Fonction et réaction organiques II

Fall Semester 2025

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1. Aromatic Chemistry

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1.4. Reactions proceeding by arenium cations

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    1.5.1. Reactivity of condensed aromatic substrates

1.6. Nucleophilic Aromatic Substitution S_NAr

1.7. Reactions of diazonium salts

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1.10. Construction of the aromatic ring: metal-catalyzed [2+2+2]-cyclization

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3. Diels-Alder Cycloaddition

3.1. Diels-Alder Cycloadditions
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4. 1,3-dipolar cycloaddition and concerted molecular rearrangements

4.1. 1,3-dipolar cycloadditions
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- 4.1.2. Huisgen azide-alkyne cycloaddition, Click chemistry
- 4.1.3. Nitrile-oxide cycloaddition

4.2. Pericyclic reactions; concerted molecular rearrangements
- 4.2.1. Cope rearrangement
- 4.2.2. Claisen rearrangement
- 4.2.3. Ene reactions

1.1. Aromaticity

Definition of aromaticity :

- Ancient : smelling compounds, originally coming from coal tar destillates containing aromatic compounds
- Nowadays: lower reactivity through stabilization of an unsaturated molecule.

Example:

1.1.1. Hückel theory

Hückel theory is a simple theory to estimate if a compound is aromatic

Basic requirements:

1)
2)

Rules:

1)

2)

Anti-aromatic is the contrary of aromatic: higher reactivity than expected and/or difficult or impossible to synthesize.

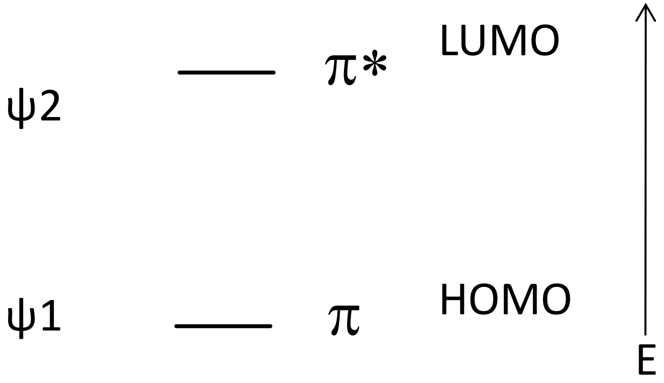
1.1.1. Hückel theory

Aromatic / Non-Aromatic / Antiaromatic ? Examples:

1.1.1. Hückel theory

Molecular orbital (MO): scheme for unsaturated hydrocarbons

The π-system of ethene:

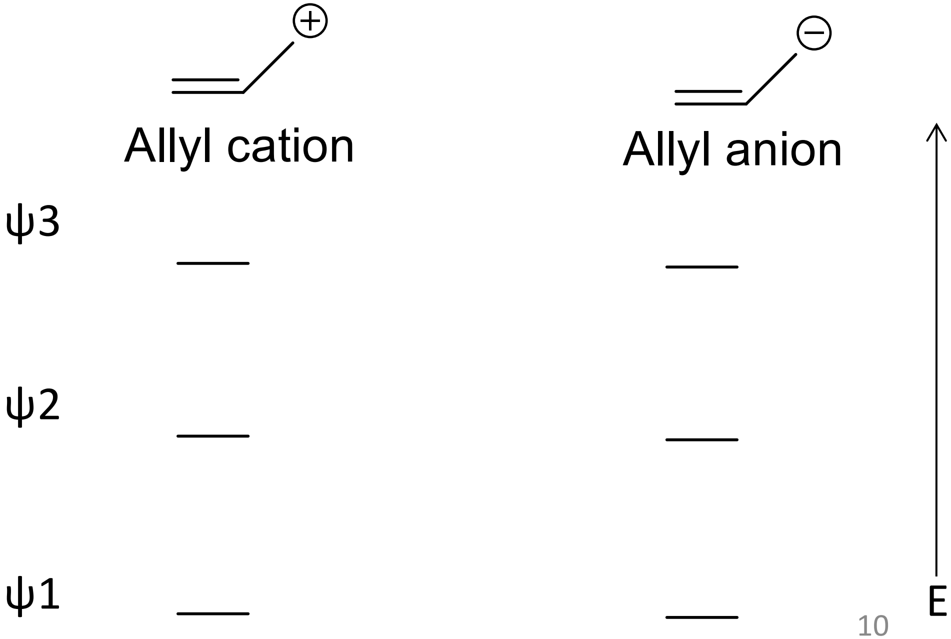


ψ2 π* LUMO

ψ1 π HOMO

E

The Allyl-system



Allyl cation

Allyl anion

ψ3

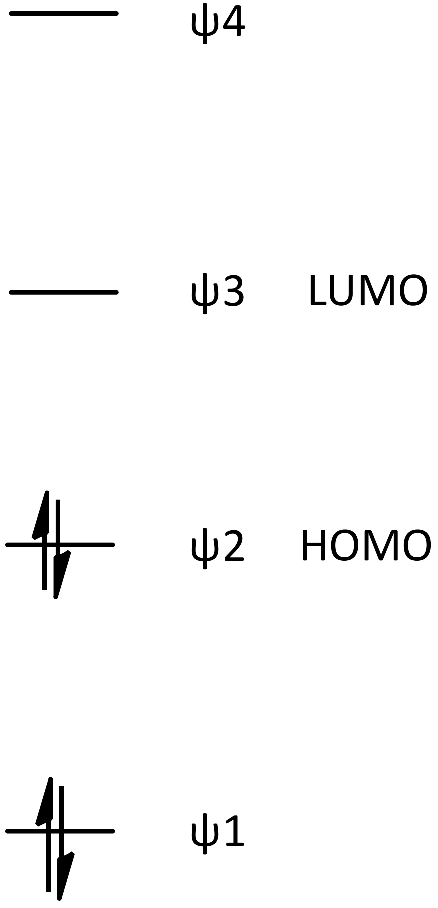
ψ2

ψ1

E

1.1.1. Hückel theory

Butadiene



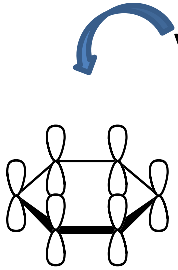
ψ4

ψ3 LUMO

ψ2 HOMO

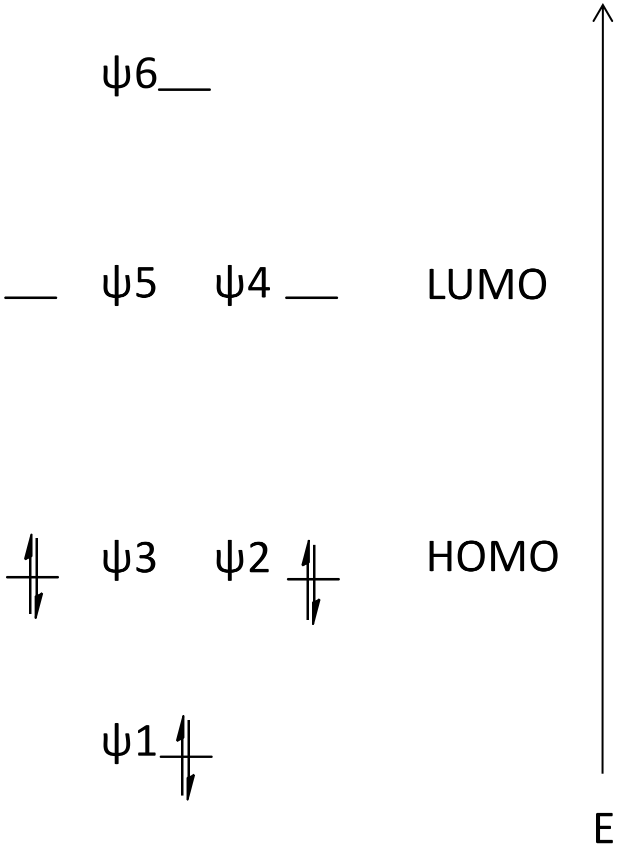
ψ1

1.1.1. Hückel theory



View from top

Benzene



ψ6

ψ5 ψ4 LUMO

ψ3 ψ2 HOMO

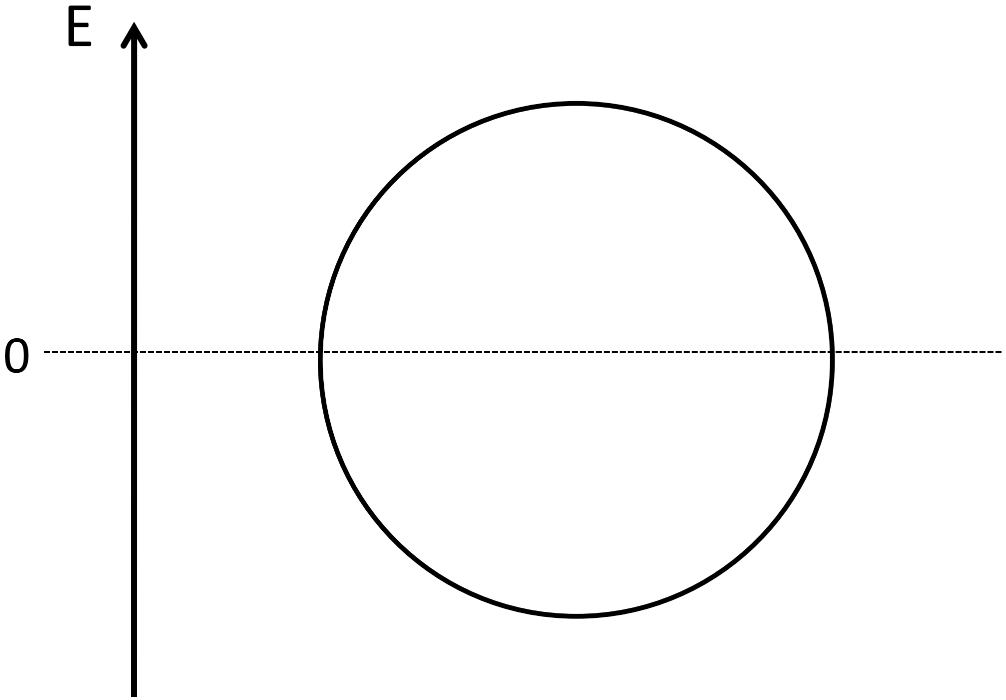
ψ1

E

1.1.2. Frost-Musulin cycle

It is a tool for monocyclic aromatic compounds to estimate the degree of aromaticity by relative energy of their Molecular Orbital (MO).

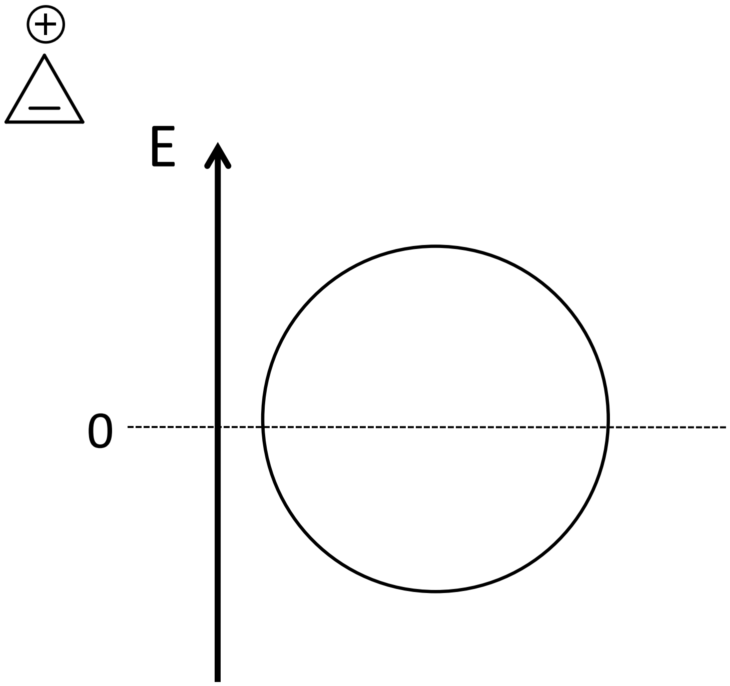
Constructed : molecule sits on an edge!



