Rh(I)-catalyzed Coupling Cyclization of *N*-Aryl Trifluoroacetimidoyl Chlorides with Alkynes: One-pot Synthesis of Fluorinated Quinolines

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General. ^{1}H and ^{19}F NMR spectra were recorded at 200 and 188 MHz (or 500 and 470 MHz) respectively, using $CDCl_3$ as a solvent. The chemical shifts are reported in δ (ppm) values relative to TMS (δ 0 ppm for ^{1}H NMR) and C_6F_6 (δ 0 ppm for ^{19}F NMR). Coupling constants are reported in hertz (Hz).

All air and/or water sensitive reactions were carried out under nitrogen atmosphere with dry, freshly distilled solvents using standard syringe-cannula/septa techniques. Toluene and xylene were distilled from CaH_2. All other reagents and solvents were employed without further

purification.

Typical procedure for the syntheses of 2-fluoroalkyl quinolines: **3,4-Dipropyl-6-methoxy-2-trifluoromethylquinoline (3a).** A toluene solution (1.0 mL) of [Rh_2 $(cod)_2Cl_2$] (6.0 mg, 13 μmol), dppe (9.9 mg, 25 μmol), **1a** (119 mg, 0.50 mmol), 4-octyne (0.22 mL, 1.5 mmol) and Et_3N (0.14 mL, 1.0 mmol) under a nitrogen atmosphere was heated at 110 °C for 24 h. The cooled reaction mixture was filtered through a pad of silica gel and the filtrate was purified by silica gel column chromatography (hexane:Et_2O = 10:1) to afford **3a** (112.0 mg, 72%) as a colorless solid: Mp. 92.0 ^oC; IR (KBr) 2972, 1624 cm^{-1}; ^1H NMR δ 8.00 (d, *J* = 9.0, 1 H), 7.37 (dd, *J* = 9.0, 3.0, 1 H), 7.21 (d, *J* = 3.0, 1 H), 3.97 (s, 3 H), 3.06-3.03 (m, 2 H), 2.88-2.84 (m, 2 H), 1.75-1.67 (m, 2 H), 1.64-1.57 (m, 2 H), 1.14 (t, *J* = 7.5, 3 H), 1.10 (t, *J* = 7.5, 3 H); ^{19}F NMR (470 MHz, $CDCl_3$) δ 98.5 (s, 3 F); MS *m/z* 311 (M^+, 100), 282 (75). Anal. Calcd for $C_{17}H_{20}F_3NO$: C, 65.58; H, 6.47; N, 4.50. Found: C, 65.52; H, 6.53; N, 4.90.

3,4-Dipropyl-6-methyl-2-trifluoromethylquinoline (3b). Colorless solid; Mp. 64.0 ^oC; IR (KBr) 2972, 1626 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 8.04 (d, *J* = 8.7, 1 H), 7.75 (s, 1 H), 7.54 (d, *J* = 8.7, 1 H), 3.13-3.02 (m, 2 H), 2.93-2.80 (m, 2 H), 2.58 (s, 3H), 1.75-1.50 (m, 4 H), 1.20-1.05 (m, 6 H) ; ^{19}F NMR (188 MHz, $CDCl_3$) δ 98.3 (s, 3 F); MS *m/z* 295 (M^+, 48),

266 (100). Anal. Calcd for $C_{17}H_{20}F_3NO$: C, 69.13; H, 6.83; N, 4.74. Found: C, 69.27; H, 6.92; N, 4.85.

3,4-Dipropyl-2-trifluoromethylquinoline (3c). Pale yellow oil; IR (neat) 2972, 1646 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.15 (d, *J* = 7.9, 1 H), 8.03 (d, *J* = 7.9, 1 H), 7.76-7.58 (m, 3 H), 3.18-3.05 (m, 2 H), 2.95-2.88 (m, 2 H), 1.78-1.55 (m, 4 H), 1.18-1.07 (m, 6 H) ; ^{19}F NMR (188 MHz, $CDCl_3$) δ 98.1 (s, 3 F); MS m/z 281 (M^+, 49), 252 (100). Anal. Calcd for $C_{16}H_{18}F_3N$: C, 68.31; H, 6.45; N, 4.98. Found: C, 67.94; H, 6.61; N, 5.27.

