An Improved Access to 4-Trifluoromethyl-2(1*H*)-quinolinones: The "Watering Protocol"

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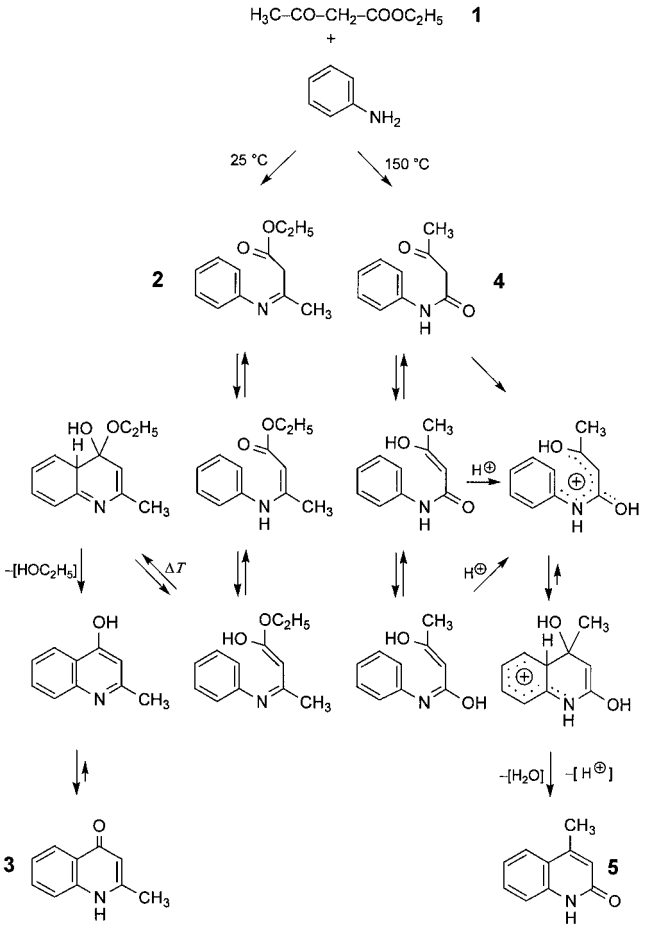
Condensation of anilines with ethyl 4,4,4-trifluoroacetoacetate (**7**) to afford the corresponding 4,4,4-trifluoro-3-oxobutaneanilides (**10**), precursors to 4-(trifluoromethyl)-2-quinolinones (**11**), can be favored and the competing condensation to produce the ethyl 4,4,4-trifluoro-3-(phenylimino)butanoate, the precursor to 2-(trifluoromethyl)-4-quinolinones, avoided if water is occasionally added to the reaction mixture while ethanol is continuously removed by distillation. The anilides **10** also form selectively when 4,4,4-trifluoroacetoacetyl chloride (**6**) is allowed to react with anilines. The cyclization of the anilides has to be accomplished under carefully controlled conditions. The resulting 4-(trifluoromethyl)-2-quinolinones (**11**) can be converted into 4-(trifluoromethyl)quinolines (**13**), 4-(trifluoromethyl)-2-quinolinecarboxylic acids (**14**), and 2-bromo-4-(trifluoromethyl)quinolines (**12**), the last of which may in turn be converted into 2-bromo-4-(trifluoromethyl)-3-quinolinecarboxylic acids (**15**) and eventually 4-trifluoromethyl-3-quinolinecarboxylic acids (**16**).

Introduction

Following literature precedents, we have recently prepared a variety of 2-trifluoromethyl-4(1*H*)-quinolinones[1] and 4-trifluoromethyl-2(1*H*)-quinolinones.[2] In the latter series, however, yields were poor at best (21−36%). Whenever the aniline carried an electron-withdrawing substituent, even if only a moderately powerful one, the isomeric 4-quinolinone was obtained rather than the expected 2-quinolinone. To gain insight, we embarked on a systematic study.

The 2-/4-quinolinone dichotomy was first recognized by L. Knorr.[3−5] Leaving a mixture of aniline and ethyl acetoacetate (**1**) at ambient temperature for a few days was found to give the anil **2** (or rather the tautomeric ethyl β-anilinocrotonate).[3−5] In contrast, the acetoacetanilide **4** results when the two components are briefly heated to about 150 °C.[4,6] When treated with concentrated sulfuric acid at 85 °C (or 100 °C), the anilide **4** undergoes smooth cyclization to the 4-methyl-2(1*H*)-quinolinone (**5**), whereas the cyclization to the isomeric 2-methyl-4(1*H*)-quinolinone (**3**) is generally brought about by heating the crotonate to approximately 250 °C.[7,8] These reaction conditions suggest an intramolecular Friedel−Crafts-type process operating in the former case and an electrocyclic ring-closure in the latter. Crotonates and anilides can be mutually interconverted by heating them in the presence of water or in ethanol (the latter in the presence of a drying agent), respectively.[5,8]



Replacement of ethyl acetoacetate by ethyl 4,4,4-trifluoroacetoacetate (**7**), a bulk material made from 4,4,4-trifluo-

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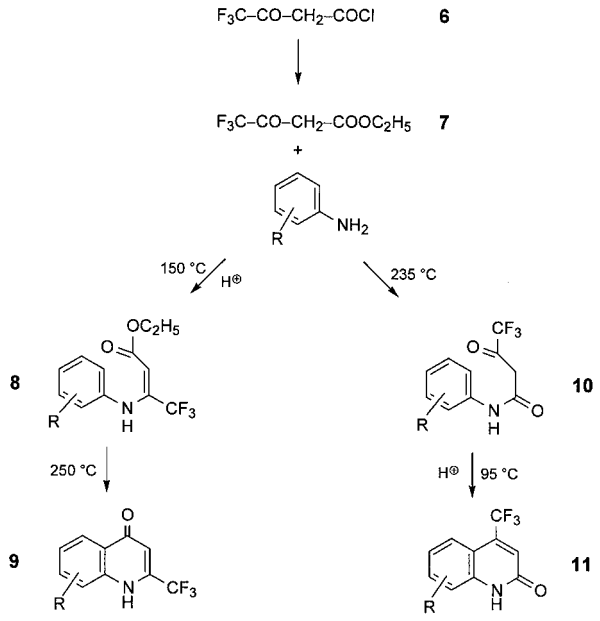
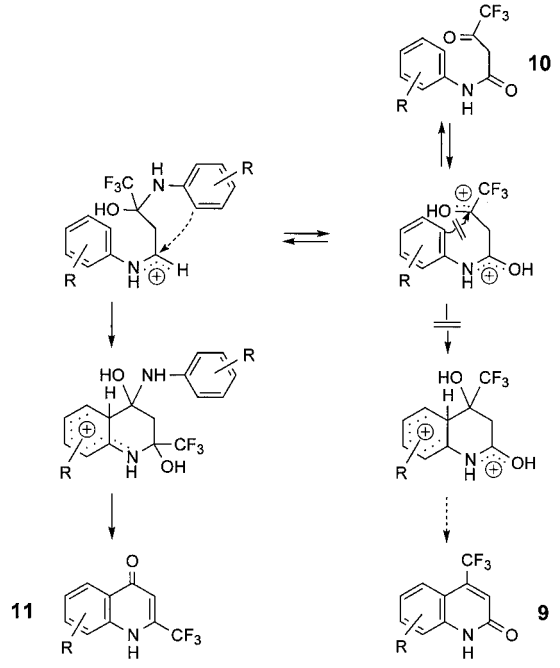
roacetoacetyl chloride[1] (**6**), does not alter the fundamentals but requires adjustment of the experimental conditions. To prepare the crotonates **8**, the reactants have to be heated in the presence of polyphosphoric acid for 90 min at 150 °C.[9,10] The anilides **10** have been obtained, although generally in poor yields, by heating the aniline and ethyl 4,4,4-trifluoroacetoacetate (**7**) either to 235 °C for a few minutes[11] or to 155 °C for a prolonged period of time (typically 18 h).[12] The cyclization of the crotonates **8** can be brought about thermally, at temperatures ranging from 170 °C to 250 °C,[9,10] and that of the anilides **10** by heating with concentrated sulfuric acid at 90−95 °C.[11,12]



Results

A modified procedure[13] employs methanesulfonic acid in the presence of phosphorus pentoxide for the cyclization of 4,4,4-trifluoroacetoacetanilides (4,4,4-trifluoro-3-oxobutananilides, **10**). We applied this method to the parent compound 4,4,4-trifluoroacetoacetanilide and the anilides derived from 2- and 3-toluidine, 2-fluoroaniline, and 2- and 4-anisidine, but invariably isolated the 2-(trifluoromethyl)-4(1*H*)quinolinones (**9**; 41−51%) rather than the expected 4-(trifluoromethyl)-2(1*H*)quinolinones (**11**). This is reminiscent of the surprising outcome of the acid-catalyzed cyclization of 4-anilino-1,1,1-trifluoro-3-buten-2-ones to 2- rather than 4-(trifluoromethyl)quinolines.[14] The suggested mechanism[15] may also provide a clue as to how to explain the present findings. Under strongly acidic conditions, protonation of both carbonyl groups, the one residing in the ketone part and the other one belonging to the amide function, may occur simultaneously. Free aniline, always present in minute amounts due to unavoidable hydrolysis, might come by and add to the activated carbenium-oxonium ion. Alternatively, aniline could add directly to the oxo group, which is already sufficiently activated by the neighboring fluorine atoms. The protonated carboxamide function, being part of the newly formed hemiaminal, would now dock at the *ortho*-position of the aromatic ring, whereas the other one would remain electronically passive because the protonation of the carboxamide immobilizes the lone pair. Dehydration and elimination of the initial aniline would terminate the reaction sequence.



As demonstrated in a recent series of publications,[16−18] the preparation of the anilides and their cyclization can be contracted into a single operational step merely by heating the condensation components aniline and ethyl 4,4,4-trifluoroacetoacetate for several hours under reflux in ethanol and in the presence of zinc chloride. From our own experience, however, this method suffers from an extremely narrow scope of applicability. It appears to work well only with markedly electron-rich anilines such as 3-anisidine[19] and 1,3-diaminobenzene[20] and its congeners. Even 3-hydroxyaniline provides only small amounts of 7-hydroxy-4-trifluoromethyl-2(1*H*)-quinolinone, along with a further byproduct and the main component, 7-amino-4-trifluoromethyl-2*H*-1-benzopyran-2-one, resulting from a Pechmann reaction.[19] No quinolinone at all was formed when aniline, 4-toluidine, 2- or 3-fluoroaniline, and 4-trifluoromethoxyaniline were used as the starting materials.

