

Chapter 3

Synthesis of aromatic heterocycles

SYNTHESIS OF AROMATIC HETEROCYCLES

CONSTRUCTION OF THE RING SKELETON

I. Carbonyl condensation type reactions

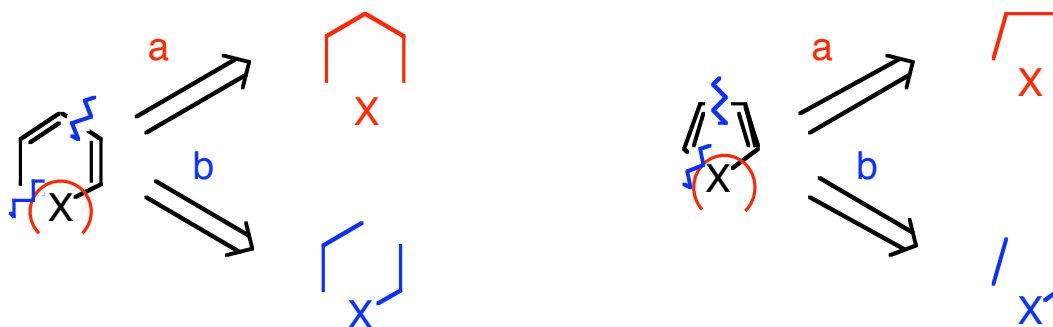
II. Cycloadditions

a) with 1,3-dipoles

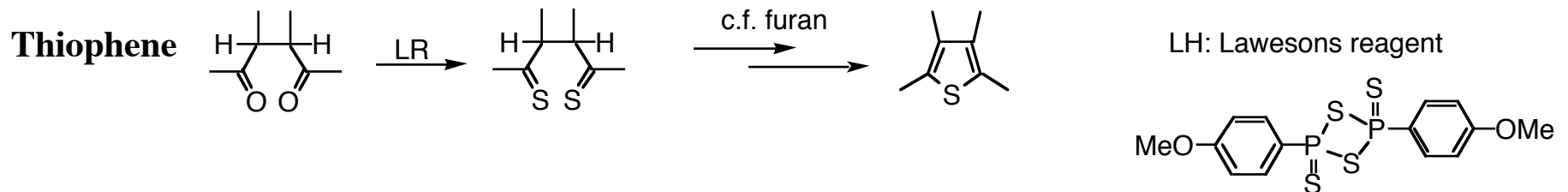
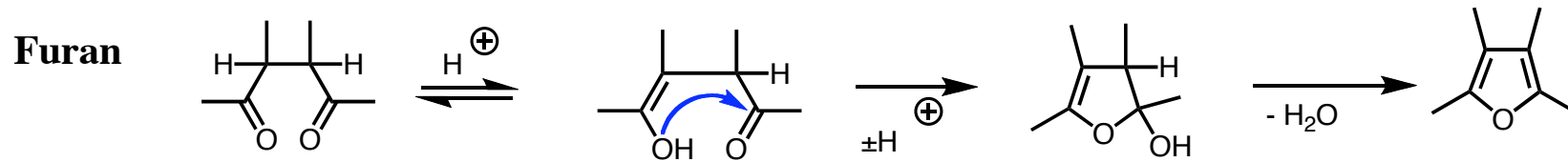
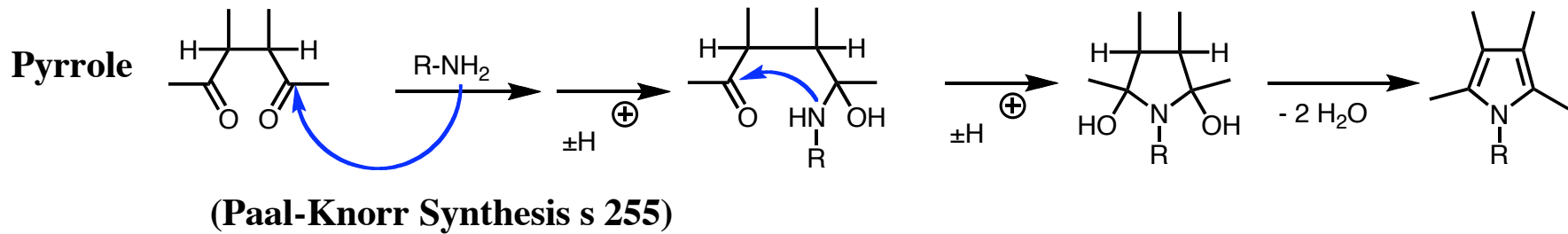
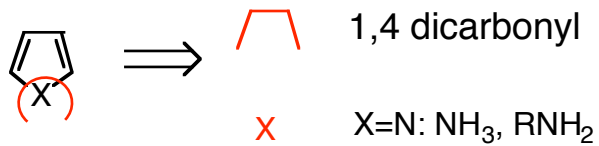
b) with *ortho*-quinodimethanes (DA type react.)

III. Nitrene insertion

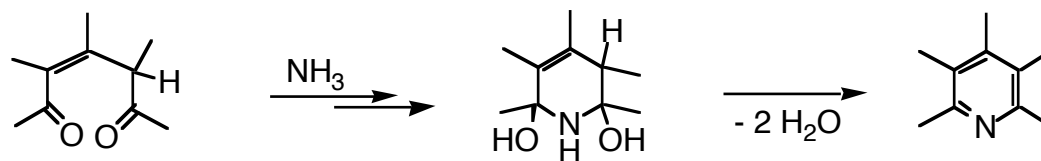
Carbonyl condensations



Strategy a) - 5-membered rings

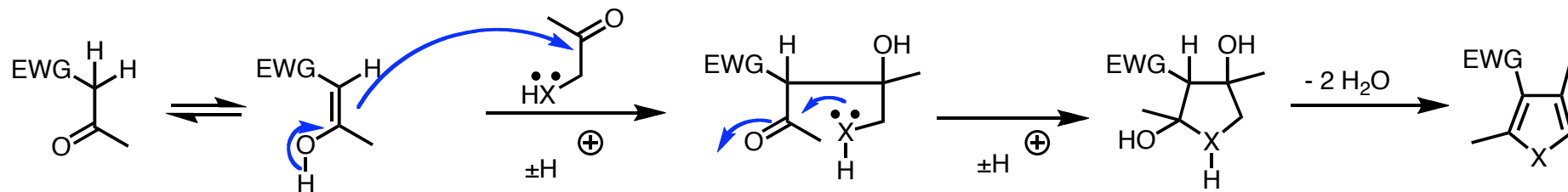
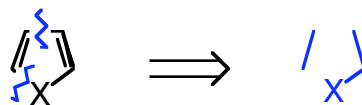


Strategy a) - 6-membered rings



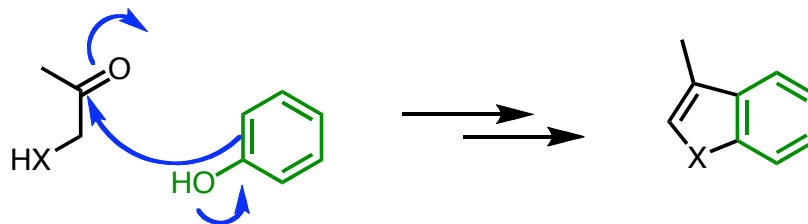
Strategy b

5-membered rings

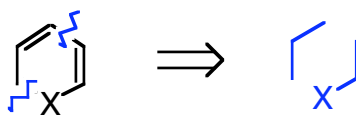


EWG: CN, COR etc.
X: NR; O, S

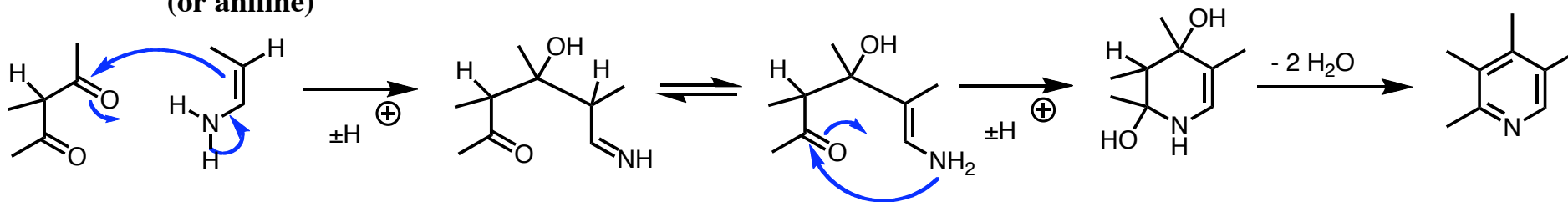
Enol
(or phenol)



6-membered rings



Enamine
(or aniline)



I. Carbonyl condensation type reactions

II. Cycloadditions

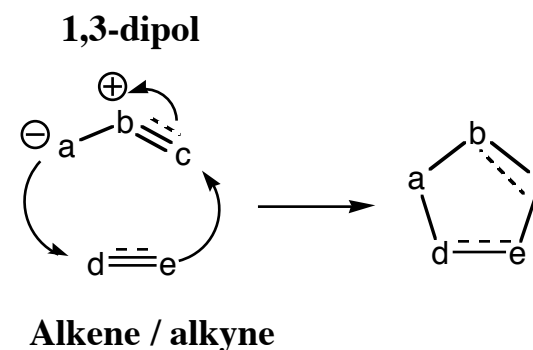
a) with 1,3-dipoles

b) with *ortho*-quinodimethanes (DA type react.)

