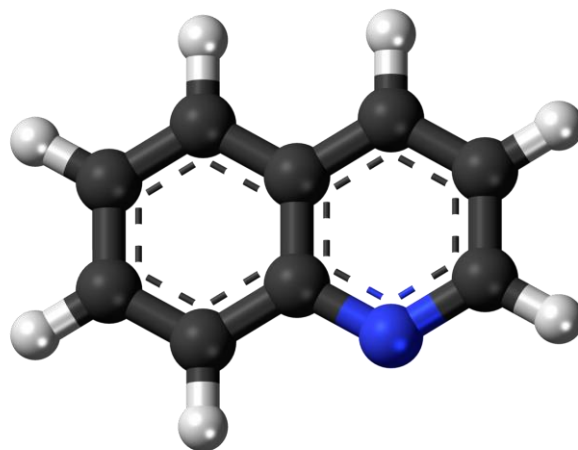


Reaction of Pyridine Part 1



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Recommended Textbook:

Heterocyclic Chemistry, 5th Edition, J. A. Joule, K. Mills, **2010**, Wiley

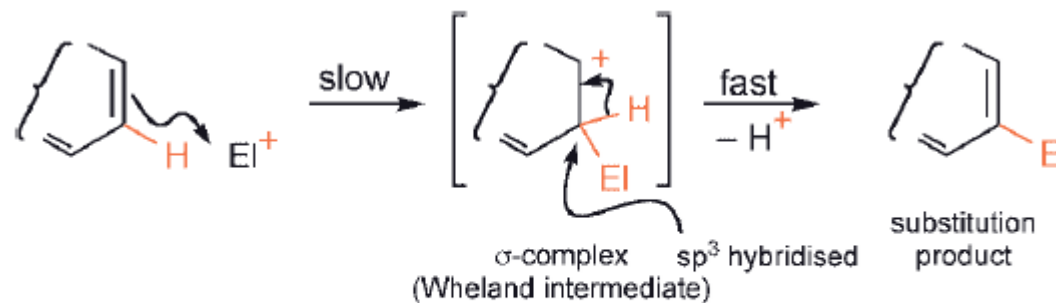
Reactions of Pyridine – Reaction with Electrophiles

1)

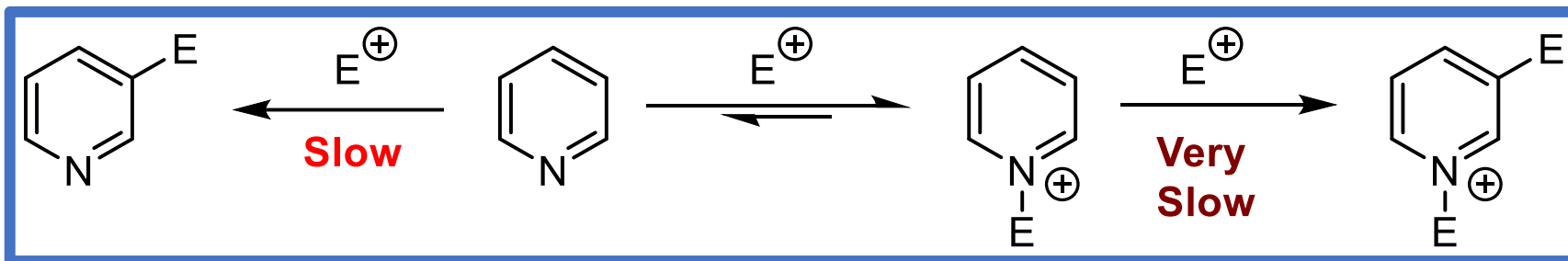


Pyridines react with electrophiles by donation of the nitrogen lone pair

2)



