

**B.Sc. Semester-IV
Core Course-IX (CC-IX)
Organic Chemistry-III**



III. Heterocyclic Compounds

**24. Pyridines : Nucleophilic Reactions, Metal-Halogen Exchange,
Direct Metallation and Other Reactions**



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Heterocyclic Compounds

22 Lectures

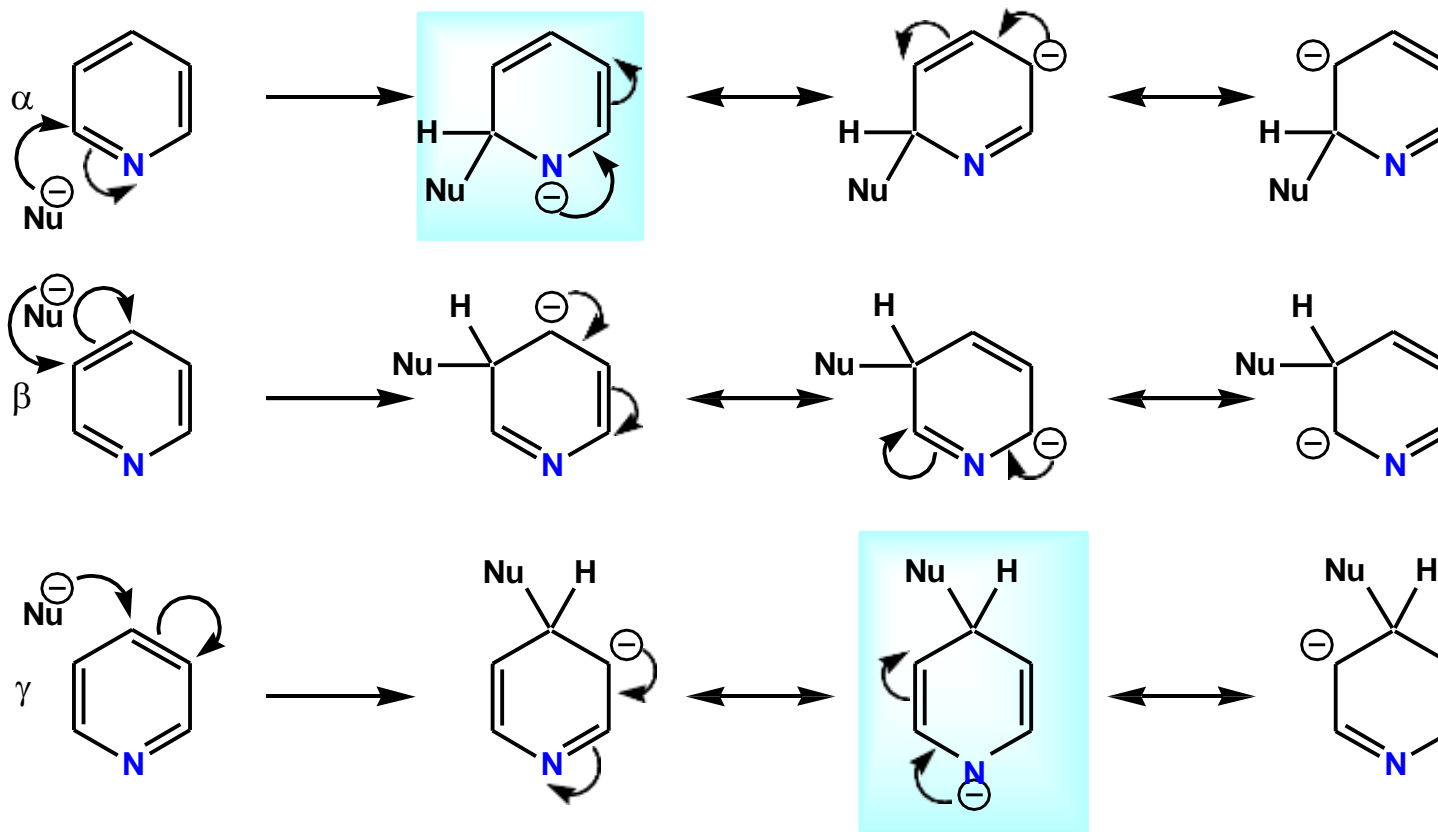
Classification and nomenclature, Structure, aromaticity in 5-numbered and 6-membered rings containing one heteroatom; Synthesis, reactions and mechanism of substitution reactions of: Furan, Pyrrole (Paal-Knorr synthesis, Knorr pyrrole synthesis, Hantzsch synthesis), Thiophene, Pyridine (Hantzsch synthesis), Pyrimidine, Structure elucidation of indole, Fischer indole synthesis and Madelung synthesis), Structure elucidation of quinoline and isoquinoline, Skraup synthesis, Friedlander's synthesis, Knorr quinoline synthesis, Doebner- Miller synthesis, Bischler-Napieralski reaction, Pictet-Spengler reaction, Pomeranz-Fritsch reaction
Derivatives of furan: Furfural and furoic acid.

