Iron-Catalyzed C(sp²)–C(sp³) Cross-Coupling at Low Catalyst Loading

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Electronic Supplementary Information

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List of Known Compounds/General Methods

All compounds reported in the manuscript are commercially available or have been previously described in literature unless indicated otherwise. <u>All experiments involving iron were performed using standard Schlenk techniques under argon or nitrogen atmosphere unless stated otherwise.</u> All solvents were purchased at the highest commercial grade and used as received or after purification by distillation from sodium/benzophenone under nitrogen. All solvents were deoxygenated prior to use. All other chemicals were purchased at the highest commercial grade and used as received. Reaction glassware was oven-dried at 140 °C for at least 24 h or flame-dried prior to use, allowed to cool under vacuum and purged with argon (three cycles). All products were identified using ^{1}H NMR analysis and comparison with authentic samples. All yields refer to yields determined by ^{1}H NMR using an internal standard unless stated otherwise. GC and/or GC/MS analysis was used for volatile products. ^{1}H NMR and ^{13}C NMR spectra were recorded in CDCl$_3$ on Bruker spectrometers at 400 (^{1}H NMR) and 100 MHz (^{13}C NMR). All shifts are reported in parts per million (ppm) relative to residual CHCl$_3$ peak (7.27 and 77.2 ppm, ^{1}H NMR and ^{13}C NMR, respectively). All coupling constants (J) are reported in hertz (Hz). Abbreviations are: s, singlet; d, doublet; t, triplet; q, quartet; brs, broad singlet. GC-MS chromatography was performed using Agilent HP5890/2 GC system using helium as the carrier gas at a flow rate of 1 mL/min and an initial oven temperature of 50 °C. The injector temperature was 250 °C. The detector temperature was 250 °C. For runs with the initial oven temperature of 50 °C, temperature was increased with a 10 °C/min ramp after 50 °C hold for 3 min to a final temperature of 250 °C, then hold at 250 °C for 15 min (splitless mode of injection, total run time of 35.0 min). High-resolution mass spectra (HRMS) were measured on a 7T Bruker Daltonics FT-MS instrument (for HRMS). Melting points were measured on Melt EMP (laboratory devices). All flash chromatography was performed using silica gel, 60 Å, 300 mesh. TLC analysis was carried out on aluminum plates coated with silica gel 60 F254, 0.2 mm thickness. The plates were visualized using a 254 nm ultraviolet lamp or aqueous potassium permanganate solutions. ^{1}H NMR and ^{13}C NMR data are given for all products in the Supplementary Experimental for characterization purposes. ^{1}H NMR, ^{13}C NMR and HRMS data are reported for all new compounds. All products have been previously reported, unless stated otherwise.

Experimental Procedures and Characterization Data

General Procedure for Iron-Catalyzed C(sp^2)–C(sp^3) Cross-Coupling. An oven-dried vial equipped with a stir bar was charged with an aryl chloride substrate (neat, typically, 0.50 mmol, 1.0 equiv) and Fe(acac)$_3$ (typically, 0.10 or 0.05 mol%), placed under a positive pressure of argon and subjected to three evacuation/backfilling cycles under vacuum. Tetrahydrofuran (0.50 M) and ligand (neat, typically, 100-600 mol%) were sequentially added with vigorous stirring at room temperature, the reaction mixture was cooled to 0 °C, a solution of Grignard reagent (typically, 1.20 equiv) was added dropwise with vigorous stirring and the reaction mixture was stirred for the indicated time at 0 °C. After the indicated time, the reaction mixture was diluted with HCl (1.0 N, 1.0 mL) and Et$_2$O (1 x 30 mL), the organic layer was extracted with HCl (1.0 N, 2 x 10 mL), dried and concentrated. Note: for products containing basic nitrogen, NaOH (1.0 N) was used instead of HCl (1.0 N). The sample was analyzed by ^{1}H NMR (CDCl$_3$, 400 MHz) to obtain conversion, yield and selectivity using internal standard and comparison with authentic samples. Analytical sample was purified by chromatography on silica gel (EtOAc/hexanes).

