Hiyama Cross-Coupling of Chloro-, Fluoro- and Methoxy- pyridyl trimethylsilanes : Room-temperature Novel Access to Functional Bi(het)aryl

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SUPPORTING INFORMATION

General Methods. All solvents were distilled before use. All pyridylsilanes were prepared according to literature procedures,¹ CuI was dried overnight under vacuum before use. All other reagents were commercially available and used as such. ¹H and ¹³C were obtained in CDCl₃ on a Bruker DRX400 instrument at 400 and 100 MHz respectively. GC experiments were performed on a Shimadzu chromatograph fitted with a 15m capillary column. GC/MS (EI) were obtained on a HP5971 spectrometer.

General procedure for cross-coupling of silanes 1,2,7-9.

To a stirred mixture of PdCl₂(PPh₃)₂ (35mg, 0.05mmol), PPh₃ (26mg, 0.1mmol) and CuI (188 mg, 1mmol) in degassed DMF (5mL) at room temperature were added successively (Het)ArX (0.5mmol), the appropriate silane (185 mg, 1 mmol) and TBAF (2mL of a 1M solution in THF, 2 mmol). The reaction medium became instantly dark. After 12h of stirring at room temperature, the mixture was filtered through a Celite pad. After successive washings with NH₄OH, H₂O, THF and Et₂O, the filtrate was extracted twice with diethylether. After drying (MgSO₄) of the organic layer, the solvents were evaporated under reduced pressure and the crude product purified by column chromatography on silica gel.

3-Chloro-2-(para-anisyl)-pyridine (1a)²: 70mg (80%), white solid, eluent hexane/AcOEt (90 :10). - ¹H NMR (400MHz, CDCl₃) : δ = 3.86 (s, 1H), 7.0 (d, J = 7 Hz, 2H), 7.18 (dd, J = 8 and 5 Hz, 1H), 7.72 (d, J = 7 Hz, 2H), 7.77 (d, J = 8 Hz, 1H), 8.57 (d, J = 5 Hz, 1H). - ¹³C NMR (100 MHz, CDCl₃): δ = 55.7, 113.8, 122.9, 130.3, 131.1, 138.5, 147.9, 156.1, 156.5, 161.8. -MS (EI) ; m/z (%): 221 (34), 219 [M⁺] (100), 184 (35), 141 (39), 114 (7.7), 76 (2.8), 51 (3).

¹ For preparation of **1-3** with BuLi-LiDMAE see Choppin, S. Gros, Ph. Fort, Y. *Org. Lett.*, **2000**, 2, 803-805. Choppin, S. Gros, Ph. Fort, *Eur. J. Org. Chem.*, **2001**, 3, 603-606. For preparation of **5-6** with LDA or LTMP see Gribble, G.W. Saulnier, M.G. *Tetrahedron Lett.* **1980**, 21, 4137-4140. Comins, D.L.; Myoung, Y. *J. Org. Chem.* **1990**, 55, 292-298. **4** was prepared by reaction of BuLi with 2-chloro-5-bromopyridine in THF at -78°C and quenching with TMSCl.

² Simkovsky, N. M.; Ermann, M.; Roberts S.M.; Parry D.M.; Baxter, A. *J. Chem. Soc. Perkin Trans. 1*, **2002**, (16), 1847-1849.

3-Chloro-2-(phenyl)-pyridine (1b)³ : 53mg (71%), colorless oil, eluent hexane/AcOEt (90 :10). – ¹H NMR (400MHz, CDCl₃) : δ = 7.22 (dd, J = 8 and 3 Hz, 1H), 7.47 (m, 3H), 7.72 (d, J = 7 Hz, 2H), 7.80 (d, J = 8 Hz, 1H), 8.6 (d, J = 3 Hz, 1H). – ¹³C NMR (100 MHz, CDCl₃): δ = 123.4, 128.4, 129.2, 129.7, 130.6, 138.5, 138.6, 148.0, 157.0. –MS (EI) ; *m/z* (%): 191 (13), 189 [M⁺] (48), 154 (100), 144 (16), 127 (19), 77 (9.5), 51 (5).

