Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 62 (2006) 6166–6171
Tetrahedron

$TMSCH_2Li$–LiDMAE: a new nonnucleophilic reagent for C-2 lithiation of halopyridines

Abdelatif Doudouh,[a] Philippe C. Gros,[a,*] Yves Fort[a] and Christopher Woltermann[b,*]

[a]*Synthèse Organométallique et Réactivité, UMR CNRS 7565, Université Henri Poincaré, Bd des Aiguillettes, 54506 Vandoeuvre-lès-Nancy, France*
[b]*FMC Corporation, Lithium Division, Highway 161 Box 795, Bessemer City, NC 28016, USA*

Received 21 March 2006; revised 18 April 2006; accepted 20 April 2006
Available online 19 May 2006

Abstract—A new superbasic reagent has been discovered by combining $TMSCH_2Li$ and LiDMAE in hexane. This reagent was found highly efficient for the C-2 lithiation of sensitive chloro- and fluoropyridines. The metallation occurred chemo- and regioselectively at 0 °C avoiding the nucleophilic addition or substrate degradation commonly obtained with other alkyllithiums even at lower temperatures.

1. Introduction

The C-2 lithiation of the pyridine ring has proved to be a synthetically important process to introduce opportune functionalities subsequently giving access to numerous pharmacophores, polydentate ligands (e.g., bipyridines) and chiral catalysts. Several methodologies have been developed to lithiate selectively the C-2 position. The bromine–lithium exchange was probably the most useful since adequately placed bromine ensured the selectivity.[1] However, the reactions were performed at low temperatures to avoid substrate degradation and the availability of C-2 brominated pyridines often restricted the reaction to derivatives with a low degree of functionality. Another way was to increase the alpha proton's acidity by reacting the substrate with a Lewis acid.[2] The intermediate pyridinium salt was then efficiently lithiated with LiTMP but mixtures of mono- and bifunctional derivatives are always obtained. The hydrogen–lithium exchange appeared as the more elegant process since brominated precursors and a tedious activation step were avoided. However, this was probably the more complicated approach since the base used had to be sufficiently basic to abstract the alpha protons while not nucleophilic to prevent side addition at the electrophilic C-2 position. The success was met by associating *n*-BuLi with $Me_2N(CH_2)_2OLi$ in nonpolar solvents such as hexane or toluene.[3] The obtained reagent named BuLi–LiDMAE effected clean alpha metallations of numerous pyridine derivatives with tolerance of sensitive functionalities such as chlorine,[4] acidic methyles,[5] anisyles[6] and pyrrolyl groups.[7] BuLi–LiDMAE is now a well-recognized reagent included in the portfolio of metallating agents.[8] However, it still suffers from drawbacks, which need to be overcome. All lithiations require an excess of base (typically 3–4 equiv) implying the use of the corresponding excess of electrophilic reagent to avoid its consumption by the base before trapping the lithiopyridine. This was problematic when an expensive electrophile was used or could complicate the purification step, the side addition product being present in the medium. Furthermore the newly introduced substituent could be attacked by the excess of basic reagent if sensitive such as an aldehyde. Since BuLi–LiDMAE is an *n*-BuLi-containing reagent, nucleophilicity towards the most electrophilic heterocycles remains problematic and low temperatures (typically −80 to −100 °C) are required to metallate substrates such as halopyridines.

Since we are continuously looking for the most efficient and easily handled reagent we have launched a research program aiming at replacing *n*-BuLi by other alkyllithiums. It is well known that the degrees of aggregation and solvation have a significant impact on the reactivity and selectivity of organolithium complexes. Generally the smaller the aggregate size the more reactive they are. In contrast to *n*-BuLi, branched *i*-PrLi, *s*-BuLi and *t*-BuLi are not hexameric, but rather tetrameric, in hexanes. So the association of such bases with LiDMAE should provide more reactive lithiating agents usable in lower amounts than *n*-BuLi–LiDMAE. The steric effects are also expected to induce lower nucleophilicity towards sensitive heterocycles potentially allowing the metallation to be performed at more practical higher temperatures (0 °C or rt). Unfortunately, our first attempts to associate LiDMAE with classical branched alkyllithiums (*s*-BuLi or *t*-BuLi) only led to insoluble mixtures unreactive

* Corresponding authors. Tel.: +33 3 83 68 4979; +1 704 868 5421; fax: +33 3 383 68 4785; +1 704 868 5496; e-mail addresses: philippe.gros@sor.uhp-nancy.fr; chris_woltermann@fmc.com

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.04.059

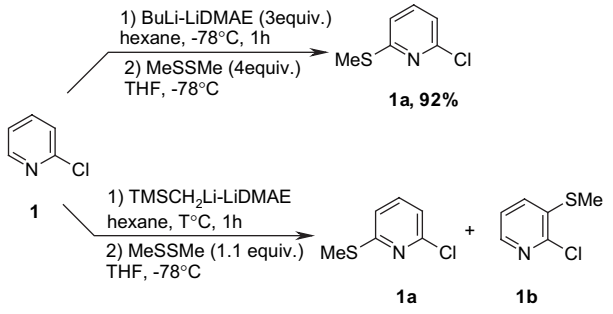
or slightly nucleophilic towards pyridines,[9] and we decided to examine other lithiating agents.

