

Organic Chemistry II

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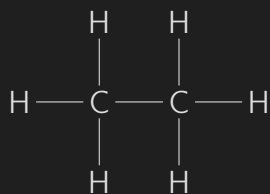
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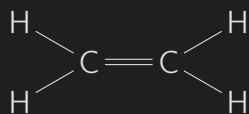
14: Alkenes

Alkenes Basics/Review

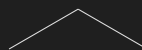
- Alkanes vs alkenes:



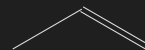
Saturated
alkanes ethane



Unsaturated
alkenes ethene



propane



propene

- We will fully investigate the nomenclature of alkenes ↗ later.
- Some relevant facts to start:
 - Alkene:** a hydrocarbon that contains a carbon-carbon double bond.
 - IUPAC recommends using alkene for only acyclic hydrocarbons with just one double bond; an **olefin** is a hydrocarbon with one or more double bonds.
 - Generally prepared through beta elimination, which results in the formation of alkenes from alkanes.

Types of Alkenes

- Basic types of alkenes:



Terminal Alkene

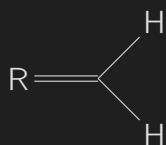


Internal Alkene



Cycloalkene

- Types of terminal alkenes:



Methylene



Vinyl

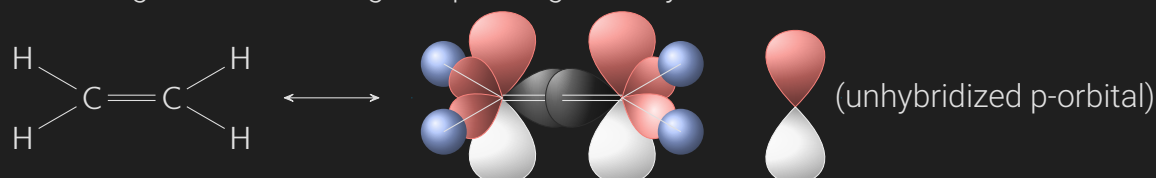


Allyl

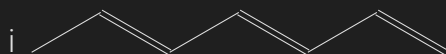
- "R" always tells you it's a carbon containing functional group, or hydrogen.
- "A" can be used to represent any functional group.

Relevant Review

- **Electronegativity:** negative charges on atoms with lower hybridization result in greater stability due to proximity (overlap) to positive nucleus. More s character results in greater stability.
 - I.e., sp (50% s) > sp^2 (33% s) > sp^3 (25% s)
 - E.g., ethene has two carbons that are both sp^2 due to one unhybridized p-orbital. This gives ethene a trigonal planar geometry.



- **Hydrogen deficiency index (HDI):** the measure of degrees of unsaturation.
 - E.g., two degrees of unsaturation results in a HDI of 2.
 - Degrees of freedom help represent possible structures, indicating possible double bonds, triple bonds, rings, or various combinations of each.
 - Only helpful when molecular formula is known for certainty.
 - Formula: $HDI = \frac{1}{2}(2C + 2 + N - H - X)$
 - X: halogen atoms.
- What is the HDI for the following molecules?

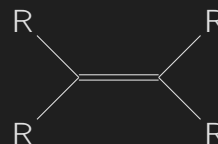


i $\frac{1}{2}(2(7) + 2 + (0) - (3 + (5(1)) + 2) - 0) = 3$



ii $\frac{1}{2}(2(6) + 2 + 0 - (6(1)) - 0) = 4$

- **Degree of substitution:** not a substitution reaction, but the number of groups connected to the double bond.



Monosubstituted

Disubstituted

Trisubstituted

Tetrasubstituted

Common Patterns Between Formal Charge and Lone Pairs

- **Associated Patterns for Oxygen**
 - A negative (\ominus) charge corresponds with 1 bond and 3 lone pairs.

- The absence of charge corresponds with 2 bonds and 2 lone pairs.
- A **positive** (\oplus) charge corresponds with 3 bonds and 1 lone pair.
- **Associated Patterns for Nitrogen**
 - A **negative** charge corresponds with 2 bonds and 2 lone pairs.
 - The absence of charge corresponds with 3 bonds and 1 lone pair.
 - A **positive** charge corresponds with 4 bonds and 0 lone pairs.

Chirality

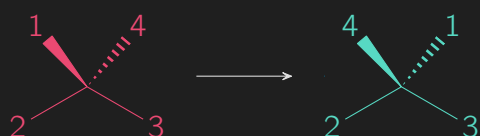
- **Achiral (nonsuperimposable)**: when an object's mirrored version is identical to the actual object.
- **Chiral**: objects that are not superimposable.
 - The most common source of molecular chirality is the presence of a **carbon bearing four different groups**.
- All three-dimensional objects can be classified as either chiral or achiral.
- **Enantiomer**: the nonsuperimposable mirror image of a chiral compound.
 - Can be used in speech the same way the word **twin** is used
 - The easiest way to draw enantiomers is to simply change wedges and dashes, but there are multiples ways to mirror a molecule, so it can be more complex.
- **Diastereomers**: non-identical stereoisomers (nonsuperimposable) that are **not mirror images** of one another.
 - Enantiomers have the same physical properties, while diastereomers have **different physical properties**.
 - Differences between enantiomers and diastereomers are especially relevant when comparing compounds with **more than one chiral center**.
 - **Maximum** (could be less) number of stereoisomers: 2^n
 - n : number of chiral centers
 - $\frac{2^n}{2}$: max pairs of enantiomers.

Cahn-Ingold-Prelog System

- **Cahn-Ingold-Prelog system**: a system of nomenclature for identifying each enantiomer individually.
 1. Assign priorities to each of the four groups based on atomic number; the highest atomic number has the highest priority.
 2. Rotate the molecule so that the fourth priority group is on a dash (behind)

3. Determine the configuration, i.e., sequence of 1–2–3 groups;
 - clockwise (*R*, *rectus*, right) or counterclockwise (*S*, *sinister*, left).
- If there is a tie between the atoms connected, then continue outward until a difference is found.
 - Do not add the sum all atomic numbers attached to each atom, just the first in which the atoms differ.
 - Any multiple bonded atom, (2 or 3) is treated as if connected to multiple atoms equal to number of bonds.

- Switching any two groups on a chiral center will invert the configuration, e.g.,



- Switching twice results in a change without changing configuration, e.g.,



- **Configuration in IUPAC nomenclature:**

- The configuration of the chiral center is indicated at the beginning of the name, italicized, and surrounded by parentheses.
- When multiple centers are present, then each must be preceded by a locant.

Rearrangements

- There are several kinds of rearrangements, but only those relating to carbocation rearrangements are focused here.
- **Hyperconjugation:** carbocations that can be stabilized by neighboring groups due to molecular orbitals that slightly overlap with empty *p* orbitals, placing some of its electron density there.
 - **Primary (1°), secondary (2°), and tertiary (3°):** refers to the number of groups directly attached to the carbocation.
 - Tertiary are the most stable (more slight overlap) and primary are the least (less overlap)
- **Hydride shift:** involves the migration of a H^- .
 - Involves the rearrangement of the carbocation to a more stable variant due to change migration of the H^- .

- **Methyl shift:** similar to a hydride, except a whole methyl group is migrated instead.
 - The methyl group must be attached to the carbon atom that is adjacent to the carbocation for this to occur.

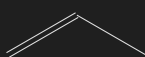
Nomenclature of Alkenes

Basic Alkene Nomenclature Rules

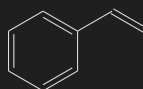
- Alkenes are named using the same four steps in the previously used nomenclature, though the suffix of "ane" is replaced with "ene."
- When choosing the parent chain, choose the parent chain that **includes** the double bond.
- When numbering the parent chain, the double bond should receive the **lowest** number possible.
 - Define the location k of the double bond as being the number of its first carbon.
 - The locant (k) of the double bond should be placed right before the suffix of "ene," though, it was previously recommended before the parent (both are acceptable), e.g., 2-pentene = pent-2-ene
- Name and the side groups (other than hydrogen) according to the appropriate rules.
- Define the position of each side group as the number of the chain carbon it is attached to.
- E-Z notation:** recommended instead of *cis* and *trans* in order to account for cases that has more than two different groups attached to the double bond by first determining the **CIP priority** ↗.
 - E**, *entgegen*, "opposite".
 - Z**, *zusammen*, "together"; "on ze same side."
- Commonly recognized alternative names:



Ethylene



Propylene



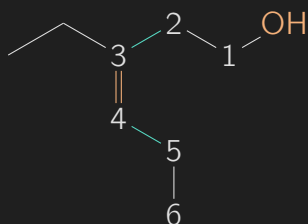
Styrene

- Groups containing C=C have common names as well, which can be found under **types of alkenes** ↗.

Alkenes Containing an Alcohol

- If there is **more than 1** functional group, then the **alcohol** has the **higher priority** over alkenes.
- There are more rules depending on functional groups, but for now the distinction between alcohol and alkenes are all that is needed.
- I.e., find the longest chain and number in a way that the carbon **containing the OH** gets the **lowest** possible number while still including both the OH and alkene.

- An example with alcohol:

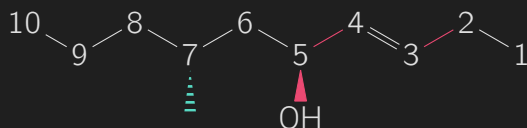


(3Z)-3-propyl-hex-3-en-1-ol

or

(3Z)-3-propyl-3-hexen-1-ol

- An example with OH still being lowest (name still ends with -ol), but alkene happens to be lower:



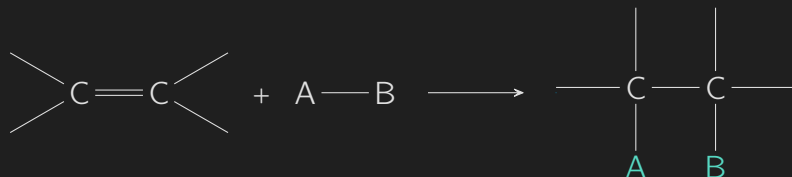
(3E,5S,7R)-4-methyl-3-en-5-ol

- Note: if planar geometry was not given, R and S could not be determined. Check out the [Cahn-Ingold-Prelog System](#) for review.

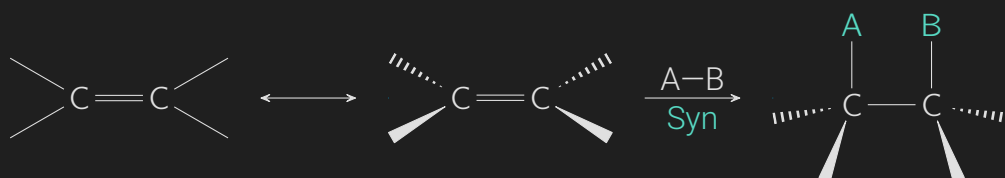
Addition Reactions of Alkenes

Syn Addition

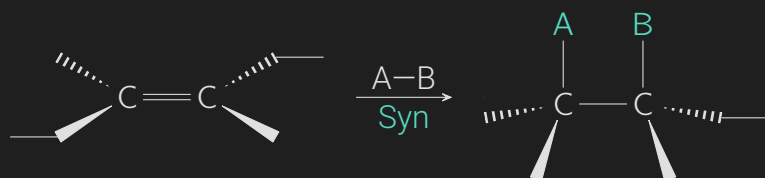
- Syn addition means that both components (A & B) came in from the same side.



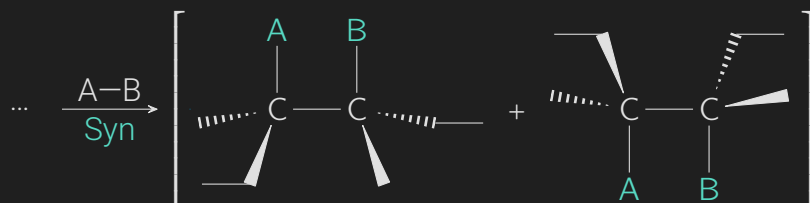
- When there is mixture of products, then the stereochemistry is important—A & B could come from different directions.
- Switching to a 3D perspective, with groups pointing towards and away from the viewer, rather than a flat view:



- The final product above results in no chiral compounds (no carbons contain four different groups). If a product does have chiral compounds, you must show the other possible products.

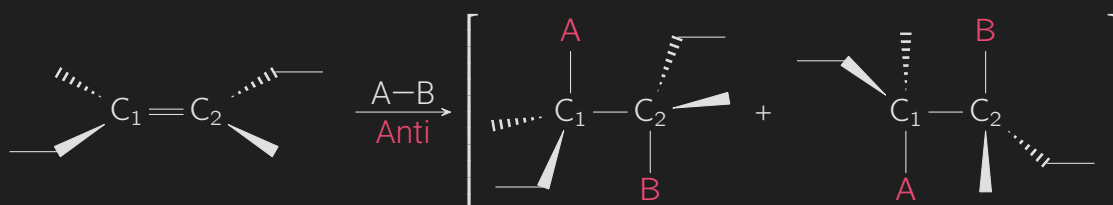


- The product in this case has **chiral centers**, so enantiomers must be considered.



Anti Addition

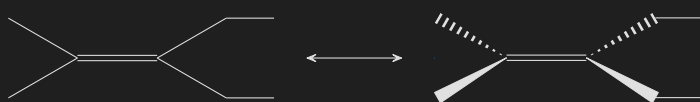
- Anti addition means that the added components come in from different sides.



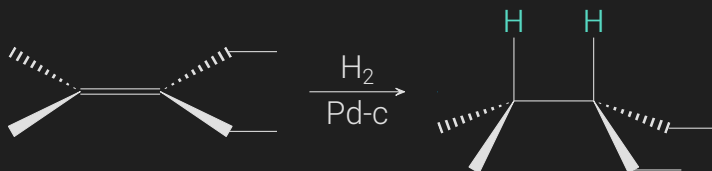
Hydrogenation

- **Hydrogenation:** a chemical reaction between molecular hydrogen H_2 and another compound or element, usually in the presence of a catalyst such as nickel, palladium (typically Pd , due to cost) or platinum.
 - Commonly employed to **reduce** (π bonds) or **saturate** (add hydrogens) organic compounds.
 - Usually constitutes the addition of pairs of hydrogen atoms to a molecule, often an alkene.
 - Catalysts are required for the reaction to be usable; non-catalytic hydrogenation takes place only at very high temperatures.
 - Always occurs with **syn addition**, with hydrogen entering from the least hindered side.
- Hydrogenation of 2-methyl-3-ethyl-2-pentene:

- First convert to 3D view:

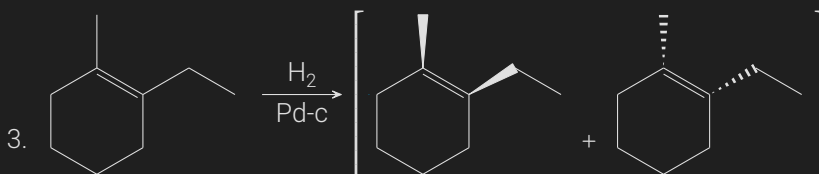
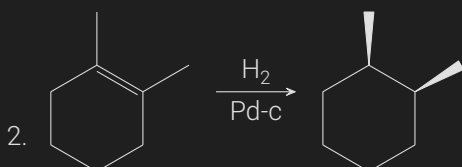
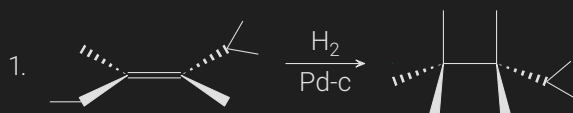


- Then apply H_2 with catalyst to trigger syn addition:



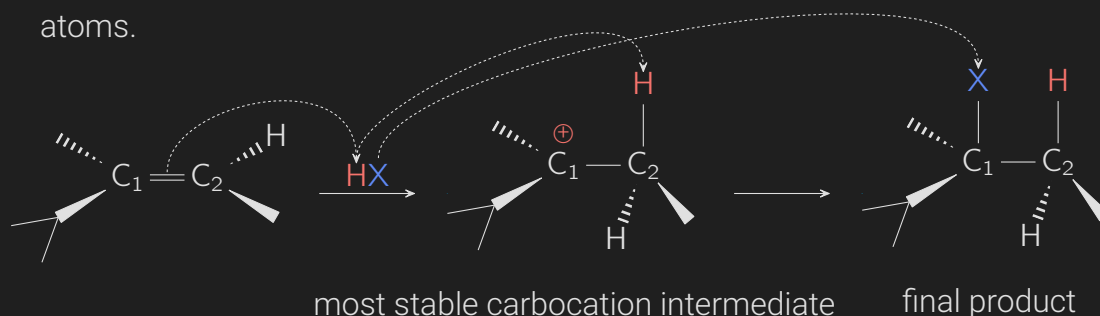
- Product is achiral; no enantiomers. Bottom would attack just flips the orientation; not a different product.

