Ring-Fluorinated Isoquinoline and Quinoline Synthesis: Intramolecular Cyclization of *o*-Cyano- and *o*-Isocyano-β,β-difluorostyrenes

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Supporting Information

General. NMR spectra were obtained on a Bruker DRX-500 or a Bruker Avance-500 spectrometer. Chemical shift values were given in ppm relative to internal Me_4Si (for ^{1}H NMR: δ 0.00), $CDCl_3$ (for ^{13}C NMR: δ 77.0), and C_6F_6 (for ^{19}F NMR: δ_F 0.00). IR spectra were recorded on a Horiba FT-300S spectrometer. Mass spectra were taken with JEOL JMS-DX-300 or a JEOL JMS-SX-102A spectrometer under electron impact (EI) unless otherwise noted. _Elemental analyses were performed with a YANAKO MT-6 CHN Corder apparatus. Mass spectra were taken with JEOL JMS-DX-300 or JEOL JMS-SX-102A spectrometer under electron inpact (EI) unless otherwise noted. THF was distilled from sodium benzophenone ketyl prior to use. Column chromatography and preparative thin-layer chromatography (PTC) were performed on silica gel.

Experimental

o-(1-Butyl-2,2-difluorovinyl)benzonitrile (3a)

Butyllithium (6.63 ml, 1.60 M, in hexane, 10.6 mmol) was added to a solution of 2,2,2-trifluoroethyl *p*-toluenesulfonate (1.28 g, 5.05 mmol) in THF (25 ml) at –78 °C over 10 min under nitrogen. The reaction mixture was stirred for 20 min at –78 °C, and then tributylborane (5.56 ml, 1.00 M in THF, 5.56 mmol) was added at –78 °C. After being stirred for 1 h, the reaction mixture was warmed to room temperature and stirred for an additional 3 h. The solution was treated with hexamethylphosphoric triamide (HMPA, 6 ml), triphenylphosphine (106 mg, 0.404 mmol), and tris(dibenzylideneacetonyl)bispalladium-chloroform (1/1) (105 mg, 0.101 mmol) and stirred for 15 min. To the resulting solution was added *o*-iodobenzonitrile (1.11 g, 4.88 mmol) and copper(I) iodide (1.06 g, 5.55 mmol). After the mixture had been stirred for 1 h at room temperature, the reaction was quenched with phosphate buffer (pH 7). The mixture was filtered through Celite, and then organic materials were extracted with AcOEt three times. The combined extracts were washed with brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography on silica gel (hexane–AcOEt 5:1) to give **3a** (906 mg, 84%) as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87 (3H, t, J = 7.3 Hz), 1.26–1.38 (4H, m), 2.44 (2H, tt, J = 7.3 Hz, J_{CF} = 2.2 Hz), 7.35 (1H, d, J = 7.7 Hz), 7.42 (1H, ddd, J = 7.7, 7.7, 1.2 Hz), 7.60 (1H, ddd, J = 7.7, 7.7, 1.2 Hz) 7.70 (1H, dd, J = 7.7, 1.2 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ 13.7, 22.1, 28.2, 29.6 (d, J_{CF} = 2 Hz), 90.6 (dd, J_{CF} = 24, 15 Hz), 113.4, 117.6, 128.2, 130.4 (d, J_{CF} = 2 Hz), 132.7, 133.2, 138.2 (dd, J_{CF} = 5, 2 Hz), 153.4 (dd, J_{CF} = 290, 290 Hz).

^{19}F NMR (471 MHz $CDCl_3$) δ_F 71.7 (1F, dt, J_{FF} = 39 Hz, J_{FH} = 2 Hz), 74.1 (1F, dt, J_{FF} = 39 Hz, J_{FH} = 3 Hz).

IR (neat) 2970, 2940, 2870, 2240, 1740, 1280, 1240, 1140, 975, 765 cm^{-1}.

MS (70 eV) *m/z* (%) 221 (M^+; 36), 179 (100), 131 (45).

HRMS calcd for $C_{13}H_{13}NF_2$ 221.1016 (M^+); found 221.1000.

Anal. Calcd for $C_{13}H_{13}NF_2$; C, 70.57; H, 5.92; N, 6.33. Found: C, 70.93; H, 5.95; N, 6.17.

***o*-(1-*sec*-Butyl-2,2-difluorovinyl)benzonitrile (3b)**

Compound **3b** was prepared by the method described for **3a** using 2,2,2-trifluoroethyl *p*-

toluenesulfonate (749 mg, 2.95 mmol), butyllithium (4.15 ml, 1.49 M in hexane, 6.19 mmol), tri-*sec*-butylborane (3.24 ml, 1.0 M in THF, 3.24 mmol), HMPA (3 ml), triphenylphosphine (62 mg, 0.24 mmol), tris(dibenzylideneacetonyl)bispalladium-chloroform (1/1) (61 mg, 0.059 mmol), *o*-iodobenzonitrile (606 mg, 2.64 mmol), and copper(I) iodide (561 mg, 2.95 mmol) in THF (15 ml). Purification by column chromatography on silica gel (hexane–AcOEt 5:1) gave **3b** (433 mg, 74%) as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.99 (3H, t, J = 7.1 Hz), 1.09 (3H, d, J = 7.1 Hz), 1.38 (1H, ddq, J = 14.3, 7.1, 7.1 Hz), 1.53 (1H, ddq, J = 14.3, 7.1, 7.1 Hz), 2.61 (1H, ddq, J = 7.1, 7.1, 7.1 Hz), 7.30 (1H, d, J = 6.7 Hz), 7.43 (1H, td, J = 6.7, 1.2 Hz), 7.59 (1H, td, J = 6.7, 1.2 Hz), 7.71 (1H, dd, J = 6.7, 1.2 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ 12.2, 18.6 (dd, J_{CF} = 3, 3 Hz), 28.0 (dd, J_{CF} = 3, 3 Hz), 35.7, 94.0 (dd, J_{CF} = 23, 13 Hz), 114.5, 117.9, 128.3, 130.9 (dd, J_{CF} = 2, 2 Hz), 132.4, 133.2, 137.0 (d, J_{CF} = 6 Hz), 153.4 (dd, J_{CF} = 292, 292 Hz).

