$TMSCH_2Li$-induced regioselective lithiation of (*S*)-nicotine

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The first regioselective C-4 lithiation of (*S*)-nicotine has been realized using $TMSCH_2Li$ as basic reagent in toluene. The reaction proceeded under mild conditions with a small excess of electrophile. The 4-chloro derivative was subsequently metallated at C-5 with the same basic reagent in THF at −78 °C. This methodology opens a straightforward access to functional diversity in (*S*)-nicotine chemistry.

Introduction

Much interest is currently focused on the chemical modification of naturally occurring bioactive molecules. The aim is to modulate the properties of the natural product using only a few reaction steps. This time- and money-saving approach becomes even more important when optically active compounds are needed. The preparation of a chiral molecule analogue often draws the chemist to design sophisticated multistep synthetic sequences from achiral precursors, implying yield-consuming asymmetric resolutions as the final step. (*S*)-Nicotine **1** is a naturally abundant chiral alkaloid, efficient for the treatment of neurodegenerative diseases.[1] However, there are many drawbacks of using (*S*)-nicotine, such as addiction and intrinsic toxicity leading to dramatic cardiovascular and digestive complications.

The synthesis of new (*S*)-nicotine analogues potentially displaying weaker side effects is thus of critical importance and opens an exciting challenge for chemists. Also important is the synthesis of nicotine vaccines for fighting against tobacco addiction.[2] Besides multistep reaction sequences reported in the literature,[1c] some attractive straightforward one-step modifications *via* lithiation of the pyridine ring have been reported recently by Comins and co-workers (Scheme 1).[3]

For example, a range of moieties was introduced at the C-6 position of **1** by lithiation with the BuLi–LiDMAE reagent[3a] previously developed by Gros and Fort.[4] The C-2 position was metallated using LiTMP.[3a] Unfortunately, the functionalization was made possible only by trapping the lithio intermediate with base-compatible electrophiles, obviously limiting the functional diversity. Kondo's TMP-zincate[5] was also tried, leading to mixtures of C-2- and C-4-substituted compounds in poor yield. To date, the best reported way to functionalize cleanly the C-4 position is the nucleophilic addition of a Grignard or cuprate reagent to activated (*S*)-nicotine.[6] However, two additional steps are needed, since the nucleophilic agents have first to be prepared, and a sulfur treatment is subsequently necessary to release the target compounds.

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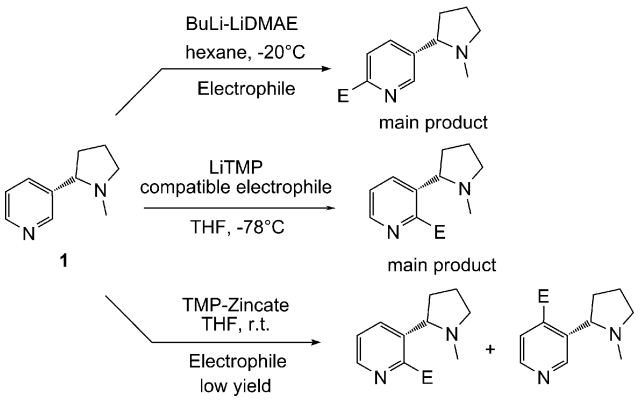
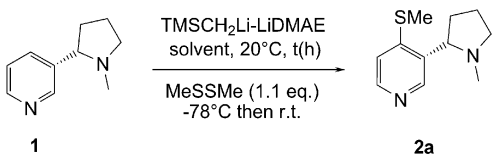


Scheme 1 Metallations of (*S*)-nicotine reported in the literature. LiDMAE = $LiO(CH_2)_2NMe_2$.

Recently, we have reported the efficient metallation of pyridine derivatives using $TMSCH_2Li$-based lithiating agents.[7] The new non-nucleophilic $TMSCH_2Li$–LiDMAE reagent used in stoichiometric amount led to an unexpected regioselectivity in the metallation of 4-DMAP, which was functionalized exclusively at C-3 for the first time.[8] We felt that such a reagent could provide new levels of selectivity with other amino-substituted pyridines such as **1**.

