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REVIEW ON THE METALLATION OF π-DEFICIENT HETEROAROMATIC COMPOUNDS

REGIOSELECTIVE ORTHO-LITHIATION OF 3-FLUOROPYRIDINE: DIRECTING EFFECTS AND APPLICATION TO SYNTHESIS OF 2,3- OR 3,4-DISUBSTITUTED PYRIDINES

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Abstract—Metallation of π-deficient heterocyclic compounds is first reviewed, which shows the important recent developments in this research area. A particular aspect of this reaction is then given with the study of the 3-fluoropyridine metallation regioselectivity.

Lithiation of 3-fluorophyridine is chemoselective at low temperatures using butyllithium–polyamine chelates or lithium diisopropylamide. Protophilic attack by these strong bases can be directed either at the 2- or 4-position depending on the lithiation conditions. Various reaction parameters are thus studied such as solvent, temperature, reaction time, lithium-chelating agent as well as metallating agent. The high regioselectivity of 3-fluoropyridine lithiation is theoretically discussed, in particular in terms of kinetic of thermodynamic control of the metallation. Chelation between butyllithium and 3-fluoropyridine is proposed, which completely modifies the heterocycle reactivity toward the lithiating agent. This is confirmed by theoretical quantum calculations performed on different models of 3-fluoropyridine using the CNDO/2.

These results allow to select the best 3-fluoropyridine-metallation conditions which lead to 3-fluoro-2-lithiopyridine on the one hand and to 3-fluoro-4-lithiopyridine on the other hand. Each of the lithiated isomers is then reacted with a great variety of electrophiles which gives very conveniently the corresponding 2, 3- or 3, 4-disubstituted pyridines.

INTRODUCTION

Many substituents can induce beta (or ortho) metallation[1] in the *homoaromatic* or the π-excessive heteroaromatic series (thiophene, furan, pyrrole . . .). These ortho-directing groups generally contain one heteroatom (N, O, S, halogen . . .) and may act according to two different ways:[2]

Chelation effect. Metal chelation by the heteroatom enhances the strong base reactivity (alkyllithiums) and deprotonation occurs at the nearest acidic site.

Inductive effect. The substituent heteroatom provides an inductive electron-withdrawing effect which first increases the ortho-hydrogen acidity and secondly stabilizes the resulting lithiated species.

Borderline mechanism often manages the proton-abstraction step (Fig. 1).

Metallation of π-deficient heterocycles (pyridine, quinoline, diazines . . .) by metal–hydrogen exchange has been only recently studied, mainly during the last five years. This reaction is a very attractive functionalization method, in as much as electrophilic substitutions are often difficult to insert in these series. (It is frequently hard to prepare polysubstituted derivatives, some of which are key synthons to new potentially active products.)

Metallation of π-deficient heterocycles (promoted by lithium alkyls and amides) has been masked for a long time by numerous competitive reactions.[3] Nucleophilic attacks on these moieties produce these reactions which must be avoided and which will be first summarized. We shall then show that metallation can be achieved at low temperatures by use of strong metallating reagents and by introducing suitable ortho-directing substituents on the substrates.

I. *Competitive reactions during metallation of π-deficient heterocycles*

As early as 1930, Ziegler[4] studied the organolithium addition to the pyridine imine bond, which leads to 2-alkyl-1, 2-dihydropyridine (I). 1, 2-Addition is fol-

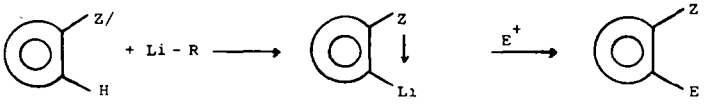
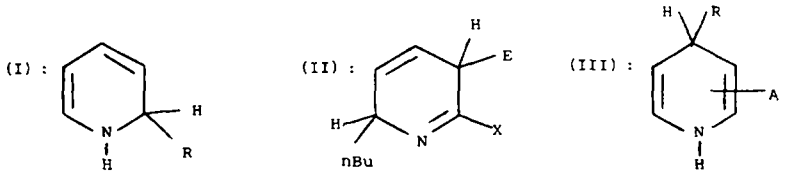


Fig. 1.

lowed in some cases by electrophilic reaction at the 5-position and 5-substituted-2-alkylpyridines are obtained.[5] This reaction proceeds via 2, 5-dihydropyridines,[6] which are known to be very unstable. However, we proved[7] that butyllithium reacts with 2-chloro- or 2-fluoropyridine to give 2-butyl-6-halogeno-2,5-dihydropyridine (II) which are isolated and structurally studied. 1,4-Additions are sometimes observed with Grignard reagents and NADH analogues are obtained (III). This type of reaction, which occurs more rarely with alkyl- or aryllithiums, has been reported by Meyers[8] on 3-oxazolinylpyridine.



Additions are often followed by rearomatization either by oxidation or by elimination ($SNAr_2$) in the case of halogenated heterocyclic derivatives.[9] Strong bases such as alkyllithiums also induce on halogenopyridines and quinolines elimination–addition reactions via an hetaryne-mechanism.[10]

Some nucleophilic attacks on pyridine or quinoline compounds cause ring-openings.[11] Substituted butadienes[12] are obtained, which can then cyclise[13] again, as described in the pyrimidine series[11] (Fig. 2).

Coupling reactions have been reported by Kauffmann[14] and Meth-Cohn[15] when reacting lithium dialkylamides in the presence of HMPT with pyridine, pyrimidine,[16] quinoline and isoquinoline: these reactions were recently showed by Newkome[17] to proceed via a radical anion. Reaction between alkyllithium and brominated derivatives of pyridine[18] and quinoline sometimes gives rise to halogen-dance reactions.[19]

II. *Main directed metallation of π-deficient heterocycles*

The previous side reactions can be avoided by use of low temperatures and powerful metallating agents as well as by introducing a convenient ortho-directing group on the heterocycles. The most important ortho-directing substituents in lithiation of pyridines, quinolines, and pyrimidines are halogens, alkoxy, and protected amines, ketones and carboxylic acids derivatives.

Historically, as early as 1967 numerous pyridine N-oxides have been metallated by Abramovich,[20] but the first pyridine metallation was reported by Wakefield in 1969 with highly activated polychloropyridines.[21] In 1972, we succeeded in metallating various monohalo-[22] and dihalo-pyridines,[23] which already showed the synthetic usefulness of this reaction. At the same time we lithiated 3-ethoxypyridine[22] and Narasimhan[24] reported metallation of 2-ethoxyquinoline. When butyllithium addition becomes too fast (in the case of monofluoroquinolines for examples) we proved that the use of a less nucleophilic reagent such as LDA (lithium diisopropylamide)[25] makes metallation completely chemoselective. Research of new ortho-directing groups and applications to heterocyclic synthesis will then be the two main axis of metallation development in these series.

(1) *Metallation of halogenated π-deficient heterocycles*

Lithiation of *2-chloro- and 2-fluoropyridines* with alkyllithiums is competitive with additions, which can be avoided as for haloquinolines[25] by use of a less nucleophilic metallating agent such as LDA.[26]

This reagent allows lithiation of *2-bromopyridine* without halogen–metal exchange.[27] Metallation proves to be a powerful functionalization method starting from readily prepared compounds. 2-Halo-3-substituted pyridines have been obtained which are attractive due to the 2-halogen moiety: 2-Amino-3-acyl or aroyl pyridines are synthetized[26] by the fast and convenient method shown below (Fig. 3).

Some of these derivatives are key molecules in the elaboration of azaacridines,[28] pyridodiazepines[29] and azaellipticines.[30] Metallation of *2-bromopyridine* shows an additional interest due to the great reactivity of the 2-bromine via SRN_1 reactions, in particular with enolates.[31] Excess metallating agent induces the 2-bromopyridine ring-opening and the same time lithiation (Fig. 4).

3-Halopyridines give with an excellent regioselectivity the corresponding 4-carbanions by action of butyllithium in polar solvent[22] or by reaction with LDA.[32] A great variety of 3, 4-disubstituted pyridines are thus prepared. Even though 3-chloro- and 3-fluoro-4-lithiopyridines are quite stable at low temperatures, the brominated isomers give rise to a "halogen dance" reaction: 3-bromo-4-substituted or the more stable 4-bromo-3-substituted pyridines[33] are obtained depending on the reaction conditions. Halogen migration proceeds likely via a dibromo species[33] (Fig. 5).

