Selective and Efficient Structural Elaboration of 2-(Trifluoromethyl)quinolinones

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The acid-catalyzed cyclization-condensation between anilines and ethyl 4,4,4-trifluoroacetoacetate affords 1,4-dihydro-2-trifluoromethyl-4*H*-4-quinolinones (**1**), which can easily be converted into 4-bromo-2-(trifluoromethyl)quinolines. These undergo halogen/metal exchange, generating 2-trifluoromethyl-4-quinolyllithiums, when treated with butyllithium, and hydrogen/metal exchange, generating 4-bromo-2-trifluoromethyl-3-quinolyllithiums, when treated with lithium diisopropylamide. Trapping of the latter intermediates provides 3-functionalized products that may be further elaborated by electrophilic substitution of the bromine atom. A few unexpected findings resulted from these investigations, the most noteworthy being an unprecedented buttressing effect and a counterintuitive halogen reactivity.
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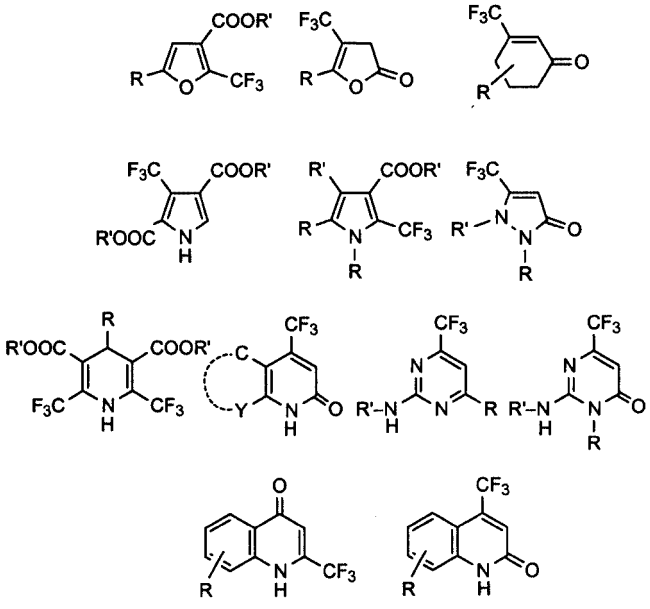
Ethyl 4,4,4-trifluoroacetoacetate, technically manufactured by addition of trifluoroacetyl chloride to ketene,[1] is a most versatile component for condensation and cyclization reactions. From this building block, considerable numbers of 2-(trifluoromethyl)furans,[2] 2,5-dihydro-4-trifluoromethyl-2-furanones,[3] trifluoromethyl-substituted sugars[4,5] or cyclohexenones[6] and 4-trifluoromethyl-2-benzopyranones have been prepared. An even greater variety of five- and six-membered nitrogen heterocycles has also been made available in such a way: 3-(trifluoromethyl)pyrroles,[7,8] 5-(trifluoromethyl)pyrazoles,[9,10] 3-(trifluoromethyl)-5-pyrrolinones,[11–15] 1,4-dihydro-2,6-bis(trifluoromethyl)pyridines,[16] 2-hetero-substituted 4-trifluoromethyl-6-pyridinones,[17–19] 2-amino-substituted 4-(trifluoromethyl)-pyrimidines[20,21] or -pyrimidones[22–25] and (trifluoromethyl)quinolinones.[25–29]

The purpose of this report is to draw attention to the synergies which can be exploited when an electronegative substituent such as trifluoromethyl is allowed to interfere with a polar organometallic reaction. We shall substantiate



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the point by showing how easily 2-trifluoromethyl-4(1*H*)-quinolones (**1**) can be converted into 4-bromo-2-(trifluoromethyl)-quinolines (**2**) and, by use of the latter as kind of a turntable, into 2-(trifluoromethyl)quinolines (**3**) and various families of quinolinecarboxylic acids (**4**, **5**, **6**, and **7**).

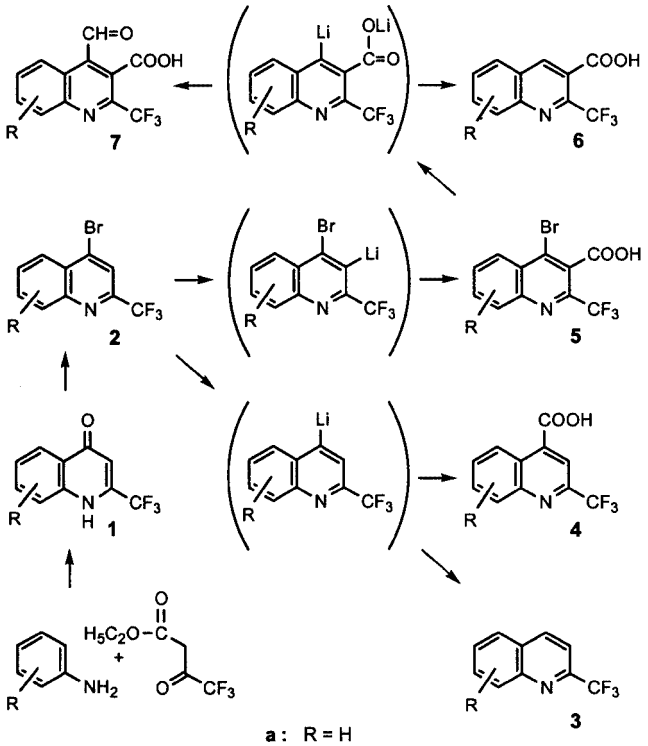
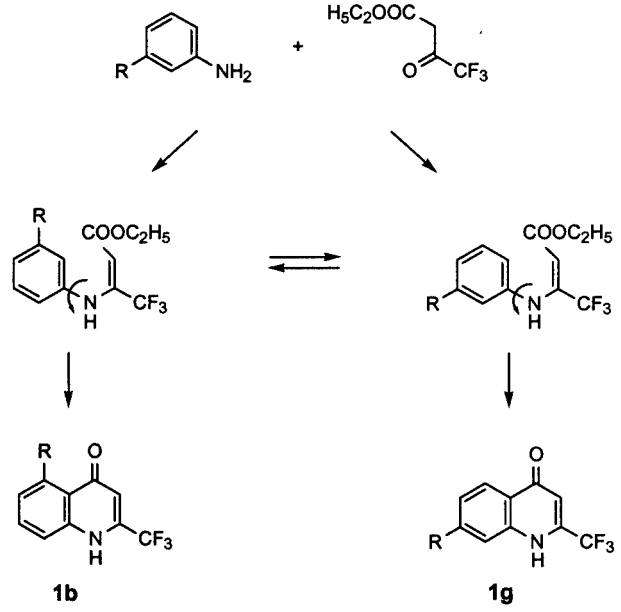


Table 1. 2-Trifluoromethyl-4(1*H*)-quinolones (**1**) from anilines and ethyl 4,4,4-trifluoroacetoacetate (yields of isolated and purified products)

	R	Reaction cond.	Yield
1a	H	[a]	51%
1b	5-H_3CO	[a]	22%[c]
1c	5-F	[a]	14%[d]
1d	6-H_3C	[a]	62%
1e	6-F	[a]	69%
1f	6-F_3CO	[a]	63%
1g	7-H_3CO	[b]	51%
1h	7-F	[b]	55%
1i	8-F	[a]	79%
1j	8-Br	[a]	64%
1k	8-I	[a]	46%

[a] The reaction components were heated for 2 h at 150 °C in the presence of a large excess of polyphosphoric acid. [b] The reaction components were dissolved in diphenyl ether and heated under reflux, in the presence of a few drops of concentrated hydrochloric acid, for 45 min. [c] Along with 32% of **1g**. [d] Along with 36% of **1h**.

The cyclization with ethyl 4,4,4-trifluoroacetoacetate proceeded without any problem when *ortho*- or *para*-substituted anilines were employed (Table 1). On the other hand, two regioisomeric 4-quinolinones **1** can result from *meta* isomers of anilines, with the substituent emerging either at the 5- or at the 7-position. Depending on the reaction conditions, either a mixture (e.g. **1b** + **1g** or **1c** + **1h**) was obtained or the latter isomer (e.g. **1g** or **1h**) was formed almost exclusively (see formula scheme and Table 1).



The conversion of the 4-quinolones **1** into the corresponding 4-bromo-2-(trifluoromethyl)quinolines **2** was accomplished with phosphorus oxytribromide as described previously.[26] Despite considerable losses during workup, yields of isolated products were generally high (Table 2).

Table 2. 4-Bromo-2-(trifluoromethyl)quinolines (**2**) from 2-trifluoromethyl-4(1*H*)-quinolones (**1**) and phosphorus oxytribromide: yields of isolated and purified products

	Subst. R	React. cond.	Yield
2a	H	[a]	88%
2b	5-H_3CO	[a]	55%[b]
2c	5-F	[a]	52%
2d	6-H_3C	[a]	87%
2e	6-F	[a]	84%
2f	6-F_3CO	[a]	78%
2g	7-H_3CO	[a]	70%
2h	7-F	[a]	68%
2i	8-F	[a]	81%
2j	8-Br	[a]	83%
2k	8-I	[a]	49%[c]

[a] The reaction components were heated, without solvent, for 2 h at 150 °C. [b] Along with 14% of 4,8-dibromo-5-methoxy-2-(trifluoromethyl)quinoline as a by-product. [c] Along with 22% of **2j**.

As already reported,[26] the bromine in the heterocyclic compounds can be exchanged for lithium by treatment with butyllithium, although the yields of trapping products were only moderate. When the diethyl ether solvent was replaced with tetrahydrofuran and the temperature was lowered from −35 °C to −75 °C, the 2-(trifluoromethyl)quinolines **3** were formed almost quantitatively upon quenching with methanol (Table 3).

Table 3. Removal of the heavy halogen from 4-bromo-2-(trifluoromethyl)quinolines (**2**) by consecutive treatment with butyllithium and methanol: yields of isolated and purified 2-(trifluoromethyl)quinolines (**3**)

	Subst. R	React. cond.[a]	Yield
3a	H	[b]	81%
3d	6-H_3C	[b]	74%
3e	6-F	[b]	89%
3g	7-H_3CO	[b]	79%
3h	7-F	[b]	80%

[a] The bromine/lithium permutation requires only two or three minutes if *tert*-butyllithium is employed instead of butyllithium. [b] Butyllithium in tetrahydrofuran at −75 °C for 15 min, then quenching with methanol.

The organometallic intermediates emanating from the halogen/metal interconversion can, of course, be intercepted with other electrophiles. Thus, carboxylation followed by neutralization afforded the acids **4** (Table 4).

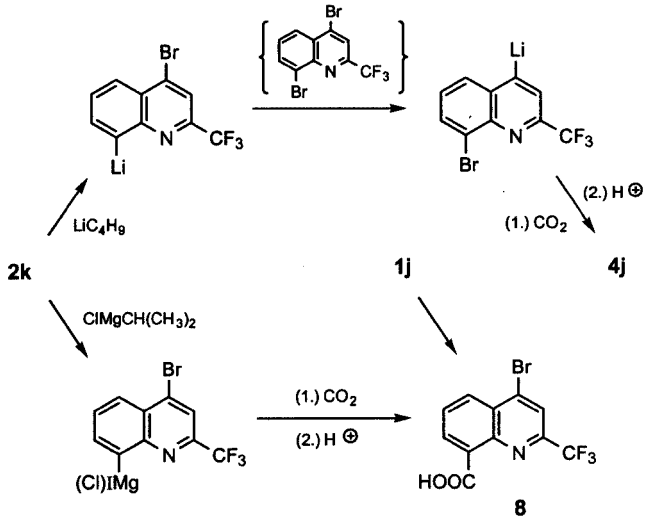
Table 4. 2-Trifluoromethyl-4-quinolinecarboxylic acids (**4**) made from 4-bromo-2-(trifluoromethyl)quinolines (**2**) with butyllithium and carbon dioxide: yields of isolated and purified products

	Subst. R	React. cond.	Yield
4a	H	[a]	74%
4b	5-H_3CO	[a]	89%
4c	5-F	[a]	82%
4d	6-H_3C	[a]	77%
4e	6-F	[a]	83%
4f	6-F_3CO	[a]	74%
4g	7-H_3CO	[a]	74%
4h	7-F	[a]	84%
4i	8-F	[a]	79%
4j	8-Br	[a]	57%[b,c]

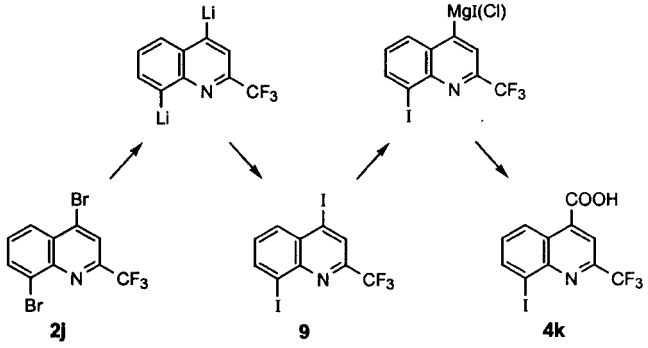
[a] Butyllithium was added at −75 °C to the bromo compound **2** in tetrahydrofuran, and after 45 min the mixture was poured onto an excess of freshly crushed dry ice. [b] Not even a trace of the regioisomer resulting from halogen/metal interconversion at the 8-position was detected. [c] If the halogen/metal exchange is performed with isopropylmagnesium chloride (in tetrahydrofuran at 0 °C for 2 h) instead with butyllithium, acid **4j** can be isolated in 89% yield.

The same carboxylic acid **4j** was obtained regardless of whether the 4,8-dibromoquinoline **2j** or the 4-bromo-8-iodoquinoline **2k** was used as the substrate. Obviously, the latter had initially undergone a halogen/metal exchange at the 8-position. However, the generated intermediate was subsequently isomerized to the 8-bromo-2-trifluoromethyl-4-quinolyllithium in another intermolecular halogen/metal exchange, trace amounts of the dibromo compound **2j** presumably acting as a turntable.

When the halogen/metal permutation was carried out with isopropylmagnesium chloride, the resulting 8-magnesium species proved stable. Upon carboxylation, the quinolinecarboxylic acid **8** was obtained in 84% yield. The same compound was prepared independently from 8-bromo-2-trifluoromethyl-4(1*H*)-quinolinone (**1j**), in a six-step sequence passing through 8-bromo-4-methoxy-2(trifluoromethyl)quinoline, 4-methoxy-2-trifluoromethyl-8-quinolinecarboxylic acid, the corresponding methyl ester and methyl 4-bromo-2-trifluoromethyl-8-quinolinecarboxylate as the key intermediates (see Exp. Sect.).



We were nevertheless able to obtain the 8-iodo-2-trifluoromethyl-4-quinolinecarboxylic acid (**4k**). The dibromoquinoline **2j** was subjected to a double halogen/metal permutation with butyllithium, and the generated dilithio species was intercepted with iodine to afford 4,8-diiodo-2-(trifluoromethyl)quinoline (**9**; 69%). A fresh halogen/metal interconversion, this time carried out with isopropylmagnesium chloride, followed by carboxylation and neutralization gave the desired acid **4k** (59%).



