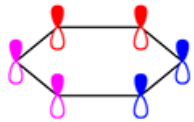
Aromaticity

Hückel's rule states that if a **cyclic, planar, conjugated** molecule having **(4n+2) π electrons** (n = 0, 1, 2 etc), is known as **aromatic conpound**.

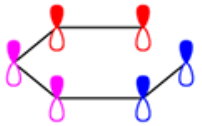
benzene



1. Cyclic
2. *p*-orbital for each member of the ring
3. Planar ring (sp^2 hybridized)
4. **4n+2 π–bond electron count.**

Aromatic

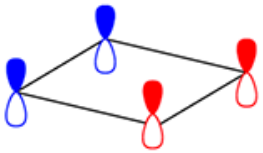
hexatriene



1. NOT Cyclic
2. *p*-orbital for each member of the ring
3. Planar ring (sp^2 hybridized)
4. **4n+2 π–bond electron count.**

Non-Aromatic

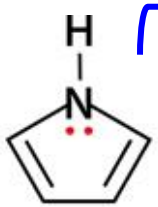
cyclobutadiene



1. Cyclic
2. *p*-orbital for each member of the ring
3. Planar ring (sp^2 hybridized)
4. **Closed 4n π–bond electron count.**

Anti-Aromatic

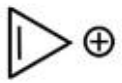
Aromatic



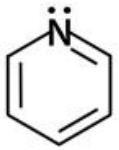
Pyrrole
Pi electrons = 6
n = 1

Furan
Pi electrons = 6
n = 1

Thiophene
Pi electrons = 6
n = 1



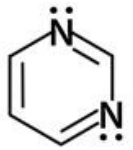
Cyclopropenyl ion
Pi electrons = 2
n = 0



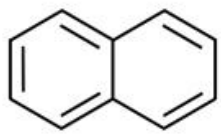
Pyridine
Pi electrons = 6
n = 1

Imidazole
Pi electrons = 6
n = 1

Oxazole
Pi electrons = 6
n = 1

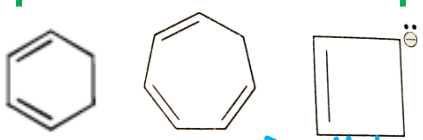


Pyrimidine
Pi electrons = 6
n = 1

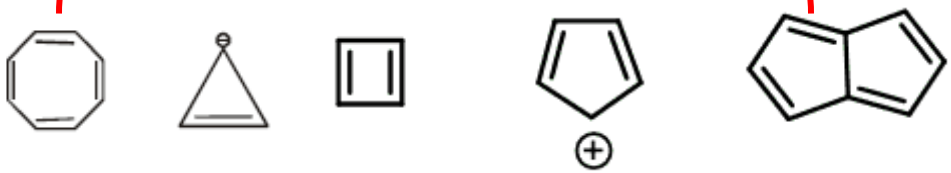


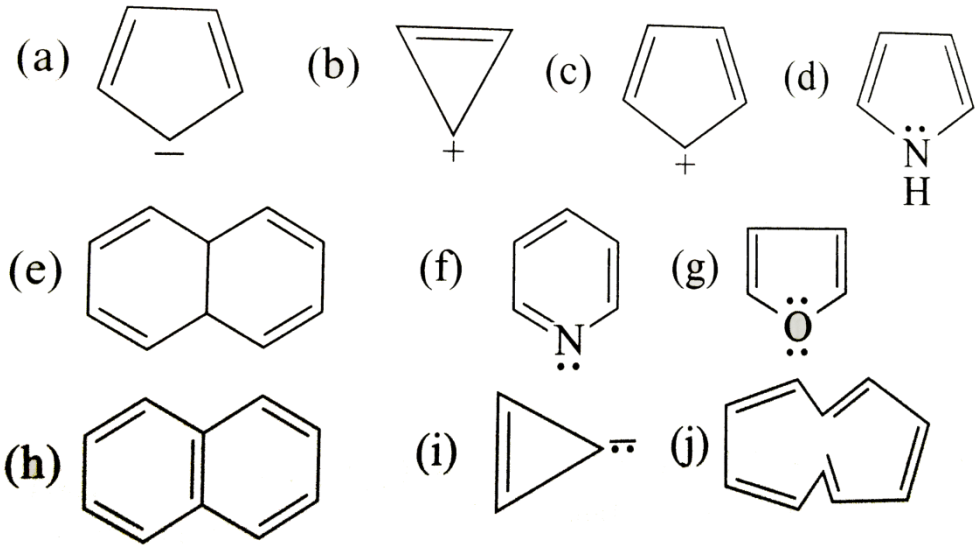
Napthalene
Pi electrons = 10
n = 2

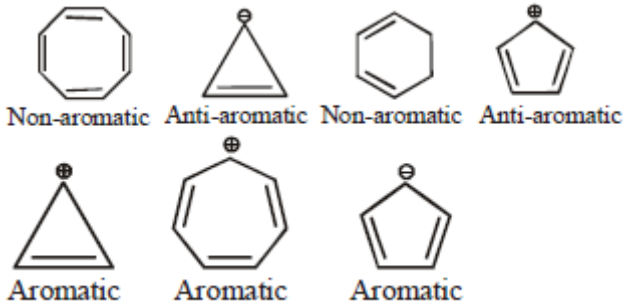
Non aromatic

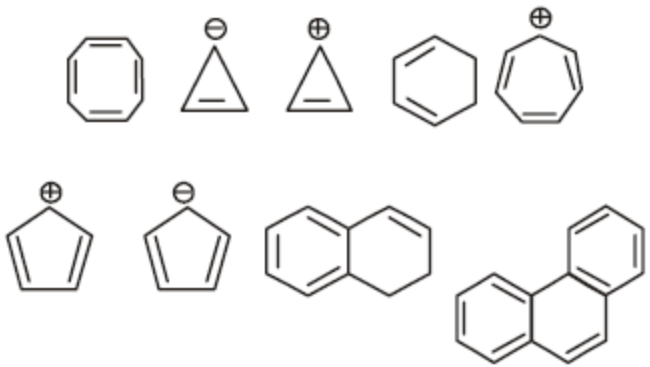


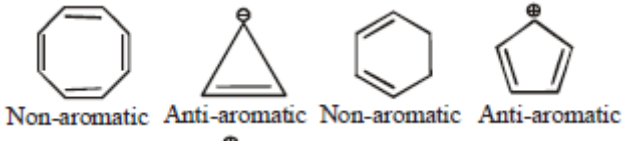
Anti aromatic




(a)
(b)
(c)
(d)
N
H
(e)
(f)
N
(g)
O
(h)
(i)
(j)

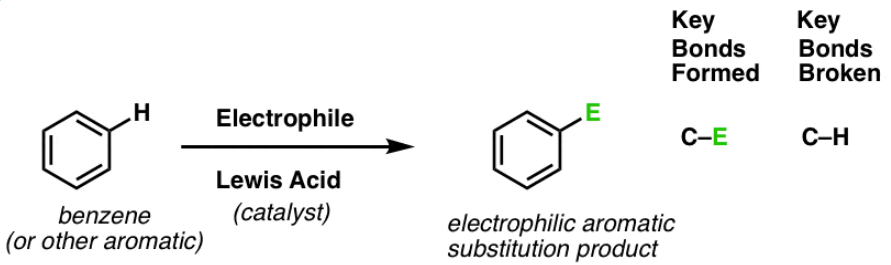

Non-aromatic
Anti-aromatic
Non-aromatic
Anti-aromatic
Aromatic
Aromatic
Aromatic



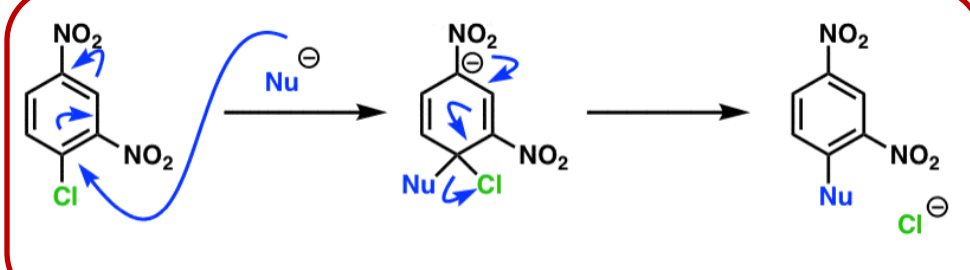

Non-aromatic
Anti-aromatic
Non-aromatic
Anti-aromatic

Aromatic substitution reactions

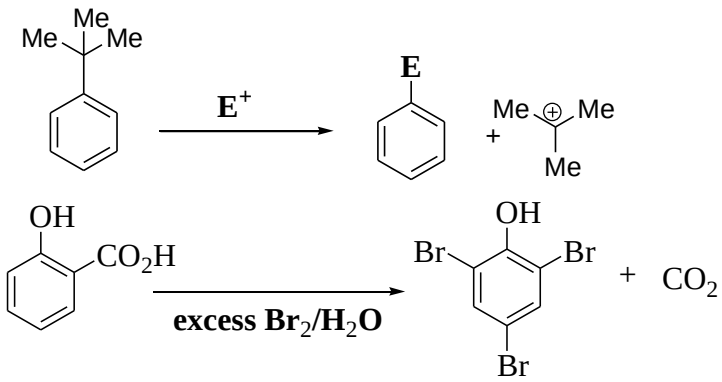
Electrophilic aromatic substitution reactions



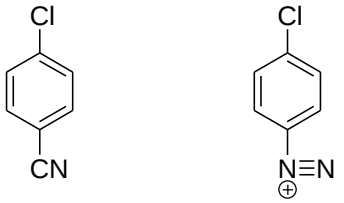
Nucleophilic aromatic substitution reaction



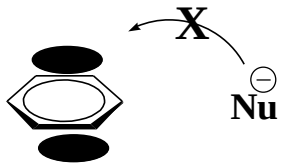
IPSO substitution



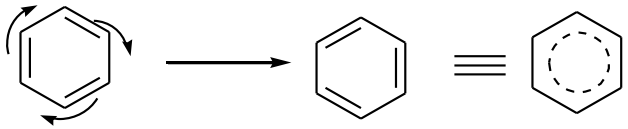
More example of nucleophilic substitution reaction



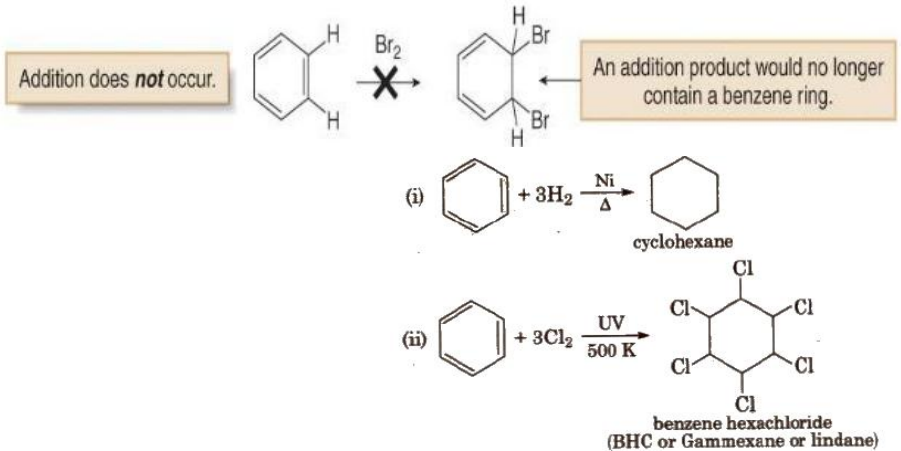
Why simple benzene does not under goes normal nucleophilic substitution or addition reactions??



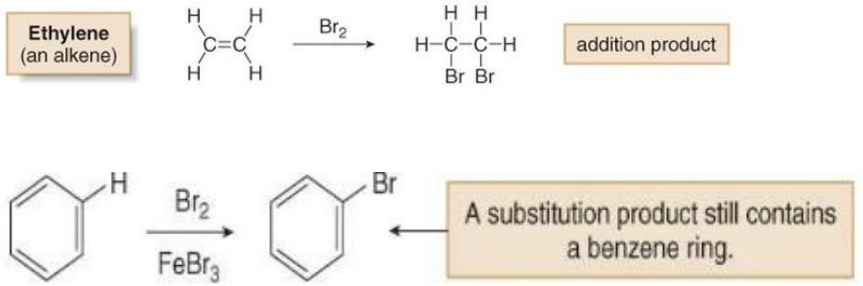
In **benzene**, the π-electrons are delocalised and makes the structure more stable. Delocalization of π electron is called resonance. Thus, **benzene does not** give **addition reactions** because of resonance stabilisation



- Benzene does not react with Br_2 to yield an addition product. Instead, in the presence of a Lewis acid, bromine substitutes for a hydrogen atom, yielding a product that retains the benzene ring.

