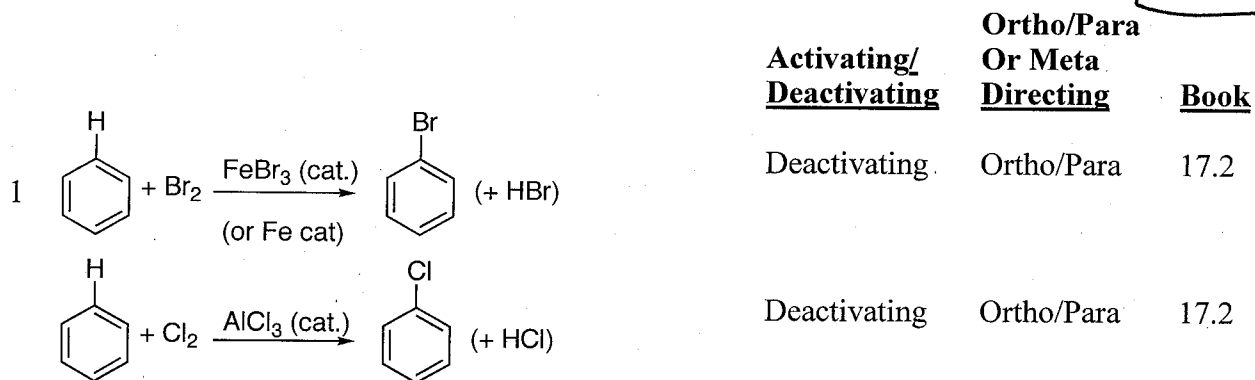
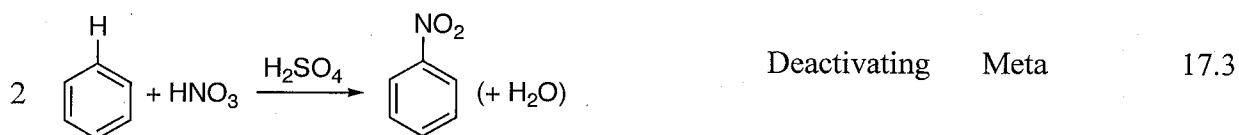


## 5 Major Electrophilic Aromatic Substitution Reactions

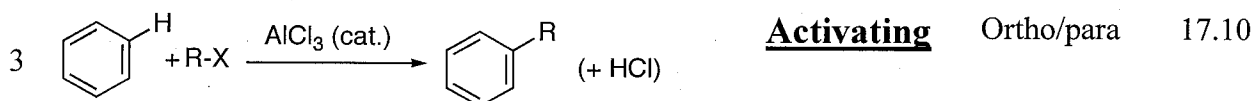
Answers



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**

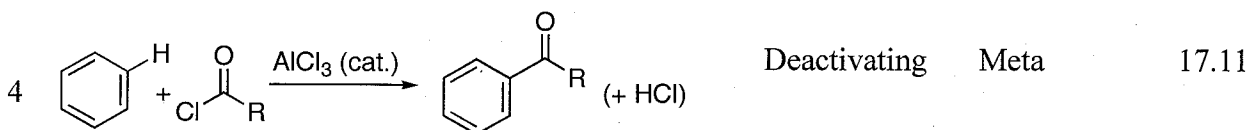


The product can be reduced to Ar-NH<sub>2</sub> by Fe/HCl or Sn/HCl. Nitration/Reduction provides an effective way to introduce an NH<sub>2</sub> group. Reduction converts m-directing NO<sub>2</sub> group into an o/p-directing NH<sub>2</sub> group. **Mech required.**



- Restricted to 3°, 2°, or ethyl halides. 1° halides suffer carbocation rearrangements.
- Since product is more active than starting material, polyalkylation is often a serious problem.
- Fails with strongly deactivated benzenes.

**Mech required.**



- The product can be reduced to -CH<sub>2</sub>R by Zn(Hg)/HCl.
- The acylation-reduction sequence provides an effective way to introduce a 1° alkyl group.
- Reduction converts meta-directing acyl group into an ortho/para-directing alkyl group.

**Mech required.**



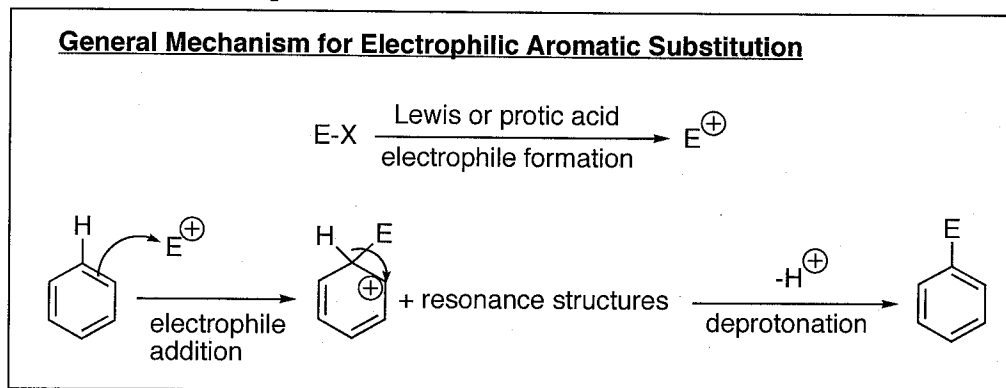
The sulfonyl group is a useful para-blocking group, since it can later be removed upon treatment with H<sub>2</sub>O/H<sup>+</sup>. **No mech required.**

**5 Major Aromatic Support Reactions**

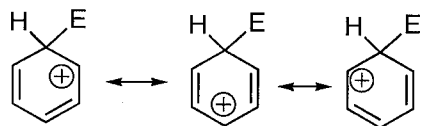
		<b>Activating/ Deactivating</b>	<b>Ortho/Para Or Meta Directing</b>	<b>Book</b>
6		Activating	Ortho/Para	19.21
	<ul style="list-style-type: none"> <li>Reduction converts meta-director into an ortho-para director.</li> <li>Fe, Sn, or several other reducing metals can work.</li> </ul>		No mech required.	
7		Activating	Ortho/Para	17.12
	<ul style="list-style-type: none"> <li>Clemmensen reduction converts meta-director into an ortho-para director.</li> <li>Acylation (#4) followed by Clemmensen Reduction (#7) is the standard method for introducing a 1° alkyl group. (Direct alkylation with a 1° alkyl halide, reaction #3, fails due to cation rearrangement problems...)</li> </ul>		No mech required.	
8		-----	-----	17.4
	<ul style="list-style-type: none"> <li>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<sub>2</sub>O/H<sup>+</sup> (reaction 8).</li> <li>The sulfonation/other reaction/desulfonation sequence is crucial for clean ortho-substitution of an o/p director.</li> </ul>		No mech required.	
9		Deactivating	Meta	17.14
	<ul style="list-style-type: none"> <li>Oxidation converts ortho/para-director into a meta-director.</li> <li>Side alkyl chains longer than methyl can also be oxidized to benzoic acid in the same way, although more time and heat is required.</li> <li>For test purposes, just writing KMnO<sub>4</sub> will be OK. But the real reaction requires a basic solution for the KMnO<sub>4</sub> to work, so an acidic workup step is actually required to isolate the neutral carboxylic acid.</li> </ul>		No mech required.	
10		-----	-----	17.14
	<ul style="list-style-type: none"> <li>Bromination occurs via free-radical mechanism.</li> <li>It is selective for substitution at the benzylic position because the benzylic radical intermediate is resonance-stabilized.</li> <li>Note: keep distinct Br<sub>2</sub>/FeBr<sub>3</sub> from Br<sub>2</sub>/peroxides!</li> <li>Product is subject to S<sub>N</sub>2 substitutions (benzylic bromides are especially good, better than normal 2° bromides) and E2 eliminations with bulky bases.</li> <li>"NBS" is N-bromosuccinimide, which functions just like Br<sub>2</sub>/peroxides, but is much more convenient and cleaner because it avoids competing reactions caused by lots of Br<sub>2</sub> and HBr.</li> </ul>			

