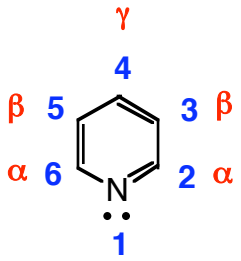
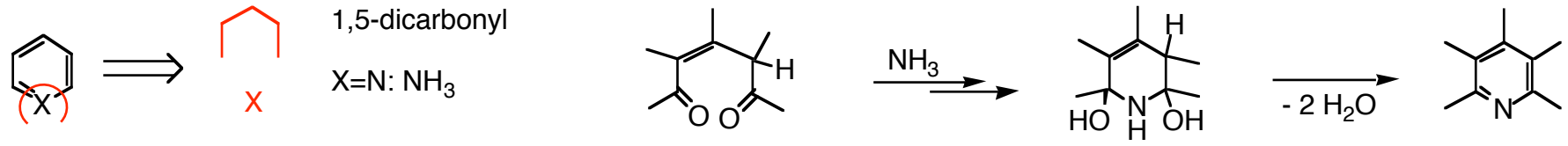
PYRIDINES

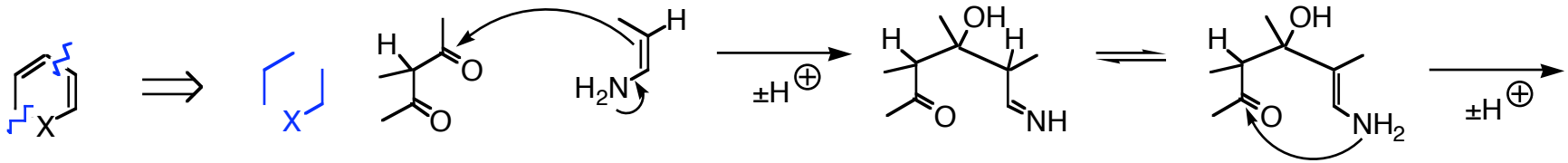


Synthesis of Pyridines

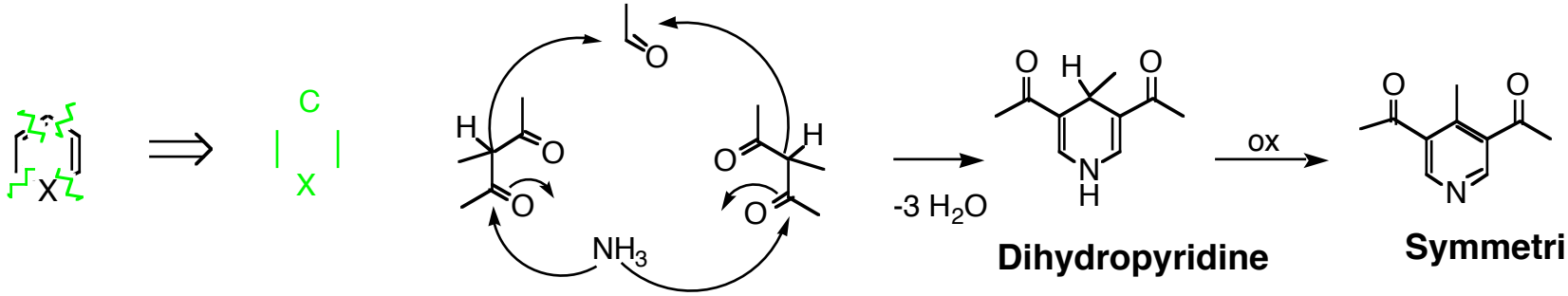
From 1,5-dicarbonyl and ammonia (c.f. chapt. 3)



From 1,3-dicarbonyl and enamine (c.f. chapt. 3)

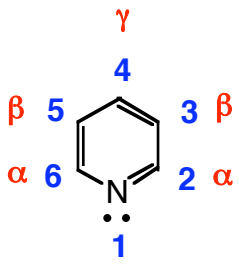


From 2 equivs. 1,3-dicarbonyl , aldehyde and ammonia - Hantzsch Synthesis



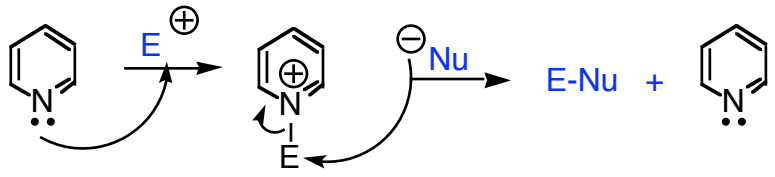
Various syntheses from other heterocycles

PYRIDINES

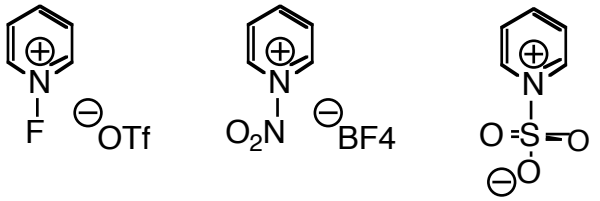


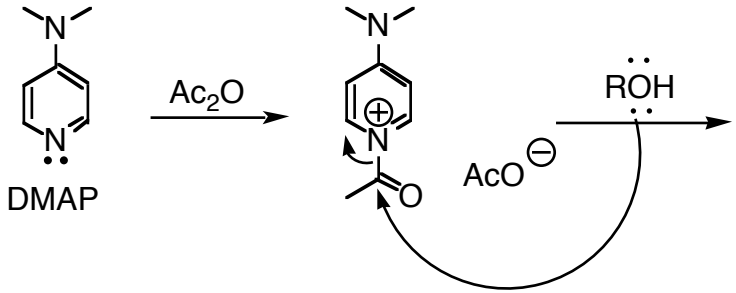
Reaction with electrophiles - react. on N:

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



Mild, not acidic electrophile





Reaction with electrophiles - react. on C:
Electrophilic Aromatic Substitution

Difficult

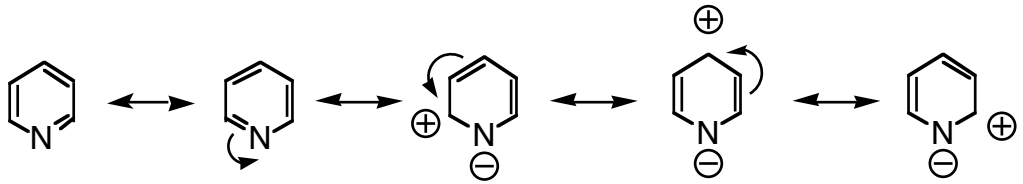
- Electron defficient / Poor nucleophiles
- Electrophiles may react at N

- Nitration
- Sulfonation
- Halogenation

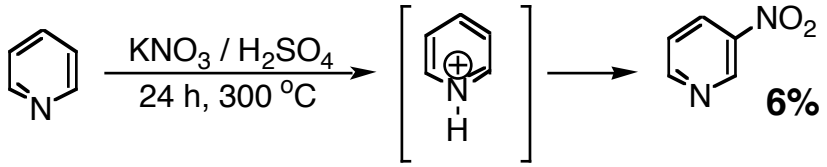
} React. in 3-pos.