Coverage:

1. Pyridines : Nucleophilic Reactions, Metal-Halogen Exchange, Direct Metallation and Synthesis of Natural Products
2. Pyridinium Ions : Nucleophilic Reactions
3. Pyridines : Formation, Nucleophilic Reactions

Pyridines – Nucleophilic Reactions

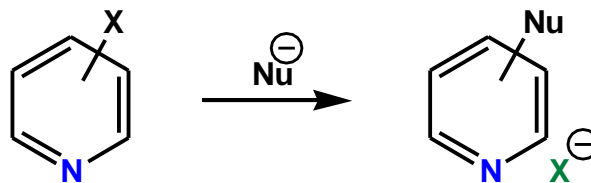
Regiochemical Outcome of Nucleophilic Addition to Pyridines



- 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 be regained by loss of hydride or a leaving group, or by oxidation

Pyridines – Nucleophilic Reactions

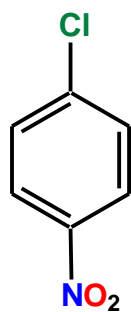
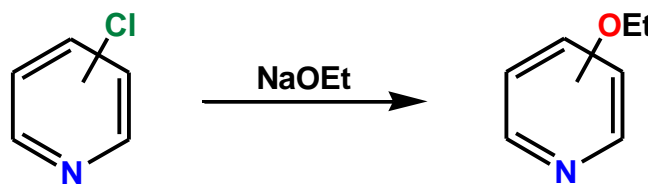
Nucleophilic Substitution



X = Cl, Br, I, (NO₂)

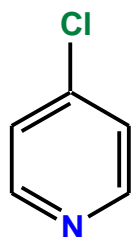
Nu = MeO[⊖], NH₃, PhSH etc.

