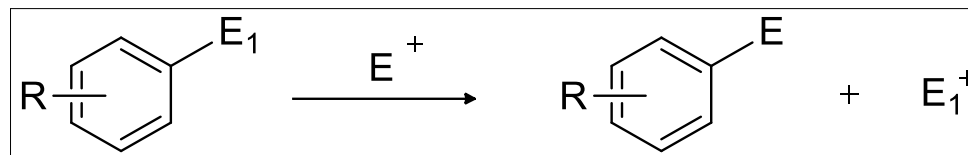


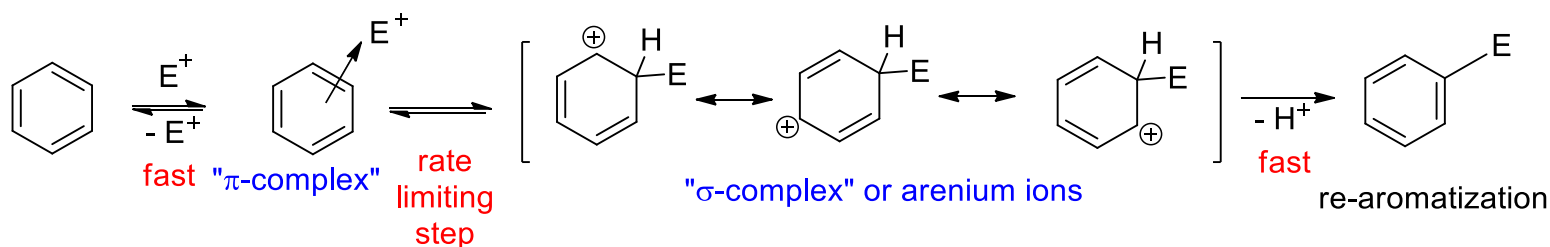
Fonction et réaction organiques II, week 2

1.2. Electrophilic aromatic substitution S_EAr

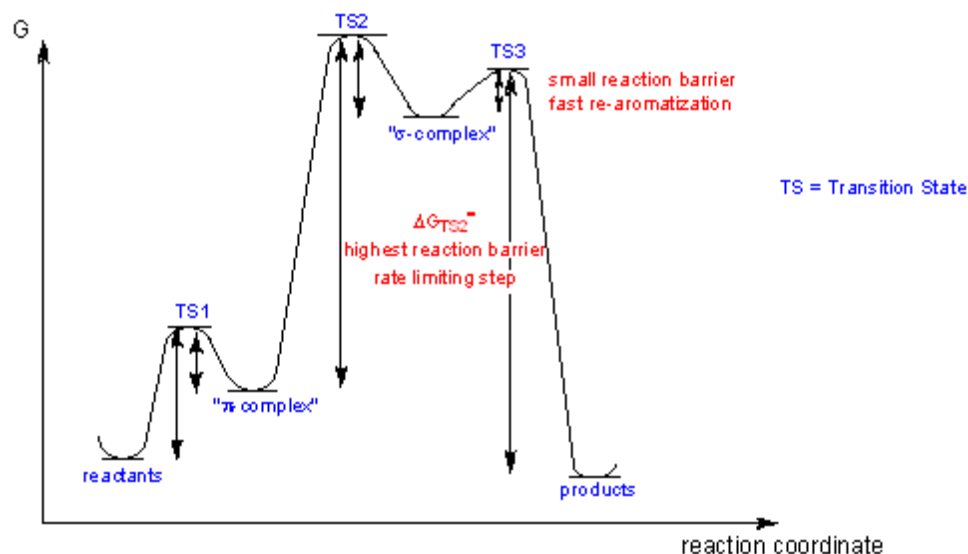
- General reaction:



- $E_1 = H$
- Rare cases where $E_1 = SiR_3$, tBu , SO_3H is then called ipso-substitution
- Formally, the reaction is the substitution of H^+ by an electrophile E^+
- Mechanistically, it is an addition / elimination process



1.2.1. General principles



- Polanyi-Hammond postulate:
When two neighboring species on the reaction coordinate are related in their energy, they are as well in their structure.
TS2 much closer to the σ -complex than to the π -complex
- Applications:
 - Lowering the activation barrier makes a reaction faster
 - For S_EAr : TS2 looks rather similar to the σ -complex
 - Everything stabilizing the σ -complex accelerates the reaction rate
 - Everything destabilizing the σ -complex decrease the reaction rate

1.2.1. General principles

- How can one speed up the reaction? How are the substituents chosen?