As initially demonstrated with 3-bromofuran, halogenated heterocycles undergo hydrogen/metal rather than halogen/metal permutation when the organolithium reagent is replaced by a lithium dialkylamide.[30] In the same way, 4-

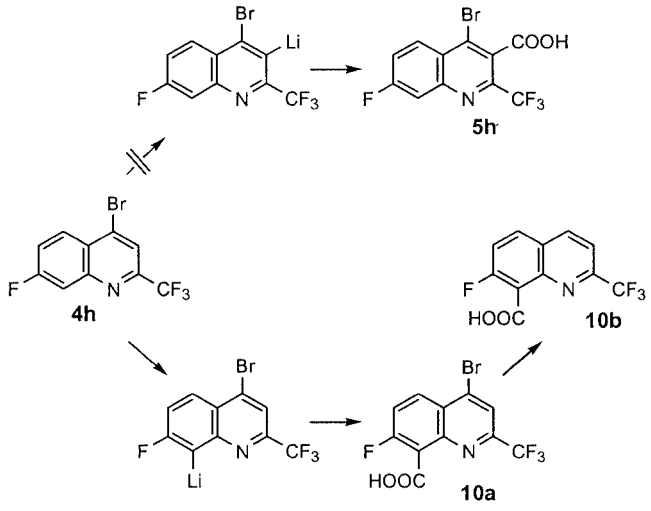
bromo-2-(trifluoromethyl)quinoline (**2a**) and its 6-, 7- or 8-substituted congeners (**2d** − **2j**) react smoothly with lithium diisopropylamide with deprotonation at the 3-position and give the corresponding acids **5** upon carboxylation in almost quantitative yield (Table 5). In contrast, the 5-substituted analogues proved to be totally inert under the same conditions (Table 5). This once again suggests the operation of a buttressing effect.[31−33]

Table 5. Production of 4-bromo-2-trifluoromethyl-3-quinolinecarboxylic acids (**5**) by consecutive treatment of 4-bromo-2-(trifluoromethyl)quinolines (**2**) with lithium diisopropylamide and carbon dioxide: yields of isolated and purified products

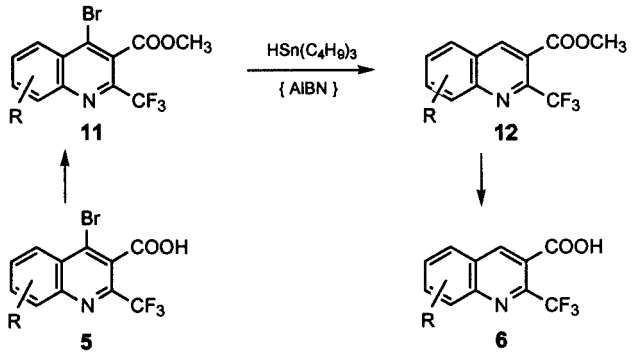
	Subst. R	React. cond.	Yield
5a	H	[a]	88%
5b	5-H_3CO	[a]	0%[b]
5c	5-F	[a]	0%[b]
5d	6-H_3C	[a]	74%
5e	6-F	[a]	81%
5f	6-F_3CO	[a]	89%
5g	7-H_3CO	[a]	86%
5h	7-F	[a]	0%[c]
5i	8-F	[a]	86%
5j	8-Br	[a]	62%
5k	8-I	[a]	78%

[a] The substrate **2** was treated consecutively with LIDA (2 h at −75 °C) and with an excess of freshly crushed dry ice. [b] Starting materials **2b** and **4b** were recovered almost quantitatively. For an explanation, see text. [c] Deprotonation and functionalization at the 8- rather than the 3-position; 80% of product **9**, see text and Exp. Sect.

Another surprise was the behavior of 4-bromo-7-fluoro-2-(trifluoromethyl)quinoline (**4h**). Deprotonation did not, as expected, occur at the 3-position to produce acid **5h** after carboxylation, but rather at the nitrogen-adjacent 8-position, providing the corresponding carboxylic acid **10a** in 80% yield and, after bromine/lithium exchange and subsequent neutralization, the acid **10b**.



When the quinoline starting materials **2** are treated with secondary lithium amides, the bromine substituent serves two purposes simultaneously, protecting the 4-position against deprotonation and also facilitating the hydrogen/metal exchange at the 3-position. Having fulfilled its task, it may be removed. The dehalogenation of the 4-bromo-2-trifluoromethyl-3-quinolinecarboxylic acids **5** can be accomplished in two ways. Firstly, the acid **5** may be converted into its methyl (**11**) or ethyl ester, and this can be treated with tributyltin hydride to provide the debrominated congener (**12**), and finally hydrolyzed to the reduced acid **6** (Table 6, Method A).



Alternatively, the acid **5** may be treated at −75 °C or −100 °C with two equivalents of butyllithium. The *O*,*C*-dilithio species thus generated can subsequently be protonated to afford the debrominated acid **6** in high yield (Table 6, Method B).

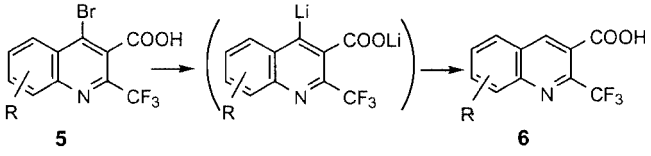


Table 6. 2-Trifluoromethyl-3-quinolinecarboxylic acids (**6**) by reduction of 4-bromo-2-trifluoromethyl-3-quinolinecarboxylic acids (**5**): yields of isolated and purified products

	R	Method A[a]	Method B[b]
6a	H	71%	91%
6d	6-H_3C	60%	83%
6f	6-F_3CO	59%	87%
6g	7-H_3CO	59%	86%
6i	8-F	64%	81%

[a] Overall yields: esterification, reduction with tributyltin hydride, and ester hydrolysis. [b] Consecutive treatment with butyllithium and methanol.

The *O*,*C*-dilithio species can also, of course, be trapped by electrophiles other than a proton source. Aldehydes **7** were obtained when *N*,*N*-dimethylformamide was used. However, the yields were poor and the 4-unsubstituted acids **6** were inevitably formed as by-products (Table 7, Method C, M = Li). Apparently the *O*,*C*-dilithio intermediates, as soon as generated, cluster with unmodified

acids **6**, thus promoting proton transfer within mixed aggregates.[34−35] Such complications can be avoided if the acids **5** are converted into tetrabutylammonium rather than lithium carboxylates before subjection to halogen/metal exchange and subsequent electrophilic trapping. Under such conditions, pure aldehyde-acids **7** were isolated (Table 7, Method D, M = $N(C_4H_9)_4$].

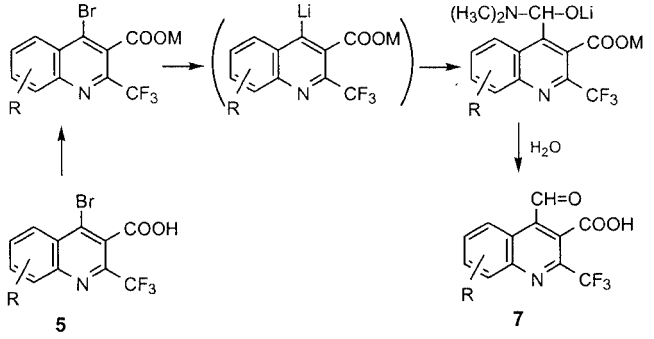


Table 7. Conversion of 4-bromo-2-trifluoromethyl-3-quinolinecarboxylic acids (**5**) into 4-formyl-2-trifluoromethyl-3-quinolinecarboxylic acids (**7**) through their lithium or tetrabutylammonium carboxylates

	R	Method C [a,b,c]	Method D[d,e]
7a	H	15% (+ 22% **6a**)	56%
7f	6-F_3CO	39% (+ 20% **6f**)	83%
7g	7-H_3CO	−	63%

[a] Treatment with 2.0 equiv. of butyllithium in diethyl ether at −100 °C. [b] Trapping with *N*,*N*-dimethylformamide, followed by hydrolysis. [c] Gas chromatographically determined yields. [d] Neutralization of the acid **5** with tetrabutylammonium hydroxide, removal of water, and consecutive treatment with 1.0 equiv. of butyllithium, *N*,*N*-dimethylformamide, and water. [e] Yields of isolated and purified products **7**.

Experimental Section

Details concerning standard operations and abbreviations can be found in previous publications from this laboratory.[36−38] ^1H, ^{13}C, and ^{19}F NMR spectra were recorded at 400, 101, and 376 MHz, respectively, the samples having been dissolved in deuteriochloroform or, if marked by an asterisk (*), deuterioacetone, unless stated otherwise. 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 standard conditions, chemical ionization ("c.i.") in an ammonia atmosphere at 100 °C source temperature was applied.

2-Trifluoromethyl-4(1*H*)-quinolones (1)

An aniline (0.25 mmol) was added dropwise, over 15 min and with mechanical stirring, to a mixture of ethyl 4,4,4-trifluoro-3-oxobutanoate (38 mL, 50 g, 0.25 mol) and polyphosphoric acid (0.20 kg), heated at 100 °C. The temperature was then raised to 150 °C and kept there for 2 h. When cold, the mixture was diluted with aqueous sodium hydroxide (5%, 0.80 L). The precipitate formed was dissolved in a 10% aqueous solution (0.30 L) of sodium hydroxide. After some insoluble material had been removed by filtration, the clear solution was acidified with concentrated (32%) hydrochloric acid. The solid obtained was collected and crystallized from ethanol.

2-(Trifluoromethyl)-4-quinolinone (1a): This compound was prepared from aniline (23 mL, 23 g, 0.25 mol); short colorless needles; m.p. 206−208 °C (repr.; ref.[26] 210.5−211.5 °C); yield: 21.0 g (51%). ^1H NMR*: δ = 11.39 (br. s, 1 H), 8.32 (dd, *J* = 8.3, 0.9 Hz, 1 H), 7.98 (d, *J* = 8.4 Hz, 1 H), 7.84 (td, *J* = 6.9, 1.4 Hz, 1 H), 7.61 (t, *J* = 7.6 Hz, 1 H), 7.05 (s, 1 H) ppm. ^{13}C NMR*: δ = 168.3, 148.5, 147.7 (qr, *J* = 34.4 Hz), 133.1, 128.6, 128.0, 124.7, 123.4 (qr, *J* = 274.8 Hz), 118.3, 103.3 ppm. ^{19}F NMR*: δ = −67.3 (s) ppm. MS (c.i.): *m*/*z* (%) = 214 (100) [M^+ + 1], 213 (89) [M^+], 185 (13), 165 (19), 144 (17). $C_{10}H_6F_3NO$ (213.16): calcd. C 56.35, H 2.84; found C 56.19, H 3.00.

5-Methoxy-2-(trifluoromethyl)-4-quinolinone (1b): This compound was prepared from *m*-anisidine (28 mL, 31 g, 0.25 mol). The crude reaction mixture was adsorbed on silica gel and eluted with a 1:9 (v/v) mixture of ethyl acetate and hexanes to afford **1b** and **1g** in a 2:3 ratio; colorless needles; m.p. 130−132 °C (ref.[29] 131−132 °C); yield: 13.3 g (22%). ^1H NMR*: δ = 10.52 (br. s, 1 H), 7.76 (dd, *J* = 8.4, 8.1 Hz, 1 H), 7.66 (d, *J* = 8.5 Hz, 1 H), 7.20 (d, *J* = 7.9 Hz, 1 H), 7.10 (s, 1 H), 4.22 (s, 3 H) ppm. ^{13}C NMR*: δ = 165.3, 157.3, 151.5, 150.0 (qr, *J* = 33.1 Hz), 132.0, 123.5, 122.5 (qr, *J* = 274.4 Hz), 112.8, 107.0, 102.5, 57.2 ppm. ^{19}F NMR*: δ = −67.5 (s) ppm. MS (c.i.): *m*/*z* (%) = 244 (100) [M^+ + 1)], 243 (22) [M^+], 228 (1), 200 (1).

5-Fluoro-2-(trifluoromethyl)-4-quinolinone (1c) and 7-Fluoro-2-(trifluoromethyl)-4-quinolinone (1h): These compounds were obtained from 3-fluoroaniline (24 mL, 28 g, 0.25 mol); 28.9 g (50%). Attempts to separate the two regioisomers by chromatography or by fractional crystallization failed.

6-Methyl-2-(trifluoromethyl)-4-quinolinone (1d): This compound was prepared from *p*-toluidine (27 g, 0.25 mol); m.p. 251−253 °C (repr.); yield: 43.0 g (62%). ^1H NMR (D_3CSOCD_3): δ = 8.02 (s, 1 H), 7.93 (br. s, 1 H), 7.66 (d, *J* = 8.6 Hz, 1 H), 7.16 (br. s, 1 H), 2.53 (s, 3 H) ppm. ^{13}C NMR (D_3CSOCD_3): δ = 164.4, 148.6 (qr, *J* = 35.3 Hz), 138.2, 134.8, 130.3, 125.0, 123.4 (qr, *J* = 273.1 Hz), 123.2, 118.1, 102.1, 22.4 ppm. ^{19}F NMR (D_3CSOCD_3): δ = −62.0 (s) ppm. MS (c.i.): *m*/*z* (%) = 228 (100) [M^+ + 1], 227 (38), [M^+], 207 (2), 184 (1), 158 (2). $C_{11}H_8F_3NO$ (277.18): calcd. C 58.16, H 3.55; found C 57.89, H 3.80.

6-Fluoro-2-(trifluoromethyl)-4-quinolinone (1e): This compound was prepared from 4-fluoroaniline (24 mL, 28 g, 0.25 mol). Short, colorless needles; m.p. 250−251 °C (repr.; ref.[27] 255−260 °C); yield: 39.8 g (69%). ^1H NMR*: δ = 8.09 (dd, *J* = 9.2, 5.1 Hz, 1 H), 7.89 (dd, *J* = 9.3, 2.9 Hz, 1 H), 7.69 (td, *J* = 8.4, 2.9 Hz, 1 H), 7.15 (br. s, 1 H) ppm. ^{13}C NMR*: δ = 164.1, 160.2 (d, *J* = 251.5 Hz), 146.2 (qr, *J* = 32.9 Hz), 144.5, 131.3 (d, *J* = 9.6 Hz), 125.6, 121.4 (qr, *J* = 276.3 Hz), 121.5 (d, *J* = 25.7 Hz), 106.2 (d, *J* = 23.3 Hz), 100.9 ppm. ^{19}F NMR*: δ = −67.0 (s, 3 F), −111.3 (m, 1 F) ppm. MS (c.i.): *m*/*z* (%) = 232 (100) [M^+ + 1], 231 (699 [M^+], 212 (6), 183 (8), 162 (16), 134 (12), 107 (18).