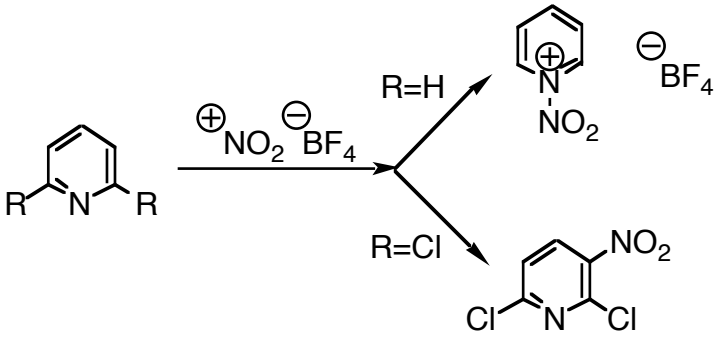
Not:

- FC alkylation
- FC acylation

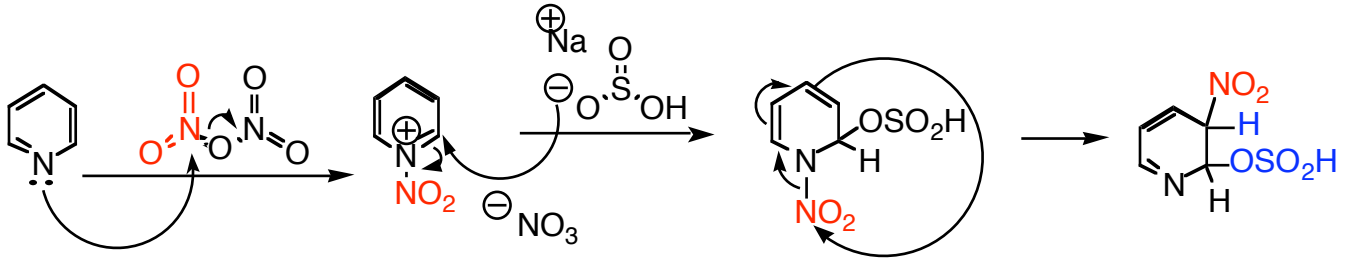


Nitration

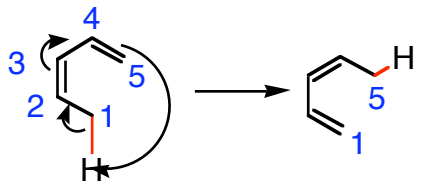




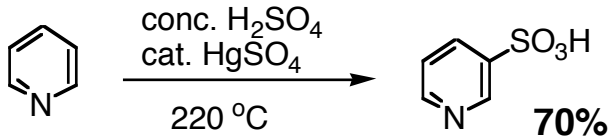
Bakke:



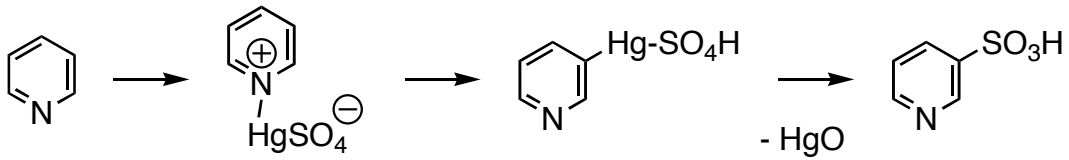
[1,5]-sigmatropic rearrang.



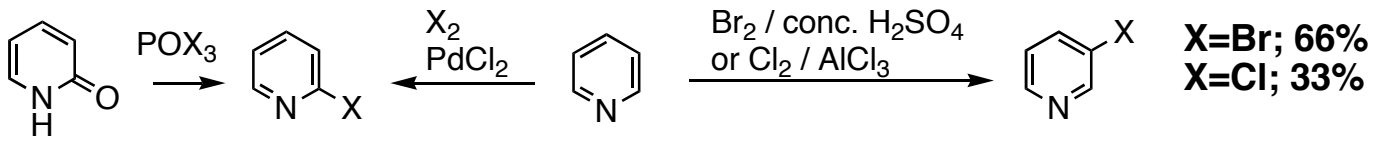
Sulfonation



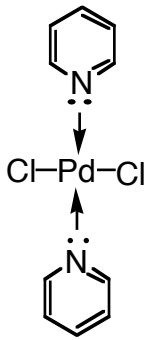
Possible intermediates



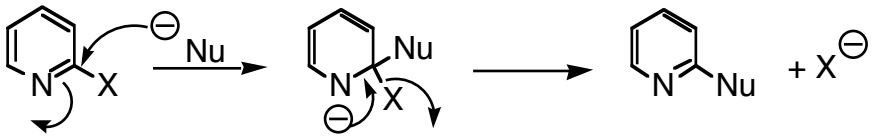
Halogenation



Via:



Reaction with Nucleophiles



a) X=H
b) X=Good leaving group

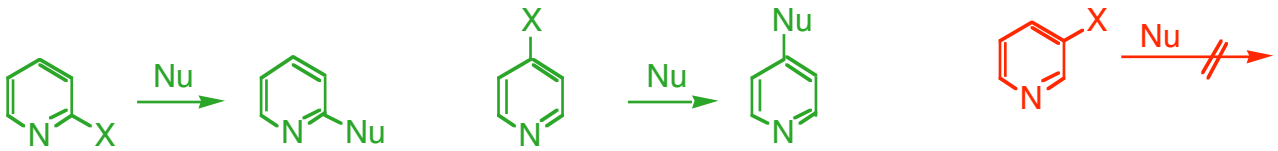
a) X=H, Substitution with "hydride" transfer

Nu: $NaNH_2$ - amination - Chichibabin reaction
Nu: BuLi, PhLi etc - alkylation / arylation
Nu: NaOH - "hydroxylation" - NB! High temp

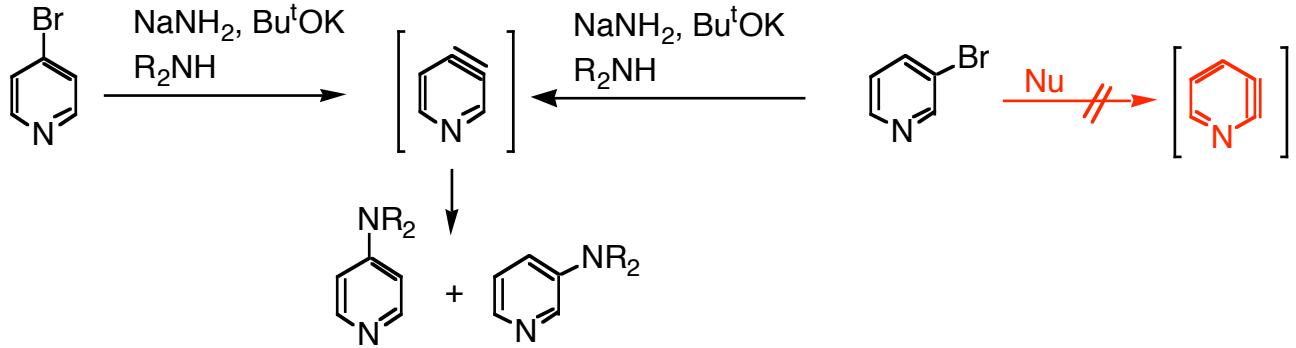
} **Attack in the 2-pos (not 4-pos)**

b) X=LG, Displacement of good leaving group

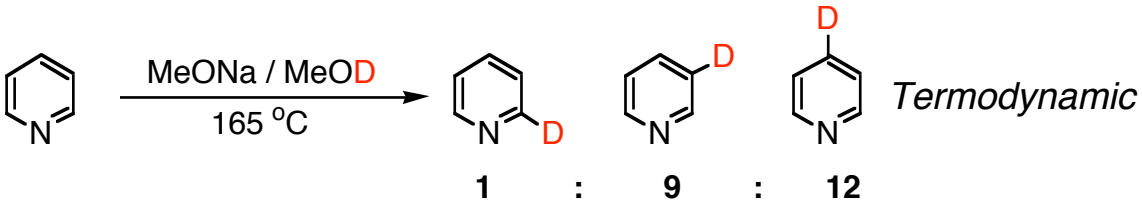
X: Halogen (F>>Cl,>Br,>I), $-OSO_2R$, $-NO_2$, -OR