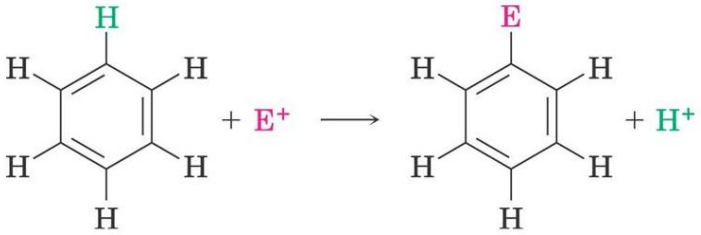


Whereas unsaturated hydrocarbons such as alkenes, alkynes and dienes readily undergo addition reactions, benzene does not.



Electrophilic aromatic substitution

- Electrophilic aromatic substitution is the most common reaction of aromatic compounds
  - It replaces a proton (H^+) on an aromatic ring with another electrophile (E^+)
  - It leads to the retention of the aromatic core



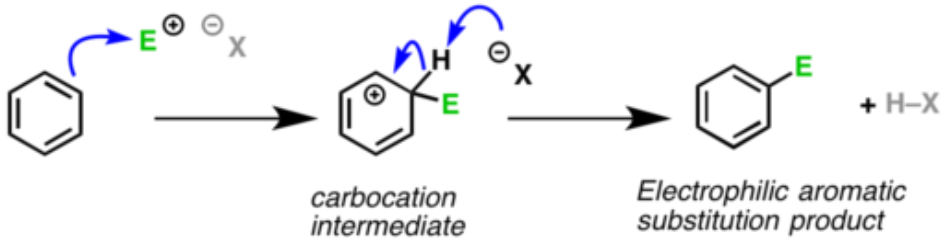
Electrophilic Aromatic Substitution: The General Mechanism

Step 1: attack of electrophile by aromatic pi bond

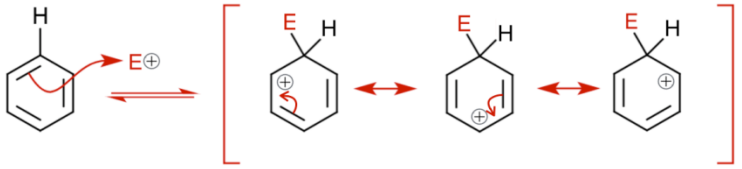
Form C–E
Break C–C (π)

Step 2: deprotonation adjacent to carbocation restores aromaticity

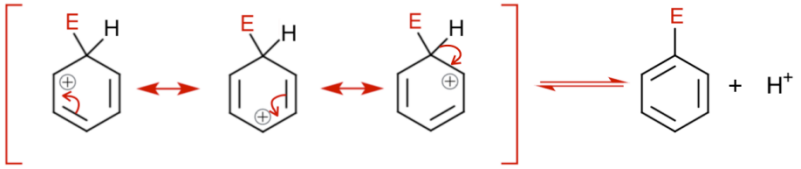
Break C–H
Form C–C (π)
(and also H–X)



Step 1: Electrophilic Attack

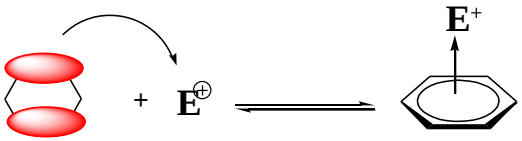


Step 2: Proton Loss



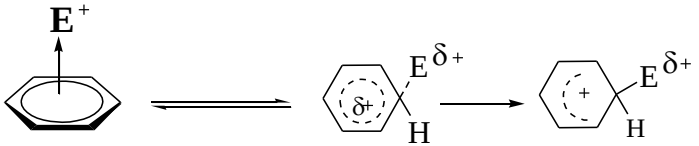
Step wise mechanism of Ar.S_E2 reaction

Step I. Formation of Π complex



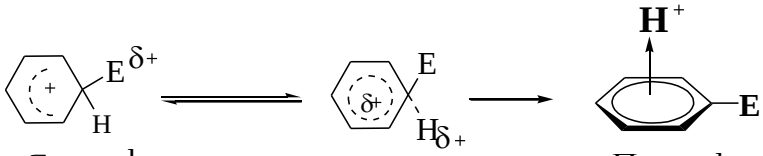
Π complex

Step II. Conversion of Π complex to σ complex



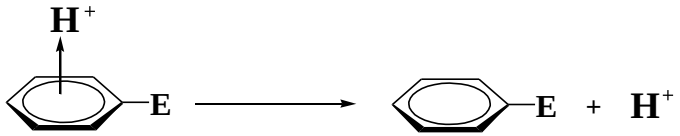
σ complex

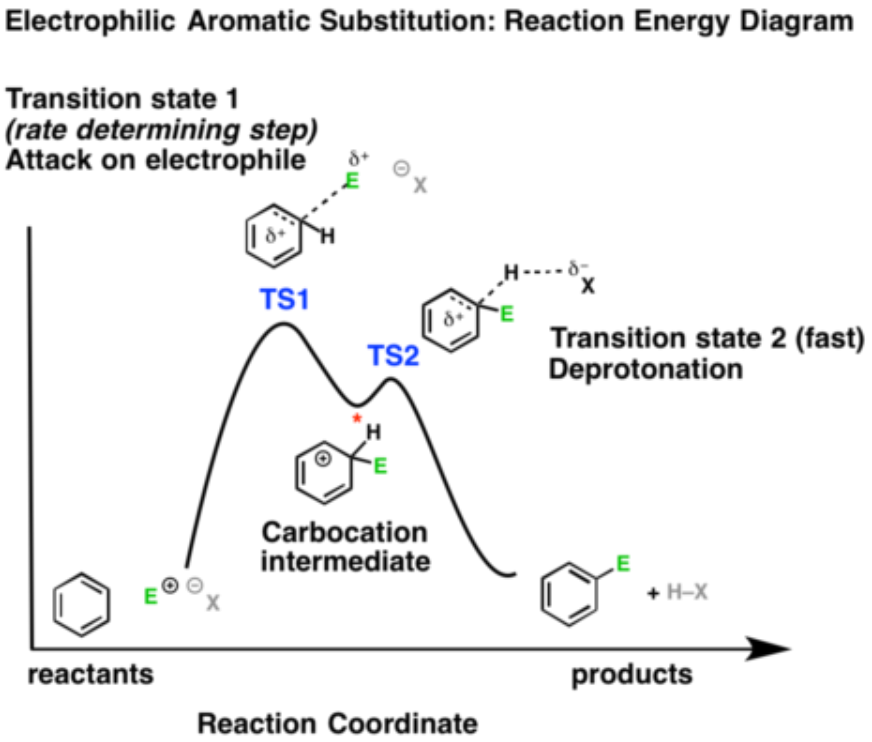
Step III. Conversion of σ complex to Π complex



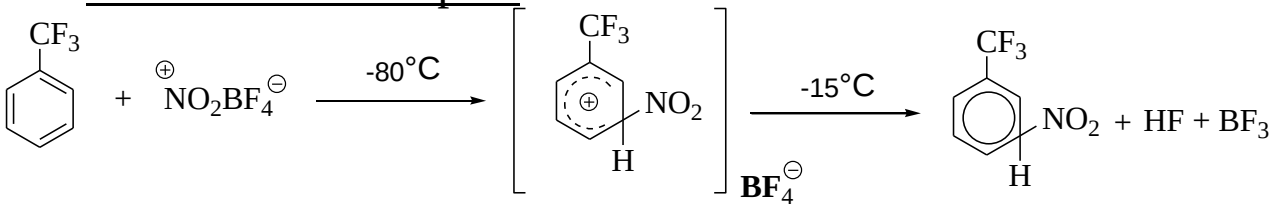
σ complex Π complex

Step III. Decomposition of Π complex to products





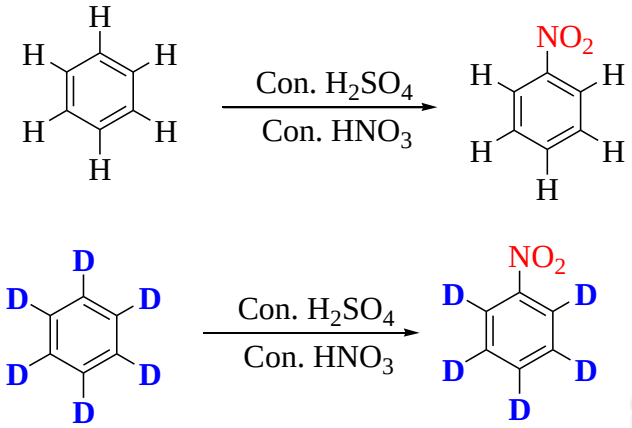
1. Isolation of σ complex



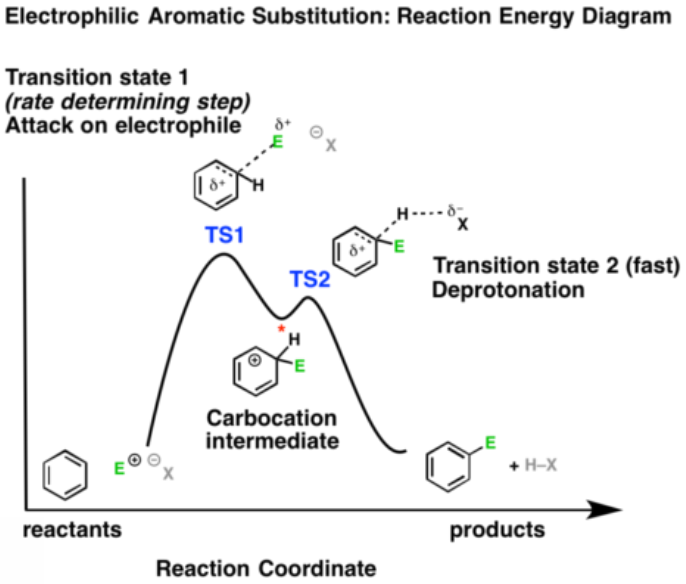
intermediate **σ complex**

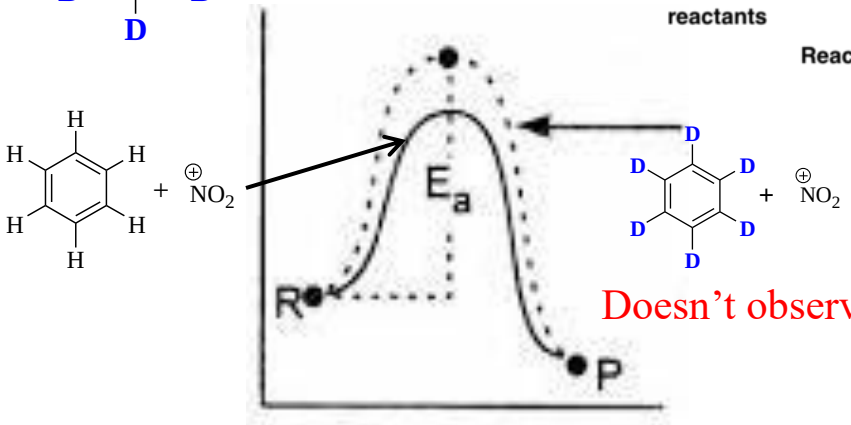
intermediate **σ complex has been isolated**

2. Primary kinetic isotope effect



$$\frac{K_H}{K_D} = 1$$



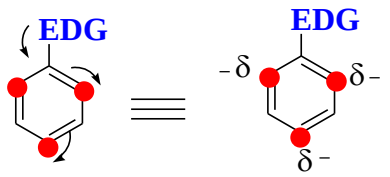


Doesn't observed

The effect of substituents on the rate of electrophilic aromatic substitution

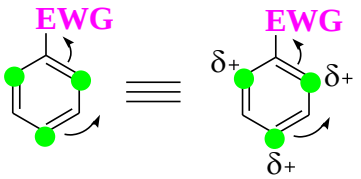
Table 14.2 Polar effects and directing nature of some groups

	Groups	Polar effects	Directing nature
(a)	$-O^-$	+R	*o*, *p*
	$-NR_2$, $-NH_2$, $-OH$, $-NHCOR$,		
	$-OR$, $-SR$, $-O-$, $-COR$	–I, +R	*o*, *p*
	$-F$, $-Cl$, $-Br$, $-I$, $-Ph$	–I, +R	*o*, *p*
(b)	$-Me$, $-CH_2Me$, $-CHMe_2$	+ I, hyperconjugative	*o*, *p*
	$-CMe_3$	+I	*o*, *p*
	$-CH=CH_2$	+I	*o*, *p*
(c)	$-\overset{\oplus}{N}H_3$, $-\overset{\oplus}{N}R_3$, $-\overset{\oplus}{S}R_2$, $-\overset{\oplus}{P}R_3$	–I	*m*
	$-CF_3$, $-CCl_3$		
(d)	$-NO_2$, $-CN$, $-SO_3H$, $-COOH$,	–I, –R	*m*
	$-SO_3R$, $-B(OH)_2$, $-CHO$, $-COR$		



