Side-Chain Retention During Lithiation of 4-Picoline and 3,4-Lutidine: Easy Access to Molecular Diversity in Pyridine Series

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The first direct ring-selective lithiation of 4-picoline and 3,4-lutidine has been achieved through the use of BuLi/LiDMAE aggregates to prevent the usual side-chain metallation. Several functionalities have been introduced at the C-2, C-6 and C-5 positions by ring-selective sequential lithiation, opening a simple and fast route to polysubstituted pyridine building blocks.

Introduction

The search for productive short synthetic sequences is a challenge in modern organic chemistry. Selective functionalization of compounds with retention of reactive substituents is thus an attractive process, avoiding protection/deprotection sequences while allowing immediate transformation of the reactive moiety. In this context, the selective ring lithiation of 4-picoline (**1**) and 3,4-lutidine (**7**) with retention of the side chain could provide a new route to useful heterocyclic building blocks, since the methyl group can subsequently be converted into an aldehyde[1] or carboxylic acid,[2] or subjected to olefination to prepare conjugated molecules (Scheme 1).[3]

The higher acidity of the methyl protons in **1**[4] means that they are exclusively abstracted by LDA, LTMP or *n*BuLi in THF.[5] The only methodology for ring lithiation known to date is through the enhancement of acidity of protons at C-2 by formation of a pyridinium moiety. This was accomplished by treatment of **1** with $BF_3{\cdot}OEt_2$ and subsequent lithiation with an excess of LTMP, and is known as Kessar's reaction.[6] Although efficient, this process implies the regeneration of neutral substituted pyridine from the BF_3−pyridinium species. Our approach is to incorporate the pyridine nitrogen atom into *n*BuLi-containing lithium aggregates,[7] the enhancement of proton acidities and proximity effects being expected to promote selective C-2 lithiation (Figure 1).

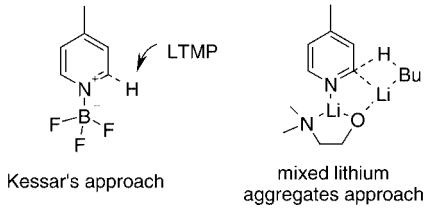
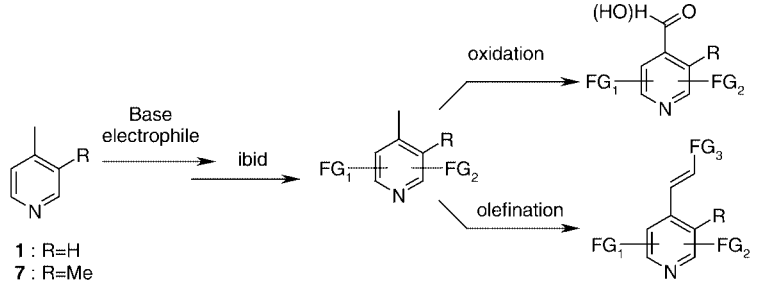


Figure 1. The two concepts for ring lithiation of **1**



Scheme 1

Results and Discussion

Lithiation of 4-Picoline

We performed an initial set of experiments to determine the best conditions for ring metallation of **1** (Table 1). Di-

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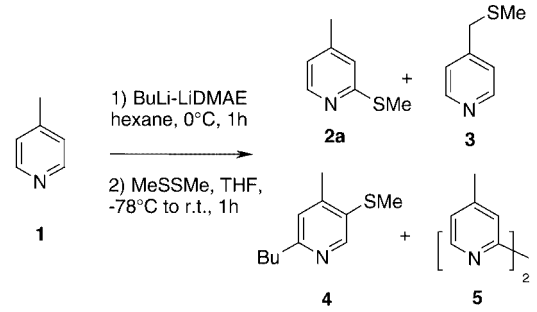
Table 1. Metallation of **1** with BuLi-LiDMAE

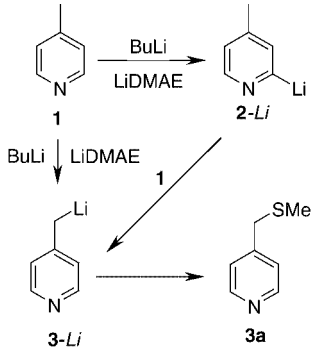


Entry[a]	Base (equiv.)	Conv.(%)[b]	Hexane (mL)	**2a** (%)[b]	**3** (%)[b]	**4** (%)[b]	**5** (%)[b]
1	1	86	20	11	41	15	19
2	1	> 99	40	80	3	17	–
3	1	55	60	11	16	6	22
4	1.2	> 99	40	94	trace	6	–
5	1.5	> 99	40	96	trace	4	–
6	2	> 99	40	> 99	–	–	–
7	3	> 99	20	> 99	–	–	–