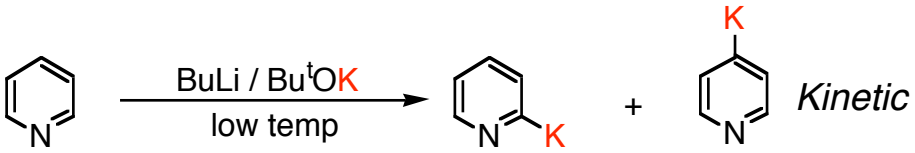


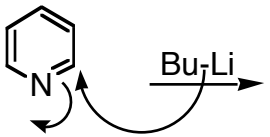
Via Pyridyne



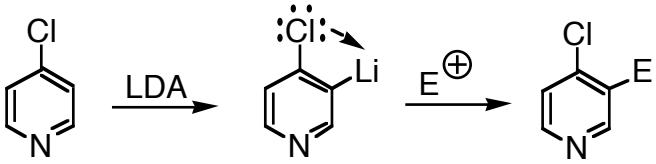
Metallation and Reactions with Electrophiles



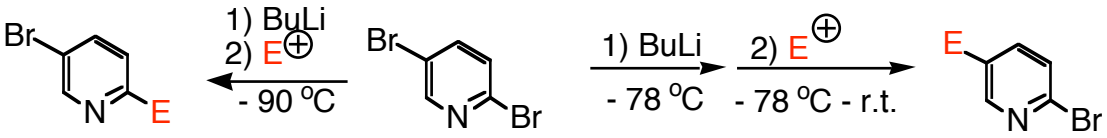




***Ortho* directing subst.**

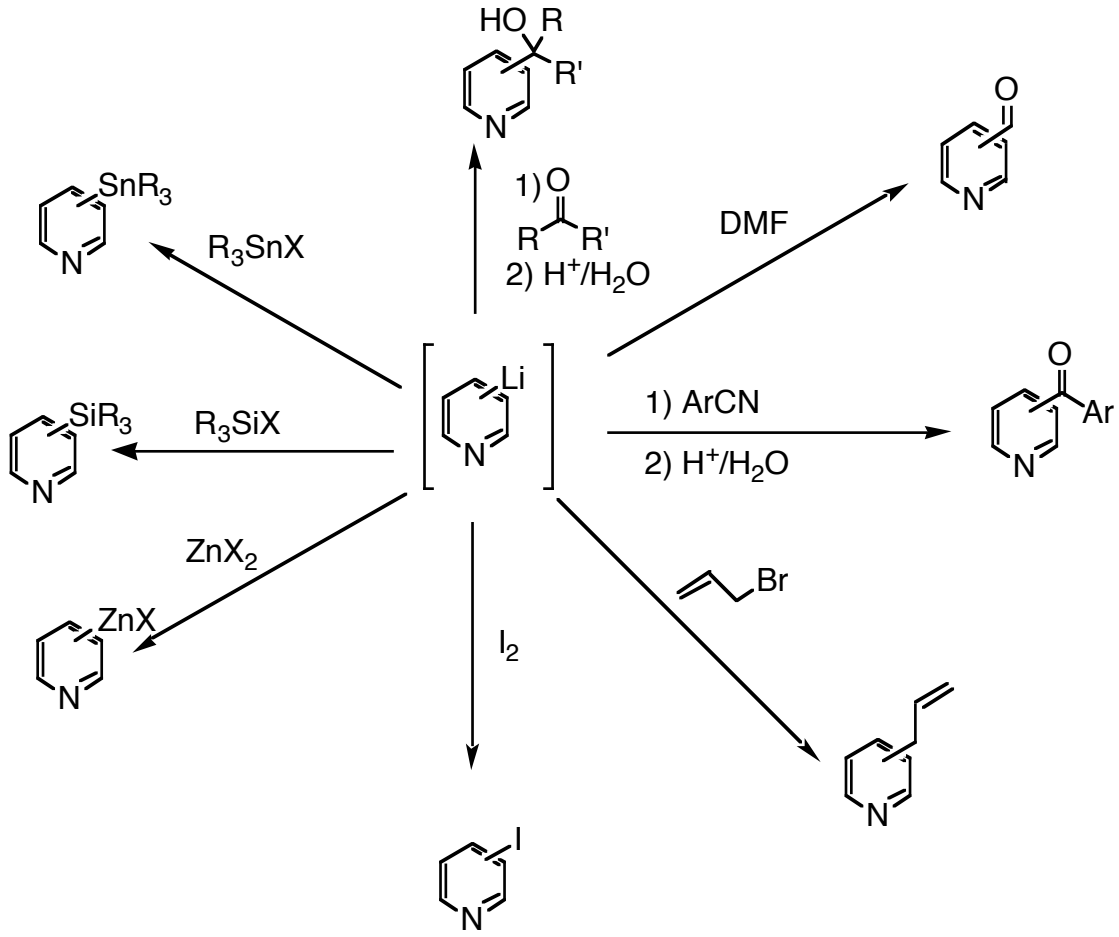


Metal - Halogen Exchange



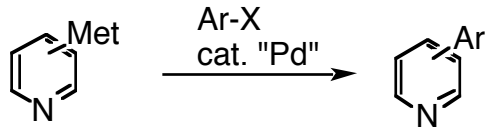
Direct Reactions with Electrophiles: Additions, Substitutions

Some examples (c.f. react. with ArLi)



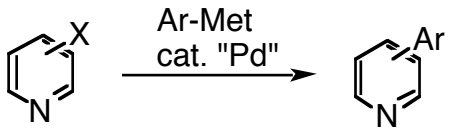
Pd-Catalyzed Coupling reactions

a) On metallated pyridines

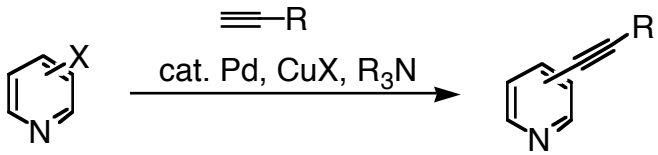


Met = -SnR_3; Stille coupling
Met= -$B(OR)_2$; Suzuki
Met= -ZnX; Negishi

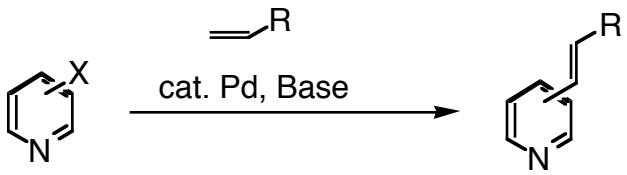
b) On halopyridines



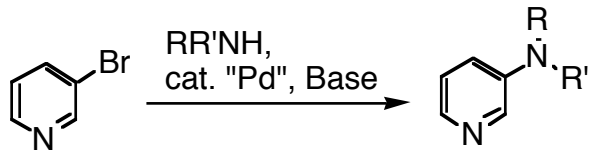
Met = -SnR_3; Stille coupling
Met= -$B(OR)_2$; Suzuki
Met= -ZnX; Negishi