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

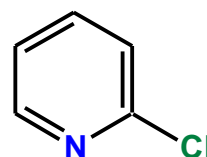


Relative rate

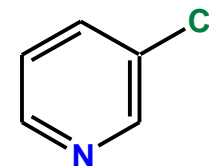
80



40



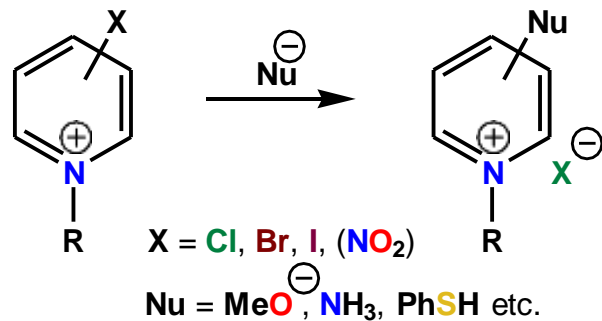
1



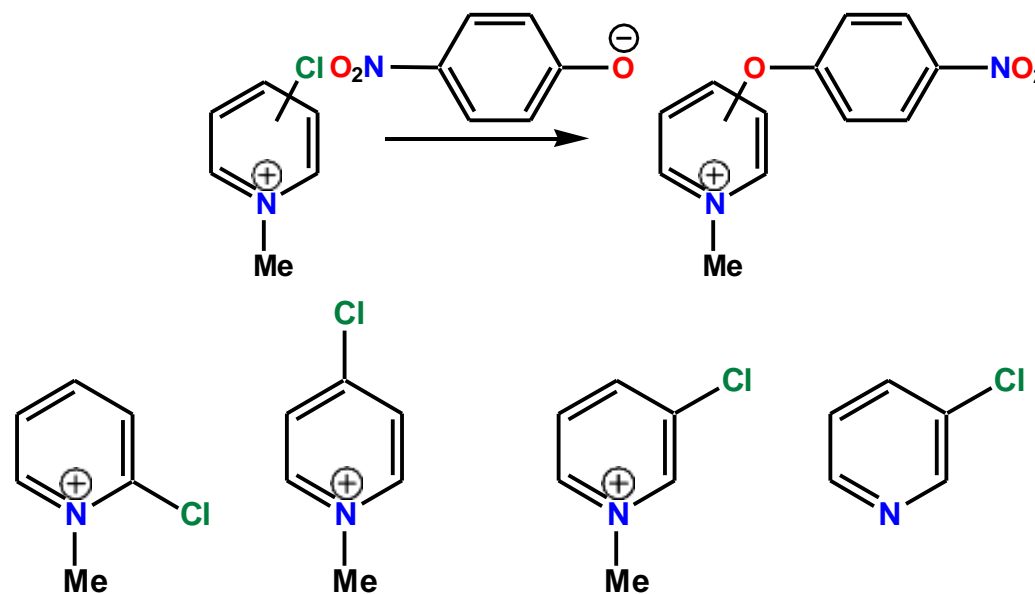
3×10^{-4}

Pyridinium Ions – Nucleophilic Reactions

Nucleophilic Substitution



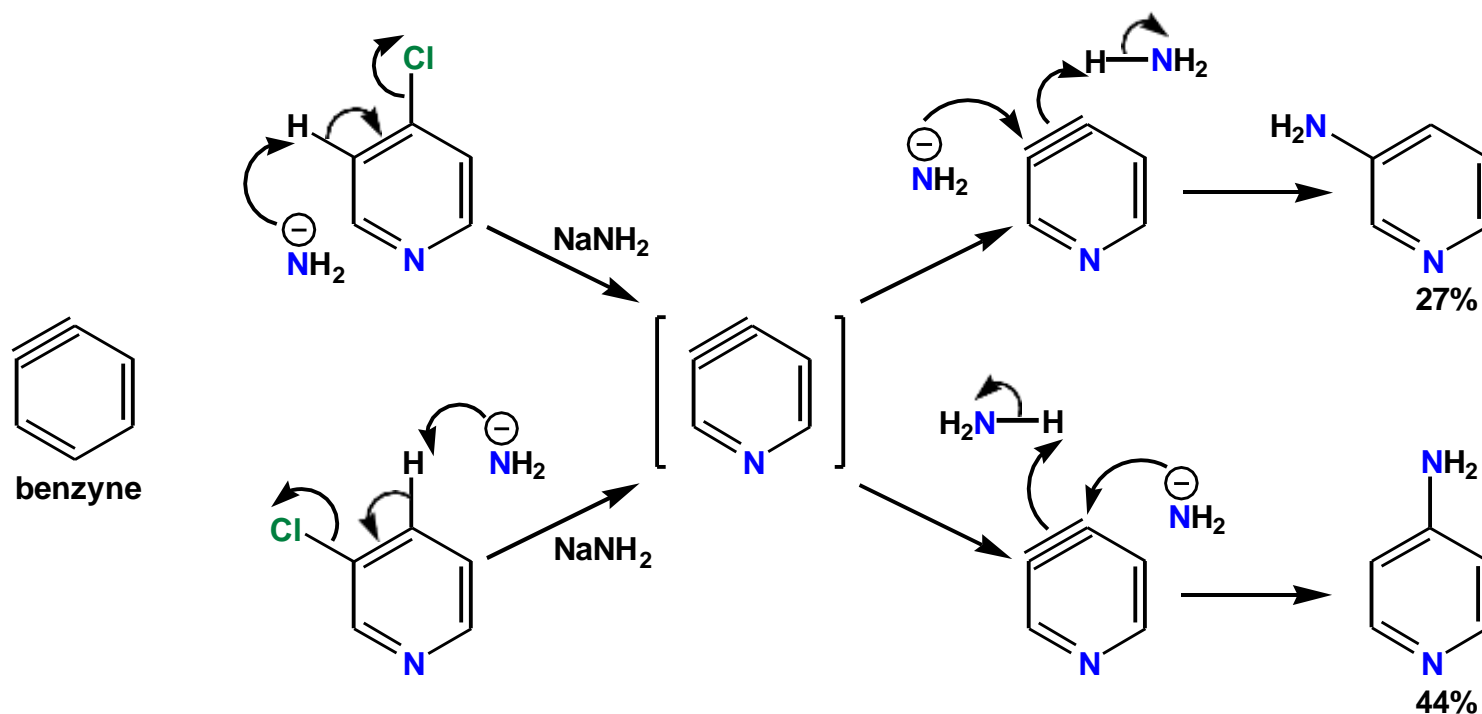
- Conversion of a pyridine into the pyridinium salt greatly accelerates substitution
- Substituent effects remain the same ($\alpha, \gamma \gg \beta$) but now $\alpha > \gamma$