Representative Procedure for Iron-Catalyzed C(sp^2)–C(sp^3) Cross-Coupling. 1.0 g Scale. An oven-dried, two-necked flask (100 mL) equipped with a stir bar was charged with 4-chloro-*N*,*N*-diisopropylbenzenesulfonamide (1.00 g, 3.63 mmol, 1.0 equiv) and Fe(acac)$_3$ (1.28 mg, 3.63 μmol, 0.10 mol%). Tetrahydrofuran (2.12 mL, 0.50 M) and DMI (0.78 ml, 200 mol%) were sequentially added with vigorous stirring at room temperature, the reaction mixture was cooled to 0 °C, a solution of *n*-C$_{14}$H$_{29}$MgCl (1.0 M in THF, 4.36 mL, 1.20 equiv) was added dropwise with vigorous stirring and the reaction mixture was stirred for 5 h at 0 °C. After the indicated time, the reaction mixture was diluted with HCl (1.0 N, 3 mL) and Et$_2$O (1 x 50 mL), the organic layer was extracted with HCl (1.0 N, 2 x 10 mL), dried and concentrated. The sample was analyzed by ^{1}H NMR (CDCl$_3$, 400 MHz) and GC-MS to obtain conversion, yield and selectivity using internal standard and comparison with authentic samples. Purification by recrystallization from Et$_2$O afforded the title product. Yield 95% (1.51 g). White solid. Characterization data are included in the section below.

Iron-Catalyzed Cross-Coupling at Low Catalyst Loading

### 1-Tetradecyl-4-(trifluoromethyl)benzene (Table 2, 2a)
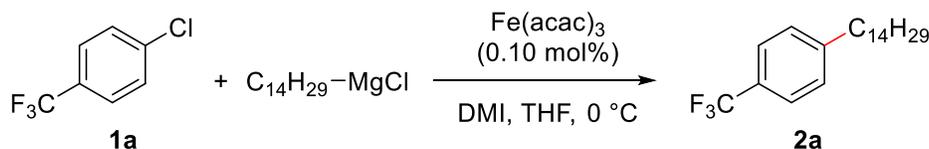
Prepared according to the general procedure using 1-chloro-4-(trifluoromethyl)benzene (0.50 mmol), Fe(acac)$_3$ (0.10 mol%), DMI (200 mol%), THF (0.50 M), and n-C$_{14}$H$_{29}$MgCl (1.0 M in THF, 1.20 equiv). The reaction mixture was stirred for 10 min at 0 °C. Yield 93%. Colorless oil. **¹H NMR (400 MHz, CDCl₃)** δ 7.51 (d, J = 8.0 Hz, 2H), 7.27 (d, J = 8.0 Hz, 2H), 2.64 (t, J = 7.8 Hz, 2H), 1.66-1.56 (m, 2H), 1.37-1.18 (m, 22H), 0.88 (t, J = 6.8 Hz, 3H). **¹³C NMR (100 MHz, CDCl₃)** δ 147.23, 128.86, 128.16 (q, J^F = 32.3 Hz), 125.33 (q, J^F = 3.7 Hz), 124.63 (q, J^F = 271.7 Hz), 36.01, 32.16, 31.44, 29.93, 29.89, 29.78, 29.68, 29.60, 29.45, 22.92, 14.32. Spectroscopic properties matched those described previously.[1,2]

4-Tetradecylbenzonitryle (Table 2, 2b)
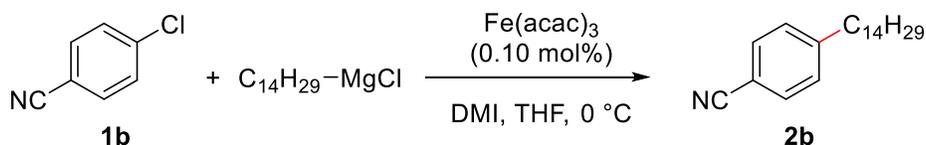
Prepared according to the general procedure using 4-chlorobenzonitrile (0.50 mmol), Fe(acac)$_3$ (0.10 mol%), DMI (600 mol%), THF (0.50 M), and n-C$_{14}$H$_{29}$MgCl (1.0 M in THF, 1.20 equiv). The reaction mixture was stirred for 18 h at 0 °C. Yield 74%. White solid. **¹H NMR (400 MHz, CDCl₃)** δ 7.56 (d, J = 8.3 Hz, 2H), 7.27 (d, J = 8.4 Hz, 2H), 2.65 (t, J = 7.7 Hz, 2H), 1.67-1.53 (m, 2H), 1.34-1.23 (m, 22H), 0.88 (t, J = 6.9 Hz, 3H). **¹³C NMR (100 MHz, CDCl₃)** δ 148.81, 132.28, 129.37, 119.41, 109.62, 36.30, 32.11, 31.17, 29.87, 29.84, 29.81, 29.71, 29.59, 29.55, 29.36, 22.88, 14.32. Spectroscopic properties matched those described previously.[1,2]