Aromatic electrophilic substitution *via* an addition/elimination sequence

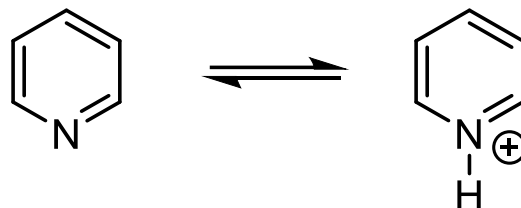


Electrophilic substitution of pyridines occurs much **less readily** than for the correspondingly substituted benzene

Reactions of Pyridine – Addition to Nitrogen

1.1) Protonation

- Pyridines ($pK_{aH} = 5.2$) form crystalline, hygroscopic, salts with most protic acids
- It is a much weaker base than saturated aliphatic amines ($pK_{aH} = 9$ to 11)



1.2) Halogenation

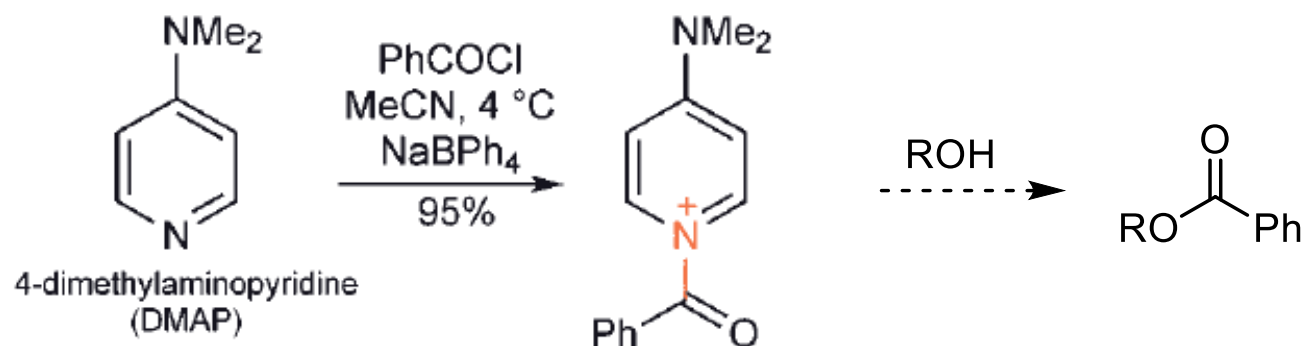
- Pyridines react easily with halogens to give crystalline compounds, largely undissociated



Reactions of Pyridine – Addition to Nitrogen

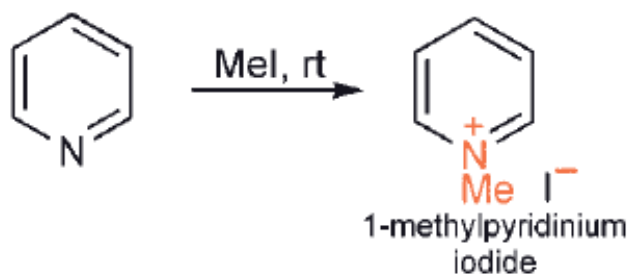
1.3) Acylation

Acid halides react rapidly with pyridines generating 1-acyl-pyridinium salts in solution, and in suitable cases some of these can even be isolated as crystalline, non-hygroscopic solids



They are commonly used for the **preparation of esters from alcohols, and of amides from amines**

