Lecture 8

Aromatic Compounds and Aromatic Substitution Reactions

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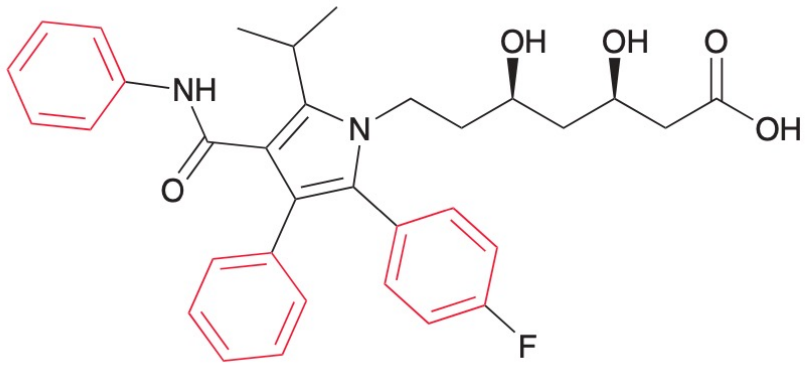
2022/4/20

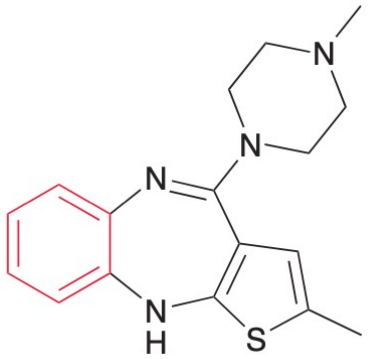
Aromatic Compounds

Introduction to Aromatic Compounds, Basic Reactions of Benzene,

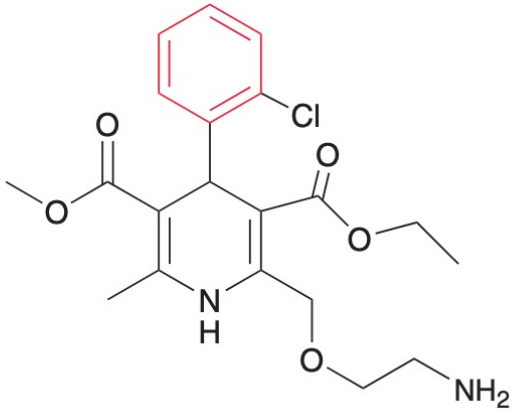
Spectroscopy of Aromatic Compounds



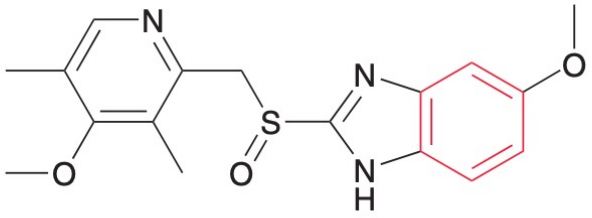
Lipitor
(atorvastatin)
Lowers cholesterol levels and reduces risk of heart attack and stroke



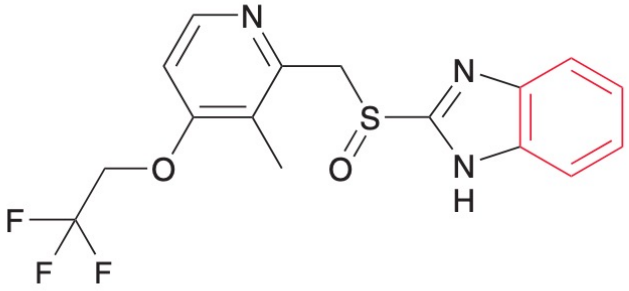
Zyprexa
(olanzapine)
An antipsychotic used in the treatment of schizophrenia and bipolar disorder



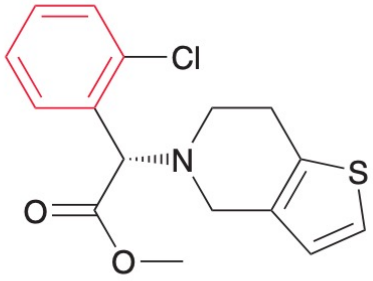
Norvasc
(amlodipine)
Used in the treatment of angina and high blood pressure



Prilosec
(omeprazole)
A proton-pump inhibitor used in the treatment of ulcers and acid reflux

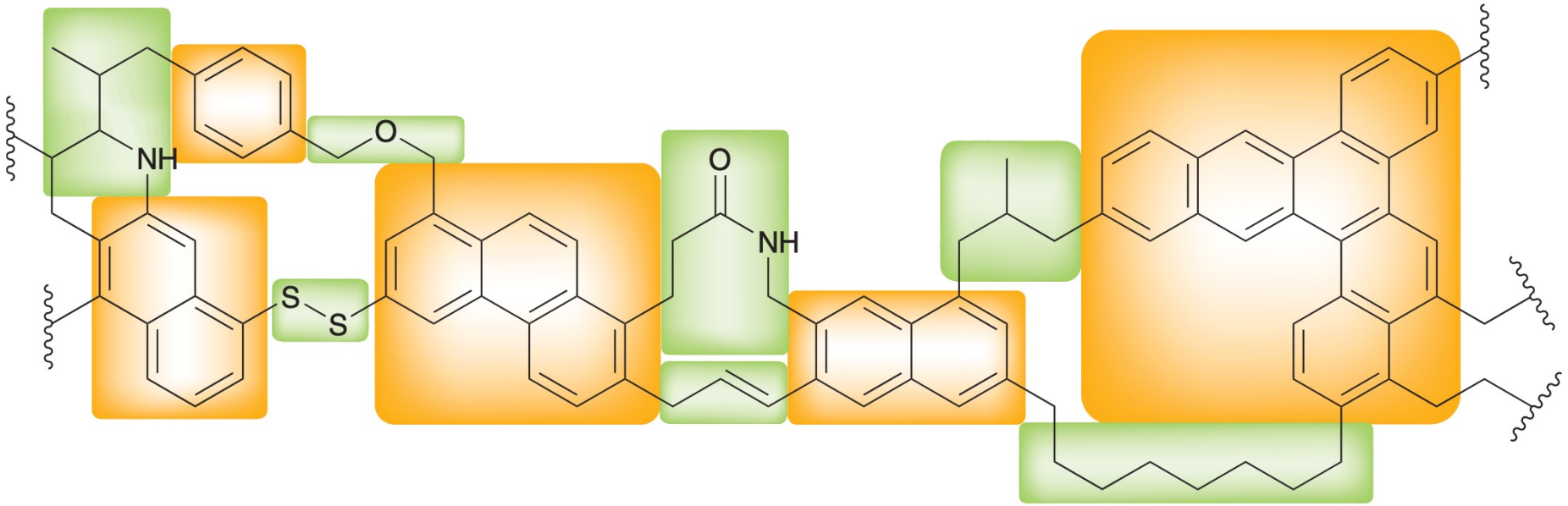


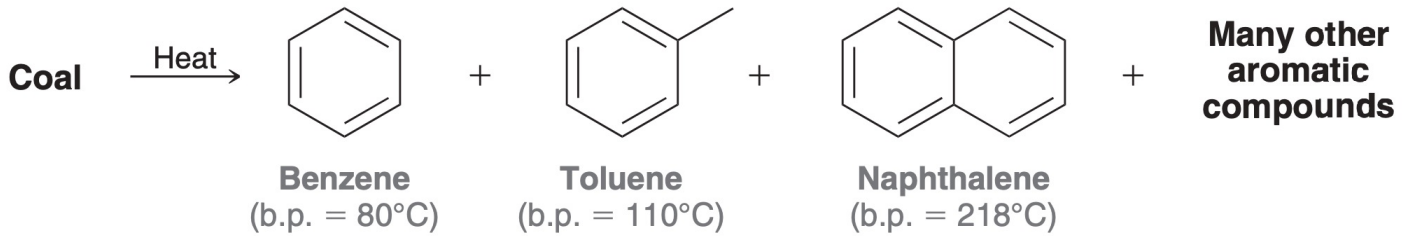
Prevacid
(lansoprazole)
A proton-pump inhibitor used in the treatment of ulcers and acid reflux



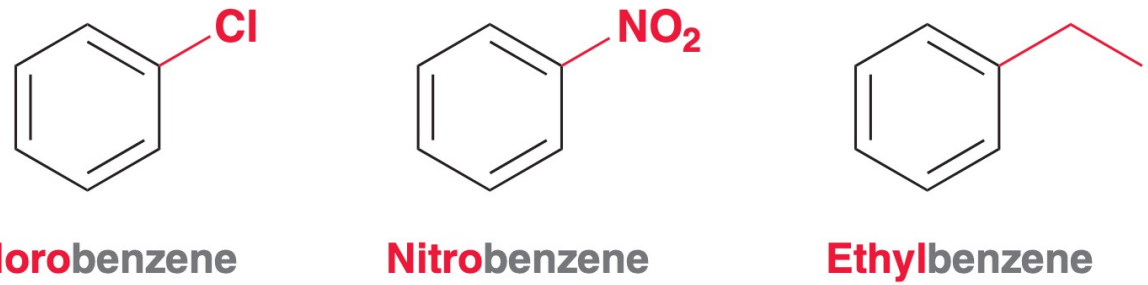
Plavix
(clopidogrel)
An antiplatelet agent (prevents formation of blood clots) used in the treatment of coronary artery disease

- The model of coal

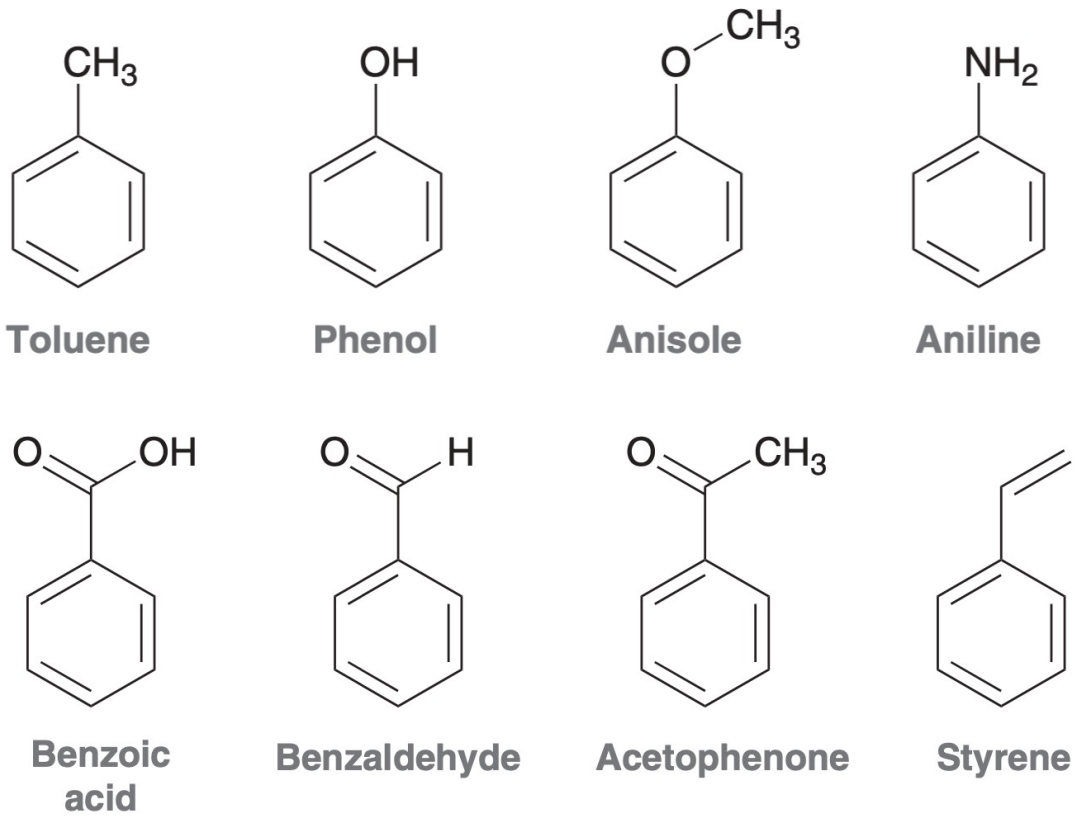




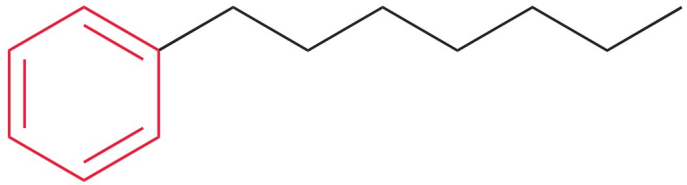
- Nomenclature of benzene derivatives
  - Using benzene as the parent
  - Listing the substituent as a prefix



- Common names accepted by IUPAC



- Benzene as a substituent – phenyl group

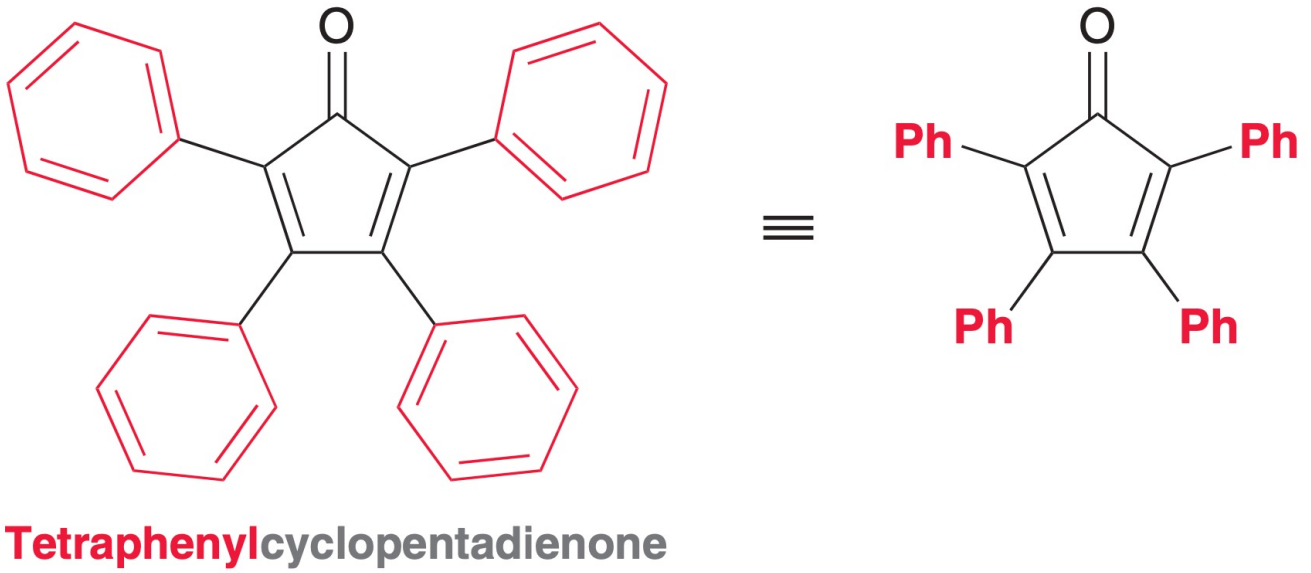


1-Phenylheptane

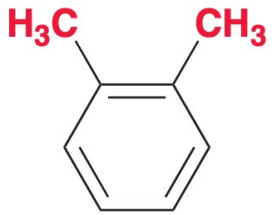
if the carbon chain is quite large (> 6 carbons)

phenyl can be treated as a substituent

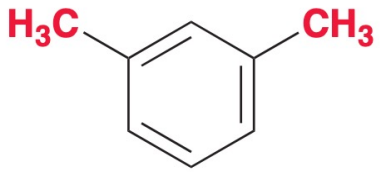
- The abbreviation of phenyl: **Ph**



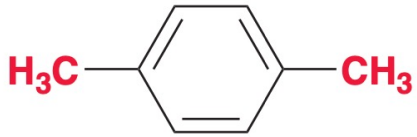
- Disubstituted derivatives of benzene
  - Using descriptors: *ortho* (*o*-), *meta* (*m*-), *para* (*p*-)
  - Using locants: 1,2 (the same as *ortho*); 1,3 (*meta*); 1,4 (*para*)



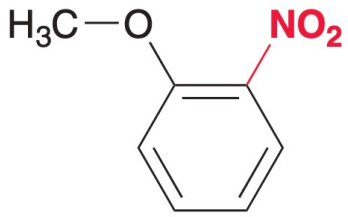
***ortho*-Xylene**
(1,2-dimethylbenzene)



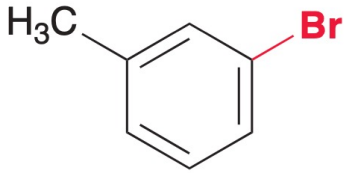
***meta*-Xylene**
(1,3-dimethylbenzene)



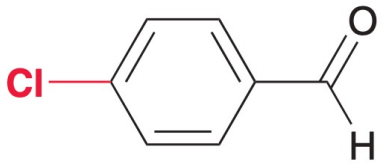
***para*-Xylene**
(1,4-dimethylbenzene)



***ortho*-Nitroanisole**
(2-Nitroanisole)



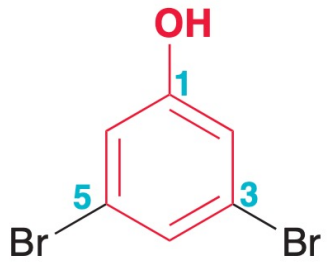
***meta*-Bromotoluene**
(3-Bromotoluene)



***para*-Chlorobenzaldehyde**
(4-Chlorobenzaldehyde)

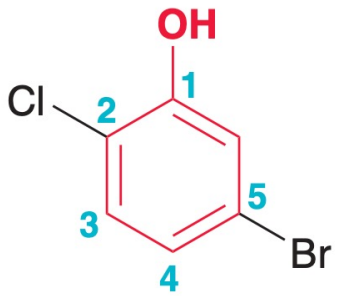
- Polysubstituted derivatives of benzene
  - Identify and name the parent
  - Identify and name the substituents
  - Assign a locant to each substituent
  - Arrange the substituents alphabetically

- Using common name as the parent

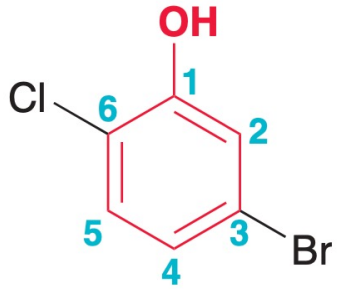


3,5-Dibromophenol

Correct

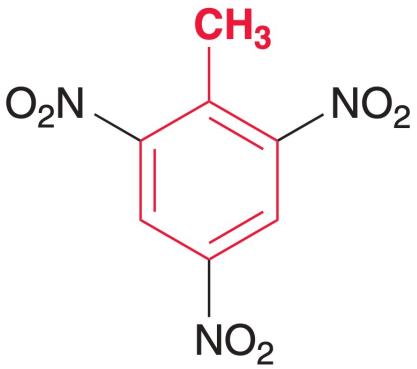


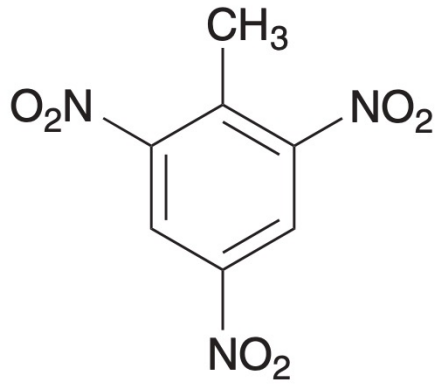
Incorrect



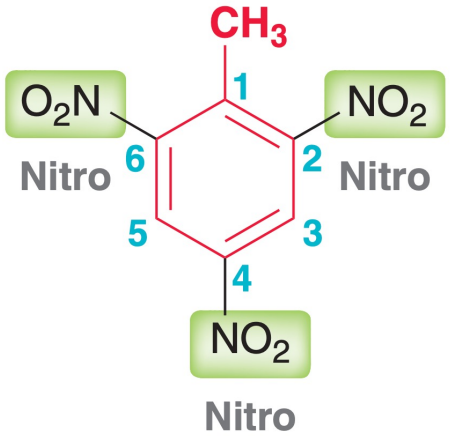
hint: carefully assign the locant!

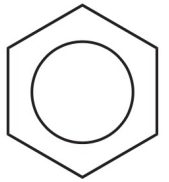
- Practice: provide a systematic name for TNT, a well-known explosive with the following molecular structure:





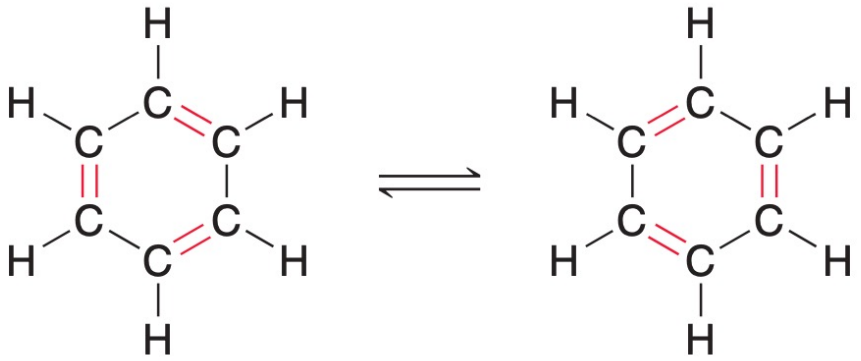
2,4,6-Trinitrotoluene

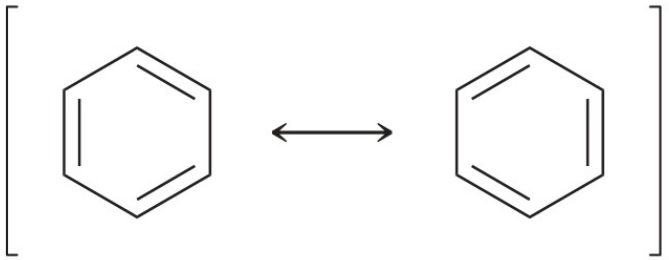




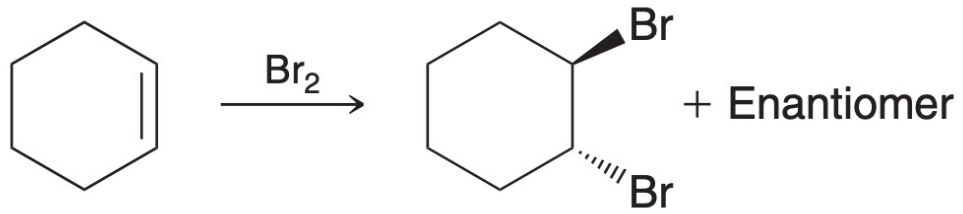
not recommended!

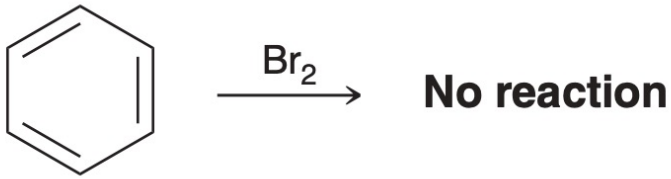
- Structure of benzene: from the *Kekulé* formula



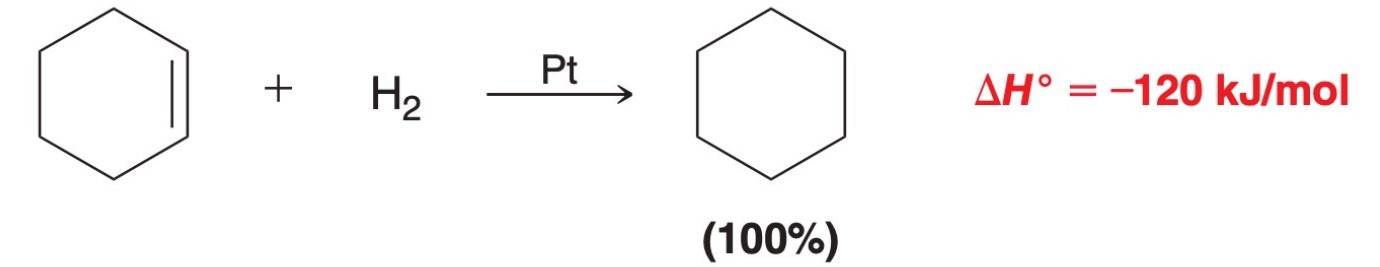


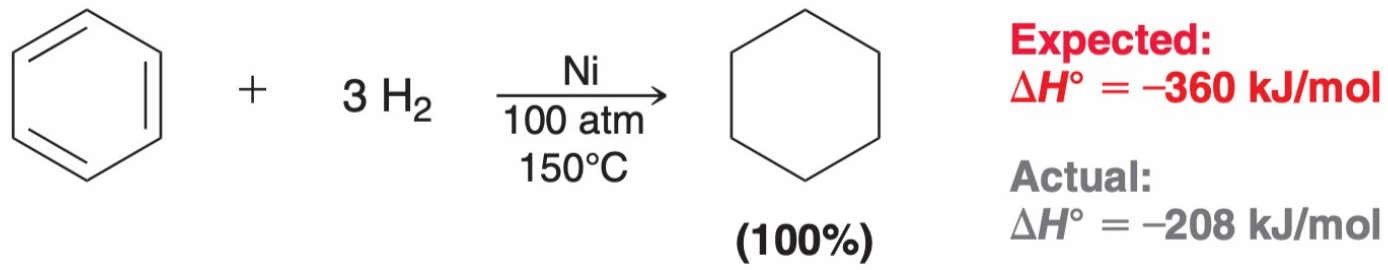
- Stability of benzene



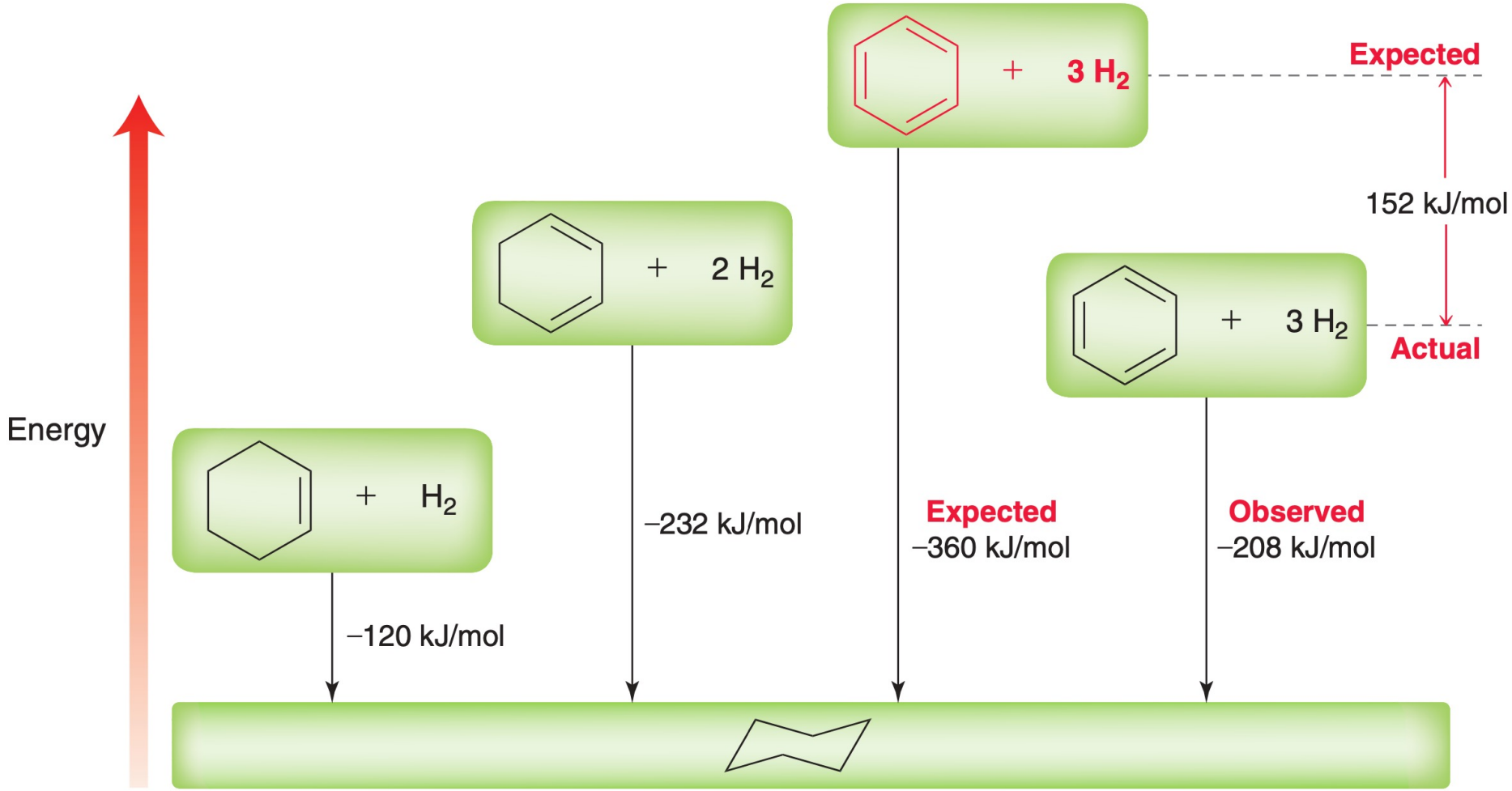


- Evidence for unusual stability

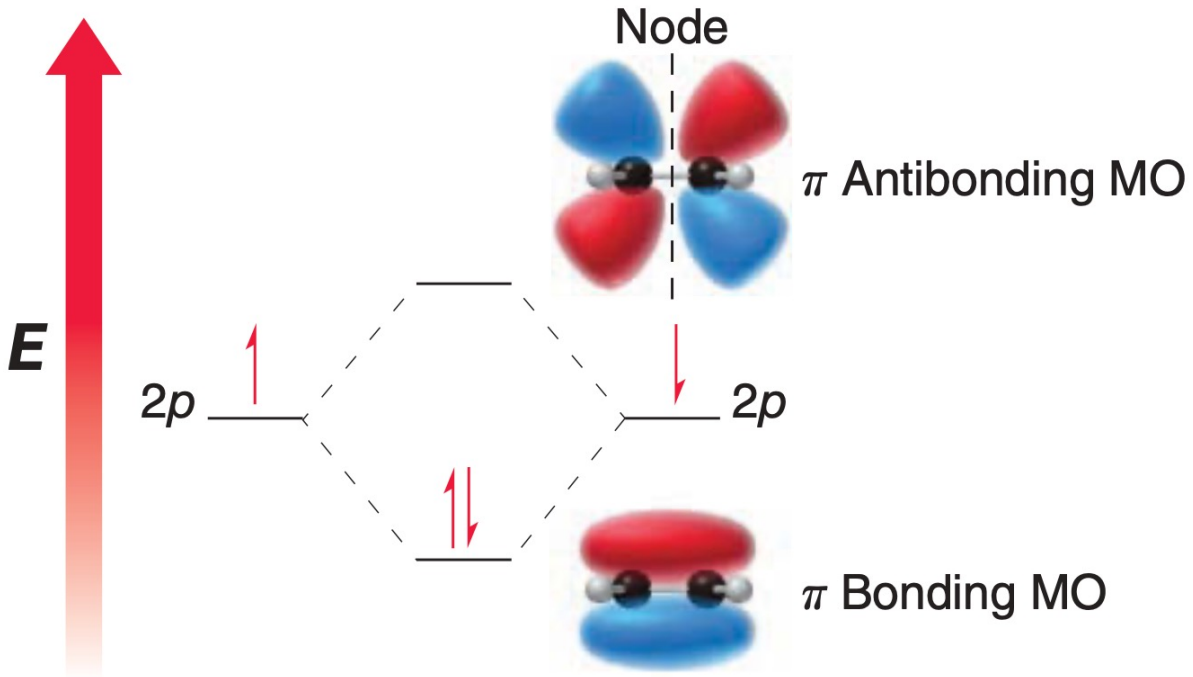




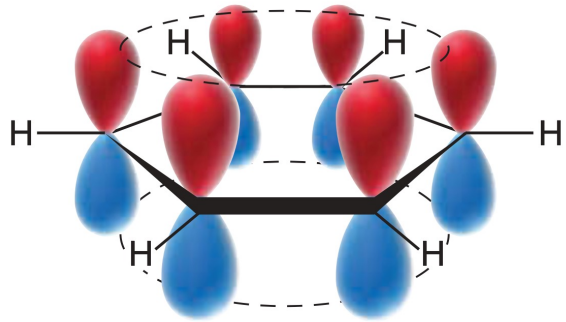
- Energy diagram of hydrogenation



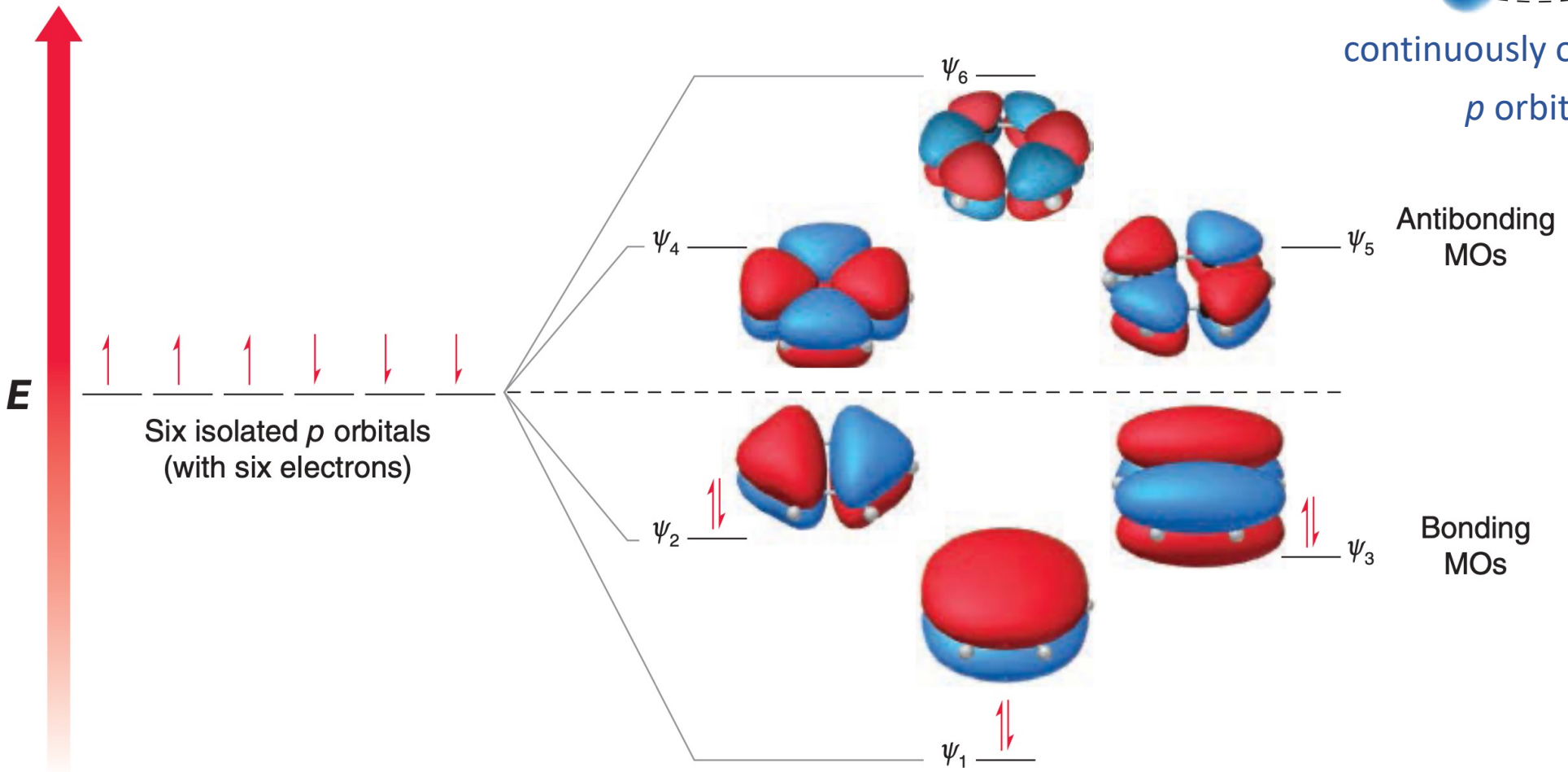
- Molecular orbital theory



- Source of stability: MO description

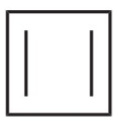


continuously overlapped *p* orbitals

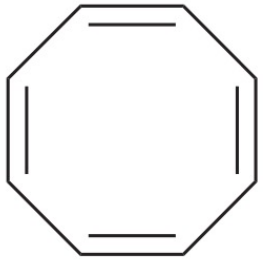


- Conclusion from the MO description
  - There are six molecular orbitals, each of which is associated with the entire molecule (rather than being associated with any specific bond)
  - Three of the six MOs (those below the dashed line) are bonding MOs, while the other three MOs (those above the dashed line) are antibonding MOs
  - Since each MO can contain two electrons, the three bonding MOs can collectively accommodate up to six π electrons
  - By occupying the bonding MOs, all six electrons achieve a lower energy state and are delocalized
  - Since the bonding MOs are filled with paired electrons while the antibonding MOs are empty, benzene is said to have a **closed-shell electron configuration** – the source of stability

- Are they also exhibit aromatic stabilization?

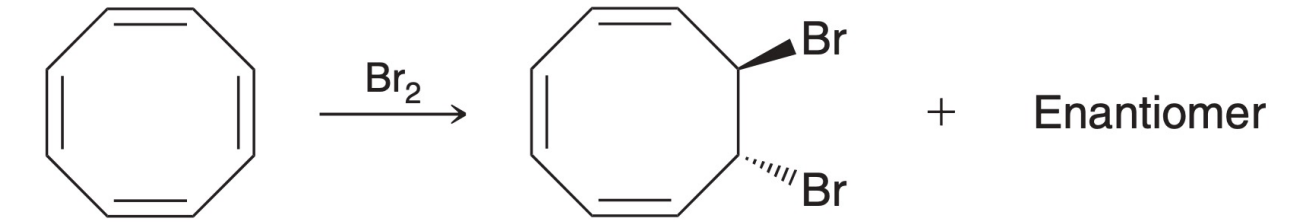


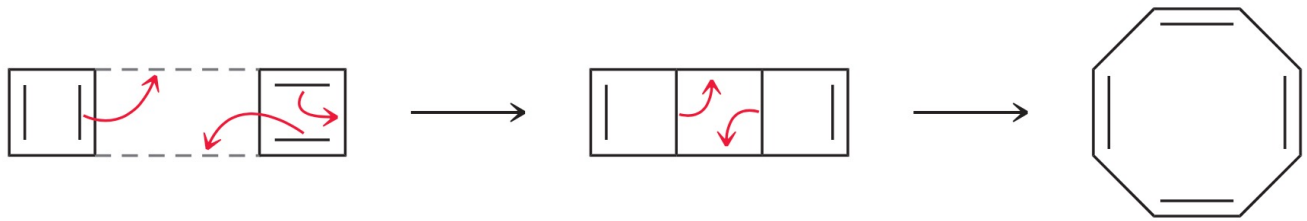
Cyclobutadiene
(C_4H_4)



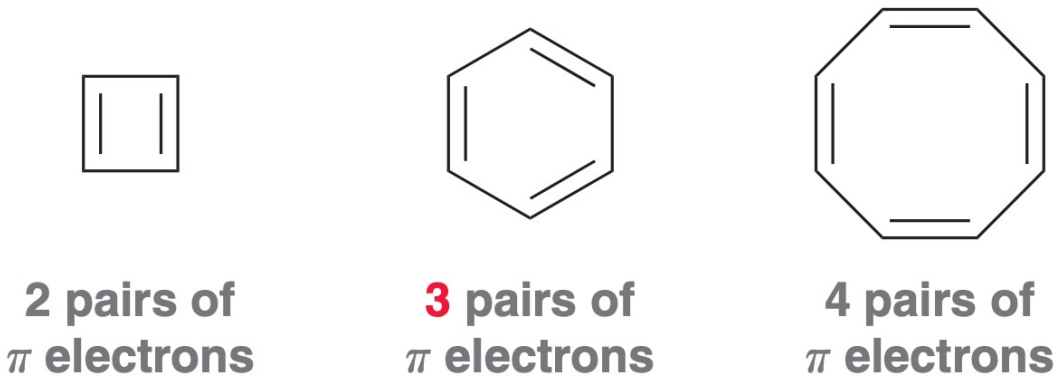
Cyclooctatetraene
(C_8H_8)

- Actually not…

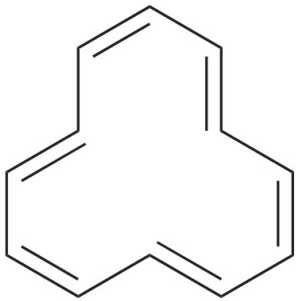




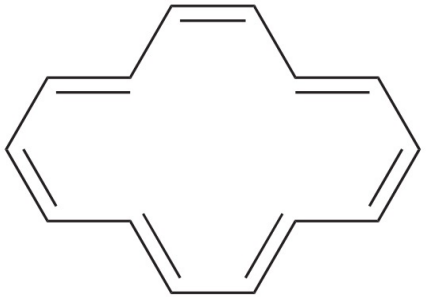
- Hückel's rule: **π electrons should be 4*n* + 2 for aromaticity**



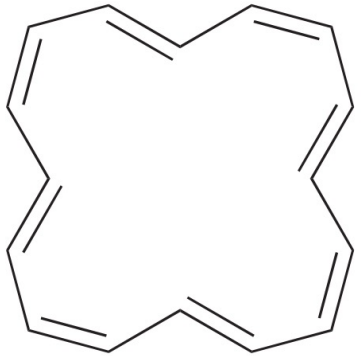
- Practice: predict whether each of the following compounds should be aromatic:

