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Metalation/functionalization sequences applied to 2-bromo-3-fluoroquinolines

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Abstract—Mono- and disubstituted 2-bromo-3-fluoroquinolines **3** are readily accessible. They can be converted into the 3-fluoroquinoline-2-carboxylic acids **5** by consecutive halogen/metal permutation and into the 2-bromo-3-fluoroquinoline-4-carboxylic acids **6** by consecutive deprotonation and carboxylation. The latter compounds can be reduced to afford the 3-fluoroquinoline-4-carboxylic acids **7**. The yields are excellent throughout. Rather than to introduce one functional group alternatively at the 2- or 4-position, one may also attach two different functional groups sequentially to both sites.

1. Introduction

2-Fluoro-3-methoxy-2-propenoic acid, generally employed as its methyl ester[1,2] or acyl chloride,[3] is an extremely versatile building block for the construction of a variety of heterocyclic compounds.[3] The condensation with anilines provides 2-fluoro-3-methoxy-prop-2-enanilides and, after acid catalyzed cyclization, 3-fluoroquinolin-2(1*H*)-ones. The latter react with phosphoric trichloride (phosphorus oxychloride) to give 2-chloro-3-fluoro-quinolines which can be reduced to the 3-fluoroquinolines.[1]

2. Results

We wish now to report on an extension of these earlier studies. As key intermediates serve 2-bromo-3-fluoroquinolines **3** which were readily obtained by the treatment of 3-fluoroquinolin-2(1*H*)-ones **2** with phosphoric tribromide. The immediate precursors to the fluoroquinolinones **2** were the open-chain anilides **1** which in turn were made from the ultimate starting materials, aniline itself and four monosubstituted and one disubstituted congeners (Scheme 1).

Unlike chlorine, bromine atoms can be displaced against lithium in butyllithium-mediated halogen/metal permutation processes, which can be performed in tetrahydrofuran, diethyl ether or, often more cleanly, in toluene. The organometallic intermediates thus generated may be trapped with any electrophile. Reaction with dry ice afforded the 3-fluoroquinoline-2-carboxylic acids **5** in an average yield of 75%. To accomplish a site-selective displacement of the nitrogen-adjacent bromine atom at the 2-position of the dibromo compound **3e**, the interconversion reaction had to be conducted in toluene at −100 °C as at −75 °C a 9:1 mixture of 2- and 8-lithiated intermediates was produced. When lithium diisopropylamide was employed as the base instead, deprotonation occurred at the vacant 4-position and subsequent carboxylation afforded the 2-bromo-3-fluoroquinoline-4-carboxylic acids **6** in 84% average yield. Pyridine being, particularly at the 4-position, far more acidic than benzene, the 3,7-difluorinated substrate **3c** underwent deprotonation and subsequent functionalization selectively in the heterocyclic part. Reductive removal of the heavy halogen from the acids **6** (by either catalytic hydrogenation or with tin dichloride[4]) gave the 3-fluoroquinoline-4-carboxylic acids **7**, yields averaging 79% this time. The same compounds **7** are accessible by an operational inversion of the carboxylation and reduction steps. Debromination of the 2-bromo-3-fluoroquinolines **3** leads to the 3-fluoroquinolines **4** which, as demonstrated previously,[1] can be deprotonated effectively with lithium diisopropylamide in the presence of potassium *tert*-butoxide ('Mordini mixture') in order to be carboxylated subsequently (Scheme 2).

Keywords: Bromine replacement by hydrogen; Carboxylation; Formylation; 3-Fluoroquinoline-2- and -4-carboxylic acids; Halogen/metal permutation ('halogen exchange') reactions; Hydrogen/metal permutation ('metalation') reactions.
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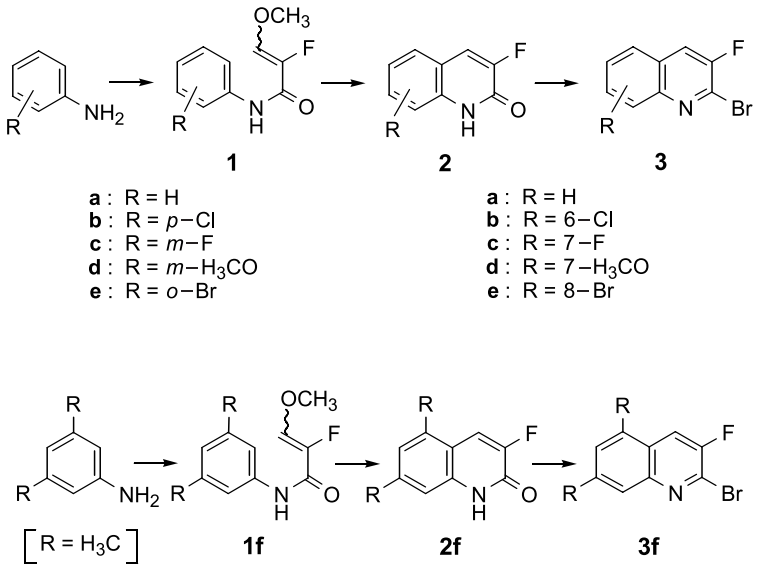


Scheme 1.

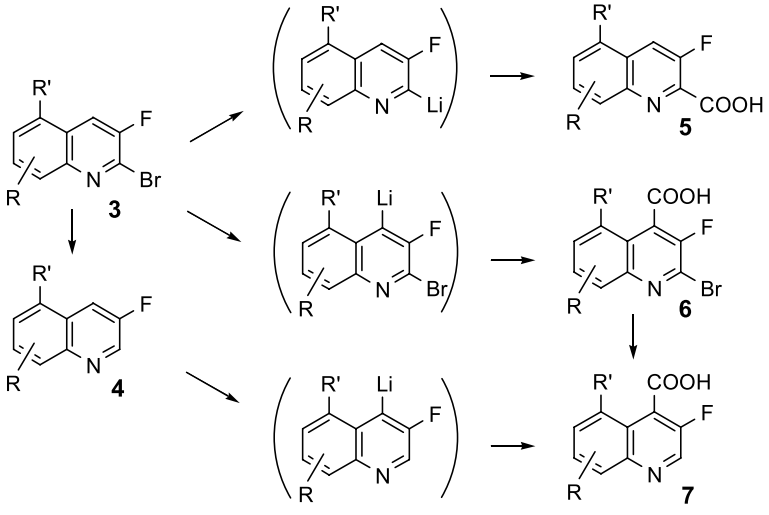
Carboxy groups or another functionality may not only be introduced alternatively into either the 2- or the 4-position of 2-bromo-3-fluoroquinolines **3** but also sequentially in both sites. Two series of reactions have been performed to illustrate this possibility.

2-Bromo-3-fluoro-5,7-dimethylquinoline **3f** was converted into the quinoline-4-carboxylic acid **6f**, as described above, before being subjected to a halogen/metal permutation with lithium tributylmagnesate[5] followed by trapping with dimethylformamide. The formylacid **8a** thus formed was isolated as the crystalline thiosemicarbazone **8b** (78%) (Scheme 3).

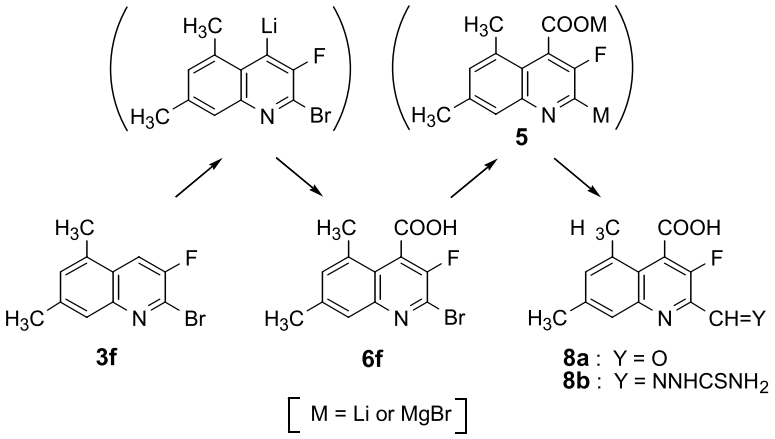
When dimethylformamide was added to the 4-lithiated 2-bromo-3-fluoroquinoline (**3a**) and thus the formyl entity was introduced as the first functional group, the aldehyde **9a** (98%) had to be protected by acetalization with ethylene glycol, thus producing the 1,3-dioxole **9b** (97%). Ensuing halogen/metal permutation, carboxylation and acetal hydrolysis gave the formylcarboxylic acid **10b** (74%) (Scheme 4).

