Regioflexibility in the Functionalization of Multiply Halogenated Quinolines

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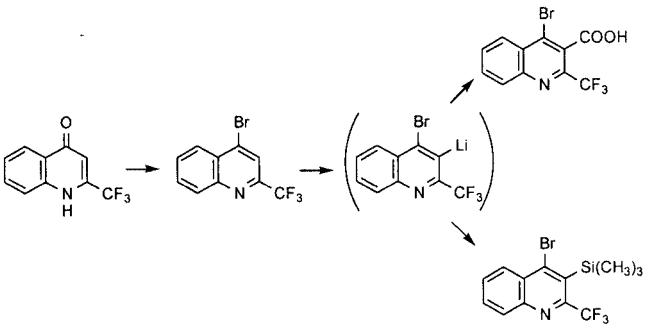
4-Bromo-6-fluoro-2-(trifluoromethyl)quinoline (**1**) and 4-bromo-7-fluoro-2-(trifluoromethyl)quinoline (**13**) were selected as model substrates to explore under what conditions regiochemically exhaustive functionalization reactions can be carried out. This goal was achieved by using trimethylsilyl entities and iodine atoms as the sole auxiliary substituents. The organolithium intermediates could be generated and the protective groups removed without impairing the bromine atom present at the 4-position.

Introduction

The metal-mediated, regiochemically exhaustive functionalization of bulk materials is a concept which, although new, has already passed an impressive series of benchmark tests.[1−5] The present case study goes beyond previous limits in so far as for the first time two fused rings, an aromatic and a heterocyclic one, are optionally subjected to site-specific functionalization.

4-Bromo-2-(trifluoromethyl)quinolines are readily accessible from the corresponding 4-quinolinones which in turn can be conveniently prepared by the condensation of anilines with ethyl 4,4,4-trifluoroacetoacetate and the subsequent cyclization of the resulting 3-anilino-2-butenoate ("anil").[6−8] Sequential treatment of 4-bromo-2-(trifluoromethyl)quinoline with lithium diisopropylamide (LIDA) and carbon dioxide or chlorotrimethylsilane provides the quinoline-3-carboxylic acid or the 3-quinolylsilane, respectively.



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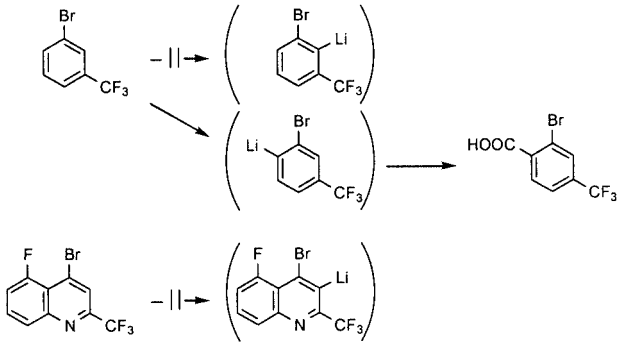
The smooth lithiation observed was by no means granted from the outset. The benzene-analogous 3-bromobenzotrifluoride is known to undergo metalation at the CF_3-remote 6-position and not at all at the 2-position flanked by both electronegative substituents.[9] Moreover, even when applied to quinolines, the hydrogen/metal permutation process appears to be quite sensitive to structural biases as one may deduce from the reluctance of 4-bromo-5-fluoro-2-(trifluoromethyl)quinoline to tolerate any deprotonation.[8]



In order to gain further insight, the two regioisomers **1** and **13** of just the latter quinoline were selected as model substrates for regioexhaustive derivatization. In either case each of the four vacant sites were targeted for the introduction of a carboxy unit, arguably the most typical functional group. A major challenge was not to lose the bromine substituent before delivering it into the final products. Under these circumstances only a restricted choice of organometallic methods rather than the entire "2 × 3 toolbox"[1] qualified for this task. In fact, complete regiocontrol was achieved throughout relying on merely two stratagems, steric shielding by trimethylsilyl groups and deprotonation-triggered iodine migration.

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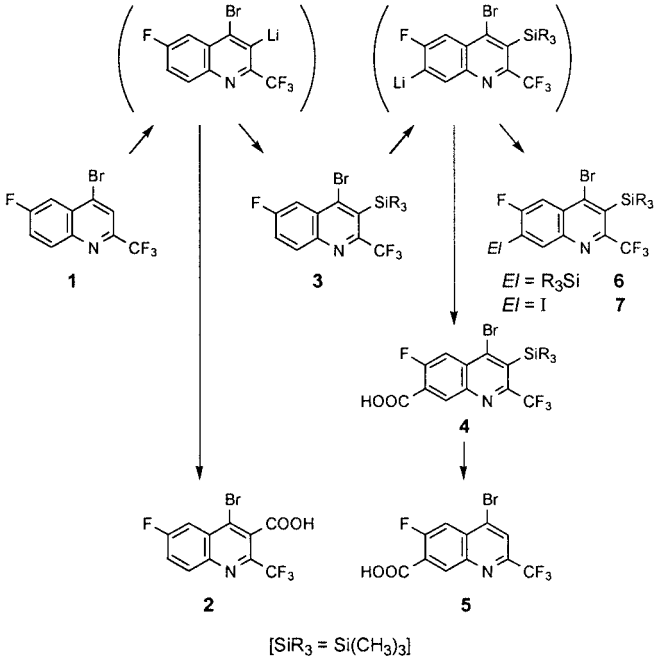
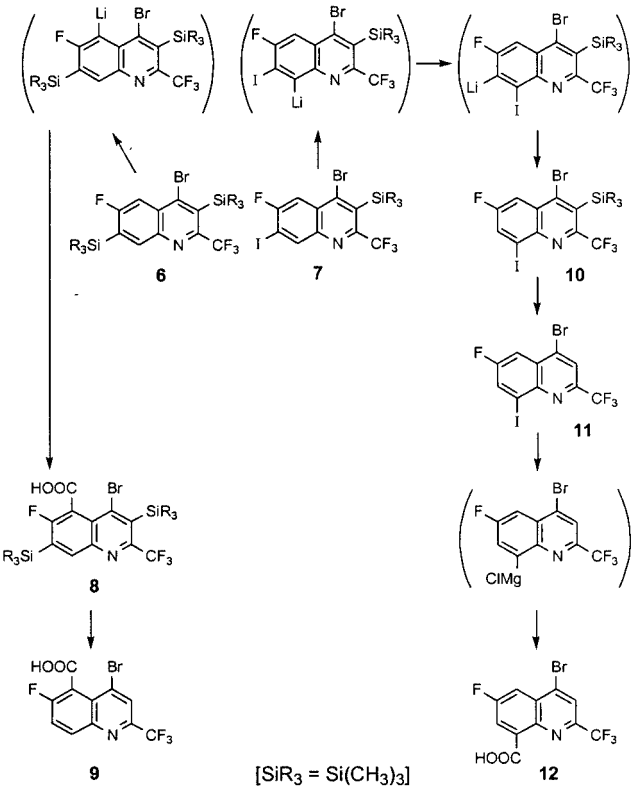
Results

