

KJM5220 - Heterocyclic chemistry

<http://www.uio.no/studier/emner/matnat/kjemi/KJM5220/h09/>

Rings containing one or more heteroatom (atom other than C)

Heteroatoms: N, O, S

Aromatic rings

5 and 6 membered rings + fused rings

Synthesis and *reactivity*

Chapter 1

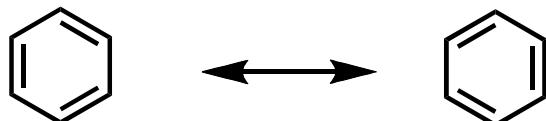
Structure (and spectroscopic) properties of aromatic heterocycles

Aromaticity

Hückel

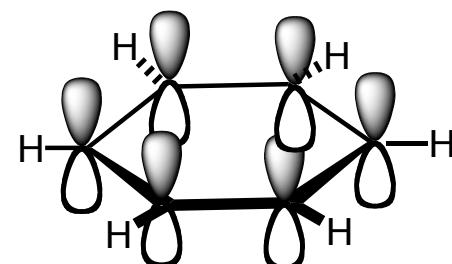
$$4n + 2$$

Benzene



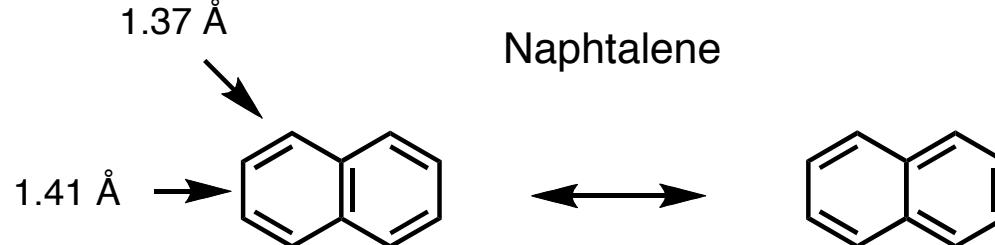
All C-C bonds 1.39 Å

All C sp²



1.37 Å

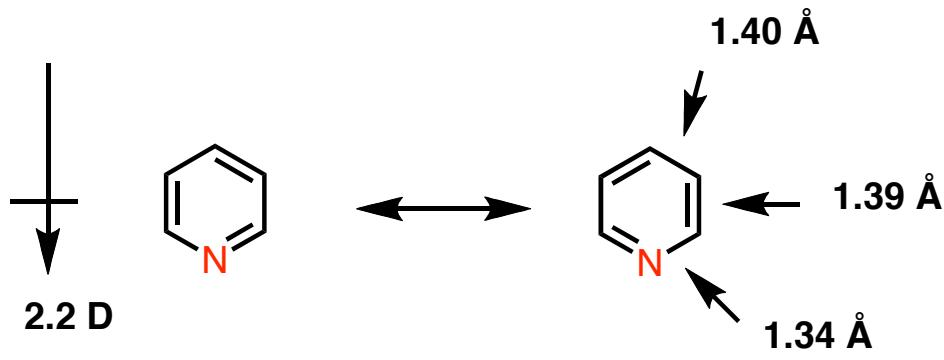
Naphthalene



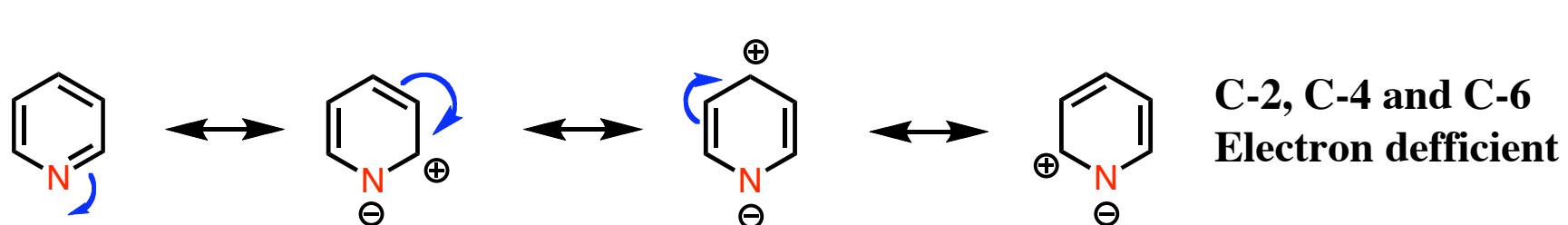
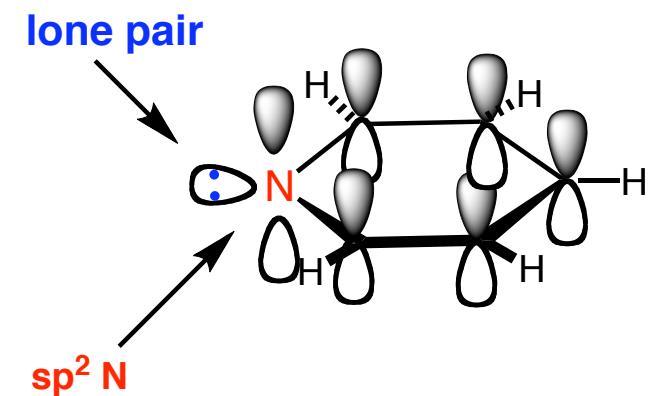
6-Membered heterocyclic rings

Heteroatom: N (or O)

Pyridine



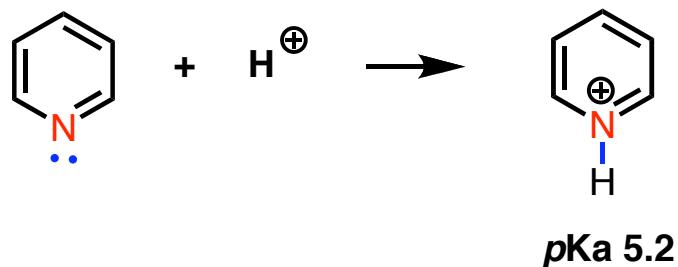
N more electroneg. than C



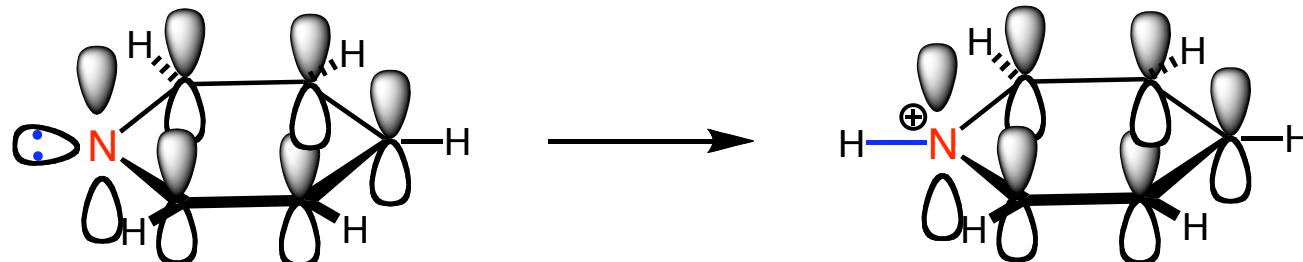
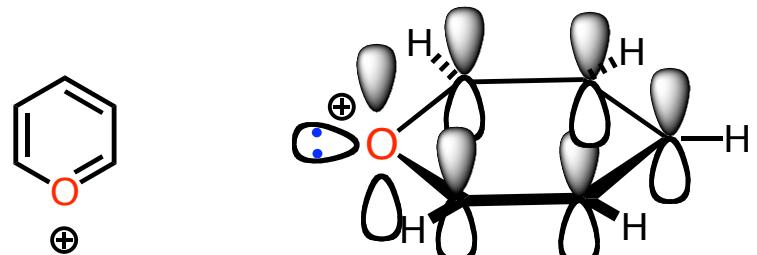
6-Membered heterocyclic rings

Heteroatom: N (or O)

Pyridine as a base



Pyrylium cation

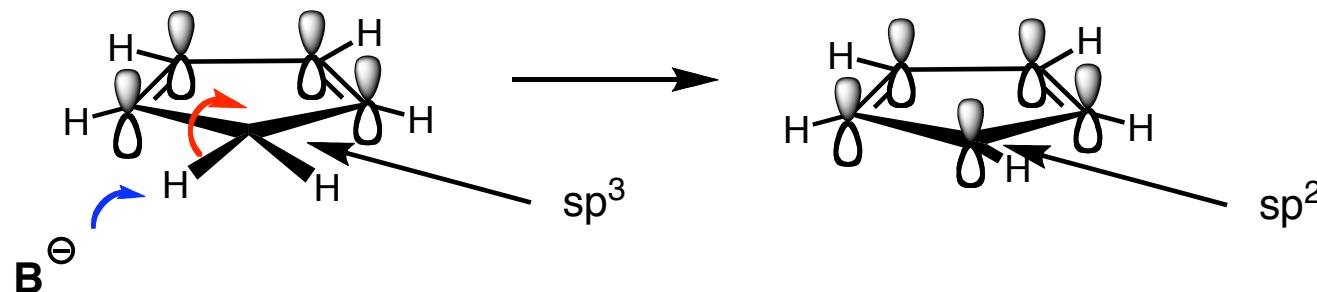


Still aromatic!