3. Conclusions

The present investigation features methods designed to install flexibility into the derivatization and, in particular, functionalization of quinolines. This class of compounds represents a key segment of heterocyclic chemistry. As



Scheme 2.



Scheme 3.

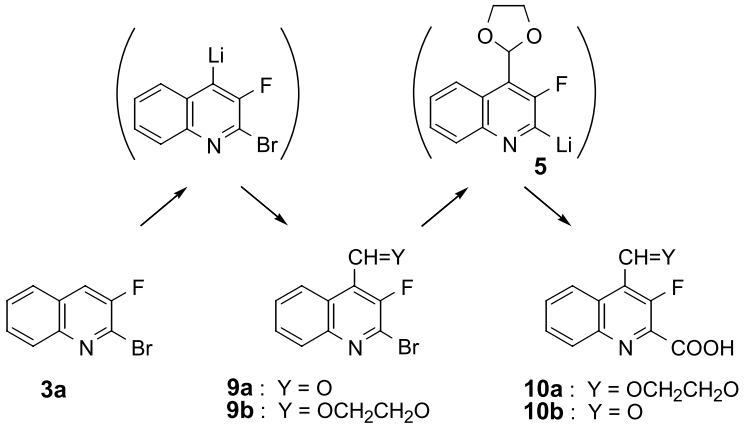
demonstrated, the elaborated procedures tolerate the presence of a great variety of substituents located in the benzo ring.

Notwithstanding such general statements, it deems appropriate to examine in detail to what extent this work is novel and significant. Neither bromofluoroquinolines, readily accessible on our route, nor organometallic derivatives thereof have ever been reported. These compounds offer a manifold of possibilities for further elaboration. Whereas 3-fluoroquinoline itself and its 2-butoxy congener require mixed-metal reagents to undergo metalation efficaciously,[1] lithium diisopropylamide suffices to deprotonate 2-bromo-3-fluoroquinolines cleanly at the 4-position. The menacing nucleophilic bromide/amide displacement can be perfectly controlled and avoided. The lithiated species resulting from 4-deprotonation can be trapped by standard electrophilic reagents such as carbon dioxide. Alternatively, 2-lithio species may be generated by permutational halogen/metal interconversion and subsequently be intercepted again with dry ice or another electrophile.

So far without precedent is the combination of both processes, the metalation followed by functionalization and the halogen/metal permutation followed by another functionalization. The feasibility of such a sequence has been demonstrated in two model cases.

We have previously investigated the functionalization of 4-bromo-2-(trifluoromethyl)quinolines[6,7] and 2-bromo-4-(trifluoromethyl)quinolines.[8,9] They differ in two respects from the present substrates. On one hand they contain a doubly acidified 3-position and on the other hand, the trifluoromethyl entity provides relatively little neighboring group assistance to the deprotonation of *ortho* positions but has a long-ranging effect whereas the fluorine atom is an excellent *ortho*-metalation-promoting substituent the activating effect of which, however, rapidly levels off with distance.[10]

The preparation and subsequent transformations of 2-bromo-3-fluoroquinolines **3** deserves attention even if the outcome might have been anticipated on the basis of earlier work. The metal was cleanly introduced in the 4-position when lithium dialkylamide-type bases were employed. Remarkably, these deprotonations were not accompanied by any bromine migration.[11,12] In comparison with chlorine, trifluoromethyl and alkoxy, bromine disposes of additional reaction modes. It can be easily and selectively replaced by hydrogen through metal-mediated reduction or catalytic hydrogenation;[12] it can participate in permutational halogen/metal interconversions to leave its place to lithium; and it can undergo carbon–carbon linking Suzuki couplings.[13–16]



Scheme 4.

4. Experimental

4.1. General

Details concerning standard operations and abbreviations have been given in previous publications from this laboratory.[17,18] ^{1}H and (^{1}H-decoupled) ^{13}C NMR spectra were recorded at 400 and 101 MHz, respectively. If not specified otherwise the samples were dissolved in deuteriochloroform or, if marked by an asterisk, in dimethylsulfoxide-d_6. 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 [^{35}Cl] and [^{79}Br] fragments and not the [^{37}Cl] and [^{81}Br] isotopomers are listed.

The anilides **1a**, **1c** and **1d** have been isolated and characterized previously.[2] In the present work, all anilides were collected as crude products and cyclized by heating in 70% sulfuric acid without prior purification. The preparation of the quinolinones **2a**,[1] **2c**,[2] and **2d**[2] has already been reported.

4.1.1. 6-Chloro-3-fluoroquinol-2(1*H*)-one (2b). Butyllithium (0.50 mol) in hexanes (0.33 L) and methyl 2-fluoro-3-methoxyprop-2-enoate[1] (*Z*/*E*∼1:1; 27 mL, 34 g, 0.25 mol) were added consecutively to 4-chloroaniline (45 mL, 47 g, 0.50 mol) in tetrahydrofuran (2.7 L) at 0 °C. After 1 h at 25 °C, the mixture was poured into 2.0 M hydrochloric acid (0.70 L). The two phases were separated and the aqueous one extracted with diethyl ether (3×0.25 L). The combined organic layers were washed with a saturated aqueous solution (0.25 L) of sodium hydrogen carbonate, brine (0.25 L) and dried with anhydrous sodium sulfate. After evaporation, a brownish-yellow solid residue was left behind. It was heated in 96% sulfuric acid (2.0 L) to 50 °C for 5 h. The mixture was poured on crushed ice. The precipitate was collected by filtration and washed with water (2×0.10 L); colorless needles (from aqueous *N*,*N*-dimethylformamide); mp 306–308 °C (reprod.); yield: 89.9 g (88%). ^{1}H NMR: δ=11.29 (s, broad, 1H), 7.75 (d, J=2.4 Hz, 1H), 7.71 (d, J=10.1 Hz, 1H), 7.52 (dd, J=8.9, 2.4 Hz, 1H), 7.46 (d, J=8.8 Hz, 1H) ppm. ^{13}C NMR*: δ=155.4 (d, J=27 Hz), 151.2 (d, J=253 Hz), 134.5 (s), 129.2 (s), 126.5 (d, J=6 Hz), 126.4 (s), 119.4 (d, J=8 Hz), 118.3 (d, J=18 Hz), 117.0 (s) ppm. MS: *m*/*z* (%)=199 (41) [M$^+$+2], 198 (44) [M$^+$+1], 197 (100) [M$^+$], 164 (14), 134 (11), 107 (10). Anal. Calcd for C_9H_5ClFNO (197.60): C, 54.71; H, 2.55. Found: C, 54.51; H, 2.61.

4.1.2. 8-Bromo-3-fluoroquinol-2(1*H*)-one (2e). Prepared analogously from 2-bromoaniline (0.10 kg, 0.60 mol) with 96% aqueous sulfuric acid at 50 °C for 5 h; tiny colorless needles (from aqueous *N*,*N*-dimethylformamide); mp 202–204 °C (reprod.); yield: 71.4 g (64%). ^{1}H NMR: δ=9.30 (s, broad, 1H), 7.71 (d, J=8.0 Hz, 1H), 7.51 (dd, J=8.0, 1.3 Hz, 1H), 7.46 (d, J=9.0 Hz, 1H), 7.16 (t, J=8.0 Hz, 1H) ppm. ^{13}C NMR*: δ=155.7 (d, J=27 Hz), 150.7 (d, J=252 Hz), 133.4 (s), 133.0 (s), 127.7 (d, J=6 Hz), 123.8 (s), 119.8 (d, J=8 Hz), 119.3 (dd, J=18, 4 Hz), 108.0 (s) ppm. MS: *m*/*z* (%)=242 (32) [M$^+$+1], 241 (100) [M$^+$], 215 (15), 134 (21), 107 (28), 81 (21). Anal. Calcd for C_9H_5BrFNO (242.05): C, 44.66; H, 2.08. Found: C, 44.66; H, 2.03.

