Objective 7. Apply addition and elimination concepts to predict electrophilic aromatic substitution reactions (EAS) of benzene and monosubstituted benzenes.

Skills: Draw structure
ID structural features and reactive sites (alpha C, beta C, LG, etc.)
ID Nu^- and E^+
use curved arrows to show bonds breaking and forming
show delocalized electrons with resonance structures.

Key ideas:
In EAS, pi bond is Nu and undergoes addition.

Carbocation intermediate undergoes elimination to form substitution product, not addition product.

Some groups activate ring, others deactivate ring.

π Bonds are Nucleophiles
π Bonds undergo Addition Reactions
Simple Alkenes, Conjugated Dienes, and Arenes have π Bonds

What is the correct ranking in order of $Nu:^-$ strength (reactivity with E^+)?

a. Arenes > Conjugated Dienes > Simple Alkenes

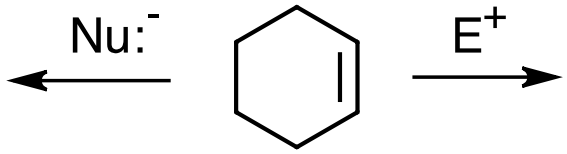
b. Conjugated Dienes > Arenes > Simple Alkenes

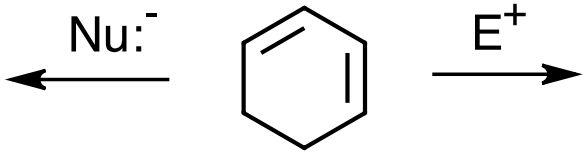
c. Simple Alkenes > Conjugated Dienes > Arenes

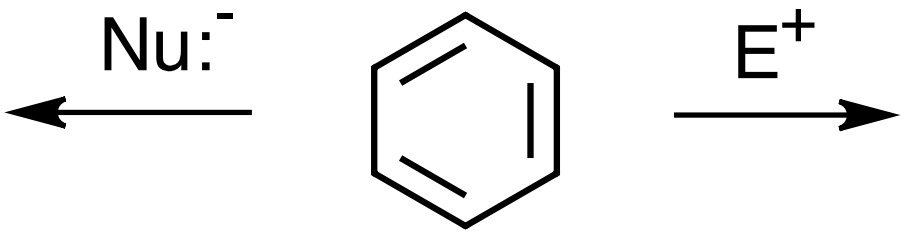
Give reasons for your ranking.

OChem Objectives:

(1) given reactants and reaction conditions ==> predict products. Determine all possible products. Use curved arrows to show bonds breaking and forming.





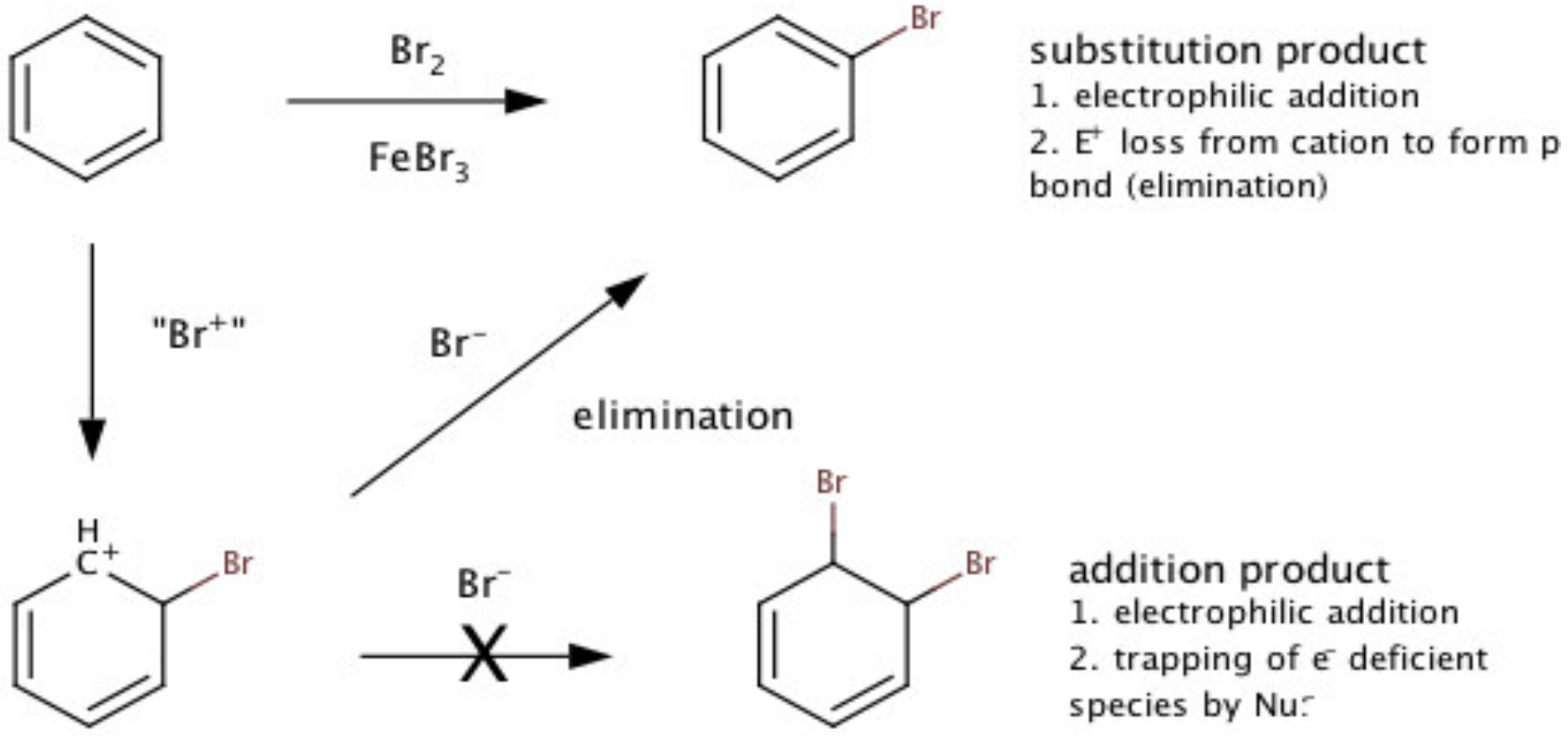


Remember: Keep track of the H's.

How do carbocations react?