Methyl 4-tetradecylbenzoate (Table 2, 2c)
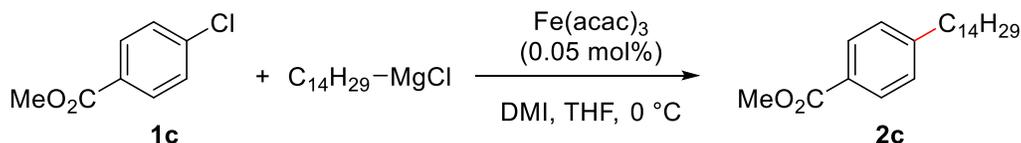
Prepared according to the general procedure using methyl 4-chlorobenzoate (0.50 mmol), Fe(acac)$_3$ (0.05 mol%), DMI (200 mol%), THF (0.50 M), and n-C$_{14}$H$_{29}$MgCl (1.0 M in THF, 1.05 equiv, added dropwise over 1 h at 0°C). The reaction mixture was stirred for 1 h at 0 °C. Yield 90%. White solid. **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.95 (d, J = 8.4 Hz, 2H), 7.24 (d, J = 8.5, 2H), 3.90 (s, 3H), 2.65 (t, J = 7.7 Hz, 2H), 1.67-1.56 (m, 2H), 1.35-1.20 (m, 22H), 0.88 (t, J = 6.9 Hz, 3H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 167.39, 148.71, 129.78, 128.60, 127.74, 52.12, 36.19, 32.11, 31.33, 29.88, 29.84, 29.74, 29.64, 29.55, 29.44, 22.88, 14.31. Spectroscopic properties matched those described previously.[1,2]

N,N-Diisopropyl-4-tetradecylbenzenesulfonamide (Table 2, 2d)
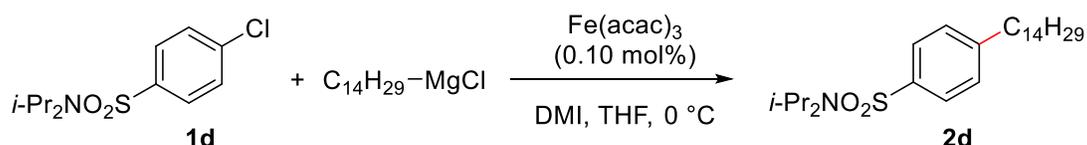
Prepared according to the general procedure using 4-chloro-*N,N*-diisopropylbenzenesulfonamide (0.50 mmol), Fe(acac)$_3$ (0.10 mol%), DMI (200 mol%), THF (0.50 M), and n-C$_{14}$H$_{29}$MgCl (1.0 M in THF, 1.20 equiv). The reaction mixture was stirred for 3 h at 0 °C. Yield 99%. White solid. **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.76 (d, J = 8.4 Hz, 2H), 7.26 (d, J = 8.4 Hz, 2H), 3.75-3.63 (m, 2H), 2.65 (t, J = 7.7 Hz, 2H), 1.66-1.55 (m, 2H), 1.35-1.20 (m, 34H), 0.88 (t, J = 6.8 Hz, 3H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 147.54, 139.94, 128.85, 127.31, 48.65, 35.91, 32.08, 31.23, 29.85, 29.81, 29.78, 29.70, 29.58, 29.52, 29.34, 22.85, 22.08, 14.28. Spectroscopic properties matched those described previously.[1,2]

