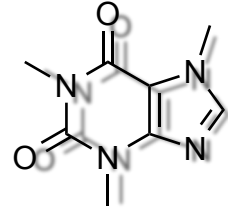


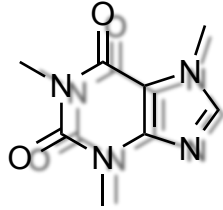
Chem 2500

Chapter 10

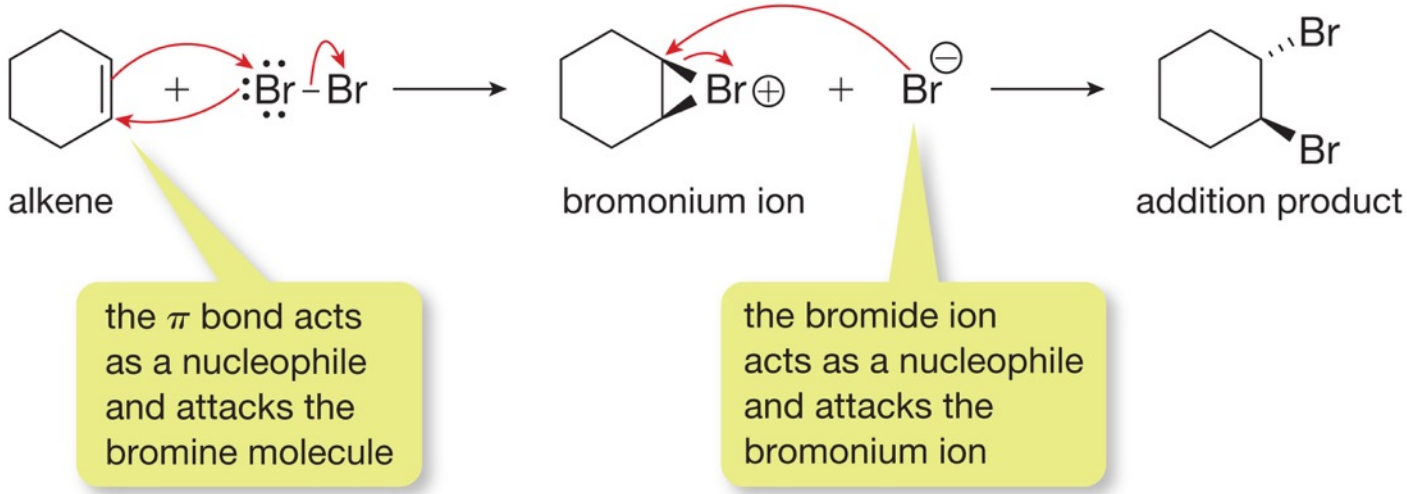
Synthesis Using Aromatic Materials

(sections 10.1-10.10 excluding 10.7 and 10.8)

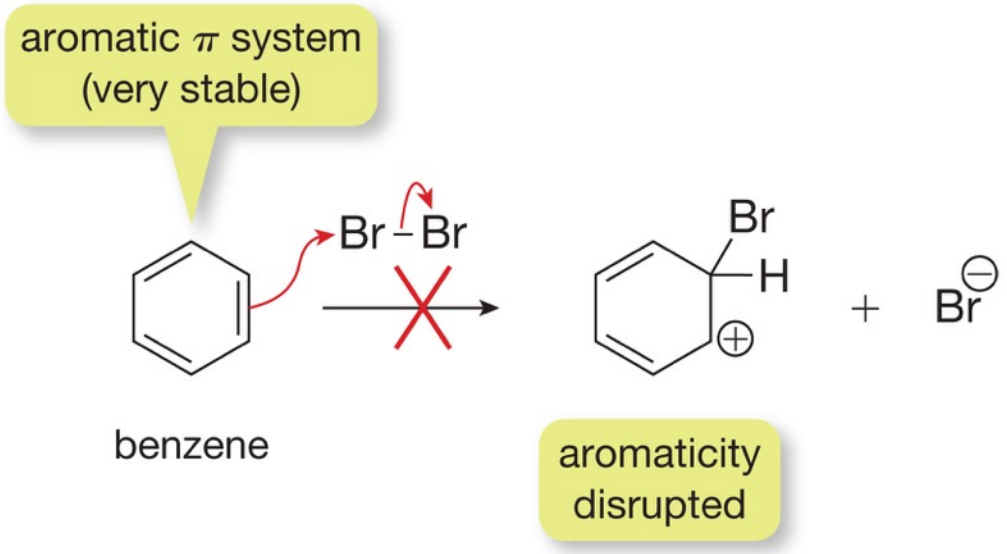
π Bonds Acting as Nucleophiles



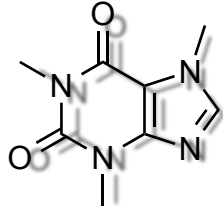
- We saw in chapter 8 how alkenes are nucleophilic in the presence of electrophiles.



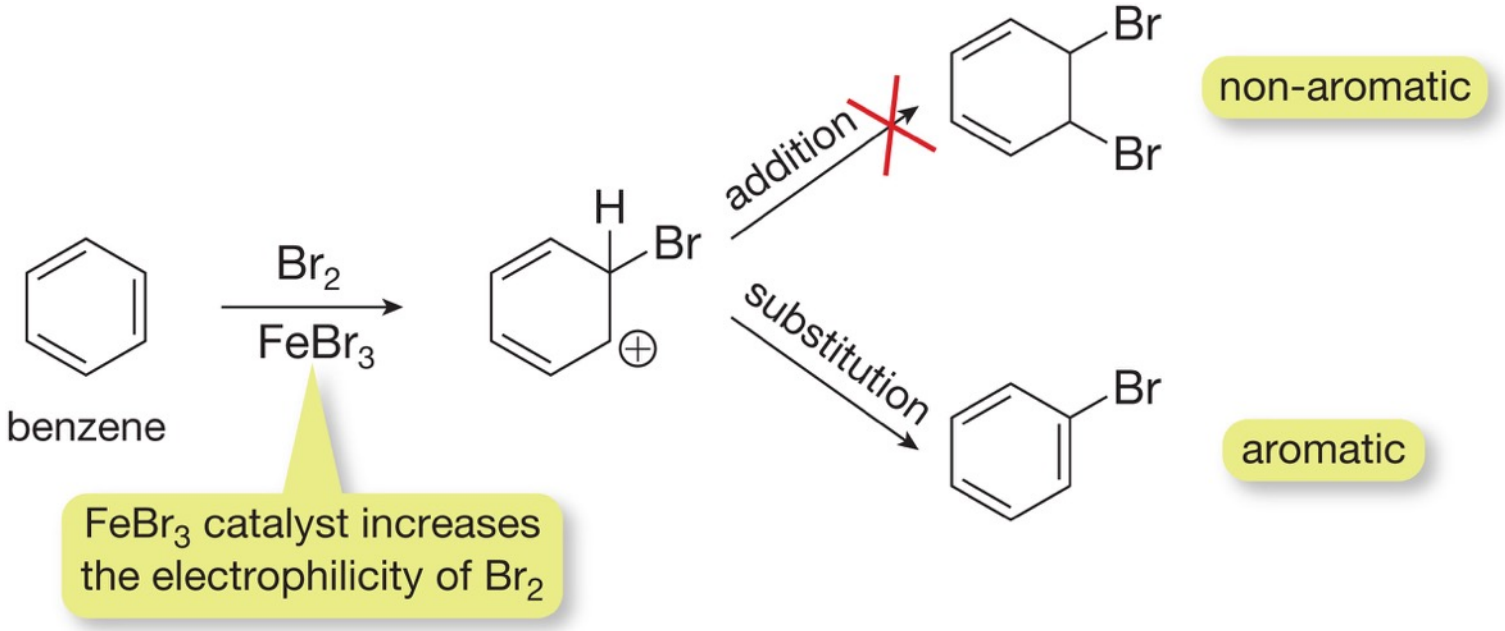
- Although benzene has π electrons, the stability imparted by its aromaticity makes it much less reactive towards electrophiles.



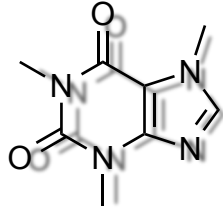
π Bonds Acting as Nucleophiles



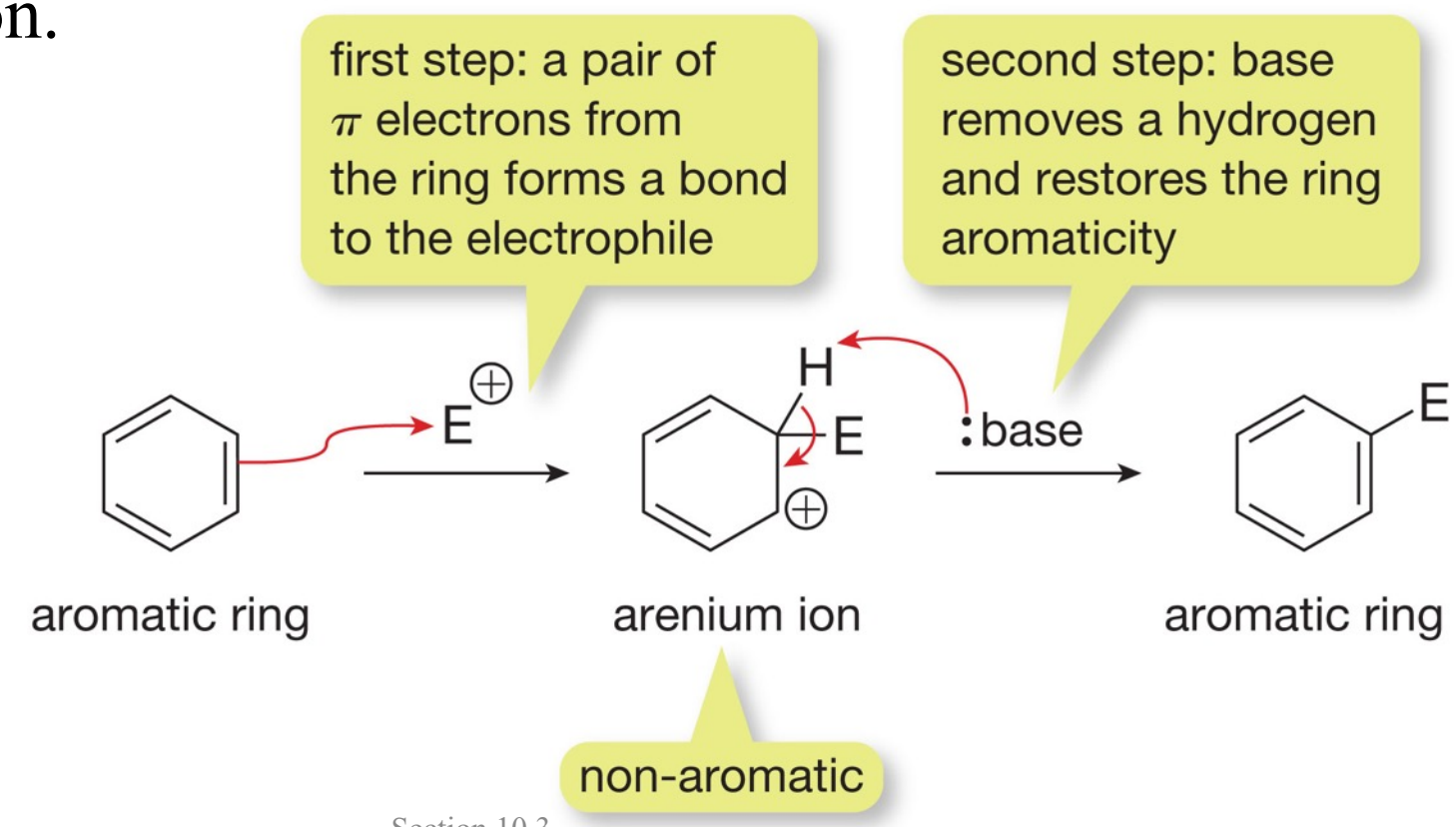
- Benzene can be made to react with reactive electrophiles in the presence of a catalyst.
- The overall reaction, however, is different; aromatic rings undergo ***substitution***, not addition, with electrophiles.
- This is known as ***electrophilic aromatic substitution*** **(S_EAr)**.



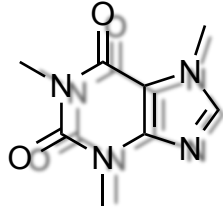
Electrophilic Aromatic Substitution



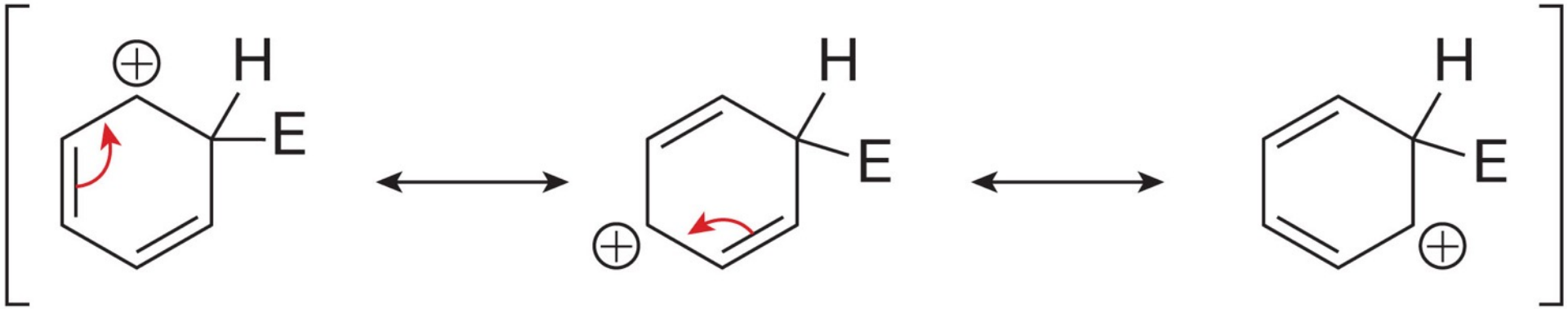
- Electrophilic aromatic substitution reactions proceed by a general 2-step mechanism: (1) addition of the electrophile, and (2) elimination.
- The combination of addition and elimination steps leads to a net substitution reaction.



Electrophilic Aromatic Substitution

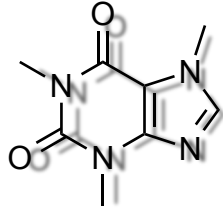


- In the first step of the mechanism, a carbocation intermediate, called an arenium ion, is formed.
- The arenium ion is resonance stabilized, however, it is no longer aromatic.
- This first step is identical to the addition of electrophiles to alkenes.

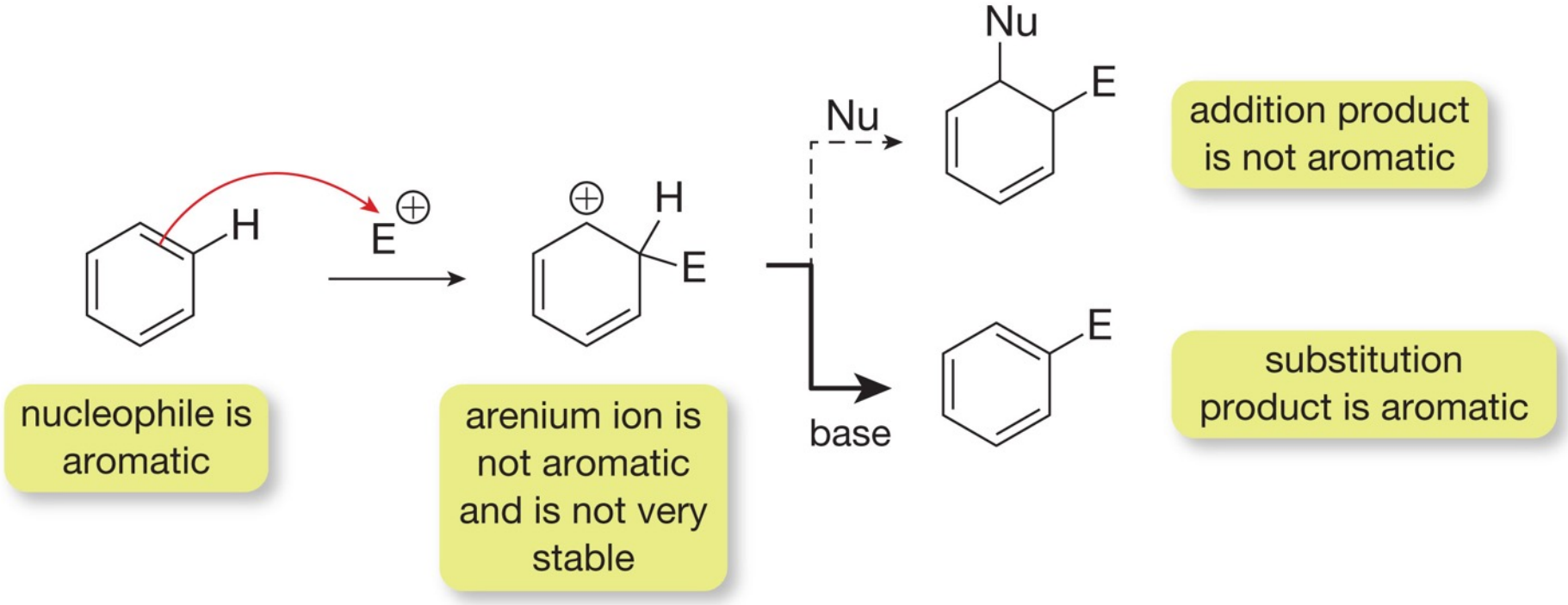


arenium ion is stabilized by conjugation but is not aromatic

Electrophilic Aromatic Substitution

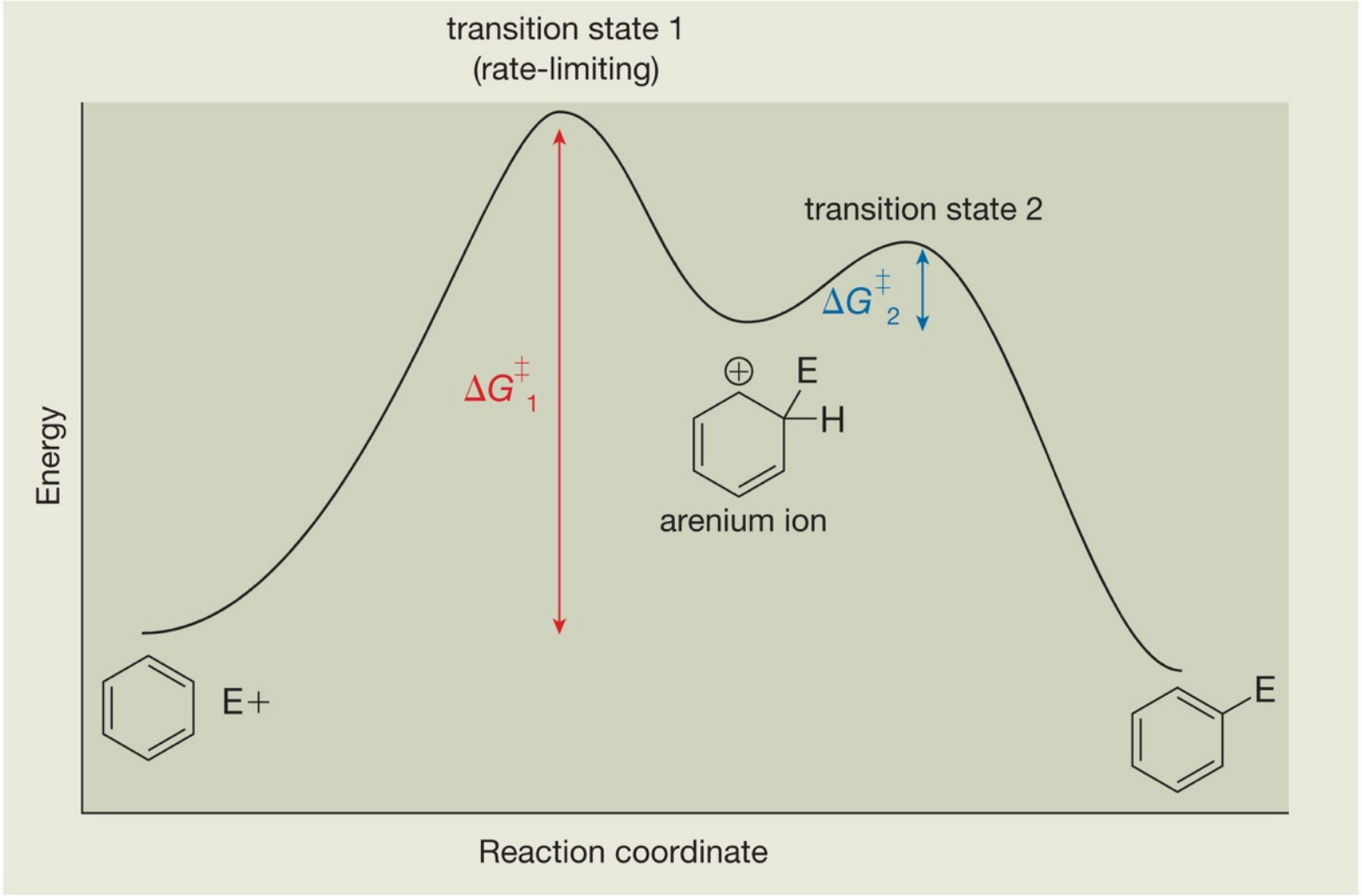


- In the second step of the mechanism, a base removes a hydrogen atom to restore the ring aromaticity.
- It is the re-aromatization of the ring which is the main driving force for the formation of the substitution product.

