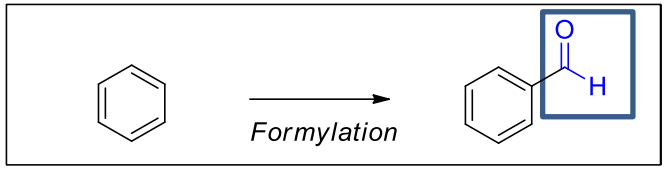
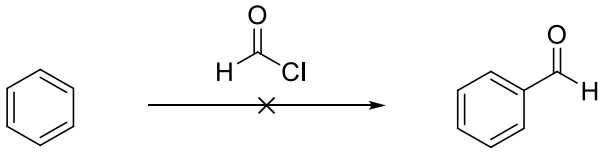
# Fonction et réaction organiques II
# Week 3

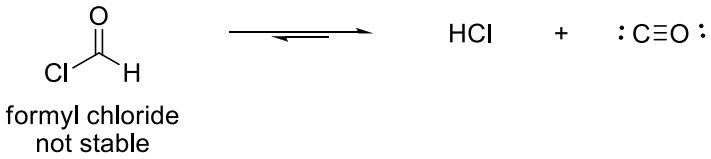
# 1.2.2.7. Formylation




Introduction of a formyl group

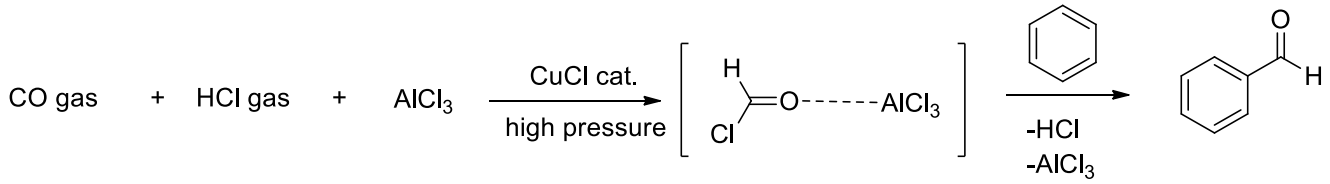
The obtained products are aromatic aldehydes.




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

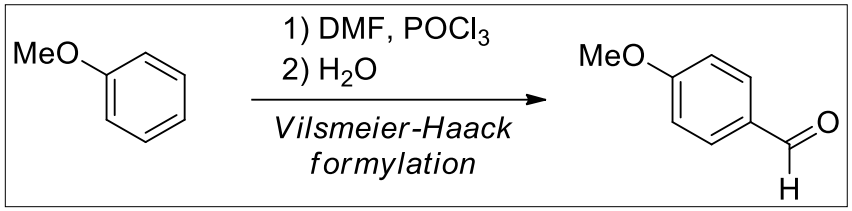
- Used with limitations in the Gattermann-Koch-Process