● δ– More electron dense **C**

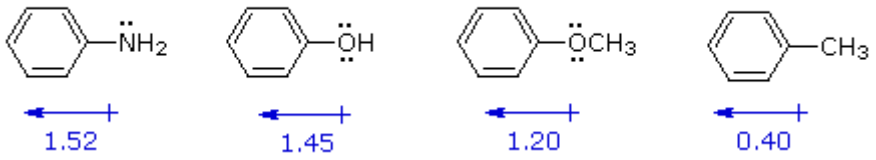
EDG = electron donating group



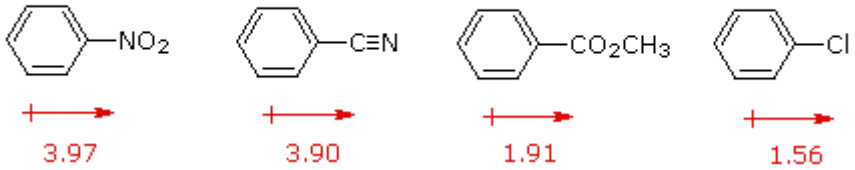
● δ+ More electron deficient **C**

EWG = electron withdrawing group

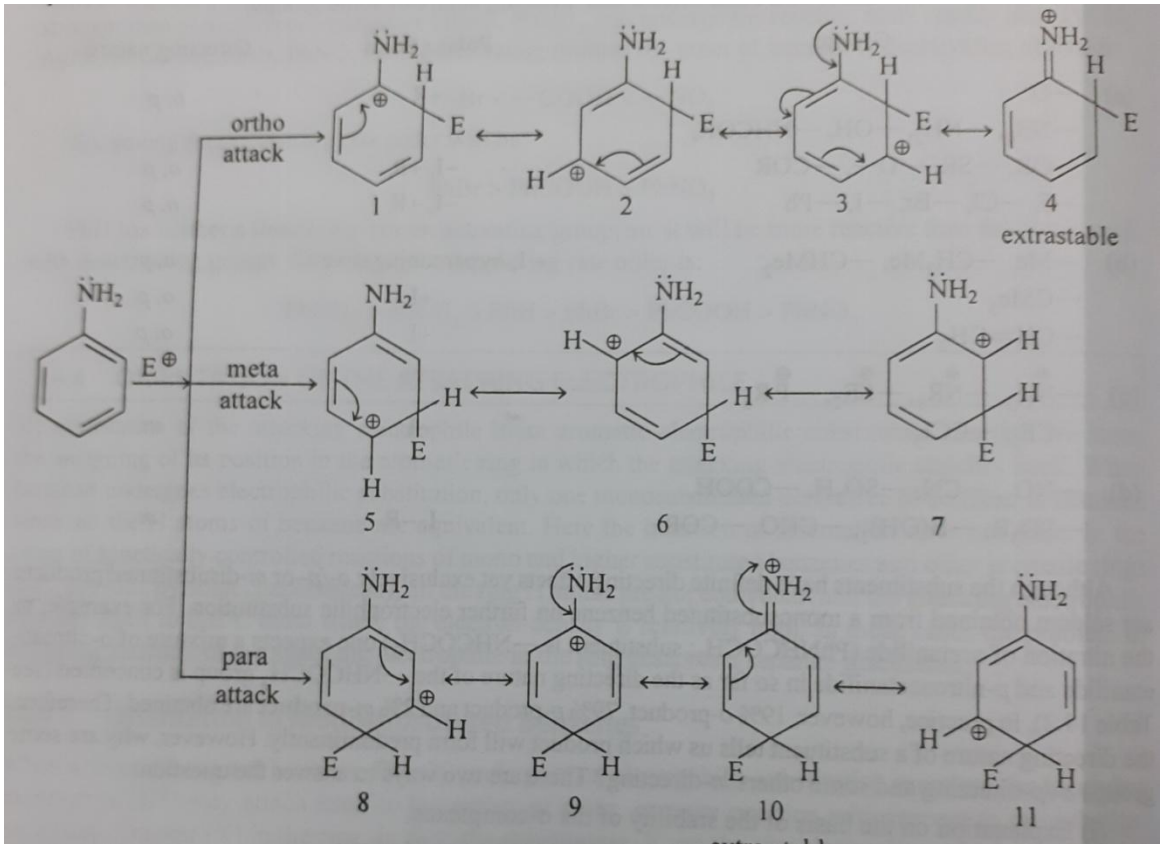
Activating Substituents



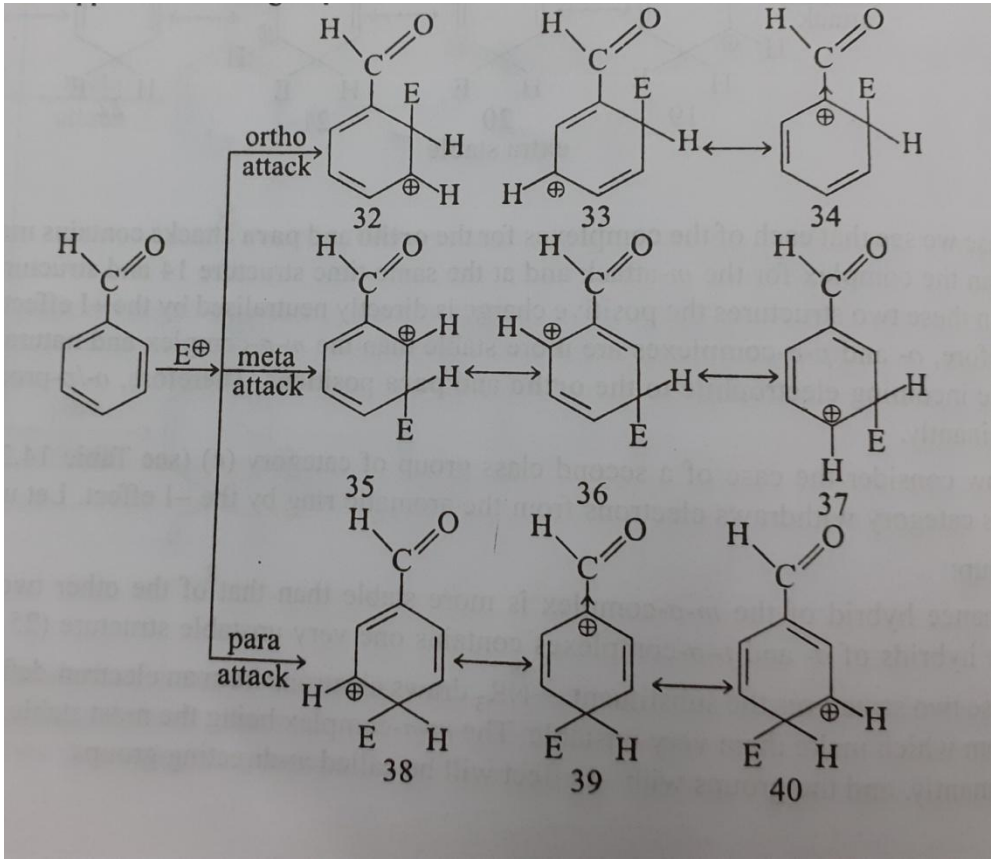
Deactivating Substituents



Orientation in presence of electron donating (activating) group



Orientation in presence of electron withdrawing (deactivating) group



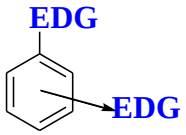
$$\bar{O} > NR_2 > NH_2 > OH > NHAc, OMe > Ar > Me > X$$

(iii) If both groups belong to the second class, isomeric compounds are formed. However, the order of decreasing directing powers are:

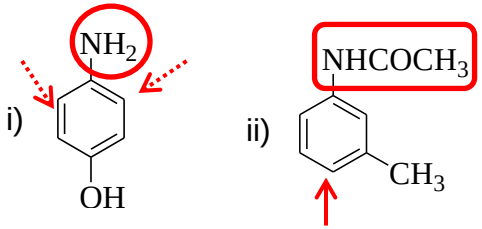
$$\overset{\oplus}{N}Me_3 > NO_2 > CN > SO_3H > CHO > COMe > CO_2H$$

Orientation of Attacking E^+ in Di-substituted Benzenes

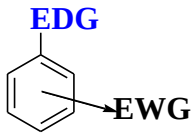
Case 1. Both are electron donating groups



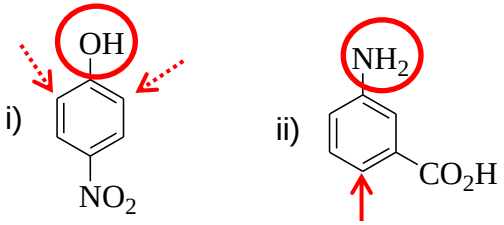
Example



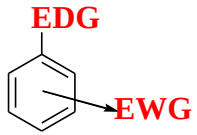
Case 2. One is electron donating group and other is EWG



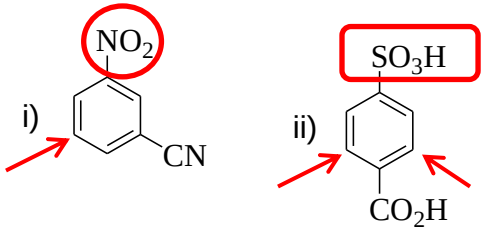
Example



Case 3. Both are electron withdrawing groups



Example



O/P ratio

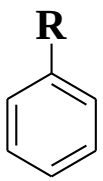
a) Steric effect

Me

Et

i-Pr

t-Bu



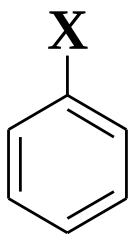
a) Electronic effect of the group already present in the ring

F

Cl

Br

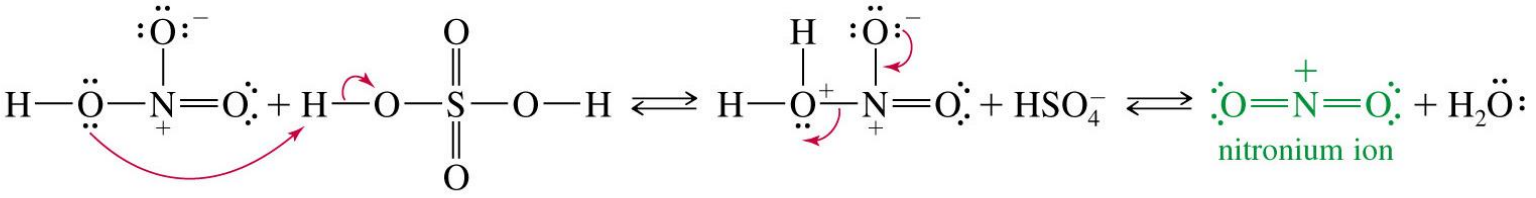
I



a) Interaction between the substitutent and attacking E+

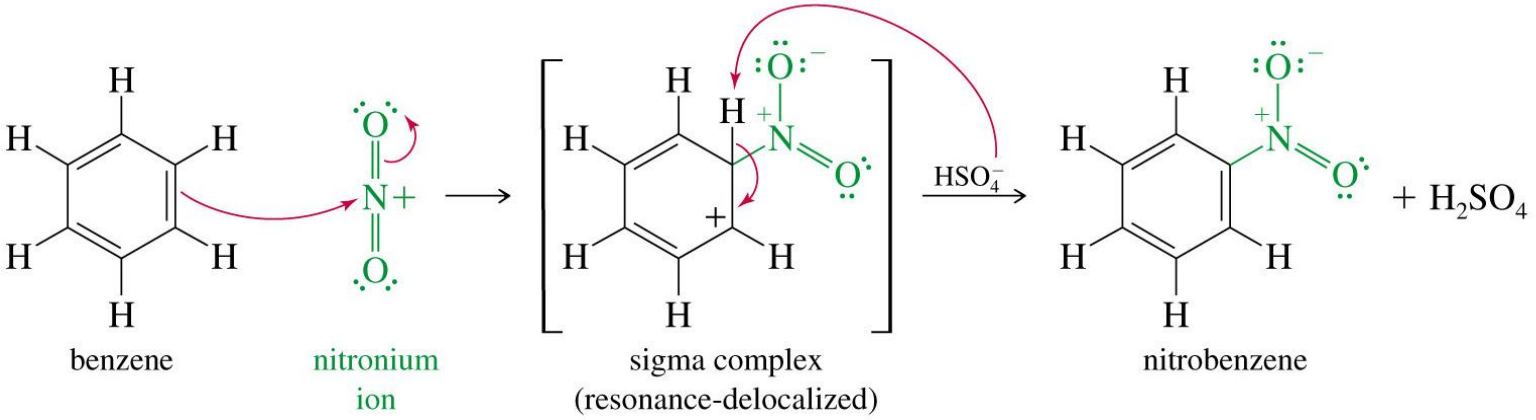
Nitration:

Formation of the nitronium ion.



Step 1: Electrophilic attack.