A literature survey reported the beneficial effects of silicon-containing reagents and substrates on several transformations. Accelerating effects and enantiomeric excess enhancement have been observed in asymmetric additions in the presence of silylated catalysts.[10] Moreover, silyl moieties are also known to bring some thermal and air stability to lithiating agents such as in lithium hexamethyldisilazide (LiHMDS).[11] Unfortunately, the consequence is also a decrease of the basicity (p*K*a 29.5 vs 35.7 for LDA in THF) impeding, for example, abstraction of acidic pyrimidinone protons.[12] Recently, the bulky Me_3SiCH_2Li ($TMSCH_2Li$) has been reported to be a promising base for ortholithiation of some pyridine derivatives when reacted in the presence of small amounts of diisopropylamine (DIA) in THF.[13] Thus, we felt that such an apparently nonnucleophilic reagent could be an excellent candidate for promoting alpha lithiation of pyridine derivatives when associated with LiDMAE in nonpolar solvents. Therefore, we investigated the reactivity of various $TMSCH_2Li$–LiDMAE combinations towards electrophilic chloro- and fluoropyridines.

2. Results and discussion

2.1. Lithiation of chloropyridines

The study was initiated with the metallation of 2-chloropyridine for which the behaviour towards *n*-BuLi–LiDMAE is well known (Scheme 1). As shown 3 equiv of this reagent at −78 °C in hexane were needed to metallate selectively **1** in 92% yield.[4a] Higher temperatures (e.g., 0 °C) gave nucleophilic addition and substrate degradation.[4a] **1** was then treated with $TMSCH_2Li$–LiDMAE combinations in hexane under various temperatures and stoichiometries (Table 1). $TMSCH_2Li$–LiDMAE mixtures were prepared according to procedures previously reported for BuLi–LiDMAE.[4–7]



Scheme 1. Lithiation of **1** with BuLi–LiDMAE and $TMSCH_2Li$–LiDMAE.

The experiments in Table 1 clearly underline the differences between *n*-BuLi and $TMSCH_2Li$. At first, the latter did not react with **1** even at 0 °C (entries 1–3) while *n*-BuLi gave addition even at −70 °C leading to a dihydropyridone.[14] Another interesting feature was the effect of the $TMSCH_2Li$–LiDMAE ratio on the selectivity. Indeed while BuLi and LiDMAE had to be used in a 1/1 ratio to ensure selective C-6 lithiation, such a stoichiometry gave mixtures of **1a** and **1b** with the new reagent (entries 4–6). In contrast the 2/1 ratio gave the best selectivities leading exclusively to **1a** whatever the temperature (entries 7–10). The best result was obtained when the metallation was performed at 0 °C yielding **1b** cleanly in an excellent yield (96%, entry 10) without any nucleophilic addition product. Entries 11 and 13 demonstrated that the 2/1 ratio must be adopted since a decrease of the amount of $TMSCH_2Li$ or the use of a 2/2 ratio induced a loss of the regioselectivity. Attempts to metallate at rt did not give any reaction, maybe due to the reagent degradation at such a temperature (entry 12). Finally LiDMAE used in substoichiometric amount also effected a clean metallation despite a slight decrease in the conversion (entry 14). Lower amounts led to much less efficient processes. The low nucleophilicity of $TMSCH_2Li$ is remarkable since all experiments were realized using only 1–1.1 equiv of electrophile. This means that $TMSCH_2Li$ was less nucleophilic than the formed pyridyllithium allowing efficient introduction of the functionality on the ring. Such a reagent stoichiometry was prohibited with BuLi–LiDMAE and excess of electrophile was necessary (Scheme 1) except on rare occasions when base compatible electrophiles such as TMSCl or $ClSnBu_3$ were used.[15]

Table 1. Conditions screening for lithiation of **1** with $TMSCH_2Li$–LiDMAE[a]