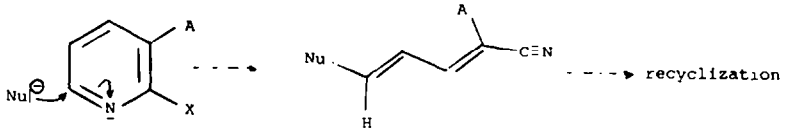


Fig. 2.

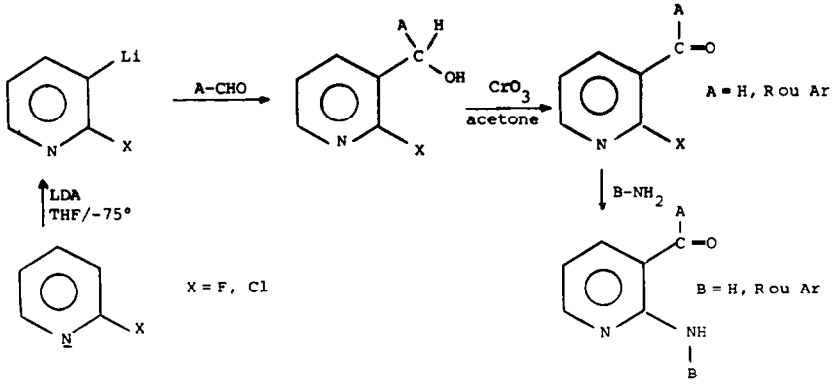
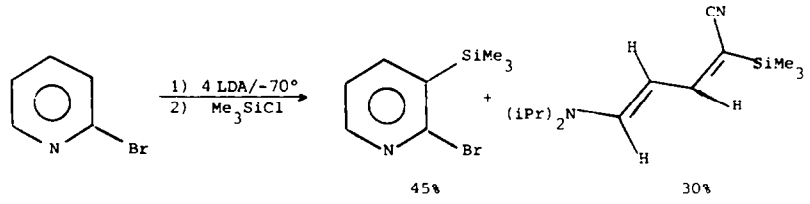


Fig. 3



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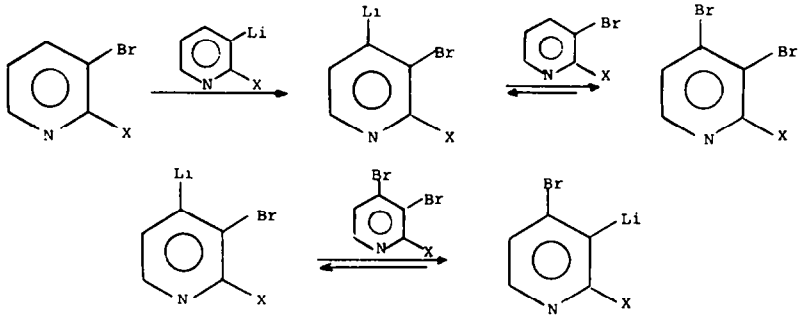


Fig. 5.

3-*Chloro-*[34] *and* 3-*fluoropyridines* can be lithiated at the 2-position by use of butyllithium–polyamine chelates. The surprising solvent dependent regioselectivity will be studied in the second part of this report.

4-Halo-3-substituted pyridines have been prepared by lithiation of 4-*fluoro- and* 4-*chloropyridines*,[35] respectively, by the butyllithium–TMEDA chelate and LDA.

Metallation of *fluoroquinolines* is difficult to realize due to the particular reactivity of this heterocycle toward nucleophiles. Butyllithium leads exclusively to 1, 2-additions excepted with 2-*fluoro- and* 7-*fluoro-quinolines* which are competitively metallated at position 3 and 8,[25] respectively (Fig. 6).

Reactions become completely chemoselective by use of LDA at $-60°$ and regioselectivity is directed by relative acidities of the hydrogens ortho to

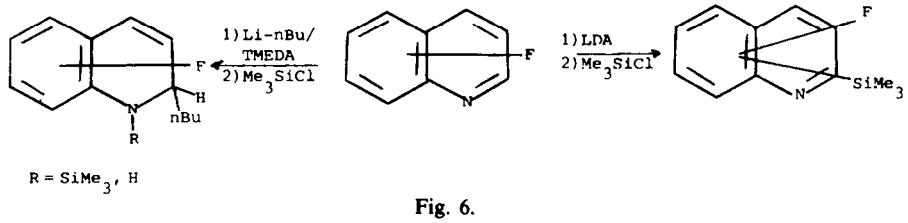


Fig. 6.

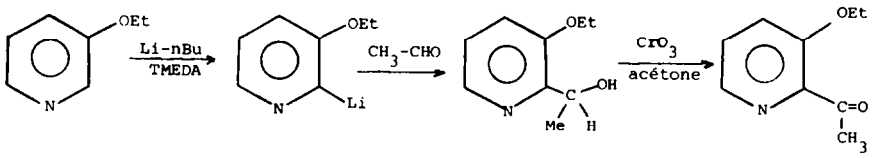


Fig. 7.

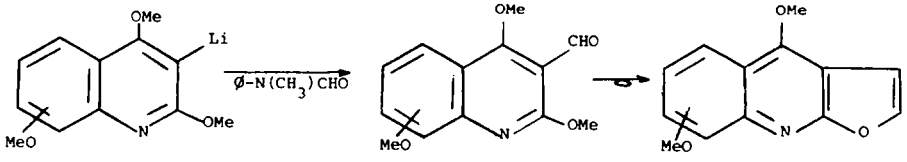


Fig. 8.

fluorine. Thus 3-*fluoro*-, 5-*fluoro*- *and* 7-*fluoroquinolines* react, respectively, at position 4, 6 and 8; whereas, 6-*fluoroquinoline* is lithiated at positions 5 and 7 (80 and 20%).[25]

It should be pointed out however that attempts to metallate 8-*fluoroquinoline* remained unsuccessful, most likely because the fluorine and nitrogen juxtaposition forms a powerful lithium chelating site which keeps the metallating agent too far from proton 7.

In the pyramidine series, Kress[36] reported metallation of the 5-*bromo compound* in the position ortho to bromine. This reaction can be followed by formation of a dimeric derivative.

(2) *Metallation of alkoxylated π-deficient heterocycles*

Several 3-alkoxypyridines have been lithiated by the butyllithium/TMEDA chelate[22] and best yields were obtained with 3-*ethoxypyridines*.[37] The reaction is completely regioselective at position 2 and leads to new 2, 3-disubstituted pyridines (Fig. 7).

3-Ethoxy-2-lithiopyridine is an exceptionally stable carbanion in these series (stable up to 0°) but it slowly changes to the thermodynamically more stable 4-lithio isomer after several hours at room temperature.

Whereas 2-*ethoxyquinoline* has been metallated only in poor yields,[24,38] 2, 4-*dimethoxyquinoline* has been lithiated at position 3 in good conditions. Narasimhan[39] thus has prepared many natural alkaloids such as pteline, evolitrine, γ-tagarine... (Fig. 8) using this technique.

Ranade[40] reacted 2, 4-dimethoxy-3-lithioquinoline with benzonitrile, which gave after acidification pyrimido[4, 5-c]quinoline.

(3) *Metallation of a protected pyridine ketone*

Metallation of *pyridine ketones* (blocked as ketal or otherwise) seems very attractive, but only one reaction was reported by Newkome.[13] Butyllithium reacts with bis(2-pyridyl)ketone-1, 3-dioxolane at different temperatures (from $-78°$ to $-20°$) and the lithiated species are quenched by deuteriolysis. Newkome also described a ring-opening reaction resulting from nucleophilic attack (Fig. 9).