6-Trifluoromethoxy-2-(trifluoromethyl)-4-quinolinone (1f): This compound was prepared from 4-(trifluoromethoxy)aniline (34 mL, 44 g, 0.25 mol). Short, colorless needles; m.p. 229−230 °C (repr.); yield: 46.8 g (63%). ^1H NMR*: δ = 8.14 (d, *J* = 9.2 Hz, 1 H), 8.11 (d, *J* = 1.4 Hz, 1 H), 7.76 (dd, *J* = 9.3, 2.4 Hz, 1 H), 7.21 (br. s, 1 H) ppm. ^{13}C NMR*: δ = 166.9, 149.5, 148.5, 147.4 (qr, *J* = 35.5 Hz), 132.3, 126.9, 124.5, 123.3 (qr, *J* = 256.2 Hz), 122.4 (qr,

J = 274.7 Hz), 115.0, 103.7 ppm. ^{19}F NMR*: δ = −57.5 (s, 3 F), −67.3 (s, 3 F) ppm. MS (c.i.): *m/z* (%) = 298 (100) [M$^+$ + 1], 297 (2) [M$^+$], 278 (2), 228 (3), 200 (4). $C_{11}H_5F_6NO_2$ (297.15): calcd. C 44.46, H 1.70; found C 44.43, H 1.87.

7-Methoxy-2-(trifluoromethyl)-4-quinolinone (1g): This compound was prepared from *m*-anisidine (28 mL, 31 g, 0.25 mol); colorless needles; m.p. 249−251 °C (repr.; ref.[29] 254−255 °C); yield: 19.4 g (32%). ^{1}H NMR*: δ = 11.00 (br. s, 1 H), 8.19 (d, J = 9.1 Hz, 1 H), 7.31 (s, 1 H), 7.23 (d, J = 8.9 Hz, 1 H), 6.94 (br. s, 1 H), 3.99 (s, 3 H) ppm. ^{13}C NMR*: δ = 164.1, 161.9, 151.5, 149.0 (qr, J = 35.4 Hz), 124.7, 122.7, (qr, J = 275.6 Hz), 120.7, 117.1, 108.5, 100.0, 56.8. −^{19}F NMR*: δ = −67.3 (s) ppm. MS (c.i.): *m/z* (%) = 244 (100) [M$^+$ + 1], 243 (50) [M$^+$], 200 (4), 144 (4).

Product **1g** could be prepared regioisomerically pure by application of a modified procedure. *m*-Anisidine (0.25 mol) and ethyl 4,4,4-trifluoro-3-oxobutanoate (38 mL, 50 g, 0.25 mol) were dissolved in warm diphenyl ether (0.25 L) containing 5 drops of concentrated hydrochloric acid. The mixture was heated at reflux (≈ 265 °C) for 45 min. After a few hours at 25 °C, a white solid deposited and was collected, washed with pentanes, and crystallized from ethanol as colorless needles; **1g**: m.p. 249−251 °C (ref.[29] 254−255 °C); yield: 29.5 g (51%).

7-Fluoro-2-(trifluoromethyl)-4-quinolinone (1h): This compound was prepared from 3-fluoroaniline (24 mL, 28 g, 0.25 mol); colorless needles; m.p. 248−250 °C (repr.); yield: 31.8 g (55%). ^{1}H NMR (D_3CSOCD_3): δ = 8.36 (dd, J = 9.2, 6.2 Hz, 1 H), 7.64 (dd, J = 10.2, 2.5 Hz, 1 H), 7.48 (td, J = 8.5, 2.5 Hz, 1 H), 7.06 (s, 1 H) ppm. ^{13}C NMR (D_3CSOCD_3): δ = 164.8, 164.7 (d, J = 251.5 Hz), 150.2 (qr, J = 34.4 Hz), 132.5, 126.9, 122.4 (qr, J = 277.0 Hz), 120.0, 118.0, 113.1, 101.5. −^{19}F NMR (D_3CSOCD_3): δ = −67.5 (s, 3 F), −107.5 (m, 1 F) ppm. MS (c.i.): *m/z* (%) = 232 (100) [M$^+$ + 1], 231 (72) [M$^+$], 203 (7), 183 (16), 162 (15), 107 (22). $C_{10}H_5F_4NO$ (231.15): calcd. C 51.96, H 2.18, N 6.06; found C 51.92, H 2.08, N 6.09.

The same procedure (45 min in refluxing diphenyl ether) that enabled the regioselective preparation of **1g** gave also pure **1h**; m.p. 248−250 °C; yield: 31.8 g (55%).

8-Fluoro-2-(trifluoromethyl)-4-quinolinone (1i): This compound was prepared from 2-fluoroaniline (24 mL, 28 g, 0.25 mol); short colorless needles; m.p. 150−151 °C (ref.[27] 144−145 °C); yield: 45.6 g (79%). ^{1}H NMR*: δ = 11.21 (br. s, 1 H), 8.12 (dd, J = 7.4 Hz, 1 H), 7.65 (m, 2 H), 7.29 (br. s, 1 H) ppm. ^{13}C NMR*: δ = 154.5, 158.5 (d, J = 251.0 Hz), 149.1 (qr, J = 35.3 Hz), 139.5, 128.0 (d, J = 6.6 Hz), 124.5, 122.6 (qr, J = 274.8 Hz), 119.3, 116.5 (d, J = 18.5 Hz), 102.8 ppm. ^{19}F NMR*: δ = −67.3 (s, 3 F), −123.5 (m, 1 F) ppm. MS (c.i.): *m/z* (%) = 232 (100) [M$^+$ + 1], 231 (39) [M$^+$], 203 (5), 183 (10). $C_{10}H_5F_4NO$ (231.15): calcd. C 51.96, H 2.18, N 6.06; found C 52.37, H 2.09, N 6.26.

8-Bromo-2-(trifluoromethyl)-4-quinolinone (1j): This compound was prepared from 2-bromoaniline (43 g, 0.25 mol); colorless needles; m.p. 137−139 °C; yield: 46.7 g (64%). ^{1}H NMR*: δ = 8.27 (dd, J = 8.4, 1.3 Hz, 1 H), 8.16 (dd, J = 7.4, 1.1 Hz, 1 H), 7.53 (t, J = 7.8 Hz, 1 H), 7.33 (s, 1 H) ppm. ^{13}C NMR*: δ = 164.8, 150.7 (qr, J = 35.2 Hz), 147.3, 136.5, 129.1, 126.3, 124.5, 123.8, 123.2 (qr, J = 274.0 Hz), 102.6 ppm. ^{19}F NMR*: δ = −67.3 (s) ppm. MS (c.i.): *m/z* (%) = 294 (97) [M$^+$ + 1], 293 (44) [M$^+$], 292 (100) [M$^+$ + 1], 291 (24) [M$^+$], 214 (10), 134 (25). $C_{10}H_5BrF_3NO$ (292.05): calcd. C 41.73, H 1.73; found C 40.92, H 1.96.

8-Iodo-2-(trifluoromethyl)-4-quinolinone (1k): This compound was prepared from 2-iodoaniline (55 g, 0.25 mol); short colorless needles; m.p. 157−158 °C; yield: 39.0 g (46%). ^{1}H NMR*: δ = 11.28 (br. s, 1 H), 8.51 (1dd, J = 7.3, 1.2 Hz, 1 H), 8.37 (dd, J = 7.4, 1.2 Hz, 1 H), 7.45 (t, J = 7.6 Hz, 1 H), 7.32 (s, 1 H) ppm. ^{13}C NMR*: δ = 165.5, 150.6 (qr, J = 35.3 Hz), 149.3, 143.4, 129.8, 124.8, 123.7, 123.2 (qr, J = 275.5 Hz), 104.3, 102.5 ppm. ^{19}F NMR*: δ = −67.3 (s) ppm. MS (c.i.): *m/z* (%) = 340 (100) [M$^+$ + 1], 339 (35) [M$^+$], 311 (5), 268 (2), 214 (4). $C_{10}H_5F_3INO$ (339.05): calcd. C 35.42, H 1.49; found C 35.36, H 1.63.

4-Bromo-2-(trifluoromethyl)quinolines (2 and 9)

The 2-trifluoromethyl-4(1*H*)-quinolinone (0.15 mol) was slowly added, with mechanical stirring, to phosphorus oxybromide (43 g, 0.15 mol) while the temperature was raised from 75 °C to 150 °C. After 2 h at 150 °C, the mixture was poured into ice-water (0.40 L). The insoluble material was collected and crystallized from methanol.

4-Bromo-2-(trifluoromethyl)quinoline (2a): This compound was prepared from quinolinone **1a** (32 g, 0.15 mol); colorless needles; m.p. 37−38 °C (ref.[26] 38−39 °C); yield: 31.6 g (88%). ^{1}H NMR: δ = 8.17 (d, J = 6.8 Hz, 1 H), 8.14 (dd, J = 8.4, 1.0 Hz, 1 H), 7.97 (s, 1 H), 7.81 (td, J = 7.0, 1.3 Hz, 1 H), 7.69 (td, J = 6.9, 1.2 Hz, 1 H) ppm. ^{13}C NMR: δ = 147.4, 147.3 (qr, J = 36.0 Hz), 135.7, 131.5, 130.5, 129.3, 128.7, 126.6, 120.9 (qr, J = 274.9 Hz), 120.8 ppm. ^{19}F NMR: δ = −67.8 (s) ppm. MS (c.i.): *m/z* (%) = 278 (24) [M$^+$ + 1], 277 (100) [M$^+$], 276 (239 [M$^+$ + 1], 275 (99) [M$^+$], 258 (5), 213 (16), 149 (16).

4-Bromo-5-methoxy-2-(trifluoromethyl)quinoline (2b): This compound was prepared from quinolinone **1b** (36 g, 0.15 mol), the crude reaction mixture being adsorbed on silica and eluted with a mixture 9:1 (v/v) of hexanes and dichloromethane to afford colorless needles; m.p. 140−141 °C; yield: 21.9 g (55%). ^{1}H NMR: δ = 7.95 (s, 1 H), 7.80 (dd, J = 8.5, 1.0 Hz, 1 H), 7.70 (dd, J = 8.4, 8.0 Hz, 1 H), 7.03 (d, J = 7.8 Hz, 1 H), 3.98 (s, 3 H) ppm. ^{13}C NMR: δ = 155.6, 149.8, 147.1 (qr, J = 35.0 Hz), 131.2, 130.8, 125.0, 123.0, 120.8 (qr, J = 273.7 Hz), 120.5, 108.3, 55.8 ppm. ^{19}F NMR: δ = −68.3 (s) ppm. MS (c.i.): *m/z* (%) = 308 (23) [M$^+$ + 1], 307 (100) [M$^+$], 306 (99) [M$^+$ + 1], 305 (98) [M$^+$], 264 (20), 262 (19), 214 (3), 212 (3), 183 (17). $C_{11}H_7BrF_3NO$ (306.08): calcd. C 43.17, H 2.31; found C 43.22, H 2.18.

4,8-Dibromo-5-methoxy-2-(trifluoromethyl)quinoline, a by-product of longer retention time, followed; colorless needles; m.p. 170−172 °C; yield: 7.0 g (14%). ^{1}H NMR: δ = 8.05 (d, J = 8.6 Hz, 1 H), 8.03 (s, 1 H), 6.93 (d, J = 8.5 Hz, 1 H), 3.99 (s, 3 H) ppm. ^{13}C NMR: δ = 155.6, 149.8, 147.3 (qr, J = 35.2 Hz), 131.3, 130.6, 125.0, 123.0, 120.8 (qr, J = 274.0 Hz), 120.4, 108.3, 55.2 ppm. ^{19}F NMR: δ = −68.1 (s) ppm. MS (c.i.): *m/z* (%) = 388 (12) [M$^+$ + 1], 387 (50) [M$^+$], 386 (57) [M$^+$ +1], 385 (100) [M$^+$], 384 (81) [M$^+$ +1], 383 (52) [M$^+$], 342 (20), 305 (5). $C_{11}H_6Br_2F_3NO$ (384.98): calcd. C 34.32, H 1.77; found C 34.18, C 1.66.

4-Bromo-5-fluoro-2-(trifluoromethyl)quinoline (2c): A mixture of **2c** and **2h** was obtained in a 27:73 ratio (determined by GC 30 m, DB 1701, 130 °C; 30 m, DB 210, 120 °C) from the mixture of quinolinones **1c** and **1h** (34 g, 0.15 mol). The quinolinone **2c** was separated by elution from silica gel (0.30 L) with hexanes; m.p. 62−64 °C; yield: 7.3 g (19%). ^{1}H NMR: δ = 8.09 (d, J = 8.6 Hz, 1 H), 8.04 (s, 1 H), 7.80 (td, J = 8.4, 5.2 Hz, 1 H), 7.44 (ddd, J = 11.4, 7.9, 1.0 Hz, 1 H) ppm. ^{13}C NMR: δ = 157.3 (d, J = 264.1 Hz), 149.1, 148.0 (m), 131.0 (d, J = 9.5 Hz), 129.3, 127.1 (d, J = 4.5 Hz), 123.1, 120.7 (qr, J = 273.0 Hz), 119.2, 114.5 (d, J = 22.0 Hz) ppm. ^{19}F NMR: δ = −68.1 (s, 3 F), −111.0 (dd, J = 11.5, 5.0 Hz, 1 F) ppm. MS (c.i.): *m/z* (%) = 296 (100) [M$^+$ + 1], 295 (78) [M$^+$], 294

(97) [M^+ + 1], 293 (66) [M^+], 250 (9), 216 (17). $C_{10}H_4BrF_4N$ (294.04): calcd. C 40.85, H 1.37, N 4.76; found C 41.14, H 1.35, N 4.87.

4-Bromo-6-methyl-2-(trifluoromethyl)quinoline (2d): This compound was prepared from quinolinone **1d** (41 g, 0.15 mol); m.p. 71−72 °C (ref.[26] 70−71 °C); yield: 32.8 g (87%). ^{1}H NMR: δ = 8.07 (d, *J* = 8.6 Hz, 1 H), 7.96 (s, 2 H), 7.66 (dd, *J* = 8.7, 1.7 Hz, 1 H), 2.61 (s, 3 H) ppm. ^{13}C NMR: δ = 146.5 (qr, *J* = 35.3 Hz), 146.0, 140.6, 135.0, 134.0, 130.4, 126.5, 125.0, 121.0 (qr, *J* = 274.8 Hz), 120.9, 22.0 ppm. ^{19}F NMR: δ = −67.8 (s) ppm. MS (c.i.): *m/z* (%) = 292 (90) [M^+ + 1], 291 (34) [M^+], 290 (100) [M^+ + 1], 289 (23) [M^+], 271 (1), 212 (24), 140 (5).