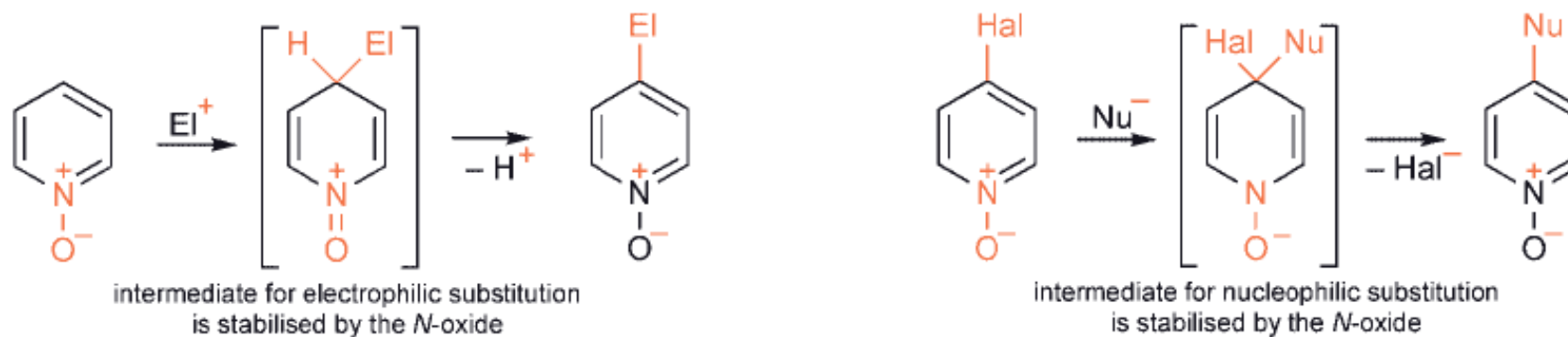
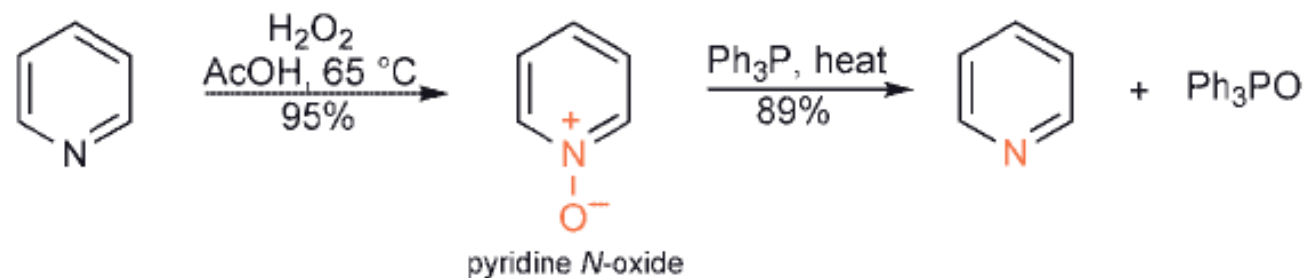
1.4) Alkylation