(4) *Metallation of protected pyridine carboxylic acids*

Easily accessible pyridinecarboxylic acids are interesting starting products for preparation of orthodisubstituted pyridines. Elaboration of such synthons has been attempted by metallation of pyridinecarboxylic acids, whose hydroxy carbonyl group has been protected as *oxazolines, amides or esters*. Metallation of 3- *or* 4-(4,4-*dimethyl*-2-*oxazolinyl*)-*pyridines* (prepared from nicotinic or isonicotinic acid) was achieved by Meyers.[41] Lithiation was regioselectively directed by oxazolinyl group at position 4 and 3 respectively, and various lactones were obtained (Fig. 10).

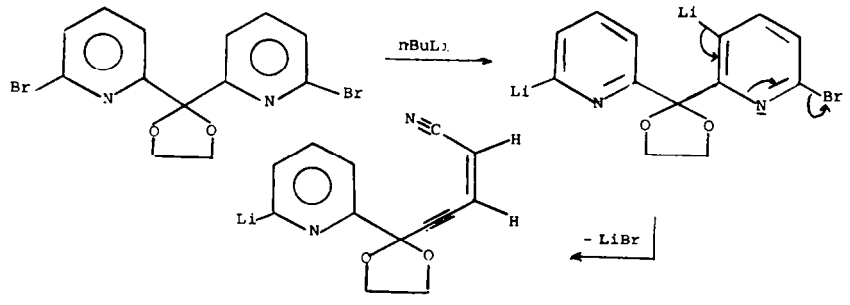


Fig. 9.

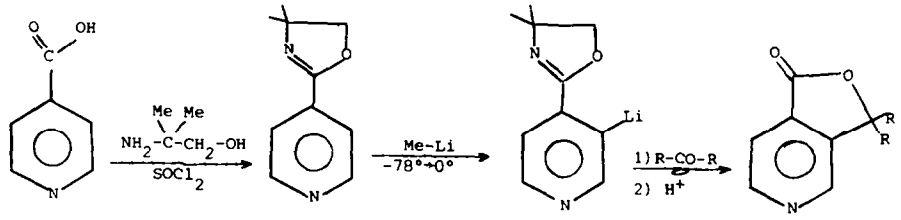


Fig. 10.

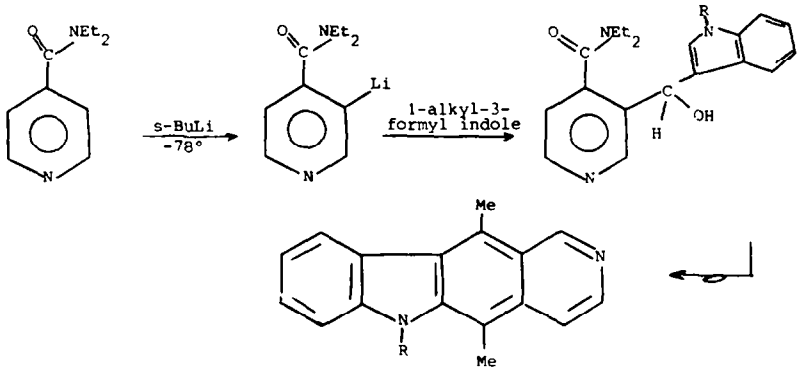


Fig. 11.

Snieckus successfully metallated 4-(*N,N-diethylaminocarbonyl*) *pryidines*;[42] this reaction gives rise to a very convenient synthesis of ellipticines[43] (Fig. 11).

Lithiation of 2-(N-*benzylaminocarbonyl*)*pyridine* was reported by Katritzky,[44] who used butyllithium in THF at $-78°$ before reacting the lithiated intermediate with acid chlorides (Fig. 12).

Metallation of 2-, 3- *and* 4-(N, N-*diisopropylaminocarbonyl*)*pyridines* was achieved by Epsztajn[45] with LDA at $-78°$. Under the same conditions diethylamides gave self-condensation; whereas, dimethylamides gave nitrogen trans-alkylation.

Sole ester metallation has been described by Ferles,[46] who reacted *ethyl nicotinate* with LDA. As with ethyl benzoate,[47] the resulting carbanion adds to the starting compound, which leads to the corresponding ketone.

We have been recently interested in metallation of *aminopyridines* and the various reaction conditions were checked with 3-*aminopyridine* (amine function was protected as pivalamido group). Lithiation by the butyllithium/TMEDA chelate at room temperature is chemoselective and regioselective at position 4 (Fig. 13).

This reaction is a powerful synthetic method to

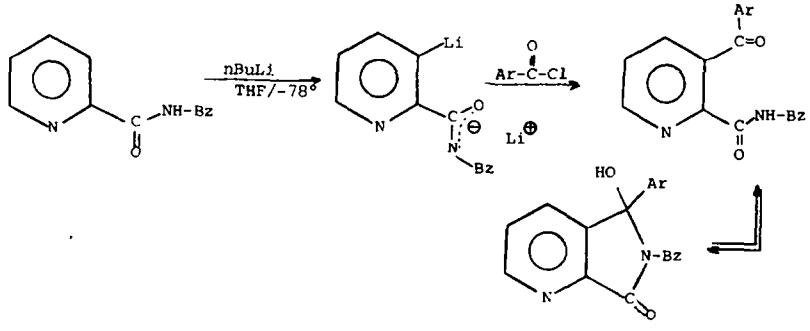


Fig. 12.

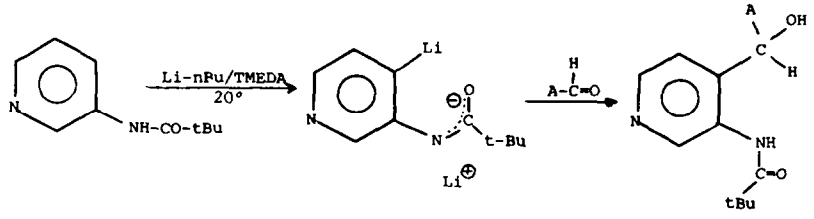


Fig. 13.

3-amino-4-carbonylated pyridines, since it is always difficult to introduce an amino group at position 3 of substituted pyridines. Some of these ortho-difunctional derivatives should afford a new and fast synthesis of polycyclic compounds such as ellipticines, diazepines...

In the same way Tamura[49] achieved the lithiation of a *bis*-activated pyridine, 3-methoxy-5-pivalamidopyridine.

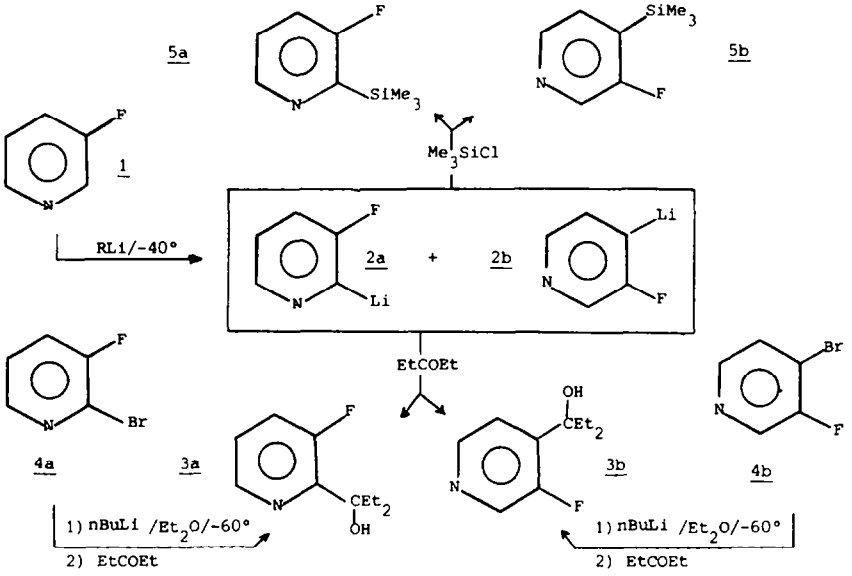
At the present time we can observe a real development in the π-deficient heterocyclic metallation field. The main part ot this work is synthetic however some work has been done on the theoretical aspects, neither about the lithiation mechanism nor the lithiated species structure. Newkome recently suggested a mechanism for the reaction between pyridine and LDA.[17] In the same manner nobody has been interested in the 3-substituted pyridines-lithiation regioselectivity, thus we report here in that 3-fluoropyridine can be metallated either at position 2 or position 4, depending on the reaction conditions. The regioselectivity of that reaction is very high and can be theoretically discussed. It opens the field to 2, 3- or 3,4-disubstituted pyridines starting from 3-fluoropyridine by simple modification of the metallation conditions.