2-Difluoromethyl-3,4-dipropyl-6-methoxyquinoline (3e). (The reaction was carried out at 160 ^oC in mesitylene. Na_2CO_3 was used instead of Et_3N.); Colorless solid; Mp. 65.0 ^oC; IR (KBr) 2964, 1624 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.98 (d, *J* = 9.2, 1 H), 7.34 (dd, *J* = 9.2, 2.8, 1 H), 7.21 (d, *J* = 2.8, 1 H), 6.84 (t, $^2J_{HF}$ = 55.0, 1 H), 3.96 (s, 3 H), 3.07-2.87 (m, 4 H), 1.80-1.52 (m, 4 H), 1.21-1.05 (m, 6 H); ^{19}F NMR (188 MHz, $CDCl_3$) δ 50.6 (d, $^2J_{HF}$ = 55.0, 2 F); MS *m/z* 293 (M^+, 100), 264 (84), 244 (43). Anal. Calcd for $C_{17}H_{21}F_2NO$: C, 69.60; H, 7.22; N, 4.77. Found: C, 69.52; H, 7.31; N, 4.77.

3,4-Dipropyl-2-heptafluoropropyl-6-methoxy-quinoline (3f). (The reaction was carried out at 160 ^oC in mesitylene.); Colorless solid; Mp. 66.0^oC; IR (KBr) 2980, 1624 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.01 (d, *J* = 9.2, 1 H), 7.36 (dd, *J* = 9.2, 2.6, 1 H), 7.20 (d, *J* = 2.6, 1 H), 3.96 (s, 3

H), 3.06-2.98 (m, 2 H), 2.90-2.79 (m, 2 H), 1.80-1.50 (m, 4 H), 1.20-1.05 (m, 6 H); ^{19}F NMR (188 MHz, $CDCl_3$) δ 83.0 (t, *J* = 9.5, 3 F), 56.7-56.4 (m, 2 F), 38.7-38.5 (m, 2 F); MS *m/z* 411 (M^+, 88), 382 (100). Anal. Calcd for $C_{19}H_{20}F_7NO$: C, 55.48; H, 4.90; N, 3.40. Found: C, 55.14; H, 5.10; N, 3.46.

3,4-Diethyl-6-methoxy-2-trifluoromethylquinoline (3g). (The reaction was carried out in a sealed glass tube at 140 ^{o}C.); Colorless solid; Mp. 88.5 ^{o}C; IR (KBr) 2984, 1624 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.06 (d, *J* = 9.2, 1 H), 7.38 (dd, *J* = 9.2, 2.8, 1 H), 7.24 (d, *J* = 2.8, 1 H), 3.98 (s, 3 H), 3.15 (q, *J* = 7.7, 2 H), 2.96 (q, *J* = 7.3, 2 H), 1.35 (t, *J* = 7.7, 3 H), 1.28 (t, *J* = 7.3, 3 H); ^{19}F NMR (188 MHz, $CDCl_3$) δ 98.5 (s, 3 F); MS *m/z* 283 (M^+, 100), 268 (47). Anal. Calcd for $C_{15}H_{16}F_3NO$: C, 63.60; H, 5.69; N, 4.94. Found: C, 63.44; H, 5.49; N, 5.11.

3,4-Dimethoxymethyl-6-methoxy-2-trifluoromethylquinoline (3h). Colorless solid; Mp. 86.0 ^{o}C; IR (KBr) 2932, 1626 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.09 (d, *J* = 9.2, 1 H), 7.50 (d, *J* = 2.6, 1 H), 7.45 (dd, *J* = 9.2, 2.6, 1 H), 5.00 (s, 2 H), 4.77 (s, 2 H), 3.99 (s, 3 H), 3.49 (s, 3 H), 3.48 (s, 3 H) ; ^{19}F NMR (188 MHz, $CDCl_3$) δ 99.8 (s, 3 F); MS *m/z* 315 (M^+, 10), 283 (87), 268 (100), 240 (38). Anal. Calcd for $C_{15}H_{16}F_3NO_3$: C, 57.14; H, 5.11; N, 4.44. Found: C, 56.97; H, 4.97; N, 4.37.