3-Chloro-2-(ortho-anisyl)-pyridine (1c) : 36mg (38%), white solid, eluent hexane/AcOEt (70 :30). – ¹H NMR (200MHz, CDCl₃) : δ = 3.79 (s, 3H), 6.90 (d, J = 8 Hz, 1H), 7.08 (t, J = 7.4 Hz, 1H), 7.2 (m, 1H), 7.3 (d, J = 8 Hz, 1H), 7.4 (t, J = 9 Hz, 1H), 7.77 (d, J = 8 Hz, 1H), 8.58 (d, J = 4.5 Hz, 1H). – ¹³C NMR (50 MHz, CDCl₃): δ = 47, 115.3, 115.6, 123.6, 130.5, 131.7, 131.8, 134.62, 134.68, 138.6, 148.04, 155.9, 162.2, 164.7. –MS (EI) ; *m/z* (%): 219 [M⁺] (16), 218 [M⁺-1] (15), 184 (100), 169 (5.6), 154 (44), 140 (10), 144 (10), 77 (7.3), 51 (4.7).

3-Chloro-2-(meta-anisyl)-pyridine (1d) : 60mg (55%), white solid, eluent hexane/AcOEt (70 :30). – ¹H NMR (400MHz, CDCl₃) : δ = 3.86 (s, 3H), 6.98 (d, J = 7 Hz, 1H), 7.26 (m, 2H), 7.30 (d, J = 8 Hz, 1H), 7.80 (d, J = 7 Hz, 1H), 8.58 (d, J = 3.5 Hz, 1H). – ¹³C NMR (100 MHz, CDCl₃): δ = 55.7, 115.0, 115.28, 122.2, 123.5, 129.5, 138.5, 139.9, 146.3, 147.9, 159.7. MS (EI) ; *m/z* (%): 220 [M⁺+1] (40), 219 [M⁺] (75), 218 [M⁺-1] (100), 189 (34), 154 (35), 127 (8.6), 88 (3.4), 74 (3.6), 51 (5.7).

3-Chloro-2-(para-fluoro)-pyridine (1e) : 91mg (88%), white solid, eluent hexane/AcOEt (90 :10). – ¹H NMR (400MHz, CDCl₃) : δ = 7.15 (t, J = 9 Hz, 2H), 7.22 (dd, J = 8 and 4 Hz, 1H), 7.73 (t, J = 9 Hz, 2H), 7.79 (d, J = 8 Hz, 1H), 8.58 (d, J = 4 Hz, 1H). – ¹³C NMR (100 MHz, CDCl₃): δ = 115.4, 123.5, 130.5, 131.7, 134.62, 138.6, 148.0, 155.9, 162.2, 164.7. –MS (EI) ; *m/z* (%): 209 (34), 207 [M⁺] (62), 172 (100), 152 (5.6), 145 (19), 125 (6.8), 103 (2), 86 (9), 51 (6.9).

³ Maerten, E.; Hassouna, F.; Couve-Bonnaire, S.; Mortreux, A.; Carpentier, J.-F.; Castanet, Y., *Synlett*, **2003**, (12), 1874-1876.

3-Chloro-2-(para-acetophenone)-pyridine (1f) : 93mg (80%), white solid, eluent hexane/AcOEt (70 :30). - ^1H NMR (400MHz, CDCl_3) : δ = 2.58 (s, 3H), 7.20 (dd, J = 4.7 and 8 Hz, 1H), 7.76 (d, J = 8.5 Hz, 3H), 7.90 (d, J = 8.5 Hz, 1H), 8.54 (d, J = 6 Hz, 1H). - ^{13}C NMR (100 MHz, CDCl_3): δ =27.83, 124.75, 129.10, 130.74, 131.35, 138.0, 139.32, 143.64, 148.81, 156.42, 198.86. -MS (EI) ; m/z (%): 231 [M^+] (-35), 218 (32), 217 (13), 216 (100), 188 (46), 153 (33), 126 (22), 125 (13), 76 (19), 51 (19).