(a) 

not aromatic

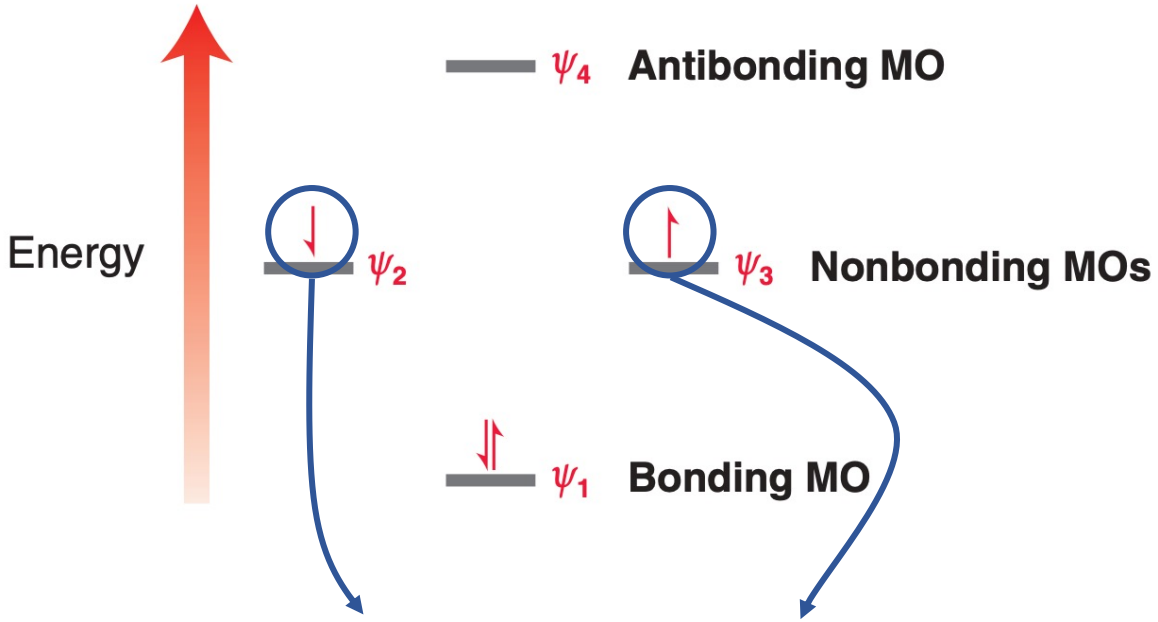
(b) 

aromatic

(c) 

not aromatic

- MO description of Hückel's rule: cyclobutadiene



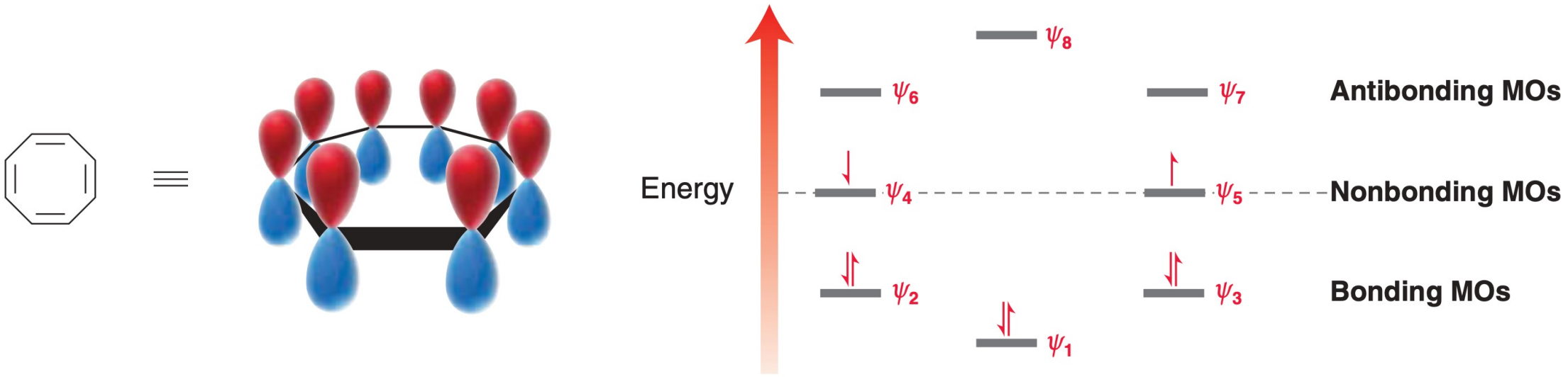
unpaired electrons (a diradical)

open-shell configuration – **antiaromaticity**

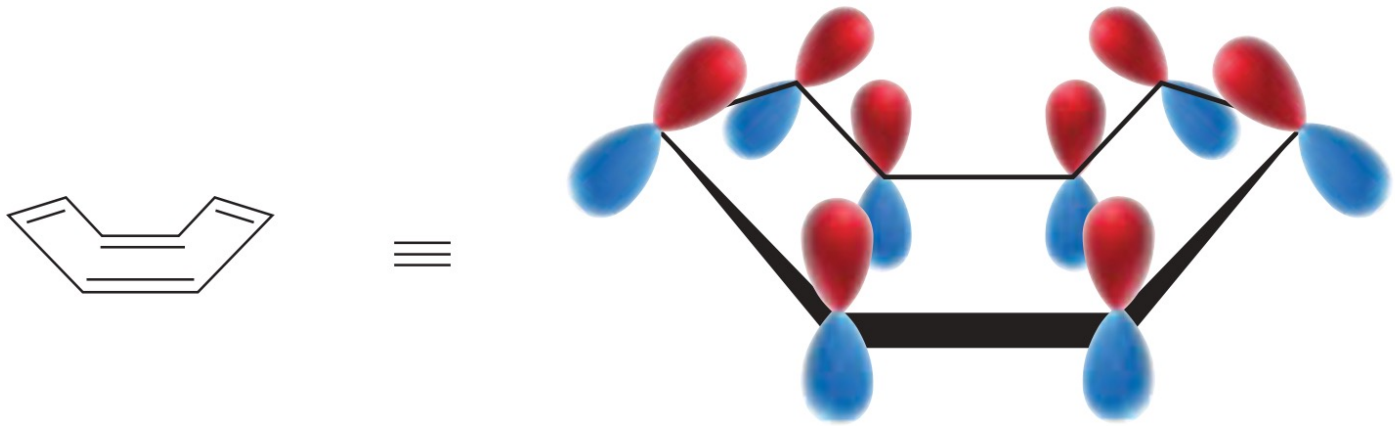
- Avoiding antiaromaticity by changing the shape

two isolated π bonds

- MO description of Hückel's rule: cyclooctatetraene

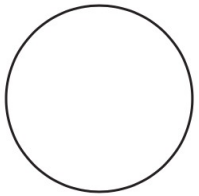
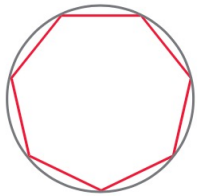
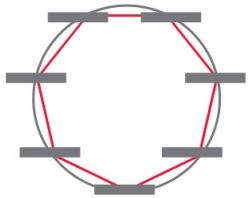
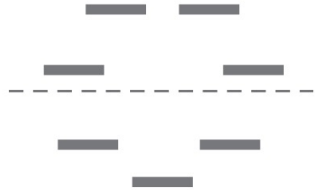
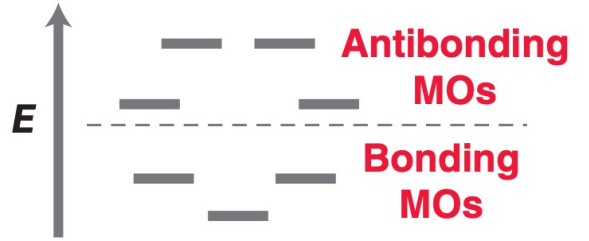


- Changing to a tub shape to avoid unnecessary instability

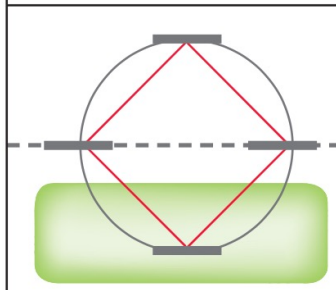
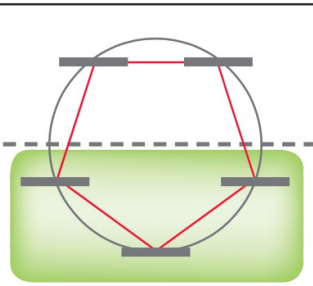
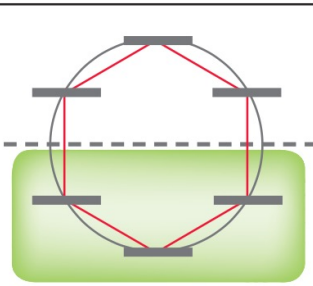
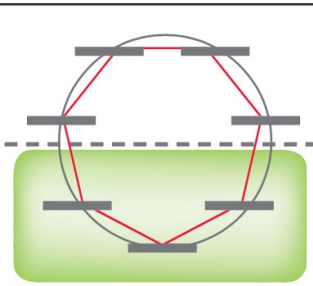
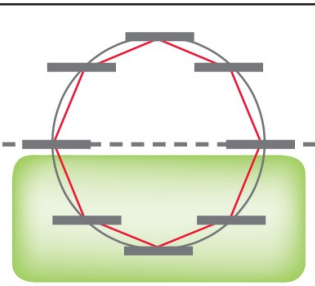
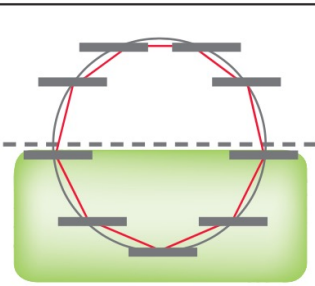
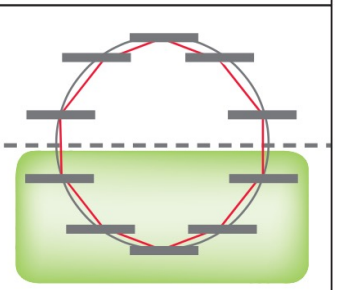


four isolated π bonds

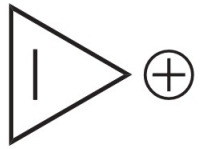
- Frost circle: a method for determining relative MO energy levels

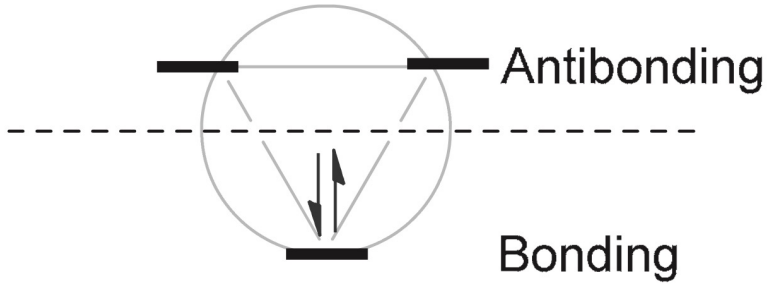
STEP 1 Draw a circle. 	**STEP 2** Inscribe a polygon, making sure that one of the connecting points is at the bottom of the circle. 	**STEP 3** Draw a horizontal line at each point of intersection. 	**STEP 4** Draw a dotted horizontal line through the center of the circle, and then erase the circle and polygon. 	**STEP 5** Identify all bonding MOs (below the line), nonbonding MOs (on the line), and antibonding MOs (above the line). 

- Frost circles for different-size ring systems

Four-membered ring	Five-membered ring	Six-membered ring	Seven-membered ring	Eight-membered ring	Nine-membered ring	Ten-membered ring
						
1 Bonding MO	**3** Bonding MOs	**3** Bonding MOs	**3** Bonding MOs	**3** Bonding MOs	**5** Bonding MOs	**5** Bonding MOs

- Practice: the cyclopropenyl cation has a three-membered ring that contains a continuous system of overlapping p orbitals. This system contains a total of two π electrons. Using a Frost circle, draw an energy diagram showing the relative energy levels of all three MOs and then predict whether this cation is expected to exhibit aromatic stabilization.

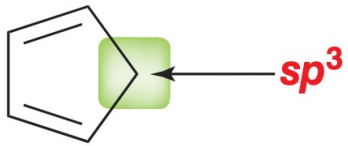




it is expected to exhibit aromatic stabilization

- The criteria for aromaticity
  - The compound must contain a ring comprised of continuously overlapping *p* orbitals – if not, it is said to be **nonaromatic**
  - The number of π electrons in the ring must be a Hückel number ($4n + 2$) – if there are **$4n$** electrons, the compound is said to be **antiaromatic**

Not a ring

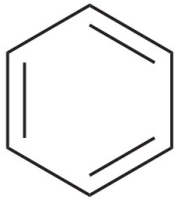


Not a continuous system of *p* orbitals

Molecule is not planar, so the *p* orbitals are not overlapping

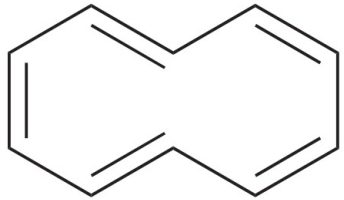
examples of nonaromatic

- Annulenes

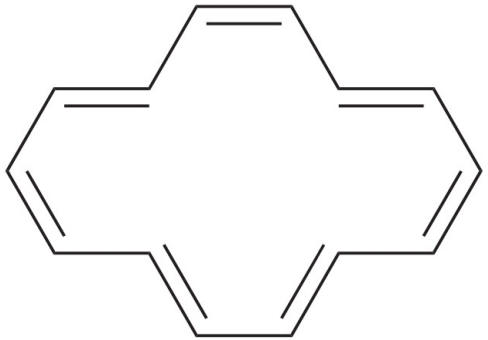


[6]Annulene

(benzene)

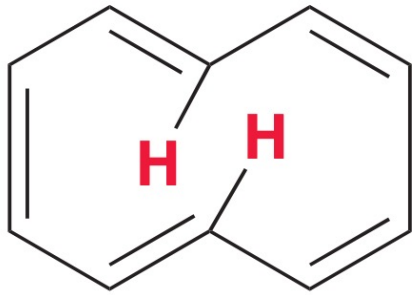


[10]Annulene



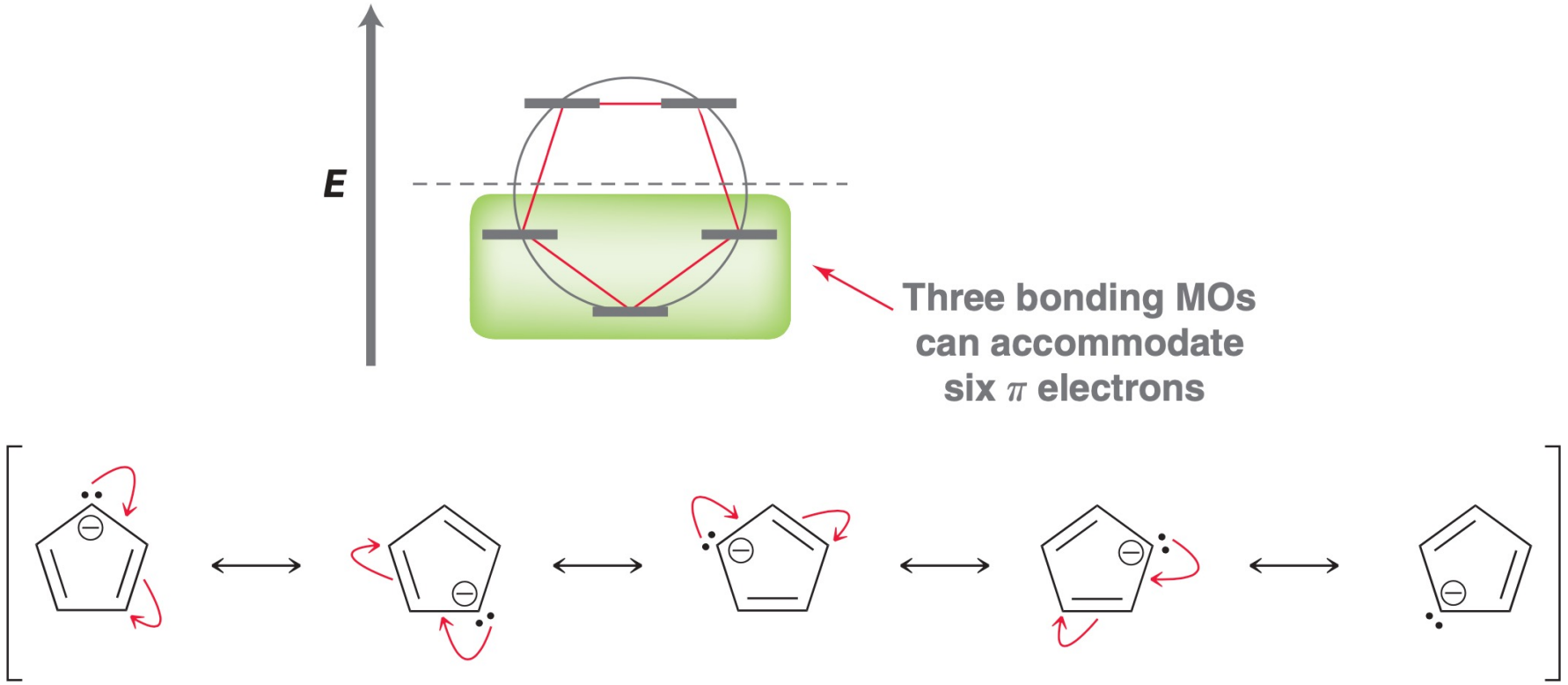
[14]Annulene

- [10]annulene – steric interaction forces out of planarity

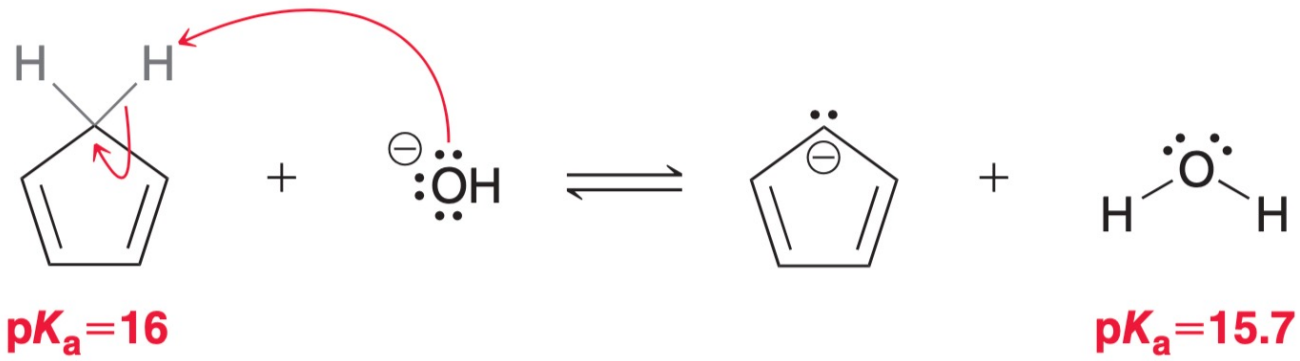


larger annulene has less pronounced effect

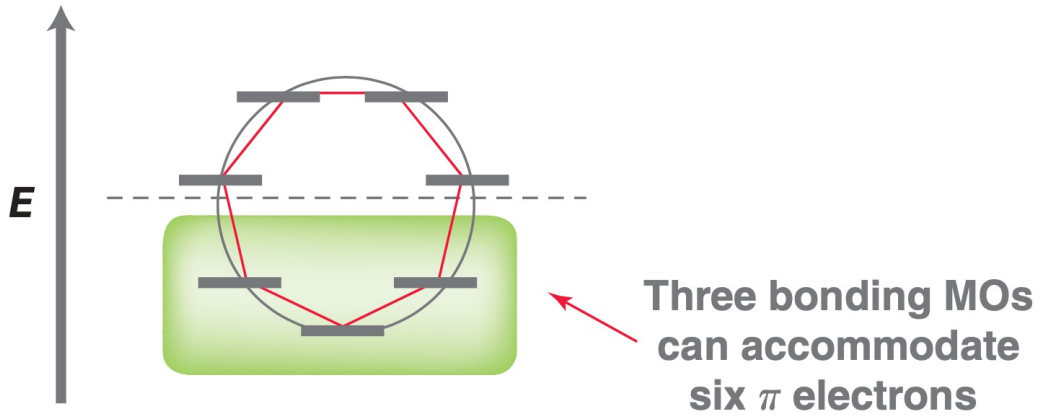
- Aromatic ions: five-membered ring

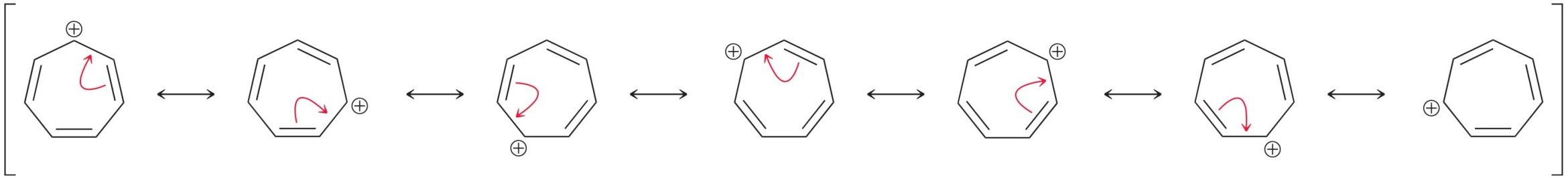


- Unusually low pK_a for cyclopentadiene

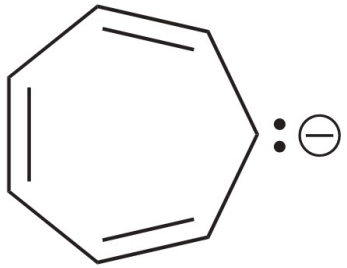


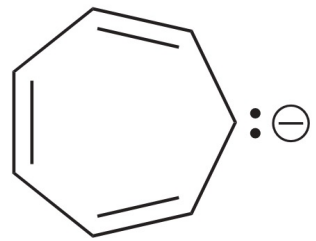
- Aromatic ions: seven-membered ring





- Practice: determine whether the following anion is aromatic, nonaromatic, or antiaromatic:



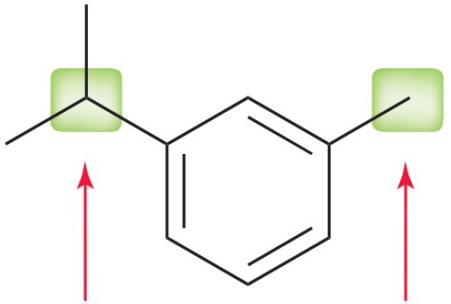


To determine if this anion is aromatic, we must ask two questions:

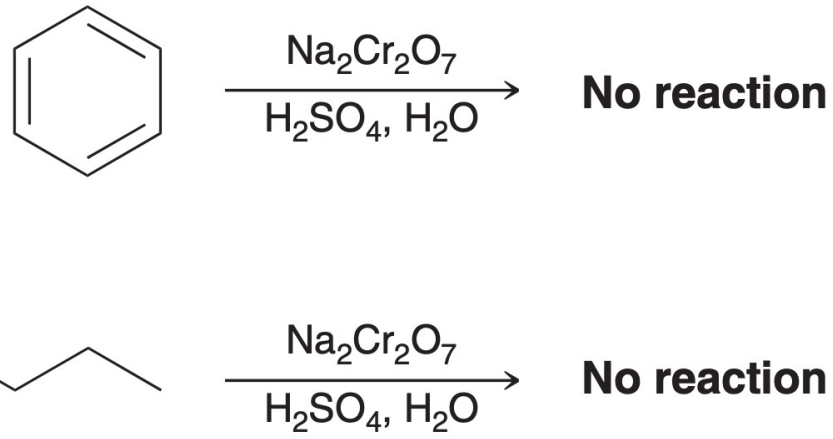
1. Does the compound contain a ring comprised of continuously overlapping *p* orbitals?
2. Is there a Hückel number of π electrons in the ring?

The answer to the first question appears to be yes; that is, the lone pair can occupy a *p* orbital, providing for continuous overlap of *p* orbitals around the ring. However, when we try to answer the second question, we discover that this anion has eight π electrons, which renders the anion antiaromatic. As such, we expect the geometry of this anion to change and become nonplanar, in order to avoid some of the instability associated with antiaromaticity.

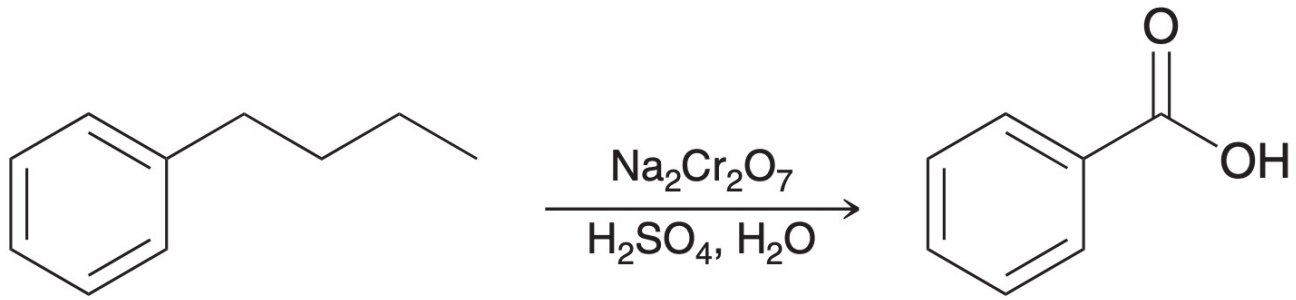
- Benzylic position



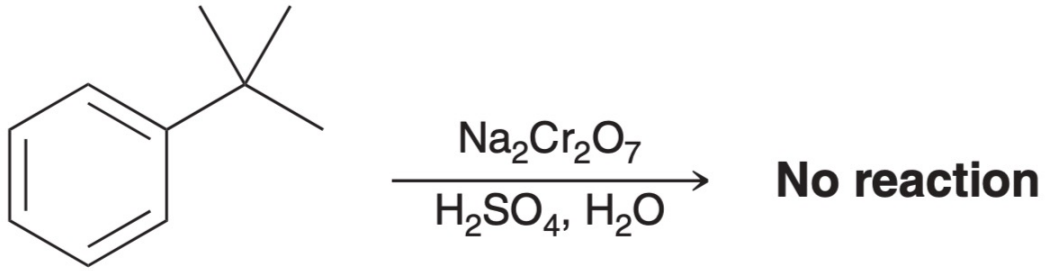
- *Recall*: chromic acid does not readily react with benzene or alkanes



- Benzylic oxidation

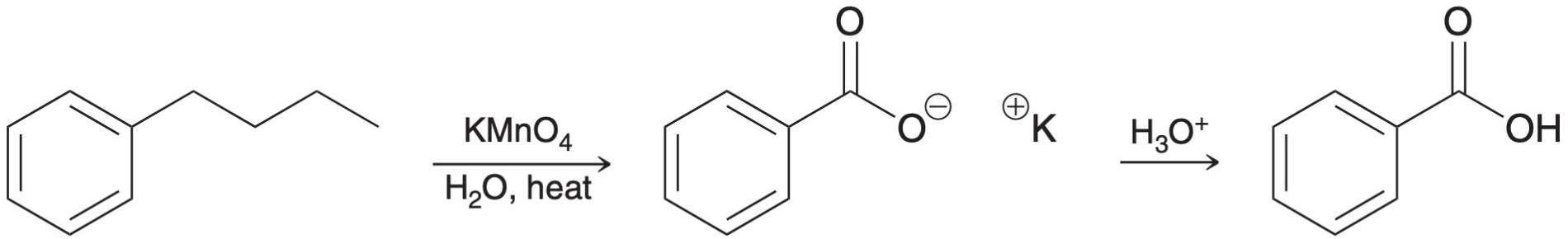


no matter the alkyl group is, the product must be benzoic acid



the benzylic position must have at least one H

- Using other oxidizing agents like $KMnO_4$

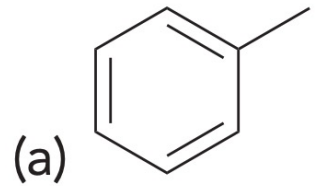


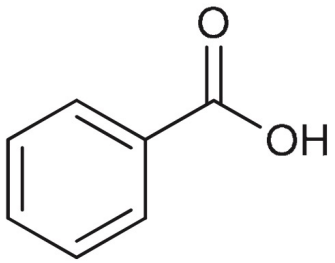
protonation is needed

for acquiring benzoic acid

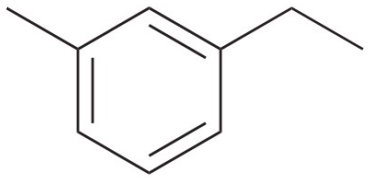
- Practice: draw the expected product when each of the following compounds is oxidized with chromic acid:

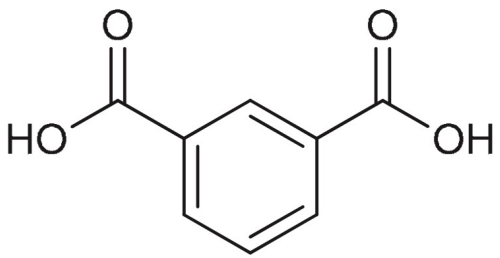
(a)



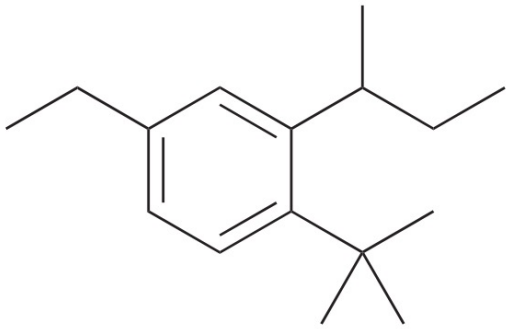


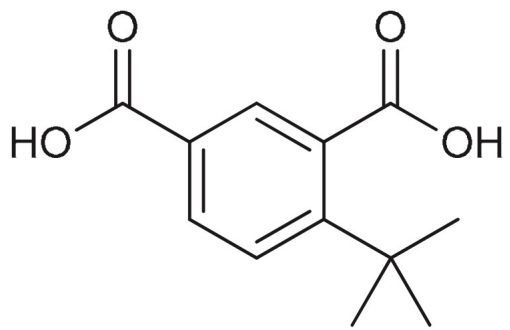
(b)

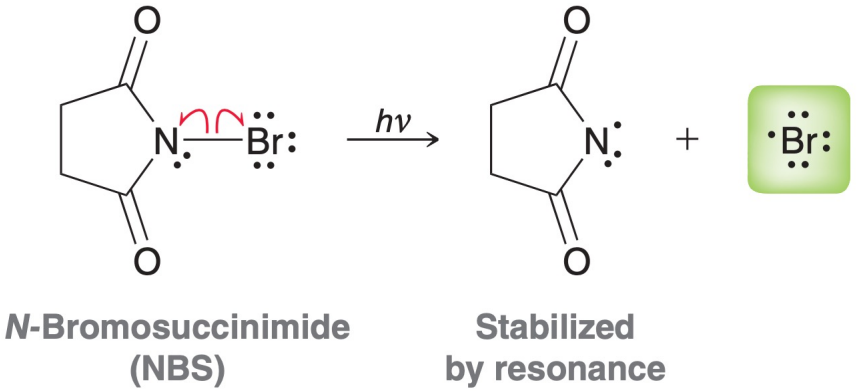




(c)



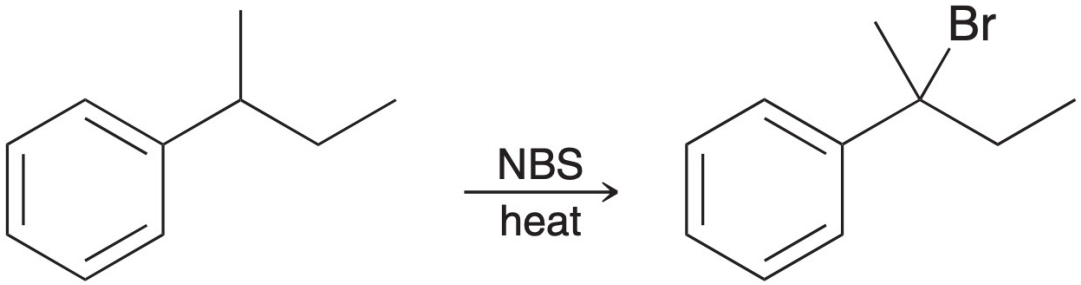




N-Bromosuccinimide (NBS)

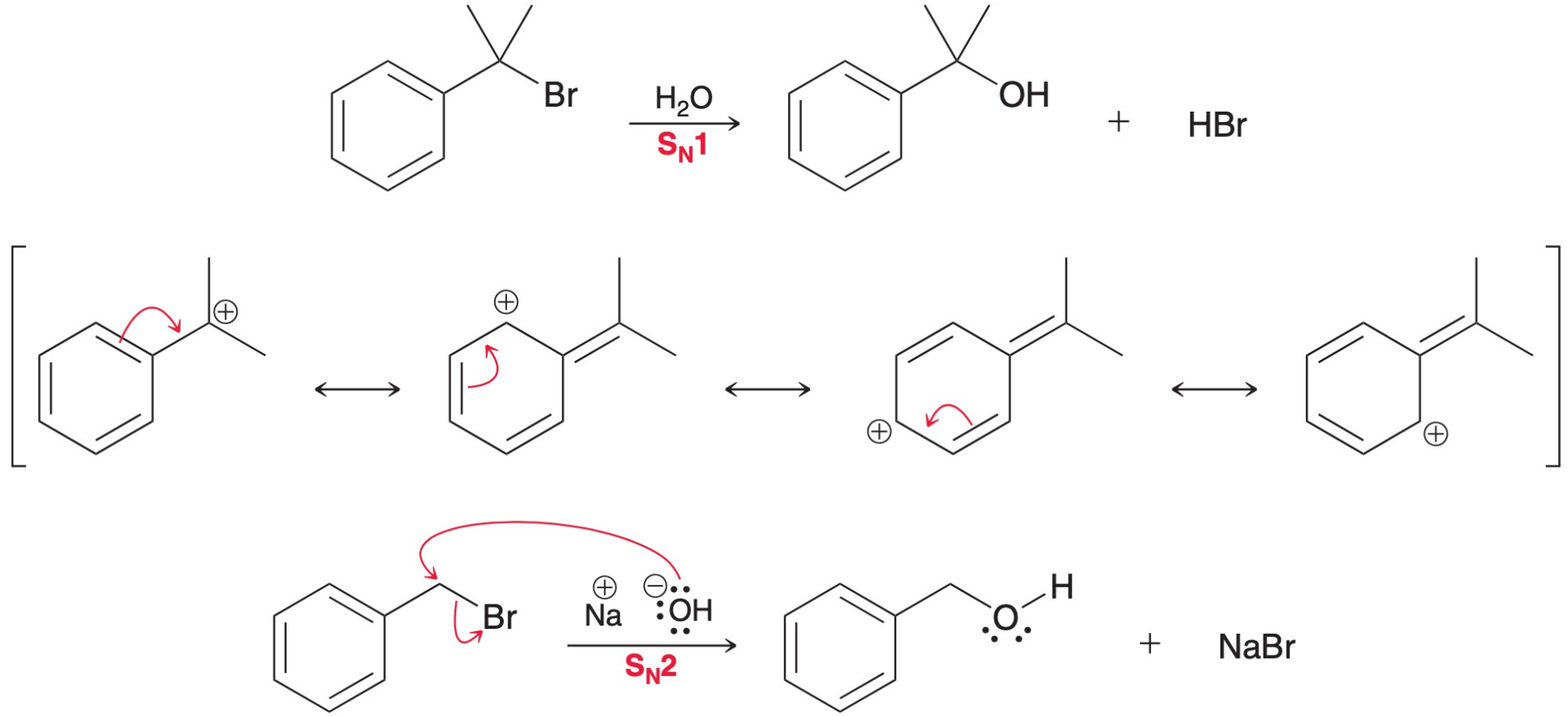
Stabilized by resonance

- Free-radical bromination

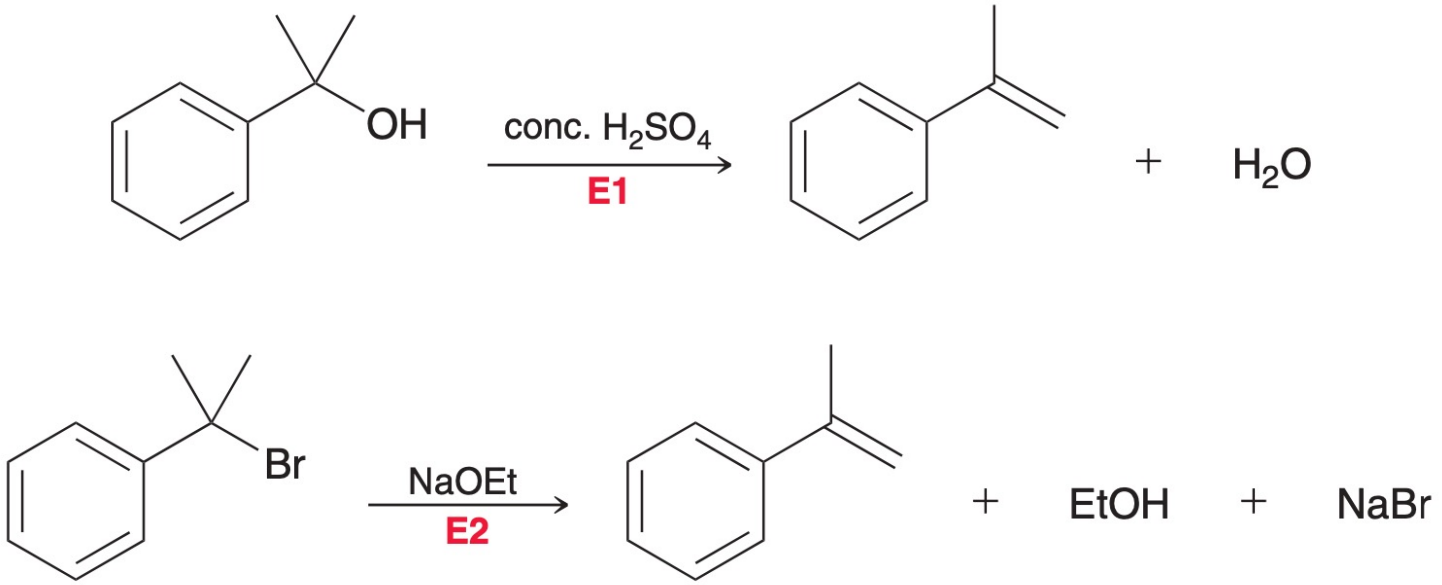


highly regioselective for benzylic position

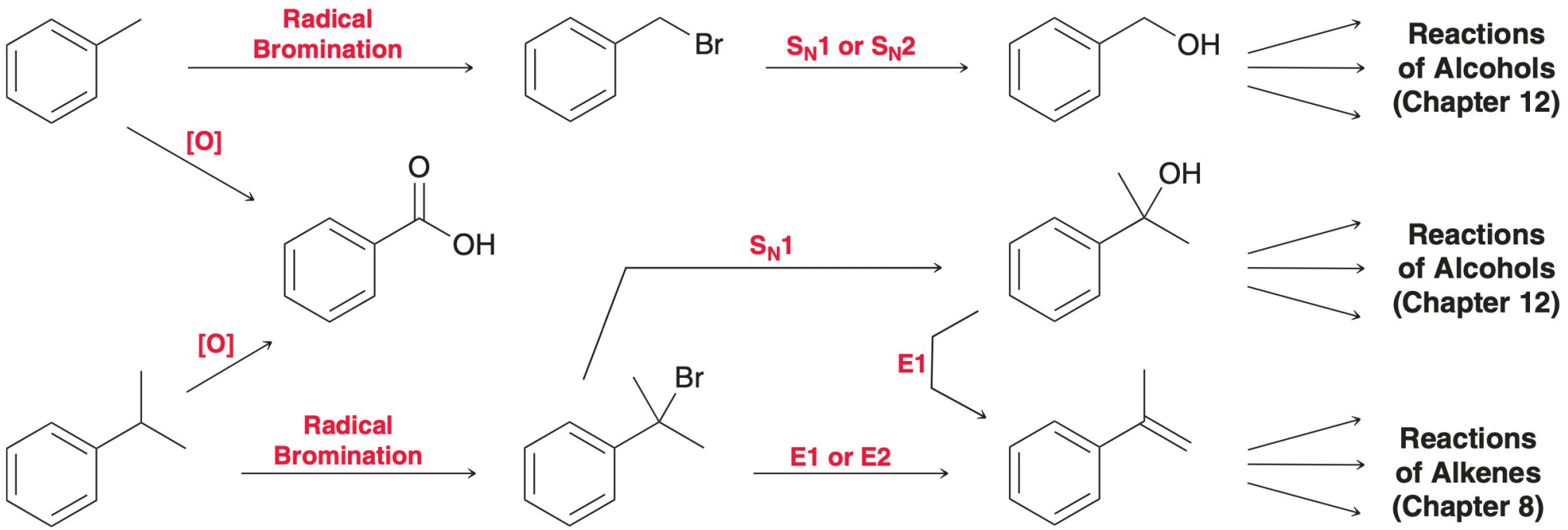
- Substitution reactions of benzylic halides



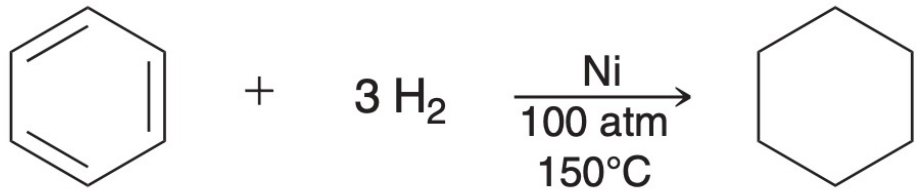
- Elimination reactions of benzylic halides



- Summary of reactions at the benzylic position

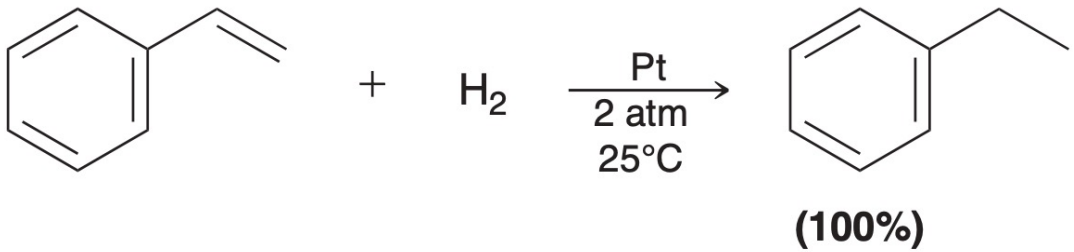


- Benzene hydrogenation



$\Delta H° = -208$ kJ/mol

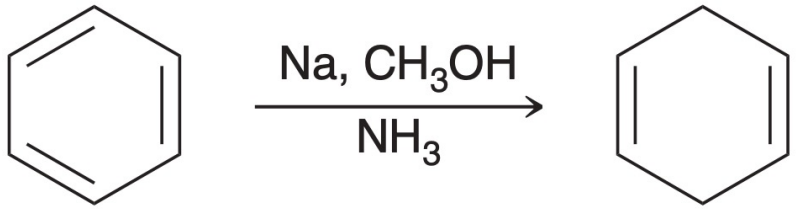
fully reduction



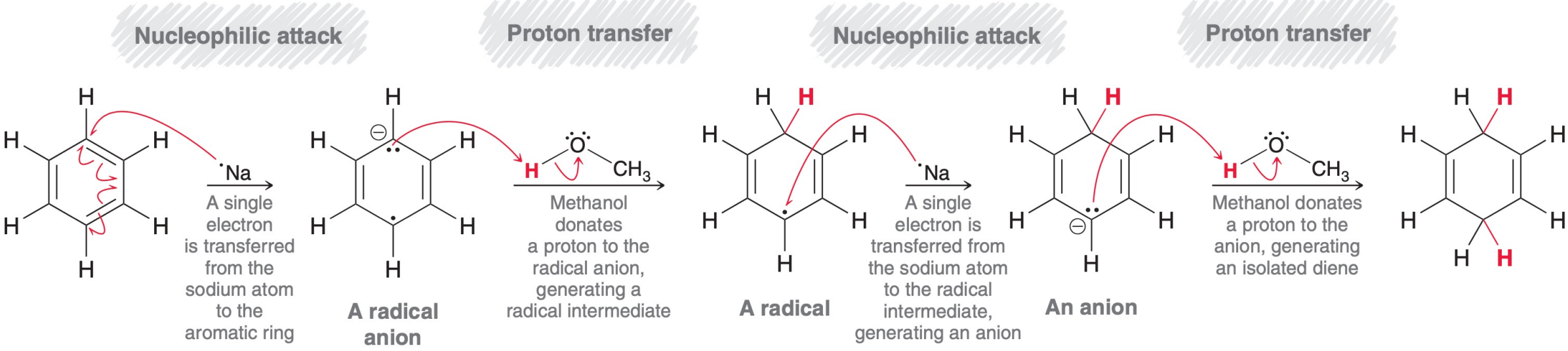
$\Delta H° = -117$ kJ/mol

controlled selective reduction of vinyl group

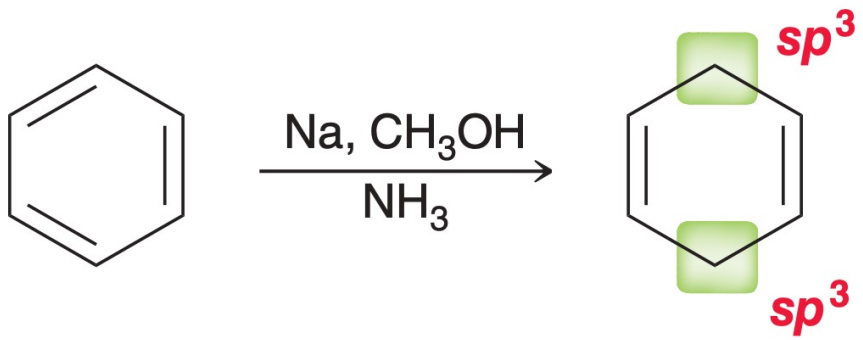
- Birch reduction



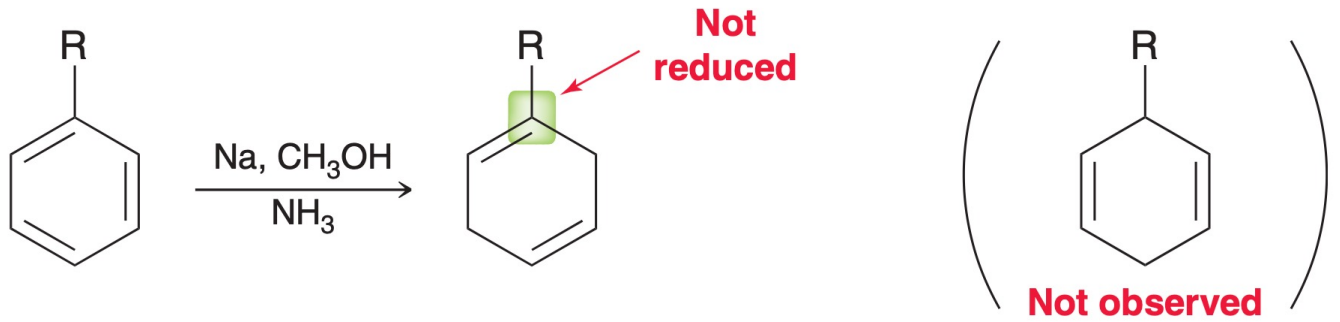
- **Mechanism: the Birch Reduction**



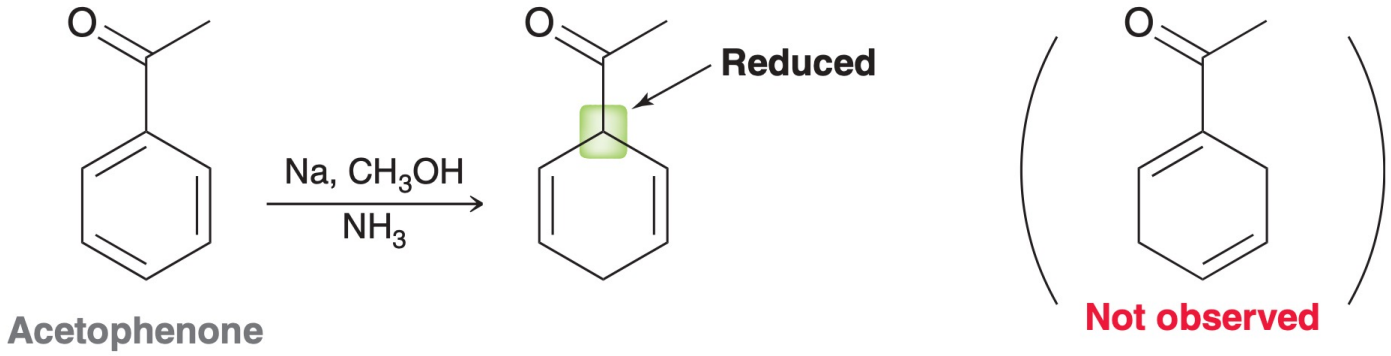
- Only two carbons are reduced in Birch reduction



