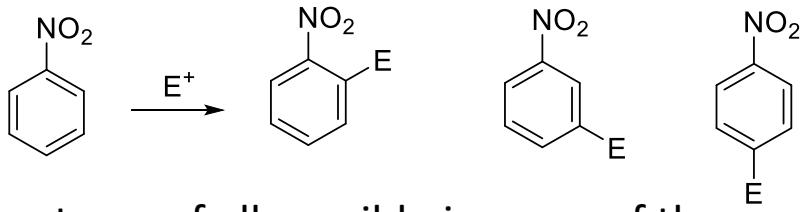
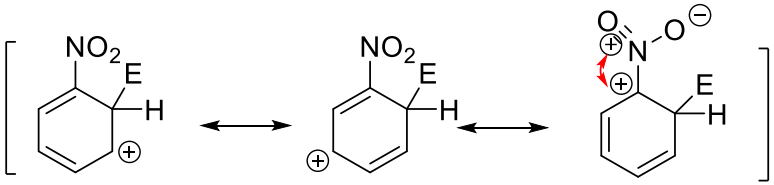
1.2.3. Secondary substitution on the benzene ring

π-acceptors: all positions are deactivated as electron density of the ring is decreased



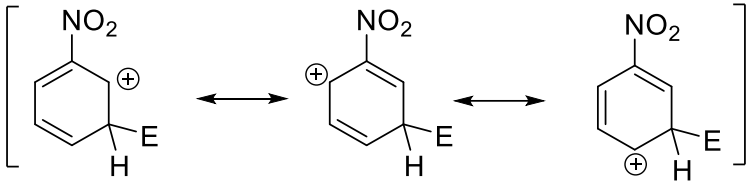
Mesomeric structures of all possible isomers of the σ-complex:

ortho



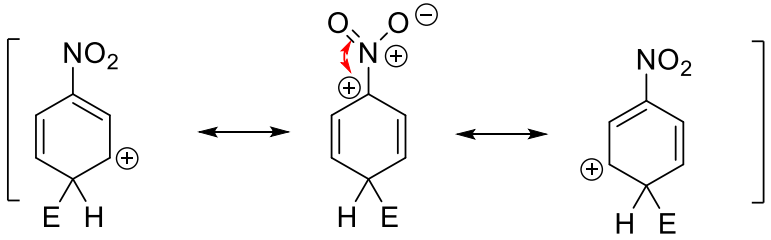
charge repulsion
not a good mesomeric structure

meta



no charge repulsion

para



charge repulsion
not a good mesomeric structure

-M: slows the reaction down and directs meta

1.2.3. Secondary substitution on the benzene ring

• What happen in a formally contradicting case?
(substituent with –I and +M or with +I and –M)

- Generally the M-effect dominates I-effect
- Quantitative assessment with the Hammet equation

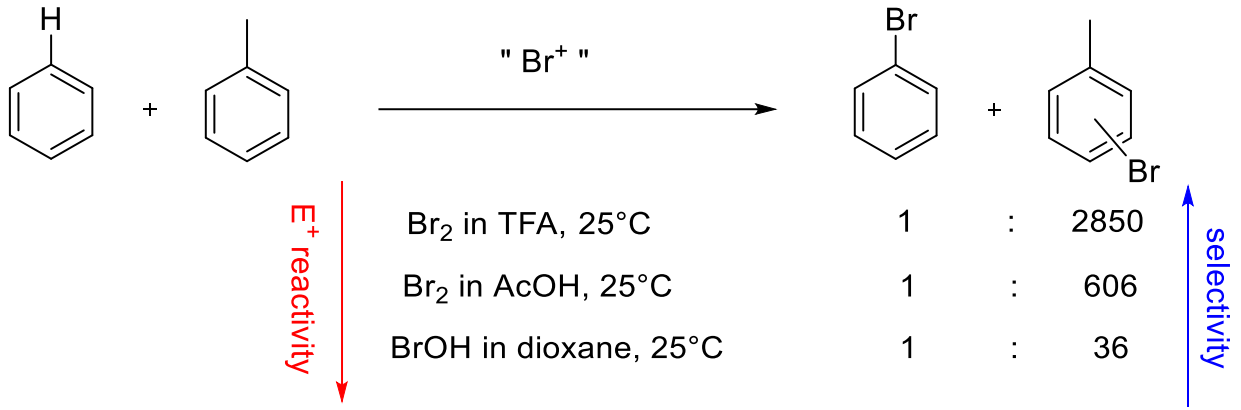
• Special case: halogens –Cl and –Br which have a –I and +M effect