3-Chloro-2-(pyridyl)-pyridine (1g) : 62mg (65%), gummy white solid , eluent hexane/AcOEt (0 :100). - ^1H NMR (200MHz, CDCl_3) : δ = 7.18 - 7.30 (m, 2H), 7.70 - 7.77 (m, 3H), 8.54 (d, J = 4.3 Hz, 1H), 8.66 (d, J = 3.5 Hz, 1H). - ^{13}C NMR (50 MHz, CDCl_3) : δ = 124.48, 125.18, 125.53, 133.02, 137.88, 139.46, 148.62, 150.34, 156.04, 157.08. -MS (EI) ; m/z (%) : 193 (2.3), 192 [$\text{M}^+ + 2$] (19), 190 [M^+] (60), 162 (10), 155 (100), 128 (19), 112 (4.5), 78 (24), 51 (37).

3-Chloro-2-(thienyl)-pyridine (1h) : 76mg (78%), yellow oil, eluent hexane/AcOEt (90 :10). - ^1H NMR (400MHz, CDCl_3) : δ = 7.09 (dd, J = 4.5 and 8 Hz, 1H), 7.14 (dd, J = 4 and 6 Hz, 1H), 7.46 (d, J = 5.2 Hz, 1H), 7.73 (dd, J = 1.4 and 8 Hz, 1H), 8.09 (d, J = 3.8 Hz, 1H), 8.49 (dd, J = 3.8 and 1.4 Hz, 1H). - ^{13}C NMR (100 MHz, CDCl_3): δ =122.61, 128.29, 128.33, 129.18, 129.45, 139.21, 142.74, 147.66, 149.78. -MS (EI) ; m/z (%): 196 [$\text{M}^+ + 1$] (14), 195 [M^+] (100), 194 [$\text{M}^+ - 1$] (9.3), 162 (8.5), 151 (12), 116 (14), 89 (14), 76 (9.2), 51 (16).

4-Chloro-2-(para-anisyl)-pyridine (2a) : 96mg (87%), white solid, eluent hexane/AcOEt (90 :10). - ^1H NMR (400MHz, CDCl_3) : δ = 3.86 (s, 3H), 6.98 (d, J = 8.8 Hz, 2H), 7.16 (dd, J = 5.3 and 1.8 Hz, 1H), 7.66 (d, J = 1.8 Hz, 1H), 7.92 (d, J = 8.8 Hz, 2H), 8.52 (d, J = 5.3 Hz, 1H). - ^{13}C NMR (100 MHz, CDCl_3): δ = 55.80, 114.64, 120.43, 121.98, 128.73, 131.12, 145.02, 150.78, 159.06, 161.35. -MS (EI) ; m/z (%): 221 (33), 220 [$\text{M}^+ + 1$] (33), 219 [M^+] (100), 204 (26), 141 (42), 113 (9.2), 87 (4.3), 63 (6.7), 51 (4.4).

4-Chloro-2-(ortho-anisyl)-pyridine (2b) : 63mg (57%), white solid, eluent hexane/AcOEt (90 :10). - ^1H NMR (400MHz, CDCl_3) : δ = 3.81 (s, 3H), 6.92 (d, J = 8 Hz, 1H), 7.01 (d, J = 7.5 Hz, 1H), 7.13 (dd, J = 5 and 2 Hz, 1H), 7.29 (dt, J = 7.5 and 1.8 Hz, 1H), 7.71 (dd, J = 7.5 and 1.8 Hz, 1H), 7.82 (d, J = 1.5 Hz, 1H), 8.50 (d, J = 5 Hz, 1H). - ^{13}C NMR (100 MHz, CDCl_3): δ = 56.65, 112.39, 122.12, 122.98, 126.37, 128.76, 131.61, 132.18, 151.12, 157.97, 158.47. -MS (EI) ; m/z (%): 220 [$\text{M}^+ + 2$] (38), 219 [$\text{M}^+ + 1$] (73), 218 [M^+] (92), 154 (100), 141 (21), 114 (97), 77 (36), 51 (32).