4-Bromo-6-fluoro-2-(trifluoromethyl)quinoline (2e): This compound was prepared from quinolinone **1e** (34 g, 0.15 mol); colorless needles; m.p. 90−91 °C (ref.[27] 93−95 °C); yield: 32.0 g (84%). ^{1}H NMR: δ = 8.24 (dd, *J* = 9.3, 5.3 Hz, 1 H), 8.04 (s, 1 H), 7.89 (dd, *J* = 9.3, 2.8 Hz, 1 H), 7.64 (ddd, *J* = 8.6, 7.9, 2.8 Hz, 1 H) ppm. ^{13}C NMR: δ = 162.8 (d, *J* = 251.5 Hz), 147.1 (qr, *J* = 35.2 Hz), 144.7, 134.9 (d, *J* = 6.4 Hz), 133.7 (d, *J* = 9.6 Hz), 130.1, 122.3 (d, *J* = 26.4 Hz), 121.6, 120.8 (qr, *J* = 275.6 Hz), 110.7 (d, *J* = 24.8 Hz) ppm. ^{19}F NMR: δ = −67.8 (s, 3 F), −107.1 (m, 1 F) ppm. MS (c.i.): *m/z* (%) = 296 (100) [M^+ + 1], 295 (58) [M^+], 294 (97) [M^+ + 1], 293 (51) [M^+], 276 (3), 274 (3), 216 (12), 145 (17).

4-Bromo-6-trifluoromethoxy-2-(trifluoromethyl)quinoline (2f): This compound was prepared from quinolinone **1f** (44 g, 0.15 mol); colorless needles; m.p. 70−71 °C; yield: 32.1 g (78%). ^{1}H NMR: δ = 8.44 (d, *J* = 11.1 Hz, 1 H), 8.17 (m, 2 H), 7.76 (dd, *J* = 11.0, 3.1 Hz, 1 H) ppm. ^{13}C NMR: δ = 149.8, 148.3 (qr, *J* = 35.5 Hz), 145.8, 135.5, 133.5, 129.3, 125.8, 120.4 (qr, *J* = 259.3 Hz), 120.3 (qr, *J* = 264.1 Hz), 122.0, 116.8 ppm. ^{19}F NMR: δ = −58.3 (s, 3 F), −68.3 (s, 3 F) ppm. MS (c.i.): *m/z* (%) = 362 (53) [M^+ + 1], 361 (80) [M^+], 360 (62) [M^+ + 1], 359 (100) [M^+], 342 (17), 282 (64), 281 (84). $C_{11}H_4BrF_6NO$ (360.05): calcd. C 36.70, H 1.12; found C 36.84, H 1.11.

4-Bromo-7-methoxy-2-(trifluoromethyl)quinoline (2g): This compound was prepared from quinolinone **1g** (36 g, 0.15 mol); colorless needles; m.p. 126−128 °C; yield: 28.3 g (71%). ^{1}H NMR: δ = 8.12 (d, *J* = 9.3 Hz, 1 H), 7.87 (s, 1 H), 7.54 (d, *J* = 2.5 Hz, 1 H), 7.34 (dd, *J* = 9.3, 2.5 Hz, 1 H), 3.98 (s, 3 H) ppm. ^{13}C NMR: δ = 162.5, 149.6, 147.3 (qr, *J* = 35.2 Hz), 135.6, 127.8, 123.9, 123.5, 121.0 (qr, *J* = 274.8 Hz), 118.8, 107.7, 56.1 ppm. ^{19}F NMR: δ = −68.1 (s, 3 F) ppm. MS (c.i.): *m/z* (%) = 308 (90) [M^+ + 1], 307 (34) [M^+], 306 (100) [M^+ + 1], 305 (25) [M^+], 278 (3), 228 (57), 114 (7). $C_{11}H_7BrF_3NO$ (306.08): calcd. C 43.17, H 2.31; found C 43.12, H 2.04.

4-Bromo-7-fluoro-2-(trifluoromethyl)quinoline (2h): This compound was prepared from quinolinone **1h** (34 g, 0.15 mol); colorless needles; m.p. 64−65 °C; yield: 26.0 g (68%). ^{1}H NMR: δ = 8.27 (dd, *J* = 9.3, 5.8 Hz, 1 H), 7.98 (s, 1 H), 7.84 (dd, *J* = 9.4, 2.6 Hz, 1 H), 7.55 (ddd, *J* = 9.3, 7.9, 2.6 Hz, 1 H) ppm. ^{13}C NMR: δ = 164.1, (d, *J* = 254.6 Hz), 148.8 (d, *J* = 12.9 Hz), 148.7 (qr, *J* = 35.3 Hz), 138.3, 129.3 (d, *J* = 9.8 Hz), 125.5, 120.7 (qr, *J* = 275.5 Hz), 120.5 (2 C), 144.0 (d, *J* = 21.0 Hz) ppm. ^{19}F NMR: δ = −68.3 (s, 3 F), −106.3 (m, 1 F,) ppm. MS (c.i.): *m/z* (%) = 296 (91) [M^+ + 1], 295 (37) [M^+], 294 (100) [M^+ + 1], 293 (30) [M^+], 278 (3), 276 (4), 216 (94), 145 (9). $C_{10}H_4BrF_4N$ (294.04): calcd. C 40.85, H 1.37; found C 40.96, H 1.20.

4-Bromo-8-fluoro-2-(trifluoromethyl)quinoline (2i): This compound was prepared from quinolinone **1i** (34 g, 0.15 mol); colorless needles; m.p. 69−71 °C, (ref.[27] 68−69 °C); yield: 35.7 g (81%). ^{1}H NMR: δ = 8.07 (s, 1 H), 8.02 (d, *J* = 8.6 Hz, 1 H), 7.72 (ddd, *J* = 8.3, 8.1, 5.0 Hz, 1 H), 7.59 (ddd, *J* = 9.5, 7.9, 1.1 Hz, 1 H) ppm. ^{13}C NMR: δ = 157.9 (d, *J* = 256.6 Hz), 147.5 (qr, *J* = 35.5 Hz), 144.3, 138.1 (d, *J* = 12.5 Hz), 135.8 (d, *J* = 4.0 Hz), 129.8 (d, *J* = 8.2 Hz), 122.6 (d, *J* = 4.5 Hz), 122.0, 120.6 (qr, *J* = 274.8 Hz), 115.5 (d, *J* = 18.0 Hz) ppm. ^{19}F NMR: δ = −67.8 (s, 3 F), −121.3 (dd, *J* = 10.0, 5.0 Hz, 1 F) ppm. MS (c.i.): *m/z* (%) = 296 (89) [M^+ + 1], 295 (47) [M^+], 294 (100) [M^+ + 1], 293 (26) [M^+], 250 (6), 216 (6). $C_{10}H_4BrF_4N$ (294.04): calcd. C 40.85, H 1.37, N 4.76; found C 40.56, H 1.18, N 4.76.

4,8-Dibromo-2-(trifluoromethyl)quinoline (2j): This compound was prepared from quinolinone **1j** (44 g, 0.15 mol); colorless needles; m.p. 86−87 °C; yield: 38.3 g (83%). ^{1}H NMR: δ = 8.25 (d, *J* = 8.5 Hz, 1 H), 8.20 (d, *J* = 7.5 Hz, 1 H), 8.08 (s, 1 H), 7.61 (t, *J* = 8.3 Hz, 1 H) ppm. ^{13}C NMR: δ = 148.0 (qr, *J* = 35.9 Hz), 144.7, 136.2, 135.3, 130.0, 129.6, 126.7, 126.2, 121.9, 120.7 (qr, *J* = 276.4 Hz) ppm. ^{19}F NMR: δ = −68.0 (s) ppm. MS (c.i.): *m/z* (%) = 358 (63) [M^+ + 1], 357 (22) [M^+], 356 (100) [M^+ + 1], 355 (19) [M^+], 354 (70) [M^+ + 1], 353 (5) [M^+], 278 (5), 276 (5). $C_{10}H_4Br_2F_3N$ (354.95): calcd. C 33.84, H 1.14; found C 33.72, H 1.24.

4-Bromo-8-iodo-2-(trifluoromethyl)quinoline (2k): This compound was prepared from quinolinone **1k** (51 g, 0.15 mol); colorless needles; m.p. 112−113 °C; yield: 25.6 g (49%). ^{1}H NMR: δ = 8.48 (dd, *J* = 7.4, 1.2 Hz, 1 H), 8.26 (dd, *J* = 8.5, 1.2 Hz, 1 H), 8.06 (s, 1 H), 7.47 (dd, *J* = 8.4, 7.5 Hz, 1 H) ppm. ^{13}C NMR: δ = 148.1 (qr, *J* = 36.5 Hz), 146.5, 142.4, 136.3, 131.1 (qr, *J* = 278.0 Hz), 130.8, 128.9, 127.6, 121.8, 104.3 ppm. ^{19}F NMR: δ = −67.9 (s) ppm. MS (c.i.): *m/z* (%) = 404 (91) [M^+ + 1], 403 (89) [M^+], 402 (100) [M^+ + 1], 401 (73) [M^+], 356 (16), 324 (23), 276 (9), 156 (11). $C_{10}H_4BrF_3IN$ (401.95): calcd. C 29.88, H 1.00, N 3.48; found C 29.78, H 1.03, N 3.54.

4,8-Diiodo-2-(trifluoromethyl)quinoline (9): 4,8-Dibromo-2-(trifluoromethyl)quinoline (28 g, 79 mmol) in tetrahydrofuran (0.10 L) and butyllithium (0.16 mol) in hexanes (0.10 L) were mixed at −75 °C and kept for 45 min. Iodine (41 g, 0.16 mol) in tetrahydrofuran (50 mL) was added. The solvents were evaporated and the residue was taken up in diethyl ether (0.10 L). The organic layer was washed with aqueous sodium thiosulfate (1.0 M, 2 × 50 mL) and dried, and the solvents were evaporated. The residue was crystallized from methanol; colorless prisms; m.p. 157−159 °C; yield: 24.6 g (69%). ^{1}H NMR: δ = 8.45 (dd, *J* = 7.5, 1.1 Hz, 1 H), 8.30 (s, 1 H), 8.07 (dd, *J* = 8.3, 1.1 Hz, 1 H), 7.42 (dd, *J* = 8.3, 7.5 Hz, 1 H) ppm. ^{13}C NMR: δ = 148.0 (qr, *J* = 36.0 Hz), 145.3, 142.4, 135.3, 132.5, 131.0, 129.1, 120.2 (qr, *J* = 276.0 Hz), 113.5, 104.5 ppm. ^{19}F NMR: δ = −67.8 (s) ppm. MS (c.i.): *m/z* (%) = 450 (25) [M^+ + 1], 449 (100) [M^+], 448 (81), 403 (11), 322 (12). $C_{10}H_4F_3I_2N$ (448.94): calcd. C 26.75, H 0.90, N 3.12; found C 26.96, H 0.96, N 3.17.

2-(Trifluoromethyl)quinolines (3)

The 4-bromo-2-(trifluoromethyl)quinoline (**2**; 25 mmol) was added to a precooled solution of butyllithium (25 mmol) in tetrahydrofuran (15 mL) and hexanes (15 mL). After the mixture had been kept for 15 min at −75 °C, methanol (2.0 mL, 50 mmol) was added by syringe and the product was isolated by crystallization from pentanes.

2-(Trifluoromethyl)quinoline (3a): This compound was prepared from **2a** (4.1 g, 15 mmol); colorless needles; m.p. 57−58 °C (ref.[39] 57.0−57.5 °C); yield: 2.39 g (81%). ^{1}H NMR: δ = 8.37 (d, *J* = 8.5 Hz, 1 H), 8.24 (d, *J* = 8.5 Hz, 1 H), 7.93 (d, *J* = 8.3 Hz, 1 H),

7.84 (dd, J = 8.5, 7.2 Hz, 1 H), 7.75 (d, J = 8.5 Hz, 1 H), 7.69 (t, J = 8.5 Hz, 1 H) ppm. ^{13}C NMR: δ = 147.8 (qr, J = 34.4 Hz), 147.0, 137.9, 130.7, 129.9, 128.8, 128.3, 127.5, 121.6 (qr, J = 275.6 Hz), 116.5 ppm. ^{19}F NMR: δ = −68.0 (s) ppm. MS (c.i.): m/z (%) = 198 (10) [M^+ + 1], 197 (45) [M^+], 128 (28), 96 (30), 83 (100).

6-Methyl-2-(trifluoromethyl)quinoline (3d): This compound was prepared from **2d** (4.4 g, 15 mmol); colorless prisms; m.p. 89.5−91.5 °C (ref.[39] 88−89 °C); yield: 2.34 g (74%). ^{1}H NMR: δ = 8.26 (d, J = 8.6 Hz, 1 H), 8.12 (d, J = 9.4 Hz, 1 H), 7.70 (d, J = 8.6 Hz, 1 H), 7.65 (m, 2 H), 2.58 (s, 3 H) ppm. ^{13}C NMR: δ = 147.1 (qr, J = 34.4 Hz), 145.9, 139.0, 137.4, 133.3, 129.7, 129.0, 126.5, 122.0 (qr, J = 274.8 Hz), 116.8, 21.7 ppm. ^{19}F NMR: δ = −67.9 (s) ppm. MS (c.i.): m/z (%) = 212 (100) [M^+ + 1], 211 (37) [M^+], 191 (4), 142 (2).

6-Fluoro-2-(trifluoromethyl)quinoline (3e): This compound was prepared from **2e** (4.4 g, 15 mmol); colorless needles; m.p. 59−60 °C; yield: 2.87 g (89%). ^{1}H NMR: δ = 8.30 (d, J = 8.6 Hz, 1 H), 8.14 (dd, J = 9.4, 5.4 Hz, 1 H), 7.75 (d, J = 8.6 Hz, 1 H), 7.60 (ddd, J = 11.0, 9.2, 2.7 Hz, 1 H), 7.51 (dd, J = 8.6, 2.7 Hz, 1 H) ppm. ^{13}C NMR: δ = 161.4 (d, J = 251.7 Hz), 147.3 (qr, J = 34.4 Hz), 144.1, 137.3 (d, J = 5.6 Hz), 132.7 (d, J = 9.6 Hz), 129.6 (d, J = 10.4 Hz), 121.4 (qr, J = 274.8 Hz), 121.3 (d, J = 25.6 Hz), 117.5, 111.1 (d, J = 21.6 Hz) ppm. ^{19}F NMR: δ = −68.0 (s), −110.0 (m, 1 F) ppm. MS (c.i.): m/z (%) = 216 (100) [M^+ + 1], 215 (42) [M^+], 193 (2), 146 (4). $C_{10}H_5F_4N$ (215.15): calcd. C 55.83, H 2.34, N 6.51; found C 55.67, H 2.50, N 6.32.

7-Methoxy-2-(trifluoromethyl)quinoline (3g): This compound was prepared from **2g** (4.6 g, 15 mmol); colorless needles; m.p. 69−71 °C (ref.[39] 65−66 °C); yield: 2.69 g (79%). ^{1}H NMR: δ = 8.21 (d, J = 8.3 Hz, 1 H), 7.73 (d, J = 9.1 Hz, 1 H), 7.58 (d, J = 8.3 Hz, 1 H), 7.48 (d, J = 2.4 Hz, 1 H), 7.28 (dd, J = 8.9, 2.4 Hz, 1 H), 3.94 (s, 3 H) ppm. ^{13}C NMR: δ = 161.6, 149.3, 148.1 (qr, J = 34.4 Hz), 137.7, 128.8, 124.4, 122.2, 121.7 (qr, J = 275.5 Hz), 114.7, 107.5, 55.8 ppm. ^{19}F NMR: δ = −67.9 (s) ppm. MS (c.i.): m/z (%) = 228 (100) [M^+ + 1], 227 (61) [M^+], 216 (12), 197 (11), 128 (5).