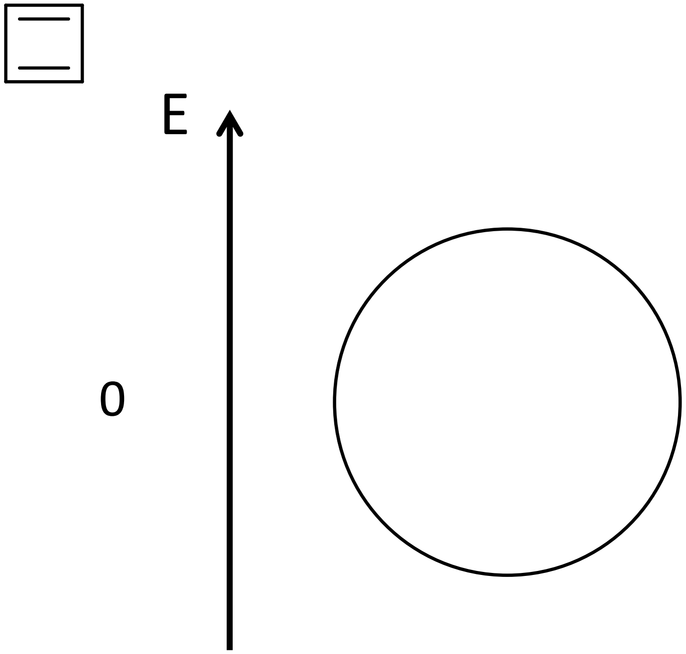
- All corners represent energy-levels
- Fill in electron from buttom
- Read out stabilization / destabilization

1.1.2. Frost-Musulin cycle

Example: Cyclopropenylium cation and cyclobutadiene



Stabilized / aromatic

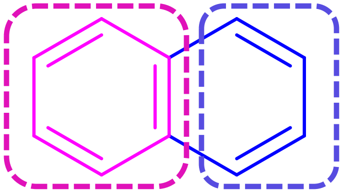


4 π; biradical species
anti aromatic

1.1.3. Polycyclic aromatic compounds

Important example:

Benzoide



Quinoide

Naphthaline

Quinoide rings are more reactive than benzoide rings

Example:

1.1.3. Polycyclic aromatic compounds

Indene - Anion

Azulene: blue color! Observation of color is due to its high dipole moment.

- Color comes from charge transfer

- ‘composed’ from the aromatic compounds cyclopentadienide and cycloheptatrienylium

1.1.3. Polycyclic aromatic compounds

Examples:

Benzo[a]pyrene is produced by incomplete combustion at 300-600°C from:

- coal tare
- diesel engine exhaust fumes
- cigarrette
- barbecue

⬇

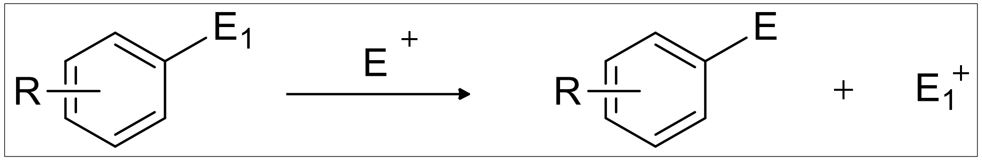
pyrene, aromatic

Benzo [a] pyrene
very cancerogenic
mutagenic tetratogenic

Toxicity of benzene v.s toluene

1.2. Electrophilic aromatic substitution S_EAr

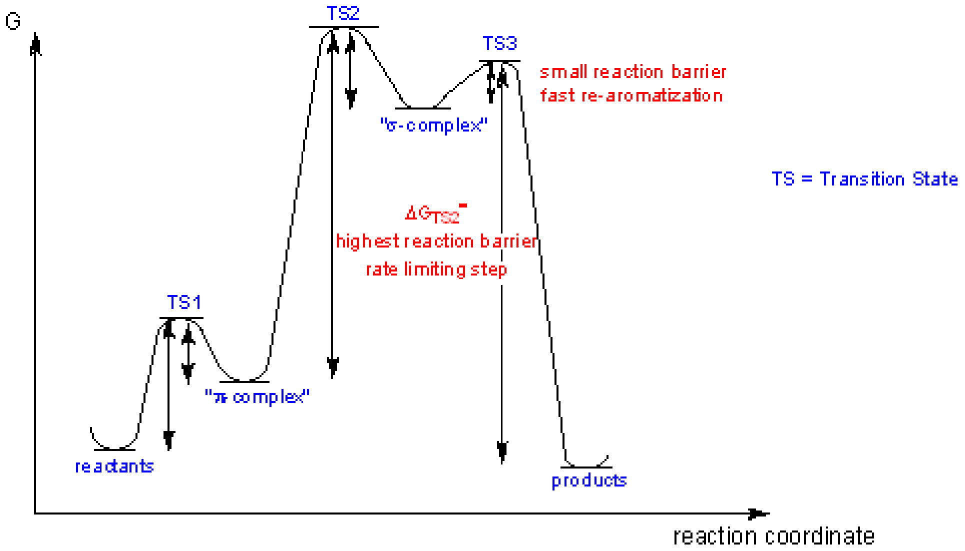
- General reaction:



- $E_1 = H$
- 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. –OMe, having +M / +I effect
  - EWG (Electron Withdrawing Group) e.g. –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: $-NR_2$, $-NH_2$, -OH, -OR
EDG with +I effect: -Alkyl, $-SiR_3$
EWG with –M effect: $-NO_2$, -COOR, -COR, -CHO, -CN, $-SO_3H$, $-SO_2R$
EWG with –I effect: $-NH_3^+$, $-NR_3^+$, $-CF_3$

1.2.2.1. Nitration

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

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

$$2HNO_3 \rightleftharpoons \overset{+}{N}O_2 + H_2O + NO_3^-$$

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

$$HNO_3 + 2H_2SO_4 \rightleftharpoons \overset{+}{N}O_2 + H_3O^+ + 2HSO_4^-$$

  - Strongest conditions: nitroniumtetrafluoroborat salt $NO_2^+ BF_4^-$

- 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

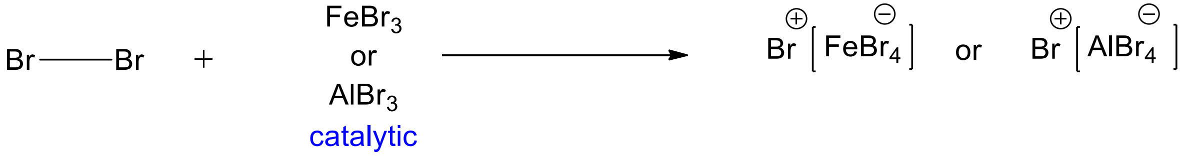
Application for dyes, explosives (TNT, picric acid) and basic industrial processes

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

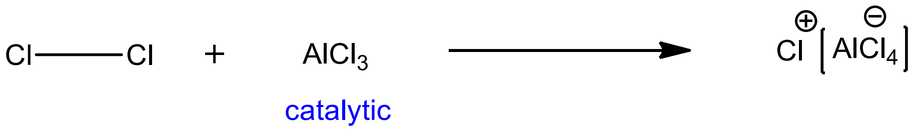
- Electrophile = Br^+ / Cl^+
  - Fluorination: not controlable
  - Iodination: requires promoters

- Practical methods to generate the electrophile:
  - Bromination:



$$Br{-}Br + \begin{matrix} FeBr_3 \\ \text{or} \\ AlBr_3 \\ \text{catalytic} \end{matrix} \longrightarrow \overset{\oplus}{Br}\left[FeBr_4\right]^{\ominus} \text{ or } \overset{\oplus}{Br}\left[AlBr_4\right]^{\ominus}$$

  - Chlorination:



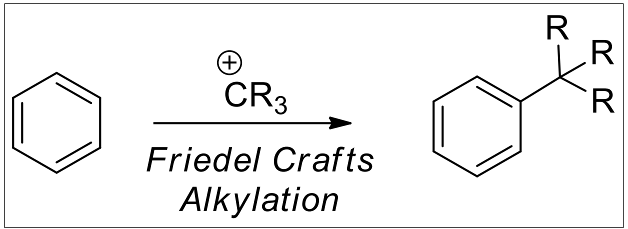
$$Cl{-}Cl + \underset{\text{catalytic}}{AlCl_3} \longrightarrow \overset{\oplus}{Cl}\left[AlCl_4\right]^{\ominus}$$

- 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:

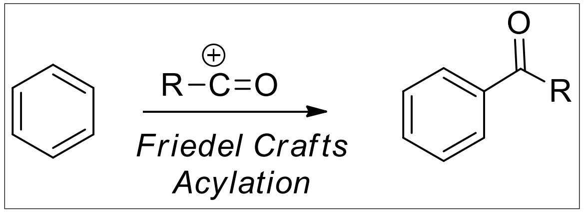
1.2.2.3. Friedel-Crafts reaction

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

Example:

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

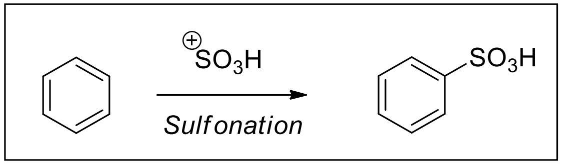
Typical examples:

- 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)

1.2.2.4. Sulfonation



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

– Autoprotolysis of sulfuric acid

$$2\ H_2SO_4 \rightleftharpoons H_2SO_4 .\ SO_3 + H_2O \rightleftharpoons SO_3 + HSO_4^- + H_3O^+$$

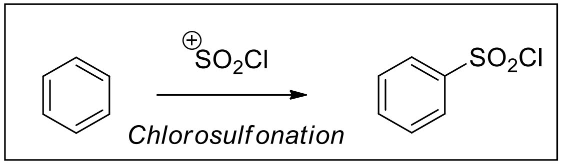
– More forcing condition: Oleum (mixture of H_2SO_4(100%) and SO_3 (up to 30%))

Representative examples:

A)

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

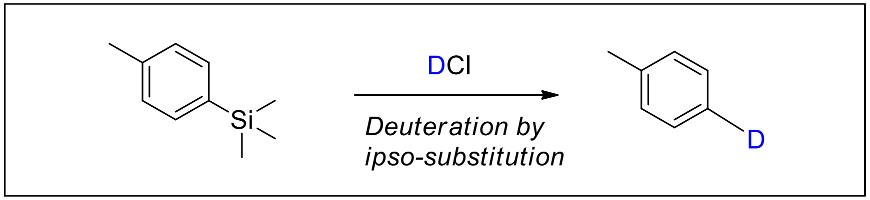
1.2.2.5. Chlorosulfonation



Reagent: Chlorosulfonic acid $ClSO_3H$

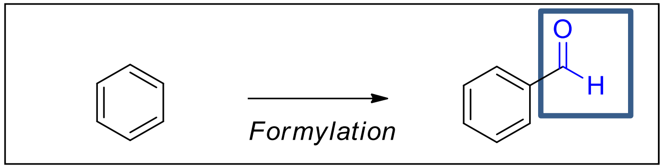
Representative example: sulfochlorides are synthetically very versatiles

1.2.2.6. Deuteration by ipso-substitution



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

1.2.2.7. Formylation

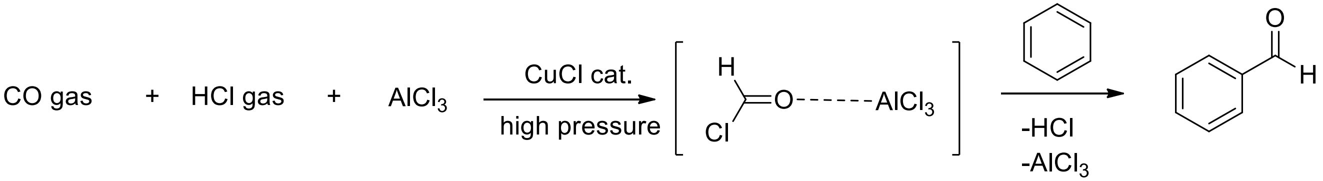


Introduction of a formyl group

The obtained products are aromatic aldehydes.