Sonogashira coupling

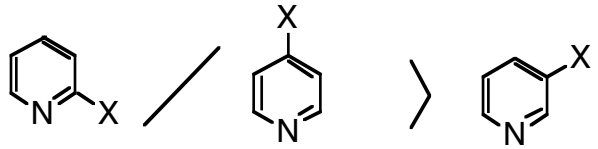


Heck coupling



Hartvig - Buchwald

Reactivity

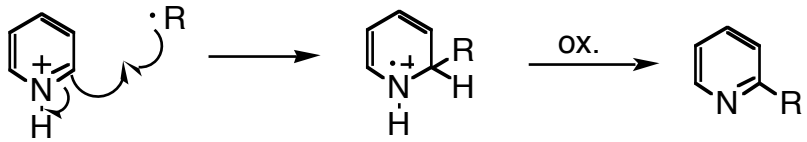


X=I>X=Br/OTf>X=Cl

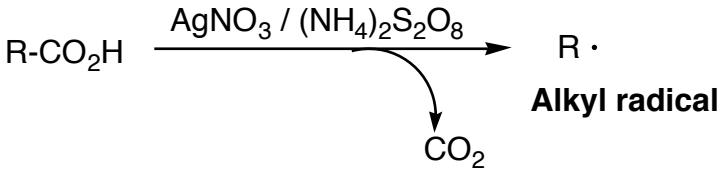
Radical Reactions

a) Reactions with C-radicals: Minisci React.

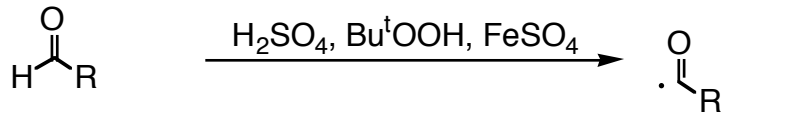
Nucleophilic radical



Reactivity: Pyridinum cation > neutral pyridine
2-pos. > 4-pos. > >3-position



Alkyl radical

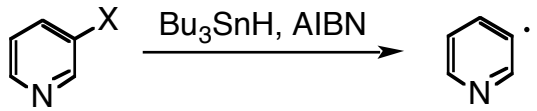


R=Alkyl, Aryl, -NR_2

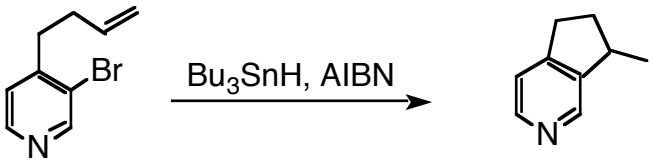
(aldehyd / formamid)

Acyl radical

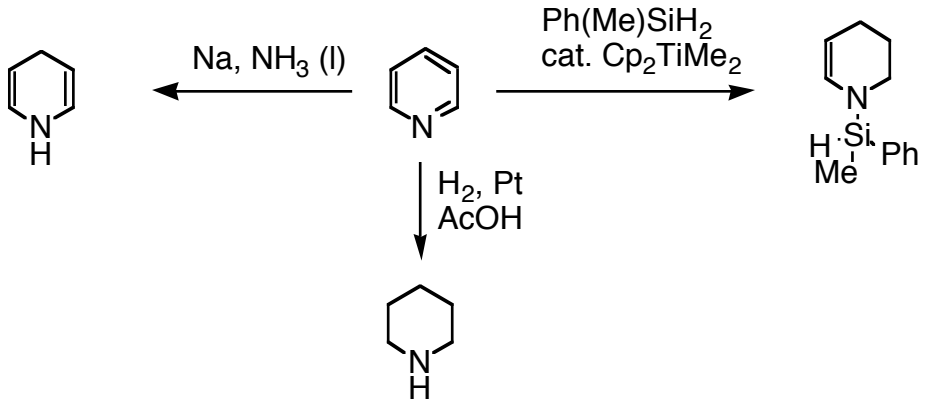
b) Generation of / Reaction on pyridylradicals