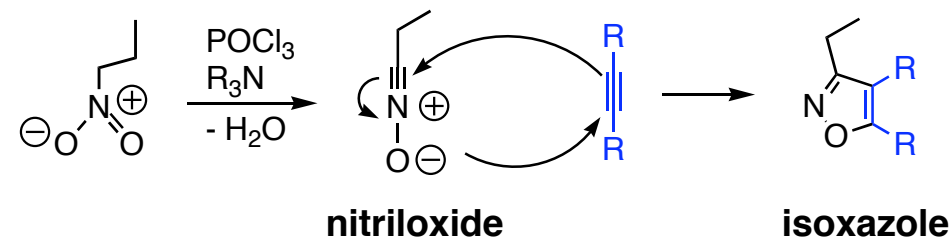
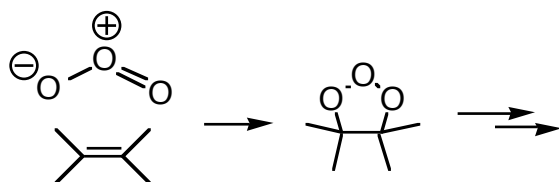
III. Nitrene insertion

1,3-Dipolar Cycloaddition

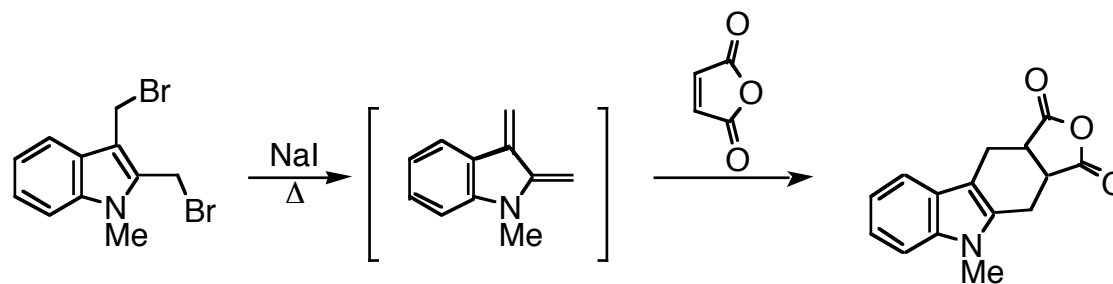
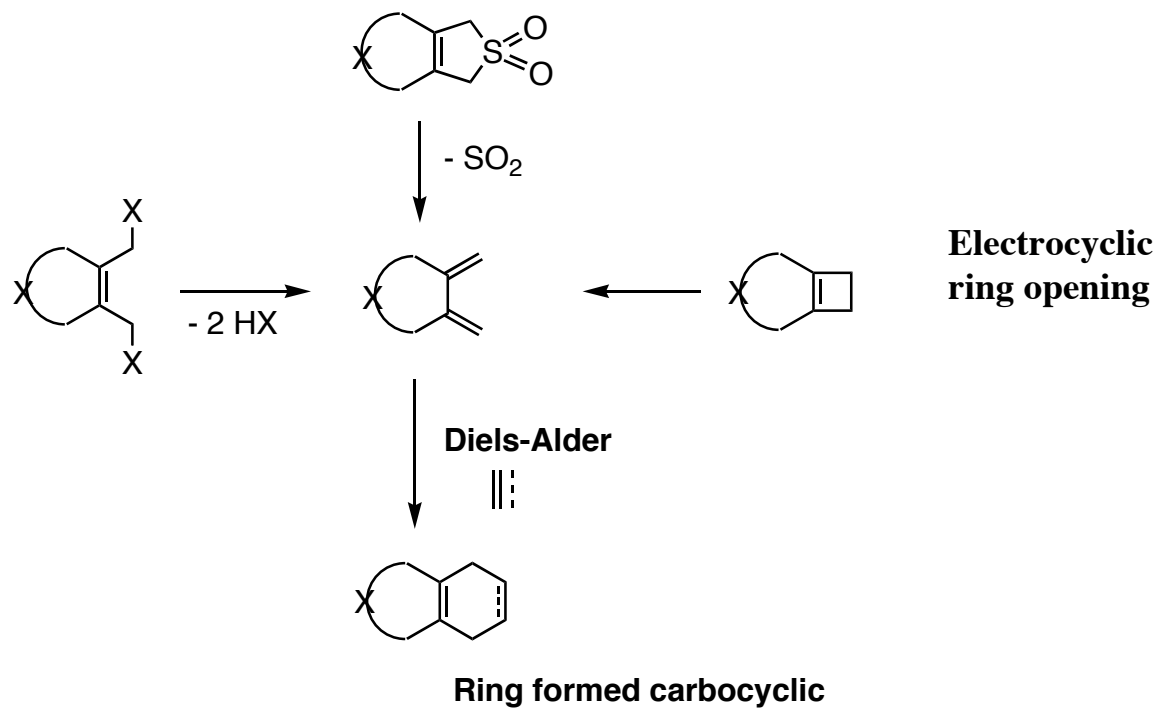
Only 5-membered rings



Ex. ozonolysis



Cycloaddition with *ortho*-Quinodimethanes



I. Carbonyl condensation type reactions

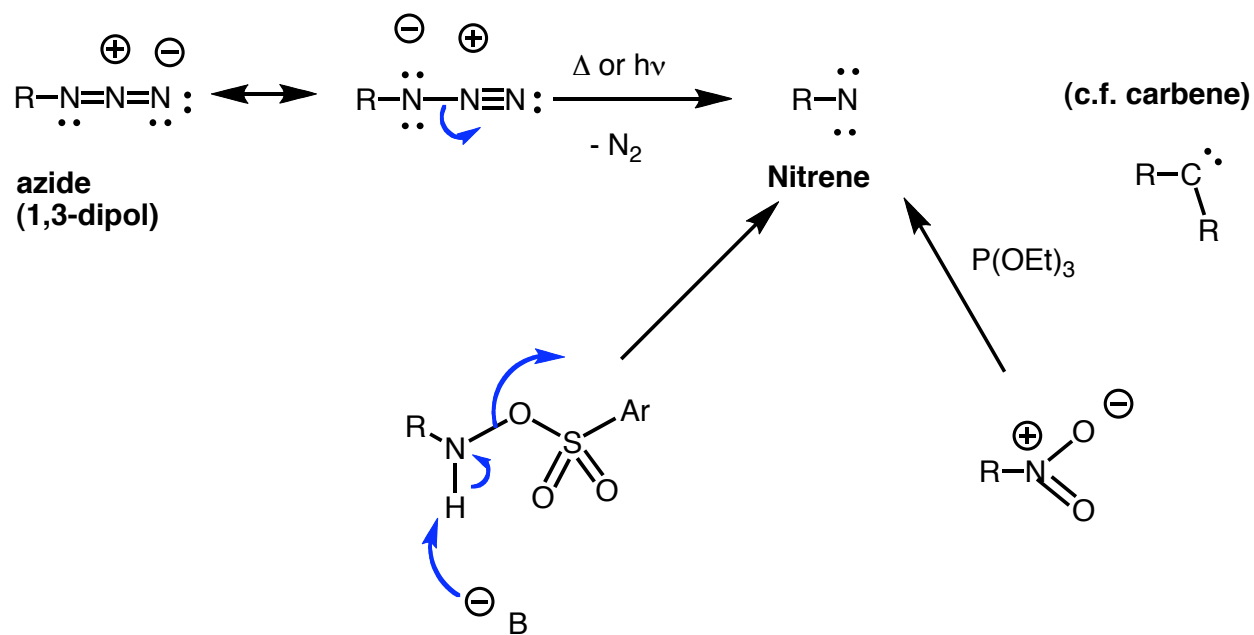
II. Cycloadditions

a) with 1,3-dipoles

b) with *ortho*-quinodimethanes (DA type react.)

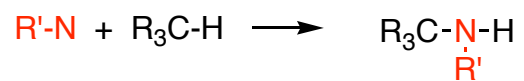
III. Nitrene insertion

Generation of nitrenes

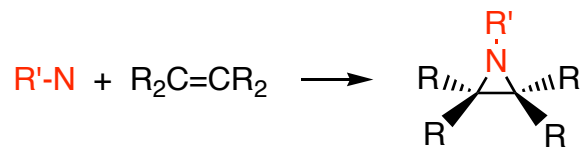


React. of nitrenes

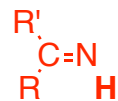
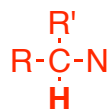
Insertion



Add. to double bonds

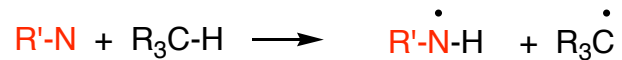


Rearrangement

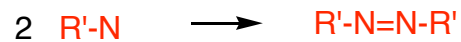


Dominating react alkyl nitrenes

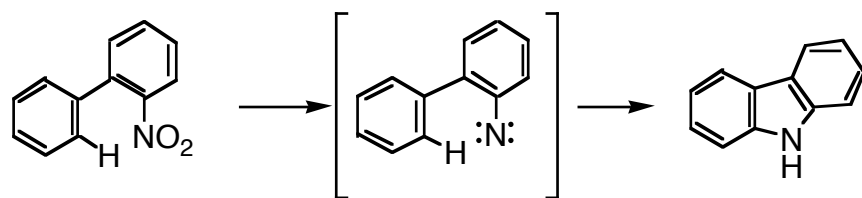
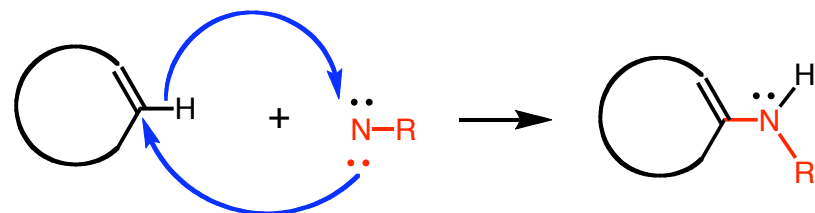
Abstraction



Dimerisation

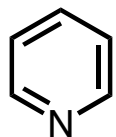


Nitrene insertion - Heterocyclic synthesis

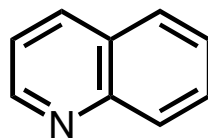


Chapter 4

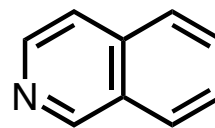
Typical reactivity of pyridines, quinolines and isoquinolines



Pyridine



Quinoline

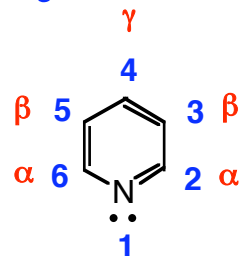


Isoquinoline

Chapter 5

Pyridines: reactions and synthesis

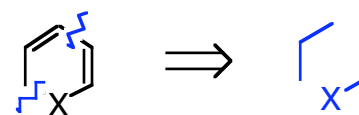
Pyridine



Synthesis - Carbonyl condensations

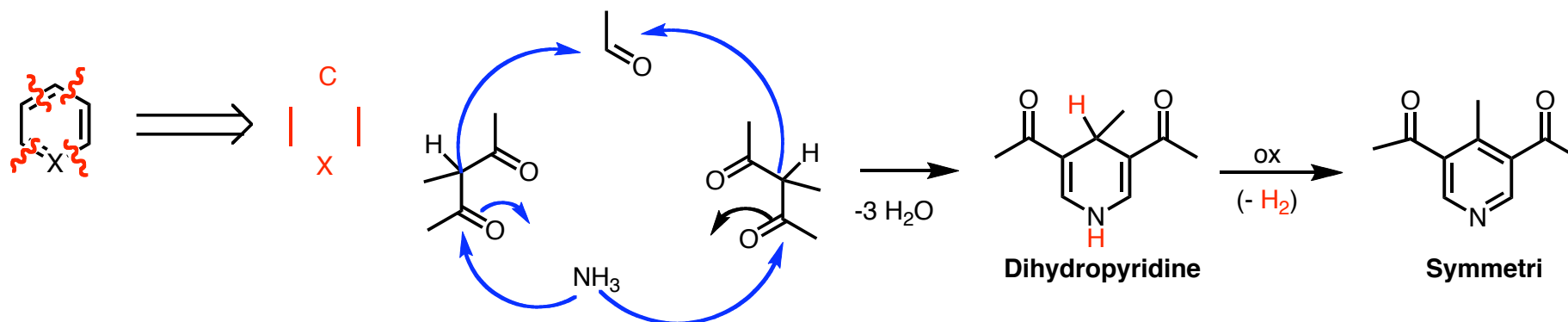


Strategy a - Chapt 3



Strategy b - Chapt 3

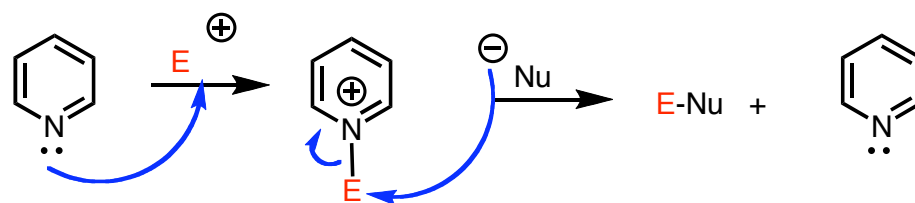
From 2 equivs. 1,3-dicarbonyl, aldehyde and ammonia - Hantzsch Synthesis