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

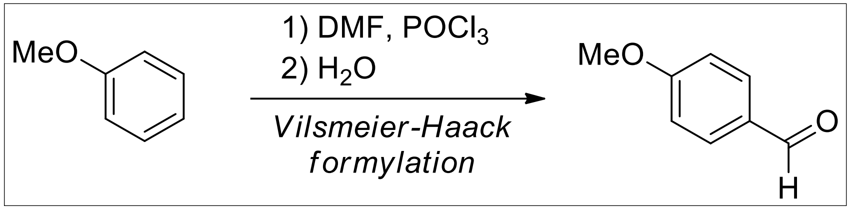
- Used with limitations in the Gattermann-Koch-Process



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

1.2.2.7. Formylation

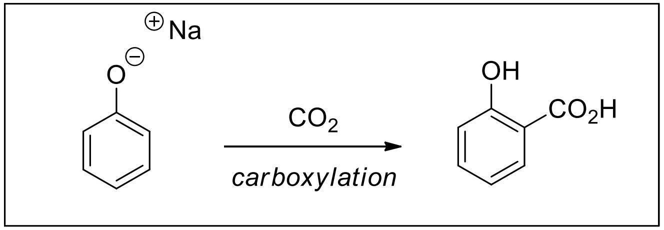
- Vilsmeier-Haack formylation: (requires an **electron rich** aromatic substrate)



Mechanism:

1.2.2.8. Carboxylation

- Kolbe-Schmitt reaction:



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

Most important example: synthesis of aspirin

1.2.2.9. Hydroxy methylation

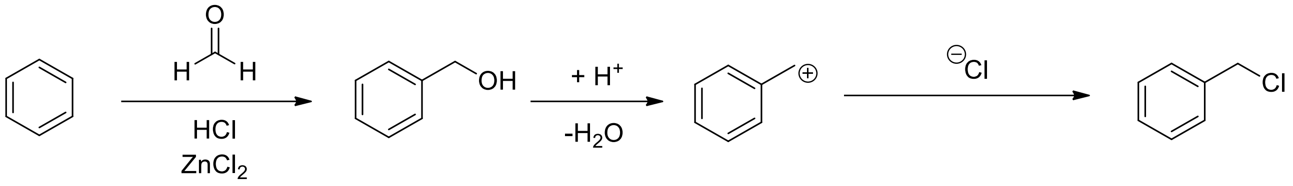
Only with **activated** aromatic substrates

- Reaction under basic conditions:

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

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

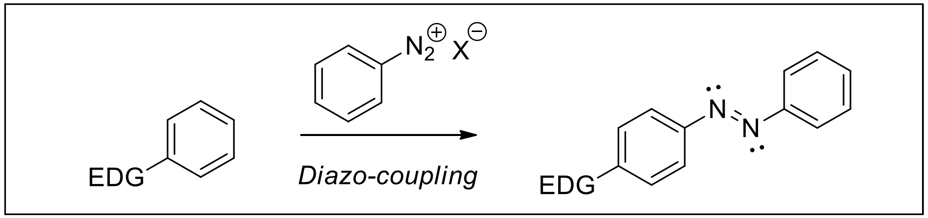
1.2.2.10. Chloromethylation



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

Application: preparation of Merrifield resins

1.2.2.11 Diazo-coupling



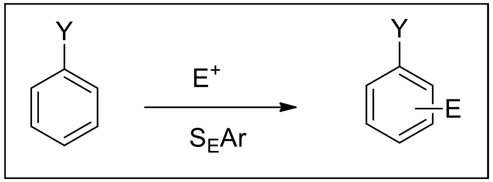
Diazo coupling requires **activated** aromatic substrates!

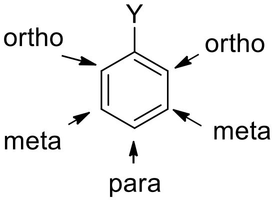
Preparation of the diazonium electrophile:

Illustrative example:

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

1.2.3. Secondary substitution on the benzene ring





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

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

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

1.2.3. Secondary substitution on the benzene ring

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

Reactivity can be modulated by pH:

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

Slightly deactivating substituent (~ 30 times compared to Y=H)

But ortho- / para- directing group

1.2.3. Secondary substitution on the benzene ring

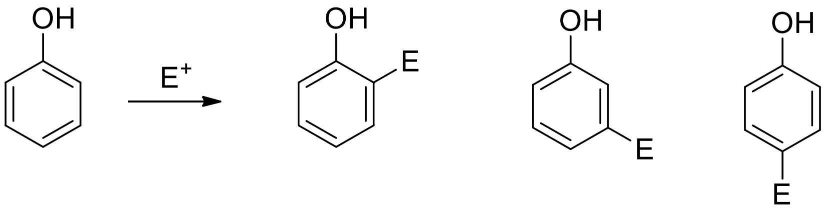
Illustrative examples between EDG and EWG directing groups

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

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

1.2.3. Secondary substitution on the benzene ring

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

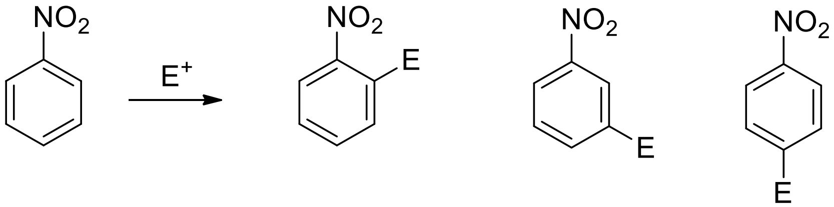


Mesomeric structures of the possible isomers of the σ-complex:

+M: accelerate the reaction and direct ortho and para

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:

-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

- <u>Special case</u>: 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

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

K_H: reaction rate for the unsubstituted aromatic compound

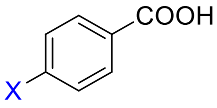
K_X reaction rate for X substituted aromatic compound

σ: substitution parameter (changes with X)

ρ: reaction parameter (changes with the reaction)

–σ-values:

Characteristic for the individual substituent



X = H: $\sigma = 0$

X = EDG: $\sigma < 0$

X = EWG: $\sigma > 0$

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

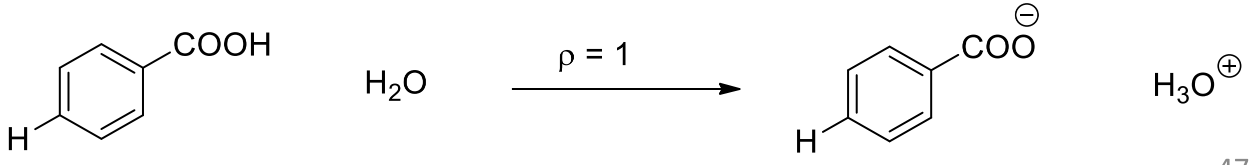
–ρ-values:

$\rho > 0$: a negative charge is developing in the transition state

$\rho = 0$: rare case where the reaction rate is not influenced by substitution

$\rho < 0$: 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:

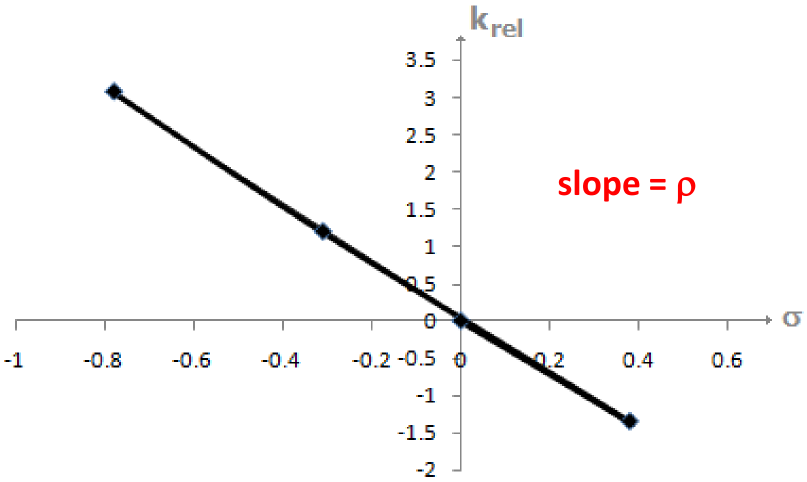
1) A known reaction (ρ known) can be used to determine the donor or acceptor properties of an unknown substituent X: measure its σ value.

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
$\text{Log}(K_{rel})$	0	-1.35	1.2	3.08



slope = ρ

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

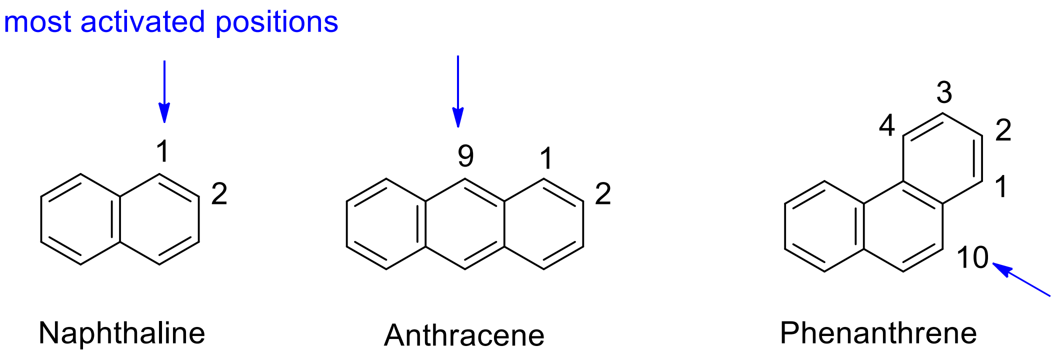
Example:

Kinetic:

Thermodynamic:

Application: a trick for a removable directing group

1.5.1. Reactivity of condensed aromatic substrates

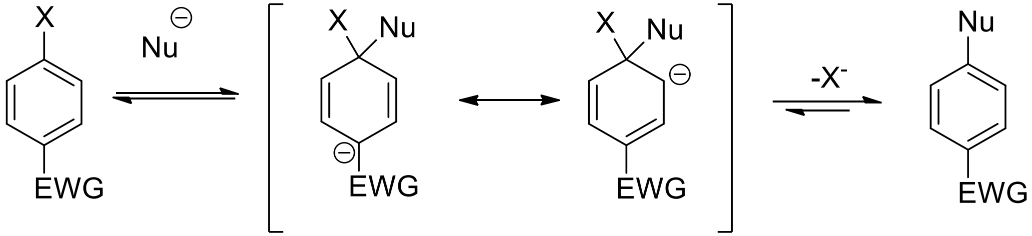


Naphthaline: reactivities differences between position 1 and 2 in S_EAr

Position 2:

Position 1:

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

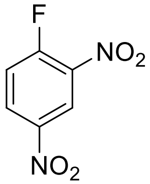
→ EWG substituents must stabilize the negative charge of the Meisenheimer intermediate.