7-Fluoro-2-(trifluoromethyl)quinoline (3h): This compound was prepared from **2h** (4.4 g, 15 mmol); colorless prisms; m.p. 49−50 °C (ref.[39] 52−53 °C); yield: 2.58 g (80%). ^{1}H NMR: δ = 8.35 (d, J = 8.6 Hz, 1 H), 7.91 (dd, J = 9.1, 5.9 Hz, 1 H), 7.83 (dd, J = 9.7, 2.4 Hz, 1 H), 7.73 (d, J = 8.6 Hz, 1 H), 7.46 (td, J = 8.6, 2.7 Hz, 1 H) ppm. ^{13}C NMR: δ = 163.8 (d, J = 252.5 Hz), 149.2 (qr, J = 35.2 Hz), 148.3 (d, J = 13.6 Hz), 138.1, 130.0 (d, J = 9.6 Hz), 126.0, 121.5 (qr, J = 274.8 Hz), 119.5 (d, J = 25.6 Hz), 116.3, 113.7 (d, J = 20.8 Hz) ppm. ^{19}F NMR: δ = −68.1 (s, 3 F), −107.3 (m, 1 F) ppm. MS (c.i.): m/z (%) = 216 (100) [M^+ + 1], 215 (57) [M^+], 193 (7), 146 (11).

2-(Trifluoromethyl)-4-quinolinecarboxylic Acids (4)

The 4-bromo-2-(trifluoromethyl)quinoline (**2**; 25 mmol) was added at −75 °C to a solution of butyllithium (25 mmol) in tetrahydrofuran (15 mL) and hexanes (15 mL). After 45 min at this temperature, the mixture was poured onto an excess of freshly crushed dry ice. Water (0.10 L) was added, and the aqueous phase was washed with diethyl ether (3 × 50 mL) before being acidified to pH 4 with concentrated hydrochloric acid. Extraction with ethyl acetate (3 × 50 mL), drying of the combined organic layers, and evaporation gave a residue, which was crystallized from a 2:1 (v/v) mixture of chloroform and ethyl acetate.

2-Trifluoromethyl-4-quinolinecarboxylic Acid (4a): This compound was prepared from **2a** (6.9 g, 25 mmol); colorless prisms; m.p. 181−182 °C (ref.[26] 196−197 °C); yield: 4.46 g (74%). ^{1}H NMR*: δ = 8.96 (dd, J = 8.6, 0.8 Hz, 1 H), 8.35 (s, 1 H), 8.27 (d, J = 8.4 Hz, 1 H), 8.01 (ddd, J = 8.5, 6.8, 1.4 Hz, 1 H), 7.91 (ddd, J = 8.5, 6.7, 1.3 Hz, 1 H) ppm. ^{13}C NMR*: δ = 167.5, 150.0, 148.8 (qr, J = 34.4 Hz), 139.7, 133.0, 132.0 (2 C), 127.8 (2 C), 123.4 (qr, J = 274.0 Hz), 119.7 ppm. ^{19}F NMR*: δ = −67.1 (s) ppm. MS (c.i.): m/z (%) = 242 (27) [M^+ + 1], 241 (100) [M^+], 224 (7), 196 (6), 185 (1). $C_{11}H_6F_3NO_2$ (241.17): calcd. C 54.78, H 2.51; found C 54.78, H 2.88.

5-Methoxy-2-trifluoromethyl-4-quinolinecarboxylic Acid (4b): This compound was prepared from **2b** (7.6 g, 25 mmol); colorless prisms; m.p. 249−250 °C (repr.); yield: 6.03 g (89%). ^{1}H NMR*: δ = 7.91 (m, 1 H), 7.84 (s, 1 H), 7.81 (dd, J = 8.6, 0.8 Hz, 1 H), 7.31 (d, J = 8.0 Hz, 1 H), 4.03 (s, 3 H) ppm. ^{13}C NMR*: δ = 169.1, 155.6, 149.5, 148.3 (qr, J = 35.0 Hz), 142.6, 132.9, 123.0, 122.5 (qr, J = 274.0 Hz), 117.6, 114.8, 109.3, 56.8 ppm. ^{19}F NMR*: δ = −67.3 (s) ppm. MS (c.i.): m/z (%) = 272 (51) [M^+ + 1], 271 (100) [M^+], 270 (42), 253 (6), 239 (18), 224 (5). $C_{12}H_8F_3NO_3$ (271.19): calcd. C 53.15, H 2.97; found C 53.13, H 3.23.

5-Fluoro-2-trifluoromethyl-4-quinolinecarboxylic Acid (4c): This compound was prepared from **2c** (7.3 g, 25 mmol); colorless prisms; m.p. 237−239 °C (repr.); yield: 5.31 g (82%). ^{1}H NMR*: δ = 8.15 (d, J = 8.5 Hz, 1 H), 8.10 (s, 1 H), 8.05 (ddd, J = 8.4, 7.9, 5.7 Hz, 1 H), 7.68 (ddd, J = 11.2, 7.9, 0.9 Hz, 1 H) ppm. ^{13}C NMR*: δ = 169.0, 158.5 (d, J = 257.8 Hz), 150.0 (qr, J = 35.3 Hz, 2 C), 141.5, 133.5 (d, J = 8.8 Hz), 128.3 (d, J = 3.2 Hz), 123.1 (qr, J = 275.5 Hz), 117.0 (2 C), 116.0 (d, J = 20.1 Hz) ppm. ^{19}F NMR*: δ = −67.3 (s, 3 F), −111.9 (m, 1 F) ppm. MS (c.i.): m/z (%) = 260 (100) [M^+ + 1], 259 (76) [M^+], 234 (36), 215 (9), 183 (12). $C_{11}H_5F_4NO_2$ (259.16): calcd. C 50.98, H 1.94, N 5.40; found C 50.82, H 1.86, N 5.44.

6-Methyl-2-trifluoromethyl-4-quinolinecarboxylic Acid (4d): This compound was prepared from **2d** (7.2 g, 25 mmol); colorless prisms; m.p. 212−213 °C (repr.; ref.[26] 215−216 °C); yield: 4.91 g (77%). ^{1}H NMR*: δ = 8.71 (s, 1 H), 8.31 (s, 1 H), 8.11 (d, J = 8.7 Hz, 1 H), 7.80 (dd, J = 8.7, 1.9 Hz, 1 H), 2.62 (s, 3 H) ppm. ^{13}C NMR*: δ = 168.3, 148.7, 147.8 (qr, J = 34.5 Hz), 142.4, 140.0, 135.0, 131.6, 127.7, 126.5, 123.4 (qr, J = 273.9 Hz), 119.3, 23.0 ppm. ^{19}F NMR*: δ = −67.0 (s) ppm. MS (c.i.): m/z (%) = 256 (100) [M^+ + 1], 255 (25) [M^+], 212 (13), 117 (1).

6-Fluoro-2-trifluoromethyl-4-quinolinecarboxylic Acid (4e): This compound was prepared from **2e** (7.3 g, 25 mmol); colorless prisms; m.p. 194−196 °C (ref.[27] 207−09 °C); yield: 5.37 g (83%). ^{1}H NMR*: δ = 8.66 (dd, J = 11.0, 2.9 Hz, 1 H), 8.40 (s, 1 H), 8.30 (dd, J = 9.3, 5.7 Hz, 1 H), 7.83 (ddd, J = 9.3, 8.0, 2.9 Hz, 1 H) ppm. ^{13}C NMR*: δ = 166.3, 163.8 (d, J = 251.5 Hz), 162.5, 147.8 (qr, J = 37.2 Hz), 146.5, 137.5 (d, J = 6.4 Hz), 134.3 (d, J = 10.0 Hz), 128.3 (d, J = 11.8 Hz), 122.5 (d, J = 26.7 Hz), 122.4 (qr, J = 274.6 Hz), 110.5 (d, J = 25.7 Hz) ppm. ^{19}F NMR*: δ = −67.0 (s), −106.5 (m, 1 F) ppm. MS (c.i.): m/z (%) = 260 (96) [M^+ + 1, 259 (100) [M^+], 242 (13), 214 (9), 194 (3).

6-Trifluoromethoxy-2-trifluoromethyl-4-quinolinecarboxylic Acid (4f): This compound was prepared from **2f** (9.0 g, 25 mmol); colorless prisms; m.p. 201−202 °C (repr.); yield: 6.02 g (74%). ^{1}H NMR*: δ = 9.00 (d, J = 1.3 Hz, 1 H), 8.48 (s, 1 H), 8.40 (d, J = 9.3 Hz, 1 H), 7.95 (dd, J = 9.3, 1.6 Hz, 1 H) ppm. ^{13}C NMR*: δ = 165.3, 149.5, 147.8 (qr, J = 34.5 Hz), 146.5, 137.5, 133.0, 126.8, 125.0, 121.4 (qr, J = 256.3 Hz), 120.8 (qr, J = 275.5 Hz), 119.5, 116.0 ppm. ^{19}F NMR*: δ = −57.3 (s, 3 F), −67.3 (s, 3 F) ppm.

MS (c.i.): *m/z* (%) = 326 (100) [M^+ + 1], 325 (81) [M^+], 308 (10), 281 (14). $C_{12}H_5F_6NO_3$ (325.16): calcd. C 44.33, H 1.55; found C 44.09, H 1.75.

7-Methoxy-2-trifluoromethyl-4-quinolinecarboxylic Acid (4g): This compound was prepared from **2g** (7.6 g, 25 mmol); colorless prisms; m.p. 235−236 °C (repr.); yield: 5.02 g (74%). ^{1}H NMR*: δ = 8.85 (d, *J* = 9.5 Hz, 1 H), 8.18 (s, 1 H), 7.58 (d, *J* = 2.7 Hz, 1 H), 7.49 (dd, *J* = 9.5, 2.7 Hz, 1 H), 4.06 (s, 3 H) ppm. ^{13}C NMR*: δ = 166.8, 162.7, 151.5, 148.1 (qr, *J* = 34.4 Hz), 138.3, 127.8, 124.4, 122.6 (qr, *J* = 274.8 Hz), 122.3, 116.4, 108.8, 56.3 ppm. ^{19}F NMR*: δ = −67.1 (s) ppm. MS (c.i.): *m/z* (%) = 272 (32) [M^+ + 1], 271 (100) [M^+], 254 (1), 223 (3), 185 (2). $C_{12}H_8F_3NO_3$ (271.19): calcd. C 53.15, H 2.97; found C 53.09, H 2.92.

7-Fluoro-2-trifluoromethyl-4-quinolinecarboxylic Acid (4h): This compound was prepared from **2h** (7.3 g, 25 mmol); colorless prisms; m.p. 215−217 °C (repr.): yield: 5.44 g (84%). ^{1}H NMR*: δ = 9.05 (dd, *J* = 9.6, 6.1 Hz, 1 H), 8.33 (s, 1 H), 7.91 (dd, *J* = 9.6, 2.7 Hz, 1 H), 7.76 (ddd, *J* = 9.5, 8.3, 2.7 Hz, 1 H) ppm. ^{13}C NMR*: δ = 167.2, 165.3 (d, *J* = 253.0 Hz), 151.3 (d, *J* = 12.9 Hz), 150.0 (qr, *J* = 35.3 Hz), 139.9, 131.1 (dd, *J* = 12.1, 9.6 Hz), 125.0, 123.0 (qr, *J* = 274.7 Hz), 122.4 (d, *J* = 25.7 Hz), 119.3, 115.3 (d, *J* = 20.9 Hz) ppm. ^{19}F NMR*: δ = −67.4 (s, 3 F), −107.0 (m, 1 F) ppm. MS (c.i.): *m/z* (%) = 260 (100) [M^+ + 1], 259 (21) [M^+], 216 (50), 130 (15). $C_{11}H_5F_4NO_2$ (259.16): calcd. C 50.98, H 1.94; found C 50.65, H 2.15.

8-Fluoro-2-trifluoromethyl-4-quinolinecarboxylic Acid (4i): This compound was prepared from **2i** (7.3 g, 25 mmol); colorless prisms; m.p. 214−216 °C (repr.; ref.[27] 218−220 °C); yield: 5.12 g (79%). ^{1}H NMR*: δ = 8.74 (d, *J* = 8.8 Hz, 1 H), 8.44 (s, 1 H), 7.89 (m, 1 H), 7.74 (ddd, *J* = 10.5, 7.8, 1.0 Hz, 1 H) ppm. ^{13}C NMR*: δ = 165.2, 157.9 (d, *J* = 261.6 Hz), 147.3 (qr, *J* = 35.4 Hz), 138.5 (d, *J* = 12.5 Hz), 138.0, 130.4 (d, *J* = 8.0 Hz), 127.4, 121.8, 121.3 (qr, *J* = 274.0 Hz), 119.0, 115.1 (d, *J* = 18.5 Hz) ppm. ^{19}F NMR*: δ = −67.0 (s, 3 F), −122.0 (m, 1 F) ppm. MS (c.i.): *m/z* (%) = 260 (100) [M^+ + 1], 259 (22) [M^+], 242 (3), 203 (2). $C_{11}H_5F_4NO_2$ (259.16): calcd. C 50.98, H 1.94, N 5.40; found C 51.05, H 1.95, N 5.72.

8-Bromo-2-trifluoromethyl-4-quinolinecarboxylic Acid (4j): This compound was prepared from **2j** (8.9 g, 25 mmol); colorless prisms; m.p. 220−222 °C (repr.); yield: 4.56 g (57%). ^{1}H NMR*: δ = 8.97 (dd, *J* = 8.7, 1.2 Hz, 1 H), 8.45 (s, 1 H), 8.37 (dd, *J* = 7.5, 1.2 Hz, 1 H), 7.82 (dd, *J* = 8.7, 7.5 Hz, 1 H) ppm. ^{13}C NMR*: δ = 167.1, 149.5 (qr, *J* = 36.1 Hz), 146.8, 144.0, 140.8, 136.8, 135.8, 132.5, 129.3, 122.8 (qr, *J* = 274.7 Hz), 120.6 ppm. ^{19}F NMR*: δ = −67.0 (s) ppm. MS (c.i.): *m/z* (%) = 322 (32) [M^+ + 1], 321 (100) [M^+], 320 (40) [M^+ + 1], 319 (95) [M^+], 303 (6), 276 (8), 184 (4). $C_{11}H_5BrF_3NO_2$ (320.06): calcd. C 41.28, H 1.57; found C 41.10, H 1.53.

Methyl Ester: This was prepared from acid **4j** (10 mmol) and diazomethane; colorless needles; m.p. 131−132 °C; yield: 3.21 g (96%). ^{1}H NMR: δ = 8.85 (d, *J* = 8.7 Hz, 1 H), 8.29 (s, 1 H), 8.21 (d, *J* = 7.5 Hz, 1 H), 7.63 (dd, *J* = 8.2, 7.9 Hz, 1 H), 4.12 (s, 3 H) ppm. ^{13}C NMR: δ = 165.1, 148.1 (qr, *J* = 35.9 Hz), 145.5, 135.0, 131.2, 130.5, 127.4, 126.4, 125.5, 121.1 (qr, *J* = 275.6 Hz), 119.1, 53.3 ppm. ^{19}F NMR: δ = −67.9 (s, 3 F) ppm. MS (c.i.): *m/z* (%) = 336 (86) [M^+ + 1], 335 (43) [M^+], 334 (100) [M^+ + 1], 333 (16) [M^+], 304 (4), 302 (4), 271 (11), 256 (3). $C_{12}H_7BrF_3NO_2$ (334.09): calcd. C 43.14, H 2.11; found C 43.56, H 1.99.