[a] All reactions performed on 4 mmol of **1**. [b] GC yields.

methyl disulfide was chosen as the electrophile because of its good ability to trap lithiated species. As mentioned previously,[7] BuLi/aminoalkoxide reagents have to be used in hexane in order to favour lithium aggregate formation. A first attempt with BuLi in hexane (1 equiv., 0 °C) provided **4** as a single product in 76% yield. With 1 equiv. of BuLi/LiDMAE, in contrast, nucleophilic addition was dramatically reduced. The target compound **2a** was obtained in 11% yield, together with the side chain metallation product **3** as the main product and dimer **5** (Table 1, Entry 1). The formation of **5** probably results from an intermolecular reaction of the nucleophilic **2**-Li with unreacted **1**.

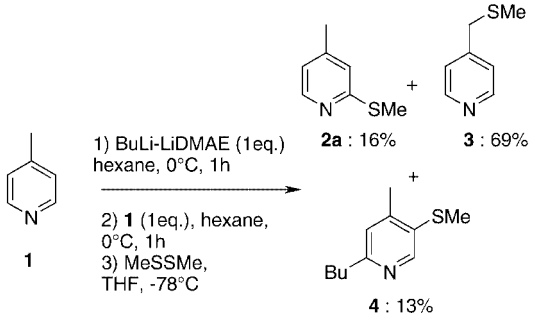
At this stage, however, we wondered whether **3** might be the result of direct lithiation of **1** or rather from a reaction between **2**-Li and unchanged **1** (Scheme 2).



Scheme 2. Proposed pathway for methyl deprotonation by **2**-Li

We thus decided to perform the metallation at greater dilution, expecting the prevention of such an intermolecular reaction and a better stabilization of **2**-Li. The dilution effect was remarkable. When the metallation was carried out in twice the volume of hexane, **2a** was formed as the main product in 80% yield (Table 1, Entry 2) while use of higher dilution was found to be deleterious, probably due to a strong decrease in the reaction rate.

To check the ability of **2**-Li to deprotonate the methyl group in **1**, the substrate was first lithiated under the conditions listed in Entry 2 (Table 1), giving **2**-Li in 80% yield, and was then treated with an additional amount of **1** (1 equiv.). After quenching with electrophile, **3** was formed as the main product in 69% yield, in full agreement with the expected deprotonation (Scheme 3).



Scheme 3. Evidence for intermolecular deprotonation of the methyl group

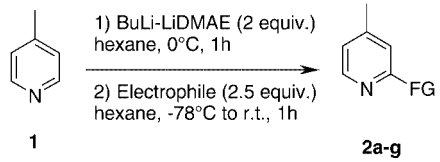
An increase in the amount of base to 2 equiv. induced the cleanest reaction and yielded **2a** quantitatively (Table 1, Entry 6). Interestingly, this procedure offers the same efficiency and selectivity as a reaction with 3 equiv. of base under less dilute conditions (Table 1, Entry 7).

For synthetic purposes, the excellent yields obtained with 1.2 or 1.5 equiv. of BuLi/LiDMAE make the methodology competitive with halogen/metal exchange, which also generally requires the same amount of BuLi and availability of starting bromopyridine.

Compound **1** was next treated with a range of electrophiles under the optimised conditions (Table 2, Entry 6).

The expected C-2-substituted derivatives **2a**−**f** were obtained in good yields, especially the reactive halo and stannyl compounds.