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

1.6. Nucleophilic Aromatic Substitution S_NAr

Prominent example of S_NAr

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



Sanger's reagent

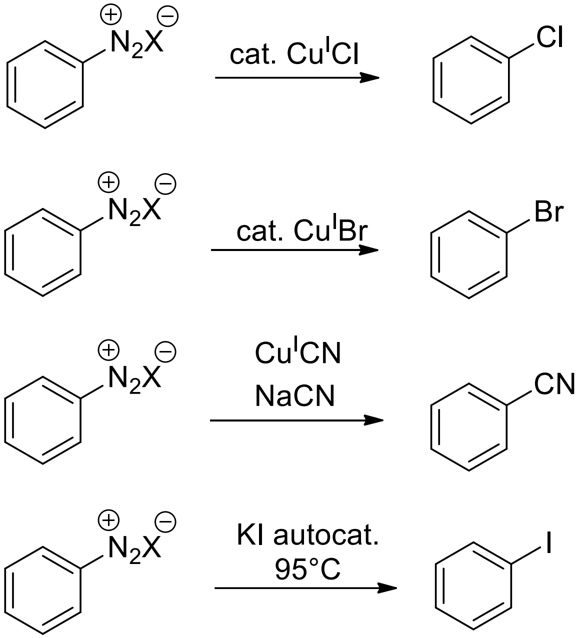
1.6. Nucleophilic Aromatic Substitution S_NAr

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

1.7. Reaction of diazonium salts

- Sandmeyer reaction



- General mechanism:

Exception: no copper needed with iodide, iodide act as a redox catalyst itself

1.7. Reaction of diazonium salts

- Meerwein reduction: removal of the diazonium group

- Reduction of a diazonium salt maintaining the N-N single bond: preparation of aromatic hydrazines

1.7. Reactions proceeding by arenium cations

Only possible with the very best leaving group: N_2

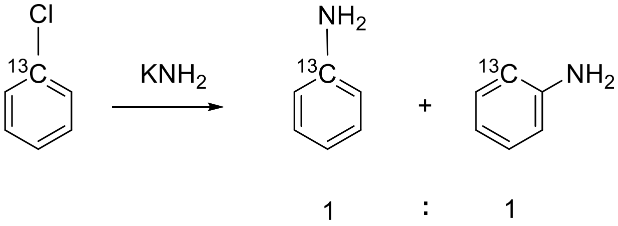
- Generation of arene cations: “Phenol cooking”

- Balz-Schiemann reaction: introduction of a fluorine substituent

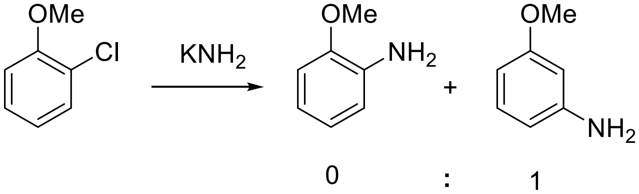
1.8. Substitution by the aryne mechanism

Experimental observations:

A)



B)



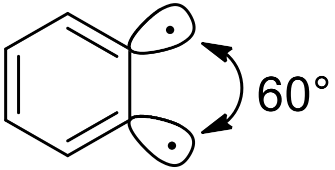
Explanation by a new mechanism:

1.8. Substitution by the aryne mechanism

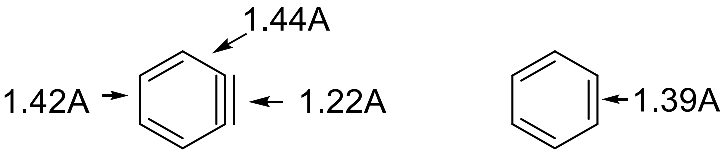
General properties of the arynes

- Are not real/normal triple bond with two sp-hybridized carbon atoms
- Only a partial orbital overlap possible, remain mostly sp^2-hybridized

- Arynes are reactive singulett species



- Bond lengths in comparison to benzene



1.8. Substitution by the aryne mechanism

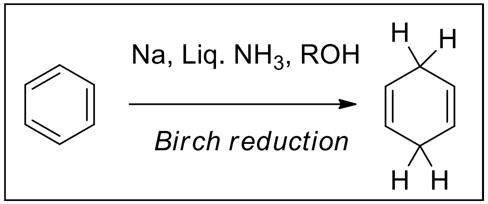
Other reactions of arynes:

Additional methods for their preparation:

Modern method:

1.9. Reduction of the aromatic ring

Birch reduction: reduction of the aromatic ring to give 1,4-cyclohexadienes



Solvent: liquid ammonia
Reaction below -31°C

Mechanism:

1.9. Reduction of the aromatic ring

Regioselectivity of the reduction:

Case 1: Electron-donating substituents

Case 2: Electron-withdrawing substituents

1.9. Reduction of the aromatic ring

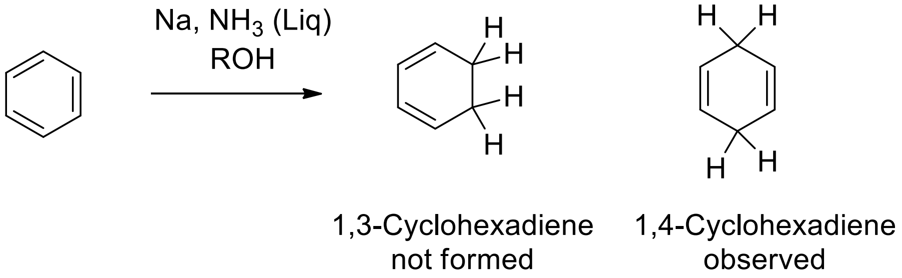
Example for a Birch alkylation:

interception of the carbanion by an electrophile, e.g. alkylhalide instead of proton

1.9. Reduction of the aromatic ring

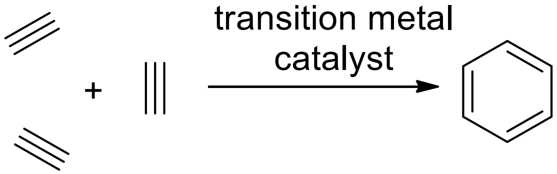
The Birch reduction yields selectively 1,4-Cyclohexadienes.

Why are 1,3-Cyclohexadienes not formed?



Explanation by the electron densities of the pentadienyl anion

1.10. Construction of the aromatic ring: metal-catalyzed [2+2+2]-cyclization



Several different metal complexes of Ni^0, Rh^I, Ir^I, Ru, Co, Pd are known for this reactivity.

Simplified mechanism:

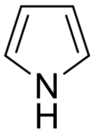
Well suited and excellent for intramolecular reactions

Problems of regioselectivity and chemoselectivity with different substituted alkynes

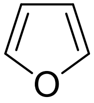
2.1.1. Nomenclature: trivial names

- Most important heterocycles:

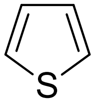
  - 5-membered ring series:



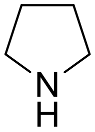
pyrrole



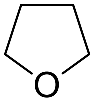
furan



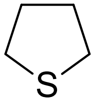
thiophene



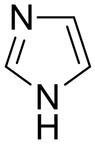
pyrrolidine



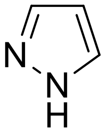
tetrahydrofuran



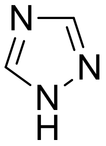
tetrahydrothiophene



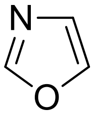
imidazole



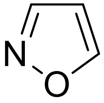
pyrazole



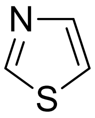
triazole



oxazole

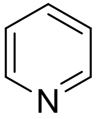


isoxazole

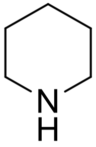


thiazole

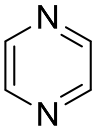
  - 6-membered ring series:



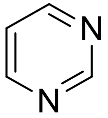
pyridine



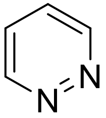
piperidine



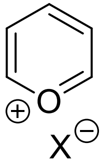
pyrazine



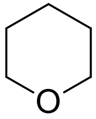
pyrimidine



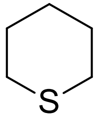
pyridazine



pyrilium salts



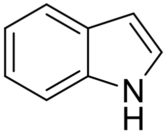
pyran



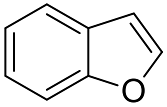
thiopyran

2.1.1. Nomenclature: trivial names

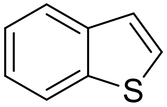
- Most important heterocycles:
  - Condensed series:



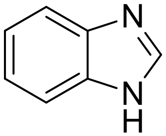
indole



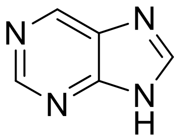
benzofuran



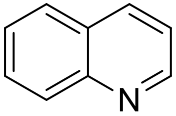
benzothiophene



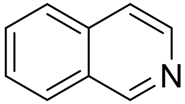
benzimidazole



purine



quinoline



isoquinoline

2.1.2. Nomenclature: The Hantsch-Widman system

- the essentials:

– Name is composed by number + prefixe(s) + suffix

– Numbering rules:

  1) heteroatom is always number 1
  2) If multiple heteroatoms priority: O > S > N
  3) The smallest numbering combination for the heteroatoms is then correct

– Prefix originates from the heteroatom: N = az(a)

O = ox(a)

S = thi(a)

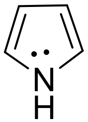
2.1.2. Nomenclature: The Hantsch-Widman system

- Suffix determines the ring size:

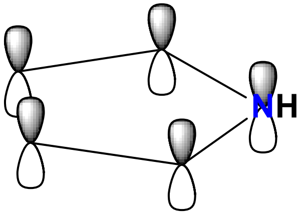
Ring size	Unsaturated ring	Saturated ring	N-Saturated ring
3	irene	irane	iridine
4	ete	etane	etidine
5	ole	olane	olidine
6	ine	inane	
7	epine	epane	
8	ocine	ocane	
9	onine	onane	

- Examples:

2.2.1. Comparison between pyrrole and pyridine

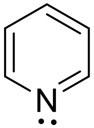


5 membered ring
electron rich

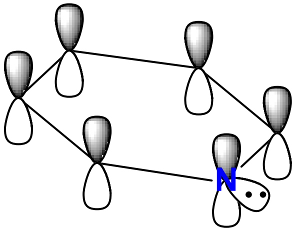


N is not basic (cannot be protonated)
lone pair is integral part of the aromatic system

why electron rich?
for benzene: 6 π electrons on 6 atoms
here: 6 π electrons on 5 atoms
-> higher electron density



6 membered ring
electron poor



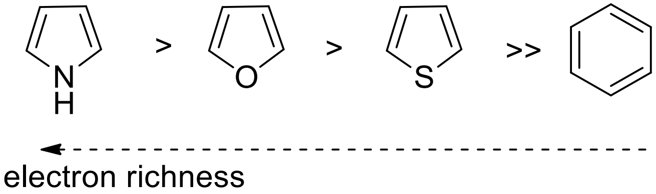
N is basic (can be protonated)
lone pair available; orthogonal to the aromatic system

why electron poor?
6 π electrons on 6 atoms
N has a higher electronegativity than carbon
and pulls elctrons

- Examples:

2.2.2. Reactivity of electron rich heteroaromatics

- S_EAr for electron rich heteroaromatics:



- The 2-position is the most activated:

One additionnal mesomeric structure possible by an addition to the 2-position
→ better stabilization

Similar reactivity for furane and thiophene

2.2.2. Reactivity of electron rich heteroaromatics

- S_EAr for indole:

- The 3-position is the most activated:

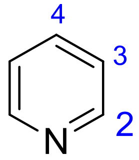
- Example: gramine synthesis

2.2.2. Reactivity of electron rich heteroaromatics

- N-Alkylation / N-Acylation of indoles or pyrroles:

2.2.3. Reactivity of electron poor heteroaromatics

- S_EAr for electron poor heteroaromatics:



Pyridine is electron poor and therefore a very deactivated substrate for S_EAr
All positions are deactivated

- The 3 position is the least deactivated one and reacts preferentially:

2.2.3. Reactivity of electron poor heteroaromatics

S_EAr on pyridines require forcing conditions:

Examples:

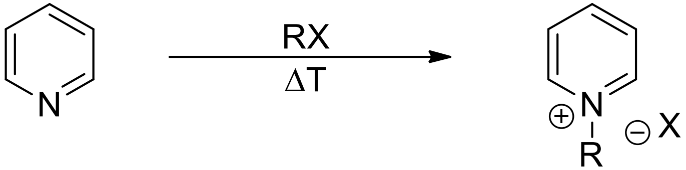
2.2.3. Reactivity of electron poor heteroaromatics

- Method to address the 2- and 4-position of pyridine with S_EAr

→ oxidation into the more electron rich pyridine N-oxide

2.2.3. Reactivity of electron poor heteroaromatics

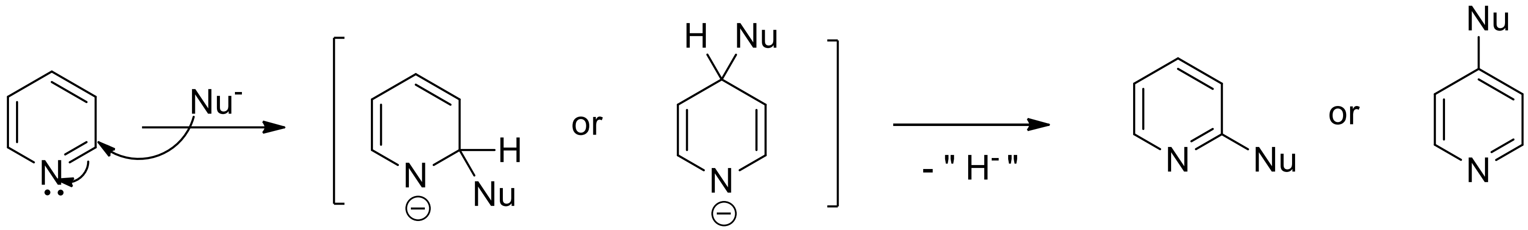
- Under forcing conditions the nitrogen atom of the pyridine can be alkylated or acylated to give pyridinium salts:



- Examples:

2.2.4. The Tschitschibabin reaction

- The Tschitschibabin reaction is equivalent to S_NAr reaction on a pyridine:

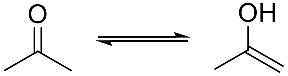


- Example for the synthesis of 2-aminopyridine:

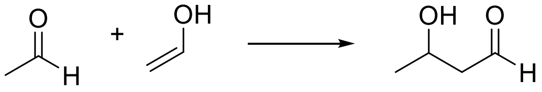
2.3.1. Synthesis of five-membered ring heteroaromatics

- Recapitulation of some relevant carbonyl chemistry

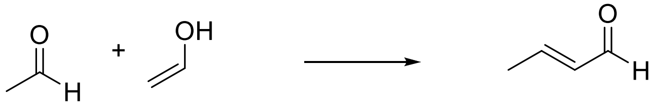
Keto-Enol tautomerization:



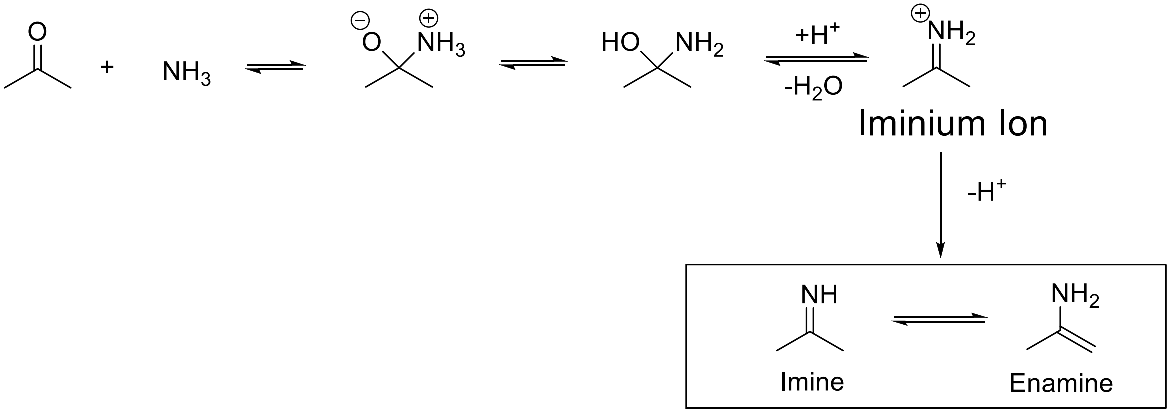
Aldol-addition:



Aldol condensation:

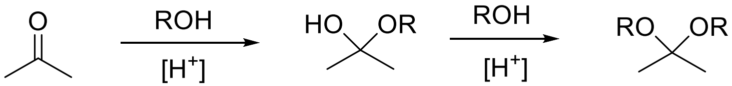


Formation of Iminium ion:

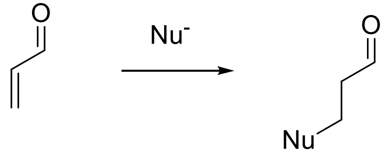


Imine-Enamine tautomerization

Acetalization:



Conjugate Additions:

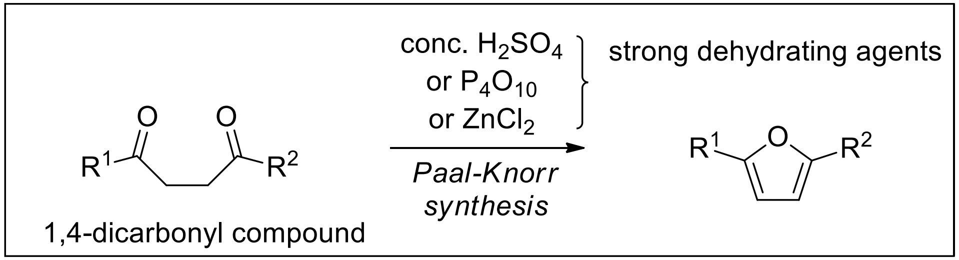


2.3.1. Furane syntheses

From a formal retrosynthesis perspective:
same starting materials, two different pathways

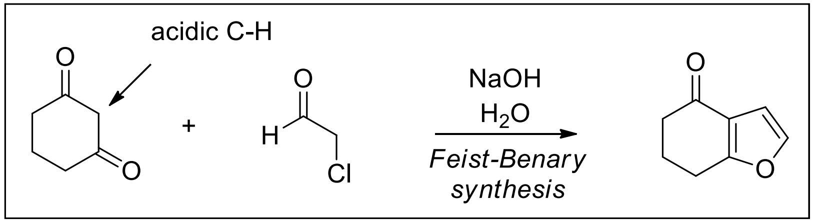
2.3.1. Furane syntheses

- Paal-Knorr synthesis:



Mechanism:

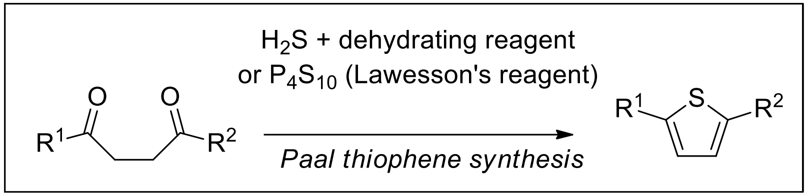
- Feist-Benary synthesis:



Mechanism:

2.3.2. Thiophene syntheses

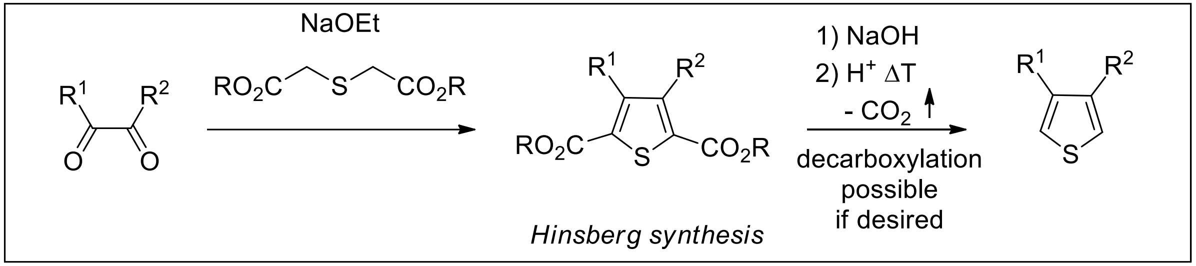
- Paal-Knorr thiophene synthesis:



P_4S_{10}: transfer of sulfur and dehydrating agent at once

Mechanism:

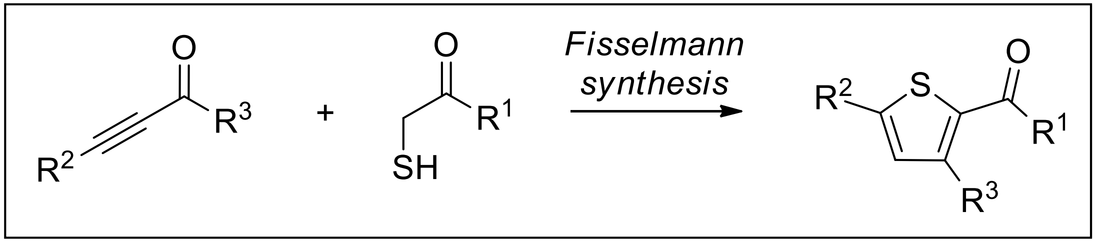
- Hinsberg synthesis:



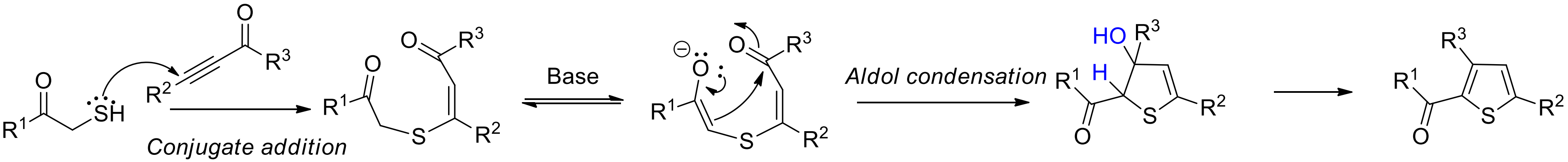
Mechanism:

2.3.2. Thiophene syntheses

- Fisselmann thiophene synthesis:

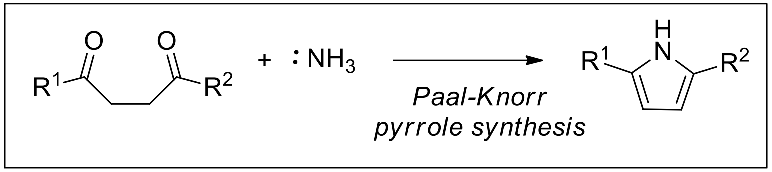


Mechanism:



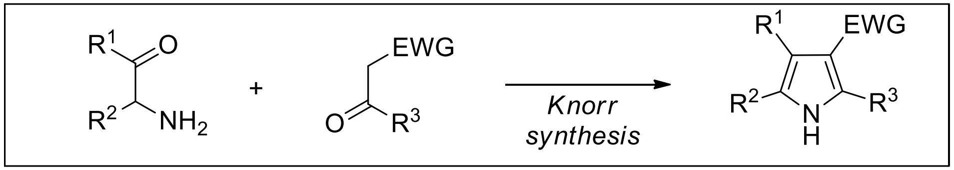
2.3.3. Pyrrole syntheses

- Paal-Knorr pyrrole synthesis:



Mechanism:

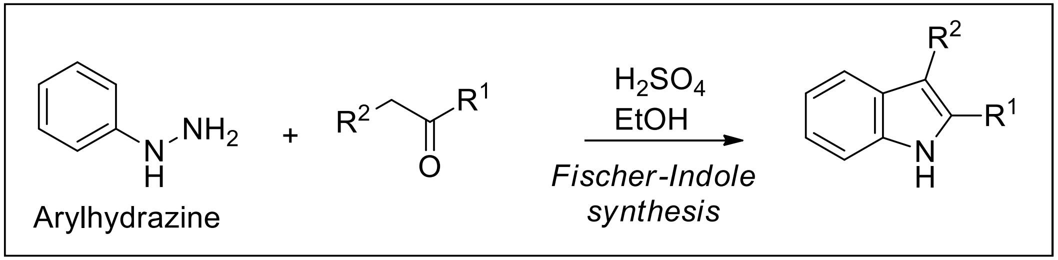
- The Knorr synthesis:



Mechanism:

2.3.4. Indole syntheses

- Fischer-Indole synthesis:



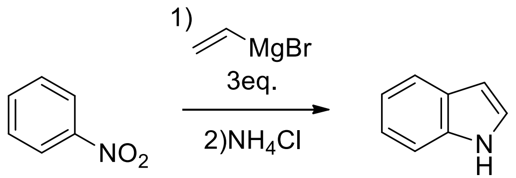
Mechanism:

2.3.4. Indole syntheses

- Reissert synthesis:

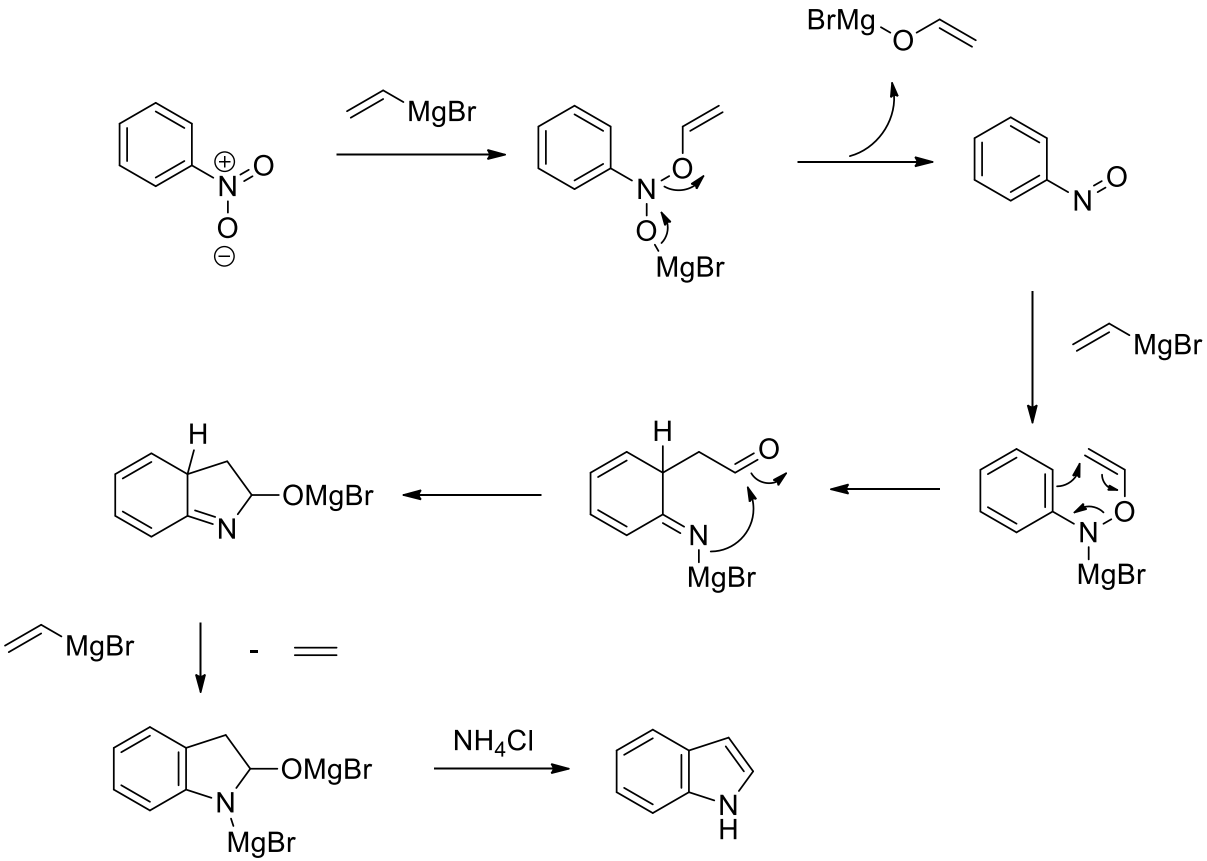
2.3.4. Indole syntheses

- Bartoli-Indole synthesis:



Bartoli-Indole Synthesis

Mechanism:

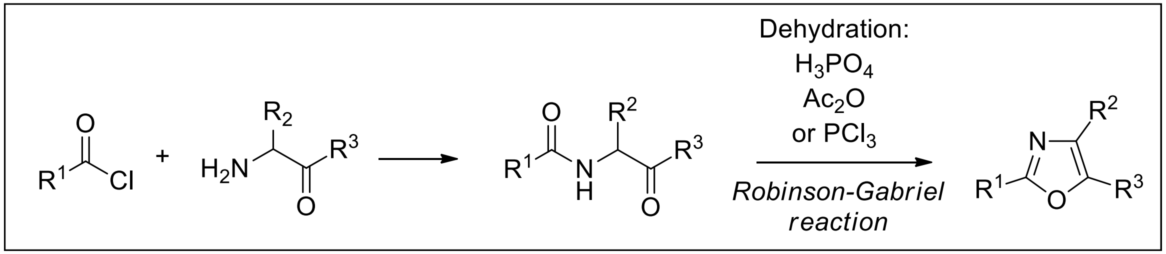


2.3.4. Indole syntheses

- Example: technical synthesis of Indigo (dye for blue jeans)

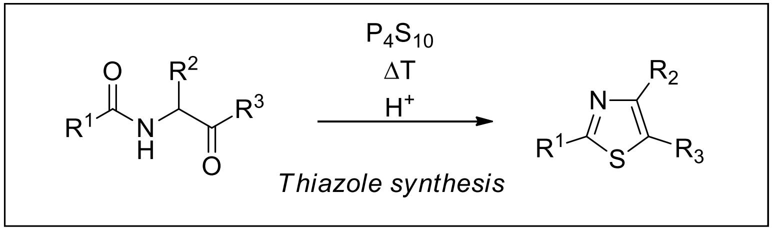
2.3.5. Oxazole syntheses

- Robinson-Gabriel reaction:



Mechanism:

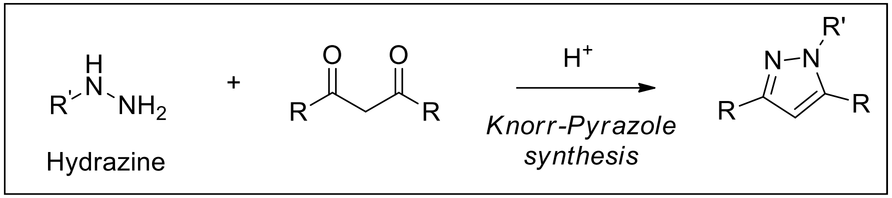
- Analog for thiazole synthesis:



Mechanism:

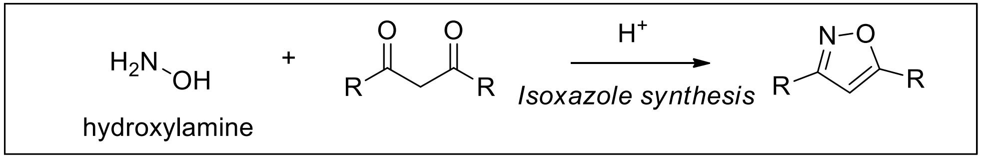
2.3.6. Pyrazole and Isoxazole syntheses

- Knorr-Pyrazole synthesis:



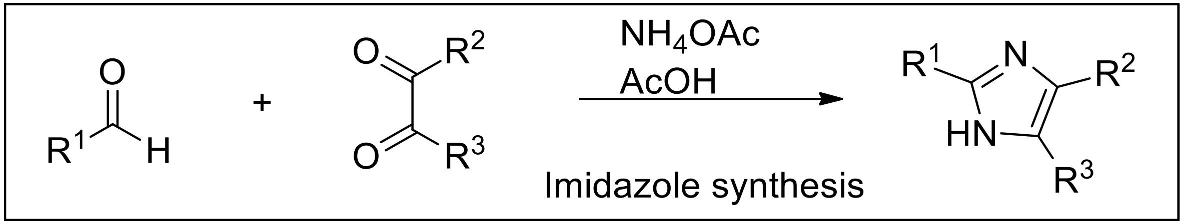
Mechanism:

- Similar for isoxazole synthesis:



Mechanism:

2.3.7. Imidazole syntheses

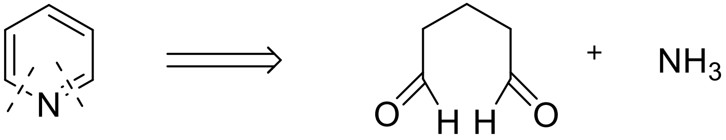


Mechanism:

2.4.1. Pyridine syntheses

- Retrosynthesis:

Common strategy: cuts around the heteroatom

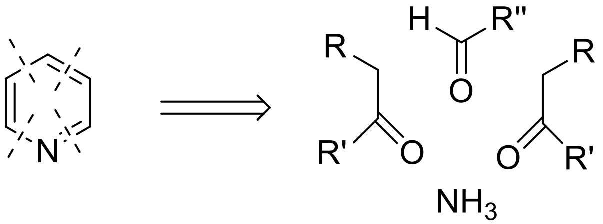


Reaction can be performed differently:

2.4.1. Pyridine syntheses

- Hantzsch (dihydro)pyridine synthesis:

- Strategic disconnections:



- Synthesis

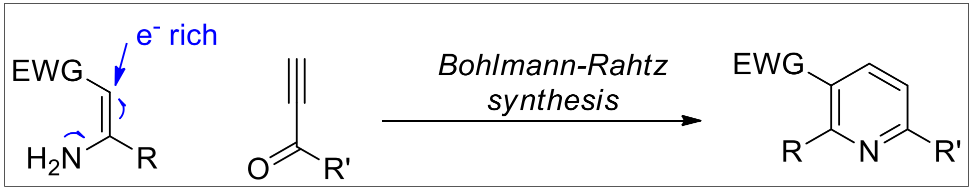
2.4.1. Pyridine syntheses

- Mechanism:

2.4.1. Pyridine syntheses

- **Bohlmann-Rahtz pyridine synthesis:**

- Synthesis:



- Mechanism:

2.4.1. Pyridine syntheses

- [2+2+2] cyclotrimerization for pyridine synthesis

- The Ciamician Dennstedt reaction: pyridines by ring enlargment of a pyrrole

2.4.2. Quinoline syntheses

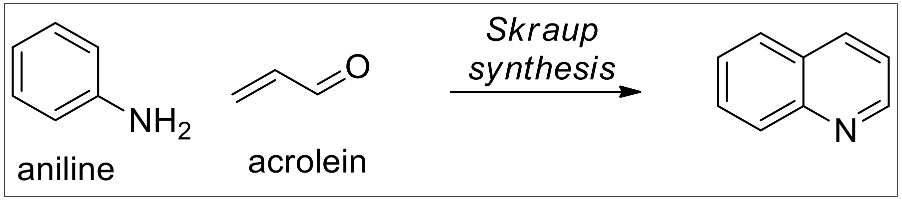
- General strategies:

→ The ring containing the heteroatom is the one which is constructed

→ There are several possibilities to perform it always starting with an aniline

2.4.2. Quinoline syntheses

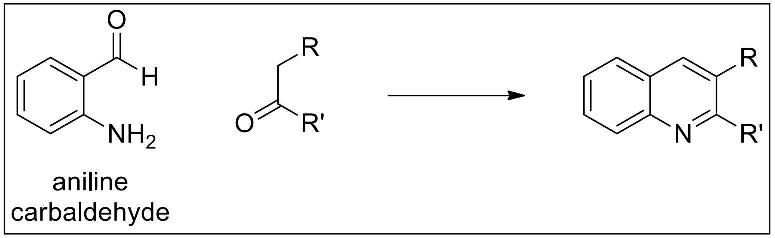
- Skraup quinoline synthesis:



- Mechanism

2.4.2. Quinoline syntheses

- Friedländer quinoline synthesis

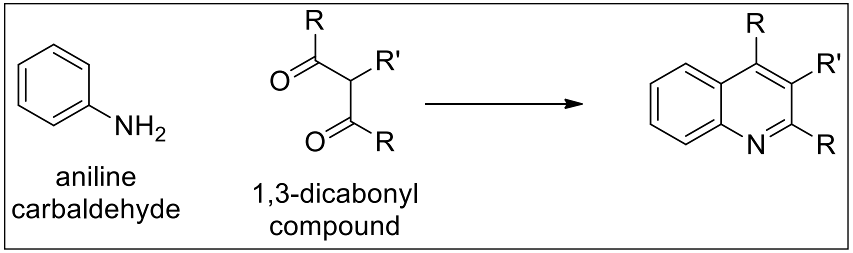


- Advantage: flexibility in the substitution pattern

- Mechanism:

2.4.2. Quinoline syntheses

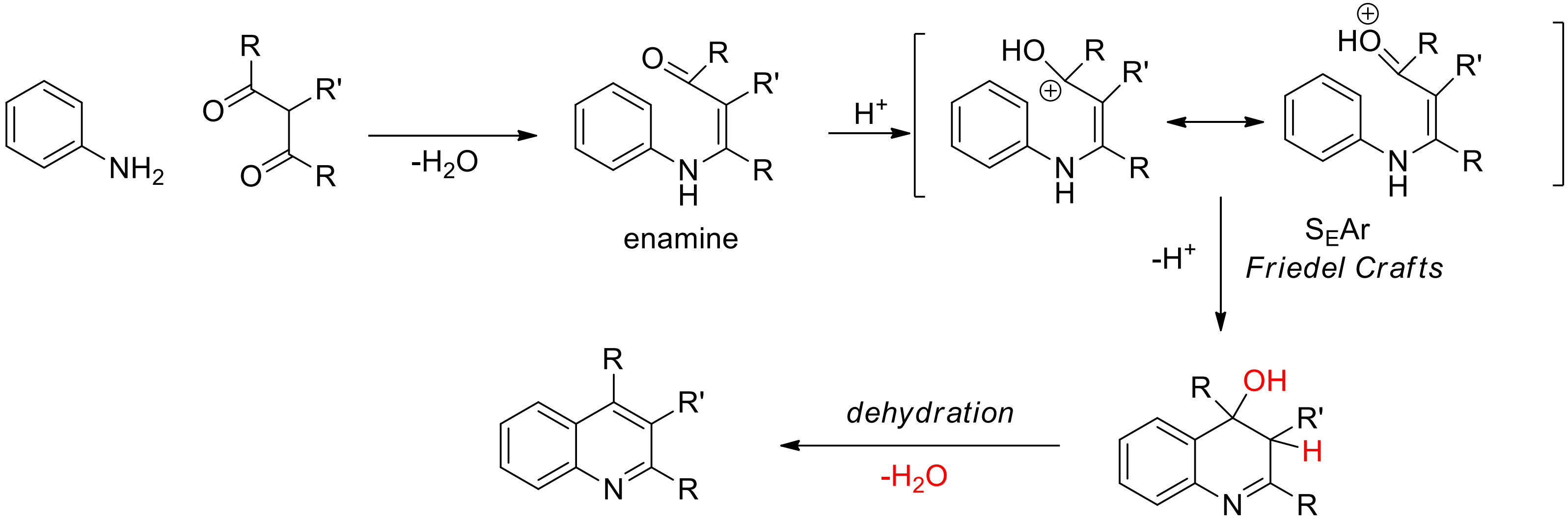
- Combes quinoline synthesis:



aniline carbaldehyde

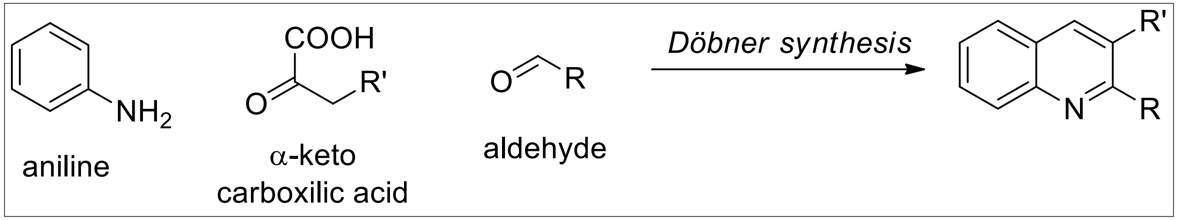
1,3-dicabonyl compound

- Mechanism:



2.4.2. Quinoline syntheses

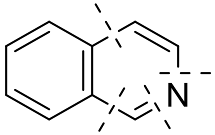
- Döbner quinoline synthesis:



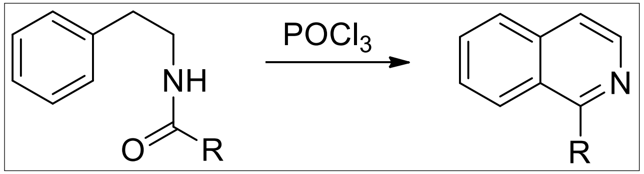
- Mechanism:

2.4.2. Isoquinoline syntheses

- Strategic disconnections:



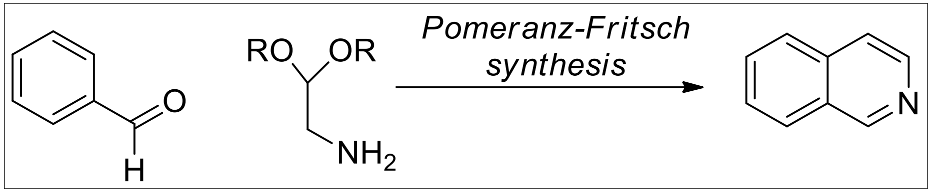
- Bischler-Napieralski isoquinoline synthesis:



- Mechanism:

2.4.2. Isoquinoline syntheses

- Pomeranz-Fritsch isoquinoline synthesis:

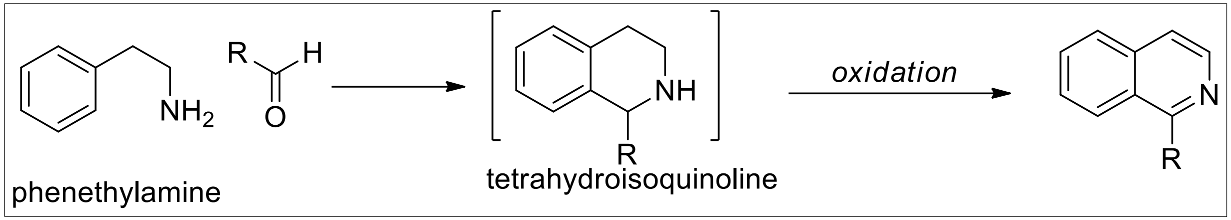


- Mechanism:

2.4.2. Isoquinoline syntheses

- Pictet-Spengler reaction:

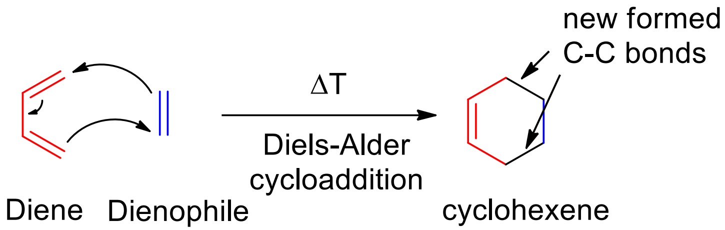
This is a more general reaction for several ring size, but used here for the synthesis of isoquinolines



- Mechanism:

3.1.1. General reaction principle

The Diels-Alder reaction was discovered by Otto Diels and Kurt Alder (Nobel prize in 1950)



Diene: 4 π-electrons
Dienophile: 2 π-electrons
Diels-Alder reaction: [4+2]-cycloaddition

Molecular Orbital picture of the Diels-Alder Cycloaddition:

For the Diels-Alder cycloaddition, the interaction between the butadiene HOMO and the ethene LUMO is relevant.

⇨ The smaller the Gap $\Delta G_{HOMO/LUMO}$, the easier and faster the cycloaddition reaction proceeds.

3.1.1. General reaction principle

Interaction of the HOMO of the diene with the LUMO of the olefin

Concerted cycloaddition, no intermediate

An interaction is possible when allowed by the orbital symmetry: $\text{HOMO}_{\text{Diene}}/\text{LUMO}_{\text{Dienophile}}$ and $\text{LUMO}_{\text{diene}}/\text{HOMO}_{\text{Dienophile}}$

The better the energetic overlap, the better and faster the Diels-Alder reaction

Minimize energy difference between HOMO of the diene and LUMO of the dienophile:

- Diene needs to be electron-rich = high lying HOMO
- Dienophile needs to be electron-poor = low lying LUMO

3.1.2 The nature of the diene

The diene component must be able to adopt s-*cis* conformation: A Diels-alder cycloaddition is only possible from the s-*cis* conformer.

Examples:

Electron-rich dienes react faster:

Electron-rich Dienes > Electronically neutral Dienes >> Electron-poor Diene

3.1.3. The nature of the dienophile

Electron-poor dienophiles are best suited and react fast

Examples of Dienophiles:

- Electron-poor alkynes can be used as dienophiles as well, and yield 1,4-cyclohexadienes as products:

3.2.1. Diene and dienophile isomers

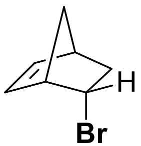
The Diels-Alder reaction is a concerted cycloaddition and obeys the Woodward-Hoffmann rules for pericyclic reactions.
In that respect, the Diels-Alder cycloaddition is a thermally allowed process.