^{19}F NMR (471 MHz, $CDCl_3$) δ_F 71.9 (1F, d, J_{FF} = 41 Hz), 75.6 (1F, d, J_{FF} = 41 Hz).

IR (neat) 2970, 2930, 2880, 2230, 1735, 1720, 1460, 1235, 1060, 760, 670 cm^{-1}.

MS (70 eV) m/z (%) 221 (M^+; 30), 192 (100), 172 (40), 165 (76), 152 (35).

Anal. Calcd for $C_{13}H_{13}NF_2$: C, 70.57; H, 5.92; N, 6.33. Found: C, 70.51; H, 5.98; N, 6.39.

o-(1-Butyl-2,2-difluorovinyl)aniline (4a)

Compound **4a** was prepared by the method described for **3a** using butyllithium (1.56 ml, 1.63 M in hexane, 2.54 mmol), 2,2,2-trifluoroethyl *p*-toluenesulfonate (301 mg, 1.21 mmol), THF (10 ml), tributylborane (1.33 ml, 1.0 M in THF, 1.33 mmol), HMPA (3 ml), triphenylphosphine (25 mg, 0.10 mmol), tris(dibenzylideneacetonyl)bispalladium-chloroform (1/1) (25 mg, 0.02 mmol), *N*-butylmagnesio-*o*-iodoaniline [generated from *o*-iodoaniline (238 mg, 1.09 mmol) and dibutylmagnesium (2.47 ml, 0.44 M in Et_2O, 1.09 mmol) in THF (3 ml) at 0 °C for 30 min], and copper(I) iodide (230 mg, 1.21 mmol). Purification by thin layer chromatography on silica gel (hexane–AcOEt 5:1) gave **4a** (176 mg, 77%) as a pale yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87 (3H, t, *J* = 7.1 Hz), 1.30–1.35 (4H, m), 2.29 (2H, tdd, *J* = 7.0 Hz, J_{HF} = 2.3, 2.3 Hz), 3.66 (2H, br s), 6.70–6.77 (2H, m), 7.00 (1H, dd, *J* = 7.6, 1.5 Hz), 7.12 (1H, ddd, *J* = 7.6, 7.6, 1.5 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ 13.8, 22.4, 27.7, 29.8 (dd, J_{CF} = 3, 3 Hz), 89.1 (dd, J_{CF} = 22, 17 Hz), 115.6, 118.4, 119.0 (d, J_{CF} = 3 Hz), 128.9, 130.6, (d, J_{CF} = 2 Hz), 144.3, 152.8 (dd, J_{CF} = 290, 288 Hz).

^{19}F NMR (470 MHz, $CDCl_3$) δ_F 68.7 (1F, d, J_{FF} = 43 Hz), 72.7 (1F, d, J_{FF} = 43 Hz).

IR (neat) 3475, 3375, 2960, 2930, 2860, 1740, 1620, 1495, 1230 cm^{-1}.

MS (70 eV) *m/z* (%) 211 (M^+; 100), 168 (59), 148 (43).

Anal. Calcd for $C_{12}H_{15}NF_2$: C, 68.23; H, 7.16; N, 6.63. Found: C, 68.14; H, 7.07; N, 6.52.

o-(1-*sec*-Butyl-2,2-difluorovinyl)aniline (4b)

Compound **4b** was prepared by the method described for **3a** using butyllithium (1.56 ml, 1.63 M in hexane, 2.54 mmol), 2,2,2-trifluoroethyl *p*-toluenesulfonate (301 mg, 1.21 mmol), THF (10 ml), tributylborane (1.33 ml, 1.0 M in THF, 1.33 mmol), HMPA (3 ml), triphenylphosphine (25 mg, 0.10 mmol), tris(dibenzylideneacetonyl)bispalladium-chloroform (1/1) (25 mg, 0.02 mmol), *N*-butylmagnesio-*o*-iodoaniline [generated from *o*-iodoaniline (238 mg, 1.09 mmol) and dibutylmagnesium (2.47 ml, 0.44 M in Et_2O, 1.09 mmol) in THF (3 ml) at 0 °C for 30 min], and copper(I) iodide (230 mg, 1.21 mmol). Purification by PTLC on silica gel (hexane–AcOEt 5:1) gave **4b** (157 mg, 68%) as a pale yellow liquid.

^{1}H NMR (126 MHz, $(CD_3)_2SO$, 100 °C) δ 0.99 (3H, t, *J* = 7.3 Hz), 1.03–1.15 (3H, m), 1.31–1.45 (1H, m), 1.54–1.66 (1H, m), 2.44–2.58 (1H, m), 4.58 (2H, br s), 6.62 (1H, ddd, *J* = 7.4, 7.4, 1.4 Hz), 6.79 (1H, d, *J* = 7.4 Hz), 6.92 (1H, d, *J* = 7.4 Hz), 7.07 (1H, ddd, *J* = 7.4, 7.4, 1.4 Hz).

^{13}C NMR (126 MHz, $(CD_3)_2SO$, 100 °C) δ 10.1, 17.2, 26.9, 34.5, 92.4 (dd, J_{CF} = 16, 16 Hz), 114.5, 115.4, 116.1, 127.8, 129.6, 145.8, 151.7 (dd, J_{CF} = 290, 288 Hz).