Results and discussion

The metallation of **1** was investigated with several $TMSCH_2Li$–LiDMAE combinations under various conditions (Scheme 2, Table 1). Preliminary experiments showed that **1** was entirely recovered when reacted at 0 °C. In contrast, C-4 lithiation was obtained exclusively at 20 °C whatever the $TMSCH_2Li$/LiDMAE ratio or solvent used.



Scheme 2 Metallation of **1** with $TMSCH_2Li$-containing reagents.

All reactions were very clean, providing easily separable **2a** and unreacted **1**. The best yield (90% isolated) was obtained using 2 equiv. of $TMSCH_2Li$ in toluene for 5 h at room temperature

Table 1 Condition screening for lithiation of **1**[a]

Entry	$TMSCH_2Li$ (equiv.)	LiDMAE (equiv.)	Solvent	t/h	**2a** (%)[b]
1	2	1	Hexane	1	14
2	2	2	Hexane	4	72
3	2	0	Hexane	4	81
4	2	0	Hexane	5	88
5	1.5	0	Hexane	5	82
6	2	0	Toluene	5	95 (90[c])
7	1.5	0	Toluene	5	88
8	2	1	Toluene	3	91

[a] All reactions performed on 1.84 mmol of **1**. [b] Yield determined by ^{1}H NMR of the crude product; the remaining material is unreacted **1**. [c] Isolated yield.

(entry 6). However, excellent yields could be also attained using 1.5 equiv. of the basic reagent (entry 7). The metallation time could be shortened (to 3 h) using $TMSCH_2Li$ and LiDMAE in a 2 : 1 ratio (entry 8). Interestingly, all reactions were performed with only a stoichiometric amount of electrophile. This illustrated the low nucleophilicity of $TMSCH_2Li$, since an excess of this reagent did not consume the electrophile before its reaction with the lithiated pyridine.

This lithiation regioselectivity was unexpected, since the metallation affected the less acidic proton, as shown by the calculated charge on protons in **1** (Fig. 1(a)).[9] A tentative explanation of this selectivity could be a cooperative chelating effect of the pyrrolidine nitrogen, placing $TMSCH_2Li$ at the appropriate place to abstract the H-4 proton (Fig. 1(b)).

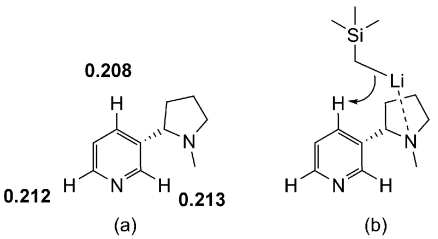
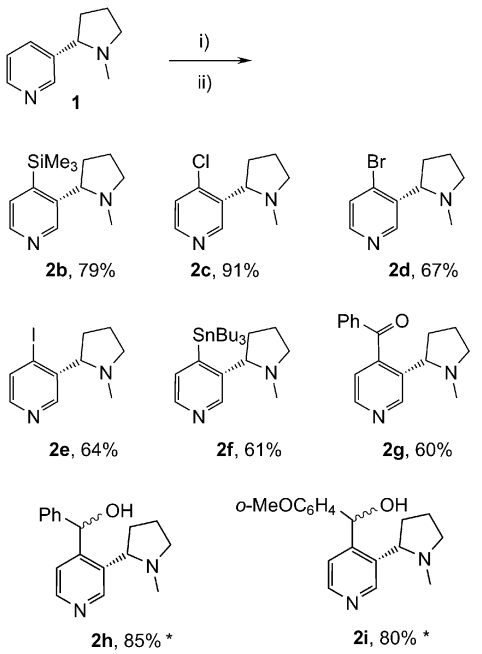


Fig. 1 (a) PM3 proton charge calculations in **1**. (b) Proposed coordination mode of $TMSCH_2Li$ to pyrrolidine nitrogen.