**Mech required.**

## Section 17.1 Electrophilic Aromatic Substitution



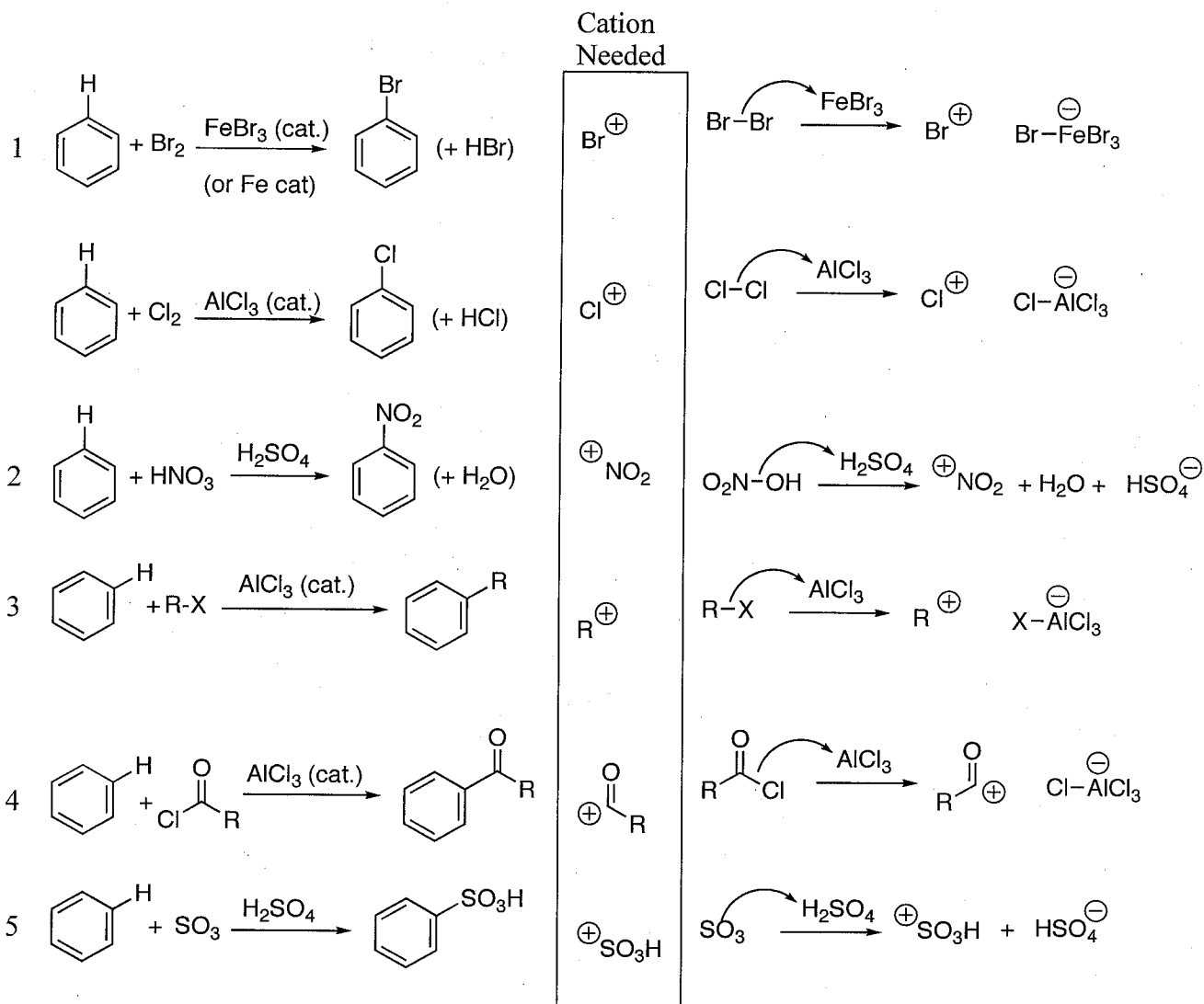
- The **addition step**, generating the carbocation, is the **rate-determining** step
- Any extra **substituents that stabilize the carbocation will make the reaction faster** (the product stability-reactivity principle). And vice-versa...
  - Electron-donating groups** will stabilize carbocations and accelerate (**activate**) addition
  - Electron-withdrawing groups** that destabilize carbocations will decelerate (**deactivate**) addition
- 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
- 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**

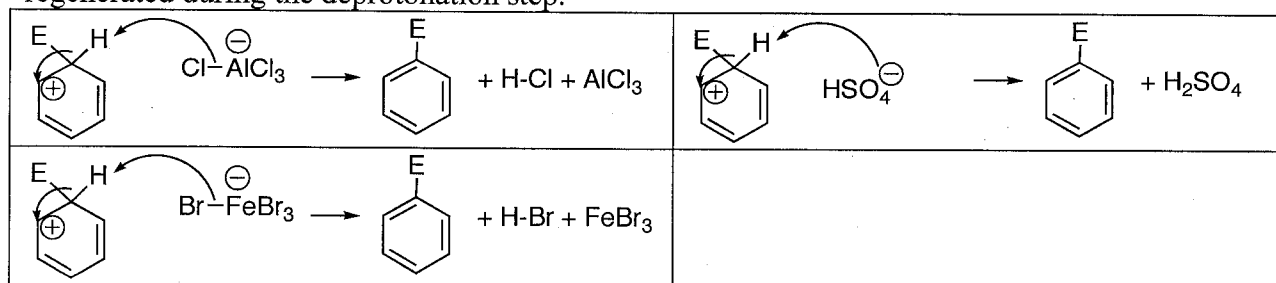
- A substituent that's good for one of these cation forms (donor) is good for the addition:
  - This results in activation (kinetics)
  - and ortho/para addition (orientation)
- A substituent that's bad for one of these cation forms (withdrawer) is bad for the addition:
  - This results in deactivation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

**Formation of the Active Electrophiles**

- In each case, the cationic form of the thing that adds must be generated
- The arrow pushing in the E<sup>+</sup> generation always involves an arrow going from the cation precursor to the Lewis or Bronsted acid
- For class, we will focus on sulfuric acid as Bronsted acid, and AlCl<sub>3</sub> or FeBr<sub>3</sub> 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

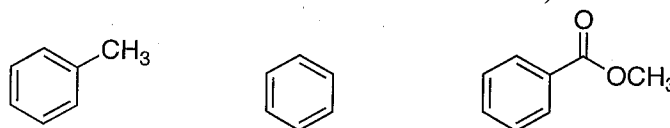
1. Activators versus Deactivators
2. Electron Donors versus Electron Withdrawing Groups
3. Ortho-Para directors versus Meta Directors

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)

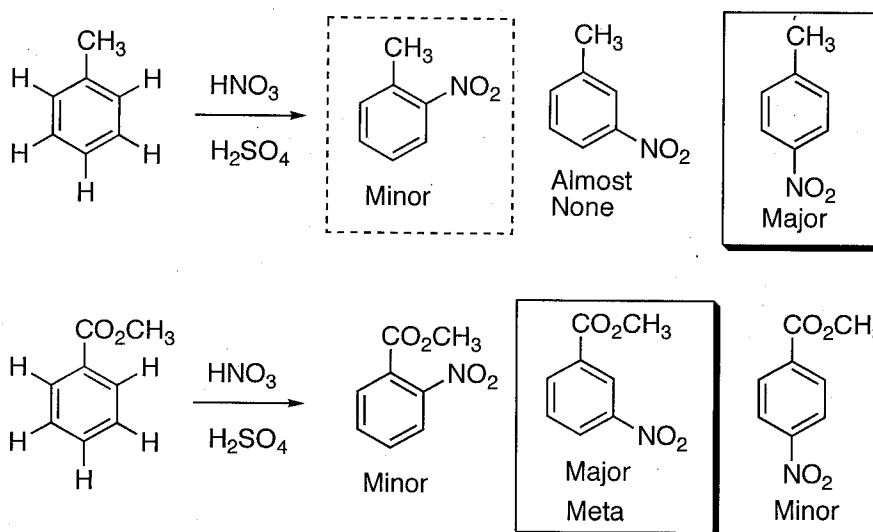
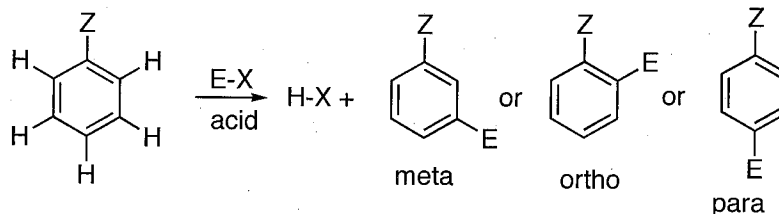
Cation stabilizers = **electron donors** → good for cations → good for rates = **activators**  
 Cation destabilizers = **electron withdrawers** → bad for cations → bad for rates = **deactivators**