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

Pyridines – Pyridyne Formation

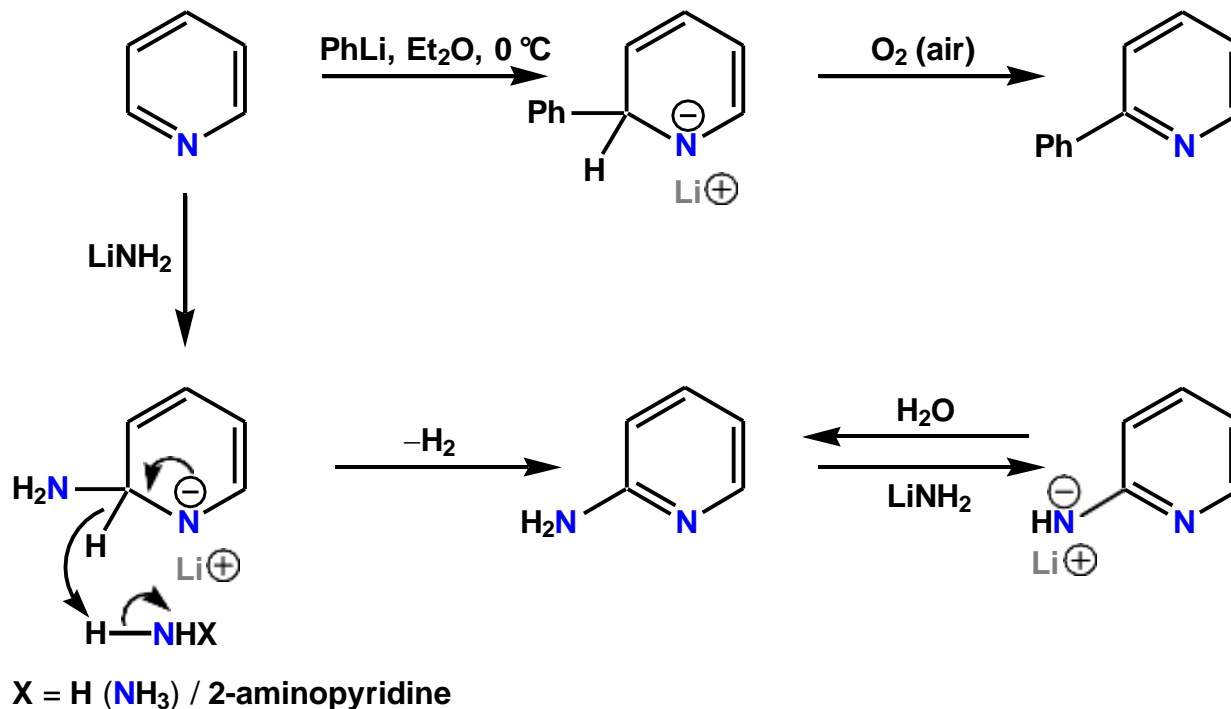
Substitution via an Intermediate Pyridyne