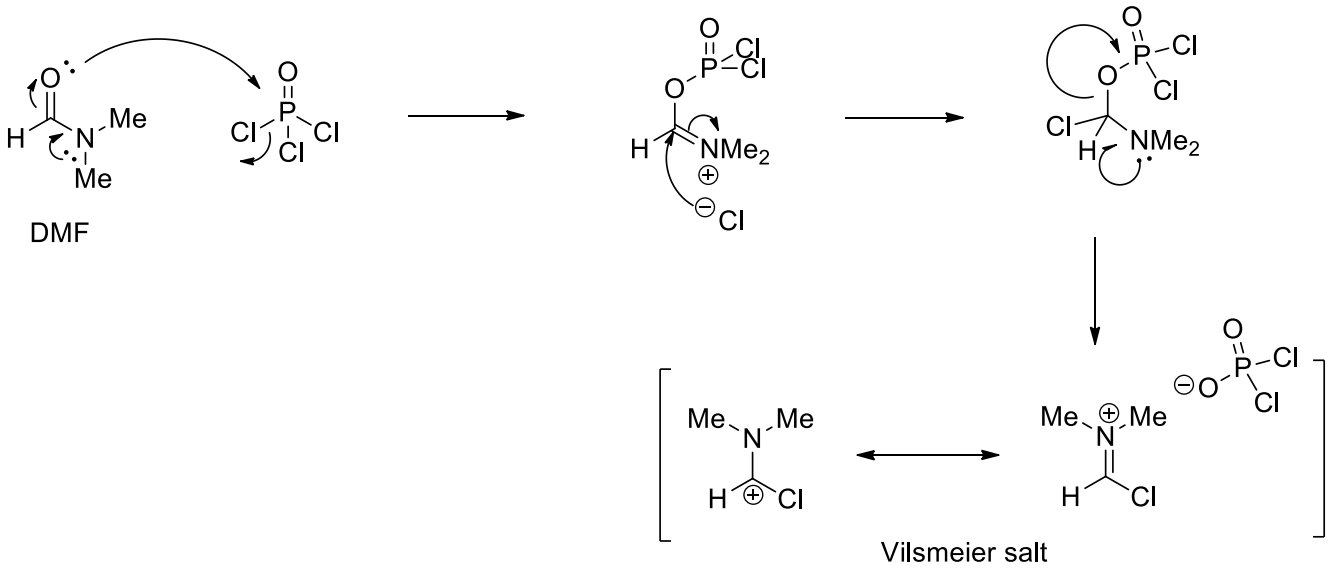

The method is not convenient on a laboratory scale. The process requires high pressures of the gases to shift the equilibrium towards the formyl chloride.

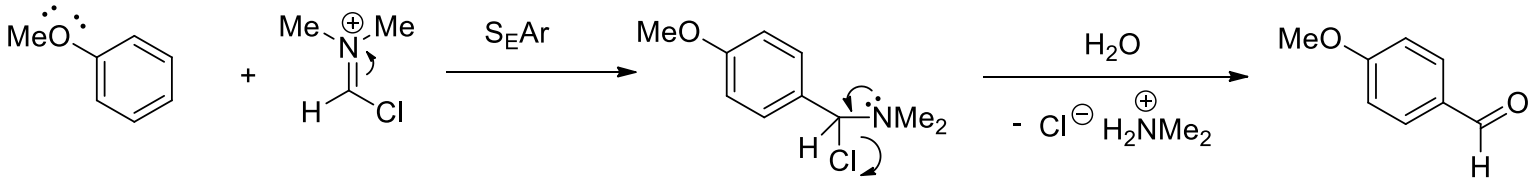
# 1.2.2.7. Formylation

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



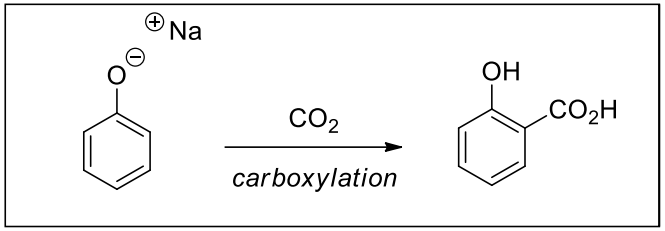

Mechanism:



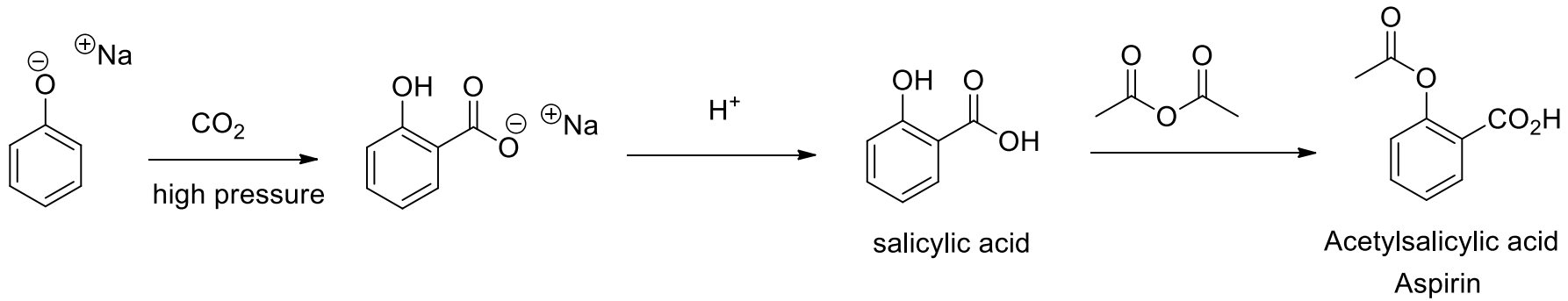
# 1.2.2.8. Carboxylation

- Kolbe-Schmitt reaction:




Carbon dioxide $CO_2$ is a weak electrophile ⟹ Only react with very activated aromatic susbtrates

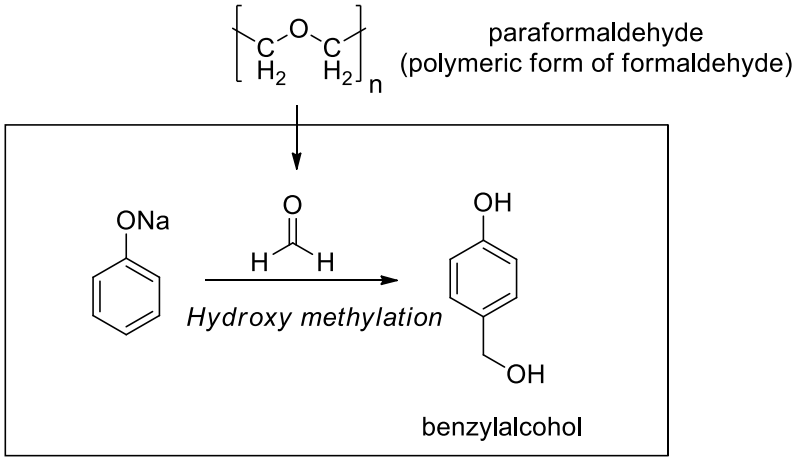
Most important example: synthesis of aspirin



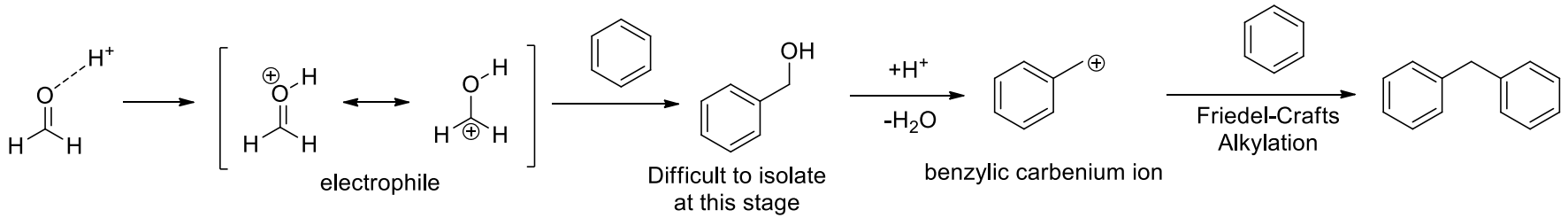
# 1.2.2.9. Hydroxy methylation

Only with **activated** aromatic substrates

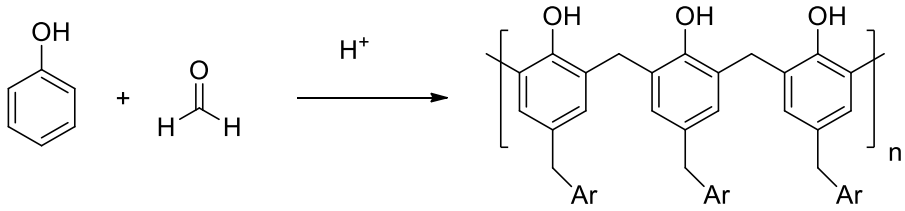
- Reaction under basic conditions:



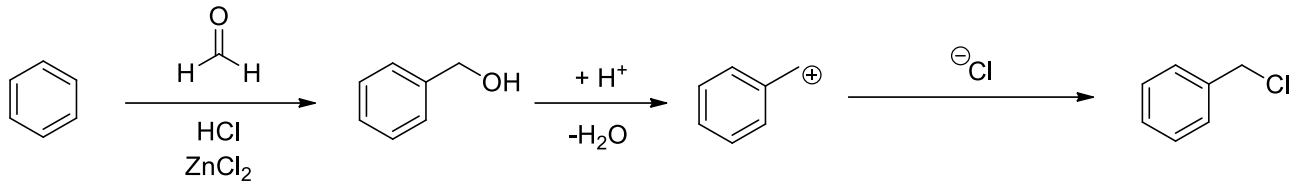

- Reaction under acidic condition: less reactive aromatic substrates can be used




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

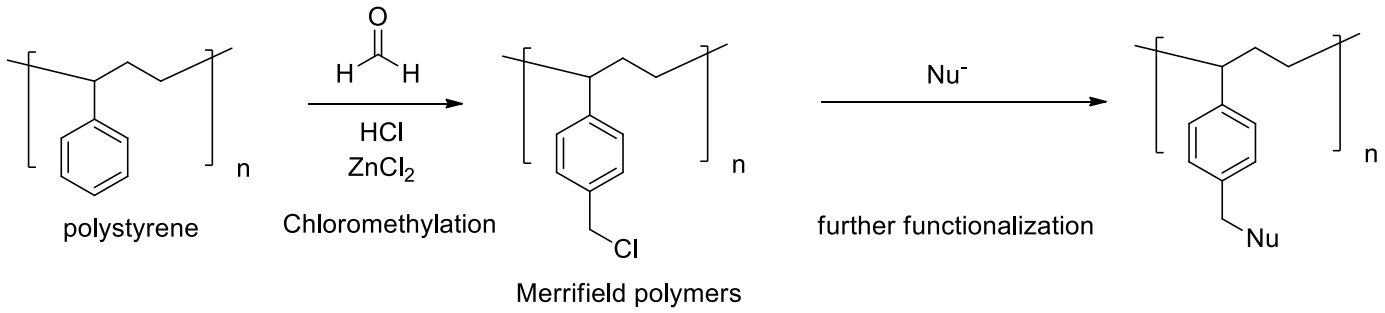


# 1.2.2.10. Chloromethylation

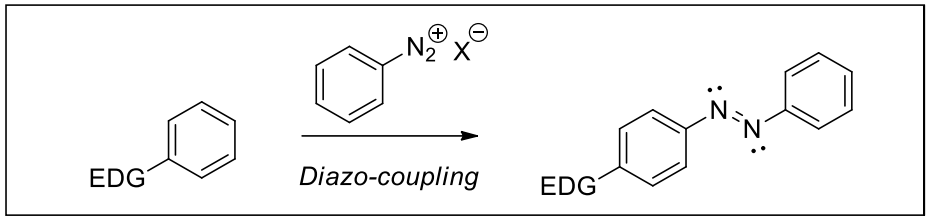



Benzylhalides are important synthetic intermediates and as well relevant for solid phase chemistry