Table 2. Preparation of 2,4-disubstituted pyridines

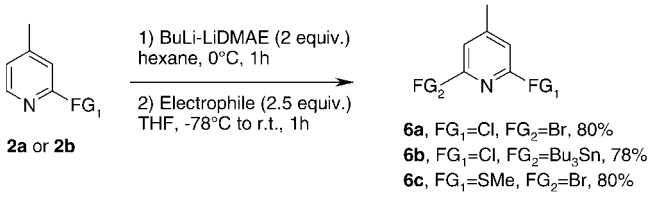


1 **2a-g**

Electrophile[a]	FG	Product	Yield (%)[b]
MeSSMe	SMe	**2a**	90
C_2Cl_6	Cl	**2b**	80
CBr_4	Br	**2c**	70
$ClSnBu_3$	$SnBu_3$	**2d**	80
$PhCONMe_2$	COPh	**2e**	78
PhCHO	CH(OH)Ph	**2f**	60
MeEtCO	C(OH)MeEt	**2g**	68

[a] All metallations performed on 4 mmol of **1** in 40 mL of hexane. [b] Isolated yields after column chromatography.

The availability of another acidic proton α to nitrogen atom in **2** was viewed as an opportunity to introduce further substitution at this position. We thus examined the lithiation of **2a** and **2b**, bearing base-compatible substituents (Scheme 4).[8]



Scheme 4. Preparation of 2,4,6-trisubstituted pyridines

We were pleased to observe that the methyl group was no more affected by the second lithiation, which occurred exclusively at C-6 to give the 2,4,6-trisubstituted derivatives **6a**−**c** in high yields.

Lithiation of 3,4-Lutidine

We next investigated the lithiation of 3,4-lutidine (**7**). The presence of an additional acidic side chain and different environment for hydrogen atoms α to the pyridine nitrogen atom were expected to modify the reaction pathway. Indeed, four products could be envisioned besides those resulting from nucleophilic addition (Figure 2).

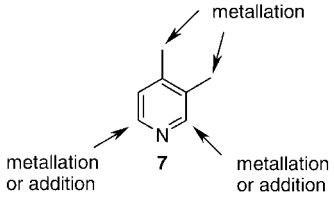
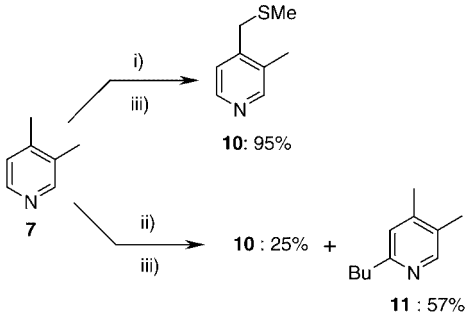


Figure 2. Potential reactive sites in **7**

Control experiments first showed that *n*BuLi in THF at −78 °C gave only compound **10**, in agreement with the higher acidity of the methyl group at C-4.[4] The same reaction performed in hexane mainly afforded addition product **11**, probably due to the ability of the pyridine nitrogen atom to chelate the lithium ion in non-complexing hexane (Scheme 5).



Scheme 5. Reaction of **7** with *n*BuLi in hexane and THF

When the reaction was attempted with the BuLi/LiDMAE superbase, under the conditions used above with **1**, large amounts of addition product and side chain metallation product were obtained (Table 3, Entry 1). We investigated the reaction with larger amounts of base under various conditions.

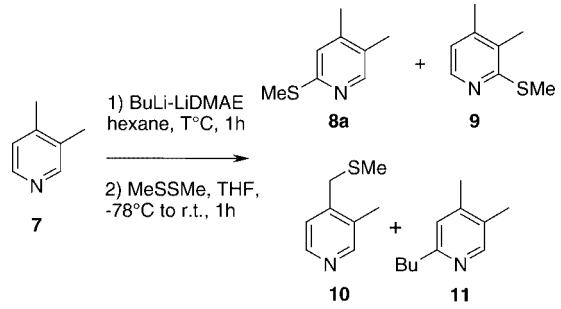
All the experiments resulted in efficient ring lithiation with formation of isomer **8a** as the main product. Good conversions were obtained provided that metallation was performed at 0°C. An increase in the amount of base to 5 equiv. gave **8a** in 78% yield while the amount of isomer **9** resulting from lithiation at C-2 was decreased (Table 3, Entry 4). Dilution was also beneficial, allowing the use of 3 equiv. of base (Table 3, Entry 5), but addition product **11** was formed. Finally, we were unable to obtain total suppression of side-chain lithiation, which was even enhanced at −45°C, giving **10** in 34% yield.

In order to verify that the observed selectivity actually reflected the content of the reaction medium after lithiation, we performed a deuteration experiment (Scheme 6). The ^1H NMR spectrum revealed the same product distribution as obtained in Entry 4 (Table 3), indicating the absence of any combination between lithiated species during the quenching step.