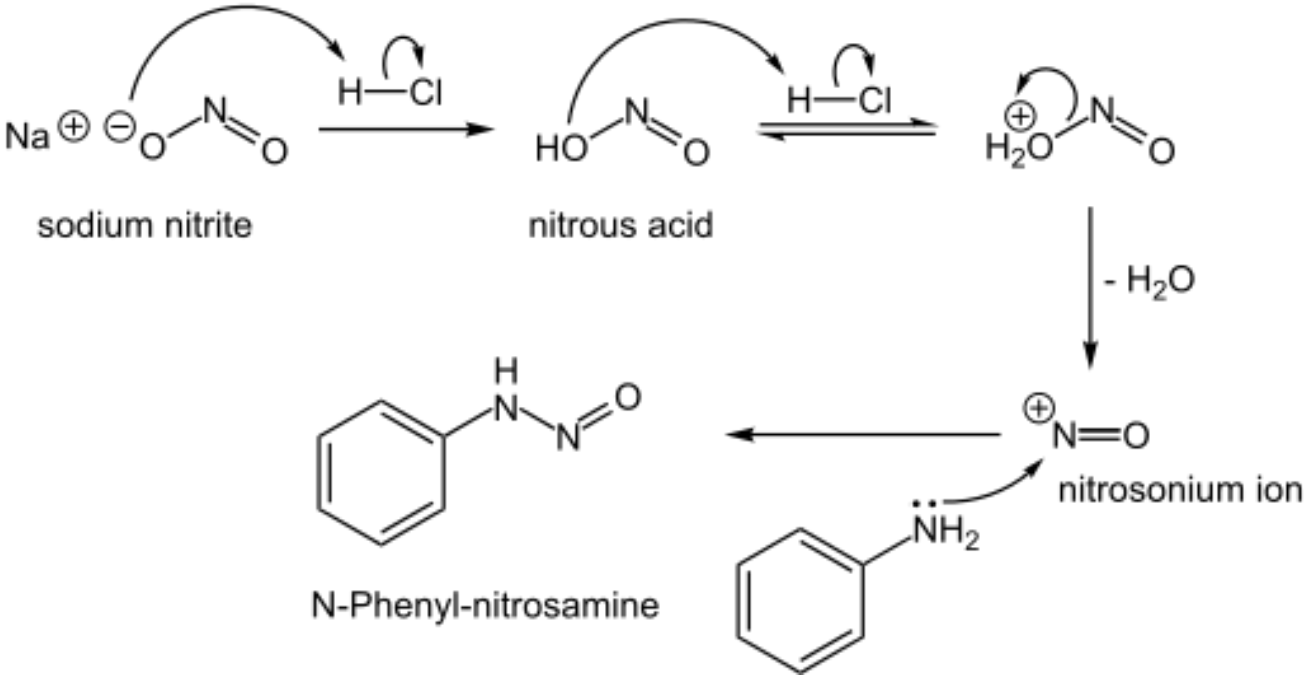
Step 2: Loss of a proton.



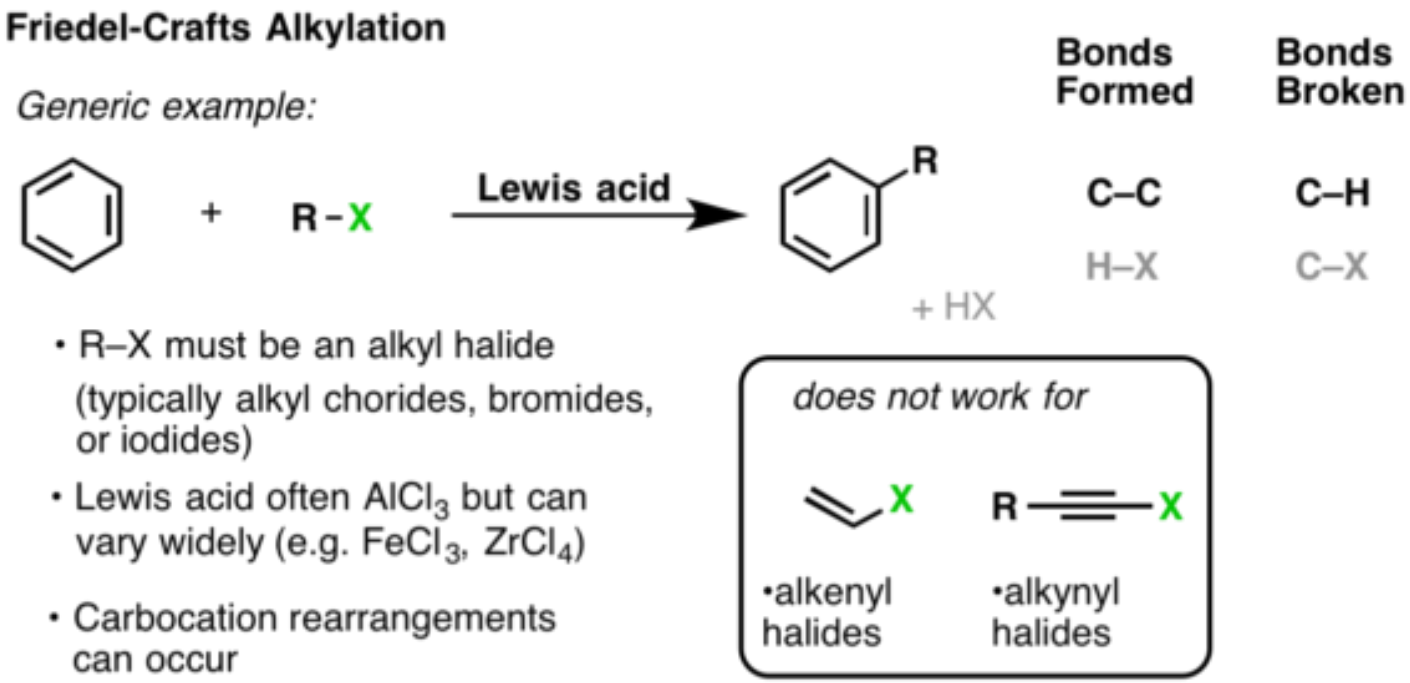
Nitrating agents

i) Conc. H_2SO_4 and conc. HNO_3
ii) HNO_3 in water
iii) Conc. HNO_3 and glacial AcOH
iv) Fuming HNO_3 and fuming H_2SO_4
v) Acylnitrates e.g. CH_3COONO_2, $PhCOONO_2$
vi) $^{+}NO_2BF_4^{-}$
vii) N_2O_5

Nitrosation is a process of converting organic compounds into nitroso derivatives, i.e. compounds containing the R-NO functionality.



Friedel-Crafts reaction



❖ Alkylating agents are $R{-}X$, $H_2C{=}CH_2$, $R{-}OH$, $HC{\equiv}CH$

➢ reactivity order of all type reagent is 3° >Allyl, benzyl > 2° >1°

❖ Reactivity among halide is fluoride > chloride > bromide > Iodide

❖ Reactivity order of Lewis acid catalyst is $AlCl_3$ > $AlBr_3$ >$GdCl_3$ >$FeCl_3$ >$SbCl_3$ > $SnCl_4$ >BF_3, BCl_3. When ROH is used, HF, H_2SO_4 or BF_3

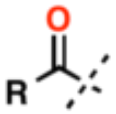
❖ Nitrobenzene is used as a solvent for Fridel-Crafts alkylation reaction.

Friedel-Crafts reaction

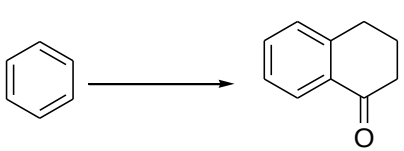
Friedel-Crafts Acylation

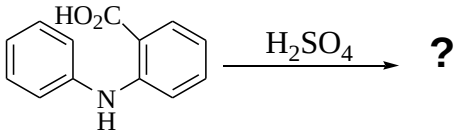
Generic example:

Bonds Formed	Bonds Broken
C–C	C–H
H–X	C–X

"acyl group": 

X is usually a halogen
e.g. Cl, Br, I
(although anhydrides can also be used)

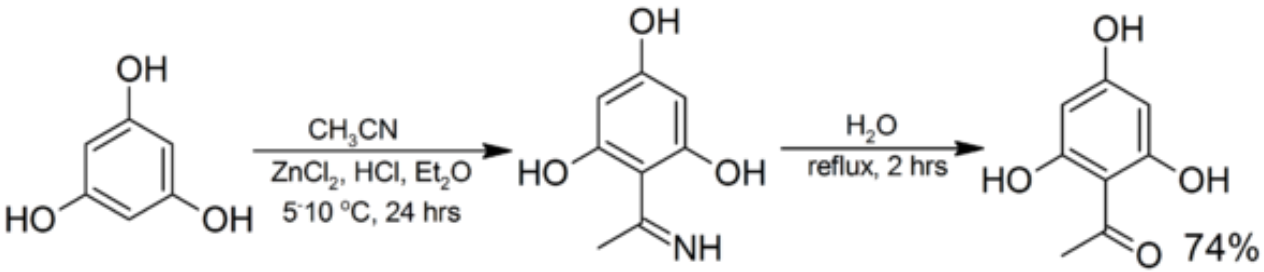


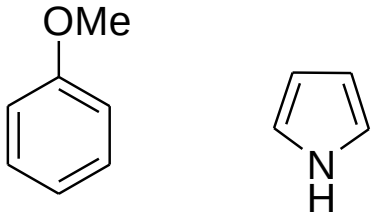


?

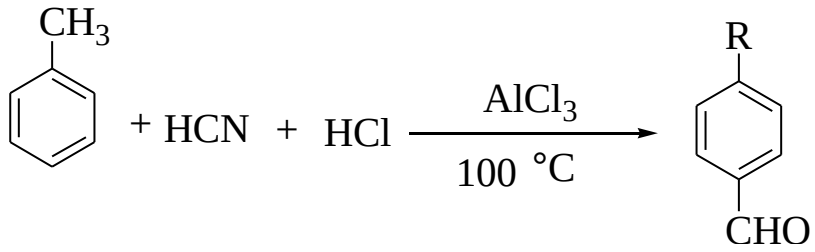
Houben–Hoesch reaction: It is a reaction where a nitrile reacts with an arene compound to form an aryl Ketone . The reaction is a type of Friedel-Crafts acylation with hydrogen chloride and a Lewis acid catalyst.

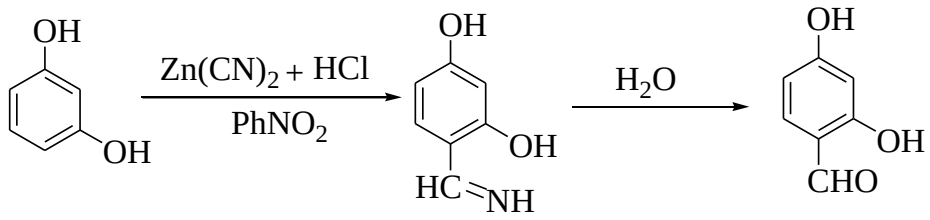
The synthesis of 2,4,6-Trihydroxyacetophenone from phloroglucinol is representative. If two-equivalents are added, 2,4-Diacetylphloroglucinol is the product.





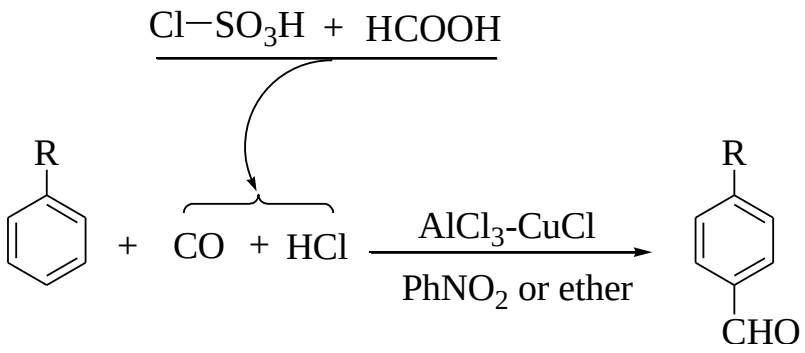
Gattermann reaction





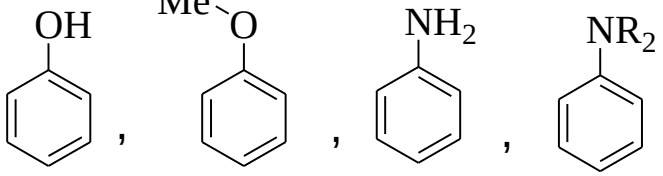
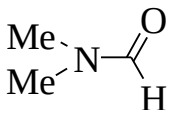
Benzene, alkylbenzene, Phenols, phenolic ethers, and some heterocyclic compounds under go this reaction, but nitrobenzene, amines and m-directing group do not under go this reaction.

