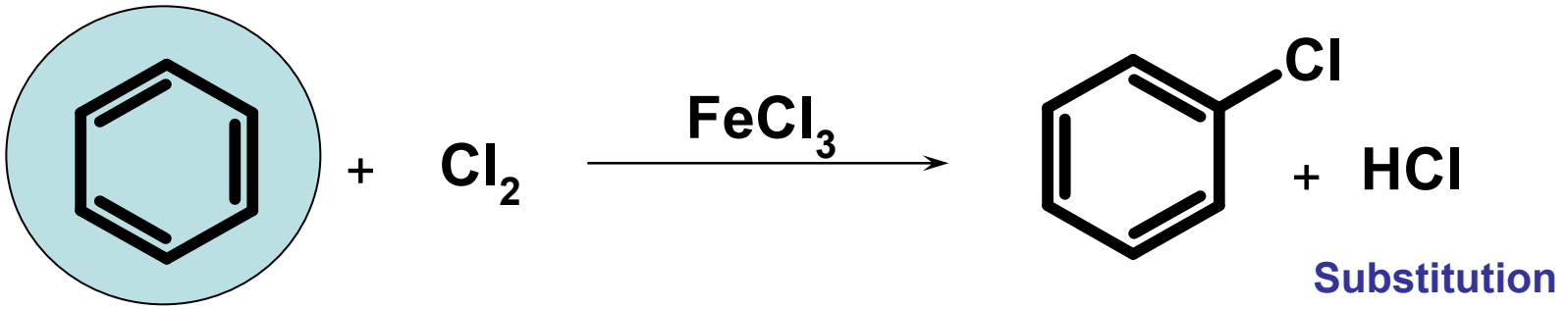
# AROMATIC SUBSTITUTION REACTIONS

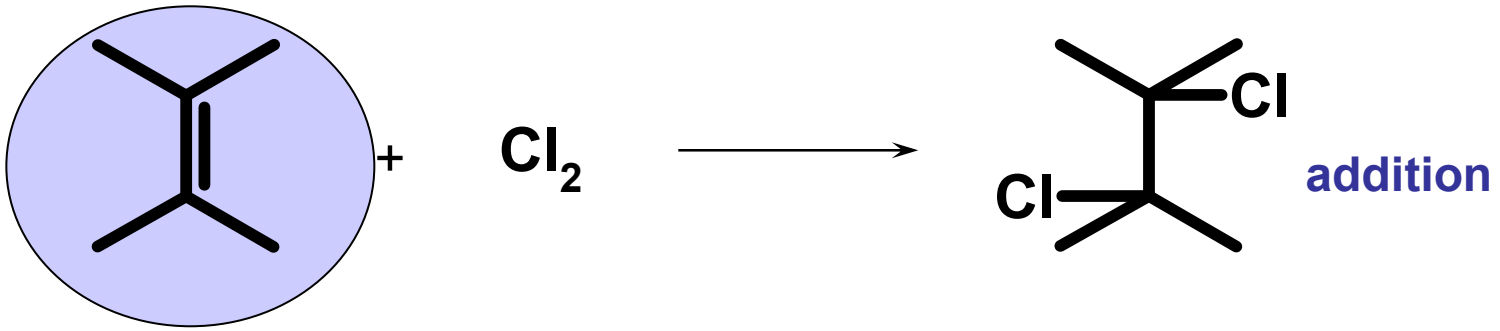
- **Electrophilic**
- **Nucleophilic**

# Benzene Reactivity

Benzene undergoes **substitution reactions** instead of **addition**.
It requires a strong electrophile




compare:



# Substitution….

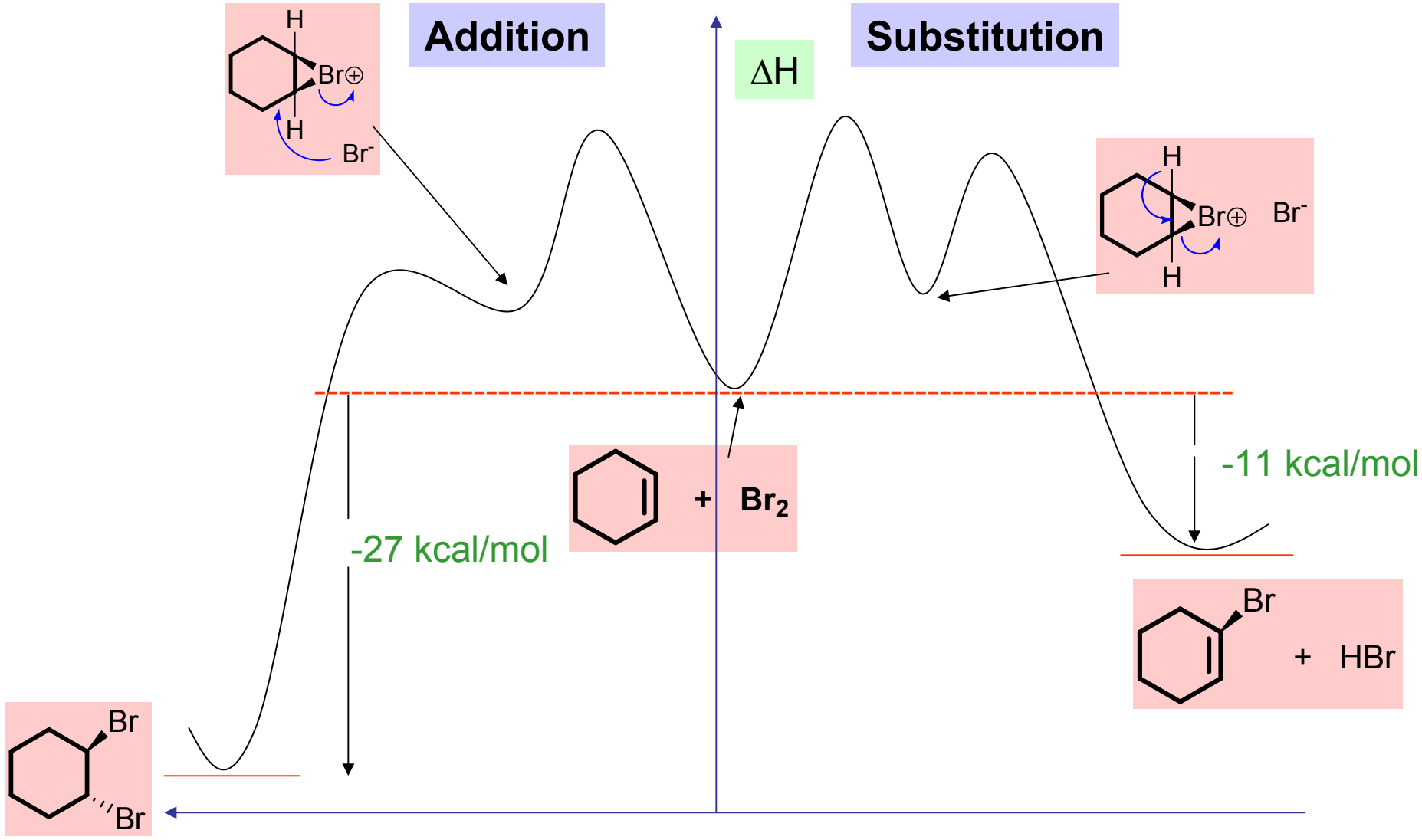
Why??

How??

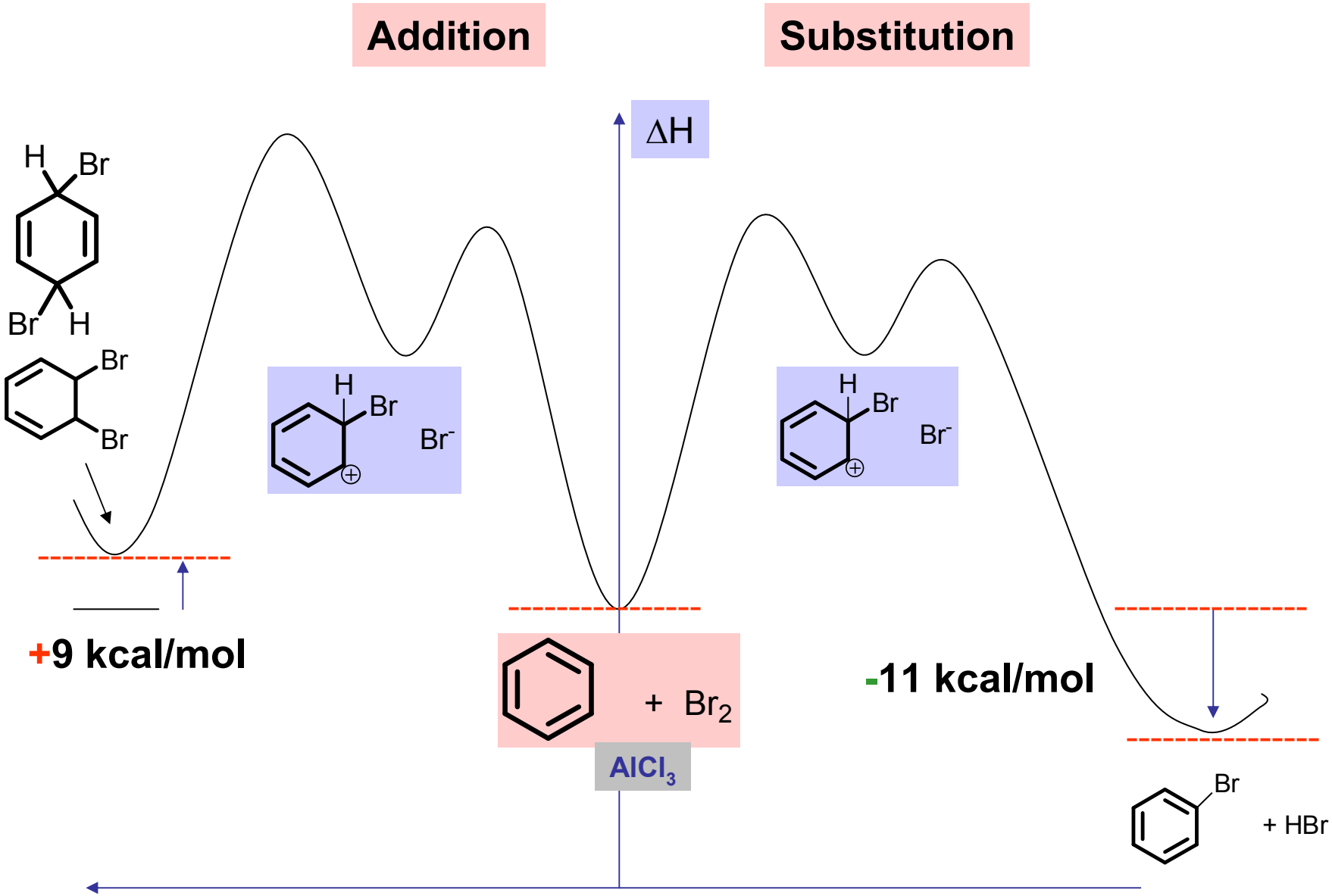
Influence of preexisting groups

Synthetic utility

Energy profile in the case of Olefins – Addition vs. Substitution

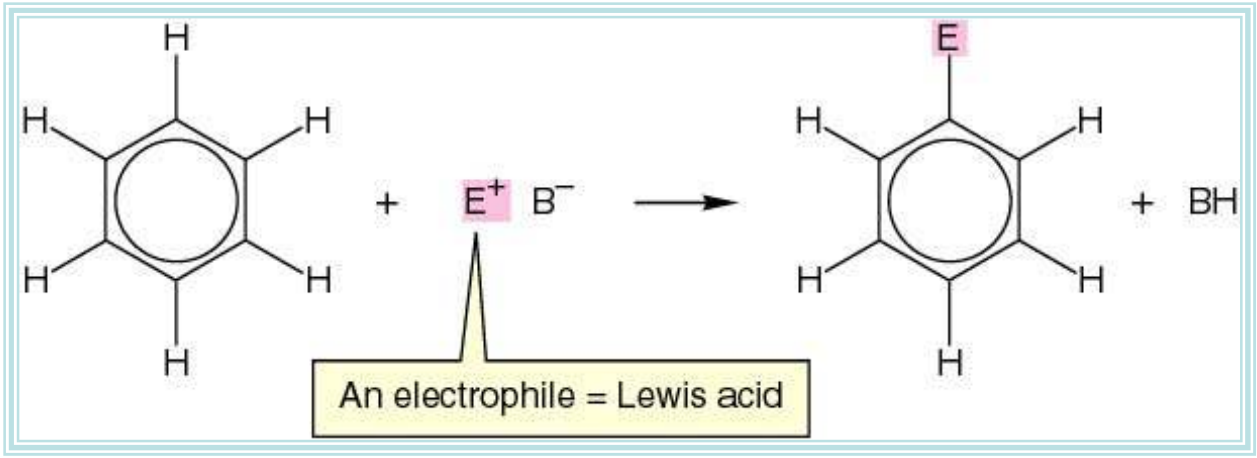


Energy profile in the case of Benzene – Addition vs. Substitution

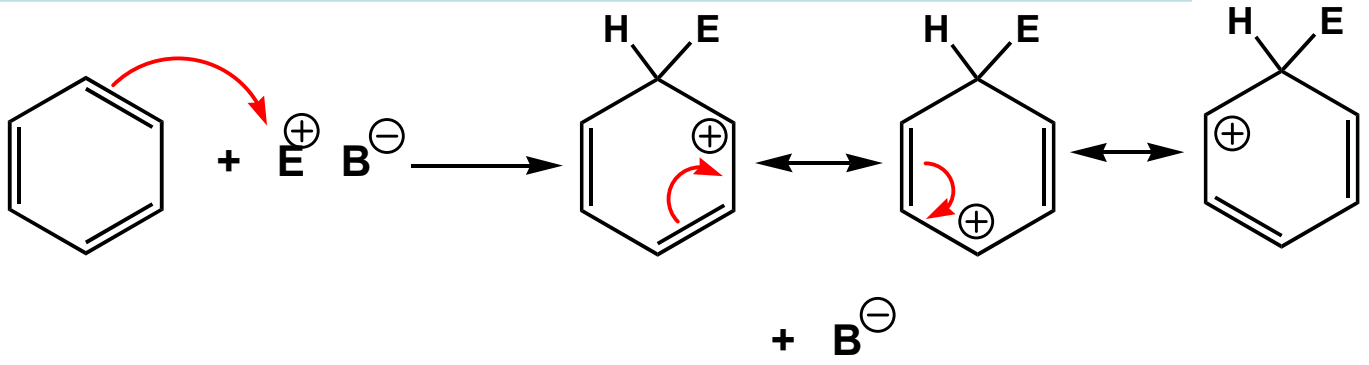


**How???**

# General reaction:

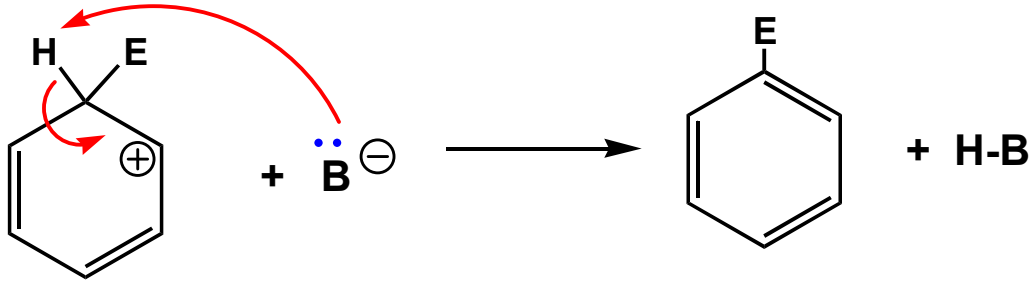



Step 1:

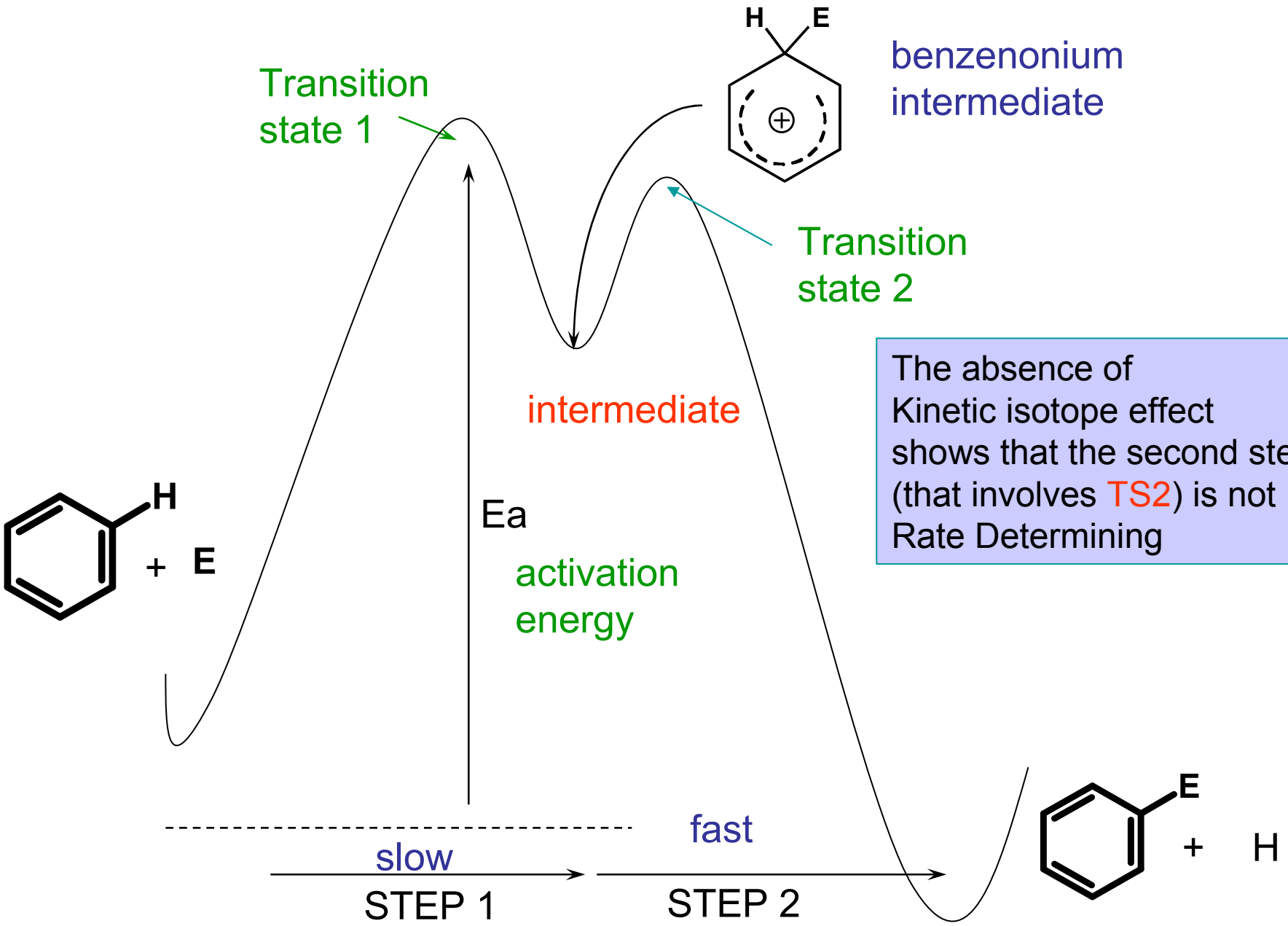



a stabilized cyclohexadienyl cation
(also called a benzenonium ion)

Step 2:



# Energy profile of aromatic substitution reaction



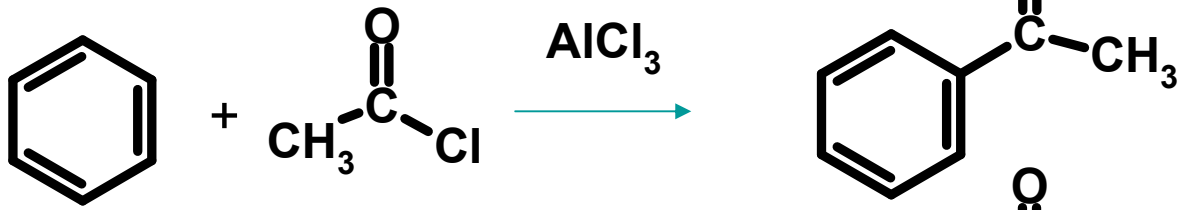

The absence of Kinetic isotope effect shows that the second step (that involves TS2) is not Rate Determining

