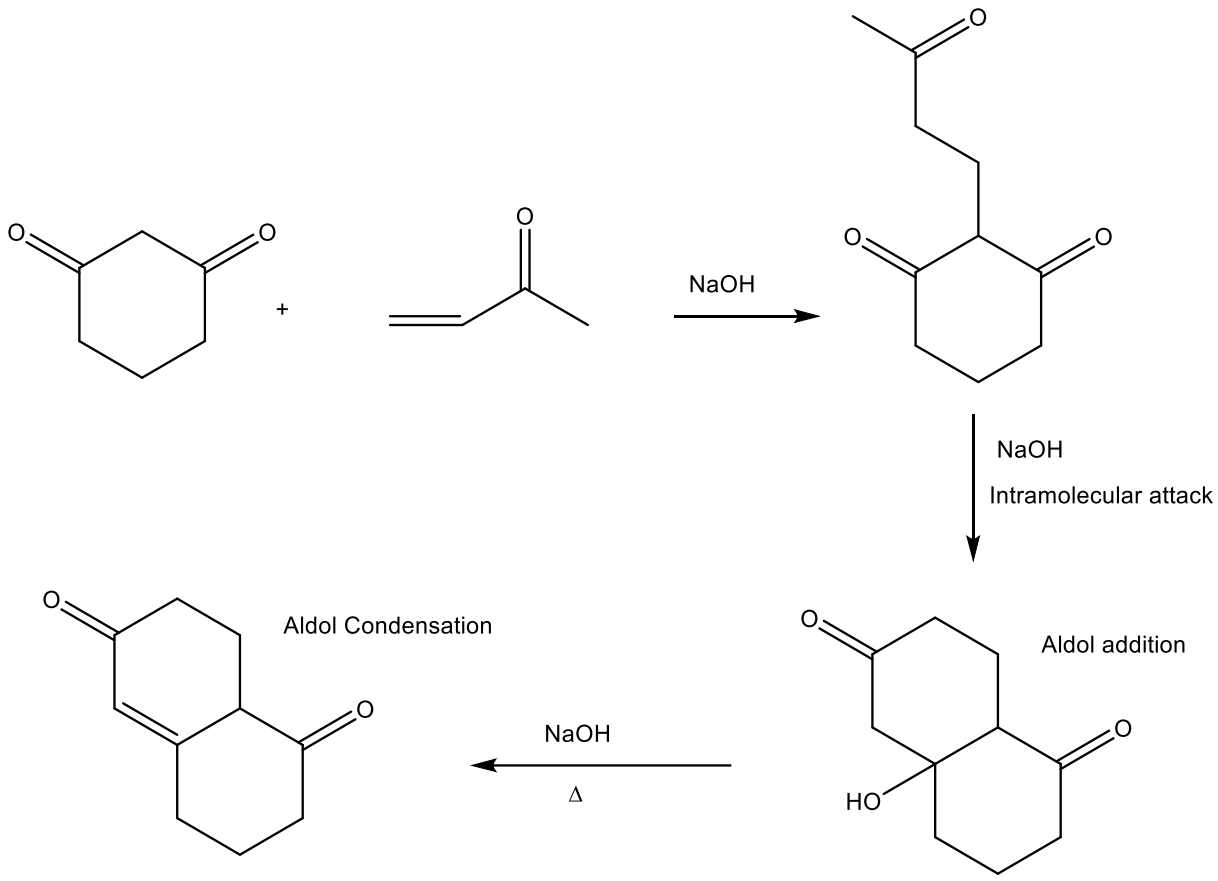

LDA/THF
E/Z isomerism
NaOCH3
HCl
NaOCH3
HCl
NaOH
NaOH
CH3Br
NaOH
CH3CH2Br



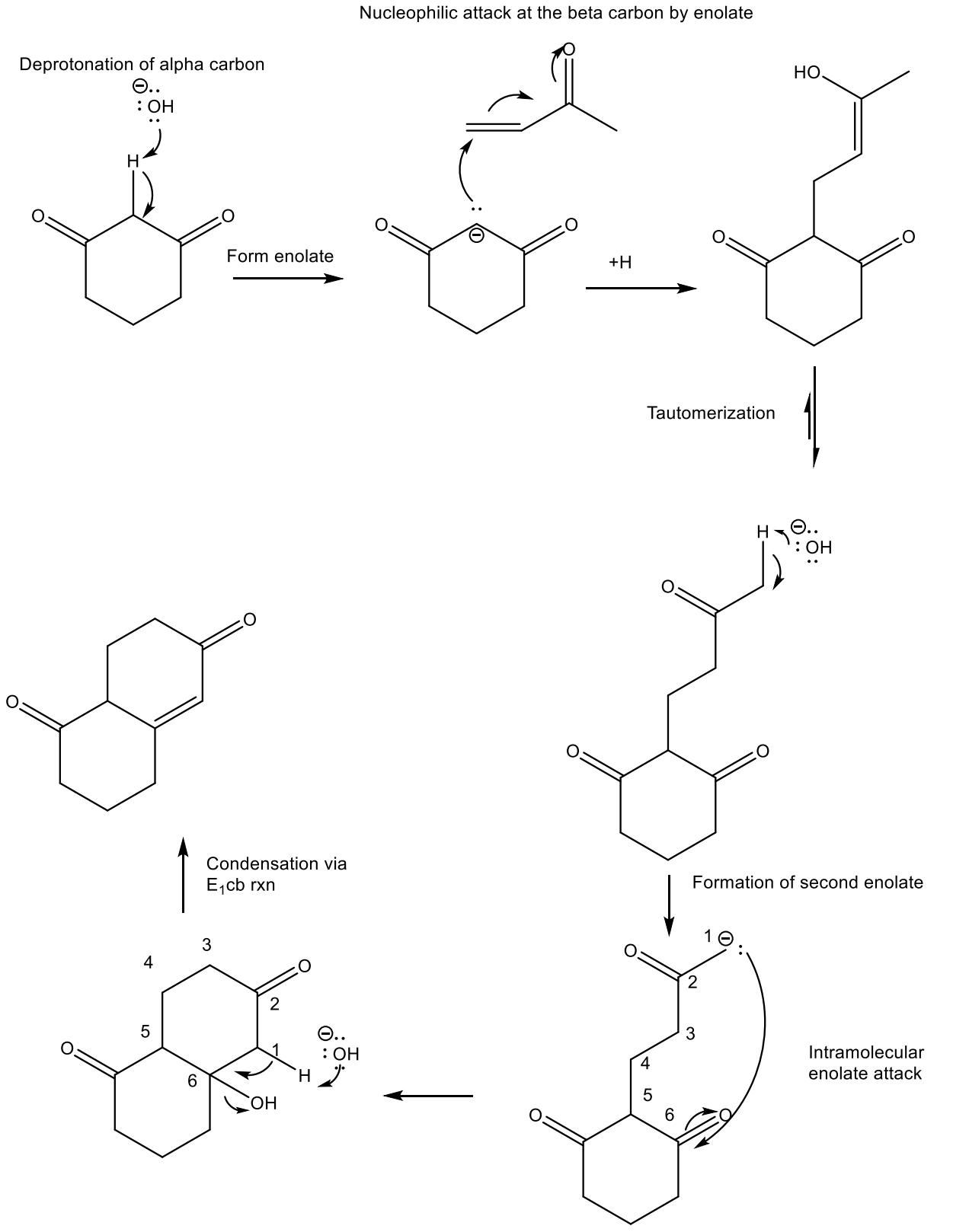
No methyl group off the benzene ring therefore had to be a benzaldehyde derivative

These next few reactions that we will discuss are essentially just applications for the reactions that we have already discussed just in a specific sequence. They combine all of the previous carbonyl chapters to give us very useful products.

The first of these application reactions is the Robinson Annulation reaction, which has been immensely useful to create steroids and it is the only reaction other than the Diels Alder that is designed specifically to make 6 membered rings. Fundamentally, the Robinson Annulation reaction is a Michael reaction followed by an intramolecular aldol condensation reaction. Let's see what I mean with an example reaction followed by a mechanism:


NaOH
NaOH
Intramolecular attack
Aldol addition
Aldol Condensation
NaOH
Δ
HO

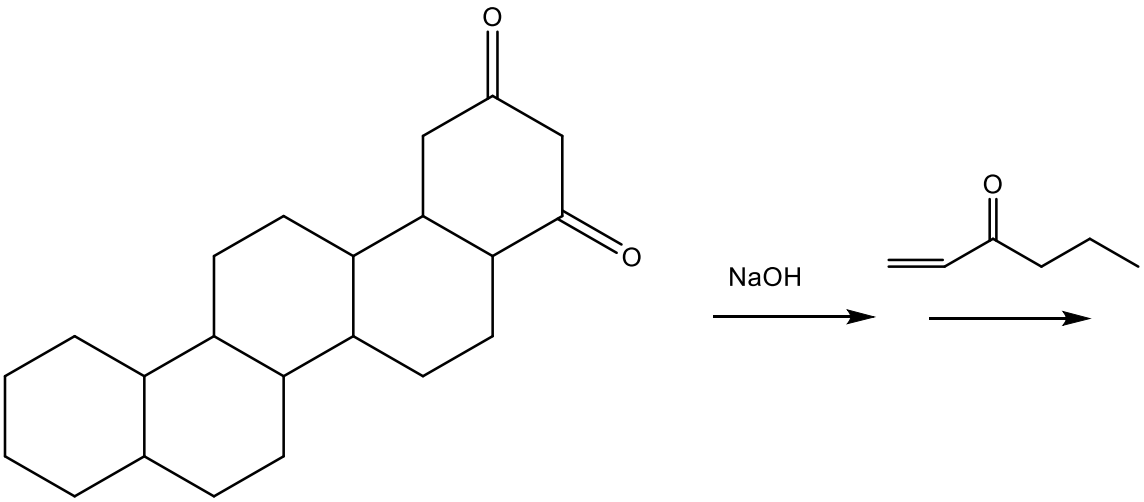
Mechanism:

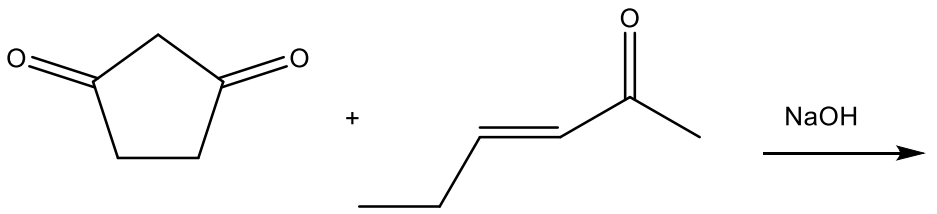

Deprotonation of alpha carbon
Nucleophilic attack at the beta carbon by enolate
Form enolate
+H
Tautomerization
Formation of second enolate
Intramolecular
enolate attack
Condensation via
E1cb rxn

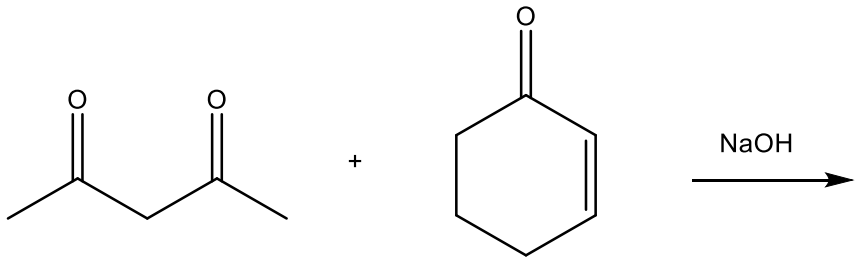
The driving force for this reaction is the formation of the very stable six-membered ring, those rings, as we recall from our discussion of structure way back when, are the most stable and have 0 angle or ring strain, so an intramolecular Aldol reaction is highly likely. The chemical logic for all the other steps is the same from their respective reactions. Remember, this is simply an extension of the knowledge that you have already. I know this is a difficult reaction to visualize, but let's see if we can do some examples:

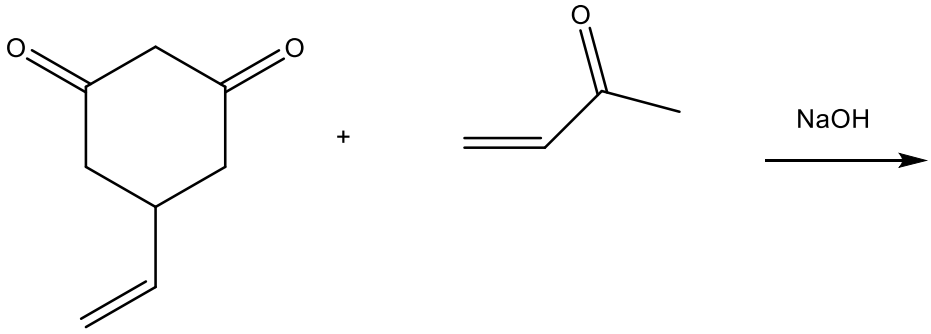
Practice questions:

Predict the major organic products for the following reactions:

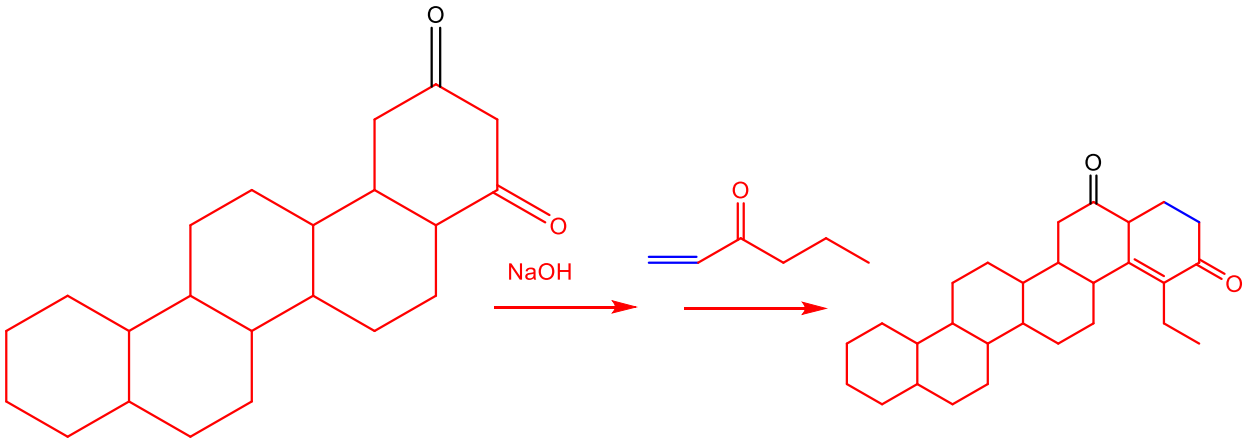

O
O
NaOH
O

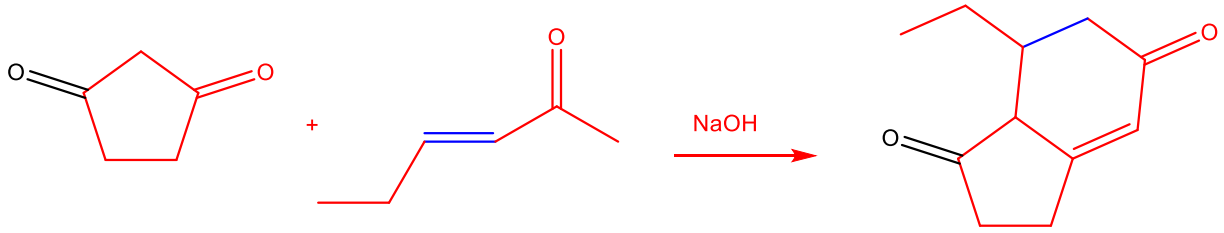

O
O
+
O
NaOH

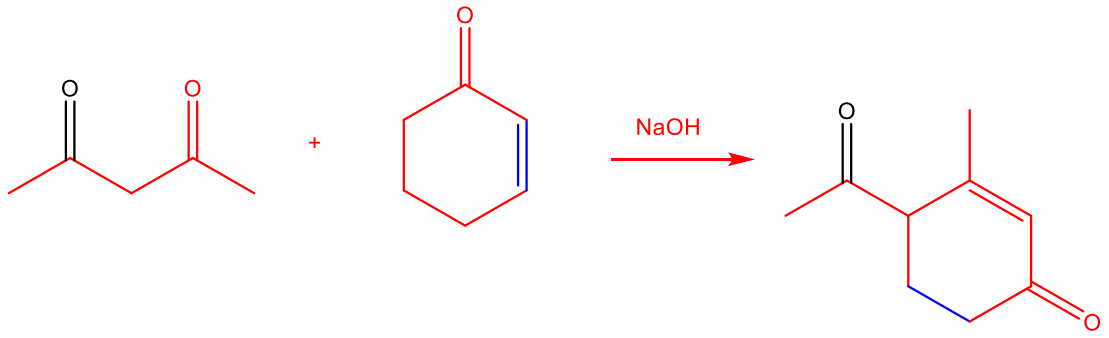

O
O
+
O
NaOH

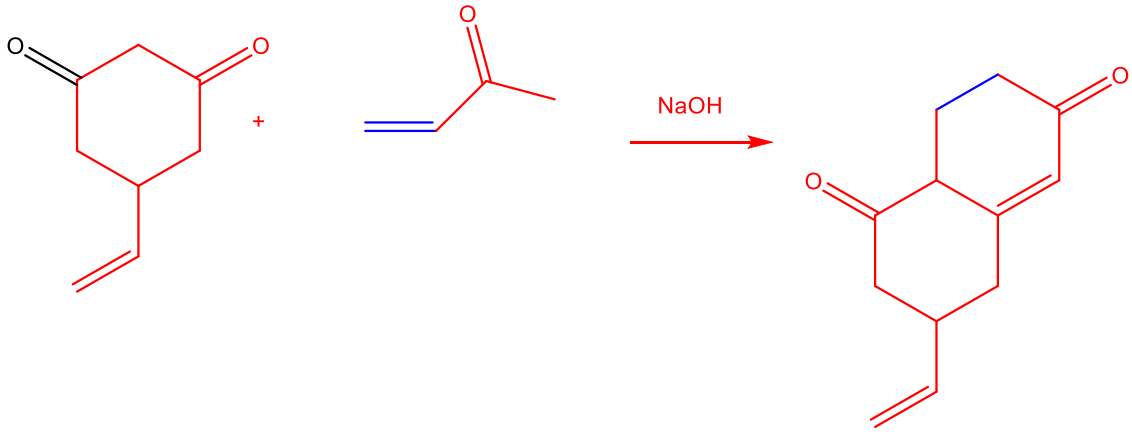

O
O
+
O
NaOH

Answers:

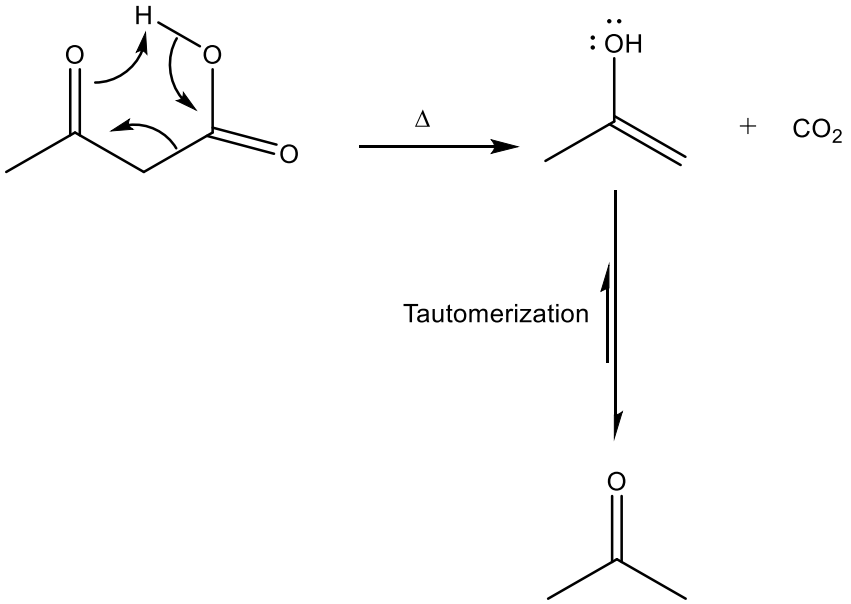








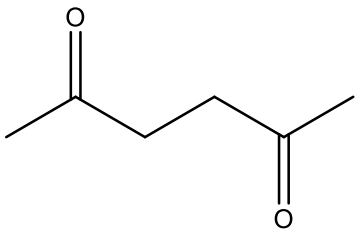
Before we get to the other application reactions, we have one more foundational reaction to cover, decarboxylation. Decarboxylation occurs when you have *1,3-dicarbonyl compounds* where one of the carbonyls is a carboxylic acid. When a decarboxylation reaction occurs, part of the molecule is removed and escapes as CO_2, this is promoted with acid and heat. The mechanism is not super important to understand, however, the reason it has to be 1,3-dicarbonyl is because the electrons in the C-C bond that breaks in this reaction pushes onto a carbon, the 1,3-dicarbonyls give resonance stabilization to these extra electrons and allow them to sit happier. This is the mechanism:

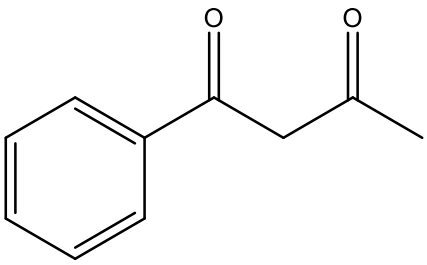


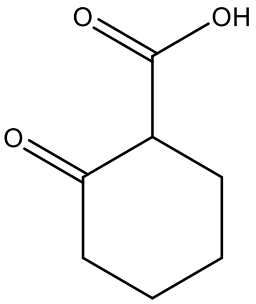
Because the mechanism is not super important to understand, we will not go over the chemical logic, all you need to know is that *1,3-dicarbonyl compounds will undergo decarboxylation if one of the carbonyl groups is a carboxylic acid and it is heated under acidic conditions.*

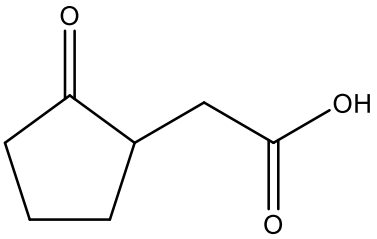
Practice questions:

Determine which of the following carbonyl compounds will decarboxylate:

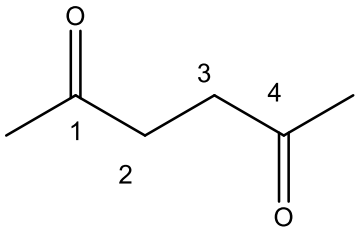






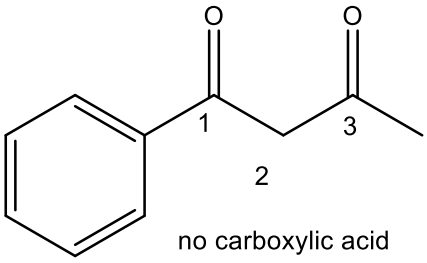


Answer:

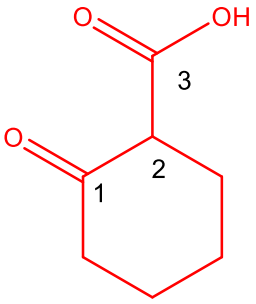


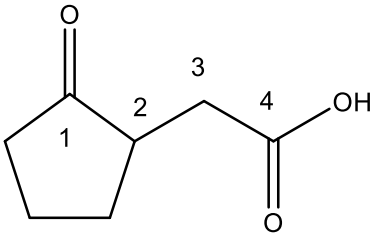
1,4 not 1,3

no carboxylic acid



no carboxylic acid

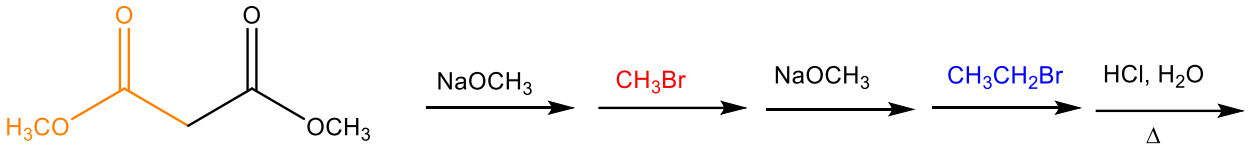


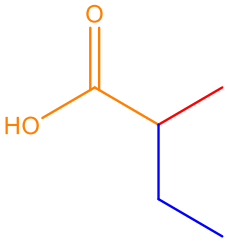


1,4 not 1,3

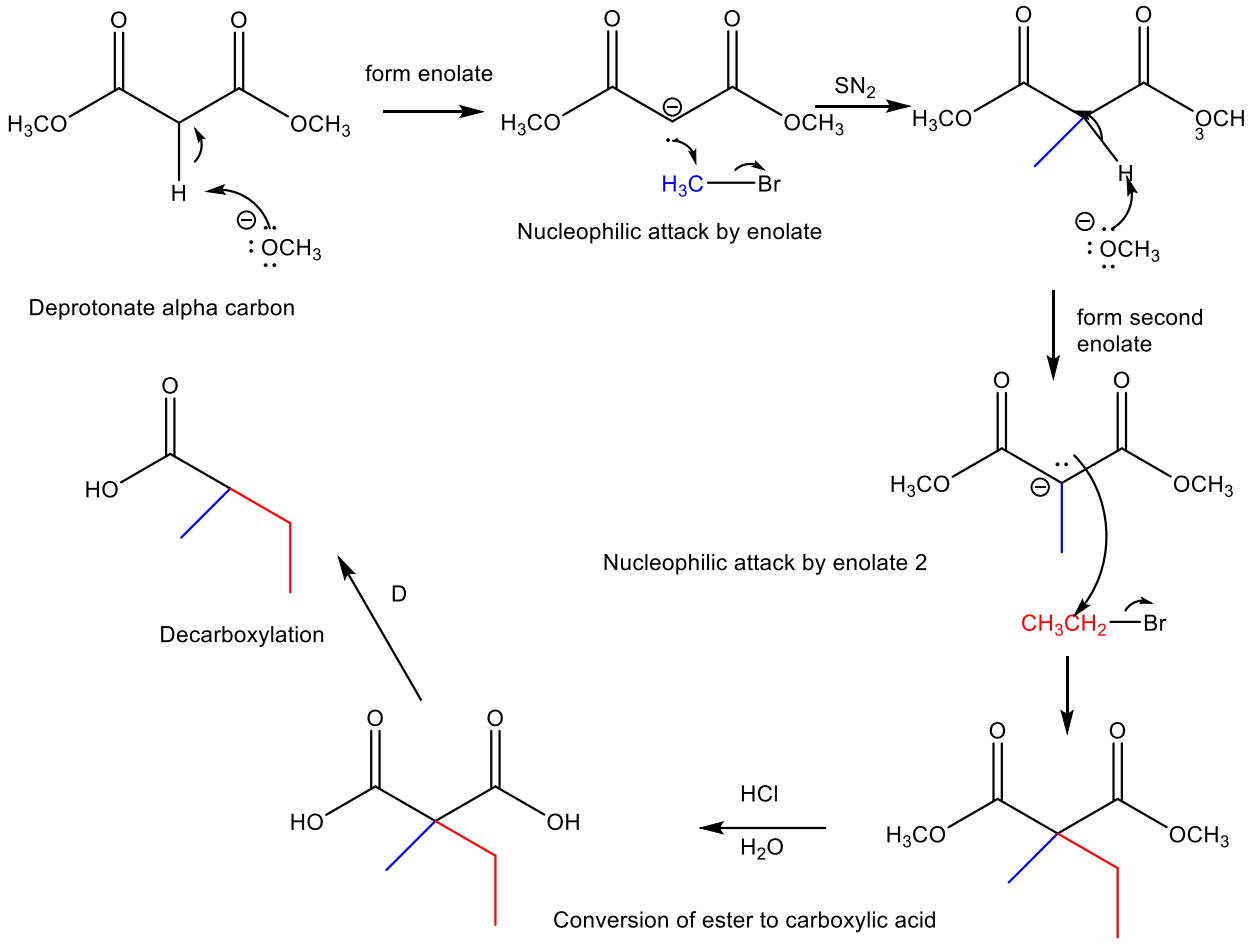
Now we will discuss the application of this decarboxylation reaction and its ability to give us sophisticated carboxylic acids and methyl ketones using malonic esters and acetoacetic esters.