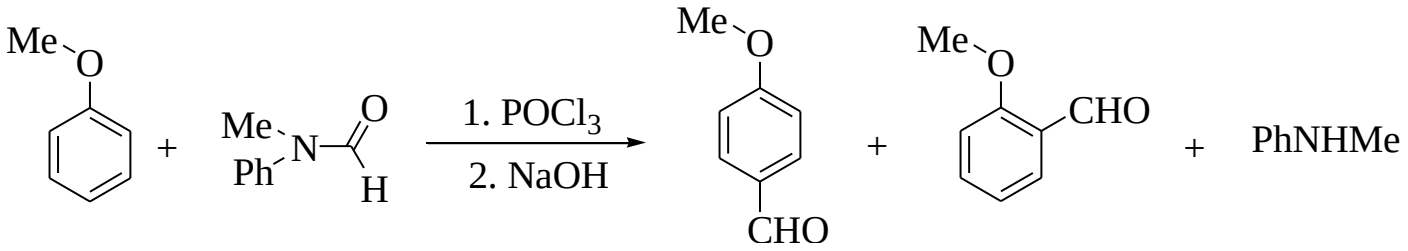
Gattermann-Koch reaction (aldehyde synthesis)



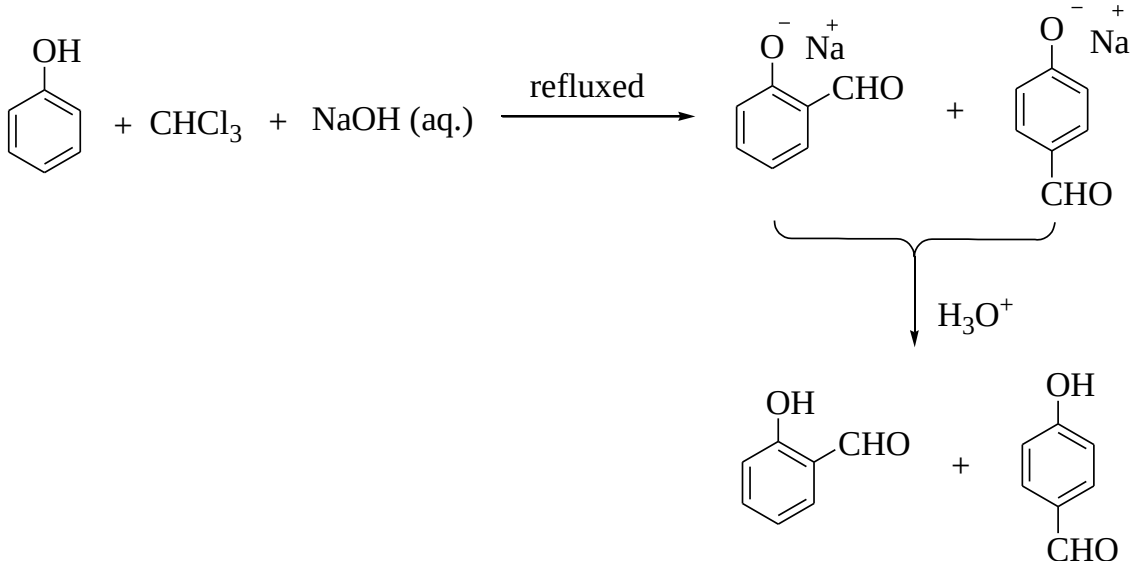
Phenols, phenolic ethers, and m-directing group do not under go this reaction

Vilsmeier-Haak reaction

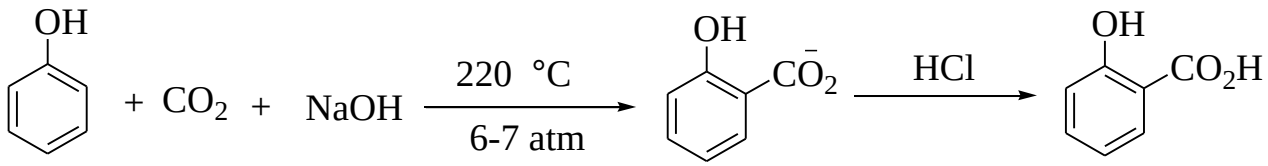
Formylation of  By  & $POCl_3$



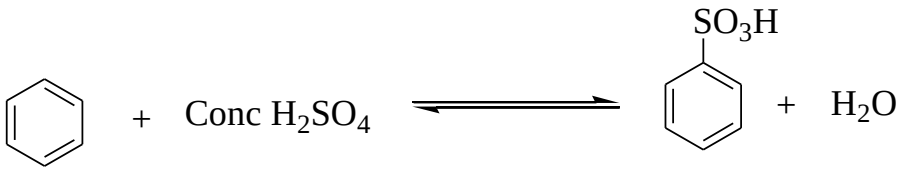
Reimer-Tiemann reaction



Kolbe smith reaction



Sulfonylation reaction

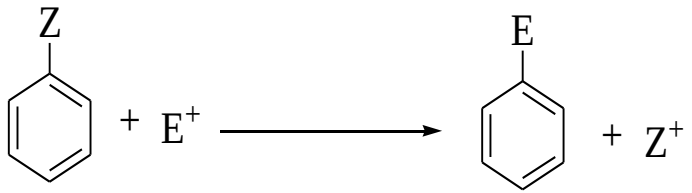


Other Sulfonating agent fuming H_2SO_4,
Olium (SO_3 in H_2SO_4,),
SO_3 in organic solvent (CH_3NO_2,pyridine,
$ClHSO_3$ in CCl_4 etc

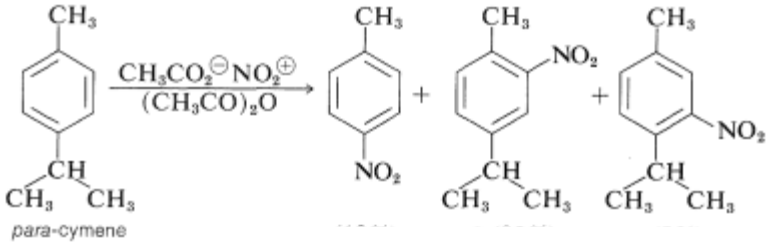
The **kinetic isotope effect** for the sulfonylation of **benzene** at 25.0° was found to be kH/kD = 0.86 ± 0.06.

Basically, it states that at equilibrium each individual reaction occurs in such a way that the forward and reverse rates are equal.

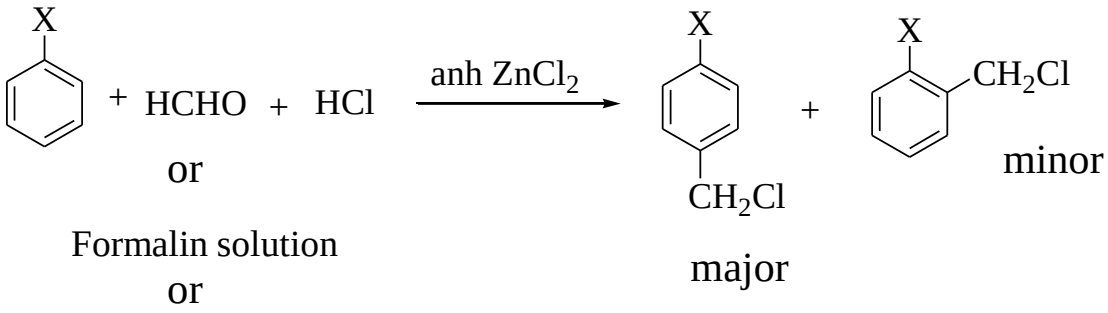
IPSO substitution

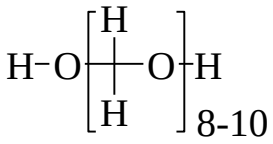


Z = -SO_3H, -CO_2H, I, -$SiMe_3$, -CMe_3

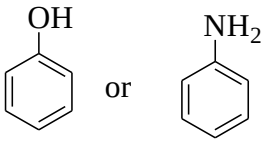


Chloromethylation reaction



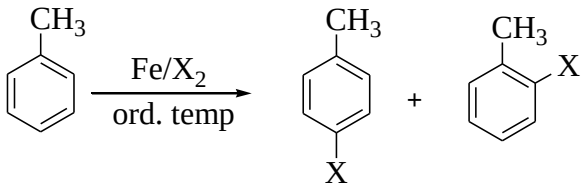
paraformaldehyde 

8-10



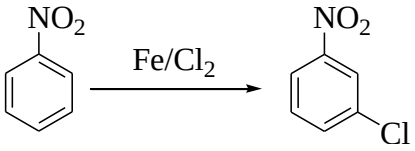
Under goes polymerisation

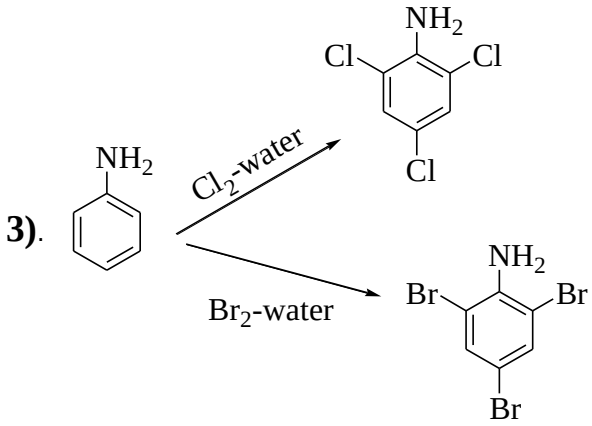
Halogenation:

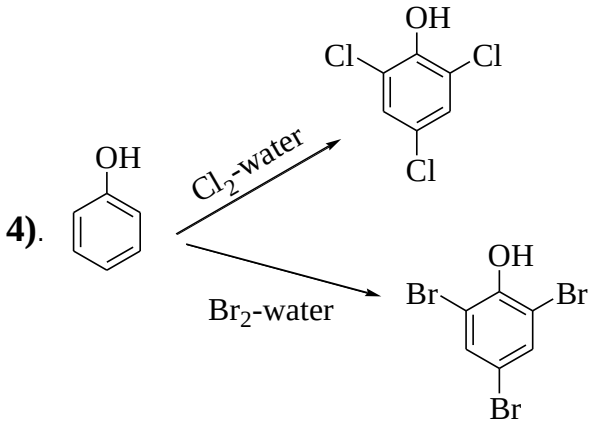
1). 

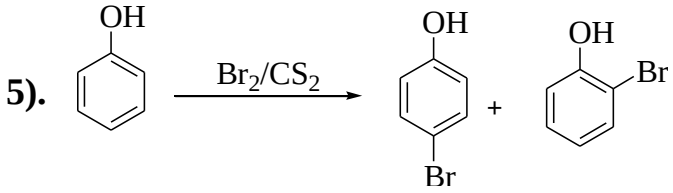
major

X = Cl, Br

2). 

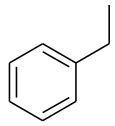
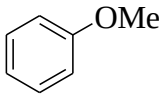
3). 

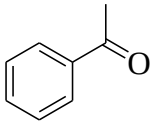
4). 

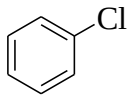
5). 

Model questions

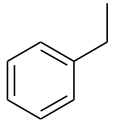
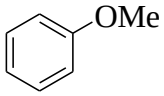
Q1. Which is most (and least reactive) reactive in electrophilic substitution?

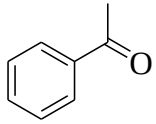
a)  b) 

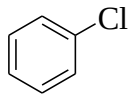
c) 

d) 

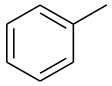
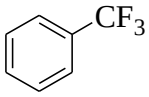
Q2. Which gives a *meta* nitro compound as the main product upon nitration with mix acid?

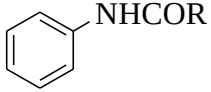
a)  b) 

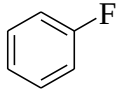
c) 

d) 

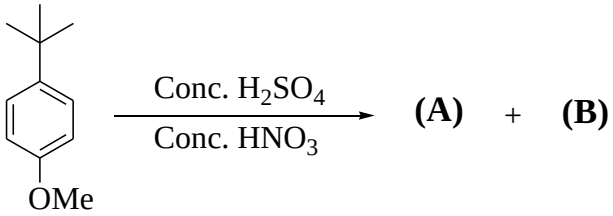
Q3. Which is most reactive in electrophilic substitution?

a)  b) 

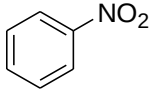
c) 

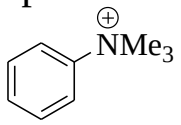
d) 

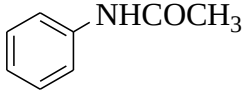
Q4. Which will be the main product upon chlorination of *m*-nitrotoluene with $Cl_2/AlCl_3$?

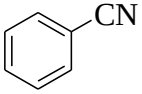
Q5. 

Q6. Write down the pdt in each case on treatment with nitric acid-sulfuric acid mixture?

a) 

b) 

c) 

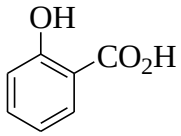
d) 

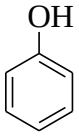
Model questions

Q7. What are the major products from the reactions of phenyl ethanoate and ethyl benzoate with HNO_3 / H_2SO_4 / heat ?