# Substitution Reactions of Benzene

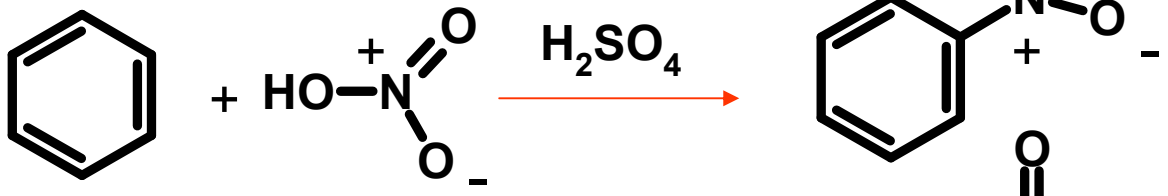
Halogenation


Friedel-Crafts Alkylation

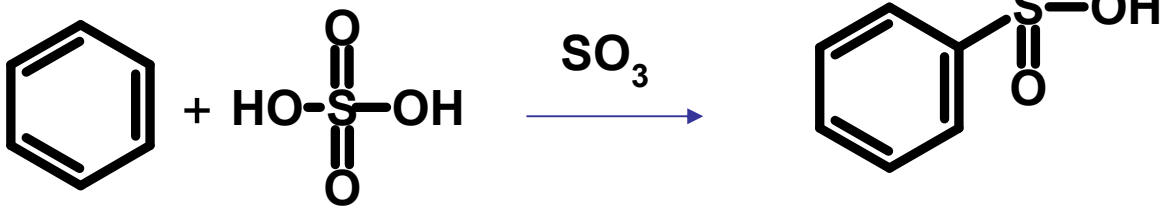

Friedel-Crafts Acylation



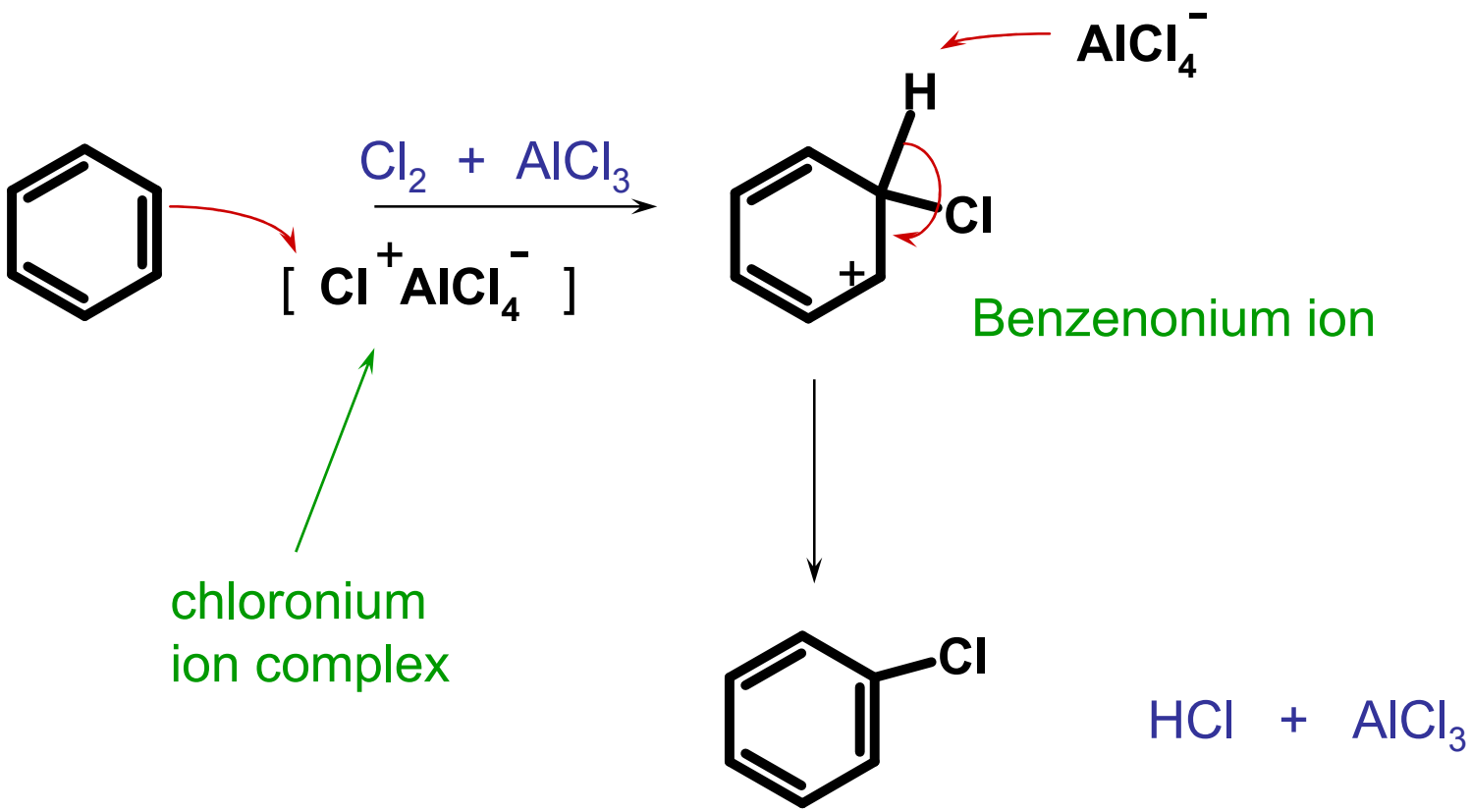

Nitration



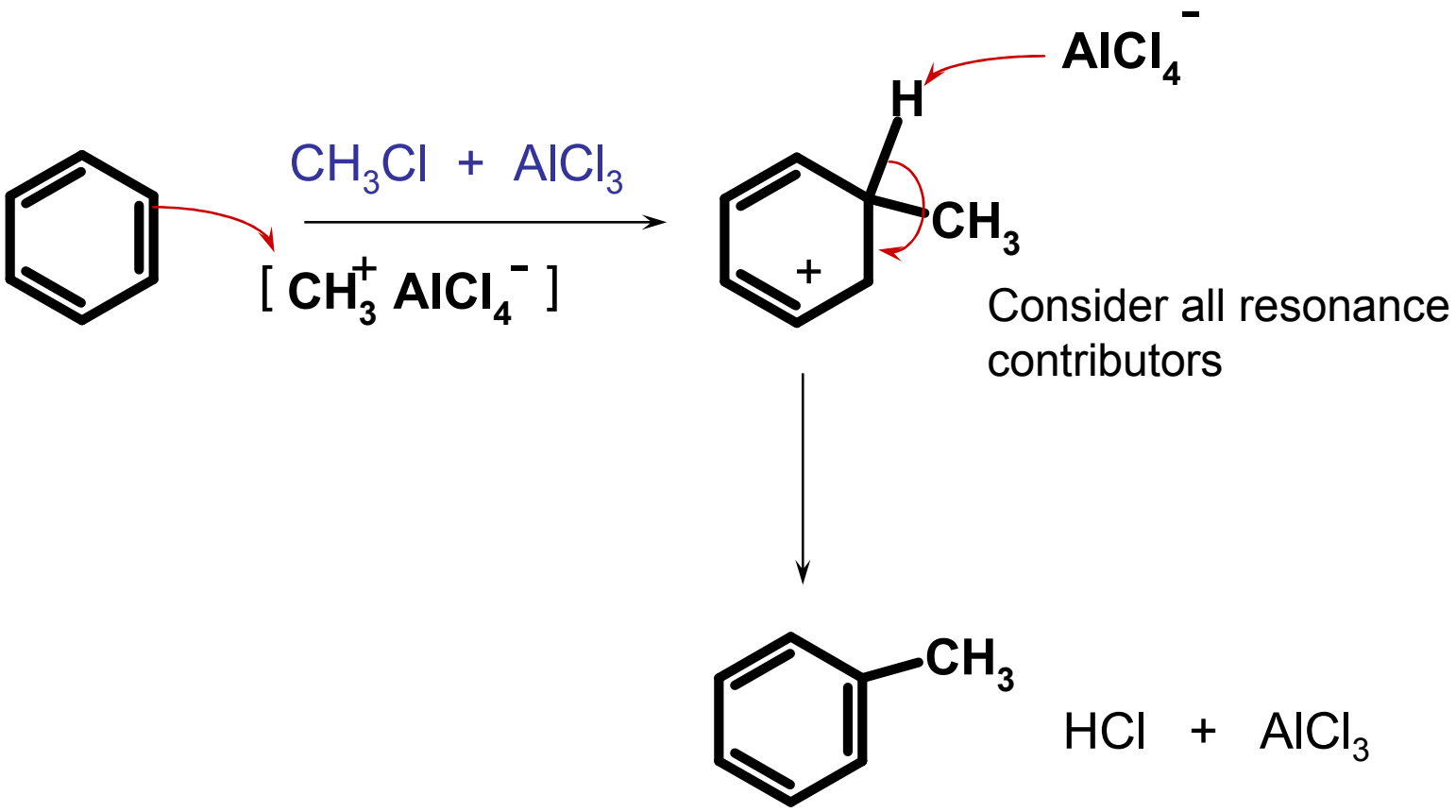

Sulfonation



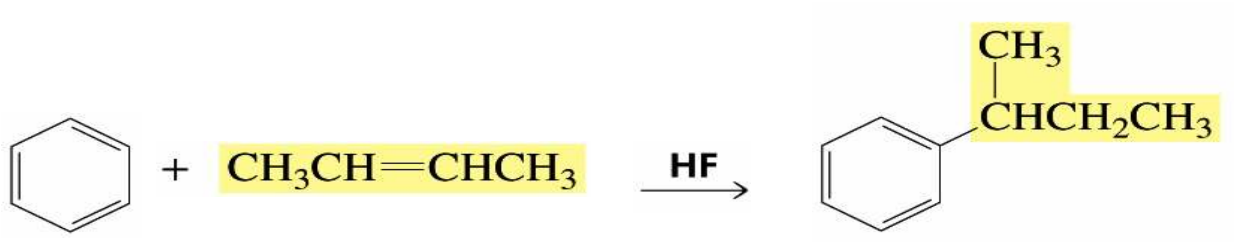
# Chlorination of Benzene



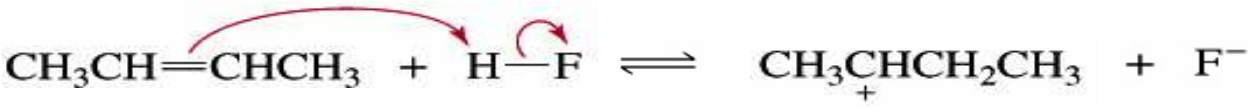
# Friedel-Crafts Alkylation

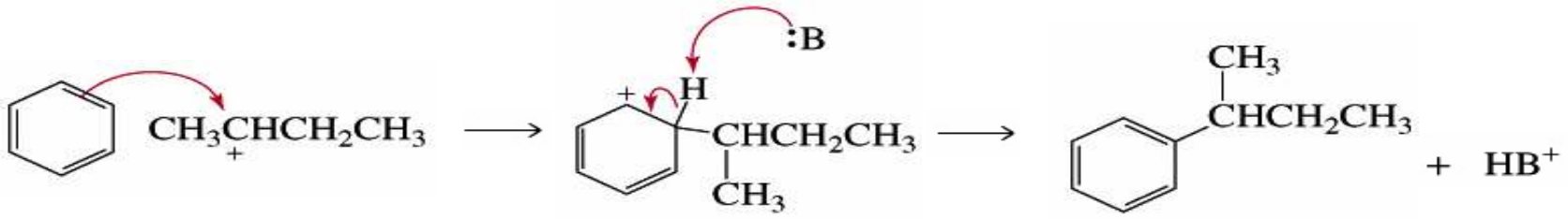


## alkylation of benzene by an alkene

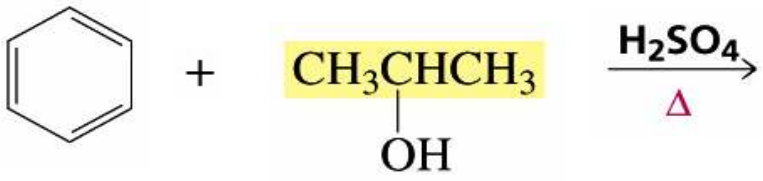


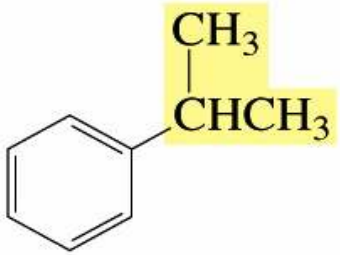

*sec*-butylbenzene



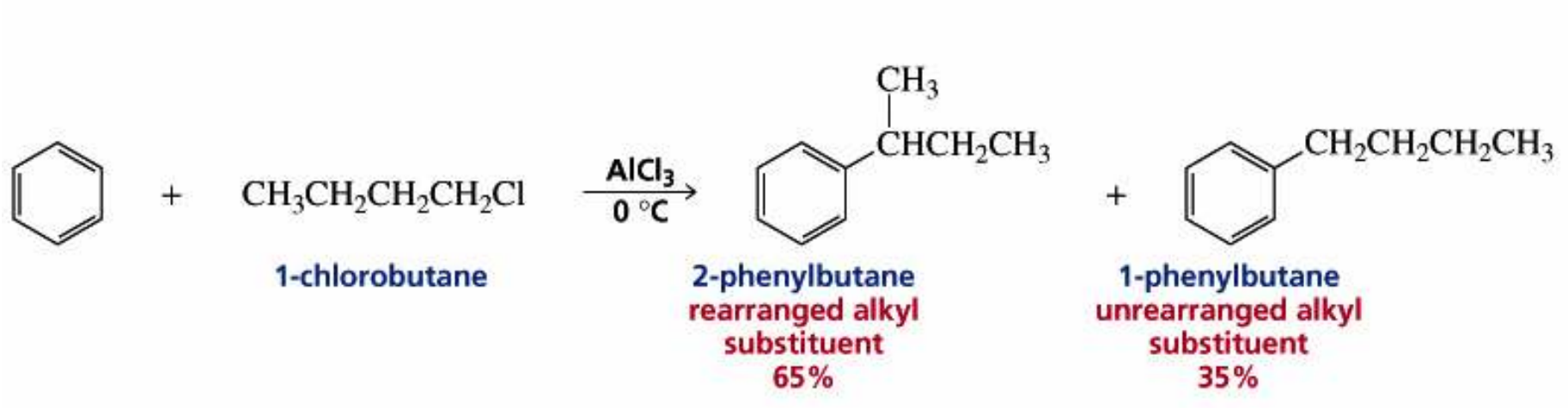

## alkylation of benzene by alcohol

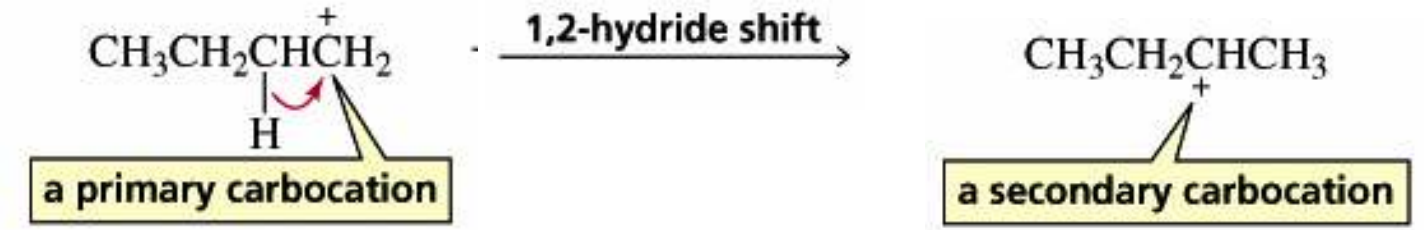


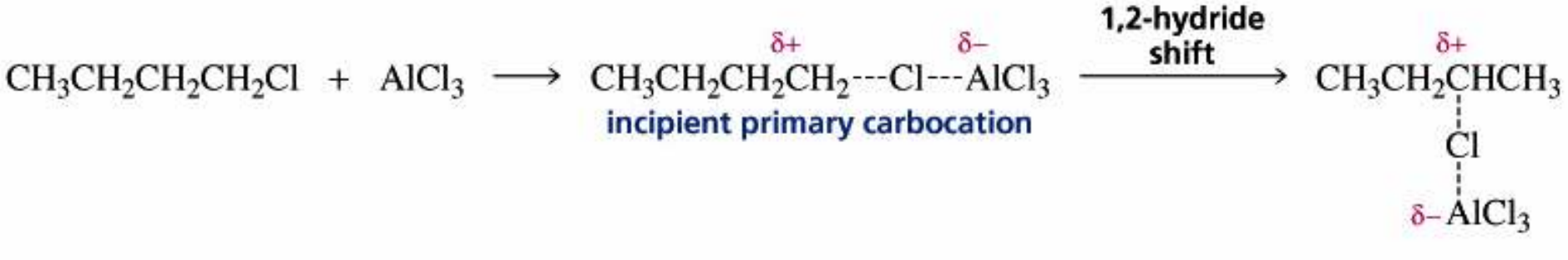



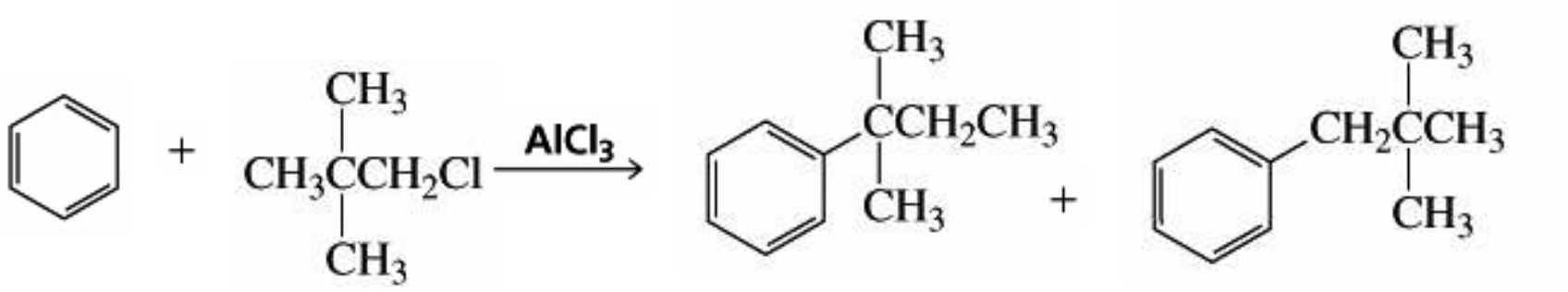

isopropylbenzene
cumene

# FC alkylations can give problems due to rearrangement of carbocations to more stable ones





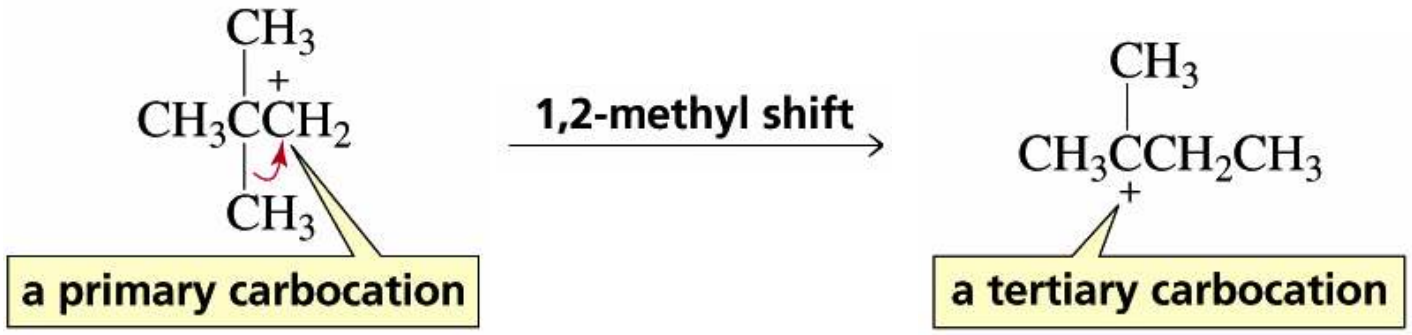

1-chloro-2,2-dimethylpropane

2-methyl-2-phenylbutane

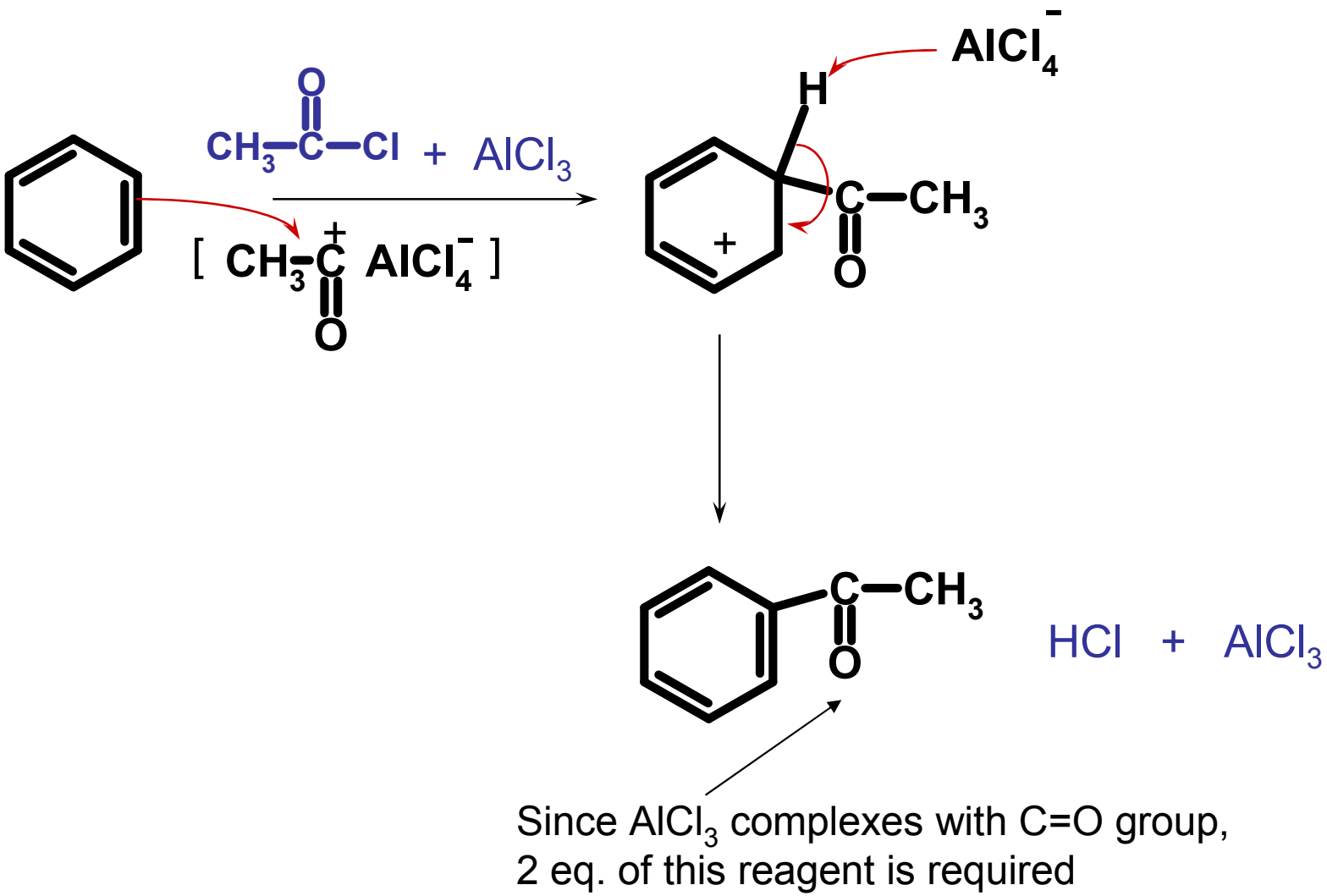
rearranged alkyl substituent 100%

2,2-dimethyl-1-phenylpropane

unrearranged alkyl substituent 0%

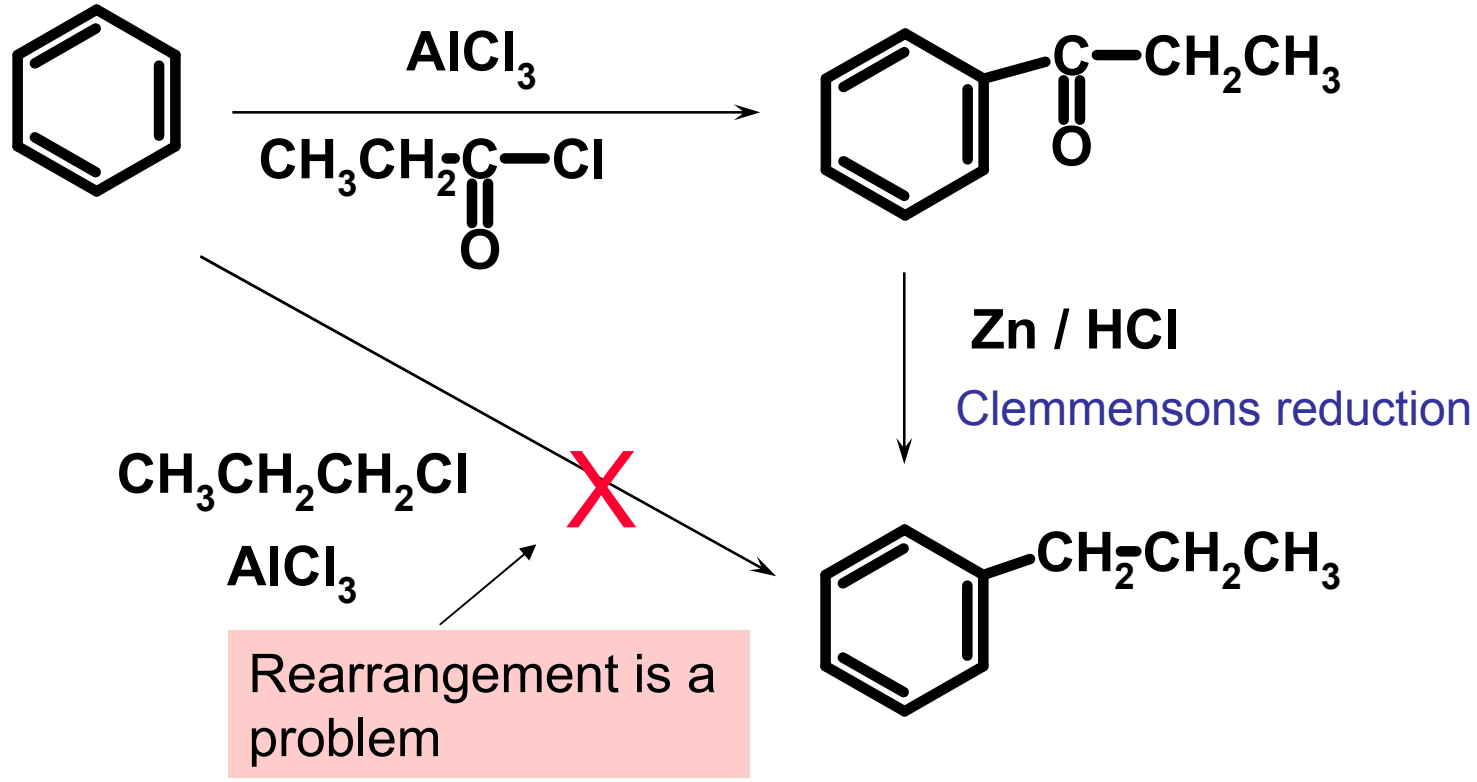


# Friedel-Crafts Acylation

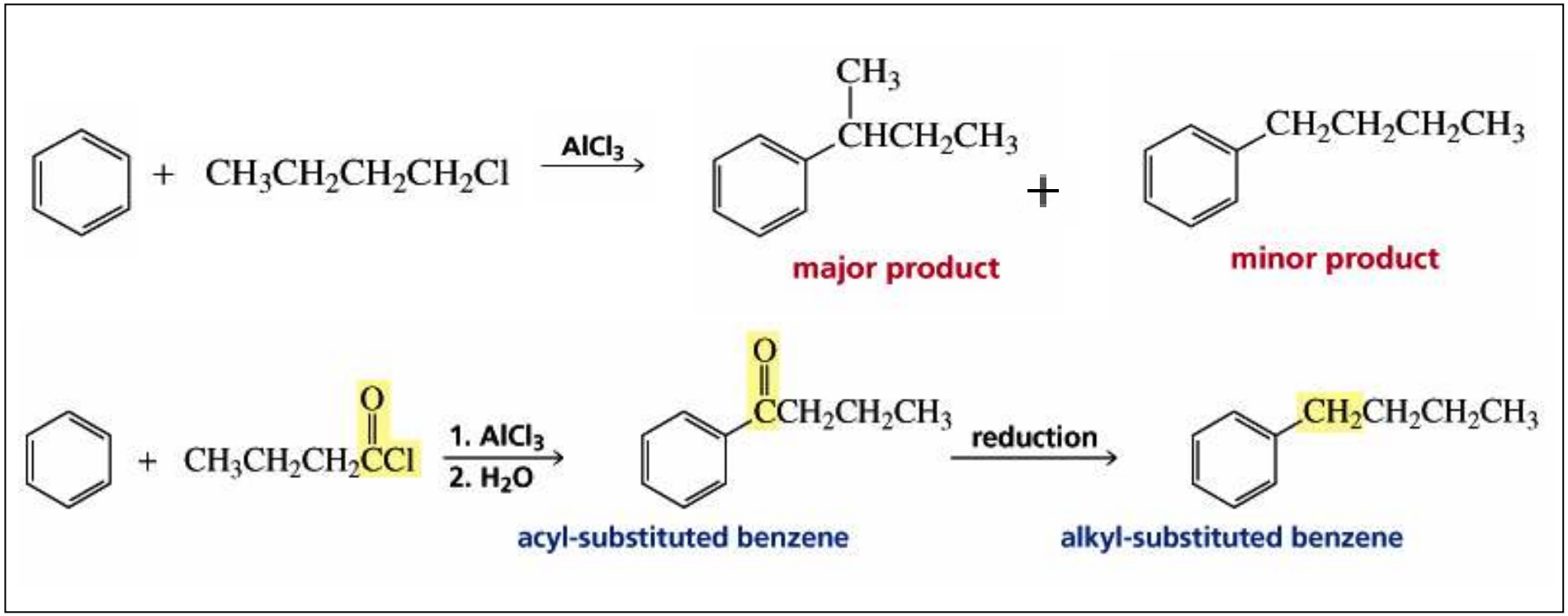



Since $AlCl_3$ complexes with C=O group,
2 eq. of this reagent is required

Acylation followed by Reduction is a convenient route to introduce long alkyl chains on aromatic ring; No problem of rearrangement !



