4-(Trifluoromethyl)quinoline Derivatives

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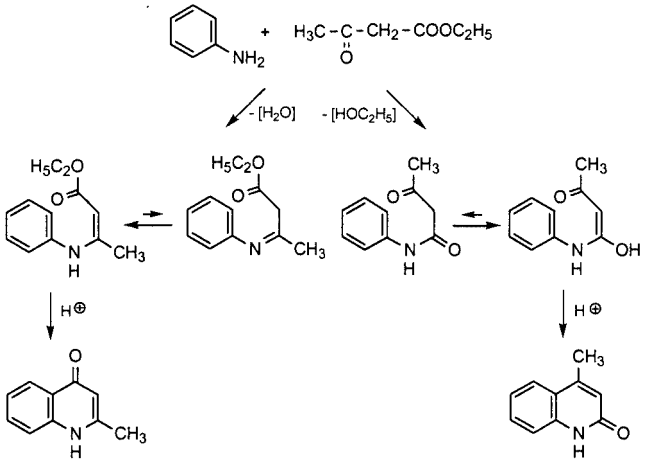
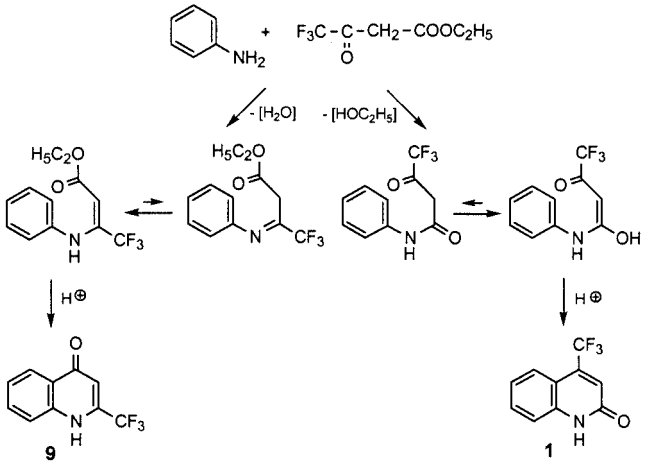
Under carefully controlled conditions, ethyl 4,4,4-trifluoroacetoacetate (ethyl 4,4,4-trifluoro-3-oxobutanoate) can be condensed with anilines and subsequently cyclized to give 4-trifluoromethyl-2-quinolinones **1** although only in poor yield. Heating these products with phosphoryl tribromide affords 2-bromo-4-(trifluoromethyl)quinolines **2** which can be converted into 4-(trifluoromethyl)quinolines **3** by reduction, 4-trifluoromethyl-2-quinolinecarboxylic acids **4** by permutational halogen/metal exchange followed by carboxylation, and 2-bromo-4-trifluoromethyl-3-quinolinecarboxylic acids **5** by consecutive treatment with lithium diisopropylamide and dry ice. Debromination of acids **5** makes 4-trifluoromethyl-3-quinolinecarboxylic acids **6** available. As at any time 2-trifluoromethyl-4-quinolinones **9** may form instead of the expected isomers **1**, the structures have to be assigned on the basis of unequivocal NMR spectral criteria.

"To kill two birds with one stone" is a saying that finds its chemical equivalent in the conversion of the same starting material into two different products. An early example was published more than a century ago by R. Knorr.[1] Aniline and ethyl acetoacetate react with each other at ambient temperature to form an imino ester (in equilibrium with the tautomerically predominent ethyl 3-anilino-2-butenoate) which gives 4-quinolinone upon acid-catalyzed cyclization [1] whereas the acetoacetanilide (or the tautomeric enol) and, after acid treatment, the 2-quinolinone are obtained when the condensation between aniline and the dicarbonyl compound is carried out at temperatures around 150 °C.[1,2]



The same dichotomy is encountered with ethyl 4,4,4-trifluoroacetoacetate, a versatile technical bulkware.[3] When combined with aniline in the presence of polyphosphoric acid at 150 °C, it produces the anil, which predominantly exists in the tautomeric 3-amino-2-butenoate form. Ring closure to the 2-trifluoromethyl-4-quinolinone occurs upon prolonged heating to 170 °C.[4] However, if aniline and ethyl trifluoroacetate are very briefly kept at 235 °C, the 4,4,4-trifluoroacetoacetanilide (or the enol-like tautomer) is obtained. Subsequent treatment with concentrated sulfuric acid at 95 °C yields the 4-trifluoromethyl-2-quinolinone.[5−7]



As described in a preceding article,[3] we have prepared a considerable number of 2-trifluoromethyl-4-quinolinones and have converted them into several families of functionalized, mainly carboxy-substituted, derivatives. We have

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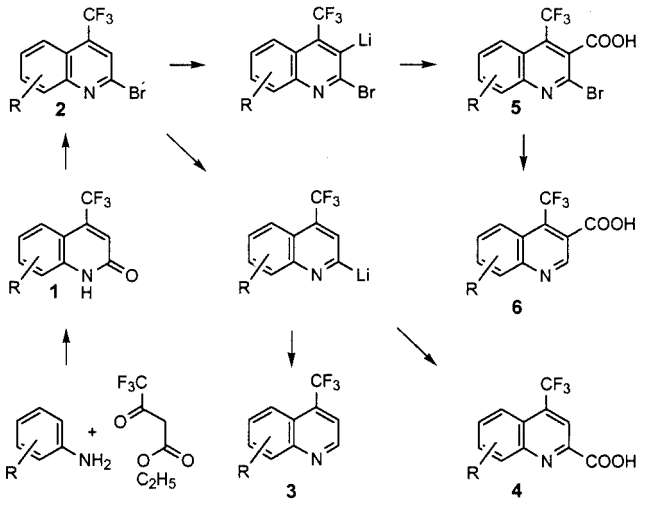
now extended this work to the 4-trifluoromethyl series and have prepared several 2-quinolinones **1**, 2-bromoquinolines **2**, quinolines **3**, 2-quinolinecarboxylic acids **4**, 2-bromo-3-quinolinecarboxylic acids **5**, and 3-quinolinecarboxylic acids **6**.



We immediately faced logistical problems caused by the poor accessibility of the 4-trifluoromethyl-2-quinolinone starting materials **1**, the yields hardly exceeding 30% even after extensive attempts to optimize the reaction and workup conditions (see Table 1). In several cases, the method failed completely when anilines carrying just moderately, not even strongly, electron-withdrawing substituents such as chlorine or bromine were employed. We shall come back to this point in the near future[8] and publish a modified protocol that ensures significantly improved yields.

Table 1. 4-Trifluoromethyl-2-quinolinones **1** by condensation of ethyl 4,4,4-trifluoroacetoacetate with a variety of anilines followed by the acid-catalyzed cyclization of the amide intermediate

Compound	Precursor	R	Yield[a]
1a	aniline	H	34%[b]
1b	*p*-toluidine	6-H_3C	32%
1c	*p*-fluoroaniline	6-F	11%
1d	*m*-toluidine	7-H_3C	29%
1e	*m*-anisidine	7-H_3CO	30%
1f	*m*-fluoroaniline	7-F	31%
1g	*o*-toluidine	8-H_3C	21%

[a] Yields of isolated and purified products. [b] See also ref.[9]

The conversion of the quinolinones **1** into the 2-bromoquinolines **2** was accomplished with phosphoryl tribromide by applying a standard procedure. The yields were acceptable, though far from quantitative (see Table 2).

The next step, the butyllithium-mediated halogen/metal permutation and subsequent neutralization, also gave the 4-(trifluoromethyl)quinolines **3** in yields below our expectations (see Table 3). The well-known reactivity of pyridinic and quinolinic 2-positions presumably opens pathways for side reactions and compromises the chemical stability of the organometallic intermediates.