Electrophilic Aromatic Substitution (EAS) Occurs in Ring

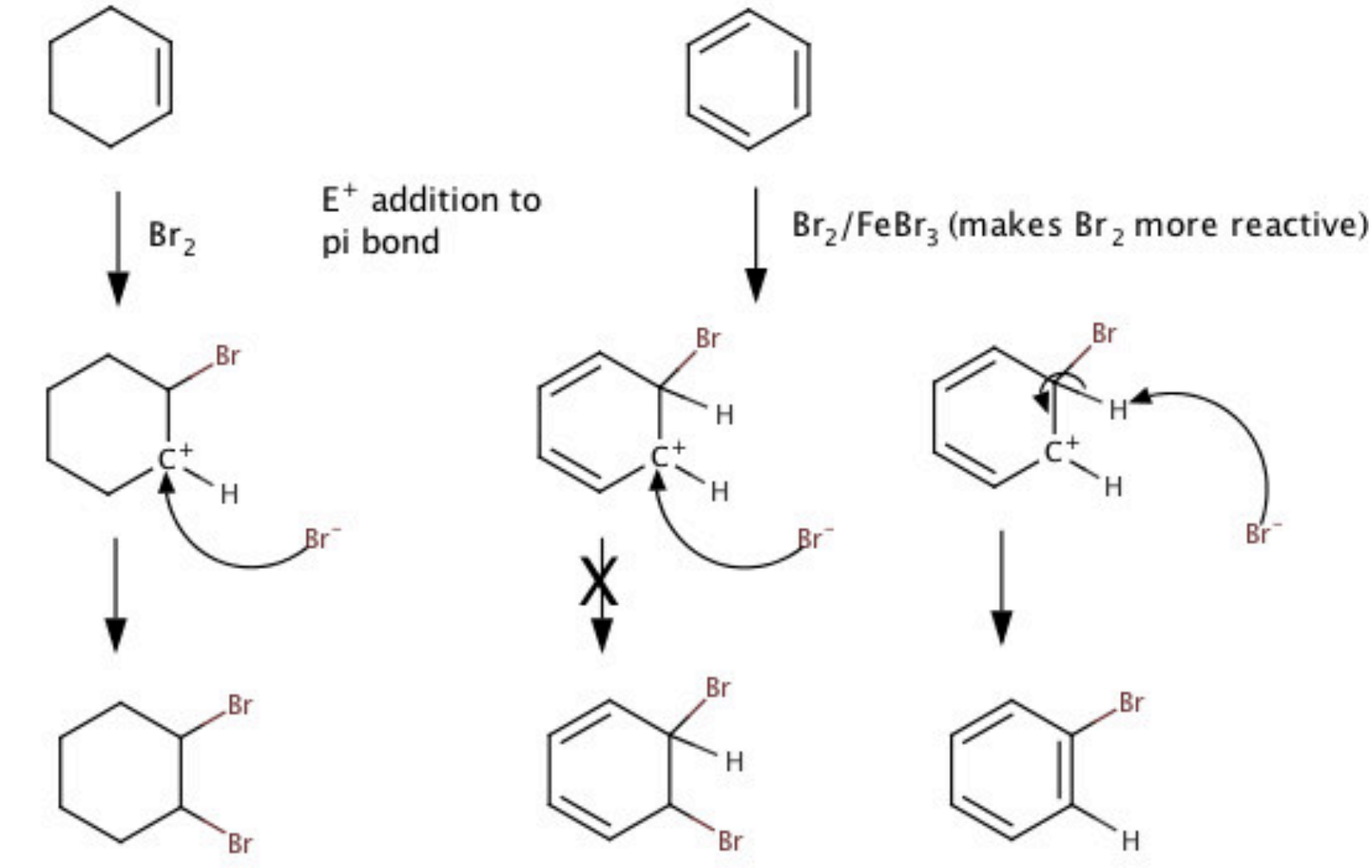
Aromatic pi bond is a **weaker** nucleophile than simple pi bond. So, aromatic pi bond needs a **stronger** electrophile than simple pi bond for a reaction to occur.



EAS: Why Substitution and Not Addition?

Objective: describe EAS mechanism

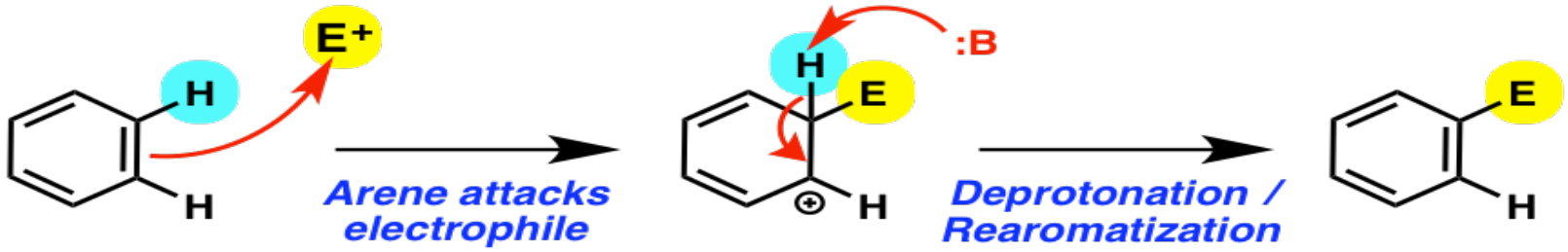
Alkenes undergo addition but aromatics undergo substitution



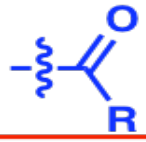
Conjugated diene is *less* stable than aromatic

From LearnBacon.com

Electrophilic Aromatic Substitution (EAS)

