

# Heterocyclic Chemistry

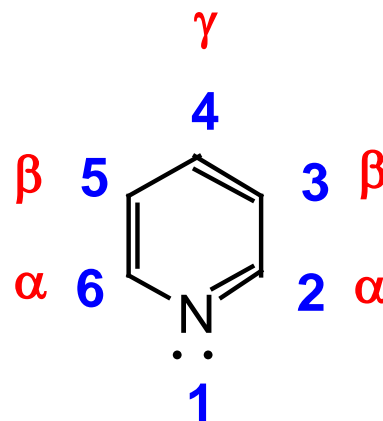
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*Department of Chemistry*

*Iran University of Science & Technology*

# فصل ششم:

## Pyridines



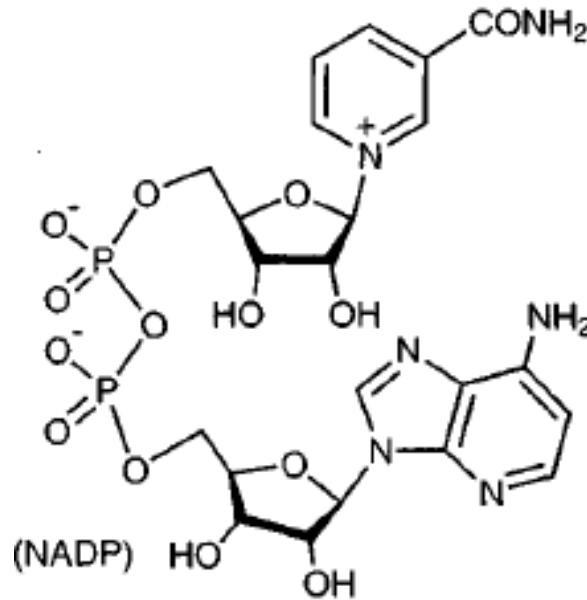
Based on:

J. A. Joule & K. Mills's Heterocyclic Chemistry, Ch. 8

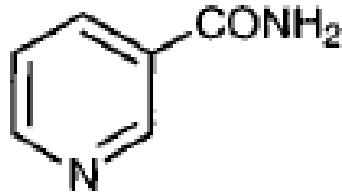
With special thanks to Dr. M. G. Dekamin

The pyridine ring **plays a key role in several biological processes**, most notably in

- 1) the oxidation/reduction coenzyme nicotina adenine dinucleotide phosphate (NADP);

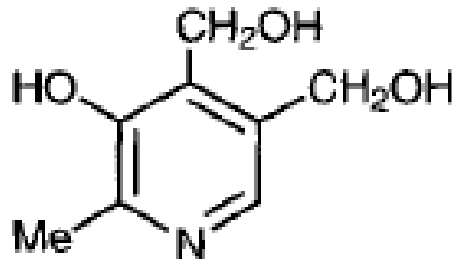


2) The **vitamin niacin** (or the corresponding acid) is required for its biosynthesis.



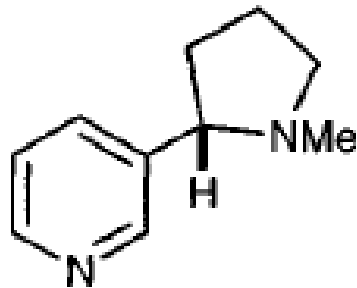
niacin  
(nicotinamide)

3) **Pyridoxine (vitamin B6)** plays a key role as the coenzyme in transaminases.



pyridoxine

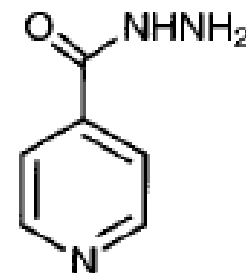
- 4) Nicotine, a highly toxic alkaloid, is the major active component in tobacco, and the most addictive drug known.



nicotine

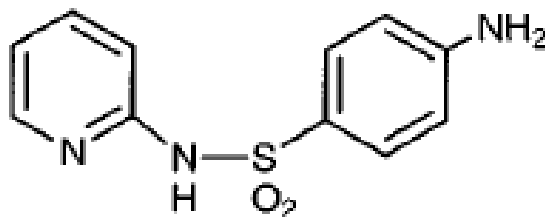
Many synthetic pyridine derivatives are important as therapeutic agents, for example :

1) Isoniazide is a major antituberculosis agent,



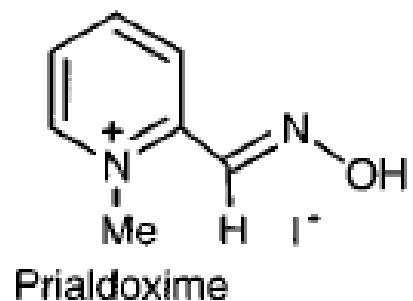
Isoniazide

2) Sulphapyridine is one of the sulfonamide antibacterials,

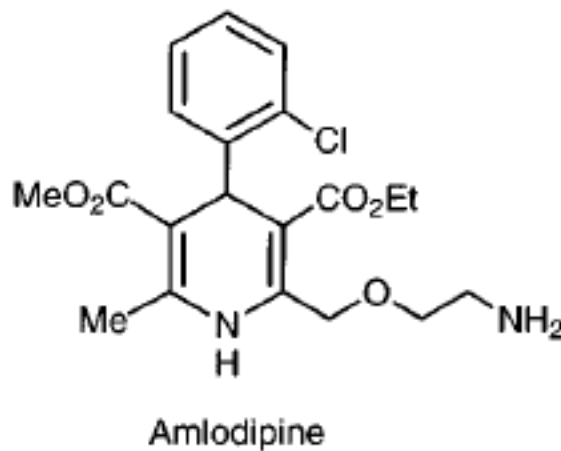


Sulphapyridine

3) Pralidoxime is an antidote for poisoning by organophosphates,



4) Amlodipine is one of several antihypertensive 1,4-dihydropyridines.



# Chapter 6: Pyridines: Reactions & Synthesis

Pyridine and its simple derivatives are stable and relatively unreactive liquids, with strong penetrating odors that are unpleasant to some people.

- 1) Pyridine was first isolated, like pyrrole, from bone pyrolysates: the name is constructed from the Greek for fire, *'pyr\* and the suffix *'idine\* which was at the time being used for all aromatic bases - phenetidine, toluidine, etc.
- 2) They are much used as solvents and bases, especially pyridine itself, in reactions such as N- and O-tosylation and -acylation.
- 3) Pyridine and the monomethylpyridines (picolines) are completely miscible with water.



## Pyridine and its simple alkyl derivatives

- 1) were for a long time produced by isolation from coal tar, in which they occur in quantity.
- 2) In recent years this source has been displaced by synthetic processes:

A) pyridine itself, for example, can be produced on a commercial scale in 60-70% yields by the gas-phase high-temperature interaction of crotonaldehyde, formaldehyde, steam, air and ammonia over a silica-alumina catalyst.

B) Processes for the manufacture of alkylpyridines involve reaction of acetylenes and nitriles over a cobalt catalyst.

# 6 Pyridines: Reactions

## 6.1 Reactions with electrophilic reagents

### 6.1.1 Addition to nitrogen

In reactions which involve bond formation using the lone pair of electrons on the ring nitrogen, such as protonation and quaternisation, pyridines behave just like tertiary aliphatic or aromatic amines.

When a pyridine reacts as a base or a nucleophile it forms a pyridinium cation in which the aromatic sextet is retained and the nitrogen acquires a formal positive charge.

# 6 Pyridines: Reactions

## 6.1 Reactions with electrophilic reagents

### 6.1.1 Addition to nitrogen

#### 6.1.1.1 Protonation of nitrogen

Pyridines form crystalline, frequently hygroscopic salts with most protic acids.

- a) Pyridine itself, with  $pK_a$  5.2 in water, is a much weaker base than saturated aliphatic amines which have  $pK_a$  values mostly between 9 and 11.
- b) Since the gas-phase proton affinity of pyridine is actually very similar to those of aliphatic amines, this difference may in turn be related to the mesomerically delocalised charge in pyridinium ions and the consequent reduced requirement for external stabilisation *via* solvation. In other words, the observed solution values reflect relatively strong solvation of aliphatic ammonium cations.

# 6 Pyridines: Reactions

## 6.1 Reactions with electrophilic reagents

### 6.1.1 Addition to nitrogen

#### 6.1.1.1 Protonation of nitrogen

- c) Electron-releasing substituents generally increase the basic strength; 2-methyl ( $\text{pK}_a$  5.97), 3-methyl (5.68) and 4-methylpyridine (6.02) illustrate this.
- d) The basicities of pyridines carrying groups which can interact mesomerically as well as inductively vary in more complex ways, for example:
  - 1) 2-methoxypyridine (3.3) is a weaker, but 4-methoxypyridine (6.6) a stronger base than pyridine; the effect of inductive withdrawal of electrons by the electronegative oxygen is felt more strongly when it is closer to the nitrogen, i.e. at C-2.

# 6 Pyridines: Reactions

## 6.1 Reactions with electrophilic reagents

### 6.1.1 Addition to nitrogen

#### 6.1.1.1 Protonation of nitrogen

2) Large 2- and 6-substituents impede solvation of the protonated form:

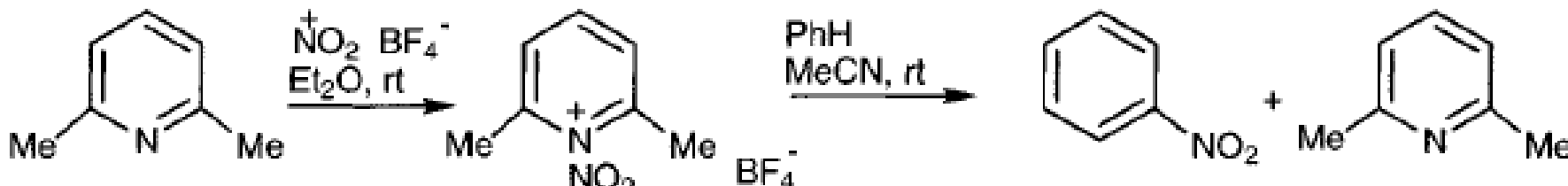
2,6-di-*t*-butylpyridine is less basic than pyridine by one pK<sub>a</sub> unit and

2,6-di(tri-*i*-propylsilyl)pyridine will not dissolve even in 6N hydrochloric acid.

### 6.1.1 Addition to nitrogen

### 6.1.1.2 Nitration at nitrogen

1-Nitro-2,6-dimethylpyridinium tetrafluoroborate is one of several *N*-nitropyridinium salts which can be used as **non-acidic nitrating agents** with good substrate and positional selectivity.

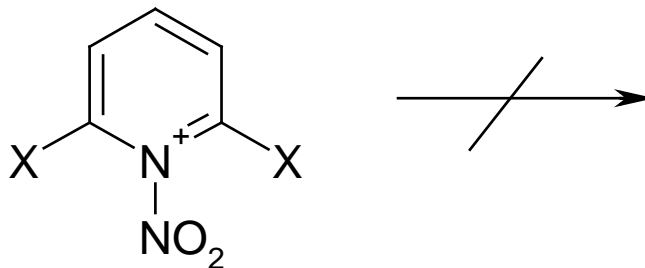


# 6 Pyridines: Reactions

## 6.1.1 Addition to nitrogen

### 6.1.1.2 Nitration at nitrogen

The 2,6-disubstitution serves to **sterically inhibit resonance overlap between nitro group and ring** and consequently increase reactivity as a nitronium ion donor, however the balance between this advantageous effect and hindering approach of the aromatic substrate is illustrated by **the lack of transfer nitration reactivity in 2,6-dihalo-analogues**.

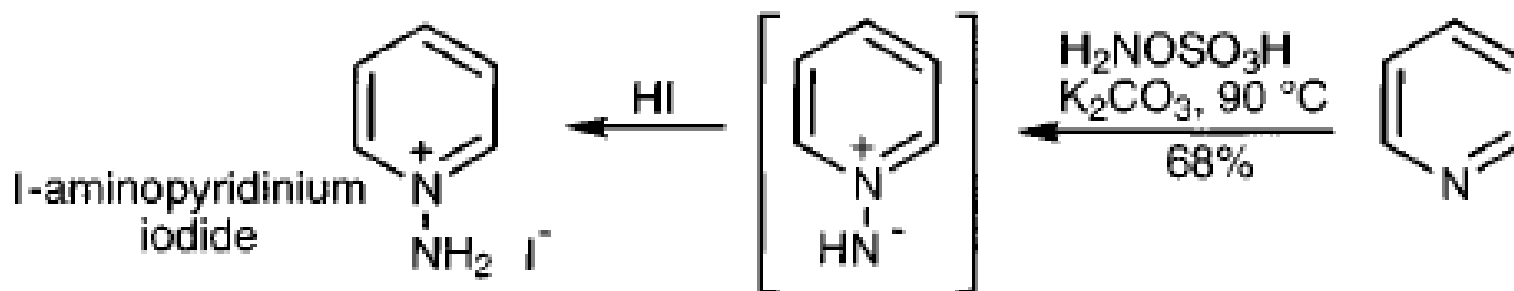


# 6 Pyridines: Reactions

## 6.1.1 Addition to nitrogen

### 6.1.1.3 Amination of nitrogen

The introduction of nitrogen at a different oxidation level can be achieved with hydroxylamine *O*-sulfate.



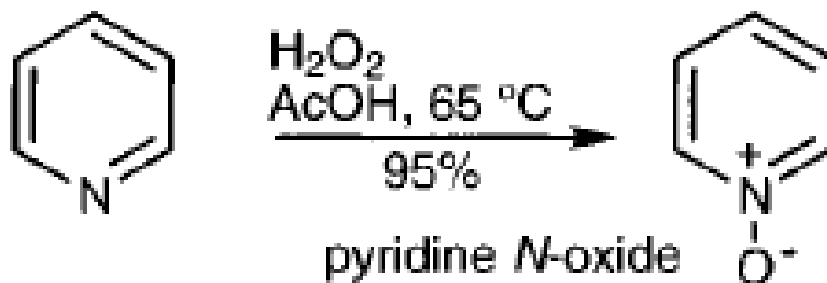


# 6 Pyridines: Reactions

## 6.1.1 Addition to nitrogen

### 6.1.1.4 Oxidation of nitrogen

In common with other tertiary amines, pyridines react smoothly with **percarboxylic acids** to give *N*-oxides, which have their own rich chemistry.

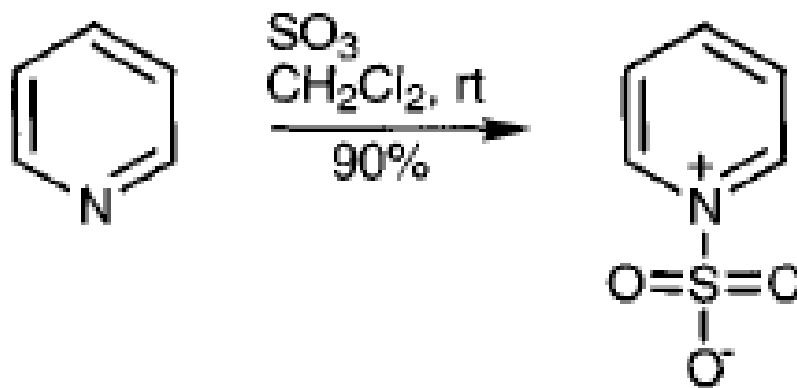


# 6 Pyridines: Reactions

## 6.1.1 Addition to nitrogen

### 6.1.1.5 Sulfonation at nitrogen

Pyridine reacts with sulfur trioxide to give the commercially available, crystalline, zwitterionic pyridinium-1-sulfonate, usually known as the pyridine sulfur trioxide complex.

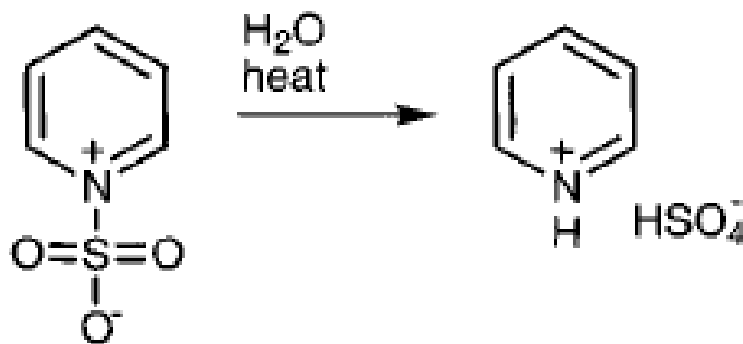


# 6 Pyridines: Reactions

## 6.1.1 Addition to nitrogen

### 6.1.1.5 Sulfonation at nitrogen

This compound is hydrolysed in **hot water** to **sulfuric acid** and **pyridine**,

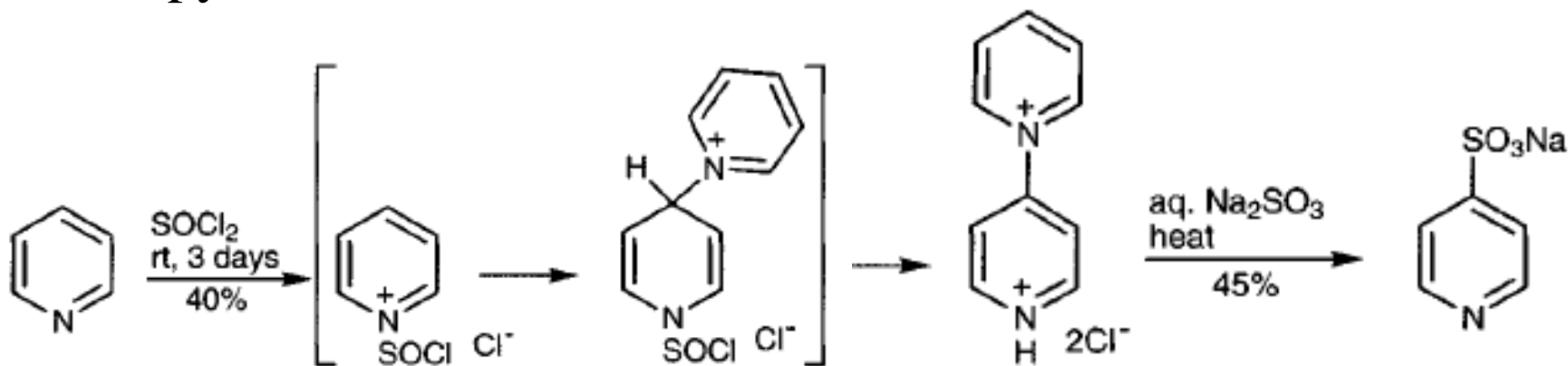


but more usefully it can serve as **a mild sulfonating agent**.

# 6 Pyridines: Reactions

## 6.1.1.5 Sulfonation at nitrogen

When pyridine is treated with **thionyl chloride** a **synthetically useful dichloride salt** is formed, which can, for example, be transformed into pyridine-4-sulfonic acid. The reaction is believed to involve initial attack by sulfur at nitrogen, followed by nucleophilic addition of a second pyridine at C-4.

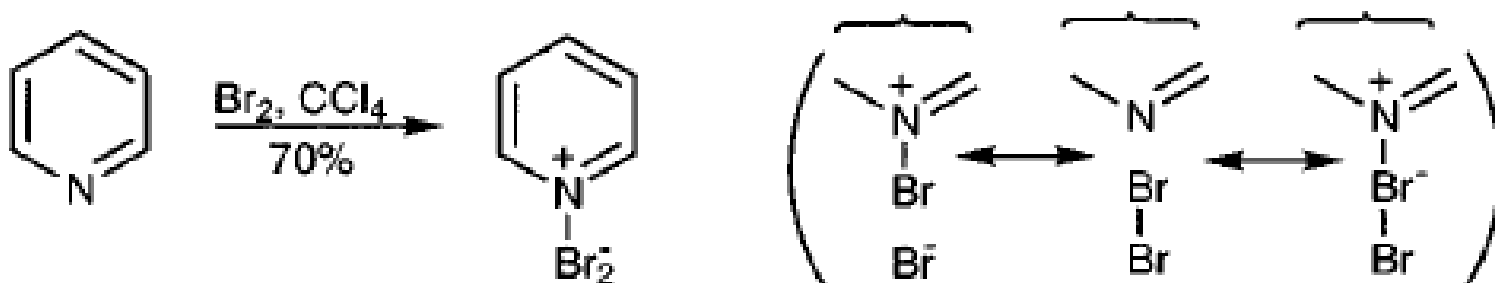


dichloride salt

# 6 Pyridines: Reactions

## 6.1.1.6 Halogenation at nitrogen

a) Pyridines react easily with halogens and interhalogens to give crystalline compounds, largely undissociated when dissolved in solvents such as carbon tetrachloride.

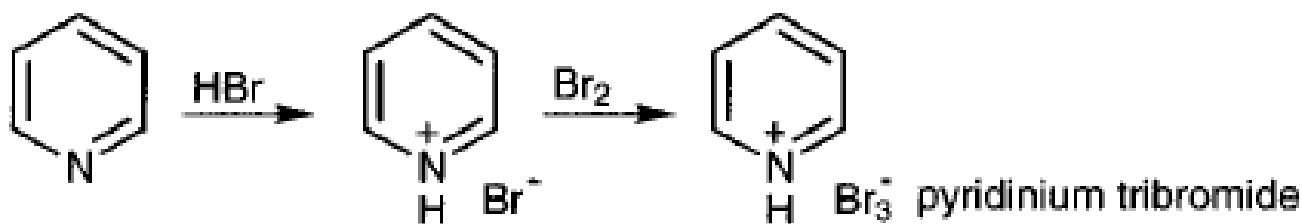


b) Structurally they are best formulated as resonance hybrids related to trihalide anions.