Reactions of Pyridine – Addition to Nitrogen

1.5) Oxidation

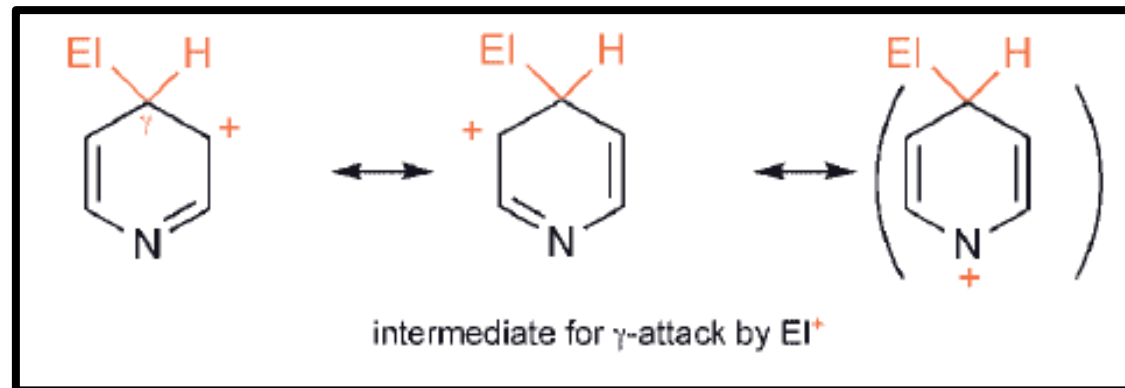
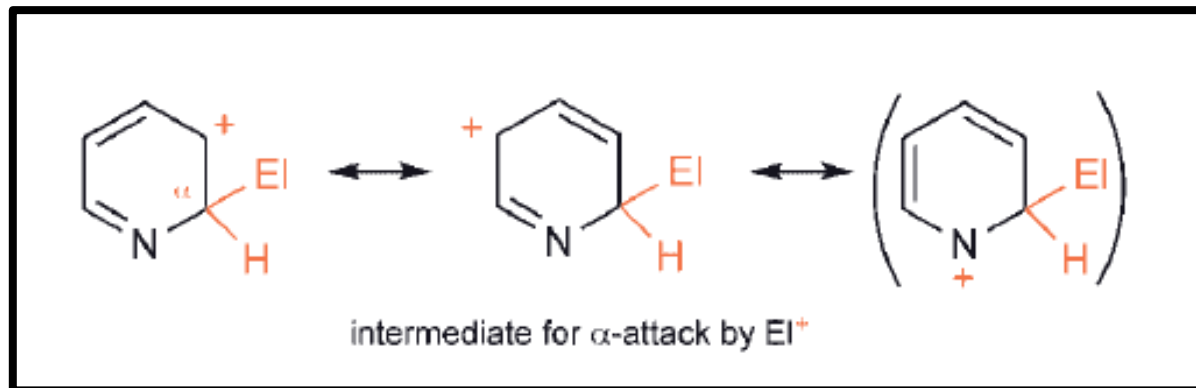
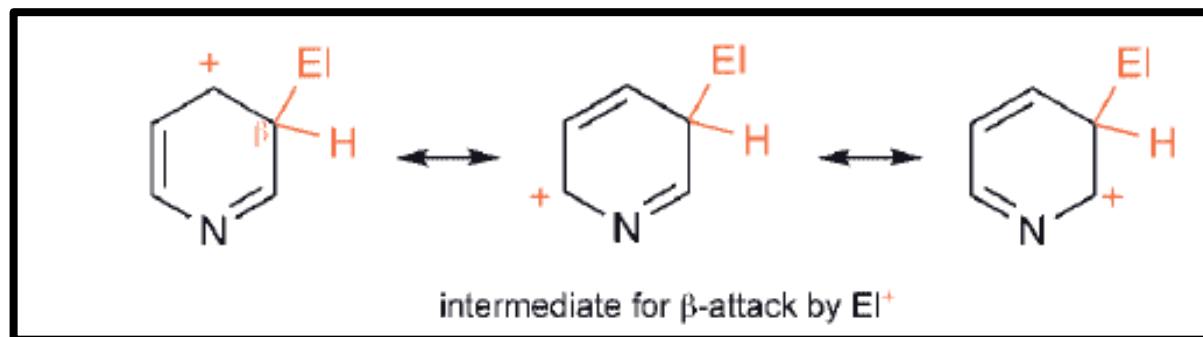
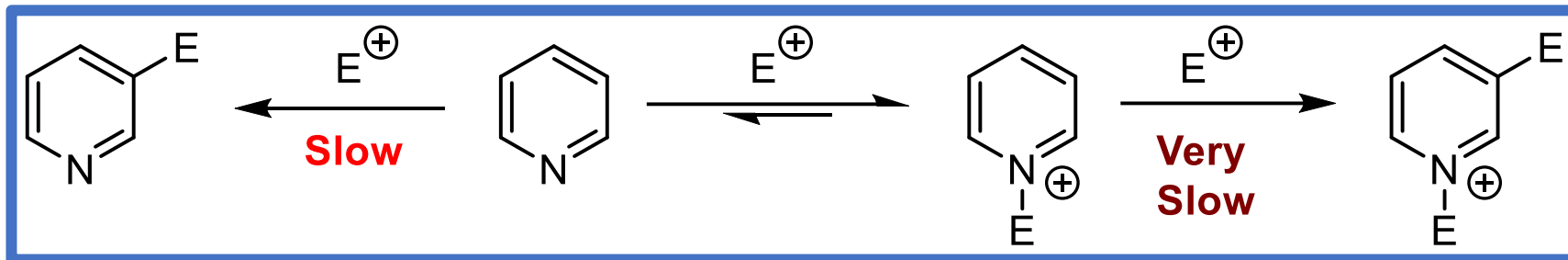
- Pyridines react smoothly with **peroxides** or **percarboxylic acids** to give *N*-oxides, which have their own rich chemistry
- It is converted back to pyridine by oxygen transfer to **trivalent phosphorus**