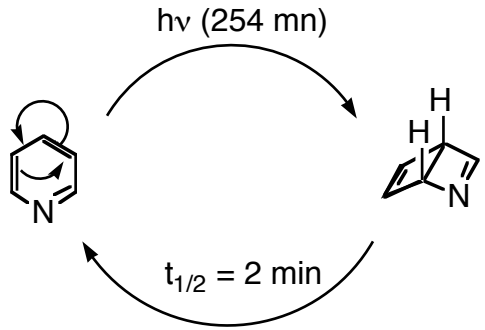
Intramolecuar cyclisations



Reductions

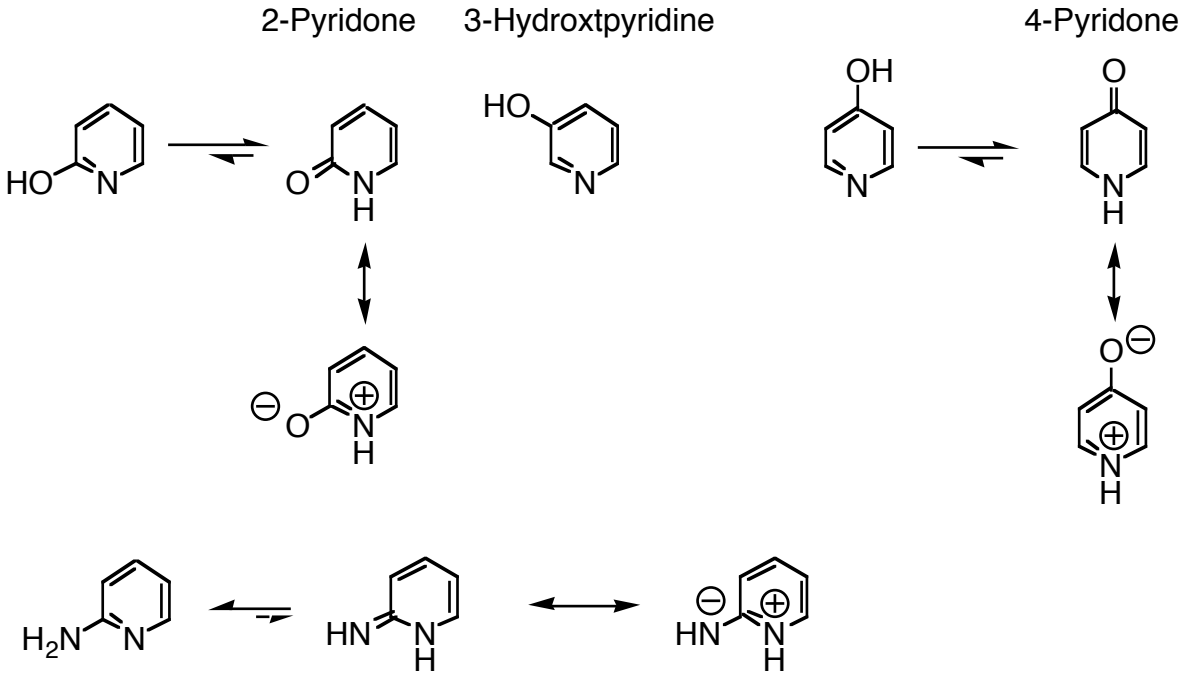


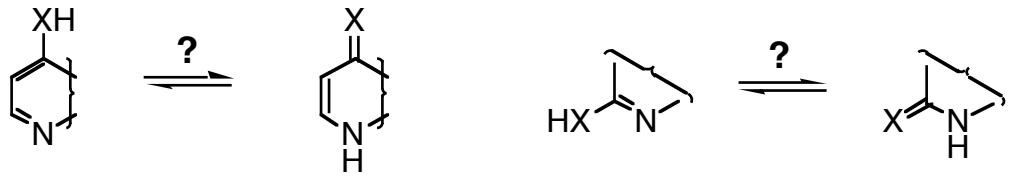
Photochemistry



Oxy-, Thio- and Aminopyridines

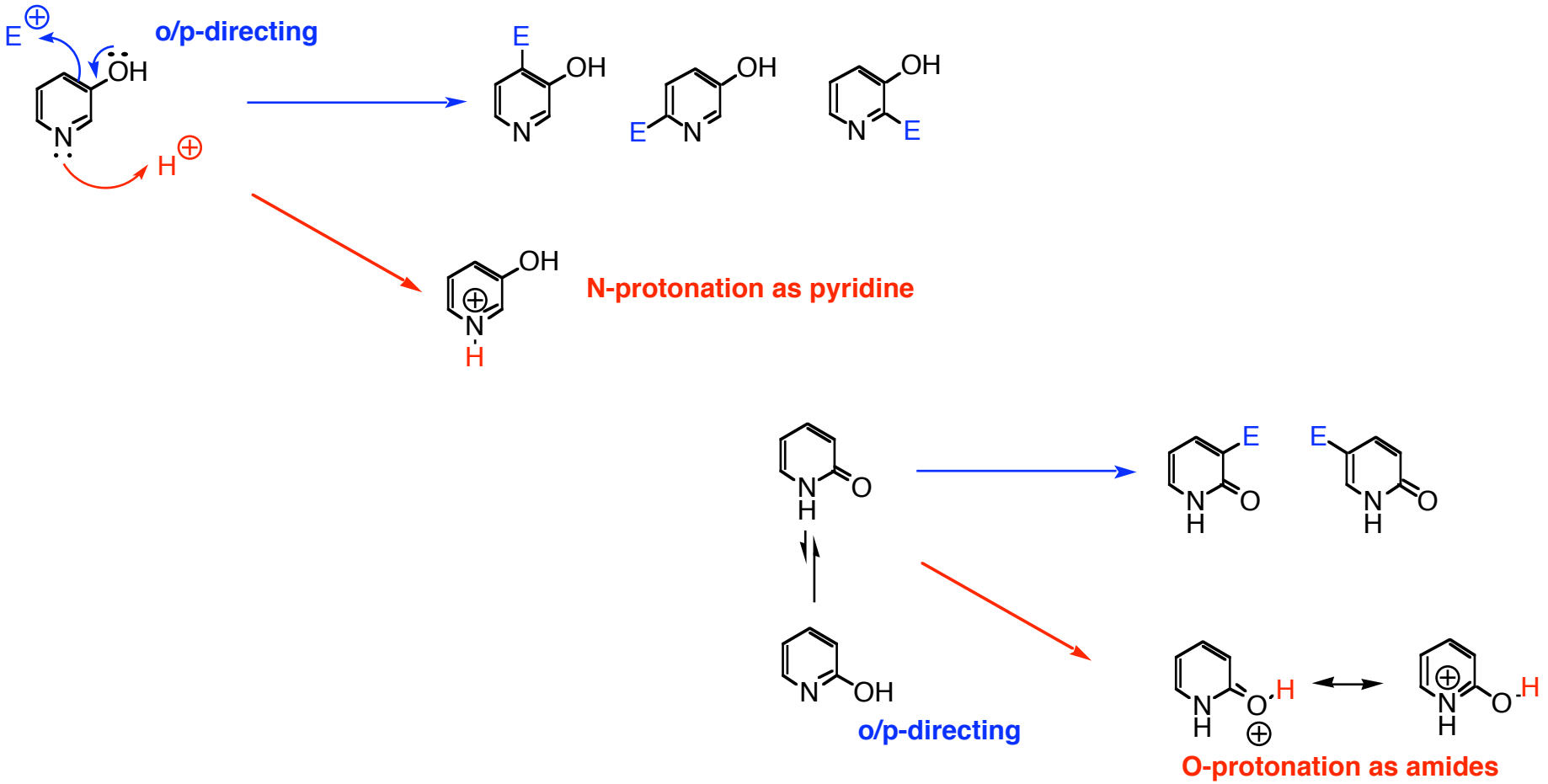
Structure - Tautomerism



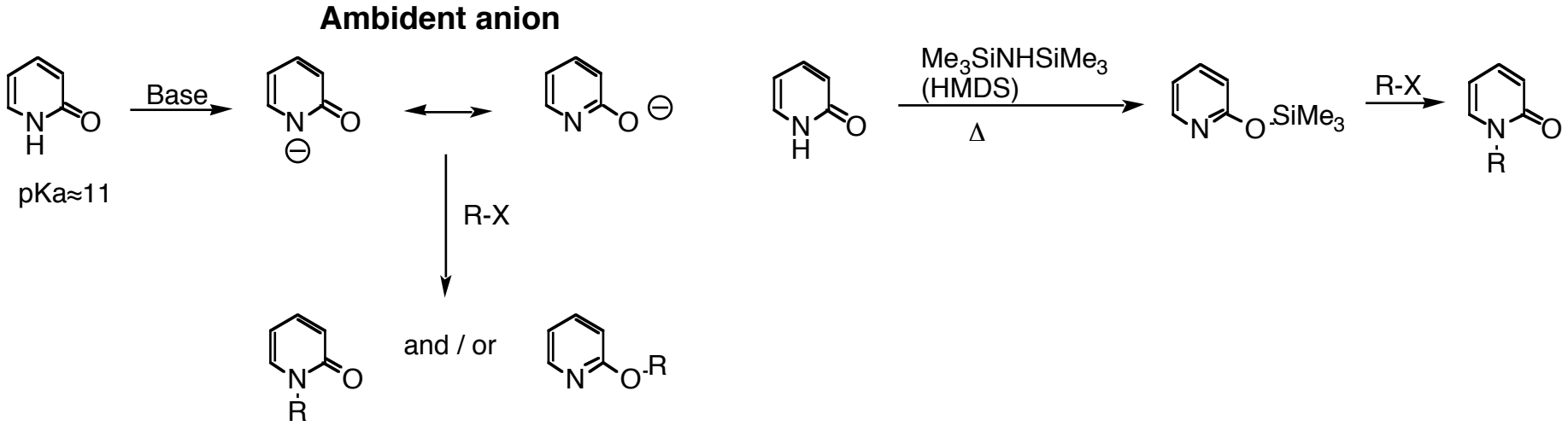


X=O: **one** / hydroxy
X=NR: imino / **amino**
X=S: thione (6-membered rings) /
thiol (5 membered)