Derivatization of the 6-Fluoro Compound

The LIDA-promoted metalation and subsequent carboxylation of quinoline **1** to afford the acid **2** (81%) has already been reported.[8] When the lithiated intermediate was trapped with chlorotrimethylsilane instead, the silane **3** (89%) was obtained. It was found to be attacked by LIDA or lithium 2,2,6,6-tetramethylpiperidide (LITMP) exclusively at the 7-position. Subsequent treatment with carbon dioxide, chlorotrimethylsilane and elemental iodine gave the acid **4** (78%), and after protodesilylation the acid **5** (89%), the bis(silane) **6** (85%), and the iodo compound **7** (78%), respectively.

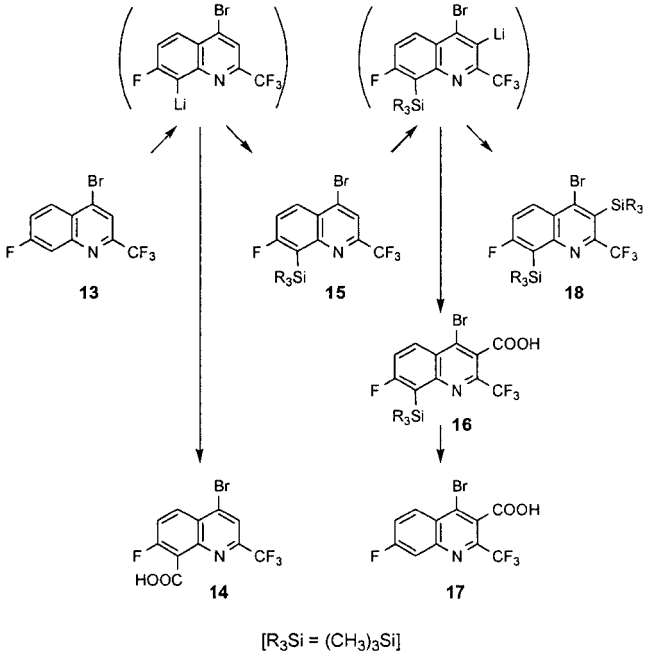


As expected, the bis(silane) **6** underwent deprotonation at the 5-position. Carboxylation provided the silylated acid **8** (74%) and deprotection the quinoline-5-carboxylic acid **9** (93%). When the iodo compound **7** was treated with LIDA, heavy halogen migration[9] occurred. The regioisomer **10** (89%) which resulted upon hydrolysis was subjected consecutively to protodesilylation, producing the quinoline **11** (92%), halogen/metal permutation, executed with isopropylmagnesium chloride, and carboxylation with dry ice to furnish the quinoline-8-carboxylic acid **12** (78%).



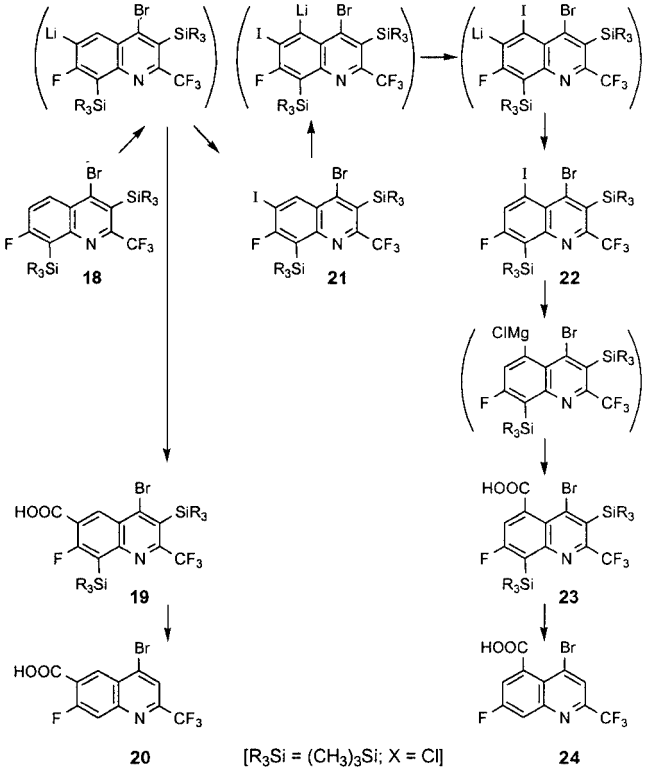
Derivatization of the 7-Fluoro Compound

The first deprotonation of 4-bromo-7-fluoro-2-(trifluoromethyl)quinoline (**13**) occurs not at the 3-position, but rather at the 8-position and thus leads directly to the quinoline-8-carboxylic acid **14** (80%).[8] When the lithiated intermediate was trapped with chlorotrimethylsilane instead of dry ice, the silane **15** (68%) was formed. When this was



treated again with LIDA, metalation occurred this time at the 3-position. Carboxylation afforded the silylated acid **16** (87%) and, after deprotection, the quinoline-3-carboxylic acid **17** (74%) whereas the interception with chlorotrimethylsilane produced the bis(silane) **18** (89%).

