JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

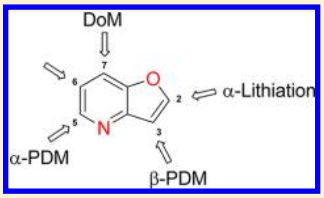
Successive Regioselective Metalations of Fused Heterocycles: Synthesis of Polyfunctionalized Furo[3,2-*b*]pyridines

Adeline Jasselin-Hinschberger, Corinne Comoy,* Anthony Chartoire, and Yves Fort*

Groupe Hétérocycles: Réactivité et Interaction (HECRIN), SRSMC UMR CNRS 7565, Université de Lorraine, B.P. 239, Boulevard des Aiguillettes, F-54506 Vandoeuvre-lès-Nancy, France

Supporting Information

ABSTRACT: The furopyridine framework was chosen as a target for a lithiation study, in order to define the most effective conditions leading to the total functionalization of the heterocycle. Consequently, a detailed procedure for successive regioselective lithiations/electrophilic trapping of furo[3,2-*b*]pyridines is described and afforded several polyfunctionalized derivatives in good overall yields. A Pd-catalyzed cross-coupling reaction is also described and easily yielded the 7,7′-bifuro[3,2-*b*]pyridine.



INTRODUCTION

In our ongoing research in heterocyclic chemistry, we are interested in the development of new strategies for the polyfunctionalization of aromatic heterocycles, especially fused heterocycles such as furopyridines.[1−5] The functionalities of such heterocycles are most frequently introduced before or during the construction of one of the aromatic rings, which has the effect of limiting potential subsequent functionalization as well as increasing the number of steps. Indeed, in the literature, the most reported processes for the preparation of substituted furopyridines usually involve a Pd-catalyzed furan ring formation starting from alkynyl-substituted pyridine derivatives.[6−15] In contrast, only few papers discuss the preparation of substituted furopyridines by direct functionalization of the bare heterocycles. Whereas this has been reported on the furan unit (C-2 or C-3 positions of furopyridines) using hydrogen lithium (H−Li) exchange reactions with these substrates,[2,16] regioselective lithiations of the pyridinic ring proved to be much more challenging. However, Shiotani[17−21] and more recently Baran[22] achieved the targeted functionalization using activated pyridinic rings (e.g., *N*-oxide derivative). Carrër and co-workers[23] also proposed an alternative sequence involving a palladium-catalyzed C−H activation leading to the introduction of aryl groups at the C-3 and C-7 positions. We have also recently reported new detailed procedures to achieve successive lithiation/functionalization of the furo[2,3-*c*]pyridine isomer, displaying control of the regioselectivity.[5] In a polar organometallic chemistry context, furopyridines, and especially furo[3,2-*b*]pyridines, appear of interest because of their characteristic reactivity resulting from the annulation. Indeed, the presence of two "nonconnected" heteroatoms is an additional interesting parameter to understand the complexation phenomena observed with the lithiated species. With the aim of controlling regioselectivities during metalation processes, the direct functionalization of such substrates always remains an interesting challenge.

In recent decades, significant researches have been reported concerning the development of regioselective lithiation reactions of aromatic or heteroaromatic substrates. From our perspective, the challenge today is to successfully introduce a different group on each position of selected substrates.

Among the five hydrogen atoms present on the furo[3,2-*b*]pyridine, H2, H3, H5 and H7 appear to be prime candidates for lithiation reactions. Indeed, due to their proximity to the heteroatoms (O or N), directed metalations such as *α*-lithiation, *β*- or *α*-pyridinodirected metalation (*β*- or *α*-PDM) or directed ortho-metalation (DoM) may respectively be envisioned as competitive (Figure 1). This diversity involves

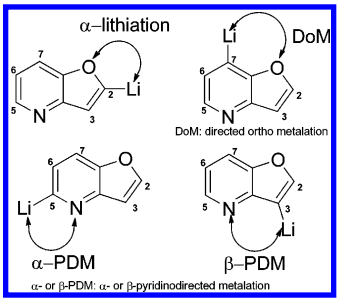


Figure 1. Potential directed lithiations of the furo[3,2-*b*]pyridine scaffold.

a judicious choice first of the lithiated basic system used for the metalation and second, of the considered sequence (because of the problem of functional tolerance between the introduced features and lithium reagents).[24] For example, while iodine (I_2) is useful as an electrophile to trap lithiated species during metalation studies, it proves to be an unsuitable electrophile for polyfunctionalizations because of side reactions (e.g., I−Li exchange, "halogen dance" rearrangement,[25] reduction, ...).

We report here the development of efficient successive functionalizations of the furo[3,2-*b*]pyridine scaffold combining several lithiation/electrophilic trapping steps. The major

Received: April 9, 2013

   dx.doi.org/10.1021/jo400748n | *J. Org. Chem.* XXXX, XXX, XXX−XXX

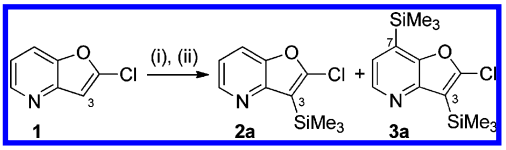
concern of this study was to carry out the various stages of functionalization with high chemioselectivity. Our aim was to propose a methodology that allows the introduction of functional groups in the presence of sensitive moieties without risking side-reactions. We have focused our attention on the reactivity of three classical basic systems: *n*-butyllithium (*n*-BuLi), lithium 2,2,6,6-tetramethylpiperidide (LiTMP) and Fort's superbase [*n*-BuLi/LiDMAE].

RESULTS AND DISCUSSION

In a preliminary study,[2] we reported that whatever basic conditions were used (*n*-BuLi, LiTMP or [*n*-BuLi/LiDMAE]), the lithiation of the furo[3,2-*b*]pyridine was occurring exclusively at the C-2 position of this fused heterocycle. No trace of deprotonation of the C-7 position invoking an ortho-metalation process, or deprotonation of the C-3 or C-5 positions potentially obtained through a pyridinodirected metalation (*α*- or *β*-PDM)[26−28] was observed. This regioselective *α*-lithiation reaction,[29] which proceeds with greater facility than the other lithiation processes, highlights the competition between coordination and "acid-base" mechanisms in favor of the acidic character of hydrogen H2. Starting from this point, we next envisioned to prepare 2,3-disubstituted furo[3,2-*b*]pyridines **2**. It appeared that the functionalization of the C-2 position of the furo[3,2-*b*]pyridine ring was easily and selectively produced by the action of *n*-BuLi.[2,30] However, to reach complete conversion, the use of 2 equivalents of *n*-BuLi is required. Under these conditions, the 2,3-dichlorofuro[3,2-*b*]pyridine **2e** was also obtained as a byproduct in 12% yield.[30] As expected, the acidity of H3 is greatly increased by the immediate vicinity of the chlorine atom at the C-2 position. This was confirmed by DFT calculations of Mulliken charges (see Supporting Information for more details about DFT calculations). As an extension of this result, we then examined the lithiation of the C-3 position starting from 2-chlorofuro-[3,2-*b*]pyridine **1** as substrate. The directed ortho-lithiation of heterocycle **1** by *n*-BuLi as lithiated agent was studied, and trimethysilyl chloride (Me_3SiCl) was chosen as representative electrophile to circumvent the potential lack of stability of polyhalogenated derivatives. The more significant results of this study are reported in Table 1. All reactions were monitored by GC using an internal standard. Lithiation of **1** was then carried out using *n*-BuLi (2 equiv) at −80 °C for 1 h in tetrahydrofuran (THF) as solvent, followed by treatment of the lithiated intermediate with Me_3SiCl (2.0 equiv) for 1 h at −80 °C to room temperature (25 °C). These conditions did not lead to complete conversion of the substrate (only 80%), but the expected 2-chloro-3-trimethylsilylfuro[3,2-*b*]pyridine **2a** was nevertheless obtained in 75% yield (GC), in the presence of a trace of 2-chloro-3,7-bis(trimethylsilyl)furo[3,2-*b*]pyridine **3a** (entry 1). The temperature of lithiation was then set at −60 °C or −45 °C (entries 2 and 3), leading to an increase of conversion (92 and 100%, respectively). However, the presence of compound **3a** was also detected (10 and 24% respectively) as a result of the double lithiation of **1** by the excess of *n*-BuLi present in the reaction medium. Consequently, the amount of *n*-BuLi was reduced (1.5 or 1.2 equiv versus 2 equiv, entries 4−8) and various metalation temperatures were probed.

When 1.5 equivalents of *n*-BuLi were used at −45 °C for 1 h followed by trapping with Me_3SiCl (2.0 equiv) at −45 °C to room temperature, byproduct **3a** was always detected in the reaction medium (11%, entry 4). The amount of *n*-BuLi was consequently adjusted to 1.2 equiv and metalation was performed at −60, −45 or −20 °C for 1 h in THF (entries 5−7). After electrophilic trapping, the 2-chloro-3-trimethylsilylfuro[3,2-*b*]pyridine **2a** was obtained in 79−87% yields (GC) and only traces of **3a** (<2%) were detected (GC). To lead to total consumption of substrate **1**, we envisioned to achieve the lithiation at 0 °C for 15 min (entry 8). Under these conditions, the conversion rate was not improved, the degradation of the lithiated intermediate was observed, and **2a** was detected in a moderate yield (57%). For a synthetic purpose, the scope of the reaction was investigated using the optimized lithiation conditions (entry 7) and various representative electrophiles as trapping agents. Furopyridine derivatives **2a−e** were then easily obtained in very good yields (58−85%, Scheme 1).

