WILEY

Organic Chemistry

Third Edition

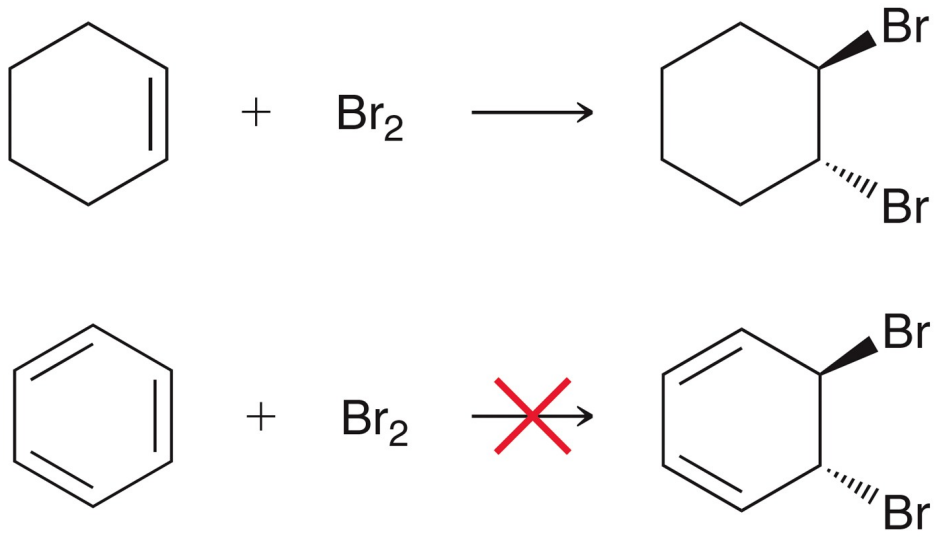
David Klein

Chapter 18

Aromatic Substitution Reactions

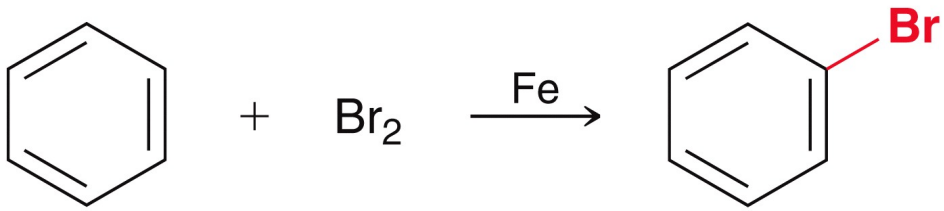
18.1 Electrophilic Aromatic Substitution

- We have already seen how **aromatic π bonds are less reactive** than typical alkenes (chapter 17)



18.1 Electrophilic Aromatic Substitution

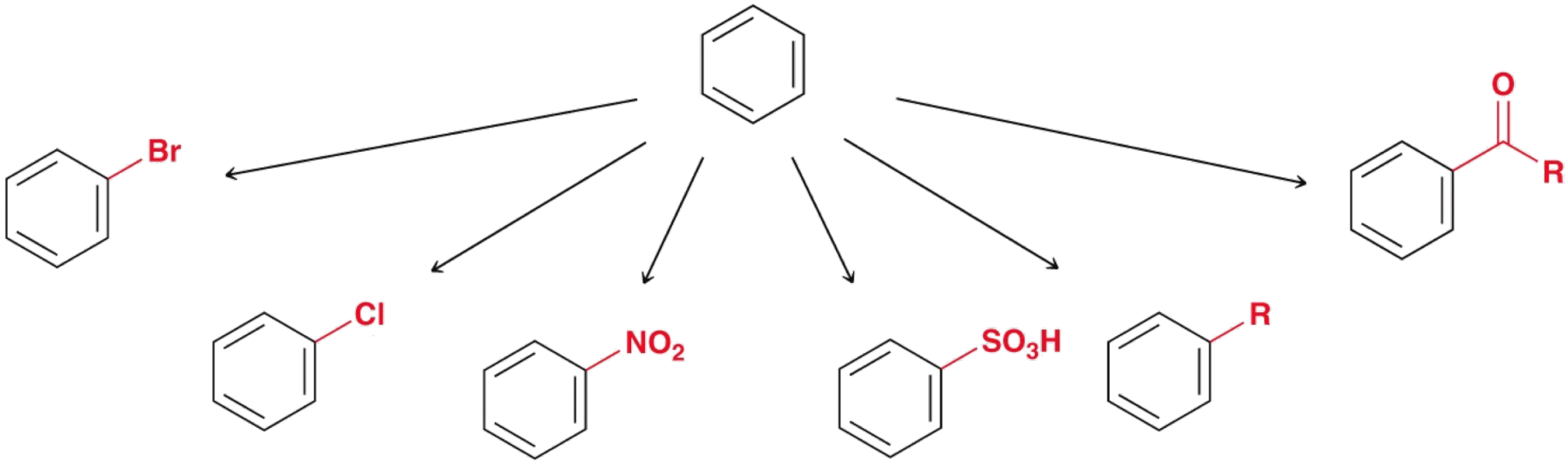
- However, when Fe is introduced, a **substitution reaction** occurs



- The observed reaction is **Electrophilic Aromatic Substitution**

18.1 Electrophilic Aromatic Substitution

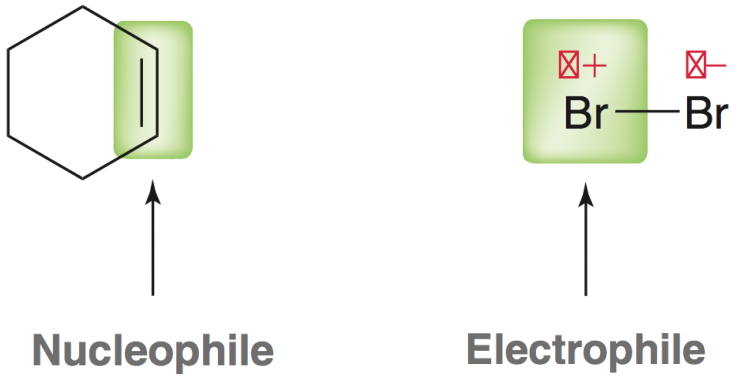
- **Electrophilic Aromatic Substitution (EAS) –** an aromatic proton is replaced by an electrophile
- The ring acts as the nucleophile



- the aromaticity of the ring is preserved

18.2 Halogenation

- In bromination of an alkene (chapter 8.9), **Br_2 functions as an electrophile**



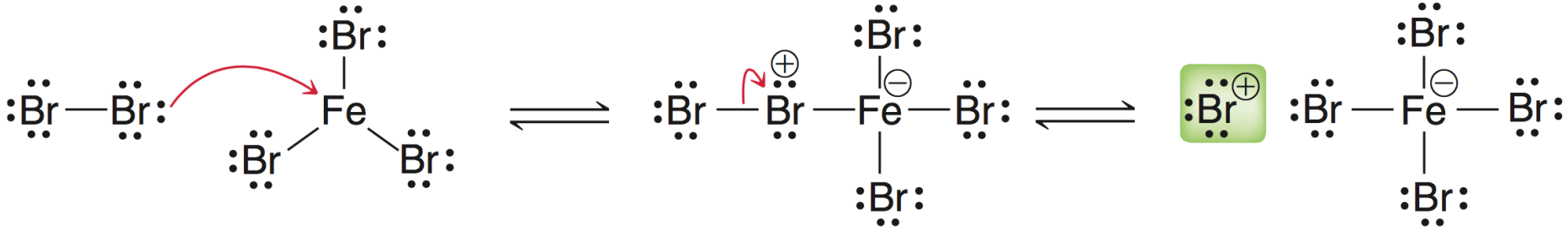
- A Lewis acid catalyst is needed to make Br_2 electrophilic enough to be attacked by the more stable p electrons of an aromatic ring

$$2\ Fe + 3\ Br_2 \longrightarrow 2\ FeBr_3$$

Lewis acid catalyst

18.2 Halogenation

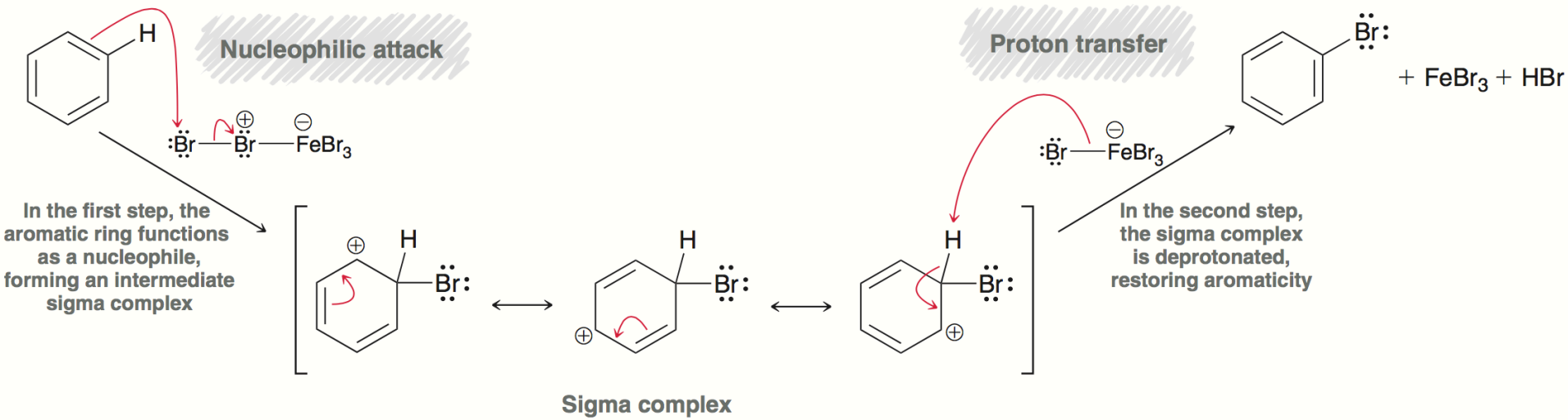
- FeBr3 activates the Br2, making it even more electron-poor (i.e. more electrophilic)



More potent electrophile

18.2 Halogenation

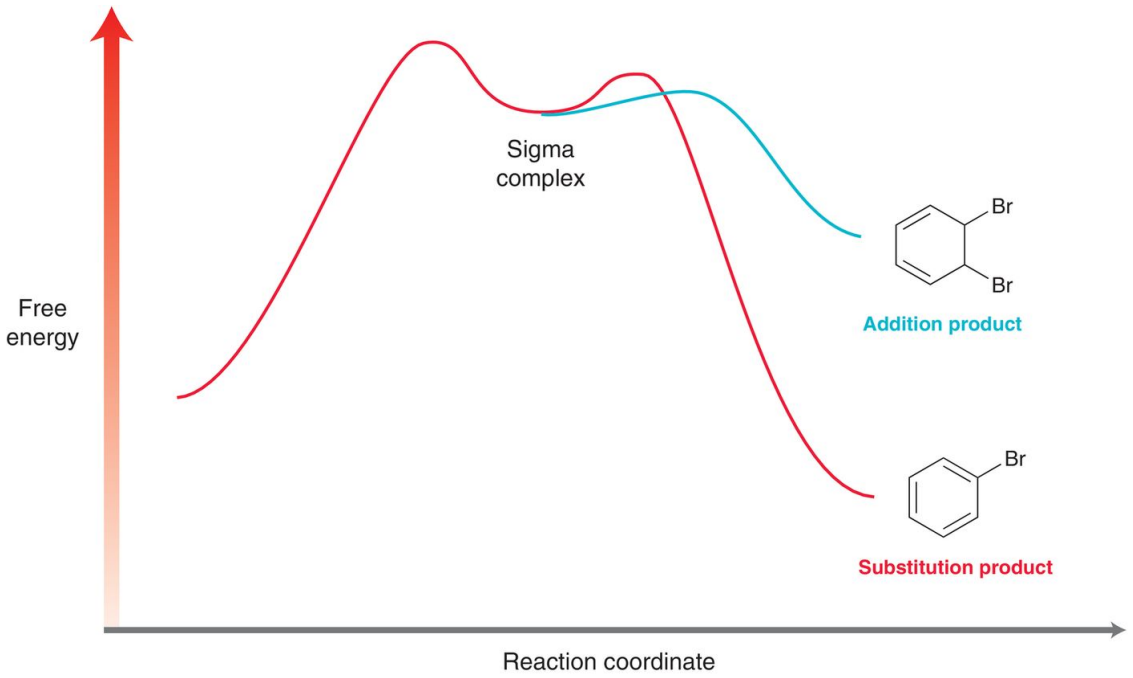
- Bromination of benzene mechanism:



- **Step 1** – aromatic ring attacks the electrophile; sigma complex intermediate is formed
- **Step 2** – deprotonation of the sigma complex (rearomatization)

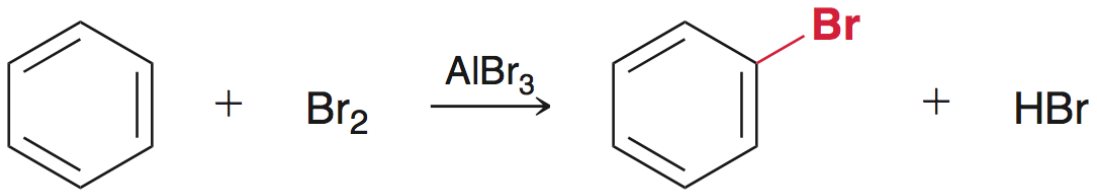
18.2 Halogenation

- **Addition reaction** to an aromatic ring would be **endergonic**, which is why **substitution is observed** instead.



18.2 Halogenation

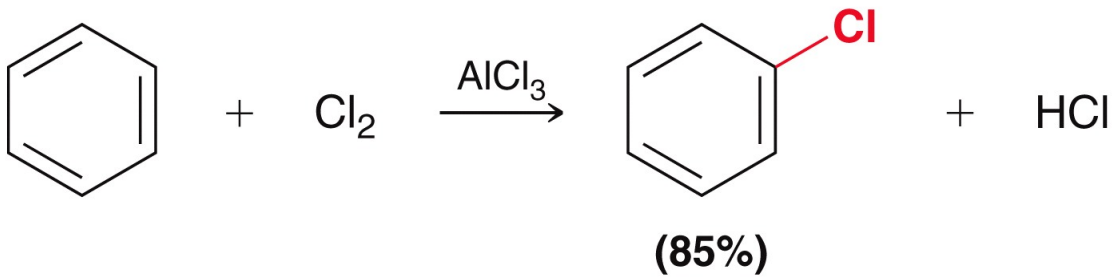
- Aluminum tribromide could also be used as the Lewis acid catalyst for bromination of benzene:



- The mechanism of bromination would be the same as when $FeBr_3$ is used

18.2 Halogenation

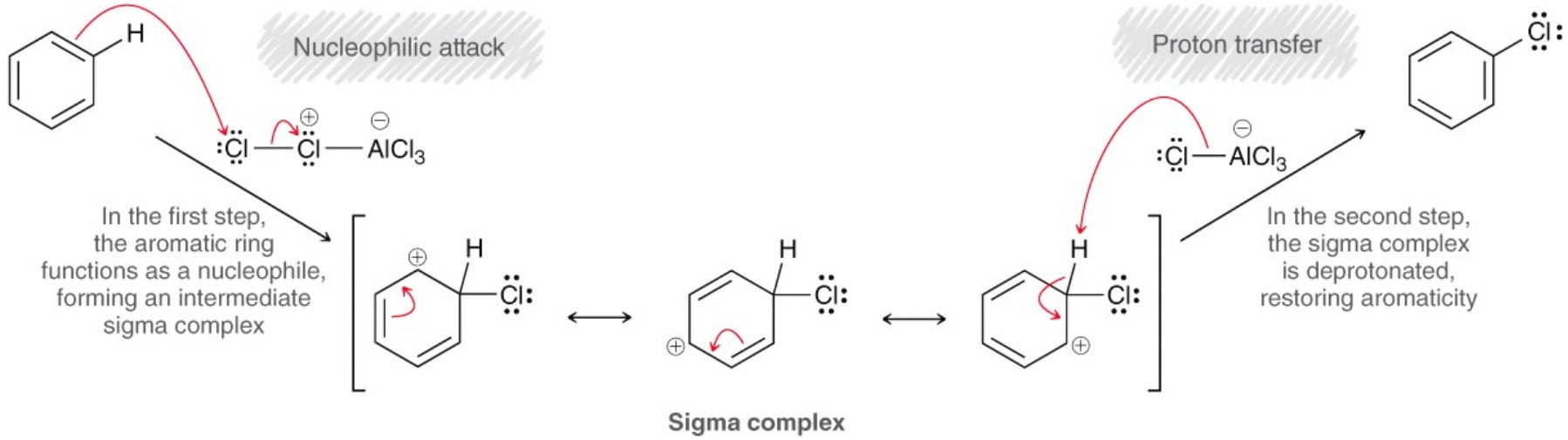
- Benzene can also undergo chlorination by using Cl_2 instead of Br_2



- Using F_2 or I_2 does not work well:
  - Fluorination too violent to be practical
  - iodination is generally slow with low yields

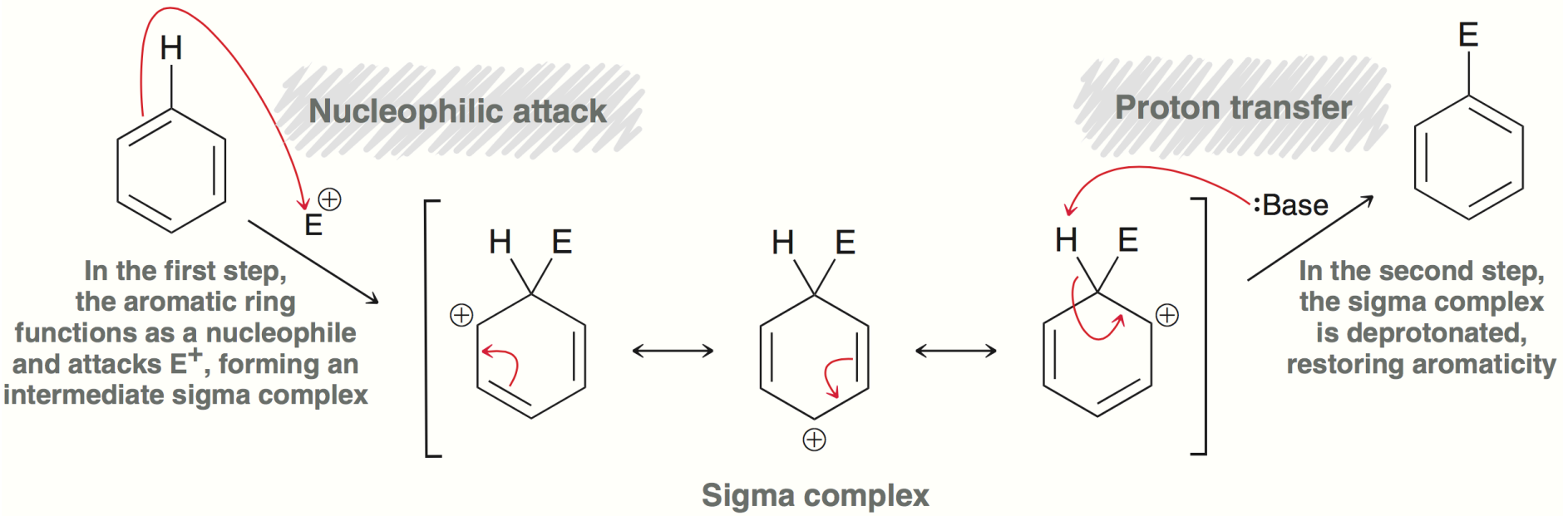
18.2 Halogenation

- Note the EAS mechanism for chlorination is analogous to bromination



18.2 Halogenation

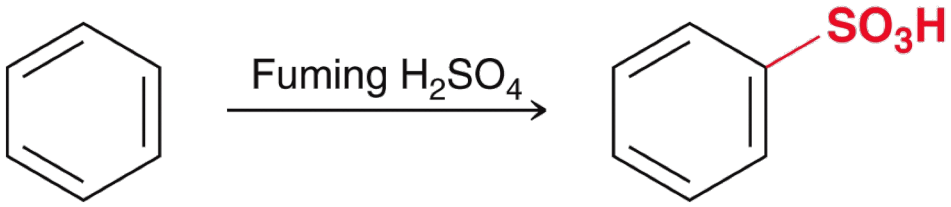
- In fact, all EAS reactions discussed in this chapter follow the same 2-step mechanism:



