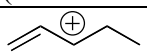
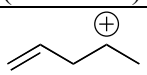
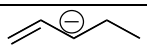
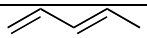
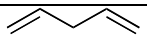
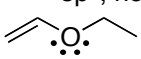
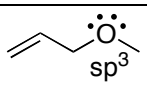
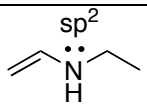
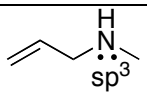
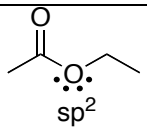
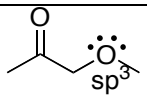
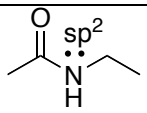
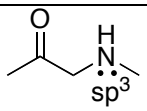
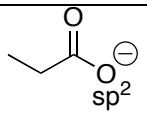
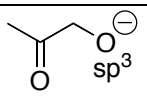
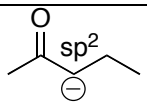
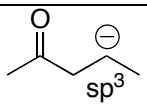
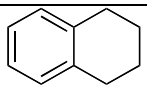
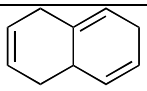
Ch. 15 Conjugated Systems

The General Stabilization Effect of Conjugation (Section 15.1, 2, 3, 8, 9)

		Conjugated (more stable)	Isolated (less stable)	Notes:
1	Cations			
2	Radicals			
3	Anions			
4	Dienes			
5	Ethers	sp^2, not sp^3!! 		An N or O next to a double bond becomes sp^2. An isolated N or O is sp^3
6	Amines			
7	Esters			
8	Amides			Very special, chapter 23, all of biochemistry, proteins, enzymes, etc.
9	Oxyanions (Carboxylates)			Very special, chapter 21
10	Carbanions (Enolates)			Very special, chapter 22
11	Aromatics			Very special, chapters 16 + 17

Conjugation: Anything that is or can be sp^2 hybridized is stabilized when next to π bonds.
- oxygens, nitrogens, cations, radicals, and anions

Notes:
1. Any atom that can be sp^2 will be sp^2 when next to a double bond
2. "Conjugation" is when sp^2 centers are joined in an uninterrupted series of 3 or more, such that an uninterrupted series of π-orbitals is possible
3. Any sp^2 center has one p orbital

Impact of Conjugation

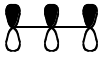
4. **Stability:** Conjugation is **stabilizing** because of π-orbital overlap (Sections 15.2, 4, 7)
   - Note: In the allyl family, **resonance = conjugation**

One p
Unstabilized
Isolated

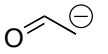
Two p's
π-bond
C=C

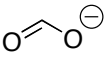
C=O

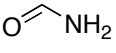
C=N

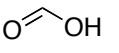


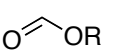
Three p's
Allyl type

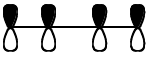




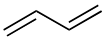


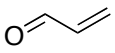


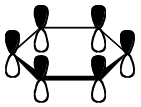




Four p's
Butadiene type



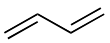




Six p's in circuit
Aromatic

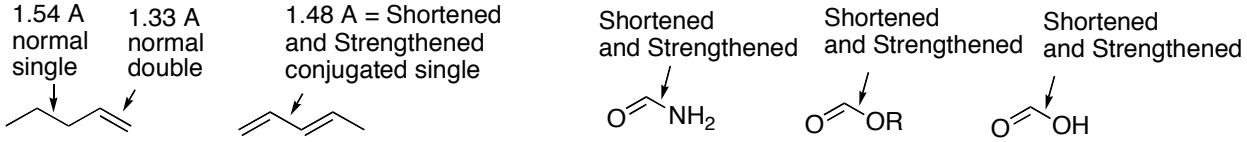
5. **Reactivity:** Conjugation-induced stability impacts **reactivity** (Sections 15.4-7) • If the **product** of a rate-determining step is stabilized, the reaction rate will go **faster** (product stability-reactivity principle) o Common when allylic cations, radicals, or carbanions are involved • If the **reactant** in the rate-determining step is stabilized, the reaction rate will go **slower** (reactant stability-reactivity principle) o Why aromatics are so much less reactive o Why ester, amide, and acid carbonyls are less electrophilic than aldehydes or ketones

6. **Molecular shape** (Sections 15.3, 8, 9)
   - The π-orbitals must be aligned in parallel for max overlap and max stability
   - The sp^2 centers must be coplanar



All four sp^2 carbons must be flat for the p's to align

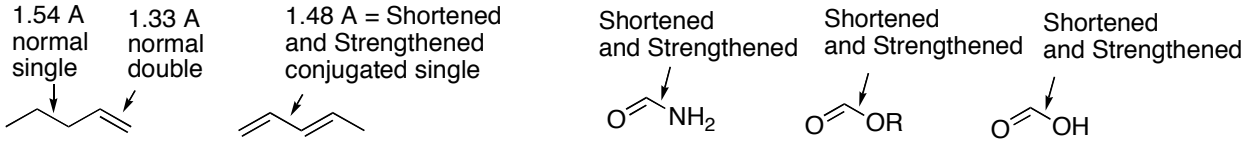
7. **Bond Length:** Bonds that look like singles but are actually between conjugated sp^2 centers are **shorter** than ordinary single bonds



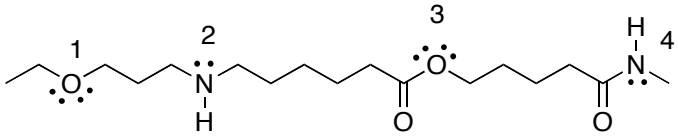
- In amides, esters, and acids, the bond between the carbonyl and the heteroatom is shortened

8. **Bond Strength:** Bonds that look like singles but are actually between conjugated sp^2 centers are **stronger** than ordinary single bonds

9. **Bond Rotation Barrier:** Bonds that look like singles but are actually between conjugated have much larger rotation barriers than ordinary single bonds
   - Because in the process of rotating, the π-overlap and its associated stability would be temporarily lost



10. **Hybridization:** Conjugated sp^2 atoms have both sp^2 and p orbitals. You should always be able to classify the hybridization of **lone pairs on nitrogen and oxygen**.
    - **Isolated** oxygens or nitrogens: sp^3 atom hybridization, sp^3 lone-pair hybridization, and tetrahedral, 109º bond angles
    - **Conjugated nitrogens**: sp^2 atom hybridization, **p lone-pair hybridization (needed for conjugation)**), and 120º bond angles
    - **Conjugated oxygens**: sp^2 atom hybridization, **one p lone-pair hybridization** (needed for conjugation), **one sp^2 lone-pair**, and 120º bond angles



Atom	O-1	N-2	O-3	N-4
Isolated vs. Conjugated				
Atom Hybridization				
Lone-Pair(s) Hybridization				
Bond Angles				

15.2 Diene Stability and the Stability of other Acyclic Systems with 2 Elements of Unsaturation

Q1: Rank the stability of the following dienes:

Stability Factors for Simple Dienes:

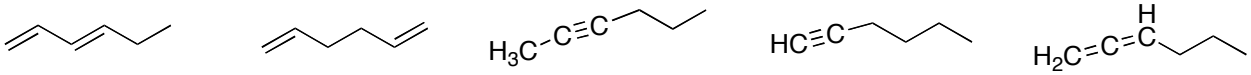
1. Isolated versus Conjugated: Conjugation stabilizes
2. Substitution: More highly substituted are more stable.

Stability Patterns for Regular Dienes versus Other Systems with 2 elements of unsaturation

3. **Allenes** = "Cumulated Dienes": **Less stable than dienes or alkynes**
   - in allenes, the central carbon is sp rather than sp^2 hybridized

4. **Alkynes**: **Less stable than dienes, but more stable than allenes**.
   As for alkenes and dienes, more substituted alkynes are more stable less substituted alkynes

Q2: Rank the stability of the following isomers:



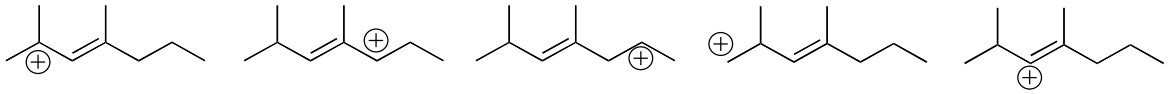
Q3: Rank the amount of heat produced if the isomers above were hydrogenated? Burned?

15.4 Stability of Allylic/Benzylic (Conjugated) Cations

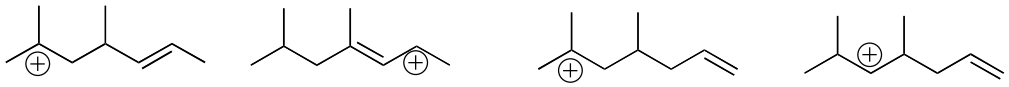
Stability Factors for Cations:

1. Isolated versus Conjugated/Allylic: Conjugation stabilizes
2. Substitution: More highly substituted are more stable.
    - Conjugation/allylic is more important than the substitution pattern of an isolated cation (i.e. 1º allylic > 3º isolated)

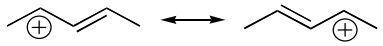
Q1: Rank the stability of the following cations?

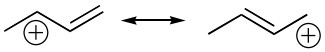


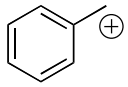
Q2: Rank the stability of the following alkene cations?



Allylic Cations, Resonance, and Allylic Symmetry/Asymmetry

a. 

b. 

c. 
”Benzylic”

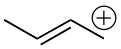
1. Two resonance structures each (at least)
2. Charge is delocalized, shared
3. **Allylic cations can be symmetric or asymmetric**
4. When an allylic cation is asymmetric, it’s helpful to evaluate which form would make a larger contribution to the actual hybrid
    - Cation substitution is more important than alkene substitution

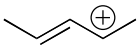
Q3: For above cations, identify as symmetric or asymmetric.

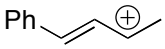
Q4: For the following cations:

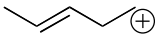
a. identify which are allylic (would have a resonance structure).
b. For those that are allylic, identify which are symmetric vs. asymmetric?
c. For any asymmetric allylic cations, draw the resonance structure
d. For any asymmetric allylic cations, identify which resonance structure would make the larger contribution to the actual resonance hybrid

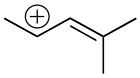
a. 

b. 

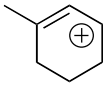
c. 

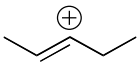
d. 

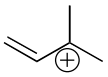
e. 

f. 

g. 

h. 

i. 

j. 

Impact of Allylic Cation Resonance on Reaction Rates and on Whether One or Two Products Form (S_N1 Reactions)

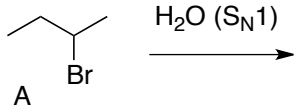
1. **Rates**: Resonance/conjugation stability enhances rates when cation formation is rate-determining

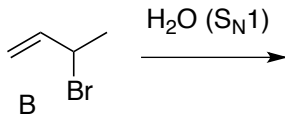
2. **One Product or Two?** Product mixtures result if an allylic cation is asymmetric.
   - two unequal resonance structures can lead to two products (structural isomers).

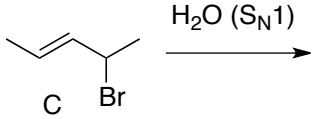
3. **Product Distribution**
   - When two isomeric products can form, consider two things:
     1. Which product is more stable?
        - This will impact "product stability control" = "thermodynamic control" = "equilibrium control"
        - To assess product stability, focus on the alkene substitution
     2. Which resonance form of the cation would have made a larger contribution?
        - This will often favor "kinetic control", in which a product which may not ultimately be the most stable forms preferentially
4. **Position of Cation Formation**: When a conjugated diene is protonated, consider which site of protonation would give the best allylic cation.

Q1: Key: Think about the cation! For the bromides A-C:

a. Draw the cation intermediates.
b. If an allylic cation is involved, recognize as symmetric or asymmetric.
c. Rank the reactivity of the three bromides.
d. Draw the product or products. Be clear to notice whether you'd get one isomer or two.
e. If two products are possible, identify which is more stable (the "thermodynamic product") based on product alkene stability.
f. For the asymmetric allylic cation, identify which resonance structure makes a larger contribution to the resonance hybrid. Does this lead to the "thermodynamic" (more stable) product, or to the "kinetic" (less stable) product?







Impact of Allylic Cation Resonance on Addition of H-X to Conjugated Dienes.

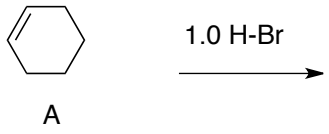
- Notes on predicting products when H-X adds to a diene.

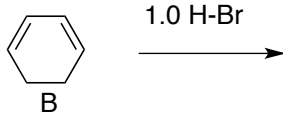
Questions/Issues to Deal With When Predicting Product(s).

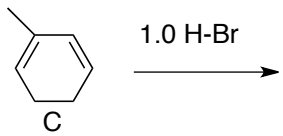
1. Always protonate first on an outside rather than inside carbon.
   - This will give an allylic rather than isolated cation
2. Is the diene symmetric or asymmetric?
   - If it's symmetric, it doesn't matter which outside carbon you add to first.
   - If it's asymmetric, then protonating at different ends will likely give allylic cations of unequal stability. Thus you should decide which protonation site will give the best allylic cation.
3. Is the allylic cation (once you have protonated) symmetric or asymmetric?
   - If it's symmetric, you'll get one structural isomer.
   - Is it's asymmetric, you'll get two structural isomers.

Question 2: Key: Think about the cation! For the dienes A-C,

a. Draw the cation intermediates.
b. If an allylic cation is involved, recognize as symmetric or asymmetric.
c. Rank the reactivity of the three bromides.
d. Draw the product or products. Be clear to notice whether you'd get one isomer or two.
e. If two products are possible, identify which is more stable (the "thermodynamic product") based on product alkene stability.
f. For the asymmetric allylic cation, identify which resonance structure makes a larger contribution to the resonance hybrid. Does this lead to the "thermodynamic" (more stable) product, or to the "kinetic" (less stable) product?
g. When two products form, classify each as a "1,2" or "1,4" product



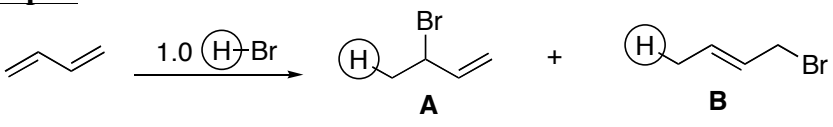




Sections 15.5,6 **1,2 vs. 1,4 Addition to Conjugated Dienes: "Kinetic" vs. "Thermodynamic" Control**

1. **"Thermodynamic Control" = "Product-Stability Control" = "Equilibrium Control"**
   - This is when **the most stable** of two possible **products** predominates.
     - **Use Alkene Stability to identify which product is more stable.**
     - The most stable product will be preferred if either:
       - The two products can equilibrate, or
       - The more stable product involves a more stable transition state
2. **Kinetic Control:** If **the less stable** of two possible products predominates.
   - This will always require that for some reason the less stable product forms via a better transition state (transition-state stability/reactivity principle). Common reasons:
     - Charge distribution in an allylic cation or radical.
     - Proximity of reactants. In an H-X addition to a diene, often the halide anion is closer to the "2" carbon than to the "4" carbon of the allylic cation.
     - Steric factors. (Why bulky E2 base give less stable Hoffman alkenes.)
3. **Temperature Factor**: When allylic halides are produced, the "thermodynamic" product increases at higher temperature due to equilibration.

Example:



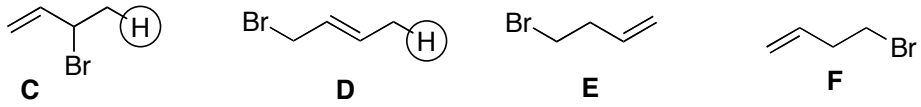
Kinetic vs Thermodynamic Control Conditions

1,2- vs 1,4 Addition Product:

at -80°C	80% (major)	20% (minor)
at +40°C	15% (minor)	85% (major)
More/Less stable:		

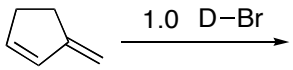
Mech (and why)

What about the following? Do they form, and if not why not?