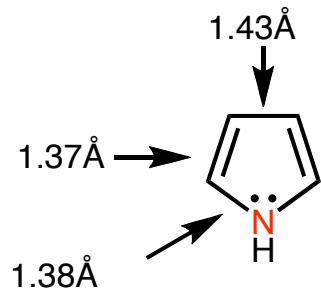
5-Membered heterocyclic rings

Heteroatom: N, O, S

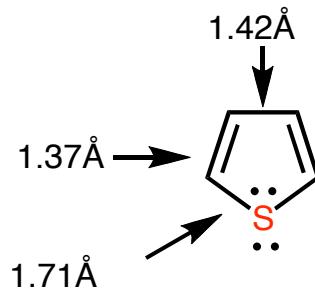
Cyclopentadiene



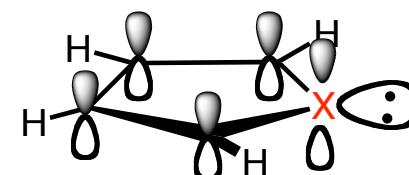
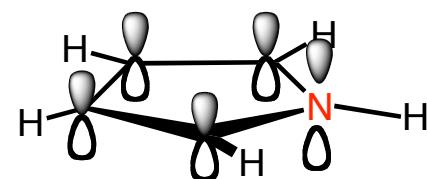
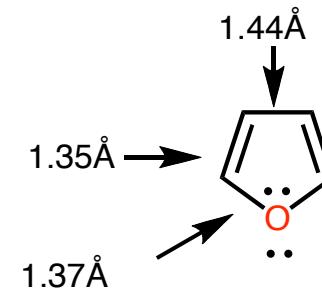
Pyrrole



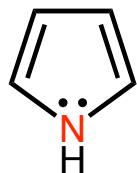
Thiophene



Furan



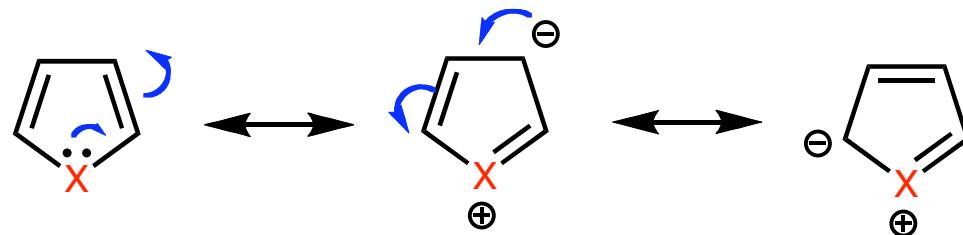
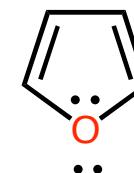
Pyrrole



Thiophene

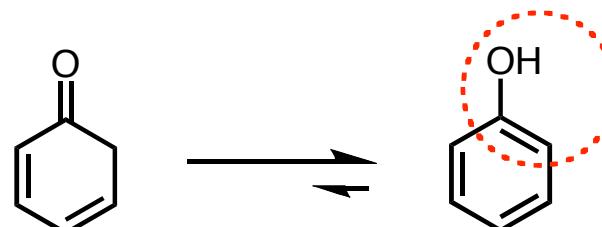
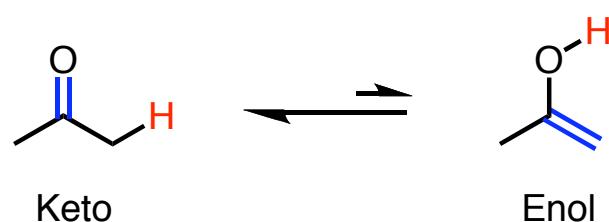


Furan

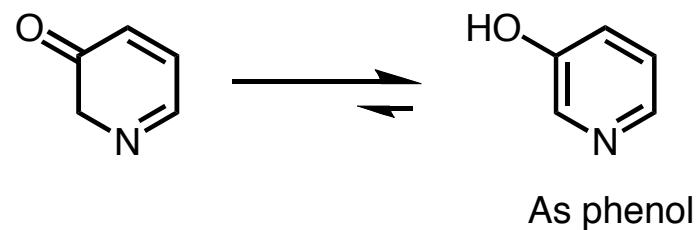


All C electron rich

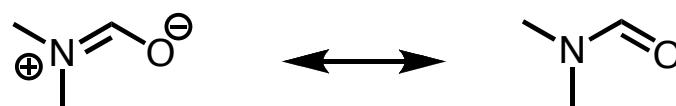
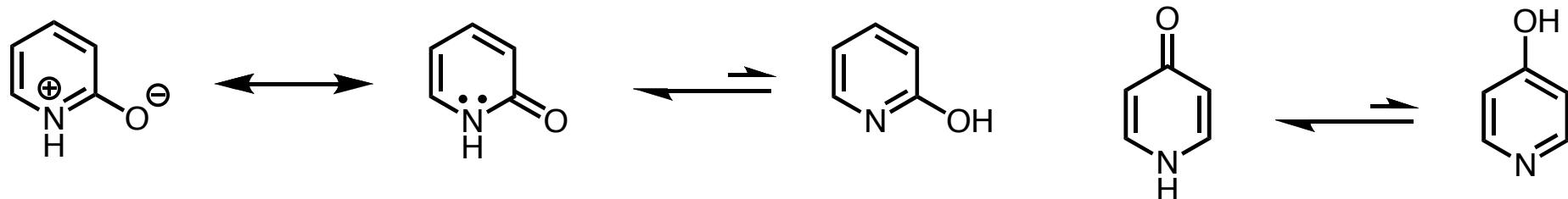
Tautomerism



Pyridones (keto) - Hydroxypyridines (enol)

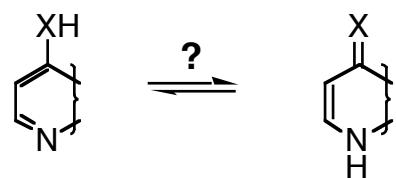
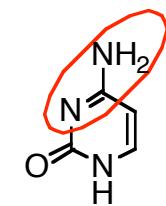
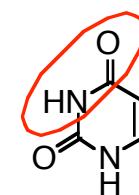
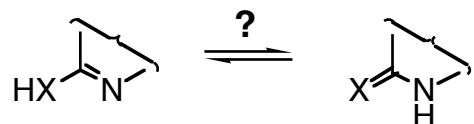


Pyridones (keto) - Hydroxypyridines (enol)



DMF

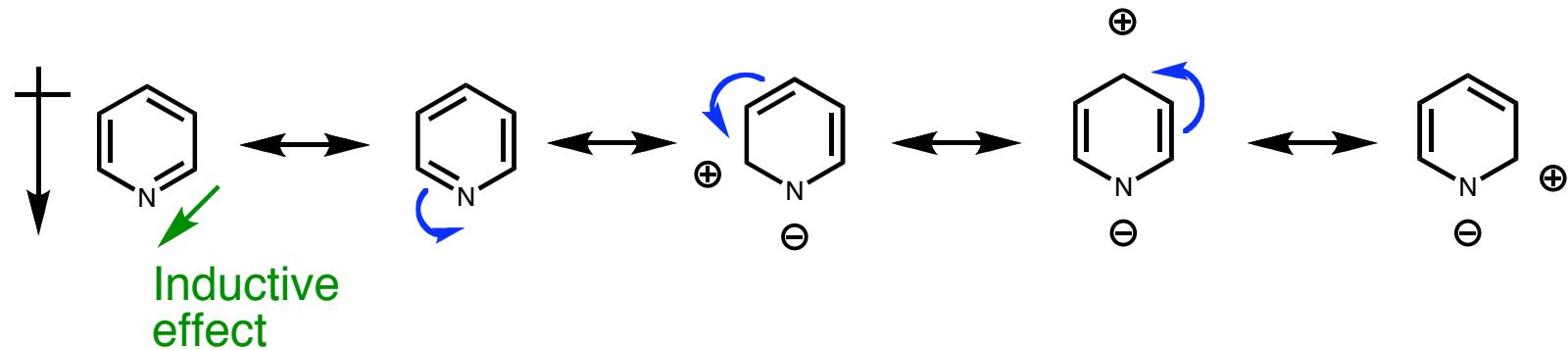
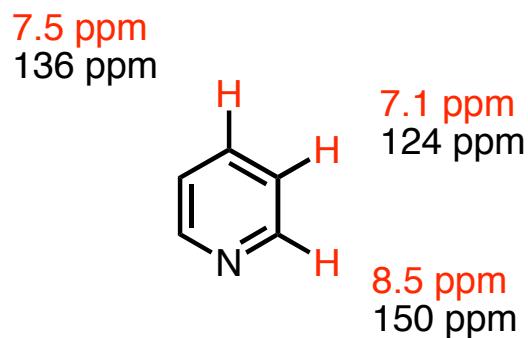
Summary taut. - 5 and 6-membered rings