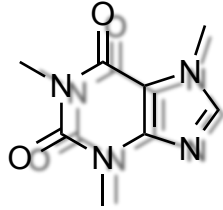


Electrophilic Aromatic Substitution

- From the reaction profile diagram, the disruption of the aromaticity of the ring in the first step has the highest activation barrier and is therefore the rate determining step.

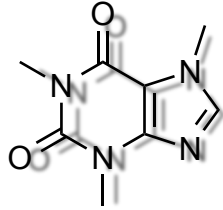


Types of Electrophiles used in S_EAr

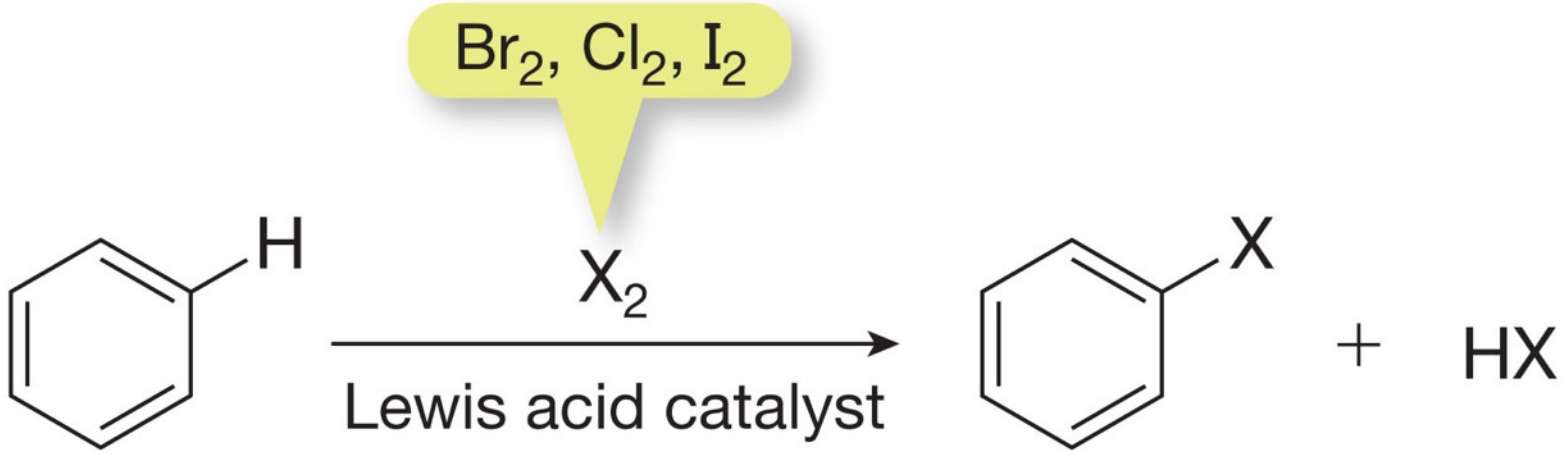


- Many electrophiles can be used to react with aromatic rings to generate a variety of different functional groups, including halogens, nitro groups, sulfonic acids, alkyl, and acyl groups.
- Mechanistically, all electrophiles react the same way with an aromatic ring. The only difference is the way the strong electrophile is generated.

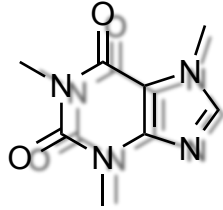
Halogenation



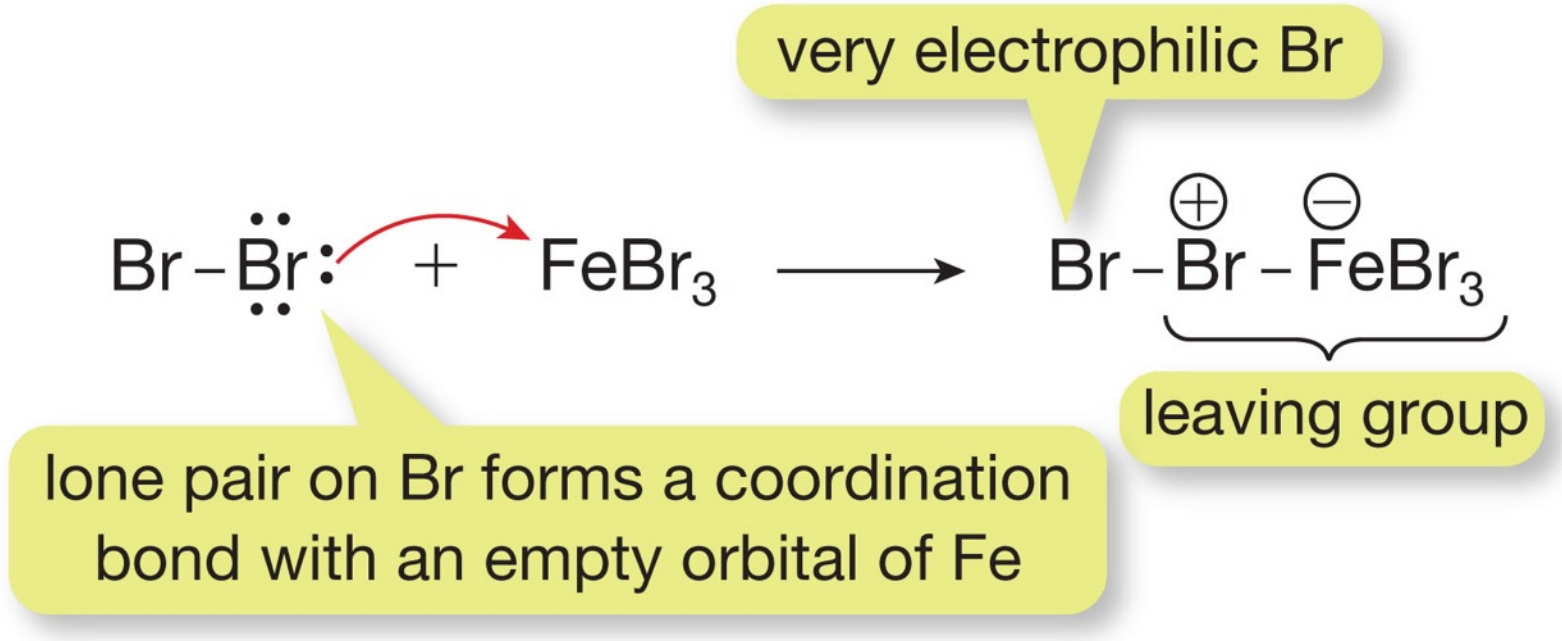
- Aromatic rings can be halogenated with chlorine, bromine, or iodine using a Lewis acid catalyst.
- Fluorine is reactive enough that a catalyst is not required, though the reaction is not a practical lab procedure.
- In halogenation, a hydrogen atom is substituted by a halogen.



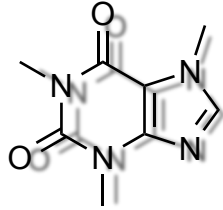
Halogenation



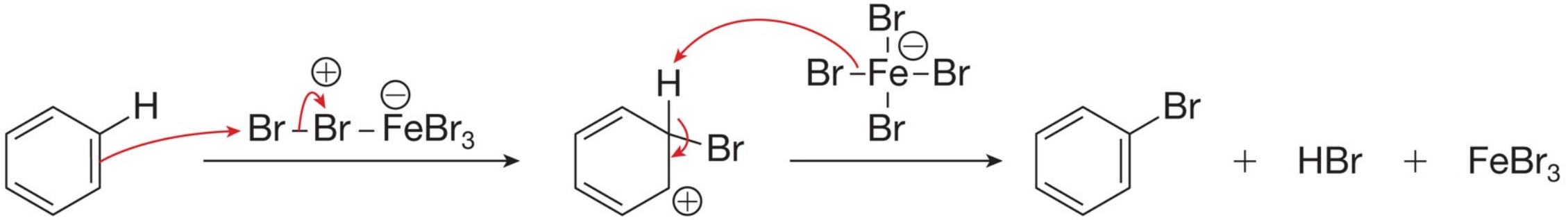
- The halogen molecule is activated by first forming a Lewis acid-base adduct with the catalyst.
- This creates a highly electrophilic halogen atom and a good leaving group.



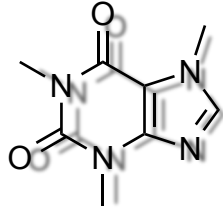
Halogenation



- The aromatic ring can now react with the activated electrophile, producing the arenium ion intermediate.
- A bromide ion from the Lewis acid-base adduct removes the proton from the arenium ion, re-aromatizing the ring.
- Notice how the catalyst, $FeBr_3$, is regenerated.
- The bromobenzene product is less reactive than the starting benzene causing the reaction to stop after one substitution.



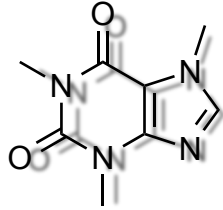
Halogenation



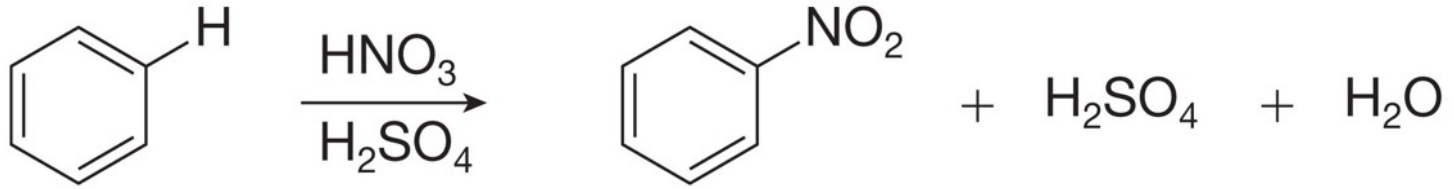
- The other halogens can be added in a similar fashion, the only difference being the Lewis acid catalyst used.

Halogen Added	Electrophile	Lewis Acid
F	F_2	None
Cl	Cl_2	$FeCl_3$
Br	Br_2	$FeBr_3$
I	I_2	$CuCl_2$

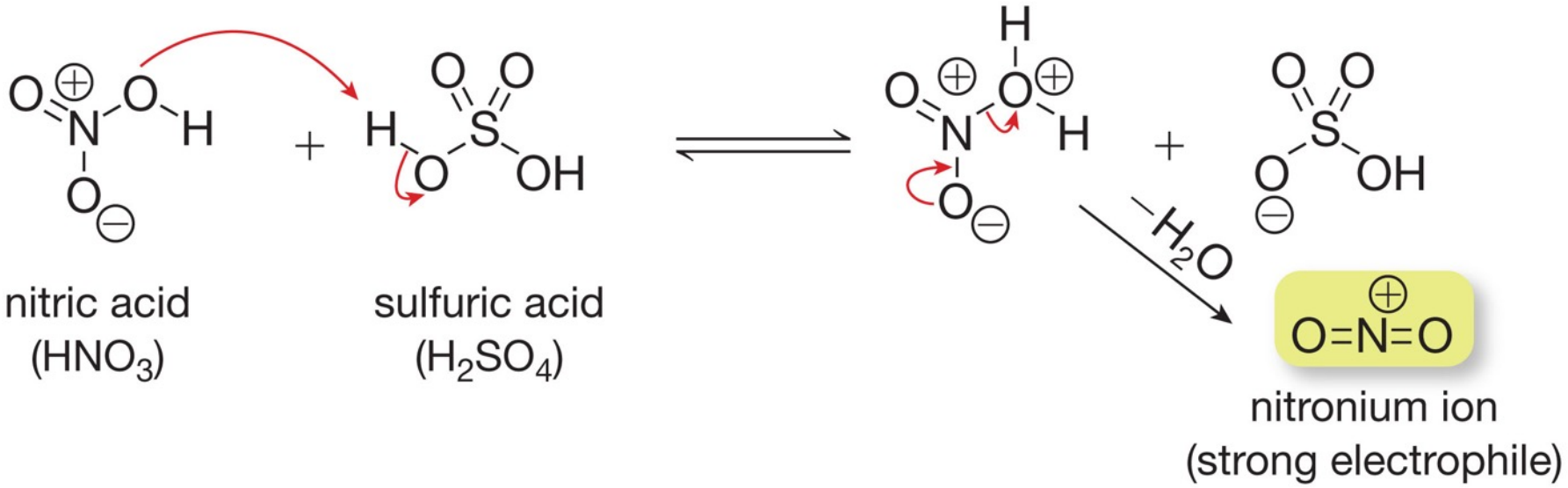
Nitration



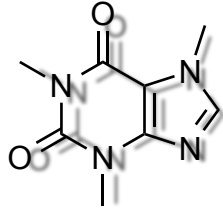
- In nitration, a hydrogen atom is substituted by a nitro group (NO_2)



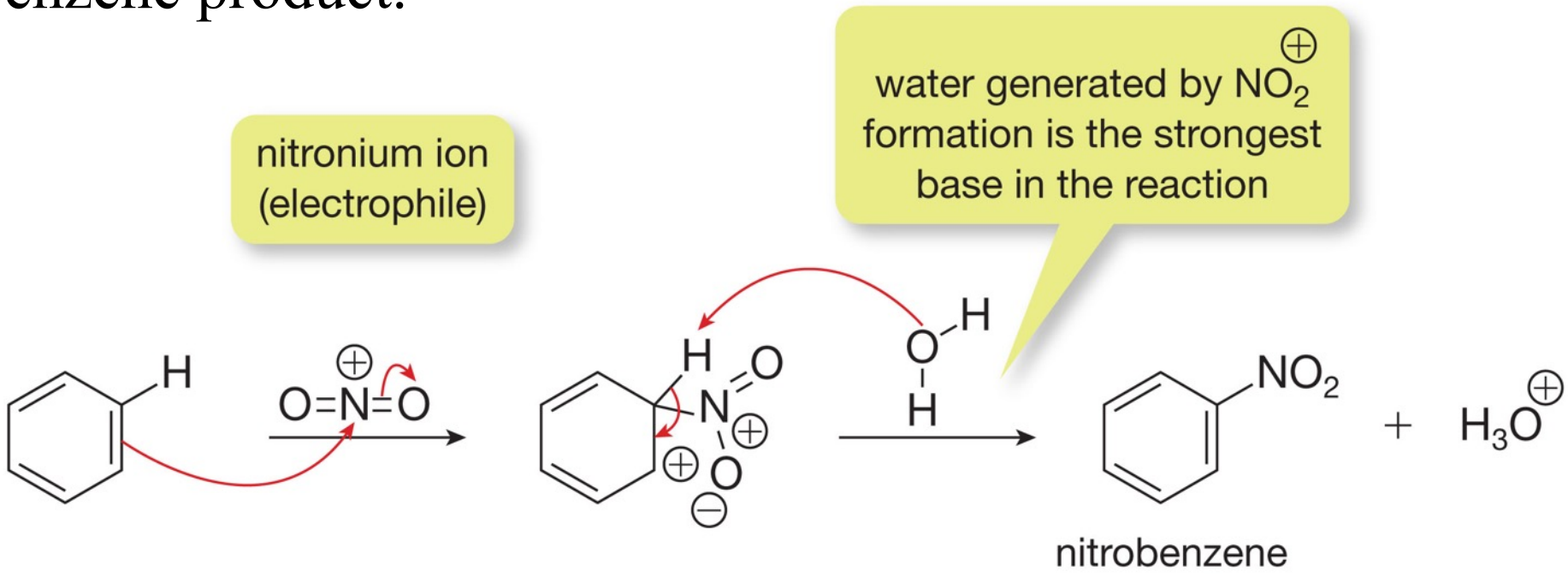
- The electrophile in this reaction is the nitronium ion (NO_2^+), which is generated by reacting HNO_3 with H_2SO_4.



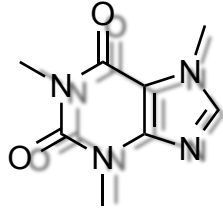
Nitration



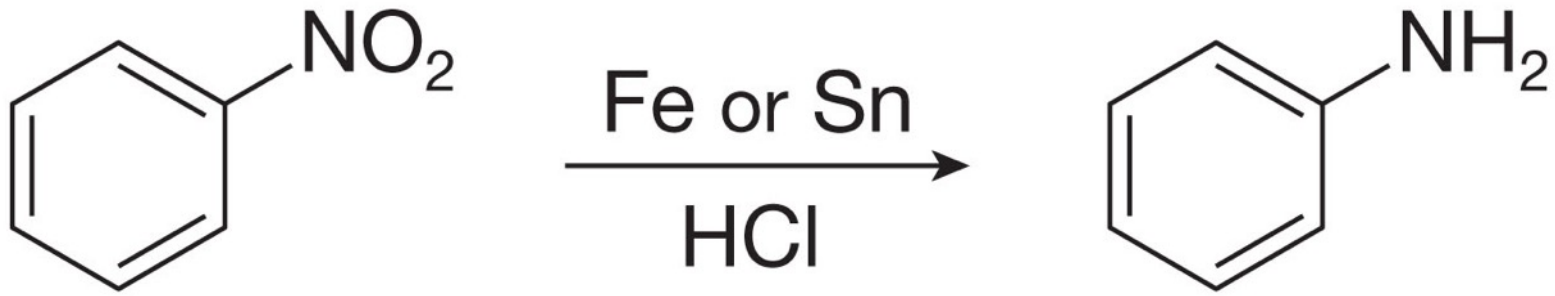
- Nitration then proceeds via the two-step electrophilic aromatic substitution mechanism.
- In this strongly acidic medium, water is basic enough to remove a proton from the arenium ion to re-aromatize the ring and form the nitrobenzene product.



Nitration

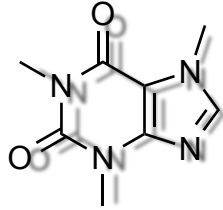


- An important functional group conversion is the reduction of nitro groups to an amine using a dissolving metal reaction.
- This is typically done using iron or tin with a strong acid, such as HCl.

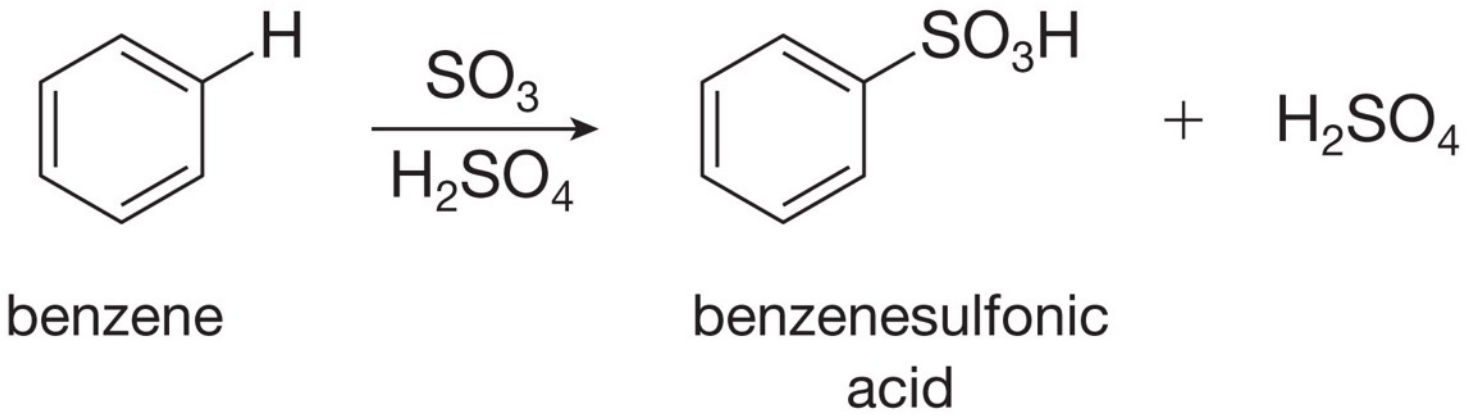


- The reduction of a nitro group to an amine is a key method to making aromatic amines, which are important synthetic synthons.

Sulfonation

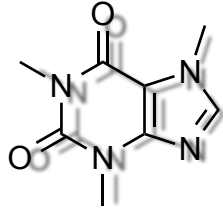


- In sulfonation, a hydrogen atom is substituted by a sulfonic acid group, SO_3H.



- The active electrophile is SO_3H^+, produced either by the dehydration of sulfuric acid or the protonation of SO_3.

