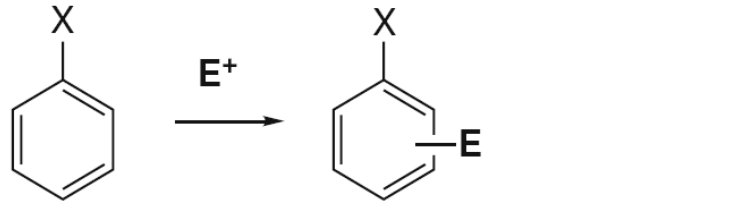
AROMATIC SUBSTITUTION REACTIONS (S_{Ar})

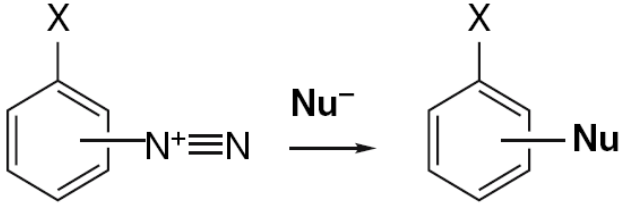
Reactions of Aromates:

1) Electrophilic S_{Ar} (EAS)



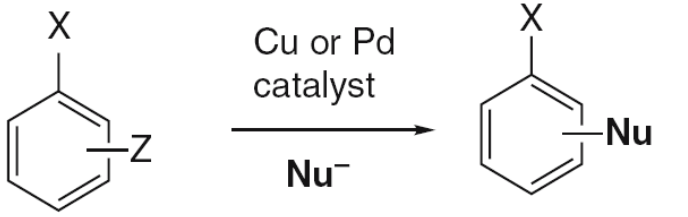
E = NO_2, F, Cl, Br. I, SO_3H, SO_2Cl, R, RC = O

2) Nuclephilic S_{Ar}



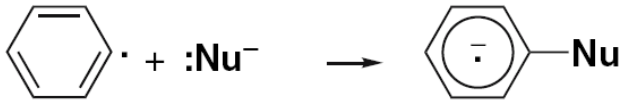
Nu = F, Cl, Br, I, CN, N_3, OH, CH = CHR

3) Transition Metal-catalyzed S_{Ar}



Z = I, Br, Cl, O_3SAr **Nu** = CN, R_2N, RO

4) S_{Ar} Involving Radical Intermediates



Electrophilic Aromatic Substitution (EAS)

EAS:

- the most thoroughly studied classes of organic reactions
- substitution of some FG for H (not always – Si, Hg FG)
- various electrophiles

1) Electrophiles capable of substituting both activated and deactivated Ar

Electrophile	Typical means of generation
$O{=}N^{+}{=}O$	$2\ H_2SO_4 + HNO_3 \rightleftharpoons NO_2^{+} + 2\ HSO_4^{-} + H_3O^{+}$
Br_2 or $Br_2{-}MX_n$	$Br_2 + MX_n \rightleftharpoons Br_2{-}MX_n$
$BrO^{+}H_2$	$BrOH + H_3O^{+} \rightleftharpoons BrO^{+}H_2$
Cl_2 or $Cl_2{-}MX_n$	$Cl_2 + MX_n \rightleftharpoons Cl_2{-}MX_n$
$ClO^{+}H_2$	$ClOH + H_3O^{+} \rightleftharpoons ClO^{+}H_2$
SO_3 or $SO_2O^{+}H$	$H_2S_2O_7 \rightleftharpoons HSO_4^{-} + SO_2O^{+}H$
RSO_2^{+}	$RSO_2Cl + AlCl_3 \rightleftharpoons RSO_2^{+} + AlCl_4^{-}$

Electrophilic Aromatic Substitution (EAS)

2) Electrophiles capable of substituting activated but NOT deactivated Ar

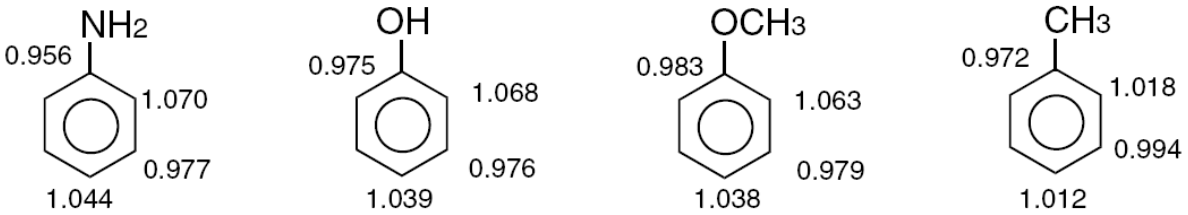
Electrophile	Typical means of generation
R_3C^+	$R_3CX + MX_n \rightleftharpoons R_3C^+ + [MX_{n+1}]^-$
R_3C^+	$R_3COH + H^+ \rightleftharpoons R_3C^+ + H_2O$
$R_2C^+CHR'_2$	$R_2C{=}CR'_2 + H^+ \rightleftharpoons R_2C^+CHR'_2$
$RCH_2X{-}MX_n$	$RCH_2X + MX_n \rightleftharpoons RCH_2X{-}MX_n$
$RC{\equiv}O^+$	$RCOX + MX_n \rightleftharpoons RC{\equiv}O^+ + [MX_{n+1}]^-$
$RCOX{-}MX_n$	$RCOX + MX_n \rightleftharpoons RCOX{-}MX_n$
$RC^+{=}O^+H$	$RCOX + MX_n + H^+ \rightleftharpoons RC^+{=}O^+H + [MX_{n+1}]^-$
H^+	$HX \rightleftharpoons H^+ + X^-$
$R_2C{=}O^+H$	$R_2C{=}O + H^+ \rightleftharpoons R_2C{=}O^+H$
$R_2C{=}O^+{-}M^-X_n$	$R_2C{=}O + MX_n \rightleftharpoons R_2C{=}O^+{-}M^-X_n$
$HC^+{=}N^+H_2$	$HC{\equiv}N + 2H^+ \rightleftharpoons HC^+{=}N^+H_2$

Electrophilic Aromatic Substitution (EAS)

3) Electrophiles capable of substitution only strongly activated Ar

Electrophile	Typical means of generation
$HC{\equiv}N^+H$	$HC{\equiv}N + HX \rightleftharpoons HC{\equiv}N^+H + X^-$
$N{\equiv}O^+$	$HONO + H^+ \rightleftharpoons N{\equiv}O^+ + H_2O$
$ArN^+{\equiv}N$	$ArNH_2 + HONO + H^+ \rightleftharpoons ArN^+{\equiv}N + 2H_2O$

- strongly activated Ar:



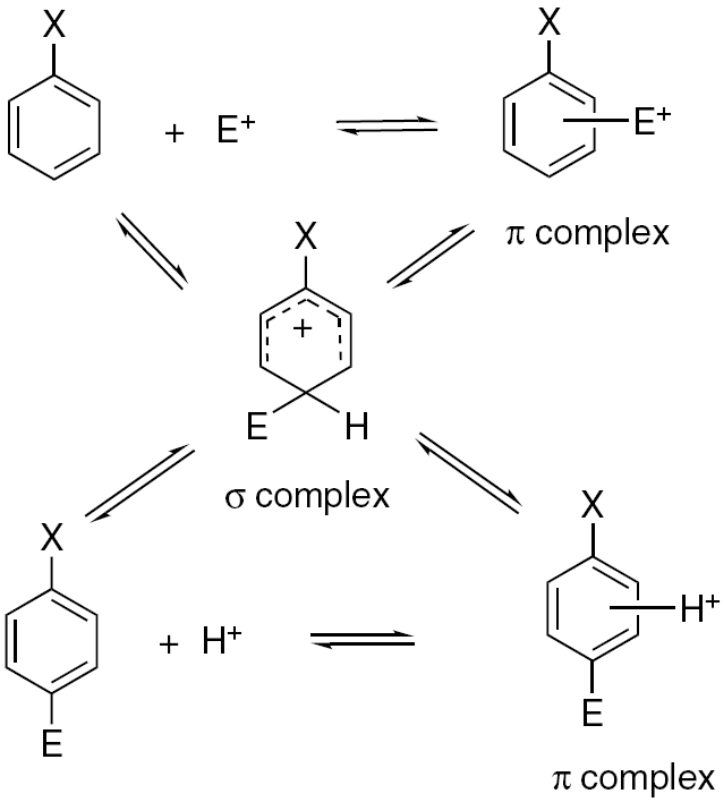
Electrophilic Aromatic Substitution (EAS)

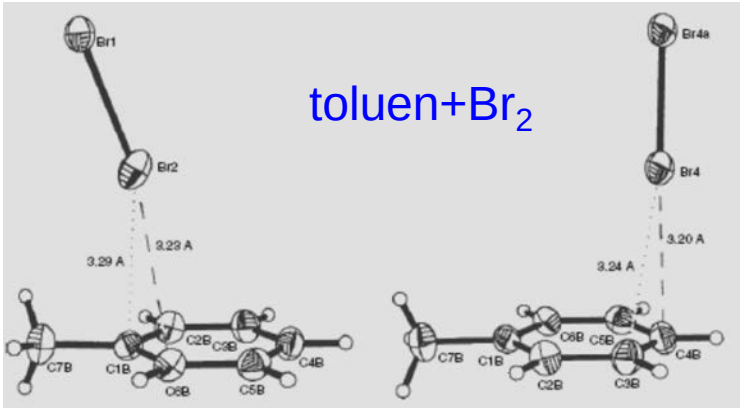
Mechanism:

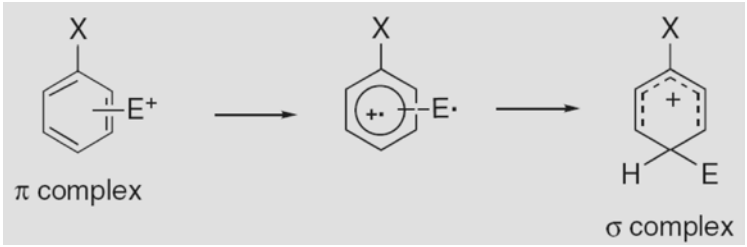
1.step – complexation of **Ar** + **E** forming **π-complex**

2.step – formation of **σ-complex**
(*cyclohexadienylium cation*)

3.step – deprotonation

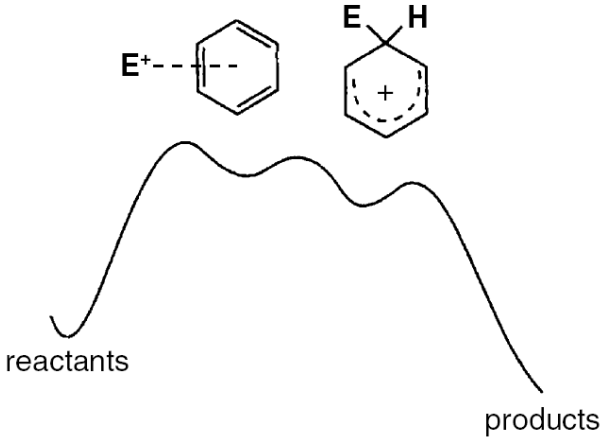




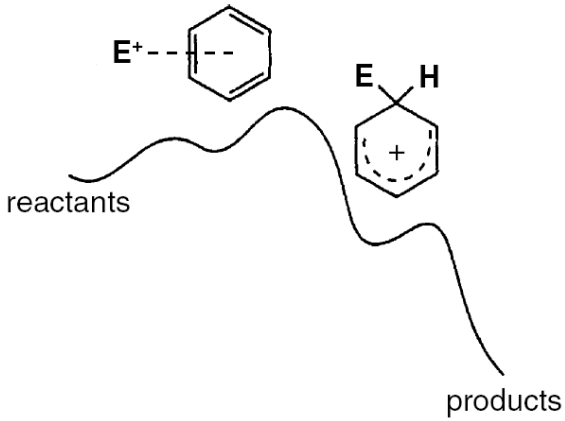


Electrophilic Aromatic Substitution (EAS)

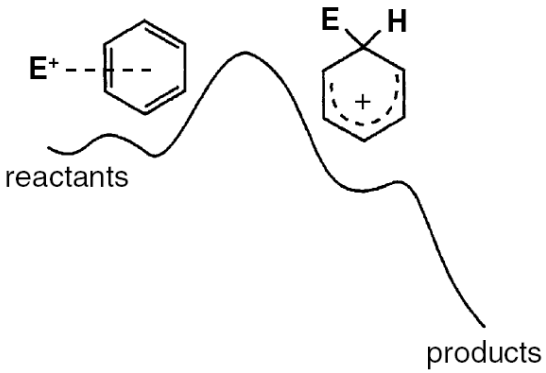
Energy profiles:



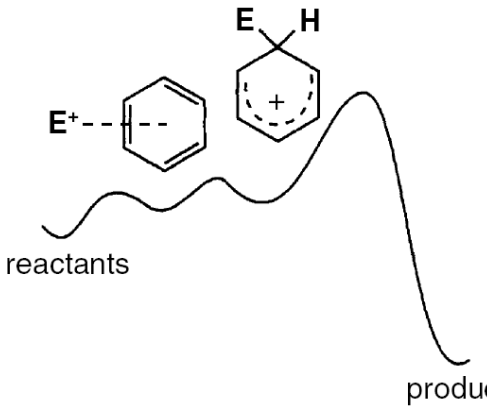
rate-controlling formation of E^+



rate-controlling σ complex formation
(non-selective electrophile)



rate-controlling σ complex formation
(selective E^+)

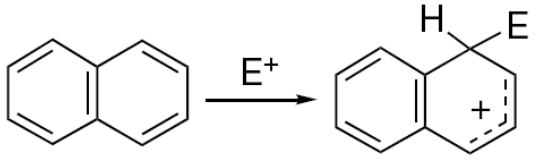


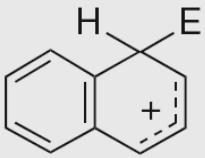
rate-controlling deprotonation

Electrophilic Aromatic Substitution (EAS)

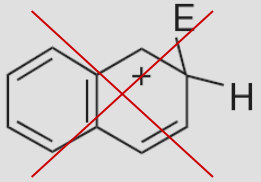
Other Aromatics:

- naphthalene





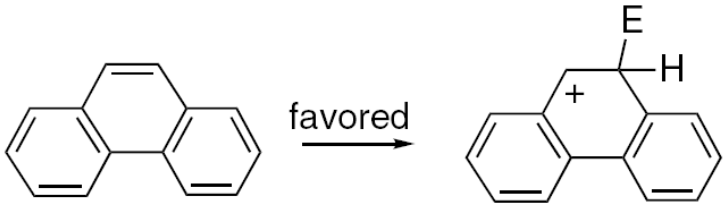
cationic intermediate has both allylic and benzylic stabilization



cationic intermediate has benzylic but not allylic stabilization

- antracene

- phenanthrene

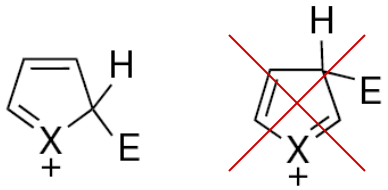


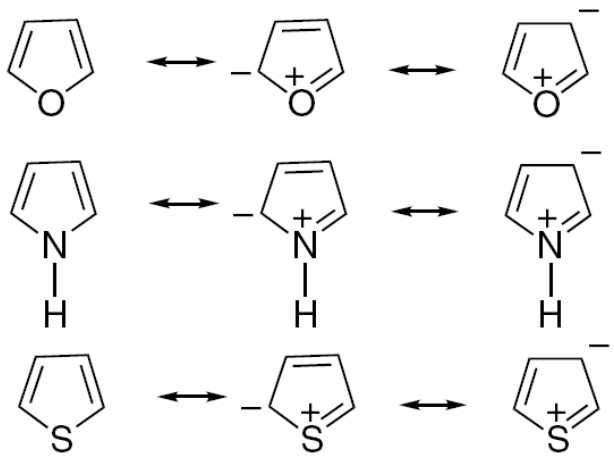
Electrophilic Aromatic Substitution (EAS)

Heteroaromatics:

π-excessive

- reactivity order: pyrrole > furan > thiophene
- order in electron-donating capacity N > O > S
- reactivity toward EAS: 2 > 3

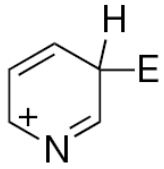




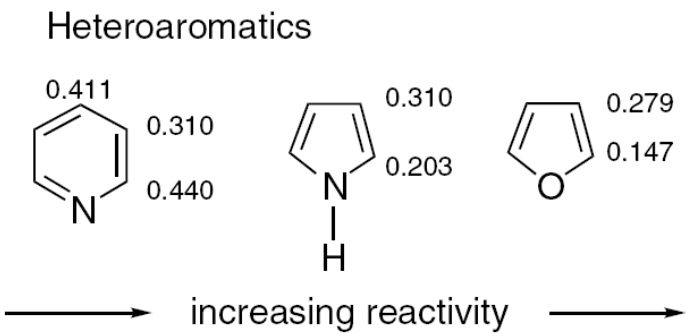
π-deficient

−N=CH− unit is „deficient“

- reactivity toward EAS: 3 > 4 ~ 2



less
unfavorable

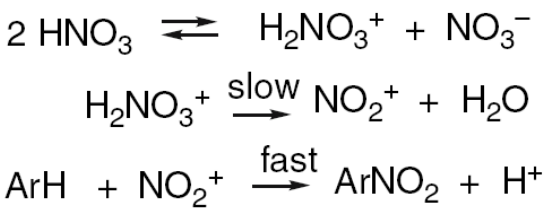


Electrophilic Aromatic Substitution (EAS)

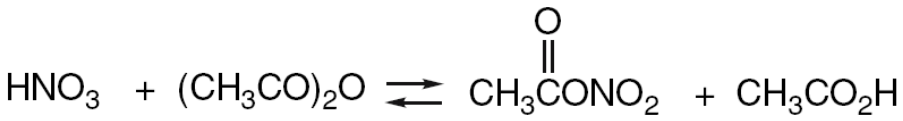
Nitration

- general reaction, normally for both activated and deactivated Ar
- nitro group reduces the reactivity → easy to control (mononitration x polynitration)
- nitration reagents:

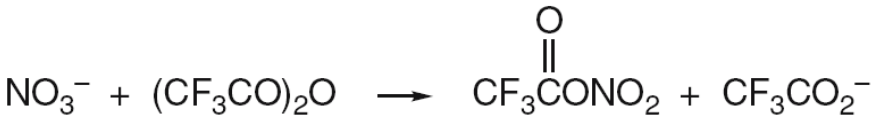
1) HNO_3 2) HNO_3/H_2SO_4



3) HNO_3/Ac_2O (*o- selectivity*)



4) CF_3COONO_2 (*o*-, *p*- selectivity + zeolites)



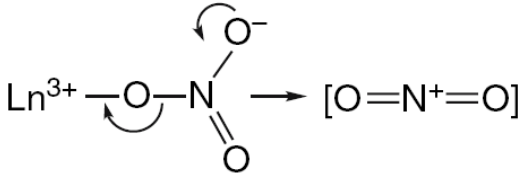
Electrophilic Aromatic Substitution (EAS)

Nitration

- nitration reagents:

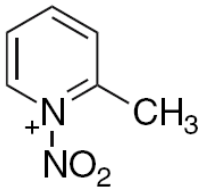
5) $HNO_3/Yb(OTf)_3$
   - stoichiometric amount of nitric acid
   - various systems:

$Sc(OTf)_3$/ $LiNO_3$ or $Al(NO_3)_3$ and Ac_2O



6) NO_2BF_4 (NO_2OTf)
   - salts containing the nitronium ion (very reactive)

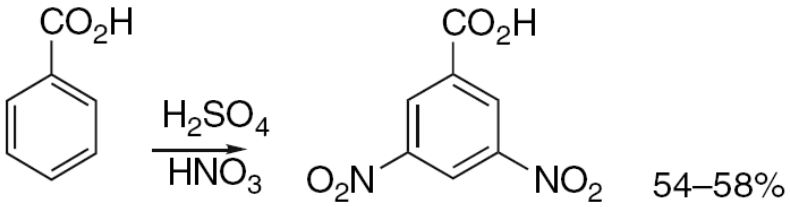
7) „transfer nitration“
   - mild conditions

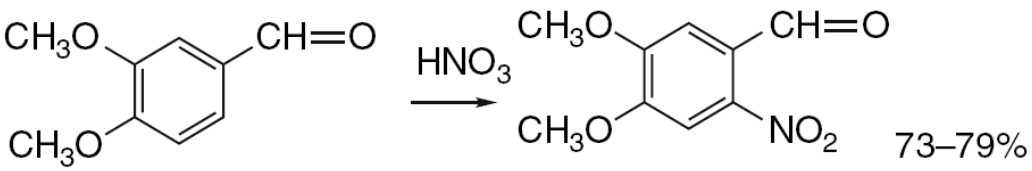


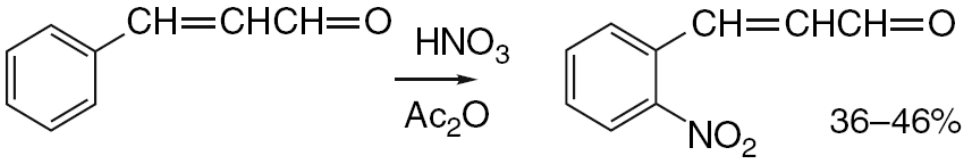
8) NO_2+O_3

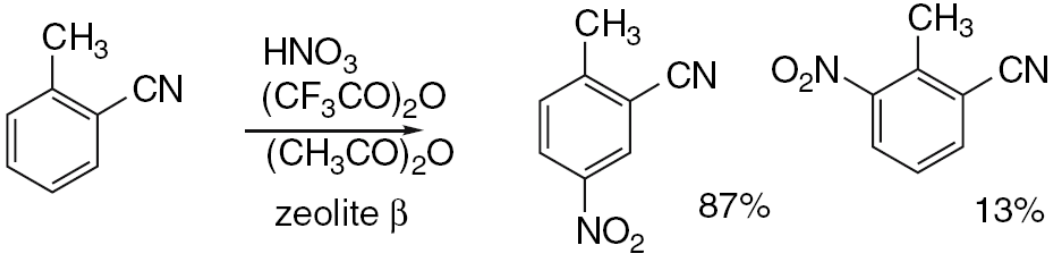
Electrophilic Aromatic Substitution (EAS)

Examples:



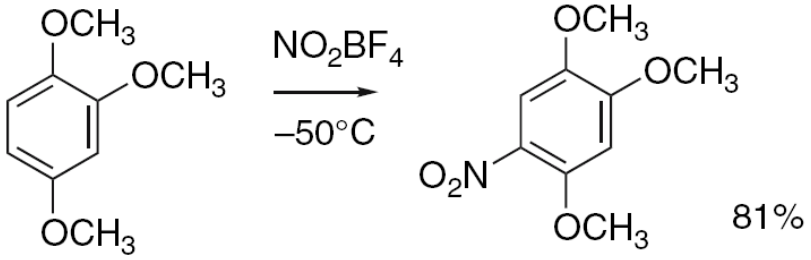


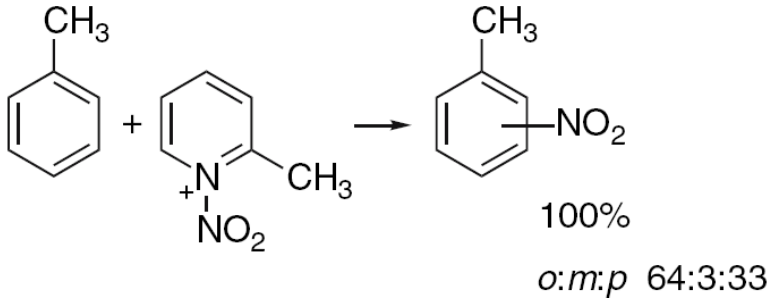


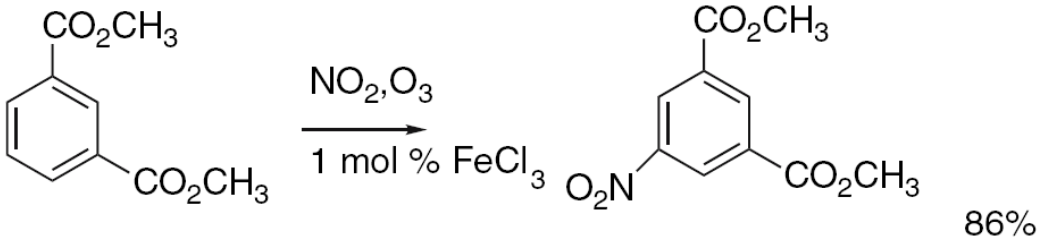


Electrophilic Aromatic Substitution (EAS)

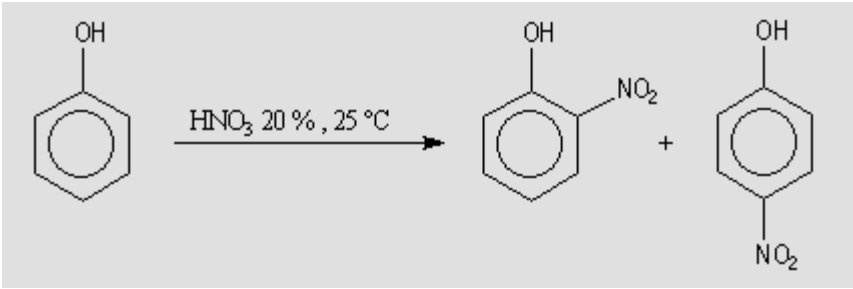
Examples:







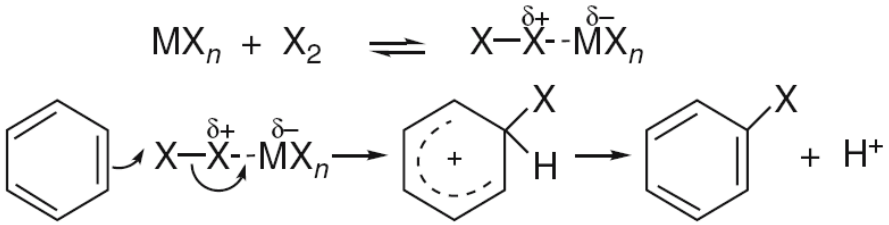
Q.1?



Electrophilic Aromatic Substitution (EAS)

Halogenation

- the order of reactivity of the halogens: $I_2 < Br_2 < Cl_2 < F_2$.
- LA $\rightarrow$ cleavage of the halogen-halogen bond



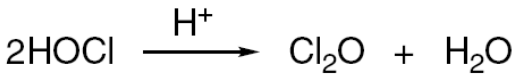
Chlorination

1) Cl_2 /LA ($ZnCl_2$, $FeCl_3$, $AlCl_3$)

2) NCS/HCl ($HClO_4$)

3) HOCl (weak)
   - very reactive (for non-activated Ar)

4) $Cl_2/Hg(OOCCF_3)_2$ or $Hg(OTf)_2$

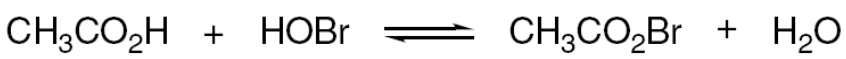


Electrophilic Aromatic Substitution (EAS)

Bromination

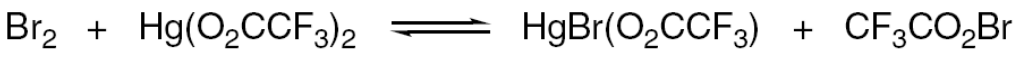
1) Br_2 /LA (Fe) 2) NBS/HBr 3) $Br_2/CCl_4/H_2SO_4$

4) HOBr/AcOH

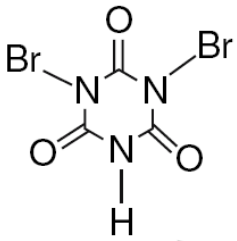


5) $Br_2/Hg(OAc)_2$ or $Hg(OTf)_2$

- very reactive (for non-activated Ar)



6) dibromoisocyanuric acid/H_2SO_4



(The estimated order of reactivity: Br_2, CH_3CO_2Br and CF_3CO_2Br: $1:10^6:10^{10}$)

Electrophilic Aromatic Substitution (EAS)

Iodination

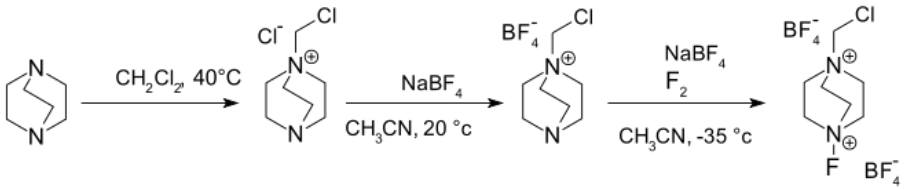
- I_2 not a very powerful halogenating agent (only anilines or phenolate anions)

1) ICl/HCl or LA ($ZnCl_2$)
2) I_2/oxidant (HIO_4, I_2O_5, CAN = $Ce(NH_3)_2(NO_3)_6$)
3) $I_2/CuCl_2$
4) $I_2/Hg(OAc)_2$ or $AgOOCCF_3$
   - very reactive
5) py_2I^+/TfOH, etc.

Fluorination

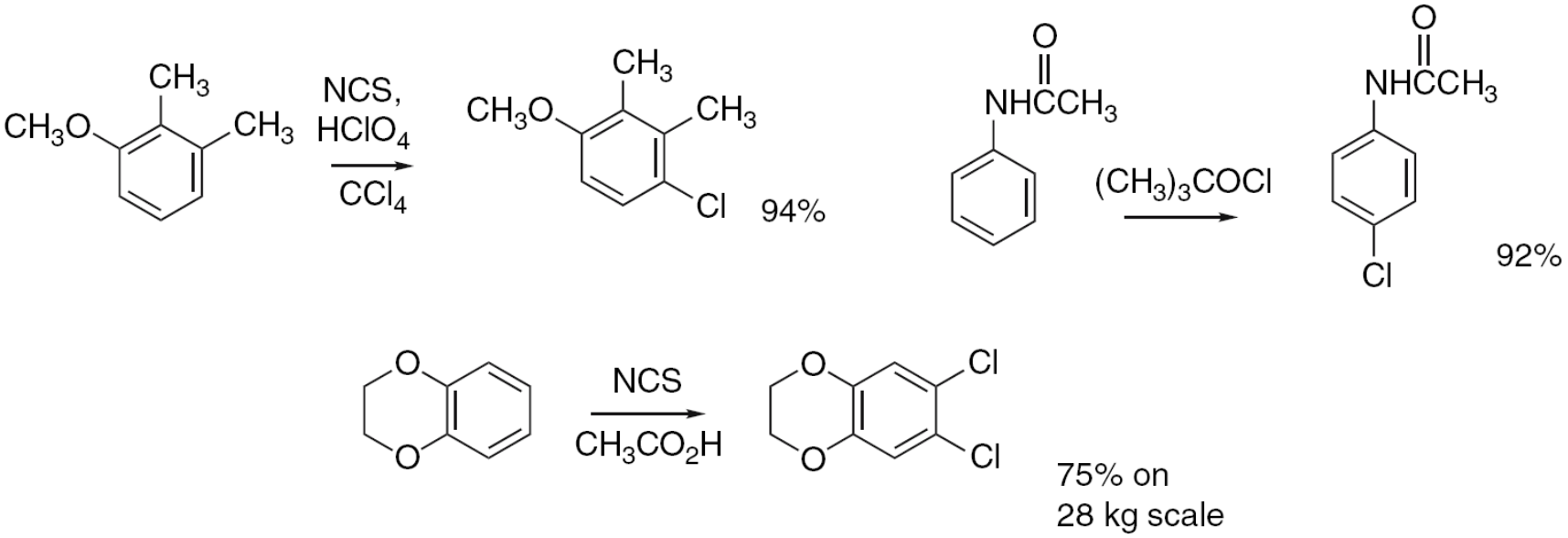
- not very important in lab
- with F_2 „uncontrolled reaction“ – use of inert gas

1) AcOF, CF_3OF (for activated Ar)
2) *N*-fluorotriflimide $(CF_3SO_2)_2NF$
3) Selectfluor, etc.



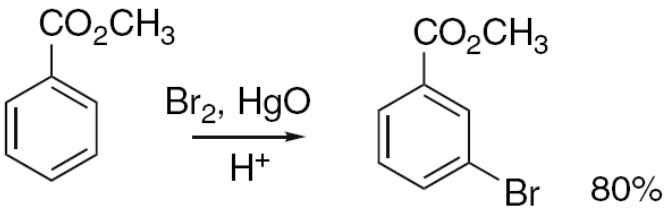
Electrophilic Aromatic Substitution (EAS)

Examples:

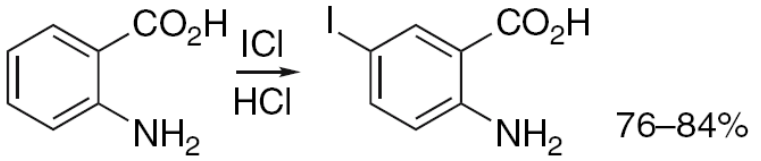


Electrophilic Aromatic Substitution (EAS)

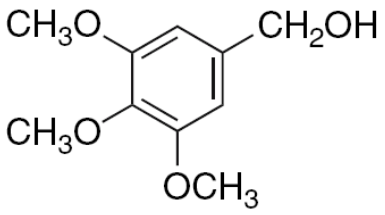
Examples:

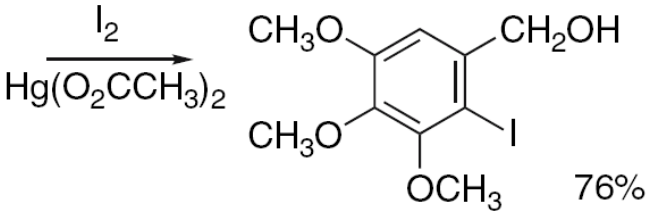


80%

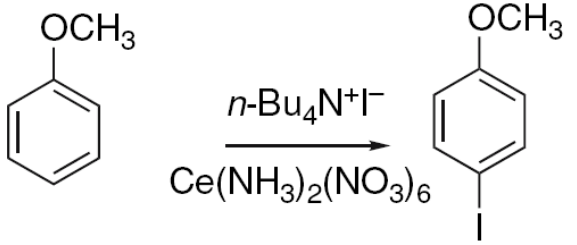


76–84%

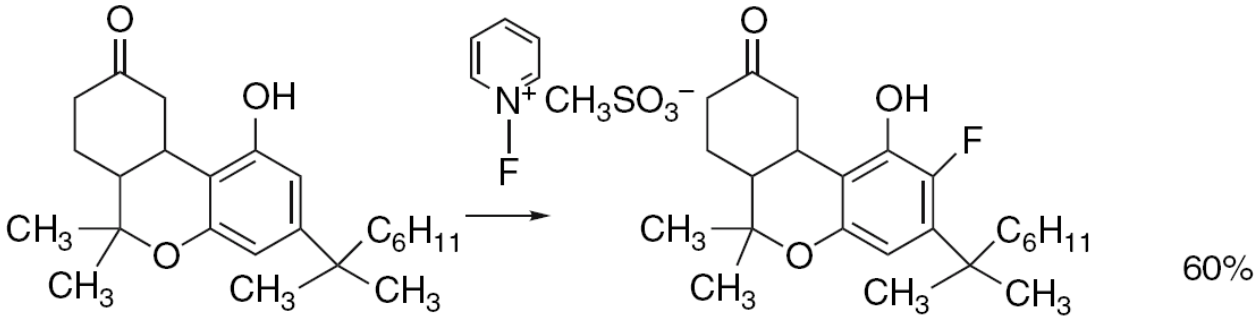




76%



84%

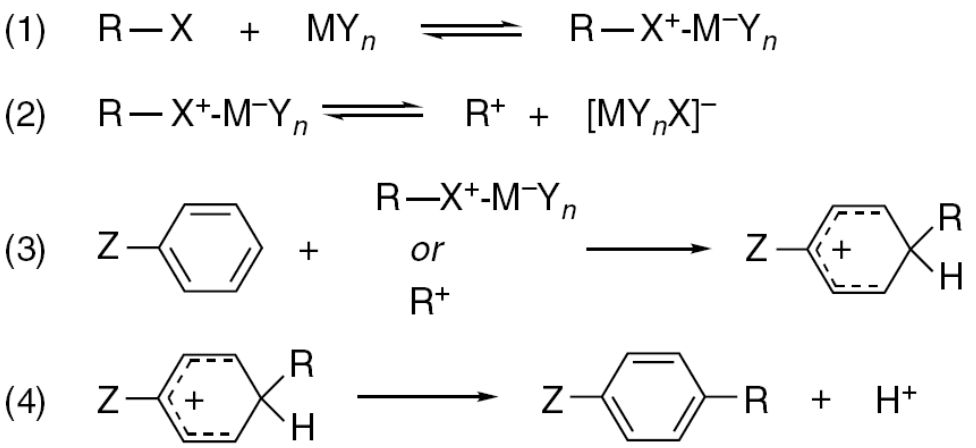


60%

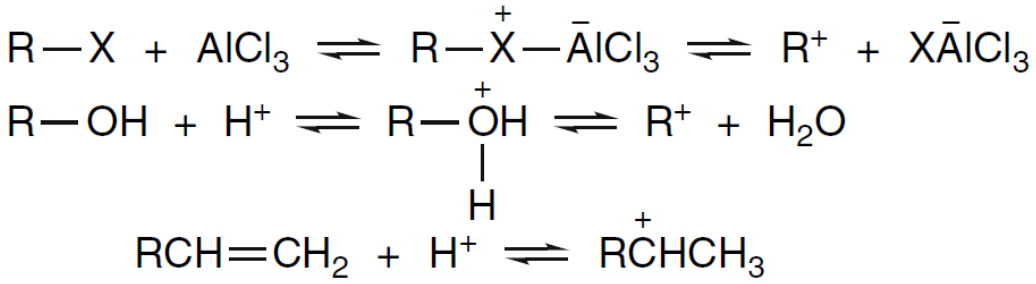
Electrophilic Aromatic Substitution (EAS)

Friedel-Crafts Alkylation

Mechanism



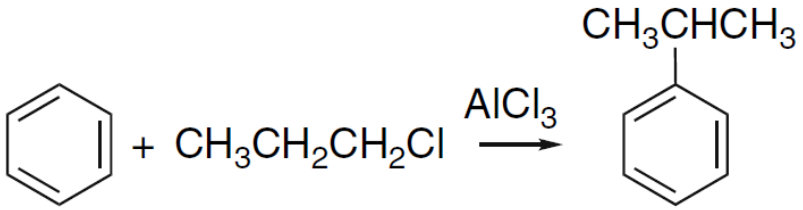
Alkylation reagents



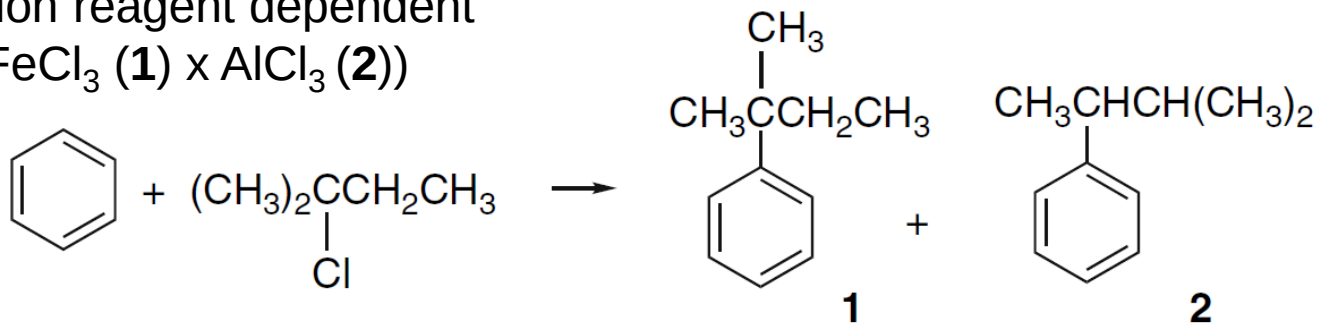
Electrophilic Aromatic Substitution (EAS)

Friedel-Crafts Alkylation

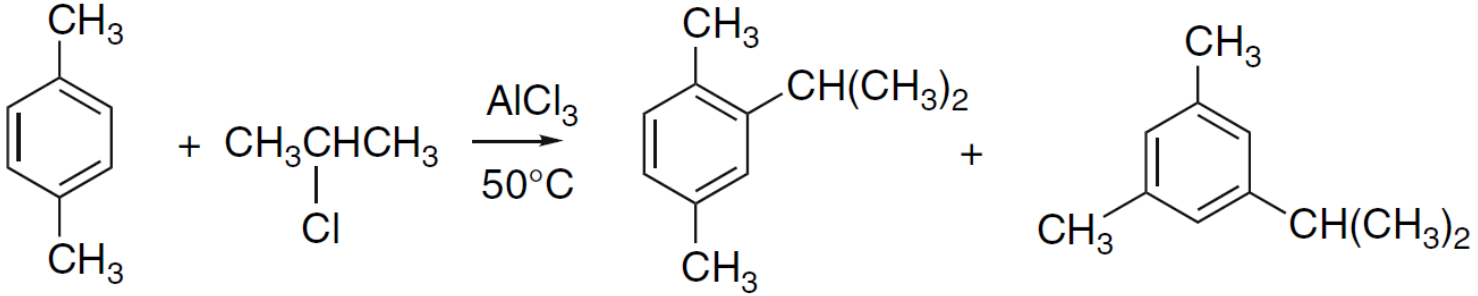
Rearrangements



- alkylation reagent dependent (BF_3, $FeCl_3$ (**1**) x $AlCl_3$ (**2**))



- migration of groups



Electrophilic Aromatic Substitution (EAS)

Friedel-Crafts Alkylation

Polyalkylation

- increase of reactivity toward S_{Ar}
- excess of Ar

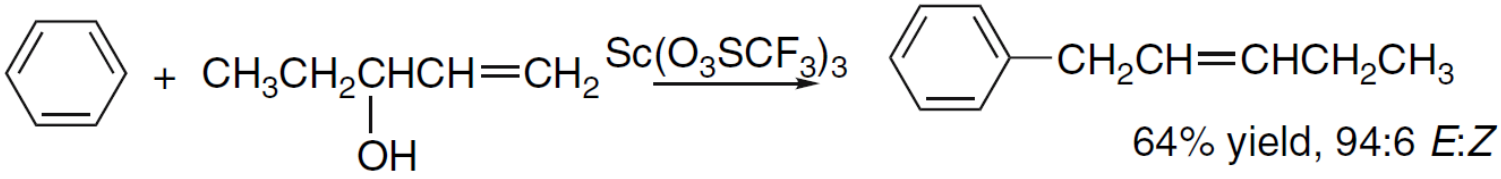
Catalysts

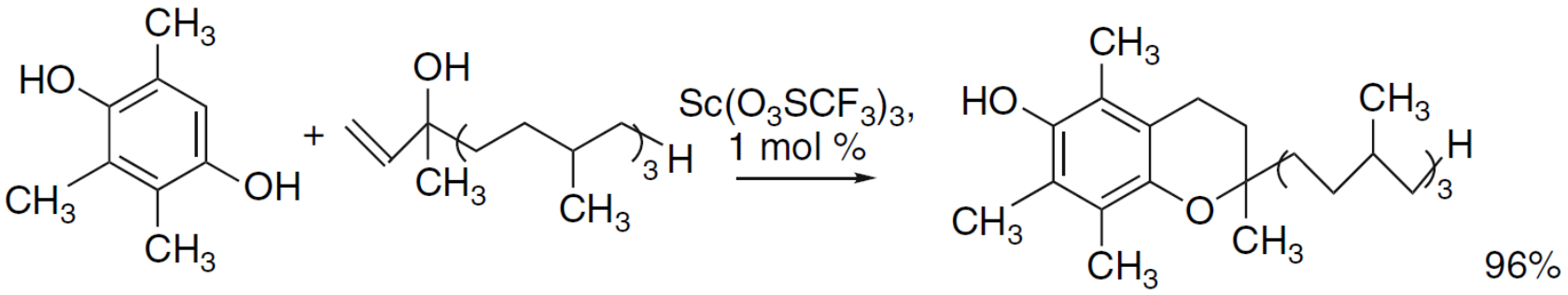
BF_3, $FeCl_3$ (**RX, ROH**)
H_2SO_4, H_3PO_4, HF, BF_3, $FeCl_3$ (**alkenes**)
$Sc(OTf)_3$ - **allylic, benzylic carbcations**
$Sc(OTf)_3$, $Cu(OTf)_2$ (**ROMs**)

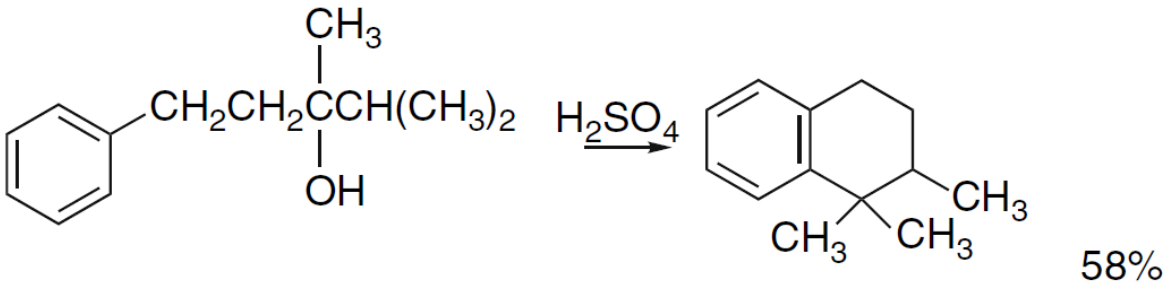
Very active	Moderately active	Mild
$AlCl_3$, $AlBr_3$,	$InCl_3$, $InBr_3$, $SbCl_4$,	BCl_3, $SnCl_4$,
$GaCl_3$, $GaCl_2$,	$FeCl_3$, $AlCl_3-CH_3NO_2$,	$TiCl_4$, $TiBr_4$,
SbF_5, $MoCl_5$,	$SbF_5-CH_3NO_2$	$FeCl_2$

Electrophilic Aromatic Substitution (EAS)

Examples



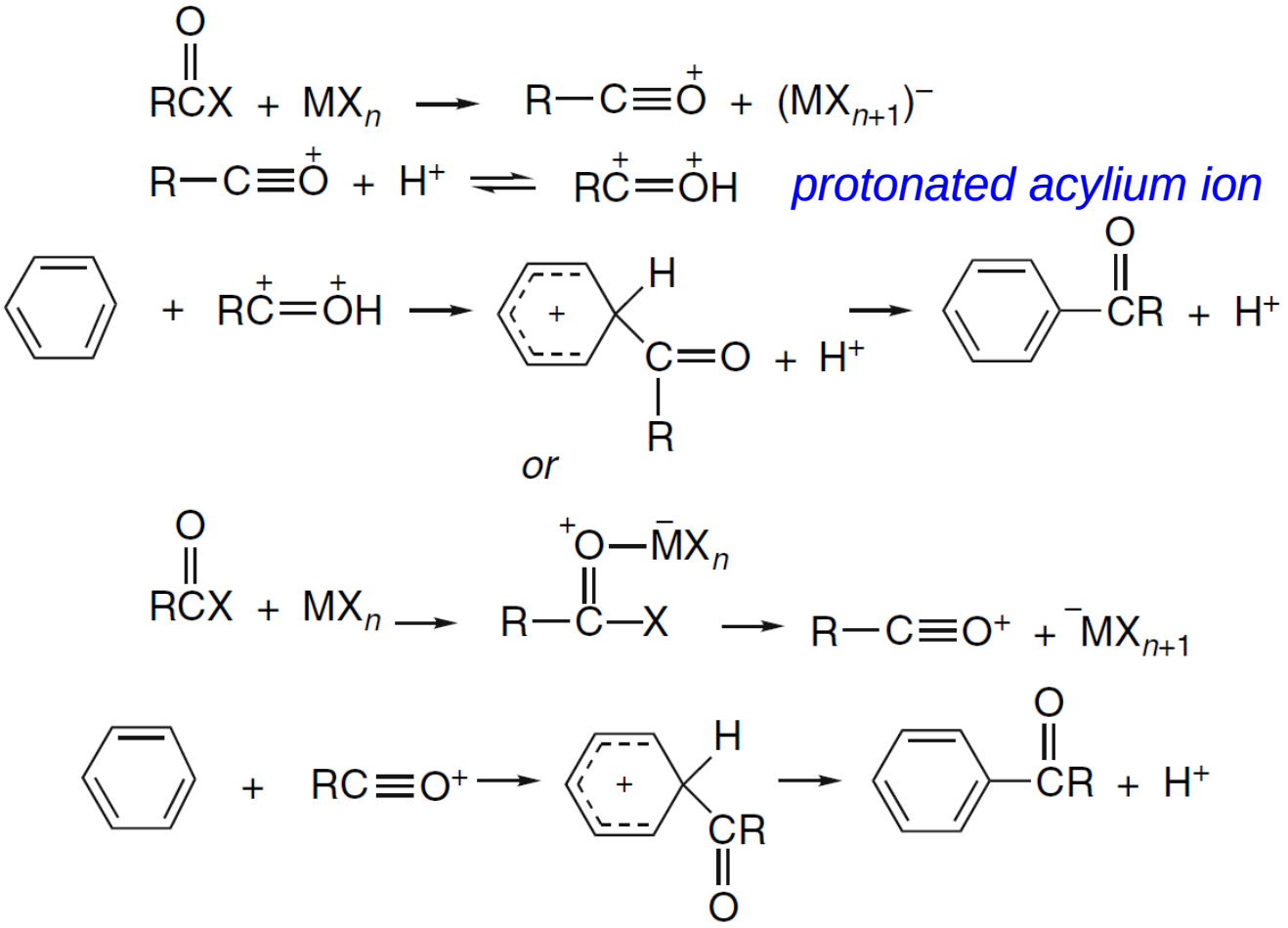




Electrophilic Aromatic Substitution (EAS)

Friedel-Crafts Acylation

Mechanism



Electrophilic Aromatic Substitution (EAS)

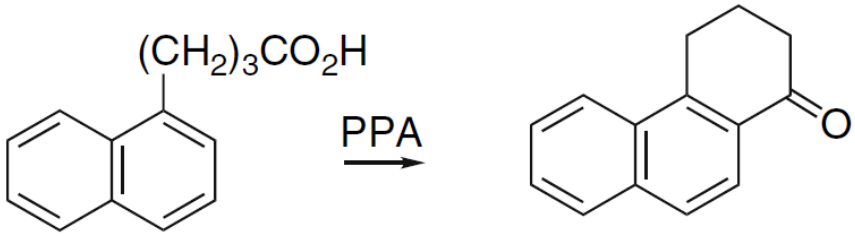
Friedel-Crafts Acylation

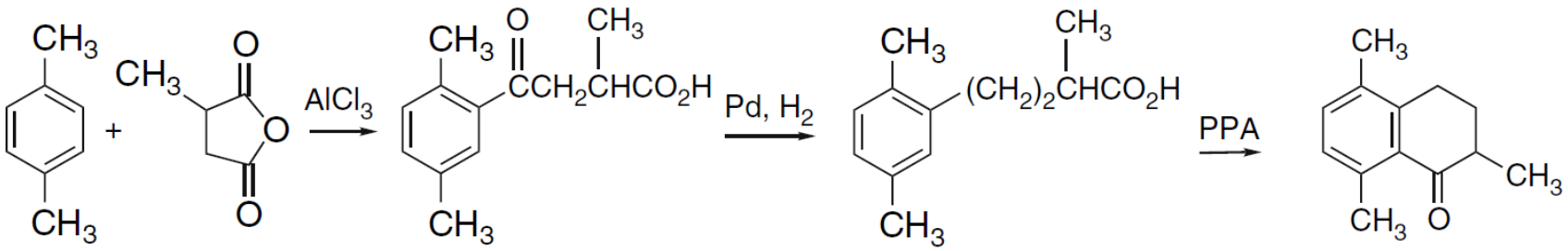
Acylation catalysts

$AlCl_3$, SbF_5, BF_3,$Bi(OTf)_3$ - **RCOX**
$Hf(OTf)_2$, $LiClO_4$ - **$(RCO)_2O$**
H_3PO_4, (H^+) – **RCOOTf**

Regioselectivity

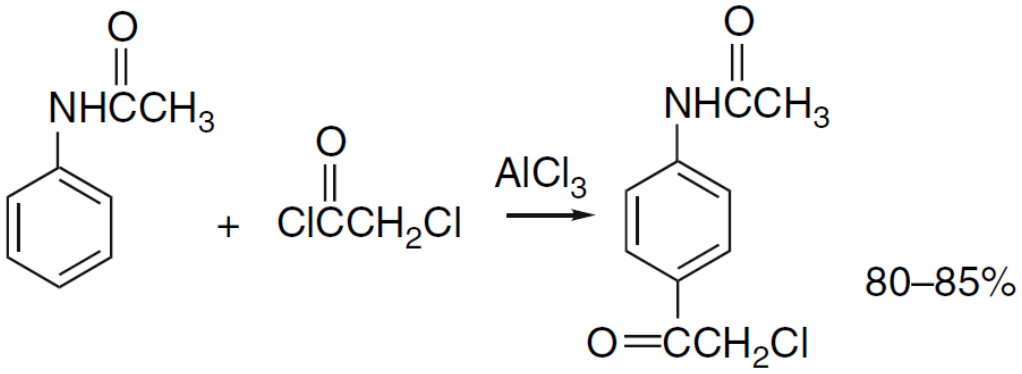
para **–** alkylated aromatics, *ortho* – increased with electrophilicity of acylium ion
no rearrangements
monoacylation products
intramolecular acylation

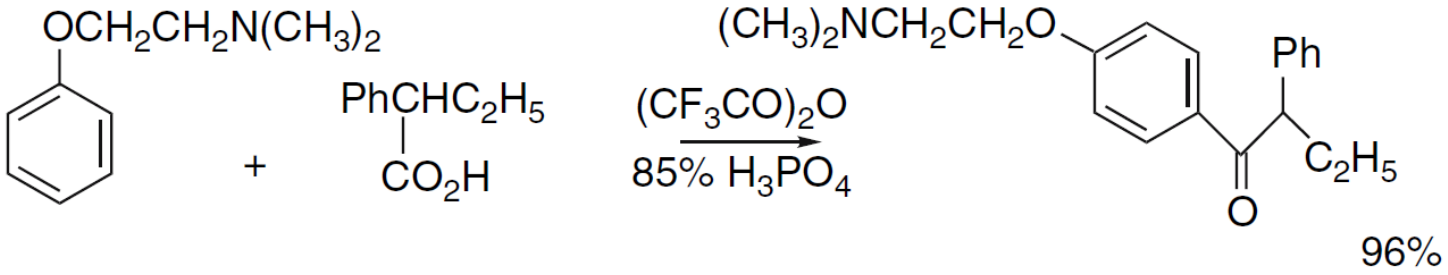


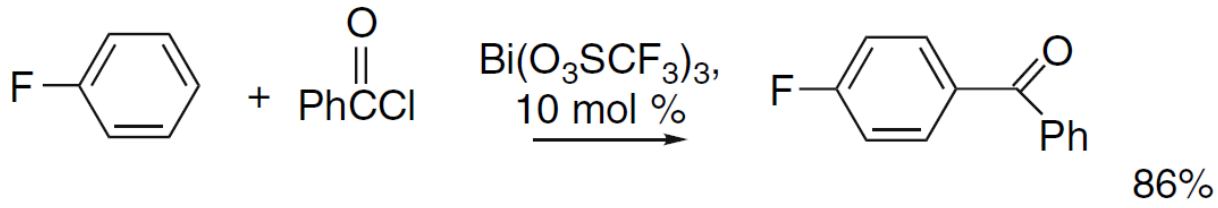


Electrophilic Aromatic Substitution (EAS)

Examples

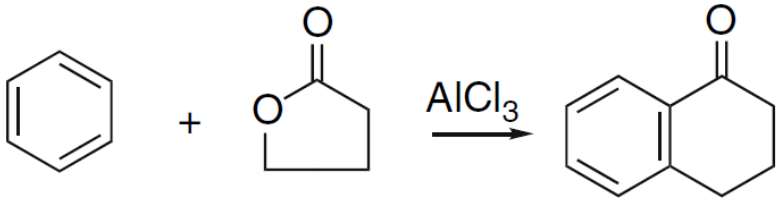




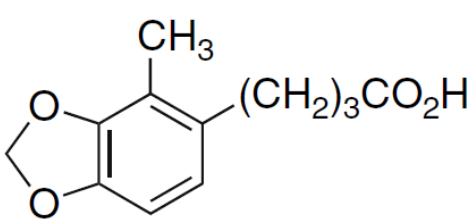


Electrophilic Aromatic Substitution (EAS)

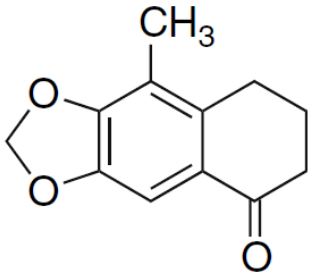
Examples



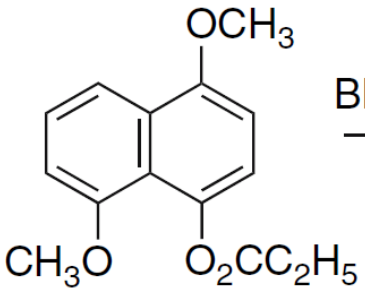
91–96%



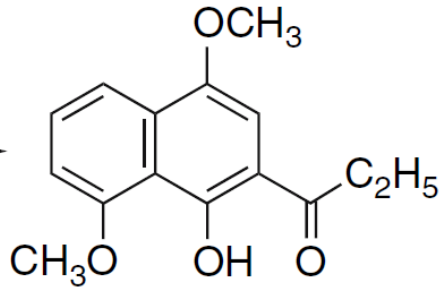
polyphosphate ester



87%



BF_3



92%

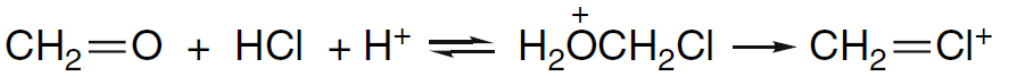
Fries r.

Electrophilic Aromatic Substitution (EAS)

Related Alkylation and Acylation Reactions

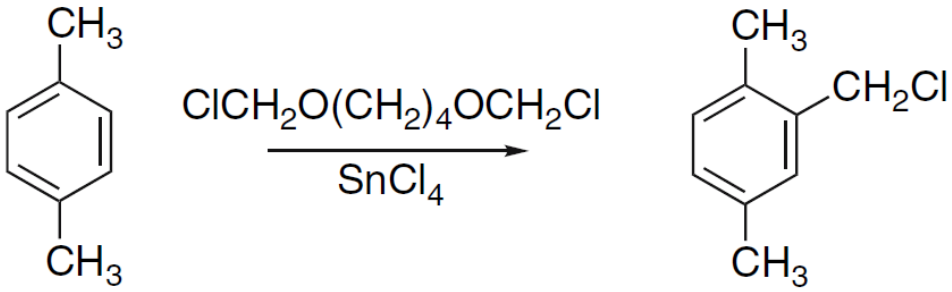
Chlormethylenation

HCOH/HCl – benzene, activated Ar



chlormethylium ion

$ROCH_2Cl/SnCl_4$

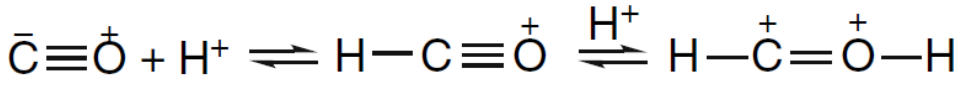


Electrophilic Aromatic Substitution (EAS)

Related Alkylation and Acylation Reactions

Formylation

a. Formylation with carbon monoxide:



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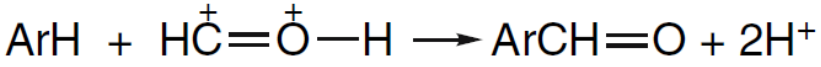
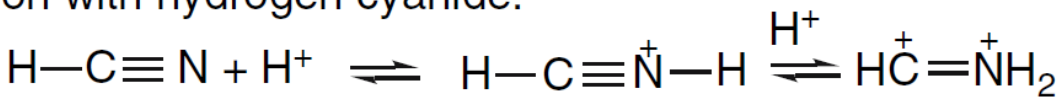
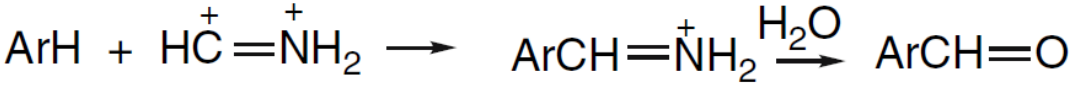
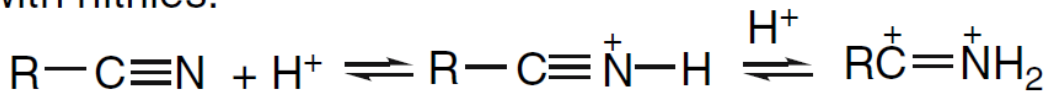


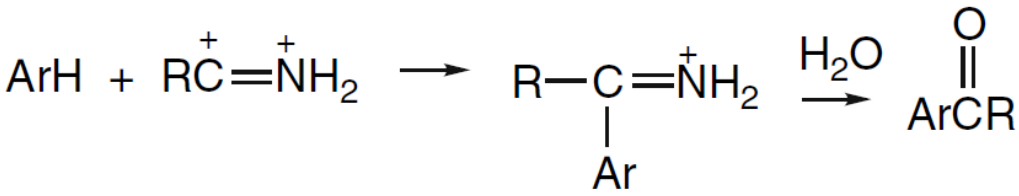
b. Formylation with hydrogen cyanide:





c. Acylation with nitriles:





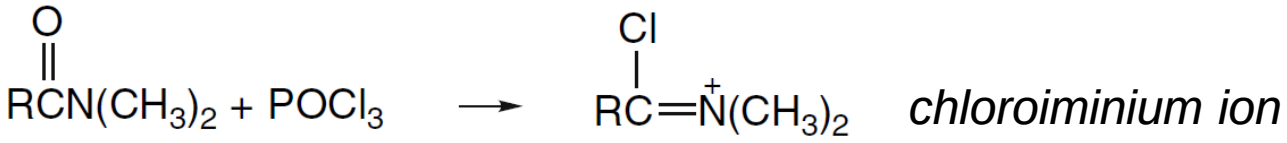
Electrophilic Aromatic Substitution (EAS)

Related Alkylation and Acylation Reactions

Formylation

Vilsmeier-Haack reaction

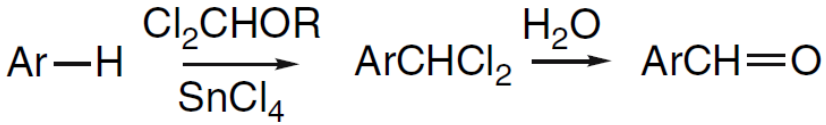
N,*N*-dialkylamides + $POCl_3$ ($ClOCCOCl$)



chloroiminium ion

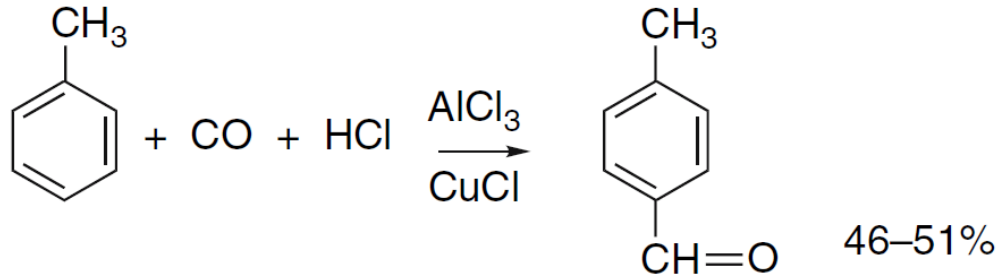
- no LA, activated Ar

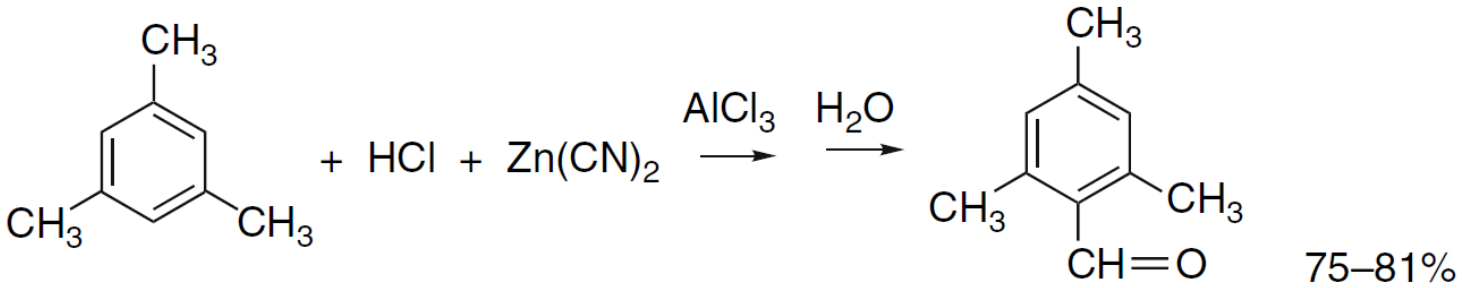
Dichloromethylethers ($SnCl_4$, $TiCl_4$)

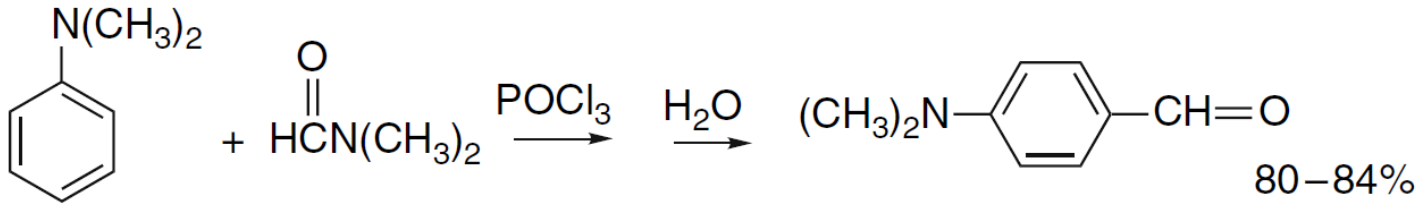


Electrophilic Aromatic Substitution (EAS)

Examples



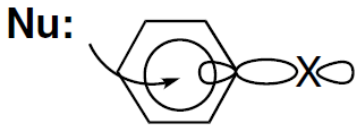




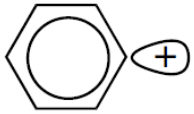
Nucleophilic Aromatic Substitution (NAS)

NAS:

- different to other nucleophilic substitution (S_N1, S_N2)



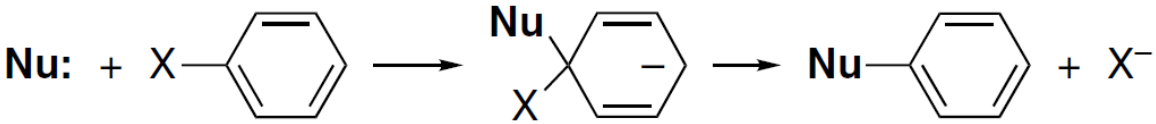
back-side approach of the nucleophile with inversion is impossible



phenyl cation is a high-energy intermediate

- addition-elimination and elimination-addition mechanism

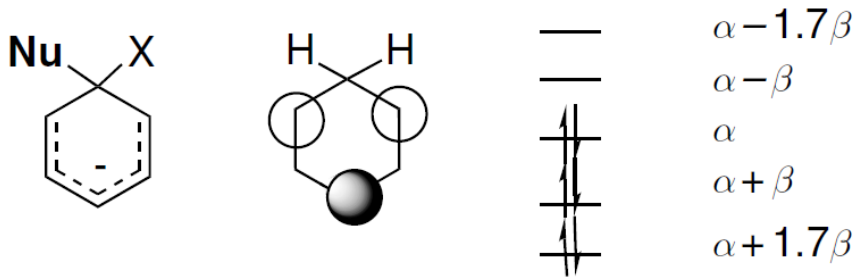
Addition-Elimination Mechanism



Nucleophilic Aromatic Substitution (NAS)

Addition-Elimination Mechanism

- one of the vacant π^* orbitals for bonding interaction with the nucleophile
- intermediate isoelectric with a cyclohexadienyl anion



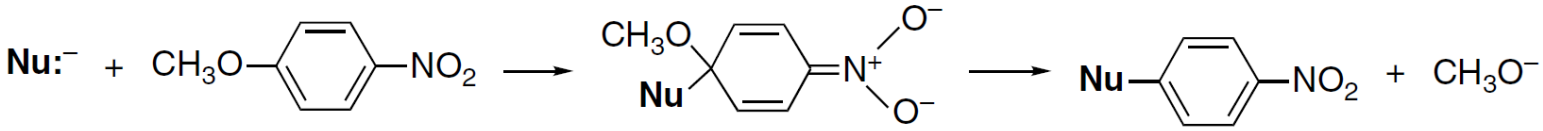
- stabilization of intermediate with EWG (NO_2, CN, COR)
- extreme reaction conditions

- LG:
  halogens: association of Ar with Nu (*slow*) $\rightarrow$ F > Cl > Br > I
  (S_N1, S_N2: strength dominant $\rightarrow$ I > Br > Cl > F)
  alkoxy: (poor in S_N1 and S_N2)
  nitro, sulfonyl groups

Nucleophilic Aromatic Substitution (NAS)

Addition-Elimination Mechanism

- *Meisenheimer complexes*

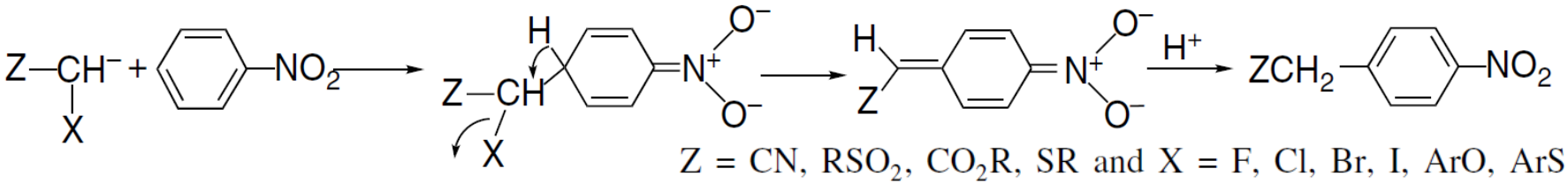


- Nucleophiles: (the same with S_N2 reactions)
  RS^-, RO^-, ArO^-, F^-, RNH_2, etc.

- Solvents: (the same with S_N2 reactions)
  DMF, DMSO, etc.

- Heteroaromatics:
  2-halopyridines, 2-haloquinolines, 1-haloisoquinolines, etc.

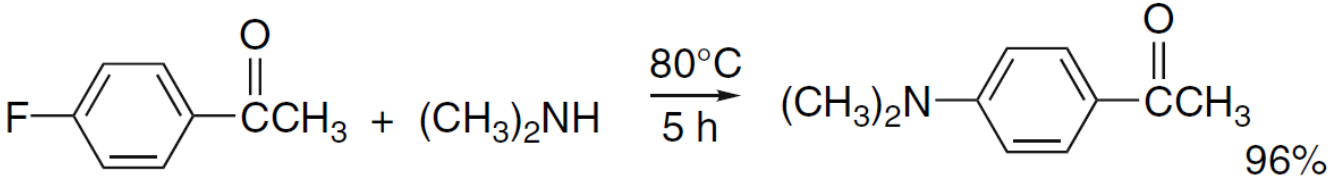
- *Vicarious Nucleophilic Aromatic Substitution*

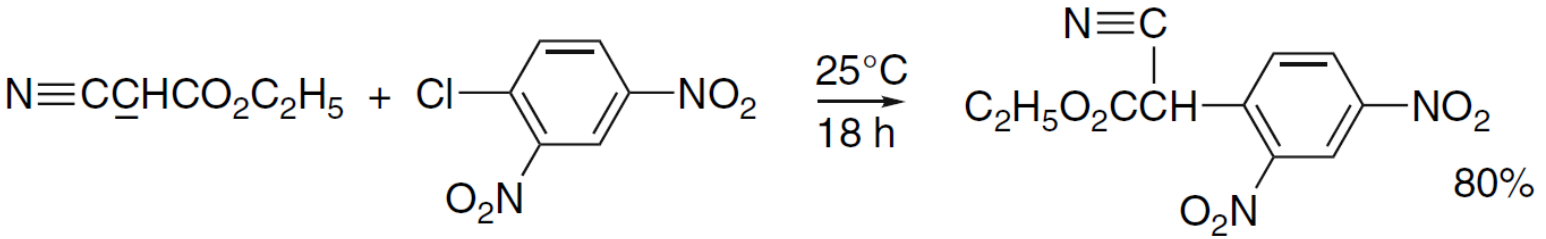


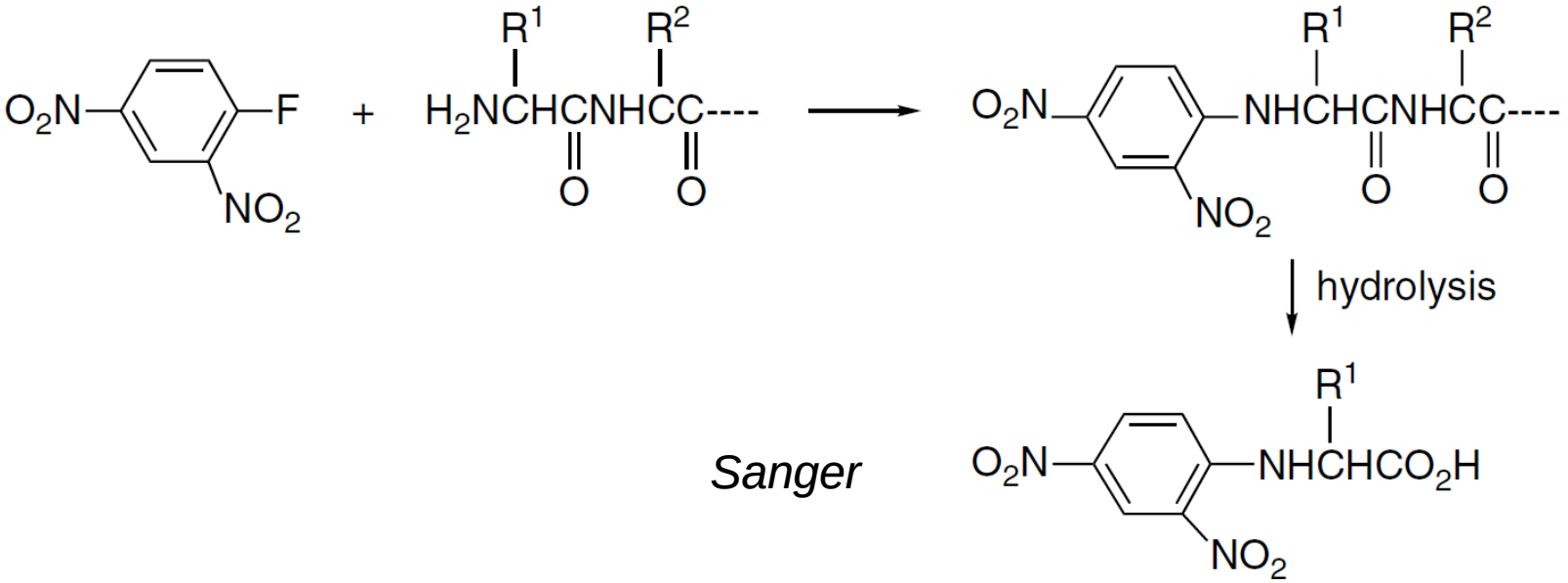
Z = CN, RSO_2, CO_2R, SR and X = F, Cl, Br, I, ArO, ArS

Nucleophilic Aromatic Substitution (NAS)

Examples





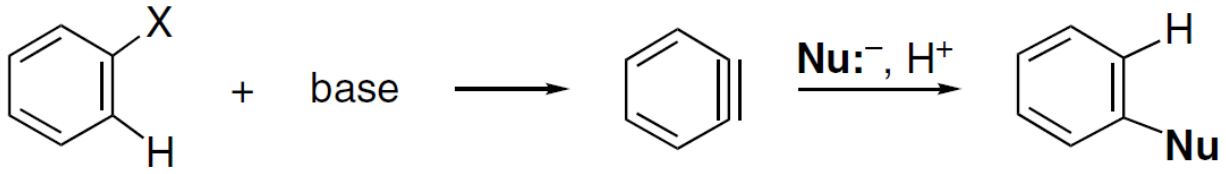


Sanger

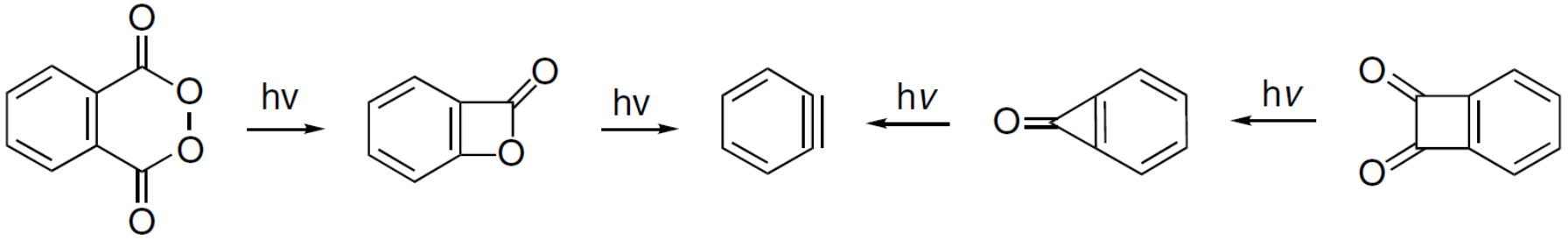
Nucleophilic Aromatic Substitution (NAS)

Elimination-Addition Mechanism

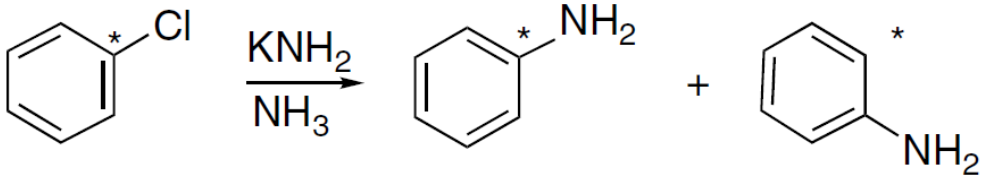
- *via* benzyne



- generation of benzyne



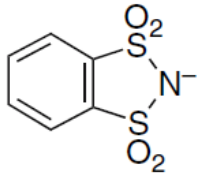
- relative reactivity: Br > I > Cl > F



Nucleophilic Aromatic Substitution (NAS)

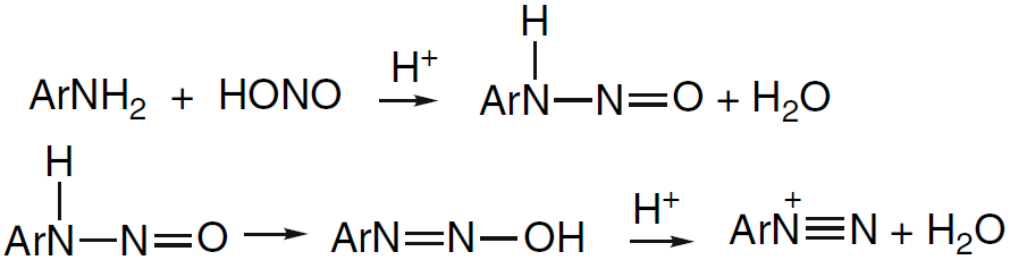
Aryl Diazonium Ions

- aliphatic diazonium salts → carbocation + N_2
- aryl diazonium salts: „stable“ ← aniline + „HNO_2“
- anions: BF_4, CF_3COO^-, $C_6H_4S_2O_4N^-$

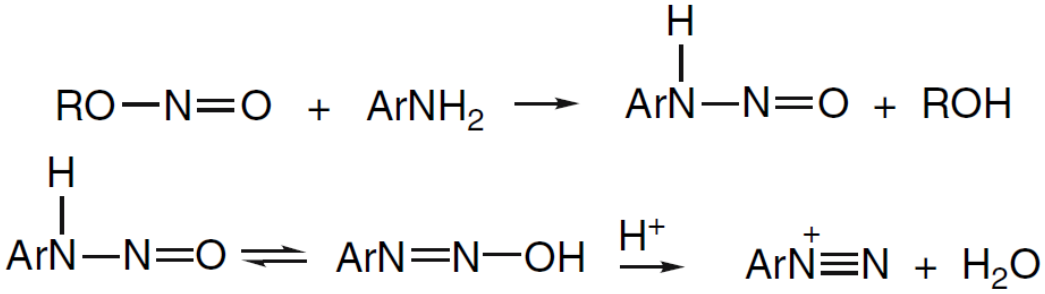


benzenedisulfonimidate anion

- mechanism:



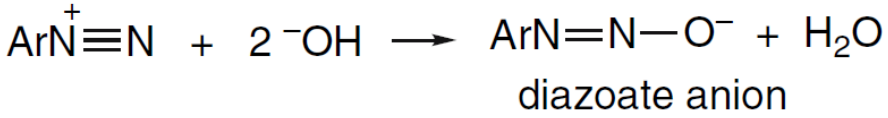
- another generation of ArN_2^+ (from alkylnitrites)

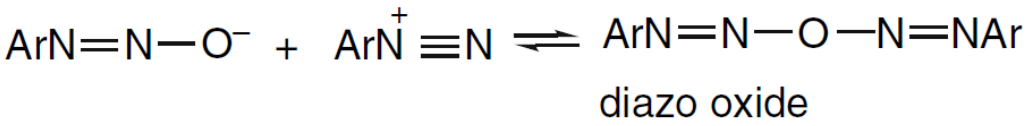


Nucleophilic Aromatic Substitution (NAS)

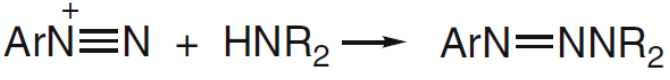
Aryl Diazonium Ions

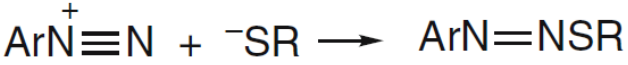
- stability:





- stable adducts:



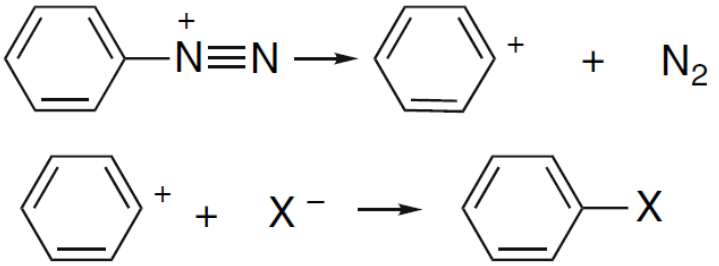


Nucleophilic Aromatic Substitution (NAS)

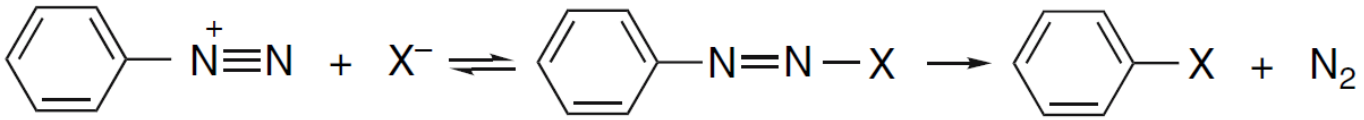
Aryl Diazonium Ions

General Mechanisms of NAS:

- unimolecular thermal decomposition
  (hydrolyzis of ArN_2^+ to phenols)



- formation of adduct and collabse (the loss of N_2)



- redox process (Cu)

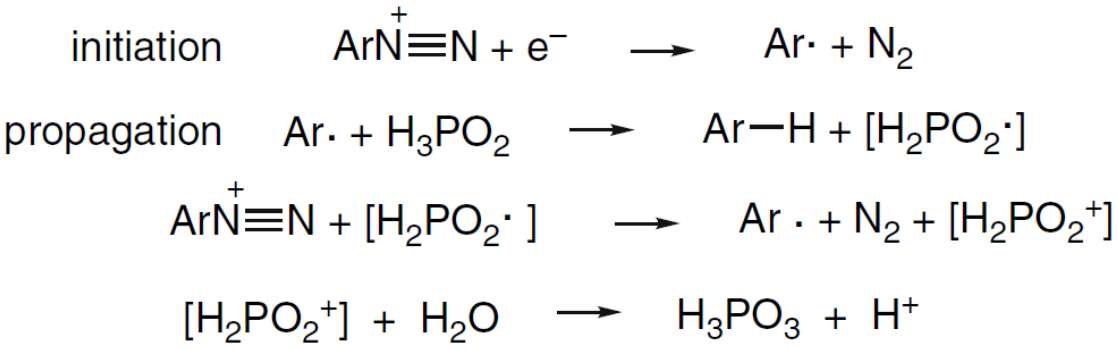
$$ArN_2^+ + [Cu(I)X_2]^- \rightarrow Ar{-}Cu(III)X_2 + N_2$$

$$Ar{-}Cu(III)X_2 \rightarrow ArX + Cu(I)X$$

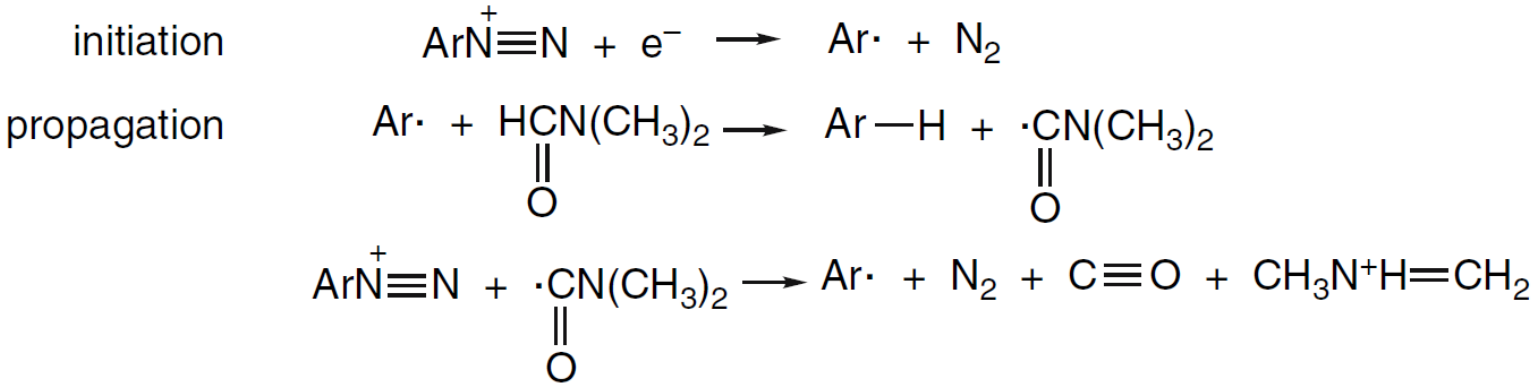
Nucleophilic Aromatic Substitution (NAS)

Reductive Dediazonization

- H_3PO_2
- single-electron process



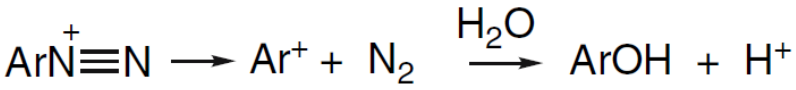
- another reagents ($NaBH_4$, $DMF/FeSO_4$ or RONO)



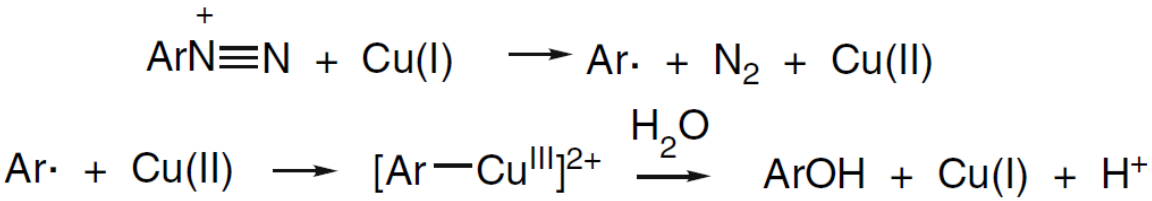
Nucleophilic Aromatic Substitution (NAS)

Phenols from Aryl Diazonium Ions

- H_2O
- formation of a phenyl cation



- redox mechanism (Cu)



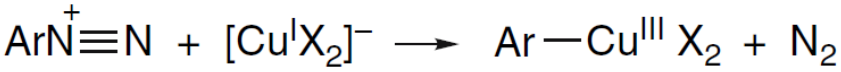
Aryl Halides from Diazonium Ion Intermediates

- ArCl, ArBr *via* Cu(I) - *Sandmayer*

Nucleophilic Aromatic Substitution (NAS)

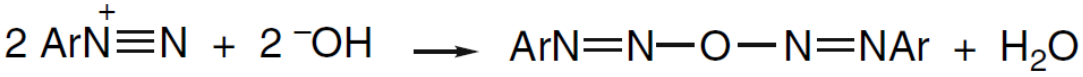
Aryl Halides from Diazonium Ion Intermediates

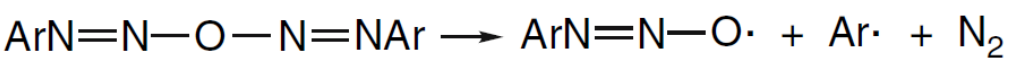
Sandmayer reaction - mechanism



($FeCl_2$-$FeCl_3$)

X aryl free radicals

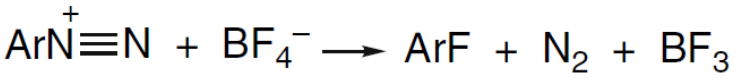




- crownethers, PTC, solvents (CCl_4, $CHBr_3$, CCl_3Br, MeI, CH_2I_2)

Schiemann reaction (BF_4^-, PF_6^-)

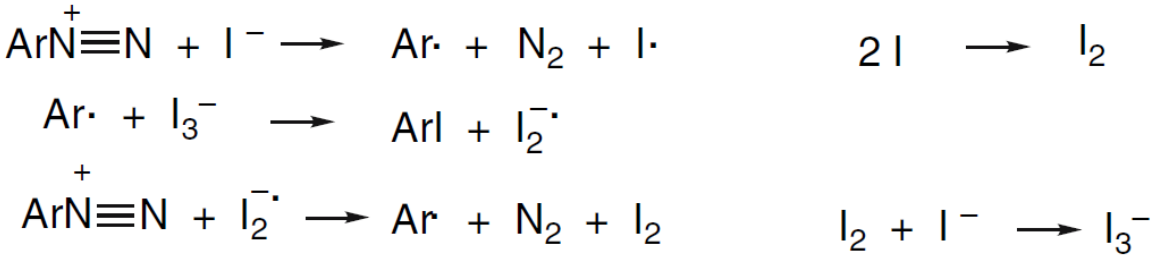
- *via* Ar^+



Nucleophilic Aromatic Substitution (NAS)