Problem: Rank the reactivity towards  $\text{HNO}_3/\text{H}_2\text{SO}_4$  (The fastest is 25 times faster than the middle, the slowest one is less than  $1/100^{\text{th}}$  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



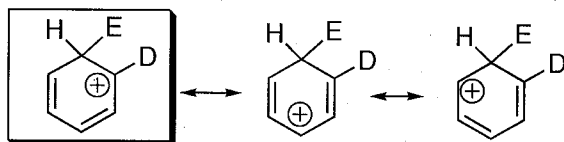
Cation-stabilizing donors are **ortho-para** directors

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

Cation-destabilizing withdrawers are **meta** directors

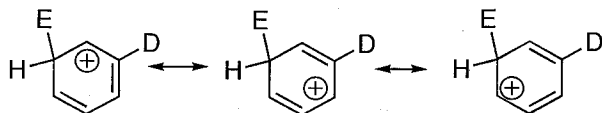
The Situation with an Electron Donor/Cation Stabilizer (Ortho-Para Director) (Section 17-6)

Ortho  
Addition  
Relative to a  
Donor



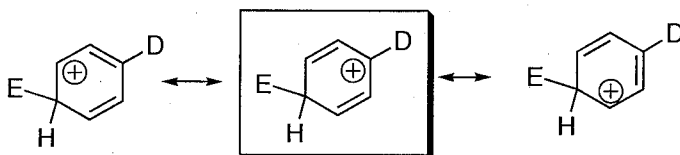
Boxed form is especially good electronically.  
Ortho addition often has some steric destabilization.

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.

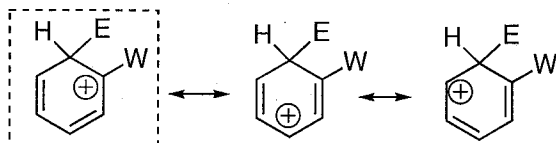
**Summary: Electronic Factor:** An electron donor (cation stabilizer) is especially beneficial electronically when the electrophile adds ortho or para relative to the donor.

- 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.

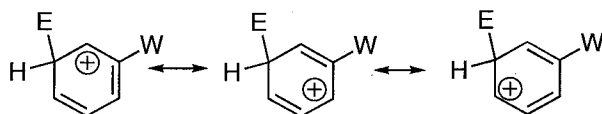
The Situation with an Electron Withdrawer/Cation Destabilizer (Ortho-Para Director) (17-7)

Ortho  
Addition  
Relative to a  
Withdrawer



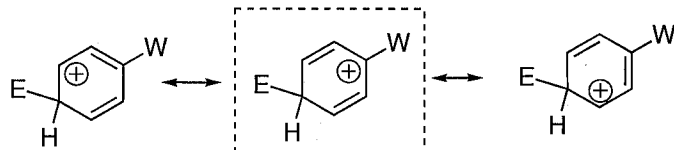
Boxed form is especially bad electronically.

Meta  
Addition  
Relative to a  
Withdrawer



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

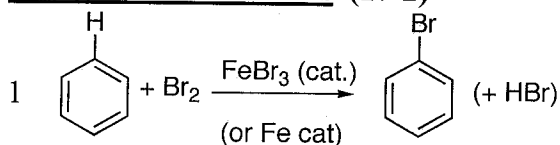
Para  
Addition  
Relative to a  
Withdrawer



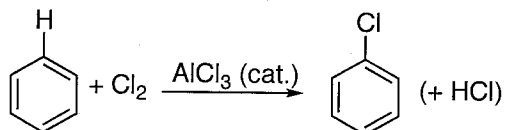
Boxed form is especially bad electronically.

**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)**

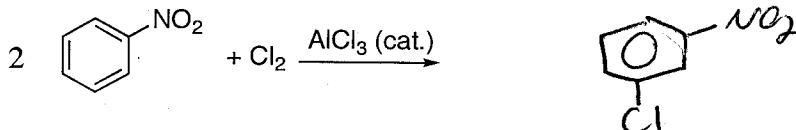
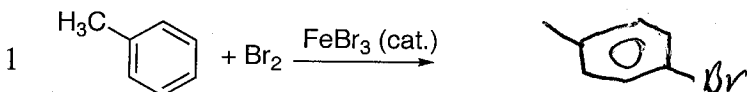
Deactivating Ortho/Para 17.2



Deactivating Ortho/Para 17.2

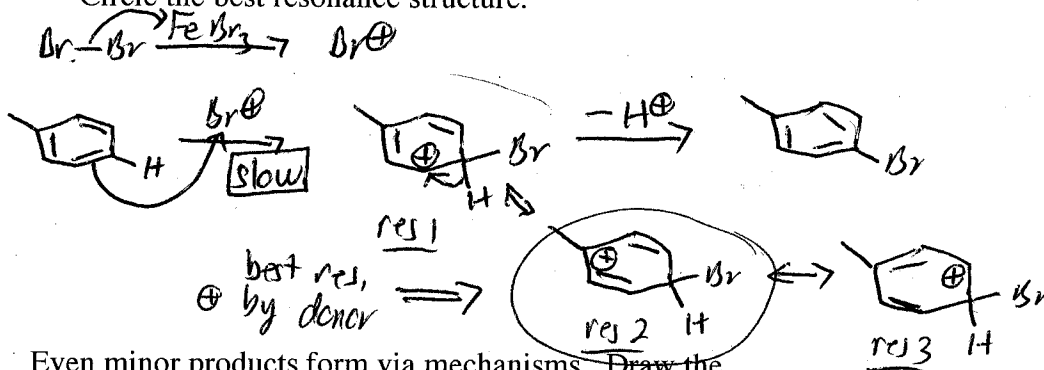
- Note: In the presence of Br<sub>2</sub>, Fe metal is converted directly into FeBr<sub>3</sub>, so sometimes Fe rather than FeBr<sub>3</sub> is used
- Many other Lewis acids can accomplish the same reactions

Draw the products for the following reactions.

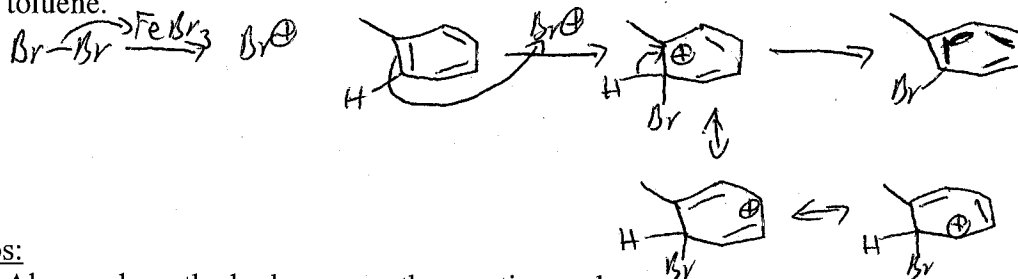


3 Draw the mechanism for the first reaction above.

- Identify the slow step.
- Draw in all three resonance structures for the cation.
- Circle the best resonance structure.