The reactivity of $TMSCH_2Li$ here contrasts with that of *n*-BuLi, since BuLi–LiDMAE has been reported to induce selectively the C-6 lithiation of **1** (Scheme 1).[2]

We then focused on the synthetic potential of this new methodology for the preparation of several C-4-substituted nicotine derivatives. The simplest and most practical conditions (Table 1, entry 6) were chosen to examine the reaction with several electrophilic reagents (Scheme 3).

A range of new functionalities was introduced for the first time at C-4 of **1**. Good yields were obtained using small excesses of electrophiles. This was found to be highly valuable for the preparation of stannane **2f**, avoiding the usual tedious separation of tin by-products. Note that the iodo derivative **2e** was obtained as a single product in 64% yield, while the same compound could be obtained only in 24% yield (in non-selective manner) using Kondo's reagent.[3a] Our compound **2e** gave an optical rotation comparable to the literature value under similar conditions, indicating the absence of racemization during our metallation process (see Experimental section). We also demonstrated the



Scheme 3 Preparation of 4-substituted nicotine derivatives. *Reagents and conditions*: i) $TMSCH_2Li$ (2 equiv.), toluene, 20 °C, 5 h. ii) $ClSiMe_3/C_2Cl_6/CBr_4/I_2/ClSnBu_3/PhCONMe_2$, as appropriate (1.1 equiv.), toluene, −78 °C to rt. For **2h** and **2i** the electrophiles were respectively PhCHO and *o*-$MeOC_6H_4CHO$ (2 equiv.) added in THF. * ^{1}H NMR showed a 1 : 1 diastereoisomeric ratio.

applicability of the process for the multigram scale preparation of the useful chloro derivative **2c**.[10] The reaction proceeded as well on 28 mmol of **1**, producing 5 g of **2c** (88% yield). The reaction of prochiral aldehydes was also investigated for a straightforward access to chiral alcohols. The ^{1}H NMR spectra did not reveal any diastereoselection, indicating the weak influence of the chiral pyrrolidine moiety during the aldehyde condensation step. However, both the diastereoisomers from **2h** and **2i** were found to be separable by column chromatography.

Finally, we examined the metallation of the chloro derivative **2c**. The aim was to exploit the *ortho*-directing power of chlorine at C-4 to introduce functionalities at C-5. Our first attempts at applying the previous metallation conditions led to sluggish and poorly selective reactions. The solvent was then changed and the reaction was performed at 0 °C with 2 equiv. of $TMSCH_2Li$ in THF. Under these conditions, only the C-5-substituted product **3** was obtained (Scheme 4). The formation of **3** can be explained by pyridyne

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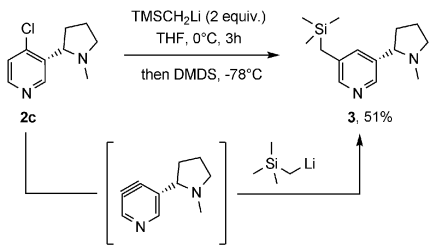
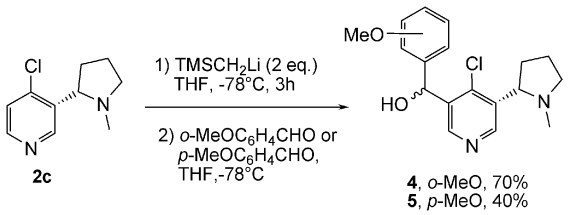


Scheme 4 Introduction of the $TMSCH_2$ group at C-5.

formation and subsequent attack at the more electrophilic site by the remaining equivalent of $TMSCH_2Li$.

This reaction clearly indicated that lithium was successfully introduced at the C-5 position but was too instable to be trapped at 0 °C. Thus, the temperature was lowered to improve the stabilization. After a short temperature screening, we found that performing the reaction at −78 °C, while decreasing the conversion, cleanly provided alcohols **4** and **5** (as 1 : 1 mixtures of inseparable diastereoisomers) in acceptable yields (Scheme 5). Note that the starting material was recovered in 25 and 47% respectively. This iterative lithiation is also of particular interest, since the C–Cl bond at C-4 is known to be easily reduced under several conditions, giving a straightforward access to C-5-substituted derivatives.



Scheme 5 Synthesis of 4,5-disubstituted nicotine derivatives.