The *N*-oxide group facilitates both electrophilic *and* nucleophilic substitutions

Reactions of Pyridine – Substitution at Carbon

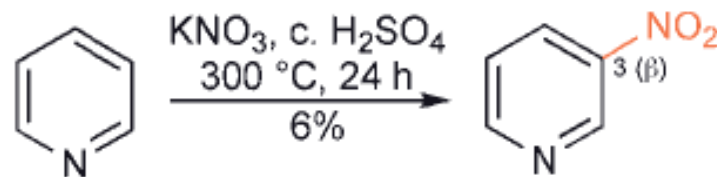
Selectivity at β -position



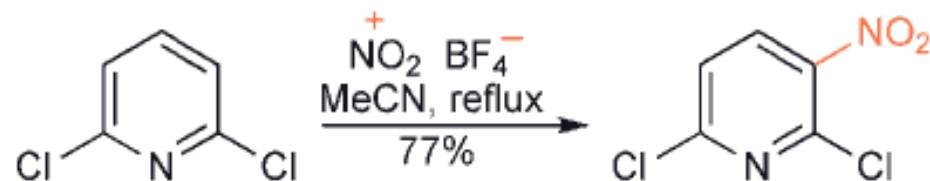
Reactions of Pyridine – Substitution at Carbon

2.1) Nitration

- Pyridine itself can undergo nitration only **inefficiently** by direct nitration, even with extremely vigorous conditions



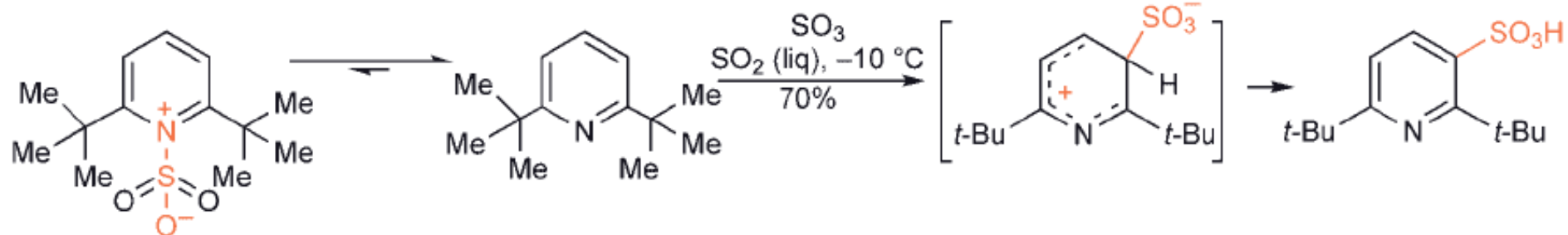
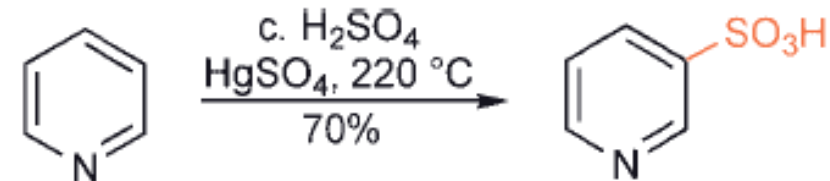
- Steric or/and inductive inhibition of *N*-nitration allows C-3-substitution using nitronium tetrafluoroborate