6-Methoxy-3-methyl-4-phenyl-2-trifluoromethylquinoline (3k).

Colorless solid; Mp. 92.0 ^{o}C; IR (KBr) 1624 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, *J* = 9.5, 1 H), 7.53-7.49 (m, 3 H), 7.36 (dd, *J* = 7.5, 3.0, 1 H), 7.26-7.24 (m, 2 H), 6.59 (d, *J* = 3.0, 1 H), 3.69 (s, 3 H), 2.31 (q, J_{HF} = 6.5, 3 H) ; ^{19}F NMR (470 MHz, $CDCl_3$) δ 96.8 (s, 3 F); MS *m/z* 317 (M^+, 100). Anal. Calcd for $C_{18}H_{14}F_3NO$: C, 68.13; H, 4.45; N, 4.41. Found: C, 67.78; H, 4.64; N, 4.64.

6-Methoxy-4-methyl-3-phenyl-2-trifluoromethylquinoline (4k). Colorless solid; Mp. 202 ^{o}C; IR (KBr) 1624 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (d, *J* = 9.0, 1 H), 7.50-7.44 (m, 4 H), 7.28-7.22 (m, 3 H), 3.99 (s, 3 H), 2.36 (s, 3 H) ; ^{19}F NMR (470 MHz, $CDCl_3$) δ 100.0 (s, 3 F); MS *m/z* 317 (M^+, 100). Anal. Calcd for $C_{18}H_{14}F_3NO$: C, 68.13; H, 4.45; N, 4.41. Found: C, 68.15; H, 4.64; N, 4.37.

Ethyl 6-Methoxy-4-phenyl-2-trifluoromethylquinoline-3-carboxylate (4l). (Ethyl phenylpropiolate (4.5 eq) was used, and Na_2CO_3 was used as a base instead of Et_3N.); Colorless solid; Mp. 151 ^{o}C; IR (KBr) 1734, 1622 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.17 (d, *J* = 9.2, 1 H), 7.56-7.32 (m, 6 H), 6.84 (d, *J* = 2.7, 1 H), 4.07 (q, *J* = 7.0, 2 H), 3.74 (s, 3 H), 1.01 (t, *J* = 7.0, 3 H); ^{19}F NMR (188 MHz, $CDCl_3$) δ 97.7 (s, 3 F); MS *m/z* 375 (M^+, 100), 330 (68). Anal. Calcd for $C_{20}H_{16}F_3NO_3$: C, 64.00; H, 4.30; N, 3.73. Found: C, 64.04; H, 4.53; N, 3.57.

3,4-Diphenyl-6-methoxy-2-trifluoromethylquinoline (3i). Colorless solid; Mp. 186 ^{o}C; IR (KBr) 1622 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.20 (d, *J* = 9.4, 1 H), 7.46 (dd, *J* = 9.4, 2.9, 1 H), 7.3-7.0 (m, 10 H), 6.76 (d, *J* = 2.9, 4 H), 3.71 (s, 3 H); ^{19}F NMR (188 MHz, $CDCl_3$) δ 100.4 (s, 3 F); MS *m/z* 379 (M^+, 100). Anal. Calcd for $C_{23}H_{16}F_3NO$: C, 72.82; H, 4.25; N, 3.69. Found: C, 72.46; H, 4.42; N, 4.09.

Dimethyl 6-Methoxy-2-trifluoromethylquinoline-3,4-dicarboxylate (3j). (The reaction was carried out at 140 ^{o}C in *o*-xylene for 36 h, dimethyl acetylenedicarboxylate was added 1.5 eq every 12 h (total 4.5 eq). In addition, $[RhCl(cod)]_2$ was used 10 mol%, DPPE was 20 mol%.); Colorless solid; Mp. 155 ^{o}C; IR (KBr) 2956, 1736, 1624 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.15 (d, *J* = 9.7, 1 H), 7.55 (dd, *J* = 9.7, 2.7, 1 H), 7.42 (d, *J* = 2.7, 1 H), 4.03 (s, 3 H), 3.98 (s, 3 H), 3.97 (s, 3 H); ^{19}F NMR (188 MHz, $CDCl_3$) δ 97.8 (s, 3 F); MS *m/z* 343 (M^+, 67), 312 (100). Anal. Calcd for $C_{15}H_{12}F_3NO_5$: C, 52.49; H, 3.52; N, 4.08. Found: C, 52.31; H, 3.36; N, 4.01.

