JOC Article

Lithiation of 2-Chloro- and 2-Methoxypyridine with Lithium Dialkylamides: Initial Ortho-Direction or Subsequent Lithium Ortho-Stabilization?

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The lithiation pathway of 2-chloro and 2-methoxypyridine with LDA and LTMP has been investigated using deuterated probes. The availability of both H-6 and H-3 protons on the pyridine nucleus was found to be critical to ensure complete C-3 lithiation. We thus concluded that the C-3 lithiation was not a straightforward process. A mechanism involving precomplexation of lithium dialkylamides near the H-6 proton and formation of a 3,6-dilithio pyridine intermediate is proposed.

Introduction

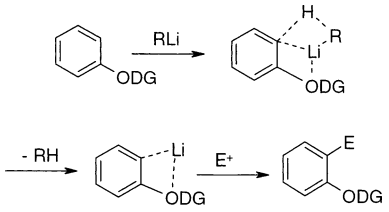
For years, directed ortho-metalation (DOM) of aromatic derivatives has proved to be a powerful synthetic tool for functionalization (Scheme 1).[1] Besides the synthetic value, many interrogations remain concerning the origin of the observed ortho-selectivity. Investigations on the mechanistic pathway revealed that formation of a complex-induced proximity effect (CIPE)[2] is generally admitted. However, other interpretations involving inductive effects of substituents as a source of acidification have also been developed.[3]

More recently, the DOM methodology has been applied to π-deficient aromatic compounds, especially in the pyridine series, offering an elegant route to new heterocyclic compounds.[4] The DOM mechanism, which has been the topic of considerable debate, appears even more complicated with N-containing heteroaromatic compounds, since the nitrogen atom is expected to modify inductive effects while offering an additional lithium complexation site. This was clearly demonstrated by the new regioselectivity obtained using a modified alkyllithium. Indeed, we have already reported that the superbase BuLi−$Me_2N(CH_2)_2OLi$ (BuLi−LiDMAE) used in apolar solvents (e.g. hexane) opened access to a new metalation site.[5] We have subsequently shown that the H-6 proton of 2-chloropyridine **1** and 2-methoxypyridine **6** was directly abstracted by the superbase BuLi−LiDMAE (Scheme 2).[6]

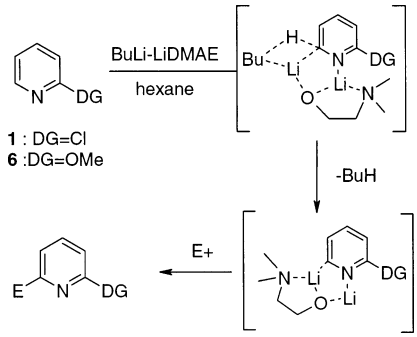
This unprecedented selectivity strongly contrasted with those usually obtained with LDA[7] or LTMP,[8] which lithiated exclusively the C-3 position according to the DOM selectivity (Figure 1).

Since the PM3-calculated acidity values were very close for H-3 and H-6, especially in **1**,[6] only the formation of

SCHEME 1



SCHEME 2



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(2) Anderson, D. R.; Faibish N. C.; Beak, P. *J. Am. Chem. Soc.* **1999**, *121*, 7553.

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(6) Gros, Ph.; Choppin, S.; Mathieu, J.; Fort, Y. *J. Org. Chem.* **2002**, 67, 234.

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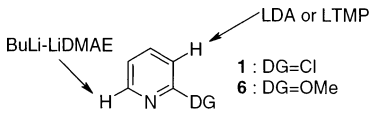


FIGURE 1.

