Recommendable Routes to Trifluoromethyl-Substituted Pyridine- and Quinolinecarboxylic Acids

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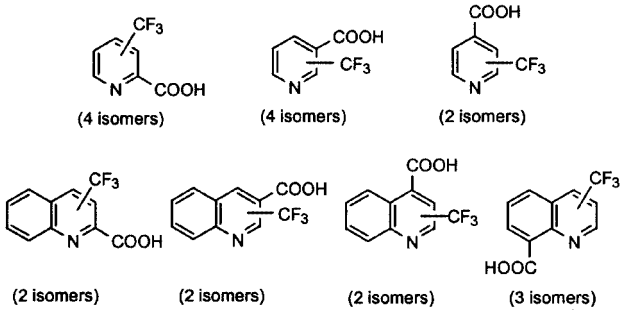
As part of a case study, rational strategies for the preparation of all ten 2-, 3-, or 4-pyridinecarboxylic acids and all nine 2-, 3-, 4-, or 8-quinolinecarboxylic acids bearing trifluoromethyl substituents at the 2-, 3-, or 4-position were elaborated. The trifluoromethyl group, if not already present in the precursor, was introduced either by the deoxygenative fluorination of suitable carboxylic acids with sulfur tetrafluoride or by the displacement of ring-bound bromine or iodine by trifluoromethylcopper generated in situ. The carboxy function was produced by treatment of organolithium or organomagnesium intermediates, products of halogen/metal or hydrogen/metal permutation, with carbon dioxide.

Introduction

After nitrogen, fluorine occupies the position of second favorite heteroelement in life science-oriented research.[1−5] Over 10% of newly registered pharmaceutical drugs[6,7] and some 40% of newly registered agrochemicals[8,9] contain one or more fluorine atoms. The halogen is often incorporated as a *p*-fluorophenyl group, but (trifluoromethyl)phenyl entities are also not infrequent. In contrast, fluorinated or, even more so, trifluoromethyl-substituted heterocycles are relatively rare. This is especially true if the simultaneous presence of a carboxy or similar functional group is required.

We have previously investigated[10] how (trifluoromethyl)-pyridines and (trifluoromethyl)quinolines can be directly converted into functional derivatives by application of a simple metalation/carboxylation sequence. Thus, four pyridinecarboxylic acids and five quinolinecarboxylic acids, all bearing trifluoromethyl substituents, were made accessible in a most straightforward manner. With this achieved, we started to look for another set of methods that would allow one to prepare, in a rational − even if more lengthy − way, all ten trifluoromethyl-substituted 2-, 3-, and 4-pyridinecarboxylic acids and all nine 2-, 3-, 4-, and 8-quinolinecarboxylic acids bearing the trifluoromethyl group in the heterocyclic ring.



Obviously the crucial issue is at what stage and how to introduce the trifluoromethyl substituent. The most advantageous solution to this problem would of course be to identify a suitable precursor already containing the CF_3 group. Thus, 2-chloro-3-(trifluoromethyl)pyridine and 2-chloro-5-(trifluoromethyl)pyridine are commercially available at a reasonable cost (400 and 100 EUR/mol, respectively) whereas the prices of three other isomers, 2-chloro-4-(trifluoromethyl)pyridine,2-chloro-6-(trifluoromethyl)pyridine, and 3-chloro-5-(trifluoro-methyl)pyridine (at 14000, 70000, and 10000 EUR/mol, respectively) are prohibitive. Three methods for the de novo creation of trifluoromethyl

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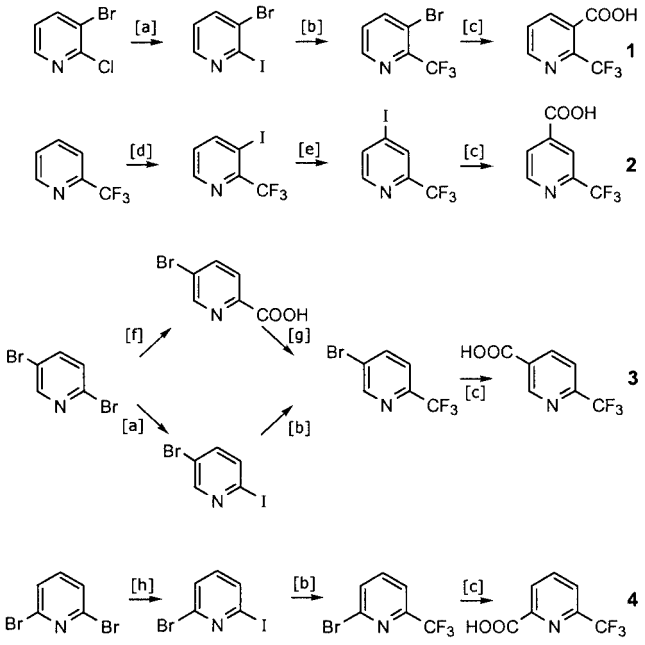
substituents warrant consideration. Perchloration of pyridine- or quinoline-attached methyl groups and subsequent Lewis acid-catalyzed chlorine/fluorine displacement with hydrogen fluoride is most attractive from an industrial point of view,[11] while the fluorinative deoxygenation of carboxylic acids with sulfur tetrafluoride[12] or, particularly, the treatment of bromo or iodo derivatives of pyridines and quinolines with trifluoromethylcopper generated in situ[13–16] can be accomplished more conveniently on a laboratory scale.