4.1.3. 3-Fluoro-5,7-dimethyquinol-2(1*H*)-one (2f). Prepared analogously from 3,5-dimethylaniline (0.14 L, 0.14 kg, 1.2 mol) using 32% hydrochloric acid at 50 °C for 5 h; colorless platelets (from *N*,*N*-dimethylformamide); mp 278–280 °C (reprod.); yield: 81.8 g (72%). ^{1}H NMR: δ=7.70 (d, J=10.9 Hz, 1H), 7.13 (s, 1H), 6.95 (s, 1H), 2.50 (s, 3H), 2.42 (s, 3H) ppm. ^{13}C NMR*: δ=155.4 (d, J=27 Hz), 149.8 (d, J=249 Hz), 139.0 (s), 136.3 (s), 134.9 (d, J=6 Hz), 125.1 (s), 116.5 (d, J=17 Hz), 114.5 (d, J=6 Hz), 113.0 (s), 21.1 (s), 18.3 (s) ppm. MS: *m*/*z* (%)=208 (19%), 192 (24) [M$^+$+1], 191 (100) [M$^+$], 190 (27), 175 (7). Anal. Calcd for $C_{11}H_{10}FNO$ (191.20): C, 69.10; H, 5.27. Found: C, 68.88; H, 5.10.

4.1.4. 2-Bromo-3-fluoroquinoline (3a). 3-Fluoroquinol-2(1*H*)-one (**2a**; 33 g, 0.20 mol) and phosphoric tribromide (0.12 kg, 0.40 mol) were heated together for 30 min to 150 °C before the mixture was poured on crushed ice (0.50 kg), neutralized with a 5.0 M aqueous solution of sodium hydroxide (0.30 L) and subjected to a steam distillation; colorless needles (from hexanes); mp 82–83 °C (reprod.); yield: 40.8 g (90%). ^{1}H NMR: δ=8.07 (d, J=8.6 Hz, 1H), 7.80 (d, J=8.1 Hz, 2H), 7.71 (t, J=7.5 Hz, 1H), 7.61 (t, J=7.3 Hz, 1H) ppm. ^{13}C NMR: δ=151.9 (d, J=260 Hz), 145.3 (s), 132.1 (d, J=26 Hz), 129.6 (s), 128.7 (s), 128.1 (s), 127.1 (d, J=5 Hz), 119.7 (d, J=18 Hz) ppm. ^{19}F NMR: δ=−115.5 (d, J=8.2 Hz) ppm. MS: *m*/*z* (%)=242 (30), 226 (62) [M$^+$+1], 225 (100) [M$^+$], 162 (42), 146 (14). Anal. Calcd for C_9H_5BrFN (226.04): C, 47.82; H, 2.23. Found: C, 47.78; H, 2.26.

4.1.5. 2-Bromo-6-chloro-3-fluoroquinoline (3b). Prepared analogously from 6-chloro-3-fluoroquinol-2(1*H*)-one (**2b**; 59 g, 0.30 mol). The reaction mixture was kept for 30 min at 190 °C; colorless needles (from ethanol); mp 139–141 °C (reprod.); yield: 61.1 g (78%). ^{1}H NMR: δ=7.97 (d, J=9.3 Hz, 1H), 7.76 (d, J=2.3 Hz, 1H), 7.69 (d, J=7.5 Hz, 1H), 7.62 (dd, J=9.3, 2.3 Hz, 1H) ppm. ^{13}C NMR: δ=153.0 (d, J=263 Hz), 143.5 (s), 134.2 (s), 132.4 (d, J=27 Hz), 130.6 (s), 130.1 (s), 128.8 (d, J=4 Hz), 125.8 (d, J=5 Hz), 118.7 (d, J=19 Hz) ppm. MS: *m*/*z* (%)=260 (52) [M$^+$+1], 259 (100) [M$^+$], 196 (11), 181 (5), 144 (9). Anal. Calcd for $C_9H_5BrClFNO$ (260.49): C, 41.50; H, 1.55. Found: C, 41.50; H, 1.51.

4.1.6. 2-Bromo-3,7-difluoroquinoline (3c). Prepared analogously as described for quinoline **3a** from the 5:95 mixture of 3,5- and 3,7-difluoroquinol-2(1*H*)-one (**2c**; 47 g, 0.26 mol); colorless needles (from hexanes); mp 105–107 °C (reprod.); yield: 47.6 g (75%). ^{1}H NMR: δ=7.8 (m, 2H), 7.70 (dd, J=8.5, 2.4 Hz, 1H), 7.42 (dt, J=8.5, 2.4 Hz, 1H) ppm. ^{13}C NMR: δ=162.4 (d, J=252 Hz), 151.7 (d, J=258 Hz), 145.4 (s), 133.3 (dd, J=26, 7 Hz), 129.0 (dm, J=164 Hz), 124.6 (s), 119.4 (ddd, J=165, 20, 5 Hz), 118.4 (ddd, J=165, 26, 5 Hz), 112.4 (dd, J=165, 22 Hz) ppm. ^{19}F NMR: δ=−116.3 (t, J=7.6 Hz), −109.5 (quint, J=7.6 Hz) ppm. MS: *m*/*z* (%)=244 (62) [M$^+$+1],

243 (100) [M^+], 242 (45), 180 (7), 163 (8). Anal. Calcd for $C_9H_4BrF_2N$ (244.04): C, 44.30; H, 1.65. Found: C, 44.32; H, 1.82.

4.1.7. 2-Bromo-3-fluoro-7-methoxyquinoline (3d). The 1:4 mixture of 3-fluoro-5- and 3-fluoro-7-methoxyquinol-2(1*H*)-one (**2d**; 28 g, 0.15 mol) was heated together with phosphoric tribromide (84 g, 0.29 mol) in anhydrous propionitrile (0.30 L) under reflux for 4 h. After evaporation of the solvent, the residue was poured on ice (0.30 kg). A 5.0 M aqueous solution (0.20 L) of sodium hydroxide was added. The precipitate was collected by filtration and washed with water (4×50 mL). The crude product was dissolved in ethyl acetate, filtered through a pad of silica gel and crystallized from a mixture of ethyl acetate and hexanes; colorless needles; mp 136–138 °C (reprod.); yield: 24.5 g (62%). ^{1}H NMR: δ=7.73 (d, J=7.7 Hz, 1H), 7.66 (d, J=9.1 Hz, 1H), 7.38 (d, J=2.5 Hz, 1H), 7.25 (dd, J=9.1, 2.5 Hz, 1H), 3.93 (s, 3H) ppm. ^{13}C NMR: δ=160.8 (s), 151.4 (d, J=256 Hz), 146.3 (s), 131.9 (d, J=26 Hz), 127.9 (d, J=4 Hz), 122.9 (d, J=3 Hz), 121.4 (s), 119.9 (d, J=19 Hz), 106.9 (s), 55.7 (s) ppm. MS: *m/z* (%)=256 (62) [M^++1], 255 (100) [M^+], 254 (48), 211 (6), 175 (7), 132 (6). Anal. Calcd for $C_{10}H_7BrFNO$ (256.07): C, 46.90; H, 2.76. Found: C, 46.90; H, 2.71.