Hydrogenation Practice Problems

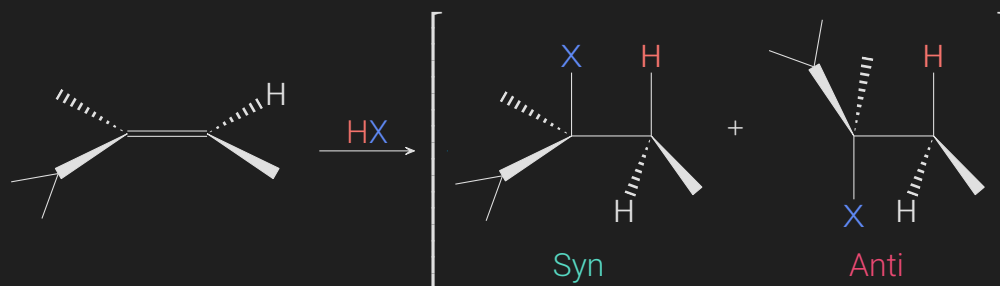


Hydrohalogenation

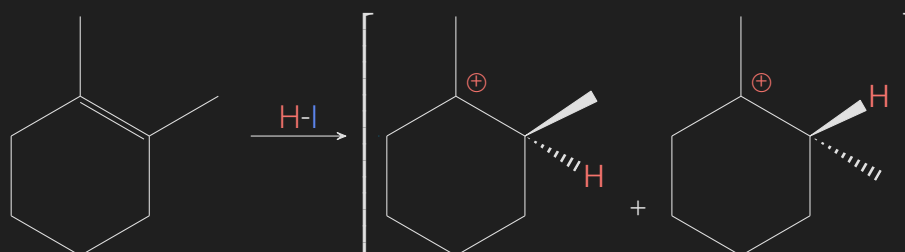
- **Hydrohalogenation:** the electrophilic addition ($\pi \rightarrow 2\sigma$ bonds) of hydrohalic acids (HX, e.g., HCl or HBr) to alkenes to yield the corresponding haloalkanes.
- **Markovnikov's Rule:** an addition of a protic acid (HX) or other polar reagent to an asymmetric alkene results in the **electropositive part (usually H)** gets attached to the carbon with **more hydrogen substituents**, and the **electronegative part (usually the halide)** attaches to the carbon with **more alkyl substituents**.
 - Alternatively: H^+ is added to the carbon with the **greatest** number of hydrogen atoms while the X^- component is added to the carbon with the **fewest** hydrogen atoms.



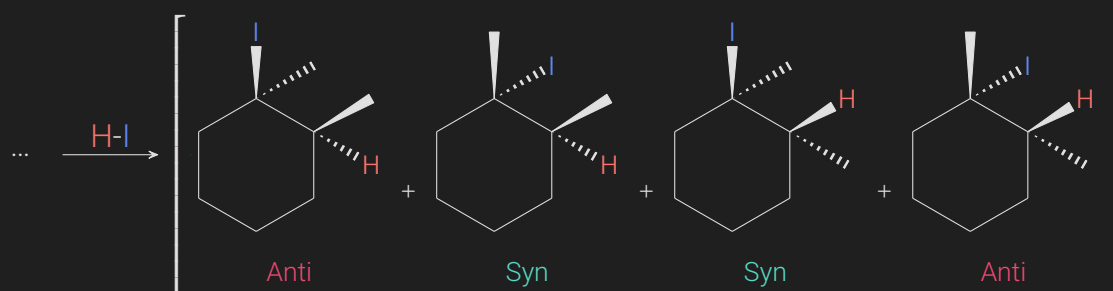
- However, we have a chiral carbon, so we have to take enantiomers into account:



- The previous example is an example of a regioselective reaction, i.e., it's a chemical reaction where one reaction site is preferred over another.
 - Markovnikov additions are common examples of regioselective reactions since there is a specific region in where the hydrogen is supposed to go.
- Another example that contains multiple products:

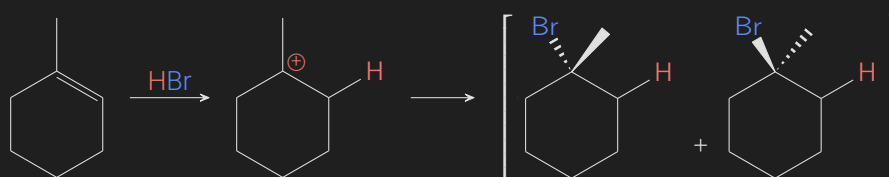


- Again, this first step shows the most stable carbocation intermediate, which helps determine where the H^+ will attach to. In this case either location works, so four products are formed, each with syn and anti enantiomers.



- The above products are all **stereoisomers** of each other. Note: not all chemical reactions produce all possible stereoisomers.

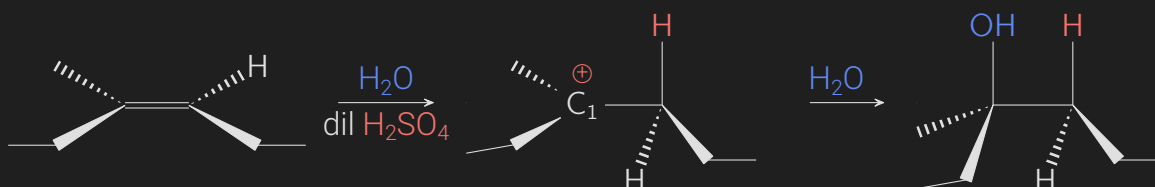
Hydrohalogenation Practice Examples



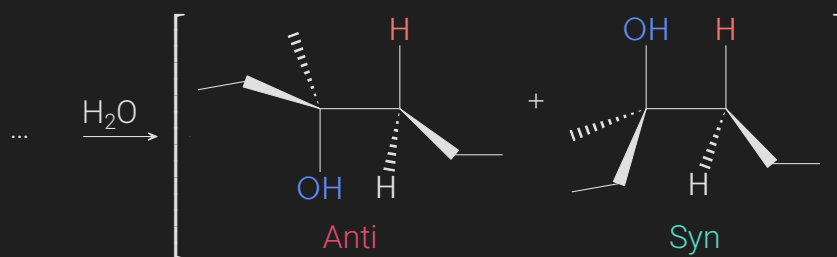
Addition of Water or Alcohol

Addition of Water or Alcohol (ROH): analogous to that of hydrohalogenation (HX); both of which involve a carbocation intermediate, syn/anti stereochemistry, and Markovnikov regioselectivity.

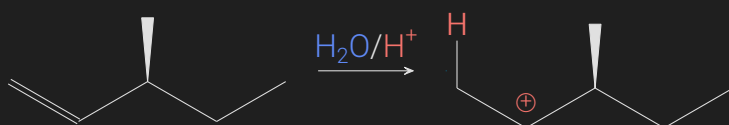
- Note: the hydronium ion (H_3O^+) forms via the reaction of H_2SO_4 with H_2O , and is the source of the proton that reacts with the starting alkene.
- $\text{H}-\text{OH}$ and $\text{RO}-\text{H}$ helps to visualize where the proton is coming from. What ever works with water also works with alcohol and vice versa.
- An example that is very similar to the example from **hydrohalogenation** \nearrow :



- Note: H_2SO_4 is a **strong acid** and can be generalized to H^+ or HA .
- Note: I occasionally use **red** for **cations**, **acids**, and E^+ (electrophile). I also use **blue** for **anions**, **bases**, and nu^- (nucleophile) to help easily keep track of things. This is an arbitrary color choice, but it holds weight in these notes. However, not all bases/acids are nucleophile/electrophiles, so keep that in mind.
- Again, this reaction is stereoselective, so there is actually more than one product:

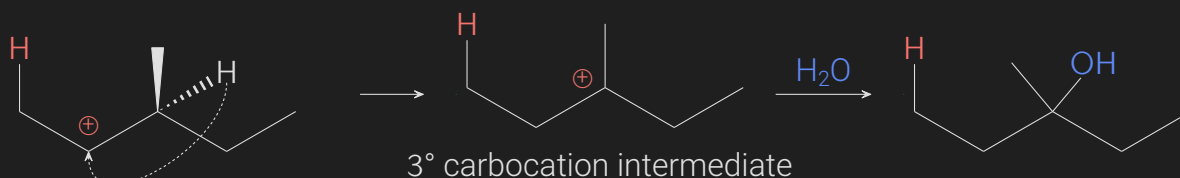


- Example 2:

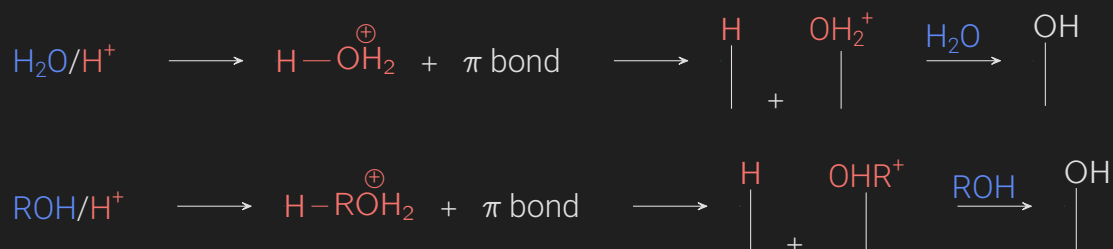


- **Rearrangement** \rightarrow is always a possibility to be considered when cation are generated. In this case, a 2° carbocation was generated, but we can do better:

- Note: showing H is not necessary, but useful to visualize the hydride shift and avoid the urge to move the methyl. "Why move a sofa when you can move a chair?"



- Note: the carbocation intermediate changes planar geometry due to change in hybridization ($sp^3 \rightarrow sp^2$).
- Top and bottom attacks do not need to be considered in this case, as there are chiral centers; no enantiomers.
- Reminder, H_2O and alcohols (ROH) behave very similarly; the reduction of the π bond generates 2 σ bonds, one of which that takes a **hydrogen**, and the other (with possible carbocation rearrangement first) which first takes up the **cation** generated in the medium, then interacts with **base**, removing an **H** and leaving **OH**.
 - Note: the OH is not actually negatively charged on the end, I just keep the blue there to help show where it's coming from; it helps determine syn/anti if needed.



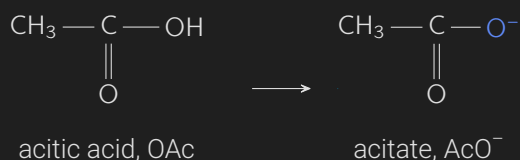
- **Problems of going through carbocation intermediate:**

- Carbocations are sp^2 , which makes them trigonal planar, so nu^- can attack from top or bottom.

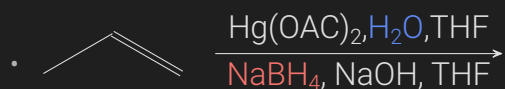
- C^+ can cause rearrangements leading to **multiple products**.

Oxymercuration-Demercuration

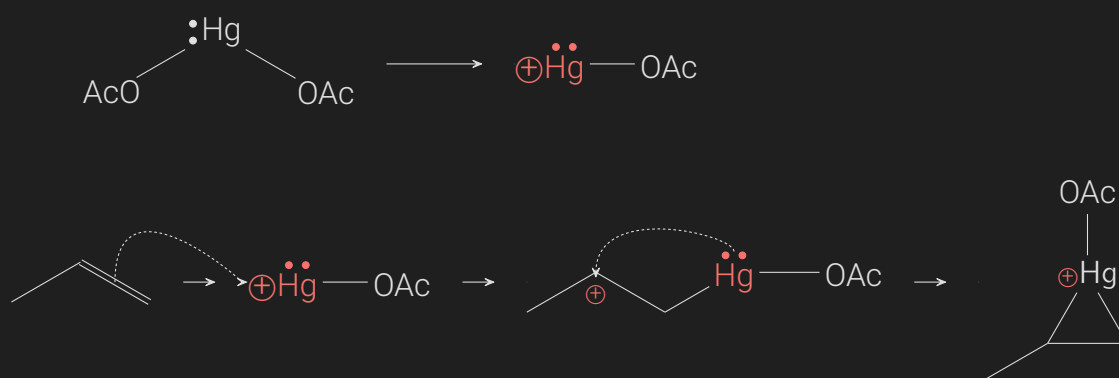
- **Oxymercuration-Demercuration** is another electrophilic addition organic reaction that transforms an alkene into a neutral alcohol.
- Reacts with mercuric acetate ($AcO-Hg-OAc$) in aqueous solution to yield the addition of an acetoxymcury ($HgOAc$) group and a hydroxy (OH) group across the double bond.



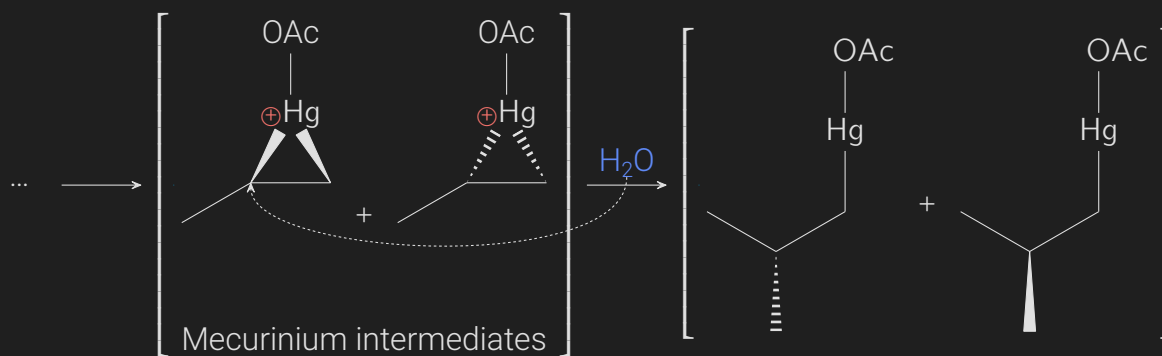
- Carbocations are not formed in this process and thus rearrangements are not observed.
- The reaction follows **Markovnikov's rule**.
- The reaction is stereospecific—it is always an **anti addition**.
- Example using propylene:



- H_2O is nu^- ; ROH can be used instead.
- THF has no function directly; it is the solvent.
- $NaBH_4$ is the reducing agent.

