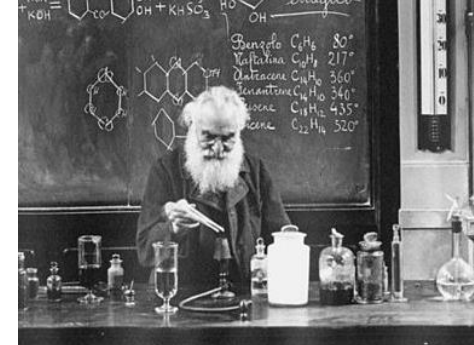
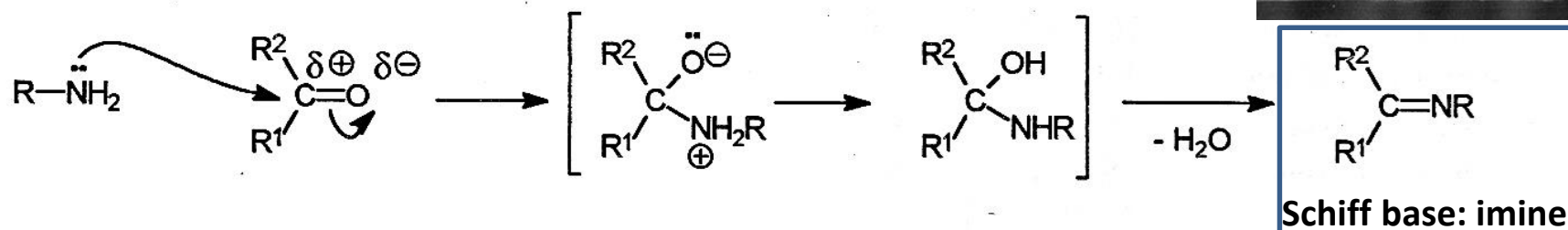


## Chemical properties of amines 6.



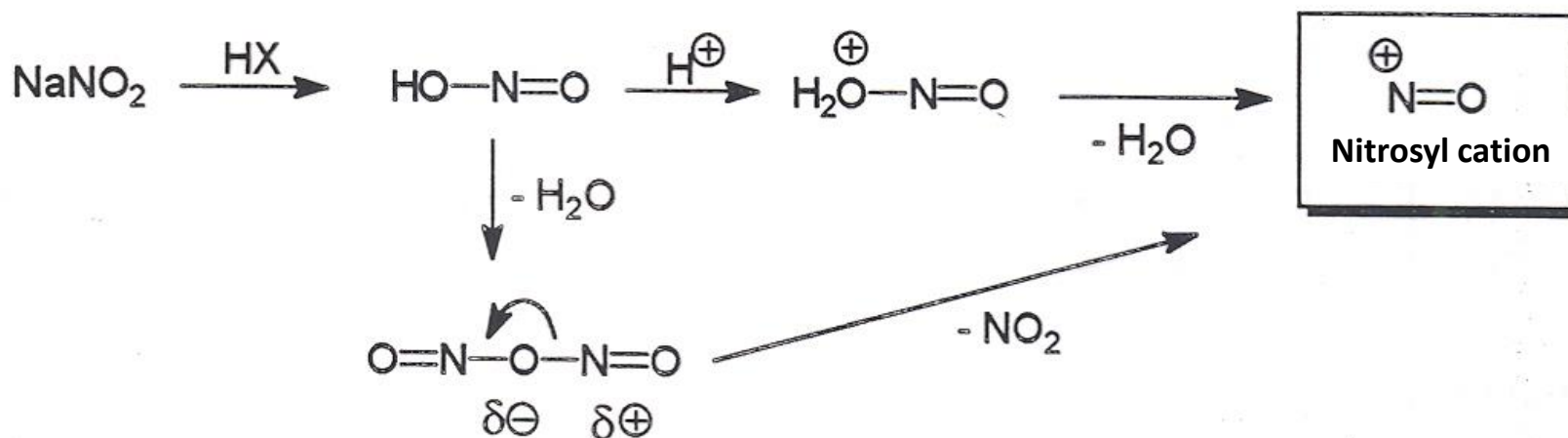
### 5. Reaction with oxo compounds

Primary amines can attack on  $sp^2$  electrophilic C



Condensation reaction – Ad + E = Condensation  
difference to acylation: no leaving group, different elimination (E) step