4-Chloro-2-(meta-anisyl)-pyridine (2c) : 83mg (77%), white solid, eluent hexane/AcOEt (90 :10). - ^1H NMR (200MHz, CDCl_3) : δ = 3.82 (s, 3H), 6.90 (dd, J = 8.1 and 2.2 Hz, 1H), 7.16 (dd, J = 5.3 and 1.8 Hz, 1H), 7.28 (t, J = 8.1 Hz, 1H), 7.43 (s, 1H), 7.49 (d, J = 1.8 Hz, 1H), 8.50 (d, J = 5.3 Hz, 1H). - ^{13}C NMR (50 MHz, CDCl_3): δ = 56.44, 113.09, 116.79, 120.36, 122.05, 123.48, 130.91, 140.62, 145.77, 151.47, 159.82, 161.17. -MS (EI) ; m/z (%): 221 [$\text{M}^+ + 2$] (41), 220 [$\text{M}^+ + 1$] (72), 219 [M^+] (100), 190 (47), 189 (51), 188 (38), 154 (34), 141 (34), 114 (17), 113 (13), 78 (3.7), 63 (21), 51 (19).

4-Chloro-2-(para-fluorobenzyl)-pyridine (2d) : 96mg (95%), white solid, eluent hexane/AcOEt (90 :10). - ^1H NMR (400MHz, CDCl_3) : δ = 7.13 (t, J = 8.7 Hz, 2H), 7.22 (dd, J = 5.3 and 1.8 Hz, 1H), 7.67 (d, J = 1.8 Hz, 1H), 7.94 (dd, J = 9.9 and 5.3 Hz, 2H), 8.55 (d, J = 5.3 Hz, 1H). - ^{13}C NMR (100 MHz, CDCl_3): δ = 116.36, 120.94, 122.65, 129.24, 134.69, 145.24, 150.91, 158.34, 163.02, 165.50. -MS (EI) ; m/z (%): 208 [$\text{M}^+ + 1$] (17), 207 [M^+] (100), 206 [$\text{M}^+ - 1$] (14), 173 (11), 172 (90), 145 (42), 125 (18), 86 (19), 75 (18), 51 (21).

4-Chloro-2-(para-acetophenone)-pyridine (2e) : 50mg (42%), yellow solid, eluent hexane/AcOEt (80 :20). - ^1H NMR (400MHz, CDCl_3) : δ = 2.58 (s, 3H), 7.21 (dd, J = 5.2 and 1.8 Hz, 1H), 7.70 (d, J = 1.8 Hz, 1H), 7.99 (s, 4H), 8.53 (d, J = 5.2 Hz, 1H). - ^{13}C NMR (100 MHz, CDCl_3): δ = 27.84, 122.42, 124.14, 128.19, 129.92, 138.65, 143.27, 146.03, 151.77, 158.62, 198.75. -MS (EI) ; m/z (%): 232 [$\text{M}^+ + 1$] (4.1), 231 [M^+] (29), 216 (100), 188 (40), 153 (29), 126 (20), 76 (12), 51 (10).

4-Chloro-2-(pyridyl)-pyridine (2f) : 82mg (85%), white solid, eluent hexane/AcOEt (90 :10). - ^1H NMR (400MHz, CDCl_3) : δ = 7.20 – 7.28 (m, 2H), 7.69 (dt, J = 8 and 1.8 Hz, 1H), 8.29 (d, J = 8 Hz, 1H), 8.37 (d, J = 2 Hz, 1H), 8.46 (d, J = 5 Hz), 8.58 (d, J = 5 Hz, 1H). - ^{13}C NMR (100 MHz, CDCl_3): δ = 122.36, 122.51, 124.91, 125.32, 138.07, 146.25, 150.28, 151.01, 155.86, 158.67. MS (EI) ; m/z (%): 192 [$\text{M}^+ + 2$] (32), 191 [$\text{M}^+ + 1$] (17), 190 [M^+] (100), 155 (80), 128 (39), 112 (8.8), 78 (40), 51 (45).