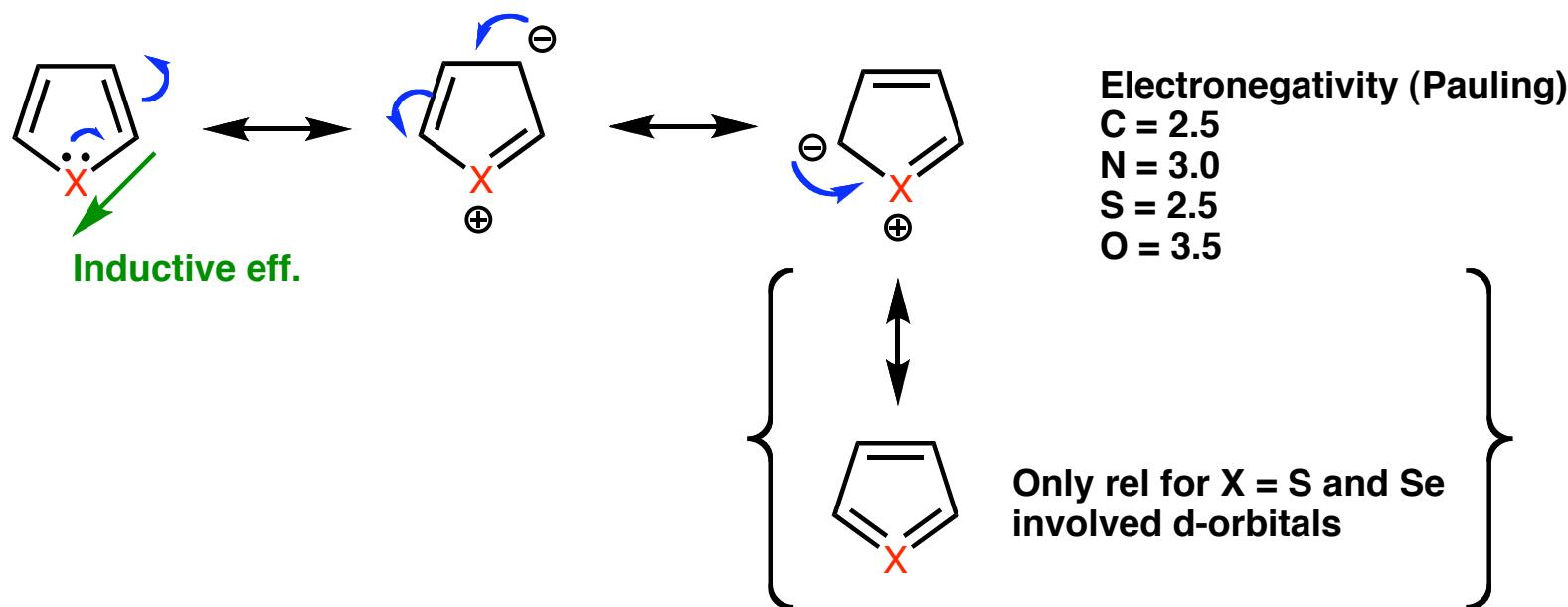
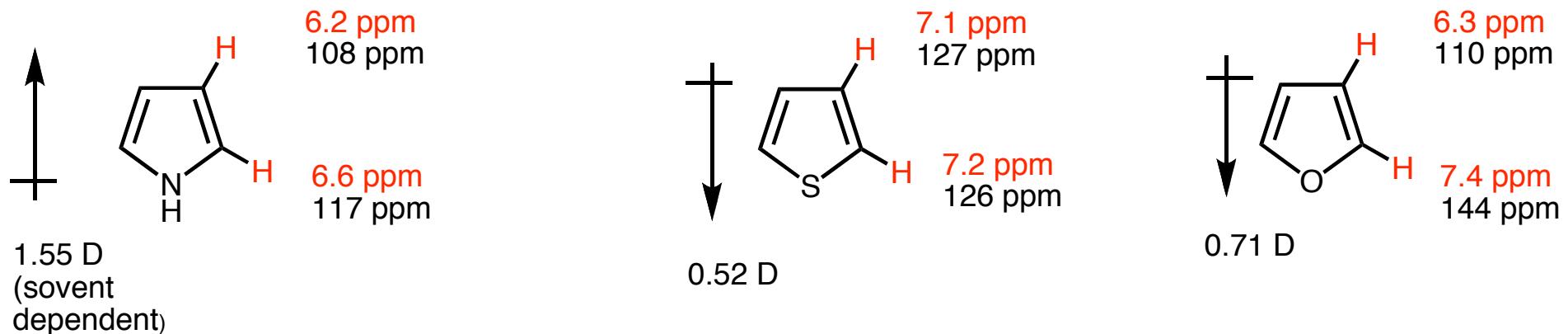
X=O: **one** / hydroxy
 X=NR: imino / **amino**
 X=S: thione (6-membered rings) /
 thiol (5 membered)

NMR

Benzene: 7.3ppm, 128ppm



(^{15}N NMR)



Chapter 2

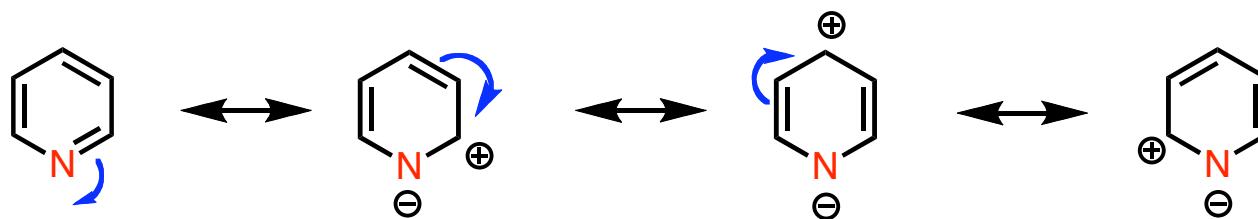
Reactivity

of

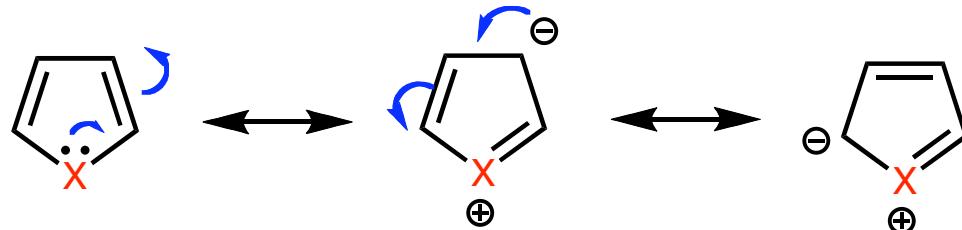
aromatic heterocycles

We already know !!!!!