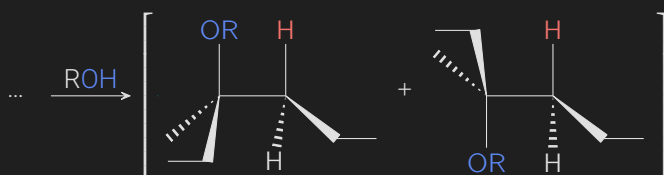
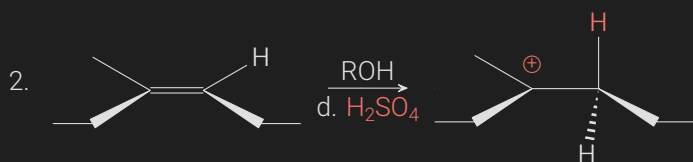


- Note: the above is a concerted (one step) process, but drawn out for illustration.
- Also, we are not done, we have a chiral center that forms, plus it is just an intermediate step, a nucleophilic attack will occur on the strained (highly reactive) epoxide:

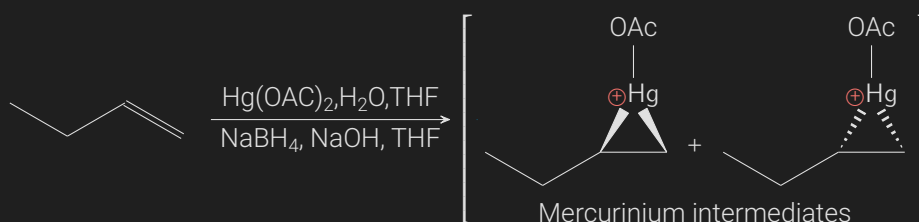


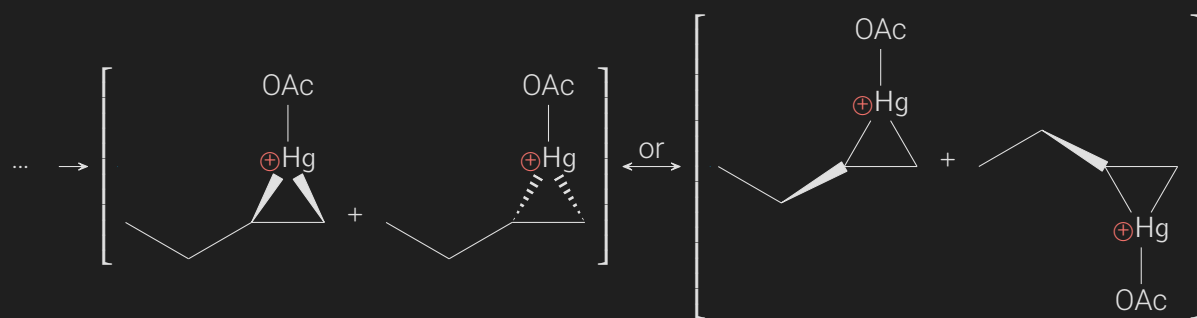
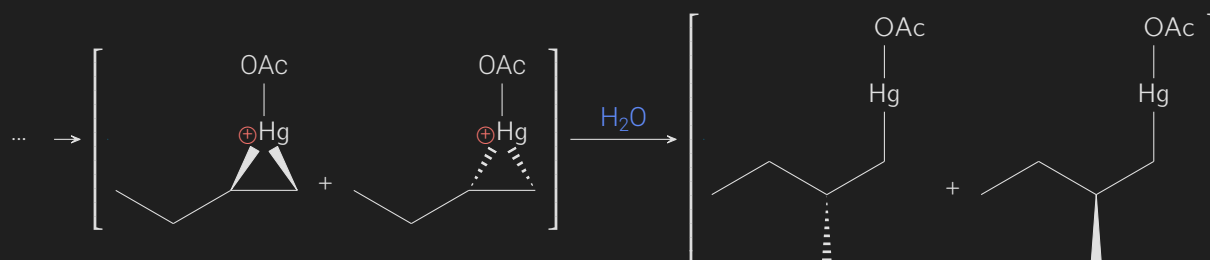
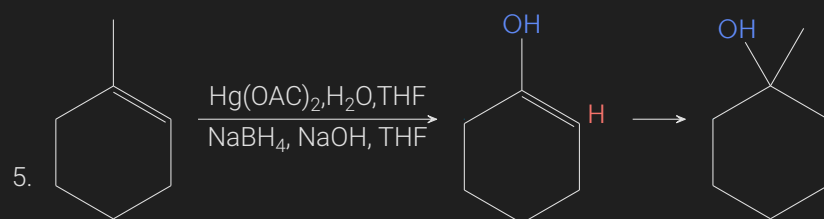
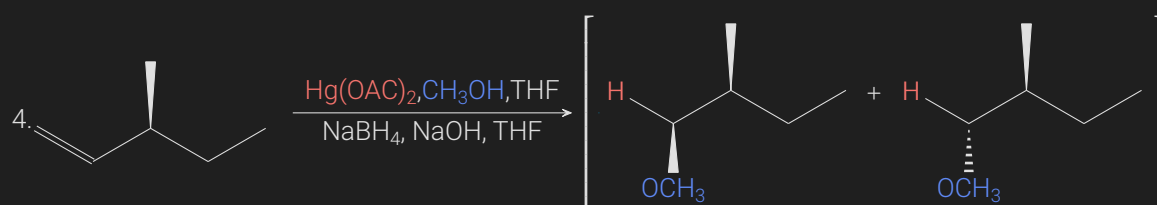
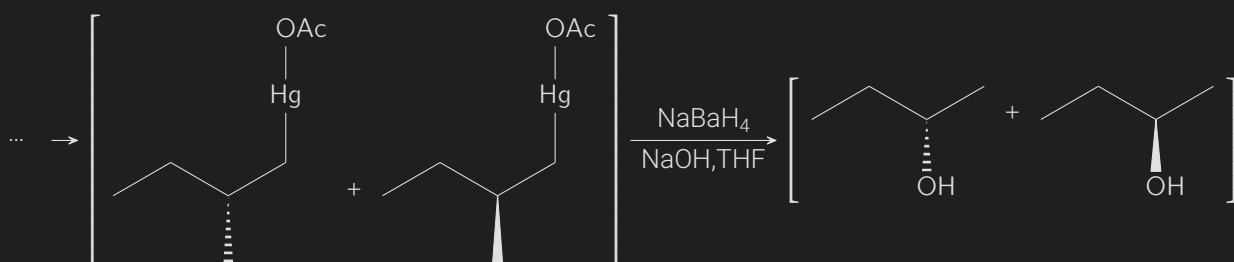
- Notice the nucleophile attack the carbon with the greater flow of electrons (more substituted), since there was a positive charge on mercury. Epoxides with no charge are attacked on the side with less steric hindrance.
- Also, the nucleophilic attack occurs on the opposite side of the plane since there is less hindrance on that side.

Related Practice Problems

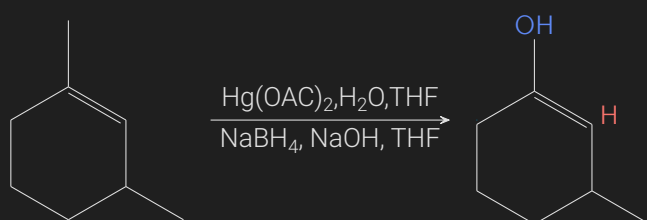


3. + Alternate ways of drawing rings (was done in lecture):

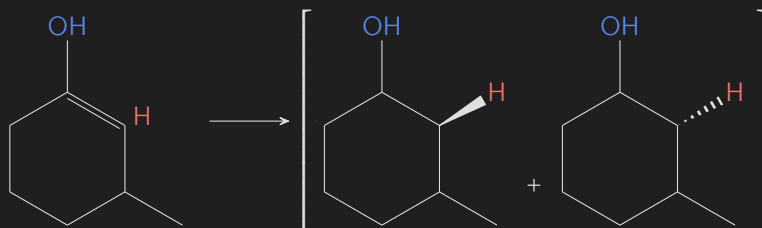


**Oxymercuration:****Demercuration:**

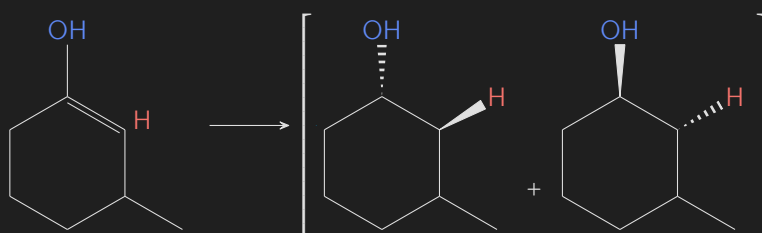
6. (was done in lecture)



- We know these are the locations of the H and OH, so we can start by labeling them.



- The methyl will be the same no matter what, so we can ignore that.
- H has two options, which gives us the above.
- Since oxymercuration-demercuration is always an **anti addition**, then we know OH must be **anti** to the hydrogen in both of the products:

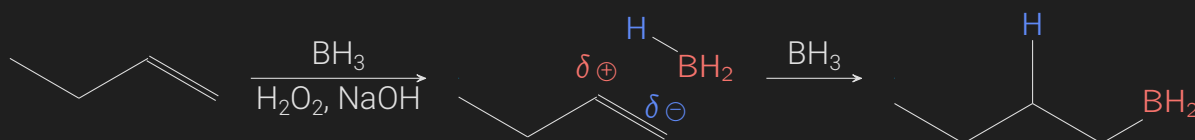


Hydroboration-Oxidation

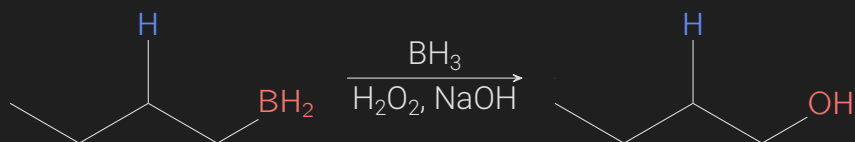
- Hydroboration-Oxidation:** a two-step hydration reaction that converts an alkene into an alcohol.
 - Results in the **syn addition** of a hydrogen and a hydroxyl group where the double bond had been.
 - An **anti-Markovnikov reaction**—the hydroxyl group attaches to the less-substituted carbon.
 - Provides a more stereospecific and complementary regiochemical alternative to other hydration reactions such as acid-catalyzed addition (stereoselective) and oxymercuration-demercuration (stereospecific for anti).
 - Usually BH_3 , B_2H_6 , R_2BH are used. The presence of Boron is key.
- Like H_2O and ROH , it's useful to think of them in the following way:



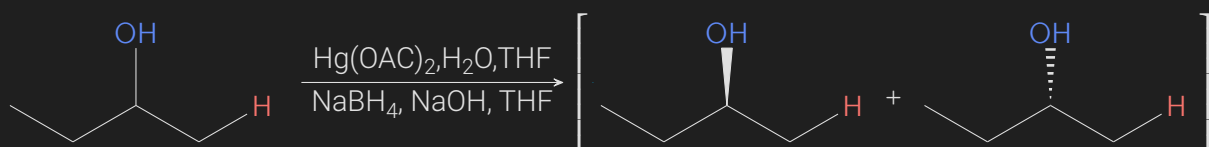
- Unlike water/alcohol, the hydrogen is now the partial negative component and the boron is the positive.



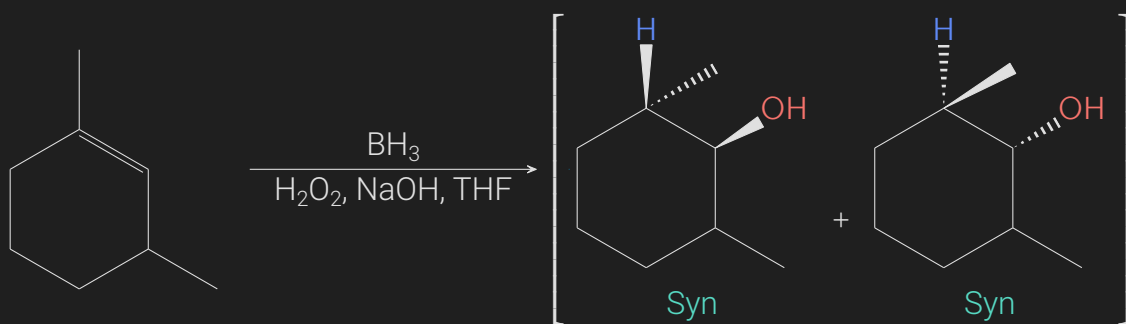
- There are no chiral centers, but there is still one more step—the oxidation:



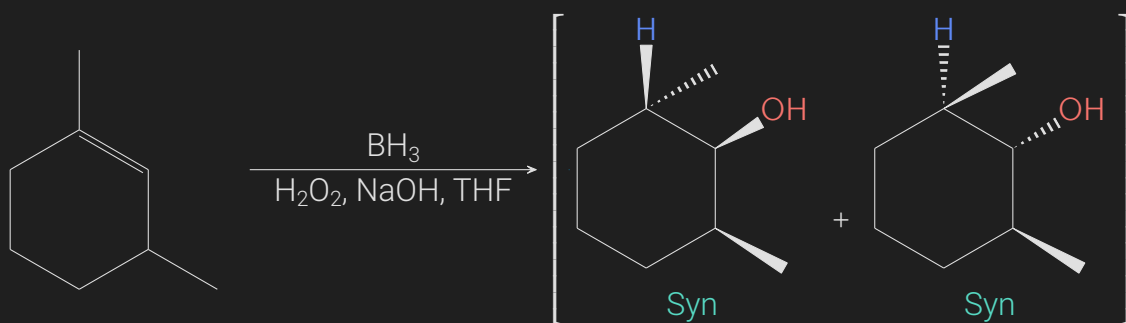
- If we had used $\text{Hg}(\text{OAc})_2$, then the above reaction would be different; partial charges change the possible final products: $\overset{\delta^-}{\text{H}}-\overset{\delta^+}{\text{BH}_2}$ vs. $\overset{\delta^+}{\text{H}}-\overset{\delta^-}{\text{OH}_2}$:



- Revisiting a practice example, using different reagents:

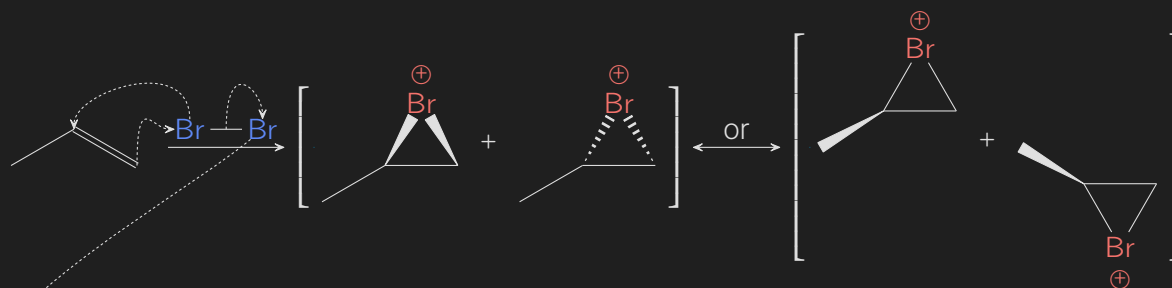


- If the untouched methyl happened to be above or below the plane initially, then you would keep that the same, e.g:

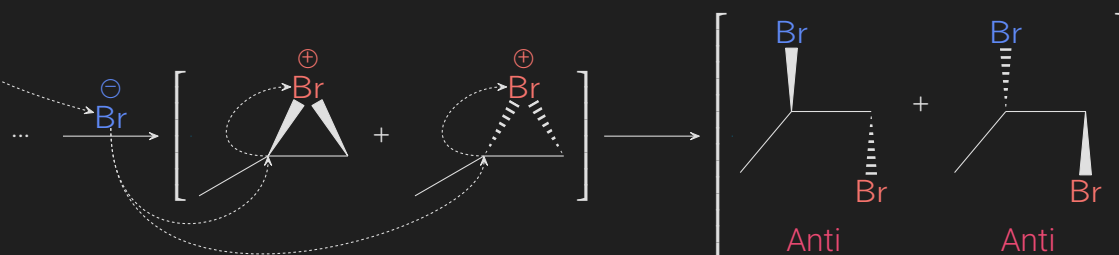


Halogenation

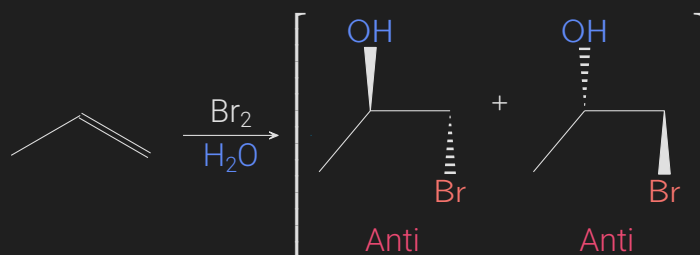
- Halogenation:** a reaction that involves the addition of one or more halogens to a compound or material.
 - The addition of halogens to alkenes proceeds via intermediate halonium ions.
 - Halonium ion:** any onium ion containing a halogen atom carrying a positive charge. This cation has the general structure: $\text{R}-\text{X}^+-\text{R}'$
 - Onium ion:** a cation formally obtained by the protonation of mononuclear parent hydride of a pnictogen (group 15 of the periodic table), chalcogen (group 16), or halogen (group 17).