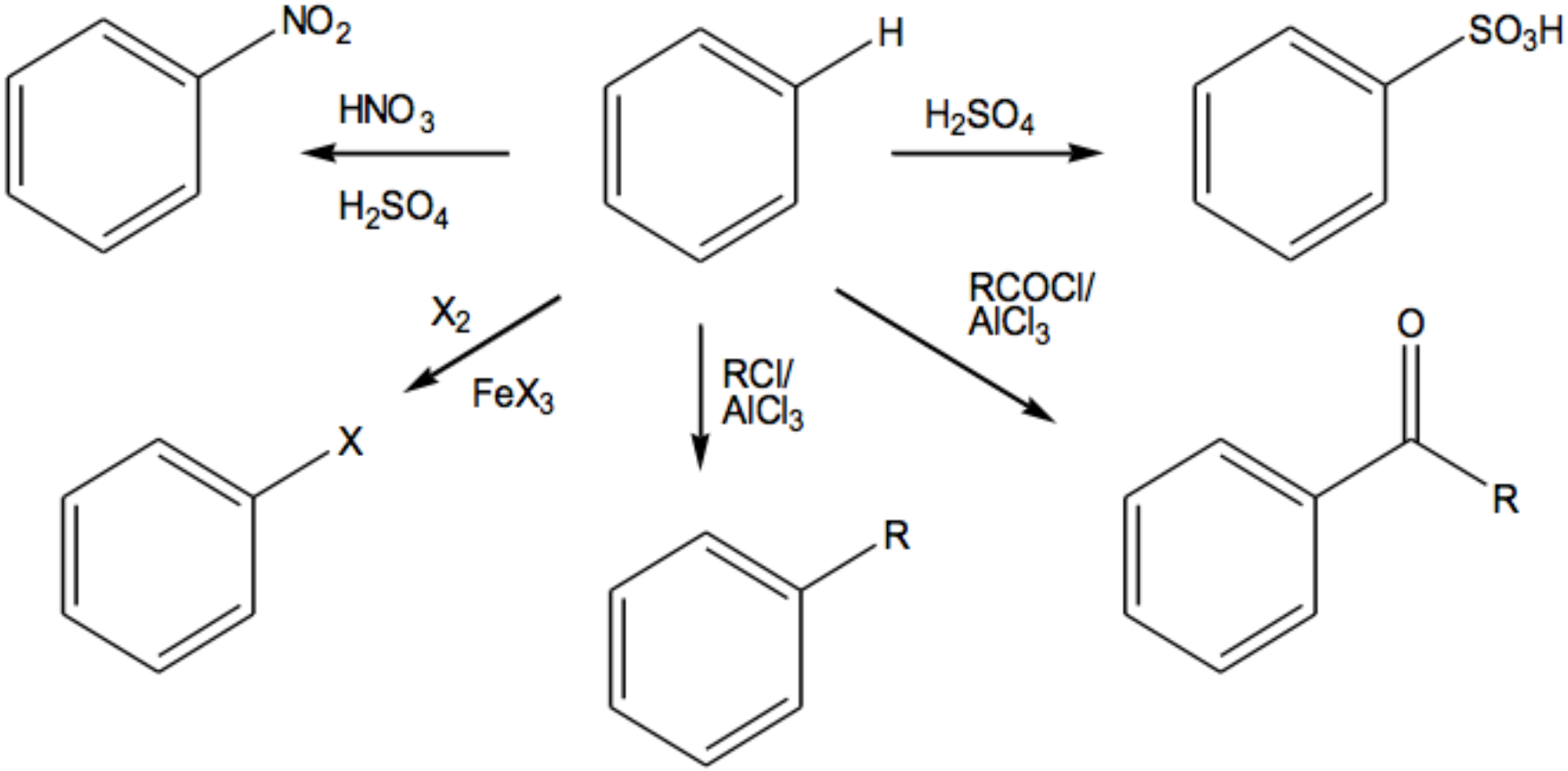


Several common EAS reactions are shown below. Pay special attention to the boxed ones in red, as you will see these within this tutorial.

E =		
	-alkyl	Friedel–Crafts Alkylation
		Friedel–Craft Acylation
	$-NO_2$	Nitration
	$-SO_3H$	Sulfonylation
	-halide	Halogenation

Use Electrophilic Aromatic Substitution (EAS) to Replace H with Functional Group

Benzene --> monosubstituted benzene --> di-, trisub benzene

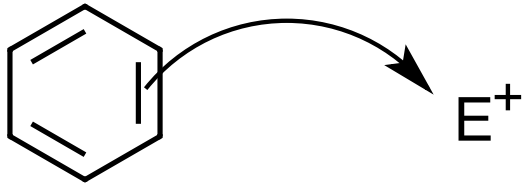


Substitute NO_2, SO_3H, X, R, COR for H

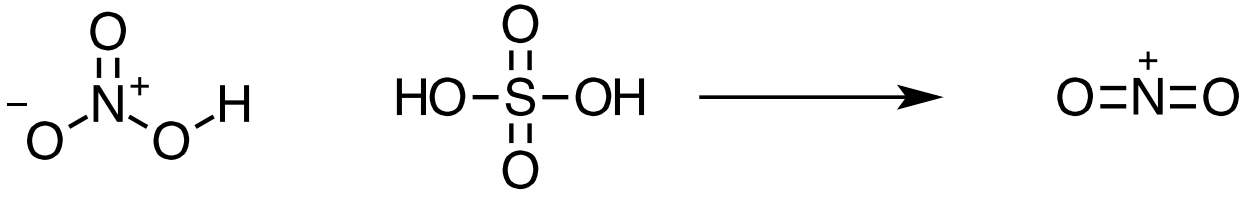
-R and -COR are Friedel-Crafts rxns. See Klein, p. 870 for limitations.