Conclusion

In summary, the first regioselective C-4 lithiation of (*S*)-nicotine has been realized. The metallation proceeded smoothly at room temperature using $TMSCH_2Li$ as a basic reagent in toluene, leading to a range of new derivatives. The C-4-chlorinated derivative was prepared on a multigram scale and successfully functionalized at C-5 using the same metallating agent in THF at −78 °C. The new methodology disclosed here is a significant advance in (*S*)-nicotine chemistry in terms of selectivity and functional diversity. Work is now progressing to investigate in more detail the origin of the selectivity at C-4 as well as the scope of this reaction.

Experimental

General procedure for lithiation of (*S*)-nicotine. Preparation of compounds 2a–i

A solution of **1** (299 mg, 1.84 mmol) in anhydrous toluene (4 mL) was cooled to 0 °C, and $TMSCH_2Li$ (3.68 mmol, 4 mL of a 0.92 M solution in hexanes) was added dropwise. At the end of the addition (*ca.* 5 min), the reaction medium was allowed to warm to rt (typically 20 °C) and stirred for 5 h at this temperature. The orange solution was then cooled to −78 °C and treated with a solution of the appropriate electrophile (2 mmol) in toluene (2 mL), added dropwise. After the addition, stirring was maintained for 30 min at −78 °C, and then for 1 h at room temperature. Hydrolysis was performed at −78 °C with H_2O (10 mL). After extraction with Et_2O, drying and evaporation of the organic phase, the crude product was purified by column chromatography using AcOEt–hexane–Et_3N (30 : 70 : 10) as eluent (this was found to be convenient for all compounds). For the preparation of alcohols **2h** and **2i**, the above procedure was employed except that 3.68 mmol of benzaldehyde or *ortho*-anisaldehyde were used. For reasons of solubility *ortho*-anisaldehyde was added as a solution in THF (4 mL).

(*S*)-4-(Methylsulfanyl)nicotine (2a). Yield 90%, white solid, mp 76 °C. $[\alpha]_D^{27}$ −191.5 (*c* 1.03, $CHCl_3$). (Found: C, 63.51; H, 7.63; N, 13.58. $C_{11}H_{16}N_2S$ requires C, 63.42; H, 7.74; N, 13.45%). δ_H (200 MHz, $CDCl_3$) 1.47–2.01 (m, 3H), 2.22 (s, 3H), 2.10–2.40 (m, 2H), 2.46 (s, 3H), 3.25 (t, $J = 7.2$ Hz, 1H), 3.42 (t, $J = 8.4$ Hz, 1H), 7.01 (d, $J = 5.3$ Hz, 1H), 8.35 (d, $J = 5.3$ Hz, 1H), 8.58 (s, 1H). δ_C (50 MHz, $CDCl_3$) 14.1, 22.7, 32.7, 40.6, 57.1, 65.9, 117.5, 134.9, 147.4, 147.8, 149.0. *m/z* (EI) 209 (3%), 208 (M^+, 13%), 207 (13%), 193 (41%), 165 (24%), 159 (14%), 84 (100%).

(*S*)-4-(Trimethylsilyl)nicotine (2b). Yield 79%, pale yellow oil. $[\alpha]_D^{27}$ −169.0 (*c* 1.04, $CHCl_3$). (Found: C, 66.74; H, 9.53; N, 12.08. $C_{13}H_{22}N_2Si$ requires C, 66.61; H, 9.46; N, 11.95%). δ_H (200 MHz, $CDCl_3$) 0.36 (s, 9H), 1.48–1.85 (m, 3H), 2.22 (s, 3H), 2.28–2.41 (m, 2H), 3.23–3.49 (m, 2H), 7.27 (d, $J = 4.6$ Hz, 1H), 8.43 (d, $J = 4.6$ Hz, 1H), 8.86 (s, 1H). δ_C (50 MHz, $CDCl_3$) 0.8, 23.1, 36.8, 40.7, 57.2, 69.2, 128.1, 144.8, 147.3, 147.9, 149.4. *m/z* (EI) 234 (M^+, 4%), 219 (7%), 205 (3%), 84 (100%), 73 (11%).

