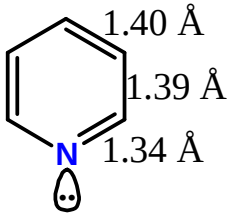
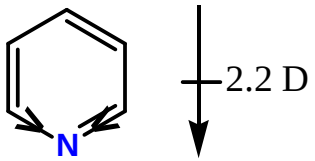
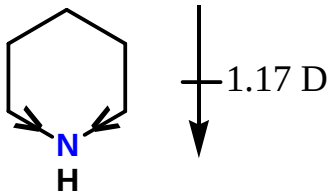
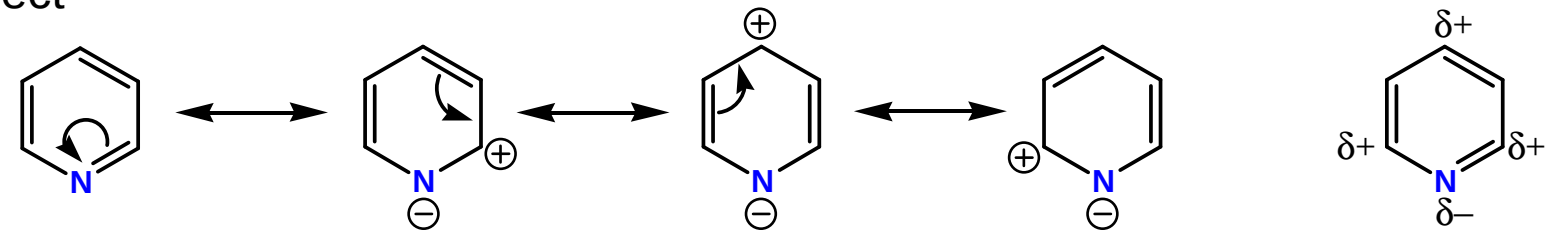
Pyridines – Structure



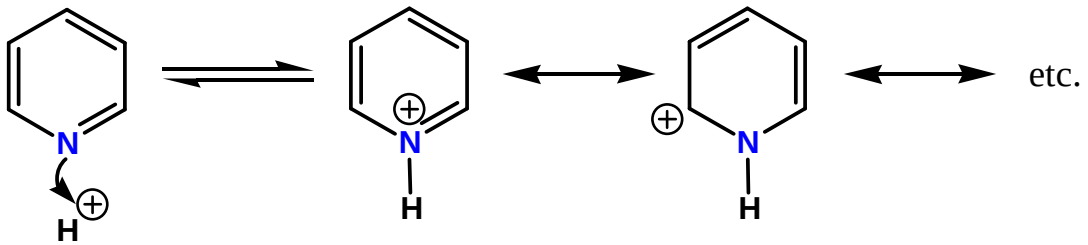




- Isoelectronic with and analogous to benzene
- Stable, not easily oxidised at *C*, undergoes substitution rather than addition
- –I Effect (inductive electron withdrawal)
- –M Effect

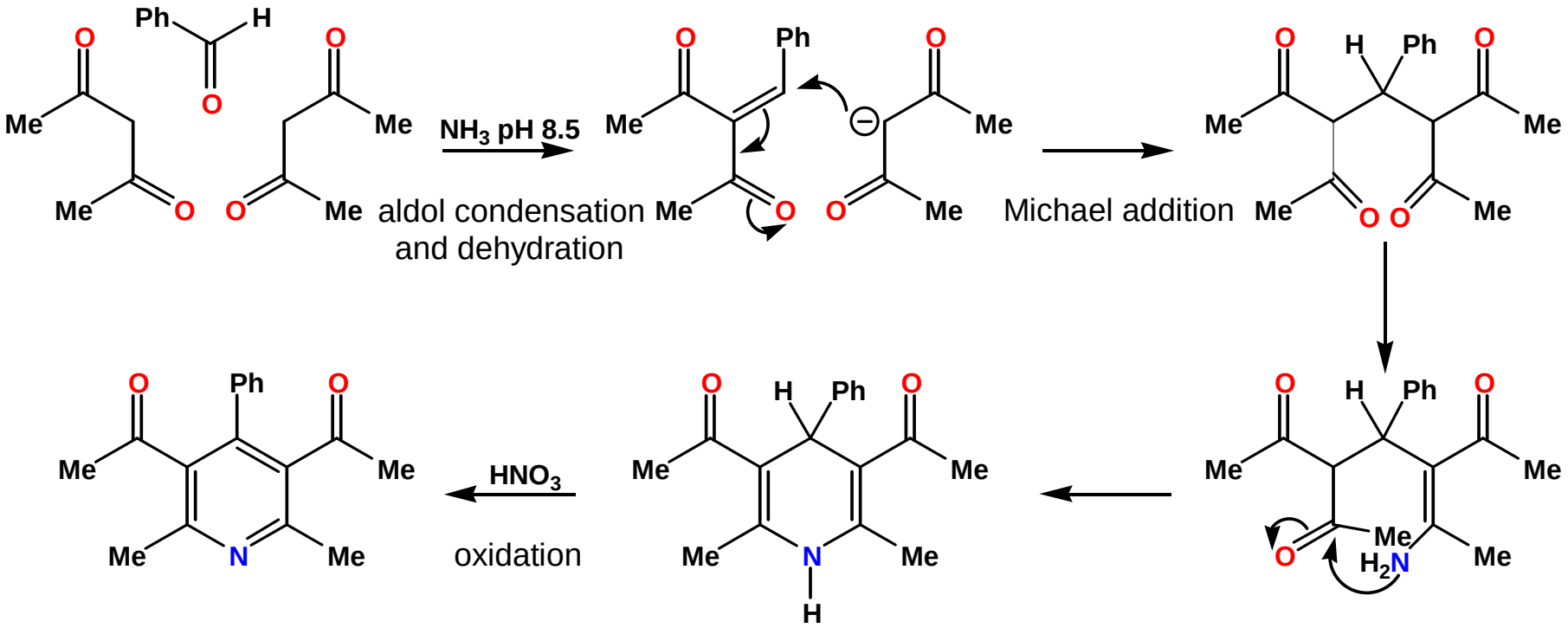


- Weakly basic – pK_a ~5.2 in H_2O (lone pair is **not** in aromatic sextet)
- Pyridinium salts are also aromatic – ring carbons are more δ+ than in parent pyridine



Pyridines – Synthesis

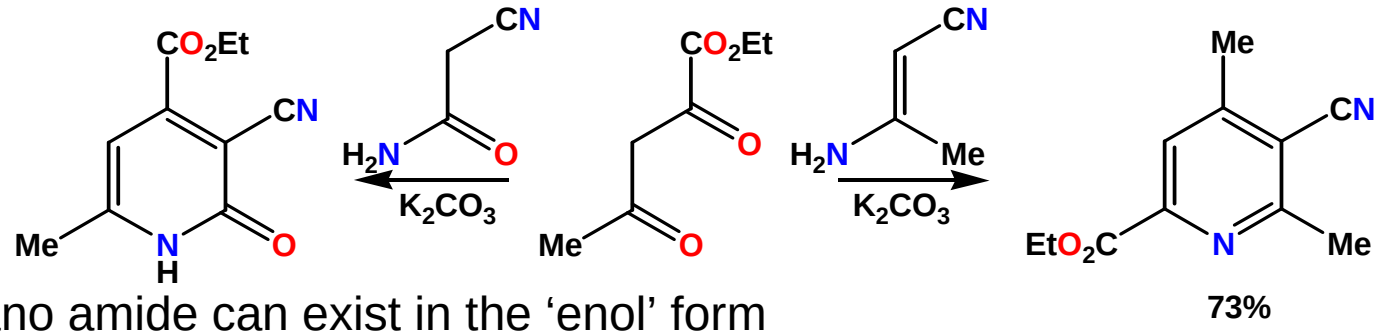
The Hantzsch synthesis (“5+1”)



- The reaction is useful for the synthesis of symmetrical pyridines
- The 1,5-diketone intermediate can be isolated in certain circumstances
- A separate oxidation reaction is required to aromatise the dihydropyridine

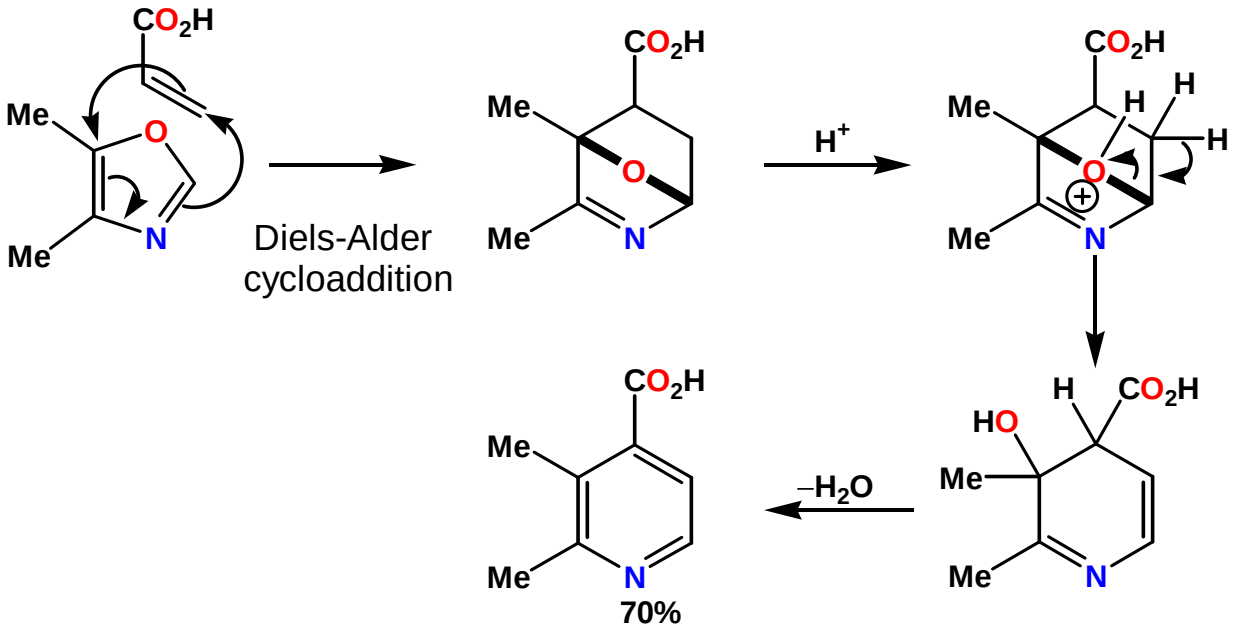
Pyridines – Synthesis

From Enamines or Enamine Equivalents – the Guareschi synthesis (“3+3”)