The lesson thus learned was that none of the literature procedures offers an expedient and universal entry to the family of 4-trifluoromethyl-2-quinolinones. As the cyclization proceeds reliably and with satisfactory yields when brought about with concentrated sulfuric acid, the problem can be narrowed down to the preparation of the required 4,4,4-trifluoroacetoacetanilide intermediates **10**. A possible solution is to be found in the patent literature.[21] The acyl carbonyl group of 4,4,4-trifluoroacetoacetyl chloride (**6**) be-

ing far more electrophilic than any ester carbonyl group, nucleophiles − including anilines − directly attack the terminal functionality. In this way, we have been able to obtain six different 4,4,4-trifluoroacetoanilides in yields ranging from 71−81% (see Table 1).

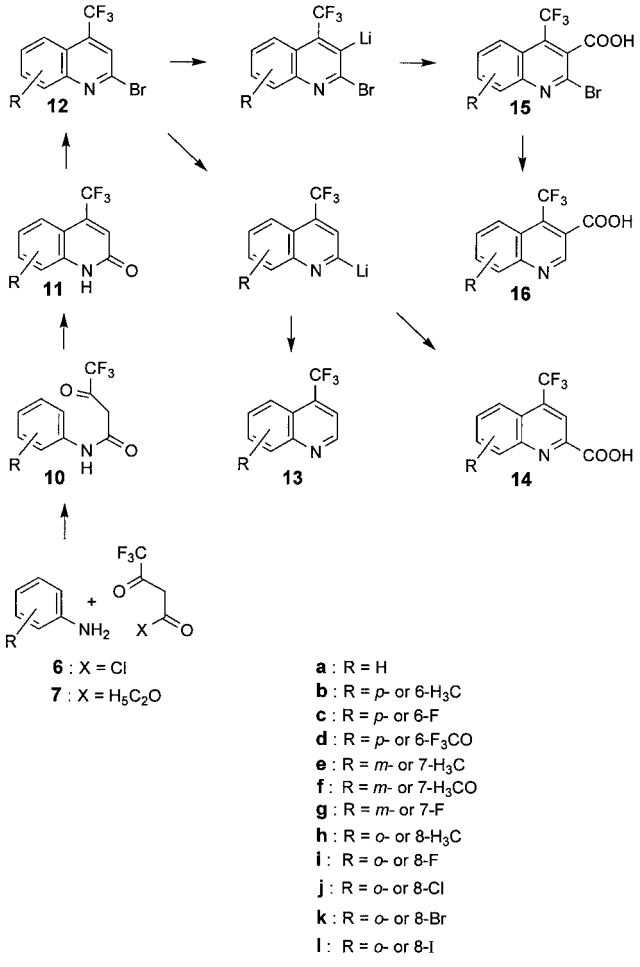
Table 1. 4,4,4-Trifluoroacetoacetanilides **10** produced by condensation between anilines and 4,4,4-trifluoroacetoacetyl chloride (**6**) or ethyl 4,4,4-trifluoroacetoacetate (**7**): yields of isolated products

Compound	R [a]	From **6**	From **7**[b]
a	H	81%	91%
b	*p*-H_3C	78%	88%
c	*p*-F	−	82%
d	*p*-F_3CO	74%	72%
e	*m*-H_3C	81%	92%
f	*m*-H_3CO	76%	87%
g	*m*-F	−	93%
h	*o*-H_3C	−	87%
i	*o*-F	−	56%
j	*o*-Cl	71%	51%
k	*o*-Br	−	44%
l	*o*-I	−	41%

[a] Substituent R as present in the aniline starting material and its position (*ortho*, *meta*, or *para*) in the aromatic ring. [b] Application of the "watering protocol".

This approach, of course, depends totally on the availability of 4,4,4-trifluoroacetoacetyl chloride (**6**),[22,23] which is difficult to make and unstable at ambient temperature. We have therefore reinvestigated the condensation reaction between aniline and ethyl 4,4,4-trifluoroacetoacetate (**7**). The amino function should rapidly add to the extremely electrophilic carbonyl group activated by the neighboring trifluoromethyl entity without even requiring acid catalysis. The hemiacetal thus produced should give the crotonate upon loss of water. Despite the enhanced thermodynamic stability of the anilide, its formation is sluggish because it has to be preceded by the energetically unattractive addition of the aniline to the ethoxycarbonyl unit. The only chance to reorient the course of the condensation-cyclization sequence towards the 4-(trifluoromethyl)quinolinones **11** is to make all reaction steps reversible and to shift the equilibrium from the crotonate **8** to the anilide intermediates **10** by allowing the by-product ethanol to escape while retaining water, the by-product resulting from crotonate formation. As we have found, this can most conveniently be achieved by keeping the mixture of the two reactants in an open vessel at 130 °C and replenishing it portionwise with water in 30 min intervals. In this way, we have been able to make a variety of 4,4,4-trifluoroacetoacetanilides (see Table 1), mostly in excellent yields (**10a**−**h**: 72−92%), although only in moderate yields when *o*-haloanilines were employed as the starting materials (**10i**−**l**: 44−56%).

The cyclization of the anilides **10** proceeded smoothly when promoted by concentrated sulfuric acid at 95 °C, and provided the 4-(trifluoromethyl)-2(1*H*)-quinolinones **11** in high yields (80−92%; see Table 2). Those quinolinones (**11d**, **11i**, **11j**, **11k**, and **11l**) prepared for the first time were converted into the 2-bromo-4-(trifluoromethyl)quinolines **12** (Table 3), and these in turn into the 4-(trifluoromethyl)quinolines **13** (Table 3), the 4-(trifluoromethyl)quinoline-2-carboxylic acids **14** (Table 3), the 2-bromo-4-(trifluoromethyl)quinoline-3-carboxylic acids **15** (Table 3), and the 4-(trifluoromethyl)quinoline-3-carboxylic acids **16** (Table 3) by application of the same methods as described previously.[2]



As already reported,[24] 2-bromo-8-iodo-4-(trifluoromethyl)quinoline (**12l**) undergoes a selective iodine/lithium permutation to afford, upon carboxylation, the 2-bromo-4-(trifluoromethyl)quinoline-8-carboxylic acid (**17**) and, after reductive debromination, the 4-(trifluoromethyl)quinoline-8-carboxylic acid. To introduce lithium into the 2-position rather than the 8-position and thus to pave the way to the 8-iodo-4-(trifluoromethyl)quinoline-2-carboxylic acid (**14l**), one would first have to exchange[25] the bromine in quinoline **12l** with another iodine atom. 2,8-Dibromo-4-(trifluoromethyl)quinoline (**12k**) preferentially underwent the permutational interconversion at the 2-position with alkyllithium reagents, although perfect regioselectivity was achieved only under carefully optimized conditions (lithium tributylmagnesiate[26−28] in toluene). In contrast, 8-bromo-2-iodo-4-(trifluoromethyl)quinoline (**18**), readily obtained

Table 2. Acid-promoted cyclization of the anilides **10** to the 4-trifluoromethyl-2(1*H*)-quinolinones **11**: yields of isolated products

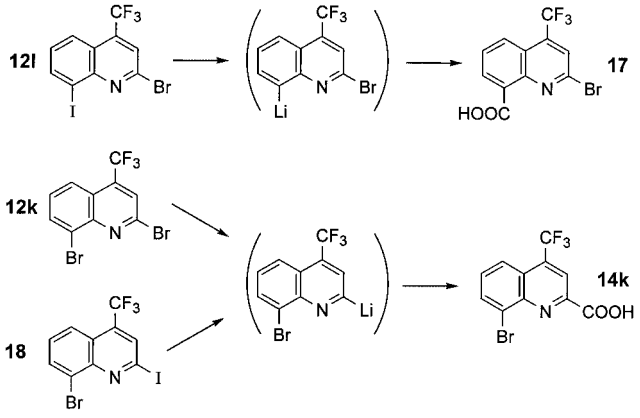
	R [a]	Position [b]	Product **11**
a	H	–	90%
b	*p*-H_3C	6	89%
c	*p*-F	6	92%
d	*p*-F_3CO	6	84%
e	*m*-H_3C	7[c]	87%
f	*m*-H_3CO	7[c]	83%
g	*m*-F	7[c]	91%
h	*o*-H_3C	8	89%
i	*o*-F	8	57%
j	*o*-Cl	8	80%
k	*o*-Br	8	22%
l	*o*-I	8	39%

[a] Substituent R as present in the aniline starting material and its position (*ortho*, *meta*, or *para*) in the aromatic ring. [b] Position of the substituent R in the cyclization product (quinolinone **11**). [c] No 5-isomer detected.

Table 3. Conversion of the quinolinones **11** into 2-bromo-4-(trifluoromethyl)quinolines **12**, 4-(trifluoromethyl)quinolines **13**, 4-(trifluoromethyl)quinoline-2-carboxylic acids **14**, 2-bromo-4-(trifluoromethyl)quinoline-3-carboxylic acids **15**, and 4-(trifluoromethyl)quinoline-3-carboxylic acids **16**: yields of isolated products

	R (in **11**)	**12**	**13**	**14**	**15**	**16**
d	6-F_3CO	89%	75%	69%	40%	81%
i	8-F	55%	63%	73%	83%	83%
j	8-Cl	79%	86%	61%	78%	89%
K	8-Br	59%	92%	58%	81%	78%
l	8-I	88%	82%	–	89%	83%

from the dibromo compound **12k** by halogen/halogen displacement,[25] was found to react exclusively at the 2-position, where the heaviest halogen was located, thus opening a convenient and clean entry to the 2-bromo-4-(trifluoromethyl)quinoline-2-carboxylic acid (**14k**).



Experimental Section

Details regarding standard operations and abbreviations can be found in previous publications from this laboratory.[29,30] ^{1}H, ^{1}H-decoupled ^{13}C, and ^{19}F NMR spectra of samples dissolved in deuteriochloroform or, if marked by an asterisk, in hexadeuterioacetone were recorded at 400, 101, and 376 MHz, respectively, chemical shifts being given relative to tetramethylsilane and trichlorofluoromethane as the internal standards.