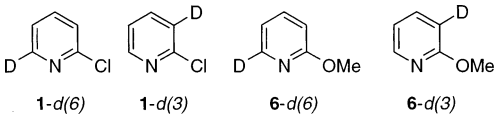
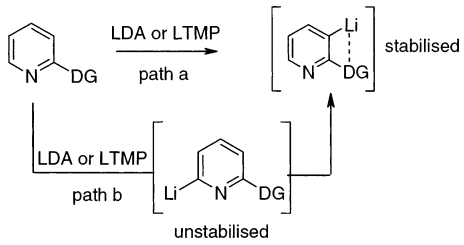


FIGURE 2.

SCHEME 3



aggregates at the nitrogen atom could explain the regioselectivity observed with BuLi−LiDMAE.[6] This result again opened interrogations about the lithiation mechanism with lithium dialkylamides. Indeed, one could wonder why these basic systems did not promote lithiation at C-6. The immediate answer is that the lithiation is initiated at C-3 and follows the DOM principles (path a, Scheme 3). Another explanation could be the absence of stabilization of the initially formed 6-lithio intermediate in the reaction medium, allowing equilibration toward the more stabilized 3-lithio species (path b, Scheme 3).

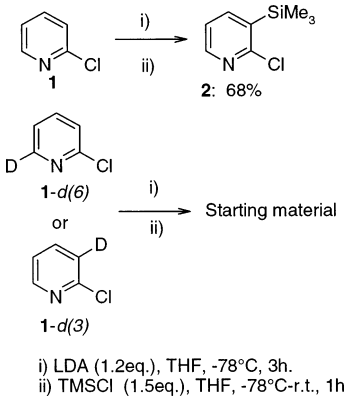
From these considerations, we decided to revisit the metalation of **1** and **6** with LDA and LTMP following the methodology previously used to study our reagent.[6] Thus, the deuterated compounds **1**-*d(6)*, **1**-*d(3)*, **6**-*d(6)*, and **6**-*d(3)* (Figure 2)[9] were chosen as probes to investigate the lithiation pathway.[10] Replacement of the prospective hydrogens (H-3 or H-6) by a deuterium was expected to effect protection by KIE.[11]

Lithiation of 1, 1-*d(6)*, and 1-*d(3)* with LDA.

Lithiation of **1** and its derivatives was performed with 1.2 equiv of the LDA reagent at −78 °C in THF.[7e] (Scheme 4).

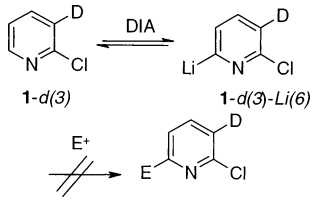
The results obtained were surprising when considering the classical interpretation of ortho-lithiation. Indeed, C-3 lithiation was obtained only when H-3 and H-6 were present on the pyridine ring. The absence of any reactivity of **1**-*d(6)* strongly supported the involvement of the H-6 proton in the lithiation process, since the starting material was recovered with an unchanged deuterium content (>98%). In the same way, the metalation of **1**-*d(3)* did not give any metalation product. According to the result obtained above with **1**-*d(6)* and taking into account

SCHEME 4[a]



[a] Conditions: (i) LDA (1.2 equiv), THF, −78 °C, 3 h. (ii) TMSCl (1.5 equiv), THF, −78 °C to rt, 1 h.

SCHEME 5



our hypothesis of a possible metalation at C-6, a 6-silylated product should have been detected at least in small amounts from **1**-*d(3)*. An explanation could be the protonation of the 6-lithio intermediate **1**-*d(3)*-Li*(6)* by diisopropylamine delivered in the reaction medium before electrophilic quenching (Scheme 5).

Thus, we studied the reaction with the more basic LTMP ($pK_a = 37.3$; $pK_a = 35.7$ for LDA).[4b] With such a reagent, the delivery of a less acidic conjugated amine (TMP) in the reaction medium could be expected to prevent protonation of lithiated intermediates and thus to allow efficient trapping by electrophile. The metalation was performed with 1.2 equiv of LTMP (Scheme 6).

