université PARIS-SACLAY | FACULTÉ DE PHARMACIE

TU 07 - The Medicinal Chemist's Toolbox 1 : Aromatic and Heteroaromatic chemistry

Pr Sandrine Piguel – sandrine.piguel@universite-paris-saclay.fr
Laboratoire BioCIS, 1er étage, bureau 1716, bât. HM1

BioCIS
Biomolécules :
Conception, Isolement, Synthèse

General information

- 4 sessions (8h) : Room 1402a, building HM4
  - Friday 21/03/2025 13h30-16h00
  - Monday 24/03/2025 13h30-15h00
  - Tuesday 25/03/2025 13h30-15h00
  - Monday 31/03/2025 13h30-16h00
- Documents on eCampus
- Joint exam : Monday 30/04/2025 9h00-11h00

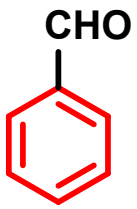
General information

- Contents
  - **Chapter 1** : Chemistry of benzene and its derivatives
    1. Introduction to aromatic compounds
    2. Structure and resonance of benzene
    3. Aromaticity
    4. Naming the benzenes
    5. Electrophilic aromatic substitution of benzene
    6. Electrophilic aromatic substitution of monosubstituted benzenes
    7. Electrophilic aromatic substitution of polysubstituted benzenes
    8. Nucleophilic aromatic substitution
  - **Chapter 2** : Chemistry of aromatic heterocycles

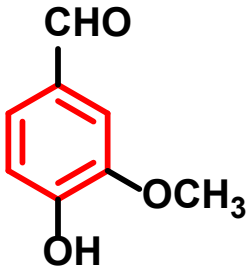
Chapter 1 :
Chemistry of benzene and its derivatives

1. Introduction to aromatic compounds

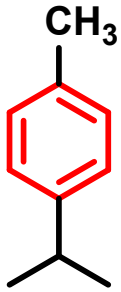
- Benzene and its derivatives were originally called aromatic compounds → strong aroma



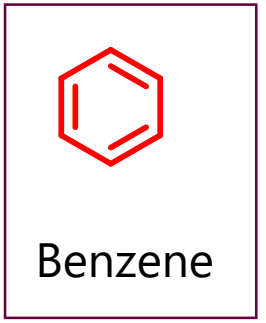
Benzaldehyde
Bitter almond



Vanillin
Vanilla

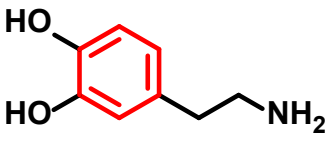


p-cymene
Cumin

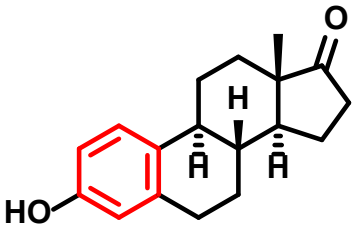


Benzene

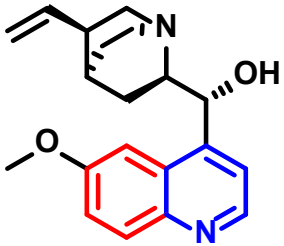
- Aromatic compounds in life sciences



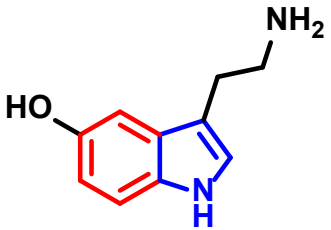
Dopamin



Oestron



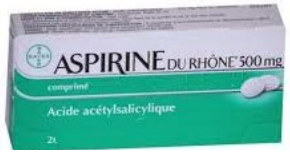
Quinin

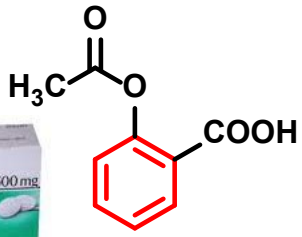


Serotonin

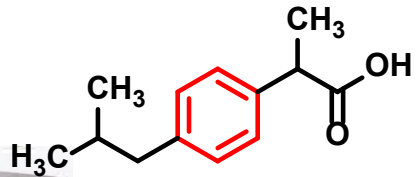
1. Introduction to aromatic compounds

- Aromatic compounds as pharmaceuticals

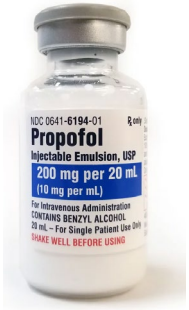


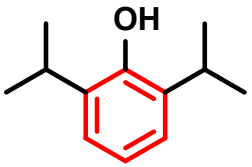


Aspirin®

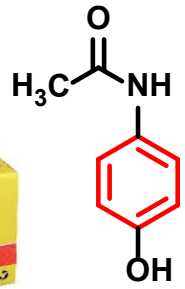


Ibuprofen®

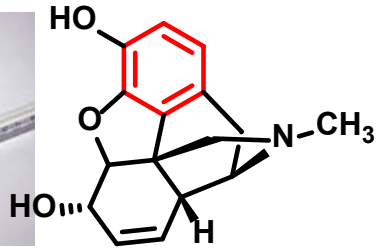




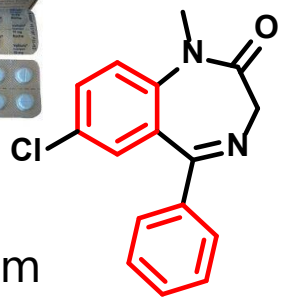
Propofol



Paracetamol



Morphine



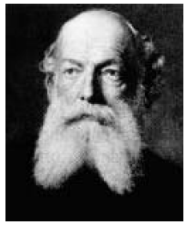
Diazepam

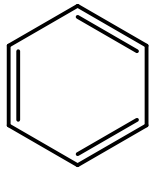
2. Structure and resonance of benzene

- C_6H_6
- Isolated in1825 par Michael Faraday
- Obtained from the distillation of coal

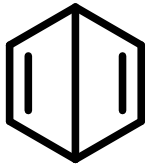
- Physico-chemical properties
  - ✓ Colorless liquid
  - ✓ Boiling point 80 °C
  - ✓ Melting point 5,5 °C

- Proposed benzene structures between 1865-1870 :



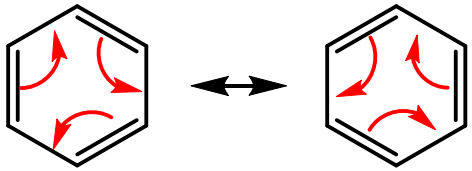


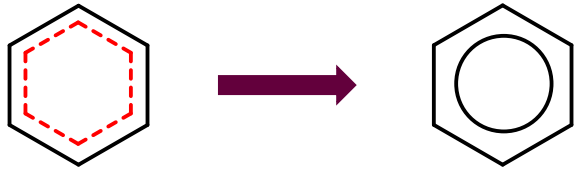
Kékulé, 1865



Dewar, 1867

Ladenburg, 1869



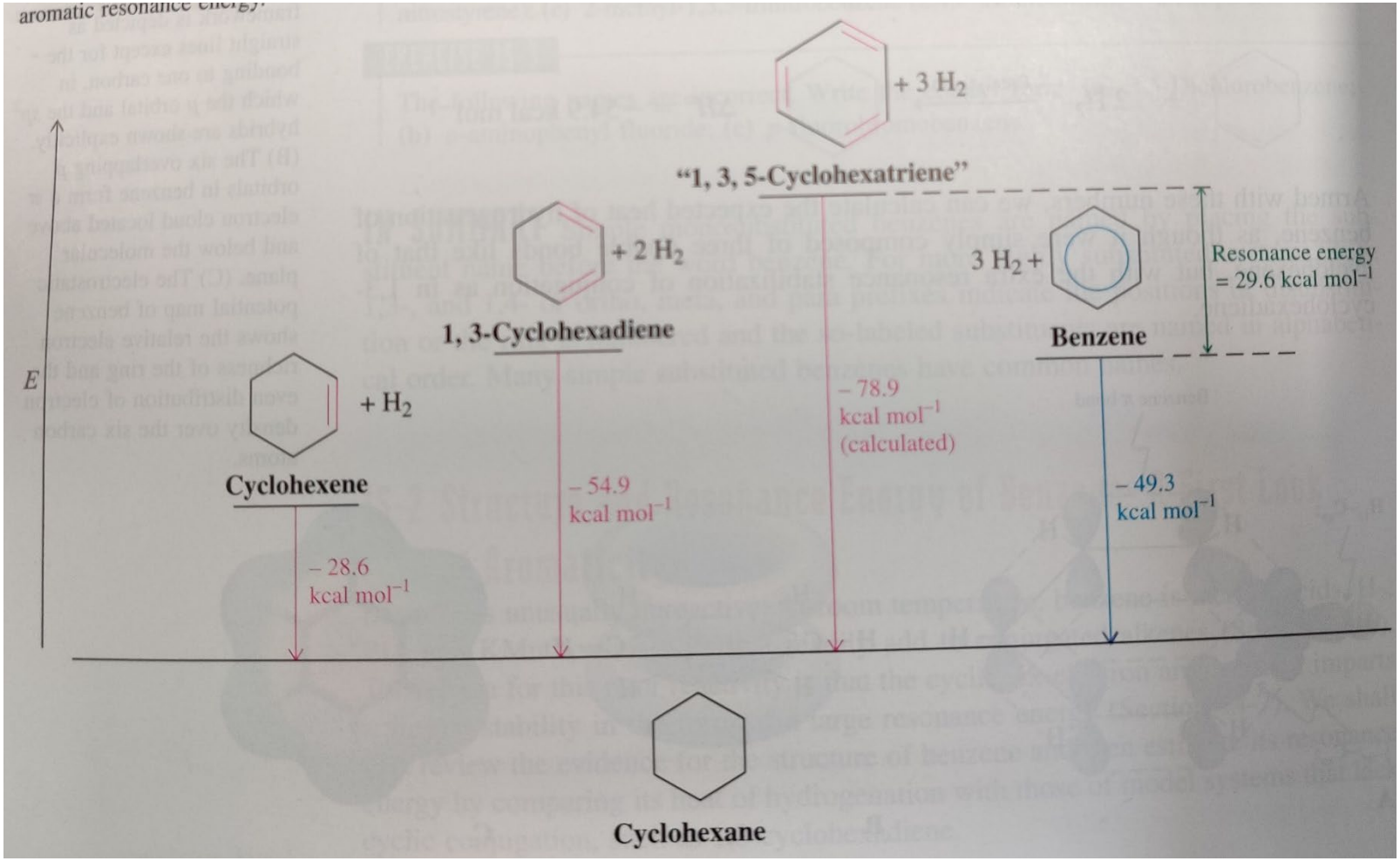


Hybrid resonance

- Unsual stability and chemical inertness

2. Structure and resonance of benzene

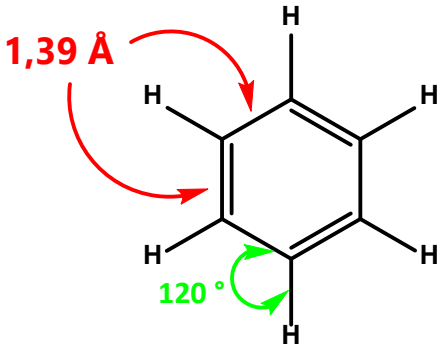
- Stability of benzene → resonance energy → aromaticity



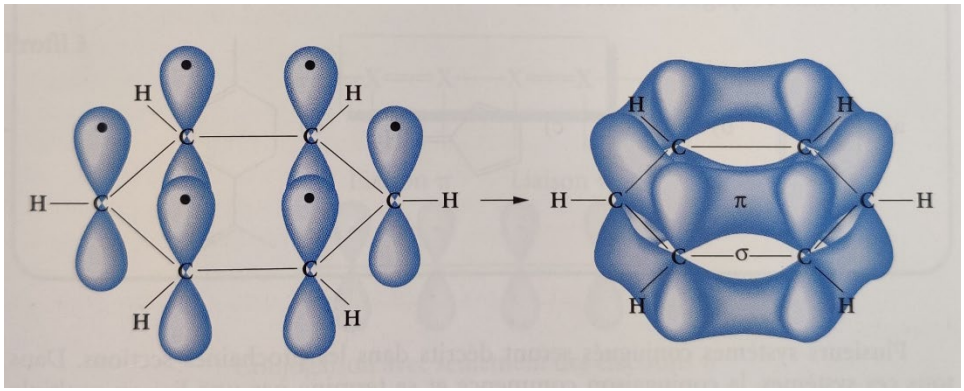
Extrait de Vollhardt et al., organic Chemistry @freeman

2. Structure and resonance of benzene

- C = C (alkene) < C – C (benzene) < C – C (alcane)
  1,33 Å 1,39 Å 1,54 Å



All 6 C are hydridized sp^2



Lateral overlap of the 6 atomic orbitals *p*
Electron delocalization of the 6 e^- π