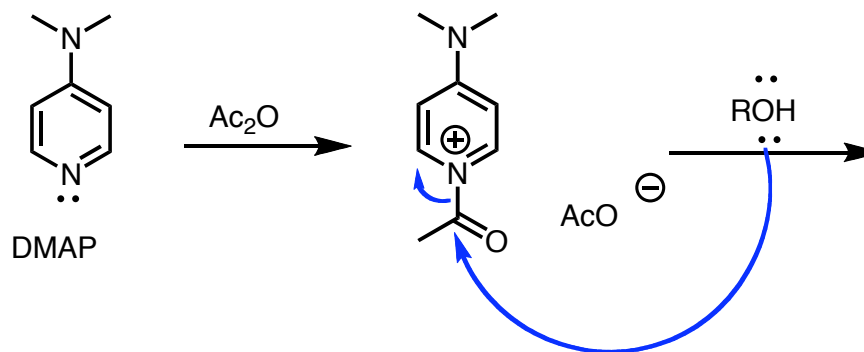
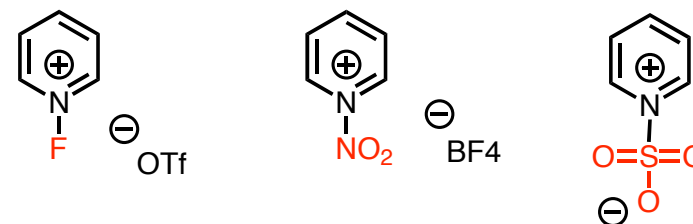
Pyridine - Reactivity

Reaction with electrophiles - react. on N:

- Protonation
- Nitration
- Sulfonation
- Amination
- Halogenation
- Alkylation
- Acylation



Mild, not acidic
electrophile

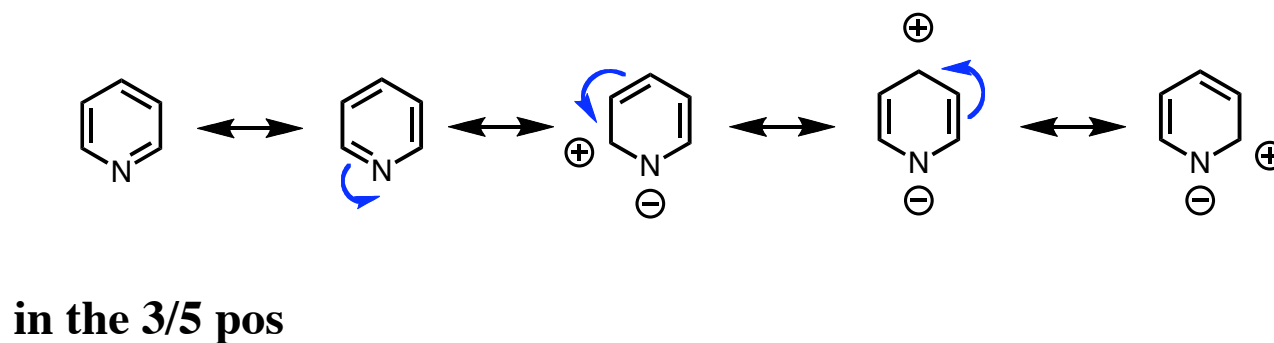


Reaction with electrophiles - react. on C - E-fil Ar subst

Difficult:

- Electron deficient ring (poor Nu)
- Electrophiles may react at N

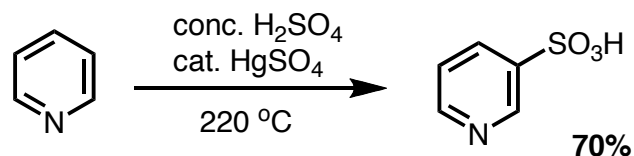
- Nitration
- Sulfonation
- Halogenation



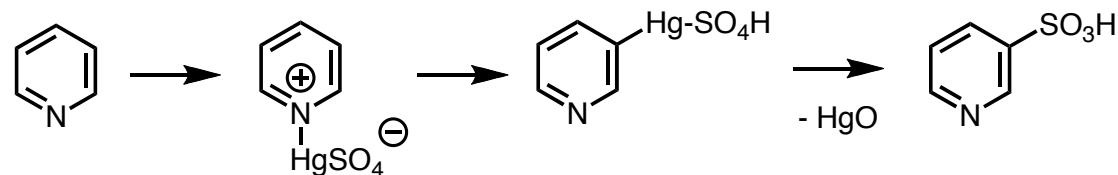
Sulfonation

NOT:

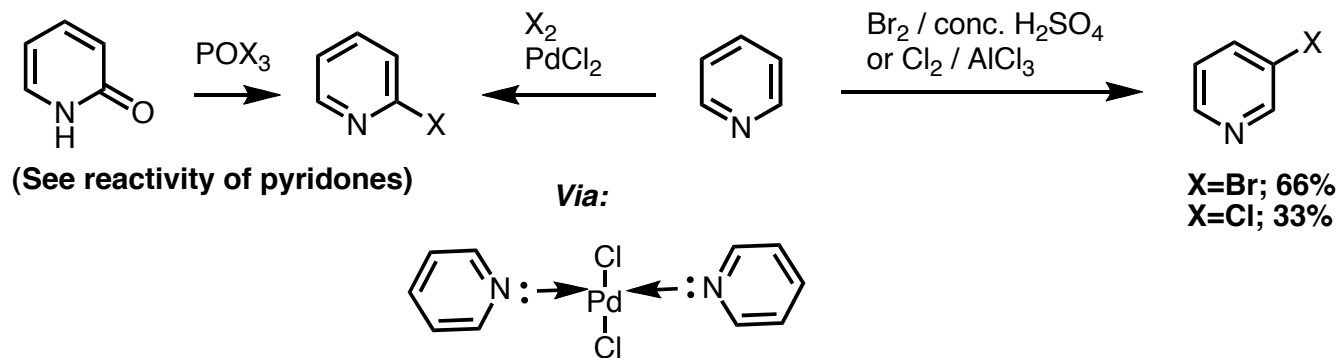
- FC Alkylation
- FC Acylation



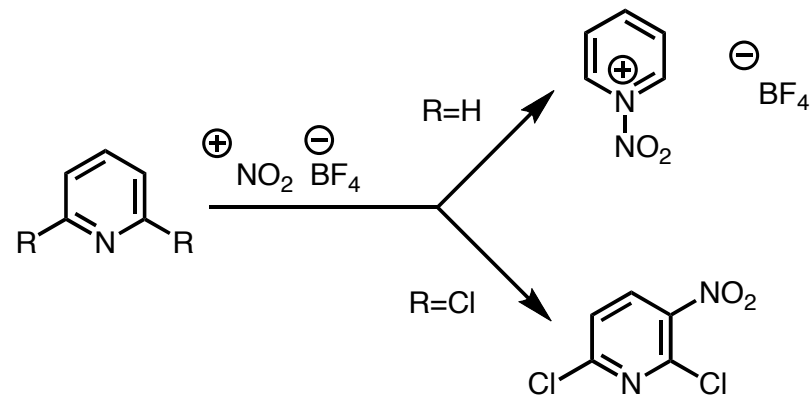
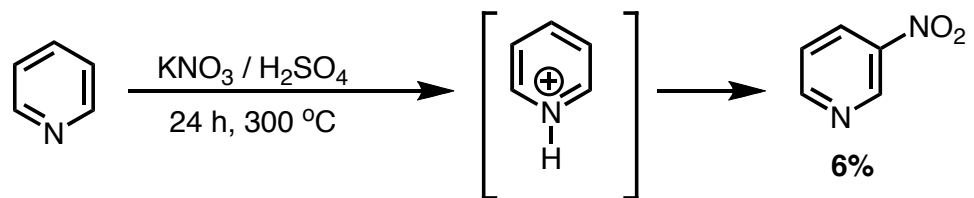
Possible intermed.