# 6 Pyridines: Reactions

## 6.1.1.6 Halogenation at nitrogen

c) These salts must be distinguished from **pyridinium tribromide**, obtained by treating pyridine hydrobromide with bromine, which does not contain an *N*-halogen bond, but does include a **trihalide anion**. The stable, crystalline, commercially available salt can be used as a source of molecular bromine especially where small accurately known quantities are required.

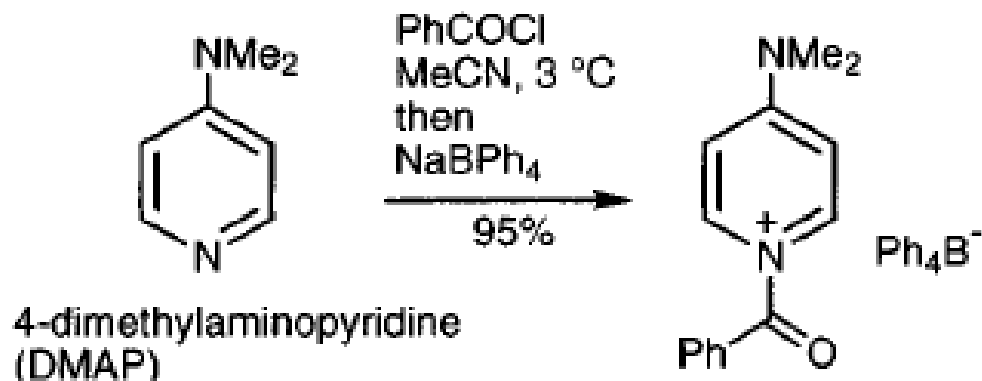


1-Fluoropyridinium triflate is also crystalline and serves as an electrophilic fluorinating agent.

# 6 Pyridines: Reactions

## 6.1.1.7 Acylation at nitrogen

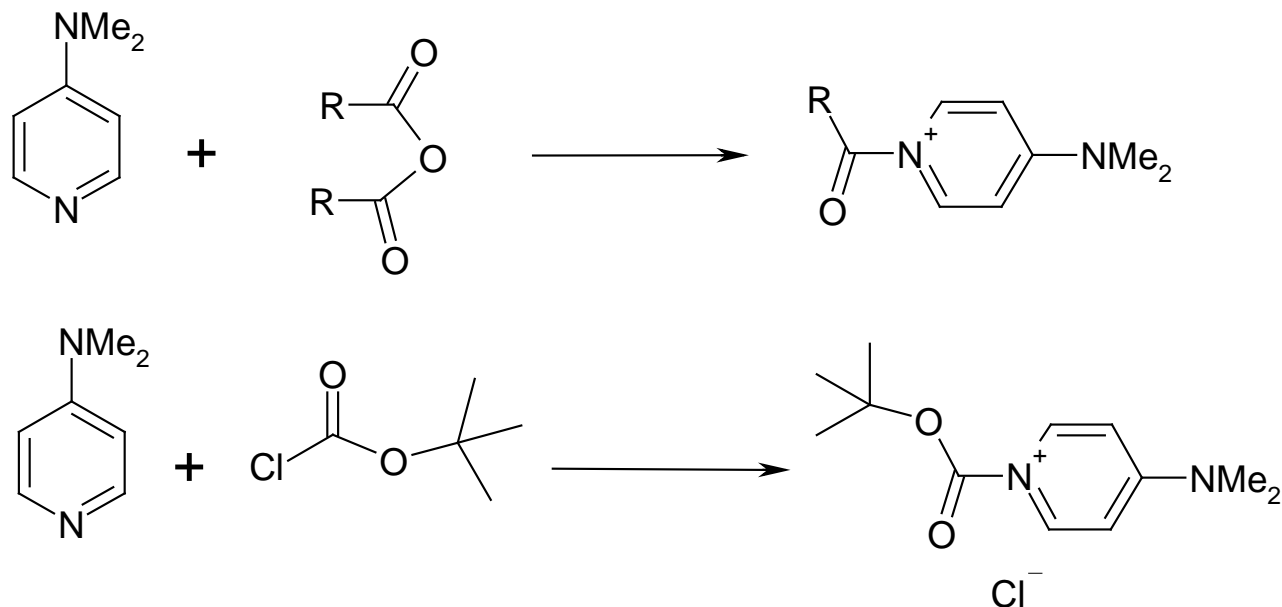
Carboxylic, and arylsulfonic acid halides react rapidly with pyridines generating 1-acyl- and 1-arylsulfonylpyridinium salts in solution, and in suitable cases some of these can even be isolated as crystalline solids. The solutions, generally in excess pyridine, are commonly used for the preparation of esters and sulfonates from alcohols and of amides and sulfonamides from amines.



# 6 Pyridines: Reactions

## 6.1.1.7 Acylation at nitrogen

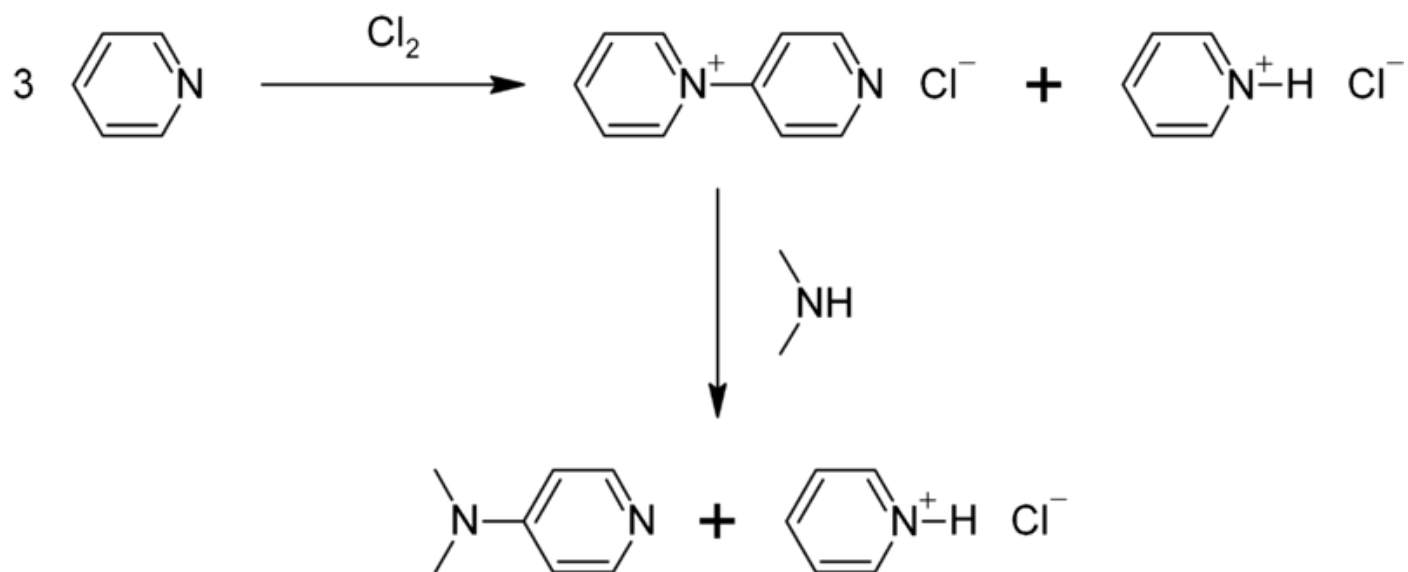
4-Dimethylaminopyridine (DMAP) is widely used (in catalytic quantities) to activate anhydrides in a similar manner.



The salt derived from **DMAP** and ***t*-butyl chloroformate** is stable even in aqueous solution at room temperature.



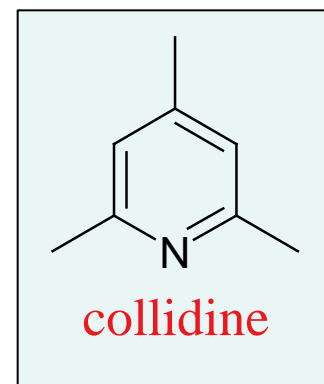
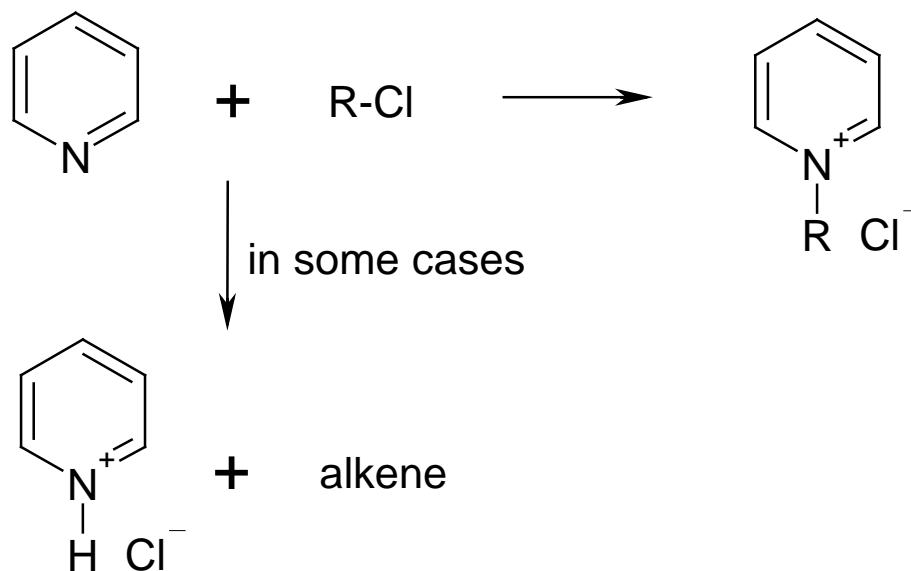
DMAP can be prepared in a two-step procedure from pyridine, which is first oxidized to 4-pyridylpyridinium cation. This cation then reacts with dimethylamine:



# 6 Pyridines: Reactions

## 6.1.1.8 Alkylation at nitrogen

Alkyl halides and sulfates react readily with pyridines giving quaternary pyridinium salts.

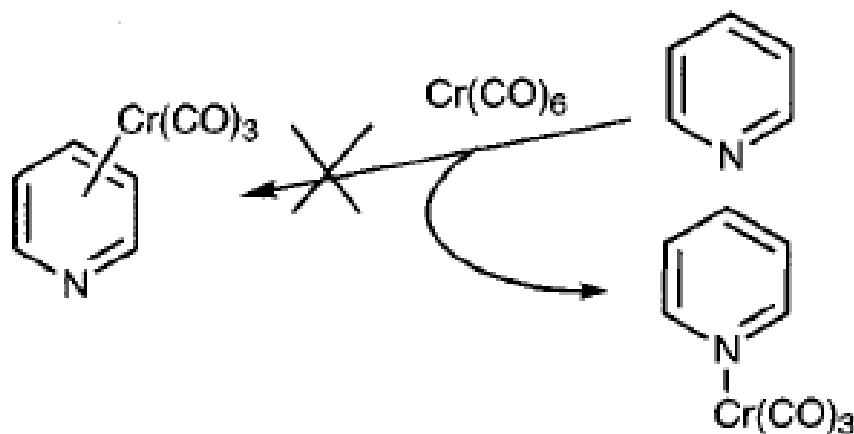


As with aliphatic tertiary amines, increasing substitution around the nitrogen, or around the halogen-bearing carbon, causes an increase in the alternative, competing, elimination process which gives alkene and *N*-proto-pyridinium salt, thus 2,4,6-trimethylpyridine (collidine) is useful as a base in dehydrohalogenation reactions.

# 6 Pyridines: Reactions

## 6.1.1.9 Reaction with metal centres

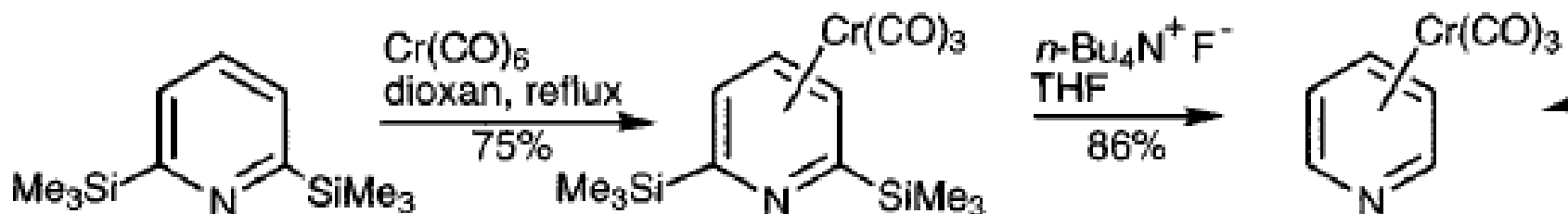
The normal behaviour of pyridines in the presence of **metal cations** is complexation involving donation of the nitrogen lone pair to the metal centre. This means that for **simple pyridines**, formation of  $\pi$ -complexes like benzene-chromium carbonyl complexes, **does not take place**.



# 6 Pyridines: Reactions

## 6.1.1.9 Reaction with metal centres

However, if the nitrogen lone pair is hindered, then  $\eta^6$ -complexes can be formed.



# 6 Pyridines: Reactions

## 6.1.2 Substitution at carbon

In most cases, electrophilic substitution of pyridines occurs **very much less readily than for the correspondingly substituted benzene**. The main reason is that the **electrophilic reagent, or a proton** in the reaction medium, adds preferentially to the pyridine nitrogen, **generating a pyridinium cation**.

# 6 Pyridines: Reactions

## 6.1.2 Substitution at carbon

- a) Some of the typical electrophilic substitution reactions **do not occur at all**. Friedel-Crafts alkylation and acylation are examples - but it is worth recalling that these **also fail with nitrobenzene**.
- b) Milder reagents, such as **Mannich reactants, diazonium ions and nitrous acid**, which in any case require activated benzenes for success, naturally fail with pyridines.

# 6 Pyridines: Reactions

## 6.1.2.1 Proton exchange

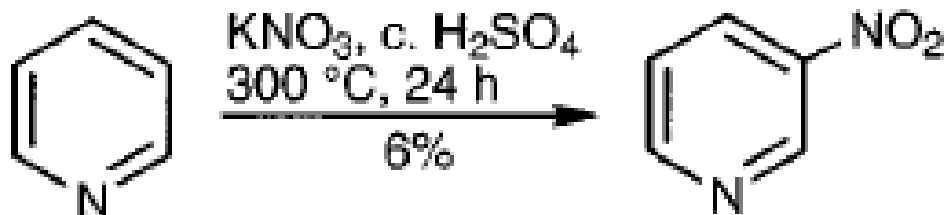
H-D exchange *via* an electrophilic addition process, such as operates for benzene, **does not take place with pyridine**. A special mechanism allows **selective exchange at the two  $\alpha$ -positions** in DCl-D<sub>2</sub>O or even in water at 200 °C, the key species being **an ylide formed by 2/6-decarboxylation of the 1H-pyridinium cation**.



# 6 Pyridines: Reactions

## 6.1.2.2 Nitration

a) Pyridine itself can be converted into 3-nitropyridine only inefficiently by direct nitration even with vigorous conditions, as shown below,



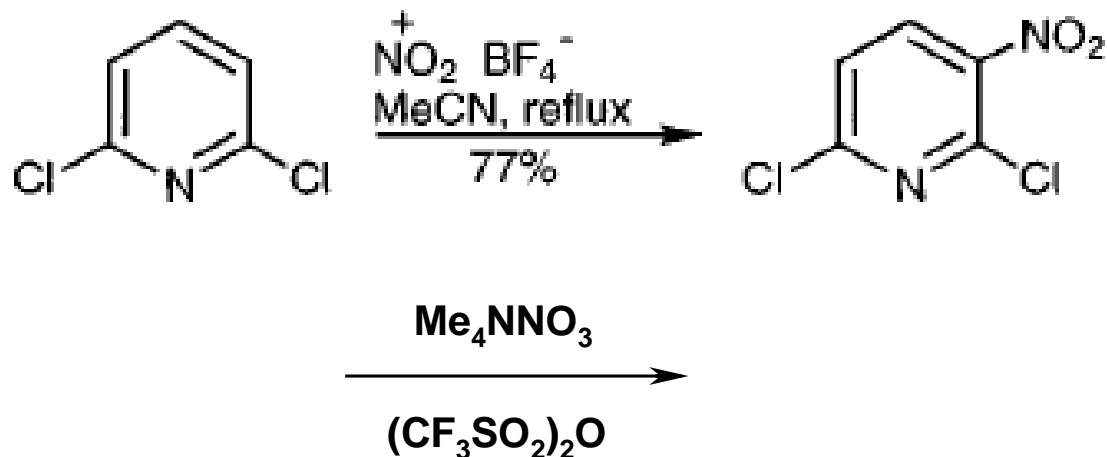


# 6 Pyridines: Reactions

## 6.1.2.2 Nitration

b) However a couple of ring methyl groups facilitate electrophilic substitution sufficiently to allow nitration.

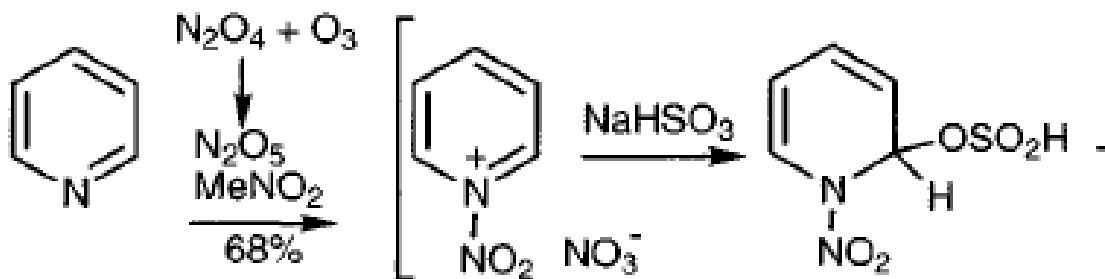
c) Steric or/and inductive inhibition of *N*-nitration allows C-substitution using nitronium tetrafluoroborate, an example is nitration of 2,6-dichloropyridine.



# 6 Pyridines: Reactions

## 6.1.2.2 Nitration

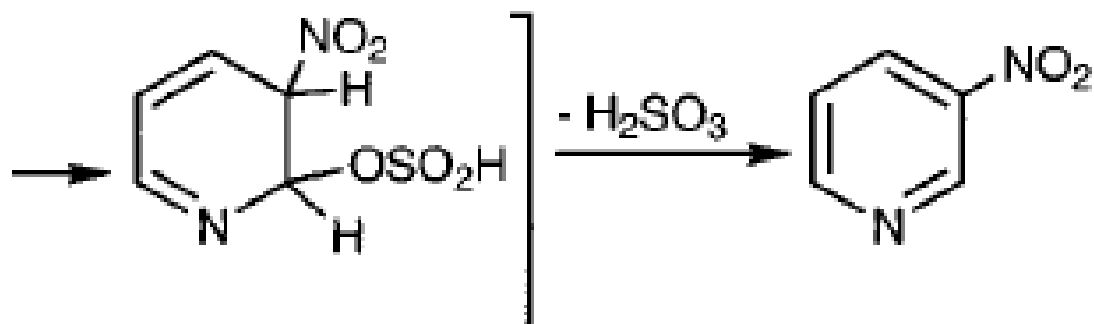
b) 3-Nitropyridine itself, and some of its substituted derivatives, can now be prepared efficiently by reaction with **dinitrogen pentoxide** as shown below. The initially formed *N*-nitropyridinium nitrate suffers **addition of a nucleophile-sulfur dioxide** (when this is used as solvent or co-solvent), **or sulfite**, added subsequently - forming a 1,2-dihydropyridine.