6-Membered rings - electron deficient on carbons



5-Membered rings - electron rich on carbons



Electrophilic reactions

on Nitrogen

6-membered rings

5-membered rings

on Carbon

6-membered rings

5-membered rings

Deprotonation

of N-H

of C-H / C-metallation

C-Litiation

Direct litiation

Metal-halogen exchange

C-metallation (Met not Li)

Transmetallation

Insertion

Nucleophilic reactions

on Carbon

6-membered rings

5-membered rings

Reactions on metallated heterocycles

Pd-cat. cross couplings

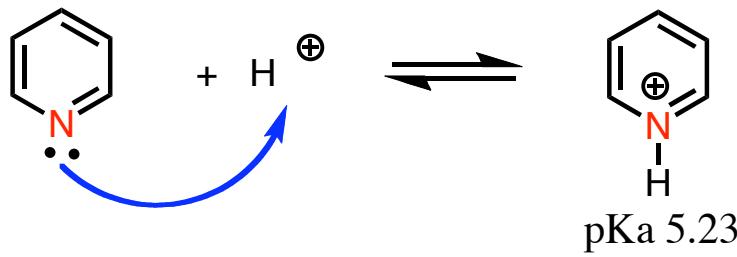
ipso-substitution

(Radical reactions)

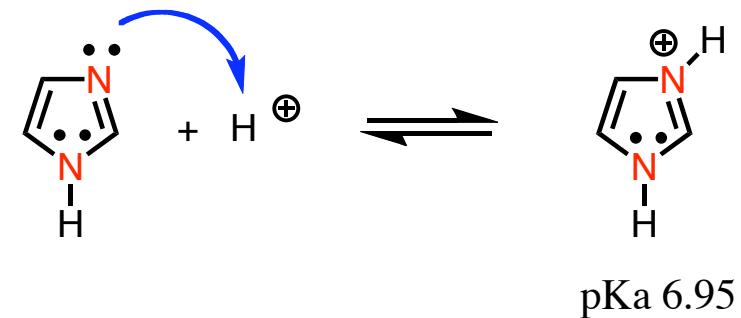
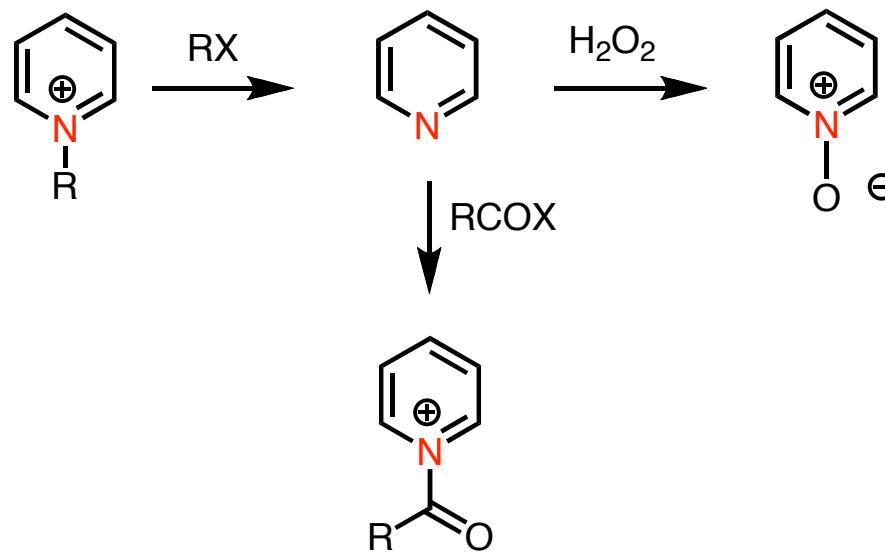
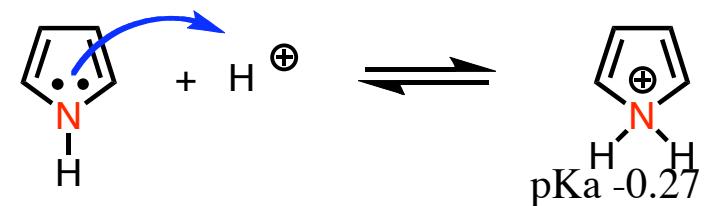
Metallation (deprotonation) in
alkyl side chains

Electrophilic reactions on Nitrogen

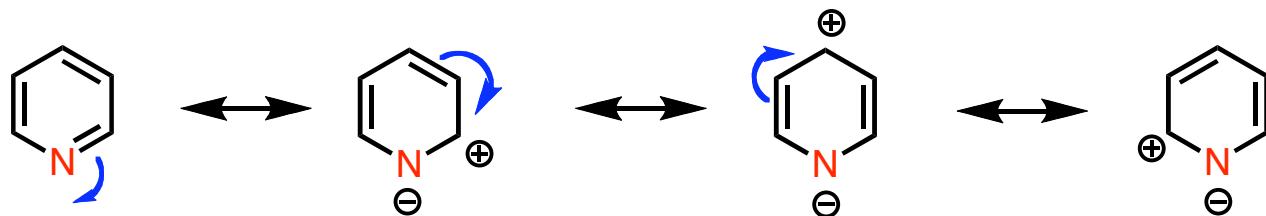
6-Membered rings



5-Membered rings

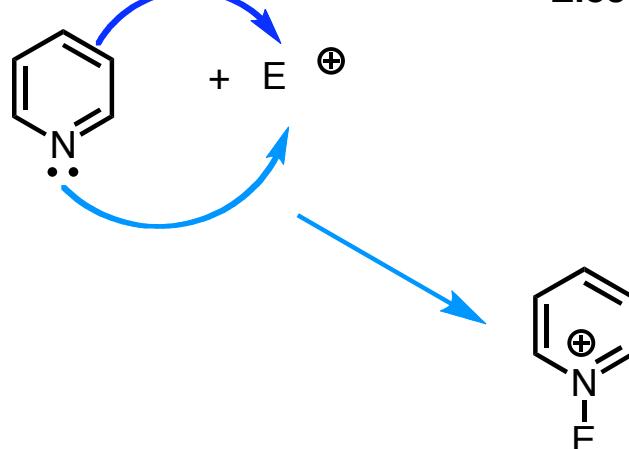
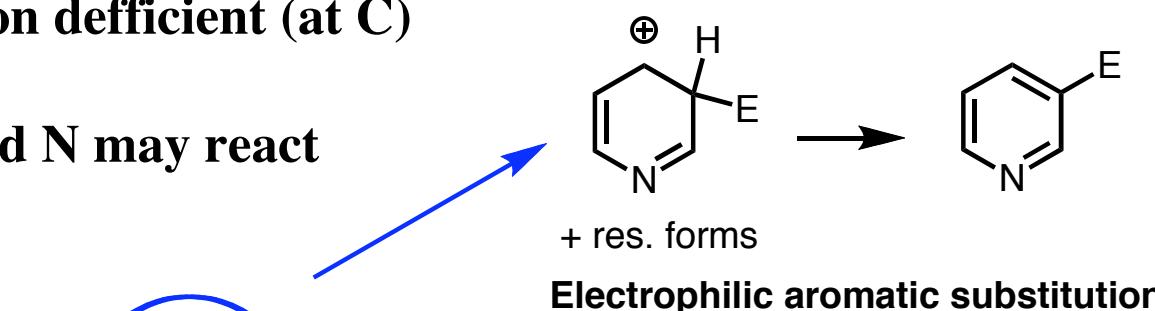


Electrophilic reactions on Carbon 6-membered rings

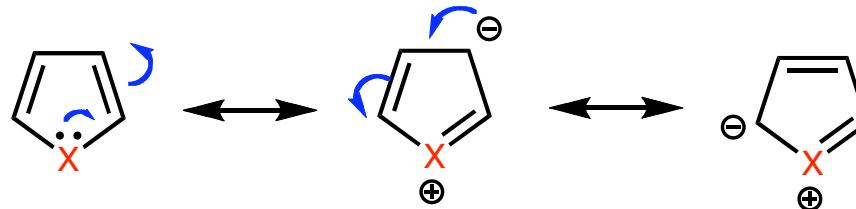


6-membered rings - electron deficient (at C)

- Decreased reactivity
- Both C (C-3 / C-5) and N may react
- Diazines less reactive