- In the above example we see a cyclic bromonium ion intermediate being formed. Next, one bromine is now left to act as the nu^\ominus :



- Alternatively, if you did the reaction in H_2O , then water would become the dominant nu^\ominus , leaving OH.



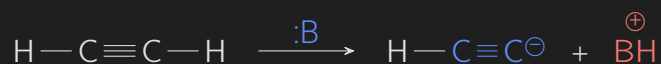
15: Alkynes

Alkynes Basics/Review

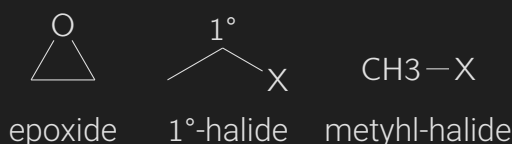
- **Alkynes**: an unsaturated hydrocarbon containing at least one carbon—carbon triple bond.
 - Contains two unhybridized p-orbitals (sp) on each carbon.
- $$\begin{array}{ccccccc} \delta+ & \delta- & \delta- & \delta+ & & & \\ \text{H} & -\text{C} & \equiv & \text{C} & -\text{H} & & \end{array}$$
- Large amount of s character (sp: 50% s) makes the hydrogens very acidic and the carbons very basic.
 - 1 mole of base takes off 1 hydrogen (1 equivalent, equiv, eq), which can be done twice to take off both (2 equivalent).
 - Traditionally known as acetylenes, though acetylene refers specifically to C₂H₂ (ethyne)

Acetylides

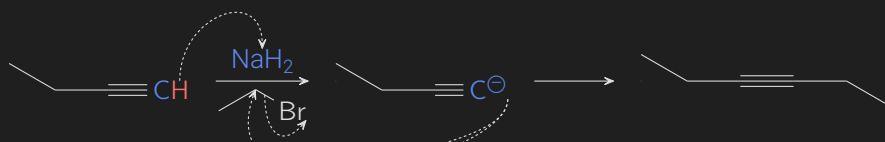
- **Acetylide**: an alkyne with a negatively charged carbon on one end, e.g.,



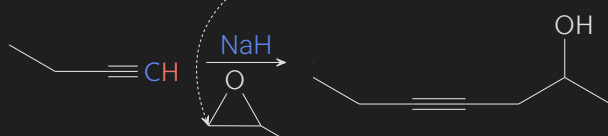
- :B is a name of generic base, typical bases used:
 - NaNH₂ → sodamide, or NaH → sodium hydride.
- Acetylide acts as a nucleophile when it reacts with an epoxide, 1°-halide, or a methyl-halide.



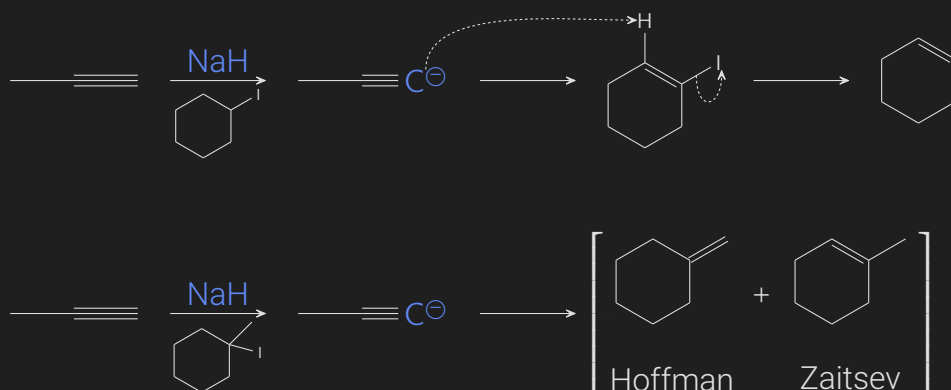
- Is a S_N2 reaction.
- Can be used for chain extension, e.g.,



- Example two:



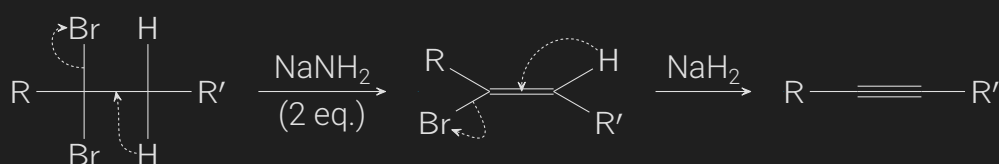
- Acetylide acts as a **base** when it reacts with 2°-halide or a 3°-halide due to steric crowding.
 - Is an E2 reaction.



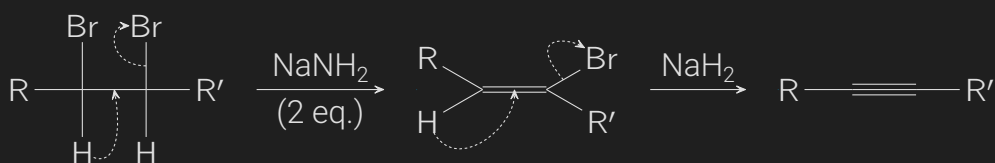
- The Zaitsev product is more likely to be the major product due to the thermodynamics (more energetically stable) than the Hofmann product; a bulkier base would likely increase the Hofmann product.

Preparation of Alkynes

- Introductory example of a geminal dihalide going through two E2 reactions to generate an alkyne:



- Related example with a vicinal dihalide (halide on adjacent carbons):



Regioselectivity and Stereospecificity of E2 Reactions

- Regiochemistry:** when a chemical reaction is said to produce two different regiochemical outcomes.
 - Regiochemical:** preference of chemical bonding or breaking **direction**.
- Regioselective:** when there is a preference in products of a regiochemical reaction.
- Zaitsev product:** name of the **more substituted** alkene that is generally observed to be the major product.
- Hofmann product:** name of the **less substituted** alkene.

- There ratio between the Zaitsev and Hofmann product is dependent on a number of factors and often difficult to predict.
 - Steric hindrance of the base often plays a major role, often increasing the Hofmann product.
 - The outcome of E2 reactions can often be carefully **controlled by choosing the base**, despite difficulty in overall prediction.
- **Stereospecific**: when the stereoisomeric product of the E2 process depends on the configuration of the starting stereoisomeric substrate.
 - The stereospecificity is only relevant when the **β position has only one proton**.
- **Stereoselective**: when the substrate itself is not necessarily stereoisomeric, but can yield two stereoisomeric products, one of which that often has a higher yield.
 - Occurs when there are **more than one proton in the β position**.
- **Coplanar**: when the proton in the β position, the leaving group, and the two carbons atoms that form a double bond lie on the same plane.
 - Often leads only one stereoisomer product being formed, thus more often stereospecific.
 - If it stereoselective, then usually *trans* conformation is favored.
 - **Periplanar**: when the proton and leaving group are **nearly coplanar**; often is used in place of coplanar to incorporate both situations.
- **Syn-coplanar**: when the proton and the leaving group are **eclipsed** in a coplanar conformation.
 - Elimination in this state involves a higher energy transition state due to eclipsed geometry, and is **slower** than anti-coplanar arrangement.
- **Anti-coplanar**: when the proton and the leaving group are **staggered** in a coplanar conformation.
 - Elimination in this state involves a lower energy transition state due to staggered geometry, leading to a **faster** reaction relative to syn-coplanar.

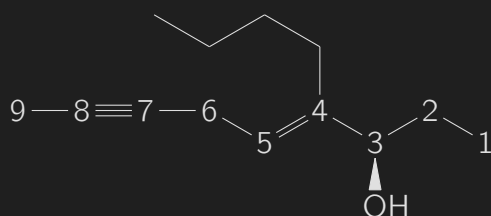
Alkyne Nomenclature

Basic Alkyne Nomenclature

- All other basic IUPAC rules still apply; the suffix is "yne".
- Find the longest carbon chain that includes both carbons of the triple bond.
- Number the longest chain starting at the end closest to the triple bond.
- Compounds with > 1 triple bond are called diynes, triynes, etc.
- Enynes are compounds that contain both double and triple bonds, and enynols also contain an alcohol.
- The functional groups have their assigned carbon numbers written directly before their name.

Priority Rules

- More functional groups will change the as we get introduced to more, but for now we only need to know the following (somewhat follows electronegativity):
 1. Alcohol
 2. Alkenes
 3. Alkynes
 4. Alkyls
 5. Halogens
- Preference for naming order if multiple functional groups are present in the same chain: OH + DB + TB > OH + DB > OH + TB.
- When alkynes are substituents, then they are named as *k*-alkynyl. (*k* = locant)
- Example containing all three:

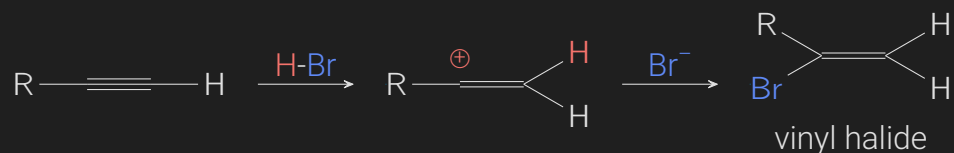


(3R,4E)-butylnon-4-en-7-yn-3-ol

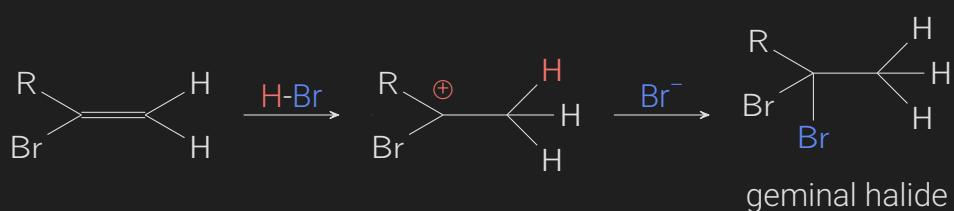
Addition Reactions of Alkynes

Hydrohalogenation of Alkynes

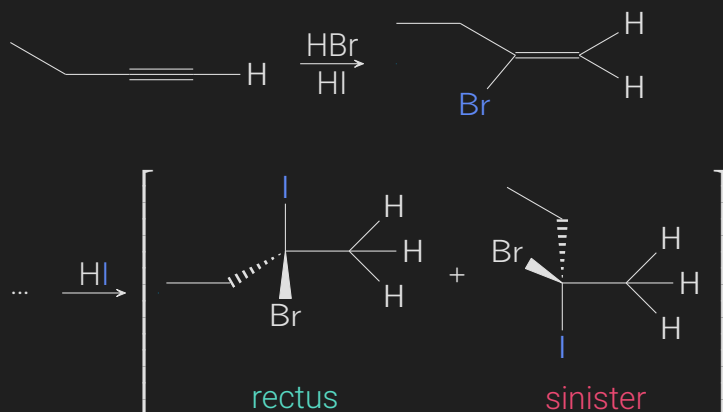
- Introductory example:



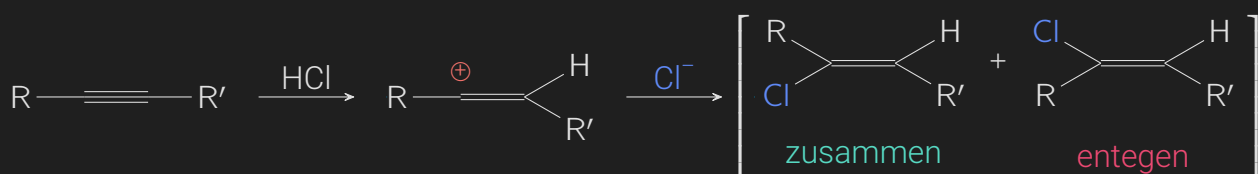
- Is **Regioselective** ↗
- Follows **Markovnikov's Rule** ↗
- This reaction can be done again (2 equiv):



- Geminal halide: a carbon that contains two halides.
- Related practice problem that generates chiral carbon due to use of different reagents for each equivalence (needs to be verified still, I might be wrong):

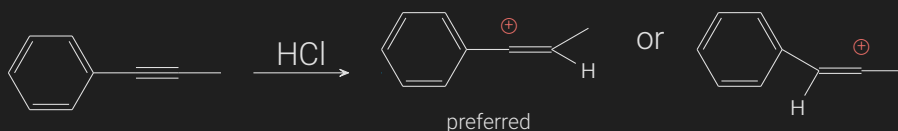


- Example with an internal alkyne; either side can be chosen if the R groups are not specified:

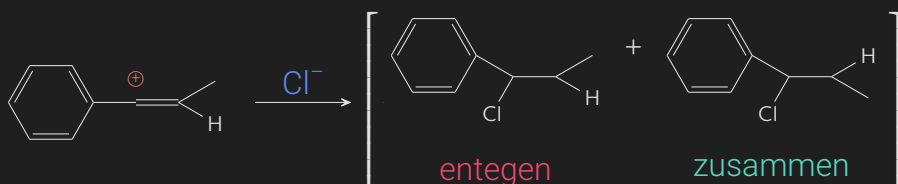


- Cl is higher priority than any carbon containing group (R), and any R' is higher than H, so both top and bottom attacks are possible.

- Related practice problem:

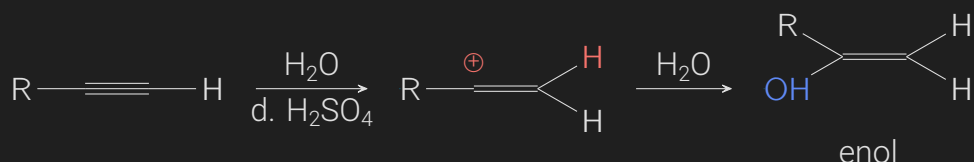


- The former carbocation intermediate is preferred due to resonance of the benzene ring, which does a better job stabilizing the carbocation.
- Continuing the reaction:

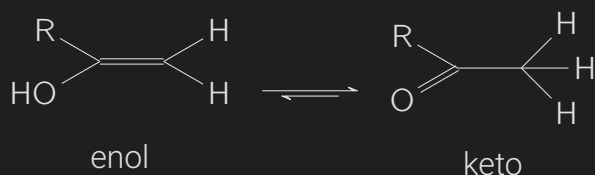


Hydration of Alkynes

- Introductory example:

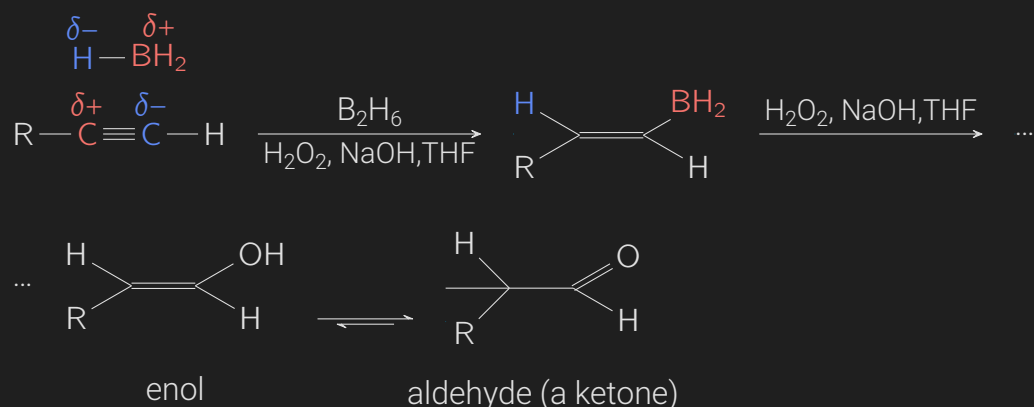


- Follows **Markonikov's Rule** ↗
- However, enols readily interconvert with more stable form:



- **Tautomers:** a class of structural isomers (constitutional isomers) that readily interconvert, commonly due to the relocation of a proton (protonation-deprotonation) across a π bond.
 - The chemical reaction is called tautomerization; the concept is referred to tautomerism, which is sometimes desmotropism.
- Keto-enol tautomerism major product is the keto form, which does not allow for a second addition reaction.
- HgSO_4 is frequently used instead of d. H_2SO_4 , due to the mercurinium intermediate vs. the carbocation intermediate, which is both **faster** and a means to **reduce the probability** of byproducts.