4,4,4-Trifluoroacetoacetanilides (10): Ethyl 4,4,4-trifluoro-3-oxobutanoate (**7**; 58 mL, 74 g, 0.40 mol) and the aniline (0.20 mol) were heated at 130 °C. Water (4.0 mL) was added every 30 min over a period of 6 h. At 0 °C, after spontaneous crystallization, the solid mass was filtered and washed with hexanes (3 × 0.20 L) before being recrystallized from a 1:1 (v/v) mixture of ethyl acetate and hexanes.

Alternatively, 4,4,4-trifluoro-3-oxobutanoyl chloride[1] (**6**; 0.20 mol) in dichloromethane (85 mL) was added dropwise, over the course of 2 h, to a solution of aniline (0.20 mol) and triethylamine (28 mL, 20 g, 0.20 mol) in dichloromethane (50 mL), kept in an ice bath. The volatiles were evaporated, and the residue was taken up in diethyl ether (0.25 L) and washed with water (3 × 0.25 L). The product was again purified by crystallization.

4,4,4-Trifluoro-3-oxo-*N*-phenylbutanamide (10a): This compound was prepared from aniline (18 mL, 19 g, 0.20 mol) and ethyl 4,4,4-trifluoroacetoacetate; colorless prisms; m.p. 94–95 °C; yield 42.1 g (91%). ^{1}H NMR: δ = 7.50 (d, *J* = 8.4 Hz, 2 H), 7.37 (t, *J* = 8.6 Hz, 2 H), 7.19 (t, *J* = 7.19 Hz, 1 H), 2.81 (s, 2 H) ppm. ^{13}C NMR*: δ = 170.0, 138.6, 129.3, 125.2, 124.1 (q, *J* = 286 Hz), 120.5, 93.5 (q, *J* = 32 Hz), 39.0 ppm. MS (c.i.): *m*/*z* (%) = 249 (5) [M^+ + 18], 232 (40) [M^+ + 1], 231 (42) [M^+], 93 (100). $C_{10}H_8F_3NO_2$ (231.16): calcd. C 51.96, H 3.49; found C 51.44, H 3.44. When 4,4,4-trifluoroacetoacetyl chloride was used instead of the ester, amide **10a** was obtained in 81% yield (37.3 g).

4,4,4-Trifluoro-*N*-(4-methylphenyl)-3-oxobutanamide (10b): This compound was prepared from 4-methylaniline (*p*-toluidine; 21 g, 0.20 mol) and ethyl 4,4,4-trifluoroacetoacetate; colorless prisms; m.p. 92–94 °C; yield 43.2 g (88%). ^{1}H NMR: δ = 7.37 (d, *J* = 8.0 Hz, 2 H), 7.16 (d, *J* = 8.0 Hz, 2 H), 2.79 (s, 2 H), 2.34 (s, 3 H) ppm. ^{13}C NMR*: δ = 170.0, 136.4, 134.8, 130.1, 123.9 (q, *J* = 286 Hz), 119.8, 94.0 (q, *J* = 32 Hz), 39.1, 20.9 ppm. MS (c.i.): *m*/*z* (%) = 263 (45) [M^+ + 18], 246 (67) [M^+ + 1], 245 (13) [M^+], 198 (1), 176 (6), 107 (100). $C_{11}H_{10}F_3NO_2$ (245.20): calcd. C 53.88, H 4.11; found C 53.94, H 4.04. When 4,4,4-trifluoroacetoacetyl chloride was used instead of the ester, amide **10b** was obtained in 78% yield (38.3 g).

4,4,4-Trifluoro-*N*-(4-fluorophenyl)-3-oxobutanamide (10c): This compound was prepared from 4-fluoroaniline (19 mL, 22 g, 0.20 mol) and ethyl 4,4,4-trifluoroacetoacetate; colorless prisms; m.p. 102–104 °C; yield 40.9 g (82%). ^{1}H NMR: δ = 7.44 (dd, *J* = 9.1, 4.6 Hz, 2 H), 7.05 (dd, *J* = 8.9, 8.3 Hz, 2 H), 5.59 (s, 1 H) ppm. ^{13}C NMR: δ = 168.3, 160.2 (d, *J* = 247 Hz), 159.3 (q, *J* = 37 Hz), 132.0, 128.3 (q, *J* = 9 Hz), 122.6, 119.3 (q, *J* = 276 Hz), 117.0, (d, *J* = 21 Hz), 116.0 (d, *J* = 23 Hz), 93.3 (d, *J* = 23 Hz) ppm. MS (c.i.): *m*/*z* (%) = 267 (6) [M^+ + 18], 250 (37) [M^+ + 1], 249 (42) [M^+], 180 (9), 111 (100), 83 (23). $C_{10}H_7F_4NO_2$ (249.16): calcd. C 48.21, H 2.83; found C 48.06, H 2.60.

4,4,4-Trifluoro-3-oxo-*N*-[4-(trifluoromethoxy)phenyl]butanamide (10d): This compound was prepared from 4-(trifluoromethoxy)aniline (27 mL, 35 g, 0.20 mol) and ethyl 4,4,4-trifluoroacetoacetate; colorless prisms; m.p. 63–65 °C; yield 45.4 g (72%). ^{1}H NMR: δ = 7.55 (d, *J* = 9.0 Hz, 2 H), 7.22 (d, *J* = 8.8 Hz, 2 H), 5.61 (s, 1 H) ppm. ^{13}C NMR*: δ = 170.5, 146.1, 138.2, 123.9 (q, *J* = 286 Hz), 122.6, 122.2, 120.4, 94.0 (q, *J* = 33 Hz) ppm. MS (c.i..): *m*/*z* (%) =

333 (93) [M^+ + 18], 316 (43) [M^+ + 1], 315 (71) [M^+], 246 (4), 177 (100), 108 (35). $C_{11}H_7F_6NO_3$ (315.16): calcd. C 41.92, H 2.24, N 4.44; found C 42.06, H 2.17, N 4.53. When 4,4,4-trifluoroacetoacetyl chloride was used instead of the ester, amide **10d** was obtained in 74% yield (46.6 g).

4,4,4-Trifluoro-*N*-(3-methylphenyl)-3-oxobutanamide (10e): This compound was prepared from 3-methylaniline (*m*-toluidine; 22 g, 0.20 mol) and ethyl 4,4,4-trifluoroacetoacetate; colorless prisms; m.p. 78−80 °C; yield 45.1 g (92%). ^{1}H NMR: δ = 7.48 (s, 1 H), 7.34 (s, 1 H), 7.23 (m, 1 H), 7.00 (d, *J* = 6.7 Hz, 1 H), 2.79 (s, 2 H), 2.35 (s, 3 H) ppm. ^{13}C NMR: δ = 168.7, 159.4 (q, *J* = 37 Hz), 139.6, 136.4, 129.4, 126.8, 121.5, 118.7 (q, *J* = 276 Hz), 118.1, 93.8, 21.4 ppm. MS (c.i.): *m*/*z* (%) = 263 (2) [M^+ + 18], 246 (53) [M^+ + 1], 245 (36) [M^+], 176 (5), 107 (100). $C_{11}H_{10}F_3NO_2$ (245.20): calcd. C 53.88, H 4.11, N 5.71; found C 53.86, H 4.07, N 5.69. When 4,4,4-trifluoroacetoacetyl chloride was used instead of the ester, amide **10e** was obtained in 81% yield (39.7 g).

4,4,4-Trifluoro-*N*-(3-methoxyphenyl)-3-oxobutanamide (10f): This compound was prepared from 3-methoxyaniline (*m*-anisidine; 22 mL, 25 g, 0.20 mol) and ethyl 4,4,4-trifluoroacetoacetate; colorless prisms; m.p. 168−170 °C; yield 45.4 g (87%). ^{1}H NMR*: δ = 7.58 (d, *J* = 8.7 Hz, 1 H), 6.73 (dd, *J* = 8.9, 2.5 Hz, 1 H), 6.63 (d, *J* = 2.5 Hz, 1 H), 5.89 (s, 1 H), 3.86 (s, 3 H), 2.98 (s, 2 H) ppm. ^{13}C NMR*: δ = 167.2, 162.4, 140.2, 129.4, 126.9 (q, *J* = 286 Hz), 113.9, 109.0, 101.9, 72.9 (q, *J* = 30 Hz), 55.8, 40.3 ppm. MS (c.i.): *m*/*z* (%) = 279 (0) [M^+ + 18], 262 (42) [M^+ + 1], 261 (38) [M^+], 243 (10), 192 (100), 174 (14). $C_{11}H_{10}F_3NO_3$ (261.20): calcd. C 50.58, H 3.86; found C 50.85, H 3.60. When 4,4,4-trifluoroacetoacetyl chloride was used instead of the ester, amide **10f** was obtained in 76% yield (39.7 g).

4,4,4-Trifluoro-*N*-(3-fluorophenyl)-3-oxobutanamide (10g): This compound was prepared from 3-fluoroaniline (19 mL, 22 g, 0.20 mol) and ethyl 4,4,4-trifluoroacetoacetate; colorless prisms; m.p. 93−95 °C (dec.), yield 46.3 g (93%). ^{1}H NMR: δ = 7.46 (dm, *J* = 10.9 Hz, 1 H), 7.29 (m, 2 H), 7.13 (dd, *J* = 7.7, 1.0 Hz, 1 H), 6.88 (ddd, *J* = 8.6, 8.3, 1.9 Hz, 1 H), 5.60 (s, 1 H) ppm. ^{13}C NMR: δ = 168.8, 163.0 (d, *J* = 245 Hz), 159.5 (q, *J* = 37 Hz), 130.5 (d, *J* = 10 Hz), 118.6 (q, *J* = 275 Hz), 116.0 (d, *J* = 3 Hz), 112.4, (d, *J* = 21 Hz), 108.4 (d, *J* = 27 Hz), 93.5 (q, *J* = 4 Hz), 38.6 ppm. MS (c.i.): *m*/*z* (%) = 267 (0) [M^+ + 18], 250 (8) [M^+ + 1], 249 (8) [M^+], 180 (2), 111 (100). $C_{10}H_7F_4NO_2$ (249.16): calcd. C 48.21, H 2.83; found C 48.17, H 2.78.