Sulfonation



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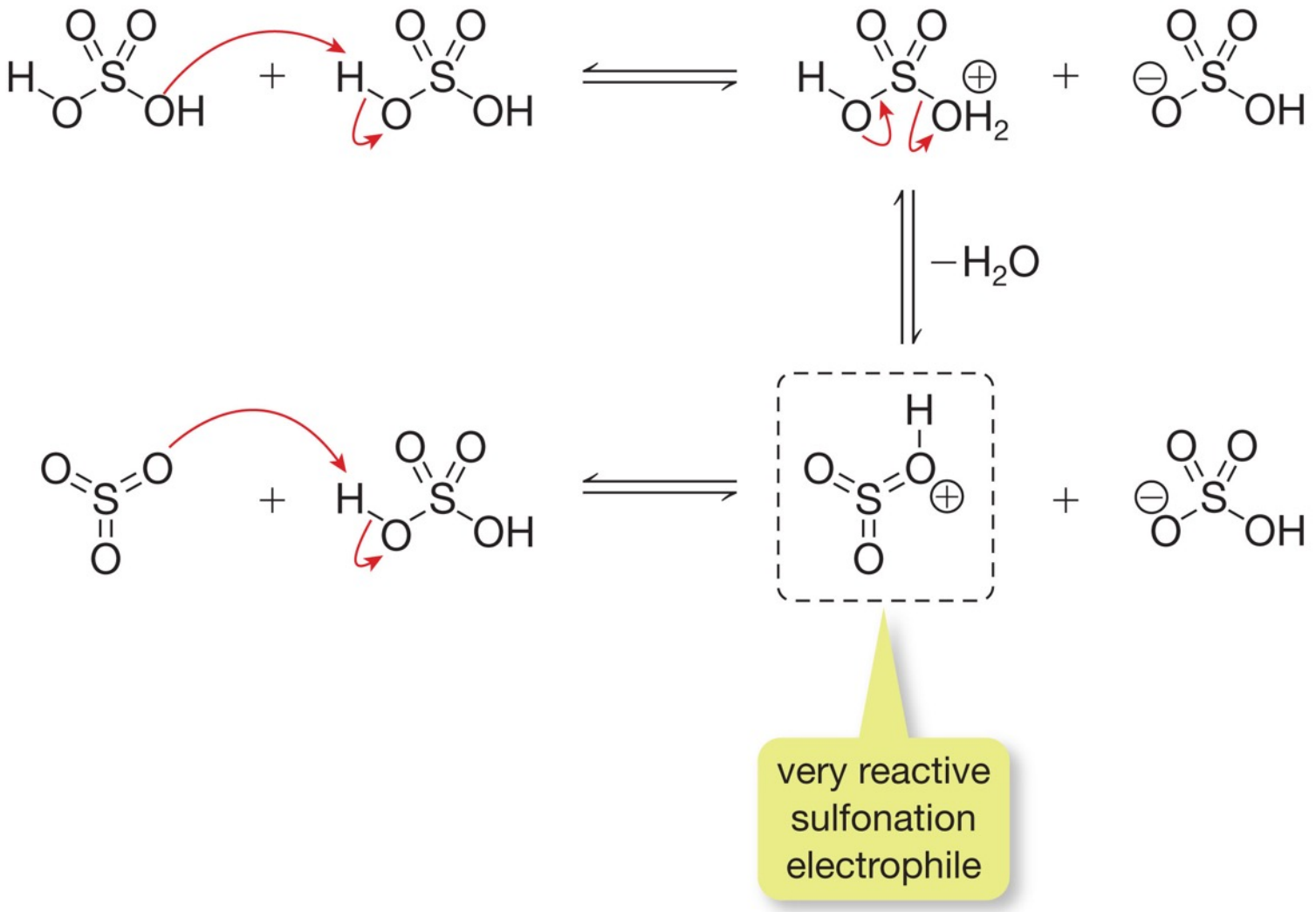
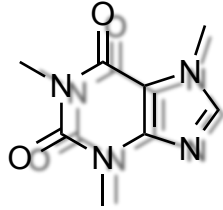
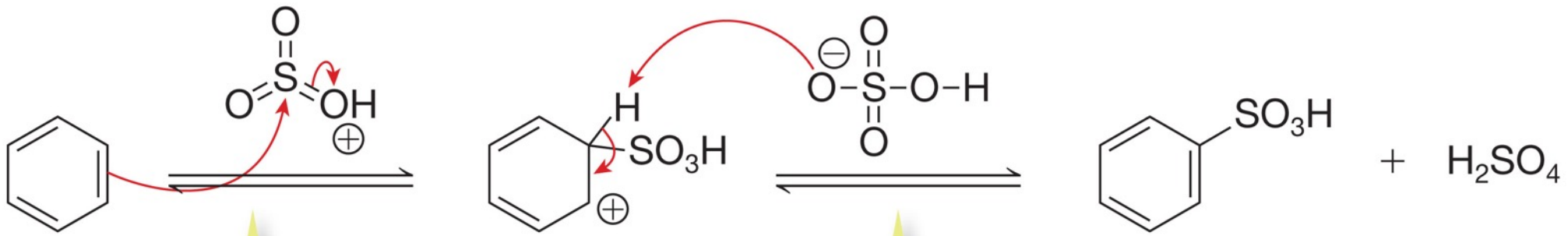


Sulfonation



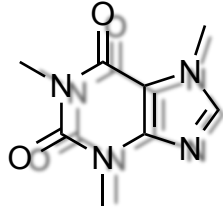
- Once the SO_3H^+ electrophile is formed, the reaction proceeds as normal; addition of the electrophile, followed by re-aromatization of the ring.



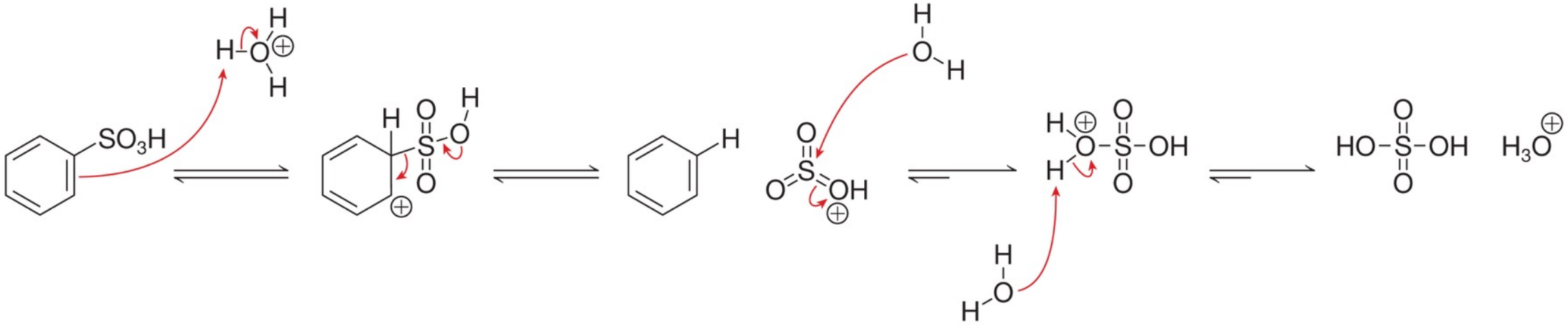
one pair of π electrons of the aromatic ring attacks the SO_3H electrophile

the conjugate base of H_2SO_4 abstracts a proton from the sp^3-hybridized carbon

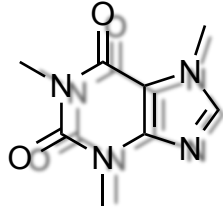
Sulfonation



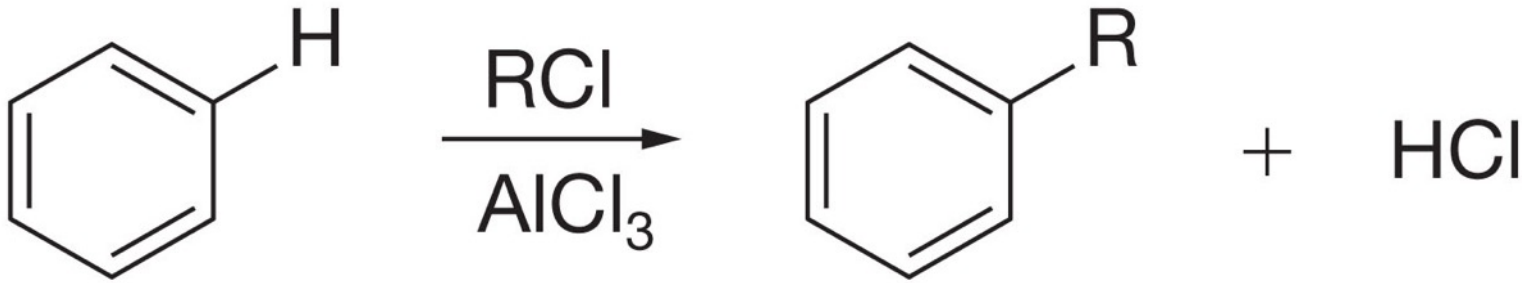
- Sulfonation is reversible in strong, aqueous acid
- The mechanistic process is the exact reverse of the sulfonation reaction.



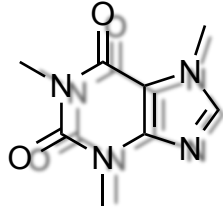
Friedel-Crafts Alkylation



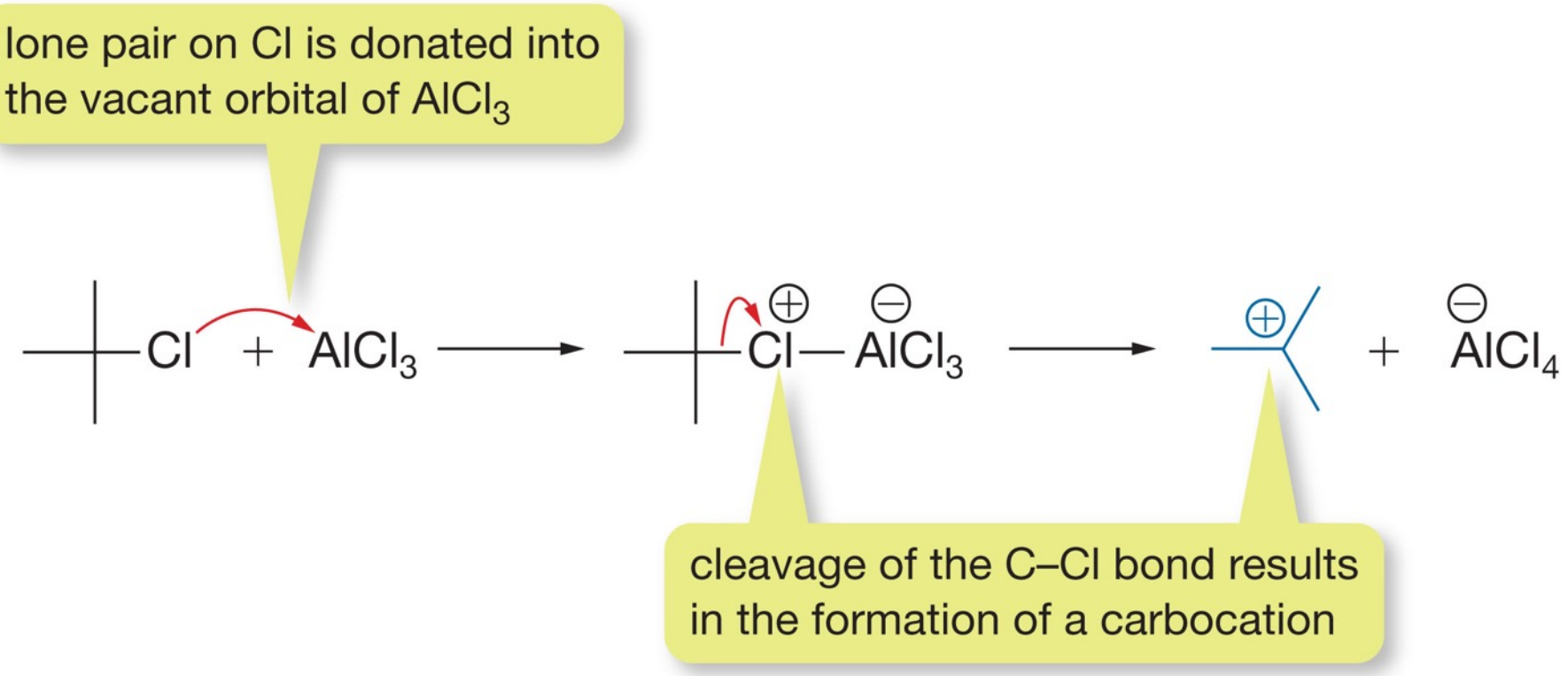
- Friedel-Crafts alkylation is a method of adding alkyl groups to aromatic rings via electrophilic aromatic substitution.
- An alkyl halide and Lewis acid catalyst are used to substitute the hydrogen atom.



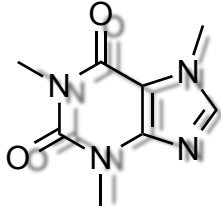
Friedel-Crafts Alkylation



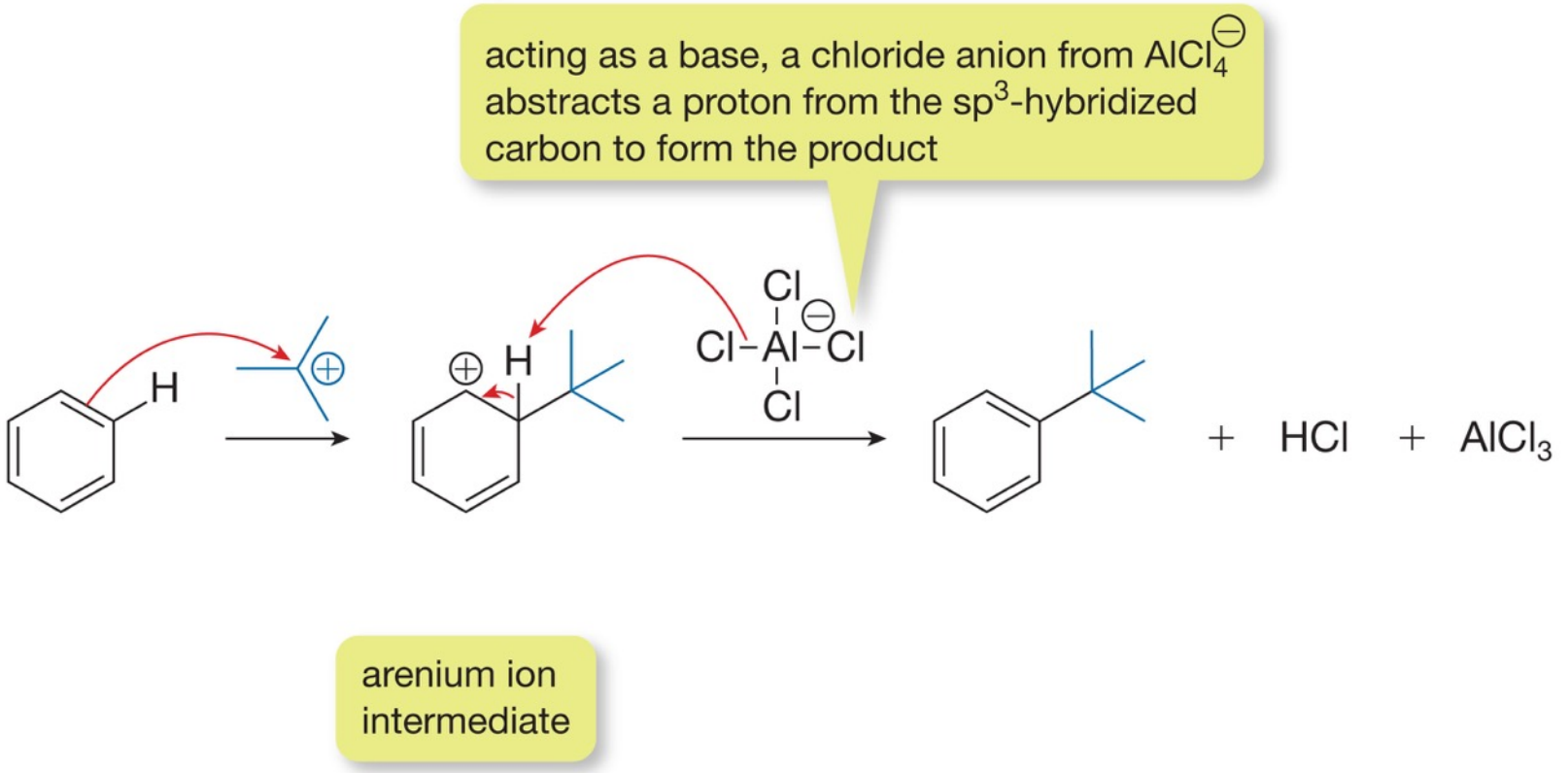
- The active electrophile is a carbocation, produced by interaction of the Lewis acid catalyst with the alkyl halide.



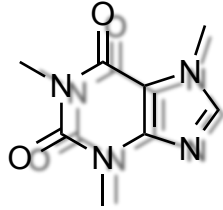
Friedel-Crafts Alkylation



- Once the electrophile is produced, the mechanism proceeds as usual with addition of the electrophile followed by re-aromatization of the ring.

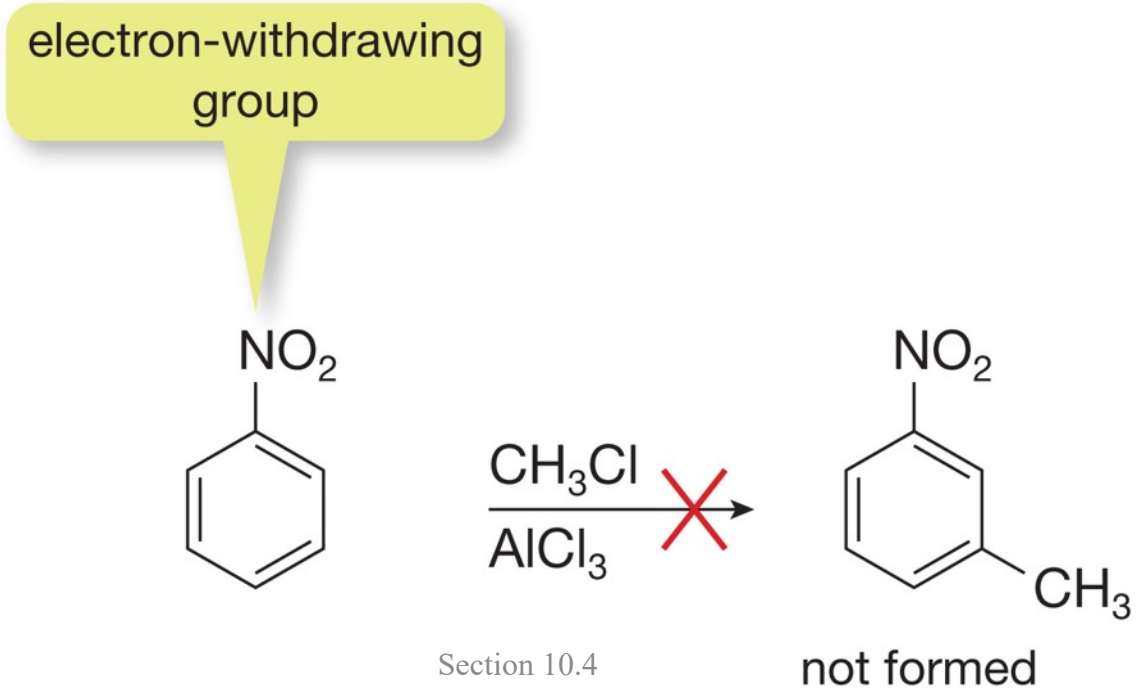


Limitations of Friedel-Crafts Alkylations

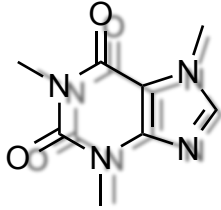


- There are 3 main limitations to Friedel-Crafts reactions.

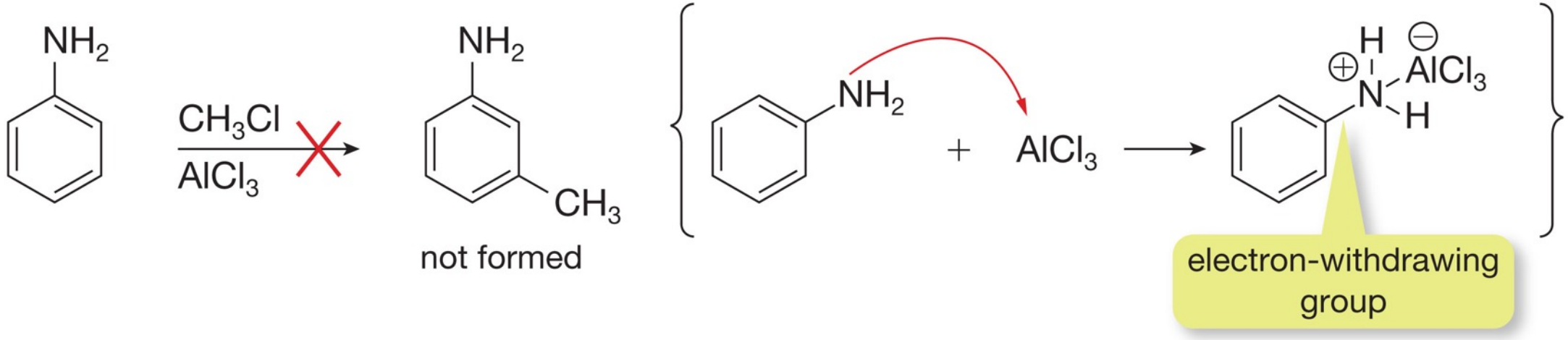
1. Friedel-Crafts reactions do not work with electron deficient aromatic rings. Therefore, aromatic rings with attached electron withdrawing groups (EWG) are deactivated and will not couple with the electrophilic carbocation.