Application: preparation of Merrifield resins

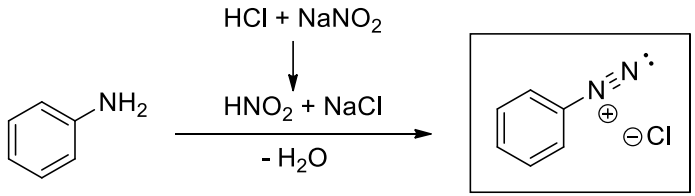


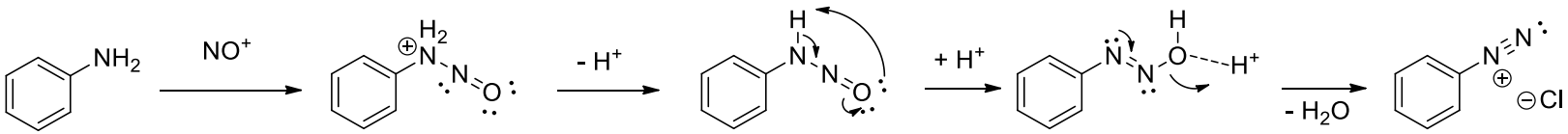
# 1.2.2.11 Diazo-coupling



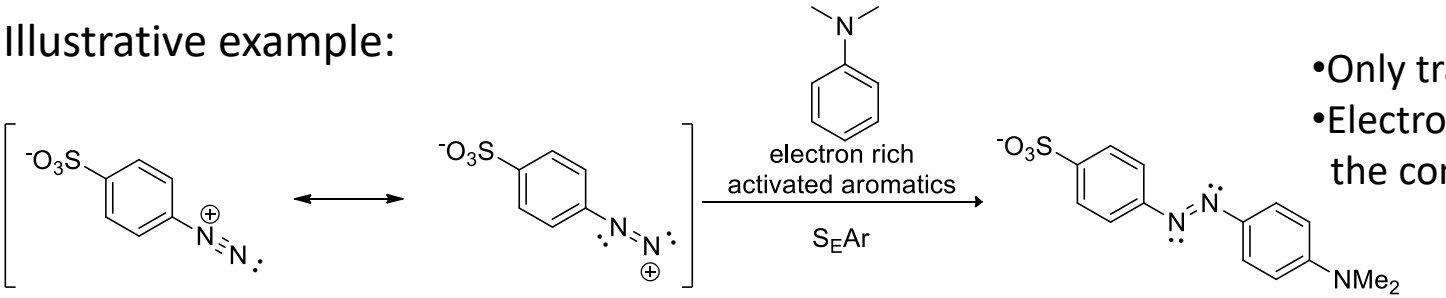

Diazo coupling requires **activated** aromatic substrates!

Preparation of the diazonium electrophile:



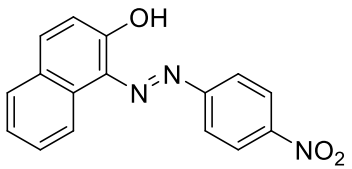




Illustrative example:

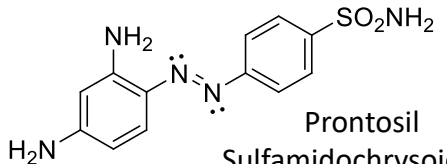



Methyl orange
pH indicator, yellow to orange scheme

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

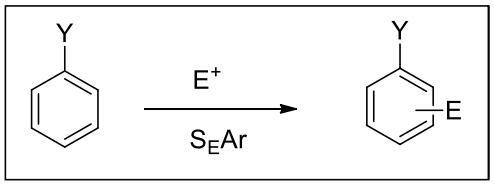


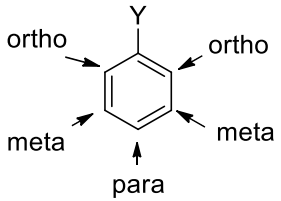

Para-red




Prontosil
Sulfamidochrysoidine
antibiotic

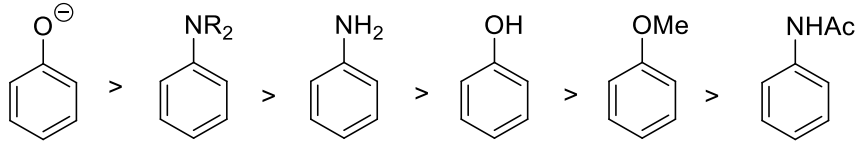
# 1.2.3. Secondary substitution on the benzene ring



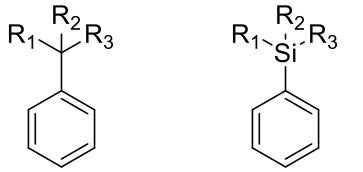




Y=EDG, π-donor, +M-effect ➡ strongly activating ortho-/para- directing; reactivity increases up to $10^{20}$ times compared to Y=H

inportant substituents
strongly activating

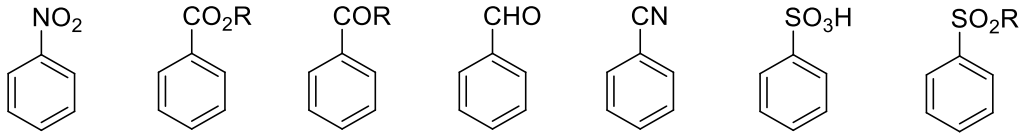



Y=σ-donor, +I-effect ➡ slightly activating, ortho-/para- directing; reactivity increases up to 20 times faster compared to Y=H