Table 2. 2-Bromo-4-(trifluoromethyl)quinolines **2** from 2-quinolinones **1** by the reaction with phosphorus oxybromide

Compound	R	Precursor	Yield
2a	H	**1a**	66%
2b	6-H_3C	**1b**	59%
2c	6-F	**1c**	59%
2d	7-H_3C	**1d**	62%
2e	7-H_3CO	**1e**	59%
2f	7-F	**1f**	51%
2g	8-H_3C	**1g**	64%

Table 3. 4-(Trifluoromethyl)quinolines **3** by consecutive treatment of 2-bromoquinolines **2** with butyllithium and methanol

Compound	R	Precursor	Yield
3a	H	**2a**	63%
3b	6-H_3C	**2b**	72%
3c	6-F	**2c**	68%
3d	7-H_3C	**2d**	71%
3e	7-H_3CO	**2e**	68%
3f	7-F	**2f**	55%
3g	8-H_3C	**2g**	74%

Of course the choice of the electrophile does not affect the lability of the 2-lithiated species. Consequently, carboxylation of the latter affords the 2-quinolinecarboxylic acids **4**, again in satisfactory, though not excellent, yields (Table 4).

Table 4. 4-Trifluoromethyl-2-quinolinecarboxylic acids **4** from 2-bromoquinolines **2** by consecutive reaction with butyllithium and dry ice

Compound	R	Precursor	Yield
4a	H	**2a**	72%
4b	6-H_3C	**2b**	72%
4c	6-F	**2c**	71%
4d	7-H_3C	**2d**	73%
4e	7-H_3CO	**2e**	66%
4f	7-F	**2f**	52%
4g	8-H_3C	**2g**	75%

The carboxylation could be directed to the 3-position by employing lithium diisopropylamide (LIDA) as a base. The resulting 2-bromo-3-quinolinecarboxylic acids **5** were isolated in high yields (Table 5). The only exception was found with 2-bromo-7-fluoro-4-(trifluoromethyl)quinoline (**2f**), which underwent the deprotonation exclusively at the 8-position to give the 2-bromo-7-fluoro-8-quinolinecarboxylic acid (**7**) in 87% yield.

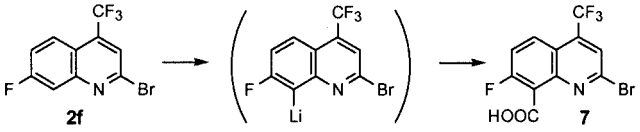


Table 5. 2-Bromo-4-trifluoromethyl-3-quinolinecarboxylic acids **5** by consecutive treatment of 2-bromoquinolines **2** with lithium diisopropylamide and carbon dioxide

Compound	R	Precursor	Yield
5a	H	**2a**	81%
5b	6-H_3C	**2b**	66%
5c	6-F	**2c**	69%
5d	7-H_3C	**2d**	88%
5e	7-H_3CO	**2e**	82%
5f	7-F	**2f**	0%[a]
5g	8-H_3C	**2g**	89%

[a] Acid **7** (87%) instead (see text).

A few of the acids **5** were subjected to reductive debromination (Table 6). This was accomplished either by bromine/lithium permutation and subsequent quenching with methanol or by catalytic hydrogenation. In addition, the 2-formyl-8-methyl-4-trifluoromethyl-3-carboxylic acid (**8**; 57%) was obtained from the halogen/metal permutation performed with the carboxylate of the bromo acid **5g** followed by addition to *N*,*N*-dimethylformamide and hydrolysis.

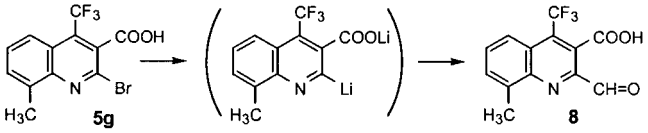


Table 6. 4-Trifluoromethyl-3-quinolinecarboxylic acids **6** by two-step debromination of the bromo analogs **5**

Compound	R	Precursor	Yield
6a	H	**5a**	64%[a]
6c	6-F	**5c**	71%[b]
6g	8-H_3C	**5g**	67%[a]

[a] After consecutive treatment with butyllithium and methanol. [b] Bromine removal by catalytic hydrogenation.

This report has to close with a word of warning. There is no a priori certainty about the structural identity of the aniline/β-oxo ester condensation/cyclization products. A minor change in the protocol (e.g. the use of methanesulfonic acid in the presence of phosphorus pentoxide[8] rather than concentrated sulfuric acid) suffices to switch back from the 4-trifluoromethyl-2-quinolone to the 2-trifluoromethyl-4-quinoline family. To avoid erroneous assignments, a careful evaluation of the spectroscopic data is warranted. Characteristic differences between the two isomeric series are displayed by the ^{1}H NMR spectra of the 4- or 2-(trifluoromethyl)quinolines (**3** and **10**, respectively: δ ≈ 8.3 vs. 9.0 ppm; see Table 7) and, even more markedly, by the ^{13}C NMR spectra of the 4- or 2-trifluoromethyl-2- or -4-quinolinones (**1** and **9**, respectively: δ ≈ 149 vs. 137 ppm; see Table 8).

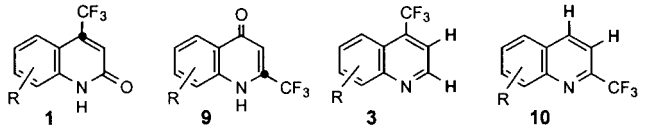


Table 7. The ^{1}H NMR shifts (in ppm relative to tetramethylsilane) at the 2- and 3-position of representative 4-trifluoromethyl-2-quinolines **3** and at the 3- and 4-position of the isomeric 2-(trifluoromethyl)quinolines **10**

R	Compound	δ(2-H)[a]	δ(3-H)[b]	Compound	δ(3-H)[a]	δ(4-H)[a]
H	**3a**	9.05	7.70	**10a**	8.37	7.75
6-H_3C	**3b**	8.97	7.70	**10b**	8.26	7.70
6-F	**3c**	9.00	7.72	**10c**	8.30	7.75
7-H_3C	**3d**	8.99	7.62	**10d**	–	–
7-H_3CO	**3e**	8.94	7.54	**10e**	8.21	4.58
7-F	**3f**	9.06	7.69	**10f**	8.35	7.73
8-H_3C	**3g**	9.01	7.66	**10g**	–	–

[a] ^3J = 8.3–8.7 Hz. [b] ^3J = 4.0–4.7 Hz.

Table 8. ^{13}C NMR shifts (in ppm relative to tetramethylsilane) and coupling constants (in Hz) of C-4 and C-2 of representative 4-trifluoromethyl-2-quinolones **1** and 2-trifluoromethyl-4-quinolones **9**, respectively

R	Compound	δ(CF_3)	$^2J_{C,F}$	Compound	δ(CF_3)	$^2J_{C,F}$
H	**1a**	136.6	34.5	**9a**	147.7	34.4
6-H_3C	**1b**	137.3	34.0	**9b**	147.8	35.3
6-F	**1c**	135.7	32.7	**9c**	146.2	32.9
7-H_3C	**1d**	136.2	31.2	**9d**	–	–
7-H_3CO	**1e**	137.5	30.8	**9e**	149.0	35.4
7-F	**1f**	137.4	31.4	**9f**	150.2	34.4
8-H_3C	**1g**	137.9	30.6	**9g**	–	–

Experimental Section

Generalities: Working practices and abbreviations are specified in previous articles from this laboratory.[10–12] ^{1}H and ^{13}C NMR spectra were recorded at 400 and 101 MHz relative to the internal standard tetramethylsilane (δ = 0.00 ppm), samples having been dissolved in deuteriochloroform or, if marked by an asterisk (*), in perdeuterioacetone.

4-Trifluoromethyl-Substituted 2-Quinolinones 1

4-Trifluoromethyl-2(1*H*)-quinolinone (1a): Aniline (9.1 mL, 9.3 g, 0.10 mol) and ethyl 4,4,4-trifluoro-3-oxobutanoate (29 mL, 37 g, 0.20 mol) were heated at 110 °C for 45 min before the excess of ester was evaporated under reduced pressure. Then 75% aqueous sulfuric acid (80 mL) was added to the oily mass formed. The mixture was heated for 45 min at 90 °C, then poured on milled ice (0.25 L). The precipitate formed was collected by filtration and crystallized from ethanol; colorless needles; m.p. 246–247 °C (ref.[9] 245–246 °C; reprod.); yield: 7.25 g (34%). ^{1}H NMR (D_3CSOCD_3): δ = 7.71 (d, *J* = 8.4 Hz, 1 H), 7.65 (td, *J* = 7.6,

1.0 Hz, 1 H), 7.43 (d, J = 8.5 Hz, 1 H), 7.32 (td, J = 7.7, 1.0 Hz, 1 H), 6.98 (s, 1 H) ppm. ^{13}C NMR (D_3CSOCD_3): δ = 160.0, 139.8, 136.6 (q, J = 31 Hz), 131.7, 124.3, 122.8, 122.6 (q, J = 277 Hz), 122.0 (q, J = 5 Hz), 116.5, 113.1 ppm. MS (c.i.): m/z (%) = 231 (27) [M^+ + 18], 214 (100) [M^+ + 1], 213 (34) [M^+], 185 (8), 166 (2). $C_{10}H_6F_3NO$ (213.16): calcd. C 56.35, H 2.84; found C 56.19, H 3.00.