The most economical route to the carboxy function would presumably be palladium-catalyzed halogen/cyano exchange[17,18] and subsequent hydrolysis of the resulting nitrile, or the palladium- or nickel-catalyzed carbonylation[19] of chloro or bromo derivatives of hetarenes. However, for operational simplicity, we preferred to make the acids by carboxylation of organolithium or organomagnesium intermediates, which could easily be generated by hydrogen/metal or halogen/metal permutation.

Many of the required halopyridines were obtained by silane-mediated chlorine/bromine exchange.[20] A final key step in several preparative sequences was the reductive removal of bromine that had temporarily served as a protective group and deprotonation promoter.

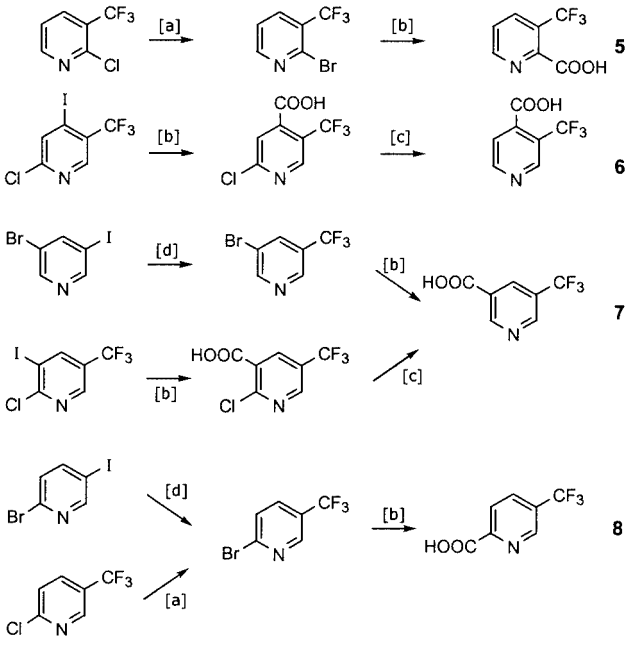
Trifluoromethyl-Substituted Pyridinecarboxylic Acids

2-Trifluoromethyl-3-pyridinecarboxylic acid (**1**; 61% overall) was prepared from 3-bromo-2-iodopyridine (made in four steps from 2-chloropyridine) by trifluoromethylating displacement of iodine at the 2-position, followed by consecutive halogen/metal permutation and carboxylation. To obtain 2-trifluoromethyl-4-pyridinecarboxylic acid (**2**; 45% overall), 2-(trifluoromethyl)pyridine[16] was deprotonated and iodinated at the 3-position before being subjected to a base-mediated halogen migration[21,22] and subsequent halogen/metal permutation and carboxylation. When 2,5-dibromopyridine was treated with butyllithium in toluene, halogen/metal permutation occurred regioselectively at the 2-position.[23] The 5-bromo-2-pyridinecarboxylic acid (64%) obtained upon carboxylation was converted into 5-bromo-2-(trifluoromethyl)pyridine (33%) by use of sulfur tetrafluoride. The 6-trifluoromethyl-3-pyridinecarboxylic acid (**3**; 85%) was again prepared by application of the halogen/metal permutation and carboxylation sequence to 5-bromo-2-(trifluoromethyl)pyridine. The latter compound was in turn made from 2,5-dibromopyridine, either through the 5-bromo-2-pyridinecarboxylic acid (by selective bromine/lithium exchange[23]), which was then treated with sulfur tetrafluoride (21% overall) or through 5-bromo-2-iodopyridine, which was then subjected to a halogen/trifluoromethyl displacement (60% overall[16]). In the same way, 6-trifluoromethyl-2-pyridinecarboxylic acid (**4**; 87%) was obtained from 2-bromo-6-(trifluoromethyl)pyridine, which was in turn derived from 2-bromo-6-iodopyridine by trifluoromethylating displacement of iodine.[16]