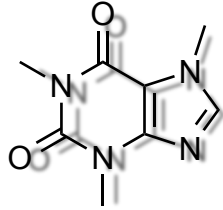
Limitations of Friedel-Crafts Alkylations



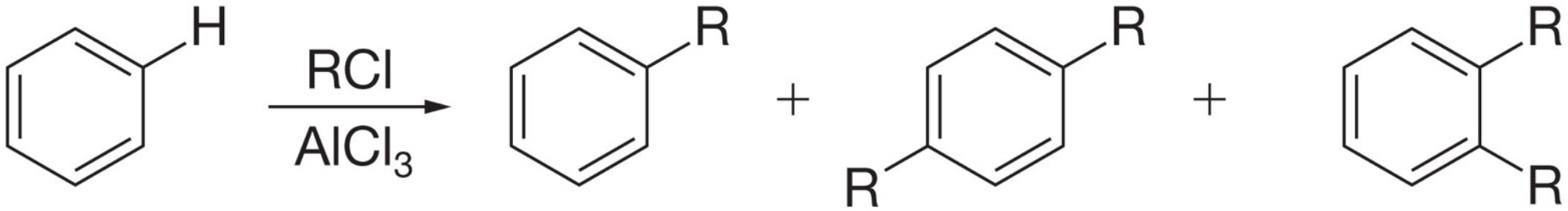
- While it may seem contradictory, anilines do not undergo Friedel-Crafts alkylation either. Amine are electron donating groups (EDG) and should facilitate the alkylation, however, the amine nitrogen atom is Lewis basic and forms a Lewis acid-base adduct with the catalyst which converts it to an EWG.



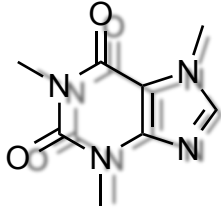
Limitations of Friedel-Crafts Alkylations



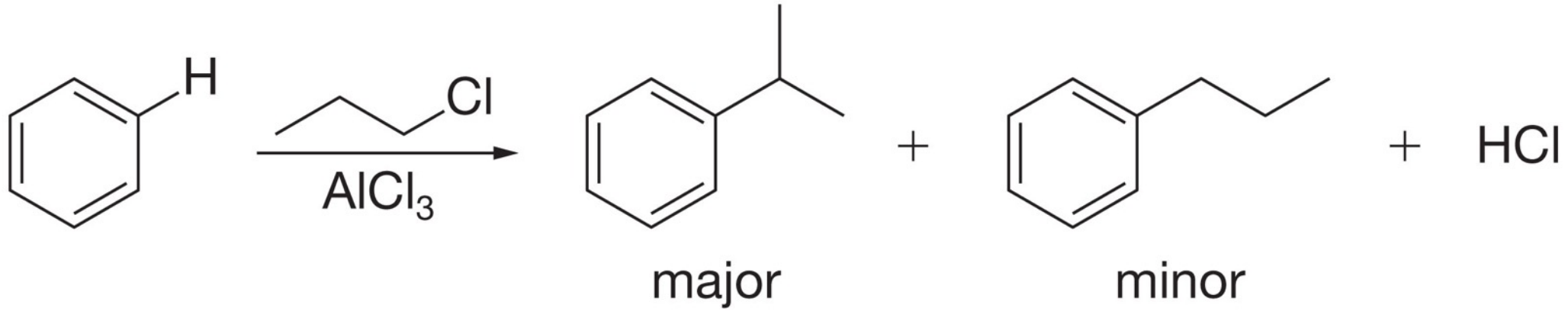
2. Alkyl groups are mildly electron donating, making the Friedel-Crafts alkylation products more nucleophilic than the starting reactant. For this reason, over-alkylation is common unless special measures are taken.



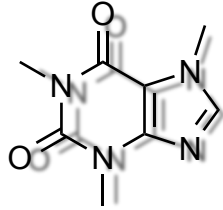
Limitations of Friedel-Crafts Alkylations



3. Because the active electrophile is a carbocation, Friedel-Crafts alkylations are prone to carbocation rearrangements and give a mixture of products. For this reason, the alkyl halides used are typically tertiary or secondary.

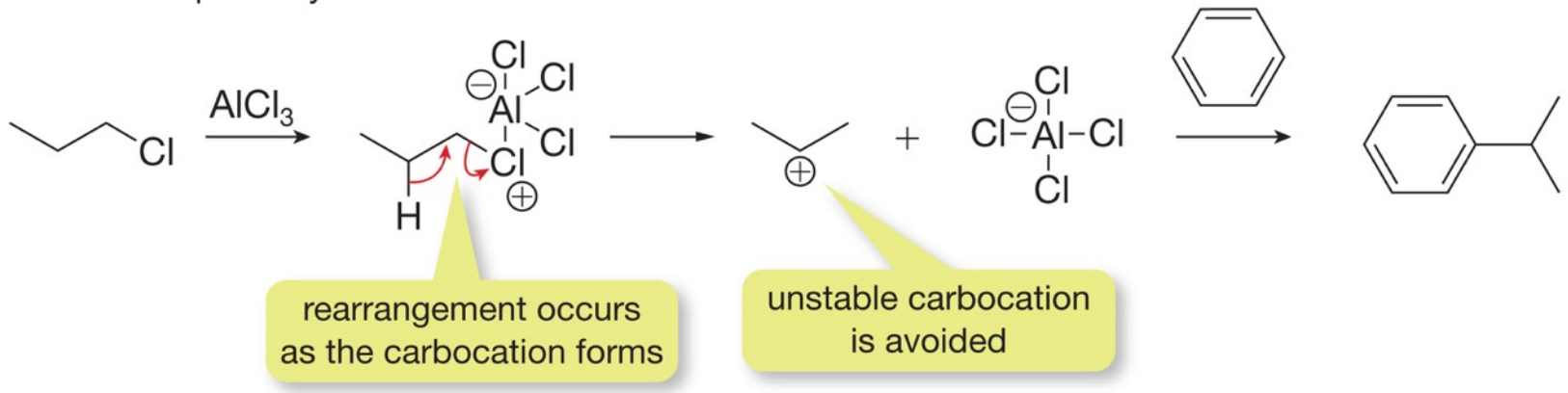


Limitations of Friedel-Crafts Alkylations

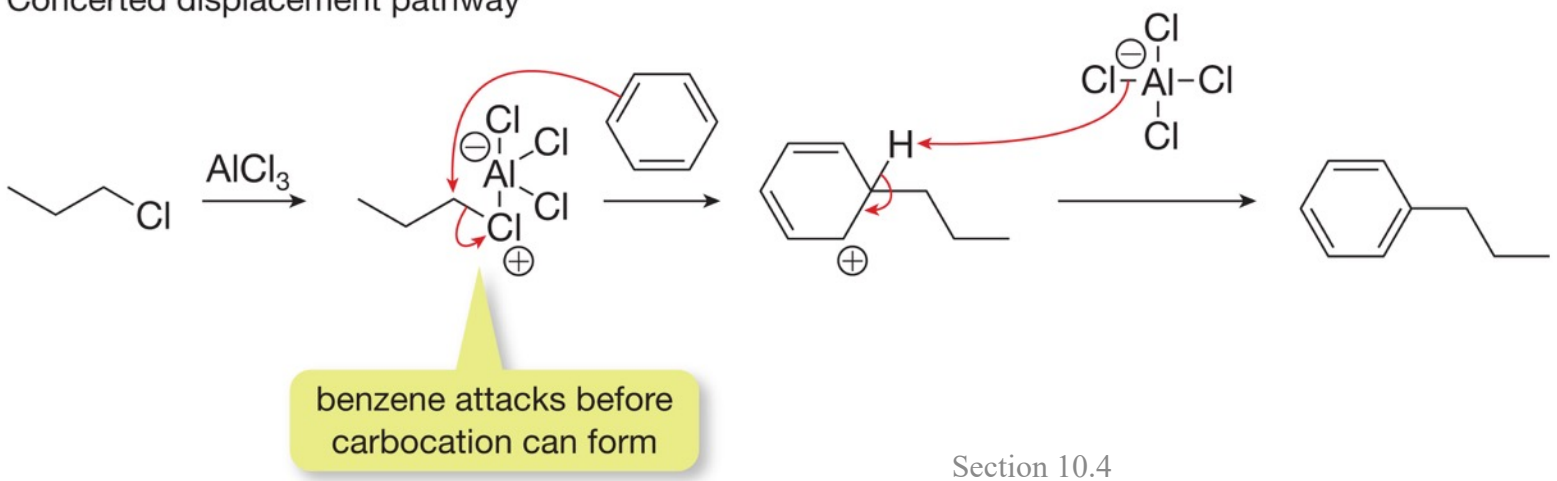


- The stability of a primary carbocation is so low that it is unlikely that it actually forms:

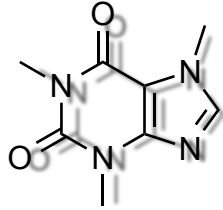
Carbocation pathway



Concerted displacement pathway

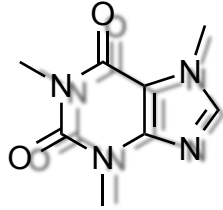


Limitations of Friedel-Crafts Alkylations

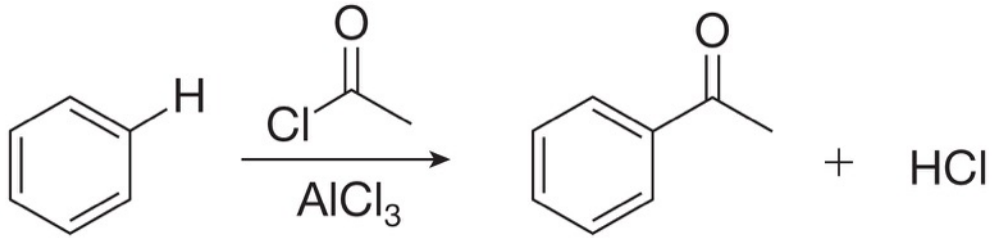


- The reality is that primary alkyl halides, which do not form 1° carbocations and are prone to rearrangements, do not reliably add to aromatic rings.
- These problems can be solved by a variation of the Friedel-Crafts alkylation reaction, the Friedel-Crafts ***acylation*** reaction.

Friedel-Crafts Acylation

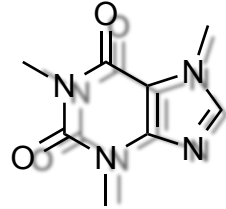


- In the Friedel-Crafts acylation reaction, an acyl group, instead of an alkyl group, substitutes the hydrogen atom on an aromatic ring.
- The reagents used are an acyl chloride and a Lewis acid catalyst.

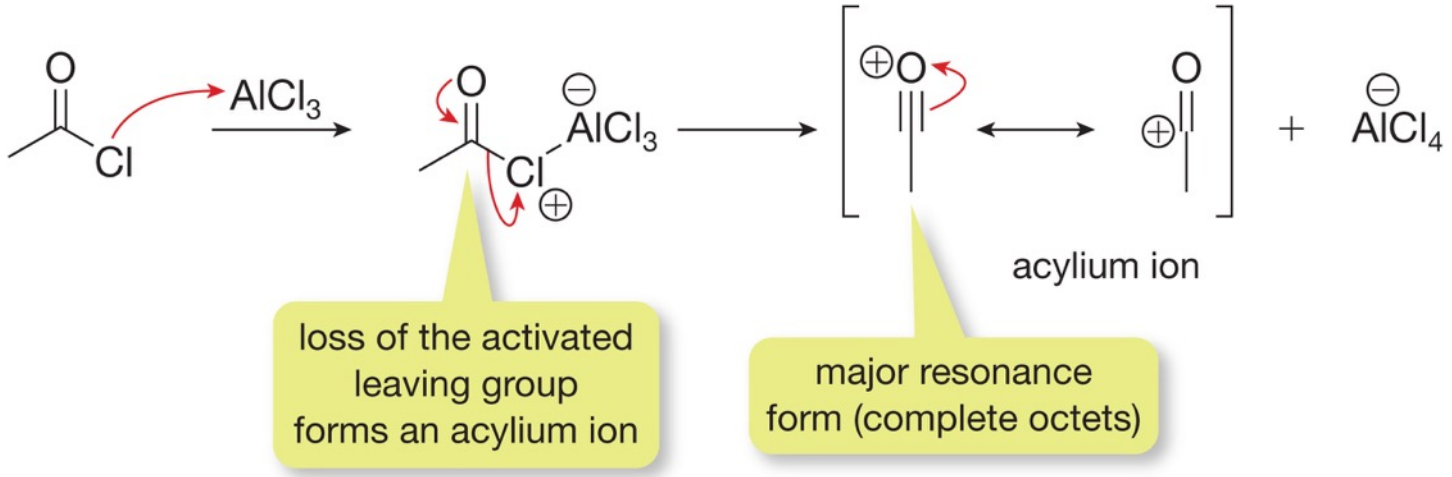


- The active electrophile is an acylium ion, produced by interaction of the Lewis acid catalyst with the alkyl halide.
- Once the electrophile is produced, the mechanism proceeds as usual with addition of the electrophile followed by re-aromatization of the ring.

Friedel-Crafts Acylation



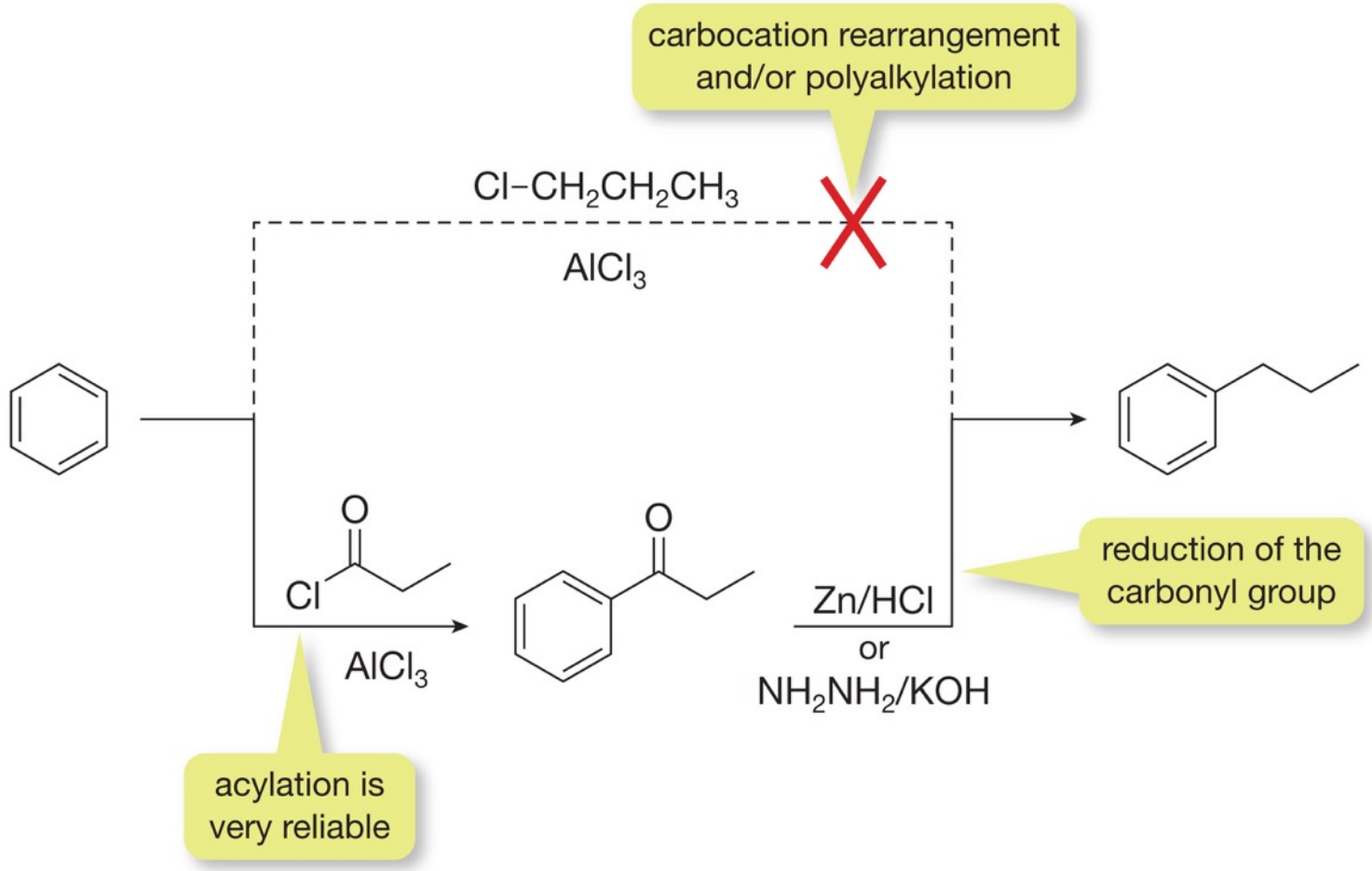
- Once the electrophile is produced, the mechanism proceeds in the usual fashion.



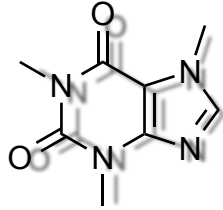
- Friedel-Crafts acylation is more reliable than alkylation.
- Because the acyl group is electron withdrawing, subsequent acylation is avoided. Also, the acylium ion is not prone to rearrangement as it is resonance stabilized.

Friedel-Crafts Acylation

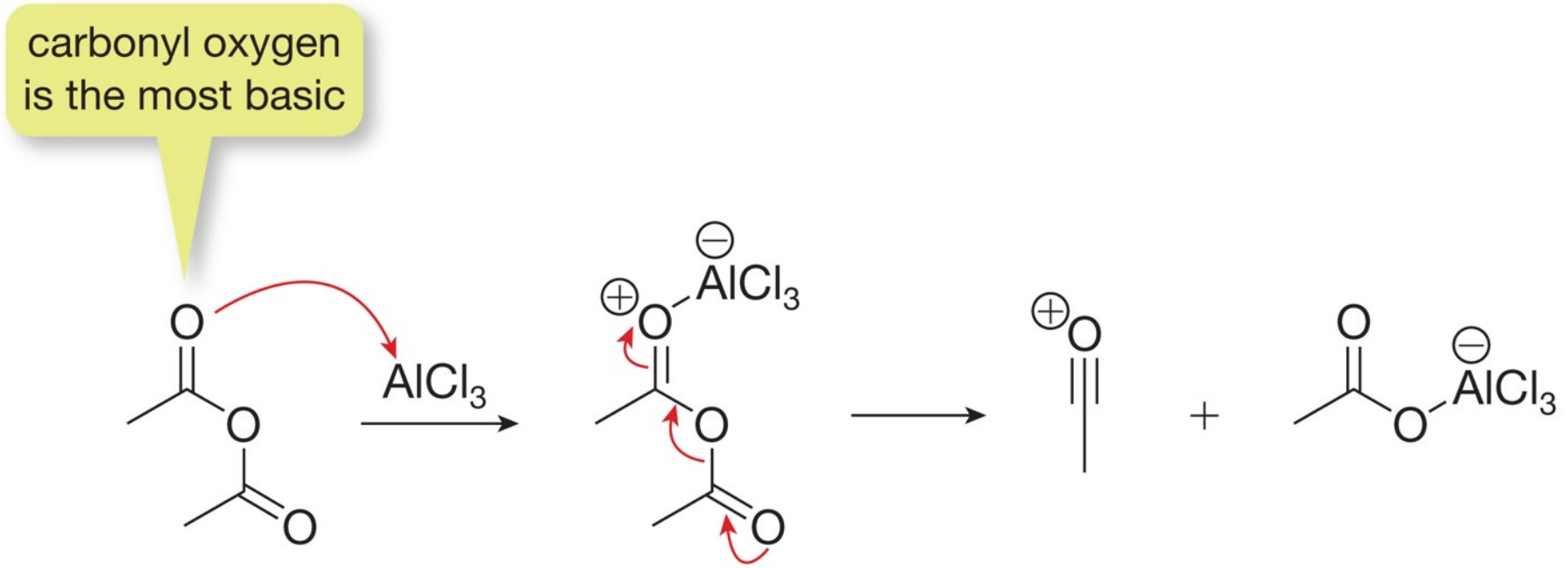
- Once added, acyl groups can be reduced with NH2NH2/KOH (Wolff-Kischner) or with Zn(or Sn)/HCl (Clemmenson) to give the alkyl group.
- This produces the overall equivalent of a Friedel-Crafts alkylation without the side-reactions.



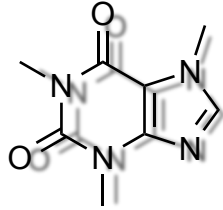
Friedel-Crafts Acylation



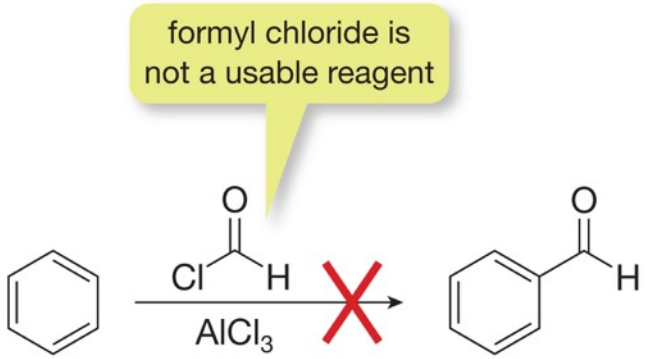
- Friedel-Crafts acylations can also be carried out with an acid anhydride instead of an acid chloride.



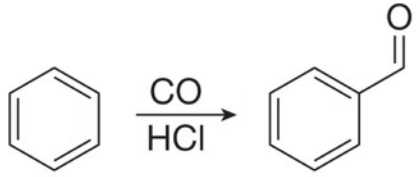
Friedel-Crafts Acylation

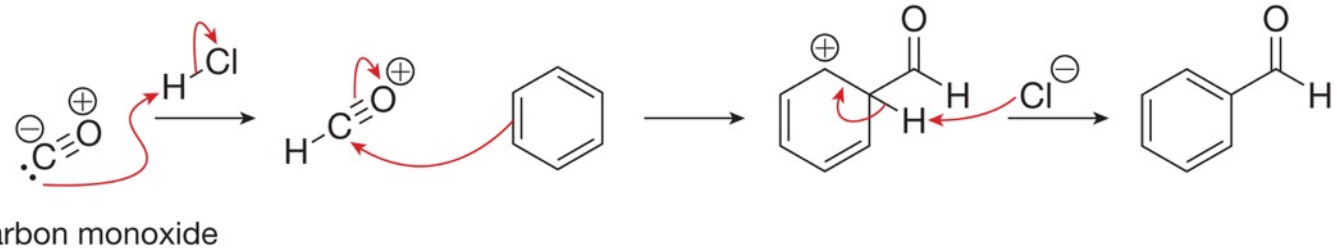


- One limitation of the Fridel-Crafts acylation is that the unstable formyl chloride cannot be used to form aldehydes.