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

Pyridines – Nucleophilic Reactions

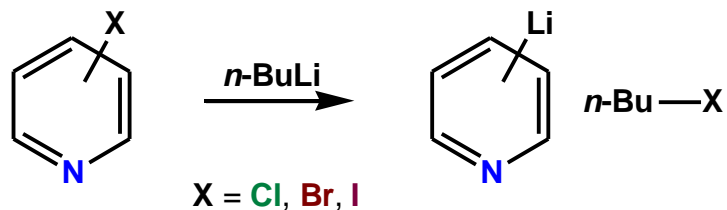
Nucleophilic Attack with Transfer of Hydride



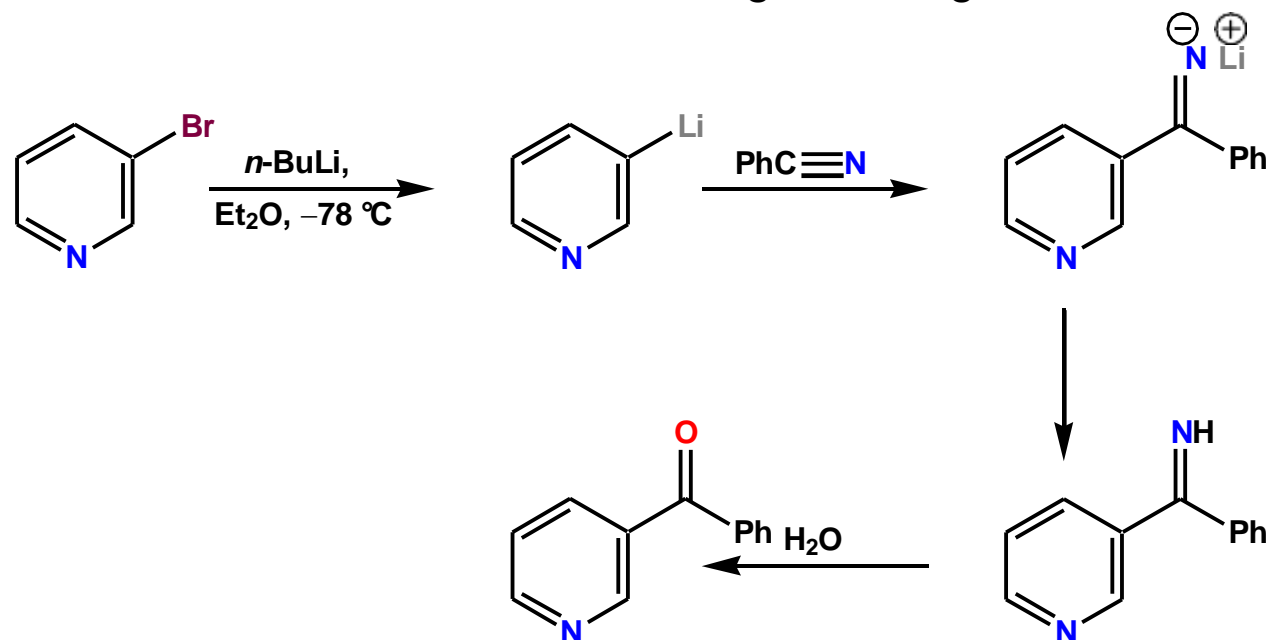
- A hydride acceptor or oxidising agent is required to regenerate aromaticity
- The reaction with LiNH_2 is referred to as the **Chichibabin reaction**