• The β-cyano amide can exist in the ‘enol’ form

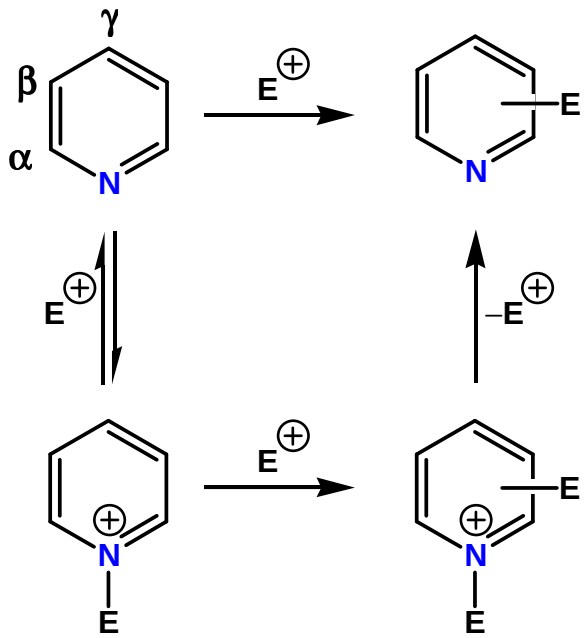
Using Cycloaddition Reactions (“4+2”)



• Oxazoles are sufficiently low in aromatic character to react in the Diels-Alder reaction

Pyridines – Electrophilic Reactions

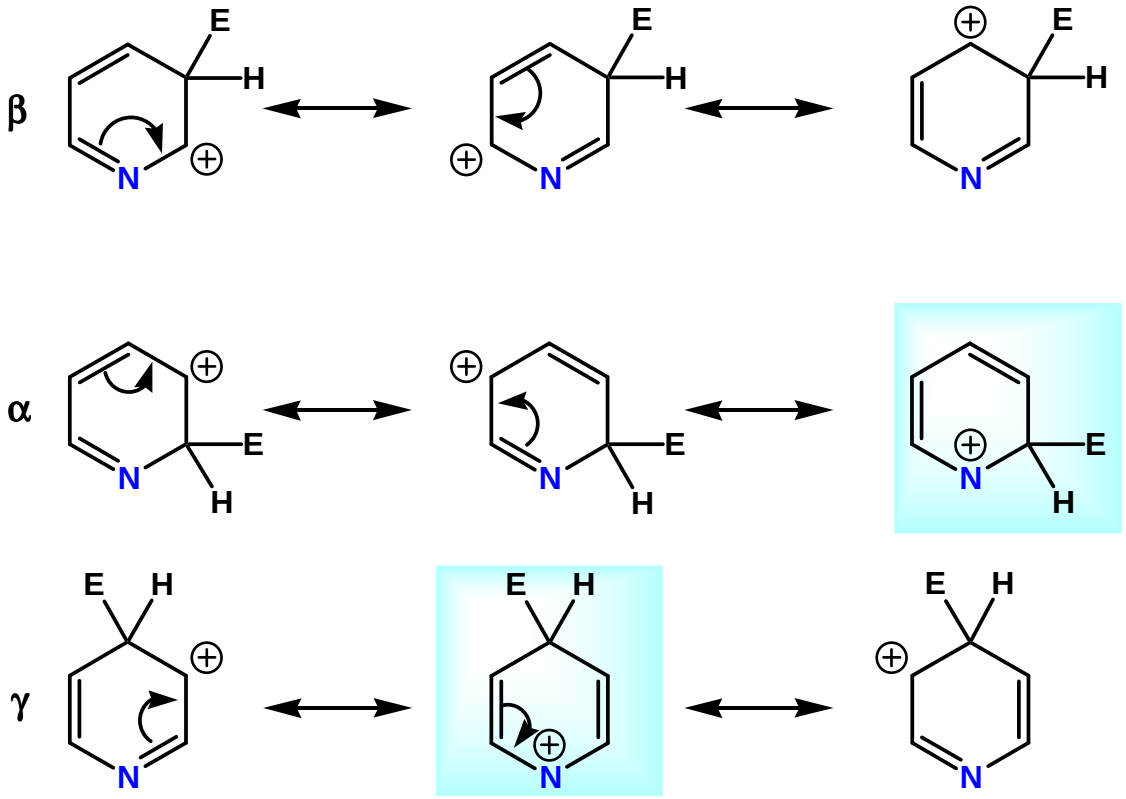
Pathways for the Electrophilic Aromatic Substitution of Pyridines



- The position of the equilibrium between the pyridine and pyridinium salt depends on the substitution pattern and nature of the substituents, but usually favours the salt

Pyridines – Electrophilic Reactions

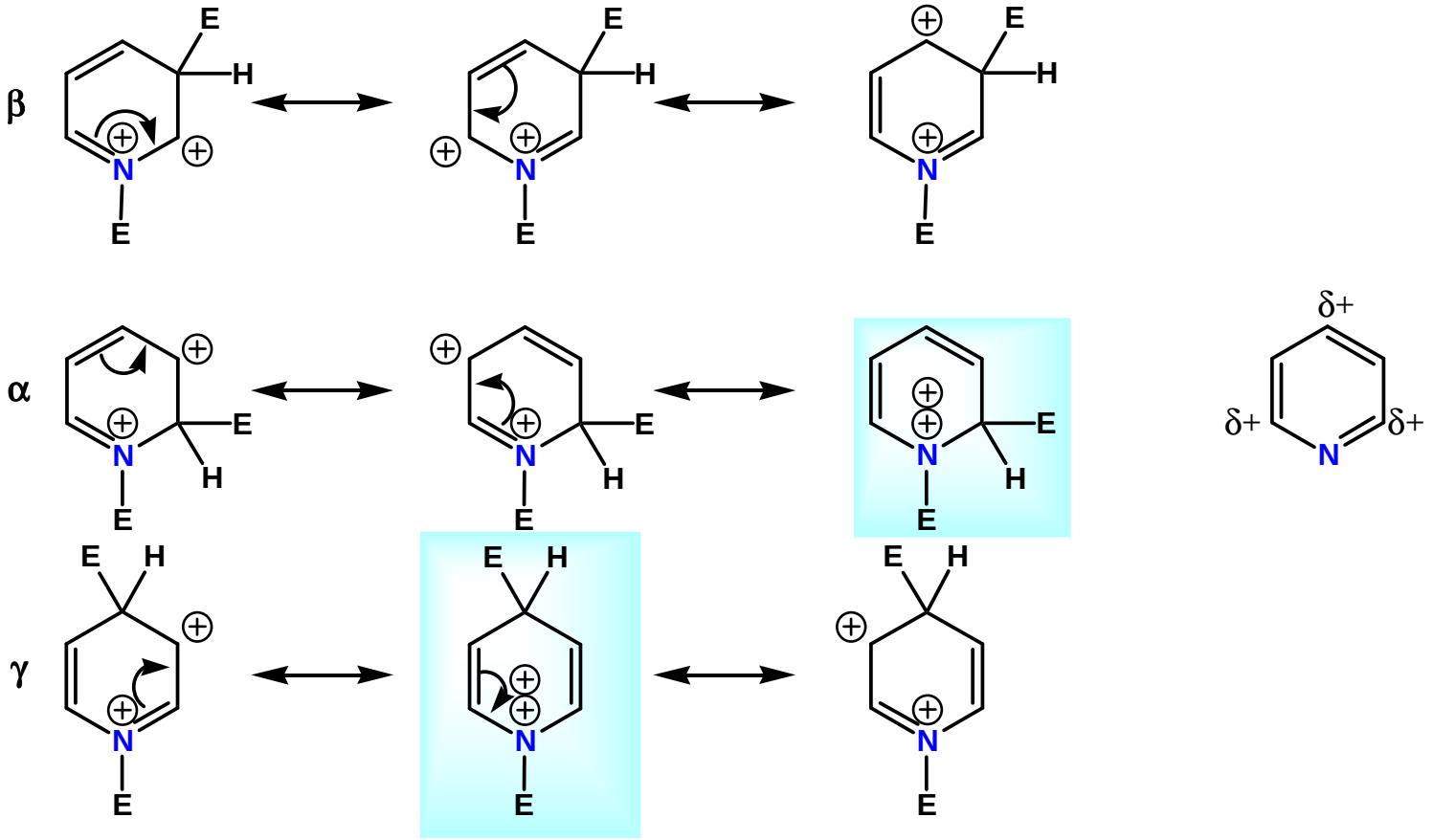
Regiochemical Outcome of Electrophilic Substitution of Pyridines