# Alkylation of Benzene by Acylation-Reduction



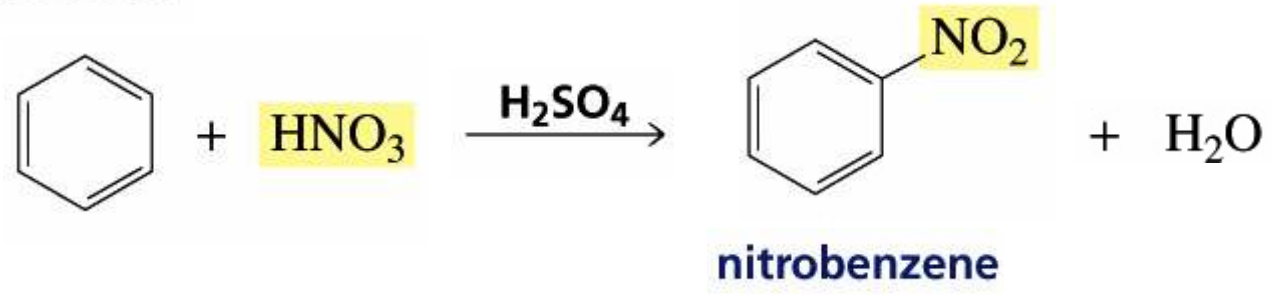

**Advantages :**

**(1) No rearrangement**

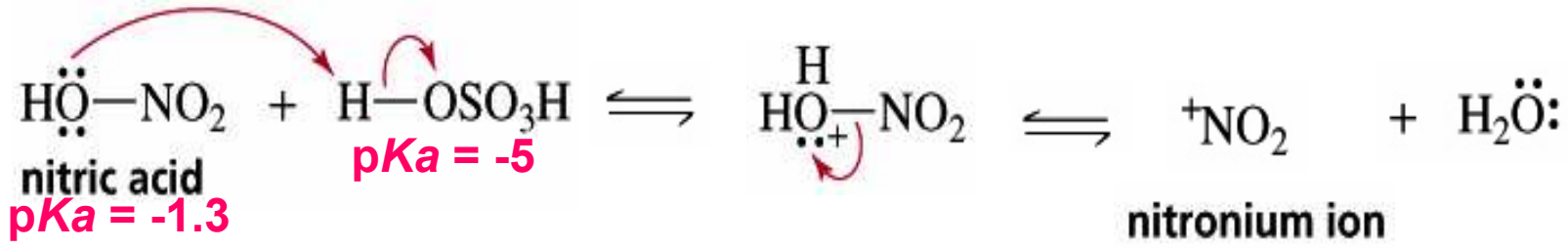
**(2) No multiple substitutions (acyl- group is de-activating)**

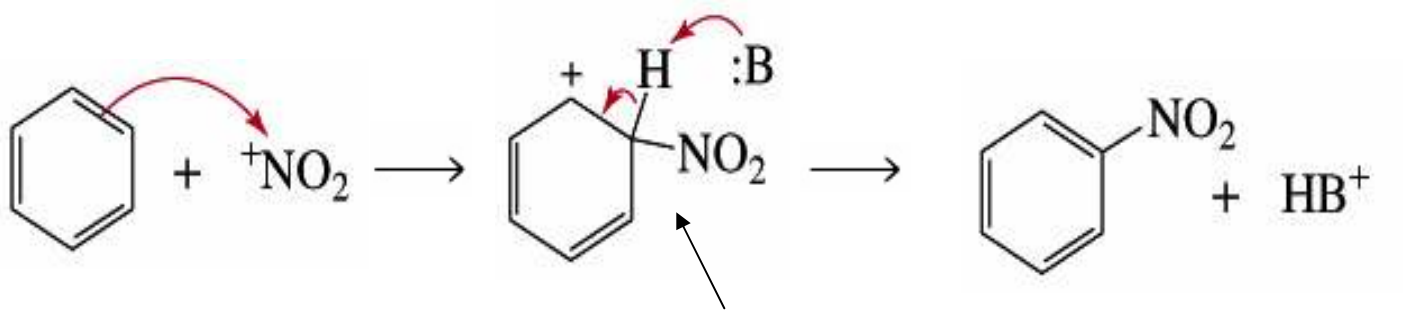
# Nitration of Benzene

**nitration**



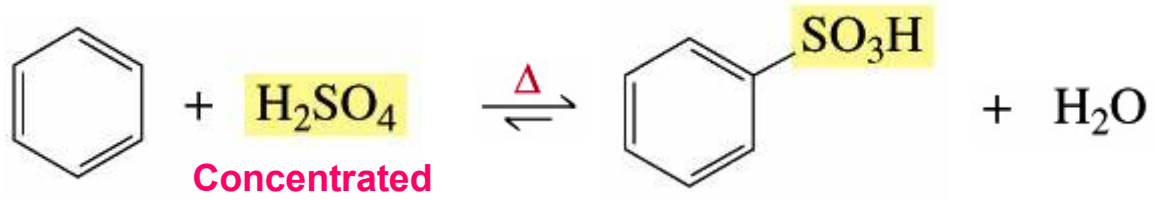

**mechanism for nitration**



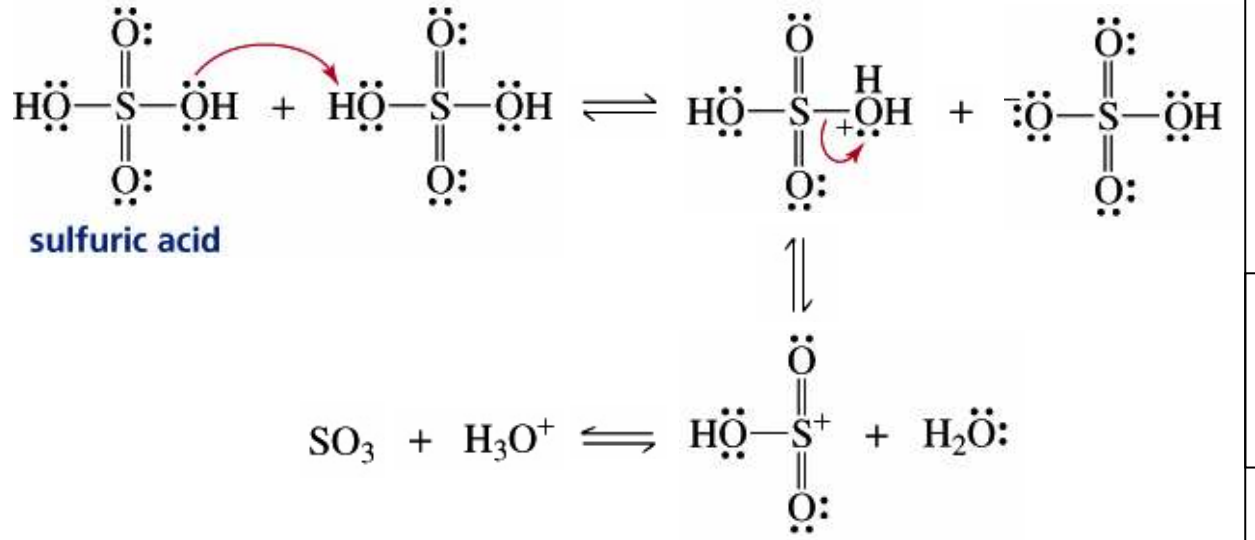



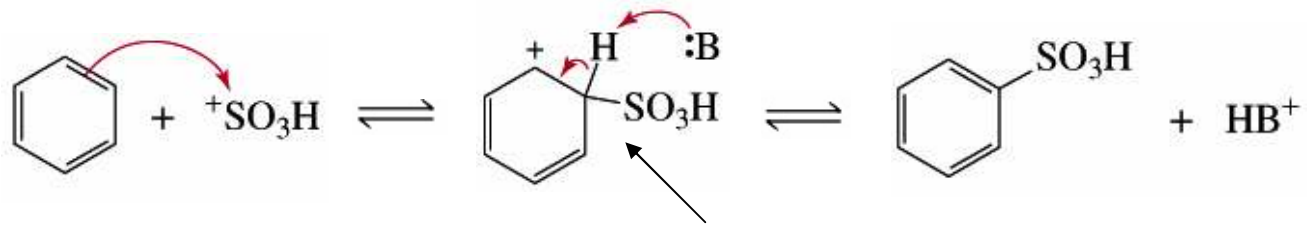

(consider all resonance forms)

# Sulfonation of Benzene




## mechanism for sulfonation

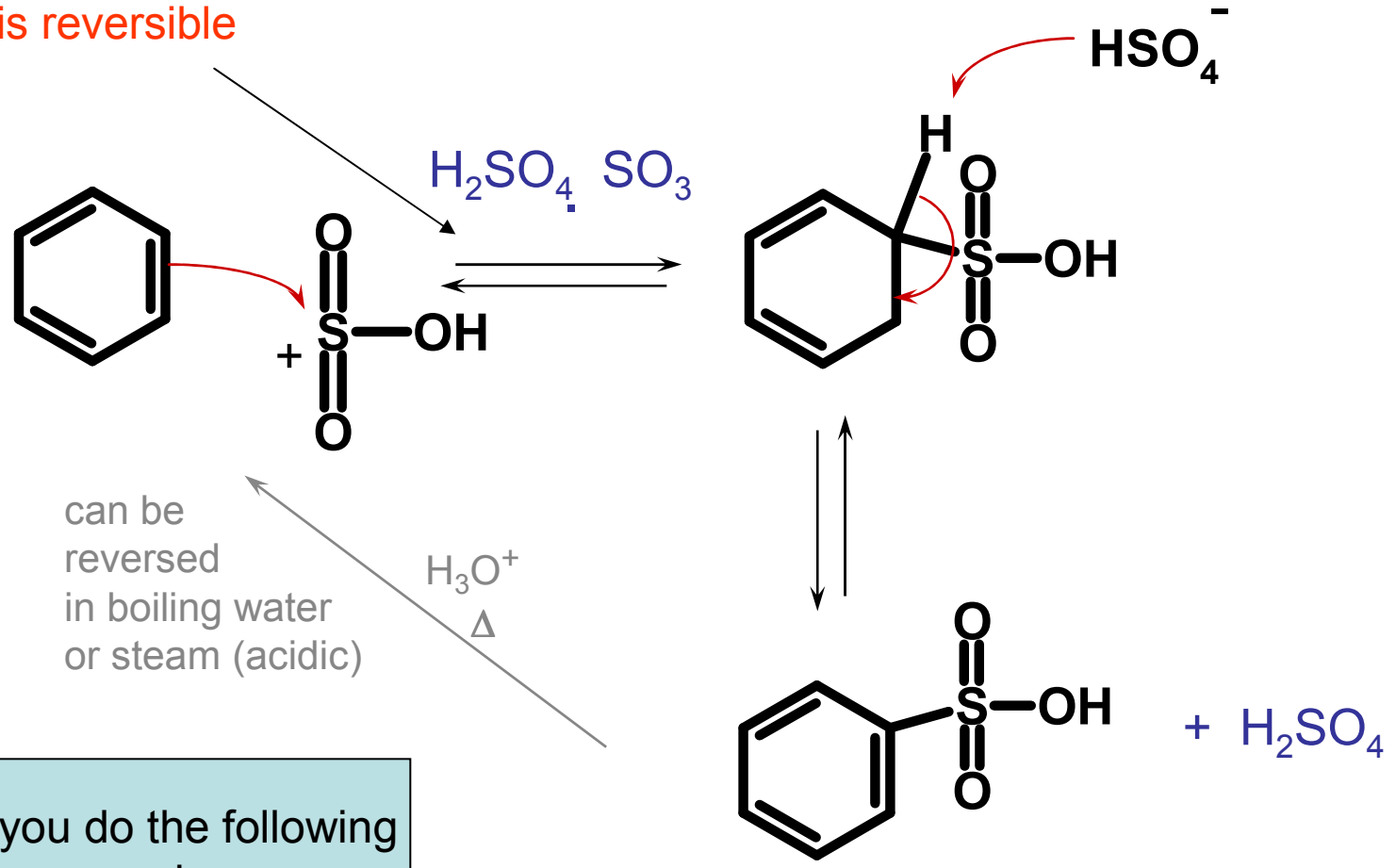


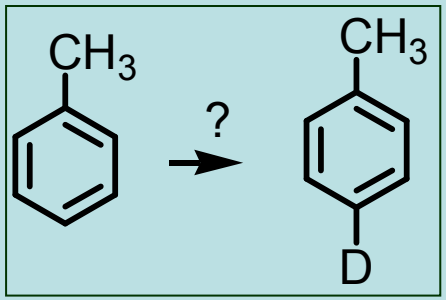

(Consider all resonance forms)

# Sulfonation of Benzene

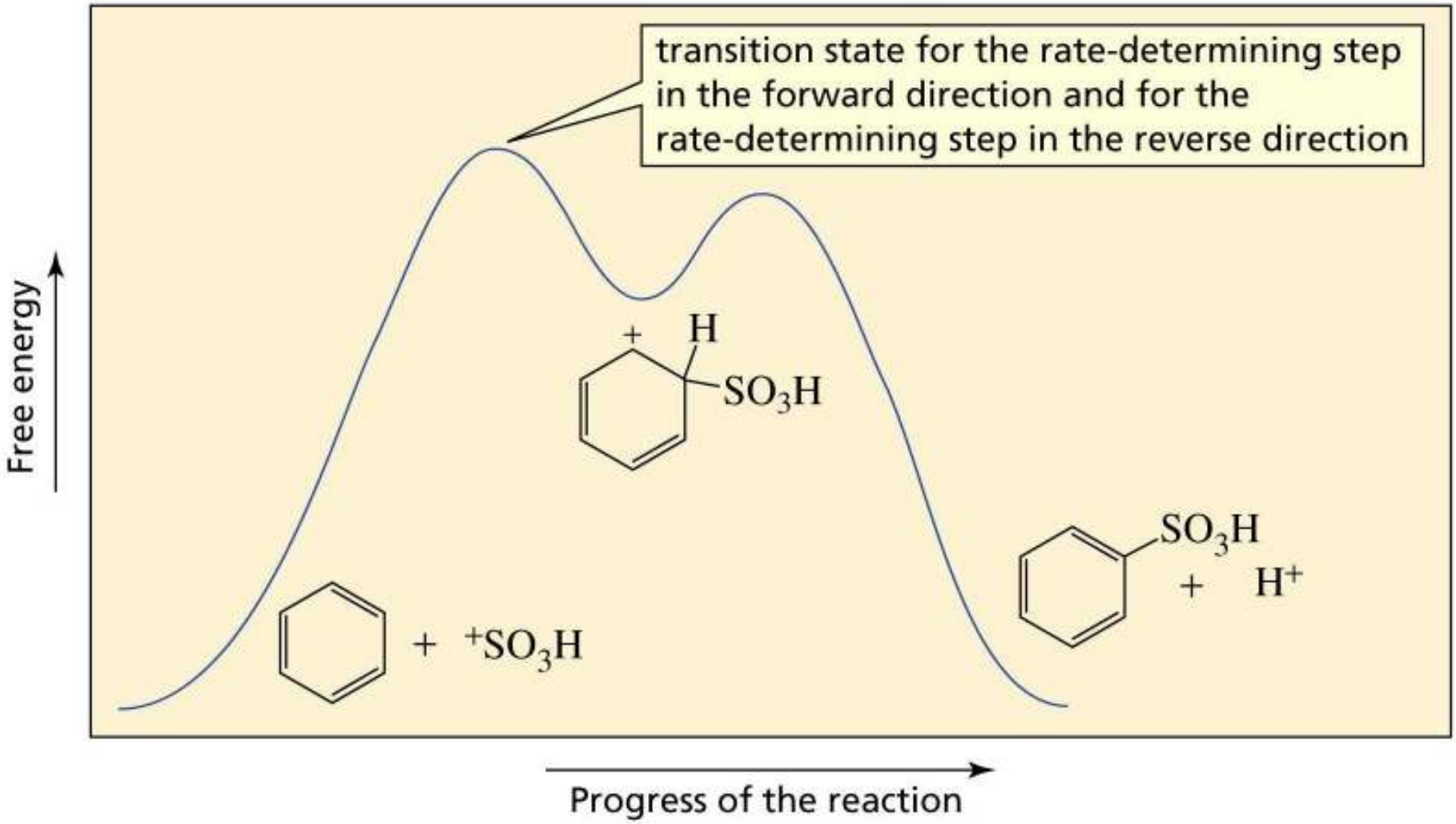
Look.. It is reversible



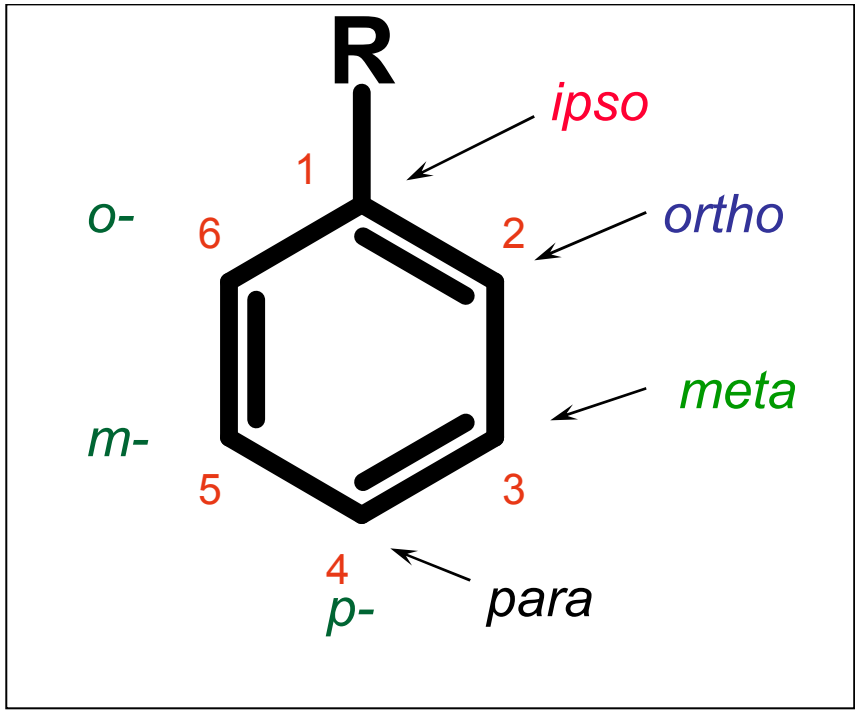

How would you do the following conversion



# Energy profile in Sulfonation

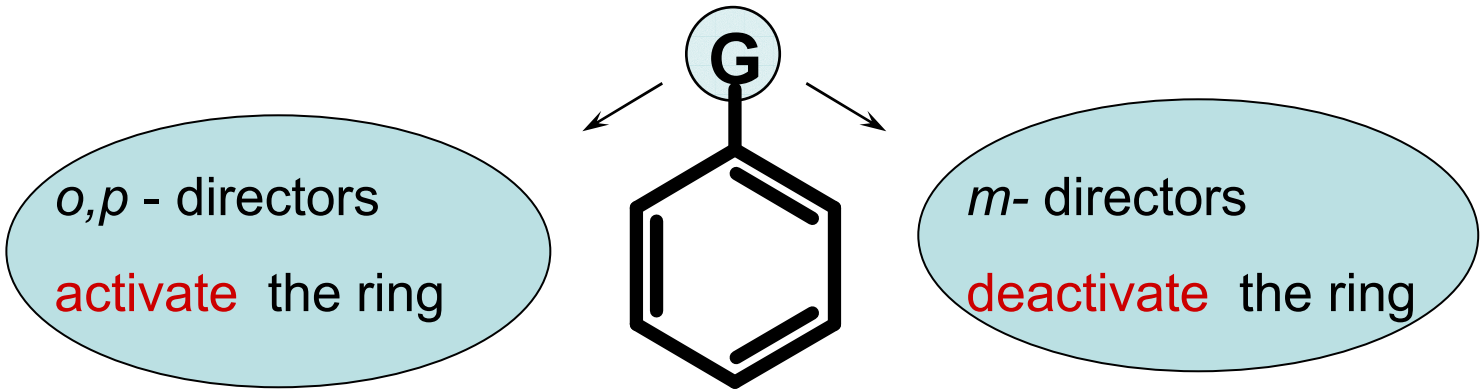


# Directing effect of groups,
## ring activation and deactivation



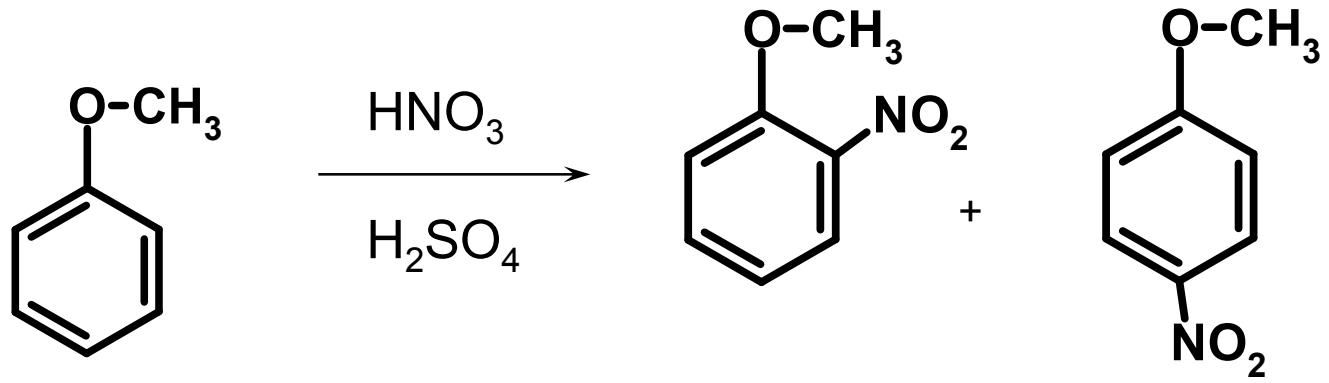

## Substitution categories

Depending upon whether they are electron donating or electron withdrawing, substituents fall into one of the following categories:



# ACTIVATED RING

## Example, Nitration of Anisole




anisole *ortho* *para*

Reacts faster than benzene = "activated"

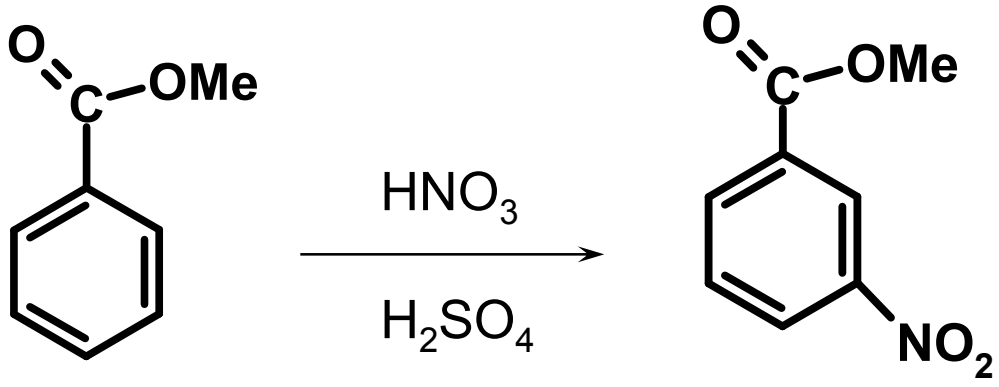
The -$OCH_3$ (or other electron donating groups) if present on the ring, give preferentially *ortho* and *para* products, and no meta.

⇨ Substituents that cause this effect are called *o,p* directors

and they usually activate the ring

# DEACTIVATED RING

## Example Nitration of Methyl Benzoate




methyl benzoate

*meta*

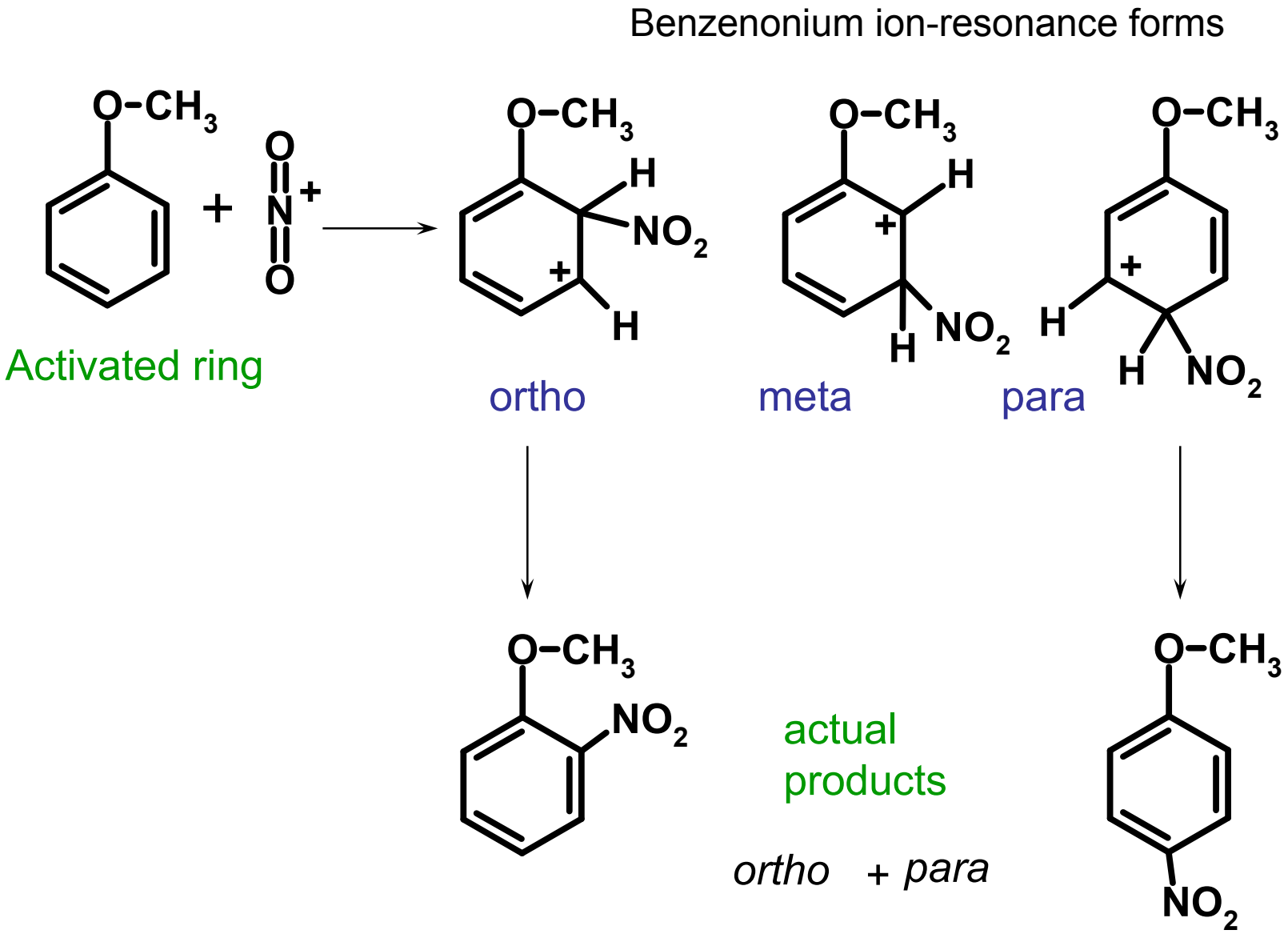
Reacts slower than benzene = "deactivated"

The -COOMe (or other electron withdrawing groups) if present on the ring give only *meta*, and no *ortho* or *para* products.

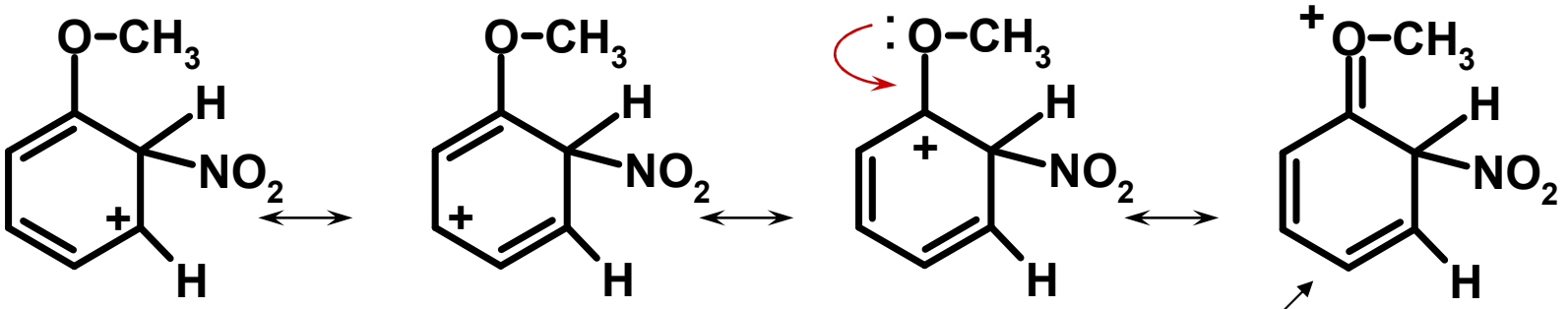
⇨ Substituents that cause this result are called *m* directors

and they usually deactivate the ring.