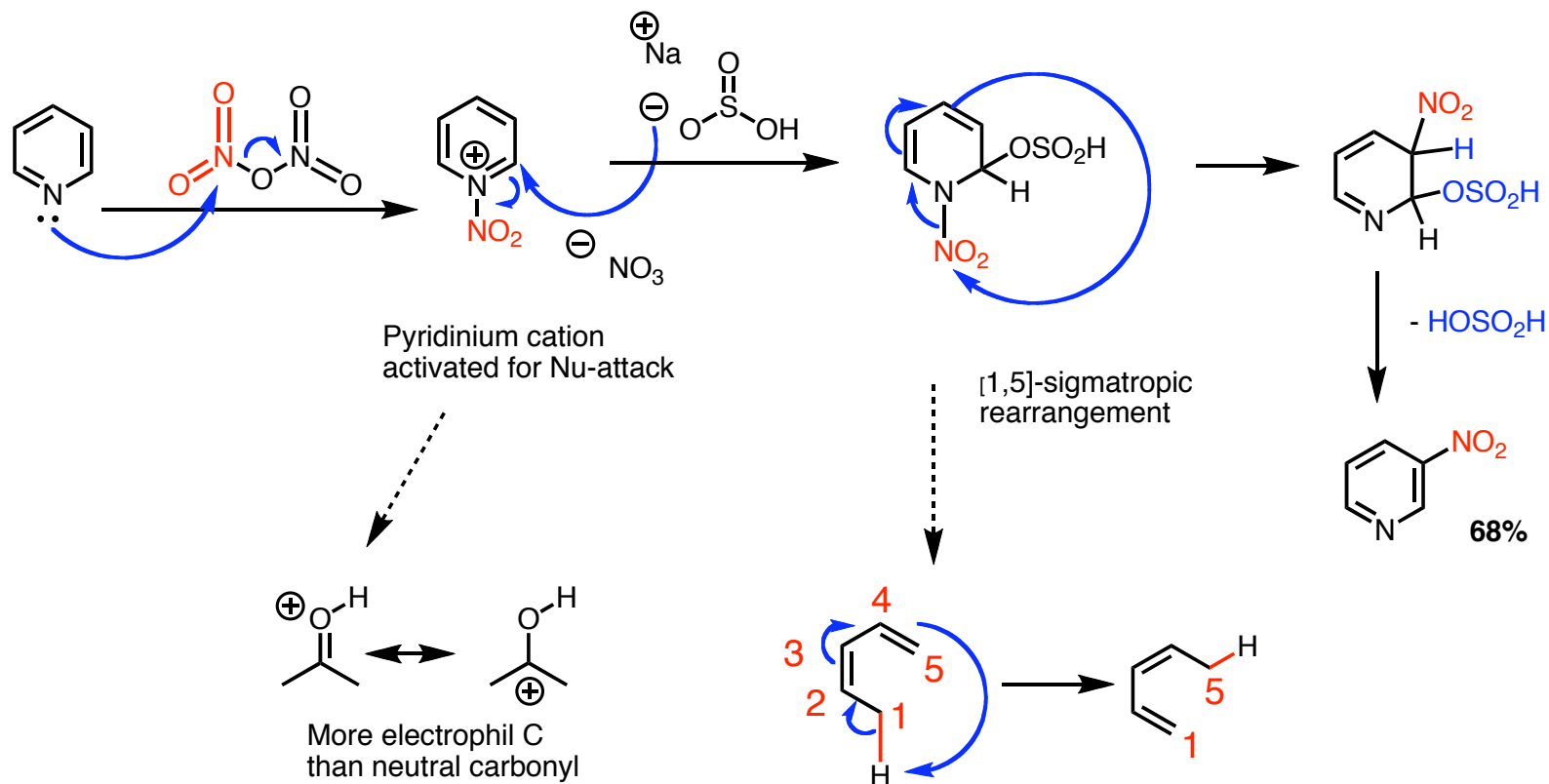
Halogenation



Nitration

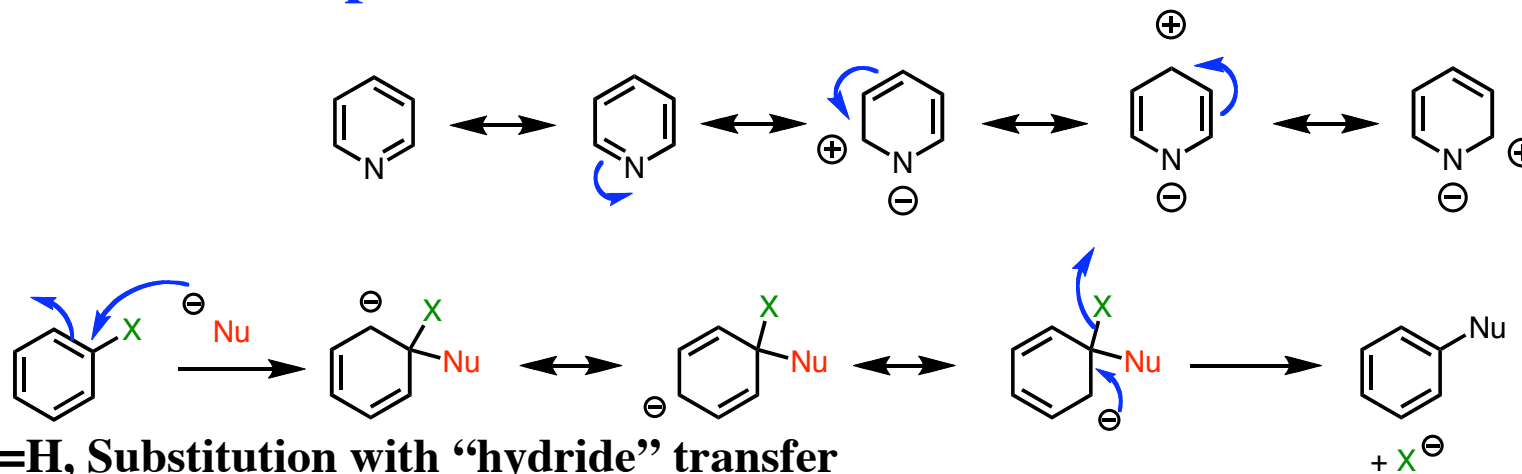


Nitration - Bakke (NTNU, <http://www.chem.ntnu.no/organisk/ansatte/Bakke/jb.html>)



Reaction with nucleophiles

S_NAr



Nu: $NaNH_2$ - amination - Chichibabin reaction

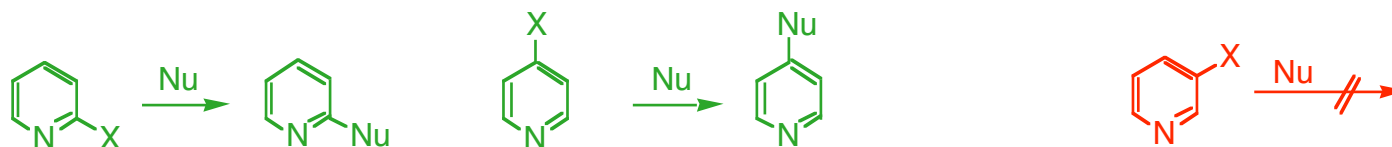
Nu: $BuLi$, $PhLi$ etc - alkylation / arylation

Nu: $NaOH$ - “hydroxylation” - NB! High temp

} Attack in the 2-pos (not 4-pos)

b) $X=LG$, Displacement of good leaving group

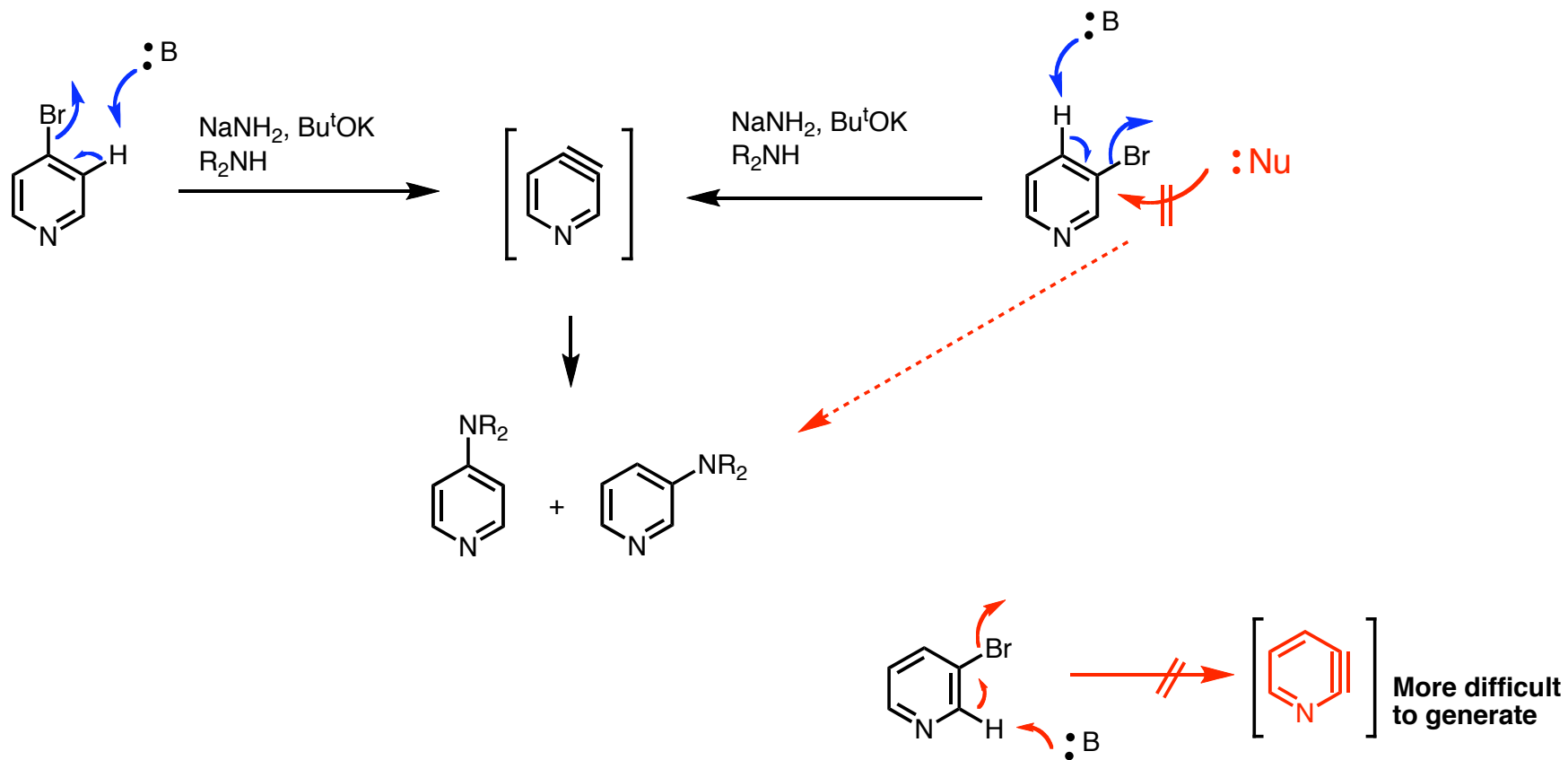
X: Halogen ($F \gg Cl > Br > I$), $-OSO_2R$, $-NO_2$, $-OR$



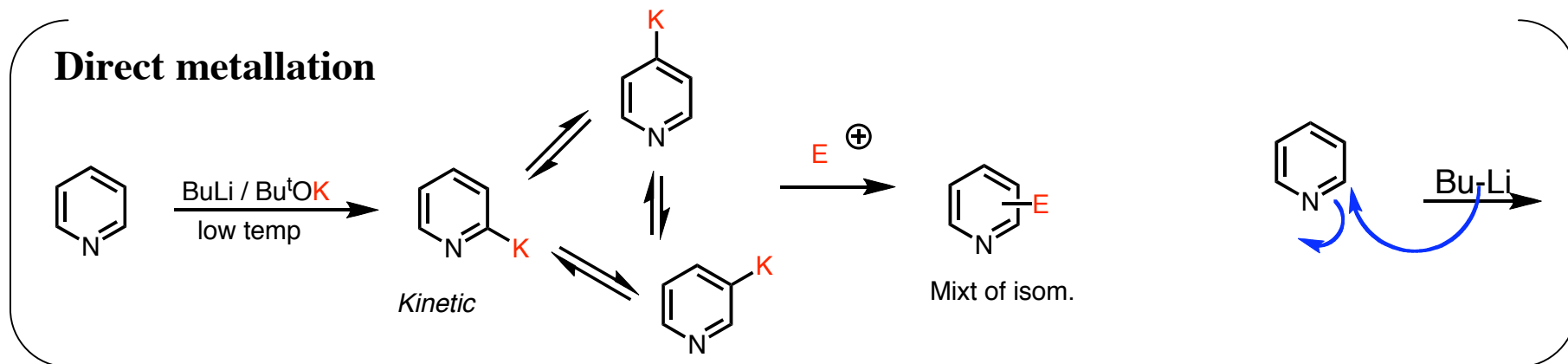
a) $X=H$

b) $X=$ Good leaving group

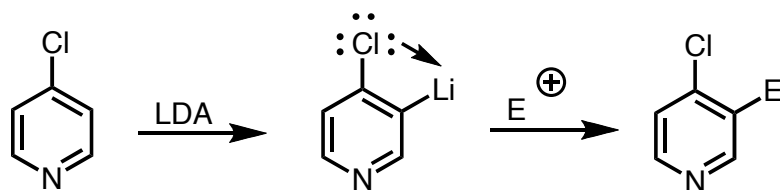
- S_NAr
- S_N1 : Via diazonium salts and aryl cation
- Benzyne
- SRN1: Involves radicals
- VNS: Vicarious nucl. Subst.