Despite the formation of side products **9** and **10**, we nevertheless found this new lithiation to be efficient for the preparation of 3,4,6-trisubstituted and 2,3,4,6-tetrasubstituted derivatives (Table 4).

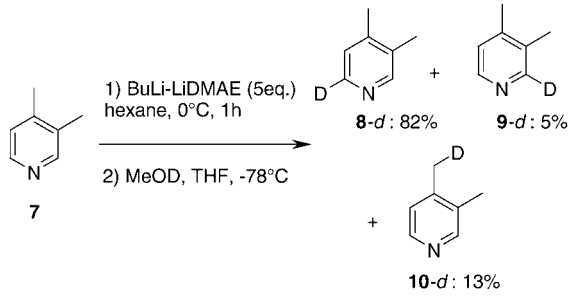
Compounds **8a**−**c** were obtained in good yield after easy separation from **9** and **10** by column chromatography. The second lithiation of **8b** also proceeded efficiently, giving **12a** and **12b**, respectively. In this case, the reaction proceeded cleanly with 3 equiv. of reagent without side-chain lithiation, which could be prevented by a concomitant complexation of lithium aggregates by nitrogen and heteroatom at C-6 (Scheme 7).

Table 3. Metallation of **7** with BuLi/LiDMAE



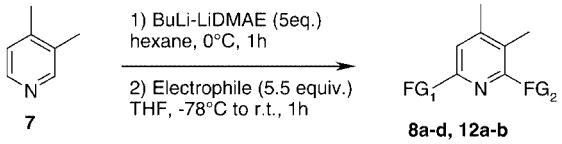
Entry[a]	Base (equiv.)	*T* (°C)	Conv. (%)[b]	**8a** (%)[b]	**9** (%)[b]	**10** (%)[b]	**11** (%)[b]
1	1.5[c]	0	93	52	6	21	14
2	3[d]	0	95	61	10	20	–
3	4[d]	0	92	73	10	9	–
4	5[d]	0	> 99	78	4	17	–
5	3[c]	0	> 99	70	5	15	8
6	3[c]	−78	n. r.[e]	–	–	–	–
7	3[c]	−45	81	40	3	34	4
8	3[c]	room temp.	> 99	62	3	12	19
9	3[c] [f]	0	> 99	54	6	9	29
10	3[g]	0	> 99	77	4	12	7

[a] All reactions performed on 2 mmol of **1**. [b] GC yields. Metallations performed in hexane. [c] 40 mL. [d] 20 mL. [e] No reaction occurred. [f] 4 h metallation time. [g] Metallation performed in hexane/toluene (10:30).



Scheme 6

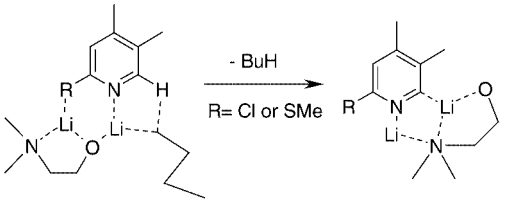
Table 4. Preparation of polysubstituted pyridines



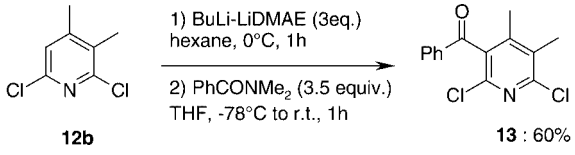
Substrate[a]	Electrophile	Product	FG_1	FG_2	Yield (%)[b]
7	MeSSMe	**8a**	MeS	H	65
7	C_2Cl_6	**8b**	Cl	H	83
7	CBr_4	**8c**	Br	H	80
8b	Me_2NCOPh	**12a**	Cl	COPh	75[c]
8b	C_2Cl_6	**12b**	Cl	Cl	70[c]

[a] All reactions performed on 1.6 mmol of substrate. [b] Isolated yields. [c] Metallation performed with 3 equiv. of base in 40 mL of hexane.

Finally, the remaining ring-free site in compound **12b** was efficiently lithiated by a third reaction, which gave the pentasubstituted derivative **13** in good yield (Scheme 8).