[a] $ClSi(CH_3)_3$ and NaI in H_5C_2CN, 100 °C. [b] $(H_3C)_3SiCF_3$, CuI, KF, 25 °C. [c] (1.) LiC_4H_9 in tetrahydrofuran (THF), -75 °C; (2.) CO_2; (3.) neutralization. [d] (1.) Lithium diisopropylamide (LIDA) in THF, -75 °C; (2.) I_2. [e] (1.) LIDA in THF, -75 °C; (2.) H_2O. [f] (1.) LiC_4H_9 in toluene, -75 °C; (2.) CO_2; (3.) neutralization. [g] SF_4, HF, 125 °C [h] (1.) $ClMgCH(CH_3)_2$ in THF, 25 °C; (2.) I_2.

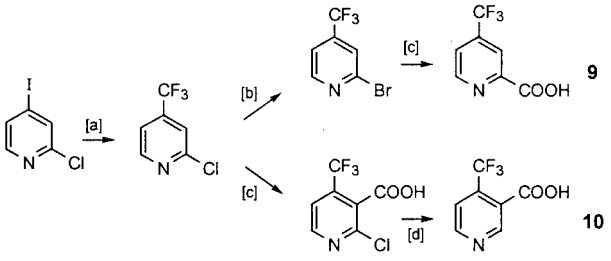
The preparation of the four pyridinecarboxylic acids **5**–**8**, each bearing the trifluoromethyl group in the 3-position, again relied heavily on halogen/metal permutation followed by carboxylation. Thus, 2-bromo-3-(trifluoromethyl)-pyridine, 3-bromo-5-(trifluoromethyl)pyridine, and 2-



[a] $BrSi(CH_3)_3$ in H_5C_2CN at 100 °C. [b] (1.) LiC_4H_9 in toluene or tetrahydrofuran (THF) at -75 °C; (2.) CO_2; (3.) neutralization. [c] $HCOONH_4$, Pd/C in $HOCH_3$, 25 °C. [d] $(H_3C)_3SiCF_3$, CuI, KF, 25 °C.

bromo-5-(trifluoromethyl)pyridine, produced either through silane-mediated chlorine/bromine exchange[20] or by copper-promoted iodine/trifluoromethyl displacement,[16] were converted into 3-trifluoromethyl-2-pyridinecarboxylic acid (**5**; 68%), 5-trifluoromethyl-3-pyridinecarboxylic acid (**7**; 33%), and 5-trifluoromethyl-2-pyridinecarboxylic acid (**8**; 67%), respectively. An alternative reaction sequence consisted of the deprotonation and subsequent carboxylation of commercially available 2-chloro-5-(trifluoromethyl)pyridine derivatives and subsequent reductive removal of the heavier halogen. In this way, the 3-trifluoromethyl-4-pyridinecarboxylic acid (**6**; 70%) and, again, the 5-trifluoromethyl-3-pyridinecarboxylic acid (**7**; 57%) were prepared.

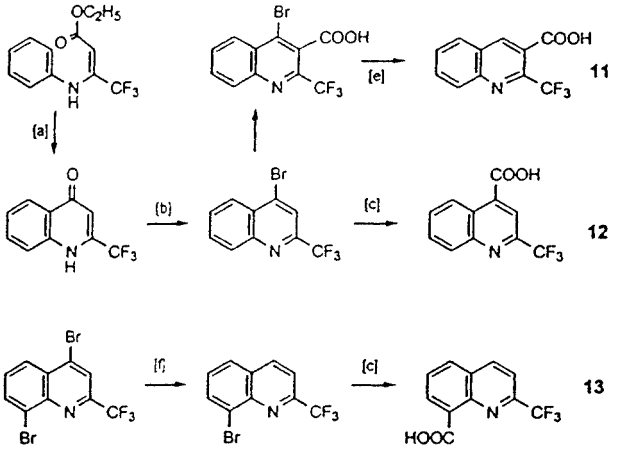
The route to the 4-trifluoromethyl-substituted pyridinecarboxylic acids **9** and **10** was once more based on the methodical principles already outlined. 2-Bromo-4-(trifluoromethyl)pyridine (65%) was obtained by the reaction of 2-chloro-4-(trifluoromethyl)pyridine[16] with bromotrimethylsilane.[20] Consecutive treatment with butyllithium, carbon dioxide and hydrochloric acid provided the 4-trifluoromethyl-2-carboxylic acid (**9**; 54%), whereas deprotonation with lithium diisopropylamide followed by carboxylation, neutralization, and dechlorinative hydrogenation produced the isomeric 4-trifluoromethyl-3-pyridinecarboxylic acid (**10**; overall 73%).