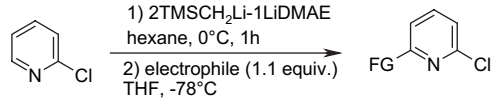
Entry	$TMSCH_2Li$ (equiv)	LiDMAE (equiv)	*T* (°C)	S.M. (%)[b]	**1a** (%)[b]	**1b** (%)[b]
1	1	0	−78	>99[c]	—	—
2	2	0	−78	>99[c]	—	—
3	2	0	0	99	tr	—
4	1	1	−78	72	22	6
5	1.5	1.5	−78	43	47	10
6	2	2	−78	64	17	19
7	2	1	−78	54	46	tr
8	2	1	−40	20	80	tr
9	2	1	−20	7	93	tr
10	2	1	0	3	96 (92)[d]	—
11	2	2	0	30	38	30
12	2	1	20	>99[c]	—	—
13	1.5	1	0	25	42	32
14	2	0.5	0	20	80	—

[a] All reactions performed on 1.8 mmol of **1**.
[b] GC yields, S.M.=starting material.
[c] No reaction occurred.
[d] Isolated yield in parentheses.

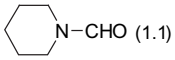
To gain additional information about the reactivity of the new superbase, we examined various conditions for the quenching step in order to examine the pyridyllithium versus $TMSCH_2Li$ nucleophilicity. The temperature was first maintained at 0 °C (conditions: entry 10, Table 1) after the metallation step, the electrophile was then introduced at the same temperature. Under these conditions, **1a** was obtained in very good yield (85%). Moreover, when THF usually added to release the pyridyllithium from aggregates to enhance its reactivity was omitted, **1a** was still obtained in excellent yield (89%). These experiments additionally stress the low nucleophilicity of $TMSCH_2Li$ allowing one to perform the metallation in more practical conditions.

The scope of the reaction was then investigated by reaction with a range of electrophiles such as halides, aldehydes or amides, which were introduced in stoichiometric amounts (Table 2). For reasons of solubility and to minimize degradation of these sensitive reagents, it was preferred to perform the trapping step at −78 °C using THF as a co-solvent.

Table 2. Metallation of **1** and reaction with sensitive electrophiles[a]

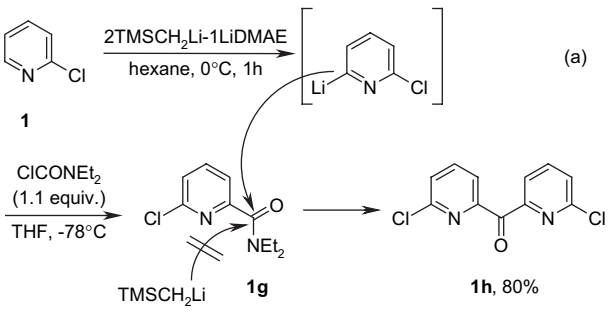


1 **1c-g**

Entry	Electrophile (equiv)	FG	Product, yield (%)[b]
1	CBr_4 (1.1)	Br	**1c**, 58
2	DMF (1.1)	CHO	**1d**, 62
3	 (1.1)	CHO	**1d**, 81
4	$PhCONMe_2$ (1.1)	COPh	**1e**, 46
5	$PhCONMe_2$ (1.1)	COPh	**1e**, 95[c]
6	PhCHO (1.1)	PhCH(OH)	**1f**, 60[d]
7	PhCHO (2)	PhCH(OH)	**1f**, 80
8	$ClCONEt_2$ (1.1)	$CONEt_2$	**1g**, 7[e]
9	$ClCONEt_2$ (3)	$CONEt_2$	**1g**, 20[e]
10	$ClCONEt_2$ (3)	$CONEt_2$	**1g**, 32[e,f]

[a] All reactions performed on 1.8 mmol of **1**.
[b] Isolated yields.
[c] The electrophile was added at 0 °C.
[d] The remaining part was unreacted **1**.
[e] Bis-(6-chloro-pyridin-2-yl)-methanone **1h** was the main product.
[f] Reverse addition.

As shown, all the expected products were synthetized in good yields using only 1.1 equiv of electrophile. Impressive was the stability of aldehyde **1d** that is usually highly electrophilic towards *n*-BuLi. A notable improvement was obtained using piperidine carboxaldehyde instead of DMF. Expectedly, PhCHO was found to be more sensitive to nucleophilic attack by the excess of $TMSCH_2Li$ nevertheless providing the corresponding alcohol **1f** in 60% yield, the remaining product being only unreacted **1**. The yield could be raised to 80% by employing an additional equivalent of benzaldehyde. Finally, the reaction of the diethylcarbamide (entries 8–10) was handicapped by fast subsequent reaction of the lithiopyridine with the target amide **1g** leading to the corresponding bis-(6-chloro-pyridin-2-yl)-methanone **1h** in good yields (60–83%) (see Scheme 2). A 32% yield of **1g** could, however, be obtained using an excess of carbamide and a reversed addition order. Interestingly, the amide **1g** was not attacked by the excess of $TMSCH_2Li$ but only by the pyridyllithium. This contrasted with the reactivity of BuLi–LiDMAE which always led to the corresponding pyridylbutylketone.[16]

