Fonction et réaction organiques II

Fall Semester 2025

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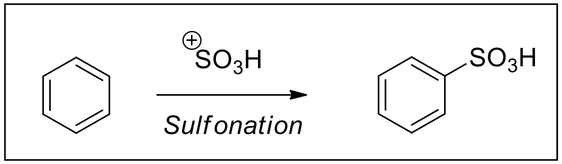
1.2.2.4. Sulfonation



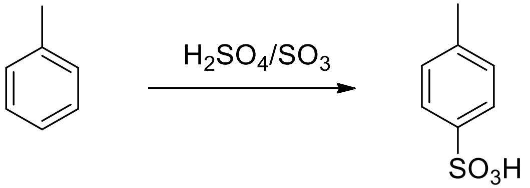
- Electrophile = SO_3H^+ , sulfonium ion
- Preparative Methods for Electrophile SO_3H^+ preparation:
  - Autoprotolysis of sulfuric acid

$$2\ H_2SO_4 \rightleftharpoons H_2SO_4 .\ SO_3 + H_2O \rightleftharpoons SO_3 + HSO_4^- + H_3O^+$$

  - More forcing condition: Oleum (mixture of H_2SO_4(100%) and SO_3 (up to 30%))

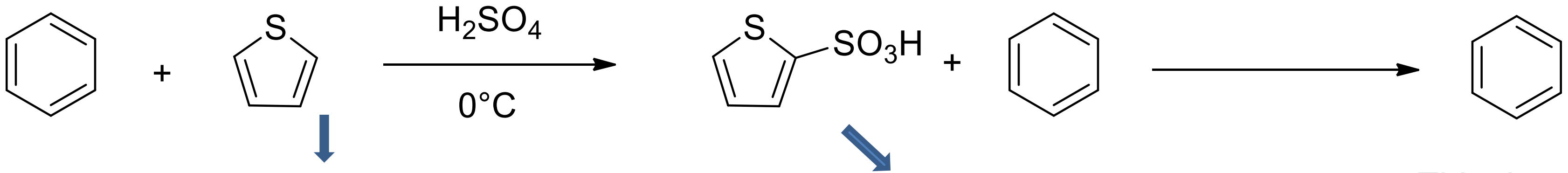
Representative examples:

A)



p-toluenesulfonic acid

B) Historical purification of benzene by removal of thiophene after distillation of crude oil

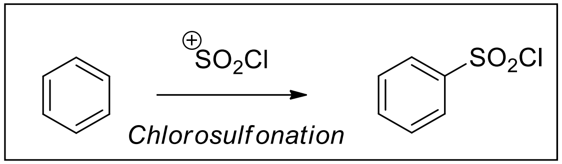


Electron-rich reacts faster then benzene

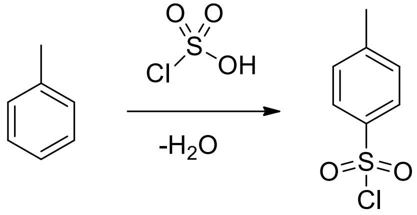
Washed out by water

Thiophene-free benzene

1.2.2.5. Chlorosulfonation

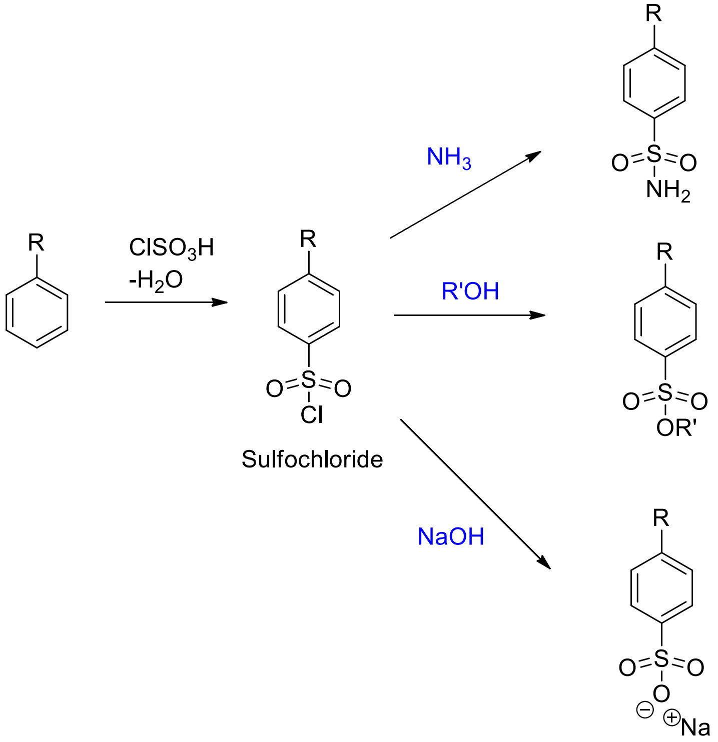


Reagent: Chlorosulfonic acid $ClSO_3H$



TsCl (Tosylchloride)
very useful activating group
for hydroxyl groups

Representative example: sulfochlorides are synthetically very versatiles

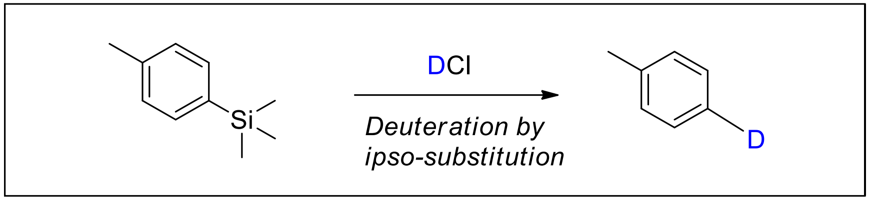


sulfonamides (antibiotics)

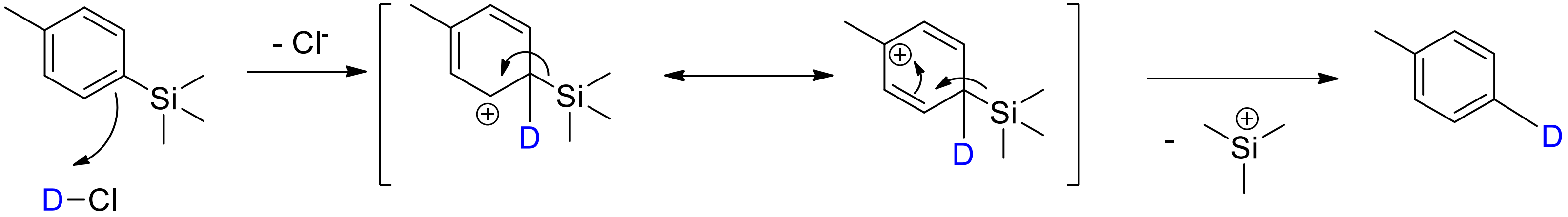
activation of hydroxyl
groups R'OH

sulfonates (detergents)

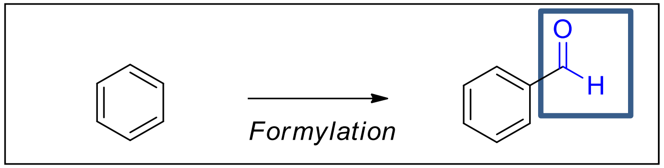
1.2.2.6. Deuteration by ipso-substitution



Selective method to introduce a ^{2}H (D) deuterium label

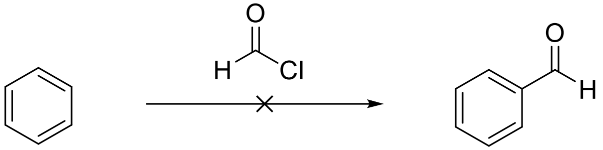


1.2.2.7. Formylation

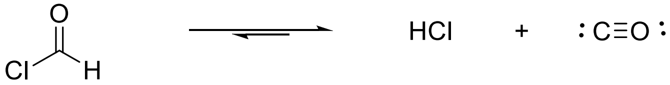


Introduction of a formyl group

The obtained products are aromatic aldehydes.

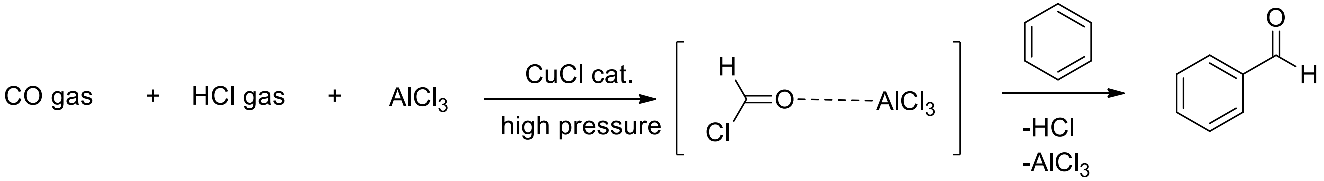


Not possible by using the Friedel-Crafts acylations, formyl chloride is not stable and decomposes to HCl and CO



formyl chloride
not stable

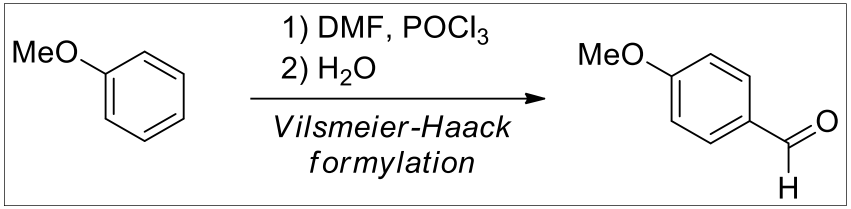
- Used with limitations in the Gattermann-Koch-Process



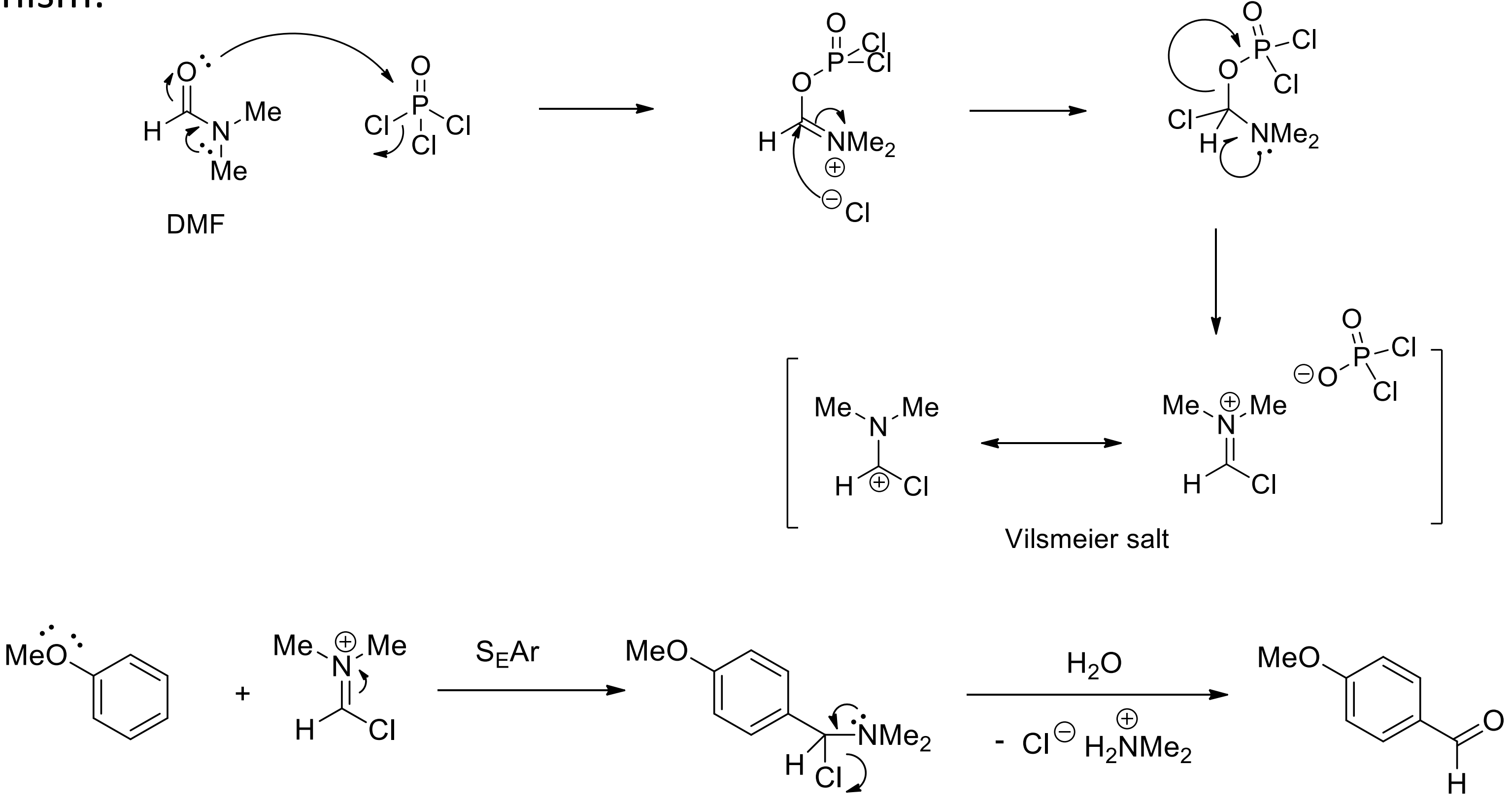
The method is not convenient on a laboratory scale. The process requires high pressures of the gases to shift the equilibrium towards the formyl chloride.

1.2.2.7. Formylation

- Vilsmeier-Haack formylation: (requires an **electron rich** aromatic substrate)

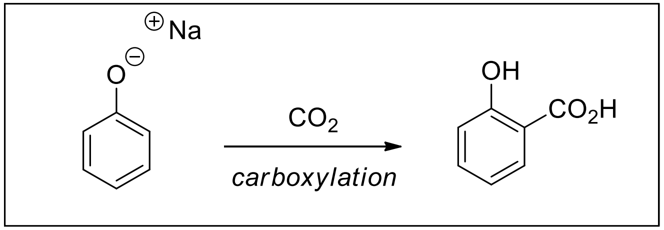


Mechanism:



1.2.2.8. Carboxylation

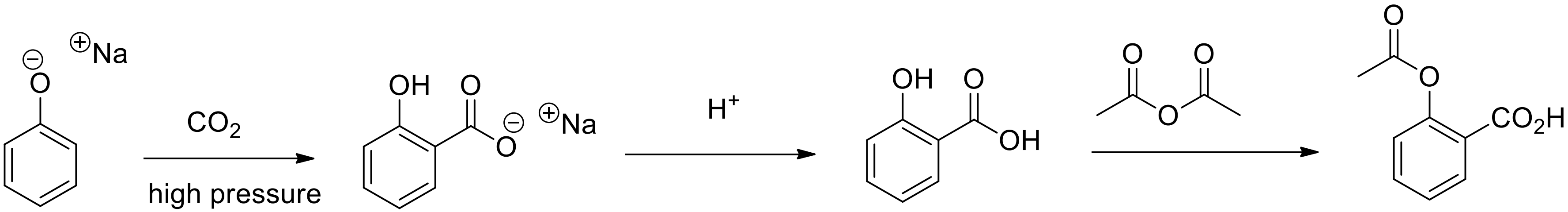
- Kolbe-Schmitt reaction:



Carbon dioxide CO_2 is a weak electrophile

Only react with very activated aromatic susbtrates

Most important example: synthesis of aspirin



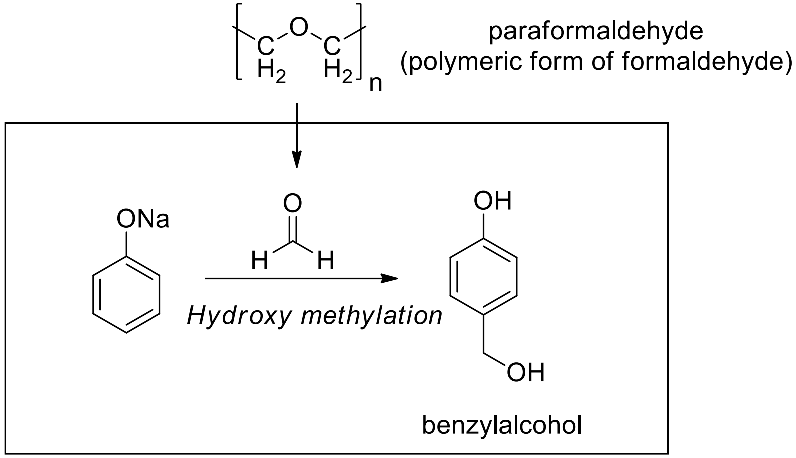
salicylic acid

Acetylsalicylic acid
Aspirin

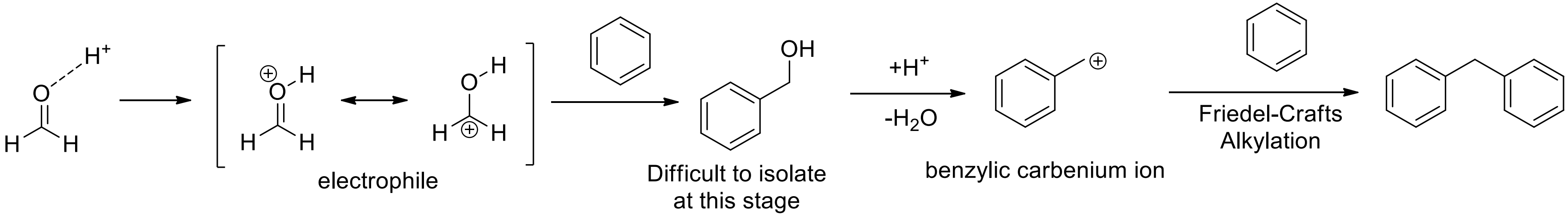
1.2.2.9. Hydroxy methylation

Only with **activated** aromatic substrates

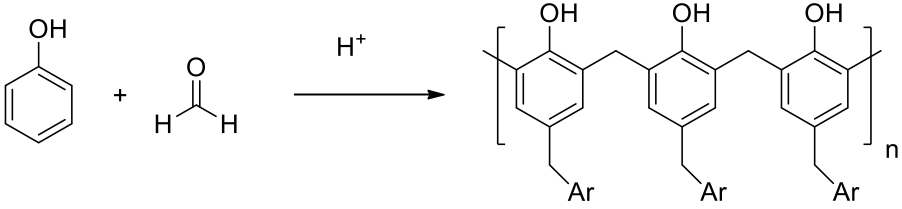
- Reaction under basic conditions:



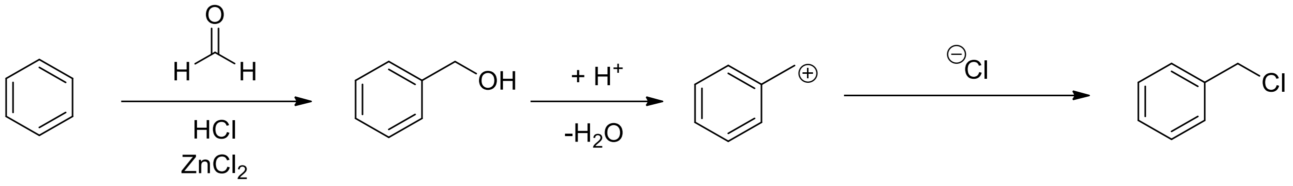
- Reaction under acidic condition: less reactive aromatic substrates can be used



Reaction used in manufacture of Bakelite, one of the first synthetic plastic polymers in 1907-1909

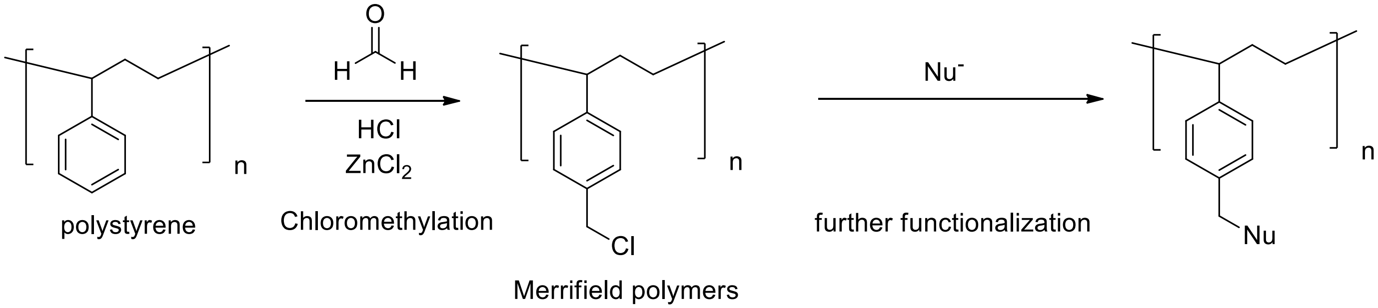


1.2.2.10. Chloromethylation

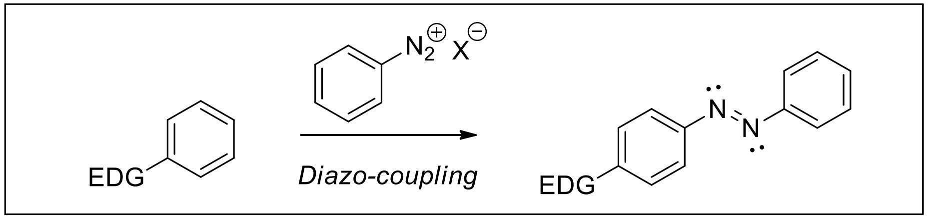


Benzylhalides are important synthetic intermediates and as well relevant for solid phase chemistry

Application: preparation of Merrifield resins

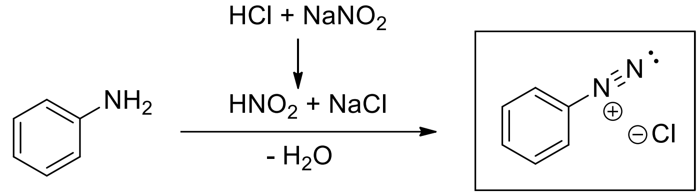


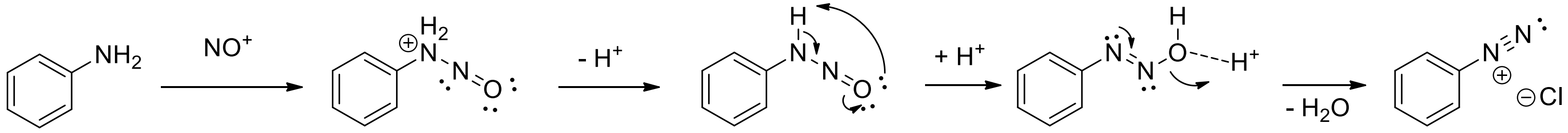
1.2.2.11 Diazo-coupling



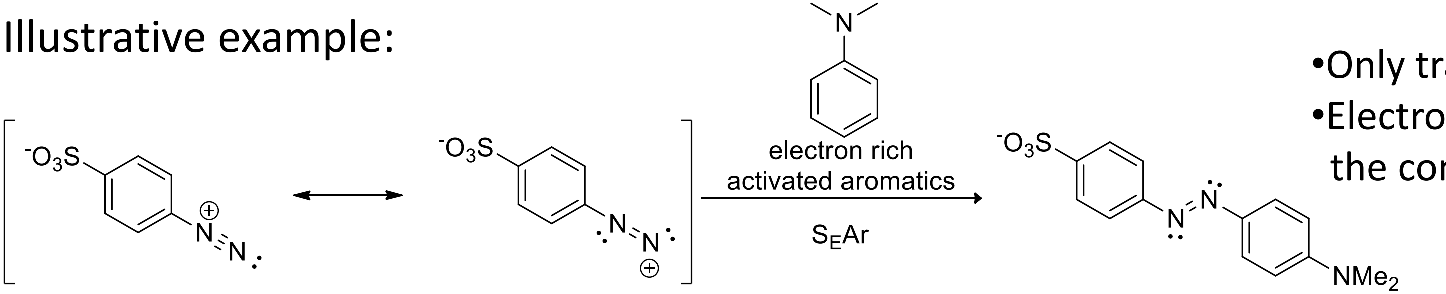
Diazo coupling requires **activated** aromatic substrates!

Preparation of the diazonium electrophile:



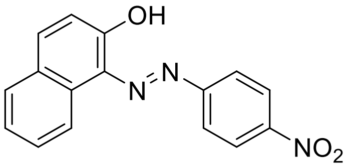


Illustrative example:

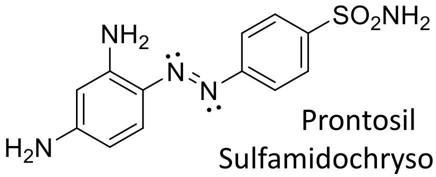


Methyl orange
pH indicator, yellow to orange scheme

- Only trans isomers are formed
- Electron delocalized over the complete π-systeme

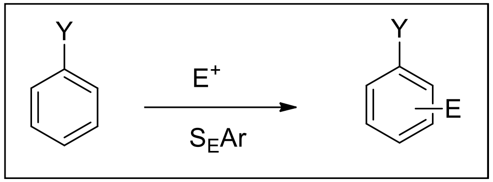


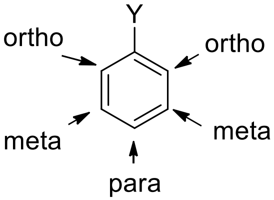
Para-red



Prontosil
Sulfamidochrysoidine
antibiotic

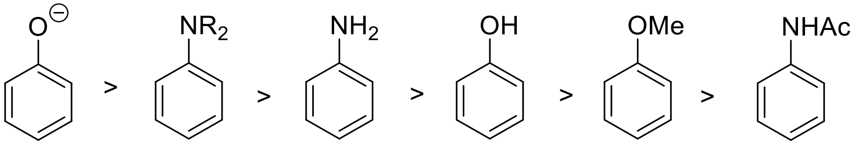
1.2.3. Secondary substitution on the benzene ring



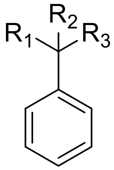


Y=EDG, π-donor, +M-effect ➡ strongly activating ortho-/para- directing; reactivity increases up to 10^{20} times compared to Y=H

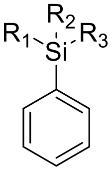
inportant substituents strongly activating



Y=σ-donor, +I-effect ➡ slightly activating, ortho-/para- directing; reactivity increases up to 20 times faster compared to Y=H

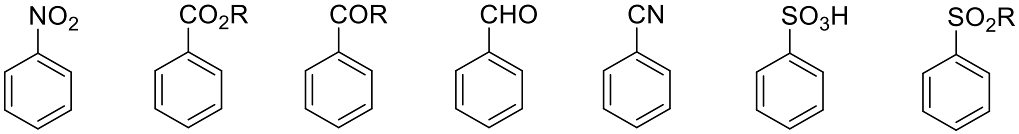


alkyl groups



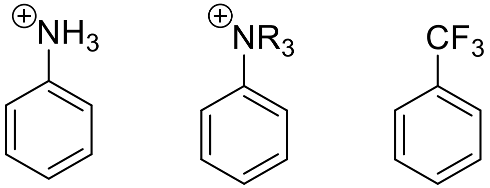
silyl groups

X=EWG, π-acceptor, -M-effect ➡ strongly deactivating; meta-directing; up to 10^{-7} decreased reactivity compared to Y=H

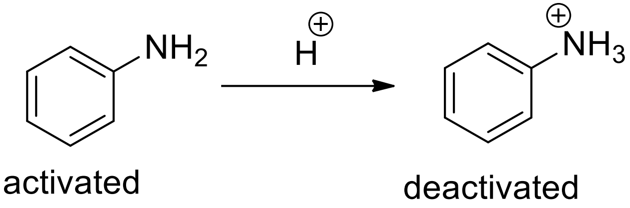


1.2.3. Secondary substitution on the benzene ring

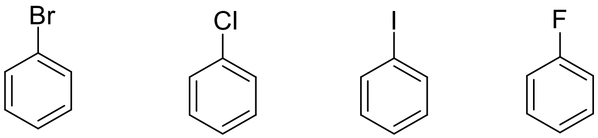
X=σ-acceptor, deactivating, *m*-directing



Reactivity can be modulated by pH:



Halogens are a special case: -I and +M effect



Slightly deactivating substituent (~ 30 times compared to Y=H)
But ortho- / para- directing group