# Nitration of Anisole

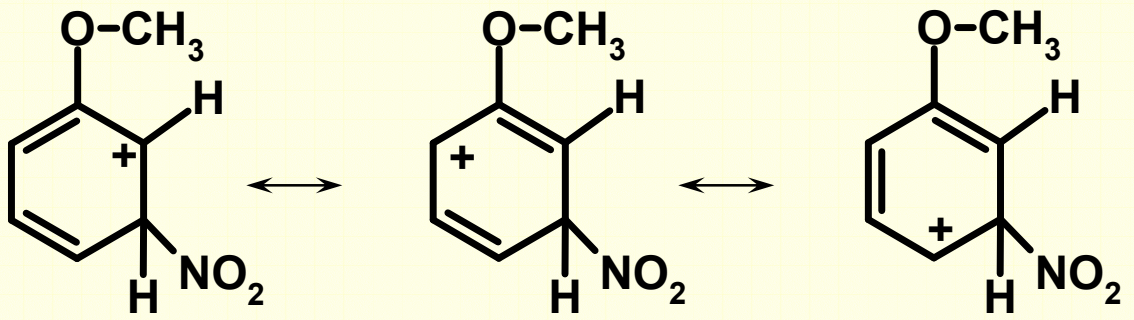


*ortho*

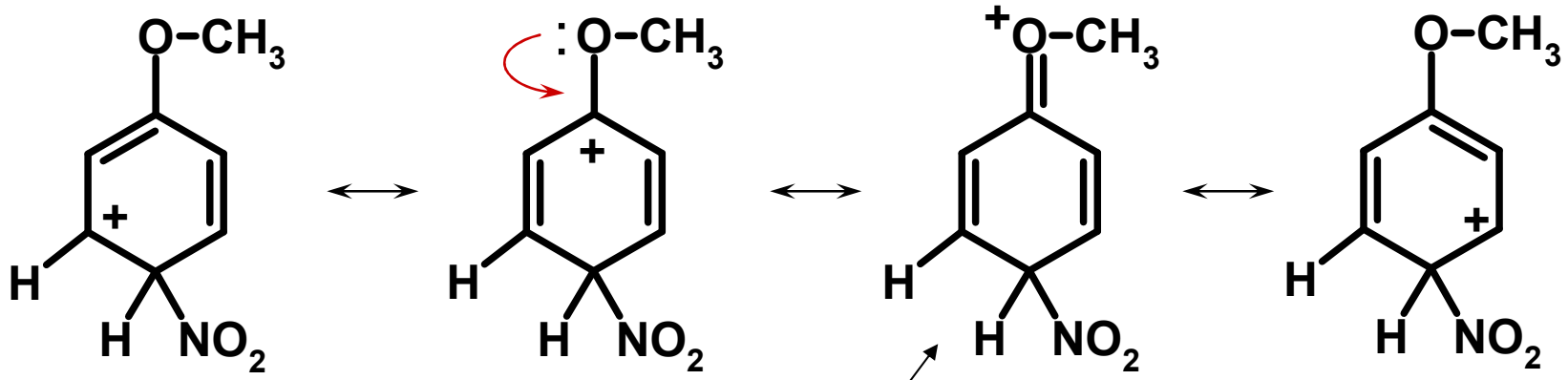



Extra stabilization and extra resonance structure

*meta*

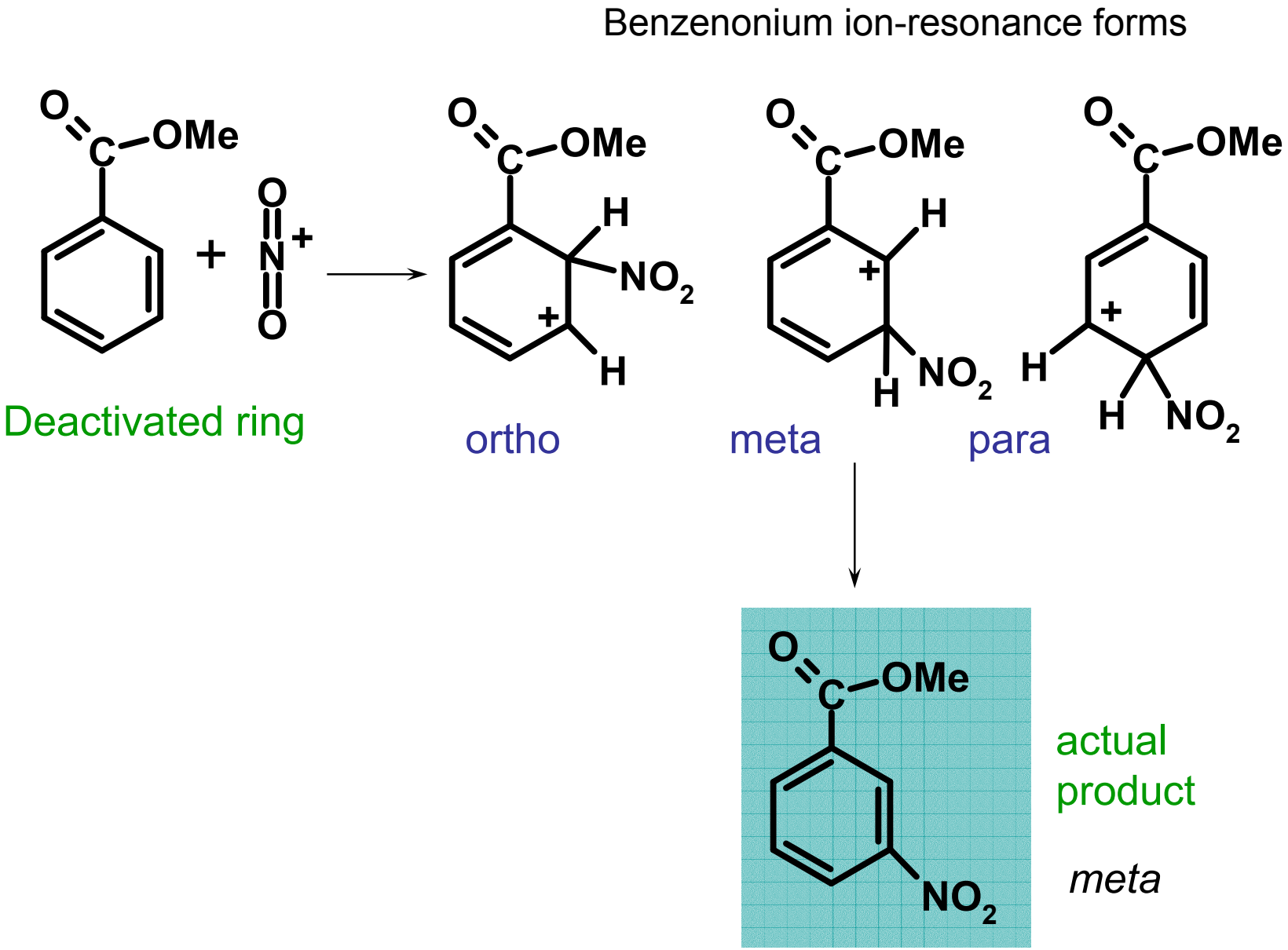



*para*

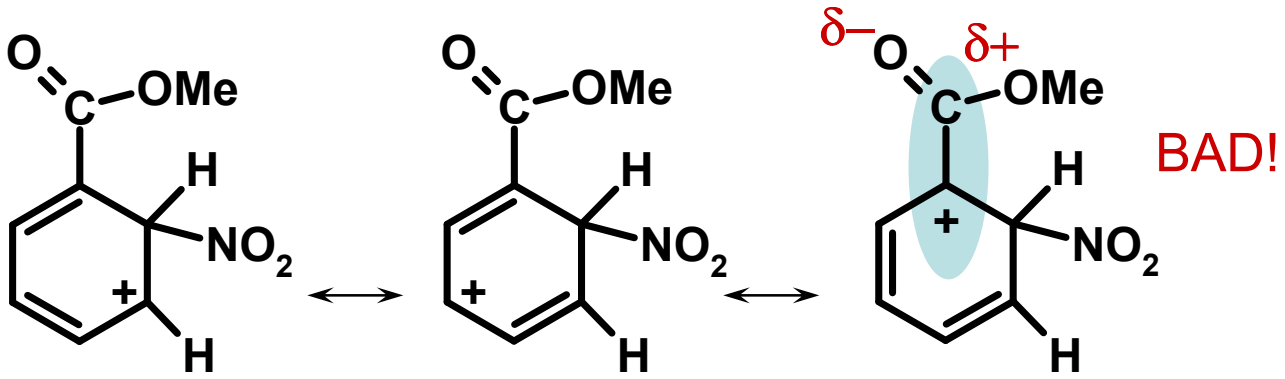



Extra stabilization and extra resonance structure

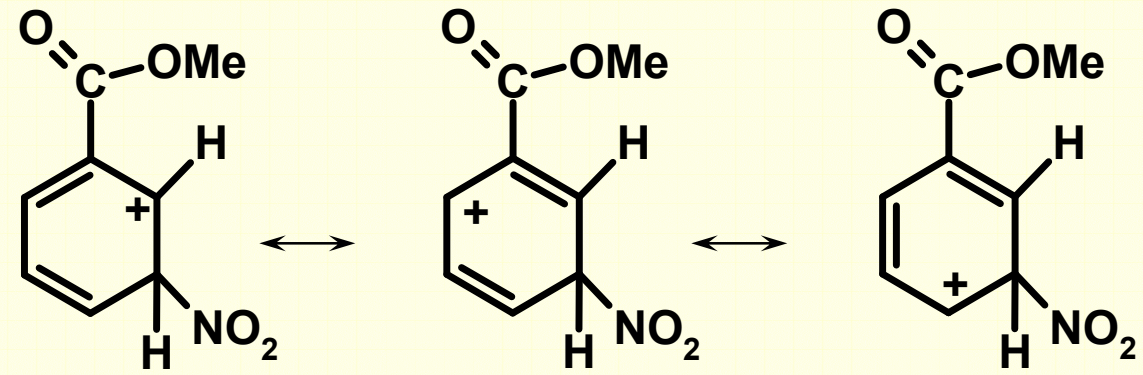
# Nitration of Methyl Benzoate



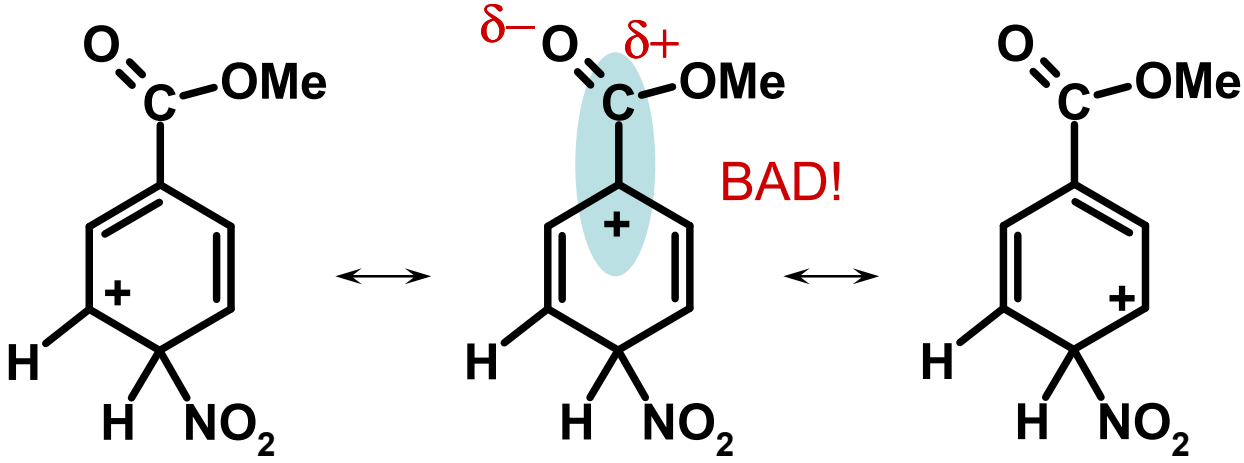
*ortho*




*meta*




*para*

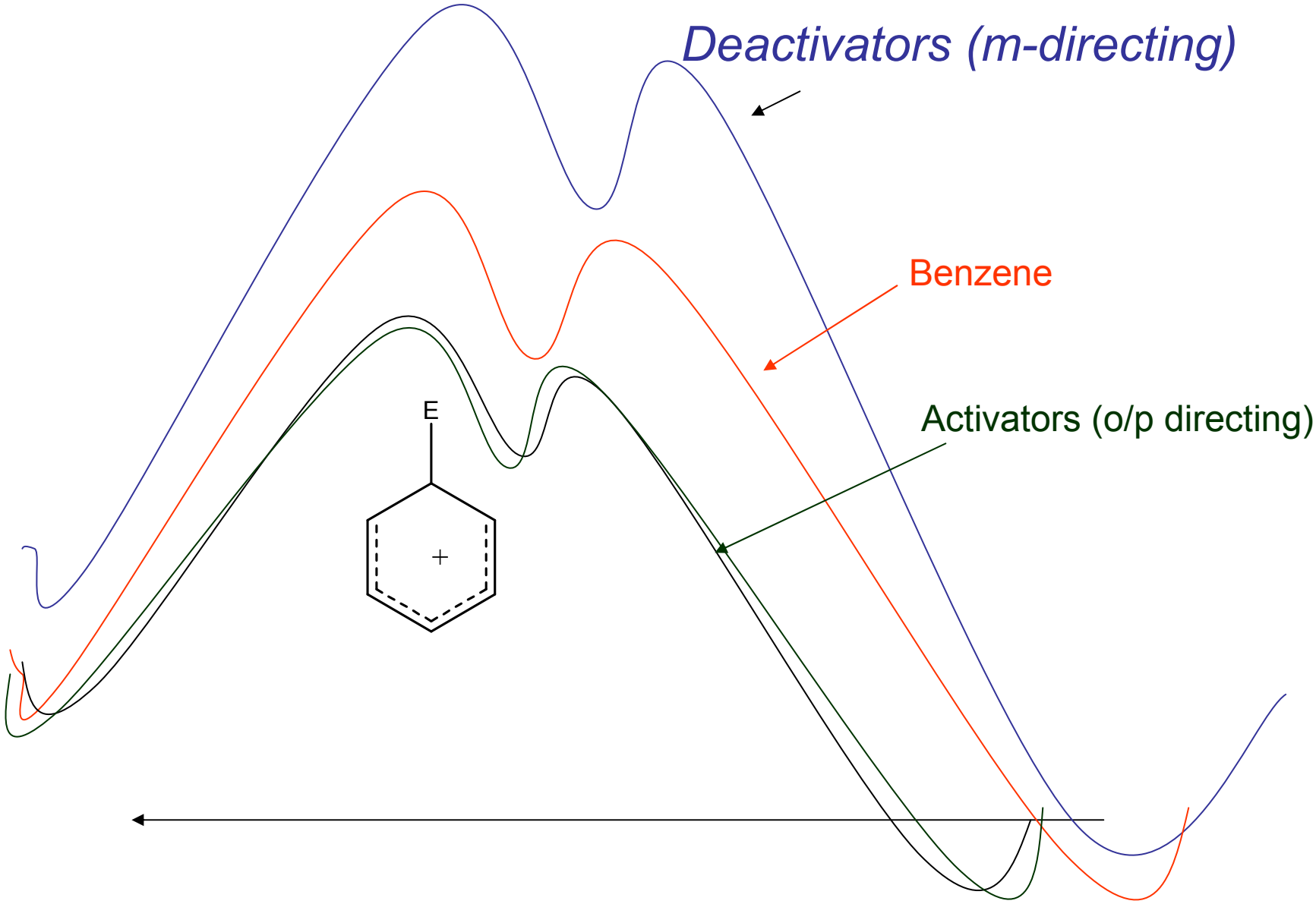


- Classification of Substitutents

| Ortho–Para Directors | Meta Directors |
| --- | --- |
| **Strongly Activating**<br>$-\ddot{N}H_2$, $-\ddot{N}HR$, $-\ddot{N}R_2$<br>$-\ddot{O}H$, $-\ddot{O}:^-$ | **Moderately Deactivating**<br>$-C\equiv N$<br>$-SO_3H$<br>$-CO_2H$, $-CO_2R$<br>$-CHO$, $-COR$ |
| **Moderately Activating**<br>$-\ddot{N}HCOCH_3$, $-\ddot{N}HCOR$<br>$-\ddot{O}CH_3$, $-\ddot{O}R$ | **Strongly Deactivating**<br>$-NO_2$<br>$-NR_3^+$<br>$-CF_3$, $-CCl_3$ |
| **Weakly Activating**<br>$-CH_3$, $-C_2H_5$, $-R$<br>$-C_6H_5$ | |
| **Weakly Deactivating**<br>$-\ddot{F}:$, $-\ddot{Cl}:$, $-\ddot{Br}:$, $-\ddot{I}:$ | |

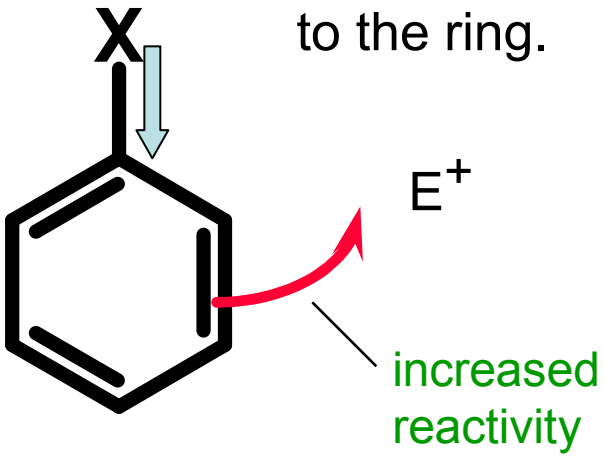
# Comparison of Activators and deactivators

## Relative energy states of intermediates with respect to that of benzene



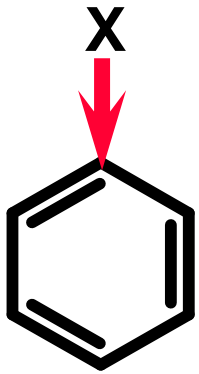
# *ortho, para* - Directing Groups

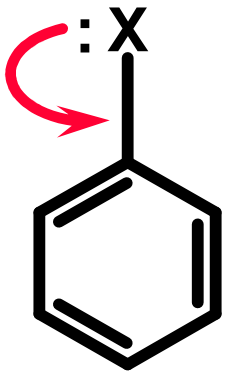
Groups that donate electron density to the ring.




These groups "activate" the ring, or make it more reactive.

PROFILE:



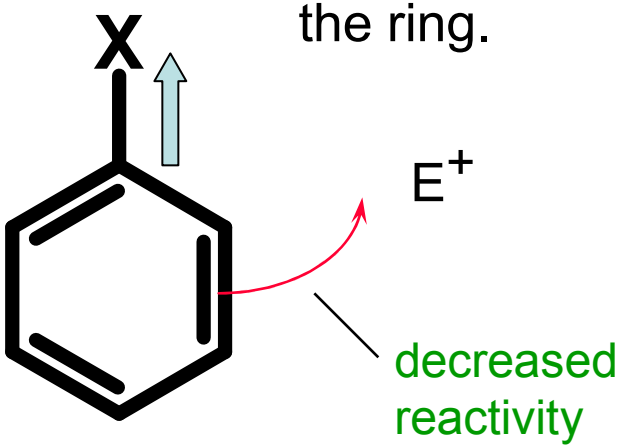




| +I Substituent | +R Substituent |
|---|---|
| $CH_3$- | $CH_3$-O- |
| R- | $CH_3$-N- |
| | -$NH_2$ |
| | -O-H |

The +R groups activate the ring more strongly than +I groups.

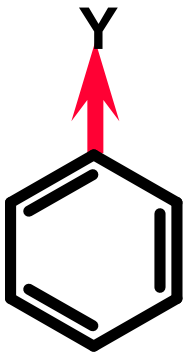
# *meta* - Directing Groups

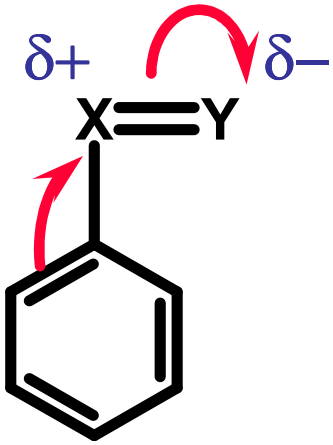
Groups that withdraw electron density from the ring.



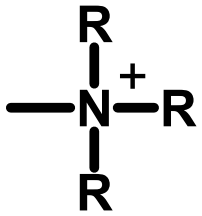

These groups "deactivate" the ring, or make it <u>less reactive</u>.

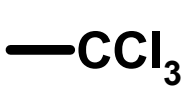
PROFILE:



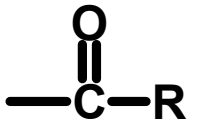




## -I Substituent



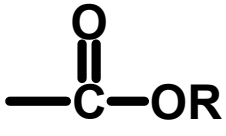



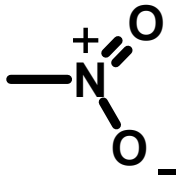

## -R Substituent

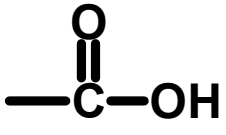


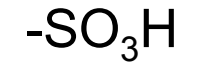






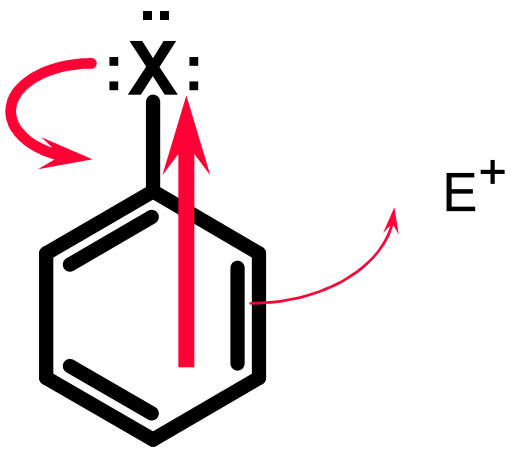



# Halides - *o,p* Directors / Deactivating;

## an exception to the trend we saw in the previous slide



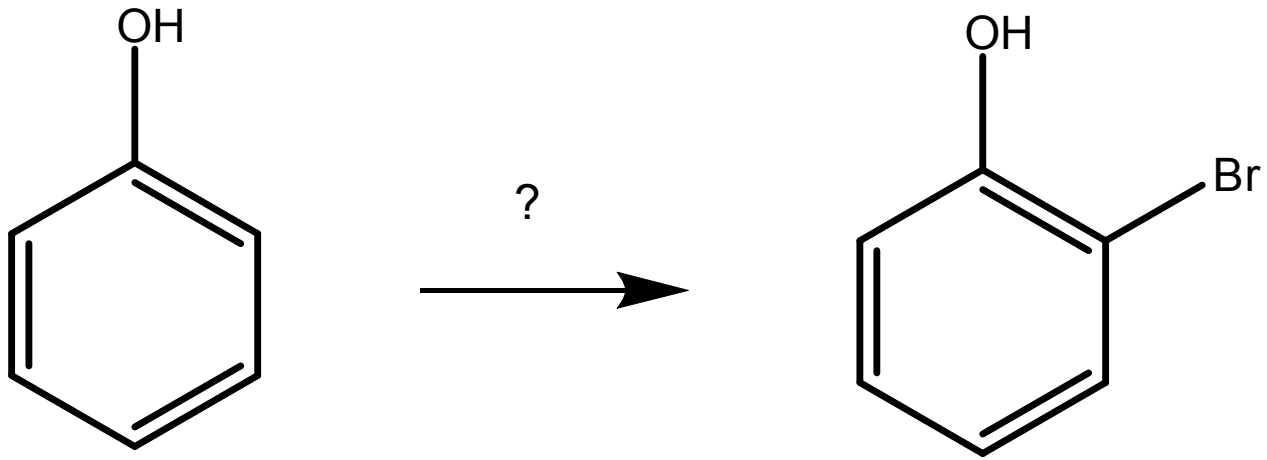

**X =** -F
-Cl
-Br
-I

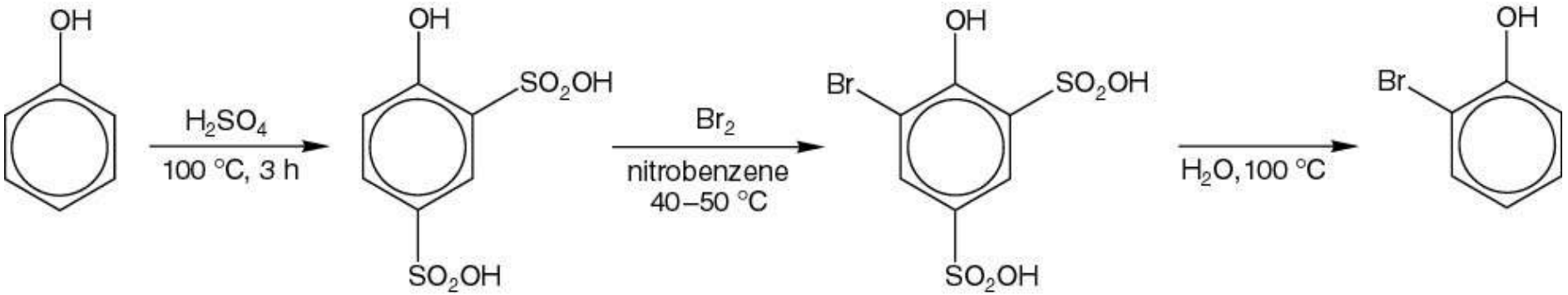
Halides represent a special case:

They are *o,p* directors (+M effect )

They are deactivating ( -I effect )

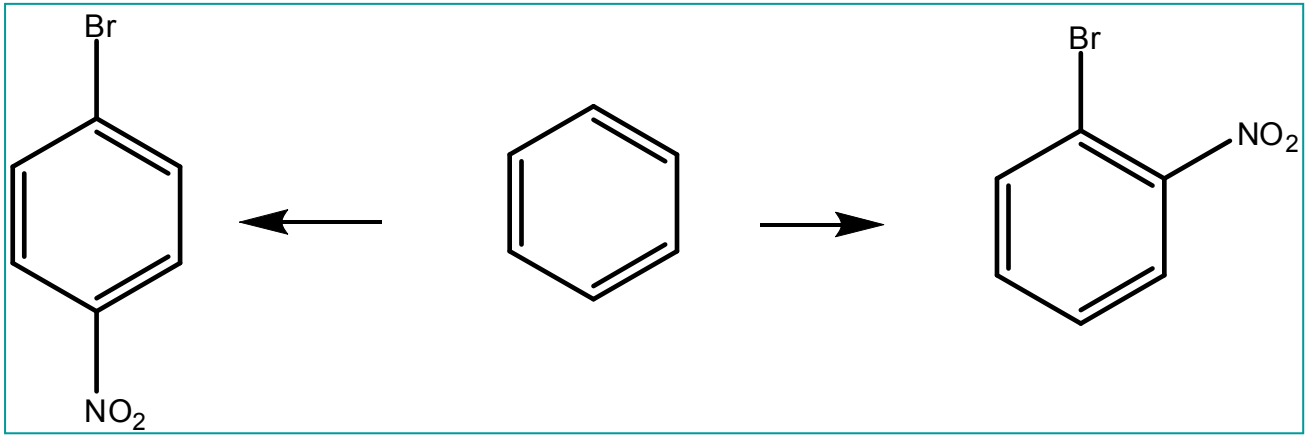
How would you bring about the following conversion efficiently?