More H-X to Conjugated Dienes Practice

1. Draw the mechanism, including both resonance structures for the best allylic cation.
2. Predict the products for the following reaction.
3. Identify each product as 1,2 or 1,4 product.
4. Identify which product is the "thermodynamic" product, and which might be the "kinetic".
5. One product **X** is the major product at low temp, but the other product **Y** is major at higher temperatures. Assign "**X**" and "**Y**" to the appropriate products.



Review on predicting products when H-X adds to a diene.

1. Always protonate first on an outside rather than inside carbon.
   - This will give an allylic rather than isolated cation
2. Is the diene symmetric or asymmetric?
   - If it's symmetric, it doesn't matter which outside carbon you add to first.
   - If it's asymmetric, then protonating at different ends will likely give allylic cations of unequal stability. Thus you should decide which protonation site will give the best allylic cation.
3. Is the allylic cation (once you have protonated) symmetric or asymmetric?
   - If it's symmetric, you'll get one structural isomer.
   - Is it's asymmetric, you'll get two structural isomers.

Mixtures of 1,2 and 1,4 addition also occur when dihalogens (Br_2, Cl_2) add to dienes

Q2: Draw the major products when the diene above reacts with Br_2. Which would you expect to be the "thermodynamic" product?

15.7 Allylic/Benzylic Radicals and Allylic Halogenation

Stability Factors for Radicals:

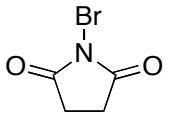
1. Isolated versus Conjugated/Allylic: Conjugation stabilizes
2. Substitution: More highly substituted are more stable.
    - Conjugation/allylic is more important than the substitution pattern

Impact of Radical Resonance on Reactivity and Product Formation: Allylic Radical Bromination is Fast!

1. **Rates**: Allylic bromination is fast.
2. **Position of Radical Formation: Allylic positions react.**
3. **Product Distribution A:** Unequal allylic positions can each lead to products.
4. **Product Distribution B:** Asymmetric allylic radicals product two bromide isomer.

Review on predicting products in allylic radical brominations.

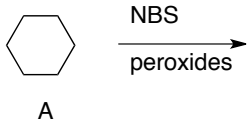
1. Is the alkene symmetric or asymmetric?
    - If it's symmetric, it doesn't matter which allylic carbon you convert to a radical.
    - If it's asymmetric, then you can remove a hydrogen from different allylic sites and make different allylic radicals, each of which can lead to products.
2. For each allylic radical, is it symmetric or asymmetric?
    - If it's symmetric, it will lead to one structural isomer bromide.
    - Is it's asymmetric, it will lead to two structural isomer bromides.



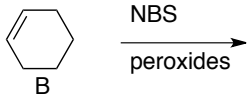
"**NBS**" = N-Bromosuccinimide = More commonly used than Br_2/hv for allylic/benzylic radical brominations. Maintains dilute [Br_2], absorbs HBr. Prevents Br_2 or HBr from undergoing ionic addition to alkenes. More convenient to weigh out (solid). Some mechanistic complexity. Often higher yields.

Practice Problems

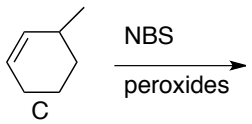
a. Draw the radical intermediates, including resonance structures
b. Ranks the reactivity of **A**, **B**, and **C**.
c. Draw the product or products for the following reactions



A



B



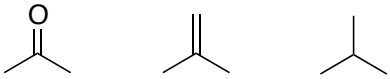
C

Allylic Anions

1. Allylic anions are stabilized, just as are cations and radicals
2. Anion stability impacts acidity
   - when something neutral functions as an acid, it releases H^+ and produces an anion

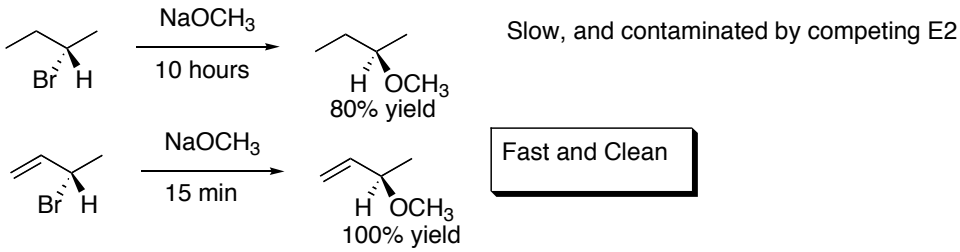
Question 1: Compare the acidity of cyclpentene to cyclopentane. One is a quintillion times more acidic than the other. Which is it, and why?

Question 2: Compare the acidity of acetone, 2-methylpropene, and 2-methylpropane

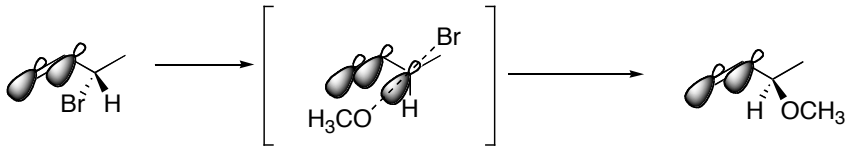


Section 15.10 **Allylic Halides and S_N2 Reactions. Allylic Systems Are Really Fast**

Ex.



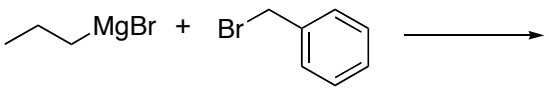
Why? Because the backside-attack transition-state is stabilized by conjugation!
(Transition state-stability-reactivity principle).

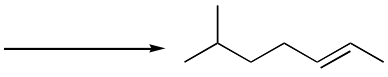


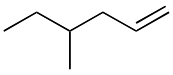
1. Neither the product nor the reactant has conjugation, so it's hard to see why conjugation should apply
2. However, in the 5-coordinate T-state the reactive carbon is sp^2 hybridized
   - the nucleophile and the electrophile are essentially on opposite ends of a temporary p-orbital.
3. That transient sp^2 hybridization in the transition-state is stabilized by π-overlap with the adjacent p-bond.
4. This stabilization of the transition-state lowers the activation barrier and greatly accelerates reaction

Key Application: RMgBr can do Clean S_N2 Reactions on 1° Allylic Bromides

- RMgBr carbanionic nucleophiles can't do good S_N2's on normal 1° or 2° allylic bromides because of competing elimination and single-electron-transfer reactions.
- But they work well on allylic halides

1 

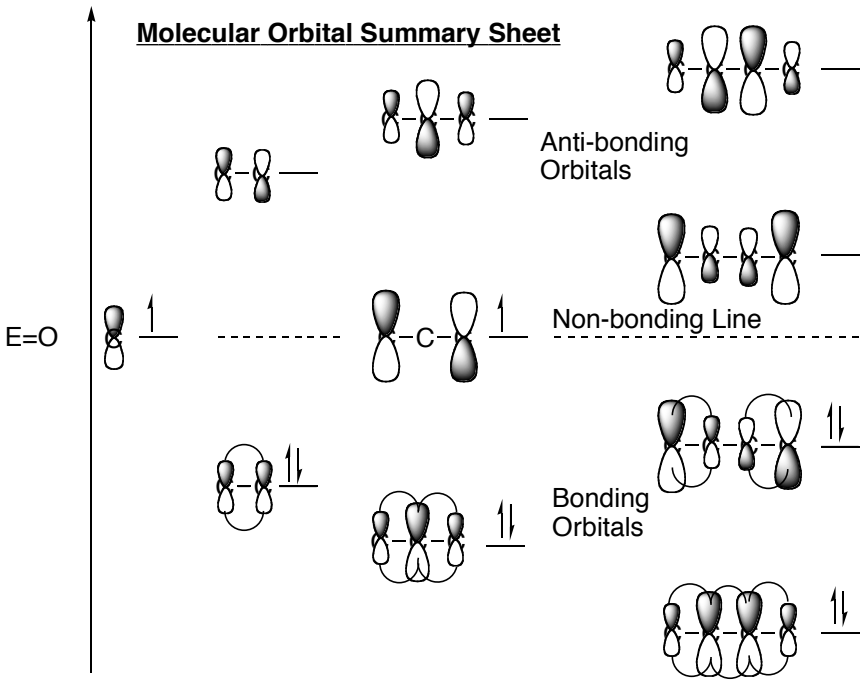
2 

3 

Retrosynthesis.
Make from bromides
that began with 4 or fewer carbons

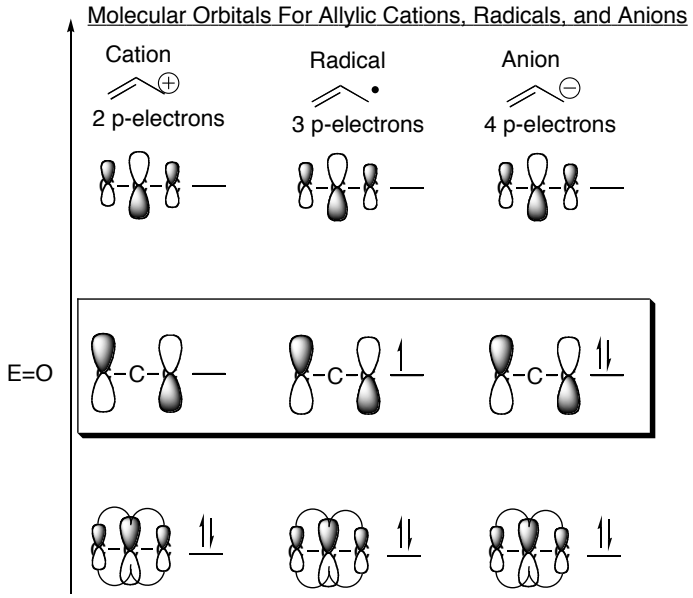
Note: When thinking backwards, identify the allylic carbon and the next carbon removed from the alkene. Those will be the two carbons that were linked.

Sections 15.3, 8, 9 Molecular Orbitals and Conjugation (not for test)



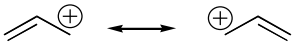
Observations:

1. Shown are an isolated radical, a double bond, an allyl radical, and butadiene.
2. "**MO**" = "**M**olecular **O**rbital"
3. MO's lower/stabler in energy than the non-bonding line are referred to as "bonding MO's", while those that are higher (less stable) in energy are called "antibonding MO's"
4. The number of π MO's equals the number of contributed π (p) orbitals. (One p in gives one MO. Two p's in gives two MO's. Three p's in gives three MO's. Four p's in gives four MO's. Etc.)
5. Any bonding MO is mirrored by an antibonding MO, whose energy is as high above nonbonding as the bonding MO is above it.
6. Thus the sum energies of the MO's (ignoring electron occupancy) equals 0.
7. However, not all MO's are occupied by electrons. Electron occupancy proceeds from the lowest MO's up. And it's the energies of the electrons that determine the molecular energy. Thus explains why it's energetically profitable for a molecule to be conjugated. CONJUGATING THE P ORBITALS LOWERS THE ENERGIES OF THE ELECTRONS AND THUS IS STABILIZING.
8. The **h**ighest **o**ccupied **m**olecular **o**rbital is called the "**HOMO**", and the **l**owest **u**noccupied **m**olecular **o**rbital is called the "**LUMO**". These are also referred to as the Frontier Molecular Orbitals (**FMO**'s). The frontier molecular orbitals are the orbitals involved as nucleophiles or electrophiles in reactions. If electrons are donated (nucleophile), they will come from the HOMO. If electrons are accepted (electrophile), they will go to the LUMO. Thus the energies and shapes of the HOMO/LUMO are really important.
9. The lowest MO keeps getting lower and lower (more and more stable). But, the energy level of the HOMO does **not** get progressively lower. Notice that the diene HOMO is higher than the simple alkene HOMO.
10. Notice that not all atoms have the same sized π-orbitals in the FMO's. When reactions happen, atoms with the big p-lobes are the ones that react.



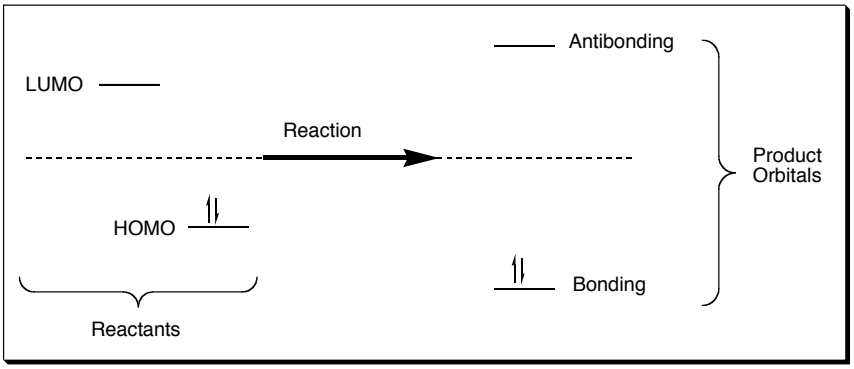
11. For allylic systems, notice that the energies and shapes of the MO's stay the same.

12. However, the occupancy does change. An allylic cation has two π-electrons, an allylic radical has three, and an allylic anion has four. Thus the key reactive middle MO goes from empty (strongly electrophilic) to full (strongly nucleophilic) across the series.

13. The MO picture tells the same story that resonance pictures show: there is no reactivity on the central carbon, but the outside carbons are the ones that react, whether in an allylic cation, radical, or anion.
    - MO theory explains this with the orbital lobes
    - Resonance theory explains this with 

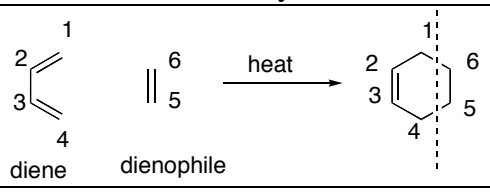
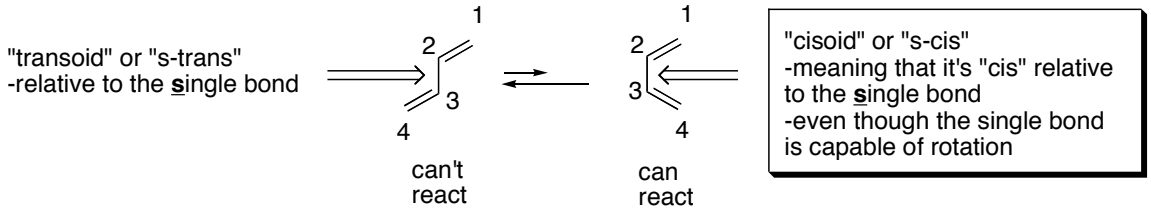
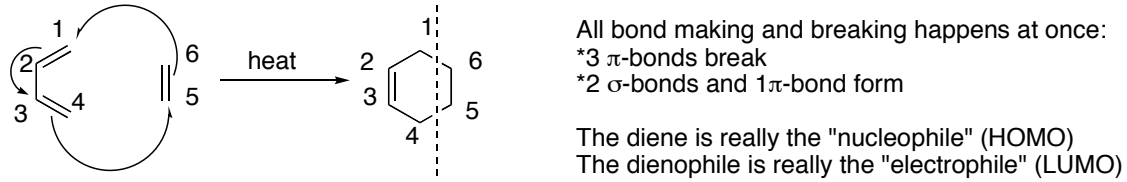
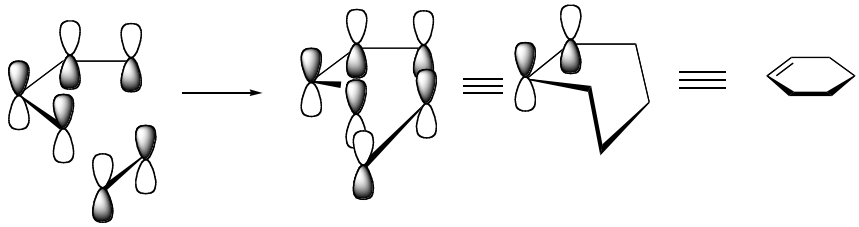
14. Sometimes MO can explain things that the simpler resonance theory can't.

15. In an actual reaction, the HOMO and LUMO interact
    - As usual two orbitals in produce two new orbitals (molecular orbitals) out.
    - The electrons end up lower in energy: more stable
    - MO fact: the closer the HOMO and LUMO are to each other in energy, the more favorable and profitable the reaction will be

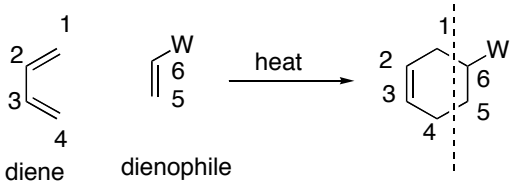


Section 15.11 The Diels-Alder Reaction. The Reaction of Conjugated Dienes (Dienes) with Electron-Poor Alkenes (Dienophiles) to make Cyclohexenes.