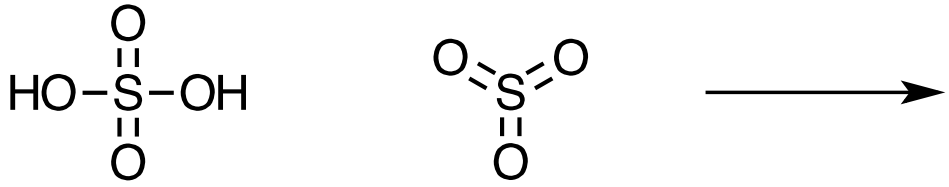
Aromatic pi bonds are poor Nu:$^-$

Need a very strong E^+



X_2/AlX_3 ⟶ X^+ AlX_4^-





concentrated (fuming) H_2SO_4

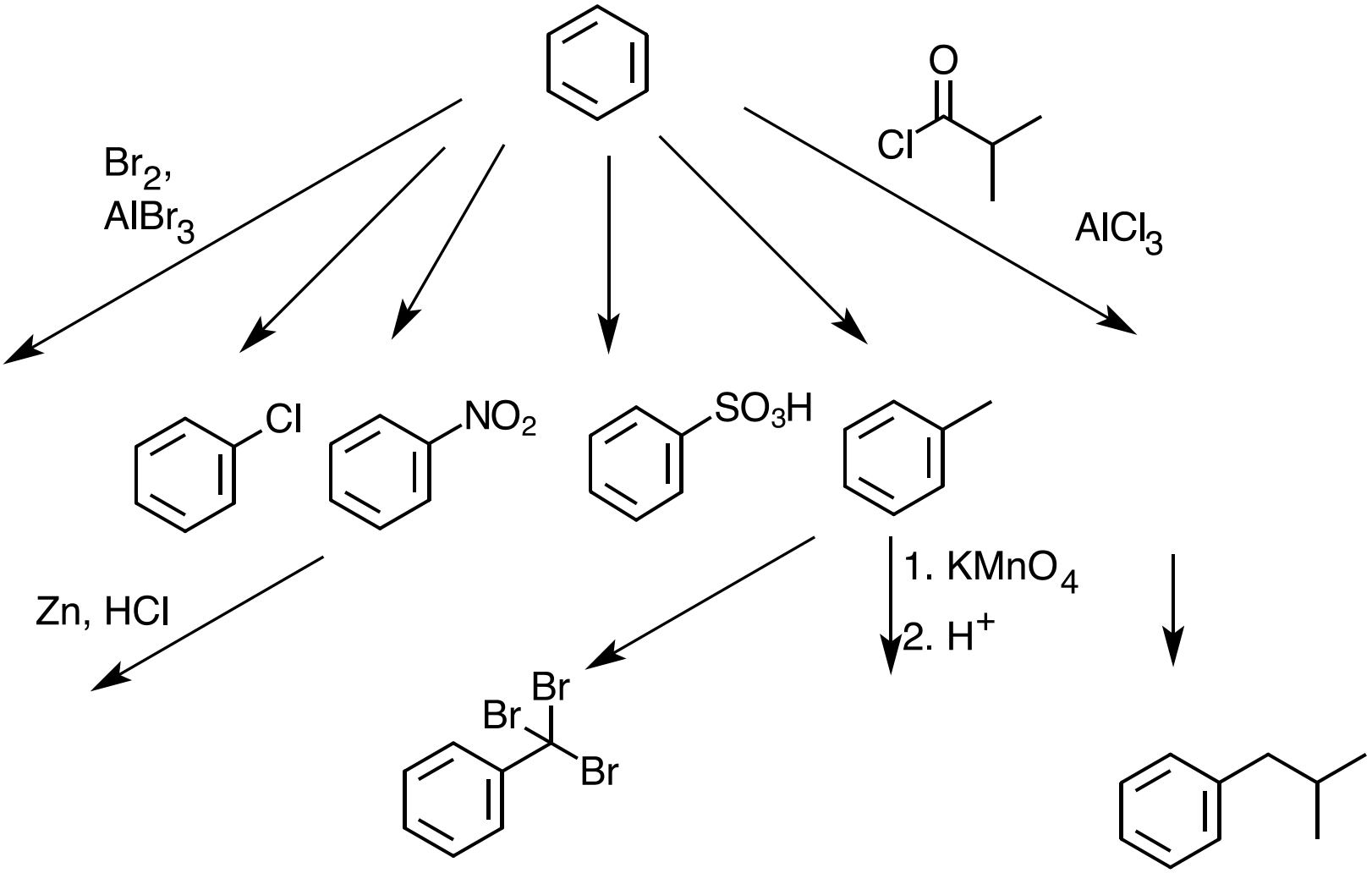
See Practice Problems

$RCl/AlCl_3$ ⟶ R^+ AlX_4^-

$RCOCl/AlCl_3$ ⟶ ??

Problem solving steps: 1. Identify functional group(s)
2. Relate reaction conditions to reaction type

Objective: Predict the product or ID the reaction conditions



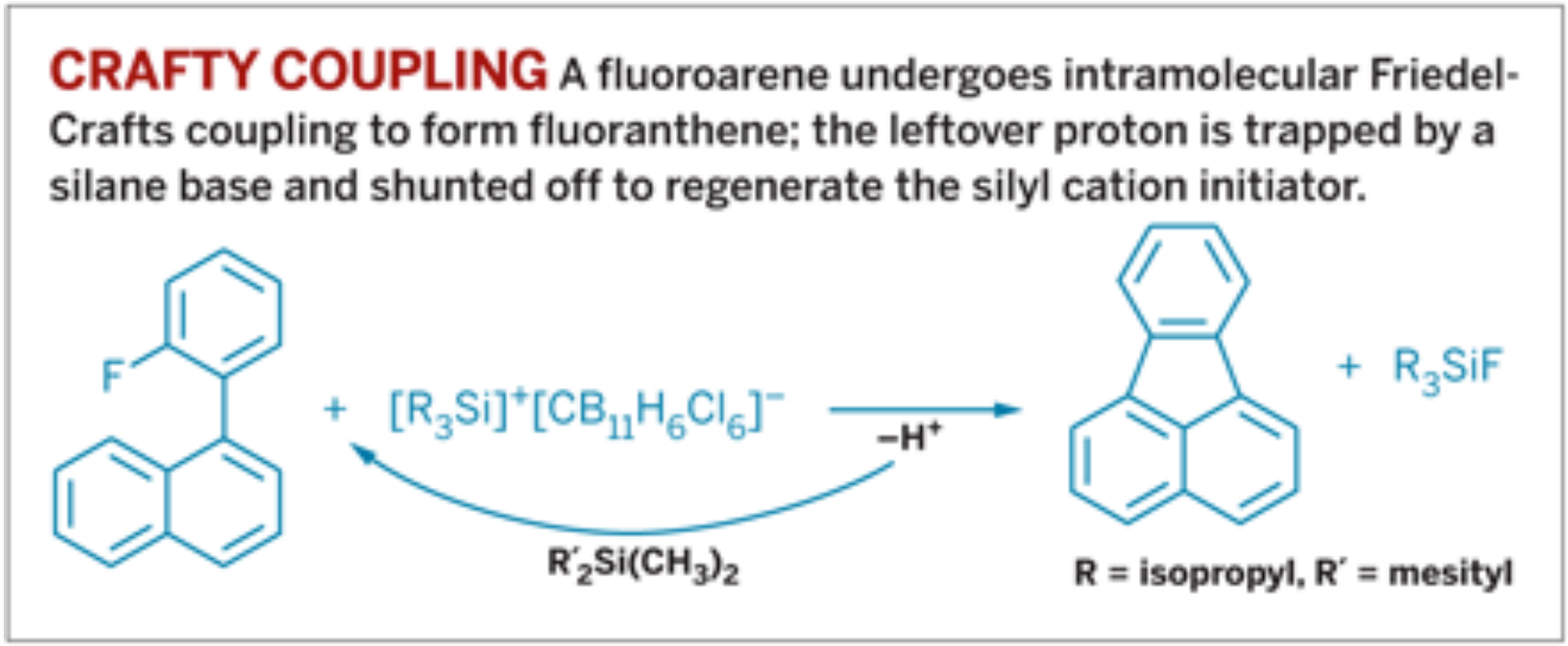
http://cen.acs.org/articles/89/i18/Friedel-Crafts-Takes-New-Gig.html