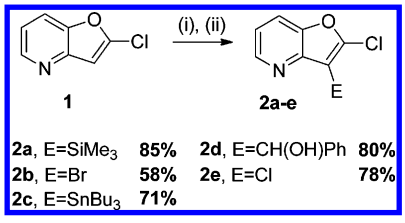
Table 1. Lithiation of 2-Chlorofuro[3,2-*b*]pyridine 1a



	metalation conditions[a]	trapping step conditions[a]	conversion (%)[b,c]	yields (%)[b,c]
	n equiv/*T* (°C)	*T* (°C)		**2a/3a**
1	2.0 equiv/−80	−80 to 25	80	75/trace
2	2.0 equiv/−60	−60 to 25	92	80/10
3	2.0 equiv/−45	−45 to 25	100	75/24
4	1.5 equiv/−45	−45 to 25	97	86/11
5	1.2 equiv/−60	−60 to 25	82	79/trace
6	1.2 equiv/−45	−45 to 25	91	85/trace
7	**1.2 equiv/−20**	**−20 to 25**	**91**	**87(85)[d]/trace**
8	1.2 equiv/0[e]	0 to 25	92	57/trace

[a]Reagents and conditions: (i) *n*-BuLi (*n* equiv), THF, T °C, 1 h. (ii) Me_3SiCl (2.0 equiv), THF, T °C to 25 °C, 1 h then H_2O. [b]Reaction performed on 0.8 mmol of **1**. [c]GC yields determined by internal standard method. [d]Isolated yield after centrifugal thin-layer chromatography purification. [e]Metalation was performed for 15 min.

Scheme 1. Preparation of 2,3-Disubstituted Furo[3,2-*b*]pyridines 2a−e[a,b]



[a]Reagents and conditions: (i) *n*-BuLi (1.2 equiv), THF, −20 °C, 1 h. (ii) E^+ = Me_3SiCl, CBr_4, Bu_3SnCl, PhCHO, C_2Cl_6 (2.0 equiv), THF, −20 to 25 °C, 1 h then H_2O. [b]Isolated yields after centrifugal thin-layer chromatography purification.

We next envisioned to achieve a third functionalization of the furo[3,2-*b*]pyridine moiety using a step by step procedure. As trimethylsilyl substitution at the C-3 position can act as a protective group, 2-chloro-3-trimethylsilylfuro[3,2-*b*]pyridine **2a** was chosen as substrate. Both C-5 and C-7 positions of the fused ring have attracted our attention for this study because of potential competing lithiations. Since the work by Gilman[31] and Wittig,[32] directed ortho-metalation (DoM) proved to be a powerful tool for the functionalization of

dx.doi.org/10.1021/jo400748n | J. Org. Chem. XXXX, XXX, XXX−XXX

aromatic or heteroaromatic scaffolds. Heteroatoms contained in the structures of directing metalation groups (DMGs) facilitate ortho-lithiations and provide predictable regioselectivities. Then, considering the structure of **2a**, the oxygen atom can allow a regioselective DoM[29,33] using classical *n*-BuLi or LiTMP[34] bases. DFT calculations of Mulliken charges (see Supporting Information) confirmed that the hydrogen atom at the C-7 position can be considered as the most acidic. In contrast, the use of the [*n*-BuLi/LiDMAE] superbase in aprotic solvents is known to favor the formation of aggregates near the nitrogen atom.[26−28] Indeed, in such conditions, and despite the fact that H5 is less acidic than H7, the lithiation may take place at the C-5 position as a competitive α-pyridinodirected metalation (α-PDM) (Figure 2).

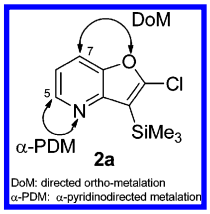
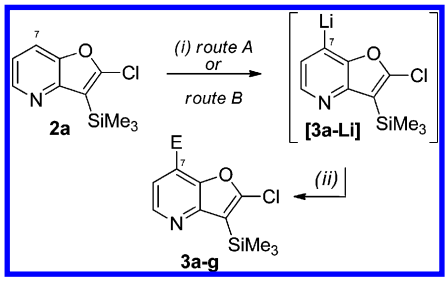


Figure 2. Potential directed lithiations of derivative **2a**.

We first decided to examine the action of *n*-BuLi as base toward derivative **2a**. After several attempts, best results were obtained when using *n*-BuLi (1.2 equiv) in THF for 1 h at −20 °C, followed by electrophilic trapping (2.0 equiv) (Table 2, route A). As expected, under these conditions, functionalization of **2a** was only observed at the C-7 position. Despite total conversion, the expected derivatives **3a−d** were obtained only in moderate yields (38−55%), in the presence of byproducts resulting from desilylation[5] and reaction medium degradation. To avoid side reactions due to the nucleophilic character of *n*-BuLi, we next decided to carry out the lithiation using LiTMP, because of its non-nucleophilic behavior (Table 2, route B).

Table 2. Preparation of 7-Substituted-2-chloro-3-trimethylsilylfuro[3,2-*b*]pyridines 3a−g



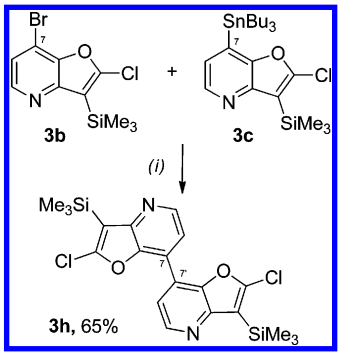
		yields[a−c] (%)			yields[a−c] (%)
	E	route B (route A)		E	route B
3a	$SiMe_3$	78 (40)	**3e**	Cl	92
3b	Br	88 (38)	**3f**	SMe	67
3c	$SnBu_3$	87 (55)	**3g**	CHO	85
3d	CH(OH)Ph	90 (46)			

[a]Reagents and conditions: (i) route A = *n*-BuLi (1.2 equiv), THF, −20 °C, 1 h/route B = LiTMP (2.0 equiv), THF, −20 °C, 1 h. (ii) E^+ = Me_3SiCl, CBr_4, Bu_3SnCl, PhCHO, C_2Cl_6, Me_2S_2 or DMF (2.0 equiv), THF, −20 to 25 °C, 1 h then H_2O. [b]Reaction performed on 0.53 mmol of **2a**. [c]Isolated yields after centrifugal thin-layer chromatography purification.

Indeed, LiTMP (2.0 equiv) in THF as solvent, at −20 °C for 1 h, afforded efficient lithiation at the C-7 position. This was evidenced by trapping the lithiated intermediate with various electrophiles, producing the highly functionalized 2,3,7-trisubstituted derivatives **3a−g** in very good yields (78−92%, Table 2).

The synthetic potential of the trisubstituted scaffolds was further exemplified by involving the 7-bromo derivative **3b** and the 7-stannyl compound **3c** into a Pd-catalyzed cross-coupling reaction. Interestingly, under usual Stille conditions, the 7,7′-bifuropyridine **3h** was efficiently prepared in good yield (65%, Scheme 2).

Scheme 2. Preparation of 7,7′-Bifuro[3,2-*b*]pyridine Derivative 3h[a,b]



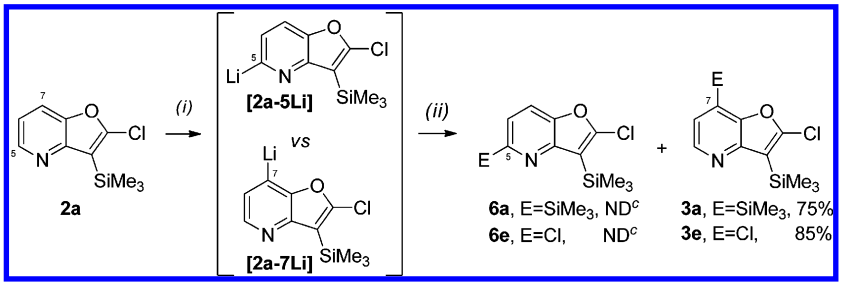
[a]Reagents and conditions: (i) **3b** (1.0 equiv), **3c** (1.1 equiv), $PdCl_2(PPh_3)_2$ (5 mol %), DMF, 110 °C, 24 h. [b]Reaction performed on 0.53 mmol of **3b**. Isolated yields after centrifugal thin-layer chromatography purification.

We next turned our attention to the direct functionalization at the C-5 position, involving the deprotonation of the less acidic hydrogen atom H5 (Scheme 3). Such a metalation may be considered by using the monometallic non-nucleophilic superbase [*n*-BuLi/LiDMAE] which generally exhibits specific aggregation[35] on the pyridinic nitrogen atom. We then carried out deprotonation of furopyridine derivative **2a** using the [*n*-BuLi/LiDMAE] superbase (3.0 equiv) in hexanes as solvent followed by electrophilic trapping using Me_3SiCl or hexachloroethane (C_2Cl_6) (3.0 equiv). When the metalation step was carried out at −78 °C for 1, 2 or 4 h, starting material **2a** was recovered unchanged. In contrast, H−Li exchange partially occurred at −45 °C (less than 30%) to become complete at −20 °C. Unfortunately, deprotonation of the C-7 position was revealed since only 7-trimethylsilyl or 7-chloro isomers **3a** and **3e** were isolated in excellent yields (75 and 85%, respectively) without any trace of 5-substituted furo[3,2-*b*]pyridine **6a** or **6e**. Despite the fact that the [*n*-BuLi/LiDMAE] superbase usually promotes deprotonation of the α-position of the pyridinic nitrogen even in the presence of DMGs (Cl, SMe, OMe, etc.),[3,4,36] we note that in the case of furopyridines, the deprotonation always occurs at the C-7 position. This is probably due to the fact that the complexation of the superbase, preferred on the oxygen atom at the expense of the nitrogen one, enhances the H7 acidity versus H5 acidity,[5,37] then only the deprotonation at the C-7 position can be observed.