Substituents are generally divided in two groups:

- EDG (Electron Donating Group) e.g. $-\text{OMe}$, having +M / +I effect
- EWG (Electron Withdrawing Group) e.g. $-\text{COOMe}$, having -M / -I effect

EDG stabilizes the σ -complex making the reaction faster

EWG destabilizes the σ -complex making the reaction slower

(how much faster/slower is depending on the substituent properties)

- Examples of EDG / EWG:

EDG with +M effect: $-\text{NR}_2$, $-\text{NH}_2$, $-\text{OH}$, $-\text{OR}$

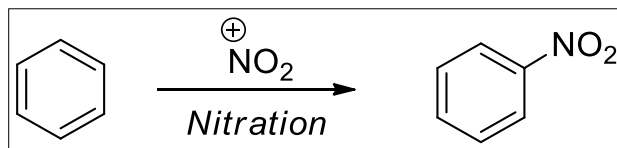
EDG with +I effect: $-\text{Alkyl}$, $-\text{SiR}_3$

EWG with -M effect: $-\text{NO}_2$, $-\text{COOR}$, $-\text{COR}$, $-\text{CHO}$, $-\text{CN}$, $-\text{SO}_3\text{H}$, $-\text{SO}_2\text{R}$

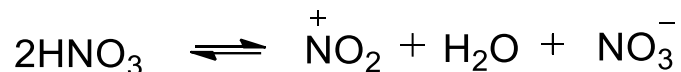
EWG with -I effect: $-\text{NH}_3^+$, $-\text{NR}_3^+$, $-\text{CF}_3$

1.2.2.1. Nitration

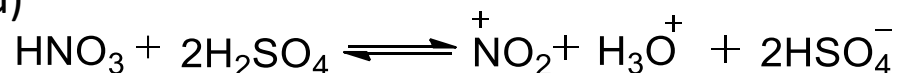
- Electrophile = NO_2^+ , nitronium ion $\text{O}=\text{N}^+=\text{O}$



- Practical methods to generate the electrophile:
 - Mild: autoprotolysis of nitric acid, in concentrated HNO_3 (68%) the amount of NO_2^+ is 3-4%

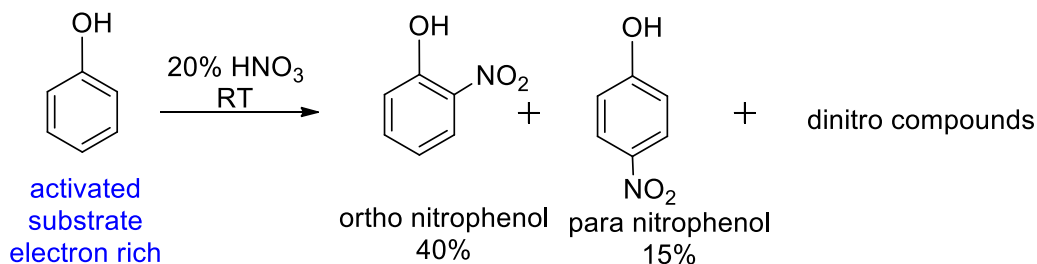


- More forcing conditions: mixture of concentrated HNO_3 + concentrated H_2SO_4 (nitrosulfuric acid)