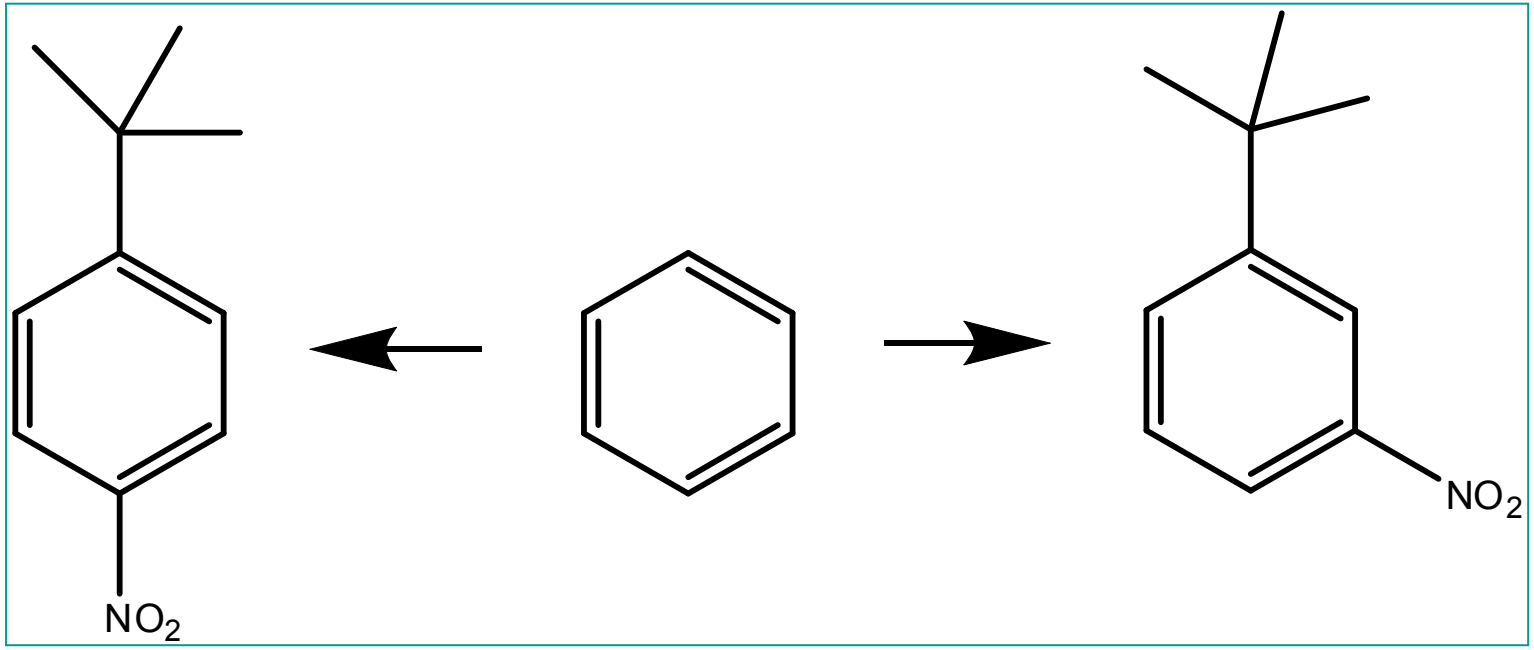


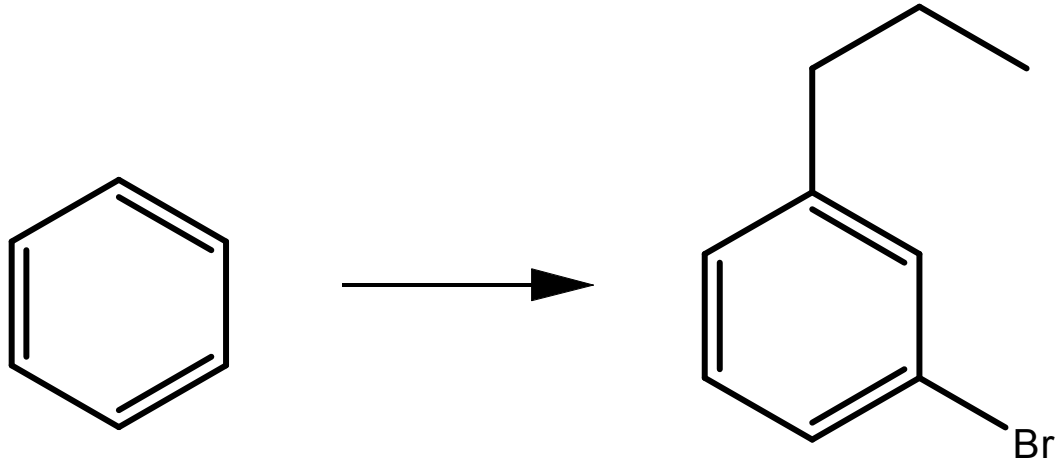



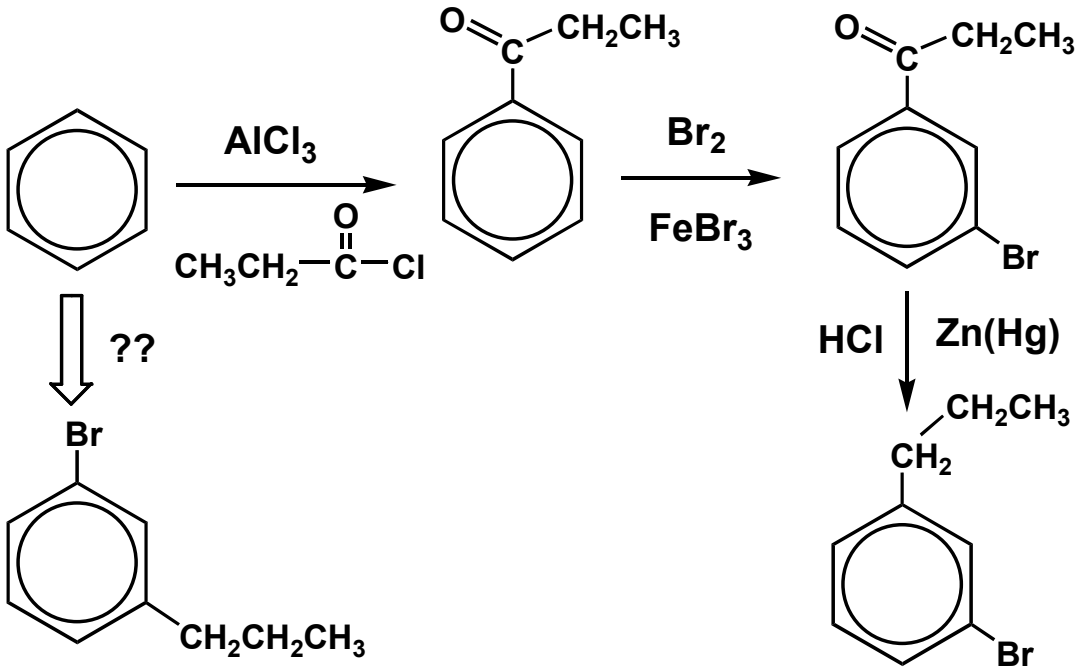
# Directing effect of groups: Application in synthesis

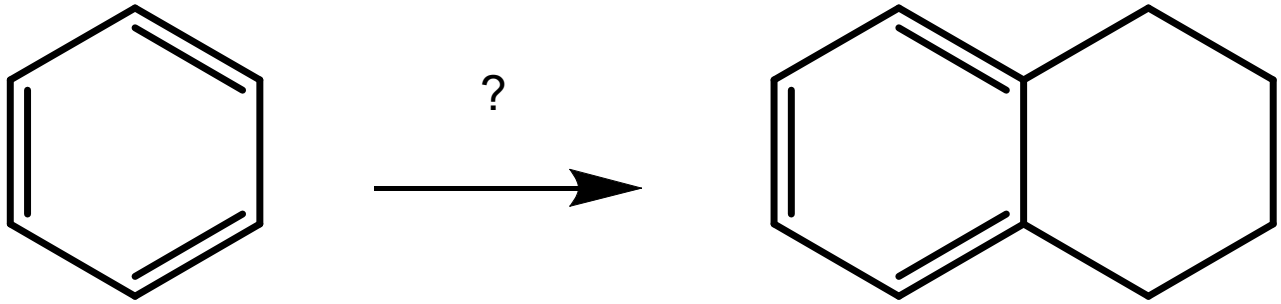
How would you bring about the following conversions efficiently?



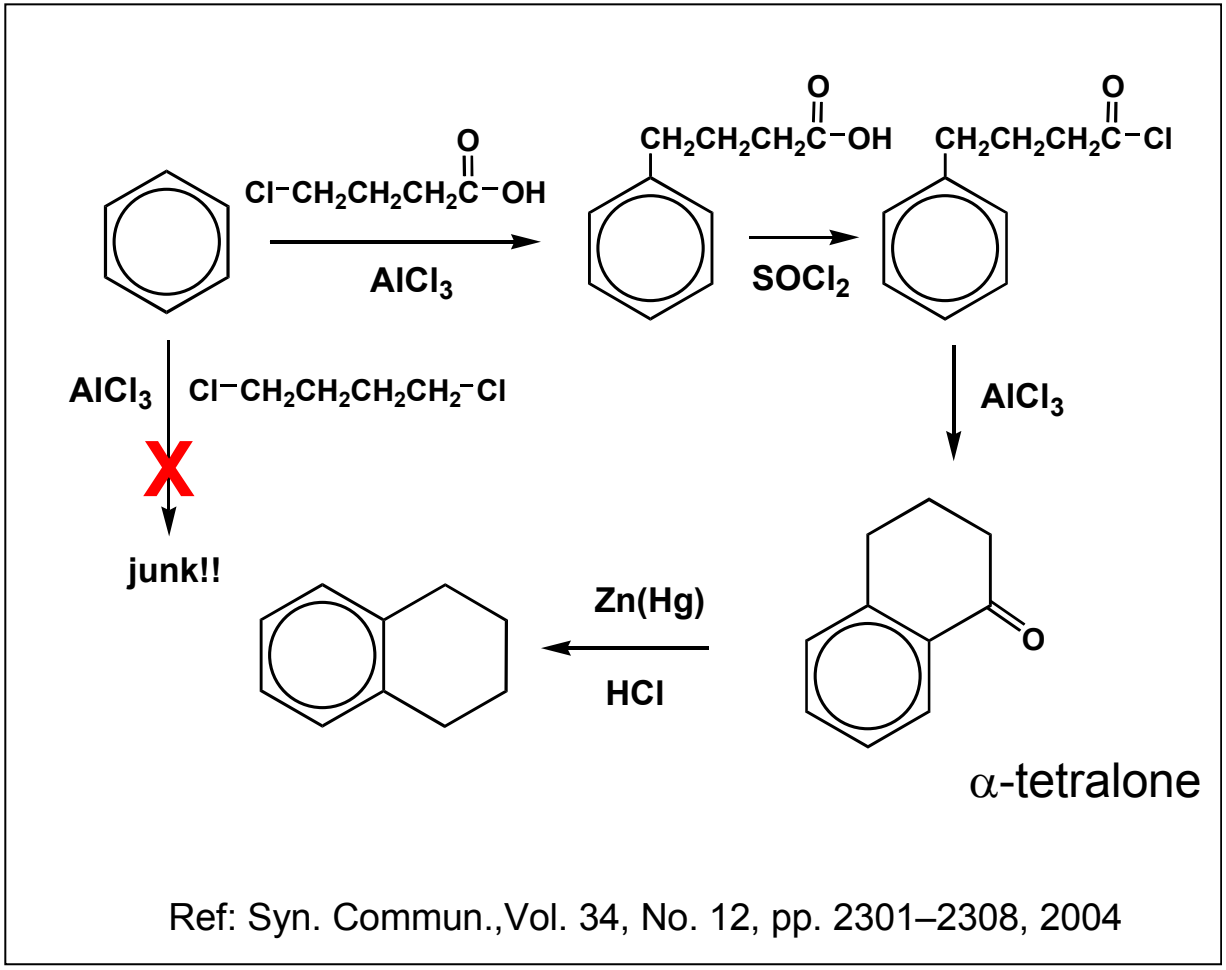




Br

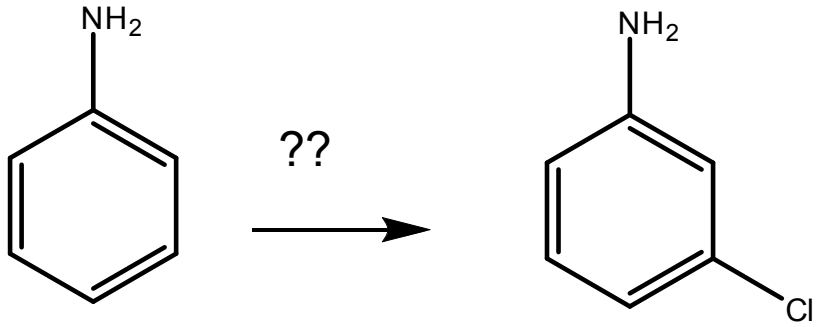

AlCl3
CH3CH2—C(=O)—Cl
O
C
CH2CH3
Br2
FeBr3
HCl
Zn(Hg)
??
Br
CH2CH2CH3
CH2

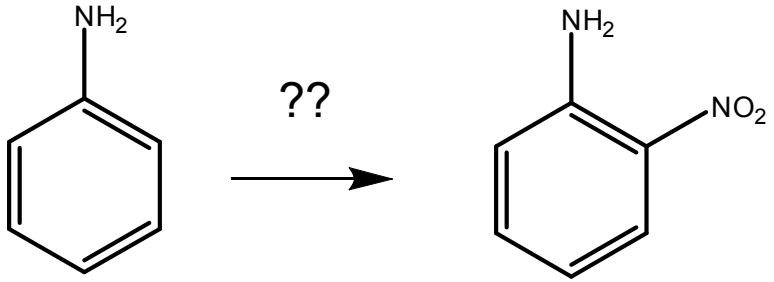



You can also consider a route through succinic anhydride (draw the sequence)

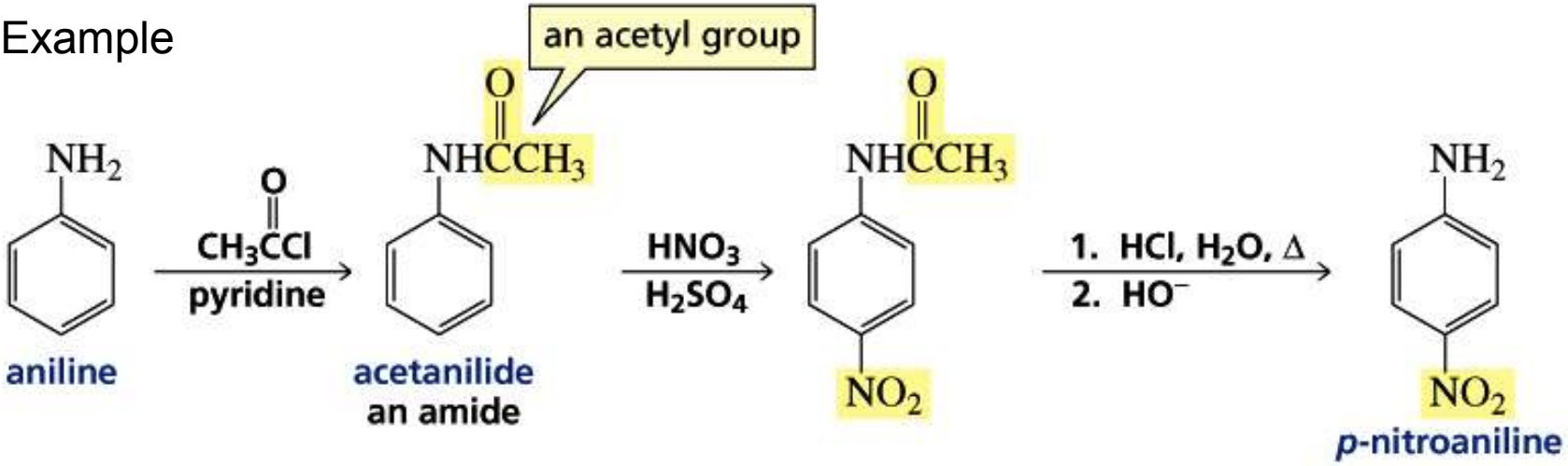


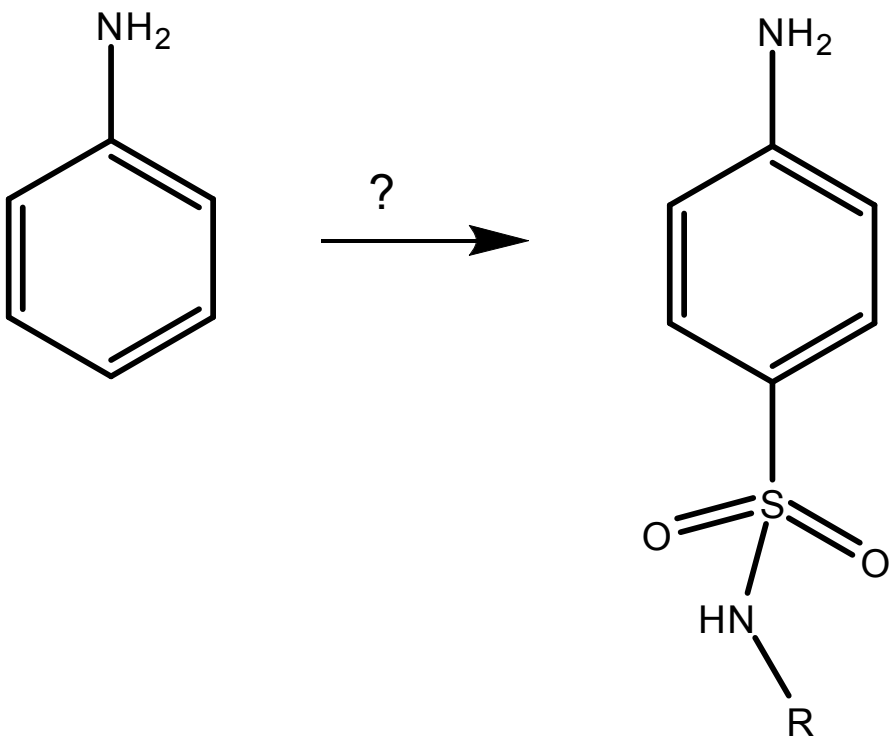

Ref: Syn. Commun.,Vol. 34, No. 12, pp. 2301–2308, 2004


NH2
??
NH2
Cl


NH2
??
NH2
NO2

Example

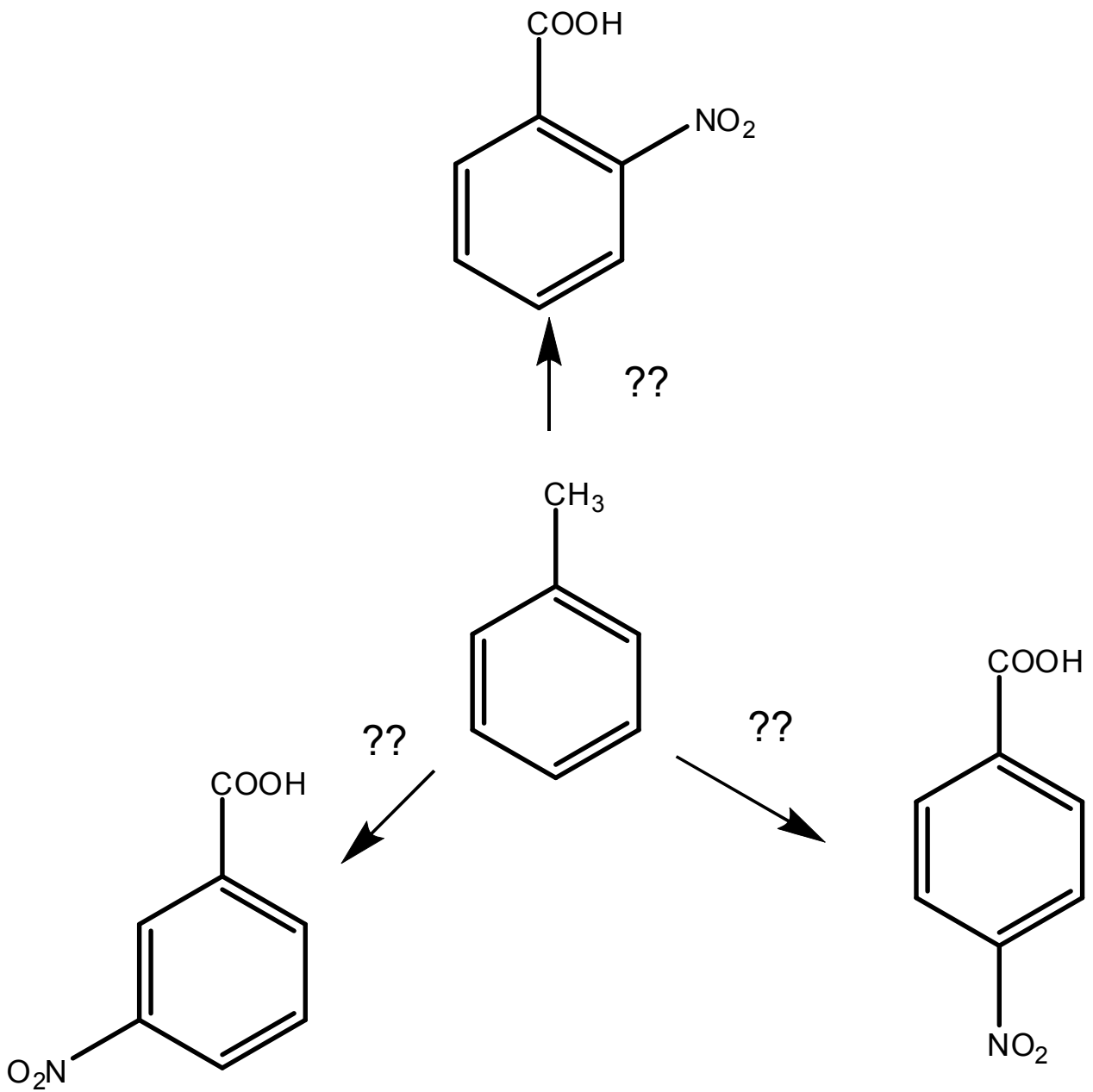

an acetyl group
NH2
O
CH3CCl
pyridine
NHCCH3
aniline
acetanilide
an amide
HNO3
H2SO4
NO2
1. HCl, H2O, Δ
2. HO−
p-nitroaniline




Sulfa drugs (very important class of Antibacterials)

Clue: steps in random order
chlorosulfonation, amination, N-acetylation, de-acetylation

Give reasons for N-acetylation????


COOH
NO2
??
CH3
??
??
COOH
O2N
COOH
NO2

# Directing effect if more than one substituent is present

## General rules

1) Activating (*o,p*) groups (+R, +I) win over deactivating (*m*) groups (-R,-I)

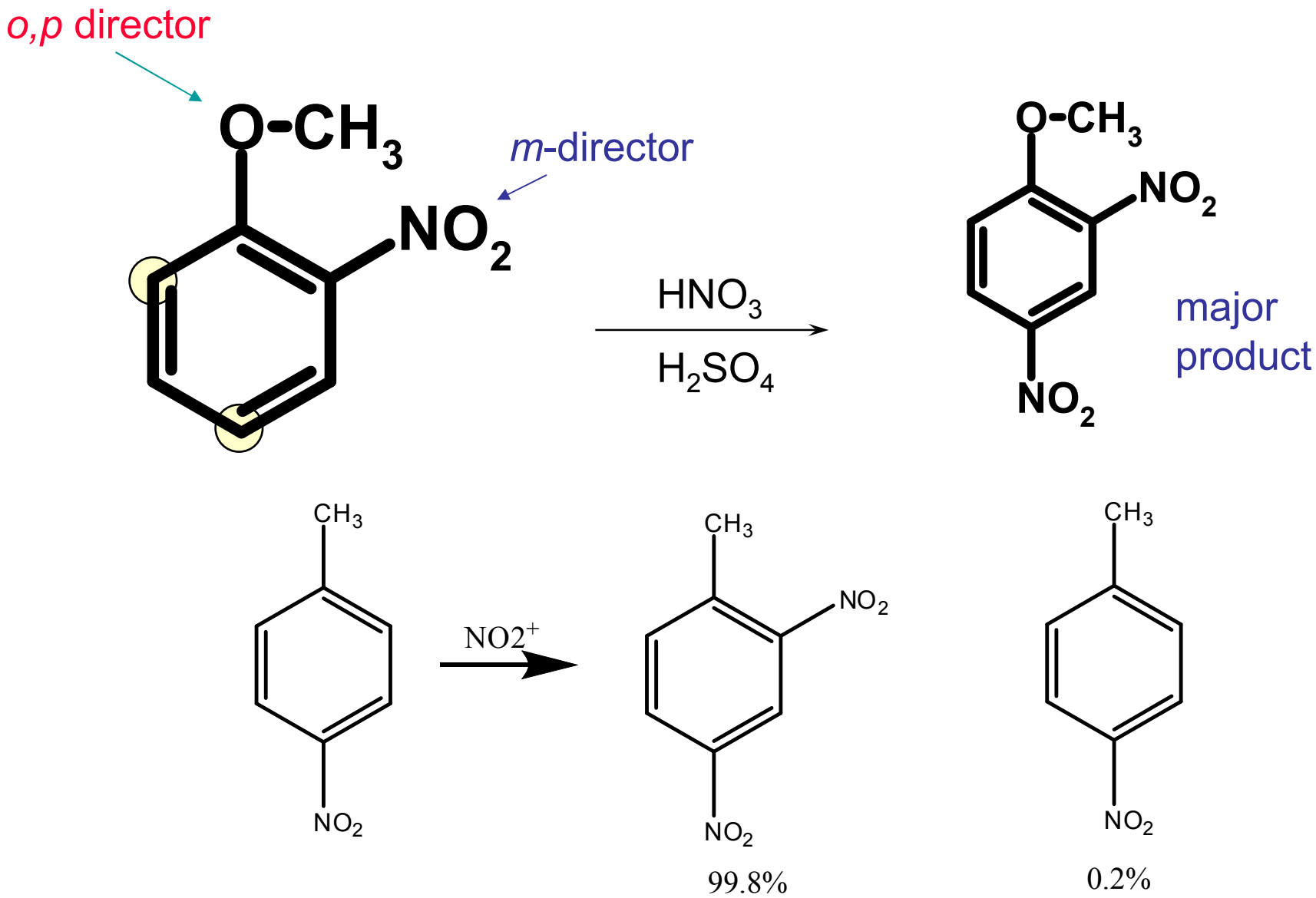
2) Resonance groups (+R) win over inductive (+I) groups

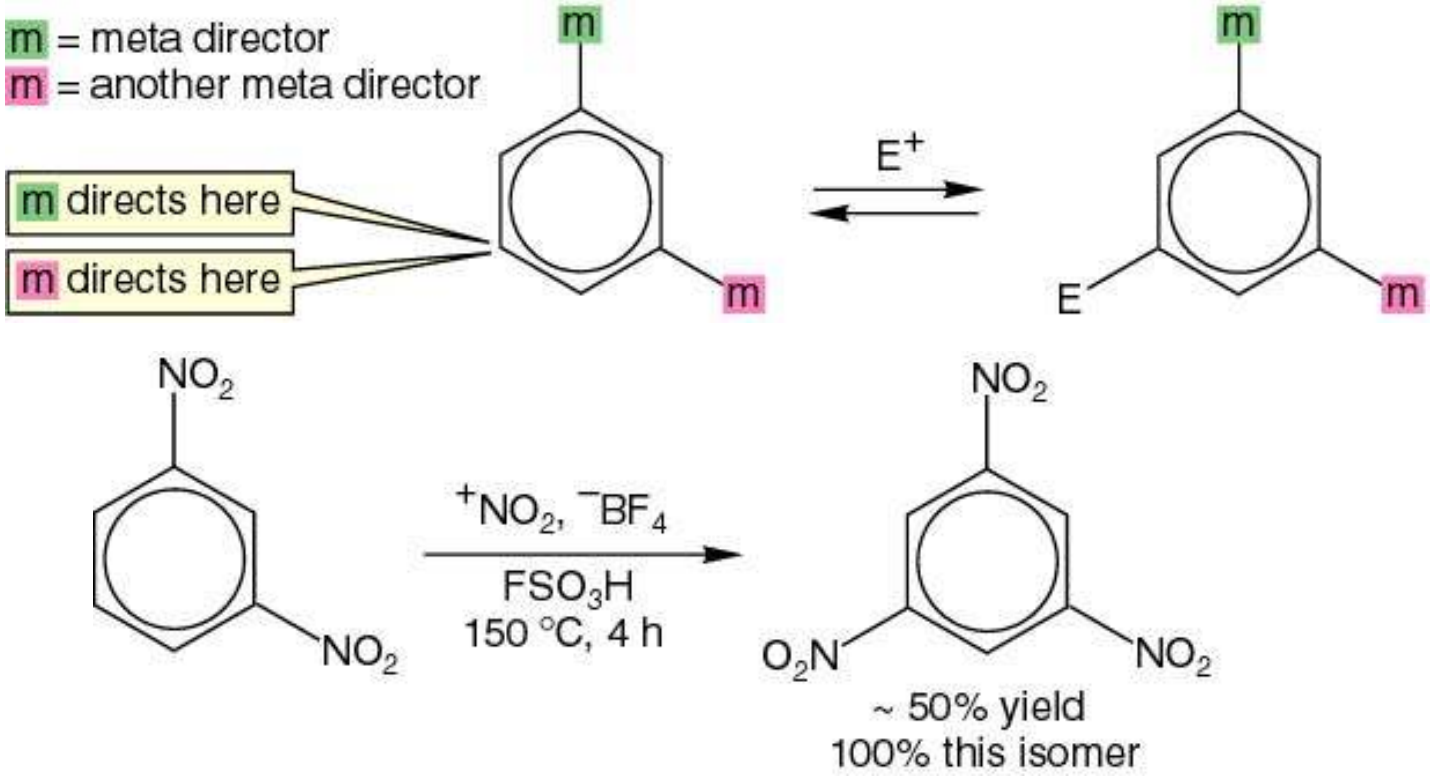
3) 1,2,3-Trisubstituted products rarely form due to steric crowding