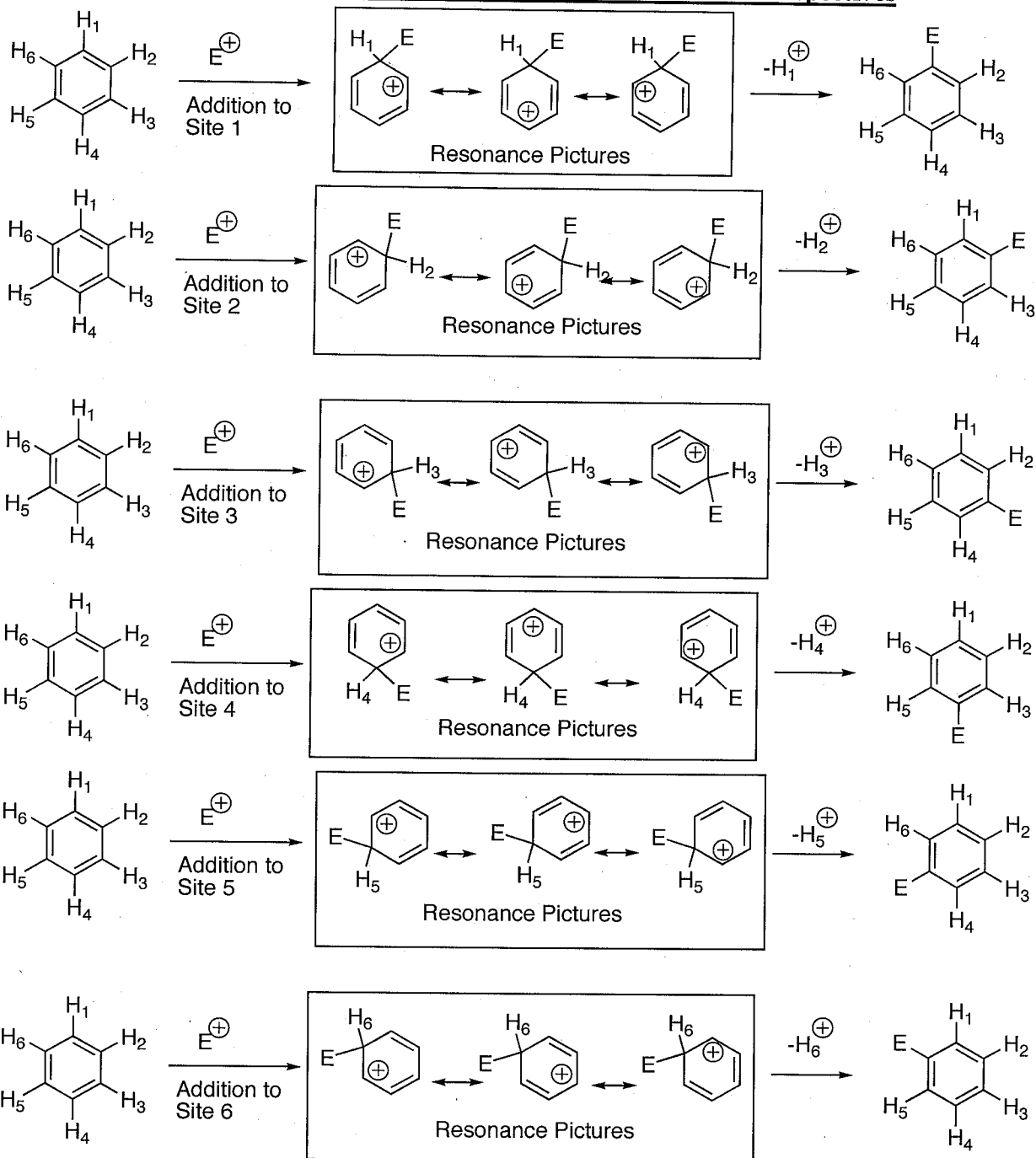


4 Even minor products form via mechanisms. Draw the mechanism for formation of ortho-bromotoluene from toluene.

**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)**

<u>Donating?</u>	<u>Memorize the list</u>	<u>Activating/Deactivating</u>	<u>Directing Effect</u>
	OH, OR, NH <sub>2</sub> , NHR, NR <sub>2</sub>	Strong Activators	Ortho/para directors
	R, Ar	Weak Activators	Ortho/para directors
	Cl, Br	Weak Deactivators	Ortho/para directors
	Carbonyl, NO <sub>2</sub> , CN, SO <sub>3</sub> H	Strong Deactivators	Meta directors

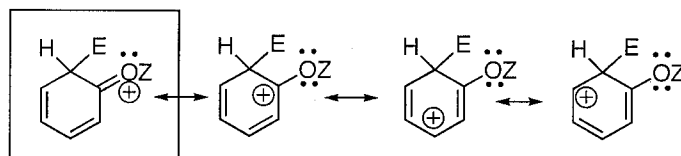
**Note:** Halogens are a special case that are ortho-para directors despite being deactivating

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



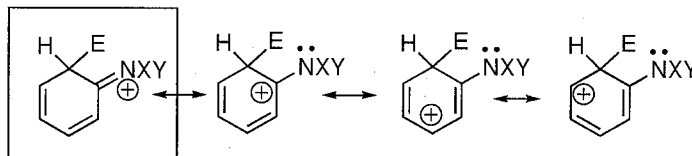
-extra resonance structure  
-best resonance structure

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 a Nitrogen Donor



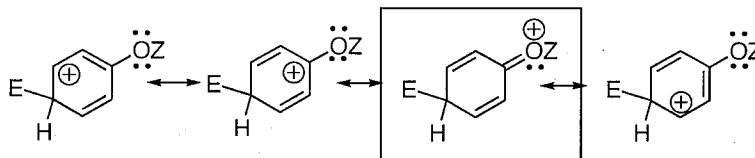
-extra resonance structure  
-best resonance structure

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.

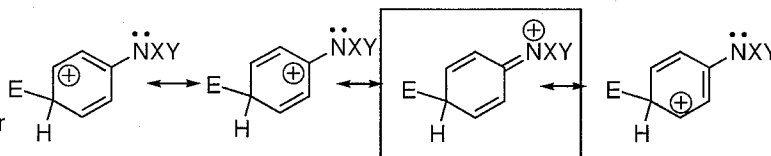
Para Addition Relative to a Oxygen Donor



-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



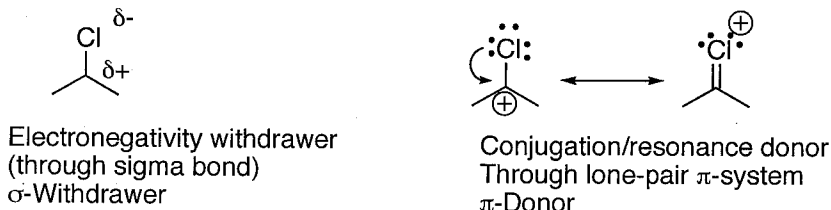
-extra resonance structure  
-best resonance structure

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

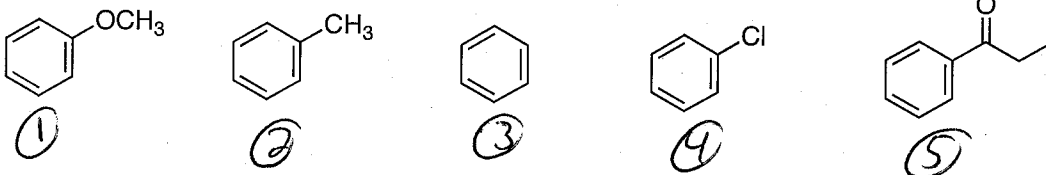
**Section 7-8. Halogens. Special Case: Weak Deactivators, but still ortho-para directors.**

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

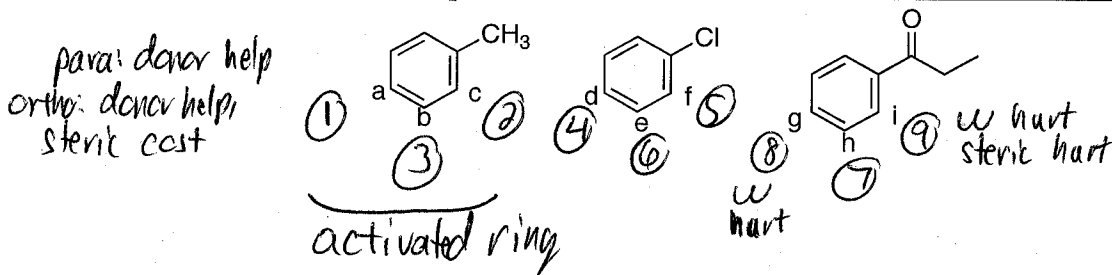
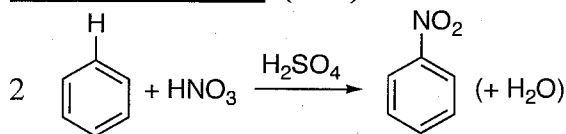
- Withdrawers, because of the polarized, electronegative C-X bond
- Donors via the  $\pi$ -conjugation
- The withdrawing effect is stronger, thus they are overall deactivators, whether ortho, meta, or para
- The  $\pi$ -conjugation only benefits with ortho-para addition
- Because of the conjugation/resonance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



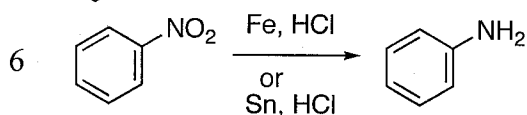
Rank the reactivity of the following towards  $\text{Br}_2/\text{FeBr}_3$ .