4,4,4-Trifluoro-*N*-(2-methylphenyl)-3-oxobutanamide (10h): This compound was prepared from 2-methylaniline (*o*-toluidine; 21 mL, 21 g, 0.20 mol) and ethyl 4,4,4-trifluoroacetoacetate; colorless prisms; m.p. 91−92 °C; yield 42.7 g (87%). ^{1}H NMR: δ = 7.61 (d, *J* = 8.0 Hz, 1 H), 7.16−7.27 (m, 3 H), 2.83 (s, 2 H), 2.29 (s, 3 H) ppm. ^{13}C NMR*: δ = 170.3, 136.2, 132.6, 131.2, 126.8, 126.7, 125.8, 124.1 (q, *J* = 287 Hz), 94.0 (q, *J* = 30 Hz), 38.8, 17.9 ppm. MS (c.i.): *m*/*z* (%) = 263 (0) [M^+ + 18], 246 (12) [M^+ + 1], 245 (9) [M^+], 107 (100). $C_{11}H_{10}F_3NO_2$ (245.20): calcd. C 53.88, H 4.11; found C 53.74, H 3.92.

4,4,4-Trifluoro-*N*-(2-fluorophenyl)-3-oxobutanamide (10i): This compound was prepared from 2-fluoroaniline (19 mL, 22 g, 0.20 mol) and ethyl 4,4,4-trifluoroacetoacetate; colorless prisms; m.p. 85−87 °C; yield 27.9 g (56%). ^{1}H NMR: δ = 8.20 (dd, *J* = 8.5, 7.4 Hz, 1 H), 7.40 (s, 1 H), 7.08 (m, 3 H), 5.66 (s, 1 H) ppm. ^{13}C NMR: δ = 168.5, 159.4 (q, *J* = 36 Hz), 152.9 (d, *J* = 245 Hz), 125.8 (d, *J* = 7 Hz), 124.5 (q, *J* = 2 Hz), 122.5, 118.4 (q, *J* = 275 Hz), 115.3 (d, *J* = 19 Hz), 93.5 (q, *J* = 3 Hz), 38.5 ppm. MS (c.i.): *m*/*z* (%) = 267 (44) [M^+ + 18], 250 (77) [M^+ + 1], 249 (24) [M^+], 134 (23), 111 (100). $C_{10}H_7F_4NO_2$ (249.16): calcd. C 48.21, H 2.83; found C 48.07, H 2.76.

***N*-(2-Chlorophenyl)-4,4,4-trifluoro-3-oxobutanamide (10j):** This compound was prepared from 2-chloroaniline (21 mL, 26 g, 0.20 mol) and ethyl 4,4,4-trifluoroacetoacetate; colorless prisms; m.p. 79−81 °C; yield 27.1 g (51%). ^{1}H NMR: δ = 8.24 (d, *J* = 8.2 Hz, 1 H), 7.89 (s, 1 H), 7.39 (d, *J* = 8.1 Hz, 1 H), 7.29 (t, *J* = 8.0 Hz, 1 H), 7.12 (t, *J* = 7.6 Hz, 1 H), 2.89 (s, 2 H) ppm. ^{13}C NMR: δ = 168.6, 133.5, 129.5, 128.2, 128.1, 126.4, 122.8, 118.9 (q, *J* = 275 Hz), 93.6 (q, *J* = 33 Hz), 38.8 ppm. MS (c.i.): *m*/*z* (%) = 285 (19) [M^+ + 18], 283 (45) [M^+ + 18], 268 (34) [M^+ + 1], 267 (27) [M^+], 266 (76) [M^+ + 1], 265 (38) [M^+], 230 (60), 196 (9), 127 (100). $C_{10}H_7ClF_3NO_2$ (265.62): calcd. C 45.22, H 2.66, N 5.28; found C 45.52, H 2.59, N 5.30. When 4,4,4-trifluoroacetoacetyl chloride was used instead of the ester, amide **10j** was obtained in 71% yield (37.7 g).

***N*-(2-Bromophenyl)-4,4,4-trifluoro-3-oxobutanamide (10k):** This compound was prepared from 2-bromoaniline (34 g, 0.20 mol) and ethyl 4,4,4-trifluoroacetoacetate; colorless prisms; m.p. 84−86 °C; yield 27.3 g (44%). ^{1}H NMR: δ = 8.20 (dd, *J* = 8.2, 1.5 Hz, 1 H), 7.57 (dd, *J* = 8.1, 1.4 Hz, 1 H), 7.33 (td, *J* = 7.8, 1.3 Hz, 1 H), 7.06 (td, *J* = 7.9, 1.5 Hz, 1 H), 2.91 (s, 3 H) ppm. ^{13}C NMR: δ = 168.4, 136.8, 132.5, 128.5, 123.0, 122.3 (q, *J* = 286 Hz), 114.3, 93.0 (q, *J* = 33 Hz), 38.8 ppm. MS (c.i.): *m*/*z* (%) = 329 (96) [M^+ + 18], 327 (100) [M^+ + 18], 312 (28) [M^+ + 1], 311 (11) [M^+], 310 (30) [M^+ + 1], 309 (9) [M^+], 230 (12), 173 (20), 171 (21). $C_{10}H_7BrF_3NO_2$ (310.07): calcd. C 38.74, H 2.28; found C 38.01, H 2.20.

4,4,4-Trifluoro-*N*-(2-iodophenyl)-3-oxobutanamide (10l): This compound was prepared from 2-iodoaniline (44 g, 0.20 mol) and ethyl 4,4,4-trifluoroacetoacetate; colorless prisms; m.p. 102−104 °C; yield 29.3 g, (41%). ^{1}H NMR: δ = 8.09 (dd, *J* = 8.3, 1.3 Hz, 1 H), 7.82 (dd, *J* = 8.0, 1.0 Hz, 1 H), 7.63 (s, 1 H), 7.38 (ddd, *J* = 8.0, 7.4, 1.3 Hz, 1 H), 6.94 (ddd, *J* = 8.0, 7.7, 1.3 Hz, 1 H), 2.88 (s, 2 H) ppm. ^{13}C NMR: δ = 168.5, 139.0, 137.4, 128.9, 127.3, 126.6, 122.5 (q, *J* = 286 Hz), 93.5, 92.8 (q, *J* = 32 Hz), 38.9 ppm. MS (c.i.): *m*/*z* (%) = 375 (100) [M^+ + 18], 358 (41) [M^+ + 1], 357 (7) [M^+], 230 (11), 134 (3). $C_{10}H_7F_3INO$ (357.06): calcd. C 33.64, H 1.98; found C 33.54, H 2.39.

4-(Trifluoromethyl)quinolin-2(1*H*)-ones (11): The anilide (**10**; 0.10 mol) was dissolved in sulfuric acid (96%, 0.10 L) and the mixture was heated at 90 °C for 50 min before being poured into water (0.25 L). The precipitate formed was filtered and crystallized from ethanol.

4-(Trifluoromethyl)quinolin-2(1*H*)-one (11a): This compound was prepared from amide **10a** (23 g, 0.10 mol); colorless needles; m.p. 246−247 °C (reprod.); yield 19.2 g (90%). ^{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)quinolin-2(1*H*)-one (11b): This compound was prepared from amide **10b** (24 g, 0.10 mol); colorless needles; m.p. 257−260 °C (reprod.); yield 20.2 g (89%). ^{1}H NMR (D_3CSOCD_3): δ = 7.6 (m, 2 H), 7.47 (d, *J* = 8.50 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* (%) = 245 (2) [M$^+$ + 18], 228 (100) [M$^+$ + 1], 227 (61) [M$^+$], 198 (4). $C_{11}H_8F_3NO$ (227.18): calcd. C 58.16, H 3.55, N 6.17; found C 58.09, H 3.55, N 6.12.

6-Fluoro-4-(trifluoromethyl)quinolin-2(1*H*)-one (11c): This compound was prepared from amide **10c** (25 g, 0.10 mol); short colorless needles; m.p. 252−253 °C (decomp.); yield 21.3 g (92%). ^{1}H NMR (D_3CSOCD_3): δ = 7.59 (ddd, *J* = 9.2, 8.4, 4.6 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* = 36 Hz), 123.1 (q, *J* = 5 Hz), 121.9 (q, *J* = 275 Hz), 120.0 (d, *J* = 25 Hz), 118.4 (d, *J* = 18 Hz), 113.3 (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). $C_{10}H_5F_4NO$ (231.15): calcd. C 51.96, H 2.18; found C 52.03, H 2.10.

4-Trifluoromethyl-6-(trifluoromethoxy)quinolin-2(1*H*)-one (11d): This compound was prepared from amide **10d** (32 g, 0.10 mol); colorless needles; m.p. 178−180 °C; 25.0 g (84%). ^{1}H NMR (D_3CSOCD_3): δ = 7.71 (dd, *J* = 8.8, 1.6 Hz, 1 H), 7.56 (d, *J* = 9.7 Hz, 1 H), 7.52 (s, 1 H), 7.11 (s, 1 H) ppm. ^{13}C NMR (D_3CSOCD_3): δ = 161.0, 144.0, 139.7, 136.8 (q, *J* = 32 Hz), 126.2, 124.6, 123.2 (q, *J* = 257 Hz), 121.0 (q, *J* = 276 Hz), 119.6, 117.2, 114.4 ppm. MS (c.i.): *m*/*z* (%) = 315 (0) [M$^+$ + 18], 298 (27) [M$^+$ + 1], 297 (100) [M$^+$], 269 (3), 228 (10), 200 (10). $C_{11}H_5F_6NO_2$ (297.15): calcd. C 44.46, H 1.70, N 4.71; found C 44.46, H 1.90, N 4.68.

7-Methyl-4-(trifluoromethyl)quinolin-2(1*H*)-one (11e): This compound was prepared from amide **10e** (25 g, 0.10 mol); colorless needles; m.p. 210−213 °C (reprod.); yield 19.8 g (87%). ^{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 (1) [M$^+$ + 18], 228 (100) [M$^+$ + 1], 227 (47) [M$^+$], 198 (7), 130 (3), 102 (1). $C_{11}H_8F_3NO$ (227.18): calcd. C 58.16, H 3.55, N 6.17; found C 58.06, H 3.64, N 6.31.