4.1.8. 2,8-Dibromo-3-fluoroquinoline (3e). Prepared analogously as described for quinoline **3a** from 8-bromo-3-fluoroquinol-2(1*H*)-one (**2e**; 58 g, 0.24 mol); colorless needles (from ethanol); mp 129–131 °C (reprod.); yield: 56.5 g (77%). ^{1}H NMR: δ=7.99 (d, J=7.5 Hz, 1H), 7.77 (d, J=7.5 Hz, 1H), 7.74 (d, J=8.4 Hz, 1H), 7.43 (t, J=7.5 Hz, 1H) ppm. ^{13}C NMR: δ=153.0 (d, J=263 Hz), 142.4 (s), 133 (m), 129.2 (d, J=4 Hz), 128.5 (s), 126.9 (d, J=5 Hz), 123.6 (s), 119.9 (d, J=19 Hz) ppm. MS: *m/z* (%)=304 (56) [M^++1], 303 (100) [M^+], 224 (42), 145 (76), 118 (16). Anal. Calcd for $C_9H_4Br_2FN$ (304.94): C, 35.45; H, 1.32. Found: C, 35.64; H, 1.17.

4.1.9. 2-Bromo-3-fluoro-5,7-dimethylquinoline (3f). 3-Fluoro-5,7-dimethylquinol-2(1*H*)-one (**2f**; 4.8 g, 25 mmol) and phosphoric tribromide (14 g, 50 mmol) were heated in anhydrous propionitrile (50 mL) under reflux for 2 h. After evaporation of the volatiles, the residue was poured on ice (50 g). A 2.0 M aqueous solution (84 mL) of sodium hydroxide was added. The precipitate was collected by filtration, and washed with water (4×10 mL). The crude product was dissolved in ethyl acetate, filtered through a pad of silica gel and recrystallized from ethanol; colorless needles; mp 126–128 °C (reprod.); yield: 5.21 g (82%). ^{1}H NMR: δ=7.86 (d, J=8.3 Hz, 1H), 7.68 (s, 1H), 7.27 (s, 1H), 2.60 (s, 3H), 2.50 (s, 3H) ppm. ^{13}C NMR: δ=151.7 (d, J=258 Hz), 145.8 (s), 139.6 (s), 133.7 (d, J=5 Hz), 131.0 (d, J=26 Hz), 130.7 (s), 125.7 (s), 125.5 (s), 116.5 (d, J=19 Hz), 21.7 (s), 18.6 (s) ppm. MS: *m/z* (%)=254 (93) [M^++1], 253 (100) [M^+], 252 (18), 240 (22), 238 (27). Anal. Calcd for $C_{11}H_9BrFN$ (254.10): C, 51.99; H, 3.57. Found: C, 52.16; H, 3.59.

4.1.10. 3-Fluoroquinoline[1] (4a). Palladium (10% on charcoal, 0.20 g) was added to a solution of 2-bromo-3-fluoroquinoline (**3a**; 7.9 g, 35 mmol) and triethylamine (9.8 mL, 7.1 g, 70 mmol) in methanol (60 mL), stirred under an atmosphere of hydrogen (1 atm) at 25 °C. After 2 h, the required amount of hydrogen had been taken up. Distillation afforded a colorless oil; bp 47–48 °C/1.9 mmHg; mp 4–5 °C (reprod.); yield: 4.34 g (87%). ^{1}H NMR: δ=8.82 (d, J=2.6 Hz, 1H), 8.13 (d, J=8.3 Hz, 1H), 7.79 (d, J=8.6 Hz, 1H), 7.76 (dd, J=9.0, 2.9 Hz, 1H), 7.68 (t, J=8.0 Hz, 1H), 7.57 (t, J=8.0 Hz, 1H) ppm. ^{13}C NMR: δ=156.2 (d, J=256 Hz), 145.4 (s), 141.5 (d, J=27 Hz), 129.5 (s), 128.5 (s), 127.6 (s), 127.2 (s), 118.2 (d, J=16 Hz) ppm. MS: *m/z* (%)=148 (19) [M^++1], 147 (100) [M^+], 120 (9).

4.1.11. 8-Bromo-3-fluoroquinoline (4e). A solution containing 2,8-dibromo-3-fluoroquinoline (**3e**; 7.6 g, 25 mol) and butyllithium (25 mmol) in toluene (0.10 L) and hexanes (20 mL) was kept for 45 min at −100 °C, before being treated with methanol (10 mL, 8.0 g, 0.25 mol). Afterwards the solvents were stripped off and the residue was crystallized; colorless needles (aqueous methanol); mp 67–68 °C (reprod.); yield: 5.09 g (90%). ^{1}H NMR: δ=8.94 (d, J=2.9 Hz, 1H), 8.04 (dd, J=7.4, 1.3 Hz, 1H), 7.81 (dd, J=8.3, 2.9 Hz, 1H), 7.78 (dd, J=8.3, 1.3 Hz, 1H), 7.44 (t, J=8.0 Hz, 1H) ppm. ^{13}C NMR: δ=156.7 (d, J=259 Hz), 142.4 (s), 142.1 (s), 132.4 (s), 129.8 (d, J=5 Hz), 128.2 (s), 127.3 (d, J=4 Hz), 124.9 (s), 118.9 (d, J=17 Hz) ppm. MS: *m/z* (%)=226 (22) [M^++1], 225 (49) [M^+], 146 (100), 126 (35), 119 (30), 100 (20). Anal. Calcd for C_9H_5BrFN (226.05): C, 47.82; H, 2.23. Found: C, 47.54; H, 2.07.

4.1.12. 3-Fluoroquinoline-2-carboxylic acid (5a). A solution containing 2-bromo-3-fluoroquinoline (**3a**; 10 g, 45 mol) and butyllithium (45 mmol) in diethyl ether (0.20 L) and hexanes (20 mL) was kept for 45 min at −75 °C before being poured onto an excess of freshly crushed dry ice. After addition of water (0.10 L), the reaction mixture was extracted with diethyl ether (3×45 mL) and the aqueous layer was acidified with 2.0 M aqueous solution of hydrochloric acid (10 mL) to pH 1. The precipitate was collected by filtration and washed with water (2×10 mL); colorless needles (from aqueous *N*,*N*-dimethylformamide); mp 129–130 °C (decomp.); yield: 6.19 g (72%). ^{1}H NMR: δ=8.17 (d, J=8.6 Hz, 1H), 8.06 (d, J=10.2 Hz, 1H), 7.91 (d, J=8.3 Hz, 1H), 7.83 (td, J=7.8, 1.4 Hz, 1H), 7.75 (t, J=7.5 Hz, 1H) ppm. ^{13}C NMR: δ=161.0 (s), 155.9 (d, J=271 Hz), 143.0 (s), 136.0 (d, J=11 Hz), 131.9 (d, J=6 Hz), 130.5 (m), 129.6 (s), 127.4 (d, J=4 Hz), 123.4 (d, J=18 Hz) ppm. MS: *m/z* (%)=208 (31), 193 (10) [M^++2], 192 (45) [M^++1], 191 (100) [M^+], 147 (78). Anal. Calcd for $C_{10}H_6FNO_2$ (191.16): C, 62.83; H, 3.16. Found: C, 63.18; H, 3.29.

4.1.13. 6-Chloro-3-fluoroquinoline-2-carboxylic acid (5b). Prepared analogously from 2-bromo-6-chloro-3-fluoroquinoline (**3b**; 6.5 g, 25 mmol) but, to improve the yield, using toluene (0.11 L) rather than diethyl ether as the solvent; colorless needles (from acetone) mp 147–149 °C (decomp.); yield: 4.60 g (82%). ^{1}H NMR: δ=8.11 (d, J=9.1 Hz, 1H), 7.97 (d, J=10.2 Hz, 1H), 7.90 (d, J=2.3 Hz, 1H), 7.75 (dd, J=9.1, 2.3 Hz, 1H) ppm. ^{13}C NMR (D_3CCOCD_3): δ=163.4 (d, J=6 Hz), 156.4 (d, J=267 Hz), 143.0 (s), 140.9 (d, J=14 Hz), 135.8 (s), 132.3 (s), 132.1 (d, J=6 Hz), 131.4 (s), 126.9 (d, J=4 Hz), 121.8

(d, $J=19$ Hz) ppm. MS: m/z (%)=226 (24) [$M^+ +1$], 225 (7) [M^+], 208 (24), 181 (100), 146 (21). Anal. Calcd for $C_{10}H_5ClFNO_2$ (225.60): C, 53.24; H, 2.32. Found: C, 53.13; H, 1.91.