^{19}F NMR (254 MHz, $(CD_3)_2SO$, 100 °C) δ_F 71.2 (1F, d, J_{FF} = 49 Hz), 74.1 (1F, d, J_{FF} = 49 Hz).

IR (neat) 3390, 2960, 1730, 1615, 1495, 1455, 1300, 1215, 935, 750 cm^{-1}.

MS (20 eV) *m/z* (%) 211 (M$^+$; 100), 182 (57), 162 (82).

HRMS calcd for $C_{12}H_{15}NF_2$ 211.1173 (M$^+$); found 211.1184.

N-[2-(1-Butyl-2,2-difluorovinyl)phenyl]formamide (5a)

To a solution of **4a** (1.46 g, 6.92 mmol) in pyridine (30 ml) was added formic acid (0.65 ml, 17.3 mmol), acetic anhydride (1.63 ml, 17.3 mmol), and a catalytic amount of DMAP at room temperature under nitrogen. After being stirred for 1 h, the reaction mixture was quenched with phosphate buffer (pH 7). Organic materials were extracted with AcOEt three times. The combined extracts were washed with aq. HCl (2 M) and brine, and then dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography on silica gel (hexane–AcOEt 2:1) to give **5a** (1.49 g, 90%) as a pale yellow liquid.

^{19}F NMR (470 MHz, $CDCl_3$) δ_F 70.9 (1F, dt, J_{FF} = 39 Hz, J_{HF} = 2Hz), 74.6 (1F, dd, J_{FF} = 39, 39 Hz).

IR (neat) 3309, 2958, 2931, 2862, 1738, 1676, 1522, 1246, 1130, 968, 912, 725 cm^{-1}.

Anal. Calcd for $C_{13}H_{15}NF_2O$: C, 65.26; H, 6.32; N, 5.85. Found: C, 65.46; H, 6.44, N; 5.66.

***N*-[2-(1-*sec*-Butyl-2,2-difluorovinyl)phenyl]formamide (5b)**

Compound **5b** was prepared by the method described for **5a** using **4b** (1.66 g, 7.85

mmol), pyridine (20 ml), formic acid (0.59 ml, 19.6 mmol), acetic anhydride (1.49 ml, 19.6 mmol), and catalytic amount of DMAP. Purification by column chromatography on silica gel (hexane–AcOEt 2:1) gave **5b** (1.63 g, 87%) as a pale yellow liquid.

^{19}F NMR (470 MHz, $C_6D_5CD_3$) 72.4 (1F, dd, J_{FF} = 41, 41 Hz), 75.8 (1F, d, J_{FF} = 41, 41 Hz).

IR (neat) 3303, 2966, 2933, 1730, 1672, 1520, 1448, 1284, 1248, 1059, 912, 752 cm^{-1}.

Anal. Calcd for $C_{13}H_{15}NF_2O$: C, 65.26; H, 6.32; N, 5.85. Found: C, 65.03; H, 6.40, N; 5.67.

2-(1-Butyl-2,2-difluorovinyl)phenyl isocyanide (6a)

To a solution of **5a** (166 mg, 0.70 mmol) in CH_2Cl_2 (6 ml) was added triethylamine (0.21 ml, 1.53 mmol) and phosphorus oxychloride (0.08 ml, 0.83 mmol) at 0 °C under nitrogen. After being stirred for 0.5 h, the reaction mixture was poured into 10% aqueous sodium carbonate. Organic materials were extracted with CH_2Cl_2 three times. The combined extracts were washed with brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by PTLC on silica gel (hexane–AcOEt 10:1) to give **6a** (130 mg, 85%) as a pale yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87 (3H, t, J = 7.0 Hz), 1.25–1.37 (4H, m), 2.38–2.43 (2H, m), 7.28 (1H, dd, J = 7.7, 1.4 Hz), 7.35 (1H, ddd, J = 7.7, 7.7, 1.6 Hz), 7.38–7.44 (2H, m).

^{13}C NMR (126 MHz, $CDCl_3$) δ 13.7, 22.1, 27.8, 29.6 (dd, J_{CF} = 3, 3 Hz), 88.9 (dd, J_{CF} = 26, 16 Hz), 127.4, 128.7, 129.4, 130.6, 131.7, 131.8, 153.2 (dd, J_{CF} = 290, 290 Hz), 166.7.

^{19}F NMR (470 MHz, $CDCl_3$) δ_F 70.5 (1F, d, J_{FF} = 39 Hz), 74.5 (1F, d, J_{FF} = 39 Hz).

IR (neat) 2960, 2930, 2860, 2130, 1740, 1705, 1275, 1240, 1135, 760 cm^{-1}.

MS (20 eV) *m/z* (%) 221 (M$^+$; 14), 167 (45), 149 (100).

HRMS calcd for $C_{13}H_{13}NF_2$ 221.1016 (M$^+$); found 221.1022.

2-(1-*sec*-Butyl-2,2-difluorovinyl)phenyl isocyanide (**6b**)

Compound **6b** was prepared by the method described for **6a** using **5b** (526 mg, 2.20 mmol), CH_2Cl_2 (15 ml), triethylamine (0.77 ml, 5.50 mmol), and phosphorus oxychloride (0.30 ml, 3.29 mmol). Purification by column chromatography on silica gel (hexane–AcOEt 10:1) gave **6b** (398 mg, 82%) as a pale yellow liquid.

^{1}H NMR (500 MHz, $C_6D_5CD_3$) δ 0.86 (3H, t, J = 7.0 Hz), 0.99 (3H, dd, J = 7.0 Hz, J_{HF} = 0.9 Hz), 1.22 (1H, ddq, J = 14.0, 7.0, 7.0 Hz), 1.47 (1H, ddq, J = 14.0, 7.0, 7.0 Hz), 2.44 (1H, ddqd, J = 7.0, 7.0, 7.0 Hz, J_{HF} = 1.2 Hz), 6.78 (1H, ddd, J = 7.6, 7.6, 1.6 Hz), 6.85–7.00 (3H, m).