As stated earlier, our aim was to achieve the functionalization of each position of the heterocycle. At this stage of our study, the functionalization of the C-6 position became possible thanks to the activation generated by the group introduced at

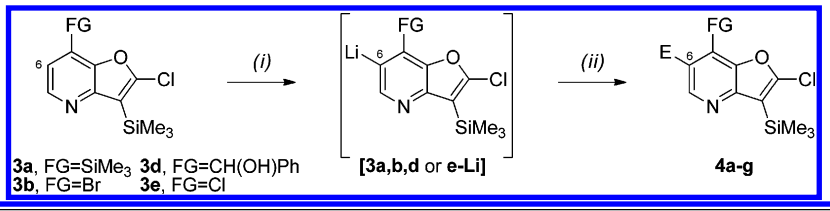
dx.doi.org/10.1021/jo400748n | J. Org. Chem. XXXX, XXX, XXX−XXX

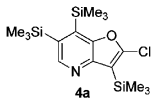
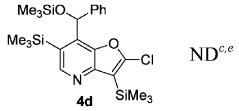
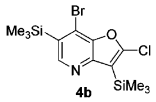
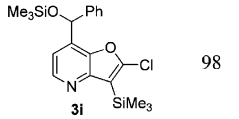
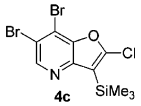
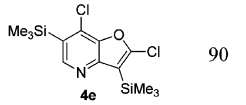
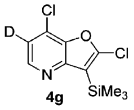
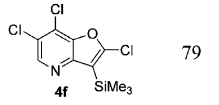
Scheme 3. Competitive Lithiation of the C-5 and C-7 Positions with the [*n*-BuLi/LiDMAE] Superbase[a,b]



[a]Reagents and conditions: (i) [*n*-BuLi/LiDMAE] (3.0 equiv), hexanes, −20 °C, 1 h. (ii) Me_3SiCl or C_2Cl_6 (3.0 equiv), THF, −20 to 25 °C, 1 h then H_2O. [b]Isolated yields after centrifugal thin-layer chromatography purification. [c]ND: not detected.

Table 3. Preparation of 6,7-Disubstituted-2-chloro-3-trimethylsilylfuro[3,2-*b*]pyridines 4a−g



Substrate	E^+	Product	Yield[a,b] (%)	Substrate	E^+	Product	Yield[a,b] (%)
3a FG=$SiMe_3$	Me_3SiCl	 **4a**	ND[c]	**3d** FG=CH(OH)Ph	Me_3SiCl	 **4d**	ND[c,e]
3b FG=Br	Me_3SiCl	 **4b**	73[d]			 **3i**	98
3b FG=Br	CBr_4	 **4c**	41[d]	**3e** FG=Cl	Me_3SiCl	 **4e**	90
3e FG=Cl	CD_3OD	 **4g**	82	**3e** FG=Cl	C_2Cl_6	 **4f**	79

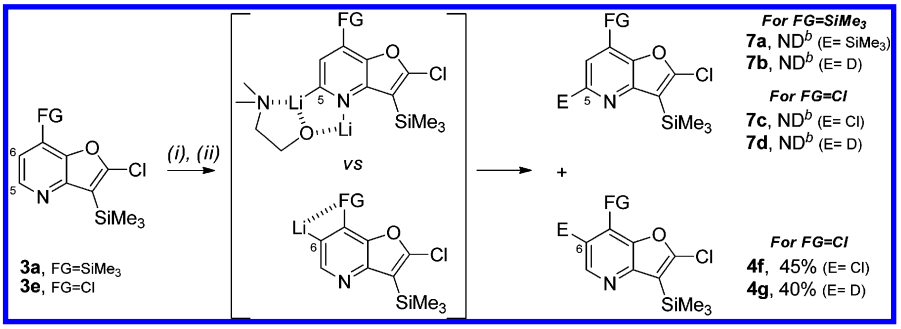
[a]Reagents and conditions: (i) LiTMP (3.0 equiv), THF, −20 °C, 1 h. (ii) E^+= Me_3SiCl, CBr_4, CD_3OD or C_2Cl_6 (3.0 equiv), THF, −20 to 25 °C, 1 h then H_2O. [b]Isolated yields after centrifugal thin-layer chromatography purification. [c]ND: not detected. [d]**4b−c** are unstable and lead to degradation compounds. [e]4.0 equiv of LiTMP then 4.0 equiv of Me_3SiCl were used.

the C-7 position. Lithiations of trisubstituted derivatives **3a**,**b** or **3e** were then performed using LiTMP (3.0 equiv) as base (to avoid nucleophilic attack on the silyl group), at −20 °C for 1 h and in THF as solvent. The lithiated species were next trapped with Me_3SiCl, CBr_4, C_2Cl_6 or CD_3OD as electrophiles (3.0 equiv). Main results are reported in Table 3. As expected and according to the DFT calculation of Mulliken charges (see Supporting Information for more details about DFT calculations), H6−Li exchange takes place only if a halogen atom is present at the C-7 position (Br or Cl, **3b** or **3e** respectively). This ortho-metalation could be attributed to a complex induced proximity effect (CIPE). The complexation between LiTMP and the halogen leads at first to a close relationship between the lithiated base and H6. Then, because the electrons of the heteroatom are shared with the metal, the inductive effect of the halogen is increased. This has the effect of accentuating the acidity of H6 and thus facilitates the deprotonation.[38] In the above-described conditions, no reaction was observed starting from silyl derivative **3a** while halogenated isomers **3b**,**e** gave the desired tetrasubstituted heterocycles **4b**,**c**,**e**−**g** in very good yields (41−90%, Table 3). On the other hand, we studied the metalation of **3d**. The hydroxymethyl group at the C-7 position does not increase the acidity of the H6 hydrogen atom, however the oxyanion unit which is generated in basic medium can be considered as a potential directing group and may facilitate the expected selective reaction. Unfortunately, no trace of furopyridine **4d** was detected, **3d** being converted into silyl ether **3i** in quantitative yield.

The results described above from **2a**, **3a** and **3d** suggest that the lithiation of furopyridines can be achieved only if an "acid-base" mechanism is possible. To check this hypothesis, we next planned to carry out lithiations using the superbase [*n*-BuLi/LiDMAE] starting from 7-silyl or 7-chloro isomers **3a** and **3e**. Without activating substituent (**3a**), H−Li exchange could be envisioned only at the C-5 position according to an α-PDM involving an initial coordination step. On the other hand, in the case of **3e** and using the superbase [*n*-BuLi/LiDMAE] as lithiated base, two reaction pathways can be proposed: (a) a

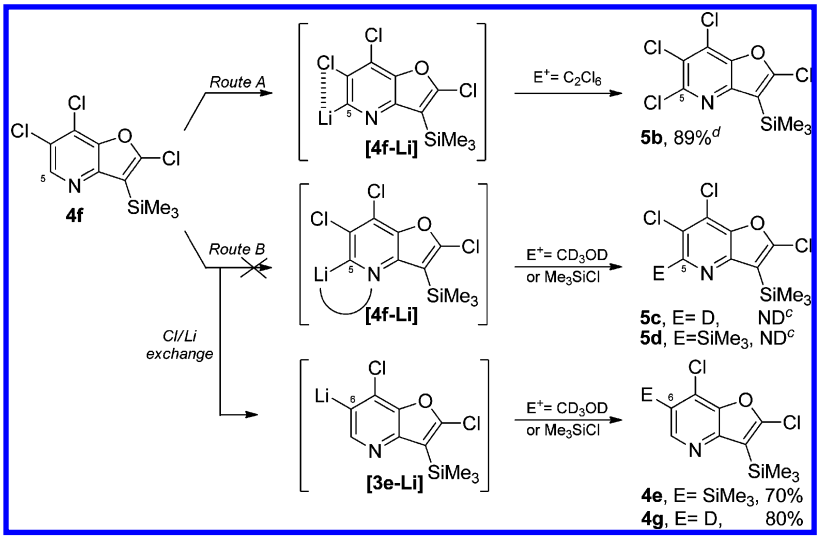
dx.doi.org/10.1021/jo400748n | J. Org. Chem. XXXX, XXX, XXX−XXX

Scheme 4. Lithiation of the C-5 or C-6 Positions of 3a or 3e with the [*n*-BuLi/LiDMAE] Superbase[a]



[a]Reagents and conditions: (i) [*n*-BuLi/LiDMAE] (3.0 to 12.0 equiv), hexanes, −45 or −20 °C, 1 h to 4h. (ii) E^+= Me_3SiCl or C_2Cl_6 (3.0 or 4.0 equiv) or CD_3OD (40.0 equiv), THF, −45 or −20 to 25 °C, 1 h then H_2O. [b]ND: Not detected.