### 6. Reaction with nitrous acid --- Generation of electrophile - $^+\text{NO}$

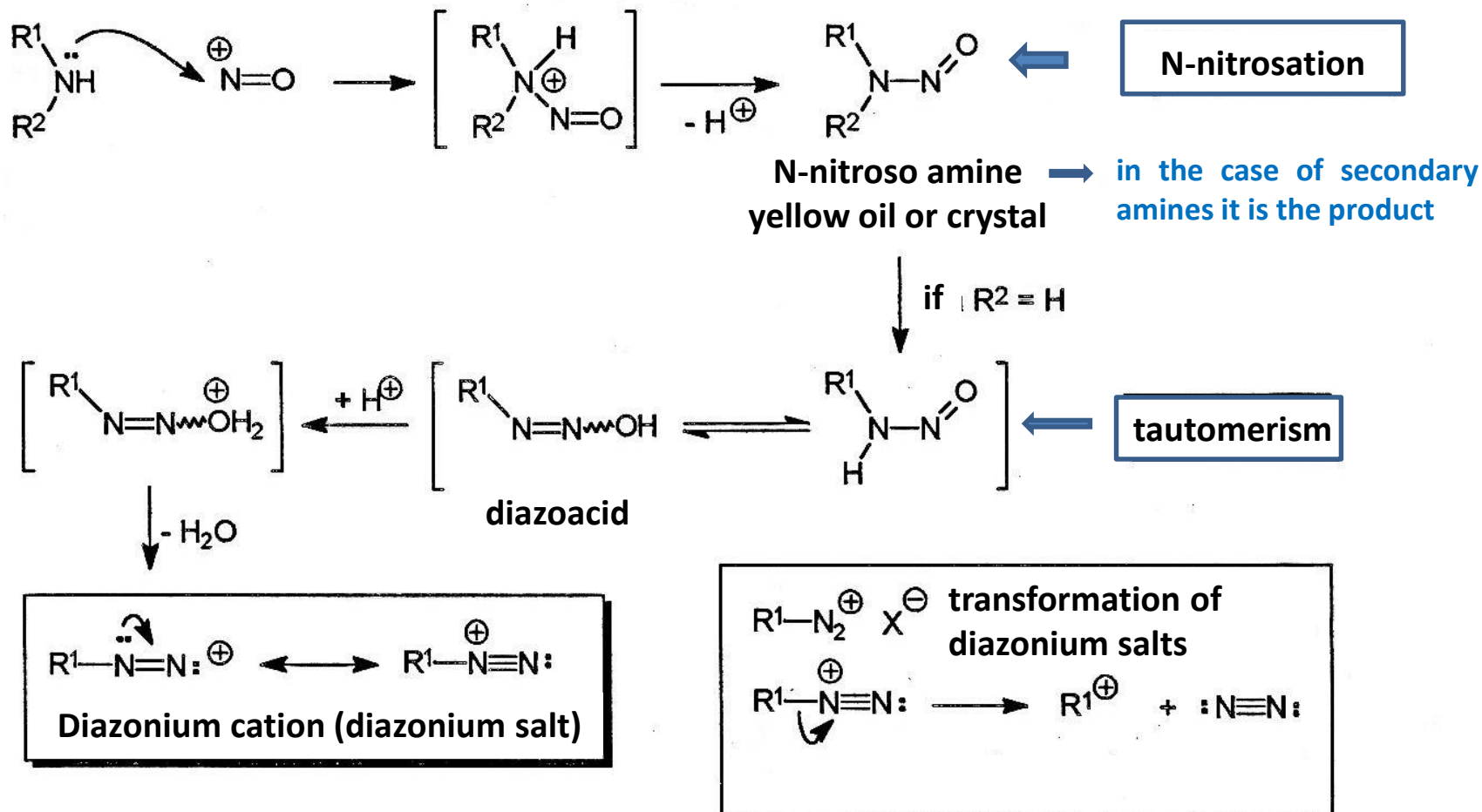


Reaction with different amines →

## Chemical properties of amines 7.

### Reaction of primary and secondary amines with nitrous acid

#### Mechanism



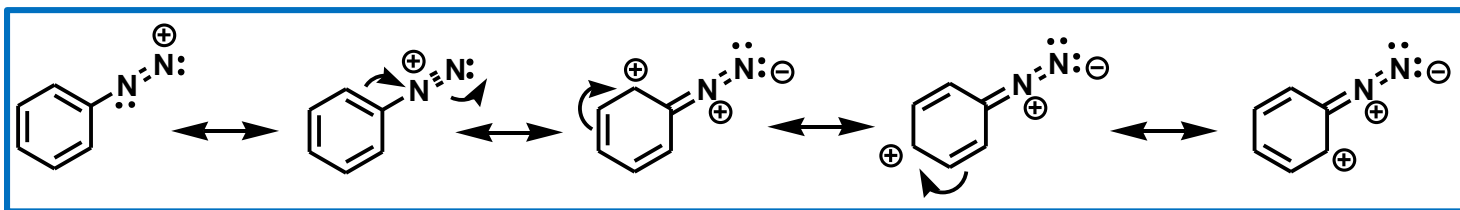
# Reaction of primary, secondary and tertiary amines with nitrous acid

## Primary amines (Properties of diazonium salts)

- Aliphatic primary amines – yield aliphatic diazonium salts. Alkyl diazonium salts are very unstable and yield carbocation-derived products (rapid spontaneous decomposition even at low temperature carbocations are formed by losing nitrogen) generally little practical importance
- Aromatic primary amines – arenediazonium salts are stable at low temperature (0-5 ° C) in aqueous solutions, they are of considerable synthetic importance because the diazonium group can be replaced by a variety of other functional groups (synthetic applications of aromatic diazonium salts see later) **BUT! In solid, dry form it is unstable!**

Resonance structures

8 centred, 10 electrons:  
delocalized system

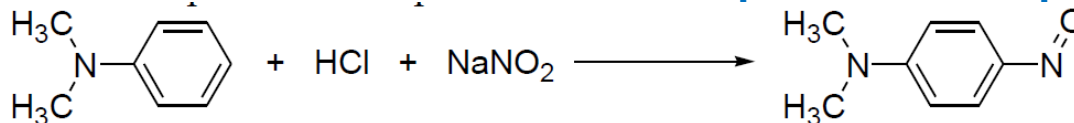


## Secondary amines – stable N-nitroso compounds

**Tertiary amines** – tertiary *aliphatic amines*: possibility of proton loss is missing, there is no effective reaction. Actually very slow C-N bond cleavage



– tertiary *arylamines* react with nitrous acid to form C-nitroso aromatic compounds. Nitrosation takes place almost exclusively at the para position if it is open and, if not, at the ortho position. The reaction is an example of electrophilic aromatic substitution:



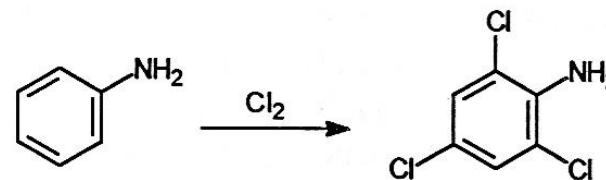
## Chemical properties of amines 8.

### 7. Reaction of aromatic ring of aniline derivatives – $\text{ArS}_E$

$-\text{NH}_2, -\text{NHR}, -\text{NR}_2$   $|+M| > |-I|$ , I. order, activating agent

#### Similarity to phenols:

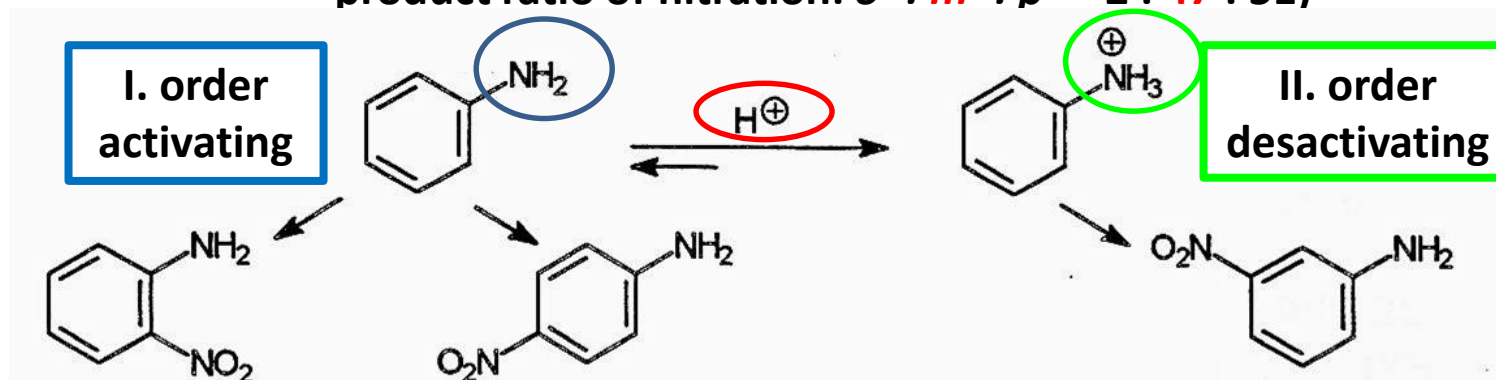
- Reaction with weak electrophiles
- Reaction without catalyst
- Polysubstitution



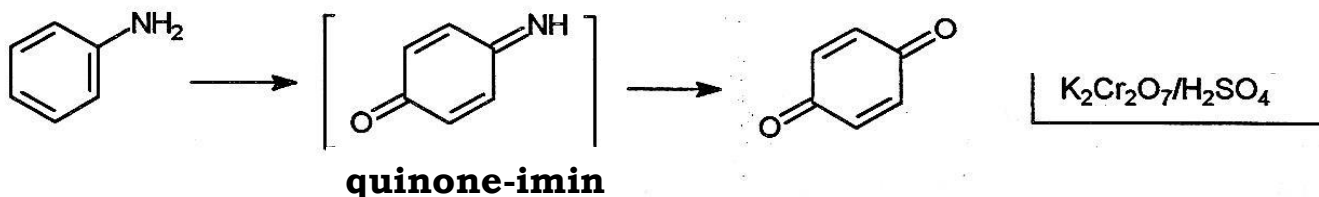
In  $\text{CHCl}_3$  solution too!