# 6 Pyridines: Reactions

## 6.1.2.2 Nitration

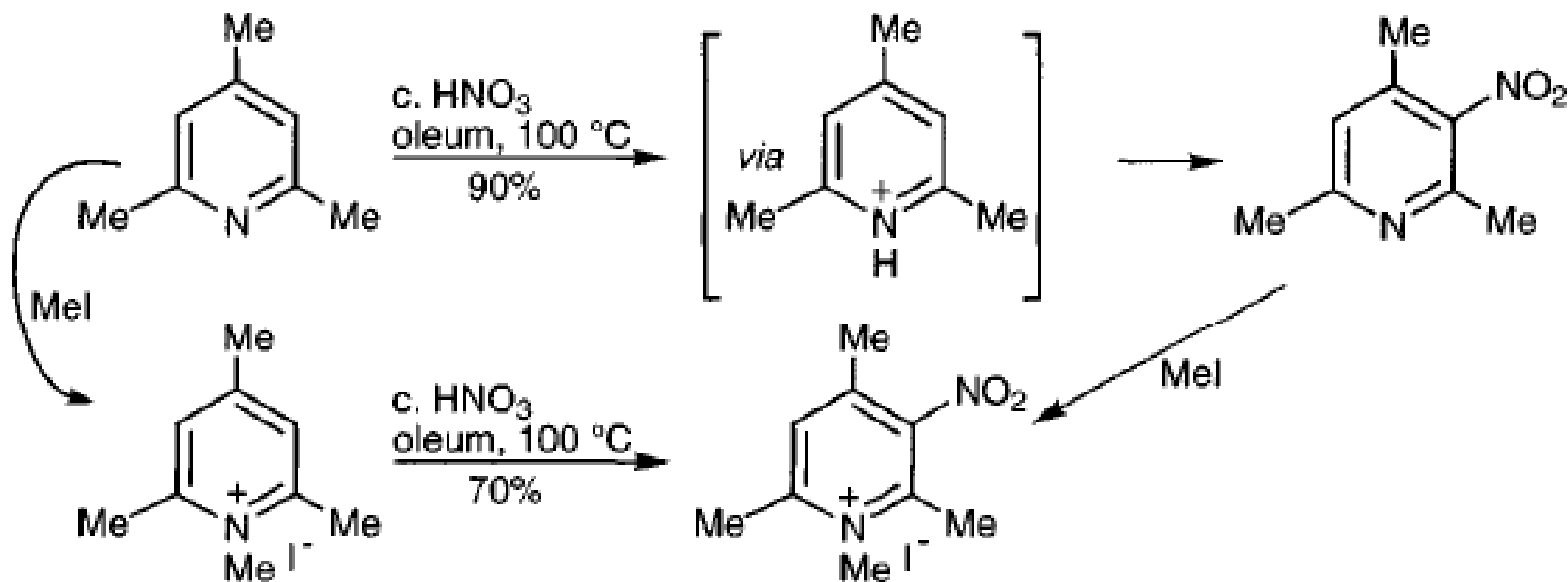
Transfer of the nitro group to a 3- or 6-position, via a [1,5]-sigmatropic migration, is then followed by elimination of the nucleophile regenerating the aromatic system.



# 6 Pyridines: Reactions

## 6.1.2.2 Nitration

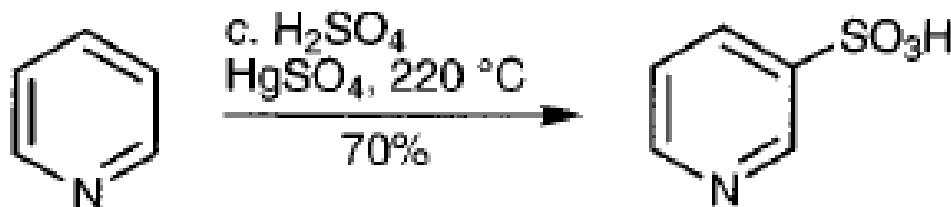
Both **collidine** and its **quaternary salt** are nitrated at similar rates under the same conditions, showing that the **former reacts via its N-protonic salt**.



# 6 Pyridines: Reactions

## 6.1.2.3 Sulfonation

a) Pyridine is very resistant to sulfonation using concentrated sulfuric acid or oleum, only very low yields of the 3-sulfonic acid being produced after prolonged reaction periods at 320 °C. However, addition of mercuric sulfate in catalytic quantities allows smooth sulfonation at a somewhat lower temperature. The role of the catalyst is not established; one possibility is that C-mercuration is the first step (cf. section 6.1.2.5)

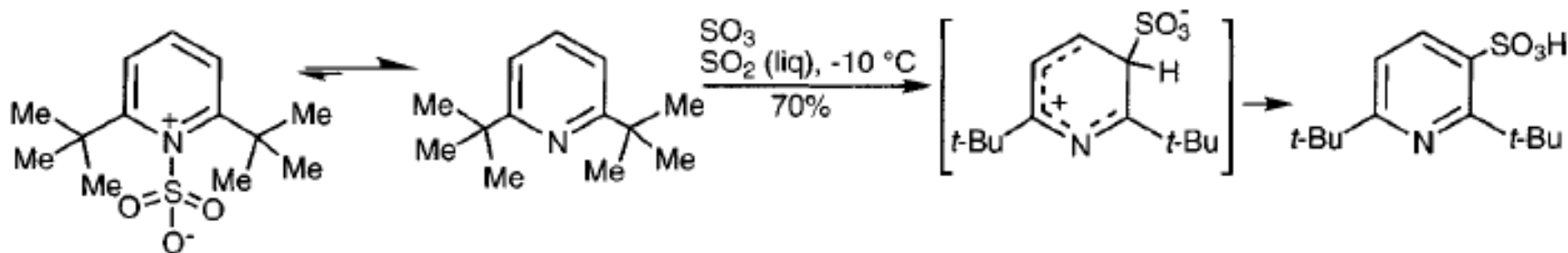


# 6 Pyridines: Reactions

## 6.1.2.3 Sulfonation

b) The C-sulfonation of 2,6-di-*t*-butylpyridine is a good guide to the intrinsic reactivity of a pyridine ring, for in this situation the bulky alkyl groups effectively prevent addition of sulfur trioxide to the ring nitrogen allowing progress to a 'normal' electrophilic C-substitution intermediate, at about the same rate as for sulfonation of nitrobenzene.

A maximum conversion of 50% is all that is achieved because for every C-substitution a proton is produced which 'consumes' a molecule of starting material by *N*-protonation.

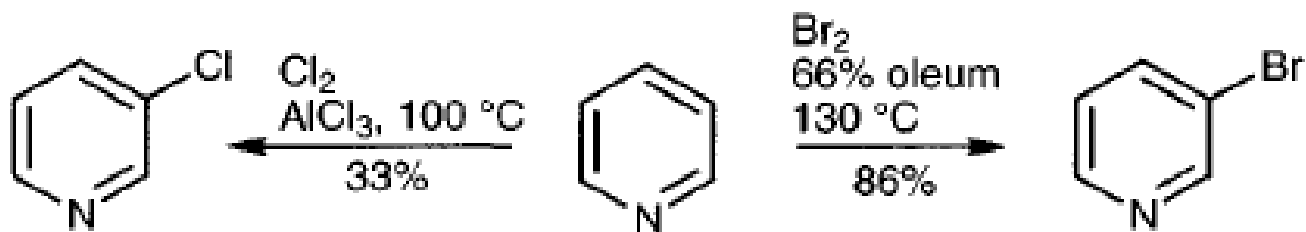


# 6 Pyridines: Reactions

## 6.1.2.4 Halogenation

a) **3-Bromopyridine** is produced in good yield by the action of **bromine in oleum**. The process is thought to involve **pyridinium-1-sulfonate** as the reactive species, since no bromination occurs in **95% sulfuric acid**.

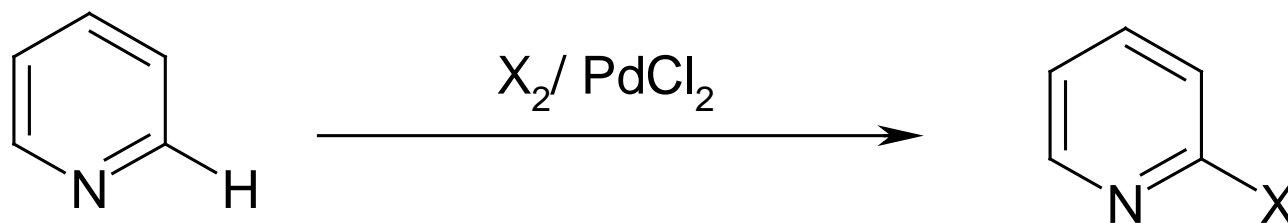
b) **3-Chloropyridine** can be produced by **chlorination** at **200 °C** or at **100 °C** in the presence of **aluminium chloride**.



# 6 Pyridines: Reactions

## 6.1.2.4 Halogenation

c) 2-Bromo- and 2-chloropyridines can be made extremely efficiently by reaction of pyridine with the halogen, at 0-5 °C in the presence of palladium(II) chloride.

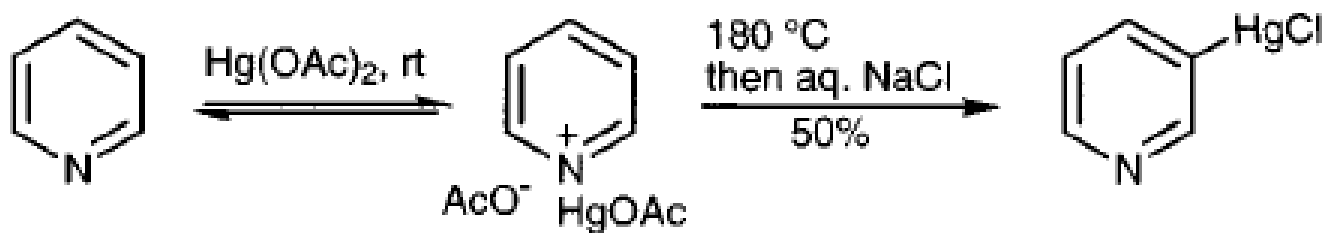




# 6 Pyridines: Reactions

## 6.1.2.5 Acetoxymercuration

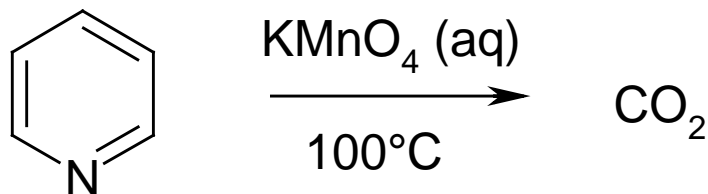
The salt formed by the interaction of pyridine with mercuric acetate at room temperature can be rearranged to 3-acetoxymercuripyridine by heating to only 180 °C. This process, where again there is C-attack by a relatively weakly electrophilic reagent, like that described for mercuric sulfate-catalysed sulfonation, may involve attack on an equilibrium concentration of free pyridine.



# 6 Pyridines: Reactions

## 6.2 Reactions with oxidising agents

- a) The **pyridine ring** is generally resistant to oxidising agents, vigorous conditions being required, thus **pyridine itself is oxidised** by neutral aqueous **potassium permanganate at about the same rate as benzene** (sealed tube, 100 °C), to give **carbon dioxide**.

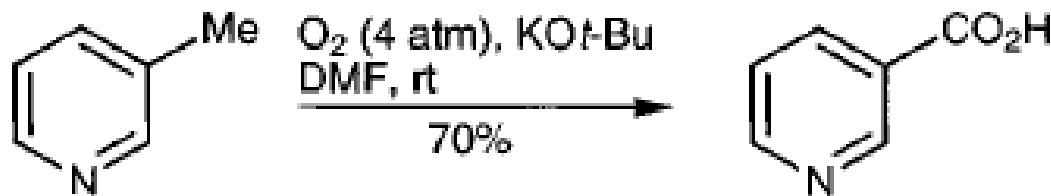


- b) In **acidic solution** pyridine is more resistant, but in **alkaline media** more rapidly oxidised, than benzene.

# 6 Pyridines: Reactions

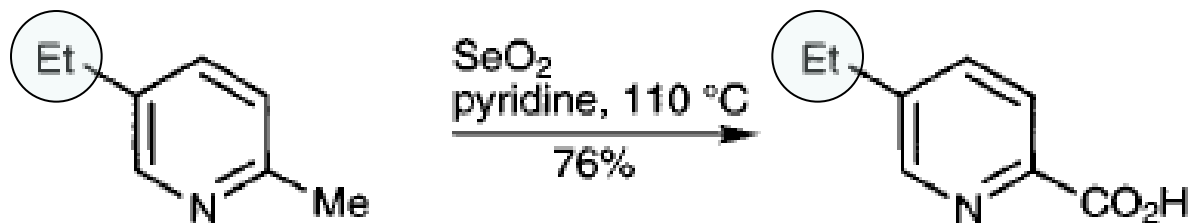
## 6.2 Reactions with oxidising agents

c) In most situations, carbon substituents can be oxidised with survival of the ring, thus alkyldiarynes can be converted into pyridine carboxylic acids with a variety of reagents.



Some selectivity can be achieved:

1) only  $\alpha$ - and  $\gamma$ -groups (and not  $\beta$ -) are attacked by selenium dioxide.



# 6 Pyridines: Reactions

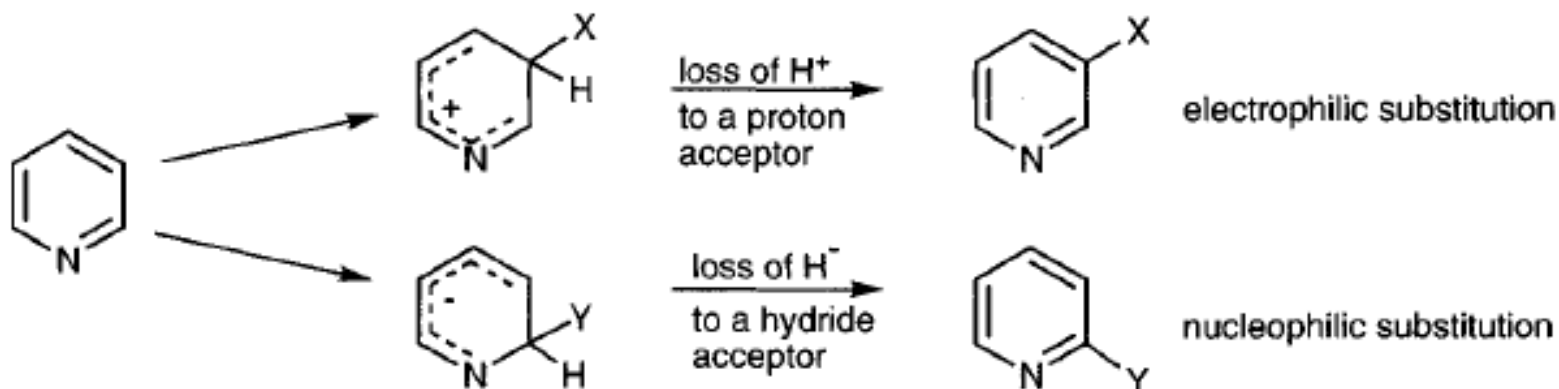
## 6.3 Reactions with nucleophilic reagents

a) Just as electrophilic substitution is the characteristic reaction of benzene and electron-rich heteroaromatic compounds (pyrrole, furan etc.), so substitution reactions with nucleophiles can be looked on as characteristic of pyridines.

# 6 Pyridines: Reactions

## 6.3 Reactions with nucleophilic reagents

b) It is important to realise that nucleophilic substitution of hydrogen differs in an important way from electrophilic substitution: whereas the last step in electrophilic substitution is loss of proton, an easy process, the last step in nucleophilic substitution of hydrogen has to be a hydride transfer, which is less straightforward and generally needs the presence of an oxidising agent as hydride acceptor.



# 6 Pyridines: Reactions

## 6.3 Reactions with nucleophilic reagents

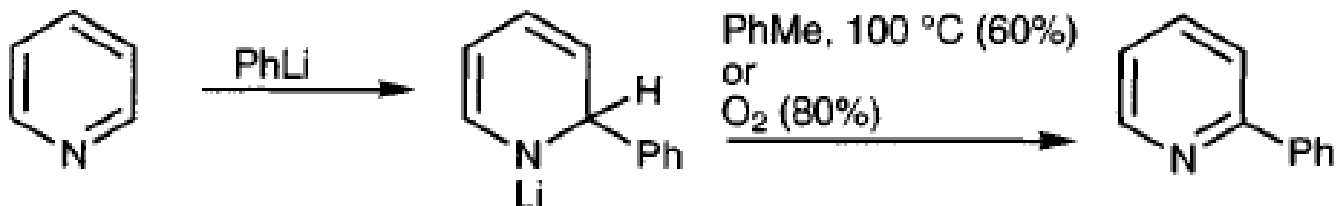
c) Nucleophilic substitution of an atom or group which is a good anionic leaving group however is an easy and straightforward process.

# 6 Pyridines: Reactions

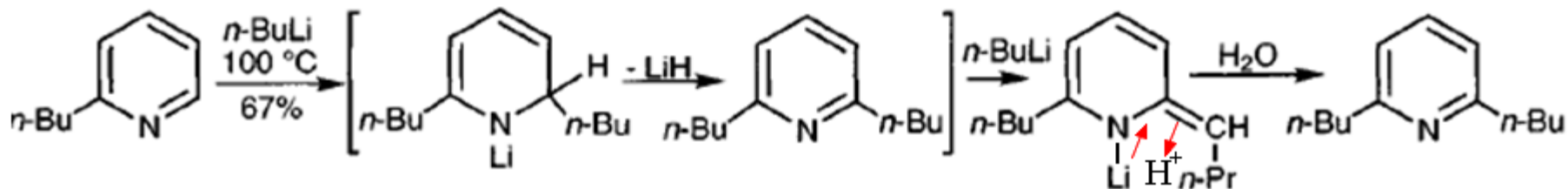
## 6.3 Reactions with nucleophilic reagents

### 6.3.1 Nucleophilic substitution with 'hydride' transfer

- a) Reaction with **alkyl-** or **aryllithiums** proceeds in two discrete steps:
- 1) **addition** to give a dihydropyridine N-Lithio-salt which,
  - 2) can then be converted into the **substituted aromatic pyridine by oxidation** (e.g. by air),



disproportionation, or **elimination of lithium hydride**.



# 6 Pyridines: Reactions

## 6.3 Reactions with nucleophilic reagents

### 6.3.1 Nucleophilic substitution with 'hydride' transfer

b) The N-lithio-salts can be observed spectroscopically and in some cases isolated as solids.

c) Attack is nearly always at an  $\alpha$ -position:  
reaction with 3-substituted-pyridines usually takes place at both available  $\alpha$ -positions, but predominantly at C-2. This regioselectivity may be associated with relief of strain when the 2-position rehybridises to  $sp^3$  during addition.



# 6 Pyridines: Reactions

## 6.3 Reactions with nucleophilic reagents

### 6.3.1 Nucleophilic substitution with 'hydride' transfer

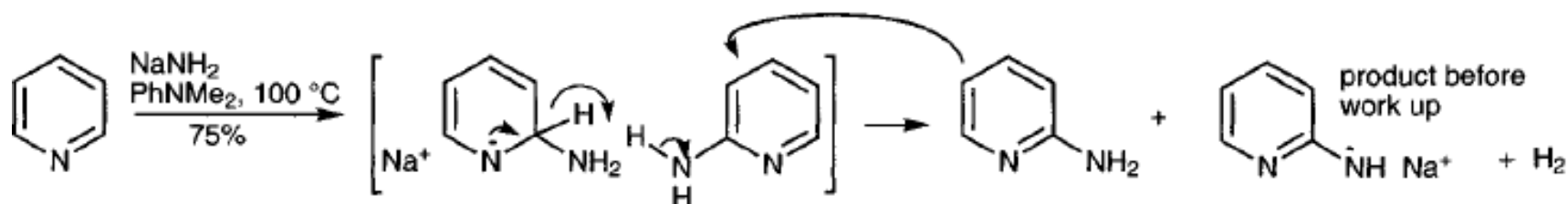
d) From the preparative viewpoint nucleophilic alkylations can be greatly facilitated by the device of prior quaternisation of the pyridine in such a way that the *N*-substituent can be subsequently removed - these processes are dealt with in section 6.13.2.

# 6 Pyridines: Reactions

## 6.3 Reactions with nucleophilic reagents

### 6.3.1.2 Amination

a) Amination of pyridines and related heterocycles, generally at a position *a* to the nitrogen, is called the Chichibabin reaction, the pyridine reacting with sodamide with the evolution of hydrogen. The 'hydride' transfer and production of hydrogen probably involve interaction of aminopyridine product, acting as an acid, with the anionic intermediate.



# 6 Pyridines: Reactions

## 6.3 Reactions with nucleophilic reagents

### 6.3.1.2 Amination

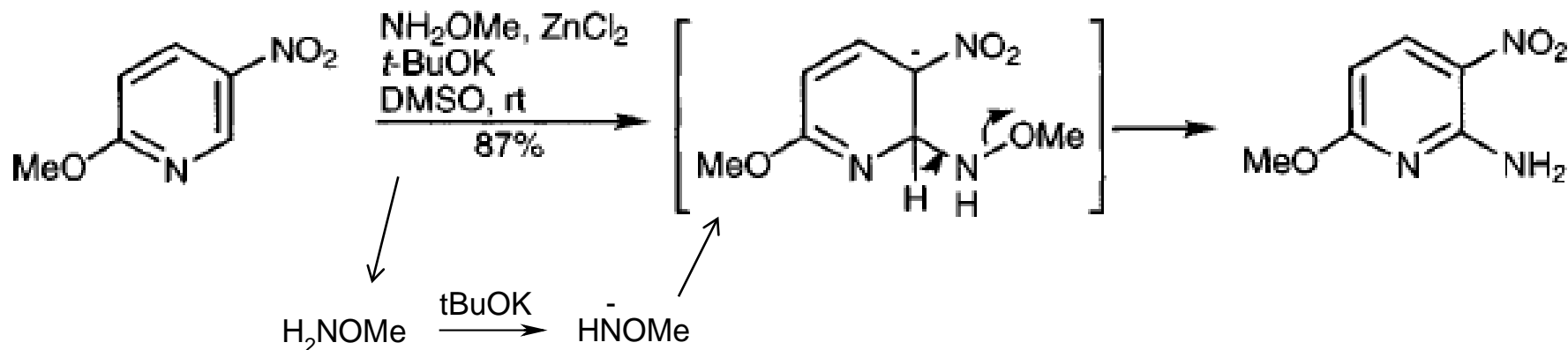
- b) The preference for  $\alpha$ -substitution may be associated with an intramolecular delivery of the nucleophile, perhaps guided by complexation of ring nitrogen with metal cation.
- c) More vigorous conditions are required for the amination of 2- or 4-alkylpyridines since proton abstraction from the side-chain by the amide occurs first and ring attack must therefore involve a dianionic intermediate. Amination of 3-alkylpyridines is regioselective for the 2-position.