6-Methyl-4-trifluoromethyl-2(1*H*)-quinolinone (1b): Analogously, using *p*-toluidine (11 g, 0.10 mol); colorless needles; m.p. 257−269 °C (from ethanol; reprod.); yield: 7.27 g (32%). ^{1}H NMR (D_3CSOCD_3): δ = 7.6 (m, 2 H), 7.47 (d, J = 8.5 Hz, 1 H), 7.07 (s, 1 H), 2.54 (s, 3 H) ppm. ^{13}C NMR (D_3CSOCD_3): δ = 160.9, 138.9, 137.3 (q, J = 33 Hz), 134.9, 133.3, 133.1, 123.7, 123.5 (q, J = 277 Hz), 117.4, 114.0, 21.7 ppm. MS (c.i.): m/z (%) = 246 (0) [M^+ + 18], 228 (100) [M^+ + 1], 198 (4). $C_{11}H_8F_3NO$ (227.15): calcd. C 58.16, H 3.55, N 6.17; found C 58.09, H 3.55, N 6.12.

6-Fluoro-4-trifluoromethyl-2(1*H*)-quinolinone (1c): Analogously, using *p*-fluoroaniline (9.5 mL, 11 g, 0.10 mol); colorless needles; m.p. 252−253 °C (from ethanol; decomp.); yield: 2.54 g (11%). ^{1}H NMR (D_3CSOCD_3): δ = 7.59 (td, J = 9.2, 2.6 Hz, 1 H), 7.49 (dd, J = 9.1, 4.9 Hz, 1 H), 7.41 (d, J = 9.5 Hz, 1 H), 7.08 (s, 1 H) ppm. ^{13}C NMR (D_3CSOCD_3): δ = 159.6, 156.4 (d, J = 238 Hz), 136.5, 135.7 (q, J = 34 Hz), 123.1 (d, J = 5 Hz), 121.9 (q, J = 275 Hz), 120.0 (d, J = 25 Hz), 118.4 (d, J = 18 Hz), 113.4 (d, J = 9 Hz), 109.3 (d, J = 25 Hz) ppm. MS (c.i.): m/z (%) = 249 (0) [M^+ + 18], 232 (40) [M^+ + 1], 231 (100) [M^+], 203 (26), 184 (19), 107 (9). $C_{10}H_5F_4NO$ (231.15): calcd. C 51.96, H 2.18, N 6.06; found C 52.03, H 2.10, N 6.11.

7-Methyl-4-trifluoromethyl-2(1*H*)-quinolinone (1d): Analogously, using *m*-toluidine (11 mL, 11 g, 0.10 mol); colorless needles; m.p. 210−213 °C (from ethanol; reprod.); yield: 6.59 g (29%). ^{1}H NMR (D_3CSOCD_3): δ = 7.59 (d, J = 8.6 Hz, 1 H), 7.22 (s, 1 H), 7.14 (d, J = 8.2 Hz, 1 H), 6.89 (s, 1 H), 2.41 (s, 3 H) ppm. ^{13}C NMR (D_3CSOCD_3): δ = 160.1, 142.0, 139.7, 136.2 (q, J = 31 Hz), 124.2, 123.8, 122.5 (q, J = 276 Hz), 120.5 (q, J = 5 Hz), 116.0, 110.9, 21.1 ppm. MS (c.i.): m/z (%) = 245 (0) [M^+ + 18], 228 (100) [M^+ + 1], 198 (7), 130 (3), 102 (1). $C_{11}H_8F_3NO$ (227.15): calcd. C 58.16, H 3.55, N 6.17; found C 58.06, H 3.64, N 6.31.

7-Methoxy-4-trifluoromethyl-2(1*H*)-quinolinone (1e): Analogously, using *p*-anisidine (11 mL, 12 g, 0.10 mol); tiny yellowish needles; m.p. 219−222 °C (from ethanol; reprod.); yield: 7.29 g (30%). ^{1}H NMR (D_3CSOCD_3): δ = 7.72 (dm, J = 8.0 Hz, 1 H), 7.05 (dd, J = 9.5, 2.5 Hz, 1 H), 7.04 (s, 1 H), 6.89 (s, 1 H), 3.94 (s, 3 H) ppm. ^{13}C NMR (D_3CSOCD_3): δ = 162.9, 161.7, 143.0, 137.5 (q, J = 31 Hz), 126.8, 123.8 (q, J = 278 Hz), 119.4 (q, J = 6 Hz), 113.3, 108.1, 100.2, 56.7 ppm. MS (c.i.): m/z (%) = 261 (0) [M^+ + 18], 244 (100) [M^+ + 1]. $C_{11}H_8F_3NO_2$ (243.14): calcd. C 54.34, H 3.32, N 5.76; found C 54.46, H 3.32, N 5.88.

7-Fluoro-4-trifluoromethyl-2(1*H*)-quinolinone (1f): Analogously, using *m*-fluoroaniline (11 mL, 11 g, 0.10 mol); tiny colorless needles; m.p. 166−167 °C (from ethanol; decomp.); yield: 7.16 g (31%). ^{1}H NMR (D_3CSOCD_3): δ = 7.87 (tm, J = 8.0 Hz, 1 H), 7.30 (m, 2 H), 7.05 (s, 1 H) ppm. ^{13}C NMR (D_3CSOCD_3): δ = 164.2 (d, J = 247 Hz), 161.2, 142.6 (d, J = 12 Hz), 137.4 (d, J = 31 Hz), 128.0 (d, J = 10 Hz), 123.2 (q, J = 267 Hz), 121.5, 112.4 (d, J = 23 Hz), 111.2, 103.1 (d, J = 26 Hz) ppm. MS (c.i.): m/z (%) = 249 (0) [M^+ + 18], 232 (100) [M^+ + 1], 231 (88) [M^+], 203 (19), 184 (8). $C_{10}H_5F_4NO$ (231.10): calcd. C 51.97, H 2.18, N 6.06; found C 52.03, H 1.95, N 6.18.

8-Methyl-4-trifluoromethyl-2(1*H*)-quinolinone (1g): Analogously using *o*-toluidine (11 mL, 11 g, 0.10 mol); tiny colorless needles; m.p. 248−251 °C (from ethanol; reprod.); yield: 4.77 g (21%). ^{1}H NMR (D_3CSOCD_3): δ = 7.68 (d, J = 7.3 Hz, 1 H), 7.60 (d, J = 7.0 Hz, 1 H), 7.34 (t, J = 7.6 Hz, 1 H), 7.11 (s, 1 H), 2.61 (s, 3 H) ppm. ^{13}C NMR (D_3CSOCD_3): δ = 161.3, 139.0, 137.9 (q, J = 31 Hz), 133.8, 125.9, 123.7 (q, J = 272 Hz), 123.5, 123.0, 122.6, 114.1, 18.8 ppm. MS (c.i.): m/z (%) = 245 (0) [M^+ + 18], 228 (100) [M^+ + 1], 227 (35), 198 (2), 130 (1). $C_{11}H_8F_3NO$ (227.15): calcd. C 58.16, H 3.55, N 6.17; found C 57.93, H 3.29, N 6.18.