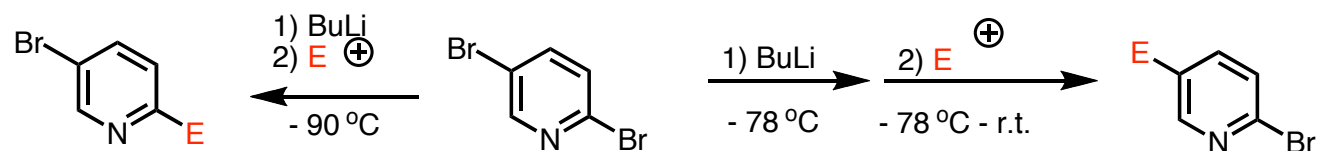
Metallation and reactions with electrophiles



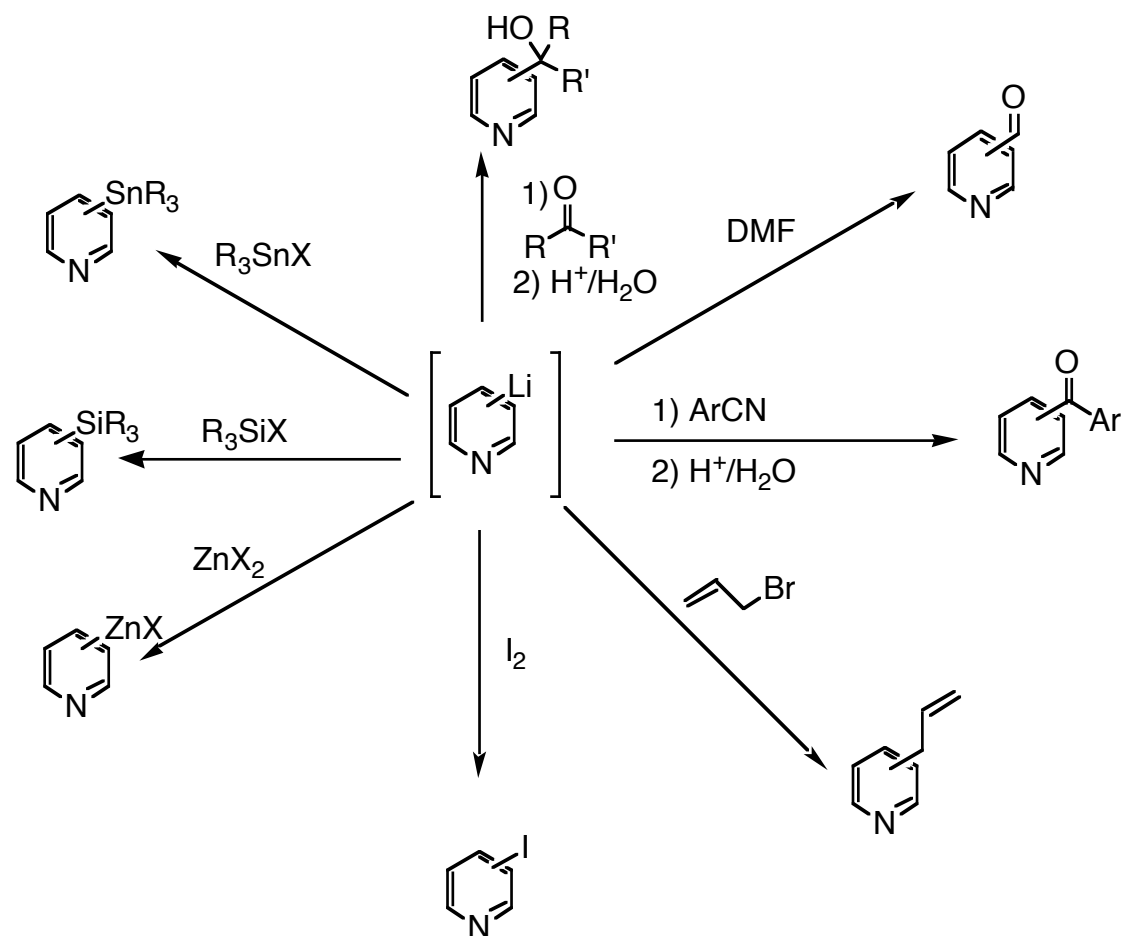
Direct metallation with ortho directing group (ODG)



Metal halogen exchange

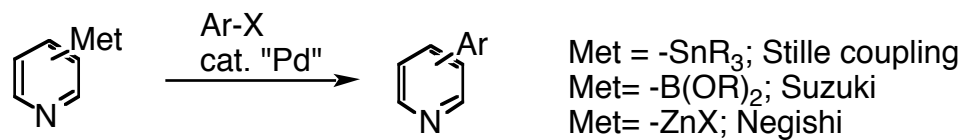


Metallation and reactions with electrophiles

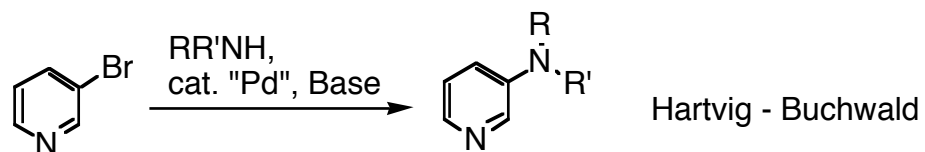
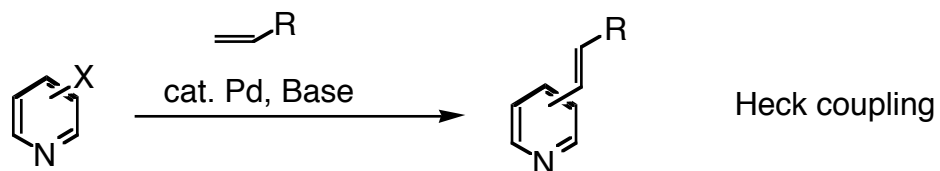
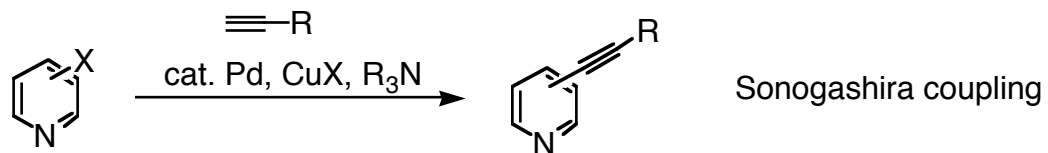
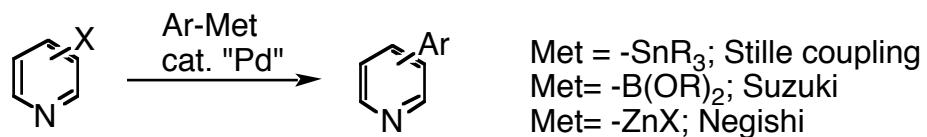


Pd-Catalyzed Coupling reactions

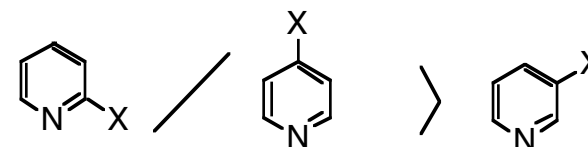
a) On metallated pyridines



b) On halopyridines



Reactivity

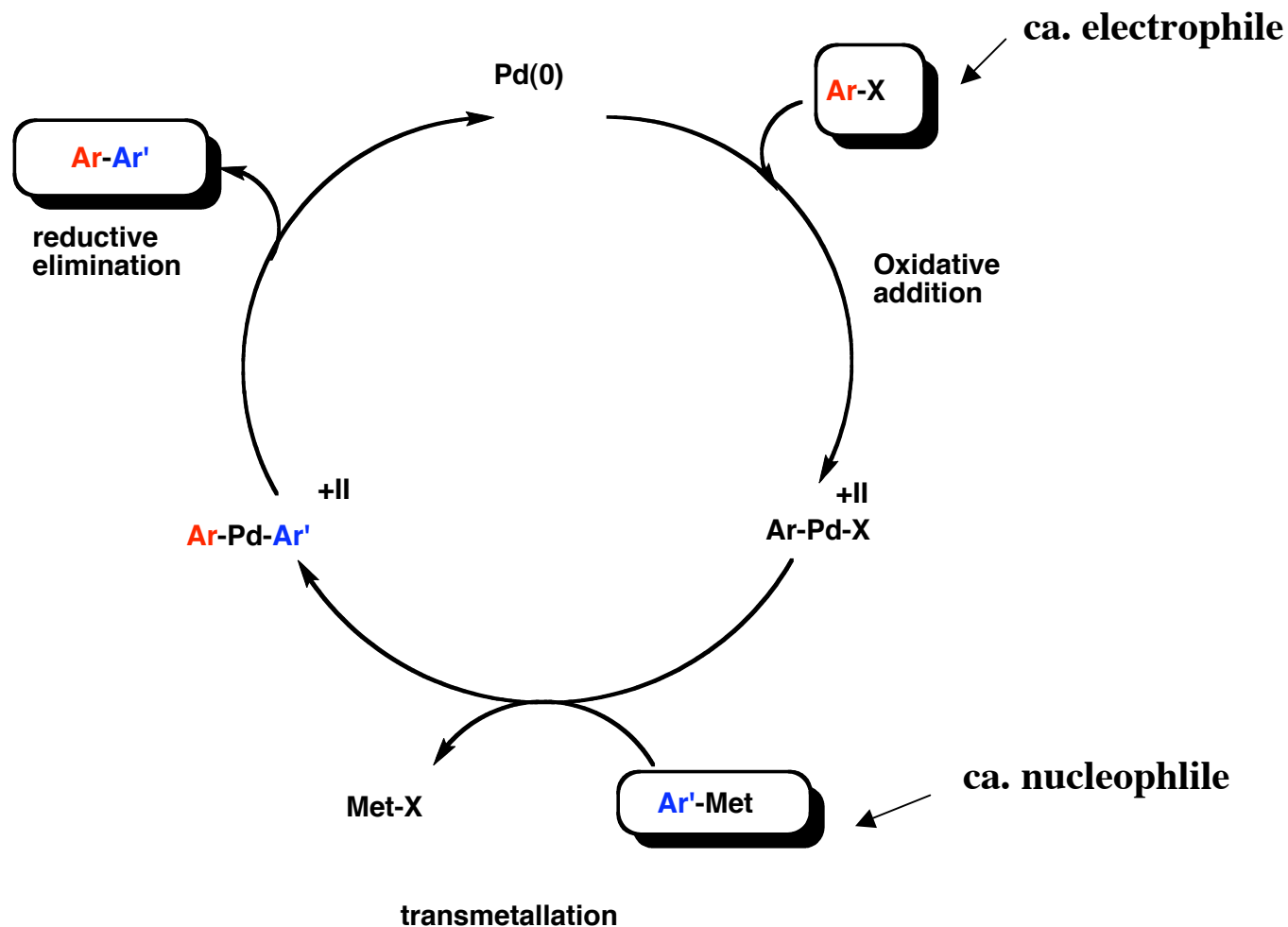
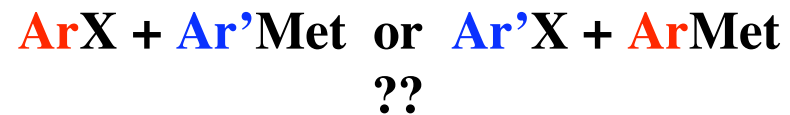