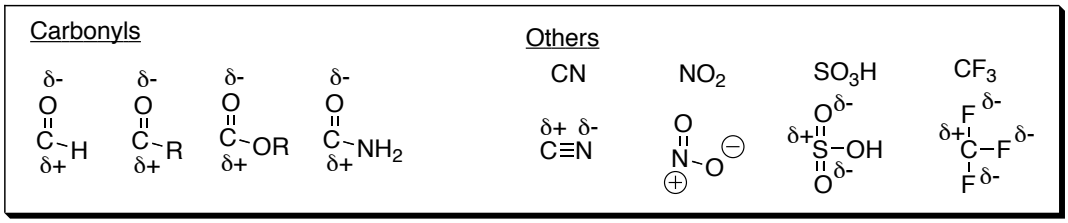
Quick Overview Summary

1.	
2.	s-cis diene conformational requirement: The diene must be locked or be able to single-bond rotate it's way into the "s-cis" conformation in order to react 
3.	Rate Factors 1. Dienophile ▪ activated by electron withdrawing groups ("W" or "EWG") for electronic reasons 2. Diene: ▪ Deactivated by substituents that make it harder or less stable to exist in the s-cis conformation. This is true when a diene alkene has a Z-substituent. ▪ Steric factors equal, activated somewhat by electron donating groups ("D" or "EDG")
4.	Concerted Mechanism 
5.	Orbital Picture 
6.	Product Prediction Highlights ▪ Try to match up the 4 diene and 2 dienophile carbons with the product o The product double bond will be between C2 and C3 of the diene ▪ Substituents are spectators ▪ 1,4/1,2 Rule: when asymmetric dienes react with asymmetric dienophiles o Match δ- end of nucleophilic diene with δ+ end of electrophilic dienophile ▪ For disubstituted dienophiles: o cis-substituents end up cis, and trans-substituents end up trans

A. The General Diels-Alder Reaction

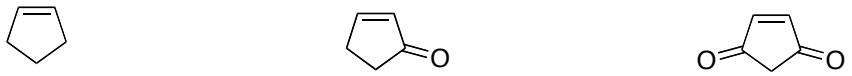


1. **Electronics**: The diene HOMO reacts with the dienophile LUMO
   - Effectively the diene is the nucleophile and the dienophile functions as the electrophile
2. The **dienophile** usually **needs an electron-withdrawing attachment** ("W") (at least one)
   - This makes the dienophile more electrophilic
   - Electron Withdrawing Groups to Memorize:

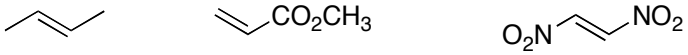


   - Keys:
     - The atom that is connected to the alkene has δ+ charge
     - Anything with a double-bond to a heteroatom tends to have this
       - C=O, C≡N, N=O, S=O

Q1/example: Rank the reactivity of the following alkenes as dienophiles. The actual relative reactivity ratios are 50,000 : 1,000 : 1. Huge differences.

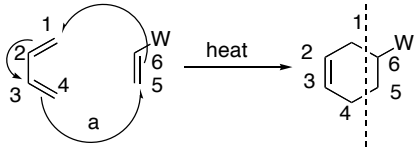


Q2: Rank the reactivity of the following dienophiles:



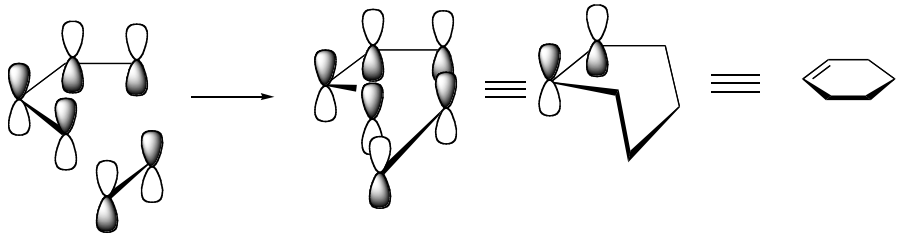
3. **Energetics**:
   - **Bonds broken**: 3 π bonds
   - **Bonds made**: 2 σ bonds, 1 π bond
   - **Enthalpy:** The net replacement of 2 π bonds (weaker) with 2 σ bonds is normally **strongly enthalpy favored**
   - **Entropy:** The high required organization of the concerted transition state makes the reaction **entropy disfavored**.
   - Heat normally required to overcome entropy

4. **Simple Mechanism (Good enough for test)**



Concerted: All bond making and breaking happens at once
-three arrows show each of the three p-bonds breaking and the three new bonds forming
-the arrow "a" from the diene to the dienophile is really key

5. **Orbital Picture**



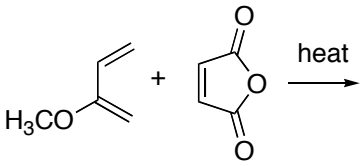
a. the p orbitals on the dienophile overlap with the p-orbitals on C1 and C4 of the diene
b. the overlapped p orbitals from the diene and dienophile end up being σ bonds in product
c. the leftover p orbitals on C2 and C3 end up overlapping to give the π bond in product
d. the diene must be in the s-cis conformation; in the zigzag s-trans layout, can't react
e. Not tested: perfect HOMO/LUMO orbital symmetry match (Section 15.12)

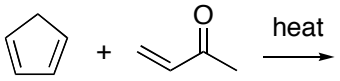
B. Predicting Products When the Diene or the Dienophile (or both) is Symmetric

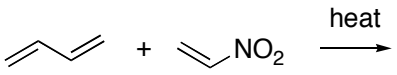
1. Always make a cyclohexene 6-ring product
2. Number the diene from 1-4, and identify those four carbons in the product ring.
3. A double bond in the product will always exist between carbons 2 and 3.
4. Any substituents on the diene or dienophile are spectators: they will be attached to the same carbons at the end.

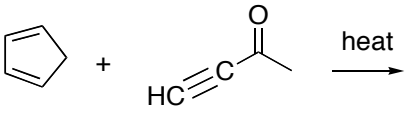
- Beware of cyclic dienes
- Beware of dienes that are drawn in their zigzag s-trans form, but could react following rotation into an s-cis form

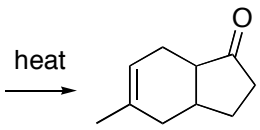
Noteworthy

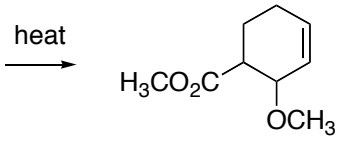
1 

2 

3 

4 

5 

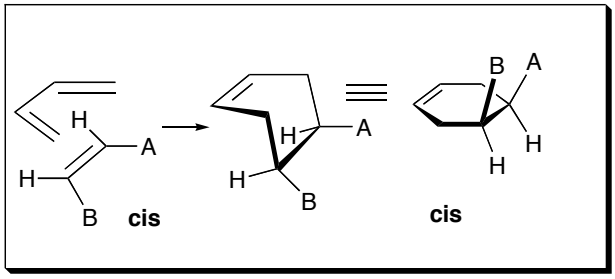
6 

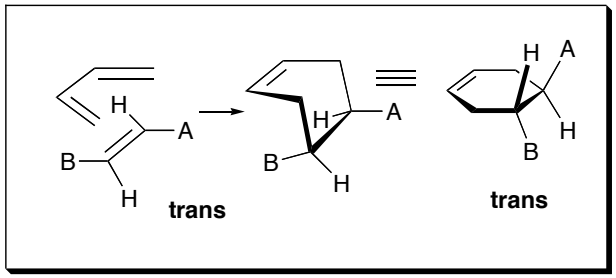
C. Stereochemistry: For Cis- or Trans- **Disubstituted Dienophiles**

- Both carbons of a disubstituted dienophile usually turn into stereocenters.

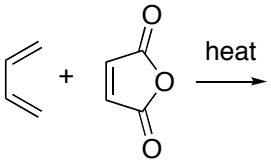
1. **Cis in → cis out**: If two substituents on the **dienophile** are cis to begin with, they will still have a cis relationship on the product cyclohexene
2. **Trans in → trans out**: If two substituents on the **dienophile** are cis to begin with, they will still have a cis relationship on the product cyclohexene

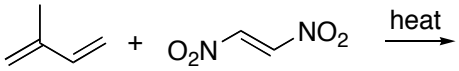
- **Note**: this is for the **dienophile only**. The diene alkenes may also have substitution such that one or both diene double bonds are cis or trans, but the "cis-in-cis-out" guideline does not apply to the diene.

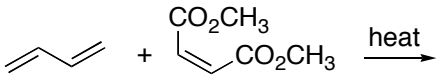


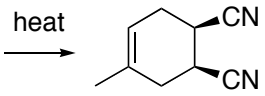


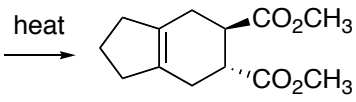
- **Why**: Because of the concerted mechanism. The diene is basically doing a concerted "cis" addition to the dienophile. The attachments on the dienophile never have opportunity to change their position relative to each other.

1 

2 

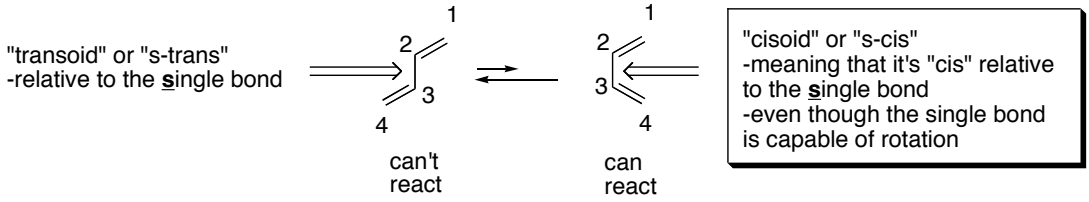
3 

4 

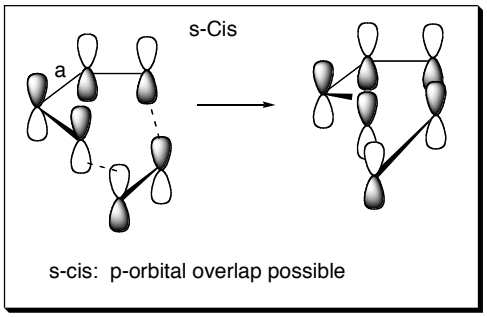
5 

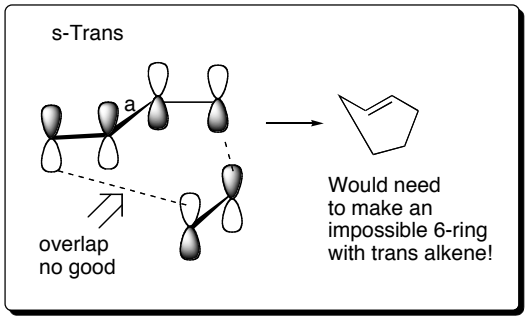
D. Structural Factors for **Dienes**

1. s-cis (cisoid) diene conformational requirement: The diene must be locked "s-cis" or be able to single-bond rotate it's way into the "s-cis" (cisoid) conformation in order to react



Why? Because the concerted, p-orbital overlap mechanism is impossible from s-trans.



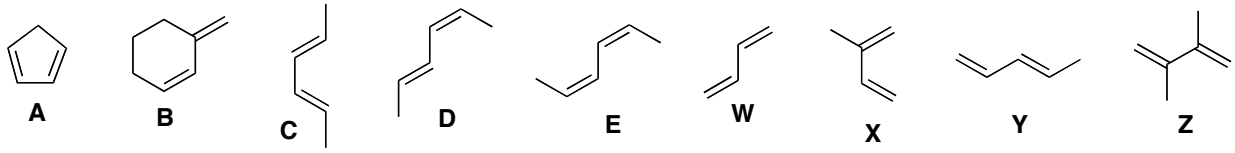


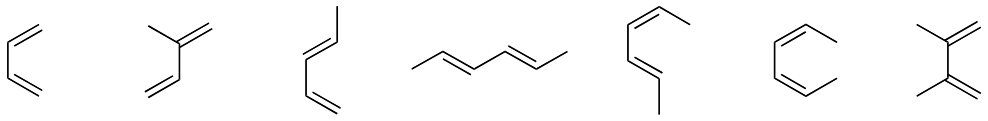
- Normally the s-cis conformation is less stable than the s-trans conformation (sterics).

- Only the minor fraction of a diene in the s-cis conformation is able to react
- The larger the equilibrium population in the s-cis conformation, the greater the reactivity

2. For an acyclic diene, a "Z" substituent on either (or both) of the diene alkenes causes major steric problems for the s-cis conformation, reduces the equilibrium population of s-cis diene, and thus reduces Diels-Alder reactivity

Q1: For the dienes **A-Z**, circle the letters for those that are in a reactive s-cis conformation.
Q2: For the acyclic dienes **C-Z**, identify any double bonds the are E or Z.
Q3: Match acyclic dienez **C-Z** with the alternate s-cis/s-trans form shown below.
Q4: For the dienes **A-E**, try to rank their probable Diels-Alder reactivity based on the probable relative population of their s-cis conformations. (or match: 100%, 3%, 001%, 0.000001%, 0%)
Q5: Try to redraw **D** and **E** into their s-cis forms





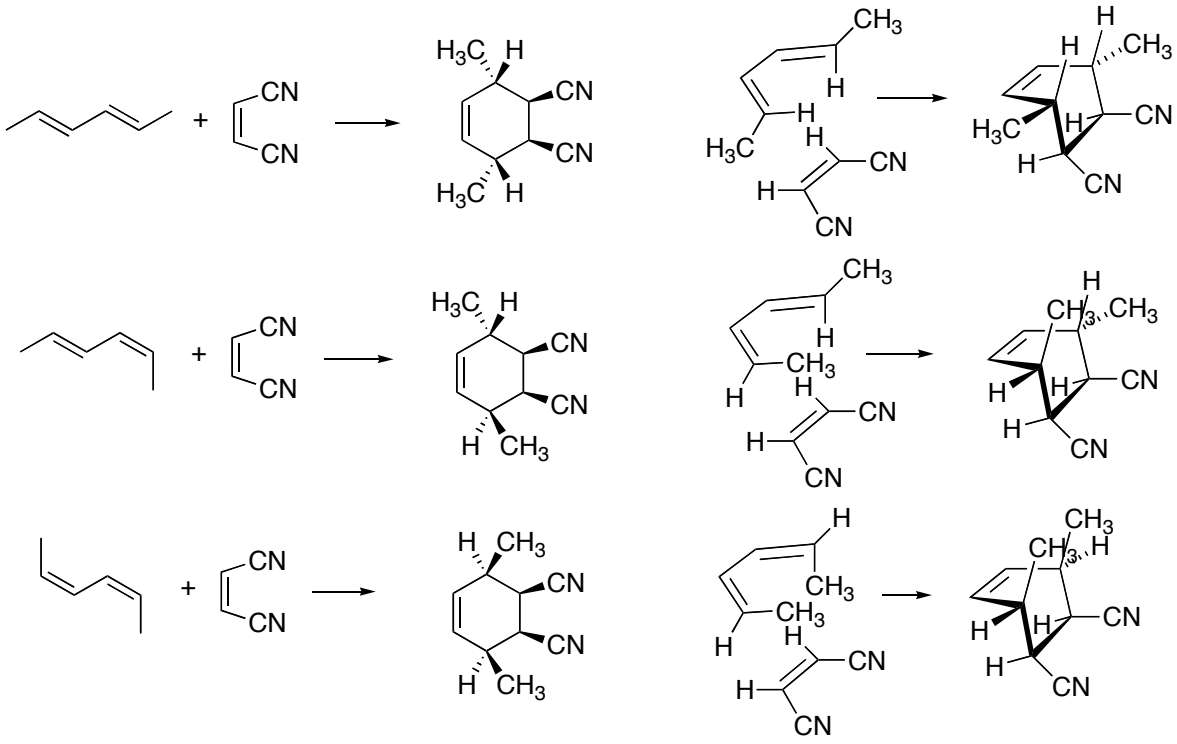
When steric factors are not a problem (in other words, when not in a "Z" position), electron donating groups ("D" or "EDG") have a mild activating effect

- OR, NR_2, R (memorize)
- Why: The diene functions as the nucleophile. A donor makes the diene more electron rich and thus more nucleophilic.