- Resonance forms with a positive charge on *N* (i.e. 6 electrons) are very unfavourable
- The β-substituted intermediate, and the transition state leading to this product, have more stable resonance forms than the intermediates/transition states leading to the α/γ products

Pyridines – Electrophilic Reactions

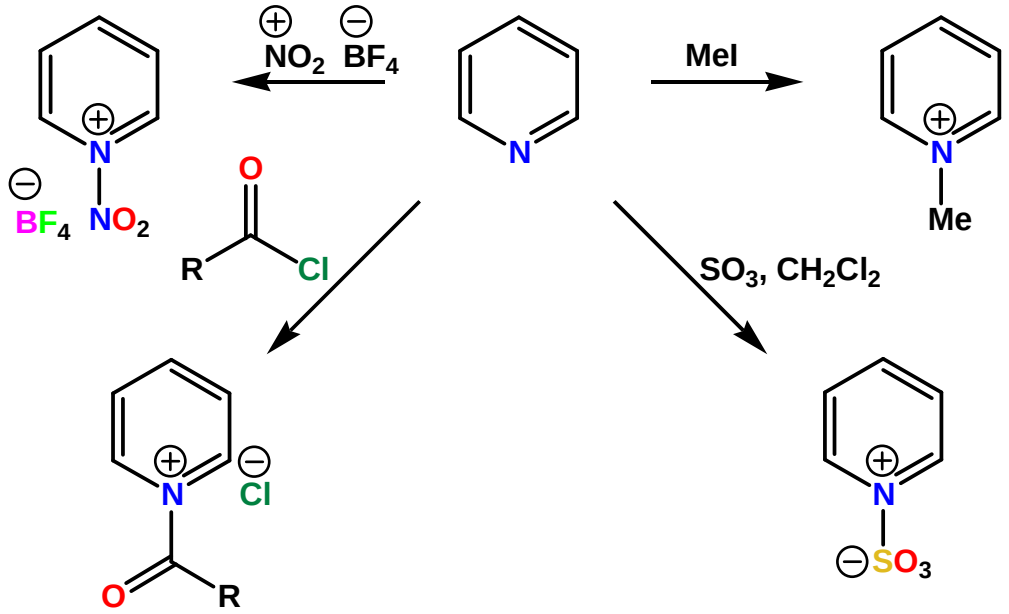
Regiochemical Outcome of Electrophilic Substitution of Pyridinium Ions



- Regiochemical control is even more pronounced in the case of pyridinium ions
- In both pyridine and pyridinium systems, β substitution is favoured but the reaction is slower than that of benzene
- Reaction will usually proceed through the small amount of the free pyridine available

Pyridines – Electrophilic Reactions

N Substitution

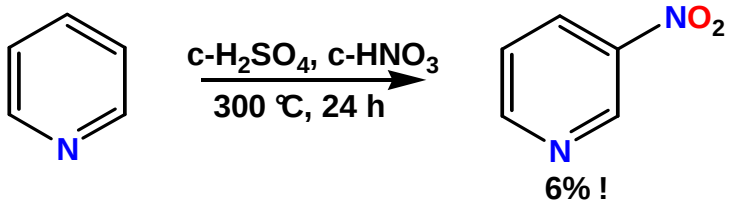


C Substitution

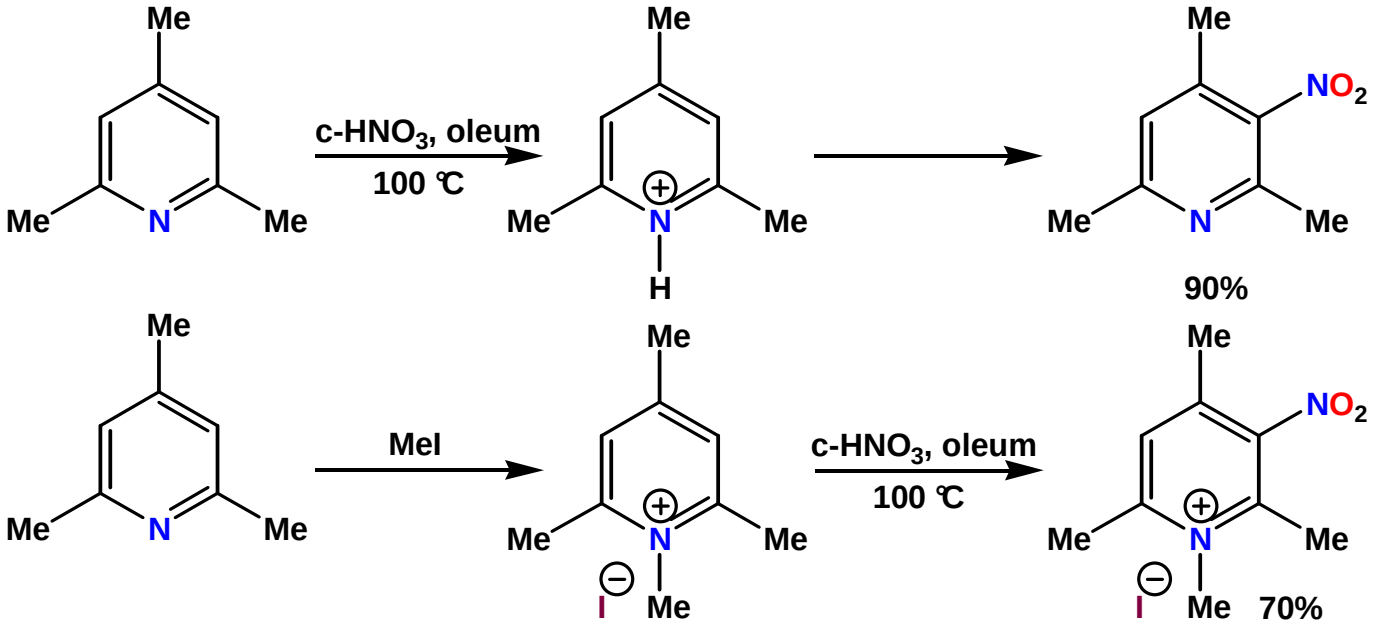
- Reaction at *C* is usually difficult and slow, requiring forcing conditions
- Friedel-Crafts reactions are not usually possible on free pyridines

Pyridines – Electrophilic Reactions

Nitration of Pyridine



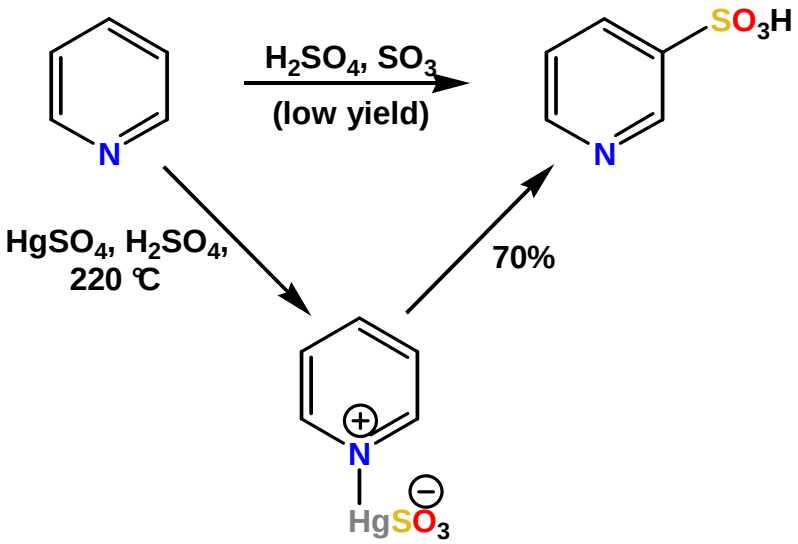
Use of Activating Groups



- Multiple electron-donating groups accelerate the reaction
- Both reactions proceed at similar rates which indicates that the protonation at *N* occurs prior to nitration in the first case