As expected, LTMP led to **2** in better yield (95%) than LDA (68%, Scheme 4), and compounds **1**-*d(3)* and **1**-*d(6)* underwent metalation. Surprisingly, the lithiation of **1**-*d(3)* resulted in a mixture of regioisomers. Deuterium at C-3 induced a strong decrease in the yield of **2** (25%) as well as the formation of 4-silyl and 3,6-disilyl derivatives **4**-*d(3)* and **5**, respectively, in notable amounts. The 6-silyl derivative **3**-*d(3)* was also obtained in significant yield (6%), underlining the ability of LTMP to lithiate the 6 position.[12] Finally, **2**-*d(6)* was obtained in lower yield from **1**-*d(6)* than was **2** from **1**. Indeed, this compound was obtained in 80% yield besides 15% of unreacted **1**-*d(6)*, which displayed unchanged deuterium content. Although this result did not allow us to exclude direct lithiation at C-3, it also revealed the role of H-6 in the lithiation process.

We then studied the metalation of 2-methoxypyridine derivatives **6**, **6**-*d(6)*, and **6**-*d(3)* with the aim to examine

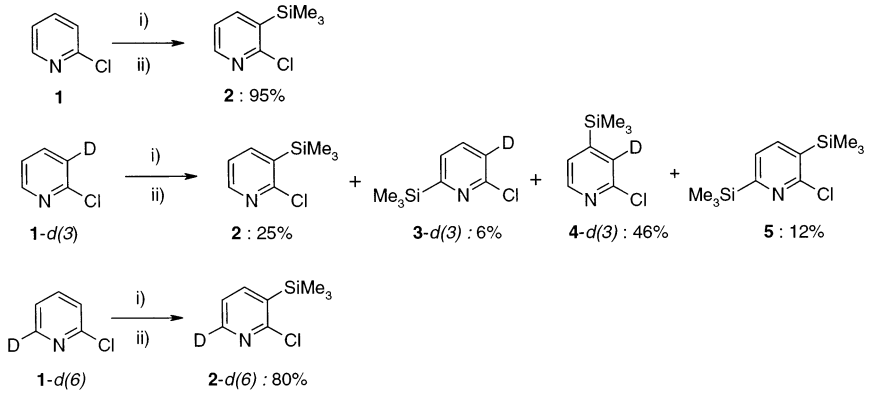
(9) **1**-*d(6)*, **6**-*d(6)*, **1**-*d(3)*, and **6**-*d(3)* were prepared according to refs 5d, 5a, 7e, and 8, respectively

(10) The reported yields are average values calculated for at least two runs. A reproducibility of ±2% was observed.

(11) Examples using KIE to elucidate reaction pathways have been reported. See for instance: (a) Kopach, M.; Meyers, A. I. *J. Org. Chem.*, **1996**, *61*, 6764. (b) Clayden, J.; Pink, J.; Westlund, N.; Wilson, F. *Tetrahedron Lett.* **1998**, *39*, 303.

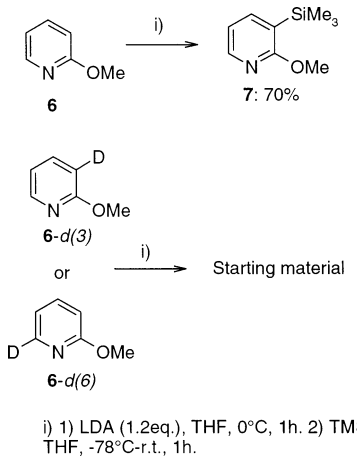
(12) Recently, Kondo and co-workers have reported a C-6 silylation of 2-bromopyridine with LTMP in Et_2O using an in situ trapping technique. Imahori, T.; Uchiyama, M.; Sakamoto, T.; Kondo, Y. *Chem. Commun.* **2001**, *23*, 2450.