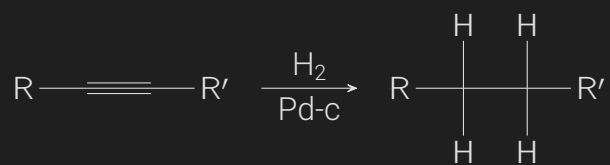
- Example of an alkyne in a hydroboration-oxidation reaction ↗:



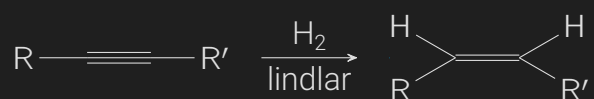
- Aldehyde:** generally created by removing a hydrogen from an alcohol; in our case it is generated by the **anti-Markovnikov** reaction that results in a terminal enol, which then undergoes tautomerization and produces the aldehyde as the major product.

Hydrogenation of Alkynes

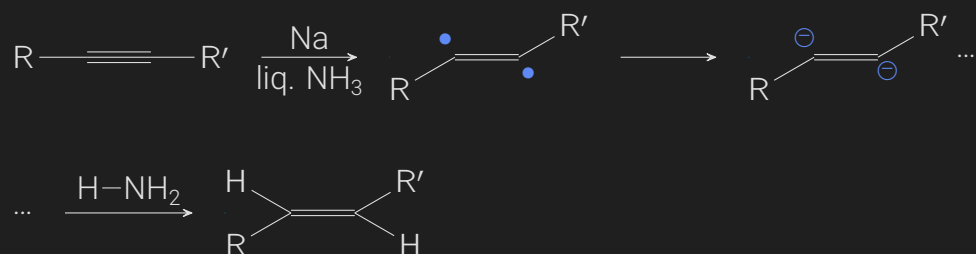
- Complete hydrogenation of an alkyne:



- Alkyne → **cis**-alkene; use of lindlar catalyst (Pd-c poisoned with lead) limits further reduction by controlling hydrogens available:



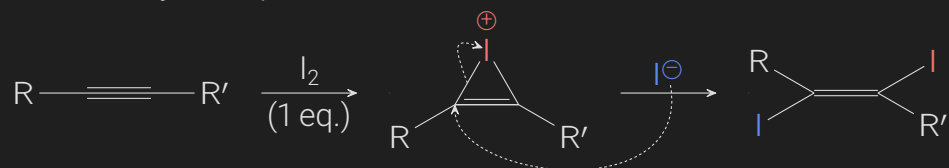
- Alkyne → **trans**-alkene; using generation of free radicals (•, single electron) that pair up with another electron generated by the dissociation of $\text{Na} \rightarrow \text{Na}^+ + \text{e}^-$ to create a free pair of electrons that then receive a hydrogen from NH_3 :



- Note, in lecture the added hydrogens were drawn separately; I am unsure, but I assume they happen near-simultaneously.

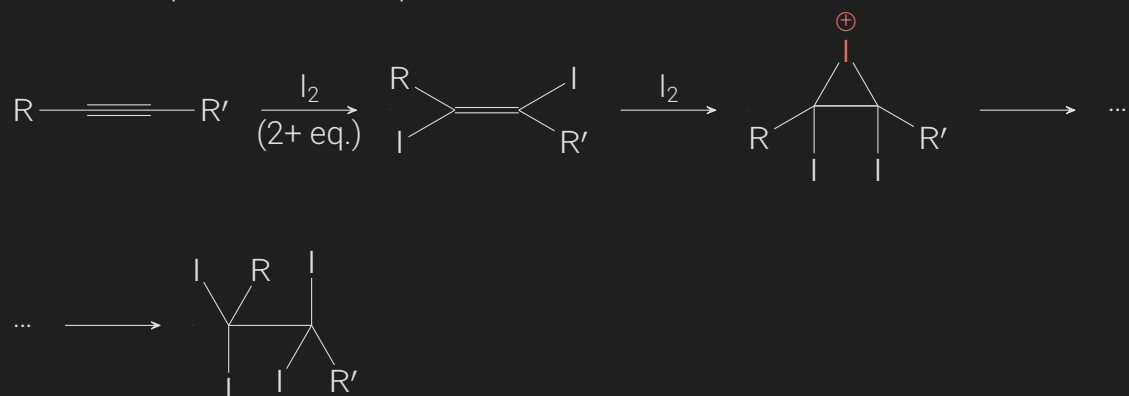
Halogenation of Alkynes

- Introductory example:



- The 3-membered cationic ring with a double bond is not very stable, so it does not form readily with a rate that is 10^3 – 10^7 times slower than that on an alkene.

- Same example, but with 2 equivalent or excess:

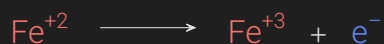


- Note: if you had controlled the second addition and added a different halide, then stereochemistry would have been important to consider since the products would have had chiral carbons.

16: Oxidation and Reduction

Redox Basics/Review

- **Oxidation:** is the **loss of electrons** or an **increase in the oxidation state** of an atom, an ion, or of certain atoms in a molecule.



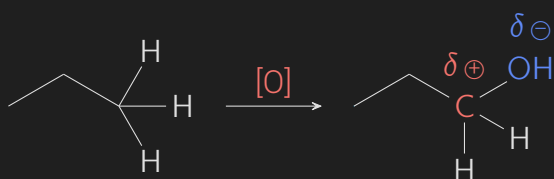
- **Reduction:** is the **gain of electrons** or a **decrease in the oxidation state** of an atom, an ion, or of certain atoms in a molecule (a reduction in oxidation state).



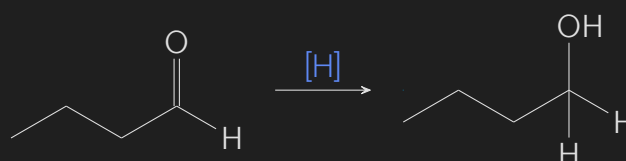
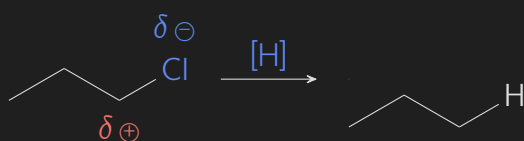
- **Redox (reduction-oxidation):** a type of chemical reaction in which the oxidation states of atoms are changed.
 - Characterized by the actual or formal transfer of electrons between chemical species.
 - Most often one species (**the reducing agent**) undergoing **oxidation** while another species (**the oxidizing agent**) undergoes **reduction**.
- Many reactions in organic chemistry are redox reactions due to changes in oxidation states but without distinct electron transfer; rather changes in **electron density**.
 - **Oxidation [O]:** going from a C–H \rightarrow C– δ^{\ominus} bond; pulls **electron density away** from the carbon.
 - **Reduction [H]:** going from a C– δ^{\ominus} \rightarrow C–H bond; pulls **electron density towards** the carbon.

Redox Practice Examples

- Examples of oxidation reactions:



- Examples of reduction reactions:



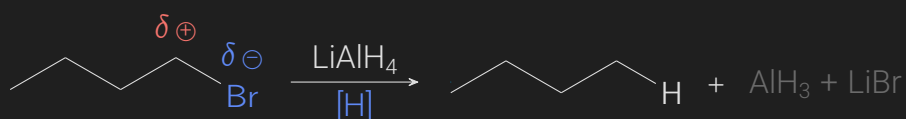
Reduction Reactions

Reduction Agents

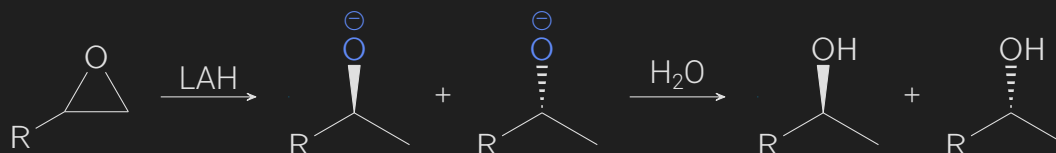
- **Hydride:** H^- , a negatively charged hydrogen ion (anion); commonly used as a **strong base** that react with **weak acids**, releasing H_2 .
- NaBH_4 : sodium borohydride.
- LiAlH_4 (LAH): lithium aluminum hydride.
- Both NaBH_4 and LiAlH_4 are **hydride donors**; they give up a hydride to become neutral.
 - Boron < aluminum in terms of size; electrons are attracted to boron to a greater degree, making it harder to remove the hydride for boron vs. aluminum. Thus:
 - LiAlH_4 is a **stronger** reducing agent.
 - NaBH_4 is a **weaker** reducing agent.

Reduction with LiAlH_4

- Example with an alkyl halide:



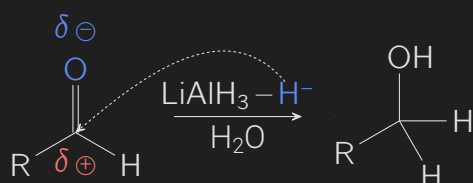
- Example with an epoxide:



- Remember: epoxide rings **no positive charge** will have the **less sterically hindered** side attacked.
- **Quenching:** deactivation of any unreacted reagents (adding a hydrogen source using H_2O for the negatively charged oxygen in this case).

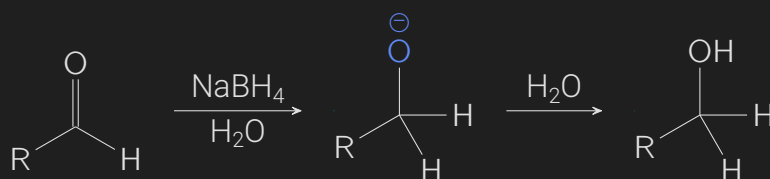
Reduction of Aldehydes

- Example of reduction to 1° alcohol:



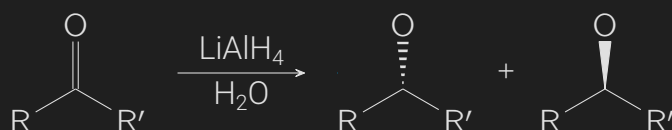
- Note: the reaction is done in two steps, but the addition of water was omitted here.

- The partial charge on the carbon double bonded to oxygen gives a slight **electrophilic** center for the **hydride** to attack due to the **inductive effect**.
- Same example as above, but with NaBH_4 and showing the intermediate step:



Reduction of Ketones

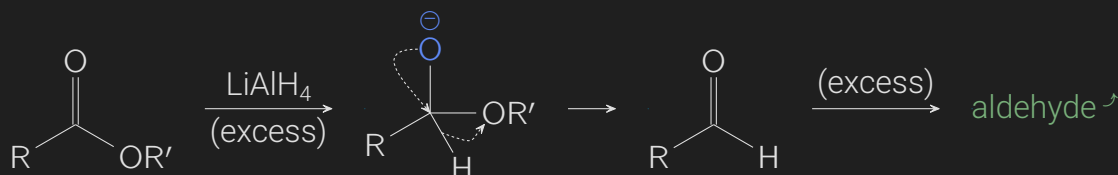
- Examples of generating racemic mixtures of 2° alcohols:



- Note: the above can be done with NaBH_4 , it's just slower.
- The inductive effect is slightly increased vs. aldehydes, since there are now two alkyl groups pushing electron density.

Reduction of Esters

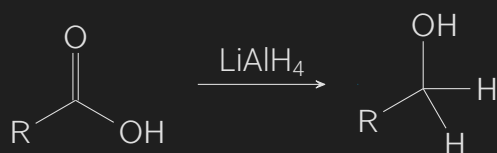
- First the ester is reduced to an aldehyde, then in presence of excess it will be further reduced from an aldehyde to a 1° alcohol.



- Resonance (shared electron density due to delocalization of electrons between either oxygen) is stronger than inductive effect, so **only reduction using LiAlH_4** works.

Reduction of Carboxylic Acids

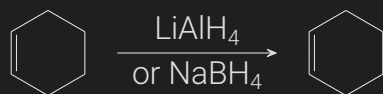
- Very similar to Esters, which ends up producing a 1° alcohol:



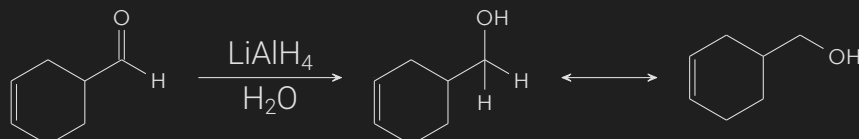
- Again, the presence of resonance will only allow the use of LiAlH_4 ; the first step will not occur if NaBH_4 is used as it is too weak to be a reagent.

Reduction Practice Problems

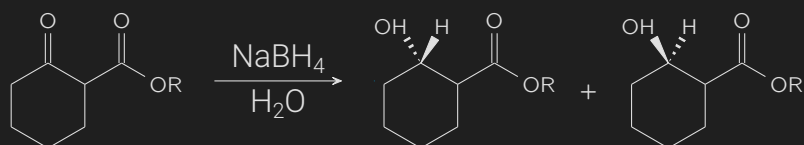
1. No reaction, needs carbonyl (C=O) functional group to proceed:



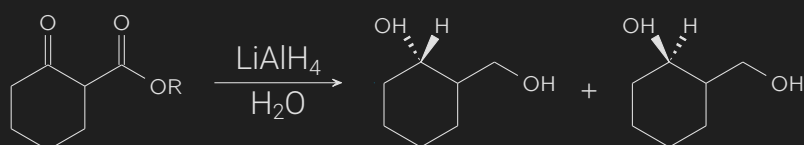
2. Example that contains a carbonyl group:



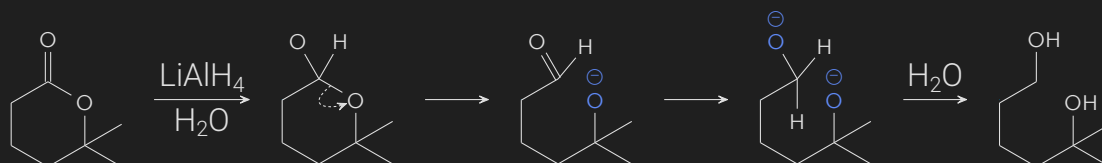
3. Example with a ketone and an acyclic ester:



- 3b. Same example as above but with LiAlH₄ (assuming excess):



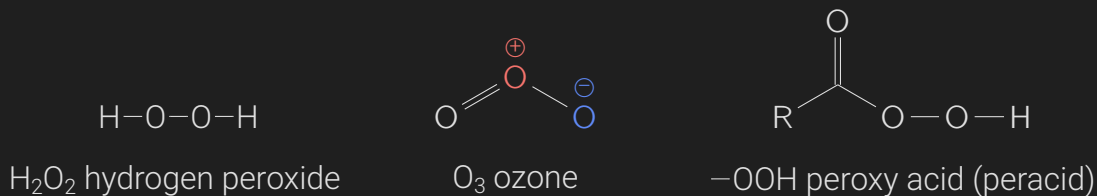
4. Example with a cyclic ester (assuming excess):



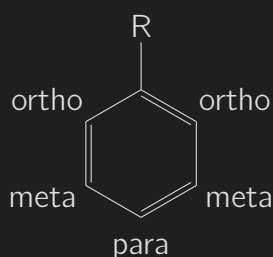
Oxidation Reactions

Oxidizing Agents

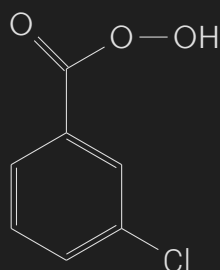
- **Peroxide reagents:** reagents that contain O—O linkage of some kind:



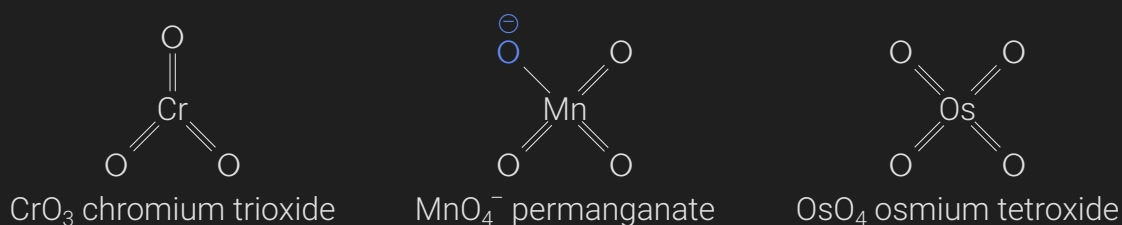
- **Arene substitution patterns:** IUPAC nomenclature for naming substituents other than hydrogen in relation to each other on an aromatic hydrocarbon:



- **meta-Chloroperoxybenzoic acid (mCPBA):** a strong and widely used oxidant in organic synthesis due to relative ease of handling.