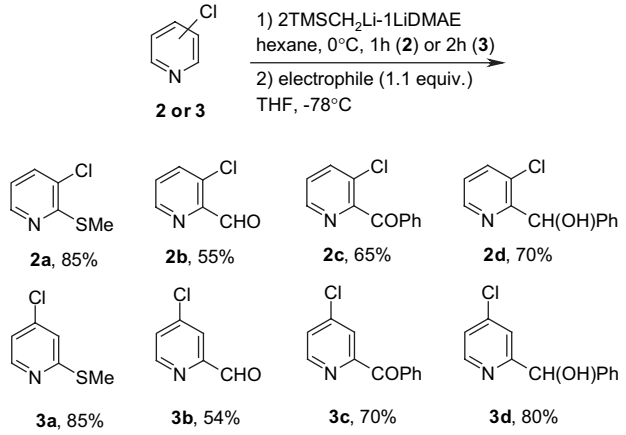


Scheme 2. Formation of dipyridylketone **1h** (a) and classical reaction with *n*-BuLi (b).

Thus the new $TMSCH_2Li$–LiDMAE reagent effected the first clean alpha lithiation of **1** at 0 °C while temperatures under −78 °C were needed with other lithiating agents. Thanks to its low nucleophilicity, the reagent also generally allowed the use of electrophiles in stoichiometric amounts.

Then we turned to the extension of this promising selective reagent to the metallation of 3- and 4-chloropyridines **2** and **3**, the latter being the most electrophilic in this series. First conditions screening showed that $TMSCH_2Li$ behaved in the same way with these isomers. No reaction occurred in the absence of LiDMAE and the conditions used for 2-chloropyridine could be applied successfully for the C-2 lithiation of **2** and **3** except that the metallation time had to be extended to 2 h for the complete conversion of **3**. The reaction performed at 0 °C did not give any nucleophilic addition product even with **3** nor did it result in isomerisation leading to C-4 lithiation with **2**. The reactivity was different from those of *n*-BuLi–LiDMAE which had to be used in excess (3–4 equiv) at −60 and −78 °C for the metallation of **2** and **3**, respectively, to avoid nucleophilic addition and C-4 lithiation of **2**.[4b]

A range of sensitive electrophiles was then reacted with lithiated **2** and **3**. All reactions were clean and gave the expected products in good to high yields (Scheme 3).



Scheme 3. Preparation of C-2 substituted chloropyridines under mild conditions.

From these excellent results obtained under mild conditions and using low amounts of reagents we decided to examine further the scope of the reaction by investigating the metallation in the fluoropyridine series.

2.2. Lithiation of fluoropyridines

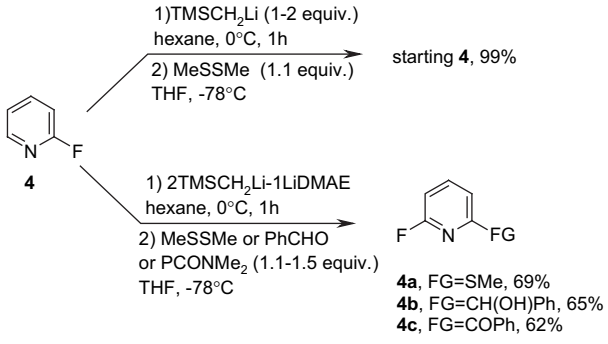
Fluoropyridines are important substrates for many reasons. At first fluorine is far more electronegative than chlorine inducing dramatic changes in the reactivity of the pyridine ring. The consequences are a strong increase of the electrophilicity[17] and proton acidities especially for those *ortho* to fluorine, so major changes could be expected on chemo- and regioselectivity.

These electronic properties have also made the introduction of fluorine in heterocyclic structures of high interest for the pharmaceutical purpose. Indeed, fluorine and hydrogen are isosteric atoms; consequently, steric or chelating effects

able to interfere with the substrate–biological site interactions never accompany the electronic effect.

Recently, 2-fluoropyridine (**4**) has been lithiated successfully at C-6 using 3 equiv of BuLi–LiDMAE. The temperature had to be maintained at −100 °C to avoid substrate degradation.[18] 3-Fluoropyridine (**5**) has been lithiated with various basic systems and low temperatures were always employed (−40 to −78 °C). The C-2 lithiation of this substrate was less easily directed since protons at C-4 were also highly activated by the fluorine group. This implied a thorough control of temperature and the appropriate lithiating agent.[8c,d,19] A few examples of 4-fluoropyridine lithiation have been reported also at low temperatures. The formed C-3 lithio intermediate was often instable leading to pyridine formation lowering the synthetic interest of this substrate.[19] Moreover, 4-fluoropyridine is not easily available from standard commercial sources and its preparation is quite tedious.