5/2/11, CEN, p. 9 Intramolecular Friedel-Crafts alkylation

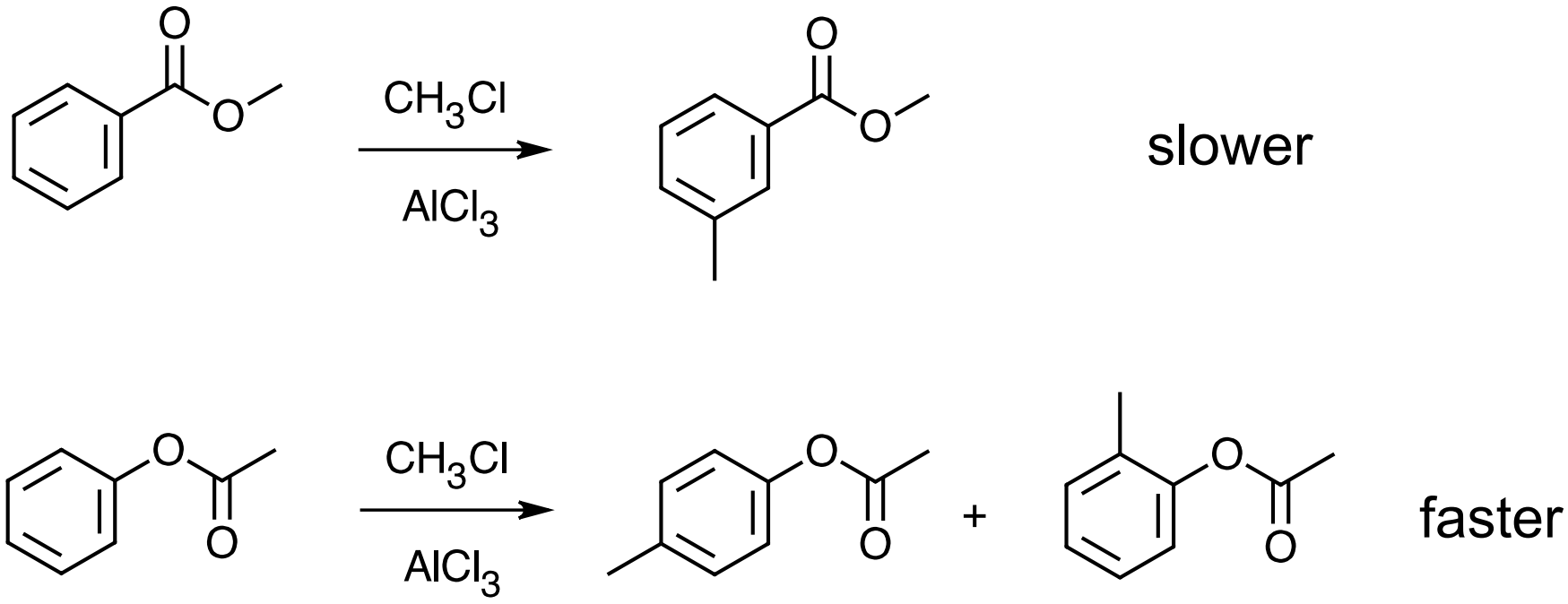
Lewis acid: triisopropylsilyl cation as a paired with a weakly coordinating carborane anion (compare to $AlCl_3$).

The R_3Si^+ activates C-F bond (compare to CH_3Cl).

Favored by thermo: Si-F bond is stronger than C-F bond

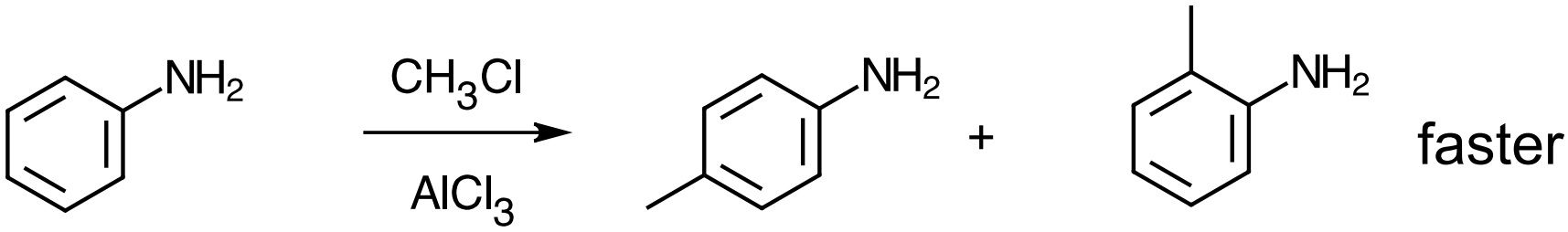


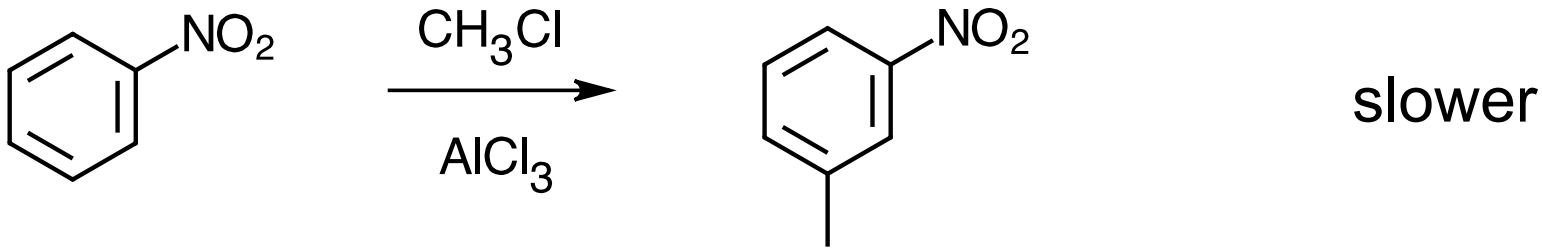
EAS of monosubstituted benzenes:



Experiments show different rates and substitution at different position.

EAS of monosubstituted benzenes:



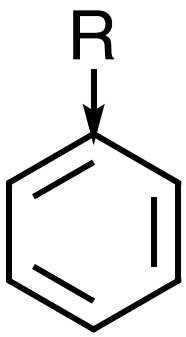


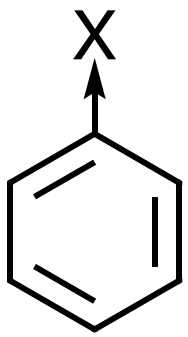
Experiments show different rates and substitution at different position.

For substituted (mono or higher) benzene, the *Substituent* (group) on benzene determines the:

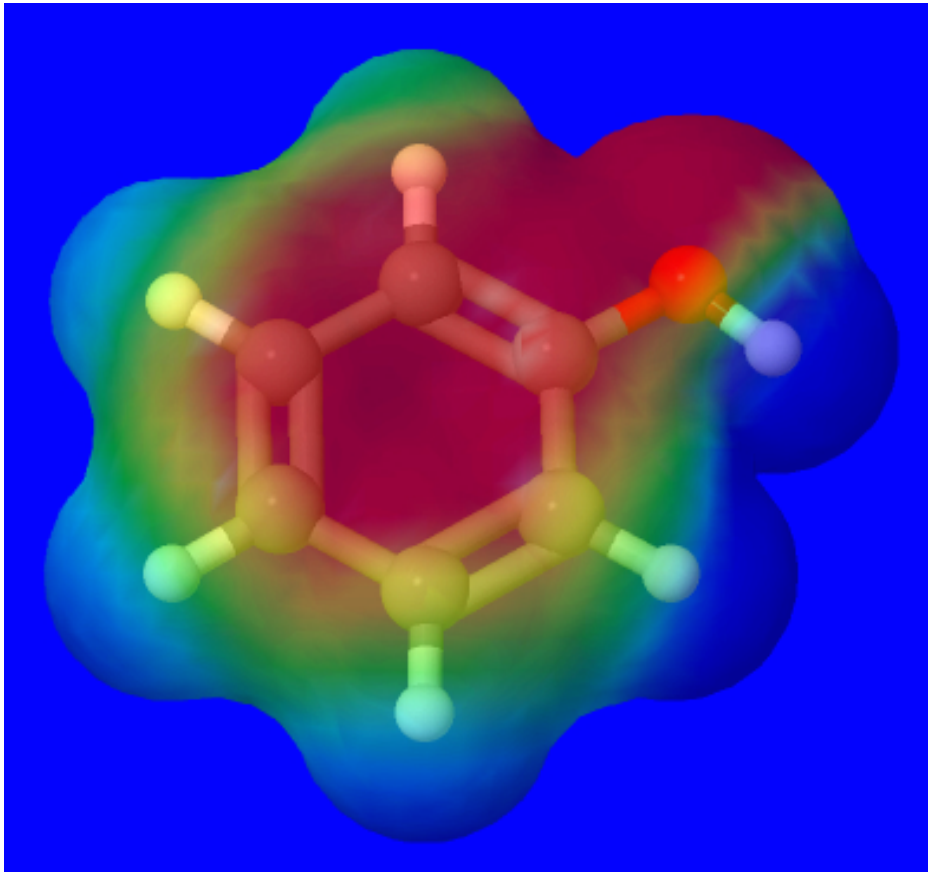
- position of substitution (ortho, meta, or para)
- rate of reaction

Electron Donating Group	Electron Withdrawing Group
Activates π e^- in ring	Deactivates π e^- in ring
Faster reaction	Slower reaction
Ortho, para director	Meta director
-NHR -OH, -OR, -OCOR -R	-X (but o, p director) -COR, -CHO, -COOH, -COOR -CN, $-NO_2$

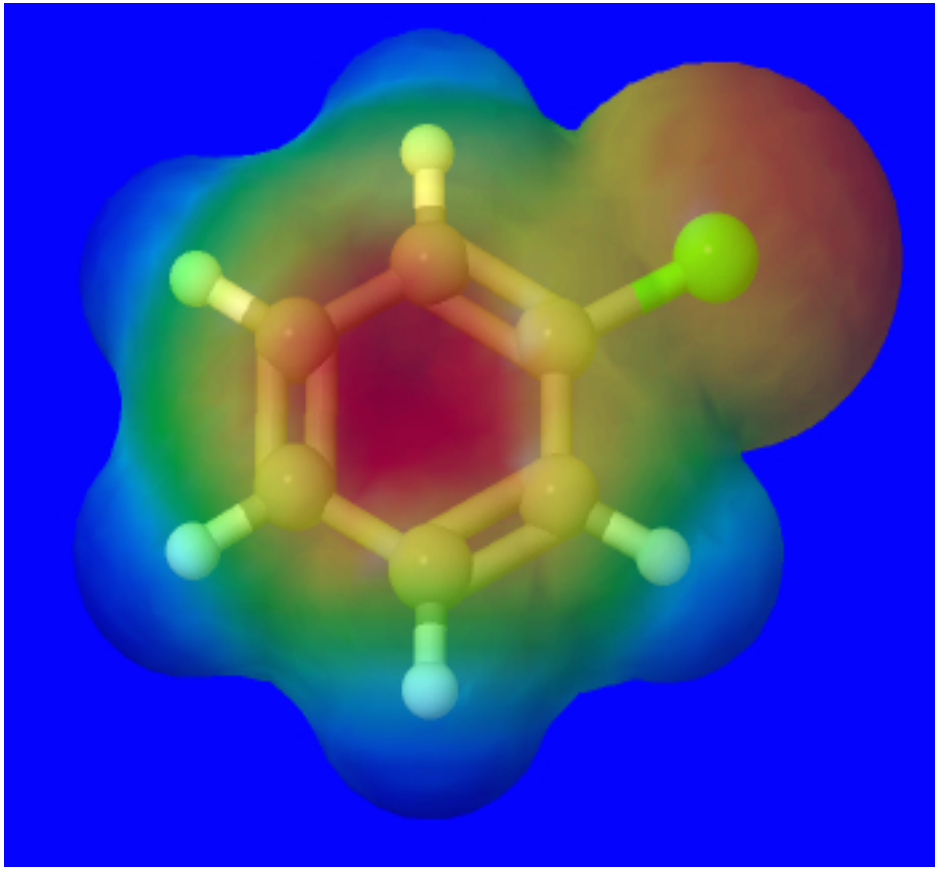




Electron donating groups Activate Ring
E.g., OH (see chemagic.com)



Electron withdrawing groups Deactivate Ring
E.g., Cl (see chemagic.com)