7-Methoxy-4-(trifluoromethyl)quinolin-2(1*H*)-one (11f): This compound was prepared from amide **10f** (26 g, 0.10 mol); short pale yellow needles; m.p. 219−222 °C (reprod.); yield 20.2 g (83%). ^{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* = 21 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 (14) [M$^+$ + 18], 244 (100) [M$^+$ + 1], 243 (24) [M$^+$]. $C_{11}H_8F_3NO_2$ (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)quinolin-2(1*H*)-one (11g): This compound was prepared from amide **10g** (25 g, 0.10 mol); short colorless needles; m.p. 166−167 °C (decomp.); yield 21.2 g (91%). ^{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)quinolin-2(1*H*)-one (11h): This compound was prepared from amide **10h** (25 g, 0.10 mol); short colorless needles; mp. 248−251 °C (reprod.); yield 20.2 g (89%). ^{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.

8-Fluoro-4-(trifluoromethyl)quinolin-2(1*H*)-one (11i): This compound was prepared from amide **10i** (25 g, 0.10 mol); colorless needles; m.p. 220−222 °C (reprod.); yield 13.2 g (57%). ^{1}H NMR*: δ = 11.0 (s, 1 H), 7.61 (m, 1 H), 7.53 (ddd, *J* = 10.8, 8.2, 1.3 Hz, 1 H), 7.34 (td, *J* = 8.2, 5.3 Hz, 1 H), 7.03 (s, 1 H) ppm. ^{13}C NMR*: δ = 161.3, 151.0 (d, *J* = 246 Hz), 130.5 (d, *J* = 15 Hz), 124.6 (q, *J* = 5 Hz), 124.0 (d, *J* = 7 Hz), 123.9 (q, *J* = 274 Hz), 121.4, 118.0 (d, *J* = 17 Hz), 116.8 ppm. MS (c.i.): *m*/*z* (%) = 249 (2) [M$^+$ + 18], 232 (100) [M$^+$ + 1], 231 (71) [M$^+$], 203 (9), 184 (7). $C_{10}H_5F_4NO$ (231.15): calcd. C 51.96, H 2.18; found C 51.83, H 2.10.

8-Chloro-4-(trifluoromethyl)quinolin-2(1*H*)-one (11j): This compound was prepared from amide **10j** (27 g, 0.10 mol); colorless needles; m.p. 203−205 °C (reprod.); yield 19.8 g (80%). ^{1}H NMR (D_3CSOCD_3): δ = 7.83 (d, *J* = 7.9 Hz, 1 H), 7.72 (d, *J* = 8.2 Hz, 1 H), 7.36 (t, *J* = 8.0 Hz, 1 H), 7.13 (s, 1 H) ppm. ^{13}C NMR (D_3CSOCD_3): δ = 161.2, 137.4 (q, *J* = 31 Hz), 133.0, 128.3, 128.2, 125.6, 125.4, 124.5, 123.0 (q, *J* = 273 Hz), 112.4 ppm. MS (c.i.): *m*/*z* (%) = 267 (0) [M$^+$ + 18], 265 (0) [M$^+$ + 18], 250 (10) [M$^+$ + 1], 249 (37) [M$^+$], 248 (36) [M$^+$ + 1], 247 (100) [M$^+$], 219 (20), 200 (13). $C_{10}H_5ClF_3NO$ (247.60): calcd. C 48.51, H 2.04, N 5.66; found C 48.45, H 2.00, N 5.66.

8-Bromo-4-(trifluoromethyl)quinolin-2(1*H*)-one (11k): This compound was prepared from amide **10k** (31 g, 0.10 mol); colorless needles; m.p. 178−180 °C; yield 6.43 g, (22%). ^{1}H NMR (D_3CSOCD_3): δ = 8.00 (d, *J* = 7.9 Hz, 1 H), 7.76 (d, *J* = 8.0 Hz, 1 H), 7.30 (t, *J* = 8.1 Hz, 1 H), 7.13 (s, 1 H) ppm. ^{13}C NMR (D_3CSOCD_3): δ = 160.3, 138.2 (q, *J* = 32 Hz), 136.0, 129.7, 125.5 (q, *J* = 3 Hz), 124.7, 124.0 (q, *J* = 3 Hz), 123.5 (q, *J* = 276 Hz), 116.2, 110.2 ppm. MS (c.i.): *m*/*z* (%) = 311 (0) [M$^+$ + 18], 309 (0) [M$^+$ + 18], 294 (65) [M$^+$ + 1], 293 (100) [M$^+$], 292 (80) [M$^+$ + 1], 291 (95) [M$^+$], 263 (16). $C_{10}H_5BrF_3NO$ (292.05): calcd. C 41.13, H 1.73; found C 41.13, H 1.73.

8-Iodo-4-(trifluoromethyl)quinolin-2(1*H*)-one (11l): This compound was prepared from amide **10l** (36 g, 0.10 mol); colorless needles; m.p. 199−201 °C (reprod.); yield 13.2 g, (39%). ^{1}H NMR*: δ = 8.22 (dd, *J* = 8.0, 1.2 Hz, 1 H), 7.85 (d, *J* = 8.1 Hz, 1 H), 7.19 (t, *J* = 7.6 Hz, 1 H), 7.03 (s, 1 H) ppm. ^{13}C NMR*: δ = 161.2, 144.8, 143.1, 138.1 (q, *J* = 31 Hz), 128.4, 125.8, 123.9 (q, *J* = 275 Hz), 123.5, 112.4, 102.3 ppm. MS (c.i.): *m*/*z* (%) = 357 (25) [M$^+$ + 18], 341 (29) [M$^+$ +2], 340 (100) [M$^+$ + 1], 339 (93) [M$^+$], 338 (40), 311 (7). $C_{10}H_5F_3INO$ (339.05): calcd. C 35.43, H 1.49; found C 35.72, H 1.88.

2-Bromo-4-(trifluoromethyl)quinolines (12): The 4-(trifluoromethyl)quinolin-2(1*H*)-one (**11**; 50 mmol) was added whilst stirring to phosphorus oxybromide (29 g, 0.10 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 precipitate was collected and crystallized from methanol.

2-Bromo-6-trifluoromethoxy-4-(trifluoromethyl)quinoline (12d): This compound was prepared from quinolone **11d** (14.9 g, 50 mmol); colorless needles; m.p. 55−56 °C; yield 16.0 g (89%). ^{1}H NMR:

δ = 8.19 (d, *J* = 9.3 Hz, 1 H), 7.91 (s, 1 H), 7.87 (s, 1 H), 7.70 (d, *J* = 9.3, 2.0 Hz, 1 H) ppm. ^{13}C NMR: δ = 148.4, 147.4, 141.1, 136.4 (q, *J* = 33 Hz), 131.9, 125.1, 124.3 (q, *J* = 6 Hz), 122.4, 122.2 (q, *J* = 276 Hz), 120.4 (q, *J* = 261 Hz), 115.0 ppm. MS (c.i.): *m*/*z* (%) = 379 (0) [M$^+$ + 18], 377 (0) [M$^+$ + 18], 362 (5) [M$^+$ + 1], 361 (2) [M$^+$], 360 (6) [M$^+$ + 1], 359 (1) [M$^+$], 282 (7), 116 (46), 76 (100), 75 (63). $C_{11}H_4BrF_6NO$ (360.05): calcd. C 36.69, H 1.12; found C 36.59, H 1.14.

2-Bromo-8-fluoro-4-(trifluoromethyl)quinoline (12i): This compound was prepared from quinolone **11i** (11.6 g, 50 mmol); colorless needles; m.p. 80−81 °C; yield 8.09 g (55%). ^{1}H NMR: δ = 7.90 (m, 2 H), 7.68 (ddd, *J* = 13.1, 8.0, 5.1 Hz, 1 H), 7.55 (ddd, *J* = 9.6, 8.0, 1.3 Hz, 1 H) ppm. ^{13}C NMR: δ = 157.7 (d, *J* = 260 Hz), 141.6, 139.9 (d, *J* = 13 Hz), 136.7 (qd, *J* = 33, 3 Hz), 129.3 (d, *J* = 8 Hz), 124.8 (q, *J* = 6 Hz), 123.8, 122.6 (q, *J* = 275 Hz), 120.3 (sext, *J* = 3 Hz), 116.1 (d, *J* = 19 Hz) ppm. MS (c.i.): *m*/*z* (%) = 313 (0) [M$^+$ + 18], 311 (0) [M$^+$ + 18], 296 (3) [M$^+$ + 1], 295 (41) [M$^+$], 294 (7) [M$^+$ + 1], 293 (35) [M$^+$], 214 (47), 194 (100). $C_{10}H_4BrF_4N$ (294.04): calcd. C 40.85, H 1.37; found C 41.09, H 1.12.

2-Bromo-8-chloro-4-(trifluoromethyl)quinoline (12j): This compound was prepared from quinolone **11j** (12.4 g, 50 mmol); colorless needles; m.p. 66−68 °C; yield 12.3 g (79%). ^{1}H NMR: δ = 8.02 (d, *J* = 8.8 Hz, 1 H), 7.94 (d, *J* = 7.4 Hz, 1 H), 7.89 (s, 1 H), 7.63 (t, *J* = 8.1 Hz, 1 H) ppm. ^{13}C NMR: δ = 145.7, 141.6, 136.7 (q, *J* = 33 Hz), 133.9, 131.5, 128.6, 124.4 (q, *J* = 6 Hz), 123.4, 123.1 (q, *J* = 3 Hz), 122.2 (q, *J* = 277 Hz) ppm. MS (c.i.): *m*/*z* (%) = 331(0) [M$^+$ + 18], 329 (4) [M$^+$ + 18], 327 (3) [M$^+$ + 18], 314 (25) [M$^+$ + 1], 313 (19) [M$^+$], 312 (100) [M$^+$ + 1], 311 (23) [M$^+$], 310 (81) [M$^+$ + 1], 309 (8) [M$^+$], 291 (8), 247 (14). $C_{10}H_4BrClF_3N$ (310.50): calcd. C 38.68, H 1.30; found C 38.63, H 1.46.