[a] $(H_3C)_3SiCF_3$, CuI, KF, 25 °C. [b] $BrSi(CH_3)_3$ in H_5C_2CN at 100 °C. [c] (1.) LiC_4H_9 in toluene or THF at −75 °C; (2.) CO_2; (3.) neutralization. [d] (1.) LIDA in THF at −75 °C; (2.) CO_2; (3.) neutralization. [e] $HCOONH_4$, Pd/C in $HOCH_3$ at 25 °C.

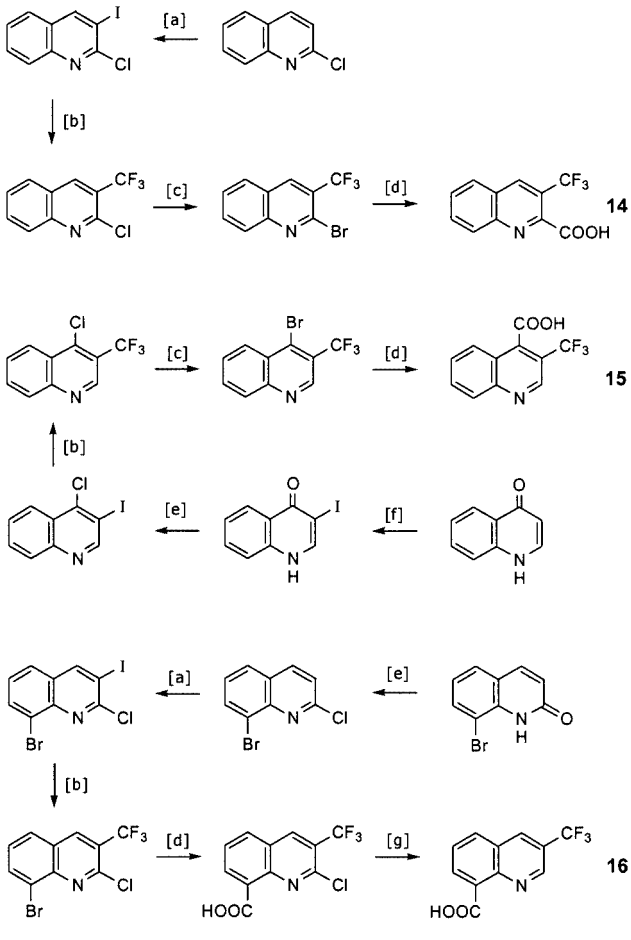
Trifluoromethyl-Substituted Quinolinecarboxylic Acids

4-Bromo- and 4,8-dibromo-2-(trifluoromethyl)quinoline, the key intermediates in the production of the 2-trifluoromethyl-substituted 3-, 4- and 8-quinolinecarboxylic acids, emanated from the acid-catalyzed cyclocondensation of ethyl 4,4,4-trifluoroacetoacetate with aniline and 2-bromoaniline, respectively.[24] 4-Bromo-2-(trifluoromethyl)quinoline was transformed into the 2-trifluoromethyl-4-quinolinecarboxylic acid (**12**; 88%) by butyllithium-promoted halogen/metal permutation followed by carboxylation and neutralization, and also into the isomeric 2-trifluoromethyl-3-quinolinecarboxylic acid (**11**; 80%) by consecutive deprotonation with LIDA, carboxylation and reductive hydrogenation. The 4,8-dibromo-2-(trifluoromethyl)quinoline was first selectively debrominated at the 4-position[24] before being subjected to a halogen/metal permutation and carboxylation, to afford the 2-trifluoromethyl-8-quinolinecarboxylic acid (**13**) in 73% yield.



[a] PPA, 150 °C. [b] $POBr_3$, 150 °C. [c] (1.) LiC_4H_9 in THF, -75 °C; (2.) CO_2; (3.) neutralization. [d] (1.) LIDA in THF, -75 °C; (2.) CO_2; (3.) neutralization. [e] (1.) LiC_4H_9 in THF, -100 °C; (2.) $HOCH_3$. [f] (1.) LiC_4H_9 in THF, -75 °C; (2.) $HOCH_3$.