- **Practice with Conceptual Checkpoint 18.1**

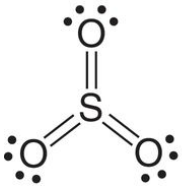
18.3 Sulfonation

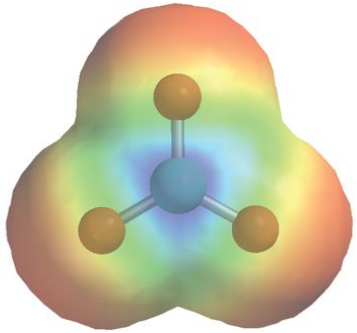
- **Sulfonation** occurs by using **SO_3** as the **electrophile**, and **H_2SO_4** as the **acid catalyst**:



(95%)

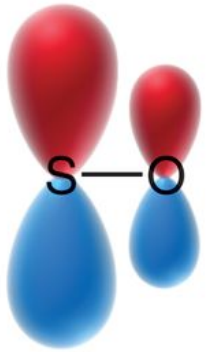
- Fuming H_2SO_4 contains SO_3 (gas)





18.3 Sulfonation

- SO_3 is a potent electrophile; the sulfur atom has a significant partial positive charge due to inefficient π overlap with the oxygen atoms:

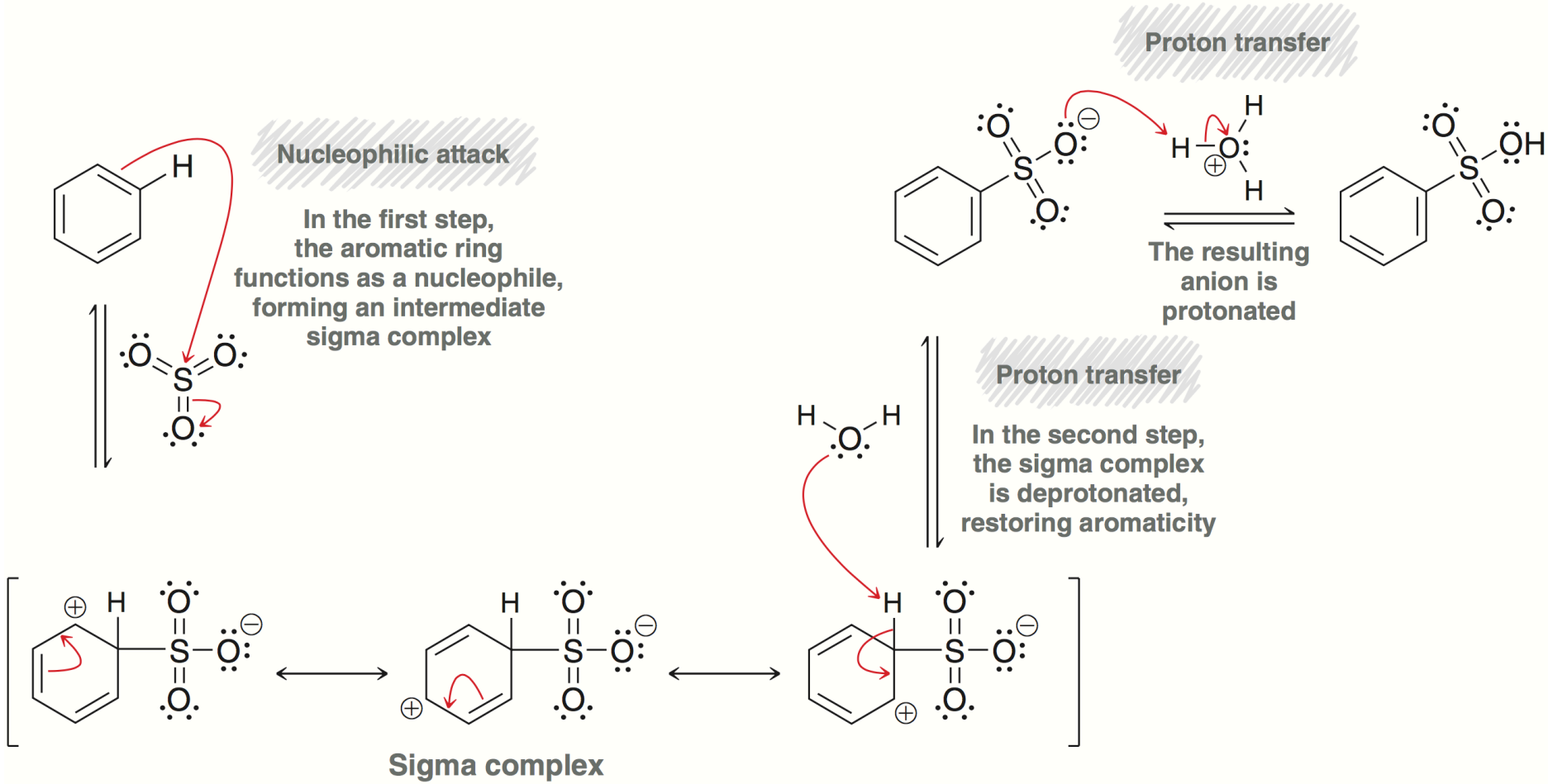


Inefficient overlap

- As a result, the S-O bond has significant single-bond character

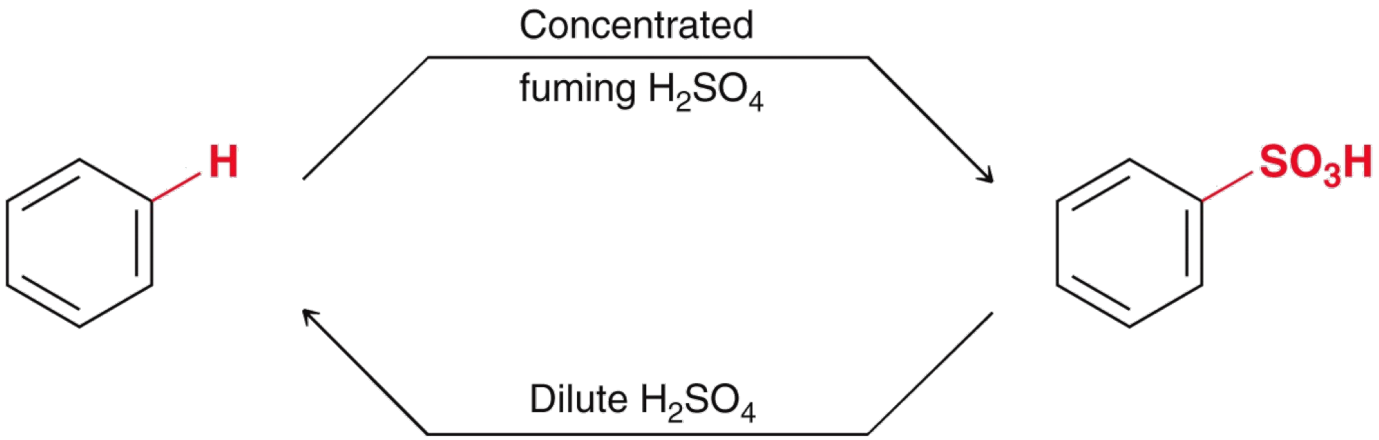
18.3 Sulfonation

- Sulfonation of benzene mechanism:



18.3 Sulfonation

- **Sulfonation** is sensitive to reagent concentration; it **is a reversible process:**

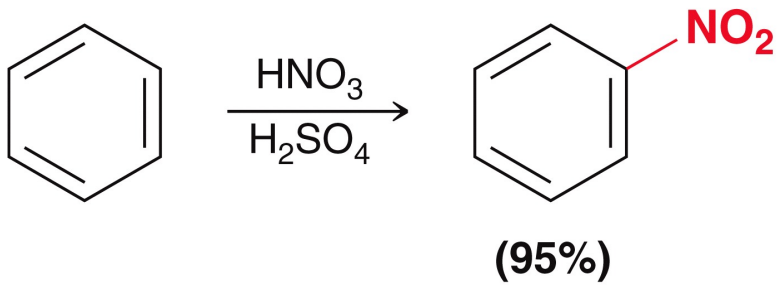


- This process is examined in more detail later in the chapter

- **Practice with Conceptual Checkpoint 18.2 – 18.3**

18.4 Nitration

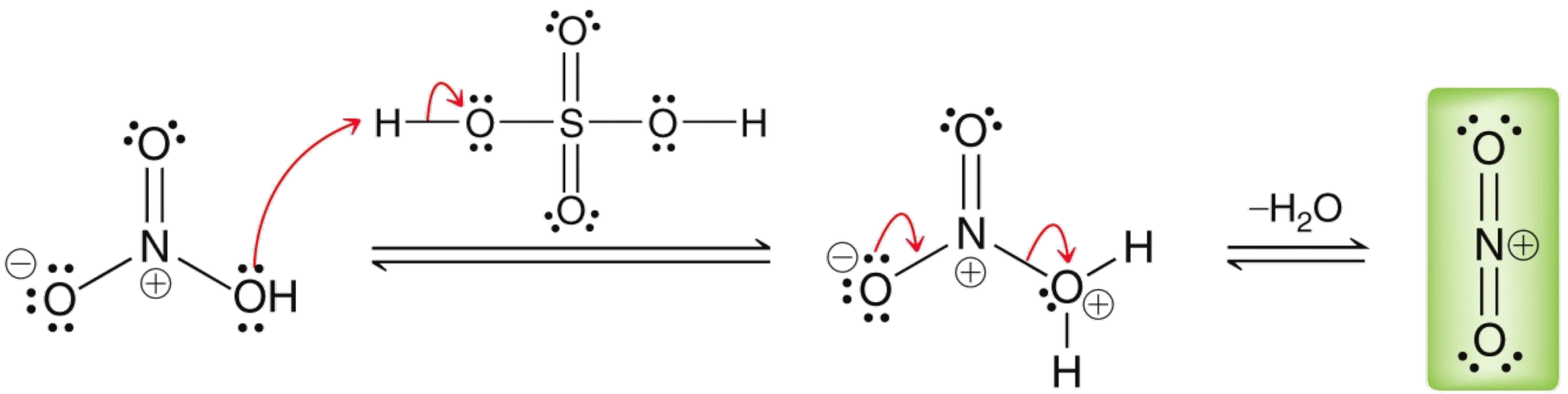
- **Nitration** occurs by using **HNO_3** as the **source of the electrophile**, and **H_2SO_4** as the **acid catalyst**:



- It is believed a **nitronium ion** (NO_2^+)is the **active electrophile**

18.4 Nitration

- It is believed a **nitronium ion** (NO_2^+)is the **active electrophile**

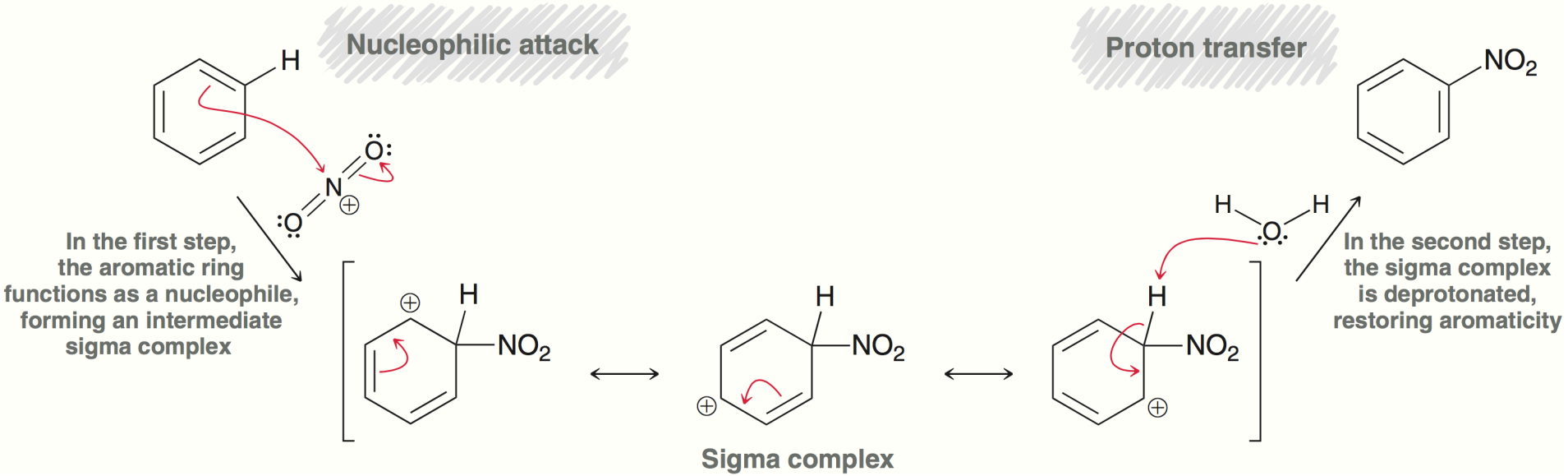


Active electrophile

- The nitronium ion is highly electrophilic

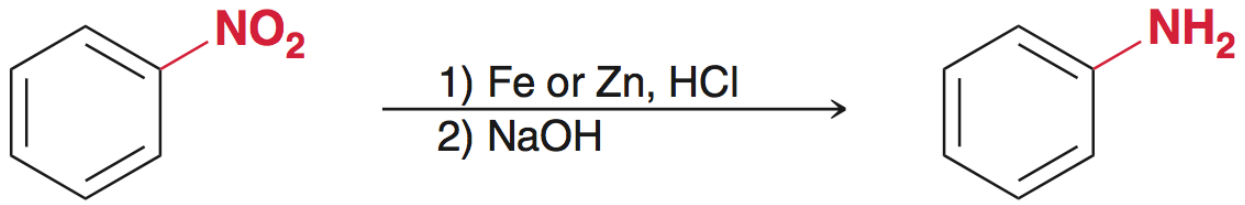
18.4 Nitration

- Nitration of benzene mechanism:

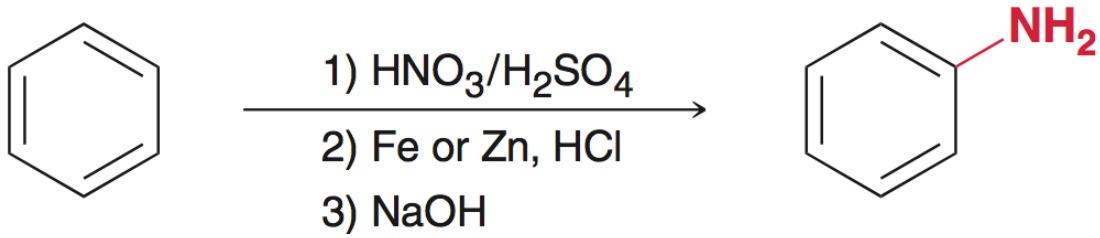


18.4 Nitration

- A nitro group can be reduced to form an amine



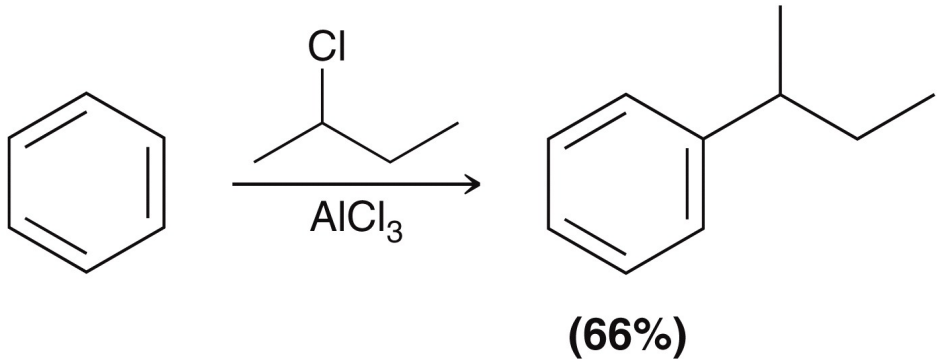
- Combining these reactions gives a general process for installing an amino group on a benzene ring:



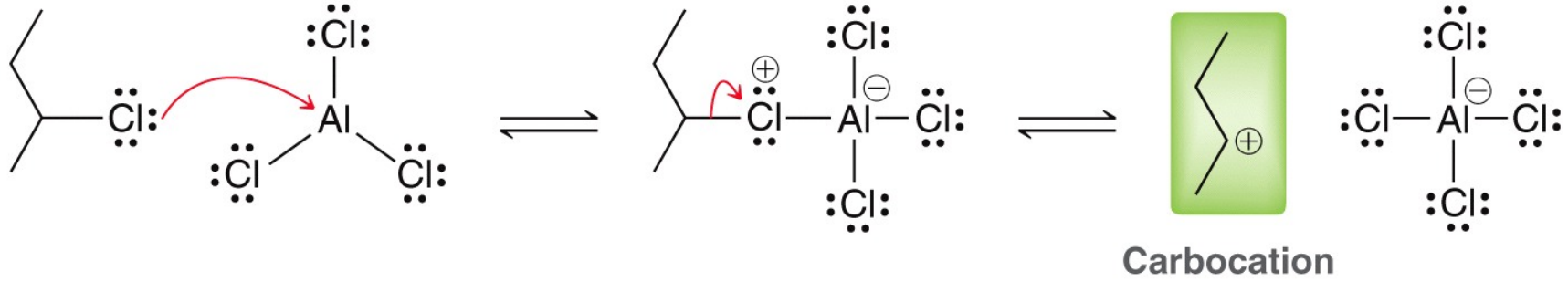
- **Practice with Conceptual Checkpoint 18.4**

18.5 Friedel-Crafts Alkylation

- **Alkylation** occurs by using an **alkyl halide** as the **electrophile** and **$AlCl_3$** as the Lewis **acid catalyst**