# 6 Pyridines: Reactions

## 6.3 Reactions with nucleophilic reagents

### 6.3.1.2 Amination

d) **Vicarious nucleophilic substitution** (section 2.3.3) permits the **introduction of amino groups *ortho* to nitro groups** by reaction with methoxyamine as illustrated below.



# 6 Pyridines: Reactions

## 6.3 Reactions with nucleophilic reagents

### 6.3.1.3 Hydroxylation

a) **Hydroxide ion**, being a much weaker nucleophile than amide, attacks pyridine **only at very high temperatures** to produce a **low yield of 2-pyridone**, which can be usefully **contrasted with the much more efficient reaction of hydroxide with quinoline and isoquinoline and with pyridinium salts**.

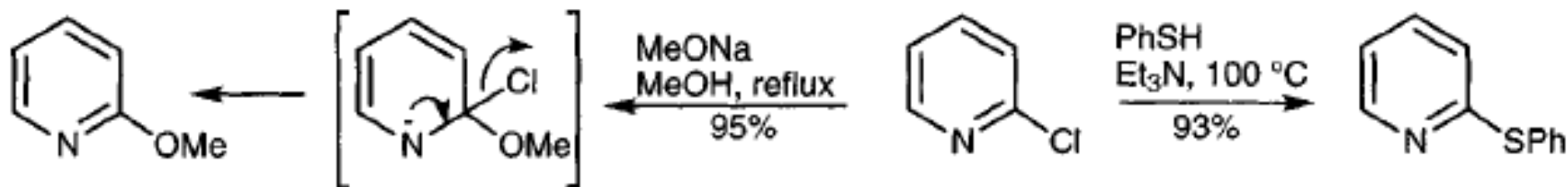
# 6 Pyridines: Reactions

## 6.3 Reactions with nucleophilic reagents

### 6.3.2 Nucleophilic substitution with displacement of good leaving groups

a) Halogen, and also, though with fewer examples, nitro, alkoxy sulfonyl, and methoxy substituents at  $\alpha$ - or  $\gamma$ -positions, *but not at  $\beta$ -positions*, are relatively easily displaced by a wide range of nucleophiles *via an addition-elimination mechanism facilitated by:*

- (1) electron withdrawal by the substituent and
- (2) the good leaving ability of the substituent.

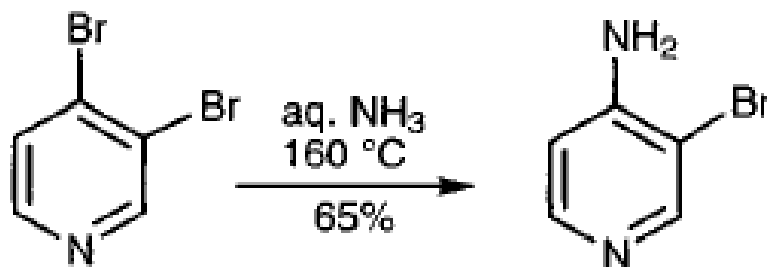


# 6 Pyridines: Reactions

## 6.3 Reactions with nucleophilic reagents

### 6.3.2 Nucleophilic substitution with displacement of good leaving groups

b) reactivity:  $\gamma$ -Halopyridines  $>$   $\alpha$ -isomers  $>$   $\beta$ -isomers

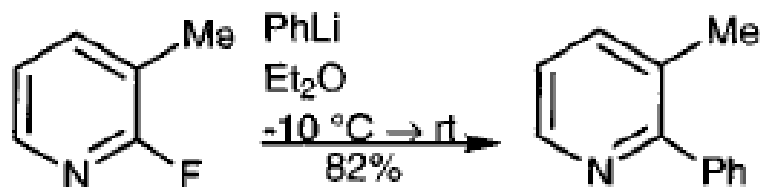


# 6 Pyridines: Reactions

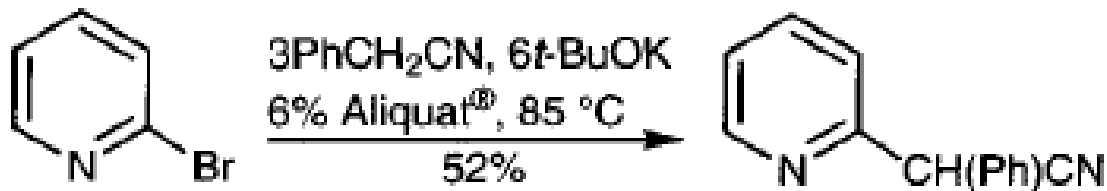
## 6.3 Reactions with nucleophilic reagents

### 6.3.2 Nucleophilic substitution with displacement of good leaving groups

c) **Fluorides** are more reactive than the other halides.

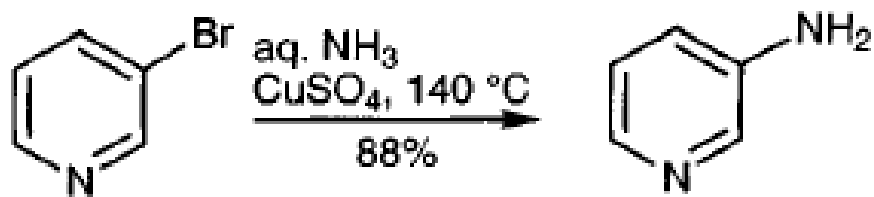


d) **Replacement of halide by reaction with ammonia** can be achieved at considerably **lower temperatures under 6-8 kbar pressure**. The inclusion of **Aliquat** is an alternative means for improving the efficiency of such nucleophilic displacements.





$\beta$ -halopyridines are very much less reactive and needs some catalysis , but still somewhat more reactive than halobenzenes.

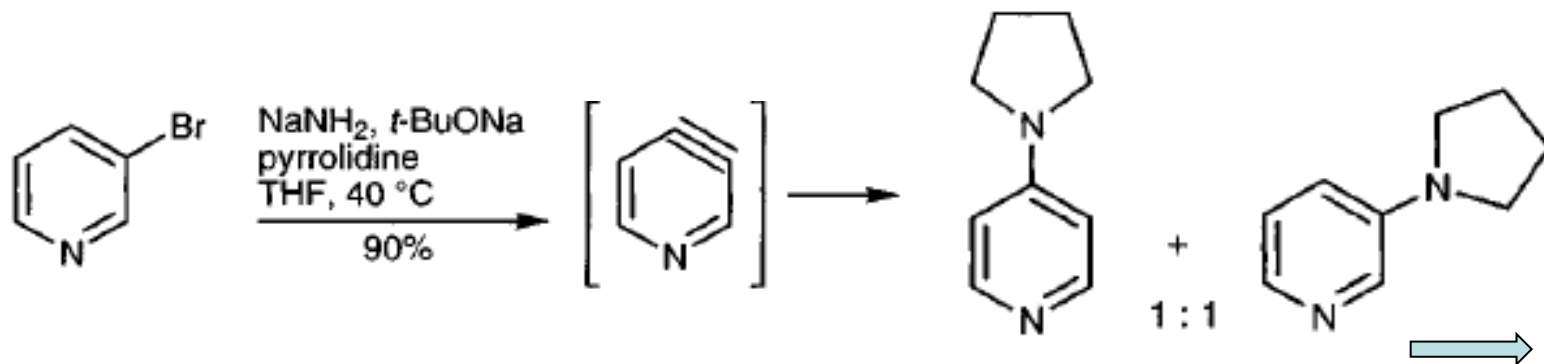


## 6 Pyridines: Reactions

### 6.3 Reactions with nucleophilic reagents

#### 6.3.2 Nucleophilic substitution with displacement of good leaving groups

e) In some, apparently straightforward displacements, more detailed mechanistic study reveals the operation of **alternative mechanisms**. For example the reaction of either 3- or 4-bromopyridine with **secondary amines** in the presence of **sodamide/sodium t-butoxide**, produces the **same mixture of 3- and 4-dialkylaminopyridines**; this proceeds *via an elimination process (SN(EA) - Substitution Nucleophilic Elimination Addition)* and the intermediacy of 3,4-didehydropyridine (3,4-pyridyne).



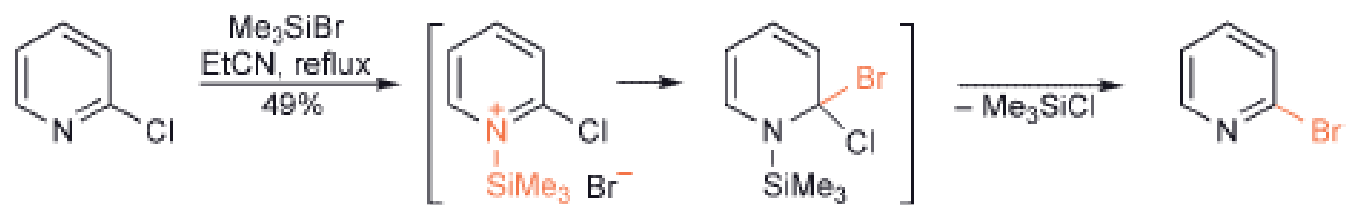
# 6 Pyridines: Reactions

## 6.3 Reactions with nucleophilic reagents

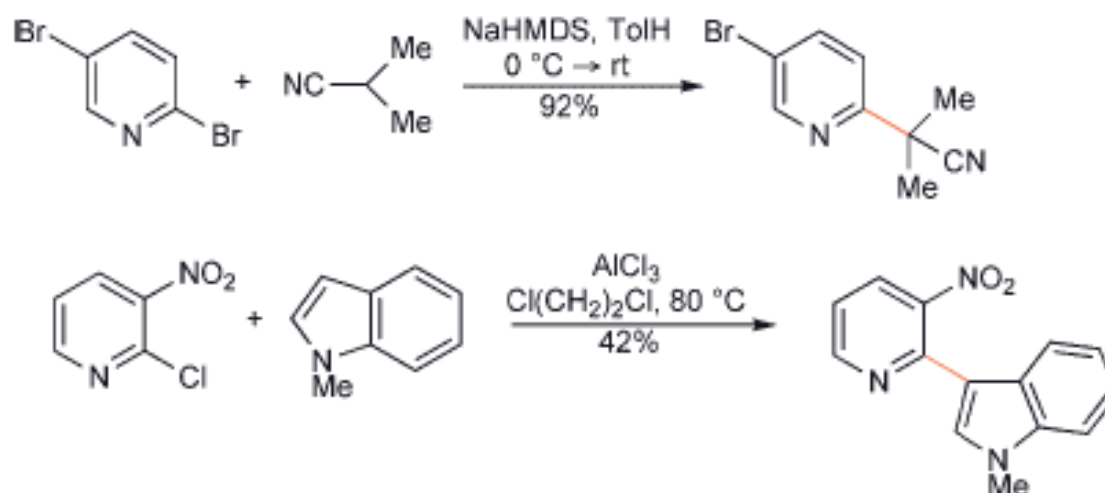
### 6.3.2 Nucleophilic substitution with displacement of good leaving groups

f) The fact that no 2-aminated pyridine is produced shows a greater difficulty in generating 2,3-pyridyne, it can however be formed by reaction of 3-bromo-2-chloropyridines with butyllithium, or via the reaction of 3-trimethylsilyl-2-trifluoromethanesulfonyloxy pyridine with fluoride.

It is possible to replace  $\alpha$ -chlorine with bromine or iodine by reaction with the halotrimethylsilane; no doubt this involves an intermediate pyridinium salt, as shown (see also 8.12.2).<sup>68</sup>



Carbon nucleophiles can also be used: deprotonated nitriles will displace a halogen;<sup>69,70</sup> electron-rich aromatic compounds will displace  $\alpha$ -halogen *ortho* or *para* to nitro or cyano, using aluminium chloride catalysis.<sup>71</sup>

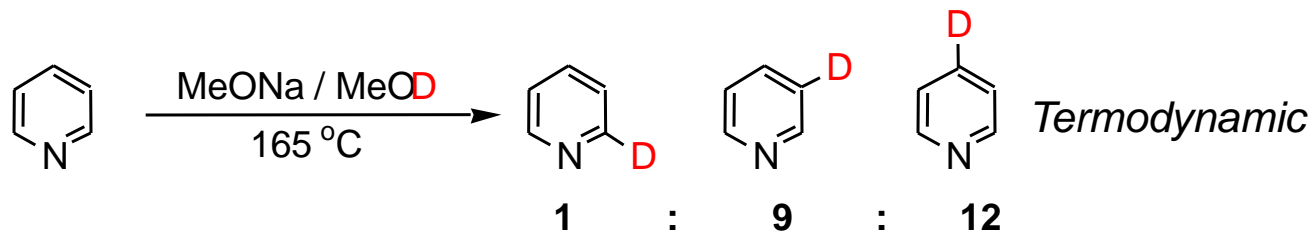


# 6 Pyridines: Reactions

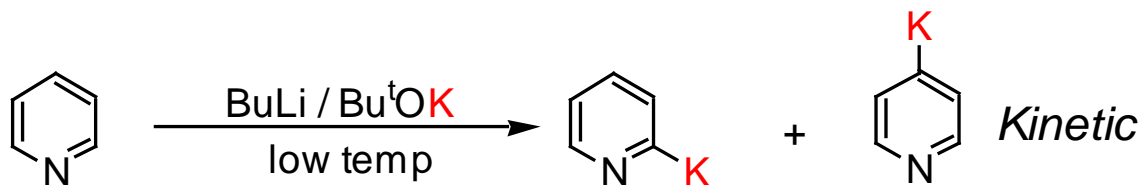
## 6.4 Reactions with bases

### 6.4.1 Metallation of C-hydrogen

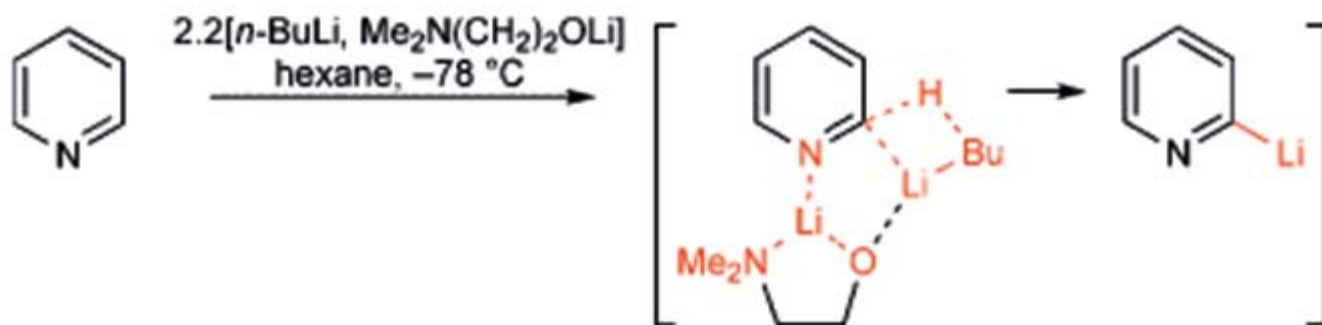
- a) When pyridine is heated to  $165^{\circ}\text{C}$  in  $\text{MeONa-MeOD}$ , H-D exchange occurs at all positions *via small concentrations of deprotonated species*, at the relative rates of  $\alpha: \beta: \gamma$ , 1: 9: 12.



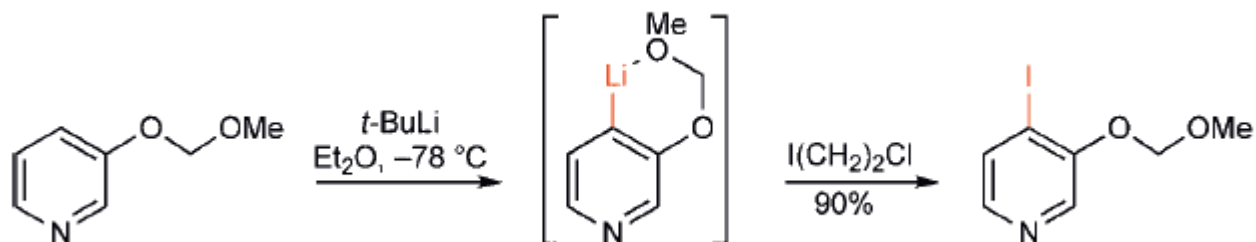
- a) However, using the combination *t*-butyllithium/*t*-BuOK, efficient formation of 2-pyridylpotassium or 4-pyridylpotassium has been achieved.



Regioselective metallation at an  $\alpha$  - position of a pyridine can be achieved with the mixed base produced from two mole equivalents of *n* - butyllithium with one of dimethylaminoethanol i.e. it is a 1 : 1 mixture of *n* - BuLi and  $\text{Me}_2\text{N}(\text{CH}_2)_2\text{OLi}$  (BuLi - LiDMAE)



3-Halo- and 3-alkoxy pyridines react mainly at C-4, and 2- and 4-halo-pyridines necessarily lithiate at a  $\beta$  - position.



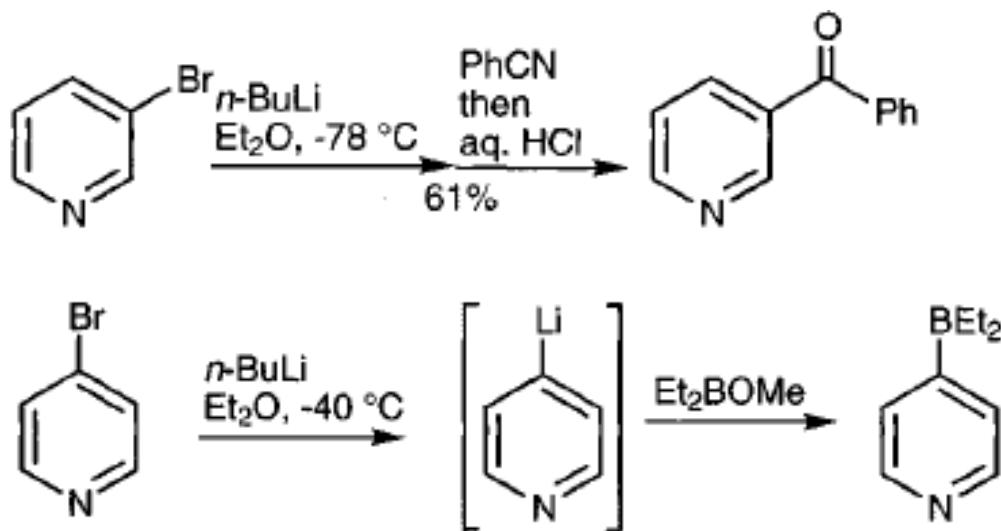


# 6 Pyridines: Reactions

## 6.5 Reactions of C-metallated pyridines

### 6.5.1 Metal- Halogen Exchange

Lithium derivatives are easily prepared and **behave as typical organometallic nucleophiles**, thus for example, **3-bromopyridine** undergoes efficient exchange with n-butyllithium in ether at -78 °C.

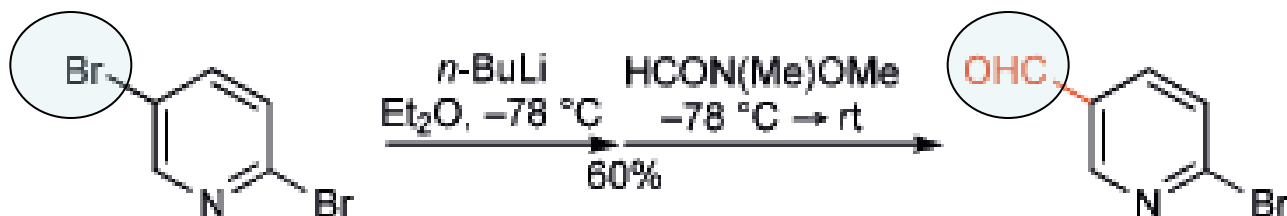


# 6 Pyridines: Reactions

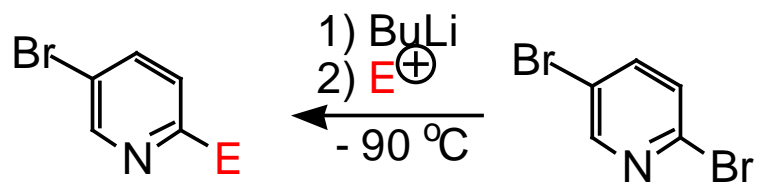
## 6.5 Reactions of C-metallated pyridines

### 6.5.1 Lithium and magnesium derivatives

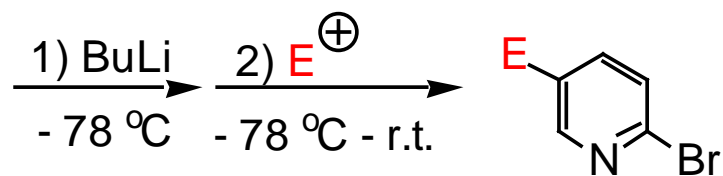
Metal/halogen exchange with 2,5-dibromopyridine leads exclusively and efficiently to 2-bromo-5-lithiopyridine in a thermodynamically controlled process; it has been suggested that the 2-pyridyl anion is destabilised by electrostatic repulsion between nitrogen lone pair and the adjacent anion; The example below illustrates the use of the 'Weinreb amide' of formic acid as a formyl transfer reagent.