4-Trifluoromethyl-Substituted 2-Bromoquinolines 2

2-Bromo-4-(trifluoromethyl)quinoline (2a): At 60 °C, quinolinone **1a** (11 g, 50 mmol) was added to an excess of phosphorus oxybromide (29 g, 0.10 mol). The mixture was heated at 140 °C for 2 h before being poured onto ice (0.20 L). The precipitated brown mass was collected and dissolved in methanol (0.20 L) containing charcoal (3 g). The slurry was stirred at 25 °C for 1 h before being filtered through a pad of diatomaceous earth. The residue left after evaporation of the solvent was crystallized from methanol; colorless needles; m.p. 56−57 °C (after sublimation); yield: 9.11 g (66%). ^{1}H NMR: δ = 8.15 (d, J = 8.5 Hz, 1 H), 8.11 (d, J = 8.5 Hz, 1 H), 7.83 (m, 2 H), 7.71 (ddd, J = 8.4, 7.0, 1.3 Hz, 1 H) ppm. ^{13}C NMR: δ = 149.5, 140.6, 136.2 (q, J = 33 Hz), 131.4, 129.6, 128.6, 124.1, 123.1 (q, J = 6 Hz), 122.5 (q, J = 277 Hz), 121.9 ppm. MS (c.i.): m/z (%) = 294 (0) [M^+ + 18], 277 (100) [M^+ + 1], 276 (82) [M^+], 213 (14), 196 (67), 176 (47). $C_{10}H_5BrF_3N$ (276.05): calcd. C 43.51, H 1.83; found C 43.43, H 1.71.

2-Bromo-6-methyl-4-(trifluoromethyl)quinoline (2b): Analogously, from quinolinone **1b** (11 g, 50 mmol); colorless needles; m.p. 97−99 °C (from methanol); yield: 8.56 g (59%). ^{1}H NMR: δ = 8.03 (d, J = 8.5 Hz, 1 H), 7.83 (s, 1 H), 7.76 (s, 1 H), 7.65 (dd, J = 8.5, 1.7 Hz, 1 H), 2.57 (s, 3 H) ppm. ^{13}C NMR: δ = 147.8, 139.3, 139.2, 135.7 (qr, J = 32 Hz), 133.6, 129.0, 122.9, 122.4 (qr, J = 276 Hz), 121.7, 22.0 ppm. MS (c.i.): m/z (%) = 308 (0) [M^+ + 18], 291 (38) [M^+ + 1], 290 (100) [M^+], 227 (11), 212 (5). $C_{11}H_7BrF_3N$ (290.06): calcd. C 44.55, H 2.43, N 4.83; found C 45.15, H 2.32, N 4.89.

2-Bromo-6-fluoro-4-(trifluoromethyl)quinoline (2c): Analogously, from quinolinone **1c** (12 g, 50 mmol); colorless needles; m.p. 108−109 °C (from methanol); yield: 8.67 g (59%). ^{1}H NMR: δ = 8.16 (dd, J = 9.3, 5.4 Hz, 1 H), 7.85 (s, 1 H), 7.73 (dm, J = 9.4 Hz, 1 H), 7.61 (ddd, J = 9.2, 7.9, 2.7 Hz, 1 H) ppm. ^{13}C NMR: δ = 161.4 (d, J = 257 Hz), 146.5, 139.8, 136.1 (qr, J = 35 Hz), 132.2 (qr, J = 5 Hz), 124.0 (d, J = 25 Hz), 122.8, 122.2 (qr, J = 275 Hz), 121.8 (d, J = 26 Hz), 108.7 (d, J = 25 Hz) ppm. MS (c.i.): m/z (%) = 312 (0) [M^+ + 18], 295 (62) [M^+ + 1], 294 (100) [M^+], 276 (2), 214 (5), 145 (2). $C_{10}H_4BrF_4N$ (294.04): calcd. C 40.85, H 1.37; found C 40.82, H 1.81.

2-Bromo-7-methyl-4-(trifluoromethyl)quinoline (2d): Analogously, from quinolinone **1d** (11 g, 50 mmol); colorless needles; m.p. 49−51 °C (from methanol); yield: 8.99 g (62%). ^{1}H NMR: δ = 8.00 (d, J = 8.9 Hz, 1 H), 7.92 (s, 1 H), 7.75 (s, 1 H), 7.55 (d, J = 8.9 Hz, 1 H), 2.60 (s, 3 H) ppm. ^{13}C NMR: δ = 149.7, 142.3, 140.7, 136.2 (qr, J = 32 Hz), 131.0, 128.7, 123.7, 122.7 (qr, J = 276 Hz), 122.1, 120.9, 21.6 ppm. MS (c.i.): m/z (%) = 308 (0) [M^+ + 18], 290 (100) [M^+], 227 (7), 190 (3). $C_{11}H_7BrF_3N$ (290.06): calcd. C 45.55, H 2.43, N 4.83; found C 45.55, H 2.23, N 4.90.

2-Bromo-7-methoxy-4-(trifluoromethyl)quinoline (2e): Analogously, from quinolinone **1e** (12 g, 50 mmol); colorless needles; m.p. 76−78 °C (from methanol); yield: 8.11 g (53%). ^{1}H NMR: δ = 7.96 (dd, J = 9.2, 2.0 Hz, 1 H), 7.66 (s, 1 H), 7.44 (d, J = 2.3 Hz, 1 H), 7.31 (dd, J = 9.2, 2.8 Hz, 1 H), 3.95 (s, 3 H) ppm. ^{13}C NMR: δ = 161.9, 151.4, 141.0, 136.1 (qr, J = 32 Hz), 125.1, 122.5 (qr, J = 282 Hz),

121.7, 120.6, 116.8, 107.7, 55.8 ppm. MS (c.i.): *m/z* (%) = 324 (0) [M^+ + 18], 307 (40) [M^+ + 1], 306 (100) [M^+]. $C_{11}H_7BrF_3NO$ (306.05): calcd. C 43.17, H 2.31, N 4.58; found C 43.06, H 2.51, N 4.56.

2-Bromo-7-fluoro-4-(trifluoromethyl)quinoline (2f): Analogously, from quinolinone **1f** (12 g, 50 mmol); colorless needles; m.p. 60−62 °C (from methanol); yield: 7.50 g (51%). ^{1}H NMR: δ = 8.13 (dq, *J* = 7.8, 2.0 Hz, 1 H), 7.81 (s, 1 H), 7.78 (dd, *J* = 9.3, 2.9 Hz, 1 H), 7.51 (ddd, *J* = 9.5, 8.1, 2.9 Hz, 1 H) ppm. ^{13}C NMR: δ = 163.9 (d, *J* = 256 Hz), 150.5 (d, *J* = 13 Hz), 142.1, 136.2 (qr, *J* = 33 Hz), 127.1 (d, *J* = 10 Hz), 122.5, 122.1 (qr, *J* = 276 Hz), 119.1 (d, *J* = 26 Hz), 119.0, 113.8 (d, *J* = 21 Hz) ppm. MS (c.i.): *m/z* (%) = 312 (0) [M^+ + 18], 295 (100) [M^+ + 1], 226 (14), 194 (7), 145 (18). $C_{10}H_4BrF_4N$ (294.01): calcd. C 40.85, H 1.37, N 4.76; found C 40.99, H 1.25, N 4.94.

2-Bromo-8-methyl-4-(trifluoromethyl)quinoline (2g): Analogously, from quinolinone **1g** (11 g, 50 mmol); colorless needles; m.p. 17−19 °C (from methanol); b.p. 90−93 °C/5 Torr; yield: 9.28 g (64%). ^{1}H NMR: δ = 7.94 (d, *J* = 8.2 Hz, 1 H), 7.81 (s, 1 H), 7.67 (d, *J* = 7.1 Hz, 1 H), 7.59 (dd, *J* = 8.2, 7.3 Hz, 1 H), 2.78 (s, 3 H) ppm. ^{13}C NMR: δ = 148.4, 139.4, 137.8, 136.4 (qr, *J* = 32 Hz), 134.4, 128.3, 122.8 (qr, *J* = 6 Hz), 122.6 (qr, *J* = 276 Hz), 122.0, 121.9, 15.8 ppm. MS (c.i.): *m/z* (%) = 318 (0) [M^+ + 18], 292 (100) [M^+ + 2], 291 (39) [M^+ + 1], 227 (2), 99 (2). $C_{11}H_7BrF_3N$ (290.06): calcd. C 45.55, H 2.43, N 4.83; found C 45.59, H 2.18, N 4.90.