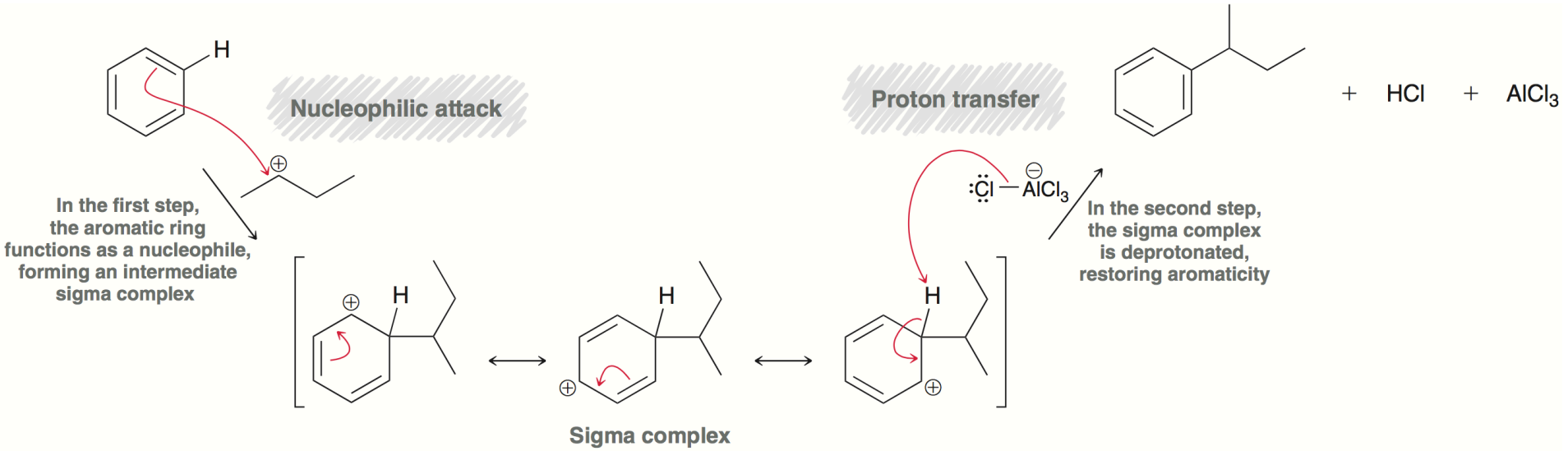


- The catalyst functions as expected:



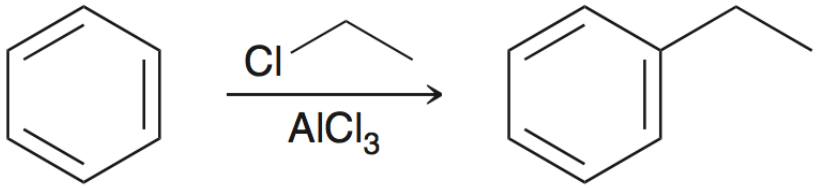
18.5 Friedel-Crafts Alkylation

- **Alkylation** mechanism:

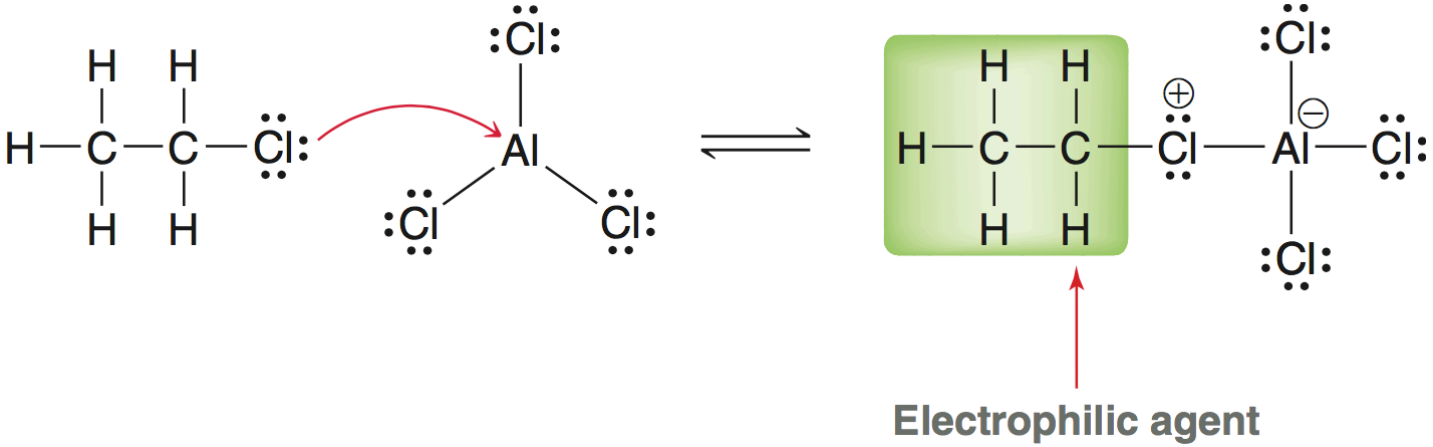


18.5 Friedel-Crafts Alkylation

- Simple 1˚ halides can be used effectively:

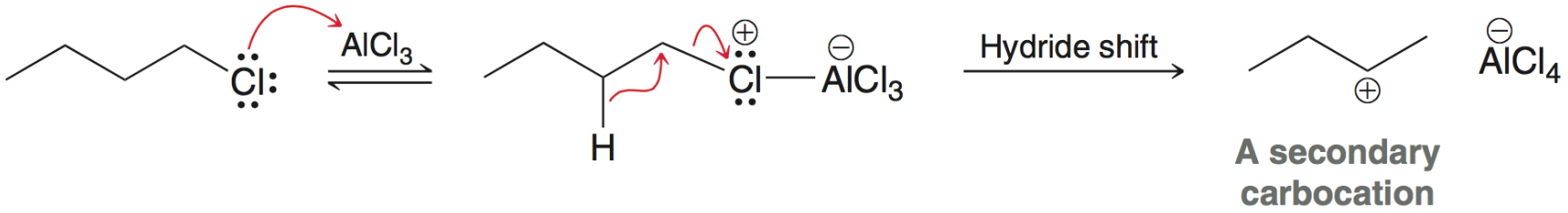


- Since 1˚ carbocations cannot form, the electrophile is presumed to be a complex:

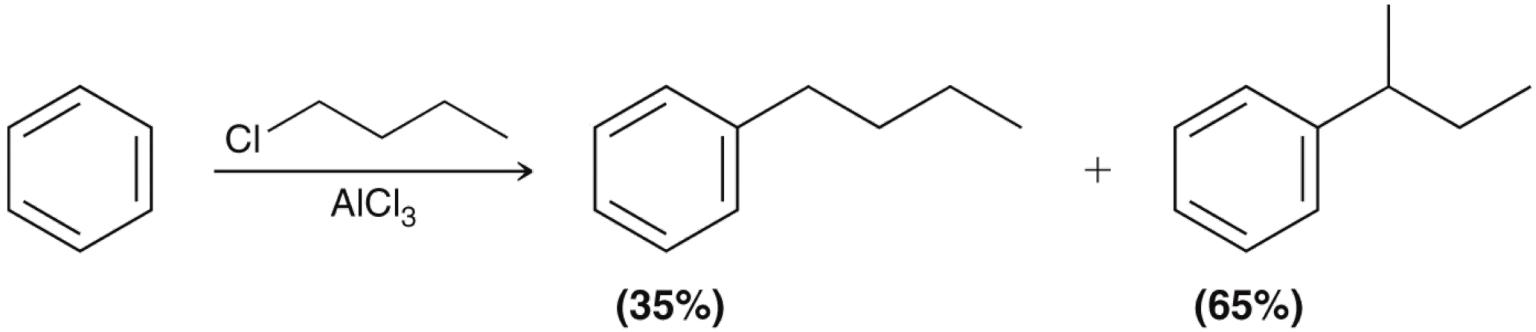


18.5 Friedel-Crafts Alkylation

- However, most 1˚ alkyl halides are susceptible to rearrangement…



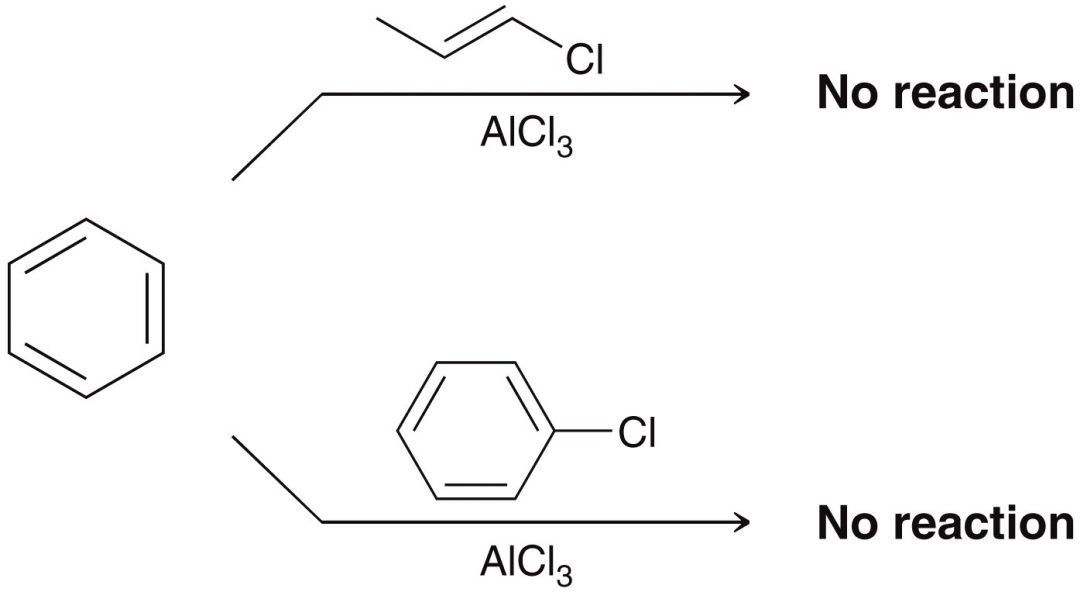
… and give rearranged products:



18.5 Friedel-Crafts Alkylation

- There are three other limitations to Friedel-Crafts alkylation:

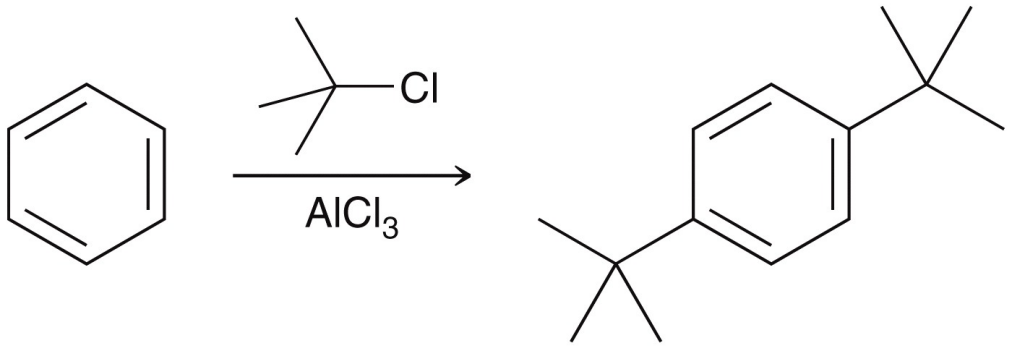
1. The halide leaving group must be attached to an sp^3 hybridized carbon



18.5 Friedel-Crafts Alkylation

- There are three other limitations to Friedel-Crafts alkylation:

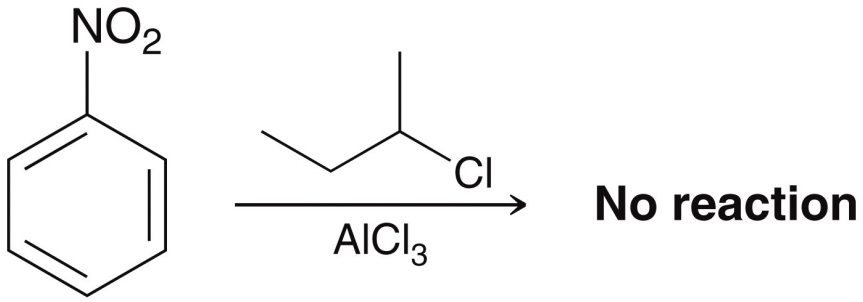
2. Polyalkylation often results



18.5 Friedel-Crafts Alkylation

- There are three other limitations to Friedel-Crafts alkylation:

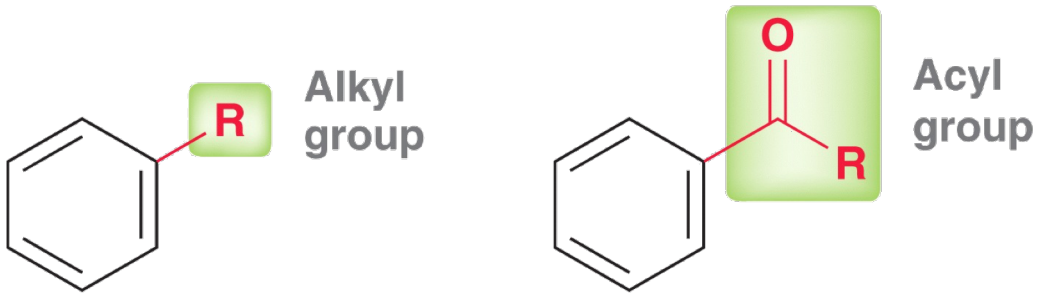
3. Some substituted aromatic rings such as nitrobenzene are too deactivated to react



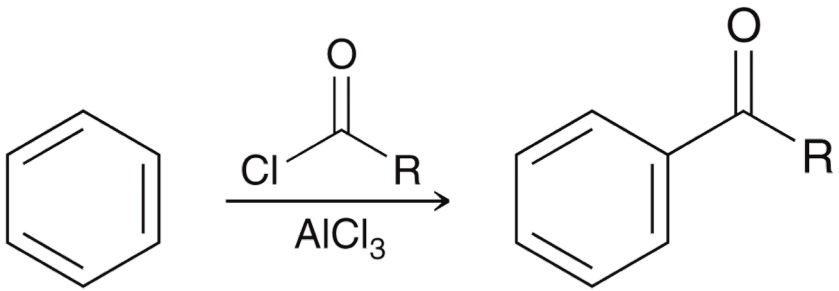
- **Practice with Conceptual Checkpoints 18.5, 18.6, and 18.7**

18.6 Friedel-Crafts Acylation

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

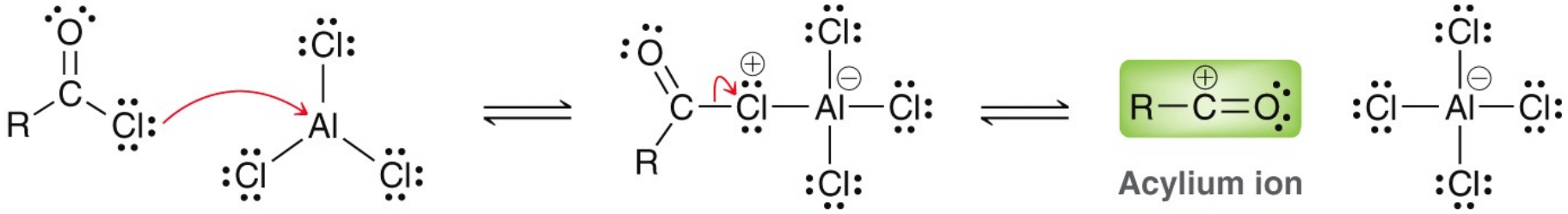


- Acylation reactions are also catalyzed by $AlCl_3$ as the Lewis acid



18.6 Friedel-Crafts Acylation

- The **active electrophile** is an **acylium ion**



18.6 Friedel-Crafts Acylation

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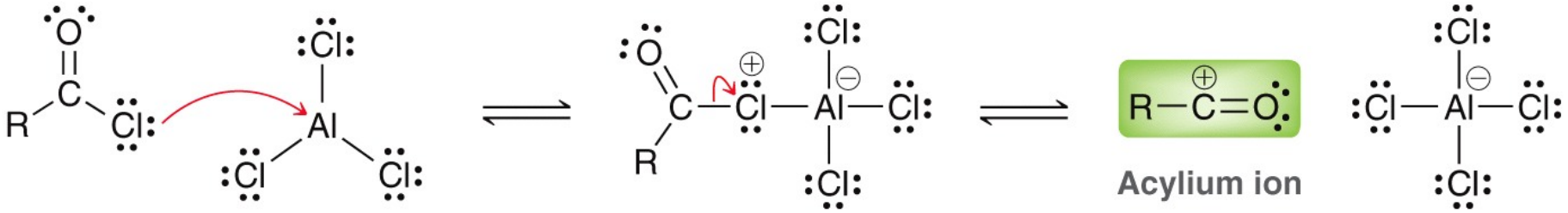
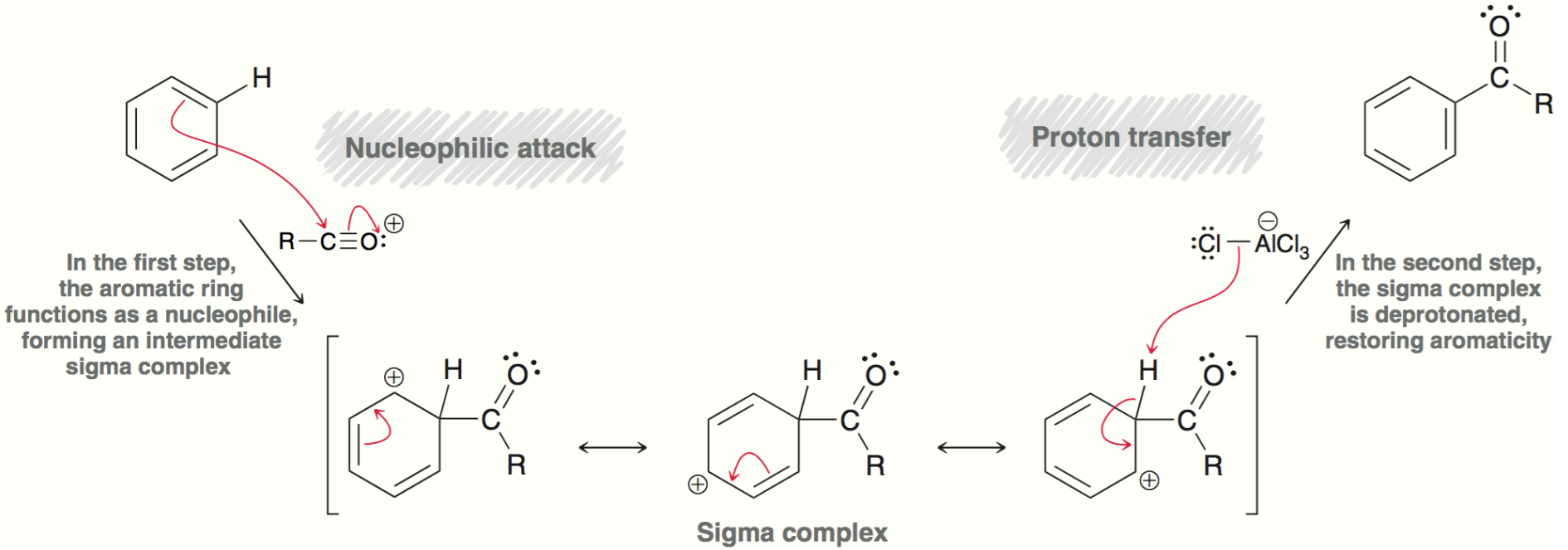


- Acylium ions are resonance stabilized, and not subject to rearrangement:

18.6 Friedel-Crafts Acylation

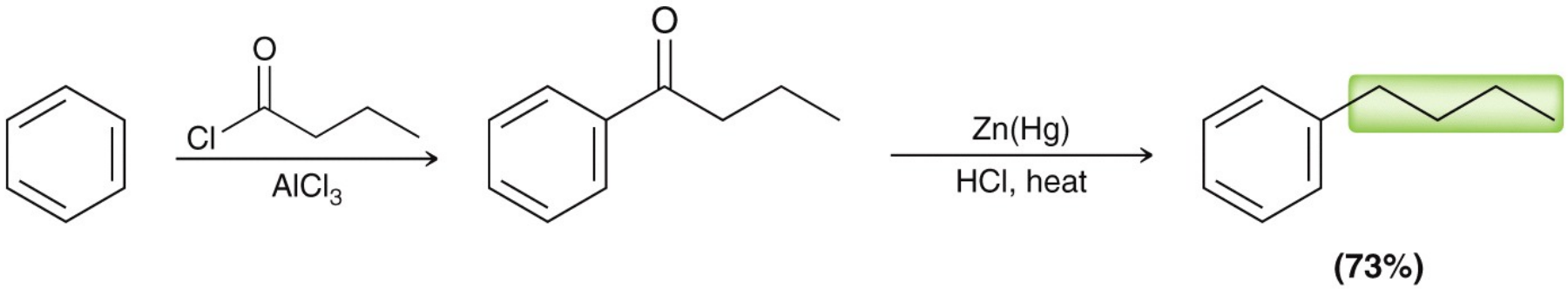
- Acylation mechanism:



18.6 Friedel-Crafts Acylation

- Some alkyl groups cannot be attached to a ring by Friedel-Crafts alkylation because of rearrangements

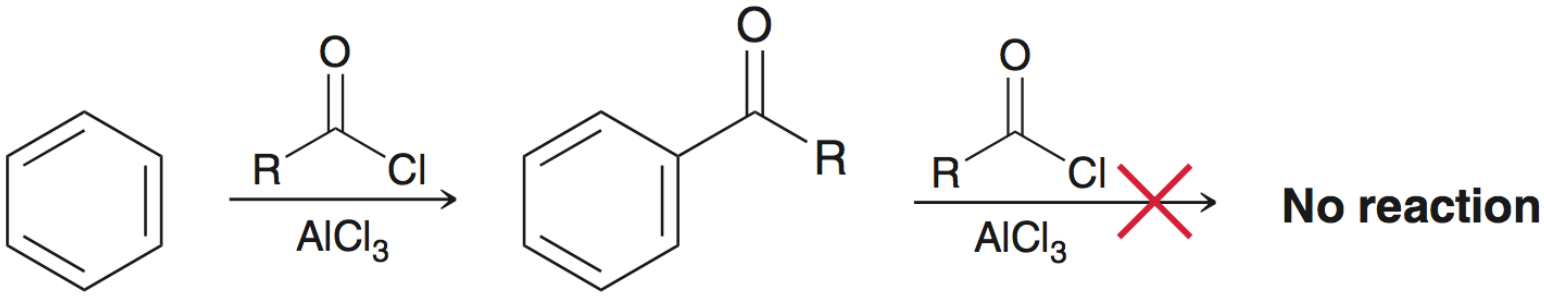
- An acylation followed by a Clemmensen reduction is a good alternative



(73%)

18.6 Friedel-Crafts Acylation

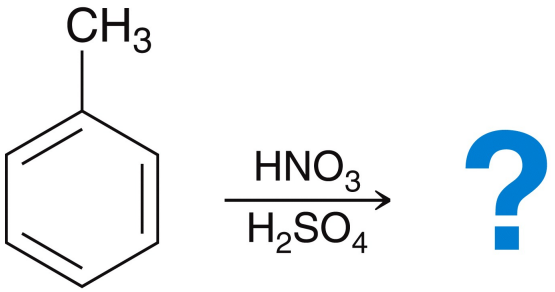
- Unlike polyacylation is generally not observed (which is a problem with ***alkylation***)



- **Practice with Conceptual Checkpoint 18.8 - 18.10**

18.7 Activating Groups

- Two issues arise when adding a group to a ring which already possesses one or more substituents. Consider the nitration of toluene:

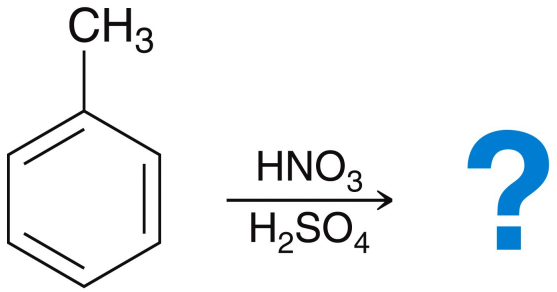


1. What is the effect of the methyl group on the **rate** of nitration?

Toluene reacts much faster than benzene. The CH_3 group is electron-donating, making the ring a better nucleophile

18.7 Activating Groups

- Two issues arise when adding a group to a ring which already possesses one or more substituents. Consider the nitration of toluene:

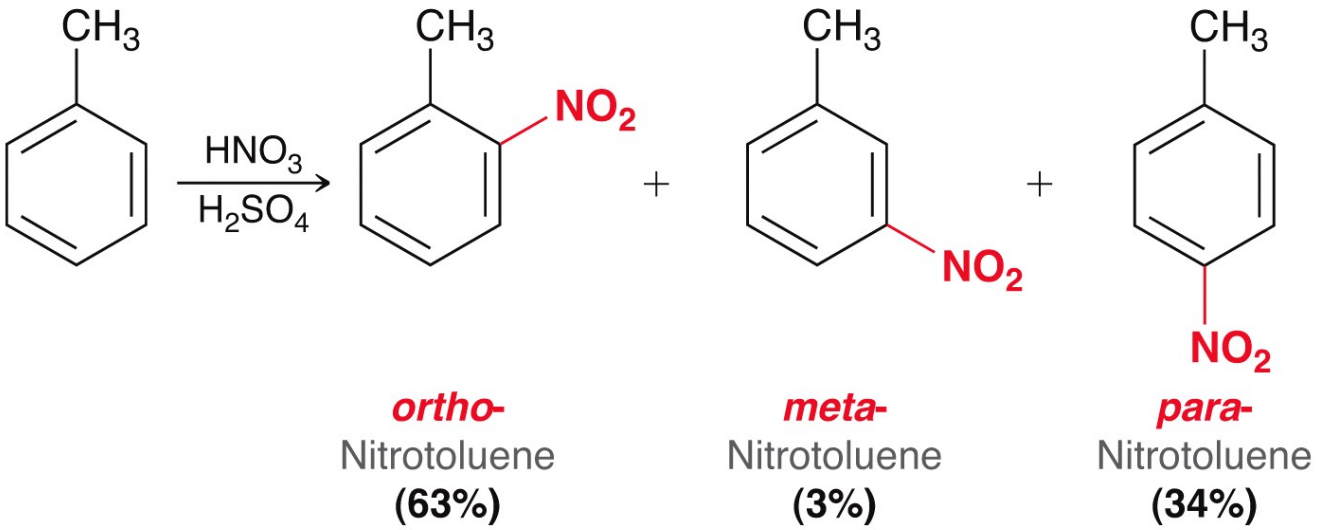


2. What is the effect of the methyl group on the **regioselectivity** of the reaction?

*there are **three possible products**: the nitro group could be installed **ortho, meta or para.***

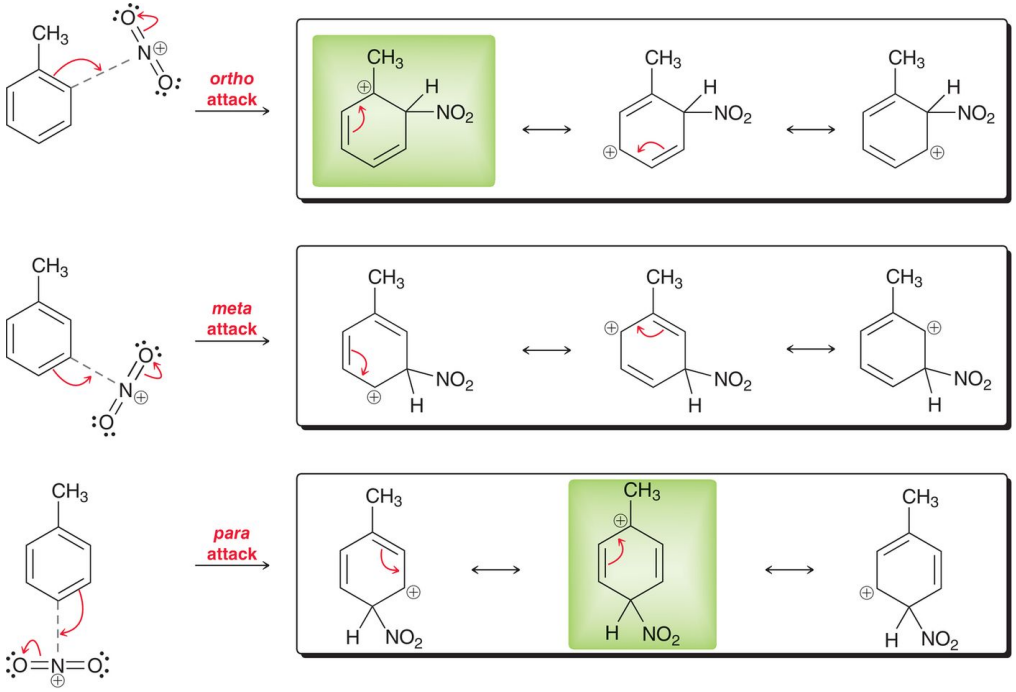
18.7 Activating Groups

- The ***ortho* and *para*** products **predominate**. Very little *meta* product is formed:



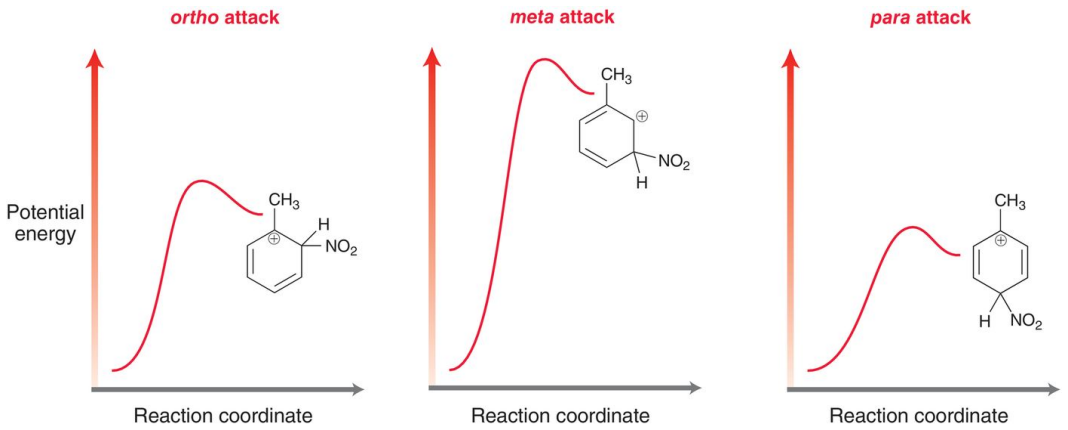
18.7 Activating Groups

- Compare the relative stability of the sigma-complex intermediate:



18.7 Activating Groups

- The sigma-complex obtained from *ortho* and *para* attack has positive charge delocalized adjacent to the electron donating CH_3 group, giving a more stable sigma complex intermediate:



18.7 Activating Groups

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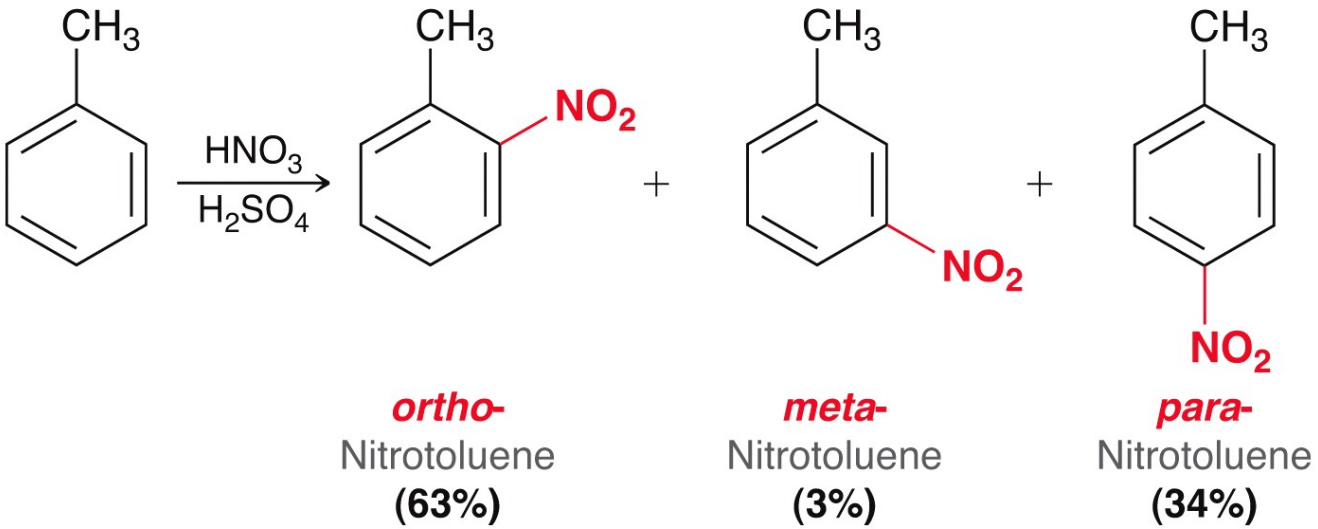
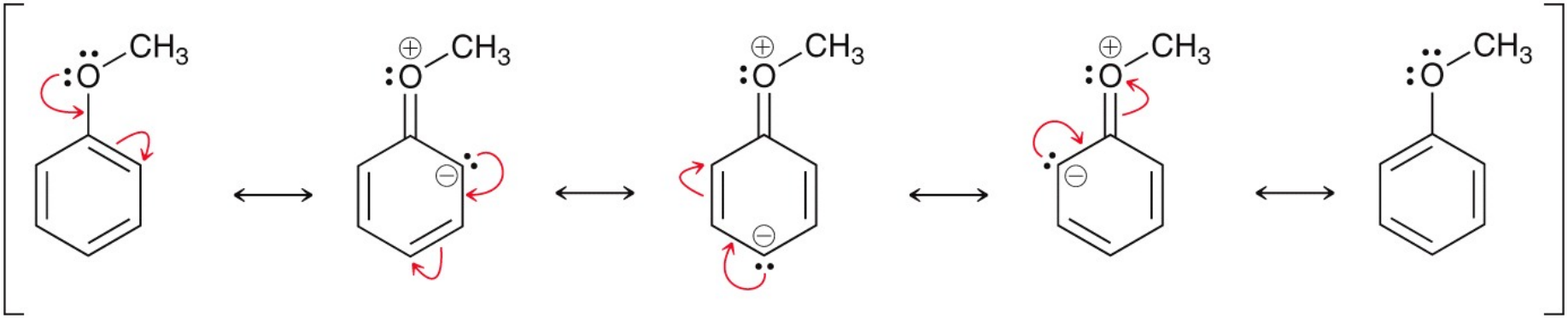


- More *ortho* is formed because there are two *ortho* positions and only one *para* position

18.7 Activating Groups

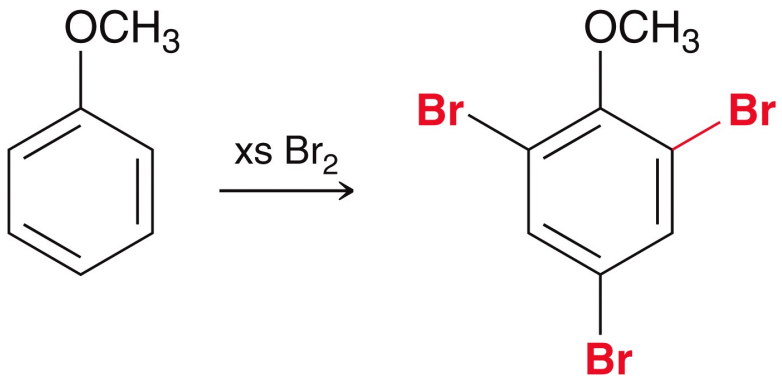
- The methoxy group in anisole activates the ring 400 times more than benzene

- The methoxy group donates electron density via resonance:



18.7 Activating Groups

- The methoxy group activates the ring so strongly that a lewis acid catalyst isn't necessary, and polysubstitution is difficult to avoid

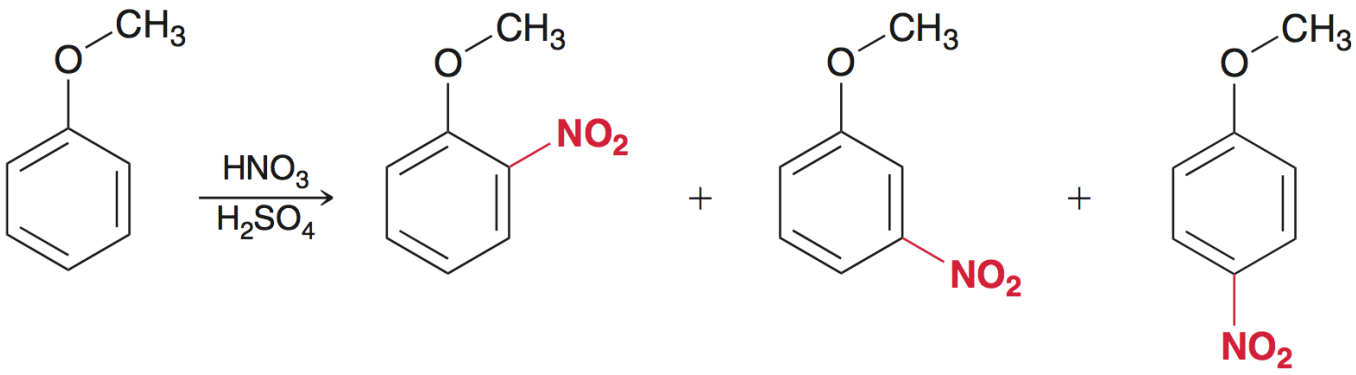


(100%)

- Activators are generally *ortho-para* directors

18.7 Activating Groups

- Like the $-CH_3$ group, the $-OCH_3$ group is activating and an *ortho-para* director:



ortho- Nitroanisole **(31%)**

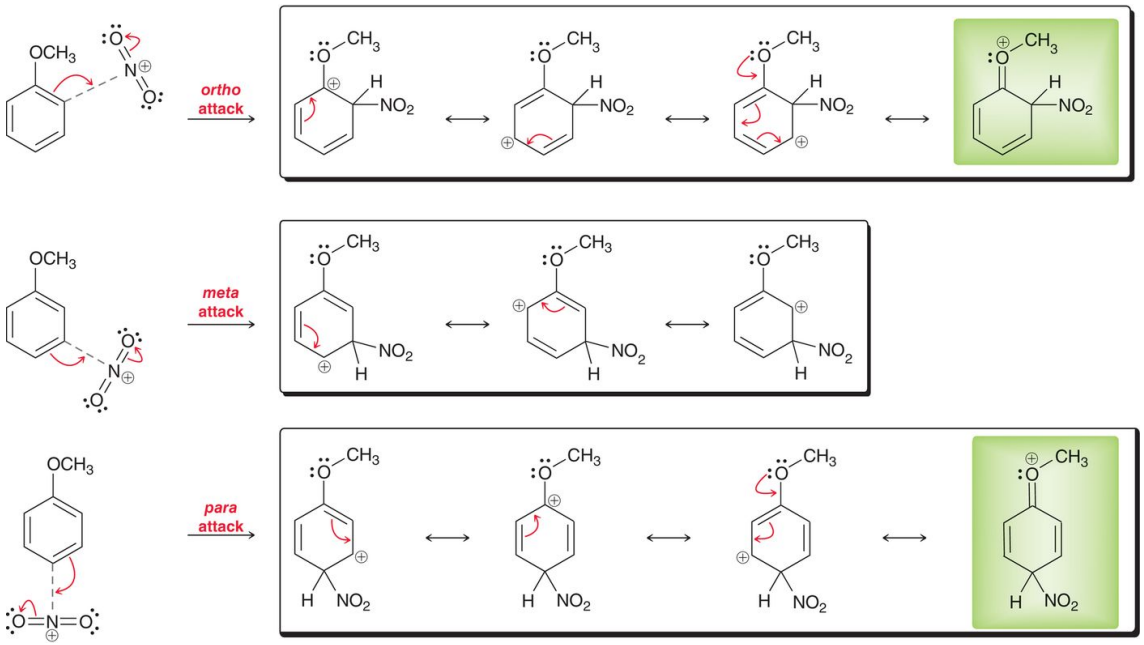
meta- Nitroanisole **(2%)**

para- Nitroanisole **(67%)**

- Here, *para* is the major, due to the *ortho* position(s) being more sterically hindered

