WILEY

Organic Chemistry

Second Edition

David Klein

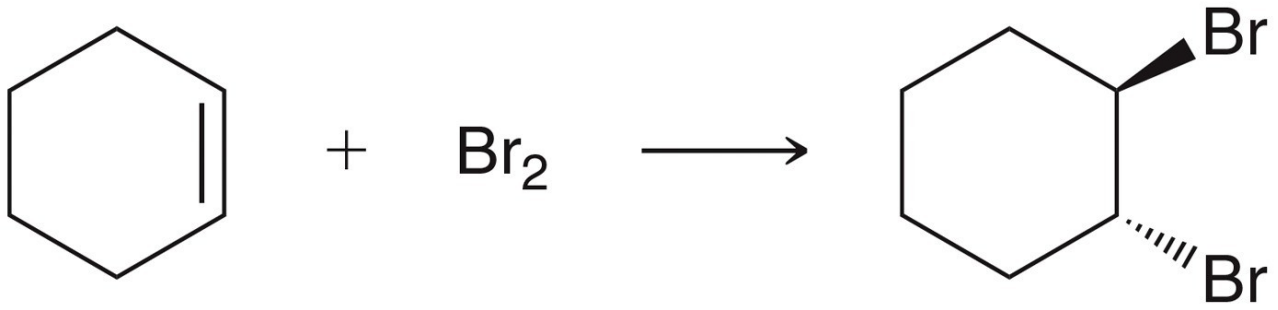
Chapter 19

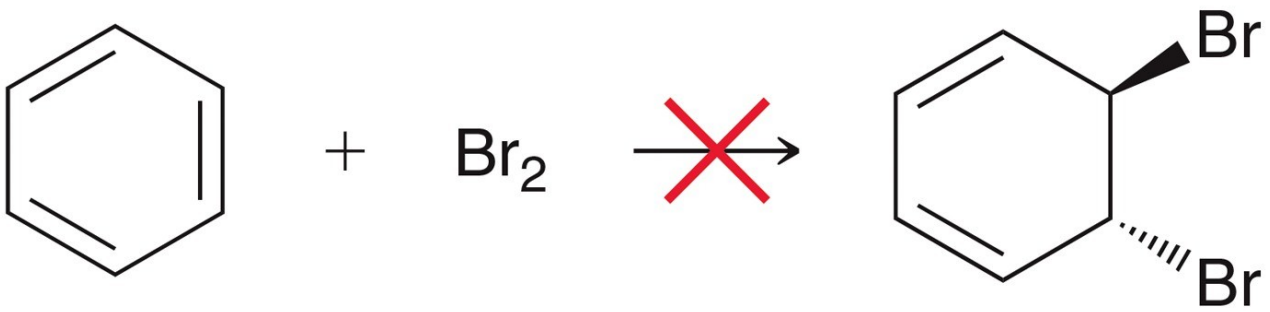
Aromatic Substitution Reactions

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19.1 Introduction to Electrophilic Aromatic Substitution

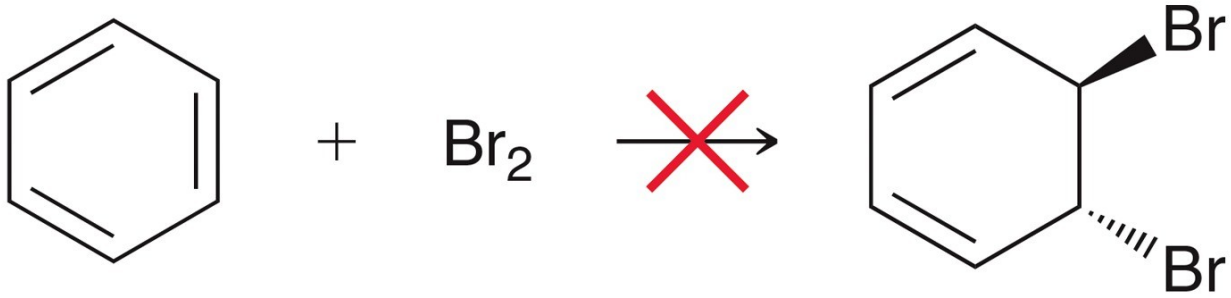
- In chapter 18, we saw how aromatic C=C double bonds are less reactive than typical alkene double bonds
- Cons



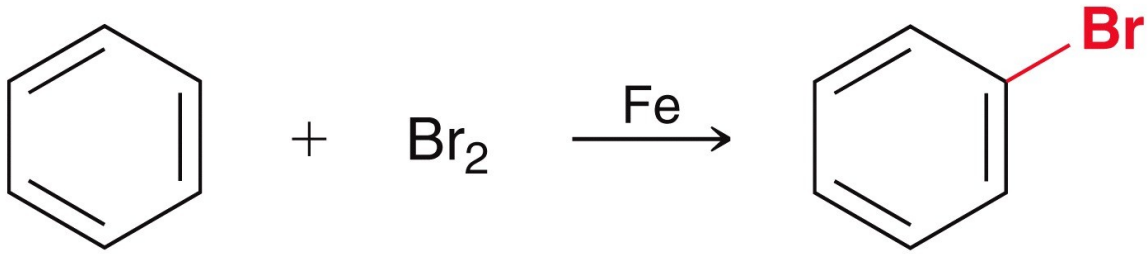


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19.1 Introduction to Electrophilic Aromatic Substitution



- When Fe is introduced a reaction occurs



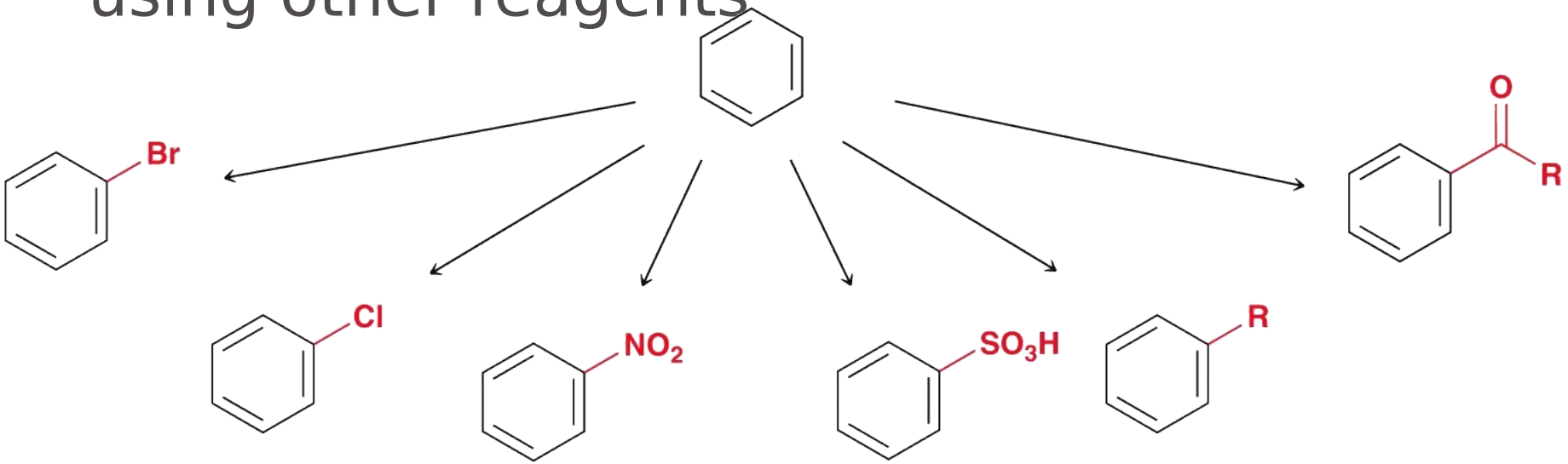
(75%)

- Is the reaction substitution, elimination, addition or pericyclic?

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19.1 Introduction to Electrophilic Aromatic Substitution

- Similar reactions occur for aromatic rings using other reagents



- Such reactions are called **Electrophilic Aromatic Substitution (EAS)**
- Explain each term in the EAS title

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19.2 Halogenation

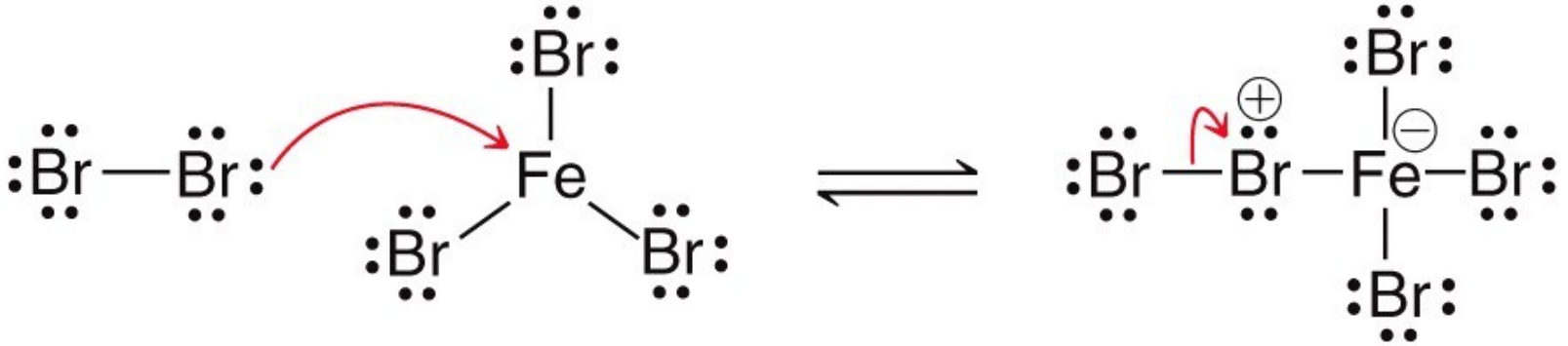
- Do you think an aromatic ring is more likely to act as a nucleophile or an electrophile? WHY?

- Do you think Br_2 is more likely to act as a nucleophile or an electrophile? WHY?

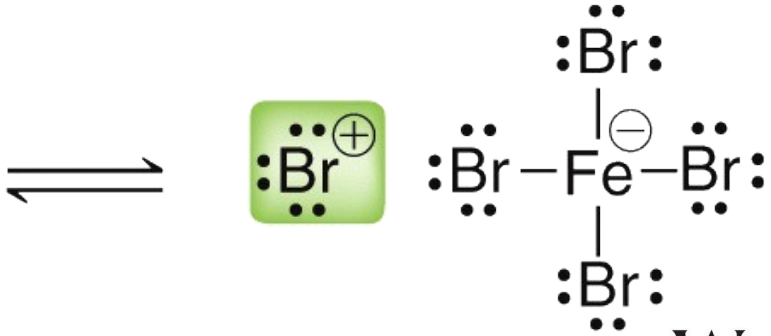
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19.2 Halogenation

- To promote the EAS reaction between benzene and Br_2, we saw that Fe is necessary
- $2\ Fe + 3\ Br_2 \longrightarrow 2\ FeBr_3$

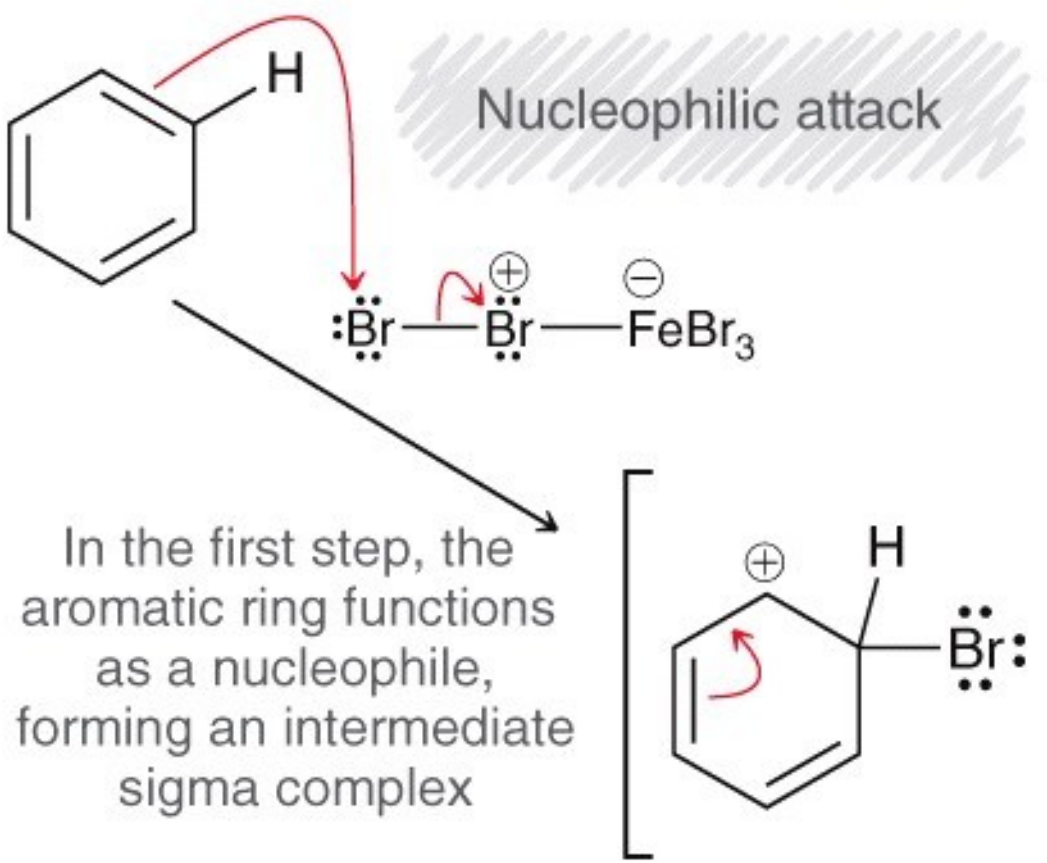


- Does this process make Bromine a better or worse electrophile? HOW?



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19.2 Halogenation

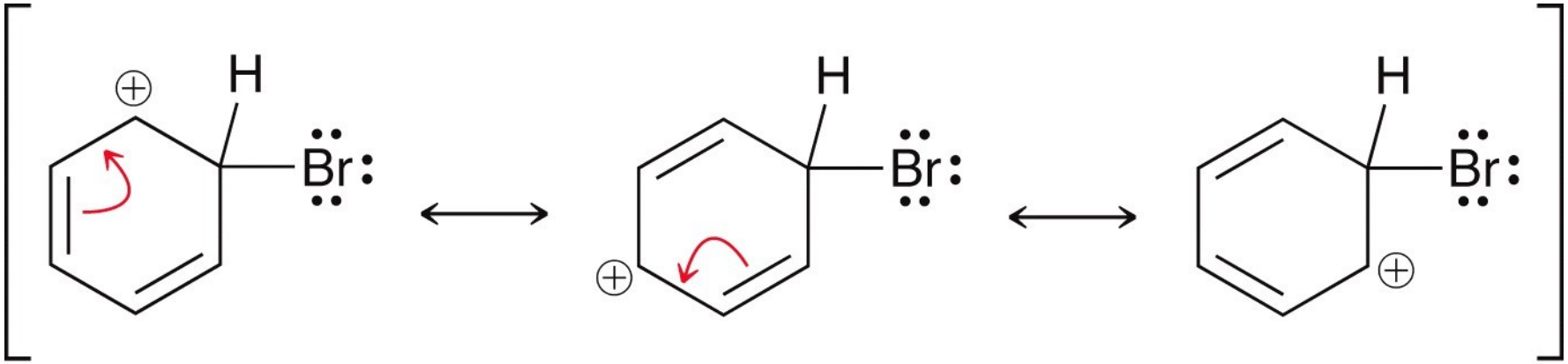


- The $FeBr_3$ acts as a Lewis acid. HOW?
- $AlBr_3$ is sometimes used instead of $FeBr_3$
- A resonance-stabilized carbocation is formed

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19.2 Halogenation

- The resonance stabilized carbocation is called a Sigma Complex or arenium ion



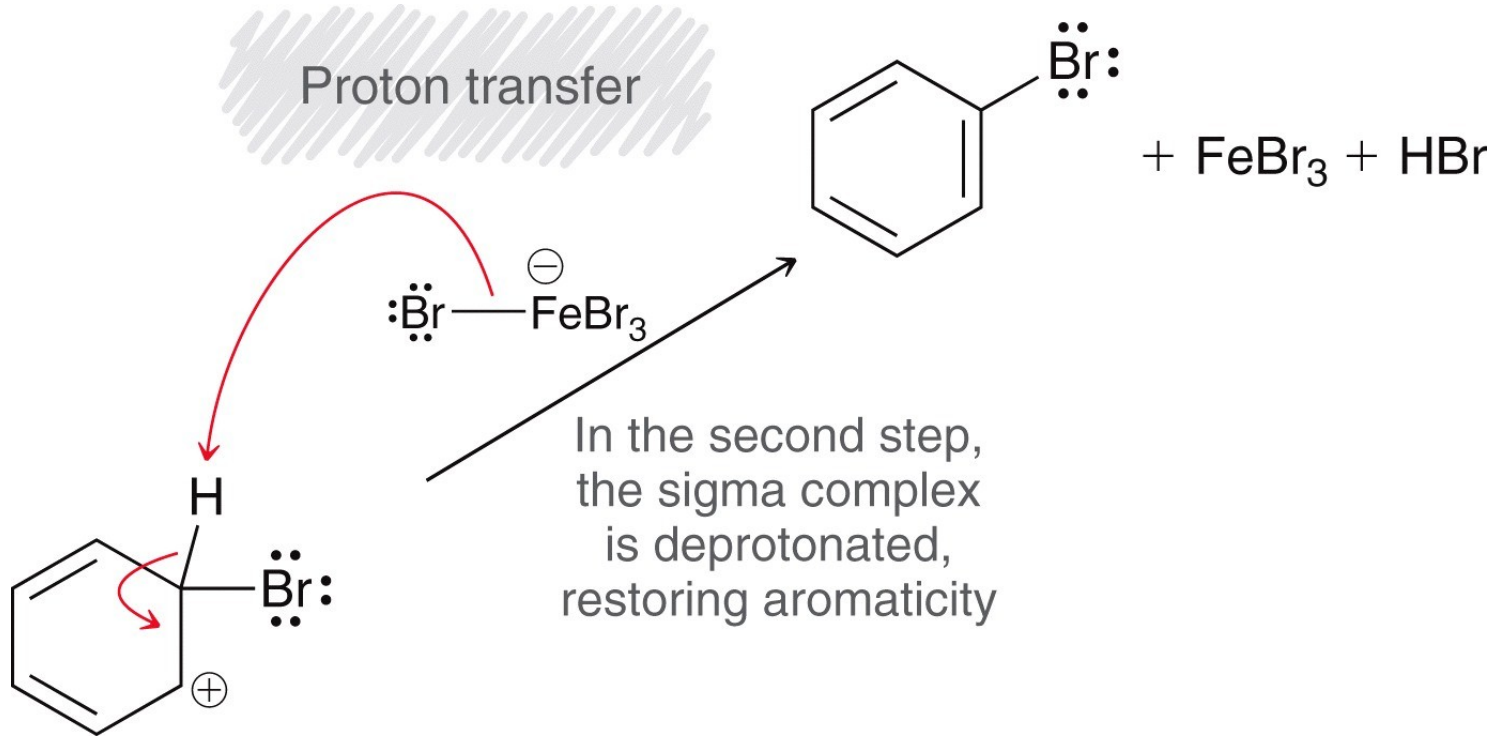
Sigma complex

- Draw the resonance hybrid

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19.2 Halogenation

- The Sigma Complex is re-aromatized

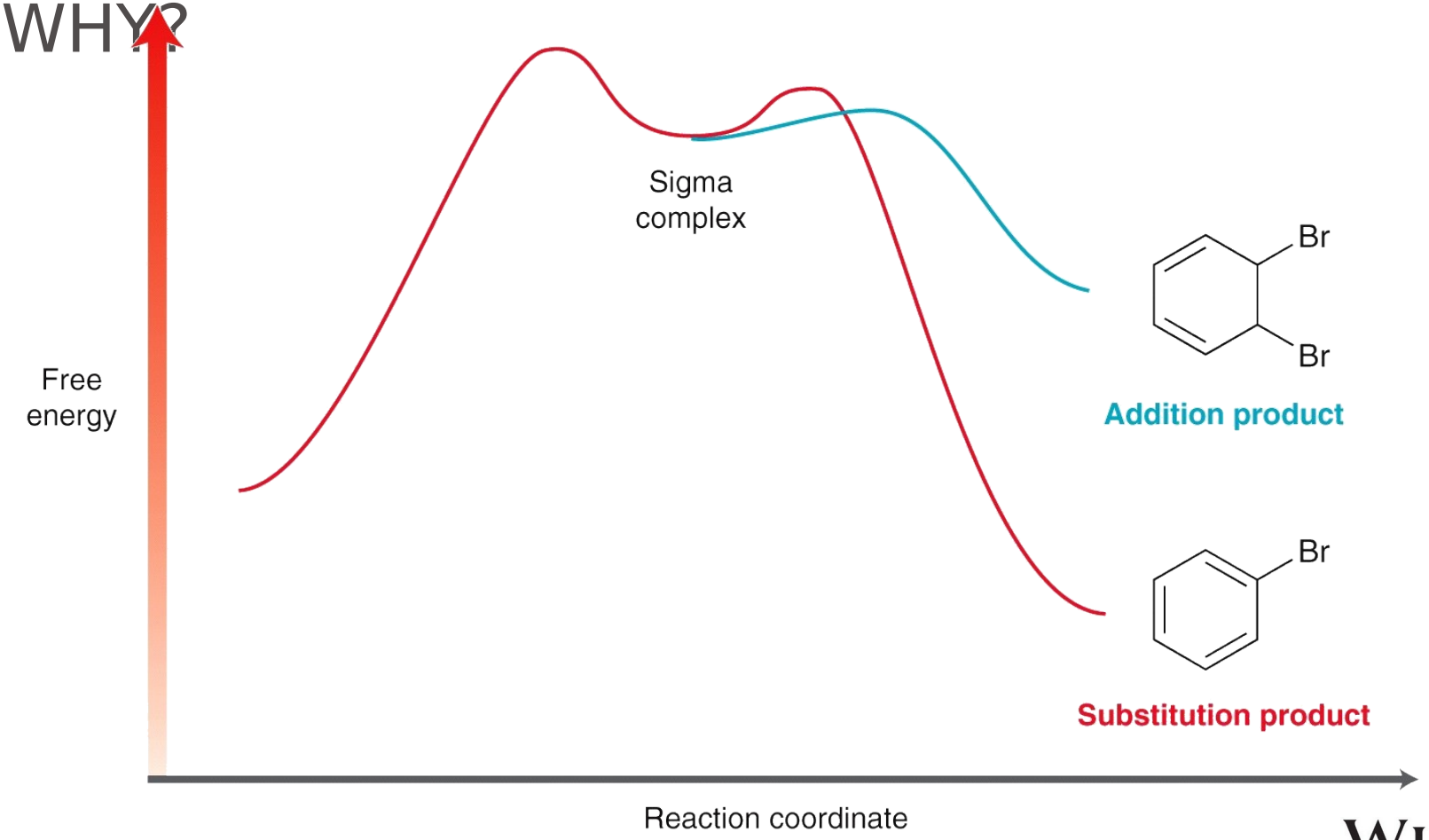


- Does the $FeBr_3$ act as catalyst?

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19.2 Halogenation

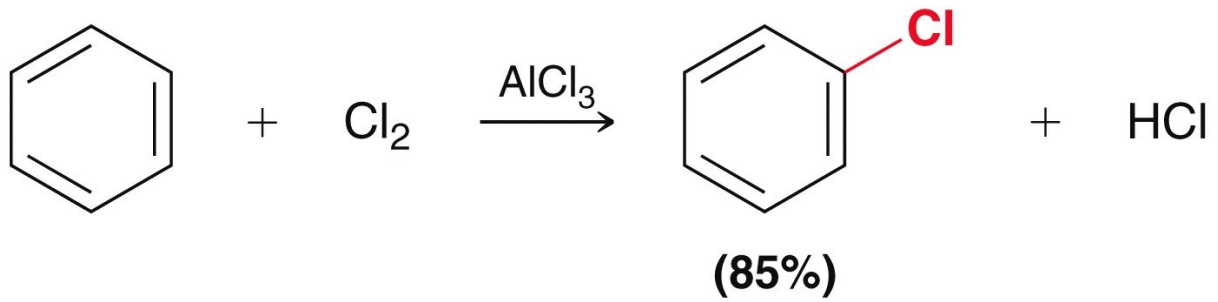
- Substitution occurs rather than addition. WHY?



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19.2 Halogenation

- Cl_2 can be used instead of Br_2

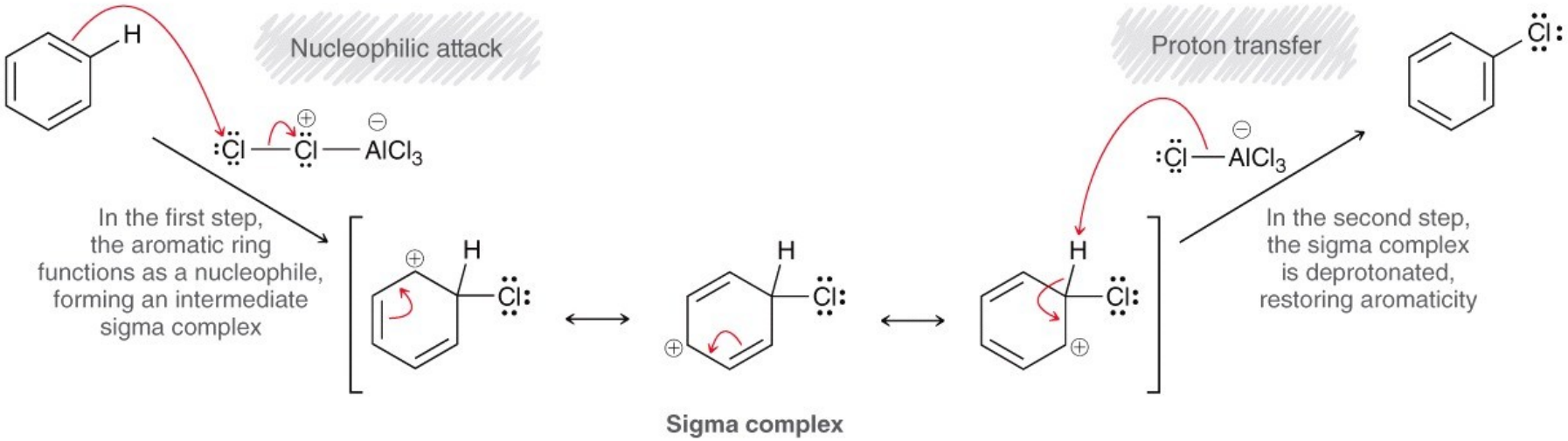


- Draw the EAS mechanism for the reaction between benzene and Cl_2 with $AlCl_3$ as a Lewis acid catalyst

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19.2 Halogenation

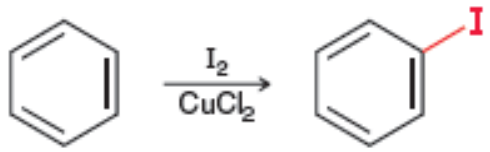
- Note the general EAS mechanism



- Practice with conceptual checkpoint 19.1

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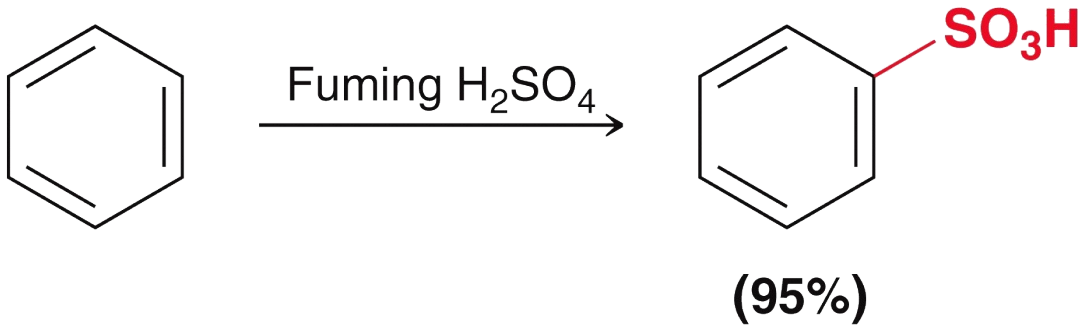
19.1 When benzene is treated with I_2 in the presence of $CuCl_2$, iodination of the ring is achieved with modest yields. It is believed that $CuCl_2$ interacts with I_2 to generate I^+, which is an excellent electrophile. The aromatic ring then reacts with I^+ in an electrophilic aromatic substitution reaction. Draw a mechanism for the reaction between benzene and I^+. Make sure that your mechanism has two steps, and make sure to draw all of the resonance structures of the sigma complex.