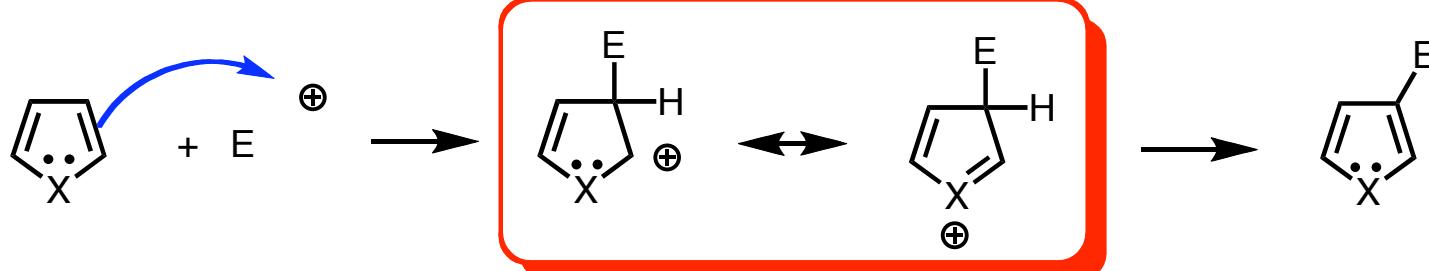
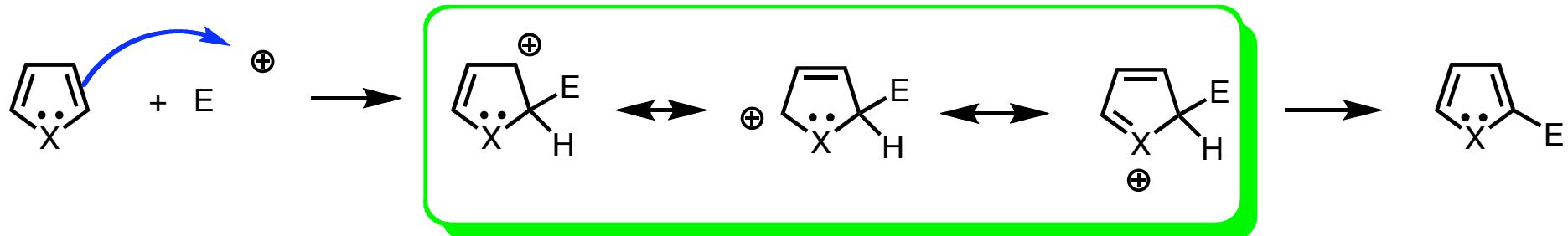


Electrophilic reactions on Carbon 5-membered rings



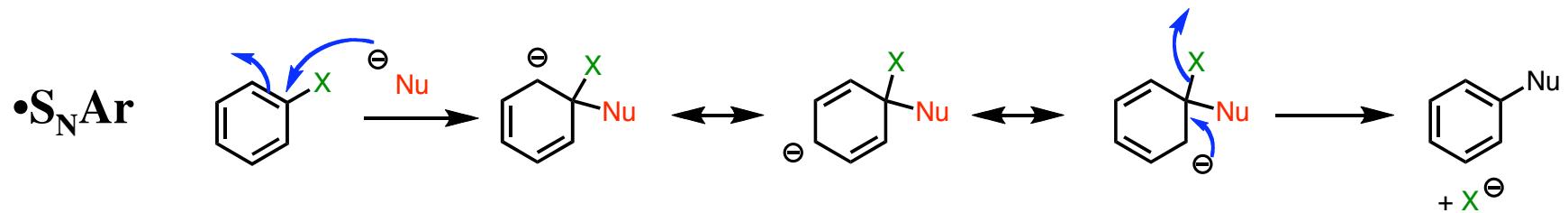
Electron rich (on all C) - reactive in electrophilic Ar. subst

Selectivity (not always good) ?



Nucleophilic reactions on Carbon

Nucleophilic aromatic substitution (KJM4200)



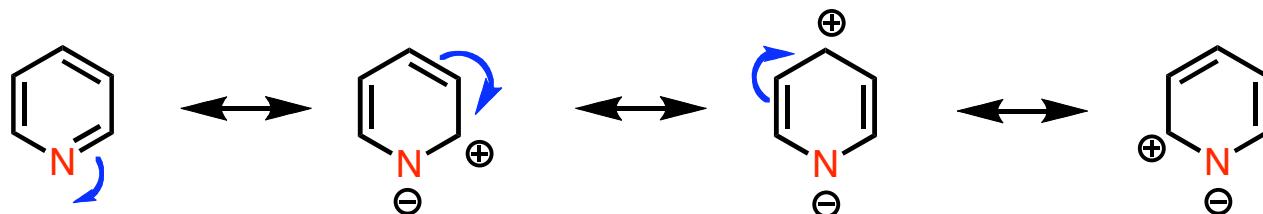
• S_N1 : Via diazonium salts and arylic cation

• Benzyne

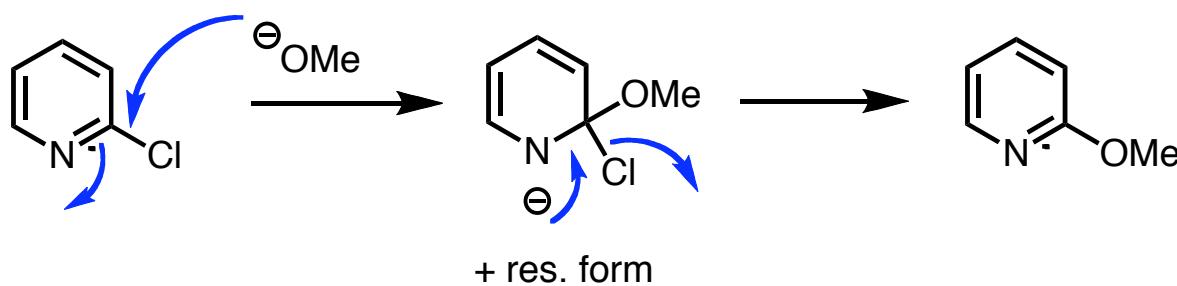
• $SRN1$: Involves radicals

• VNS : Vicarious nucl. Subst.

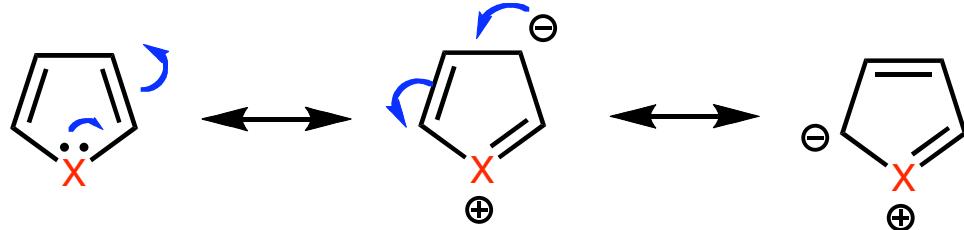
Nucleophilic reactions on Carbon 6-membered rings



6-membered rings - electron deficient (at C-2 / C-4 / C-6)
Reactive in nucleophilic Ar subst

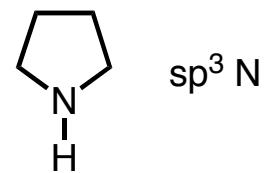
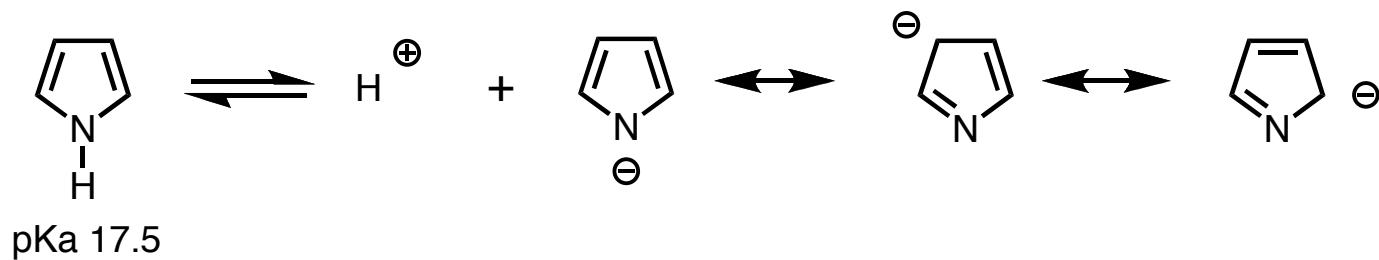


Nucleophilic reactions on Carbon 5-membered rings

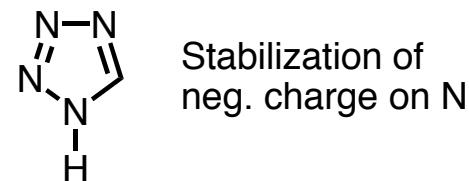


electron rich (at C)
not reactive Nu Ar subst

Deprotonation of N-H

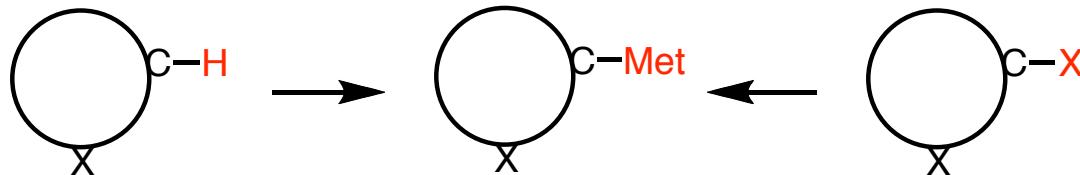


pKa ≈ 44



pKa 4.8

Deprotonation of C-H / C-metallation



C-Litiation: a) Direct litiation (C-H – C-Li)