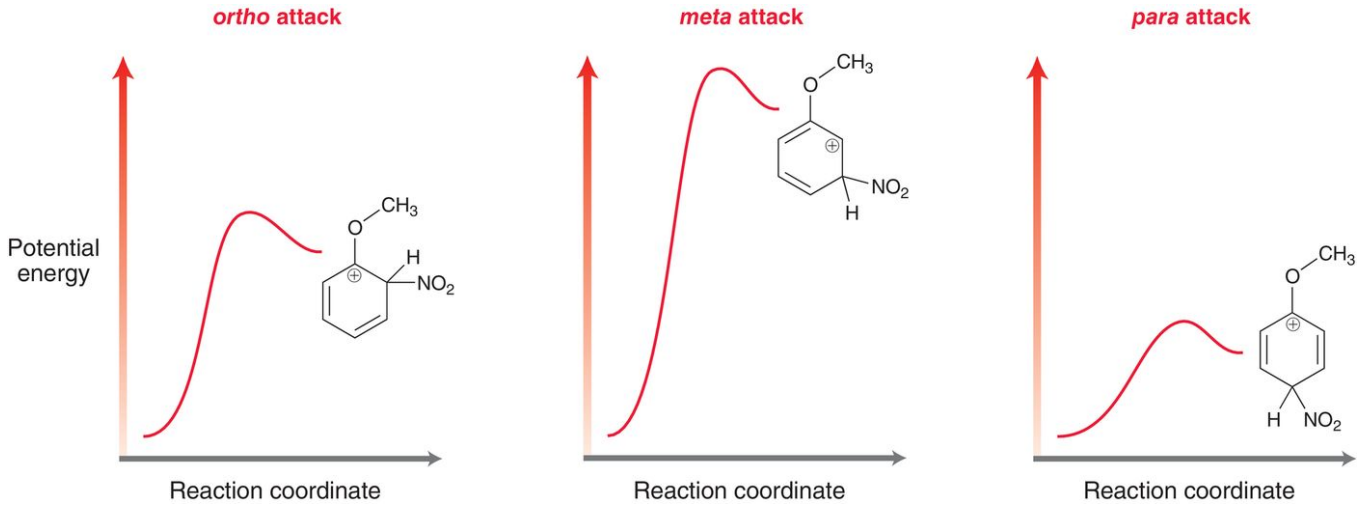
18.7 Activating Groups

- Resonance stabilizes sigma-complex of *ortho* and *para* attack:



18.7 Activating Groups

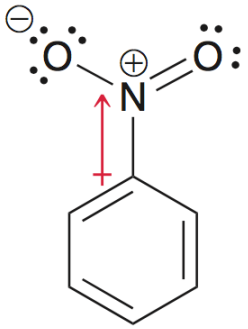
- Resonance stabilizes sigma-complex of *ortho* and *para* attack:



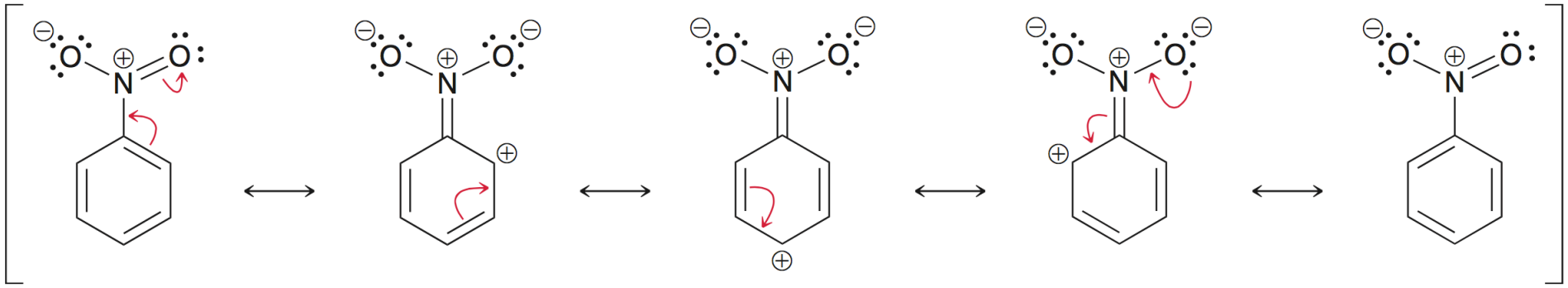
- **Practice with Conceptual Checkpoint 18.11-18.12**

18.8 Deactivating Groups

- The nitro group is an example of a **deactivating** group.
- It is both inductively electron withdrawing…

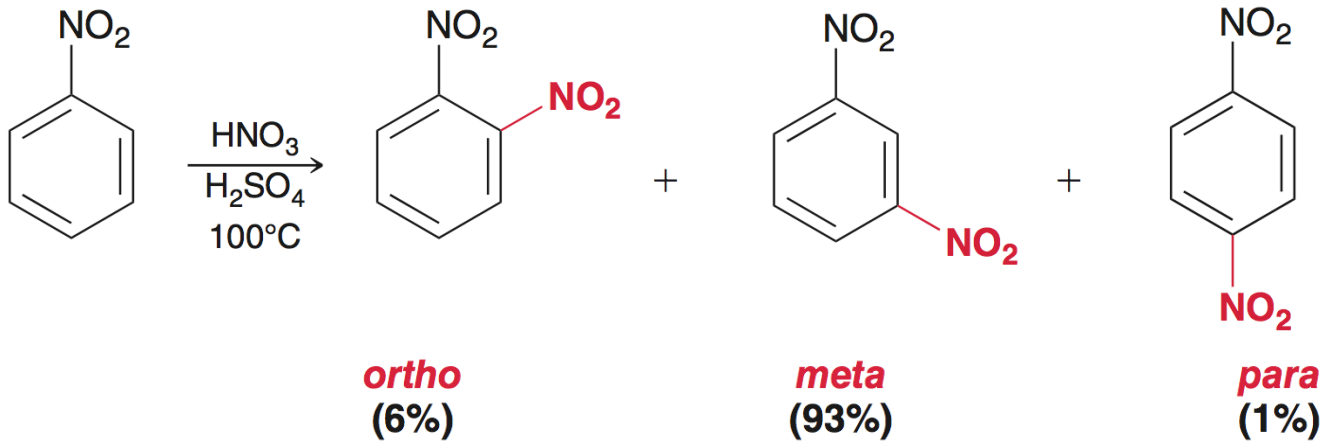


… and withdraws electron density from the ring via resonance:



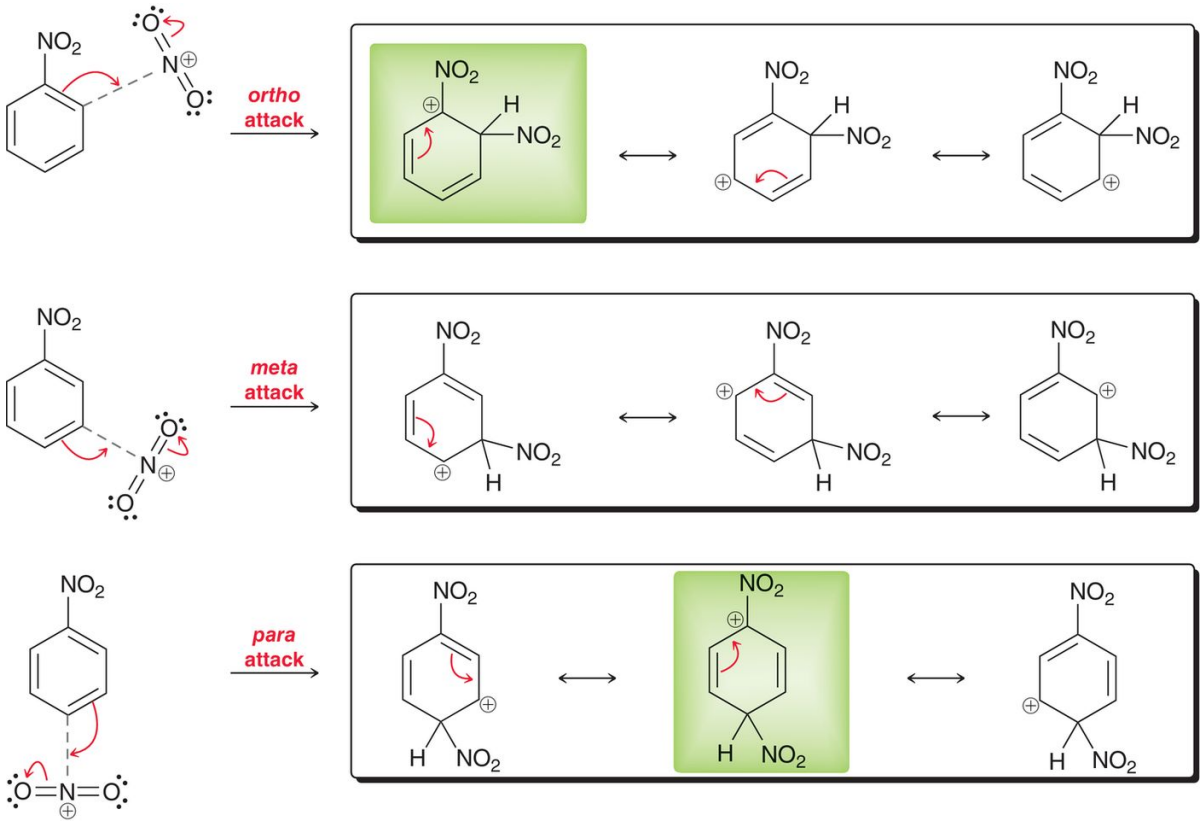
18.8 Deactivating Groups

- Nitrobenzene undergoes nitration 100,000 times slower than benzene



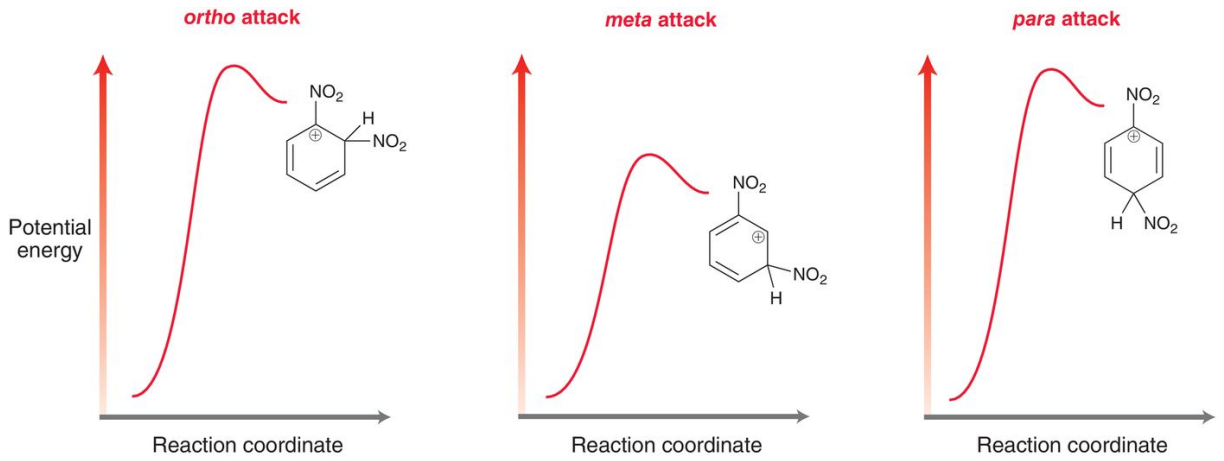
- The *meta* product is the major product

18.8 Deactivating Groups



18.8 Deactivating Groups

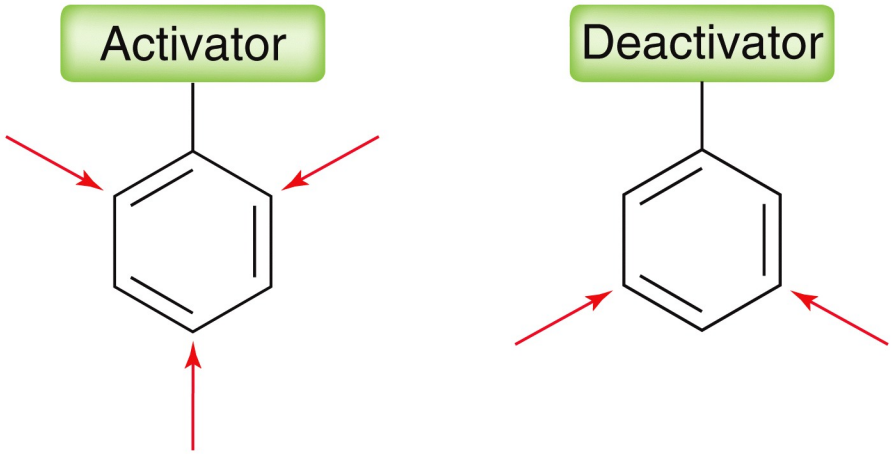
- The electron-withdrawing group deactivates the sigma-complex formed from *ortho* and *para* attack
- **The nitro group is a *meta* director**



- **Practice with Conceptual Checkpoint 18.13**

18.9 Halogens: The Exception

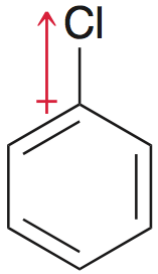
- All electron donating groups are *ortho-para* directors
- All electron-withdrawing groups are *meta*-directors, EXCEPT the halogens



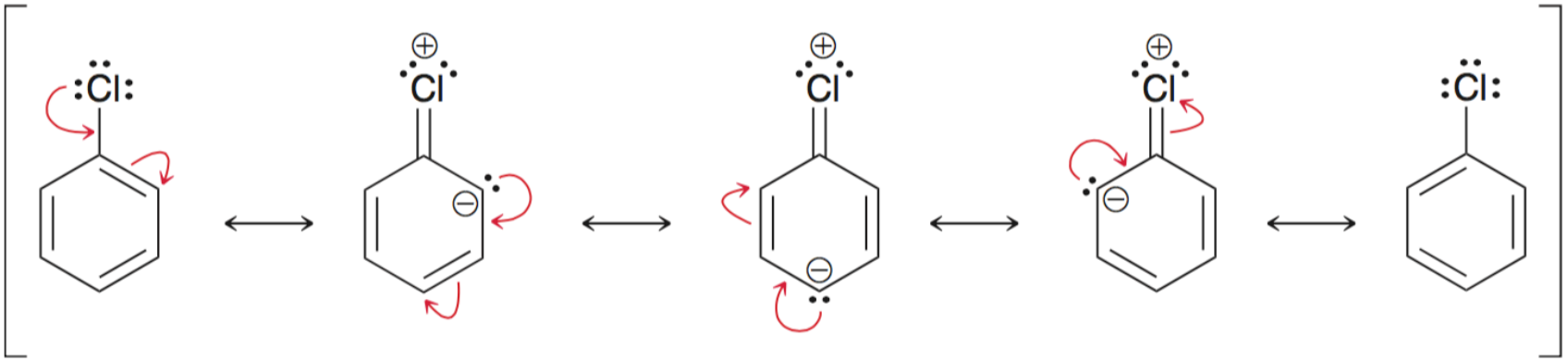
- Halogens withdraw electrons by induction (deactivating)
- Halogens donate electrons through resonance (*ortho-para* directing)

18.9 Halogens: The Exception

- Halogens withdraw electrons by induction **(deactivating)**

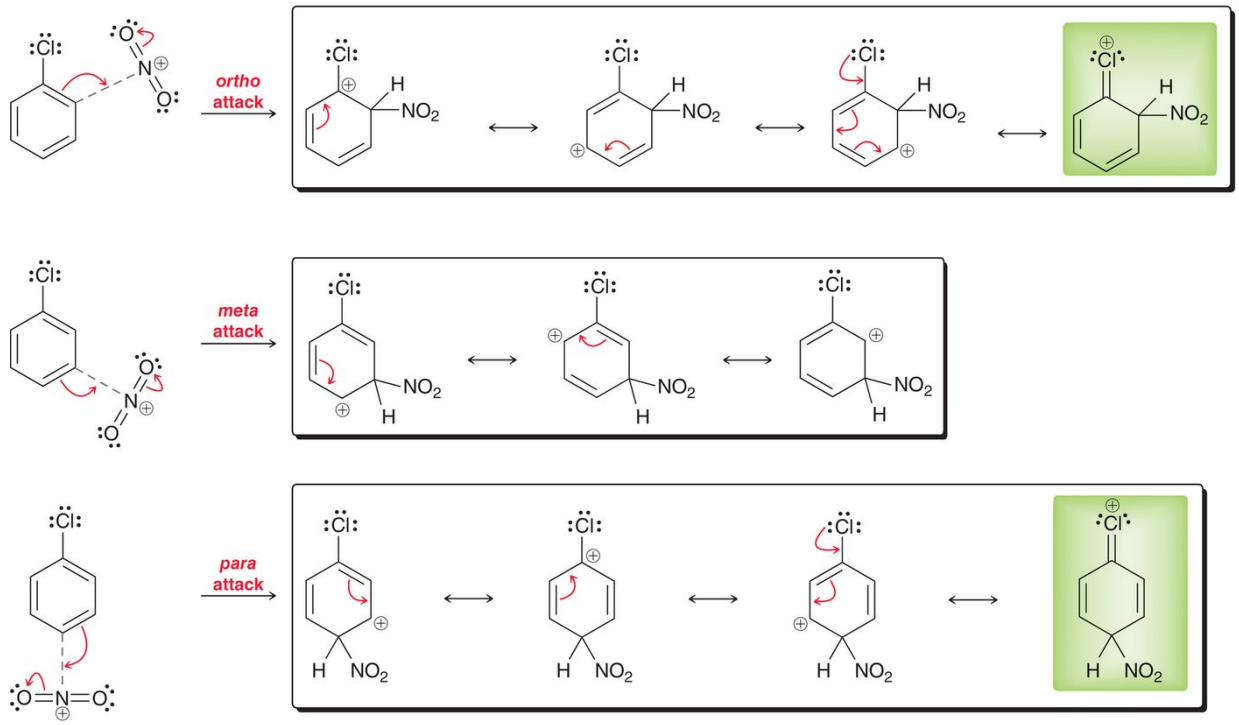


- Halogens donate electrons through resonance **(*ortho-para* directing)**



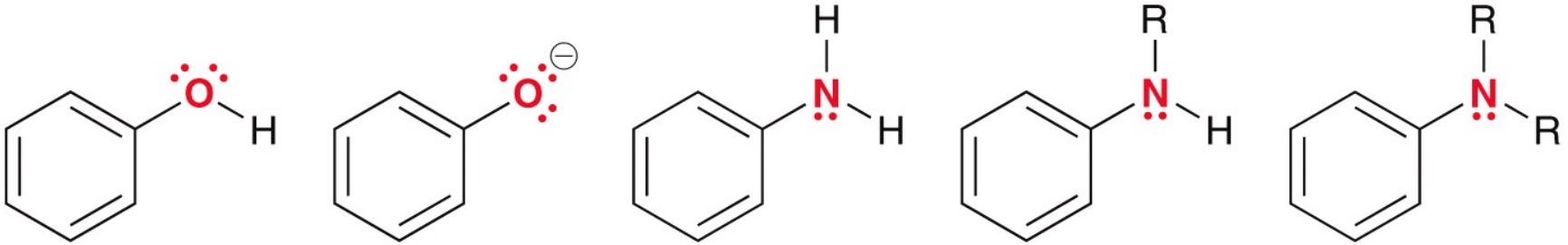
18.9 Halogens: The Exception

- Halogens donate electrons through resonance

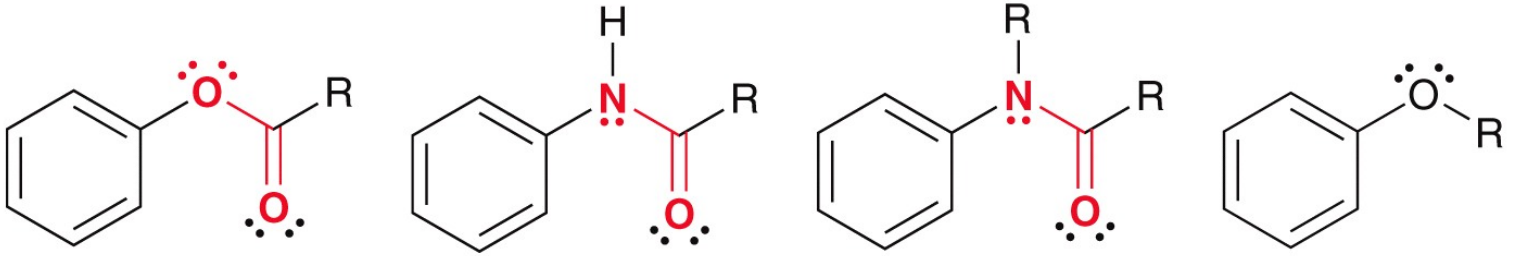


18.10 Directing Effects of a Substituent

- **STRONG activators** (*ortho/para* directing)