4-Trifluoromethyl-Substituted Quinolines 3

4-(Trifluoromethyl)quinoline (3a): 2-Bromo-4-(trifluoromethyl)-quinoline **2a** (2.8 g, 10 mmol) was added to butyllithium (10 mmol) in toluene (15 mL) and hexanes (6.0 mL), cooled in a methanol/dry ice bath. After 15 min at −75 °C, methanol (1.0 mL, 0.79 g, 25 mmol) was injected. The product was isolated by direct distillation; colorless liquid; b.p. 135−137 °C/23 Torr (ref.[9] 139 °C); n_D^{20} = 1.5375; d_4^{20} = 1.364; yield: 1.24 g (63%). ^{1}H NMR: δ = 9.05 (d, *J* = 4.2 Hz, 1 H), 8.23 (d, *J* = 8.5 Hz, 1 H), 8.12 (dm, *J* = 8.5 Hz, 1 H), 7.83 (ddd, *J* = 8.5, 6.9, 1.4 Hz, 1 H), 7.70 (m, 2 H) ppm. ^{13}C NMR: δ = 149.5, 149.0, 134.4 (qr, *J* = 32 Hz), 130.4 (2 C), 128.5, 124.0, 123.4 (qr, *J* = 275 Hz), 123.0, 118.0 ppm. MS (c.i.): *m/z* (%) = 215 (0) [M^+ + 18], 198 (12) [M^+ + 1], 197 (51) [M+], 175 (5), 157 (3), 83 (100).

6-Methyl-4-(trifluoromethyl)quinoline (3b): Analogously, from the 2-bromoquinoline **2b** (2.9 g, 10 mmol); colorless needles; m.p. 37−39 °C (from hexanes); yield: 1.53 g (72%). ^{1}H NMR: δ = 8.97 (d, *J* = 4.4 Hz, 1 H), 8.13 (d, *J* = 8.7 Hz, 1 H), 7.90 (s, 1 H), 7.7 (m, 2 H) ppm. ^{13}C NMR: δ = 148.3, 147.3, 138.7, 133.7 (qr, *J* = 32 Hz), 132.7, 130.0, 123.4 (qr, *J* = 275 Hz), 123.1, 122.8, 117.9 (qr, *J* = 6 Hz), 22.0 ppm. MS (c.i.): *m/z* (%) = 229 (0) [M^+ + 18], 212 (24) [M^+ + 1], 211 (100) [M^+], 192 (4), 142 (7). $C_{11}H_8F_3N$ (211.19): calcd. C 62.56, H 3.82, N 6.63; found C 62.46, H 3.82, N 6.67.

6-Fluoro-4-(trifluoromethyl)quinoline (3c): Analogously, from 2-bromoquinoline **2c** (2.9 g, 10 mmol); colorless needles; m.p. 51−53 °C (from hexanes); yield: 1.45 g (68%). ^{1}H NMR: δ = 9.00 (d, *J* = 4.4 Hz, 1 H), 8.22 (dd, *J* = 9.1, 5.8 Hz, 1 H), 7.76 (dm, *J* = 9.8 Hz, 1 H), 7.72 (d, *J* = 4.2 Hz, 1 H), 7.59 (ddd, *J* = 12.1, 10.3, 3.8 Hz, 1 H) ppm. ^{13}C NMR: δ = 161.3 (d, *J* = 252 Hz), 148.7 (d, *J* = 2 Hz), 146.0, 133.9 (qd, *J* = 32, 6 Hz), 132.9 (d, *J* = 10 Hz), 123.7 (d, *J* = 10 Hz), 123.2 (qr, *J* = 275 Hz), 120.6 (d, *J* = 26 Hz), 118.6 (d, *J* = 5 Hz), 108.0 (d, *J* = 23 Hz) ppm. MS (c.i.): *m/z* (%) = 233 (1) [M^+ + 18], 216 (85) [M^+ + 1], 215 (5) [M^+], 170 (12), 122 (40), 99 (100). $C_{10}H_5F_4N$ (215.15): calcd. C 55.83, H 2.34; found C 55.57, H 2.20.

7-Methyl-4-(trifluoromethyl)quinoline (3d): Analogously, from the 2-bromoquinoline **2d** (2.9 g, 10 mmol); colorless needles; m.p. 48−50 °C (from hexanes); yield: 1.50 g (71%). ^{1}H NMR: δ = 8.99 (d, *J* = 4.5 Hz, 1 H), 8.04 (dq, *J* = 8.8, 2.0 Hz, 1 H), 8.00 (qr, *J* = 0.8 Hz, 1 H), 7.62 (d, *J* = 4.2 Hz, 1 H), 7.54 (dd, *J* = 9.0, 2.0 Hz, 1 H), 2.61 (s, 3 H) ppm. ^{13}C NMR: δ = 149.5, 149.2, 140.6, 133.8 (qr, *J* = 32 Hz), 130.6, 129.2, 124.0, 123.9 (qr, *J* = 275 Hz), 120.8, 117.2, 21.8 ppm. MS (c.i.): *m/z* (%) = 229 (0) [M^+ + 18], 212 (22) [M^+ + 1], 211 (100) [M^+], 192 (4), 142 (9), 115 (4). $C_{11}H_8F_3N$ (211.19): calcd. C 62.56, H 3.82; found C 62.29, H 3.94.

7-Methoxy-4-(trifluoromethyl)quinoline (3e): Analogously, from the 2-bromoquinoline **2e** (3.1 g, 10 mmol); colorless needles; m.p. 41−43 °C (from hexanes); yield: 1.55 g (68%). ^{1}H NMR: δ = 8.03 (d, *J* = 4.3 Hz, 1 H), 7.54 (d, *J* = 8.9 Hz, 1 H), 7.52 (s, 1 H), 7.33 (d, *J* = 4.5 Hz, 1 H), 3.99 (s, 3 H) ppm. ^{13}C NMR: δ = 161.0, 150.7, 148.7, 134.2 (qr, *J* = 32 Hz), 125.1, 123.3 (qr, *J* = 276 Hz), 121.6, 118.0, 115.6, 108.1, 55.7 ppm. MS (c.i.): *m/z* (%) = 262 (0) [M^+ + 18], 245 (0) [M^+ + 1], 227 (100) [M^+], 208 (4), 197 (19), 147 (5). $C_{11}H_8F_3NO$ (227.18): calcd. C 58.16, H 3.55, N 6.17; found C 58.00, H 3.48, N 6.08.

7-Fluoro-4-(trifluoromethyl)quinoline (3f): Analogously, from the 2-bromoquinoline **2f** (2.9 g, 10 mmol); colorless needles; m.p. 62−64 °C (from hexanes); yield: 1.17 g (55%). ^{1}H NMR: δ = 9.06 (d, *J* = 4.3 Hz, 1 H), 8.17 (tq, *J* = 8.0, 1.9 Hz, 1 H), 7.86 (dd, *J* = 7.0, 2.6 Hz, 1 H), 7.69 (d, *J* = 4.7 Hz, 1 H), 7.50 (ddd, *J* = 9.6, 8.0, 2.8 Hz, 1 H) ppm. ^{13}C NMR: δ = 163.1 (d, *J* = 253 Hz), 150.7, 150.3 (qr, *J* = 13 Hz), 134.6 (qr, *J* = 32 Hz), 126.4 (d, *J* = 9 Hz), 123.3 (qr, *J* = 275 Hz), 120.0, 118.9 (d, *J* = 26 Hz), 117.3, 114.1 (d, *J* = 20 Hz) ppm. $C_{10}H_5F_4N$ (215.15): calcd. C 53.83, H 2.34, N 6.51; found C 53.71, H 2.49, N 6.51.