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

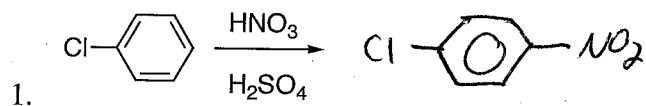
**Nitration Reaction (17-3)**

Deactivating    Meta    17.3

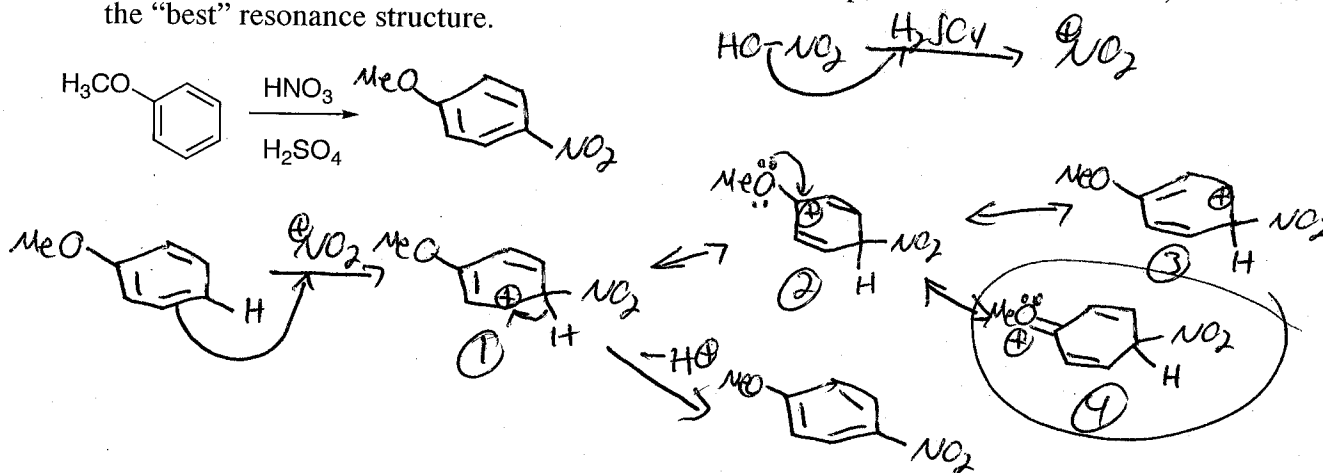


Activating    Ortho/Para    19.21

Draw the major product.



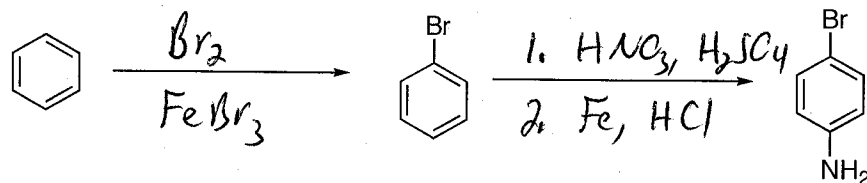
2. Anisole is more than 1000 times faster than benzene. Draw the mechanism, including all of the resonance structures for the cation intermediate in the p-bromination of anisole, and circle the "best" resonance structure.



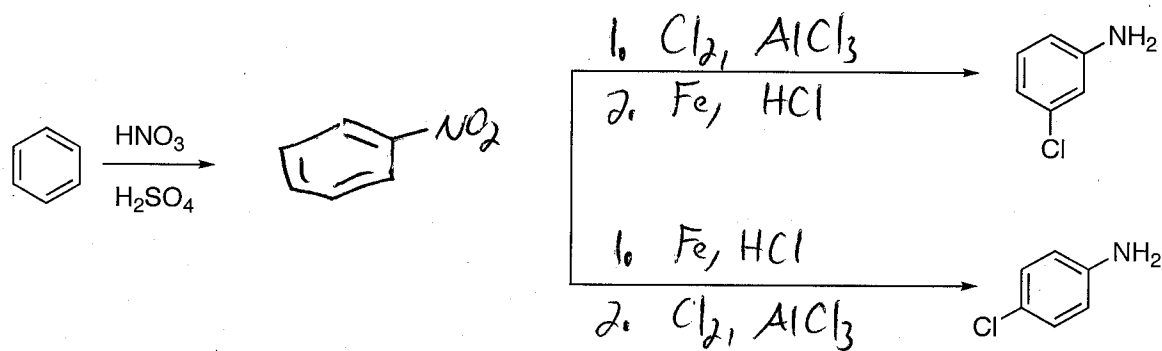
2-Step Route to Add  $\text{NH}_2$ : 1)  $\text{HNO}_3, \text{H}_2\text{SO}_4$  2)  $\text{Fe}, \text{HCl}$

- 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.



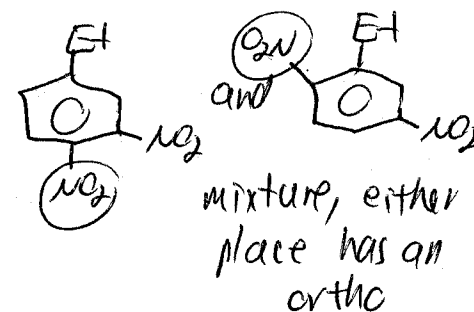
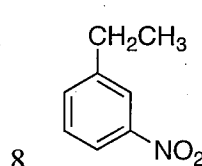
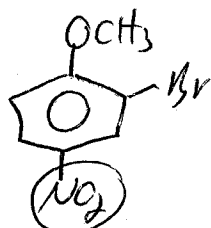
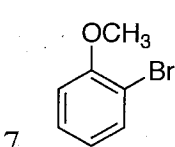
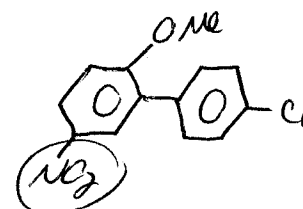
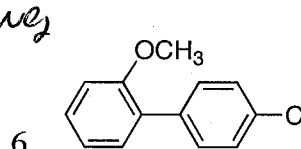
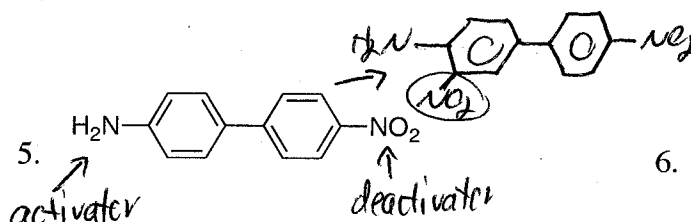
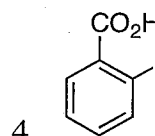
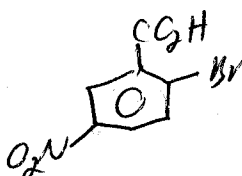
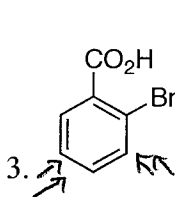
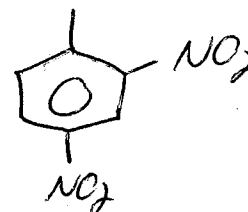
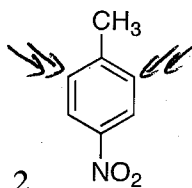
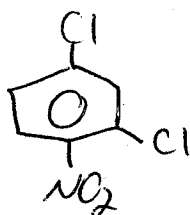
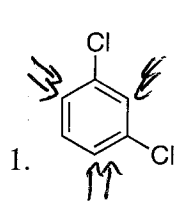
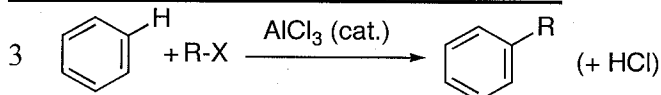
4. Design synthetic routes for the following transformations.



**Rules for Additions to Disubstituted/Polysubstituted Aromatics (17.9)**

- Effects are additive if both direct to the same spot
- If there is a conflict of interest, the more activating group controls the outcome
  - You need to know the relative activating/deactivating strengths!
- 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?