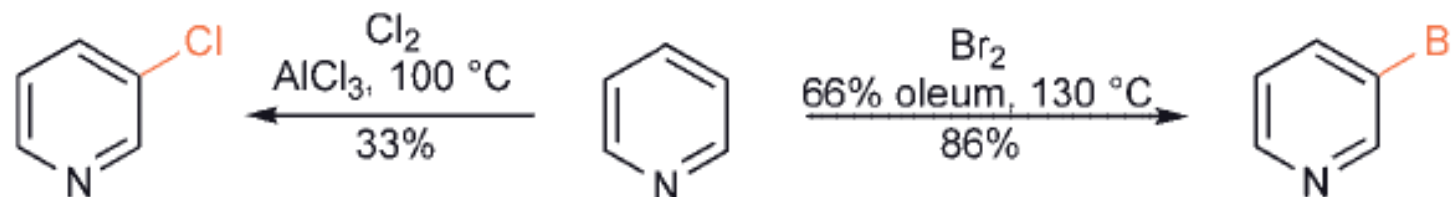
Reactions of Pyridine – Substitution at Carbon

2.2) Sulfonation

- Pyridine is very resistant to sulfonation; however, addition of cat. mercuric sulfate allows smooth sulfonation



2.3) Halogenation

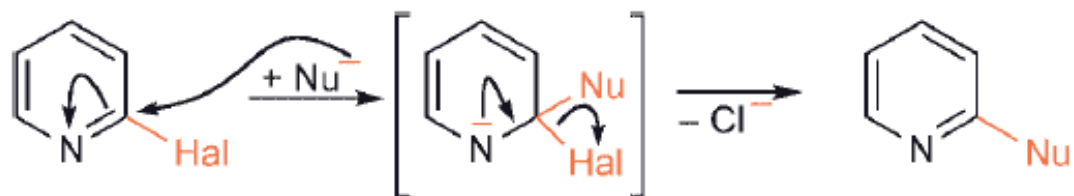


Reactions of Pyridine – Reactions with Nucleophiles

Substitution reactions with nucleophiles is characteristic to pyridines

3.1) Nucleophilic Substitution with Displacement of Halides

Aromatic nucleophilic substitution *via* an addition/elimination sequence

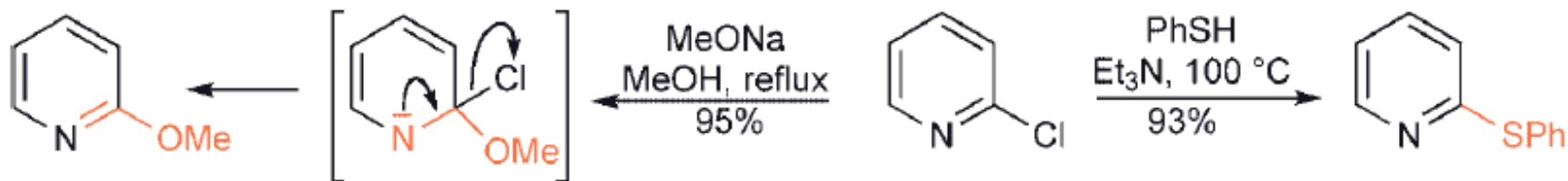


compare



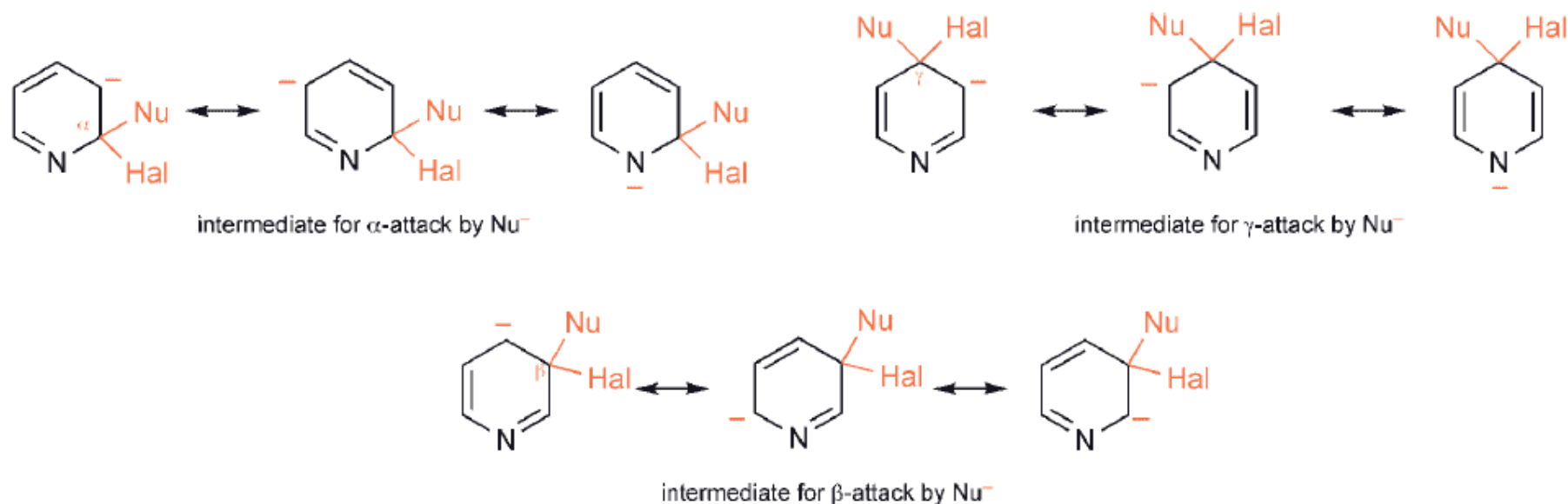
Comparison of the reactivity of an α -halopyridine with an acid chloride

Examples



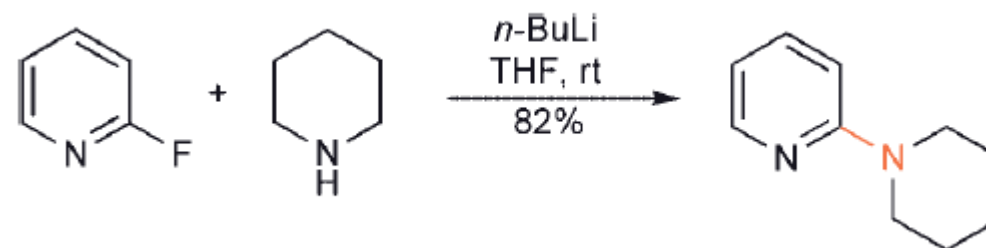