Rank the reactivity:

E. Stereochemistry: For **Dienophiles with Substituents on C1 and/or C4 (**Not test responsible)

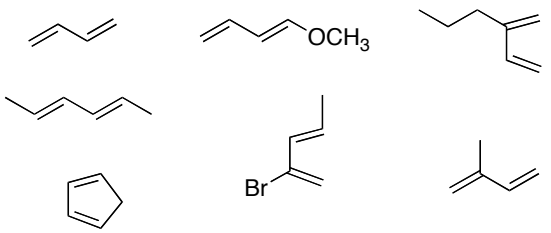
- Need to convert diene into s-cis conformation, then envision the transition state
- The "inside" (Z) substituents on C1/C4 end up "up" (cis); the "outside" (E) substituents on C1/C4 end up "down" (and cis to each other); inside/outside attachments on C1/C4 end up trans



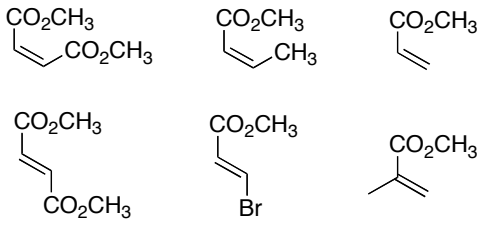
F. Predicting Products When **Both Diene and Dienophile are Asymmetric** (****)

Q. Circle the symmetric dienes or dienophiles

Dienes

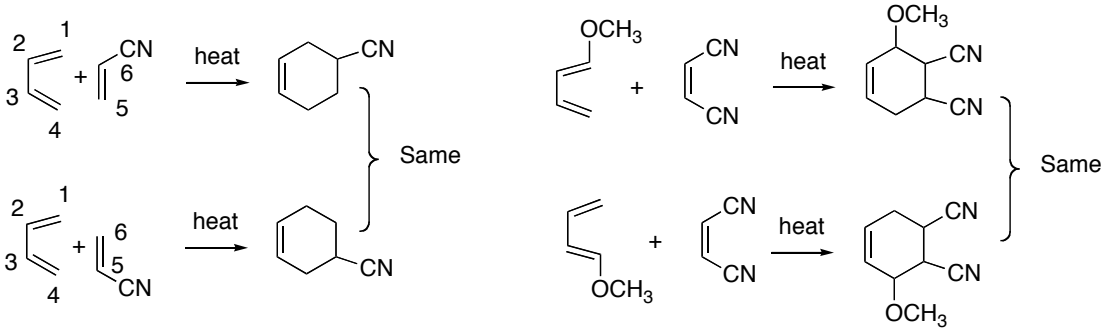


Dienophiles



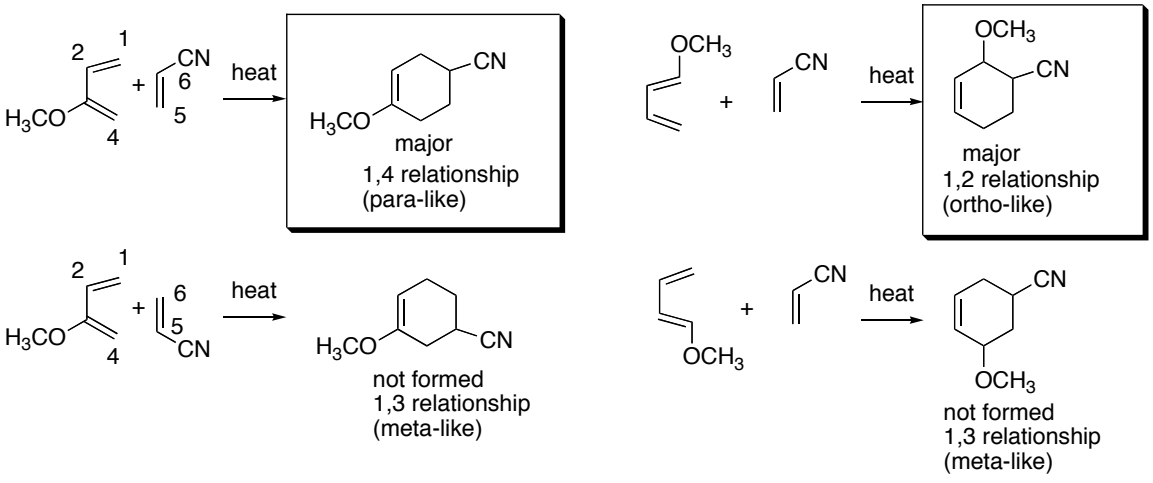
- Any monosubstituted diene or monosubstituted dienophile is asymmetric
- You can be trans and still symmetric
- Symmetry requires equal attachments on: C1+C4, C2+C3 (dienes), C5+C6 (dienophile)

If either component is symmetric, you don't have structural isomer issues.



1. If both ends of diene are the same, it doesn't matter which adds to which end of dienophile
2. If both ends of dienophile are the same, it doesn't matter which adds to which end of diene

If both components are asymmetric: two structural isomers are possible; one dominates.

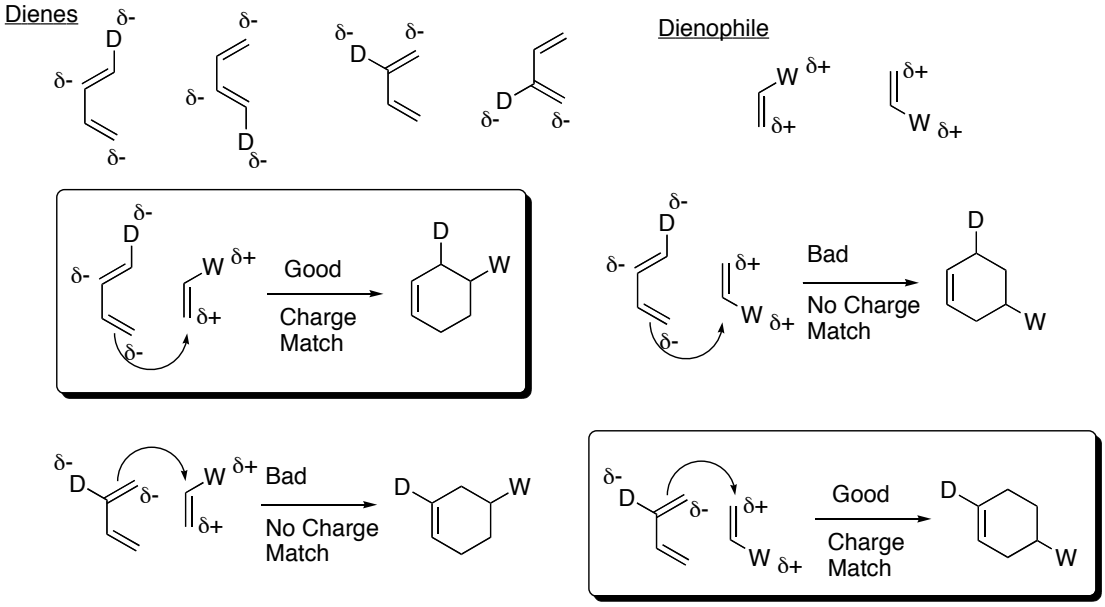


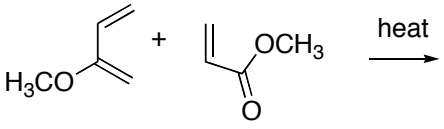
***** A 1,2 or 1,4 relationship is always preferred over a 1,3 relationship, if possible *****

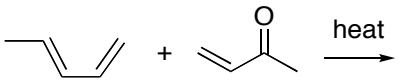
- Although ortho/meta/para terms don't really correctly apply to cyclohexenes, many students remember this is an "**ortho/para preferred**" rule, to avoid number confusion

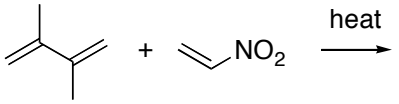
Explanation for Structural Isomer Selectivity in Addition of Asymmetric Dienes to Asymmetric Dienophiles: Electronics

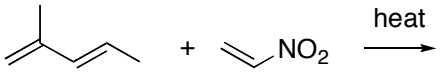
- Donors function as electron rich (δ-); withdrawers function as electron poor (δ+)
- δ- or δ+ partial charges are shared on **alternating atoms** (ala allylic) over π-systems
- For an asymmetric diene, one of the two terminal carbons ends up δ- and nucleophilic
- For an asymmetric dienophile, one of the alkene carbons ends up δ+ and electrophilic.
- Matching the δ- diene terminus with the δ+ dienophile carbon gives major structural isomer.

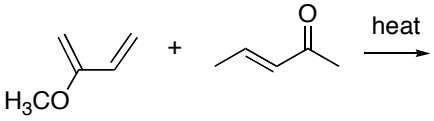


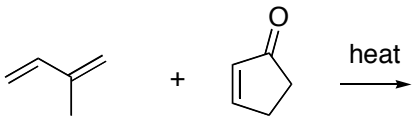
1 

2 

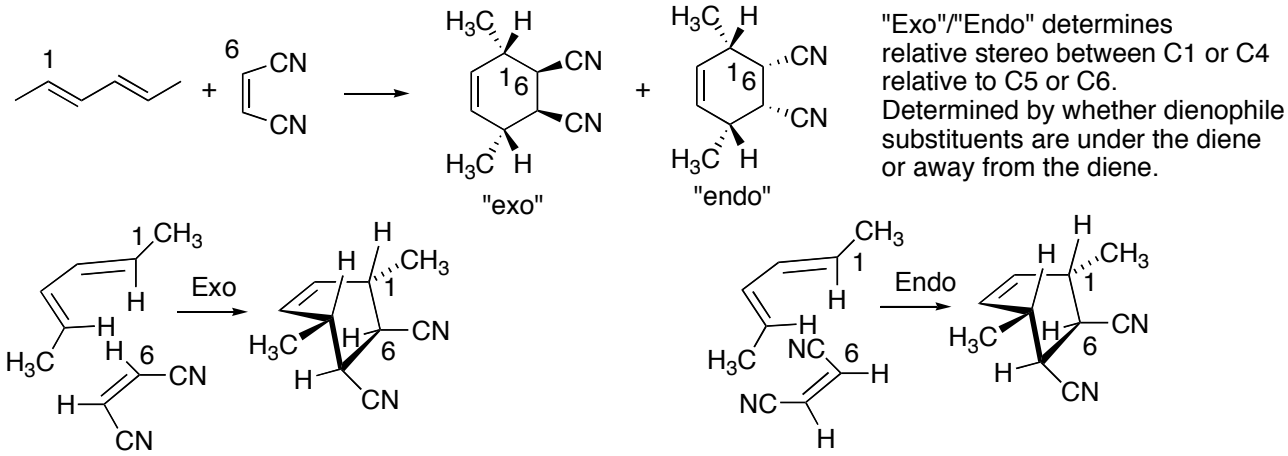
3 

4 

5 

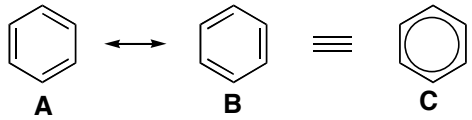
6 

G. Endo/Exo Stereochemistry: Relative stereochemistry when both diene and dienophile generate stereocenters. (This will involve **Dienophiles with Substituents on C1 and/or C4)** (p 684. Not test responsible)



1. In the exo product, the relative stereochemistry at C1-C6 is trans.
2. In the endo product, the relative stereochemistry at C1-C6 is cis.
3. The difference results from how the dienophile lays out under the diene.
   - In the exo case, the dienophile substituent extends away from the diene, while the dienophile hydrogens extend underneath the diene. (Sterically preferable)
   - In the endo case, the dienophile substituent extends under the diene, while the dienophile hydrogens extend away from the diene. (Some electronic advantage.)

Ch. 16 Aromatic Compounds

C_6H_6 

2 Resonance Structures

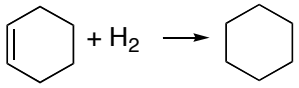
Facts to Accommodate

1. 4 elements of unsaturation
2. All C-C bonds are same length, not alternating (contrary to expectation based on structure **A**)
3. Only 1 isomer of 1,2-dibromobenzene (contrary to expectation based on structure **A**)
4. Unlike alkenes, does not undergo addition reactions (contrary to expectations based on **A**)
5. Extreme stability indicated by combustion or hydrogenation tests

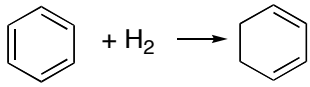
	H_2/Pt	Br_2	HBr	BH_3	$Hg(OAc)_2/H_2O$	Etc.
 **D**	Reacts	Reacts	Reacts	Reacts	Reacts	
 **A**	No Reaction	No Reaction	No Reaction	No Reaction	No Reaction	

Hydrogenation: Measurement Tests for the Extraordinary Stability of Benzene

Normal Alkene



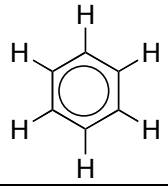
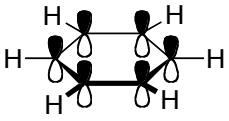
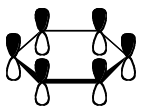
Benzene



- Hydrogenation is normally very exothermic, but not for benzene
- The less favorable hydrogenation reflects **greater stability**
- The stability difference is over 30 kcal/mol: huge
  - Butadiene gains <4 kcal/mol of stability from it's conjugation

16.3,4 Benzene Molecular, Structural Details, and Molecular Orbitals

1. Some different pictures of benzene

			
a) Simplest **b) Ideal for mechanisms**, helps keep track of the electrons	Illustrates: a) delocalization of b) equivalence of bonds d)complete planarity	**a) Easy to see π-system** b) Helps explain why the C-C bonds are all the same	**a) Easy to see the π-system**, undistracted by the hydrogens

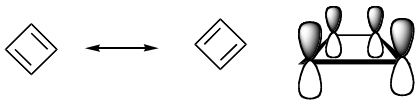
2. Notes on Pictures and Structural Features

1. All 6 carbons are sp^2, with one p orbital each
2. 120º angles, so all 6 carbons and each of their attached hydrogens are all co-planar.
3. Perfectly flat.
4. Perfect 120º angles, no angle strain whatsoever
5. Complete symmetry
6. Each C-C bond is equal in length and strength
7. Each C-C bond is longer than a normal double but shorter than a normal single bond

Normal Bond Lengths:	C-C: 1.54A	C=C: 1.34 A	Benzene CC: 1.39A

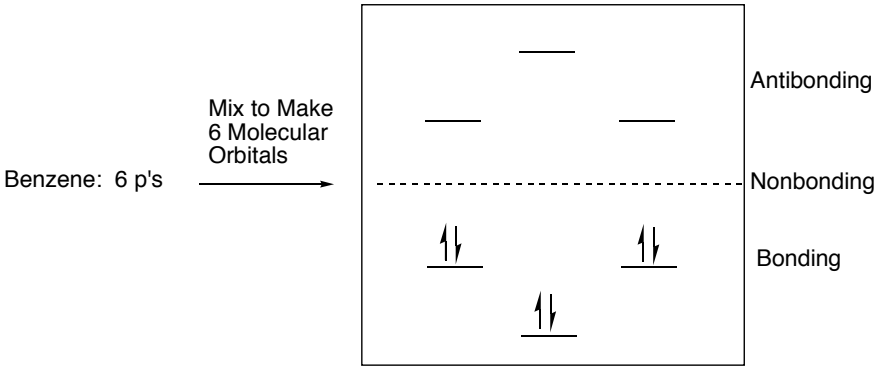
- "1.5" bonds, as we see from resonance.

8. 6 π -electrons are delocalized throughout the ring.
   - Complete racetrack
9. Resonance delocalization, stabilization
10. Note: not all "π racetracks" are stabilized



No extra stability
Actually somewhat destabilized

3. Molecular Orbital for Benzene (11.5)



- All and only the bonding molecular orbitals are completely filled. Special stability
- But how can you know what the molecular orbitals will look like for other rings?