First, we will discuss the Malonic ester carboxylic acid synthesis. The good news is that you know all of these reactions, now it is just a matter of putting together what you have learned. The following is the Malonic ester carboxylic acid synthesis reaction:





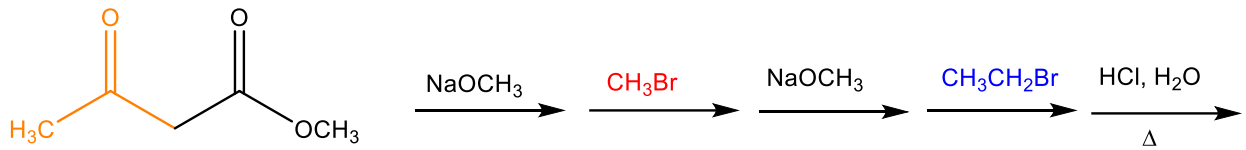
This reaction is just alkylation at the alpha carbon via enolate SN2 reactions followed by conversion of the esters to carboxylic acids (HCl, H_2O) and then finally decarboxylation of one of the carboxyl groups (the heat). The mechanism is shown below:

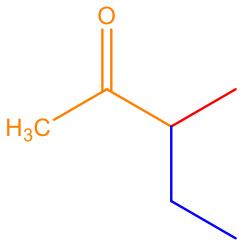


The conversion of ester to carboxylic acid is a reaction that we covered in the very first carbonyl chapter, if you are fuzzy on how that works, it is covered in there.

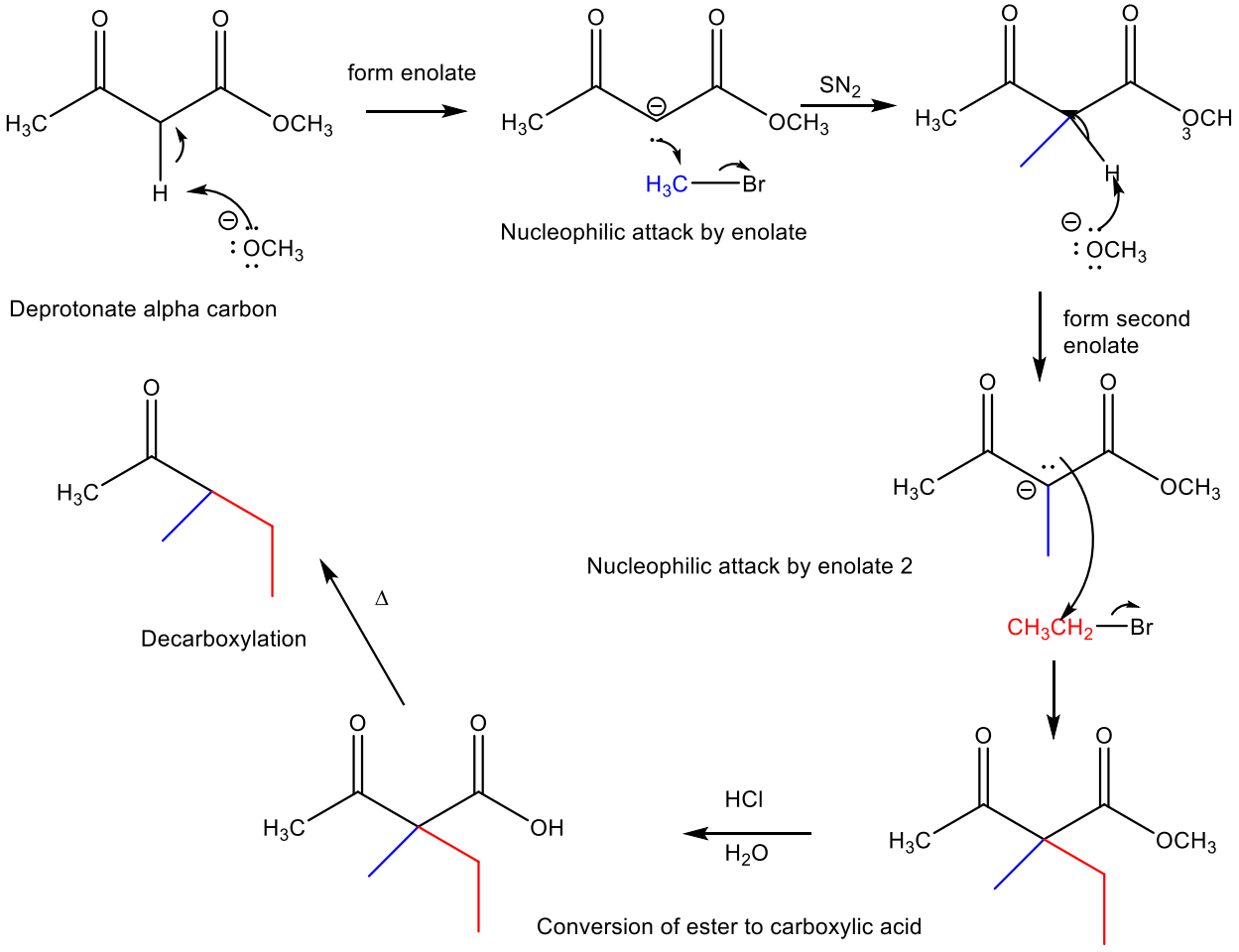
The last reaction that we will cover in this chapter is the acetoacetic ester methyl ketone synthesis reaction. Guess what, you basically just did it. The ONLY difference between these two reactions is the starting material, instead of having a 1,3-diester, we have a 1,3-ketoester, this way, we aren't left with a carboxylic acid at the end, but a methyl ketone. The mechanism is the exact same, all I changed was the starting reagent and the product by changing one of the OCH_3 groups with a CH_3 instead. Magic right?

The reaction:



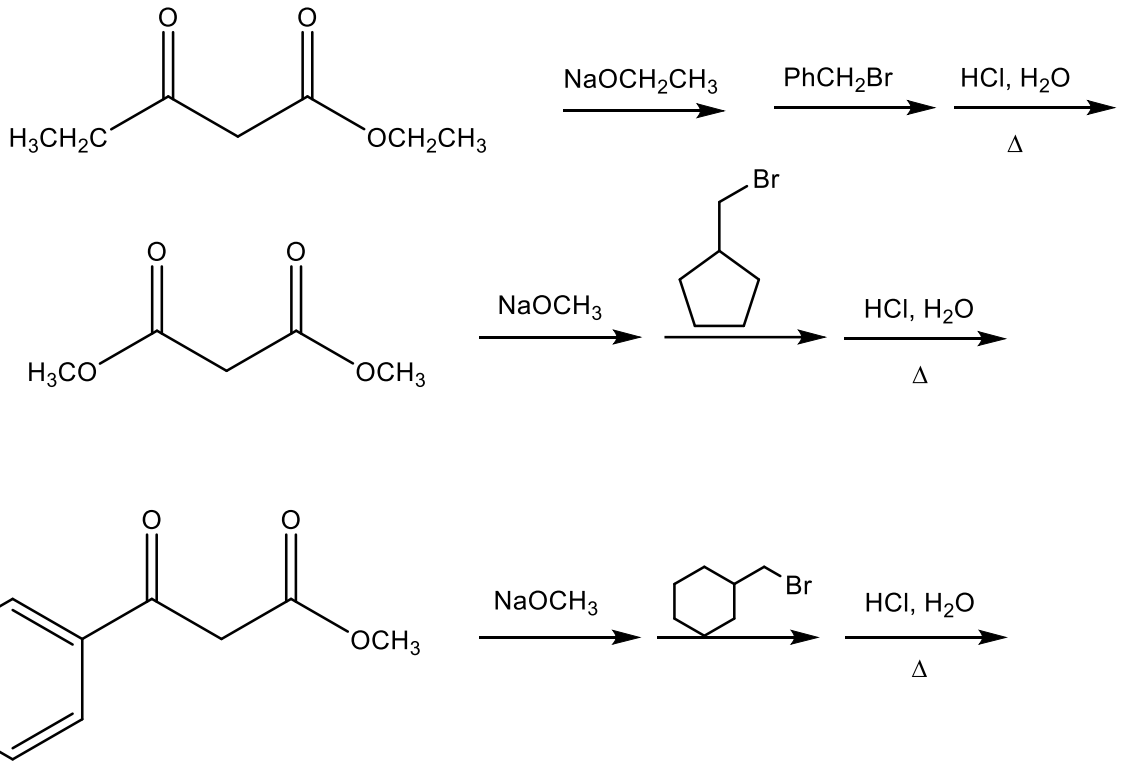


The mechanism:

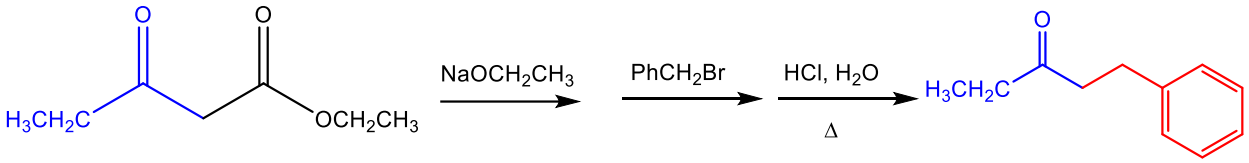


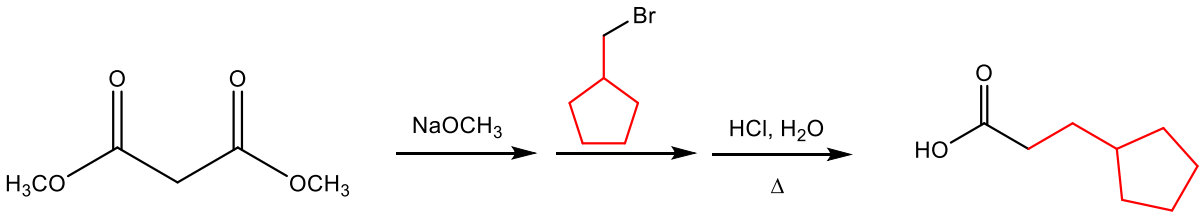
Practice questions:

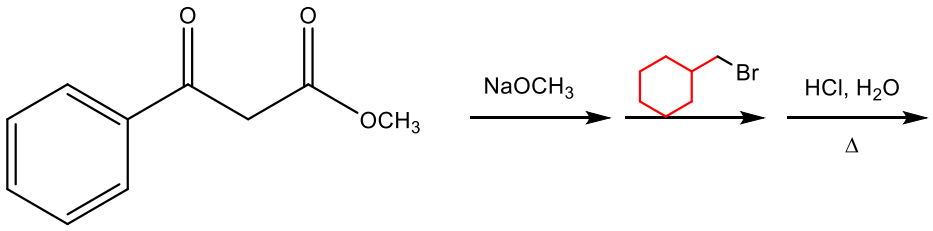
Predict the major organic products for the following reactions:

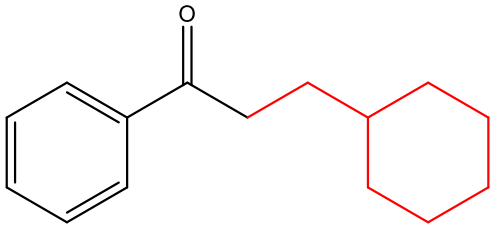


Answer:


O
O
H3CH2C
OCH2CH3
NaOCH2CH3
PhCH2Br
HCl, H2O
Δ
H3CH2C
O


O
O
H3CO
OCH3
NaOCH3
Br
HCl, H2O
Δ
HO
O

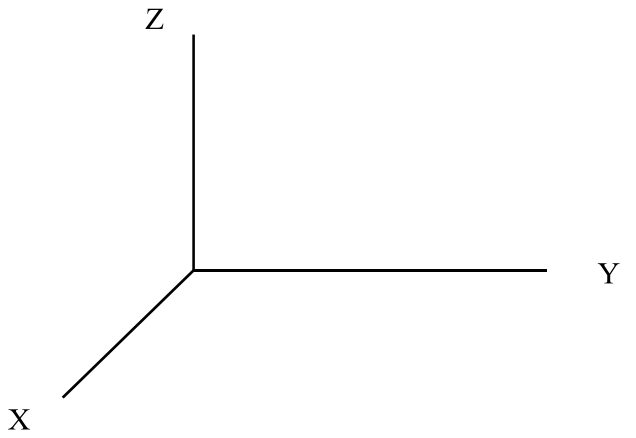

O
O
OCH3
NaOCH3
Br
HCl, H2O
Δ


O

Chapter 15: UV and IR Spectroscopy

Now we move onto the spectroscopy unit of the course. This is not super related to anything that we have discussed previously, rather than determine what a product of a reaction is given the reactants, we can use technology and instrumentation to determine its *structure*. UV spectroscopy is also referred to as simply "UV-Vis" spectroscopy and the purpose of this type of spectroscopy is to determine excitations and absorbance of high energy light. These transitions correspond to electrons being promoted from one orbital to another. These orbitals exist as discrete energy values. For organic chemistry at the typical introductory, undergraduate level, it is not necessary to go too deeply into MO theory, if you want more information regarding MO theory, you can look at my physical chemistry resources on the site. Organic chemistry is primarily interested in two MOs in particular, the HOMO and LUMO. The HOMO is the highest occupied molecular orbital and these typically correspond to the highest energy electrons that are available to a molecule, the LUMO is a lowest unoccupied molecular orbital. The LUMO is the next highest energy level *after* the HOMO. It is the interaction between the HOMO and LUMO of organic molecules that give rise to all of the reactions that we have discussed so far. UV-Vis spectroscopy concerns itself with determining the wavelength that corresponds to certain transitions, like the HOMO to LUMO transition or the HOMO-1 to LUMO, etc. Because energy is quantized, these transitions correspond to specific wavelengths of light that we can measure using some kind of detector to evaluate absorbance. If the photon from the light source of the UV-Vis instrument is of the right energy to excite an electron from an occupied orbital to an unoccupied orbital, then that photon is absorbed and a hump will appear in the UV-Vis spectrum. For a typical organic chemistry course, the only thing that you have to concern yourself with is knowing how many pi electrons there are in a conjugated system and knowing how to fill a wavefunction MO diagram. We will go over these first and then we will discuss IR spectroscopy.

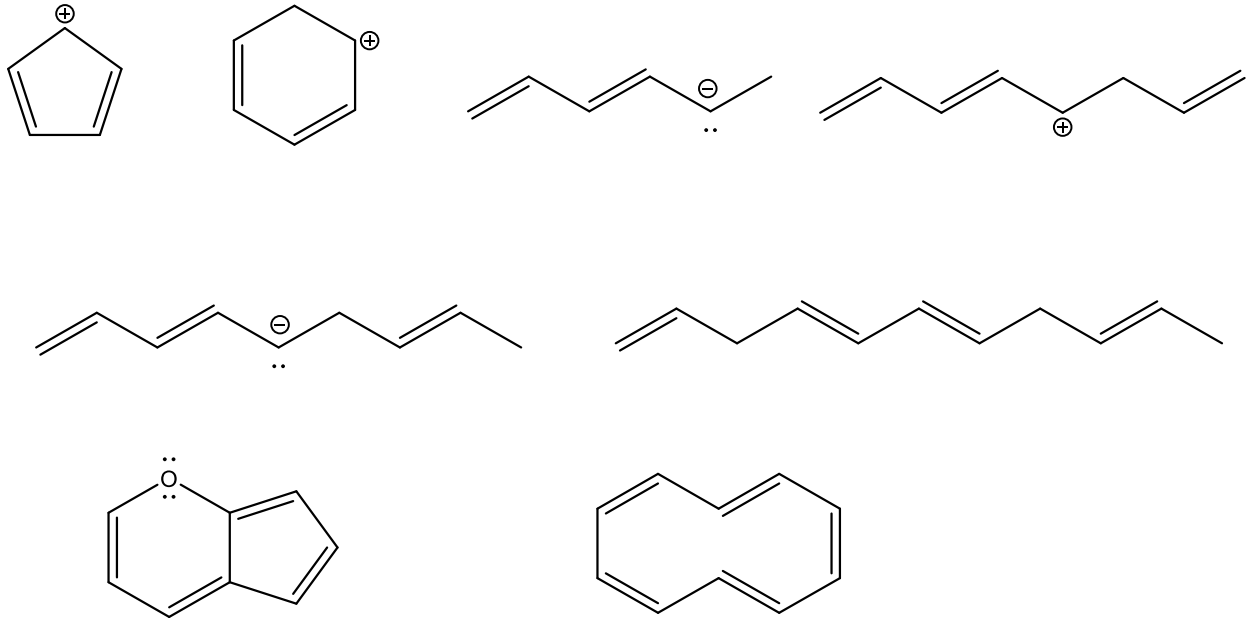
A p orbital can face three different directions, x, y, and z. In benzene for example, the p orbitals that were interacting to form a highway of electrons in the benzene molecule (that gives the aromatic properties) point above and below the plane of the ring. Therefore, these p orbitals are oriented about the z axis, a typical coordinate diagram is shown below:



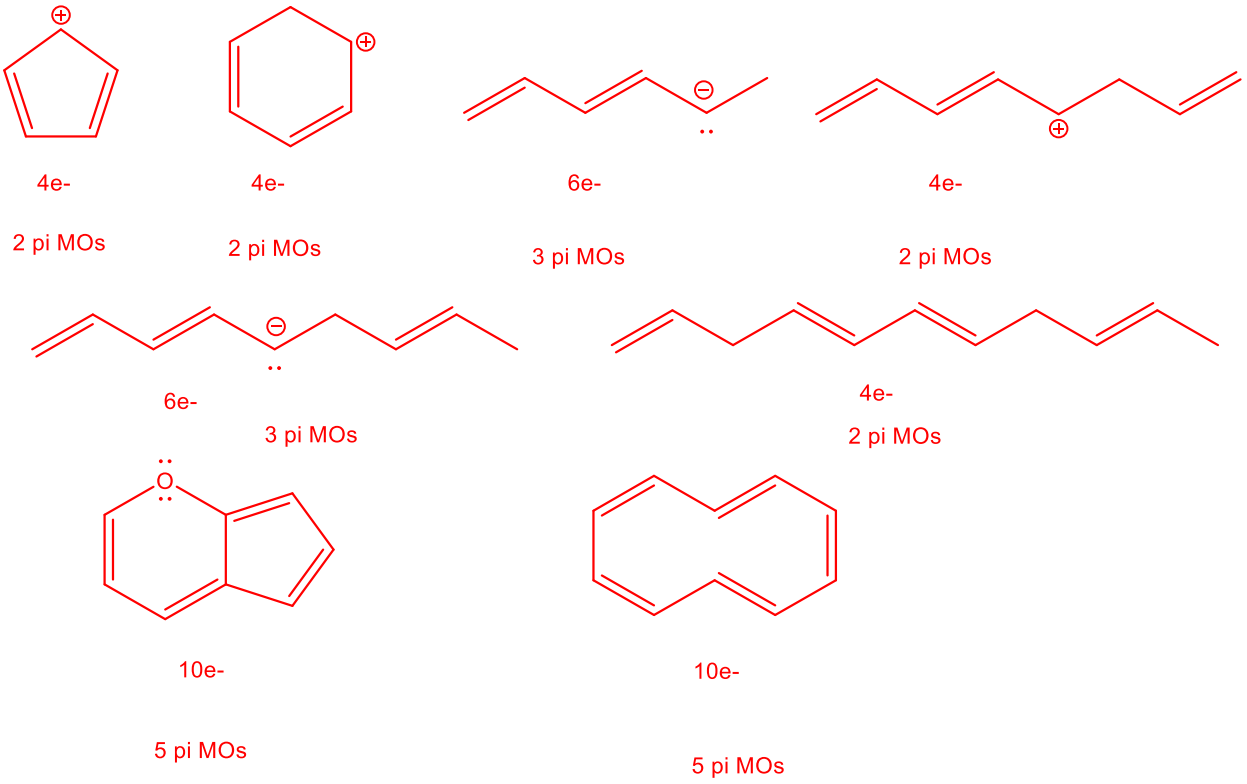
The p orbitals are all oriented along the z axis for the benzene molecule and because they are all interacting to make the pi bonds, they are said to be conjugated and form a continuous highway of electrons along the z axis. This should all be review. In each of the pi bonds, there are two p orbitals interacting, therefore each pi bond gives two pi electrons to that total that we used to determine aromaticity. If there is a positive charge in conjugation with the pi system, that contributes no electrons and if there is a lone pair in conjugation with the pi system, that contributes two electrons as well. For each pair of pi electrons, there is one MO, so for benzene that has 6 pi electrons, there are 3 MOs, each of which have 2 electrons in them to give the 6 we counted.

Practice questions:

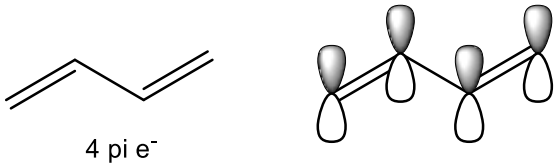
Determine the number of pi electrons and pi MOs in the delocalized electron systems below:

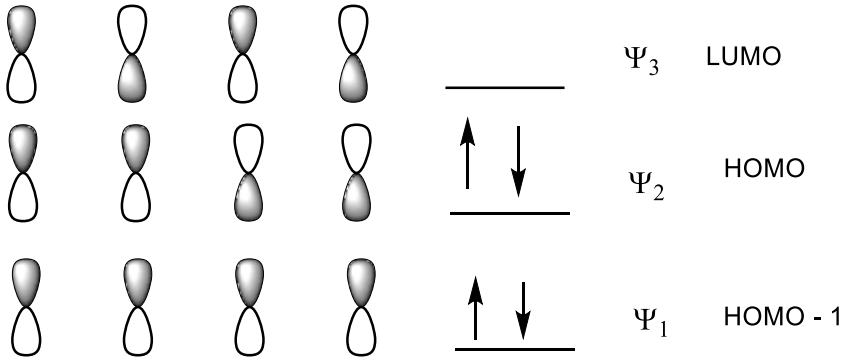


Answers:



Now we will discuss how we will fill out the MO diagram and put electrons in their respective MOs. For each MO, there will be a corresponding series of p orbitals that will display a certain symmetry and have certain nodes. The lowest energy level will have 0 nodes and the number of nodes will increase by one after each energy level. Nodes are places where there are antibonding interactions, meaning that the p orbitals are not in phase (both not dark or both not white). We will take 1,3-butadiene as an example. 1,3-butadiene has 4 pi electrons and therefore two occupied pi MOs, the MO diagram for 1,3-butadiene is the following:

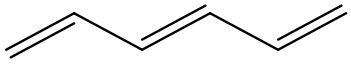




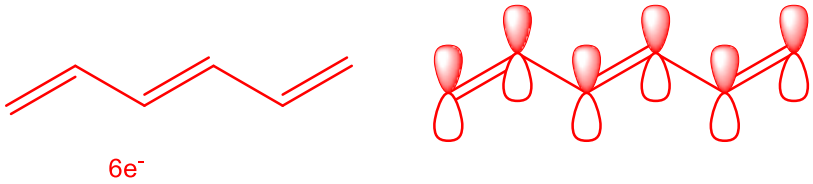
1,3-butadiene has 4 pi electrons and each MO can contain only two electrons, therefore the first two MOs will be occupied and the third will not. This is because after the second MO, we have no more electrons to put into the third one. As we said previously, a node occurs when there is a mismatch of phases and the lowest energy MO has no nodes. The HOMO-1 MO has no nodes because all p orbitals have dark on top and light on bottom, they are all in phase. The HOMO has one node, specifically in the middle because the second p orbital from the left has dark on top while the next p orbital to the right has light on top, therefore they are out of phase and that is one node. This pattern continues with the LUMO.