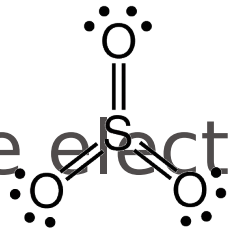
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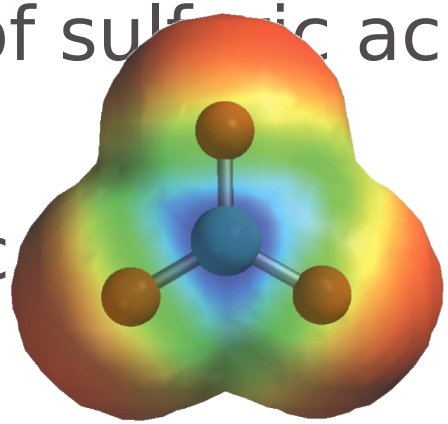
19.3 Sulfonation

- There are many different electrophiles that can be attacked by an aromatic ring



- Fuming H_2SO_4 consists of sulfuric acid and SO_3 gas
- SO_3 is quite electrophilic

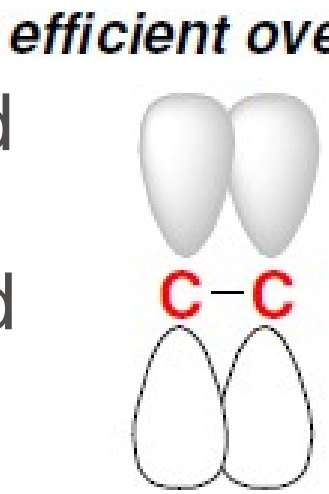


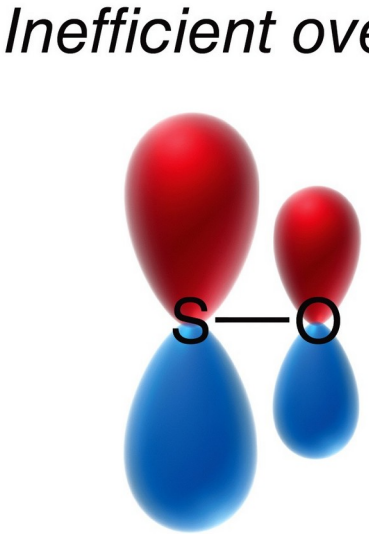


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19.3 Sulfonation

- Let's examine SO_3 in more detail
- The S=O double bond involves *p*-orbital overlap that is less effective than the orbital overlap in a C=C double bond. WHY?
- As a result, the S=O double bond behaves more as a S-O single bond with formal charges. WHAT are the charges?

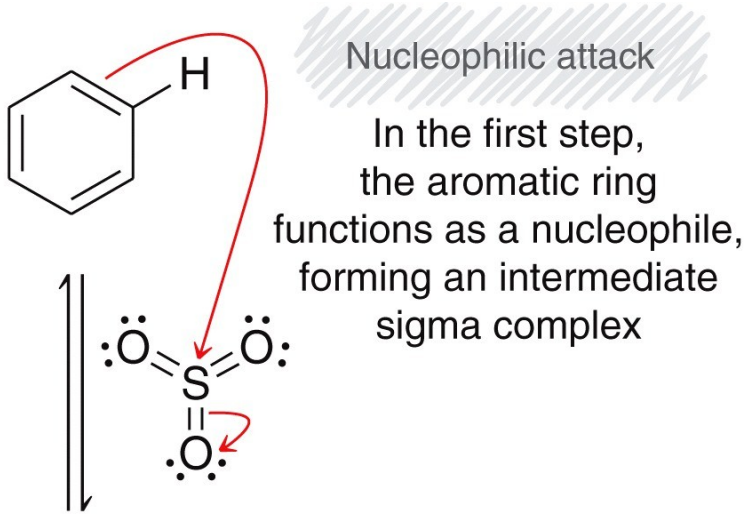


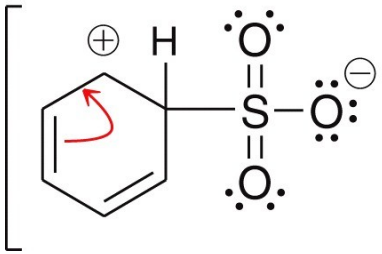


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19.3 Sulfonation

- The S atom in SO_3 carries a great deal of positive charge
- The aromatic ring is stable, but it is also electron-rich
- When the ring attacks SO_3, the resulting carbocation is resonance stabilized
- Draw the resonance contributors and the

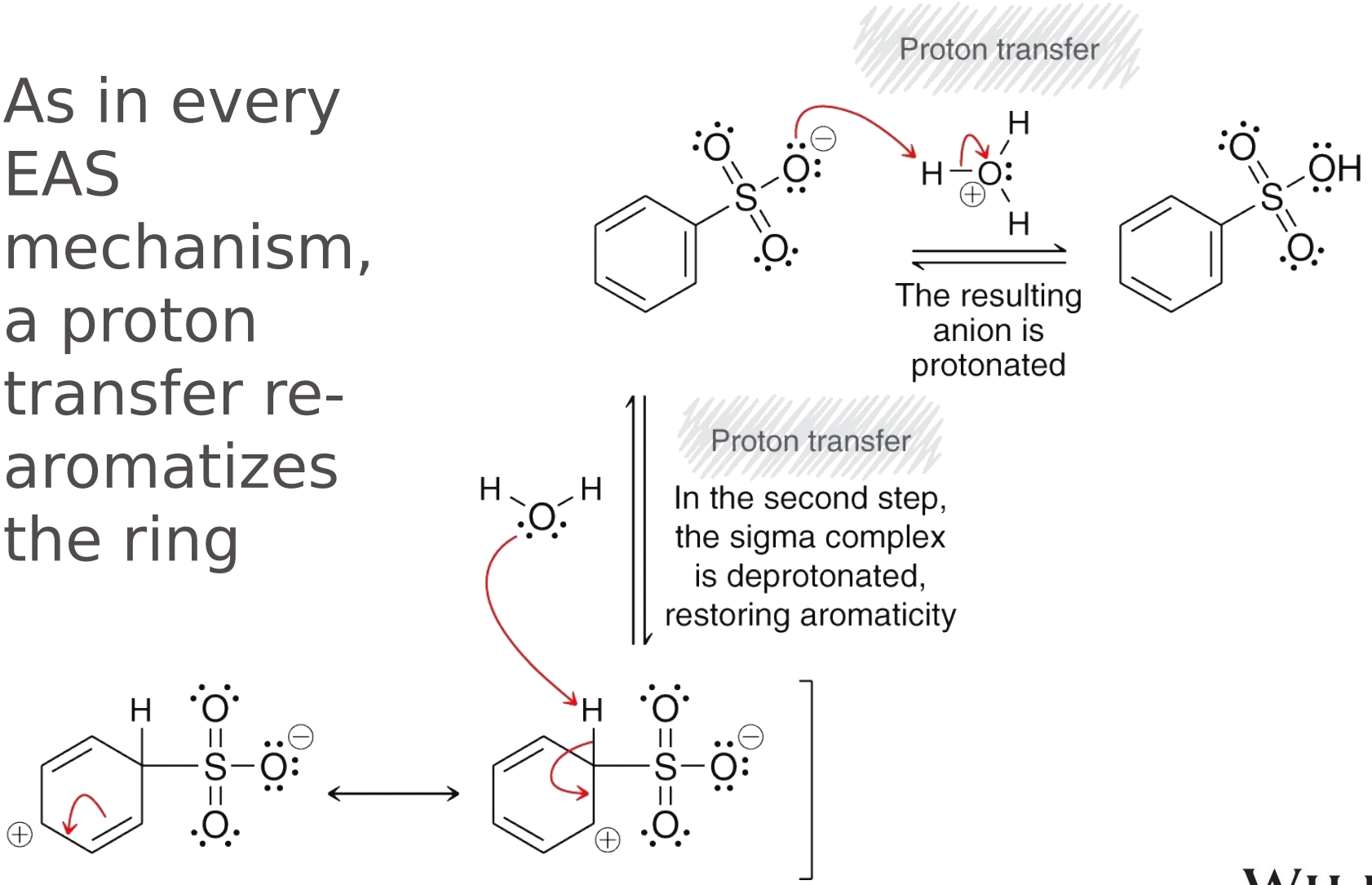




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19.3 Sulfonation

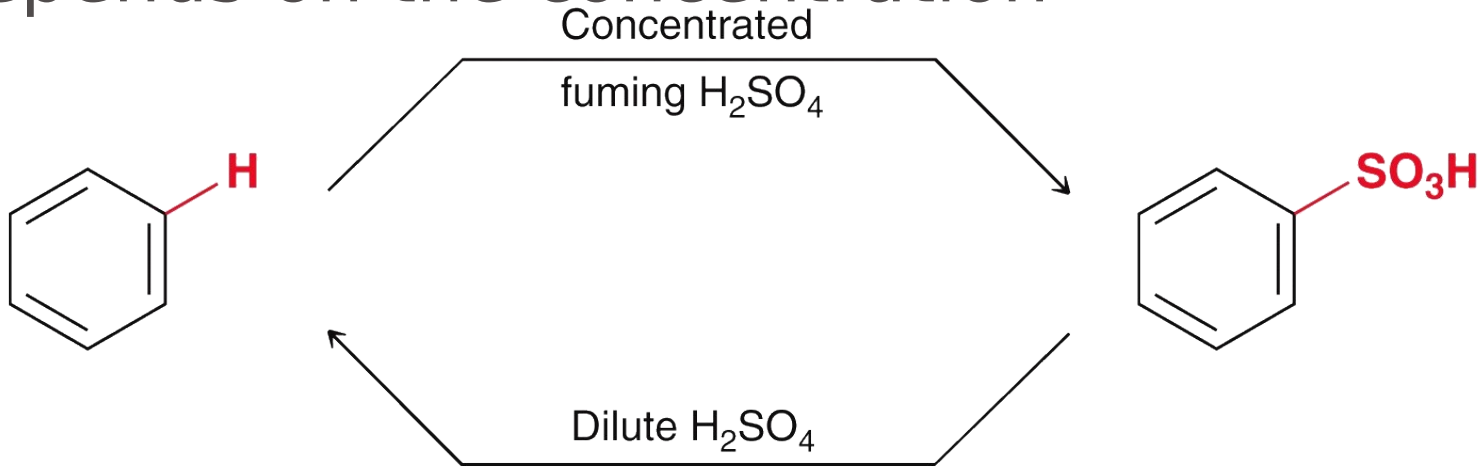
- As in every EAS mechanism, a proton transfer re-aromatizes the ring



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19.3 Sulfonation

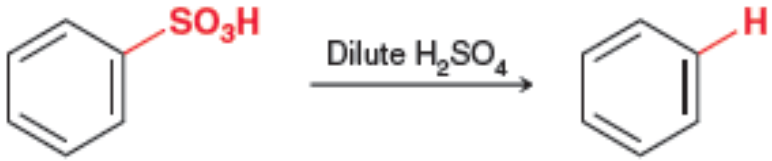
- The spontaneity of the sulfonation reaction depends on the concentration



- We will examine the equilibrium process in more detail later in this chapter
- Practice with conceptual checkpoints 19.2 and 19.3

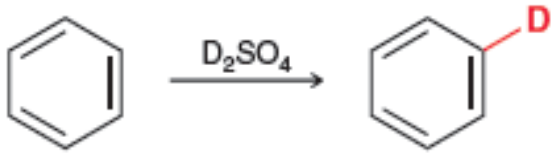
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19.2 Draw a mechanism for the following reaction. **Hint:** This reaction is the reverse of sulfonation, so you should read the sulfonation mechanism backward. Your mechanism should involve a sigma complex (positively charged).



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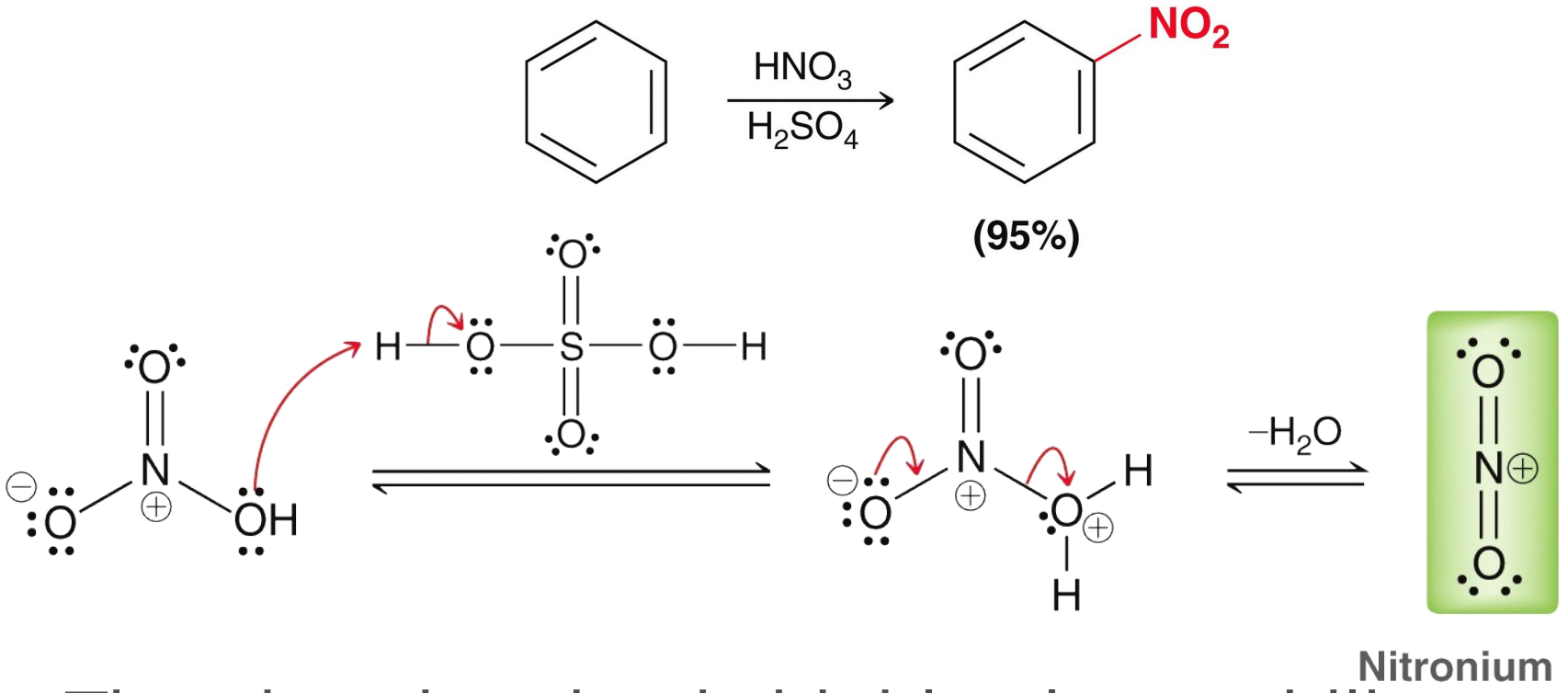
19.3 When benzene is treated with D_2SO_4, a deuterium atom replaces one of the hydrogen atoms. Propose a mechanism for this reaction. Once again, make sure that your mechanism involves a sigma complex.



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19.4 Nitration

- A mixture of sulfuric acid and nitric acid causes the ring to undergo nitration

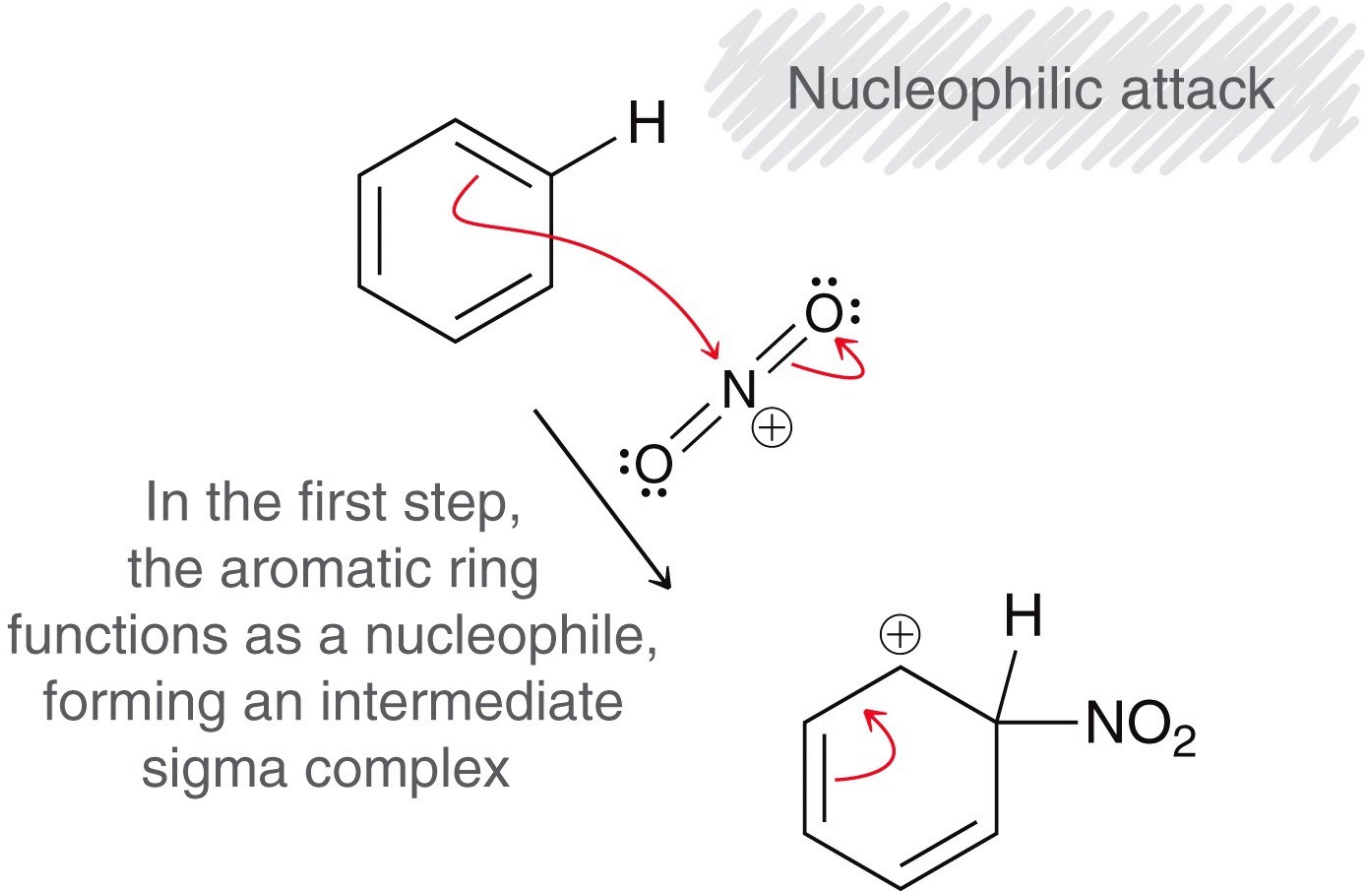


- The nitronium ion is highly electrophilic

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19.4 Nitration

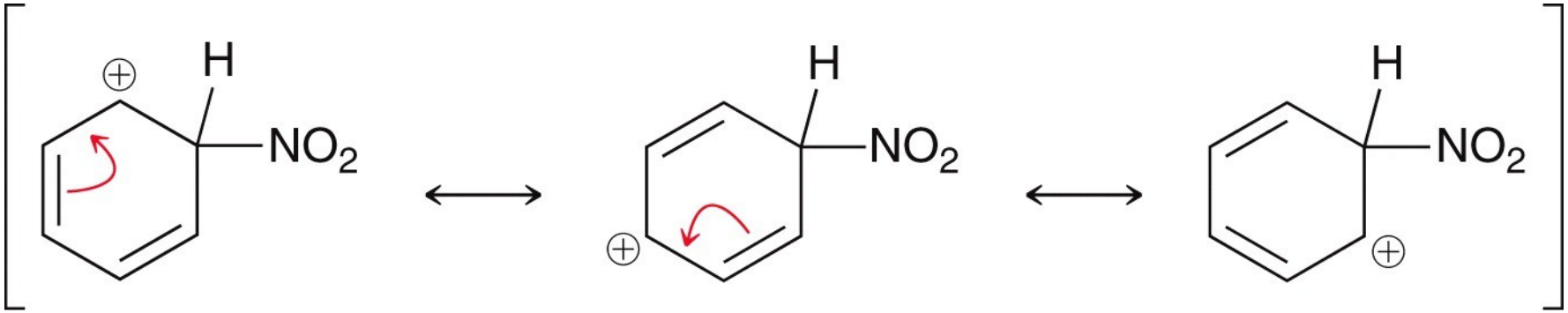
- The ring attacks the nitronium ion



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19.4 Nitration

- The sigma complex stabilizes the carbocation

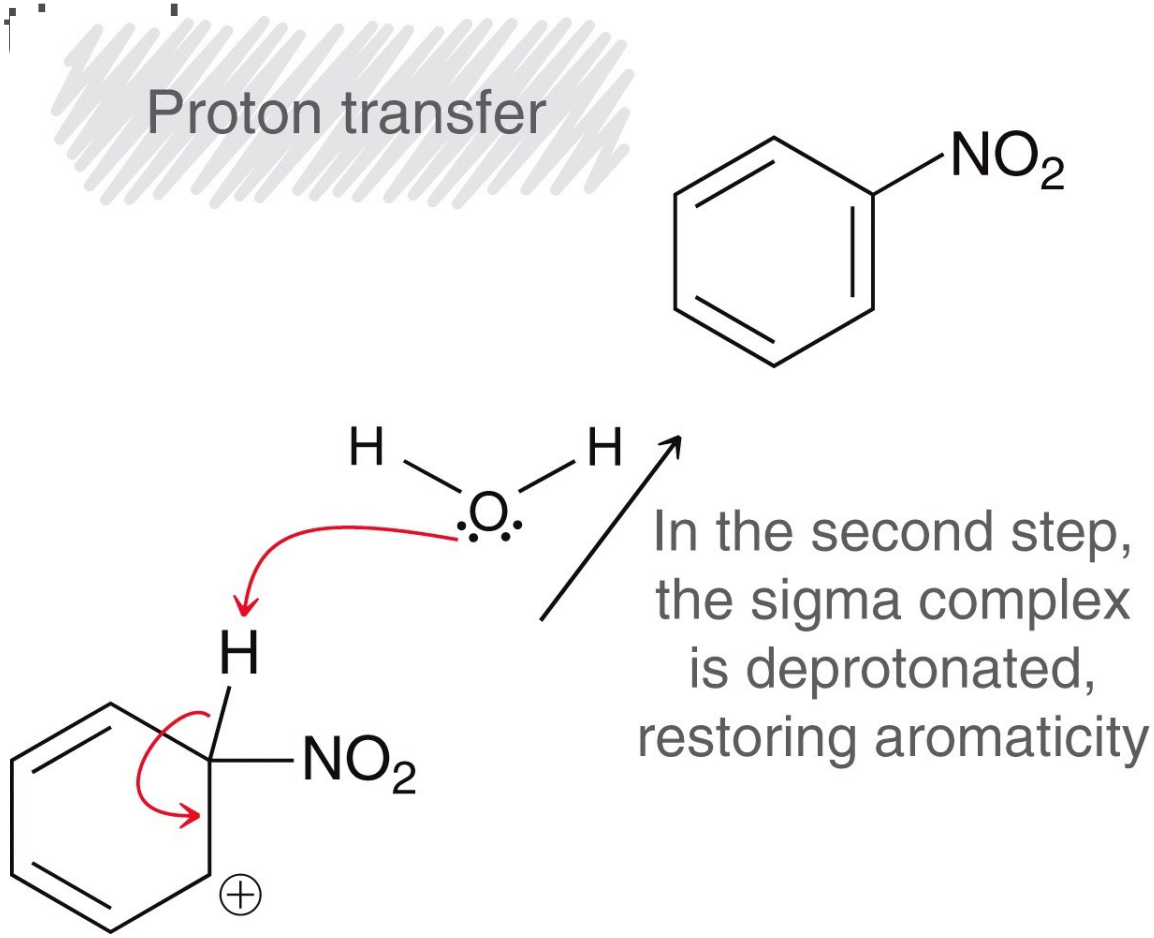


Sigma complex

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19.4 Nitration

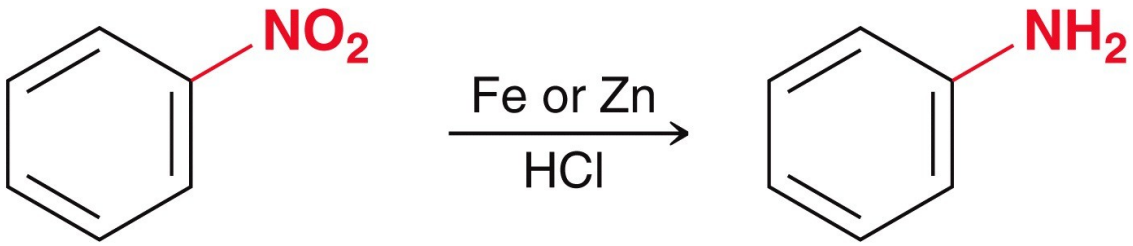
- As with any EAS mechanism, the ring is re-aromatized.