LIDA-promoted deprotonation followed by carboxylation readily converted the bis(silane) **18** into the acid **19** (61%) and, after deprotection, into the quinoline-6-carboxylic acid **20** (73%). Trapping of the organolithium intermediate with iodine rather than carbon dioxide furnished the 6-iodo compound **21** (58%) which was isomerized[9] to the 5-iodo analog **22** (56%) when exposed to LIDA. Halogen/metal permutation with isopropylmagnesium chloride and subsequent carboxylation afforded the acid **23** (79%) and after removal of the silyl groups, the quinoline-5-carboxylic acid **24** (88%).



Conclusions

The projected functionalization of the two model substrates, 4-bromo-6-fluoro- and 4-bromo-7-fluoro-2-(trifluoromethyl)quinoline, was achieved by employing merely two auxiliary substituents. Trimethylsilyl groups protected not alone the *ipso* center but also their immediate vicinity against any attack of a base. At the end of the reaction sequence they were readily removed by treatment with a soluble fluoride (such as tetrabutylammonium fluoride) in the presence of small amounts of a proton source (such as water or methanol). Iodine atoms, equally easily introduced at a targeted acidic site, could be dislocated by a deprotonation-triggered heavy halogen migration[9] to an otherwise inaccessible neighboring position. It could subsequently be selectively exchanged against magnesium halide, and eventually an electrophile, without affecting the bromo substituent at the 4-position.

Experimental Section

Details concerning standard operations and abbreviations have been given in previous publications from this laboratory.[10−12] ^{1}H and (^{1}H-decoupled) ^{13}C NMR spectra were recorded at 400 and 101 MHz, respectively. If not specified otherwise, samples having been dissolved in deuteriochloroform or, if marked by an asterisk, in hexadeuterioacetone. Mass spectra were obtained at 70 eV ionization potential while a source temperature of 200 °C was maintained. Whenever no molecular peak was observed under such conditions, chemical ionization ("c.i.") in an ammonia atmosphere at 100 °C source temperature was applied. To avoid redundancy, in all cases only the [^{79}Br] fragments and not the [^{81}Br] isotopomers are listed.

4-Bromo-6-fluoro-2-(trifluoromethyl)quinoline-3-carboxylic Acid (2): From 4-bromo-6-fluoro-2-(trifluoromethyl)quinoline (**1**; 4.4 g, 15 mmol), same procedure as described;[8] colorless prisms (from chloroform/ethyl acetate); m.p. 181−183 °C; yield: 4.11 g (81%).

4-Bromo-6-fluoro-2-trifluoromethyl-3-(trimethylsilyl)quinoline (3): Diisopropylamine (14 mL, 10 g, 0.10 mol) and 4-bromo-6-fluoro-2-(trifluoromethyl)quinoline (**1**; 29 g, 0.10 mol) were added consecutively to a solution of butyllithium (0.10 mol) in tetrahydrofuran (0.12 L) and hexanes (63 mL) kept in a dry ice/methanol bath. After 2 h at −75 °C, chlorotrimethylsilane (25 mL, 22 g, 0.20 mol) was added. After 2 h, methanol (8.0 mL, 6.4 g, 0.20 mol) was added, the solvents were evaporated and the residue was crystallized from methanol; colorless needles; m.p. 86−87 °C; yield: 32.6 g (89%). ^{1}H NMR: δ = 8.17 (dd, *J* = 9.6, 5.8 Hz, 1 H), 8.03 (dd, *J* = 9.9, 2.9 Hz, 1 H), 7.59 (ddd, *J* = 10.6, 7.7, 2.9 Hz, 1 H), 0.60 (d, *J* = 1.0 Hz, 9 H) ppm. ^{13}C NMR: δ = 162.5 (d, *J* = 252 Hz), 150.0 (qd, *J* = 34, 3 Hz), 145.0 (d, *J* = 6 Hz), 142.9, 133.6 (d, *J* = 10 Hz), 133.0 (d, *J* = 10 Hz), 129.9 (d, *J* = 10 Hz), 122.0 (d, *J* = 26 Hz), 121.4 (q, *J* = 276 Hz), 111.1 (d, *J* = 25 Hz), 2.7 (q, *J* = 3 Hz) ppm. MS (c.i.): *m*/*z* (%) = 383 (0) [M$^+$ + 18], 366 (34) [M$^+$ + 1], 365 (1) [M$^+$], 194 (82), 170 (56), 133 (34). $C_{13}H_{12}BrF_4NSi$ (366.23): calcd. C 42.64, H 3.30; found C 42.74, H 3.16.

4-Bromo-6-fluoro-2-trifluoromethyl-3-(trimethylsilyl)quinoline-7-carboxylic Acid (4): Analogously starting from silane **3** (9.2 g, 25 mmol), the mixture was poured onto an excess of freshly crushed dry ice after 2 h at −75 °C. A 1.8 M ethereal solution (20 mL) of hydrochloric acid was added. After evaporation of the volatiles, the residue was crystallized from methanol; colorless prisms; m.p. 238−240 °C (reprod.); yield: 8.00 g (78%). ^{1}H NMR*: δ = 8.70 (d, *J* = 7.0 Hz, 1 H), 8.19 (d, *J* = 11.8 Hz, 1 H), 0.64 (q, *J* = 1.3 Hz, 9 H) ppm. ^{13}C NMR*: δ = 164.0 (d, *J* = 4 Hz), 161.4 (d, *J* = 261 Hz), 151.1 (qd, *J* = 34, 3 Hz), 145.4 (d, *J* = 6 Hz), 147.8 (d, *J* = 10 Hz), 136.5 (d, *J* = 3 Hz), 136.0, 132.5 (d, *J* = 10 Hz), 126.0 (d, *J* = 16 Hz), 122.4 (q, *J* = 275 Hz), 113.8 (d, *J* = 27 Hz), 2.6 (q, *J* = 3 Hz) ppm. MS (c.i.): *m*/*z* (%) = 427 (0) [M$^+$ + 18], 410 (33) [M$^+$ + 1], 409 (7) [M$^+$], 373 (65), 371 (63), 143 (60). $C_{14}H_{12}BrF_4NO_2Si$ (410.24): calcd. C 40.99, H 2.95; found C 41.08, H 2.86.