Scheme 7. Concomitant complexation of lithium aggregates



Scheme 8. Lithiation of remaining ring-free site in **12b**

Conclusion

We have performed the first direct ring-selective lithiation of 4-picoline and 3,4-lutidine. The use of BuLi/LiDMAE aggregates, formed through anchoring at the pyridine nitrogen atom, prevents the exclusive side-chain metallation obtained with common reagents (BuLi, dialkylamides). Several functionalities have been introduced at the C-2, C-6 and C-5 positions through ring-selective sequential lithiations. This methodology opens a simple and fast route to polysubstituted pyridine building blocks. Work to investigate the functionalization of free methyl groups on polysubstituted pyridines obtained by our methodology is now in progress.

Experimental Section

General Methods: ^{1}H and ^{13}C NMR spectra were recorded at 200 and 50 MHz, respectively, with $CDCl_3$ as solvent and TMS as internal standard for ^{1}H NMR spectroscopy. GC/MS (EI, 70 eV) spectra was recorded with a HP5871 spectrometer.

Materials and Solvents: THF and hexane were distilled and stored with sodium wire before use. 2-(Dimethylamino)ethanol was distilled under nitrogen and stored over molecular sieves. *n*BuLi was used as a 1.6 M solution in hexanes.

General Procedure for C-2 Lithiation of 4-Picoline (1) and C-6 Lithiation of 2a−b: A solution of 2-(dimethylamino)ethanol (0.8 mL, 8 mmol) in hexane (25 mL) was cooled to 0 °C and treated dropwise with *n*BuLi (10 mL, 16 mmol). After this mixture had been kept at 0 °C for 15 min, a solution of 4-picoline (0.39 mL, 4 mmol) in hexane (5 mL) was added dropwise. After 1 h at 0 °C, the orange solution was cooled to −78 °C and treated with a solution of the appropriate electrophile (10 mmol) in THF (10 mL). After 1 h at −78 °C, the mixture was warmed to room temperature. Hydrolysis was then performed at 0 °C with H_2O (15 mL). The organic layer was then extracted twice with diethyl ether and dried with $MgSO_4$, and the solvents were evaporated under vacuum. The crude product was then purified by column chromatography with hexane/EtOAc mixtures as eluent and gave compounds **2a−g**. The same procedure was repeated with compounds **2a** and **2b**, to afford derivatives **6a−c**.

4-Methyl-2-(methylsulfanyl)pyridine (2a):[9] Column chromatography (hexanes/EtOAc, 90:10) yielded **2a** (500 mg, 90%) as a dark yellow oil. ^{1}H NMR ($CDCl_3$, 25 °C): δ = 2.26 (s, 3 H), 2.54 (s, 3 H), 6.77 (d, *J* = 5.2 Hz, 1 H), 6.98 (s, 1 H), 8.27 (d, *J* = 5.2 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 25 °C): δ = 13.2, 20.9, 120.5, 121.9, 146.9, 149, 159.8 ppm. MS (EI): *m*/*z* (%) = 139 (100) [M^+], 138 (74), 93 (50).

2-Chloro-4-methylpyridine (2b):[10] Column chromatography (hexanes/EtOAc, 70:30) yielded **2b** (405 mg, 80%) as a yellow liquid. ^{1}H NMR ($CDCl_3$, 25 °C): δ = 2.30 (s, 3 H), 7.0 (d, *J* = 5.2 Hz, 1 H), 7.15 (s, 1 H), 8.22 (d, *J* = 5.2 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 25 °C): δ = 20.8, 123.6, 125.1, 149.3, 150.5, 151.6 ppm. MS (EI): *m*/*z* (%) : 129 (32) [M + 2], 127 (100) [M^+], 92 (83).

2-Bromo-4-methylpyridine (2c):[10] Column chromatography (hexanes/EtOAc, 90:10) yielded **2c** (484 mg, 70%) as a yellow liquid. ^{1}H NMR ($CDCl_3$, 25 °C): δ = 2.41 (s, 3 H), 7.0 (d, *J* = 4.8 Hz, 1 H), 7.33 (s, 1 H), 8.21 (d, *J* = 4.8 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 25 °C): δ = 20.1, 122.7, 128.2, 141.7, 149.1, 149.7 ppm. MS (EI): *m*/*z* (%) = 173 (40) [M^+], 171 (40), 92 (100).