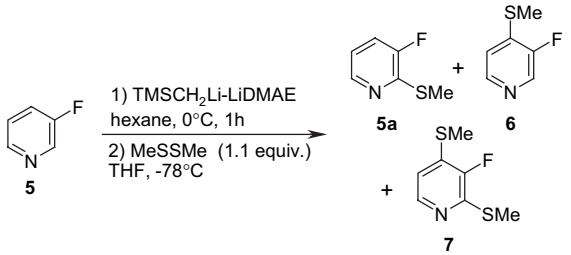
So we rather focused on the lithiation of 2-fluoropyridine **4** and 3-fluoropyridine **5**. Our first observation was surprising since **4** did not react at all with $TMSCH_2Li$ (1–2 equiv) at 0 °C in hexane indicating the low nucleophilicity of the reagent towards the substrate. This first positive outcome encouraged us to attempt the lithiation with $TMSCH_2Li$–LiDMAE. We were pleased to obtain a quantitative C-6 lithiation at 0 °C! The reaction medium did neither reveal nucleophilic addition product nor material loss due to degradation. The 2/1 $TMSCH_2Li$–LiDMAE ratio was found to be the best to ensure efficient reaction. Sulfenyl, alcohol and ketone functionalities were introduced in good yields. It must be pointed out here that the isolated yields were lower than the GC yields due to the volatility of the products (Scheme 4).



Scheme 4. Clean lithiation of **4** with $TMSCH_2Li$–LiDMAE and preparation of derivatives.

The lithiation of 3-fluoropyridine **5** was then investigated (Table 3). A first blank test was realized with $TMSCH_2Li$ at 0 °C (entry 1). The absence of nucleophilicity was clearly established since the metallation was complete and gave a mixture of C-2 and C-4 functionalized derivatives **5a** and **6**. At this stage a decrease of the metallation temperature could have been envisioned but we first decided to maintain the temperature at 0 °C and to attempt to control the selectivity only by adding LiDMAE to the basic system. Under these conditions, the incorporation of LiDMAE in the 2/1 ratio significantly favoured the C-2 versus C-4 lithiation

Table 3. Effect of the $TMSCH_2Li$–LiDMAE ratio on the lithiation selectivity of **5**[a]

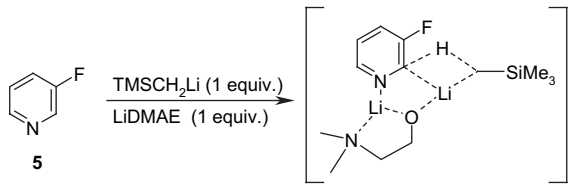


Entry	$TMSCH_2Li$ (equiv)	LiDMAE (equiv)	S.M. (%)[b]	**5a** (%)[b]	**6** (%)[b]	**7** (%)
1	2	0	—	53	45	—
2	2	1	—	61	38	—
3	1	1	—	87	12	tr
4	2	2	—	90	—	9

[a] All reactions performed on 1.84 mmol of **1**.
[b] GC yields, S.M.=starting material.

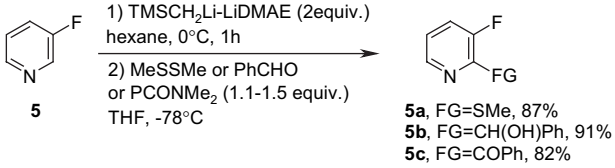
(entry 2). A stoichiometric amount of LiDMAE led to a far more selective metallation giving mainly **5a** in 87% besides **6** in 12% yield. An increase of the global base amount to 2 equiv gave the best selectivity affording **5a** in 90% yield with the formation of the bismetallation product **7**.

As shown in Table 3, the **5a**–**6** ratio was strongly dependent on the amount of LiDMAE. This underlined the severe competition between the acidities of H-4 and H-2. The $TMSCH_2Li$–LiDMAE (1/1) reagent probably ensured the formation of an aggregate with the pyridine nitrogen which was sufficiently robust to maintain the basic reagent near the H-2 proton and promote the selective lithiation (Scheme 5). This was different with the 2/1 ratio where $TMSCH_2Li$ could be released from the aggregates to deprotonate the other position.



Scheme 5. Proposed aggregate for selective C-2 lithiation.