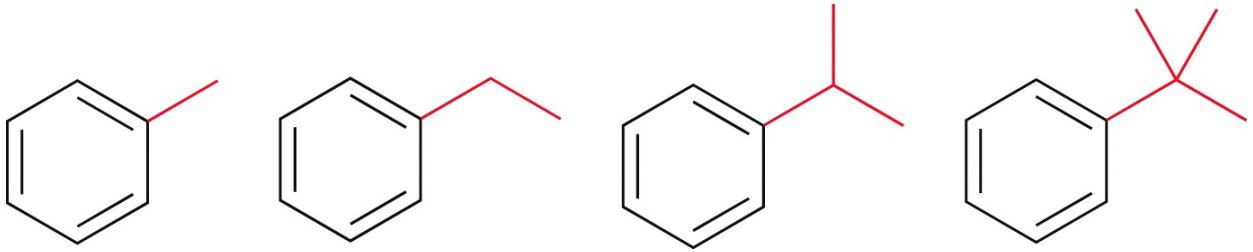


- **MODERATE activators** (*ortho/para* directing)



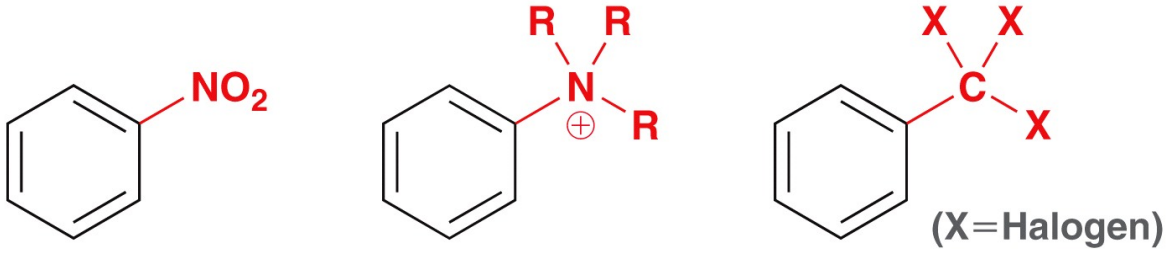
18.10 Directing Effects of a Substituent

3. **WEAK activators** (*ortho/para* directing)

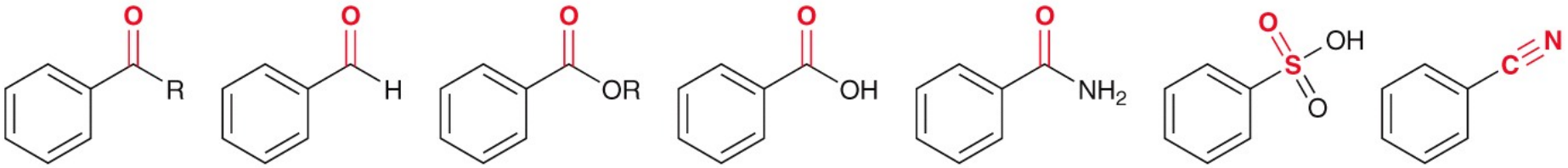


18.10 Directing Effects of a Substituent

- **STRONG deactivators** (*meta* directing)

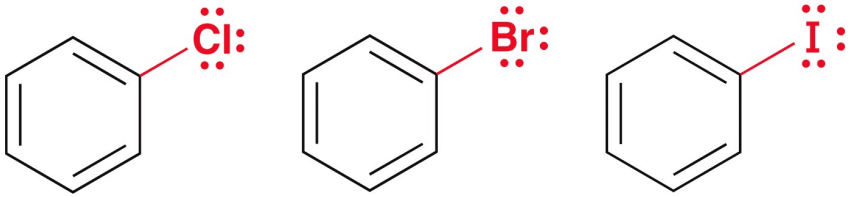


- **MODERATE deactivators** (*meta* directing)



18.10 Directing Effects of a Substituent

- **WEAK deactivators** (*ortho/para* directing)



- REMEMBER! The halides are the only **deactivating groups that are *ortho/para* directors!**

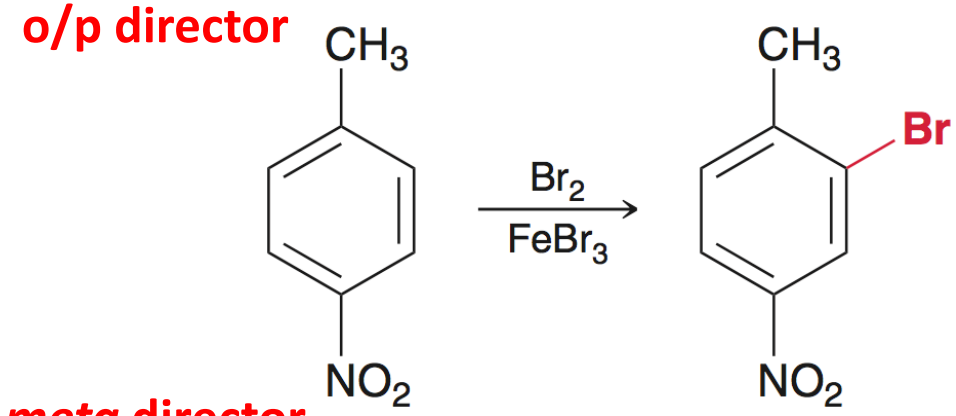
- Activators and deactivators are summarized in Table 18.1

- **Practice with SkillBuilder 18.1**

18.11 Multiple Substituents

- The directing effects of all substituents attached to a ring must be considered in an EAS reaction

- The directing effects of $-CH_3$ and the $-NO_2$ direct the bromine to the same carbon: one product is obtained

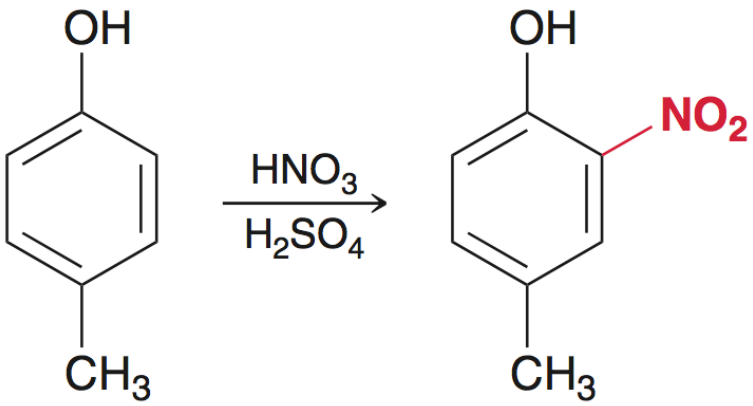


bromine goes *ortho* to the CH_3 group, and *meta* to the NO_2 group

18.11 Multiple Substituents

- IF the groups direct to different carbons, the stronger group will dominate the directing effects

Strong o/p director



Weak o/p director

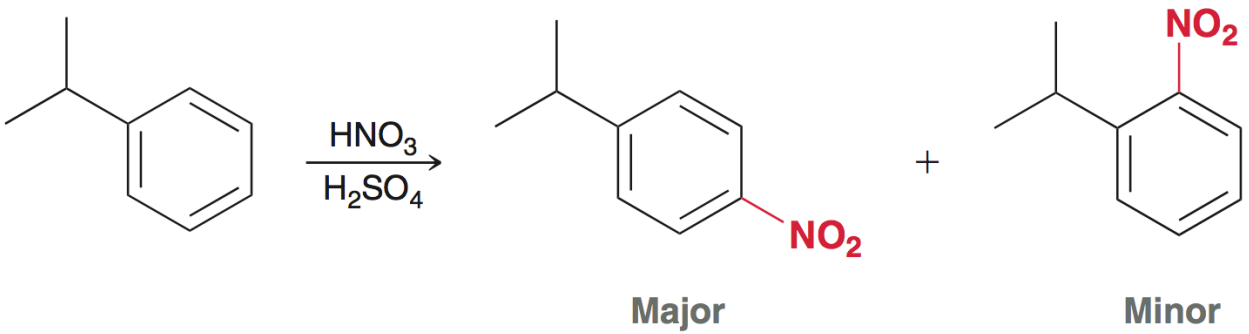
NO_2 group is ortho to the stronger OH group

- **Practice with SkillBuilder 18.2**

18.11 Multiple Substituents

- Steric hindrance must be considered when more than one product is possible, using these guidelines:

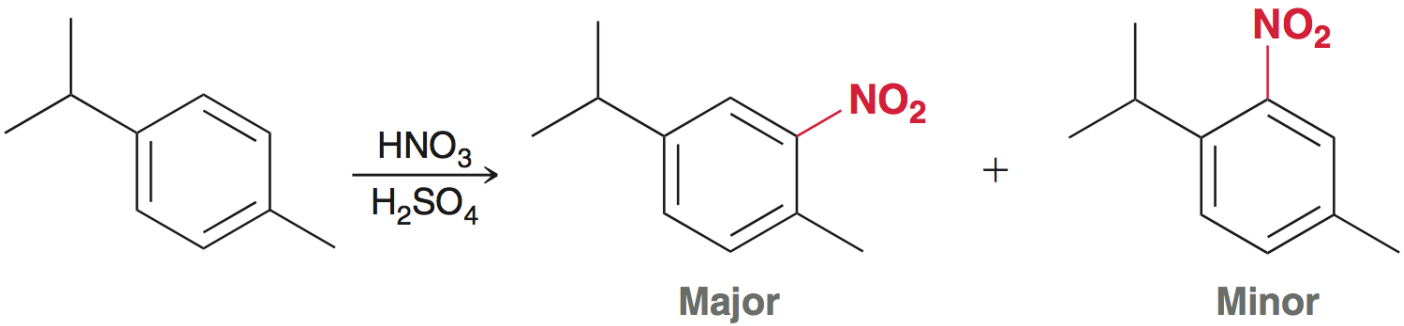
1. For a monosubstituted ring, the *para* product typically dominates, due to sterics



18.11 Multiple Substituents

- Steric hindrance must be considered when more than one product is possible, using these guidelines:

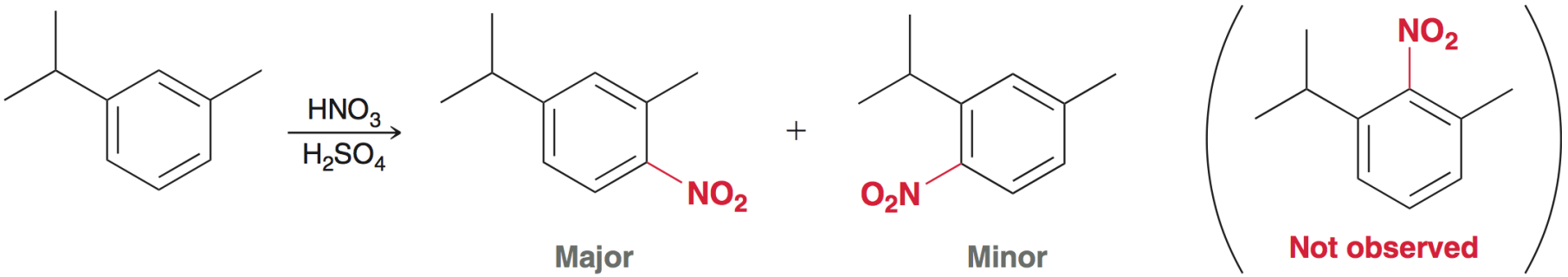
2. For 1,4 disubstituted rings, substitution will occur at the less sterically hindered site (if more than one site is favored by directing effects)



18.11 Multiple Substituents

- Steric hindrance must be considered when more than one product is possible, using these guidelines:

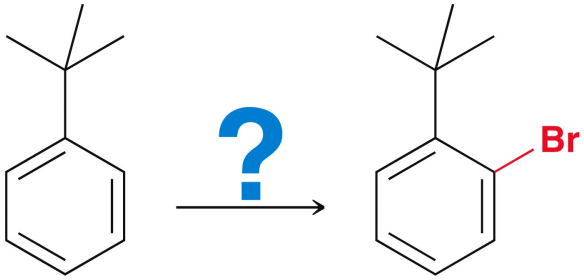
3. For 1,3 disubstituted rings, substitution typically does not occur between the existing substituents:



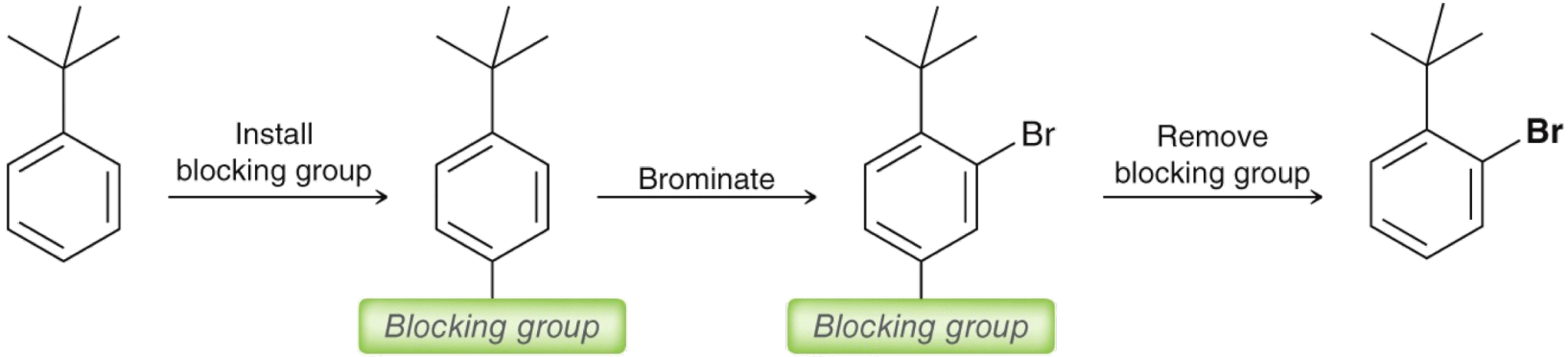
- **Practice with SkillBuilder 18.3**

18.11 Blocking Groups

- Consider how one might force a substituent to add *ortho* (instead of *para*) in the presence of an *ortho/para* director:

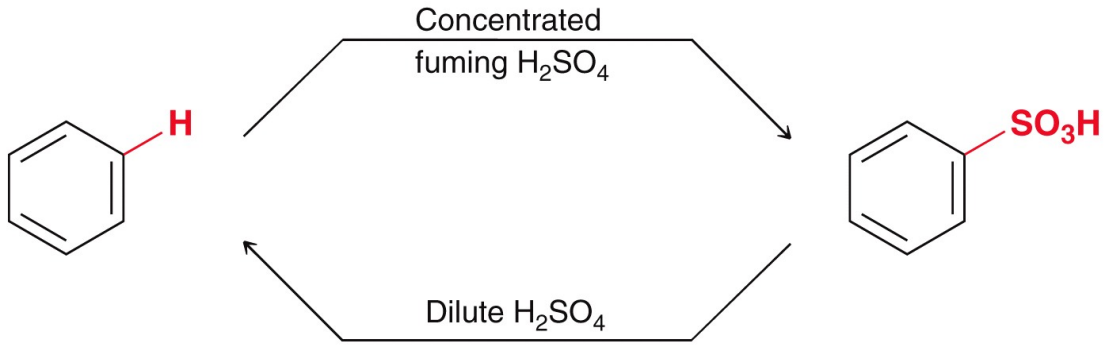


- A **blocking group** could be used prevent substitution at the *para* position:

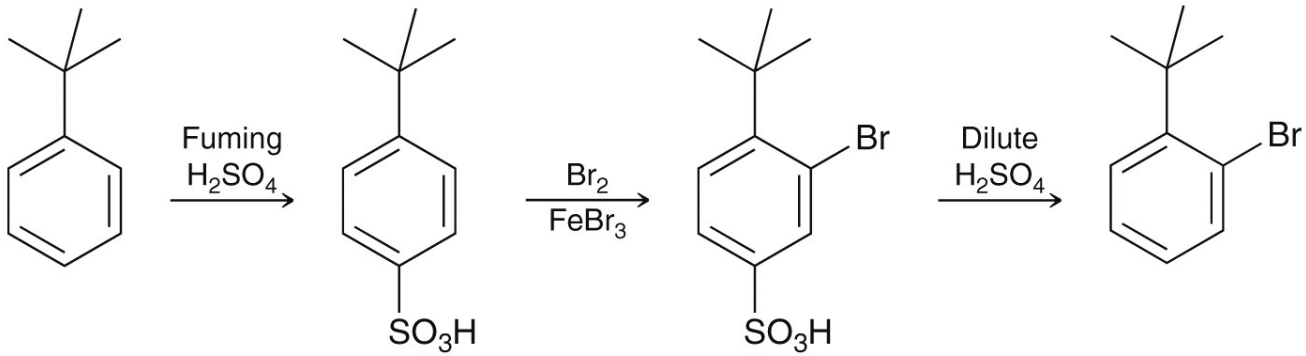


18.11 Multiple Substituents

- Sulfonation, since it is reversible, is commonly used as a **blocking group:**



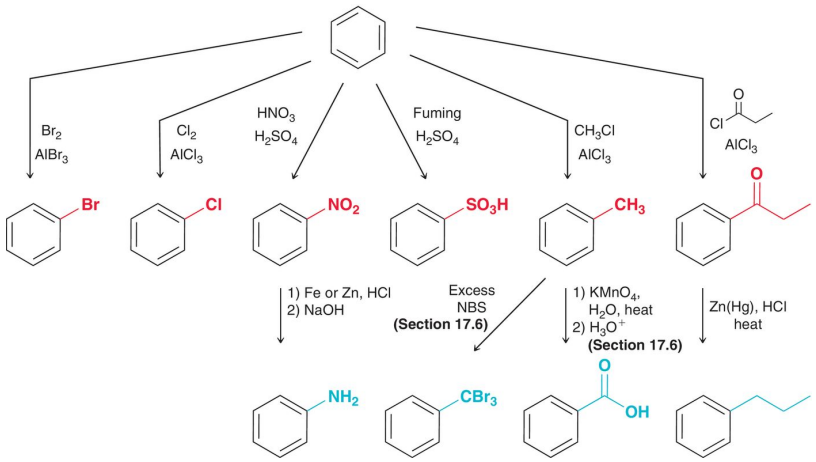
- So the synthesis can be accomplished as follows:



- **Practice with SkillBuilder 18.4**

18.12 Synthesis Strategies

- 10 different groups can be installed on a benzene ring using the reactions covered so far:



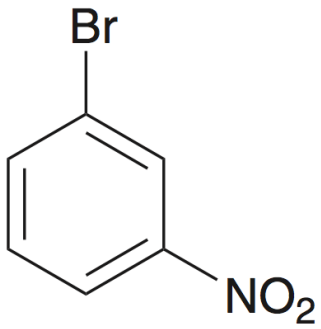
- Practice with

  Checkpoints

  18.24-18.25

18.12 Synthesis Strategies

- Synthesis of disubstituted benzene rings requires careful analysis of directing effects to decide which group to install first:

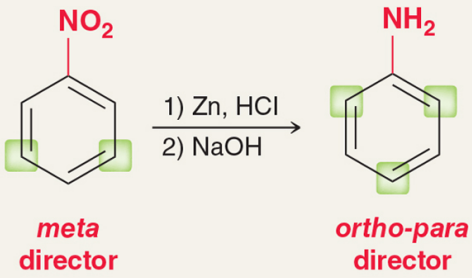
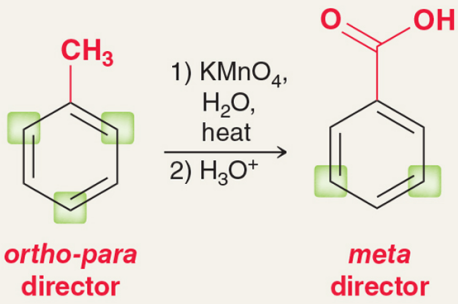
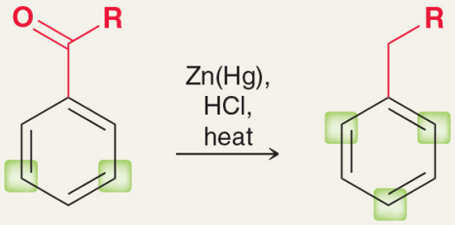
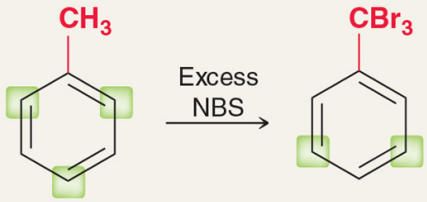


Groups need to be *meta*, so the first group installed must be a *meta* director

- Br is an *o/p* director, and NO_2 is a *meta* director. So the nitro group must be added first, so that the Br will be directed to the *meta* position.

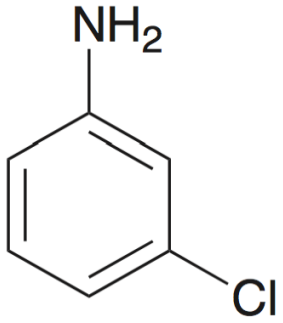
18.12 Synthesis Strategies

TABLE 18.2 FUNCTIONAL GROUP CONVERSIONS THAT CHANGE DIRECTING EFFECTS

meta director ⟶ *ortho-para* director	*ortho-para* director ⟶ *meta* director
 *meta* director ⟶ *ortho-para* director	 *ortho-para* director ⟶ *meta* director
 *meta* director ⟶ *ortho-para* director	 *ortho-para* director ⟶ *meta* director

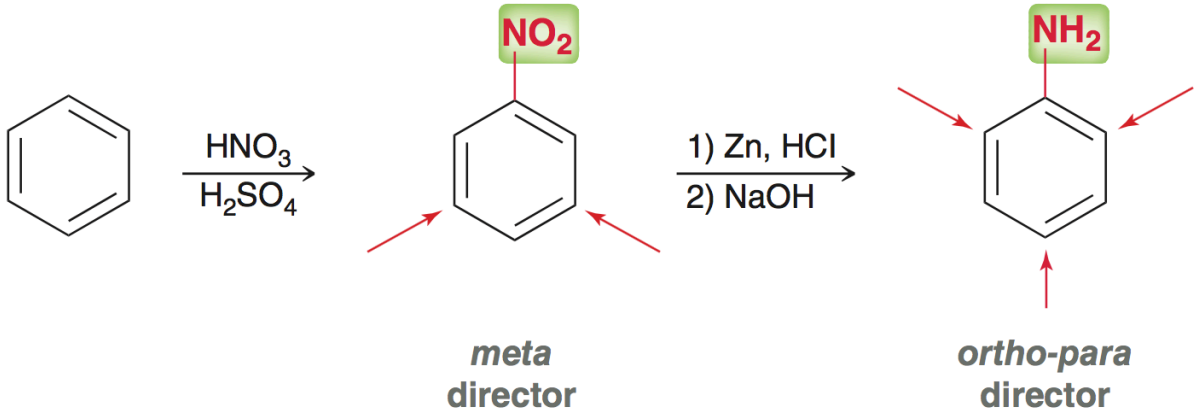
18.12 Synthesis Strategies

- Additional consideration is necessary when one of the groups require more than one step to install:



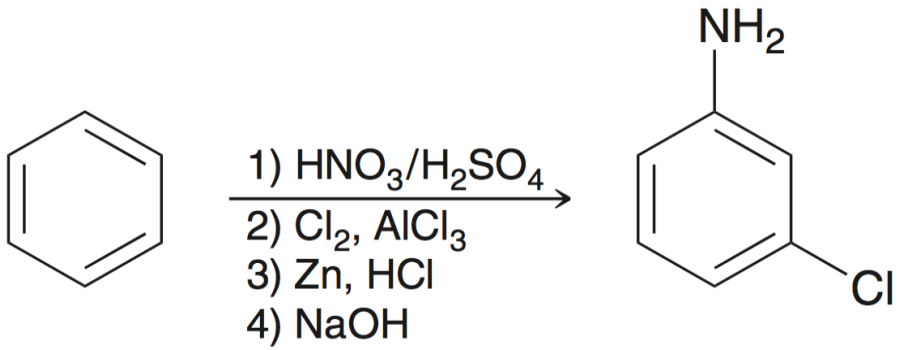
Groups need to be *meta*, but both of these substituents are o/p directors

- Recall that adding the –NH2 groups requires (1) nitration, then (2) reduction.



18.12 Synthesis Strategies

- So, We need to take advantage of the *meta* directing ability of the $-NO_2$ group before reducing it to the $-NH_2$ group:

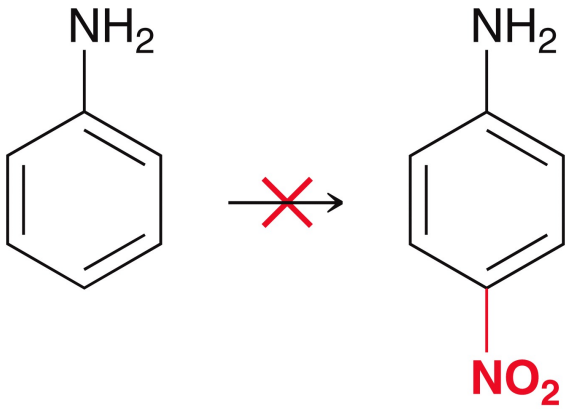


In most cases, changing the order of the reactions will change the substitution pattern on the ring

18.12 Synthesis Strategies

- Other limitations that must be considered when planning a synthesis:

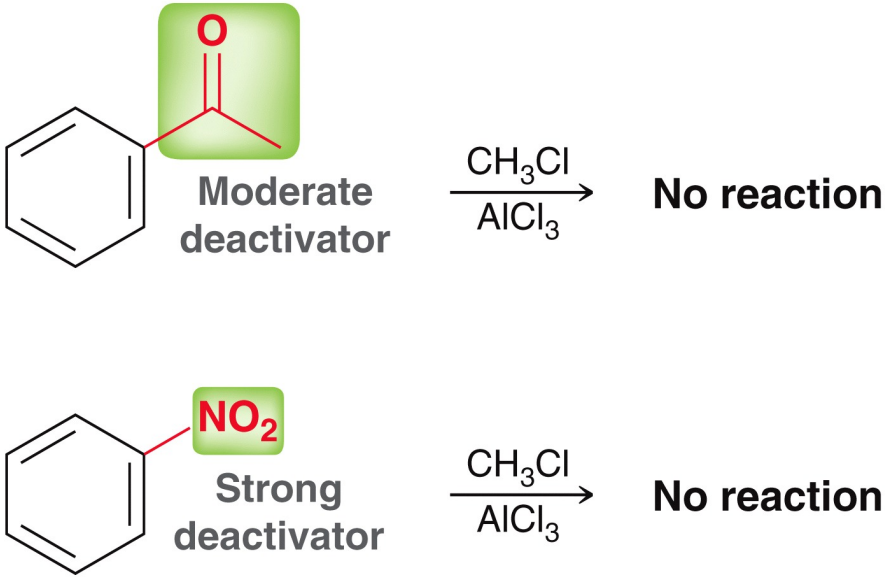
1. **Nitration cannot be done on a ring that already contains an amino group** (it can be oxidized with HNO_3/H_2SO_4)



18.12 Synthesis Strategies

- Other limitations that must be considered when planning a synthesis:

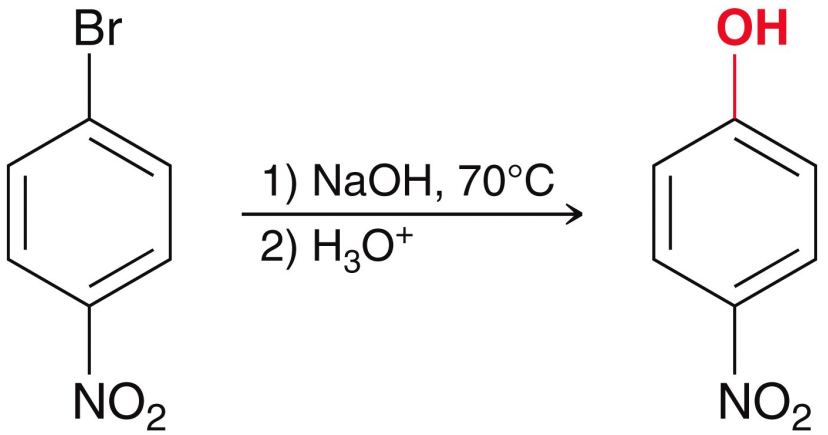
2. **Friedel-Crafts reactions do not work on a ring that is moderately or strongly deactivated:**



- **Practice with SkillBuilders 18.5 and 18.6**

18.13 Nucleophilic Aromatic Substitution

- **Nucleophilic Aromatic Substitution** – a reaction where the benzene is attacked by a nucleophile:



- Here, **OH^-** is the **nucleophile**, and the **–Br** acts as a **leaving group**

18.13 Nucleophilic Aromatic Substitution

- **Three requirements** must be met **for Nucleophilic Aromatic Substitution (S_NAr)** to occur:

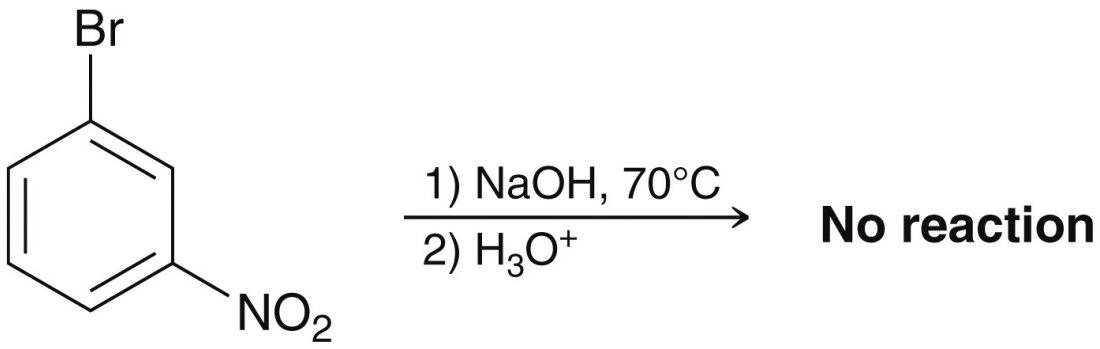
1. The benzene ring must possess a strong electron-withdrawing group (i.e. the ring must be electron poor)

2. The ring must possess a good leaving group (e.g. halide)

3. The leaving group must be positioned *ortho* or *para* to the withdrawing group.

18.13 Nucleophilic Aromatic Substitution

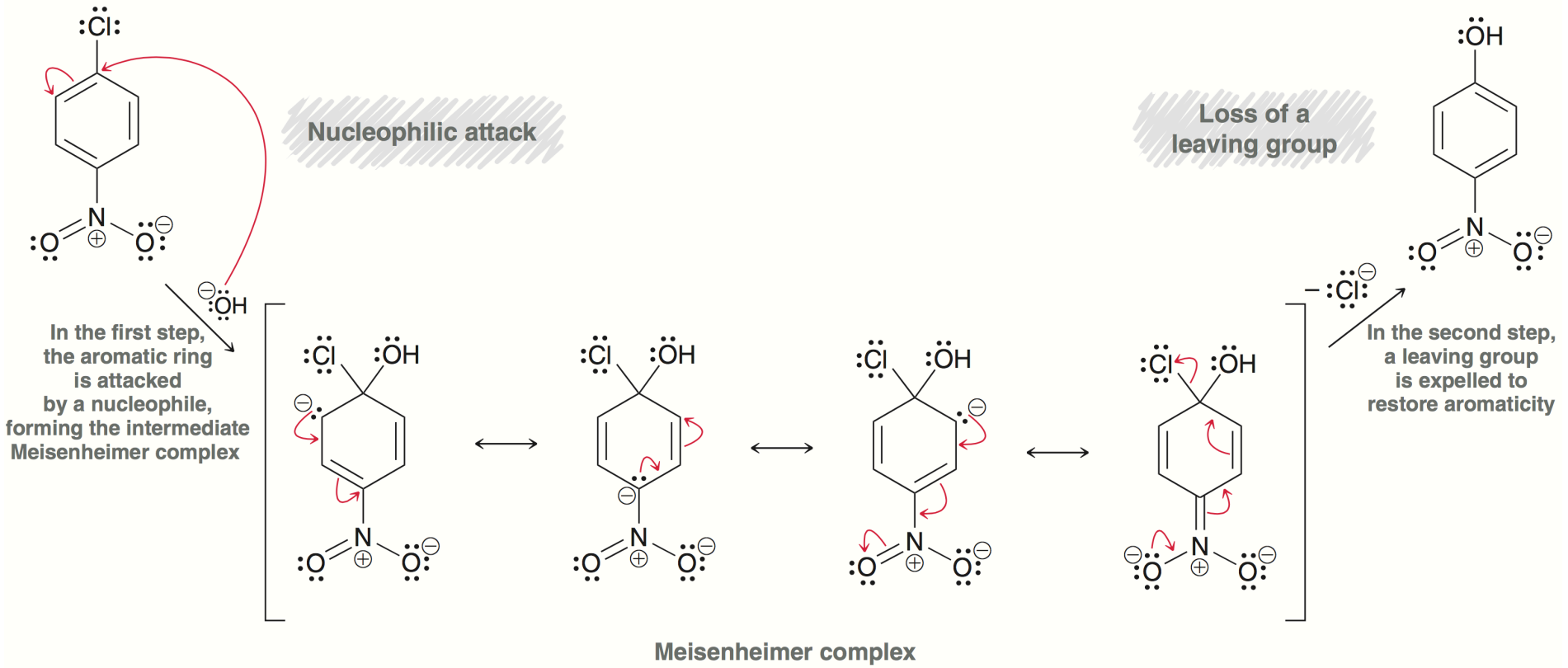
- If the leaving group and withdrawing group are meta, no reaction is observed:



- With the electron withdrawing group in the *meta* position, it is unable to stabilize the **Meisenheimer complex intermediate**.