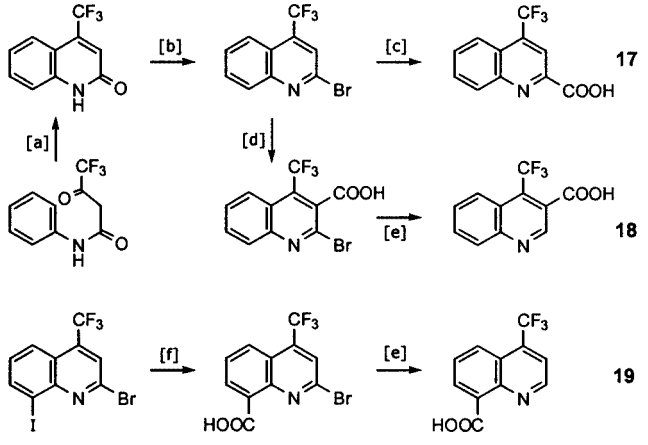
The trifluoromethyl group at the 3-position of the quinolinecarboxylic acids **14**−**16** was introduced by the re-



[a] (1.) LIDA in THF, -75 °C; (2.) I_2. [b] $(H_3C)_3SiCF_3$, CuI, KF, 50 °C. [c] $BrSi(CH_3)_3$ in H_5C_2CN, 100 °C. [d] (1.) LiC_4H_9 in toluene or THF, -75 °C; (2.) CO_2; (3.) neutralization. [e] $POCl_3$, 125 °C. [f] ICl in H_3CCOOH at 80 °C. [g] $HCOONH_4$, Pd/C in $HOCH_3$, 25 °C.

action of a suitable chloro-3-iodoquinoline with trifluoromethylcopper generated in situ.[16] Subsequent chlorine/bromine displacement[20] at the 2- and 4-positions gave intermediates which, when consecutively subjected to halogen/metal permutation and carboxylation, provided the acids **14** and **15** in 54% and 59% overall yields, respectively. The remaining isomer **16** was produced from 8-bromo-2-chloro-3-iodoquinoline by a sequence comprising iodine/trifluoromethyl substitution (64%), halogen/metal permutation followed by carboxylation (68%), and dechlorinating hydrogenation (54%).

By means of a high-temperature protocol, the cyclocondensation between ethyl 4,4,4-trifluoroacetylacetate and aniline can be reoriented towards the 4-trifluoromethyl-2(1*H*)-quinolinone and, from 2-iodoaniline, towards the 8-iodo-4-trifluoromethyl-2(1*H*)-quinolinone.[25] The corresponding 2-bromoquinolines were obtained by the reaction with phosphorus oxybromide. Upon consecutive treatment with butyllithium and dry ice, they afforded the 4-trifluoromethyl-2-quinolinecarboxylic acid (**17**; 72%) and 2-bromo-4-trifluoromethyl-3-quinolinecarboxylic acid (88%), respectively. Debromination of the latter compound gave 4-(trifluoromethyl)-8-quinolinecarboxylic acid (**19**; 79%). The 2-bromo-4-trifluoromethyl-3-quinolinecarboxylic acid (88%) was formed by deprotonation of 2-bromo-4-(trifluoromethyl)quinoline with LIDA and subsequent carboxylation. Butyllithium-promoted debromination gave the 4-trifluoromethyl-3-quinolinecarboxylic acid (**18**; 64%).



[a] 76% H_2SO_4, 90 °C. [b] $POBr_3$, 140 °C. [c] (1.) LiC_4H_9 in THF, -75 °C; (2.) CO_2; (3.) neutralization. [d] (1.) LIDA in THF, -75 °C; (2.) CO_2; (3.) neutralization. [e] (1.) LiC_4H_9 in diethyl ether, -100 °C; (2.) $HOCH_3$. [f] (1.) $ClMgCH(CH_3)_2$ in THF, -75 °C; (2.) CO_2; (3.) neutralization.

In summary, the trifluoromethyl-substituted quinolinecarboxylic acids **11**–**19** and the corresponding pyridinecarboxylic acids **1**–**10** can be prepared in a few uncomplicated and generally high-yielding steps. This once more illustrates the versatility and operational advantages of organometallic methods in synthesis.

Experimental Section

^1H and ^{13}C NMR spectra of samples dissolved in deuteriochloroform (or, if marked by an asterisk, in perdeuterioacetone) were recorded at 400 and 101 MHz, respectively, chemical shifts being given relative to tetramethylsilane (δ = 0.00 ppm). Working habits and abbreviations have been explained in previous publications from this laboratory.[26–28]

1. Bromochloro- and Bromoiodopyridines

3-Bromo-2-chloropyridine: A solution of 2-chloro-3-(trimethylsilyl)pyridine[29,30] (56 g, 0.30 mol) and bromine (23 mL, 72 g, 0.45 mol) in tetrachloromethane (0.15 L) was heated under reflux for 3 days (75 h). Upon immediate distillation, a yellowish oil was collected. This solidified; m.p. 54–56 °C (colorless needles from pentanes) (ref.[31] m.p. 55 °C); b.p. 95–97 °C/10 Torr; yield: 53.1 g (92%).

2,3-Dibromopyridine: A mixture of 3-bromo-2-chloropyridine (38 g, 0.20 mol) and bromotrimethylsilane (37 mL, 46 g, 0.30 mol) in propionitrile (0.10 L) was heated under reflux for 2 days (50 h) in a flask connected to a reflux condenser, the cooling jacket of which was kept at +75 °C by a continuous flow of warm water. The chlorotrimethylsilane formed was allowed to escape through the calcium chloride tube attached at the condenser outlet. The propionitrile and excess bromotrimethylsilane were evaporated off. The residue was taken up in aqueous sodium hydroxide (2.0 M, 0.10 L) and extracted with diethyl ether (3 × 0.10 L). The combined organic layers were dried and the solvents were evaporated. Distillation of the residue afforded a colorless oil, which rapidly solidified; m.p. 58–59 °C (ref.[32] m.p. 58.5–59.5 °C); b.p. 117–119 °C /15 Torr; yield: 42.2 g (89%).

3-Bromo-2-iodopyridine: A mixture of 2,3-dibromopyridine (47 g, 0.20 mol), chlorotrimethylsilane (25 mL, 22 g, 0.20 mol), sodium iodide (90 g, 0.60 mol), and propionitrile (0.20 L) was heated under reflux for 3 days (75 h). The product was isolated by distillation as a light yellow oil, which later solidified; colorless needles (from hexanes); m.p. 50–52 °C; b.p. 137–139 °C/13 Torr; yield: 42.0 g, (74%). ^1H NMR: δ = 8.31 (dd, *J* = 4.6, 1.7 Hz, 1 H), 7.82 (dd, *J* = 8.1, 1.9 Hz, 1 H), 7.16, (dd, *J* = 8.1, 4.6 Hz, 1 H) ppm. ^{13}C NMR: δ = 148.2, 139.7, 129.8, 124.0, 123.7. C_5H_3BrIN (283.89): calcd. C 21.15, H 1.06; found C 21.33, H 1.02. If 2,3-dibromopyridine was replaced by its precursor 3-bromo-2-chloropyridine, only a 41% yield of 3-bromo-2-iodopyridine was obtained under otherwise identical conditions.

5-Bromo-2-iodopyridine: This compound was prepared analogously, from 2,5-dibromopyridine (47 g, 0.20 mol), except that the reflux time was extended to 5 days (125 h); colorless platelets (from acetone); m.p. 110–111 °C (ref.[33] m.p. 113 °C); yield: 49.4 g (87%).

2. Bromo-, Iodo- and Chloroiodo(trifluoromethyl)pyridines

3-Bromo-2-(trifluoromethyl)pyridine: Copper(I) iodide (21 g, 0.11 mol) and spray-dried anhydrous potassium fluoride (6.4 g, 0.11 mol) were heated with a Bunsen burner under reduced pressure (1 Torr) while being gently shaken until a homogeneously greenish powder was obtained. After the addition of 3-bromo-2-iodopyridine (28 g, 0.10 mol), (trifluoromethyl)trimethylsilane (15 mL, 14 g, 0.10 mol), and *N*-methylpyrrolidinone (0.10 L), the suspension was vigorously stirred at +25 °C, until after 3–6 h it had turned into a brown solution and all the fluorotrimethylsilane formed had escaped. The mixture was poured into aqueous ammonia (12%, 0.20 L) and extracted with diethyl ether (3 × 50 mL). The com-

bined organic layers were washed with aqueous ammonia (12%, 3 × 50 mL) and brine (2 × 50 mL) and dried, and the solvents were evaporated. The residue was purified by distillation; m.p. 34−36 °C (colorless prisms from hexanes); b.p. 97−99 °C/35 Torr; yield: 23.0 g (74%). ^{1}H NMR: δ = 8.63 (dd, *J* = 4.6, 1.0 Hz, 1 H), 8.08 (dm, *J* = 8.1 Hz, 1 H), 7.39, (dd, *J* = 8.1, 4.6 Hz, 1 H) ppm. ^{13}C NMR: δ = 147.1, 146.0 (q, *J* = 34 Hz), 143.0, 127.3, 121.0 (q, *J* = 275 Hz), 118.1. $C_6H_3BrF_3N$ (225.99): calcd. C 31.89, H 1.34; found C 32.02, H 1.33.