(*S*)-4-Chloronicotine (2c). Yield 91%, pale yellow oil. $[\alpha]_D^{27}$ −182.1 (*c* 1, $CHCl_3$). (Found: C, 61.29; H, 6.74; N, 14.18. $C_{10}H_{13}ClN_2$ requires C, 61.07; H, 6.66; N, 14.24%). δ_H (200 MHz, $CDCl_3$) 1.48–1.62 (m, 1H), 1.72–1.85 (m, 2H), 2.21 (s, 3H), 2.32–2.38 (m, 2H), 3.23 (dt, $J = 9.2$ and 1.8 Hz, 1H), 3.58 (t, $J = 8.3$ Hz, 1H), 7.21 (d, $J = 5.2$ Hz, 1H), 8.31 (d, $J = 5.2$ Hz, 1H), 8.75 (s, 1H). δ_C (50 MHz, $CDCl_3$) 23.2, 33.8, 40.9, 57.2, 65.6, 124.4, 137.3, 143.7, 148.8, 150.5 *m/z* (EI) 197 (3%), 196 (M^+, 8%), 195 (8%), 169 (5%), 167 (15%), 85 (8%), 84 (100%).

(*S*)-4-Bromonicotine (2d). Yield 67%, orange gummy solid. $[\alpha]_D^{27}$ −51.9 (*c* 0.92, $CHCl_3$). (Found: C, 49.93; H, 5.54; N, 11.71. $C_{10}H_{13}BrN_2$ requires C, 49.81; H, 5.43; N, 11.62%). δ_H (200 MHz, $CDCl_3$) 1.48–1.92 (m, 3H), 2.22 (s, 3H), 2.30–2.50 (m, 2H), 3.20–3.32 (m, 1H), 3.57 (t, $J = 8.0$ Hz, 1H), 7.46 (d, $J = 5.3$ Hz, 1H), 8.27 (d, $J = 5.3$ Hz, 1H), 8.74 (s, 1H). δ_C (50 MHz, $CDCl_3$) 22.9, 33.5, 40.7, 56.9, 67.7, 127.5, 134.3, 147.9, 148.4, 150.2. *m/z* (EI) 242 (4%), 241 (M^+, 4%), 239 (4%), 199 (2%), 84 (100%).

(*S*)-4-Iodonicotine[3] (2e). Yield 64%, white solid, mp 96 °C (lit.[3] 97–98 °C). $[\alpha]_D^{27}$ −130.5 (*c* 1.03, $CHCl_3$) and (for comparison) $[\alpha]_D^{25}$ −118 (*c* 4.05, CH_2Cl_2) (lit.[3] $[\alpha]_D^{23}$ −120 (*c* 4.2, CH_2Cl_2)). δ_H (200 MHz, $CDCl_3$) 1.42–1.65 (m, 1H), 1.75–1.95 (m, 2H), 2.24 (s, 3H), 2.32–2.45 (m, 2H), 3.20–3.35 (m, 1H), 3.39 (t, $J = 8.3$ Hz, 1H), 7.70 (d, $J = 5.3$ Hz, 1H), 8.04 (d, $J = 5.3$ Hz, 1H), 8.61 (s, 1H). δ_C (50 MHz, $CDCl_3$) 23.1, 34.1, 40.9, 57.2, 72.7, 111.5, 134.5, 142.2, 148.5, 149.9. *m/z* (EI) 288 (M^+, 6%), 287 (6%), 259 (5%), 84 (100%), 82 (10%), 63 (10%).