Frost Diagram/Polygon Rule: (11.19) For a **complete ring** of **sp^2 centers**,

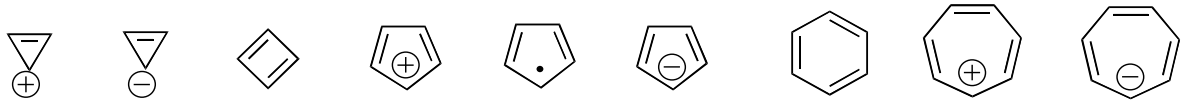
1. Draw the ring/polygon with a vertex down, basically inside what would be a circle
2. Each apex represents a molecular orbital
3. A horizontal line through the middle of the ring provides the non-bonding reference point
4. Populate the MO's as needed depending on how many π-electrons are available

Molecular Orbital Rules for a cyclic π-system:

1. If all and only bonding molecular orbitals are occupied→ good ("aromatic")
2. If any nonbonding or antibonding MO's are occupied, or if any bonding MO's are not completely occupied → bad, poor stability ("antiaromatic")
   - Below nonbonding line → bonding
   - Above nonbonding line → antibonding
   - On nonbonding line → nonbonding

Practice Problem

1. Draw the MO's for 3-, 4-, 5-, and 6-membered cyclic π systems.
2. Fill in the orbitals and circle the following as good=stable=aromatic or not.



3

4

5

6

NOTE: 5-, 6-, 7-, and 8-membered rings all end up with 3 molecular orbitals below the non-bonding line

(11.19) **Aromatic, Antiaromatic, Nonaromatic**. **Huckel's Rule**: For a **planar**, **continuous ring** of **π-orbitals**, (sp^2 all around):

- If the number of π-electrons = 2,6,10 etc. (4N + 2) → AROMATIC, STABILIZED
- If the number of π-electrons = 4,8,12 etc. (4N) → Anti-aromatic, destabilized

- Why: the 4N+2 rule always goes with favorable Frost diagrams: bonding and only bonding MO's are always filled.

- Generality: Huckel's Rule applies for cycles, bicycles, ionic compounds, and heterocycles.

a. Cycles (one-ring) b. Polycycles (2 or more) c. Ionic rings d. Heterocycles

-

e. Cycles (one-ring) f. Polycycles (2 or more) g. Ionic rings h. Heterocycles

Practice Problems: Classify each of the following as Aromatic (circle them) or not. For those that aren't, are there any that are Antiaromatic? (square them)

Keys:

1. Do you have an uninterrupted sp^2 ring?
2. Apply Huckel's Rule: Do you have 2,6,10 etc. π electrons?
3. Applying Huckel's Rule requires that you can accurately count your π-electrons. Be able to count:
   - Anions: contribute 2 π-electrons
   - Cations: contribute 0 π-electrons
   - Heteroatoms (O or N): can provide 2 π-electrons if it helps result in aromatic stability.

Note: For those that are not aromatic, why not?

1. Lacks cyclic sp^2 ring
2. Lacks Huckel's rule electron count

1. 
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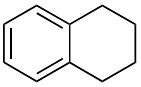
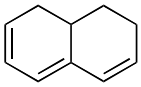
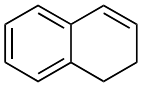
9. 
10. 
11. 
12. 
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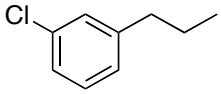
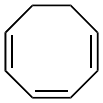
15. 

16. 
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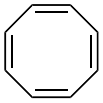
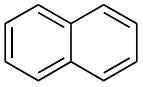
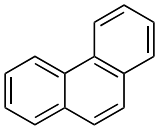
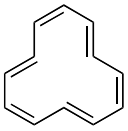
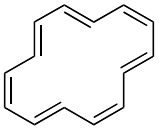
19. 
20. 
21. 
22. 
23. 
24. 
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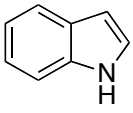
26. 

27. 

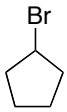
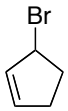
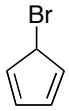
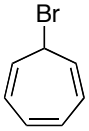
28. 

16.8 Aromatic Ions

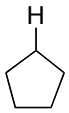
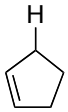
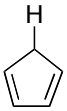
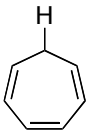
- 3 common, important Aromatic Ions



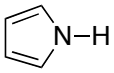
Problem 1: The following substrates have widely differing reactivity toward **H_2O solvolyis**. (The fastest is more than a million times faster than 2nd fastest, and the slowest more than a hundred times slower than the second slowest). Rank the reactivity. (Key: What kind of reaction would happen, and what determines reactivity?)

Problem 2: The following have enormous differences in **acidity**. (10^{-20}, 10^{-42}, 10^{-50}, 10^{-56})
Key:

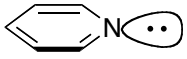
(11.22,23) Heterocyclic Aromatics. Memorize 3.


Pyridine

N-hybridization: sp^2
N-lone-pair: sp^2
N-basicity: reasonably normal

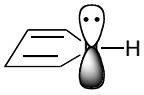
The lone pair is not used in the π-system; the sp^2 points in plane of paper, and has normal basicity.



Pyrrole

N-hybridization: sp^2
N-lone-pair: p
N-basicity: Nonbasic

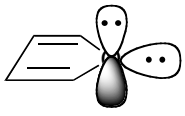
The lone pair is used in the π-system and is counted toward the 6 electrons for Huckel's rule. Because the lone pair is p, pyrrole is nonbasic.



Furan

O-hybridization: sp^2
O-lone-pairs: one p, one sp^2

The p lone pair is used in the π -system and is needed to get the 6 electrons needed for Huckel's rule. But the sp^2 lone pair is in the plane of the ring, extending straight out.



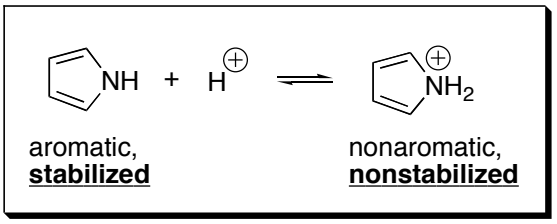
Nitrogens: Atom hybridization, Lone-Pair hybridization, and Basicity

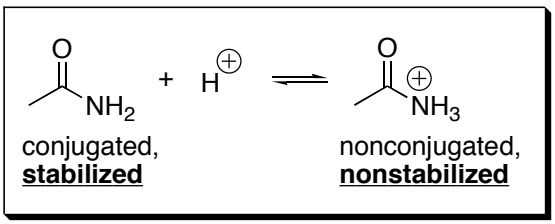
- Amine nitrogens are normally basic, but not when the N-lone pair is p-hybridized
- Rule: If a nitrogen lone pair is p (used in conjugation) → nonbasic
- Nitrogen lone-pair basicity: $sp^3 > sp^2 >>> p$

Situations	N-Atom	N-Lone Pair	N-Basicity
1. Isolated	sp^3	sp^3	Normal
2. Double Bonded	sp^2	sp^2	Normal (a little below, but not much)
3. Conjugated (not itself double bonded, but next to a double bond)	sp^2	p	Nonbasic

Why are p-lone pairs so much less basic?

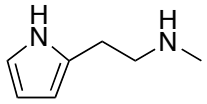
- Because conjugation/aromatic stability in the reactant is lost upon protonation.

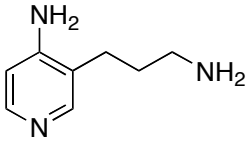


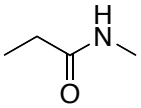


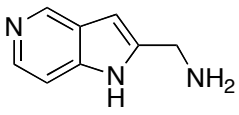
Problem: For each nitrogen, classify:

a) hybridization of the Nitrogen atom
b) hybridization of the Nitrogen lone-pair
c) basicity of the Nitrogen (basic or nonbasic)

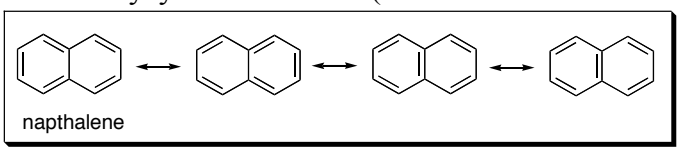
1. 

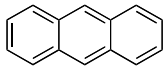
2. 

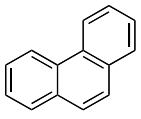
3. 

4. 

16.10 Polycyclic Aromatics (needn't memorize names)


napthalene

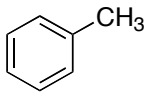

anthracene


phenanthrene

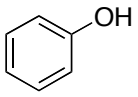
16.13 AROMATIC NOMENCLATURE

1. **Memorize** Special Names.

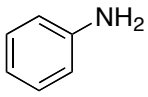
- Six Special Monosubstituted Names You Must **Memorize**



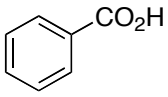
Toluene



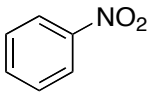
Phenol



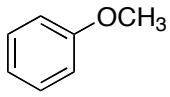
Aniline



Benzoic Acid



Nitrobenzene



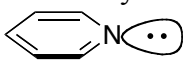
Anisole

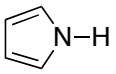
- Three Special Heterocyclic Common Names You Must **Memorize**

Pyridine

N-hybridization: sp^2
N-lone-pair: sp^2
N-basicity: reasonably normal

The lone pair is not used in the π-system; the sp^2 points in plane of paper, and has normal basicity.

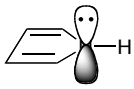




Pyrrole

N-hybridization: sp^2
N-lone-pair: p
N-basicity: Nonbasic

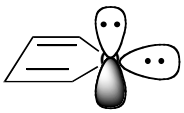
The lone pair is used in the π-system and is counted toward the 6 electrons for Huckel's rule. Because the lone pair is p, pyrrole is nonbasic.



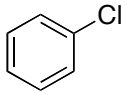
Furan

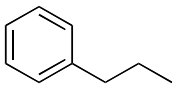
O-hybridization: sp^2
O-lone-pairs: one p, one sp^2

The p lone pair is used in the π -system and is needed to get the 6 electrons needed for Huckel's rule. But the sp^2 lone pair is in the plane of the ring, extending straight out.

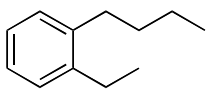


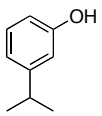
2. Mono-substituted benzenes, if not one of the special memory names: use "benzene" as core name

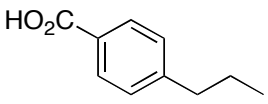




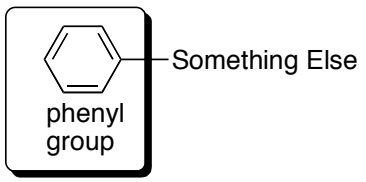
3. Di- or polysubstituted aromatics
   a. If one of the "special" memory names can be used, use that as the core name and number with the special substituent on carbon 1.
   b. Special Terms:
      - "ortho" or o- 1,2 relationship
      - "meta" or m- 1,3 relationship
      - "para" or p- 1,4 relationship

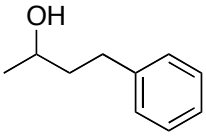
1. 

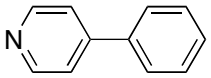
2. 

3. 

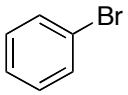
4. As a substituent, benzene is named "phenyl"
   - "phenyl" = C_6H_5- = a benzene group attached to something else, named as a substituent





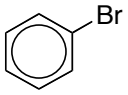


5. Three Shorthands for phenyl

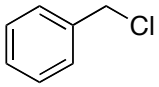


PhBr

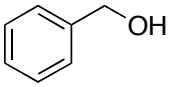
C_6H_5Br



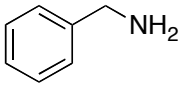
6. "Benzyl" = $PhCH_2$



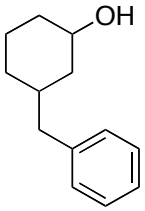
benzyl chloride



benzyl alcohol



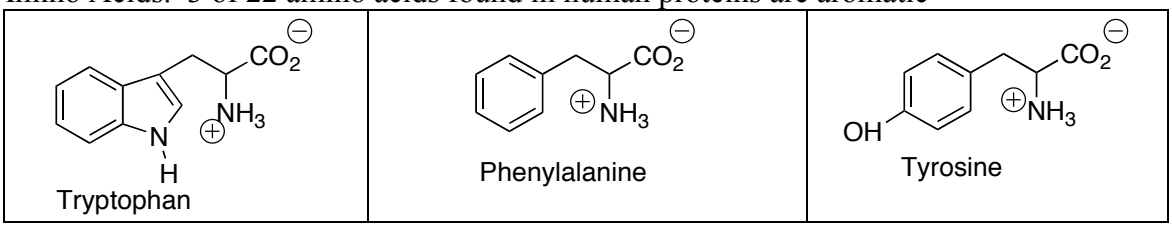
benzyl amine



3-benzylcyclohexanol

Some Complex Aromatics in Nature

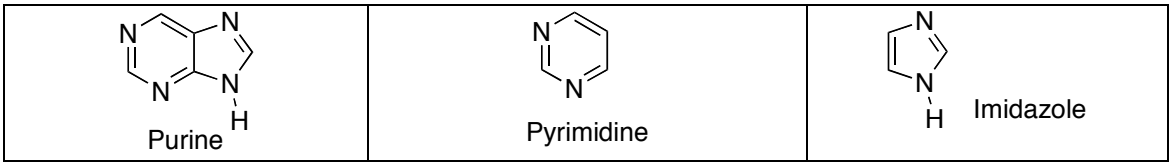
1. Amino Acids. 3 of 22 amino acids found in human proteins are aromatic



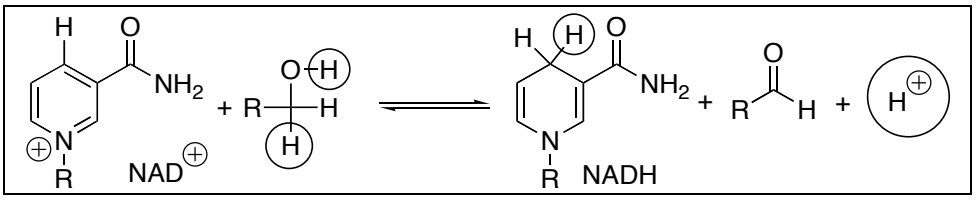
"Essential"-have to eat them, since body can't make the benzene rings

2. Nitrogen Bases: Purine, Pyrimidine, Imidazole.

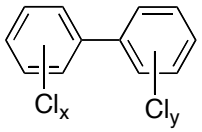
Nitrogen Bases Purine, Pyrimidine, Imidazole. Substituted derivatives of purine and pyrimidine are the stuff of DNA and RNA. The basicity of their nitrogens is crucial to genetics, replication, enzymes, and protein synthesis.



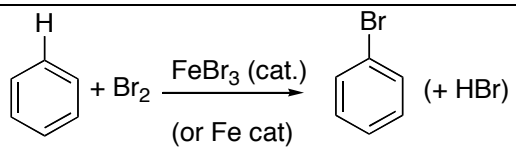
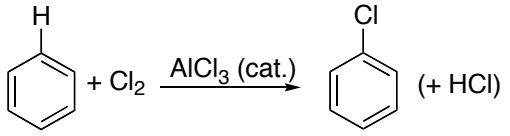
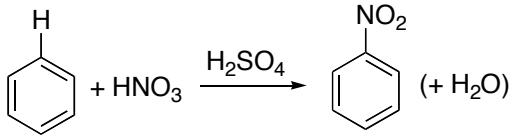
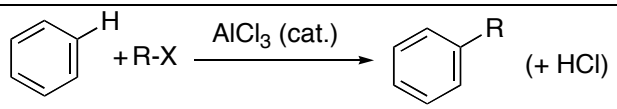
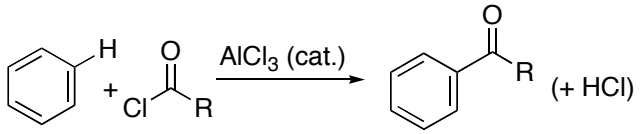
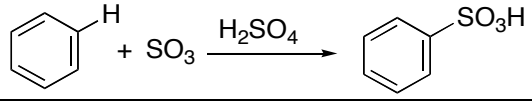
3. Nitrogen Bases: Purine, Pyrimidine, Imidazole. Nicotinamide Adenine Dinucleotide (NAD+) and NADH. Important Redox reagents.