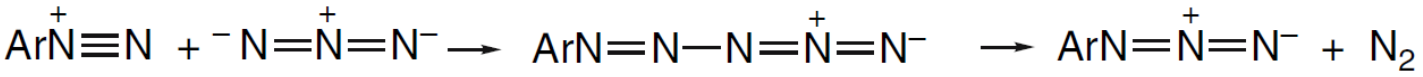
Aryl Halides from Diazonium Ion Intermediates

Aryl Iodides
- iodine salts
- reduction of ArN_2^+ by I^-
- mechanism



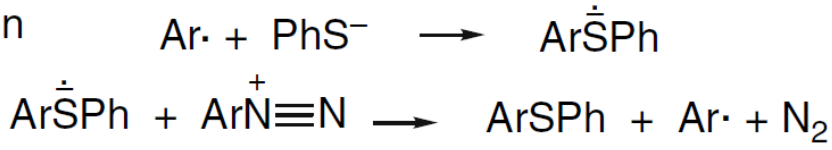
Introduction of Other Nuclephiles from Diazonium Ion Intermediates

- ArCN, ArN_3, ArSR, etc.



x *„Sandmayer“* (Cu)

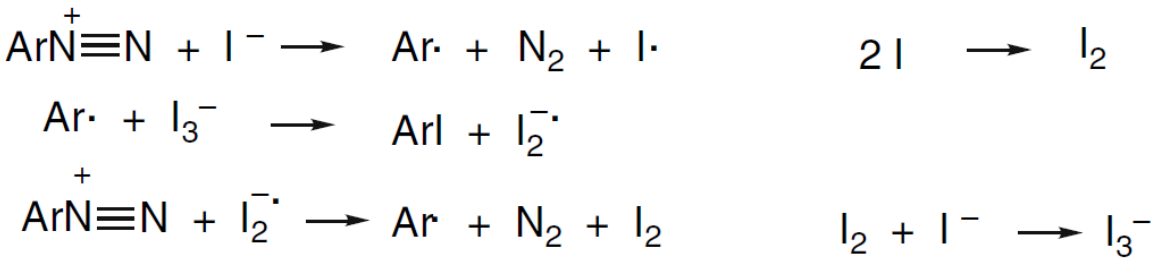
propagation



Nucleophilic Aromatic Substitution (NAS)

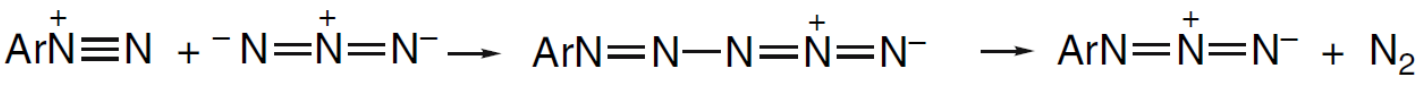
Aryl Halides from Diazonium Ion Intermediates

Aryl Iodides
- iodine salts
- reduction of ArN_2^+ by I^-
- mechanism



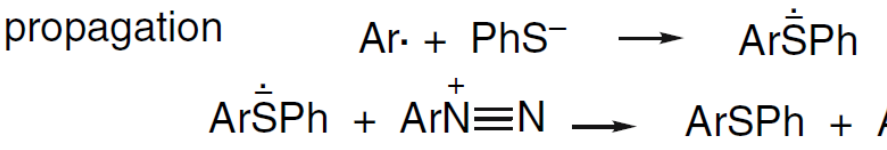
Introduction of Other Nuclephiles from Diazonium Ion Intermediates

- ArCN, ArN_3, ArSR, *Meerwein Arylation Reactions,* etc.

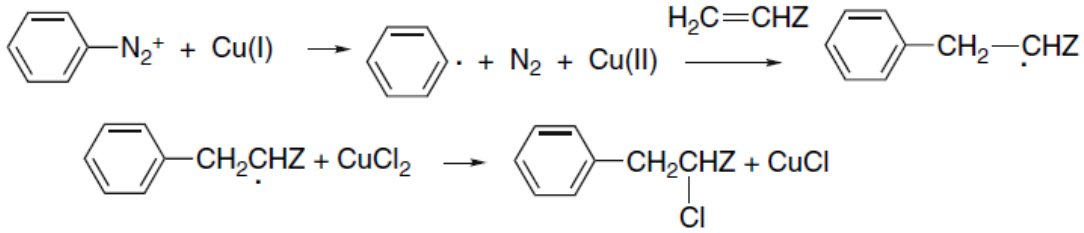


x *„Sandmayer“* (Cu)

propagation

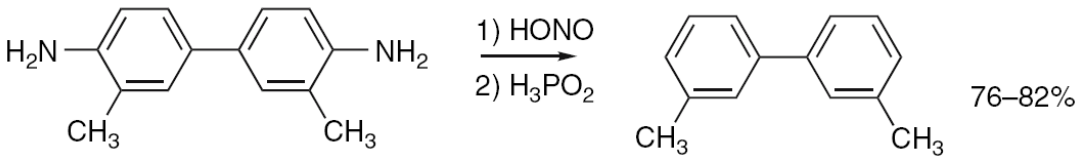


x

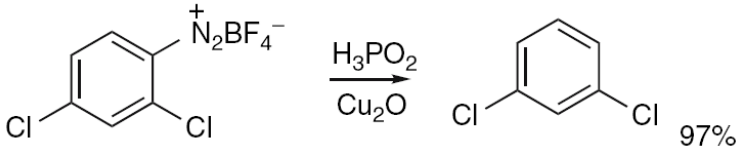


Nucleophilic Aromatic Substitution (NAS)

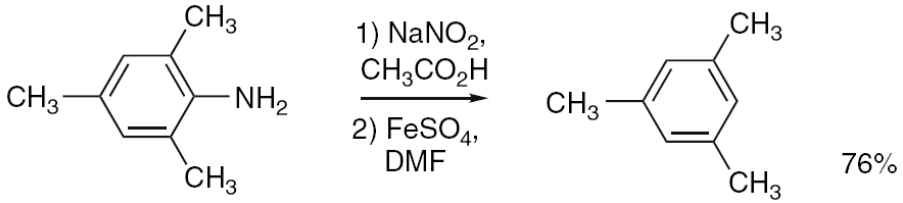
Examples



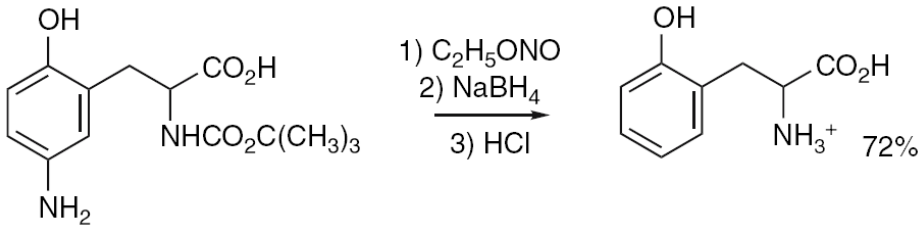
76–82%



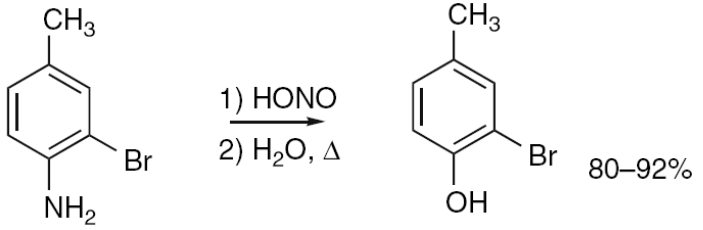
97%



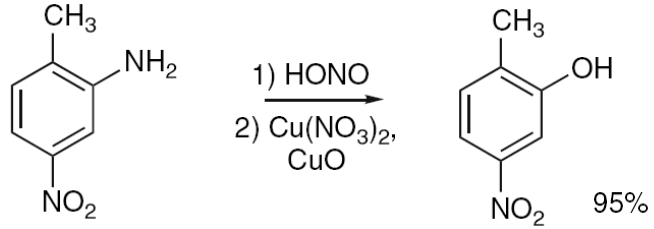
76%



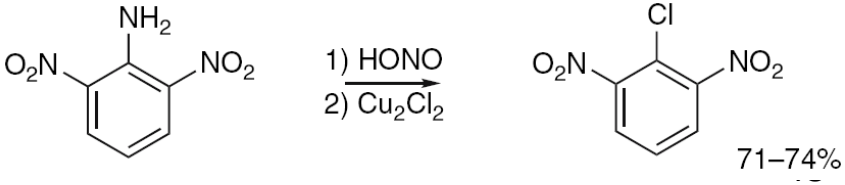
72%



80–92%



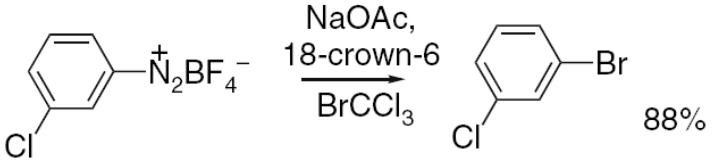
95%



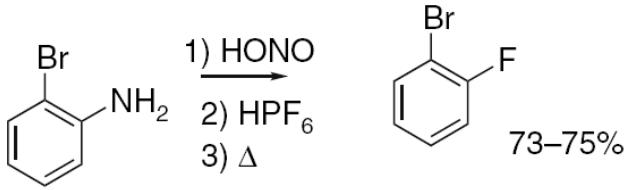
71–74%

Nucleophilic Aromatic Substitution (NAS)

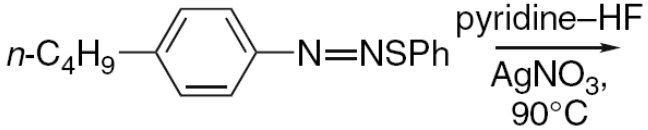
Examples



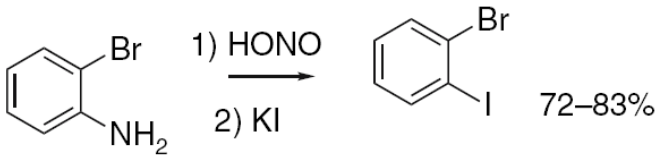
88%



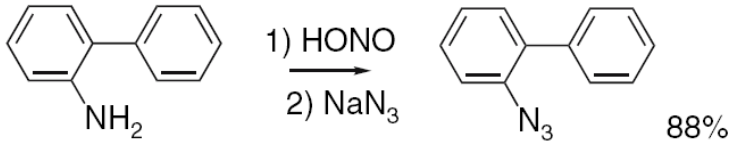
73–75%



39%



72–83%



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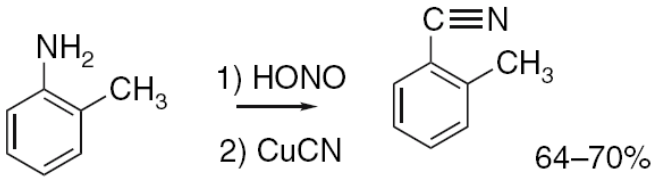
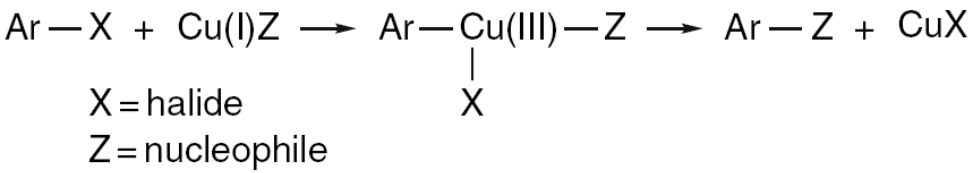


64–70%

Transition Metal-catalyzed Reactions S_{Ar}

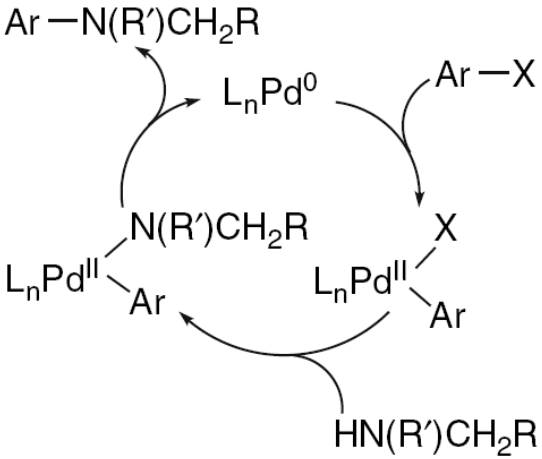
Cu-catalyzed Reactions

- heterogeneous condition
- I > Br> Cl > OSO_2R
- aryl halides with either EWG or ERG substituents



Palladium-Catalyzed Reactions

- I, Br, Cl, OTf, ONf, etc.
- with either EWG or ERG substituents
- ligand-control



Transition Metal-catalyzed Reactions S_{Ar}

Examples