The reaction was finally examined with a range of electrophiles leading selectively to the corresponding derivatives in excellent yields, which were found better than with 2-fluoropyridine (Scheme 6). The bismetallation product was never obtained after reaction with aldehydes of amides supporting a subsequent lithiation of **5a** during the quenching step with MeSSMe.[7]



Scheme 6. C-2 lithiation of 3-fluoropyridine.

3. Conclusion

A new superbasic reagent has been discovered by combining $TMSCH_2Li$ and LiDMAE in hexane. This reagent, when used in a 2/1 ratio was found highly efficient for the C-2 lithiation of sensitive chloro- and fluoropyridines. The metallation occurred chemoselectively at 0 °C without any trace of the nucleophilic addition commonly observed with other alkyllithiums even at lower temperatures. The usually tedious regioselective control of 3-fluoropyridine lithiation was achieved by simply adjusting the $TMSCH_2Li$–LiDMAE ratio to 1/1. Moreover, the low nucleophilicity of the base allowed using only stoichiometric amounts of electrophilic reagents. Although using the more expensive $TMSCH_2Li$, the newly reported C-2 lithiating reagent is a profound improvement of the known BuLi–LiDMAE superbase for lithiation of halopyridines. Work is now progressing to further investigate the scope of the $TMSCH_2Li$–LiDMAE superbase especially with more electrophilic heterocycles.

4. Experimental

4.1. General

All solvents were distilled and stored over sodium wire before use. 2-Dimethylaminoethanol was distilled under nitrogen and stored on molecular sieves. $TMSCH_2Li$ (FMC Lithium) was used as a 0.92 M solution in hexanes. All reagents were commercially available and used as such except for 4-chloropyridine, which was released from its hydrochloride salt by basic treatment (aq K_2CO_3). ^1H and ^{13}C NMR spectra were obtained in $CDCl_3$ (unless otherwise stated) on a Bruker AC400 instrument at 200 and 50 MHz, respectively. GC experiments were performed on a Shimadzu chromatograph (FID detection) through a 15 m capillary HP1 column. Products **1a**, **1c–e**,[4a] **1f**,[18] **2a–c**,[4b] **3a–c**[4b] and **4b**[18] were found spectroscopically identical to the previously reported compounds.

4.2. General procedure for C-2 lithiation of chloropyridines 1–3 and 2-fluoropyridine 4

$TMSCH_2Li$ (6 mL, 5.52 mmol) was added dropwise to a solution of 2-dimethylaminoethanol (164 mg, 1.84 mmol) in hexane (6 mL) at 0 °C. After 30 min of stirring, a solution of the appropriate halopyridine (1.84 mmol) in hexane (6 mL) was then added dropwise. The solution was then stirred for 1 h (2 h for **3**) at the same temperature and then treated at −78 °C with a solution of the appropriate electrophile (2.02 mmol), except for benzaldehyde (3.68 mmol), in THF (18 mL). The temperature was maintained at −78 °C for 1 h and at 0 °C for 30 min. Hydrolysis was then performed at this temperature with water (10 mL). The reaction medium was then extracted twice with ether (25 mL), the organic layer dried over $MgSO_4$ and evaporated under vacuum. The crude product was first subjected to GC analysis and purified if needed by chromatography on silica gel eluting with hexane–AcOEt mixtures using a gradient from 95/5 to 90/10.

4.2.1. 6-Chloro-pyridine-2-carboxylic acid diethylamide (1g).[20] Yield, 32%. ^1H NMR ($CDCl_3$): δ=1.35 (t, J=7.3 Hz, 6H), 3.49 (q, J=7.3 Hz, 4H), 7.38 (d, J=7.6 Hz, 1H), 7.54 (d, J=7.6 Hz, 1H), 7.75 (t, J=7.6 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ=15.4, 43.5, 121.9, 125.1, 139.7, 150.1, 155.3, 203.1.

4.2.2. Bis-(6-chloro-pyridin-2-yl)-methanone (1h). Yield, 80%. ^1H NMR ($CDCl_3$): δ=7.55 (d, J=8.0 Hz, 2H), 7.87 (t, J=7.5 Hz, 2H), 8.04 (d, J=7.5 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ=124.1, 127.8, 139.5, 151.1, 153.7, 189.6. Anal. Calcd for $C_{11}H_6Cl_2N_2O$: C, 52.20; H, 2.39; N, 11.07%. Found: C, 51.97; H, 2.23; N, 11.16%.

4.2.3. (3-Chloro-pyridin-2-yl)-phenyl-methanol (2d).[21] Yield, 70%. ^1H NMR ($CDCl_3$): δ=5.31 (br s, 1H), 6.03 (s, 1H), 7.24–7.39 (m, 6H), 6.69 (dd, J=7.9 and 1.3 Hz, 1H), 8.57 (dd, J=4.8 and 1.3 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ= 72.1, 123.8, 126.9, 128.1, 128.4, 128.5, 130.1, 137.9, 141.7, 146.2, 157.5.