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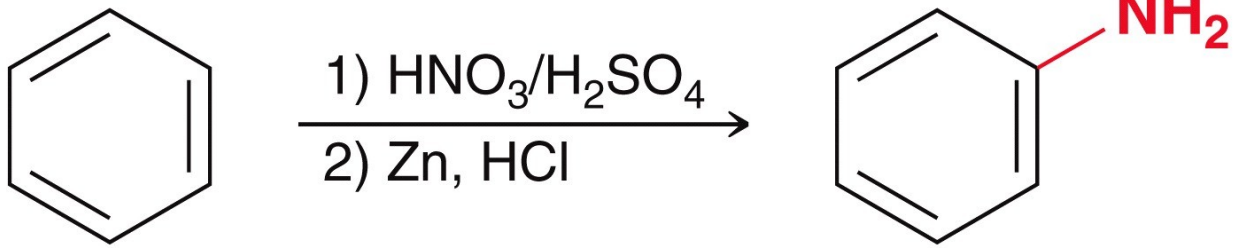
19.4 Nitration

- A nitro group can be reduced to form an amine



(95%)

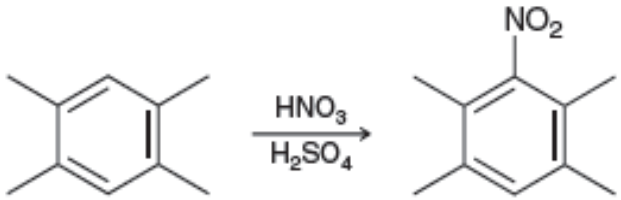
- Combining the reactions gives us a 2-step process



- Practice with conceptual checkpoint 19.4

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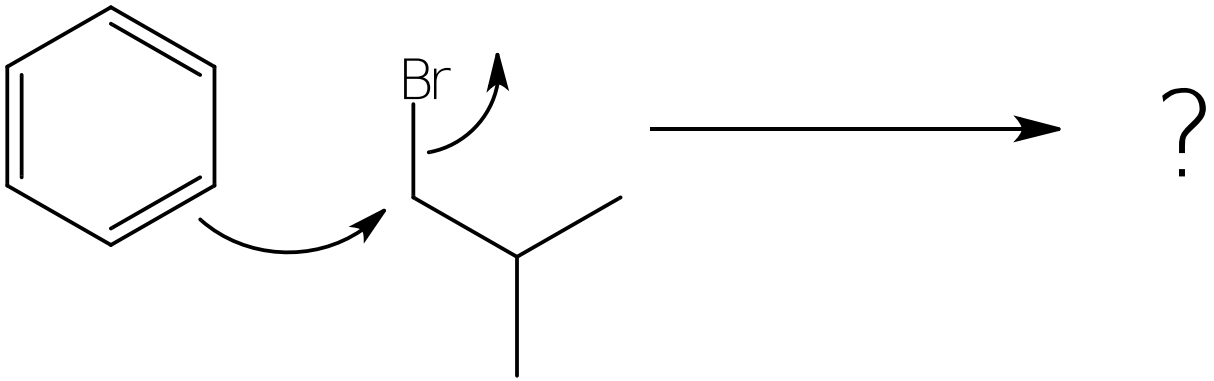
19.4 Draw a mechanism for the following reaction and make sure to draw all three resonance structures of the sigma complex:



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19.5 Friedel-Crafts Alkylation

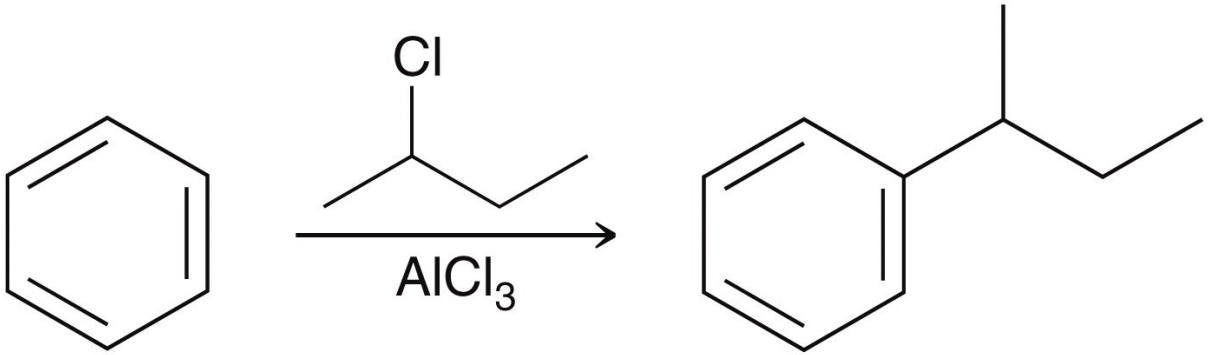
- Do you think that an alkyl halide is an effective nucleophile for EAS?



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19.5 Friedel-Crafts Alkylation

- In the presence of a Lewis acid catalyst, alkylation is generally favored

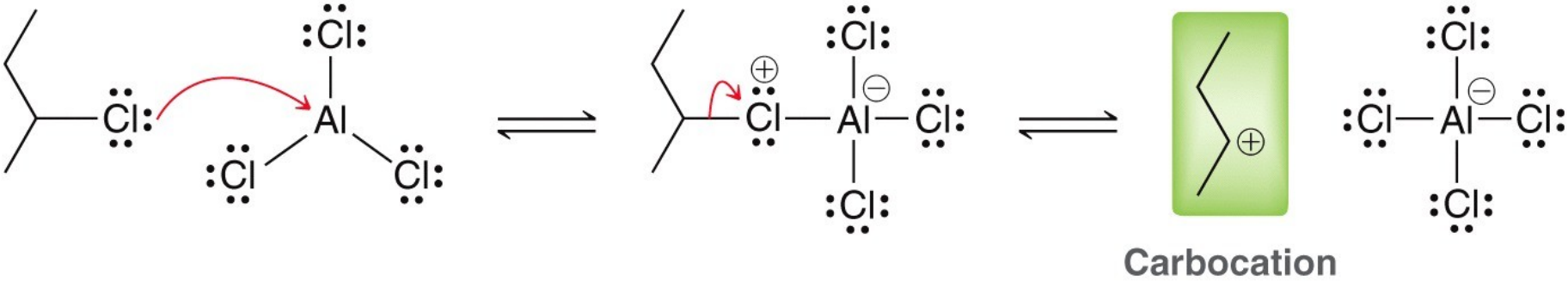


(66%)

- What role do you think the Lewis acid plays?

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19.5 Friedel-Crafts Alkylation

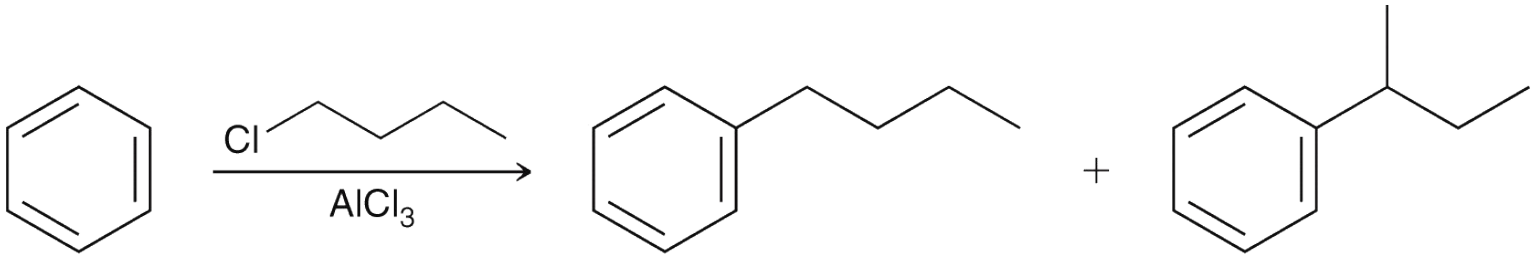


- A carbocation is generated
- The ring then attacks the carbocation
- Show a full mechanism

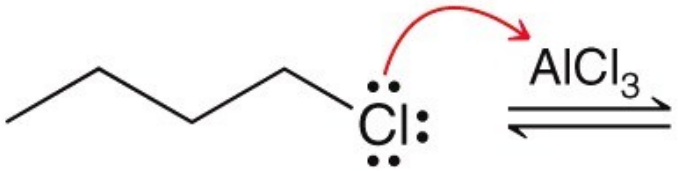
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19.5 Friedel-Crafts Alkylation

- Primary carbocations are too unstable to form, yet primary alkyl halides can react under Friedel-Crafts conditions



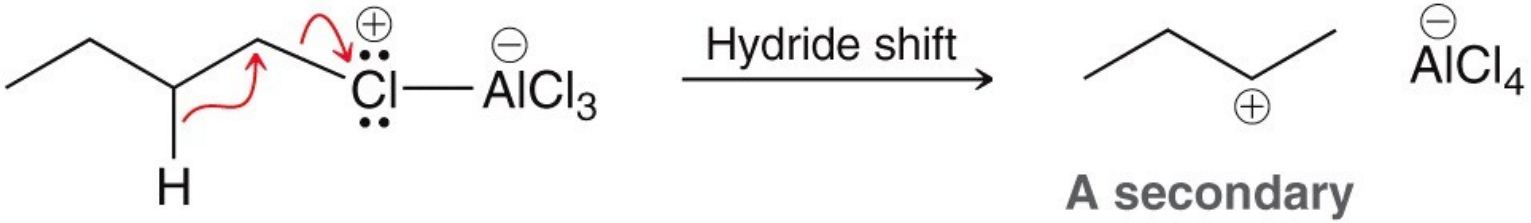
- First the alkyl halide reacts with the Lewis acid – show the product



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19.5 Friedel-Crafts Alkylation

- The alkyl halide / Lewis acid complex can undergo a hydride shift

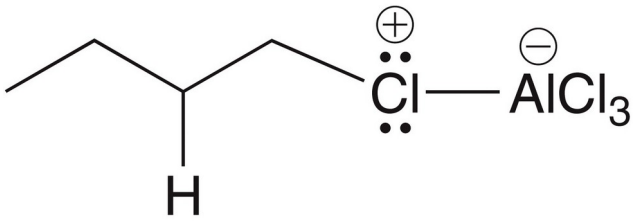


- Show how the mechanism continues to provide the major product of the reaction

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19.5 Friedel-Crafts Alkylation

- The alkyl halide / Lewis acid complex can also be attacked directly by the aromatic ring

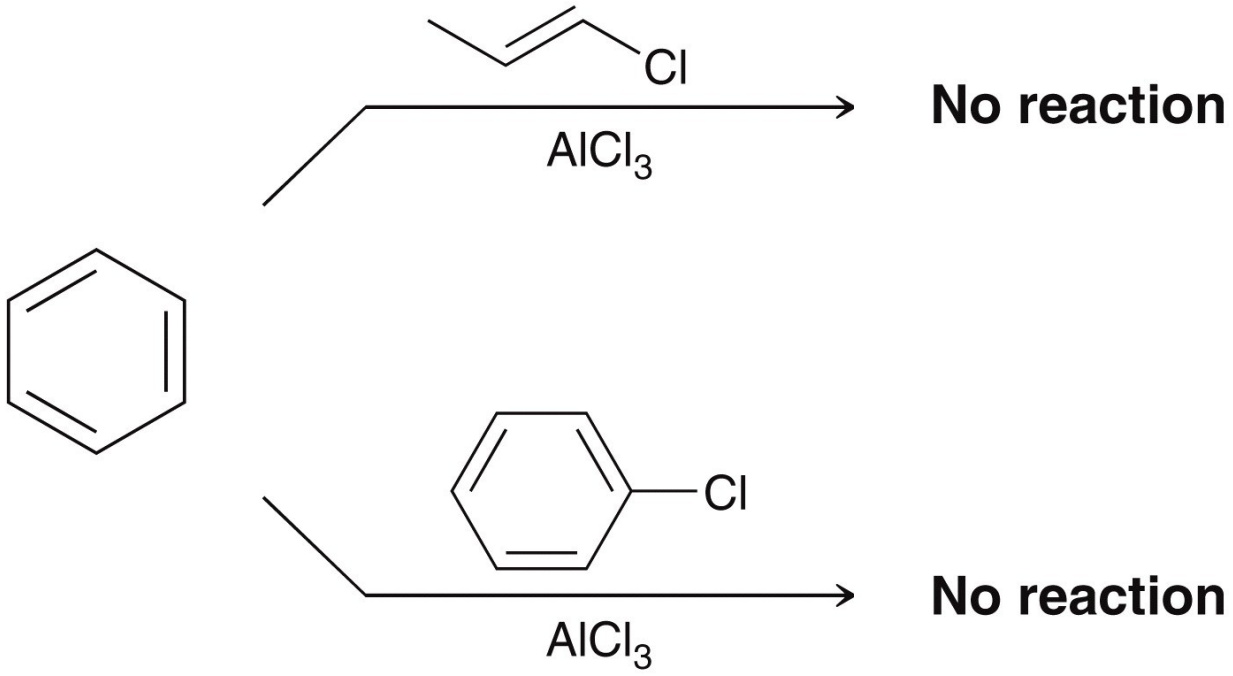


- Show how the mechanism provides the minor product
- Why might the hydride shift occur more readily than the direct attack?
- Why are reactions that give mixtures of products often impractical?

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19.5 Friedel-Crafts Alkylation

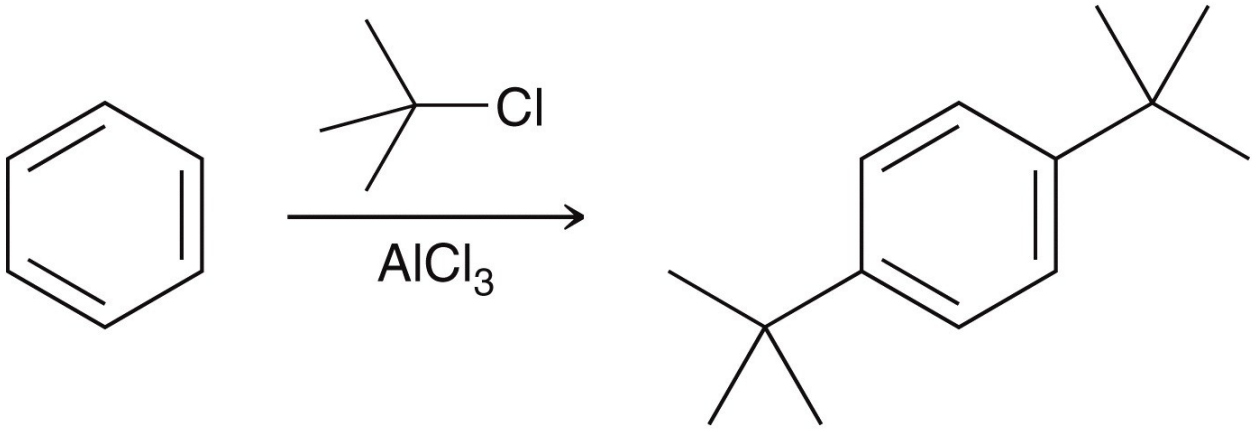
- There are three major limitations to Friedel-Crafts alkylations
  1. The halide leaving group must be attached to an sp^3 hybridized carbon



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19.5 Friedel-Crafts Alkylation

- There are three major limitations to Friedel-Crafts alkylations
  2. Polyalkylation can occur

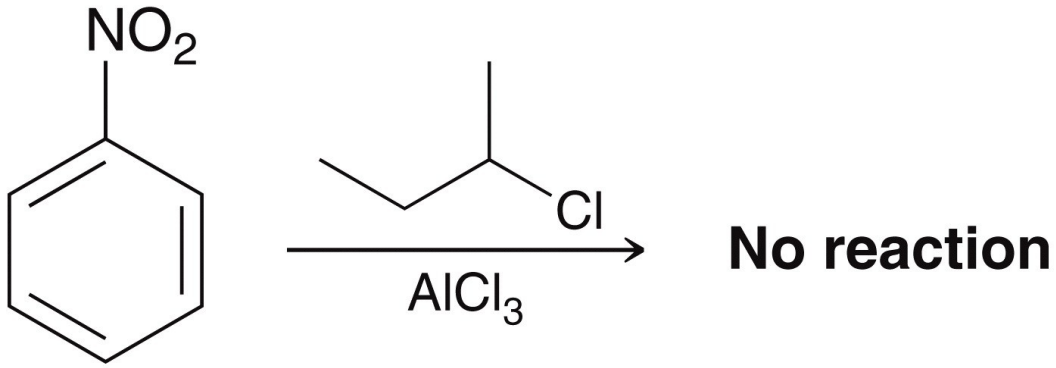


We will see later in this chapter how to control polyalkylation

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19.5 Friedel-Crafts Alkylation

- There are three major limitations to Friedel-Crafts alkylations
  3. Some substituted aromatic rings such as nitrobenzene are too deactivated to react

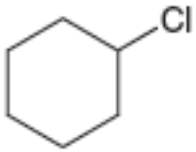


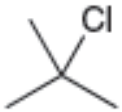
We will explore deactivating groups later in this chapter

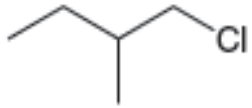
- Practice with conceptual checkpoints 19.5, 19.6, and 19.7

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19.5 Predict the expected product(s) when benzene is treated with each of the following alkyl halides in the presence of $AlCl_3$. In each case, assume conditions have been controlled to favor mono-alkylation.

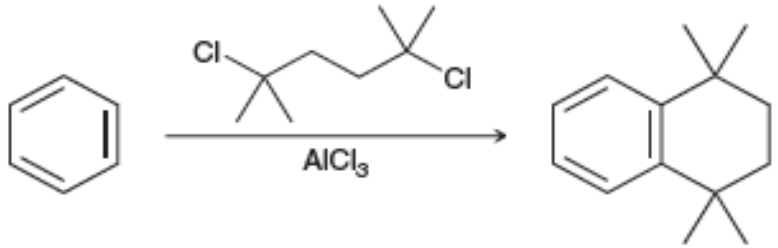
(a) 

(b) 

(c) 

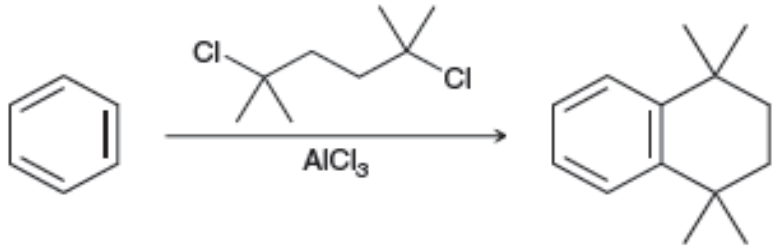
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19.6 Draw a mechanism for the following reaction, which involves two consecutive Friedel-Crafts alkylations. When drawing the mechanism, do not try to draw the two alkylations as occurring simultaneously (such a mechanism would have too many curved arrows and too many simultaneous charges). First draw the steps that install one alkyl group and then draw the steps that install the second alkyl group.



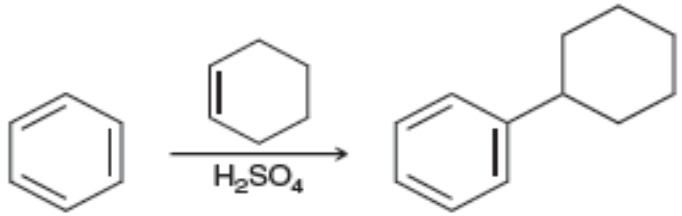
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19.6 Draw a mechanism for the following reaction, which involves two consecutive Friedel-Crafts alkylations. When drawing the mechanism, do not try to draw the two alkylations as occurring simultaneously (such a mechanism would have too many curved arrows and too many simultaneous charges). First draw the steps that install one alkyl group and then draw the steps that install the second alkyl group.



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19.7 A Friedel-Crafts alkylation is an electrophilic aromatic substitution in which the electrophile (E^+) is a carbocation. In previous chapters, we have seen other methods of forming carbocations, such as protonation of an alkene using a strong acid. The resulting carbocation can also be attacked by a benzene ring, resulting in alkylation of the aromatic ring. With this in mind, draw a mechanism for the following transformation:

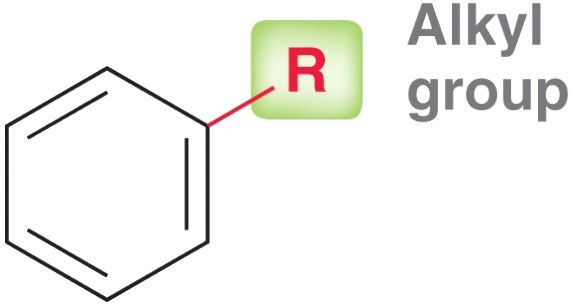


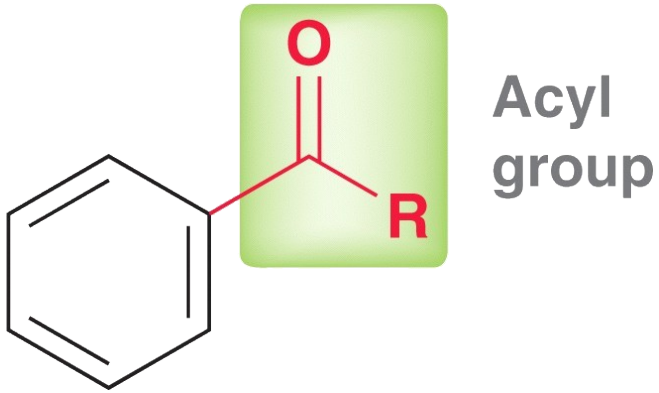
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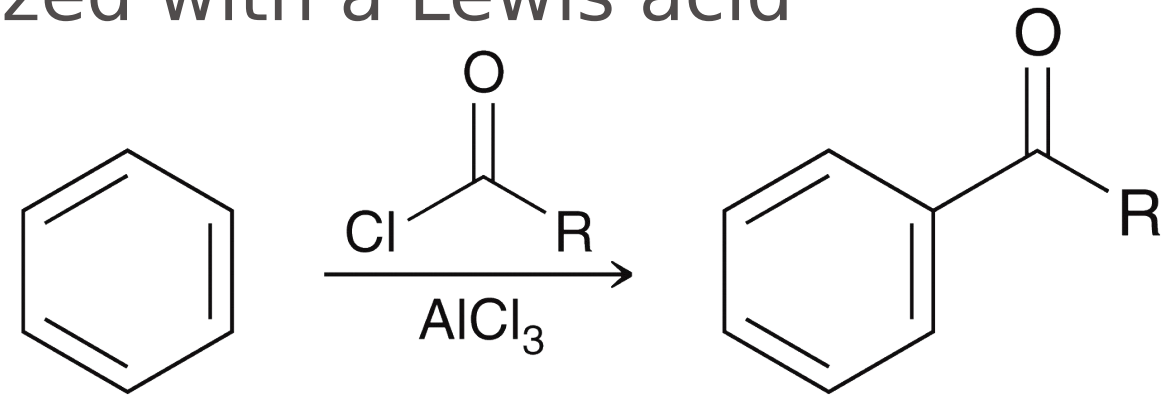
19.6 Friedel-Crafts Acylation

- Acylation and alkylation both form a new carbon-carbon bond





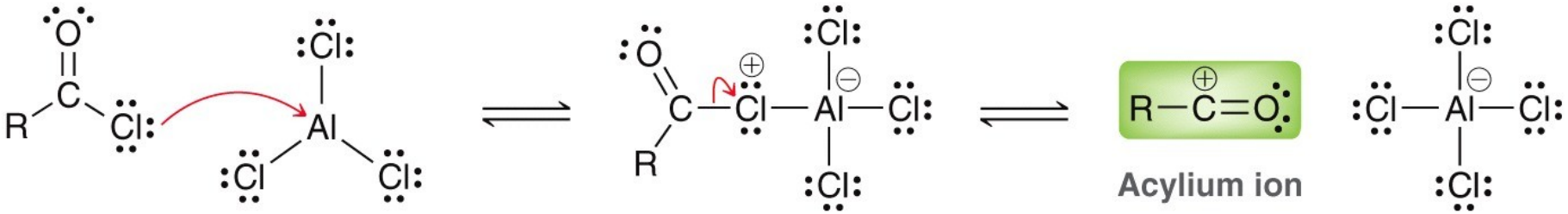
- Acylation reactions are also generally catalyzed with a Lewis acid



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19.6 Friedel-Crafts Acylation

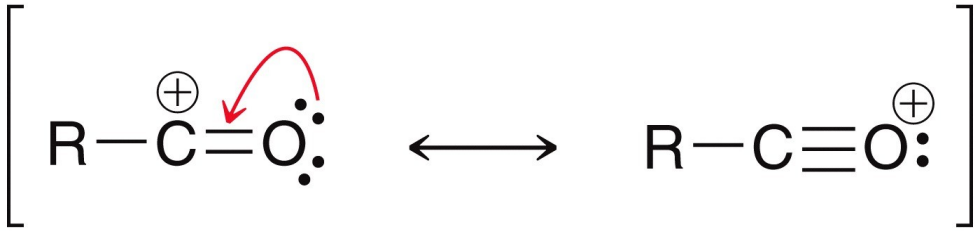
- Acylation proceeds through an acylium ion



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19.6 Friedel-Crafts Acylation

- The acylium ion is stabilized by resonance



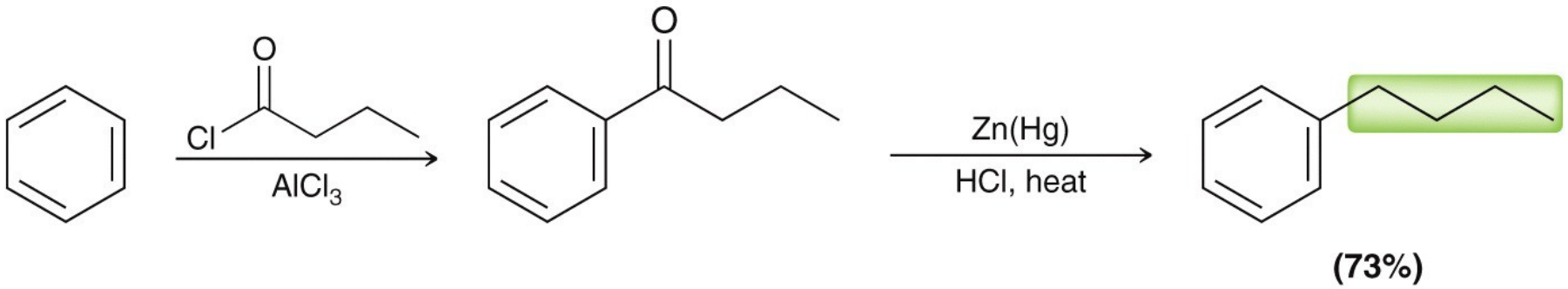
Resonance stabilized

- The acylium ion generally does not rearrange because of the resonance
- Draw a complete mechanism for the reaction between benzene and the acylium ion

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19.6 Friedel-Crafts Acylation

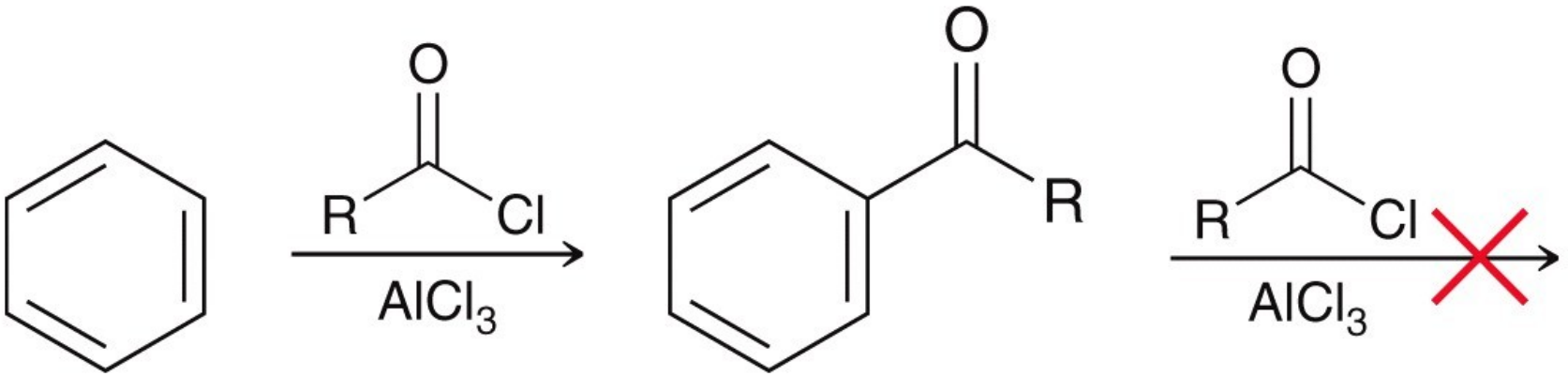
- Some alkyl groups cannot be attached to a ring by Friedel-Crafts alkylation because of rearrangements
- An acylation followed by a Clemmensen reduction is a good alternative



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19.6 Friedel-Crafts Acylation

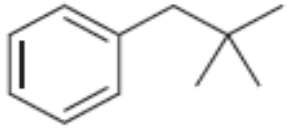
- Unlike polyalkylation, polyacylation is generally not observed. We will discuss WHY later in this chapter

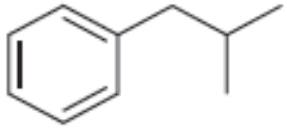


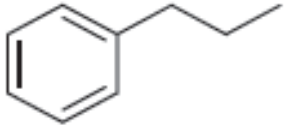
- Practice with conceptual checkpoint 19.8 through 19.10

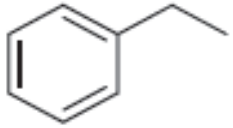
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19.8 Identify whether each of the following compounds can be made using a direct Friedel-Crafts alkylation or whether it is necessary to perform an acylation followed by a Clemmensen reduction to avoid carbocation rearrangements:

(a) 

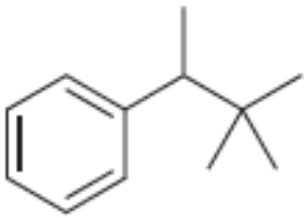
(b) 

(c) 

(d) 

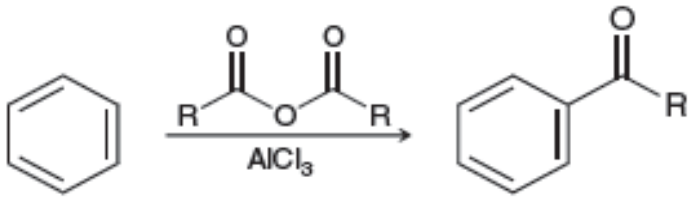
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19.9 The following compound cannot be made with either a Friedel-Crafts alkylation or acylation. Explain.