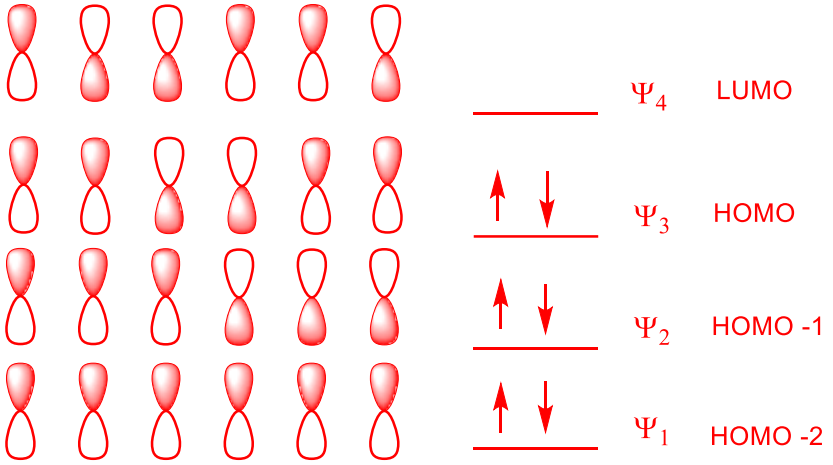
Practice question:

Draw the MO diagram for 1,3,5-hexatriene:



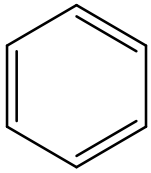
Answer:



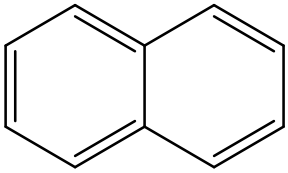


The key when drawing MOs and figuring out where the p orbitals will orient themselves is by looking at the symmetry. *Initially, there is a vertical plane of symmetry down the middle. The next MO has a rotation of symmetry, if you rotate the MOs 180 degrees about an axis perpendicular to the plane of the screen, it will be the same. This pattern alternates, vertical axis of symmetry down the middle, then 180 degrees turn along an axis pointing into the page/screen. Then the number of nodes has to increase by one starting from zero.* In general, the HOMO MO will be the number of pi electrons divided by 2 and it will have $\frac{n}{2} - 1$ nodes where n is the number of pi electrons.

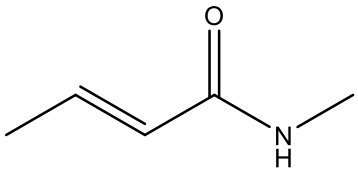
But enough about MOs for a second, what does this have to do with UV spectroscopy? Well the short answer is everything, all of these excitations that UV spectroscopy is able to observe has to do with exciting electrons from an occupied state to an unoccupied state using light as the energy source. The wavelength that has the maximum absorption is referred to as the lambda max for the compound and generally this corresponds will with the HOMO to LUMO transition. This wavelength can be determined by looking at the degree of conjugation in the molecule, the more conjugated bonds and the better the conjugation is (easier it is to delocalize the electrons), the larger the lambda max wavelength. For example:



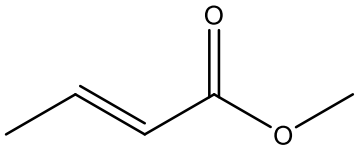
Vs



The molecule on the right has more extensive conjugation than the one on the left, therefore the one on the right will have a larger lambda max wavelength, so if benzenes lambda max is 255 nm, naphthalene's will be greater than 255 nm. Along the same vein, if the atom donating its electrons through resonance is more willing to give its electrons, the wavelength will be larger, for example:



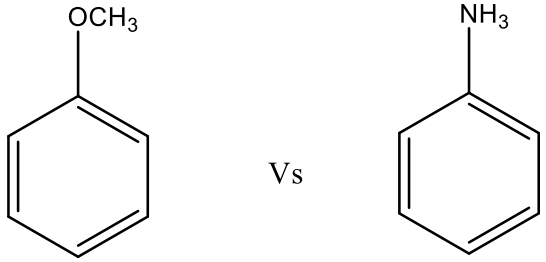
vs

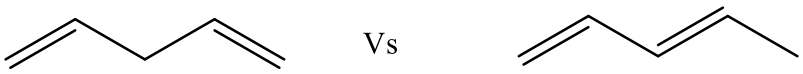


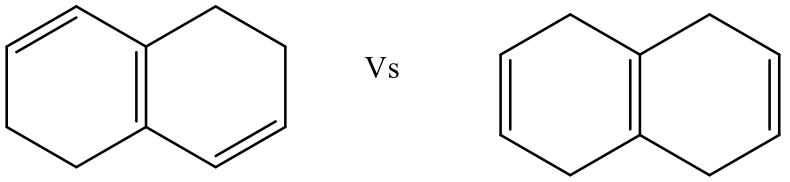
Because nitrogen is less electronegative than oxygen, it is more willing to donate its electrons to the conjugated molecule, therefore, despite having everything else equal, the amide will have a larger lambda max than the ester because nitrogen is more efficient at conjugation than oxygen.

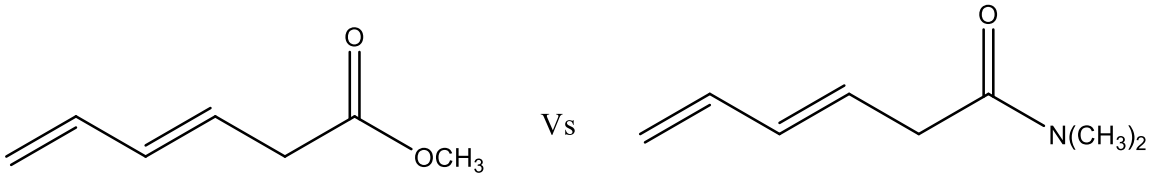
Practice questions:

Determine which molecules of each pair will have the longer lambda max:

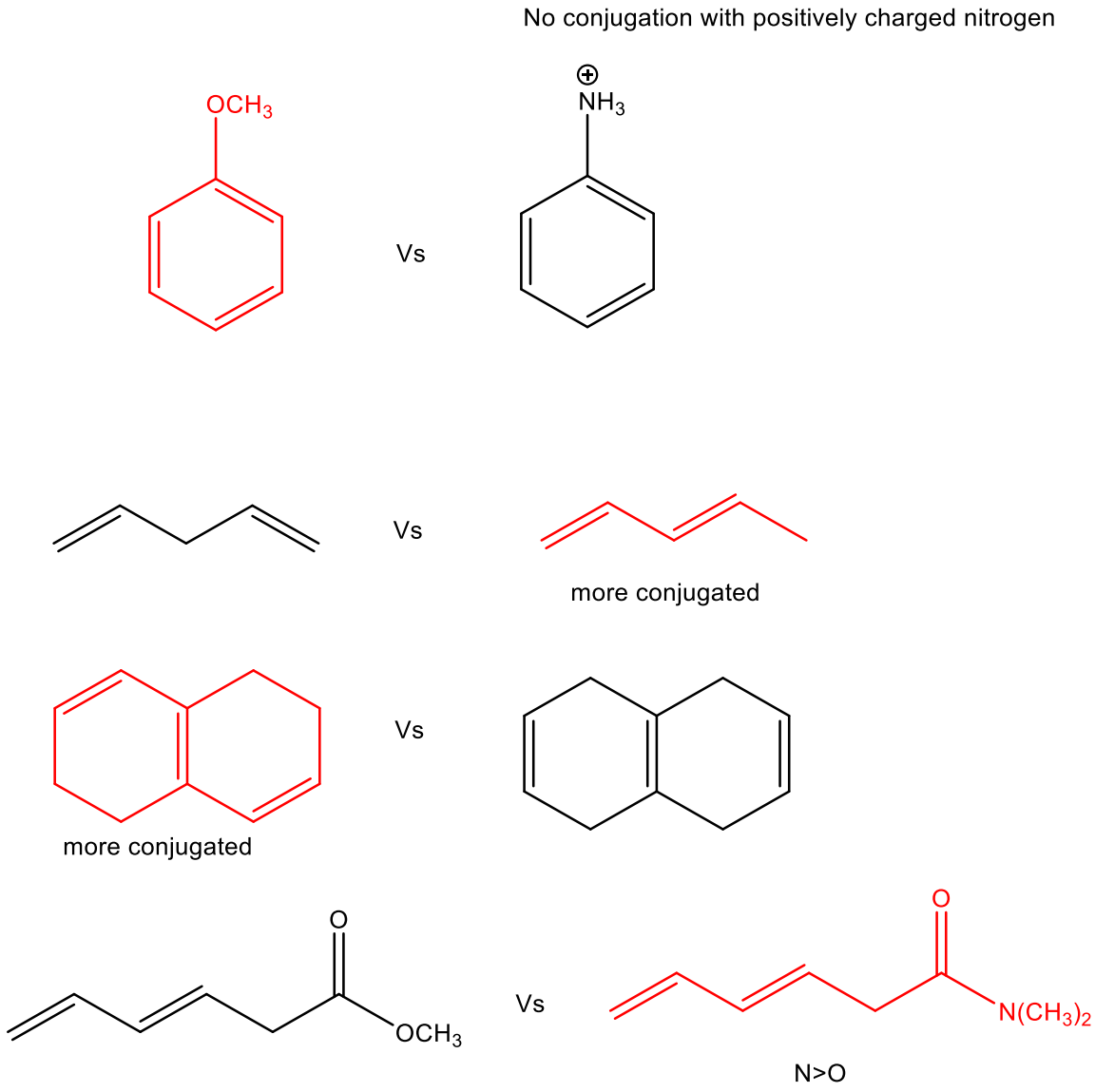








Answers:



The real power of UV-vis spectroscopy doesn't really come into play until you have taken or learned p-chem, otherwise, it isn't super useful for much, so we will now turn our attention to the thing that is way more important for our study of organic chemistry, IR spectroscopy.

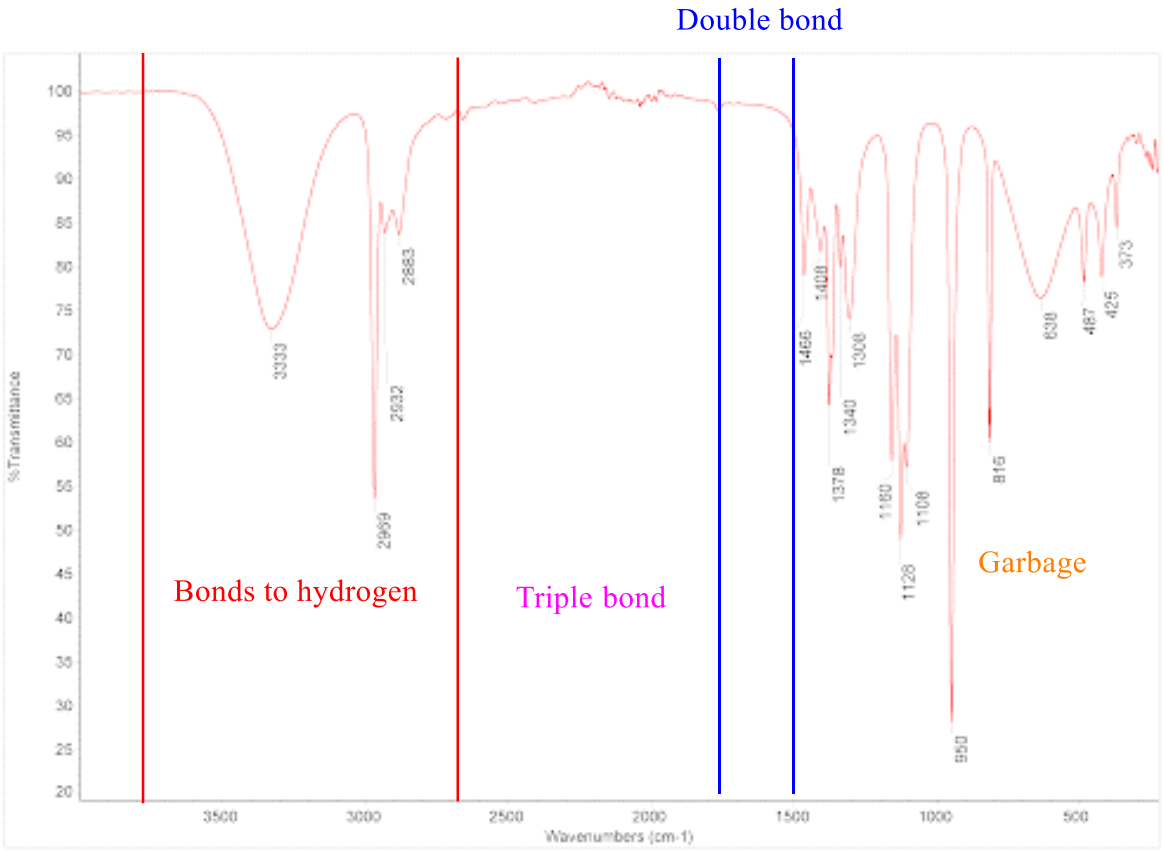
IR spectroscopy at its base level measures vibrations, specifically vibrations that cause changes in dipole moment. This turns out to be exceptionally useful because IR coincidentally is the region of the electromagnetic spectrum that causes different functional groups to vibrate. *Therefore, IR spectroscopy is useful to determine the kinds of functional groups an organic molecule has based off its vibrational profile.* These vibrations are measured in energy units called wavenumbers or cm^{-1}. *The higher the wavenumber the larger the energy that photon has.* Perhaps intuitively, *the shorter and stronger the bond is, the harder it is to vibrate,* therefore, *stronger bonds will appear at higher wavenumbers.* Looking at an IR spectrum is a multidimensional issue, just like during college admissions you cannot only look at test scores, *you can't only look at wavenumbers to figure out which functional group the vibration corresponds to. Other factors like shape and intensity come into play.* Luckily, these differences all have physical meaning and can be explained if you understand that IR spectroscopy looks at vibrations.

Let's first by discussing intensity, bonds that are more polar will be more intense. Therefore, things like C=O and OH bonds will appear as very intense peaks, often being absorbed far more than other peaks. Other nonpolar bonds like C=C or C-C bonds will appear as weaker peaks because the change in dipole moment is not as strong when these bonds vibrate, after all, there is very little difference in electronegativity for those bonds.

The shape of the peak mainly has to do with hydrogen bonding. Like you have learned in general chemistry, hydrogen bonding is directional, meaning the orientation of the groups participating in these interactions matters a lot for strength. The strongest hydrogen bonds are when the groups are collinear, i.e. they are directly next to each other and point towards each other. The farther the groups are from one another and the larger the angle between them, the weaker the hydrogen bonding is. But wait, I thought we were measuring vibrations and changes in dipole moment, why does hydrogen bonding have anything to do with this? The reason is that hydrogen bonding makes it harder for vibrations to happen. This should make sense, hydrogen bonding is a favorable interaction, it increases stability, if you are already stable, why would you move. That's like asking someone to move off the sofa during their favorite part of a movie, they're not gonna do it without you pushing them, or supplying extra energy. Because of this directionality and wide differences in hydrogen bonding strength, the wavenumber corresponding to that vibration will change. Hydrogen bonds that are weak will only weakly prevent a bond from vibrating, think of yourself watching TV because you're just bored and aren't particularly interested in watching it, it doesn't take that much additional energy for your friend to get you to get food with them. Likewise, if hydrogen bonds are strong and have the optimal orientation, they will really stop you from vibrating that bond and they will make the functional group vibrate at larger wavenumbers. Think of it as if you're watching your favorite movie with your significant other and randomly the phone rings from a number you don't recognize, you're not going to move because you'd rather stay put, you really need a lot of energy to push you to leave that situation (I know it would for me!). Therefore, broad peaks are those peaks that correspond to groups that can participate in hydrogen bonding, think OH and NH bonds.

In summary, wavenumber has to do with bond strength, shape has to do with hydrogen bonding, and intensity has to do with how polar the vibrating bond is.

Here is essentially a cheat sheet for IR that will tell you generally where the overall types of bonds vibrate:



We can rationalize the placement for all of these regions. Remember from the very first chapter, the most important criteria for determining bond length and strength is size, since hydrogen is the smallest element, it will also form the smallest bonds and generally the strongest bonds for organic compounds. Because bonds to hydrogen are strong, they appear at larger wavenumbers than the rest of them. Then we look at the number of pi bonds, that was second on our criteria, triple bonds are shorter and stronger than double bonds, therefore they will appear at larger wavenumbers than double bonds. All the peaks after 1500 cm^{-1} are generally useless and are only useful in fingerprinting a molecule, that is why it is generally referred to as the fingerprint region. I will also provide a table for you to look at for all the general IR vibrations that you will likely encounter, the most important ones will be OH, NH, and C=O bonds, these are characteristic bonds that you should be familiar with.

Functional group	Type of vibration	Wavenumber	Shape
Alcohol	O-H stretch	3500-3200	Strong, broad, parabolic
Amine	N-H stretch	3500-3200	Medium and broad, number of peaks = number of hydrogens
Carboxylic acid	O-H stretch	3300-2700	Strong, broad, screwed up bottom
Aldehyde	C-H stretch	2830-2700	Medium, sharp
Nitrile	C≡N stretch	2300-2200	Weak
Alkyne	C≡C stretch	2300-2200	Weak
Ketone/Aldehyde	C=O stretch	1730	Strong, sharp
Ester	C=O stretch	1750	Strong, sharp
Carboxylic acid	C=O stretch	1760	Strong, sharp
Amide	C=O stretch	1700-1650	Strong, sharp
Alkene	C=C stretch	1680-1600	Medium, sharp

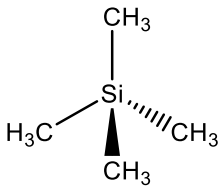
Notice how I did not give you the alkane C-H stretches, this is because these are beyond useless. I see a bunch of orgo students every semester constantly obsessing over these peaks, STOP! Every single organic molecule will have a C-H stretch, therefore they are USELESS when looking at an IR. All those tell you is that you have an organic molecule… well geez, that's helpful, not like you're taking an ORGANIC chemistry course or anything. Rant aside, please ignore those peaks, they are not worth discussing because every molecule has them. *Your focus when looking at IR should be on the unique peaks, not on the peaks everything has*! *Look for differences, NOT similarities.* Not every molecule will have an alcohol, but almost every molecule you have seen so far has an alkane C-H bond.

Unfortunately, there are no practice IR spectra I have off hand, so I cannot provide you with any practice problems without stealing them from textbooks or my previous exams, which I can't do. Therefore, I highly recommend you look at your actual textbook, look for practice problems and apply the concepts you have learned here to help you delineate each peak in the IR. If you want additional reading on IR, there is stuff posted in the physical chemistry section of the site.

Chapter 16: NMR Spectroscopy

IR is great and everything, *but it tells you nothing about how the atoms in the molecule are connected*. For that information, you need other tools, like NMR spectroscopy to help you determine what the structure of the compound is.

For a typical organic chemistry course, the actual theory behind NMR is not super important to know or understand, so it will not be covered in this text (also because I am not super comfortable explaining it in truth). What IS important to know is the concept of shielding and deshielding. When a molecule is being analyzed through NMR, the extent to which an atom is shielded by electrons plays a big role in determining its "chemical shift". *A chemical shift is essentially a measure of how deshielded that atom is relative to some standard.* For a typical organic chemistry course, there are two flavors of NMR: proton (or hydrogen) and carbon. The standard for proton NMR is tetramethylsilane or TMS, which is shown below:



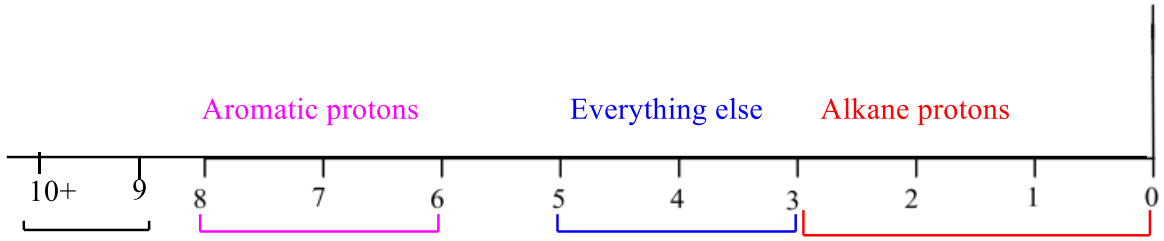
The protons in that molecule are set to be the 0 for the proton NMR scale. *If an atom is shielded, that means it is electron-rich and has a bunch of electrons protecting the nucleus from the magnetic field. If an atom is deshielded, that means that it is electron-deficient and is more exposed to the magnetic field. The more deshielded your atom is, the larger its chemical shift value.* If you recall, Si is less electronegative than carbon, therefore, there are more electrons on those carbons than typical alkanes, therefore, these protons and carbons are more shielded than they would be if they were in a purely organic molecule with no Si. This leads us to a general rule:

The closer you are to an EWG, the more deshielded you are and the higher your chemical shift

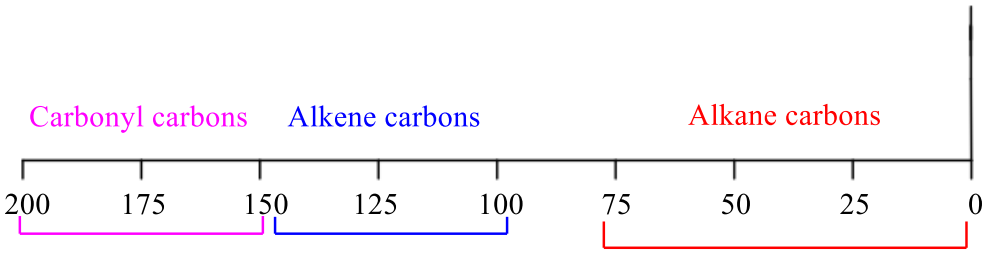
The closer you are to an EDG, the more shielded you are and the lower your chemical shift.

The following is a proton and carbon NMR cheat sheet that tells you the general region of each type of signal:

x axis is the chemical shift measured in ppm

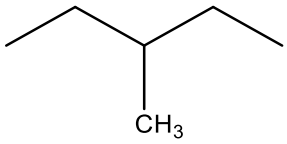


Aldehydes + carboxylic acid

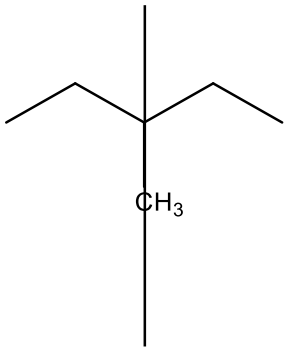


Keep in mind, these are general regions. There is some wiggle room and ultimately it depends upon the chemical environment of the protons and carbons in the molecule (if they are close to an EDG or EWG). What may stand out to you is the aromatic protons, why do those have such a high chemical shift (downfield)? The reason why is a bit confusing, but it will be covered in every official organic textbook, so I refer you to your actual textbook for that explanation.