SCHEME 6[a]



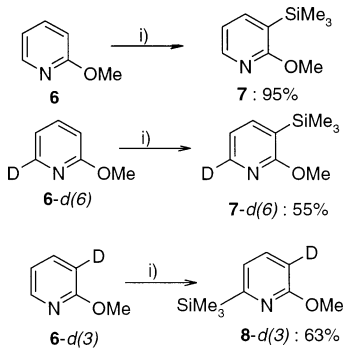
[a] Conditons: (i) LTMP (1.2 equiv), THF, −78 °C, 1.5 h. (ii) TMSCl (1.5 equiv), THF, −78 °C to rt, 1 h.

SCHEME 7[a]



[a] Conditions: (i) (1) LDA (1.2 equiv), THF, 0 °C, 1 h; (2) TMSCl (1.5 equiv) THF, −78 °C to rt, 1 h.

SCHEME 8[a]



[a] Conditions: (i) (1) LTMP (1.2 equiv), THF, −78 °C, 1 h; (2) $ClSiMe_3$ (1.5 equiv), THF, −78 °C, 1 h.

the effect of the methoxy group, known as a better lithium complexing agent than chlorine, on the selectivity.

Lithiation of 6, 6-*d(6)*, and 6-*d(3)* with LDA.

These substrates were lithiated according to literature procedures. The classical conditions required 1.2 equiv of LDA in THF at 0 °C (Scheme 7).

As shown, like with 2-chloropyridine derivatives, LDA gave no reaction with both 6- and 3-deuterated derivatives **6**-*d(6)* and **6**-*d(3)*, which were totally recovered with unchanged deuterium content. This again supported the high probability of the H-6 proton involvement in the lithiation pathway.

Lithiation of 6, 6-*d(6)*, and 6-*d(3)* with LTMP.

As already observed with LDA, H-3 and H-6 had to be present to ensure the complete C-3 lithiation of **6** with LTMP (Scheme 8).

Expectedly, the reaction of **6**-*d(3)* allowed us to trap of the 6-lithio intermediate, leading to compound **8**-*d(3)* in 63% yield, underlining the ability of LTMP to directly abstract H-6. This supported the hypothesis of the intermediate protonation in previous reaction with LDA. Protection of the C-3 position by deuterium was here noteworthy, allowing a complete reversal of usual selectivity. In addition, introduction of deuterium at C-6 resulted in the strong decrease of the yield of the C-3 silylated derivative.

TABLE 1. PM3-Calculated Mulliken Charges for 1 and 6[a]

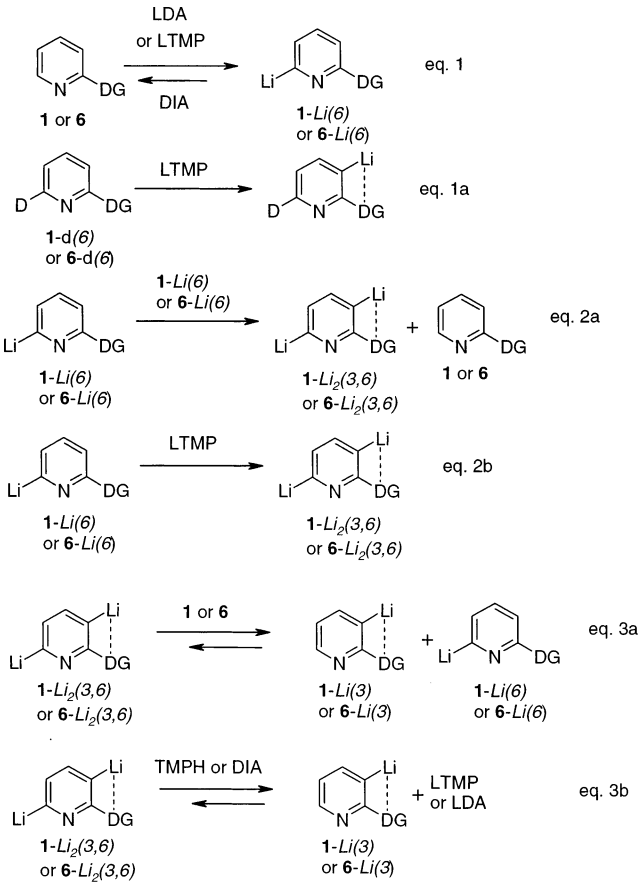
substrate	H-3	H-4	H-5	H-6
1	0.126	0.109	0.117	0.121
6	0.125	0.104	0.118	0.117

[a] Calculated with PM3 method.