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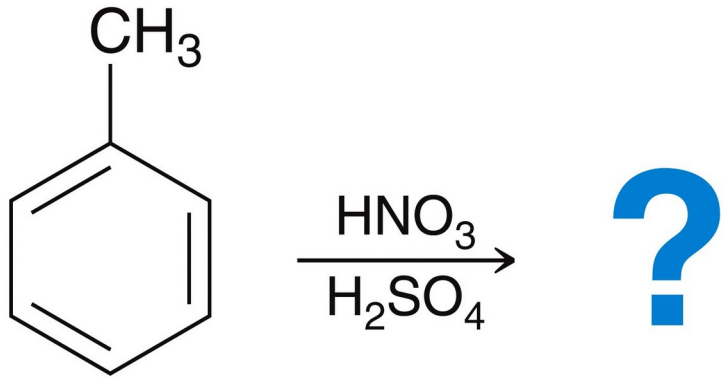
19.10 A Friedel-Crafts acylation is an electrophilic aromatic substitution in which the electrophile (E^+) is an acylium ion. There are other methods of forming acylium ions, such as treatment of an anhydride with a Lewis acid. The resulting acylium ion can also be attacked by a benzene ring, resulting in acylation of the aromatic ring. With this in mind, draw a mechanism for the following transformation:



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19.7 Activating Groups

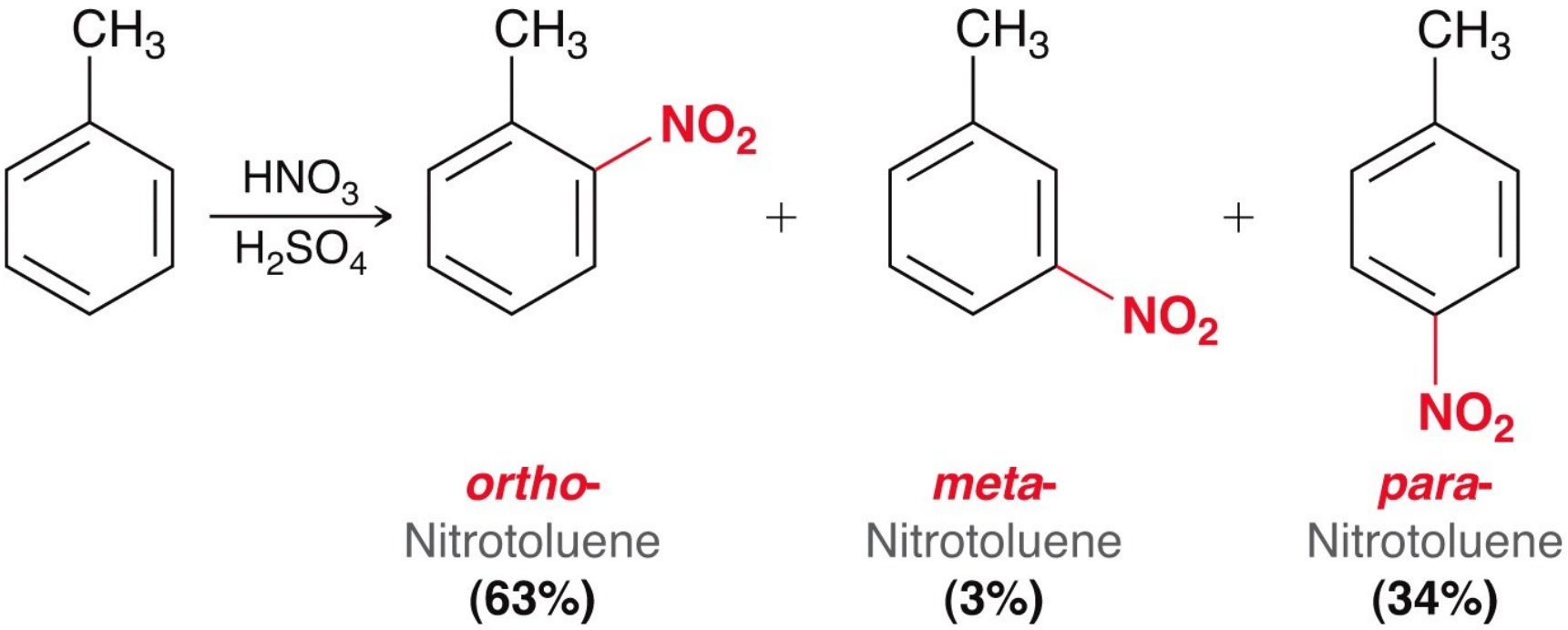
- Substituted benzenes may undergo EAS reactions with faster **RATES** than unsubstituted benzene. What is rate?
- Toluene undergoes nitration 25 times faster than benzene
- The methyl group activates the ring through induction (hyperconjugation). Explain HOW



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19.7 Activating Groups

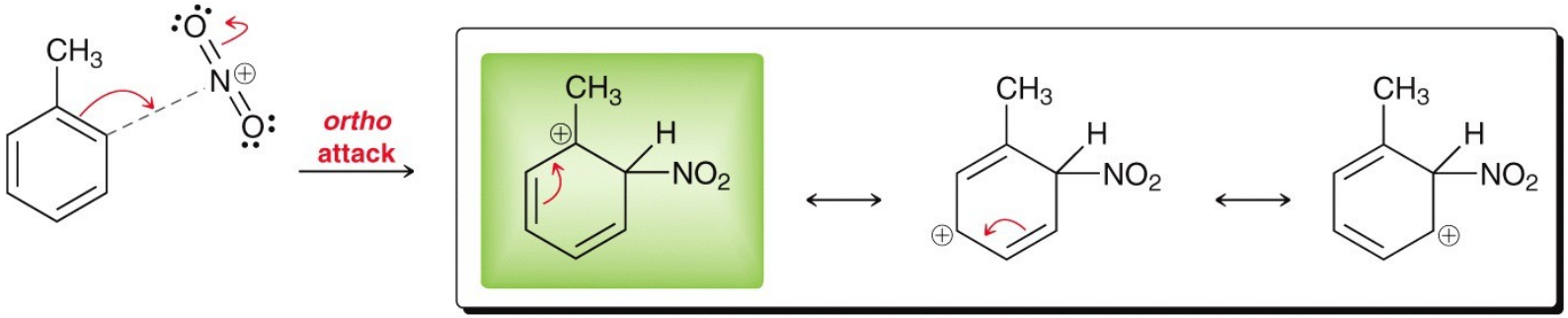
- Substituted benzenes generally undergo EAS reactions regioselectively



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19.7 Activating Groups

- The relative position of the methyl group and the approaching electrophile affects the stability of the sigma complex

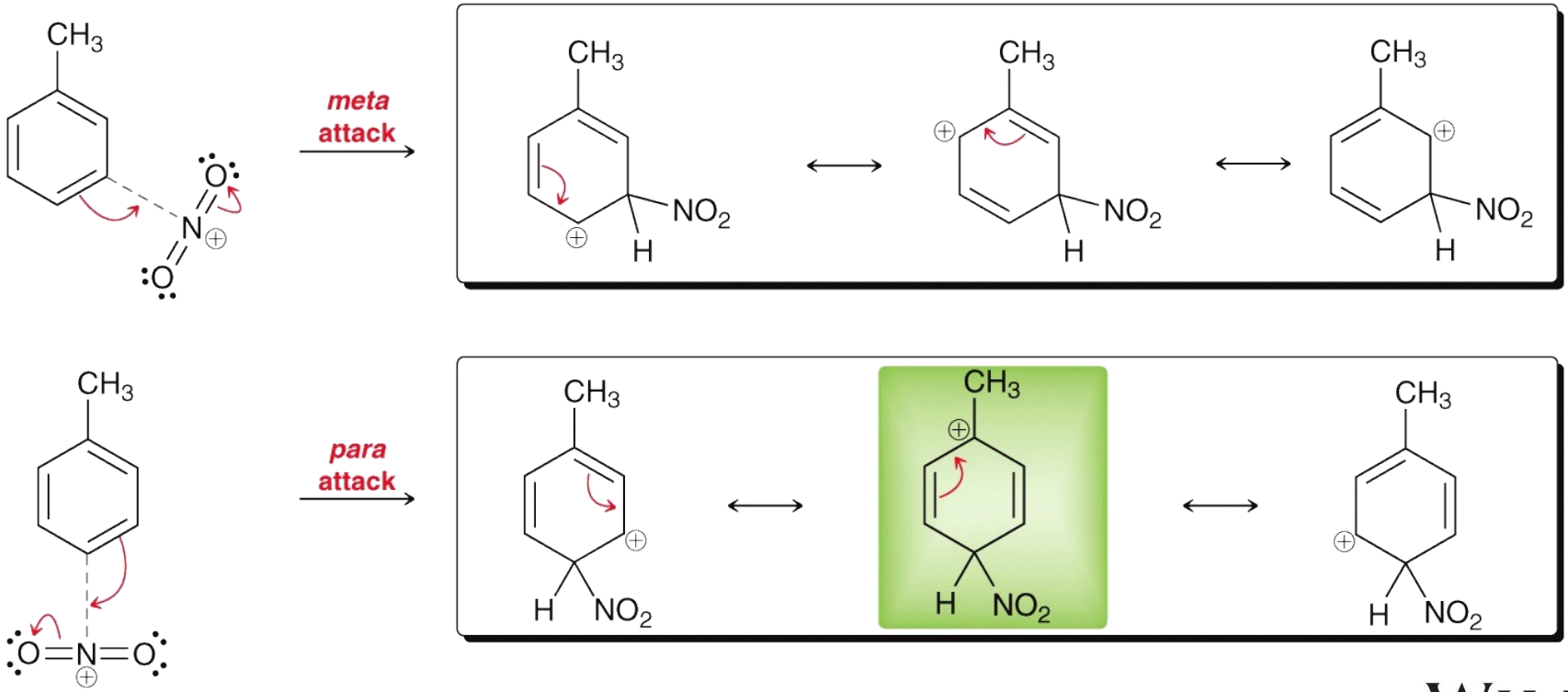


- If the ring attacks from the *ortho* position, the first resonance contributor of the sigma complex is stabilized. HOW?
- Is the transition state also affected?

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19.7 Activating Groups

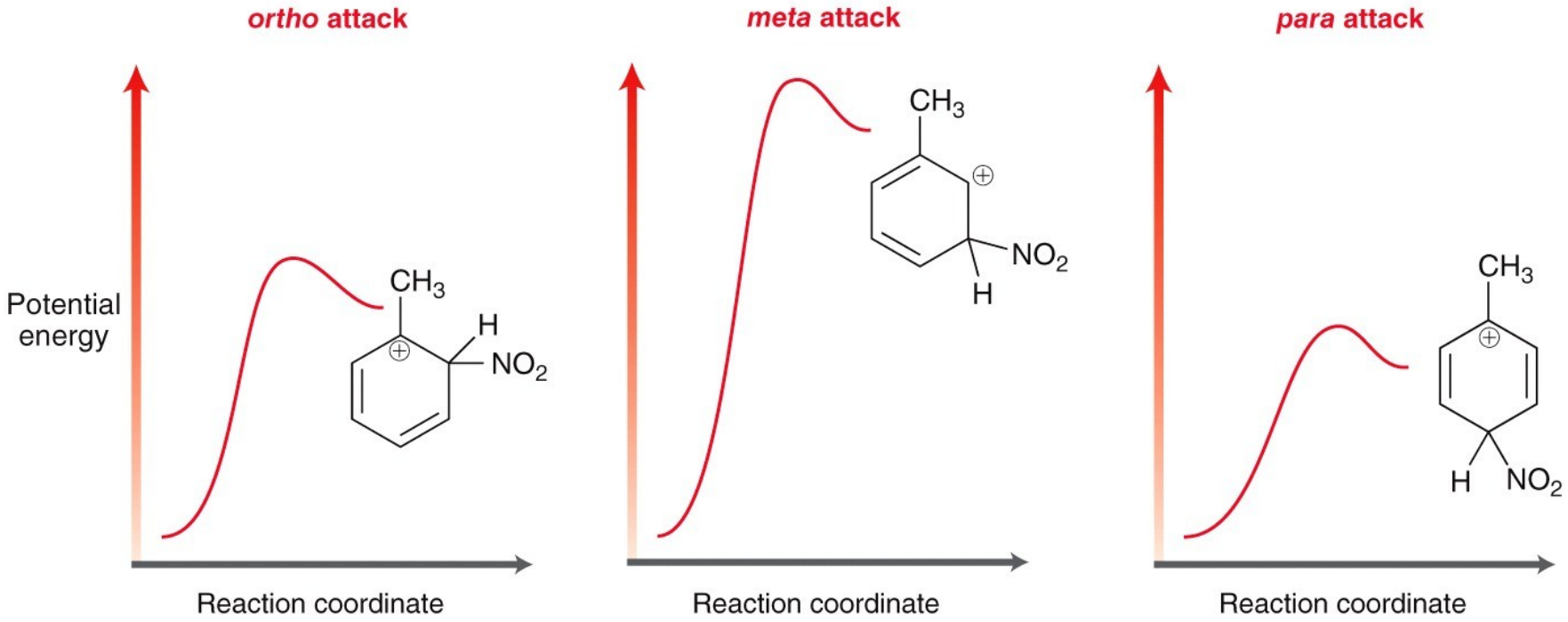
- The relative position of the methyl group and the approaching electrophile affects the stability of the sigma complex



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19.7 Activating Groups

- Explain the trend below



- The *ortho* product predominates for statistical reasons despite some slight steric

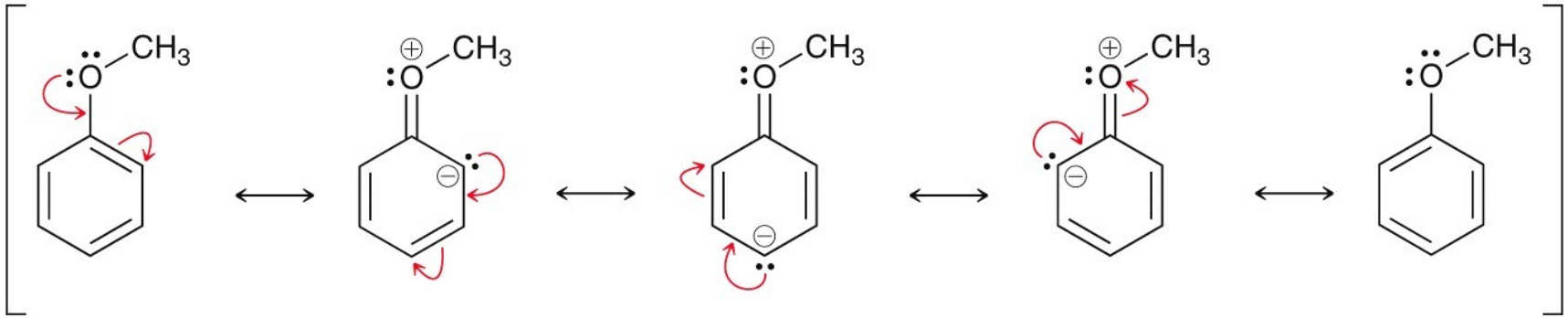
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19.11 Draw the two major products obtained when toluene undergoes monobromination.

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19.7 Activating Groups

- The methoxy group in anisole activates the ring 400 times more than benzene
- Through **induction**, is a methoxy group electron withdrawing or donating? HOW?
- The methoxy group donates through

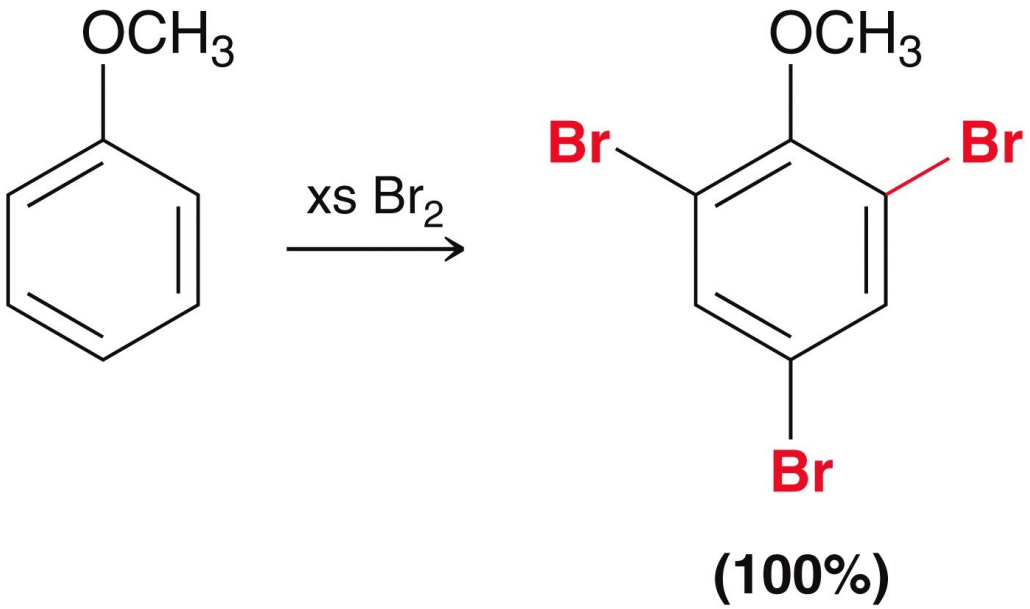


- Which resonance structure contributes most to the resonance hybrid?

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19.7 Activating Groups

- The methoxy group activates the ring so strongly that polysubstitution is difficult to avoid

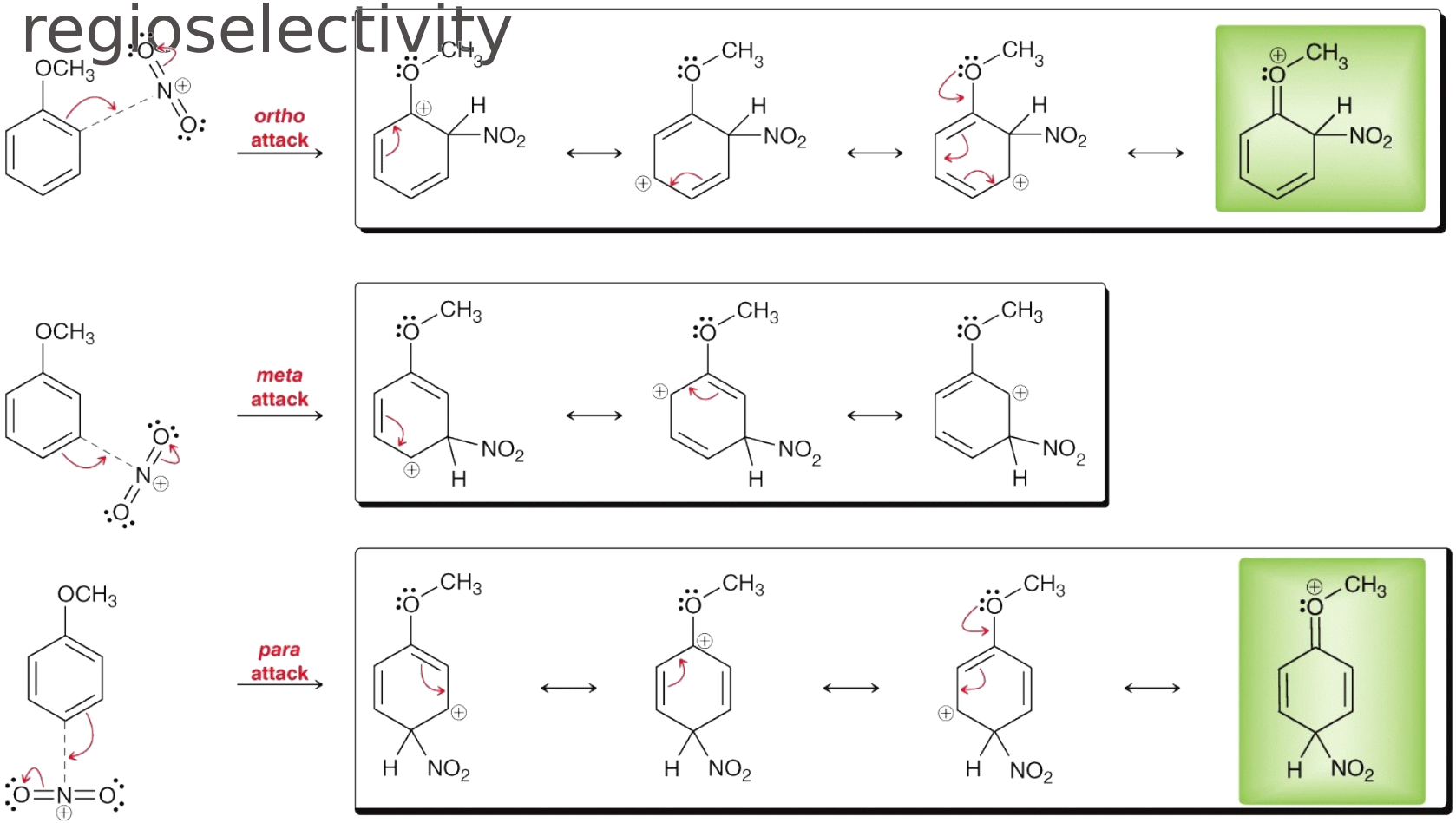


- Activators are generally *ortho-para* directors

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19.7 Activating Groups

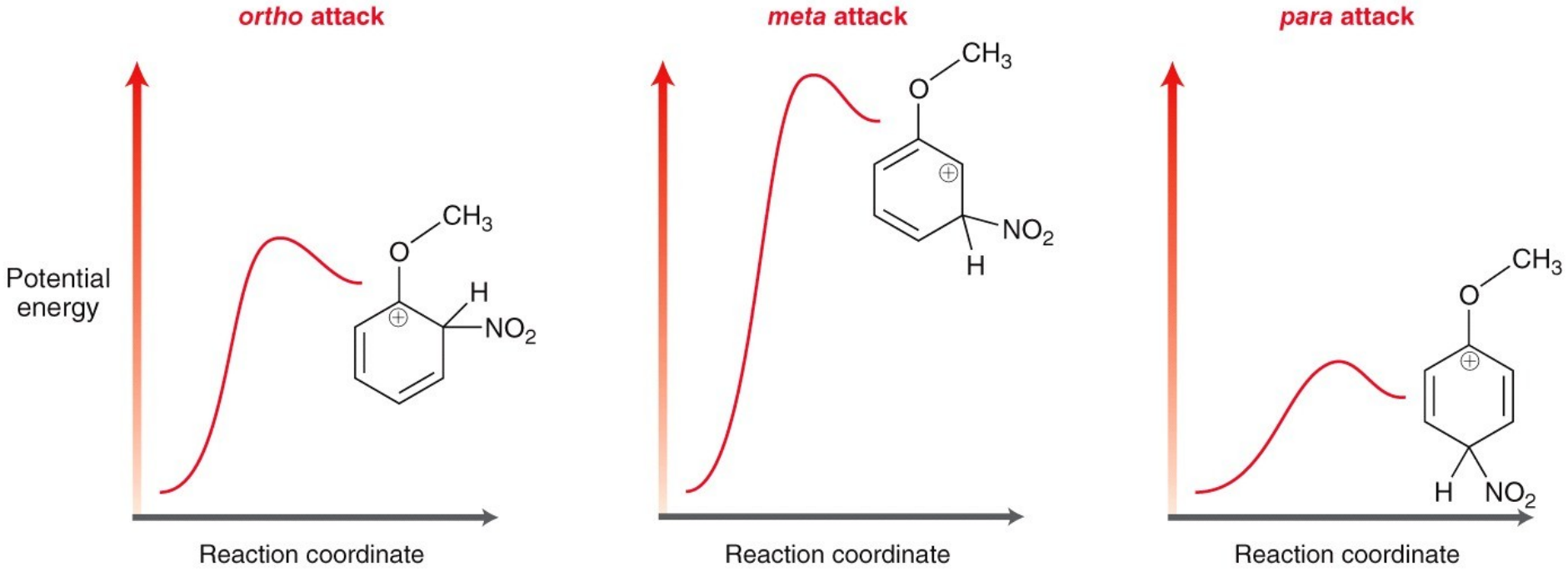
- The resonance stabilization affects the regioselectivity



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19.7 Activating Groups

- How will the methoxy group affect the transition state?

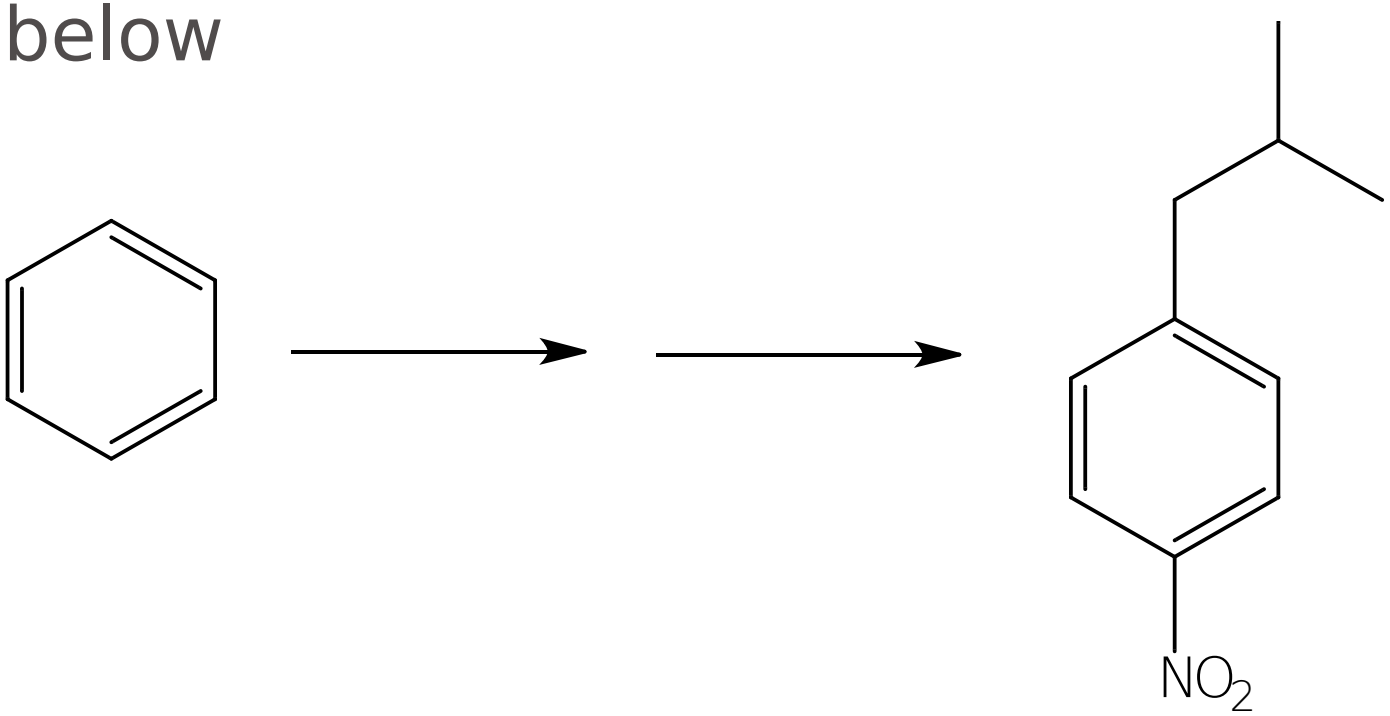


- The *para* product is the major product. WHY?