The same acid **4j** was isolated after consecutive treatment of quinoline **2k** (10.0 g, 25 mmol) with butyllithium (in tetrahydrofuran, 15 min at −75 °C), dry ice, and acid; m.p. 220−222 °C; yield 6.9 g (86%).

8-Iodo-2-trifluoromethyl-4-quinolinecarboxylic Acid (4k): 4,8-Iodo-2-(trifluoromethyl)quinoline (**9**; 11.2 g, 25 mmol) was added to an ice-cold solution of isopropylmagnesium chloride (25 mmol) in tetrahydrofuran (25 mL). The mixture was kept 45 min at 0 °C before being poured onto an excess of freshly crushed dry ice. After evaporation of the solvent, the residue was taken up in water (0.10 L). The aqueous phase was washed with diethyl ether (3 × 50 mL), acidified to pH 4 with concentrated hydrochloric acid, and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine (50 mL), dried, and concentrated. The product was collected after crystallization from a 1:1 (v/v) mixture of chloroform and ethyl acetate; colorless prisms; m.p. 273−275 °C (dec.); yield 4.13 g (45%). ^{1}H NMR*: δ = 8.97 (dd, *J* = 8.7, 1.1 Hz, 1 H), 8.65 (dd, *J* = 7.4, 1.1 Hz, 1 H), 8.41 (s, 1 H), 7.65 (dd, *J* = 8.7, 7.4 Hz, 1 H) ppm. ^{13}C NMR*: δ = 167.0, 149.0 (qr, *J* = 35.2 Hz), 148.8, 144.0, 137.0, 133.3, 128.3, 127.6, 122.9 (qr, *J* = 274.8 Hz), 120.5, 105.4 ppm. ^{19}F NMR*: δ = −66.9 (s) ppm. MS (c.i.): *m/z* (%) = 368 (100) [M^+ + 1], 367 (15) [M^+], 323 (8), 242 (7). $C_{11}H_5F_3INO_2$ (367.06): calcd. C 35.99, H 1.37, N 3.82; found C 36.19, H 1.39, N 3.88.

The yield of isolated acid **4k** dropped to 45% when the halogen/metal exchange was performed with butyllithium in tetrahydrofuran at −75 °C. Deiodination of the acid **4k** (10 mmol) with zinc (20 mmol) suspended in a 10% aqueous solution of sodium hydroxide (50 mL) at 0 °C and with vigorous stirring for 2 h afforded the acid **4a** almost quantitatively; m.p. and mix-m.p. 181−183 °C.

4-Bromo-2-trifluoromethyl-8-quinolinecarboxylic Acid (8): Quinoline **2k** (10.0 g, 25 mmol) was added at 0 °C to a 0.5 M ethereal solution of isopropylmagnesium chloride (25 mmol). After 45 min at 0 °C, the mixture was poured onto dry ice and neutralized with a saturated aqueous solution (50 mL) of ammonium chloride. The organic phase was decanted and the aqueous one was extracted with ethyl acetate (2 × 25 mL). The combined organic layers were dried and the solvents were evaporated. The residue was crystallized from ethyl acetate; colorless needles; m.p. 128−130 °C (from chloroform/ethyl acetate); yield: 6.72 g (84%).

Methyl Ester: This was prepared from acid **8** (10 mmol) and diazomethane; colorless needles; m.p. 75−76 °C; yield: 3.11 g (93%). ^{1}H NMR: δ = 8.39 (dd, *J* = 8.5, 1.1 Hz, 1 H), 8.14 (dd, *J* = 7.1, 1.2 Hz, 1 H), 8.07 (s, 1 H), 7.80 (dd, *J* = 8.5, 7.2 Hz, 1 H), 4.05 (s, 3 H) ppm. ^{13}C NMR: δ = 167.4, 148.1 (qr, *J* = 35.2 Hz), 144.8, 136.0, 133.6, 132.0, 129.6, 129.1, 128.6, 121.5, 120.6 (qr, *J* = 275.6 Hz), 52.8 ppm. ^{19}F NMR: δ = −68.3 (s) ppm. MS (c.i.): *m/z* (%) = 336 (94) [M^+ + 1], 335 (41) [M^+], 334 (100) [M^+ + 1], 333 (3) [M^+], 277 (4), 275 (4), 256 (13). $C_{12}H_7BrF_3NO_2$ (334.09): calcd. C 43.14, H 2.11; found C 43.21, H 2.21.

The same acid (**8**) was prepared (93%) by hydrolysis (with formic acid and catalytic amounts of boron trifluoride, 15 h 25 °C) of **methyl 4-bromo-2-trifluoromethyl-8-quinolinecarboxylate** (m.p. 75−76 °C), obtained from methyl **4-methoxy-2-trifluoromethyl-8-quinolinecarboxylate** (m.p. 123−125 °C) in 11% yield by treatment with phosphorus tribromide (2 h, 75 °C). The latter compound was made by esterification of **4-methoxy-2-trifluoromethyl-8-quinolinecarboxylic acid** (m.p. 210−211 °C) with methyl iodide in the presence of potassium carbonate in 83% yield. This compound (74%) was obtained by consecutive treatment with butyllithium, carbon dioxide, and acid of **8-bromo-4-methoxy-2-(trifluoromethyl)quinoline** (m.p. 174−175 °C), which in turn was almost quantitatively formed by the *O*-alkylation of quinoline **1j** with dimethyl

sulfate in the presence of potassium carbonate in acetone. Elemental analyses, ^1H, ^{13}C, and ^{19}F NMR spectra, and mass spectra were in agreement with the assigned structure of all intermediates mentioned in this paragraph.

4-Bromo-2-trifluoromethyl-3-quinolinecarboxylic Acids (5)

Diisopropylamine (3.5 mL, 2.5 g, 25 mmol) and the bromoquinoline **2** (25 mmol) were added consecutively, at −75 °C, to a solution of butyllithium (25 mmol) in tetrahydrofuran (30 mL) and hexanes (15 mL). After 2 h at −75 °C, the mixture was poured onto an excess of freshly crushed dry ice before being worked up as specified for the acids **3**.

A few of these 4-bromo-2-trifluoromethyl-3-quinolinecarboxylic acids (each time 20 mmol) were converted into the methyl esters by addition of methyl iodide (2.0 mL, 4.6 g, 32 mmol), potassium carbonate (4.1 g, 30 mmol), and acetone (0.10 L) to the acid **5** and stirring of the suspension at 25 °C for 6 h. The volatiles were evaporated and the residue was extracted with diethyl ether (5 × 50 mL) after water had been added. The combined organic layers were dried and concentrated. The ester was crystallized from hexanes.

4-Bromo-2-trifluoromethyl-3-quinolinecarboxylic Acid (5a): This compound was prepared from quinoline **2a** (6.9 g, 25 mmol); colorless prisms; m.p. 207−208 °C (dec.); yield: 7.04 g (88%). ^1H NMR*: δ = 8.42 (dd, *J* = 8.4, 0.9 Hz, 1 H), 8.27 (d, *J* = 8.5 Hz, 1 H), 8.08 (ddd, *J* = 9.8, 6.9, 1.4 Hz, 1 H), 8.01 (ddd, *J* = 9.7, 7.0, 1.3 Hz, 1 H) ppm. ^{13}C NMR*: δ = 165.8, 147.0, 143.8 (m), 134.0, 133.5, 132.3, 130.7, 129.0, 128.0, 127.5, 121.7 (qr, *J* = 275.8 Hz) ppm. ^{19}F NMR*: δ = −63.3 (s) ppm. MS (c.i.): *m/z* (%) = 322 (27) [M$^+$ + 1], 321 (100) [M$^+$], 320 (27) [M$^+$ + 1], 319 (95) [M$^+$], 305 (7), 304 (59), 303 (8), 302 (68), 277 (59), 276 (26), 275 (61), 274 (18), 176 (31). $C_{11}H_5BrF_3NO_2$ (320.06): calcd. C 41.28, H 1.57; found C 41.27, H 1.78.

Methyl Ester 11a: Colorless needles; m.p. 90−92 °C; yield: 6.35 g (95%). ^1H NMR: δ = 8.30 (d, *J* = 8.4 Hz, 1 H), 8.21 (d, *J* = 8.5 Hz, 1 H), 7.91 (td, *J* = 7.2, 1.1 Hz, 1 H), 7.81 (td, *J* = 7.2, 1.1 Hz, 1 H), 4.06 (s, 3 H). −^{13}C NMR: δ = 165.4, 146.4, 143.4 (qr, *J* = 35.3 Hz), 134.2, 132.3, 130.7 (2 C), 127.6, 127.1 (2 C), 120.5 (qr, *J* = 276.3 Hz), 53.6. −^{19}F NMR: δ = −65.3 (s) ppm. MS (c.i.): *m/z* (%) = 336 (96) [M$^+$ + 1], 335 (40) [M$^+$], 334 (100) [M$^+$ + 1], 333 (12) [M$^+$], 304 (12), 302 (12), 271 (10), 256 (15). $C_{12}H_7BrF_3NO_2$ (334.09): calcd. C 43.14, H 2.11; found C 43.30, H 2.25.

4-Bromo-6-methyl-2-trifluoromethyl-3-quinolinecarboxylic Acid (5d): This compound was prepared from quinoline **2d** (7.2 g, 25 mmol); colorless platelets; m.p. 224−225 °C (dec.); yield: 6.16 g (74%). ^1H NMR*: δ = 8.12 (s, 1 H), 8.09 (d, *J* = 8.6 Hz, 1 H), 7.86 (dd, *J* = 8.6, 1.8 Hz, 1 H), 2.66 (s, 3 H) ppm. ^{13}C NMR*: δ = 167.0, 146.5, 144.1, 143.5 (qr, *J* = 35.3 Hz), 136.6, 133.8, 131.9, 130.3, 129.5, 127.5, 122.7 (qr, *J* = 275.5 Hz), 23.0 ppm. ^{19}F NMR*: δ = −63.6 (s) ppm. MS: 336 (99) [M$^+$ + 1], 335 (53) [M$^+$], 334 (100) [M$^+$ + 1], 333 (20) [M$^+$], 318 (3), 316 (3), 292 (8), 290 (9), 256 (9). $C_{12}H_7BrF_3NO_2$ (334.09): calcd. C 43.14, H 2.11; found C 43.30, H 2.48.

Methyl Ester 11d: Colorless needles; m.p. 104−106 °C; yield: 6.20 g (89%). ^1H NMR: δ = 8.11 (d, *J* = 8.6 Hz, 1 H), 7.06 (s, 1 H), 7.73 (dd, *J* = 8.6, 1.3 Hz, 1 H), 4.05 (s, 3 H), 2.64 (s, 3 H) ppm. ^{13}C NMR: δ = 165.4, 145.0, 142.5 (qr, *J* = 35.0 Hz), 141.7, 134.6, 133.1, 130.0, 127.8, 127.3, 125.9, 120.6 (qr, *J* = 276.3 Hz), 53.5, 22.1 ppm. ^{19}F NMR: δ = −65.3 (s) ppm. MS (c.i.): *m/z* (%) = 350 (100) [M$^+$ + 1], 349 (71) [M$^+$], 348 (72) [M$^+$ + 1], 347 (32) [M$^+$], 318 (28), 316 (29), 270 (7).

4-Bromo-6-fluoro-2-trifluoromethyl-3-quinolinecarboxylic Acid (5e): This compound was prepared from quinoline **2e** (7.3 g, 25 mmol); colorless prisms; m.p. 181−183 °C; yield: 6.85 g (81%). ^1H NMR*: δ = 8.35 (dd, *J* = 9.3, 5.4 Hz, 1 H), 8.06 (dd, *J* = 9.6, 2.8 Hz, 1 H), 7.93 (ddd, *J* = 10.1, 8.2, 2.8 Hz, 1 H) ppm. ^{13}C NMR*: δ = 167.5, 164.1 (d, *J* = 252.0 Hz), 143.5, 143.4 (qr, *J* = 36.0 Hz), 134.8 (d, *J* = 9.9 Hz), 133.7, 132.9 (d, *J* = 5.8 Hz), 130.4 (d, *J* = 10.8 Hz), 123.5 (d, *J* = 26.1 Hz), 126.9 (qr, *J* = 276.4 Hz), 111.8 (d, *J* = 25.1 Hz) ppm. ^{19}F NMR*: δ = −62.8 (s, 3 F), −105.5 (dd, *J* = 11.0, 6.8 Hz, 1 F) ppm. MS (c.i.): *m/z* (%) = 340 (40) [M$^+$ + 1], 339 (90) [M$^+$], 338 (54) [M$^+$ + 1], 337 (89) [M$^+$], 322 (45), 320 (48), 295 (87), 293 (100), 270 (10), 268 (8), 194 (23). $C_{11}H_4BrF_4NO_2$ (338.05): calcd. C 39.08, H 1.19; found C 39.10, H 1.52.

4-Bromo-6-trifluoromethoxy-2-trifluoromethyl-3-quinolinecarboxylic Acid (5f): This compound was prepared from quinoline **2f** (9.0 g, 25 mmol); colorless prisms; m.p. 170−171 °C; yield: 8.99 g (89%). ^1H NMR*: δ = 8.43 (d, *J* = 9.2 Hz, 1 H), 8.27 (s, 1 H), 8.03 (dd, *J* = 9.2, 2.6 Hz, 1 H) ppm. ^{13}C NMR*: δ = 165.8, 151.0, 145.4, 144.3 (qr, *J* = 35.3 Hz), 134.5, 133.8, 130.3, 129.8, 127.3, 121.4 (q, *J* = 258.1 Hz), 121.6 (qr, *J* = 275.1 Hz), 118.3 ppm. ^{19}F NMR*: δ = −57.3 (s, 3 F), −63.9 (s, 1 F) ppm. MS (c.i.): *m/z* (%) = 406 (49) [M$^+$ + 1], 405 (100) [M$^+$], 404 (60) [M$^+$ + 1], 403 (99) [M$^+$], 361 (44), 360 (26), 359 (50), 358 (18), 297 (18), 260 (9). $C_{12}H_4BrF_6NO_3$ (404.06): calcd. C 35.67, H 1.00; found C 35.54, H 1.22.