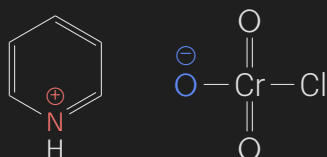


Metal Based Oxidizing Agents



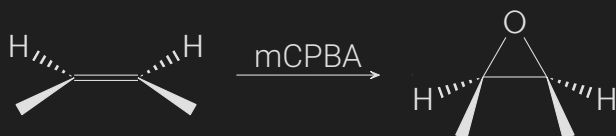
- KMnO_4 is **inexpensive**, but a very **strong oxidizing** agent and is **not soluble** in organic solvents.
 - MnO_4^- comes as KMnO_4 ; the anion must be created in order to be used as a reagent.
 - Keeping KMnO_4 cold can help reduce activation energy, leading a reduction of the more oxidized byproduct.

- OsO_4 is **very expensive**, but a **mild oxidizing** agent that is **soluble** in organic solvents.
 - N-methylmorpholine N-oxide (NMO): used with OsO_4 to reduce cost; it oxidizes the byproduct (Os^{+6}) back to OsO_4 in solution, allowing for reuse.
- CrO_3 is a **strong oxidizing** agent that is **not soluble** in most organic solvents; it tends to explode in the presence of organic compounds and solvents.
 - In water it forms chromic acid and anhydrides, from which salts such as sodium dichromate ($\text{Na}_2\text{Cr}_2\text{O}_7$) and PCC.
 - Other chromium based oxidizing reagents:
 - NaCrO_4 : sodium chromate.
 - $\text{K}_2\text{Cr}_2\text{O}_7$: potassium dichromate.
- **Pyridinium chlorochromate (PCC)**: $[\text{C}_5\text{H}_5\text{NH}]^+[\text{CrO}_3\text{Cl}]^-$ — a **mild** oxidizing reagent primarily used for **selective oxidation** of alcohols to **aldehyde or ketones** rather than carboxylic acid.

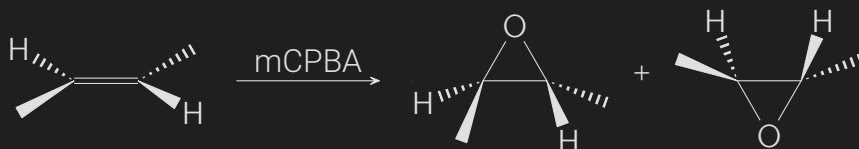


Epoxidation

- Example of oxidizing a *cis*-alkene to a *cis*-epoxide:



- Note: epoxide rings are always (commonly?) made when using mCPBA.
- The epoxide ring is an example of a **meso compound**, where there are chiral centers, but there is a plane of symmetry making it **superimposable on its mirror image**, so no other products are made.
- Similar to example of above, but with a *trans*-alkene to a *trans*-epoxide:



- The *trans*-epoxide ring is no longer a meso compound, so you must show both products; one when the ring forms on the top and one where the ring forms on the bottom.

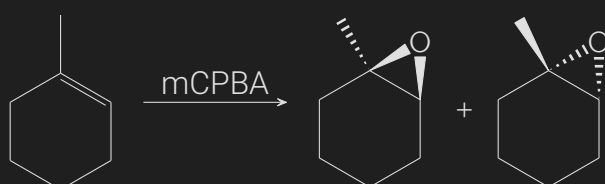
- These examples show that epoxidation reactions are **concerted** reactions, since there is no mixture of products between cis and trans products; it's dependent on the starting compound.

Epoxidation Practice Problems

1.

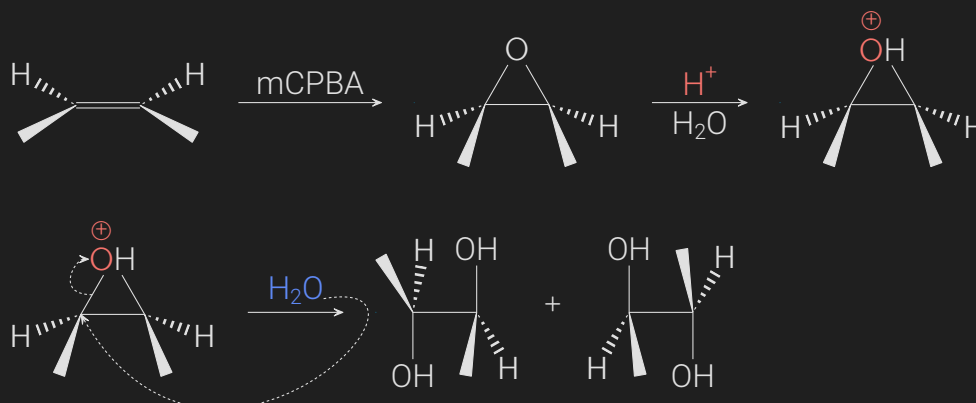


2.



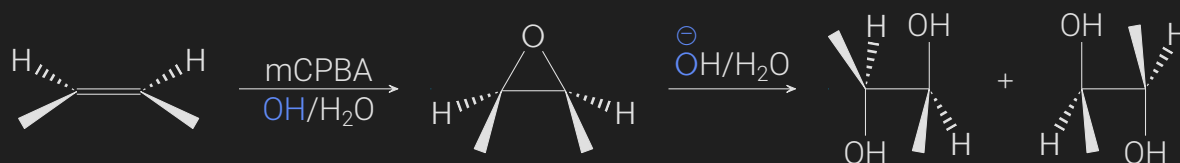
Trans Dihydroxylation

- Acid catalyzed:



- If both carbon centers in a product have the same configuration (S–S, R–R), then means it must have as corresponding enantiomer; R–S would be meso.
- Our first product is S–S, so we must show the second product, where OH comes from the top vs. the bottom.

- Base catalyzed:

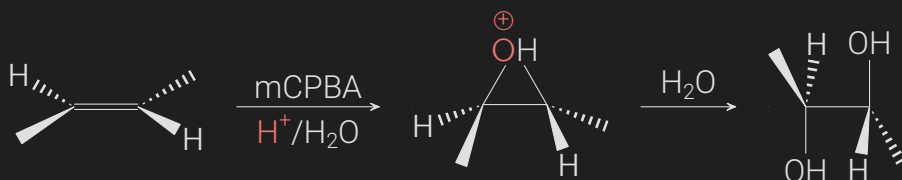


- Note: the result is the same as acid catalyzed conditions when both sides of the alkene are equally substituted.

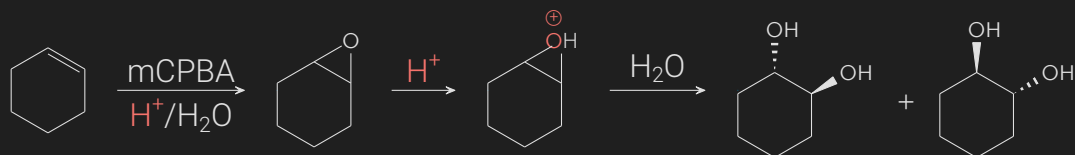
- However, under **acidic conditions** then the **more substituted** side will get attacked, while under **basic conditions** then the **less substituted** side will get attacked.

Trans Hydroxylation Practice Problems

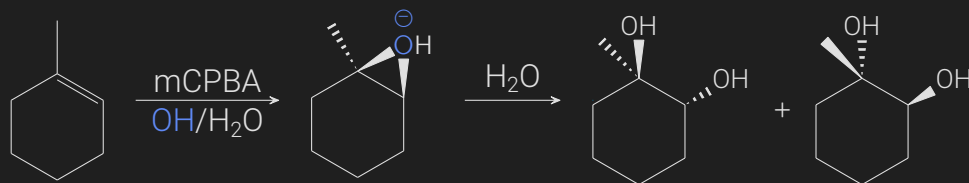
- *Trans*-alkene reactant (**acid catalyzed** in this case, but a **base catalyzed** would produce same product):



- Cyclohexene reactant:

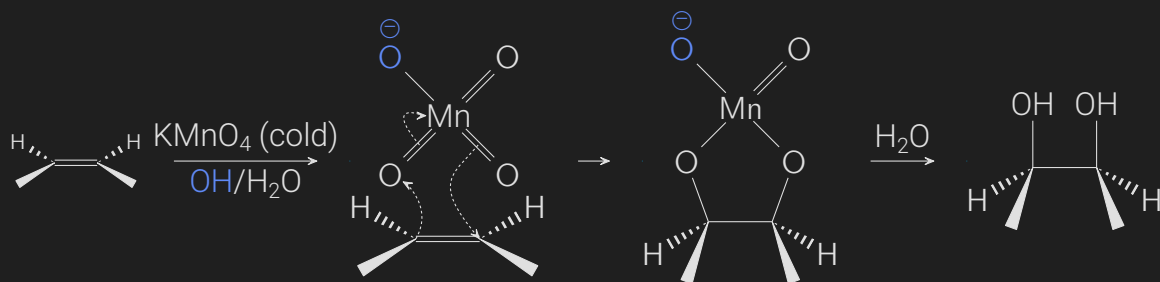


- 1-methylcyclohexene reactant:

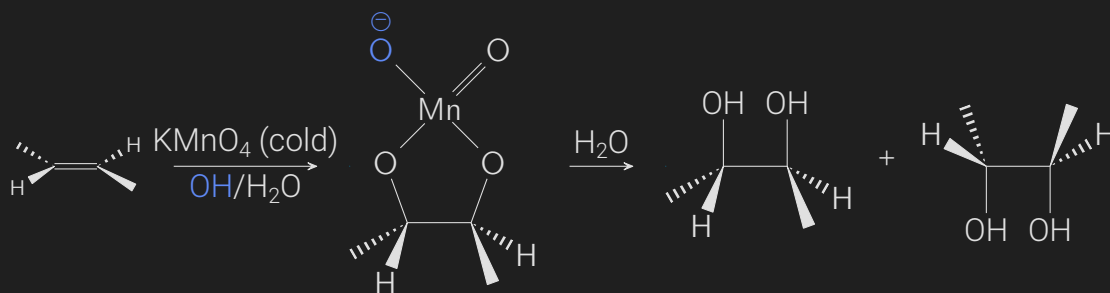


Syn Dihydroxylation

- Using potassium permanganate on a *cis*-alkene:



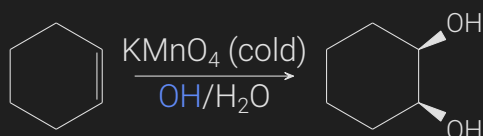
- The addition of MnO_4^- is a **concerted** reaction, which is then replaced by hydroxyl groups due to addition of water to create a syn product.
- The product is a meso compound, so it is achiral, making it have no enantiomers.
- Same reaction, but on a *trans*-alkene:



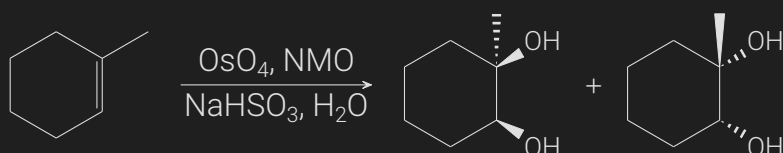
- The product is no longer chiral, giving us different products depending on which side MnO_4^- attached to.

Syn Dihydroxylation Practice Problems

- Cyclohexene with cold potassium permanganate:

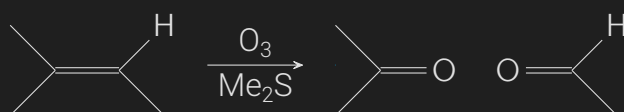


- 1-methylcyclohexene with osmium tetroxide:

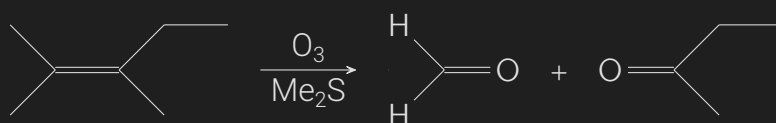


Ozonolysis

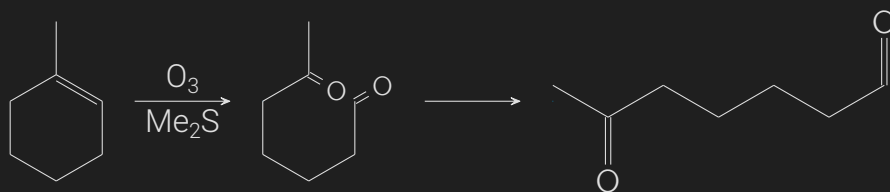
- **Ozonolysis:** when the unsaturated bonds of alkenes, alkynes, or azo compounds (azo compounds not important for this class) are **cleaved** with ozone.
- Basic example demonstrating bond cleavage:



- Me_2S : dimethyl sulfide; used as reducing agent that decomposes the intermediate (ozonide), making dimethyl sulfoxide (DMSO).
- Alkenes can be oxidized with ozone to form alcohols, aldehydes or ketones (depends on substituents), or carboxylic acids.
- Example of ozonolysis on an alkene, generating both an aldehyde and a ketone due to difference in substituents:



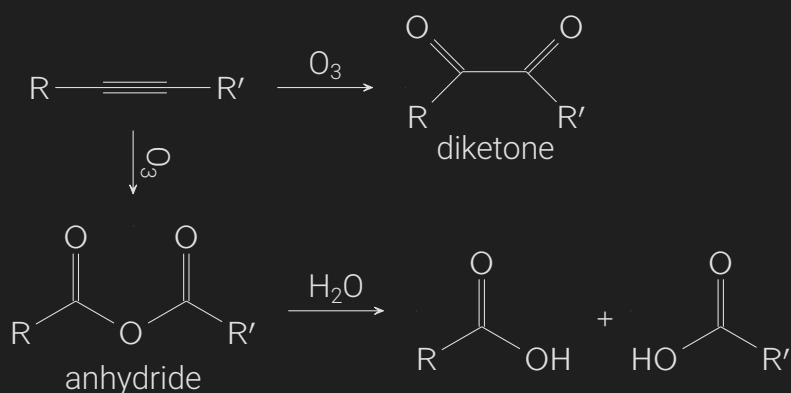
- Example with 1-methylcyclohexene:



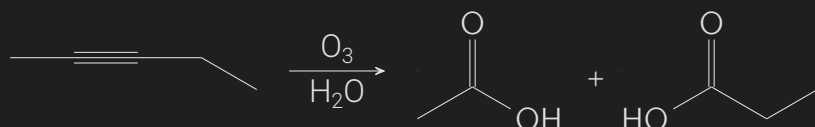
- Ozonolysis of alkynes generally gives an acid anhydride or diketone product, unlike the complete fragmentation in alkenes.