The amino group can be protonated --- **changed directing effect!!!**

product ratio of nitration:  $o- : m- : p- = 2 : 47 : 51$

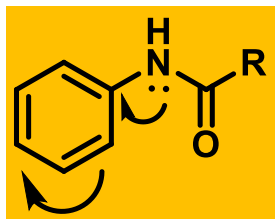


Oxidation of aromatic amines: similar than phenols



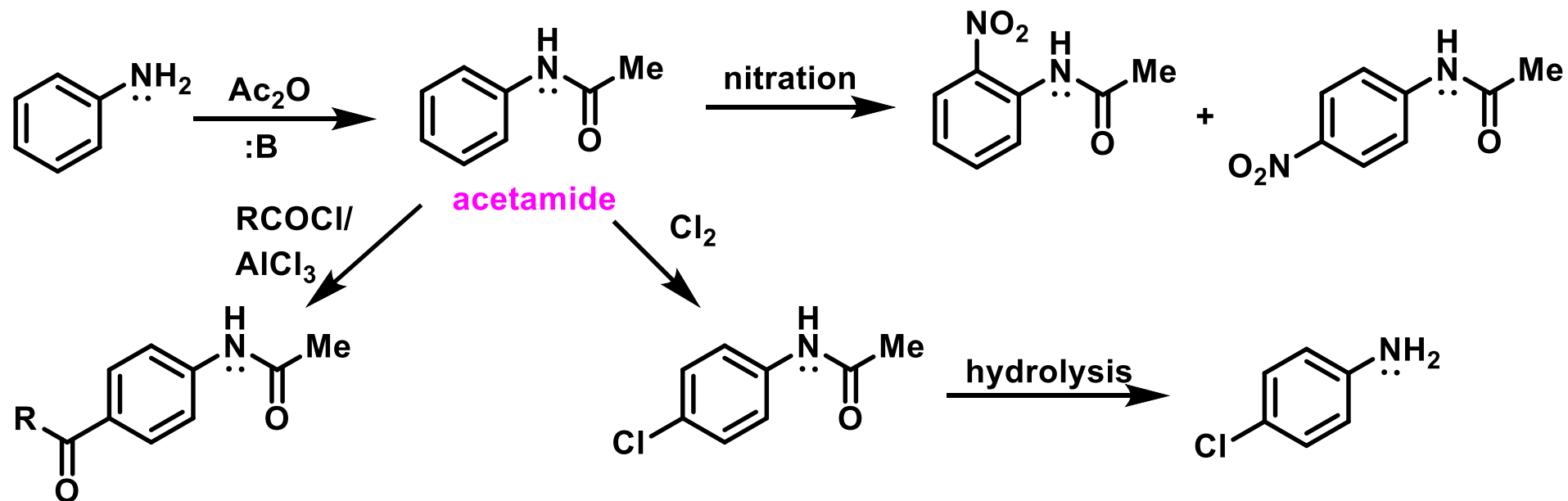
## Chemical properties of amines 9.

To avoid protonation and oxidation – protecting groups needed (eg. acylation, acetylation)



Similar + M effect as amino group  $\Rightarrow$  **RCONH** I. order (o/p) activation effect

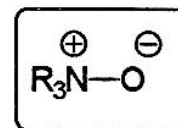
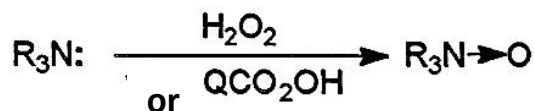
About **amide nitrogen**: it is not basic so no protonation and no sensitivity toward oxidation



## 8. Oxidation of anilines

General characteristics: due to the high electron density easy oxidizability (oxidation = electron release !!), but a wide variety of concurrent reaction  $\Rightarrow$  little synthetic value

Exception: tertiary amines

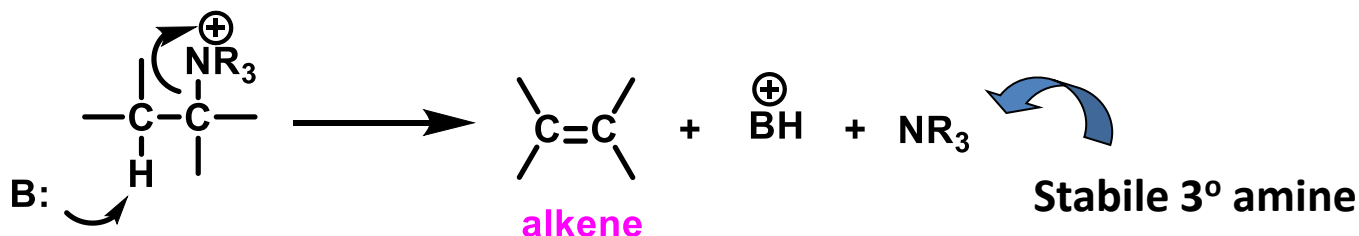


See the oxidation of aromatic amines (formerly)

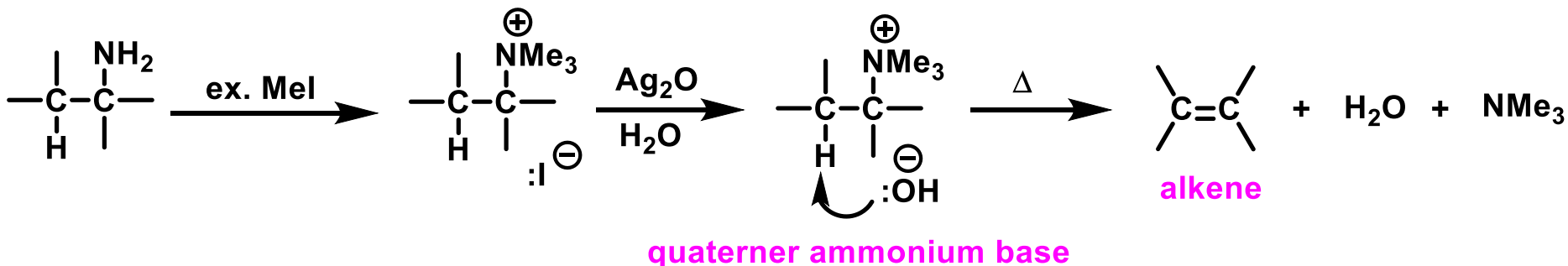
## Chemical properties of amines 10.

### 9. Elimination

Similarity to alcohols.  $\text{NH}_2/\text{NHR}/\text{NR}_2$  bad leaving groups, **BUT** transformed to cations it turns into a good leaving group (see acid catalysed dehydration of alcohols). In case of amines: **stable, isolable cations** –mostly 4° ammonium compounds



Specific application: Hofmann's "exhaustive methylation" and Hofmann elimination

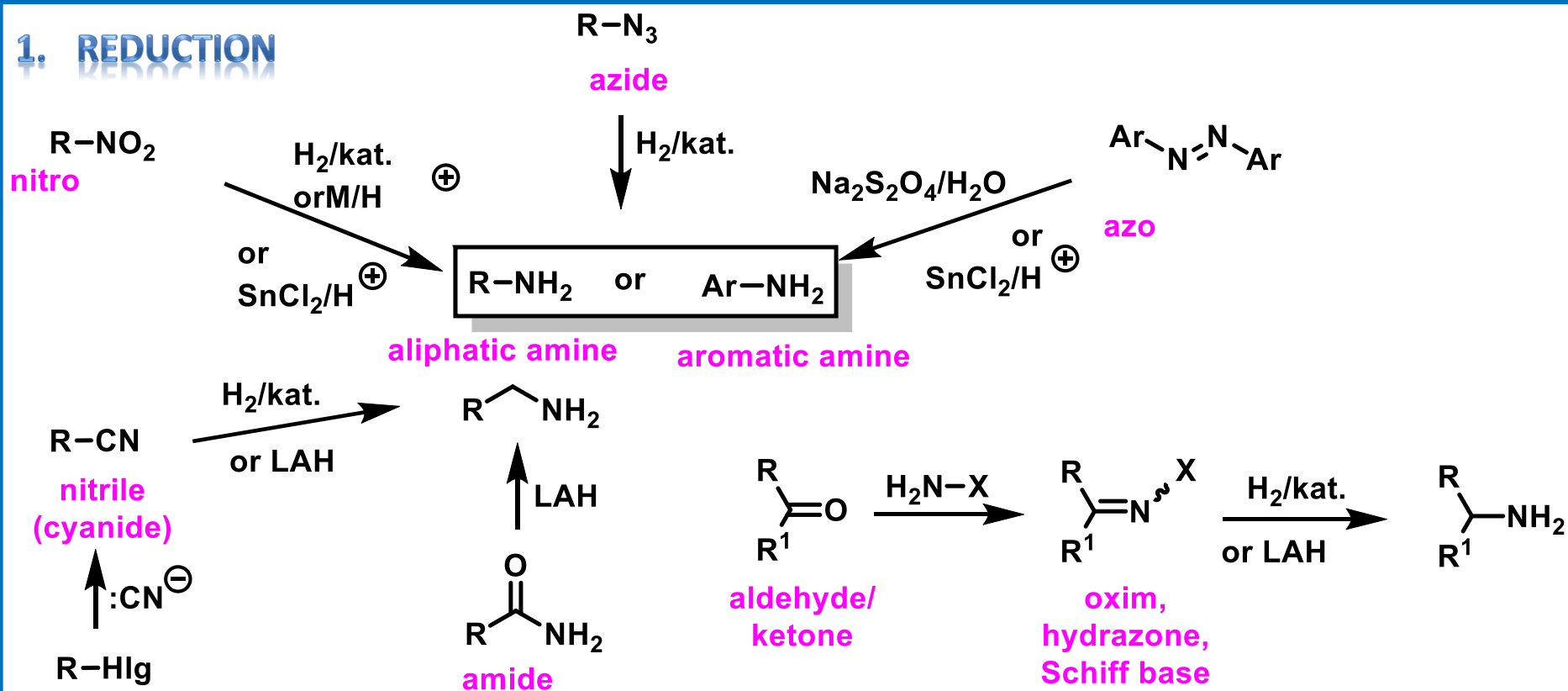


**Note:** The product with lower thermodynamic stability is favoured (less hydrocarbon group attached to the double bond (less highly substituted double bond)). So-called **Hofmann product**.