^{13}C NMR (126 MHz, $CDCl_3$) δ 12.1, 18.5, 28.5 (t, J_{CF} = 3 Hz), 36.4, 93.4 (dd, J_{CF} = 23, 13 Hz), 127.9, 128.0, 128.2, 131.2, 131.4, 131.5, 154.1 (dd, J_{CF} = 288, 288 Hz), 171.4.

^{19}F NMR (470 MHz, $C_6D_5CD_3$) δ_F 72.6 (1F, d, J_{FF} = 41 Hz), 76.8 (1F, d, J_{FF} = 41 Hz).

IR (neat) 2966, 2877, 2121, 1736, 1460, 1238, 1061, 993, 937, 762 cm^{-1}.

MS (20 eV) *m/z* (%) 221 (M^+; 46), 206 (69), 192 (100).

HRMS calcd for $C_{13}H_{13}NF_2$ 221.1016 (M^+); found 221.1000.

1,4-Dibutyl-3-fluoroisoquinoline (7a)

To a solution of **3a** (93 mg, 0.42 mmol) in Et_2O (3 ml) was added butyllithium (0.34 ml, 1.49 M in hexane, 0.50 mmol) at –78 °C under nitrogen. After the mixture had been stirred for 0.5 h at –78 °C, the reaction was quenched with phosphate buffer (pH 7). Organic materials were extracted with AcOEt three times. The combined extracts were washed with brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by PTLC on silica gel (hexane–AcOEt 5:1) to give **7a** (94 mg, 86%) as a pale yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.96 (3H, t, J = 7.6 Hz), 0.98 (3H, t, J = 7.6 Hz), 1.45 (2H, tq, J = 7.6, 7.6 Hz), 1.49 (2H, tq, J = 7.6, 7.6 Hz), 1.61–1.69 (2H, m), 1.80–1.87

(2H, m), 2.99 (2H, t, *J* = 7.6 Hz), 3.22 (2H, t, *J* = 7.9 Hz), 7.49 (1H, ddd, *J* = 8.3, 7.0, 1.0 Hz), 7.67 (1H, dd, *J* = 8.3, 7.0 Hz), 7.98 (1H, d, *J* = 8.3 Hz), 8.15 (1H, d, *J* = 8.3 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ 13.9, 14.0, 22.8, 22.9, 24.0, 31.8, 32.1, 34.5, 112.3 (d, J_{CF} = 30 Hz), 123.6 (d, J_{CF} = 7 Hz), 125.1 (d, J_{CF} = 2 Hz), 125.7 (d, J_{CF} = 2 Hz), 126.2, 130.1, 138.9 (d, J_{CF} = 6 Hz), 157.9 (d, J_{CF} = 230 Hz), 159.9 (d, J_{CF} = 16 Hz).

^{19}F NMR (471 MHz, $CDCl_3$) δ_F 78.9 (s).

IR (neat) 2960, 2930, 2875, 1620, 1595, 1560, 1505, 1460, 1350, 1115, 760 cm^{-1}.

MS (20 eV) *m/z* (%) 259 (M^+; 17), 217 (100), 174 (43).

Anal. Calcd for $C_{17}H_{22}NF$: C, 78.73; H, 8.55; N, 5.40. Found: C, 79.01; H, 8.66; N, 5.08.

1-Butyl-4-*sec*-butyl-3-fluoroisoquinoline (7b)

To a solution of **3b** (122 mg, 0.55 mmol) in Et_2O (5 ml) was added butyllithium (0.40 ml, 1.64 M in hexane, 0.66 mmol) at –78 °C over 10 min under nitrogen. After the mixture had been stirred for 7 h at –78 °C, the reaction was quenched with phosphate buffer (pH 7). Organic materials were extracted with AcOEt three times. The combined extracts were washed with brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by PTLC on silica gel (hexane–AcOEt 5:1) to give **7b** (117 mg, 82%) as a pale yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.86 (3H, t, *J* = 7.3 Hz), 0.98 (3H, t, *J* = 7.3 Hz), 1.44 (3H, dd, *J* = 7.0 Hz, J_{HF} = 1.2 Hz), 1.49 (2H, tq, *J* = 7.3, 7.3 Hz), 1.80–1.89 (3H, m), 1.94 (1H, ddq, *J* = 14.7, 7.3, 7.3 Hz), 3.23 (2H, t, *J* = 7.6 Hz), 3.45 (1H, ddq, *J* = 7.3, 7.3, 7.3 Hz), 7.49 (1H, dd, *J* = 7.6, 7.6 Hz), 7.66 (1H, dd, *J* = 7.6, 7.6 Hz), 8.14 (1H, d, *J* = 8.9 Hz), 8.17 (1H, d, *J* = 8.6 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ 12.8, 13.9, 19.3 (d, J_{CF} = 3 Hz), 22.9, 28.5 (d, J_{CF} = 4 Hz), 31.6, 32.8 (d, J_{CF} = 4 Hz), 34.5, 116.4 (d, J_{CF} = 26 Hz), 123.6 (d, J_{CF} = 6 Hz), 124.9

(d, J_{CF} = 2 Hz), 125.7, 126.2, 129.9, 139.0 (d, J_{CF} = 7 Hz), 158.1 (d, J_{CF} = 233 Hz), 159.8 (d, J_{CF} = 16 Hz).

^{19}F NMR (471 MHz, $C_6D_5CD_3$) δ_F 88.1 (s).