(“Metal-Hydrogen exchange”)

b) Metal-Halogen exchange (C-X – C-Li)

C-Met

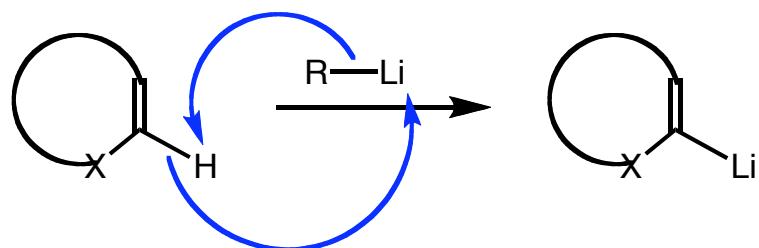
a) Transmetallation (C-Li – C-Met)

(Me not Li)

b) Insertion (C-X – C-Met-X cf Grignard)

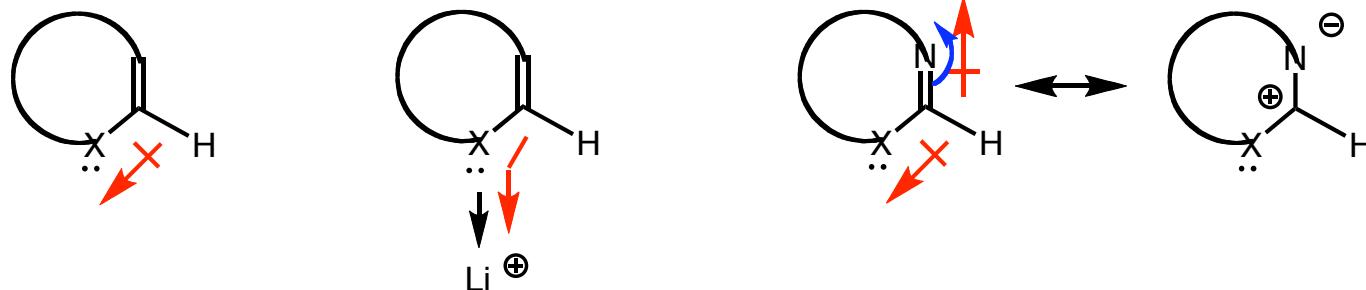
Deprotonation of C-H / C-metallation

C-Litiation: Direct lithiation



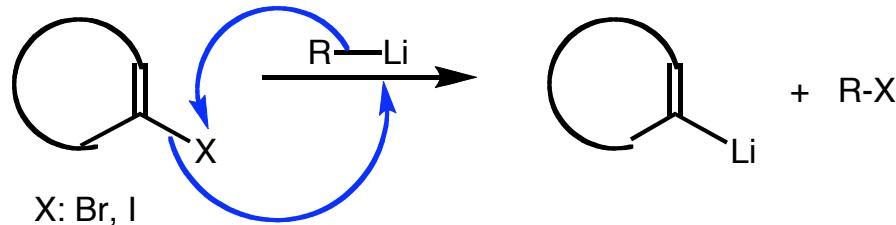
H in α -position to heteroatom

- Reactivity / Acidity / Anion Stability
- Other subst - Directed ortho metallation
- R-Li: Alkyllithium and lithium amides



Deprotonation of C-H / C-metallation

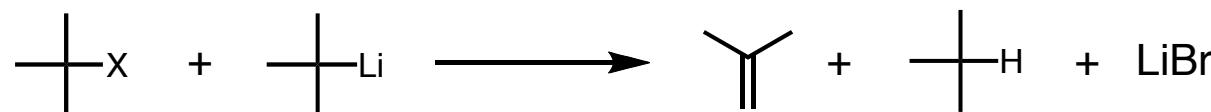
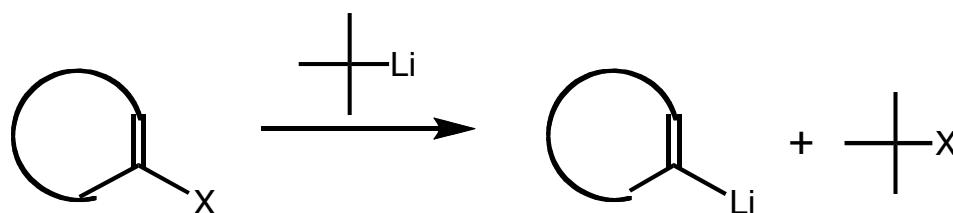
C-Litiation: Metal halogen exchange



R-Li: Alkylolithium, NOT LDA etc.

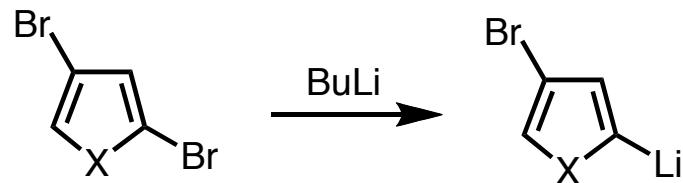
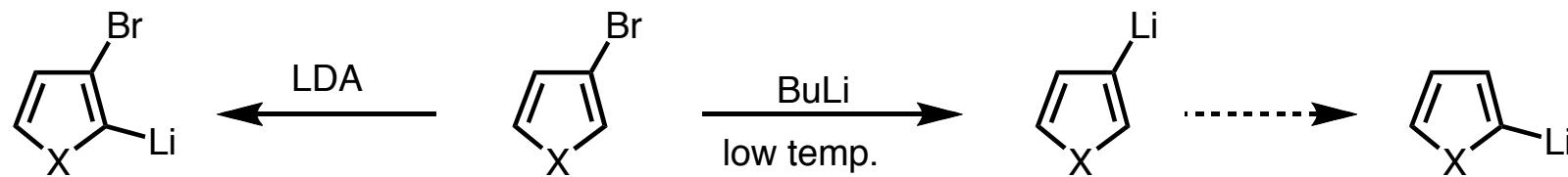
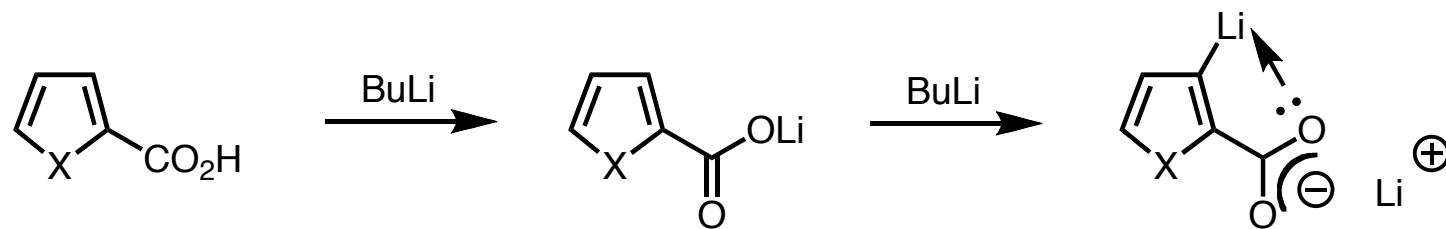
Metall - halogen exchange favored over direct lithiation, low temp.