1-Chloro-4-tetradecylbenzene (Table 2, 2e)
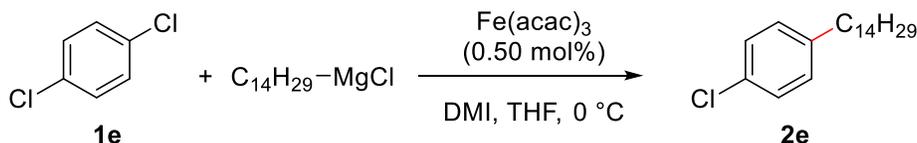
Prepared according to the general procedure using 1,4-dichlorobenzene (0.50 mmol), Fe(acac)$_3$ (0.50 mol%), DMI (600 mol%), THF (0.50 M), and n-C$_{14}$H$_{29}$MgCl (1.0 M in THF, 1.20 equiv). The reaction mixture was stirred for 18 h at 0 °C. Yield 81%. White solid. **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.23 (d, J = 8.4 Hz, 2H), 7.09 (d, J = 8.4 Hz, 2H), 2.56 (t, J = 7.7 Hz, 2H), 1.62-1.52 (m, 2H), 1.34-1.20 (m, 22H), 0.88 (t, J = 6.8 Hz, 3H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 141.51, 131.40, 129.91, 128.47, 35.49, 32.14, 31.61, 29.91, 29.88, 29.78, 29.68, 29.58, 29.40, 22.91, 14.33. Spectroscopic properties matched those described previously.[3]
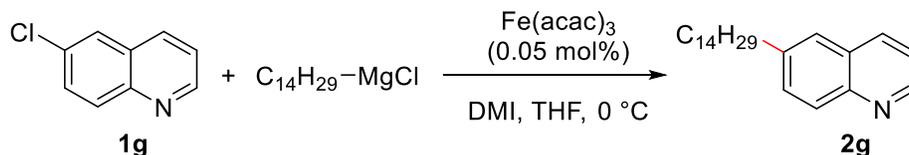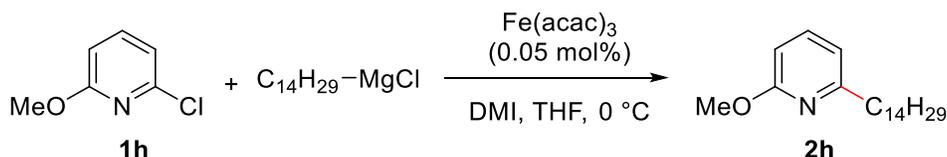
2-Tetradecylpyridine (Table 2, 2f)
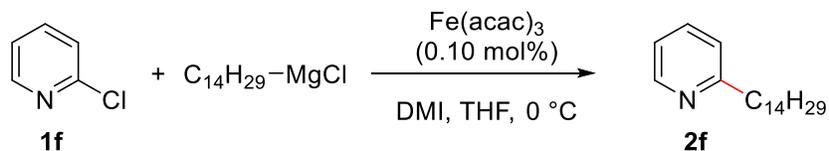
Prepared according to the general procedure using 2-chloropyridine (0.50 mmol), Fe(acac)$_3$ (0.10 mol%), DMI (600 mol%), THF (0.50 M), and n-C$_{14}$H$_{29}$MgCl (1.0 M in THF, 2.0 equiv). The reaction mixture was stirred for 18 h at 0 °C. Yield 78%. Colorless oil. **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.52 (ddd, J = 4.9, 1.8, 0.9 Hz, 1H), 7.57 (td, J = 7.7, 1.9 Hz, 1H), 7.13 (d, J = 7.8 Hz, 1H), 7.08 (ddd, J = 7.5, 4.9, 1.1 Hz, 1H), 2.78 (t, J = 7.7 Hz, 2H), 1.77-1.66 (m, 2H), 1.40-1.18 (m, 22H), 0.88 (t, J = 6.9 Hz, 3H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 162.70, 149.34, 136.31, 122.80, 120.95, 38.64, 32.08, 30.11, 29.84, 29.82, 29.73, 29.66, 29.58, 29.52, 22.85, 14.28. Spectroscopic properties matched those described previously.[1,2]

6-Tetradecylquinoline (Table 2, 2g)