- Regioselectivity of Birch reduction

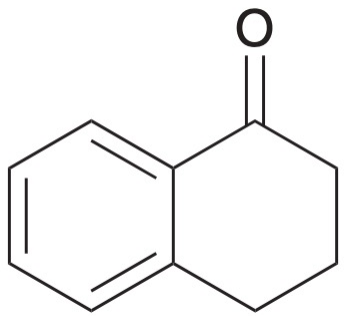


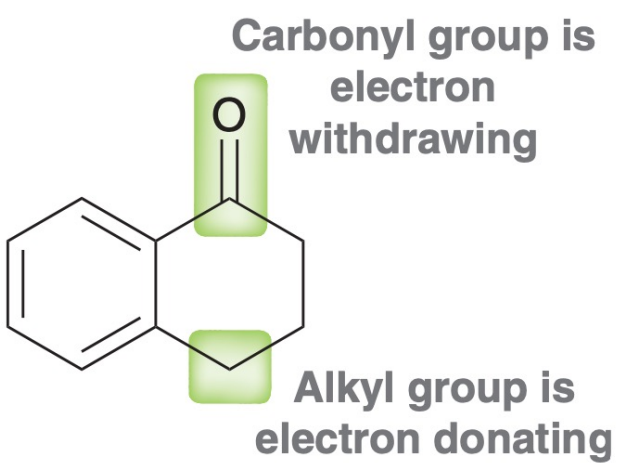
when an EDG substituent is present, carbon linked to the EDG is not reduced

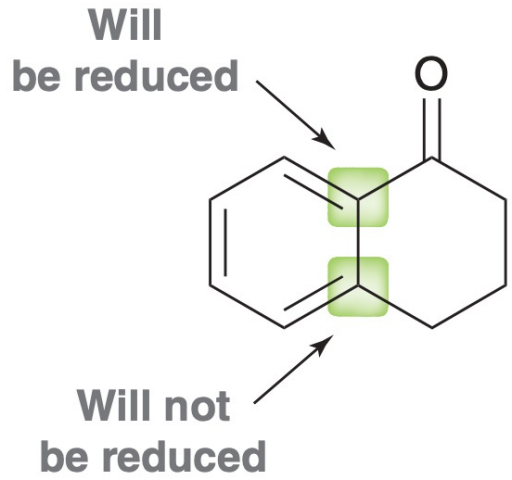


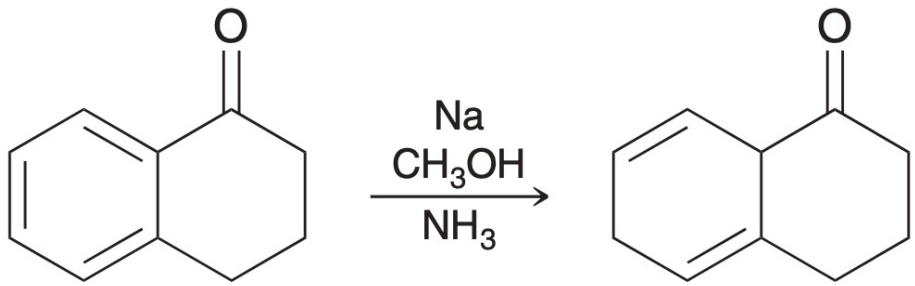
when an EWG substituent is present, carbon linked to the EWG is reduced

- Practice: predict the major product obtained when the following compound is treated with Birch conditions:

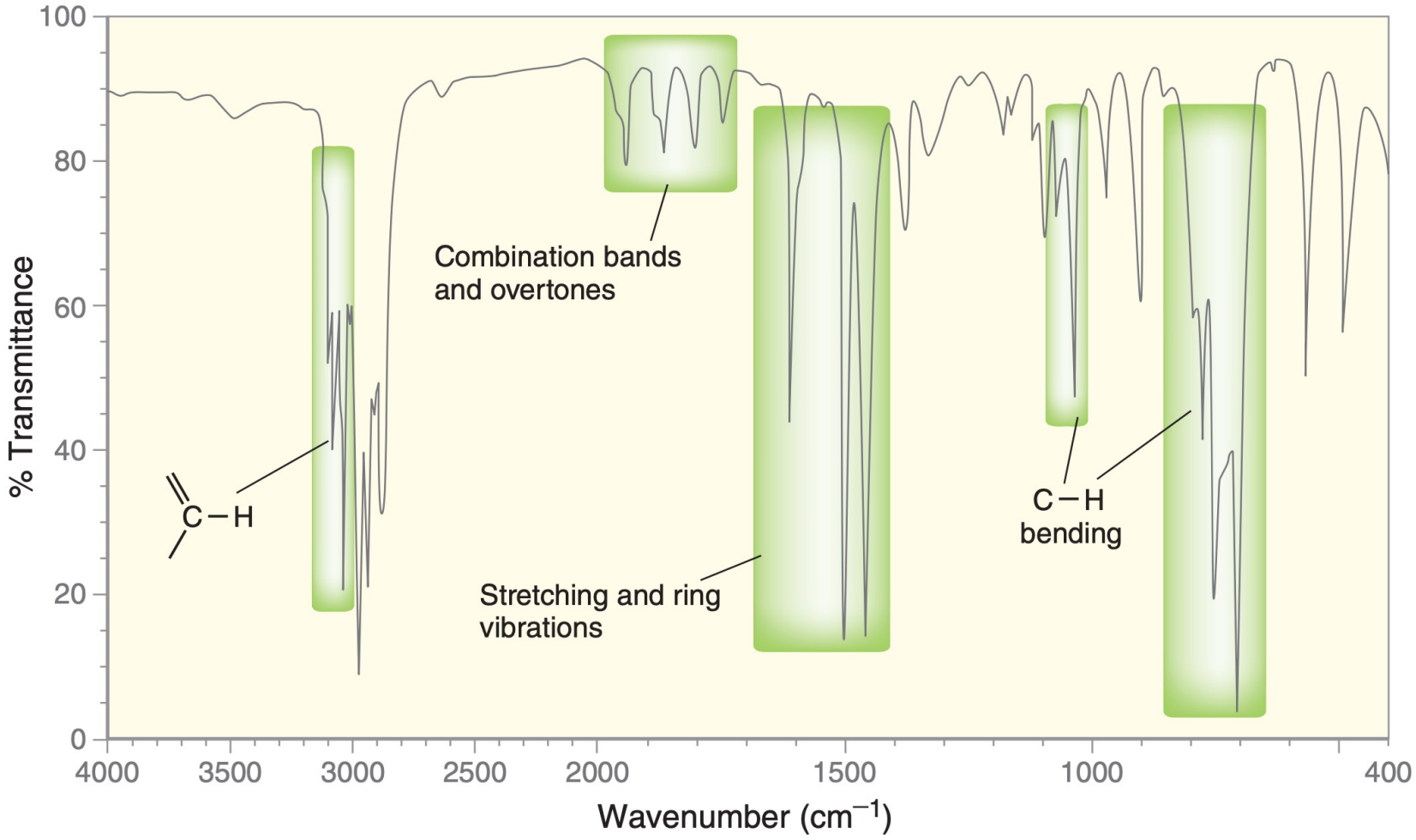



Carbonyl group is electron withdrawing
O
Alkyl group is electron donating


Will be reduced
O
Will not be reduced


O
Na
CH3OH
NH3
O

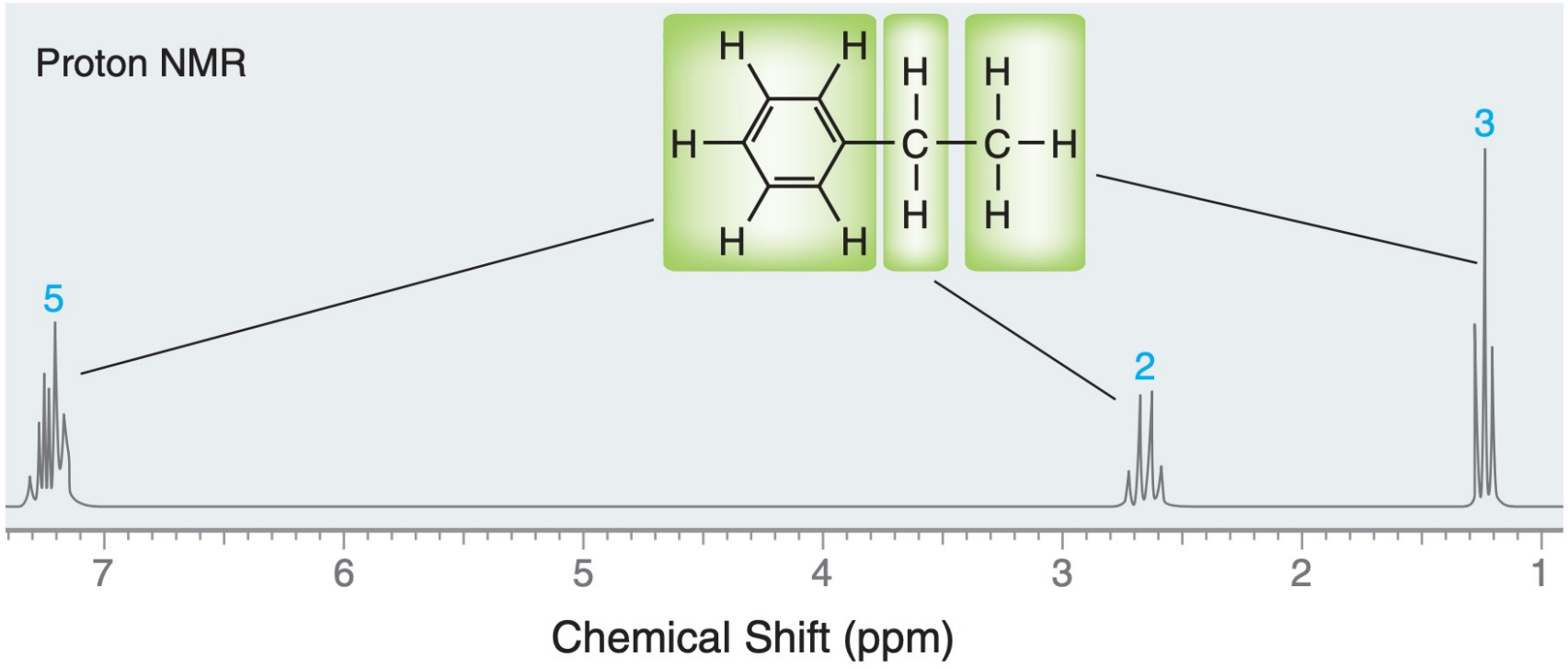
- IR spectroscopy



- Characteristic signals in the IR spectra of aromatic compounds

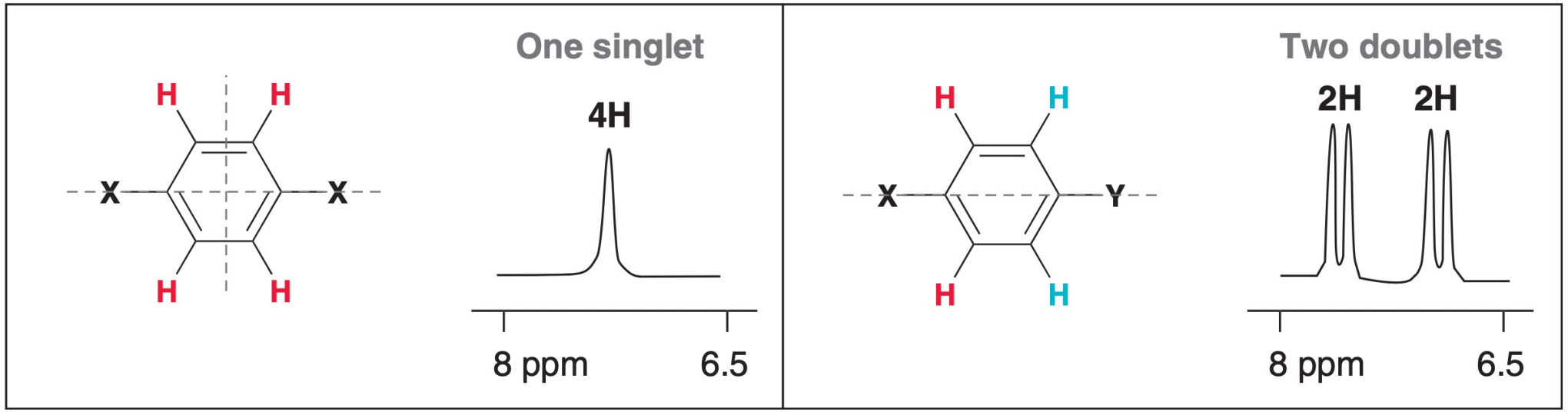
ABSORPTION	FEATURE	COMMENTS
3000–3100 cm^{-1}	C_{sp^2}—H stretching	One or more signals just above 3000 cm^{-1}. Intensity is generally weak or medium
1700–2000 cm^{-1}	Combination bands and overtones	A group of very weak signals
1450–1650 cm^{-1}	Stretching of carbon-carbon bonds as well as ring vibrations	Generally three signals (medium intensity) at around 1450, 1500, and 1600 cm^{-1}
1000–1275 cm^{-1}	C—H bending (in plane)	Several signals of strong intensity
690–900 cm^{-1}	C—H bending (out of plane)	One or two strong signals

- ^{1}H NMR spectroscopy

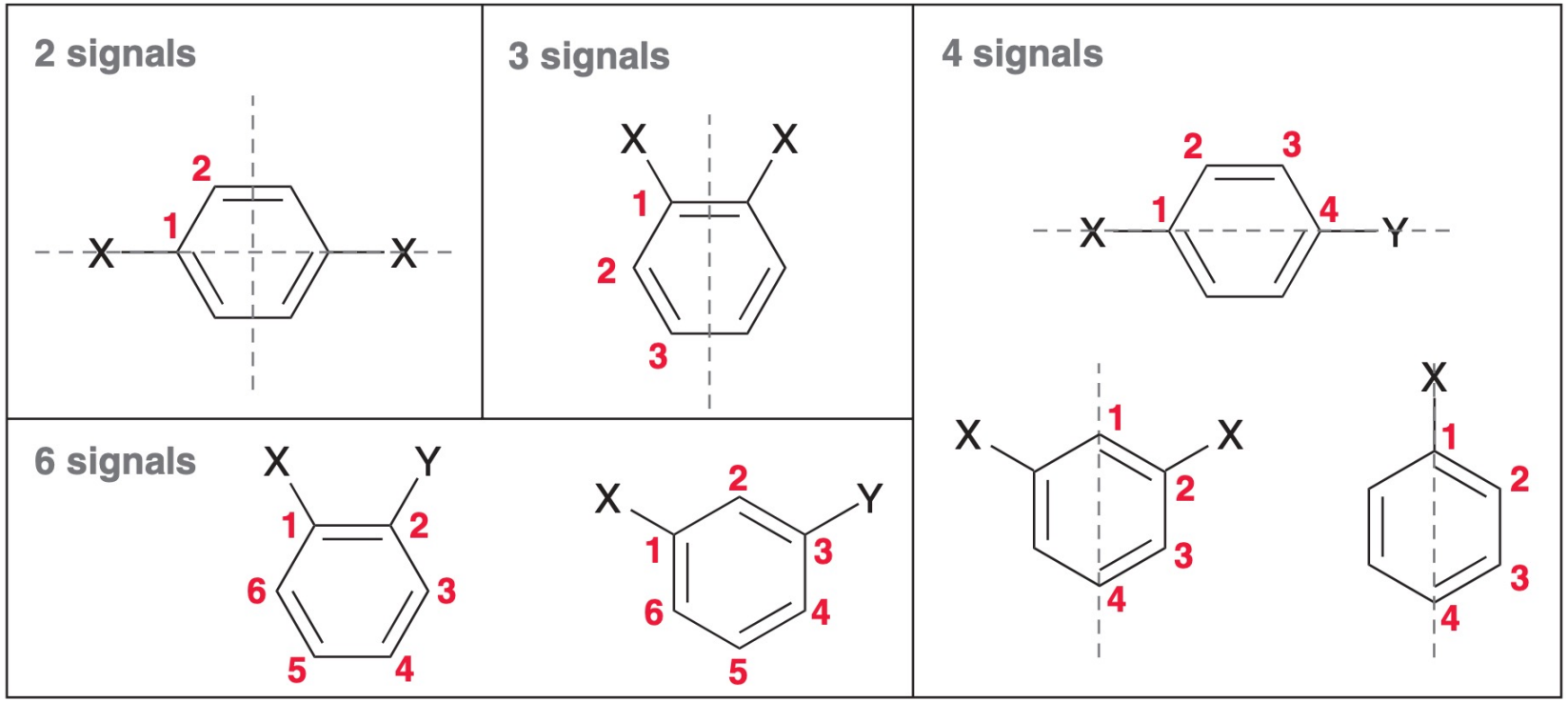


multiplet between 6.5 to 8 ppm is an evidence of aromatic ring

- Complex splitting patterns… except two *para*-disubstituted cases



- ^{13}C NMR Spectroscopy



signals typically fall in the region of 100–150 ppm

Aromatic Substitution Reactions

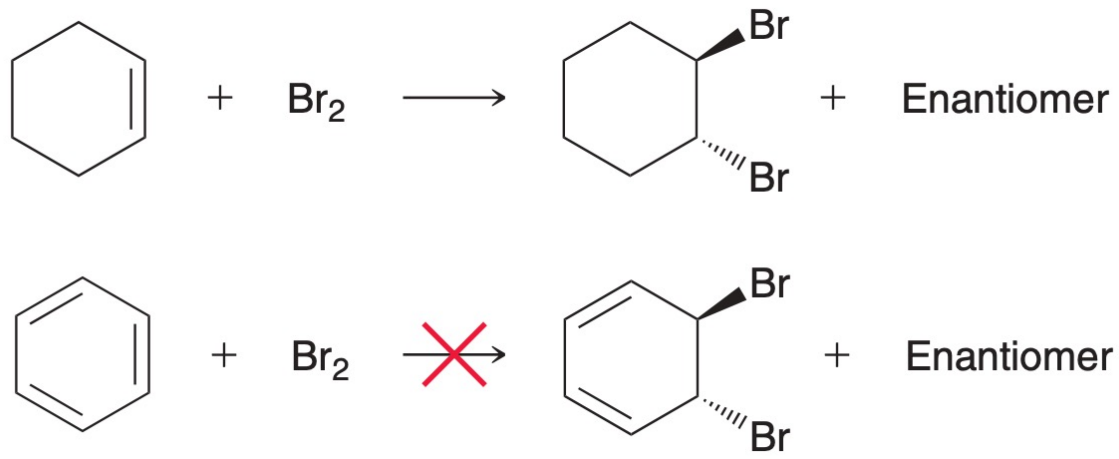
Introduction to Electrophilic Aromatic Substitution,

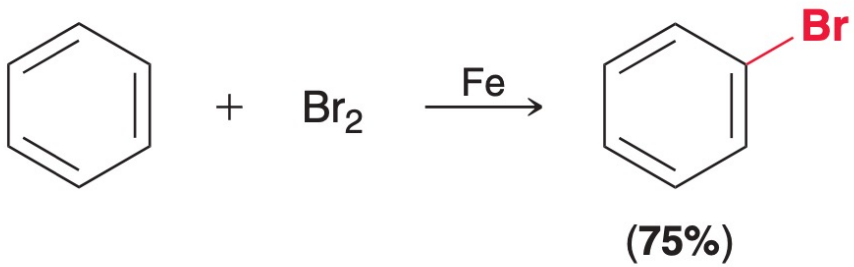
Halogenation, Sulfonation, Nitration, Friedel–Crafts Reactions,

Activating and Deactivating Groups, Directing Effect and Substituent Positions,

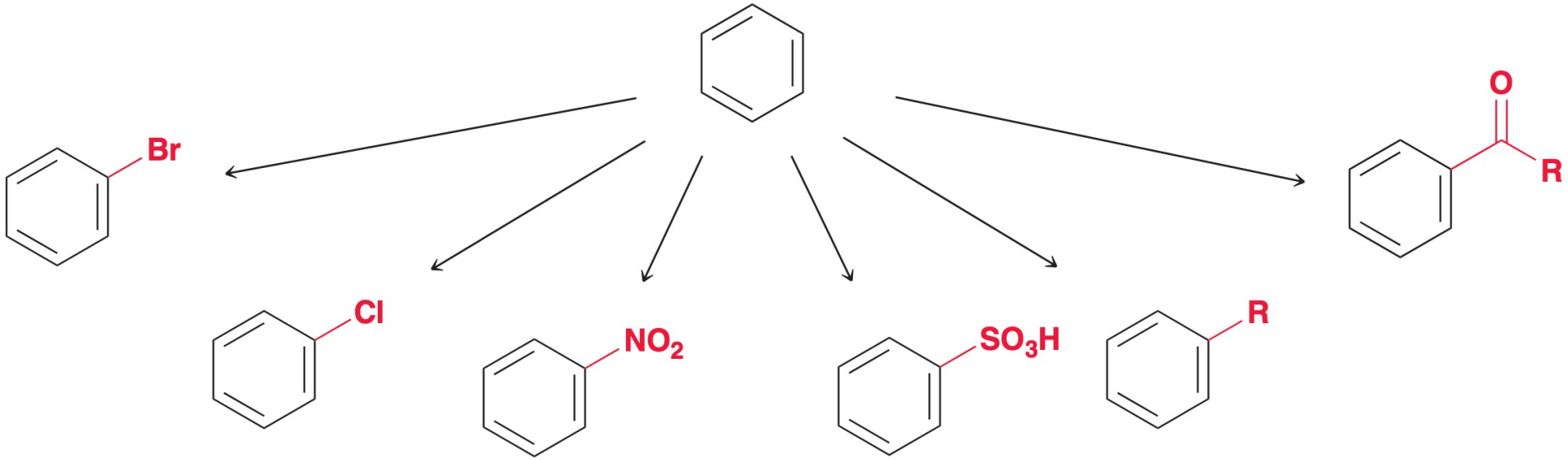
Nucleophilic Aromatic Substitution, Elimination-Addition

- Introduction to **E**lectrophilic **Ar**omatic **S**ubstitution (**EArS**)

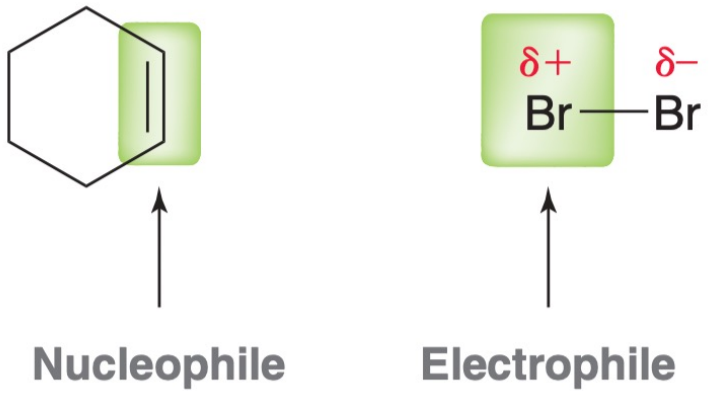




- Electrophilic aromatic substitution reactions

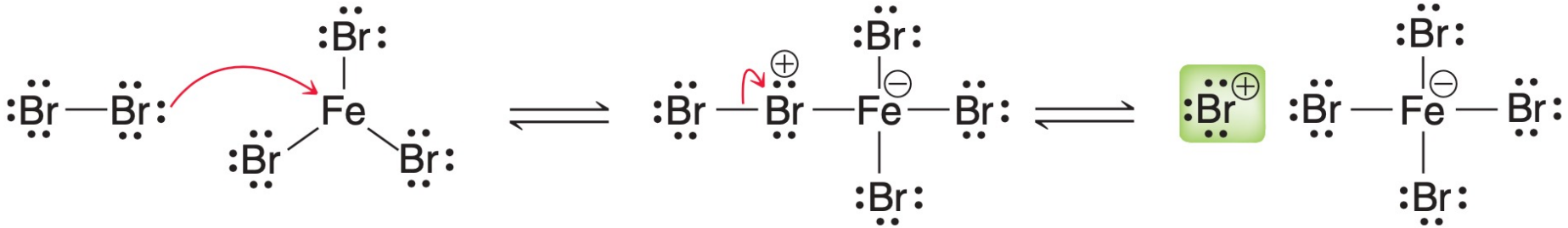


- Benzene bromination

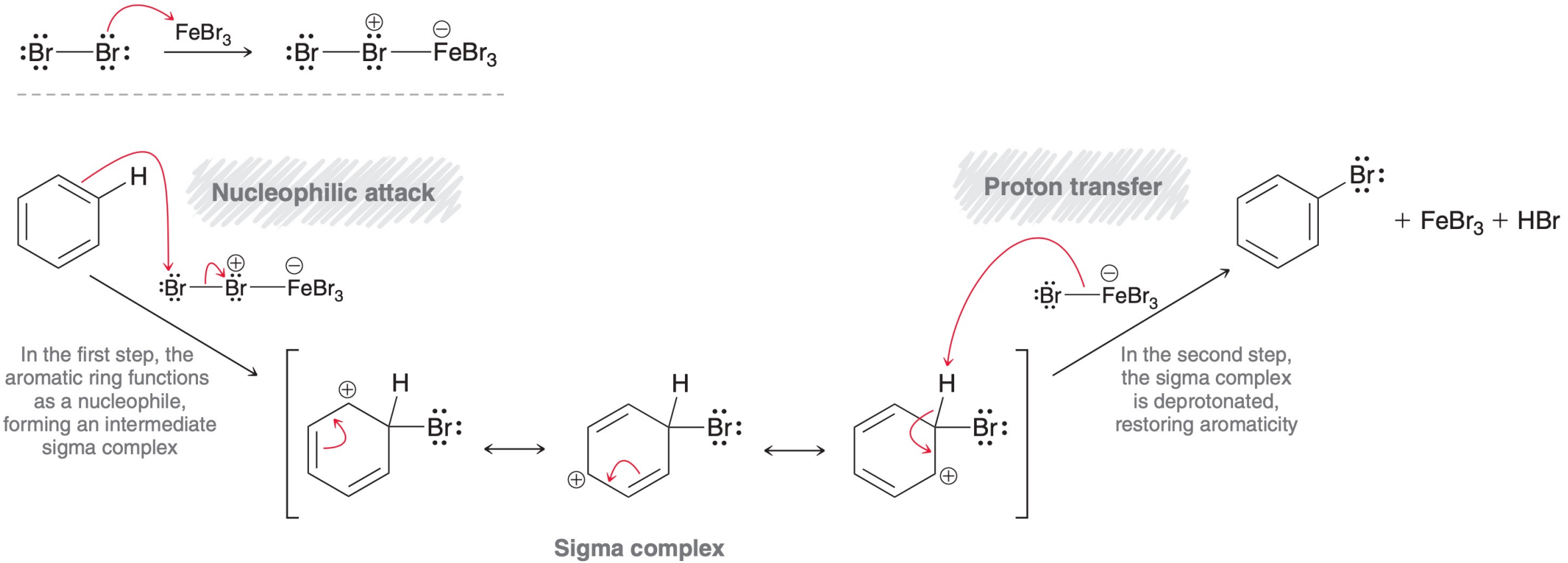


- Lewis acid-halogen complex – the halogenation reagent

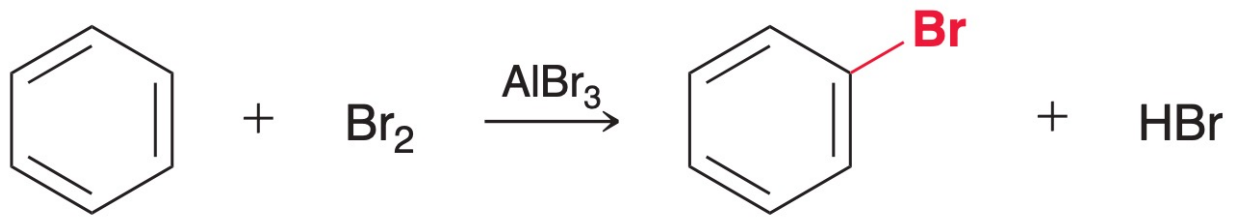
$$2\ Fe + 3\ Br_2 \rightarrow 2\ FeBr_3$$



- **Mechanism: Bromination of Benzene**

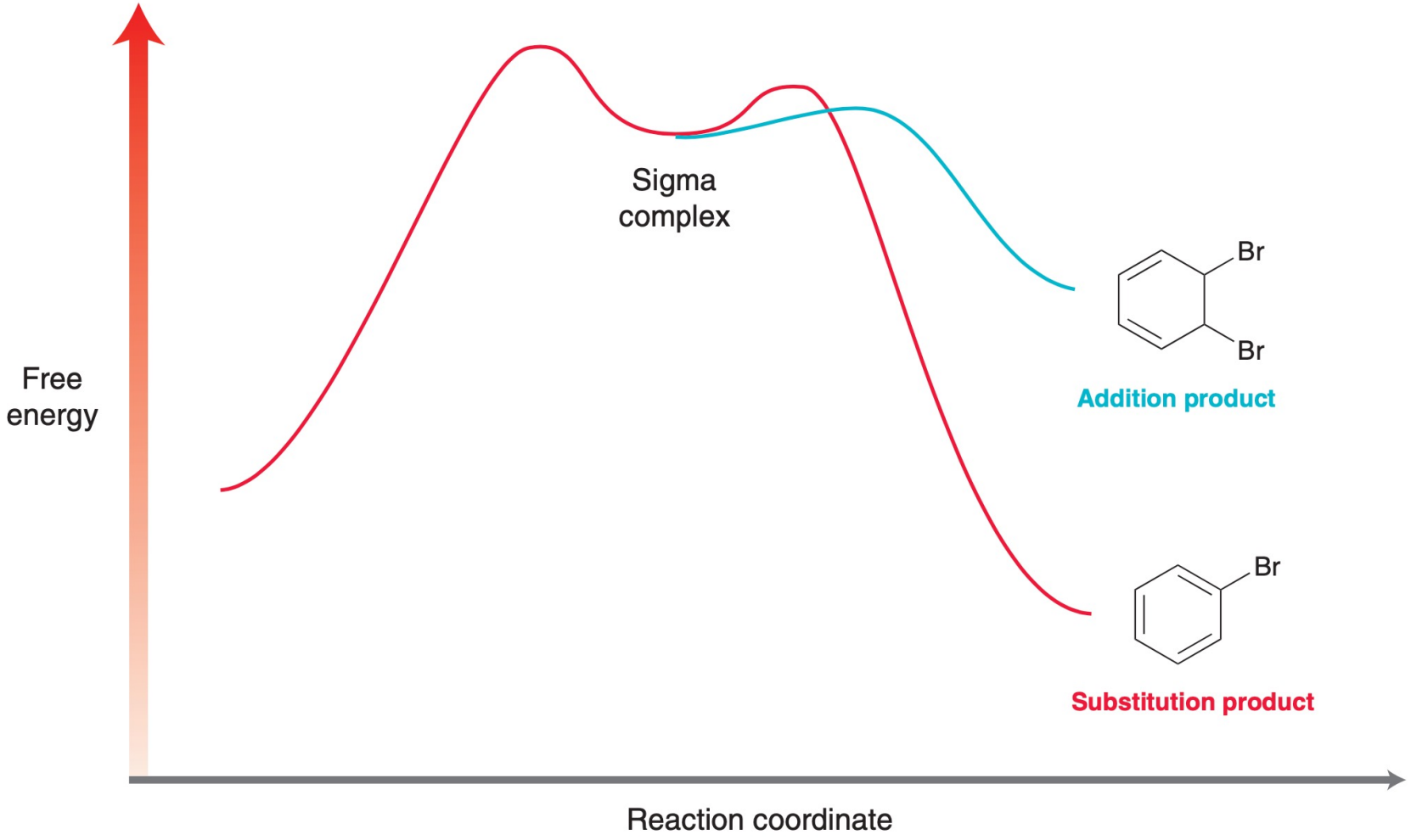


- Lewis acid is a catalyst

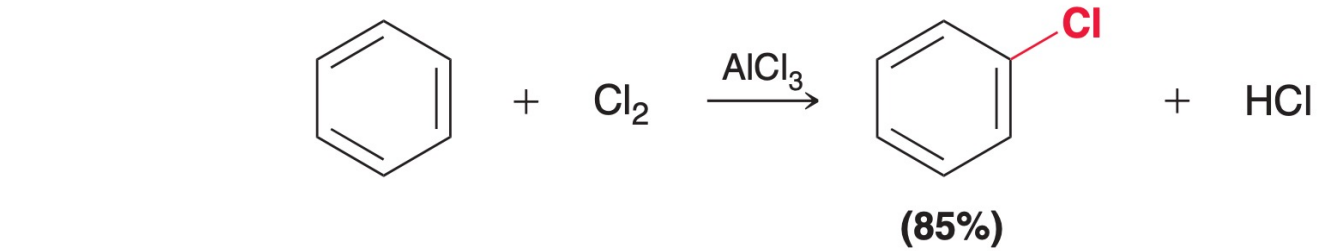


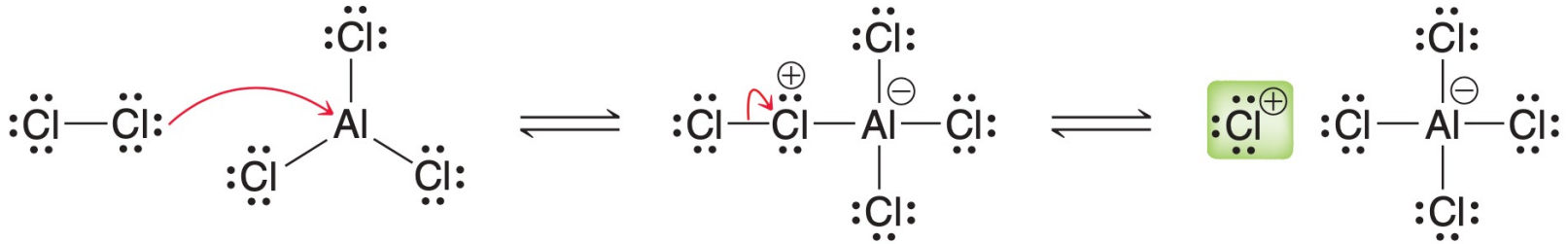
$AlBr_3$ is also applicable for catalyzing

- Addition is an endergonic process – will not happen

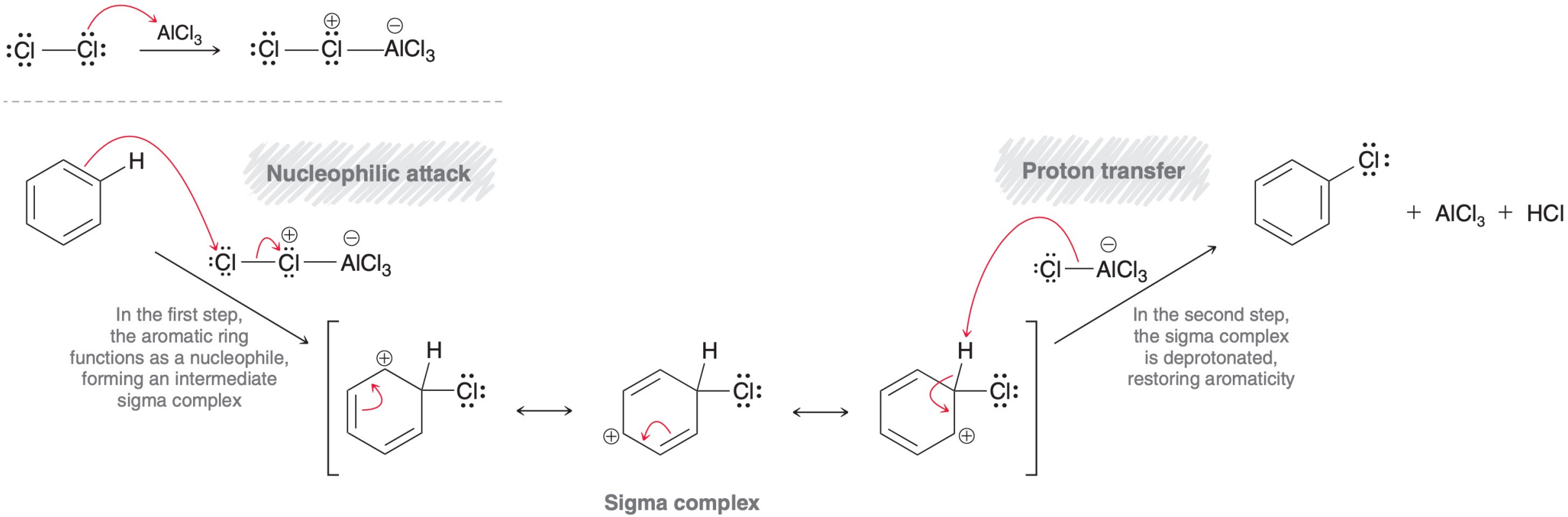


- Benzene chlorination

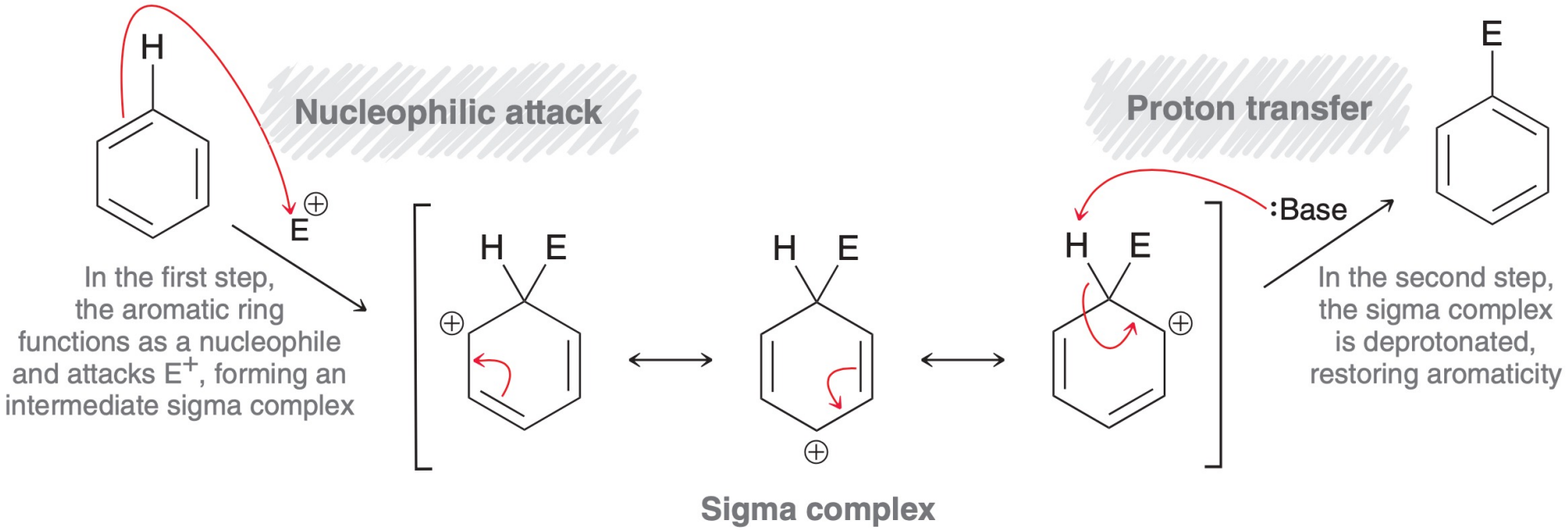




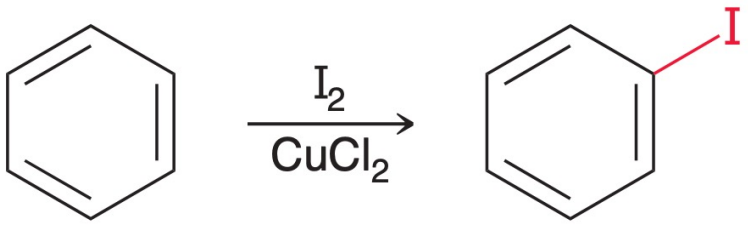
- **Mechanism: Chlorination of Benzene**

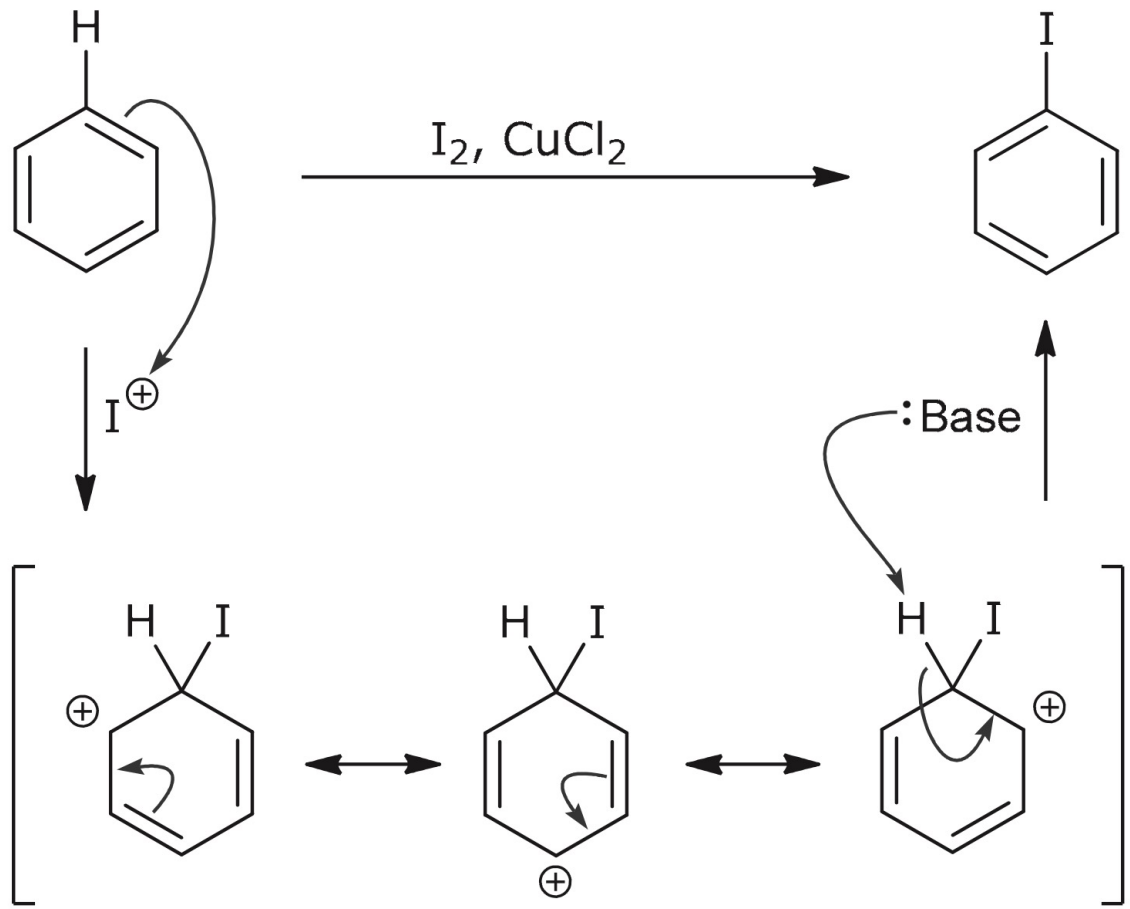


- **A General Mechanism for Electrophilic Aromatic Substitution (EArS)**

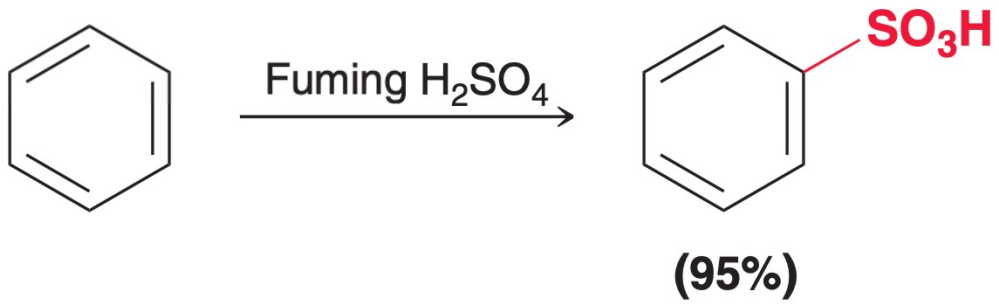


- Practice: when benzene is treated with I_2 in the presence of $CuCl_2$, iodination of the ring is achieved with modest yields. It is believed that $CuCl_2$ interacts with I_2 to generate I^+, which is an excellent electrophile. The aromatic ring then reacts with I^+ in an electrophilic aromatic substitution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