X=I

X=Br / OTf

X=Cl

Polarity in couplings

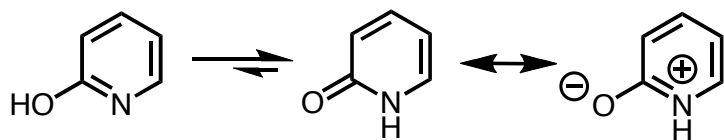


Substituted pyridines - Structure and reactivity

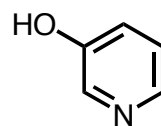
- Oxy-, Thio- and Aminopyridines
- Alkyl- and Vinylpyridines
- Quaternary Pyridinium Salts
- Pyridine *N*-oxides

Oxy-, Thio- and Aminopyridines - Structure; Tautomerism

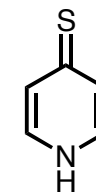
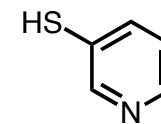
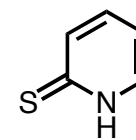
2-Pyridone



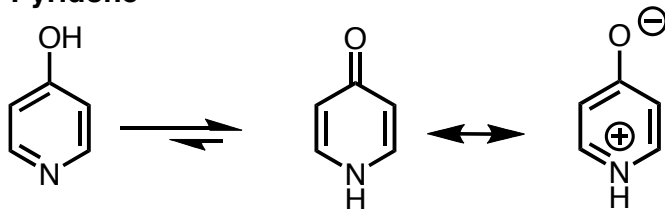
3-Hydroxypyridine
(c.f. phenol)



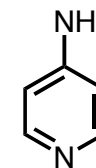
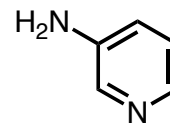
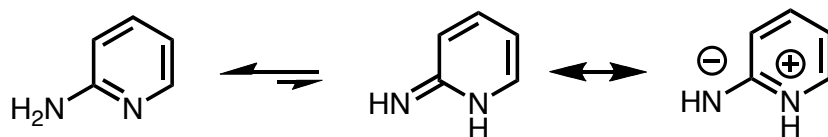
Thio:



4-Pyridone

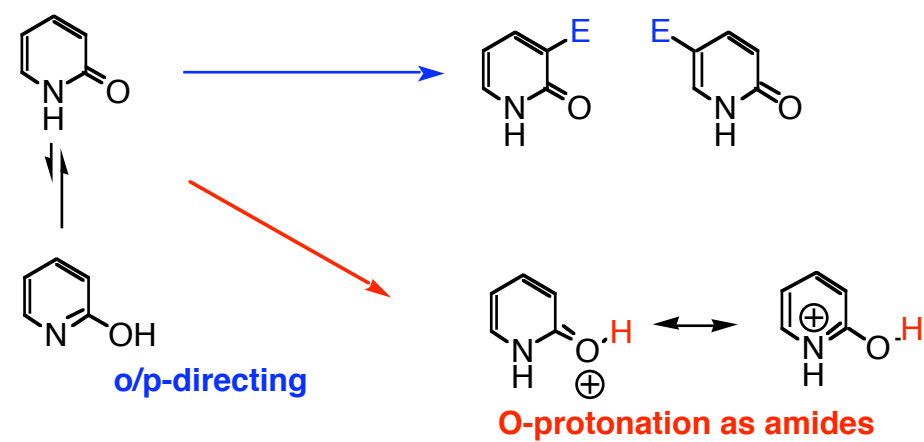
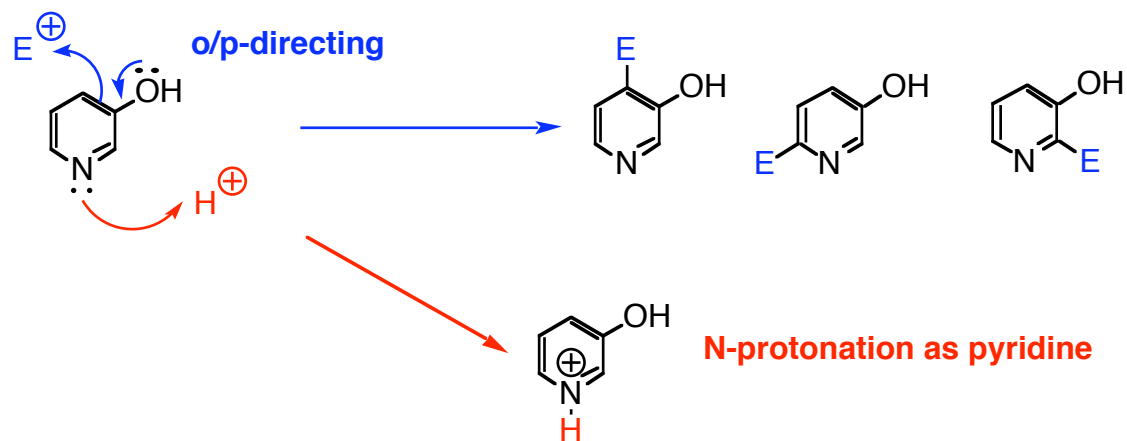


Amino

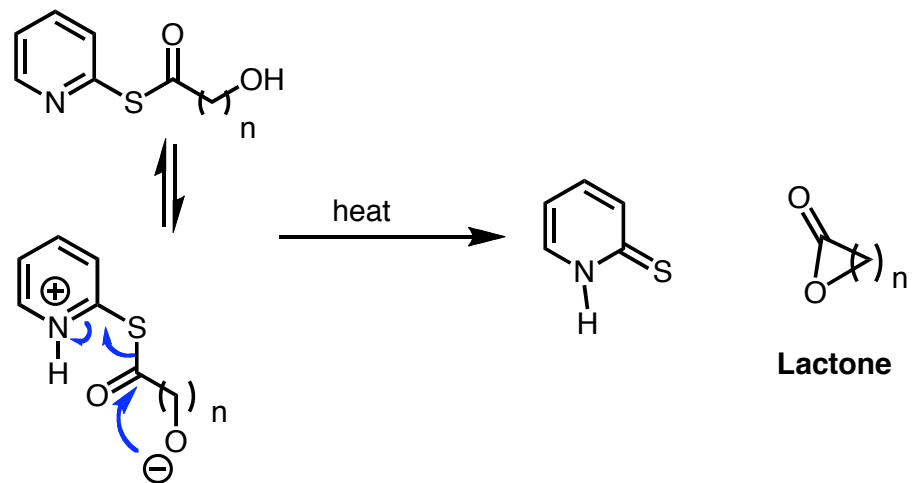
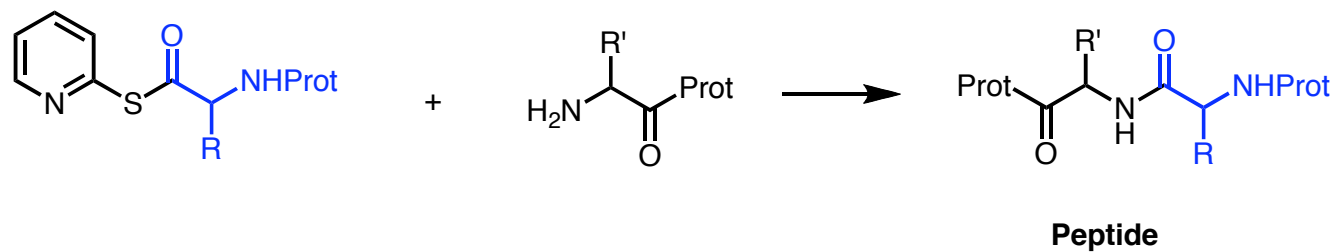
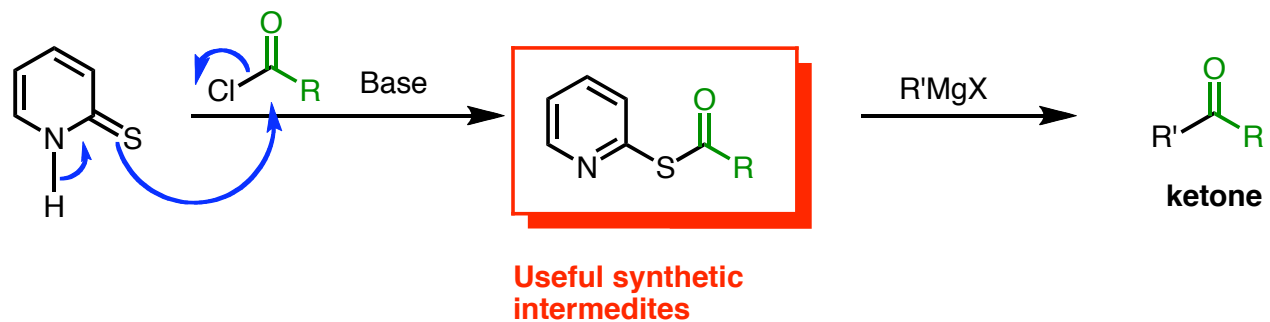