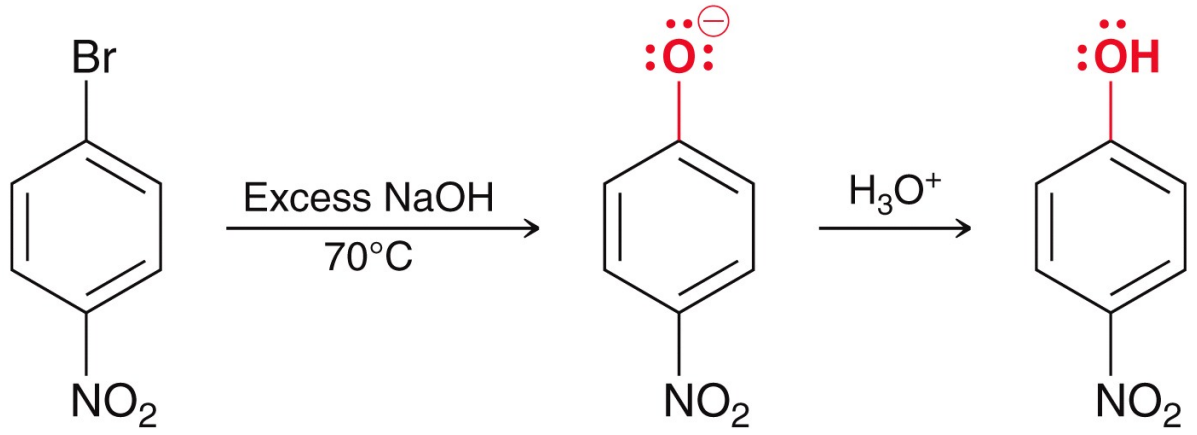
18.13 Nucleophilic Aromatic Substitution

- Mechanism:



18.13 Nucleophilic Aromatic Substitution

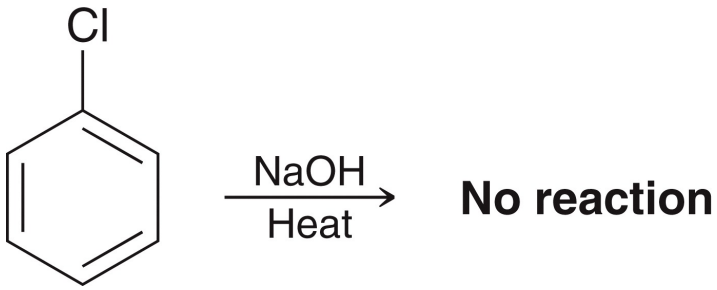
- The substituted phenol product is deprotonated under the basic hydroxide conditions. So acidic workup is necessary to obtain the neutral organic product:



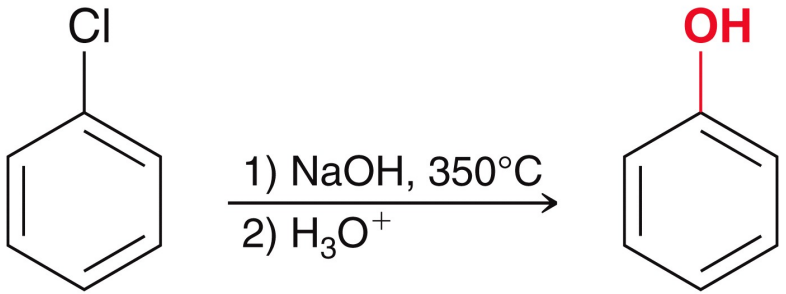
- **Practice with Conceptual Checkpoints 18.30 - 18.32**

18.14 Elimination-Addition

- Recall, a S_NAr reaction will not occur if the ring doesn't have a strong electron withdrawing group:

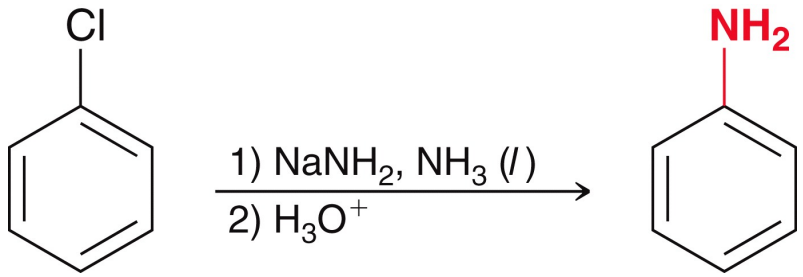


- But if **very high temperature** is used, then a **reaction occurs**:

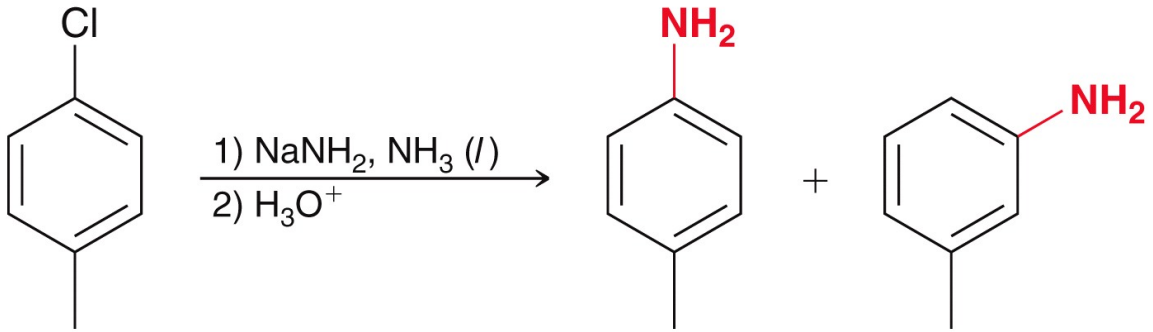


18.14 Elimination-Addition

- The reaction works even better, and doesn't require high temp, if a stronger reagent is used

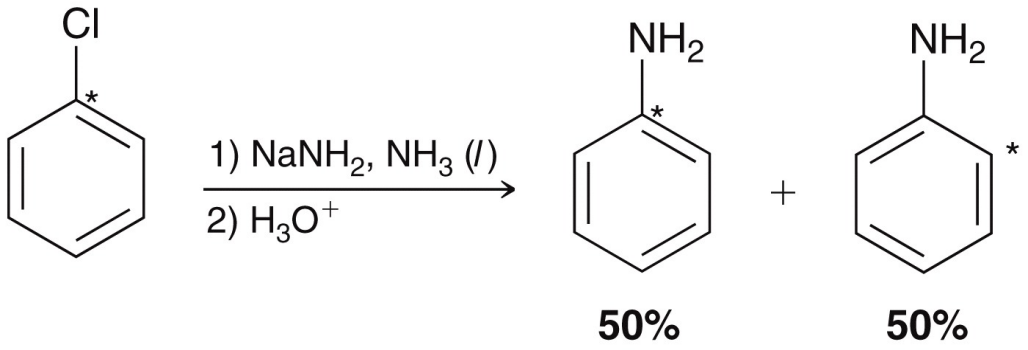


- the regiochemical outcome (below) means this reaction does not proceed through the S_NAr mechanism:

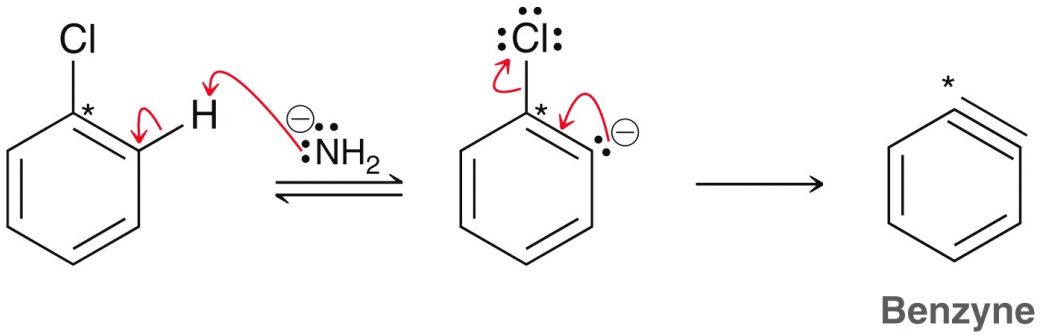


18.14 Elimination-Addition

- Using an isotopically labeled substrate, it is clear that substitution is occurring at two different carbons:

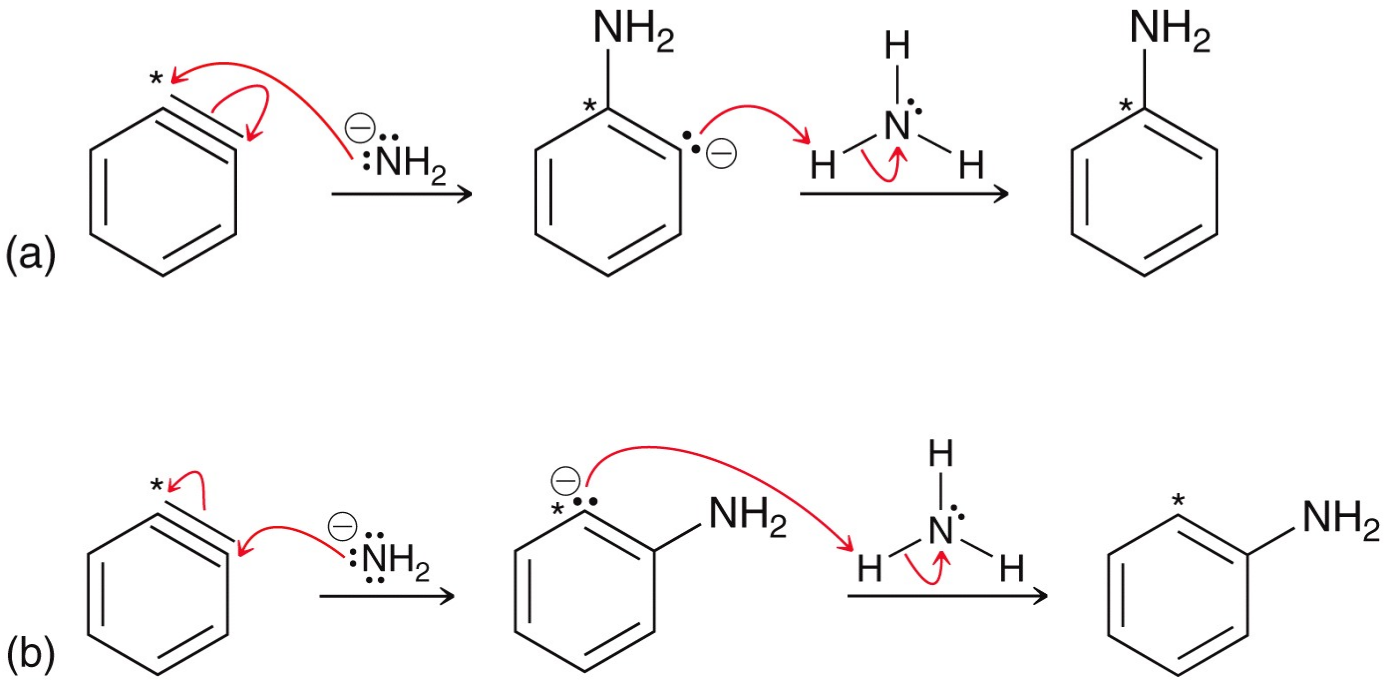


- This can be due to the formation of **benzyne intermediate**:



18.14 Elimination-Addition

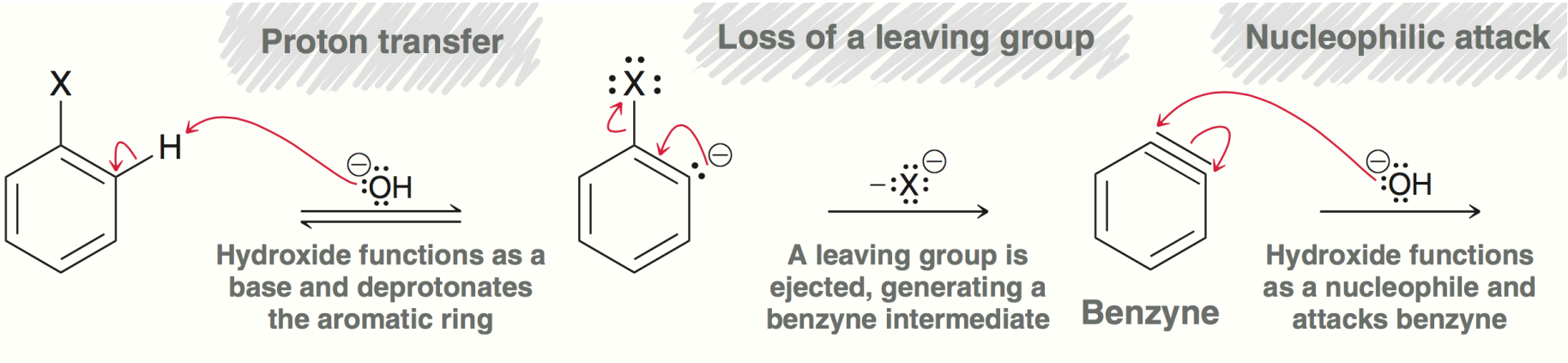
- Nucleophilic attack by NH_2^- can take place at either carbon of **benzyne**, followed by protonation of the other:

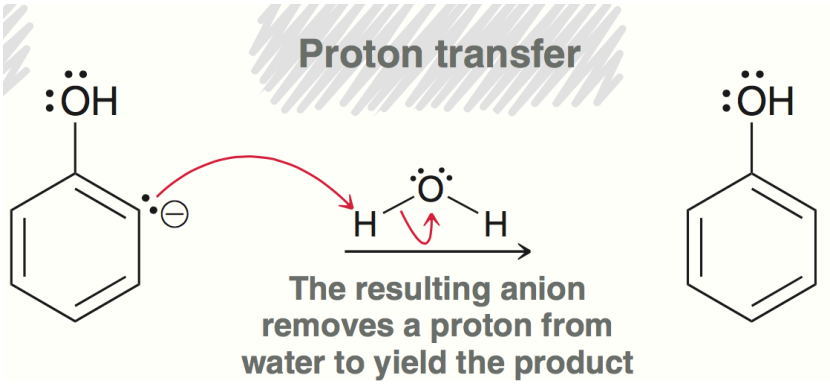


- This is an **elimination-addition** mechanism

18.14 Elimination-Addition

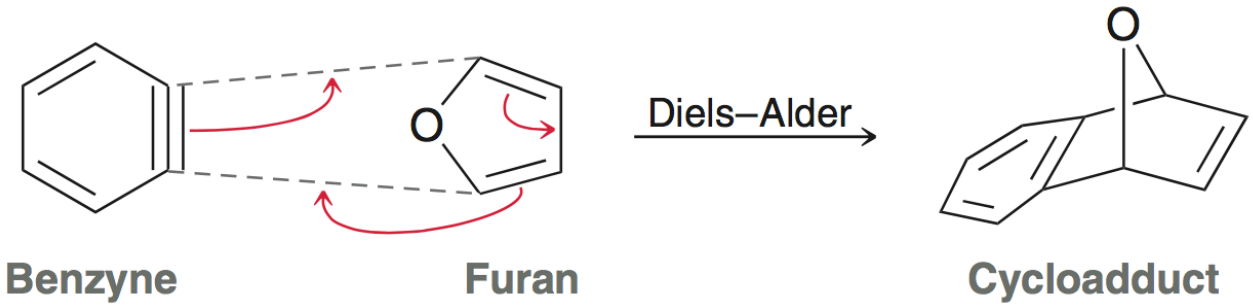
- **Elimination-addition** mechanism:





18.14 Elimination-Addition

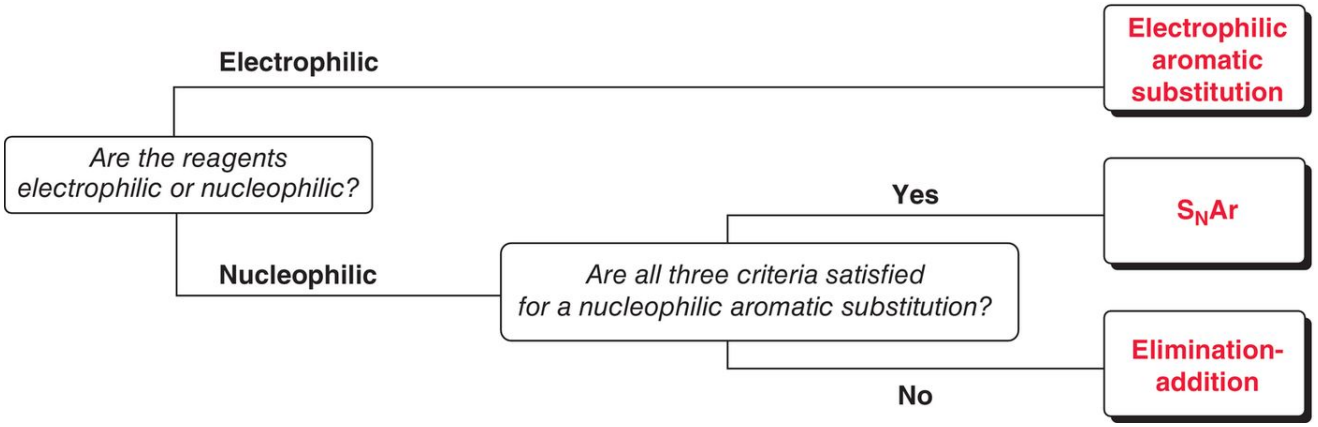
- Evidence for the formation of the benzyne intermediate come from a trapping experiment: a small amt of Diels-Alder product is obtained if furan is added



- **Practice with conceptual checkpoint 18.33 and 18.34**

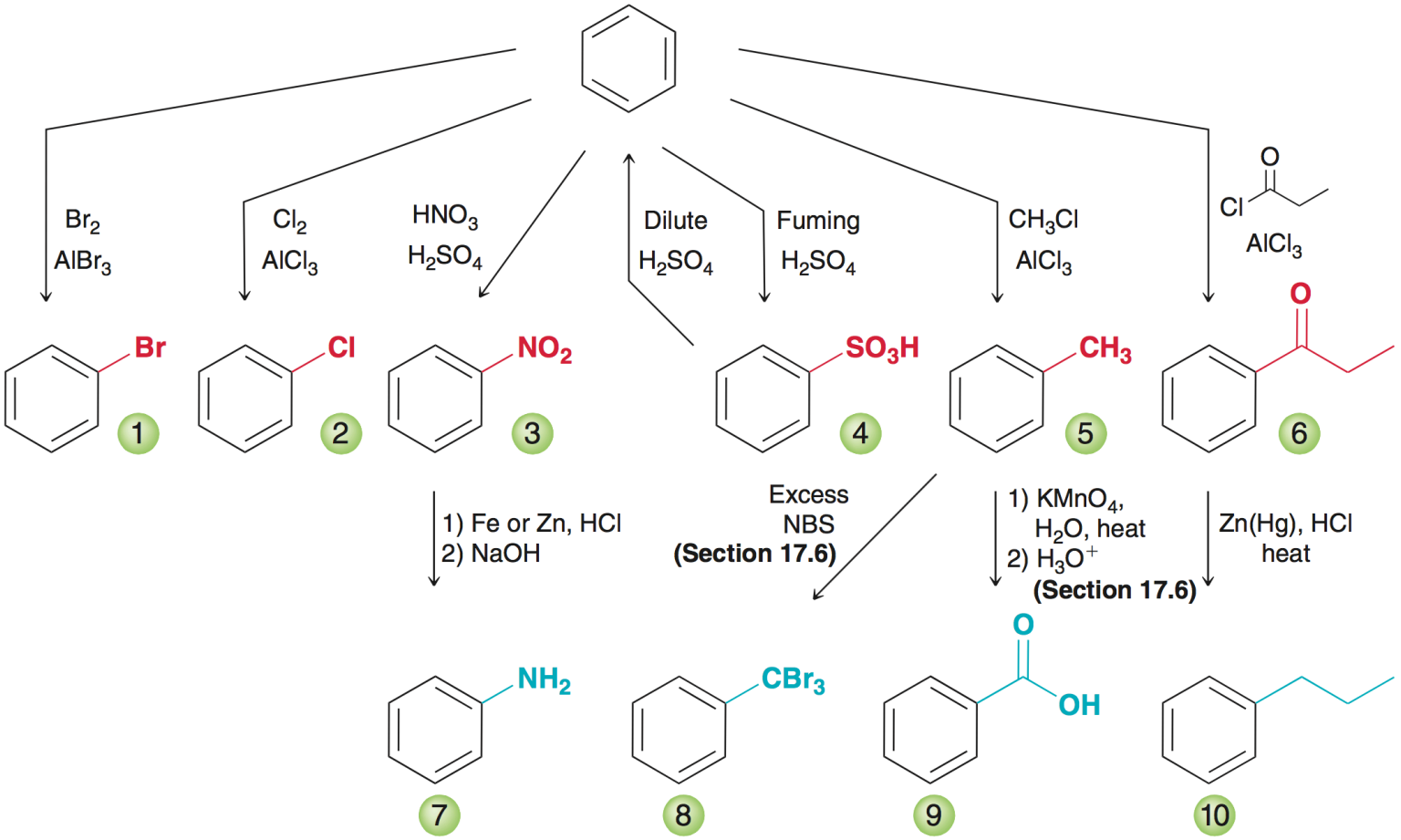
18.15 Identifying the Mechanism

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



- **Practice with SkillBuilder 18.7**

Review of Reactions

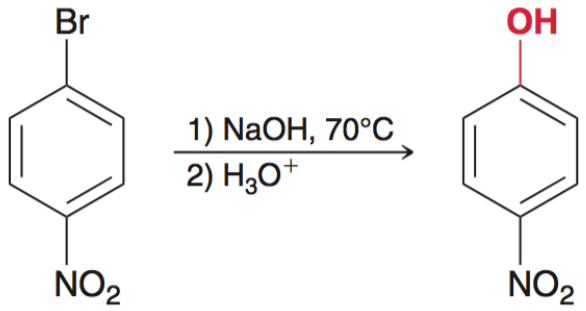


1. Bromination
2. Chlorination
3. Nitration
4. Sulfonation/desulfonation
5. Friedel–Crafts alkylation
6. Friedel–Crafts acylation
7. Reduction
8. Benzylic bromination
9. Oxidation
10. Clemmensen reduction

Review of Reactions

Other Aromatic Substitution Reactions

Nucleophilic Aromatic Substitution



Elimination-Addition