RESULTS

I. *Metallation of 3-fluoropyridine: conditions and regioselectivity*

Reaction of n-BuLi with 3-fluoropyridine (**1**) at $-40°$ in THF (tetrahydrofuran) or in Et_2O(ethyl ether) solution gives a mixture of 3-fluoro-2-lithio- (**2a**) and 3-fluoro-4-lithio-pyridine (**2b**). Lithiated derivatives **2a** and **2b** are quenched by reaction with 3-pentanone which leads after hydrolysis to the corresponding alcohols **3a** and **3b** (Scheme 1, Table 1).

Assignments of the structure **3a** and **3b** are based on the ^1H NMR spectra of the same derivatives prepared by halogen-metal exchange starting from 2-bromo-3-fluoro- (**4a**) and 4-bromo-3-fluoropyridine (**4b**), respectively (Scheme 1).



Scheme 1.

Table 1. Directing effects on the metallation of 3-fluoropyridine at $-40°$ for $\frac{1}{2}$ hr.

Metallation conditions		Metallation of the 2-position	Metallation of the 4-position
Metallating agent	Solvent	Yields of 3a	Yields of 3b
nBuLi	Et_2O	25%	15%
nBuLi	THF	10%	30%
nBuLi /TMEDA	Et_2O	65%	10%
nBuLi /TMEDA	THF	None	
		Yields of 5a	Yields of 5b
nBuLi /TMEDA	Et_2O	68%	3%
nBuLi /TMEDA	THF	None	75%

Table 2. Effect of the reaction time at $-40°$ on the metallation of 3-fluoro-pyridine in Et_2O with nBuLi/TMEDA

Reaction time at -40°	0h	1h	2h	4h	6h
Metallation at position 2 (yields of 5a)	60%	50%	40%	20%	5%
Metallation at position 4 (yields of 5b)	5%	16%	30%	50%	70%

Table 3. Effect of the relocation temperature on the metallation of 3-fluoropyridine in Et_2O with nBuLi/TMEDA

Relocation temperature θ°	-60°	-50°	-40°	-30°
Reaction time	2h	2h	2h	2h
Metallation at position 2 (yields of 5a)	60%	60%	40%	2%
Metallation at position 4 (yields of 5b)	5%	5%	30%	73%

Fluorine at position 3 is a good activating and ortho-directing substituent toward metallation, and no side reaction, such as nucleophilic addition, can be observed during the lithiation of **1** as in the case of 2-fluoropyridine.[6]

The regioselectivity of this reaction depends on the solvent since formation of the 2-lithio intermediate is favored in Et_2O; whereas lithiation leads preferentially to the 4-lithio product in THF. This solvent directing effect is greatly enhanced by using butyllithium chelated with TMEDA and so are the overall yields of lithiation (Table 1).

II. *Metallation of 3-fluoropyridine in ethereal solution: temperature and reaction time influence*

In Et_2O, the 2 and 4 positions of **1** are both reactive toward lithiation and regioselectivity is very sensitive to various parameters such as reaction time and temperature. In order to quench the two lithiated isomers **2a** and **2b** and to analyze the resulting products conveniently, the metallation mixture is reacted with Me_3SiCl (Scheme 1). Distillation of the crude reaction product affords a mixture of the silylated compounds **5a** and **5b** (Table 1). Yields of **5a** and **5b** are obtained from GPC and NMR analysis of the distillated mixture (experimental section).

Temperature and reaction time effects. 3-Fluoropyridine (**1**) is reacted with nBuLi/TMEDA in Et_2O for 2 hr at $-60°$ and the resulting mixture is then kept at $-40°$ for varying times.

Reaction of the lithiated intermediates with Me_3SiCl affords a mixture of **5a** and **5b** in varying yields (Table 2).

Lithiation of **1** first occurs at $-60°$ at the 2 position and the relocation of the lithium atom from the 2 to the 4 position is favored by an increase of the reaction time at $-40°$ without significant change of the overall yields.

When the lithiation of **1** is performed at lower temperature, the shift of the lithium from the 2 to the 4 position is quite slow. Metallation at $-75°$ for 4 hr gives 73% of **5a** and 6% of **5b**; whereas, after 24 hr at the same temperature yields are 69% and 9%, respectively.

The equilibration of the 4-lithio derivatives also depends on the reaction temperature. The 2-carbanion is first formed in Et_2O for 2 hr at $-60°$ and the resulting solution is then warmed at different temperatures for additional 2 hr before quenching with Me_3SiCl. Results show that a small increase of temperature causes an important increase of the relocation rate (Table 3).

III. *Metallation of 3-fluoropyridine with butyllithium: solvent effect*

Lithiation of 3-fluoropyridine (**1**) occurs at position 4 exclusively in THF with TMEDA and does not depend on reaction time and temperature; further reaction with Me_3SiCl gives **5b** both at $-75°$ for 18 hr and at $-40°$ for 2 hr in very similar yields (75%).

IV. *Metallation of 3-fluoropyridine with lithium diisopropylamide*

When metallation of 3-fluoropyridine is performed with lithium diisopropylamide (LDA)[32] either in THF or ethyl ether at $-75°$, 3-fluoro-4-lithio pyridine (**2b**) is exclusively obtained. Reaction of **2b** with chlorotrimethylsilane gives a 75% yield of the 4-silylated product **5b**. It is interesting to note that excess of metallating agent produces a second lithiation at position 2, that leads to the corresponding disilylated derivative **6** (Table 4).

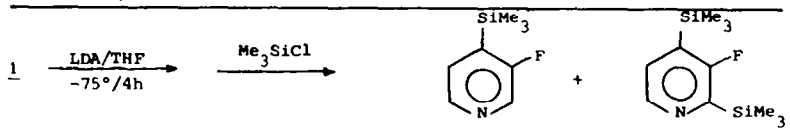
These results show that the 2 position of **1** is also reactive toward LDA but less than the 4 position.

DISCUSSION

A model widely accepted for the lithiation mechanism involves a four center transition state,[50] but it is actually too simple to give a clear idea of the intimate process.

Attempts to reveal monoelectronic transfer during

Table 4. Effect of LDA excess on the metallation of 3-fluoropyridine (1)



LDA / 1	5b	6
1	75%	0%
1,1	78%	7%
2	16%	70%

lithiation of homoaromatic derivatives[51] remained unsuccessful, which is not the case in the π-deficient heteroaromatic series.

Recently, Ashby[52] and Newkome[17] have shown that LDA can induce a monoelectronic transfer with easily reducible compounds. Newkome[17] has proposed that the pyridine dimerization occurs via an one-electron transfer. We also think that a radical anion intermediate may be the first step of π-deficient heterocycles lithiation (Scheme 2).

It is likely that 3-fluoropyridine is more reactive toward electron-donors than pyridine itself and that a radical-anion intermediate may be first formed[17], in particular with LDA. However as we identified no dipyridines at low temperatures we must suppose that the 3-fluoropyridine radical-anion is only a transient species. Abstraction of an hydrogen radical by $^{\cdot}B$ occurs quickly inside the caged radical anion radical pair[69] and leads to the corresponding carbanion. Then our first approach of the regioselectivity of the lithiation will be based on lithiated intermediates.

I. *Thermodynamic and kinetic control of the metallation in* Et_2O

These lithiation directing effects can be discussed in terms of kinetic or thermodynamic control of the reaction.