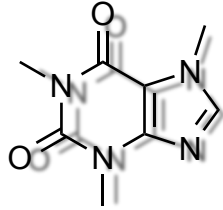


- Aldehydes can be produced by the Gatterman-Koch reaction, a variation on the Friedel-Crafts reaction.

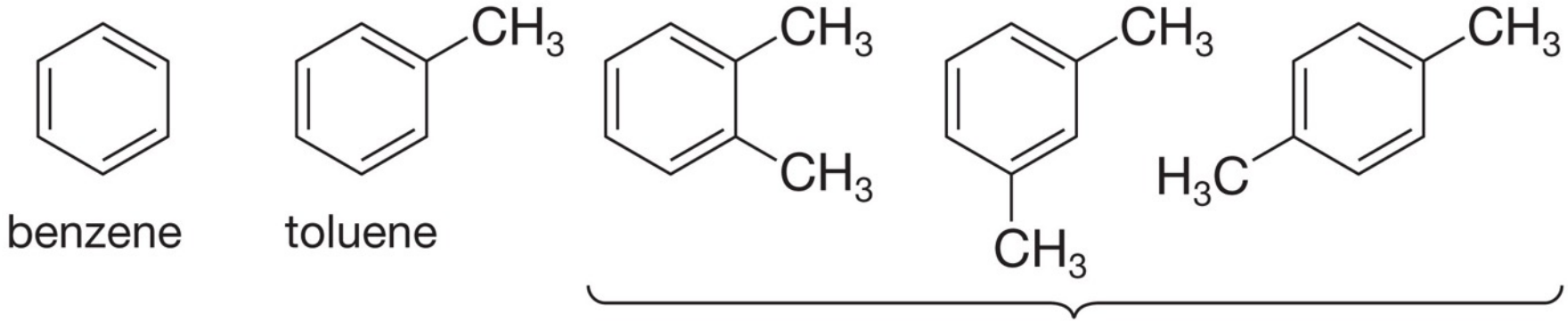


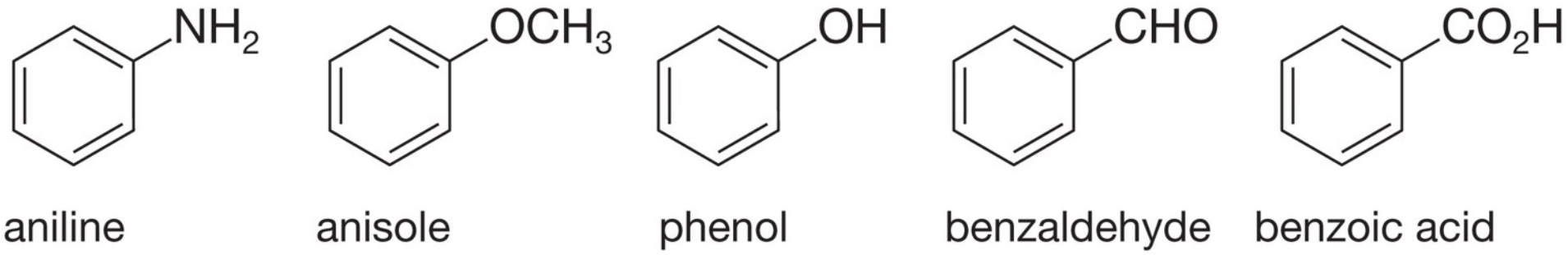


Aromatic Nomenclature

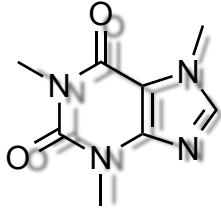


- Many aromatic molecules have ‘trivial’ names and do not follow IUPAC rules for nomenclature.

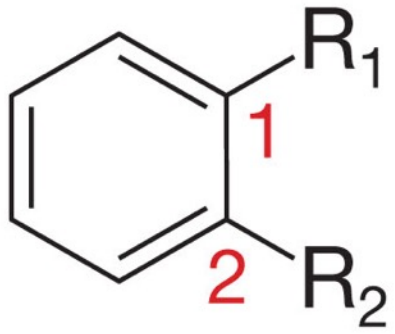




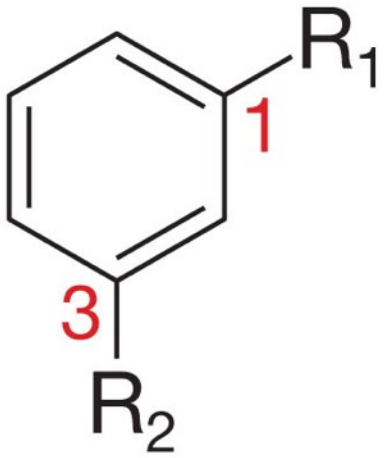
Aromatic Nomenclature



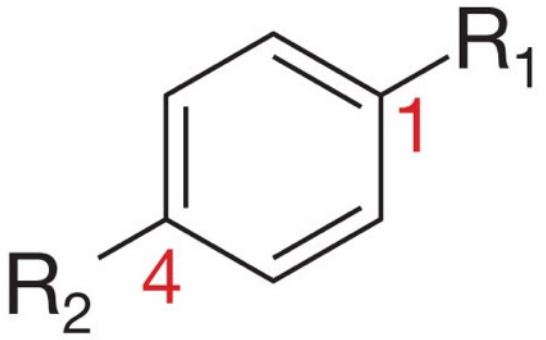
- The relative positions of ***two*** groups on an aromatic ring can be referred to by numbers or by Greek words; ortho, meta, or para.



ortho

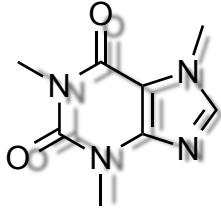


meta



para

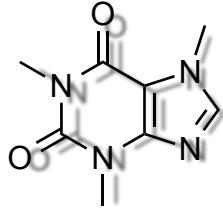
Directing Groups in S_EAr



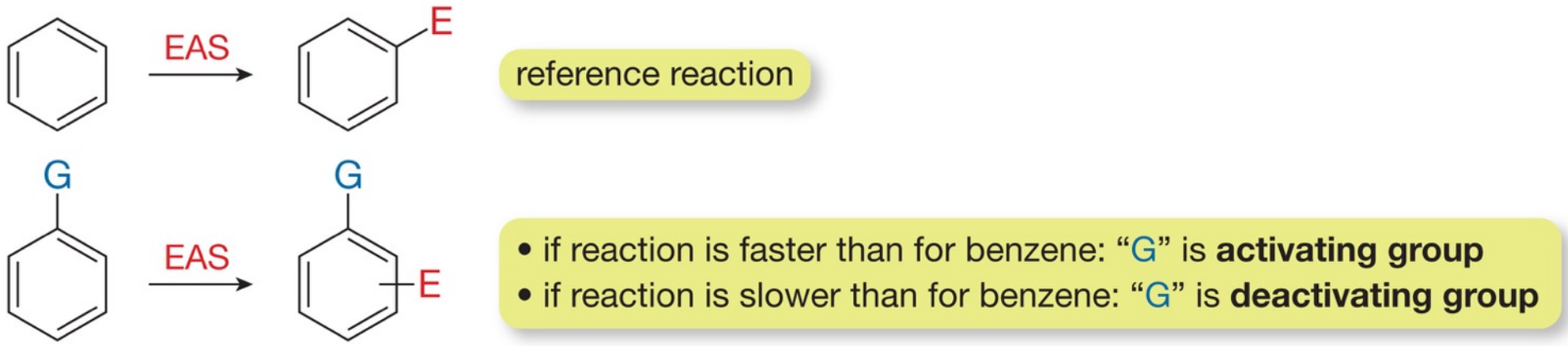
- Substituents attached to an aromatic ring affects the outcome of electrophilic aromatic substitution reaction.
- Specifically, it can affect the ***rate of the reaction*** as well as the ***regiochemistry***.

- The functional groups can be categorized based on two factors:
  1. ***Activating*** or ***deactivating*** groups
  2. ***Ortho/para*** or ***meta*** directors

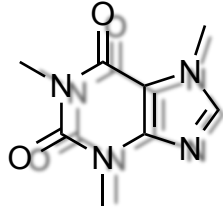
Directing Groups in S_EAr



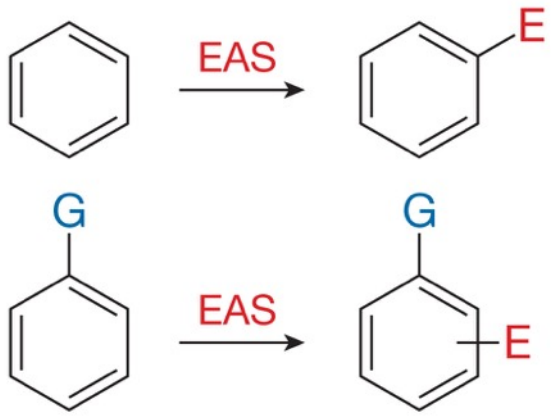
- Activating groups ***increase*** the rate of electrophilic aromatic substitution reactions relative to the rate of reaction of an unsubstituted aromatic ring (benzene).
- Deactivating groups ***decrease*** the rate of electrophilic aromatic substitution reactions relative to the rate of reaction of an unsubstituted aromatic ring (benzene).



Directing Groups in S_EAr



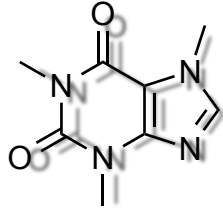
- In general, electron donating groups (EDGs) are activating because they help stabilize the arenium ion intermediate and the transition state of rate determining step.
- Electron withdrawing groups (EWGs) are deactivating because the destabilize the arenium ion intermediate and the transition state leading to them.



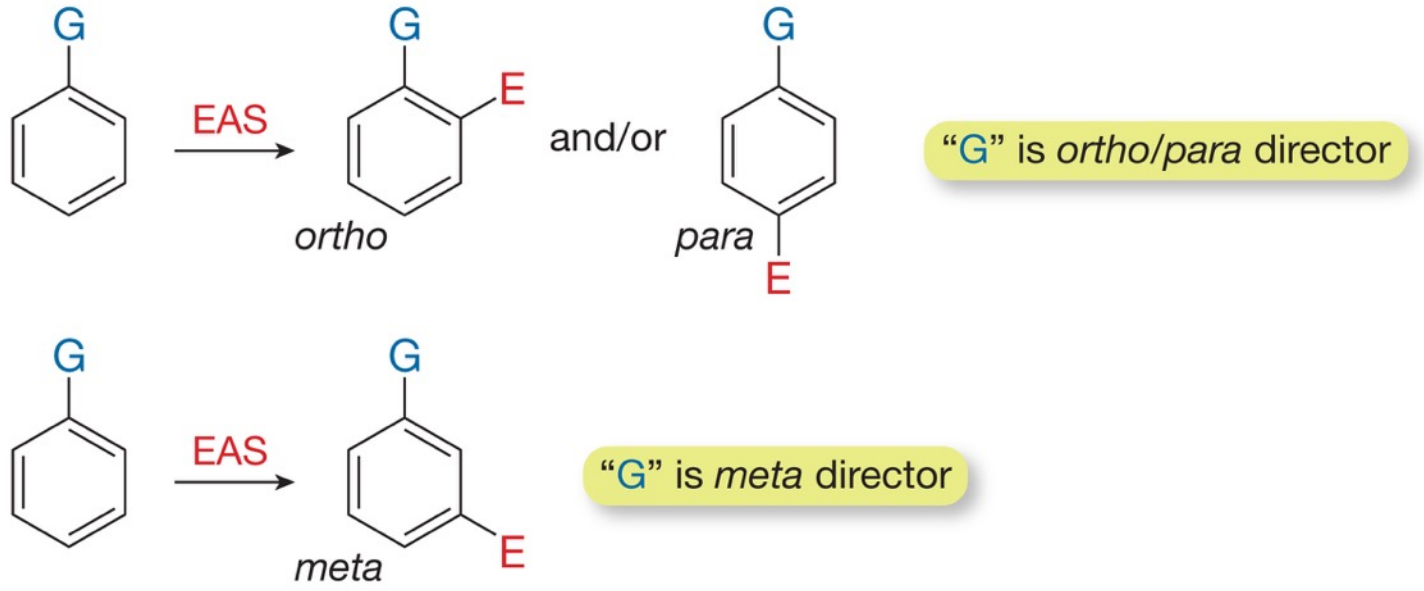
reference reaction

- if reaction is faster than for benzene: "G" is **activating group**
- if reaction is slower than for benzene: "G" is **deactivating group**

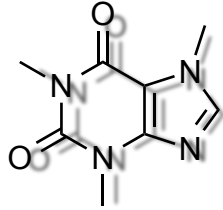
Directing Groups in S_EAr



- Directing groups refer to substituents that influence the regiochemistry of the electrophilic aromatic substitution reaction.
- Ortho/para directors favour the formation of the ortho and para regioisomers.
- Meta directors favour the formation of the meta regioisomers.



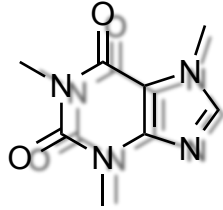
Directing Groups in S_EAr



- The influence of these substituents on the reactivity and regioselectivity is rationalized by conjugation and inductive effects.

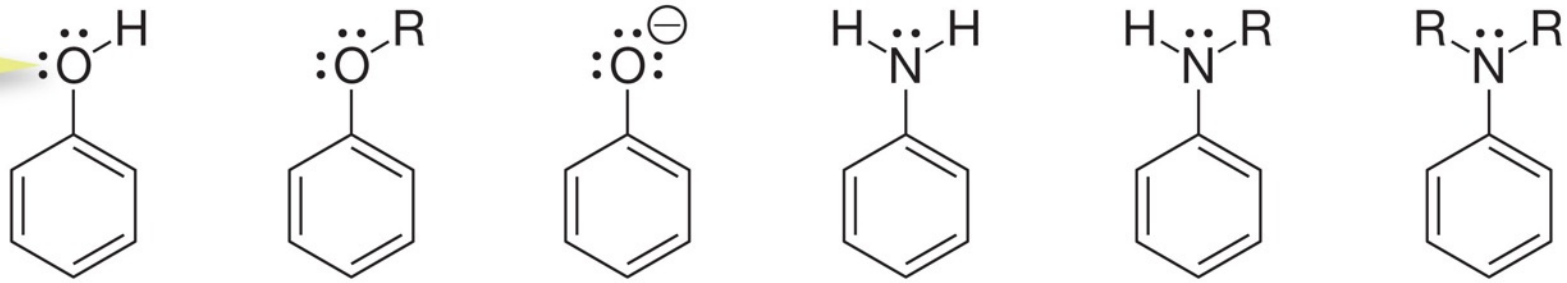
Substituent	Features	Reactivity	Direction
NH_2, NHR, NR_2, OH, O^-	Lone pair on heteroatom	Strongly activating	*Ortho/para*
NHCOR, OCOR	Electron-delocalized lone pair on heteroatom	Moderately activating	*Ortho/para*
Alkyl, aryl	Hyperconjugation or weak electron delocalization	Weakly activating	*Ortho/para*
F, Cl, Br, I	Lone pair on electronegative halogen atom	Deactivating	*Ortho/para*
COH(R), CO_2H(R), CONHR, CN	Polar π bond conjugated to ring	Moderately deactivating	*Meta*
NO_2, NR_3^+, CX_3	Strong inductive electron-withdrawing group	Strongly deactivating	*Meta*

Ortho/Para Directing Groups



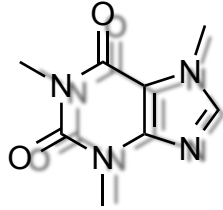
- EDGs tend to activate electrophilic aromatic substitution and they tend to direct the regioselectivity towards the ortho/para positions.
- ***Strong ortho/para directors*** all have a heteroatom with at least one lone pair which can delocalize into the ring.

strong *ortho/para* directors have lone pairs on heteroatoms that can delocalize in the ring via resonance

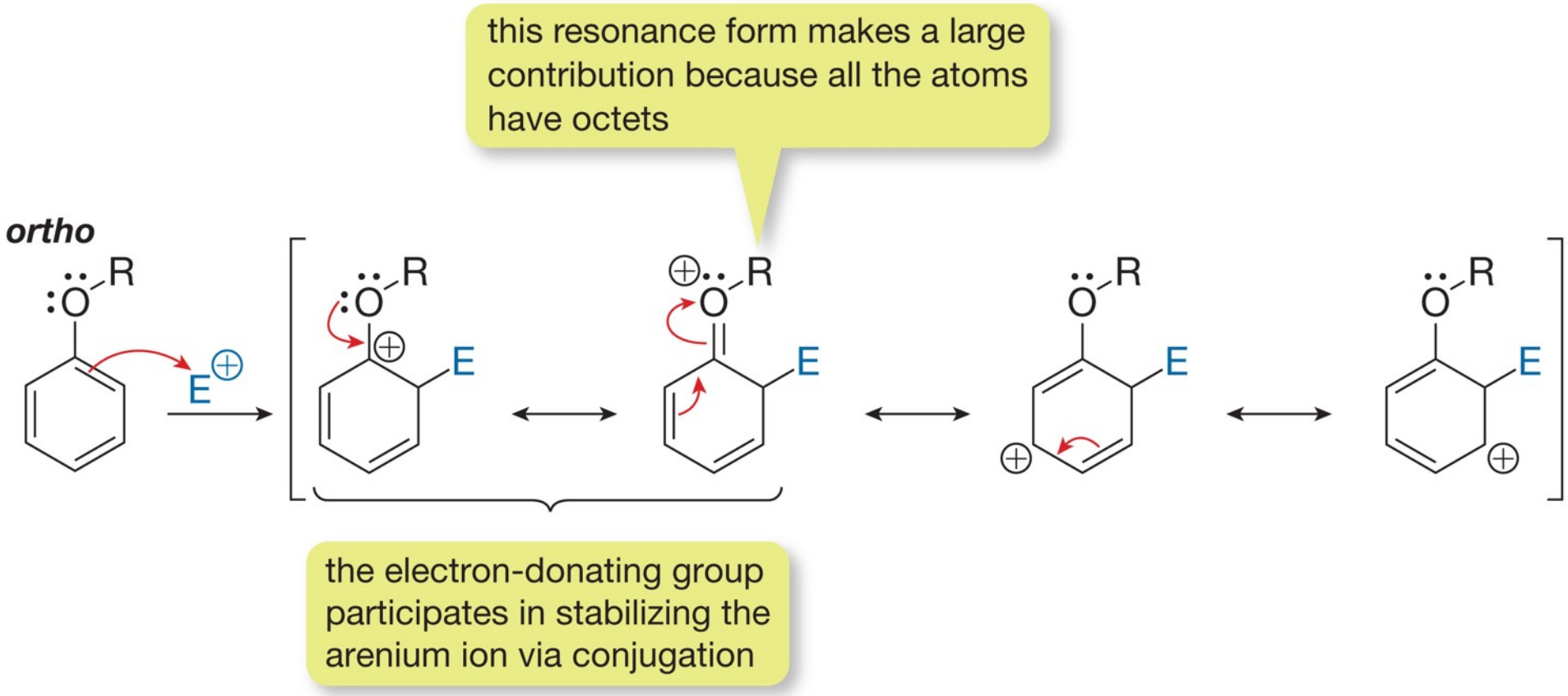


- Resonance delocalization of the arenium ion intermediate helps explain the observed regioselectivity.