(*S*)-4-(Tributylstannyl)nicotine (2f). Yield 61%, colorless oil. $[\alpha]_D^{27}$ −74.6 (*c* 1.03, $CHCl_3$). (Found: C, 58.63; H, 8.84; N, 6.32. $C_{22}H_{40}N_2Sn$ requires C, 58.46; H, 8.93; N, 6.21%). δ_H (200 MHz, $CDCl_3$) 0.9–2.0 (m, 31H), 2.19 (s, 3H), 2.30 (q, $J = 8.6$ Hz, 1H), 3.0 (t, $J = 8.6$ Hz, 1H), 3.25 (dt, $J = 7.6$ and 1.9 Hz, 1H), 7.31 (d, $J = 4.9$ Hz, 1H), 8.38 (d, $J = 4.9$ Hz, 1H), 8.67 (s, 1H). δ_C (50 MHz, $CDCl_3$) 10.9, 13.5, 22.5, 26.9, 29.2, 36.5, 40.8, 56.9, 72.8, 131.4, 145.2, 146.1, 148.5, 152.1

(*S*)-[3-(1-Methylpyrrolidin-2-yl)pyridin-4-yl](phenyl)methanone (2g). Yield 60%, yellow oil. $[\alpha]_D^{27}$ −76.4 (*c* 0.84, $CHCl_3$). (Found: C, 76.79; H, 6.71; N, 10.63. $C_{17}H_{18}N_2O$ requires C, 76.66; H, 6.81; N, 10.52%). δ_H (200 MHz, $CDCl_3$) 1.62–1.9 (m, 3H), 1.99 (s, 3H), 2.05–2.31 (m, 2H), 2.75–2.85 (m, 1H), 3.45 (t, $J = 8.0$ Hz, 1H), 7.13 (d, $J = 4.9$ Hz, 1H), 7.44 (t, $J = 6.8$ Hz, 2H), 7.56 (t, $J = 6.9$ Hz, 1H), 7.70 (d, $J = 6.8$ Hz, 2H), 8.58 (d, $J = 4.9$ Hz, 1H), 8.81 (s, 1H). δ_C (50 MHz, $CDCl_3$) 23.4, 35.4, 40.8, 56.0, 66.6, 112.1, 127.2, 128.4, 128.6, 128.9, 133.2, 137.3, 146.2, 148.1, 150.3, 194.4. *m/z* (EI) 266 (42%), 251 (58%), 210 (20%), 159 (15%), 105 (24%), 84 (100%), 82 (21%), 77 (84%), 51 (38%).

[3-(1-Methylpyrrolidin-2-yl)pyridin-4-yl](phenyl)methanol (2h). Yield 85%, obtained as a 1 : 1 mixture of diastereoisomers, which were separated. The absolute configuration was not determined.

Diastereoisomer 2h-1. Yield 47%, viscous colorless oil. $[\alpha]_D^{27}$ −38.7 (*c* 1.24, $CHCl_3$). (Found: C, 76.15; H, 7.62; N, 10.53. $C_{17}H_{20}N_2O$ requires C, 76.09; H, 7.51; N, 10.44%). δ_H (200 MHz, $CDCl_3$) 1.90–2.52 (m, 8H), 3.21–3.42 (m, 2H), 6.15 (s, 1H), 6.70 (d, $J = 5.1$ Hz, 1H), 7.25–7.45 (m, 5H), 8.33 (d, $J = 5.1$ Hz, 1H), 8.46 (s, 1H). δ_C (50 MHz, $CDCl_3$) 24.1, 32.5, 40.5, 57.1, 66.8, 69.9, 71.3, 123.3, 127.1, 127.3, 127.8, 128.5, 135.0, 137.6, 141.1, 149.6, 151.1, 152.5. *m/z* (EI) 268 (M^+, 9%), 210 (10%), 196 (15%), 168 (13%), 120 (19%), 84 (100%), 79 (22%), 77 (48%).

Diastereoisomer 2h-2. Yield 37%, white solid, mp 135 °C. $[\alpha]_D^{27}$ −28.6 (*c* 0.68, $CHCl_3$). (Found: C, 76.19; H, 7.46; N, 10.62. $C_{17}H_{20}N_2O$ requires C, 76.09; H, 7.51; N, 10.44%). δ_H (200 MHz, $CDCl_3$) 1.20–1.40 (m, 1H), 1.42–1.81 (m, 2H), 2.10–2.42 (m, 4H), 3.12–3.42 (m, 2H), 5.92 (s, 1H), 7.10–7.45 (m, 6H), 8.48 (d, $J = 5.0$ Hz, 1H), 8.54 (s, 1H). δ_C (50 MHz, $CDCl_3$) 22.4, 32.6, 40.5, 56.5, 68.7, 76.7, 123.9, 123.9, 127.3, 127.7, 128.6, 135.2, 141.1, 144.1, 148.7, 151.2, 152.4. *m/z* (EI) 268 (M+, 11%), 210 (11%), 196 (15%), 168 (13%), 120 (19%), 84 (100%), 79 (31%), 77 (60%).