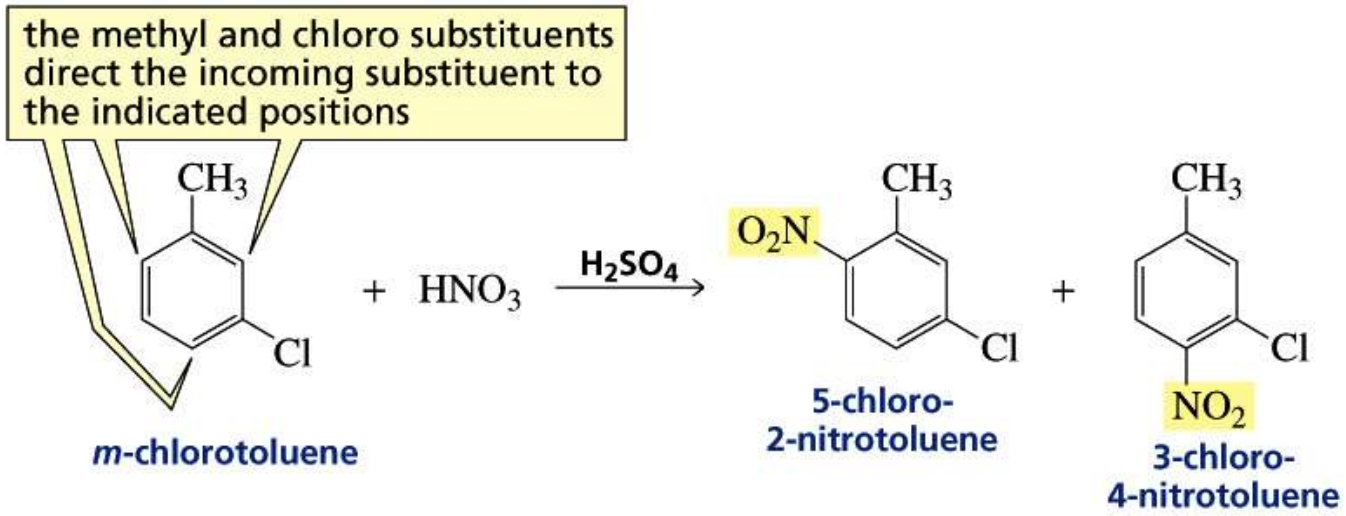
4) With bulky directing groups, there will usually be more *p*-substitution than *o*-substitution

5) The incoming group replaces a hydrogen, it will not usually displace a substituent already in place (in the case of electrophilic aromatic substitution)

# Case 1. When two substituents direct to the same position



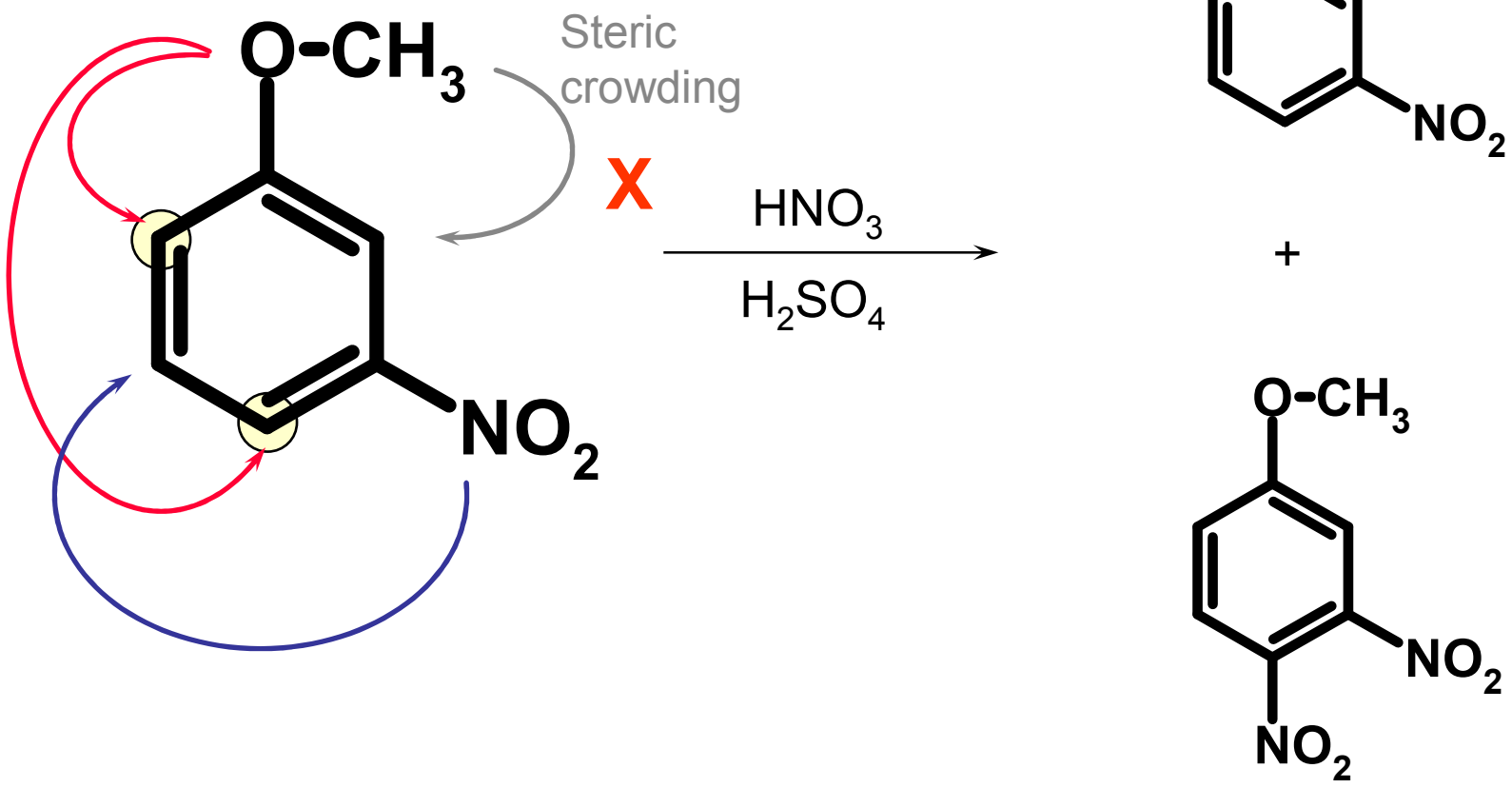



Why a mixture in this case ?? (assuming 1:1)

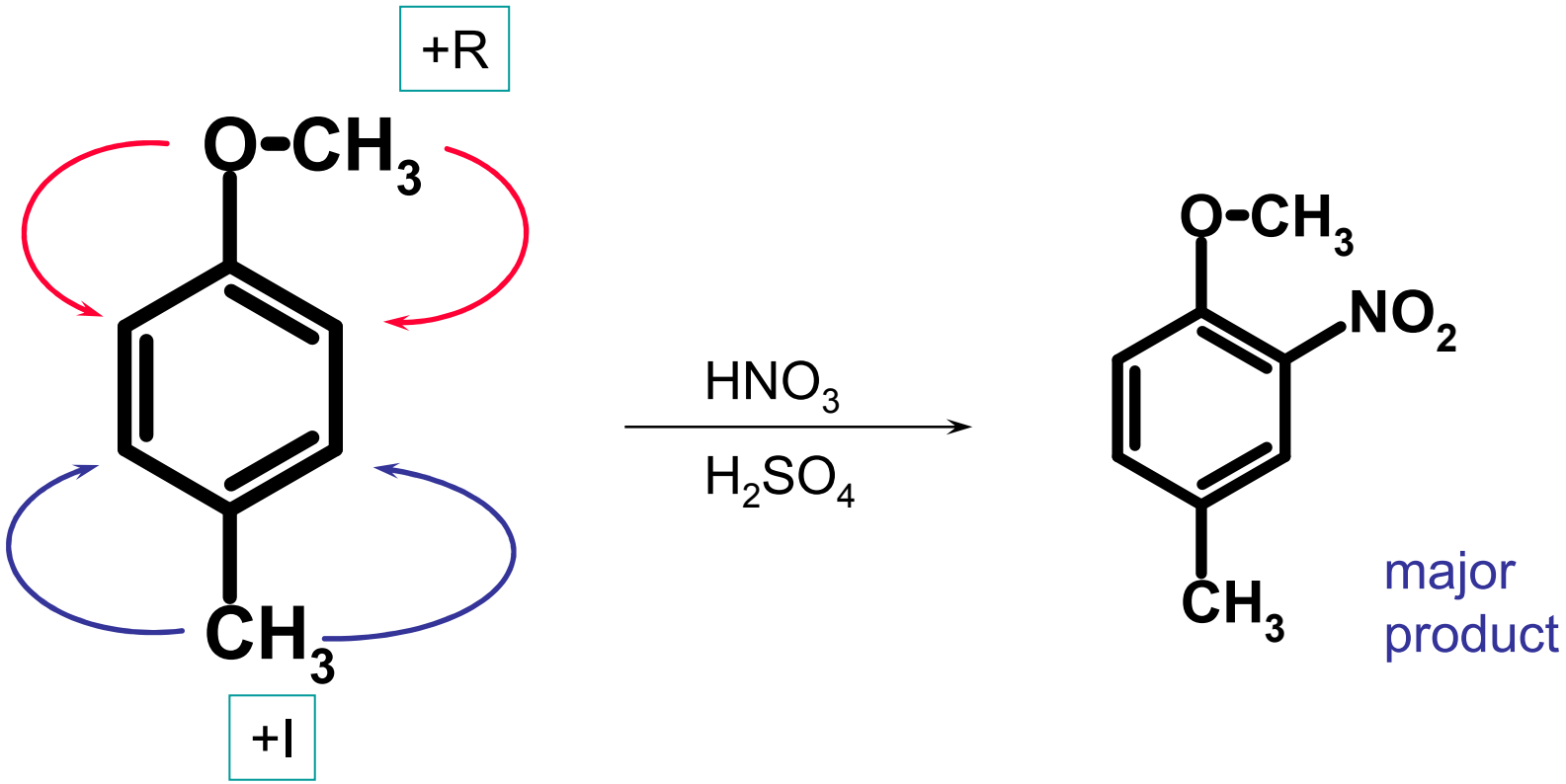
## Case 2. When two substituents direct to the different positions (activation vs. deactivation)

*o,p*-directing groups win over *m*-directing groups

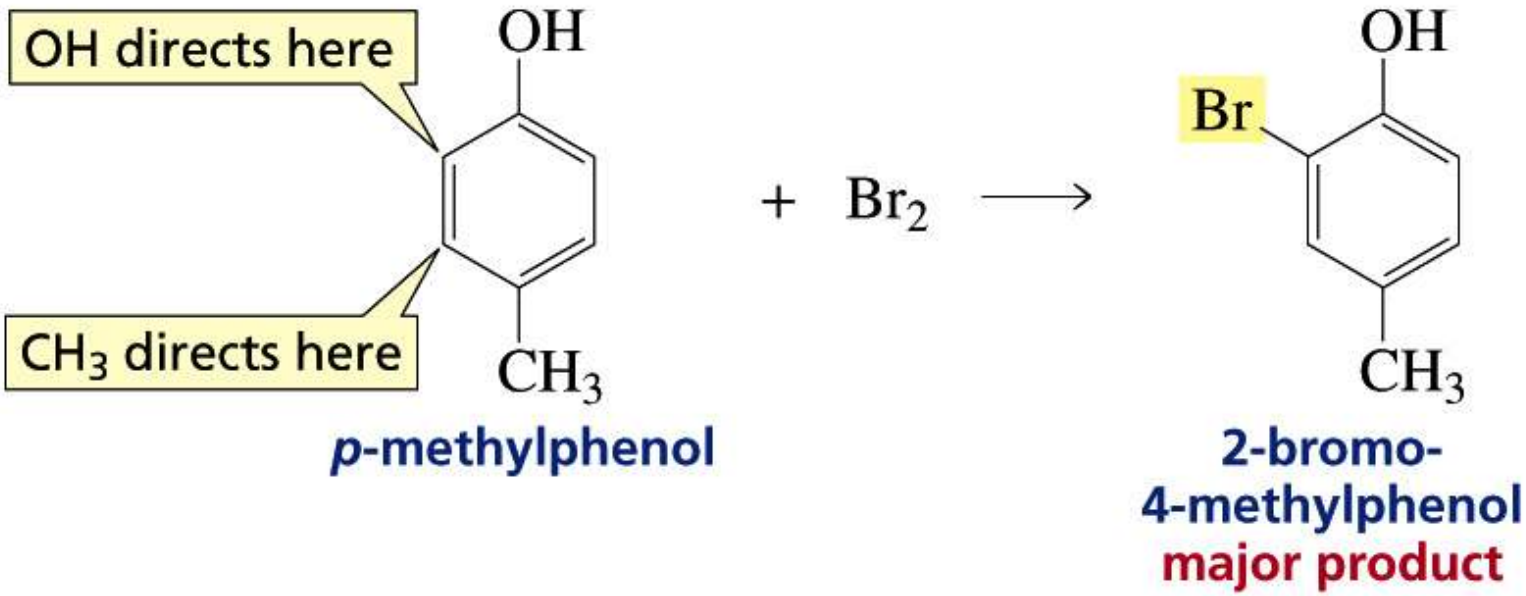


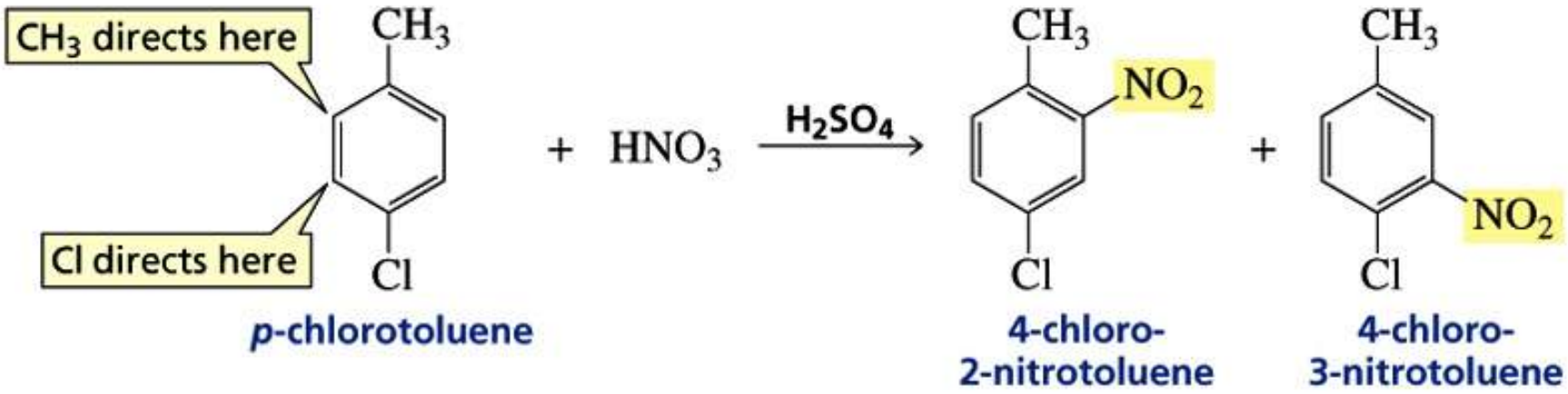

Activation effect of o,p directors are stronger than the meta directing deactivators.

## Case 3. Resonance vs. inducting effect



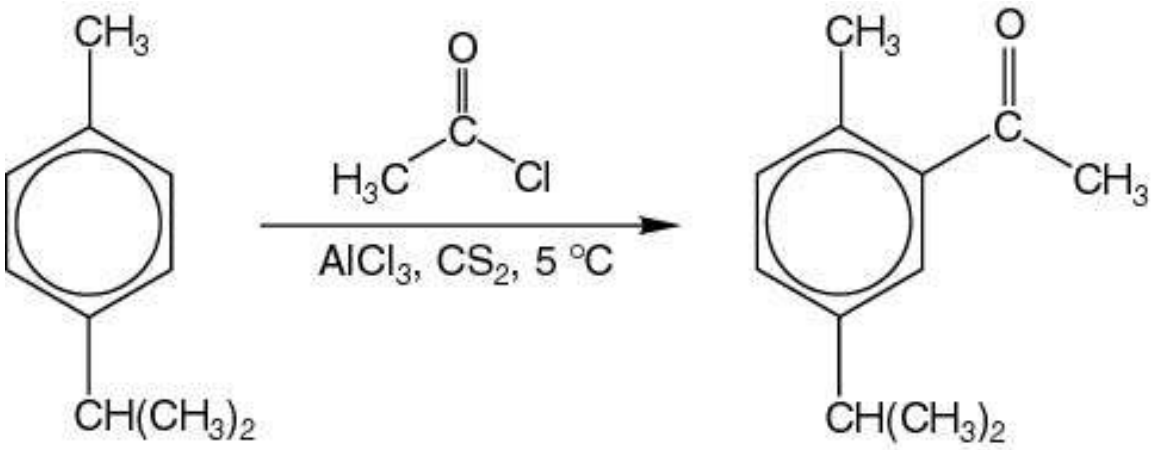

resonance effects are more
important than inductive effects



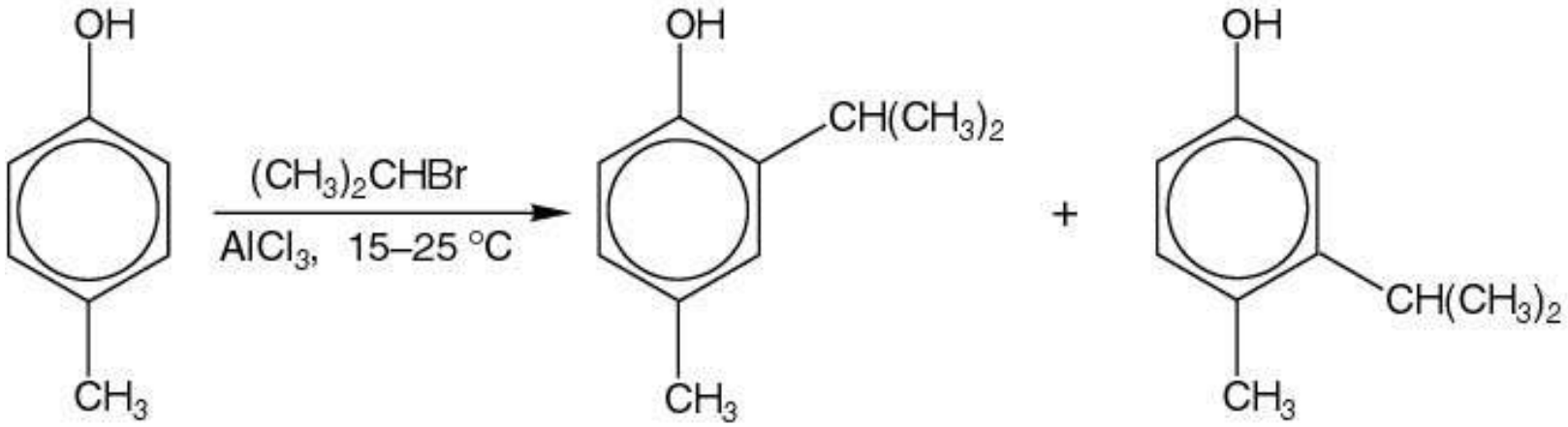




The alkyl groups and halides are in-between (mixture of products)

# Steric and electronic effects can decide the outcome

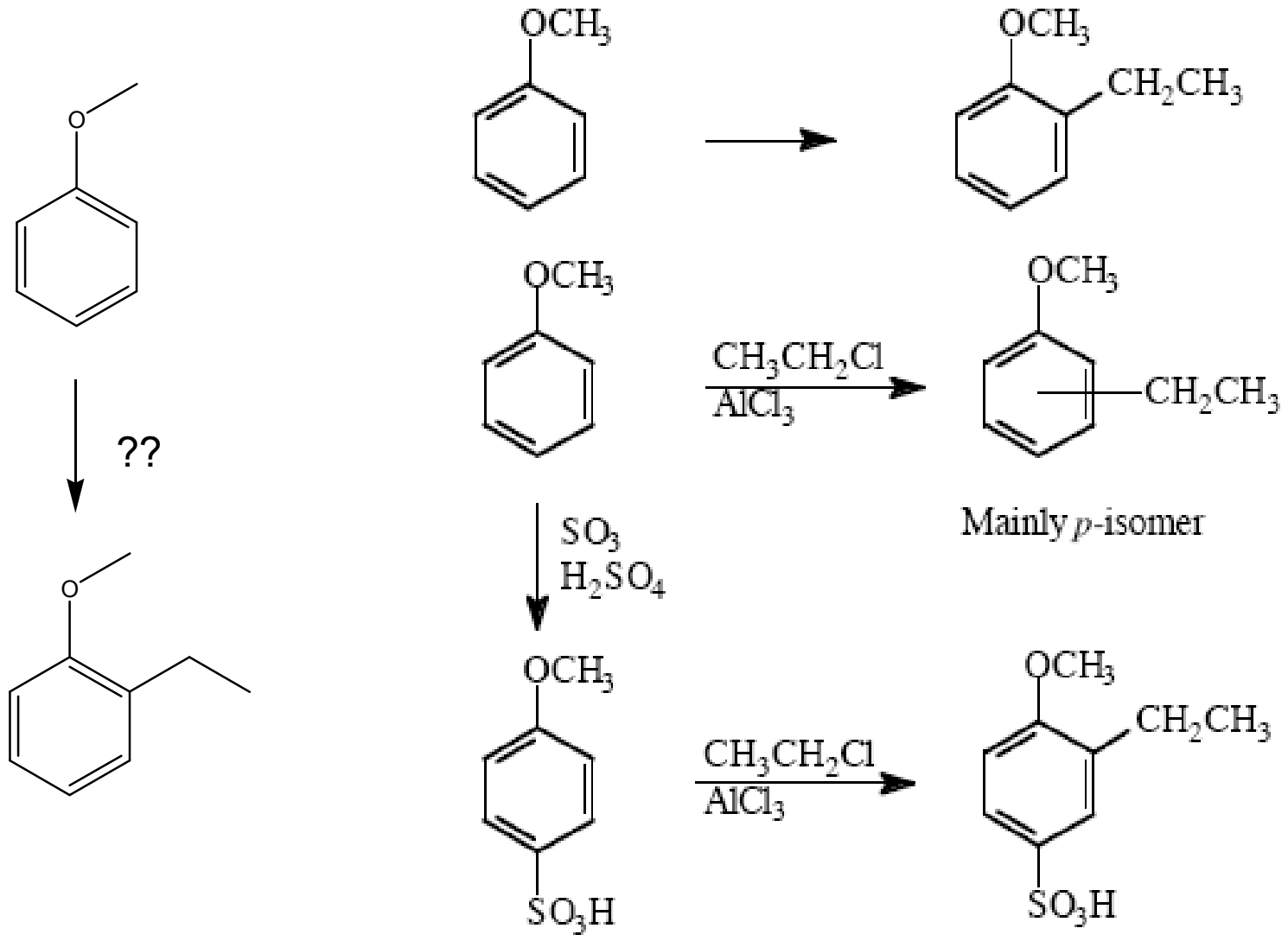



The steric influence of the large isopropyl group dominates (50% yield)




Here, electronic effects decide the issue

Problem

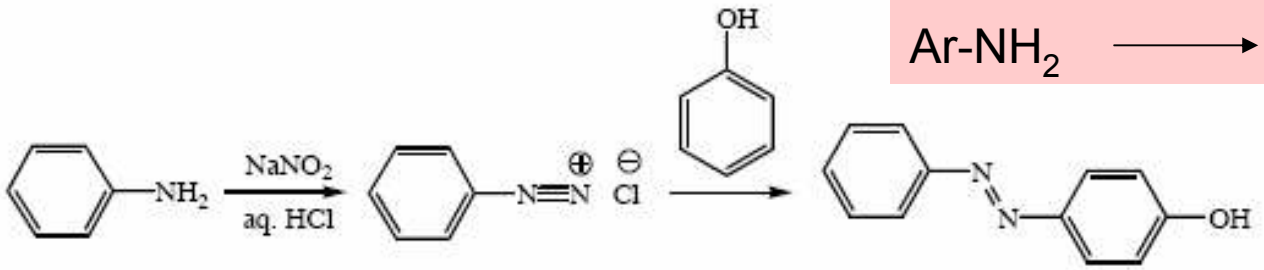


# A different electrophile

**Electrophile**

Ar-$NH_2$ ⟶ $ArN_2^+$

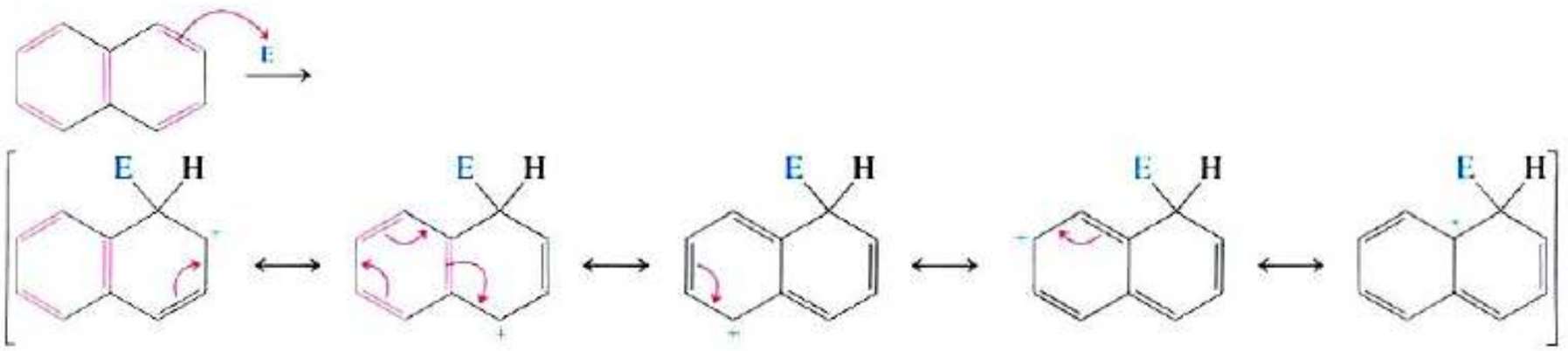
Diazo Coupling:

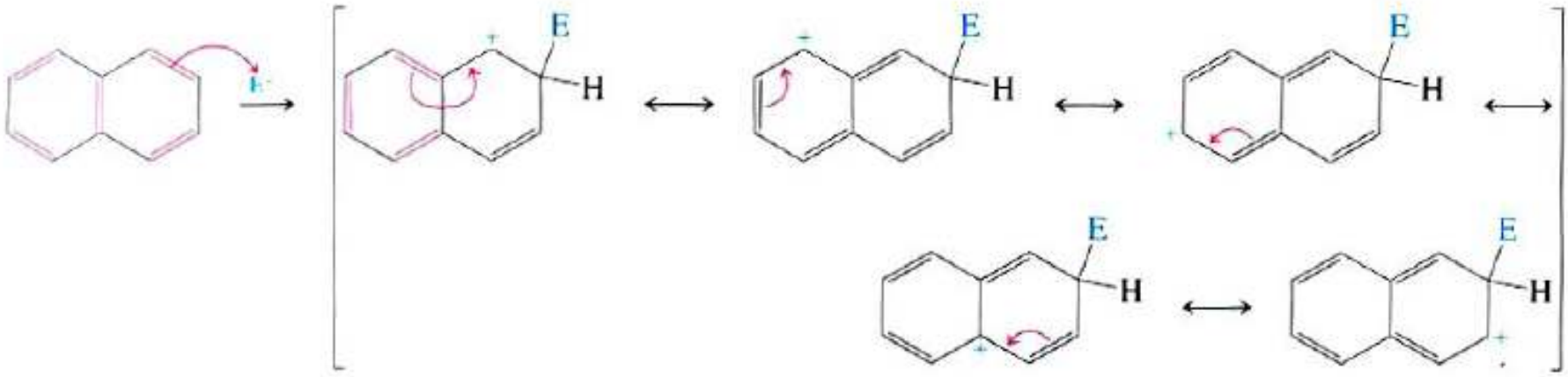



Show how $ArN_2^+$ is formed

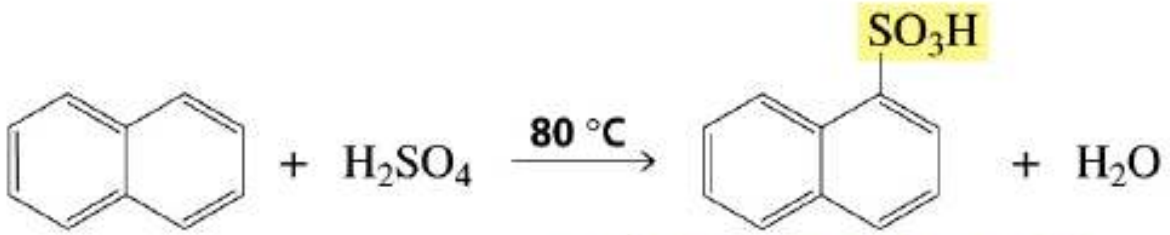
# Naphthalene- electrophilic substitution

There are two resonance structures which retain fully conjugated aromatic ring in the case of substitution at position 1.