4-Bromo-6-fluoro-2-(trifluoromethyl)quinoline-7-carboxylic Acid (5): Tetrabutylammonium fluoride trihydrate (9.5 g, 30 mmol) was dis-

solved in a solution of acid **4** (6.2 g, 15 mmol) in tetrahydrofuran (30 mL). After 6 h at 25 °C, water (30 mL) was added and the aqueous phase was washed with diethyl ether (3 × 15 mL) before being acidified to pH 4 with concentrated hydrochloric acid. Extraction with ethyl acetate (3 × 15 mL), drying of the combined organic layers and evaporation gave a residue, which was crystallized from a 4:1 (v/v) mixture of chloroform and ethyl acetate; colorless prisms; m.p. 247−248 °C (reprod.); yield: 4.15 g (89%). ^{1}H NMR*: δ = 8.81 (d, *J* = 7.0 Hz, 1 H), 8.43 (s, 1 H), 8.10 (d, *J* = 11.2 Hz, 1 H) ppm. ^{13}C NMR*: δ = 164.5 (d, *J* = 3 Hz), 161.2 (d, *J* = 262 Hz), 148.3 (qd, *J* = 35, 3 Hz), 144.2, 136.5 (d, *J* = 3 Hz), 135.3 (d, *J* = 6 Hz), 132.5 (d, *J* = 11 Hz), 127.0 (d, *J* = 16 Hz), 123.7 (q, *J* = 2 Hz), 121.6 (q, *J* = 275 Hz), 113.1 (d, *J* = 26 Hz) ppm. MS (c.i.): *m*/*z* (%) = 355 (0) [M$^+$ + 18], 338 (30) [M$^+$ + 1], 337 (99) [M$^+$], 322 (48), 320 (53), 295 (27), 293 (36). $C_{11}H_4BrF_4NO_2$ (338.05): calcd. C 39.08, H 1.19; found C 39.45, H 1.25.

4-Bromo-6-fluoro-2-trifluoromethyl-3,7-bis(trimethylsilyl)quinoline (6): 2,2,6,6-Tetramethylpiperidine (8.5 mL, 7.1 g, 50 mmol) and 4-bromo-6-fluoro-2-trifluoromethyl-3-(trimethylsilyl)quinoline[8] (**3**; 18 g, 50 mmol) were added consecutively to a solution of butyllithium (50 mmol) in tetrahydrofuran (70 mL) and hexanes (30 mL) kept in a dry ice/methanol bath. After 6 h at −75 °C, chlorotrimethylsilane (13 mL, 11 g, 0.10 mol) was added. Neutralization, evaporation and crystallization afforded colorless needles (from methanol); m.p. 89−91 °C; yield: 18.6 g (85%). ^{1}H NMR: δ = 8.22 (d, *J* = 5.4 Hz, 1 H), 7.93 (d, *J* = 9.9 Hz, 1 H), 0.60 (q, *J* = 1.0 Hz, 9 H), 0.42 (d, *J* = 1.4 Hz, 9 H) ppm. ^{13}C NMR: δ = 166.8 (d, *J* = 247 Hz), 149.8 (qd, *J* = 34, 3 Hz), 144.8 (d, *J* = 6 Hz), 142.8, 139.0 (d, *J* = 13 Hz), 135.6 (d, *J* = 36 Hz), 133.1, 130.6 (d, *J* = 11 Hz), 121.4 (q, *J* = 276 Hz), 110.0 (d, *J* = 31 Hz), 2.6 (q, *J* = 3 Hz), 1.2 (d, *J* = 2 Hz) ppm. MS (c.i.): *m*/*z* (%) = 455 (1) [M$^+$ + 18], 438 (88) [M$^+$ + 1], 437 (12) [M$^+$], 401 (31), 399 (28), 77 (74). $C_{16}H_{20}BrF_4NSi_2$ (438.41): calcd. C 43.83, H 4.60; found C 44.00, H 4.26.

4-Bromo-6-fluoro-7-iodo-2-trifluoromethyl-3-(trimethylsilyl)-quinoline (7): Diisopropylamine (7.1 mL, 5.1 g, 50 mmol) and silane **3** (18 g, 50 mmol) were added consecutively, at −75 °C, to a solution of butyllithium (50 mmol) in tetrahydrofuran (70 mL) and hexanes (30 mL) and kept at −75 °C for further 2 h. The mixture was treated with iodine (25 g, 0.10 mol) in tetrahydrofuran (25 mL). After 2 h at −75 °C, the solvents were evaporated and the residue was taken up in diethyl ether (50 mL). The organic layer was washed with a 1.0 M aqueous solution of sodium thiosulfate (2 × 50 mL), dried and the solvents evaporated; colorless needles (from methanol); m.p. 99−100 °C; yield: 19.2 g (78%). ^{1}H NMR: δ = 8.69 (d, *J* = 6.1 Hz, 1 H), 7.99 (d, *J* = 9.3 Hz, 1 H), 0.59 (q, *J* = 1.3 Hz, 9 H) ppm. ^{13}C NMR: δ = 160.9 (d, *J* = 251 Hz), 150.7 (qd, *J* = 34, 3 Hz), 145.0 (d, *J* = 6 Hz), 143.3, 142.0 (d, *J* = 4 Hz), 133.8, 129.6 (d, *J* = 9 Hz), 121.1 (q, *J* = 276 Hz), 110.6 (d, *J* = 28 Hz), 89.0 (d, *J* = 30 Hz), 2.5 (q, *J* = 3 Hz) ppm. MS (c.i.): *m*/*z* (%) = 509 (0) [M$^+$ + 18], 492 (98) [M$^+$ + 1], 491 (40) [M$^+$], 455 (16), 453 (14), 189 (6). $C_{13}H_{11}BrF_4INSi$ (492.12): calcd. C 31.73, H 2.25; found C 31.44, H 2.01.