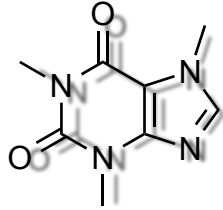
Ortho/Para Directing Groups



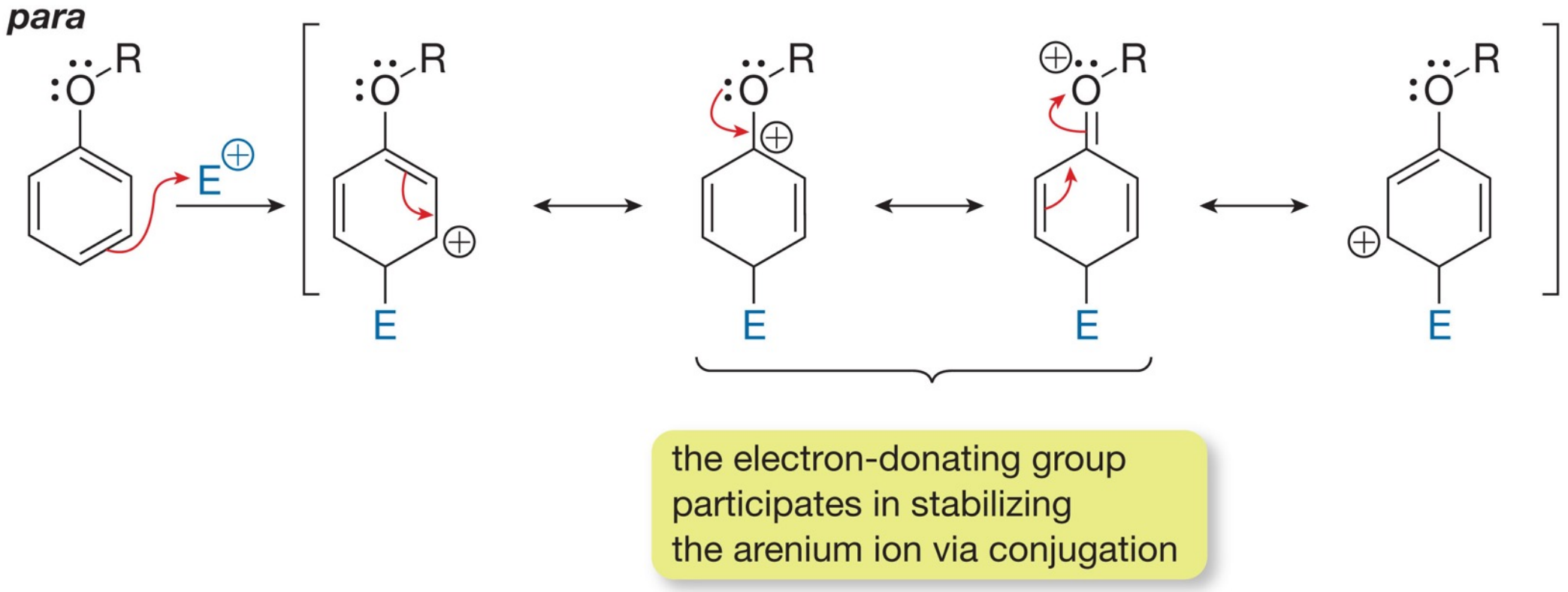
- Consider the arenium ion intermediates when substituting in the ortho or para position:



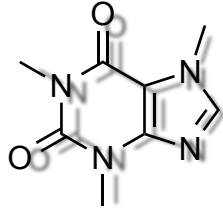
Ortho/Para Directing Groups



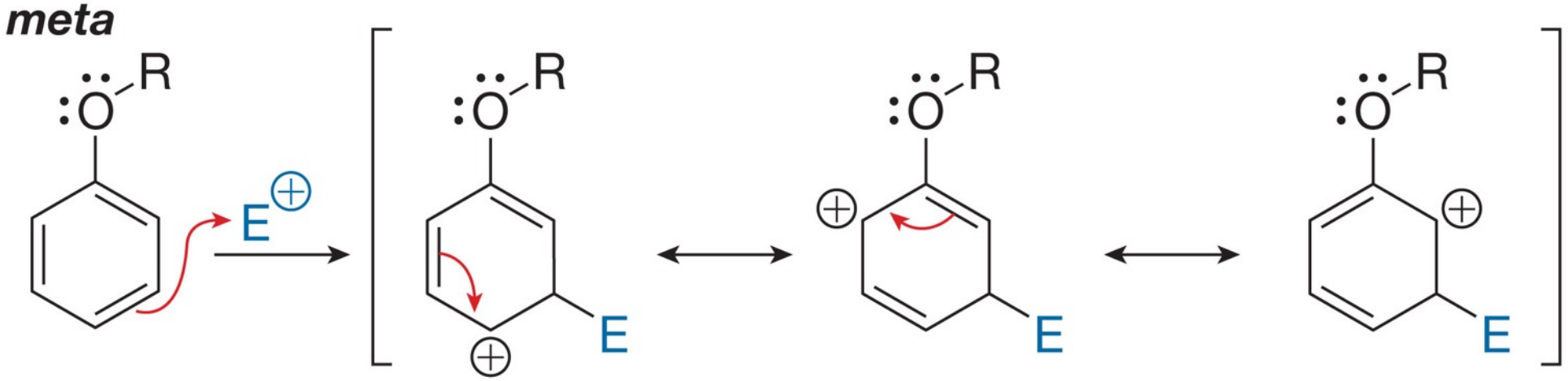
- Consider the arenium ion intermediates when substituting in the ortho or para position:



Ortho/Para Directing Groups

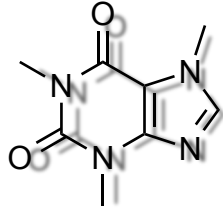


- Compare this with the arenium ion intermediate when substituting in the meta position:



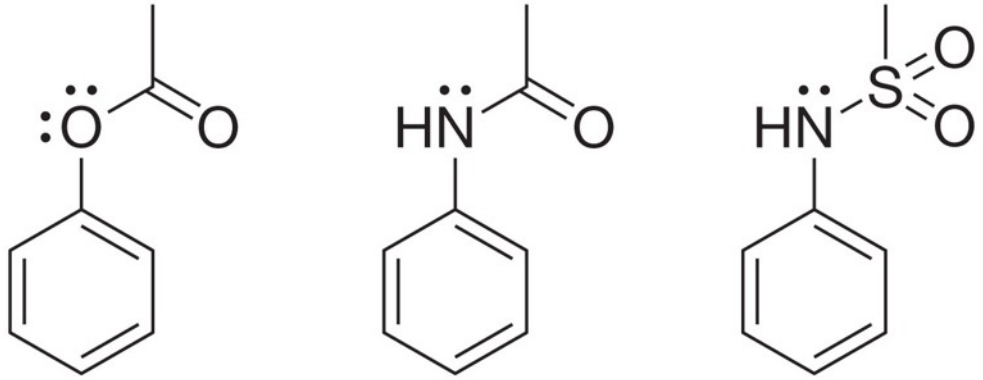
the electron-donating group cannot participate in stabilizing the arenium ion via conjugation

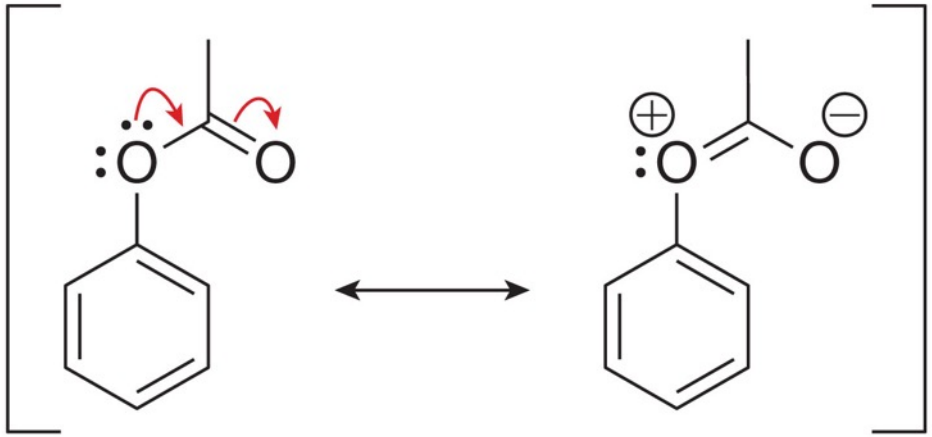
Ortho/Para Directing Groups



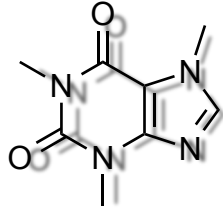
- ***Moderate ortho/para directors*** also contain a heteroatom with at least one lone pair, however, the lone pair is already delocalized into the functional group itself.

weak *ortho/para* directors have resonance-stabilized lone pairs on the heteroatom

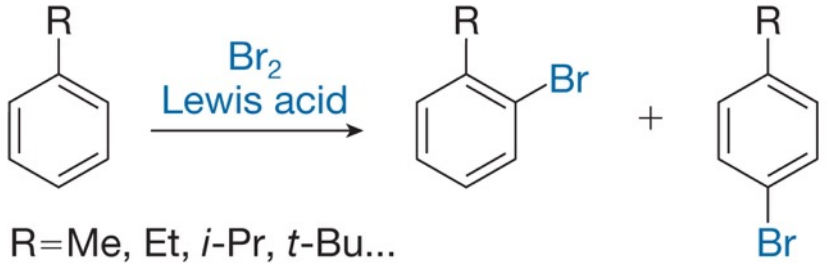


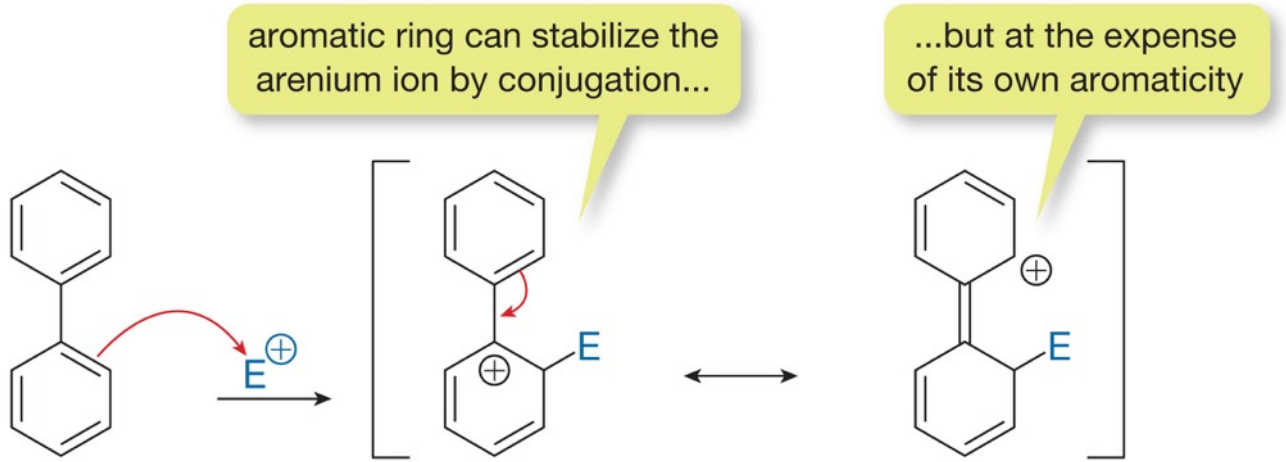


Ortho/Para Directing Groups

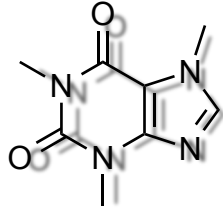


- ***Weak ortho/para directors*** are split into two categories; alkyl groups and aromatic rings.
- Alkyl groups are weakly electron donating via hyperconjugation.
- Aromatic groups are weakly electron donating via conjugation.

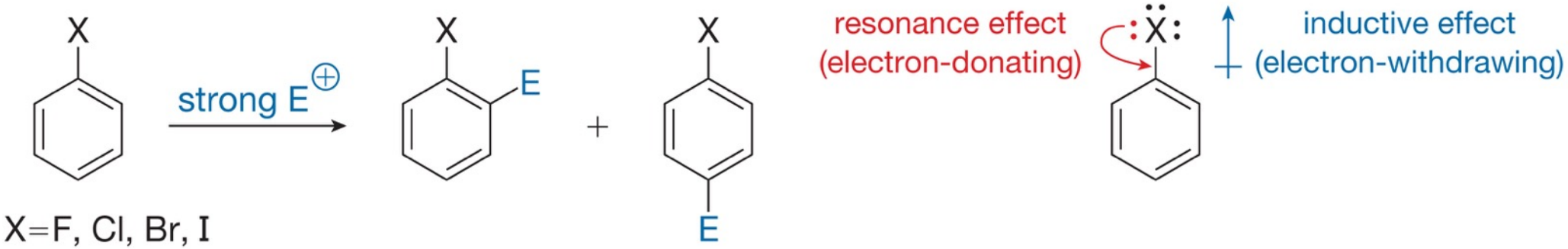




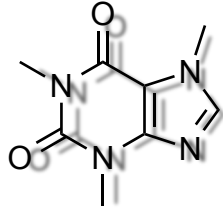
Ortho/Para Directing Groups



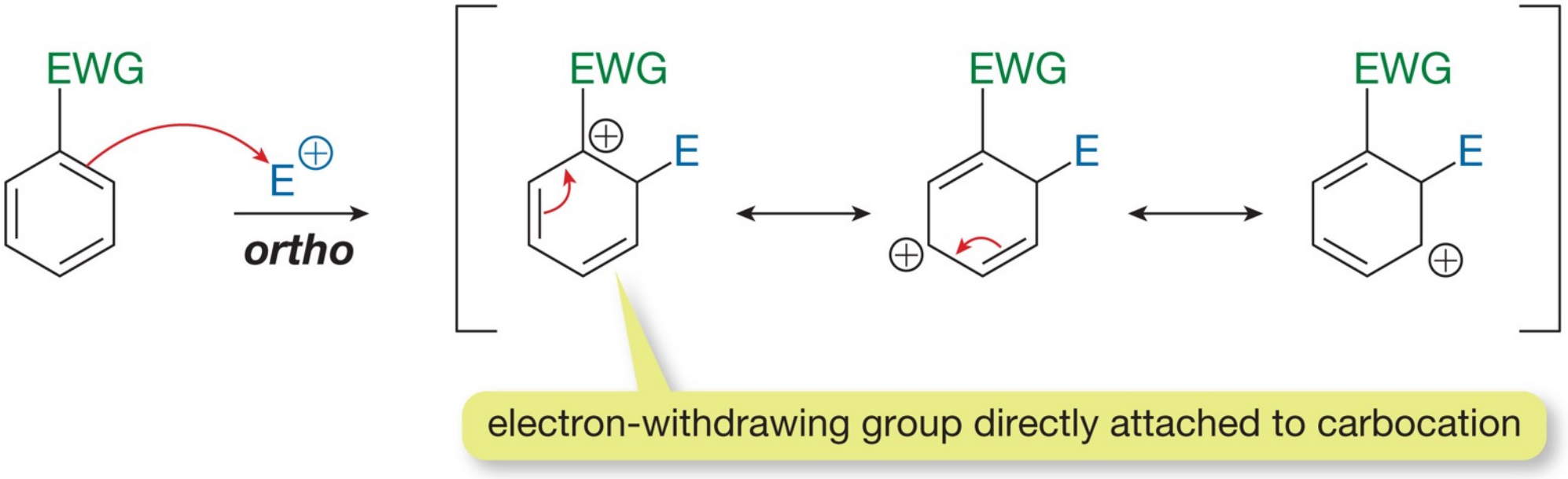
- The halogens (F, Cl, Br, I) fall into the category of ***deactivating ortho/para directors***. They are ortho/para directing because they carry lone pairs that can be delocalized with an aromatic ring.
- At the same time, the halogens are also highly electronegative and withdraw electron density from the aromatic ring via inductive effects. This makes the aromatic rings less nucleophilic and slows the overall rate of reaction – i.e. deactivating.



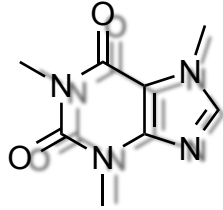
Meta Directing Groups



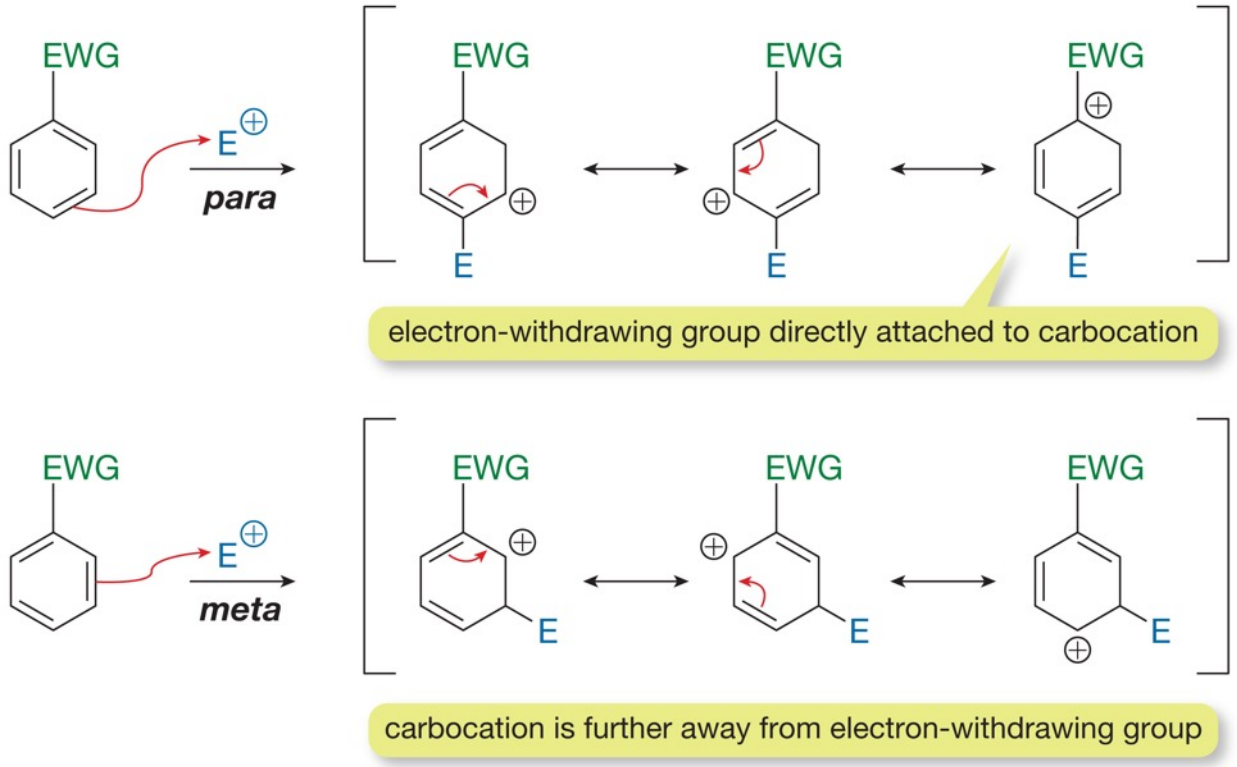
- EWGs tend to deactivate electrophilic aromatic substitution and they tend to direct the regioselectivity towards the meta positions.
- Resonance delocalization of the arenium ion intermediate helps explain the observed regioselectivity.

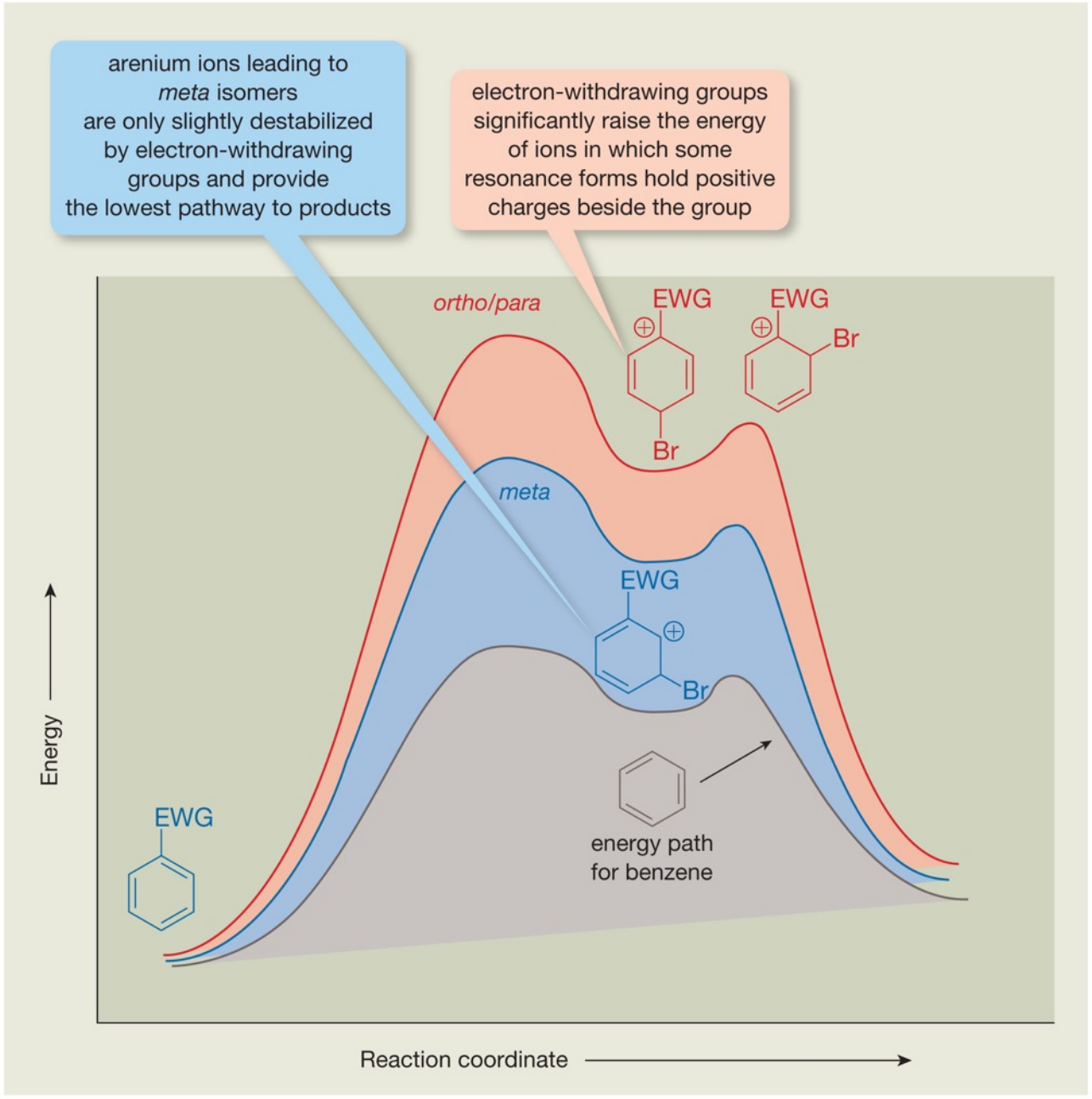


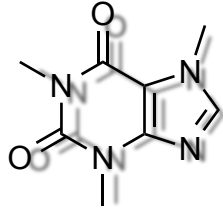
Meta Directing Groups



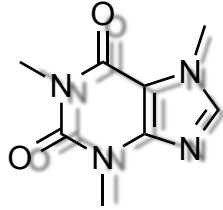
- For both ortho and para additions, one resonance structure places the carbocation adjacent to the EWG, ***destabilizing*** the charge.
- Meta addition keeps the carbocation further from the EWG.