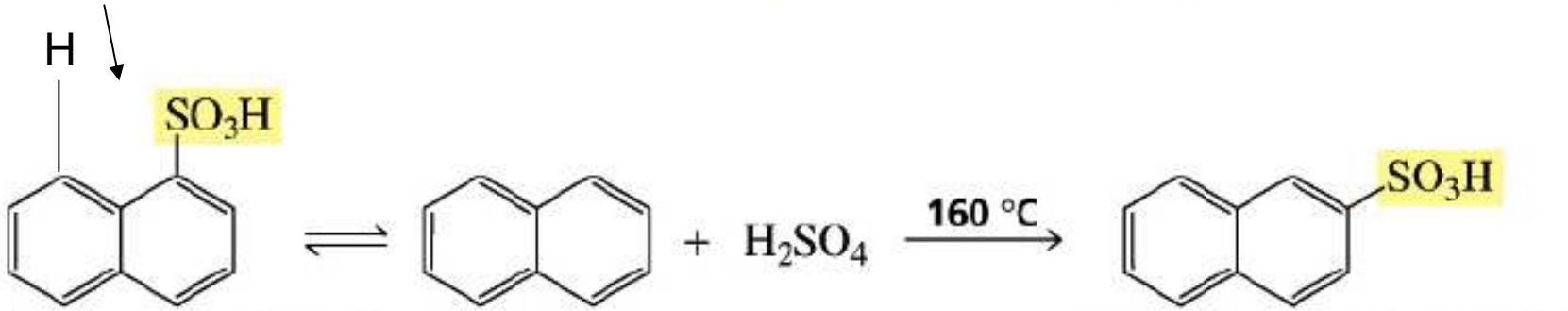



# Electrophilic substitution of Naphthalene




naphthalene-1-sulfonic acid

Peri interaction

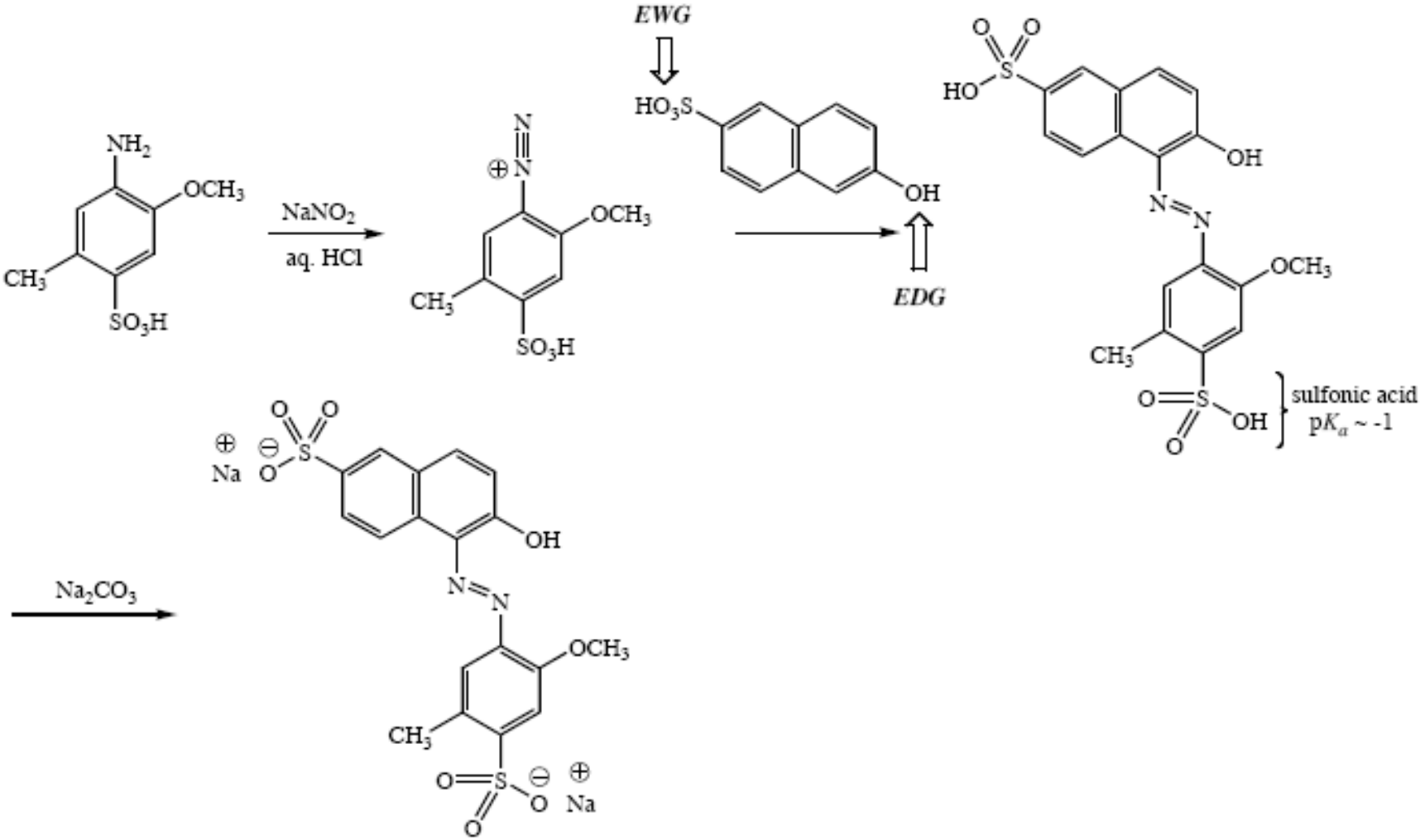



naphthalene-1-sulfonic acid
kinetic product

naphthalene-2-sulfonic acid
thermodynamic product

# Allura Red

A red azo dye, used in many food, drug and cosmetic products



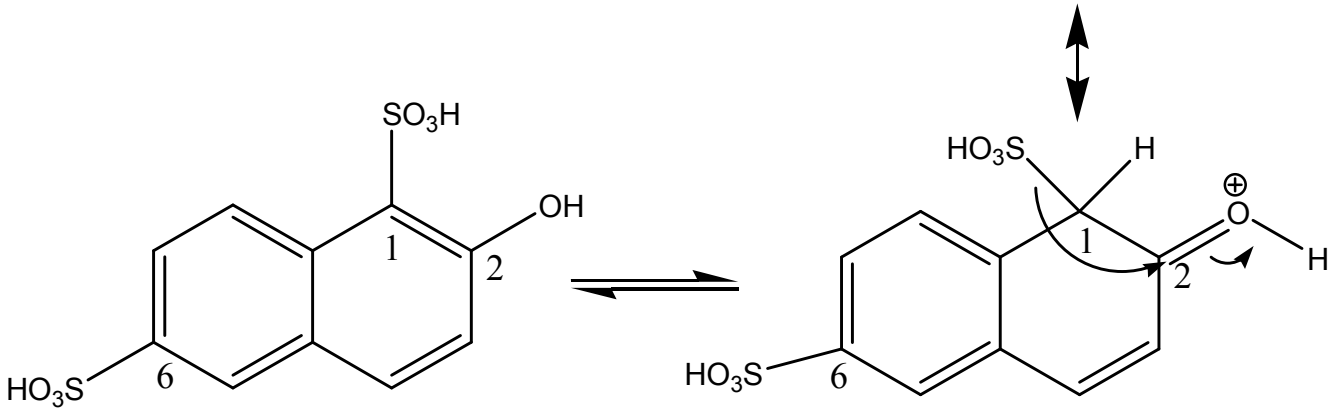

Allura Red AC

# Synthesis of Shaffer acid required for the synthesis of Allura red

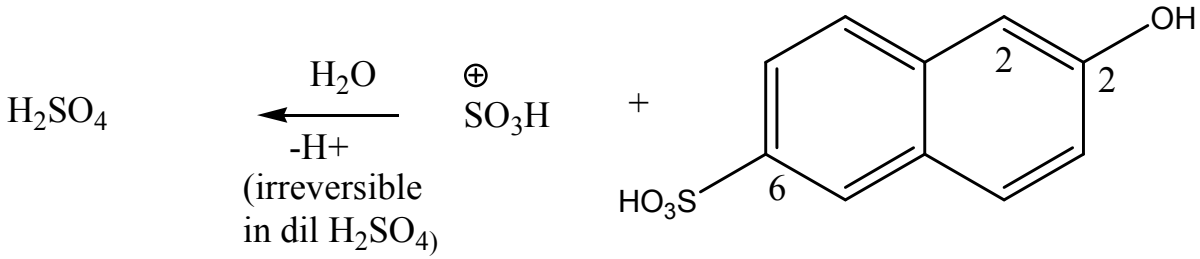
Method: Sulfonate 2-naphthol twice (ie. 1,6-disulfonate) and then desulfonate once.

Why desulfonation happens only at position 1?

Consider other resonance forms also




(First Sulfonation of 2-naphthol goes to position 1 and the second goes to position 2; First desulfonation happens at position1)




2-hydroxynaphthalene-6-sulfonic acid (shaffer acid)

# Nucleophilic Aromatic Substitution

**Neither true $SN_1$ or $SN_2$ is energetically feasible in aromatic Systems**

1. pi electrons in conjugation
2. Back side attack (as in SN2) and inversion is precluded by the geometry of the ring

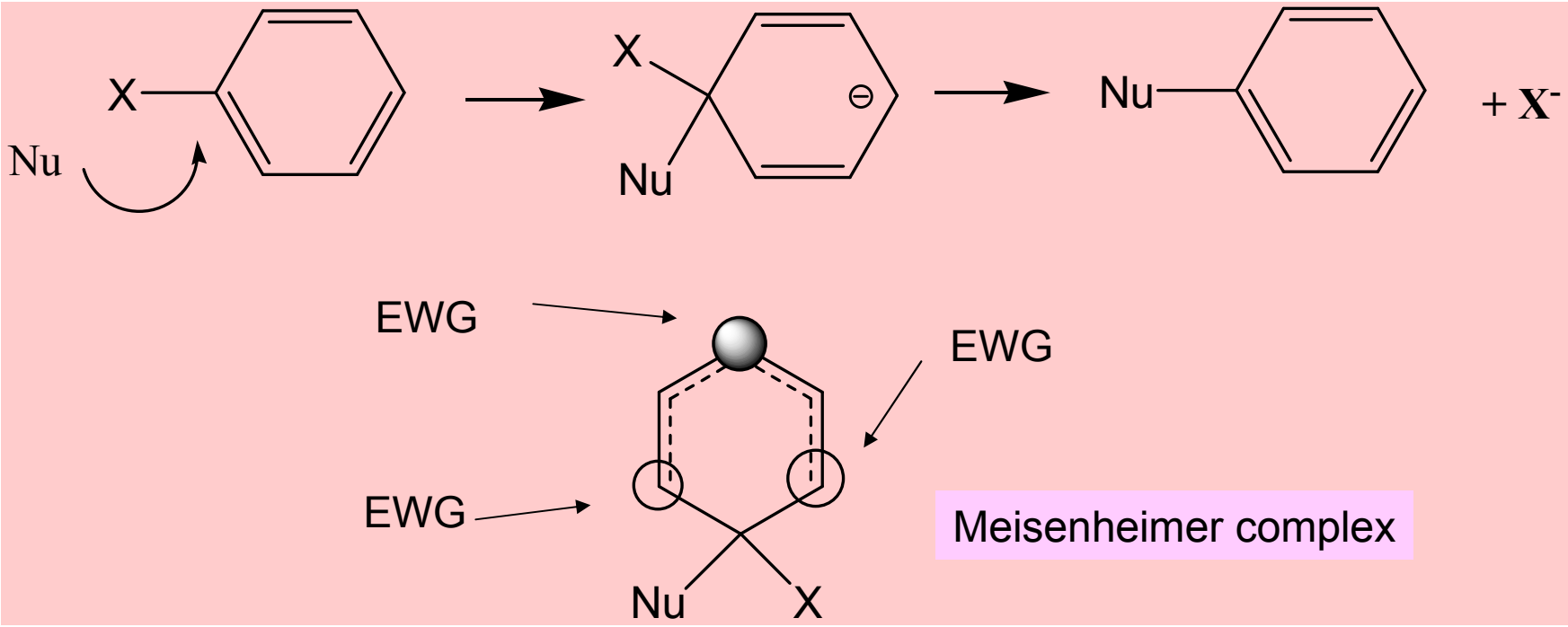
1. SN1 leads to phenyl cation which is less stable than a primary carbocation

**Two types of mechanisms that operate in Nucleophilic substitutions are,**

1. **Addition-Elimination**

2. **Elimination-Addition**

# 1. Addition-Elimination ($S_NAr$)

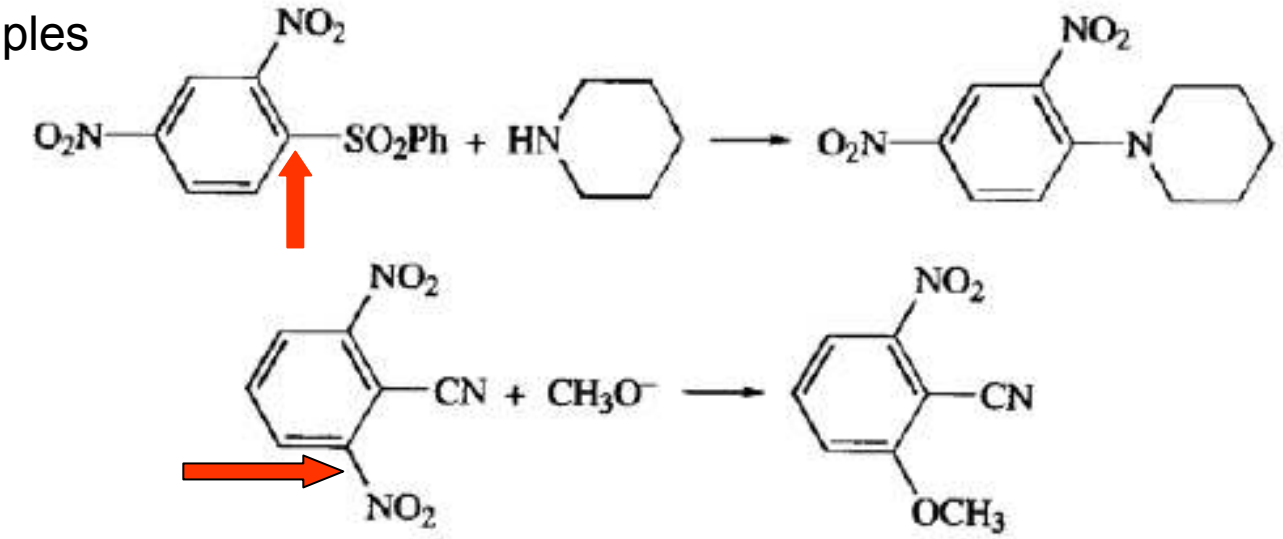



**Groups which favor substitution**
**$NO_2$, CN, -CO-**

The formation of the addition intermediate is usually the RDS
For halogens, the order of reactivity is **F > Cl > Br> I**
(stronger bond dipoles associated with the more electronegative atom favor the addition step)

**leaving groups Halogens, Alkoxy, $NO_2$, Sulfonyl**

Examples



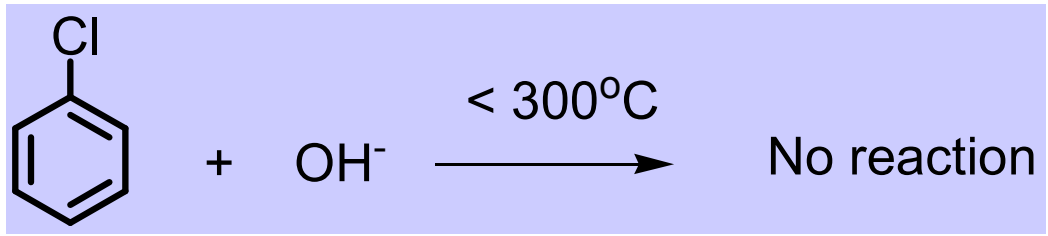

## Nucleophiles in aromatic substitution

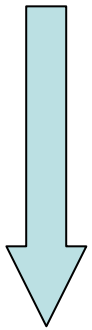
**Alkoxides, Phenoxides, Sulfides, fluoride ion or amines (similar to that in SN2)**

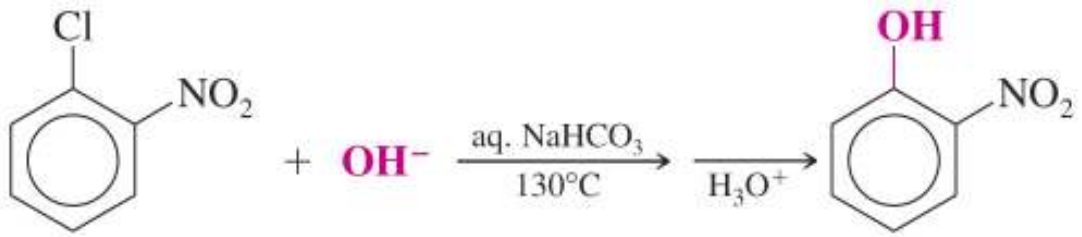
The rate of the reaction gets enhanced on using
Dipolar aprotic solvents, crown ethers or other phase transfer catalysts

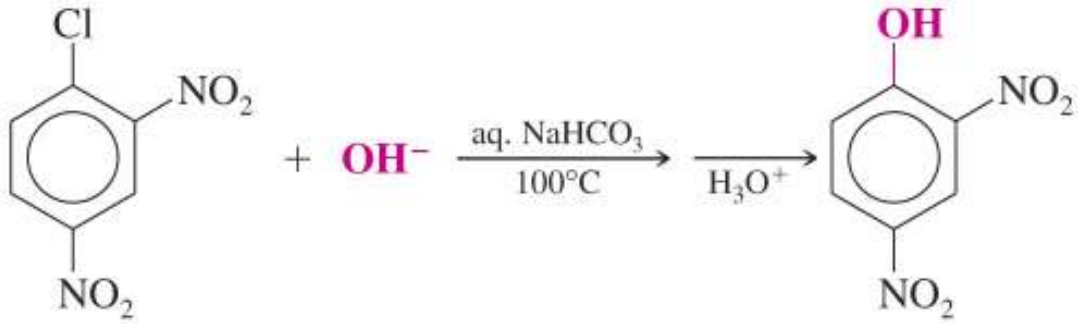
(by providing the nucleophile in a reactive state with minimum solvation)

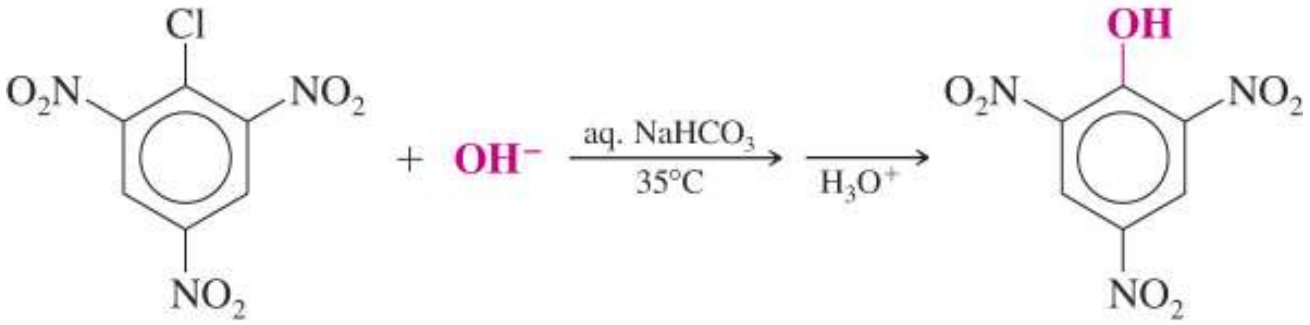
Electron withdrawing groups stabilize Meisenheimer complex and favor the reaction



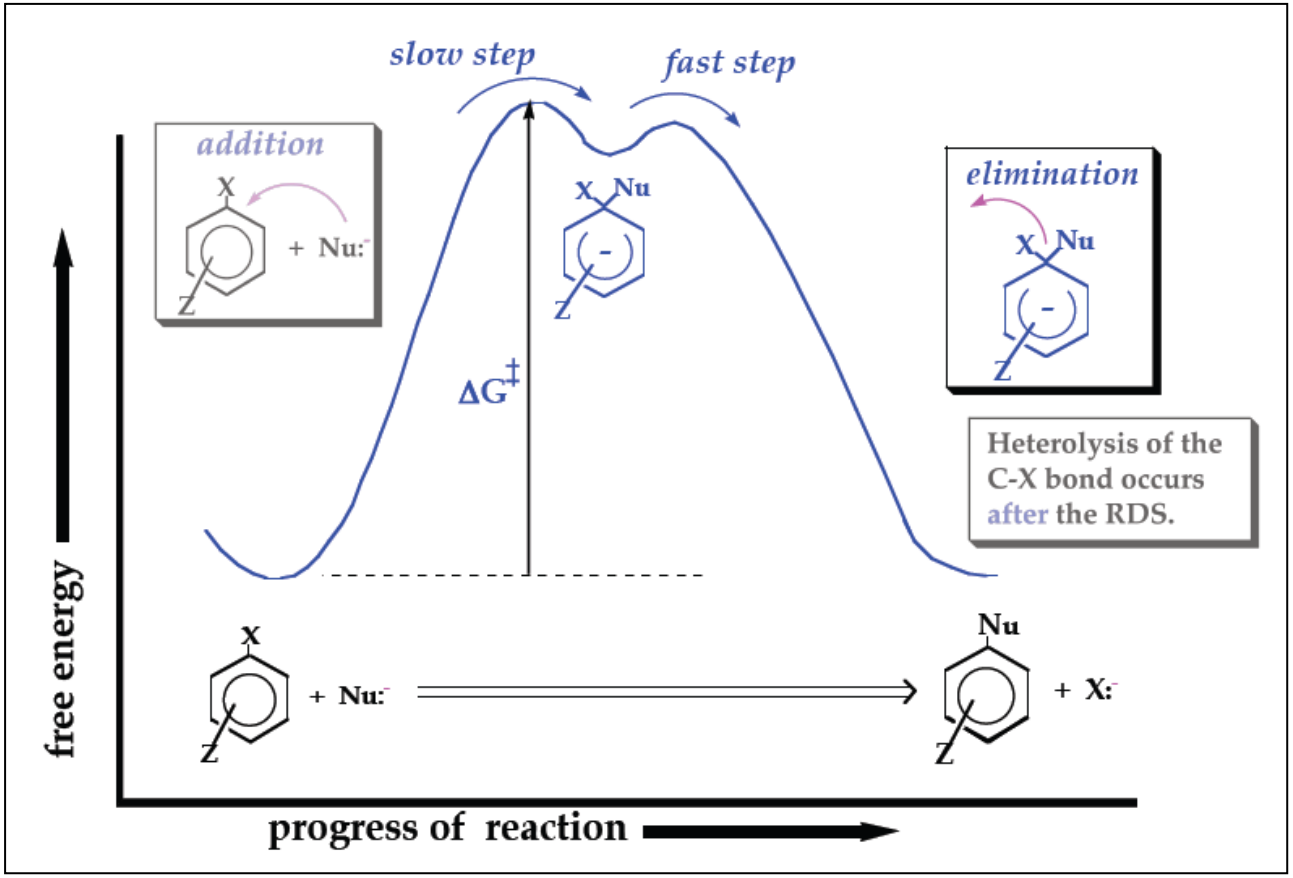





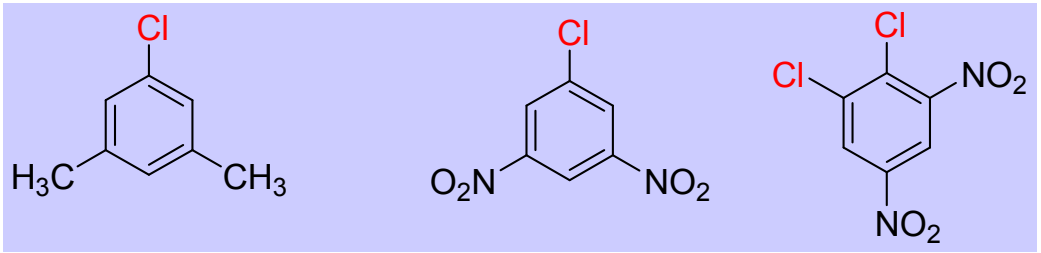



Energy profile

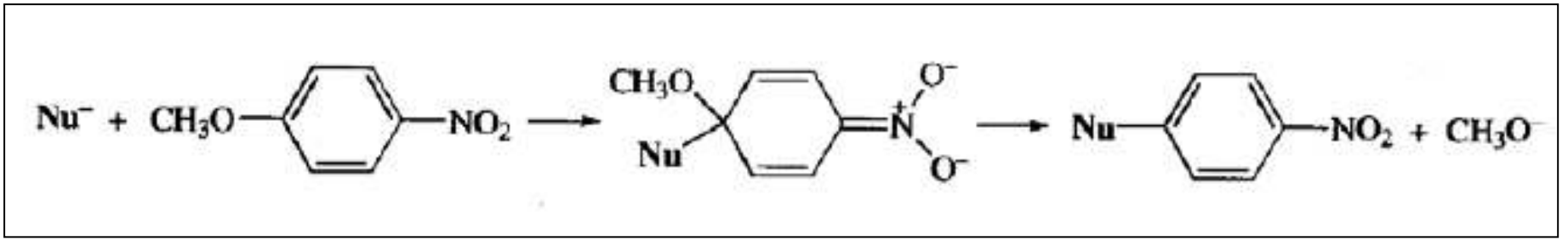


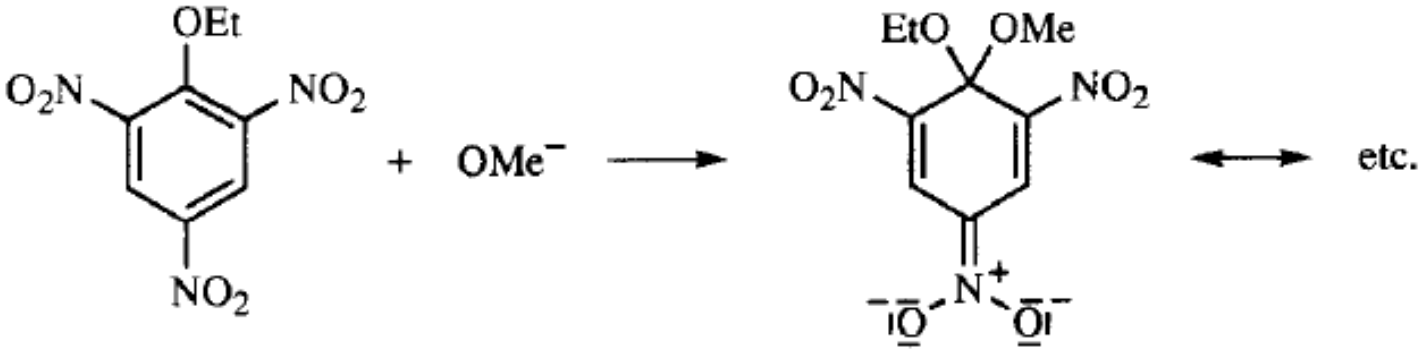

Which among these Substrates undergo the reaction efficiently




Which chloride will be nucleophilically Substituted?