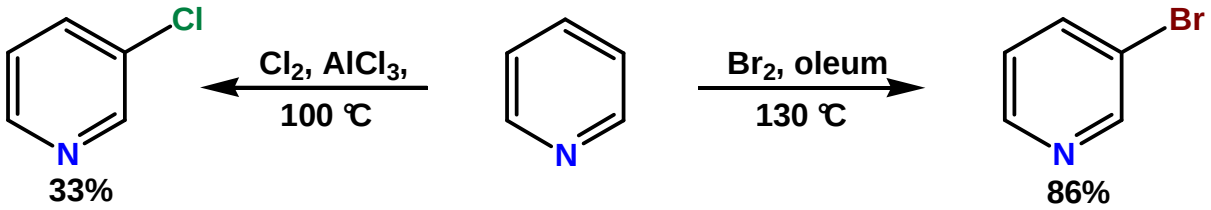
Pyridines – Electrophilic Reactions

Sulfonation of Pyridine



- Low yield from direct nitration but good yield via a mercury intermediate

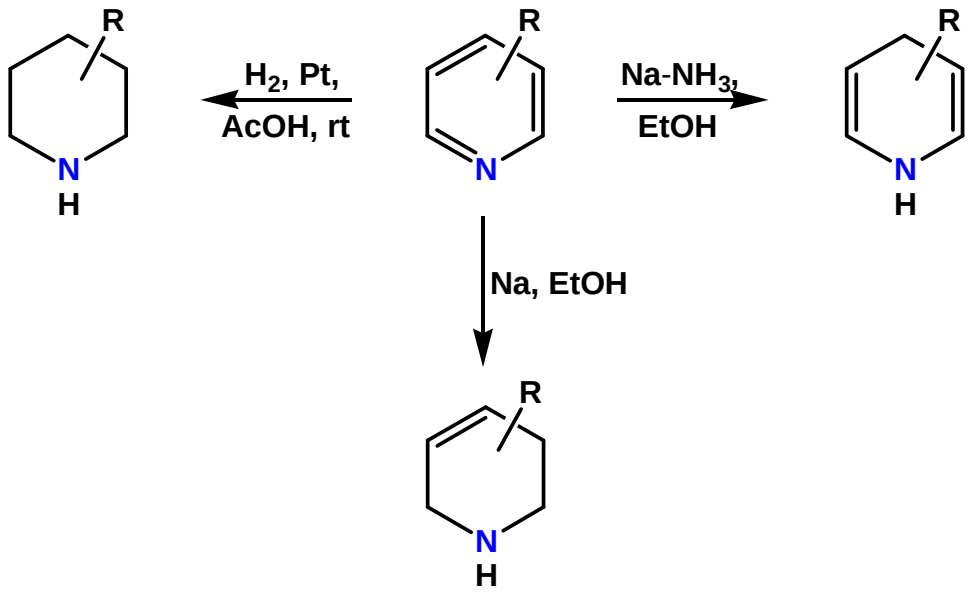
Halogenation of Pyridine



- Forcing reaction conditions are required for direct halogenation

Pyridines – Reduction

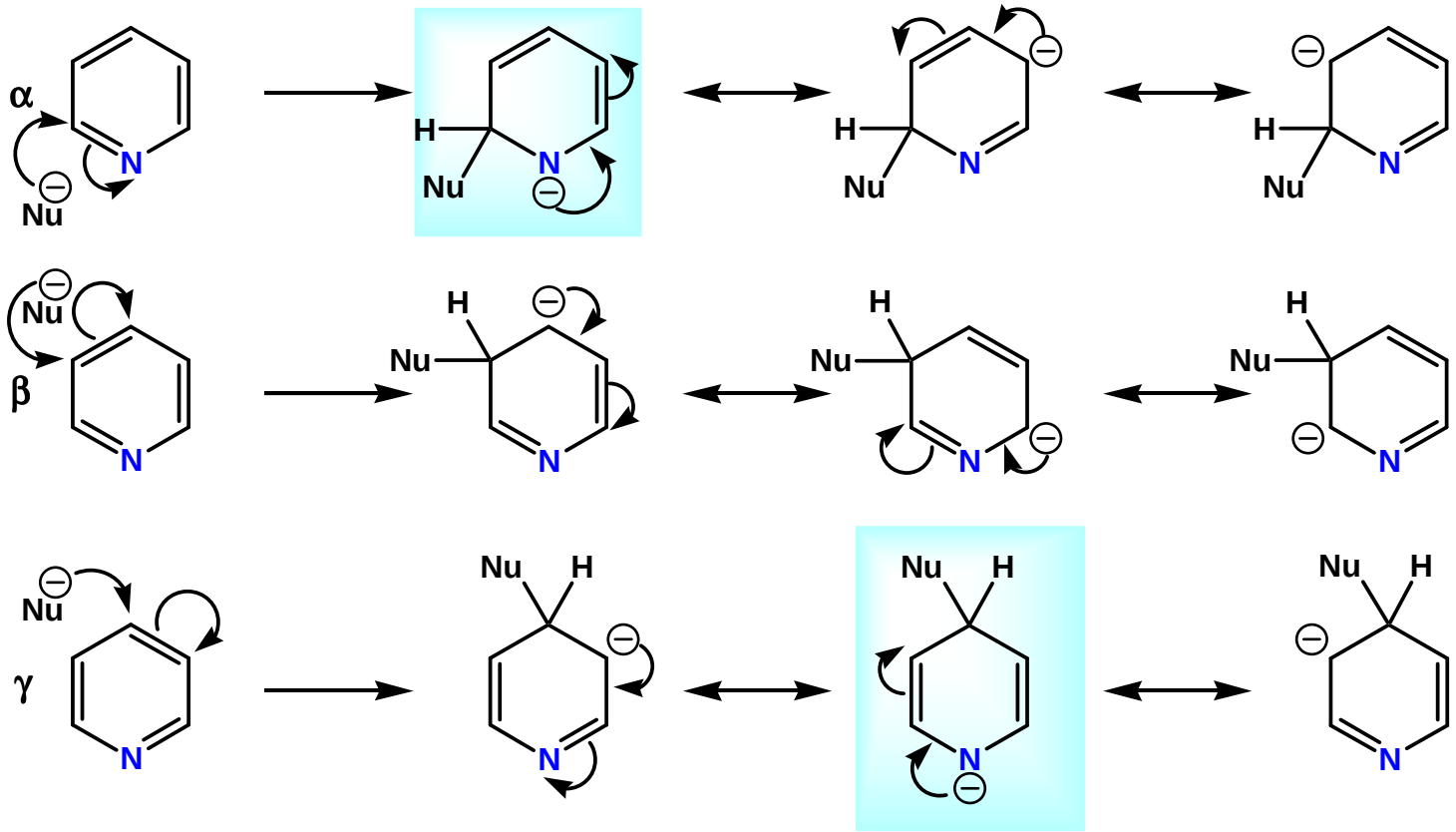
Full or Partial Reduction of Pyridines



- Pyridines generally resist oxidation at ring carbon atoms and will often undergo side-chain oxidation in preference to oxidation of the ring
- Full or partial reduction of the ring is usually easier than in the case of benzene

Pyridines – Nucleophilic Reactions

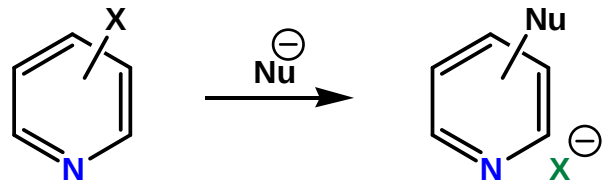
Regiochemical Outcome of Nucleophilic Addition to Pyridines



- Nitrogen acts as an electron sink
- β Substitution is less favoured because there are no stable resonance forms with the negative charge on *N*
- Aromaticity will is regained by loss of hydride or a leaving group, or by oxidation

Pyridines – Nucleophilic Reactions

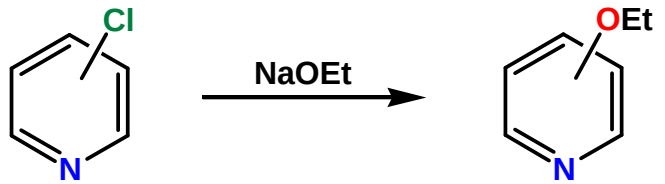
Nucleophilic Substitution

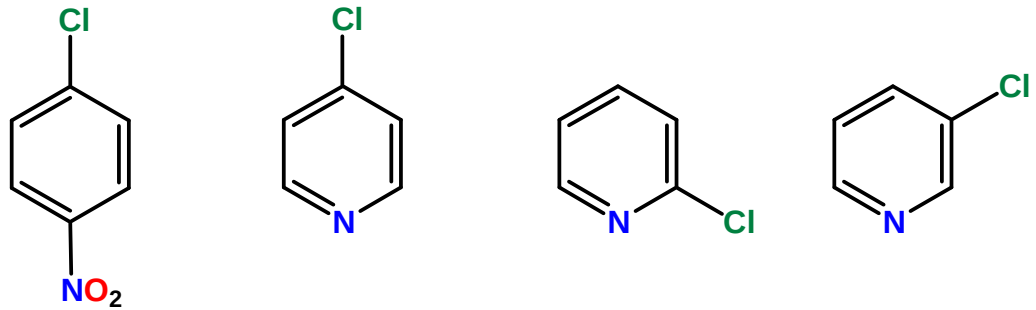


X = **Cl**, **Br**, **I**, (**NO_2**)

Nu = **$MeO^{\ominus}$**, **NH_3**, **PhSH** etc.