Interestingly, **6**-*d(3)* did not give a mixture of regioisomers such as was observed with **1**-*d(3)*. Particularly, no silylation at C-4 was detected, while such product was obtained in 46% yield from **1**-*d(3)*. To explain such a difference the net atomic charges on hydrogens in **1** and **6** have been calculated (PM3 method) as a reflection of the relative acidities of the prospective protons (Table 1).

As shown, H-4 displayed higher acidity in both substrates. Thus, acidities did not allow us to explain lithiation at C-4 exclusively with **1**. We thought that the selectivity was here rather governed by the ability of heteroatoms at C-2 to chelate lithium. Thus the better complexation by the methoxy group probably led to localization of lithium dialkylamide near the oxygen atom and the pyridine nitrogen impeding lithiation at a position other than H-3 or H-6. With chlorine, the level of complexation was probably much lower, consequently

SCHEME 9



allowing free lithium dialkylamide to abtract the more acidic H-4 proton.

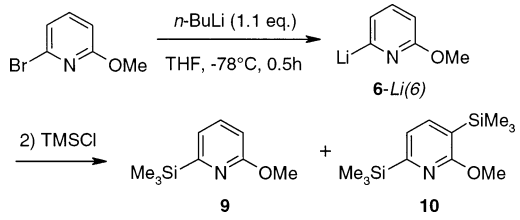
This study revealed the involvement of the H-6 proton in the lithiation pathway of **1** and **6** with LDA and LTMP and that C-3 lithiation appeared to be partly or totally initiated at C-6 with regard to the basic reagent (Scheme 9). Thus, **1**-*Li(6)* or **6**-*Li(6)* could react with itself (eq 2a) or with lithium dialkylamides (eq 2b) to give the dilithio intermediate **1**-Li_2*(3,6)* or **6**-Li_2*(3,6)*. These intermediates then could be turned into **1**-*Li(3)* or **6**-*Li(3)* following two pathways: reaction with **1** or **6** (eq 3a) or protonation at C-6 by DIA or TMPH (eq 3b). It can be seen that introduction of deuterium at C-6 prevents formation of the 6-lithio intermediate, leading to the absence of reaction with LDA or a drop of the C-3 functionalization yield with LTMP. In the same way introduction of deuterium at C-3 produces the 6-lithio derivative that is totally or partially protonated with regard to acidity of the conjugated amine delivered in the reaction medium.

Note that such a C-6 to C-3 isomerization pathway can be related to previous works dealing with lithiation of 3-chloro and 3-fluoropyridine, where lithio intermediates isomerization from C-2 to C-4 were also observed.[13]

To check the ability of the 6-lithio intermediate to produce the 3,6-dilithio derivative, **6**-*Li(6)* was prepared unambiguously from 6-bromo-2-methoxypyridine and the reaction mixture was quenched at various times and temperatures with TMSCl (Table 2).

(13) (a) Marsais, F.; Bréant, P.; Ginguene, A.; Quéguiner, G. *J. Organomet. Chem*. **1981**, *216*, 139. (b) Marsais, F.; Quéguiner, G. *Tetrahedron* **1983**, *39* (*12*), 2009.