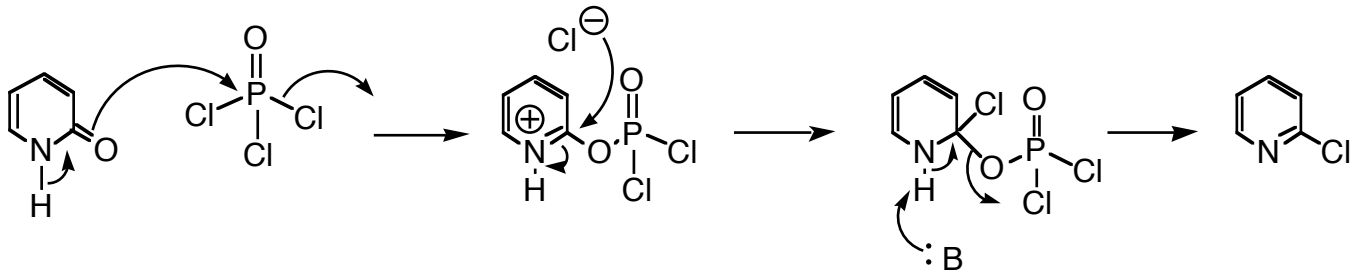
Reactions on Pyridones - With Electrophiles



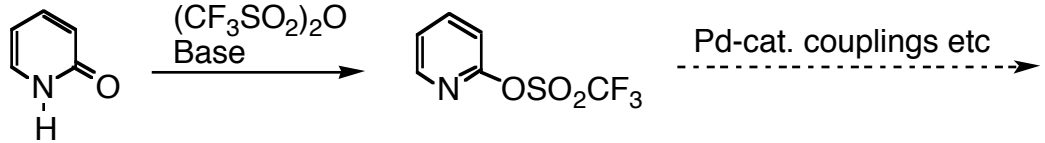
Reactions on Pyridones - Deprotonation - O or N-substitution



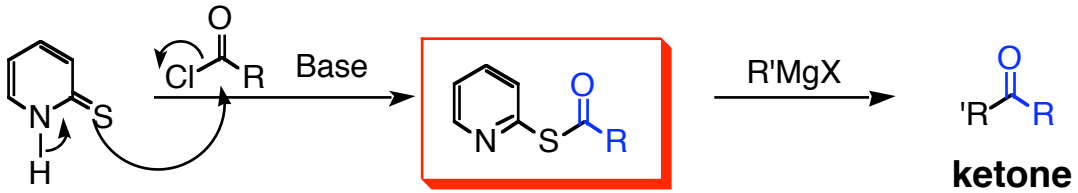
Reactions on Pyridones - Replacement of Oxygen