**Section 17-10. Friedel-Crafts Alkylation**

**Activating** Ortho/para

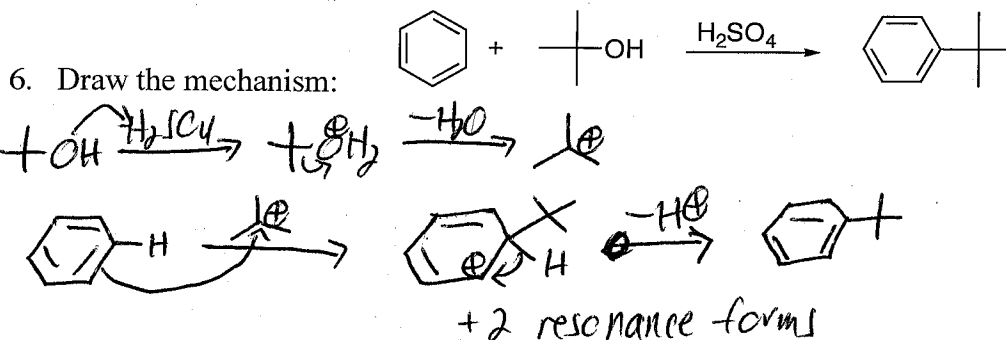
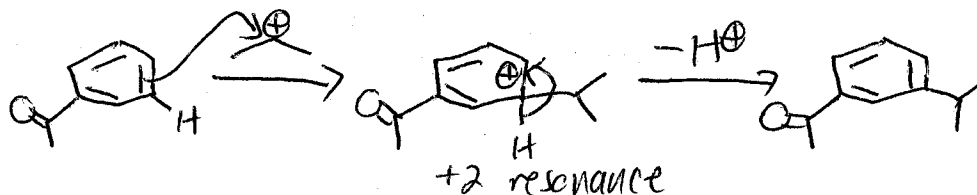
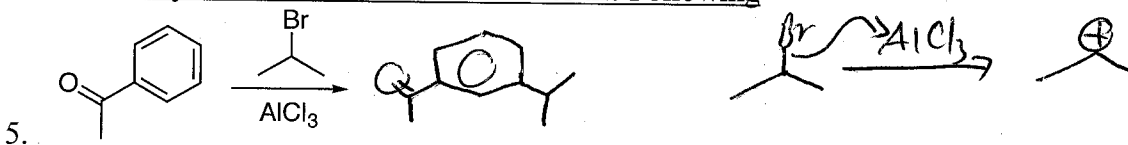
- Restricted to 3°, 2°, or ethyl halides. **1° halides suffer carbocation rearrangements.**
- Since product is more active than starting material, **polyalkylation is often a problem.**
- Fails with strongly deactivated benzenes.

**Mech required.**

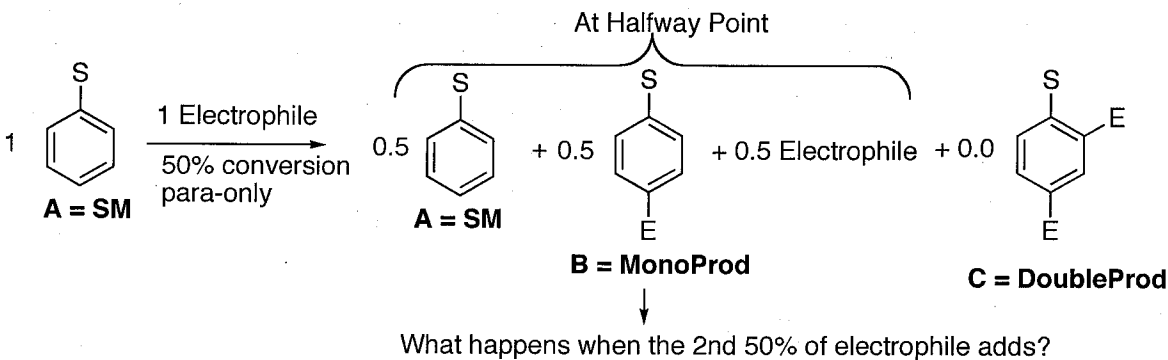
**Other Sources of Carbocations:**

- ROH + H<sub>2</sub>SO<sub>4</sub>
- ROH + BF<sub>3</sub>
- Alkene + H<sup>+</sup>

Draw the Major Product and Mechanism for the Following



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



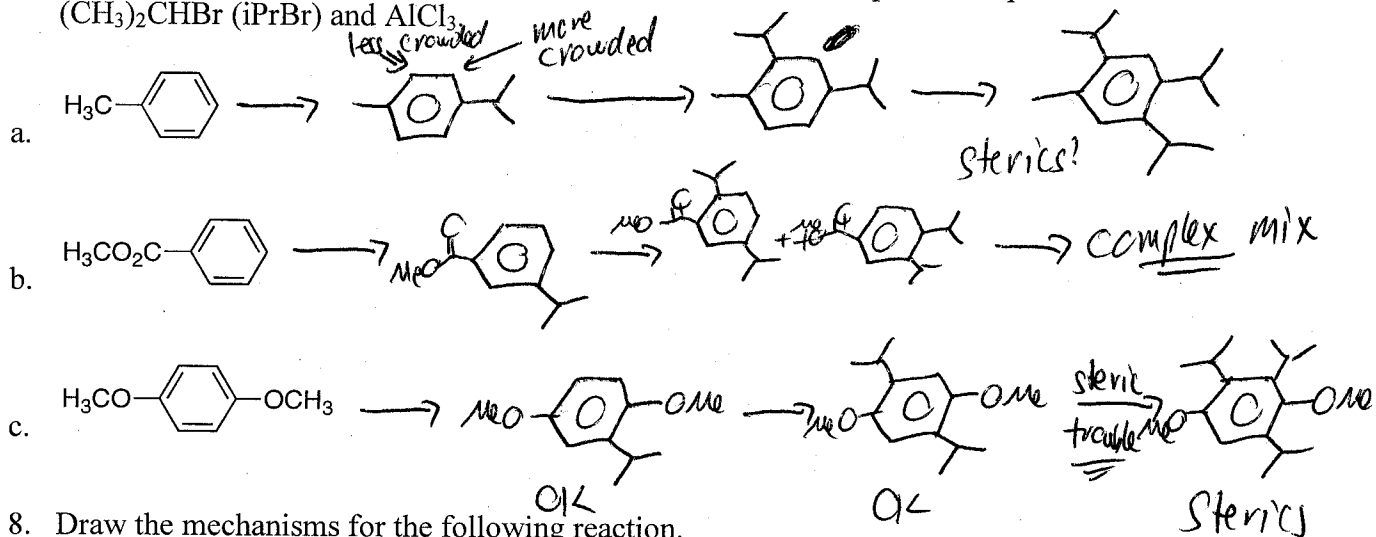
Case:	If: (hypothetically)	Activating/Deactivating Effect of Added Group "E"	Amount of A	Amount of B	Amount of C
1	Product "B" is much <b>more</b> reactive than SM "A"	Activating	0.5	0	0.5
2	Product "B" is much <b>less</b> reactive than SM "A"	Deactivating	0	1.0	0
3	Product "B" is <b>equally</b> reactive to SM "A"	No Effect	0.25	0.50	0.25

Ideal case for clean monosub.