H
I
I_2, $CuCl_2$
I⊕
:Base
H I
H I
H I
⊕
⊕
⊕

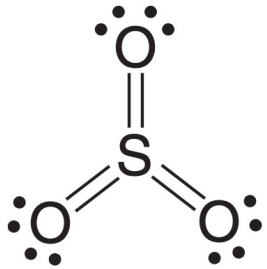
- Benzene sulfonation

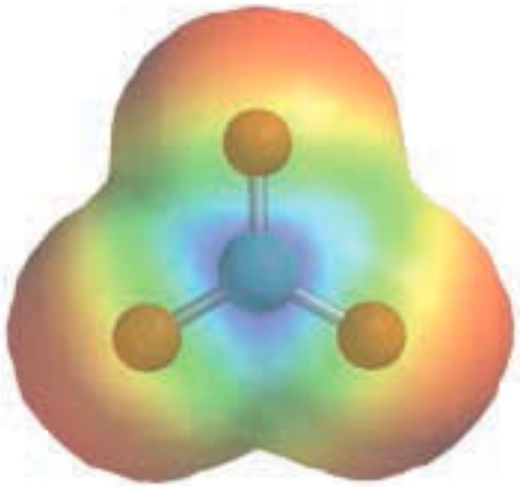


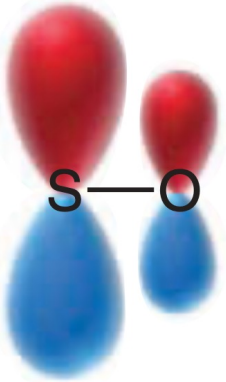
fuming H_2SO_4: a mixture of H_2SO_4 and SO_3

(supersaturated solution of SO_3)

- SO_3 is a very powerful electrophile





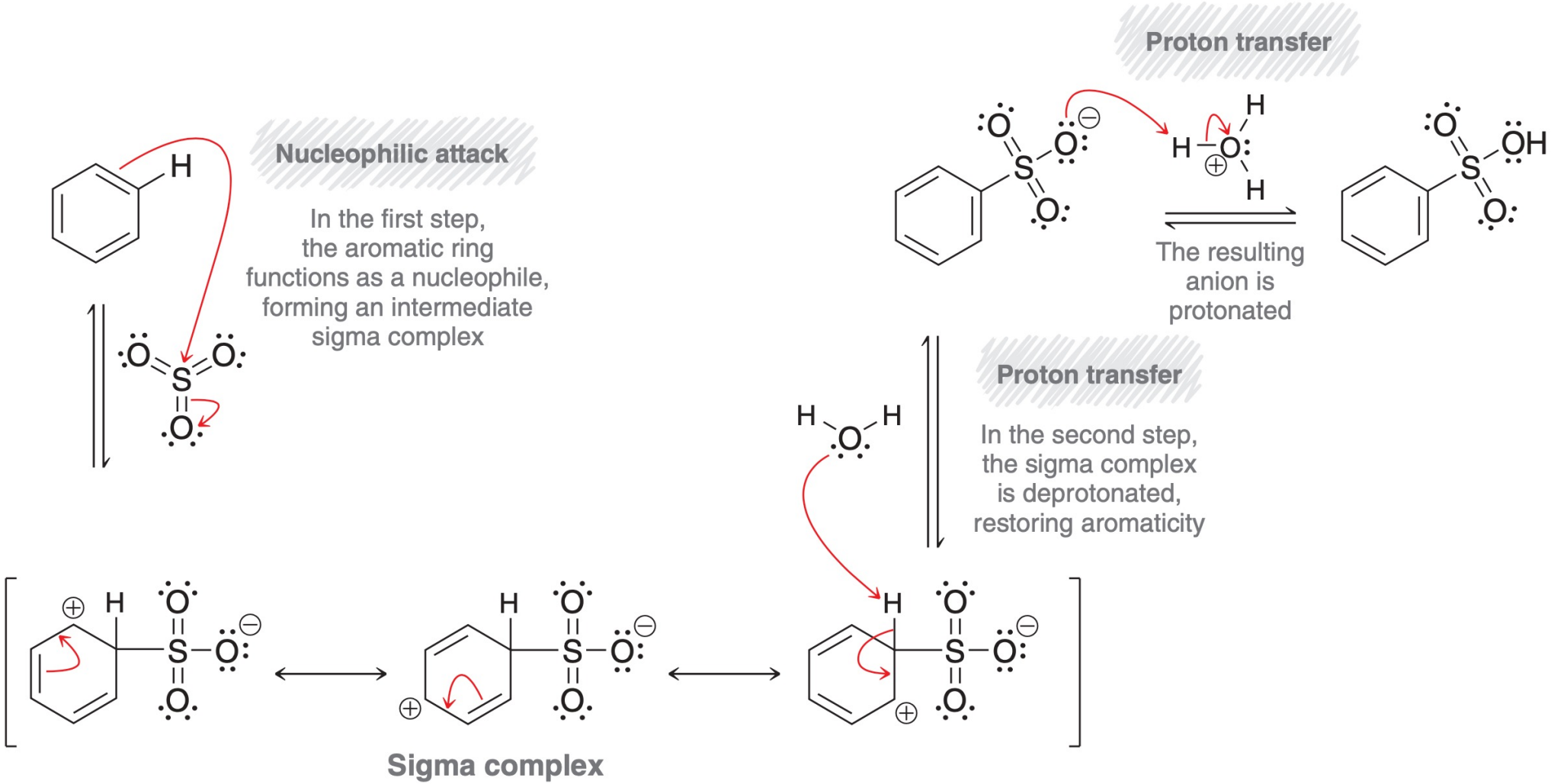


Inefficient overlap

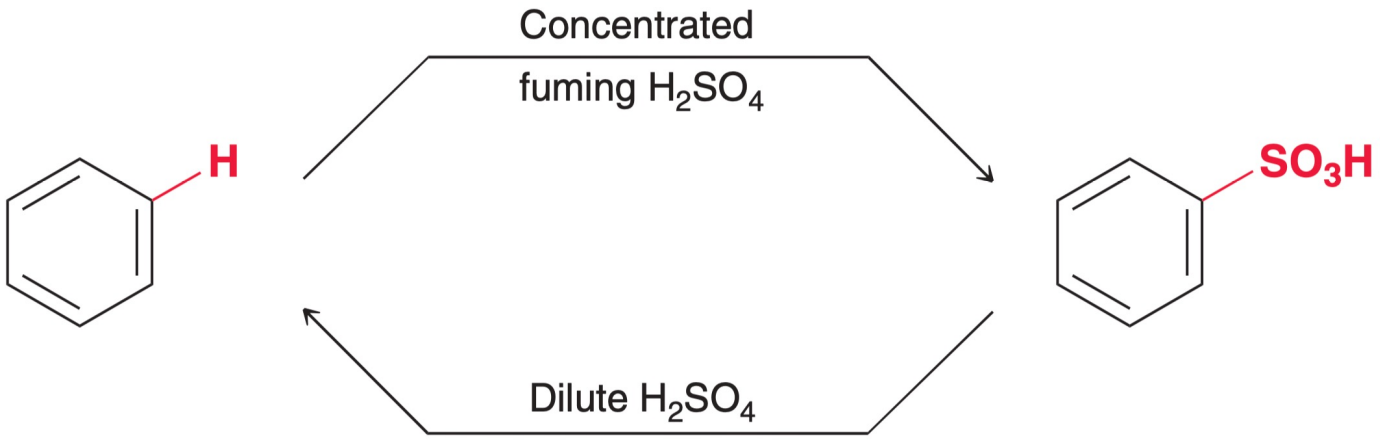
inefficient orbital overlap (between 3*p* and 2*p*)

creates charge separations (S^+ and O^-)

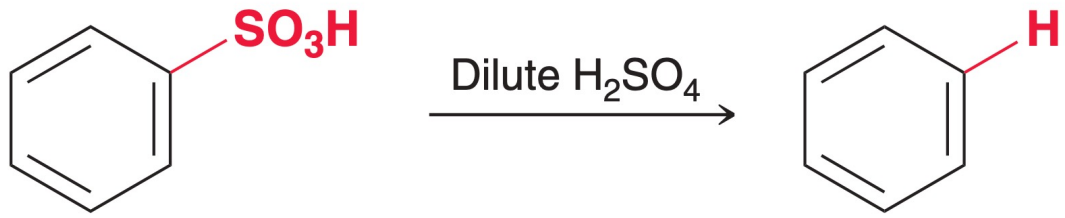
- **Mechanism: Sulfonation of Benzene**



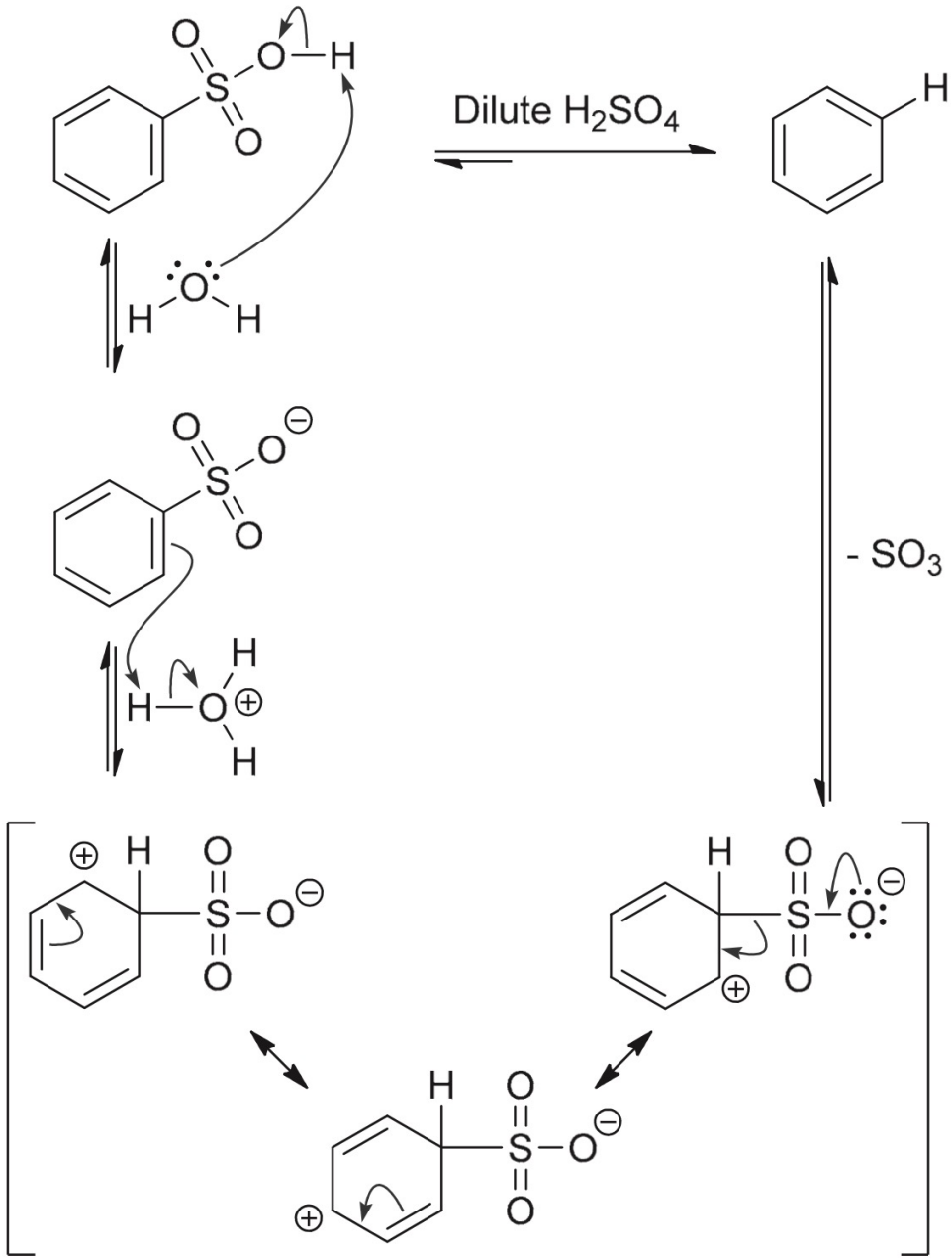
- Sulfonation is a reversible process



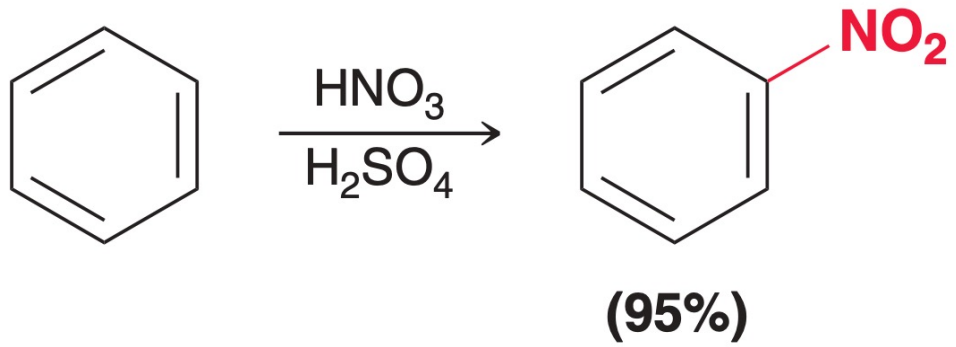
- Practice: draw a mechanism for the following reaction. **Hint:** This reaction is the reverse of sulfonation, so you should read the sulfonation mechanism backward. Your mechanism should involve a sigma complex (positively charged).



Sulfonation



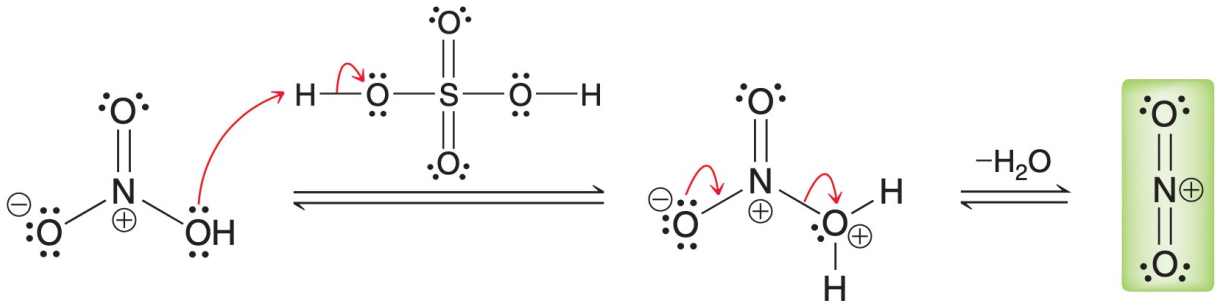
- Benzene nitration

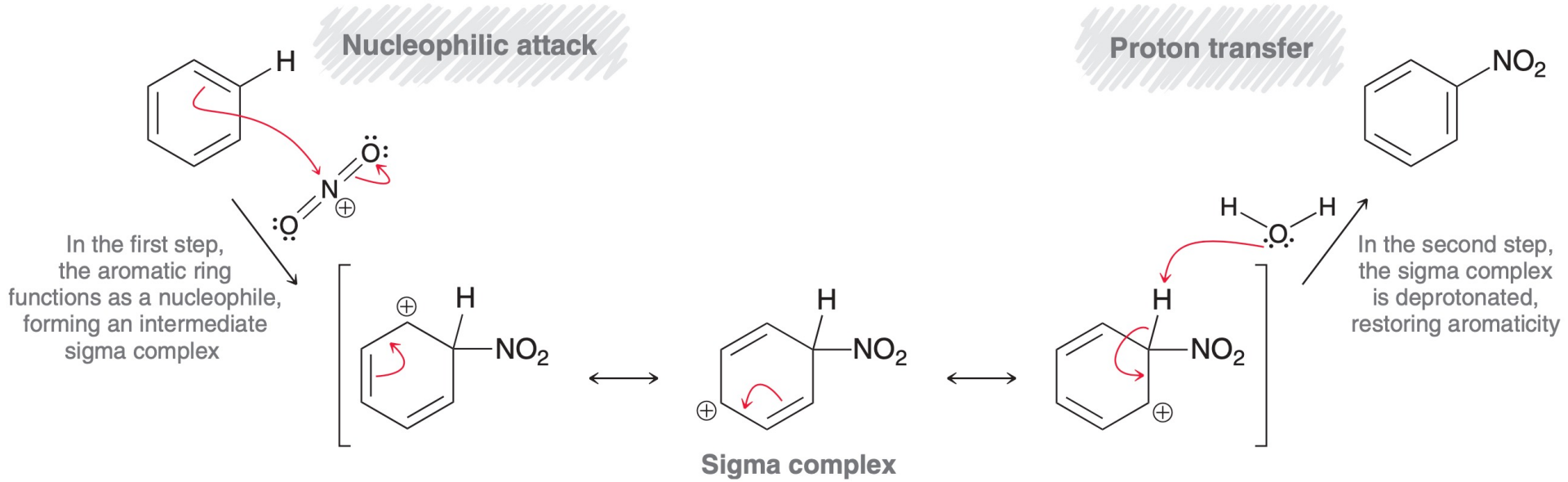


nitric acid functions as a *base* to accept a proton from sulfuric acid

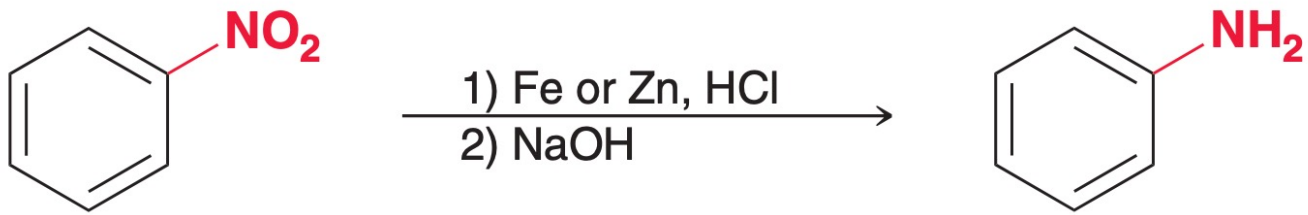
followed by loss of water to produce a nitronium ion (NO_2^+)

- **Mechanism: Nitration of Benzene**

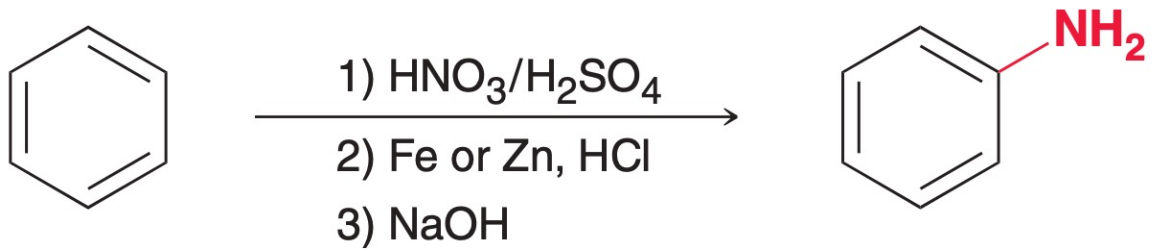




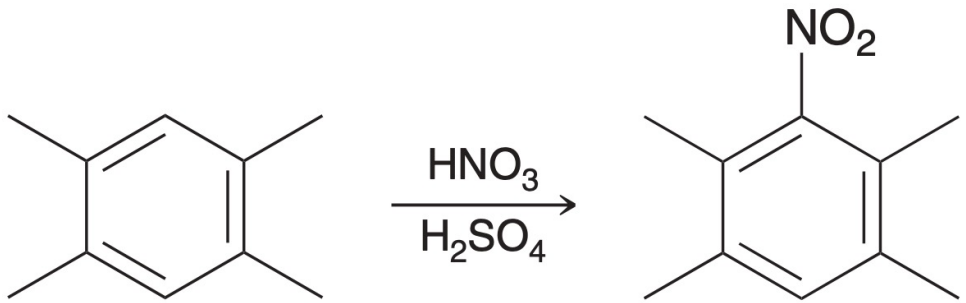
- Reduction gives an amino group

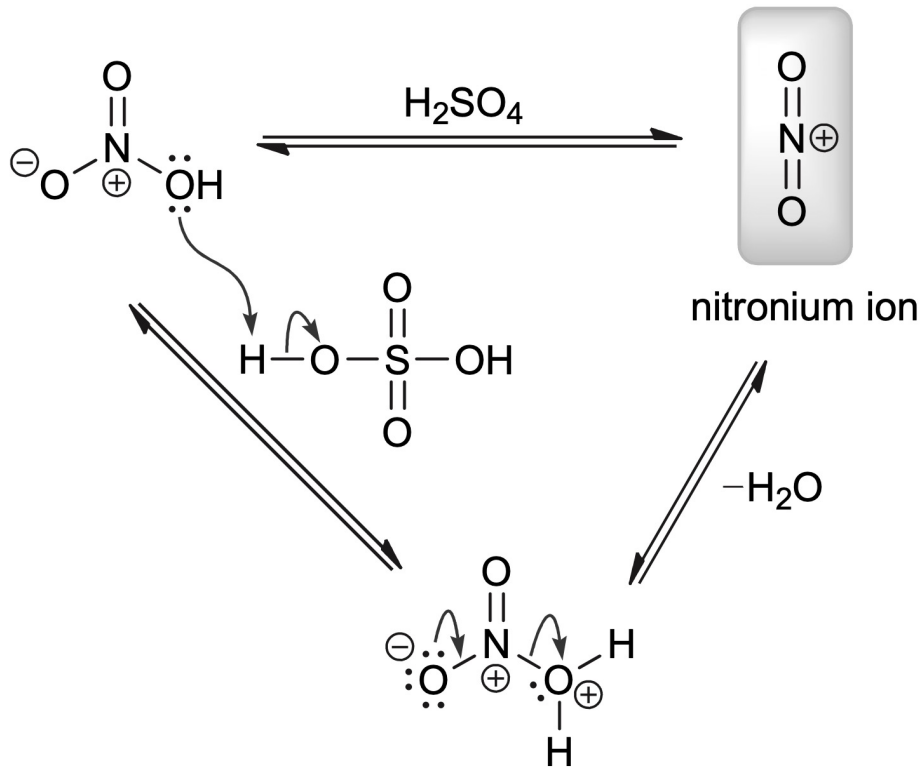


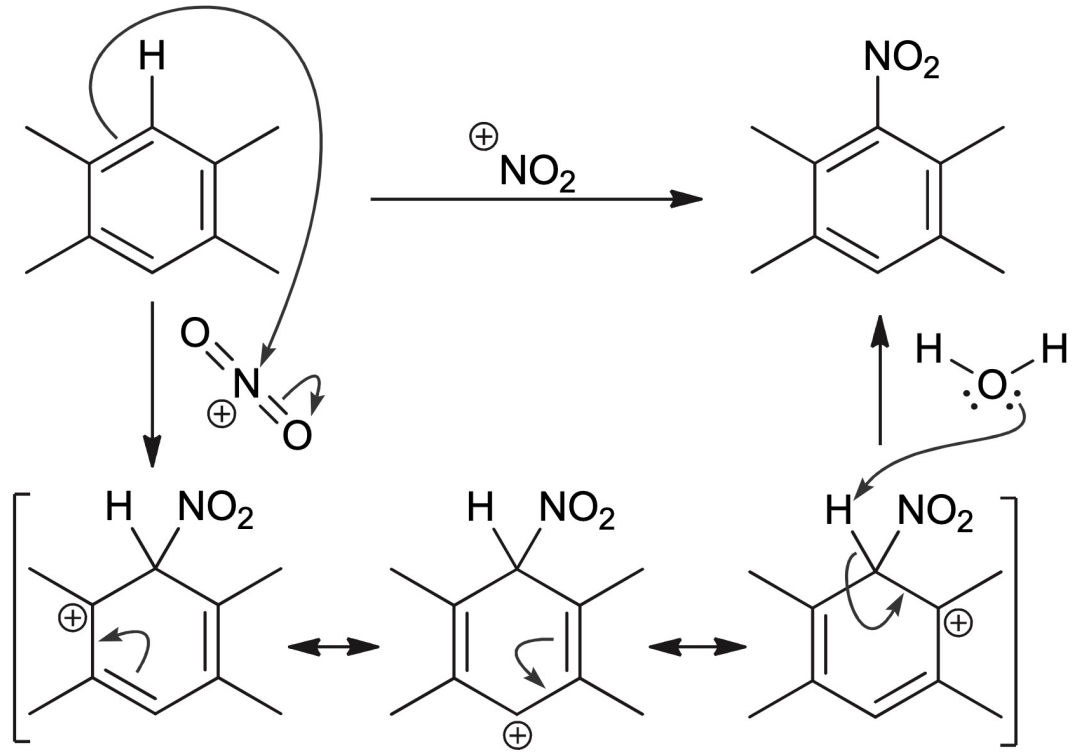
- The general process for installing an amino group on a benzene



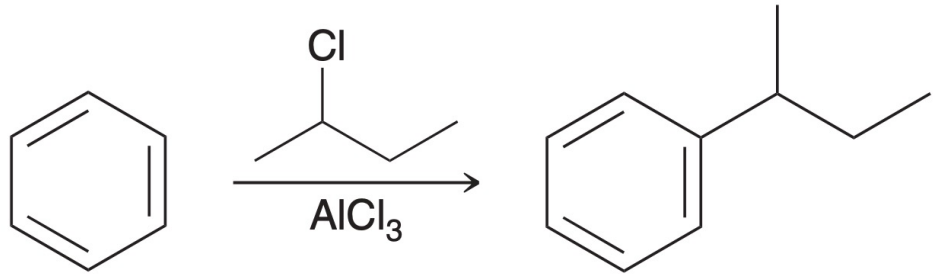
- Practice: draw a mechanism for the following reaction and make sure to draw all three resonance structures of the sigma complex:



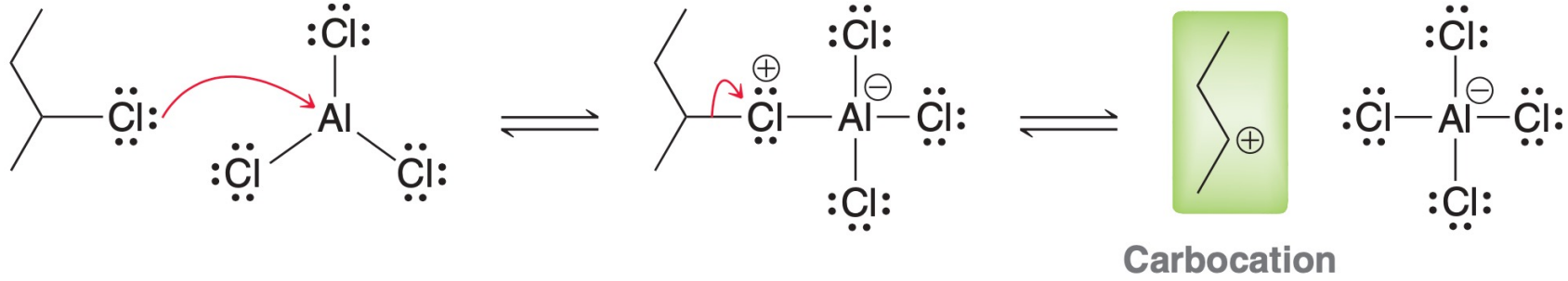

H2SO4
nitronium ion
−H2O


NO2
NO2
NO2
NO2
NO2

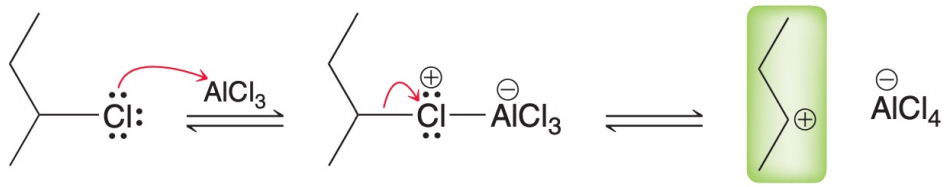
- Friedel–Crafts alkylation

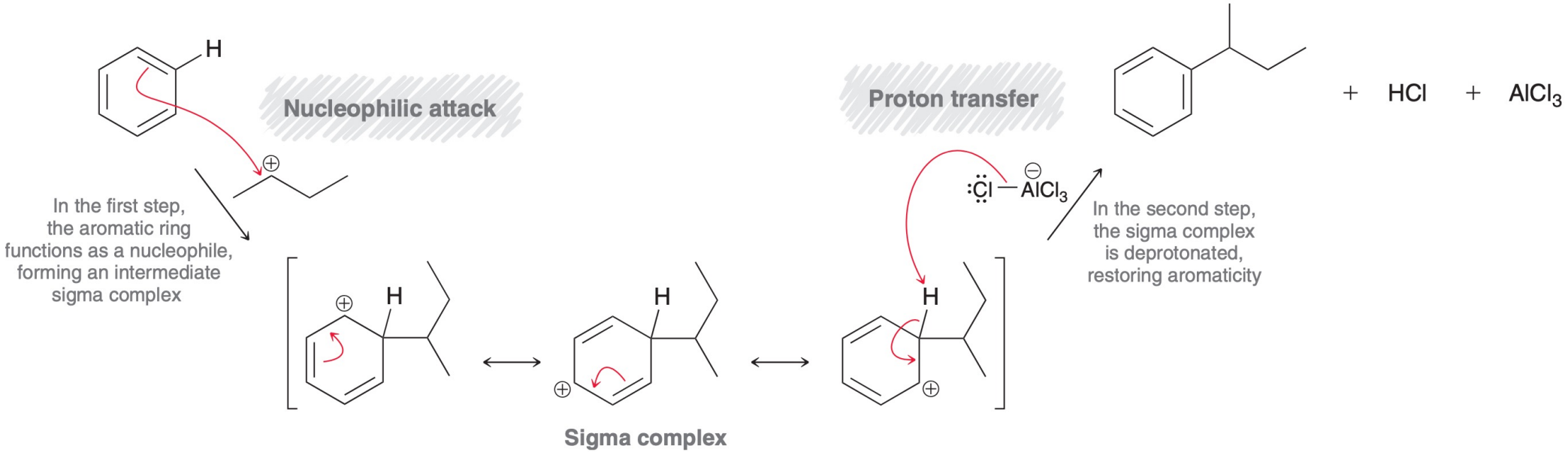


(66%)

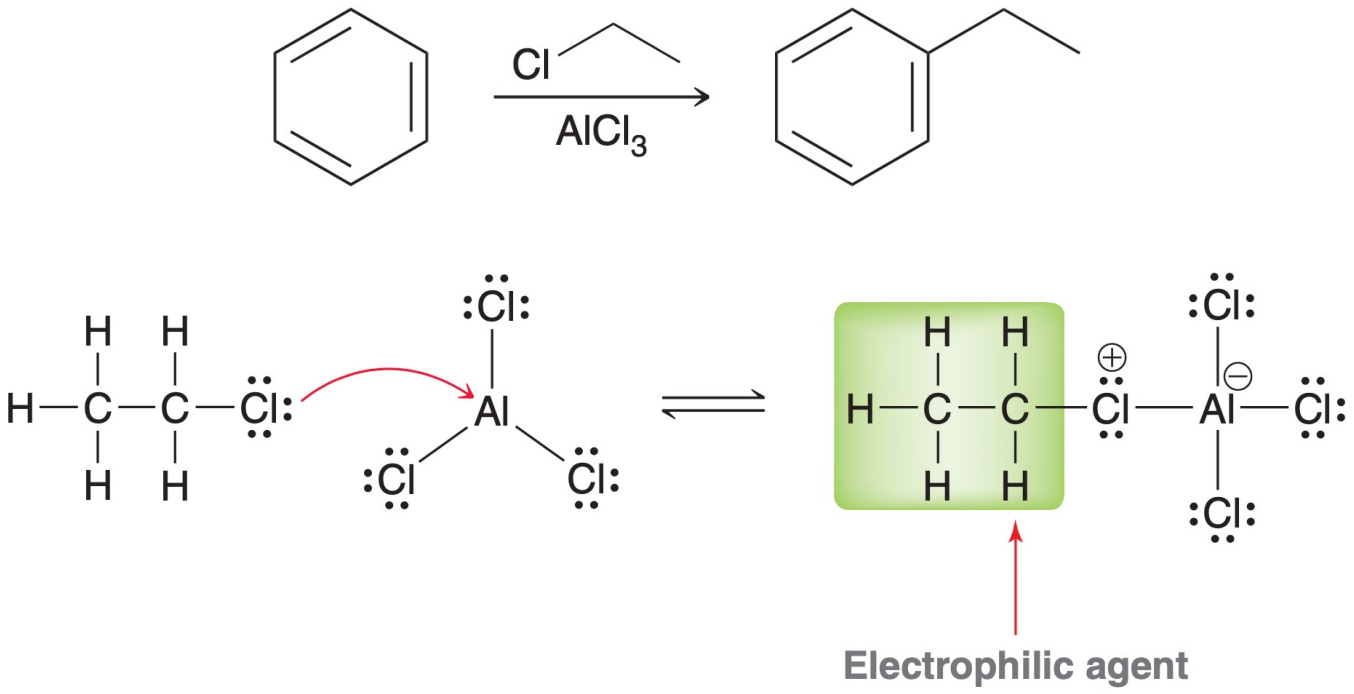


- **Mechanism: Friedel–Crafts Alkylation**

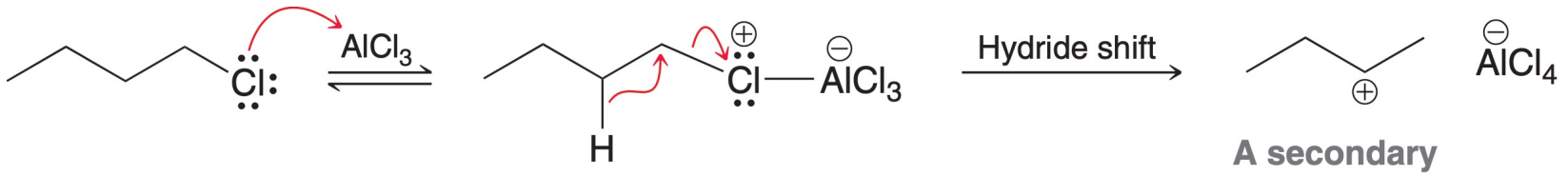


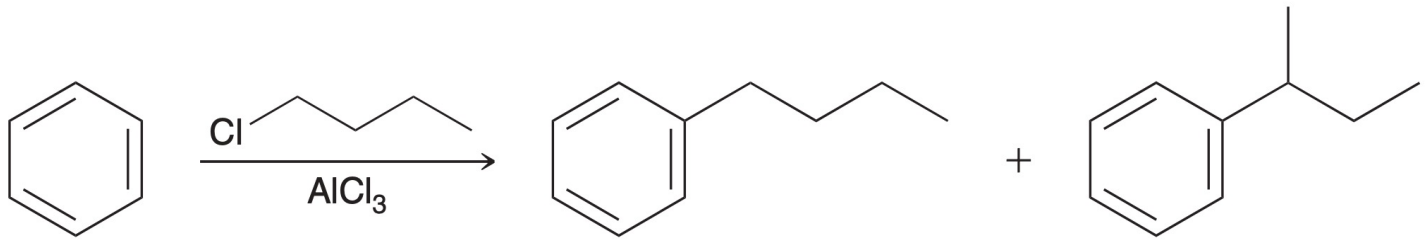


- Ethyl chloride in Friedel–Crafts alkylation



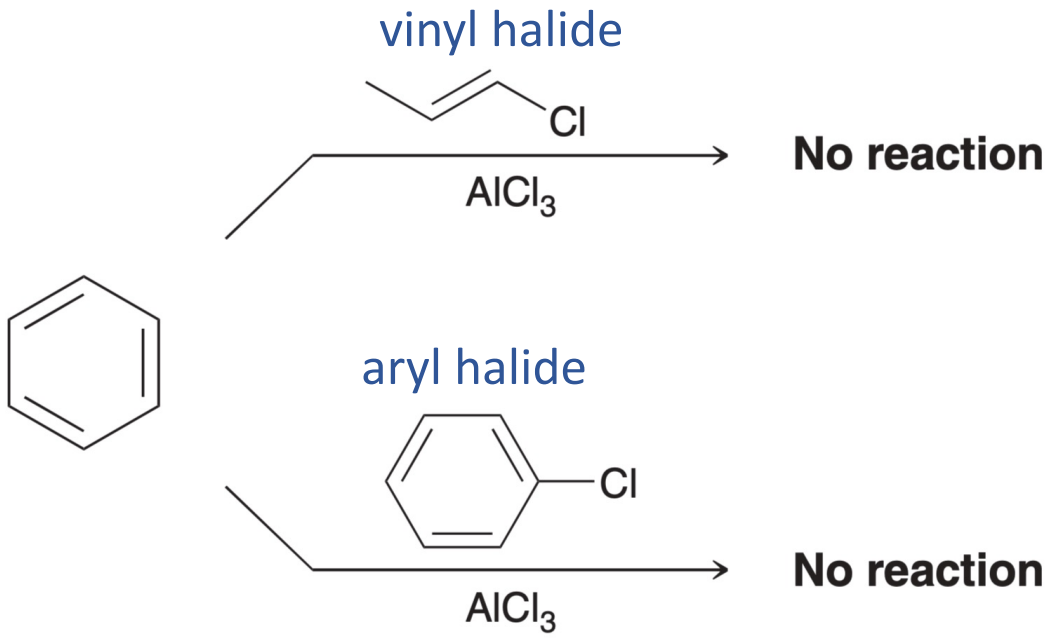
- Primary alkyl halides usually undergo rearrangement



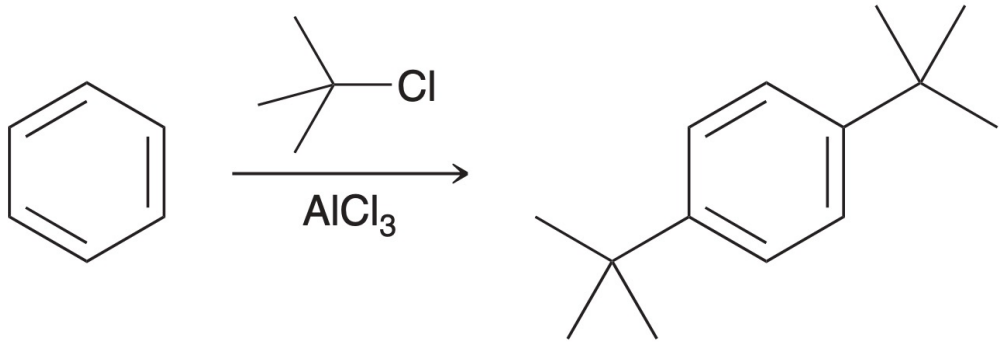


a mixture of products is obtained – *a limitation*!

- Limitation: α carbon must be sp^3 hybridized

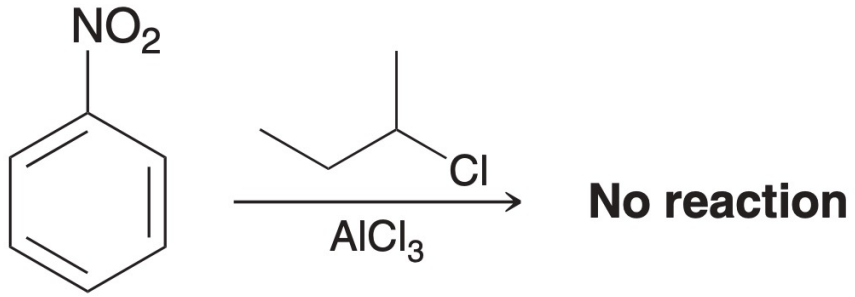


- Limitation: polyalkylations often occur

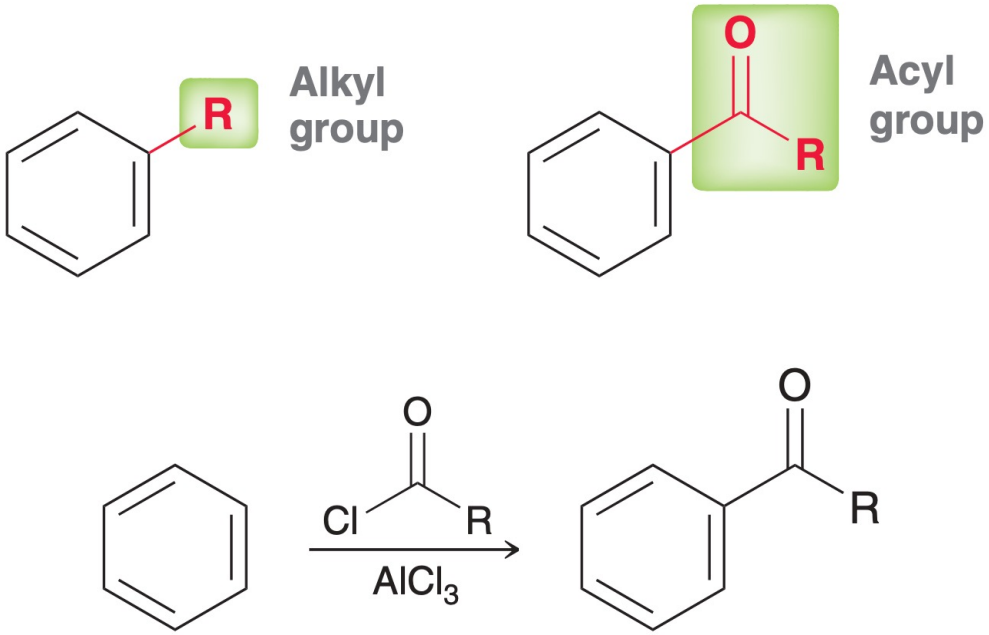


alkyl groups are *activating* groups

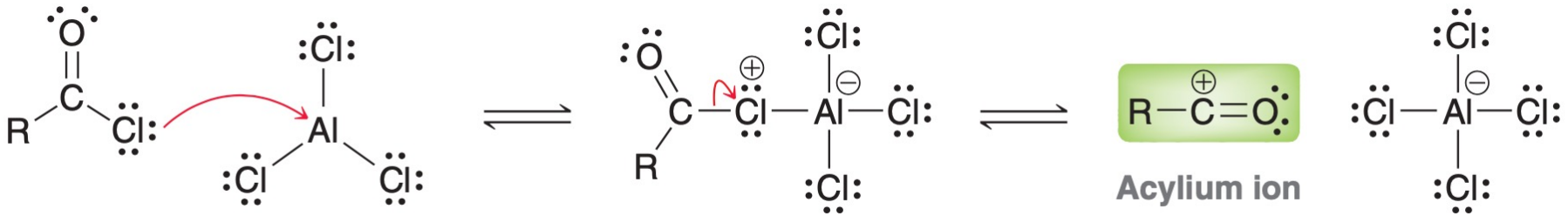
- Limitation: certain groups are incompatible with F–C reaction

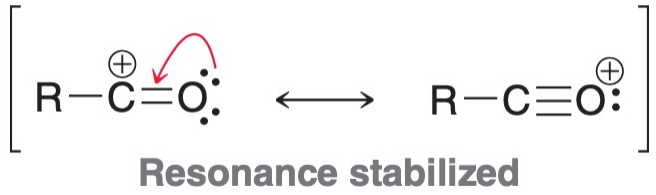


- Friedel–Crafts Acylation

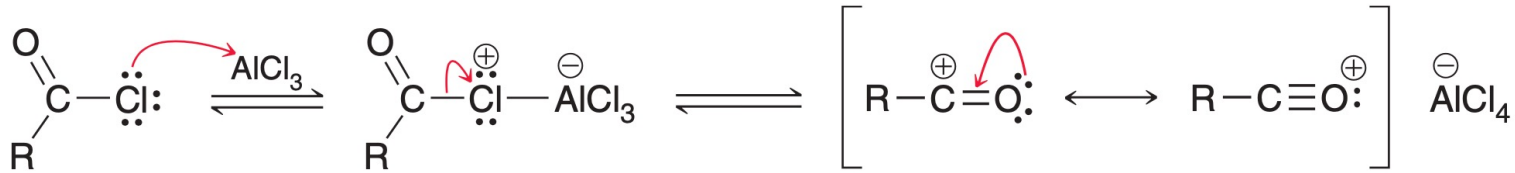


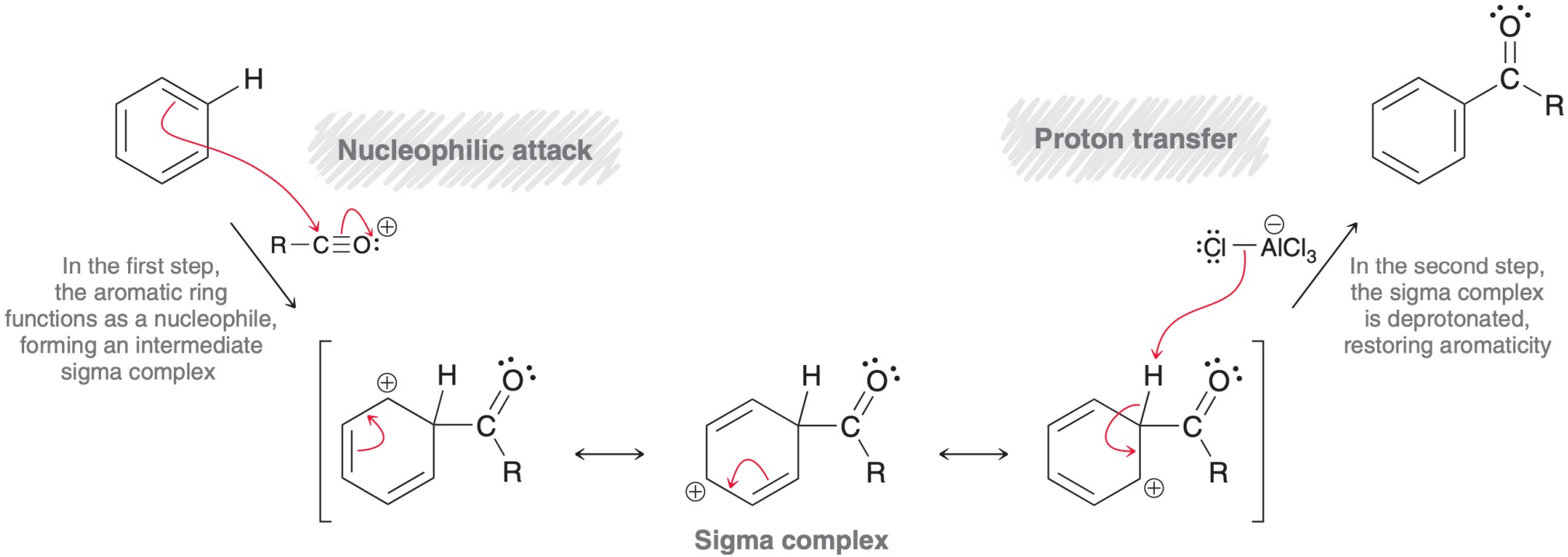
- Acylium ion formation



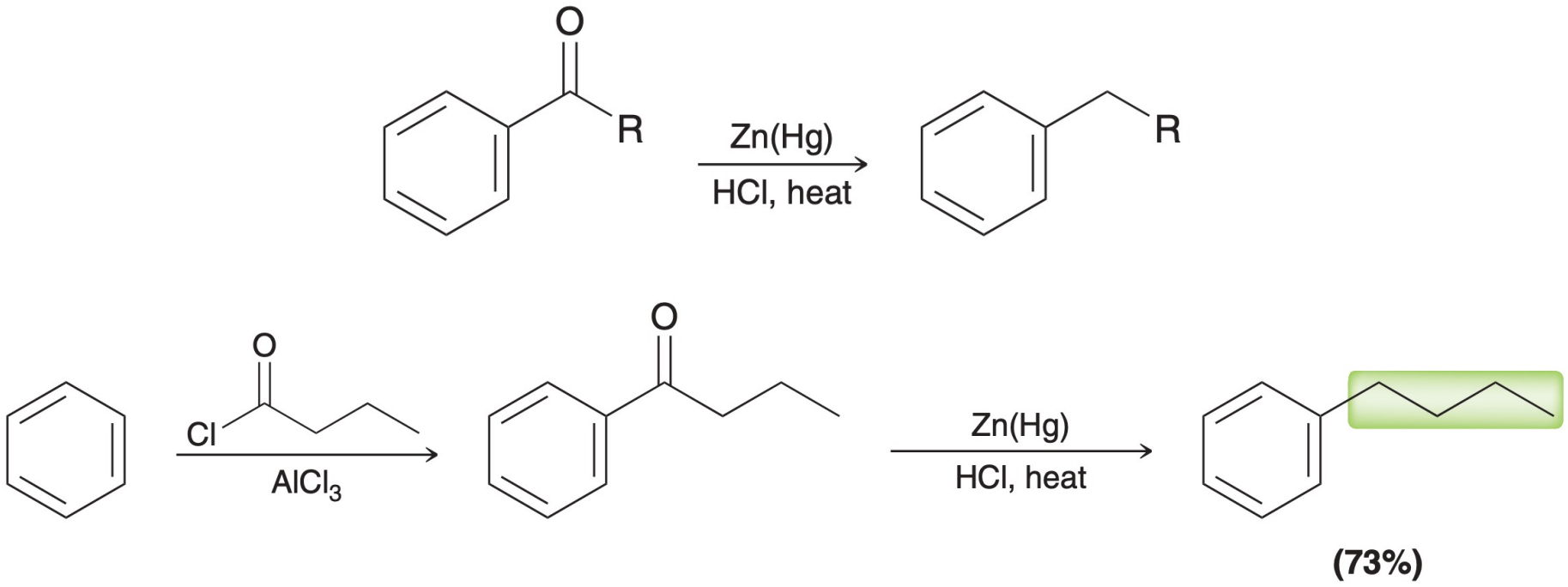


- **Mechanism: Friedel–Crafts Acylation**

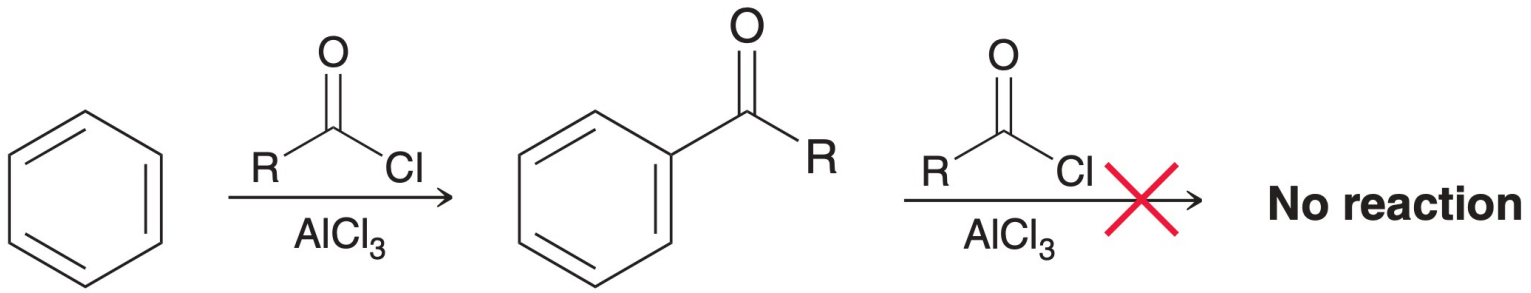




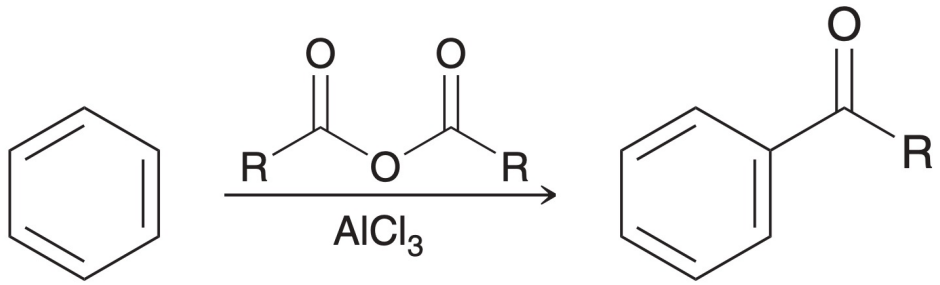
- Using Clemmensen reduction to achieve alkyl group installation

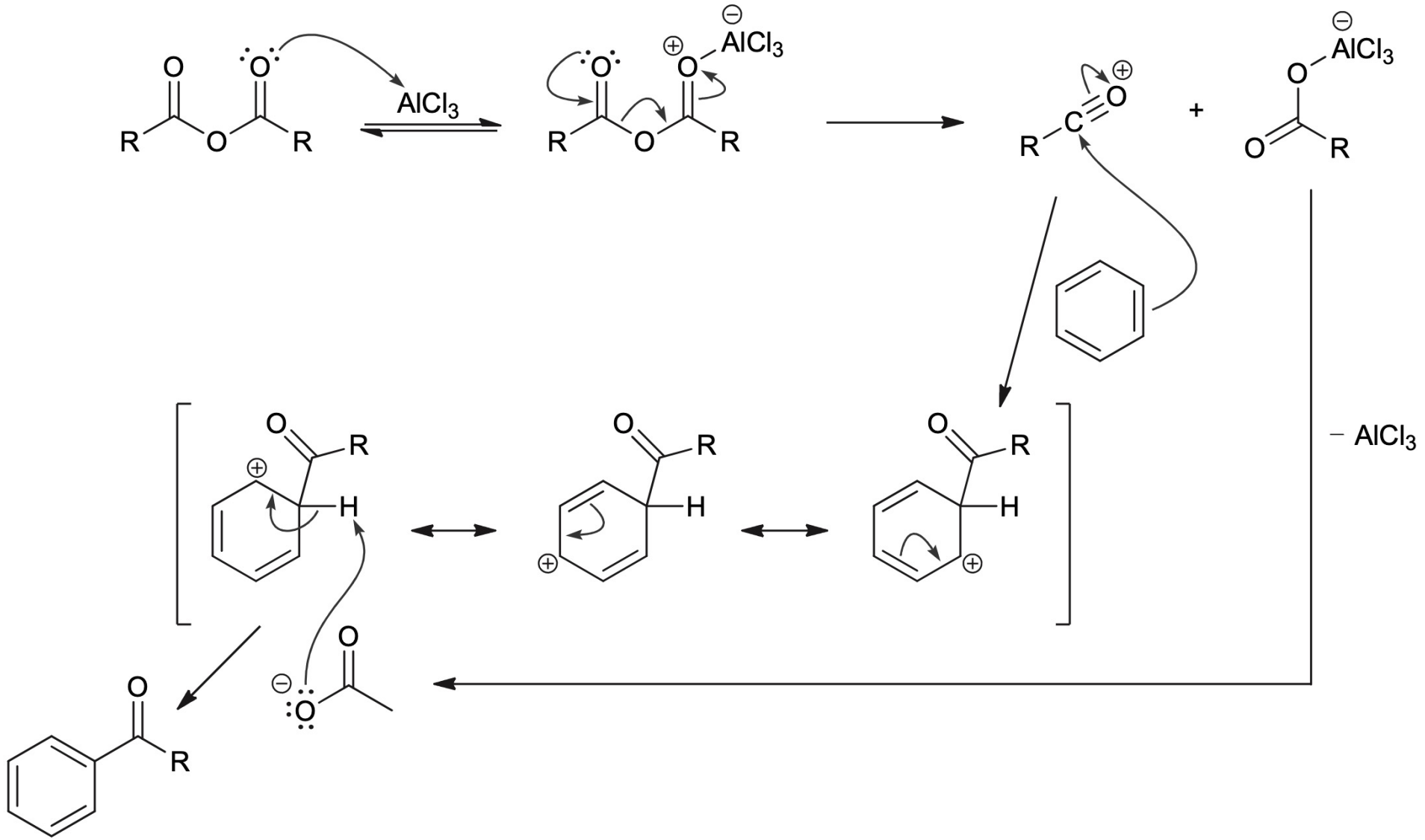


- Acyl group deactivates benzene ring – prevent further acylation

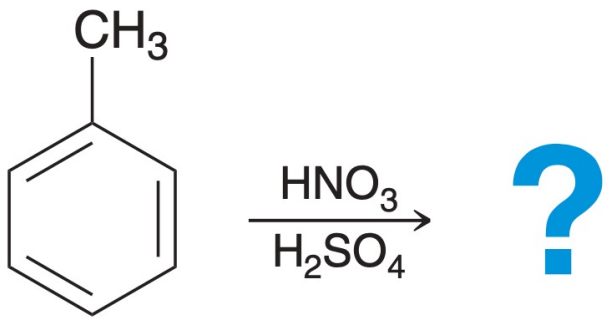


- Practice: a Friedel–Crafts acylation is an electrophilic aromatic substitution in which the electrophile (E^+) is an acylium ion. There are other methods of forming acylium ions, such as treatment of an anhydride (shown below) with a Lewis acid. The resulting acylium ion can also be attacked by a benzene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



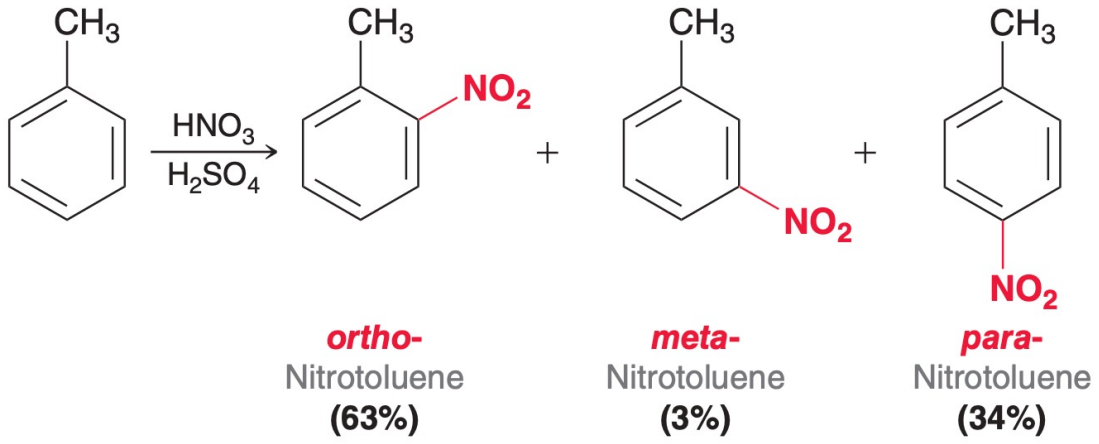

AlCl3
AlCl3
AlCl3
AlCl3
– AlCl3

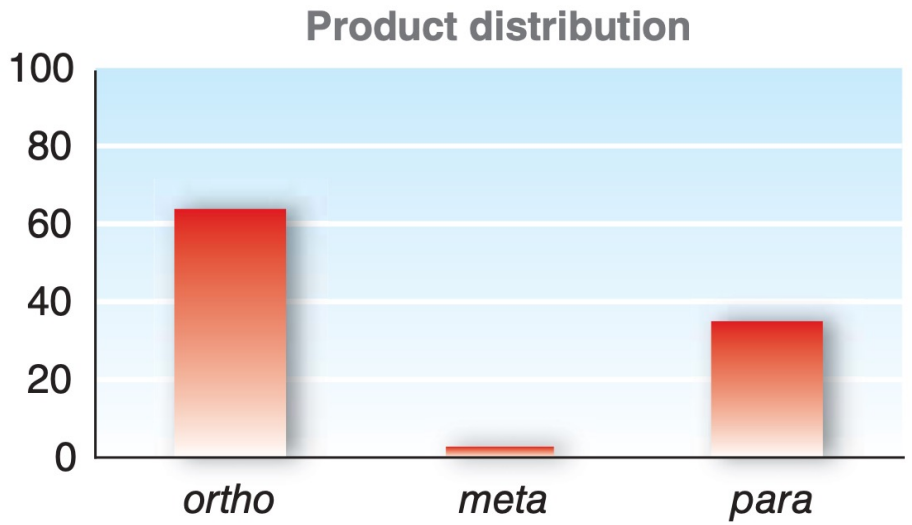
- Activating groups: nitration of toluene

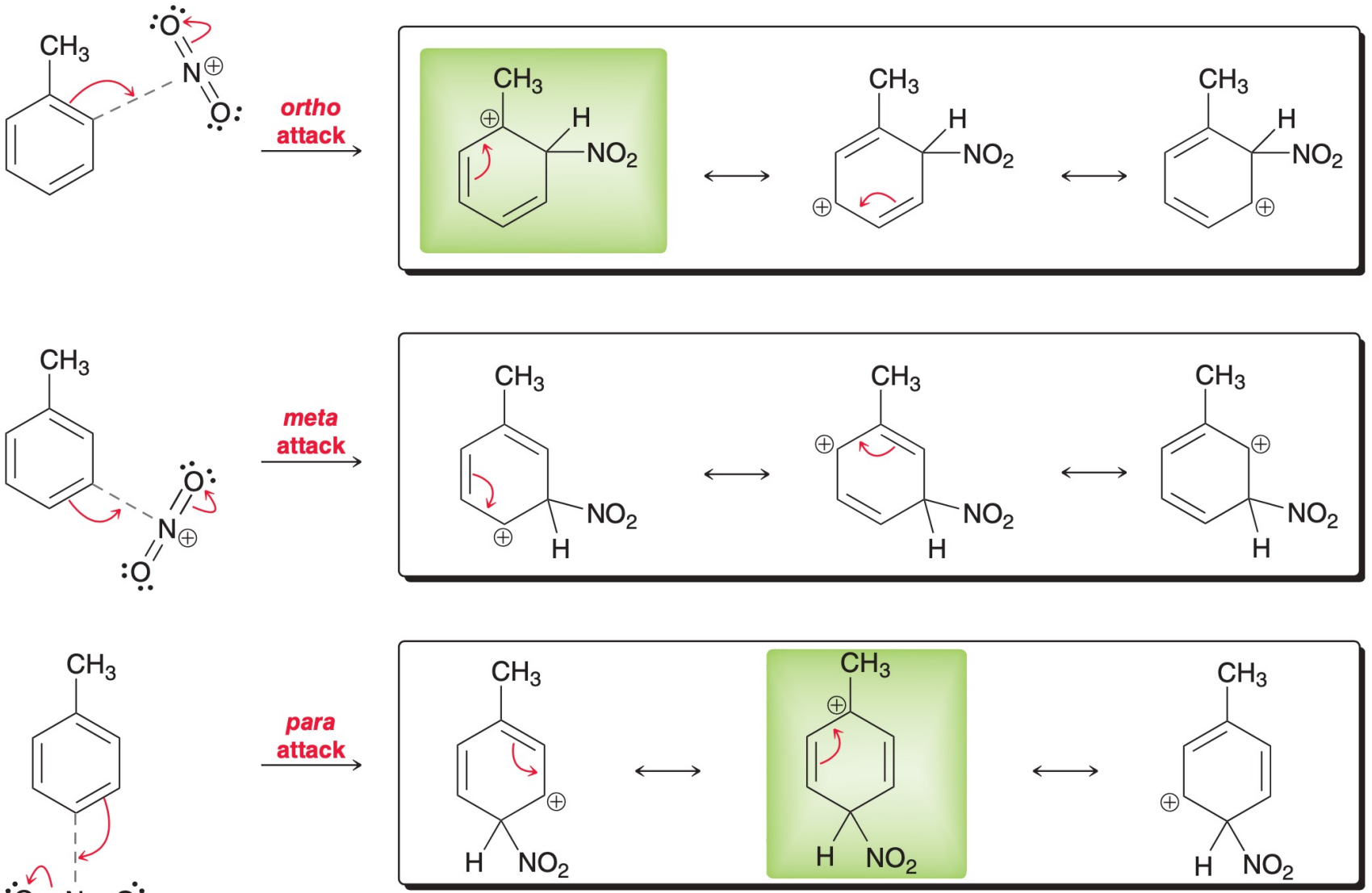


- the effect of the methyl group on the rate of reaction – 25 times faster than benzene
- the effect of the methyl group on the regiochemical outcome of the reaction…?

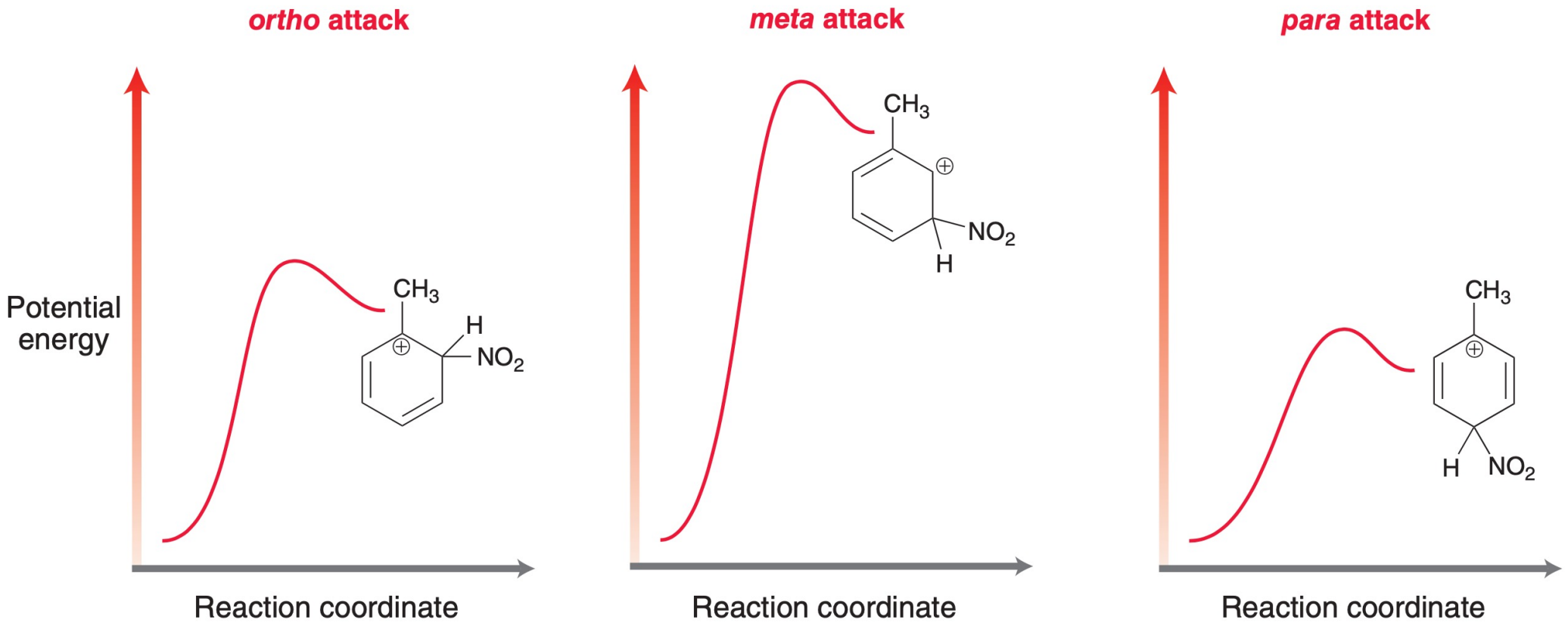
- The product distribution for nitration of toluene





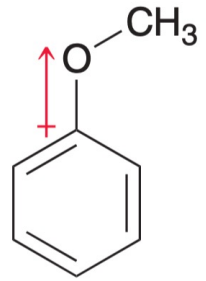

ortho attack
meta attack
para attack

- Energy diagrams for different attacking – toluene

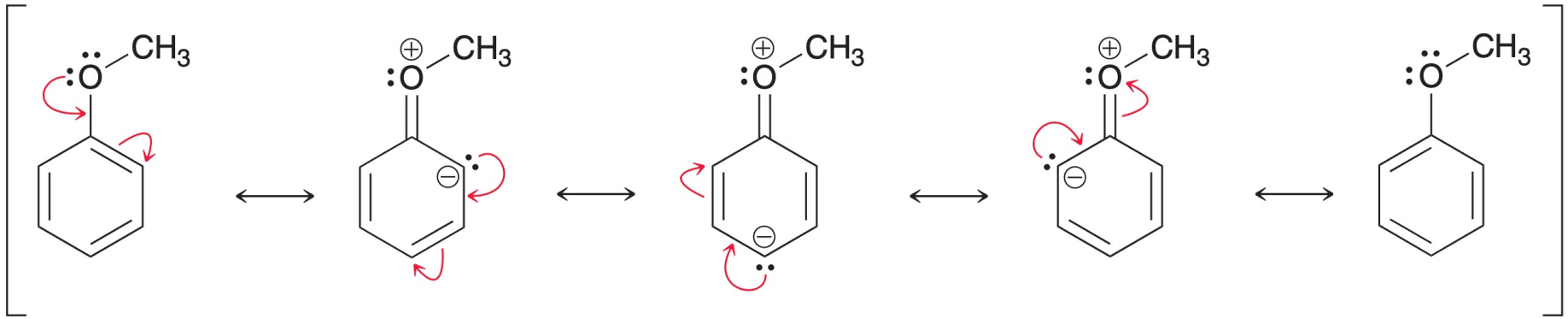


methyl group is said to be an ***ortho-para*** **director**

- Activating groups: nitration of anisole

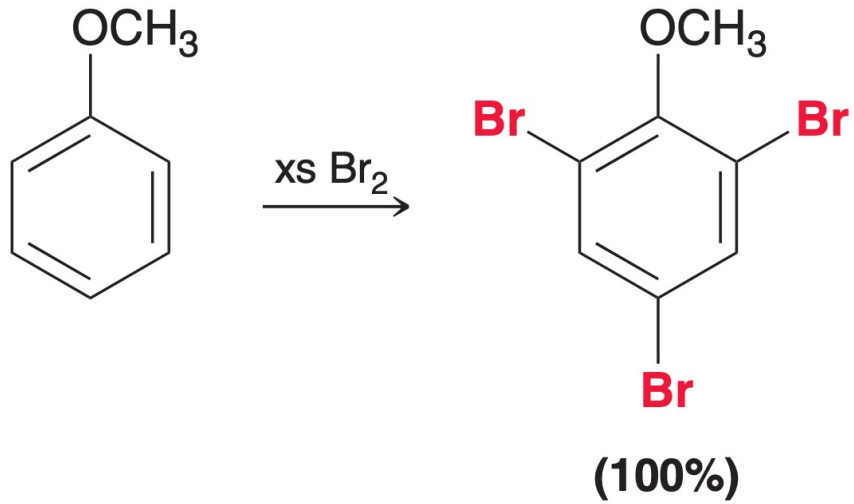


inductive effect: electron withdrawing



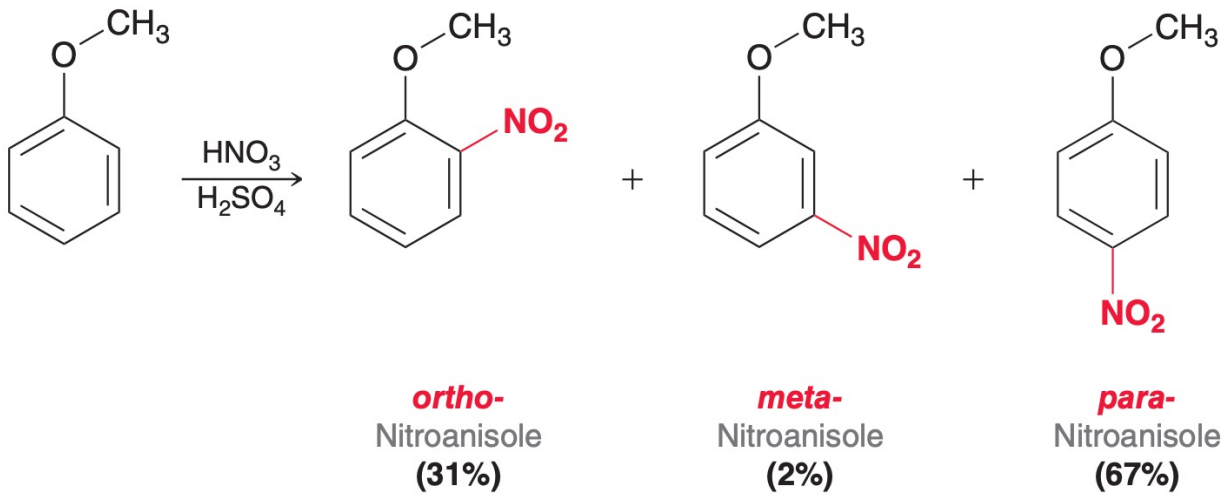
resonance effect: electron donating (dominant) – the ring is *activated*

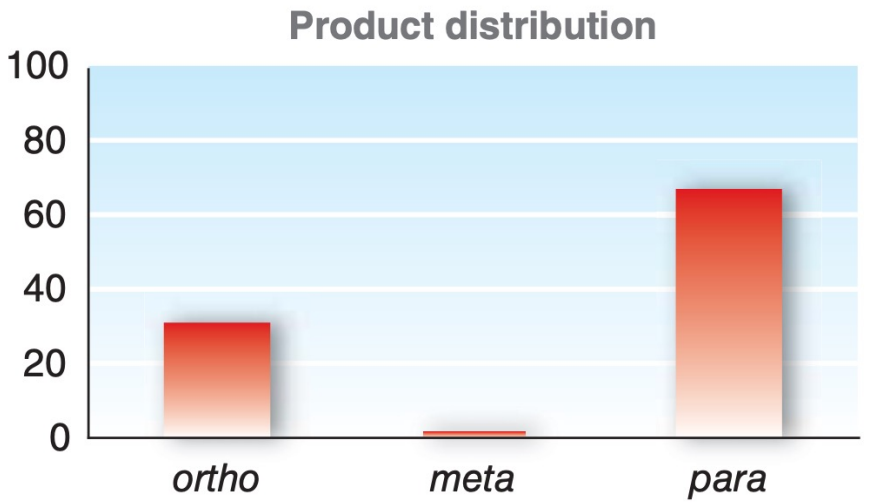
- The ring is so activated – xs. Br_2 gives a trisubstituted product

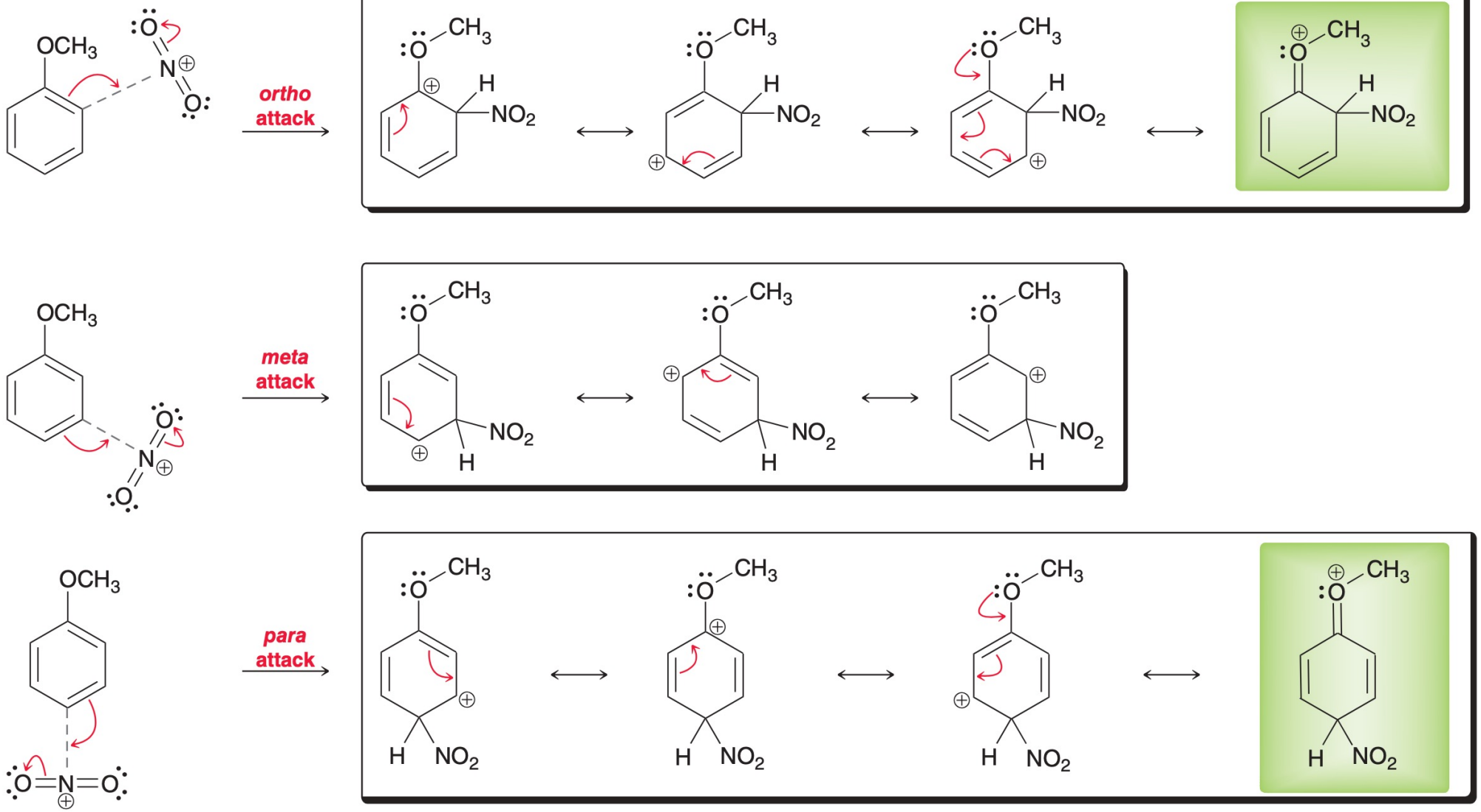


(100%)

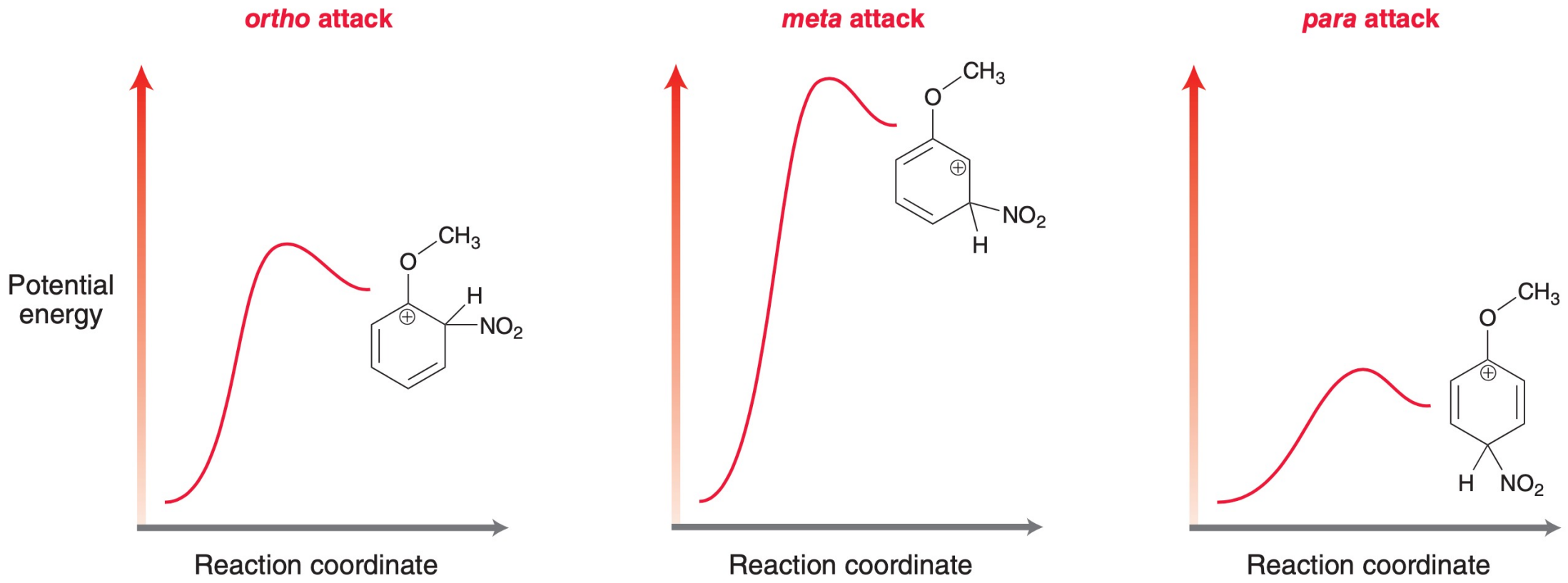
- The product distribution for nitration of anisole



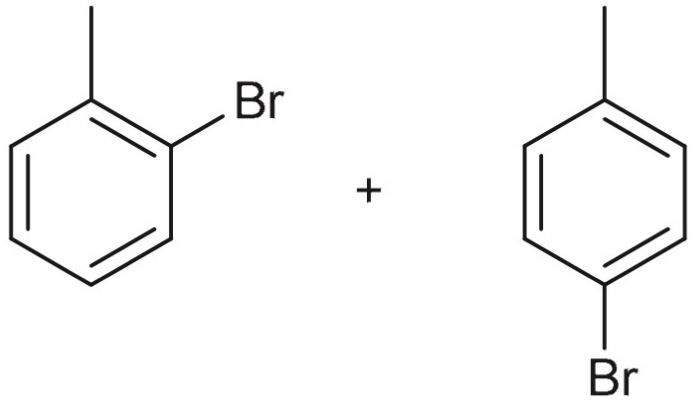



OCH3
ortho attack
CH3
H
NO2
meta attack
para attack

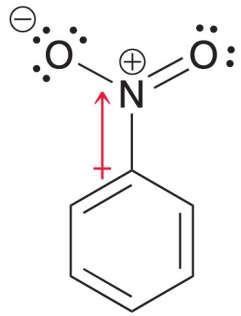
- Energy diagrams for different attacking – anisole



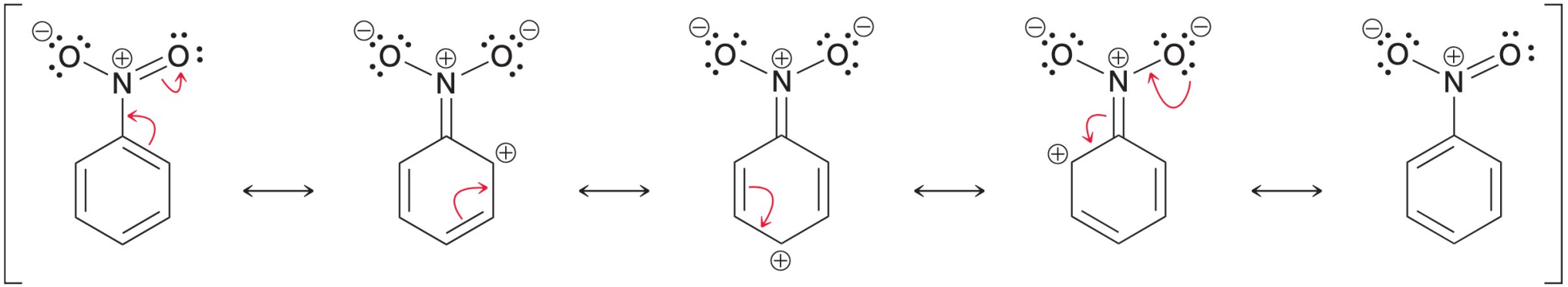
- Practice: draw the two major products obtained when toluene undergoes monobromination.



- Deactivating groups: substitution on nitrobenzene

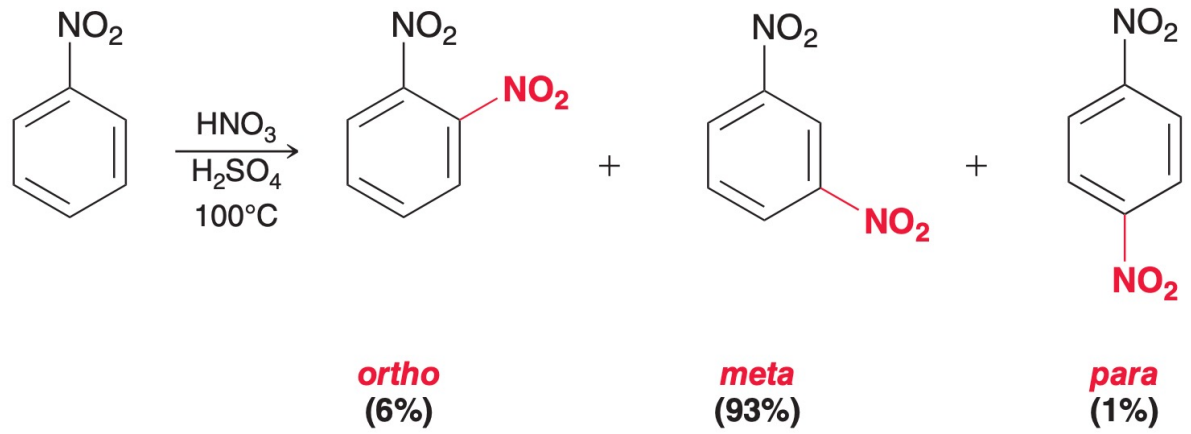


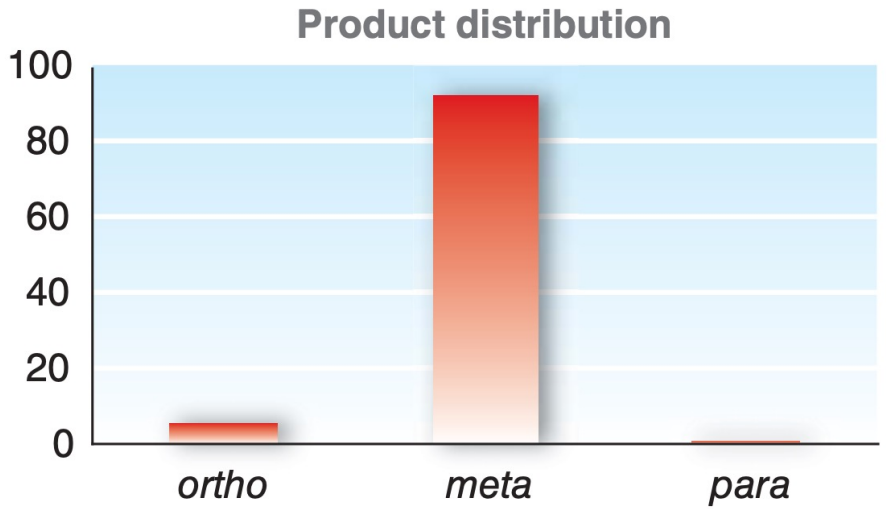
inductive effect: electron withdrawing

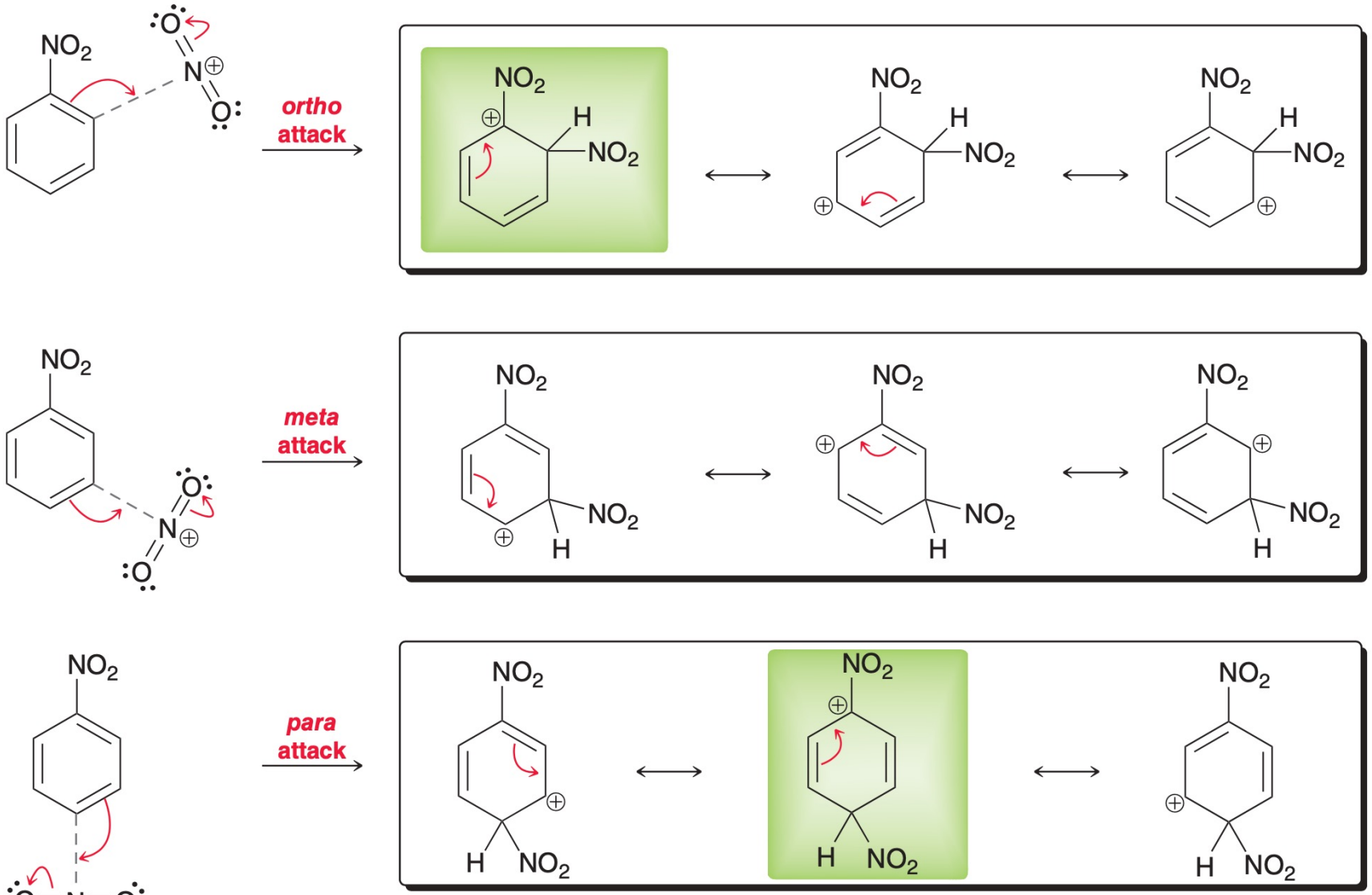


resonance effect: electron withdrawing

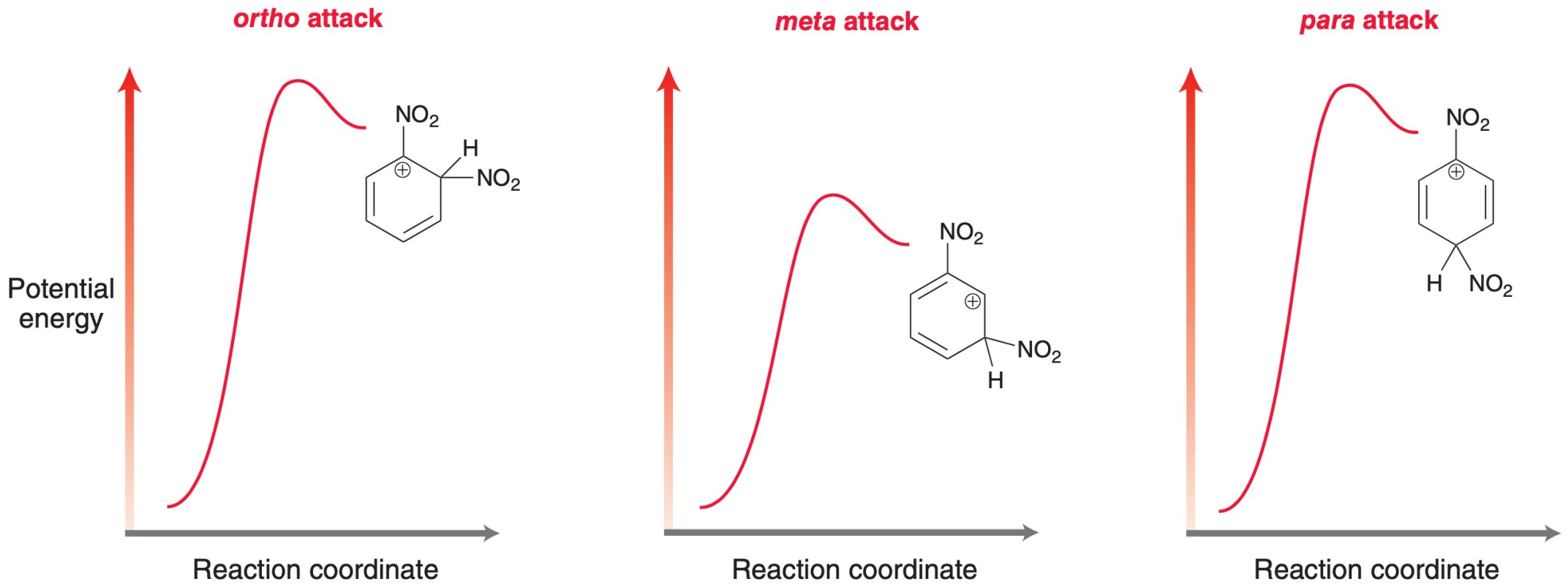
- The product distribution for nitration of nitrobenzene



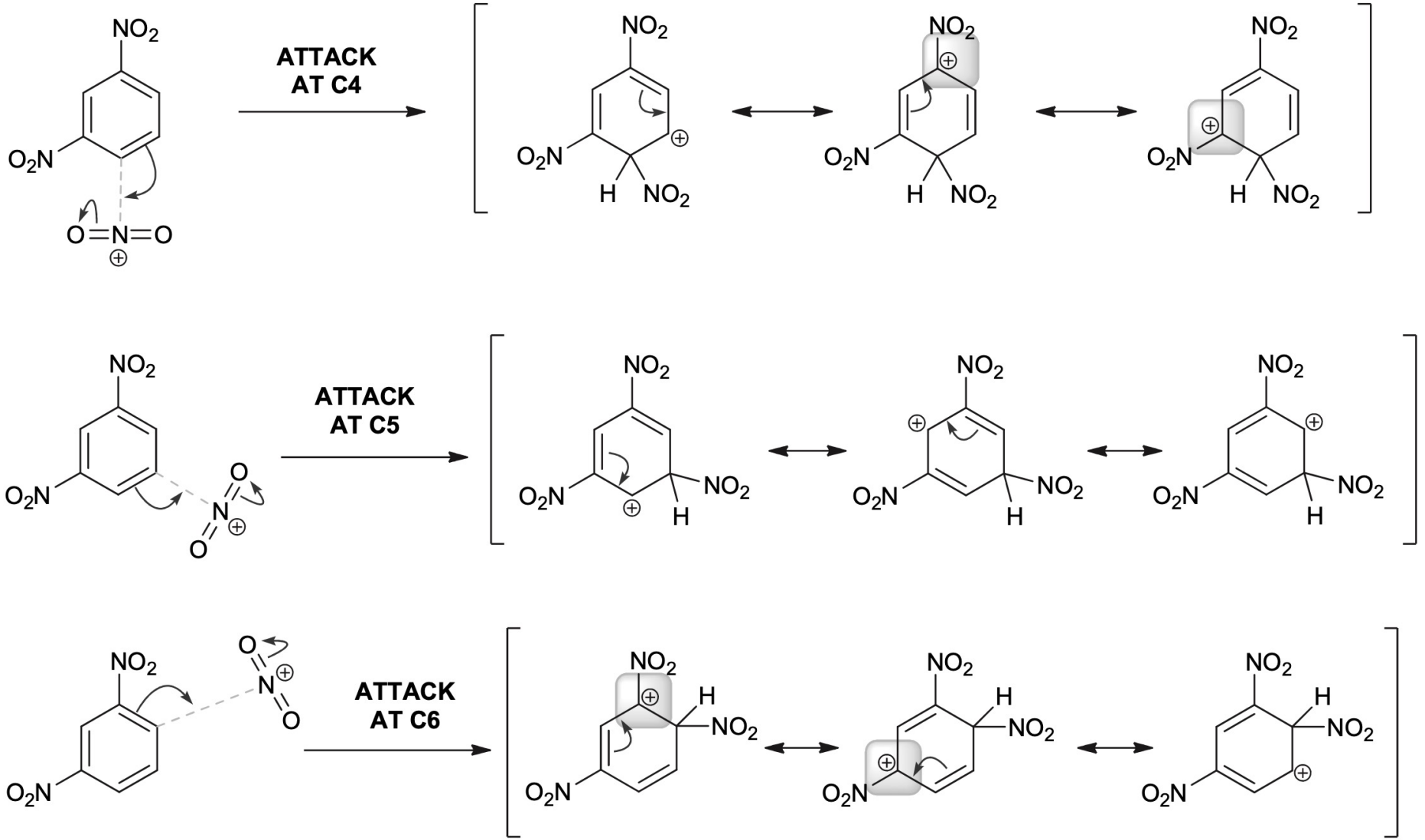



NO2
ortho attack
meta attack
para attack
H

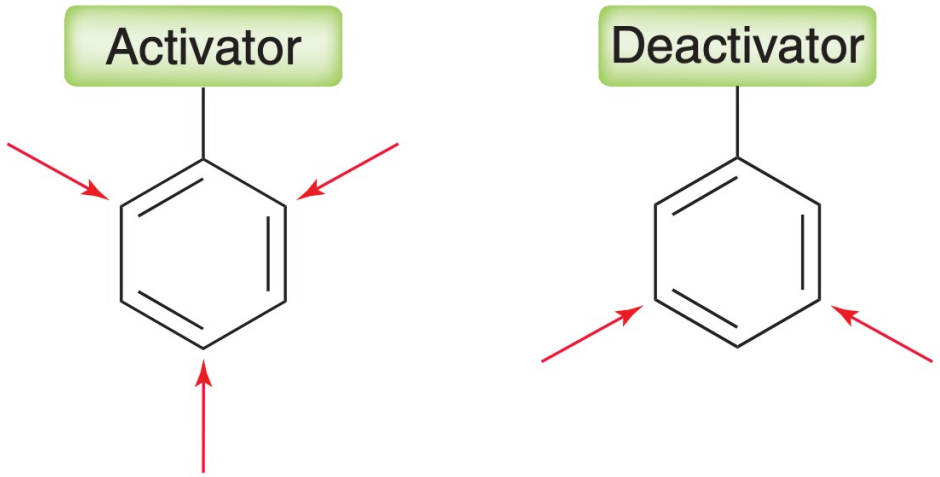
- Energy diagrams for different attacking – nitrobenzene



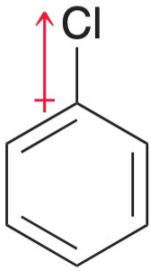
- Practice: when 1,3-dinitrobenzene is treated with nitric acid and sulfuric acid at elevated temperature, the product is 1,3,5-trinitrobenzene. Explain the regiochemical outcome of this reaction. In other words, explain why nitration takes place at the C5 position. Make sure to draw the sigma complex for each possible pathway and to compare the relative stability of each sigma complex.


ATTACK
AT C4
ATTACK
AT C5
ATTACK
AT C6

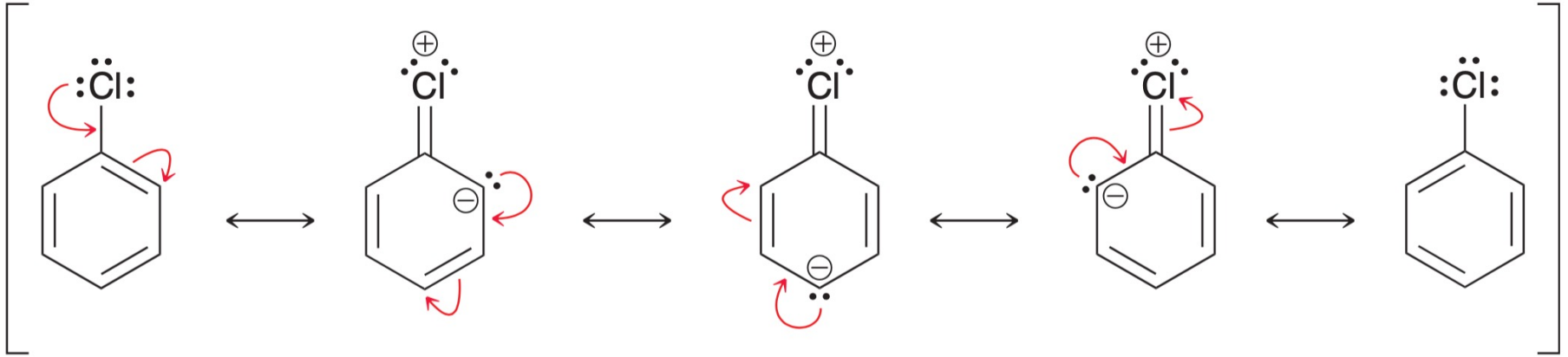
- General trend of activating and deactivating groups



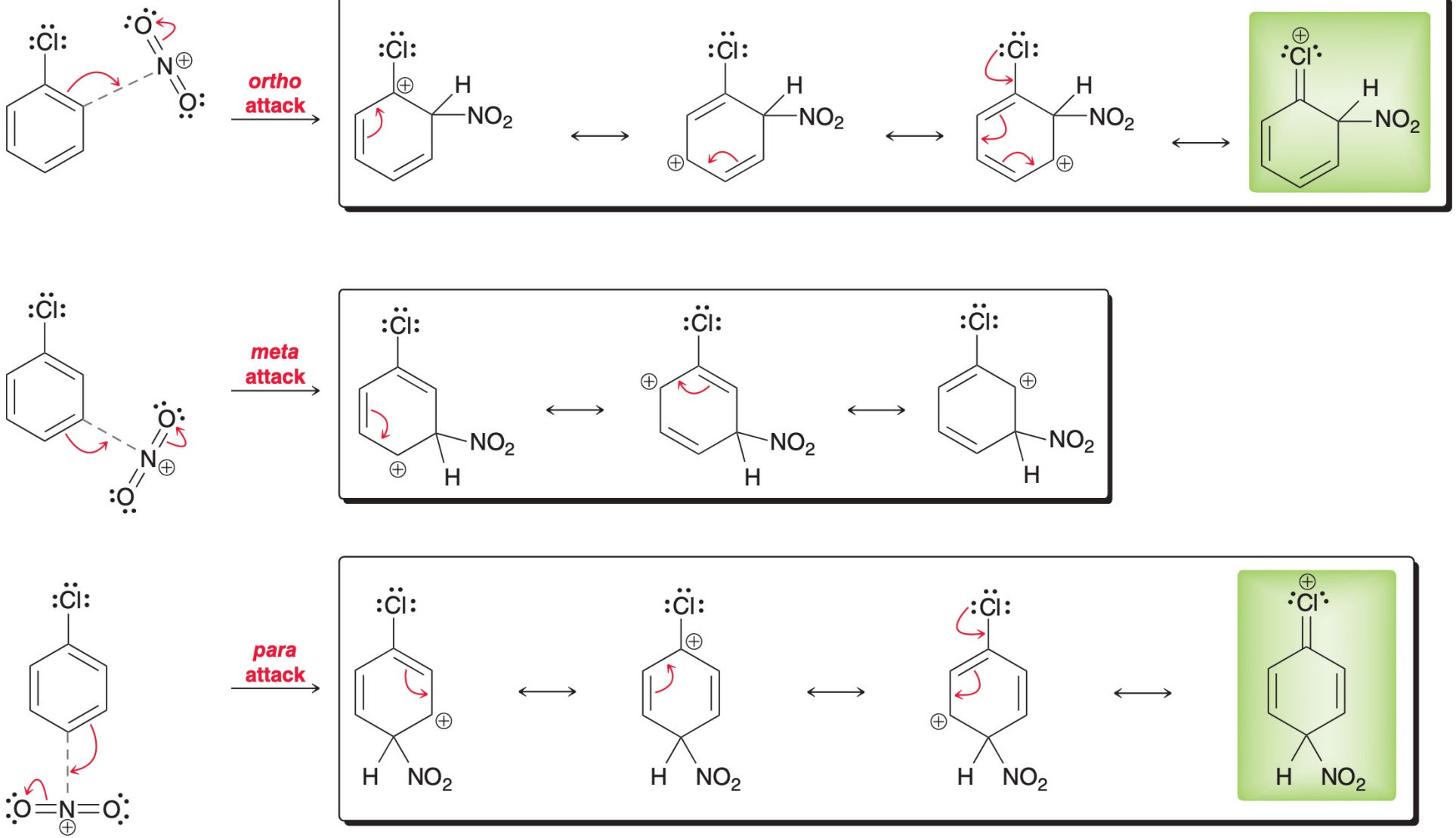
- Halogens: the exception



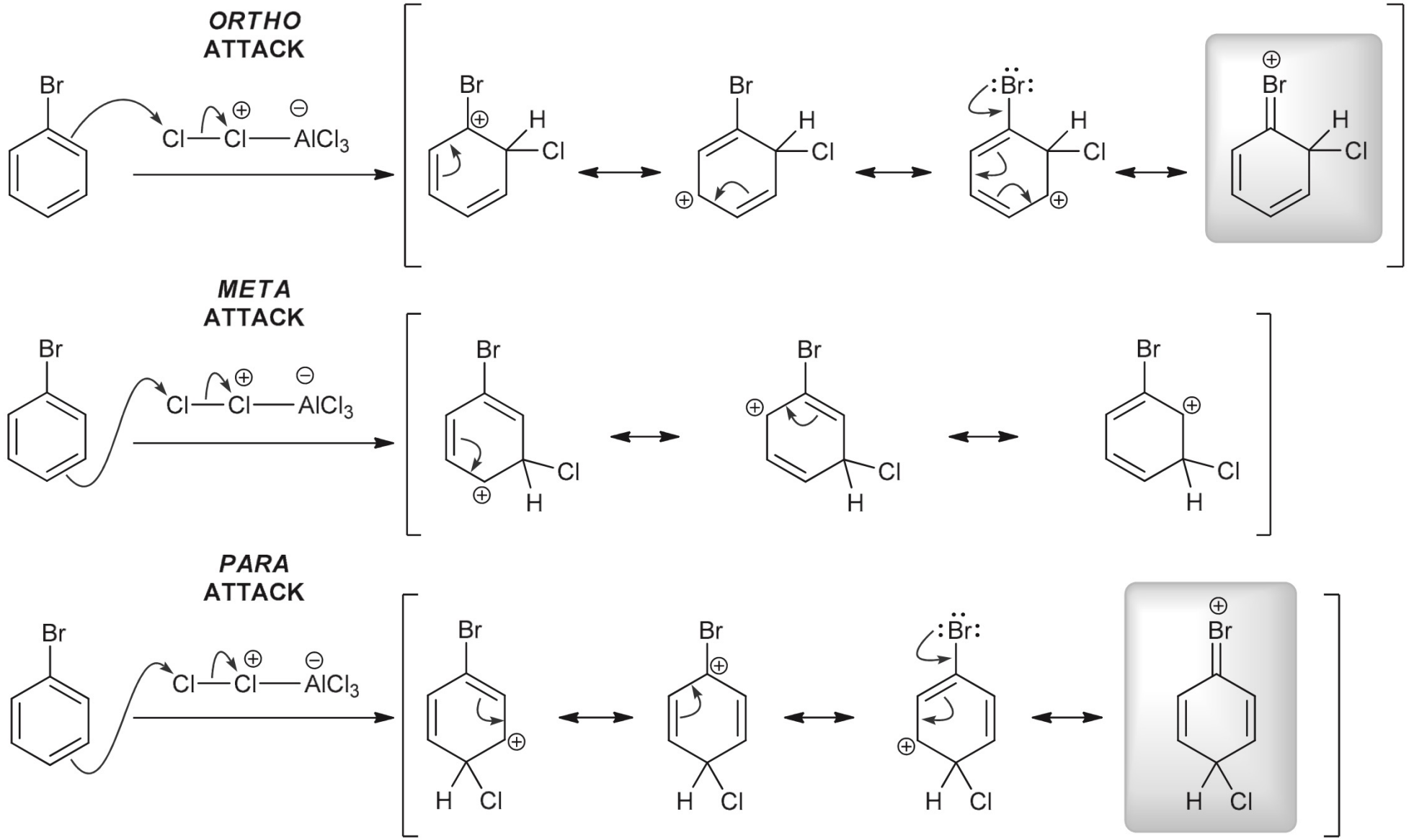
inductive effect: electron withdrawing (dominant) – the ring is *deactivated*



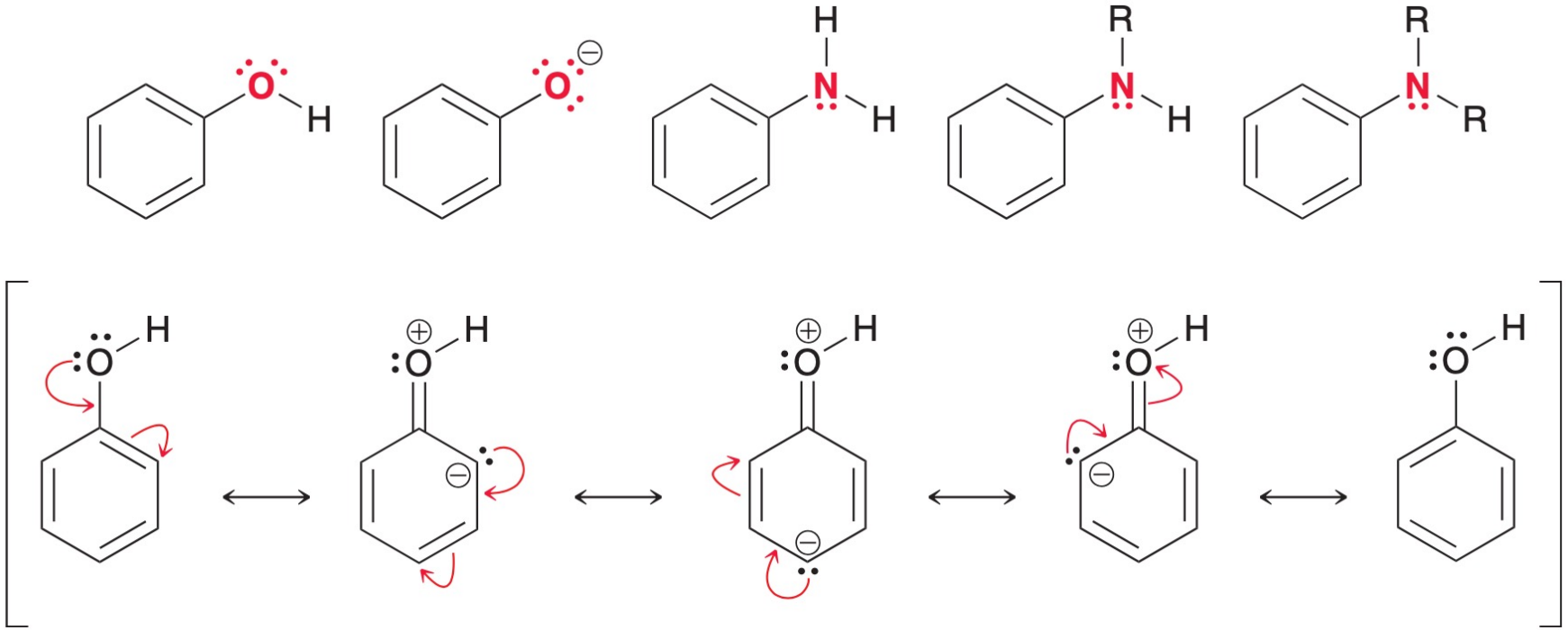
resonance effect: electron donating


ortho attack
meta attack
para attack

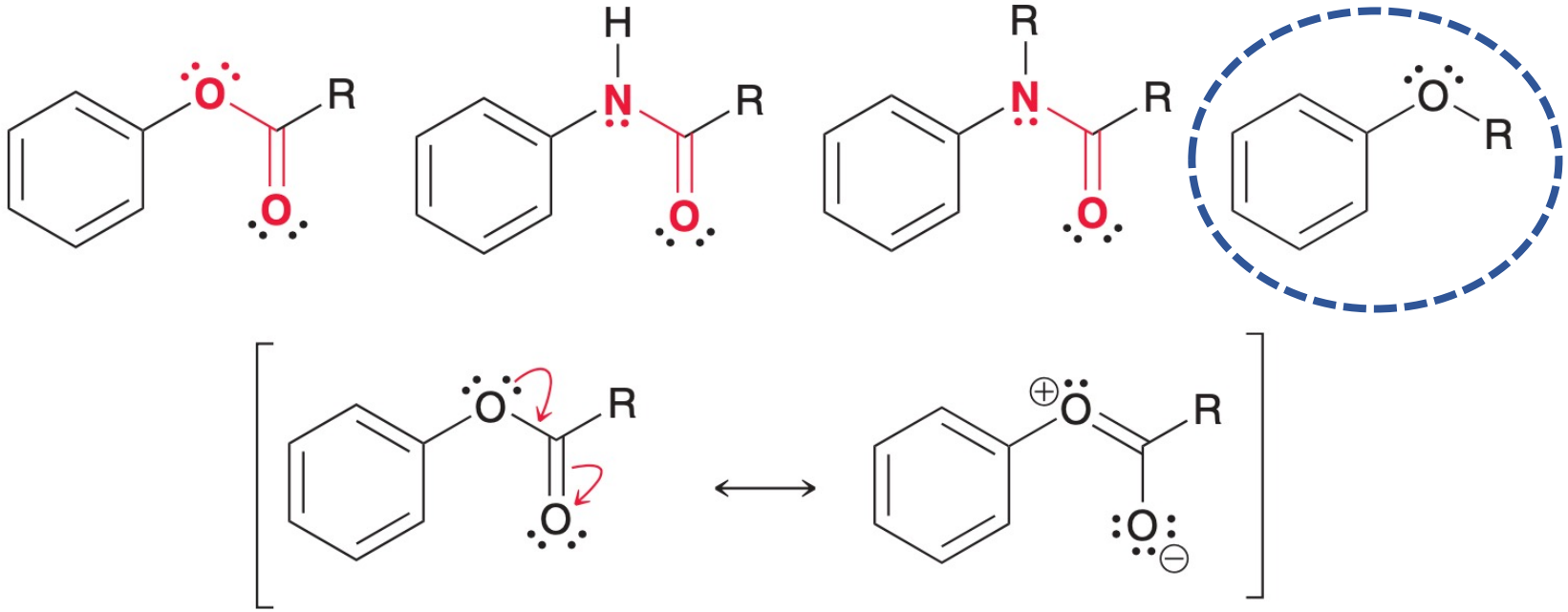
- Practice: predict and explain the regiochemical outcome for chlorination of bromobenzene.


ORTHO
ATTACK
META
ATTACK
PARA
ATTACK
Br
Cl
AlCl3
H

- Activators
  - Strong activators: a lone pair immediately adjacent to the aromatic ring

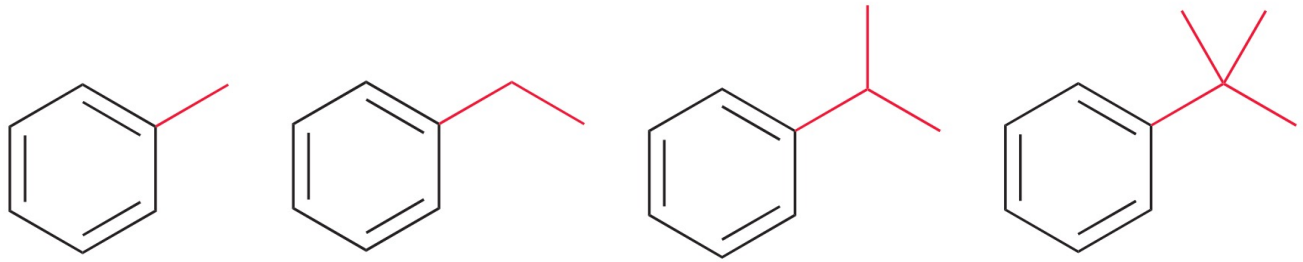


- Activators
  - Moderate activators: a lone pair that is already delocalized outside of the ring

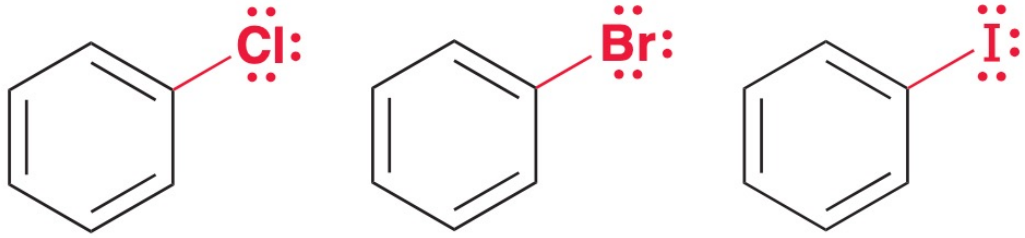


stronger than other moderate activators; less than strong deactivators

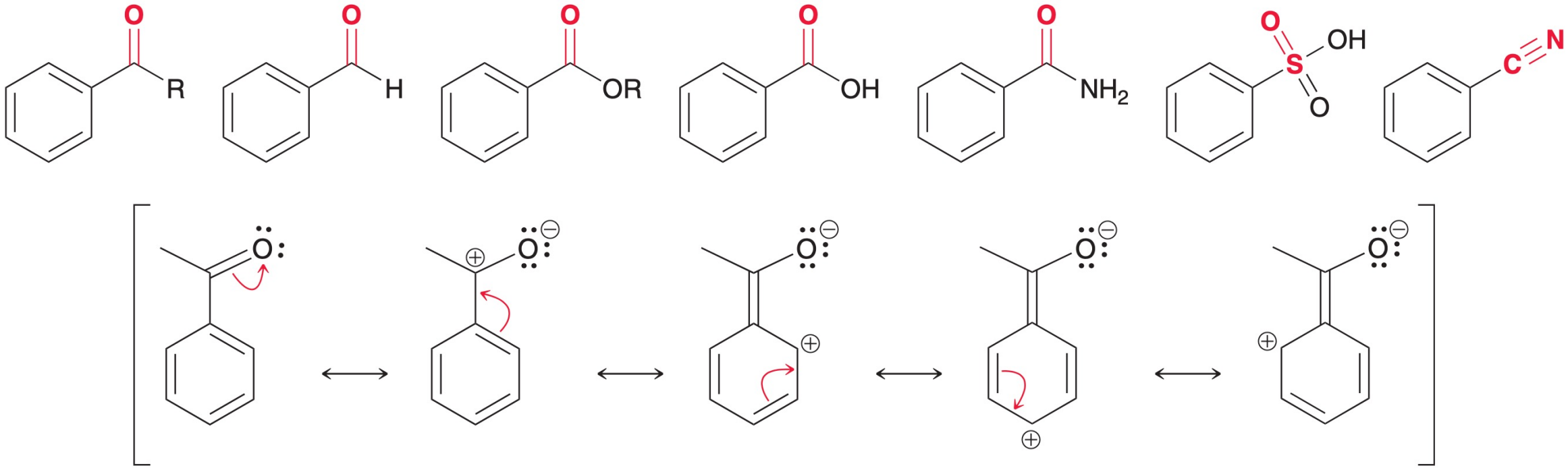
- Activators
  - Weak activators: alkyl groups – relatively weak effect of hyperconjugation



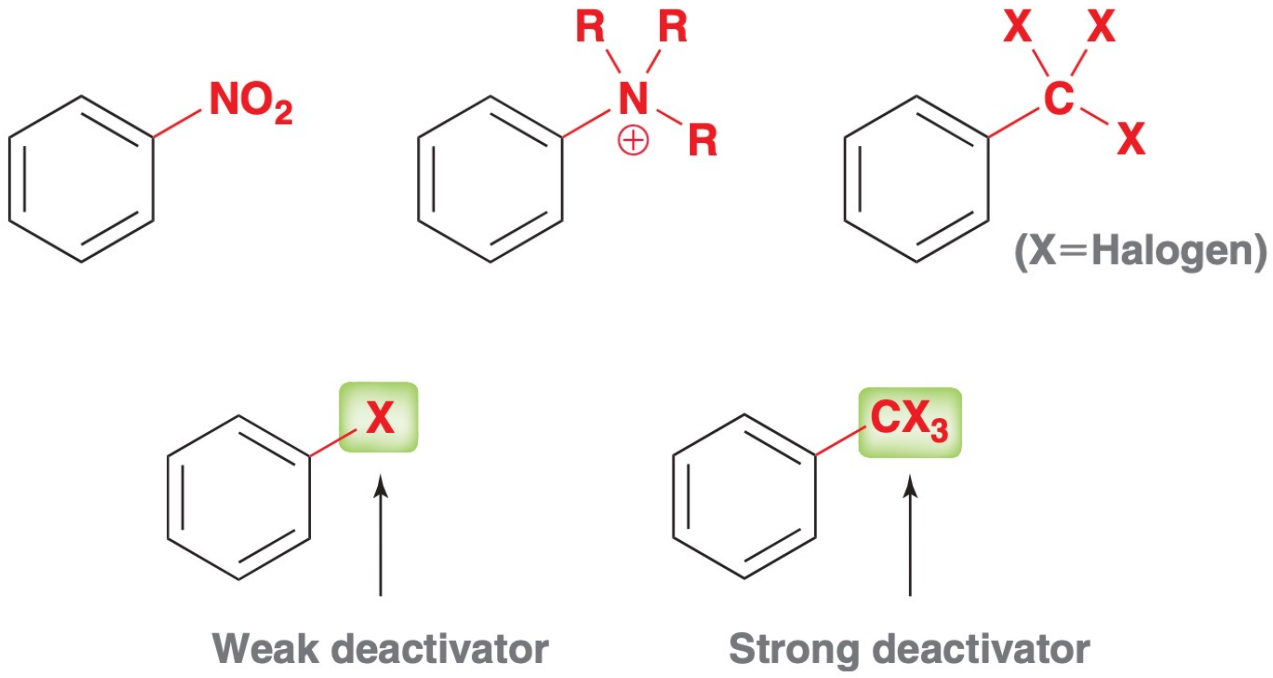
- Deactivators
  - Weak deactivators: halogens – competing inductive & resonance effects



- Deactivators
  - Moderate deactivators: a ring-conjugated π bond to an electronegative atom

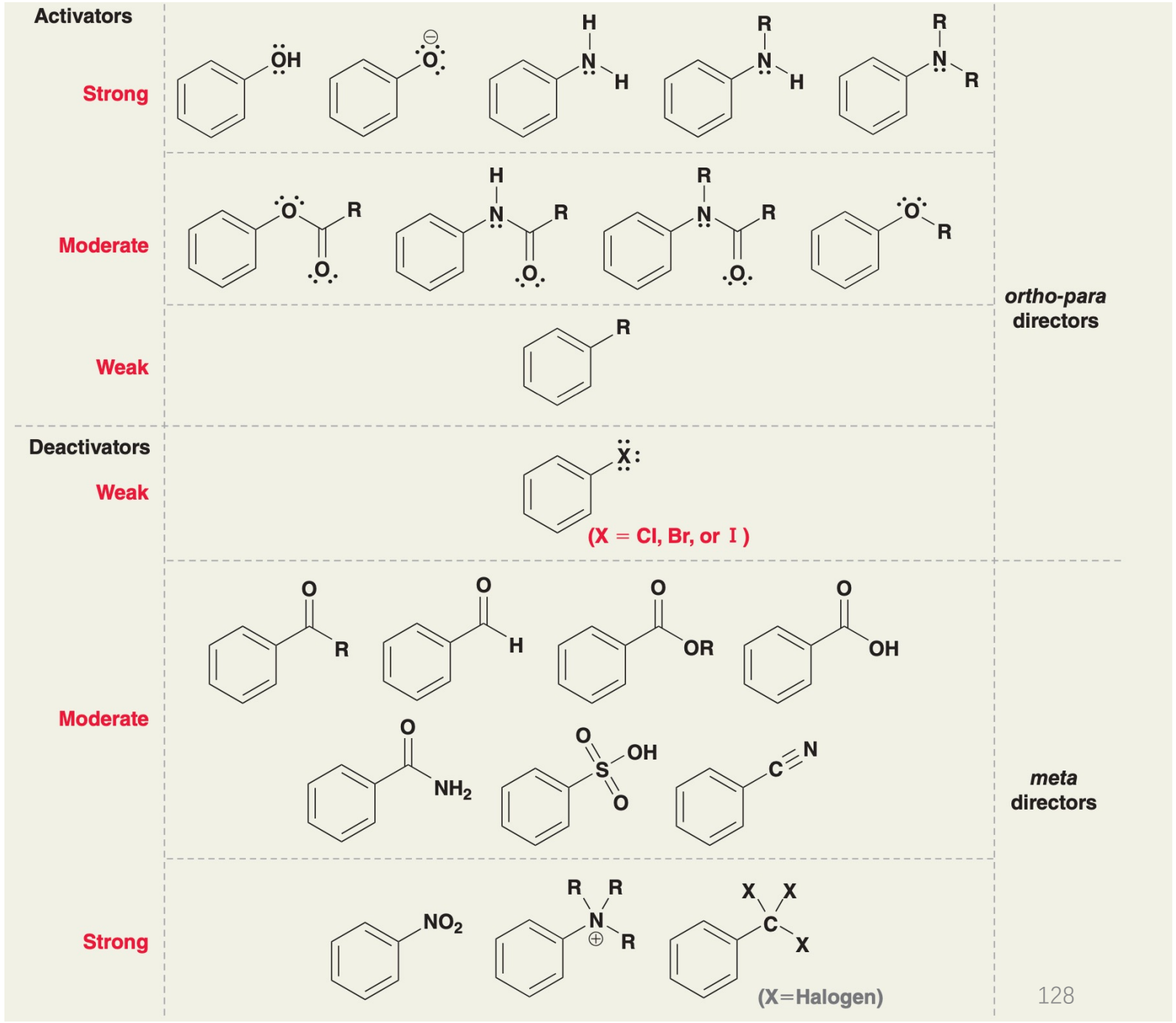


- Deactivators
  - Strong deactivators: nitro group and trihalides

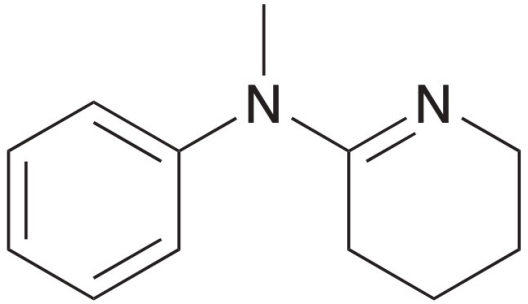


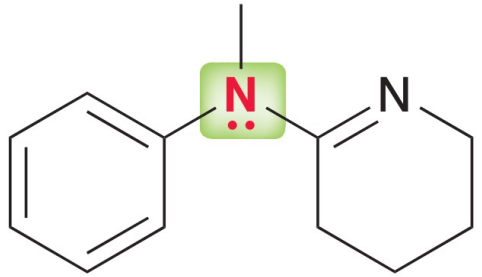
do not confuse a CX_3 group with a halogen (X)!

- A list of activators and deactivators by category
  - All activators are *ortho-para* directors
  - Most of deactivators are *meta* directors
  - Halogens are *ortho-para* directors, but they are deactivators

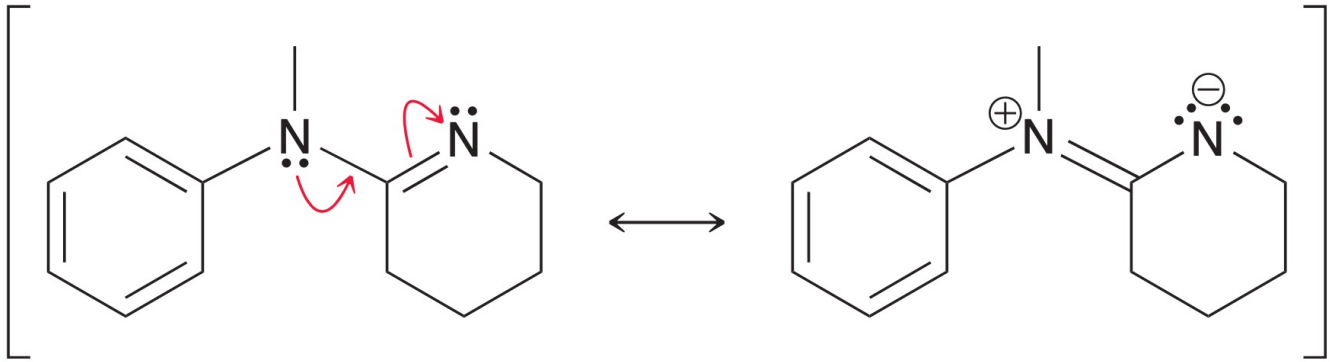


- Practice: consider the following monosubstituted aromatic ring. Predict whether this aromatic ring is activated or deactivated, and predict the strength of activation/deactivation (i.e., is it strong, moderate, or weak). Finally, predict the directing effects of the group.





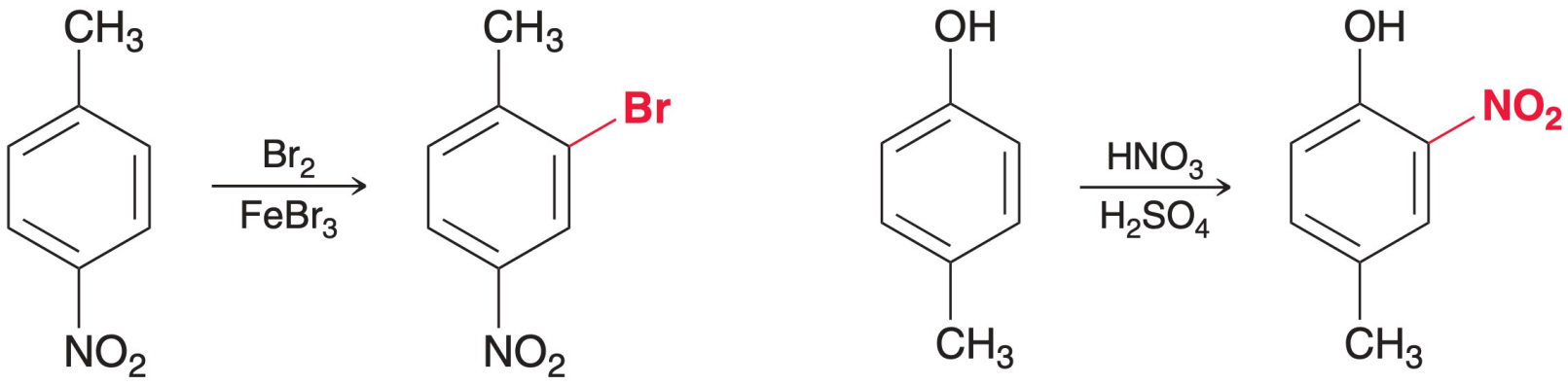
adjacent lone pair – activator



lone pair delocalized outside of the ring – moderate activator

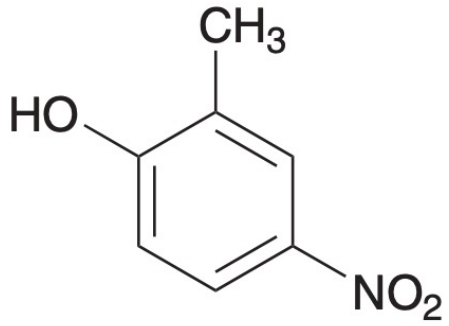
moderate activator – *ortho-para* director

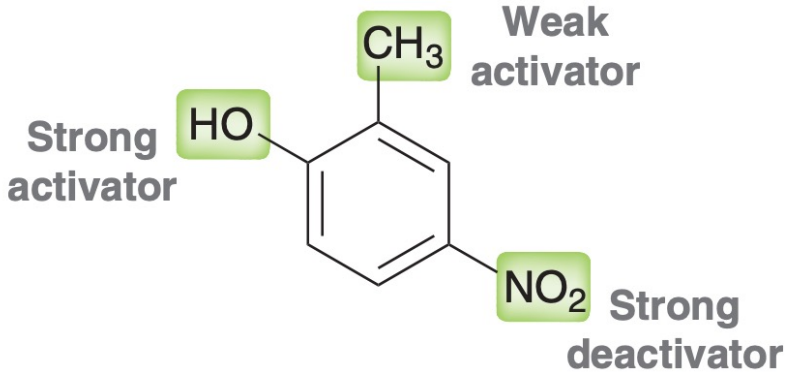
- Multiple substituents: directing effects

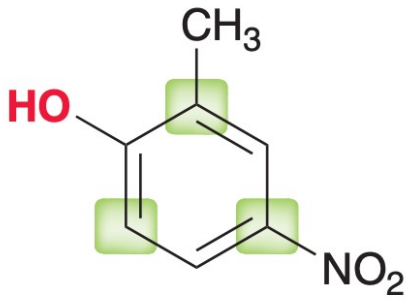


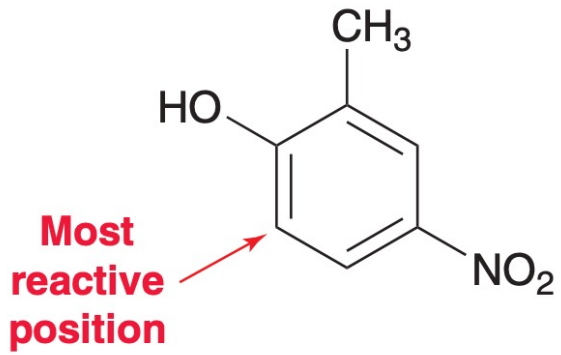
the more powerful activating group dominates the directing effects

- Practice: in the following compound, identify the position that is most likely to undergo an electrophilic aromatic substitution reaction.

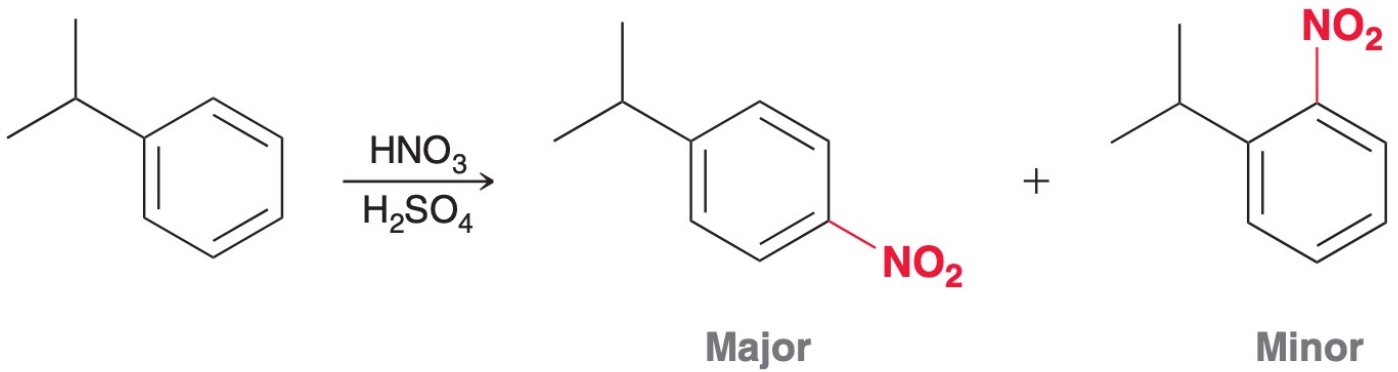



CH3
Weak activator
HO
Strong activator
NO2
Strong deactivator


CH3
HO
NO2

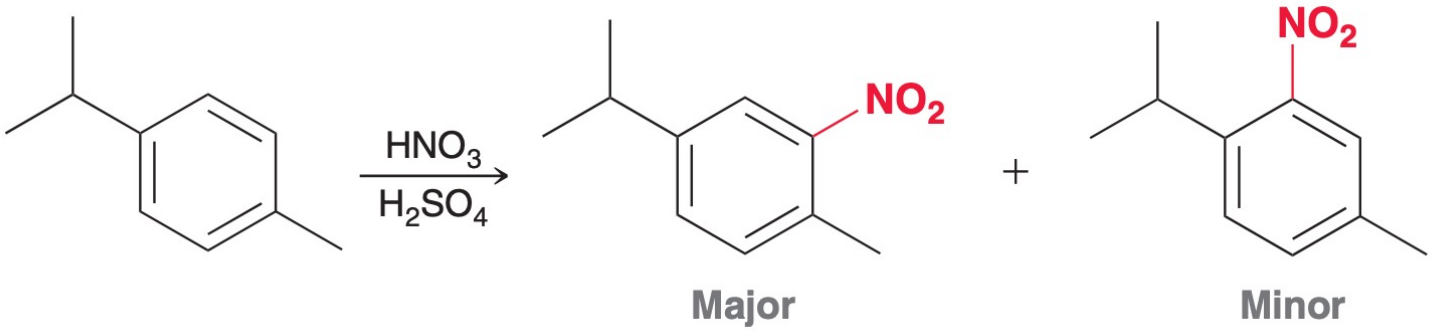

CH3
HO
Most reactive position
NO2

- Multiple substituents: steric effects
  - For most monosubstituted aromatic rings, the *para* product generally dominates over the *ortho* product as a result of steric considerations

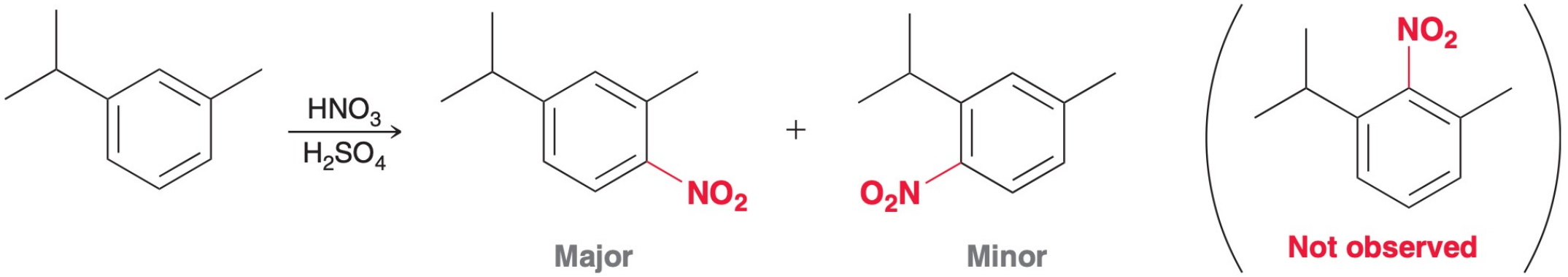


toluene is an exception – the ratio of ortho and para products is sensitive to the conditions employed

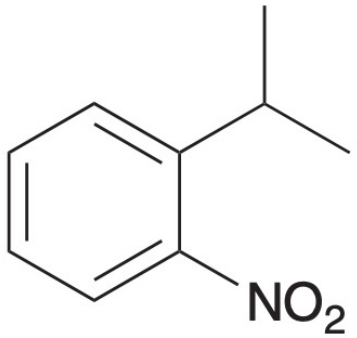
- Multiple substituents: steric effects
  - For 1,4-disubstituted aromatic rings, steric effects again play a significant role – substitution is more likely to occur at the site that is less sterically hindered

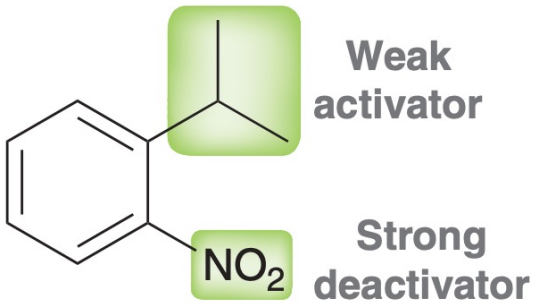


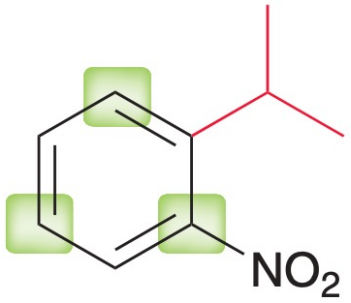
- Multiple substituents: steric effects
  - For 1,3-disubstituted aromatic rings, it is extremely unlikely that substitution will occur at the position between the two substituents

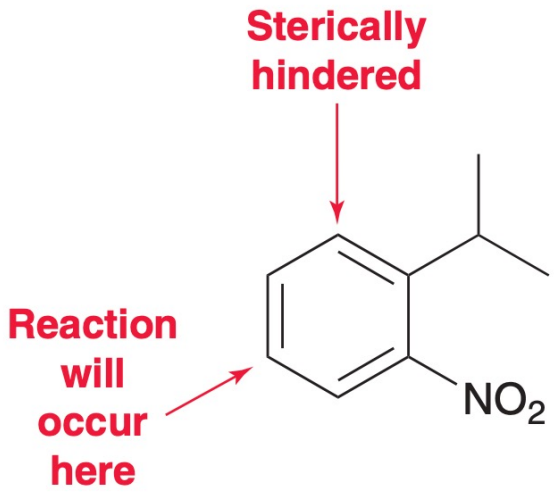


- Practice: in the following compound, determine the position that is most likely to be the site of an electrophilic aromatic substitution reaction.

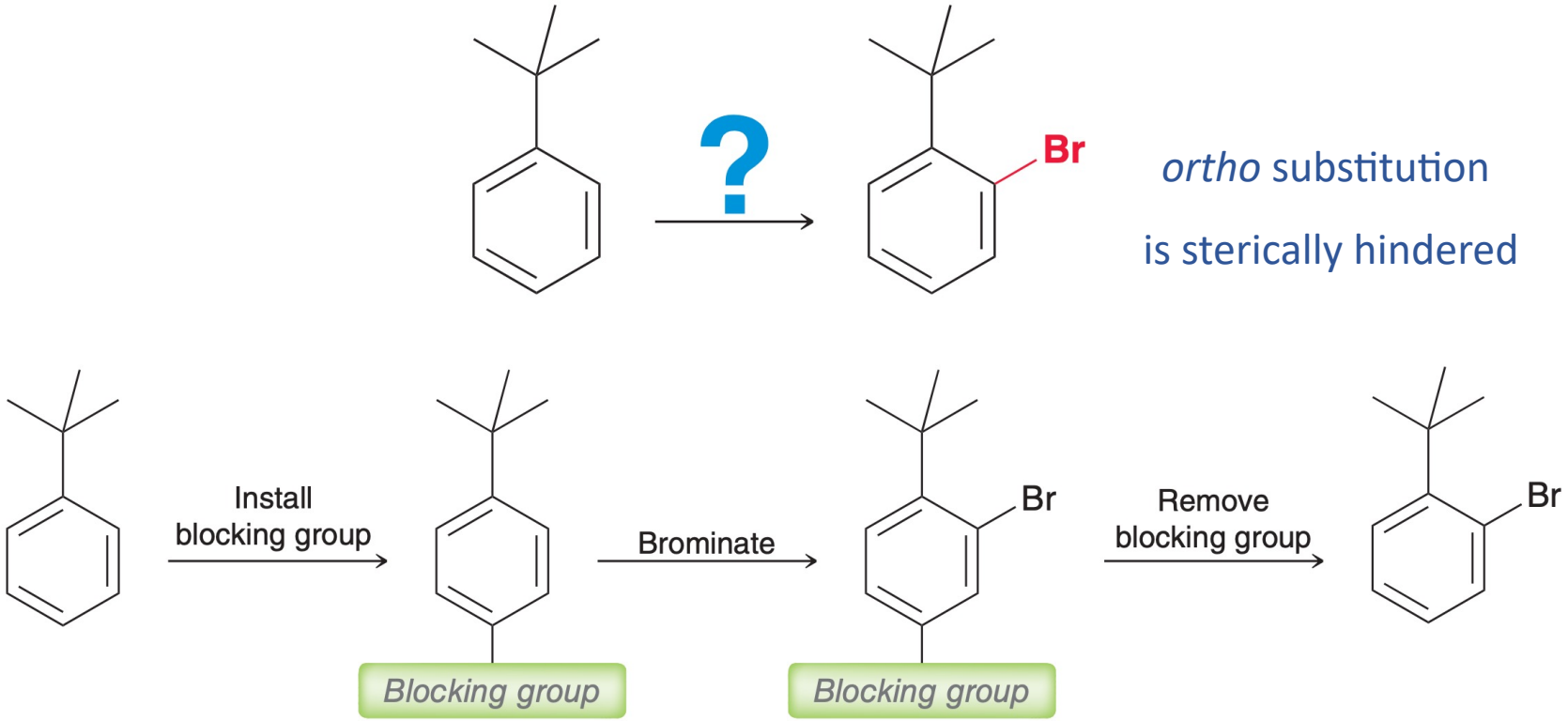



Weak
activator
NO2
Strong
deactivator

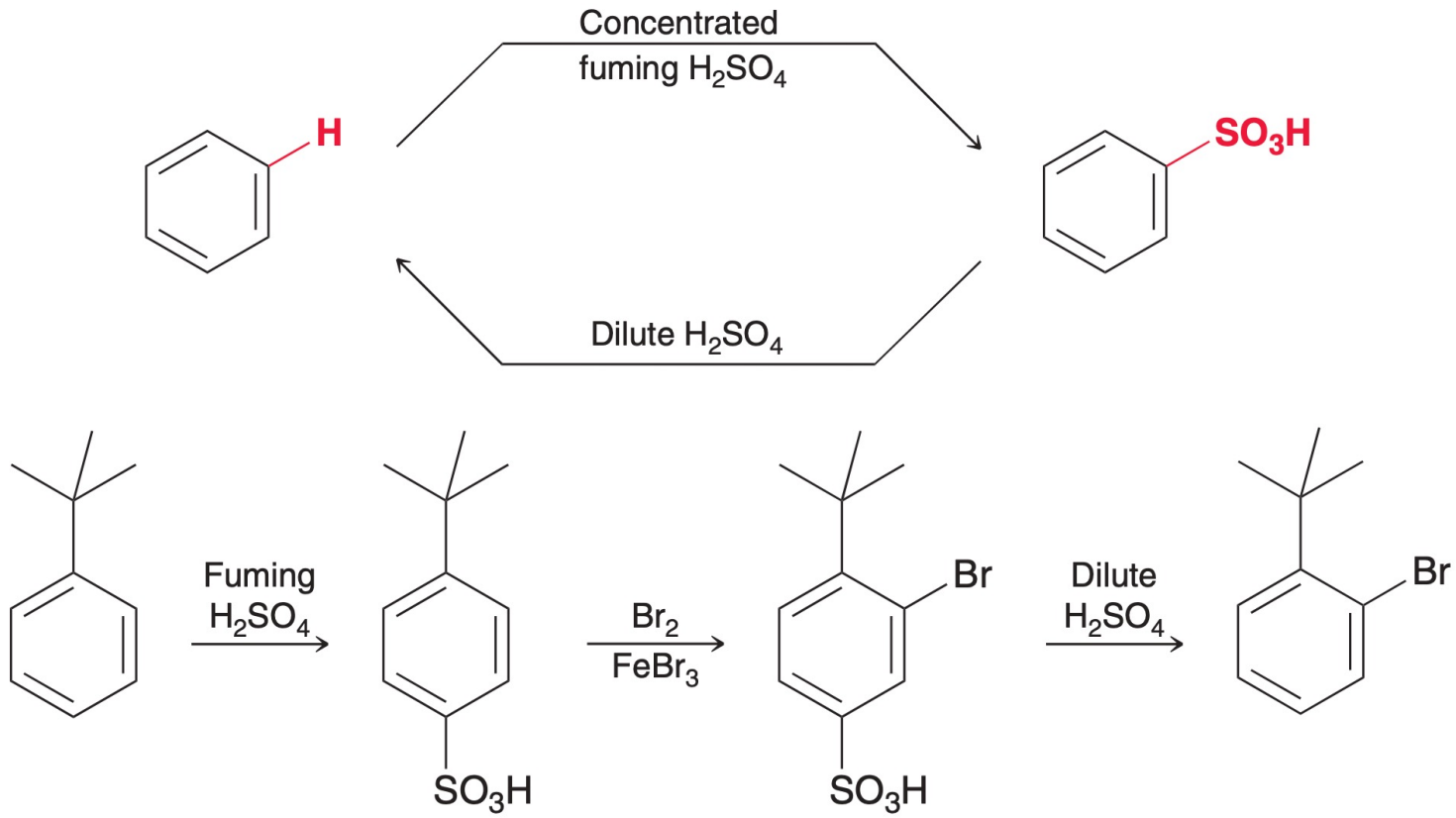

NO2


Sterically
hindered
Reaction
will
occur
here
NO2

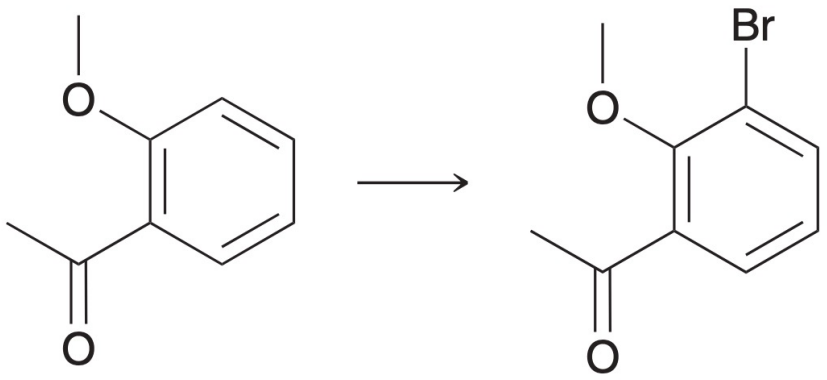
- Blocking groups

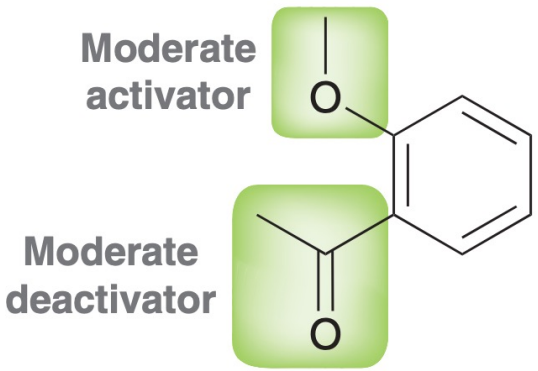


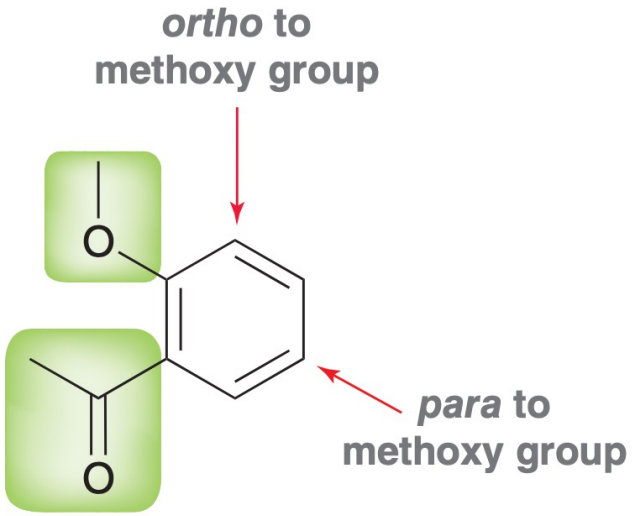
- Sulfonation is used in blocking strategy

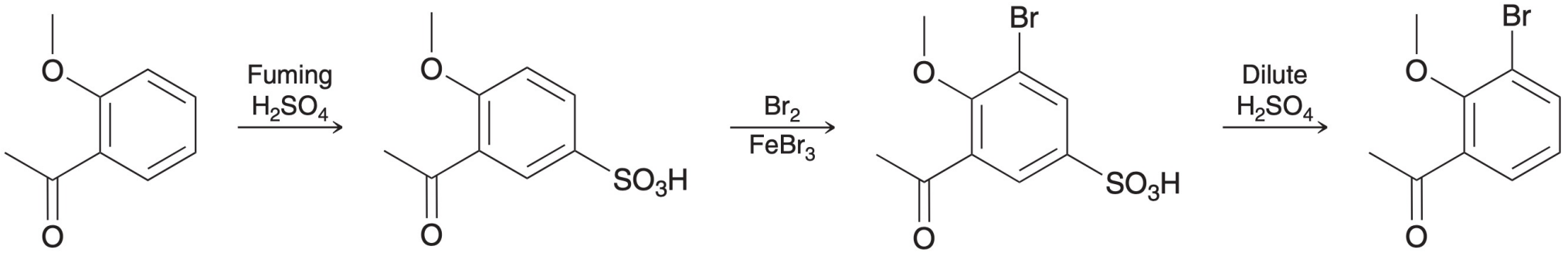


- Practice: identify whether a blocking group is necessary to accomplish the following transformation:

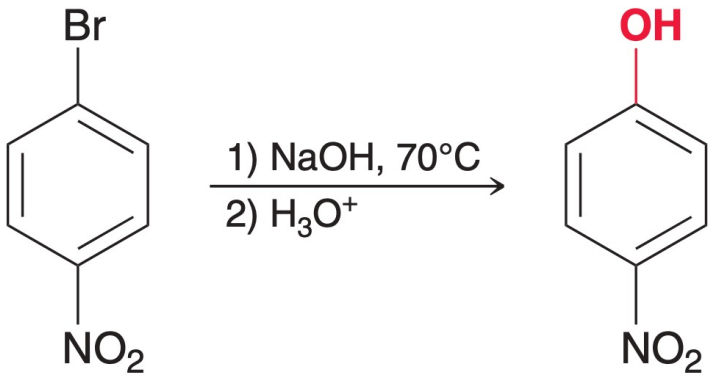



Moderate
activator
Moderate
deactivator
O
O

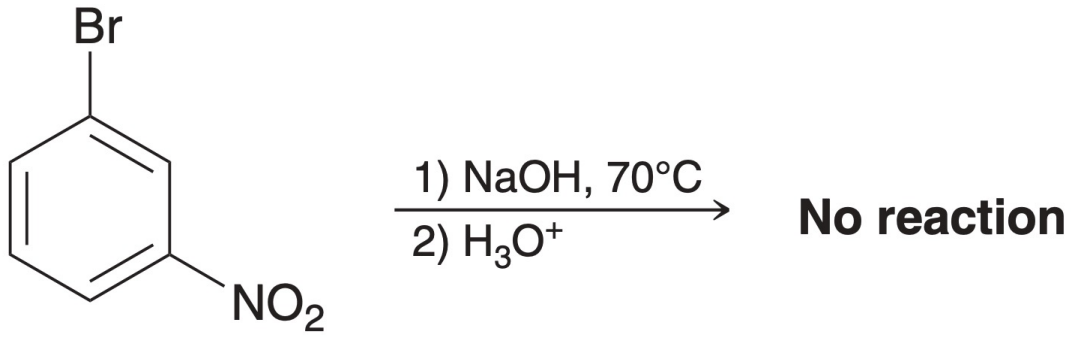

ortho to
methoxy group
para to
methoxy group
O
O


O
O
Fuming
H_2SO_4
SO_3H
Br_2
$FeBr_3$
Br
Dilute
H_2SO_4

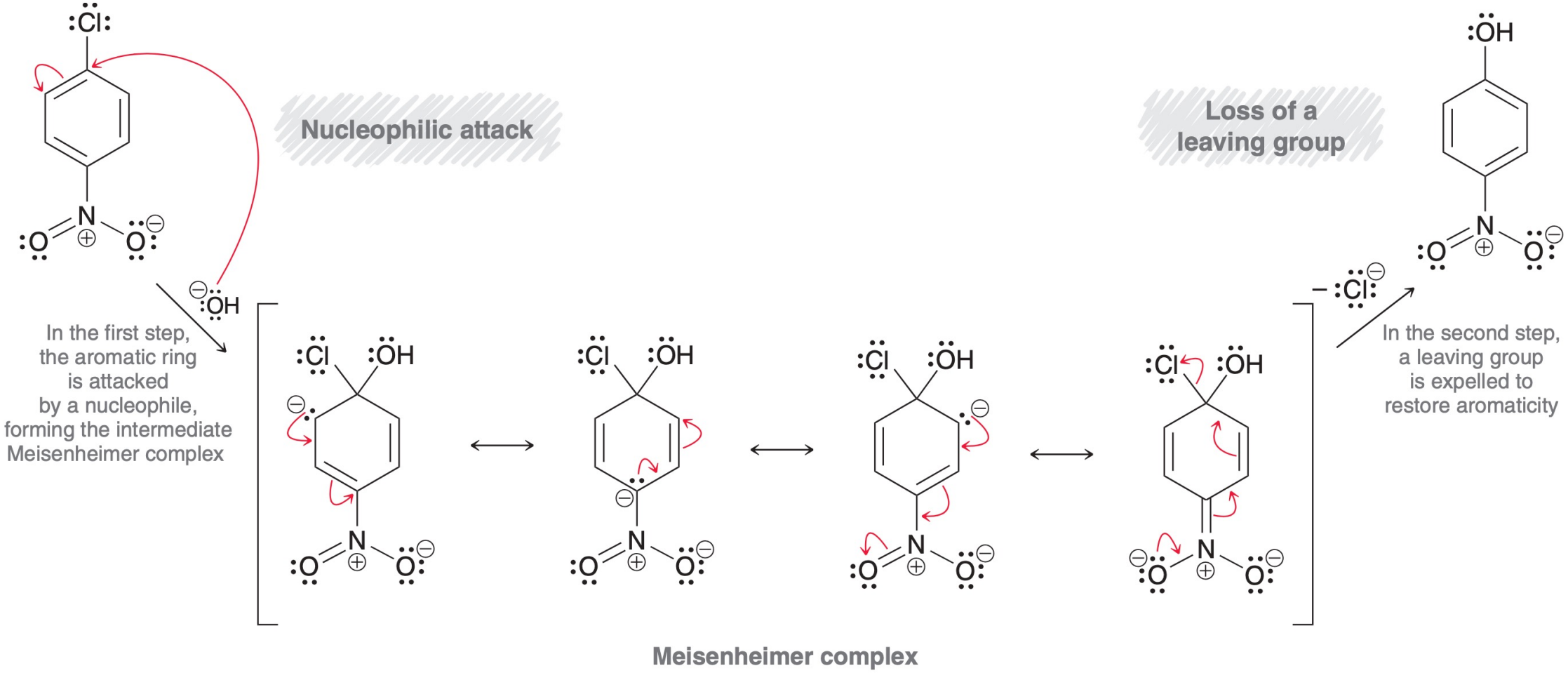
- Nucleophilic aromatic substitution ($\mathbf{S_NAr}$)
  - The ring must contain a powerful electron-withdrawing group (typically a nitro group)
  - The ring must contain a leaving group (usually a halide)
  - The leaving group must be either *ortho* or *para* to the electron-withdrawing group; if the leaving group is *meta* to the nitro group, the reaction is not observed



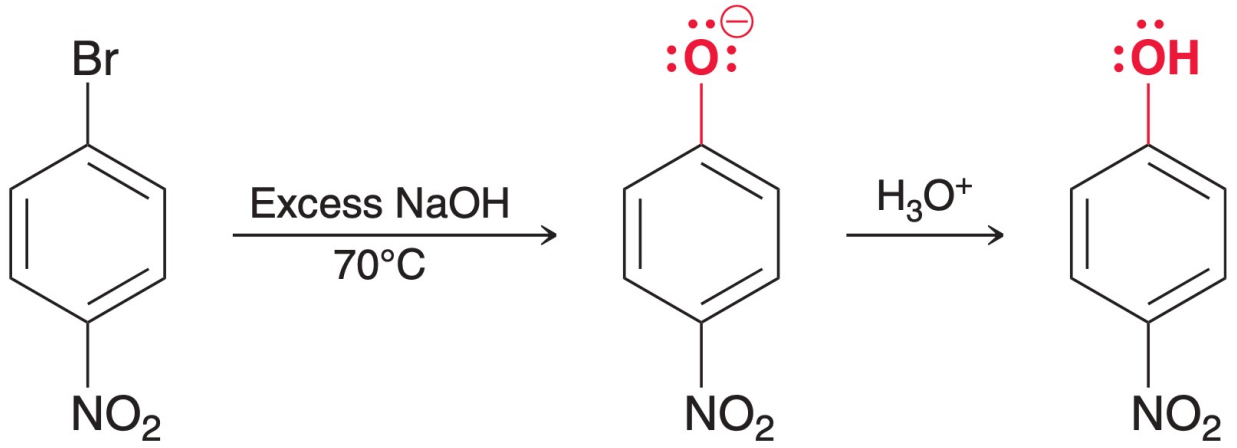
- Leaving group is *meta* to the nitro group – no reaction!



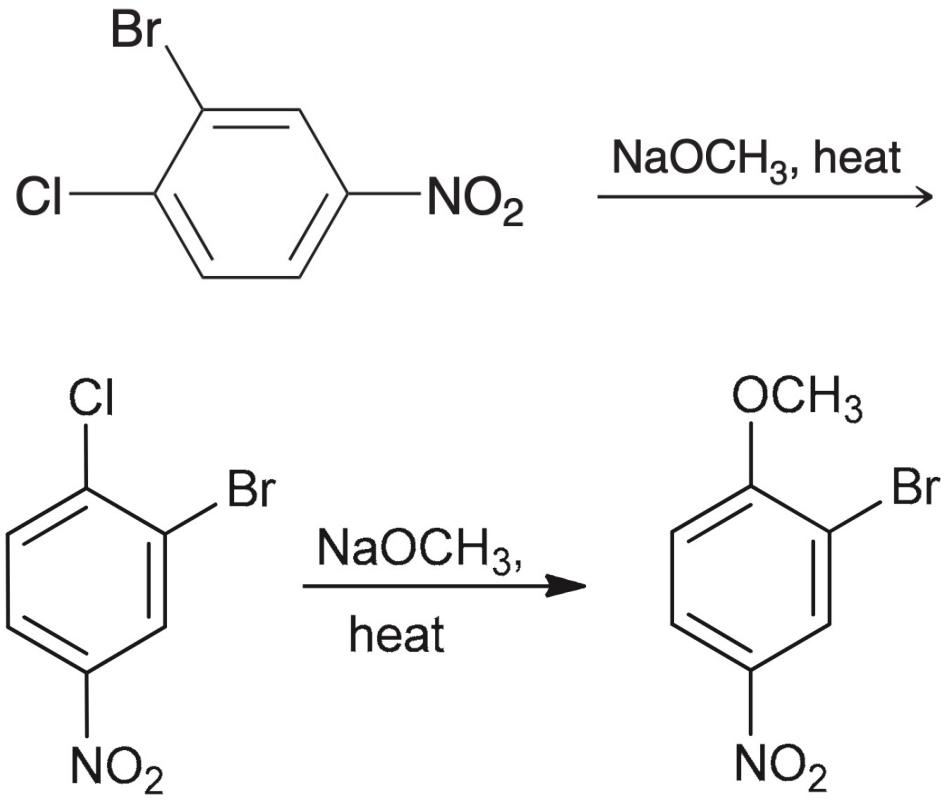
- **Mechanism: Nucleophilic Aromatic Substitution (S_NAr)**



- Acid is required when the nucleophile is a hydroxide

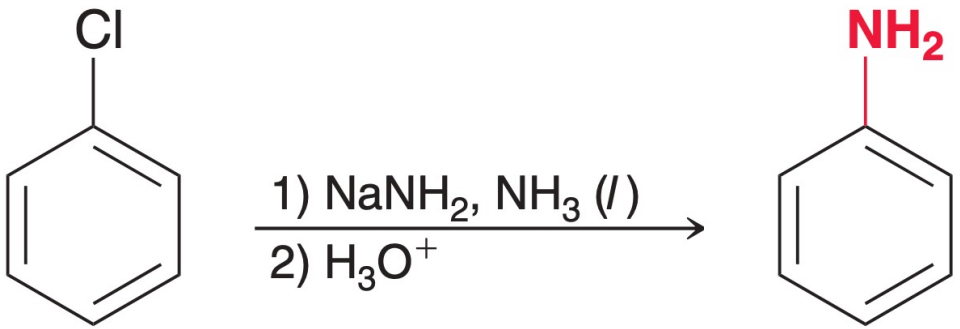


- Practice: predict the product of the following reaction:

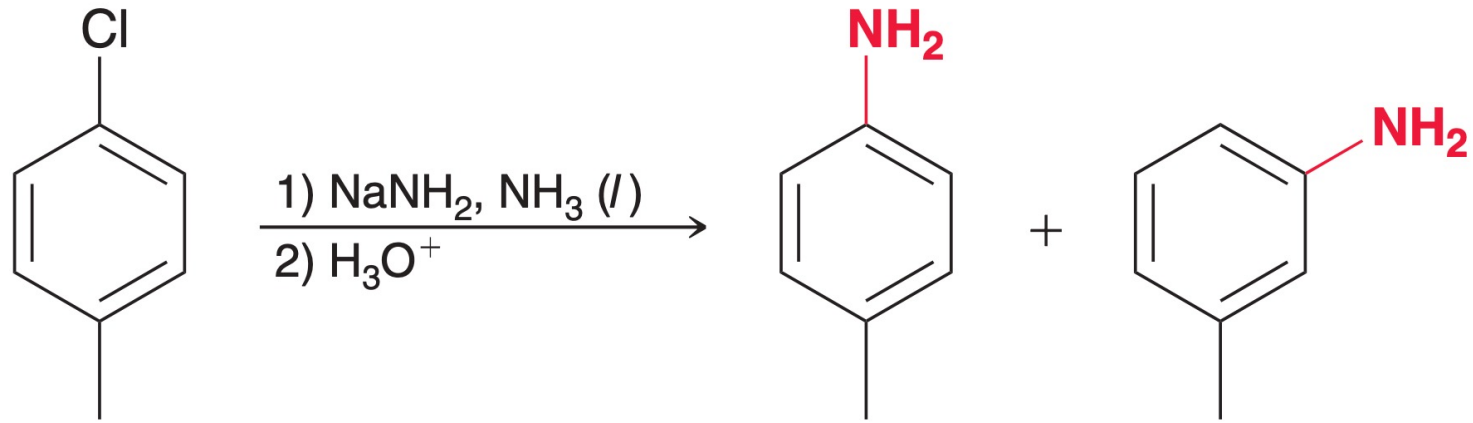


- No EWG group, but high temperature… also S_NAr?

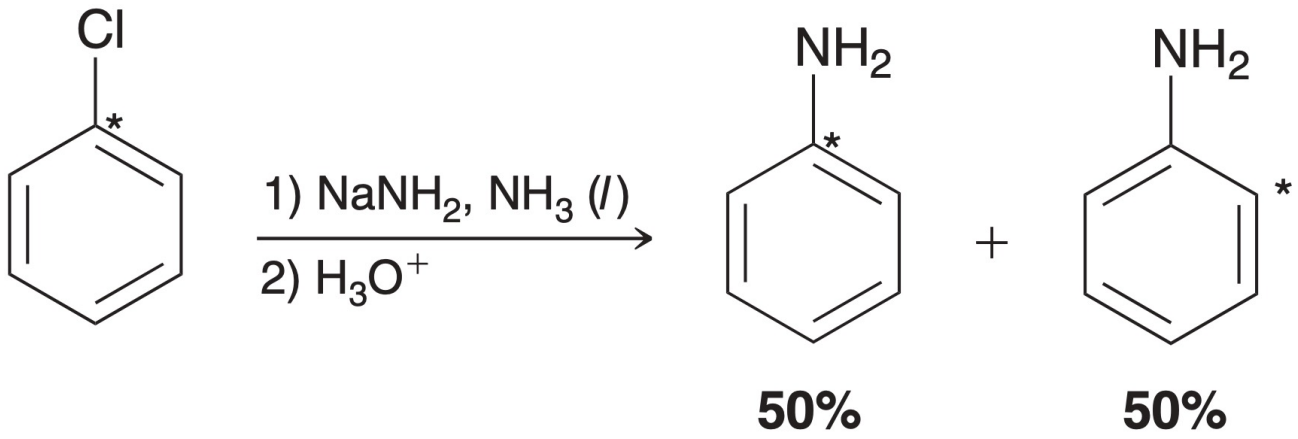
- Low temperature & H_2N^- as a nucleophile



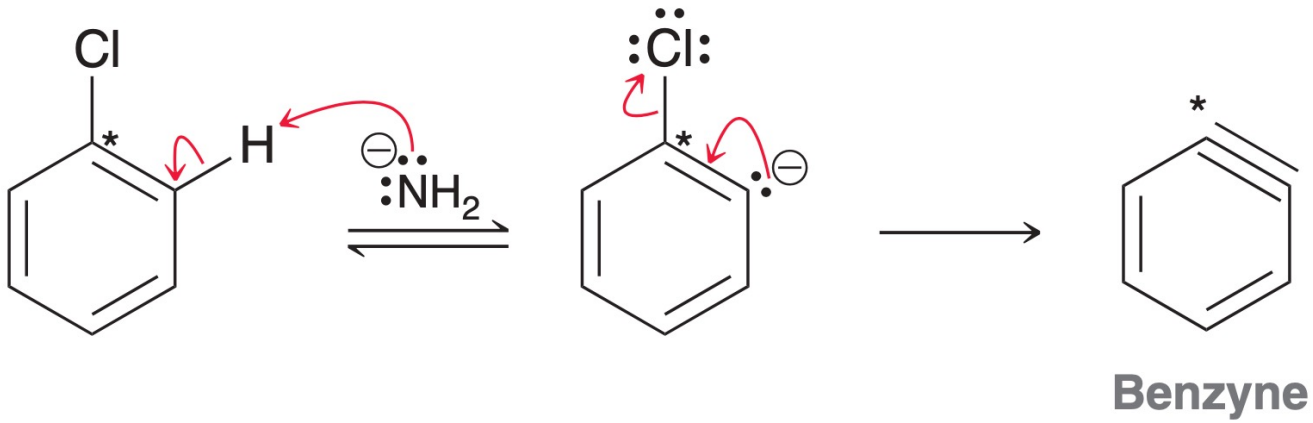
- Moreover… different regiochemical outcome



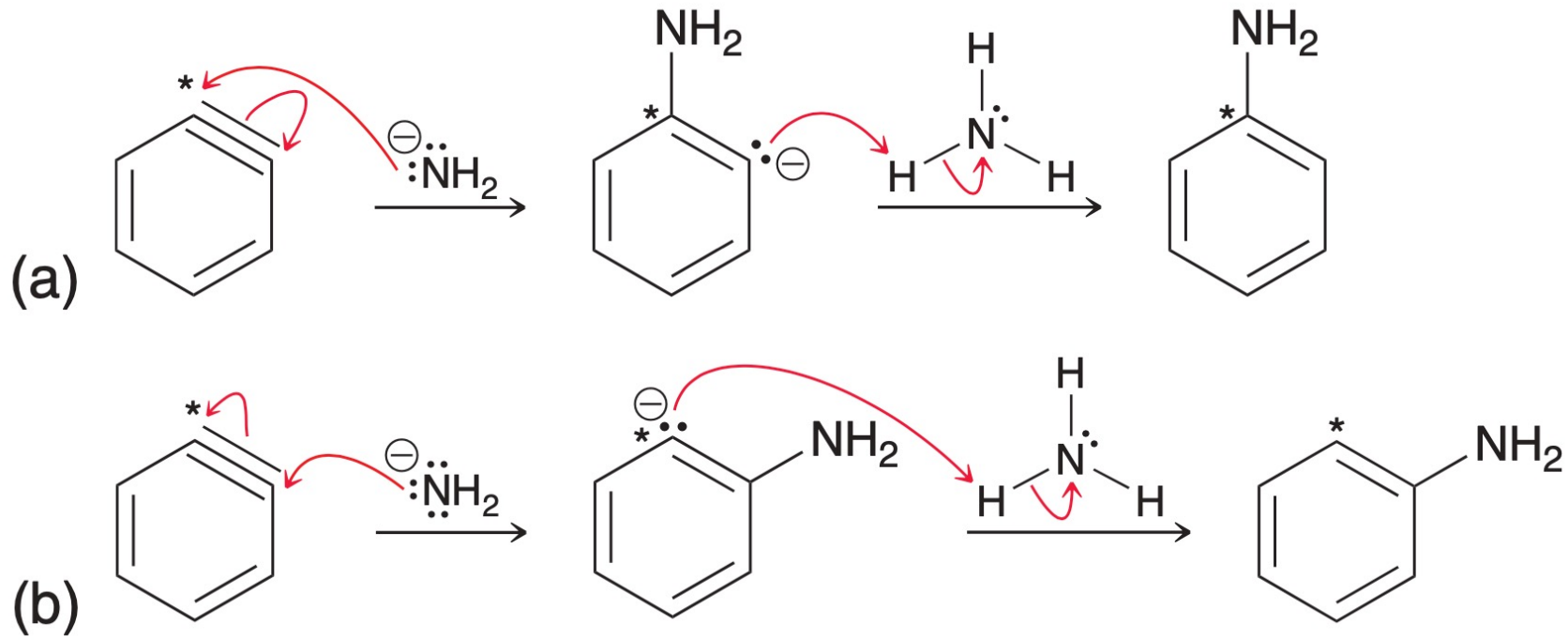
- Isotopic labeling experiment



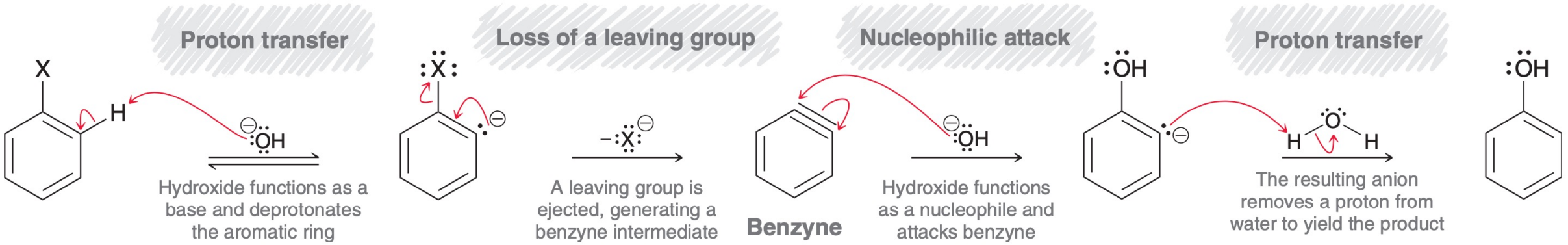
- The *benzyne* intermediate



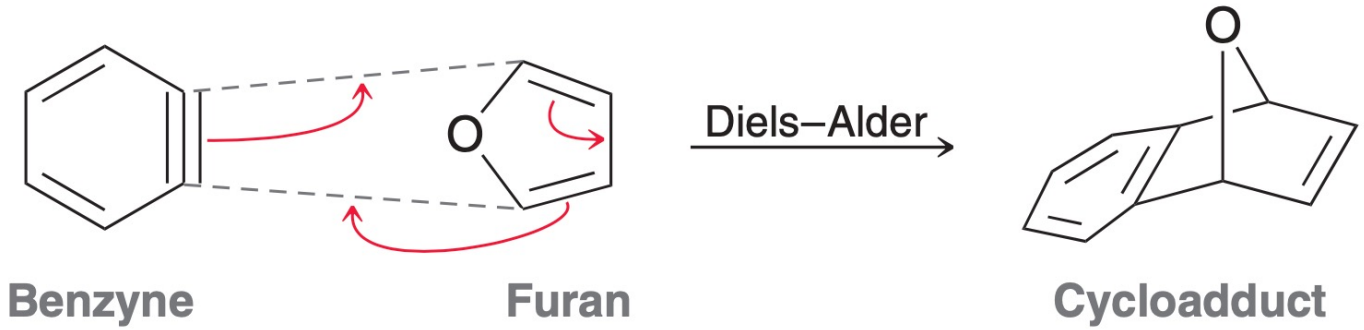
- Elimination & substitution can take place at both positions



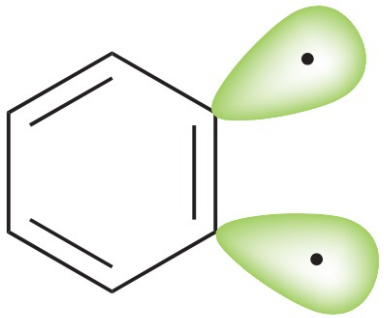
- **Mechanism: Elimination-Addition**



- Evidence: Diels-Alder cycloadduct is obtained



- The explanation of benzyne “triple bond” – a diradical



the “triple bond” is resulting from overlapping sp^2 orbitals

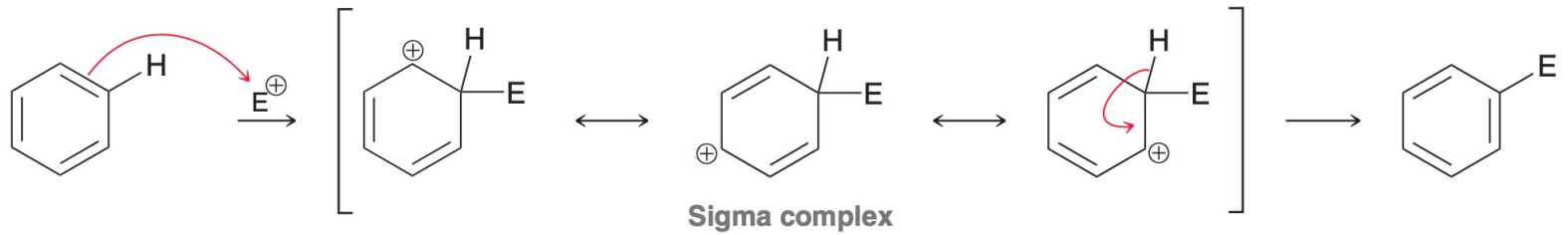
rather than overlapping *p* orbitals

Synthetic Strategies

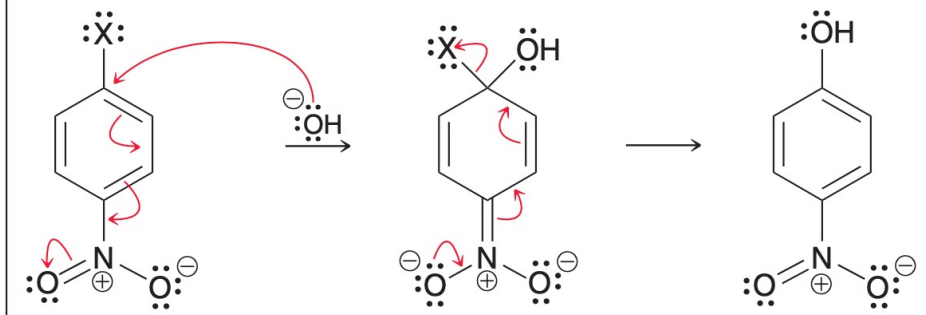
Identifying the Mechanism, Substituted Benzene Synthesizing