Methyl Ester 11f: This was prepared from the bromoacid **5a**; colorless needles; m.p. 77−78 °C; yield: 7.19 g (86%). ^1H NMR: δ = 8.31 (d, *J* = 8.1 Hz, 1 H), 8.14 (s, 1 H), 7.76 (dd, *J* = 8.2, 2.5 Hz, 1 H), 4.07 (s, 3 H) ppm. ^{13}C NMR: δ = 164.8, 150.3, 144.6, 144.0 (qr, *J* = 36.0 Hz), 133.8, 133.4, 128.3, 128.8, 126.3, 120.4 (qr, *J* = 276.4 Hz), 120.3 (q, *J* = 260.4 Hz), 117.3, 53.6 ppm. ^{19}F NMR: δ = −57.3 (s), −65.5 (s, 3 F) ppm. MS (c.i.): *m/z* (%) = 420 (100) [M$^+$ + 1], 419 (68) [M$^+$], 418 (74) [M$^+$ + 1], 417 (25) [M$^+$], 388 (24), 386 (26), 312 (24).

4-Bromo-7-methoxy-2-trifluoromethyl-3-quinolinecarboxylic Acid (5g): This compound was prepared from quinoline **2g** (7.6 g, 25 mmol); colorless needles; m.p. 211 −212 °C (dec.); yield: 7.53 g (86%). ^1H NMR*: δ = 8.26 (m, 1 H), 7.55 (m, 2 H), 4.09 (s, 3 H) ppm. ^{13}C NMR*: δ = 170.5, 168.2, 153.5, 148.3 (qr, *J* = 36.1 Hz), 137.6, 133.5, 131.4, 129.5, 128.0, 126.0 (qr, *J* = 277.1 Hz), 113.0, 60.9 ppm. ^{19}F NMR*: δ = −64.0 (s) ppm. MS (c.i.): *m/z* (%) = 352 (24) [M$^+$ + 1], 351 (87) [M$^+$], 350 (100) [M$^+$ + 1], 349 (9) [M$^+$], 334 (28), 333 (27%), 332 (30), 331 (26), 231 (34). $C_{12}H_7BrF_3NO_3$ (350.09): calcd. C 41.17, H 2.02; found C 41.16, H 2.09.

Methyl Ester 11g: This was prepared from the bromoacid **5g**; colorless prisms; m.p. 138−139 °C (from hexanes); yield: 6.34 g (87%). ^1H NMR: δ = 8.17 (d, *J* = 9.1 Hz, 1 H), 7.50 (d, *J* = 2.4 Hz, 1 H), 7.13 (dd, *J* = 9.1, 2.4 Hz, 1 H), 4.03 (s, 3 H), 3.98 (s, 3 H) ppm. ^{13}C NMR: δ = 165.5, 162.9, 148.5 (qr, *J* = 34.4 Hz), 133.5, 128.3, 125.1, 124.3, 123.0, 120.4 (qr, *J* = 277.2 Hz), 107.8, 56.0, 53.5 ppm. ^{19}F NMR: δ = −65.4 (s) ppm. MS (c.i.): *m/z* (%) = 366 (43) [M$^+$ + 1], 365 (98) [M$^+$], 364 (84) [M$^+$ + 1], 363 (100) [M$^+$],334 (89), 332 (90), 306 (17), 304 (18).

4-Bromo-7-fluoro-2-trifluoromethyl-8-quinolinecarboxylic Acid (10a): This compound was prepared from quinoline **2h** (7.3 g, 25 mmol); colorless prisms; m.p. 160−161 °C; yield: 6.76 g (80%). ^1H NMR*: δ = 8.46 (dd, *J* = 9.4, 5.7 Hz, 1 H), 8.32 (s, 1 H), 7.87 (t, *J* = 9.1 Hz, 1 H) ppm. ^{13}C NMR*: δ = 164.5, 162.5 (d, *J* = 258.6 Hz), 149.8 (qr, *J* = 36.1 Hz), 146.8 (d, *J* = 8.8 Hz), 138.2, 132.3 (d, *J* = 11.2 Hz), 127.4, 123.0, 122.7 (d, *J* = 26.5 Hz), 122.4 (qr, *J* = 274.7 Hz), 121.5 (d, *J* = 16.9 Hz) ppm. ^{19}F NMR*: δ =

−67.0 (s, 3 F), −106.8 (m, 1 F) ppm. MS (c.i.): *m/z* (%) = 340 (96) [M$^+$ + 1], 339 (23) [M$^+$], 338 (100) [M$^+$ + 1], 337 (13) [M$^+$], 296 (9), 295 (19), 294 (10), 293 (21), 194 (3), 117 (4). $C_{11}H_4BrF_4NO_2$ (338.05): calcd. C 39.08, H 1.19; found C 39.13, H 1.10.

4-Bromo-8-fluoro-2-trifluoromethyl-3-quinolinecarboxylic Acid (5i): This compound was prepared from quinoline **2i** (7.3 g, 25 mmol); colorless prisms; m.p. 182−183 °C; yield: 7.27 g (86%). ^{1}H NMR*: δ = 8.22 (d, *J* = 8.6 Hz, 1 H), 8.01 (ddd, *J* = 8.3, 8.2, 5.1 Hz, 1 H), 7.85 (ddd, *J* = 10.0, 7.9, 1.1 Hz) ppm. ^{13}C NMR*: δ = 166.5, 159.6 (d, *J* = 260.2 Hz), 144.5 (qr, *J* = 36.1 Hz), 138.2 (d, *J* = 13.6 Hz), 136.4, 134.9 (d, *J* = 3.2 Hz), 133.3 (d, *J* = 8.0 Hz), 131.1 (d, *J* = 5.6 Hz), 124.9, 122.4 (qr, *J* = 275.5 Hz), 118.1 (d, *J* = 18.5 Hz) ppm. ^{19}F NMR*: δ = −64.0 (s, 3 F), −121.7 (m, 1 F) ppm. MS (c.i.): *m/z* (%) = 340 (90) [M$^+$ + 1], 339 (75) [M$^+$], 338 (100) [M$^+$ + 1], 337 (50) [M$^+$], 296 (3), 295 (7), 294 (7), 293 (7), 194 (2). $C_{11}H_4BrF_4NO_2$ (338.05): calcd. C 39.08, H 1.19, N 4.14; found C 38.97, H 1.23, N 4.19.

Methyl Ester 11i: Colorless needles; m.p. 128−130 °C; yield: 6.45 g (92%). ^{1}H NMR: δ = 8.10 (dt, *J* = 8.8, 1.1 Hz, 1 H), 7.78 (td, *J* = 8.1, 4.8 Hz, 1 H), 7.61 (ddd, *J* = 9.2, 7.8, 1.2 Hz, 1 H), 4.06 (s, 3 H) ppm. ^{13}C NMR: δ = 165.0, 157.9 (d, *J* = 262.6 Hz), 143.5 (qr, *J* = 36.0 Hz), 136.1 (d, *J* = 12.5 Hz), 134.1 (d, *J* = 4.0 Hz), 131.0 (d, *J* = 8.0 Hz), 129.3, 128.4, 123.0 (d, *J* = 4.5 Hz), 120.3 (qr, *J* = 276.3 Hz), 116.5 (d, *J* = 18.5 Hz), 53.3 ppm. ^{19}F NMR: δ = −65.1 (s, 3 F), −121.0 (m, 1 F) ppm. MS (c.i.): *m/z* (%) = 354 (100) [M$^+$ + 1], 353 (42) [M$^+$], 352 (77) [M$^+$ + 1], 351 (15) [M$^+$], 322 (15), 320 (13), 289 (2).

4,8-Dibromo-2-trifluoromethyl-3-quinolinecarboxylic Acid (5j): This compound was prepared from quinoline **2j** (8.9 g, 25 mmol); colorless needles; m.p. 192−194 °C; yield: 6.18 g (62%). ^{1}H NMR: δ = 8.36 (dd, *J* = 8.4, 1.0 Hz, 1 H), 8.26 (dd, *J* = 7.5, 1.1 Hz, 1 H), 7.69 (dd, *J* = 8.3, 7.4 Hz, 1 H) ppm. ^{13}C NMR: δ = 167.5, 143.9 (qr, *J* = 36.9 Hz), 143.6, 136.1, 134.3, 131.0, 129.3, 128.0, 127.3, 126.3, 120.2 (qr, *J* = 277.1 Hz) ppm. ^{19}F NMR: δ = −64.9 (s) ppm. MS (c.i.): *m/z* (%) = 402 (48) [M$^+$ + 1], 401 (50) [M$^+$], 400 (100) [M$^+$ + 1], 399 (75) [M$^+$], 398 (59) [M$^+$ + 1], 397 (34) [M$^+$], 320 (27), 242 (3). $C_{11}H_4Br_2F_3NO_2$ (398.96): calcd. C 33.12, H 1.01; found C 33.00, H 1.22.

Methyl Ester 11j: colorless needles; m.p. 101−103 °C; yield: 7.76 g (94%). ^{1}H NMR: δ = 8.29 (dd, *J* = 8.5, 1.1 Hz, 1 H), 8.22 (dd, *J* = 7.5, 1.1 Hz, 1 H), 7.66 (dd, *J* = 8.3, 7.8 Hz, 1 H), 4.06 (s, 3 H) ppm. ^{19}F NMR: δ = −65.4 (s) ppm. MS (c.i.): *m/z* (%) = 415 (54) [M$^+$ + 1], 414 (64) [M$^+$], 413 (100) [M$^+$ + 1], 412 (72) [M$^+$], 382 (21), 354 (15), 319 (5), 317 (5). $C_{12}H_6Br_2F_3NO_2$ (412.98): calcd. C 34.90, H 1.46, N 3.39; found C 35.22, H 1.46, N 3.48.

4-Bromo-8-iodo-2-trifluoromethyl-3-quinolinecarboxylic Acid (5k): This compound was prepared from quinoline **2k** (10.0 g, 25 mmol); colorless needles; m.p. 207−208 °C (dec.); yield: 8.70 g (78%). ^{1}H NMR*: δ = 8.69 (dd, *J* = 7.4, 1.1 Hz, 1 H), 8.45 (dd, *J* = 8.5, 1.1 Hz, 1 H), 7.74 (dd, *J* = 8.4, 7.5 Hz, 1 H) ppm. ^{13}C NMR*: δ = 166.5, 146.9, 145.0, 144.8 (qr, *J* = 36.1 Hz), 135.5, 133.9, 130.8, 130.0, 129.8, 122.3 (qr, *J* = 275.5 Hz), 105.3 ppm. ^{19}F NMR*: δ = −63.8 (s) ppm. MS (c.i.): *m/z* (%) = 447 (90) [M$^+$ + 1], 446 (100) [M$^+$], 445 (99) [M$^+$ + 1], 444 (55) [M$^+$], 402 (22), 400 (23), 322 (6), 320 (7), 194 (10). $C_{11}H_4BrF_3INO_2$ (445.96): calcd. C 29.63, H 0.90, N 3.14; found C 29.72, H 0.97, N 3.20.

2-Trifluoromethyl-3-quinolinecarboxylic Acids (6)

By Reduction of the Ester with Tributyltin Hydride: A solution of the methyl 4-bromo-2-(trifluoromethyl)quinoline-3-carboxylate (15 mmol), tributyltin hydride (8.1 mL, 8.7 g, 30 mmol), and azoisobutyronitrile (0.24 g, 1.5 mmol) in tetrahydrofuran (30 mL) was kept under nitrogen at 75 °C for 20 h. The solvent was evaporated and the residue was recrystallized from hexanes.

Methyl 2-Trifluoromethyl-3-quinolinecarboxylate (12a): This compound was prepared from bromo compound **11a**; colorless platelets; m.p. 51−52 °C; yield: 3.45 g (90%). ^{1}H NMR: δ = 8.70 (s, 1 H), 8.26 (d, *J* = 8.6 Hz, 1 H), 7.98 (d, *J* = 8.2 Hz, 1 H), 7.92 (td, *J* = 7.7, 1.4 Hz, 1 H), 7.75 (td, *J* = 7.6, 1.0 Hz, 1 H), 4.01 (s, 3 H) ppm. ^{13}C NMR: δ = 166.0, 147.0, 144.9 (qr, *J* = 35.3 Hz), 140.4, 132.6, 130.0, 129.6, 128.3, 127.5, 123.6, 121.2 (qr, *J* = 274.7 Hz), 53.3 ppm. ^{19}F NMR: δ = −64.5 (s) ppm. MS (c.i.): *m/z* (%) = 256 (100) [M$^+$ + 1], 255 (43) [M$^+$], 236 (3), 224 (33), 196 (3). $C_{12}H_8F_3NO_2$ (255.19): calcd. C 56.48, H 3.16; found C 56.56, H 3.25.

Methyl 6-Methyl-2-trifluoromethyl-3-quinolinecarboxylate (12d): This compound was prepared from bromo compound **11f**; colorless platelets; m.p. 101−103 °C; yield: 3.11 g (77%). ^{1}H NMR: δ = 8.60 (s, 1 H), 8.14 (d, *J* = 8.6 Hz, 1 H), 7.74 (dd, *J* = 8.6, 1.7 Hz, 1 H), 7.71 (s, 1 H), 4.01 (s, 3 H), 2.60 (s, 3 H) ppm. ^{13}C NMR: δ = 166.0, 145.6, 143.8 (qr, *J* = 35.9 Hz), 140.2, 139.3, 135.0, 129.7, 127.5, 126.9, 123.5, 121.5 (qr, *J* = 277.1 Hz), 53.1, 21.8 ppm. ^{19}F NMR: δ = −64.5 (s) ppm. MS (c.i.): *m/z* (%) = 270 (100) [M$^+$ + 1], 269 (26) [M$^+$], 238 (20), 217 (4).

Methyl 6-Trifluoromethoxy-2-trifluoromethyl-3-quinolinecarboxylate (12f): This compound was prepared from bromo compound **11d**; colorless prisms; m.p. 103−105 °C; yield: 4.17 g (82%). ^{1}H NMR: δ = 8.70 (s, 1 H), 8.36 (d, *J* = 9.0 Hz, 1 H), 7.79 (s, 1 H), 7.75 (d, *J* = 9.1 Hz, 1 H), 4.03 (s, 3 H) ppm. ^{13}C NMR: δ = 165.4, 159.2, 145.3 (qr, *J* = 36.0 Hz), 145.0, 140.0, 132.5, 127.9, 126.3, 124.7, 120.4 (qr, *J* = 276.3 Hz), 120.9 (qr, *J* = 259.4 Hz), 117.4, 53.3 ppm. ^{19}F NMR: δ = −58.3 (s), −64.8 (s) ppm. MS (c.i.): *m/z* (%) = 340 (100) [M$^+$ + 1], 339 (20) [M$^+$], 308 (22), 274 (10).

Methyl 7-Methoxy-2-trifluoromethyl-3-quinolinecarboxylate (12g): This compound was prepared from the bromo compound **11g**; colorless needles; m.p. 128−129 °C (from hexanes); yield: 3.46 g (81%). ^{1}H NMR: δ = 8.63 (s, 1 H), 7.83 (d, *J* = 9.1 Hz, 1 H), 7.86 (d, *J* = 2.4 Hz, 1 H), 7.36 (dd, *J* = 9.1, 2.4 Hz, 1 H), 3.98 (s, 3 H), 4.01 (s, 3 H) ppm. ^{13}C NMR: δ = 165.8, 163.1, 149.0, 145.0 (qr, *J* = 35.2 Hz), 139.8, 129.1, 123.3, 122.5, 121.1 (qr, *J* = 275.6 Hz), 121.0, 107.5, 55.9, 52.9 ppm. ^{19}F NMR: δ = −64.6 (s) ppm. MS (c.i.): *m/z* (%) = 286 (40) [M$^+$ + 1], 285 (100) [M$^+$], 254 (95), 226 (82), 183 (8), 116 (7).