This is the **opposite orientation than** the base-induced 1,2-elimination of alkyl halides - or acid catalysed 1,2-elimination of alcohols (**Zaitsev's rule**).

# Preparation of amines

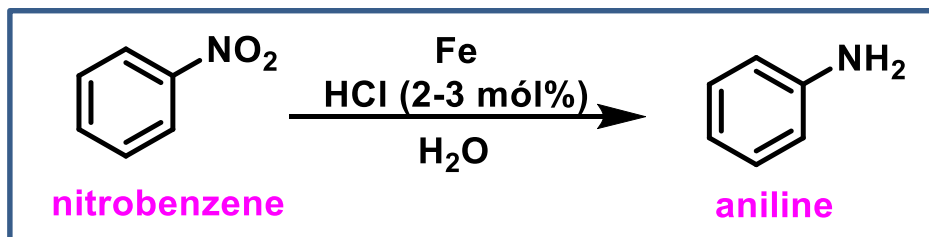
## 1. REDUCTION



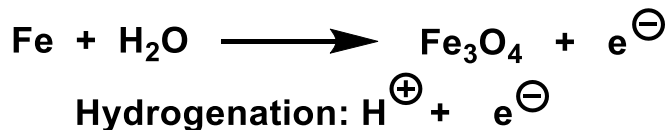
## Béchamp-reduction



Antoine Béchamp



In detail:



Nowadays:  $H_2/kat.$

World aniline consumption: ~ 4Mt

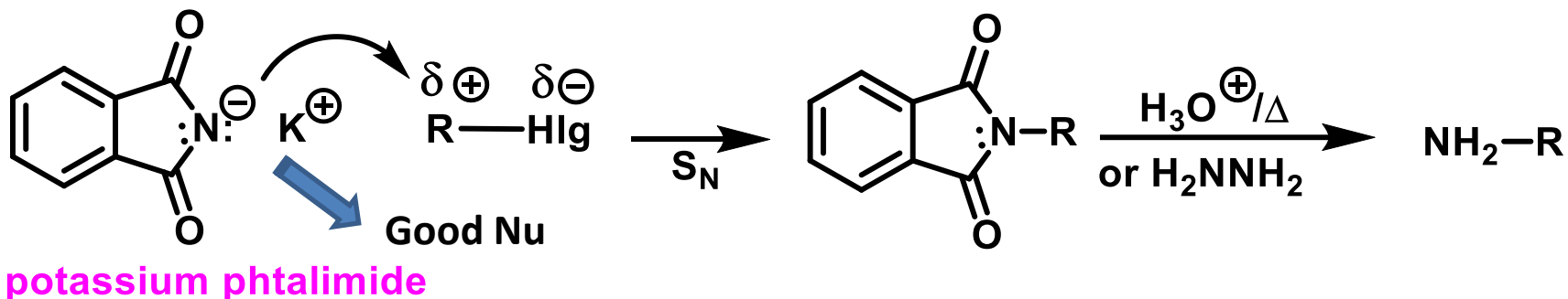
For 2015: 6.2 Mt

## Preparation of amines 2.

### 2. Nucleophile substitution

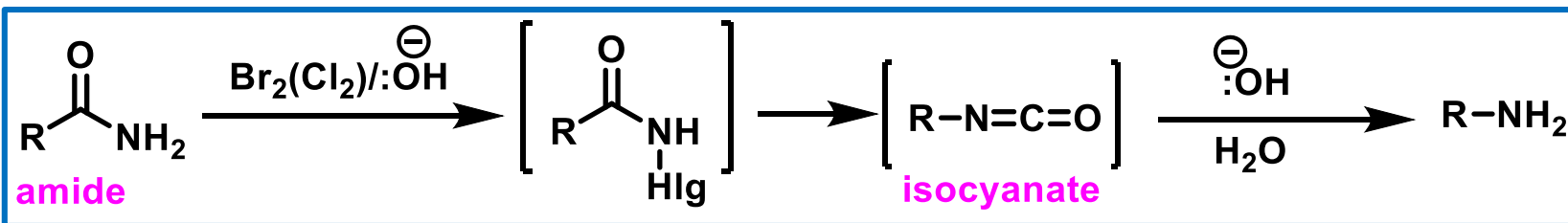
#### Gabriel's synthesis

You know:  $R-Hlg + NH_3$  gives the mixture of products

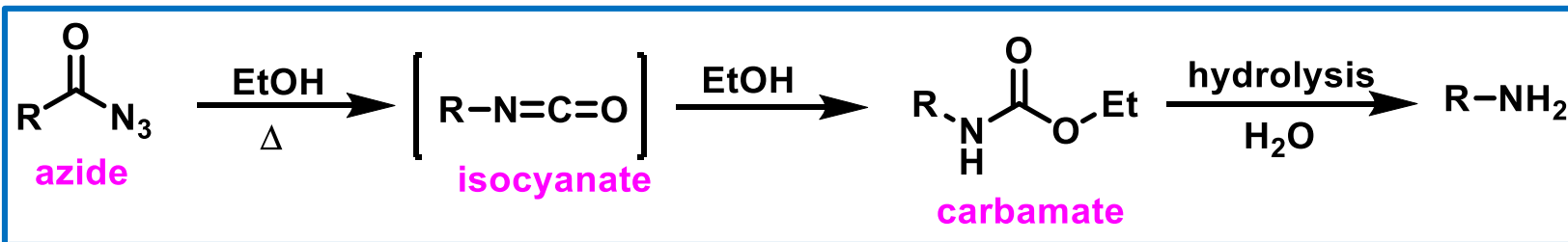


### 3. Degradation methods

Feature: 1 carbon shorter chain ----- Hofmann rearrangement



Curtius rearrangement - similar to the Hofmann rearrangement, the same isocyanate intermediate

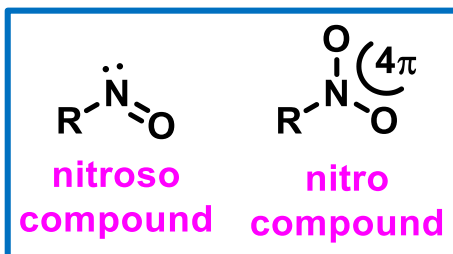




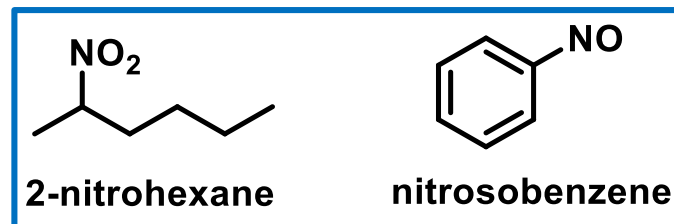
**Characterization of other compounds containing a CN single bond. Nitro compounds, nitro bonding system, the interpretation of electron-withdrawing effect, CH acidity. Preparation of nitro compounds. Preparation of diazonium salts, aromatic diazonium salts and their reactions and practical significance. Industrial significance of azo compounds.**

# Characterization of the most important compounds containing CN = X bond

## 1. Nitroso- and nitro compounds



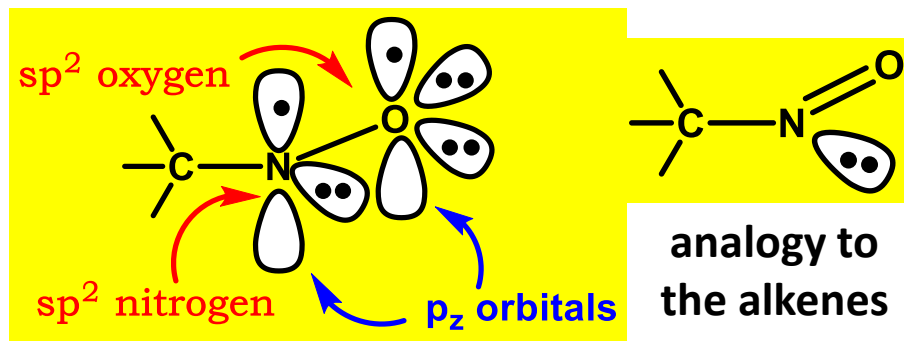
Substitution nomenclature,  
nitroso / nitro prefix (can  
only be specified as a prefix!