- If the reaction is performed in the presence of water, then the anhydride hydrolyzes to give two carboxylic acids.

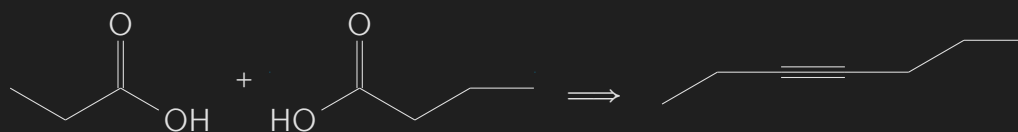
- Example of ozonolysis on alkynes:



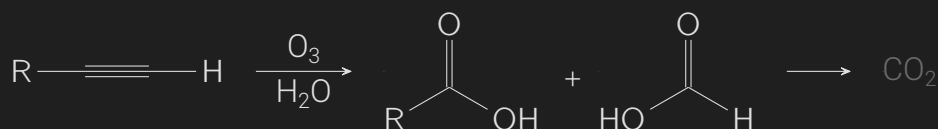
- Example of alkyne with different substituents:



- Retro synthesis (products → reactants) example:



- Example with a terminal alkyne:



- Terminal alkynes generate a carboxylic acid and a formic acid; formic acid will break down to CO₂.

17: Mass Spectrometry and Infrared Spectroscopy

Infrared Spectrometry

- **IR spectroscopy:** measurement of the interaction of infrared radiation with matter by absorption, emission, or reflection.
 - Used to study and identify chemical substances or functional groups.
 - Uses an infrared spectrometer to produce an infrared spectrum.
- The infrared spectrum is plotted on a graph with absorbance (or transmittance) vs. frequency.
- **Wavelength** λ : the distance over which a wave shape repeats.
- **Frequency** ν , f : number of occurrences per unit of time (period; T), i.e., $\nu = \frac{1}{T}$
- λ and ν are inversely proportional:

$$c = \lambda\nu \qquad \frac{c}{\lambda} = \nu \qquad \lambda \propto \frac{1}{\nu} \qquad c \left(\frac{1}{\lambda} \right) = \nu \qquad c\tilde{\nu} = \nu$$

- **Wavenumber** $\tilde{\nu} = \text{cm}^{-1}$: wave number is the spatial frequency of a wave, rather than number of waves per distance, making $\tilde{\nu} \propto \nu$
 - Energy: $E = h\nu$; h = Planck's constant.
 - Thus, $E \propto \nu \propto \tilde{\nu}$
 - Charts usually use frequency represented in wavenumbers.
- Bonds can be thought of as springs that are constantly moving. IR graphs exploits the fact that molecules absorb frequencies that are characteristic of their structure.
 - Peaks in the IR spectrum arise when a bond absorb energy that matches its vibrational energy, provides it has a dipole moment.
 - The **stronger the bond**, the faster its vibrations and the **greater the $\tilde{\nu}$** .
 - The **smaller the atoms** in a bond, the faster its vibrations and the **greater the $\tilde{\nu}$** .
- Calculating $\tilde{\nu}$:

$$\tilde{\nu} = \frac{1}{2\pi c} \sqrt{\frac{k}{\mu}}$$

Where k is the spring constant for the bond, c is the speed of light, and μ is the relative mass.

- A spectrograph is often interpreted as having two regions:
 - **Functional group region:** $\geq 1500 \tilde{\nu}$.
 - Most work done in this class will be in functional group region.
 - Shapes of the troughs help determine compounds in functional group region:

- -OH has a large wide “tongue shape”.
- -COOH has a wide and staggered “beard shape”.
- R-NH_2 has a double “fang shape”.
- $\text{R}_2\text{-NH}$ has a single “fang shape”.
- **Fingerprint region:** $< 1500 \tilde{\nu}$.
 - Generally there are many troughs which form intricate patterns, which can be used to determine certain compounds.
- **Conjugation:** alternating σ and π bonds. Allows for electron delocalization which in general lowers overall energy of the molecule and increases stability.
 - This leads to **lower $\tilde{\nu}$** due to the electron delocalization.
- Strong inductive effects towards electronegative atoms can retain double bond character if it is near one. This double bond “sealing” increases $\tilde{\nu}$ relative to resonance found in anhydrides due to increased double bond character.
 - Inversely, inductive effects towards double bonded oxygen decrease $\tilde{\nu}$ due to decreased double bond character.
- Carboxylic acid has even more increased resonance if it is close to another one, which decreases overall double bond character and thus decreases $\tilde{\nu}$.
 - Likewise, with NH_2 rather than OH , then there is even more of a tendency to enter resonance.

Mass Spectrometry

- **Mass Spectrometry (MS):** an analytical technique that is used to measure the mass-to-charge ratio of ions; typically presented as a mass spectrum.
 - **Mass-to-charge ratio $\frac{m}{Q}$:** a physical quantity that is used in electrodynamics of charged particles; two particles with the same mass-to-charge ratio move in the same path in a vacuum when subjected to same magnetic field.
 - **Mass spectrum:** an intensity of $\frac{m}{z}$ (a dimensionless unit of $\frac{m}{Q}$) representing chemical analysis; used to represent the distribution of ions by mass in a sample.
- Basic technique involves taking a sample, vaporizing it to gas form, then bombarding the ions with high energy electrons, then analyzing the unstable radical cations in order to determine relative abundance of ions by mass.
 - **Molecular ion peak M^+ :** corresponds to that of the molecule with all of its atoms intact, rather than a fragment, which themselves cause other minor peaks.
 - **Base peak:** The tallest peak, often is the same as the molecular ion peak, but not always.

- **M + 1 peak:** peaks that are due to molecular ions containing heavier isotopes of their atoms.
 - E.g., relative intensity of M+1 peak divided by 1.1 gives you the number of carbon atoms if the M peak has an intensity of 100%.
- **M + 2 peak:** used to determine if there are halogens in the molecule.
 - Relative natural abundance of chlorine: 3:1
 - Relative natural abundance of bromine: 1:1
 - Thus, roughly equal M + 2 peaks signal for Br, while uneven peaks signal for Cl.
- The atoms or molecules can then be identified by correlating known masses of the molecule or atoms to the identified masses through characteristic fragmentation patterns.
- Molecules containing only C, H and/or O atoms will have an even molecular weight.
- **Nitrogen rule:** molecules with an odd number of nitrogen atoms will have an odd molecular weight.
- In general, one can do the following to find the molecular formula:
 1. Assign M, M + 1, and M + 2 peaks.
 2. Multiple peaks by what ever factor makes M's peak 100%.
 3. Use M to determine if nitrogen is present, most of the time there will just be 1 if there is.
 4. Estimate number of carbons by dividing M + 1 relative abundance by 1.1.
 5. Determine if Cl or Br is present by comparison of M + 2 peaks. (use lower number isotope for calculation)
 6. Determine if oxygen is needed after accounting for halides and nitrogen.
 7. Add remaining hydrogens needed to reach M's amu.

18: Nuclear Magnetic Resonance Spectroscopy

NMR Basics

- **NMR spectroscopy:** a technique to observe local magnetic fields around atomic nuclei using excitation of nuclei with radio waves.
 - Radio waves triggers nuclear magnetic resonance, which changes resonance frequency, giving access to detail of the electronic structure of a molecule and its individual functional groups.
- NMR usually involves three sequential steps:
 - Alignment (polarization) of magnetic nuclear spins in an applied, constant magnetic field B_0 .
 - Perturbations of the nuclear spins by weak oscillating magnetic fields, usually referred to as a radio-frequency (RF) pulse.
 - Detection and analysis of electromagnetic waves emitted by the nuclei of the sample as a result of the perturbation.
- Organic chemist are usually limited to proton (1_1H) and carbon-13 ($^{13}_6C$), but can be used on more.

Proton NMR Spectroscopy

- **Proton NMR:** specific application of NMR spectroscopy with respect to hydrogen-1 nuclei within the molecule of a substance in order to determine structure.
 - There are four main characteristics analyzed in order to determine the structure, signal quantity, location (shift), area (integration), and shape (spin-spin).

Signal Quantity

- The number of signals identifies the number of different types of protons in the sample.
- **Chemically equivalent proton:** protons that share the same chemical environment.
 - CH_3 , CH_2 , and CH will always be non-equivalent to each other.
 - Protons are chemically equivalent if they are equivalent via symmetry considerations.
- Differences in chemical environment will show up as the same peak.
 - E.g., ethane has 6 hydrogens that all have the same chemical environment, while butane has two different chemically equivalent groups $2 \times (CH_3, CH_2)$

Signal Location

- **Chemical shift** δ : the resonant frequency of a nucleus relative to a standard in a magnetic field, i.e., **where** the signal shows up on the **x-axis** of the NMR spectrum.
 - $\delta = \frac{\nu_{sample} - \nu_{ref}}{\nu_{ref}}$
 - ν_{sample} : absolute resonance frequency of the sample.
 - ν_{ref} : absolute resonance frequency of a standard reference compound in the same applied magnetic field B_0 .
 - δ expressed in parts per million.
- Chemical shift can have deviations; exact value depends on molecular structure of solvent, temperature, magnetic field, and neighboring functional groups.
 - Tells us about the chemical or electrical environment in regard to proton NMR.
- NMR plots have an x-axis of 14–0 ppm.
 - Closer to 0 is the “upfield.”
 - Closer to 14 is the “downfield.”
 - Comparisons are relative.
- **Shielding**: an opposed magnetic field (B_i) to an applied field (B_0) induced by circulating electrons from adjacent bonds and atoms.
 - $B = B_0 - B_i$
 - **Shielded**: when nucleus of interest is surrounded by high electron density, making it more **upfield**.
 - **Deshielded**: the inverse of shielded; when electron density is pulled away from the nucleus, making it more **downfield**.
- Increased electronegativity of nearby atoms decreases shielding (increasing deshielding), thus making the chemical shift more downfield.
- Inductive effect decreases with distance, decreasing degree of chemical shift.
- Electron donating groups: OH, OCH₃, R, NR₂.
- Electron withdrawing groups: carbonyl groups (must be attached to ring), nitro groups.

Signal Integration

- NMR plots give the number of hydrogens responsible for a given peak by using an integration curve (area under the curve).

Signal Shape

- The splitting pattern of signal peaks reveal how many hydrogens neighbors exist for a particular group of equivalent hydrogens.
- In general, splitting will result in $N + 1$ peaks, where N is the number of hydrogens on the adjacent atom(s).
- **Singlet**: no hydrogens on adjacent atom.
- **Doublet**: one hydrogen on adjacent atom, resulting in two peaks of equal size.
- **Triplet**: two hydrogens on adjacent atom, with three peaks with an area ratio of 1:2:1.
- **Quartet**: three hydrogens on adjacent atoms, with four peaks with an area ratio of 1:3:3:1
- A peak is split by n identical protons into components whose sizes are the ratio of the n th row of Pascal's triangle.

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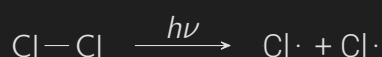
19: Free Radical Reactions

Free Radical Basics/Review

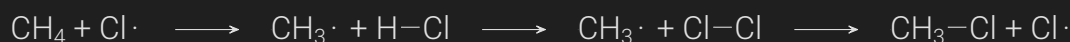
- **Free radical:** a highly reactive intermediate atom, molecule, or ion that has an unpaired valence electron formed upon homolytic cleavage, or homolysis.
 - Homolytic cleavage occurs when breaking a covalent bond, leaving each fragment with **one electron**.
 - Breaking bonds require energy, so **heat (Δ)** or **light ($h\nu$)** is needed for homolysis to take place.
 - Radical forming reactions proceed in **nonpolar solvents**, since radicals do not have a charge.
 - No rearrangements are possible with radicals.
- **Bond-dissociation energy (BDE):** one measure of strength of a chemical bond.
 - BDE is based on energy required for homolytic bond cleavage:
 - Higher BDE = less stable radical formed.
 - Lower BDE = more stable radical.
- Carbon radical geometry is not perfectly trigonal planar, instead it is a hybrid between trigonal pyramidal and trigonal planar.
- Compounds bearing C–H bonds react with radicals in the following order, reflecting C–H BDE:
 - **Least stable** $\leftarrow \text{CH}_3^\bullet < 1^\circ\text{C} < 2^\circ\text{C} < 3^\circ\text{C} < \text{benzyl} < \text{allyl} \rightarrow$ **most stable**
- **Captodative effect:** the stabilization of radicals by synergistic effect of electron-withdrawing group (EWG; “captor” group) and an electron-donating group (EDG; “dative” group)
 - Free radical can be **stabilized by resonance** in a manner directly analogous to that of carbanions and carbocations.

Radical Halogenation of Alkanes

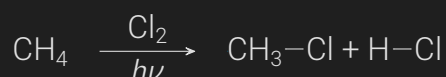
- **Free-radical halogenation:** a type of halogenation typical of alkanes and alkyl-substituted aromatics under application of UV light that proceeds by a free-radical chain mechanism.
- General mechanism (using chlorination of methane as example):
 - **Initiation:** homolysis of halogen by light or heat forming free radicals:



- **Chain propagation:** a hydrogen is pulled off the carbon leaving a methyl radical, then the methyl radical pulls a $\text{Cl}\cdot$ from Cl_2 :



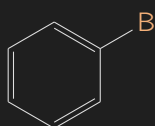
- If there is sufficient chlorine, then other products could be formed, for example a continuation to CH_2Cl_2 .
- **Chain termination:** recombination of two free radicals, needed to stop the reaction. Could result in two methyl radicals forming an impurity in final mixture. Ideally, however, the following net reaction occurs:



- Radical halogenation allows for the addition of a halogen on an alkene or other substituent, thus allowing for further reactions to take place on such normally unreactive substituents (e.g., haloalkanes) which are often needed in other reactions.
- **Statistical product distribution:** when all hydrogens in a substituent are equivalent and have equal chance of being replaced.
 - Hydrogens that form CH_2 or CH will be preferred on propane and above for alkanes.
- The reactivity of different halogens varies considerably.
 - $\text{F} > \text{Cl} > \text{Br} > \text{I}$.
 - Fluorine is difficult to control (too exothermic), with chlorine moderate to fast, bromine slow (with high UV levels) and iodine practically nonexistent (since it's endothermic).
 - Use of bromine will increase BDE preference and form a major product due to lower thermodynamic activation energy available.
 - Use of chlorine will typically create all possible products since activation energy is higher.

Allylic Bromination

- Benzylic position: the position next to a benzene ring:



- **N-Bromosuccinimide (NBS):** a chemical reagent with a weak $\text{N}-\text{Br}$ bond that is highly conducive to homolytic cleavage.
 - Leads to bromine radical formation in presence of peroxides or light.

- Avoids competitive alkene addition by limiting presence of Br present in the reaction medium.
- Allylic and benzylic radicals intermediates formed are more stable than other carbon radicals; major products are allylic and benzylic bromides.
- Use of NBS in allylic or benzylic bromination is also called Wohl-Ziegler reaction.

Anti-Markovnikov Addition of HBr to Alkenes

- Recall that normal **hydrohalogenation** follows Markovnikov's Rule due to carbocation intermediate forming on the more substituted side and the **hydrogen coming in first** on the less substituted side.
- Free radical conditions result in anti-Markovnikov reactions in contrast, since the less substituted carbon is **brominated first**, then the more substituted side forms the free radical.
- This only works well with Bromine, since chain propagations using HCl or HI is more endothermic.