IR (neat) 2960, 2930, 2870, 1615, 1585, 1560, 1505, 1460, 1340, 1120, 790, 760 cm^{-1}.

MS (70 eV) *m/z* (%) 259 (M^+; 26), 217 (100), 188 (41).

Anal. Calcd for $C_{17}H_{22}NF$: C, 78.73; H, 8.55; N, 5.40. Found: C, 78.57; H, 8.62; N, 5.26.

4-Butyl-3-fluoro-1-methylisoquinoline (7c)

To a solution of **3a** (95 mg, 0.43 mmol) in toluene (3 ml) was added methyllithium (0.58 ml, 0.89 M in Et_2O, 0.52 mmol) at 0 °C under nitrogen. After the mixture had been stirred for 0.5 h at 0 °C, the reaction was quenched with phosphate buffer (pH 7). Organic materials were extracted with AcOEt three times. The combined extracts were washed with brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by PTLC on silica gel (benzene–hexane 1:1) to give **7c** (76 mg, 81%) as a pale yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.96 (3H, t, *J* = 7.5 Hz), 1.45 (2H, tq, *J* = 7.5, 7.5 Hz), 1.61–1.69 (2H, m), 2.91 (3H, s), 3.00 (2H, t, *J* = 7.5 Hz), 7.51 (1H, ddd, *J* = 8.3, 7.2, 0.9 Hz), 7.69 (1H, dd, *J* = 8.3, 7.2 Hz), 7.98 (1H, d, *J* = 8.3 Hz), 8.11 (1H, d, *J* = 8.3 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ 13.9, 21.8, 22.7, 23.9, 32.1, 112.5 (d, J_{CF} = 30 Hz), 123.5 (d, J_{CF} = 7 Hz), 125.2 (d, J_{CF} = 2 Hz), 126.3 (d, J_{CF} = 3 Hz), 126.5, 130.3, 138.6 (d, J_{CF} = 6 Hz), 155.9 (d, J_{CF} = 17 Hz), 157.7 (d, J_{CF} = 231 Hz).

^{19}F NMR (471 MHz, $CDCl_3$) δ_F 78.5 (s).

IR (neat) 2960, 2930, 2870, 1620, 1595, 1560, 1435, 1340, 1115, 760 cm^{-1}.

MS (20 eV) *m/z* (%) 217 (M^+; 24), 174 (100), 147 (22).

Anal. Calcd for $C_{14}H_{16}NF$: C, 77.39; H, 7.42; N, 6.45. Found: C, 77.41; H, 7.49; N, 6.44.

4-Butyl-1-*tert*-butyl-3-fluoroisoquinoline (7d)

To a solution of **3a** (91 mg, 0.41 mmol) in Et_2O (3 ml) was added *tert*-butyllithium (0.31 ml, 1.60 M in pentane, 0.50 mmol) at –78 °C under nitrogen. After the mixture had been stirred for 0.5 h at –78 °C, the reaction was quenched with phosphate buffer (pH 7). Organic materials were extracted with AcOEt three times. The combined extracts were washed with brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by PTLC on silica gel (hexane–AcOEt 20:1) to give **7d** (94 mg, 88%) as a pale yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.96 (3H, t, J = 7.3 Hz), 1.42-1.52 (2H, m), 1.62-1.69 (2H, m), 1.64 (9H, s), 3.00 (2H, dt, J = 7.8 Hz, J_{HF} = 1.0 Hz), 7.46 (1H, ddd, J = 8.5, 6.7, 1.1 Hz), 7.64 (1H, ddd, J = 8.5, 6.7, 1.1 Hz), 8.01 (1H, d, J = 8.5 Hz), 8.54 (1H, d, J = 8.5 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ 13.9, 22.7, 24.0, 31.1, 32.0, 39.4, 112.3 (d, J_{CF} = 31 Hz), 123.8 (d, J_{CF} = 2 Hz), 124.1 (d, J_{CF} = 7 Hz), 125.0 (d, J_{CF} = 3 Hz), 127.9, 129.1, 139.8 (d, J_{CF} = 6 Hz), 156.6 (d, J_{CF} = 228 Hz), 165.2 (d, J_{CF} = 14 Hz).

^{19}F NMR (471 MHz, $CDCl_3$) δ_F 79.5 (1F, s).

IR (neat) 2956, 2931, 1599, 1552, 1511, 1398, 1367, 1333, 1219, 980, 769, 683 cm^{-1}.

Anal. Calcd for $C_{17}H_{22}NF$: C, 78.73; H, 8.55; N, 5.40. Found: C, 78.64; H, 8.60; N, 5.23.

4-Butyl-3-fluoro-1-phenylisoquinoline (7e)

To a solution of **3a** (92 mg, 0.42 mmol) in toluene (3 ml) was added phenyllithium (0.49 ml, 1.01 M in chexane-Et_2O, 0.50 mmol) at –78 °C under nitrogen. After the mixture had been stirred for 1 h at –78 °C, the reaction was quenched with phosphate buffer (pH 7). Organic materials were extracted with AcOEt three times. The combined extracts were washed with brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by PTLC on silica gel (hexane– AcOEt 5:1) to give **7e** (99 mg, 85%) as a pale yellow liquid.

^{1}H NMR (500 MHz, CDCl$_3$) δ 0.99 (3H, t, *J* = 7.5 Hz), 1.50 (2H, tq, *J* = 7.5, 7.5 Hz), 1.72 (2H, tt, *J* = 7.5, 7.5 Hz), 3.07 (2H, t, *J* = 7.5 Hz), 7.43 (1H, dd, *J* = 7.6, 7.6 Hz), 7.45–7.54 (3H, m), 7.64–7.72 (3H, m), 8.04 (1H, d, *J* = 8.6 Hz), 8.13 (1H, d, *J* = 8.2 Hz).