## Metal - Halogen Exchange



Kinetically controlled

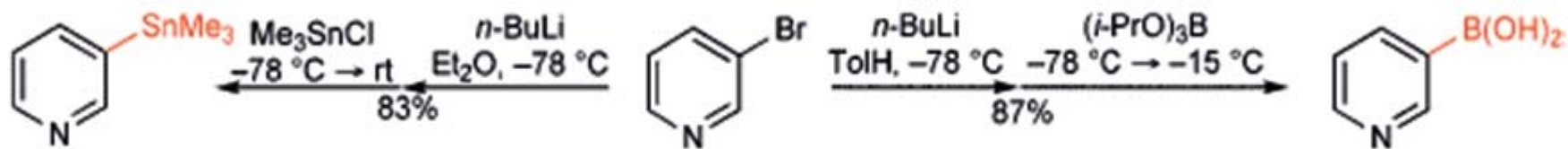


Thermodynamically controlled

# 6 Pyridines: Reactions

## 6.5 Reactions of C-metallated pyridines

### 6.5.1 Lithium and magnesium derivatives

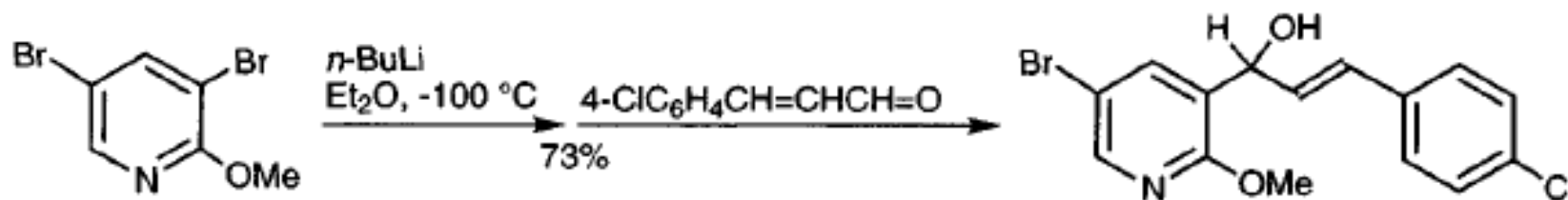


# 6 Pyridines: Reactions

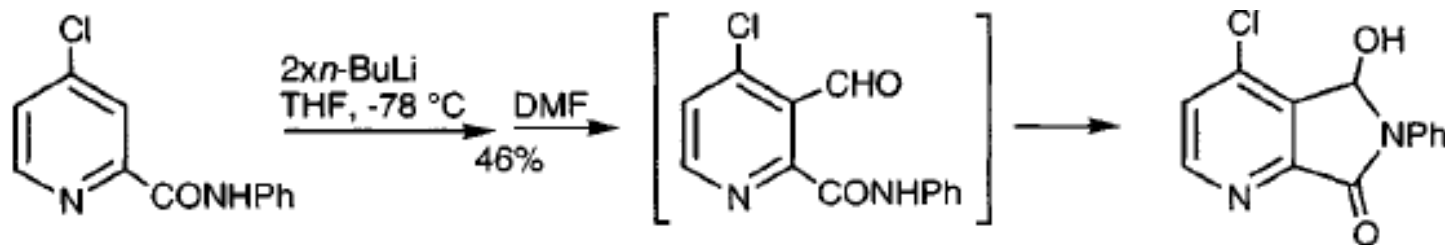
## 6.5 Reactions of C-metallated pyridines

### 6.5.1 Lithium and magnesium derivatives

The combination of metal-halogen exchange with the presence of a directing substituent can permit regioselective exchange;



two 1,3-related directing groups causes lithiation between the two groups.



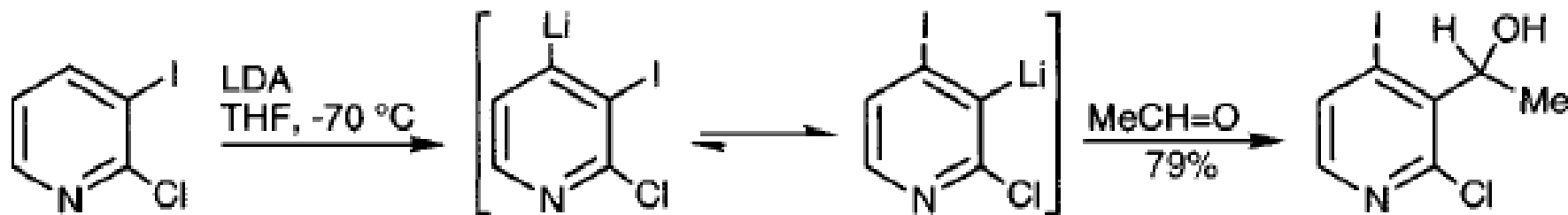
# 6 Pyridines: Reactions

## 6.5 Reactions of C-metallated pyridines

### 6.5.1 Lithium and magnesium derivatives

Bromine and iodine also direct lithiations, but isomerisation ('halogen dance') can be a problem. The sequence below shows how advantage was

taken of the isomerisation to the more stable lithio derivative i.e. that in which the formally negatively charged ring carbon is located between two halogen-bearing carbon atoms.

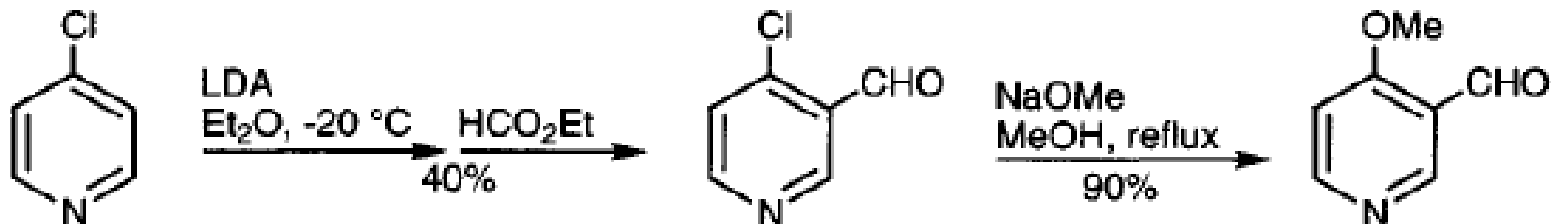


# 6 Pyridines: Reactions

## 6.5 Reactions of C-metallated pyridines

### 6.5.1 Lithium and magnesium derivatives

The use of **halogen to direct lithiation** can be combined with the ability to subsequently displace the halogen with a nucleophile.

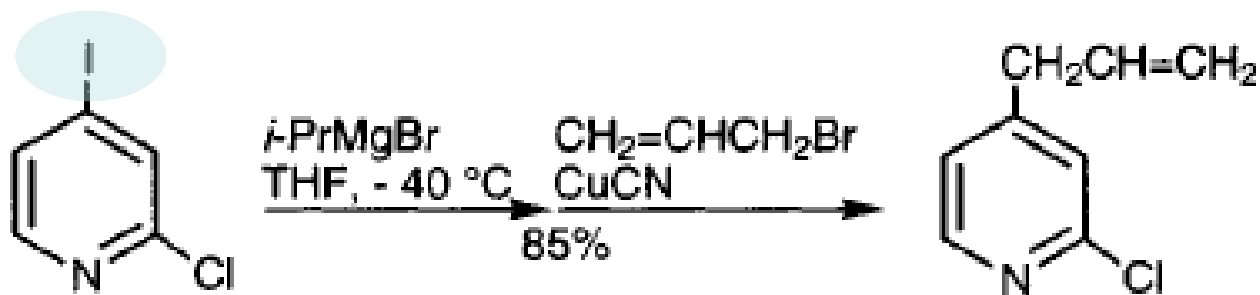


# 6 Pyridines: Reactions

## 6.5 Reactions of C-metallated pyridines

### 6.5.1 Lithium and magnesium derivatives

Pyridyl Grignard reagents are readily prepared by exchange of bromine or iodine using *i*-propyl Grignard reagents.



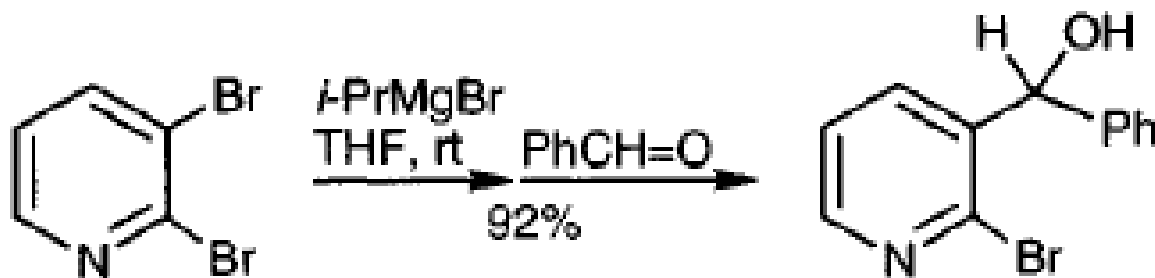


# 6 Pyridines: Reactions

## 6.5 Reactions of C-metallated pyridines

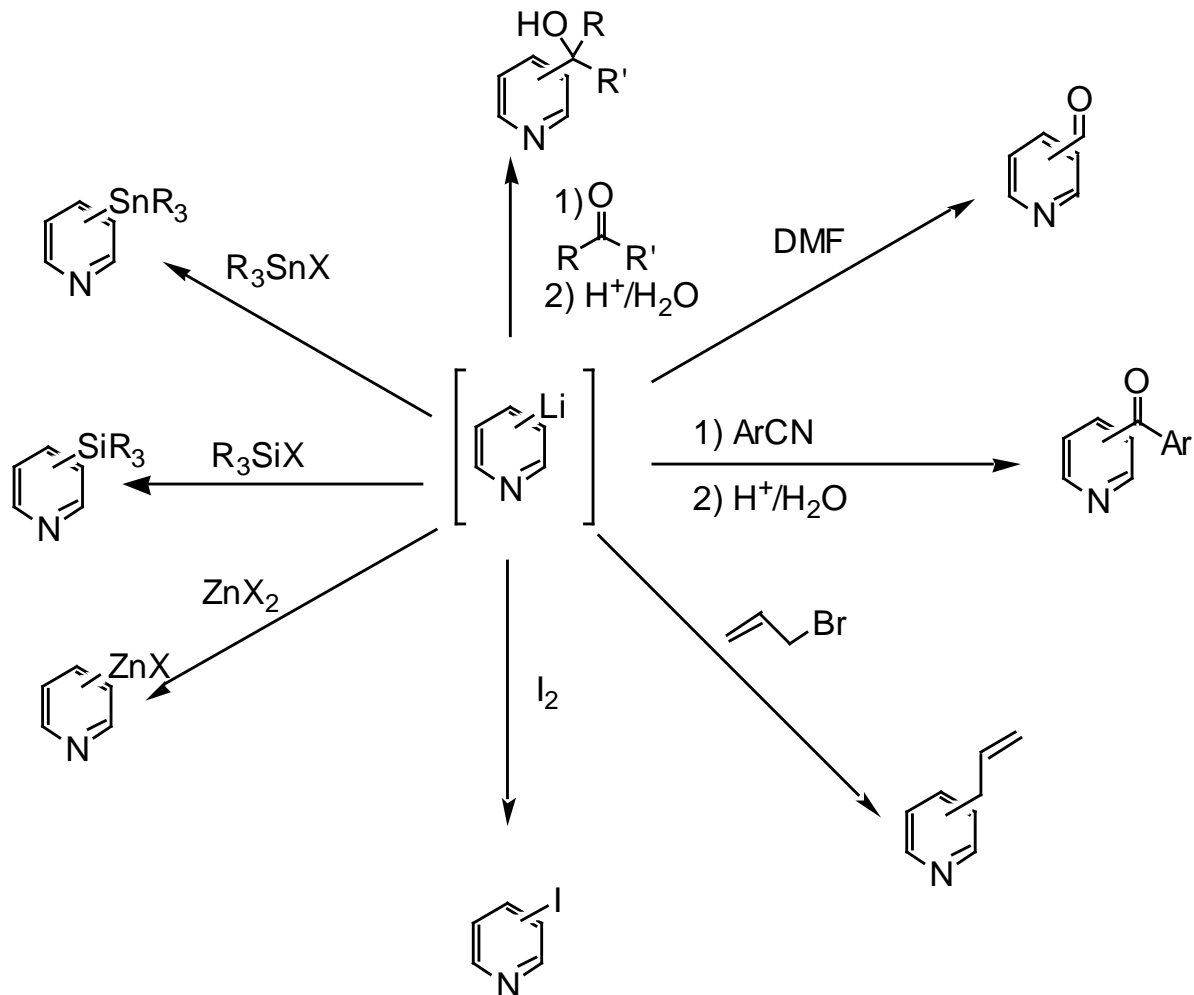
### 6.5.1 Lithium and magnesium derivatives

It is notable that in 2,5-dibromopyridine, the exchange follows the same pattern as in lithium exchange that is, selective reaction at C-5 (Thermodynamically Controlled); other dibromopyridines also give clean mono-exchange



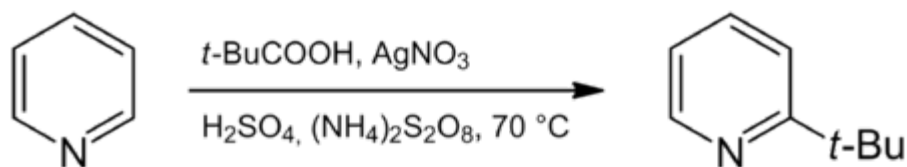
# Direct Reactions with Electrophiles: Additions, Substitutions

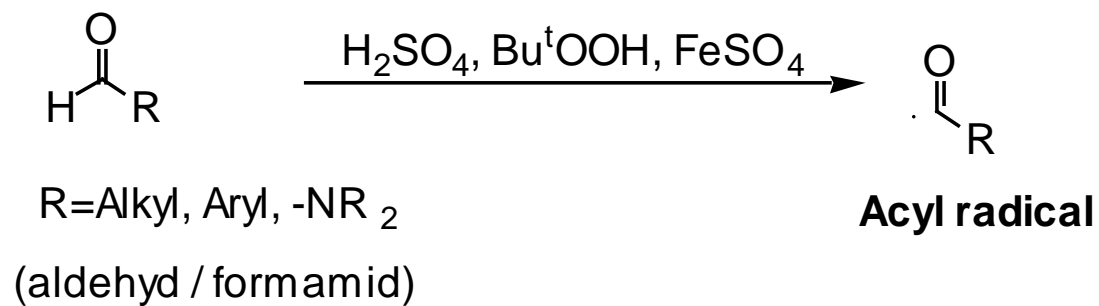
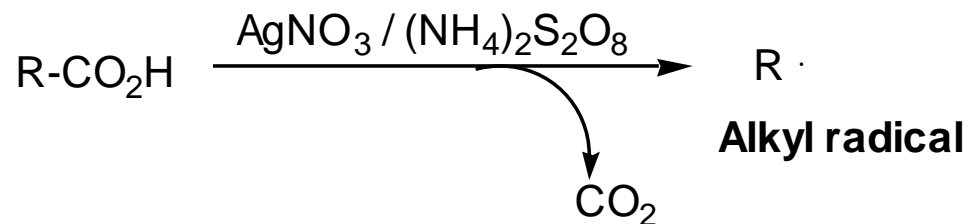
Some examples (c.f. react. with ArLi)



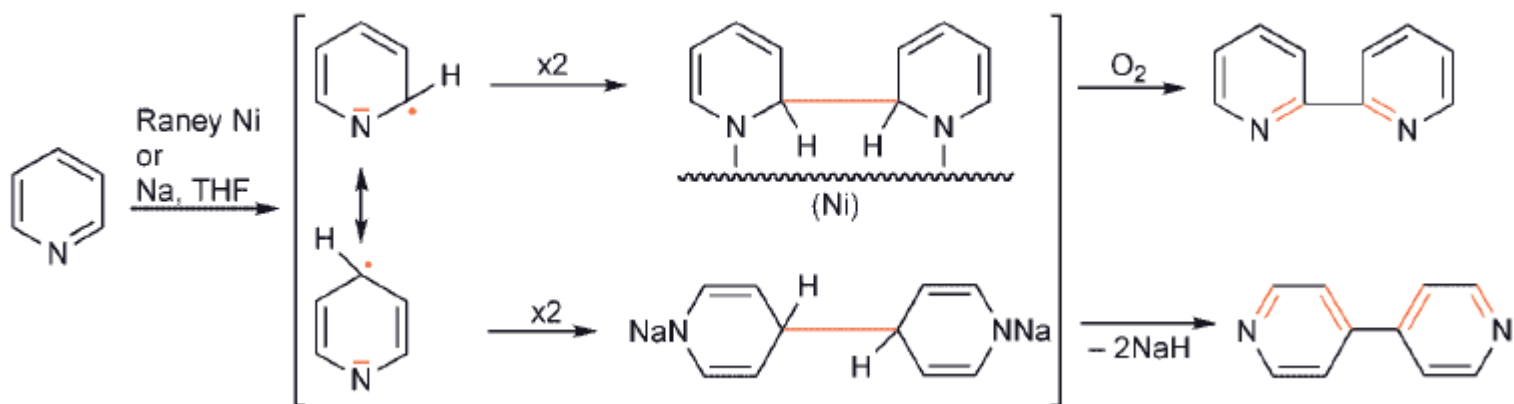
## Radical Reactions

a) Reactions with C-radicals: Minisci React.

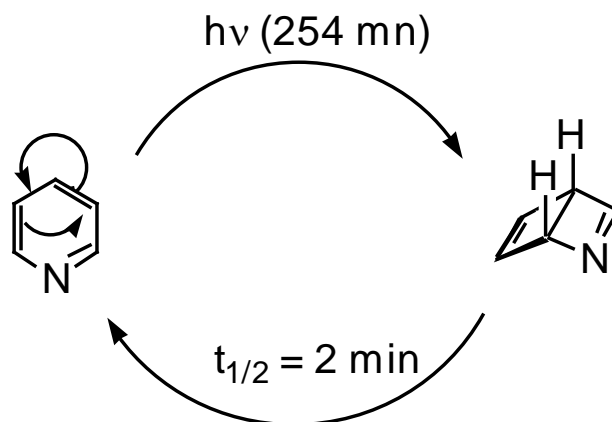




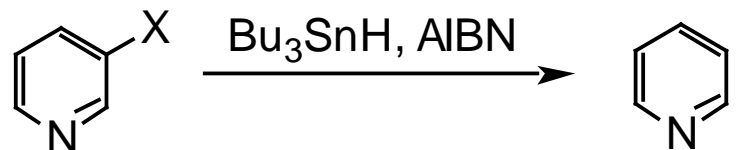
# Dimerisation



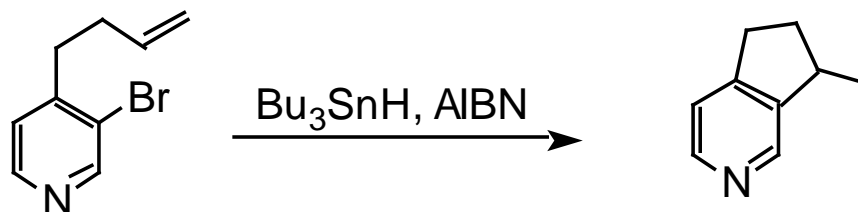
# Photochemistry



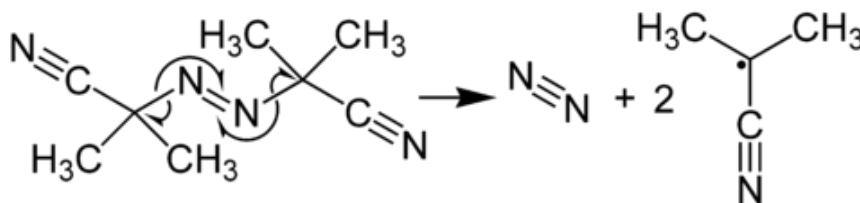
## b) Generation of / Reaction on pyridylradicals



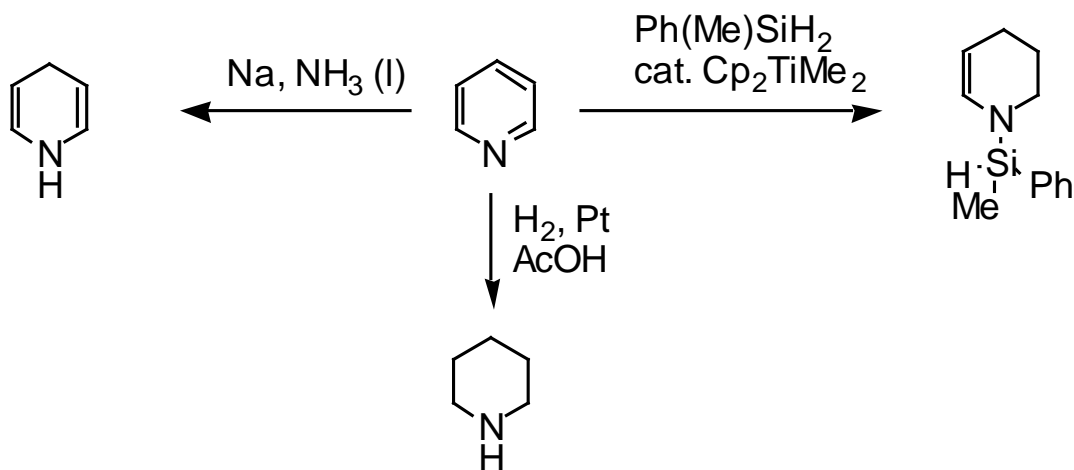
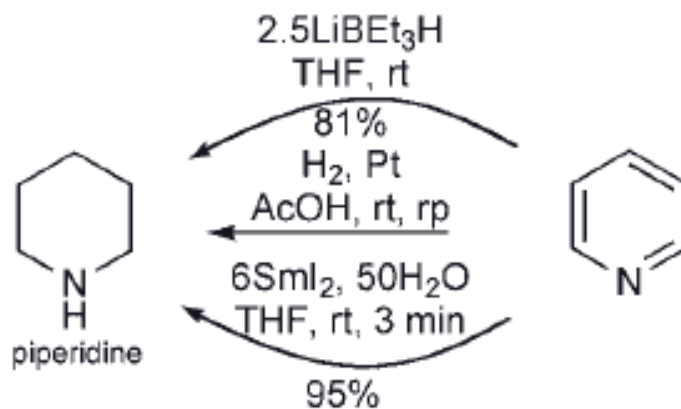
### Intramolecular cyclisations