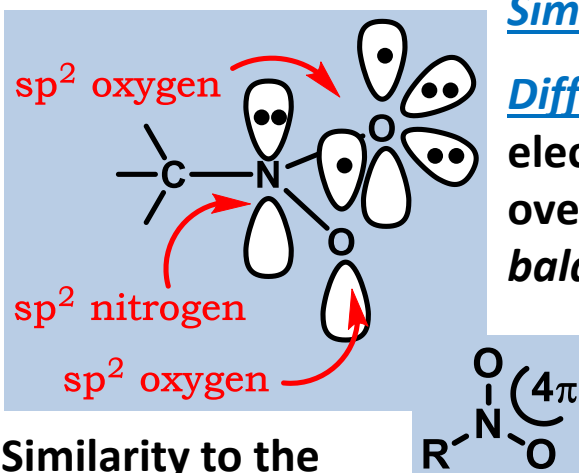
### Bonding system

#### - nitroso

$\text{sp}^2$ -hybridized nitrogen, non-bonding electron pair on the hybrid orbitals, unpaired electron in the  $\text{p}_z$  orbital



#### - nitro compounds

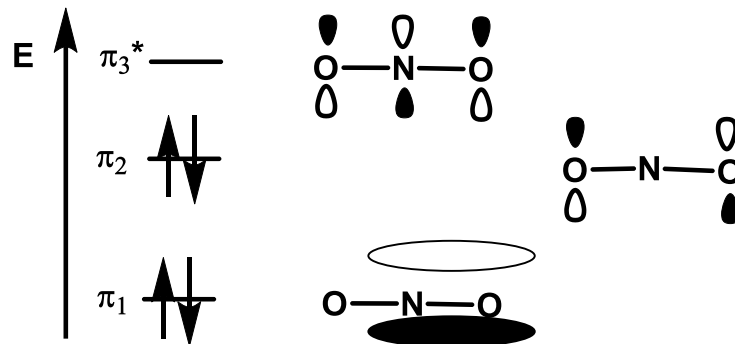


**Similarity:** both N and O  $\text{sp}^2$  hybridized

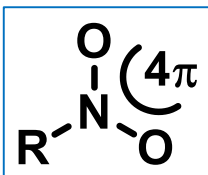
**Difference:**  $\sigma$ -skeleton built up from hybrid orbitals, a non-bonding electron pair of N exist on  $\text{p}_z$  orbitals  $\Rightarrow$  three neighbouring and overlapping  $\text{p}_z$  orbitals, four electrons - three-center bond, *fully balanced electronic structure*

Similarity to the  
carboxylate, (see later)

LCAO-MO: 3 AO  $\rightarrow$  3 MO  
growing number of nodes



## Nitro and nitroso compounds 2.



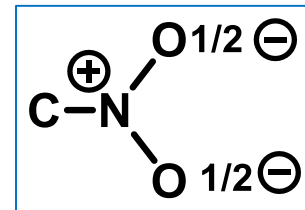
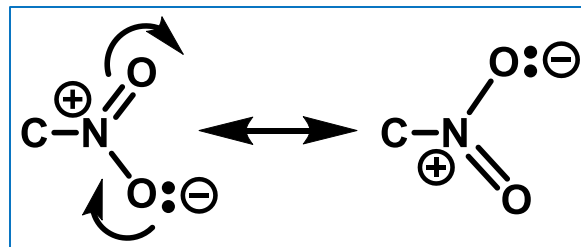
Three-center bond consequence: smooth electron distribution both on the oxygen and the nitrogen 4/3 electron

Compared to the initial state of **N charge deficiency ( $\delta^+$ )**, **O: excess charge ( $\delta^-$ )**.

This is reinforced by the EN difference!

Representation *via* resonance forms: two equivalent resonance structures!

**Two equivalent oxygens !!**



### Evidence:

- planar structure
- same NO bond distances (0.122 nm, cf.  $d(\text{NO}) = 0.136 \text{ nm}$ ,  $d(\text{N}, \text{O}) = 0.115 \text{ nm}$ ), bonding order between 1 and 2!
- O-N-O bond angle,  $126^\circ$
- large dipole moment ( $\mu = 3.5\text{-}4 \text{ D}$ )

### Consequence:

**$\text{NO}_2$  group is strongly electron-withdrawing** (due to -I and empty  $p_z$ -M effects). Attached to an aromatic ring it is a II. order, deactivating substituent (see Fig. above) Because of the empty  $p_z$  orbital the neighbouring negative charge is stabilized (mesomeric stabilization)

## Physical properties of nitro compounds

### High melting and boiling point

Cause: zwitterion structure, strong dipole-dipole interactions

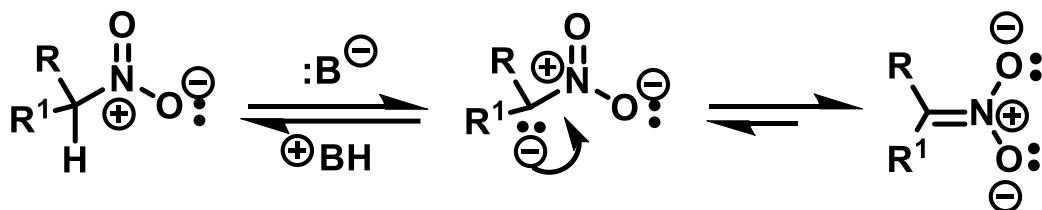
**Poor solubility in water** - because of the strong association it does not have any hydration energy gains, remains the original H-bridge and dipole-dipole-stabilized structure

Comp.	Mw	Bp ( $^\circ\text{C}$ )
$\text{MeNO}_2$	61	101
$\text{MeONO}$	61	-12
$\text{Me}_2\text{CO}$	58	56
$\text{MeCl}$	49	-24

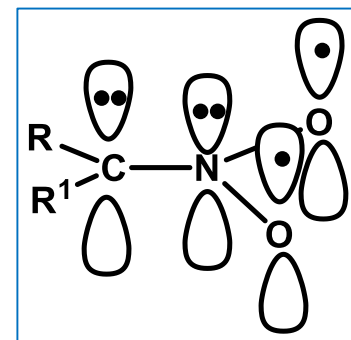
# Nitro and nitroso compounds 3.

## Chemical properties of nitro compounds

### 1. Acidity of aliphatic nitro compounds - deprotonation at $\alpha$ -position, CH acidity



LCAO MO: 4 centred, six electrons: delocalized system

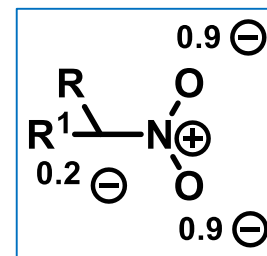


$\text{pK}_a = 7.7 - 10$  ( $\text{EtNO}_2 = 8.5$ )!!