Scheme 5. Lithiation of 6,7-Disubstituted-2-chloro-3-trimethylsilylfuro[3,2-*b*]pyridines 4e−f[a,b]



[a]Reagents and conditions: (i) route A = LiTMP (3.0 equiv), THF, −20 °C, 1 h or route B= [*n*-BuLi/LiDMAE] (3.0−6.0 equiv), hexanes, −20 °C, 1−4 h. (ii) E^+= CD_3OD (40.0 equiv), C_2Cl_6 or Me_3SiCl (3.0 to 6.0 equiv), THF, −20 to 25 °C, 1 h then H_2O. [b]Isolated yields after centrifugal thin-layer chromatography purification. [c]ND: expected derivatives were not detected. [d]**5b** is not stable at room temperature and leads to degradation compounds.

H−Li exchange at the C-6 position would highlight an "acid-base" mechanism, due to the inductive effect generated by the chlorine atom at the C-7 position which increases the acidity of H6; (b) a H−Li exchange at the C-5 position would evidence a "coordination" effect as main pathway. Various attempts were then implemented as reported in Scheme 4: (i) [*n*-BuLi/LiDMAE] (3.0−12.0 equiv), in hexanes, at −45 or −20 °C for 1−4 h; (ii) electrophile (3.0, 4.0, or 40.0 equiv), in THF, at −45 or −20 to 25 °C for 1 h. As expected (taking into account previous results), no trace of 5-substituted products **7a−d** was detected and starting materials were recovered unchanged. However, functionalization was observed at the C-6 position starting from 7-chloro derivative **3e** according to a DoM process. Reactions using 4.0 equiv of superbase, at −20 °C for 1 h followed by addition of C_2Cl_6 (4.0 equiv) or CD_3OD (40.0 equiv) as electrophile, at −20 to 25 °C for 1 h produced compounds **4f** and **4g** in 45 and 40% yields, respectively.

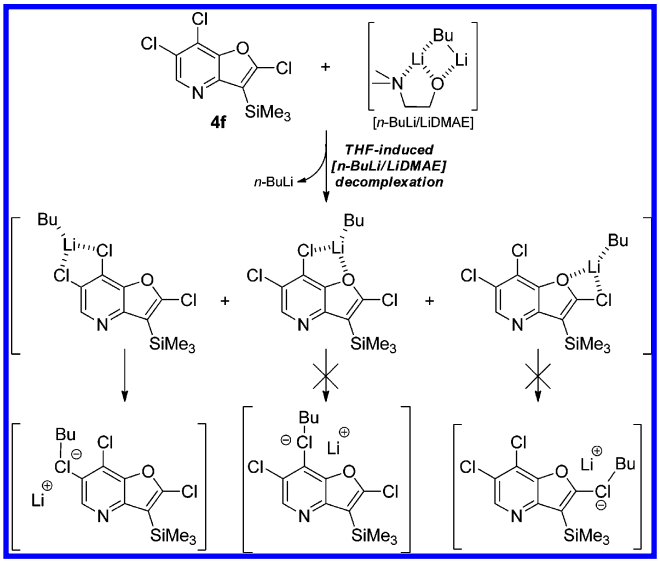
Finally, to complete our study, we focused our efforts on the functionalization of the last available position of the furopyridine. The 6-chloro derivative **4f** was chosen as representative substrate because of the activation resulting from the neighboring chlorine atom. LiTMP appeared as a good candidate to perform this last lithiation according to a DoM process. However, even if not efficient starting from **2a** or **3a**,**e**, *α*-PDM conditions using the superbase [*n*-BuLi/LiDMAE] could also be of interest because of the interesting cooperative effect[3] of nitrogen and chlorine atoms (see Supporting Information for DFT calculations). As depicted in Scheme 5, we envisioned the functionalization of chloro derivative **4f** by route A. According to our forecast, metalation of **4f** was easily obtained using LiTMP as base (3.0 equiv) in THF as solvent, at −20 °C for 1 h, followed by addition of C_2Cl_6 as electrophile, affording the expected pentasubstituted furopyridine **5b** in excellent isolated yield (89%). Compared to the results obtained above, the activation induced by the chlorine atom at the C-6 position was shown to be essential to the success of this metalation reaction. Lithiation of **4f** was next carried out according to the conditions described in route B: (i) [*n*-BuLi/LiDMAE] (3.0 to 6.0 equiv), in hexanes, at −20 °C for 1, 2 or 4 h; then (ii) addition of Me_3SiCl or CD_3OD as electrophiles (3.0 to 6.0 or 40.0 equiv respectively), in THF, at −20 to 25 °C for 1 h.

While total consumption of substrate **4f** was observed in both cases, no trace of desired products **5c** and **5d** resulting from *α*-PDM was detected. Surprisingly, the unexpected 6-trimethylsilyl and 6-deuterated derivatives **4e** and **4g** were

dx.doi.org/10.1021/jo400748n | J. Org. Chem. XXXX, XXX, XXX−XXX

isolated in excellent yields (70 and 80% respectively). These results evidence a Cl−Li exchange at the C-6 position. Although Cl−Li exchange is unusual with LiTMP, we have already observed such a permutation in the case of the lithiation of 7-chlorofuro[2,3-*c*]pyridine with [*n*-BuLi/LiDMAE].[5] A probable pathway is the following: after formation of [superbase/substrate] aggregates in apolar hexanes, the addition of THF (with the electrophile) produces a local decomplexation of the aggregates and releases *n*-BuLi near the C−Cl bonds, thus inducing a regioselective Cl−Li exchange at the C-6 position. As the mechanism of halogen/lithium exchange reactions is still under debate, it is generally admitted that in (hetero)aromatic series, the reaction proceeds through an halogen "ate"-type intermediate (nucleophilic pathway).[39] Thus, one hypothesis to explain such selectivity might be an "ate" mechanism favored at the C-6 position (Scheme 6).

Scheme 6. Postulated Mechanism for the Cl−Li Exchange at the C-6 Position[a]



[a]Reagents and conditions: (i) [*n*-BuLi/LiDMAE] (3.0 to 6.0 equiv), hexanes, −20 °C, 1−4 h. (ii) E^+, THF, −20 to 25 °C, 1 h.

To conclude, we have described here five successive regioselective lithiations of the furo[3,2-*b*]pyridine framework. Our study has required the development of specific metalation conditions involving compatibility between various lithiated reagents and different functional groups. While H2−Li or H3−Li exchanges on the furan moiety were easily achieved in very good yields, lithiations of the pyridinic ring have been more difficult to implement. Nevertheless we have managed to carry out five sequential functionalizations of the furopyridine scaffold, by exploiting activating effects of halogen atoms introduced at the C-7 or C-6 position. Regardless of the base used for the lithiation reactions (LiTMP or superbase [*n*-BuLi/LiDMAE]), the obtained results highlight mechanisms based on acid−base character rather than complexation near the pyridinic nitrogen atom. However, in particular cases, we also showed that complexation (and/or CIPE) can constitute the driving force of unusual Cl−Li exchange. Finally, as shown with the preparation of 7,7′-bifuro[3,2-*b*]pyridine **3h**, advantages of our strategy are to allow further functionalizations which could be envisioned using regioselective reactions on the furan moiety or/and on the pyridine ring (e.g., Pd-catalyzed cross couplings, Ni-catalyzed arylamination[40]). Works are in progress to explore such reactions.

EXPERIMENTAL SECTION

General. ^{1}H and ^{13}C NMR spectra were recorded at 400 or 250 or 200 and 100 or 63 or 50 MHz, respectively, with $CDCl_3$ as solvent and TMS as internal standard (for ^{1}H NMR). HRMS spectra were recorded on a microTOF-Q spectrometer. MS were recorded on a GCMS-QP2010 spectrometer. Melting temperatures are uncorrected and recorded with a thermostatic oil bath device.

Reagents. All reagents were commercially available and were purified by distillation when necessary. *n*-BuLi was used as a commercial 1.6 M solution in hexanes (titrated before use). 2-(Dimethylamino)ethanol (DMAE) was distilled and stored over molecular sieves before use. Hexanes and THF were distilled and stored on sodium wire before use. Centrifugal thin-layer chromatography purifications were performed on silica gel (silica gel 60 PF_{254} containing gypsum).

General Procedure for the Preparation of LiTMP Base. To a solution of 2,2,6,6-tetramethylpiperidine (TMP) (542 mg, 3.84 mmol, 1.0 equiv) in anhydrous tetrahydrofuran (THF) (10 mL) at −20 °C was added dropwise *n*-BuLi (2.4 mL, 1.6 M in hexanes, 3.84 mmol, 1.0 equiv) under argon atmosphere. After 30 min at 0 °C, LiTMP base (*C* = 0.31 M) is ready to be used.

General Procedure for the Preparation of the [*n*-BuLi/LiDMAE] Superbase. To a solution of 2-(dimethylamino)ethanol (DMAE) (712 mg, 8.0 mmol, 1.0 equiv) in anhydrous hexanes (14 mL) at −20 °C was added dropwise *n*-BuLi (10.0 mL, 1.6 M in hexanes, 16.0 mmol, 2.0 equiv) under argon atmosphere. After 15 min at 0 °C, the [*n*-BuLi/LiDMAE] superbase (*C* = 0.33 M) is ready to be used.