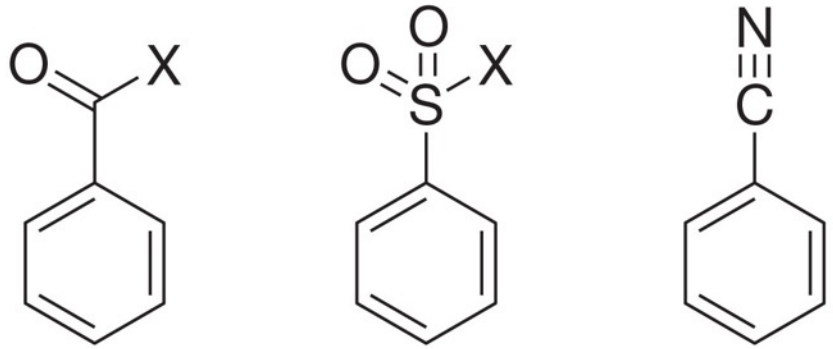

arenium ions leading to
meta isomers
are only slightly destabilized
by electron-withdrawing
groups and provide
the lowest pathway to products
electron-withdrawing groups
significantly raise the energy
of ions in which some
resonance forms hold positive
charges beside the group
ortho/para
EWG
EWG
Br
Br
meta
EWG
Br
Energy
EWG
energy path
for benzene
Reaction coordinate



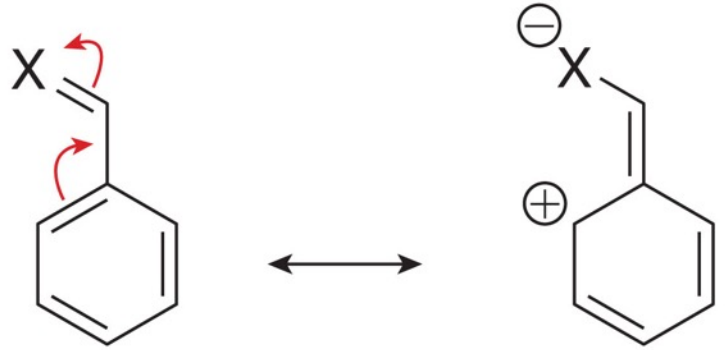
Meta Directing Groups



- ***Moderate deactivating meta directors*** have ***polar π bonds*** that can conjugated to the aromatic ring and can withdraw electron density via electron delocalization.
- Withdrawing electron density makes the ring a weaker nucleophile.

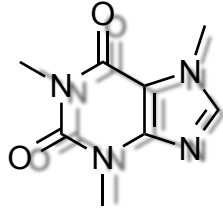


X = H, R, OH, OR, NH_2, NHR

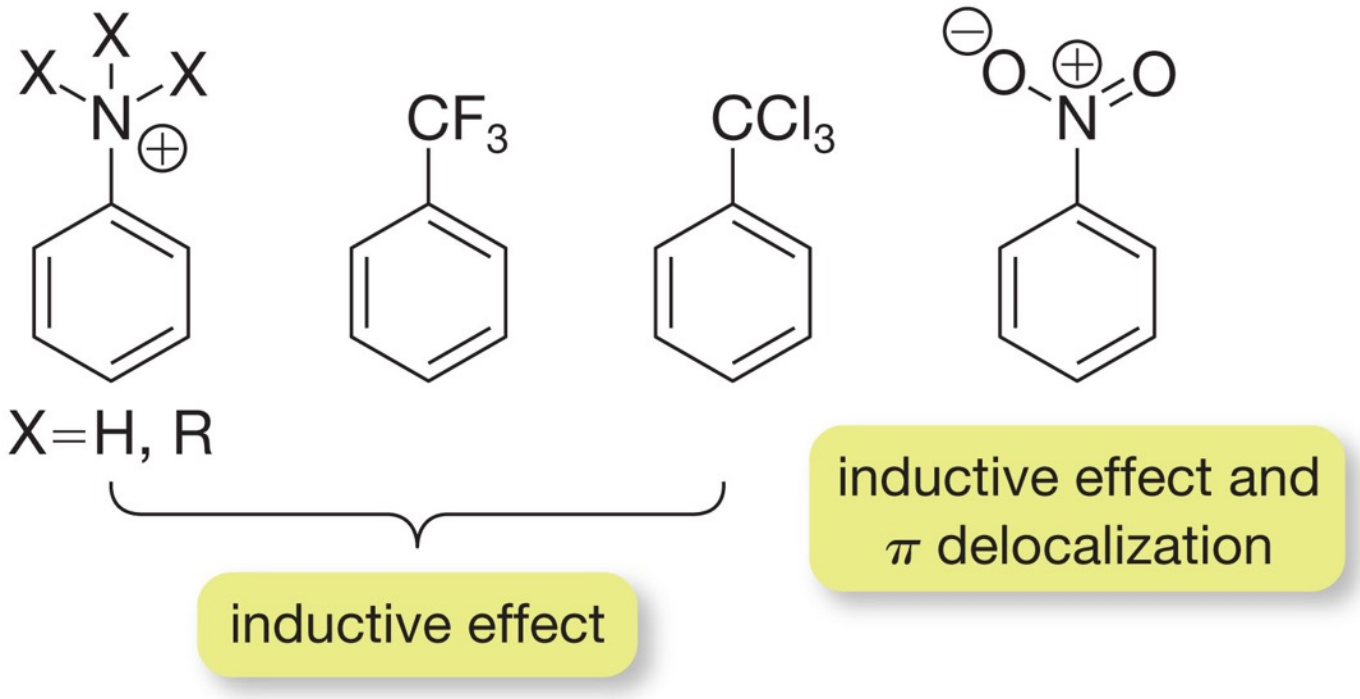


polar π bonds deactivate via conjugation

Meta Directing Groups

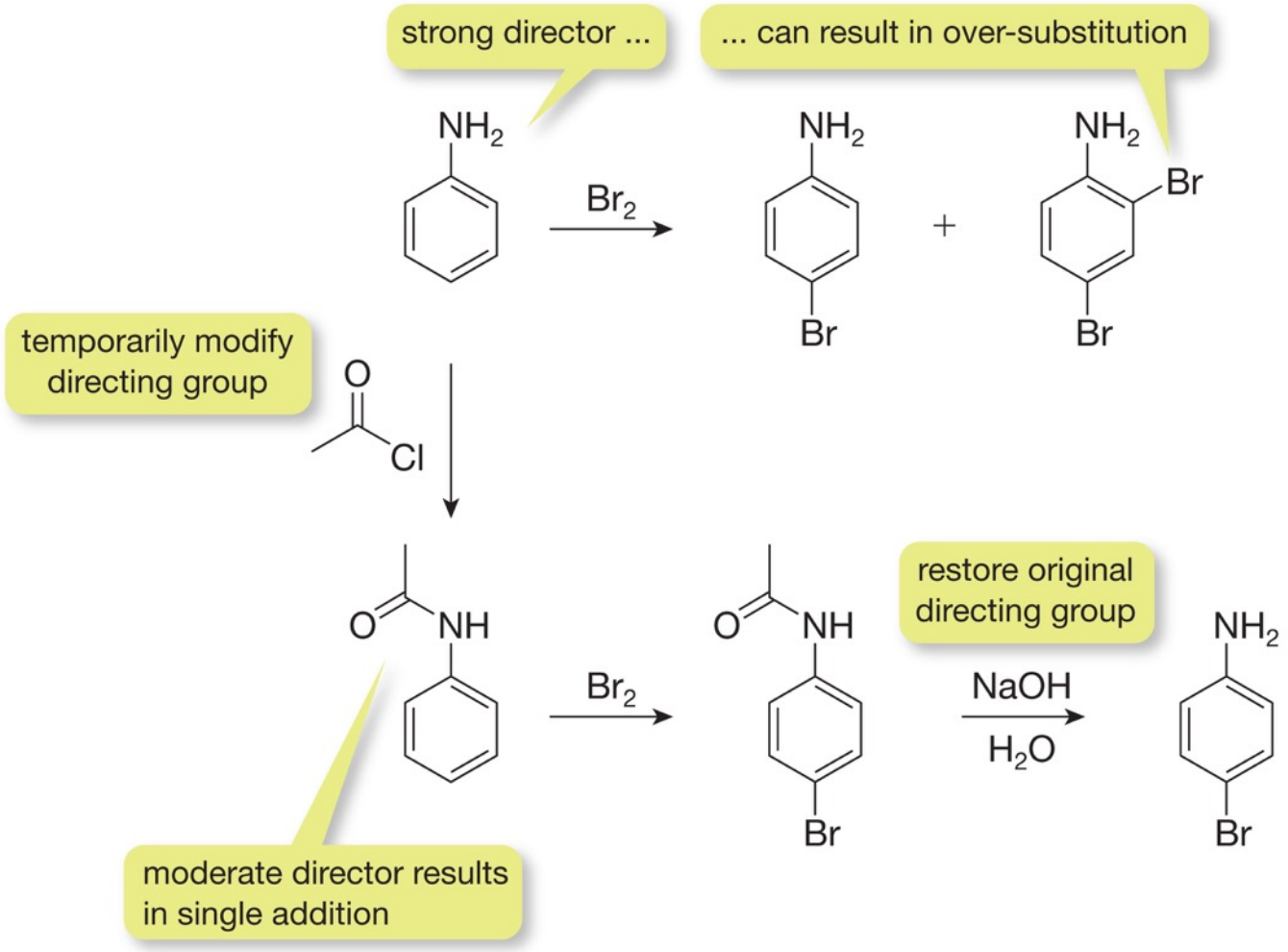


- ***Strongly deactivating meta directors*** are groups that withdraw electron density form the ring via strong inductive effects.
- Withdrawing electron density makes the ring a weaker nucleophile.

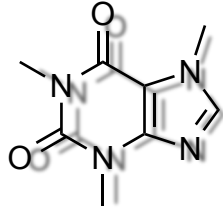


Modifying Reactivity in S_EAr

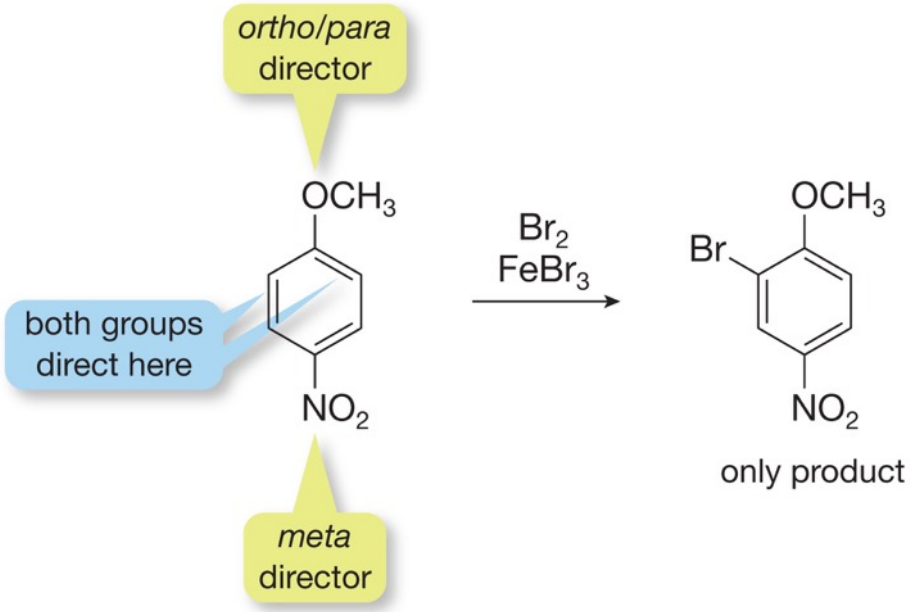
- For the strong ortho/para directors, it can be difficult to stop the reaction from undergoing multiple substitutions.
- The reactivity can be controlled to monosubstitution by modifying the strong ortho/para director into a moderate ortho/para director.



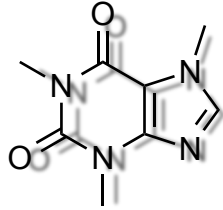
Activation on Polysubstituted Benzenes



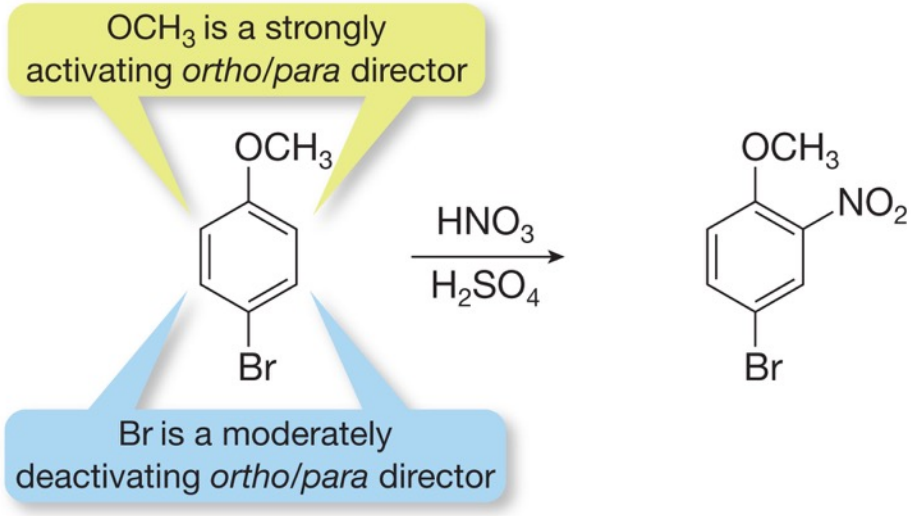
- When multiple substituents are attached to a ring, the directing effects of each substituent must be considered.
- In general, the most activating group will direct the electrophile in the major product.
- When the directing properties of the substituents reinforce each other, only one product is obtained.

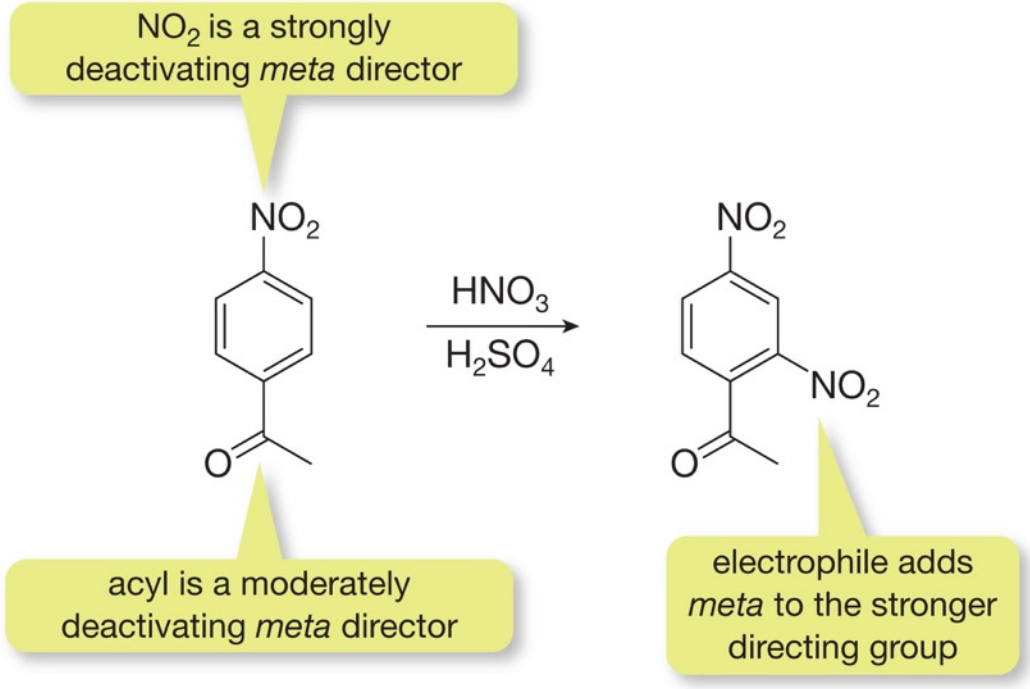


Activation on Polysubstituted Benzenes

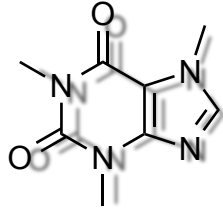


- When the directing properties of the substituents conflict each other, the most activating group will typically exert the most influence.



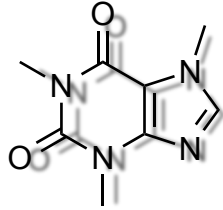


Retrosynthetic Analysis

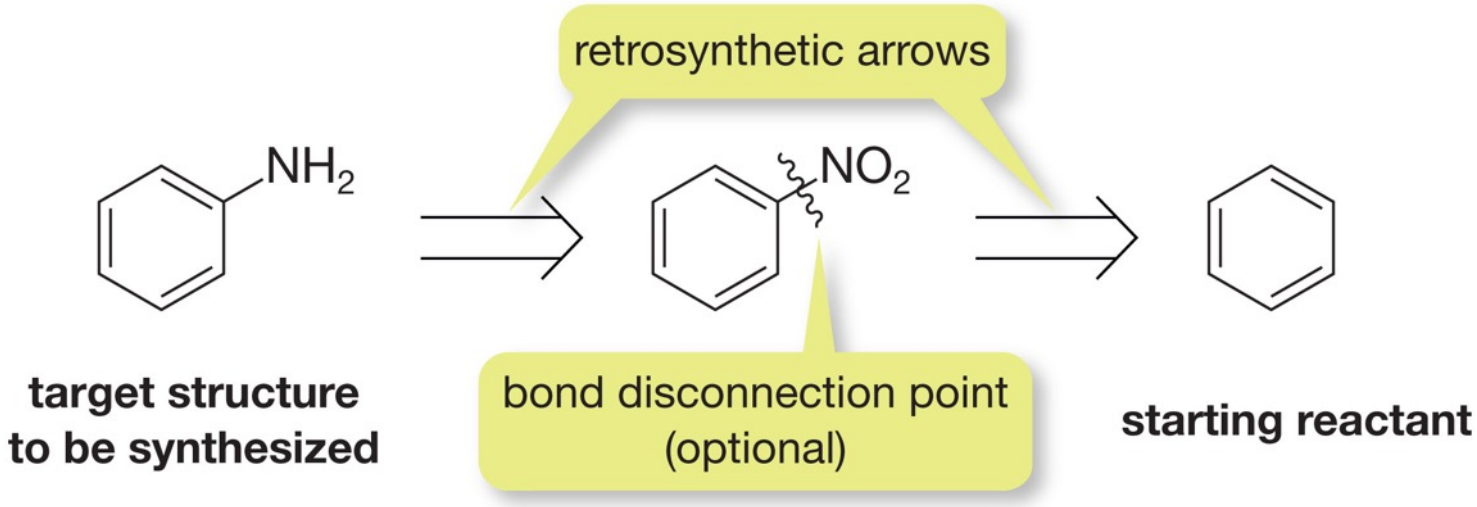


- ***Synthesis*** is the process of making complex molecules from simpler ones.
- Synthesis occurs in a stepwise fashion by modifying a given reactant in a sequence of reactions.
- One of the most challenging aspects of organic chemistry is designing a workable synthesis.
- Some syntheses are lengthy or complex, or both. The order of each reaction is important and often will determine if the overall sequence is successful or not.

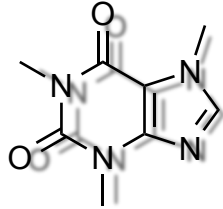
Retrosynthetic Analysis



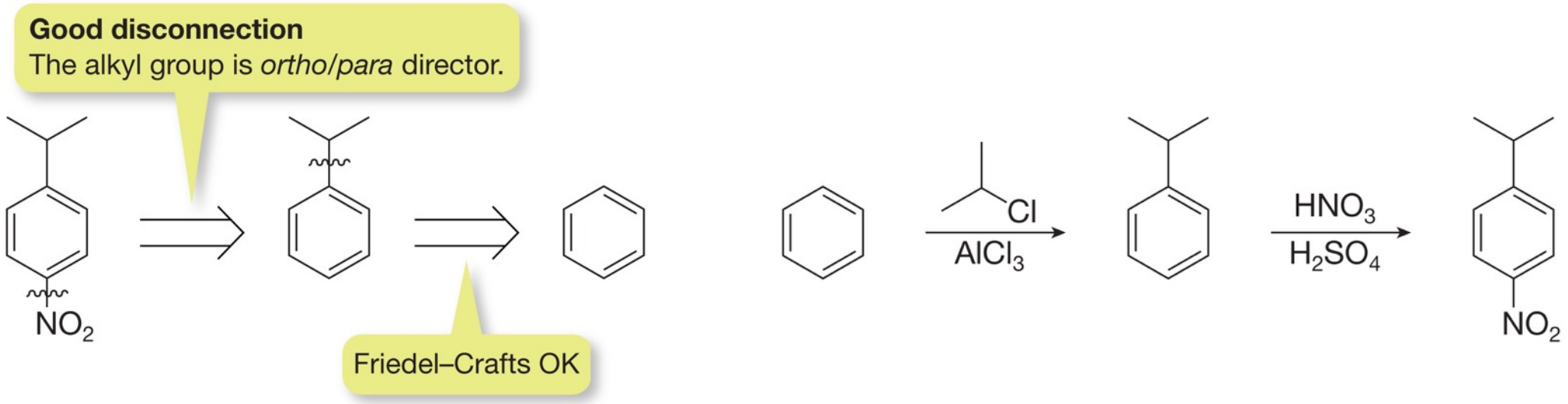
- One approach to designing a synthesis is ***retrosynthetic analysis*** (retrosynthesis). In retrosynthesis, you start with the desired end-product and work backwards to devise suitable transformations.
- Retrosynthetic analysis uses a series of ***disconnections***, imaginary processes of breaking bonds, to break a complex problem into simpler ones.