4.2.4. (4-Chloro-pyridin-2-yl)-phenyl-methanol (3d).[22] Yield, 80%. ^1H NMR ($CDCl_3$): δ=4.93 (br s, 1H), 5.72 (s, 1H), 7.17–7.41 (m, 7H), 8.44 (d, J=5.8 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ=75.2, 121.9, 124.2, 127.1, 128.7, 128.8, 142.5, 149.1, 163.2.

4.2.5. 2-Fluoro-6-methylsulfanyl-pyridine (4a).[23] Yield, 69%. ^1H NMR ($CDCl_3$): δ=2.55 (s, 3H), 6.59 (dd, J=6.9 and 0.9 Hz, 1H), 7.07 (dd, J=7.9 and 1.9 Hz, 1H), 7.59 (d, J=7.9 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ=12.5, 104.1, 118.5, 140.65, 157.5, 163.4.

4.2.6. (6-Fluoro-pyridin-2-yl)-phenyl-methanone (4c). Yield, 62%. ^1H NMR ($CDCl_3$): δ=7.15 (dd, J=8.1 and 1.2 Hz, 1H), 7.46–7.60 (m, 2H), 7.62 (q, J=6.9 Hz, 1H), 7.94–8.10 (m, 4H). ^{13}C NMR ($CDCl_3$): δ=112.8, 113.4, 122.3, 128.1, 131.2, 133.5, 142.2, 142.4, 160.2, 164.1, 192.1 ppm. Anal. Calcd for $C_{12}H_8FNO$: C, 71.64; H, 4.01; N, 6.96%. Found: C, 71.35; H, 4.23; N, 6.69%.

4.3. General procedure for C-2 lithiation of 3-fluoropyridine 5

$TMSCH_2Li$ (8 mL, 7.36 mmol) was added dropwise to a solution of 2-dimethylaminoethanol (328 mg, 3.68 mmol) in hexane (8 mL) at 0 °C. After 30 min of stirring, a solution of **5** (178 mg, 1.84 mmol) in hexane (8 mL) was then added dropwise. The solution was then stirred for 1 h at the same temperature and then treated at −78 °C with a solution of the appropriate electrophile (1.1 or 1.5 mmol for benzaldehyde) in THF (24 mL). The temperature was maintained at −78 °C for 1 h and at 0 °C for 30 min. Hydrolysis was then performed at this temperature with water (3 mL). The reaction medium was then extracted with ether (10 mL), the organic layer dried over $MgSO_4$ and evaporated under vacuum. The crude product was first subjected to GC analysis and purified if needed by eluting with hexane–AcOEt mixtures using a gradient from 95/5 to 90/10.

4.3.1. 3-Fluoro-2-methylsulfanyl-pyridine (5a). Yield, 87%. ^1H NMR ($CDCl_3$): δ=2.58 (s, 3H), 6.99 (m, 1H), 7.26 (dt, J=8.5 and 0.9 Hz, 1H), 8.28 (dd, J=5.9 and 1.5 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ=12.1, 119.7, 120.6, 120.9, 145.1, 148.3, 158.6 ppm. Anal. Calcd for C_6H_6FNS: C, 50.33; H, 4.22; N, 9.78%. Found: C, 50.47; H, 4.18; N, 9.52%.

4.3.2. (3-Fluoro-pyridin-2-yl)-phenyl-methanol (5b). Yield, 91%. ^{1}H NMR ($CDCl_3$): δ=5.35 (s, 1H), 5.98 (s, 1H), 7.14–7.41 (m, 7H), 8.36 (dd, J=4.6 and 1.5 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ=70.3, 123.5, 123.8, 124.2, 126.9, 127.9, 128.6, 142.3, 144.0, 149.1, 154.3, 158.4 ppm. Anal. Calcd for $C_{12}H_{10}FNO$: C, 70.93; H, 4.96; N, 6.89%. Found: C, 70.68; H, 4.83; N, 6.93%.

4.3.3. (3-Fluoro-pyridin-2-yl)-phenyl-methanone (5c). Yield, 87%. ^{1}H NMR ($CDCl_3$): δ=7.44–7.63 (m, 5H), 7.92 (d, J=4.9 Hz, 6H), 8.52 (dd, J=5.7 and 1.4 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ=124.7, 125.1, 127.0, 128.5, 130.5, 133.9, 135.9, 144.9, 156.1, 160.2, 191.1 ppm. Anal. Calcd for $C_{12}H_8FNO$: C, 71.64; H, 4.01; N, 6.96%. Found: C, 71.57; H, 4.10; N, 7.04%.