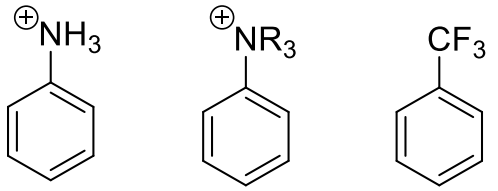

alkyl groups silyl groups

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

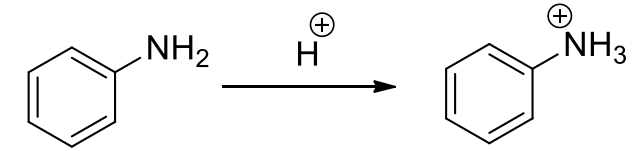


# 1.2.3. Secondary substitution on the benzene ring

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

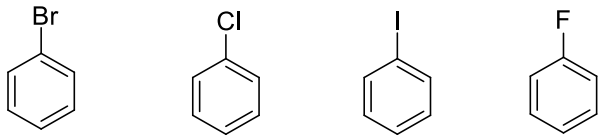



Reactivity can be modulated by pH:




activated deactivated

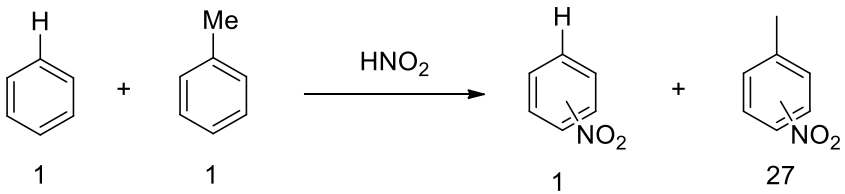
Halogens are a special case: -I and +M effect

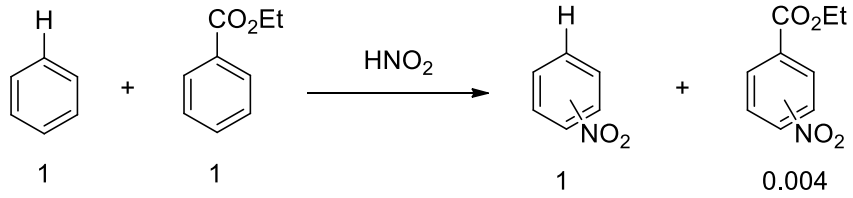


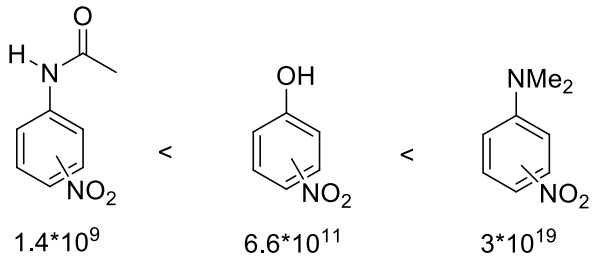

Slightly deactivating substituent (~ 30 times compared to Y=H)
**But** ortho- / para- directing group

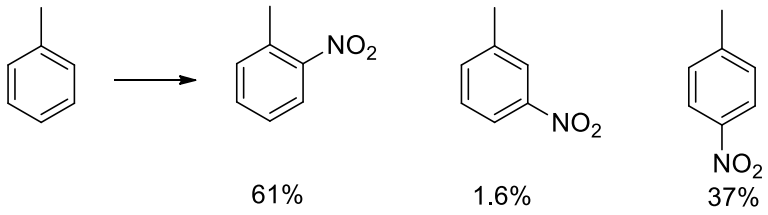
# 1.2.3. Secondary substitution on the benzene ring

Illustrative examples between EDG and EWG directing groups

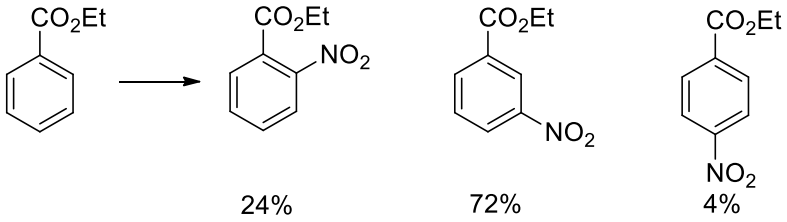


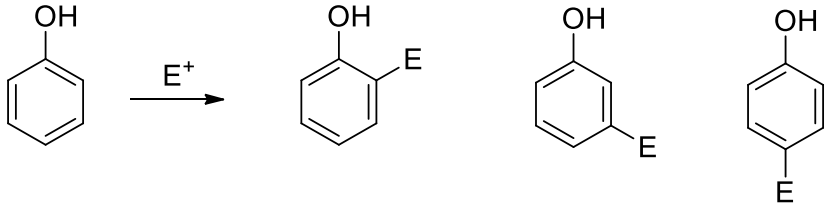

EDG activate all positions. Meta is the least activated one.