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19.7 Activating Groups

- All activators are *ortho* -*para* directors
- Give reactants necessary for the conversion below



- Practice with conceptual checkpoint 19.12

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19.12 When ethoxybenzene is treated with a mixture of nitric acid and sulfuric acid, two products are obtained, each of which has the molecular formula $C_8H_9NO_3$.

(a) Draw the structure of each product.

(b) Propose a mechanism of formation for the major product.

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19.8 Deactivating Groups

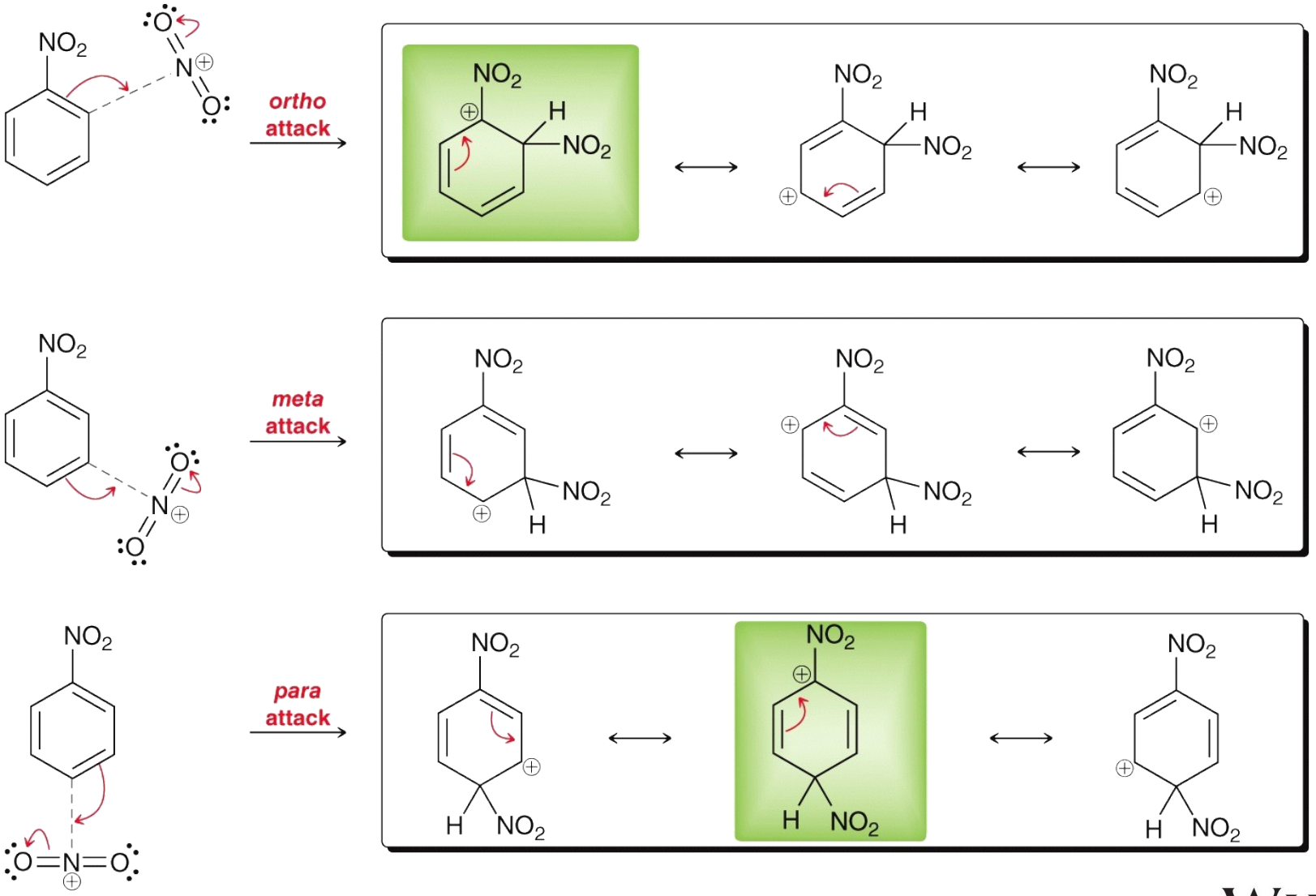
- The nitro group is electron withdrawing through both resonance and induction. Explain HOW

- Withdrawing electrons from the ring deactivates it. HOW?

- Will withdrawing electrons make the transition state or the intermediate less stable?

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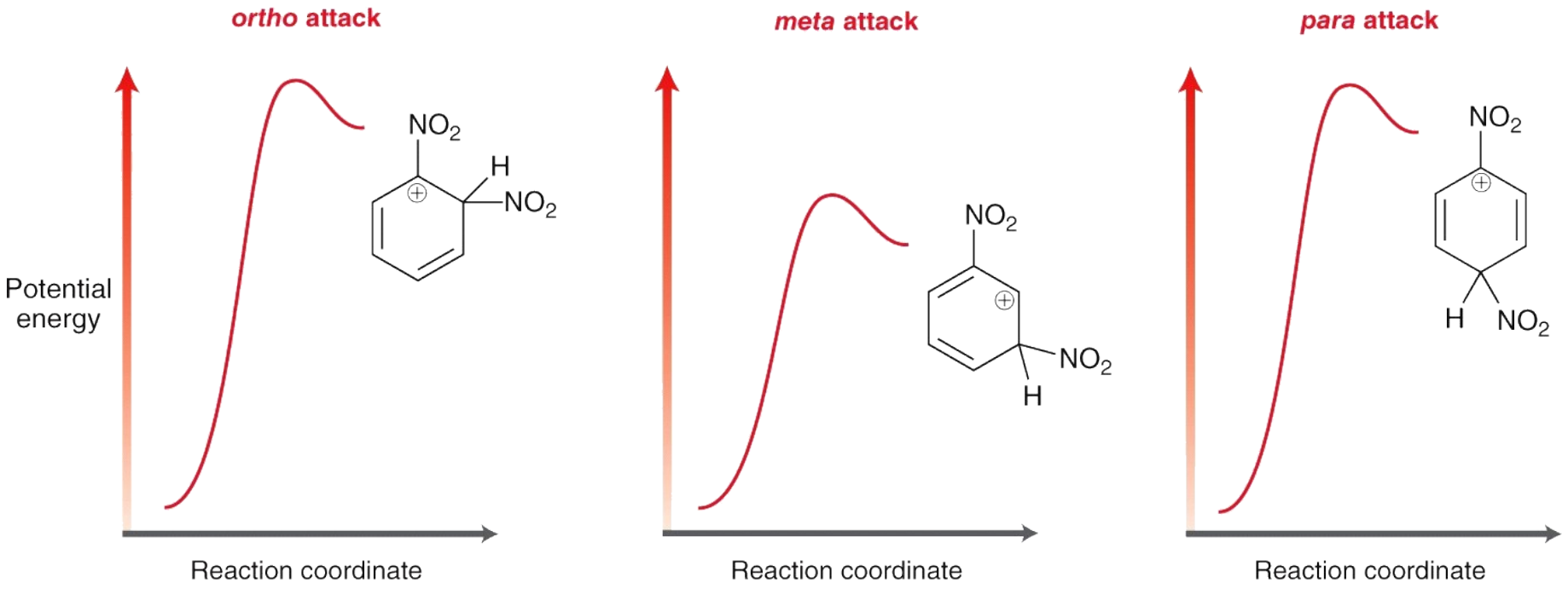
19.8 Deactivating Groups



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19.8 Deactivating Groups

- The *meta* product predominates because the other positions are deactivated



- Practice with conceptual checkpoint 19.13

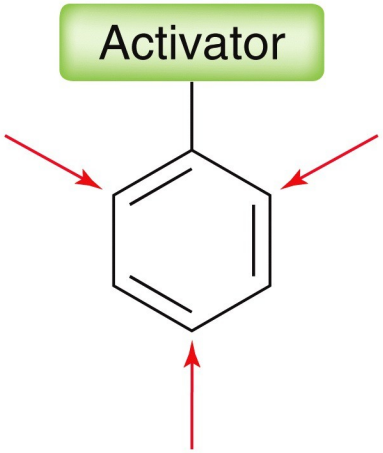
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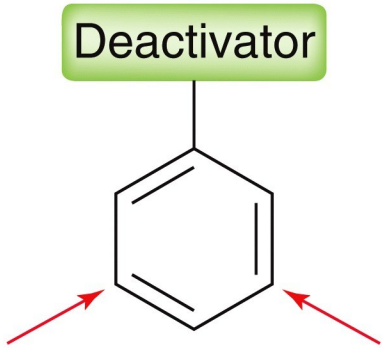
19.13 When 1,3-dinitrobenzene is treated with nitric acid and sulfuric acid at elevated temperature, the product is 1,3,5-trinitrobenzene. Explain the regiochemical outcome of this reaction. In other

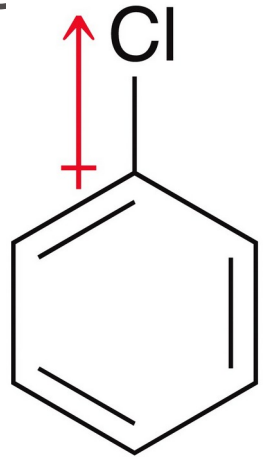
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19.9 Halogens: The Exception

- All electron donating groups are *ortho-para* directors
- All electron withdrawing groups are *meta*-dire ens





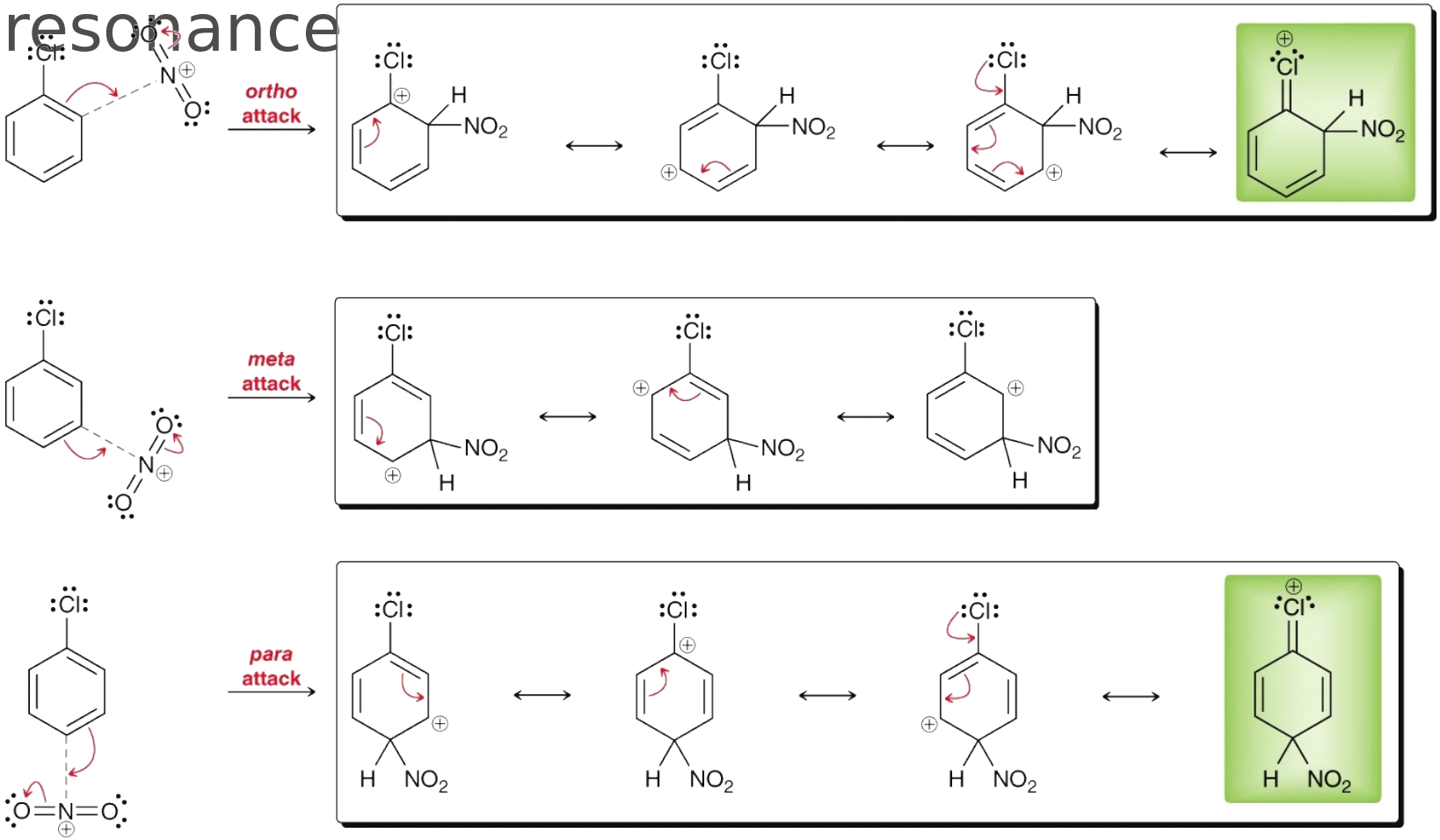


- Halogens withdraw electrons by induction (deactivating)
- Halogens donate electrons through

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19.9 Halogens: The Exception

- Halogens donate electrons through resonance



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19.14 Does chlorination of chlorobenzene require the use of a Lewis acid? Explain why or why not?

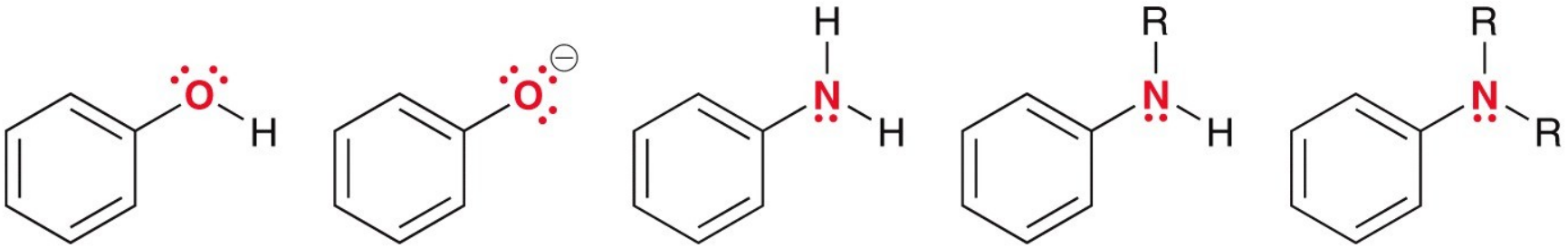
19.15 Predict and explain the regiochemical outcome for chlorination of bromobenzene.

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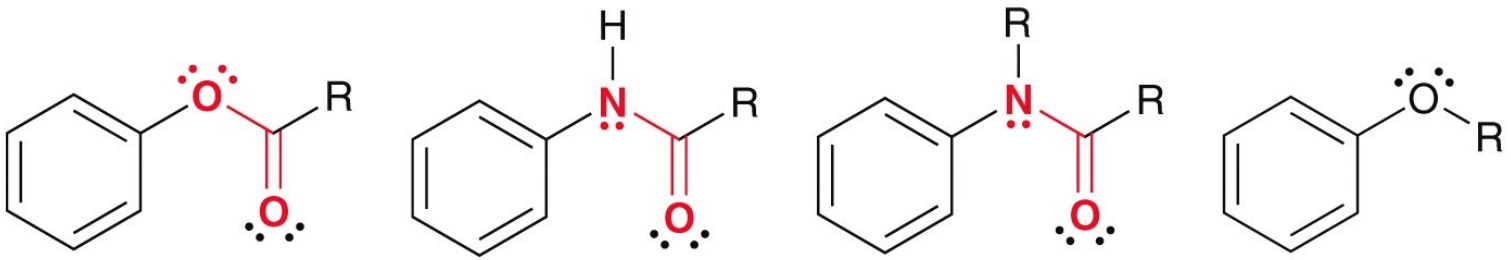
19.10 Determining the Directing Effects of a Substituent

- Let's summarize the directing effects of more substituents

1. STRONG activators. WHAT makes them



2. M
m

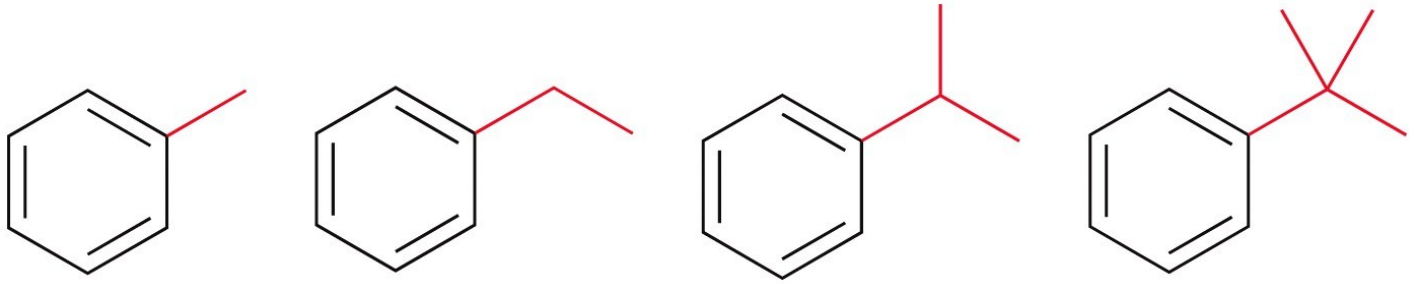


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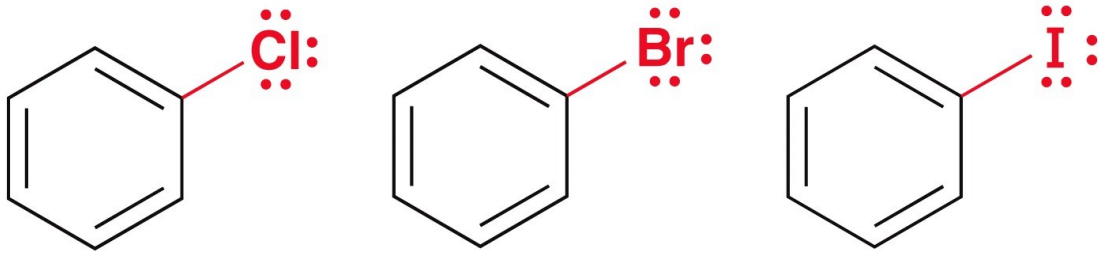
19.10 Determining the Directing Effects of a Substituent

- Let's summarize the directing effects of more substituents

3. WEAK activators. WHAT makes them weak?



4. WEAK deactivators. WHAT makes them weak?

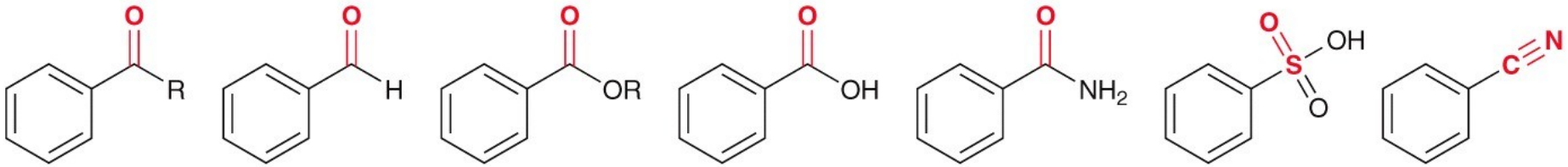


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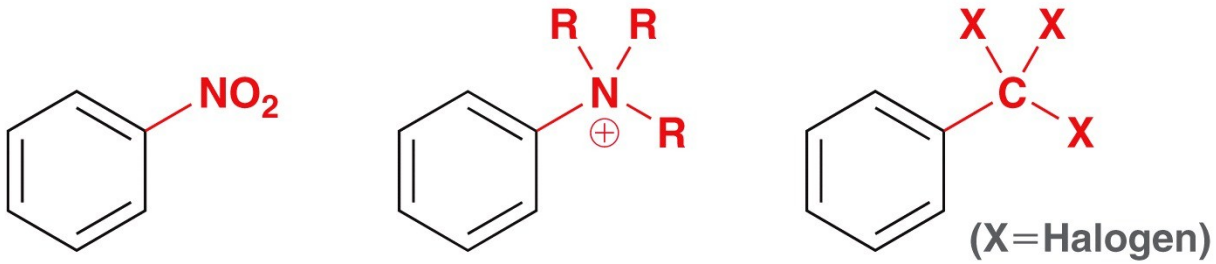
19.10 Determining the Directing Effects of a Substituent

- Let's summarize the directing effects of more substituents

5. Moderate deactivators. WHAT makes them moderate?



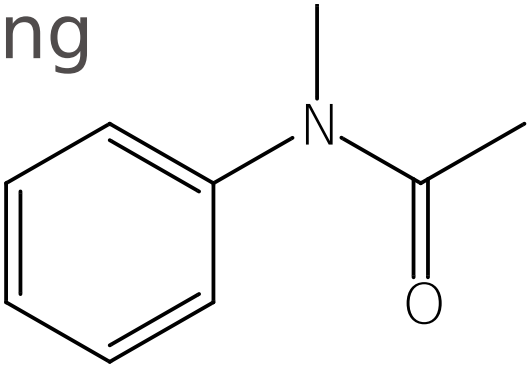
6. STRONG deactivators. WHAT makes them strong?



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19.10 Determining the Directing Effects of a Substituent

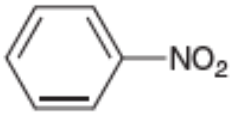
- For the compound below, determine whether the group is electron withdrawing or donating
- Also, determine if it is activating or deactivating and how strongly or weakly
- Finally, determine whether it is *ortho*, *para*, or *meta* directing

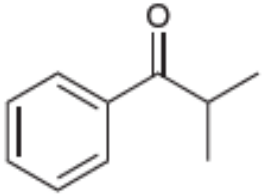


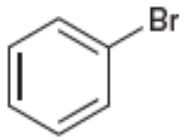
- Practice with SkillBuilder 19.1

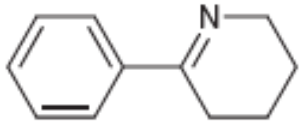
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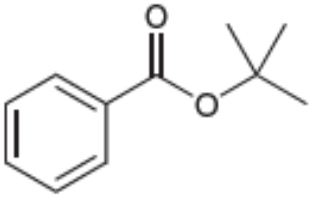
19.16 For each of the following compounds, determine whether the ring is activated or deactivated, then determine the strength of activation/deactivation, and finally determine the expected directing effects.

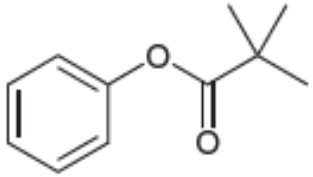
(a) 

(b) 

(c) 

(d) 

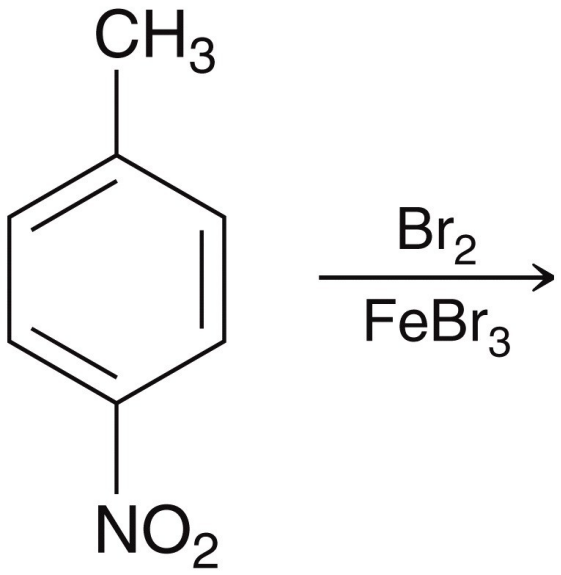
(e) 

(f) 

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19.11 Multiple Substituents

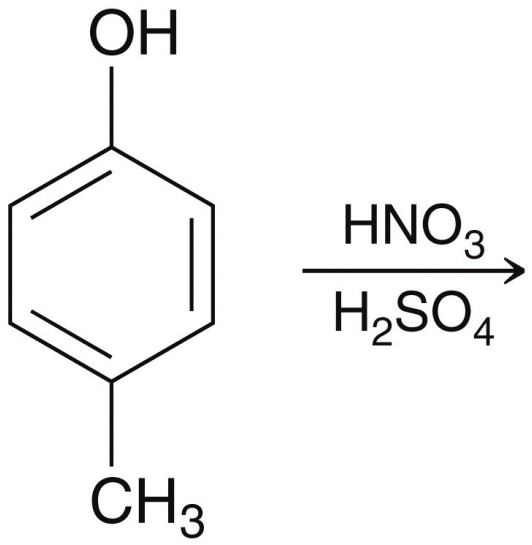
- The directing effects of all substituents attached to a ring must be considered in an EAS reaction
- Predict the major product for the reaction b[illegible]AIN



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19.11 Multiple Substituents

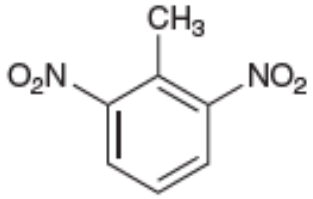
- Predict the major product for the reaction below and EXPLAIN

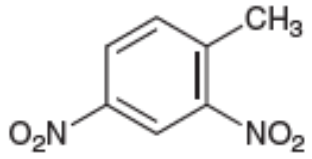


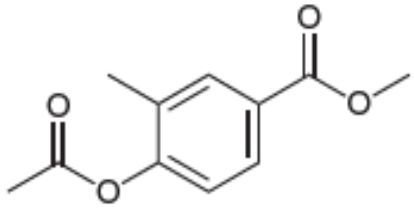
- Practice with SkillBuilder 19.2

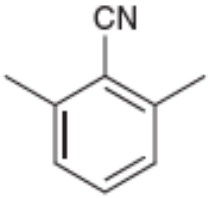
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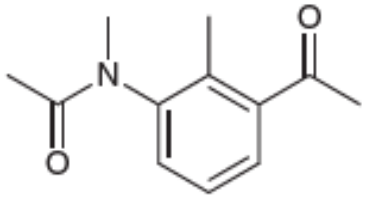
19.19 For each compound below, identify which position(s) is/are most likely to undergo an electrophilic aromatic substitution reaction.