(2-Methoxyphenyl)[3-(1-methylpyrrolidin-2-yl)pyridin-4-yl]-methanol (2i). Yield 85%, obtained as a 1 : 1 mixture of diastereoisomers, which were separated. The absolute configuration was not determined.

Diastereoisomer 2i-1. Yield 44%, colorless oil. $[\alpha]_D^{27}$ −50.0 (*c* 2.12, $CHCl_3$). (Found: C, 72.53; H, 7.56; N, 9.49. $C_{18}H_{22}N_2O_2$ requires C, 72.46; H, 7.43; N, 9.39%). δ_H (200 MHz, $CDCl_3$) 1.90–2.52 (m, 8H), 3.28–3.42 (m, 2H), 3.64 (s, 3H), 6.37 (s, 1H), 6.63 (d, $J = 5.0$ Hz, 1H), 6.88 (d, $J = 8.0$ Hz, 1H), 7.09 (t, $J = 7.6$ Hz, 1H), 7.34 (t, $J = 8.0$ Hz, 1H), 7.67 (d, $J = 7.6$ Hz, 1H), 8.29 (d, $J = 5.2$ Hz, 1H), 8.43 (s, 1H). δ_C (50 MHz, $CDCl_3$) 24.4, 40.6, 55.2, 55.3, 65.5, 70.0, 110.0, 120.8, 121.8, 127.5, 128.5, 129.2, 134.9, 149.8, 150.8, 152.5, 156.1. *m/z* (EI) 298 (M^+, 10%), 296 (18%), 281 (20%), 173 (23%), 159 (31%), 84 (100%), 77 (43%), 63 (21%).

Diastereoisomer 2i-2. Yield 33%, white solid, mp 135 °C. $[\alpha]_D^{27}$ −88.2 (*c* 0.78, $CHCl_3$). (Found: C, 72.33; H, 7.46; N, 9.25. $C_{18}H_{22}N_2O_2$ requires C, 72.46; H, 7.43; N, 9.39%). δ_H (200 MHz, $CDCl_3$) 1.22–2.23 (m, 8H), 3.10–3.45 (m, 2H), 3.80 (s, 3H), 5.37 (brs, 1H), 6.39 (s, 1H), 6.88 (m, 2H), 7.05 (dd, $J = 7.6$ and 1.2 Hz, 1H), 7.31 (t, $J = 7.6$ Hz, 1H), 7.37 (d, $J = 4.9$ Hz, 1H), 8.36 (d, $J = 4.9$ Hz, 1H), 8.63 (s, 1H). δ_C (50 MHz, $CDCl_3$) 22.6, 33.7, 40.5, 55.4, 56.6, 65.9, 66.9, 110.7, 120.8, 121.6, 128.5, 129.2, 131.2, 135.7, 147.8, 149.5, 150.7, 156.5. *m/z* (EI) 298 (M+, 10%), 296 (25%), 281 (34%), 173 (40%), 159 (50%), 135 (23%), 84 (100%), 77 (62%), 63 (27%).

Lithiation of (*S*)-4-chloronicotine (2c). A solution of **2c** (299 mg, 1.84 mmol) in anhydrous THF (4 mL) was cooled to −78 °C, and $TMSCH_2Li$ (3.68 mmol, 4 mL of a 0.92 M solution in hexanes) was added dropwise. At the end of the addition (*ca.* 5 min.), the reaction medium was stirred for 5 h at the same temperature. The orange solution was then treated dropwise with a solution of the appropriate electrophile (2 mmol) in THF (2 mL). After the addition, the stirring was maintained for 30 min at −78 °C, and then for 1 h at room temperature. Hydrolysis was performed at −78 °C with H_2O (10 mL). After extraction with Et_2O, drying, and evaporation of the organic phase, the crude product was purified by column chromatography using AcOEt–hexane–Et_3N (30 : 70 : 10) as eluent (this was found to be convenient for all compounds).