Pyridines – Metal-Halogen Exchange

Direct Exchange of Metal and a Halogen

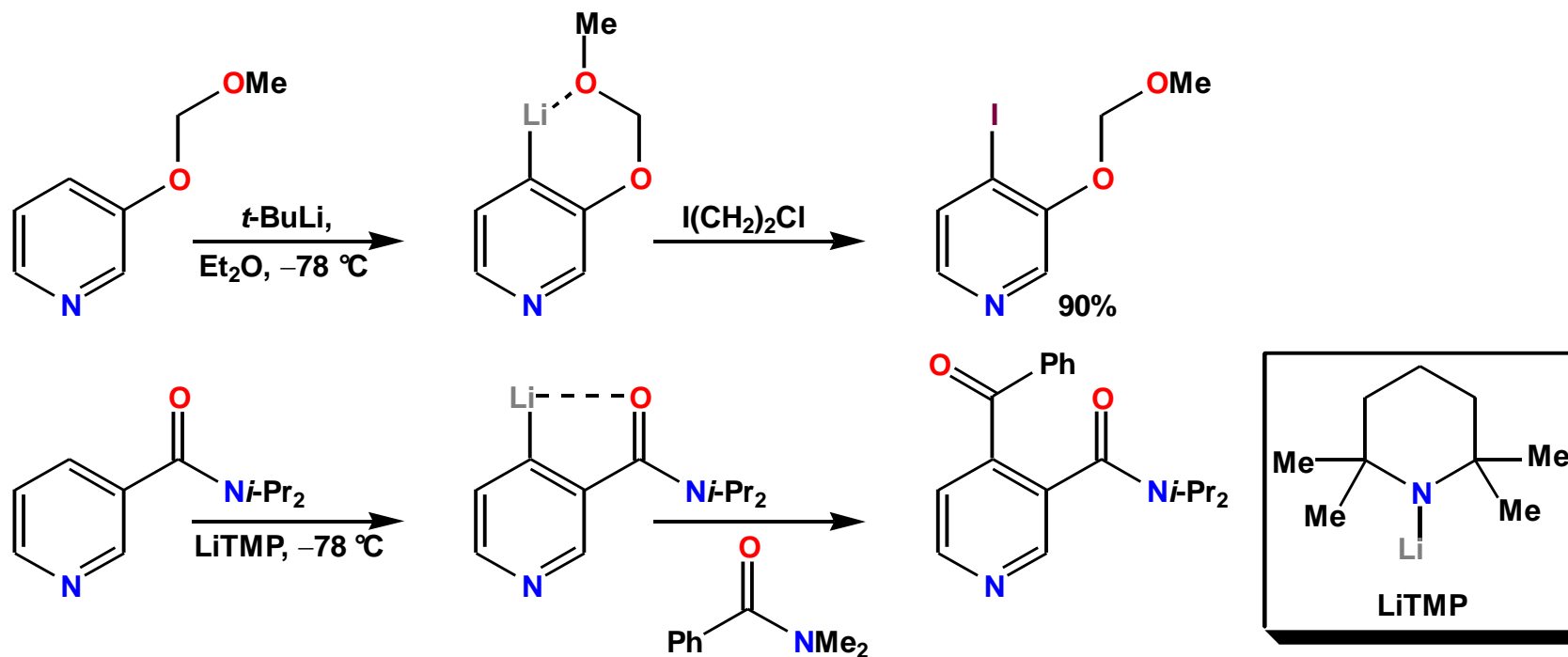


- Halogenated pyridines do not tend to undergo nucleophilic displacement with alkyl lithium or alkyl magnesium reagents
- Metallated pyridines behave like conventional Grignard reagents