4-Bromo-6-fluoro-2-trifluoromethyl-3,7-bis(trimethylsilyl)-quinoline-5-carboxylic Acid (8): Starting form bis(silane) **6** (11 g, 25 mmol), the same procedure was applied as described for preparation of **4**; colorless prisms (from methanol); m.p. 188−190 °C; yield: 8.92 g (74%). ^{1}H NMR: δ = 8.34 (d, *J* = 5.8 Hz, 1 H), 0.62 (q, *J* = 1.3 Hz, 9 H), 0.46 (d, *J* = 1.0 Hz, 9 H) ppm. ^{13}C NMR: δ = 171.9, 164.0 (d, *J* = 250 Hz), 150.4 (qd, *J* = 34, 3 Hz), 143.3, 142.1 (d, *J* = 6 Hz), 141.0 (d, *J* = 14 Hz), 136.0, 135.3 (d, *J* = 38 Hz), 127.2 (d, *J* = 6 Hz), 121.2 (q, *J* = 276 Hz), 115.9 (d, *J* = 25 Hz), 2.8 (q, *J* = 3 Hz), −1.2 (d, *J* = 1 Hz) ppm. MS (c.i.): *m*/*z* (%) = 499 (0) [M$^+$ + 18], 482 (1) [M$^+$ + 1], 481 (1) [M$^+$], 402 (6), 77 (100). $C_{17}H_{20}BrF_4NO_2Si_2$ (482.42): calcd. C 42.33, H 4.18; found C 42.50, H 4.21.

4-Bromo-6-fluoro-2-(trifluoromethyl)quinoline-5-carboxylic Acid (9): Starting from acid **8** (7.2 g, 15 mmol) and employing the same procedure as described for the preparation of acid **5** but using 3.0 (rather than 2.0) equivalents of tetrabutylammonium fluoride trihydrate (14 g, 45 mmol); colorless prisms (decomp.; from chloroform/ethyl acetate); m.p. 208−211 °C; yield: 4.72 g (93%). ^{1}H NMR*: δ = 8.41 (dd, *J* = 9.3, 5.8 Hz, 1 H), 8.39 (s, 1 H), 7.98 (dd, *J* = 9.3, 8.9 Hz, 1 H) ppm. ^{13}C NMR*: δ = 166.4, 161.3 (d, *J* = 253 Hz), 148.5 (qd, *J* = 36, 3 Hz), 146.8, 136.8 (d, *J* = 11 Hz), 133.6 (d, *J* = 6 Hz), 127.6 (d, *J* = 7 Hz), 123.7 (d, *J* = 27 Hz), 122.6 (q, *J* = 275 Hz), 121.8, 120.8 (d, *J* = 23 Hz) ppm. MS (c.i.): *m*/*z* (%) = 355 (1) [M$^+$ + 18], 338 (20) [M$^+$ + 1], 337 (3) [M$^+$], 295 (30), 293 (28), 258 (100). $C_{11}H_4BrF_4NO_2$ (338.05): calcd. C 39.08, H 1.19; found C 39.41, H 1.21.

4-Bromo-6-fluoro-8-iodo-2-trifluoromethyl-3-(trimethylsilyl)-quinoline (10): Diisopropylamine (3.5 mL, 2.5 g, 25 mmol) and silane **7** (12 g, 25 mmol) were added consecutively to a solution of butyllithium (25 mmol) in tetrahydrofuran (35 mL) and hexanes (15 mL) kept in a dry ice/methanol bath. After 6 h at −75 °C, methanol (2.0 mL, 1.6 g, 50 mmol) was added and the solvents were evaporated. The residue was crystallized three times from methanol; colorless needles; m.p. 111−113 °C; yield: 10.9 g (89%). ^{1}H NMR: δ = 8.17 (dd, *J* = 7.4, 2.5 Hz, 1 H), 7.88 (dd, *J* = 9.0, 2.5 Hz, 1 H), 0.71 (q, *J* = 1.2 Hz, 9 H) ppm. ^{13}C NMR: δ = 165.3 (d, *J* = 256 Hz), 150.7 (q, *J* = 36 Hz), 145.8, 132.7 (d, *J* = 26 Hz), 131.1 (d, *J* = 6 Hz), 128.7 (d, *J* = 10 Hz), 122.4 (d, *J* = 2 Hz), 118.8 (q, *J* = 275 Hz), 111.1 (d, *J* = 24 Hz), 104.3 (d, *J* = 9 Hz), 2.3 (q, *J* = 3 Hz) ppm. MS (c.i.): *m*/*z* (%) = 509 (0) [M$^+$ + 18], 492 (84) [M$^+$ + 1], 491 (38) [M$^+$], 270 (25), 77 (60). $C_{13}H_{11}BrF_4NSi$ (492.12): calcd. C 31.73, H 2.25; found C 31.49, H 2.39.