Acknowledgements

The authors would like to thank FMC Corporation, Lithium Division for financial support.

References and notes

1. For pioneering works in the field see Gilman, H.; Spatz, S. M. *J. Org. Chem.* **1951**, *16*, 1485–1494.
2. (a) Kessar, S. V.; Singh, P.; Singh, K. N. *J. Chem. Soc., Chem. Commun.* **1991**, 570–571; (b) Vedejs, E.; Chen, X. *J. Am. Chem. Soc.* **1996**, *118*, 1809–1810.
3. For a review see Gros, Ph.; Fort, Y. *Eur. J. Org. Chem.* **2002**, 3375–3383.
4. (a) Choppin, S.; Gros, Ph.; Fort, Y. *Org. Lett.* **2000**, *2*, 803–805; (b) Choppin, S.; Gros, Ph.; Fort, Y. *Eur. J. Org. Chem.* **2001**, *3*, 603–606.
5. (a) Mathieu, J.; Gros, Ph.; Fort, Y. *Chem. Commun.* **2000**, 951–952; (b) Kaminski, T.; Gros, Ph.; Fort, Y. *Eur. J. Org. Chem.* **2003**, 3855–3860; (c) Gros, Ph.; Viney, C.; Fort, Y. *Synlett* **2002**, 628–630.
6. Parmentier, M.; Gros, Ph.; Fort, Y. *Tetrahedron* **2005**, *61*, 3261–3269.
7. Martineau, D.; Gros, Ph.; Fort, Y. *J. Org. Chem.* **2004**, *69*, 7914–7918.
8. For recent successful applications of the reagent see (a) Ishii, T.; Fujioka, S.; Sekiguchi, Y.; Kotsuki, H. *J. Am. Chem. Soc.* **2004**, *126*, 9558–9559; (b) Février, F. C.; Smith, E. D.; Comins, D. L. *Org. Lett.* **2005**, *7*, 5457–5460; (c) Marzi, E.; Bobbio, C.; Cottet, F.; Schlosser, M. *Eur. J. Org. Chem.* **2005**, 2116–2123; (d) Bobbio, C.; Schlosser, M. *J. Org. Chem.* **2005**, *70*, 3039–3045.
9. Gros, P. C. Unpublished results.
10. Goldfuss, B.; Steigelmann, M.; Rominger, F. *Angew. Chem., Int. Ed.* **2000**, *39*, 4133–4136.
11. Zhao, P.; Lucht, B. L.; Kenkre, S. L.; Collum, D. B. *J. Org. Chem.* **2004**, *69*, 242–249.
12. Yoshimura, Y.; Kumamoto, H.; Baba, A.; Takeda, S.; Tanaka, H. *Org. Lett.* **2004**, *6*, 1793–1795.
13. Woltermann, C. J.; Sutton, D. E. PCT Int. Appl. WO 2,004,092,125, 2004; *Chem. Abstr. 141*, 366136.
14. Trécourt, F.; Marsais, F.; Güngor, T.; Quéguiner, G. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2409–2415.
15. Martineau, D.; Beley, M.; Gros, P. C. *J. Org. Chem.* **2006**, *71*, 566–571.
16. Gros, Ph.; Fort, Y.; Queguiner, G.; Caubère, P. *Tetrahedron Lett.* **1995**, *36*, 4791–4794.
17. 2-Fluoropyridine underwent nucleophilic addition by *n*-BuLi–TMEDA even at −40 °C, see Marsais, F.; Granger, P.; Quéguiner, G. *J. Org. Chem.* **1981**, *46*, 4494–4497.
18. Fort, Y.; Gros, Ph.; Rodriguez, A. L. *Tetrahedron: Asymmetry* **2001**, *12*, 2631–2635.
19. (a) Marsais, F.; Quéguiner, G. *Tetrahedron* **1983**, *39*, 2009–2021; (b) Marsais, F.; Trécourt, F.; Bréant, P.; Quéguiner, G. *J. Heterocycl. Chem.* **1988**, *25*, 81–87.
20. Najiba, D.; Carpentier, J.-F.; Castanet, Y.; Biot, C.; Brocard, J.; Mortreux, A. *Tetrahedron Lett.* **1999**, *40*, 3719–3722.
21. Shilai, M.; Uchiyama, M.; Kondo, Y.; Sakamoto, T. *J. Heterocycl. Chem.* **2001**, *38*, 481–484.
22. Negi, S.; Matsukura, M.; Mizuno, M.; Miyake, K.; Minami, N. *Synthesis* **1996**, *8*, 991–996.
23. Wada, H.; Ikemoto, T.; Mizuno, I. J.P. 10,324,688 A2, 1998; *Chem. Abstr. 130*, 66498.