8-Methyl-4-(trifluoromethyl)quinoline (3g): Analogously, from the 2-bromoquinoline **2g** (2.9 g, 10 mmol); colorless needles; m.p. 24−25 °C (from hexanes); yield: 1.56 g (74%). ^{1}H NMR: δ = 9.05 (d, *J* = 4.4 Hz, 1 H), 7.99 (d, *J* = 8.5 Hz, 1 H), 7.70 (d, *J* = 4.4 Hz, 1 H), 7.66 (d, *J* = 6.9 Hz, 1 H), 7.57 (dd, *J* = 8.4, 7.5 Hz, 1 H), 2.84 (s, 3 H) ppm. ^{13}C NMR: δ = 148.1, 148.0, 138.0, 134.1 (qr, *J* = 32 Hz), 130.2, 127.8, 123.3 (qr, *J* = 275 Hz), 122.7, 121.6, 98.9 (qr, *J* = 5 Hz), 17.9 ppm. $C_{11}H_8F_3N$ (211.19): calcd. C 62.56, H 3.82, N 6.63; found C 62.54, H 3.67, N 6.51.

4-Trifluoromethyl-Substituted 2-Quinolinecarboxylic Acids 4

4-Trifluoromethyl-2-quinolinecarboxylic Acid (4a): The 2-bromoquinoline **2a** (4.1 g, 15 mmol) was dissolved in a solution of butyllithium (15 mmol) in tetrahydrofuran (30 mL) and hexanes (10 mL) cooled in a methanol/dry ice bath. After 15 min at −75 °C, the mixture was poured onto an excess of freshly crushed solid carbon dioxide. At +25 °C, tetrafluoroboric acid−diethyl ether (2.7 mL, 3.2 g, 20 mmol) was added with shaking and the volatiles were evaporated. The residue was crystallized from ethanol to afford colorless prisms; m.p. 142−143 °C; yield: 2.50 g (69%). ^{1}H NMR*: δ = 8.47 (s, 1 H), 8.37 (ddd, *J* = 8.4, 1.43, 0.7 Hz, 1 H), 8.27 (d, *J* = 8.5 Hz, 1 H), 8.06 (td, *J* = 6.9, 1.4 Hz, 1 H), 7.99 (td, *J* = 7.0, 1.5 Hz, 1 H) ppm. ^{13}C NMR*: δ = 165.0, 158.5 (2 C), 139.0, 136.0 (qr, *J* = 35 Hz), 132.5, 131.8 (2 C), 124.7, 124.5 (qr, *J* = 274 Hz), 118.3 ppm. MS (c.i.): *m/z* (%) = 259 (0) [M^+ + 18], 242 (23) [M^+ + 1], 241 (22) [M^+], 197 (100), 176 (16) 147 (4), 128 (12). $C_{11}H_6F_3NO_2$ (241.17): calcd. C 54.78, H 2.51; found C 54.52, H 2.48.

6-Methyl-4-trifluoromethyl-2-quinolinecarboxylic Acid (4b): Analogously, from the 2-bromoquinoline **2b** (4.4 g, 15 mmol); colorless prisms; m.p. 205−208 °C (from ethanol; reprod.); yield: 2.77 g (72%). ^{1}H NMR*: δ = 8.44 (s, 1 H), 8.24 (d, *J* = 8.7 Hz, 1 H), 8.03 (s, 1 H), 7.90 (dd, *J* = 8.7, 1.7 Hz, 1 H), 2.68 (s, 3 H) ppm. ^{13}C NMR*: δ = 165.2, 147.4, 142.8, 135.8, 135.2 (qr, *J* = 32 Hz), 134.7, 131.6, 124.8, 124.3 (qr, *J* = 275 Hz), 123.4, 118.4, 22.7 ppm. MS (c.i.): *m*/*z* (%) = 273 (0) [M$^+$ + 18], 256 (43) [M$^+$ + 1], 211 (100), 190 (65), 140 (64). $C_{12}H_8F_3NO_2$ (255.19): calcd. C 56.48, H 3.16, N 5.49; found C 56.51, H 3.33, N 5.52.

6-Fluoro-4-trifluoromethyl-2-quinolinecarboxylic Acid (4c): Analogously, from the 2-bromoquinoline **2c** (4.4 g, 15 mmol); colorless prisms; m.p. 168−171 °C (from ethanol; decomp.); yield: 2.76 g (71%). ^{1}H NMR*: δ = 8.52 (s, 1 H), 8.44 (dd, *J* = 9.3, 5.6 Hz, 1 H), 7.93 (ddd, *J* = 9.3, 8.2, 2.7 Hz, 1 H), 7.88 (dm, *J* = 9.8 Hz, 1 H) ppm. ^{13}C NMR*: δ = 165.9, 164.4 (d, *J* = 253 Hz), 149.0, 146.8, 136.1 (m, 2 C), 126.5 (d, *J* = 11 Hz), 124.9 (qr, *J* = 274 Hz), 123.5 (d, *J* = 27 Hz), 120.0, 109.5 (d, *J* = 25 Hz) ppm. MS (c.i.): *m*/*z* (%) = 277 (0) [M$^+$ + 18], 260 (41) [M$^+$ + 1], 259 (22) [M$^+$], 242 (13), 215 (100), 194 (23). $C_{11}H_5F_4NO_2$ (259.16): calcd. C 50.98, H 1.94, N 5.40; found C 50.91, H 1.91, N 5.44.

7-Methyl-4-trifluoromethyl-2-quinolinecarboxylic Acid (4d): Analogously, from the 2-bromoquinoline **2d** (4.4 g, 15 mmol); colorless prisms; m.p. 145−148 °C (from ethanol; reprod.); yield: 2.80 g (73%). ^{1}H NMR*: δ = 8.42 (s, 1 H), 8.16 (dq, *J* = 8.9, 2.1 Hz, 1 H), 8.12 (qr, *J* = 0.8 Hz, 1 H), 7.85 (dd, *J* = 8.5, 1.7 Hz, 1 H), 2.66 (s, 3 H) ppm. ^{13}C NMR*: δ = 165.2, 149.0, 148.4, 143.4, 135.8 (qr, *J* = 32 Hz), 137.3, 131.2, 124.5 (qr, *J* = 275 Hz), 124.1, 122.7, 117.4 (qr, *J* = 5 Hz), 21.7 ppm. MS (c.i.): *m*/*z* (%) = 273 (0) [M$^+$ + 18], 256 (100) [M$^+$ + 1], 211 (11). $C_{12}H_8F_3NO_2$ (255.19): calcd. C 56.48, H 3.16, N 5.49; found C 56.44, H 3.07, N 5.44.

7-Methoxy-4-trifluoromethyl-2-quinolinecarboxylic Acid (4e): Analogously, from the 2-bromoquinoline **2e** (4.6 g, 15 mmol); colorless prisms; m.p. 165−168 °C (from ethanol; reprod.); yield: 2.68 g (66%). ^{1}H NMR*: δ = 8.32 (s, 1 H), 8.17 (dq, *J* = 9.2, 2.3 Hz, 1 H), 7.66 (d, *J* = 2.9 Hz, 1 H), 7.61 (dd, *J* = 9.3, 2.9 Hz, 1 H), 4.07 (s, 3 H) ppm. MS (c.i.): *m*/*z* (%) = 271 (88) [M$^+$], 227 (100). $C_{12}H_8F_3NO_3$ (271.19): calcd. C 53.15, H 2.97, N 5.17; found C 52.97, H 2.84, N 5.12.

7-Fluoro-4-trifluoromethyl-2-quinolinecarboxylic Acid (4f): Analogously, from the 2-bromoquinoline **2f** (4.4 g, 15 mmol); colorless prisms; m.p. 167−169 °C (from ethanol; decomp.); yield: 2.02 g (52%). ^{1}H NMR*: δ = 8.46 (s, 1 H), 8.37 (tq, *J* = 5.7, 1.9 Hz, 1 H), 8.01 (dd, *J* = 9.4, 2.7 Hz, 1 H), 7.87 (ddd, *J* = 9.4, 8.3, 2.7 Hz, 1 H) ppm. ^{13}C NMR*: δ = 163.9, 163.5 (qr, *J* = 255 Hz), 149.2 (qr, *J* = 13 Hz), 135.3 (qr, *J* = 32 Hz), 126.7 (d, *J* = 10 Hz), 123.2 (qr, *J* = 275 Hz), 121.2 (d, *J* = 26 Hz), 120.9, 116.9, 113.8 (d, *J* = 21 Hz) ppm. MS (c.i.): *m*/*z* (%) = 277 (0) [M$^+$ + 18], 259 (100) [M$^+$], 242 (9), 214 (15), 194 (7). $C_{11}H_5F_4NO_2$ (259.16): calcd. C 50.98, H 1.94, N 5.40; found C 51.11, H 2.06, N 5.27.