5-Bromo-2-(trifluoromethyl)pyridine:[16] This compound was prepared analogously, from 5-bromo-2-iodopyridine (28 g, 0.10 mol); purified by distillation; colorless needles (from hexanes); m.p. 37−39 °C; b.p. 76−78 °C/23 Torr; yield: 15.6 g (69%). ^{1}H NMR: δ = 8.79 (d, *J* = 1.9 Hz, 1 H), 8.02 (dd, *J* = 8.3, 1.9 Hz, 1 H), 7.59 (d, *J* = 8.3 Hz, 1 H) ppm. ^{13}C NMR: δ = 151.3, 146.6 (q, *J* = 35 Hz), 140.0, 124.0, 121.7, 121.3 (q, *J* = 274 Hz). $C_6H_3BrF_3N$ (226.00): calcd. C 31.89, H 1.34, N 6.20; found C 31.75, H 1.40, N 6.24. When 2,5-dibromopyridine was used instead of 5-bromo-2-iodopyridine, only a 1:1 mixture of starting material and 5-bromo-2-(trifluoromethyl)pyridine was obtained even after 20 h of reaction time, but the product was regioisomerically uncontaminated. 5-Bromo-2-(trifluoromethyl)pyridine was also made in 33% yield by treatment of 5-bromo-2-pyridinecarboxylic acid (see following paragraph; 35 g, 0.17 mol) with sulfur tetrafluoride (0.44 mol) and hydrogen fluoride (1.7 mol) in an autoclave for 20 h at 125 °C.

5-Bromo-2-pyridinecarboxylic Acid: 2,5-Dibromopyridine (71 g, 0.30 mol) was added to a solution of butyllithium (0.30 mol) in toluene (0.42 L) and hexanes (0.18 L), kept in a methanol/dry ice bath. After 2 h at −75 °C, the mixture was poured onto an excess of freshly crushed dry ice. After evaporation of the volatiles, the residue was dissolved in water (0.30 L). The product precipitated upon neutralization with concentrated hydrochloric acid; colorless prisms (from acetic acid); m.p. 173−174 °C (ref.[34] 175 °C); yield: 38.8 g (64%). ^{1}H NMR: δ = 8.81 (d, *J* = 2.5 Hz, 1 H), 8.27 (dd, *J* = 8.4, 2.3 Hz, 1 H), 8.10 (dd, *J* = 8.4, 1.0 Hz, 1 H) ppm. ^{13}C NMR: δ = 166.1, 152.0, 148.3, 142.1, 127.8, 126.5.

2-Bromo-3-(trifluoromethyl)pyridine: A mixture of 2-chloro-3-(trifluoromethyl)pyridine (18 g, 0.10 mol) and bromotrimethylsilane (26 mL, 31 g, 0.20 mol) in propionitrile (0.10 L) was alternately heated under reflux and cooled to +50 °C in 1 h intervals for a total period of 3 days. Upon distillation a colorless oil was collected, and was crystallized from hexanes as prisms; m.p. 37−39 °C; b.p. 67−69 °C/9 Torr; yield: 18.5 g (82%). ^{1}H NMR: δ = 8.55 (d, *J* = 4.8 Hz, 1 H), 7.99 (d, *J* = 7.7 Hz, 1 H), 7.42 (dd, *J* = 7.7, 4.8 Hz, 1 H) ppm. ^{13}C NMR: δ = 152.6, 139.6, 136.4 (q, *J* = 5 Hz), 127.9 (q, *J* = 35 Hz), 122.3 (q, *J* = 273 Hz), 122.3. $C_6H_3BrF_3N$ (225.99): calcd. C 31.89, H 1.34, N 6.20; found C 32.03, H 1.63, N 6.18.