4-Methyl-2-(tributylstannyl)pyridine (2d):[11] Column chromatography (hexanes/EtOAc, 80:20) yielded **2d** (1.14 g, 75%) as a colourless oil. ^{1}H NMR ($CDCl_3$, 25 °C): δ = 0.88−1.55 (m, 27 H), 2.26 (s, 3 H), 6.9 (d, *J* = 5.1 Hz, 1 H), 7.22 (s, 1 H), 8.58 (d, *J* = 5.1 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 25 °C): δ = 10.0, 13.7, 20.9, 27.4, 29.3, 113.1, 122.9, 133.4, 143.9, 173.1 ppm.

(4-Methylpyridin-2-yl)(phenyl)methanone (2e):[12] Column chromatography (hexanes/EtOAc, 90:10) yielded **2e** (614 mg, 78%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 25 °C): δ = 2.42 (s, 3 H), 7.25 (d, *J* = 5.2 Hz, 1 H), 7.44 (m, 3 H), 7.83 (s, 1 H), 8.01 (d, *J* = 7.9 Hz, 2 H), 8.53 (d, *J* = 5.2 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 25 °C): δ = 21.1, 125.4, 127.1, 128.2, 130.9, 132.8, 136.4, 148.1, 148.4, 154.9, 194.1 ppm. MS (EI): *m*/*z* (%) = 197 (26) [M^+], 196 (57), 169 (56), 168 (48), 105 (73), 77 (100).

(4-Methylpyridin-2-yl)-3-phenylmethanol (2f):[6] Column chromatography (hexanes/EtOAc, 70:30) yielded **2f** (476 mg, 60%) as a beige solid. ^{1}H NMR ($CDCl_3$, 25 °C): δ = 2.28 (s, 3 H), 5.34 (s, 1 H), 5.69 (s, 1 H), 6.95 (s, 1 H), 7.0 (d, *J* = 5.14 Hz, 1 H), 7.3 (m, 5 H), 8.4 (d, *J* = 5.14 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 25 °C): δ = 21.2, 75.0, 122.2, 123.8, 127.2, 127.9, 128.7, 143.5, 147.6, 148.4, 160.8 ppm.

2-(4-Methylpyridin-2-yl)butan-2-ol (2g): Column chromatography (hexanes/EtOAc, 50:50) yielded **2g** (449 mg, 68%) as an orange oil.^{1}H NMR ($CDCl_3$, 25 °C): δ = 0.75 (t, 3 H), 1.49 (s, 3 H), 2.31 (q, 2 H), 3.0 (s, 3 H), 5.3 (s, 1 H), 6.98 (d, *J* = 5.2 Hz, 1 H), 7.14 (s, 1 H), 8.36 (d, *J* = 5.2 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 25 °C): δ = 8.2, 21.2, 28.9, 36.0, 73.9, 120.0, 122.8, 146.0, 148.0, 164.9 ppm. MS (EI): *m*/*z* (%) = 164 (1) [M^+], 150 (13), 137 (35), 136 (100), 118 (23), 93 (24). $C_{10}H_{15}NO$ (165.24): calcd. C 72.69, H 9.15, N 8.48; found C 72.52, H 8.97, N 8.33.

2-Bromo-6-chloro-4-methylpyridine (6a): Column chromatography (hexanes/EtOAc, 80:20) yielded **6a** (659 mg, 80%) as a brown solid. ^{1}H NMR ($CDCl_3$, 25 °C): δ = 2.33 (s, 3 H), 7.26 (s, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 25 °C): δ = 20.7, 124.1, 127.6, 140.6, 150.0, 152.9 ppm. MS (EI): *m*/*z* (%) = 209 (21), 207 (87), 205 (67), 128 (32), 126 (100), 90 (53). C_6H_5BrClN (206.47): calcd. C 34.90, H 2.44, N 6.78; found C 34.72, H 2.55, N 6.52.

2-Chloro-4-methyl-6-(tributylstannyl)pyridine (6b): Column chromatography (hexanes/EtOAc, 80:20) yielded **6b** (1.28 g, 78%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 25 °C): δ = 0.88−1.51 (m, 27 H), 2.27 (s, 3 H), 6.96 (s, 1 H), 7.11 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 25 °C): δ = 10.2, 13.9, 20.8, 27.5, 29.2, 123.34, 132.36, 147.25, 152.3, 174.9 ppm. $C_{18}H_{32}ClNSn$ (416.61): calcd. C 51.90, H 7.74, N 3.36; found C 52.12, H 7.55, N 3.42.