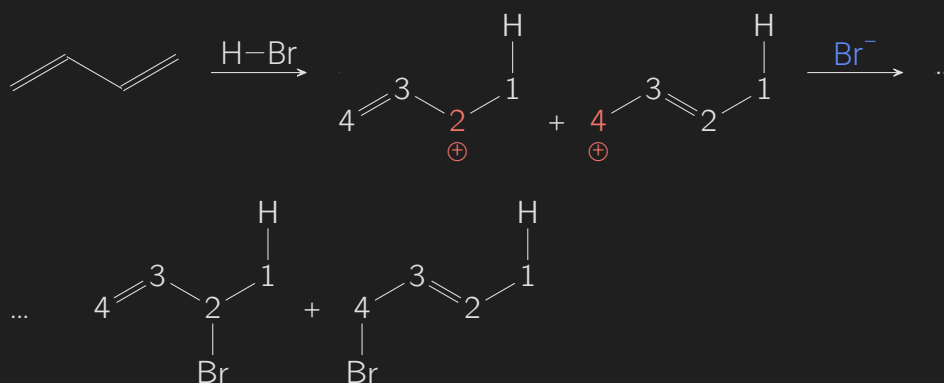
20: Conjugation and Resonance

Conjugation Basics/Review

- **Delocalization:** electrons not associated with a single atom or covalent bond.
 - Refers to resonance in conjugated systems and aromatic compounds.
- Conjugation: a system of connected p orbitals with delocalized electrons that generally lowers overall energy and increases stability.
 - Represented as alternating σ and π bonds, i.e., the overlap of a p orbital with another across an adjacent σ bond.
 - Most efficient when the p orbitals are coplanar.
- General rules of contributing significance:
 1. The greatest number of filled octets.
 2. The greatest number of covalent bonds.
 3. Minimize formally charged atoms.
 4. Minimization of unlike charged and maximization of like charges.
 5. Negative charges are on the most electronegative atoms, positive charges are on the most electropositive atoms.
 6. Do not deviate substantially from idealized bond lengths and angles.
 7. Maintain aromatic substructures locally while avoiding anti-aromatic molecules.

Conjugated Dienes

- Additions reaction of with HX and dienes result in both 1,2-addition and 1,4-addition pathways:



- **Kinetic product:** the 1,2-product, which is formed more rapidly due to low activation energy, but it is less thermodynamically stable.
- **Thermodynamic product:** the 1,4-product, which has a higher activation energy, but is more thermodynamically stable.

Pericyclic Reactions

- **Pericyclic reaction:** a concerted reaction with a transition state that has cyclic geometry and where the bond orbitals involved overlap in a continuous cycle.
 - No solvent effect; mediums make no difference.
 - No electrophile or nucleophile involved.
 - Products are highly stereospecific.
 - Conditions are either thermal (Δ) or photochemical ($h\nu$).
- There are many types of pericyclic reactions, usually being rearrangement or addition reactions.
 - **Cycloaddition:** a reaction in which two or more unsaturated molecules (or parts of same molecule) combine to form a cyclic derivative in which there is a **net reduction of bond multiplicity**, resulting in cyclization.

Diels-Alder Reaction

- **Diels-Alder reaction:** a concerted reaction between a conjugated diene and a substituted alkene (dienophile) to form a substituted cyclohexene.
 - **Diene:** a conjugated 4π electron system.
 - **Dienophiles:** the 2π electron system (generally substituted).



- **Good dienophiles** are **electron poor**, i.e., they have substituents that contain an electron withdrawing group (**EWG**).
- **Good dienes** are **electron rich**, i.e., they have substituents that contain an electron donating group (**EDG**).
- A diene is locked in *cis* form has a lower activation energy than one that is not locked (alternating *cis-trans*), leading to a faster reaction.
 - *S-trans* form is locked (closed system), meaning it cannot react.
- **Inward** facing bonds on the substituted dienophile results in the **dashed (axial)** position if a chiral carbon is created, while **outward** facing bonds results in the **wedge (equatorial)** position.
 - **Exo form (thermodynamic product):** when the substituent approaches from the **outside**.
 - **Endo form (kinetic product):** when the substituent approaches from the **inside**.

- Reactions typically occur at moderate temperatures; not much activation energy is needed to reach the more stable state.
 - **Endo-Rule:** the endo form (kinetic product) is thus generally the major product, due to better overlap of π electron system in the intermediate step.
- Diels-Alder reactions are **stereospecific** depending on approach condition, i.e., the *cis* form of dienophile leads to *cis*-type of product and the *trans* form of dienophile leads to *trans*-product.
- Diels-Alder reactions are also **regiospecific**, with the ortho product being favored in case of substituted dienes, and the para product being favored in the case of substituted dienophiles.
 - The 1-position is favored in 1,-substituted dienes.
 - The avoidance of the meta-position is due to the preference for the most **nucleophilic** of the **diene** lining up with the most **electrophilic** part of the **dienophile**.
- When reacting with **alkynes**, then the diene has inward and outward methods of approach.
 - The **outward** position of dienes leads to the **dashed** position.
 - The **inward** position of dienes, which typically forms the bridge, results in the **wedge** position.

21: Benzene and Aromaticity

Determining Aromaticity

- **Aromaticity:** a property of cyclic, planar structures with π bonds in resonance, giving increased stability relative to other arrangements with same set of atoms.
 - Most aromatic compounds are derivatives of benzene; the word aromatic often informally refers to benzene derivatives despite the existence of non-benzene aromatic compounds.
- **Characteristics of aromatic systems:**
 - A **delocalized conjugated** π system.
 - **Planar**, with all contributing atoms in the same plane.
 - **Cyclic**, arranged in one or more rings.
 - Follows **Hückel's rule**; the number of π electrons is **even**, but **not a multiple of four**.
 - **Hückel's rule:** if a molecule has $4n + 2\pi$ -electrons, it is aromatic; $n = 0$ or any integer.
 - **Antiaromatic:** when an aromatic system has $4n$ π -electrons (a multiple of four), making it highly unstable and reactive; $n \neq 0$
- **Least stable** \leftarrow **antiaromatic** $<$ **non-aromatic** $<$ **aromatic** \rightarrow **most stable**
 - Reactions will only move compounds away from the relatively more stable state if it is done in the presence of a catalyst.
 - Antiaromatic will typically become non-planar, breaking the π interactions, and typically become non-aromatic.
- Introducing a charge to a non-aromatic cyclic compound can induce a delocalized conjugated π system.
 - **Negative charges** can share in resonance, increasing number of π -electrons in the system.
 - **Positive charges** do not change the number of π electrons in the system.
 - Either one can lead to an antiaromatic or aromatic compound, depending on Hückel's rule.

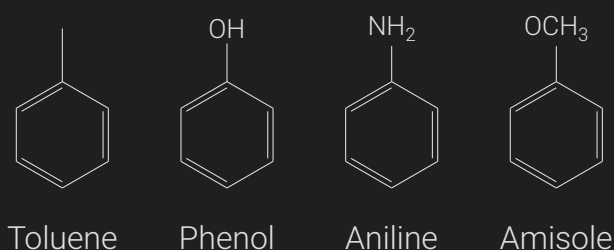
Aromatic Compounds

- **Polycyclic:** aromatic molecules containing two or more simple aromatic rings fused together by sharing two neighboring carbon atoms.
 - Not all fused carbons are necessarily equivalent, some electrons are not delocalized over the entire molecule.
- **Heterocyclic:** when one or more of the atoms in the ring is of an element other than carbon.

- Tends to lessen the ring's aromaticity, increasing reactivity.
- The addition of the lone pair electrons from unusual atoms often contributes one of the electron's p-orbital to the aromatic π system if conjugation is need to be aromatic.
- However, if the system is already aromatic, then the lone pair will act as a base, not increasing number of π -electrons.

Benzene Derivative Nomenclature

- **Monosubstituted** benzenes are named by the IUPAC system using benzene as the suffix.
 - Common monosubstituted benzene names:



- **Disubstituted** benzenes are named using numbers such as 1,2(ortho; o)- 1,3(meta; m)- and 1,4(para; p)-.
 - Differing substituents on the same ring are listed in alphabetical order.
 - The parent suffixes toluene, phenol and aniline are also used in conjunction with a second substituent.
- **Polysubstituted** benzenes substituents are alphabeticalized with the numbers around the ring to giving the lowest numerical total.
 - Use of common names described above are used when possible and designate the first position.

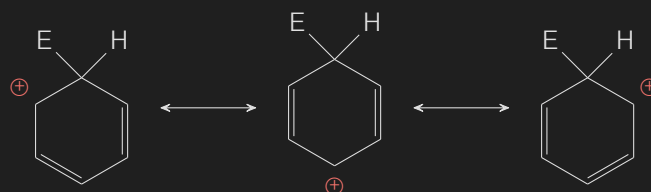
22: Reactions of Aromatic Compounds

Electrophilic Aromatic Substitution

- **Electrophilic Aromatic Substitution (EAS):** a reaction where an atom (usually hydrogen) is replaced by an **electrophile** while the product retains aromaticity.
- The electrophile typically used:
 - Br^+ or Cl^+ (via Lewis acid catalyst)
 - Nitronium ion: $\text{NO}_2^+ \rightarrow \text{O}=\text{N}^+=\text{O}$
 - SO_3H^+
 - 2° or 3°R^+ (not 1°)
 - Acylium ion: RCOX



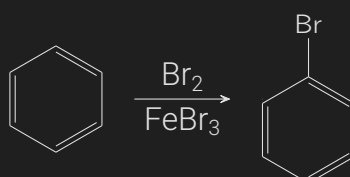
- **Arenium ion:** aka σ -complex (sigma complex); the reactive cyclohexadienyl cation that appears as a **reactive intermediate** for EAS.



Note: the hydrogen is then removed with a **base** in order to regain aromaticity.

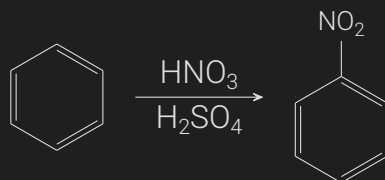
Halogenation of Benzene

- Benzene can be chlorinated or brominated in the presence of a **Lewis acid catalyst**, typically ferric (iron III) chloride (FeCl_3) or ferric bromide (FeBr_3).
 - The catalyst reacts with X_2 to form the strong electrophile; the catalyst regenerated by end of the reaction.
 - Fe^\cdot may be used instead if used in the presence of Cl_2 or Br_2 since it will form the catalyst.
 - Aluminum chloride (AlCl_3) can be used as well, cost is only real factor.



Nitration of Benzene

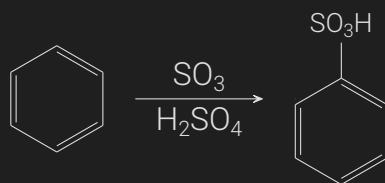
- In benzene nitration, the electrophile is the **nitronium ion, NO_2^+** ; it's formed by the protonation of nitric acid by the stronger sulfuric acid (H_2SO_4), followed by loss of H_2O .
- Sulfuric acid is regenerated and recycled in the reaction.



- Once the nitro group is added, then a reduction step using Zinc (Zn) or Tin (Sn) and hydrochloric acid is done to make an aniline (benzene with NH_2).

Sulfonation of Benzene

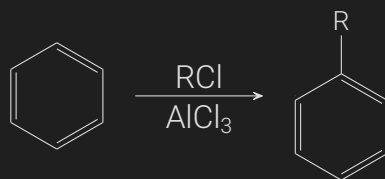
- In this reaction sulfuric acid protonates sulfur trioxide to form the **electrophilic sulfur-containing compound, SO_3H^+** .
- Sulfuric acid is regenerated and recycled in the reaction.



Friedel-Crafts Alkylation of Benzene

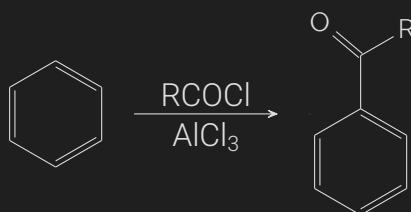
- **Friedel-Crafts alkylation (F.C. alkylation):** alkylation of an aromatic ring with an alkyl halide using a strong Lewis acid catalyst, typically **aluminum chloride, ferric chloride**, but ferric bromide is also possible, similar to **halogenation of benzene** ↗.
- F.C alkylation reactions only work with methyl or ethyl groups; will not work correctly for longer groups, e.g., addition of a propyl alkyl becomes isopropyl substituent.
- Specific structure of the electrophile can vary due to carbocation stability trends.
 - **Case 1 (MeX or EtX):** a methyl or 1° -carbocation cannot form and no rearrangements are possible; MeCl and EtCl complex with AlCl_3 is the electrophile.
 - **Case 2 (1°RX):** the 1°RCl complex with AlCl_3 loses AlCl_4^- during the rearrangement, creating a 2° or 3°R^+ .
 - **Case 3 (2° or 3°RX):** the 2° or 3°RCl complex with AlCl_3 loses AlCl_4^- directly creating the 2° or 3°R^+ (with rearrangement of 2°R^+ occurring, if feasible)

- The Lewis acid catalyst is regenerated and recycled during the reaction with the addition of HCl byproduct much like halogenation.



Friedel-Crafts Acylation of Benzene

- **Friedel-Crafts acylation:** when a new carbon-carbon bond is formed between a benzene carbon and a carbonyl carbon to create a ketone.
- Acylation is similar to alkylation, except:
 - the electrophile is an **acylium ion** derived from an acid chloride;
 - rearrangements will not occur because of the stability of the resonance-stabilized acylium ion.



- Can be used to introduce more carbons to the alkyl group than alkylation alone can with later reduction techniques to remove the oxygen.
 - **Clemmensen reduction:** zinc in presence of mercury (Zn(Hg)) with concentrated hydrochloric acid can be used in the reduction step.
 - **Wolf-Kishner reduction:** hydrazine (N₂H₄; NH₂-NH₂) in the presence of a base and heat can also be used for reduction.
 - Differences in pathways depends on substituents and their interaction with various reduction agents.
- **Intramolecular** F.C. acylation reactions can also occur to create **fused rings**.
- Addition of KMNO₄ with a strong base and heat acts as a strong oxidizing agent, resulting in any carbon attached directly to the ring becoming a carboxylic acid.

EAS Reactions of Disubstituted Benzenes

- Agents and their products remain the same as monosubstituted benzenes, but the location of the new group can vary.
- **EDG** push electron density toward the benzene ring, making it more **electron rich** (**activated**).

- $-\text{NH}_2$, $-\text{OH}$, $-\text{OR}$, $-\text{R}$, $-\text{NHR}$, $-\text{NR}_2$
- EDG are *ortho/para* directing, with para preference increasing with increasing steric hindrance; small groups are approximately equal with slight ortho preference due to charge separation distance.
- EWG pull electron density away from the benzene ring, making it *electron poor*, reducing electrophilic substitution tendency (*deactivated*).
 - $-\text{COOR}$, $-\text{CONH}_2$, $-\text{CONR}_2$, $-\text{CN}$, $-\text{NO}_2$, $-\text{COOH}$, $-\text{CHO}$, $-\text{COR}$
 - EWG are *meta* directing, as the ortho/para positions remain more *electron poor*.
- When there are two (or more) substituents, then the *strongest activator* (the *strongest EDG* or *weakest EWG*) determines where the incoming electrophile reacts.

Issues with EAS Reactions

- If the ring is *extremely activated* (typically with an $-\text{OH}$), then the product results in a *tribromophenol* product in presence of a Lewis acid catalyst.
 - Br_2 by itself can be used on a phenol to create a mono para/ortho product.
- If an *aniline* (benzene + NH_2) undergoes *halogenation* then the Lewis acid catalyst reacts with the NH_2 , *blocking the reaction*.
 - Not using a catalyst will allow the reaction, producing a mix of ortho/para products since $-\text{NH}_2$ is a strong EDG.
- *F.C. alkylation* reactions do not work with a strong EWG that *deactivates* the ring.