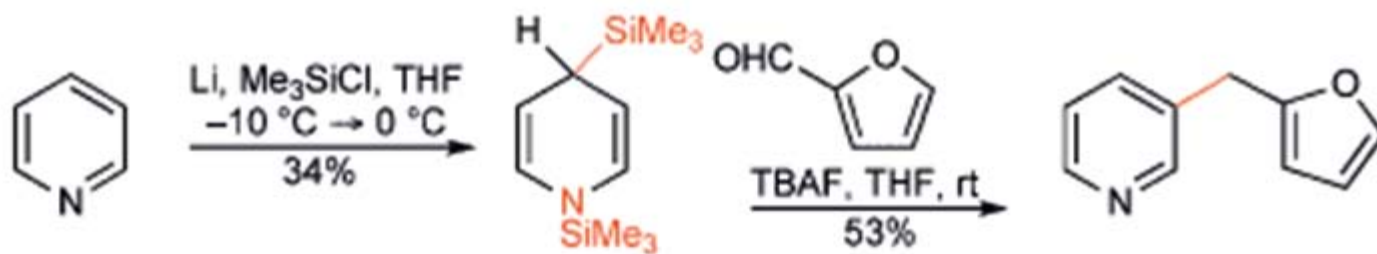
### Azobisisobutyronitrile



# Reactions with Reducing Agents





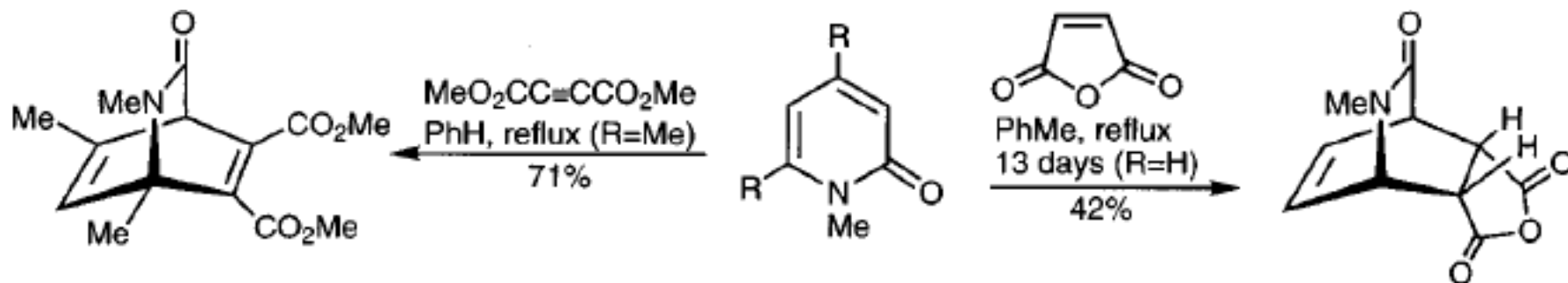


Enamine like

# 6 Pyridines: Reactions

## 6.8 Electrocyclic reactions (ground state)

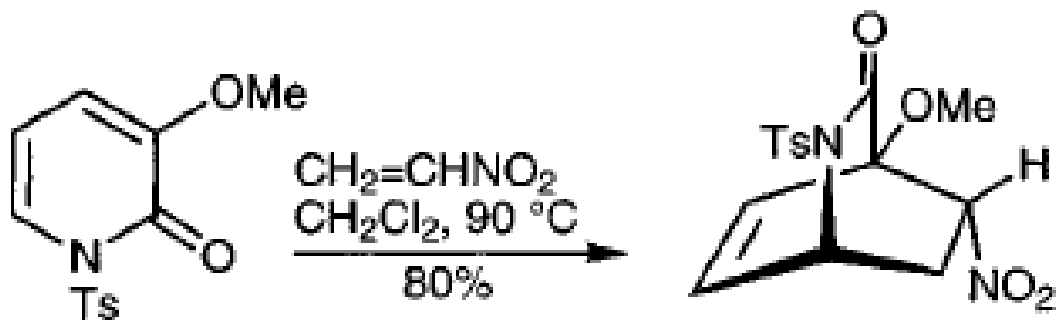
a) There are no reports of thermal electrocyclic reactions involving simple pyridines; 2-pyridones however participate as  $4\pi$  components in Diels-Alder additions, especially under high pressure.



# 6 Pyridines: Reactions

## 6.8 Electrocyclic reactions (ground state)

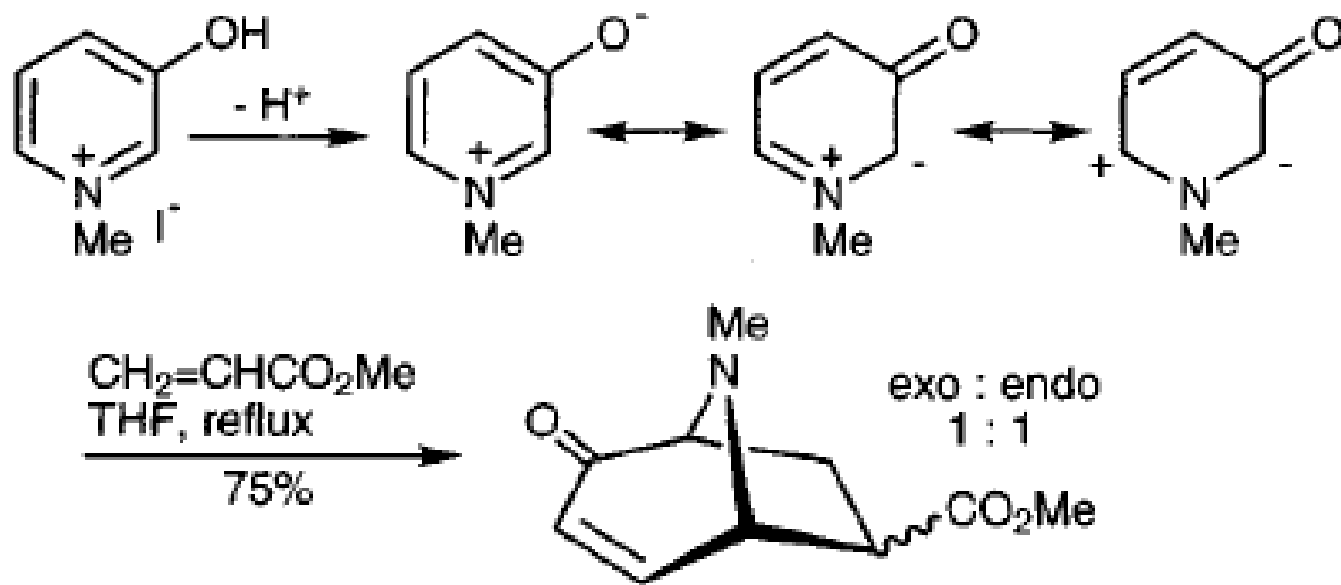
b) *N*-Tosyl-2-pyridones with a 3-alkoxy or 3-arylthio substituent, undergo cycloaddition with electron-deficient alkenes under milder conditions, as illustrated below.



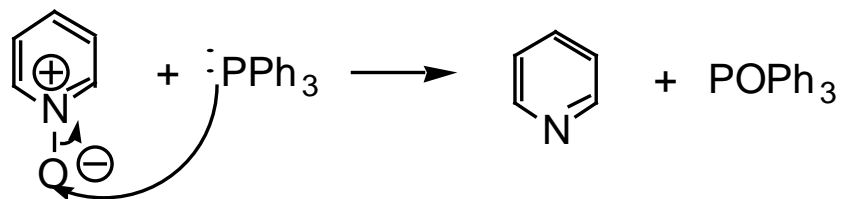
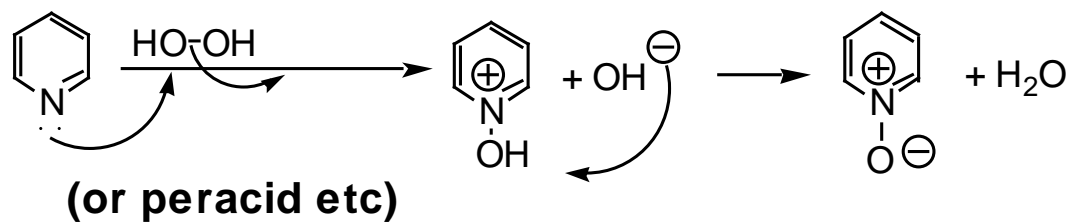
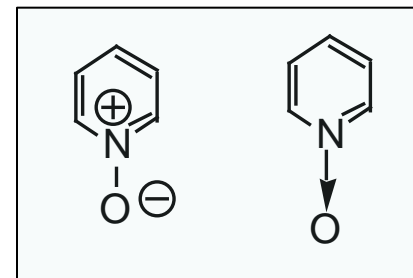
# 6 Pyridines: Reactions

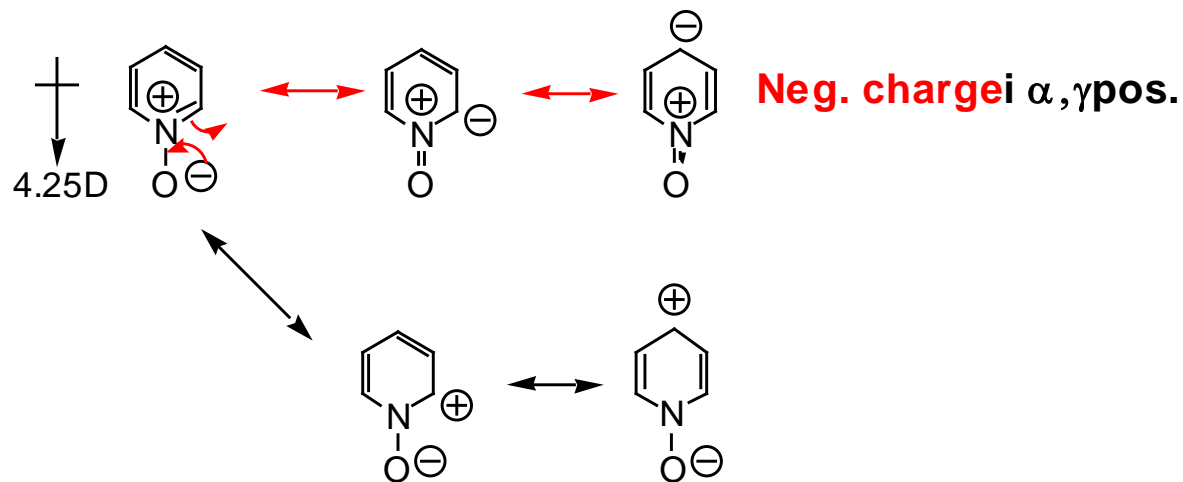
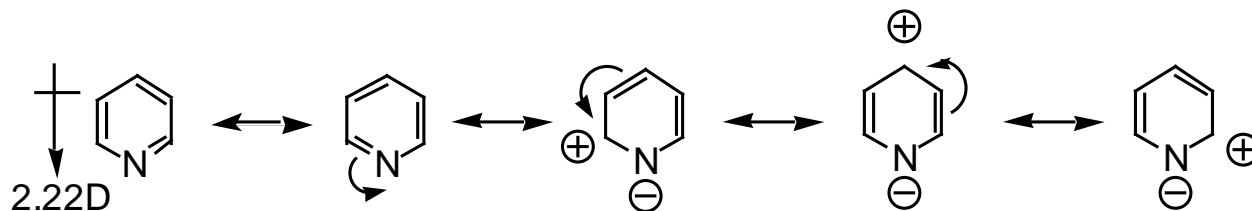
## 6.8 Electrocyclic reactions (ground state)

c) The quaternary salts of 3-hydroxypyridines are converted by mild base into zwitterionic, organic-solvent-soluble species for which no neutral canonical form can be drawn. These 3-oxidopyridiniums undergo a number of dipolar cycloaddition reactions, especially across the 2,6-positions.



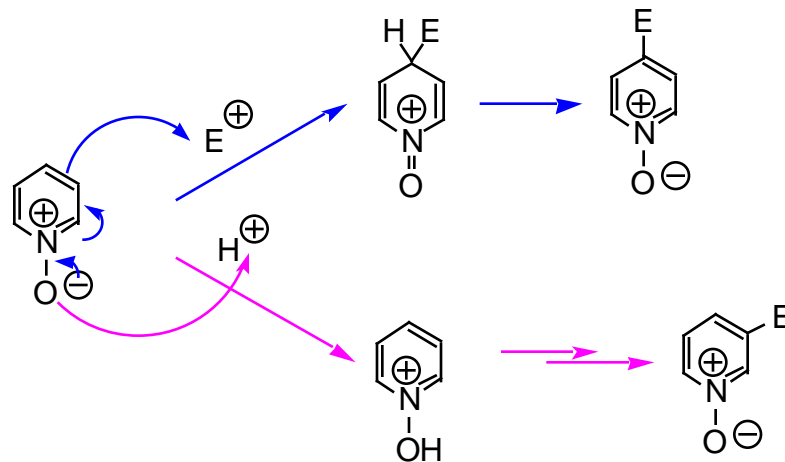
# Pyridine *N*-oxides



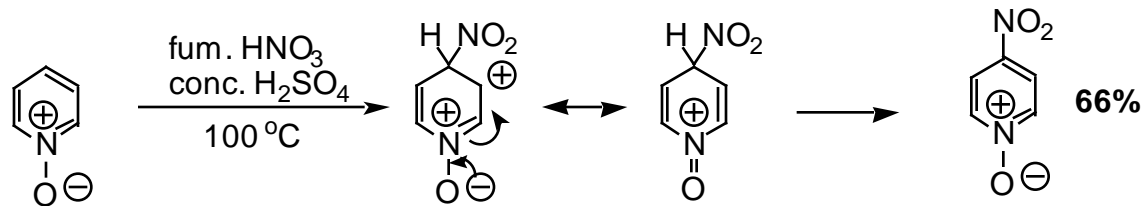
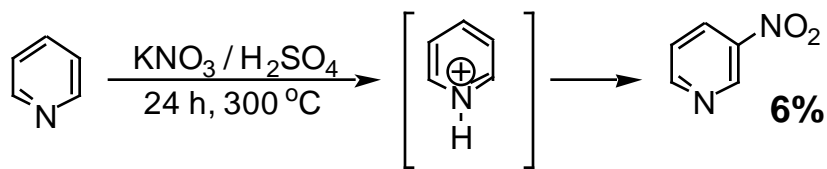


More activated for **electrophilic** and nucleophilic attack

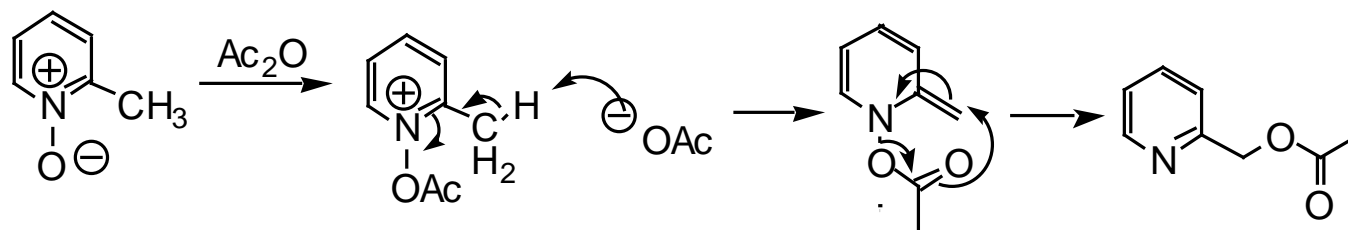
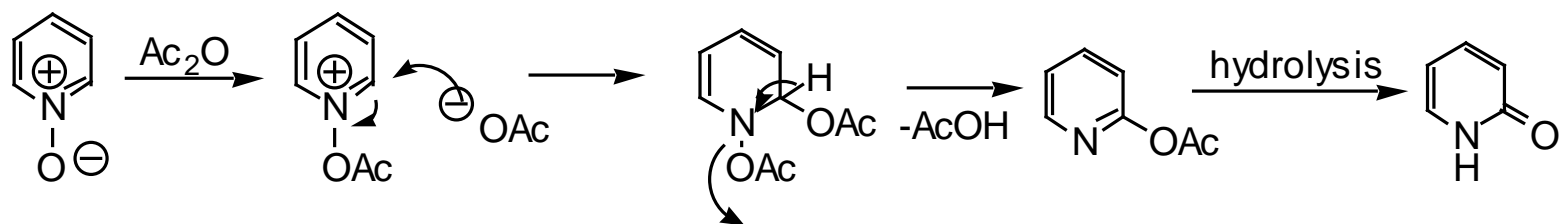
## Electrophilic Ar. subst



c.f. Electrophilic Ar. subst on pyridine  
pyridinium cation



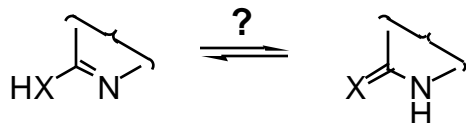
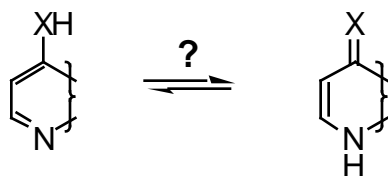
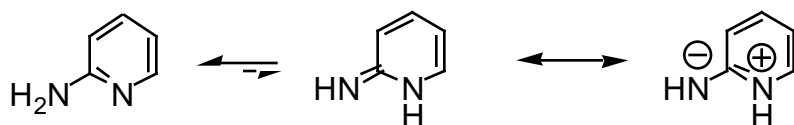
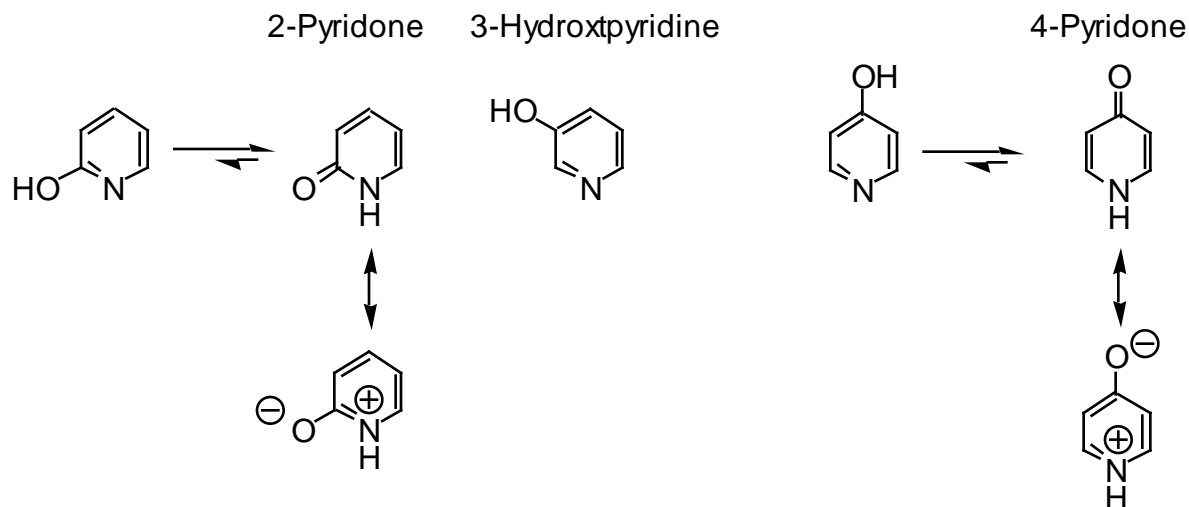
## Rearrangements