Prepared according to the general procedure using 6-chloroquinoline (0.50 mmol), Fe(acac)$_3$ (0.05 mol%), DMI (200 mol%), THF (0.50 M), and n-C$_{14}$H$_{29}$MgCl (1.0 M in THF, 1.2 equiv). The reaction mixture was stirred for 18 h at 0 °C. Yield 94%. White solid. **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.85 (dd, J = 4.2, 1.7 Hz, 1H), 8.08 (dd, J = 8.3, 1.0 Hz, 1H), 8.02 (d, J = 9.2 Hz, 1H), 7.59-7.54 (m, 2H), 7.35 (dd, J = 8.3, 4.2 Hz, 1H), 2.78 (t, J = 7.7 Hz, 2H), 1.76-1.65 (m, 2H), 1.39-1.21 (m, 22H), 0.88 (t, J = 6.9 Hz, 3H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 149.70, 147.24, 141.50, 135.67, 131.22, 129.32, 128.46, 126.14, 121.15, 36.08, 32.09, 31.43, 29.83, 29.75, 29.67, 29.53, 29.47, 22.86, 14.30. Spectroscopic properties matched those described previously.[1,2]
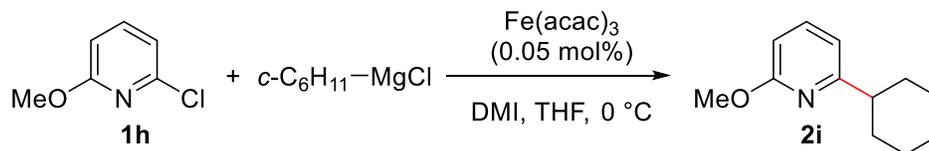
2-Methoxy-6-tetradecylpyridine (Table 2, 2h)

Prepared according to the general procedure using 2-chloro-6-methoxypyridine (0.50 mmol), Fe(acac)$_3$ (0.05 mol%), DMI (200 mol%), THF (0.50 M), and n-C$_{14}$H$_{29}$MgCl (1.0 M in THF, 1.2 equiv). The reaction mixture was stirred for 18 h at 0 °C. Yield 99%. Colorless oil. **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.45 (dd, J = 8.2, 7.3 Hz, 1H), 6.69 (d, J = 7.2 Hz, 1H), 6.52 (d, J = 8.2 Hz, 1H), 3.91 (s, 3H), 2.67 (t, J = 7.7 Hz, 2H), 1.76-1.65 (m, 2H), 1.38-1.21 (m, 22H), 0.88 (t, J = 6.9 Hz, 3H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 163.79, 160.64, 138.76, 115.21, 107.24, 53.33, 38.12, 32.12, 29.88, 29.80, 29.74, 29.59, 29.56, 22.89, 14.32. Spectroscopic properties matched those described previously.[1,2]

2-Cyclohexyl-6-methoxypyridine (Scheme 1, 2i)

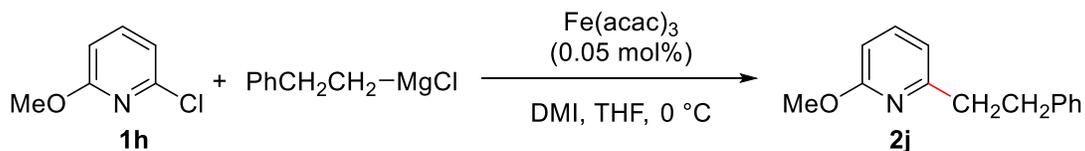
Prepared according to the general procedure using 2-chloro-6-methoxypyridine (0.50 mmol), Fe(acac)$_3$ (0.05 mol%), DMI (200 mol%), THF (0.50 M), and c-C$_6$H$_{11}$MgCl (1.0 M in THF, 2.0 equiv). The reaction mixture was stirred for 18 h at 0 °C. Yield 95%. Colorless oil. **¹H NMR (400 MHz, CDCl₃)** δ 7.47 (dd, J = 8.2, 7.3 Hz, 1H), 6.70 (d, J = 7.3 Hz, 1H), 6.52 (dd, J = 8.2, 0.6 Hz, 1H), 3.92 (s, 3H), 2.58 (tt, J = 11.7, 3.4 Hz, 1H), 1.97-1.89 (m, 2H), 1.88-1.78 (m, 2H), 1.77-1.69 (m, 1H), 1.52 (ddd, J = 24.1, 12.2, 2.7 Hz, 2H), 1.46-1.32 (m, 2H), 1.33-1.23 (m, 1H). **¹³C NMR (100 MHz, CDCl₃)** δ 164.74, 163.60, 138.87, 113.42, 107.28, 53.27, 46.16, 32.86, 26.72, 26.35. Spectroscopic properties matched those described previously.[4]

2-Methoxy-6-phenethylpyridine (Scheme 1, 2j)