4.1.14. 3,7-Difluoroquinoline-2-carboxylic acid (5c). Analogously as described in the preceding paragraph from 2-bromo-3,7-difluoroquinoline (**3c**; 4.9 g, 20 mmol); colorless needles (from aqueous *N*,*N*-dimethylformamide); mp 136–137 °C (decomp.); yield: 2.80 g (67%). ^{1}H NMR: $\delta=$ 8.09 (d, $J=9.9$ Hz, 1H), 7.93 (dd, $J=9.1$, 5.6 Hz, 1H), 7.81 (dd, $J=9.1$, 2.7 Hz, 1H), 7.56 (tm, $J=8.6$ Hz, 1H) ppm. ^{13}C NMR*: $\delta=164.8$ (d, $J=5$ Hz), 162.8 (dm, $J=247$ Hz), 154.1 (d, $J=259$ Hz), 144.9 (s), 143.0 (dd, $J=17$, 4 Hz), 130.8 (dm, $J=166$ Hz), 127.3 (d, $J=7$ Hz), 122.4 (ddd, $J=$ 169, 19, 5 Hz), 120.4 (dd, $J=166$, 26 Hz), 113.4 (dd, $J=$ 167, 20 Hz) ppm. MS: m/z %=210 (22) [$M^+ +1$], 209 (20) [M^+], 192 (14), 165 (100). Anal. Calcd for $C_{10}H_5F_2NO_2$ (209.15): C, 57.43; H, 2.41. Found: C, 57.38; H, 2.68.

4.1.15. 3-Fluoro-7-methoxyquinoline-2-carboxylic acid (5d). Prepared analogously as described for acid **5a**, from 2-bromo-3-fluoro-7-methoxyquinoline (**3d**; 6.40 g, 25 mmol); pale yellow prisms (from aqueous *N*,*N*-dimethylformamide); mp 135–136 °C (decomp.); yield: 4.52 g (82%). ^{1}H NMR: $\delta=7.98$ (d, $J=10.2$ Hz, 1H), 7.77 (d, $J=9.0$ Hz, 1H), 7.4 (m, 2H), 3.99 (s, 3H) ppm. ^{13}C NMR: $\delta=161.7$ (s), 161.4 (d, $J=6$ Hz), 155.3 (d, $J=267$ Hz), 144.9 (s), 135.5 (d, $J=10$ Hz), 128.1 (d, $J=3$ Hz), 127.3 (d, $J=5$ Hz), 124.7 (s), 123.6 (d, $J=18$ Hz), 106.7 (s), 56 (m) ppm. MS: m/z (%)=223 (5) [$M^+ +2$], 222 (31) [$M^+ +1$], 221 (45) [M^+], 204 (25), 177 (100). Anal. Calcd for $C_{11}H_8FNO_3$ (221.19): C, 59.73; H, 3.65. Found: C, 59.66; H, 3.72.

4.1.16. 8-Bromo-3-fluoroquinoline-2-carboxylic acid (5e). Prepared from 2,8-dibromo-3-fluoroquinoline (**3e**; 7.6 g, 25 mmol) in the same way as described for acid **5b** but starting the reaction at −100 °C; colorless tiny prisms (from diethyl ether); mp 137–138 °C (decomp.); yield: 4.57 g (79%). ^{1}H NMR: $\delta=8.15$ (d, $J=7.5$ Hz, 1H), 8.12 (d, $J=9.8$ Hz, 1H), 7.89 (dd, $J=8.3$, 1.1 Hz, 1H), 7.60 (t, $J=7.9$ Hz, 1H) ppm. ^{13}C NMR (D_3CCOCD_3): $\delta=163.3$ (d, $J=6$ Hz), 156.3 (d, $J=267$ Hz), 141.5 (s), 141.3 (d, $J=$ 15 Hz), 134.4 (s), 132.7 (d, $J=6$ Hz), 131.0 (s), 128.5 (d, $J=4$ Hz), 125.3 (s), 123.3 (d, $J=18$ Hz) ppm. MS: m/z (%)=270 (48) [$M^+ +1$], 269 (100) [M^+], 251 (20), 225 (40), 191 (8). Anal. Calcd for $C_{10}H_5BrFNO_2$ (270.05): C, 44.48; H, 1.87. Found: C, 44.41; H, 2.11.

4.1.17. 3-Fluoro-5,7-dimethylquinoline-2-carboxylic acid (5f). Prepared analogously from 2-bromo-5,7-dimethyl-3-fluoroquinoline (**3f**; 6.4 g, 25 mmol) as described for acid **5b**; colorless needles (from aqueous methanol); mp 125–126 °C (decomp.); yield: 3.67 g (67%). ^{1}H NMR: $\delta=$ 8.11 (d, $J=11.2$ Hz, 1H), 7.78 (s, 1H), 7.40 (s, 1H), 2.67 (s, 3H), 2.56 (s, 3H) ppm. ^{13}C NMR (D_3CCOCD_3): $\delta=163.3$ (d, $J=6$ Hz), 155.6 (d, $J=265$ Hz), 145.0 (s), 140.6 (s), 138.6 (d, $J=14$ Hz), 135.1 (d, $J=5$ Hz), 132.9 (s), 129.1 (d, $J=5$ Hz), 127.1 (s), 119.7 (d, $J=18$ Hz) ppm. MS: m/z (%)=219 (10) [M^+], 218 (100), 175 (80), 160 (70). Anal. Calcd for $C_{12}H_{10}FNO_2$ (219.21): C, 65.75; H, 4.60. Found: C, 65.46; H, 4.33.

4.1.18. 2-Bromo-3-fluoroquinoline-4-carboxylic acid (6a). Diisopropylamine (7.0 mL, 5.1 g, 50 mmol) and 2-bromo-3-fluoroquinoline (**3a**; 11 g, 50 mmol) were added consecutively to a solution of butyllithium (50 mmol) in hexanes (30 mL) and tetrahydrofuran (0.21 L) cooled in a methanol/dry ice bath. After 2 h at −75 °C, the mixture was poured onto an excess of freshly crushed solid carbon dioxide. The solvents were removed under reduced pressure. The residue was taken up in water (0.15 L) and washed with diethyl ether (3×25 mL). The aqueous layer was acidified with 2.0 M hydrochloric acid (25 mL) to pH 1. The precipitate formed was collected and washed with water (2×20 mL); colorless needles (from acetone); mp 196–197 °C (decomp.); yield: 12.7 g (94%). ^{1}H NMR*: $\delta=8.13$ (d, $J=7.6$ Hz, 1H), 8.08 (dd, $J=8.2$, 1.2 Hz, 1H), 7.92 (td, $J=7.6$, 1.2 Hz, 1H), 7.85 (td, $J=7.6$, 1.2 Hz, 1H) ppm. ^{13}C NMR*: $\delta=164.3$ (s), 148.6 (d, $J=261$ Hz), 145.6 (d, $J=$ 2 Hz), 132.5 (d, $J=27$ Hz), 131.5 (s), 130.3 (s), 129.5 (s), 126.6 (d, $J=16$ Hz), 126.1 (d, $J=5$ Hz), 124.8 (s) ppm. ^{19}F NMR*: $\delta=-114.3$ (s) ppm. MS: m/z (%)=270 [$M^+ +1$] (100), 269 (56) [M^+], 252 (2), 207 (4). Anal. Calcd for $C_{10}H_5BrFNO_2$ (270.06): C, 44.48; H, 1.87. Found: C, 44.40; H, 1.91.