3-(1-Methylpyrrolidin-2-yl)-5-(trimethylsilanylmethyl)pyridine (3). This compound was obtained when the metallation was performed at 0 °C instead of −78 °C. Yield 51%, yellow oil. (Found: C, 67.73; H, 9.66; N, 11.35. $C_{14}H_{24}N_2Si$ requires C, 67.68; H, 9.74; N, 11.28%). δ_H (200 MHz, $CDCl_3$) 0.04 (s, 9H), 1.73–2.32 (m, 9H), 3.03 (t, $J = 8.0$ Hz, 1H), 3.20–3.32 (m, 1H), 7.35 (s, 1H), 8.17 (d, $J = 1.6$ Hz, 1H), 8.24 (d, $J = 1.9$ Hz, 1H). δ_C (50 MHz, $CDCl_3$) 0.04, 22.5, 23.8, 35.3, 40.4, 57.0, 68.9, 133.9, 136.2, 137.9, 145.5, 147.9. *m/z* (EI) 248 (M^+, 9%), 247 (6%), 219 (5%), 147 (2%), 85 (6%), 84 (100%), 73 (28%).

[4-Chloro-5-(1-methylpyrrolidin-2-yl)pyridin-3-yl](2-methoxyphenyl)methanol (4). Yield 70% (as a 1 : 1 mixture of diastereoisomers), yellow solid, mp 122 °C. $[\alpha]_D^{27}$ −115.8 (*c* 1.02, $CHCl_3$). δ_H (200 MHz, $CDCl_3$) 1.52–2.10 (m, 4H), 2.25 (s, 3H), 2.26 (s, 3H), 2.25–2.50 (m, 4H), 3.23–3.65 (m, 6H), 3.86 (s, 6H), 6.42 (s, 2H), 6.91–7.08 (m, 4H), 7.09 (d, $J = 6.9$ Hz, 2H), 7.31 (t, $J = 6.9$ Hz, 2H), 8.59 (s, 1H), 8.62 (s, 1H), 8.74 (s, 2H). δ_C (50 MHz, $CDCl_3$) 23.2, 33.7, 41.1, 55.7, 57.2, 65.8, 67.2, 110.9, 121.0, 128.1, 128.9, 130.5, 136.5, 136.8, 142.7, 148.5, 157.1. *m/z* (EI) 334 (4%), 332 (M^+, 9%), 303 (5%), 152 (7%), 137 (24%), 135 (18%), 84 (100%), 77 (5%).

[4-Chloro-5-(1-methylpyrrolidin-2-yl)pyridin-3-yl](4-methoxyphenyl)methanol (5). Yield 40% (as a 1 : 1 mixture of diastereoisomers), pale yellow oil. $[\alpha]_D^{27}$ −86.2 (*c* 1.05, $CHCl_3$). δ_H (200 MHz, $CDCl_3$) 1.20–2.0 (m, 4H), 2.15 (s, 3H), 2.17 (s, 3H), 2.23–2.32 (m, 4H), 3.15–3.55 (m, 4H), 3.74 (s, 6H), 4.4 (brs, 2H), 6.09 (s, 2H), 6.83 (d, $J = 8.2$ Hz, 4H), 7.27 (d, $J = 8.2$ Hz, 4H), 8.58 (s, 2H), 8.67 (s, 1H), 8.69 (s, 1H). δ_C (50 MHz, $CDCl_3$) 23.2, 33.7, 41.1, 55.6, 57.2, 59.2, 64.8, 65.8, 71.4, 114.2, 128.9, 134.9, 137.0, 137.7, 147.7, 148.4, 148.6, 159.4. *m/z* (EI) 332 (M^+, 4%), 331 (1%), 144 (18%), 143 (98%), 130 (29%), 105 (25%), 84 (100%), 77 (15%).

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