Formation of R-X may be avoided; 2 equivs. *t*-BuLi (cf react between RLi and RX)



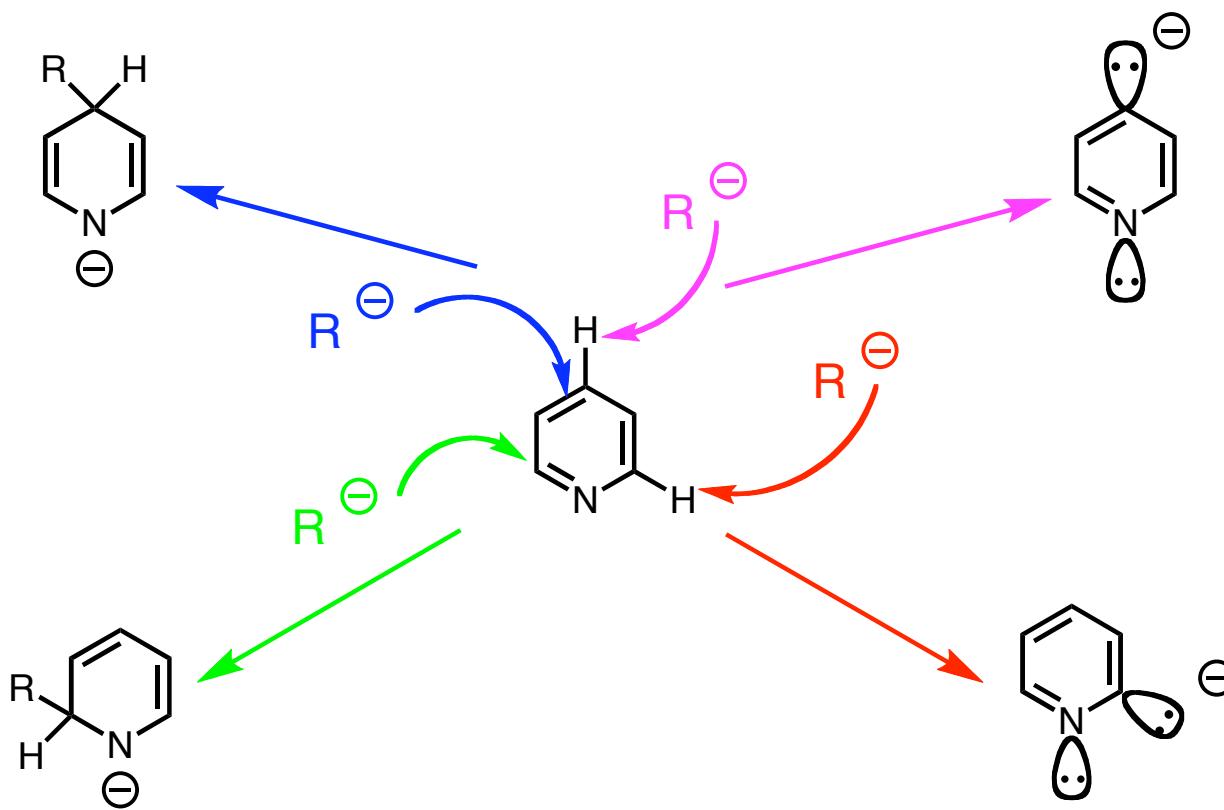
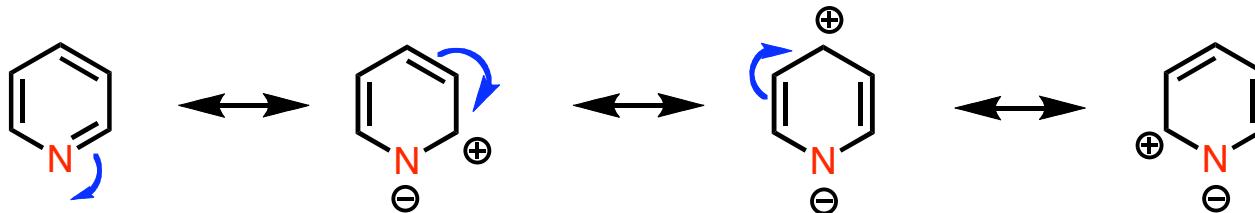
Deprotonation of C-H / C-metallation

C-Litiation: Some ex. on 5-membered rings



Deprotonation of C-H / C-metallation

C-Litiation: 6-membered rings



Met-halogen exchange
substitution?

R_3NLi : No add / subst

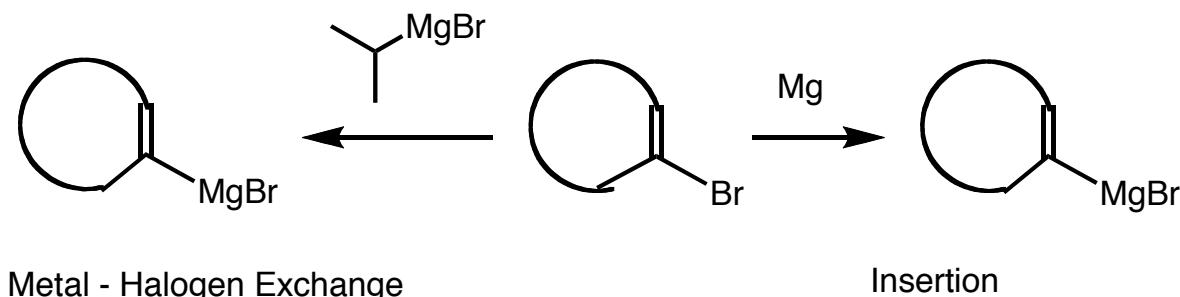
Deprotonation of C-H / C-metallation

C-metallation (Met not Li)

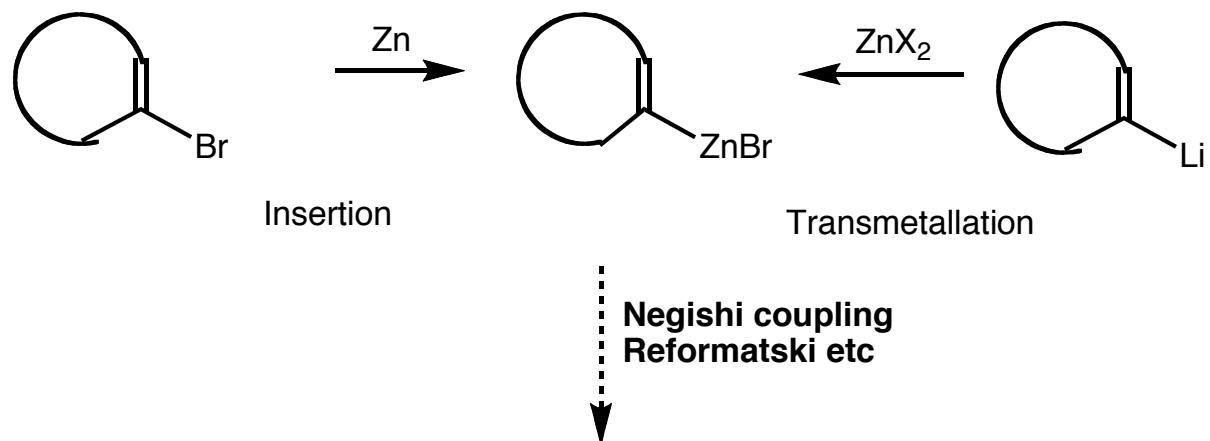
Transmetallation

Insertion

Met = **MgX** (Grignard reagents)



Met = **ZnX**



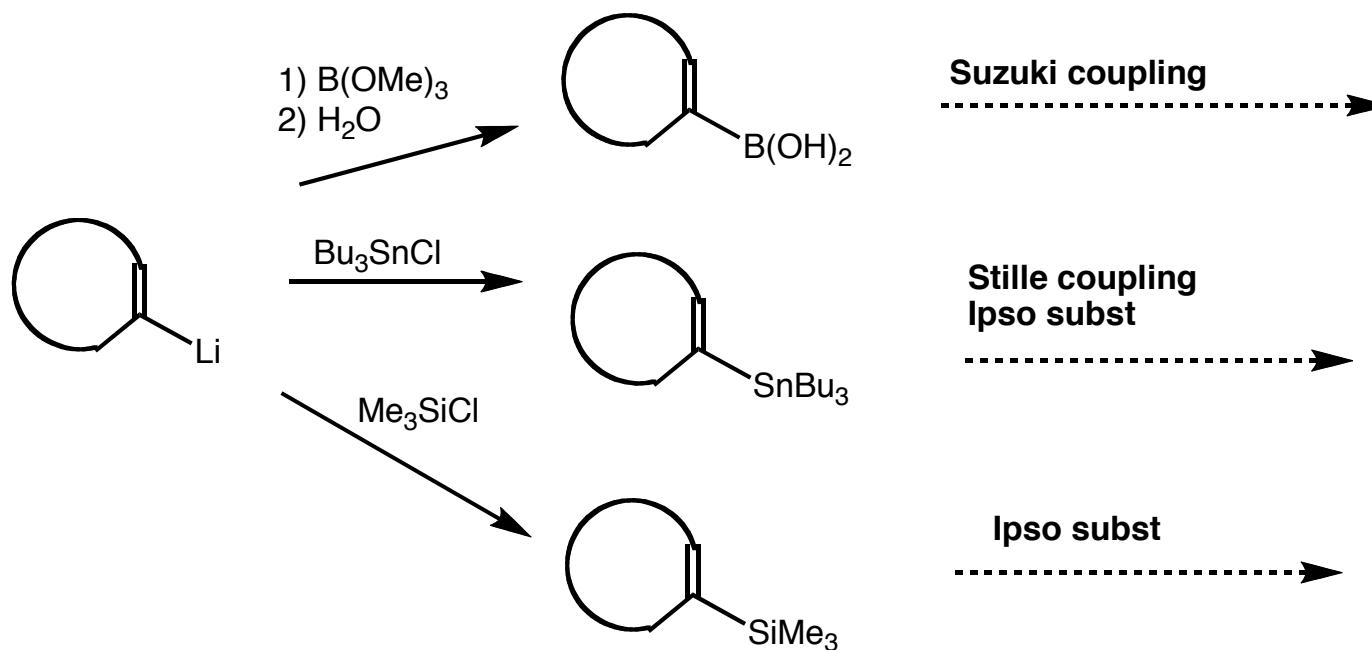
Deprotonation of C-H / C-metallation

C-metallation (Met not Li)