Prepared according to the general procedure using 2-chloro-6-methoxypyridine (0.50 mmol), Fe(acac)$_3$ (0.05 mol%), DMI (200 mol%), THF (0.50 M) and PhCH$_2$CH$_2$MgCl (1.0 M in THF, 2.0 equiv). The reaction mixture was stirred for 18 h at 0 °C. Yield 99%. Colorless oil. **¹H NMR (400 MHz, CDCl₃)** δ 7.43 (dd, J = 8.2, 7.3 Hz, 1H), 7.29-7.23 (m, 2H), 7.22-7.15 (m, 3H), 6.65 (d, J = 7.2 Hz, 1H), 6.55 (d, J = 8.2 Hz, 1H), 3.93 (s, 3H), 3.09-3.03 (m, 2H), 3.02-2.96 (m, 2H). **¹³C NMR (100 MHz, CDCl₃)** δ 163.84, 159.21, 142.10, 138.85, 128.64, 128.45, 125.98, 115.47, 107.66, 53.39, 39.74, 35.58. Spectroscopic properties matched those described previously.[5]

References

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C$_{14}$H$_{29}$

NC

2b

7.57
7.55
7.28
7.26

2.67
2.65
2.63
1.65
1.63
1.61
1.59
1.57
1.30
1.29
1.25
0.90
0.88
0.86

7.57
7.55
7.28
7.26

2.00
2.33

7.6   7.4   7.2
f1 (ppm)

2.00
2.33

2.17

2.29
23.50
3.24

14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3 -4 -5
f1 (ppm)

148.81

132.28
129.37

119.41

109.62

36.30
32.11
31.17
29.87
29.84
29.81
29.71
29.59
29.55
29.36
22.88
14.32

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

ESI-11

2d

i-Pr₂NO₂S—⟨benzene⟩—C₁₄H₂₉

¹H NMR peaks: 7.77, 7.75, 7.27, 7.25; 3.73, 3.71, 3.69, 3.68, 3.66, 2.66, 2.65, 2.63, 1.65, 1.63, 1.61, 1.59, 1.57, 1.30, 1.29, 1.27, 1.25, 0.89, 0.88, 0.86

Integrations: 2.00, 2.00, 2.00, 2.00, 2.00, 34.08, 3.00

¹³C NMR peaks: 147.54, 139.94, 128.85, 127.31, 48.65, 32.08, 29.85, 29.81, 29.78, 29.70, 29.58, 29.52, 22.85, 14.08, 14.28

2f

8.53, 8.52, 8.52, 8.51, 8.51, 7.59, 7.59, 7.57, 7.57, 7.55, 7.55, 7.14, 7.12, 7.10, 7.08, 7.07, 7.06

2.79, 2.78, 2.76, 1.76, 1.74, 1.72, 1.70, 1.68, 1.34, 1.33, 1.30, 1.28, 1.25, 0.89, 0.88, 0.86

162.70, 149.34, 136.31, 122.80, 120.95

38.64, 32.08, 30.11, 29.84, 29.82, 29.73, 29.66, 29.58, 29.52, 22.85, 14.28

$C_{14}H_{29}$

2g

2h

MeO — N — C$_{14}$H$_{29}$

7.47, 7.45, 7.45, 7.43, 6.70, 6.68, 6.53, 6.51

3.91

2.68, 2.67, 2.65, 1.74, 1.72, 1.71, 1.69, 1.67, 1.30, 1.25, 0.90, 0.88, 0.86

7.47, 7.45, 7.45, 7.43, 6.70, 6.68, 6.53, 6.51

1.00 | 1.00 | 0.91

7.6 7.4 7.2 7.0 6.8 6.6 6.4
f1 (ppm)

1.00 | 1.00 | 0.91 | 3.08 | 2.09 | 2.08 | 22.31 | 3.08

14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3 -4 -5
f1 (ppm)

163.79, 160.64

138.76

115.21

107.24

53.33

38.12, 32.12, 29.88, 29.80, 29.74, 29.59, 29.56, 22.89, 14.32

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

ESI-17

MeO — [pyridine ring] — N — CH₂CH₂Ph

2j

7.45
7.43
7.43
7.41
7.29
7.27
7.25
7.24
7.21
7.19
7.18
7.16

6.65
6.64
6.56
6.53

3.93

3.08
3.07
3.06
3.05
3.04
3.01
3.00
2.99
2.97
2.97

1.06
2.22
3.13
1.05
1.00

3.22
2.17
2.18

163.84
159.21

142.10
138.85

128.64
128.45
125.98

115.47

107.66

53.39

39.74
35.58