Lithiation of the 2-Chlorofuro[3,2-*b*]pyridine 1 with *n*-BuLi. *General procedure.* To a solution of 2-chlorofuro[3,2-*b*]pyridine **16**[2] (123 mg, 0.80 mmol, 1.0 equiv) in THF (10 mL) was added dropwise *n*-BuLi (0.6 mL, 0.96 mmol, 1.2 equiv) at −20 °C, under argon atmosphere. After stirring for 1 h at −20 °C, the appropriate electrophile (1.6 mmol, 2.0 equiv) was added in THF (5 mL) at −20 °C. The temperature was then allowed to warm to 20 °C over 20 min. After stirring for 40 min at 20 °C, the hydrolysis was performed with H_2O (10 mL) at 20 °C. The aqueous layer was then extracted twice with AcOEt (2 × 10 mL). After drying ($MgSO_4$), filtration and solvent evaporation, the crude product was purified by centrifugal thin-layer chromatography.

2-Chloro-3-trimethylsilylfuro[3,2-*b*]pyridine 2a. The product **2a** was prepared according to the general procedure described herein with chlorotrimethylsilane (TMSCl) (174 mg, 1.6 mmol, 2.0 equiv) as electrophile. Purification by centrifugal thin-layer chromatography was performed with cyclohexane/AcOEt: 10/0 to 9/1 as eluent and led to the expected compound **2a** (153 mg, 85%) as a white powder: mp 37−39 °C. ^{1}H NMR δ_H (ppm) 0.47 (s, 9H); 7.15 (dd, J = 8.3 Hz, J' = 4.8 Hz, 1H); 7.64 (dd, J = 8.3 Hz, J'= 1.4 Hz, 1H); 8.50 (dd, J = 4.8 Hz, J' = 1.4 Hz, 1H). ^{13}C NMR δ_C (ppm) −0.6 (3C); 111.4; 117.0; 118.7; 145.9; 147.7; 149.7; 152.7. SM (IE): *m*/*z* 225 ($[M]^+$, 25); 210 (100); 190 (16). ESI-HRMS calcd for $C_{10}H_{13}ClNOSi$ $(M + H)^+$: 226.0449; found: 226.0445.

3-Bromo-2-chlorofuro[3,2-*b*]pyridine 2b. The product **2b** was prepared according to the general procedure described herein with CBr_4 (531 mg, 1.6 mmol, 2.0 equiv) as electrophile. Purification by centrifugal thin-layer chromatography was performed with cyclohexane/AcOEt: 9/1 to 7/3 as eluent and led to the expected compound **2b** (108 mg, 58%) as a brown solid. This derivative is particularly unstable to the light and at room temperature: ^{1}H NMR and mp are in conformity with literature.[41] MS (EI) *m*/*z* 233 ($[M + 2]^+$, 96); 231 ($[M]^+$, 78); 205 (20); 126 (33); 124 (100). ESI-HRMS calcd for $C_7H_4BrClNO$ $(M + H)^+$: 231.9159; found: 231.9156.

2-Chloro-3-tri-*n*-butylstannylfuro[3,2-*b*]pyridine 2c. The product **2c** was prepared according to the general procedure described herein with chlorotri-*n*-butyltin (521 mg, 1.6 mmol, 2.0 equiv) as electrophile. Purification by centrifugal thin-layer chromatography was

dx.doi.org/10.1021/jo400748n | J. Org. Chem. XXXX, XXX, XXX−XXX

performed with cyclohexane/AcOEt: 10/0 to 95/5 as eluent and led to the expected compound **2c** (251 mg, 71%) as a colorless liquid: ^{1}H NMR δ_H (ppm) 0.88 (t, J = 7.3 Hz, 9H); 1.24−1.39 (m, 12H); 1.55−1.62 (m, 6H); 7.12 (dd, J = 8.2 Hz, J' = 4.8 Hz, 1H); 7.62 (dd, J = 8.2 Hz, J' = 1.4 Hz, 1H); 8.46 (dd, J = 4.8 Hz, J' = 1.4 Hz, 1H). ^{13}C NMR δ_C (ppm) 10.2 (3C); 13.8 (3C); 27.3 (3C); 29.2 (3C); 111.9; 116.7; 118.5; 145.9; 147.9; 150.2; 154.5. MS (EI) m/z 386 ([M-57]$^+$, 68); 328 (13); 272 (100). ESI-HRMS calcd for $C_{19}H_{30}ClNNaOSn$ (M + Na)$^+$: 466.0927; found: 466.0917.

1-(2-Chlorofuro[3,2-*b*]pyridin-3-yl)-1-phenylmethanol 2d. The product **2d** was prepared according to the general procedure described herein with benzaldehyde (170 mg, 1.6 mmol, 2.0 equiv) as electrophile. Purification by centrifugal thin-layer chromatography was performed with cyclohexane/AcOEt: 8/2 to 7/3 as eluent and led to the expected compound **2d** (166 mg, 80%) as beige solid: mp 80−83 °C. ^{1}H NMR δ_H (ppm) 4.90 (br s, 1H); 6.06 (s, 1H); 7.18 (dd, J = 8.4 Hz, J' = 4.9 Hz, 1H); 7.24−7.36 (m, 3H); 7.53−7.58 (m, 2H); 7.64 (dd, J = 8.4 Hz, J' = 1.3 Hz, 1H); 8.45 (dd, J = 4.9 Hz, J' = 1.3 Hz, 1H). ^{13}C NMR δ_C (ppm) 69.5; 117.9; 118.1; 119.4; 126.3 (2C); 127.9; 128.6 (2C); 142.2; 142.4; 145.8; 146.7; 146.9. MS (EI) m/z 259 ([M]$^+$, 50); 182 (100); 153 (23). ESI-HRMS calcd for $C_{14}H_{10}ClNNaO_2$ (M + Na)$^+$: 282.0292; found: 282.0291.

2,3-Dichlorofuro[3,2-*b*]pyridine 2e. The product **2e** was prepared according to the general procedure described herein with C_2Cl_6 (379 mg, 1.6 mmol, 2.0 equiv) as electrophile. Purification by centrifugal thin-layer chromatography was performed with cyclohexane/AcOEt: 10/0 to 95/5 as eluent and led to the expected compound **2e** (117 mg, 78%) as a white powder: mp 57−60 °C. ^{1}H NMR δ_H (ppm) 7.31 (dd, J = 8.4 Hz, J' = 4.8 Hz, 1H); 7.73 (dd, J = 8.4 Hz, J' = 1.2 Hz, 1H); 8.60 (dd, J = 4.8 Hz, J' = 1.2 Hz, 1H). ^{13}C NMR δ_C (ppm) 109.8; 118.5; 120.4; 142.6; 144.0; 146.4; 147.1. MS (EI) m/z 189 ([M + 2]$^+$, 60); 187 ([M]$^+$, 94); 159 (46); 126 (33); 124 (100). ESI-HRMS calcd for $C_7H_3Cl_2NNaO$ (M + Na)$^+$: 209.9484; found: 209.9484.

Lithiation of 2-Chloro-3-trimethylsilylfuro[3,2-*b*]pyridine 2a with *n*-BuLi or LiTMP: Preparation of Compounds 3a−g. *General Procedure with n-BuLi, Route A.* To a solution of 2-chloro-3-trimethylsilylfuro[3,2-*b*]pyridine **2a** (120 mg, 0.53 mmol, 1.0 equiv) in THF (10 mL) was added dropwise *n*-BuLi (0.4 mL, 0.64 mmol, 1.2 equiv) at −20 °C, under argon atmosphere. After stirring for 1 h at −20 °C, the appropriate electrophile (1.06 mmol, 2.0 equiv) was added in THF (5 mL) at −20 °C. The temperature was then allowed to warm to 20 °C over 20 min. After stirring for 40 min at 20 °C, the hydrolysis was performed with H_2O (10 mL) at 20 °C. The aqueous layer was then extracted twice with AcOEt (2 × 10 mL). After drying ($MgSO_4$), filtration and solvent evaporation, the crude product was purified by centrifugal thin-layer chromatography.

General Procedure with LiTMP, Route B. To a solution of LiTMP (3.4 mL, 0.31M, 1.06 mmol, 2.0 equiv) in THF was added dropwise 2-chloro-3-trimethylsilylfuro[3,2-*b*]pyridine **2a** (120 mg, 0.53 mmol, 1.0 equiv) in THF (10 mL) at −20 °C, under argon atmosphere. After stirring for 1 h at −20 °C, the appropriate electrophile (1.06 mmol, 2.0 equiv) was added in THF (5 mL) at −20 °C. The temperature was then allowed to warm to 20 °C over 20 min. After stirring for 40 min at 20 °C, the hydrolysis was performed with H_2O (10 mL) at 20 °C. The aqueous layer was then extracted twice with AcOEt (2 × 10 mL). After drying ($MgSO_4$), filtration and solvent evaporation, the crude product was purified by centrifugal thin-layer chromatography.