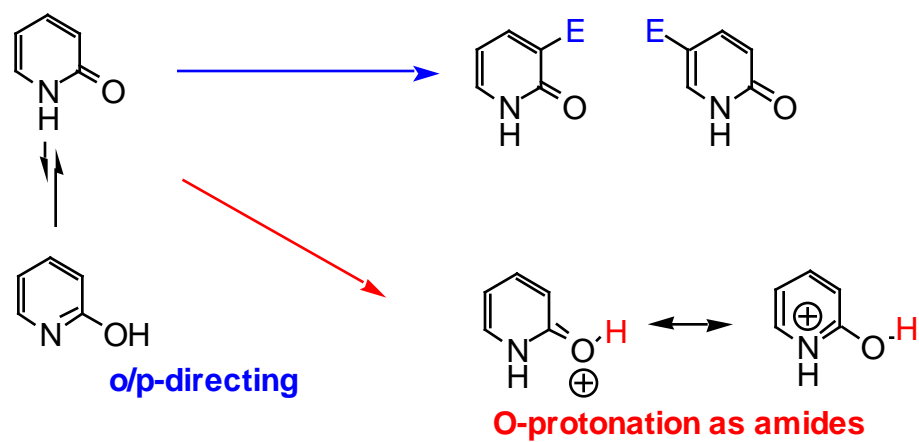
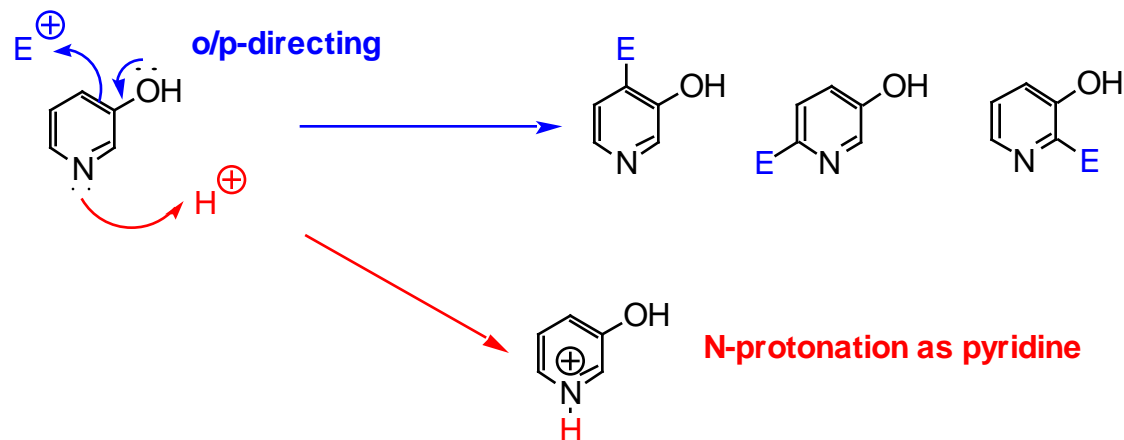
# Oxy-, Thio- and Aminopyridines

## Structure - Tautomerism

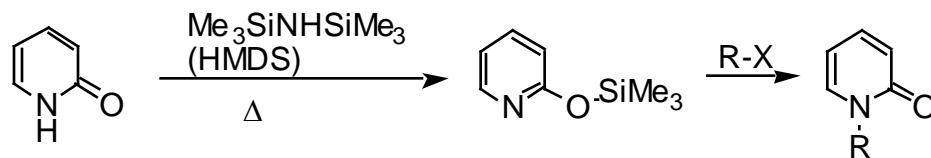
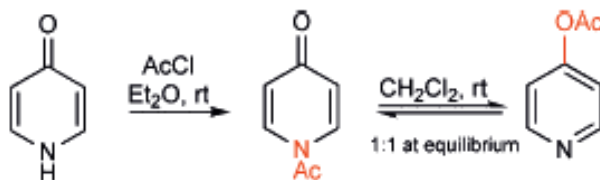
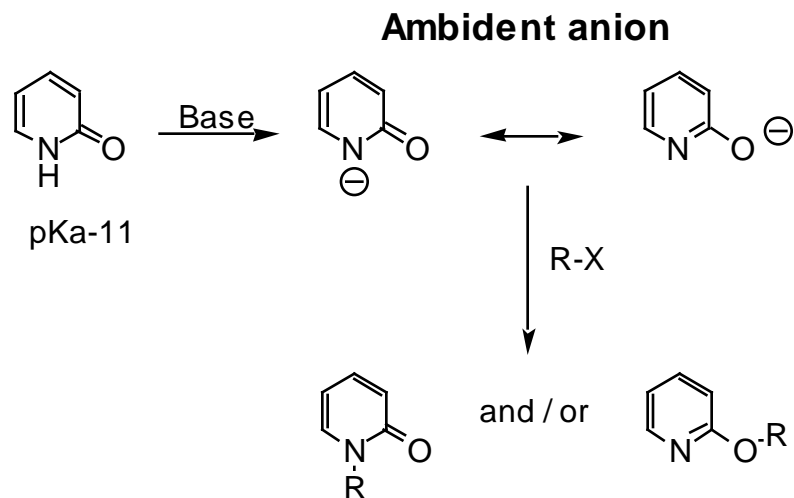


X=O: **one** / hydroxy  
 X=NR: imino / **amino**  
 X=S: thione (6-membered rings) /  
 thiol (5 membered)

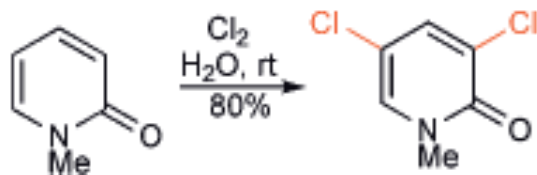
## Reactions on Pyridones - With Electrophiles



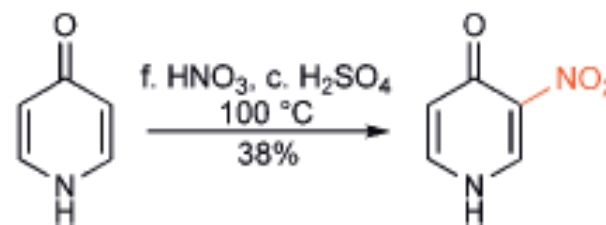
# Reactions on Pyridones - Deprotonation - O or N-substitution



Substitutions usually proceed *via* attack on the neutral pyridone,<sup>156</sup> but in very strong acid, where there is almost complete *O*-protonation, 4-pyridone undergoes a slower nitration, *via* attack on the salt, but with the same regioselectivity.<sup>157</sup>

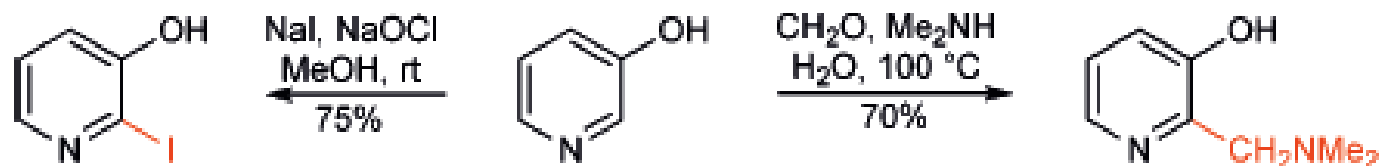


milder

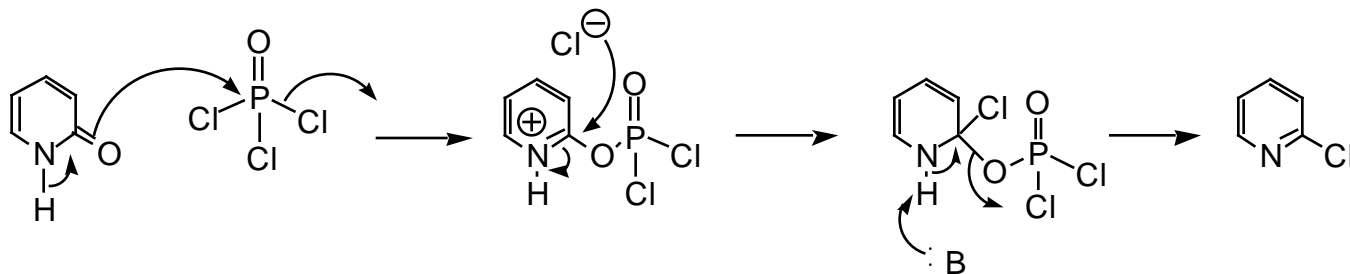


More difficult

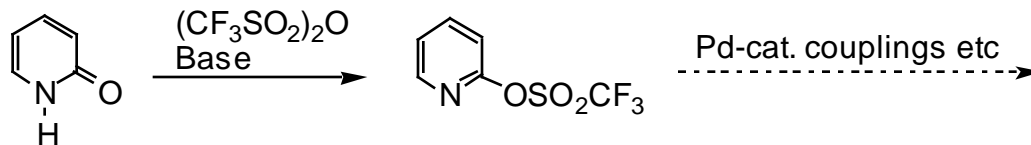
Electrophilic substitutions of 3-hydroxypyridine take place at C-2, for example nitration, Mannich substitution and iodination.



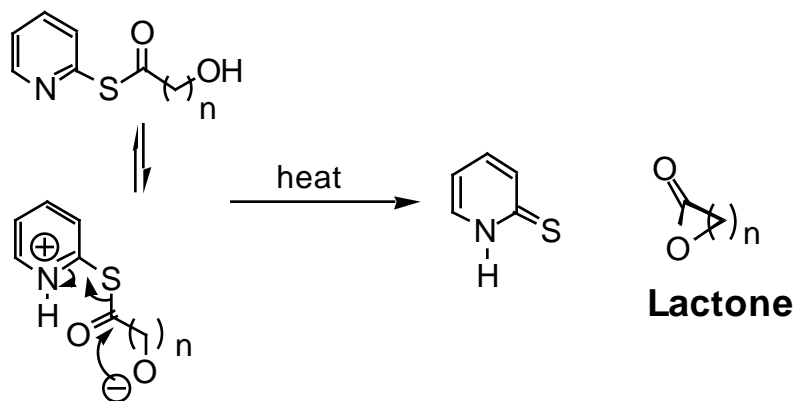
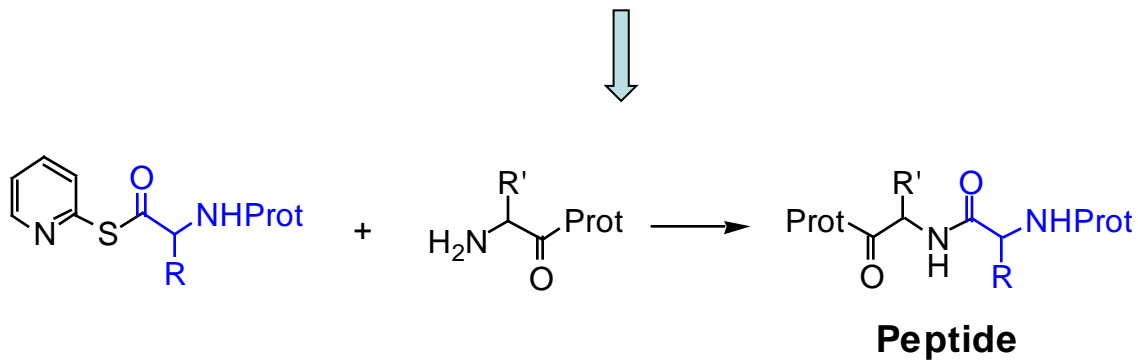
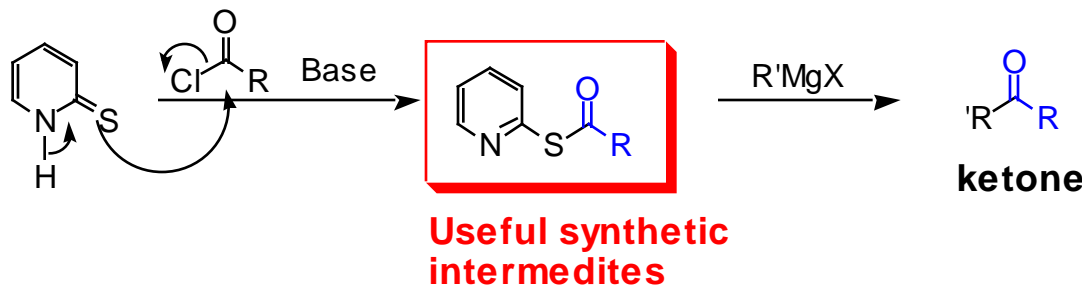
## Reactions on Pyridones - Replacement of Oxygen



### Triflate

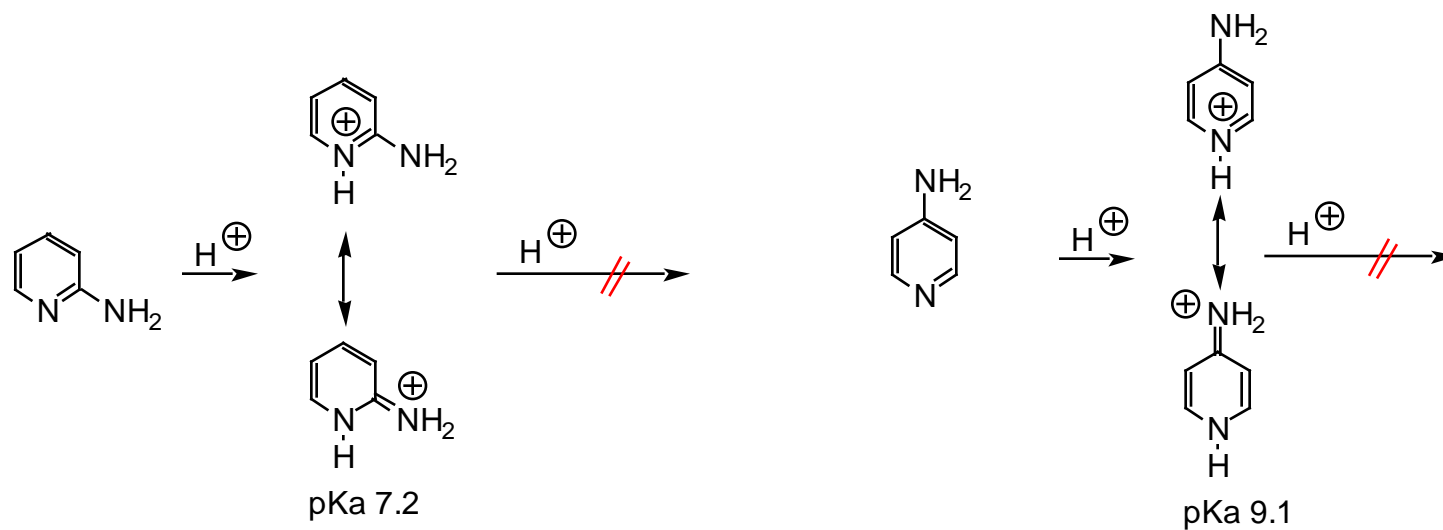


# Thiopyridones

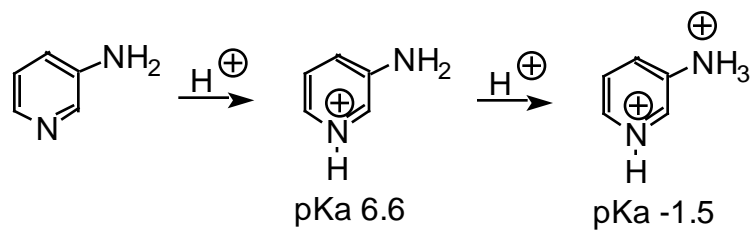


# Aminopyridines

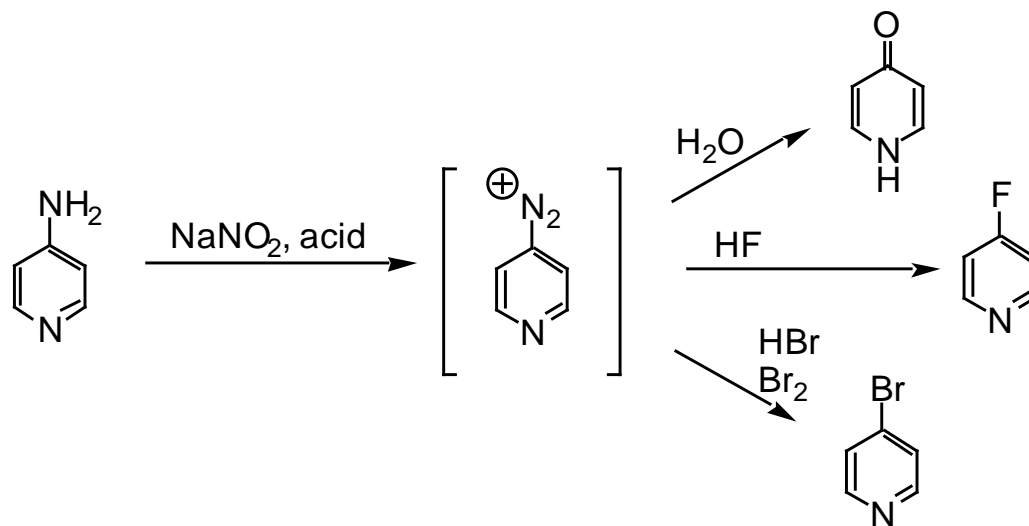
$\alpha$ - and  $\gamma$ - are monobasic:



$\beta$ - is dibasic:

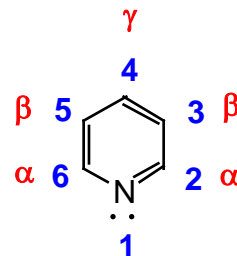




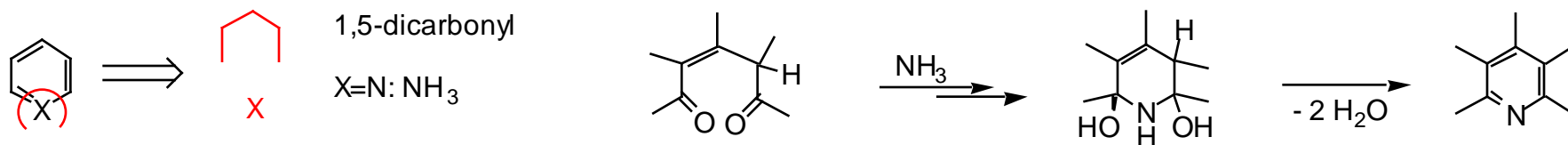


# PYRIDINES

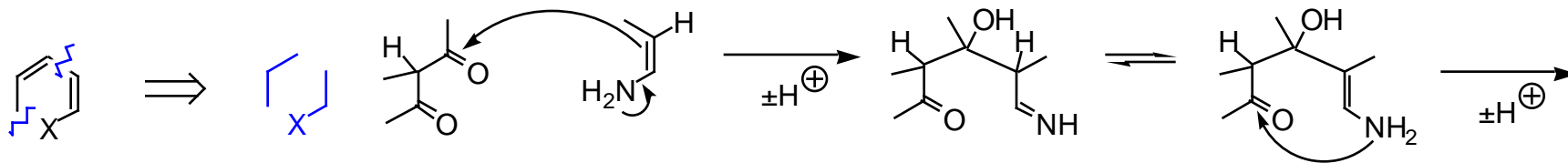
## Synthesis of Pyridines



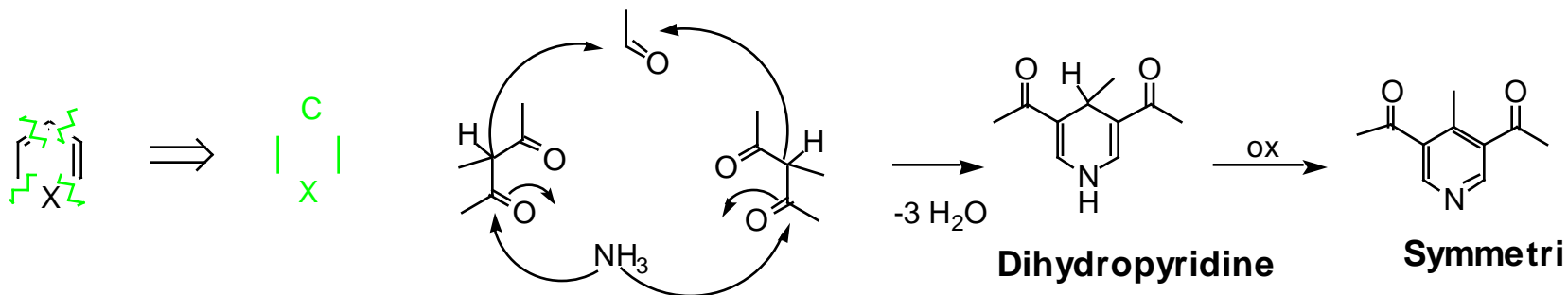
### From 1,5-dicarbonyl and ammonia (c.f. chapt. 3)



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

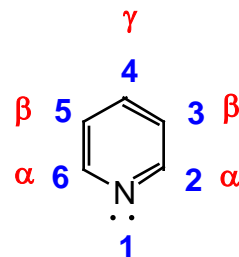


### From 2 equivs. 1,3-dicarbonyl, aldehyde and ammonia - Hantzsch Synthesis



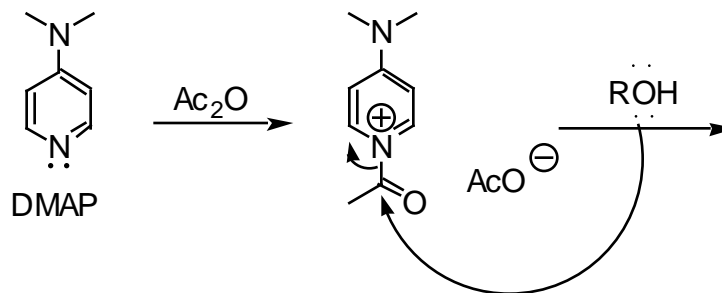
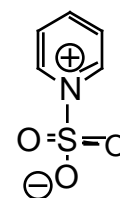
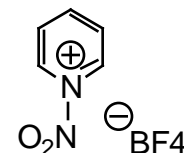
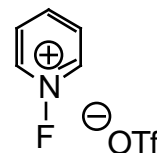
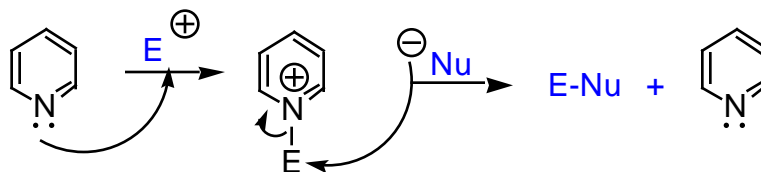
### Various syntheses from other heterocycles

# PYRIDINES

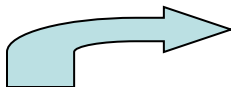


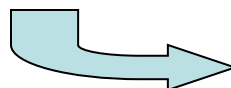
## Reaction with electrophiles - react. on N:

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



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

Difficult  Electron defficient / Poor nucleophiles

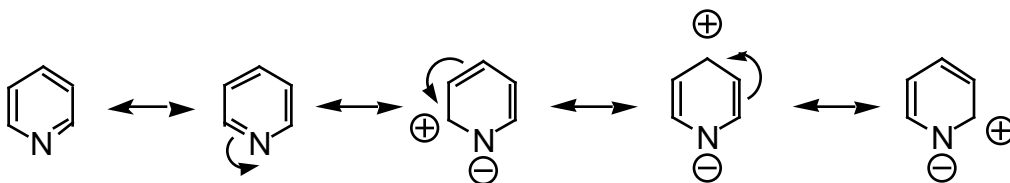
 Electrophiles may react at N

- Nitration
- Sulfonation
- Halogenation

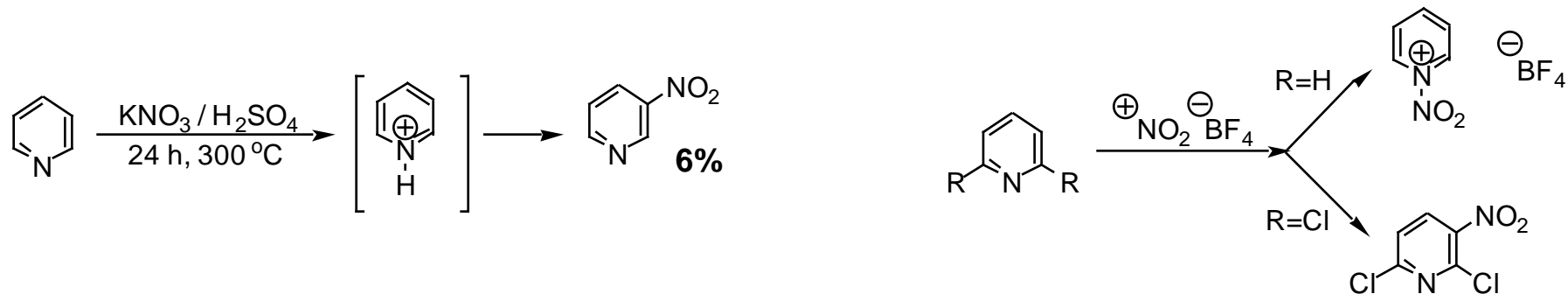
} React. in 3-pos.