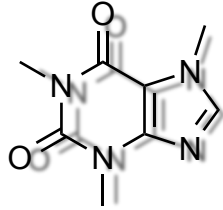
Retrosynthetic Analysis



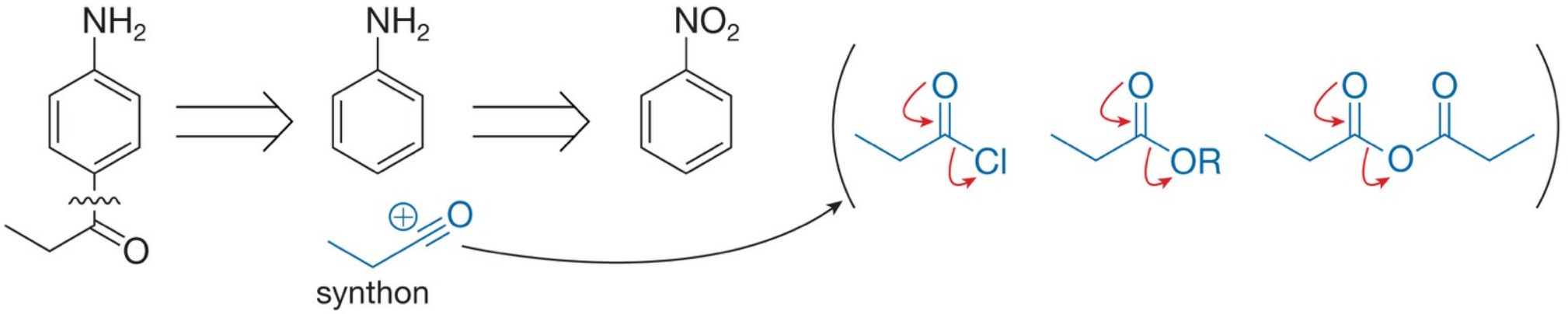
- Each synthetic step must be analyzed to ensure that the forward reaction is workable.



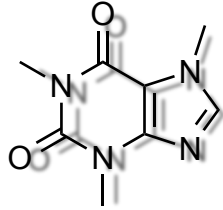
Retrosynthetic Analysis



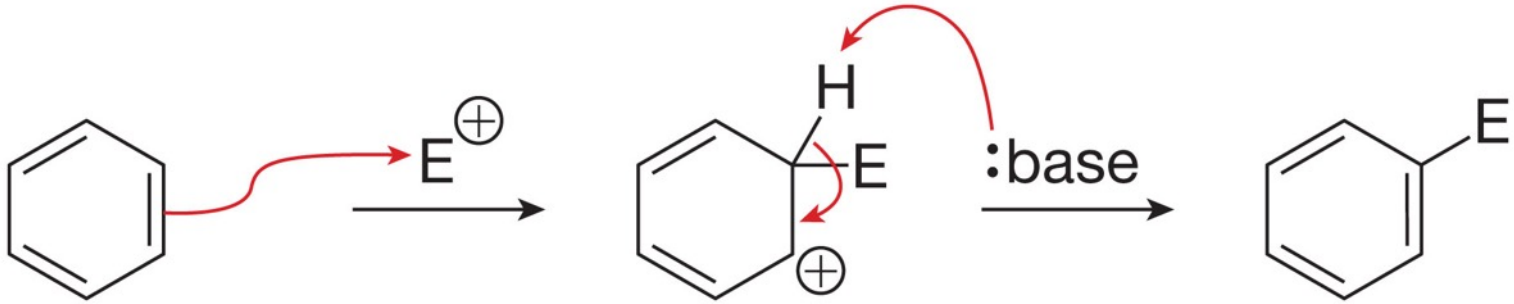
- Synthons are fragments resulting from disconnections that show the general reactivity (Nu^-/E^+) of the fragment.
- Because many different reactants can be used in synthesis, ***synthons*** are used to represent the type of reaction being considered.



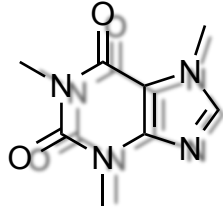
Patterns in S_EAr Reactions



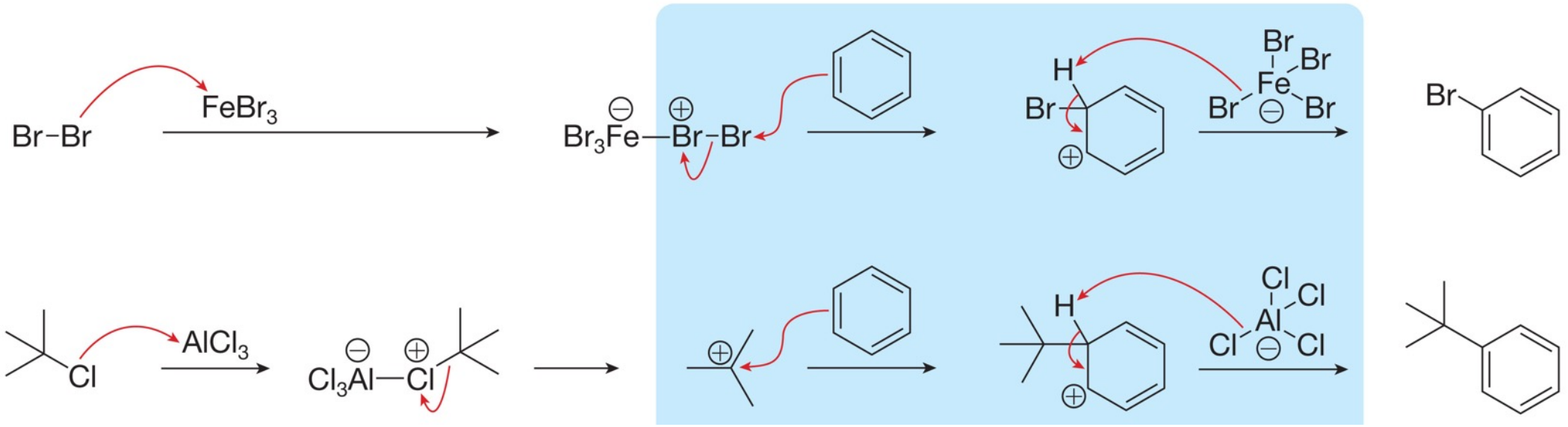
- Electrophilic aromatic substitution reactions all follow the same general pattern:
  1. Addition of an electrophile to form an arenium ion intermediate.
  2. Elimination of a hydrogen atom to restore aromaticity.
- Reactivity and regioselectivity are controlled by the stability of the arenium ions.



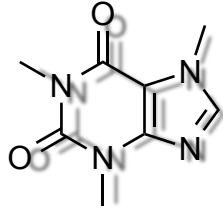
Patterns in S_EAr Reactions



- Because of the inherent stability of the starting aromatic ring, most electrophiles require activation.



Patterns in S_EAr Reactions



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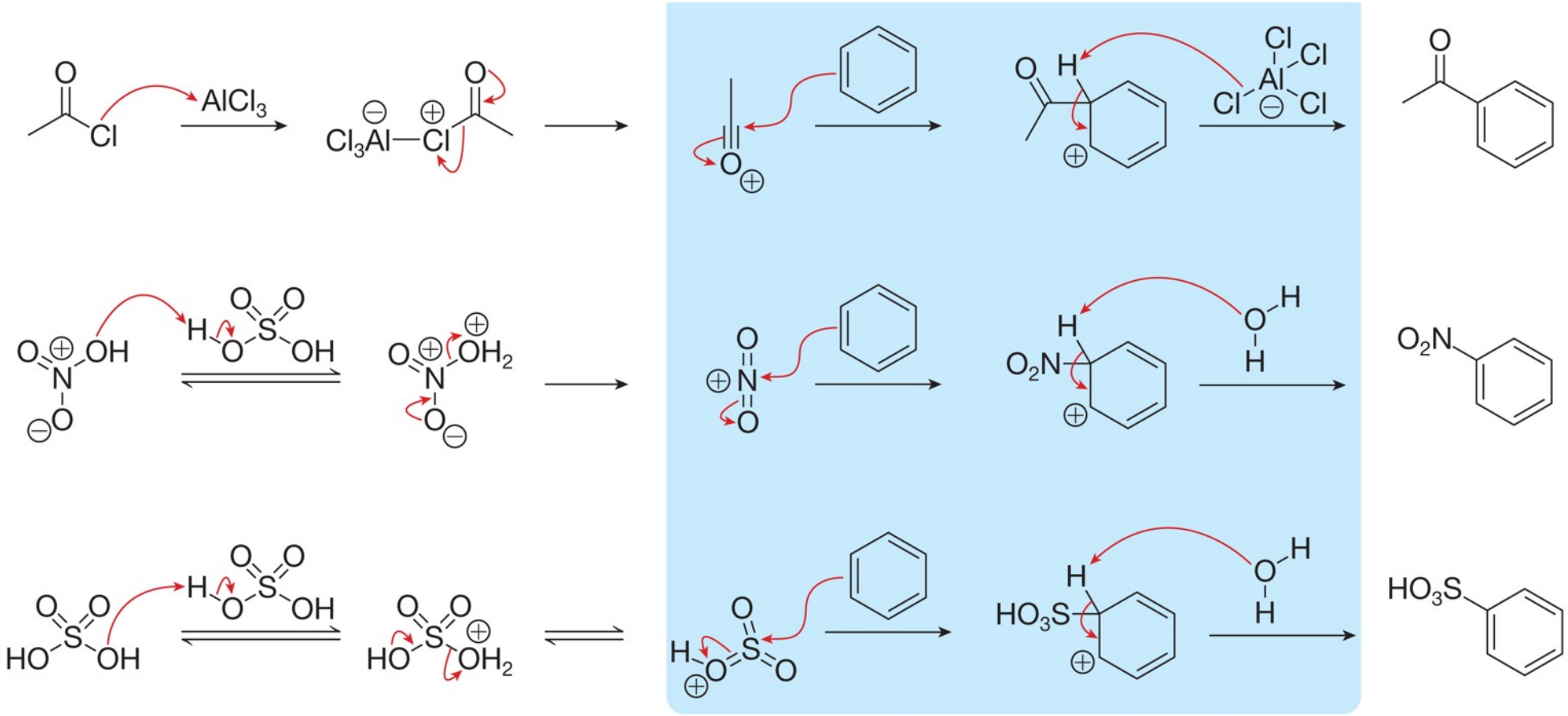
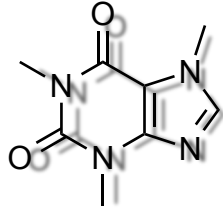
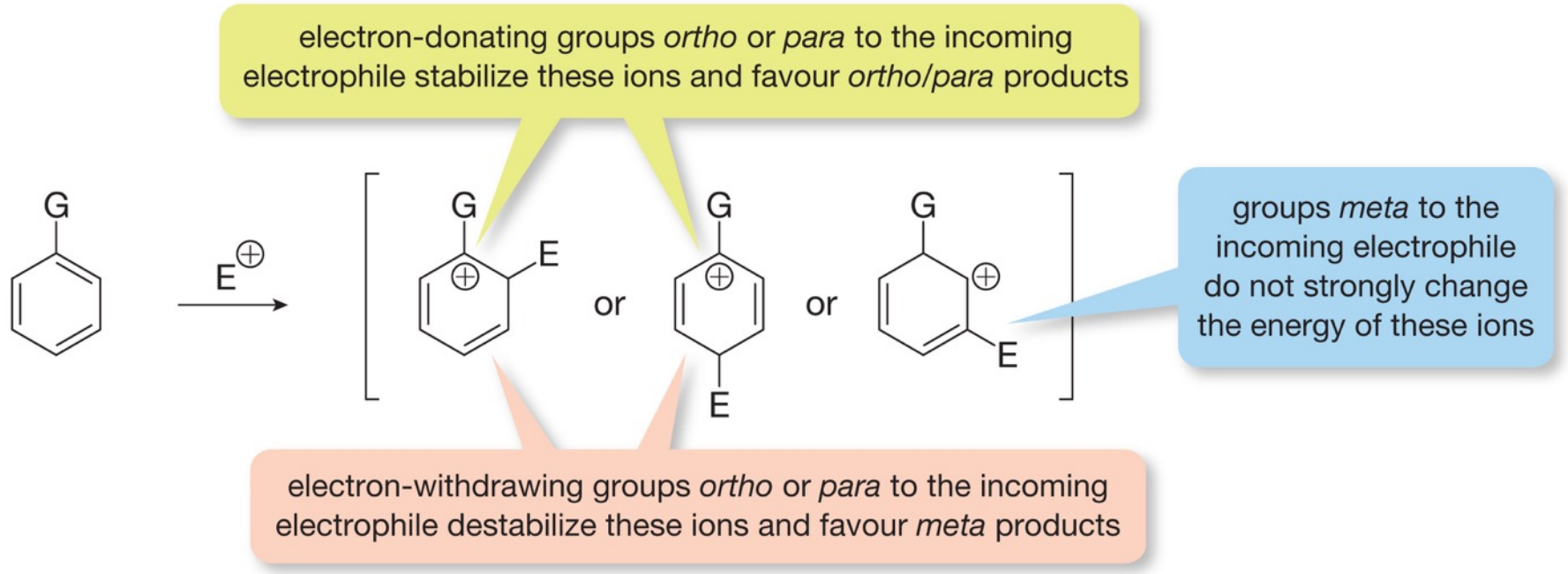


Patterns in S_EAr Reactions

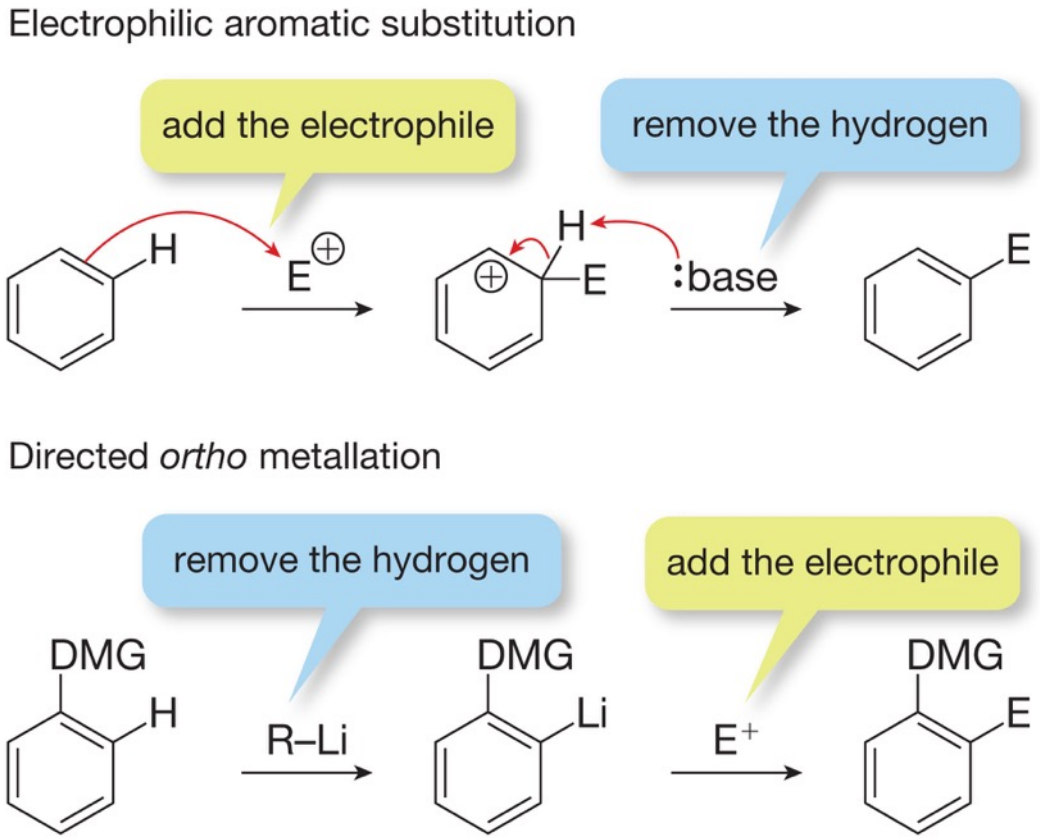


- The reactivity and regioselectivity of substituted aromatic rings is controlled by the nature of the substituents.
- In general, EDGs activate the ring and direct to the ortho/para positions. EWGs deactivate the ring and direct to the meta positions.

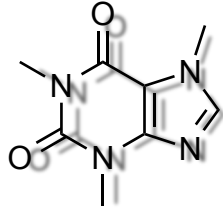


Patterns in S_EAr Reactions

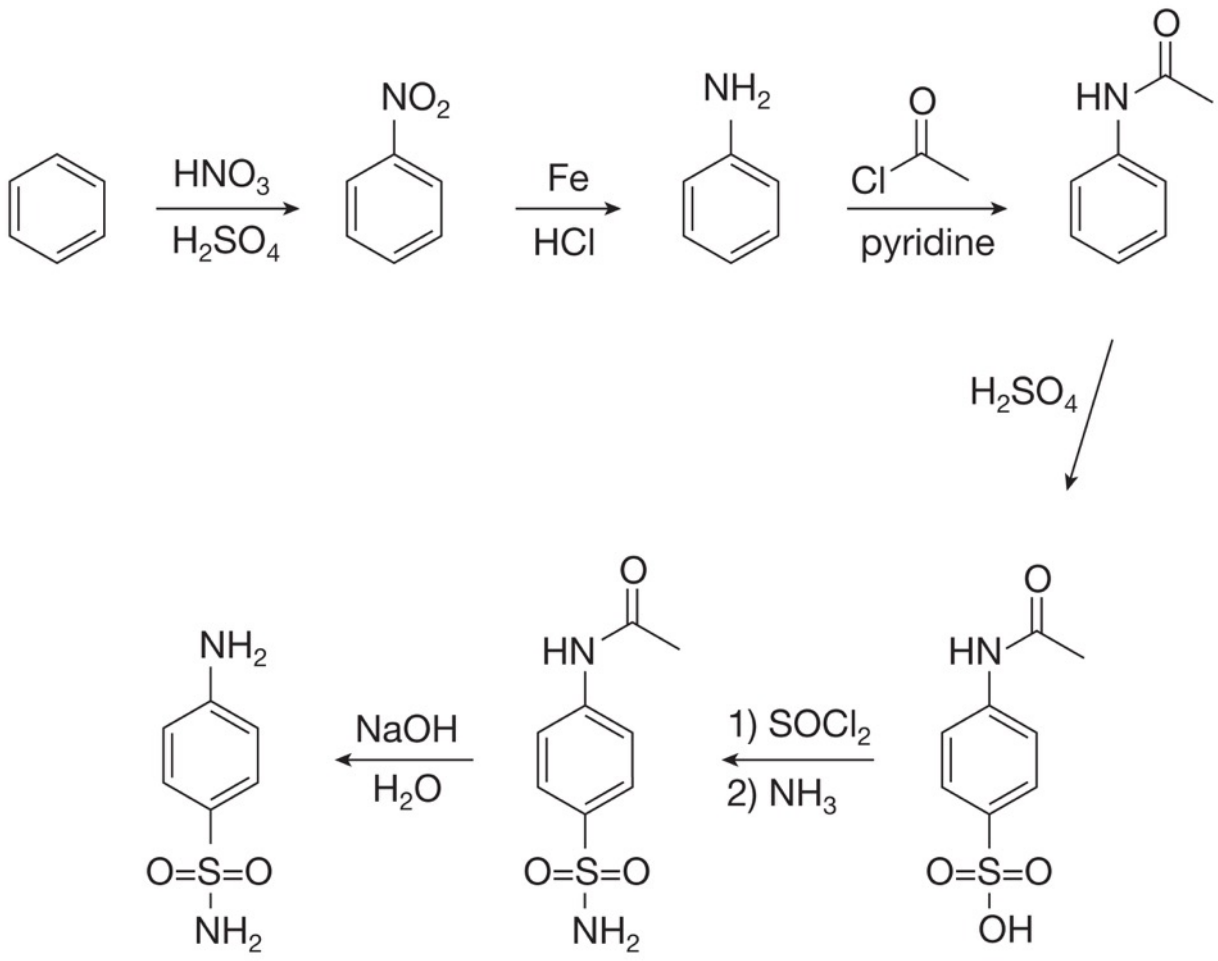
- Directed ortho metalation (DOM) is an alternative to electrophilic aromatic substitution. The steps for DOM are reversed from those of S_EAr.
- DOM requires a directed metalation group with substitution occurring only at the ortho position.



Patterns in S_EAr Reactions



- Sulfanilamide was the first antibiotic* to be a commercial success.
- It is easily made from benzene using mostly S_EAr reactions.



**Sulfanilamide is not a true antibiotic. It is more accurately described as an antimetabolite.*