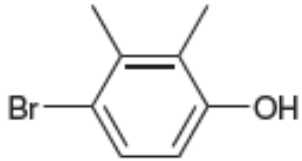
(a) 

(b) 

(c) 

(d) 

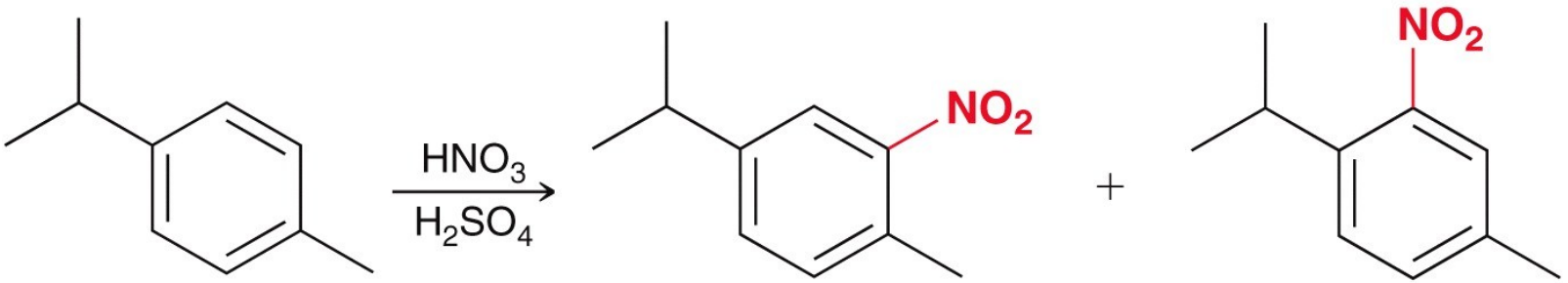
(e) 

(f) 

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19.11 Multiple Substituents

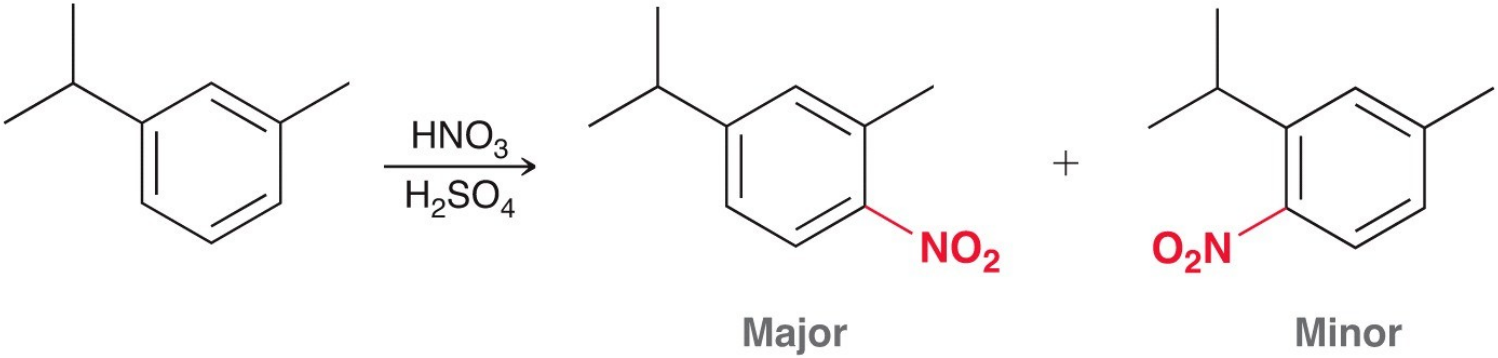
- Consider sterics in addition to resonance and induction to predict which product below is major and which is minor



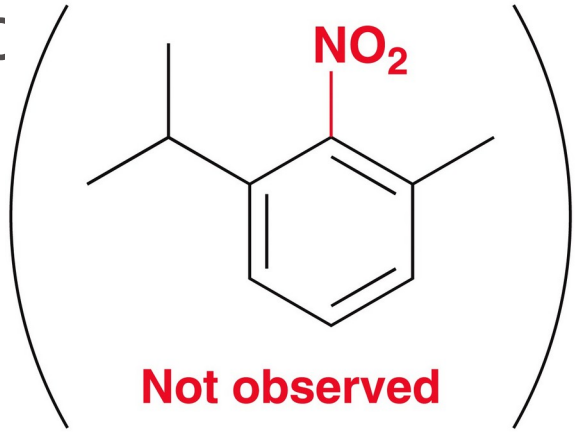
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19.11 Multiple Substituents

- Consider sterics in addition to resonance and induction to predict which product below is major



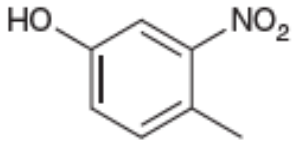
- Substitution is very unlikely to c
in between two substituents. W

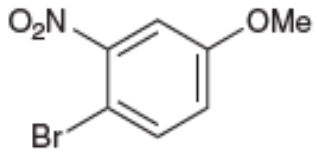


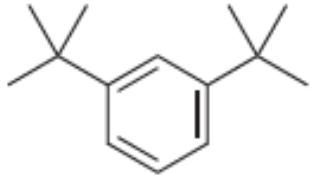
- Practice with SkillBuilder 19.3

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19.22 For each of the following compounds, determine the position that is most likely to be the site of an electrophilic aromatic substitution reaction:

(a) 

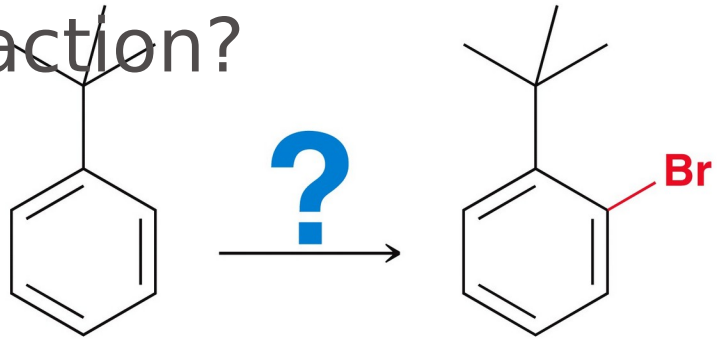
(b) 

(c) 

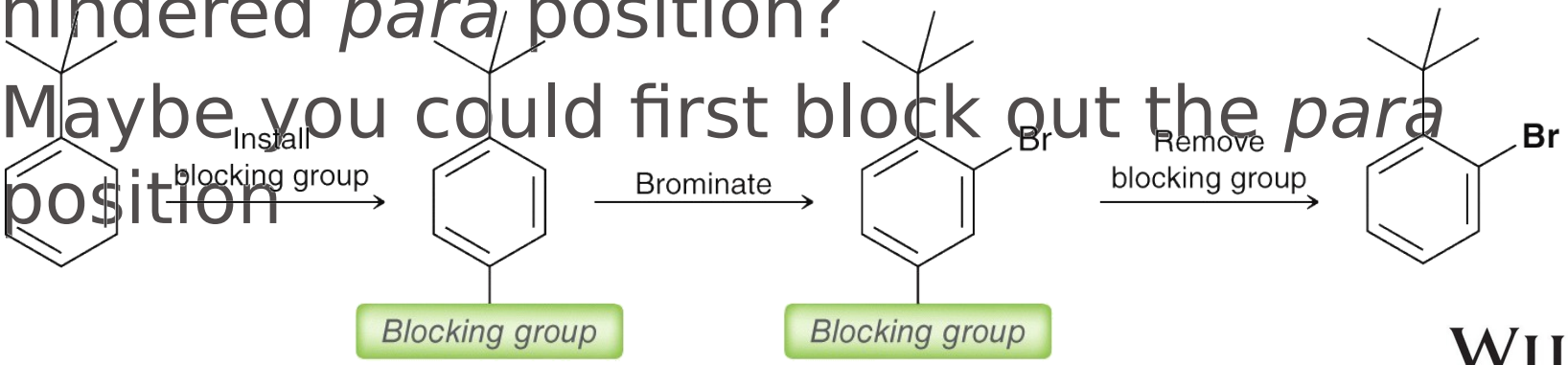
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19.11 Multiple Substituents

- What reagents might you use for the following reaction?



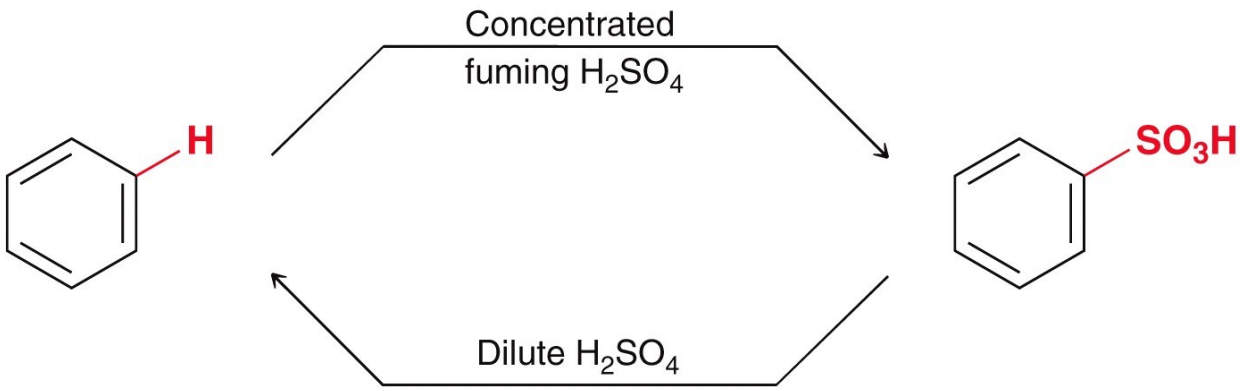
- Is there a way to promote the desired *ortho* substitution over substitution at the less hindered *para* position?
- Maybe you could first block out the *para* position

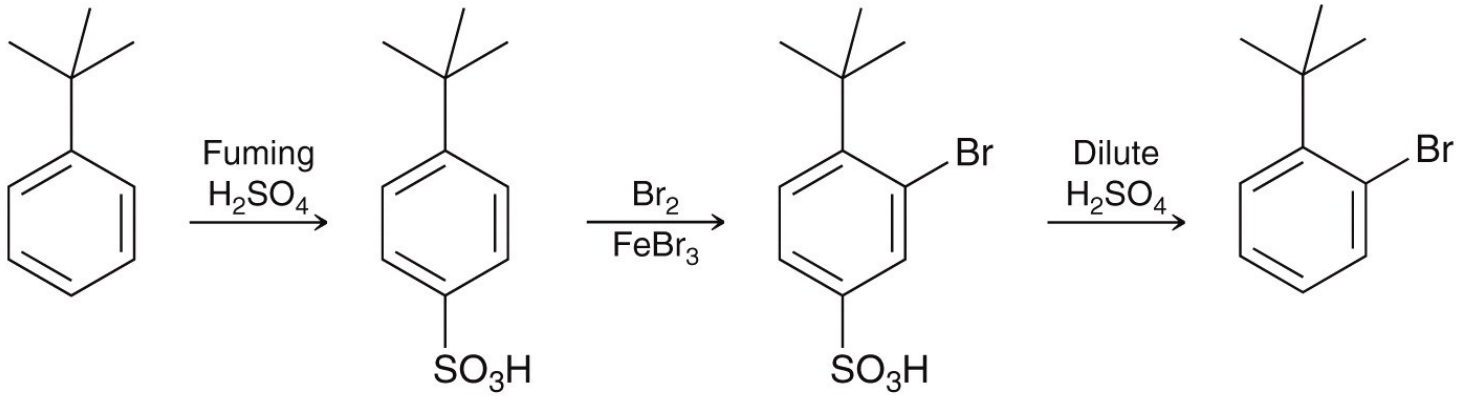


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19.11 Multiple Substituents

- Because EAS **sulfonation** i reversible, it can be used a a temporary blocking group

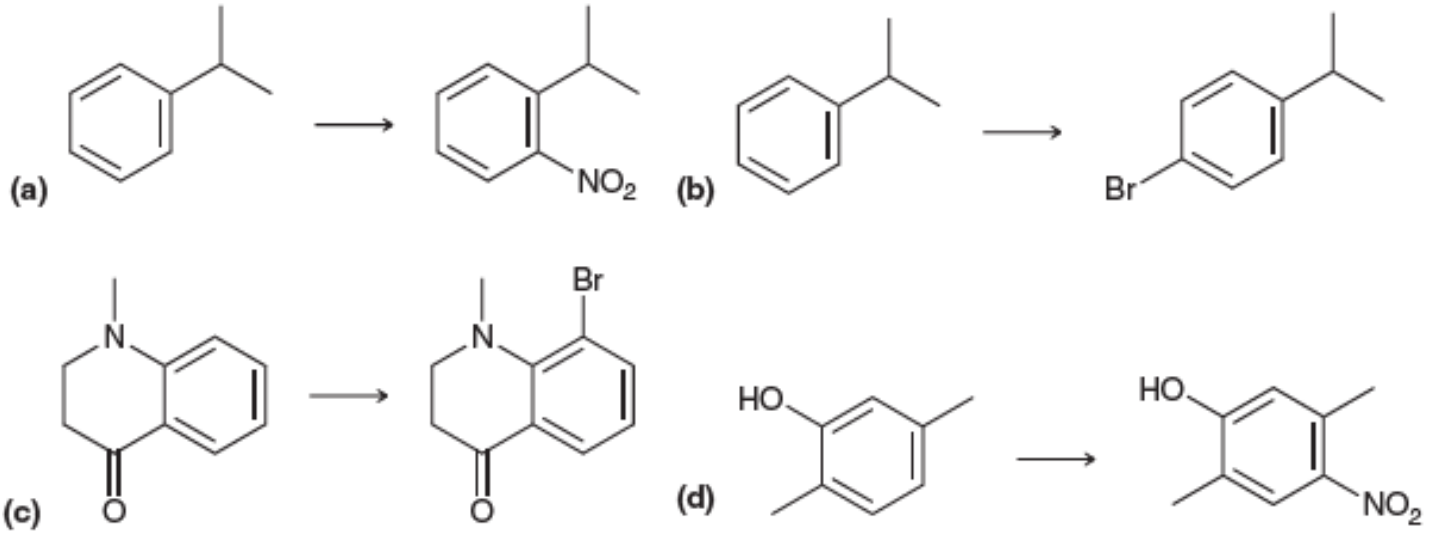




- Practice with SkillBuilder 19.4

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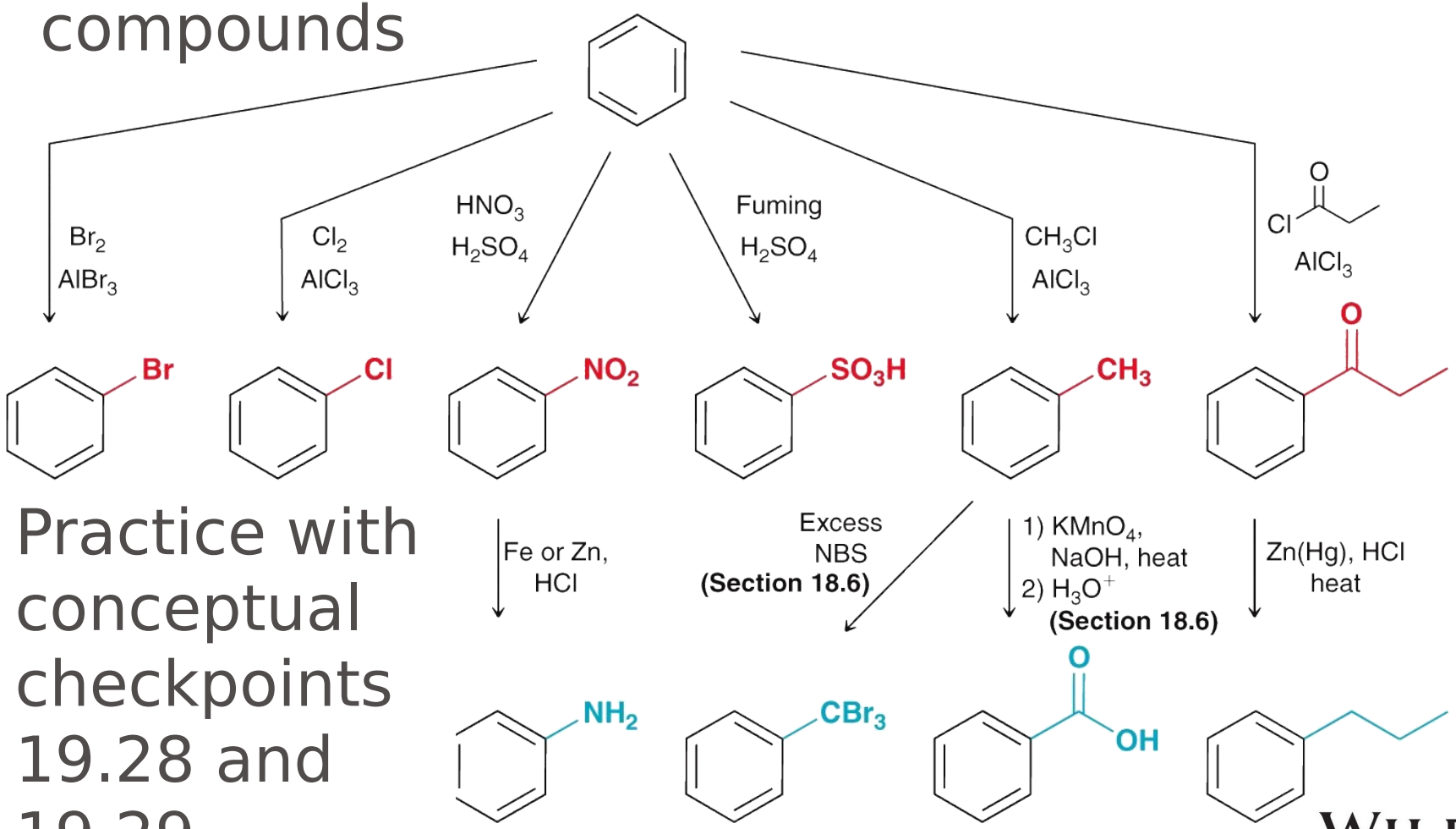
skill **19.25** Determine whether a blocking group is necessary to accomplish each of the following transformations:



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19.12 Synthetic Strategies

- Reagents for monosubstituted aromatic compounds



- Practice with conceptual checkpoints 19.28 and 19.29

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19.28 Identify the reagents necessary to convert benzene into each of the following compounds:

(a) Chlorobenzene
(b) Nitrobenzene
(c) Bromobenzene
(d) Ethylbenzene
(e) Propylbenzene
(f) Isopropylbenzene
(g) Aniline (aminobenzene)
(h) Benzoic acid
(i) Toluene

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19.28 Identify the reagents necessary to convert benzene into each of the following compounds:

(a) Chlorobenzene
(b) Nitrobenzene
(c) Bromobenzene
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(e) Propylbenzene
(f) Isopropylbenzene
(g) Aniline (aminobenzene)
(h) Benzoic acid
(i) Toluene

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19.28 Identify the reagents necessary to convert benzene into each of the following compounds:

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(d) Ethylbenzene
(e) Propylbenzene
(f) Isopropylbenzene
(g) Aniline (aminobenzene)
(h) Benzoic acid
(i) Toluene

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19.29 Identify the product obtained when benzene is treated with each of the following reagents:

(a) Fuming sulfuric acid

(b) HNO_3/H_2SO_4

(c) Cl_2, $AlCl_3$

(d) Ethyl chloride, $AlCl_3$

(e) Br_2, Fe

(f) HNO_3/H_2SO_4 followed by Zn, HCl

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19.29 Identify the product obtained when benzene is treated with each of the following reagents:

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(c) Cl_2, $AlCl_3$

(d) Ethyl chloride, $AlCl_3$

(e) Br_2, Fe

(f) HNO_3/H_2SO_4 followed by Zn, HCl

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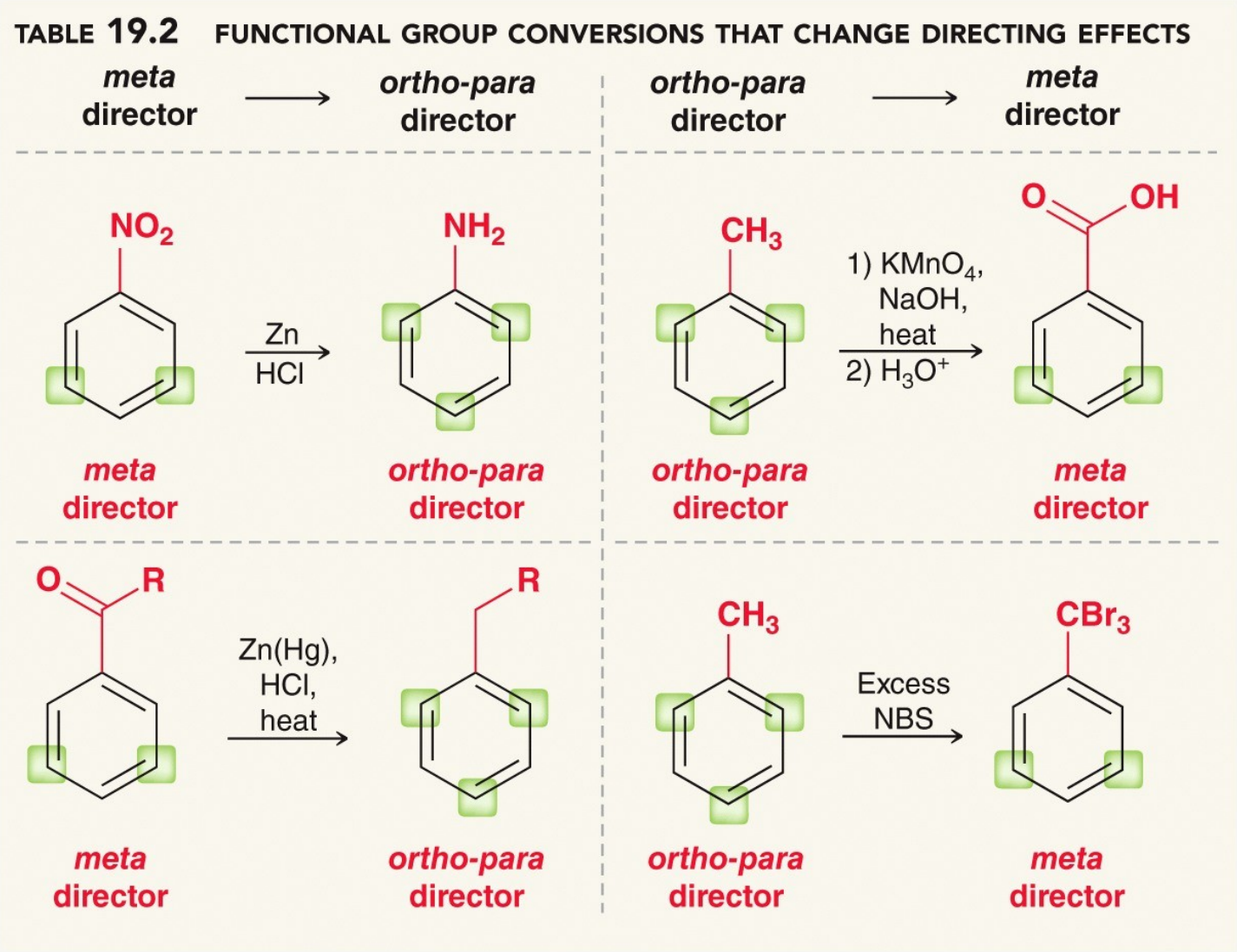
19.12 Synthetic Strategies

- To synthesize di-substituted aromatic compounds, you must carefully analysis the directing groups
- How might you make 3-nitrobromobenzene?

- How might you make 3-chloroaniline?
- Such a reaction is much more challenging, because $-NH_2$ and–Cl groups are both *para* directing
- A *meta* director will be used to install the two groups
- One of the groups will subsequently be

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19.12 Synthetic Strategies

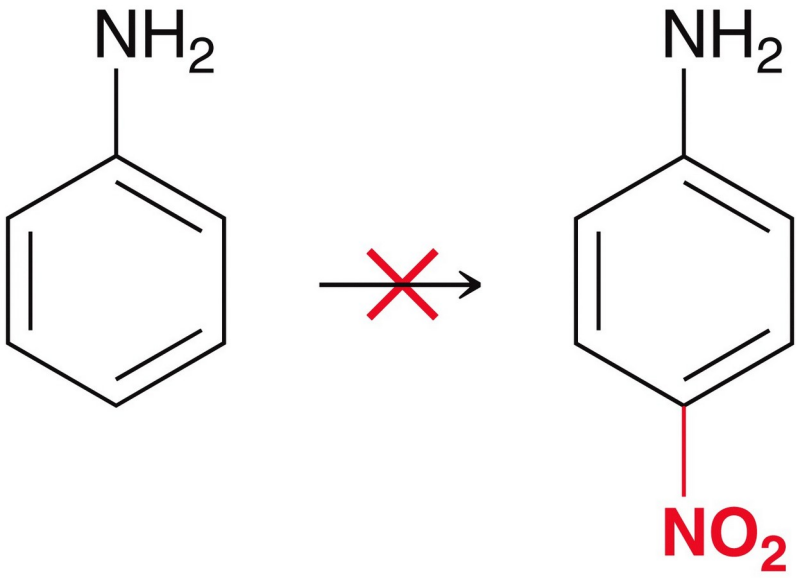


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19.12 Synthetic Strategies

- There are limitations you should be aware of for some EAS reactions

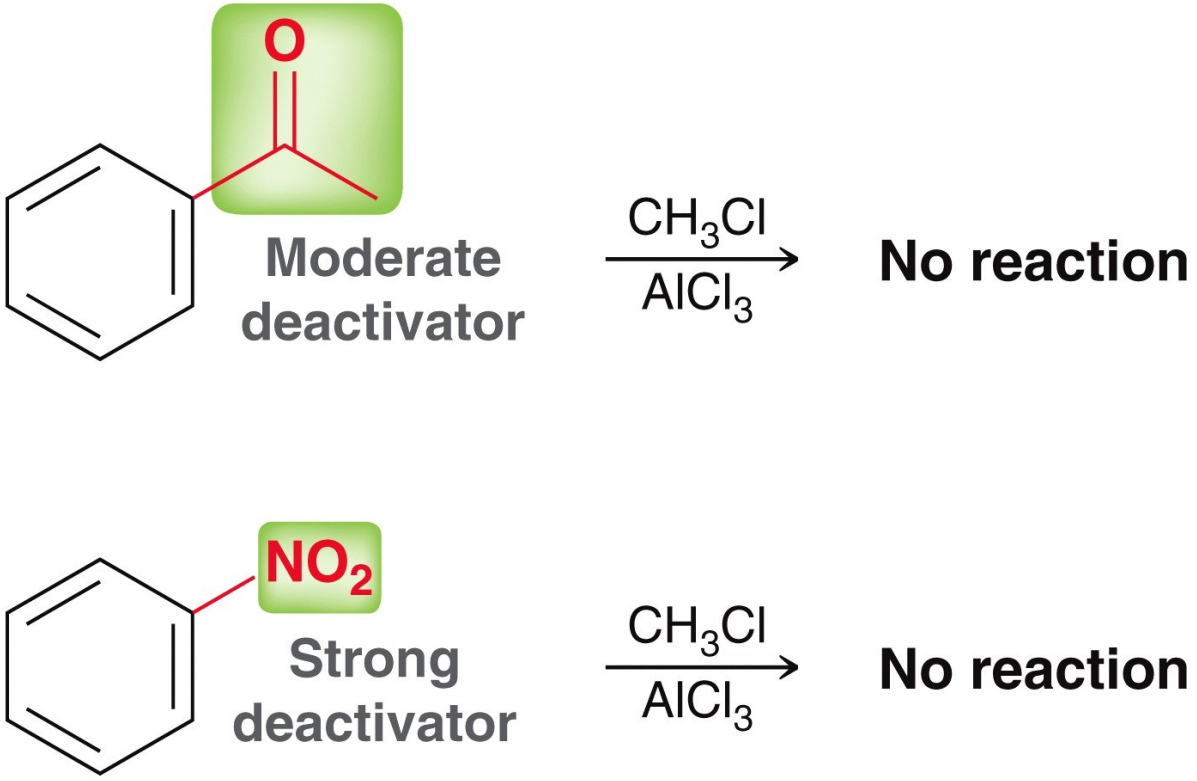
1. Nitration conditions generally cause amine oxidation leading to a mixture of undesired products



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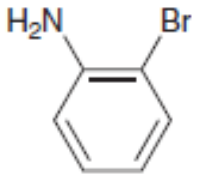
19.12 Synthetic Strategies

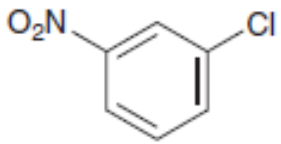
2. Friedel-Crafts reactions are too slow to be practical when a deactivating group is prese

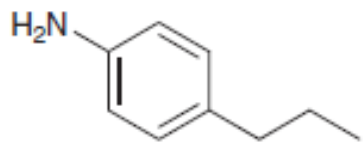


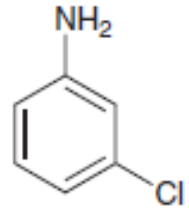
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19.30 Starting with benzene and using any other necessary reagents of your choice, design a synthesis for each of the following compounds. Note: some of these problems have more than one plausible answer.