Not:

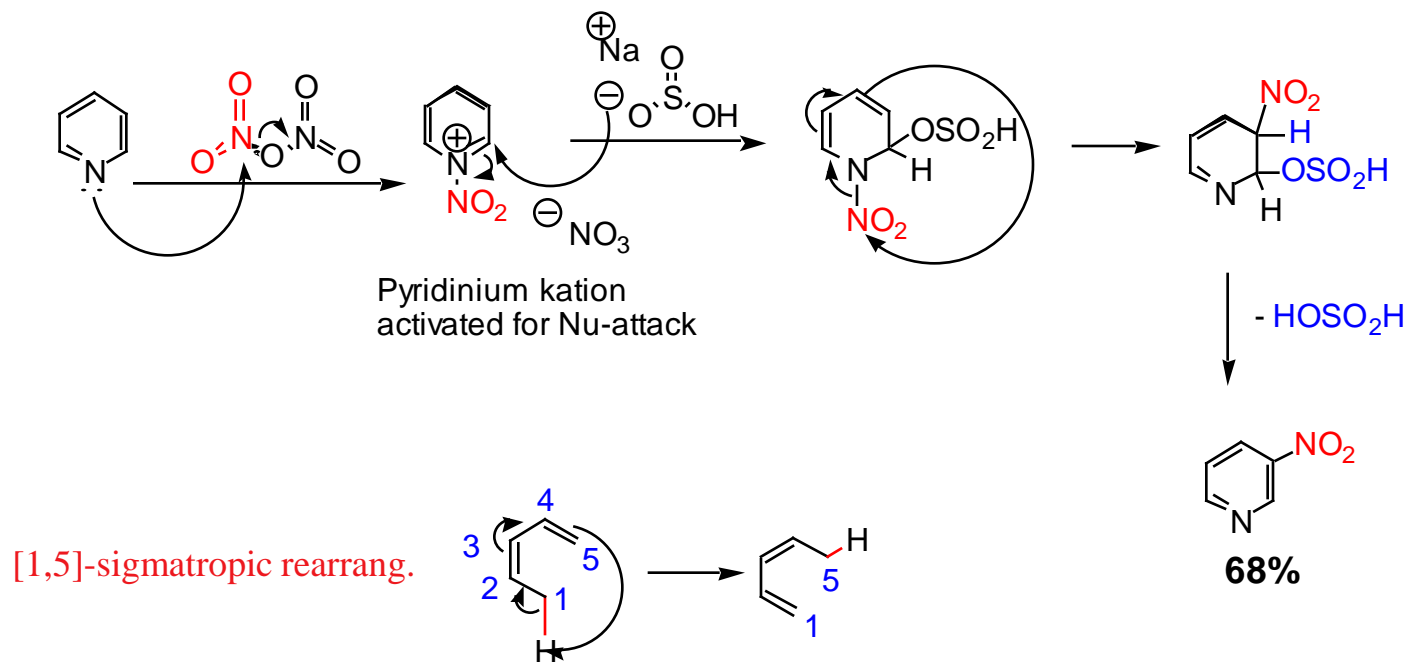
- FC alkylation
- FC acylation



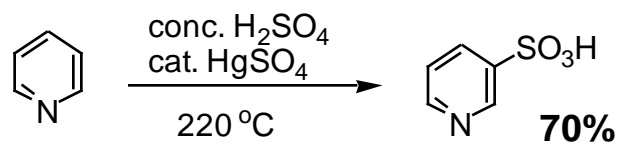
# Nitration



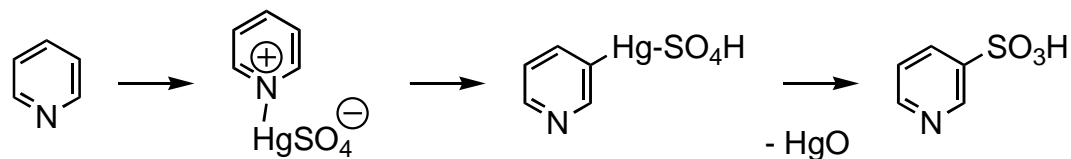
Bakke:



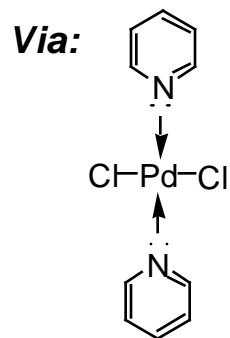
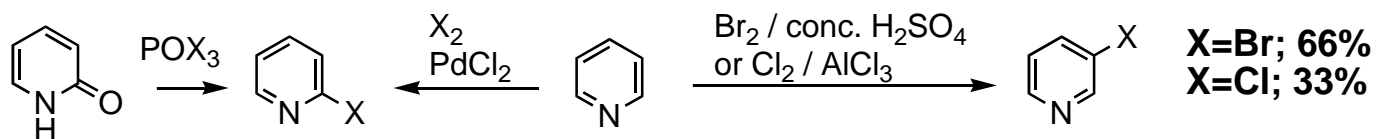
## Sulfonation



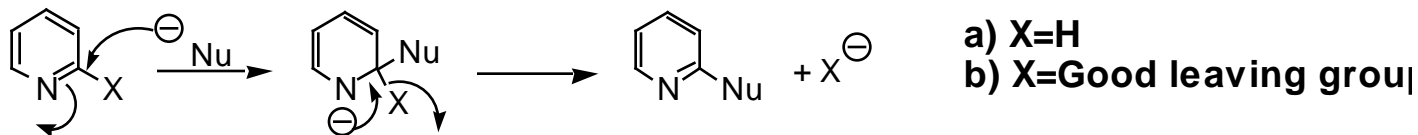
## Possible intermediates



## Halogenation



# Reaction with Nucleophiles



## a) $X=H$ , Substitution with “hydride” transfer

Nu:  $\text{NaNH}_2$  - amination - Chichibabin reaction

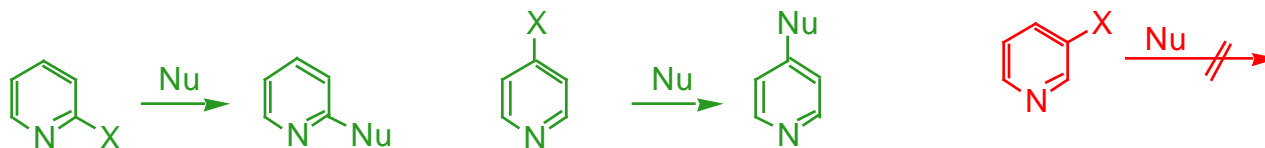
Nu:  $\text{BuLi}$ ,  $\text{PhLi}$  etc - alkylation / arylation

Nu:  $\text{NaOH}$  - “hydroxylation” - NB! High temp

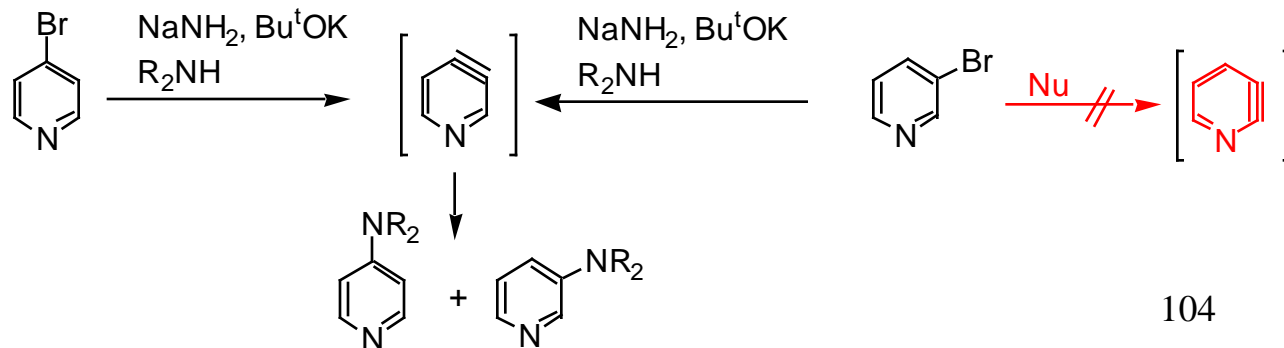
} Attack in the 2-pos (not 4-pos)

## b) $X=\text{LG}$ , Displacement of good leaving group

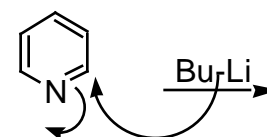
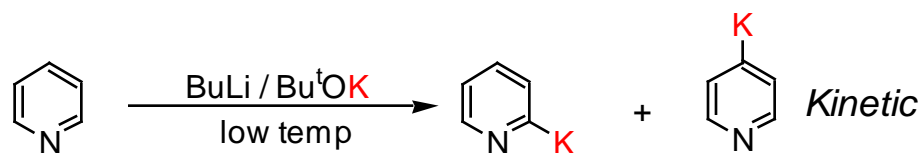
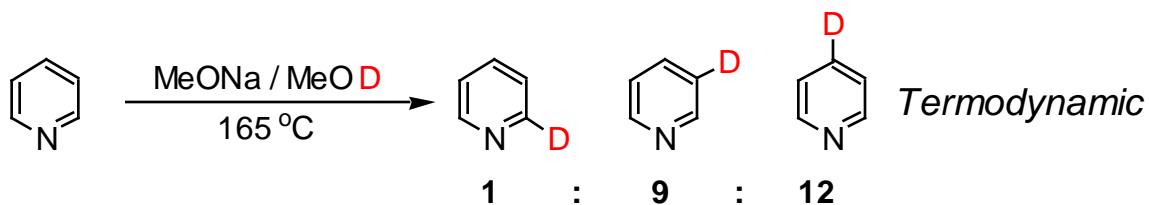
$X$ : Halogen ( $\text{F} \gg \text{Cl} > \text{Br} > \text{I}$ ),  $-\text{OSO}_2\text{R}$ ,  $-\text{NO}_2$ ,  $-\text{OR}$



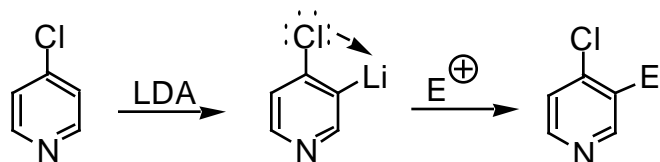
Via Pyridyne



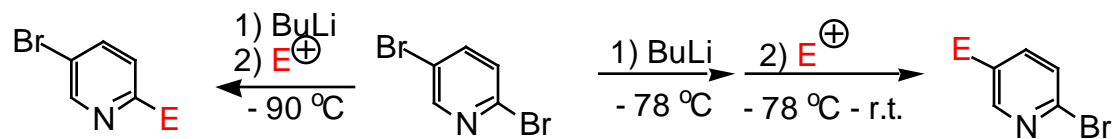
# Metallation and Reactions with Electrophiles



**Orthodirecting subst.**

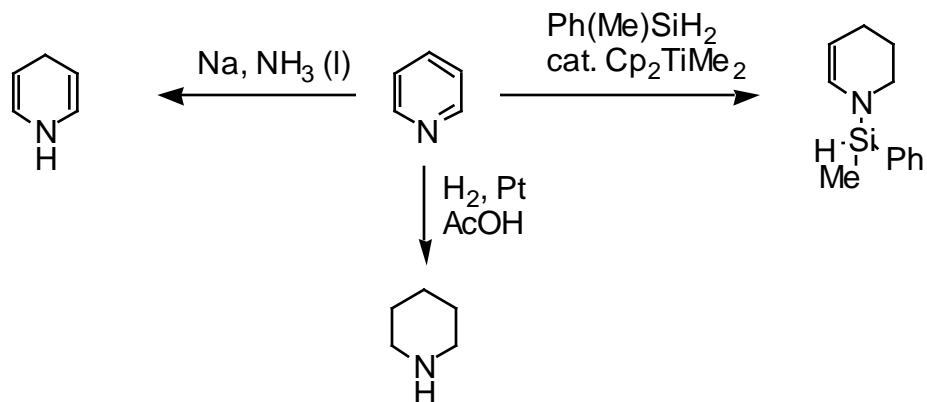


## Metal - Halogen Exchange

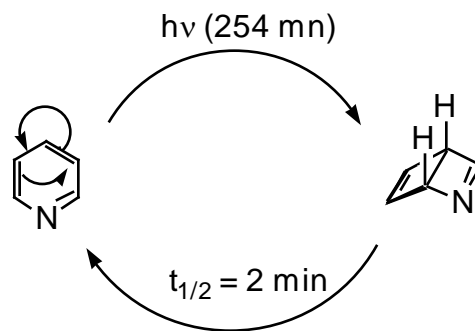




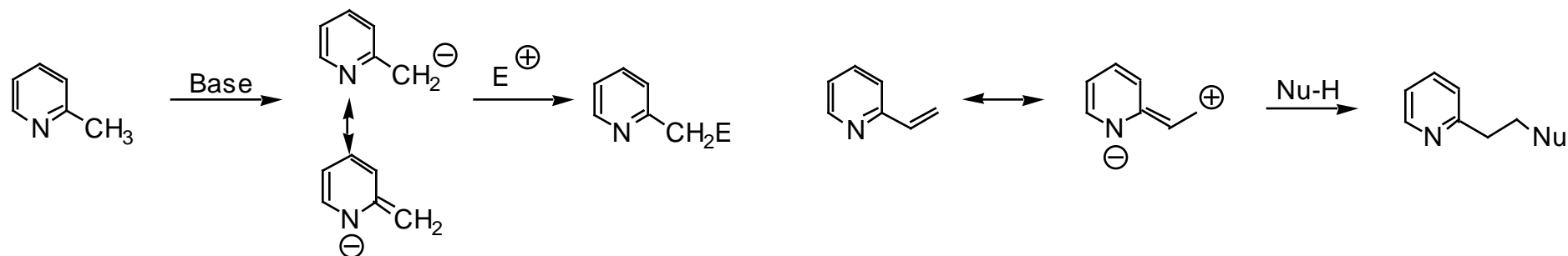
## Reductions



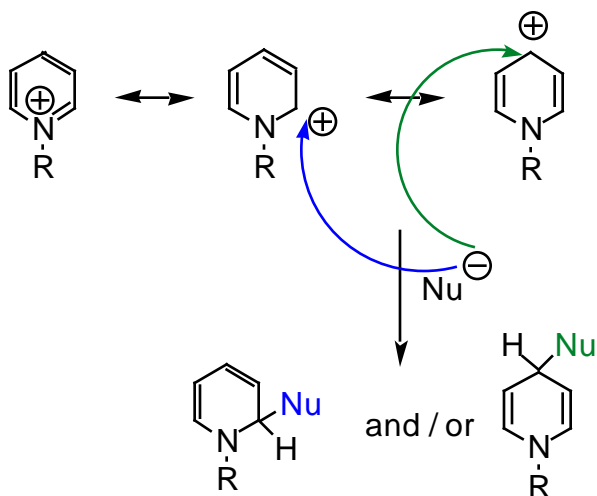
## Photochemistry



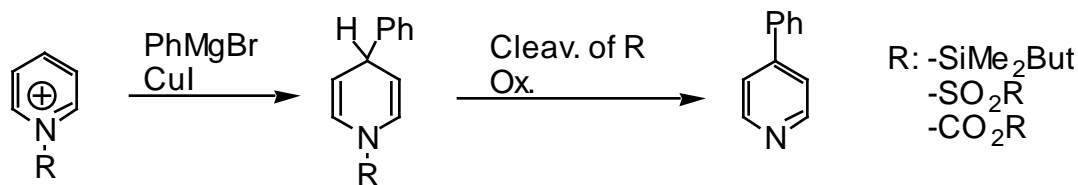
# Alkyl- and Vinylpyridines



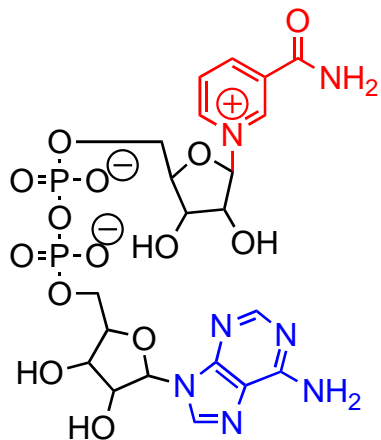
# Quaternary Pyridinium Salts



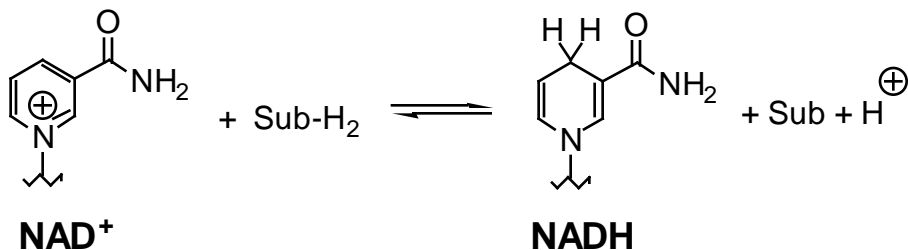
Add of: -hydrides  
-dithionite  
-organometallics  
-stab. carbanions  
etc. etc.



R: -SiMe<sub>2</sub>But  
-SO<sub>2</sub>R  
-CO<sub>2</sub>R



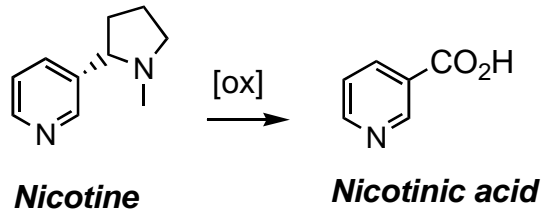
Co-enz.  
NAD<sup>+</sup>



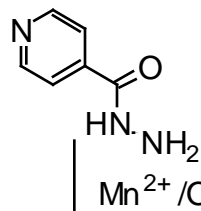
Hydride add. to NAD<sup>+</sup>, SubH<sub>2</sub> oxidized

Nicotine amide: Vit. B<sub>3</sub>

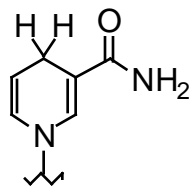
Adenine: Vit. B<sub>4</sub>



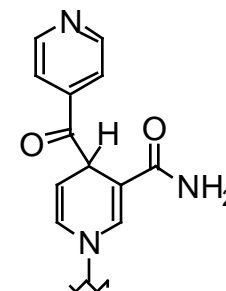
Isoniazide  
Antituberculosis drug



Active acyl radical  
formed *in vivo*



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



Inactive der. of co-en