Q8. How can you prove that the aromatic electrophilic substitution reaction is a multi steps process

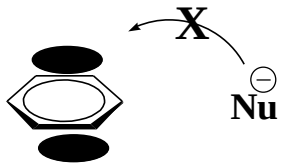
Q9. Both a) and b) gives same product on treatment with excess Br_2/H_2O, explain

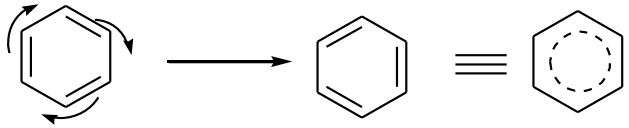
a) 

b) 

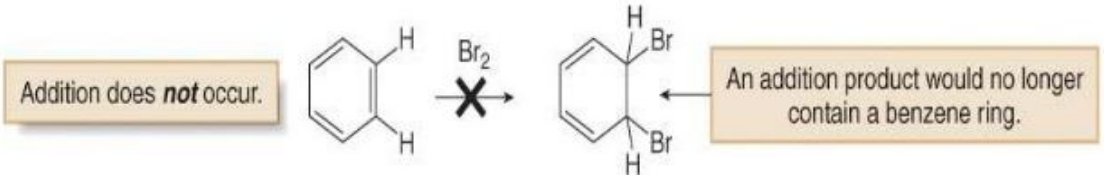
Substitution reaction in aromaic system

Why simple benzene does not under goes normal nucleophilic substitution or addition reactions??

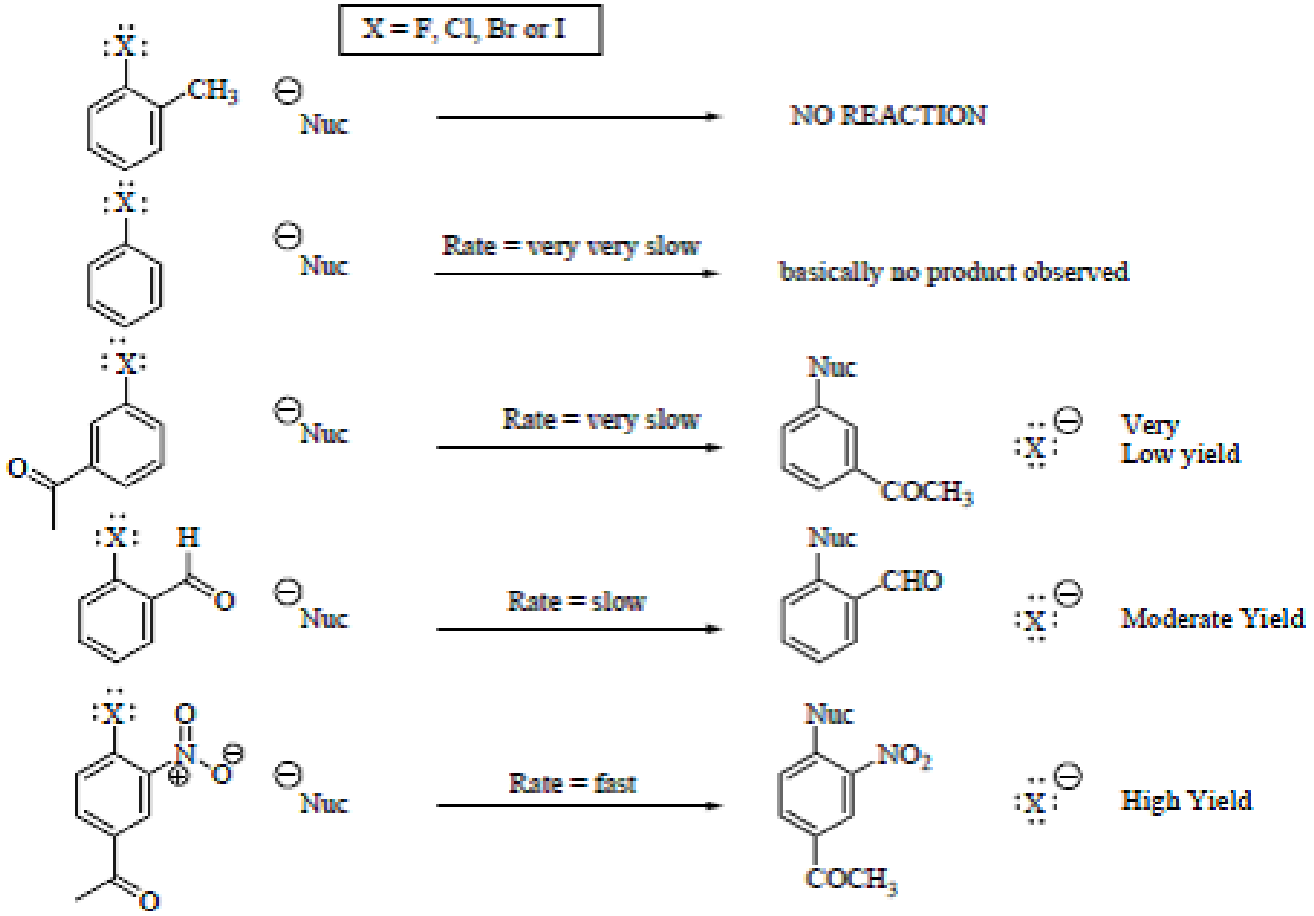




- Benzene does not react with Br_2 to yield an addition product. Instead, in the presence of a Lewis acid, bromine substitutes for a hydrogen atom, yielding a product that retains the benzene ring.



Addition-elimination reaction

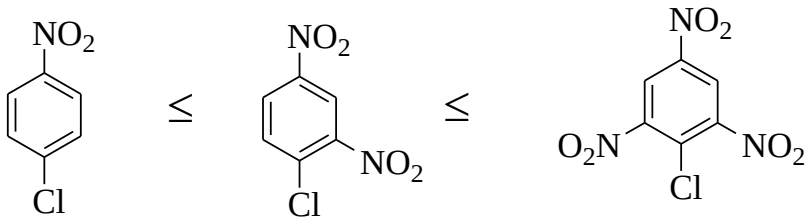


The Effect Of Substituents On The Ring

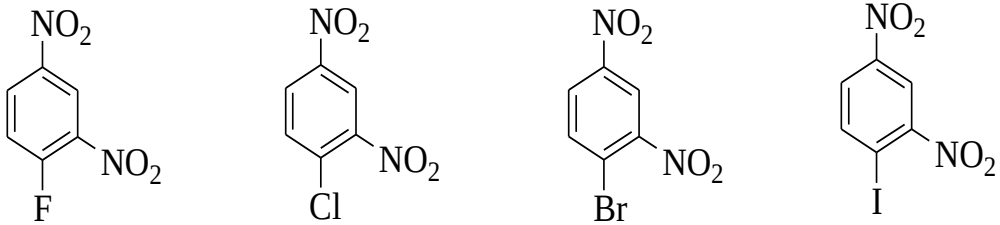
One EWG
Slowest

Two EWG
Faster
(by a factor about 10^5)

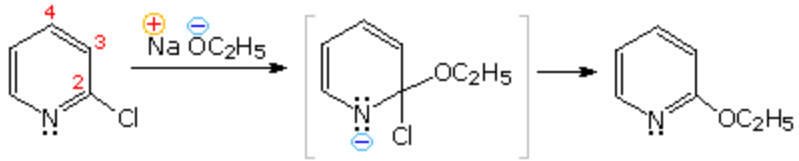
Two EWG
Fastest

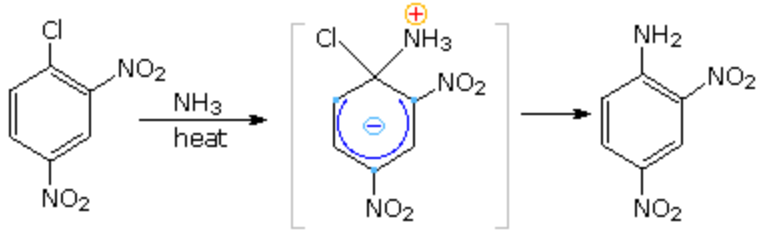


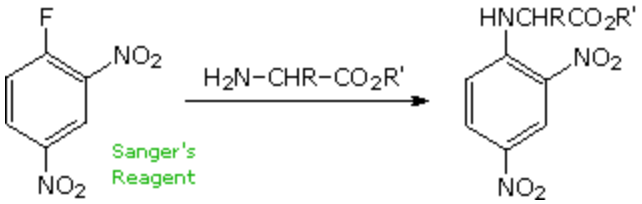
The Effect Of The Leaving Group



rate	3300	4.3	3.8	1

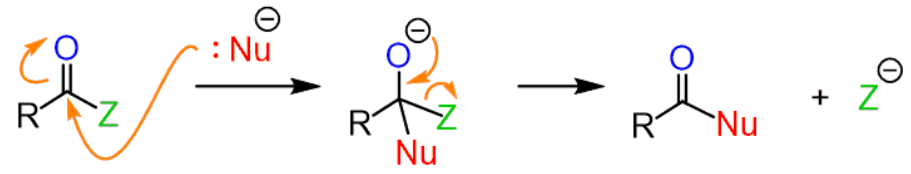






Nucleophilic Acyl Substitution by Addition-Elimination Mechanism

Nucleophilic addition ***Elimination***

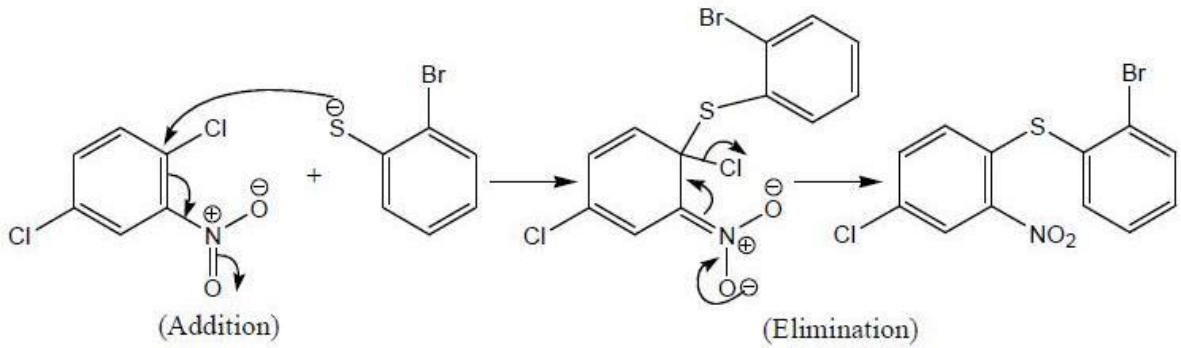


***sp*^{2} carbon**
planar

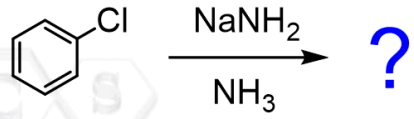
***sp*^{3} carbon**
tetrahedral

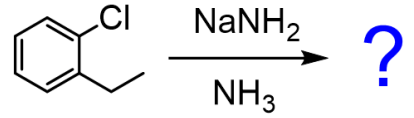
Z (leaving group) is replaced by a nucleophile. Common leaving groups

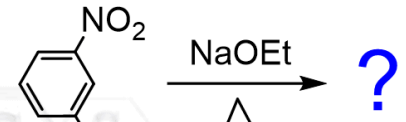
Z = Cl (**acyl chlorides**), OR (**esters**), RCOO (**anhydrides**).