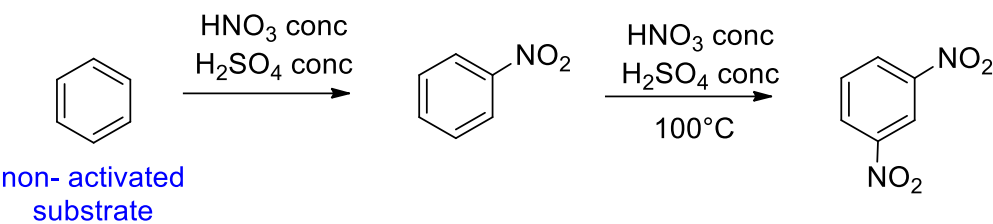
- Strongest conditions: nitroniumtetrafluoroborat salt $\text{NO}_2^+ \text{BF}_4^-$

- Examples for activated substrates: mild conditions are used

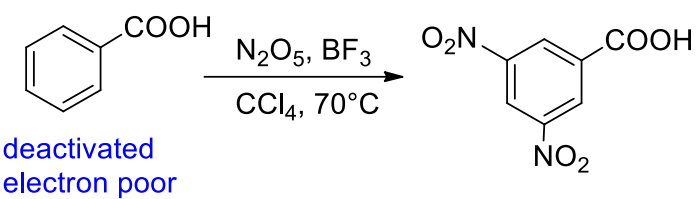


1.2.2.1. Nitration

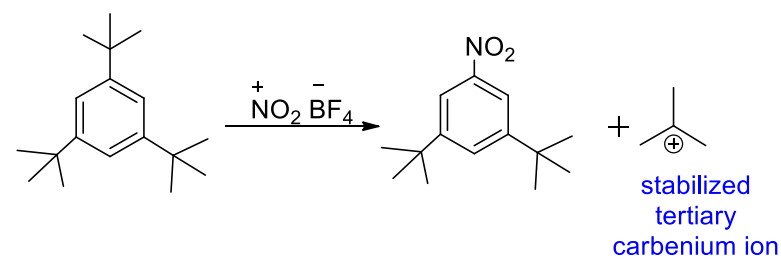
- Examples for non-activated substrates: more forcing conditions are required



- Examples for deactivated substrates:



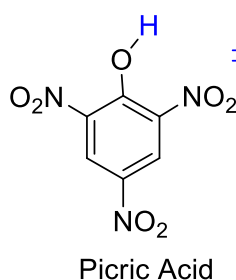
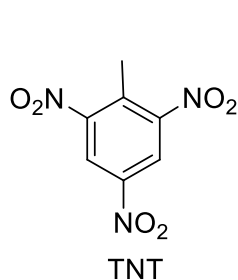
- Example for an ipso-substitution :



1.2.2.1. Nitration

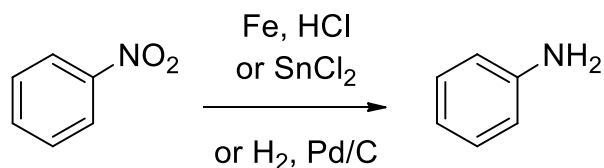
- Nitro groups are important synthetic intermediates

Application for dyes, explosives (TNT, picric acid) and basic industrial processes



very acidic due to 3EWG -NO₂ groups
⇒ crystalline salts are formed very easily
but these can be explosives !

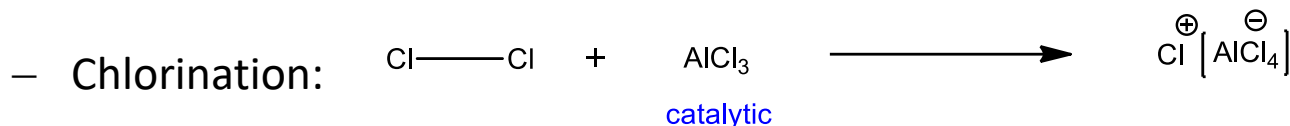
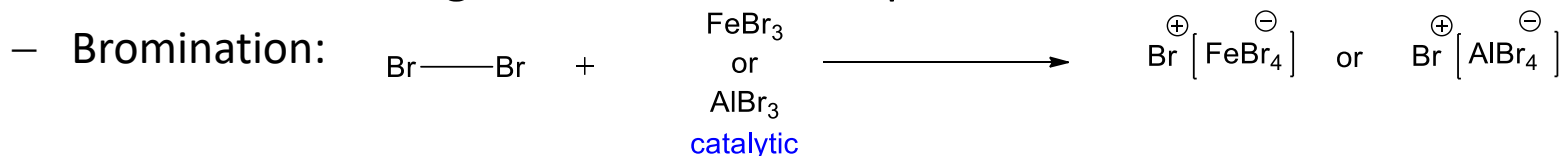
Most important follow-up reaction: reduction of the nitro group to an aniline with a variety of reducing reagents