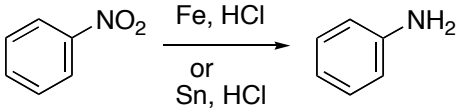
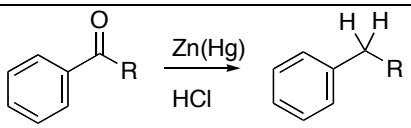
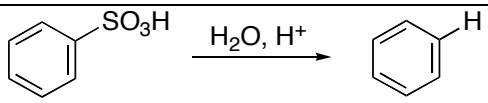
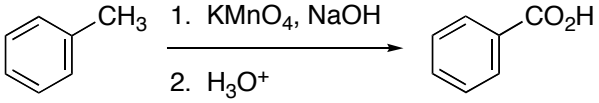
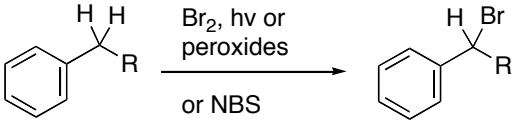
4. Polychlorinated Biphenyls (PCB's). High stability as insulators, flame-retardants make them so stable that they are hard to get rid of!



5 Major Electrophilic Aromatic Substitution Reactions

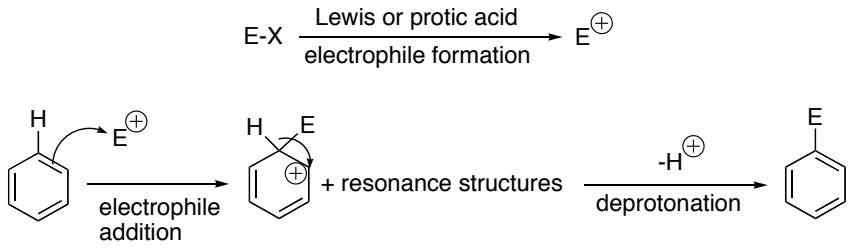
		Activating/ Deactivating	Ortho/Para Or Meta Directing	Book
1		**Deactivating**	**Ortho/Para**	17.2
		**Deactivating**	**Ortho/Para**	17.2
	The halides are unique in being deactivating but ortho/para directing. All other o/p-directors are activating, and all other deactivating groups are m-directors. **Mech required**			
2		Deactivating	Meta	17.3
	The product can be reduced to Ar-NH_2 by Fe/HCl or Sn/HCl. Nitration/Reduction provides an effective way to introduce an NH_2 group. Reduction converts m-directing NO_2 group into an o/p-directing NH_2 group. **Mech required.**			
3		**Activating**	Ortho/para	17.10
	a. Restricted to 3º, 2º, or ethyl halides. 1º halides suffer carbocation rearrangements. b. Since product is more active than starting material, polyalkylation is often a serious problem. c. Fails with strongly deactivated benzenes. **Mech required.**			
4		Deactivating	Meta	17.11
	a. The product can be reduced to -CH_2R by Zn(Hg)/HCl. b. The acylation-reduction sequence provides an effective way to introduce a 1º alkyl group. **c.** Reduction converts meta-directing acyl group into an ortho/para-directing alkyl group. **Mech required.**			
5		Deactivating	Meta	17.4
	The sulfonyl group is a useful para-blocking group, since it can later be removed upon treatment with H_2O/H^+. **No mech required.**			

5 Major Aromatic Support Reactions

		Activating/ Deactivating	Ortho/Para Or Meta Directing	Book
6		19.21	Ortho/Para	19.21
	▪ Reduction converts meta-director into an ortho-para director. ▪ Fe, Sn, or several other reducing metals can work.			
7		17.12	Ortho/Para	17.12
	▪ Clemmensen reduction converts meta-director into ortho-para director. ▪ Acylation (#4) followed by Clemmensen Reduction (#7) is the standard method for introducing a 1º alkyl group. (Direct alkylation with a 1º alkyl halide, reaction #3, fails due to cation rearrangement problems…)			
8		17.4	------	17.4
	▪ The sulfonyl group is a useful and reversible para-blocking group, since it can be temporarily put on (reaction 5) but then can be removed later upon treatment with H_2O/H^+ (reaction 8). ▪ The sulfonation/other reaction/desulfonation sequence is crucial for clean ortho-substitution of an o/p director.			
9		17.14	Meta	17.14
	▪ Oxidation converts ortho/para-director into a meta-director. ▪ Side alkyl chains longer than methyl can also be oxidized to benzoic acid in the same way, although more time and heat is required. ▪ For test purposes, just writing $KMnO_4$ will be OK. But the real reaction requires a basic solution for the $KMnO_4$ to work, so an acidic workup step is actually required to isolate the neutral carboxylic acid.			
10		17.14	------	17.14
	▪ Bromination occurs via free-radical mechanism. ▪ It is selective for substitution at the benzylic position because the benzylic radical intermediate is resonance-stabilized. ▪ Note: keep distinct $Br_2/FeBr_3$ from Br_2/peroxides! ▪ Product is subject to S_N2 substitutions (benzylic bromides are especially good) and E2 eliminations with bulky bases. ▪ "NBS" is N-bromosuccinimide, which functions just like Br_2/peroxides, but avoids competing reactions caused by Br_2 and HBr.			

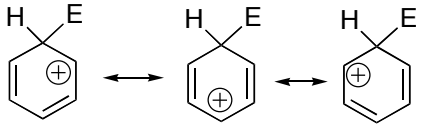
Section 17.1 Electrophilic Aromatic Substitution

General Mechanism for Electrophilic Aromatic Substitution



1. The **addition step**, generating the carbocation, is the **rate-determining** step
2. Any extra **substituents that stabilize the carbocation will make the reaction faster** (the product stability-reactivity principle). And vice-versa…
   - **Electron-donating groups** will stabilize carbocations and accelerate (**activate**)
   - **Electron-withdrawing groups** that destabilize carbocations will decelerate (**deactivate**)
3. As shown below, the **positive charge is shared by resonance** over three carbons: the carbons that are **ortho and para** relative to the carbon where the electrophile actually adds
   - Positive charge does not appear at either of the positions meta to where the electrophile adds
4. If a substituent is ortho or para relative to the carbon where the electrophile actually adds, the substituent will be next to a positive charge in one of the three resonance structure, and will have a large electronic effect, for good (donors) or bad (withdrawers)
   - If a substituent is an electron donor (cation stabilizer), it will be very beneficial if the electrophile adds ortho or para relative to the substituent. Therefore ortho or para addition will be much faster than meta addition.
     - **Thus electron donors (cation stabilizers) function as ortho/para directors.**
   - If a substituent is an electron withdrawer (cation destabilizer), it will be very harmful if the electrophile adds ortho or para relative to the substituent. Therefore ortho or para addition will be much slower than meta addition.
     - **Thus electron withdrawers (cation destabilizers) function as meta directors.**
       - Note: meta directors are meta directors not because meta addition is especially good; rather, it's because meta isn't nearly as bad as ortho or para addition, so meta addition is the best option available. But keep in mind that it still is slower than normal.

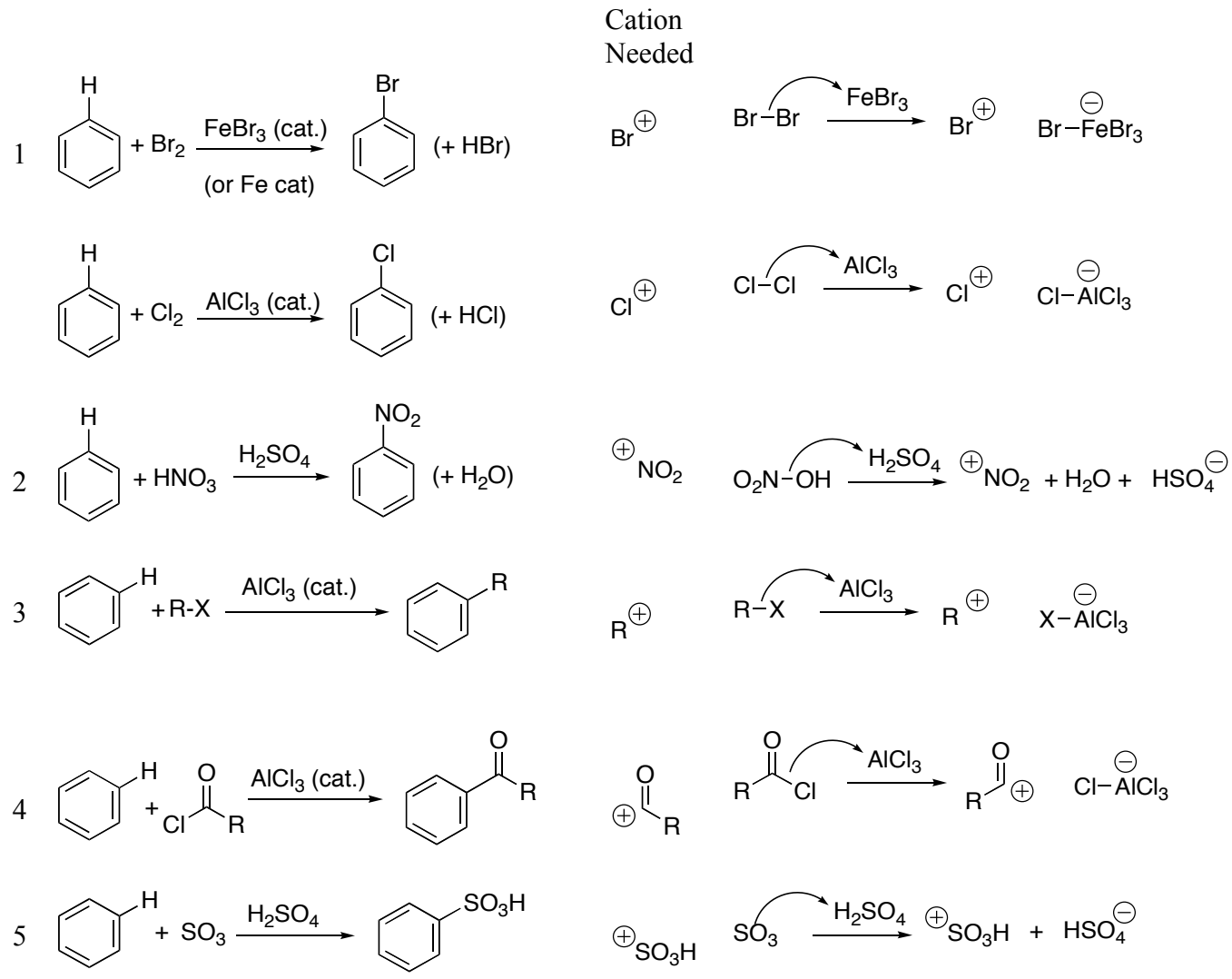
Three Resonance Structures for Every Electrophilic Aromatic Substitution



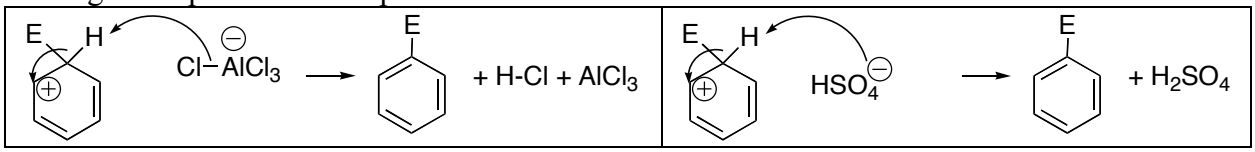
- A substituent that's good for one of these cation forms (donor) is good for the addition:
  - This results in activation (kinetics)
  - and ortho/para addition (orientation)
- A substituent that's bad for one of these cation forms (withdrawer) is bad for the addition:
  - This results in deactivation (kinetics)
  - And meta addition (orientation)

Formation of the Active Electrophiles

1. In each case, the cationic form of the thing that adds must be generated
2. The arrow pushing in the E+ generation always involves an arrow going from the cation precursor to the Lewis or Bronsted acid
3. For class, we will focus on sulfuric acid as Bronsted acid, and $AlCl_3$ or $FeBr_3$ as Lewis acids
   - But in an actual synthesis lab, other Bronsted or Lewis acids are available and may sometimes provide superior performance.



Note: The **acids** really need be used in only **catalytic** quantities. The active acids are regenerated during the deprotonation step.



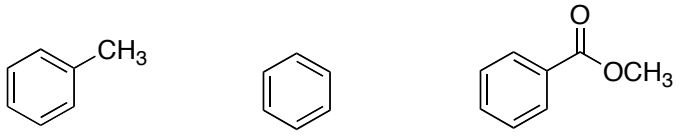
Additions to Substituted Benzenes. The Effect of Substituents on Reactivity Rates and the Position of Substitution. (17.4, 5, 6)

Three Issues
1. Activators versus Deactivators
2. Electron Donors versus Electron Withdrawing Groups
3. Ortho-Para directors versus Meta Directors

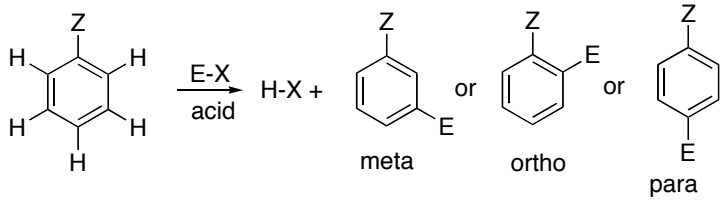
Fact: The rate determining step is the cation addition step
- The transition state much resembles the carbocationic product of that step
- What's good for the cation is good for the reaction rate (product stability-reactivity principle)

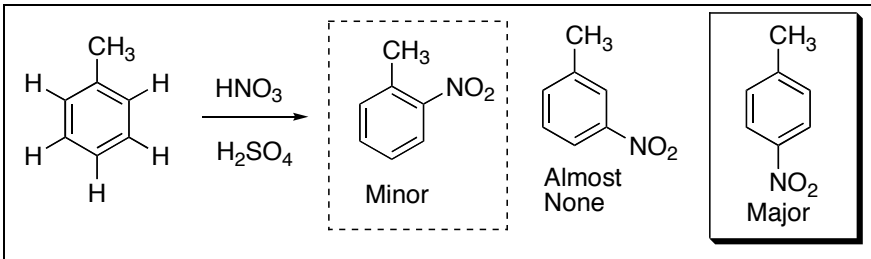
Cation stabilizers = **electron donors** → good for cations → good for rates = **activators**
Cation destabilizers = **electron withdrawers** → bad for cations → bad for rates = **deactivators**

Problem: Rank the reactivity towards HNO_3/H_2SO_4 (The fastest is 25 times faster than the middle, the slowest one is less than $1/100^{th}$ as fast as the middle.)



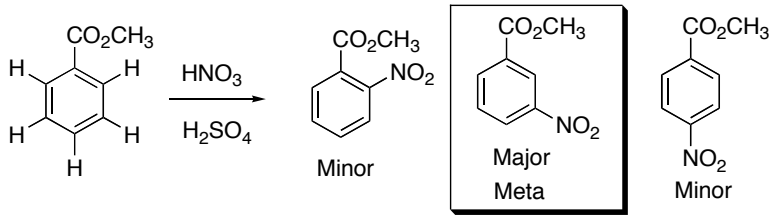
Position of Substitution: When an electrophile adds to a substituted benzene, does it add Ortho, Meta, or Para to the pre-existing substituent? Ortho-para directors versus Meta Directors
- When an electrophile adds to a substituted benzene, it can potentially come in at three different positions: ortho, meta, or para





Cation-stabilizing donors are **ortho-para** directors

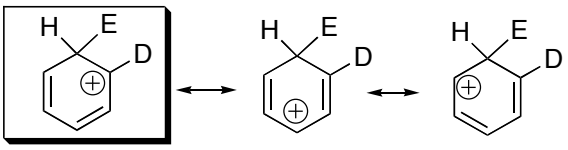
For an ortho-para director, **para predominates for steric reasons**



Cation-destabilizing withdrawers are **meta directors**

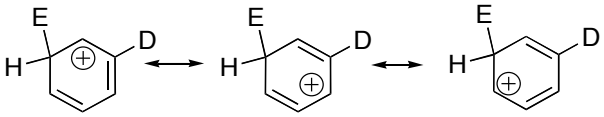
The Situation with an Electron **Donor**/Cation Stabilizer (Ortho-Para Director) (Section 17-6)

Ortho Addition Relative to a Donor



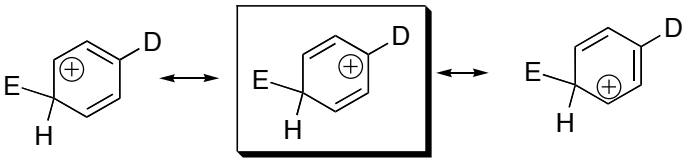
Boxed form is especially good electronically.
Ortho addition often has some steric destabilization.