- Three different mechanisms for aromatic substitution reactions
  - Electrophilic aromatic substitution (EArS)
  - Nucleophilic aromatic substitution (S_NAr)
  - Elimination-addition

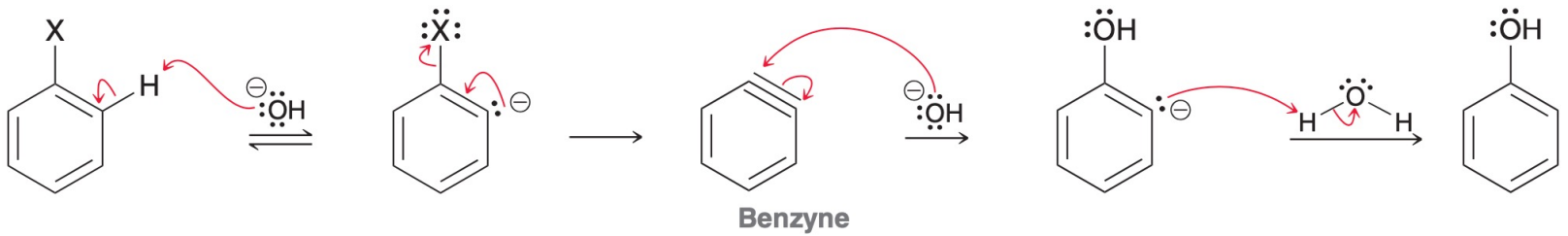
Electrophilic aromatic substitution



Nucleophilic aromatic substitution

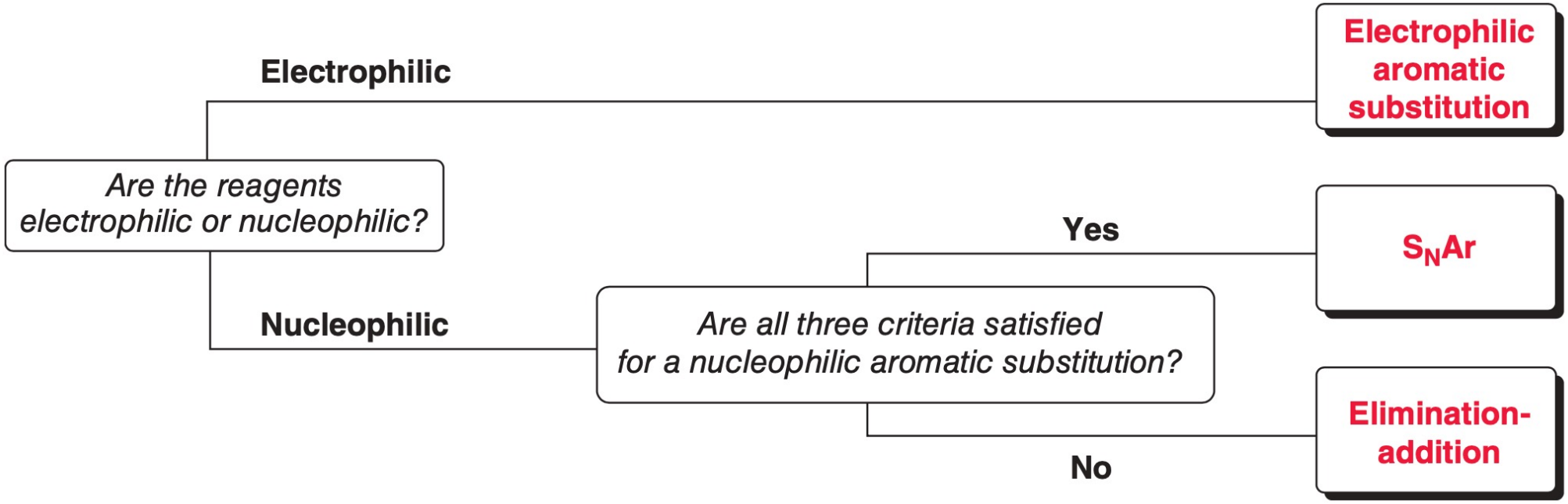


Elimination-addition

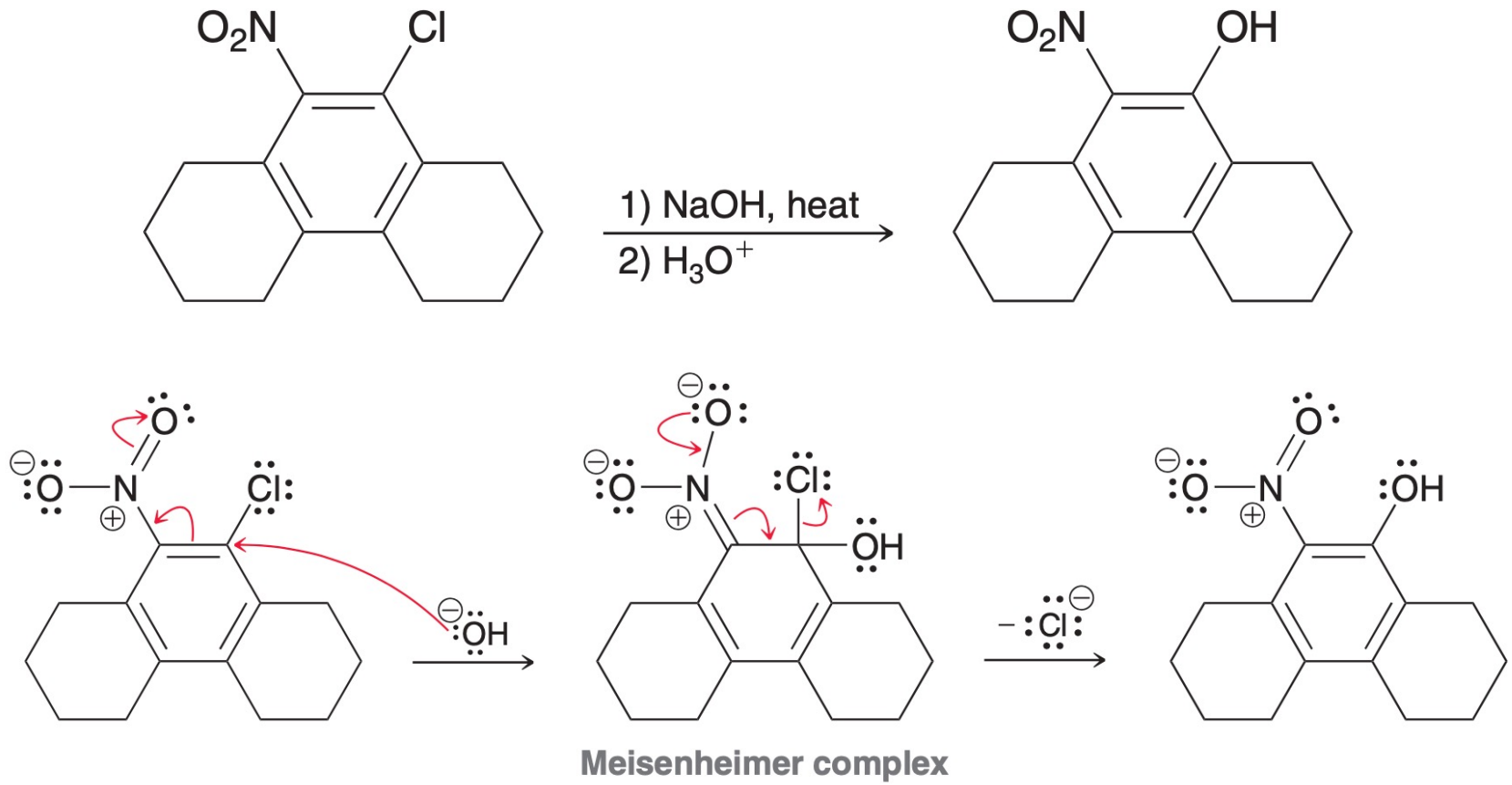


- Key differences
  - The intermediate
    - EArS: sigma complex
    - S_NAr: Meisenheimer complex
    - Elimination-addition: benzyne intermediate
  - The leaving group
    - EArS: the incoming substituent replaces a proton
    - S_NAr & elimination-addition: a negatively charged leaving group (such as a halide ion) is expelled
  - Substituent effects
    - EArS: EWGs deactivate the ring
    - S_NAr: EWGs activate the ring

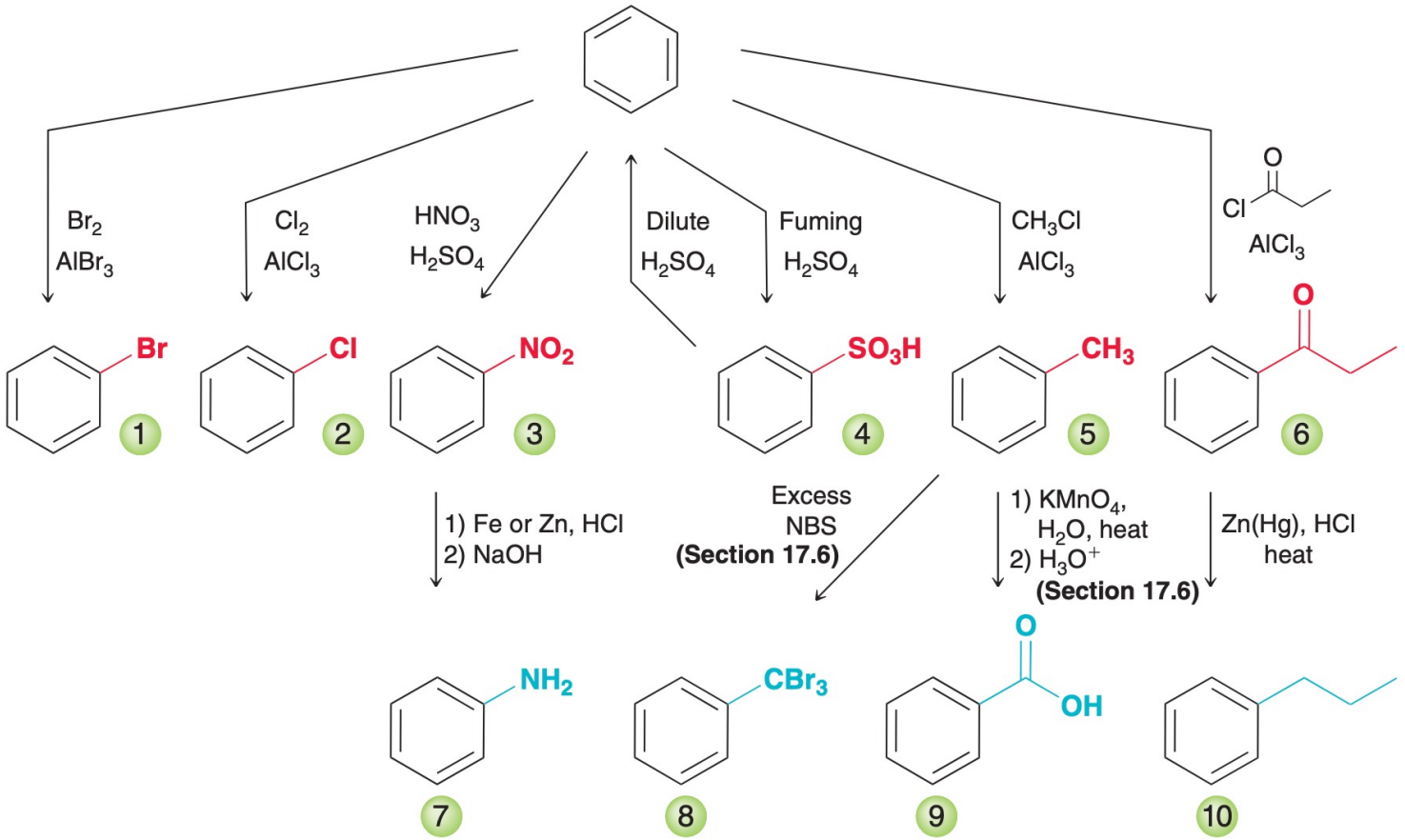
- A decision tree for mechanism determination



- Practice: draw the most likely mechanism for the following transformation:

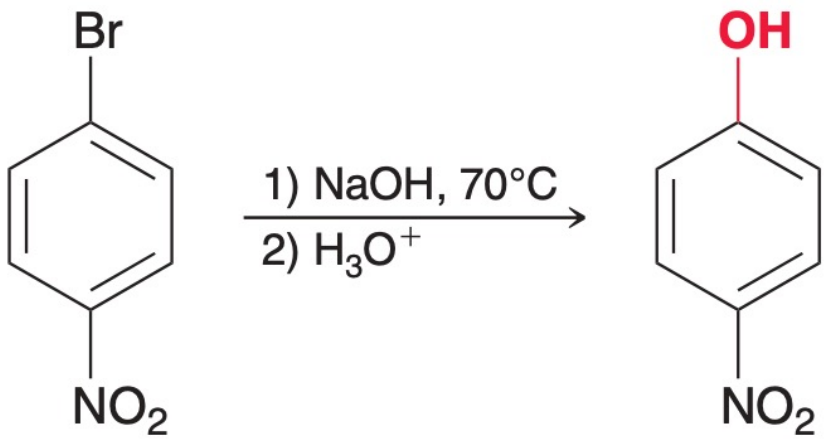


- Review: electrophilic aromatic substitution (EArS)

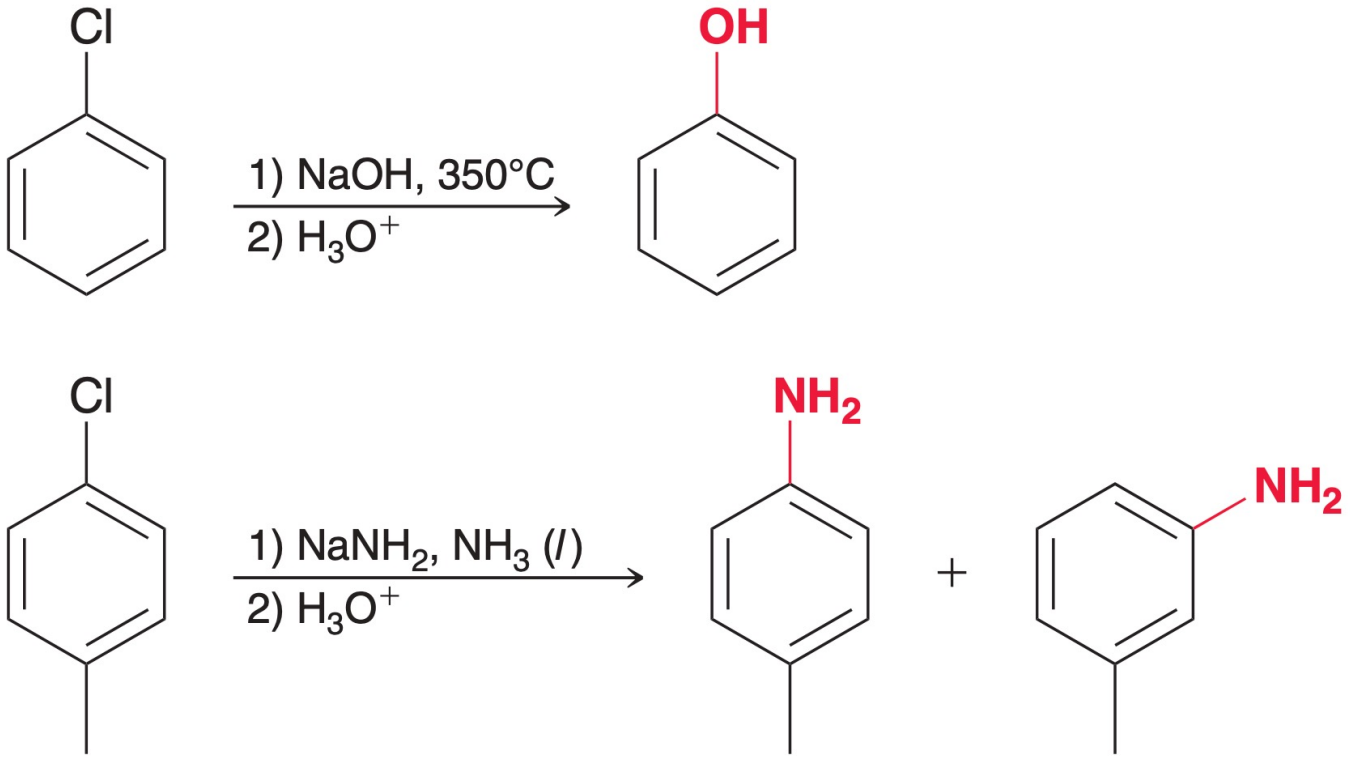


1. Bromination
2. Chlorination
3. Nitration
4. Sulfonation/desulfonation
5. Friedel–Crafts alkylation
6. Friedel–Crafts acylation
7. Reduction
8. Benzylic bromination
9. Oxidation
10. Clemmensen reduction

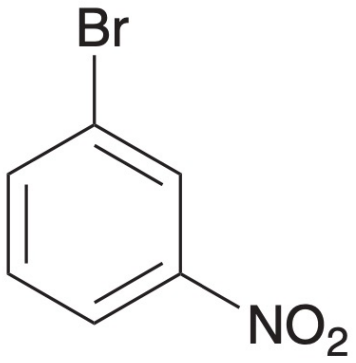
- Review: nucleophilic aromatic substitution (S_NAr)



- Review: elimination-addition

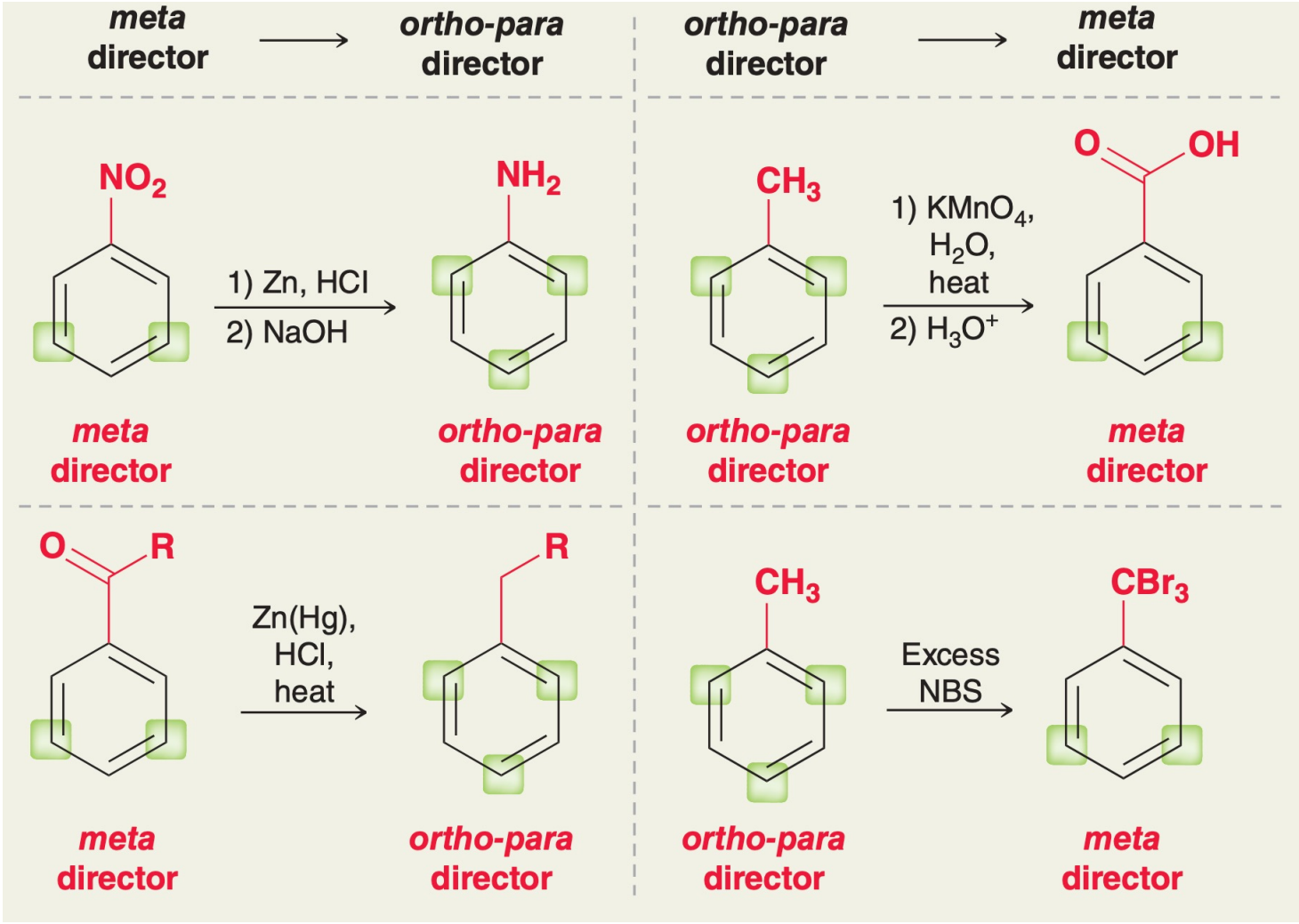


- Disubstituted benzene rings: the directing effect

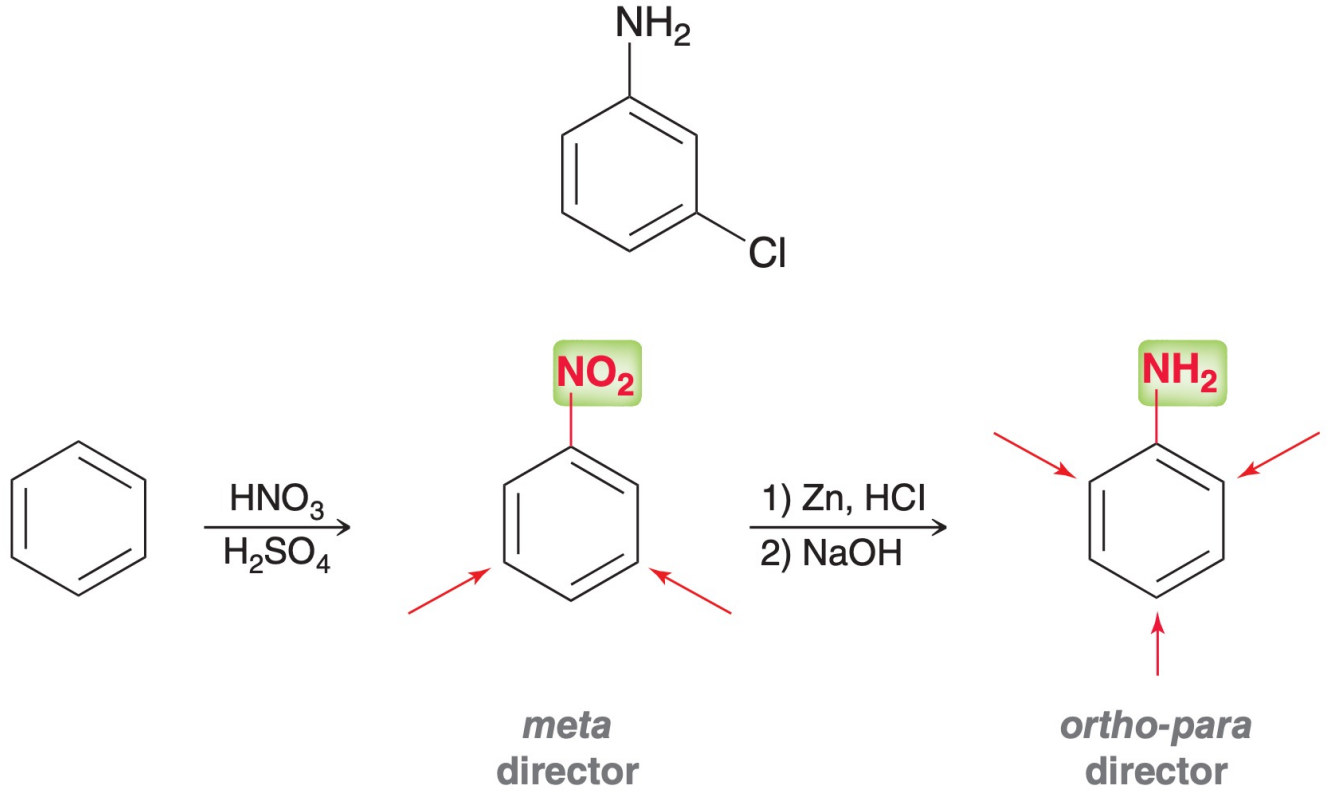


bromination, followed by nitration… or vice versa?

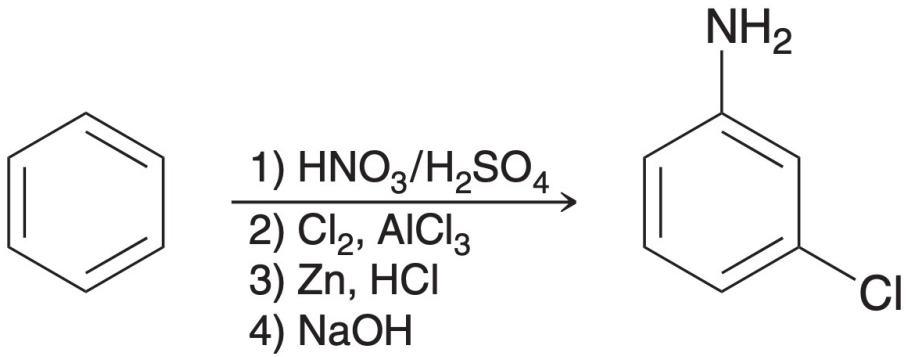
- Functional group conversions that change directing effects



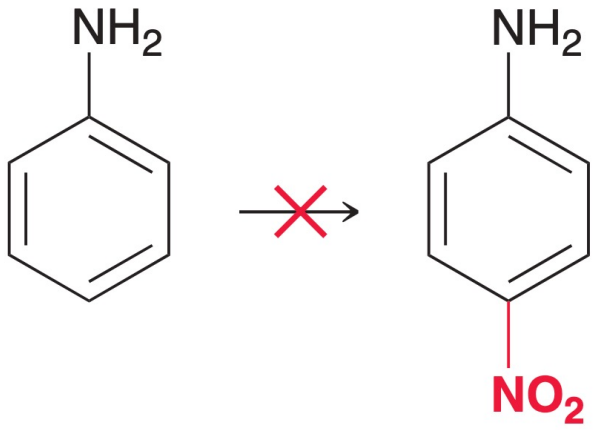
- Example: 3-chloroaniline



- The reasonable sequence of reaction



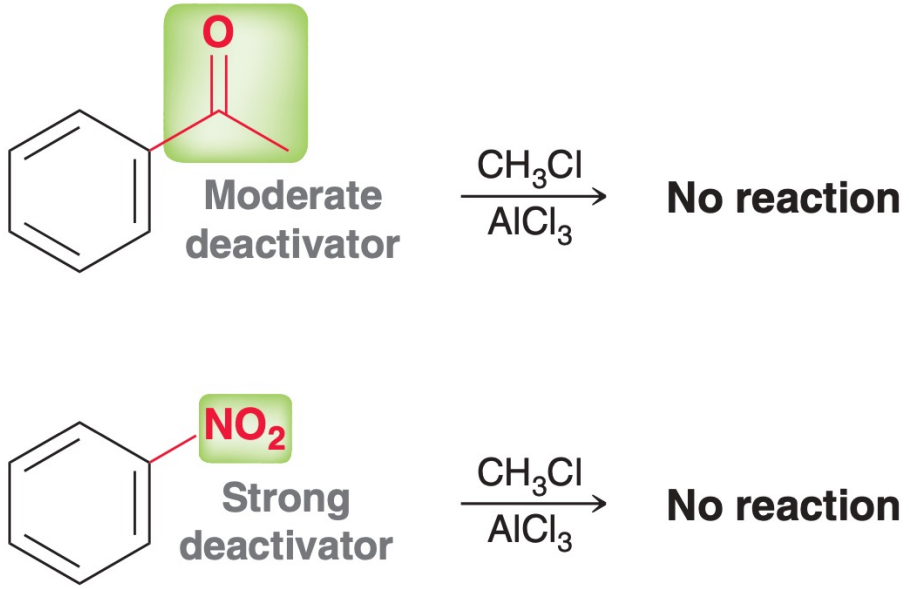
- Nitration cannot be performed on a ring that contains $-NH_2$



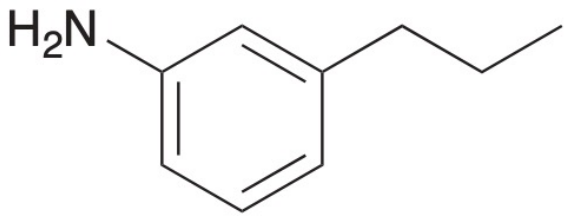
the reagents for nitration (a mixture of HNO_3 and H_2SO_4) can oxidize the amino group

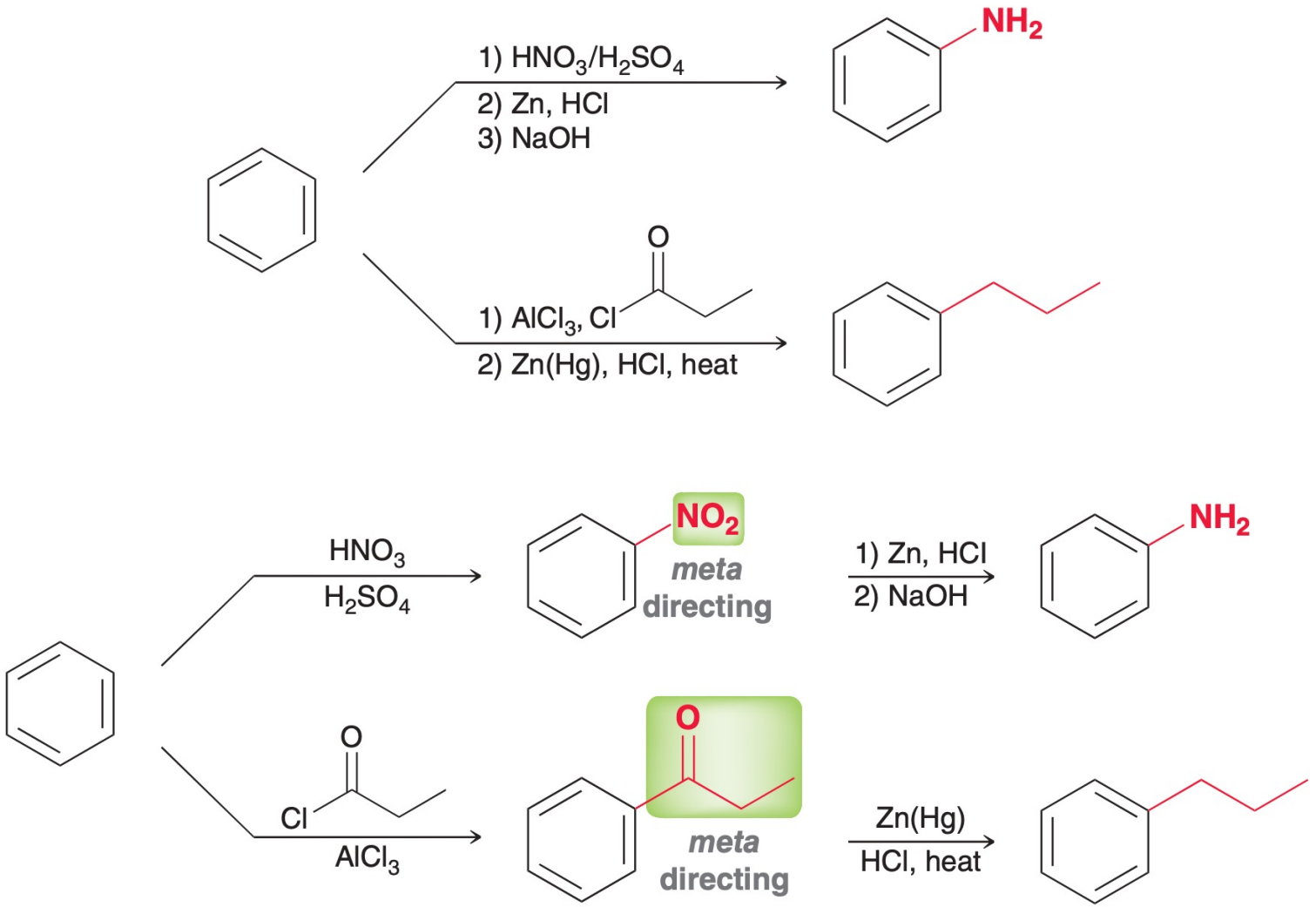
often lead to a mixture of undesirable products

- Friedel–Crafts reaction cannot be accomplished on moderate / strong deactivate rings

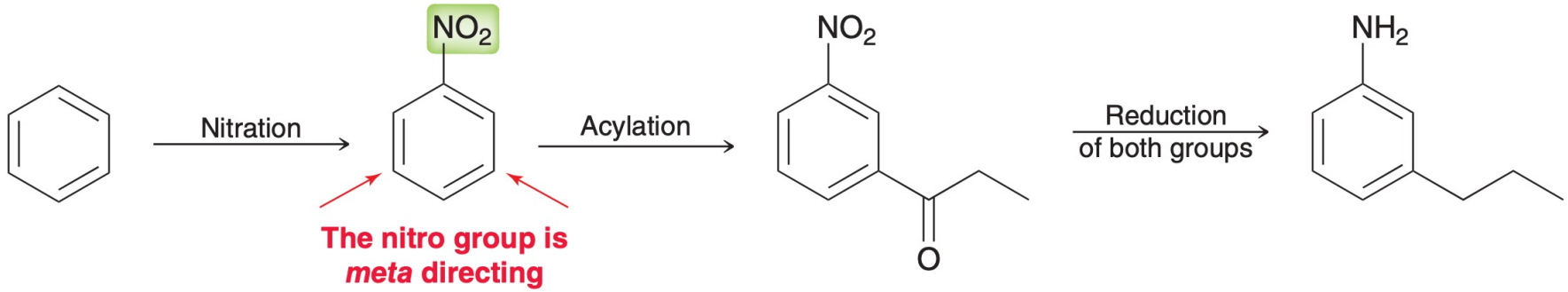


- Practice: starting with benzene and using any other necessary reagents of your choice, design a synthesis of the following compound:

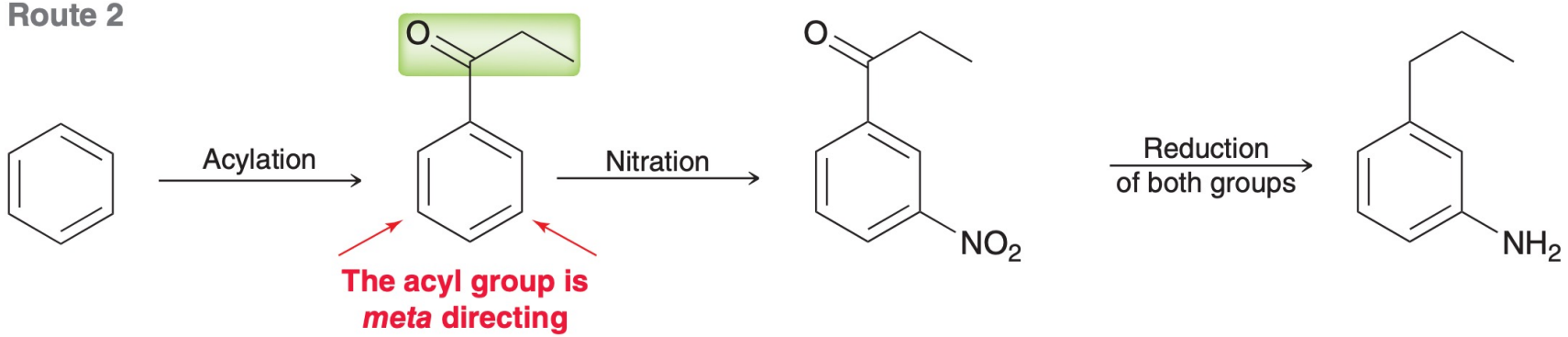


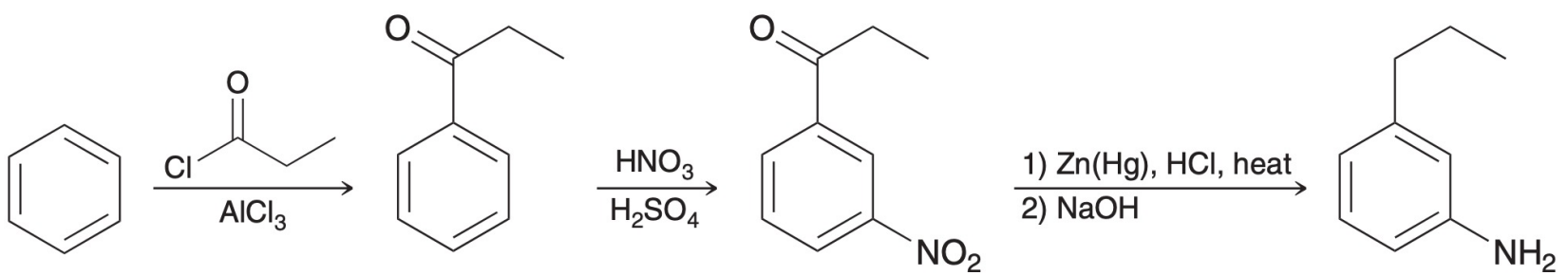

1) HNO3/H2SO4
2) Zn, HCl
3) NaOH
NH2
O
1) AlCl3, Cl
2) Zn(Hg), HCl, heat
HNO3
H2SO4
NO2
meta
directing
1) Zn, HCl
2) NaOH
NH2
O
Cl
AlCl3
O
meta
directing
Zn(Hg)
HCl, heat

Route 1



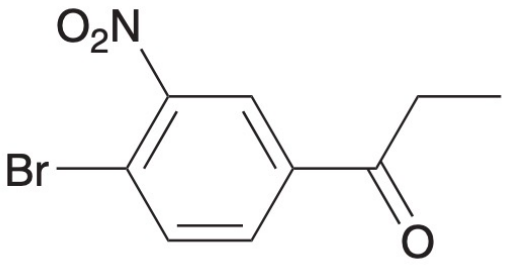
Route 2

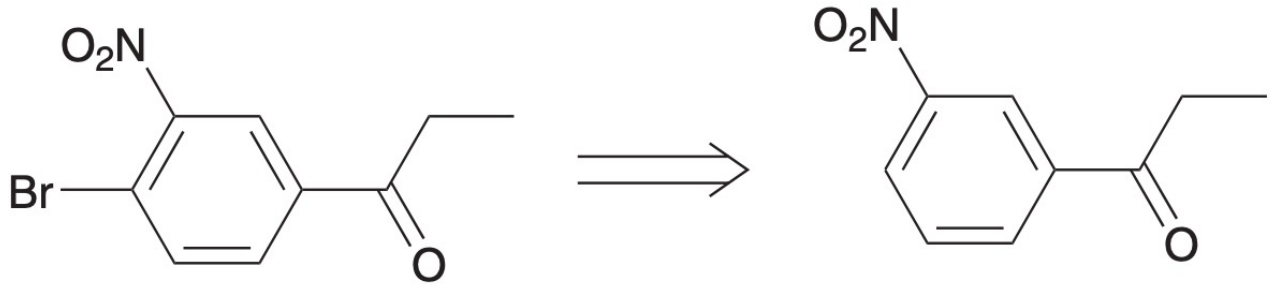


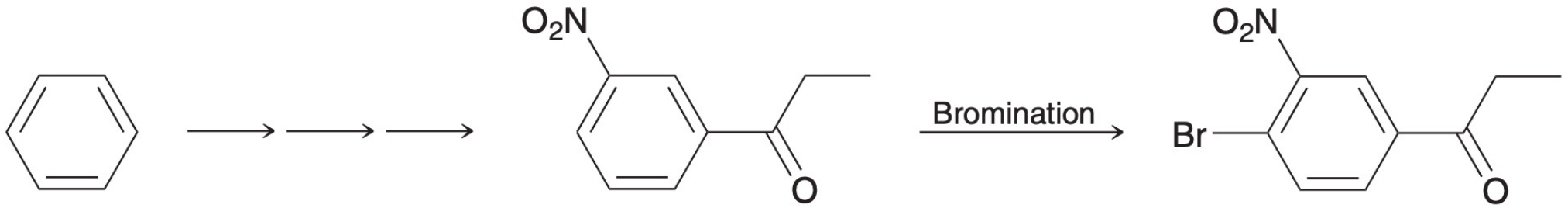


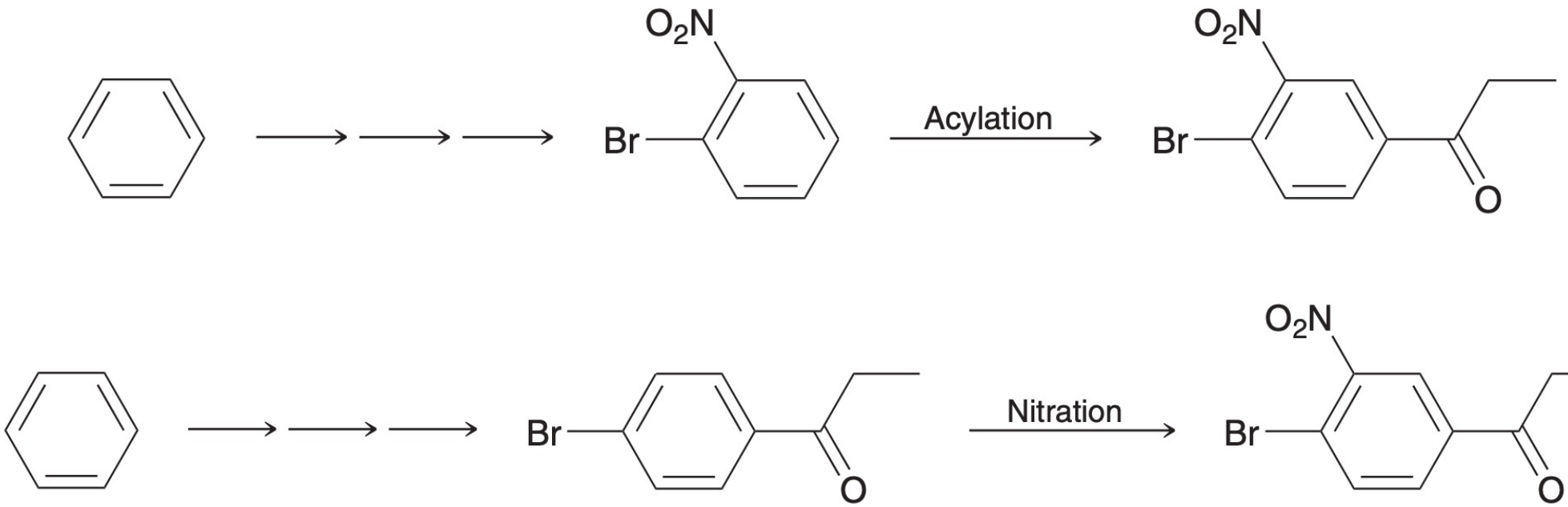
- Polysubstituted benzene rings
  - Retrosynthetic analysis is applied
  - Consider directing effects and steric effects
  - Take care of the sequence of reactions

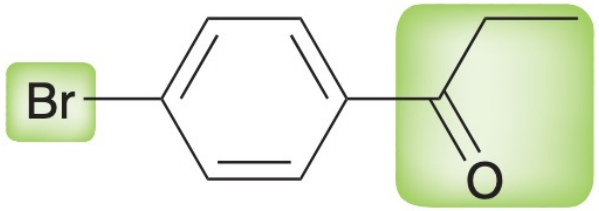
- Practice: starting with benzene and using any other necessary reagents of your choice, design a synthesis for the following compound:

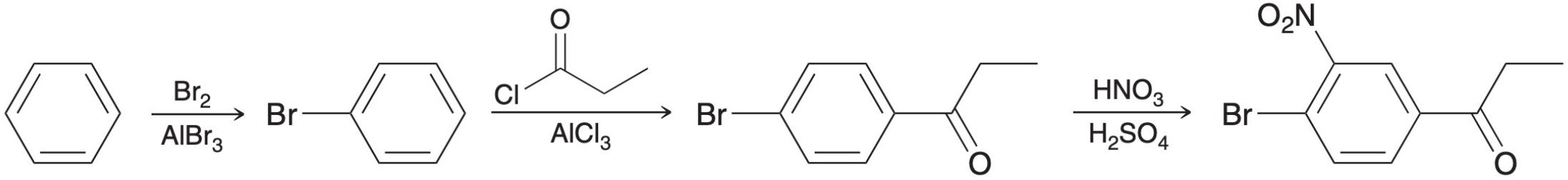



O2N
Br
O
O2N
O


O2N
O
Bromination
O2N
Br
O


O2N
Br
Acylation
O2N
Br
O
Br
O
Nitration
O2N
Br
O


Br
O


Br2
AlBr3
Br
O
Cl
AlCl3
Br
O
HNO3
H2SO4
O2N
Br
O