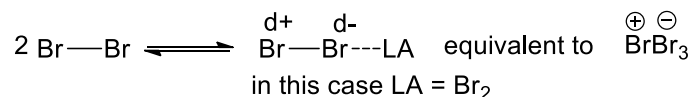
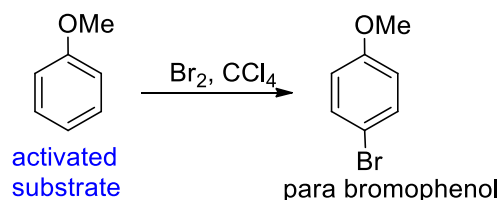
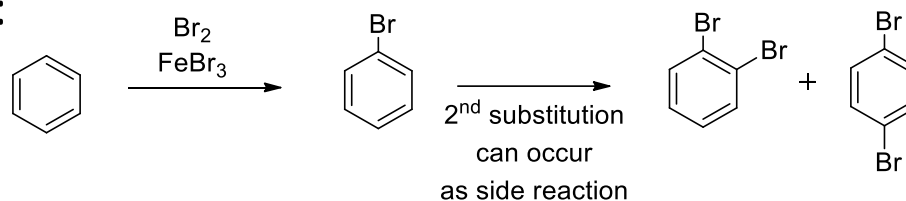
1.2.2.2. Halogenation: bromination / chlorination

- Electrophile = Br^+ / Cl^+
 - Fluorination: not controllable
 - Iodination: requires promoters

- Practical methods to generate the electrophile:



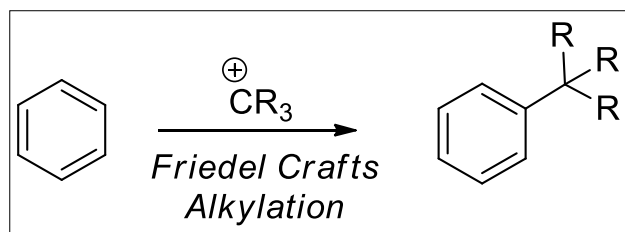
- Typical examples:



1.2.2.3. Friedel-Crafts reaction

- Friedel-Crafts alkylation: $E^+ = R_3C^+$ (carbenium ion, $R=H, alkyl$)
- Friedel-Crafts acylation: $E^+ = RCO^+$ (acylium cation, $R=alkyl, aryl$)

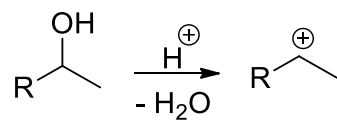
1.2.4.1. Friedel-Crafts alkylation



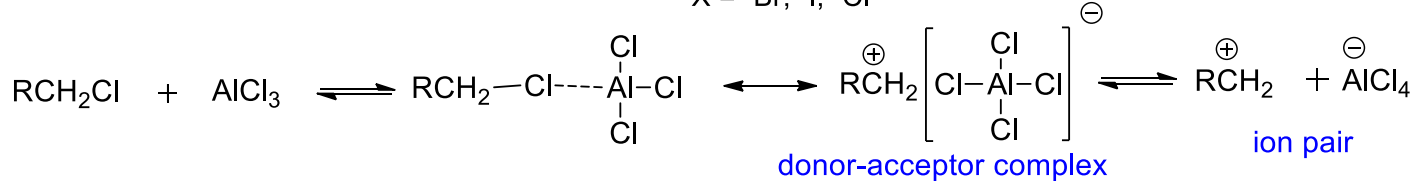
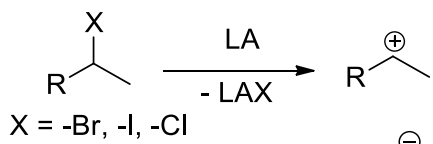
- Practical methods to generate the electrophile:
 - From protonation of alkenes: the selectivities of the carbenium ion apply