2,8-Dibromo-4-(trifluoromethyl)quinoline (12k): This compound was prepared from quinolone **11k** (14.6 g, 50 mmol); colorless needles; m.p. 70−72 °C; yield 10.5 g (59%). ^{1}H NMR: δ = 8.15 (d, *J* = 8.0 Hz, 1 H), 8.07 (dd, *J* = 8.7, 1.2 Hz, 1 H), 7.88 (s, 1 H), 7.55 (dd, *J* = 8.0, 7.6 Hz, 1 H) ppm. ^{13}C NMR: δ = 146.6, 141.8, 136.8 (q, *J* = 33 Hz), 135.2, 129.0, 124.9, 124.4 (q, *J* = 6 Hz), 123.9, 122.8, 122.0 (q, *J* = 276 Hz) ppm. MS (c.i.): *m*/*z* (%) = 375 (0) [M$^+$ + 18], 373 (0) [M$^+$ + 18], 371 (0) [M$^+$ + 18], 358 (18) [M$^+$ + 1], 357 (50) [M$^+$], 356 (33) [M$^+$ + 1], 355 (100) [M$^+$], 354 (34) [M$^+$ + 1], 353 (55) [M$^+$], 274 (40), 254 (29). $C_{10}H_4Br_2F_3N$ (354.95): calcd. C 33.84, H 1.14; found C 33.83, H 1.09.

2-Bromo-8-iodo-4-(trifluoromethyl)quinoline (12l): This compound was prepared from quinolone **11l** (17.0 g, 50 mmol); colorless needles; m.p. 102−104 °C; yield 17.7 g, (88%). ^{1}H NMR: δ = 8.45 (d, *J* = 7.4 Hz, 1 H), 8.10 (d, *J* = 8.1 Hz, 1 H), 7.87 (s, 1 H), 7.41 (dd, *J* = 8.2, 7.3 Hz, 1 H) ppm. ^{13}C NMR: δ = 148.4, 142.0, 141.7, 136.9 (q, *J* = 32 Hz), 129.5, 124.6, 124.3 (q, *J* = 6 Hz), 122.5, 122.0 (q, *J* = 276 Hz), 102.6 ppm. MS (c.i.): *m*/*z* (%) = 421 (0) [M$^+$ + 18], 419 (0) [M$^+$ + 18], 404 (70) [M$^+$ + 1], 403 (100) [M$^+$], 402 (99) [M$^+$ + 1], 401 (84) [M$^+$], 355 (16), 356 (15). $C_{10}H_4BrIF_3N$ (401.95): calcd. C 29.88, H 1.00; found C 29.90, H 1.11.

4-(Trifluoromethyl)quinolines (13): The 2-bromo-4-(trifluoromethyl)quinoline (**12d**, **12i**, or **12j**; 10 mmol) was added to a precooled solution of butyllithium (10 mmol) in toluene (40 mL) and hexanes (6.25 mL). After the mixture had been kept for 15 min at −75 °C, methanol (2.00 mL, 1.60 g, 50 mmol) was injected. The volatiles were evaporated and the residue was crystallized from pentanes.

2-Bromo-4-(trifluoromethyl)quinoline (**12k**−**l**; 10 mmol) and tin tetrachloride (1.90 g, 10 mmol) were added to a 5.0 M solution of hydrochloric acid in ethanol. After the mixture had been heated under reflux for 2 h, the solvent was evaporated and water (10 mL) was added. Extraction with hexanes (2 × 15 mL) and evaporation gave a residue, which was crystallized from pentanes.

6-Trifluoromethoxy-4-(trifluoromethyl)quinoline (13d): This compound was prepared from the bromoquinoline **12d** (3.60 g, 10 mmol); b.p. 113−114 °C/4.5 Torr; n_D^{20} = 1.4742; yield 2.11 g (75%). ^{1}H NMR: δ = 9.07 (d, *J* = 4.3 Hz, 1 H), 8.27 (d, *J* = 9.2 Hz, 1 H), 7.95 (s, 1 H), 7.76 (d, *J* = 4.4 Hz, 1 H), 7.70 (dd, *J* = 9.4, 2.0 Hz, 1 H) ppm. ^{13}C NMR: δ = 149.9, 148.1, 146.9, 134.3 (q, *J* = 33 Hz), 132.6, 124.0, 123.1, 122.9 (q, *J* = 275 Hz), 120.3 (q, *J* = 259 Hz), 118.7 (q, *J* = 6 Hz), 114.6 ppm. MS (c.i.): *m*/*z* (%) = 299 (10) [M$^+$ + 18], 282 (12) [M$^+$ + 1], 281 (84) [M$^+$], 184 (100). $C_{11}H_5F_6NO$ (281.15): calcd. C 44.99, H 1.79; found C 46.66, H 1.74.

8-Fluoro-4-(trifluoromethyl)quinoline (13i): This compound was prepared from the bromoquinoline **12i** (2.94 g, 10 mmol); colorless needles; m.p. 37−39 °C; yield 1.35 g (63%). ^{1}H NMR: δ = 9.12 (d, *J* = 4.5 Hz, 1 H), 7.95 (dm, *J* = 8.6 Hz, 1 H), 7.79 (d, *J* = 4.5 Hz, 1 H), 7.66 (ddd, *J* = 8.6, 7.7, 5.2 Hz, 1 H), 7.54 (ddd, *J* = 9.9, 7.7, 1.3 Hz, 1 H) ppm. ^{13}C NMR: δ = 158.2 (d, *J* = 258 Hz), 149.9 (d, *J* = 2 Hz), 139.4 (d, *J* = 12 Hz), 134.3 (qd, *J* = 33, 4 Hz), 128.6 (d, *J* = 8 Hz), 124.5, 123.1 (q, *J* = 274 Hz), 120.0 (sext, *J* = 3 Hz), 119.0 (q, *J* = 5 Hz), 114.7 (d, *J* = 19 Hz) ppm. MS (c.i.): *m*/*z* (%) = 233 (0) [M$^+$ + 18], 216 (28) [M$^+$ + 1], 215 (100) [M$^+$], 165 (5), 84 (9). $C_{10}H_5F_4N$ (215.15): calcd. C 55.83, H 2.34; found C 55.74, H 2.23.

8-Chloro-4-(trifluoromethyl)quinoline (13j): This compound was prepared from the bromoquinoline **12j** (3.11 g, 10 mmol); colorless needles; m.p. 35−37 °C; yield 2.0 g (86%). ^{1}H NMR: δ = 9.13 (d, *J* = 4.4 Hz, 1 H), 8.10 (dm, *J* = 8.6 Hz, 1 H), 7.97 (d, *J* = 7.7 Hz, 1 H), 7.80 (d, *J* = 4.3 Hz, 1 H), 7.63 (dd, *J* = 7.8, 7.4 Hz, 1 H) ppm. ^{13}C NMR: δ = 150.0, 145.1, 134.7 (q, *J* = 32 Hz), 134.6, 130.6, 128.3, 124.5, 123.1, 123.0 (q, *J* = 3 Hz), 118.9 (q, *J* = 5 Hz) ppm. MS (c.i.): *m*/*z* (%) = 251 (0) [M$^+$ + 18], 249 (0) [M$^+$ + 18], 234 (34) [M$^+$ + 1], 233 (53) [M$^+$], 232 (100) [M$^+$ + 1], 231 (80) [M$^+$], 162 (25), 127 (10). $C_{10}H_5ClF_3N$ (231.60): calcd. C 51.86, H 2.18; found C 51.86, H 1.90.

8-Bromo-4-(trifluoromethyl)quinoline (13k): This compound was prepared from the bromoquinoline **12k** (3.55 g, 10 mmol); colorless needles; m.p. 82−84 °C; yield 2.54 g (92%). ^{1}H NMR: δ = 9.18 (d, *J* = 4.4 Hz, 1 H), 8.18 (d, *J* = 7.5 Hz, 1 H), 8.14 (d, *J* = 9.0 Hz, 1 H), 7.79 (d, *J* = 4.3 Hz, 1 H), 7.56 (dd, *J* = 8.6, 7.5 Hz, 1 H) ppm. ^{13}C NMR: δ = 150.3, 145.9, 134.9 (q, *J* = 33 Hz), 134.0, 128.8, 125.9, 124.4, 123.8, 123.2 (q, *J* = 276 Hz), 118.9 (q, *J* = 4 Hz) ppm. MS (c.i.): *m*/*z* (%) = 295 (0) [M$^+$ + 18], 293 (0) [M$^+$ + 18], 278 (24) [M$^+$ + 1], 277 (100) [M$^+$], 276 (26) [M$^+$ + 1], 275 (94) [M$^+$], 256 (4), 196 (31), 176 (14). $C_{10}H_5BrF_3N$ (276.05): calcd. C 43.51, H 1.83; found C 43.37, H 1.73.

8-Iodo-4-(trifluoromethyl)quinoline (13l): This compound was prepared from the bromoquinoline **12l** (4.02 g, 10 mmol); colorless needles; m.p. 95−96 °C; yield 2.65 g, (82%). ^{1}H NMR: δ = 9.14 (d, *J* = 4.5 Hz, 1 H), 8.48 (d, *J* = 7.5 Hz, 1 H), 8.17 (d, *J* = 4.5 Hz, 1 H), 7.79 (d, *J* = 4.4 Hz, 1 H), 7.42 (dd, *J* = 8.2, 7.9 Hz, 1 H) ppm. ^{13}C NMR: δ = 150.6, 147.8, 141.2, 135.0 (q, *J* = 32 Hz), 129.3, 124.8 (q, *J* = 3 Hz), 123.8, 123.1 (q, *J* = 275 Hz), 119.1 (q, *J* = 5 Hz), 104.4 ppm. MS (c.i.): *m*/*z* (%) = 341 (0) [M$^+$ + 18], 324 (49) [M$^+$ + 1], 323 (100) [M$^+$], 196 (33), 176 (19), 127 (5). $C_{10}H_5F_3IN$ (323.05): calcd. C 37.18, H 1.56; found C 37.41, H 1.46.

4-(Trifluoromethyl)quinoline-2-carboxylic Acids (14): At −75 °C, 2-bromo-4-(trifluoromethyl)quinoline (**12**; 10 mmol) was added to a

solution of butyllithium (10 mmol) in tetrahydrofuran (20 mL) and hexanes (6.25 mL). After 45 min, 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 × 10 mL) before being acidified with concentrated hydrochloric acid to pH 4. Extraction with ethyl acetate (3 × 10 mL), drying of the combined organic layers, and evaporation gave a residue, which was crystallized.