- The reaction rate decrase: -I shows its influence
- ortho and para directing: +M shows its influence

1.2.3. Secondary substitution on the benzene ring

- Selectivity vs reactivity:

For the same substrate combinations, the reaction outcome is influenced by the choice of the reagents:

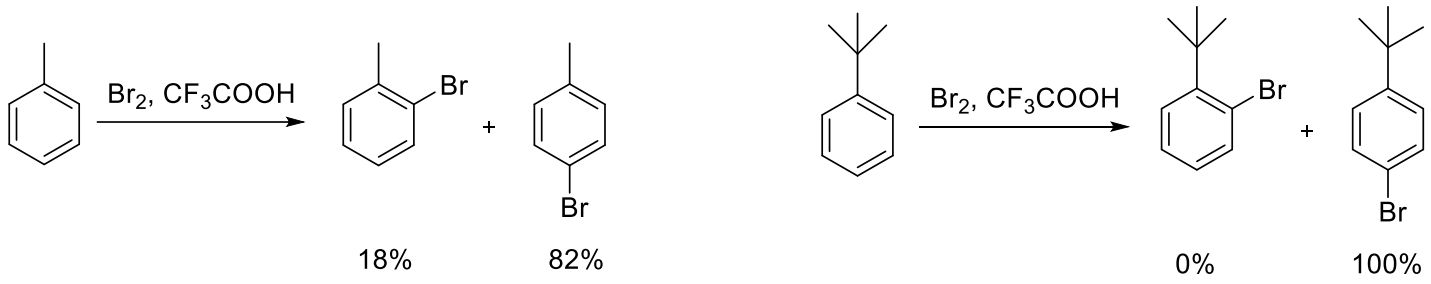


<u>Very general principle</u>:
the higher the reactivity of a reagent, the lower its selectivity is.
→ need to adapt it accordingly to the substrate

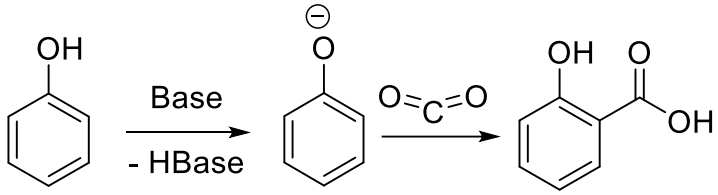
1.2.3. Secondary substitution on the benzene ring

- Ratio of ortho and para products:

1) Ortho is favored by statistics by a factor of 2
2) The para position is often preferred for sterical reasons

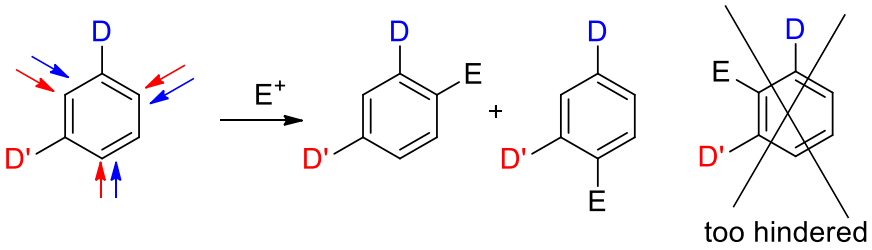


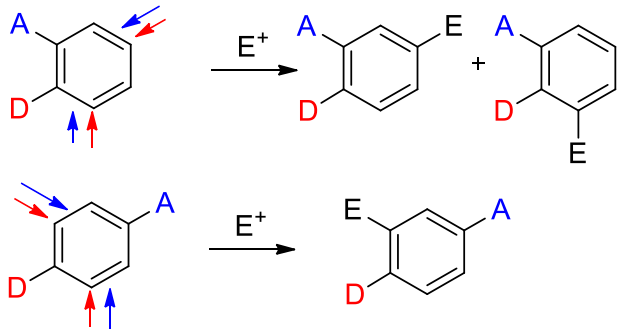
3) Coordination and directing groups can lead to a selective ortho substitution



1.2.4. Introducing a 3rd substituent

• Two substituents enhance their effects if directing in the same sense:



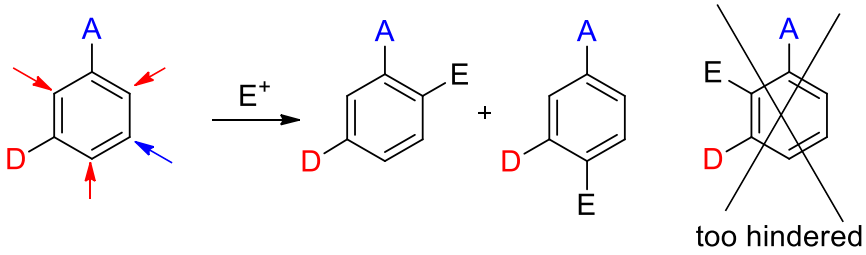


No substitution in bis-ortho position

• Case with EDG and EWG substituents: stronger subtituent wins and decides on the position

M-effects dominate I-effects

Most often activating effects are stronger than deactivating effects (-M)



1.3. Quantitative Substitution Effects

- The Hammett equation: quantitative measurement of substitution effect

$$\log \frac{K_X}{K_H} = \rho\,\sigma$$

K_H: reaction rate for the unsubstituted aromatic compound

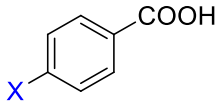
K_X reaction rate for X substituted aromatic compound

σ: substitution parameter (changes with X)

ρ: reaction parameter (changes with the reaction)

–σ-values:

Characteristic for the individual substituent



X = H: σ = 0

X = EDG: σ < 0

X = EWG: σ > 0

Its position is important (different values for a substituent in the o-, m- or p-position)

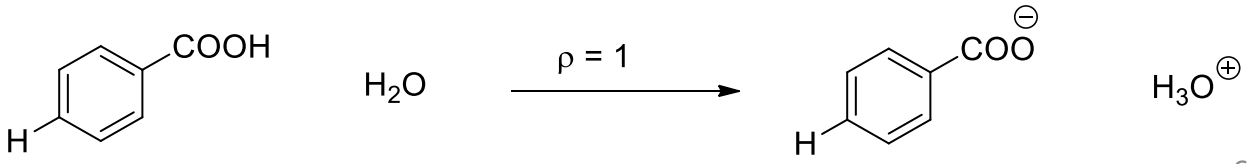
–ρ-values:

ρ>0: a negative charge is developing in the transition state

ρ=0: rare case where the reaction rate is not influenced by substitution

ρ<0: a positive charge is developing in the transition state

-Standardized reaction:



1.3. Quantitative Substitution Effects

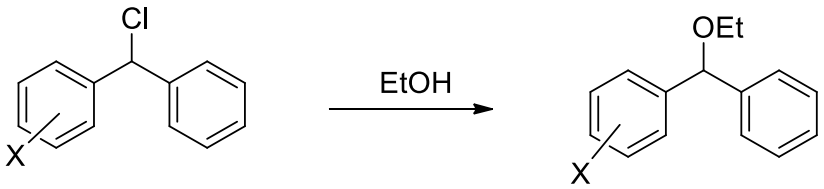
- Valuable information that can be obtained from the Hammett equation:

1) A known reaction (ρ known) can be used to determine the donor or acceptor properties of an unknown substituent X: measure its σ value.

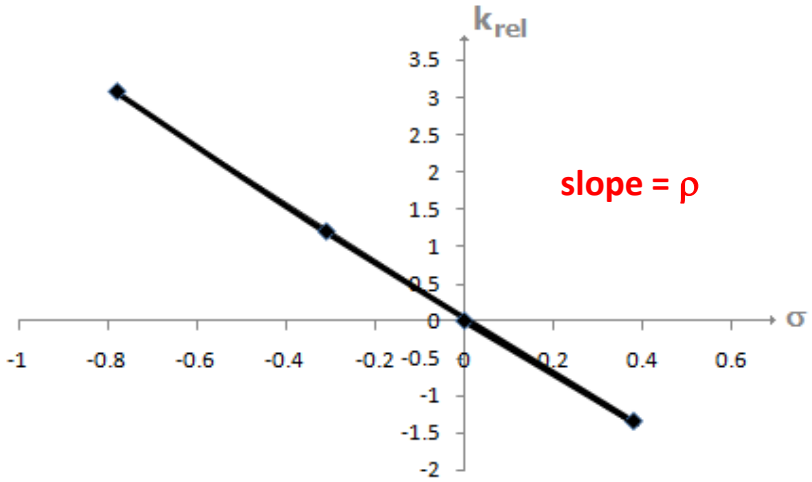
2) Investigate the mechanism of an unknown reaction (ρ unknown): with several known substituents (σ given) measure the ρ value of the reaction and draw conclusion on the charge in the transition state.