4-Hexyl-6-methoxy-2-trifluoromethylquinoline (3m). Colorless solid; Mp. 71.0 ^{o}C; IR (KBr) 2940, 1626 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (d, *J* = 9.5, 1 H), 7.52 (s, 1 H), 7.44 (dd, *J* = 9.5, 2.5, 1 H), 7.27 (d, *J* = 2.5, 1 H), 3.98 (s, 3 H), 3.07 (t, *J* = 8.0, 2 H), 1.79 (quintet, *J* = 8.0, 2 H),

1.50-1.30 (m, 6 H); ^{19}F NMR (470 MHz, $CDCl_3$) δ 94.5 (s, 3 F); MS *m/z* 311 (M^+, 100), 241 (95), 240 (70). Anal. Calcd for $C_{17}H_{20}F_3NO$: C, 65.58; H, 6.47; N, 4.50. Found: C, 65.77; H, 6.73; N, 4.51.

6-Methoxy-2-trifluoromethyl-4-trimethylsilylquinoline (3n). (The reaction was carried out at 140 ^oC in a sealed tube, and Na_2CO_3 was used instead of Et_3N.); Pale yellow solid; Mp. 65.0 ^oC; IR (KBr) 1624 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.14 (d, *J* = 9.2, 1 H), 7.78 (s, 1 H), 7.45 (dd, *J* = 9.2, 2.6, 6 H), 7.36 (d, *J* = 2.6, 1 H), 3.96 (s, 3 H), 0.53 (s, 9 H); ^{19}F NMR (188 MHz, $CDCl_3$) δ 94.6 (s, 3 F); MS *m/z* 299 (M^+, 67), 284 (100). Anal. Calcd for $C_{14}H_{16}F_3NOSi$: C, 56.17; H, 5.39; N, 4.68. Found: C, 56.39; H, 5.22; N, 4.77.

4-(Dimethylphenylsilyl)methyl-6-methoxy-2-trifluoromethyl -quinoline (3o). (Na_2CO_3 was used as a base.); Colorless solid; Mp. 90.0 ^oC; IR (KBr) 2948, 1624 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.05 (d, *J* = 9.2, 1 H), 7.42-7.28 (m, 6 H), 7.20 (s, 1 H), 6.94 (d, *J* = 2.8, 1 H), 3.72 (s, 3 H), 2.81 (s, 2 H), 0.30 (s, 6 H); ^{19}F NMR (188 MHz, $CDCl_3$) δ 94.3 (s, 3 F); MS *m/z* 375 (M^+, 2), 356 (2), 280 (2), 221 (100), 135 (47). Anal. Calcd for $C_{20}H_{20}F_3NOSi$: C, 63.98; H, 5.37; N, 3.73. Found: C, 64.14; H, 5.49; N, 3.87.

4-{(2-(*tert*-Butyldimethylsiloxy)ethyl}-6-methoxy-2-trifluoromethylquinoline (3p). (Na_2CO_3 was used, and the reaction time

was 48 h.); Pale yellow liquid; IR (neat) 2960, 1626 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.12 (d, *J* = 9.4, 1 H), 7.60 (s, 1 H), 7.45 (dd, *J* = 9.4, 2.7, 1 H), 7.29 (d, *J* = 2.7, 1 H), 4.01 (t, *J* = 6.4, 2 H), 3.30 (t, *J* = 6.4, 2 H), 0.81 (s, 9 H), -0.08 (s, 6 H); ^{19}F NMR (188 MHz, $CDCl_3$) δ 94.5 (s, 3 F); MS *m/z* 328 (M^+, 100). Anal. Calcd for $C_{19}H_{26}F_3NOSi$: C, 59.20; H, 6.80; N, 3.63. Found: C, 58.99; H, 6.78; N, 4.02.