4-Bromo-6-fluoro-8-iodo-2-(trifluoromethyl)quinoline (11): Tetrabutylammonium fluoride trihydrate (9.5 g, 30 mmol) was dissolved in tetrahydrofuran (30 mL) containing the silane **10** (7.38 g, 15 mmol). After 6 h at 25 °C, water (30 mL) was added and the aqueous phase was extracted with diethyl ether (3 × 15 mL). Drying of the combined organic layers and evaporation gave a residue which was crystallized from methanol; colorless needles; m.p. 70−71 °C; yield: 5.80 g (92%). ^{1}H NMR: δ = 8.28 (dd, *J* = 7.4, 2.6 Hz, 1 H), 8.08 (s, 1 H), 7.96 (dd, *J* = 9.0, 2.6 Hz, 1 H) ppm. ^{13}C NMR: δ = 161.4 (d, *J* = 257 Hz), 147.5 (qd, *J* = 36, 3 Hz), 143.7, 135.1 (d, *J* = 6 Hz), 132.8 (d, *J* = 28 Hz), 129.0 (d, *J* = 11 Hz), 123.3 (d, *J* = 2 Hz), 120.3 (q, *J* = 276 Hz), 111.3 (d, *J* = 24 Hz), 105.9 (d, *J* = 9 Hz) ppm. MS (c.i.): *m*/*z* (%) = 437 (0) [M$^+$ + 18], 420 (30) [M$^+$ + 1], 419 (100) [M$^+$], 294 (8), 292 (8), 118 (32). $C_{10}H_3BrF_4IN$ (419.94): calcd. C 28.60, H 0.71; found C 28.70, H 0.75.

4-Bromo-6-fluoro-2-(trifluoromethyl)quinoline-8-carboxylic Acid (12): Iodoquinoline **11** (4.2 g, 10 mmol) was added to an ice-cold solution of isopropylmagnesium chloride (10 mmol) in tetrahydrofuran (20 mL). After 45 min at 0 °C, the mixture was poured onto an excess of freshly crushed dry ice. Upon neutralization of the crude product, evaporation of the volatiles and crystallization of the residue from a 1:1 (v/v) mixture of chloroform and ethyl acetate colorless prisms were obtained; m.p. 140−142 °C; yield: 2.13 g (78%). ^{1}H NMR*: δ = 8.65 (s, 1 H), 8.59 (dd, *J* = 8.6, 2.9 Hz, 1 H), 8.36 (dd, *J* = 8.6, 2.9 Hz, 1 H) ppm. ^{13}C NMR*: δ = 164.0 (d, *J* = 3 Hz), 163.1 (d, *J* = 254 Hz), 146.1 (qd, *J* = 36, 3 Hz), 142.3, 139.0 (d, *J* = 6 Hz), 131.8 (d, *J* = 10 Hz), 131.0 (d, *J* =

9 Hz), 127.5 (d, J = 28 Hz), 124.0, 121.4 (q, J = 275 Hz), 116.5 (d, J = 25 Hz) ppm. MS (c.i.): m/z (%) = 355 (0) [M^+ + 18], 338 (30) [M^+ + 1], 337 (6) [M^+], 295 (99), 293 (97), 194 (100). $C_{11}H_4BrF_4NO_2$ (338.05): calcd. C 39.08, H 1.19; found C 39.35, H 1.17.

4-Bromo-7-fluoro-2-(trifluoromethyl)quinoline-8-carboxylic Acid (14): From 4-bromo-7-fluoro-2-(trifluoromethyl)quinoline (**13**; 7.3 g, 25 mmol) as described previously;[8] colorless prisms (from methanol); m.p. 160−161 °C; yield: 6.76 g (80%).

4-Bromo-7-fluoro-2-trifluoromethyl-8-(trimethylsilyl)quinoline (15): From 4-bromo-7-fluoro-2-(trifluoromethyl)quinoline (**13**; 29 g, 0.10 mol) analogously as described for the preparation of silane **3**; colorless needles (from methanol); m.p. 50−52 °C; yield: 24.9 g (68%). ^{1}H NMR: δ = 8.27 (dd, J = 9.1, 5.9 Hz, 1 H), 7.96 (s, 1 H), 7.44 (dd, J = 8.9, 8.6 Hz, 1 H), 0.49 (d, J = 1.9 Hz, 9 H) ppm. ^{13}C NMR: δ = 168.5 (d, J = 251 Hz), 152.9 (d, J = 18 Hz), 147.0 (q, J = 35 Hz), 135.7, 130.3 (d, J = 11 Hz), 125.8, 124.8 (d, J = 29 Hz), 120.9 (q, J = 276 Hz), 120.8 (d, J = 29 Hz), 119.8, 1.1 (d, J = 1 Hz) ppm. MS (c.i.): m/z (%) = 383 (1) [M^+ + 18], 366 (100) [M^+ + 1], 365 (6) [M^+], 322 (8), 171 (5). $C_{13}H_{12}BrF_4NSi$ (366.23): calcd. C 42.64, H 3.30; found C 42.99, H 3.14.

4-Bromo-7-fluoro-2-trifluoromethyl-8-(trimethylsilyl)quinoline-3-carboxylic Acid (16): From silane **15** (9.2 g, 25 mmol) analogously as described for the preparation of acid **4**; colorless prisms (from methanol); m.p. 187−188 °C; yield: 8.92 g (87%). ^{1}H NMR: δ = 8.37 (dd, J = 9.3, 5.6 Hz, 1 H), 7.51 (dd, J = 9.1, 8.3 Hz, 1 H), 0.51 (d, J = 1.9 Hz, 9 H) ppm. ^{13}C NMR: δ = 170.2, 169.1 (d, J = 253 Hz), 152.0 (d, J = 19 Hz), 142.5 (q, J = 36 Hz), 133.8, 130.9 (d, J = 11 Hz), 127.7 (d, J = 13 Hz), 125.3 (m, 2 C), 121.8 (d, J = 33 Hz), 120.4 (q, J = 278 Hz), 1.0 (d, J = 1 Hz) ppm. MS (c.i.): m/z (%) = 427 (0) [M^+ + 18], 410 (7) [M^+ + 1], 409 (2) [M^+], 396 (100), 394 (98), 77 (39). $C_{14}H_{12}BrF_4NO_2Si$ (410.24): calcd. C 40.99, H 2.95; found C 41.08, H 3.07.