Oxypyridines - Reactivity

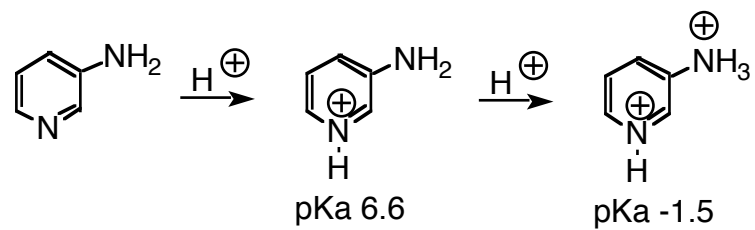
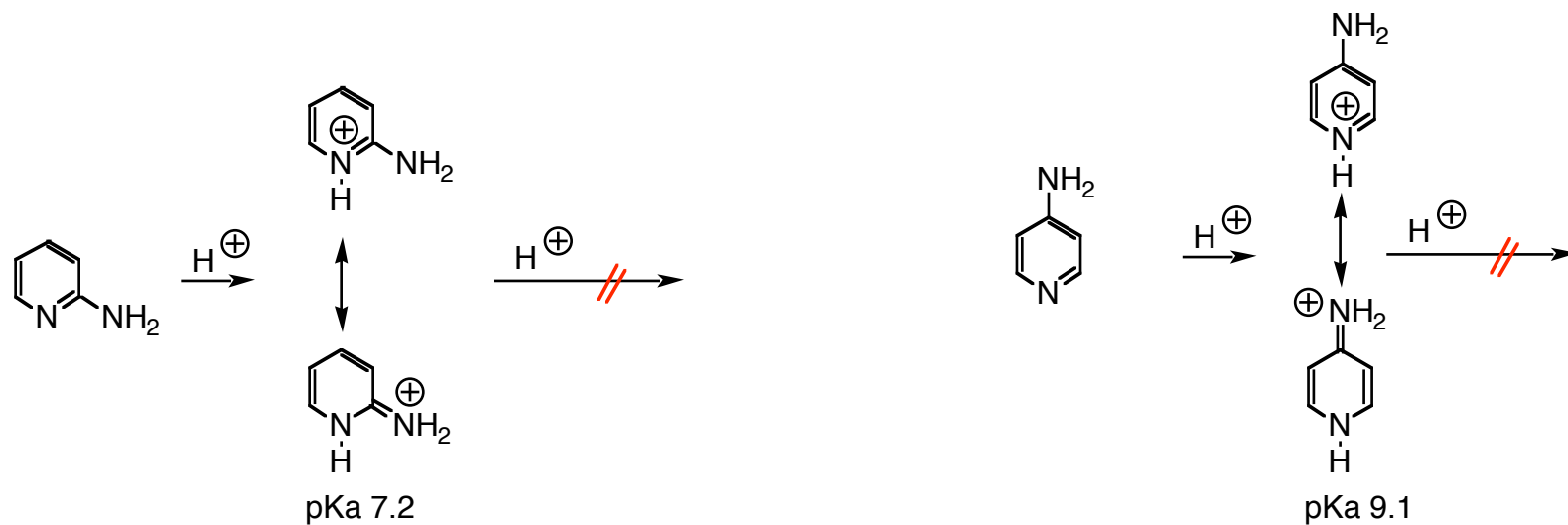
Reaction with electrophiles



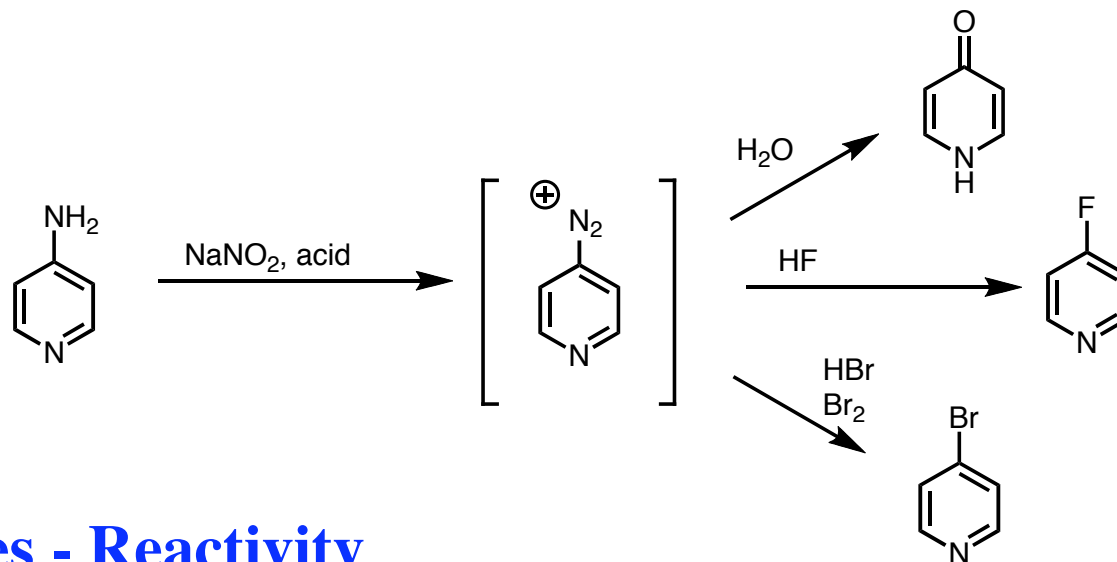
Thiopyridines - Reactivity



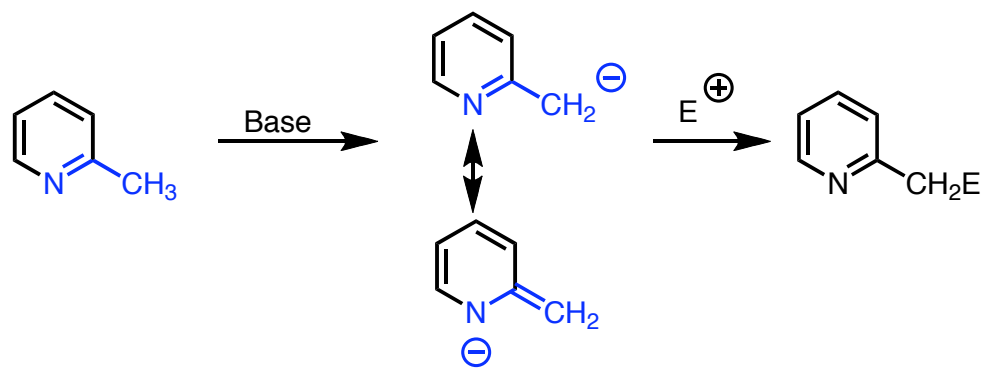
Aminopyridines - Reactivity



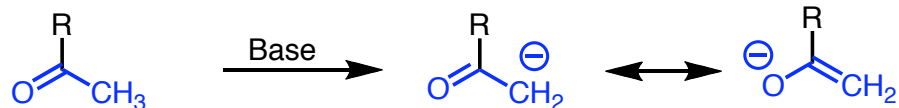
Aminopyridines - Reactivity



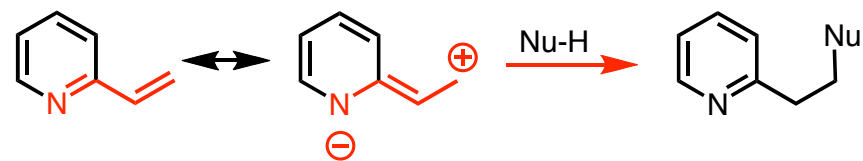
Alkylpyridines - Reactivity



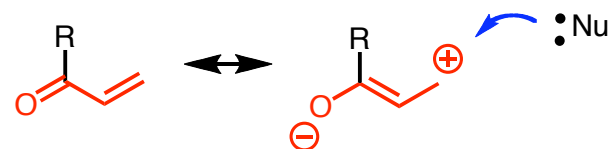
c.f. enolate anion



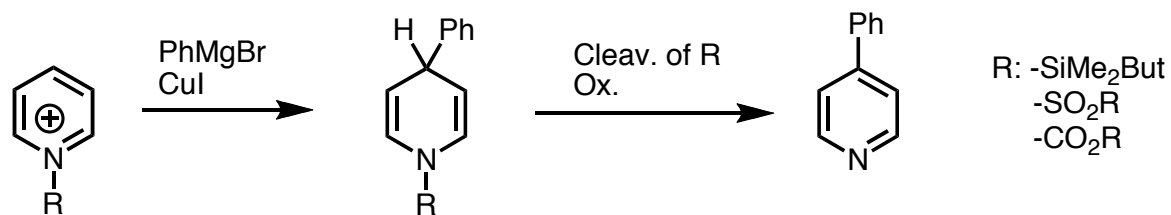
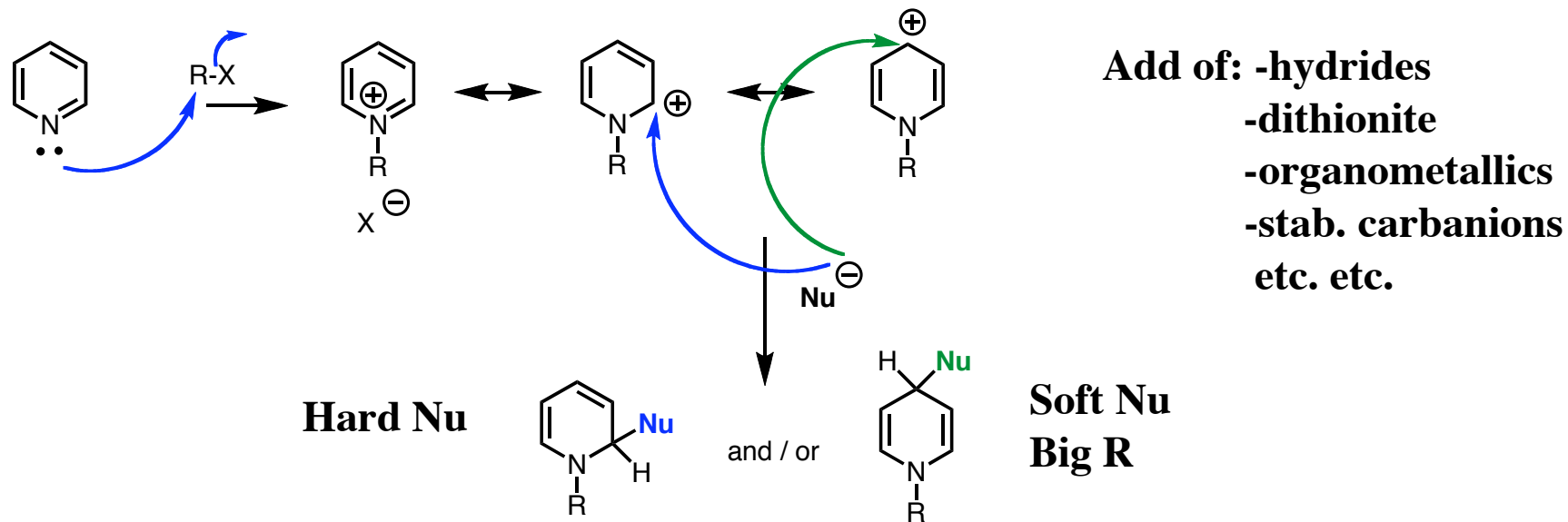
Vinylpyridines - Reactivity

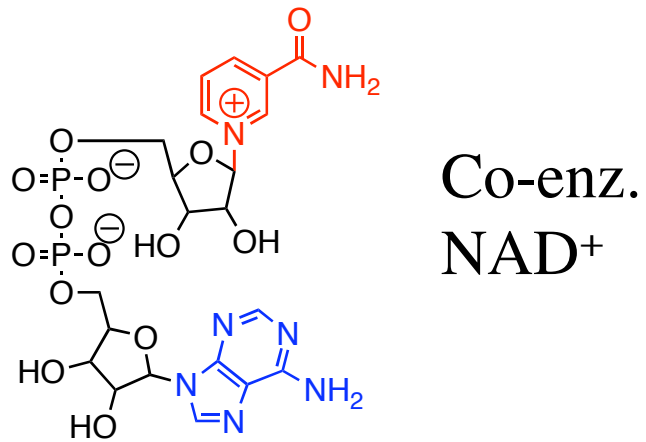


c.f. Michael type add.