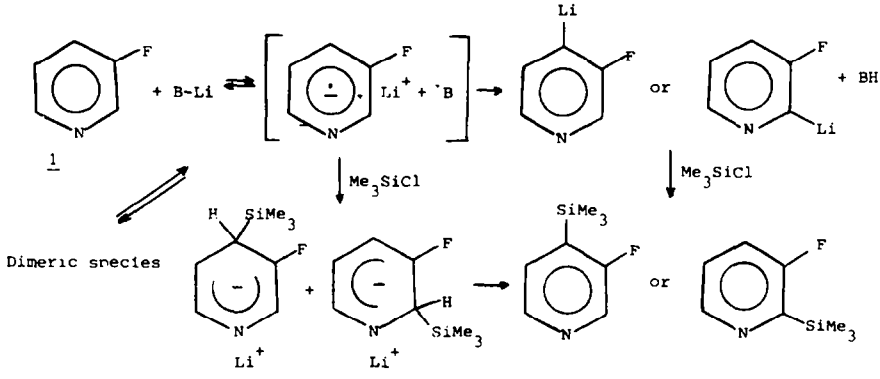
In ethyl ether at $-60°$ lithiation of **1** is kinetically controlled. We think that n-BuLi preferentially coordinates with the pyridine nitrogen (Scheme 3). Abstraction of the nearest acidic proton then leads to the 2-lithio derivative **2a** by an intramolecular route. Higher reactivity of the 2 position is also due to the Li–N chelation which increases the acidity of the 2-proton by an inductive effect.

At higher temperatures or with longer reaction times the 2-lithio compound **2a** slowly equilibrates to the thermodynamically more stable 4-lithio derivative **2b** (Scheme 3). In free 3-fluoropyridine, the position adjacent to nitrogen is thermodynamically less acidic than position 4 for two main reasons.[53]

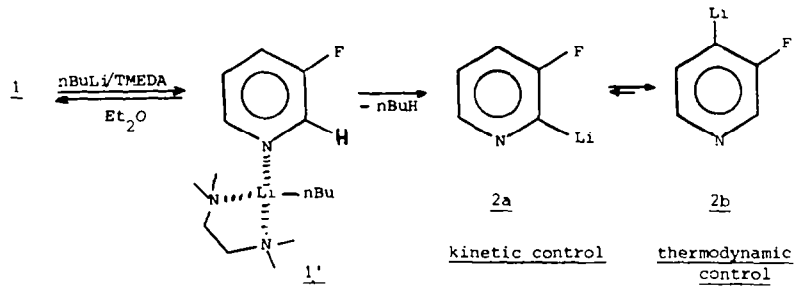
- There is electrostatic repulsive interaction between the unshared electron pair of nitrogen and the electron pair of **2a**.
- Secondly the enlarged internal ring bond angle NC_2C_3 of 122°[54] causes reduction in the s-character of the C_2–H bond.[53]

II. *Equilibration mechanism in* Et_2O

The apparent relocation of the pyridyllithium from the 2 to 4-position could occur by two routes. One would involve reaction of 3-fluoro-2-lithiopyridine (**2a**) with unreacted 3-fluoropyridine (**1**) leading to 3-fluoro-4-lithiopyridine (**2b**). Reaction of 3-fluoro-2-lithiopyridine (**2a**) (prepared in Et_2O at $-60°$) with additional[55] 3-fluoropyridine (**1**) (0.5 eq.) does not increase the relocation rate at $-40°$. Reaction with MeSiCl after one hour at $-40°$ gives the



Scheme 2.



Scheme 3.

same mixture of **5a** and **5b** than without excess of **1**, which discredits this first hypothesis. The second route would involve the initial formation of a 2, 4-dilithio-3-fluoropyridine by dismutation in a catalytic manner.[56] This could be proved by the fact that small amounts of 2, 4-disilated-3-fluoropyridine (**6**) can be isolated when lithiation of **1** is achieved by the butyllithium-TMEDA chelate in stoichiometric proportions.

III. *Influence of the solvent*

Regioselective lithiation of **1** at the 4-position using nBuLi/TMEDA in THF can be explained in connection with the greater basicity of THF beside Et_2O.

Metallation may first occur at the 2-position as in Et_2O but the isomerization rate to the 2-pyridyllithium could be highly increased in THF solution. This first hypothesis is discredited by the fact that addition of excess THF to an ethereal solution of **2a** at $-60°$ does not induce the equilibration to **2b**.

We propose that the nBuLi/TMEDA/3-fluoropyridine chelate **1'** is dissociated by THF molecules[68] and that metallation is thus kinetically controlled at the most acidic site of free 3-fluoropyridine (**1**) at the 4-position.

Very different is the influence of a strong ionizing agent such as hexamethylphosphorustriamide (HMPT). The 2-lithio derivative **2a** is prepared for two hours in Et_2O at $-60°$, and two equivalents of HMPT are added. After one additional hour at $-60°$ reaction with Me_3SiCl affords a mixture of **5a** (2%) and **5b** (68%). The shift from the 2 to the 4 carbanion was facilitated, in the presence of HMPT, likely due to its strong coordinating power. The 2-lithio derivative **2a** would be first in Et_2O in a covalent structure, whose dissociation would give a loose ion pair or a free carbanion.[57] Increase of the C–Li bond dissociation enhances the electronic repulsive destabilization[53] of the 2-lithio derivative and favors the relocation to the 4-pyridyllithium.

IV. *Metallation by LDA*

As discussed by Gschwend[2] the low Lewis-acid character of LDA makes it a "kinetically stronger base" than butyllithium and the more stable 4-pyridyllithium **2b** is exclusively obtained. It should be pointed out that formation of **2b** by action of LDA can proceed via an one-electron transfer as discussed previously.

V. *Theoretical reactivity of 3-fluoropyridine*

Attempts are made to quantify 3-fluoropyridine reactivity toward lithiation. The CNDO/2 method which was selected for this study has been widely used and its strengths and weaknesses are well-known.[58] CNDO/2 quantum calculations[59] performed on 3-fluoropyridine give electron-densities of H(2) and H(4): results show a lower net atomic charge for H(4) which is in good agreement with the observed relative acidities of **1**.

In order to explain the particular reactivity of H(2) in Et_2O we are then interested in the H(2) and H(4) electron-density change when an alkyllithium molecule approaches to pyridine nitrogen along the unshared electron-pair axis. A methyllithium model was used to simplify the calculations and the geometry of 3-fluoropyridine has been described by Sharma.[54] Scheme 4 gives the H(2) and H(4) net atomic charges when nitrogen–lithium distance is varying, as well as the total energy of the resulting chelates.

These calculations confirm that chelation between nitrogen and butyllithium makes H(2) more acidic than H(4) even if the latter is more acidic in free 3-fluoropyridine (**1**).

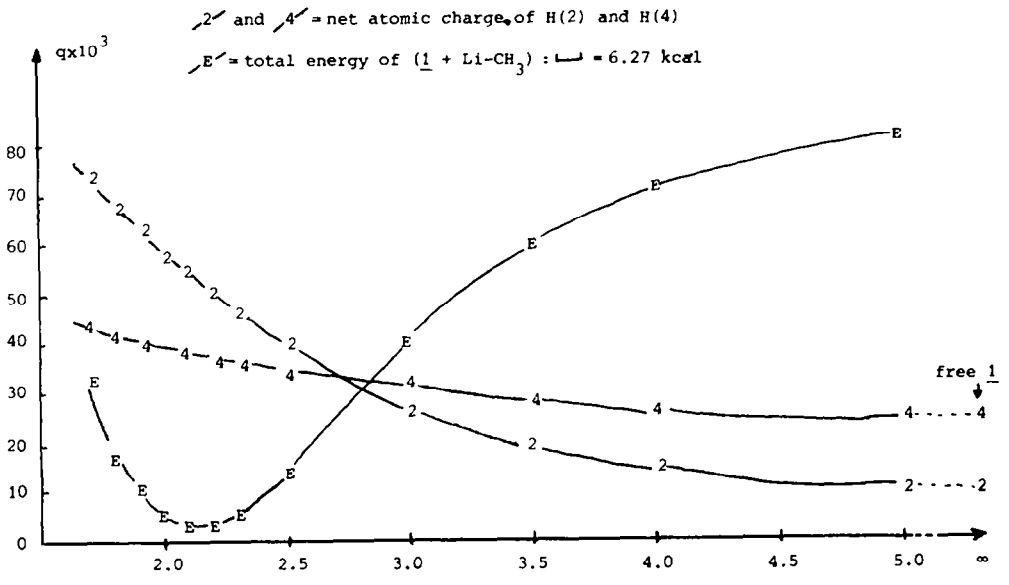
The total energy of the 2- (**2a**) and 4-pyridyllithium (**2b**) are estimated by the CNDO/2 method with covalent lithium–carbon bonds (2.2 Å). Lithium atom in **2a** is found more stabilized in a medium position between nitrogen and the 2-carbon (N–Li = 2.1 Å and C–Li = 2.2 Å). In these conditions 3-fluoro-4-lithiopyridine (**2b**) is found more stable than the 2-lithio isomer **2a** ($\Delta E = 5$ kcal).