^{13}C NMR (126 MHz, CDCl$_3$) δ 13.9, 22.8, 24.2, 32.1, 113.9 (d, J_{CF} = 30 Hz), 123.3 (d, J_{CF} = 7 Hz), 125.4 (d, J_{CF} = 2 Hz), 125.4 (d, J_{CF} = 3 Hz), 128.4, 128.5, 128.8, 130.1, 130.3, 138.4, 139.5 (d, J_{CF} = 6 Hz), 157.7 (d, J_{CF} = 14 Hz), 157.9 (d, J_{CF} = 231 Hz).

^{19}F NMR (471 MHz, CDCl$_3$) δ_F 79.6 (s).

IR (neat) 2950, 2930, 2870, 1615, 1590, 1545, 1440, 1390, 1335, 1145, 700 cm^{-1}.

MS (70 eV) *m/z* (%) 279 (M$^+$; 39), 236 (100), 179 (24), 84(97).

Anal. Calcd for $C_{19}H_{18}NF$: C, 81.69; H, 6.49; N, 5.01. Found: C, 81.71; H, 6.78; N, 4.77.

4-Butyl-3-fluoroisoquinoline (7f)

To a solution of **3a** (102 mg, 0.46 mmol) in toluene (3 ml) was added DIBAL (0.32 ml, 1.50 M in toluene, 0.49 mmol) at –45 °C over 10 min under nitrogen. After the mixture was warmed to 90 °C and stirred for 7 h, the reaction was quenched with phosphate buffer (pH 7). Organic materials were extracted with AcOEt three times. The combined extracts were washed with brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by PTLC on silica gel (hexane–AcOEt 5:1) to give **7f** (78 mg, 84%) as a pale yellow liquid.

^{1}H NMR (500 MHz, CDCl$_3$) δ 0.97 (3H, t, *J* = 7.5 Hz), 1.46 (2H, tq, *J* = 7.5, 7.5 Hz), 1.63–1.71 (2H, m), 3.03 (2H, td, *J* = 7.5 Hz, J_{HF} = 0.9 Hz), 7.52 (1H, ddd, *J* = 7.9, 7.9, 0.8 Hz), 7.71 (1H, dd, *J* = 7.9, 7.9 Hz), 7.97 (1H, d, *J* = 7.9 Hz), 7.99 (1H, d, *J* = 7.9 Hz), 8.80 (1H, s).

^{13}C NMR (126 MHz, $CDCl_3$) δ 13.9, 22.8, 24.1, 32.1, 115.0 (d, J_{CF} = 30 Hz), 122.9 (d, J_{CF} = 7 Hz), 125.6 (d, J_{CF} = 2 Hz), 127.6 (d, J_{CF} = 2 Hz), 128.4, 130.7, 138.4 (d, J_{CF} = 6 Hz), 148.6 (d, J_{CF} = 16 Hz), 159.1 (d, J_{CF} = 232 Hz).

^{19}F NMR (471 MHz, $CDCl_3$) δ_F 79.3 (s).

IR (neat) 2960, 2930, 2870, 1620, 1590, 1440, 1425, 1250, 1220, 750 cm^{-1}.

MS (20 eV) *m/z* (%) 203 (M^+; 67), 160 (100).

Anal. Calcd for $C_{13}H_{14}NF$: C, 76.82; H, 6.94; N, 6.89. Found: C, 76.54; H, 6.95; N, 6.76.

2,4-Dibutyl-3-fluoroquinoline (8a)

To a solution of **6a** (63 mg, 0.29 mmol) in toluene (2 ml) was added butylmagnesium bromide (0.31 ml, 1.12 M in THF, 0.34 mmol) at room temperature under nitrogen. After being stirred for 15 min, the reaction mixture was cooled to 0 °C and added toluene (3 ml) and HMPA (1 ml). After being stirred for 1 h, the reaction mixture was warmed to room temperature and stirred for an additional 1 h. Phosphate buffer (pH 7) was added to quench the reaction. Organic materials were extracted with AcOEt three times. The combined extracts were washed with brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography on silica gel (hexane–AcOEt 10:1) to give **8a** (51 mg, 69%) as a pale yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.97 (3H, t, *J* = 7.5 Hz), 0.97 (3H, t, *J* = 7.5 Hz), 1.41–1.51 (4H, m), 1.63–1.71 (2H, m), 1.75–1.81 (2H, m), 3.01 (2H, td, *J* = 7.6 Hz, J_{HF} = 2.4 Hz), 3.06 (2H, td, *J* = 7.6 Hz, J_{HF} = 1.7 Hz), 7.51 (1H, dd, *J* = 7.9, 7.9 Hz), 7.61 (1H, ddd, *J* = 7.9, 7.9, 0.8 Hz), 7.91 (1H, dd, *J* = 7.9, 0.8 Hz), 8.04 (1H, dd, *J* = 7.9, 0.8 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ 13.9, 14.0, 22.8, 22.8, 24.0 (d, J_{CF} = 4 Hz), 30.9, 31.9, 33.1, 123.4 (d, J_{CF} = 5 Hz), 126.1, 127.4 (d, J_{CF} = 3 Hz), 127.7 (d, J_{CF} = 2 Hz), 129.5, 130.9 (d, J_{CF} = 15 Hz), 144.8 (d, J_{CF} = 3 Hz), 153.3 (d, J_{CF} = 253 Hz), 153.4 (d, J_{CF} = 21 Hz).

^{19}F NMR (471 MHz, $CDCl_3$) δ_F 29.8 (s).

IR (neat) 2958, 2931, 2873, 1506, 1460, 1417, 1387, 1228, 1142, 760 cm^{-1}.