- Unsual stability and chemical reactivity ≠ alkenes

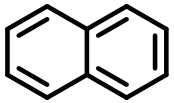
3. Aromaticity

Erich Hückel
(1896-1980)
chimiste et physicien
allemand

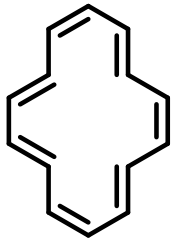
- A compound is said **aromatic** when it meets **all** the following criteria :
  - Cyclic and planar
  - Conjugated polyenes
  - Must contain **4n+2 π electrons** (n any positive number)

Hückel's rule

Benzene
6 e⁻ π



Naphthalene
10 e⁻ π



[14]annulene
14 e⁻ π

Furane
6 e⁻ π

- A compound that contains only **4n π electrons** → **antiaromatic**

Cyclobutadiene
4 e⁻ π

[12]annulene
12 e⁻ π

- ✓ Cyclic and planar
- ✓ Conjugated polyenes
- ✓ 4n electrons π delocalized

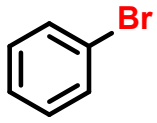
Cyclohexa-1,3-diene
→ **non aromatic**

- ✗ Cyclic and planar
- ✗ Conjugated polyenes
- ✓ 4n electrons π

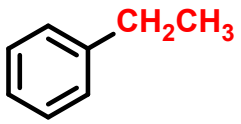
4. Naming the benzenes

a) Monosubstituted benzenes

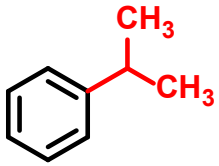
✓ They are named by adding a substituent prefix to the word benzene



Bromobenzene

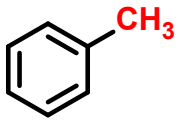


Ethylbenzene

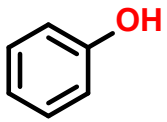


Isopropylbenzene

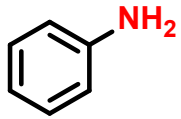
✓ Some monosubstituted benzenes have **common names**



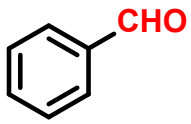
methylbenzene
Toluene



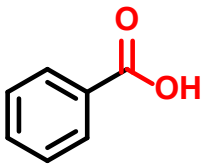
hydroxybenzene
Phenol



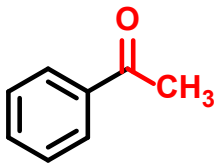
aminobenzene
Aniline



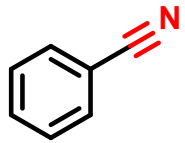
Benzaldehyde



Benzoic acid



Acetophenon



Benzonitrile

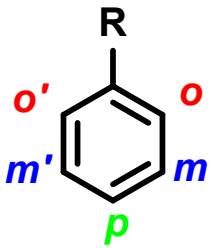
4. Naming the benzenes

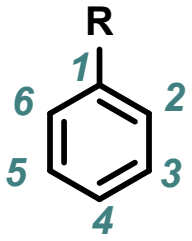
b) Disubstituted benzenes

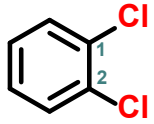
ortho- (o)

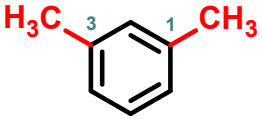
meta- (m)

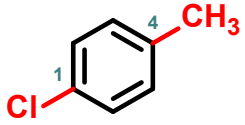
para- (p)





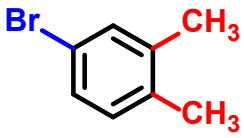


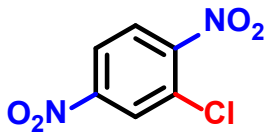


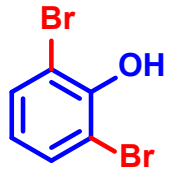


c) Polysubstituted benzenes

Numbering is done in order to give the smallest numbers to the substituents

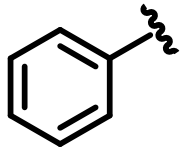




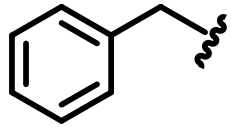


4. Naming the benzenes

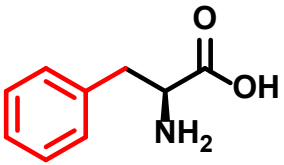
d) Miscellaneous

C_6H_5- ou 

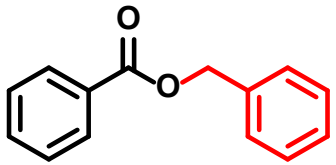
Phenyl = Ph

$C_6H_5CH_2$- ou 

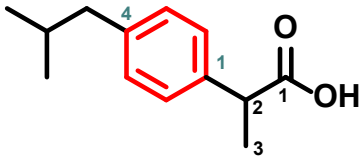
Benzyl = Bn



L- phenylalanine



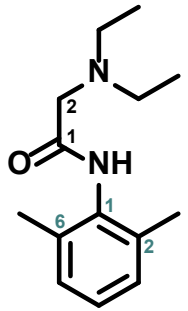
Ascabiol® - Antiparasitaire externe



2-(**4**-*iso*butylphenyl) propanoïc acid

Ibuprofen®

Anti-inflammatoire non stéroïdien (AINS)



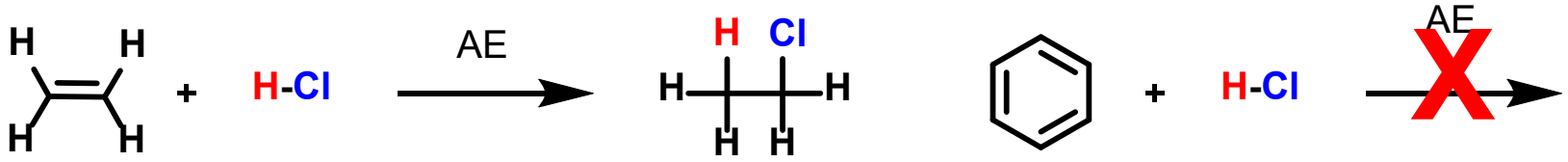
2-(diethylamino)-*N*-(**2,6**-dimethylphenyl)acetamid