APPLICATION TO SYNTHESIS

I. *Lithiation of 3-fluoropyridine at the 2-position*

Influence of the lithium-chelating agent on the regioselectivity. Metallation at position 2 using the BuLi-TMEDA chelate is not completely regioselective whatever the temperature and reaction time. The best results are obtained for 4 hr at $-75°$ and yields of the silylated derivatives **5a** and **5b** are respectively of 73% and 6%. Attempts to improve the regioselectivity by introducing cold reagents (use of a cold finger at $-70°$) remain unsuccessful.

Fast complete regioselectivity is reached using another metallating agent, the BuLi/DABCO chelate[60] in Et_2O. This reagent is prepared at $-20°$ for 1 hr in Et_2O and lithiation is then performed for 1 hr at $-60°$ before adding Me_3SiCl. 3-Fluoro-2-trimethylsilylpyridine (**5a**) is isolated in a 80% yield with less than



Scheme 4.

0.1% of the 4-silylated isomer. It should be pointed out that we have obtained similar results with 3-chloropyridine.[34]

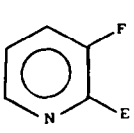
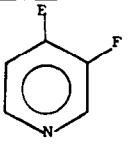
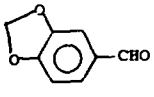
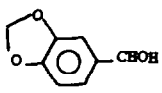
This regioselectivity improvement is due to the insolubility of the 2-lithio derivative **2a** (yellow ppt) in the presence of DABCO, whereas a solution is obtained with TMEDA: lithium relocation rate is slower in the first case, due to the low concentration of the 2-lithiated intermediate in the medium.

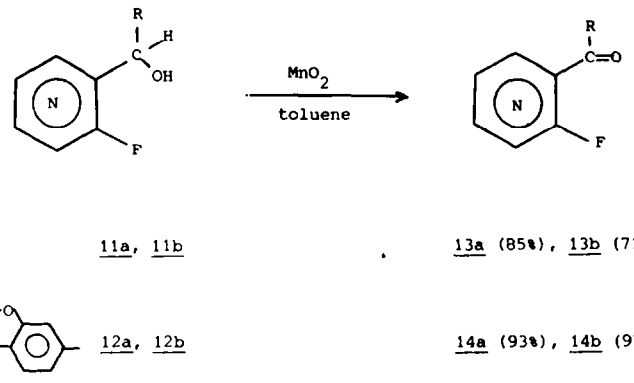
II. *Regioselective functionalization of* 3-*fluoropyridine*

Synthesis of 2, 3- *or* 3, 4-*disubstituted pyridines.* Directed metallation is a very convenient way to obtain ortho-substituted pyridyllithiums, compared with the well-known halogen–metal exchange (introduction of a Br atom on the pyridine nucleus is very often difficult, long and expensive). We previously showed that lithiation of 3-fluoropyridine (**1**) could be directed either at the 2- or 4-position with an excellent regioselectivity. Each of the resulting lithiated 3-fluoropyridine (**2a**) or (**2b**) can be reacted with a great variety of electrophiles and we can thus prepare 2, 3- or 3, 4-disubstituted pyridines. We summarize as following the best metallation conditions leading to functionalization of **1** at position 2 or 4:

Functionalization	nBuLi/TMEDA in Et_2O at $-75°$ for 4 hr.
at the 2-*position*	nBuLi/DABCO in Et_2O at $-60°$ for 1 hr.
Functionalization	nBuLi/TMEDA in THF at $-40°$ for 1 hr.
at the 4-*position*	$(iPr)_2NLi$ in THF at $-75°$ for 4 hr.

Table 5. Functionalization of 3-fluoropyridine at position 2 or 4.

Electrophile			E
Me_3SiCl	5a: 80%	5b: 75%	$SiMe_3$
Me_2AsI	8a: 55%	8b: 70%	$AsMe_2$
Br_2	9a: 25%	9b: 20%	Br
Et-CO-Et	3a: 65%	3b: 50%	CEt_2OH
Me-CO-Me	7a: 25%	7b: 15%	CMe_2OH
Me-CHO	11a: 75%	11b: 70%	CHMeOH
	12a: 79%	12b: 81%	
$H\text{-}CO_2Et$ or $H\text{-}CO\text{-}NMe_2$	10a: 45%	10b: 50%	CHO



Scheme 5.

Secondary alcohols **11a**, **11b**, **12a** and **12b** are readily oxidized with MnO_2 in toluene[61] to the corresponding ketones **13a**, **13b**, **14a** and **14b** in good yields (Scheme 5).

These fluorinated ketones would be difficult to obtain by other methods.

EXPERIMENTAL

The ^{1}NMR spectra are obtained using a Varian A-60 spectrometer and are recorded in ppm downfield of the internal standard of TmS. ^{1}H-^{1}H and ^{1}H-^{19}F coupling constants are in good agreement with the common values:[62] $J_{2\text{-}4} \simeq 2$Hz; $J_{4\text{-}5} \simeq 8$ Hz; $J_{5\text{-}6} \simeq 4.5$ Hz; $J_{2\text{-}F} < 1$ Hz; $J_{4\text{-}F} \simeq 9$ Hz; $J_{5\text{-}F} \simeq 5$ Hz; $J_{6\text{-}F} \simeq 2$ Hz. IR spectra are obtained as thin films (unless otherwise noted) from a Perkin–Elmer R-12 spectrophotometer. Elemental analyses are performed on a Technicon instrument.

Ethylether (distilled from LAH) and THF (distilled from benzophenone–sodium) are stored over molecular sieves (3 Å). Water content of the solvents is estimated by the modified Karl-Fischer method[63] (THF and Et_2O respectively less than 45 ppm and 10 ppm.) Diisopropylamine, TMEDA and Me_3SiCl are redistilled from CaH_2 and stored over CaH_2. Solvent removal on a rotary evaporator from a benzene solution of DABCO provides a dry reagent which is stored under vacuum in the presence of KOH.

Metallations are performed under a dry deoxygenated nitrogen atmosphere (pyrogallol + NaOH + H_2O; H_2SO_4; KOH; silica gel).

BuLi content of the commercial hexane solution is estimated by the Gilman double titration method.

3-Fluoropyridine (**1**) is prepared from 3-aminopyridine[64] and stored over molecular sieves (3 Å).

3-Amino-2-bromopyridine: 2-bromonicotinamide[65] (100 g, 0.5 mol) is added to a cold solution of Br_2 (90 g), NaOH (75 g), H_2O (300 g), and ice (700 g). The mixture is kept for 1/2 hr at room temperature and then warmed for 3 hr at 80°. The cold solution gives a white precipitate which is filtered, washed with cold H_2O, and dried under vacuum. 3-Amino-2-bromo-pyridine is obtained in a 75% yield. F = 79°.

NMR ($CDCl_3$) δ 7.20 (d, 2H, H_4 and H_5), 7.30 (t, 1H, H_6), 4.10 (m, 2H, NH_2); IR (KBr) 3450, 3300, 3170, 3060, 1620, 1590, 1570, 1470, 1440 cm^{-1}; (Found: C, 34.7; H, 2.90; N, 16.2. Calc for $C_5H_5N_2Br$: C, 34.71; H, 2.91; N, 16.19%.)

2-Bromo-3-fluoropyridine (**4a**): a soln of 3-amino-2-bromopyridine (10 g, 0.06 mol) in EtOH(100 mL) and HBF_4 (34% aqueous soln, 30 mL, 0.14 mol) is cooled to 0° and diazotation is performed by a stream of ethylnitrite in excess. The white ppt is filtered off, washed with cold EtOH and cold benzene before being decomposed in benzene slowly at room temp. Extraction with HCl by (10%), steam distillation at pH = 9, Et_2O extraction, drying ($MgSO_4$), and removal of the solvent afford an yellow oil. Vacuum distillation gives **4a**: 2.6 g (34%); b.p. 62° (22 mm).