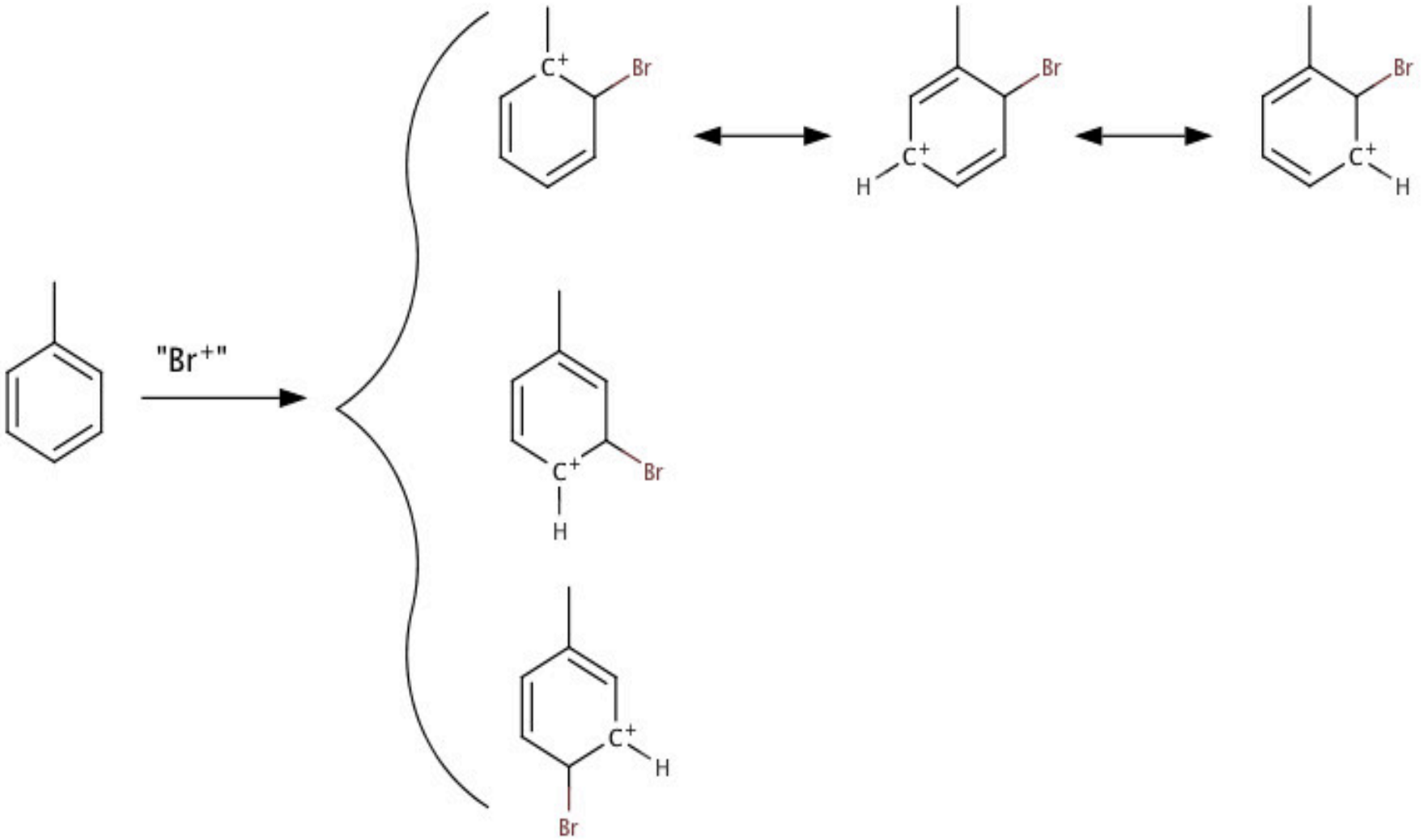


Why are electron donating groups ortho, para directors?

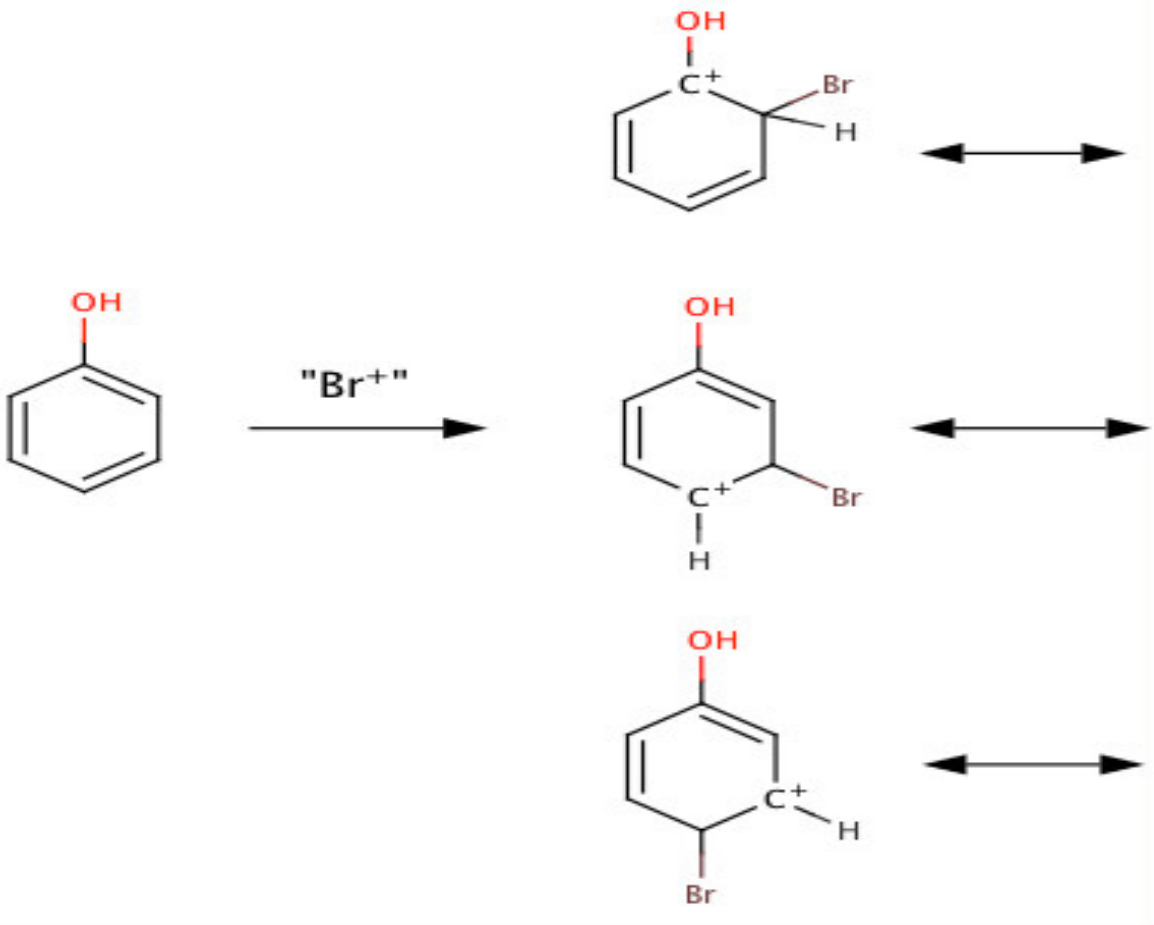
E.g., R = CH_3 is electron donating and activates ring.

Draw resonance structures for each intermediate.

Which resonance structures are the most stable?