1.3. Quantitative Substitution Effects

- Example for the Hammett equation: solvolysis reaction



X	H	p-Cl	p-Me	p-OMe
σ	0	0.38	-0.31	-0.78
K_{rel}	1	0.045	16.2	1200
$Log(K_{rel})$	0	-1.35	1.2	3.08



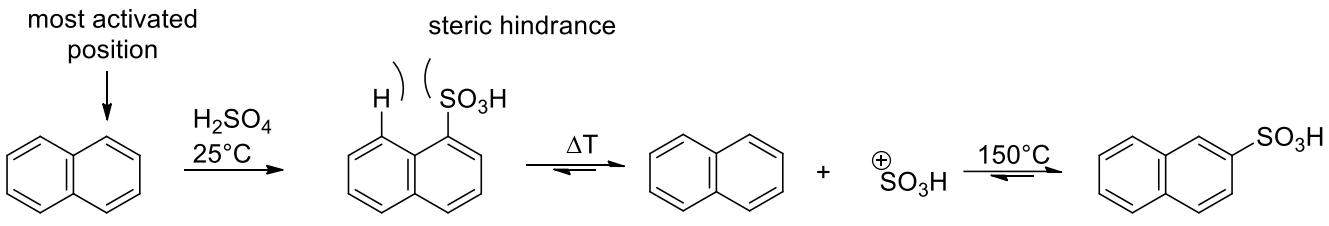
By definition the line goes via origin

Equation give the ρ-value (the slope): y = -3.828x

→ a positive charge is developing in the transition state

→ S_N1 reaction

1.4. Reversibility in S_EAr reactions

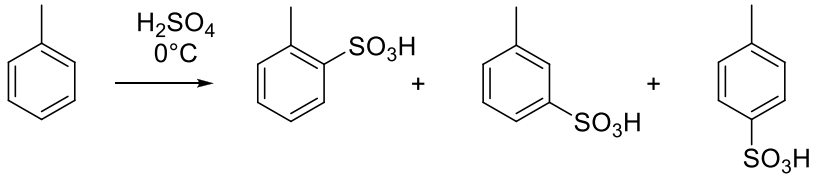


α-Naphthylsulfonic acid
kinetic product has a lower transition state and is formed faster

β-Napthylsulfonic acid
Thermodynamic product, more stable

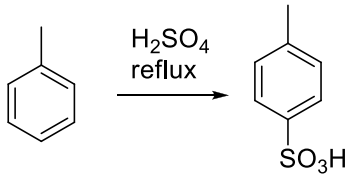
Example:

Kinetic:



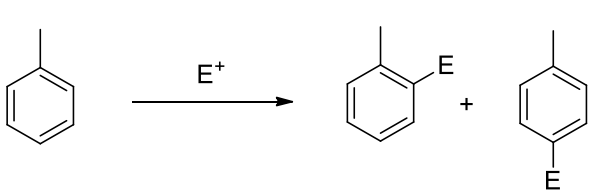
43% 4% 53%

Thermodynamic:

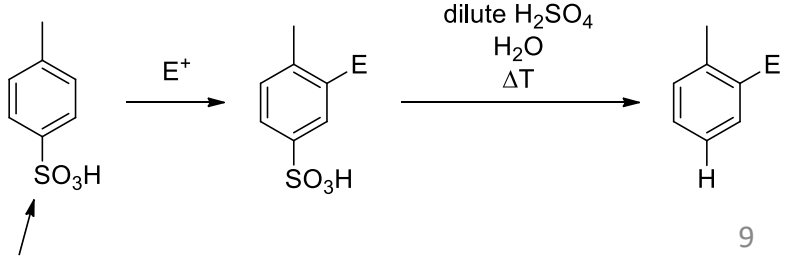


100%

Application: a trick for a removable directing group

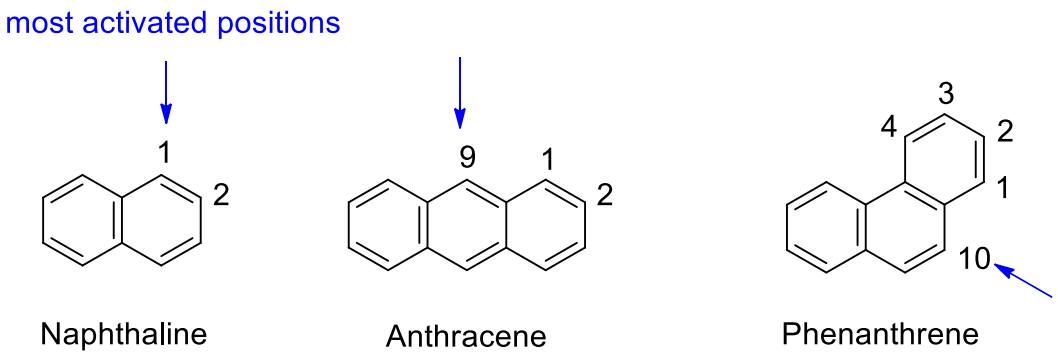


unselective!

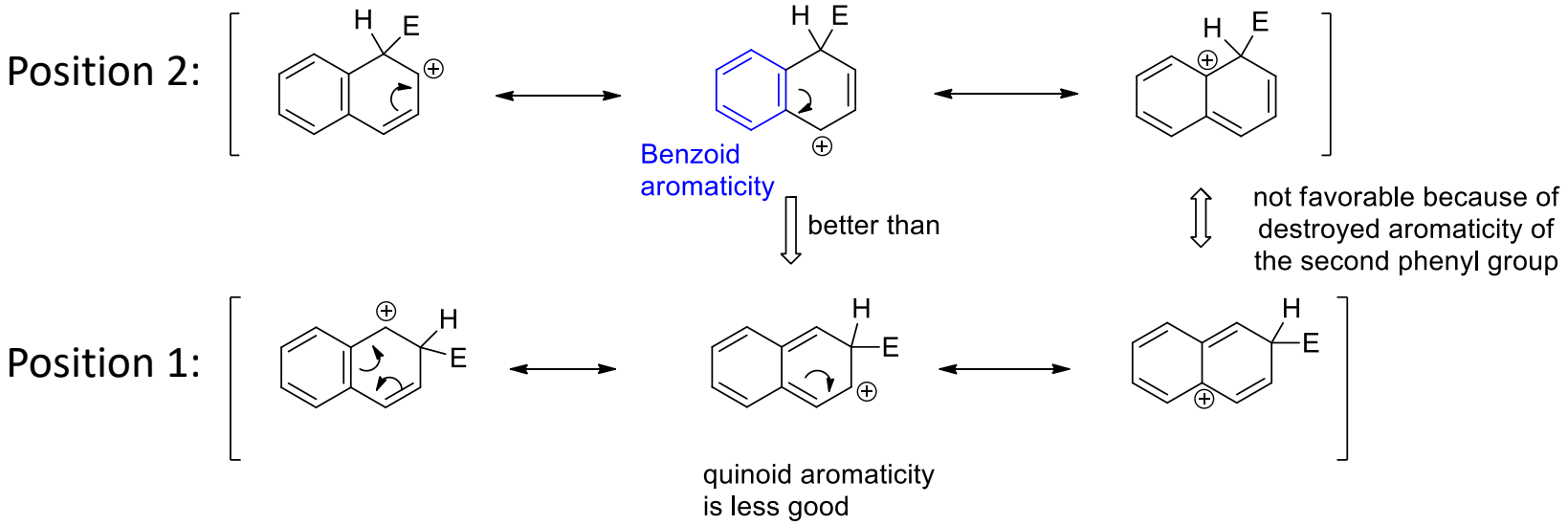


Blocks para-position

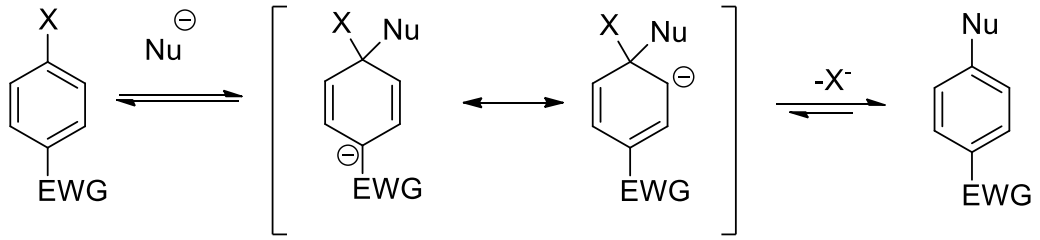
1.5.1. Reactivity of condensed aromatic substrates