MS (20 eV) *m/z* (%) 259 (M^+; 8), 217 (25), 129 (60).

HRMS calcd for $C_{17}H_{22}NF$ 259.1736 (M^+); found 259.1718.

2-Butyl-4-*sec*-butyl-3-fluoroquinoline (8b)

Compound **8b** was prepared by the method described for **8a** using **6b** (115 mg, 0.52 mmol) and butylmagnesium bromide (0.55 ml, 1.12 M in THF, 0.62 mmol). Purification by PTLC on silica gel (hexane–AcOEt 50:1) gave **8b** (81 mg, 60%) as a pale yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87 (3H, t, *J* = 7.4 Hz), 0.97 (3H, t, *J* = 7.4 Hz), 1.46 (3H, d, *J* = 7.2 Hz), 1.47 (2H, tq, *J* = 7.4, 7.4 Hz), 1.76–2.04 (4H, m), 3.01 (2H, dt, *J* = 7.9, 2.6 Hz), 3.53 (1H, ddq, *J* = 7.2, 7.2, 7.2 Hz), 7.49 (1H, dd, *J* = 7.8, 7.8 Hz), 7.61 (1H, ddd, *J* = 7.8, 7.8, 0.9 Hz), 8.05 (1H, d, *J* = 7.8 Hz), 8.07 (1H, d, *J* = 7.8 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ 12.8, 14.0, 19.2 (d, J_{CF} = 4 Hz), 22.8, 28.5 (d, J_{CF} = 4 Hz), 30.9, 33.0, 33.7, 123.4, 126.0, 127.5 (d, J_{CF} = 5 Hz), 127.6 (d, J_{CF} = 2 Hz), 129.7, 134.7 (d, J_{CF} = 10 Hz), 145.0 (d, J_{CF} = 4 Hz), 154.0 (d, J_{CF} = 254 Hz), 154.1 (d, J_{CF} = 22 Hz).

^{19}F NMR (471 MHz, $CDCl_3$) δ_F 34.2 (br s).

IR (neat) 2962, 2873, 1605, 1504, 1460, 1412, 1383, 1144, 1111, 758 cm^{-1}.

MS (20 eV) *m/z* (%) 259 (M^+; 26), 244 (49), 217 (100).

HRMS calcd for $C_{17}H_{22}NF$ 259.1736 (M^+); found 259.1735.

4-Butyl-2-ethyl-3-fluoroquinoline (8c)

Compound **8c** was prepared by the method described for **8a** using **6a** (96 mg, 0.43

mmol) and ethylmagnesium bromide (0.48 ml, 1.08 M in THF, 0.52 mmol). Purification by PTLC on silica gel (hexane–AcOEt 5:1) gave **8c** (59 mg, 59%) as a pale yellow liquid.

^{1}H NMR (500 MHz, CDCl$_3$) δ 0.97 (3H, t, *J* = 7.4 Hz), 1.38 (3H, t, *J* = 7.6 Hz), 1.46 (2H, tq, *J* = 7.4, 7.4 Hz), 1.64–1.71 (2H, m), 3.02–3.08 (4H, m), 7.51 (1H, dd, *J* = 7.6, 7.6 Hz), 7.61 (1H, ddd, *J* = 8.2, 7.6, 1.2 Hz), 7.91 (1H, d, *J* = 7.6 Hz), 8.04 (1H, d, *J* = 8.2 Hz).

^{13}C NMR (126 MHz, CDCl$_3$) δ 12.6, 13.8, 22.8, 23.9 (d, J_{CF} = 3 Hz), 26.6, 31.8, 123.3 (d, J_{CF} = 5 Hz), 126.1, 127.4 (d, J_{CF} = 3 Hz), 127.7 (d, J_{CF} = 2 Hz), 129.5, 130.9 (d, J_{CF} = 13 Hz), 144.8 (d, J_{CF} = 3 Hz), 153.2 (d, J_{CF} = 253 Hz), 154.2 (d, J_{CF} = 27 Hz).

^{19}F NMR (471 MHz, CDCl$_3$) δ_F 29.3 (s).

IR (neat) 2960, 2933, 1506, 1458, 1410, 1389, 1315, 1228, 1142, 760 cm^{-1}.

MS (20 eV) *m/z* (%) 231 (M+; 100), 230 (77).

HRMS calcd for $C_{15}H_{18}NF$ 231.1423 (M$^+$); found 231.1415.

4-Butyl-3-fluoro-2-isopropylquinoline (8d)

Compound **8d** was prepared by the method described for **8a** using **6a** (90 mg, 0.41 mmol) and isopropylmagnesium chloride (0.25 ml, 1.92 M in THF, 0.49 mmol). Purification by PTLC on silica gel (hexane–AcOEt 50:1) gave **8d** (64 mg, 64%) as a pale yellow liquid.

^{1}H NMR (500 MHz, CDCl$_3$) δ 0.97 (3H, t, *J* = 7.3 Hz), 1.41 (6H, d, *J* = 6.9 Hz), 1.43–1.50 (2H, m), 1.62–1.70 (2H, m), 3.05 (2H, td, *J* = 7.8 Hz, J_{HF} = 1.8 Hz), 3.52 (1H, (sept)d, *J* = 6.9 Hz, J_{HF} = 1.5 Hz), 7.50 (1H, dd, *J* = 8.1, 7.3 Hz), 7.60 (1H, ddd, *J* = 8.4, 7.3, 1.2 Hz), 7.90 (1H, d, *J* = 8.1 Hz), 8.05 (1H, d, *J* = 8.4 Hz).