2-Chloro-3,7-bis(trimethylsilyl)furo[3,2-*b*]pyridine 3a. The product **3a** was prepared according to the general procedure described herein with TMSCl (115 mg, 1.06 mmol, 2.0 equiv) as electrophile. Purification by centrifugal thin-layer chromatography was performed with cyclohexane/AcOEt: 10/0 as eluent and led to the expected compound **3a** (route A: 63 mg, 40%; route B: 123 mg, 78%) as a white solid: mp 42−44 °C. ^{1}H NMR δ_H (ppm) 0.41 (s, 9H); 0.46 (s, 9H); 7.17 (d, J = 4.7 Hz, 1H); 8.46 (d, J = 4.7 Hz, 1H). ^{13}C NMR δ_C (ppm) −1.4 (3C); −0.6 (3C); 110.9; 123.3; 130.5; 145.0; 149.5; 150.6; 152.4. MS (EI) m/z 297 ([M]$^+$, 26); 282 (47); 262 (30); 93 (24); 73 (100). ESI-HRMS calcd for $C_{13}H_{21}ClNOSi_2$ (M + H)$^+$ 298.0845; found: 298.0851.

7-Bromo-2-chloro-3-trimethylsilylfuro[3,2-*b*]pyridine 3b. The product **3b** was prepared according to the general procedure described herein with CBr_4 (352 mg, 1.06 mmol, 2.0 equiv) as electrophile. Purification by centrifugal thin-layer chromatography was performed with cyclohexane/AcOEt: 10/0 as eluent and led to the expected compound **3b** (route A: 61 mg, 38%; route B: 142 mg, 88%) as an orange solid: mp 42−45 °C. ^{1}H NMR δ_H (ppm) 0.46 (s, 9H); 7.33 (d, J = 5.1 Hz, 1H); 8.29 (d, J = 5.1 Hz, 1H). ^{13}C NMR δ_C (ppm) −0.8 (3C); 112.4; 122.3; 122.6; 146.3; 146.5; 150.3; 153.1. MS (EI) m/z 305 ([M + 2]$^+$, 26); 303 ([M]$^+$, 19); 290 (100); 288 (78); 268 (15). ESI-HRMS calcd for $C_{10}H_{12}BrClNOSi$ (M + H)$^+$: 303.9555; found: 303.9544.

2-Chloro-7-tri-*n*-butylstannyl-3-trimethylsilylfuro[3,2-*b*]-pyridine 3c. The product **3c** was prepared according to the general procedure described herein with chlorotri-*n*-butyltin (345 mg, 1.06 mmol, 2.0 equiv) as electrophile. Purification by centrifugal thin-layer chromatography was performed with cyclohexane/AcOEt: 10/0 to 98/2 as eluent and led to the expected compound **3c** (route A: 150 mg, 55%; route B: 237 mg, 87%) as a colorless liquid: ^{1}H NMR δ_H (ppm) 0.47 (s, 9H); 0.89 (t, J = 7.3 Hz, 9H); 1.18−1.23 (m, 6H); 1.29−1.39 (m, 6H); 1.53−1.61 (m, 6H); 7.19 (d, J = 4.6 Hz, 1H); 8.40 (d, J = 4.6 Hz, 1H). ^{13}C NMR δ_C (ppm) −0.5 (3C); 10.2 (3C); 13.8 (3C); 27.4 (3C); 29.1 (3C); 111.3; 126.5; 131.7; 144.9; 149.2; 149.8; 154.6. MS (EI) m/z 458 ([M-57]$^+$, 100); 402 (81); 346 (90); 210 (41); 73 (56). ESI-HRMS calcd for $C_{22}H_{39}ClNOSiSn$ (M + H)$^+$: 516.1503; found: 516.1490.

1-(2-Chloro-3-trimethylsilylfuro[3,2-*b*]pyridin-7-yl)-1-phenylmethanol 3d. The product **3d** was prepared according to the general procedure described herein with benzaldehyde (112 mg, 1.06 mmol, 2.0 equiv) as electrophile. Purification by centrifugal thin-layer chromatography was performed with cyclohexane/AcOEt: 10/0 to 95/5 as eluent and led to the expected compound **3d** (route A: 81 mg, 46%; route B: 158 mg, 90%) as a yellow gummy: ^{1}H NMR δ_H (ppm) 0.44 (s, 9H); 2.65 (br s, 1H); 6.25 (s, 1H); 7.29−7.37 (m, 3H); 7.46−7.49 (m, 2H); 8.48 (d, J = 5.1 Hz, 1H). ^{13}C NMR δ_C (ppm) −0.7 (3C); 70.6; 115.5; 126.6 (2C); 128.3; 128.8 (2C); 134.4; 141.6; 144.5; 146.3; 147.8; 149.6; 152.4. MS (EI) m/z 331 ([M]$^+$, 53); 316 (100); 296 (58). ESI-HRMS calcd for $C_{17}H_{19}ClNO_2Si$ (M + H)$^+$: 332.0868; found: 332.0861.

2,7-Dichloro-3-trimethylsilylfuro[3,2-*b*]pyridine 3e. The product **3e** was prepared according to the general procedure described in route B with hexachloroethane (251 mg, 1.06 mmol, 2.0 equiv) as electrophile. Purification by centrifugal thin-layer chromatography was performed with cyclohexane/AcOEt: 10/0 to 95/5 as eluent and led to the expected compound **3e** (127 mg, 92%) as a white solid: mp 48−50 °C. ^{1}H NMR δ_H (ppm) 0.46 (s, 9H); 7.19 (d, J = 5.3 Hz, 1H); 8.39 (d, J = 5.3 Hz, 1H). ^{13}C NMR δ_C (ppm) −0.8 (3C); 112.4; 119.4; 124.8; 144.5; 146.3; 150.5; 153.7. MS (EI) m/z 259 ([M]$^+$, 25); 244 (100); 224 (15); 73 (35). ESI-HRMS calcd for $C_{10}H_{12}Cl_2NOSi$ (M + H)$^+$: 260.0060; found: 260.0042.

2-Chloro-7-methylthio-3-trimethylsilylfuro[3,2-*b*]pyridine 3f. The product **3f** was prepared according to the general procedure described in route B with dimethyldisulfide (100 mg, 1.06 mmol, 2.0 equiv) as electrophile. Purification by centrifugal thin-layer chromatography was performed with cyclohexane/AcOEt: 10/0 to 95/5 as eluent and led to the expected compound **3f** (97 mg, 67%) as a yellow oil: ^{1}H NMR δ_H (ppm) 0.45 (s, 9H); 2.61 (s, 3H); 6.95 (d, J = 5.25 Hz, 1H); 8.35 (d, J = 5.25 Hz, 1H). ^{13}C NMR δ_C (ppm) −0.7 (3C); 14.1; 111.6; 114.1; 114.8; 131.3; 145.8; 149.1; 151.2. MS (EI) m/z 271 ([M]$^+$, 57); 256 (100); 236 (55); 73 (59). ESI-HRMS calcd for $C_{11}H_{15}ClNOSSi$ (M + H)$^+$: 272.0327; found: 272.0332.

2-Chloro-7-formyl-3-trimethylsilylfuro[3,2-*b*]pyridine 3g. The product **3g** was prepared according to the general procedure described in route B with dimethylformamide (77 mg, 1.06 mmol, 2.0 equiv) as electrophile. Purification by centrifugal thin-layer chromatography was performed with cyclohexane/AcOEt 10/0 to 95/5 as eluent and led to the expected compound **3g** (114 mg, 85%) as a white solid: mp 73−75 °C. ^{1}H NMR δ_H (ppm) 0.47 (s, 9H); 7.53 (d, J = 5 Hz, 1H); 8.71 (d, J = 5 Hz, 1H); 10.51 (s, 1H). ^{13}C NMR δ_C (ppm) −0.8 (3C); 111.6; 115.6; 123.8; 145.2; 146.7; 151.6; 155.5; 187.8. MS

dx.doi.org/10.1021/jo400748n | J. Org. Chem. XXXX, XXX, XXX−XXX

(EI) m/z 253 ([M]$^+$, 29); 238 (100); 218 (8); 93 (45). ESI-HRMS calcd for $C_{11}H_{13}ClNO_2Si$ (M + H)$^+$: 254.0399; found: 254.0390.

2,2′-Bischloro-3,3′-bistrimethylsilyl-7,7′-bifuro[3,2-*b*]-pyridine 3h. Under argon atmosphere, to a solution of $PdCl_2(PPh_3)_2$ (6 mg, 0.009 mmol, 5 mol %) in DMF (3 mL) was added the 7-stannanylfuro[3,2-*b*]pyridine compound **3c** (100 mg, 0.19 mmol, 1.1 equiv) and 7-bromofuro[3,2-*b*]pyridine derivative **3b** (52 mg, 0.17 mmol, 1.0 equiv). After 24h at 110 °C, the reaction medium was diluted in methylene chloride (CH_2Cl_2) (20 mL) and washed with an aqueous saturated Na_2SO_3 solution (10 mL). After drying ($MgSO_4$) and solvent evaporation, the crude product was purified by centrifugal thin layer chromatography with cyclohexane/AcOEt 10/0 as eluent and led to the expected compound **3h** (50 mg, 65%) as an oil: ^{1}H NMR δ_H (ppm) 0.50 (s, 18H); 7.78 (d, J = 5.1 Hz, 2H); 8.68 (d, J = 5.1 Hz, 2H). ^{13}C NMR δ_C (ppm) −0.6 (6C); 92.4 (2C); 102.1 (2C); 111.8 (2C); 118.8 (2C); 123.7 (2C); 146.4 (2C); 153.8 (2C). MS (EI) m/z 450 ([M]$^+$, 28); 433 (65); 413 (30); 209 (30); 73 (100). ESI-HRMS calcd for $C_{20}H_{23}Cl_2N_2O_2Si_2$ (M + H)$^+$: 449.0667; found: 449.0670.