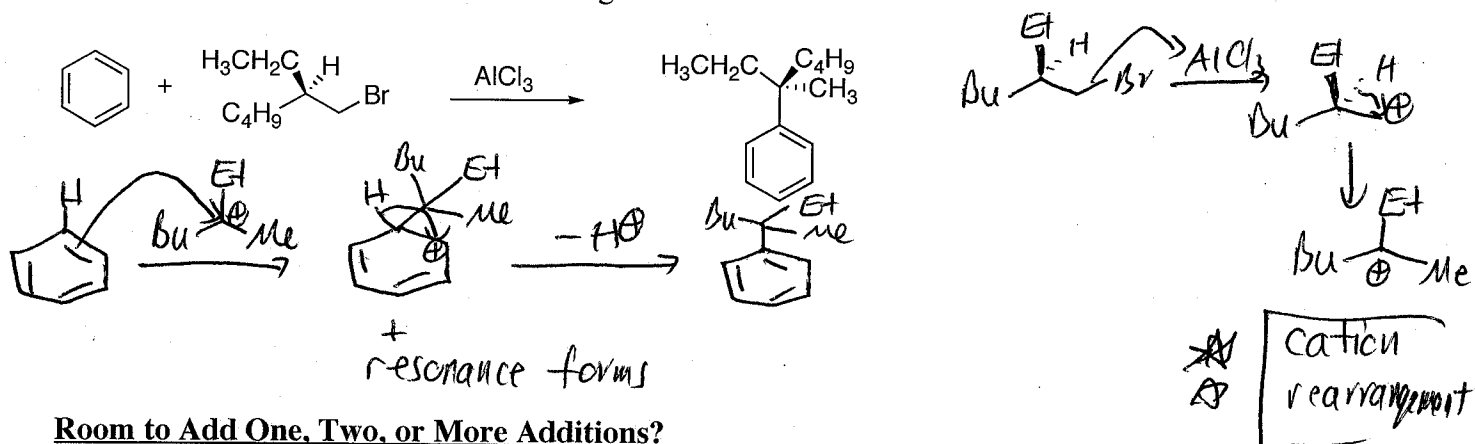
Big mess

Polyaddition Notes:

- 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
  - When a donor is added, polysubstitution can be a factor.
    - Electronically, the adduct will be more reactive than the starting material.
  - Some solutions to polyaddition.
    - Perhaps di- or tri-addition is a good and desirable thing.
    - Use a huge excess of your aromatic starting material.
      - Benzene, toluene, or anisole for example, are cheap and can be used as solvent.
      - 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
    - 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 is often the case with 2° or 3° alkyl groups
7. For each of the following, draw the 1<sup>st</sup>, 2<sup>nd</sup>, and 3<sup>rd</sup> substitution products upon treatment with (CH<sub>3</sub>)<sub>2</sub>CHBr (iPrBr) and AlCl<sub>3</sub>



8. Draw the mechanisms for the following reaction.



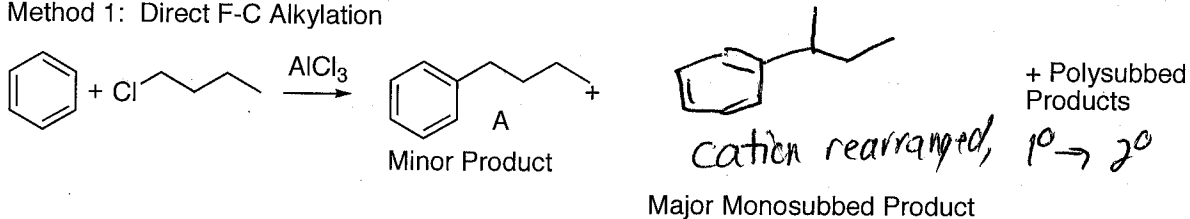
Room to Add One, Two, or More Additions?

2-Step Route to Add 1° Alkyl: 1) RCOCl, AlCl<sub>3</sub> 2) Zn(Hg), HCl

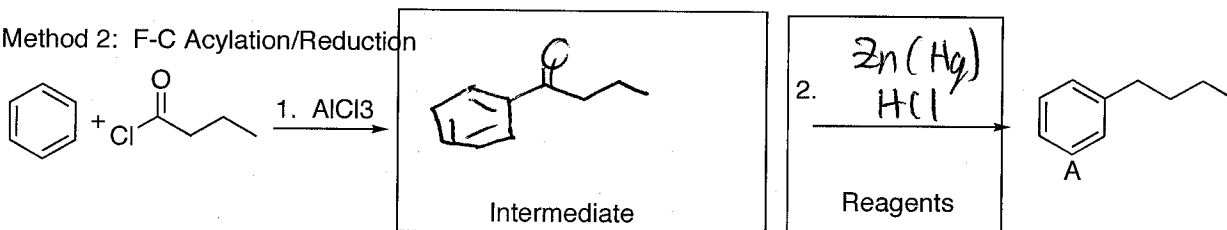
- at acyl stage, acyl carbon is a meta director
- at alkyl stage, alkyl is an ortho-para director

9. Fill in the blanks for the following reactions

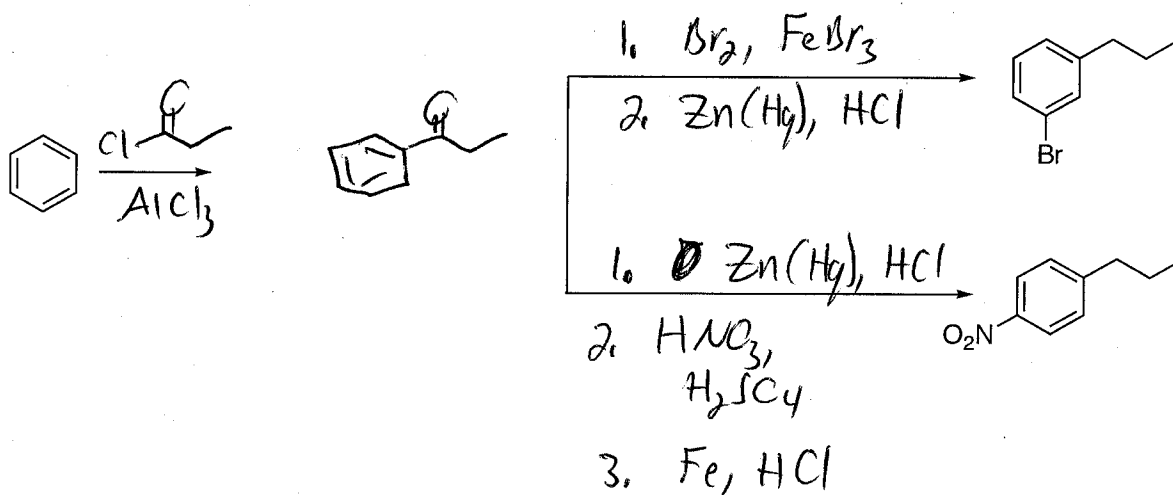
Method 1: Direct F-C Alkylation



Method 2: F-C Acylation/Reduction



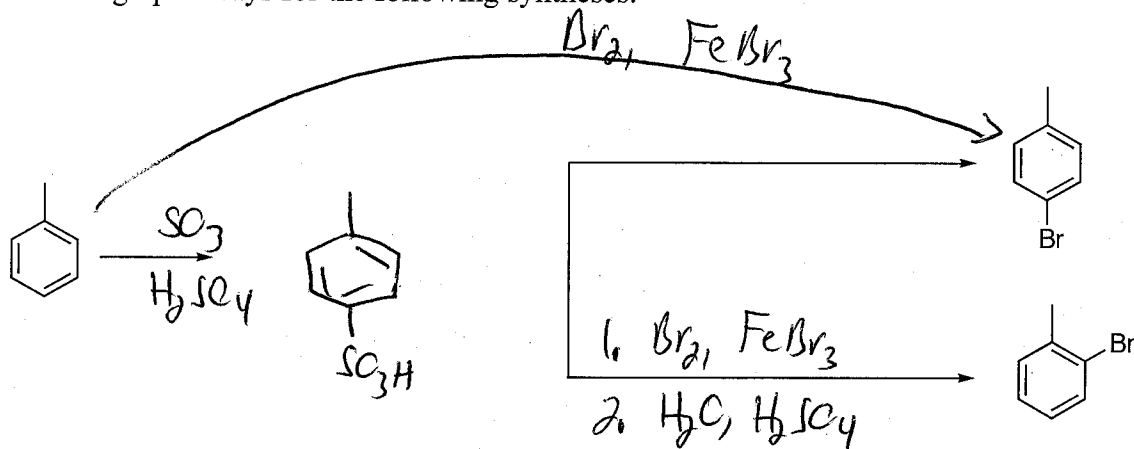
10. Design pathways for the following syntheses:



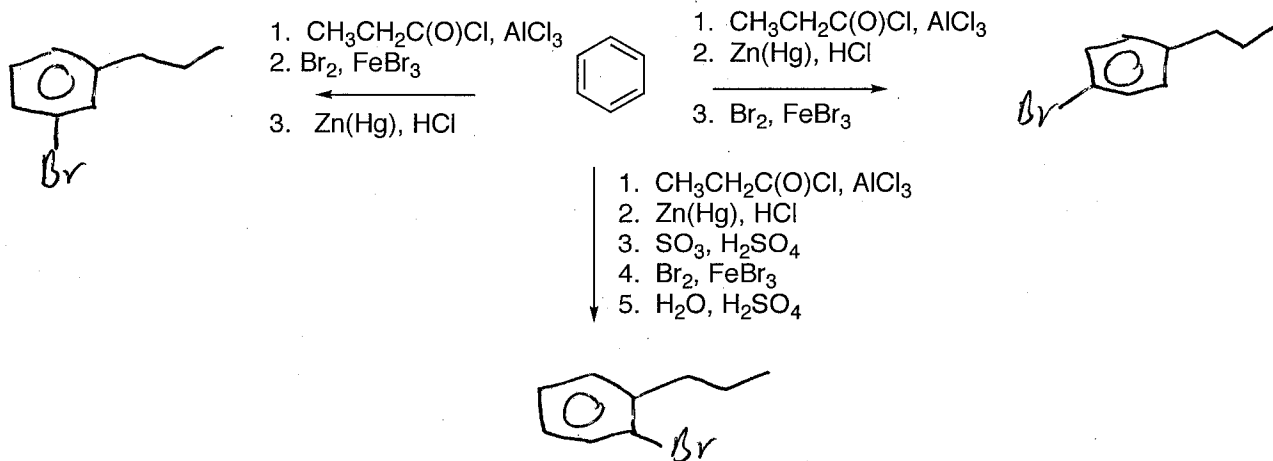
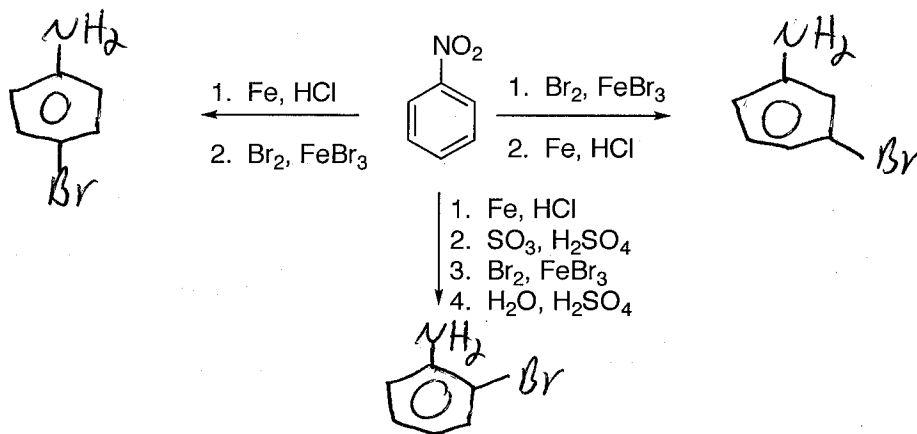
Sulfonylation/Reaction/Desulfonylation: 1.  $\text{SO}_3$ ,  $\text{H}_2\text{SO}_4$  2. Whatever 3.  $\text{H}_2\text{O}$ ,  $\text{H}_2\text{SO}_4$

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

11. Design pathways for the following syntheses:



12. Draw the products for the following reactions:

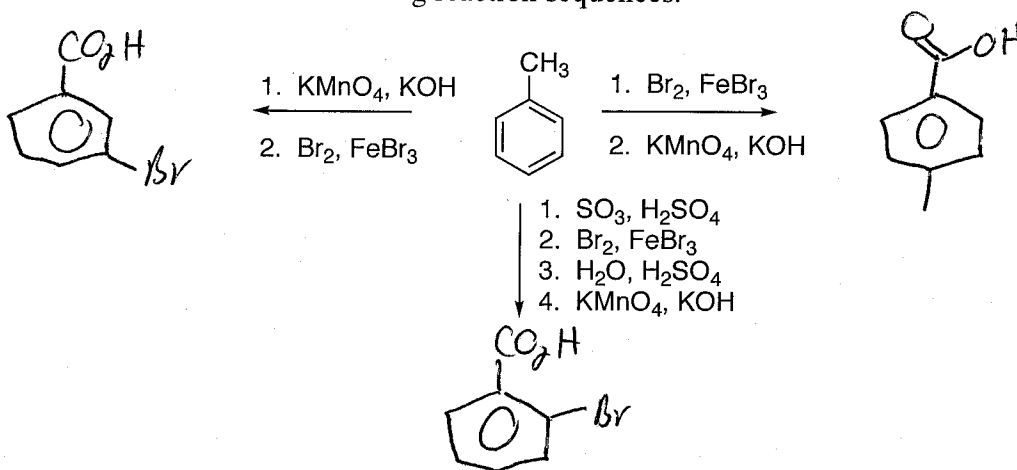




Oxidation of toluene methyl group (or other alkyl side chains):  $\text{KMnO}_4$

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

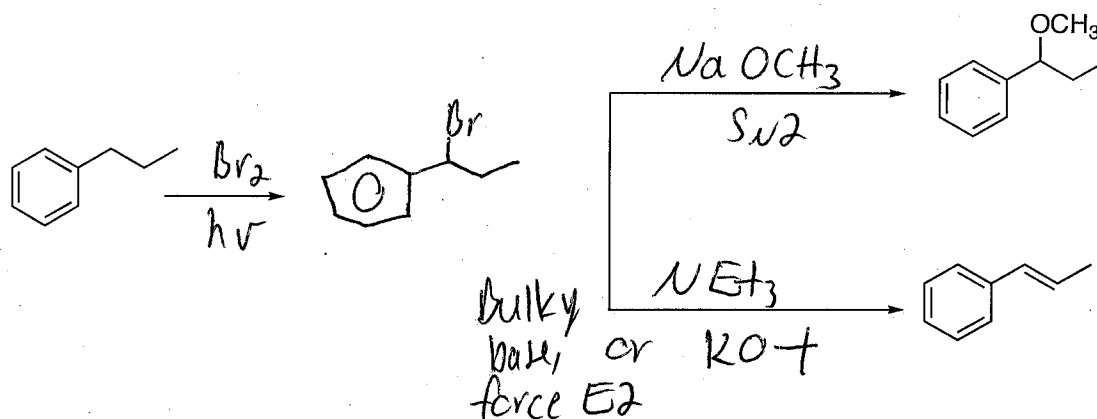
13. Draw the outcomes for the following reaction sequences.



**Benzylic Bromination Provides a Useful Functional Group:**

- Treatment with many anions results in  $S_N2$  substitution
- Treatment with bulky bases results in  $E2$  elimination  $\rightarrow$  vinyl benzenes

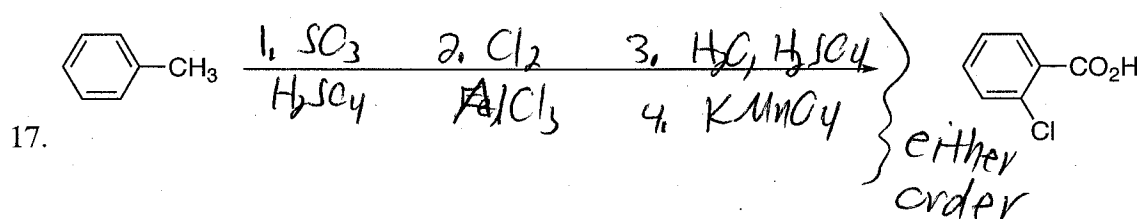
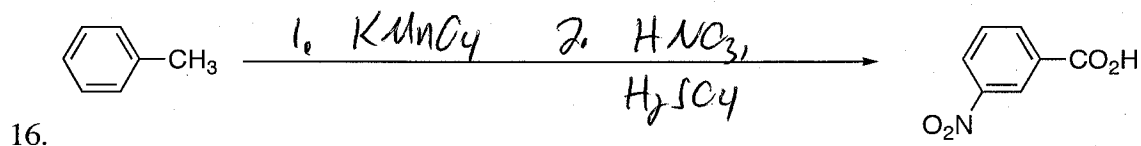
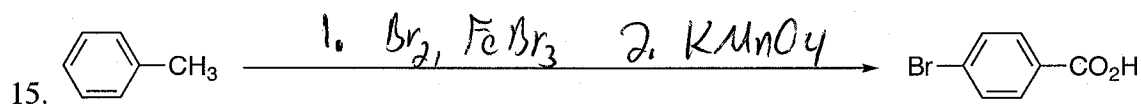
14. Design pathways.



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

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

**Design Syntheses for the Following:**



Design Syntheses for the Following: