Noncryogenic Synthesis of Functionalized 2-Methoxypyridines by Halogen–Magnesium Exchange Using Lithium Dibutyl(isopropyl)magnesate(1–) and Lithium Chloride

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Abstract: 2-Methoxypyridines functionalized in the 3-, 5-, or 6-position and 2,6-dimethoxypyridines functionalized in the 3-position were prepared from the corresponding bromo or iodo analogues by using lithium dibutyl(isopropyl)magnesate(1–) and lithium chloride under noncryogenic conditions. The procedure was optimized in terms of the choice between two magnesates and the presence or absence of lithium chloride in the reaction medium.

Key words: pyridines, magnesium, lithium, organometallic reagents

The functionalized 2-alkoxypyridine ring is a common structural motif that is present in many organic compounds that exhibit a broad spectrum of biological activities.[1] Functionalized 2-methoxypyridines are particularly valuable examples of such derivatives because, apart from their biological activities,[2] they are also useful in synthesis. Transformation of 2-methoxypyridines into N-substituted[3] or N-unsubstituted[4] 2-pyridones or replacement of the 2-methoxy substituent by chlorine by using phosphoryl chloride[5] followed by cross-coupling reactions[6] permits the preparation of hundreds of derivatives containing a pyridine ring, including alkaloids[7] and pharmacophores.[8] Moreover, the 2-methoxy group of 2-methoxypyridine can be directly replaced by an aryl moiety in a cross-coupling reaction.[9]

Halogen–metal exchange in a bromo- or iodo-substituted pyridine, followed by reaction with an electrophile, is a useful method for the functionalization of the pyridine ring. The most common synthetic approach of this type involves the use of organolithium compounds as exchange reagents; however, these reactions must be performed at low temperatures, typically between –78 and –65 °C.[10] In the case of organomagnesium compounds, Grignard derivatives, particularly isopropylmagnesium chloride,[11] or its complex with lithium chloride[12] can be used. In the past decade, increasing attention has been paid to the use of magnesate complexes of the type $[R_3Mg]Li$ as halogen–magnesium exchange reagents; these complexes are relatively stable at temperatures between –10 °C and 0 °C.[13] Magnesate reagents have been used in the functionalization of substituted pyridines,[13c–k,t,x,aa] among other reactions. Other promising candidates for use as stable halogen-exchange reagents include zincate 'ate' complexes. Recently, dilithium tetrabutylzincate and its complex with *N*,*N*,*N*′,*N*′-tetramethylethylenediamine have been used in the chemoselective zincation of bromopyridines at room temperature.[14]

In our recent study on the application of magnesates in synthesis, we introduced the use of lithium allyl(dibutyl)magnesate(1–) as a powerful allylating agent, useful in nucleophilic addition reactions of 2-(thio)pyridones.[15] Recently, we also presented some preliminary results on the use of lithium tributylmagnesate(–1) as an exchange reagent for the noncryogenic 5-functionalization of 2-methoxypyridine, starting from the 5-bromo-substituted analogue.[16] Here, we report further studies on the functionalization of 5-bromo-2-methoxypyridine by halogen–magnesium exchange and the extension of this reaction to 6-bromo- and 3-iodo-substituted 2-methoxypyridines and to 3-bromo-2,6-dimethoxypyridines. We also tested two magnesates, lithium dibutyl(isopropyl)magnesate(–1) and lithium tributylmagnesate(–1), as exchange reagents. We also investigated the effects of the presence or absence of lithium chloride in the magnesate solutions (Scheme 1).

To identify the optimal reagent for the halogen-exchange reaction, we prepared three solutions of 'ate' complexes (Scheme 1). Solution **1a**, containing lithium dibutyl(isopropyl)magnesate(–1) and lithium chloride, was prepared by mixing one equivalent of isopropylmagnesium chloride with two equivalents of butyllithium (method A). Solution **1b**, containing lithium tributylmagnesate(–1) and lithium chloride, was prepared by mixing one equivalent of butylmagnesium chloride with two equivalents of butyllithium (method B). Solution **1c**, containing lithium tributylmagnesate(–1) was prepared by mixing one equivalent of dibutylmagnesium with one equivalent of butyllithium (method C). It should be emphasized that the first two solutions each contained one equivalent of lithium chloride as a byproduct of the reaction between the Grignard reagent and butyllithium, whereas the third solution was free of lithium chloride. All three magnesate solutions were tested for the 5-functionalisation of 5-bromo-2-methoxypyridine through halogen–magnesium exchange followed by treatment with each of four electrophiles: *N*,*N*-dimethylformamide, 2-isopropoxy-4,4,5,5-

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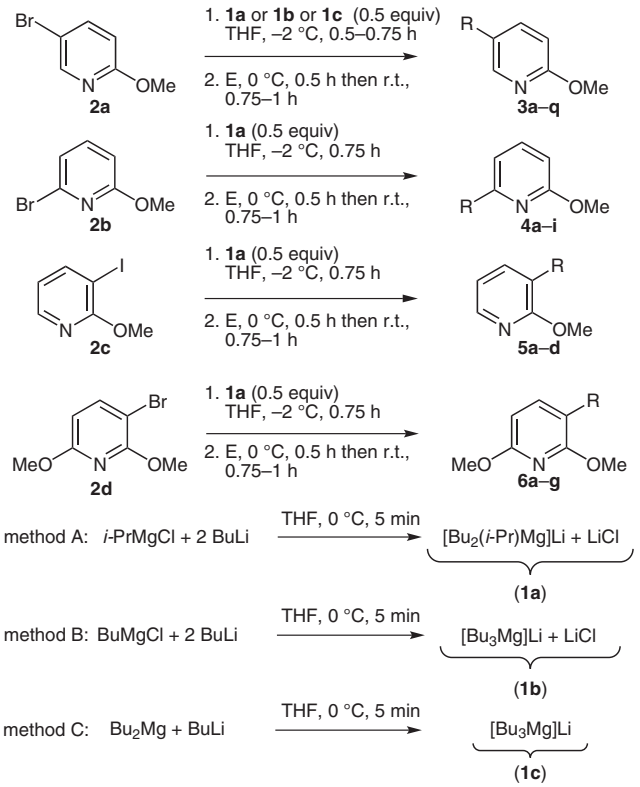


Scheme 1 Synthesis of functionalized methoxypyridines **3–6**

tetramethyl-1,3,2-dioxaborolane, diphenyl disulfide, and benzaldehyde (Table 1, entries 1–4).

The halogen–magnesium exchange step was conducted at –2 °C using 0.5 equivalents of magnesate with respect to the halide in all cases. However, the use of solution **1a** [Bu_2(Pr)Mg]Li + LiCl] or soln **1c** (Bu_3MgLi alone) required 45 minutes of stirring, whereas with solution **1b** (Bu_3MgLi + LiCl), the exchange process took 30 minutes. To optimize the amount of electrophile in the second step, various amounts between 1.0 and 3.0 equivalents with respect to the starting bromide were added at 0 °C, followed by stirring for 0.5 hours at 0 °C and for 0.75–1.0 hour at room temperature. Because the isolated yields might be affected by the purification process (especially when small amounts of product are purified by distillation), the yield was also determined by ^{1}H NMR spectroscopy of the crude product using an internal standard; the corresponding results are shown in parenthesis in the table.

The results of the optimization studies presented in Table 1 (entries 1–4) show that the presence of lithium chloride in the solution affects the course of the reaction, leading to higher yields in most cases. This suggests that the procedure involving mixing of two equivalents of RLi with one equivalent of RMgCl (solutions **1a** and **1b**) is the better choice. Comparison of the yields of functionalized products obtained by using solution **1a** and solution **1b** showed that, in general, solution **1a** gave slightly better yields than solution **1b**. As method A, involving the use of lithium dibutyl(isopropyl)magnesate(–1) and lithium chloride was also more effective for the functionalization of 5-bromo-2-methoxypyridine by reactions with other electrophiles (Table 1, entries 6–11), we subsequently used this method for the functionalization of 3-iodo- and 6-bromo-2-methoxypyridines and 3-bromo-2,6-dimethoxypyridine (Tables 2– 4, respectively).

The results presented in Tables 2– 4 show that protocol A permits successful 6- and 3-functionalization of 2-methoxypyridines and 3- functionalization of 2,6-dimethoxypyridines in the vast majority of cases. However, 6-bromo-2-methoxypyridine tended to give lower yields of functionalization products, especially with the boronic ester (Table 2, entry 2).

Overall, the protocol appears to be useful for functionalization of various halogen derivatives of methoxypyridines. The yields of the compounds obtained by using lithium dibutyl(isopropyl)magnesate(–1) and lithium chloride were, in most cases, comparable or even superior to those obtained by the classical cryogenic method (butyllithium, tetrahydrofuran, –78 °C) (Table 1, entries 1 and 2; Table 2, entries 1 and 8; Table 4, entry 1).

In summary, we developed a practical protocol that permits the introduction of a broad range of functionalities onto the 2-methoxy- or 2,6-dimethoxypyridine ring through a halogen–magnesium exchange process that does not require cryogenic conditions. In this protocol, the lithium dibutyl(isopropyl)magnesate(–1) plus lithium chloride system is used as a halogen–magnesium exchange reagent that can be prepared simply by mixing commercially available isopropylmagnesium chloride and butyllithium before use.

Melting points were determined on a Boetius hot-stage apparatus. ^{1}H and ^{13}C NMR spectroscopic measurements were performed on a Bruker DPX 400 spectrometer equipped with a 5-mm 1H/BB inverse probe head, operating at 400.13 or 100.62 MHz. TMS was used as the internal reference and 1,3,5-trimethoxybenzene was used as the internal standard. Two-dimensional spectra were acquired by using standard Bruker software. Purity and molecular mass determinations were carried out by GC-MS on a Hewlett-Packard HP 6890 equipped with an HP 5973 mass detector and a capillary column (30 m × 0.2 mm i.d.) with a 0.25 μm active phase layer of methylsiloxane modified with phenyl groups (5% Ph). Silica gel (0.04–0.063 mm, Merck) was used for preparative column chromatography. IR spectra were recorded on a Specord M80 instrument. Elemental analyses were performed on EuroEA 3000 series, EuroVector CHNS-O Elemental Analyzer. HRMS analyses were performed on Spektrometer AMD Intectra Mass AMD 402.

Before use, THF was purified over Na in under argon according to the standard procedure. 3-Iodo-2-methoxypyridine was purchased from Acros Organics. All other chemicals, including BuLi (2.5 M in hexane), BuMgCl (2.0 M in THF), *i*-PrMgCl (2.0 M in THF), Bu_2Mg (1.0 M in heptane), and 6-bromo-2-methoxypyridine, were purchased from Aldrich. 5-Bromo-2-methoxypyridine and 3-bromo-2,6-dimethoxypyridine were prepared according to the literature procedure,[26] with some modifications.

Table 1 Synthesis of 5-Functionalized 2-Methoxypyridines **3a–q** from 5-Bromo-2-methoxypyridine (**2a**)

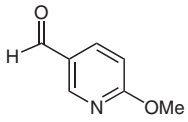
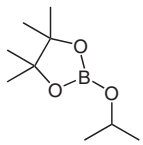
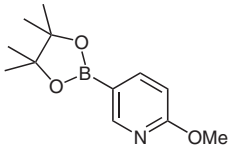
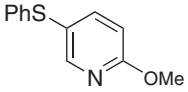
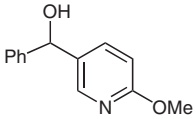
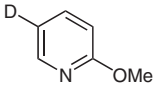
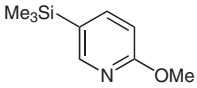
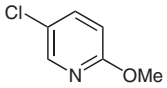
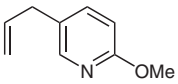
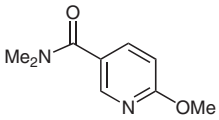
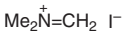
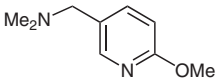
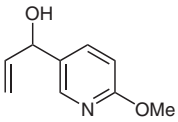
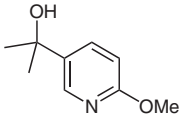
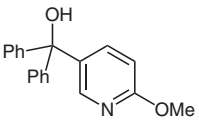
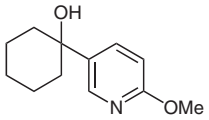
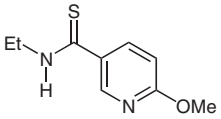
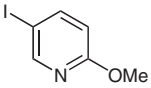
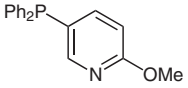
Entry	Electrophile (equiv)	Product		Method	Yield[a,b,c] (%)
1	DMF (3.0)		**3a**	A[d] B[d] C[d] (BuLi, THF, –78 °C)[17] (BuLi, Et_2O, –35 °C to 0 °C)[18]	99 (99)[a] 89 (92)[a] 83 (86)[a] 95[17] 90[18]
2	 (2.0)		**3b**	A[e] A[f] B[e] C[e] (BuLi, THF, –78 °C)[19]	73 (99)[a] 99 (99)[a] 72 (93)[a] (98) 67.5[19]
3	PhSSPh (1.0)		**3c**	A[e] B[d] C[d]	89(93)[a] 89(92)[a] (52)
4	PhCHO (2.0)		**3d**	A[d] B[f] C[d]	83 (91)[a] 93 (98)[a] (56)
5	D_2O (5.0)[g]		**3e**	A[e] B[d]	68 (76)[a] 75 (85)[a]
6	TMSCl (3.0)		**3f**	A[d] B[e]	58 (60)[a] 46 (48)[a,h]
7	Cl_3CCCl_3(1.3)		**3g**	A[d] B[d]	76 (78)[a] 63 (65)[a]
8	CH_2=$CHCH_2Br$ (3.0)		**3h**	A[d,i] B[d,i]	69 (71)[a] 63 (65)[a]
9	Me_2NCOCl (3.0)		**3i**	A[e,j] B[d,j]	76 (80)[a] 74 (76)[a]
10	 (2.0)		**3j**	A[e,k] B[e,k]	81 (83)[b] 83 (86)[b]
11	CH_2=CCHO (2.7)		**3k**	A[f] B[e]	60 (60)[a] (36)
12	acetone (5.0)[g]		**3l**	A[f]	62[a]
13	PhCOPh (2.0)		**3m**	A[d]	95[b]

Table 1 Synthesis of 5-Functionalized 2-Methoxypyridines **3a–q** from 5-Bromo-2-methoxypyridine (**2a**) (continued)

Entry	Electrophile (equiv)	Product		Method	Yield[a,b,c] (%)
14	cyclohexanone (2.0)		**3n**	A[e]	62 (63)[b]
15	EtNCS (2.0)		**3o**	A[d]	89[b]
16	I_2 (2.0)		**3p**	A[d,l]	91 (99)[a]
17	Ph_2PCl (2.0)		**3q**	A[d]	85 (90)[b]

[a] Isolated yields after distillation.
[b] Isolated yields after column chromatography.
[c] Yields estimated by ^{1}H NMR spectroscopy using an internal reference are given in parentheses.
[d] 1 mL (7.7 mmol) of substrate (5-bromo-2-methoxypyridine) was used.
[e] 0.5 mL (3.86 mmol) of substrate (5-bromo-2-methoxypyridine) was used.
[f] 3 mL (23.2 mmol) of substrate (5-bromo-2-methoxypyridine) was used.
[g] The amount of electrophile was not optimized.
[h] The yield previously reported[16] was doubled erroneously.
[i] The reaction with the electrophile was prolonged to 2 d at r.t.
[j] At the end of the reaction, Et_3N (0.5 mL) was added and reaction was prolonged for 2 h at r.t.
[k] The reaction was quenched with H_2O instead of sat. aq NH_4Cl.
[l] To remove excess I_2, sat. aq $Na_2S_2O_3$ was added after quenching with sat. aq NH_4Cl.

Table 2 Synthesis of 6-Functionalized 2-Methoxypyridines **4a–i** from 6-Bromo-2-methoxypyridine (**2b**) (Method A)

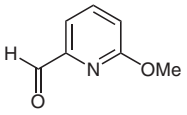
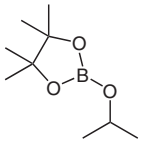
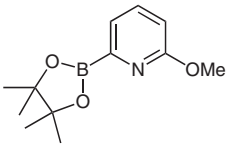
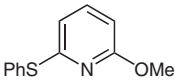
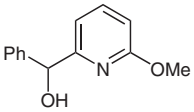
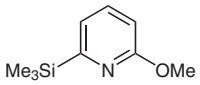
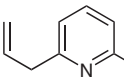
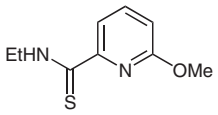
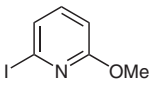
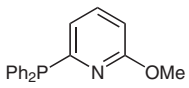
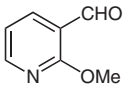
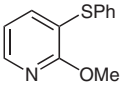
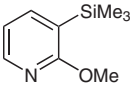
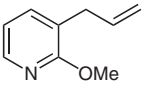
Entry	Electrophile (equiv)	Product		Yield[a,b,c] (%)
1	DMF (3.0)		**4a**	75 (86)[a,d] 76 (BuLi, THF, –78 °C)[20] 70 (BuLi, THF, –78 °C)[21]
2	 (2.0)		**4b**	– (12)[e,f]
3	PhSSPh (1.0)		**4c**	80 (85)[a,e]
4	PhCHO (2.0)		**4d**	82 (84)[a,e]
5	TMSCl (3.0)		**4e**	39 (41)[a,e] 92 (BuLi, THF, –78 °C)[22]
6	CH_2=$CHCH_2Br$ (3.0)		**4f**	55[b,d,g]

Table 2 Synthesis of 6-Functionalized 2-Methoxypyridines **4a–i** from 6-Bromo-2-methoxypyridine (**2b**) (Method A) (continued)

Entry	Electrophile (equiv)	Product		Yield[a,b,c] (%)
7	EtNCS (2.0)		**4g**	58 (59)[b,e]
8	I_2 (2.0)[h]		**4h**	92 (93)[a,e] 86 (BuLi, THF, –78 °C)[23] 80 (Bu_4ZnLi_2, TMEDA, toluene, 20 °C)[14]
9	Ph_2PCl (1.5)		**4i**	84 (91)[b,e] 79 (BuLi, Et_2O, –78 °C)[24]

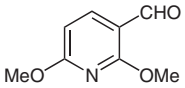
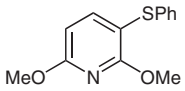
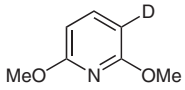
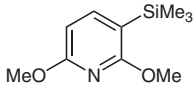
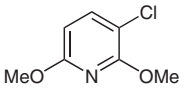
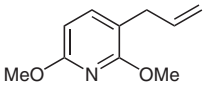
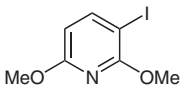
[a] Isolated yields after distillation.
[b] Isolated yields after column chromatography.
[c] Yields estimated by ^{1}H NMR spectroscopy using an internal reference are given in parentheses.
[d] 0.5 mL (4.05 mmol) of substrate (6-bromo-2-methoxypyridine) was used.
[e] 1 mL (8.1 mmol) of substrate (6-bromo-2-methoxypyridine) was used.
[f] Product decomposed during purification by column chromatography on silica gel.
[g] CuI (5 mol%) was added to the reaction mixture.
[h] To remove excess I_2, sat. aq $Na_2S_2O_3$ was added after quenching with sat. aq NH_4Cl.

Table 3 Synthesis of 3-Functionalized 2-Methoxypyridines **5a–d** from 3-Iodo-2-methoxypyridine (**2c**) (Method A)

Entry[a]	Electrophile (equiv)	Product		Yield[b,c] (%)
1	DMF (3.0)		**5a**	90 (94)
2	PhSSPh (1.0)		**5b**	88 (98)
3	TMSCl (3.0)		**5c**	90 (97)
4	CH_2=$CHCH_2Br$ (3.0)		**5d**	78[d]

[a] 0.5 mL (3.9 mmol) of substrate (3-iodo-2-methoxypyridine) was used.
[b] Isolated yields after distillation.
[c] Yields estimated by ^{1}H NMR spectroscopy using an internal reference are given in parenthesis.
[d] The reaction with the electrophile was prolonged to 1 d at r.t.

Table 4 Synthesis of 3-Functionalized 2,6-Dimethoxypyridines **6a–g** from 3-Bromo-2,6-dimethoxypyridine (**2d**) (Method A)

Entry[a]	Electrophile (equiv)	Product		Yield[b,c,d] (%)
1	DMF (3.0)		**6a**	70 (74)[c] 71 (BuLi, THF, –78 °C)[25]
2	PhSSPh (1.0)		**6b**	55 (63)[b] 61 (63)[c]
3	D_2O (5.0)[e]		**6c**	66 (72)[b]
4	TMSCl (3.0)		**6d**	69 (79)[b]
5	Cl_3CCCl_3 (1.3)		**6e**	73 (78)[b]
6	CH_2=$CHCH_2Br$ (3.0)		**6f**	70 (73)[b]
7	I_2 (2.0)		**6g**	89 (94)[b]

[a] 1.6 g (7.3 mmol) of substrate (3-bromo-2,6-dimethoxypyridine) was used.
[b] Isolated yields after distillation.
[c] Isolated yields after column chromatography.
[d] Yields estimated by ^{1}H NMR spectroscopy using an internal reference are given in parentheses.
[e] The amount of electrophile was not optimized.

Functionalization of 2-Methoxypyridine and 2,6-Dimethoxypyridine: General Procedures

Method A: A 2.5 M soln of BuLi in hexane (3.1 mL, 7.7 mmol) was added from a syringe over 1 min to a cooled (0 °C) and stirred mixture of a 2.0 M soln of *i*-PrMgCl in THF (1.9 mL, 3.9 mmol) and anhyd THF (20 mL) in a Schlenk flask under argon. The mixture was stirred for 5 min to give a yellow soln that was cooled to –2 to 0 °C. A soln of the halogenated methoxypyridine (7.7 mmol) was added from a syringe and the resulting soln was stirred for 45 min at –2 to 0 °C. The appropriate electrophile (Tables 1– 4) was then added and the mixture was continuously stirred for 30 min at 0 °C and then for 45–60 min at r.t. Sat. aq NH_4Cl (5 mL) was added and the aqueous layer was separated and then extracted with EtOAc (2 × 75 mL). The combined organic layers were dried ($MgSO_4$ or,

when alcohols were obtained as products, Na_2SO_4), filtered, concentrated in vacuo, and purified by distillation or flash column chromatography to give the corresponding product **3–6**. (Note that in the cases of **3e**, **4e**, and **6c**, Et_2O instead of EtOAc was used for extraction).

Method B: The procedure was the same as that described for Method A except that a 2.0 M soln of BuMgCl in THF (1.9 mL) was used instead of *i*-PrMgCl, and the metalation process took 30 min instead of 45 min.

Method C: A 2.5 M soln of BuLi in hexane (1.6 mL, 3.9 mmol) was added from a syringe over 1 min to a cooled (0 °C) and stirred mixture of a 1.0 M soln of Bu_2Mg in heptane (3.9 mL, 3.9 mmol) and dry THF (20 mL) in a Schlenk flask under argon. The mixture was stirred for 5 min to give a yellow soln that was cooled to –2 to 0 °C. 5-Bromo-2-methoxypyridine (1.0 mL, 7.7 mmol) was added from a syringe and the resulting soln was stirred for 45 min at –2 to 0 °C. The appropriate electrophile (Table 1) was added and the mixture was continuously stirred for 30 min at 0 °C and then for 30–60 min at r.t. Sat. aq NH_4Cl (5 mL) was added and the aq layer was separated and extracted with EtOAc (2 × 75 mL). The combined organic layers were dried ($MgSO_4$), filtered, concentrated in vacuo, and purified by distillation or by flash column chromatography.

6-Methoxypyridine-3-carbaldehyde (3a)[18]
The crude product was purified by distillation to give a colorless oil that solidified on standing at r.t.; yield: 1.05 g (99%); bp 47–49 °C (4 mbar); mp 42–46 °C (Lit.[18] 47 °C).

IR ($CDCl_3$, *c* 0.13 M, d_{NaCl} = 0.11 mm): 2952, 2836, 1694, 1606, 1568, 1496, 1364, 1320, 1292, 1022, 1068, 840 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.04 (s, 3 H, OCH_3), 6.85 (d, *J* = 8.7 Hz, 1 H, H-3), 8.07 (dd, *J* = 8.7, 2.4 Hz, 1 H, H-4), 8.64 (d, *J* = 2.4 Hz, 1 H, H-6), 9.96 (s, 1 H, CHO).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 54.1, 111.9, 126.6, 137.3, 152.7, 167.6, 189.4.

GC-MS (EI, 70 eV): *m/z* (%) = 137 (100) [M^+], 136 (97), 108 (40), 107 (58), 95 (17), 78 (20), 66 (11), 52 (14), 39 (16).

2-Methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (3b)[19]
Prepared from **2a** (3 mL, 23.1 mmol). The crude product was purified by distillation to give a colorless oil that solidified on standing in a refrigerator; yield: 5.38 g (99%); bp 100–102 °C (0.1 mbar).

IR (film): 2980, 1602, 1562, 1500, 1358, 1318, 1290, 1144, 1124, 1100, 1022, 964, 860, 840, 668 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.33 (s, 12 H, $4CH_3$), 3.96 (s, 3 H, OCH_3), 6.71 (dd, *J* = 8.3, 0.7 Hz, 1 H, H-3), 7.92 (dd, *J* = 8.3, 1.9 Hz, 1 H, H-4), 8.55 (dd, *J* = 1.9, 0.7 Hz, 1 H, H-6).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.8, 53.5, 83.8, 110.2, 144.5, 154.2, 166.1; C-5 not visible (quadrupole effect of attached B).

GC-MS (EI, 70 eV): *m/z* (%) = 235 (70) [M^+], 234 (100), 220 (20), 206 (14), 178 (11), 136 (55), 135 (39), 105 (12), 41 (6).

2-Methoxy-5-(phenylsulfanyl)pyridine (3c)
Prepared from **2a** (0.5 mL, 3.86 mmol). The crude product was purified by distillation to give a pale yellow oil; yield: 0.749 g (89%); bp 96–102 °C (0.1 mbar).

IR (film): 1588, 1556, 1480, 1440, 1360, 1304, 1282, 1250, 1124, 1022, 830, 738, 690 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.95 (s, 3 H, OCH_3), 6.74 (d, *J* = 8.6 Hz, 1 H, H-3), 7.14–7.28 (m, 5 H, C_6H_5), 7.64 (dd, *J* = 8.6, 2.4 Hz, 1 H, H-4), 8.28 (d, *J* = 2.4 Hz, 1 H, H-6).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 53.7, 111.9, 122.15, 126.2, 128.5, 129.1, 137.4, 144.1, 151.6, 164.1.

GC-MS (EI, 70 eV): *m/z* (%) = 217 (100) [M^+], 216 (50), 188 (34), 147 (13), 109 (7), 77 (9), 51 (9).

HRMS (EI): *m/z* [M^+] calcd for $C_{12}H_{11}NOS$: 217.0561; found: 217.0558.

(6-Methoxypyridin-3-yl)(phenyl)methanol (3d)[27]
The crude product was purified by distillation to give a pale yellow oil; yield: 1.38 g (83%); bp 130–135 °C (0.1 mbar) [Lit.[27] 174–176 °C (4 mbar)].

IR (film): 3400 (br), 1606, 1572, 1452, 1284, 1124, 1026, 700 cm^{-1}.

The ^1H and ^{13}C NMR spectral data for this product matched those reported previously for its enantiomer.[28]

GC-MS (EI, 70 eV): *m/z* (%) = 215 (80) [M^+], 214 (60), 198 (20), 138 (55), 136 (87), 110 (100), 105 (38), 95 (16), 77 (41), 51 (20), 42 (14).

2-Methoxy(5–^{2}H)pyridine (3e)
Prepared from **2a** (0.5 mL, 3.86 mmol). The crude product was purified by distillation to give a colorless oil; yield: 0.289 g (68%); bp 141–142 °C (1013 mbar).

IR (film): 2948, 1596, 1568, 1474, 1380, 1308, 1286, 1252, 1124, 1040, 1022, 840, 806 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.94 (s, 3 H, OCH_3), 6.75 (dd, *J* = 8.3, 0.7 Hz, 1 H, H-3), 7.56 (d, *J* = 8.3 Hz, 1 H, H-4), 8.17 (d, *J* = 0.7 Hz, 1 H, H-6).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 53.3, 110.9, 116.4 (t, J_{C-D} = 24.9 Hz), 138.4, 146.8, 164.1.

MS (EI, 70 eV): *m/z* (%) = 110 (78) [M^+], 109 (100), 80 (86), 67 (7), 53 (30), 40 (18).

HRMS (EI): *m/z* [M^+] calcd for C_6H_6DNO: 110.0589; found: 110.0585.

2-Methoxy-5-(trimethylsilyl)pyridine (3f)[16]
The crude product was purified by distillation to give a colorless oil; yield: 0.812 g (58%); bp 41 °C (4 mbar).

Spectral data for this product matched those reported previously.[16]

5-Chloro-2-methoxypyridine (3g)[29]
The crude product was purified by distillation to give a colorless oil; yield: 0.841 g (75%); bp 72–75 °C (12 mbar) [Lit.[30] 82–84 °C (27 mbar)].

IR (film): 3070, 2980, 1594, 1564, 1480, 1428, 1370, 1300, 1280, 1248, 1122, 1108, 1022, 916, 826, 782, 672 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.91 (s, 3 H, OCH_3), 6.70 (d, *J* = 8.8 Hz, 1 H, H-3), 7.51 (dd, *J* = 8.8, 2.7 Hz, 1 H, H-4), 8.10 (d, *J* = 2.7 Hz, 1 H, H-6).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 53.8, 112.0, 124.1, 138.4, 145.2, 162.6.

MS (EI, 70 eV): *m/z* (%) = 143 (72) [M^+], 142 (100), 113 (61), 78 (48), 72 (20).

5-Allyl-2-methoxypyridine (3h)
The crude product was purified by distillation to give a colorless oil; yield: 0.793 g (69%); bp 32–34 °C (5 mbar).

IR (film): 3080, 3004, 2976, 2944, 2904, 1640, 1608, 1572, 1490, 1388, 1290, 1256, 1126, 1030, 918, 828 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.30 (d, *J* = 6.5 Hz, 2 H, CH_2), 3.92 (d, *J* = 0.7 Hz, 3 H, OCH_3), 5.02–5.11 (m, 2 H, $=CH_2$), 5.92 (ddddd, *J* = 16.8, 10.3, 6.5, 6.4, 0.7 Hz, 1 H, =CH), 6.69 (d, *J* = 8.5

Hz, 1 H, H-3), 7.40 (dd, *J* = 8.5, 2.3 Hz, 1 H, H-4), 7.97 (d, *J* = 2.3 Hz, 1 H, H-6).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 36.3, 53.3, 110.5, 116.2, 127.9, 136.9, 139.2, 146.2, 162.9.

MS (EI, 70 eV): *m/z* (%) = 149 (73) [M^+], 148 (100), 120 (31), 119 (33), 118 (23), 104 (7), 91 (16), 77 (15), 65 (7), 51 (12).

HRMS (EI): *m/z* [M^+] calcd for $C_9H_{11}NO$: 149.0841; found: 149.0840.

6-Methoxy-*N*,*N*-dimethylnicotinamide (3i)
Prepared from **2a** (0.5 mL, 3.86 mmol). The crude product was purified by distillation to give a colorless oil; yield: 0.528 g (76%); bp 92–95 °C (0.1 mbar).

IR (film): 2944, 1634, 1604, 1486, 1396, 1372, 1256, 1256, 1128, 1088, 1022, 840, 776 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.08 (br s, 6 H, $2CH_3$), 3.97 (s, 3 H, OCH_3), 6.77 (dd, *J* = 8.5, 0.5 Hz, 1 H, H-3), 7.70 (dd, *J* = 8.5, 2.4 Hz, 1 H, H-4), 8.29 (dd, *J* = 2.4, 0.5 Hz, 1 H, H-6).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 35.6 (br), 39.8 (br), 53.7, 110.7, 125.0, 138.3, 146.3, 164.7, 169.3.

MS (EI, 70 eV): *m/z* (%) = 180 (30) [M^+], 179 (62), 136 (100), 108 (10), 95 (15).

HRMS (EI): *m/z* [M^+] calcd for $C_9H_{12}N_2O_2$: 180.0899; found: 180.0897.

[(6-Methoxypyridin-3-yl)methyl]dimethylamine (3j)[31]
Prepared from **2a** (0.5 mL, 3.86 mmol). The crude product was purified by column chromatography [silica gel, $CHCl_3$–MeOH (9:1)] to give a colorless oil; yield: 0.521 g (81%).

IR (film): 2980, 2944, 2820, 2772, 1610, 1572, 1494, 1460, 1392, 1356, 1292, 1270, 1124, 850, 824, 1026, cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.22 [s, 6 H, $N(CH_3)_2$], 3.34 (s, 2 H, CH_2), 3.93 (s, 3 H, OCH_3), 6.72 (d, *J* = 8.5 Hz, 1 H, H-3), 7.56 (dd, *J* = 8.5, 2.4 Hz, 1 H, H-4), 8.02 (d, *J* = 2.4 Hz, 1 H, H-6).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 45.1, 53.4, 60.8, 110.7, 126.8, 139.8, 146.9, 163.6.

GC-MS (EI, 70 eV): *m/z* (%) = 166 (65) [M^+], 165 (39), 122 (100), 94 (11), 58 (31), 53 (14), 42 (20).

1-(6-Methoxypyridin-3-yl)prop-2-en-1-ol (3k)
Prepared from **2a** (3 mL, 23.1 mmol). The crude product was purified by distillation to give a colorless oil; yield: 2.31 g (60%); bp 92–93 °C (0.1 mbar).

IR (film): 3350 (br), 1608, 1494, 1392, 1288, 1126, 1026, 932, 832 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.40 (br s, 1 H, OH), 3.92 (s, 3 H, OCH_3), 5.18 (br d, *J* = ca. 5.4 Hz, 1 H, CH), 5.22 (dt, *J* = 10.3, 1.2 Hz, 1 H, =C*H*H), 5.35 (dt, *J* = 17.1, 1.5 Hz, 1 H, =CH*H*), 6.02 (ddd, *J* = 17.1, 10.3, 5.6 Hz, 1 H, =CH), 6.74 (d, *J* = 8.5 Hz, 1 H, H-3), 7.60 (dd, *J* = 8.5, 2.4 Hz, 1 H, H-4), 8.11 (d, *J* = 2.4 Hz, 1 H, H-6).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 53.5, 72.7, 110.9, 115.5, 130.8, 137.3, 139.7, 145.1, 163.9.

GC-MS (EI, 70 eV): *m/z* (%) = 165 (63) [M^+], 164 (100), 148 (14), 138 (42), 136 (58), 122 (30), 110 (42), 95 (20), 78 (18), 67 (10), 55 (13), 42 (13).

HRMS (EI): *m/z* [M^+] calcd for $C_9H_{11}NO_2$: 165.0790; found: 165.0787.

2-(6-Methoxypyridin-3-yl)propan-2-ol (3l)
Prepared from **2a** (3 mL, 23.1 mmol). The crude product was purified by distillation to give a colorless oil; yield: 2.41 g (62%); bp 103–106 °C (9 mbar).

IR (film): 3384 (br), 2976, 1606, 1572, 1492, 1382, 1288, 1248, 1126, 1028, 834 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.57 (s, 6 H, $2CH_3$), 2.20 (s, 1 H, OH), 3.92 (s, 3 H, OCH_3), 6.71 (dd, *J* = 8.7, 0.8 Hz, 1 H, H-3), 7.72 (dd, *J* = 8.7, 2.6 Hz, 1 H, H-4), 8.24 (dd, *J* = 2.6, 0.8 Hz, 1 H, H-6).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 31.6, 53.4, 71.0, 110.2, 135.9, 137.1, 142.9, 163.1.

GC-MS (EI, 70 eV): *m/z* (%) = 167 (13) [M^+], 152 (100), 110 (28), 43 (15).

HRMS (EI): *m/z* [M^+] calcd for $C_9H_{13}NO_2$: 167.0946; found: 167.0945.

(6-Methoxypyridin-3-yl)(diphenyl)methanol (3m)
The crude product was purified by column chromatography [silica gel, hexane–EtOAc (7:3)] to give a colorless solid; yield: 2.15 g (95%); mp 135–136 °C (hexane–EtOAc).

IR (KBr): 3232 (br), 1604, 1566, 1494, 1458, 1380, 1294, 1016, 900, 840, 776, 764, 750, 708, 700 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.86 (s, 1 H, OH), 3.91 (s, 3 H, OCH_3), 6.70 (d, *J* = 8.7 Hz, 1 H, H-3), 7.24–7.35 (m, 10 H, $2C_6H_5$), 7.55 (dd, *J* = 8.7, 2.5 Hz, 1 H, H-4), 7.95 (d, *J* = 2.5 Hz, 1 H, H-6).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 53.5, 80.5, 110.2, 127.5, 127.7, 128.1, 135.3, 138.1, 138.7, 146.3, 163.2.

GC-MS (EI, 70 eV): *m/z* (%) = 291 (39) [M^+], 274 (9), 214 (100), 186 (16), 136 (46), 105 (28), 77 (22).

HRMS (EI): *m/z* [M^+] calcd for $C_{19}H_{17}NO_2$: 291.1259; found: 291.1257.

1-(6-Methoxypyridin-3-yl)cyclohexanol (3n)[32]
Prepared from **2a** (0.5 mL, 3.86 mmol). The crude product was purified by column chromatography [silica gel, hexane–EtOAc (7:3)] to give a colorless solid; yield: 0.494 g (62%); mp 72–74 °C (hexane) (Lit.[32] 74–75 °C).

IR (Nujol): 3372, 3202, 2920, 2856, 1604, 1572, 1494, 1462, 1372, 1288, 1040, 1026, 966, 924, 832 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.22–1.37 (m, 1 H, C*H*H), 1.58–1.85 (m, 10 H, $4CH_2$, CH*H*, OH), 3.93 (s, 3 H, OCH_3), 6.71 (d, *J* = 8.7 Hz, 1 H, H-3), 7.72 (dd, *J* = 8.7, 2.7 Hz, 1 H, H-4), 8.27 (d, *J* = 2.7 Hz, 1 H, H-6).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.1, 25.4, 38.7, 53.4, 71.8, 110.3, 136.1, 137.3, 143.3, 163.1.

MS (EI, 70 eV): *m/z* (%) = 207 (21) [M^+], 164 (100), 151 (29), 136 (29).

***N*-Ethyl-6-methoxypyridine-3-carbothioamide (3o)**
The crude product was purified by column chromatography [silica gel, hexane–EtOAc (8:2 then 7:3) to give a colorless solid; yield: 1.35 g (89%); mp 64–67 °C (hexane–EtOAc).

IR (KBr): 3240 (br), 2980, 2944, 1598, 1532, 1490, 1400, 1370, 1290, 1248, 1122, 1028, 968, 834, 758 cm^{-1}.

^{1}H NMR (400.1 MHz, $CDCl_3$) δ = 1.37 (t, *J* = 7.3 Hz, 3 H, CH_3), 3.84 (dq, *J* = 5.3, 7.3 Hz, 2 H, CH_2), 3.96 (s, 3 H, OCH_3), 6.71 (dd, *J* = 8.7, 0.4 Hz, 1 H, H-3), 7.58 (br s, 1 H, NH), 8.05 (dd, *J* = 8.7, 2.6 Hz, 1 H, H-4), 8.47 (d, *J* = 2.4 Hz, 1 H, H-6).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.4, 41.7, 54.2, 110.5, 131.2, 138.3, 144.2, 165.7, 195.7.

GC-MS (EI, 70 eV): *m/z* (%) = 196 (9) [M$^+$], 163 (100), 135 (75).

Anal. Calcd for $C_9H_{12}N_2OS$: C, 55.08; H, 6.16; N, 14.27; S, 16.34. Found: C, 55.11; H, 6.10; N, 14.35; S, 16.33.

5-Iodo-2-methoxypyridine (3p)[34]

The extracts were additionally washed with sat. aq $Na_2S_2O_5$ soln and the crude product was purified by distillation to give a colorless oil; yield: 1.65 g (91%); bp 73–74 °C (7 mbar) [Lit.[33]106–108 °C (40 mbar)].

IR (film): 2980, 2940, 1580, 1556, 1478, 1428, 1362, 1282, 1244, 1126, 1078, 1020, 996, 824, 638 cm^{-1}.

The ^{1}H and ^{13}C NMR spectral data for this product matched those reported previously.[34]

MS (EI, 70 eV): *m/z* (%) = 235 (100) [M$^+$], 234 (95), 206 (36), 205 (43), 165 (12), 127 (10), 93 (12), 78 (40), 64 (13), 51 (25), 38 (41).

5-(Diphenylphosphino)-2-methoxypyridine (3q)

The crude product was purified by column chromatography [silica gel, hexane–EtOAc (9:1)] to give a colorless oil; yield: 1.93 g (85%).

IR (film): 3052, 2956, 2932, 1584, 1480, 1286, 1202, 1126, 1026, 956, 742, 696 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.94 (s, 3 H, OCH_3), 6.73 (dd, *J* = 8.4, 0.7 Hz, 1 H, H-3), 7.26–7.37 (m, 10 H), 7.49 (ddd, *J* = 8.4, 6.0, 2.3 Hz, 1 H, H-4), 8.11 (ddd, *J* = 4.6, 2.3, 0.7 Hz, 1 H, H-6).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 53.5, 111.4 (d, *J* = 4.4 Hz), 124.3 (d, *J* = 11.7 Hz), 128.6, 128.7 (d, *J* = 16.1 Hz), 133.3 (d, *J* = 19.0 Hz), 136.7 (d, *J* = 10.2 Hz), 143.8 (d, *J* = 16.1 Hz), 152.6 (d, *J* = 27.8 Hz), 164.7.

GC-MS (EI, 70 eV): *m/z* (%) = 293 (100) [M$^+$], 216 (12), 183 (18), 171 (14), 107 (8).

HRMS (EI): *m/z* [M$^+$] calcd for $C_{18}H_{16}NOP$: 293.0970; found: 293.0969.

6-Methoxypyridine-2-carbaldehyde (4a)[35]

Prepared from **2b** (0.5 mL, 4.05 mmol). The crude product was purified by distillation to give a pale yellow oil; yield: 0.417 g (75%); bp 40–41 °C (5 mbar) [Lit.[36] 103–104 °C (27 mbar)].

The IR and ^{13}C NMR spectral data for this product matched those reported previously.[35]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.03 (s, 3 H, OCH_3), 6.98 (d, *J* = 8.3 Hz, 1 H, H-5), 7.56 (d, *J* = 7.3 Hz, 1 H, H-3), 7.73 (dd, *J* = 8.3, 7.3 Hz, 1 H, H-4), 9.96 (s, 1 H, CHO).

MS (EI, 70 eV): *m/z* (%) = 137 (10) [M$^+$], 136 (88), 108 (30), 107 (24), 93 (37), 79 (56), 66 (19), 52 (24), 39 (30).

2-Methoxy-6-(phenylsulfanyl)pyridine (4c)

Prepared from **2b** (1 mL, 8.1 mmol). The crude product was purified by distillation to give a pale yellow oil; yield: 1.41 g (80%); bp 110–116 °C (0.1 mbar).

IR (film): 3064, 2948, 2852, 1566, 1462, 1440, 1408, 1292, 1260, 1152, 1024, 880, 786, 748, 692 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.82 (s, 3 H, OCH_3), 6.43 (d, *J* = 8.2 Hz, 1 H, H-5), 6.47 (d, *J* = 7.6 Hz, 1 H, H-3), 7.34 (dd, *J* = 8.2, 7.6 Hz, 1 H, H-4), 7.38–7.43 (m, 3 H, C_6H_5), 7.59–7.63 (m, 2 H, C_6H_5).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 53.5, 106.7, 113.5, 128.9, 129.3, 131.1, 135.3, 139.0, 158.3, 162.5.

MS (EI, 70 eV): *m/z* = 217 (78) [M$^+$], 216 (10), 201 (31), 186 (11), 173 (11), 109 (10), 93 (13), 65 (11).

HRMS (EI): *m/z* [M$^+$] calcd for $C_{12}H_{11}NOS$: 217.0561; found: 217.0560.

(6-Methoxypyridin-2-yl)(phenyl)methanol (4d)[37]

Prepared from **2b** (1 mL, 8.1 mmol). The crude product was purified by distillation to give a pale yellow oil; yield: 1.44 g (82%); bp 103–106 °C (0.1 mbar) [Lit.[37] 160–162 °C (3 mbar)].

IR (film): 3426 (br), 2952, 1598, 1578, 1468, 1436, 1416, 1316, 1274, 1028, 800, 740, 700 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.01 (s, 3 H, OCH_3), 5.71 (s, 1 H, CH), 6.64 (d, *J* = 8.1 Hz, 1 H, H-5), 6.69 (d, *J* = 7.3 Hz, 1 H, H-3), 7.23–7.42 (m, 5 H, C_6H_5), 7.52 (dd, *J* = 8.1, 7.3 Hz, 1 H, H-4).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 53.7, 74.6, 109.3, 113.8, 127.0, 127.8, 128.5, 143.0, 139.8, 158.8, 163.6.

MS (EI, 70 eV): *m/z* (%) = 215 (100) [M$^+$], 138 (55), 110 (34), 109 (55), 79 (21), 77 (31).

2-Methoxy-6-(trimethylsilyl)pyridine (4e)[22]

Prepared from **2b** (1 mL, 8.1 mmol). The crude product was purified by distillation to give a colorless oil; yield: 0.577 g (39%); bp 42–44 °C (5 mbar) [Lit.[22] 95–100 °C (20 mbar)].

IR (film): 3060, 2956, 2898, 1568, 1458, 1328, 1248, 1140, 1028, 892, 832, 800, 754 cm^{-1}.

The ^{1}H and ^{13}C NMR spectral data for this product were almost identical with those reported previously.[22]

MS (EI, 70 eV): *m/z* (%) = 181 (15) [M$^+$], 166 (100), 150 (9), 89 (14), 73 (13), 59 (15), 43 (13).

2-Allyl-6-methoxypyridine (4f)

Prepared from **2b** (0.5 mL, 4.05 mmol). The crude product was purified by column chromatography to give a colorless oil [silica gel, hexane–EtOAc (50:1)]; yield: 0.333 g (55%).

IR (film): 3080, 2948, 1600, 1580, 1468, 1440, 1414, 1280 (br), 1148, 1036, 988, 918, 798, 760 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.51 (br d, *J* = 6.8 Hz, 2 H, CH_2), 3.93 (s, 3 H, OCH_3), 5.11 (dq, *J* = 10.2, ca. 1.5 Hz, 1 H, =C*H*H), 5.15 (dq, *J* = 17.1, 1.6 Hz, 1 H, =CH*H*), 6.08 (dddd, *J* = 17.1, 10.2, 6.9, 6.8 Hz, 1 H, =CH), 6.57 (d, *J* = 8.2 Hz, 1 H, H-5), 6.74 (d, *J* = 7.2 Hz, 1 H, H-3), 7.51 (dd, *J* = 8.2, 7.2 Hz, 1 H, H-4).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 42.2, 53.5, 107.6, 115.1, 116.6, 135.8, 139.2, 157.9, 163.6.

MS (EI, 70 eV): *m/z* (%) = 149 (53) [M$^+$], 148 (100), 133 (30), 123 (19), 118 (13), 104 (12), 91 (14), 79 (14), 65 (12), 39 (21).

HRMS (EI): *m/z* [M$^+$] calcd for $C_9H_{11}NO$: 149.0841; found: 149.0841.

***N*-Ethyl-6-methoxypyridine-2-carbothioamide (4g)**

Prepared from **2b** (1 mL, 8.1 mmol). The crude product was purified by column chromatography [silica gel, hexane–EtOAc (8:2)] to give a colorless solid; yield: 0.932 g (58%); mp 65–67 °C (hexane).

IR (Nujol): 3284, 3012, 1596, 1574, 1528, 1470, 1426, 1334, 1278, 1214, 1164, 1068, 1048, 1010, 988, 830, 818, 740, 712, 660 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.41 (t, *J* = 7.2 Hz, 3 H, CH_3), 3.86–3.95 (m, 2 H, NCH_2), 3.98 (s, 3 H, OCH_3), 6.92 (d, *J* = 8.0 Hz, 1 H, H-5), 7.71 (dd, *J* = 7.3, 8.0 Hz, 1 H, H-4), 8.30 (d, *J* = 7.3 Hz, 1 H, H-3), 9.84 (s, 1 H, NH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.3, 40.6, 53.5, 114.0, 118.3, 139.8, 148.8, 162.0, 190.4.

MS (EI, 70 eV): *m/z* (%) = 196 (67) [M$^+$], 153 (100), 138 (24), 135 (23), 123 (18), 108 (18), 93 (14).

Anal. Calcd for $C_9H_{12}N_2OS$: C, 55.08; H, 6.16; N, 14.27; S, 16.34. Found: C,55.01; H, 6.09; N, 14.30; S, 16.35.

2-Iodo-6-methoxypyridine (4h)[14]

Prepared from **2b** (1 mL, 8.1 mmol). The crude product was purified by distillation to give a colorless oil that solidified on standing at r.t.; yield: 1.76 g (92%); bp 63–67 °C (5 mbar); mp 42–45 °C (Lit.[14] 43–45 °C).

IR (Nujol): 1734, 1588, 1578, 1552, 1408, 1312, 1292, 1152, 1116, 1072, 1020, 980, 840, 784, 720 cm^{-1}.

The ^1H and ^{13}C NMR spectral data for this product matched those reported previously.[14]

MS (EI, 70 eV): *m/z* (%) = 235 (100) [M^+], 206 (8), 127 (14), 108 (78), 93 (86), 77 (10), 65 (30), 53 (17), 50 (18), 39 (51).

2-(Diphenylphosphino)-6-methoxypyridine (4i)[24]

Prepared from **2b** (1 mL, 8.1 mmol). The crude product was purified by column chromatography [silica gel, hexane–EtOAc (50:1)] to give a colorless solid; yield: 2.00 g (84%); mp 62–63 °C (hexane–EtOAc) (Lit.[24] 59 °C).

IR (Nujol): 1576, 1564, 1432, 1412, 1376, 1294, 1256, 1022, 796, 748, 696 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 3.73 (s, 3 H, OCH_3), 6.73 (dd, *J* = 7.2, 2.1 Hz, 1 H, H-3), 6.77 (d, *J* = 8.4 Hz, 1 H, H-5), 7.34–747 (m, 10 H, $2C_6H_5$), 7.65 (ddd, *J* = 8.4, 7.2, 2.3 Hz, 1 H, H-4).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 53.3, 110.2, 121.9 (d, *J* = 22.0 Hz), 128.9 (d, *J* = 7.3 Hz), 129.4, 134.0 (d, *J* = 19.0 Hz), 136.2 (d, *J* = 11.7 Hz), 139.2 (d, *J* = 4.4 Hz), 159.7, 163.4 (d, *J* = 10.2 Hz).

MS (EI, 70 eV): *m/z* (%) = 293 (100) [M^+], 292 (93), 277 (12), 216 (18), 200 (19), 183 (46), 172 (14), 107 (15).

2-Methoxypyridine-3-carbaldehyde (5a; 2-Methoxynicotinaldehyde)[38]

Prepared from **2c** (0.5 mL, 3.9 mmol). The crude product was purified by distillation to give a colorless oil; yield: 0.481 g (90%); bp 47 °C (5 mbar) [Lit.[38] 95 °C (21 mbar)].

IR (film): 2956, 2868, 1690, 1590, 1470, 1416, 1386, 1300, 1258, 1184, 1096, 1014, 858, 798, 768 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.08 (s, 3 H, OCH_3), 7.02 (dd, *J* = 7.3, 4.9 Hz, 1 H, H-5), 8.11 (dd, *J* = 7.3, 2.0, Hz, 1 H, H-4), 8.39 (dd, *J* = 4.9, 2.0 Hz, 1 H, H-6), 10.38 (s, 1 H, CHO).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 53.9, 117.3, 118.8, 137.7, 152.9, 164.5, 189.3.

MS (EI, 70 eV): *m/z* (%) = 137 (61) [M^+], 108 (100), 79 (73), 52 (30), 39 (17).

2-Methoxy-3-(phenylsulfanyl)pyridine (5b)

Prepared from **2c** (0.5 mL, 3.9 mmol). The crude product was purified by distillation to give a pale yellow oil; yield: 0.744 g (88%); bp 105–110 °C (0.1 mbar).

IR (film): 3076, 2960, 2932, 2872, 1584, 1480, 1464, 1440, 1092, 1024, 738, 690 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.01 (s, 3 H, OCH_3), 6.76 (dd, *J* = 7.3, 4.9 Hz, 1 H, H-5), 7.16 (dd, *J* = 7.3, 2.0 Hz, 1 H, H-4), 7.33–7.46 (m, 5 H, C_6H_5), 7.99 (dd, *J* = 4.9, 2.0 Hz, 1 H, H-6).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 53.9, 117.3, 121.1, 128.3, 129.5, 132.0, 133.2, 137.4, 144.1, 160.3.

MS (EI, 70 eV): *m/z* (%) = 217 (100) [M^+], 198 (16), 186 (23), 140 (30), 115 (10), 91 (25), 77 (12), 51 (20).

HRMS (EI): *m/z* [M^+] calcd for $C_{12}H_{11}NOS$: 217.0561; found: 217.0560.

2-Methoxy-3-(trimethylsilyl)pyridine (5c)[39]

Prepared from **2c** (0.5 mL, 3.9 mmol). The crude product was purified by distillation to give a colorless oil; yield: 0.637 g (90%); bp 55 °C (4 mbar) [Lit.[39] 55 °C (4 mbar)].

IR (film): 3044, 2952, 2904, 1570, 1445, 1386, 1296, 1248, 1084, 1022, 842, 784, 752 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$): δ = 0.26 (s, 9 H, $SiMe_3$), 3.95 (s, 3 H, OCH_3), 6.85 (dd, *J* = 6.8, 4.9 Hz, 1 H, H-5), 7.65 (dd, *J* = 6.8, 2.0 Hz, 1 H, H-4), 8.16 (dd, *J* = 4.9, 2.0 Hz, 1 H, H-6).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –1.6, 53.3, 116.7, 121.8, 144.6, 147.4, 167.4.

MS (EI, 70 eV): *m/z* (%) = 181 (14) [M^+], 166 (46), 136 (100), 59 (12).

3-Allyl-2-methoxypyridine (5d)

Prepared from **2c** (0.5 mL, 3.9 mmol). The crude product was purified by distillation to give a colorless oil; yield: 0.451 g (78%); bp 93–95 °C (27 mbar).

IR (film): 1592, 1464, 1410, 1312, 1256, 1022, 782 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.33 (br d, *J* = 6.7 Hz, 2 H, CH_2), 3.96 (s, 3 H, OCH_3), 5.06 (dq, *J* = 7.9, 1.6 Hz, 1 H, =CHH), 5.10 (t, *J* = 1.5 Hz, 1 H, =CHH), 5.91–6.02 (m, 1 H, =CH), 6.82 (dd, *J* = 7.2, 5.1 Hz, 1 H, H-5), 7.39 (ddt, *J* = 7.2, 1.9, 1.0 Hz, 1 H, H-4), 8.03 (dd, *J* = 5.1, 1.9 Hz, 1 H, H-6).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 33.8, 53.4, 116.3, 116.7, 122.9, 135.6, 137.7, 144.4, 161.9.

MS (EI, 70 eV): *m/z* (%) = 149 (81) [M^+], 134 (83), 120 (57), 119 (45), 118 (52), 117 (36), 116 (51), 108 (100), 106 (29), 93 (29), 92 (36), 91 (31), 90 (34), 89 (29), 79 (50), 78 (28), 77 (39), 65 (26), 52 (28), 51 (31), 39 (35).

HRMS (EI): *m/z* [M^+] calcd for $C_9H_{11}NO$: 149.0841; found: 149.0840.

2,6-Dimethoxypyridine-3-carbaldehyde (6a; 2,6-Dimethoxynicotinaldehyde)[40]

Prepared from **2d** (1.6 g, 7.3 mmol). The crude product was purified by column chromatography [silica gel, hexane–EtOAc (8:2)] to give a colorless solid; yield: 0.862 g (70%); mp 65–67 °C (hexane) (Lit.[41] 64–65 °C).

IR (KBr): 2952, 1670, 1598, 1488, 1462, 1382, 1334, 1280, 1240, 1220, 1090, 1010, 820 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.00 and 4.05 (two s, 6 H, $2OCH_3$), 6.38 (d, *J* = 8.3, 0.7 Hz, 1 H, H-5), 8.04 (d, *J* = 8.3 Hz, 1 H, H-4), 10.20 (d, *J* = 0.7 Hz, 1 H, CHO).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 53.8, 54.1, 103.4, 112.1, 140.2, 165.1, 167.1, 187.7.

MS (EI, 70 eV): *m/z* (%) = 167 (100) [M^+], 150 (42), 138 (33), 136 (25), 120 (18), 109 (14), 107 (13), 93 (14), 80 (12), 64 (12), 53 (9), 39 (8).

2,6-Dimethoxy-3-(phenylsulfanyl)pyridine (6b)

Prepared from **2d** (1.6 g, 7.3 mmol). The crude product was purified by distillation to give a pale yellow oil; yield: 1.00 g (55%); bp 115–118 °C (0.1 mbar).

IR (Nujol): 3060, 1584, 1468, 1412, 1320, 1264, 1244, 1236, 1072, 1024, 954, 808, 736, 690 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.95 and 3.96 (two s, 6 H, $2OCH_3$), 6.33 (d, *J* = 8.2, Hz, 1 H, H-5), 7.10–7.20 (m, 3 H, C_6H_5), 7.20–7.25 (m, 2 H, C_6H_5), 7.59 (d, *J* = 8.2 Hz, 1 H, H-4).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 53.8, 54.1, 102.2, 105.0, 125.3, 127.9, 128.9, 137.0, 147.2, 162.3, 163.6.

MS (EI, 70 eV): *m/z* (%) = 247 (100) [M$^+$], 204 (10), 147 (12), 77 (8).

HRMS (EI): *m/z* [M$^+$] calcd for $C_{13}H_{13}NO_2S$: 247.0667; found: 247.0669

2,6-Dimethoxy(3–^{2}H)pyridine (6c)
Prepared from **2d** (1.6 g, 7.3 mmol). The crude product was purified by distillation to give a colorless oil; yield: 0.683 g (66%); bp 30–32 °C (5 mbar).

IR (film): 2976, 2952, 1600, 1578, 1478, 1408, 1386, 1314, 1238, 1110, 1088, 1046, 1022, 948, 816, 772 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.91 (s, 6 H, $2OCH_3$), 6.30 (d, *J* = 7.8 Hz, 1 H, H-5), 7.48 (d, *J* = 7.8 Hz, 1 H, H-4).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 53.4 (2 × OMe), 100.6 (t, *J* = 24.8 Hz), 100.9, 140.8, 163.1, 163.2.

MS (EI, 70 eV): *m/z* (%) = 140 (75) [M$^+$], 139 (100), 111 (35), 110 (51), 95 (38), 81 (27), 67 (33), 54 (16), 40 (58), 29 (13).

HRMS (EI): *m/z* [M$^+$] calcd for $C_7H_8DNO_2$: 140.0695; found: 140.0693.

2,6-Dimethoxy-3-(trimethylsilyl)pyridine (6d)
Prepared from **2d** (1.6 g, 7.3 mmol). The crude product was purified by distillation to give a colorless oil; yield: 1.07 g (69%); bp 100–102 °C (12 mbar).

IR (film): 2952, 1582, 1476, 1452, 1416, 1360, 1312, 1260, 1196, 1128, 1080, 1022, 956, 840, 810, 780, 752, 688 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.22 (s, 9 H, $SiMe_3$), 3.91 and 3.92 (two s, 6 H, $2OCH_3$), 6.28 (d, *J* = 7.8 Hz, 1 H, H-5), 7.53 (d, *J* = 7.8 Hz, 1 H, H-4).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –1.1, 53.0, 53.3, 100.4, 110.2, 146.7, 164.5, 167.0.

MS (EI, 70 eV): *m/z* (%) = 211 (21) [M$^+$], 196 (26), 166 (100), 122 (14), 59 (7).

HRMS (EI): *m/z* [M$^+$] calcd for $C_{10}H_{17}NO_2Si$: 211.1029; found: 211.1028.

3-Chloro-2,6-dimethoxypyridine (6e)
Prepared from **2d** (1.6 g, 7.3 mmol). The crude product was purified by distillation to give a colorless oil; yield: 0.935 g (73%); bp 62–63 °C (5 mbar).

IR (film): 2984, 2956, 1590, 1472, 1414, 1384, 1322, 1270, 1236, 1124, 1068, 1034, 1014, 954, 808, 748, 728, 696 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.91 and 4.01 (two s, 6 H, $2OCH_3$), 6.28 (d, *J* = 8.3 Hz, 1 H, H-5), 7.50 (d, *J* = 8.3 Hz, 1 H, H-4).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 53.8, 54.1, 101.9, 107.8, 140.6, 157.6, 161.2.

MS (EI, 70 eV): *m/z* (%) = 173 (100) [M$^+$], 158 (18), 144 (64), 130 (26), 114 (13), 108 (14), 102 (14), 89 (27), 80 (35), 73 (46), 64 (56), 52 (21), 37 (20), 29 (15).

HRMS (EI): *m/z* [M$^+$] calcd for $C_7H_8ClNO_2$: 173.0244; found: 173.0244.

3-Allyl-2,6-dimethoxypyridine (6f)
Prepared from **2d** (1.6 g, 7.3 mmol). The crude product was purified by distillation to give a pale yellow oil; yield: 0.922 g (70%); bp 64–66 °C (5 mbar).

IR (film): 3080, 3008, 2980, 2948, 1640, 1604, 1588, 1480, 1420, 1388, 1322, 1248, 1206, 1112, 1024, 956, 916, 804 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.25 (d, *J* = 6.5 Hz, 2 H, CH_2), 3.89 and 3.94 (two s, 6 H, $2OCH_3$), 4.99–5.06 (m, 2 H, $=CH_2$), 5.87–5.99 (m, 1 H, =CH), 6.24 (d, *J* = 7.8 Hz, 1 H, H-5), 7.31 (dd, *J* = 7.8, 0.4 Hz, 1 H, H-4).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 32.9, 53.3, 53.5, 100.0, 113.2, 115.5, 136.6, 140.7, 160.2, 161.6.

MS (EI, 70 eV): *m/z* (%) = 179 (100) [M$^+$], 164 (31), 152 (26), 132 (12), 122 (13), 104 (14), 77 (29), 51 (23), 39 (18).

HRMS (EI): *m/z* [M$^+$] calcd for $C_{10}H_{13}NO_2$: 179.0946; found: 179.0948.

3-Iodo-2,6-dimethoxypyridine (6g)[42]
Prepared from **2d** (1.6 g, 7.3 mmol). The crude product was purified by distillation to give a pale yellow oil; yield: 1.73 g (89%); bp 95 °C (7 mbar).

IR (film): 2980, 2948, 1570, 1466, 1412, 1374, 1316, 1236, 1112, 1052, 1026, 1004, 952, 808, 746, 672 cm^{-1}.

The ^{1}H and ^{13}C NMR spectral data for this product matched those reported previously.[42]

MS (EI, 70 eV): *m/z* (%) = 265 (100) [M$^+$], 236 (22), 108 (25), 93 (21), 80 (20), 64 (23), 52 (16), 38 (14).

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis. Included are protocols for the synthesis of **2a** and **2d**.

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