4.1.19. 2-Bromo-6-chloro-3-fluoroquinoline-4-carboxylic acid (6b). Prepared analogously from 2-bromo-6-chloro-3-fluoroquinoline (**3b**; 6.5 g, 25 mmol); colorless needles (from aqueous *N*,*N*-dimethylformamide); mp 207–209 °C (decomp.); yield: 6.62 g (87%). ^{1}H NMR*: $\delta=8.1$ (m, 2H), 7.89 (dd, $J=9.1$, 2.2 Hz, 1H) ppm. ^{13}C NMR*: $\delta=162.9$ (s), 148.9 (d, $J=264$ Hz), 143.0 (d, $J=3$ Hz), 134.0 (s), 132.4 (d, $J=27$ Hz), 130.8 (s), 130.5 (s), 124.9 (s), 124.2 (d, $J=16$ Hz), 123.9 (s) ppm. MS: m/z (%)=304 (47) [$M^+ +$ 1], 303 (100) [M^+], 259 (6), 224 (15), 179 (16). Anal. Calcd for $C_{10}H_4BrClFNO_2$ (304.50): C, 39.44; H, 1.32. Found: C, 39.55; H, 1.16.

4.1.20. 2-Bromo-3,7-difluoroquinoline-4-carboxylic acid (6c). Prepared analogously from 2-bromo-3,7-difluoroquinoline (**3c**; 6.1 g, 25 mmol); colorless needles (from methanol); mp 200–202 °C (decomp.); yield: 4.90 g (68%). ^{1}H NMR (D_3CCOCD_3): $\delta=8.27$ (dd, $J=9.5$, 6.5 Hz, 1H), 7.79 (dd, $J=9.5$, 2.4 Hz, 1H), 7.70 (tdd, $J=9.3$, 2.4, 1.0 Hz, 1H) ppm. ^{13}C NMR*: $\delta=163.6$ (s), 162.9 (dm, $J=244$ Hz), 148.2 (d, $J=259$ Hz), 146.0 (symm. m), 133.7 (d, $J=$ 27 Hz), 128.5 (dm, $J=166$ Hz), 126.3 (dd, $J=16$, 3 Hz), 121.8 (symm. m), 120.2 (ddd, $J=167$, 25, 4 Hz), 113.3 (dd, $J=168$, 22 Hz) ppm. ^{19}F NMR: $\delta=-115.0$ (d, $J=7.6$ Hz), −109.0 (quint, $J=7.6$ Hz) ppm. MS: m/z (%)=288 (55) [$M^+ +1$], 287 (100) [M^+], 243 (4), 208 (16), 163 (18). Anal. Calcd for $C_{10}H_4BrF_2NO_2$ (288.05): C, 41.70; H, 1.40. Found: C, 41.75; H, 1.42.

4.1.21. 2-Bromo-3-fluoro-7-methoxyquinoline-4-carboxylic acid (6d). Prepared analogously from 2-bromo-3-fluoro-7-methoxyquinoline (**3d**; 6.4 g, 25 mmol); colorless needles (from aqueous *N*,*N*-dimethylformamide); mp 210–212 °C (decomp.); yield: 6.23 g (83%). ^{1}H NMR*: $\delta=7.94$ (d, $J=$ 9.3 Hz, 1H), 7.50 (d, $J=2.5$ Hz, 1H), 7.46 (dd, $J=9.3$, 2.5 Hz, 1H), 3.93 (s, 3H) ppm. ^{13}C NMR*: $\delta=163.5$ (s), 160.6 (s), 146.5 (d, $J=258$ Hz), 146.4 (s), 131.2 (d, $J=$ 27 Hz), 126.0 (d, $J=4$ Hz), 125.8 (d, $J=16$ Hz), 121.9 (s), 118.5 (s), 107.2 (s), 55.8 (t, $J=27$ Hz) ppm. MS: m/z (%)=

300 (100) [$M^+ + 1$], 299 (36) [M^+], 256 (4), 222 (16). Anal. Calcd for $C_{11}H_7BrFNO_3$ (300.08): C, 44.03; H, 2.35. Found: C, 44.26; H, 2.38.

4.1.22. 2,8-Dibromo-3-fluoroquinoline-4-carboxylic acid (6e). Prepared analogously from 2,8-dibromo-3-fluoroquinoline (**3e**; 24 g, 79 mmol); colorless needles (from acetonitrile); mp 175–176 °C (decomp.); yield: 25.4 g (92%). ^{1}H NMR*: $\delta=8.26$ (d, $J=7.6$ Hz, 1H), 8.05 (d, $J=7.9$ Hz, 1H), 7.70 (t, $J=7.9$ Hz, 1H) ppm. ^{13}C NMR*: $\delta=163.0$ (s), 148.5 (d, $J=263$ Hz), 141.4 (s), 134.0 (s), 132.8 (d, $J=27$ Hz), 129.0 (s), 126.1 (d, $J=17$ Hz), 125.4 (s), 125.2 (d, $J=4$ Hz), 123.0 (s) ppm. MS: *m/z* (%)=348 (75) [$M^+ + 1$], 347 (100) [M^+], 346 (8), 268 (12), 145 (15). Anal. Calcd for $C_{10}H_4Br_2FNO_2$ (348.95): C, 34.42; H, 1.16. Found: C, 34.59; H, 1.27.

4.1.23. 2-Bromo-3-fluoro-5,7-dimethylquinoline-4-carboxylic acid (6f). Prepared analogously from 2-bromo-3-fluoro-5,7-dimethylquinoline (**13**; 43 g, 0.17 mol); colorless needles (from aqueous acetone); mp 192–194 °C (decomp.); yield: 41.6 g (82%). ^{1}H NMR (D_3CCOCD_3): $\delta=7.70$ (s, 1H), 7.43 (s, 1H), 2.70 (s, 3H), 2.50 (s, 3H) ppm. ^{13}C NMR*: $\delta=165.7$ (s), 148.5 (s), 146.0 (s), 140.1 (s), 133.6 (d, $J=5$ Hz), 133.2 (s), 129.9 (d, $J=26$ Hz), 126.8 (d, $J=19$ Hz), 126.2 (s), 20.8 (s), 19.5 (s) ppm. MS: *m/z* (%)= 298 (100) [$M^+ + 1$], 297 (36) [M^+], 281 (10), 254 (18), 253 (17), 172 (26). Anal. Calcd for $C_{12}H_9BrFNO_2$ (298.11): C, 48.35; H, 3.04. Found: C, 48.76; H, 3.10.

4.1.24. 3-Fluoroquinoline-4-carboxylic acid.[1] (7a) Palladium (10% on charcoal, 0.13 g) was added to a solution of 2-bromo-3-fluoroquinoline-4-carboxylic acid (**6a**; 6.8 g, 25 mmol) and triethylamine (7.0 mL, 5.1 g, 50 mmol) in methanol (50 mL), which was stirred under an atmosphere of hydrogen (1 atm) at 25 °C. After 4 h, the required amount of hydrogen had been taken up. The reaction mixture was filtered and concentrated. Upon acidification with a 1.0 M aqueous solution of hydrochloric acid (30 mL) to pH 1, a precipitate settled out which was collected by filtration; colorless needles (from acetone); mp 242–243 °C (decomp.); yield: 4.06 g (85%). ^{1}H NMR*: $\delta=9.07$ (d, $J=1.0$ Hz, 1H), 8.14 (dd, $J=8.2$, 1.0 Hz, 1H), 8.06 (dd, $J=$ 8.2, 1.0 Hz, 1H), 7.84 (td), $J=7.0$, 1.0 Hz, 1H), 7.78 (t, $J=$ 7.0 Hz) ppm. ^{13}C NMR*: $\delta=164.3$ (s), 151.6 (d, $J=259$ Hz), 144.9 (s), 141.9 (d, $J=28$ Hz), 129.5 (s), 129.2 (s), 128.9 (s), 124.9 (d, $J=5$ Hz), 123.9 (s), 123.7 (d, $J=13$ Hz) ppm. MS: *m/z* (%)=192 (32) [$M^+ + 1$], 191 (100) [M^+], 174 (16), 173 (9), 147 (4), 135 (11).