(a) 

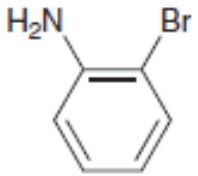
(b) 

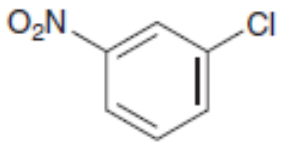
(c) 

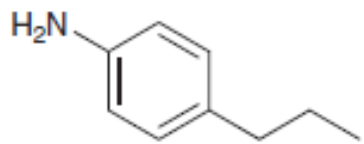
(d) 

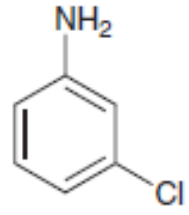
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19.30 Starting with benzene and using any other necessary reagents of your choice, design a synthesis for each of the following compounds. Note: some of these problems have more than one plausible answer.

(a) 

(b) 

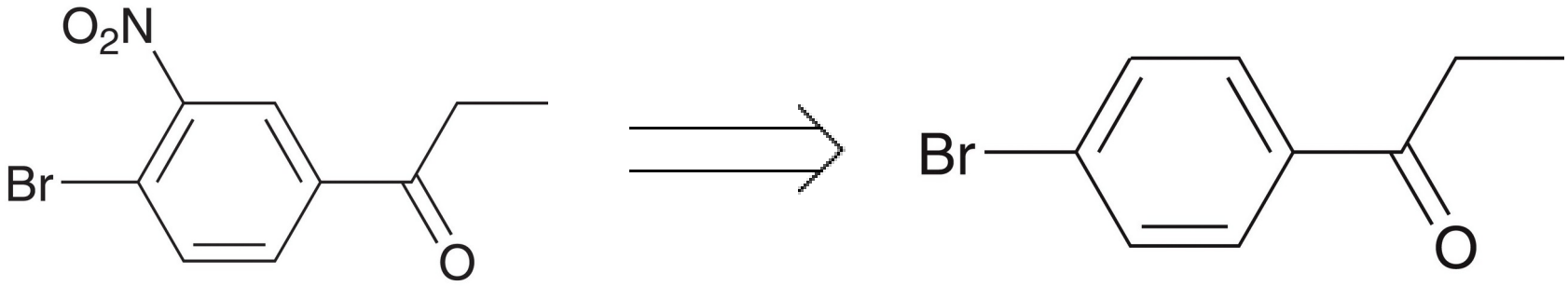
(c) 

(d) 

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19.12 Synthetic Strategies

- When designing a synthesis for a polysubstituted aromatic compound, often a retrosynthetic analysis is helpful
- Design a synthesis for the molecule below

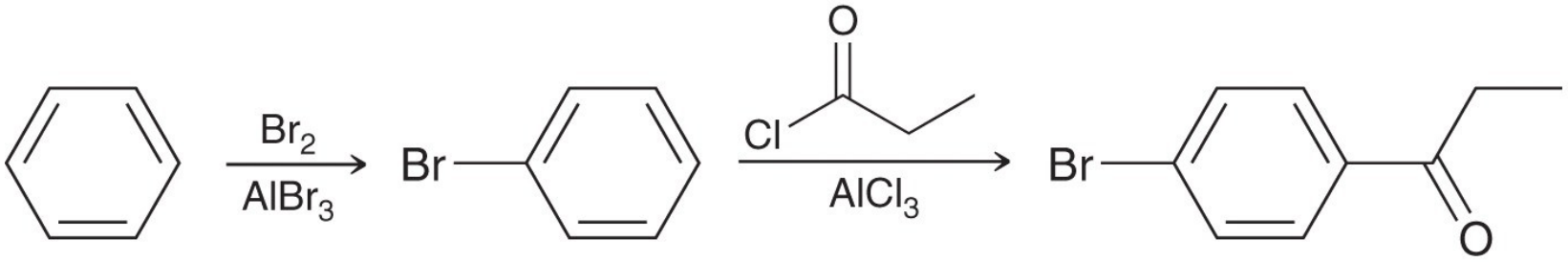


- Which group would be the LAST group attached?
- WHY can't the bromo or acyl groups be attached last?

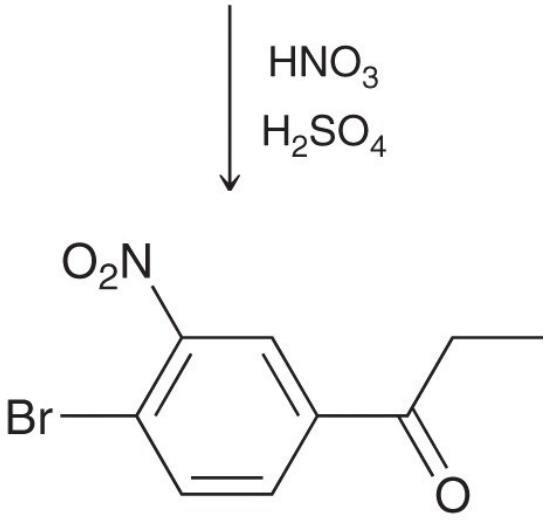
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19.12 Synthetic Strategies

- Once the ring only has two substituents, it should be easier to work forward

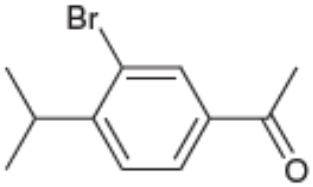


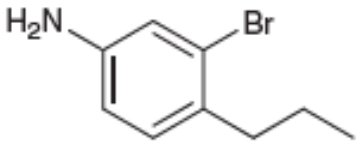
- Explain why other possible synthetic routes are not likely to yield as much of the final product
- Continue SkillBuilder 19.6

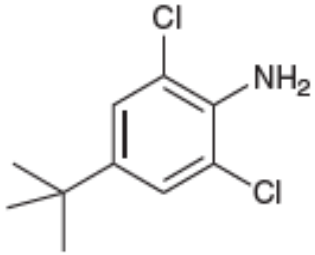


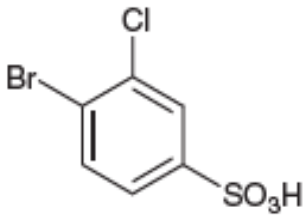
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CTICE the skill **19.33** Starting with benzene and using any other necessary reagents of your choice, design a synthesis for each of the following compounds. In some cases, there may be more than one plausible answer.

(a) 

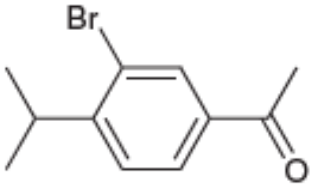
(b) 

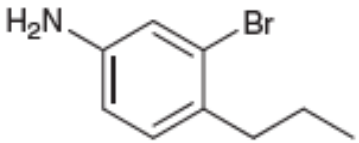
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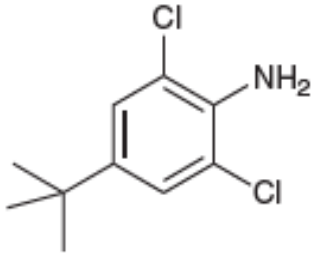
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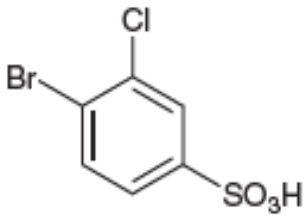
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CTICE the skill **19.33** Starting with benzene and using any other necessary reagents of your choice, design a synthesis for each of the following compounds. In some cases, there may be more than one plausible answer.

(a) 

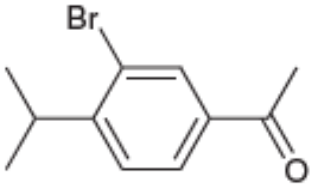
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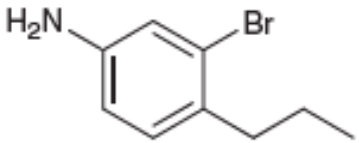
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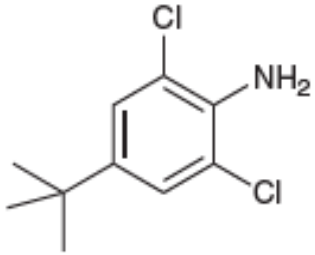
(d) 

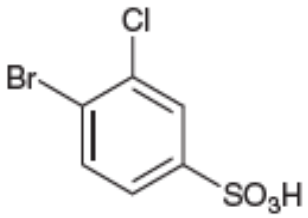
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CTICE the skill **19.33** Starting with benzene and using any other necessary reagents of your choice, design a synthesis for each of the following compounds. In some cases, there may be more than one plausible answer.

(a) 

(b) 

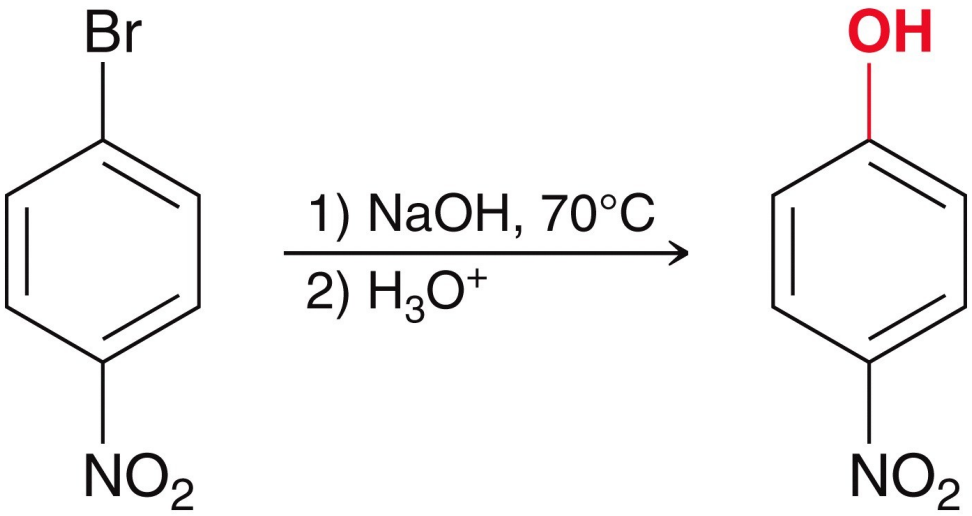
(c) 

(d) 

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19.13 Nucleophilic Aromatic Substitution

- Consider the reaction below in which the aromatic ring is attacked by a nucleophile



- Is there a leaving group?

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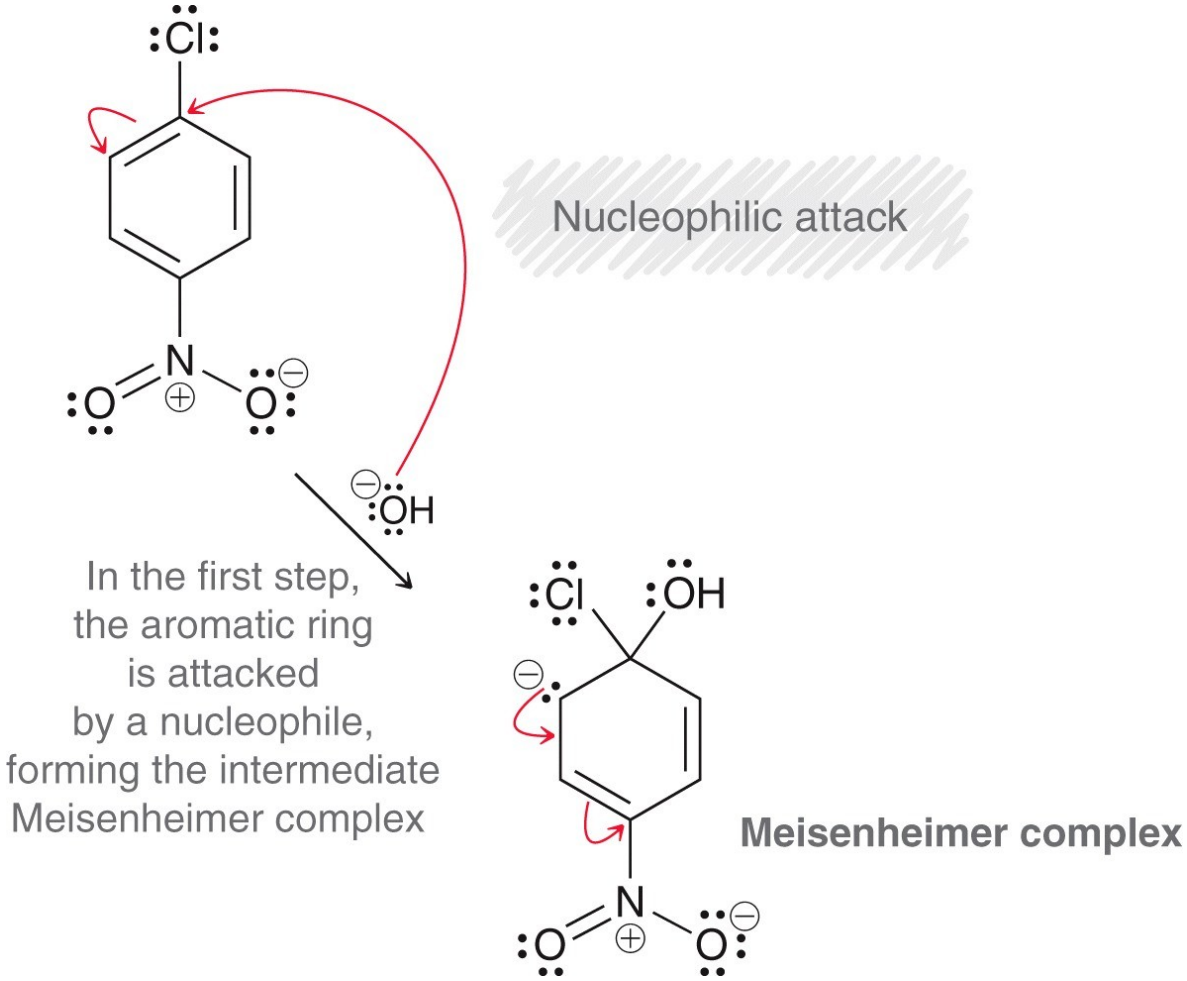
19.13 Nucleophilic Aromatic Substitution

- Aromatic rings are generally electron-rich, which allows them to attack electrophiles (EAS)
- To facilitate attack by a nucleophile:
  1. A ring must be electron poor. WHY?

     A ring must be substituted with a strong electron withdrawing group
  2. There must be a good leaving group
  3. The leaving group must be positioned *ORTHO* or *PARA* to the withdrawing group. WHY? We must investigate the mechanism – see next slide

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19.13 Nucleophilic Aromatic Substitution

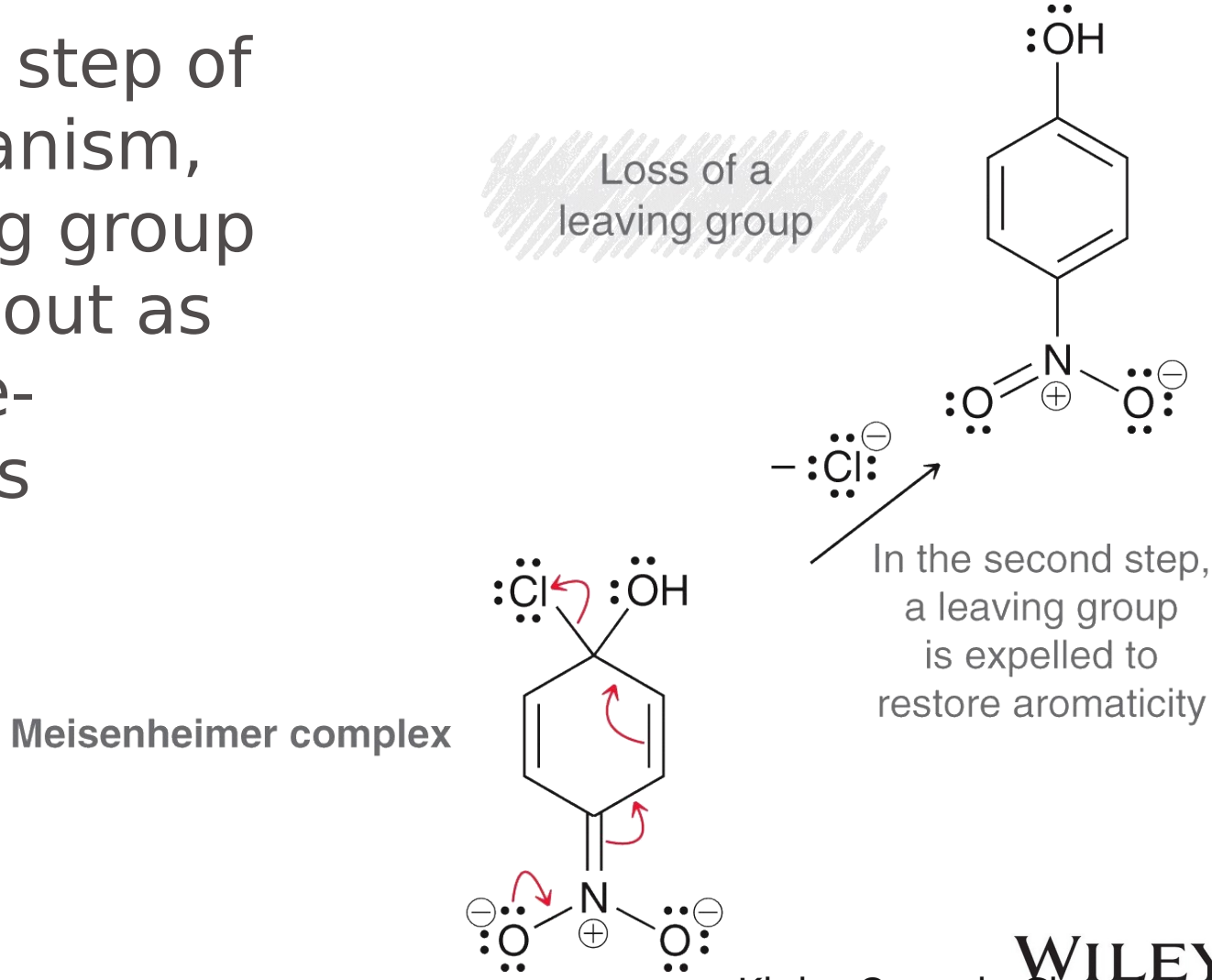


- Draw all of the resonance contributors in the intermediate

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19.13 Nucleophilic Aromatic Substitution

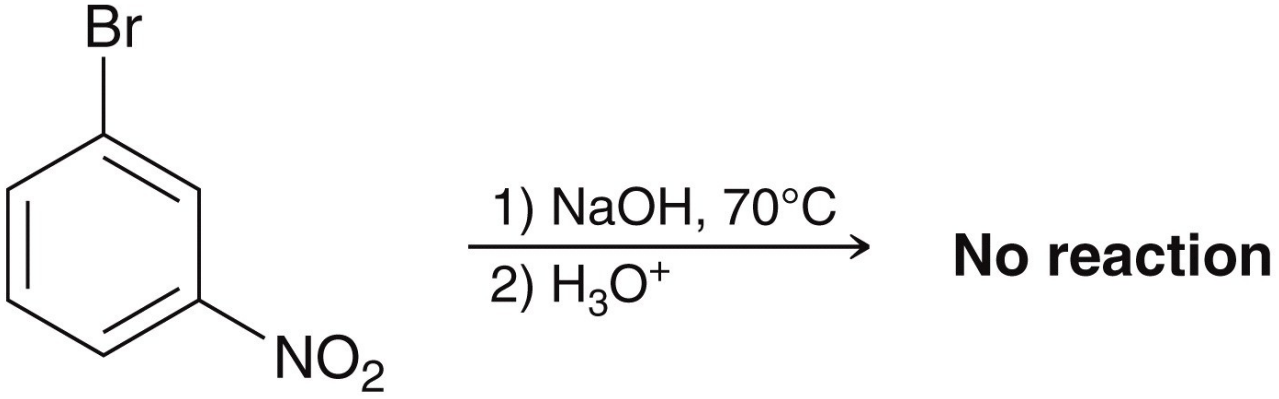
- In the last step of the mechanism, the leaving group is pushed out as the ring re-aromatizes



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19.13 Nucleophilic Aromatic Substitution

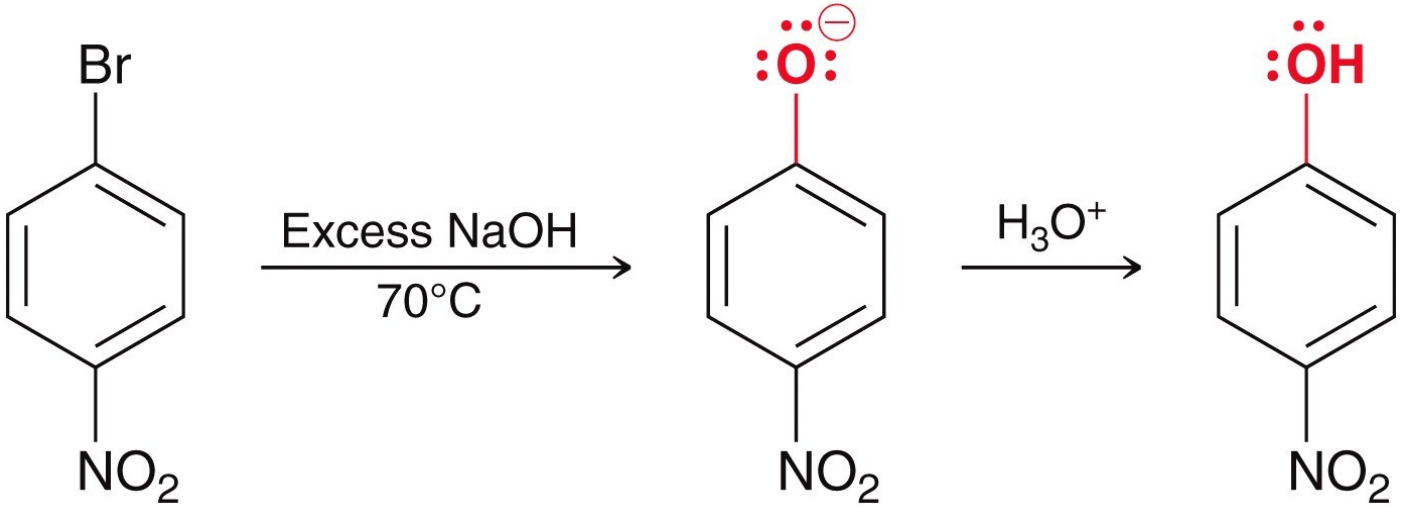
- How would the stability of the transition state and intermediate differ for the following molecule?



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19.13 Nucleophilic Aromatic Substitution

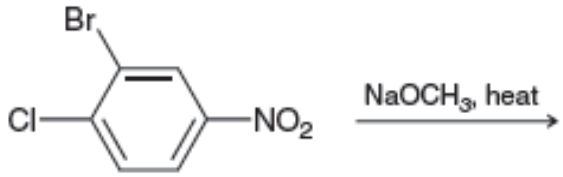
- The excess hydroxide that is used to drive the reaction forward will deprotonate the phenol, so acid must be used after the NAS st



- Practice with conceptual checkpoints 19.35 through 19.37

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19.35 Predict the product of the following reaction:



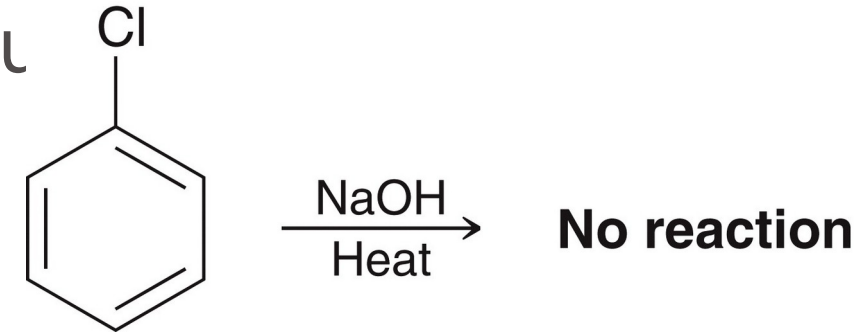
19.36 Starting with benzene and using any other necessary reagents of your choice, design a synthesis for the following compound:



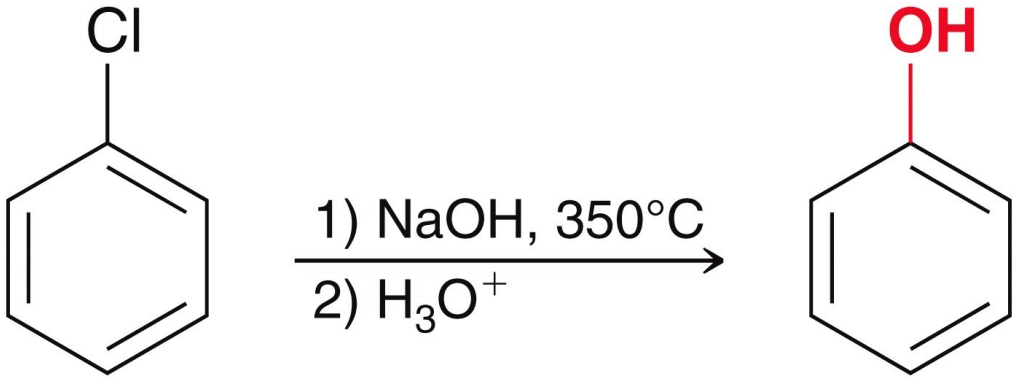
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19.14 Elimination Addition

- Without the presence of a strong electron withdrawing group, mild NAS conditions will not produ



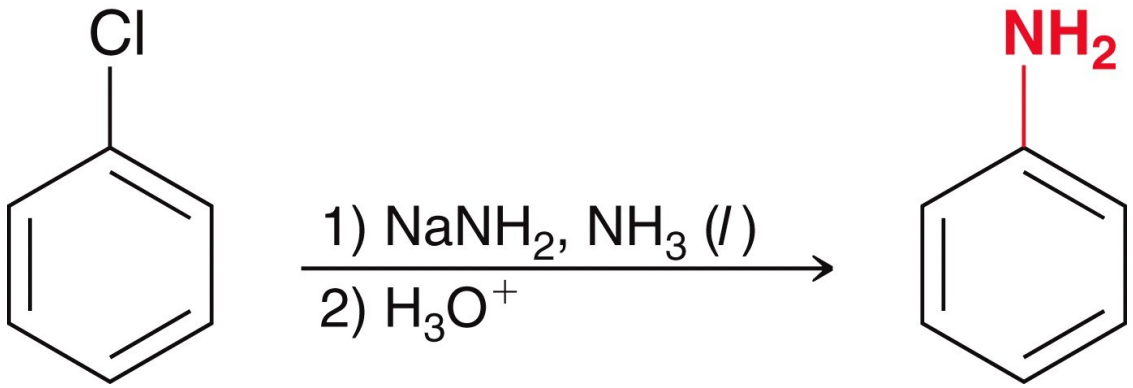
- Significantly harsher conditions are required



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19.14 Elimination Addition

- The reaction works even better when a stronger nucleophile is used

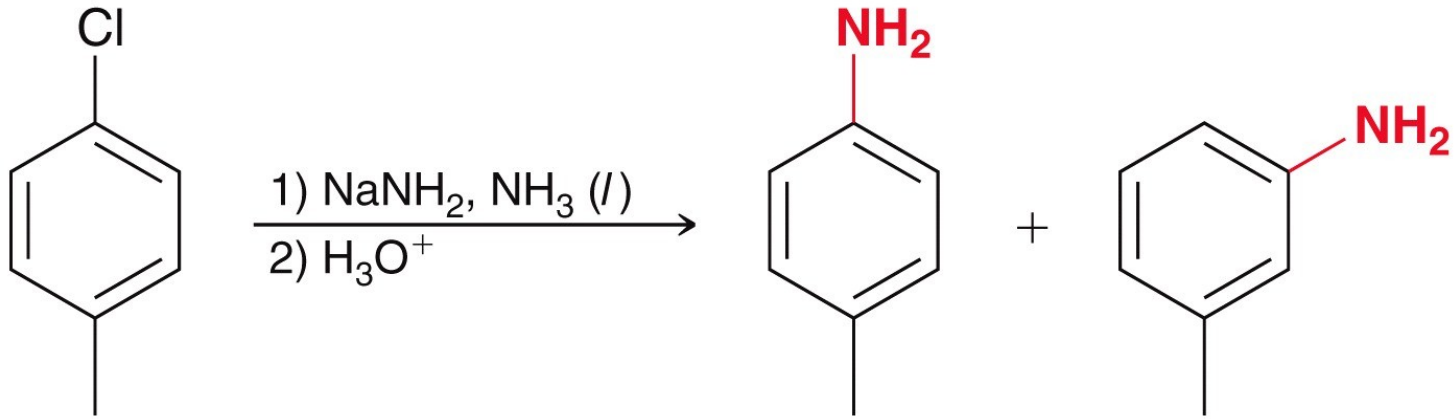


- Why is NH_2^- a stronger nucleophile than OH^-?