- Favoured by electron-withdrawing substituents that are also good leaving groups
- The position of the leaving group influences reaction rate ($\gamma > \alpha >> \beta$)

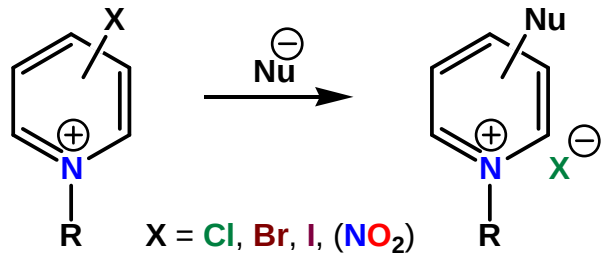




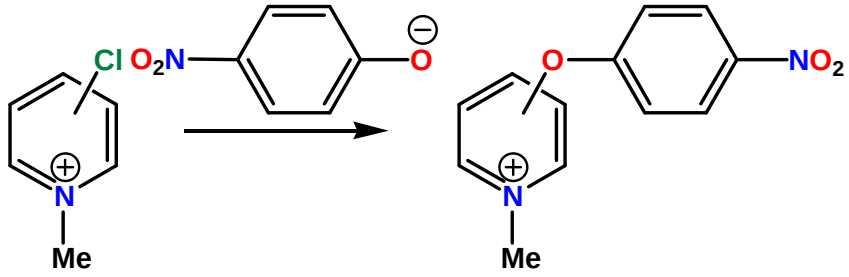
Relative rate	80	40	1	3×10^{-4}

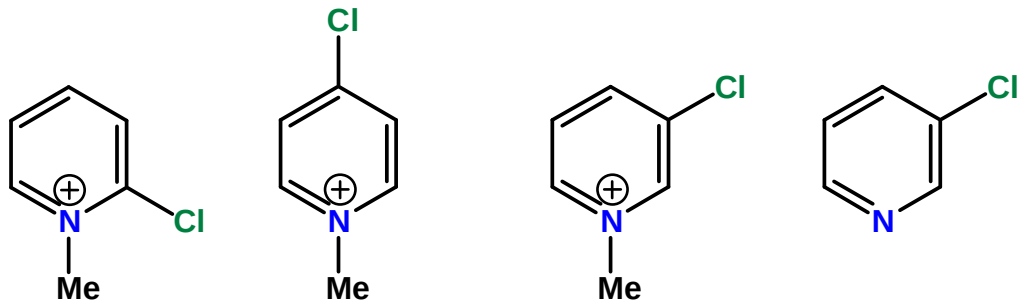
Pyridinium Ions – Nucleophilic Reactions

Nucleophilic Substitution



- Conversion of a pyridine into the pyridinium salt greatly accelerates substitution
- Substituent effects remain the same (α, γ >> β) but now α > γ

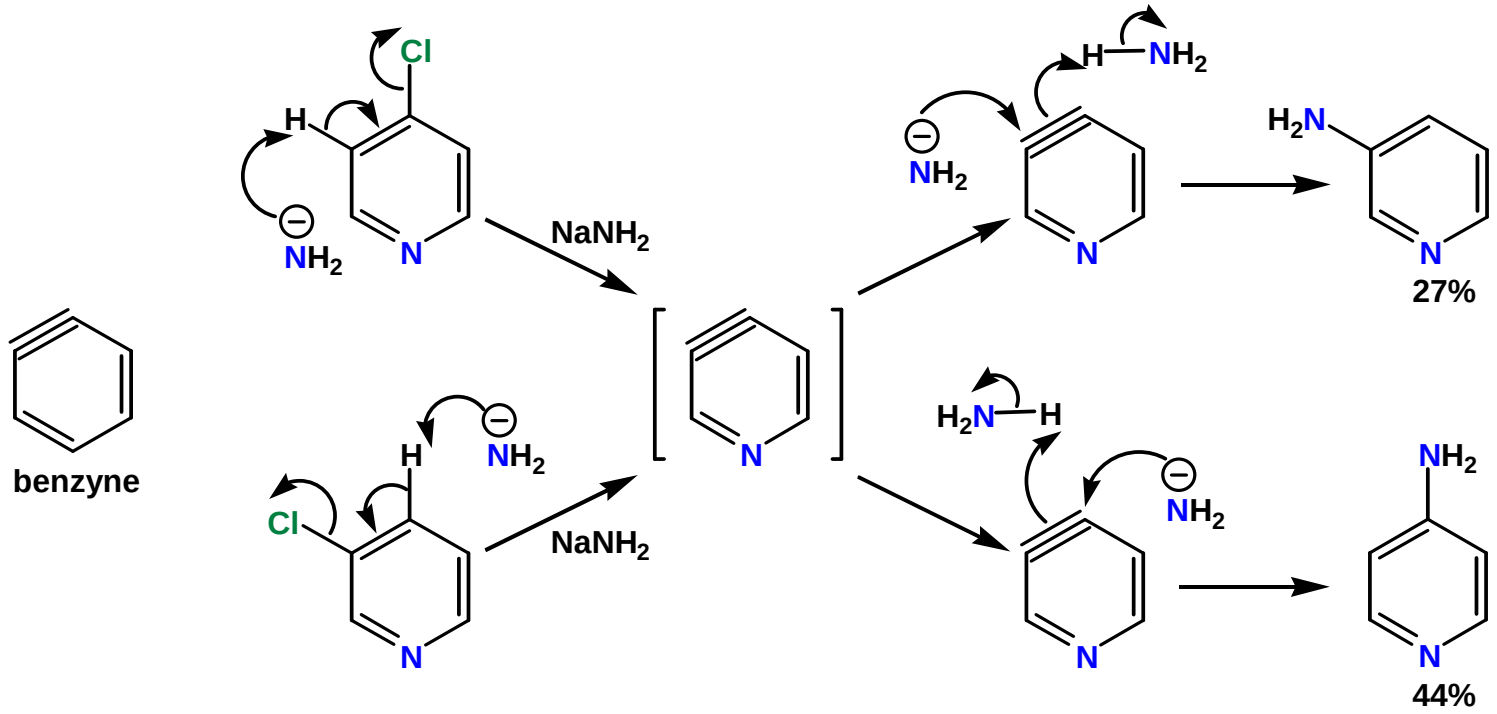




Relative rate	5×10^7	1.5×10^4	1	10^{-4}

Pyridines – Pyridyne Formation

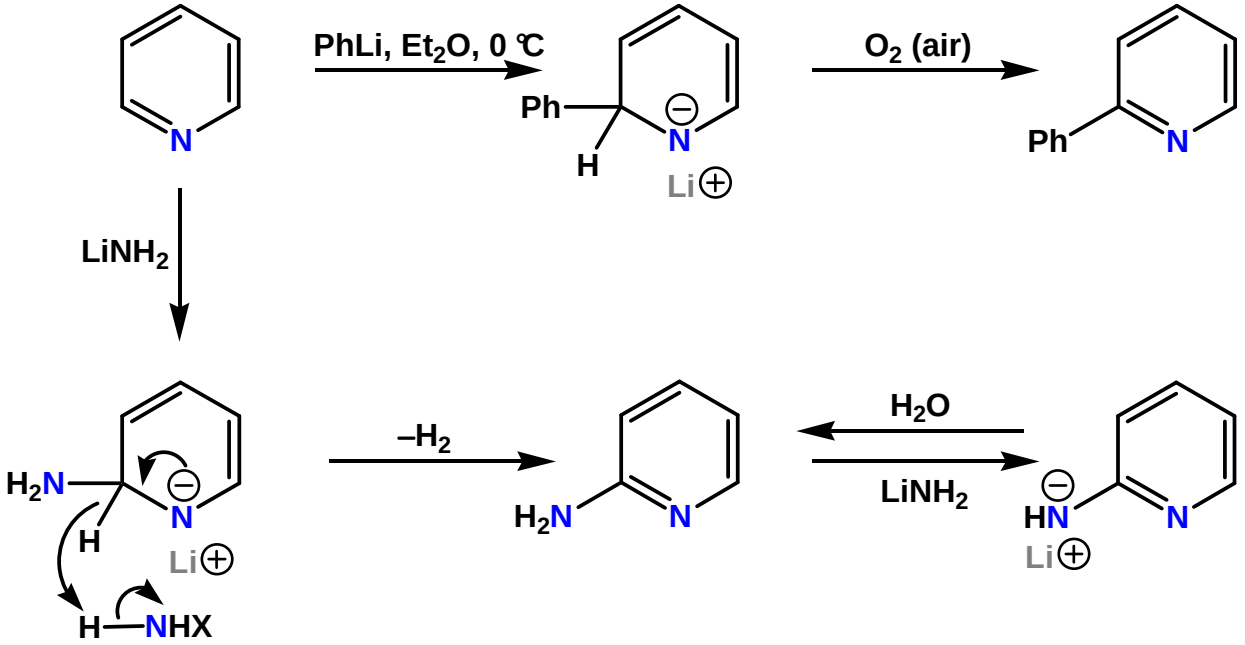
Substitution via an Intermediate Pyridyne



- When very basic nucleophiles are used, a pyridyne intermediate intervenes
- Pyridynes are similar to benzynes and are very reactive (not isolable)

Pyridines – Nucleophilic Reactions

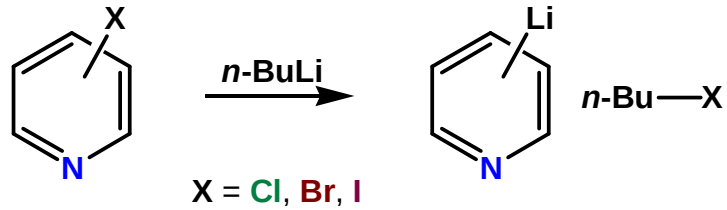
Nucleophilic Attack with Transfer of Hydride