- From alcohols and acid:



- From alkyl halides and a Lewis acid:



1.2.2.3. Friedel-Crafts reaction

Caution: all aspects of carbenium ions apply:

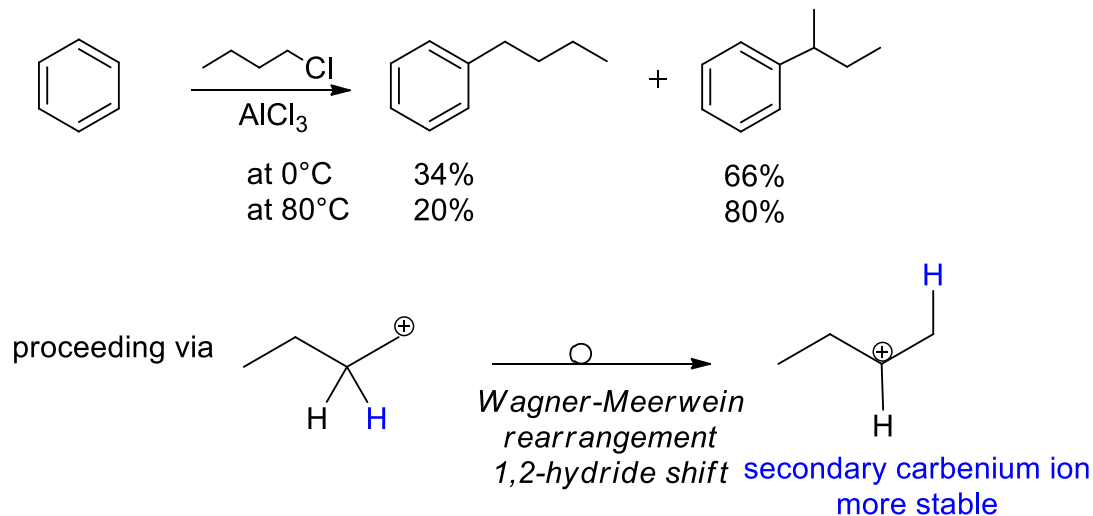
Stability: Benzylic > allylic > tertiary > secondary > primary methyl

First issue:

Wagner-Meerwein type rearrangements prone to isomerization

It is difficult to make primary alkyl chains under Wagner-Meerwein

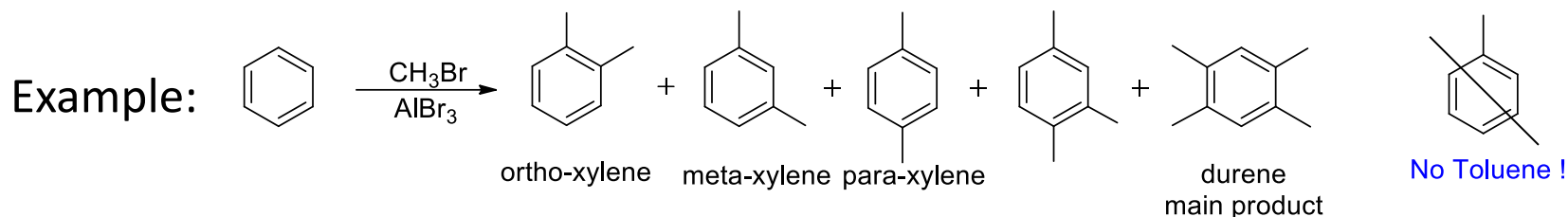
For example:



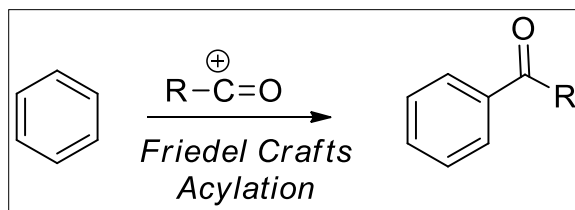
1.2.2.3. Friedel-Crafts reaction

Second issue: alkyl groups are σ -donors which means:

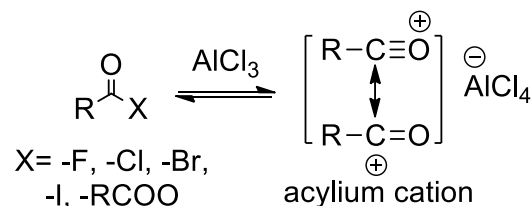
→ The product is more reactive than the starting material and therefore the reaction is difficult to stop at the mono-alkylation stage



1.2.4.2. Friedel-Crafts acylation

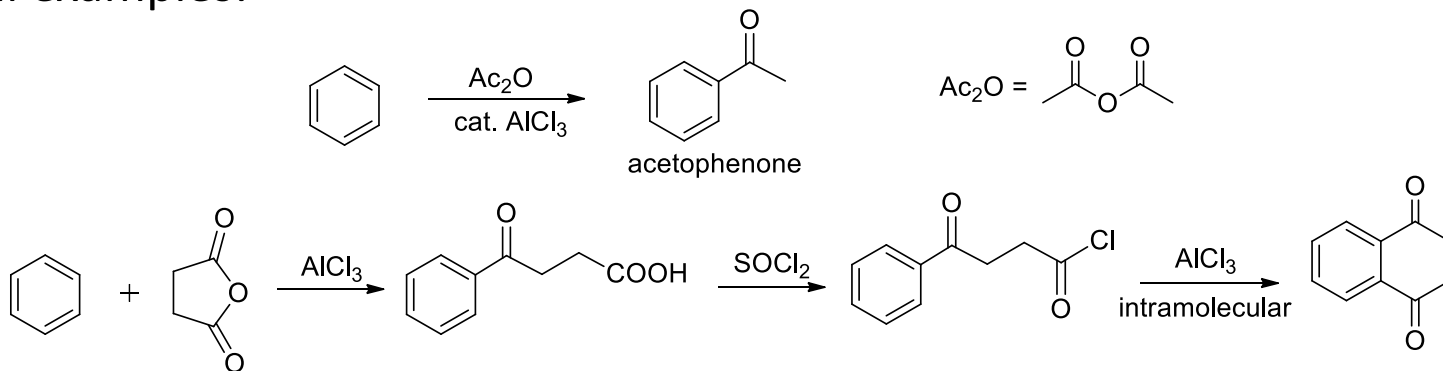


- Practical methods to generate the electrophile: from acid halogenide (acid chloride or anhydride) and a catalytic amount of a Lewis acid (AlCl_3)



1.2.2.3. Friedel-Crafts reaction

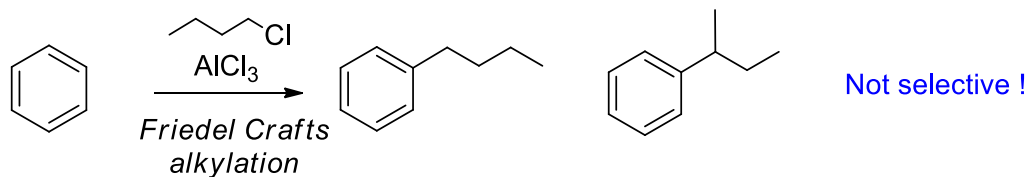
Typical examples:



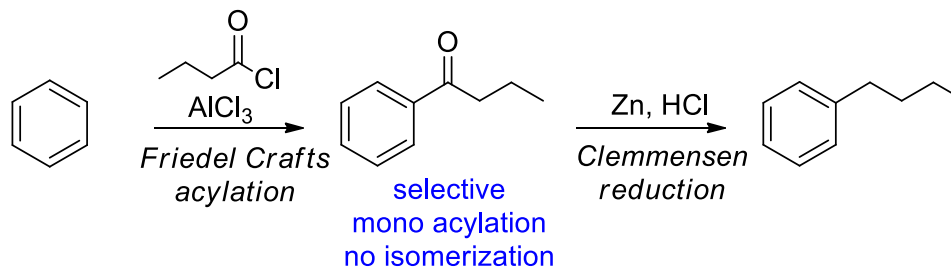
- Important characteristics compared to Friedel-Crafts alkylation:

→ The introduction of a carbonyl group (EWG) decreases the reactivity

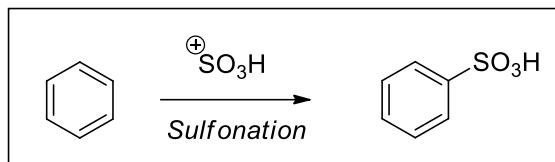
→ It prevents the risk of double acylation (however possible for intramolecular reactions)



alternative 2 steps procedure:

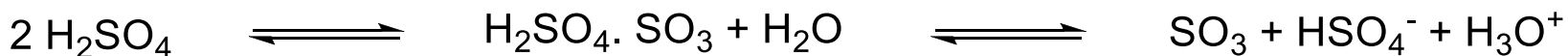


1.2.2.4. Sulfonation



- Electrophile = SO_3H^+ , sulfonium ion
- Preparative Methods for Electrophile SO_3H^+ preparation:

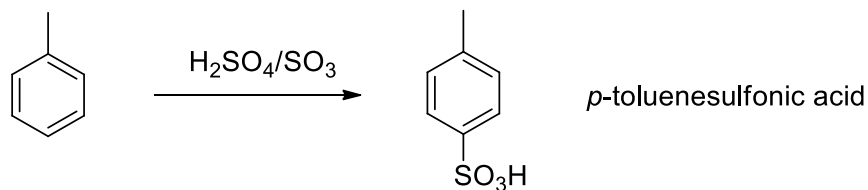
– Autoprotolysis of sulfuric acid



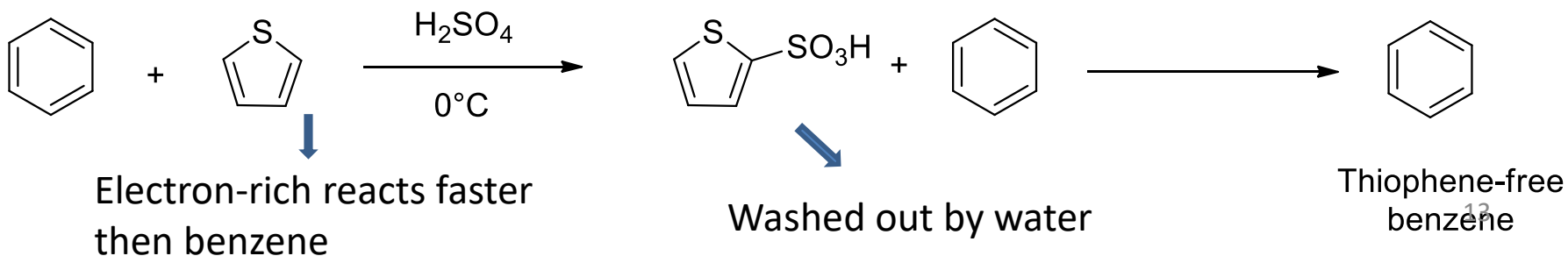
– More forcing condition: Oleum (mixture of H_2SO_4 (100%) and SO_3 (up to 30%))

Representative examples:

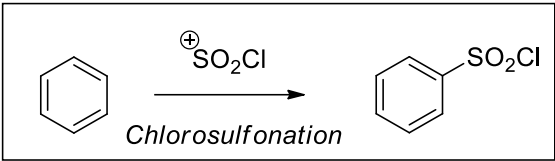
A)