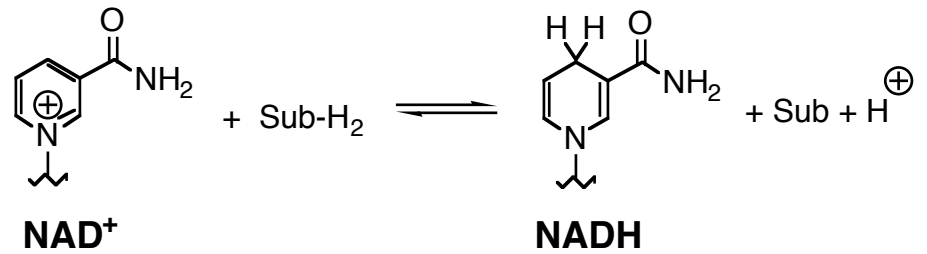


Quaternary pyridinium salts

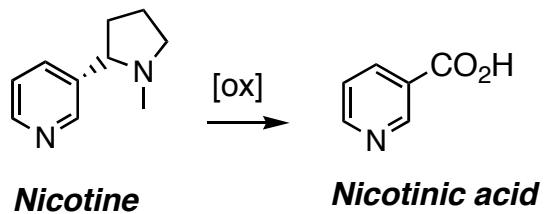




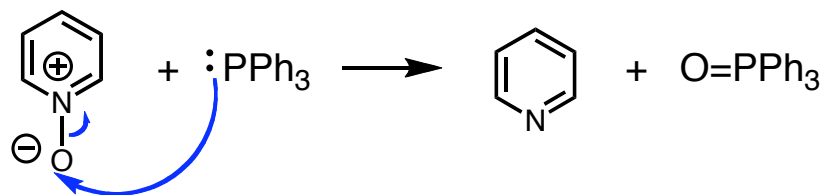
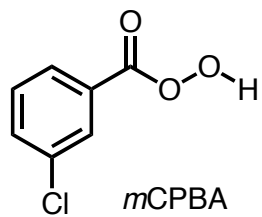
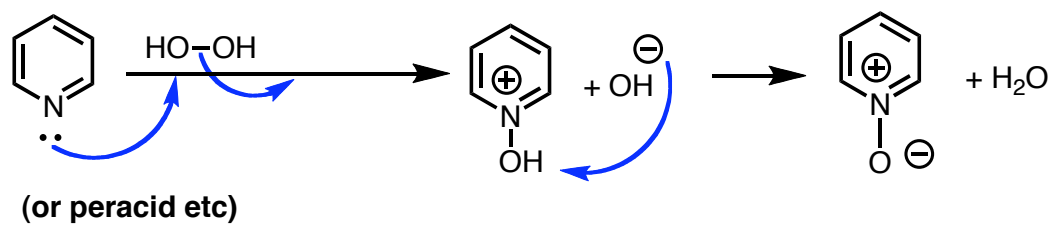
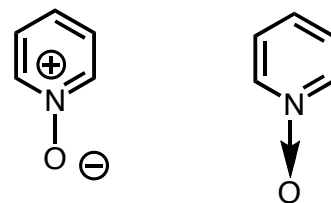
Nicotine amide: Vit. B₃
Adenine: Vit. B₄



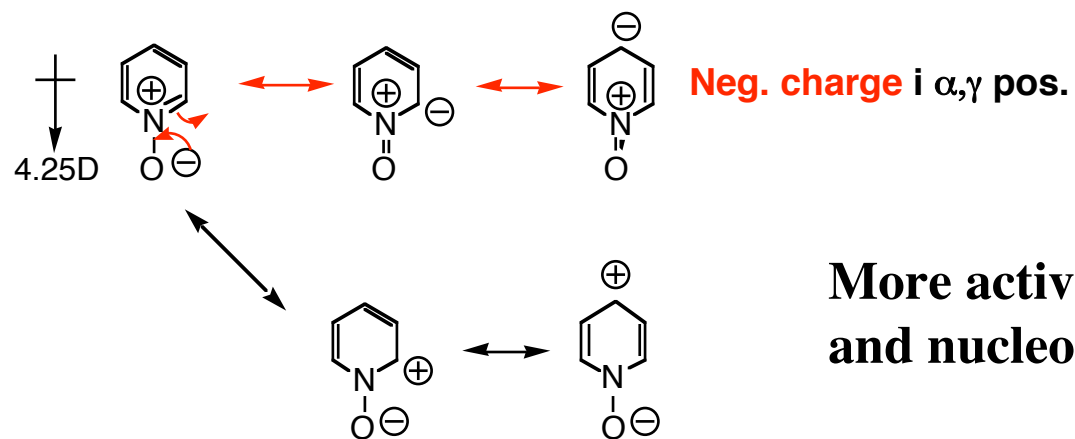
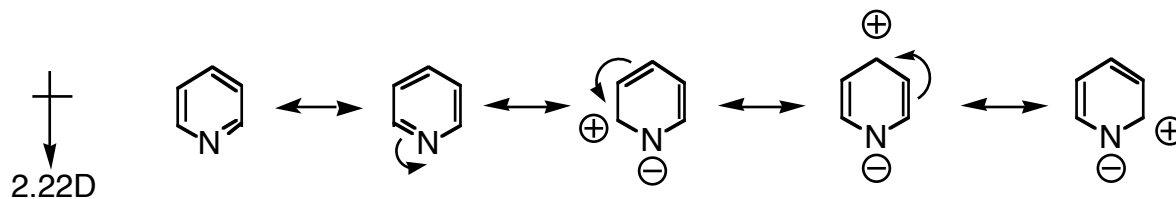
Hydride add. to NAD⁺, SubH₂ oxidized



Pyridine *N*-oxides

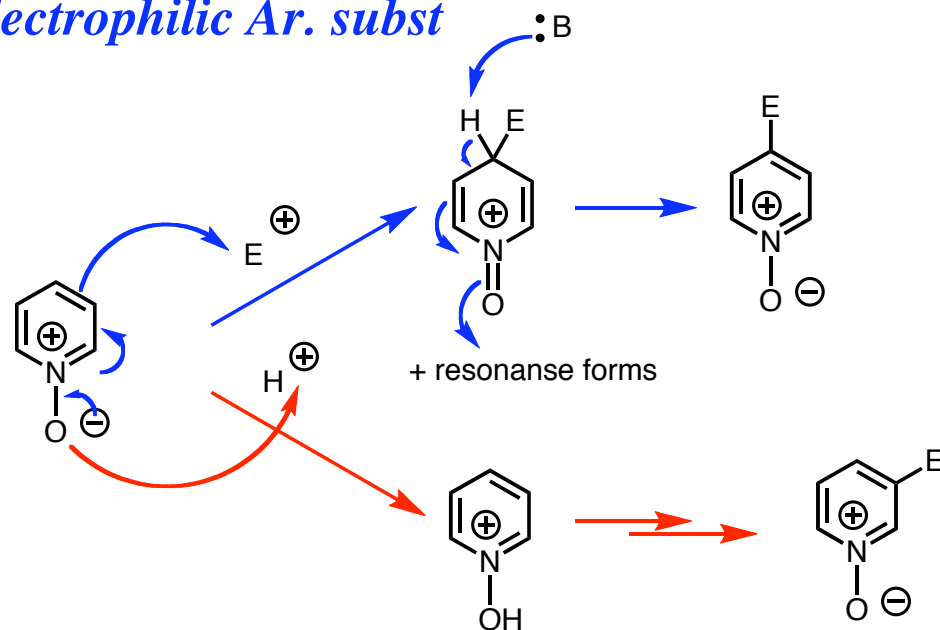


Pyridine *N*-oxides

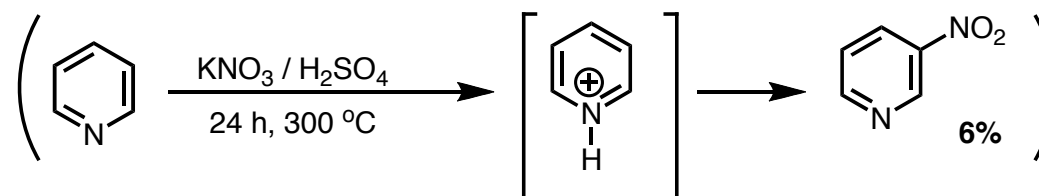
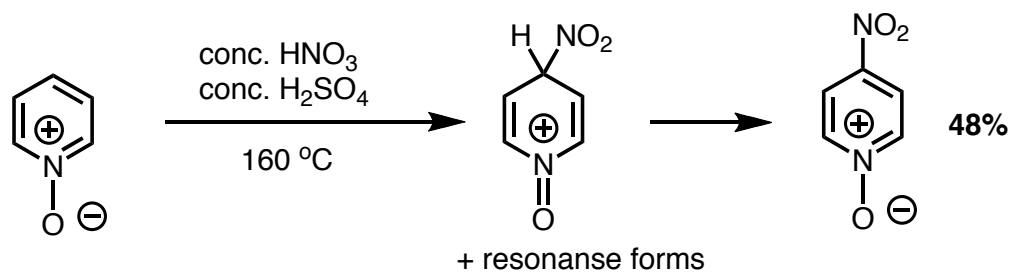


Pyridine N-oxides

Electrophilic Ar. subst



c.f. Electrophilic Ar. subst on pyridine / pyridinium cation
(difficult reactions)



Pyridine *N*-oxides

Rearrangements etc.