2-Bromo-4-methyl-6-(methylsulfanyl)pyridine (6c): Column chromatography (hexanes/EtOAc, 80:20) yielded **6c** (697 mg, 80%) as a brown oil. ^{1}H NMR ($CDCl_3$, 25 °C): δ = 2.24 (s, 3 H), 2.53 (s, 3 H), 6.92 (s, 1 H), 6.98 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 25 °C): δ = 13.7, 20.7, 120.9, 124.1, 141.7, 149.7, 160.9 ppm. MS (EI): *m*/*z* (%) = 219 (100) [M^+], 218 (70), 217 (100), 215 (62), 203 (3), 201 (3), 173 (36), 171 (37), 136 (11), 123 (24), 92 (74). C_7H_8BrNS (218.12): calcd. C 41.39, H 4.34, N 6.03; found C 41.52, H 4.41, N 5.92.

Procedure for Preparation of 3-Methyl-4-[(methylsulfanyl)methyl]-pyridine (10): A solution of 3,4-lutidine (1.8 mL, 16 mmol) in THF (15 mL) was cooled to 0 °C and treated dropwise with *n*BuLi (10 mL, 16 mmol). After 1 h at 0 °C, the orange solution was cooled to −78 °C and treated dropwise with a solution of dimethyl disulfide (1.42 mL, 16 mmol) in THF (2 mL). After 1 h at −78 °C, the mixture was warmed to room temperature. Hydrolysis was then performed at 0 °C with H_2O (15 mL). The organic layer was extracted twice with diethyl ether and dried with $MgSO_4$, and the solvents were evaporated under vacuum. Compound **10** (2.32 g, 95%) was then obtained as a yellow oil in pure form as judged by GC-MS and NMR spectra. ^{1}H NMR ($CDCl_3$, 25 °C): δ = 1.97 (s, 3 H), 2.30 (s, 3 H), 3.58 (s, 2 H), 7.09 (d, 1 H), 8.34 (d, 1 H), 8.36 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 25 °C): δ = 14.5, 15.24, 34.4, 123.3, 131.0, 144.2, 149.3, 150.5 ppm. MS (EI): *m*/*z* (%) = 153 (100), 152 (37), 107 (31), 106 (39), 105 (72), 92 (5) ppm.

General Procedure for C-6 Lithiation of 3,4-Lutidine (7): A solution of 2-(dimethylamino)ethanol (0.8 mL, 8 mmol) in hexane (5 mL) was cooled to 0 °C and treated dropwise with *n*BuLi (10 mL, 16 mmol). After the mixture had been kept at 0 °C for 15 min, a solution of 3,4-lutidine (0.18 mL, 1.66 mmol) in hexane (5 mL) was

added dropwise. After 1 h at 0 °C, the orange solution was cooled to −78 °C and treated with a solution of the appropriate electrophile (10 mmol) in THF (10 mL). After 1 h at −78 °C, the mixture was warmed to room temperature. The workup was then identical to those given above.

3,4-Dimethyl-2-(methylsulfanyl)pyridine (9): Column chromatography (hexanes/EtOAc, 80:20) yielded **9** (13 mg, 5%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 25 °C): δ = 2.20 (s, 3 H), 2.25 (s, 3 H), 2.5 (s, 3 H), 6.8 (d, *J* = 5.2 Hz, 1 H), 8.16 (d, *J* = 5.2 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 25 °C): δ = 13.6, 19.7, 22.8, 117.9, 121.3, 130.3, 146.4, 148.7 ppm. MS (EI): *m*/*z* (%) = 153 (83) [M^+], 120 (100), 106 (39).

4,5-Dimethyl-2-(methylsulfanyl)pyridine (8a): Column chromatography (hexanes/EtOAc, 80:20) yielded **8a** (165 mg, 65%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 25 °C): δ = 2.14 (s, 3 H), 2.17 (s, 3 H), 2.51 (s, 3 H), 6.92 (s, 1 H), 8.13 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 25 °C): δ = 13.2, 15.7, 19, 121.9, 127.9, 145.8, 149.3, 156.8 ppm. MS (EI): *m*/*z* (%) = 153 (100) [M^+], 152 (68), 107 (50), 106 (31). $C_8H_{11}NS$ (153.25): calcd. C 62.70, H 7.24, N 9.14; found C 62.85, H 7.12, N 9.16.