8-Methyl-4-trifluoromethyl-2-quinolinecarboxylic Acid (4g): Analogously, from the 2-bromoquinoline **2g** (4.4 g, 15 mmol); colorless prisms; m.p. 168−171 °C (from ethanol; reprod.); yield: 2.87 g (75%). ^{1}H NMR*: δ = 8.51 (s, 1 H), 8.09 (d, *J* = 7.9 Hz, 1 H), 7.9 (m, 2 H), 2.90 (s, 3 H) ppm. ^{13}C NMR*: δ = 165.1, 147.7, 147.1, 140.4, 136.2 (qr, *J* = 30 Hz), 132.4, 131.6, 124.9, 124.3 (qr, *J* = 275 Hz), 122.4, 118.0 (qr, *J* = 6 Hz), 18.4 ppm. MS (c.i.): *m*/*z* (%) = 273 (0) [M$^+$ + 18], 256 (100) [M$^+$ + 1]. $C_{12}H_8F_3NO_2$ (255.19): calcd. C 56.48, H 3.16, N 5.49; found C 56.80, H 2.93, N 5.52.

4-Trifluoromethyl-Substituted 2-Bromo-3-quinolinecarboxylic Acids 5

2-Bromo-4-trifluoromethyl-3-quinolinecarboxylic Acid (5a): Diisopropylamine (2.6 mL, 1.8 g, 18 mmol) and the 2-bromoquinoline **2a** (4.1 g, 15 mmol) were added consecutively to butyllithium (15 mmol) in tetrahydrofuran (30 mL) and hexanes (10 mL), kept in a methanol/dry ice bath. After 2 h at −75 °C, the mixture was carboxylated and worked up as described in the preceding section; colorless needles; m.p. 172−173 °C (from water; reprod.); yield: 3.88 g (81%). ^{1}H NMR*: δ = 8.22 (d, *J* = 8.6 Hz, 1 H), 8.15 (dd, *J* = 7.7, 0.8 Hz, 1 H), 8.02 (td, *J* = 7.0, 1.3 Hz, 1 H), 7.93 (td, *J* = 7.0, 1.4 Hz, 1 H) ppm. ^{13}C NMR*: δ = 167.1, 150.3 138.9, 134.0, 132.7 (qr, *J* = 33 Hz), 131.6, 131.0, 126.2 (2 C), 124.2 (qr, *J* = 278 Hz), 123.0 ppm. MS (c.i.): *m*/*z* (%) = 338 (0) [M$^+$ + 18], 321 (96) [M$^+$ + 1], 320 (100) [M$^+$], 319 (88) [M$^+$], 277 (20), 276 (22), 275 (21), 274 (21), 240 (29), 176 (12). $C_{11}H_5BrF_3NO_2$ (320.06): calcd. C 41.28, H 1.57; found C 41.12, H 1.70.

2-Bromo-6-methyl-4-trifluoromethyl-3-quinolinecarboxylic Acid (5b): Analogously, from the 2-bromoquinoline **2b** (4.4 g, 15 mmol); colorless needles; m.p. 218−220 °C (from water; reprod.); yield: 3.31 g (66%). ^{1}H NMR*: δ = 8.03 (d, *J* = 8.9 Hz, 1 H), 7.97 (broad s, 1 H), 7.85 (dd, *J* = 8.9, 1.9 Hz, 1 H), 2.63 (s, 3 H) ppm. ^{13}C NMR*: δ = 166.0, 147.9, 141.4, 136.6, 135.2, 131.4 (qr, *J* = 32 Hz), 130.0, 124.1, 123.5 (qr, *J* = 277 Hz), 122.2, 22.1 ppm. MS (c.i.): *m*/*z* (%) = 352 (0) [M$^+$ + 18], 334 (100) [M$^+$], 271 (4), 254 (9). $C_{12}H_7BrF_3NO_2$ (334.09): calcd. C 43.14, H 2.11, N 4.19; found C 43.31, H 2.03, N 4.22.

2-Bromo-6-fluoro-4-trifluoromethyl-3-quinolinecarboxylic Acid (5c): Analogously, from the 2-bromoquinoline **2c** (4.4 g, 15 mmol); colorless needles; m.p. 196−198 °C (from water; reprod.); yield: 3.50 g (69%). ^{1}H NMR*: δ = 8.25 (dd, *J* = 9.3, 5.6 Hz, 1 H), 7.90 (ddd, *J* = 9.9, 8.1, 2.6 Hz, 1 H), 7.86 (dm, *J* = 9.9 Hz, 1 H) ppm. ^{13}C NMR*: δ = 166.6, 163.6 (d, *J* = 251 Hz), 147.3, 138.0, 133.8 (d, *J* = 10 Hz), 132.6 (qr, *J* = 32 Hz), 131.5, 124.3 (2C), 124.1 (qr, *J* = 276 Hz), 110.5 (d, *J* = 26 Hz) ppm. MS (c.i.): *m*/*z* (%) = 356 (0) [M$^+$ + 18], 339 (100) [M$^+$ + 1], 338 (61) [M$^+$], 337 (99) [M$^+$], 293 (15), 258 (46), 194 (52). $C_{11}H_4BrF_4NO_2$ (338.05): calcd. C 39.08, H 1.19, N 4.14; found C 38.93, H 1.27, N 4.17.

2-Bromo-7-methyl-4-trifluoromethyl-3-quinolinecarboxylic Acid (5d): Analogously, from the 2-bromoquinoline **2d** (4.4 g, 15 mmol); colorless needles; m.p. 185−187 °C (from water; reprod.); yield: 4.41 g (88%). ^{1}H NMR*: δ = 8.13 (dq, *J* = 8.9, 2.5 Hz, 1 H), 7.96 (s, 1 H), 7.78 (dd, *J* = 9.2, 1.9 Hz, 1 H), 2.64 (s, 3 H) ppm. ^{13}C NMR*: δ = 166.2, 149.6, 144.4, 137.9, 133.1, 132.1 (qr, *J* = 32 Hz), 129.3, 129.2, 125.3 (qr, *J* = 4 Hz), 123.6 (qr, *J* = 278 Hz), 120.2, 21.7 ppm. MS (c.i.): *m*/*z* (%) = 352 (0) [M$^+$ + 18], 336 (100) [M$^+$ + 2], 254 (12), 228 (7), 140 (2). $C_{12}H_7BrF_3NO_2$ (334.09): calcd. C 43.14, H 2.11, N 4.19; found C 43.12, H 1.88, N 4.19.

2-Bromo-7-methoxy-4-trifluoromethyl-3-quinolinecarboxylic Acid (5e): Analogously, from the 2-bromoquinoline **2e** (4.6 g, 15 mmol); colorless needles; m.p. 179−180 °C (from water; reprod.); yield: 4.30 g (82%). ^{1}H NMR*: δ = 8.13 (d, *J* = 9.6 Hz, 1 H), 7.53 (d, *J* = 10.0 Hz, 1 H), 7.52 (s, 1 H), 4.08 (s, 3 H) ppm. ^{13}C NMR*: δ = 167.2, 163.2, 151.0, 138.8, 131.0 (qr, *J* = 32 Hz), 128.1, 126.7, 124.1, 123.4 (qr, *J* = 277 Hz), 116.8, 108.9, 57.4 ppm. MS (c.i.): *m*/*z* (%) = 368 (0) [M$^+$ + 18], 351 (100) [M$^+$ + 1], 332 (54), 270 (18), 225 (17). $C_{12}H_7BrF_3NO_3$ (350.04): calcd. C 41.17, H 2.02, N 4.00; found C 41.01, H 2.18, N 4.00.