4.1.25. 6-Chloro-3-fluoroquinoline-4-carboxylic acid (7b). 2-Bromo-6-chloro-3-fluoroquinoline-4-carboxylic acid (**6b**; 7.6 g, 25 mmol) and tin(II) chloride (4.8 g, 25 mmol) were added to a 5.0 M solution (0.10 mL) of hydrogen chloride in anhydrous ethanol and heated under reflux for 4 h. After evaporation of the solvent, the residue was treated with water (50 mL). The precipitate was collected and washed with water (2×20 mL); colorless needles (from acetone); mp 251–254 °C (decomp.); yield: 4.85 g (86%). ^{1}H NMR*: $\delta=9.11$ (s, 1H), 8.2 (m, 2H), 7.85 (dd, $J=11.5$, 2.3 Hz, 1H) ppm. ^{13}C NMR*: $\delta=$ 163.8 (s), 152.6 (d, $J=263$ Hz), 143.4 (s), 142.7 (d, $J=27$ Hz), 133.7 (s), 131.6 (s), 129.7 (s), 125.0 (s), 123.7 (s), 122.3 (d, $J=$ 13 Hz) ppm. MS: *m/z* (%)=226 (100) [$M^+ + 1$], 225 (72) [M^+], 190 (3), 208 (11), 181 (5). Anal. Calcd for $C_{10}H_5ClFNO_2$ (225.60): C, 53.24; H, 2.23. Found: C, 53.18; H, 1.96.

4.1.26. 3,7-Difluoroquinoline-4-carboxylic acid (7c). Prepared as described above for the acid **7a**, from 2-bromo-3,7-difluoroquinoline-4-carboxylic acid (**6c**; 7.2 g, 25 mmol); colorless tiny needles (from aqueous *N*,*N*-dimethylformamide); mp 250–251 °C (decomp.); yield: 4.90 g (70%). ^{1}H NMR (D_3CCOCD_3): $\delta=9.13$ (s, 1H), 8.17 (dd, $J=9.6$, 5.6 Hz, 1H), 7.93 (dd, $J=9.6$, 2.8 Hz, 1H), 7.73 (td, $J=8.6$, 2.8 Hz, 1H) ppm. ^{13}C NMR*: $\delta=163.8$ (s), 161.6 (d, $J=$ 245 Hz), 151.3 (d, $J=258$ Hz), 146 (symm. m), 143.1 (dd, $J=186$, 28 Hz), 127.5 (dm, $J=166$ Hz), 123.7 (d, $J=$ 14 Hz), 121.0 (s), 119.4 (dd, $J=25$, 4 Hz), 113.4 (dd, $J=26$, 4 Hz) ppm. MS: *m/z* (%)=210 (29) [$M^+ + 1$], 209 (100) [M^+], 208 (17), 192 (14), 15 (8). Anal. Calcd for $C_{10}H_5F_2NO_2$ (209.15): C, 57.43; H, 2.41. Found: C, 57.15; H, 2.44.

4.1.27. 3-Fluoro-7-methoxyquinoline-4-carboxylic acid (7d). Prepared analogously from 2-bromo-3-fluoro-7-methoxyquinoline-4-carboxylic acid (**6d**; 7.5 g, 25 mmol); golden yellow platelets (from *N*,*N*-dimethylformamide); mp 267–270 °C (decomp.); yield: 3.81 g (69%). ^{1}H NMR*: $\delta=9.00$ (s, 1H), 7.99 (d, $J=8.9$ Hz, 1H), 7.52 (d, $J=$ 2.5 Hz, 1H), 7.44 (dd, $J=8.9$, 2.5 Hz, 1H), 3.95 (s, 3H) ppm. ^{13}C NMR*: $\delta=164.5$ (s), 159.8 (s), 150.7 (d, $J=256$ Hz), 146.7 (s), 141.7 (d, $J=27$ Hz), 125.9 (s), 123.8 (d, $J=14$ Hz), 121.6 (s), 118.6 (s), 107.9 (s), 56 (m) ppm. MS: *m/z* (%)=223 (5) [$M^+ + 2$], 222 (37) [$M^+ + 1$], 221 (100) [M^+], 191 (4), 178 (11). Anal. Calcd for $C_{11}H_8FNO_3$ (221.18): C, 59.73; H, 3.65. Found: C, 59.92; H, 3.60.

4.1.28. 8-Bromo-3-fluoro-4-quinolinecarboxylic acid (7e). Prepared as described above for the acid **7b** 2,8-dibromo-3-fluoroquinoline-4-carboxylic acid (**6e**; 10 g, 30 mmol) was treated with tin(II) chloride (5.7 g, 30 mmol) to afford colorless tiny needles (from aqueous *N*,*N*-dimethylformamide); mp 224–225 °C (decomp.); yield: 6.89 g (85%). ^{1}H NMR*: $\delta=9.19$ (s, 1H), 8.23 (d, $J=7.3$ Hz, 1H), 8.07 (d, $J=8.6$ Hz, 1H), 7.67 (t, $J=8.0$ Hz, 1H) ppm. ^{13}C NMR*: $\delta=164.0$ (s), 152.2 (d, $J=262$ Hz), 142.9 (d, $J=28$ Hz), 141.5 (s), 133.0 (s), 129.5 (s), 125.6 (d, $J=3$ Hz), 125.2 (s), 124.7 (s), 124.5 (d, $J=14$ Hz) ppm. MS: *m/z* (%)=270 (56) [$M^+ + 1$], 269 (100) [M^+], 251 (6), 225 (26), 190 (8), 146 (24). Anal. Calcd for $C_{10}H_5BrFNO_2$ (270.06): C, 44.48; H, 1.87. Found: C, 44.66; H, 1.82.

4.1.29. 3-Fluoro-5,7-dimethylquinoline-4-carboxylic acid (7f). Prepared as described for the acid **7a** from 2-bromo-3-fluoro-5,7-dimethylquinoline-4-carboxylic acid (**6f**; 7.5 g, 25 mmol); colorless prisms (from ethanol); mp 196–197 °C (decomp.); yield: 4.38 g (80%). ^{1}H NMR (D_3CCOCD_3): $\delta=8.99$ (s, 1H), 7.78 (s, 1H), 7.42 (s, 1H), 2.65 (s, 3H), 2.48 (s, 3H) ppm. ^{13}C NMR*: $\delta=167.0$ (s), 151.6 (d, $J=253$ Hz), 146.2 (s), 140.4 (d, $J=27$ Hz), 133.4 (d, $J=5$ Hz), 132.8 (s), 127.3 (s), 125.1 (d, $J=17$ Hz), 120.6 (s), 20.8 (s), 19.7 (s) ppm. MS: *m/z* (%)=221 (9) [$M^+ + 2$], 220 (57) [$M^+ + 1$], 219 (100) [M^+], 201 (33), 175 (35), 172 (56). Anal. Calcd for $C_{12}H_9BrFNO_2$ (219.21): C, 65.75; H, 4.60. Found: C, 65.64; H, 4.51.

4.1.30. 3-Fluoro-5,7-dimethyl-2-[(thiocarbamoyl)hydrazonomethyl]quinoline-4-carboxylic acid (8b). Butylmagnesium chloride (25 mmol) in tetrahydrofuran (12 mL) and 2-bromo-3-fluoro-5,7-dimethylquinoline-4-carboxylic acid (**6f**, 7.5 g, 25 mmol) were added consecutively to a solution of butyllithium (50 mmol) in hexanes (35 mL) and tetrahydrofuran (80 mL) kept in an ice bath. After 2 h at 0 °C, the mixture was treated with *N*,*N*-dimethylformamide (2.1 mL, 2.0 g, 25 mmol). At 25 °C, it was poured into a 2.0 M aqueous solution of citric acid (50 mL) and extracted with ethyl acetate (3×25 mL). The combined organic layers were washed with brine (2×25 mL). The bright yellow powder obtained after the evaporation of the volatiles was dissolved in 70% aqueous ethanol (50 mL). Thiosemicarbazide (2.3 g, 25 mmol) was added and the mixture was heated under reflux for 1 h. The golden yellow tiny needles were collected by filtration and washed with 70% aqueous ethanol (2×10 mL); 195–196 °C (decomp.); 6.24 g (78%). ^{1}H NMR*: δ=11.93 (s, 1H), 8.57 (s, 1H), 8.33 (s, 1H), 7.77 (s, 1H), 7.57 (s, 1H), 7.42 (s, 1H), 2.64 (s, 3H), 2.48 (s, 3H) ppm. ^{13}C NMR*: δ=178.7 (s), 166.6 (s), 150.0 (d, J=263 Hz), 145.5 (s, broad), 142.0 (d, J=12 Hz), 139.2 (s), 138.6 (s, broad), 133.3 (s, broad), 133.1 (d, J=5 Hz), 126.9 (s), 126.5 (s), 120.6 (s), 20.8 (s), 19.4 (s) ppm. MS: *m*/*z* (%)=276 (31), 221 (96), 189 (100), 172 (61), 146 (30). Anal. Calcd for $C_{14}H_{13}FN_4O_2S$ (320.34): C, 52.49; H, 4.09. Found: C, 52.75; H, 4.17.