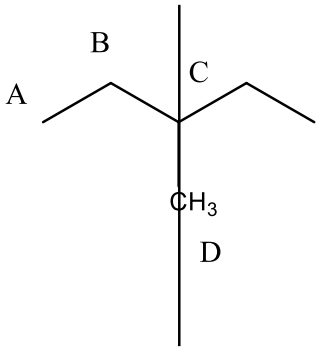
Now we will cover the basics of proton NMR and then briefly discuss carbon NMR. Proton NMR is an incredibly powerful tool because of all the information it gives you. *Each proton signal has a couple key features: chemical shift (ppm), splitting pattern, and integration. The splitting pattern gives information on the number of neighboring protons and the integration gives the number of equivalent protons coming from that signal.* But wait a second, what does it mean to be equivalent? The short answer is that if you replaced that proton with another group, you would name the molecule the exact same for all the protons you are comparing. In most cases, that means that they are connected to the exact same things and are positioned symmetrically in the molecule. This is best explained with examples, so let's consider the following molecules:



To start, I look for planes of symmetry and only do one side because I know that it is mirrored on the other side. When looking at this molecule, it is clear to see that it has a plane of symmetry down the center like so:



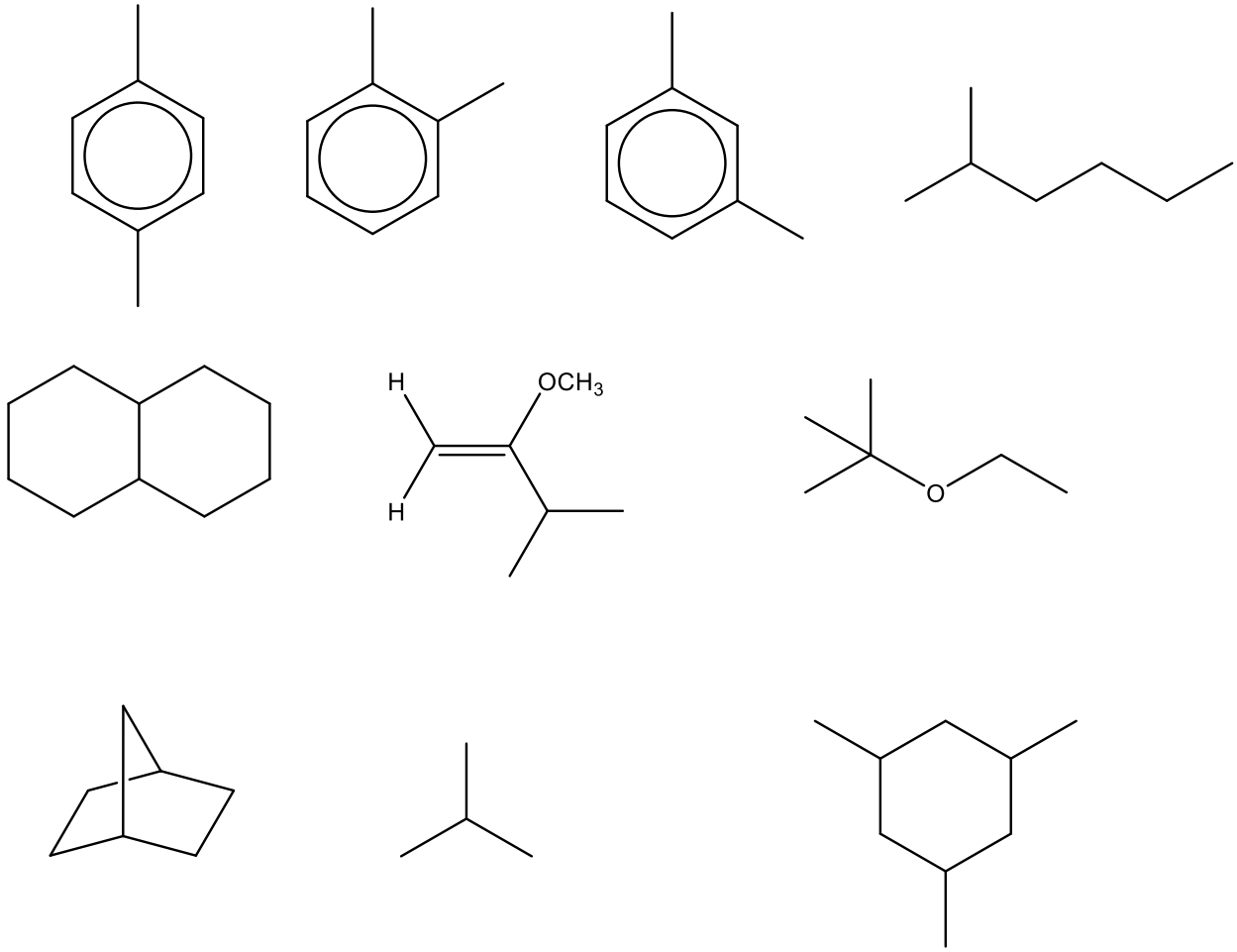
Therefore, we will turn our attention to the carbons and protons to the *left and on the plane of symmetry*. We do not know for the time being if these protons are equivalent or different, so we will assume that they are all different for the time being like so:



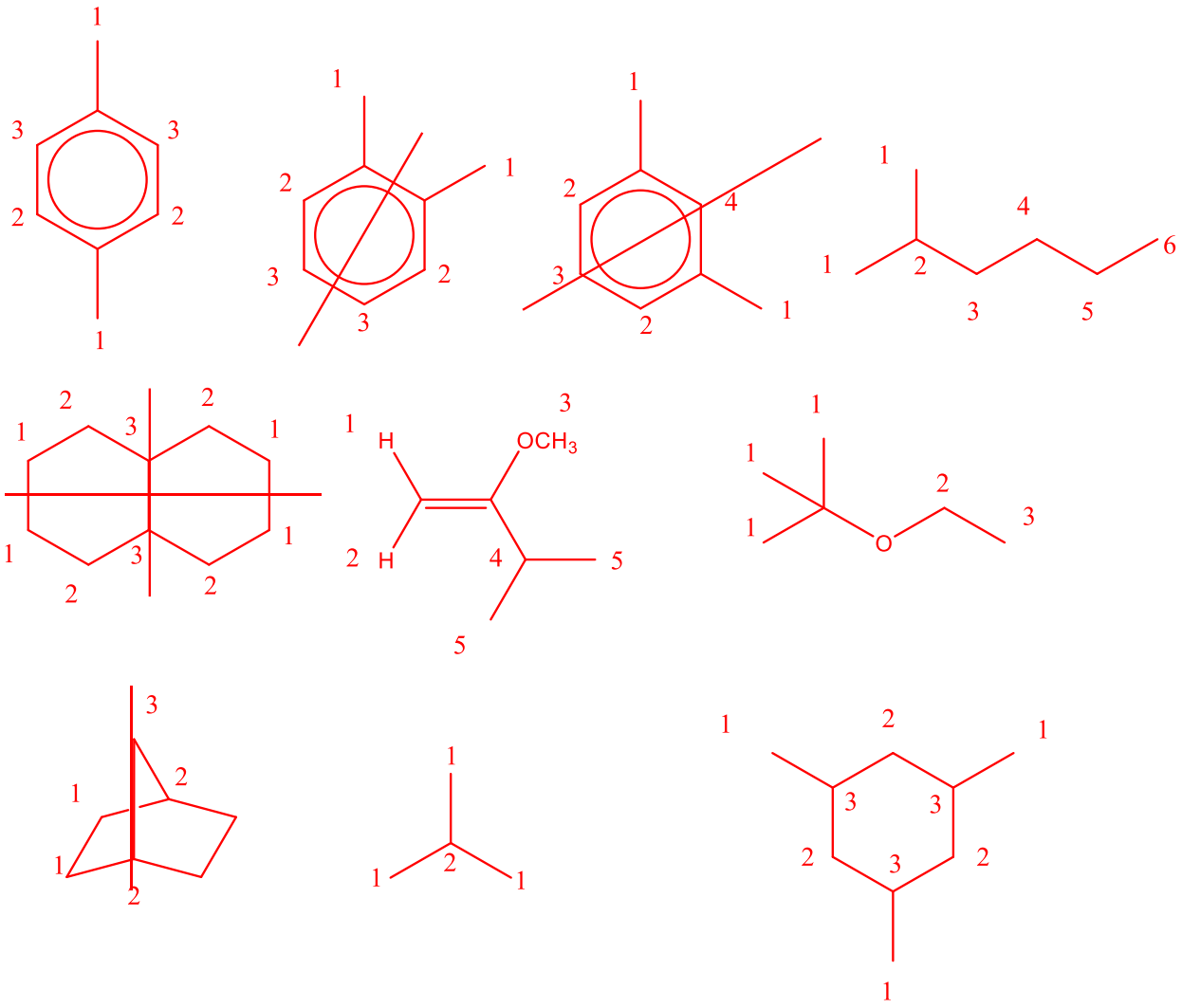
Position A has a carbon with three protons and has a connection to position B. No other carbons on the left side have the same connectivity, therefore position A has unique protons and carbons. Position B has a carbon to the left and to the right and has two protons, it is the only position directly next to position A that has 2 protons therefore position B is also unique. Position C is the only position with one proton, therefore by default it is unique. And finally, position D is the only position that is connected to position C, therefore it is also unique. This can be done for any molecule so we will do more examples:

Practice questions:

Give the number of unique proton signals in the following organic molecules:

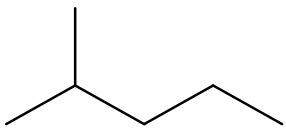


Answer:

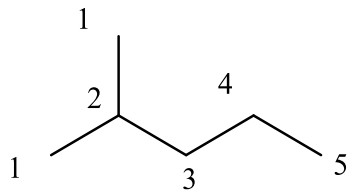


Eventually, after doing enough of these problems you will be able to almost instantly recognize the symmetry and determine the number of proton signals relatively quickly.

Now we will discuss splitting and we will discuss it using a relatively simple example. Splitting occurs because of neighboring protons, these neighboring protons will couple the signal and produce complex shapes for the peak. The number of mini peaks in the signal is given by the "N+1" rule, where N is the number of neighboring protons. Neighboring protons are those protons that are on the carbons directly next to the one of interest. Let's discuss the splitting patterns for each signal in the following compound:

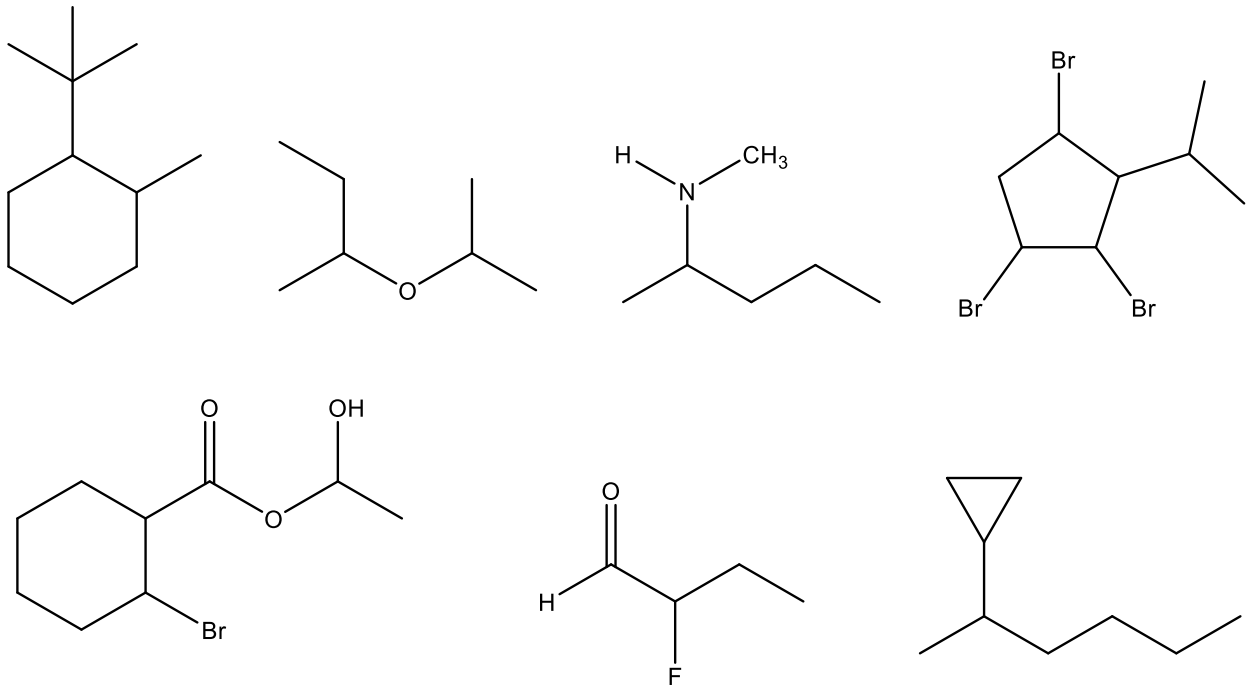


Firstly, we need to determine how many peaks there should be in that molecule and label each unique hydrogen, doing this should give you this:

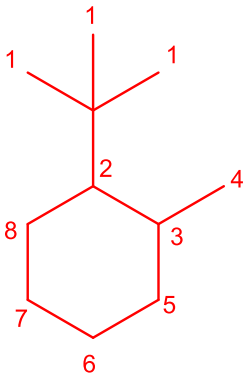


This is because every proton has a unique connectivity except for the protons in signal 1, both of them are methyl protons attached to carbon 2 and the rest of the molecule. The rest of the protons are in their own unique chemical environment, if you aren't convinced just look at each signal and look at their connectivity. If we focus our attention on the signal coming from proton 1, to figure out the splitting pattern, we look and count the number of neighboring protons. In the case of signal 1, there is only one neighboring carbon with protons, position 2. Position 2 has 1 proton, meaning that the splitting pattern for signal 1 will be a doublet because N+1 = 2. We can do the same analysis for signal 2. Signal 2 has 3 neighboring carbons (both 1's and 3), each 1 has 3 protons coming off it, and 3 has 2 protons coming off it, therefore N for signal 2 is 8. The multiplicity or splitting pattern for signal 2 is therefore 9, however, by convention, splitting patterns above 4 will be simply referred to as multiplets. Therefore, signal 2 will be split into a multiplet. The same can be done for 3, 4, and 5. The splitting pattern for those would be multiplet, multiplet, and triplet respectively. This will always work except if you have an OH or NH proton. These protons will not split or be split by other neighbors. See if you can determine the number of proton signals and the splitting patterns for the following molecules:

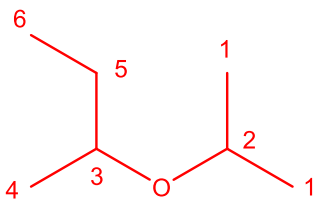
Practice questions:



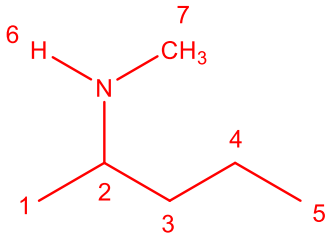
Answers:



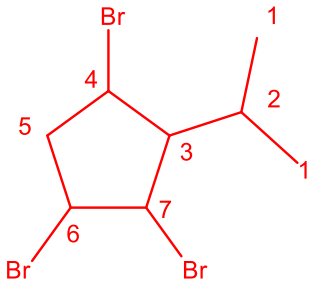
Signal splitting:
1 = singlet
2 = quartet
3 = quartet
4 = doublet
5 = quartet
6 = multiplet
7 = multiplet
8 = quartet



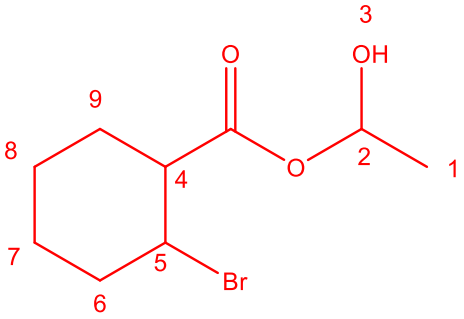
Signal splitting:
1 = doublet
2 = multiplet
3 = multiplet
4 = doublet
5 = multiplet
6 = triplet



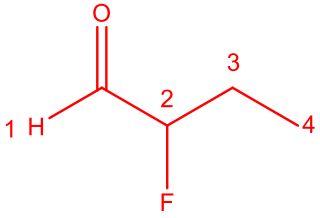
Signal splitting:
1 = doublet
2 = multiplet
3 = quartet
4 = multiplet
5 = triplet
6 = singlet
7 = singlet



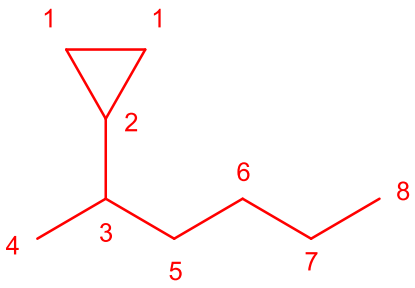
Signal splitting:
1 = doublet
2 = multiplet
3 = quartet
4 = quartet
5 = triplet
6 = quartet
7 = triplet



Signal splitting:
1 = doublet
2 = quartet
3 = singlet
4 = quartet
5 = quartet
6 = quartet
7 = multiplet
8 = multiplet
9 = quartet



Signal splitting:
1 = singlet
2 = triplet
3 = multiplet
4 = triplet



Signal splitting:
1 = doublet
2 = multiplet
3 = multiplet
4 = doublet
5 = quartet
6 = multiplet
7 = multiplet
8 = triplet

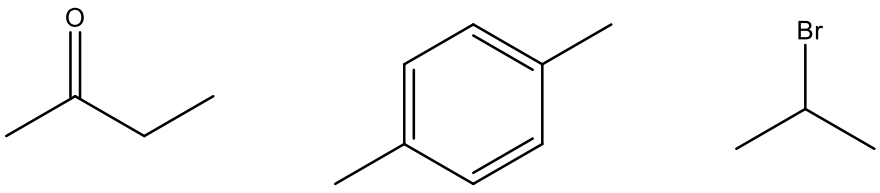
Once you know how to determine the number of signals and how those signals will be split, you can figure out the structure of unknown compounds using NMR. There are three things you need to look at when doing proton NMR: integration, shape of peak, and chemical shift. With those three things in mind, you can theoretically piece together the molecule. Let's do an example and then I will provide some practice problems. Because I do not have any NMR spectra on hand, I will provide the chemical shifts and the splitting for each peak and have you analyze it.

List of peaks in unknown NMR:

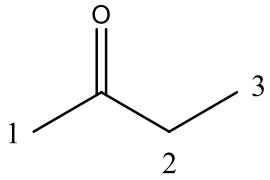
1.8 ppm, 6H, doublet

4.2 ppm, 1H, multiplet

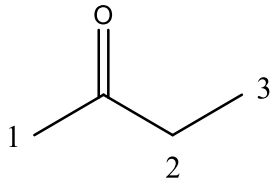
Possible candidates:

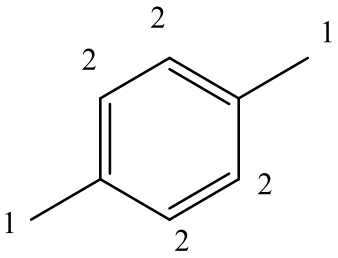


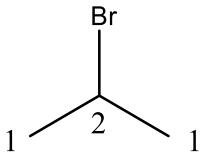
We can eliminate one of these choices just by looking at the number of peaks seen in the NMR. The first option would have three unique peaks in its NMR like so:



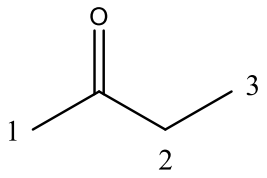
The other compounds would have two peaks, like so:

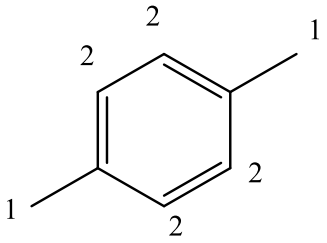


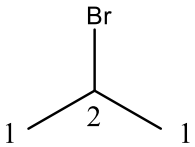


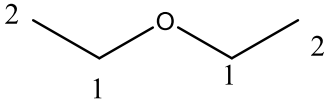


So the number of signals is a wash between the two compounds on the right, however, we can distinguish the two of them by looking for protons in the benzene ring region of the proton NMR. This region corresponds to the chemical shift values from 6 to 8 ppm, since there are no peaks in that region, we can eliminate the compound in the center, leaving only the compound on the right as the possible answer. Even if you didn't know that, you can also look at the types of groups in the compound to the right. There is an alkyl halide, that falls under the "everything else" category so it will have a peak between 3 and 5 ppm, there is a peak at 4.2, therefore, that falls directly where it should fall for an alkyl halide peak, boom, has to be the one on the right. If we wanted to make it more challenging, we could have done this:









If we add in the extra compound on the right, diethyl ether, it would be a bit harder to determine which compound is correct, but NOT impossible. Diethyl ether has more protons than the 2-bromopropane, therefore, the integration would not match, diethyl ether would have around those same chemical shifts but have 6H and 4H signals not 6H and 1H. Another tip off would be that the 6H signal from the diethyl ether would be a multiplet, not a doublet because those protons have four neighbors. You have to evaluate all information given to you to make the right decision. If you are given a molecular formula and have to determine the structure, the first thing I would recommend to do is determine the degrees of unsaturation, which tells you the number of pi bonds and rings in a compound. To calculate the degrees of unsaturation, it is a simple formula:

$$\deg_{unsat} = \frac{2C + 2 - H - X + N}{2}$$

Where C, H, X, and N are the number of carbon, hydrogen, halogen, and nitrogen atoms respectively. It is also advisable to do a fragment-based approach and analyze the highest ppm signal first. You will see an example of this in the answer key to the following questions.

Practice questions (these come from Organic Chemistry 8th edition by Paula Yurkanis Bruice, these are NOT my questions):

Identify which isomer of C_4H_9Br would make the following NMR peaks:

1.

4.1 ppm 1H multiplet

1.8 ppm 2H multiplet

1.7 ppm 3H doublet

1.1 ppm 3H triplet

2.

3.3 ppm 2H triplet

1.9 ppm 2H multiplet

1.5 ppm 2H multiplet

0.9 ppm 3H triplet

3.

3.2 ppm 2H doublet

2.0 ppm 1H multiplet

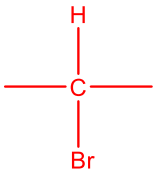
1.0 ppm 6H doublet

Answers:

Degree of unsaturation = 2(4) + 2 - 9 - 1 = 10 - 10 = 0, no pi bonds or rings

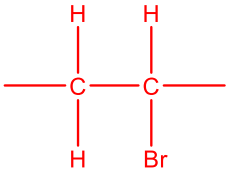
C_4H_9Br

4.1 ppm 1H multiplet indicates that the carbon having the bromine has 1 H attached, that is the only atom in the molecule that could give a signal that high



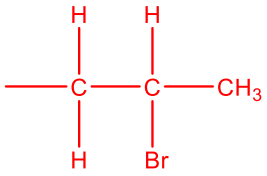
That gives this fragment

1.8 ppm 2H multiplet indicates that a carbon close to the bromine has 2H attached and has several neighbors



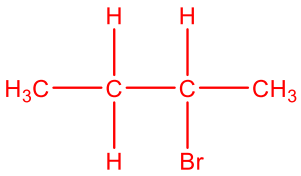
That gives this fragment

1.7 ppm 3H doublet indicates that a carbon close to the bromine has 3H attached and has 1 neighbor, that can only happen if it is a terminal methyl group next to the bromine carbon

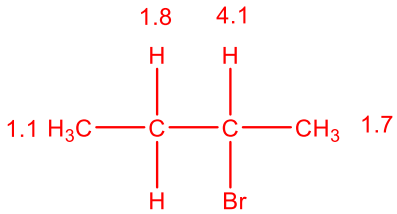


That gives this fragment

1.1 ppm 3H triplet indicates a carbon far away from the bromine has 3H attached and has 2 neighbors



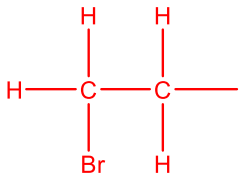
That gives this molecule



Degree of unsaturation = 2(4) + 2 - 9 - 1 = 10 - 10 = 0, no pi bonds or rings

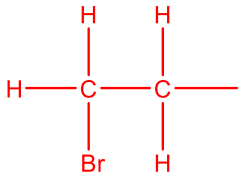
C_4H_9Br

3.3 ppm 2H triplet indicates carbon with bromine on it has 2 hydrogens and has 2 neighbors



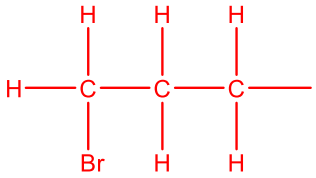
This gives this fragment

1.9 ppm 2H multiplet indicates a carbon close to the bromine has 2 hydrogens on it and several neighbors



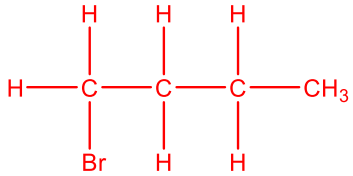
Simply reconfirms the initial fragment

1.5 ppm 2H multiplet indicates carbon farther away from bromine has 2 Hydrogens on it and has several neighbors

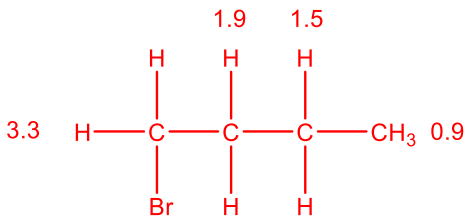


Extends the carbon chain by one linearly

0.9 ppm 3H triplet indicates terminal methyl group farthest away from bromine has 3 hydrogens and 2 neighbors



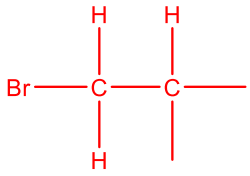
Adds the terminal methyl group to the molecule



Degree of unsaturation = 2(4) + 2 - 9 - 1 = 10 - 10 = 0, no pi bonds or rings

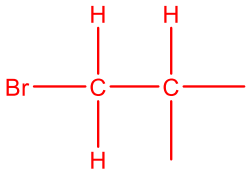
C_4H_9Br

3.2 ppm 2H doublet indicates carbon that has bromine on it has two hydrogens and has one neighbor



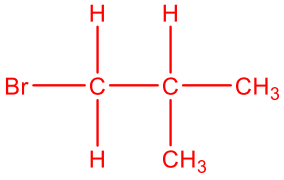
That indicates this fragment

2.0 ppm 1H multiplet indicates carbon nearest bromine has 1 hydrogen and several neighbors

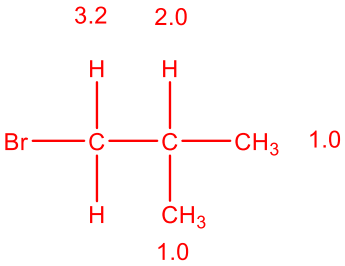


Simply reconfirms this fragment

1.0 ppm 6H doublet indicates the carbon farthest bromine have 6 hydrogens (2 methyl groups) and 1 neighbor



Adds the terminal methyl groups to the structure



This same logic can be applied to a wide variety of molecules, for example:

Determine the structure for the organic compound that has the following proton NMR with molecular formula $C_7H_{14}O$:

2.3 ppm 2H singlet

2.1 ppm 3H singlet

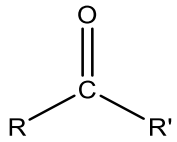
1.0 ppm 9H singlet

First we determine the degree of unsaturation, (2(7)+2-14)/2 = 1, therefore there is either one pi bond or one ring in the molecule. If there is no pi bond and there was a ring instead, then the oxygen would have to be involved in either an ether bond or an alcohol bond. Because there is no signal between 3 and 5 ppm, which is where those signals would generally reside, we can rule out that the possibility of a ring. Now that we know that there has to be a pi bond, the question is, is it a C=C bond or C=O bond. If there was a C=C bond, there would be a peak in between 3 and 5 ppm because that falls under the "everything else" category in the chart I gave you. Therefore, we know it cannot be a C=C bond, but instead is a C=O bond. Now that we know there is a carbonyl in the compound, we need to figure out what kind of carbonyl. There is only carbon, hydrogen, and one oxygen in the compound so we can rule out all carboxylic acid derivatives, therefore it can either be a ketone or aldehyde. If the carbonyl was an aldehyde, then there would be a peak at 9 ppm in the NMR, but there is not, therefore, we know it is a ketone. Now we know that the compound that we are looking at is a ketone and has the peaks that are specified above. But ketones could be symmetrical about either side, and if there is symmetry then the integration will not give the exact proton count, but simply a factor of it. We know we have 14 protons in our molecule and there are 14 protons indicated by the integration from the NMR, therefore, we know that it cannot be a symmetrical ketone, there needs to be two different carbon groups attached to either side of the ketone.

Let's summarize what we know so far:

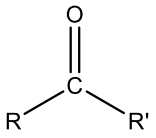
1. The molecule is a ketone
2. The molecule is an asymmetrical ketone

This gives us this as our general framework:

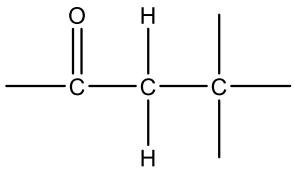


Now we have to look at each peak in turn:

$C_7H_{14}O$ 1 degree of unsaturation, ketone confirmed

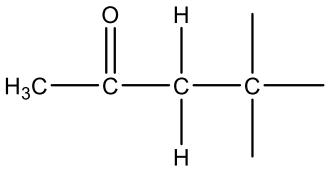


2.3 ppm 2H singlet indicates that a carbon close to the ketone has 2 hydrogens and no neighbors



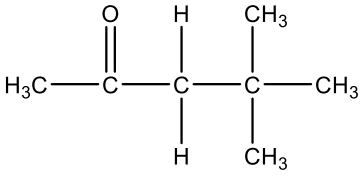
That gives this fragment

2.1 ppm 3H singlet indicates that a carbon close to the ketone has 3 hydrogens and no neighbors, has to be a terminal methyl group

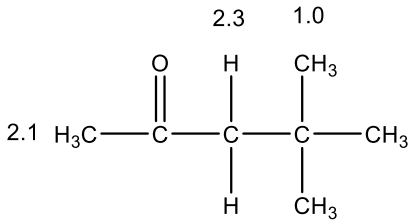


Solves one side of the asymmetrical ketone problem

1.0 ppm 9H singlet indicates that a carbon farthest away from the ketone has 9 hydrogens (probably 3 methyls) and no neighbors, have to be 3 equivalent terminal methyls



Adds the terminal methyl groups to the right side of the ketone



Now try these on your own, these will all be isomers of $C_7H_{14}O$:

1.

2.6 ppm 1H multiplet

2.4 ppm 2H triplet

1.6 ppm 2H multiplet

1.2 ppm 6H doublet

0.9 ppm 3H triplet

2.

2.9 ppm 1H multiplet

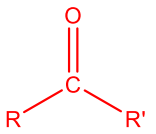
1.1 ppm 6H doublet

Answers:

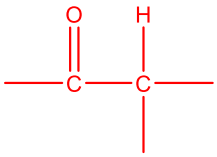
1 degree of unsaturation, ketone confirmed

1 + 2 + 2 + 6 + 3 = 14, asymmetrical ketone

$C_7H_{14}O$

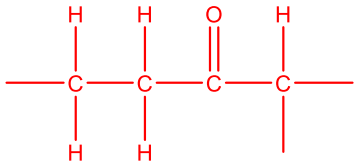


2.6 ppm 1H multiplet indicates carbon closest to ketone has 1 hydrogen and several neighbors



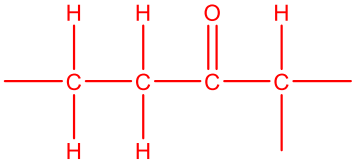
That gives this fragment

2.4 ppm 2H triplet indicates carbon closest to ketone has 2 hydrogens and 2 neighbors



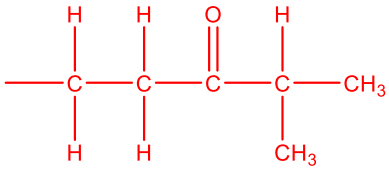
That gives this fragment

1.6 ppm 2H multiplet indicates carbon farther away from ketone has 2 hydrogens and several neighbors, forces it to be on LHS of ketone



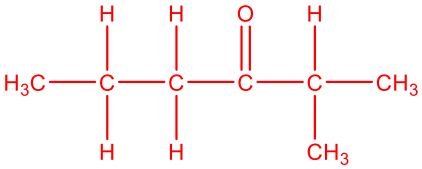
This just confirms the previous fragment

1.2 ppm 6H doublet indicates carbon even farther away from ketone has 6 protons on it (likely two equivalent methyl groups) and have one neighbor, has to be on the RHS of the ketone



Completes the RHS of the ketone by putting terminal methyls

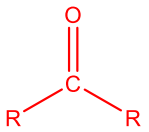
0.9 ppm 3H triplet indicates carbon even farther away from ketone has 3 hydrogens on it (likely terminal methyl) and has two neighbors, has to be on LHS of the ketone



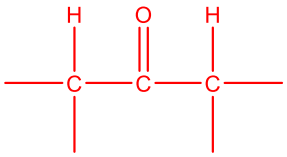
1 degree of unsaturation, ketone confirmed

1 + 6 = 7, symmetrical ketone

$C_7H_{14}O$

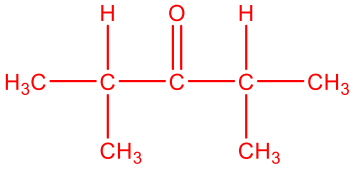


2.9 ppm 1H multiplet signal indicates that the carbons closest to the ketone have one hydrogen each and several neighbors

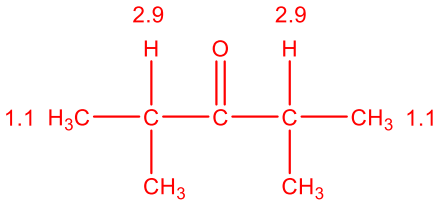


That indicates this fragment

1.1 ppm 6H doublet signal indicates the carbons farthest away from the ketone have 6 hydrogens each and one neighbor. This indicates there are two equivalent methyls on either side.



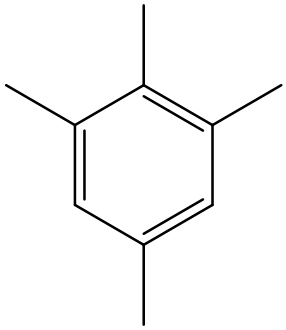
Completes both sides of ketone by putting terminal methyls on the blank bonds.

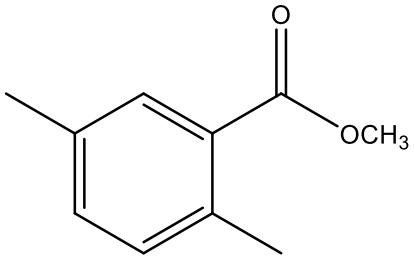


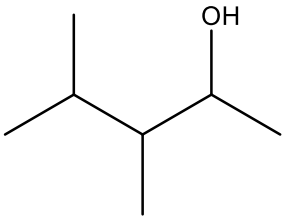
Now that we have the fundamentals of proton NMR down, we can start to discuss carbon NMR. The way we get the number of carbon peaks is exactly the same as the way we get our proton peaks, just count all of the unique carbons in the same way as we were doing protons and you can get your answer. The number of carbon signals will always be either the same or very close to the number of proton signals in any given organic molecule. Carbon NMR gives less information than proton NMR because unlike in proton NMR, there is no splitting. However, the height of the peak in carbon NMR generally tells you how many protons and how many carbons are from that signal, the higher the peak the more carbons it is associated with.

Practice questions:

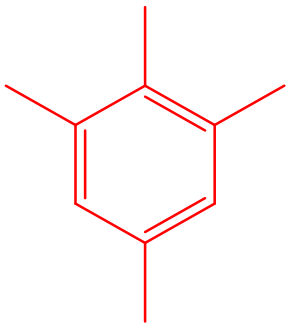
Give the number of proton and carbon signals for the following molecules:



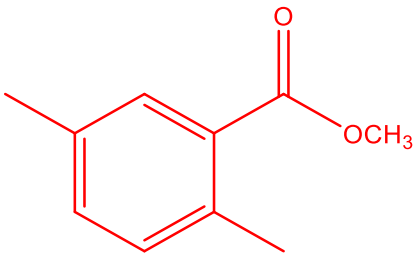




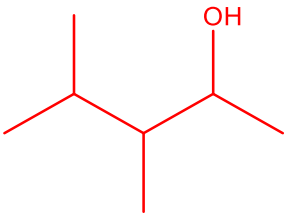
Answers:



Carbon peaks: 7
Proton peaks: 4



Carbon peaks: 10
Proton peaks: 6



Carbon peaks: 6
Proton peaks: 7

While carbon NMR may not be useful on its own, it is useful when coupled with proton NMR. These two pieces of information together provides organic chemists with powerful structural elucidation tools to determine the structure of organic molecules. Generally speaking, the carbon NMR is most useful for determining the types of carbon bonds you have in the molecule, like if you have alkenes or carbonyls, the majority of the structural information will still come from the proton NMR. For practice, we will look at an example using carbon NMR to determine the structure of an organic molecule using just the chemical shift values.

Try to determine the structure of the $C_4H_{10}O$ using the following C NMR data:

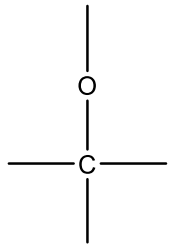
70 ppm, 30 ppm, 19 ppm signals, 19 is twice as large as 70 ppm, 30 ppm slightly lower than 70 ppm.

There are only three peaks here, meaning one of the peaks corresponds to equivalent carbons. Because 19 is twice as large as 70, that indicates that the peak coming from 19 are two equivalent carbons. Like always, we start by determining the degrees of unsaturation, in this compound it is 0, meaning that the O must be involved in either an alcohol or ether linkages. To

determine what it is, we will use the carbon NMR peaks to determine the structure of the compound.

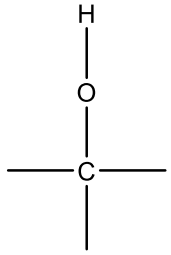
0 degrees of unsaturation, could have alcohol or ether

$C_4H_{10}O$



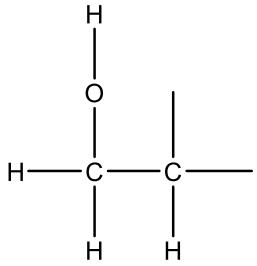
fragment we have so far

Only one peak at 70 ppm, indicating that no other carbon is attached to the electronegative oxygen atom. Therefore the oxygen acts as an alcohol here.



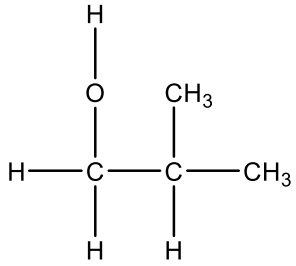
That gives us this fragment

The peak at 30 ppm has slightly lower peak than the one at 70, therefore, it has less protons and has to be attached to the 70 ppm carbon.



That gives us this fragment

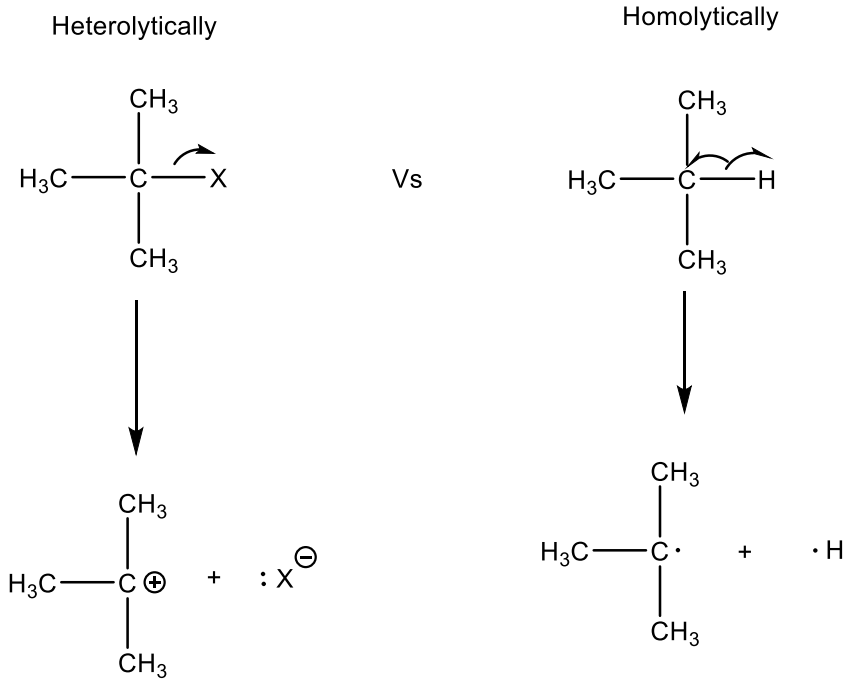
The peak at 19 ppm is taller than all the other peaks and is a bit larger than twice the size of the 70 ppm peak, therefore, the two blank bonds must be terminal CH_3 groups



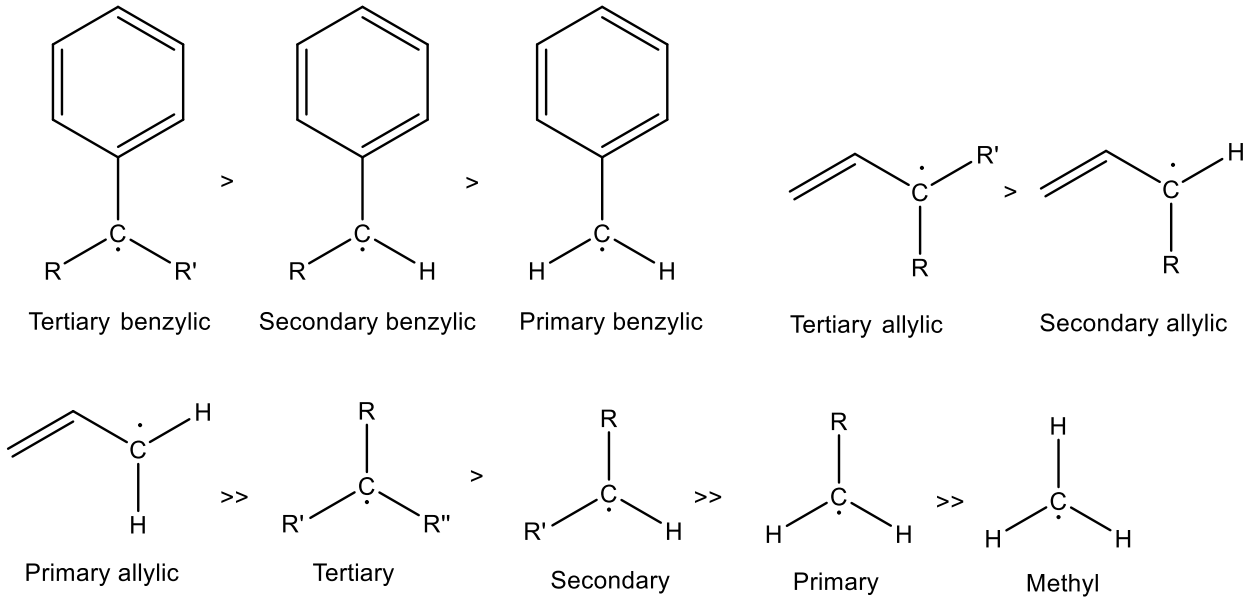
That gives us this fragment

Chapter 17: Radicals

This is the last chapter of the textbook where we will do any reactions ☹. In this chapter, we deal with the reactions of alkanes. Alkanes are mostly inert, which is the reason why we haven't been really dealing with them during this entire course. The only way that alkanes can react is through radicals, specifically, by breaking C-H bonds to make radical species. Throughout this entire course, we have been breaking bonds heterolytically, meaning that when you break a bond, both electrons go onto one atom, but in radical reactions, the bonds break homolytically:



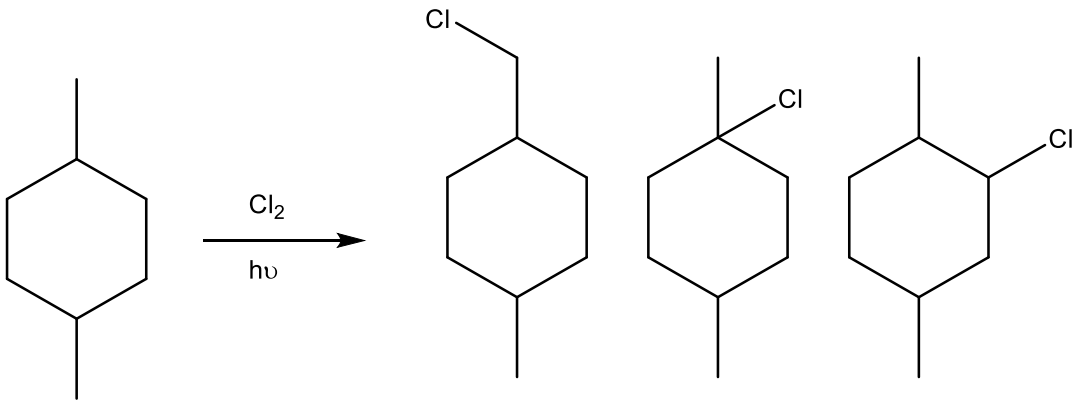
Luckily for you, radicals react very similarly to carbocations, they can rearrange through resonance if they are allylic, and the trends of stability are the exact same.



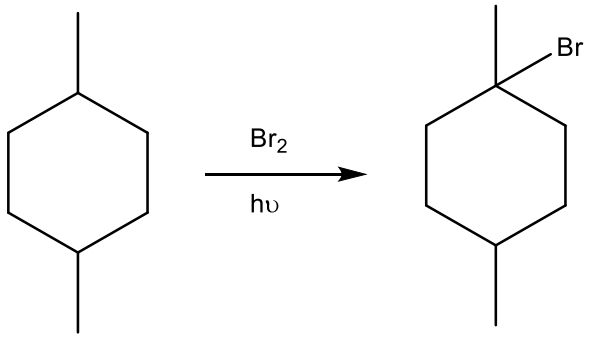
Benzylic and allylic radicals are around the same stability

First we will start by discussing the most common reaction for alkanes, halogenation. This reaction comes in two flavors, Cl_2 and Br_2. Of the two halogenation reactions Br_2 is way more selective and will add to the carbon that forms the most stable radical, Cl_2 is promiscuous and will add to whichever carbon has the highest probability to attack. The reason for this preference is because of electronegativity, Br is less electronegative than Cl, therefore, it is not as reactive as a radical and is more picky with who it wants to bond with. The Cl on the other hand, is super eager to attack anything to get its octet, so it will attack anything it comes into contact with. Ultimately, the driving force is to minimize energy, the question is, which factor plays a larger role for each, for Cl it is to become octet satisfied and for Br it is to form the more stable radical (A**M**SOW). An example of a halogenation reaction is shown below, followed by a mechanism. For all of these reactions, there are three things that cause radicals to form:

1. Heat
2. UV light often denoted as hν
3. Peroxides

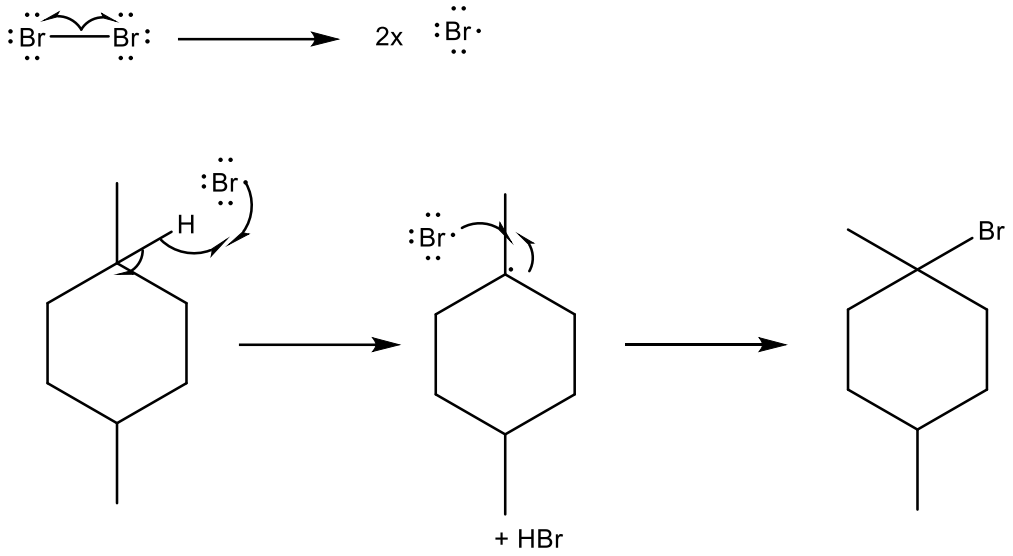


Major product because there are 4 possible secondary radicals that can form as opposed to 2 of the others



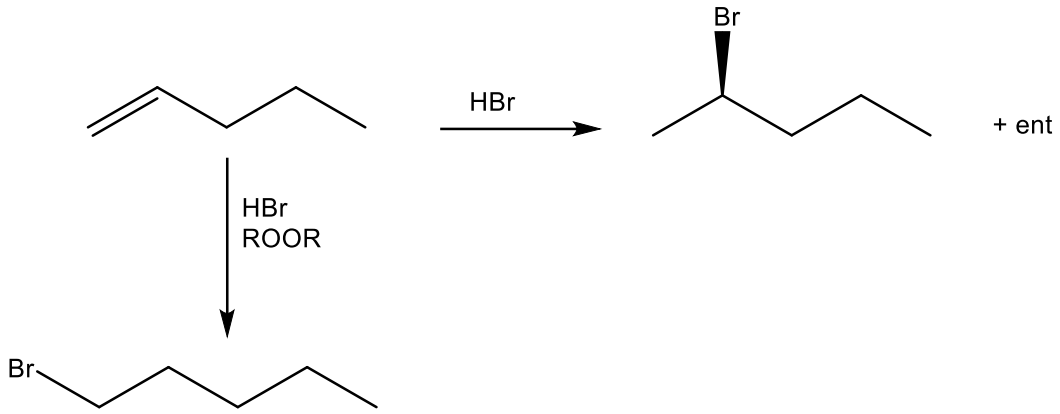
Only product because Br is selective for the tertiary radical

Because the mechanism for both halogenations are the same, we will discuss only the bromination case because that is the one that is most often used.

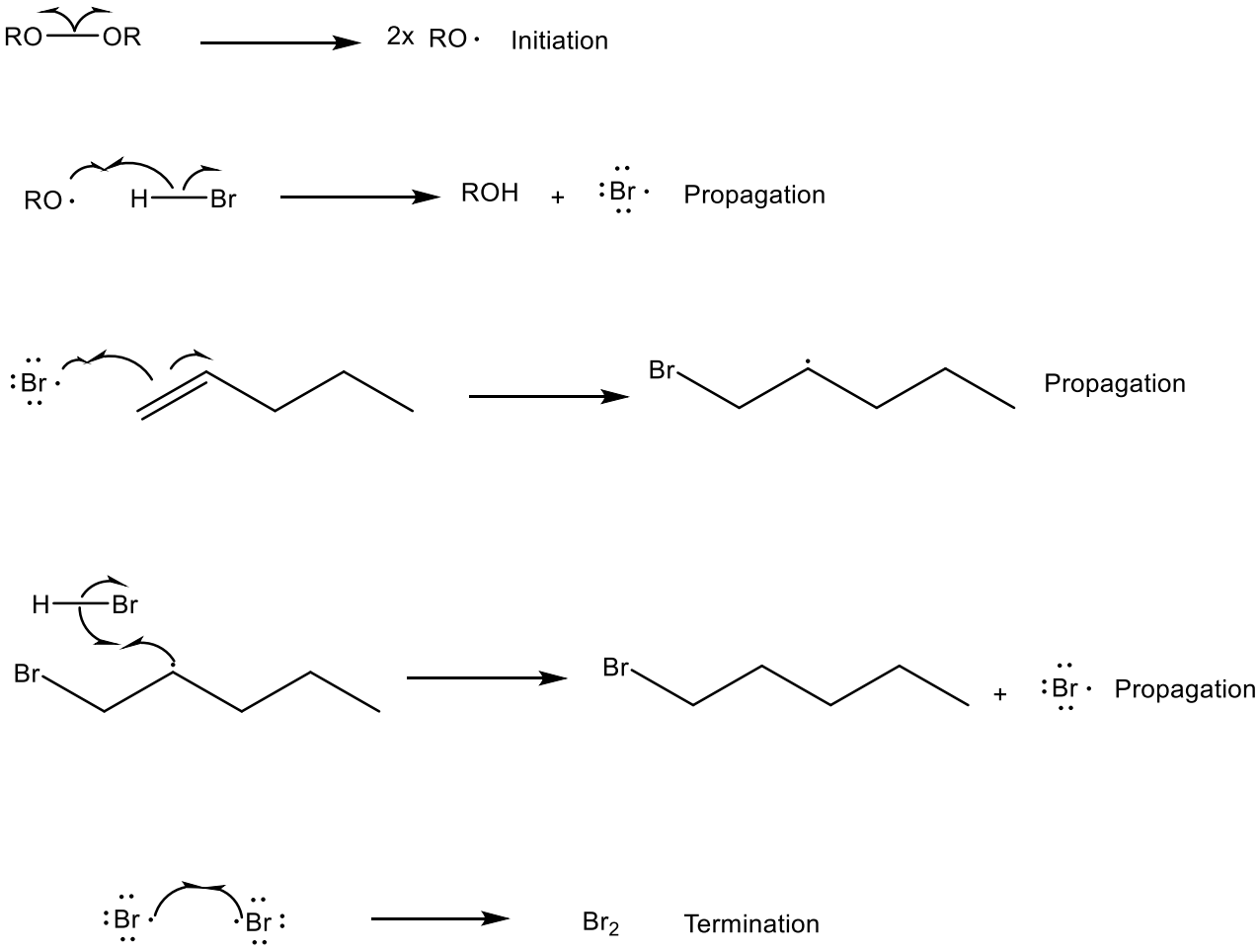


The first step is the formation of the bromine radical. This is facilitated by the energy given by the UV light or heat, recall that the Br-Br bond is extremely weak, so it does not take that much energy to cleave the bond homolytically (AMSO**W**). After this bromine radical forms, the C-H bond of the alkane gets broken homolytically and adds to one of the bromine radicals, creating a tertiary carbon radical. Breaking the C-H bond homolytically is less favorable than the Br-Br bond because C-H bonds are strong. Once the tertiary carbon radical is made, the second bromine radical can now combine with it. Remember, two electrons are required to form a bond, so one electron comes from the bromine radical and the other comes from the tertiary carbon radical, that is what forms the sigma bond between the Br and C to form the product. Now as you may have astutely pointed out, what happened to the other bromine radical and the hydrogen radical that we broke off to do this reaction? Both of those could combine together to form HBr, or they can react with other carbon radicals or they can form more radicals. THIS IS THE REASON WHY UV LIGHT IS SO DANGEROUS, IT CAUSES RADICALS THAT CAN QUICKLY CAUSE A RUNAWAY REACTION TO OCCUR. This is super dangerous and can cause such things as alkylation of DNA among other things that can have drastic effects on the cellular environment.

In addition to reacting with alkanes, radicals can also react with alkenes to give products that initially are quite unusual. For instance, if you want to add a bromine to the least substituted alkene carbon, that would be impossible with just HBr, but it is possible with HBr and peroxides (ROOR):



The mechanism for this reaction is as follows:



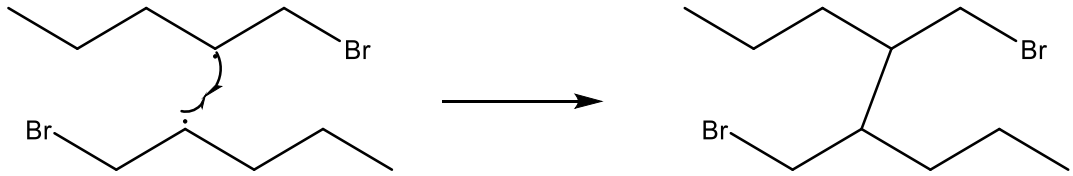
This brings us to the three phases of a radical reaction, the initiation step, the propagation step, and the termination step:

In the initiation step, two radicals are made from a nonradical

In the propagation step, one radical is made from a nonradical

In the termination step, a nonradical is made from two radicals

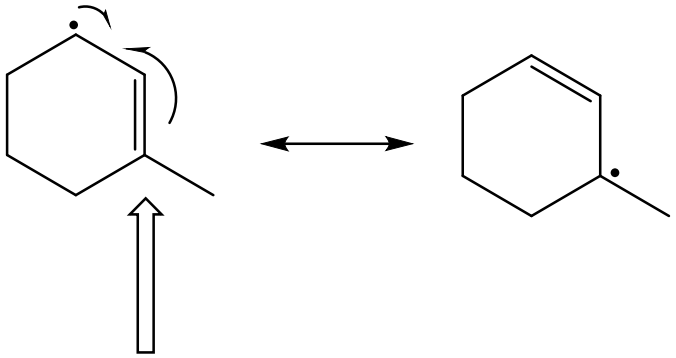
All of these are happening *at the same time*, this is the reason why these reactions are dangerous and not super great, they can cause unexpected products, the reaction that was just shown, you could also combine two carbon radicals together like so:



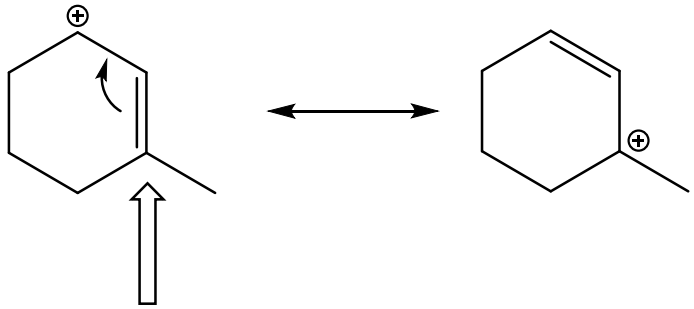
Therefore, it is generally ill advised to do these reactions to get a high-yielding synthesis, because you can get all of these side products that are hard to get out and hard to know what they are to begin with.

Just like with carbocations, radicals will form racemic mixture of products depending upon the orientation of the radical that attacks it. You will have an equal amount of R and S enantiomers when you do halogenation and create a chiral center. Also like carbocations, allylic radicals will have resonance forms that play a large role in predicting their major products. These resonance forms are done almost the same way, except we are in Bizarro world so we use half arrows for everything, which represents the transfer of one electron as opposed to two like before. An example of a resonance form for an allylic radical is shown below:

Side by side comparison between radicals and carbocation rearrangements

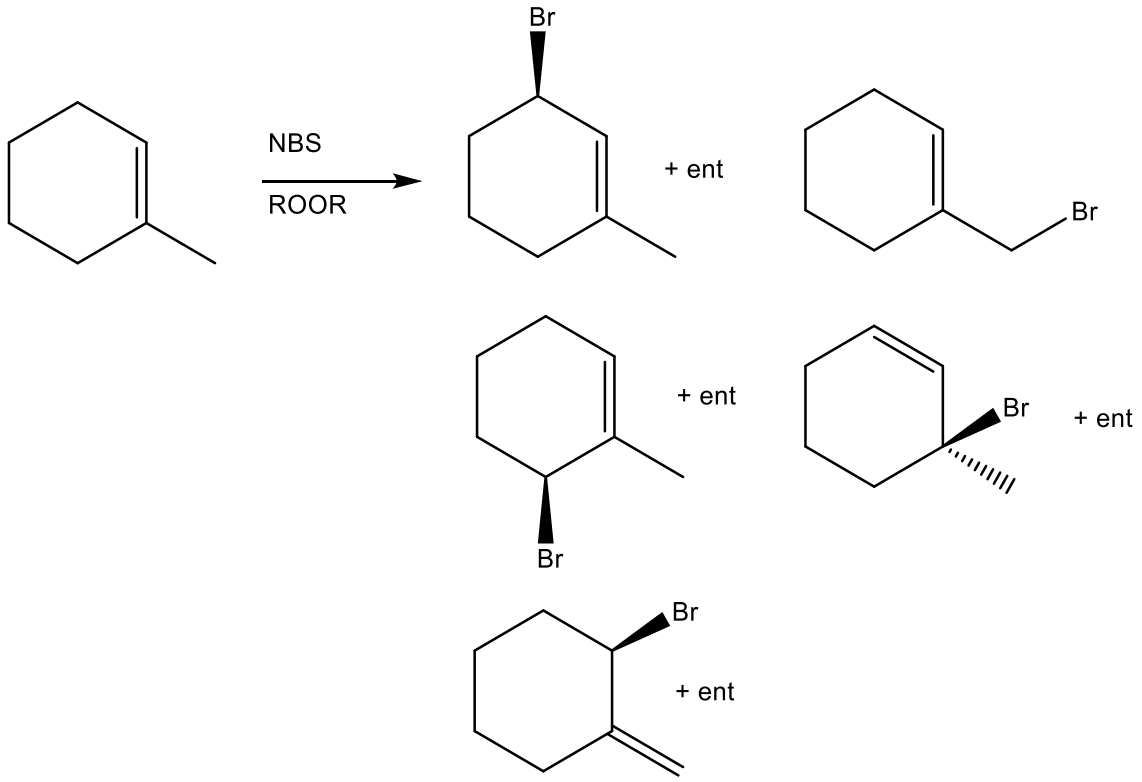


This carbon lost a single electron
when the pi bond moved

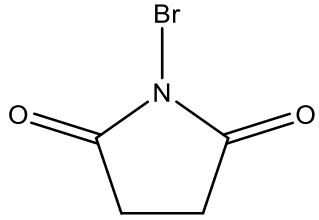


This carbon lost two electrons
when pi bond moved

When you have allylic systems like this, typically a specialty reagent is used to prevent side reactions occurring, this specialty reagent is called NBS. The reaction is shown below:



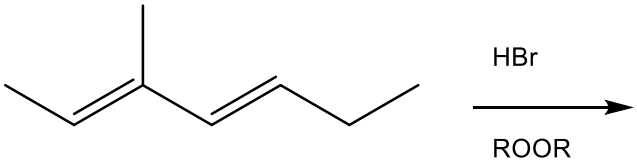
The NBS alongside peroxides makes it so that all allylic positions become radicals and therefore all allylic positions and their respective resonance forms must be evaluated. See if you can determine how all of those products were made. The reaction mechanism for this is practically the same as all the others, you can view the NBS molecule as a bromine radical source, the structure for NBS is shown below, it has a weak N-Br bond that will break homolytically to give the bromine radical.

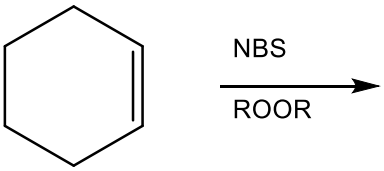


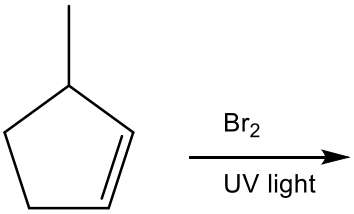
Unfortunately, this is the end of the road, this is the last reaction that I will teach in this book. Don't cry, I know this is very emotional.

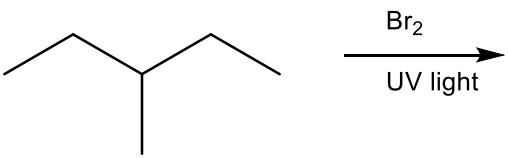
Practice problems:

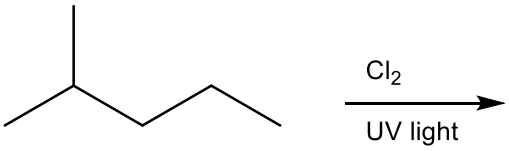
Predict the major products for the following reactions, be sure to include stereochemistry in your products where applicable:

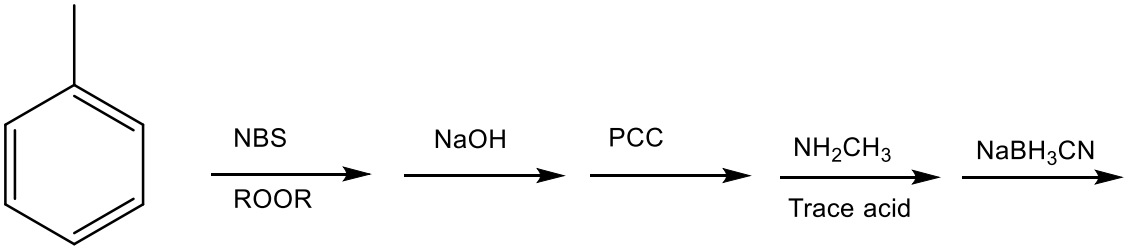

HBr
ROOR


NBS
ROOR

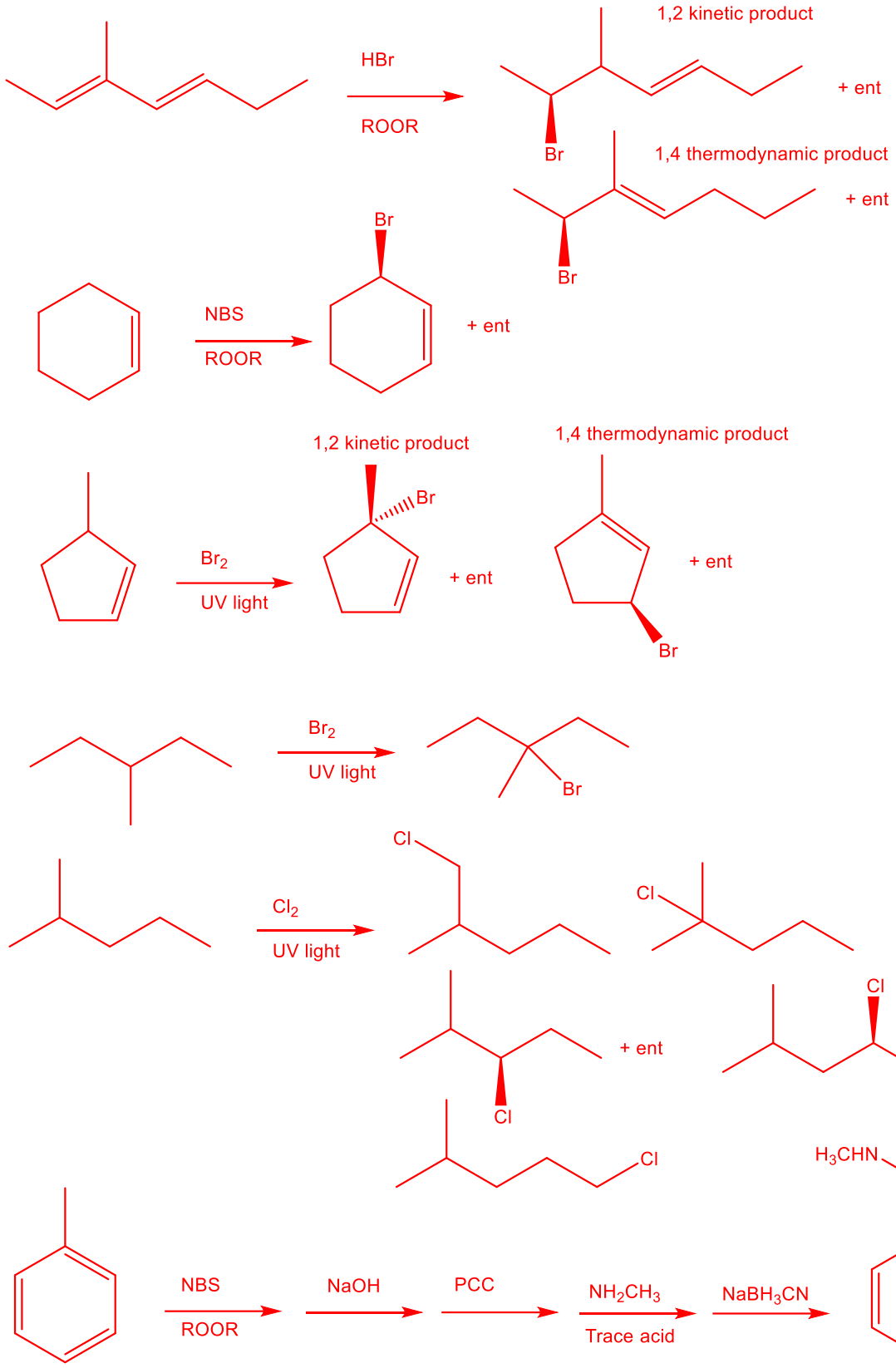

Br2
UV light


Br2
UV light


Cl2
UV light


NBS
ROOR
NaOH
PCC
NH2CH3
Trace acid
NaBH3CN

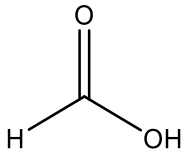
Answers:


HBr
ROOR
1,2 kinetic product
+ ent
Br
1,4 thermodynamic product
+ ent
Br
NBS
ROOR
Br
+ ent
1,2 kinetic product
1,4 thermodynamic product
Br2
UV light
Br
+ ent
+ ent
Br
Br2
UV light
Br
Cl2
UV light
Cl
Cl
+ ent
Cl
+ ent
Cl
Cl
NBS
ROOR
NaOH
PCC
NH2CH3
Trace acid
NaBH3CN
H3CHN

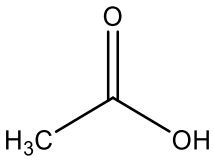
Chapter 18: Advanced Nomenclature (Carbonyls and beyond)

So far, we have discussed the nomenclature of alkanes, alkenes, alkynes, ethers, amines, and alcohols. In this chapter, we will discuss the nomenclature of carbonyls, aromatic compounds, and nitriles. The fundamental rules of nomenclature still apply, so don't panic, you will still number with the longest chain with the most amount of groups off the chain and give the highest priority group the lowest number possible, there are just more groups now to learn.

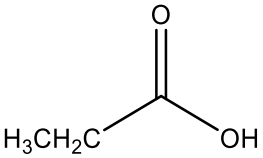
Let's start by discussing carboxylic acid derivatives, acyl chlorides, anhydrides, carboxylic acids, esters, and amides. When naming carboxylic acid chains, the ending is given by replacing the –ane with an –anoic ending. For example:



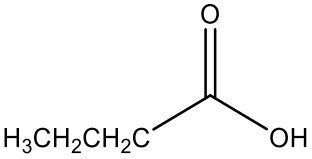
Methanoic acid



Ethanoic acid



Propanoic acid

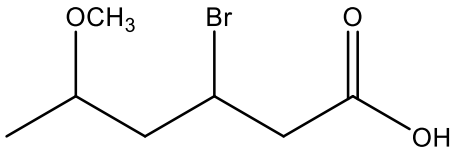


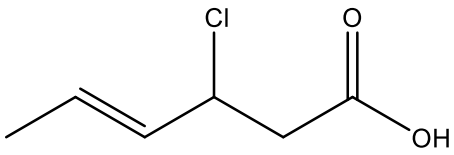
Butanoic acid

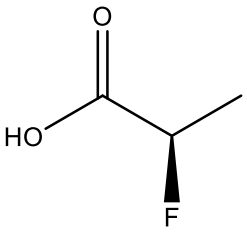
The carbonyl carbon is always counted for IUPAC nomenclature, that is why methanoic acid has only one carbon, ethanoic has two, etc. Just like before, we always give the carboxylic acid group the lowest number and we start counting from the carbonyl carbon of the carboxylic acid group.

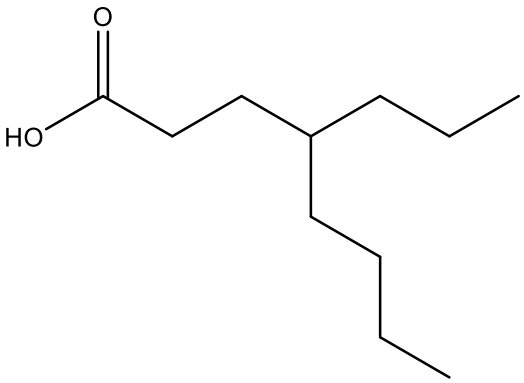
Practice problems:

Name the following organic compounds according to IUPAC nomenclature rules

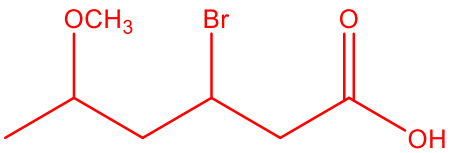




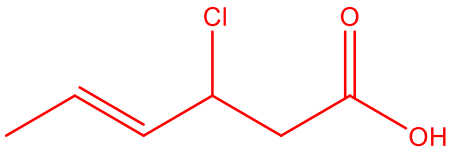




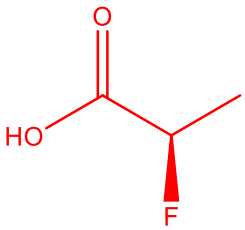
Answers:



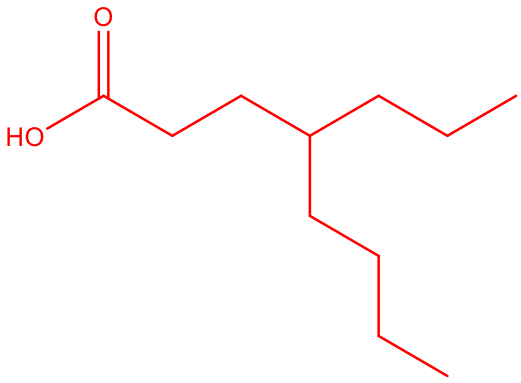
3-bromo-5-methoxyhexanoic acid



(4E) 3-chlorohex-4-enoic acid

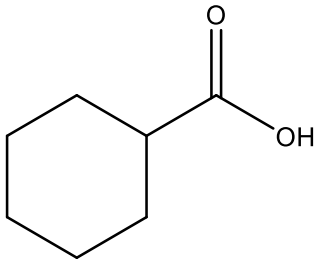


(2R) 2-fluoropropanoic acid

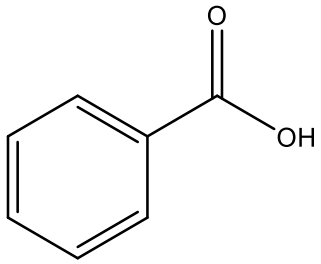


4-propyloctanoic acid

If the carboxylic acid group is on a ring, simply put the name of the ring and add “carboxylic acid” at the end of the name like so:



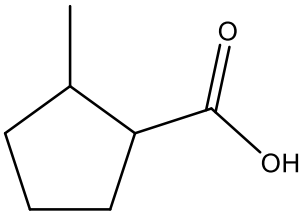
Cyclohexanecarboxylic acid

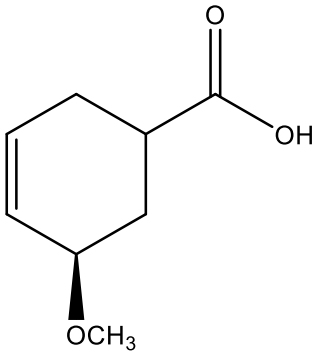


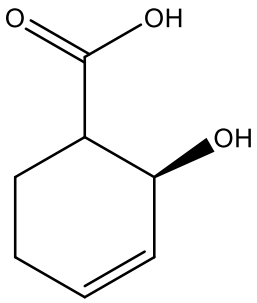
Benzenecarboxylic acid

Practice questions:

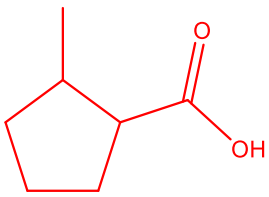
Name the following organic compounds according to IUPAC nomenclature rules



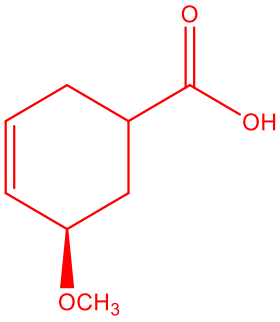




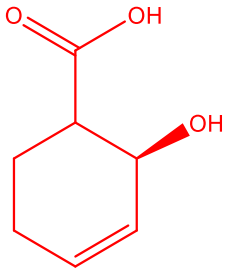
Answers:



2-methylcyclopentane-1-carboxylic acid



(5R) 5-methoxycyclohex-3-ene-1-carboxylic acid

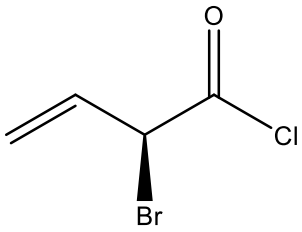


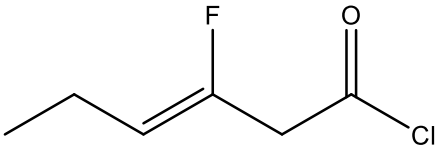
(2S) cyclohex-3-en-2-ol-1-carboxylic acid

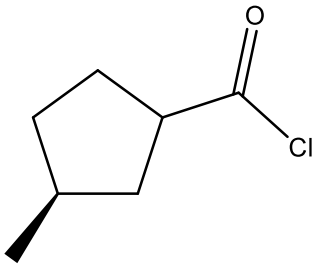
The rules to name acyl chlorides are the exact same, except the ending is now “carbonyl chloride” as opposed to carboxylic acid for cyclic compounds and –yl chloride not –oic acid for linear compounds.