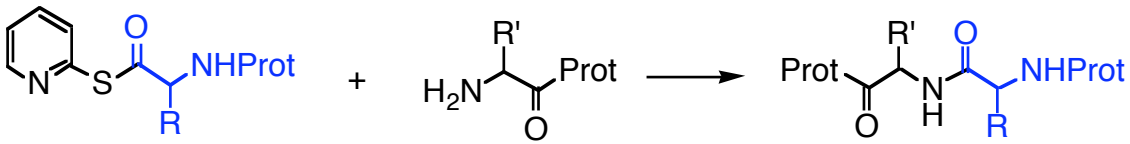
Triflate



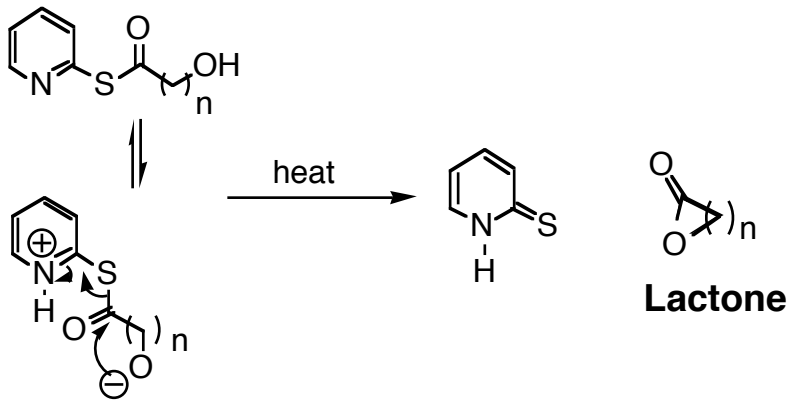
Thiopyridones



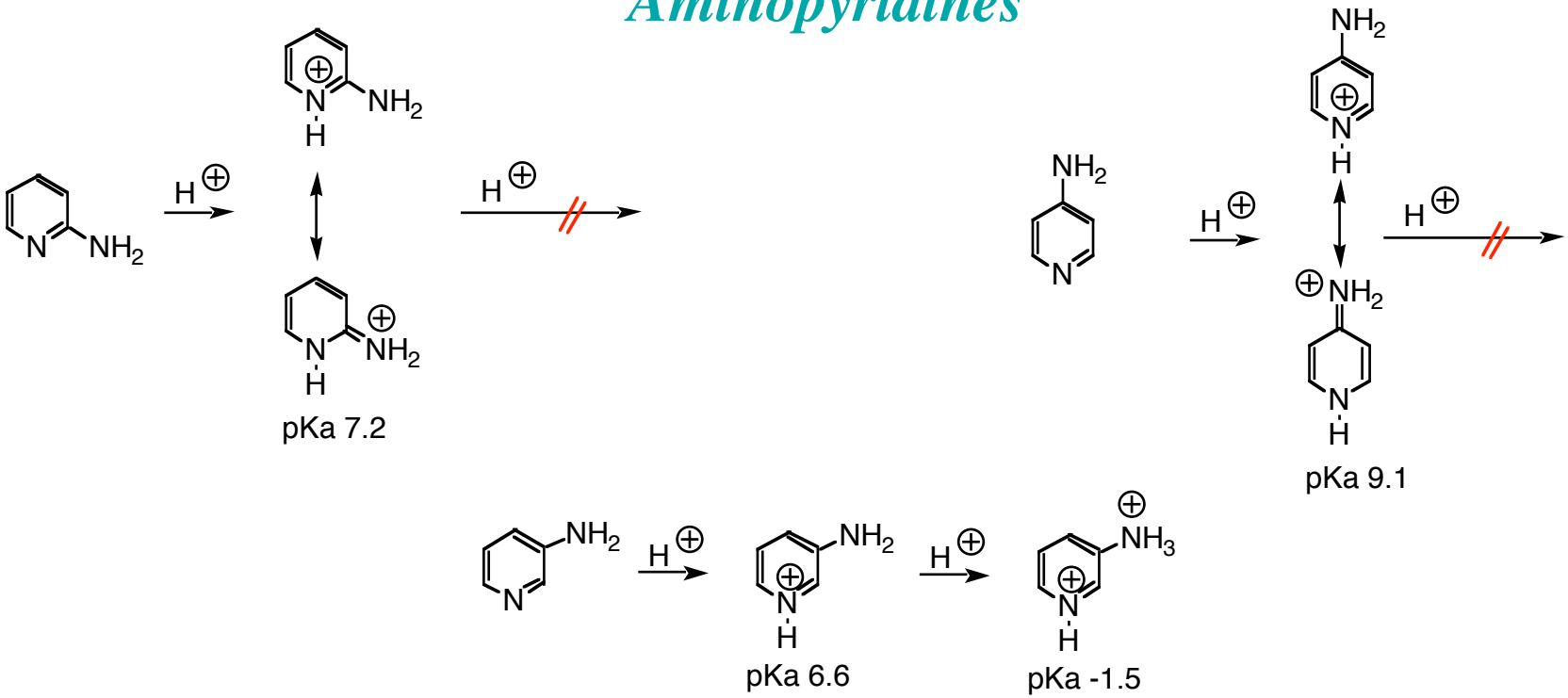
Useful synthetic intermedites

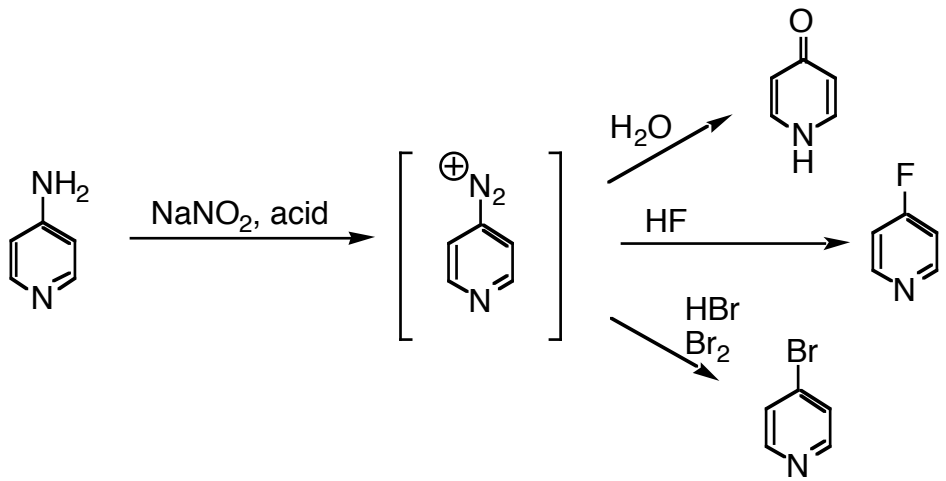


Peptide

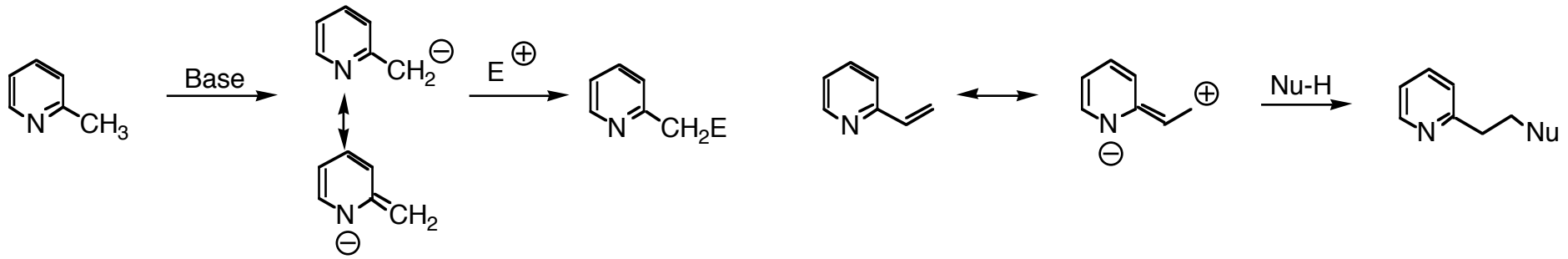


Aminopyridines

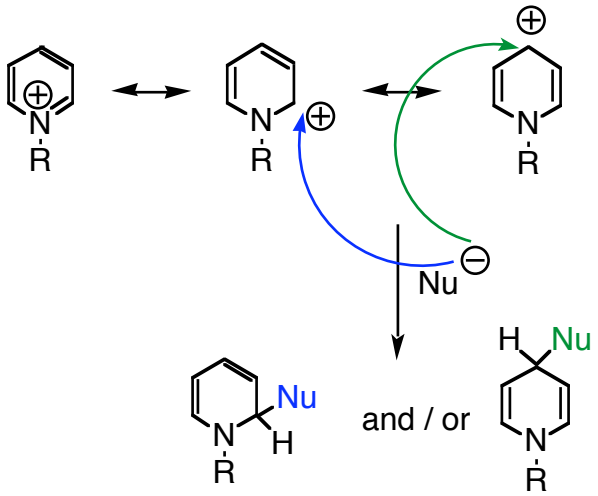




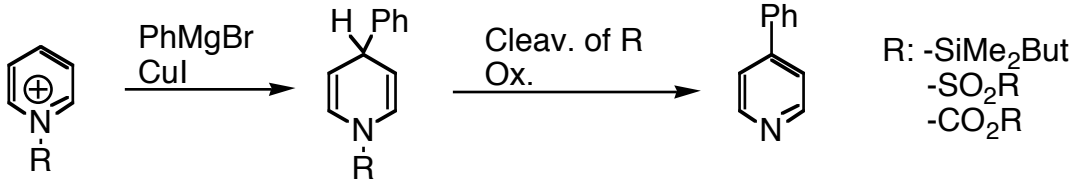
Alkyl- and Vinylpyridines

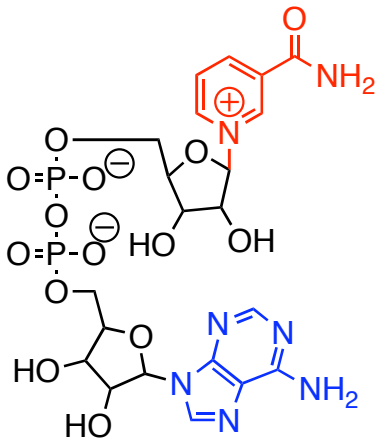


Quartenary Pyridinium Salts

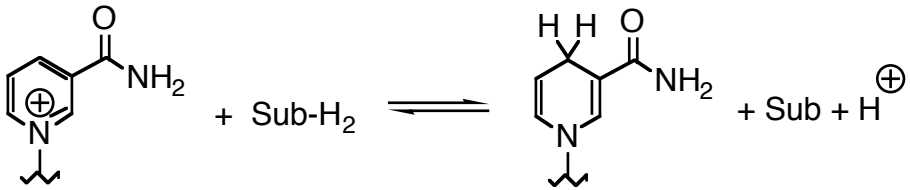


Add of: -hydrides
-dithionite
-organometallics
-stab. carbanions
etc. etc.