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19.14 Elimination Addition

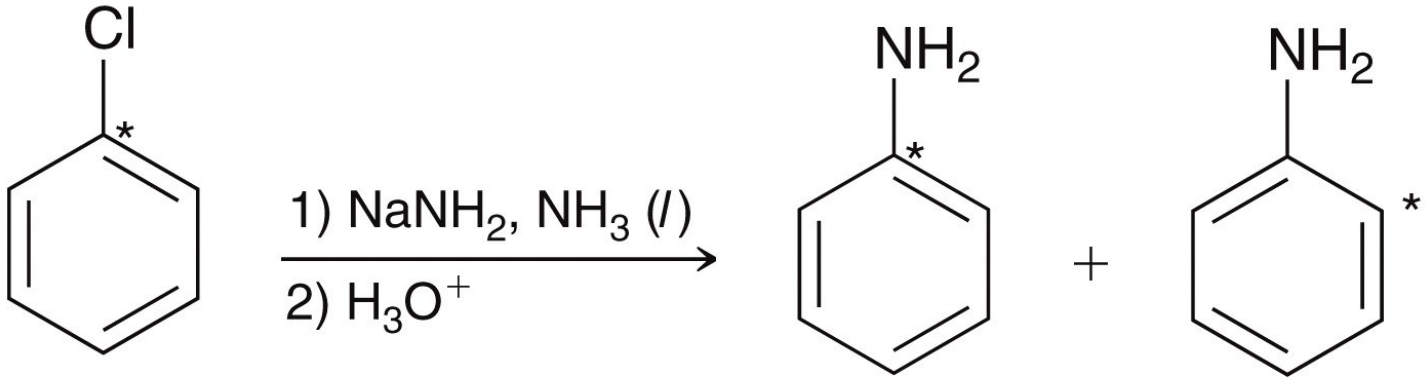
- Consider the substitution reaction using tc



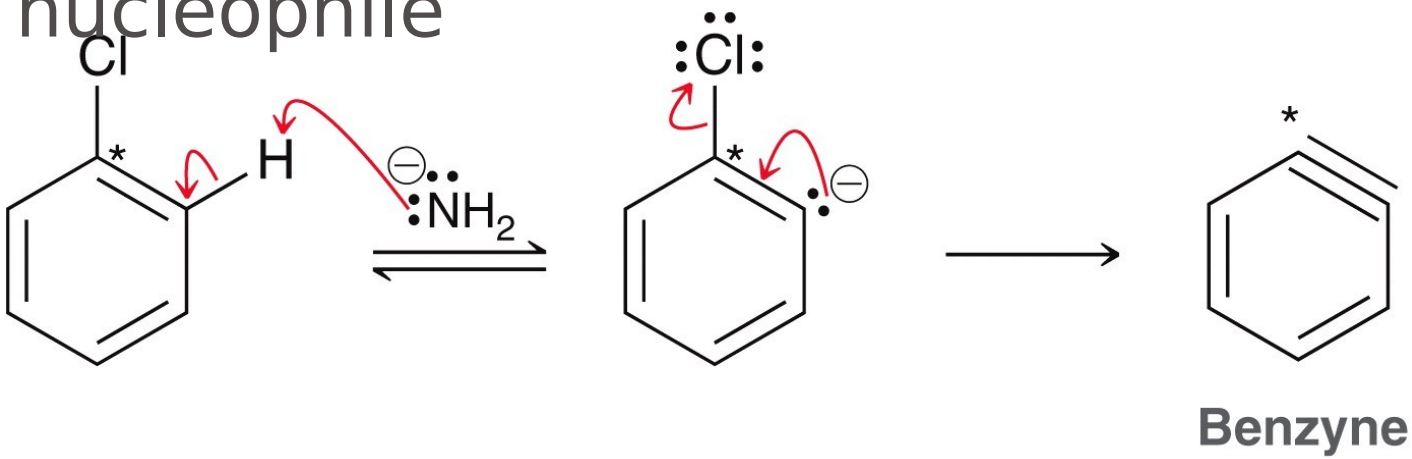
- The product regioselectivity cannot be explained using the NAS mechanism we discussed previously
- Isotopic labeling can help to elucidate the mechanism – see next slide

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19.14 Elimination Addition



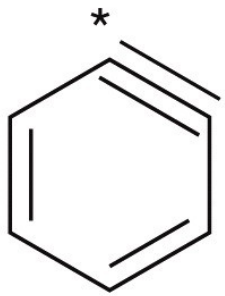
- The C* is a ^{14}C label
- The NH_2^- first acts as a base rather than as a nucleophile



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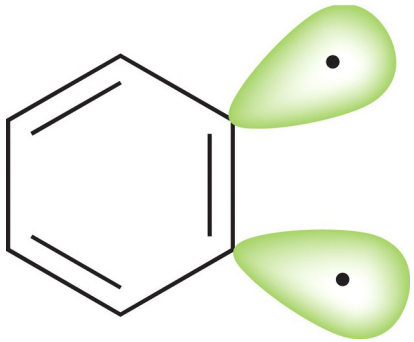
19.14 Elimination Addition

- The benzyne intermediate is a short-lived unstable intermediate
- Does a 6-membered ring allow for sp hybridized carbons?



Benzyne

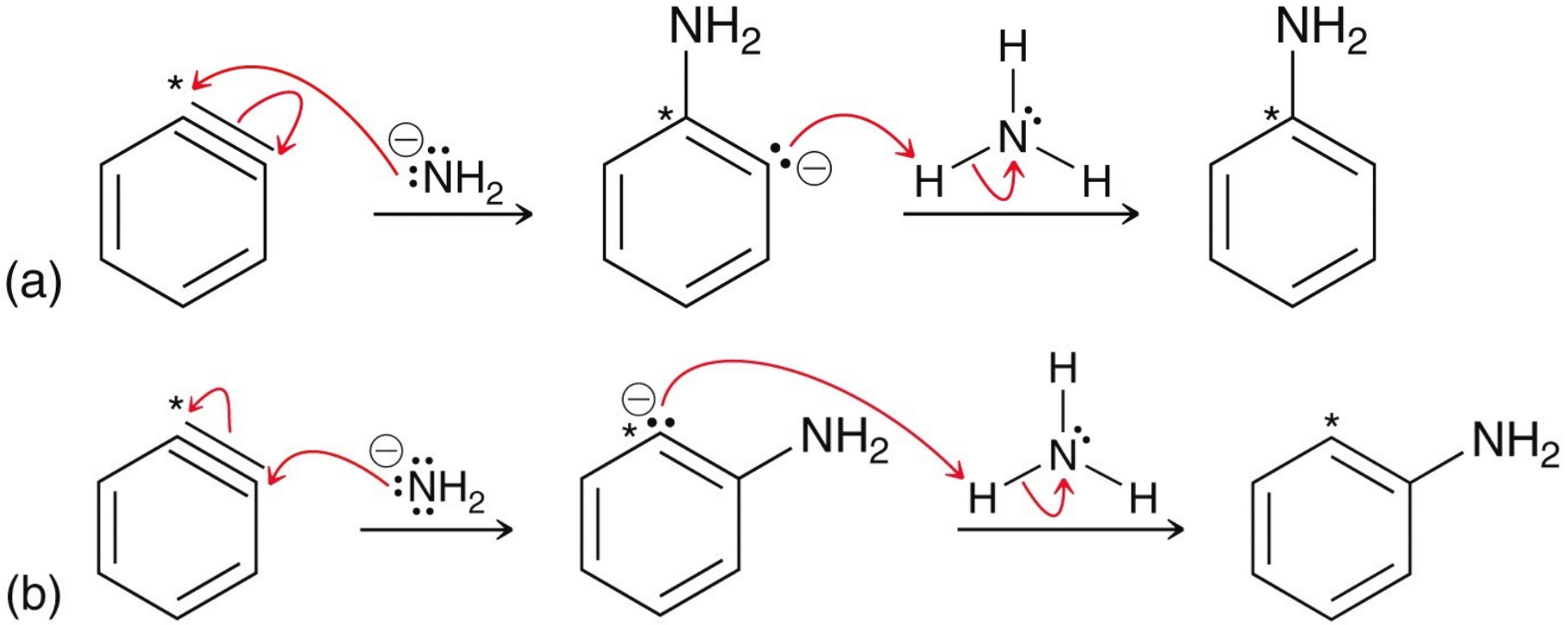
- The benzyne triple bond resembles more closely an sp^2-sp^2 overlap than it resembles a p-p overlap



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19.14 Elimination Addition

- A second molecule of NH_2^- acts as a nucleophile by attacking either side of the

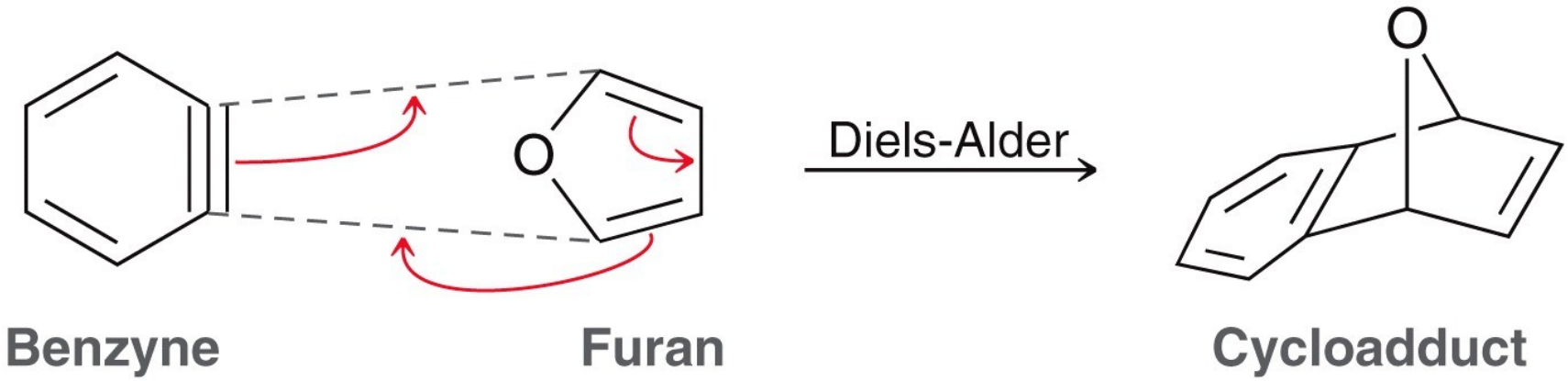


- Does NH_2^- act as a catalyst?

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19.14 Elimination Addition

- Further evidence for the existence of the benzyne intermediate can be seen when the benzyne is allowed to react with a diene via a Diels-Alder reaction



- Practice with conceptual checkpoint 19.38 and 19.39

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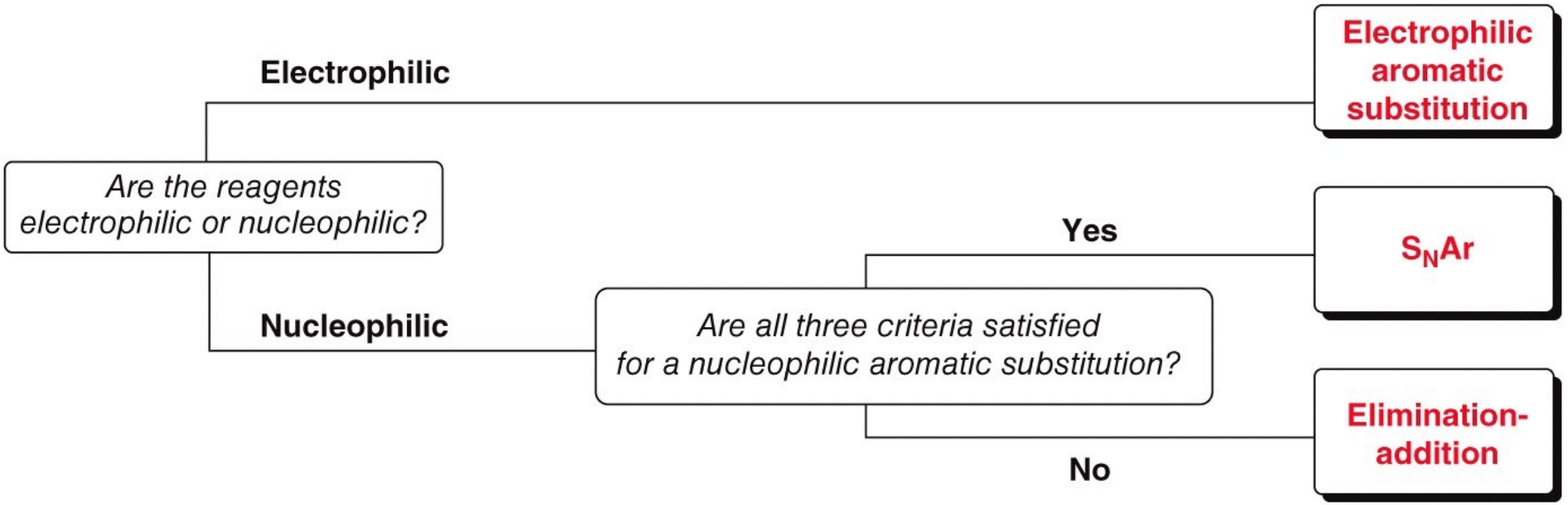
19.38 Draw both products that are obtained when 4-chloro-2-methyltoluene is treated with sodium amide followed by treatment with H_3O^+.

19.39 Starting with benzene and using any other necessary reagents of your choice, design a synthesis for anisole (methoxybenzene).

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19.15 Identifying the Mechanism of an Aromatic Substitution Reaction

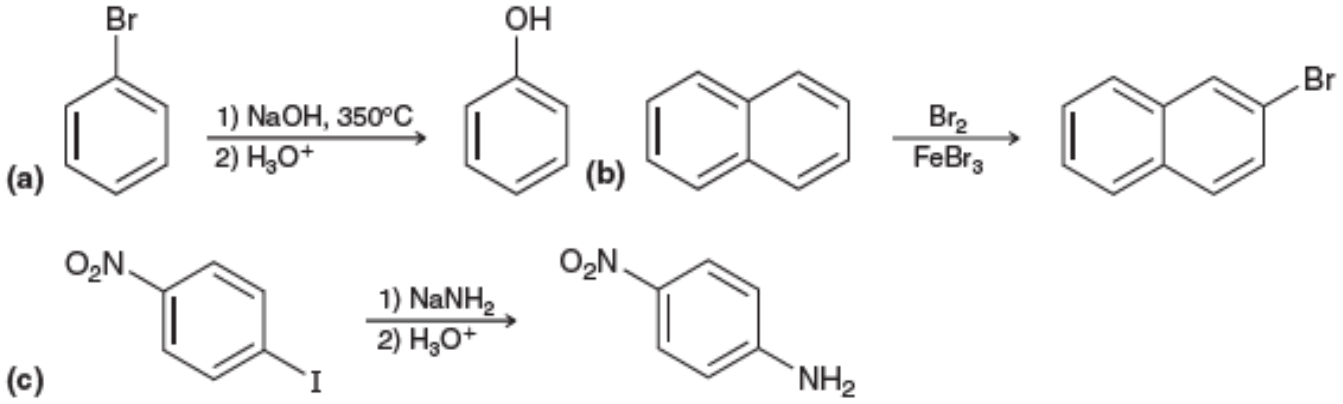
- The flow chart below can be used to identify the proper substitution mechanism



- Practice with SkillBuilder 19.7

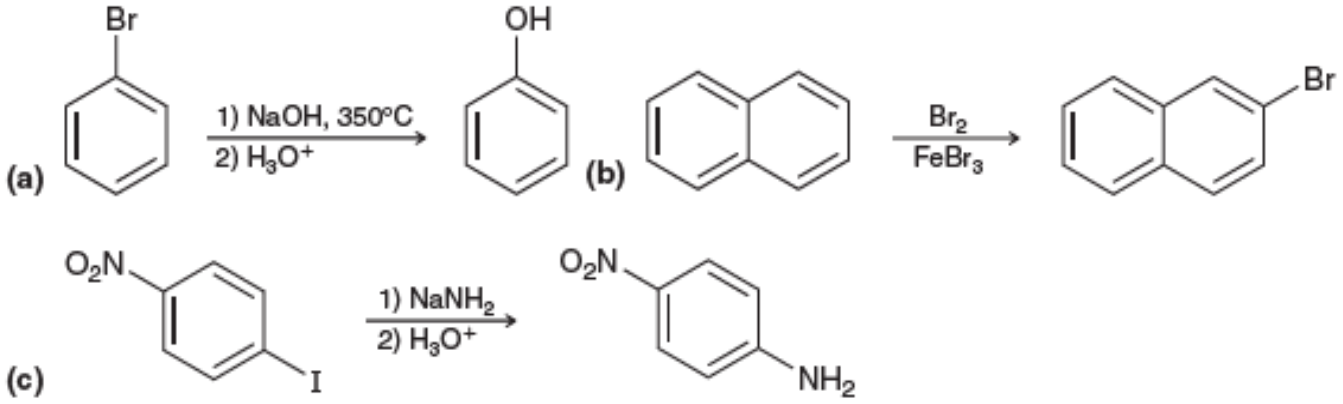
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19.40 Draw the most likely mechanism for each of the following transformations:



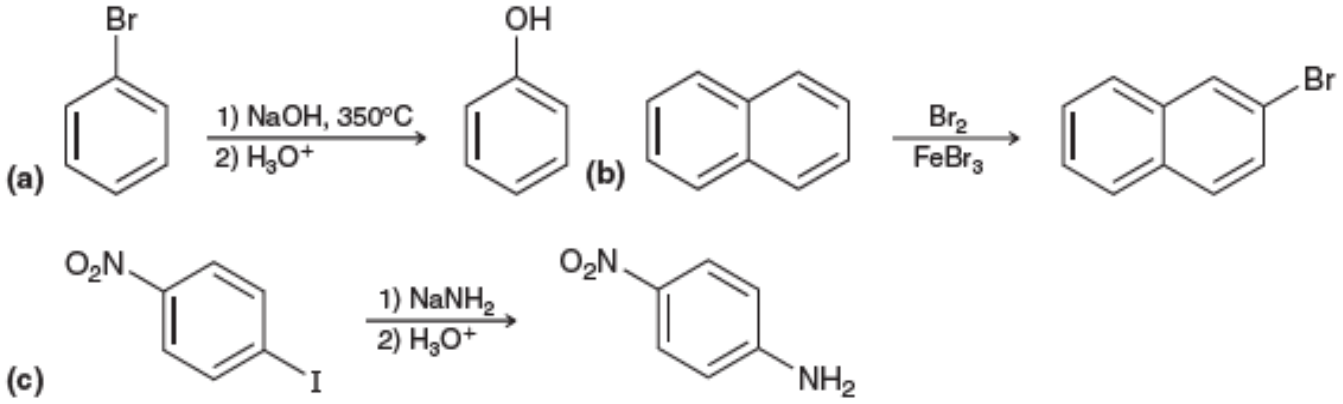
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19.40 Draw the most likely mechanism for each of the following transformations:



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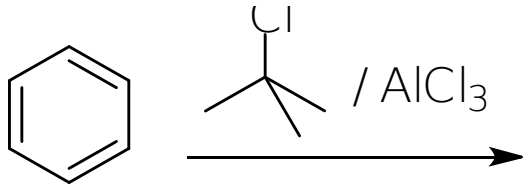
19.40 Draw the most likely mechanism for each of the following transformations:



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Additional Practice Problems

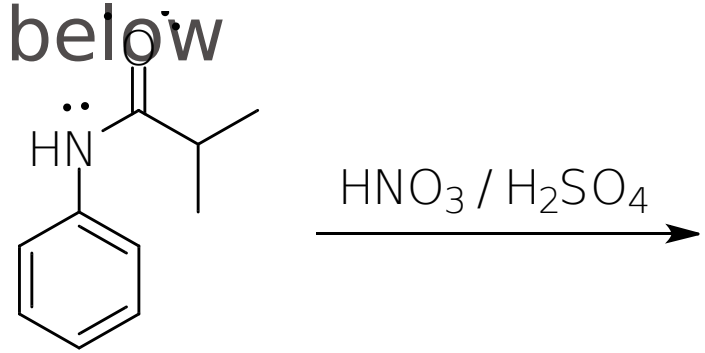
- Give the products for the reaction below and a complete mechanism

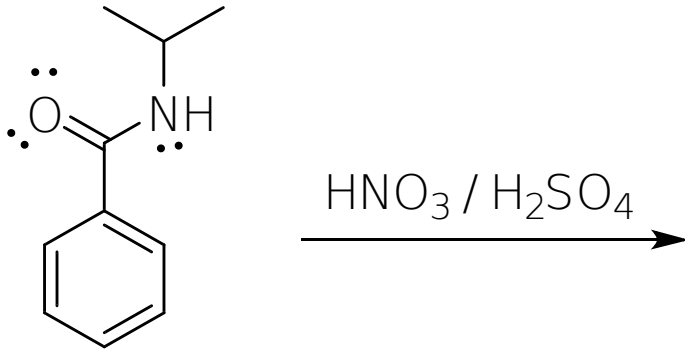


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Additional Practice Problems

- Predict the major product for each reaction below

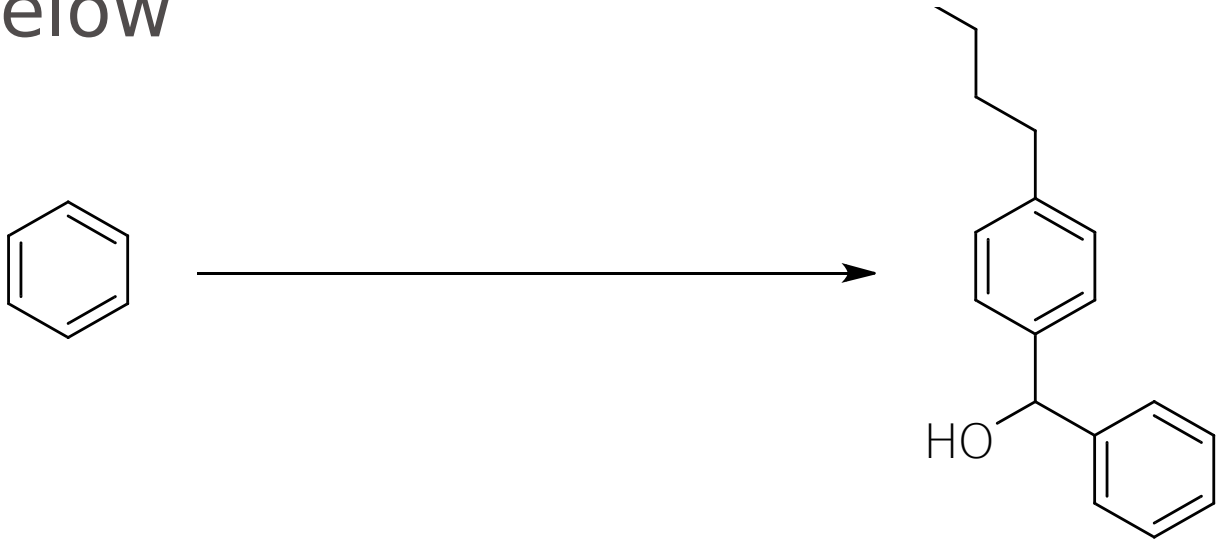




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Additional Practice Problems

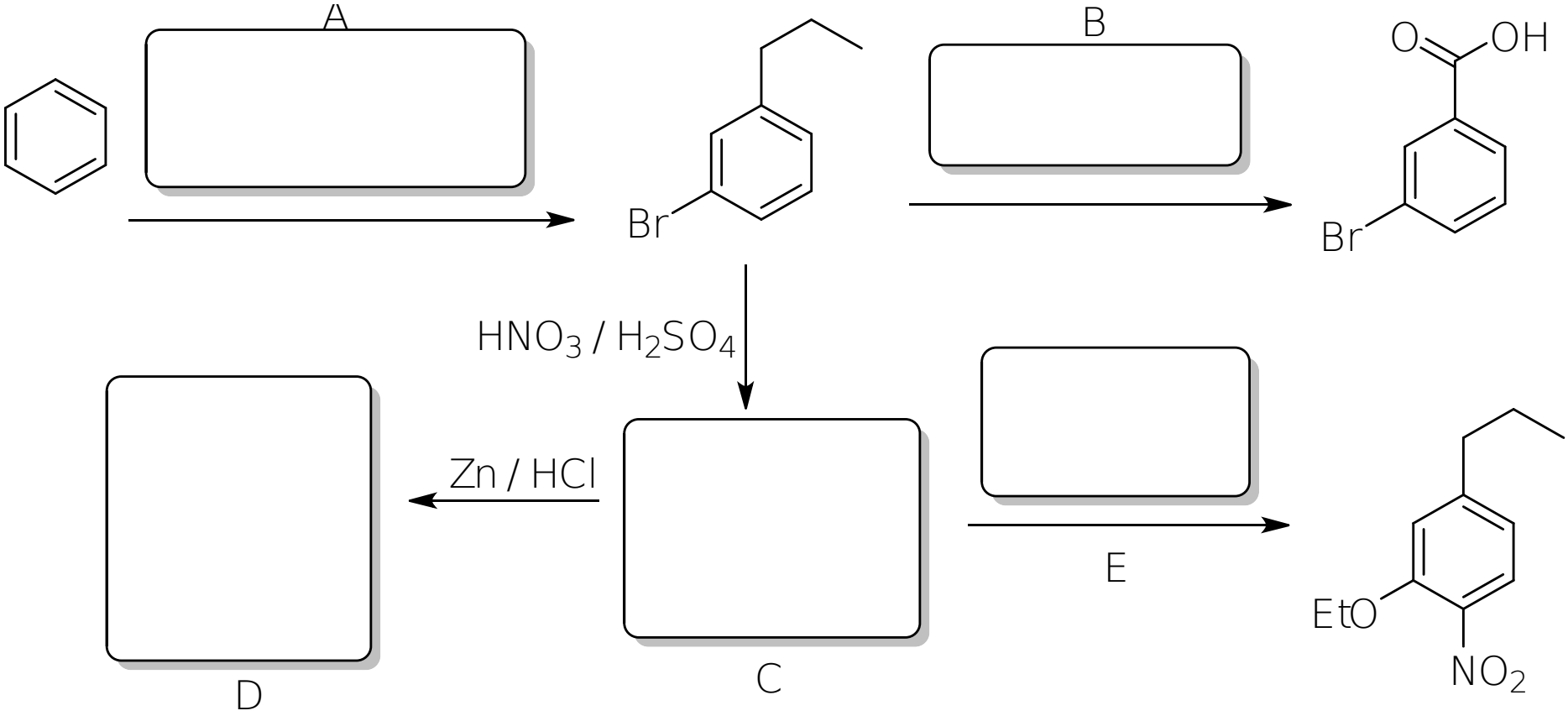
- Give necessary reagents for the synthesis below



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Additional Practice Problems

- Fill in the blanks below



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