4-Bromo-7-fluoro-2-(trifluoromethyl)quinoline-3-carboxylic Acid (17): From acid **16** (6.2 g, 15 mmol) analogously as described for the preparation of acid **5** but using 2.0 equivalents of tetrabutylammonium fluoride trihydrate (9.5 g, 30 mmol); colorless prisms (from chloroform/ethyl acetate); m.p. 180−182 °C; yield: 3.75 g (74%). ^{1}H NMR*: δ = 8.40 (dd, J = 9.5, 5.9 Hz, 1 H), 7.88 (dd, J = 9.5, 2.6 Hz, 1 H), 7.79 (ddd, J = 9.5, 8.2, 2.6 Hz, 1 H) ppm. ^{13}C NMR*: δ = 166.8, 166.2 (d, J = 255 Hz), 148.7 (d, J = 13 Hz), 145.5 (q, J = 35 Hz), 134.8, 132.3 (d, J = 27 Hz), 129.3, 126.5, 123.3 (d, J = 27 Hz), 122.2 (q, J = 276 Hz), 115.4 (d, J = 21 Hz) ppm. MS (c.i.): m/z (%) = 357 (1) [M^+ + 18], 355 (1) [M^+ + 18], 340 (100) [M^+ + 1], 339 (19) [M^+], 338 (99) [M^+ + 1], 337 (15) [M^+], 296 (22), 294 (31), 134 (13). $C_{11}H_4BrF_4NO_2$ (338.05): calcd. C 39.08, H 1.19; found C 39.40, H 1.32.

4-Bromo-7-fluoro-2-trifluoromethyl-3,8-bis(trimethylsilyl)quinoline (18): From silane **15** (18 g, 50 mmol) analogously as described for the preparation of bis(silane) **6**; colorless needles (from methanol); m.p. 79−81 °C; yield: 19.5 g (89%). ^{1}H NMR: δ = 8.38 (dd, J = 9.3, 5.8 Hz, 1 H), 7.37 (dd, J = 9.3, 8.3 Hz, 1 H), 0.58 (q, J = 1.3 Hz, 9 H), 0.48 (d, J = 1.9 Hz, 9 H) ppm. ^{13}C NMR: δ = 168.5 (d, J = 251 Hz), 151.2 (d, J = 18 Hz), 149.8 (q, J = 34 Hz), 141.6, 137.1 (d, J = 15 Hz), 131.0, 125.9, 123.9 (d, J = 28 Hz), 121.6 (q, J = 275 Hz), 120.6 (d, J = 32 Hz), 2.8 (q, J = 3 Hz), 1.0 (d, J = 4 Hz) ppm. MS (c.i.): m/z (%) = 455 (0) [M^+ + 18], 438 (93) [M^+ + 1], 437 (4) [M^+], 387 (29), 368 (48), 366 (44), 288 (29). $C_{16}H_{20}BrF_4NSi_2$ (438.41): calcd. C 43.83, H 4.60; found C 44.19, H 4.46.

4-Bromo-7-fluoro-2-trifluoromethyl-3,8-bis(trimethylsilyl)quinoline-6-carboxylic Acid (19): From bis(silane) **18** (8.77 g, 20 mmol) analogously as described for the preparation of acid **4**; colorless prisms (from methanol); m.p. 238−240 °C (decomp.); yield: 5.89 g (61%). ^{1}H NMR*: δ = 8.58 (d, J = 3.2 Hz, 1 H), 0.53 (q, J = 1.1 Hz, 9 H), 0.51 (d, J = 1.1 Hz, 9 H) ppm. ^{13}C NMR*: δ = 167.4 (d, J = 4 Hz), 164.1 (d, J = 249 Hz), 151.9 (q, J = 34 Hz), 148.9, 148.5 (d, J = 18 Hz), 145.5 (d, J = 2 Hz), 134.0 (d, J = 12 Hz), 124.3, 124.0 (q, J = 276 Hz), 121.2 (d, J = 32 Hz), 112.6 (d, J = 32 Hz), 1.9 (d, J = 4 Hz), 0.7 (q, J = 3 Hz) ppm. MS (c.i.): m/z (%) = 499 (1) [M^+ + 18], 482 (25) [M^+ + 1], 481 (8) [M^+], 469 (31), 468 (100), 467 (36), 466 (95), 77 (55). $C_{17}H_{20}BrF_4NO_2Si_2$ (482.42): calcd. C 42.33, H 4.18; found C 42.21, H 4.05.

4-Bromo-7-fluoro-2-(trifluoromethyl)quinoline-6-carboxylic Acid (20): From acid **19** (4.8 g, 10 mmol) analogously as described for the preparation of acid **5** but using 3.0 equivalents of tetrabutylammonium fluoride trihydrate (9.5 g, 30 mmol); colorless prisms (from chloroform/ethyl acetate); m.p. 230−231 °C (reprod.); yield: 2.47 g (73%). ^{1}H NMR*: δ = 8.92 (d, J = 8.0 Hz, 1 H), 7.83 (d, J = 11.5 Hz, 1 H), 7.43 (s, 1 H) ppm. ^{13}C NMR*: δ = 166.0, 164.6 (d, J = 4 Hz), 162.9 (d, J = 261 Hz), 152.8 (q, J = 34 Hz), 151.5 (d, J = 13 Hz), 129.1 (d, J = 3 Hz), 122.3 (q, J = 275 Hz), 121.8 (d, J = 15 Hz), 118.8, 115.5 (d, J = 22 Hz), 97.9 (quint, J = 2 Hz) ppm. MS (c.i.): m/z (%) = 355 (0) [M^+ + 18], 338 (31) [M^+ + 1], 337 (100) [M^+], 258 (36), 194 (58). $C_{11}H_4BrF_4NO_2$ (338.05): calcd. C 39.08, H 1.19; found C 38.70, H 1.20.