2-Bromo-8-methyl-4-trifluoromethyl-3-quinolinecarboxylic Acid (5g): Analogously, from the 2-bromoquinoline **2g** (4.4 g, 15 mmol); colorless prisms; m.p. 178−181 °C (from water; reprod.); yield: 4.46 g (89%). ^{1}H NMR*: δ = 8.09 (d, *J* = 9.8 Hz, 1 H), 7.91 (d, *J* = 7.6 Hz, 1 H), 7.83 (dd, *J* = 8.4, 7.2 Hz, 1 H), 2.78 (s, 3 H)

ppm. ^{13}C NMR*: δ = 166.2, 148.2, 138.6, 136.7, 133.1, 132.3 (qr, *J* = 30 Hz), 130.6, 129.9 (qr, *J* = 3 Hz), 123.4 (qr, *J* = 278 Hz), 123.1 (qr, *J* = 3 Hz), 122.3, 18.2 ppm. MS (c.i.): *m*/*z* (%) = 352 (0) [M$^+$ + 18], 336 (100) [M$^+$ + 2], 335 (42) [M$^+$ + 1], 290 (23), 256 (19). $C_{12}H_7BrF_3NO_2$ (334.09): calcd. C 43.14, H 2.11, N 4.19; found C 43.19, H 1.84, N 4.33.

Trifluoromethyl-Substituted 3-Quinolinecarboxylic Acids 6

4-Trifluoromethyl-3-quinolinecarboxylic Acid (6a): A solution of the 2-bromo-3-quinolinecarboxylic acid **5a** (1.5 g, 5.0 mmol) in diethyl ether (15 mL) was added dropwise, over 15 min, to butyllithium (10 mmol) in diethyl ether (15 mL) and hexanes (6.0 mL), cooled to −100 °C. The mixture was kept at this temperature for 2 h before being treated with methanol (1.0 mL, 0.80 g, 25 mmol) and worked up as described above (see the isolation of the acids **4**); colorless prisms; m.p. 182−184 °C (from acetic acid; decomp.); yield: 0.77 g (64%). ^{1}H NMR*: δ = 9.14 (s, 1 H), 8.27 (d, *J* = 8.1 Hz, 1 H), 8.26 (d, *J* = 8.7 Hz, 1 H), 8.00 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1 H), 7.90 (ddd, *J* = 8.9, 7.0, 1.6 Hz, 1 H) ppm. ^{13}C NMR*: δ = 166.9, 148.9, 147.7, 131.2, 130.4, 129.6, 126.6, 124.5 (qr, *J* = 4 Hz), 123.5 (qr, *J* = 277 Hz) ppm. MS (c.i.): *m*/*z* (%) = 259 (0) [M$^+$ + 18], 242 (100) [M$^+$ + 1], 222 (78), 197 (50). $C_{11}H_6F_3NO_2$ (241.17): calcd. C 54.78, H 2.51, N 5.80; found C 54.81, H 2.45, N 5.76.

6-Fluoro-4-trifluoromethyl-3-quinolinecarboxylic Acid (6c): Analogously, from the 2-bromoquinolinecarboxylic acid **5c** (1.7 g, 5.0 mmol); colorless prisms; m.p. 198−201 °C (from acetic acid; decomp.); yield: 0.86 g (66%). ^{1}H NMR*: δ = 9.11 (s, 1 H), 8.34 (dd, *J* = 10.2, 5.8 Hz, 1 H), 7.84−7.94 (m, 2 H) ppm. ^{13}C NMR* : δ = 167.6, 162.8 (qr, *J* = 250 Hz), 148.4 (d, *J* = 3 Hz), 147.1, 135.7 (qr, *J* = 32 Hz), 134.5 (d, *J* = 10 Hz), 124.0, (qr, *J* = 275 Hz), 123.7 (2 C), 122.3 (d, *J* = 26 Hz), 109.2 (d, *J* = 26 Hz, 3 Hz). $C_{11}H_5F_4NO_2$ (259.16): calcd. C 50.98, H 1.94; found C 51.02, H 1.85. The debromination of the acid **5c** (10 mmol) was also accomplished by transfer hydrogenation using ammonium formate (1.3 g, 20 mmol) as the hydrogen source in methanol (20 mL) in the presence of catalytic amounts of palladium on charcoal at 25 °C for 2 h; yield: 1.84 g (71%).

8-Methyl-4-trifluoromethyl-3-quinolinecarboxylic Acid (6g): Analogously, as described for acid **6a**, from the 2-bromo-3-quinolinecarboxylic acid **5g** (1.7 g, 5.0 mmol); colorless prisms; m.p. 174−176 °C (from acetic acid; reprod.); yield: 0.85 g (67%). ^{1}H NMR*: δ = 9.12 (s, 1 H), 8.09 (d, *J* = 6.3 Hz, 1 H), 7.84 (d, *J* = 6.0 Hz, 1 H), 7.77 (t, *J* = 7.9 Hz, 1 H), 2.82 (s, 3 H) ppm. ^{13}C NMR*: δ = 168.1, 148.9, 147.5, 139.3, 132.1, 130.2, 127.1, 124.3 (qr, *J* = 276 Hz), 123.2 (qr, *J* = 4 Hz), 122.8 ppm. MS (c.i.): *m*/*z* (%) = 273 (0) [M$^+$ + 18], 256 (100) [M$^+$ + 1], 236 (4), 210 (3). $C_{12}H_8F_3NO_2$ (255.19): calcd. C 56.48, H 3.16, N 5.49; found C 56.25, H 2.94, N 5.46.

Miscellaneous

2-Bromo-7-fluoro-4-trifluoromethyl-8-quinolinecarboxylic Acid (7): When the 2-bromoquinoline **2f** was treated consecutively with lithium diisopropylamide and carbon dioxide as described above (see the conversion of the bromoquinoline **2a** into the acid **5a**), deprotonation and carboxylation occurred at the 8- rather than the 3-position; colorless needles; m.p. 135−137 °C (from ethyl acetate; decomp.); yield: 4.41 g (87%). ^{1}H NMR*: δ = 8.35 (tq, *J* = 7.6, 2.0 Hz, 1 H), 8.14 (s, 1 H), 7.85 (dd, *J* = 9.6, 8.9 Hz, 1 H) ppm. ^{13}C NMR*: δ = 168.3, 165.0 (d, *J* = 256 Hz), 147.7, 140.8 (qr, *J* = 33 Hz), 132.8 (d, *J* = 10 Hz), 128.7, 128.5 (2 C), 127.3 (qr, *J* = 274 Hz), 124.5 (d, *J* = 25 Hz), 123.6 ppm. MS (c.i.): *m*/*z* (%) = 356 (0) [M$^+$ + 18], 339 (21) [M$^+$ + 1], 338 (22) [M$^+$], 295 (100), 276 (6), 214 (22). $C_{11}H_4F_4NO_2$ (338.05): calcd. C 39.08, H 1.19; found C 39.28, H 1.12.

2-Formyl-8-methyl-4-trifluoromethyl-3-quinolinecarboxylic Acid (8): The 2-bromo-3-quinolinecarboxylic acid **5g** (1.67 g, 5.0 mmol) was treated with butyllithium (10 mmol) in diethyl ether at −100 °C as described for the preparation of the debrominated acid **6a**. However, methanol was replaced by *N*,*N*-dimethylformamide (0.77 mL, 0.73 g, 10 mmol) as the reagent. After 2 h at −75 °C, tetrafluoroboric acid−diethyl ether (15 mmol) was added and, after evaporation of the volatiles, the product crystallized from ethyl acetate; colorless prisms; m.p. 217−219 °C (decomp.); yield: 0.81 g (57%). ^{1}H NMR*: δ = 8.34 (d, *J* = 8.5 Hz, 1 H), 7.97 (d, *J* = 7.0 Hz, 1 H), 7.84 (dd, *J* = 9.1, 7.1 Hz, 1 H), 7.34 (d, *J* = 7.8 Hz, 1 H), 6.81 (d, *J* = 6.5 Hz), 2.87 (s, 3 H) ppm. ^{13}C NMR*: δ = 164.0, 152.5, 140.2, 135.6 (qr, *J* = 35 Hz), 134.9, 133.6, 131.4, 125.2 (qr, *J* = 5 Hz), 124.9, 124.7 (qr, *J* = 279 Hz), 98.4, 19.5 ppm. MS (c.i.): *m*/*z* (%) = 301 (19) [M$^+$ + 18], 284 (100) [M$^+$ + 1], 283 (26) [M$^+$], 255 (11), 239 (5). $C_{13}H_8F_3NO_3$ (283.20): calcd. C 55.13, H 2.85, N 4.95; found C 55.11, H 2.91, N 4.93.

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