⇒ The stereochemical information of the starting materials is conserved in the product:

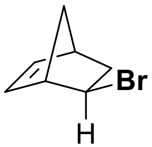
3.2.2. *Exo* / *Endo* selectivity

General and original explanation of the forms exo/endo:

Substituent of a bicyclic molecule is
•Under the ‘roof’ =endo
•Out of the ‘roof’ =exo



endo



exo

In the context of Diels Alder reaction:

Bicyclic products:

Monocyclic products:

3.2.2. *Exo* / *Endo* selectivity

Comparison between kinetic and thermodynamic product:

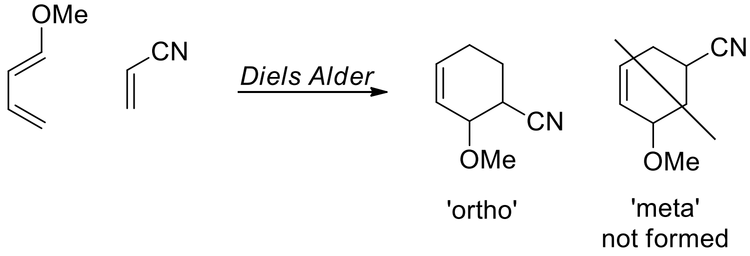
→ *Endo* is the kinetic product: the transition state is stabilized by secondary orbital interactions.

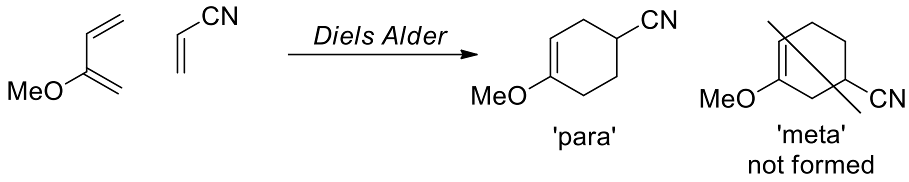
→ *Exo* is the thermodynamic product: more stable, less hindered product.

Example:

3.3. Diels-Alder regioselectivity

Observations:





Rule: Electron-donating and electron-withdrawing groups are oriented ‘ortho’ or ‘para’ to each other.

Simple explanation with the mesomeric structures:

More accurate explanation with orbital coefficients:

➡Favorable interaction: small coefficients with small, big with big

3.3. Additional examples of Diels-Alder cycloaddition

3.3.1. Extented polycyclic aromatics as diene component

Polycyclic arenes can react as diene-components in Diels-alder cycloaddition

3.3.2. Benzyne as dienophile

3.3. Additional examples of Diels-Alder cycloaddition

3.3.3. Intramolecular Diels-Alder reactions

➡ In intramolecular Diels-Alder reactions, even not very favorable Diene/Dienophile combinations which are unreactive for intermolecular Diels-alder reactions react.

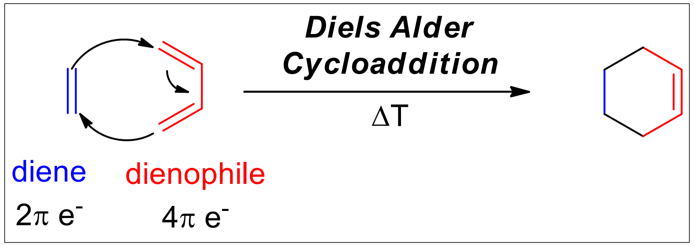
3.3.4. Self condensation and Retro-Diels-Alder reaction

Cyclopentadiene self-condenses at ambient temperature. The reaction is reversible above 140°C

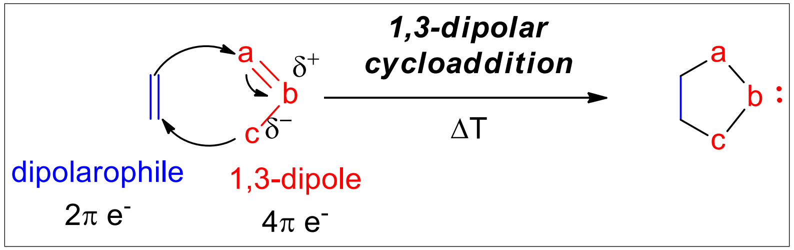
➡ All Diels-Alder cycloadditions are principally reversible at a high enough temperature (>350°C) as the entropy increases (2 molecules *v.s.* 1 molecule)

4.1.1. 1,3-dipolar cycloaddition

- Recap of the Diels-Alder cycloaddition:



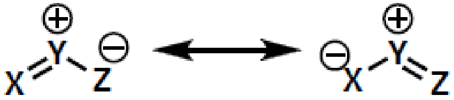
- Analogy for 1,3-dipolar cycloaddition:



Types and Classification of 1,3-Dipoles

Two Types of Dipoles:

(1) Allyl anion

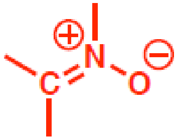


- Bent
- Y = N, O, S

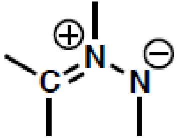
(2) Propargyl/allenyl anion

- Linear
- Y = Nitrogen

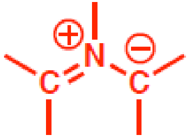
Classification of the Allyl Anion Type 1,3-Dipoles



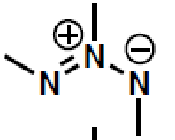
Nitrones



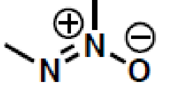
Azomethine Imines



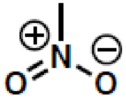
Azomethine Ylides



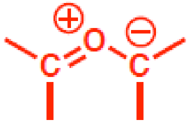
Azimines



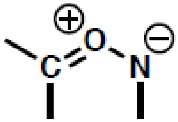
Azoxy Compounds



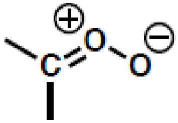
Nitro Compounds



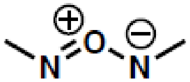
Carbonyl Ylide



Carbonyl Imines

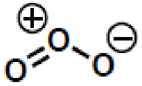


Carbonyl Oxides



Nitrosimines

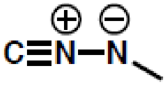
Nitrosoxides



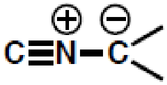
Ozone

Classification of the Propargyl/Allenyl Anion Type 1,3-Dipoles

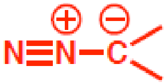
Nitrile Oxides



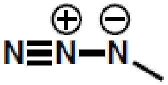
Nitrile Imines



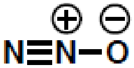
Nitrile Ylides



Diazoalkanes



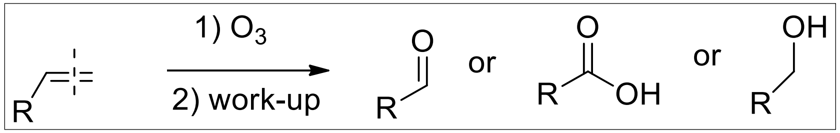
Azides



Nitrous Oxide

4.1.1. Ozonolysis

- Ozonolysis is a synthetically very important reaction converting olefins into alcohols, aldehydes, or carboxylic acids.



- Ozone O_3 is generated from O_2 (dry) by silent discharge:

$$O_2 \xrightarrow{ϟ} \text{1 to 5\% } O_3 \text{ in } O_2$$

Ozone has a blue color in solution, allowing to follow the progress of a reaction with it. When the reaction mixture turns light blue, it means that ozone is not consumed anymore and that the reaction is complete.
<u>Careful:</u> it is explosive in pure solution

- Mechanism:

4.1.1. Ozonolysis

Different work-up strategies:

- Reductive work up with $NaBH_4$ + MeOH: formation of alcohols

- Mildly reductive work up with Me_2S or PPh_3: formation of aldehydes or ketones

- Oxidative work-up with H_2O_2 + acetic acid: formation of carboxylic acids or ketones

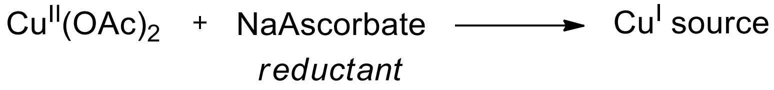
Careful with tri- or tetra-substituted alkenes:

4.1.1. Huisgen azide-alkyne cycloadditions, Click chemistry

When catalyzed by copper(I), it is known as “Click chemistry” :

It is no longer a concerted mechanism but a stepwise metal-catalyzed process.

Usually:



$$\mathrm{Cu^{II}(OAc)_2} + \underset{\textit{reductant}}{\mathrm{NaAscorbate}} \longrightarrow \mathrm{Cu^{I}}\ \text{source}$$

The reaction is very fast even at room temperature and it is proceeding in water as well.

It has found widespread applications in chemistry, chemical biology, material science, etc.

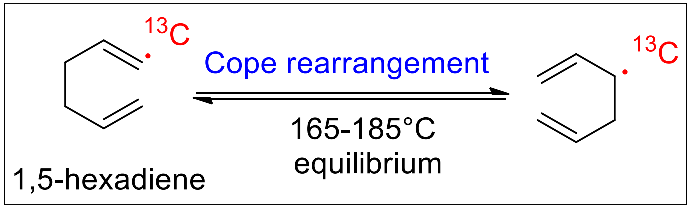
4.1.1. Nitrile-oxide cycloaddition

The nitrile-oxide dipole is not isolable, it needs to be generated in situ:

Example:

4.2.1. Cope rearrangement

Diels Alder and 1,3-cycloadditions: 4πe$^-$ + 2πe$^-$
Now, concerted molecular rearrangments: 4πe$^-$ + 2σ bonds



The equilibrium is thermally induced.

The reaction proceeds via a chair or boat transition state:

4.2.1. Cope rearrangement

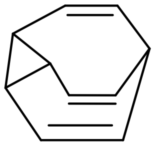
- Driving the equilibrium to one side:

• oxy-Cope rearrangement: driving force = aldehyde formation

The carbonyl tautomer is more stable, removing the enol from the equilibrium.

• Divinylcyclopropene rearrangement: driving force = release of the ring strain of cyclopropane

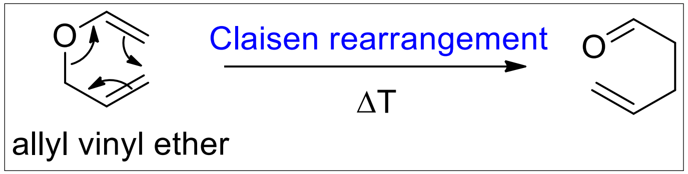
Example: bullvalene



bullvalene

fluxional molecule: degenerated Cope rearrangements lead to different (1’209’600) valence tautomers

4.2.2. Claisen rearrangement



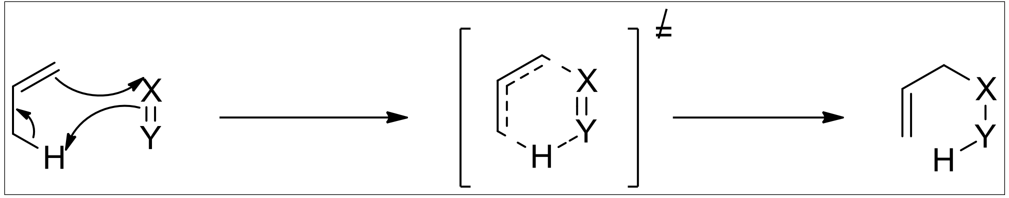
driving force of the reaction = carbonyl group formation

- Aromatic Claisen rearrangement:

When the ortho-positions are occupied:

4.2.3. Other rearrangement: the Ene reaction or Alder-Ene reaction

The Ene-reaction is a 2π + 2σ + 2π process



- Important specific example: the carbonyl Ene-reaction

Applied in the technical synthesis of menthol by the Takasago company

4.2.3. the Ene reaction or Alder-Ene reaction

- Ene-reactions with singulett oxygen :

Singulett oxygen is formed by light from “normal” triplett oxygen with a photosensitizer

Overall, this is formally an allylic oxidation with a transposition of the double bond.

- Related reactivity is observed with SeO_2:

Overall, this is formally an allylic oxidation keeping the position of the double bond.