2-Chloro-4,5-dimethylpyridine (8b): Column chromatography (hexanes/EtOAc, 60:40) yielded **8b** (194 mg, 83%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 25 °C): δ = 2.19 (s, 3 H), 2.23 (s, 3 H), 7.05 (s, 1 H), 8.04 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 25 °C): δ = 15.3, 20.5, 124.0, 131.0, 145.8, 148.8, 149.1 ppm. MS (EI): *m*/*z* (%) = 143 (31) [M + 2], 141 (100) [M^+], 105 (69). C_7H_8ClN (141.60): calcd. C,59.38, H 5.69, N 9.89; found C 59.25, H 5.63, N 9.78.

2-Bromo-4,5-dimethylpyridine (8c): Column chromatography (hexanes/EtOAc, 60:40) yielded **8c** (247 mg, 80%) as an orange oil. ^{1}H NMR ($CDCl_3$, 25 °C): δ = 2.17 (s, 3 H), 2.22 (s, 3 H), 7.23 (s, 1 H), 8.05 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 25 °C): δ = 16.0, 19.1, 128.3, 131.8, 139.6, 149.1, 150.0 ppm. MS (EI): *m*/*z* (%) = 187 (68), 186 (6) [M^+], 185 (69), 106 (96), 79 (100), 77 (88). C_7H_8BrN (186.05): calcd. C 45.19, H 4.33, N 7.13; found C 45.25, H 4.52, N 7.31.

Procedure for C-2 Lithiation of 8b and 12b: A solution of 2-(dimethylamino)ethanol (0.8 mL, 8 mmol) in hexane (25 mL) was cooled to 0 °C and treated dropwise with *n*BuLi (10 mL, 16 mmol). After the mixture had been kept for 15 min at 0 °C, a solution of **8b** or **12b** (2.66 mmol) in hexane (5 mL) was added dropwise. After 1 h at 0 °C, the orange solution was cooled to −78 °C and treated with a solution of the appropriate electrophile (10 mmol) in THF (20 mL). After 1 h at −78 °C, the mixture was warmed to room temperature. The workup was then identical to those given above.

(6-Chloro-3,4-dimethylpyridin-2-yl)(phenyl)methanone (12a): Recrystallisation from hexane yielded **12a** (488 mg, 75%) as a colourless solid. ^{1}H NMR ($CDCl_3$, 25 °C): δ = 2.19 (s, 3 H), 2.34 (s, 3 H), 7.25 (s, 1 H), 7.43 (t, *J* = 8 Hz, 2 H), 7.59 (t, *J* = 8 Hz, 1 H), 7.82 (d, *J* = 7.7 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 25 °C): δ = 14.5, 19.8, 126.1, 128.8, 130.7, 134.1, 136.0, 147.9, 151.1, 155.5, 194.5 ppm. $C_{14}H_{12}ClNO$ (245.71): calcd. C 68.44, H 4.92, N 5.70; found C 68.63, H 4.90, N 5.75.

2,6-Dichloro-3,4-dimethylpyridine (12b):[13] Column chromatography (hexanes/EtOAc, 70:30) yielded **12b** (325 mg, 70%) as yellow oil. ^{1}H NMR ($CDCl_3$, 25 °C): δ = 2.28 (s, 3 H), 2.31 (s, 3 H), 7.04 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 25 °C): δ = 15.4, 20.5, 124.2, 130.1, 146.8, 150.2, 151.5 ppm. MS (EI): *m*/*z* (%) = 179 (13) [M^+], 177 (66) [M + 2], 175 (100) [M^+], 140 (61) [M − 35], 104 (66) [M − 71].

(2,6-Dichloro-4,5-dimethylpyridin-3-yl)(phenyl)methanone (13): Recrystallisation from hexane yielded **13** (482 mg, 65) as a yellow solid. ^{1}H NMR ($CDCl_3$, 25 °C): δ = 2.96 (s, 3 H), 3.09 (s, 3 H), 7.40 (ps, 5 H) ppm. ^{13}C NMR ($CDCl_3$, 25 °C): δ = 14.2, 22.7, 127.1, 128.4, 129.5, 130.5, 132.9, 133.1, 133.9, 136.4, 171.7 ppm. $C_{14}H_{11}Cl_2NO$ (280.16): calcd. C 60.02, H 3.96, N 5.00; found C 60.15, H 3.89, N 5.21.

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