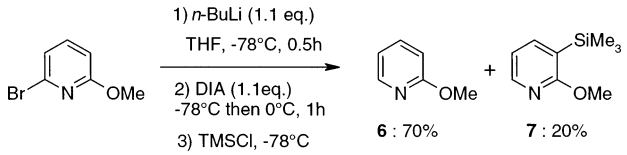
TABLE 2. Monitoring of 6-Li_2*(3,6)* Formation from 6-*Li(6)*



T (°C)	time (h)	**6** (%)[a]	**9** (%)[a]	**10** (%)[a]
−78	1		98	
−40	1		98	
0	0.5	5	80	10
0	1	12	70	15
0	2	13	68	15

[a] GC yields.

SCHEME 10



In agreement with eq 2a in Scheme 9, the above experiments revealed that **6**-Li_2*(3,6)* can be formed from **6**-*Li(6)* at 0 °C. Prolonged reaction times did not produce larger amounts of **10**, thus supporting an equilibrated process (eq 3a). Finally, we also verified that DIA could protonate **6**-*Li(6)* selectively (Scheme 10). This result also revealed the higher stability of **6**-*Li(3)* in the reaction medium.

Conclusion

This study reveals the ability of LDA or LTMP to first abstract the H-6 proton of 2-chloro and 2-methoxypyridine. Thus, the lithiation pathway could be not a direct ortho-direction but rather subsequent lithium ortho-stabilization in the reaction medium after initial lithiation at C-6. Due to its higher basicity, LTMP was found to be able to directly abstract H-3; H-6 was nevertheless probably also involved in the metalation. It is hoped that this study brings another argument to the open debate of the ortho-lithiation mechanism. Work is now in progress to investigate the structure of the proposed intermediates as well as the lithiation process with other ortho-directing groups in various positions of the pyridine nucleus.

Experimental Section

General Methods. ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, with TMS as internal standard and $CDCl_3$ as solvent.Coupling constants (*J*) are given in hertz. GC/MS spectra were recorded in EI mode.

Materials and Solvents. BuLi (1.6 M solution in hexane), 2-chloropyridine, 2-methoxypyridine, and dimethylaminoethanol were purchased from Acros. Hexane and THF were distilled and stored on sodium wire before use. All other reagents were commercially available and were purified or used as received. Compounds **2**[7e] and **7**[7a] were found to be identical to authentic samples.

Procedure for Metalation with LDA. To a solution of diisopropylamine (0.34 mL, 2.4 mmol) in THF (20 mL) cooled at −78 °C, under a nitrogen atmosphere, was added dropwise *n*-BuLi (1.5 mL, 2.4 mmol). After addition, the mixture was stirred at 0 °C for 30 min and then cooled to −78 °C and treated dropwise by a solution of the 2-chloropyridine derivative (2 mmol) in THF (5 mL). After 3 h of stirring, TMSCl (0.45 mL, 3 mmol) in THF (5 mL) was added dropwise. After one additional hour at −78 °C, the hydrolysis was performed at −10 °C with diluted aqueous HCl (10%). The aqueous layer was then extracted twice with ether. After drying ($MgSO_4$) and evaporation of solvents, the crude product was purified by column chromatography (hexane/AcOEt 95:5).

Procedure for Metalation with LTMP. To a solution of 2,2,6,6-tetramethylpiperidine (0.41 mL, 2.4 mmol) in THF (10 mL) cooled at −30 °C, under a nitrogen atmosphere, was added dropwise *n*-BuLi (1.5 mL, 2.4 mmol). After addition, the mixture was stirred at 0 °C for 30 min, cooled to −78 °C, and treated dropwise with a solution of the 2-chloropyridine derivative (2 mmol) in THF (5 mL). After 1.5 h of stirring, TMSCl (0.45 mL, 3 mmol) in THF (5 mL) was introduced dropwise. After one additional hour at −78 °C, the hydrolysis was performed at −10 °C with diluted aqueous HCl (10%). The workup was identical to that described above.