^{13}C NMR (126 MHz, CDCl$_3$) δ 13.9, 20.9 (d, J_{CF} = 2 Hz), 22.8, 24.0 (d, J_{CF} = 4 Hz), 31.1, 31.9, 123.3 (d, J_{CF} = 6 Hz), 126.1, 127.3 (d, J_{CF} = 3 Hz), 127.5 (d, J_{CF} = 2 Hz), 129.8, 130.8 (d, J_{CF} = 13 Hz), 144.8 (d, J_{CF} = 3 Hz), 153.0 (d, J_{CF} = 253 Hz), 157.3 (d,

J_{CF} = 19 Hz).

^{19}F NMR (471 MHz, CDCl$_3$) δ_F 28.8 (s).

IR (neat) 3068, 2962, 2873, 1736, 1612, 1506, 1458, 1313, 1142, 760 cm^{-1}.

MS (20 eV) *m/z* (%) 245 (M$^+$; 35), 230 (100), 187 (49).

HRMS calcd for $C_{16}H_{20}NF$ 245.1580 (M$^+$); found 245.1576.

4-Butyl-2-*tert*-butyl-3-fluoroquinoline (8e)

To a solution of **6a** (89 mg, 0.40 mmol) in toluene (4 ml) was added *tert*-butyllithium (0.302 ml, 1.60 M in pentane, 0.48 mmol) at –78 °C under a nitrogen atmosphere. After being stirred for 1 h, the reaction mixture was warmed to room temperature and stirred for an additional 1 h. Phosphate buffer (pH 7) was added to quench the reaction. Organic materials were extracted with AcOEt three times. The combined extracts were washed with brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by PTLC on silica gel (hexane–AcOEt 5:1) to give **8e** (81 mg, 78%) as a pale yellow liquid.

^{1}H NMR (500 MHz, CDCl$_3$) δ 0.96 (3H, t, *J* = 7.8 Hz), 1.43–1.49 (2H, m), 1.51 (9H, s), 1.62–1.71 (2H, m), 3.05 (2H, dt, *J* = 7.8 Hz, J_{HF} = 2.1 Hz), 7.49 (1H, dd, *J* = 7.9, 7.2 Hz), 7.59 (1H, ddd, *J* = 8.4, 7.2, 1.2 Hz), 7.88 (1H, d, *J* = 7.9 Hz), 8.04 (1H, d, *J* = 8.4 Hz).

^{13}C NMR (126 MHz, CDCl$_3$) δ 13.9, 22.8, 23.9 (d, J_{CF} = 5 Hz), 28.7 (d, J_{CF} = 4 Hz), 31.9, 38.0 (d, J_{CF} = 5 Hz), 123.0 (d, J_{CF} = 5 Hz), 126.2, 127.4 (d, J_{CF} = 2 Hz), 127.5 (d, J_{CF} = 3 Hz), 130.2, 131.5 (d, J_{CF} = 16 Hz), 144.0 (d, J_{CF} = 3 Hz), 154.1 (d, J_{CF} = 258 Hz), 158.2 (d, J_{CF} = 17 Hz).

^{19}F NMR (471 MHz, CDCl$_3$) δ_F 36.9 (s).

IR (neat) 2958, 2873, 1608, 1402, 1383, 1365, 1275, 1211, 1142, 758 cm^{-1}.

MS (20 eV) *m/z* (%) 259 (M$^+$; 12), 201 (100).

HRMS calcd for $C_{17}H_{22}NF$ 259.1736 (M$^+$); found 259.1712.

4-Butyl-3-fluoro-2-(triethylgermyl)quinoline (8f)

To a solution of triethylgermane (0.10 ml, 0.62 mmol) and TMEDA (0.12 ml, 0.62 mmol) in THF (1 ml) was added *tert*-butyllithium (0.47 ml, 1.64 M in pentane, 0.62 mmol) at 0 °C under a nitrogen atmosphere. After the reaction mixture had been stirred for 15 min, **6a** (114 mg, 0.51 mmol) in toluene (2 ml) was added at –78 °C. After being stirred for 1 h, the reaction mixture was warmed to room temperature and stirred for an additional 4 h. Phosphate buffer (pH 7) was added to quench the reaction. Organic materials were extracted with AcOEt three times. The combined extracts were washed with brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by PTLC on silica gel (hexane–AcOEt 10:1) to give **8f** (114 mg, 61%) as a pale yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.96 (3H, t, J = 7.5 Hz), 1.10–1.24 (15H, m), 1.41–1.51 (2H, m), 1.63–1.71 (2H, m), 3.04 (2H, td, J = 7.9 Hz, J_{HF} = 1.6 Hz), 7.52 (1H, dd, J = 8.1, 7.2 Hz), 7.60 (1H, ddd, J = 8.1, 7.2, 1.2 Hz), 7.94 (1H, dd, J = 8.1, 1.2 Hz), 8.13 (1H, dd, J = 8.1, 0.9 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ 4.7 (d, J_{CF} = 2 Hz), 9.1, 13.9, 22.8, 23.8 (d, J_{CF} = 3 Hz), 31.9, 123.4 (d, J_{CF} = 6 Hz), 126.5, 127.1 (d, J_{CF} = 2 Hz), 127.6 (d, J_{CF} = 4 Hz), 127.9 (d, J_{CF} = 17 Hz), 130.7, 146.6, 158.8 (d, J_{CF} = 244 Hz), 161.2 (d, J_{CF} = 43 Hz).

^{19}F NMR (470 MHz, $CDCl_3$) δ_F 39.1 (s).

IR (neat) 2956, 2872, 1600, 1460, 1317, 1138, 1020, 960, 758, 607 cm^{-1}.

MS (20 eV) *m/z* (%) 363 (M^+; 3), 335 (100), 333 (97), 278 (90), 276 (88), 231 (68), 184 (50).

HRMS calcd for $C_{19}H_{28}NFGe$ 363.1418 (M^+); found 363.1411.