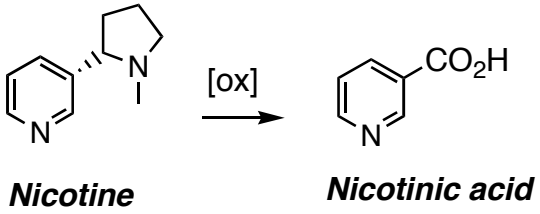
Co-enz.
NAD^+



NAD^+ **NADH**

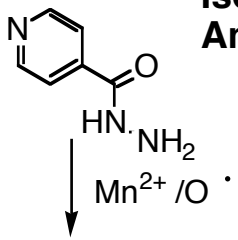
Hydride add. to NAD+, $SubH_2$ oxidized

Nicotine amide: Vit. B_3
Adenine: Vit. B_4

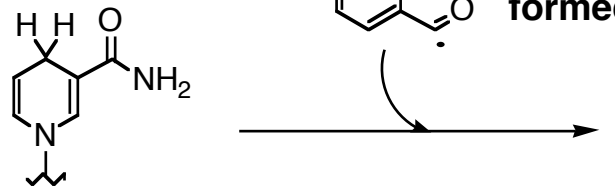


Nicotine ***Nicotinic acid***

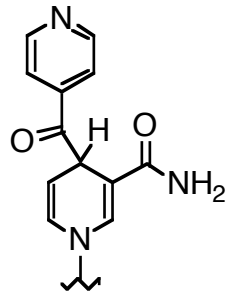
Isoniazide
Antituberculosis drug



Active acyl radical formed *in vivo*

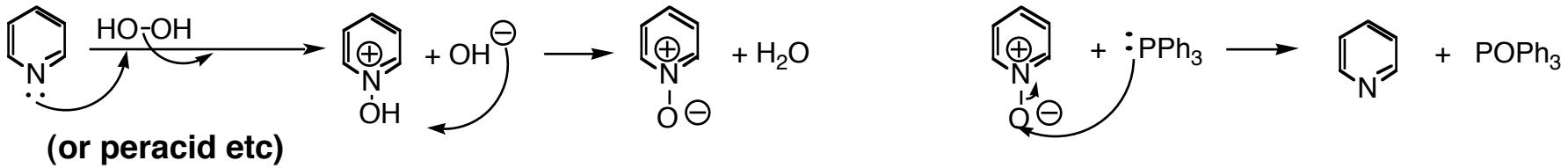


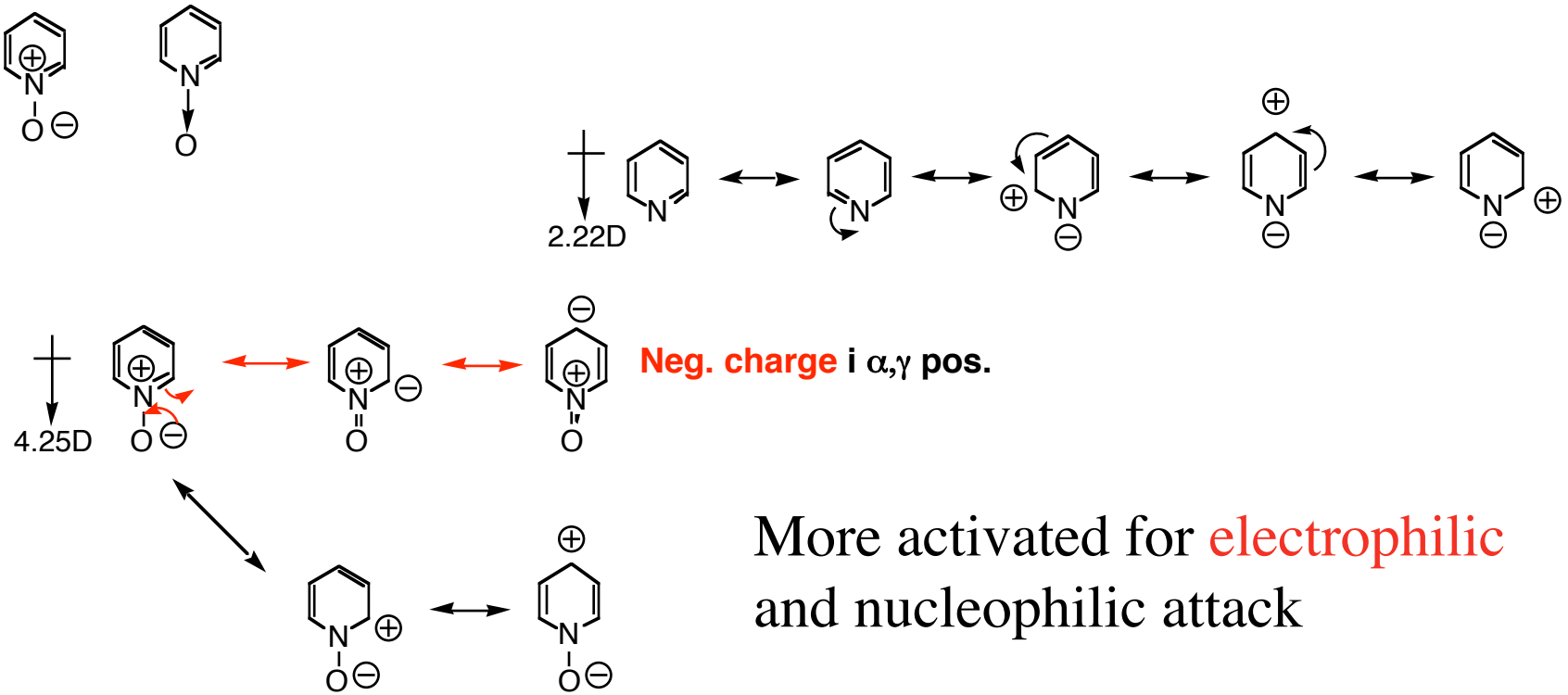
NADH co-enzyme in enzyme involved in cell wall component synth



Inactive der. of co-enz

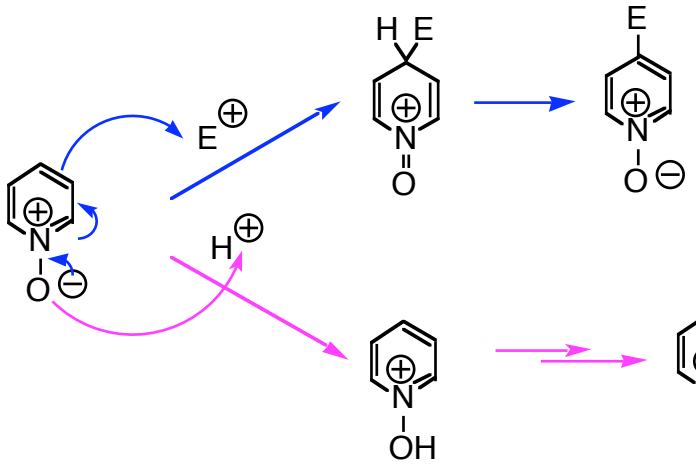
Pyridine *N*-oxides

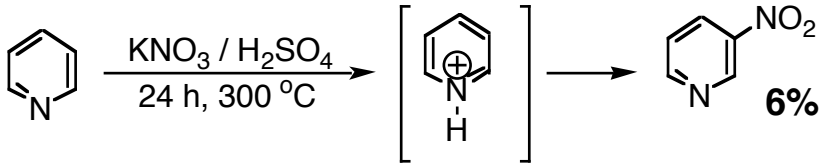




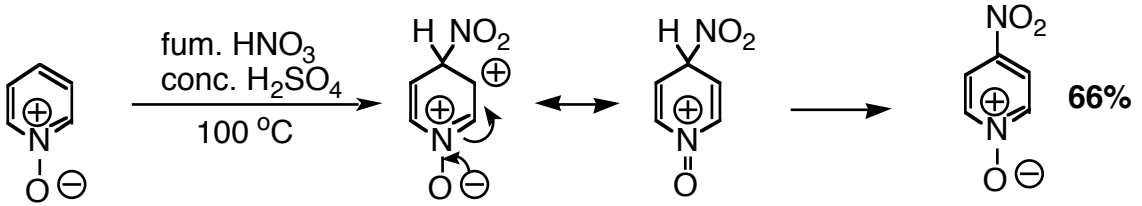
More activated for electrophilic and nucleophilic attack

Electrophilic Ar. subst





c.f. Electrophilic Ar. subst on pyridine / puridinium cation



Rearrangements