6-Trifluoromethoxy-4-(trifluoromethyl)quinoline-2-carboxylic Acid (14d): This compound was prepared from the bromoquinoline **12d** (3.60 g, 10 mmol); colorless prisms; m.p. 163−165 °C (from chloroform/ethyl acetate), yield 2.24 g (69%). ^{1}H NMR*: δ = 8.55 (s, 1 H), 8.51 (d, *J* = 9.1 Hz, 1 H), 8.07 (s, 1 H), 8.04 (d, *J* = 9.4 Hz, 1 H) ppm. ^{13}C NMR*: δ = 169.1, 154.6, 153.5, 151.3, 140.3 (q, *J* = 33 Hz), 139.2, 130.4, 129.1, 128.2 (q, *J* = 275 Hz), 125.5 (q, *J* = 258 Hz), 123.9 (q, *J* = 4 Hz), 119.4 ppm. MS (c.i.): *m/z* (%) = 343 (0) [M$^+$ + 18], 326 (4) [M$^+$ + 1], 325 (0) [M$^+$], 116 (6), 76 (100). $C_{12}H_5F_6NO_3$ (325.16): calcd. C 44.33, H 1.55; found C 44.35, H 1.52.

8-Fluoro-4-(trifluoromethyl)quinoline-2-carboxylic Acid (14i): This compound was prepared from the bromoquinoline **12i** (2.94 g, 10 mmol); colorless prisms; m.p. 188−190 °C (decomp.; from chloroform); yield 1.89 g (73%). ^{1}H NMR*: δ = 8.56 (s, 1 H), 8.08 (m, 1 H), 8.00 (ddd, *J* = 12.8, 7.7, 5.1 Hz, 1 H), 7.81 (ddd, *J* = 10.2, 7.7, 1.3 Hz, 1 H) ppm. ^{13}C NMR*: δ = 166.0, 160.3 (d, *J* = 260 Hz), 148.9 (d, *J* = 2 Hz), 140.1 (d, *J* = 13 Hz), 136.9 (qd, *J* = 33, 3 Hz), 133.3 (d, *J* = 8 Hz), 127.0, 125.0 (q, *J* = 274 Hz), 121.5 (sext, *J* = 3 Hz), 120.5 (q, *J* = 6 Hz), 117.4 (d, *J* = 19 Hz) ppm. MS (c.i.): *m/z* (%) = 277 (0) [M$^+$ + 18], 260 (10) [M$^+$ + 1], 259 (8) [M$^+$], 215 (100), 194 (32), 146 (13). $C_{11}H_5F_4NO_2$ (259.16): calcd. C 50.98, H 1.94; found C 50.87, H 1.87.

8-Chloro-4-(trifluoromethyl)quinoline-2-carboxylic Acid (14j): This compound was prepared from the bromoquinoline **12j** (3.11 g, 10 mmol); colorless prisms; m.p. 167−169 °C (from ethyl acetate); yield 1.68 g (61%). ^{1}H NMR*: δ = 8.56 (s, 1 H), 8.42 (dd, *J* = 7.7, 1.3 Hz, 1 H), 8.29 (dq, *J* = 8.6, 1.2 Hz, 1 H), 7.89 (dd, *J* = 8.6, 7.5 Hz, 1 H) ppm. ^{13}C NMR*: δ = 164.9, 149.3, 145.7, 136.6 (q, *J* = 32 Hz), 136.0, 132.2, 127.3, 126.1, 124.5 (q, *J* = 3 Hz), 124.1 (q, *J* = 275 Hz), 119.6 (q, *J* = 6 Hz) ppm. MS (c.i.): *m/z* (%) = 295 (0) [M$^+$ + 18], 293 (0) [M$^+$ + 18], 278 (0) [M$^+$ + 1], 277 (2) [M$^+$], 276 (3) [M$^+$ + 1], 275 (9) [M$^+$], 231 (100), 210 (29), 196 (19). $C_{11}H_5ClF_3NO_2$ (275.61): calcd. C 47.94, H 1.83; found C 48.18, H 1.81.

8-Bromo-4-(trifluoromethyl)quinoline-2-carboxylic Acid (14k): This compound was prepared from the iodoquinoline **18** (4.02 g, 10 mmol); colorless prisms; m.p. 199−201 °C (reprod.; from chloroform/ethyl acetate); yield 1.86 g, (58%). ^{1}H NMR*: δ = 8.58 (s, 1 H), 8.25 (dd, *J* = 8.6, 1.2 Hz, 1 H), 8.19 (dd, *J* = 7.4, 1.2 Hz, 1 H), 7.78 (ddd, *J* = 8.7, 7.5, 1.2 Hz, 1 H) ppm. ^{13}C NMR*: δ = 168.1, 151.6, 140.9, 135.8 (q, *J* = 33 Hz), 134.5, 131.1, 130.5, 126.9, 123.4, 119.3, 117.6 (q, *J* = 274 Hz) ppm. MS (c.i.): *m/z* (%) = 339 (0) [M$^+$ + 18], 337 (0) [M$^+$ + 18], 322 (52) [M$^+$ + 1], 321 (100) [M$^+$], 320 (67) [M$^+$ + 1], 319 (84) [M$^+$], 184 (8), 98 (13). $C_{11}H_5BrF_3NO_2$ (320.06): calcd. C 41.28, H 1.57; found C 41.55, H 1.40.

2-Bromo-4-(trifluoromethyl)quinoline-3-carboxylic Acids (15): At −75 °C, diisopropylamine (1.42 mL, 1.01 g, 10 mmol) and bromoquinoline (**12**; 10 mmol) were added consecutively to a solution of butyllithium (10 mmol) in tetrahydrofuran (20 mL) and hexanes (6.25 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 **14**.

2-Bromo-6-trifluoromethoxy-4-(trifluoromethyl)quinoline-3-carboxylic Acid (15d): This compound was prepared from the bromoquinoline **12d** (3.60 g, 10 mmol); colorless prisms; m.p. 176−178 °C (from ethyl acetate); yield 1.62 g, (40%). ^{1}H NMR*: δ = 8.43 (d, *J* = 9.5 Hz, 1 H), 8.28 (s, 1 H), 8.04 (d, *J* = 9.2, 2.7 Hz) ppm. ^{13}C NMR*: δ = 165.6, 151.2, 145.5, 144.4 (q, *J* = 35 Hz), 134.6, 133.9, 130.3, 129.8, 127.2, 121.7 (q, *J* = 277 Hz), 121.5 (q, *J* = 260 Hz), 118.4;) ppm. MS (c.i.): *m/z* (%) = 423 (0) [M$^+$ + 18], 421 (0) [M$^+$ + 18], 406 (33) [M$^+$ + 1], 405 (98) [M$^+$], 404 (31) [M$^+$ + 1], 403 (100) [M$^+$], 359 (59), 336 (12), 260 (7). $C_{12}H_4BrF_6NO_3$ (404.06): calcd. C 35.67, H 1.00; found C 36.03, H 0.93.

2-Bromo-8-fluoro-4-(trifluoromethyl)quinoline-3-carboxylic Acid (15i): This compound was prepared from the bromoquinoline **12i** (2.94 g, 10 mmol); colorless prisms; m.p. 211−213 °C (decomp.; from methanol); yield 2.81 g (83%). ^{1}H NMR*: δ = 8.07 (dm, *J* = 9.0 Hz, 1 H), 7.95 (ddd, *J* = 13.1, 8.0, 5.1 Hz, 1 H), 7.82 (ddd, *J* = 9.9, 8.0, 1.3 Hz, 1 H) ppm. ^{13}C NMR*: δ = 166.8, 158.7 (d, *J* = 259 Hz), 147.8, 140.1 (d, *J* = 13 Hz), 139.3 (d, *J* = 1 Hz), 133.0 (qd, *J* = 32, 3 Hz), 131.9 (d, *J* = 8 Hz), 124.5, 124.0 (q, *J* = 276 Hz), 122.3 (sext, *J* = 4 Hz), 118.2 (d, *J* = 18 Hz) ppm. MS (c.i.): *m/z* (%) = 357 (1) [M$^+$ + 18], 355 (1) [M$^+$ + 18], 340 (19) [M$^+$ + 1], 339 (77) [M$^+$], 338 (18) [M$^+$ + 1], 337 (75) [M$^+$], 293 (79), 194 (100), 101 (92). $C_{11}H_4BrF_4NO_2$ (338.05): calcd. C 39.08, H 1.19; found C 39.32, H 1.10.

2-Bromo-8-chloro-4-(trifluoromethyl)quinoline-3-carboxylic Acid (15j): This compound was prepared from the bromoquinoline **12j** (3.10 g, 10 mmol); colorless prisms; m.p. 167−169 °C (from ethyl acetate); yield 2.69 g, (78%). ^{1}H NMR*: δ = 8.19 (dm, *J* = 8.8 Hz, 1 H), 8.15 (dd, *J* = 7.7, 1.0 Hz, 1 H), 7.89 (dd, *J* = 8.5, 7.6 Hz, 1 H) ppm. ^{13}C NMR*: δ = 165.7, 145.2, 138.8, 134.0, 133.0, 132.5 (q, *J* = 32 Hz), 130.8, 125.5, 124.5 (q, *J* = 4 Hz), 123.9, 123.0 (q, *J* = 278 Hz) ppm. MS (c.i.): *m/z* (%) = 375 (0) [M$^+$ + 18], 373 (0) [M$^+$ + 18], 371 (0) [M$^+$ + 18], 358 (4) [M$^+$ + 1], 357 (17) [M$^+$], 356 (32) [M$^+$ + 1], 355 (100) [M$^+$], 354 (22) [M$^+$ + 1], 353 (84) [M$^+$], 338 (59), 311 (29), 210 (71). $C_{11}H_4BrClF_3NO_2$ (354.51): calcd. C 37.27, H 1.14; found C 36.96, H 1.18.