Lidocaïne® - anesthésique local

Inhibition des récepteurs NMDA

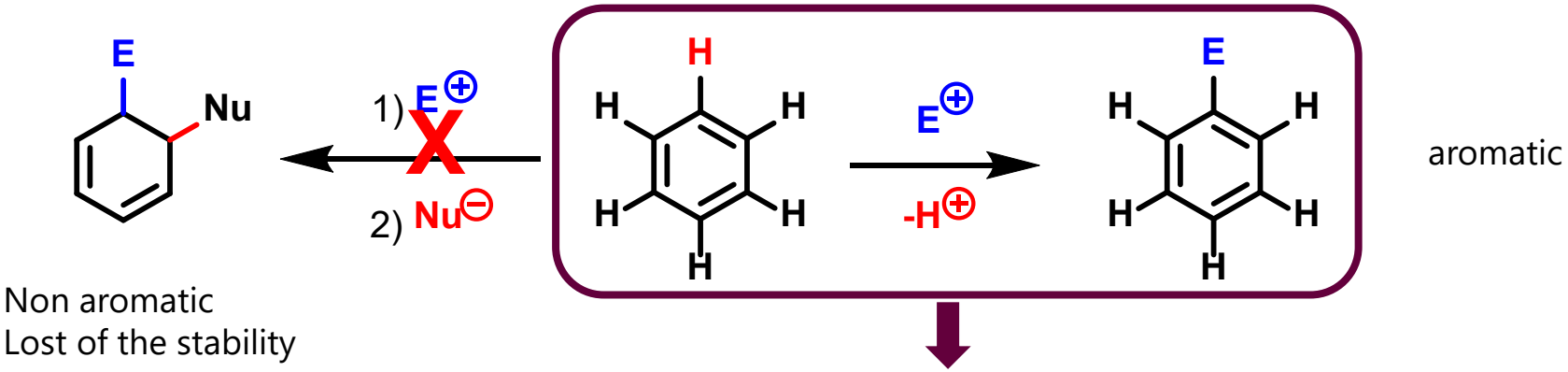
a) Introduction

- Chemical reactivity different from alkenes

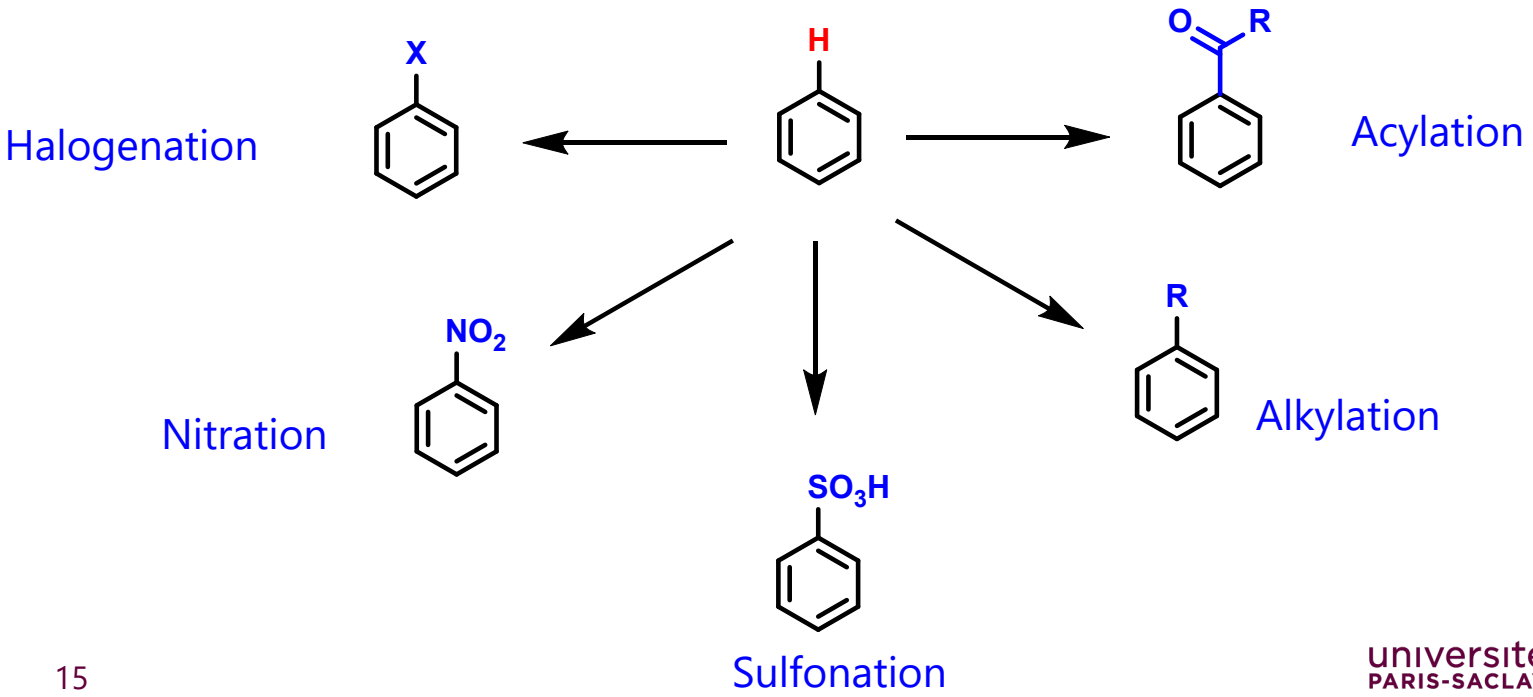


- 6 e^- π → benzene ring is **electron-rich**

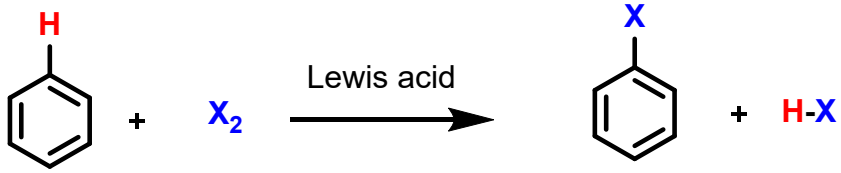
  → can react with **electrophiles**



b) General mechanism



c) Chloration/bromation

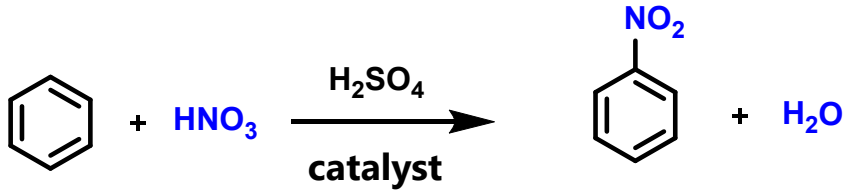


- **X_2 = Cl_2 ou Br_2**
- Lewis acid= $FeCl_3$, $FeBr_3$, $AlCl_3$

X=Cl → chlorobenzene
X=Br → bromobenzene

mechanism

d) Nitration

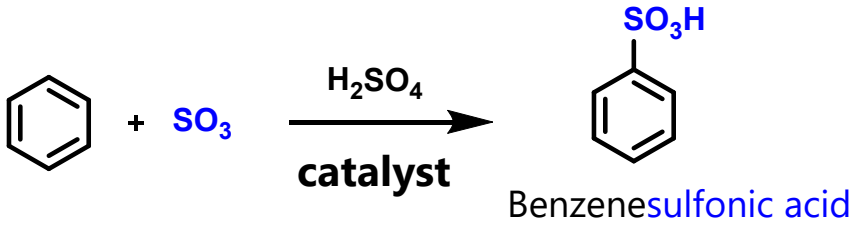


nitrobenzene

mechanism

d) Nitration

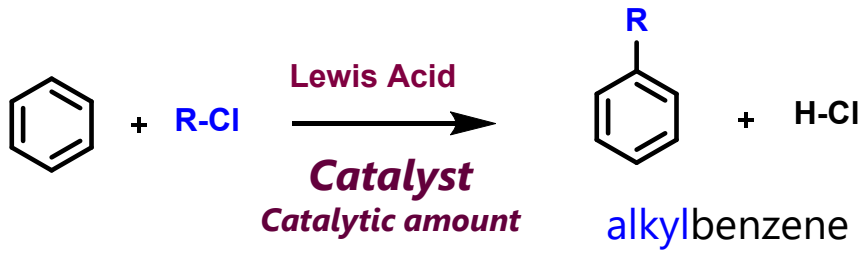
e) Sulfonation



Benzenesulfonic acid

→ mechanism

e) Friedel-Crafts alkylation

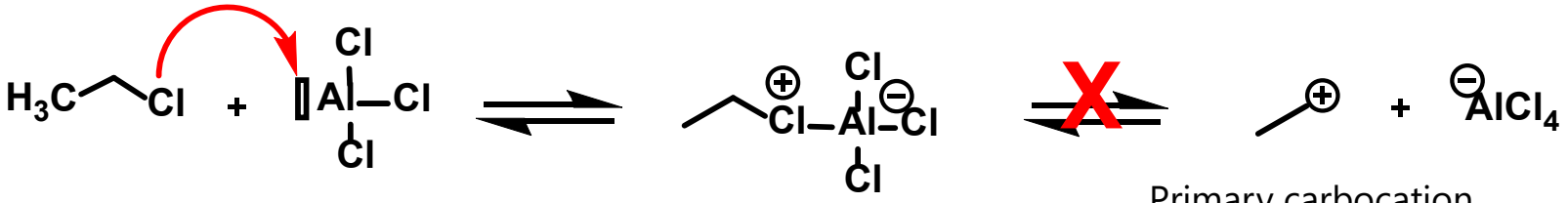


alkylbenzene

Charles Friedel
(1832-1899)
chimiste français

James Craft
(1839-1917)
chimiste américain

→ Mechanism



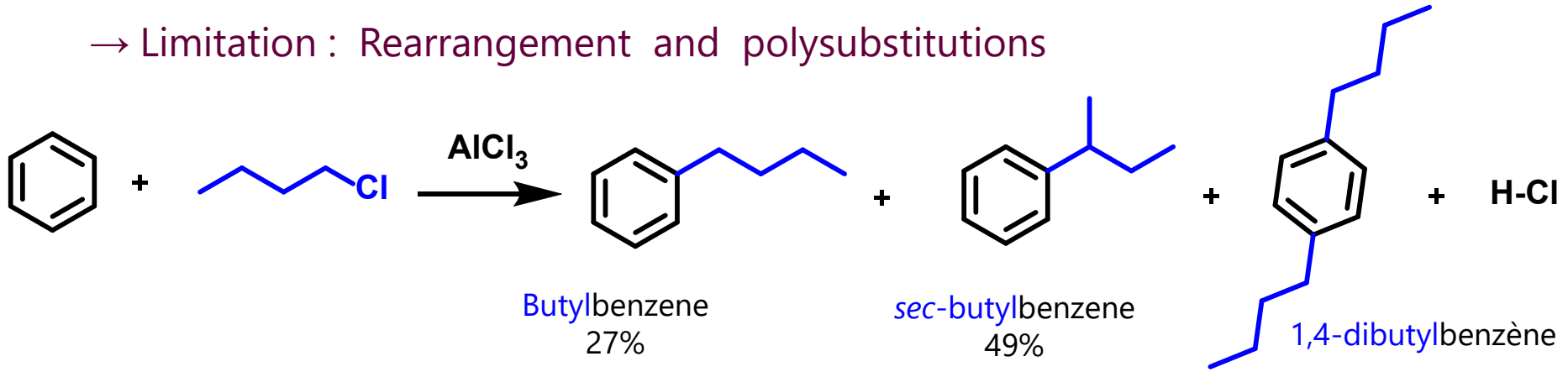
Reactive complex

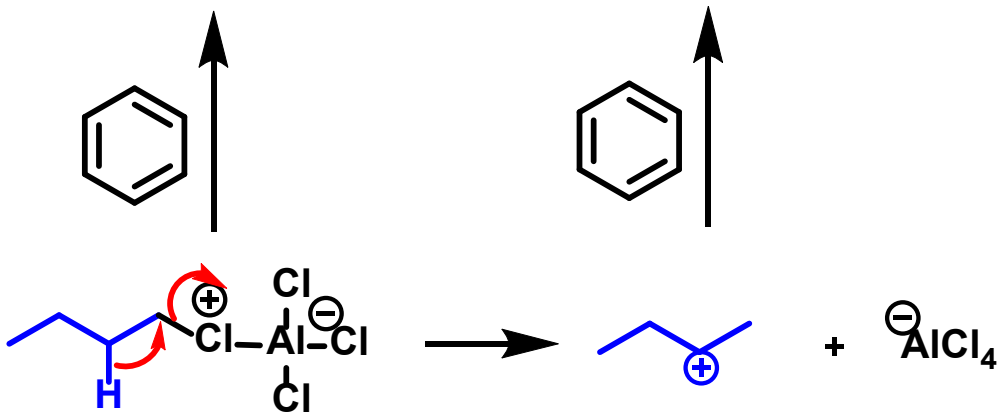
Primary carbocation
unstable

e) Alkylation : Friedel-Crafts alkylation

e) Friedel-Crafts alkylation

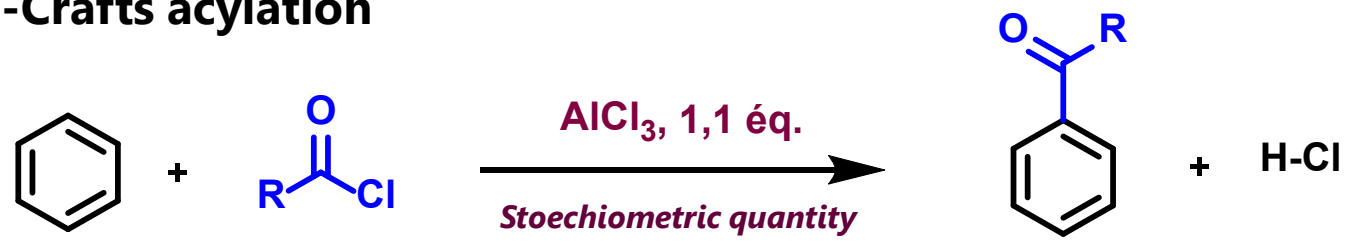
→ Limitation : Rearrangement and polysubstitutions





Rearrangement migration of hydride → *Secondary carbocation*

f) Friedel-Crafts acylation



Acyl chloride

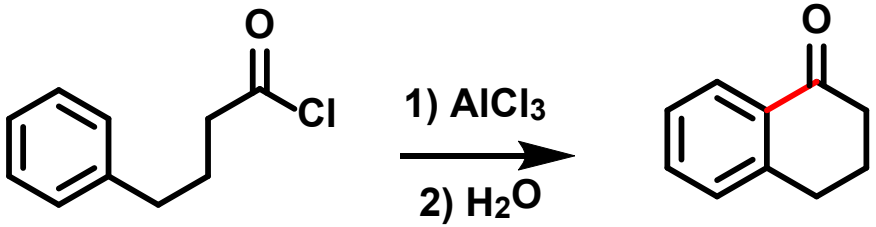
acylbenzene

→ mechanism

f) Friedel-Crafts acylation

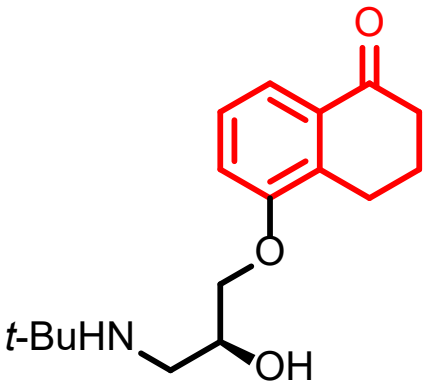
f) Friedel-Crafts acylation

→ intramolecular acylation: formation of 5 to 6-membered ring.



α-tétralone

47-91%



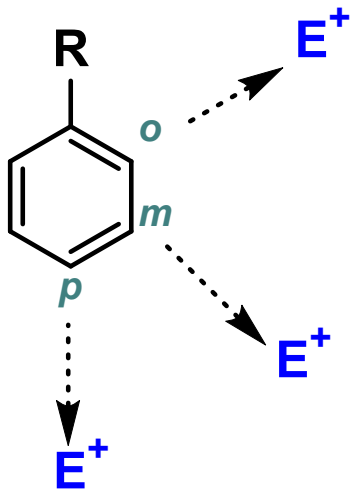
Levobunonol

Antagoniste des récepteurs β-adrénergiques

Traitement du glaucome

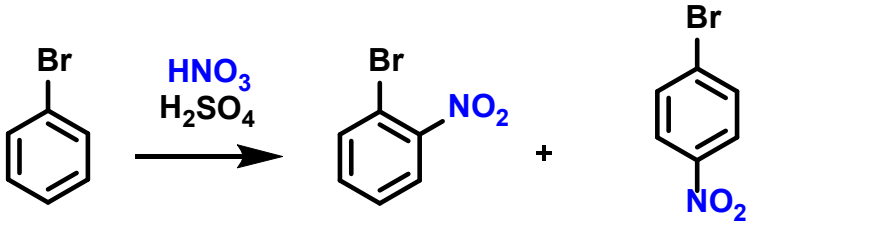
6. Electrophilic aromatic substitution of monosubstituted benzenes

a) Problematic



Regioselectivity is governed by

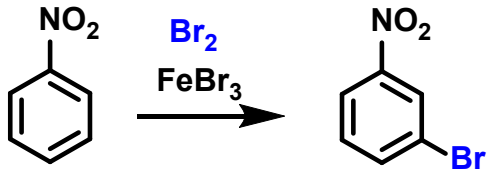
- ***electronic effects***
- ***steric effects***



o-bromonitrobenzène
36%

p-bromonitrobenzène
62%

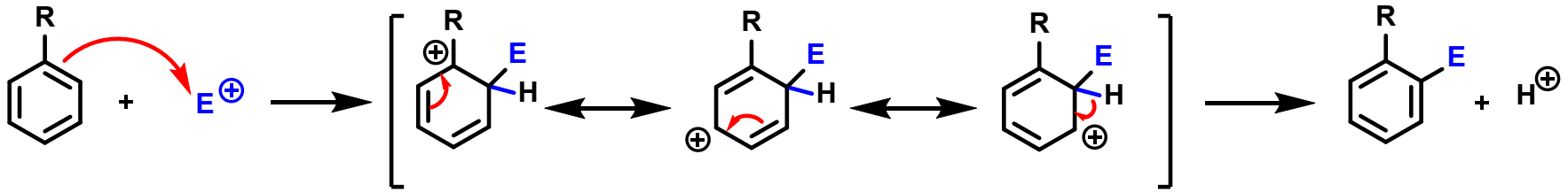
→ Br is ***ortho*** and ***para*-directing**



m-bromonitrobenzène
90%

→ NO_2 is ***meta*-directing**

b) Activation and deactivation by susbtituents on a benzene ring



- If a substituted benzene reacts more rapidly than benzene itself → R is an **activating group**
- If a substituted benzene reacts more slowly than benzene itself → R is a **deactivating group**
- The rate of the reaction is linked to the **electronic effects** of R : **inductive** effects and **resonance** effects

Relative Rates of Nitration of C_6H_5X

X =	OH	CH_3	H	Cl	$CO_2CH_2CH_3$	CF_3	NO_2
	1000	25	1	0.033	0.0037	2.6×10^{-5}	6×10^{-8}

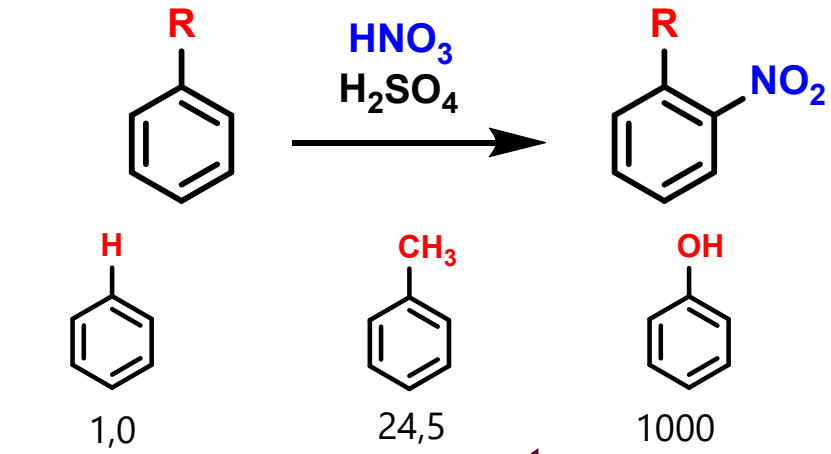
b) Activation and deactivation by susbtituents on a benzene ring

- **Activating groups**

Groupes activants†	Effet électronique*
$-NH_2$, $-NHR$, $-NR_2$	+M > –I
–OH, –OR	+M > –I
–NHCOR, –OCOR	+M > –I
–Ph, $-CH=CH_2$	+M, +I
–R	+I

Extrait de Burrows et al., Chimie[3] @de boeck

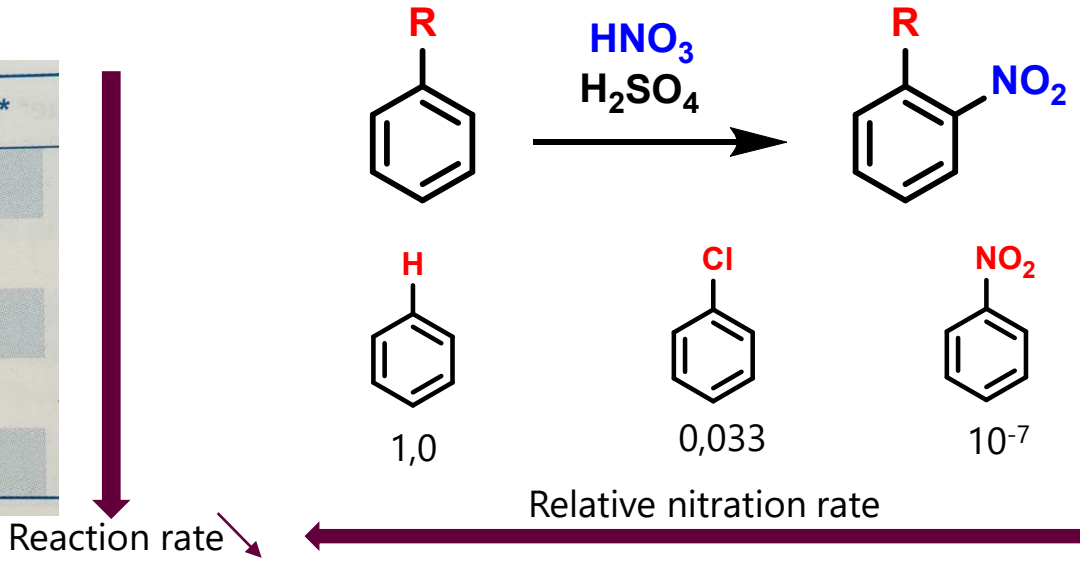
Rate of the reaction ↑



b) Activation and deactivation by susbtituents on a benzene ring

- **Deactivating groups**

Groupes désactivants	Effet électronique*
–Cl, –Br, –I	–I > +M
–CHO, –COR	–M, –I
$-CO_2H$, $-CO_2R$	–M, –I
$-SO_3H$	–M, –I
$-NO_2$	–M, –I



Extrait de Burrows et al., Chimie[3] @de boeck

c) Directing effects of substituents

c) Directing effects of substituents

c) Directing effects of substituents

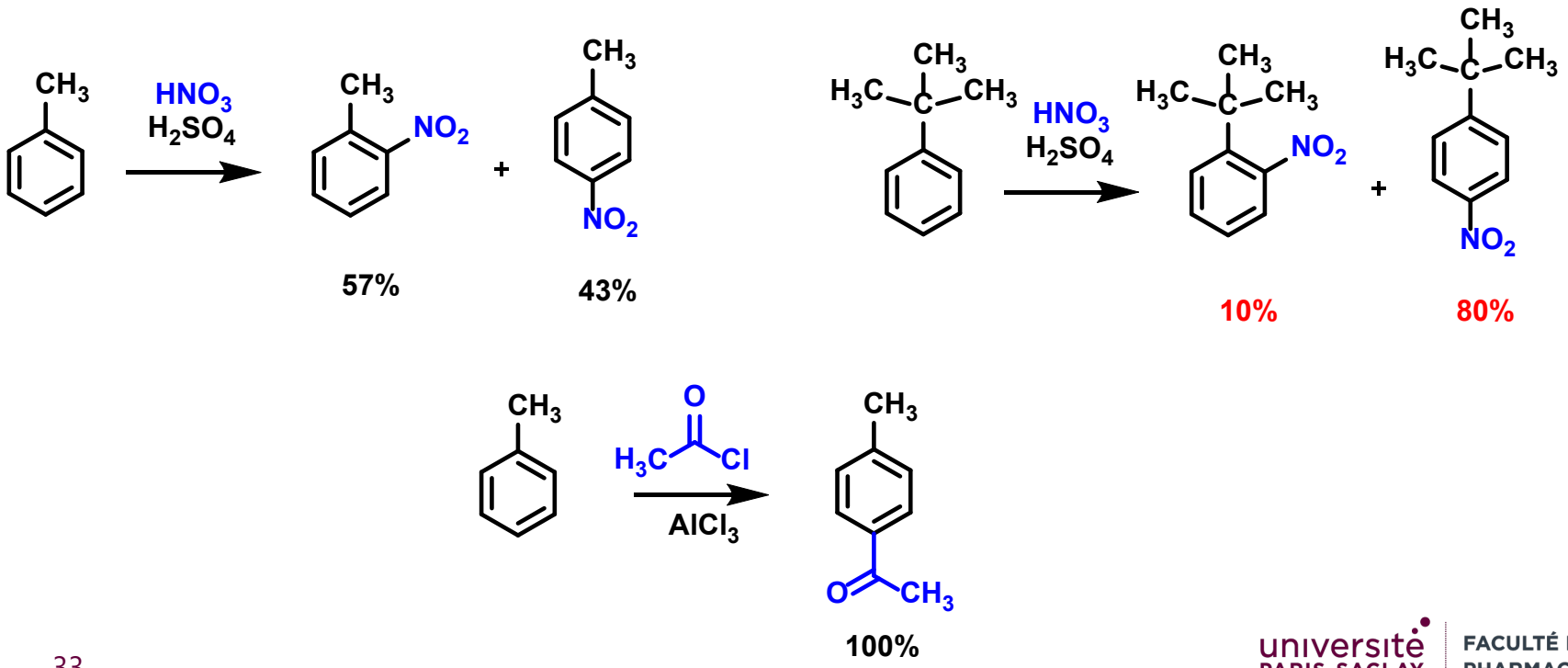
c) Directing effects of substituents

- **regioselectivity *ortho/para* : steric effects**

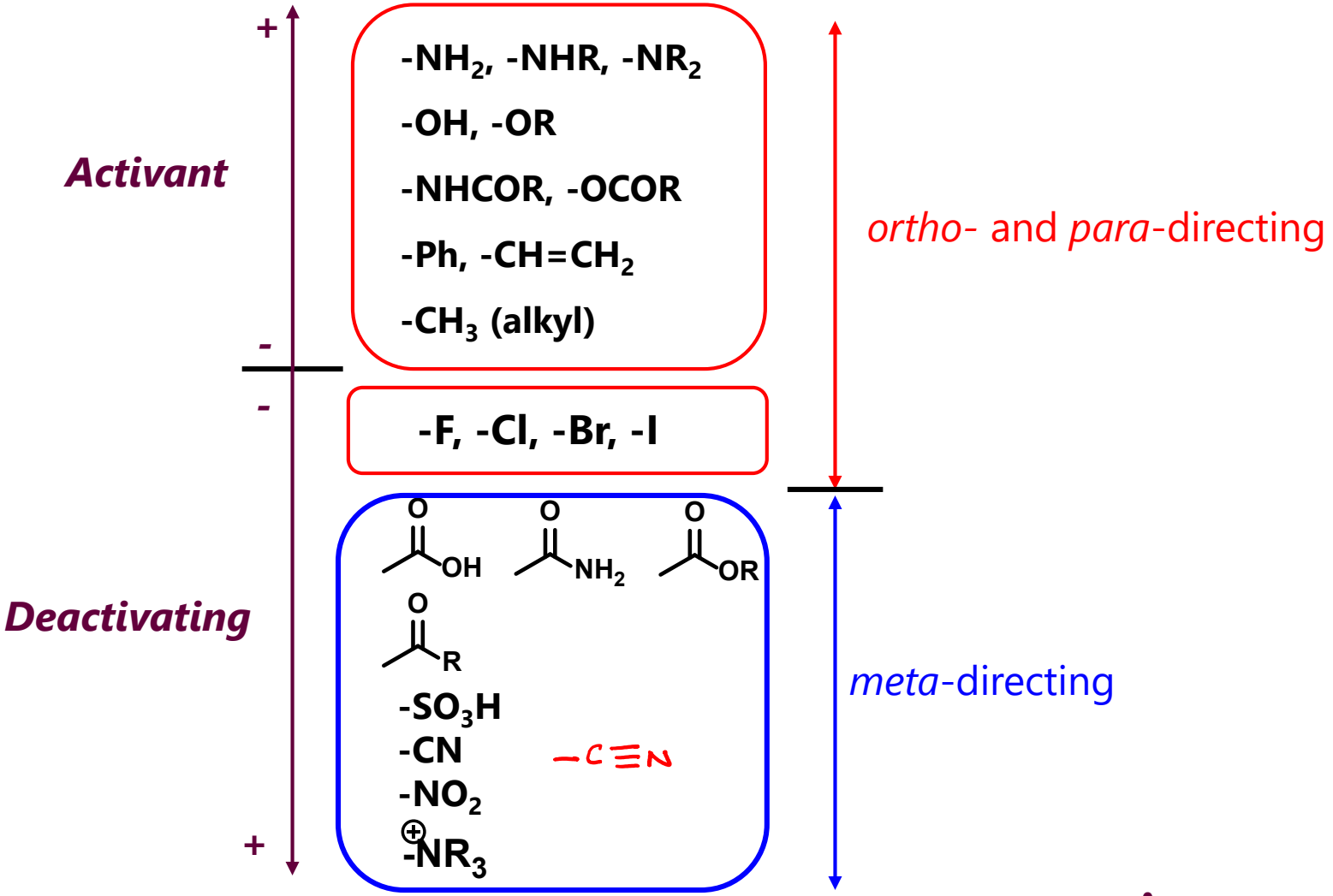
✓ *Size of the substituent on the benzene ring*

✓ *Size of the electrophile*

✓ ***In general , para substitution predominates over ortho substitution,***

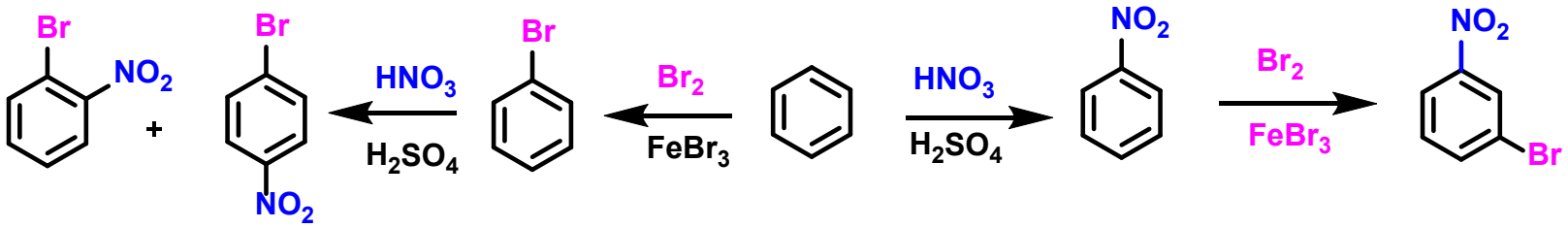


d) Summary

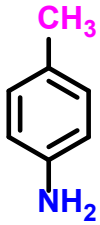

+
Activant
-NH2, -NHR, -NR2
-OH, -OR
-NHCOR, -OCOR
-Ph, -CH=CH2
-CH3 (alkyl)
-
-
-F, -Cl, -Br, -I
Deactivating
-SO3H
-CN
-NO2
-NR3
+
ortho- and para-directing
meta-directing

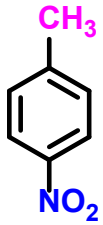
7. Electrophilic aromatic substitution of polysubstituted benzenes

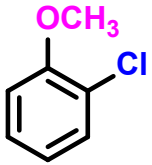
a) How to predict the regioselectivity on polysubstituted benzenes ?

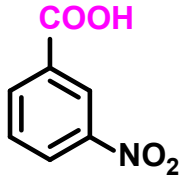


✓ *Guideline : the **most powerful activator** controls the position of the attack of the electrophile*





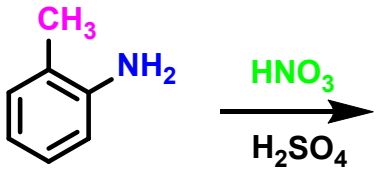


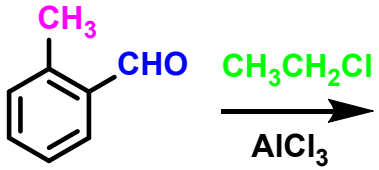


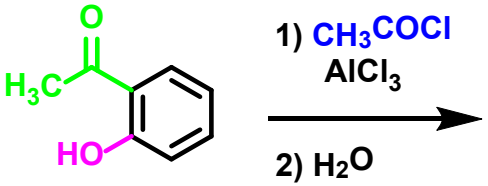
7. Electrophilic aromatic substitution of polysubstituted benzenes

Exercices

What are the compounds obtained for the following reactions? Give the ratio of the compounds and the names?

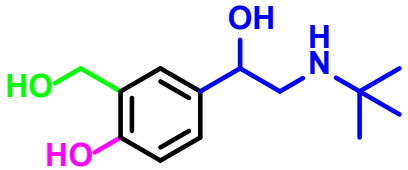
1) 

2) 

3) 

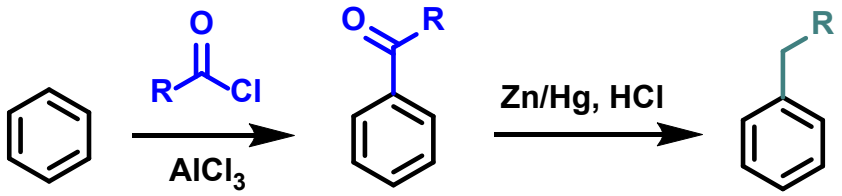
?

4 étapes

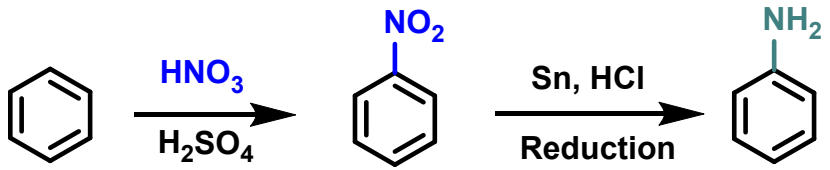


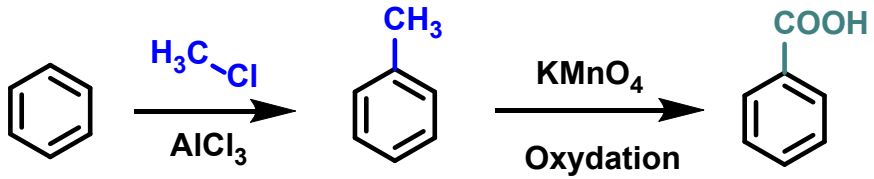
Salbutamol
Ventoline®
Agoniste des récepteurs β-adrénergiques

b) Reactivity on the substituents



Reduction de Clemmensen

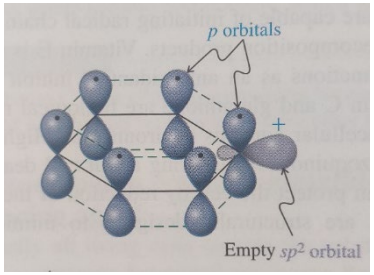


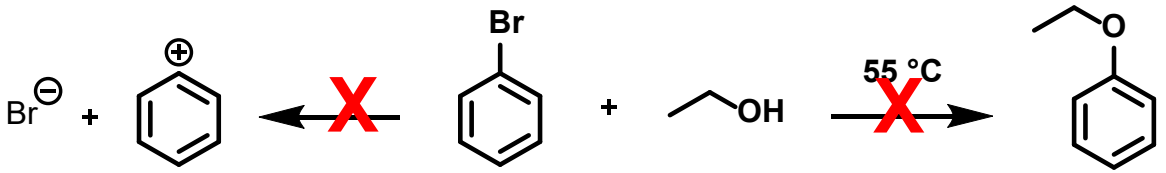


8.1 addition-elimination mechanism

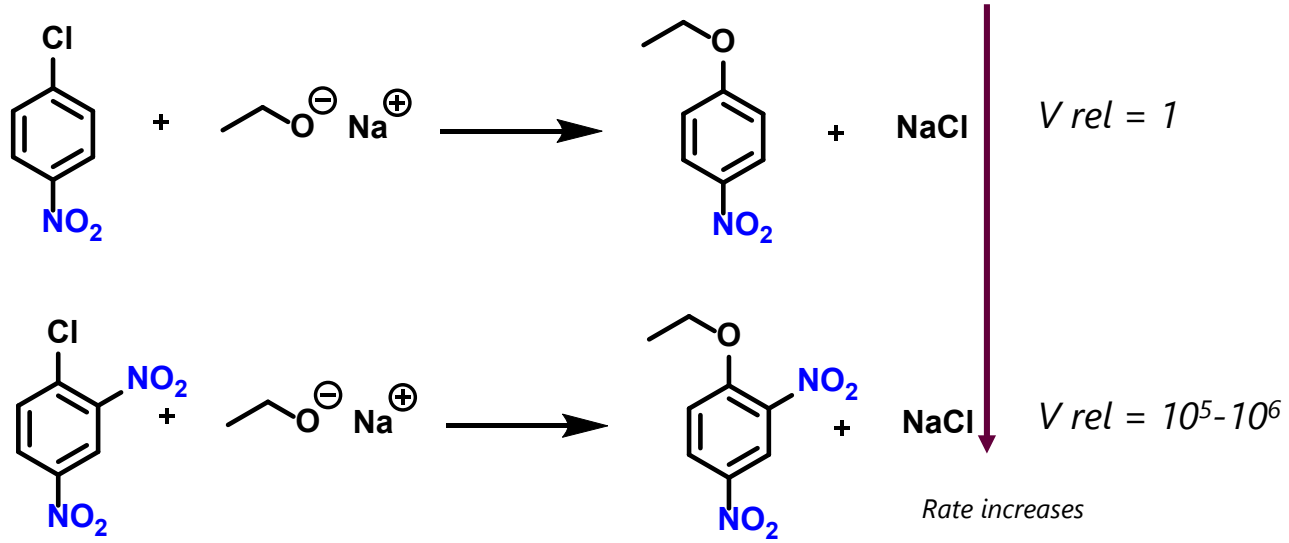
a) Introduction

✓ Lack of reactivity of aryl halides under S_N1 et S_N2 conditions ⟶ Other mechanisms





✓ Aryl halides bearing one or two strong electron-withdrawing groups ortho or para to the halogen undergo nucleophilic substitution reactions.



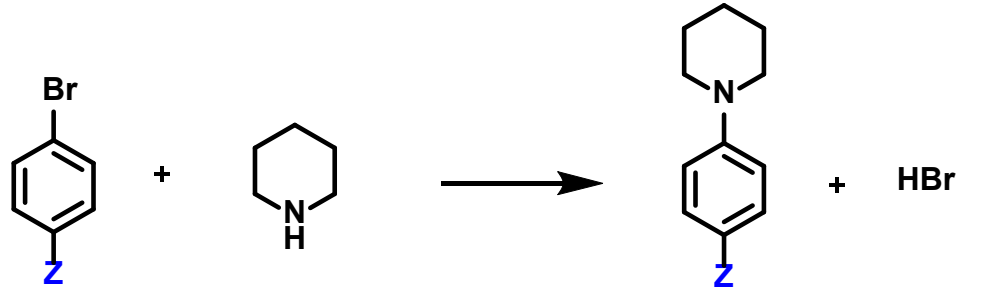
✓ Reactivity of aryl halides: Ar-F >> Ar-Cl ≈ Ar-Br ≈ Ar-I

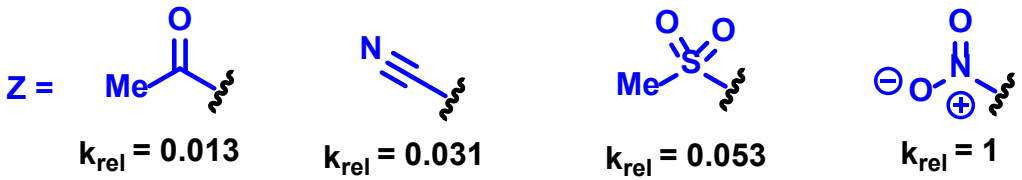
From Vollhardt Organic Chemistry @Freeman

b) addition-elimination mechanism

b) addition-elimination mechanism

- ✓ When the deactivating group is in the meta position, the SNAr is disfavored
- ✓ Any **anion-stabilizing (electron-withdrawing) group** *ortho* or *para* to a potential leaving group can be used to make nucleophilic aromatic substitution possible

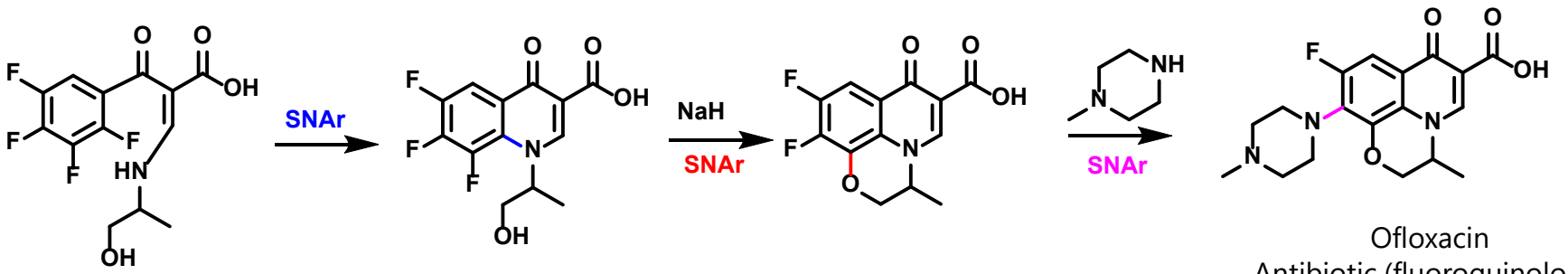




k_{rel} = 0.013 k_{rel} = 0.031 k_{rel} = 0.053 k_{rel} = 1

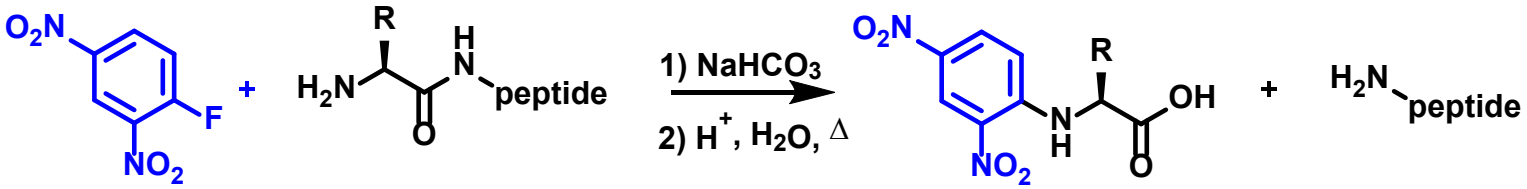
c) Applications

✓ Ofloxacin synthesis



Ofloxacin
Antibiotic (fluoroquinolone)

✓ Sanger reagent : identification of a N-terminal amino acid from a peptide

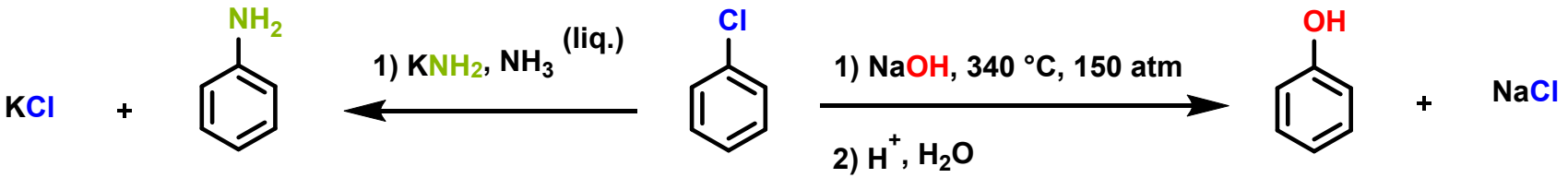


Sanger Reagent

1953, Insulin

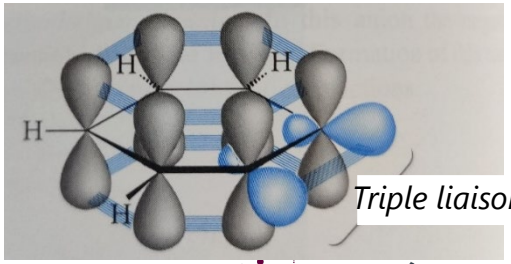
Characteristic yellow color

8.2 The benzyne mechanism



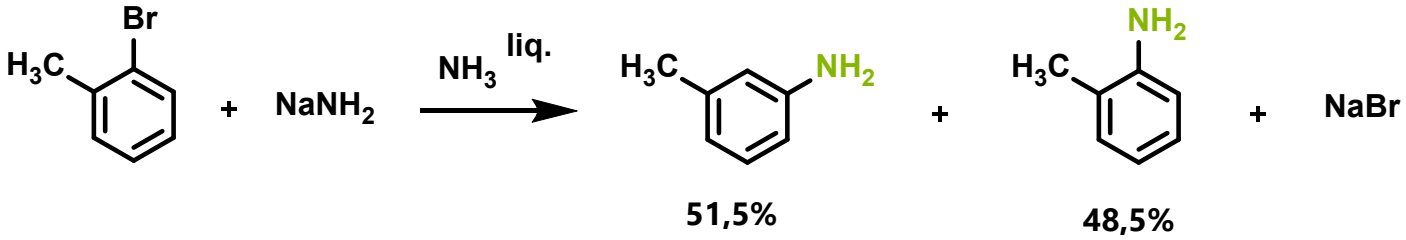
Aniline *Phénol*

Mechanism



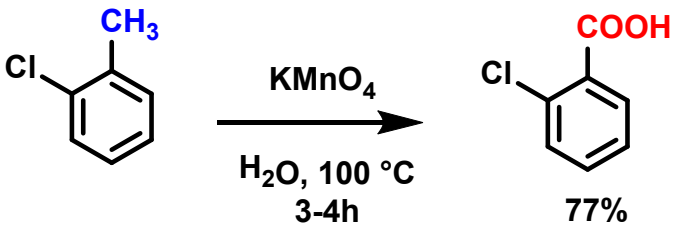
Triple liaison

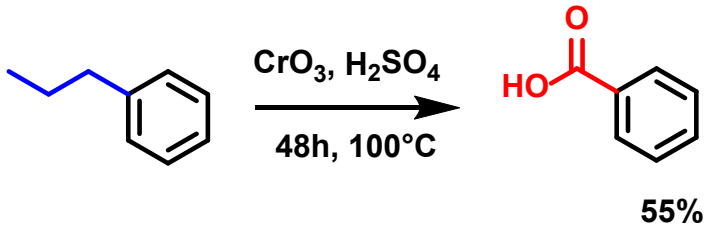
8.2 The benzyne mechanism

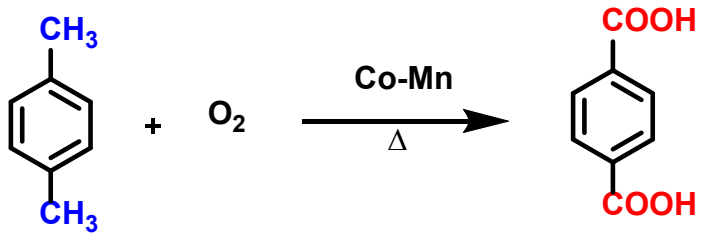


9.1 Benzylic oxidations

→ *Require at least one benzylic C-H bond*



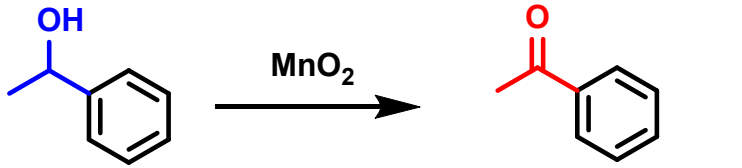




para-xylene

terephthalic acid

↳ *Polyester synthesis*



Acetophenone

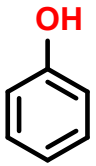
9.2 Phenols

a) Naming

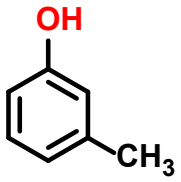
Coal (1834)

plastics

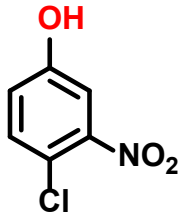
Pharmaceuticals (aspirine..)



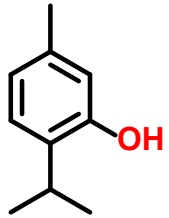
Phénol



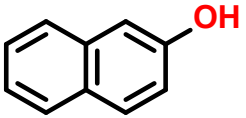
***m*-crésol**
3-méthylphenol



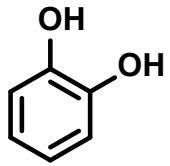
4-chloro-3-nitrophenol



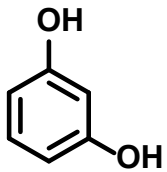
Thymol



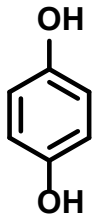
2-naphthol



Catechol

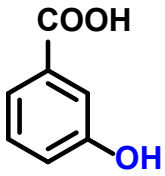


Resorcinol



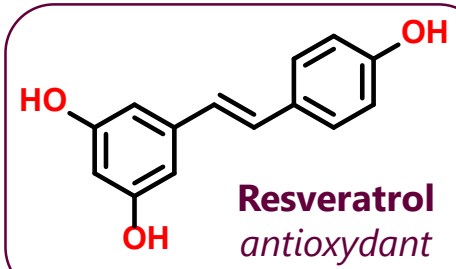
Hydroquinone

Benzenediol ou hydroxyphenol

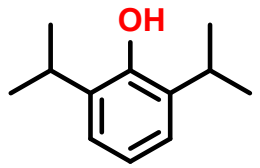


3-hydroxybenzoïc acid

→ *very important in nature*



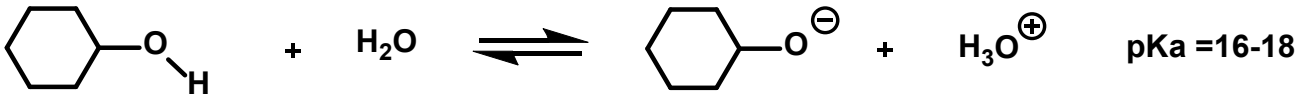
Resveratrol
antioxydant



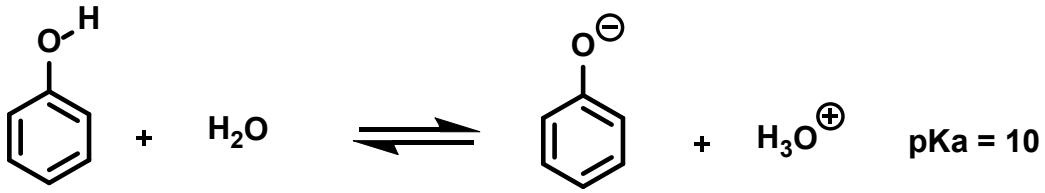
Propofol
anesthetic

9.2 Phenols

b) Acidity of phenols and use of phenoxides

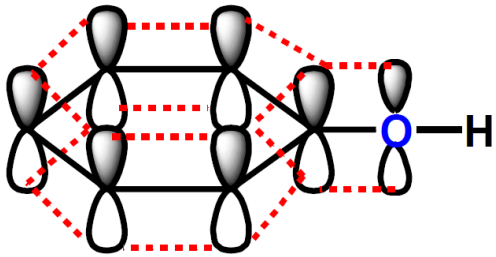


alcool alcoolate



phénol Phenoxide ion

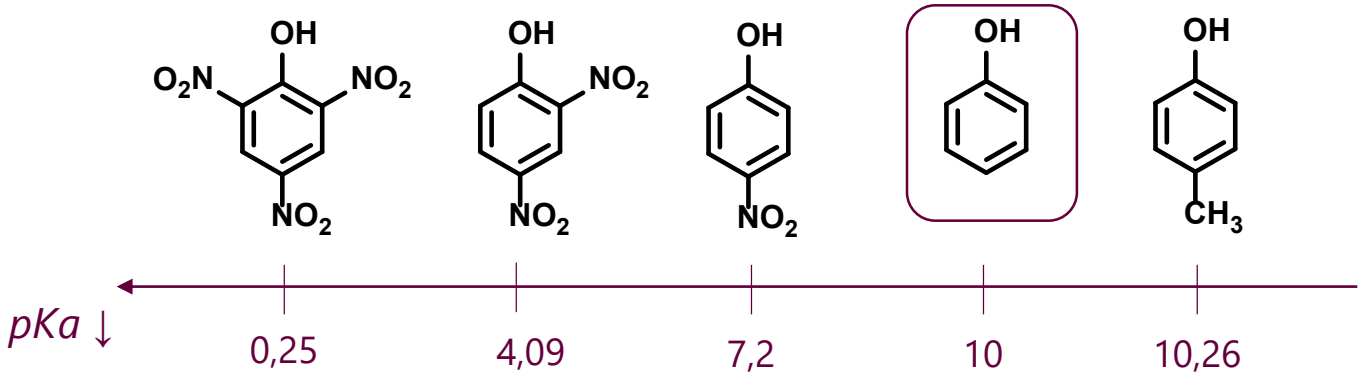
Nucleophile



9.2 Phenols

b) Acidity of phenols and use of phenoxides

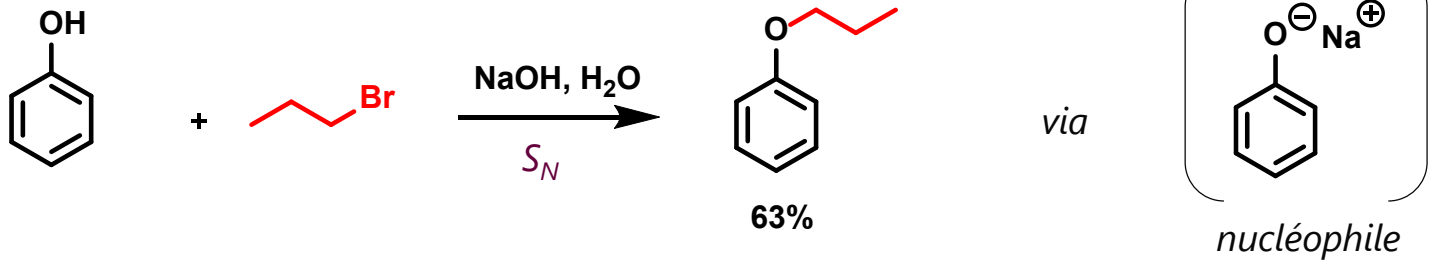
- *The acidity of phenols is greatly affected by susbtituents that are capable of resonance*



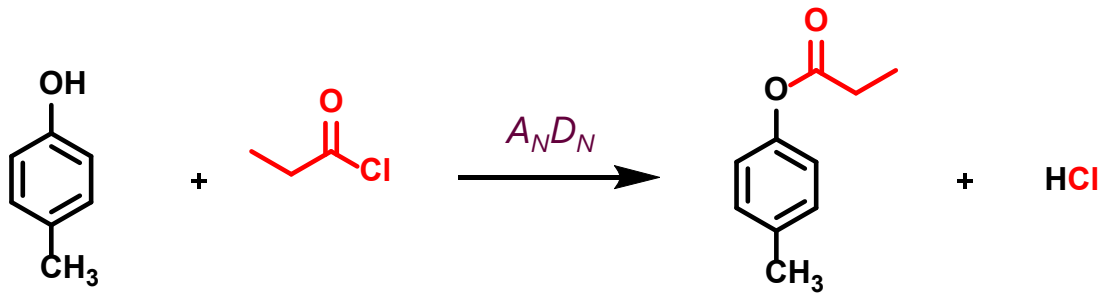
9.2 Phenols

b) Acidity of phenols and use of phenoxides

- *Williamson ether synthesis*



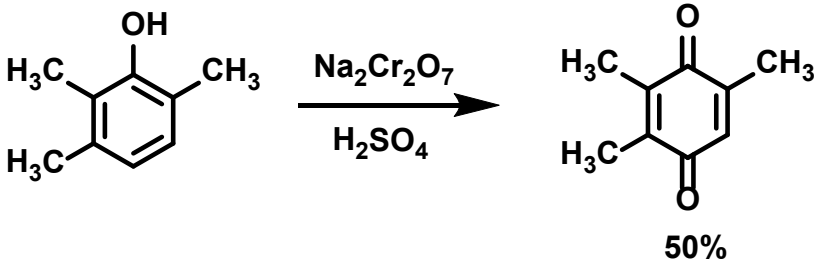
- *Esterification*

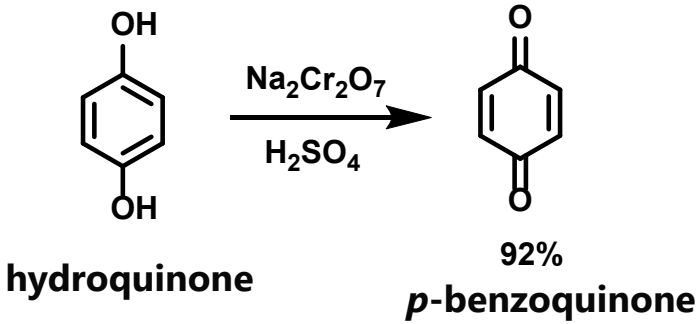


9.2 Phenols

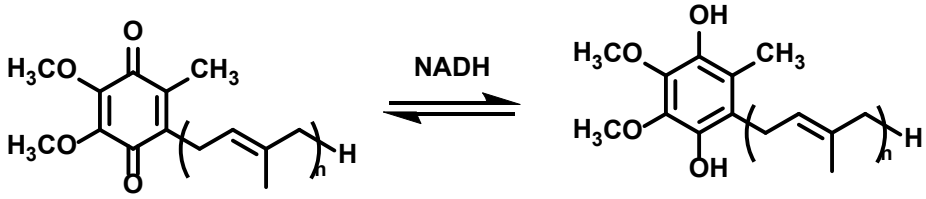
c) Oxydation of phenols to quinones

- *Oxydation*



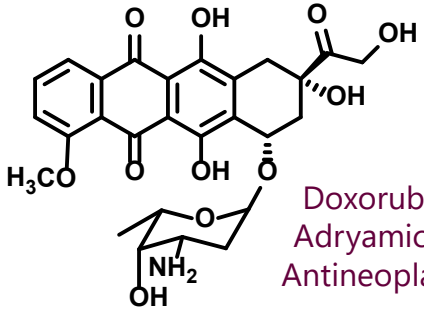


Examples of quinones in nature

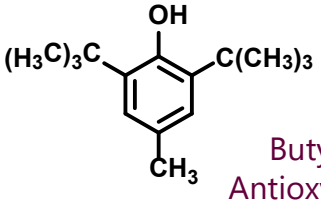


Coenzyme Q
ubiquinone

Forme réduite



Doxorubicine
Adryamicine®
Antineoplasique

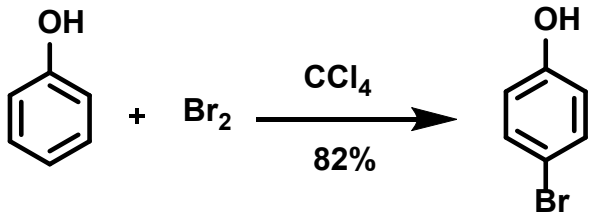


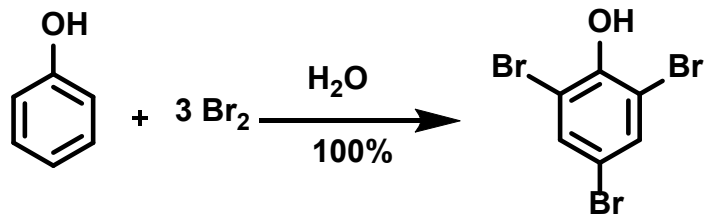
BHT
Butylhydroxytoluene
Antioxydant (cosmétique)

9.2 Phenols

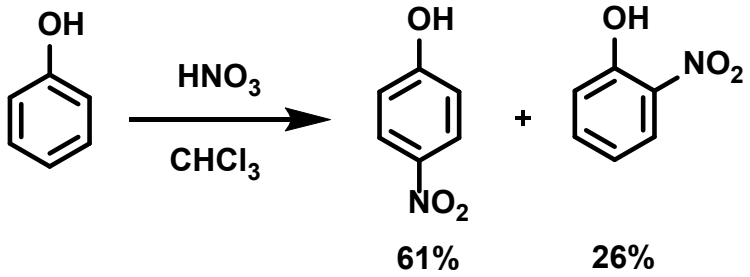
d) Electrophilic aromatic substitution of phenols

- *Halogenation*

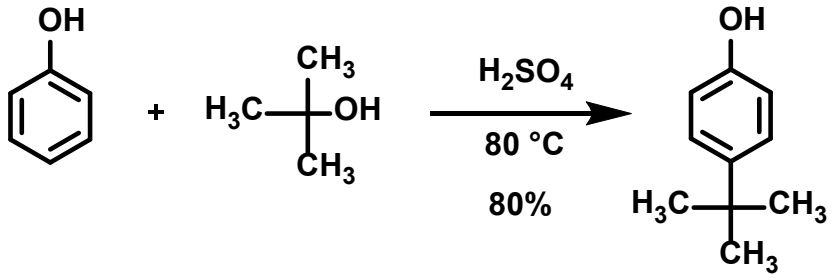




- *Nitration*

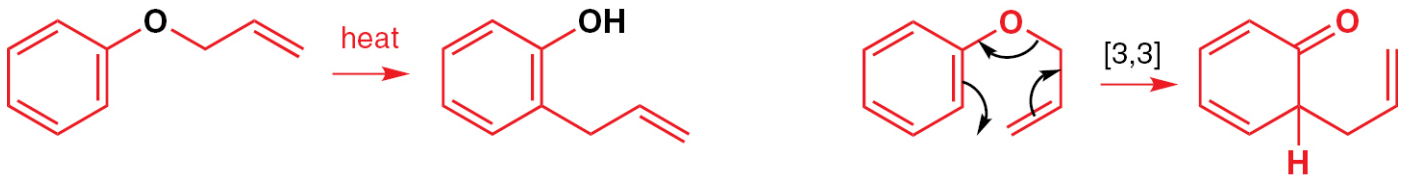


- *Alkylation de Friedel-Crafts*



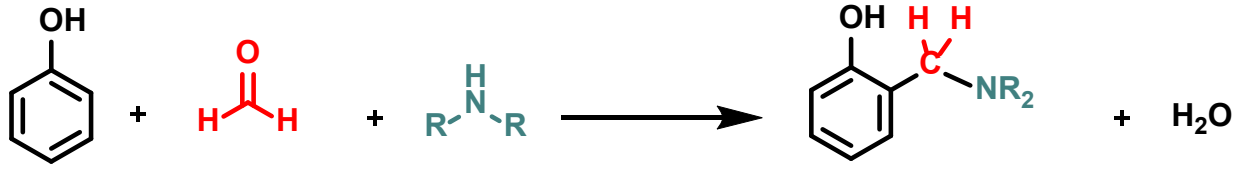
9.2 Phenols

e) The Claisen rearrangement



→ **[3,3]-sigmatropic rearrangement**

f) Mannich reaction

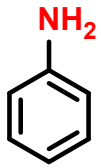


local anesthetic

9. Chemistry of benzene substituents

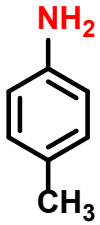
9.3 Anilines

a) Naming

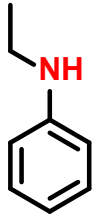


aniline
1-aminobenzene

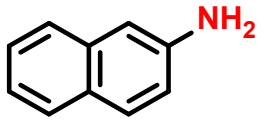
3-nitroaniline



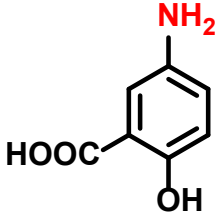
4-methylaniline
***p*-toluidine**



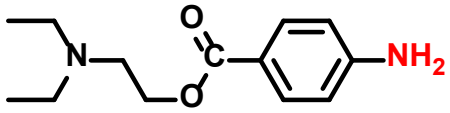
***N*-ethylaniline**



β-naphthylamine
2-aminonaphthalene



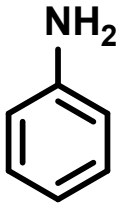
Mesalazine
Anti-inflammatory
Inflammatory bowel disease



Procaine
Local anesthetic

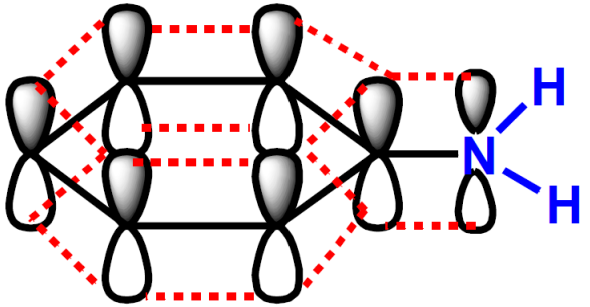
9.3 Aniline

b) Properties of aniline

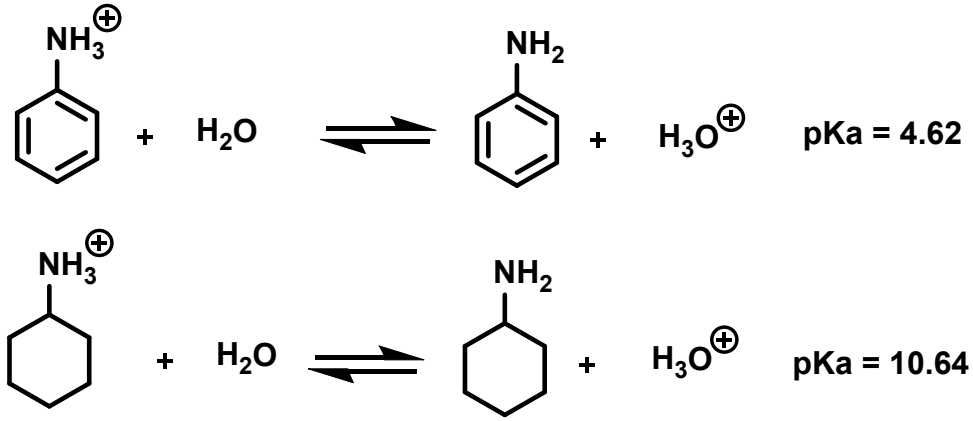


aniline
Colorless liquid
b.p. = 184 °C

C-N < C-C
1,40 Å 1,54 Å



- Aromatic amines are Bronsted bases and nucleophilic
- Aromatic amines are weaker bases as alkyl amines

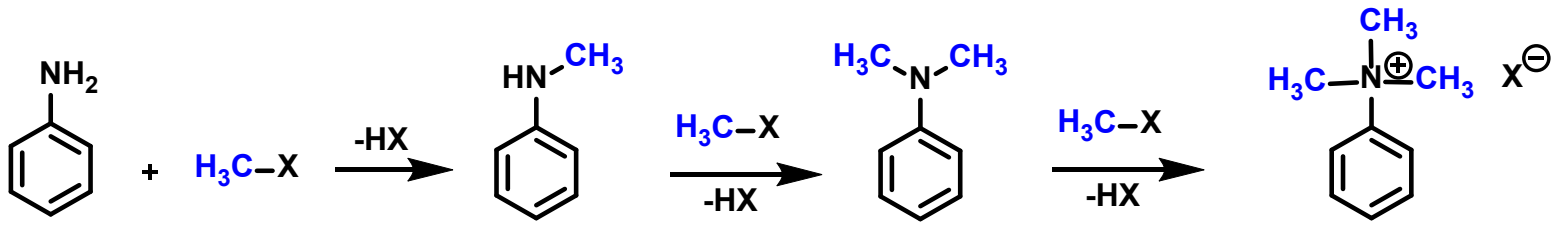


	pKa
H_3C–NH_2	5,07
Cl–NH_2	3,81
O_2N–NH_2	~1

9.3 Aniline

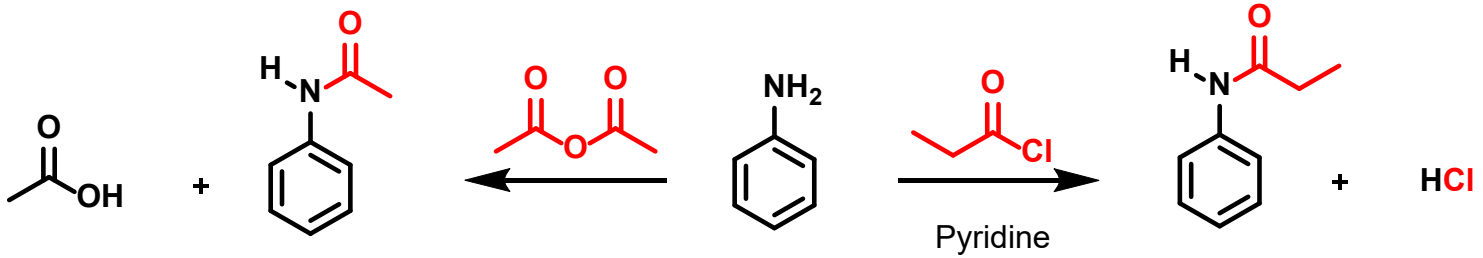
b) Reactivity of aniline

- *Alkylation reaction → polyalkylation*



Quaternary ammonium slat

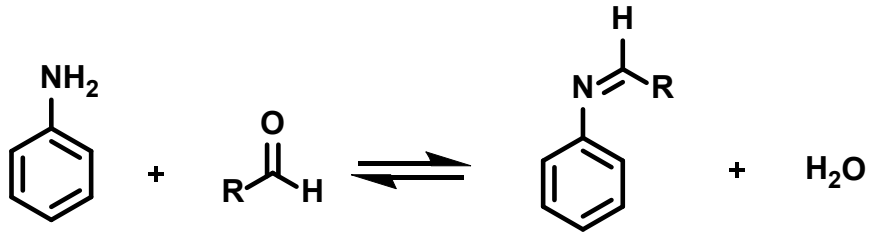
- *Acylation reaction*



9.3 Aniline

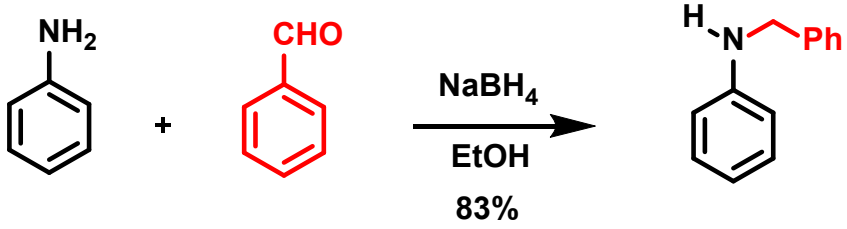
b) Reactivity of aniline

- *Condensation with aldehydes and ketones*



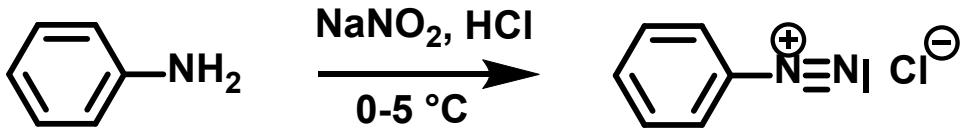
Imine
(base de Schiff)