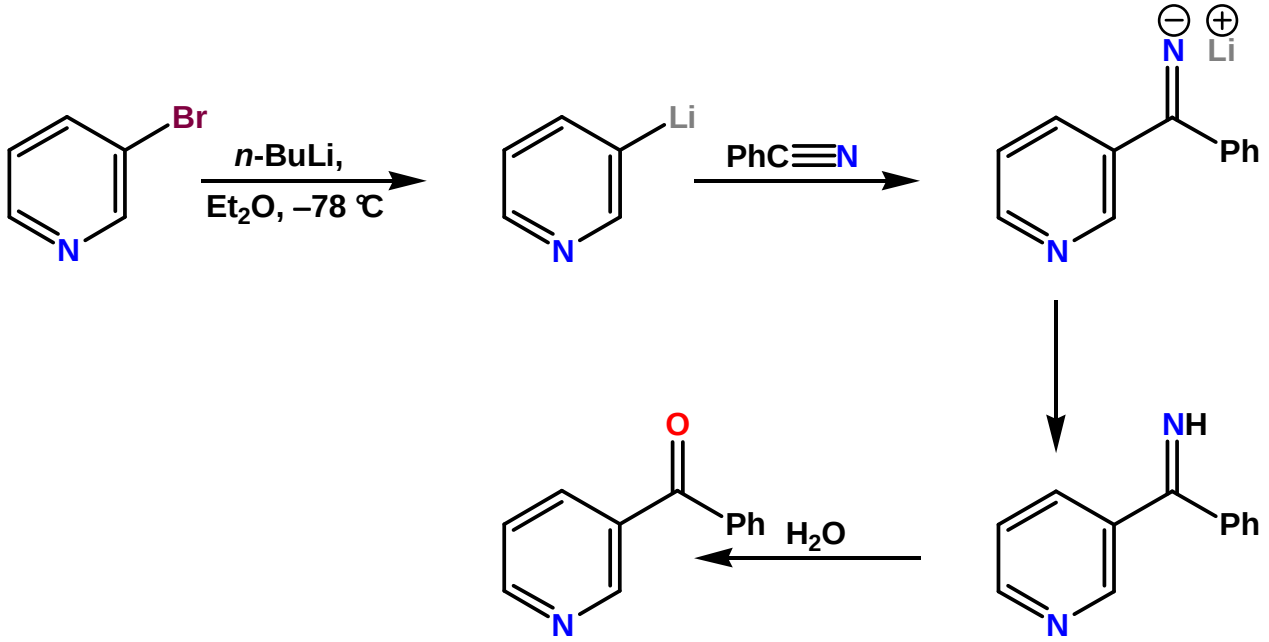
- A hydride acceptor or oxidising agent is required to regenerate aromaticity
- The reaction with $LiNH_2$ is referred to as the Chichibabin reaction

Pyridines – Metal-Halogen Exchange

Direct Exchange of Metal and a Halogen

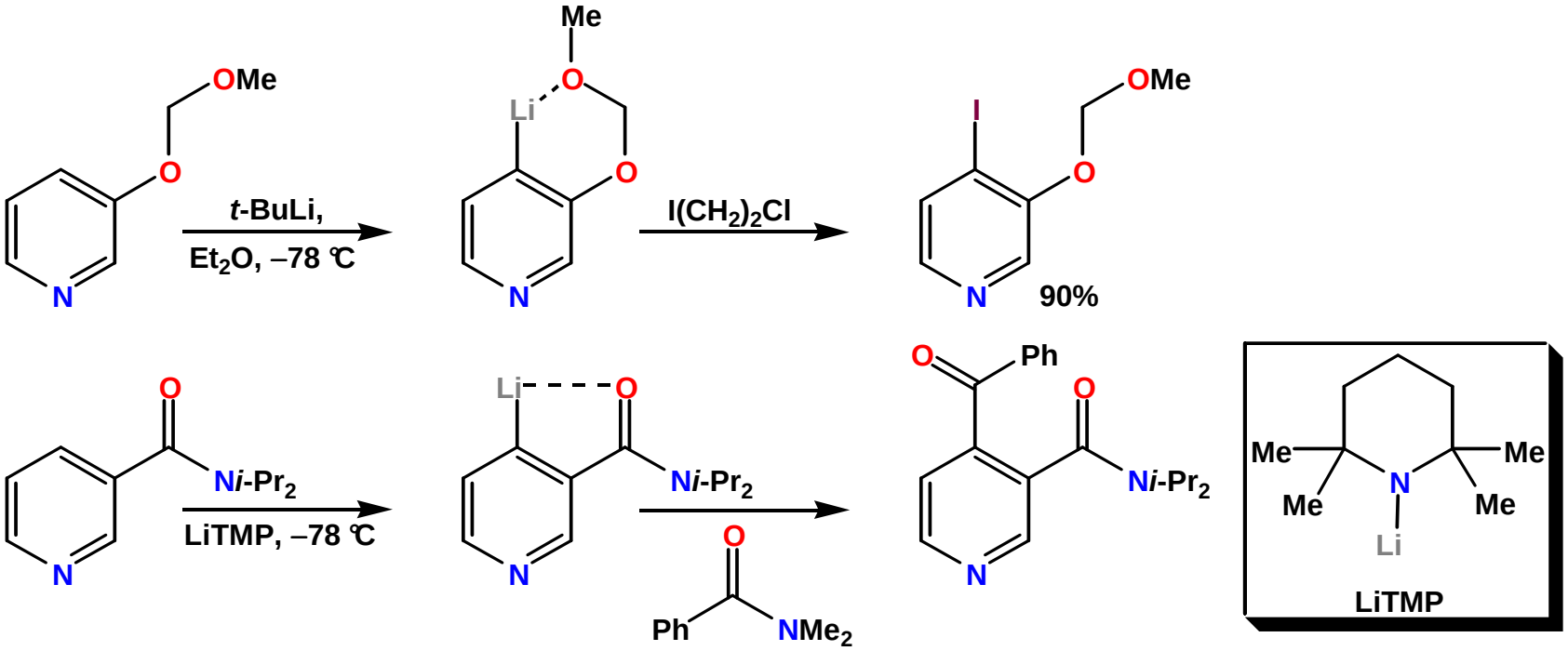


- Halogenated pyridines do not tend to undergo nucleophilic displacement with alkyl lithium or alkyl magnesium reagents
- Metallated pyridines behave like conventional Grignard reagents



Pyridines – Directed Metallation

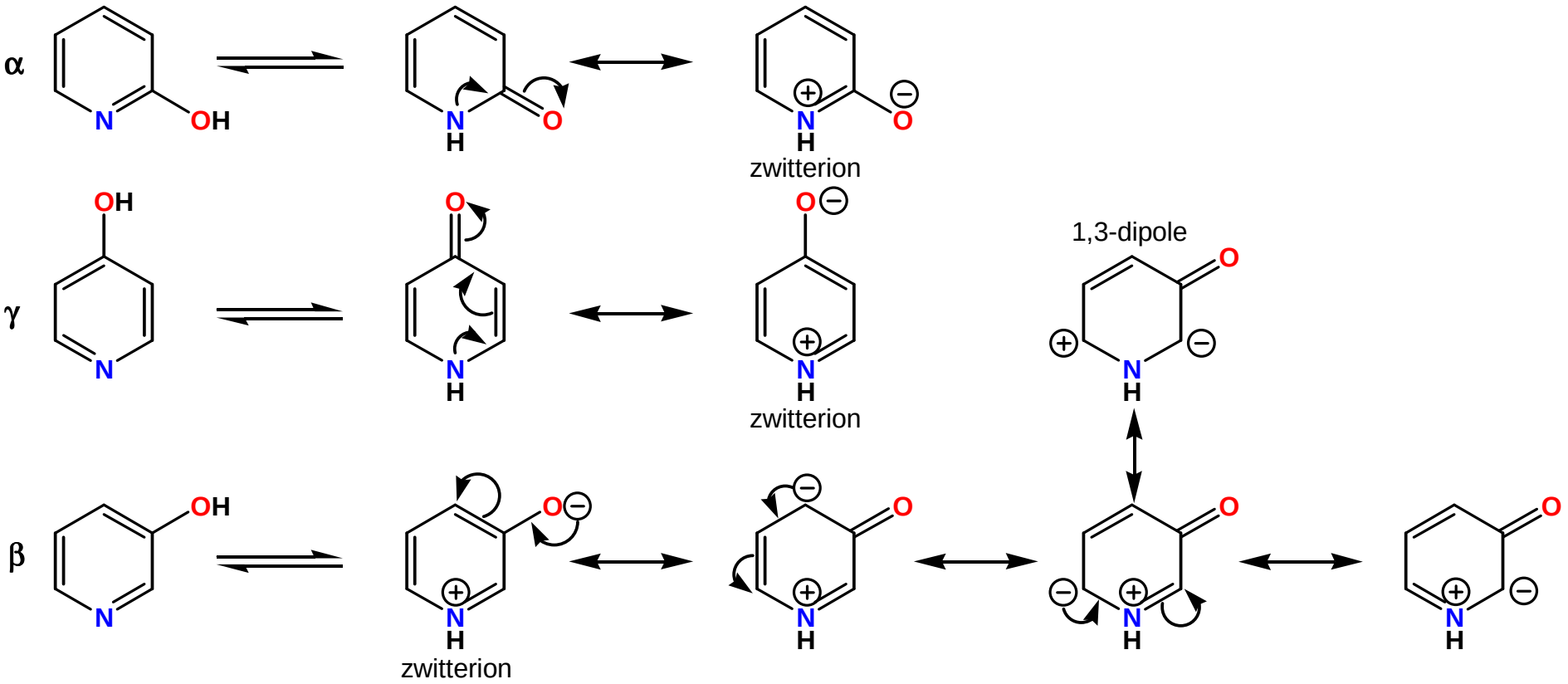
Use of Directing Groups



- Directing groups allow direct lithiation at an adjacent position
- A Lewis basic group is required to complex the Lewis acidic metal of the base

Oxy-Pyridines – Structure

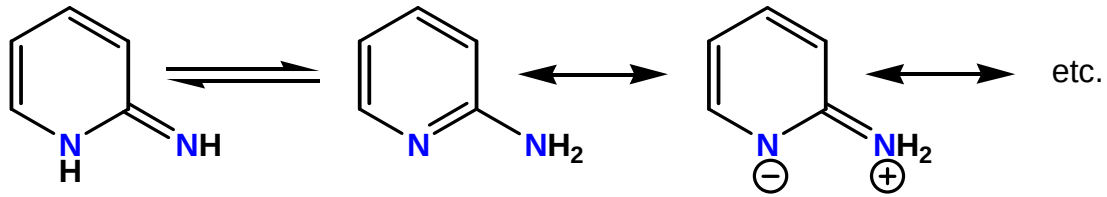
Oxy-Pyridines/Pyridones



- Subject to tautomerism
- The α, γ systems differ from the β systems in terms of reactivity and structure
- In the α case, the equilibrium is highly solvent dependent, but the keto form is favoured in polar solvents