Lithiation of 7-Substituted-2-chloro-3-trimethylsilylfuro[3,2-*b*]pyridines 3a,b,d and e. To a solution of LiTMP (5.1 mL, 0.31 M, 1.59 mmol, 3.0 equiv) in THF was added dropwise 7-substituted-2-chloro-3-trimethylsilylfuro[3,2-*b*]pyridines **3a,b,d** or **e** (0.53 mmol, 1.0 equiv) in THF (10 mL) at −20 °C, under argon atmosphere. After stirring for 1 h at −20 °C, the appropriate electrophile (1.59 mmol, 3.0 equiv) was added in THF (5 mL) at −20 °C. The temperature was then allowed to warm to 20 °C over 20 min. After stirring for 40 min at 20 °C, the hydrolysis was performed with H_2O (10 mL) at 20 °C. The aqueous layer was then extracted twice with AcOEt (2 × 10 mL). After drying ($MgSO_4$), filtration and solvent evaporation, the crude product was purified by centrifugal thin-layer chromatography.

7-Bromo-2-chloro-3,6-bistrimethylsilylfuro[3,2-*b*]pyridine 4b. The product **4b** was prepared according to the general procedure described herein with TMSCl (173 mg, 1.59 mmol, 3.0 equiv) as electrophile. Purification by centrifugal thin-layer chromatography was performed with cyclohexane/AcOEt: 10/0 as eluent and led to the expected compound **4b** (146 mg, 73%) as an yellow doughy solid. ^{1}H NMR δ_H (ppm) 0.43 (s, 9H); 0.54 (s, 9H) 8.53 (s, 1H). The product is not stable enough to have a ^{13}C spectrum. ESI-HRMS calcd for $C_{13}H_{20}BrClNOSi_2$ (M + H)$^+$: 375.9950; found: 375.9926.

6,7-Dibromo-2-chloro-3-trimethylsilylfuro[3,2-*b*]pyridine 4c. The product **4c** was prepared according to the general procedure described herein with CBr_4 (527 mg, 1.59 mmol, 3.0 equiv) as electrophile. Purification by centrifugal thin-layer chromatography was performed with cyclohexane/AcOEt: 10/0 as eluent and led to the expected compound **4c** (83 mg, 41%) as a brown solid: mp 126−128 °C. ^{1}H NMR δ_H (ppm) 0.45 (s, 9H); 8.59 (s, 1H). ^{13}C NMR δ_C (ppm) −0.8 (3C); 112.9; 115.4; 118.5; 146.8; 147.9; 150.5; 151.1. MS (EI) m/z 383 ([M]$^+$, 29); 368 (100); 73 (55). ESI-HRMS calcd for $C_{10}H_{11}Br_2ClNOSi$ (M + H)$^+$: 381.8660; found: 381.8668.

2,7-Dichloro-3,6-bistrimethylsilylfuro[3,2-*b*]pyridine 4e. The product **4e** was prepared according to the general procedure described herein with TMSCl (173 mg, 1.59 mmol, 3.0 equiv) as electrophile. Purification by centrifugal thin-layer chromatography was performed with cyclohexane/AcOEt: 10/0 as eluent and led to the expected compound **4e** (159 mg, 90%) as an yellow solid: mp 69−71 °C. ^{1}H NMR δ_H (ppm) 0.45 (s, 9H); 0.53 (s, 9H); 8.42 (s, 1H). ^{13}C NMR δ_C (ppm) −0.7 (3C); 0.2 (3C); 111.0; 117.3; 128.9; 133.1; 145.3; 149.5; 151.9. ESI-HRMS calcd for $C_{13}H_{20}Cl_2NOSi_2$ (M + H)$^+$: 332.0455; found 332.0463.

2,6,7-Trichloro-3-trimethylsilylfuro[3,2-*b*]pyridine 4f. The product **4f** was prepared according to the general procedure described herein with C_2Cl_6 (376 mg, 1.59 mmol, 3.0 equiv) as electrophile. Purification by centrifugal thin-layer chromatography was performed with cyclohexane/AcOEt: 10/0 as eluent and led to the expected compound **4f** (123 mg, 79%) as a white solid: mp 86−88 °C. ^{1}H NMR δ_H (ppm) 0.45 (s, 9H); 8.51 (s, 1H). ^{13}C NMR δ_C (ppm) −0.8 (3C); 112.8; 123.6; 126.2; 144.7; 145.9; 150.7; 151.6. MS (EI) m/z 293 ([M]$^+$, 30); 278 (100); 107 (25); 93 (45). ESI-HRMS calcd for $C_{10}H_{11}Cl_3NOSi$ (M + H)$^+$: 293.9670; found: 293.9646.

2,7-Dichloro-6-deuterio-3-trimethylsilylfuro[3,2-*b*]pyridine 4g. The product **4g** was prepared according to the general procedure described herein with CD_3OD (765 mg, 21.2 mmol, 40.0 equiv) as electrophile. Purification by centrifugal thin-layer chromatography was performed with cyclohexane/AcOEt: 10/0 to 99/1 as eluent and led to the expected compound **4g** (115 mg, 82%) as a colorless doughy solid: ^{1}H NMR δ_H (ppm) 0.48 (s, 9H); 8.50 (s, 1H). ^{13}C NMR δ_C (ppm) −0.8 (3C); 111.6; 117.0; 127.0; 145.1; 147.1; 150.3; 151.0. MS (CI) m/z 262 ([M + H], 70), 245 (100), 225 (25), 73 (13). ESI-HRMS calcd for $C_{10}H_{11}Cl_2DNOSi$ (M + H)$^+$: 261.0122; found: 261.0136.

2-Chloro-7-{phenyl[(trimethylsilyl)oxy]methyl}-3-(trimethylsilyl)furo[3,2-*b*]pyridine 3i. To a solution of LiTMP (6.8 mL, 0.31 M, 2.12 mmol, 4.0 equiv) in THF was added dropwise 1-(2-chloro-3-trimethylsilylfuro[3,2-*b*]pyridin-7-yl)-1-phenylmethanol **3d** (176 mg, 0.53 mmol, 1.0 equiv) in THF (10 mL) at −20 °C, under argon atmosphere. After stirring for 1 h at −20 °C, TMSCl (230 mg, 2.12 mmol, 4.0 equiv) was added in THF (5 mL) at −20 °C. The temperature was then allowed to warm to 20 °C over 20 min. After stirring for 40 min at 20 °C, the hydrolysis was performed with H_2O (10 mL) at 20 °C. The aqueous layer was then extracted twice with AcOEt (2 × 10 mL). After drying ($MgSO_4$), filtration and solvent evaporation, the crude product was purified by centrifugal thin-layer chromatography with cyclohexane/AcOEt 10/0 to 98/2 as eluent and led to the expected compound **3i** (210 mg, 98%) as a an orange oil: ^{1}H NMR δ_H (ppm) 0.44 (s, 18H); 1.43 (s, 18H,); 6.20 (s, 1 H); 7.24−7.47 (m, 6H); 8.46 (d, J=5.0 Hz, 1 H). ^{13}C NMR δ_C (ppm) −0.7 (3C); 27.1 (3C); 70.7; 115.8; 126.6 (2C); 127.9; 128.5 (2C); 135.5; 140.1; 142.6; 146.4; 147.8; 149.4; 152.5. MS (EI) m/z 403 ([M]$^+$, 75); 388 (100); 368 (50); 73 (94). ESI-HRMS calcd for $C_{20}H_{27}ClNO_2Si_2$ (M+H)$^+$: 404.1263; found: 404.1271.

Lithiation of 6,7-Disubstituted-2-chloro-3-trimethylsilylfuro[3,2-*b*]pyridines 4e and f. *General Procedure with the Superbase [n-BuLi/LiDMAE] Route A.* To a solution of [*n*-BuLi/LiDMAE] (4.8 mL, 0.33M, 1.59 mmol, 3.0 equiv) in *n*-hexanes was added dropwise 6,7-disubstituted-2-chloro-3-trimethylsilylfuro[3,2-*b*]-pyridine **4e** or **4f** (0.53 mmol, 1.0 equiv) in *n*-hexanes (10 mL) at −20 °C, under argon atmosphere. After stirring for 1 h at −20 °C, the appropriate electrophile (1.59 mmol, 3.0 equiv) was added in THF (5 mL) at −20 °C. The temperature was then allowed to warm to 20 °C over 20 min. After stirring for 40 min at 20 °C, the hydrolysis was performed with H_2O (10 mL) at 20 °C. The aqueous layer was then extracted twice with AcOEt (2 × 10 mL). After drying ($MgSO_4$), filtration and solvent evaporation, the crude product was purified by centrifugal thin-layer chromatography.

General Procedure with LiTMP Route B. To a solution of LiTMP (5.1 mL, 0.31M, 1.59 mmol, 3.0 equiv) in THF was added dropwise 6,7-disubstituted-2-chloro-3-trimethylsilylfuro[3,2-*b*]pyridine **4e** or **4f** (0.53 mmol, 1.0 equiv) in THF (10 mL) at −20 °C, under argon atmosphere. After stirring for 1 h at −20 °C, the appropriate electrophile (1.59 mmol, 3.0 equiv) was added in THF (5 mL) at −20 °C. The temperature was then allowed to warm to 20 °C over 20 min. After stirring for 40 min at 20 °C, the hydrolysis was performed with H_2O (10 mL) at 20 °C. The aqueous layer was then extracted twice with AcOEt (2 × 10 mL). After drying ($MgSO_4$), filtration and solvent evaporation, the crude product was purified by centrifugal thin-layer chromatography.