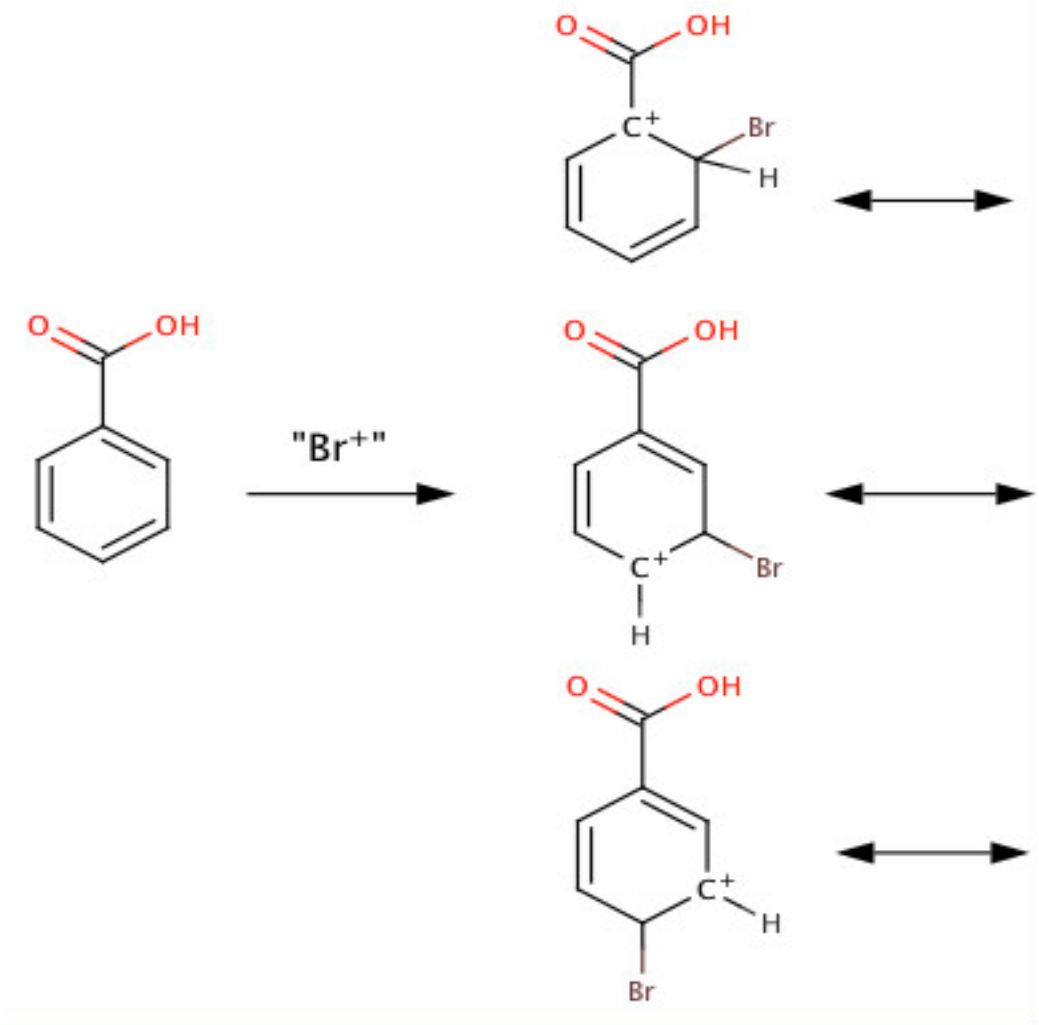
You may expect -OH to be electron withdrawing and deactivating but it is the electron donating and strongly activating. Why?



Atoms with l.p. adjacent to ring are electron _____ and ____.
E.g., O in alcohol, ether, ester; N in amine, amide

Why are electron withdrawing groups meta directors?

Which resonance structures are the most stable? Why?



C=O (carbonyl) bonded to ring are e^- _____ and _____.

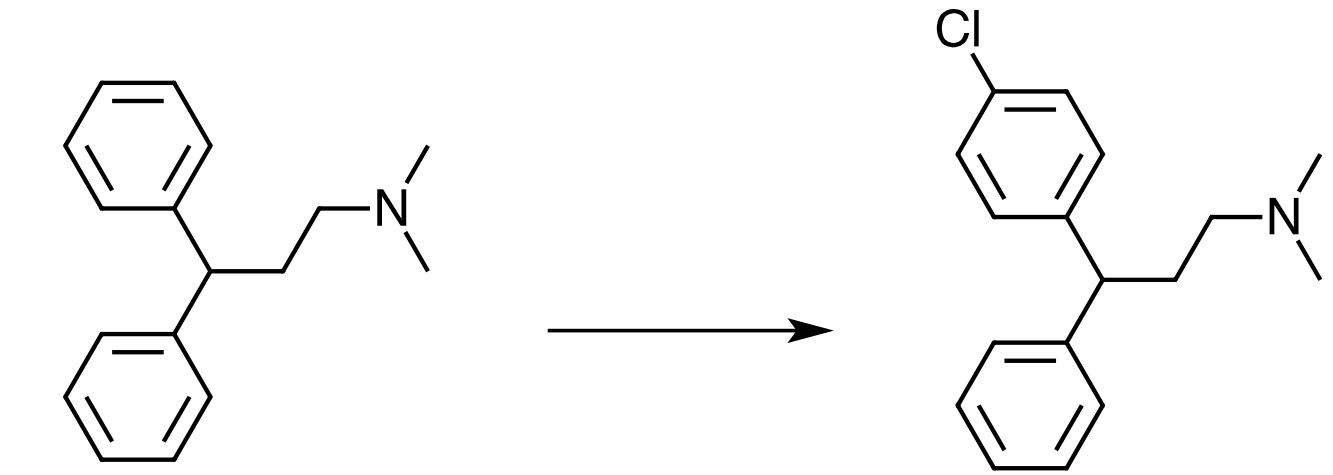
E.g., acid, aldehyde, ketone, ester.

1. Identify each group as a ortho, para director or meta director:

Cl	ortho, para director	meta director
C_2H_5	ortho, para director	meta director
CHO	ortho, para director	meta director
OH	ortho, para director	meta director
NO_2	ortho, para director	meta director
NH_2	ortho, para director	meta director

2. Name one limitation of the Friedel-Crafts alkylation reaction.

Halogenation in Drug Design (Klein, "Organic Chemistry," p. 863)



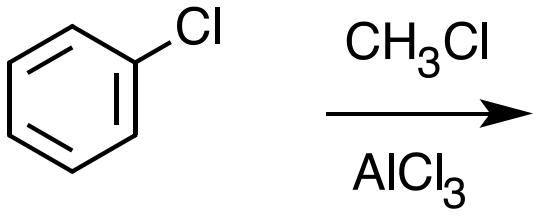
pheniramine

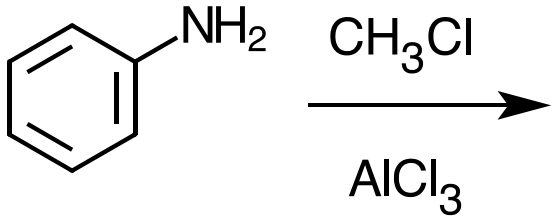
chlorpheniramine
antihistamine

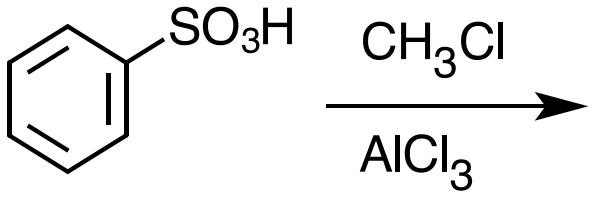
Identify the reaction conditions.

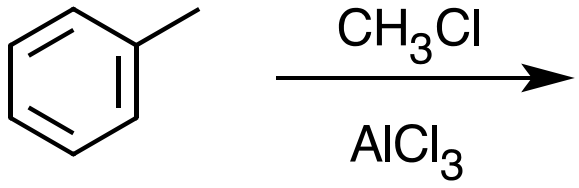
Cl substitution occurs ortho to R group because _____.

Objective: Predict EAS product of monosubstituted benzene









EAS to Functionalize Benzene

Benzene --> Substituted benzene --> disubstituted benzene