NMR ($CDCl_3$) δ 7.30 (m, 2H, H_3 and H_4), 8.20 (m, 1H, H_6); IR 3070, 1585, 1575, 1455, 1420 cm^{-1}; (Found: C, 34.2; H, 1.76; N, 8.00.) Calc for C_5H_3BrFN: C, 34.10; H, 1.70; N, 7.95%).

4-Bromo-3-fluoropyridine (**4b**) *and 4-chloro-3-fluoropyridine* (**15**) are prepared according to Talik[64] from (**1**) via 3-fluoro-4-nitro-pyridine *N*-oxide.

I. *General procedure for metallation of 3-fluoropyridine by the butyl-lithium/TMEDA chelate*

Dry THF or Et_2O (250 mL), n-BuLi (1.6 M in hexane, 31.5 mL, 0.05 mol), and dry TMEDA (5.8 g, 0.05 mol) are introduced into a 500 mL flask under a dry N_2 stream at −60° and the resulting soln is stirred for 1 hr at −20°. The mixture is cooled to −75° and a THF or Et_2O (25 mL) soln of 3-fluoropyridine (4.85 g, 0.05 mol) is added dropwise and stirring is continued at the required temp for the required time. Electrophilic reagent (0.055 mol) dissolved in dry THF or Et_2O (25 mL) is added dropwise and the mixture is allowed to stand for 2 hr at −75°. Water (150 mL) is introduced at −10°, the aqueous layer is extracted with ethyl ether (3 × 150 mL) and the combined extract is dried over anhydrous sodium sulfate. Solvent removal leads to a colored oil, which is distilled under vacuum.

II. *General procedure for metallation of 3-fluoropyridine by the butyl–lithium/DABCO chelate*

Metallation is conducted as described in I°/ using DABCO (5.6 g, 0.05 Mol) instead of TMEDA and the solvent is Et_2O. Addition of 3-fluoro-pyridine produces a pale yellow ppt which disappears after reaction with the electrophile.

III. *General procedure for metallation of 3-fluoropyridine by lithium diisopropylamide*

Into a cold solution (−20°) of THF and n-BuLi (1.6 M in hexane, 31.5 mL, 0.05 mol) under N_2, contained in a 500 mL flask, is added dropwise a THF (25 mL) soln of dry diisopropylamine (5.05 g, 0.05 mol) and the mixture is allowed to stand for 1 hr at 0°. Addition of 3-fluoropyridine (4.85 g, 0.05 mol) in THF (25 mL) at −75, slowly affords a

white solid and stirring is continued for 4 hr at −75°. The reaction procedure is then the same as described in I.

IV. *Change of the reaction temperature after metallation*

If it is necessary to keep the resulting metallation mixture for a long time at −60°, −40° or −30°, reaction temperature is regulated using a cryostat apparatus.

V. *Analysis of the mixtures of 3-fluoro-2-trimethylsilylpyridine* (**5a**) *and 3-fluoro-4-trimethylsilylpyridine* (**5b**)

After metallation of **1** and quenching with Me_3SiCl, vacuum distillation of the crude product gives a mixture of **5a** and **5b**; b.p. 70–85° (15 mm). Relative ratios of the two products are calculated by GPC using a 2 m long column (1/8 in.) filled with apiezon L over chromosorb W 80/100 at 150°. Relative response coefficient of the two isomers using a thermoconductivity dectection are respectively 1.25 and 1.00 for **5a** and **5b**. These results are in good agreement with those obtained from ^1H NMR spectra of **5a** and **5b** mixtures (6.8 to 8.6 ppm).

VI. *Halogen–metal exchange between 2-bromo-3-fluoropyridine* (**4a**) *and 4-bromo-3-fluoropyridine* (**4b**)

These reactions are performed at −60° in Et_2O (250 mL) by addition of **4a** or **4b** (8.8 g, 0.05 mol) to BuLi (0.055 mol). After ½ hr at −60°, 3-pentanone (4.8 g, 0.055 mol) is added and soln is kept at −60° for 1 hr before hydrolysis at 0°. Extraction, drying, solvent removal, and vacuum distillation leads to **3a** (85%) or **3b** (88%).

3-Fluoro-2-trimethylsilylpyridine (**5a**): b.p. 72° (15 mm). NMR ($CDCl_3$) δ 0.35 (2s, 9H, $SiMe_3$), 7.25 (m, 2H, H_4 and H_5), 8.55 (m, 1H, H_6); IR 3050, 2960, 2890, 1595, 1520, 1470, 1440, 1400 cm^{-1}; (Found: C, 56.7; H, 7.05; N, 8.30. Calc for $C_8H_{12}NFSi$: C, 56.76; H, 7.14; N, 8.27%).

3-Fluoro-4-trimethylsilylpyridine[35] (**5b**): b.p. 85° (15 mm). NMR ($CDCl_3$) δ 0.35 (2s, 9H, $SiMe_3$), 7.30 (dd, 1H, H_5), 8.40 (m, 2H, H_2 and H_6); IR 3060, 2960, 2900, 1595, 1535, 1485, 1420 cm^{-1}; (Found: C, 56.8; H, 7.12; N, 8.42. Calc for $C_8H_{12}NFSi$: C, 56.76; H, 7.14; N, 8.27%).

2, 4-*Di-trimethylsilyl-3-fluoropyridine* (**6**): b.p. 105° (15 mm). NMR ($CDCl_3$) δ 0.35 (4s, 18 H, $SiMe_3$), 7.20 (dd, 1H, H_5), 8.55 (dd, 1H, H_6); IR 3050, 2960, 2900, 1580, 1410 cm^{-1}; (Found: C, 54.9; H, 8.40; N, 5.90. Calc for $C_{11}H_{20}NFSi_2$: C, 54.72; H, 8.35; N, 5.80%).

2-Dimethylarsino-3-fluoropyridine (**8a**): b.p. 83° (16 mm). NMR ($CDCl_3$) δ 1.30 (s, 6H, $AsMe_2$), 7.20 (m, 2H, H_5 and H_4), 8.50 (m, 1H, H_6); IR 3040, 2980, 2920, 1580, 1535, 1470, 1450, 1400 cm^{-1}; (Found: C, 41.5; H, 4.40; N, 6.80. Calc for C_7H_9NFAs: C, 41.81; H 4.51; N, 6.96%).

4-Dimethylarsino-3-fluoropyridine (**8b**): b.p. 85° (16 mm). NMR ($CDCl_3$) δ 1.30 (s, 5H, $AsMe_2$), 7.30 (dd, 1H, H_5), 8.35 (m, 2H, H_2 and H_6); IR 3050, 2990, 2910, 1580, 1550, 1440, 1410 cm^{-1}; (Found: C, 41.7; H, 4.32; N, 6.95. Calc for C_7H_9NFAs: C, 41.81; H, 4.51; N, 6.96%).

2-(1-Hydroxy-1-ethylpropyl)-3-fluoropyridine (**3a**): b.p. 70° (4 mm). NMR ($CDCl_3$) δ 0.65 (t, 6H, CH_3), 1.95 (m, 4H, CH_2), 5.50 (s, 1H, OH), 7.35 (m, 2H, H_4 and H_5), 8.40 (dd, 1H, H_6); IR 3400, 3070, 2970, 2940, 2880, 2860, 1600, 1560, 1440 cm^{-1}; (Found: C, 65.7; H, 7.90; N, 7.80. Calc for $C_{10}H_{14}FNO$: C, 65.54; H, 7.70; N, 7.64%).

4-(1-Hydroxy-1-ethylpropyl)-3-fluoropyridine (**3b**): b.p. 90° (4 mm). NMR ($CDCl_3$) δ 0.80 (t, 6H, CH_3), 1.95 (m, 4H, CH_2), 2.95 (s, 1H, OH), 7.60 (dd, 1H, H_5), 8.40 (m, 2H, H_2 and H_6); IR 3260, 3060, 2990, 2970, 2950, 2890, 1615, 1555, 1490, 1430, 1420 cm^{-1}; (Found: C, 65.6; H, 7.60; N, 7.50. Calc for $C_{10}H_{14}FNO$: C, 65.54; H, 7.70; N, 7.64%).

