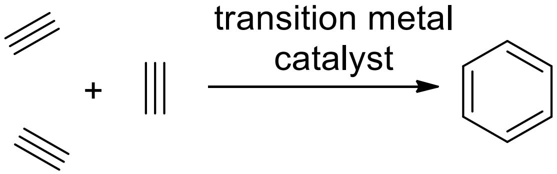
Fonction et réaction organiques II

Fall Semester 2025

Prof. Nicolai Cramer
BCH 4305
nicolai.cramer@epfl.ch

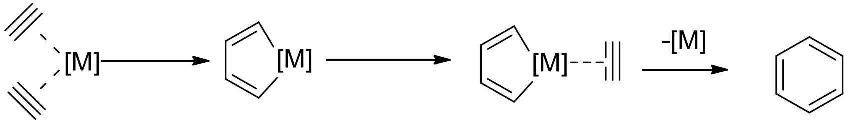
Assistants:
Jason Denizot
Jason.denizot@epfl.ch
Wilfrido Almaraz Ortiz
Wilfrido.almarazortiz@epfl.ch

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

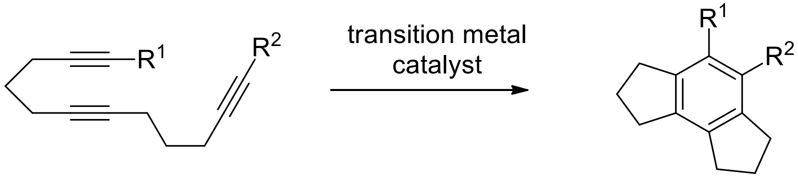


Several different metal complexes of Ni^0, Rh^I, Ir^I, Ru, Co, Pd are known for this reactivity.

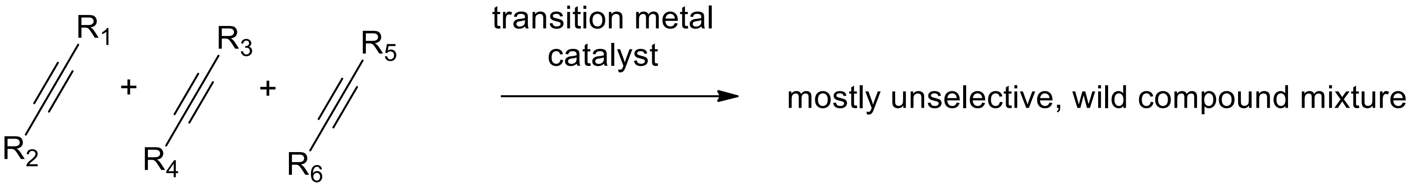
Simplified mechanism:



Well suited and excellent for intramolecular reactions



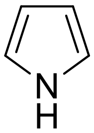
Problems of regioselectivity and chemoselectivity with different substituted alkynes



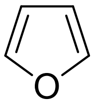
2.1.1. Nomenclature: trivial names

- Most important heterocycles:

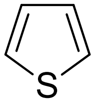
  - 5-membered ring series:



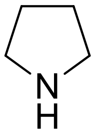
pyrrole



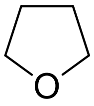
furan



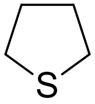
thiophene



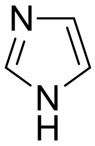
pyrrolidine



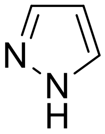
tetrahydrofuran



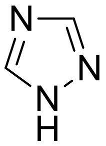
tetrahydrothiophene



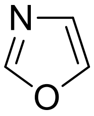
imidazole



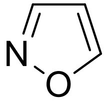
pyrazole



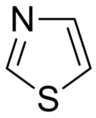
triazole



oxazole

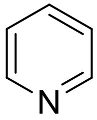


isoxazole

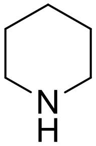


thiazole

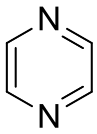
  - 6-membered ring series:



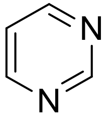
pyridine



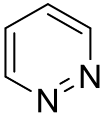
piperidine



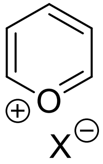
pyrazine



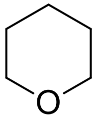
pyrimidine



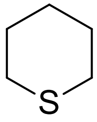
pyridazine



pyrilium salts



pyran

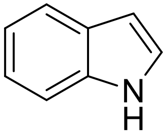


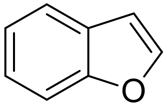
thiopyran

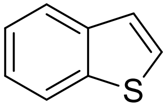
2.1.1. Nomenclature: trivial names

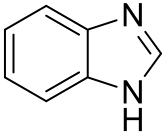
- Most important heterocycles:

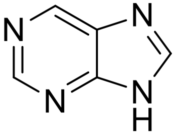
  – Condensed series:

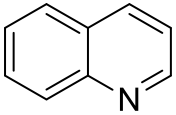

indole

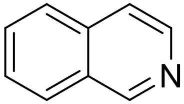

benzofuran


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

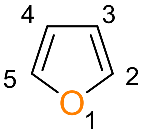
– Prefix originates from the heteroatom: N = az(a)
O = ox(a)
S = thi(a)

2.1.2. Nomenclature: The Hantsch-Widman system

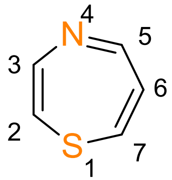
- Suffix determines the ring size:

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	

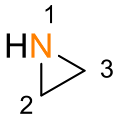
- Examples:



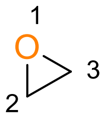
1-oxole
trivial name:
furane



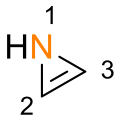
1,4-thiazepine



aziridine

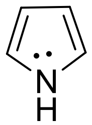


oxirane

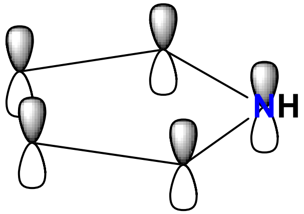


azirene

2.2.1. Comparison between pyrrole and pyridine

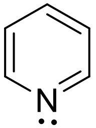


5 membered ring
electron rich

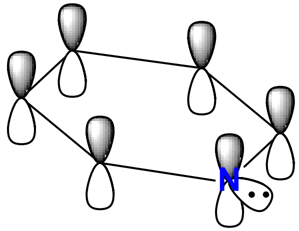


N is not basic (cannot be protonated)
lone pair is integral part of the aromatic system

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



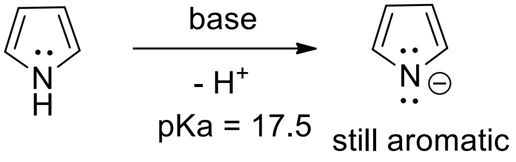
6 membered ring
electron poor



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

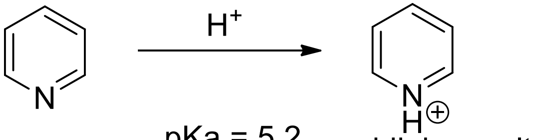
why electron poor?
6 π electrons on 6 atoms
N has a higher electronegativity than carbon
and pulls elctrons

- Examples:



pKa = 17.5 still aromatic

Pyrrole can be deprotonated

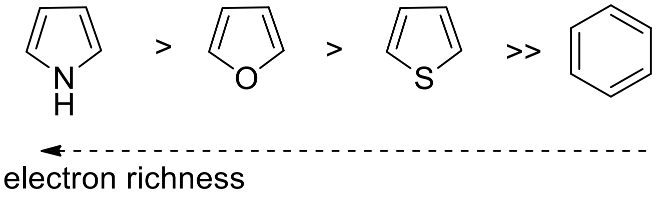


pKa = 5.2 pyridinium salt
still aromatic

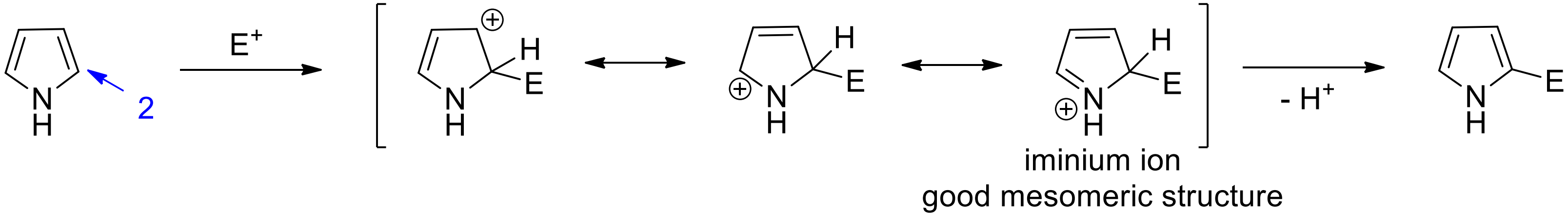
Pyridine can be protonated

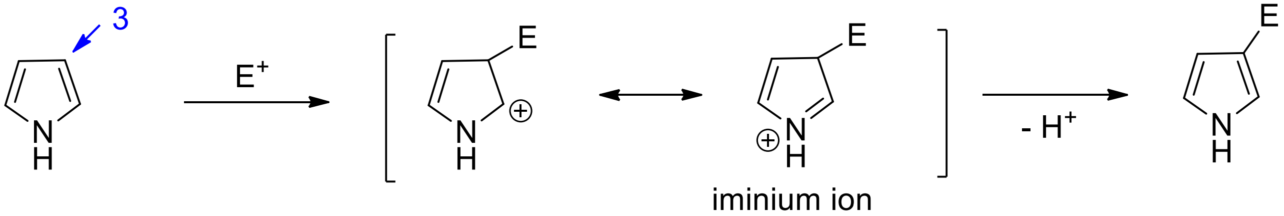
2.2.2. Reactivity of electron rich heteroaromatics

- S_EAr for electron rich heteroaromatics:



- The 2-position is the most activated:





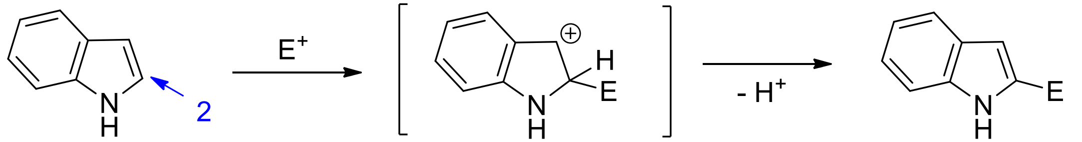
One additionnal mesomeric structure possible by an addition to the 2-position
→ better stabilization

Similar reactivity for furane and thiophene

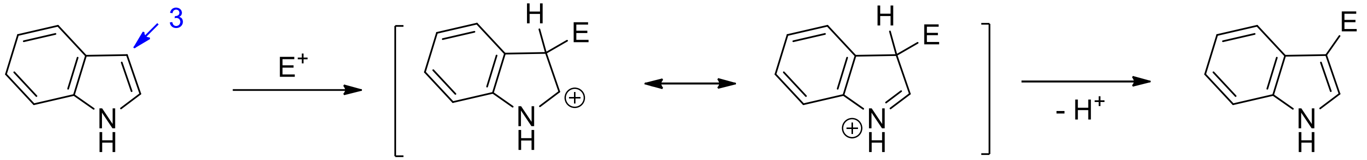
2.2.2. Reactivity of electron rich heteroaromatics

- S_EAr for indole:

- The 3-position is the most activated:

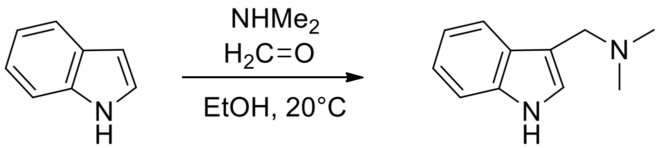


only one mesomeric structure possible without destroying the aromaticity of the annulated benzene ring

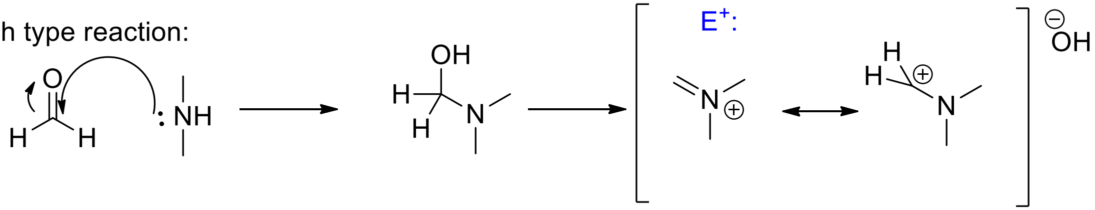


imminium salt
better stabilization

- Example: gramine synthesis



Mannich type reaction:



2.2.2. Reactivity of electron rich heteroaromatics

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