Transmetallation

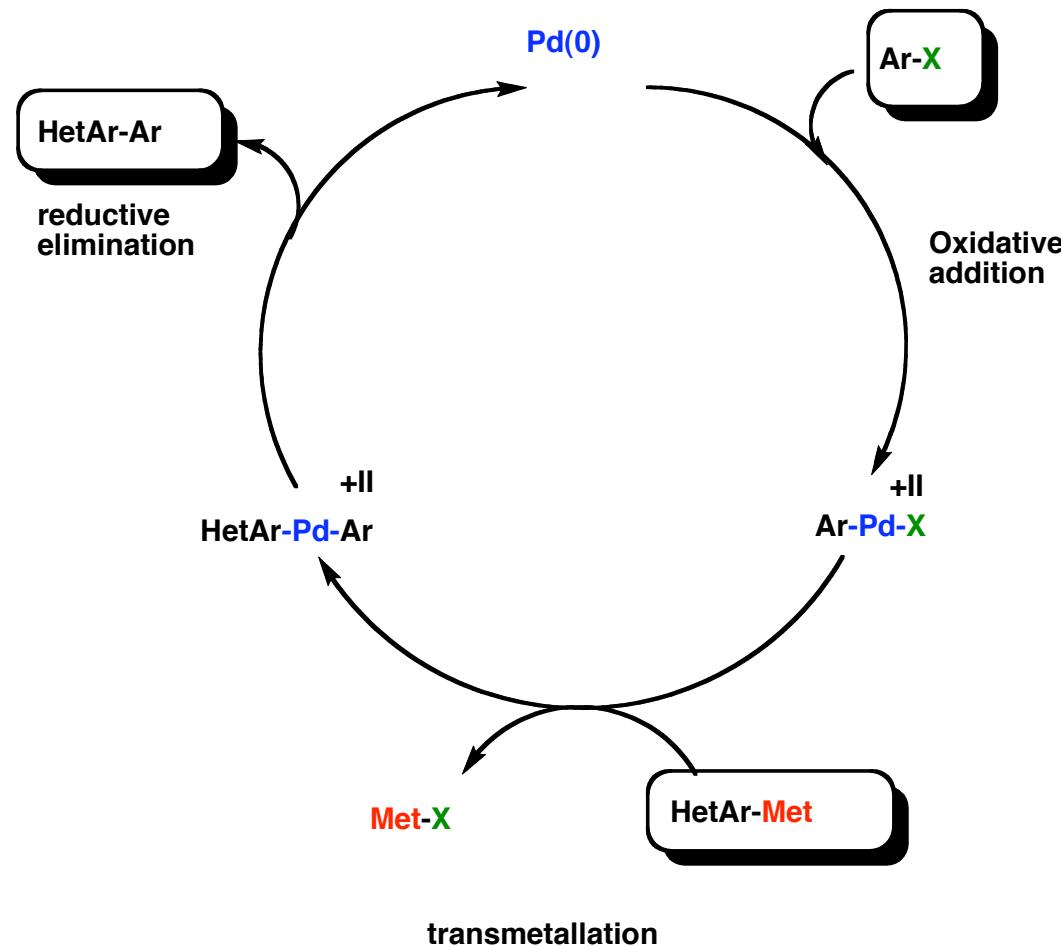
Insertion

Met = $\text{B}(\text{OR})_2$, SnR_3 , SiR_3



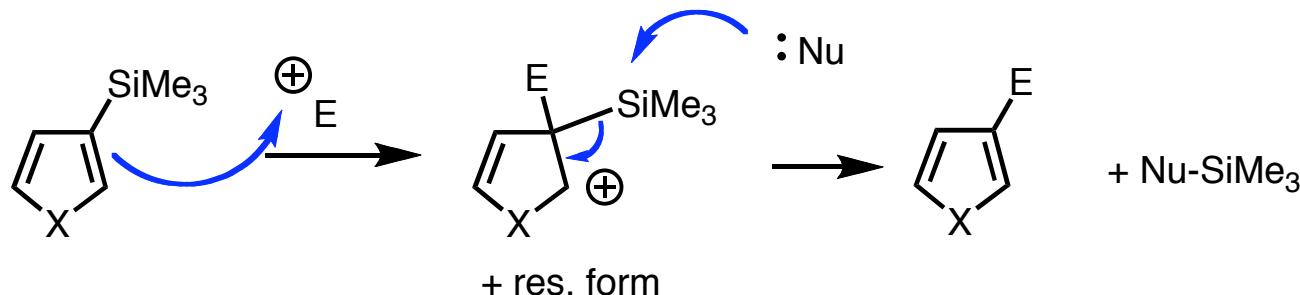
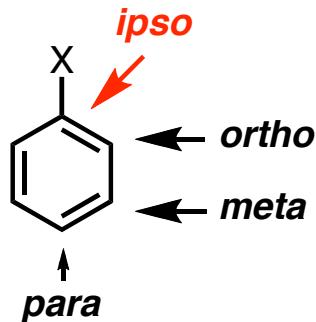
Reactions on metallated heterocycles

Pd-cat. cross couplings (KJM4200)



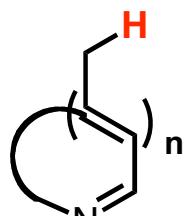
Reactions on metallated heterocycles

ipso-substitution

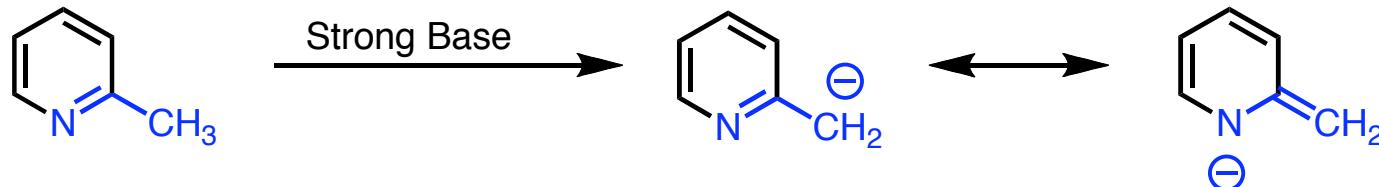
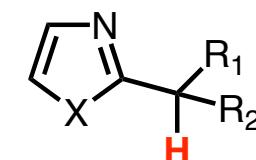
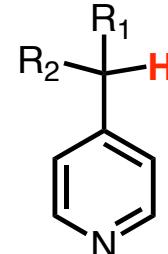
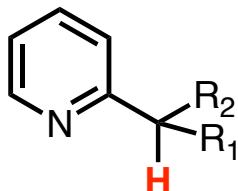


Displacement of -SiR₃, not H in E-fil Ar subst (also possible for SnR₃)

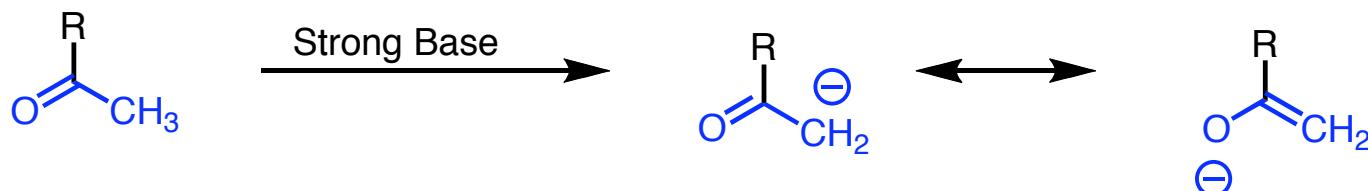
Metallation (deprotonation) in alkyl side chains



Acidic H



c.f. enolate anion



Next time:

Chapter 3 - Synthesis of aromatic heterocycles

Chapter 4: Intro to pyridines and benzofused pyridines

Chapter 5: Pyridines