Practice questions:

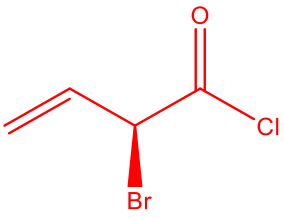
Name the following organic compounds according to IUPAC nomenclature rules



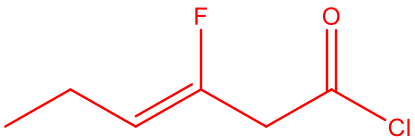




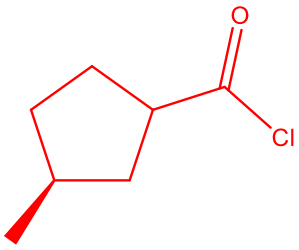
Answers:



(2S)-2-bromobut-3-enoylchloride

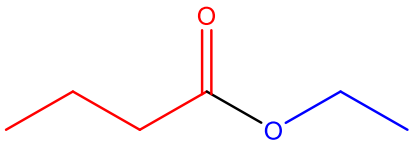


(3Z)-3-fluorohex-3-enoylchloride

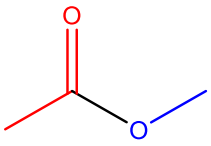


(3S)-3-methylcyclopentane-1-carbonyl chloride

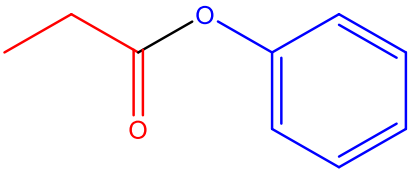
The nomenclature of esters is slightly different than that of carboxylic acids and acyl chlorides. To name esters, the group on the ester oxygen is named first followed by the other side of the carbonyl named the same as carboxylic acids except replace the ending with –oate as opposed to –oic acid. An example is shown below:



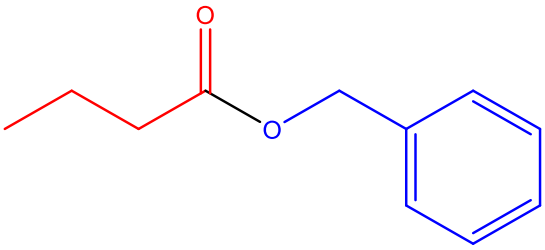
Ethyl butanoate



Methyl ethanoate



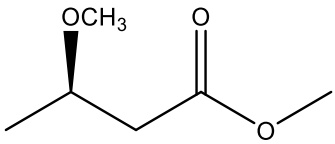
Phenyl propanoate

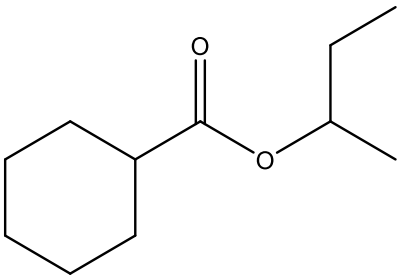


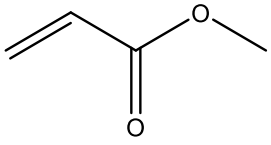
Benzyl butanoate

Practice questions:

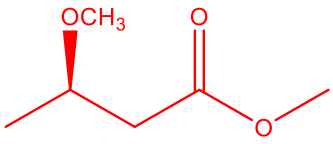
Name the following organic compounds according to IUPAC nomenclature rules



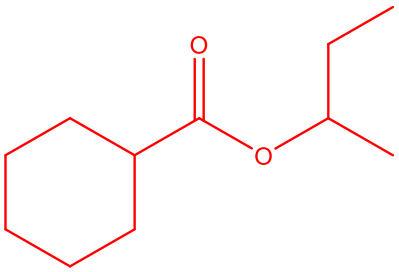




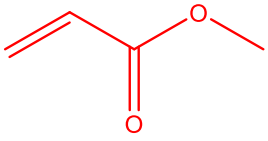
Answers:



Methyl (3R)-3-methoxybutanoate

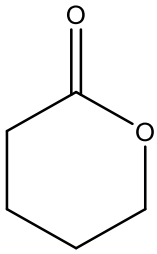


2-butylcyclohexanoate

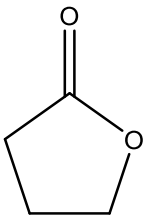


Methyl 2-propenoate

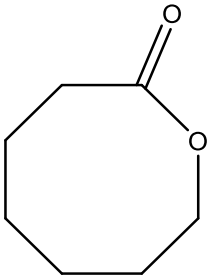
There are also cyclic esters. These compounds are called lactones and the numbering scheme starts with the carbonyl carbon moving towards the ester oxygen in that direction. The ending of lactones is –anone. An example is shown below:



2-oxacyclohexanone



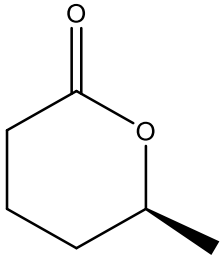
2-oxacyclopentanone

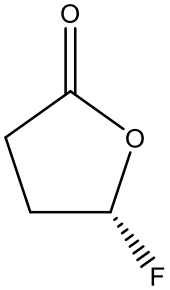


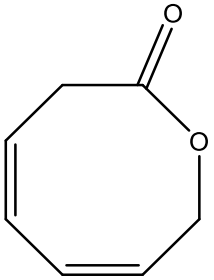
2-oxacyclooctanone

Practice questions:

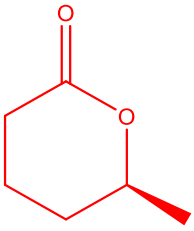
Name the following organic compounds according to IUPAC nomenclature rules



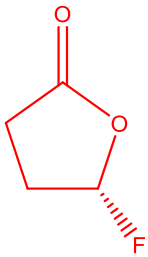




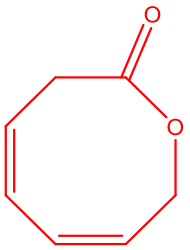
Answers:



(3S) 3-methyl-2-oxacyclohexananone

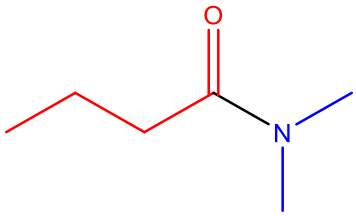


(3R) 3-fluoro-2-oxacyclopentanone

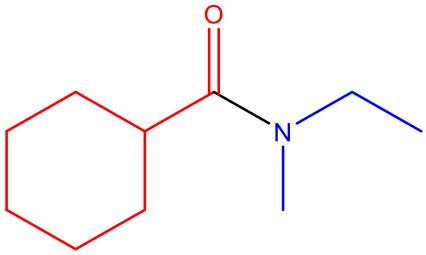


(4Z,6Z) 2-oxacycloocta-4,6-dienone

Amides are named similarly to esters, if there is any carbon group bonded to the nitrogen of the amide, those groups are named first, followed by the rest of the chain ending with –amide if the chain is linear. If the amide group is bonded to a ring, the ending is changed to carboxamide. Examples are shown below:



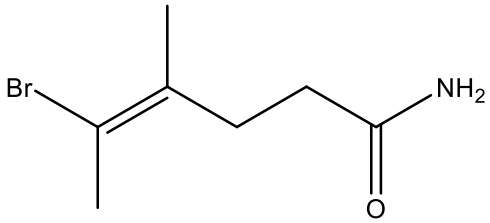
N,N-dimethylbutanamide

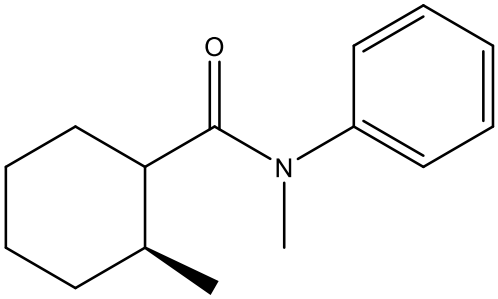


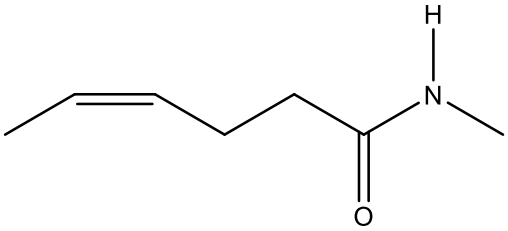
N-ethyl-N-methylcyclohexane-1-carboxamide

Practice questions:

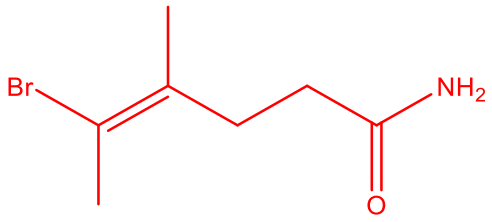
Name the following organic compounds according to IUPAC nomenclature:



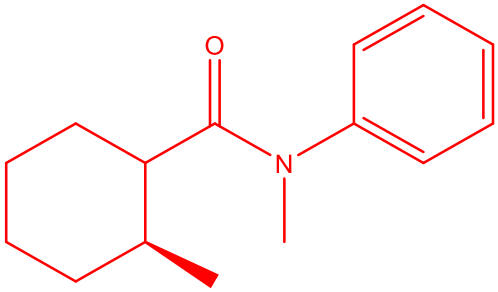




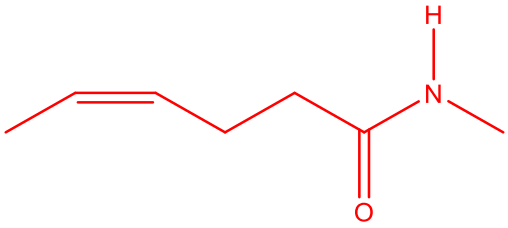
Answers:



(4E) 5-bromo-4-methylhex-4-enamide

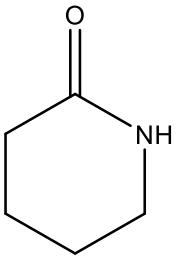


(2S)-N,2-dimethyl-N-phenylcyclohexane-1-carboxamide

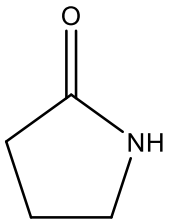


(4Z) N-methylhex-4-enamide

Just like esters, there are also cyclic amides. These compounds are called lactams. The naming convention for lactams is almost the exact same as lactones, except instead of using the –oxa to indicate the ester oxygen, you use the –aza to indicate the amide nitrogen. Examples are shown below:



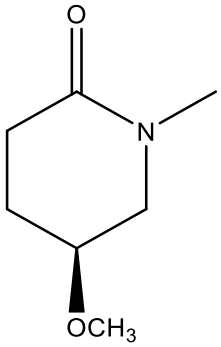
2-azacyclohexanone

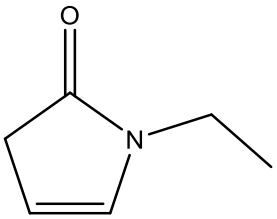


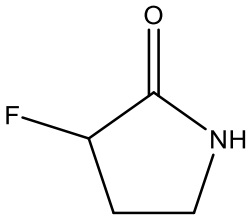
2-azacyclopentanone

Practice questions:

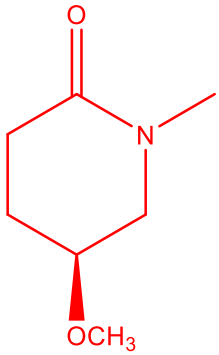
Name the following organic compounds according to IUPAC nomenclature rules:



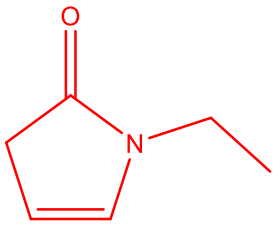




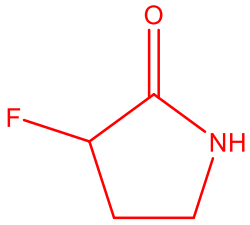
Answers:



(4S) N-methyl-2-aza-4-methoxycyclohexanone

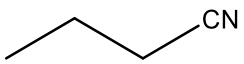


N-ethyl-2-aza-cyclopent-3-enone

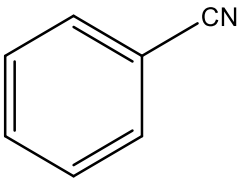


2-aza-5-fluorocyclopentanone

Taking a break from carboxylic acid derivatives for a second, we will turn our attention to the nomenclature of nitriles. To name a nitrile, simply put the alkyl chain with -nitrile as the ending, if the nitrile is on a ring, then the ending is changed to –carbonitrile for example:



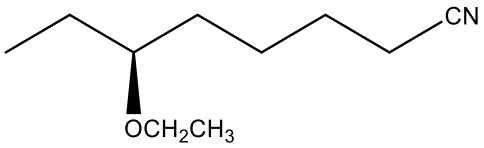
butanenitrile

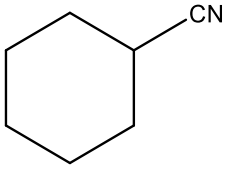


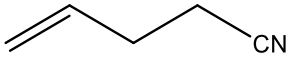
benzenecarbonitrile

Practice questions:

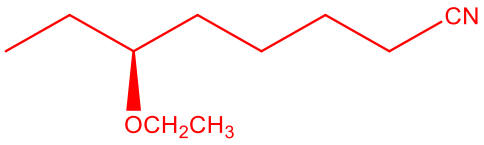
Name the following compounds according to IUPAC nomenclature rules:



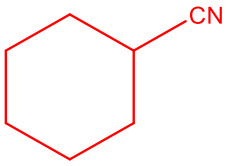




Answers:



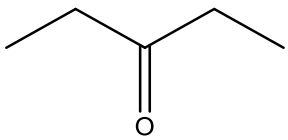
(6S) 6-ethoxyoctanenitrile



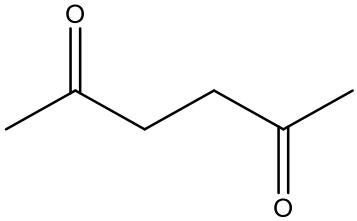
cyclohexanecarbonitrile

pent-4-en-nitrile

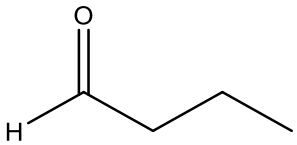
The nomenclature of aldehydes and ketones are relatively simple, they follow the same rules. For aldehydes, the compound will end with –al and for ketones, the compound will end with –one. Just like the other carbonyl compounds, the carbonyl carbon is assumed to be the lowest number possible and the carbon count includes it, an example is shown below:



3-pentanone



2,5-hexadione

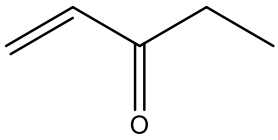


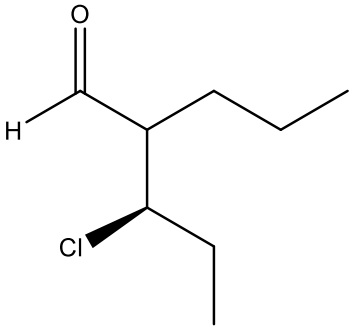
butanal

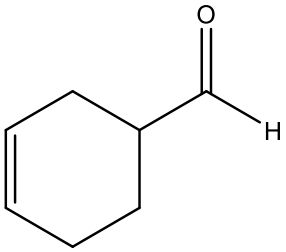
When aldehydes are attached to rings, the ending changes to –carbaldehyde.

Practice questions:

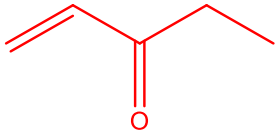
Name the following compounds according to IUPAC nomenclature:



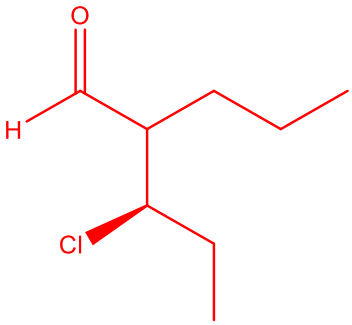




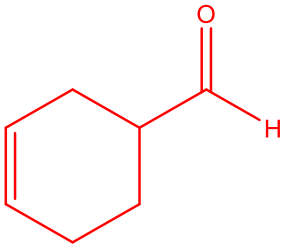
Answers:



Pent-1-en-3-one



(3R) 3-chloro-2-propylpentanal



Cyclohex-3-ene-1-carbaldehyde

We have gone through this entire nomenclature section without discussing the priority of each group. Generally speaking, the more oxidized the group is, the higher priority it holds, the following are the priorities for each group that we have discussed so far (courtesy of my friend, Kameron Farhadi) remember when the group is not the highest priority group then it must be referred to by its substituent name:

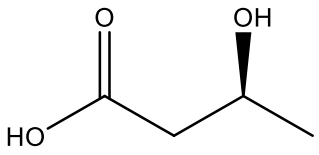
Functional group	Suffix ending	Group name
Carboxylic acid	-oic acid	Carboxy
Ester	-oate	Alkoxycarbonyl
Amide	-amide	Amido
Nitrile	-nitrile	Cyano
Aldehyde	-al	Oxo (C=O), Formyl (HC=O)
Ketone	-one	Oxo (C=O)
Alcohol	-ol	Hydroxy
Amine	-amine	Amino
Alkene	-ene	-en
Alkyne	-yne	-yn
Alkane	-ane	-yl

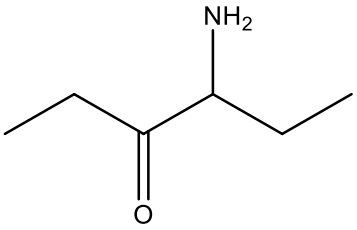
Ether	N/A	-oxy
Alkyl halide	N/A	-oro

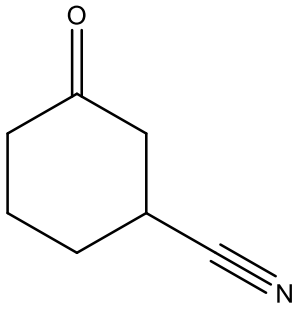
Let’s practice naming more complex compounds that contain several priority groups in one molecule.

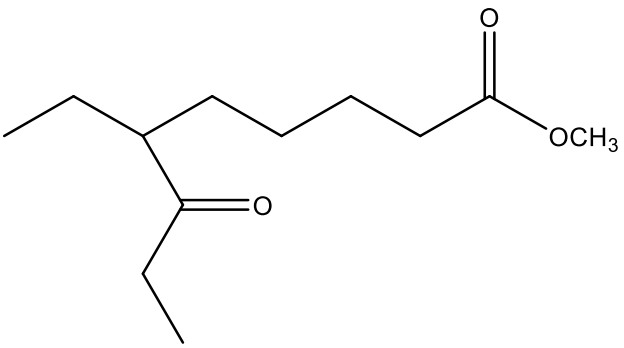
Practice questions:

Name the following organic compounds according to IUPAC nomenclature:

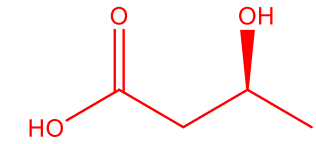




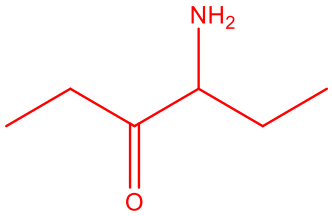




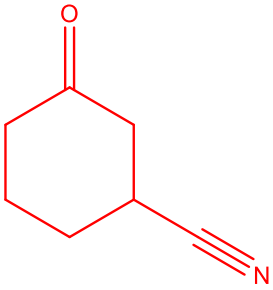
Answers:



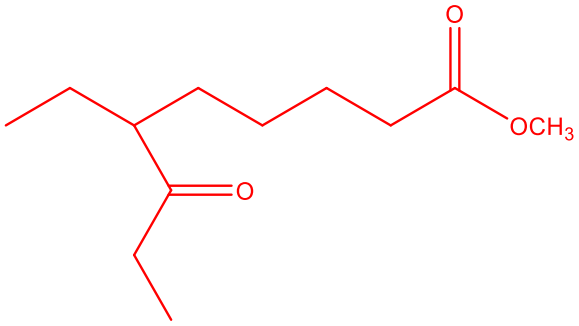
(3S) 3-hydroxybutanoic acid



4-aminohexan-3-one

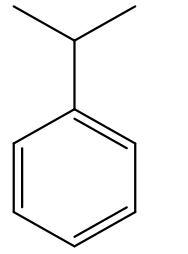


3-oxocyclohexane-1-carbonitrile

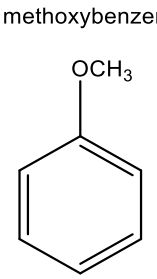


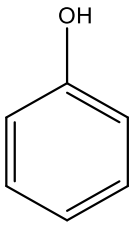
methyl-6-ethyl-7-oxonanoate

Now we will discuss the nomenclature of benzene and benzene derivatives. For monosubstituted benzenes, the benzene is named with the group that is attached to it, if it is an alkyl group, the alkyl group is given first followed by benzene if there is name for it, if there is not a common name for it then the benzene ring is listed as a phenyl substituent, for example:

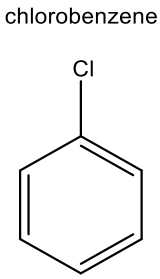


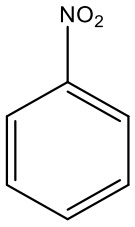
isopropylbenzene



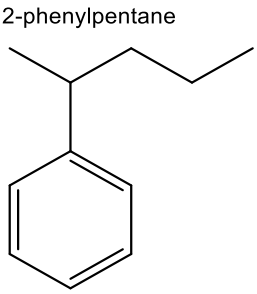


hydroxybenzene

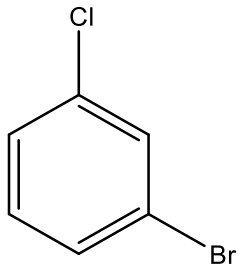




nitrobenzene

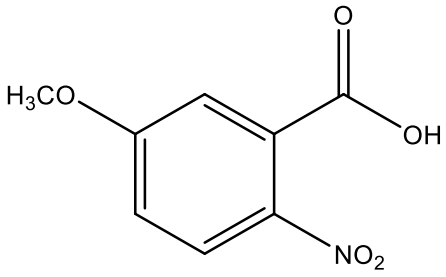


If the ring has more than one substituent on it and none of them are priority groups, then the compound is named such that the group listed first has the lowest number, for example:



1-bromo-3-chlorobenzene

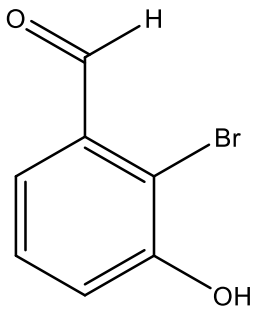
If the group on the ring has higher priority than the other groups, then they are listed such that the highest priority group is on the one carbon and the groups after that are listed to give the lowest overall numbering scheme, for example:

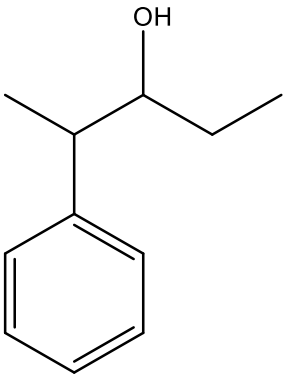


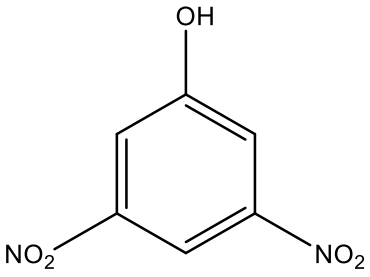
2-nitro-5-methoxybenzoic acid

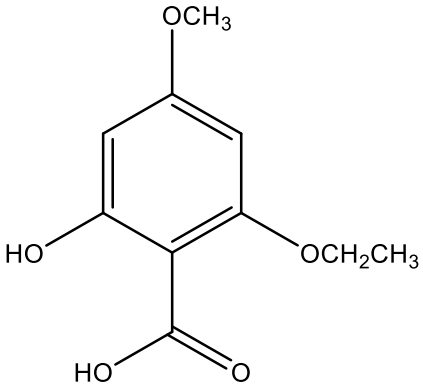
Practice questions:

Name the following organic compounds according to IUPAC nomenclature rules

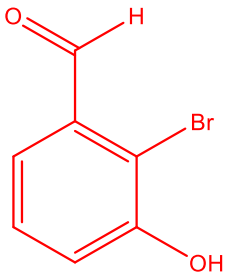






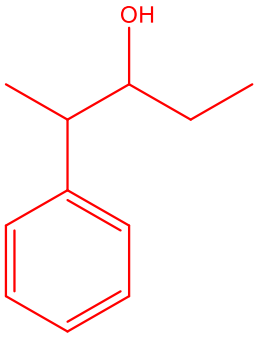


Answers:

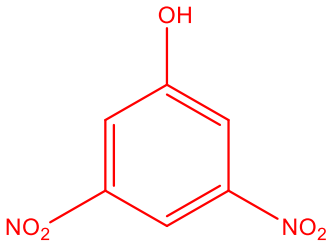


2-bromo-3-hydroxybenzaldehyde

or 2-bromo-3-hydroxybenzenecarbaldehyde

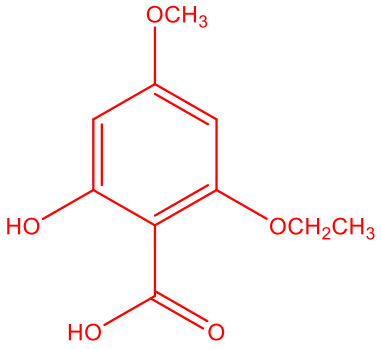


2-phenyl-pentan-3-ol



3,5-dinitrohydroxybenzene

or 3,5-dinitrophenol

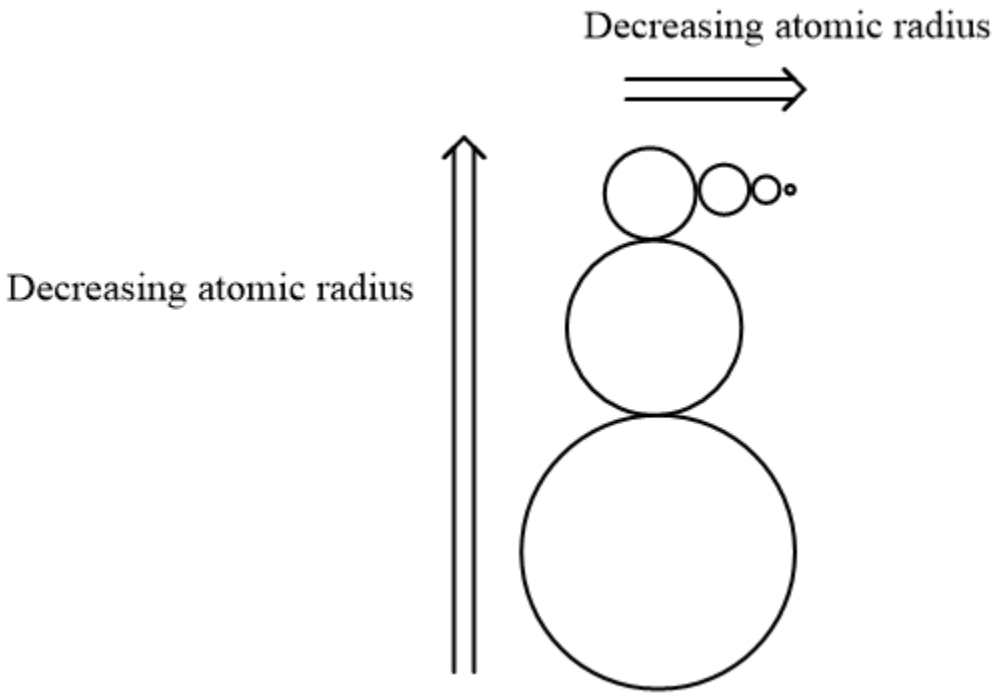


2-ethoxy-6-hydroxy-4-methoxybenzoic acid

Chapter 19: A Bunch of Helpful Guidelines and Cheat Sheets

I know this textbook is long, in fact this is probably the longest thing I have ever written so far (that will likely change when I do my PhD thesis, but that is neither here nor there). Because it is so longer, I am going to consolidate all of the helpful diagrams that I have put in this textbook into one place for easy reference. These are NOT new, these are all diagrams from previous chapters that I feel are useful.