2,5,6,7-Tetrachloro-3-trimethylsilylfuro[3,2-*b*]pyridine 5b. The product **5b** was prepared according to the general procedure described herein (route B) with C_2Cl_6 (376 mg, 1.59 mmol, 3.0 equiv) as electrophile. Purification by centrifugal thin-layer chromatography was performed with cyclohexane/AcOEt: 10/0 as eluent and led to the expected compound **5b** (155 mg, 89%) as a white solid: mp 127−129 °C. ^{1}H NMR δ_H (ppm) 0.45 (s, 9H); ^{13}C NMR δ_C (ppm) −0.9 (3C); 112.6; 124.5; 125.7; 143.9; 145.7; 149.7; 151.7. MS (EI) m/z 329 ([M]$^+$, 24); 314 (100); 113 (15); 73 (38). ESI-HRMS calcd for $C_{10}H_{10}Cl_4NOSi$ (M + H)$^+$: 327.9280; found: 327.9277.

dx.doi.org/10.1021/jo400748n | J. Org. Chem. XXXX, XXX, XXX−XXX

■ ASSOCIATED CONTENT

Supporting Information

NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: yves.fort@univ-lorraine.fr, corinne.comoy@univ-lorraine.fr.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge financial support from CNRS and Université de Lorraine. We thank Sandrine Adach, François Dupire and Brigitte Fernette for recording mass and NMR spectra.

■ REFERENCES

(1) Banaszak, E.; Comoy, C.; Fort, Y. *Tetrahedron Lett.* **2006**, *47*, 6235−6238.

(2) Chartoire, A.; Comoy, C.; Fort, Y. *Tetrahedron* **2008**, *64*, 10867−10873.

(3) Comoy, C.; Banaszak, E.; Fort, Y. *Tetrahedron* **2006**, *62*, 6036−6041.

(4) Comoy, C.; Petrignet, J.; Banaszak, E.; Chartoire, A.; Fort, Y. *Lett. Org. Chem.* **2009**, *6*, 50−56.

(5) Chartoire, A.; Comoy, C.; Fort, Y. *J. Org. Chem.* **2010**, *75*, 2227−2235.

(6) Mladenovic, S.; Castro, C. E. *J. Heterocycl. Chem.* **1968**, *5*, 227−230.

(7) Arcadi, A.; Marinelli, F.; Cacchi, S. *Synthesis* **1986**, 749−751.

(8) Wishka, D. G.; Graber, D. R.; Seest, E. P.; Dolak, L. A.; Han, F.; Watt, W.; Morris, J. *J. Org. Chem.* **1998**, *63*, 7851−7859.

(9) Sorensen, U. S.; Pombo-Villar, E. *Tetrahedron* **2005**, *61*, 2697−2703.

(10) Arcadi, A.; Cacchi, S.; Di Guiseppe, S.; Fabrizi, G.; Marinelli, F. *Synlett* **2002**, 453−457.

(11) Arcadi, A.; Cacchi, S.; Di Guiseppe, S.; Fabrizi, G.; Marinelli, F. *Org. Lett.* **2002**, *4*, 2409−2412.

(12) Cironi, P.; Tulla-Puche, J.; Barany, G.; Albericio, F.; Alvarez, M. *Org. Lett.* **2004**, *6*, 1405−1408.

(13) Yue, D.; Yao, T.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 10292−10296.

(14) Lechel, T.; Dash, J.; Bruedgam, I.; Reissig, H.-U. *Eur. J. Org. Chem.* **2008**, 3647−3655.

(15) Husain, I.; Saquib, M.; Bajpai, V.; Kumar, B.; Shaw, A. K. *J. Org. Chem.* **2011**, *76*, 8930−8943.

(16) Shiotani, S. *Heterocycles* **1997**, *45*, 975−101 and references cited therein.

(17) Shiotani, S.; Taniguhi, K. *J. Heterocycl. Chem.* **1996**, *33*, 1051−1056.

(18) Shiotani, S.; Taniguhi, K.; Ishida, T. In, Y. *J. Heterocycl. Chem.* **1996**, *33*, 647−654.

(19) Shiotani, S.; Taniguhi, K. *J. Heterocycl. Chem.* **1997**, *34*, 129−141.

(20) Shiotani, S.; Taniguhi, K. *J. Heterocycl. Chem.* **1997**, *34*, 493−499.

(21) Shiotani, S.; Taniguhi, K. *J. Heterocycl. Chem.* **1997**, *34*, 925−929.

(22) Wengryniuk, S. E.; Weickgenannt, A.; Reiher, C.; Strotman, N. A.; Chen, K.; Eastgate, M. D.; Baran, P. S. *Org. Lett.* **2013**, *15*, 792−795.

(23) Carrër, A.; Rousselle, P.; Florent, J.-C.; Bertounesque, E. *Adv. Synth. Catal.* **2012**, *354*, 2751−2756.

(24) See for example: (a) Schlosser, M.; Mongin, F. *Chem. Soc. Rev.* **2007**, *36*, 1161−1172. (b) Cottet, F.; Marull, M.; Lefebvre, O.; Schlosser, M. *Eur. J. Org. Chem.* **2003**, 1559−1568. (c) Cottet, F.; Schlosser, M. *Eur. J. Org. Chem.* **2004**, 3793−3798. (d) Marzi, E.; Bobbio, C.; Cottet, F.; Schlosser, M. *Eur. J. Org. Chem.* **2005**, 2116−32123. (e) Schlosser, M.; Ginanneschi, A.; Leroux, F. *Eur. J. Org. Chem.* **2006**, 2956−2969.

(25) Schnürch, M.; Spina, M.; Khan, A. F.; Mihovilovic, M. D.; Stanetty, P. *Chem. Soc. Rev.* **2007**, *36*, 1046−1057.

(26) (a) Gros, P.; Fort, Y.; Queguiner, G.; Caubère, P. *Tetrahedron Lett.* **1995**, *36*, 4791−4794. (b) Gros, P.; Fort, Y.; Caubère, P. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3071−3080.

(27) Gros, P.; Fort, Y. *Eur. J. Org. Chem.* **2002**, 3375−3383.

(28) Gros, P.; Fort, Y. *Eur. J. Org. Chem.* **2009**, 4199−4209.

(29) Gschwend, H. W.; Rodriguez, H. R. *Org. React.* **1979**, *26*, 1−360.

(30) Chartoire, A.; Comoy, C.; Fort, Y. *Org. Biomol. Chem.* **2011**, *9*, 1839−1845.

(31) Gilman, H.; Bebb, R. L. *J. Am. Chem. Soc.* **1939**, *61*, 109−112.

(32) Wittig, G.; Fuhrmann, G. *Ber. Dtsch. Chem. Ges. B* **1940**, *73B*, 1197−1218.

(33) For example see: (a) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879−933. (b) Quéguiner, G.; Marsais, F.; Snieckus, V.; Epsztajn, J. *Adv. Heterocycl. Chem.* **1991**, *52*, 187−304. (c) Mortier, J.; Vaultier, M. *C. R. Acad. Sci., Ser. IIc Chim.* **1998**, *1*, 465−478. (d) Hartung, C.; Snieckus, V. *Mod. Arene Chem.* **2002**, 300−367.

(34) (a) Olofson, R. A.; Dougherty, C. M. *J. Am. Chem. Soc.* **1973**, *95*, 582−584. (b) Wiedemann, S. H.; Ramirez, A.; Collum, D. B. *J. Am. Chem. Soc.* **2003**, *125*, 15893−15901 and references cited herein.

(35) Khartabil, H. K.; Gros, P. C.; Fort, Y.; Ruiz-Lopez, M. F. *J. Am. Chem. Soc.* **2010**, *132*, 2410−2416.

(36) Gros, P. C.; Choppin, S.; Mathieu, J.; Fort, Y. *J. Org. Chem.* **2002**, *67*, 234−237.

(37) Fort, Y.; Gros, P.; Rodriguez, A. L. *Tetrahedron Lett.* **2002**, *43*, 4045−4048.

(38) For example, see: (a) Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356−363. (b) Resek, J. E.; Beak, P. *J. Am. Chem. Soc.* **1994**, *116*, 405−406. (c) Whisler, M. C.; MacNeil, S.; Snieckus, V.; Beak, P. *Angew. Chem., Int. Ed.* **2005**, *43*, 2206−2225.

(39) Wittig, G.; Schöllkopf, U. *Tetrahedron* **1958**, *3*, 91−93.

(40) For example, see: (a) Leleu, A.; Fort, Y.; Schneider, R. *Adv. Synth. Catal.* **2006**, *348*, 1086−1092. (b) Desmarets, C.; Omar-Amrani, R.; Walcarius, A.; Lambert, J.; Champagne, B.; Fort, Y.; Schneider, R. *Tetrahedron* **2008**, *64*, 372−381.

(41) Yamaguchi, S.; Awajima, K.; Hirai, Y.; Yokoyama, H.; Shiotani, S. *J. Heterocycl. Chem.* **1998**, *35*, 1249−1255.