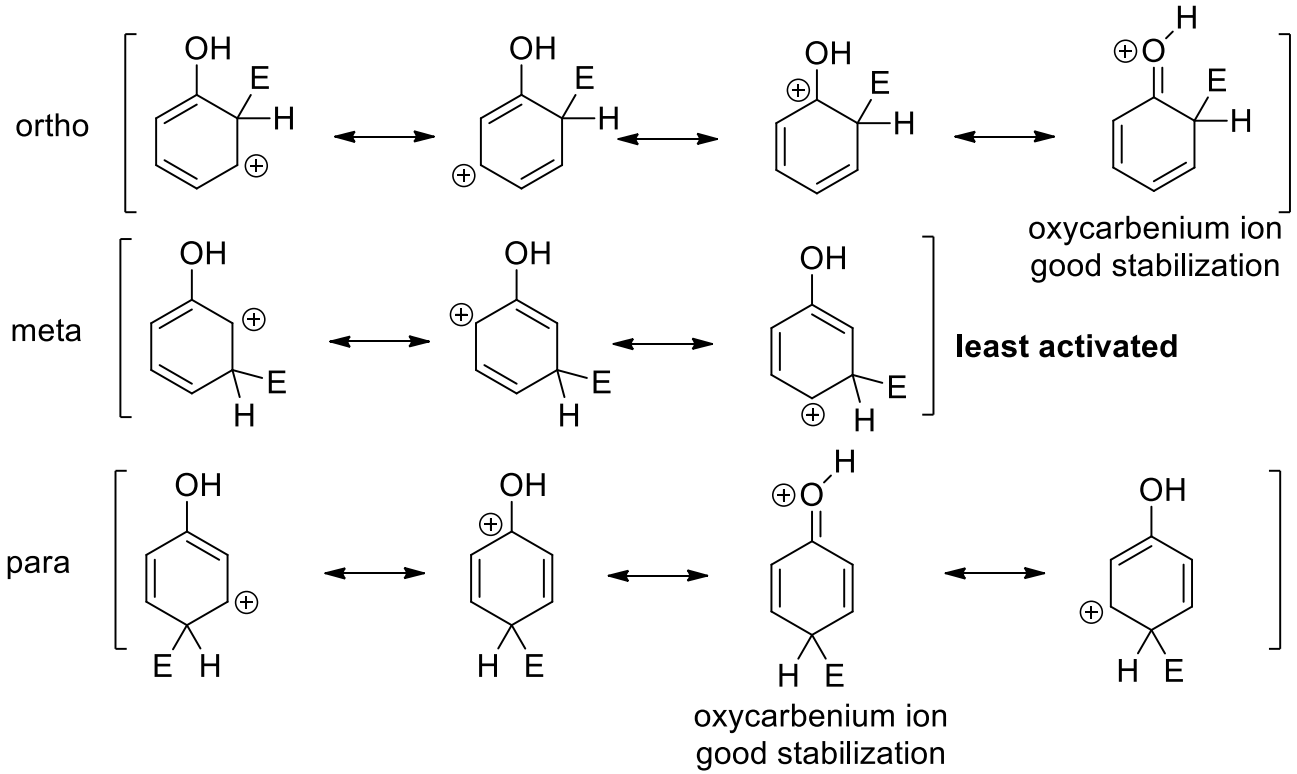

EWG deactivate all positions. Meta is the least deactivated one.

# 1.2.3. Secondary substitution on the benzene ring

π-donors: all positions are activated as electron density of the ring is increased




Mesomeric structures of the possible isomers of the σ-complex:




+M: accelerate the reaction and direct ortho and para