Methyl 8-Fluoro-2-trifluoromethyl-3-quinolinecarboxylate (12i): This compound was prepared from bromo compound **11i**; colorless needles; m.p. 96−98 °C; yield: 3.24 g (79%). ^{1}H NMR: δ = 8.75 (s, 1 H), 7.78 (d, *J* = 8.0 Hz, 1 H), 7.71 (td, *J* = 7.8, 4.6 Hz, 1 H), 7.60 (dd, *J* = 9.2, 8.0 Hz, 1 H), 4.02 (s, 3 H) ppm. ^{13}C NMR: δ = 165.3, 157.8 (d, *J* = 261.8 Hz), 144.6 (qr, *J* = 35.4 Hz), 139.8, 137.0 (d, *J* = 12.0 Hz), 130.0 (d, *J* = 9.6 Hz), 128.8, 124.5, 123.8 (d, *J* = 4.6 Hz), 120.9 (qr, *J* = 275.5 Hz), 116.6 (d, *J* = 18.5 Hz), 53.3 ppm. ^{19}F NMR*: δ = −64.6 (s, 3 F), −122.4 (m, 1 F) ppm. MS (c.i.): *m/z* (%) = 274 (100) [M$^+$ + 1], 273 (30) [M$^+$], 242 (29), 220 (14).

By Consecutive Treatment of the Lithium Carboxylate with Butyllithium and Methanol: Butyllithium (30 mmol) in hexanes (20 mL) was added to a precooled solution of bromoacid **5** (15 mmol), and the resulting suspension was stirred for 6 h at −75 °C before being treated with methanol (5 mL) and water (50 mL). The products were identical in every respect with the carboxylic acids obtained by saponification of the methyl esters described in the preceding

paragraphs (sodium hydroxide in aqueous methanol, 50 °C for 6 h; overall yields are given in Table 6).

2-Trifluoromethyl-3-quinolinecarboxylic Acid (6a): This compound was prepared from 4-bromo-3-quinolinecarboxylic acid **5a** (4.8 g, 15 mmol); colorless prisms; m.p. 207−209 °C (repr.); yield: 2.42 g (67%). ^{1}H NMR*: δ = 9.01 (s, 1 H), 8.25 (m, 2 H), 8.05 (t, *J* = 7.8 Hz, 1 H), 7.89 (t, *J* = 7.6 Hz, 1 H) ppm. ^{13}C NMR*: δ = 167.4, 148.4, 145.9 (qr, *J* = 35.0 Hz), 142.2, 134.5, 131.5 (2 C), 130.5, 128.5, 126.0, 123.2 (qr, *J* = 274.9 Hz) ppm. ^{19}F NMR*: δ = −63.5 (s) ppm. MS (c.i.): *m*/*z* (%) = 242 (35) [M$^+$ + 1], 241 (100) [M$^+$], 224 (46), 197 (48), 101 (33). $C_{11}H_6F_3NO_2$ (241.17): calcd. C 54.78, H 2.51; found C 54.78, H 2.99.

6-Methyl-2-trifluoromethyl-3-quinolinecarboxylic Acid (6d): This compound was prepared from 4-bromo-3-quinolinecarboxylic acid **5d** (5.0 g, 15 mmol), colorless platelets; m.p. 211−213 °C (dec.); yield: 2.60 g (68%). ^{1}H NMR*: δ = 8.86 (s, 1 H), 8.10 (d, *J* = 8.7 Hz, 1 H), 7.98 (s, 1 H), 7.86 (dd, *J* = 8.7, 1.9 Hz, 1 H), 2.63 (s, 3 H) ppm. ^{13}C NMR*: δ = 167.5, 147.1 (qr, *J* = 34.6 Hz), 142.1, 141.3, 136.5 (2 C), 131.0, 129.5, 128.9, 126.0, 123.1 (qr, *J* = 274.8 Hz), 22.5 ppm. ^{19}F NMR*: δ = −63.4 (s) ppm. MS (c.i.): *m*/*z* (%) = 256 (100) [M$^+$ + 1], 255 (22) [M$^+$], 238 (6), 211 (8), 186 (17). $C_{12}H_8F_3NO_2$ (255.19): calcd. C 56.48, H 3.16; found C 56.22, H 3.19.

6-Trifluoromethoxy-2-trifluoromethyl-3-quinolinecarboxylic Acid (6f): This compound was prepared from 4-bromo-3-quinolinecarboxylic acid **5f** (6.0 g, 15 mmol); colorless platelets; m.p. 191−193 °C; yield: 2.78 g (57%). ^{1}H NMR*: δ = 9.12 (s, 1 H), 8.38 (d, *J* = 9.2 Hz, 1 H), 8.26 (s, 1 H), 7.98 (dd, *J* = 9.5, 2.5 Hz, 1 H) ppm. ^{13}C NMR*: δ = 167.0, 150.4, 146.8, 146.1 (m), 142.3, 134.1, 130.0, 128.1, 126.8, 122.9 (qr, *J* = 274.7 Hz), 121.2 (qr, *J* = 257.0 Hz), 120.3 ppm. ^{19}F NMR*: δ = −57.4 (s), −63.3 (s) ppm. MS (c.i.): *m*/*z* (%) = 326 (100) [M$^+$ + 1], 325 (23) [M$^+$], 308 (23), 281 (36). $C_{12}H_5F_6NO_3$ (325.16): calcd. C 44.33, H 1.55, N 4.31; found C 44.37, H 1.61, N 4.47.

7-Methoxy-2-trifluoromethyl-3-quinolinecarboxylic Acid (6g): This compound was prepared from the bromoquinolinecarboxylic acid **5g** (5.3 g, 15 mmol); colorless prisms; m.p. 211−212 °C (from methanol); yield 3.42 g (84%). ^{1}H NMR: δ = 8.90 (s, 1 H), 8.12 (d, *J* = 9.0 Hz, 1 H), 7.55 (d, *J* = 2.6 Hz, 1 H), 7.46 (dd, *J* = 9.0, 2.6 Hz, 1 H), 4.08 (s, 3 H) ppm. ^{13}C NMR: δ = 167.4, 165.0, 150.8, 146.5 (qr, *J* = 33.7 Hz), 141.9 (2 C), 131.5, 124.8, 123.5, 123.3 (qr, *J* = 275.4 Hz), 109.1, 57.3 ppm. ^{19}F NMR: δ = −63.1 (s) ppm. MS (c.i.): *m*/*z* (%) = 272 (52) [M$^+$ + 1], 271 (100) [M$^+$], 254 (28), 226 (9). $C_{12}H_8F_3NO_3$ (271.19): calcd. C 53.15, H 2.97, N 5.16; found C 53.46, H 2.97, N 5.30.

8-Fluoro-2-trifluoromethyl-3-quinolinecarboxylic Acid (6i): This compound was prepared from 4-bromo-3-quinolinecarboxylic acid **5i** (5.1 g, 15 mmol); colorless prisms; m.p. 233−235 °C (dec.); yield: 2.25 g (58%). ^{1}H NMR*: δ = 9.07 (s, 1 H), 8.10 (d, *J* = 8.2 Hz), 7.89 (ddd, *J* = 8.2, 7.9, 4.9 Hz, 1 H), 7.79 (ddd, *J* = 10.6, 7.8, 1.2 Hz) ppm. ^{13}C NMR*: δ = 167.2, 159.5 (d, *J* = 259.4 Hz), 146.1 (qr, *J* = 36.9 Hz), 142.0 (d, *J* = 16.9 Hz), 131.9 (d, *J* = 7.2 Hz), 131.0, 127.7, 126.3 (2 C), 123.4 (qr, *J* = 275.5 Hz), 118.3 (d, *J* = 18.5 Hz) ppm. ^{19}F NMR*: δ = −63.4 (s, 3 F), −123.5 (m, 1 F) ppm. MS (c.i.): *m*/*z* (%) = 260 (100) [M$^+$ + 1], 259 (18) [M$^+$], 242 (18), 206 (17). $C_{11}H_5F_4NO_2$ (259.16): calcd. C 50.98, H 1.94, N 5.40; found C 50.88, H 2.10, N 5.44.

7-Fluoro-2-trifluoromethyl-8-quinolinecarboxylic Acid: The bromo acid **10a** (5.1 g, 15 mmol) was treated at −100 °C with butyllithium (30 mmol) in diethyl ether (40 mL) and hexanes (20 mL) for 15 min; colorless platelets; m.p. 204−206 °C (reprod.; from methanol); yield: 2.25 g (58%). ^{1}H NMR*: δ = 8.90 (d, *J* = 8.5 Hz, 1 H), 8.42 (dd, *J* = 9.2, 5.7 Hz, 1 H), 8.07 (d, *J* = 8.5 Hz, 1 H), 7.80 (t, *J* = 9.5 Hz, 1 H) ppm. ^{13}C NMR*: δ = 165.5, 162.0 (d, *J* = 256.4 Hz), 150.0 (qr, *J* = 35.0 Hz), 146.3 (d, *J* = 8.5 Hz), 141.5, 133.6 (d, *J* = 11.0 Hz), 132.0, 127.8, 123.1 (qr, *J* = 275.6 Hz), 121.9 (d, *J* = 26.4 Hz), 118.6 ppm. ^{19}F NMR*: δ = −67.0 (s, 3 F), −107.8 (m, 1 F) ppm. MS (c.i.): *m*/*z* (%) = 260 (100) [M$^+$ + 1], 259 (4), 242 (13), 215 (19). $C_{11}H_5F_4NO_2$ (259.16): calcd. C 50.98, H 1.94, N 5.40; found C 50.96, H 2.08, N 5.42.

4-Formyl-2-trifluoromethyl-3-quinolinecarboxylic Acids 7

The bromoquinolinecarboxylic acid **5** (10 mmol) was dissolved in a 1.0 M methanolic solution (10 mL) of tetrabutylammonium hydroxide (10 mmol). The solvent was replaced by toluene (0.10 L) and the mixture was heated at reflux in a Dean−Stark trap until all water had been removed. The toluene was evaporated and the residue was taken up in tetrahydrofuran (50 mL), to which butyllithium (10 mmol) in hexane (10 mL) was added at −75 °C. After 15 min, *N*,*N*-dimethylformamide (0.77 mL, 0.73 g, 10 mmol) was added. After a further 1 h at −75 °C, the mixture was poured into water (50 mL), washed with diethyl ether (2 × 15 mL), acidified to pH 1 with concentrated hydrochloric acid, and extracted with ethyl acetate (3 × 25 mL). The combined organic layers were dried, and the solvents were evaporated. The residue was crystallized from a mixture of chloroform and methanol.

4-Formyl-2-trifluoromethyl-3-quinolinecarboxylic Acid (7a): This compound was prepared from 4-bromo-2-trifluoromethyl-3-quinolinecarboxylic acid (**5a**; 5.6 g, 10 mmol); colorless platelets; m.p. 258−260 °C (dec.); yield: 1.51 g (56%). ^{1}H NMR*: δ = 8.47 (d, *J* = 8.3 Hz, 1 H), 8.40 (d, *J* = 8.5 Hz, 1 H), 8.19 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1 H), 8.04 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1 H), 7.63 (br. s, 1 H), 7.30 (s, 1 H) ppm. ^{13}C NMR*: δ = 164.5, 159.4, 148.9, 143.2 (m), 135.0, 131.6 (2 C), 126.0, 124.3, 121.5 (qr, *J* = 274.4 Hz), 118.2, 97.4 ppm. ^{19}F NMR*: δ = −67.9 (s) ppm. MS (c.i.): *m*/*z* (%) = 287 (100) [M$^+$ + NH_4^+], 270 (91) [M$^+$ + 1], 269 (11) [M$^+$], 192 (24), 134 (45). $C_{12}H_6F_3NO_3$ (269.18): calcd. C 53.55, H 2.25, N 5.20; found C 53.92, H 2.36, N 5.28.

4-Formyl-6-trifluoromethoxy-2-trifluoromethyl-3-quinolinecarboxylic Acid (7f): This compound was prepared from 4-bromo-6-trifluoromethoxy-2-trifluoromethyl-3-quinolinecarboxylic acid (**5f**; 4.0 g, 10 mmol); colorless prisms, m.p. 175−177 °C (dec.); yield: 2.93 g (83%). ^{1}H NMR*: δ = 8.56 (d, *J* = 9.3 Hz, 1 H), 8.34 (d, *J* = 1.5 Hz, 1 H), 8.14 (dd, *J* = 9.2, 2.6 Hz, 1 H), 7.79 (br. s, 1 H), 7.36 (s, 1 H) ppm. ^{13}C NMR*: δ = 164.3, 159.8, 150.4, 147.1, 144.0 (qr, *J* = 37.2 Hz), 134.5, 133.5 128.5, 127.3, 123.7 (qr, *J* = 247.4 Hz), 121.5 (qr, *J* = 274.7 Hz), 116.0, 97.5 ppm. ^{19}F NMR*: δ = −57.6 (s, 3 F), −65.6 (s, 3 F) ppm. MS (c.i.): *m*/*z* (%) = 371 (100) [M$^+$ + NH_4], 354 (48) [M$^+$ + 1], 353 (3) [M$^+$], 308 (11), 116 (2), 76 (3). $C_{13}H_5F_6NO_4$ (353.17): calcd. C 44.21, H 1.43, N 3.97; found C 44.43, H 1.56, N 4.15.

4-Formyl-7-methoxy-2-trifluoromethyl-3-quinolinecarboxylic Acid (7g): This compound was prepared from 4-bromo-7-methoxy-2-trifluoromethyl-3-quinolinecarboxylic acid (**5g**; 3.5 g, 10 mmol); colorless platelets; m.p. 232−235 °C (dec.); yield: 1.88 g (63%). ^{1}H NMR*: δ = 8.34 (d, *J* = 9.20 Hz, 1 H), 7.55 (s, 1 H), 7.74 (d, *J* = 2.6 Hz, 1 H), 7.63 (dd, *J* = 9.2, 2.6 Hz, 1 H), 7.21 (s, 1 H), 4.62 (s, 3 H) ppm. ^{13}C NMR*: δ = 166.3, 159.8, 152.4, 145.1 (qr, *J* = 35.1 Hz), 128.0, 127.5, 125.5, 122.6 (qr, *J* = 274.8 Hz), 120.0, 116.8, 110.8, 98.0, 57.6 ppm. ^{19}F NMR*: δ = −65.3 (s,) ppm. MS (c.i.): *m*/*z* (%) = 300 (100) [M$^+$ + 1], 299 (34) [M$^+$], 284 (17), 254 (6).

$C_{13}H_8F_3NO_4$ (299.20): calcd. C 52.19, H 2.69, N 4.68; found C 52.46, H 2.81, N 4.69.

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