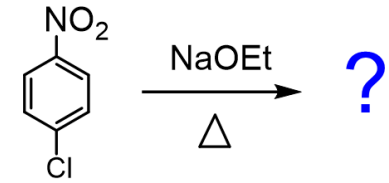


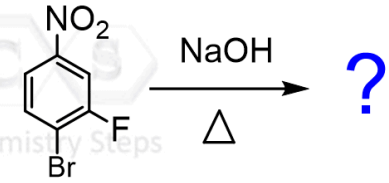
Model question

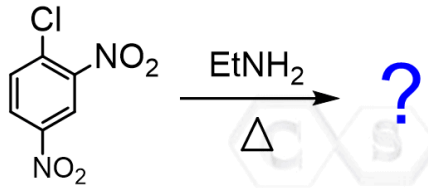
a) 

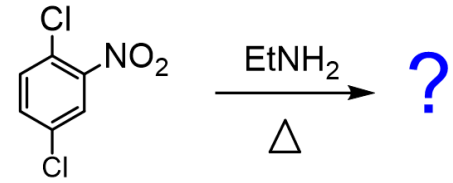
b) 

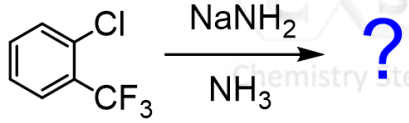
c) 

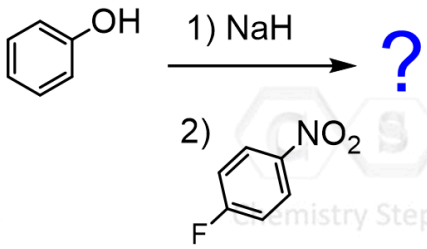
d) 

e) 

f) 

g) 

h) 

i) 

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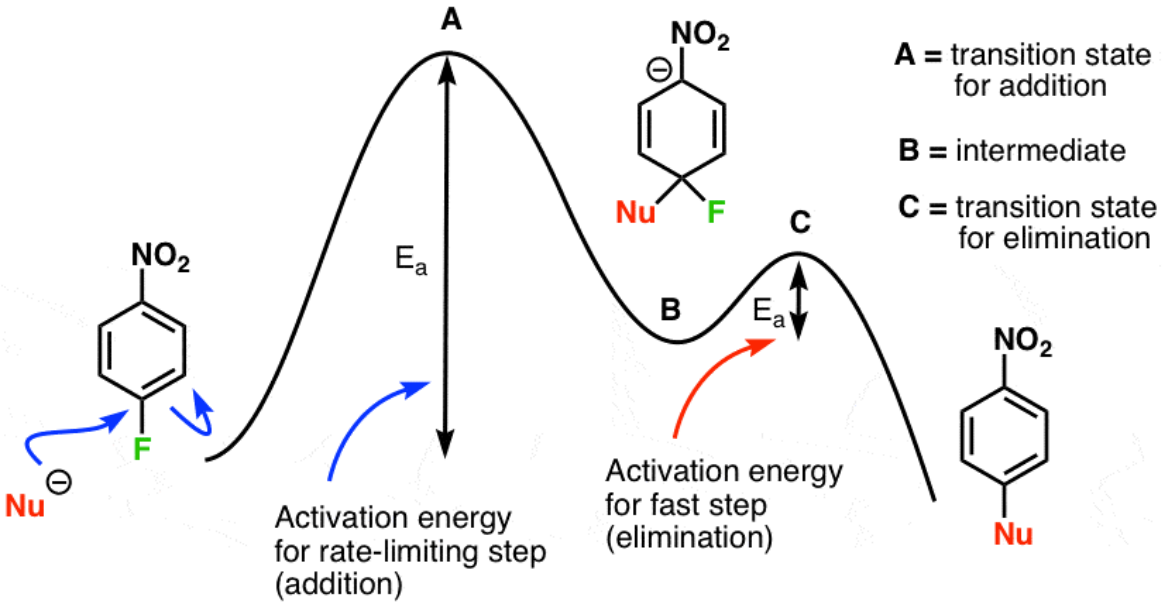
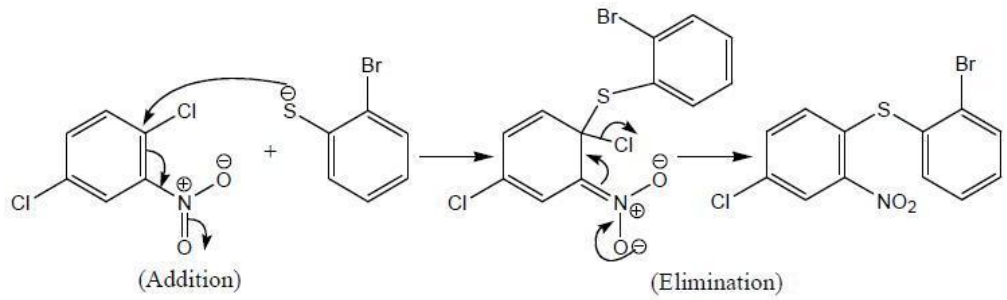
Nucleophilic aromatic substitution: Reaction Energy Diagram

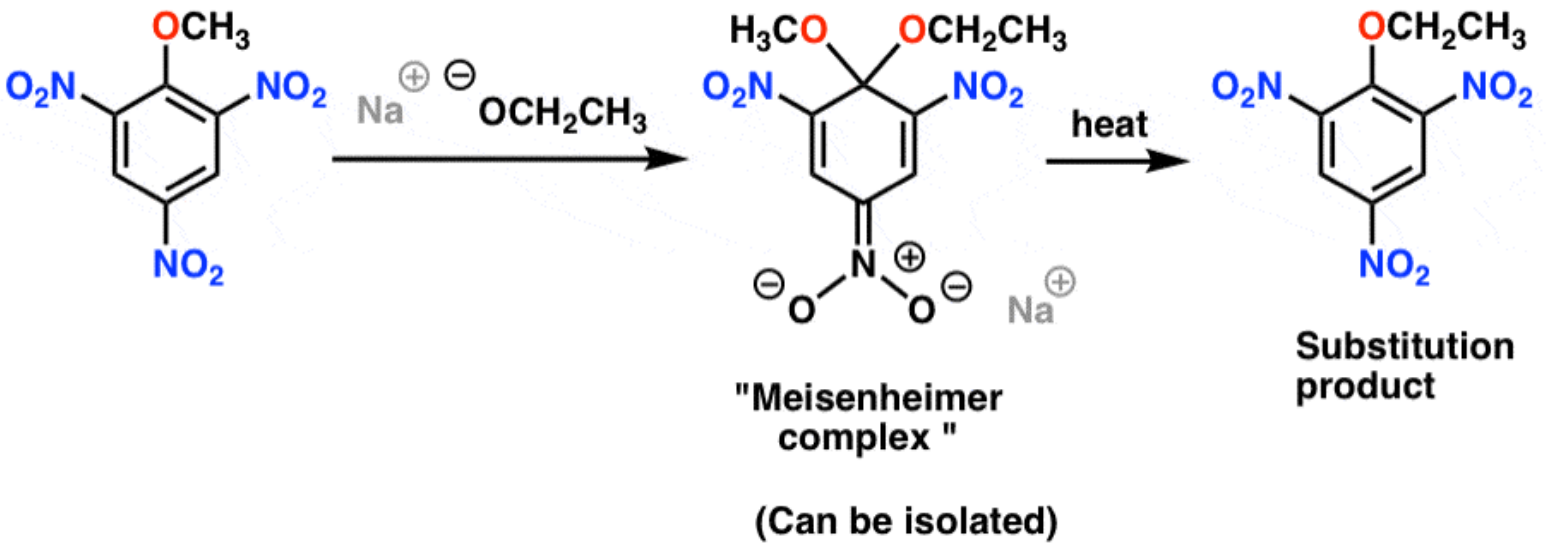




Evidences in favour S_N2Ar reaction

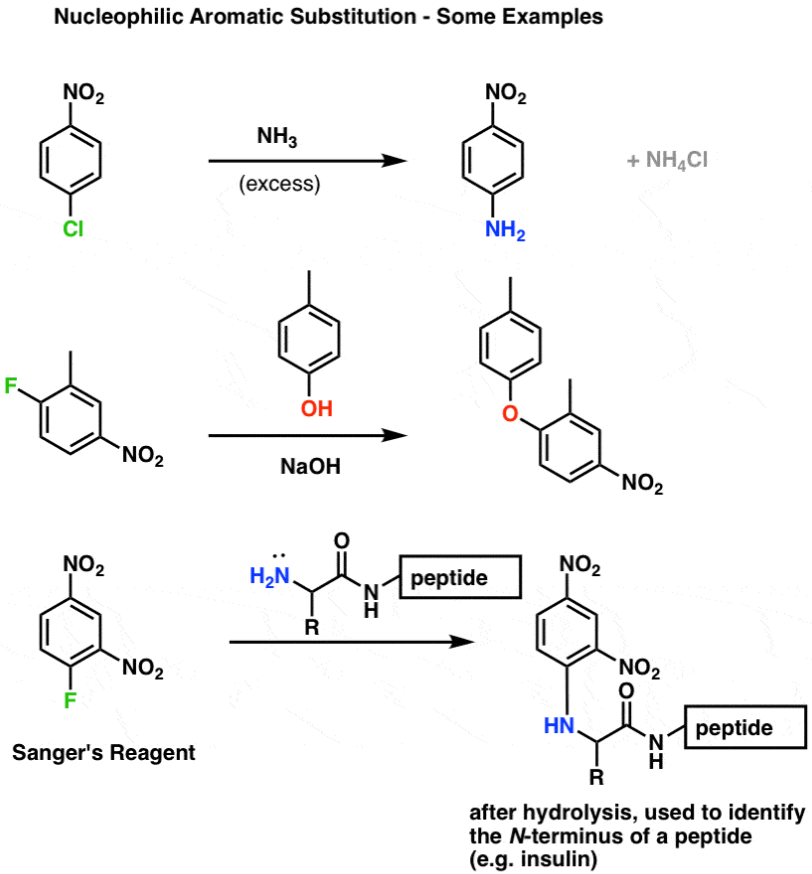
adding nucleophiles to various electron-poor aromatic molecules with a leaving group, intermediates have been isolated. One of the first was isolated in 1902 by **Jacob Meisenheimer**, and the general name "***Meisenheimer complex***" is given to these intermediates.

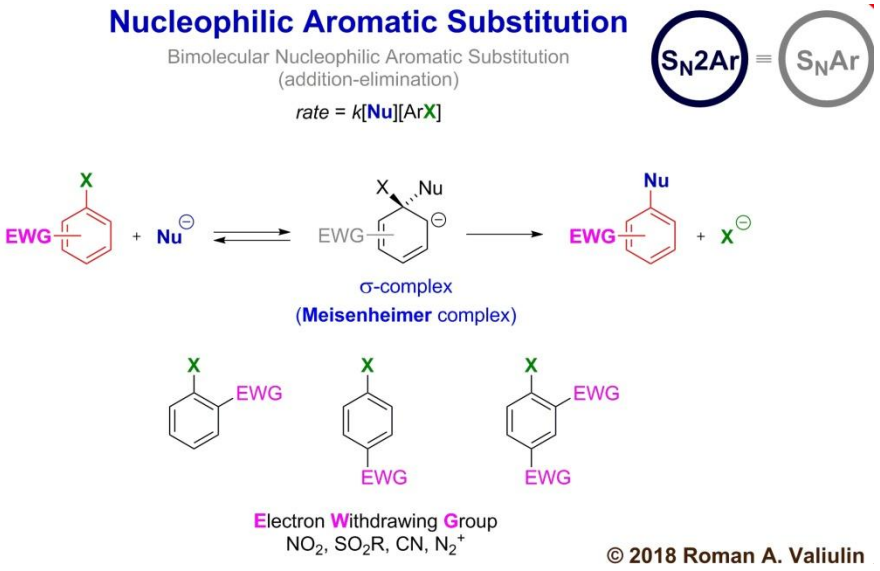
Further heating of these products results in the substitution product.

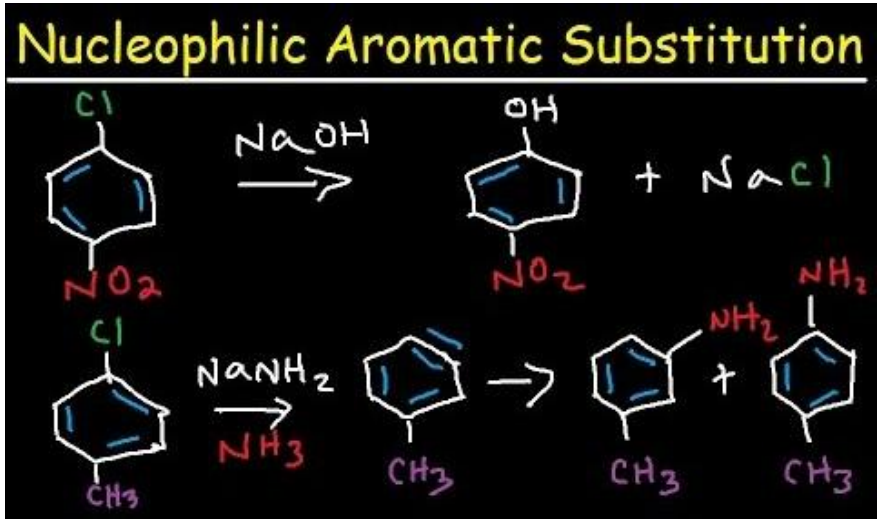


Pretty clear evidence for a two-step mechanism that proceeds through
1) attack of nucleophile on the ring
2) elimination of the leaving group