6-Methoxy-4-phenyl-2-trifluoromethylquinoline (3q). (*tert*-Butylcatecohol (TBC) was added (10^{-4} M in toluene), and phenylacetylene was used 6.0 eq.); Colorless solid; Mp. 72 ^{o}C; IR (KBr) 1624 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.19 (d, *J* = 9.3, 1 H), 7.62 (s, 1 H), 7.60-7.52 (m, 5 H), 7.47 (dd, *J* = 9.3, 2.9, 1 H), 7.22 (d, *J* = 2.9, 1 H), 3.81 (s, 3 H); ^{19}F NMR (188 MHz, $CDCl_3$) δ 94.6 (s, 3 F); MS *m/z* 303 (M^+, 100). Anal. Calcd for $C_{17}H_{12}F_3NO$: C, 67.33; H, 3.99; N, 4.62. Found: C, 67.09; H, 3.80; N, 4.58.

4-(1,1-Diethoxymethyl) -6-methoxy-2-trifluoromethylquinoline (3r). (TBC was added (10^{-4} M in toluene), and propiolaldehyde diethyl acetal (6.0 eq) was used.); Pale yellow solid; Mp. 54.0 ^{o}C; IR (KBr) 2988, 1624 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.13 (d, *J* = 9.3, 1 H), 7.97 (s, 1 H), 7.61 (d, *J* = 2.8, 1 H), 7.45 (dd, *J* = 9.3, 2.8, 1 H), 6.02 (s, 1 H), 3.97 (s, 3 H), 3.70-3.50 (m, 4 H), 1.26 (t, *J* = 7.0, 6 H); ^{19}F NMR (188 MHz, $CDCl_3$)

δ 94.6 (s, 3 F); MS *m/z* 329 (M^+, 10), 284 (30), 256 (100). Anal. Calcd for $C_{16}H_{18}F_3NO_3$: C, 58.36; H, 5.51; N, 4.25. Found: C, 58.55; H, 5.87; N, 4.16.

Ethyl 6-Methoxy-2-trifluoromethylquinoline-4-carboxylate (3s). (Reaction was carried out at 140 ^oC in *o*-xylene for 36 h, alkyne (1.5 eq) was added every 12 hours (total 4.5 eq). In addition, 10 mol % of $[RhCl(cod)]_2$ (with 20 mol% of DPPE) was used.); Colorless solid; Mp. 106 ^oC; IR (KBr) 1726, 1624 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.31 (d, *J* = 2.7, 1 H), 8.26 (s, 1 H), 8.16 (d, *J* = 9.2, 1 H), 7.51 (dd, *J* = 9.2, 2.7, 1 H), 4.53 (q, *J* = 7.1, 2 H), 4.00 (s, 3 H), 1.50 (t, *J* = 7.1, 3 H); ^{19}F NMR (188 MHz, $CDCl_3$) δ 94.6 (s, 3 F); MS *m/z* 299 (M^+, 100), 271 (27), 254 (32), 227 (61). Anal. Calcd for $C_{14}H_{12}F_3NO_3$: C, 56.19; H, 4.04; N, 4.68. Found: C, 56.28; H, 4.19; N, 4.63.

Ethyl 6-Methoxy-2-trifluoromethylquinoline-3-carboxylate (4s). Colorless solid; Mp. 66.5 ^oC; IR (KBr) 1730, 1624 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.54 (s, 1 H), 8.13 (d, *J* = 9.2, 1 H), 7.52 (dd, *J* = 9.2, 2.8, 1 H), 7.17 (d, *J* = 2.8, 1 H), 4.46 (q, *J* = 7.1, 2 H), 3.97 (s, 3 H), 1.43 (t, *J* = 7.1, 3 H); ^{19}F NMR (188 MHz, $CDCl_3$) δ 98.2 (s, 3 F); MS *m/z* 299 (M^+, 88), 271 (33), 254 (100), 226 (56). Anal. Calcd for $C_{14}H_{12}F_3NO_3$: C, 56.19; H, 4.04; N, 4.68. Found: C, 56.11; H, 3.89; N, 4.72.