Naphthaline: reactivities differences between position 1 and 2 in S_EAr



1.6. Nucleophilic Aromatic Substitution S_NAr



Meisenheimer complex

Criteria:

- X must be a leaving group with high electronegativity (F, Cl, OR…)
- EWG group (-NO_2, -CN, …)

→ The reaction proceeds by an addition/elimination mechanism.

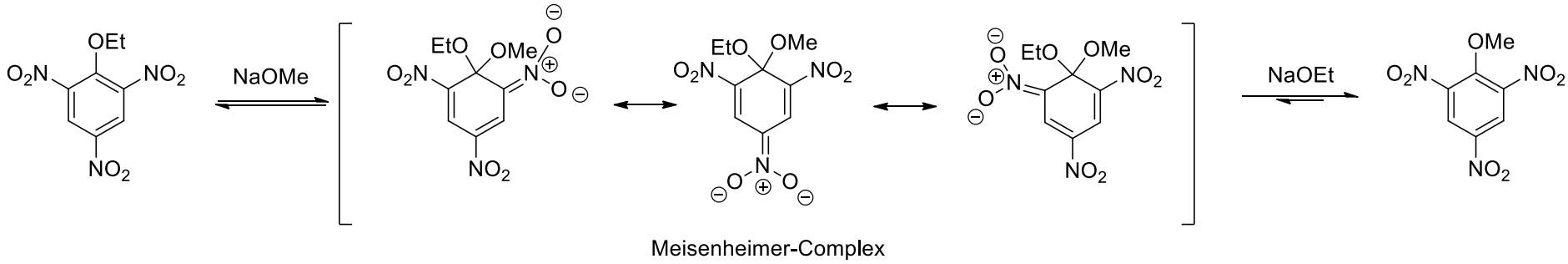
→ Obeys second order kinetics

→ EWG substituents must stabilize the negative charge of the Meisenheimer intermediate.

→ Therefore they must be in the ortho- or para- position.

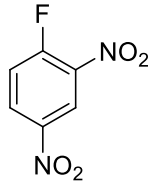
1.6. Nucleophilic Aromatic Substitution S_NAr

Prominent example of S_NAr

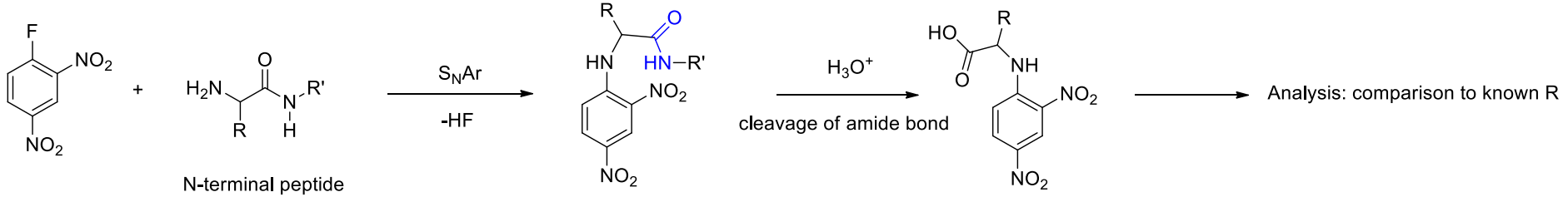


Meisenheimer-Complex

Historical very important application with Sanger's reagent using S_NAr for amino acid sequence analysis



Sanger's reagent



1.6. Nucleophilic Aromatic Substitution S_NAr

Comparaison between S_EAr and S_NAr : basic key facts

	S_EAr	**S_NAr**
Agent	E^+	Nu^-
Key Intermediate	Cationic, Wheland complex	Anionic, Meisenheimer Complex
Substituent that accelerate the reaction	+M/+I groups	strong -M groups
Leaving group	-H ($-SiR_3$; $-CR_3$)	-F, -Cl, -OR