ie). Nucleophilic aromatic Substitution



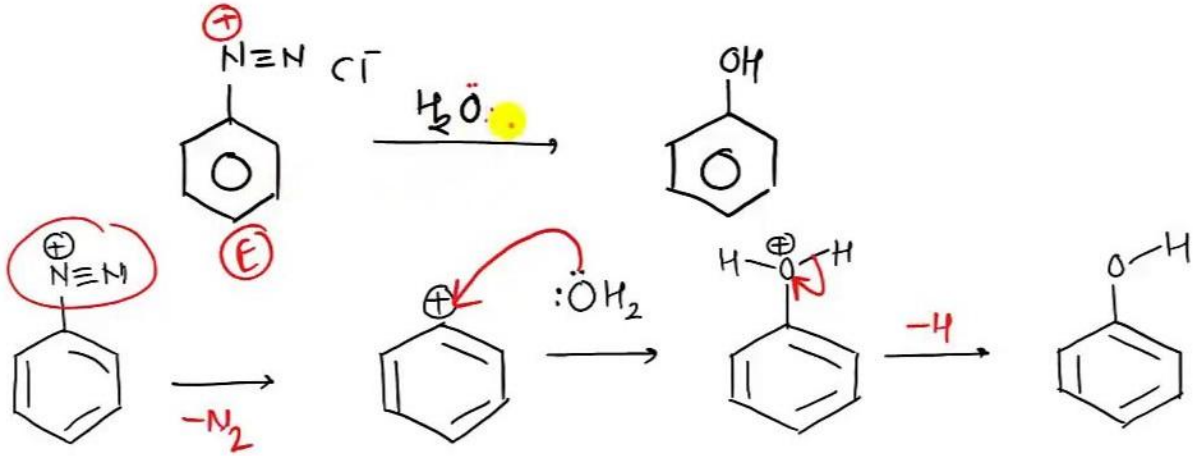




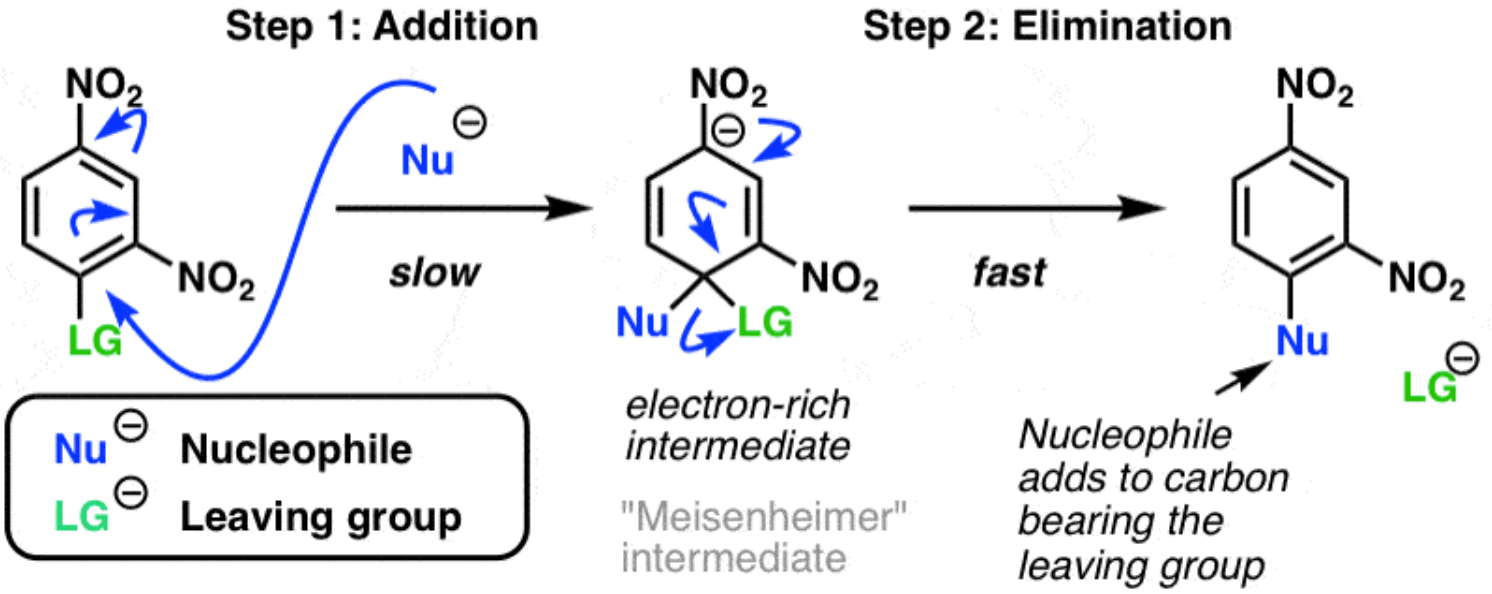
Unimolecular Aromatic Nucleophilic Substitution Reaction (S_N1Ar reaction)

SN_1Ar :-

- It is very rare mechanism and observed in benzene diazonium compounds.



Nucleophilic aromatic substitution: the addition-elimination mechanism

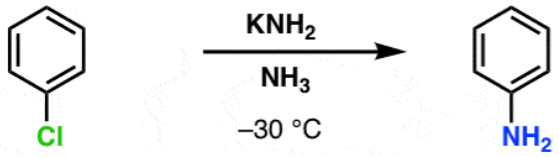


Importantly, the only substitution product is the one where the **nucleophile attached to the same carbon as that bearing the leaving group**. (This differentiates it from electrophilic aromatic substitution, where a mixture of *ortho*-, *para*– and *meta*- products can be obtained.)

A "Nucleophilic Aromatic Substitution" In Name, But By A Different Mechanism

Nucleophilic Aromatic Substitution At An Unusually Low Temperature

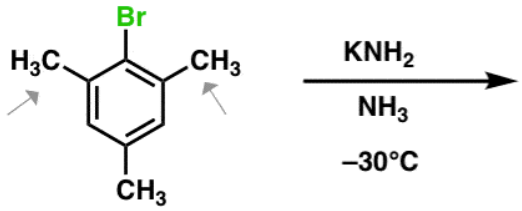
(1945)



chloro is only moderately electron-withdrawing

traditional S_NAr reactions require heat !

Observation #1: no reaction occurs without *ortho-* hydrogens!

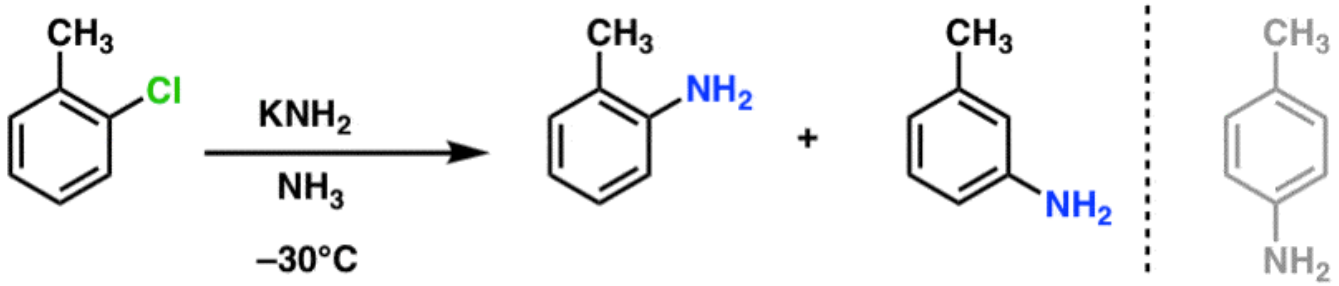


no reaction!

ortho positions blocked with substituents

Does this also go through the addition-elimination mechanism?

Observation #2 : in this example, the *ortho-* and *meta-* products are formed, but none of the *para-* is observed



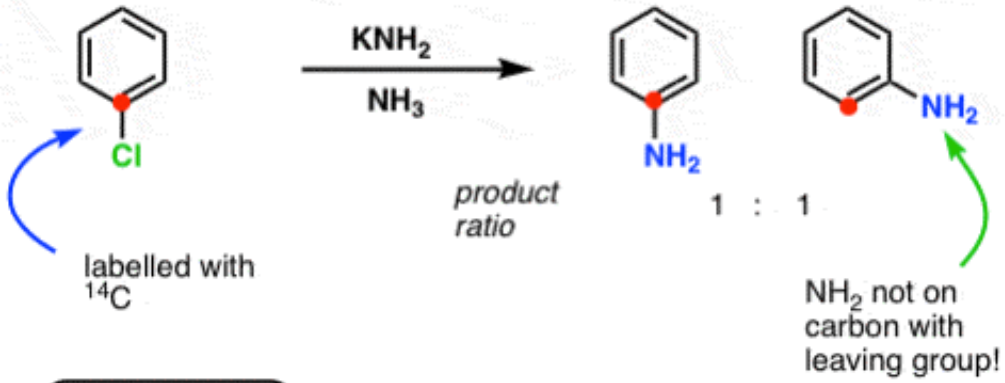
ortho- ***meta-*** ***para-***

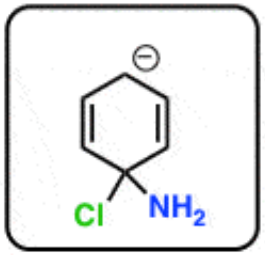
never formed!

The Benzyne Intermediate

Roberts' Classic Experiment (1953) Using ^{14}C-Labelled Chlorobenzene

- Chlorobenzene was synthesized that contained ^{14}C at the carbon attached to the leaving group (Cl)
- Hypothesis: If the reaction goes through addition-elimination, the product will NH_2 bonded exclusively to the ^{14}C labelled carbon
- In fact, the reaction produced a mixture of two products in about a 1:1 ratio !

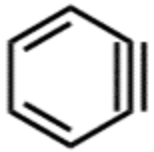




So how can this result be explained?

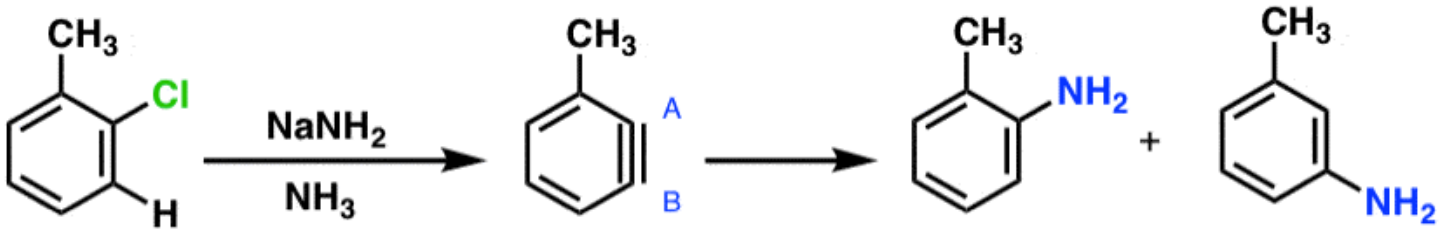
Not consistent with addition-elimination mechanism involving this intermediate!

roughly 50:50 ratio of products implies the involvement of a *symmetrical* intermediate which is attacked equally on either side. involvement of a short-lived intermediate bearing a carbon-carbon triple bond: ***"Benzyne"***



Reactions Of Substituted Benzyne ("Arynes")

Substituted benzynes ("arynes") can produce multiple products



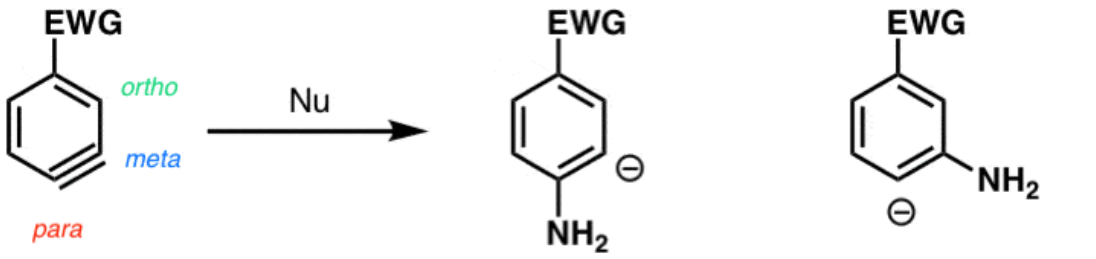
unsymmetrical aryne - can be attacked at **A** or **B**

From attack at A

From attack at B

When an electron-withdrawing group (EWG) is present, the intermediate where the negative charge is closest to the EWG will be favored

Case #1 - triple bond between meta and para carbons:



Aryne

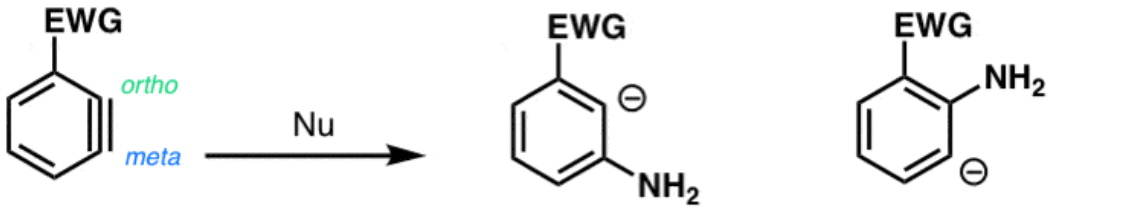
from para attack negative charge closer to EWG

Favored

from meta attack negative charge farther from EWG

Disfavored

Case #2 - triple bond between ortho and meta carbons:



Aryne

from meta attack negative charge closer to EWG

Favored

from ortho attack negative charge farther from EWG

Disfavored