3-Methoxy-2-(para-anisyl)-pyridine (7a): 91 mg (85%), yellow oil, eluent hexane/AcOEt (80:20). – ^1H NMR (400MHz, CDCl_3): δ = 3.85 (s, 6H), 6.97 (d, J = 8 Hz, 2H), 7.17 (dd, J = 8 and 4.5 Hz, 1H), 7.25 (d, J = 4.5 Hz, 1H), 7.90 (d, J = 8 Hz, 2H), 8.28 (d, J = 4.5 Hz, 1H). – ^{13}C NMR (100 MHz, CDCl_3): δ = 55.7, 55.8, 113.8, 118.7, 122.7, 131.1, 141.6, 148.2, 153.7, 160.1. –MS (EI); m/z (%): 215 [M^+] (91), 214 [$\text{M}^+ - 1$] (100), 200 (14), 172 (26), 142 (21), 129 (16), 102 (16), 63 (19), 51 (13).

2-Fluoro-2-(para-anisyl)-pyridine (8a). 63 mg (64%), yellow solid, eluent hexane/AcOEt (90:10). – ^1H NMR (200MHz, CDCl_3): δ = 3.86 (s, 3H), 6.80 (dd, J = 9 and 2.5 Hz, 1H), 7.00 (d, J = 9 Hz, 2H), 7.55 (dd, J = 8 and 2.5 Hz, 1H), 7.80 (dd, J = 8 and 9 Hz, 1H), 7.99 (d, J = 9 Hz, 2H). – ^{13}C NMR (50 MHz, CDCl_3): δ = 56.42, 107.38, 108.12, 115.19, 117.43, 117.51, 129.33, 131.18, 142.65, 162.06, 166.78, 170.78. –MS (EI); m/z (%): 204 [$\text{M}^+ + 1$] (13), 203 [M^+] (100), 188 (27), 160 (70), 134 (17), 107 (9.4), 76 (7.1), 51 (5.7).

3-Fluoro-2-(para-anisyl)-pyridine (9a). 73 mg (75%), white solid, eluent hexane/AcOEt (90:10). – ^1H NMR (200MHz, CDCl_3): 3.81 (s, 3H), 6.95 (d, J = 9 Hz, 2H), 7.18–7.26 (m, 1H), 7.46 (dd, J = 7 and 5 Hz, 1H), 7.96 (d, J = 9 Hz, 2H), 8.49 (d, J = 5 Hz, 1H). – ^{13}C NMR (50 MHz, CDCl_3): δ = 55.34, 113.87, 122.68, 122.72, 123.84, 124.05, 127.89, 127.95, 130.14, 130.20, 145.20, 145.25, 156.01, 158.59, 160.43. –MS (EI); m/z (%): 204 [$\text{M}^+ + 1$] (13), 203 [M^+] (100), 188 (31), 160 (66), 134 (10), 106 (13), 63 (12), 51 (6.5).

3.799

2.93

3-Chloro-2-(2-methoxy-phenyl)-pyridine

8.598
8.590
7.804
7.784
7.737
7.720
7.472
7.453
7.233
7.221
7.213
7.201

3-Chloro-2-phenyl-pyridine **1b**

3.864

- 8.610
- 8.586
- 8.491
- 8.465
- 8.381
- 8.371
- 8.331
- 8.291
- 7.783
- 7.774
- 7.744
- 7.736
- 7.705
- 7.696
- 7.284
- 7.260
- 7.246
- 7.236
- 7.220
- 7.209

- 158.670
- 155.868
- 151.019
- 150.288
- 146.256
- 138.080
- 125.321
- 124.912
- 122.514
- 122.366

165.509
 163.030
 158.349
 150.919
 145.242
 134.722
 134.691
 129.326
 129.240
 122.659
 120.949
 116.363

4-Chloro-2-(4-fluoro-phenyl)-pyridine

1

8.533
8.509
7.827
7.820
7.760
7.751
7.722
7.713
7.332
7.299
7.291
7.173
7.163
7.147
7.137
7.054
7.017
6.979
6.965
6.924

149.783
147.686
142.748
139.213

129.451
129.183
128.291
122.612