Pyridines – Directed Metallation

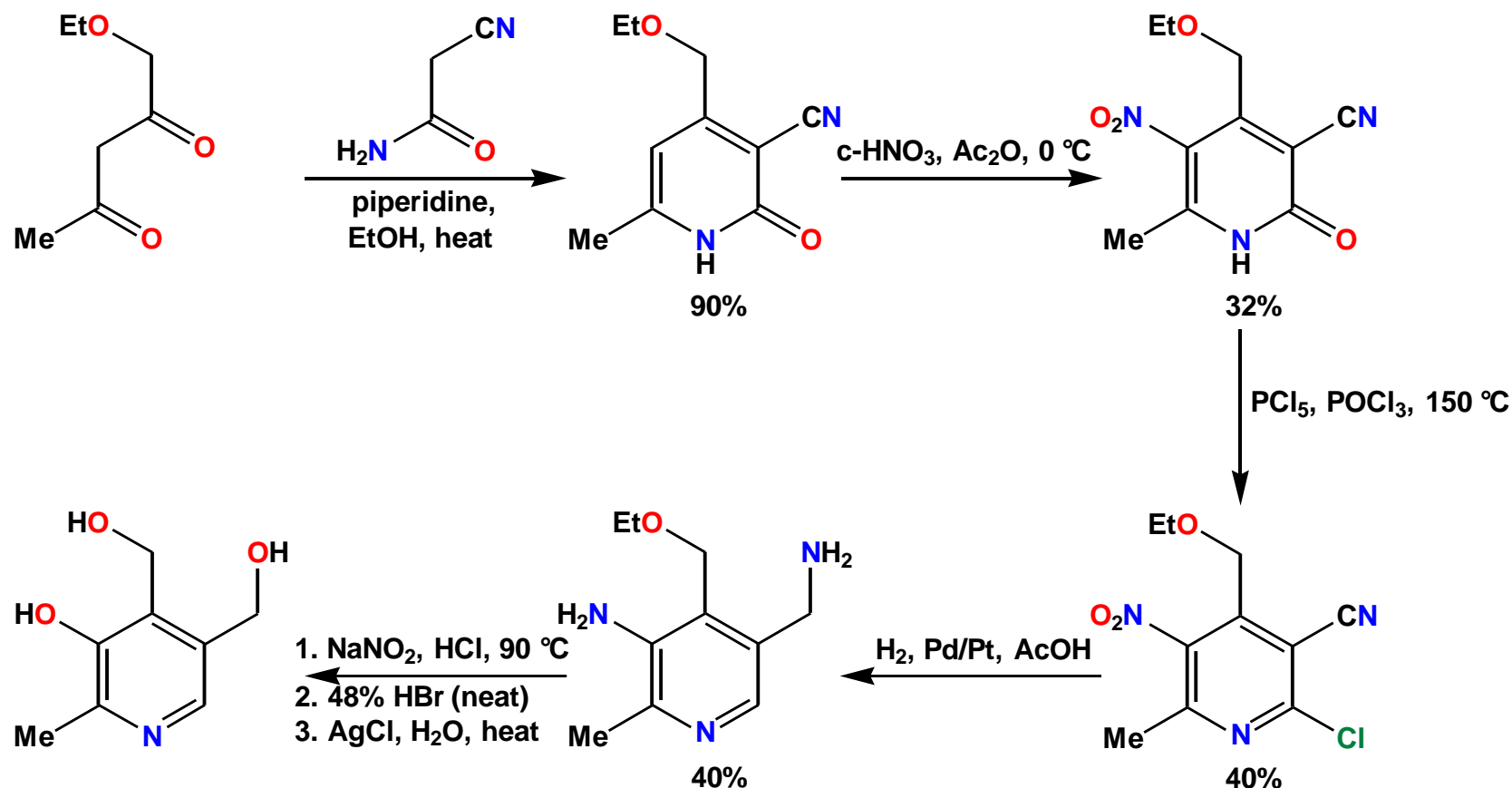
Use of Directing Groups



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

Pyridines – Synthesis of a Natural Products

Synthesis of Pyridoxine (Vitamin B₆) Using the Guareschi Synthesis



- The final sequence of steps involves formation of a *bis*-diazonium salt from a diamine
- Pyridoxine performs a key role as the coenzyme in transaminases

THANK YOU