- *Reductive amination*



9.3 Aniline

c) Diazotization



Aryl diazonium salt

- ✓ Stable @ < 5 °C
- ✓ Can be isolated
- ✓ Very reactive towards substitution reaction

With loss of N_2

Without loss of N_2

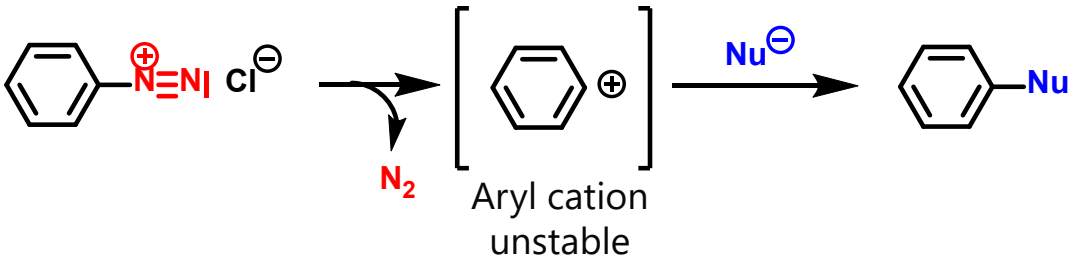
9.3 Aniline

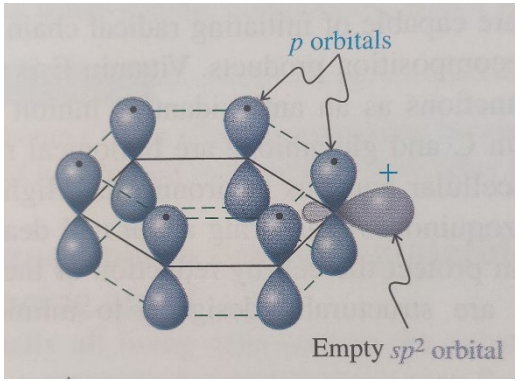
c) Diazotization

9.3 Aniline

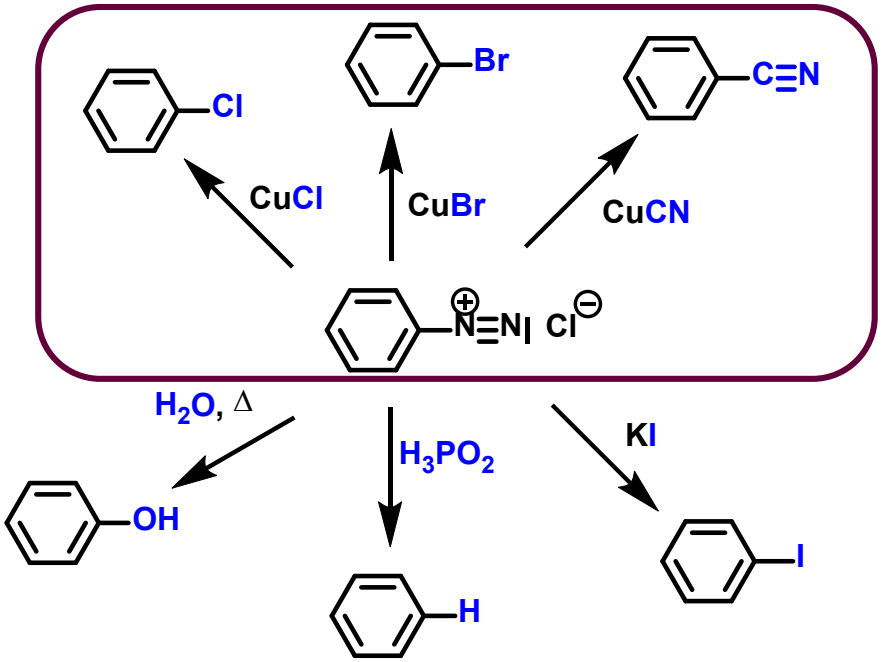
d) Reactions of diazonium salts

- Substitution reactions of diazonium salts **with loss of N_2**





From Vollhardt Organic Chemistry @Freeman



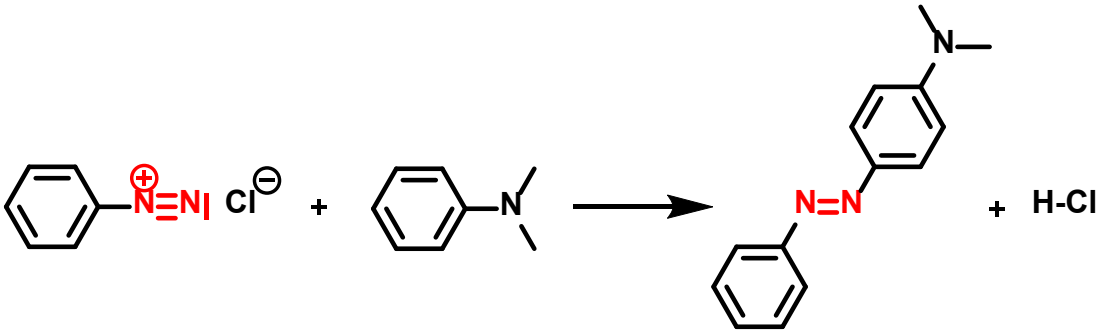
Sandmeyer reaction
→ radical-like mechanism

9.3 Aniline

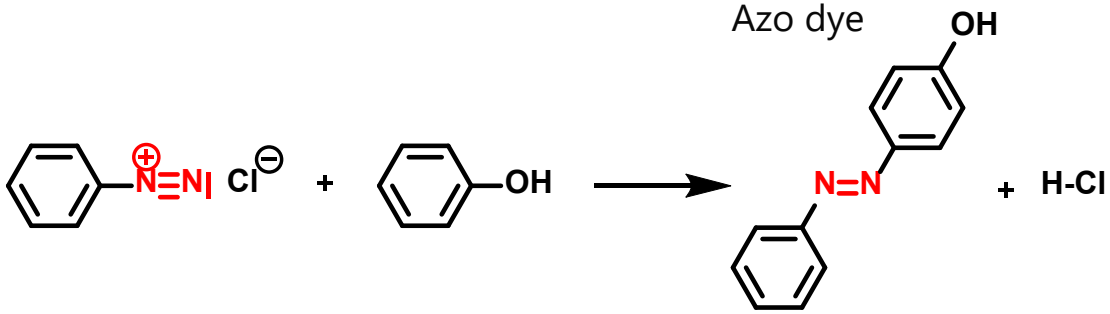
d) Reactions of diazonium salts

- Electrophilic Substitution reactions with diazonium salts **without loss of N_2 : diazo coupling**

  → reaction with compounds containing strongly activating substituents groups : amines and phenols → **azobenzenes**



Butter yellow
Azo dye



9.3 Aniline

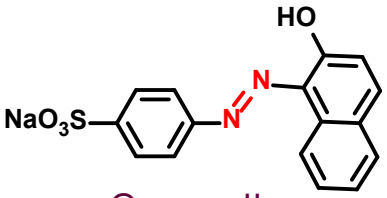
d) Reactions of diazonium salts

- Electrophilic Substitution reactions with diazonium salts **without loss of N_2 : diazo coupling**

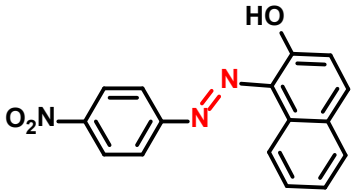
9.3 Aniline

d) Reactions of diazonium salts

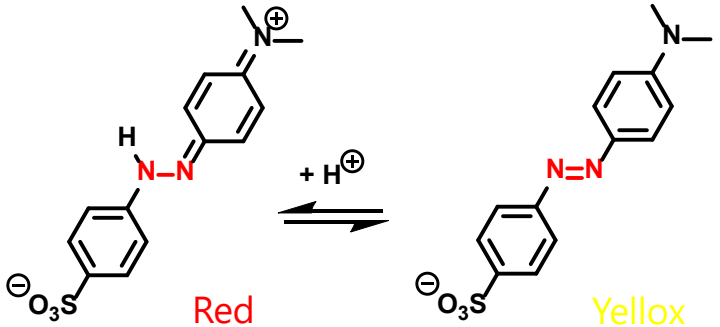
- Electrophilic Substitution reactions with diazonium salts **without loss of N_2 : diazo coupling**



Orange II



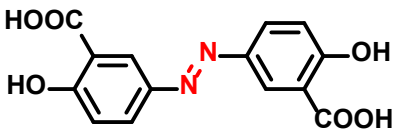
Para Red



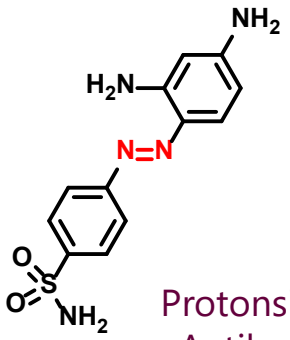
Red
(pH<3,1)

Yellox
(pH> 4,4)

Methyl orange



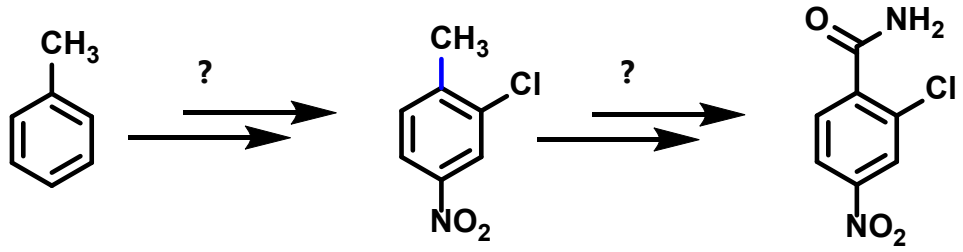
Olsalazine
Anti-inflammatory
Inflammatory bowel disease



Protonsil, 1931
Antibacterial

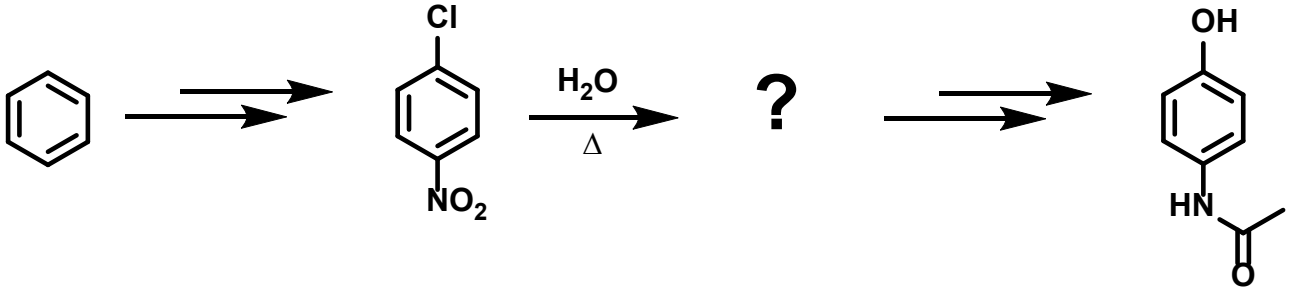
10. Exercices

1)



Aklomide

2)



Paracetamol