Reactions of Pyridine – Reactions with Nucleophiles

Selectivity at α - and γ -positions



Intermediates explain selectivity of nucleophilic attack on halopyridines

- Fluorides are more reactive than the other halides

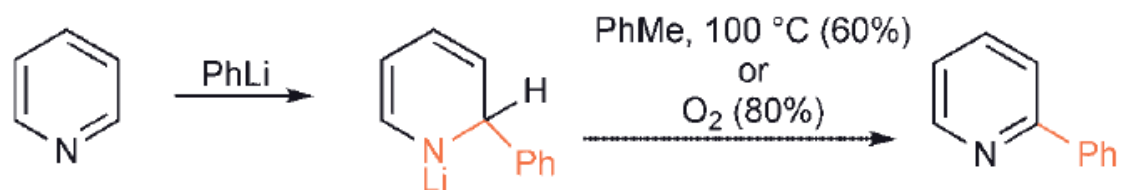


Reactions of Pyridine – Reactions with Nucleophiles

3.2) Nucleophilic Substitution with 'Hydride' Transfer

- In the **absence of an α - or γ -halogen**, pyridines are **less reactive** and do not have a substituent suitable for leaving to complete a nucleophilic substitution
- Nucleophilic additions do however take place, but the resultant dihydropyridine adduct requires **removal of 'hydride'**, to complete an overall substitution

- Alkylation and Arylation*



- Ammination*