2-(1-Hydroxy-1-méthylethyl)-3-fluoropyridine (**7a**): b.p. 80° (16 mm). NMR ($CDCl_3$) δ 1.60 (2s, 6H, CH_3), 5.55 (s, 1H, OH), 7.85 (m, 2H, H_4 and H_5), 8.35 (m, 1H, H_6); IR 3410, 3080, 2980, 2940, 1610, 1445 cm^{-1}; (Found: C, 62.0; N, 9.30; H, 6.60; Calc for $C_8H_{10}FNO$: C, 61.95; H, 6.45; N, 9.03%).

4-(-Hydroxy-1-methylethyl)-3-fluoropyridine (**7b**): b.p. 90° (16 mm). NMR ($CDCl_3$) δ 1.65 (2s, 6H, CH_3), 4.50 (s, 1H, OH), 7.70 (dd, 1H, H_5), 8.30 (m, 2H, H_2 and H_6); IR 3600, 3230, 3060, 2990, 2940, 1615, 1555, 1490, 1415 cm^{-1}; (Found: C, 61.8; H, 6.60; N, 8.80. Calc for $C_8H_{10}FNO$: C, 61.95; H, 6.45; N, 9.03%).

4-(1-Hydroxyethyl)-3-fluoropyridine (**11b**): b.p. 124° (20 mm). NMR ($CDCl_3$) δ 1.50 (d, 3H, CH_3), 5.15 (m, 2H, CH and OH), 7.50 (dd, 1H, H_5), 8.20 (m, 2H, H_2 and H_6); IR 3300, 3080, 2990, 2970, 1600, 1560, 1480, 1450, 1410 cm^{-1}; (Found: C, 59.4; H, 5.61; N, 10.2. Calc for C_7H_8FNO: C, 59.54; H, 5.71; N, 9.92%).

2-(1-Hydroxyethyl)-3-fluoropyridine (**11a**): b.p. 93° (20 mm). NMR ($CDCl_3$) δ 1.45 (d, 3H, CH_3), 4.45 (s, 1H, OH), 5.15 (dq, 1H, CH), 7.30 (m, 2H, H_3 and H_4); 8.35 (m, 1H,H_6); IR 3400, 3070, 2980, 2920, 1600, 1570, 1450, 1400; (Found: C, 59.8; H, 6.07; N, 9.62. Calc for C_7H_8FNO: C, 59.54; H, 5.71; N, 9.92%).

2 - [Hydroxy(3', 4' - methylenedioxyphenyl)methyl] - 3 - fluoropyridine (**12a**): m.p. 83°. Addition of anhyd Et_2O to the crude oil produces crystallisation of **12a**. NMR ($CDCl_3$) δ 5.10 (s, 1H, OH), 5.90 (s, 3H, CH and CH_2), 6.80 (m, 3H, phenyl), 7.30 (m, 2H, H_4 and H_5), 8.35 (m, 1H, H_6); IR (KBr) 3130, 3070, 3020, 2900, 2840, 1610, 1560, 1500, 1490, 1440, 1420; (Found: C, 63.3; H, 4.00; N, 5.60. Calc for $C_{13}H_{10}FNO_3$: C, 63.16; H, 4.08; N, 5.67%).

4-[Hydroxy(3', 4'-methylenedioxyphenyl)methyl]-3-fluoropyridine (**12b**): m.p. 175°. Addition of anhyd Et_2O to the crude oil produces crystallisation of **12b**. NMR (DMSO) δ 5.85 (s, 1H, CH), 5.90 (s, 2H, CH_2), 6.80 (m, 3H, phenyl), 7.55 (dd, 1H, H_5), 8.35 (m, 2H, H_2 and H_6); IR (KBr) 3200, 3060, 3020, 2900, 1600, 1570, 1490, 1440, 1400 cm^{-1}; Found: C, 63.3; H, 4.10; N, 5.65. Calc for $C_{13}H_{10}FNO_3$: C, 63.16; H, 4.08; N, 5.67%).

3-Fluoro-2-formylpyridine[66] (**10a**): b.p. 112° (50 mm). NMR ($CDCl_3$) δ 7.70 (m, 2H, H_4 and H_5), 8.60 (m, 1H, H_6), 9.50 (s, 1H, CHO); IR 3070, 3020, 2870, 2840, 1720, 1590, 1460, 1440 cm^{-1}; Found: C, 57.5; H, 3.20; N, 11.1. Calc for C_6H_4FNO: C, 57.61; H, 3.22; N, 11.19%).

3-Fluoro-4-formylpyridine (**10b**): b.p. 70° (25 mm). NMR ($CDCl_3$) δ 7.70 (dd, 1H, H_5), 8.70 (m, 2H, H_2 and H_6), 10.50 (s, 1H, CHO); IR 3060, 2890, 1710, 1605, 1570, 1485, 1415 cm^{-1}; (Found: C, 57.4; H, 3.30; N, 11.0 Calc for C_6H_4FNO: C, 57.61; H, 3.22; N, 11.19%).

General procedure of oxidation of secondary alcohols **11a**, **11b**, **12a**, and **12b**:

Oxidation is carried in toluene soln by 4 equivalents of active MnO_2[67] at ebullition temp using a Dean–Stark apparatus (reaction is monitored by IR spectroscopy). Filtration of MnO_2, drying ($MgSO_4$), and evaporation afford a crude oil, which is purified either by vacuum distillation or crystallisation (ethyl ether).

2-Acetyl-3-fluoropyridine (**13a**): b.p. 75° (50 mm). NMR ($CDCl_3$) δ 2.70 (d, 3H, CH_3), 7.55 (m, 2H, H_4 and H_5), 8.50 (m, 1H, H_6), $J_{CH_3\text{-}F}$ = 2 Hz; IR 3060, 3010, 2950, 2930, 1700, 1640, 1590, 1450, 1440 cm^{-1}; (Found: C, 60.4; H, 4.38; N, 10.3. Calc for C_7H_6FNO: C, 60.43; H, 4.35; N, 10.06%).

4-Acetyl-3-fluoropyridine (**13b**): b.p. 78° (45 mm). NMR ($CDCl_3$) δ 2.65 (d, 3H, CH_3), 7.60 (dd, 1H, H_5), 8.50 (m, 2H, H_2 and H_6); $J_{CH_3\text{-}F}$ = 4 Hz; IR 3050, 3010, 2980, 2930, 1700, 1600, 1480, 1420 cm^{-1}; (Found: C, 60.3; H, 4.25; N, 9.90. Calc for C_7H_6FNO: C, 60.43; H, 4.35; N, 10.06%).

2-(3', 4'-Methylenedioxybenzoyl)-3-fluoropyridine (**14a**): m.p. 139°. NMR ($CDCl_3$) δ 6.05 (s, 2H, CH_2O), 6.80 (d, 1H, H'_5), 7.50 (m, 4H, H_4, H_5, H'_2, H'_6), 8.45 (m, 1H, H_6), $J_{5'\text{-}6'}$ = 9 Hz; IR (KBr) 3080, 3060, 2920, 1660, 1625, 1605, 1595, 1510, 1495, 1450, 1440; (Found: C, 63.5; H, 3.20; N, 5.70. Calc for $C_{13}H_8FNO_3$: C, 63.68; H, 3.29; N, 5.71%).

4-(3',4'-Methylenedioxybenzoyl)-3-fluoropyridine (**14b**): m.p. 102°. NMR ($CDCl_3$) δ 6.10 (s, 2H, CH_2O), 6.80 (d, 1H, H'_5), 7.30 (m, 3H, H_5, H'_2 and H'_6), 8.50 (m, 2H, H_2 and H_6), $J_{5'\text{-}6'}$ = 9 Hz; IR (KBr) 3070, 3010, 2900, 1655, 1625, 1605, 1560, 1505, 1495, 1455, 1415 cm^{-1}; (Found: C, 63.6; H, 3.25; N, 5.65. Calc for $C_{13}H_8FNO_3$: C, 63.68; H, 3.29; N, 5.71%).

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