Meta Addition with a Donor



None of the three resonance forms benefits from the electron donor.

Para Addition Relative to a Donor



Boxed resonance form is especially benefitted electronically.

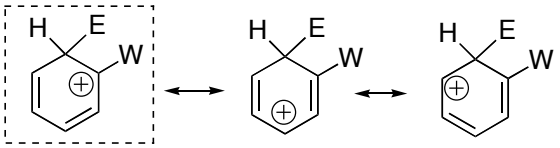
Summary: Electronic Factor: An electron donor (cation stabilizer) is especially beneficial electronically when the electrophile adds ortho or para relative to the donor.

- **Thus donors are ortho/para directors.**

Steric Factor: Ortho addition relative to the donor is always destabilized somewhat by steric interactions. Thus, when addition para relative to the donor does not involve any steric interactions, (usually but not always the case), para addition is faster than ortho addition.

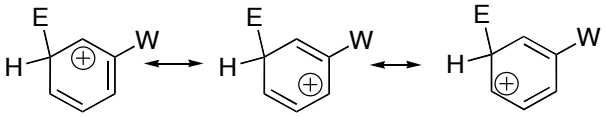
The Situation with an Electron **Withdrawer**/Cation Stabilizer (Ortho-Para Director) (12.13)

Ortho Addition Relative to a Withdrawer



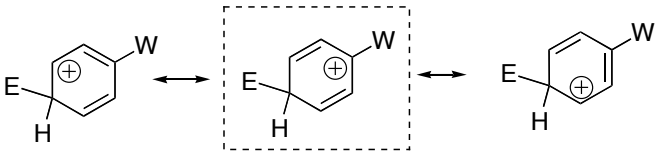
Boxed form is especially bad electronically.

Meta Addition Relative to a Withdrawer



None of the three resonance forms suffers badly from the electron donor.

Para Addition Relative to a Withdrawer

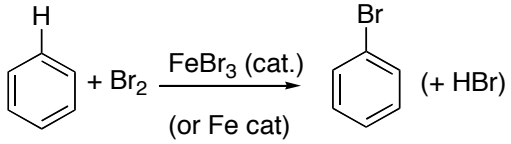


Boxed form is especially bad electronically.

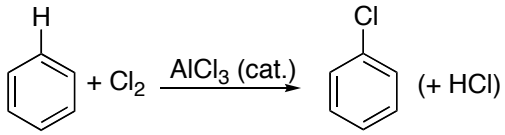
Summary: An electron withdrawer (cation destabilizer) is especially harmful electronically when the electrophile adds ortho or para relative to the withdrawer. Thus withdrawers are meta directors. Not because meta is that good; it's just not as bad as ortho or para.

Note: Meta is still deactivated somewhat, it's just not as slow as ortho or para addition.

Halogenation Reactions (17-2)

1 

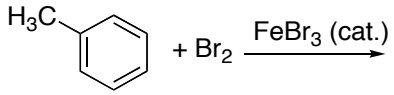
Deactivating Ortho/Para 17.2

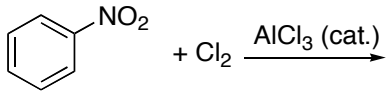


Deactivating Ortho/Para 17.2

- Note: In the presence of Br_2, Fe metal is converted directly into $FeBr_3$, so sometimes Fe rather than $FeBr_3$ is used
- Many other Lewis acids can accomplish the same reactions

Draw the products for the following reactions.

1 

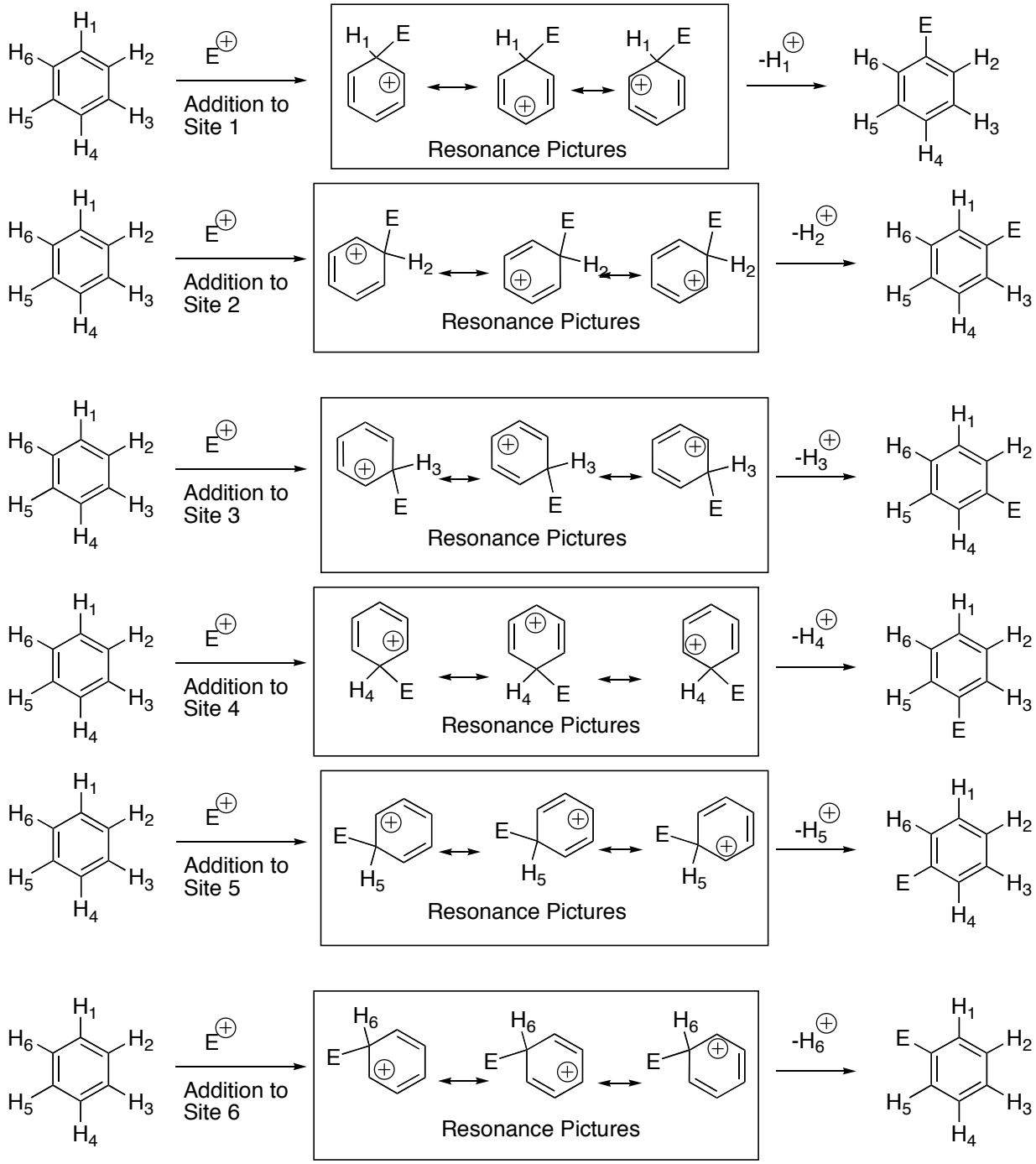
2 

3 Draw the mechanism for the first reaction above.
- Identify the slow step.
- Draw in all three resonance structures for the cation.
- Circle the best resonance structure.

4 Even minor products form via mechanisms. Draw the mechanism for formation of ortho-bromotoluene from toluene.

Tips:
- Always draw the hydrogen on the reacting carbon
- For resonance structures, keep substituent, key H, and adding group in each picture
- Never draw the + charge on the tetrahedral center
- At the cation stage, make sure you never draw a double bond to the tetrahedral center (that would make 5 bonds!)

Seeing the Mechanism and Resonance Structures from Different Perspectives



NOTES:

1. These focus on drawing the resonance structures and seeing how the positive charge is delocalized in the cation.
2. Notice that regardless of which position the electrophile adds to, the positive charge still ends up delocalized onto the positions ortho and para **relative to the site of addition**
3. Notice that the site of addition does not have positive charge
4. Notice that the hydrogen that is lost is from the same carbon where the electrophile adds, not from an ortho carbon

4 Classes of Substituents: Memorize! (Sections 17-6-8)

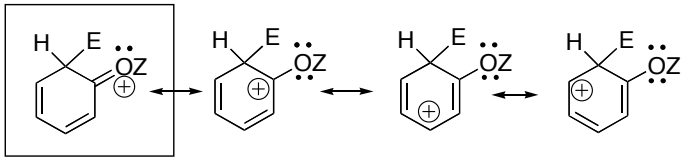
Donating?	Memorize the list	Activating/Deactivating	Directing Effect
	OH, OR, NH_2, NHR, NR_2	Strong Activators	Ortho/para directors
	R, Ar	Weak Activators	Ortho/para directors
	Cl, Br	Weak Deactivators	Ortho/para directors
	Carbonyl, NO_2, CN, SO_3H	Strong Deactivators	Meta directors

Note: Halogens are a special case that are ortho-para directors despite being deactivating
Otherwise, the following pattern is general:

- Activator = ortho-para director (and vice versa,with exception of halides)
- Meta director = deactivator (and vice versa,with exception of halides)

Special Resonance/Conjugation with Oxygen and Nitrogen Substituents

Ortho Addition Relative to an Oxygen Donor



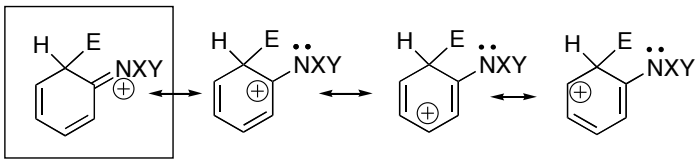
-extra resonance structure
-best resonance structure

Boxed resonance form is especially benefitted electronically.

The two electrons in the extra bond come from an oxygen lone pair.

This is why oxygen is such a strong donor.

Ortho Addition Relative to an Nitrogen Donor



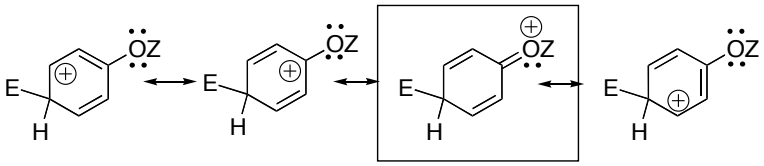
-extra resonance structure
-best resonance structure

Boxed resonance form is especially benefitted electronically.

The two electrons in the extra bond come from a nitrogen lone pair.

This is why nitrogen is such a strong donor.

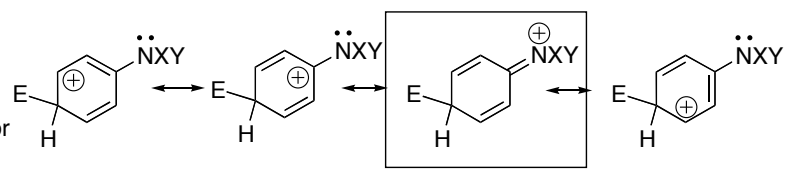
Para Addition Relative to a Oxygen Donor



-extra resonance structure
-best resonance structure

-Boxed form is best
-The two electrons in the extra bond come from a nitrogen lone pair.

Para Addition Relative to a Nitrogen Donor



-extra resonance structure
-best resonance structure

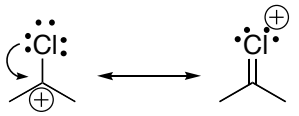
-Boxed form is best
-The two electrons in the extra bond come from a nitrogen lone pair.

Section 7-8. Halogens. Special Case: Weak Deactivators, but still ortho-para directors.

Explanation (not for test): Halogens are both withdrawers (based on their electronegativity) but also donors (through resonance/conjugation/π-donation)

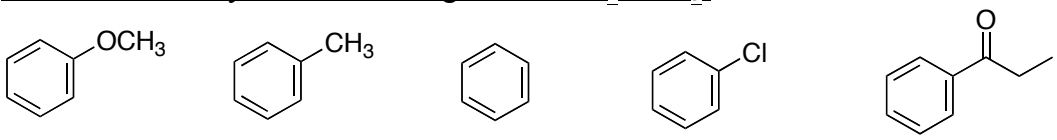
- Withdrawers, because of the polarized, electronegative C-X bond
- Donors via the π-conjugation
- The withdrawing effect is stronger, thus they are overall deactivators, whether ortho, meta, or para
- The π-conjugation only benefits with ortho-para addition
- Because of the conjugation/resonance factor, ortho-para addition isn't as destabilized as meta addition.

Electronegativity withdrawer
(through sigma bond)
σ-Withdrawer

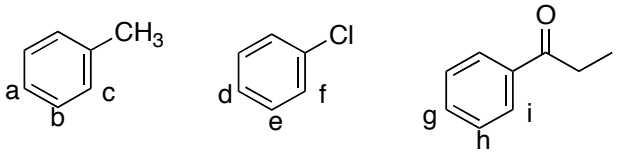


Conjugation/resonance donor
Through lone-pair π-system
π-Donor

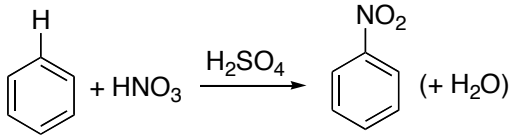
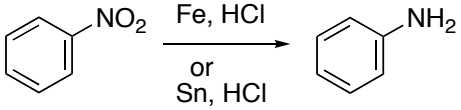
Rank the reactivity of the following towards $Br_2/FeBr_3$.



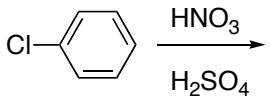
Shown are 9 different sites for possible addition. Rank all 9, from most to least reactive.



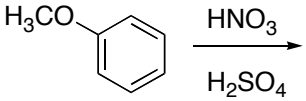
Nitration Reaction (17-3)

2		Deactivating	Meta	17.3
6		Activating	Ortho/Para	19.21

Draw the major product.

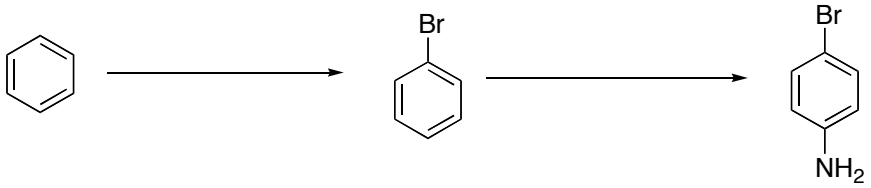
1. 

2. Anisole is more than 1000 times faster than benzene. Draw the mechanism, including all of the resonance structures for the cation intermediate in the p-bromination of anisole, and circle the "best" resonance structure.

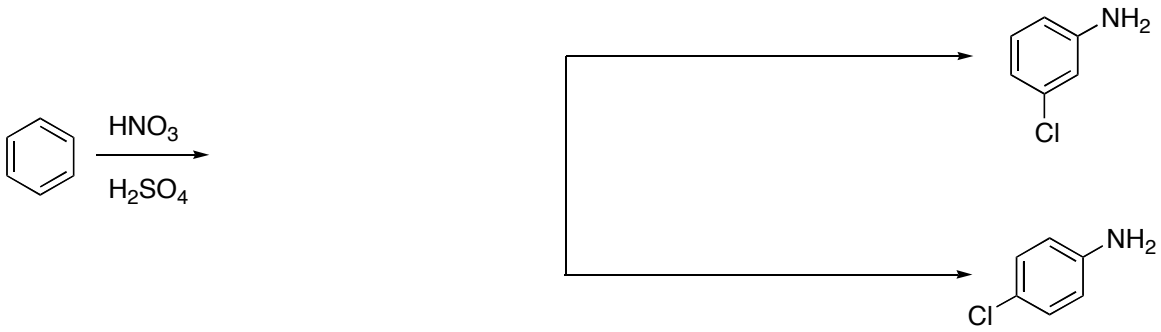


2-Step Route to Add NH_2: 1) HNO_3, H_2SO_4 2) Fe, HCl
▪ at nitro stage, Nitrogen is a meta director
▪ at amino stage, Nitrogen is an ortho-para director

3. Provide the reagents for the following transformation.



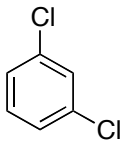
4. Design synthetic routes for the following transformations.