2,8-Dibromo-4-(trifluoromethyl)quinoline-3-carboxylic Acid (15k): This compound was prepared from the bromo quinoline **12k** (3.55 g, 10 mmol); colorless prisms; m.p. 196−198 °C (decomp.; from chloroform/ethyl acetate); yield 3.23 g, (81%). ^{1}H NMR*: δ = 8.42 (d, *J* = 8.4 Hz, 1 H), 8.28 (d, *J* = 7.5 Hz, 1 H), 7.87 (dd, *J* = 8.4, 7.3 Hz, 1 H) ppm. ^{13}C NMR*: δ = 160.6, 147.1, 139.9, 137.6, 133.6 (qr. *J* = 32 Hz), 132.1, 132.0 (q, *J* = 3 Hz), 126.2 (q, *J* = 4 Hz), 126.0, 124.8, 124.0 (q, *J* = 277 Hz) ppm. MS (c.i.): *m/z* (%) = 419 (0) [M$^+$ + 18], 417 (0) [M$^+$ + 18], 415 (0) [M$^+$ + 18], 402 (23) [M$^+$ + 1], 401 (36) [M$^+$], 400 (54) [M$^+$ + 1], 399 (61) [M$^+$]; 398 (32) [M$^+$ + 1], 397 (31) [M$^+$], 123 (71), 99 (100). $C_{11}H_4Br_2F_3NO_2$ (398.96): calcd. C 33.12, H 1.01; found C 33.44, H 0.85.

2-Bromo-8-iodo-4-(trifluoromethyl)quinoline-3-carboxylic Acid (15l): This compound was prepared from the bromo quinoline **12l** (4.02 g, 10 mmol); colorless prisms; m.p. 193−194 °C (decomp.; from ethyl acetate); yield 3.93 g, (89%). ^{1}H NMR*: δ = 8.66 (dd, *J* = 7.5, 1.4 Hz, 1 H), 8.27 (dm, *J* = 8.7 Hz, 1 h), 7.69 (dd, *J* = 8.6, 7.2 Hz, 1 H) ppm. ^{13}C NMR*: δ = 165.8, 148.4, 143.8, 138.9, 133.1 (q, *J* = 32 Hz), 131.8, 126.2 (q, *J* = 3 Hz), 123.2, 122.9 (q, *J* = 276 Hz), 102.9 ppm. MS (c.i.): *m/z* (%) = 465 (0) [M$^+$ + 18], 463 (0) [M$^+$ + 18], 448 (1) [M$^+$ + 1], 447 (2) [M$^+$], 446 (1) [M$^+$

+ 1], 445 (1) [M$^+$], 403 (94), 402 (100), 322 (19). $C_{11}H_4BrF_3INO_2$ (445.96): calcd. C 29.63, H 0.90; found C 29.94, H 1.02.

4-(Trifluoromethyl)quinoline-3-carboxylic Acids (16): These compounds were prepared as described above (see the preparation of quinolines **12 k-l**) from the 2-bromo-4-(trifluoromethyl)quinoline-3-carboxylic acids (**15**; 10 mmol) and tin chloride (1.90 g, 10 mmol).

6-(Trifluoromethoxy)-4-(trifluoromethyl)quinoline-3-carboxylic Acid (16d): This compound was prepared from bromo acid **15d** (4.04 g, 10 mmol); colorless needles; m.p. 188−189 °C (decomp.; from hexanes/ethyl acetate); yield 2.63 g, (81%). ^{1}H NMR*: δ = 9.24 (s, 1 H), 8.44 (d, J = 9.2 Hz, 1 H), 8.10 (s, 1 H), 8.01 (d, J = 9.3 Hz, 1 H) ppm. ^{13}C NMR*: δ = 167.3, 149.6, 148.0, 133.9, 130.2 (q, J = 34 Hz), 128.5, 126.2, 123.9 (q, J = 276 Hz), 123.3, 121.5 (q, J = 259 Hz), 116.2 ppm. MS (c.i.): m/z (%) = 343 (0) [M$^+$ + 18], 326 (40) [M$^+$ + 1], 325 (100) [M$^+$], 281 (40), 104 (43). $C_{12}H_5F_6NO_3$ (325.17): calcd. C 44.33, H 1.55; found C 44.55, H 1.37.

8-Fluoro-4-(trifluoromethyl)quinoline-3-carboxylic Acid (16i): This compound was prepared from bromo acid **15i** (3.38 g, 10 mmol); colorless prisms; m.p. 217−219 °C (reprod.; from chloroform/ethyl acetate); yield 2.15 g, (83%). ^{1}H NMR*: δ = 9.19 (s, 1 H), 8.09 (m, 1 H), 7.91 (ddd, J = 8.6, 7.9, 5.3 Hz, 1 H), 7.77 (ddd, J = 10.2, 8.0, 1.3 Hz, 1 H) ppm. ^{13}C NMR*: δ = 168.3, 159.7 (d, J = 257 Hz), 149.8 (d, J = 2 Hz), 140.8 (d, J = 13 Hz), 131.5 (d, J = 8 Hz), 131.2 (qd, J = 32, 3 Hz), 129.0 (d, J = 3 Hz), 125.3, 124.9 (q, J = 276 Hz), 122.3 (m), 117.0 (d, J = 19 Hz) ppm. MS (c.i.): m/z (%) = 277 (0) [M$^+$ + 18], 260 (100) [M$^+$ + 1], 259 (99) [M$^+$], 194 (15). $C_{11}H_5F_4NO_2$ (259.16): calcd. C 50.98, H 1.94; found C 50.88, H 1.82.

8-Chloro-4-(trifluoromethyl)quinoline-3-carboxylic Acid (16j): This compound was prepared from bromo acid **15j** (3.55 g, 10 mmol); colorless prisms; m.p. 210−212 °C (reprod.; from hexanes/ethyl acetate); yield 2.45 g, (89%);^{1}H NMR*: δ = 9.24 (s, 1 H), 8.25 (dm, J = 8.7 Hz, 1 H), 8.17 (dd, J = 7.7, 1.4 Hz, 1 H), 7.88 (dd, J = 9.0, 7.8 Hz, 1 H) ppm. ^{13}C NMR*: δ = 167.4, 149.4, 145.9, 135.5, 132.3, 130.9 (q, J = 32 Hz), 130.5, 128.2 (q, J = 3 Hz), 124.7 (q, J = 4 Hz), 124.5 (q, J = 276 Hz) ppm. MS (c.i.): m/z (%) = 295 (0) [M$^+$ + 18], 293 (0) [M$^+$ + 18], 278 (26) [M$^+$ + 1], 277 (50) [M$^+$], 276 (86) [M$^+$ + 1], 275 (100) [M$^+$], 258 (52), 99 (26). $C_{11}H_5ClF_3NO_2$ (275.61): calcd. C 47.94, H 1.83; found C 47.97, H 1.54.

8-Bromo-4-(trifluoromethyl)quinoline-3-carboxylic Acid (16k): This compound was prepared from bromo acid **15k** (3.39 g, 10 mmol); colorless prisms; m.p. 191−192 °C (from hexanes/ethyl acetate); yield 2.87 g, (78%). ^{1}H NMR*: δ = 9.24 (s, 1 H), 8.39 (dd, J = 7.6, 1.0 Hz, 1 H), 8.30 (d, J = 8.6 Hz, 1 H), 7.83 (dd, J = 8.7, 7.6 Hz, 1 H) ppm. ^{13}C NMR*: δ = 169.7, 148.6, 143.7, 136.0, 132.3 (q, J = 32 Hz), 129.0, 128.3, 125.0, 124.5 (q, J = 276 Hz), 122.3, 110.8 ppm. MS (c.i.): m/z (%) = 339 (18) [M$^+$ + 18], 337 (20) [M$^+$ + 18], 322 (100) [M$^+$ + 1], 321 (36) [M$^+$], 320 (84) [M$^+$ + 1], 319 (2) [M$^+$], 277 (30), 275 (29). $C_{11}H_5BrF_3NO_2$ (320.06): calcd. C 41.28, H 1.57; found C 41.47, H 1.60.

8-Iodo-4-(trifluoromethyl)quinoline-3-carboxylic Acid (16l): This compound was prepared from bromo acid **15l** (4.46 g, 10 mmol); short colorless needles; m.p. 174−176 °C (from hexanes/ethyl acetate); yield 3.05 g, (83%). ^{1}H NMR*: δ = 9.13 (s, 1 H), 8.10 (dm, J = 8.6 Hz, 1 H), 7.85 (d, J = 7.0 Hz, 1 H), 7.77 (dd, J = 8.6, 7.1 Hz, 1 H) ppm. ^{13}C NMR*: δ = 168.8, 149.6, 148.3, 140.2, 133.0, 132.3 (q, J = 32 Hz), 130.9, 127.9 (q, J = 3 Hz), 125.2 (q, J = 276 Hz), 124.0 (q, J = 4 Hz), 123.6 ppm. MS (c.i.): m/z (%) = 385 (0) [M$^+$ + 18], 368 (100) [M$^+$ + 1], 367 (86) [M$^+$], 322 (8), 100 (22). $C_{11}H_5F_3INO_2$ (367.06): calcd. C 35.99, H 1.37; found C 36.25, H 1.61.

8-Bromo-2-iodo-4-(trifluoromethyl)quinoline (18): A mixture of 2,8-dibromo-4-(trifluoromethyl)quinoline (**12k**; 5.32 g, 15 mmol), sodium iodide (6.75 g, 45 mmol), and propionitrile (15 mL) was heated under reflux for 2 h. After distillation of the solvent, the residue was crystallized in pentanes, affording colorless needles; m.p. 97−99 °C; yield 5.37 g, (89%). ^{1}H NMR: δ = 8.15 (d, J = 7.6 Hz, 1 H), 8.07 (s, 1 H), 8.05 (d, J = 9.1 Hz, 1 H), 7.55 (dd, J = 8.6, 7.5 Hz, 1 H) ppm. ^{13}C NMR: δ = 147.1, 134.9 (q, J = 33 Hz), 134.7, 130.0 (q, J = 6 Hz), 129.1, 125.2, 123.9, 123.3, 121.8 (q, J = 276 Hz), 117.2 ppm. MS (c.i.): m/z (%) = 421 (0) [M$^+$ + 18], 419 (0) [M$^+$ + 18], 404 (99) [M$^+$ + 1], 403 (83) [M$^+$], 402 (100) [M$^+$ + 1], 401 (33) [M$^+$], 293 (9), 291 (9). $C_{10}H_4BrF_3IN$ (401.95): calcd. C 29.88, H 1.00; found C 30.18, H 1.00.

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