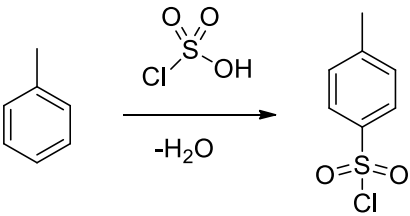
B) Historical purification of benzene by removal of thiophene after distillation of crude oil



1.2.2.5. Chlorosulfonation

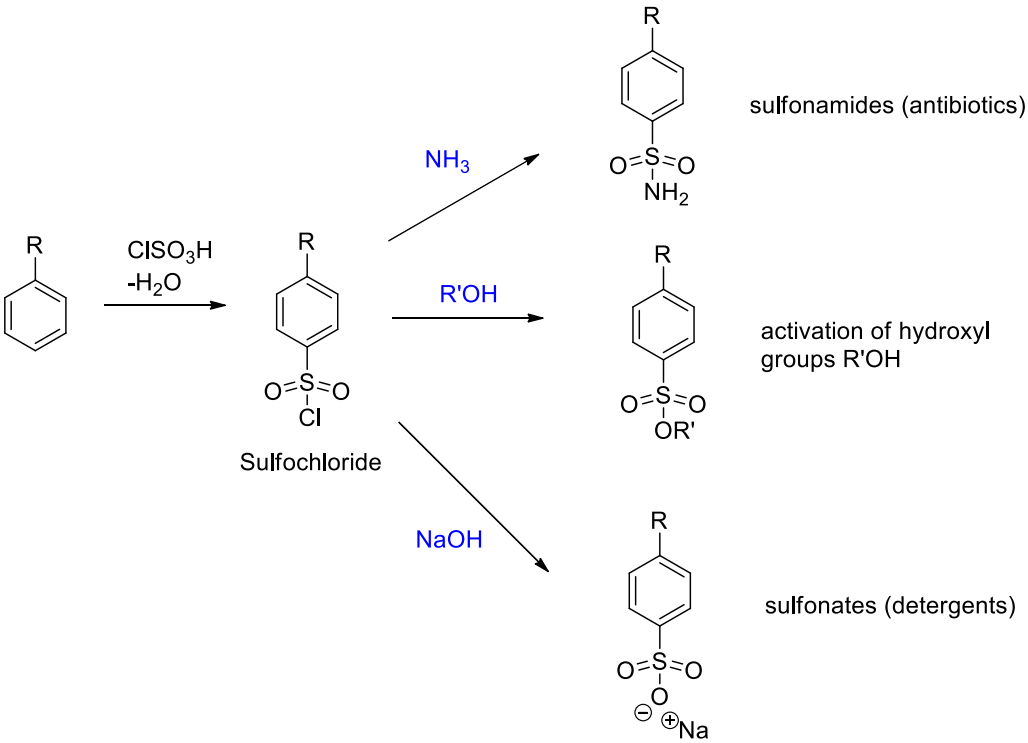


Reagent: Chlorosulfonic acid ClSO_3H

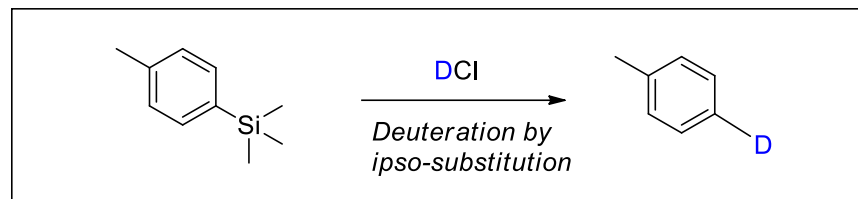


TsCl (Tosylchloride)
very useful activating group
for hydroxyl groups

Representative example: sulfochlorides are synthetically very versatile



1.2.2.6. Deuteration by ipso-substitution



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