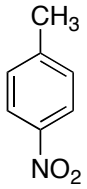


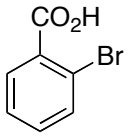
Rules for Additions to Disubstituted/Polysubstituted Aromatics (17.9)

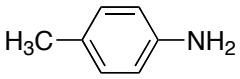
1. Effects are additive if both direct to the same spot
2. If there is a conflict of interest, the more activating group controls the outcome
   - You need to know the relative activating/deactivating strengths!
3. Steric considerations: if two substituents have a 1,3 (meta) relationship, addition in between (to give a 1,2,3 relationship) is prohibitively slow for steric reasons

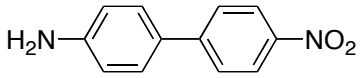
For each of the following, imagine what would happen if a mono-nitration took place. Would there be one main product, or more than one? If so, where?

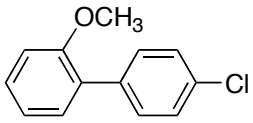
1. 

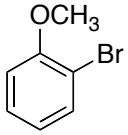
2. 

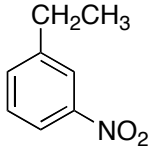
3. 

4. 

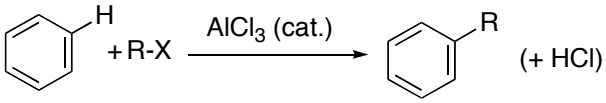
5. 

6. 

7. 

8. 

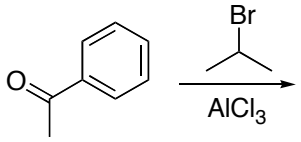
Section 17-10. Friedel-Crafts Alkylation

3		**Activating**	Ortho/para
	a. Restricted to 3º, 2º, or ethyl halides. **1º halides suffer carbocation rearrangements**. b. Since product is more active than starting material, **polyalkylation is often a problem**. c. Fails with strongly deactivated benzenes. **Mech required.**		

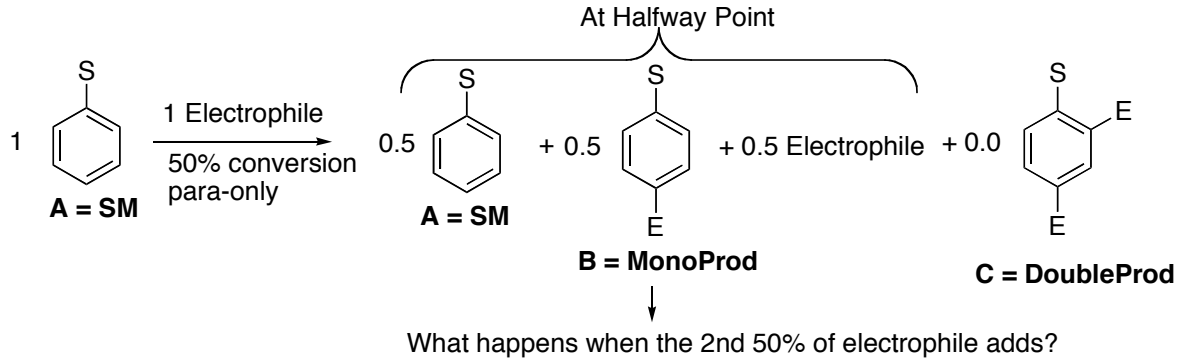
Other Sources of Carbocations:

- ROH + H_2SO_4
- ROH + BF_3
- Alkene + H^+

Draw the Major Product and Mechanism for the Following (Assume a single substitution)

5. 

Problem: Activating or Deactivating Effect by a Newly Added Substituent. Polysubstitution vs. Clean Monosubstitution. A thought exercise.



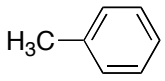
Case:	If: (hypothetically)	Activating/Deactivating Effect of Added Group "E"	Amount of **A**	Amount of **B**	Amount of **C**
1	Product "**B**" " is much **more** reactive than SM "**A**"	Activating			
2	Product "**B**" " is much **less** reactive than SM "**A**"	Deactivating			
3	Product "**B**" " is **equally reactive** to SM "**A**"	No Effect			

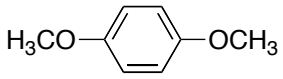
Polyaddition Notes:

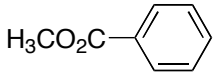
1. When a deactivator is added, monosubstitution is easy.
   - The adduct is always deactivated relative to the starting material
   - Most of the best aromatic substitutions add deactivators
2. When a donor is added, polysubstitution can be a factor.
   - Electronically, the adduct will be more reactive than the starting material.
3. Some solutions to polyaddition.
   a. Perhaps di- or tri-addition is a good and desirable thing.
   b. Use a huge excess of your aromatic starting material.
      - Benzene, toluene, or anisole for example, are cheap and can be used as solent.
      - The probability of an electrophile reacting with an adduct molecule may be statistically modest if there are thousands of times as many solvent starting materials available
   c. Steric suppression. Often steric reasons can reduce the reactivity of the adduct.
      - Frequently the only available sites might be ortho to something or other, and experience at least some steric interactions
      - This may be increased with bulky electrophiles/substituents, as if often the case with 2º or 3º alkyl groups

Practice Problem: Assume each of the following are treated with $(CH_3)_2CHBr$ (iPrBr) and $AlCl_3$. For each of the following:

a. draw the product of the first substitution
b. Draw the product of the second substitution (in other words, if the first product reacts again.)
c. In every case, the second substitution will have some electronic advantage (because you just added an activator/donor.) But in which cases will the second substitution have a steric disadvantage?

a. 

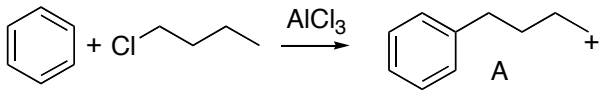
b. 

c. 

2-Step Route to Add 1º Alkyl: 1) RCOCl, $AlCl_3$ 2) Zn(Hg), HCl ▪ at acyl stage, acyl carbon is a meta director ▪ at alkyl stage, alkyl is an ortho-para director

6. Fill in the blanks for the following reactions

Method 1: Direct F-C Alkylation



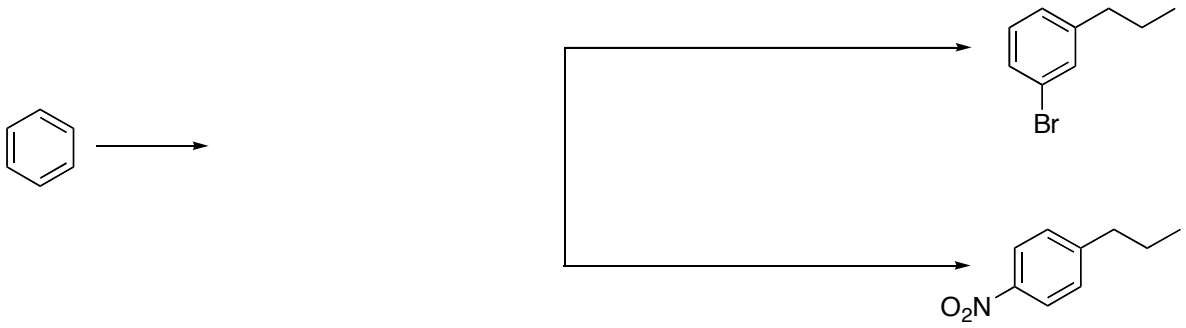
Minor Product

+ Polysubbed Products

Major Monosubbed Product

Method 2: F-C Acylation/Reduction

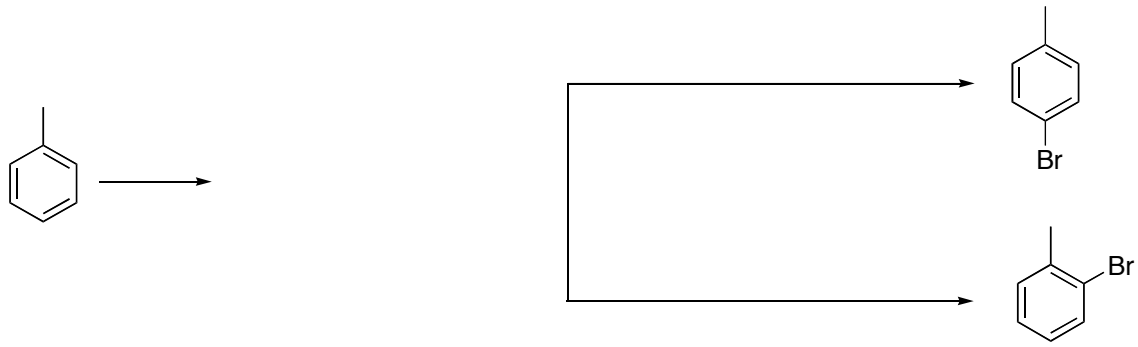
7. Design pathways for the following syntheses:



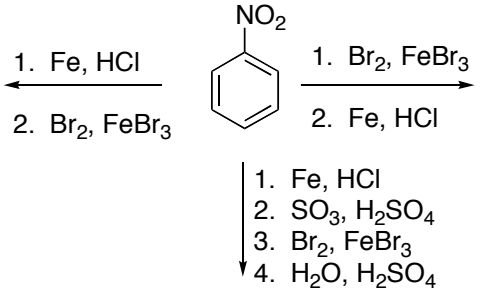
Sulfonylation/Reaction/Desulfonylation: 1. SO_3, H_2SO_4 2. Whatever 3. H_2O, H_2SO_4

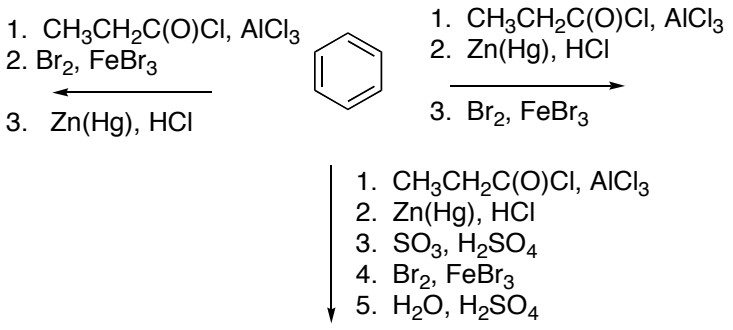
- Ideal procedure for when you have an ortho/para director, but you want an electrophile to end up ortho rather than para

8. Design pathways for the following syntheses:



9. Draw the products for the following reactions:

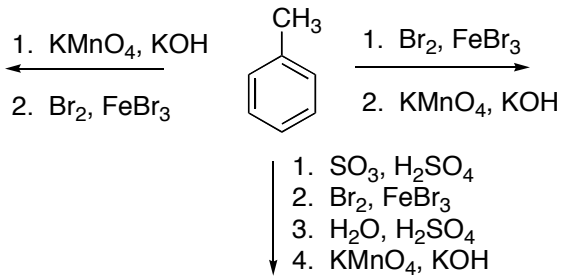




Oxidation of toluene methyl group (or other alkyl side chains): $KMnO_4$

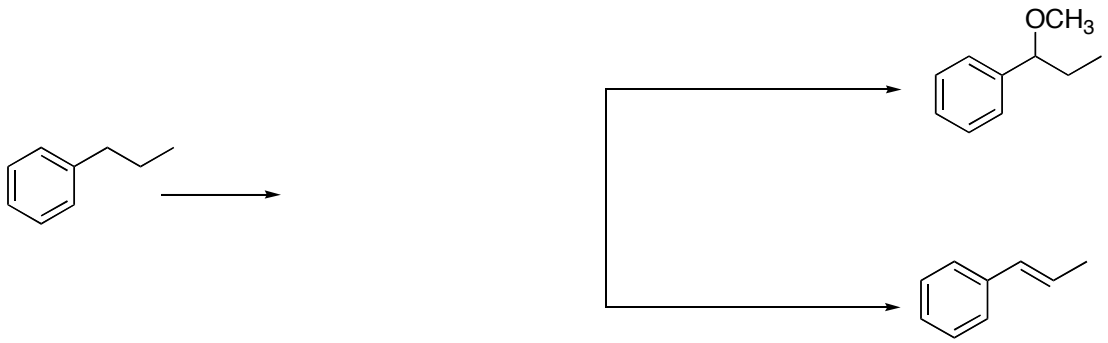
- The original alkyl group is an activating ortho-para director
- The resulting carboxylic acid is a deactivating meta director

10. Draw the outcomes for the following reaction sequences.



Benzylic Bromination Provides a Useful Functional Group:
▪ Treatment with many anions results in S_N2 substitution ▪ Treatment with bulky bases results in E2 elimination → vinyl benzenes

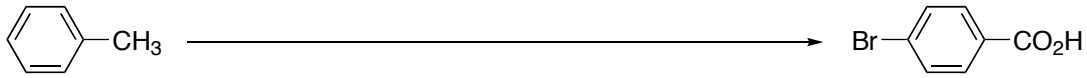
11. Design pathways.

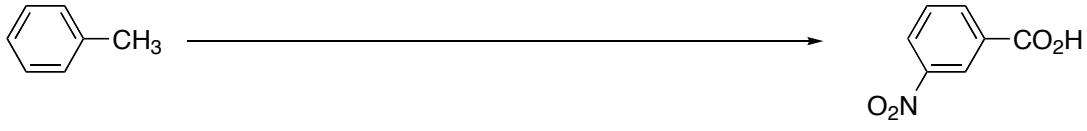


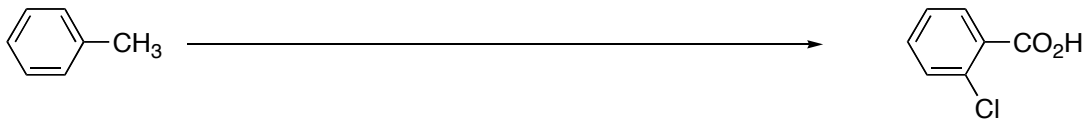
Synthetic Planning: To make multisubstituted aromatics, choose sequence with care!

If:	Make From:
Para Disubbed	An ortho-para director (a donor)
Meta Disubbed	A meta director (a strong, deactivating withdrawer)
Ortho Disubbed	An ortho-para director **and** para position blocked using the sulfonation/desulfonation trick

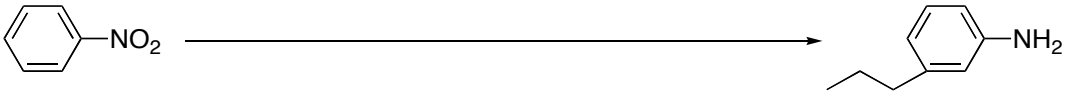
Design Syntheses for the Following:

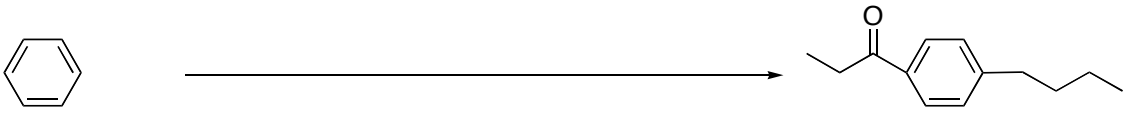
12. 

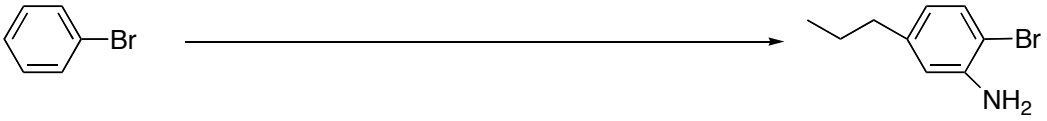
13. 

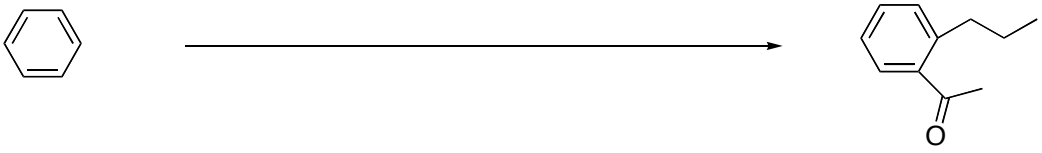
14. 

Design Syntheses for the Following:

15. 

16. 

17. 

18. 

19.