Amino Pyridines – Structure

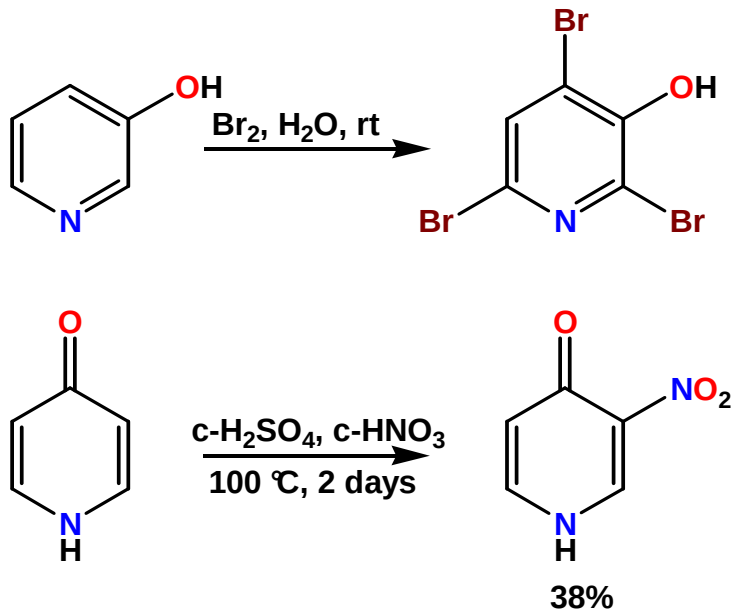
Amino Pyridine Systems



- Contrast with oxy-pyridines
- Amino pyridines are polarised in the opposite direction to oxy-pyridines

Oxy-Pyridines – Reactions

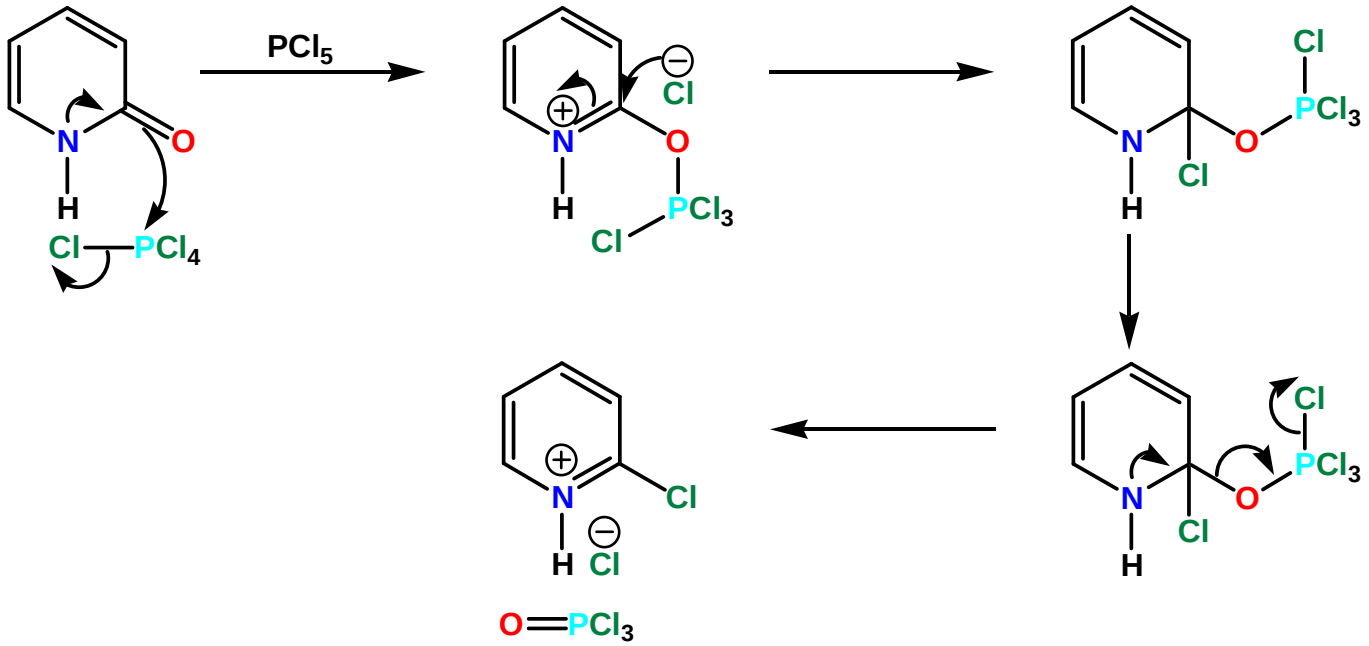
Electrophilic Substitution



- Reactions such as halogenation, nitration, sulfonation etc. are possible
- *N* is much less basic than that in a simple pyridine
- Substitution occurs ortho or para to the oxygen substituent (cf. phenols)

Oxy-Pyridines – Reactions

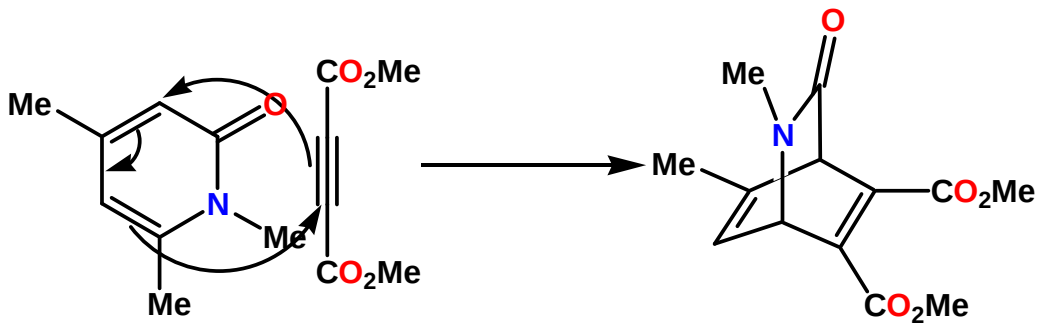
Nucleophilic Substitution



- Replacement of the oxygen substituent is possible
- In this case, the reaction is driven by the formation of the very strong P=O bond

Oxy-Pyridines – Reactions

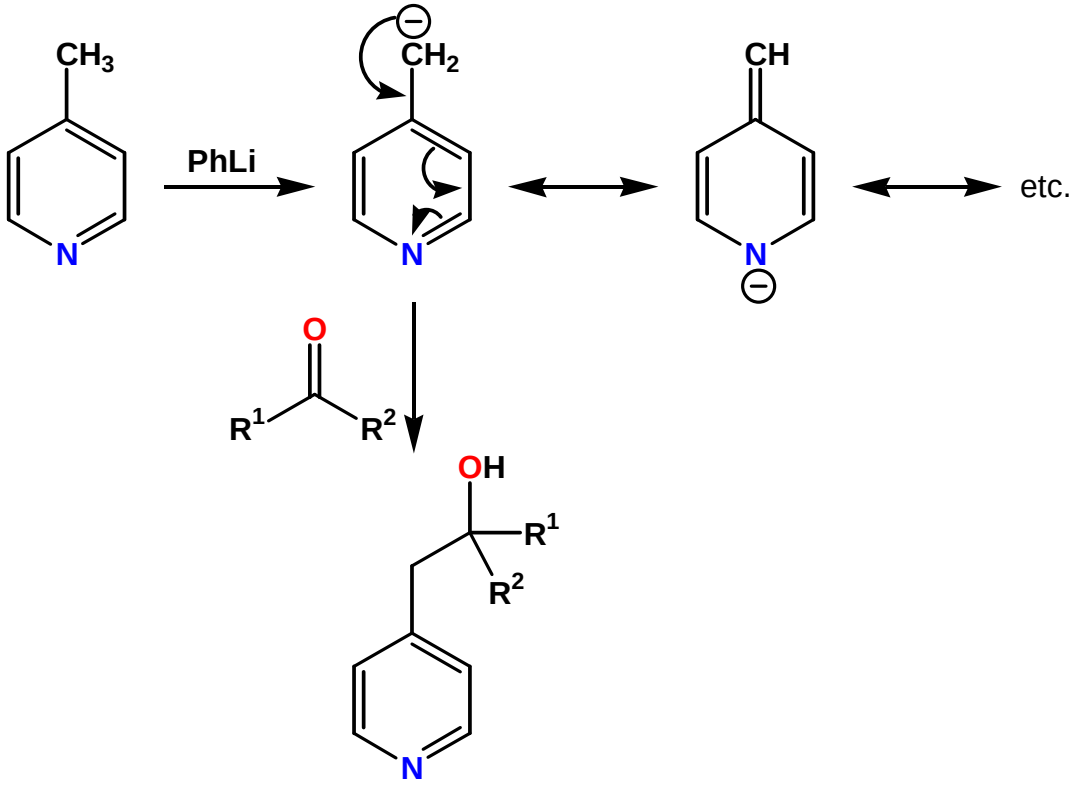
Cycloaddition



- Oxy-pyridines have sufficiently low aromatic character that they are able to participate as dienes in Diels-Alder reactions with highly reactive dienophiles