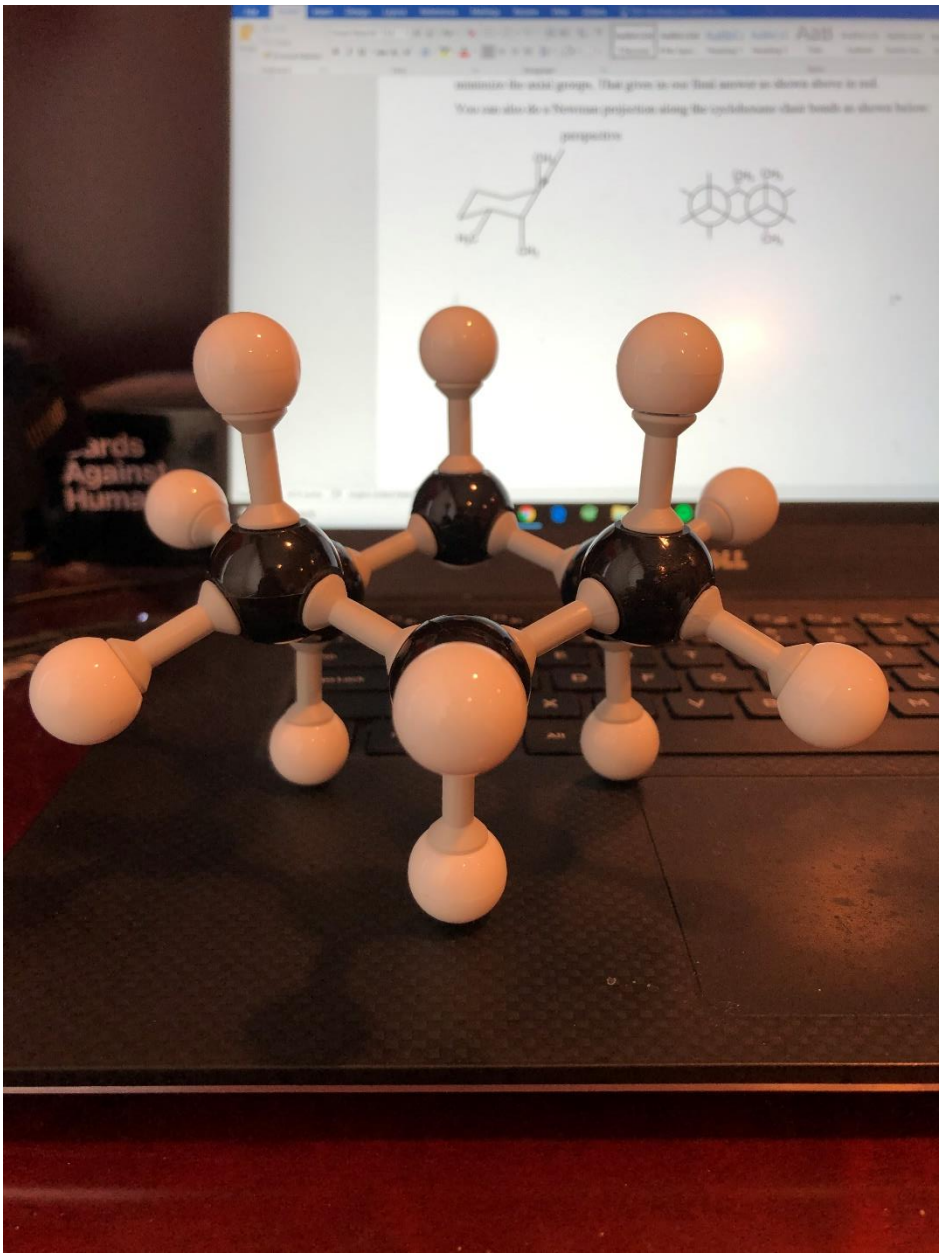
Atomic radius:



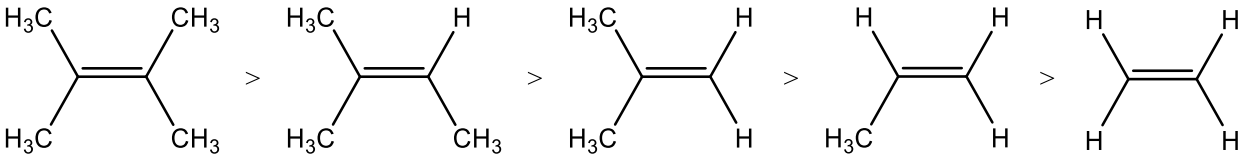
Bonding preferences:

Li	Be	B	C	N	O	F
1	2	3	4	3	2	1

Cyclohexane Newman Perspective:



Alkene stability trends:



Effects of EWG and EDG on acidity

Guide to Electronic Effects on pKa

Electron-Withdrawing Groups:
Increase Acidity
Typically have double bonds in conjugation with the ring

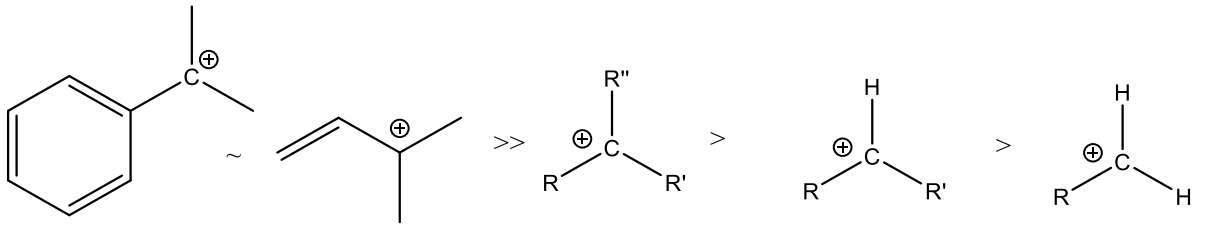
In order of decreasing strength:
NO2
SO3H
Carbonyls
Nitriles
F
Cl
Br

Electron-Donating Groups:
Decrease Acidity
Typically have lone pairs in conjugation with ring

In order of decreasing strength:
NH2
OCH3
OH
CH3

Blue = Resonance contributing groups
Red = Inductive groups

Carbocation stability:

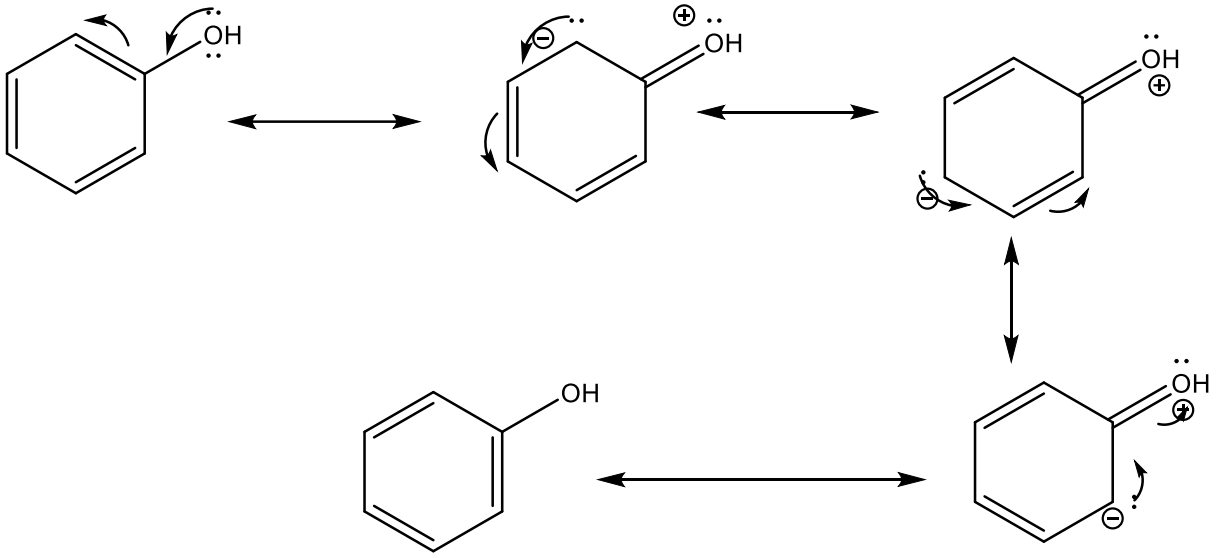


Benzylic carbocation | Allylic carbocation | Tertiary carbocation | Secondary carbocation | Primary carbocation

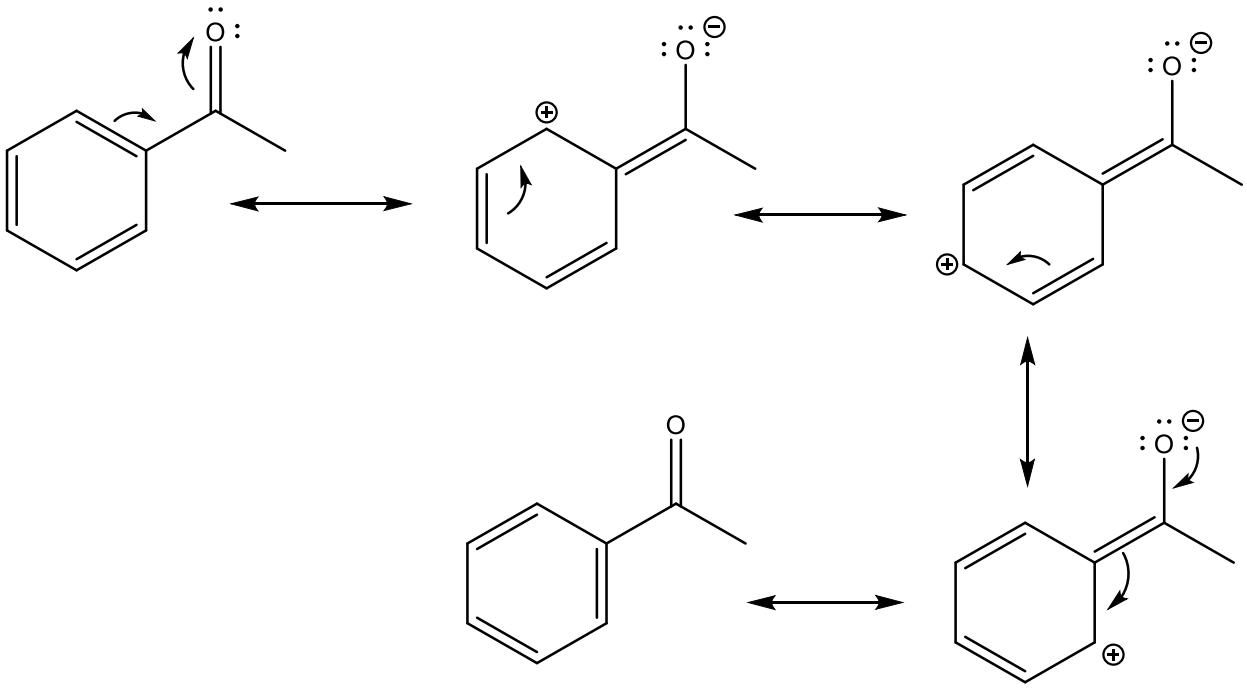
Substitution/Elimination Chart:

Reaction type	Preferred alkyl halide	Preferred reactant	Preferred solvent	Preferred temperature	Stereochemistry/Preferred product	Special conditions
SN1	More substituted	Weak nucleophile	ROH and HOH	Low/ RT	Racemic mixture	Carbocation rearrange
SN2	Primary or methyl	Strong nucleophile	Polar aprotic	Low/ RT	Total inversion	None
E1	More substituted	Weak base	ROH and HOH	High	Zaitsev (except for fluoroalkanes and bulky bases)	Carbocation rearrange
E2	More substituted	Strong base	ROH and HOH	High	Zaitsev (except for fluoroalkanes and bulky bases)	Anti-periplanar H

Example of EDG on the benzene ring, resonance form:



Example of EWG on the benzene ring, resonance form:



Benzene ring direction preferences for EAS reactions (this is flipped for NAS reactions)

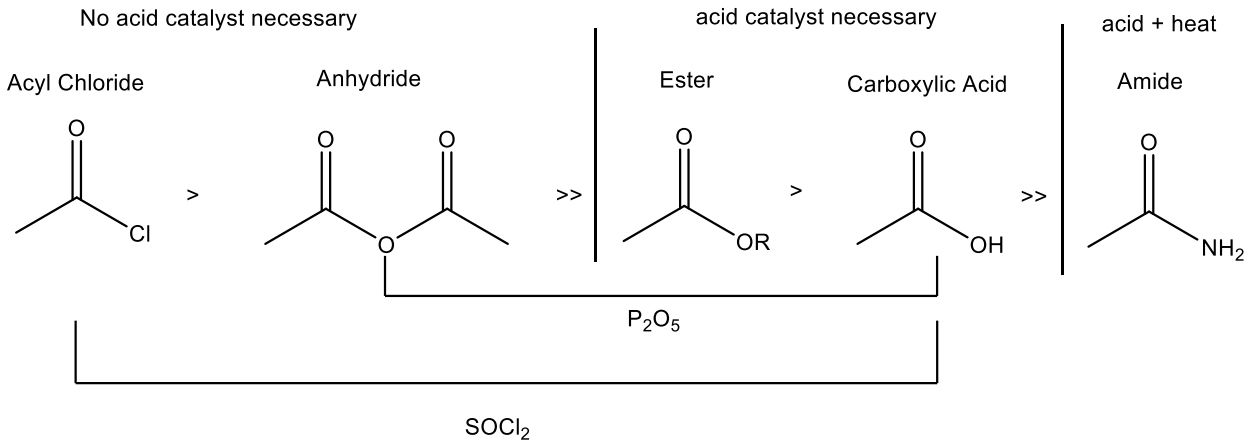
Guide to Benzene Reaction Positions

Meta Directors
Typically have a double bond or positive charge in conjugation with ring
In order of decreasing strength:
NO2
SO3H
Carbonyls
Nitriles
NH3+

Ortho/Para Directors
Typically have lone pairs in conjugation with ring
In order of decreasing strength:
NH2
OCH3
OH
N-Carbonyl
O-Carbonyl
CH3
Halogens

Blue = Resonance contributing groups
Red = Inductive groups

Carboxylic acid derivative reactivity chart:

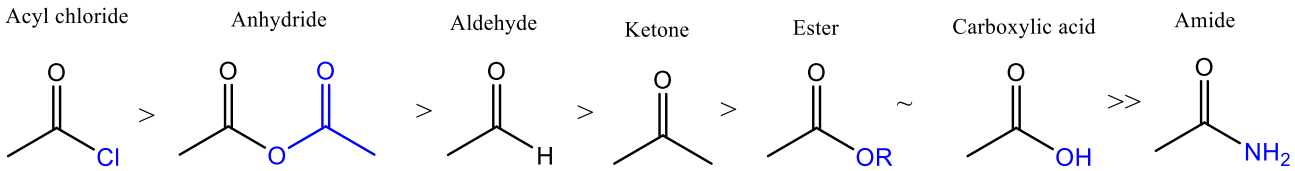


Reaction with water gives a carboxylic acid

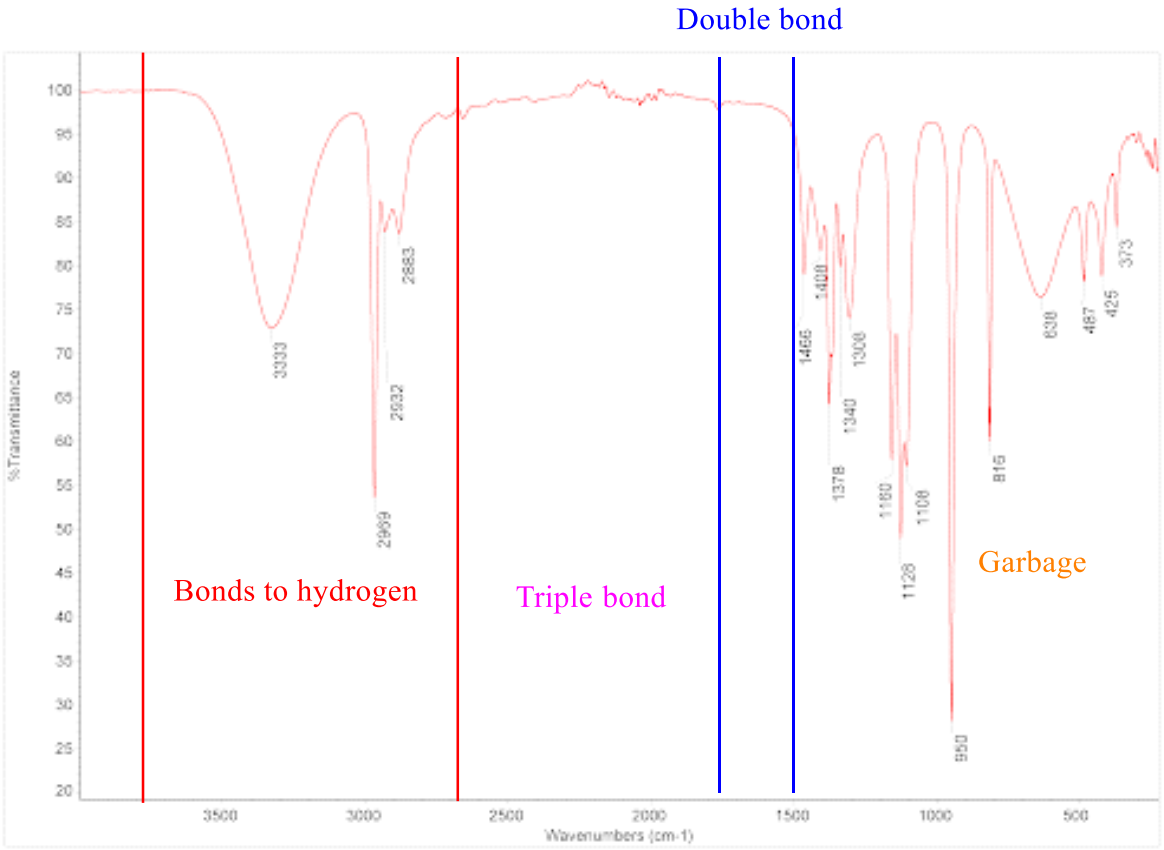
Reaction with amines gives an amide

Reaction with alcohols gives an ester

Overall reactivity chart:



IR spectroscopy cheat sheet:

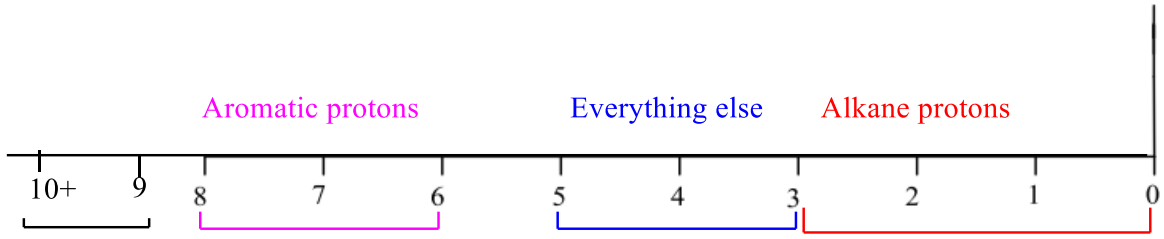


Functional group vibrations:

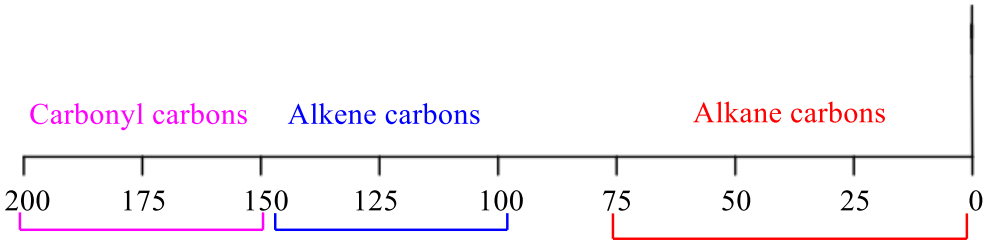
Functional group	Type of vibration	Wavenumber	Shape
Alcohol	O-H stretch	3500-3200	Strong, broad, parabolic
Amine	N-H stretch	3500-3200	Medium and broad, number of peaks = number of hydrogens
Carboxylic acid	O-H stretch	3300-2700	Strong, broad, screwed up bottom
Aldehyde	C-H stretch	2830-2700	Medium, sharp
Nitrile	C≡N stretch	2300-2200	Weak
Alkyne	C≡C stretch	2300-2200	Weak
Ketone/Aldehyde	C=O stretch	1730	Strong, sharp
Ester	C=O stretch	1750	Strong, sharp
Carboxylic acid	C=O stretch	1760	Strong, sharp
Amide	C=O stretch	1700-1650	Strong, sharp
Alkene	C=C stretch	1680-1600	Medium, sharp

NMR cheat sheets for proton and carbon NMR:

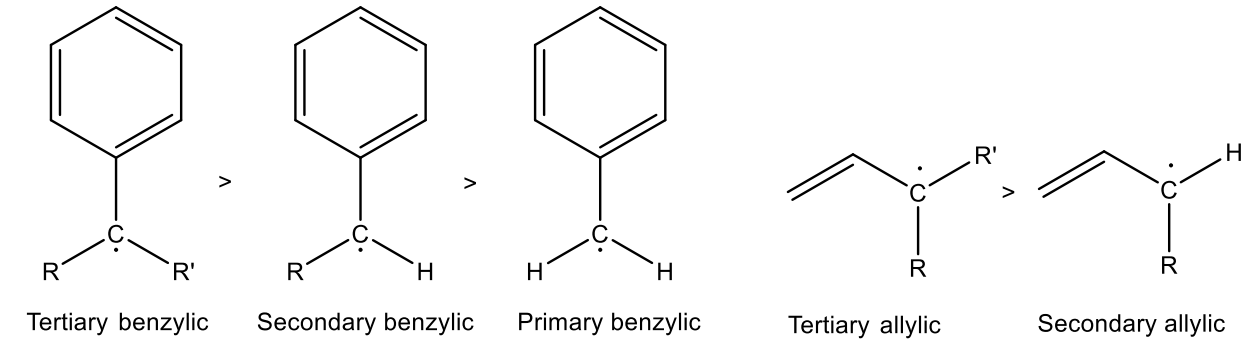
x axis is the chemical shift measured in ppm



Aldehydes + carboxylic acid



Radical stability trends:



Benzylic and allyic radicals are around the same stability

Overall nomenclature priority list in order of descending priority:

Functional group	Suffix ending	Group name
Carboxylic acid	-oic acid	Carboxy
Ester	-oate	Alkoxycarbonyl
Amide	-amide	Amido
Nitrile	-nitrile	Cyano
Aldehyde	-al	Oxo (C=O), Formyl (HC=O)
Ketone	-one	Oxo (C=O)
Alcohol	-ol	Hydroxy
Amine	-amine	Amino
Alkene	-ene	-en
Alkyne	-yne	-yn
Alkane	-ane	-yl
Ether	N/A	-oxy
Alkyl halide	N/A	-oro