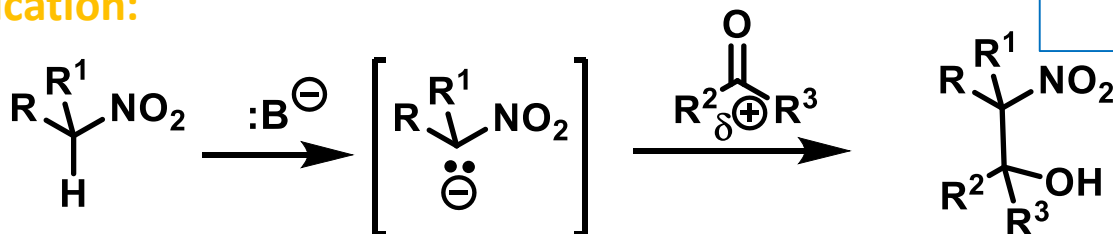
Consequence: **alkali solubility**

**Application:**

Resonance stabilized anion  
Actual charge distribution:



Most of the charge on the oxygen: a proof is the deprotonation



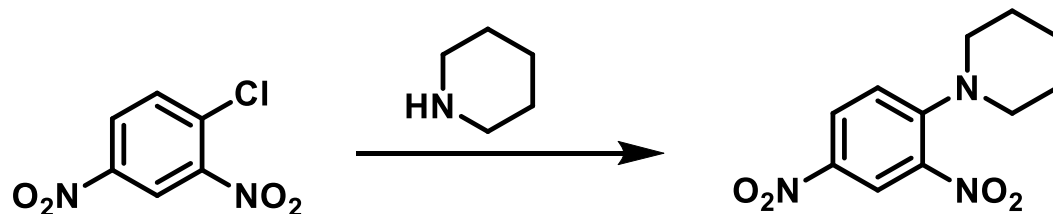
**Henry reaction**

It is generally true: nitro alkanes containing hydrogen in  $\alpha$ -position can be easily substituted in  $\alpha$ - position (bromination, nitration, etc.).

### 2. Reduction of nitro group – to aliphatic/aromatic amines (see earlier)

### 3. Aromatic nitro compounds – difficult SE reaction, a $\text{NO}_2$ group is a II. order desactivating substituent

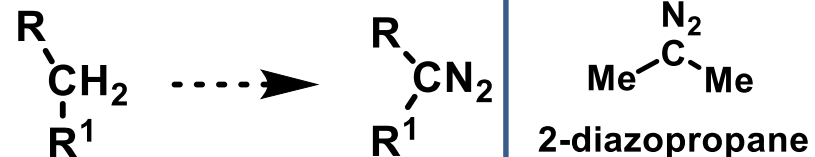
**BUT!  $\text{S}_\text{N}$  reaction of aryl halides** containing nitro groups is easier (see earlier) - Meisenheimer complex!



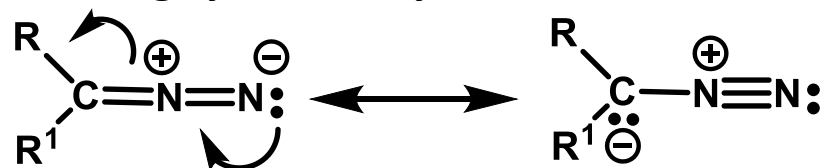
# Diazo compounds

Formally alkene derivatives - see. nomenclature

Substitution ~ diazo prefix



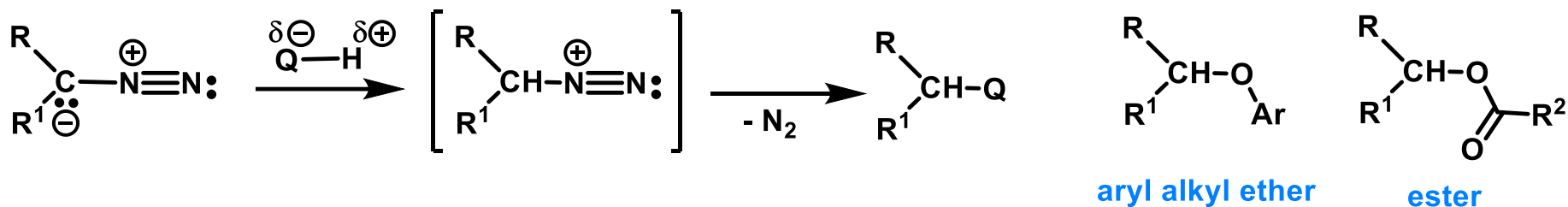
Bonding system: only resonance structures, there is no classical Lewis-Langmuir formula



LCAO-MO description: Three centred bond with four electrons

Its reactions can be derived from its resonance structure

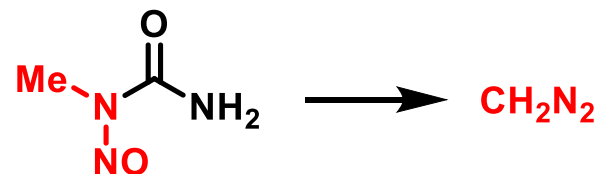
1. Reaction with strongly acidic hydrogen results nitrogen elimination - alkylation / methylation (diazomethane)



Phenols, carboxylic acids: their selective methylation is easy - alcohols do not react

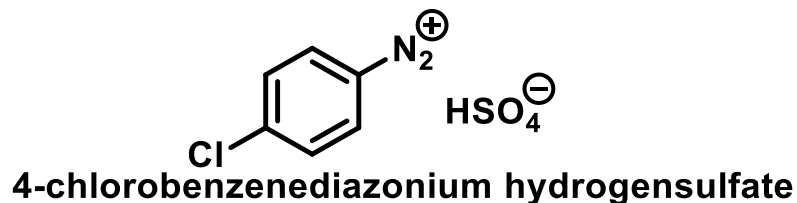
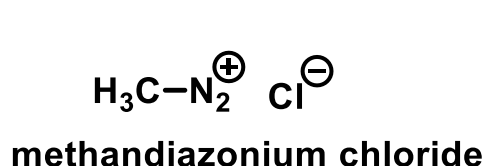
2. In 1,3-dipolar cycloaddition reactions reacts as a dipole (see later)

Preparation of diazo compounds: alkaline cleavage of N-nitroso ureas; *in situ* generation

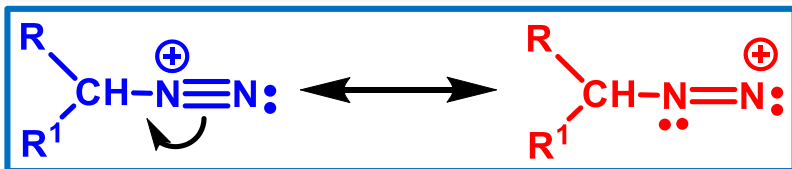


## Diazonium salts

Primarily substitution nomenclature - the main cation  $\Rightarrow$  name of the hydrocarbon group + diazonium suffix + name of counter ion



Formal derivation from diazo compounds – by removal of an electron (also described by resonance structural forms). Preparation (see earlier).

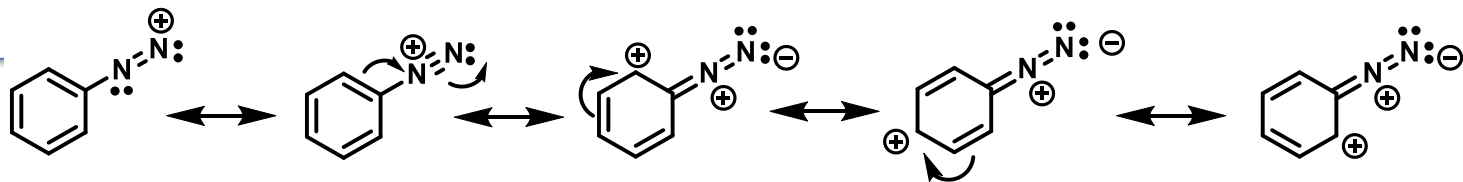


Reactivity derived from resonance structure

1. Reactions with nitrogen loss
2. N electrophile

Aryl diazonium ions are considerably more stable than their alkyl counterparts.