Alkyl Pyridines – Deprotonation

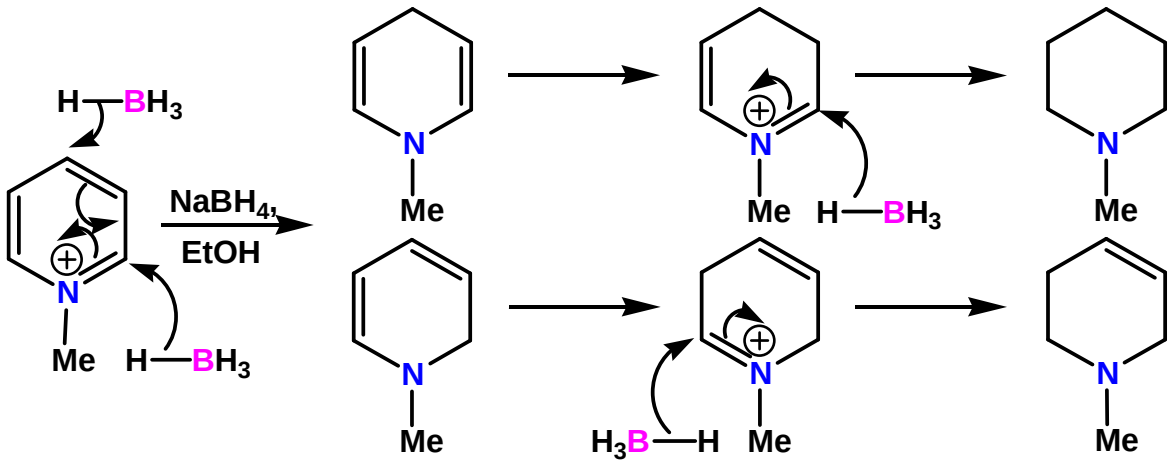
Deprotonation with a Strong Base



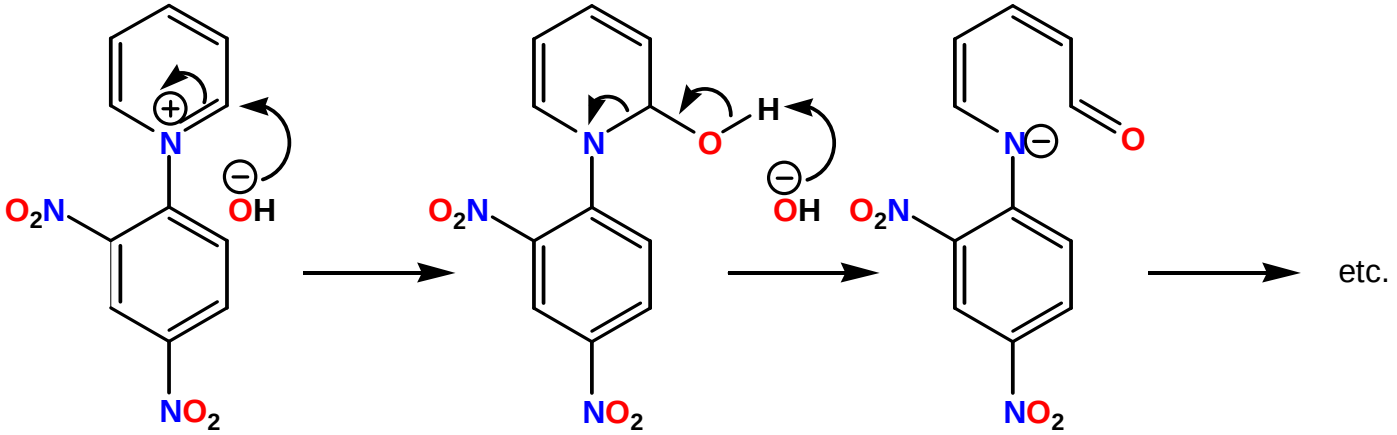
- Deprotonation of α and γ alkyl groups proceeds at a similar rate, but β alkyl groups are much more difficult to deprotonate
- Bases are also potential nucleophiles for attack of the ring

Pyridinium Salts – Reactions

Nucleophilic Attack with Reducing Agents

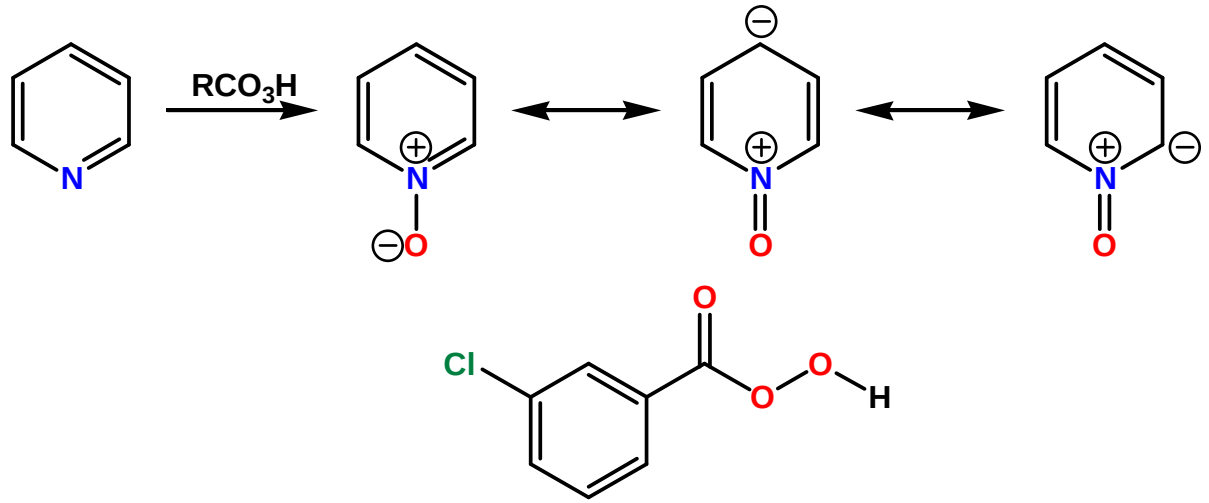


- Nucleophilic attack is much easier (already seen this)
- Deprotonation of alkyl substituents is easier (weak bases are suitable)
- Ring opening is possible by attack of hydroxide



Pyridine *N*-Oxides

N-Oxide Formation

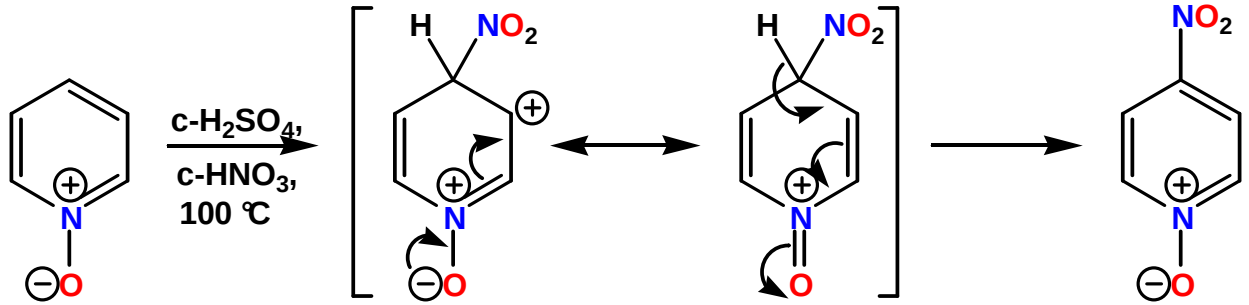


***meta*-chloroperoxybenzoic acid (*m*-CPBA)**

- The reactivity *N*-oxides differs considerably from that of pyridines or pyridinium salts
- A variety of peracids can be used to oxidise *N* but *m*-CPBA is used most commonly
- *N*-Oxide formation can be used to temporarily activate the pyridine ring to both nucleophilic and electrophilic attack

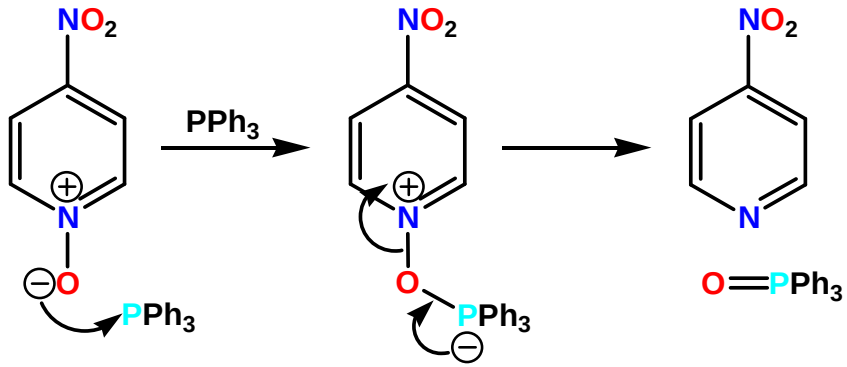
Pyridine *N*-Oxides

Electrophilic Substitution



- The *N*-oxide is activated to attack by electrophiles at both the α and γ positions
- Nitration of an *N*-oxide is easier than nitration of the parent pyridine
- Reactivity is similar to that of a pyridinium salt in many cases e.g. nucleophilic attack, deprotonation of alkyl groups etc.

Removal of *O*



- Deoxgenation is driven by the formation of the very strong P=O bond