2-Chloro-[6-2*H*]-3-pyridyl(trimethyl)silane, 2-*d(6)*. ^{1}H NMR δ: 0.35 (s, 9H), 7.2 (d, J = 7.5 Hz, 1H), 7.75 (d, J = 7.5 Hz, 1H). ^{13}C NMR δ: −1.33 (C_3), 121.8, 135.2, 144.9, 152.3, 153.2, 153.9 156.8 ppm. MS (EI) *m*/*z* (%): 186 (M^+, 5), 171 (100), 135 (20), 107 (6), 93 (14), 78 (7), 63 (20), 53 (6).

2-Chloro-[3-2*H*]-6-pyridyl(trimethyl)silane, 3-*d(3)*. ^{1}H NMR δ: 0.3 (s, 9H), 7.40 (d, J = 7 Hz, 1H), 7.55 (d, J = 7 Hz, 1H). ^{13}C NMR δ: −1.9, 122.8, 122.9, 123.0, 127.3, 136.7, 151.3, 170.2 ppm. MS (EI) *m*/*z* (%): 187 (M^+ + 1, 20), 186 (M^+, 31), 171 (100), 151 (44), 93 (59), 72 (44), 63 (19).

2-Chloro-[3-2*H*]-4-pyridyl(trimethyl)silane, 4-*d(3)*. ^{1}H NMR δ: 0.3 (s, 9H), 7.3 (d, J = 4.8 Hz, 1H), 8.35 (d, J = 4.8 Hz, 1H). ^{13}C NMR δ: ∠2.1, 126.1, 127.2, 128.3, 128.9, 148.5, 151.1, 154.4 ppm. MS (EI) (*m*/*z*): 186 (M^+) (23), 171 (100), 93 (7), 83 (5), 73 (20), 63 (10), 52 (5).

2-Chloro-3,6-bis(trimethylsilyl)pyridine, 5. ^{1}H NMR δ: 0.3 (s, 9H), 0.35 (s, 9H), 7.4 (d, J = 7.1 Hz, 1H), 7.65 (d, J = 7.1 Hz, 1H). ^{13}C NMR δ: ∠1.8, −1.3, 127, 133.9, 142.9, 157.6 (C_2), 170.5 (C_6). MS (EI) (*m*/*z*): 258 (M^+ + 1, 17), 257 (M^+, 28), 256 (M^{+-} 1, 5), 243 (90), 223 (79), 185 (17), 151 (22), 93 (33).

Lithiation of 2-Methoxypyridines 6, 6-*d(6)*, and 6-*d(3)*. The procedure was identical to that with 2-chloropyridines, excepted that the metalation with LDA was carried out at 0 °C.

2-Methoxy-[6-2*H*]-3-pyridyl(trimethyl)silane, 7-*d(6)*. ^{1}H NMR δ: 7.64 (d, J = 7.2 Hz, 1H), 6.84 (d, J = 7.2 Hz, 1H), 3.93 (s, 3H), 0.26 (s, 9H). ^{13}C NMR δ: −2.1, 53.9, 120.2, 127.8, 136.5, 152.9, 153.5, 154.2, 167.3 ppm. MS (EI) *m*/*z* (%): 183 (M^+ + 1) (2), 182 (M^+) (14), 167 (40), 137 (100), 59 (11).

2-Methoxy-[3-2*H*]-6-pyridyl(trimethyl)silane, 8-*d(3)*. ^{1}H NMR δ: 7.44 (d, J = 8.0 Hz, 1H), 7.11 (d, J = 8.0 Hz, 1H), 3.93 (s, 3H), 0.27 (s, 9H).^{13}C NMR δ: −1.8, 53.9, 108.7, 109.3, 109.95, 125.7, 130.3, 162.9, 170.7 ppm. MS (EI) *m*/*z* (%): 183 (M^+ + 1) (5), 182 (M^+) (30), 167 (100), 137 (42), 59 (13).

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