4.1.31. 2-Bromo-3-fluoroquinoline-4-carbaldehyde (9a). Diisopropylamine (10 mL, 7.1 g, 70 mmol) and 2-bromo-3-fluoroquinoline (**3a**; 16 g, 70 mmol) were added consecutively to a solution of butyllithium (70 mmol) in hexanes (45 mL) and tetrahydrofuran (0.30 L) cooled in a dry ice/methanol bath at -75 °C. After 2 h the mixture was treated with *N*,*N*-dimethylformamide (5.9 mL, 5.6 g, 70 mmol). Again 2 h later, it was poured into a 2.0 M aqueous solution of citric acid (0.15 L) and extracted with diethyl ether (3×70 mL). The combined organic layers were washed with brine (0.10 L) and evaporated; pale yellow needles (from heptanes); mp 76–78 °C (reprod.); yield: 17.4 g (98%). ^{1}H NMR: δ=10.81 (s, 1H), 9.0 (m, 1H), 8.1 (m, 1H), 7.77 (symm. m, 2H) ppm. ^{13}C NMR: δ=188.7 (symm. m), 155.5 (d, J=274 Hz), 145.8 (d, J=3 Hz), 132.5 (d, J=27 Hz), 130.7 (s), 130.1 (s), 129.1 (s), 125.2 (d, J=6 Hz), 123.3 (s), 122.0 (d, J=4 Hz) ppm. MS: *m*/*z* (%)=254 (23) [M^++1], 253 (55) [M^+], 225 (24), 146 (100), 126 (40). Anal. Calcd for $C_{10}H_5BrFNO$ (254.06): C, 47.28; H, 1.98. Found: C, 47.50; H, 1.90.

4.1.32. 2-Bromo-4-(1,3-dioxolan-2-yl)-3-fluoroquinoline (9b). At 0 °C, the boron trifluoride diethyl ether complex (25 mL, 28 g, 80 mmol) was added to a solution of 2-bromo-3-fluoro-quinoline-4-carbaldehyde (**9a**; 10 g, 40 mmol) and ethylene glycol (3.4 mL, 3.7 g, 60 mmol) in anhydrous dichloromethane (0.44 L). After 24 h at 25 °C, the mixture was poured into a 1.0 M aqueous solution of sodium hydrogen carbonate (0.30 L). The aqueous layer was extracted with dichloromethane (3×40 mL). The combined organic layers were washed with water (2×40 mL) and dried. Evaporation of the solvent afforded the product as colorless needles (from a mixture of hexanes and diethyl ether); mp 121–123 °C (reprod.); yield: 11.5 g (97%). ^{1}H NMR: δ=8.25 (d, J=8.6 Hz, 1H), 8.06 (d, J=8.6 Hz, 1H), 7.70 (t, J=8.3 Hz, 1H), 7.61 (t, J=8.3 Hz, 1H), 6.49 (s), 4.4 (symm. m, 2H), 4.2 (symm. m, 2H) ppm. ^{13}C NMR: δ=150.7 (d, J=264 Hz), 145.5 (d, J=3 Hz), 132.2 (d, J=28 Hz), 129.3 (s), 128.0 (s), 126 (m), 124.8 (d, J=5 Hz), 98.1 (d, J=4 Hz), 665.7 (s) ppm. MS: *m*/*z* (%)=298 (98) [M^++1], 297 (22) [M^+], 254 (5), 218 (9), 145 (25). Anal. Calcd for $C_{12}H_9BrFNO_2$ (298.11): C, 48.35; H, 3.04. Found: C, 48.40; H, 2.80.

4.1.33. 4-(1,3-Dioxolan-2-yl)-3-fluoroquinoline-2-carboxylic acid (10a). A solution containing 2-bromo-4-(1,3-dioxolan-2-yl)-3-fluoroquinoline (**9b**; 10 g, 35 mmol) and butyllithium (35 mmol) in tetrahydrofuran (50 mL), diethyl ether (0.10 L) and hexanes (25 mL) was stored 6 h at −100 °C before being poured onto an excess of freshly crushed dry ice. After addition of water (0.15 L) the reaction mixture was washed with diethyl ether (3×35 mL). When the aqueous layer was acidified to pH 1, the product precipitated. It was collected and washed with water (2×20 mL); colorless prisms (from acetone); mp 117–118 °C (decomp.); yield: 8.66 g (94%). ^{1}H NMR (D_3CCOCD_3): δ=8.49 (d, J=8.6 Hz, 1H), 8.17 (d, J=8.6 Hz, 1H), 7.85 (dd, J=8.3, 7.0 Hz, 1H), 7.76 (dd, J=8.0, 6.7 Hz, 1H), 6.56 (s, 1H), 4.4 (m, 2H), 4.2 (m, 2H) ppm. ^{13}C NMR*: δ=164.4 (d, J=5 Hz), 152.2 (d, J=267 Hz), 143.9 (d, J=3 Hz), 141.9 (d, J=19 Hz), 130.1 (s broad), 129.6 (s), 129.3 (s), 126.4 (d, J=6 Hz), 125.0 (d, J=5 Hz), 96.9 (d, J=7 Hz), 65.4 (s) ppm. MS: *m*/*z* (%)=263 (2) [M^+], 219 (46), 200 (8), 147 (64), 73 (100). Anal. Calcd for $C_{13}H_{10}FNO_4$ (263.22): C, 59.32; H, 3.83. Found: C, 59.05; H, 3.70.

4.1.34. 3-Fluoro-4-formylquinoline-2-carboxylic acid (10b). 4-(1,3-Dioxolan-2-yl)-3-fluoro-quinoline-2-carboxylic acid (**10a**; 6.6 g, 25 mmol) in tetrahydrofuran (60 mL) and 2.0 M hydrobromic acid (0.19 L) was stored 24 h at 25 °C before being extracted with diethyl ether (3×25 mL). The combined organic layers were washed with brine (2×25 mL) and dried with anhydrous sodium sulfate. After evaporation of the volatiles a light yellow solid was left behind, which crystallized from aqueous acetone and was isolated as colorless tiny needles; mp 114–115 °C (decomp.); 8.65 g (79%). ^{1}H NMR*: δ=10.75 (s, 1H), 8.90 (symm. m, 1H), 8.2 (symm. m, 1H), 7.9 (symm. m, 2H) ppm. ^{13}C NMR*: δ=189.4 (symm. m), 163.8 (d, J=4 Hz), 156.1 (d J=277 Hz), 143.8 (d J=3 Hz), 142.2 (d, J=18 Hz), 131.6 (s)129.9 (s), 124.6 (s), 124.4 (d, J=4 Hz), 122.7 (d, J=4 Hz) ppm. MS: *m*/*z* (%)=219 (4) [M^+], 218 (10), 200 (8), 175 (94), 147 (100), 127 (20), 120 (20). Anal. Calcd for $C_{11}H_6FNO_3$ (219.17): C, 60.28; H, 2.76. Found: C, 60.22; H, 2.75.

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