It is possible to isolate the Meisenheimer complex in some cases! Stable!



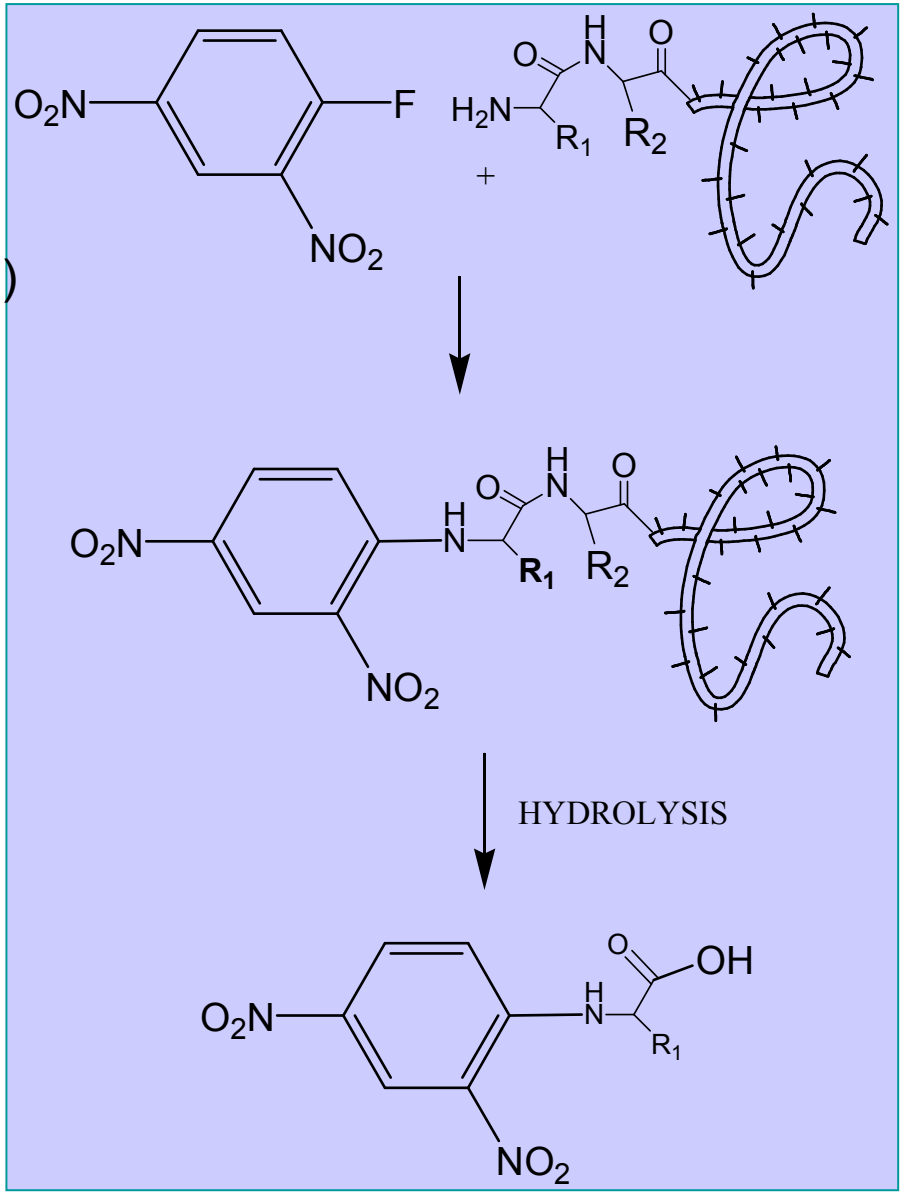




Meisenheimer complex

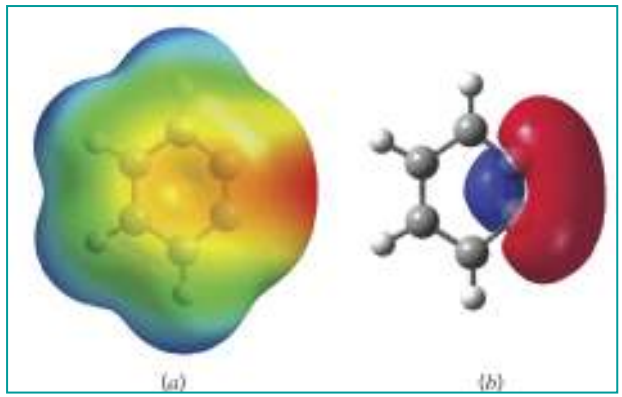
One important application of nucleophilic aromatic substitution reaction

## Sanger's Method of N-terminal Amino acid determination in proteins

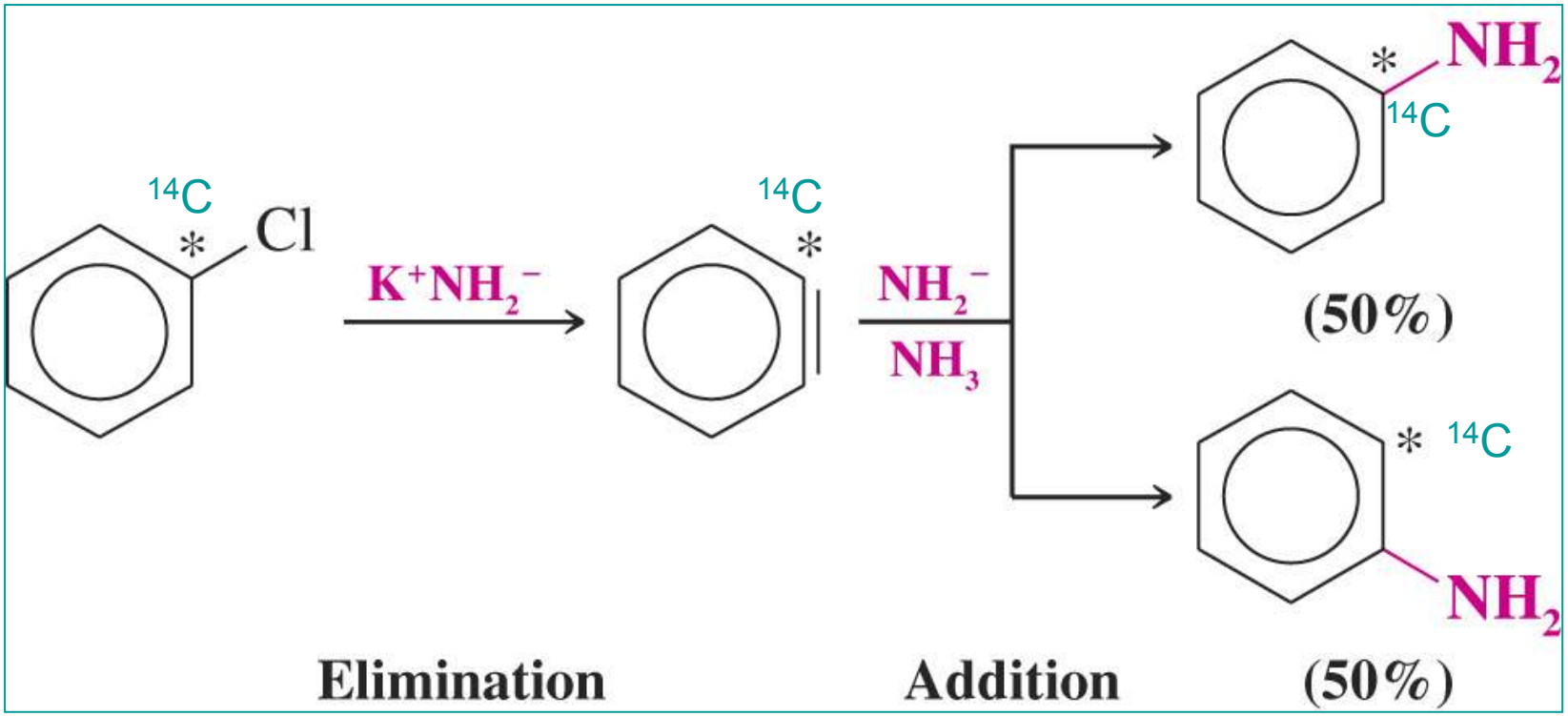
- The 2,4-dinitrofluorobenxene (2,4-DNP) is treated with the protein of interest under mild alkaline conditions (doesn't cause cleavage of peptide bonds)
- The DNP-protein adduct is then subjected to acid hydrolysis which lead to the cleavage of peptide bonds, leaving the N-terminal residue in the form of its DNP-derivative
- This derivative can be identified by chromatographic methods

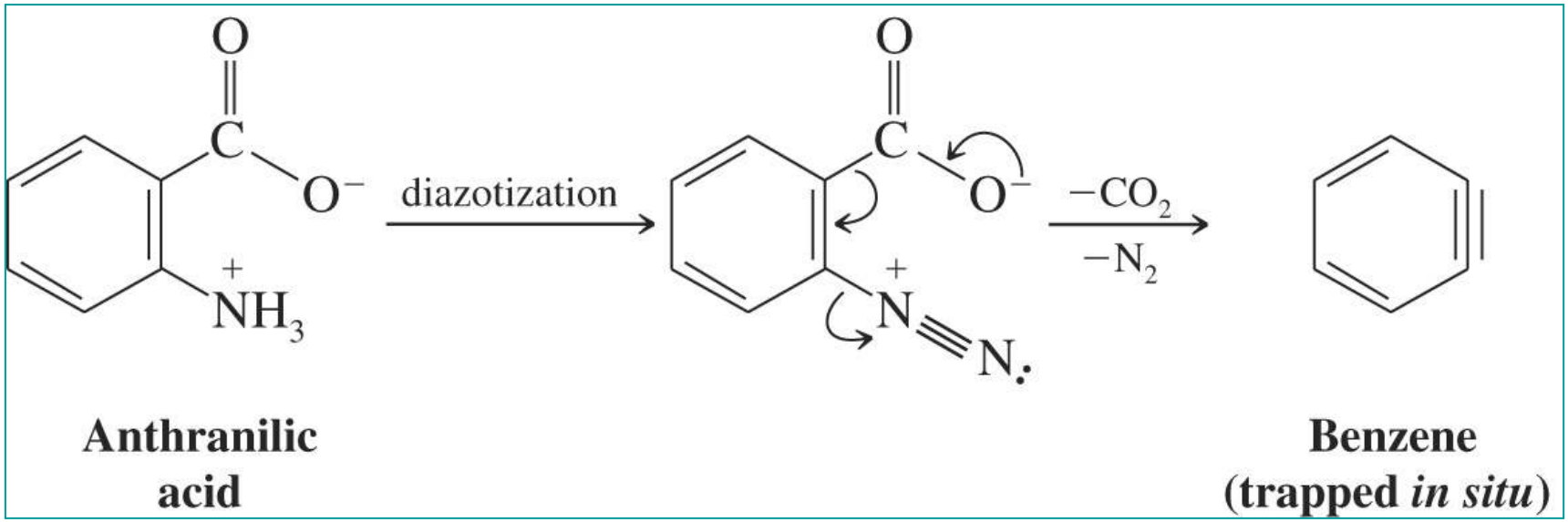


# Elimination-Addition (Benzyne mechanism)



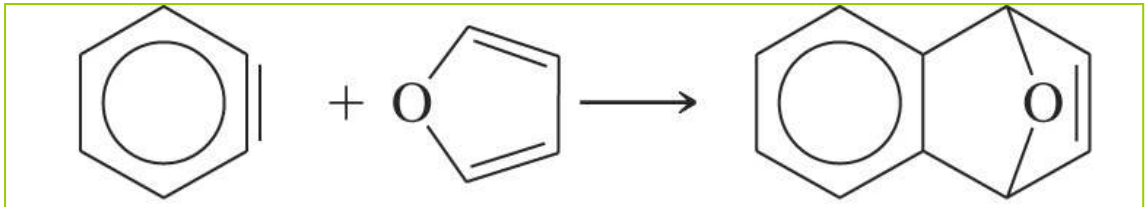
‘Cine’ Mechanism- evidence






**Anthranilic acid**

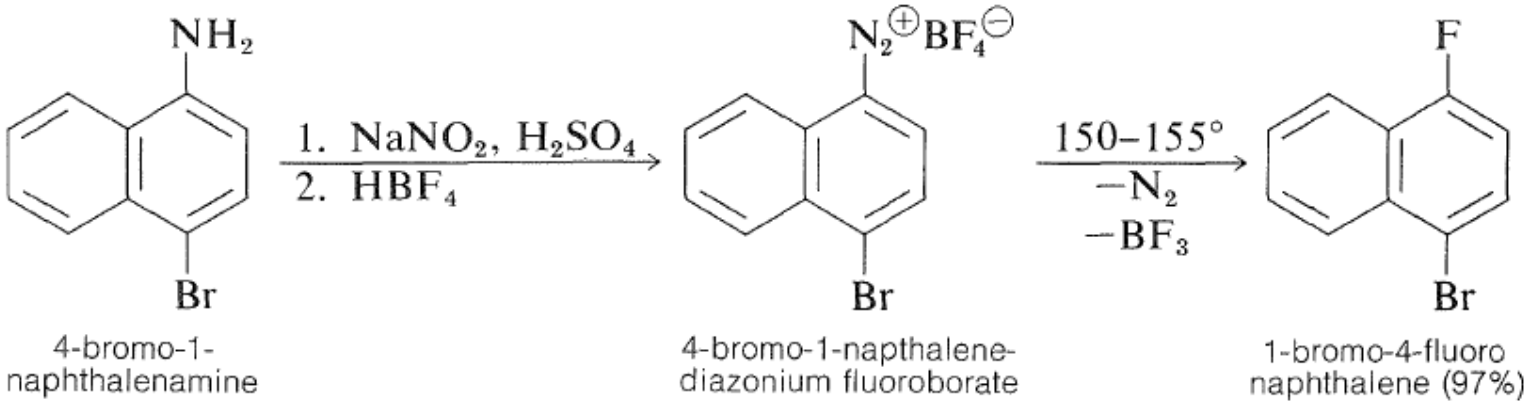
**Benzene (trapped *in situ*)**




**Benzyne (generated by an elimination reaction)**

**Furan**

**Diels–Alder adduct**



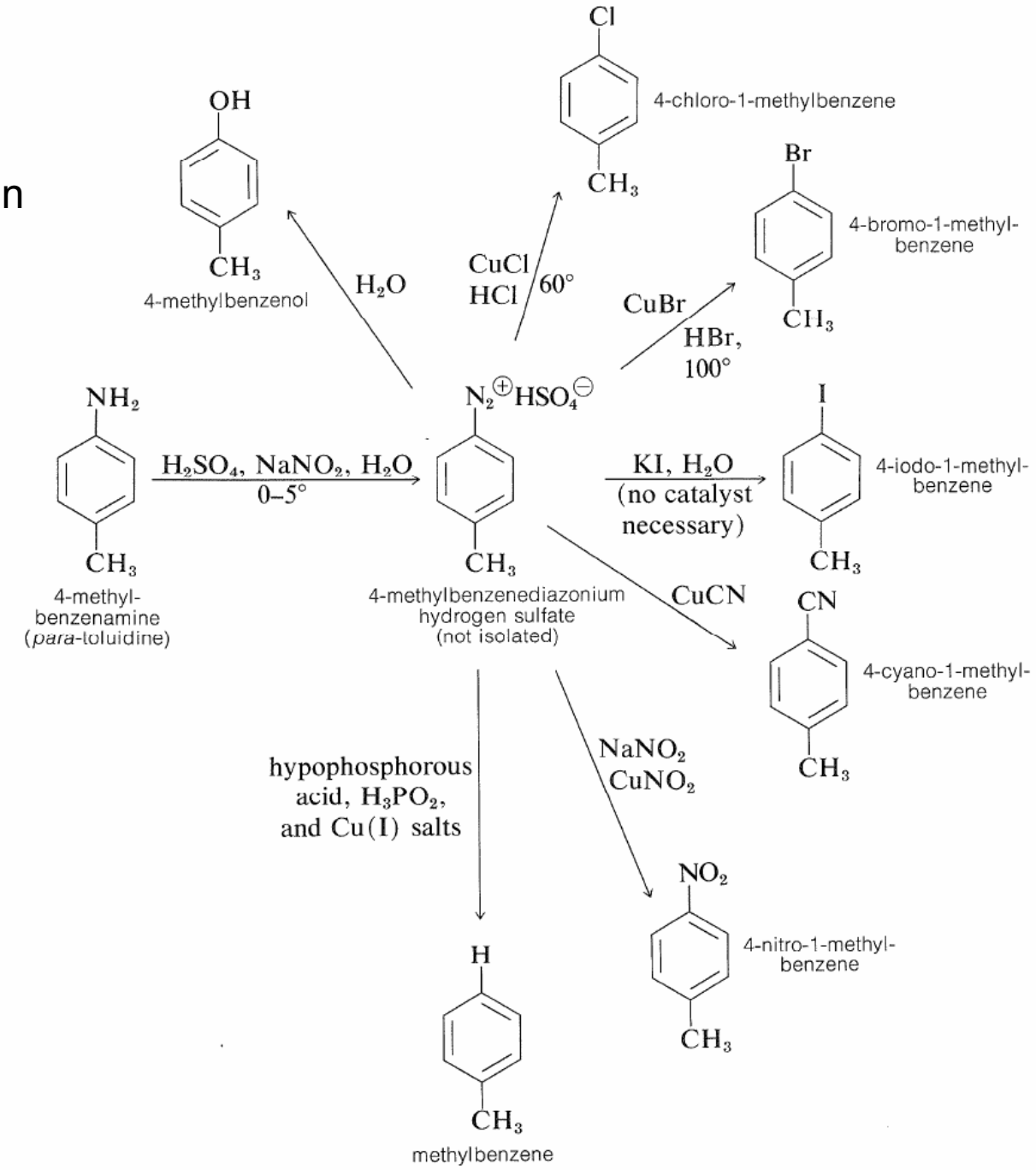

4-bromo-1-naphthalenamine

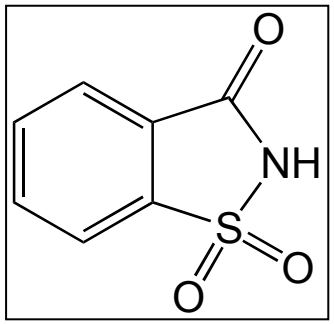
4-bromo-1-napthalene-diazonium fluoroborate

1-bromo-4-fluoro naphthalene (97%)

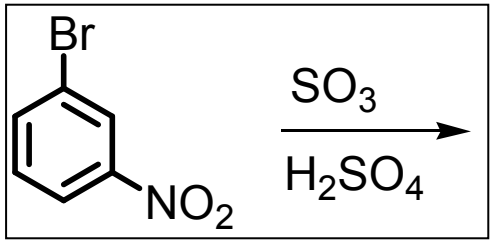
What is the electrophilic species generated from $HNO_2/H_2SO_4$ ?

Some functional group Inter-conversions you can consider while writing a sequence

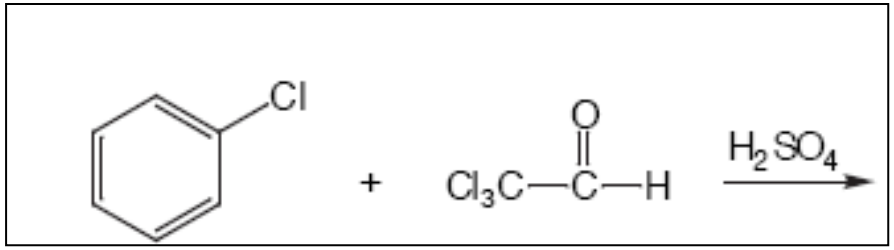




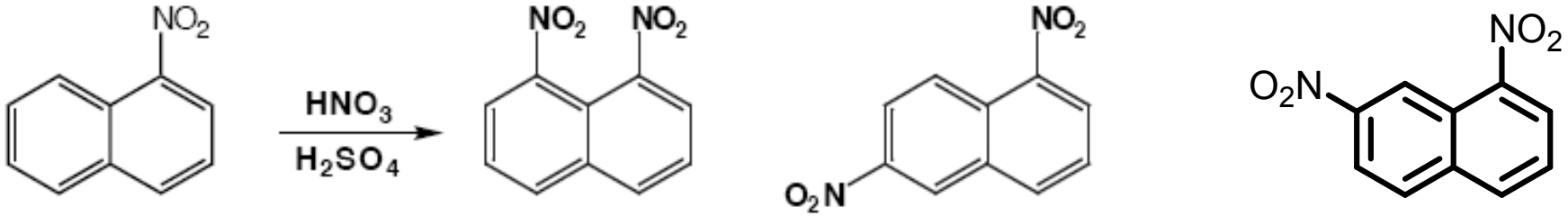

How would you make this compound



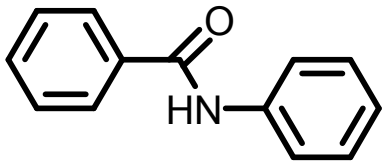

Predict the product



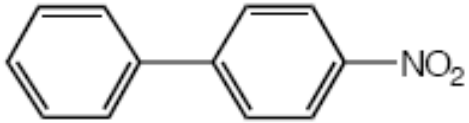

Predict the product



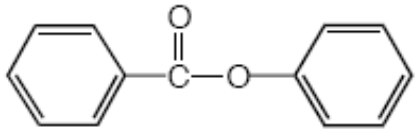

Which among these products are most likely to be formed?
Answer by analyzing resonance structures of intermediates



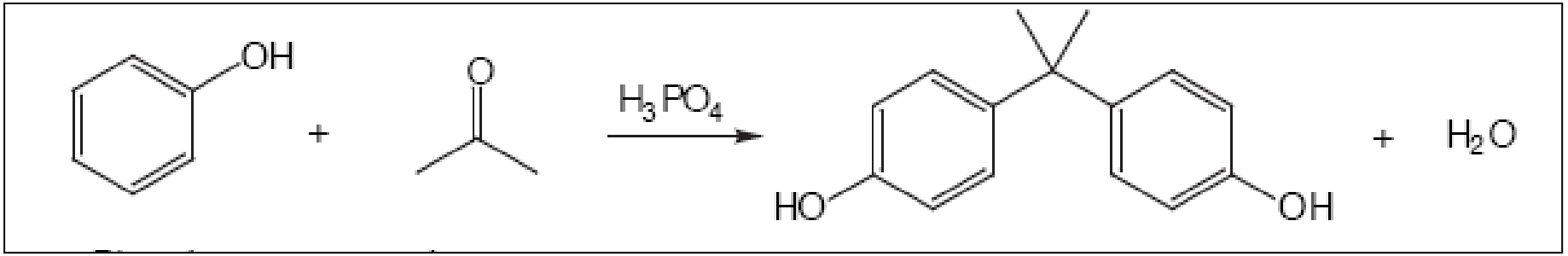

$\xrightarrow[HNO_3]{H_2SO_4}$



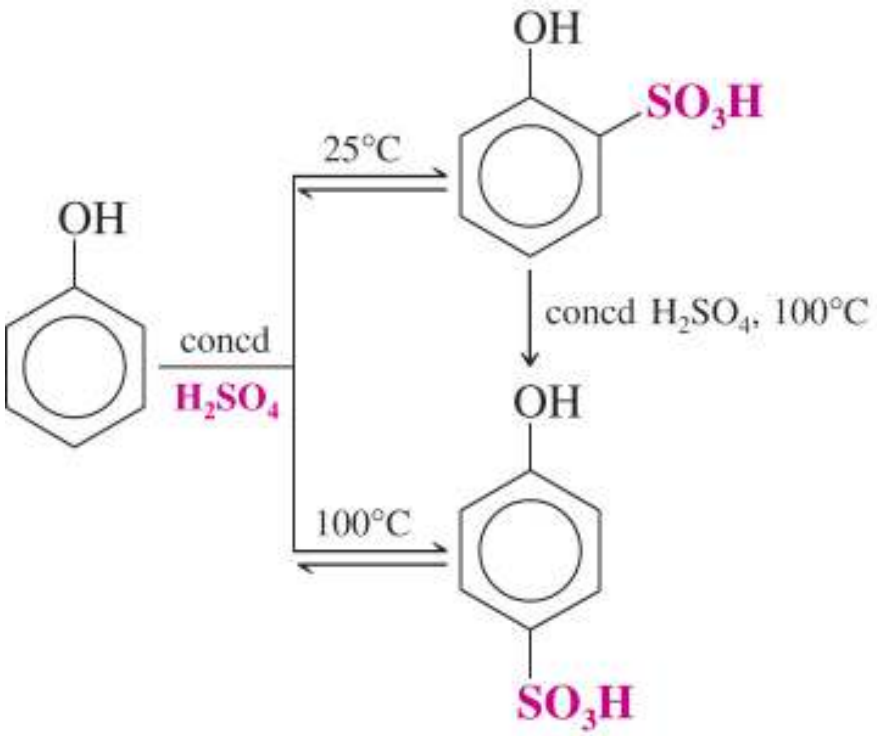

$\xrightarrow[HNO_3]{H_2SO_4}$



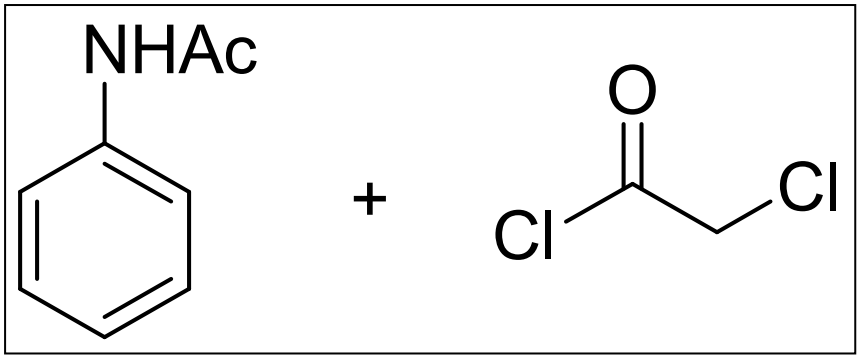

$\xrightarrow[HNO_3]{H_2SO_4}$




How??




Which is kinetic and which is thermodynamic product?




What is the product if 1 eq. of $AlCl_3$ is used