4-Bromo-7-fluoro-6-iodo-2-trifluoromethyl-3,8-bis(trimethylsilyl)quinoline (21): From bis(silane) **18** (11 g, 25 mmol) analogously as described for the preparation of the iodosilane **7** but extending the treatment with the base from 2 h to 20 h; colorless needles (from methanol); m.p. 147−149 °C; yield: 8.18 g (58%). ^{1}H NMR: δ = 8.91 (d, J = 6.4 Hz, 1 H), 0.61 (q, J = 1.3 Hz, 9 H), 0.56 (d, J = 2.2 Hz, 9 H) ppm. ^{13}C NMR: δ = 165.6 (d, J = 249 Hz), 149.9 (q, J = 34 Hz), 144.4 (d, J = 1 Hz), 140.3 (d, J = 4 Hz), 134.8 (d, J = 2 Hz), 131.6 (d, J = 3 Hz), 127.0, 124.6 (d, J = 32 Hz), 121.3 (q, J = 276 Hz), 88.6 (d, J = 32 Hz), 2.8 (q, J = 3 Hz), 1.0 (d, J = 4 Hz) ppm. MS (c.i.): m/z (%) = 581 (0) [M^+ + 18], 564 (22) [M^+ + 1], 563 (12) [M^+], 550 (100), 548 (88), 77 (27). $C_{16}H_{19}BrF_4NSi_2$ (564.30): calcd. C 34.06, H 3.39; found C 34.19, H 3.69.

4-Bromo-7-fluoro-5-iodo-2-trifluoromethyl-3,8-bis(trimethylsilyl)quinoline (22): From bis(silane) **21** (8.5 g, 15 mmol) analogously as described for the preparation of the iodosilane **10**; colorless needles (from methanol); m.p. 135−137 °C; yield: 4.74 g (56%). ^{1}H NMR: δ = 8.81 (d, J = 8.0 Hz, 1 H), 0.50 (d, J = 1.9 Hz, 9 H), 0.47 (d, J = 1.0 Hz, 9 H) ppm. ^{13}C NMR: δ = 162.4 (d, J = 251 Hz), 151.2 (d, J = 18 Hz), 150.7 (q, J = 34 Hz), 147.5 (d, J = 2 Hz), 133.5 (d, J = 2 Hz), 132.4 (d, J = 11 Hz), 131.1 (d, J = 2 Hz), 128.8, 121.9 (q, J = 276 Hz), 119.3 (d, J = 33 Hz), 0.9 (d, J = 4 Hz), −0.1 (q, J = 2 Hz) ppm. MS (c.i.): m/z (%) = 581 (0) [M^+ + 18], 364 (94) [M^+ + 1], 563 (36) [M^+], 494 (8), 492 (7), 360 (17). $C_{16}H_{19}BrF_4INSi_2$ (564.30): calcd. C 34.06, H 3.39; found C 33.77, H 3.15.

4-Bromo-7-fluoro-2-trifluoromethyl-3,8-bis(trimethylsilyl)quinoline-5-carboxylic Acid (23): From bis(silane) **22** (5.6 g, 10 mmol) analogously as described for the preparation of acid **12**; colorless prisms (from hexanes); m.p. 261−263 °C (decomp.); yield: 3.81 g (79%). ^{1}H NMR*: δ = 9.07 (d, J = 7.4 Hz, 1 H), 0.63 (q, J = 1.3 Hz, 9 H), 0.53 (d, J = 2.2 Hz, 9 H) ppm. ^{13}C NMR*: δ = 167.9 (d, J = 259 Hz), 165.8 (d, J = 4 Hz), 158.7 (d, J = 17 Hz), 152.8 (q, J = 34 Hz), 149.0, 136.2 (d, J = 4 Hz), 133.5, 127.1 (d,

J = 29 Hz), 126.8, 125.5 (d, J = 21 Hz), 123.2 (d, J = 276 Hz), 3.6 (q, J = 3 Hz), 2.1 (d, J = 4 Hz) ppm. MS (c.i.): m/z (%) = 497 (1) [M^+ + 18], 482 (23) [M^+ + 1], 481 (7) [M^+], 468 (100), 466 (94), 388 (14), 77 (52). $C_{17}H_{20}BrF_4NO_2Si_2$ (482.42): calcd. C 42.33, H 4.18; found C 42.28, H 4.02.

4-Bromo-7-fluoro-2-(trifluoromethyl)quinoline-5-carboxylic Acid (24): From acid **23** (4.8 g, 10 mmol) analogously as described for the preparation of acid **4** but using 3.0 equivalents of tetrabutylammonium fluoride trihydrate (9.5 g, 30 mmol); colorless prisms (from chloroform/ethyl acetate); m.p. 241−244 °C (decomp.); yield: 2.97 g (88%). ^{1}H NMR*: δ = 8.97 (d, J = 7.4 Hz, 1 H), 8.36 (s, 1 H), 8.06 (d, J = 11.2 Hz, 1 H) ppm. ^{13}C NMR*: δ = 163.9 (d, J = 263 Hz), 165.0 (d, J = 4 Hz), 151.6 (q, J = 35 Hz), 151.4 (d, J = 13 Hz), 138.7 (d, J = 2 Hz), 134.4 (d, J = 3 Hz), 126.8, 125.5 (d, J = 15 Hz), 123.1 (quint, J = 2 Hz), 122.4 (q, J = 275 Hz), 117.4 (d, J = 23 Hz) ppm. MS (c.i.): m/z (%) = 355 (1) [M^+ + 18], 338 (99) [M^+ + 1], 337 (53) [M^+], 296 (28), 294 (30), 186 (67). $C_{11}H_4BrF_4NO_2$ (338.05): calcd. C 39.08, H 1.19; found C 38.95, H 1.17.

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