Whereas alkyl diazonium ions decompose under the conditions of their formation, aryl diazonium salts are stable enough to be stored in aqueous solution at 0–5°C for reasonable periods of time. Loss of nitrogen from an aryl diazonium ion generates an unstable aryl cation and is much slower than loss of nitrogen from an alkyl diazonium ion. **Stability is due to: interaction with the aromatic electron system (8-center, 10-electron bonding system and 5 resonance structures)**

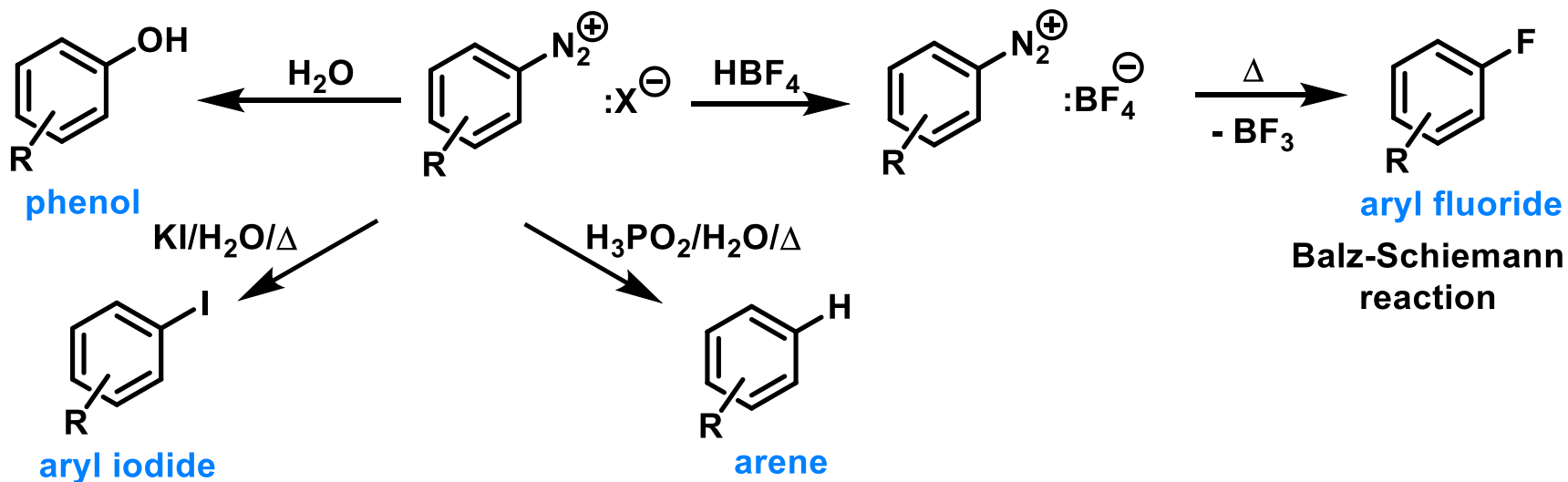


## Diazonium salts 2.

### 1. Reactions involving nitrogen departure (replacement, substitution)

Aryl diazonium ions undergo a variety of reactions that make them versatile intermediates for the preparation of a host of ring-substituted aromatic compounds. In these reactions molecular nitrogen acts as a leaving group and is replaced by another atom or group. All the reactions are regiospecific; the entering group becomes bonded to precisely the ring position from which nitrogen departs.

#### 1.1. Non-catalyzed reactions

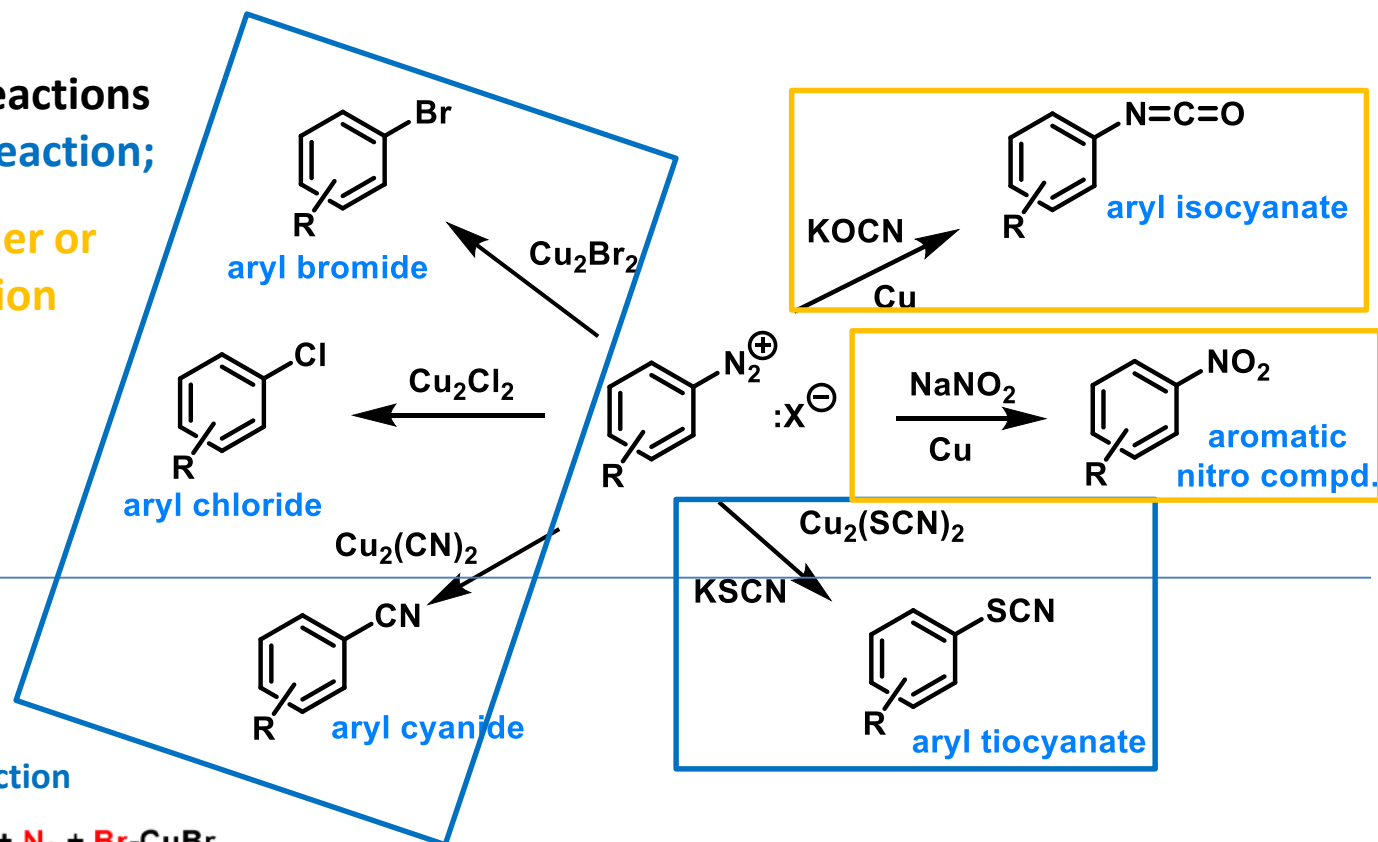


## Diazonium salts 3.

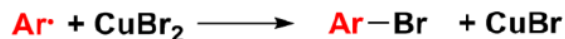
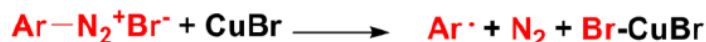
### 1.2. Copper catalyzed reactions

**Cu (I) salt: Sandmeyer reaction;**

**activated copper (powder or alloy): Gatterman reaction**



#### Mechanism of Sandmeyer reaction



The value of diazonium salts in synthetic organic chemistry rests on two main points. Through the use of diazonium salt chemistry:

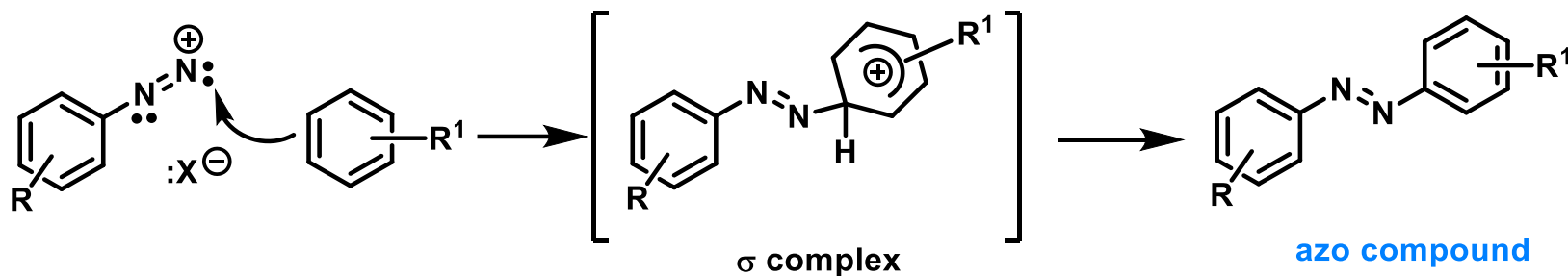
1. Substituents that are otherwise accessible only with difficulty, such as fluoro, iodo, cyano, and hydroxyl, may be introduced onto a benzene ring.
2. Compounds that have substitution patterns not directly available by electrophilic aromatic substitution can be prepared.



## Diazonium salts 4.

### 2. Reactions without nitrogen departure - N-electrophilic attack to a nucleophile

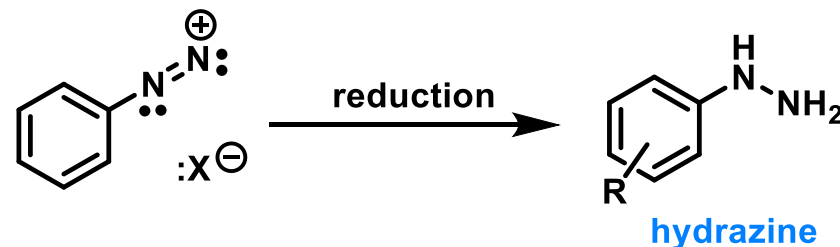
Practical significance: azo coupling -  $S_EAr$  reaction !! (The nitrogens of an aryl diazonium salt are retained on reaction with e.g. the electron-rich ring of a phenol. Azo coupling occurs.)



BUT! diazonium salt is a weak electrophile  $\rightarrow$  **strongly activated aromatic reactant required**  
(R = electron-withdrawing,  $R^1$  = electron-donating = OH,  $NH_2$ )

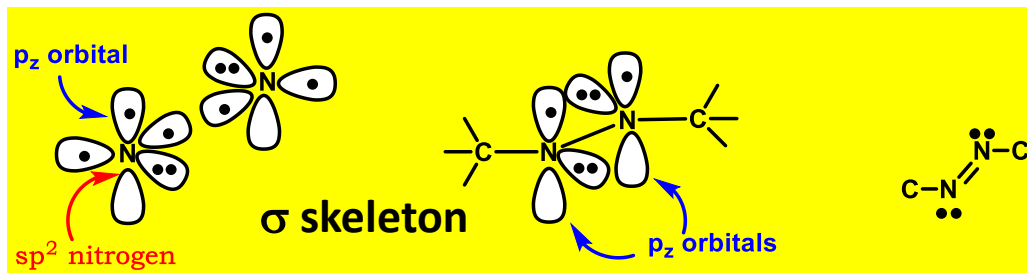
Typically, para substituted product is formed

**A further reaction without nitrogen departure- reduction to aryl hydrazine**



## Azo compounds

Bonding system: Classic  $\sigma + \pi$  bond  $sp^2$  hybridized pillar N atoms ("pyridine-type" nitrogens)



Complete analogy to alkenes  
- diastereomers exist in the same way

## Azo compounds 2.

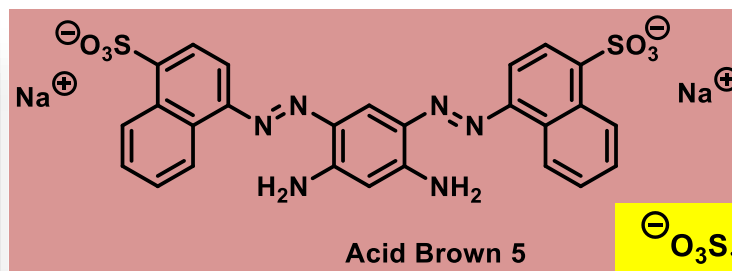
Practical significance of azo compounds: conjugated electron system, light absorption in the visible region  $\Rightarrow$  **COLOR!**

(if exists an appropriate binding these can be used as **textile dye!**)

An important aspect of using **different substituents** the colour is tuneable.



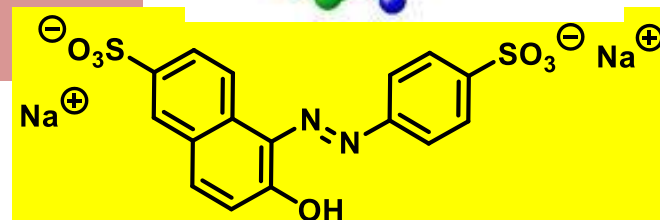
Mordant red 19



Acid Brown 5



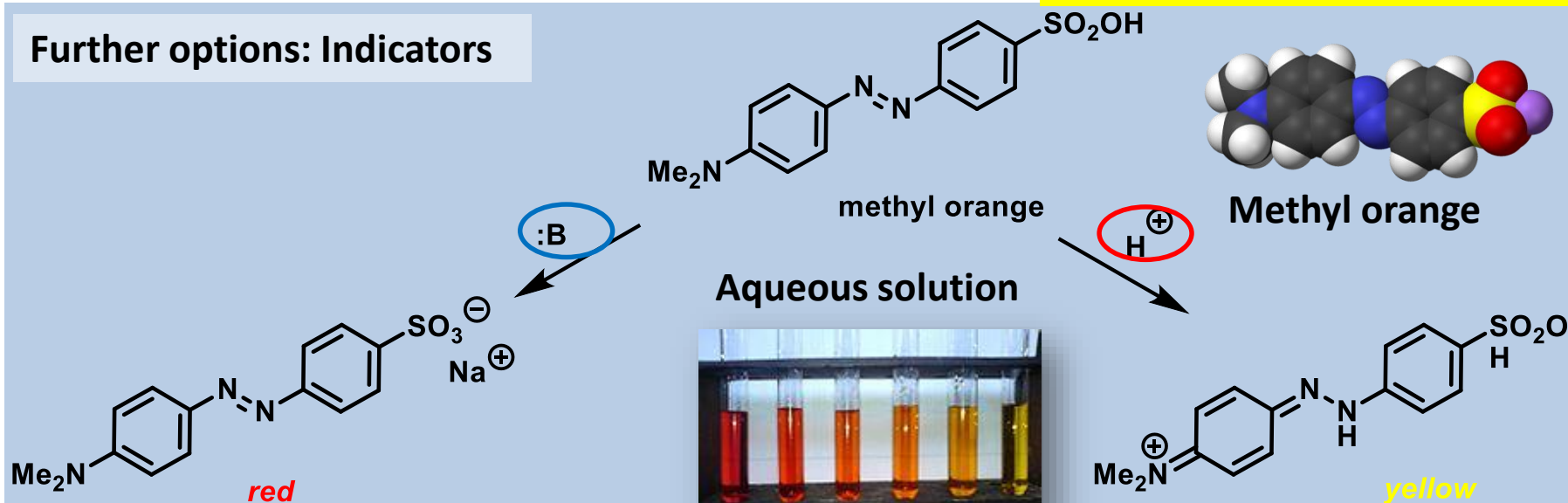
Yellow 6



yellow 6 (orange yellow, E110)

Further options: food colouring

Further options: Indicators



### Azo compounds 3.

Transformation of azo compounds – reduction of N=N double bond