2-Bromo-5-(trifluoromethyl)pyridine:[16] A solution of 2-chloro-5-(trifluoromethyl)pyridine (18 g, 0.10 mol) and bromotrimethylsilane (26 mL, 31 g, 0.20 mol) in propionitrile (0.10 L) was heated under reflux for 20 h, after which the product was isolated by distillation; colorless prisms (from hexanes); m.p. 43−44 °C; b.p. 98−99 °C/50 Torr; yield: 17.2 g (76%). ^{1}H NMR: δ = 8.66 (s, 1 H), 7.80 (dd, *J* = 8.5, 2.5 Hz, 1 H), 7.66 (d, *J* = 8.4 Hz, 1 H) ppm. ^{13}C NMR: δ = 147.1 (q, *J* = 4 Hz), 145.9, 135.3(q, *J* = 3 Hz), 128.3, 126.0 (q, *J* = 33 Hz), 123.1 (q, *J* = 273 Hz). $C_6H_3BrF_3N$ (225.99):calcd. C 31.89, H 1.34, N 6.20; found C 32.12, H 1.33, N 6.30.

2-Bromo-4-(trifluoromethyl)pyridine: This compound was prepared analogously, from 2-chloro-4-(trifluoromethyl)pyridine[16] (18 g, 0.10 mol); colorless oil; m.p. −21 to − 20 °C; b.p. 161−162 °C; yield: 14.8 g (65%). ^{1}H NMR: δ = 8.60 (d, *J* = 5.8 Hz, 1 H), 7.75 (symm. m, 1 H), 7.51 (d, *J* = 5.1 Hz, 1 H) ppm. ^{13}C NMR: δ = 151.3, 143.0, 140.6 (q, *J* = 35 Hz), 124.3, 121.9 (q, *J* = 274 Hz), 118.5. $C_6H_3BrF_3N$ (225.99): calcd. C 31.89, H 1.34, N 6.20; found C 32.03, H 1.63, N 6.18.

2-Iodo-5-(trifluoromethyl)pyridine: This compound was prepared from 2-chloro-5-(trifluoromethyl)pyridine (36 g, 0.20 mol) and chlorotrimethylsilane (24 mL, 22 g, 0.20 mol) in the presence of sodium iodide (60 g, 0.40 mol) in propionitrile (0.10 L) as described above (see the preparation of 3-bromo-2-iodopyridine); colorless needles (from hexanes); m.p. 82−83 °C (ref.[35] m.p. 77−80 °C); yield: 44.6 g (82%). ^{1}H NMR: δ = 8.64 (s, 1 H), 7.91 (d, *J* = 8.2 Hz, 1 H), 7.56 (d, *J* = 8.2 Hz, 1 H) ppm. ^{13}C NMR: δ = 147.3 (q, *J* = 4 Hz), 135.0, 134.2 (q, *J* = 3 Hz), 126.2 (q, *J* = 33 Hz), 123.3 (q, *J* = 272 Hz), 122.1. $C_6H_3F_3IN$ (272.99): calcd. C 26.40, H 1.11, N 5.13; found C 26.27, H 1.32, N 5.06.

3-Iodo-2-(trifluoromethyl)pyridine: 2,2,6,6-Tetramethylpiperidine (8.5 mL, 7.1 g, 50 mmol) and 2-(trifluoromethyl)pyridine[16,36] (5.8 mL, 7.4 g, 50 mmol) were added consecutively to a solution of butyllithium (50 mmol) in tetrahydrofuran (50 mL) and hexanes (30 mL), cooled in a dry ice/methanol bath. After 2 h at −75 °C, the mixture was treated with iodine (0.10 mol) and then poured into aqueous sodium thiosulfate (1.0 M, 50 mL), which was then extracted with diethyl ether (3 × 50 mL). The product was purified by steam distillation and subsequent crystallization from hexanes; colorless needles; m.p. 42−43 °C; yield: 12.2 g (89%). ^{1}H NMR: δ = 8.63 (dd, *J* = 4.6, 1.2 Hz,1 H), 8.36 (d, *J* = 8.0 Hz, 1 H), 7.20 (dd, *J* = 8.0, 4.6 Hz, 1 H) ppm. ^{13}C NMR: δ = 149.8, 148.9 (q, *J* = 33 Hz), 147.4, 127.1, 121.0 (q, *J* = 275 Hz), 88.8. $C_6H_3F_3IN$ (272.99): calcd. C 26.40, H 1.11, N 5.13; found C 26.22, H 1.19, N 5.15.

4-Iodo-2-(trifluoromethyl)pyridine: Diisopropylamine (1.4 mL, 1.0 g, 20 mmol) and 3-iodo-2-(trifluoromethyl)pyridine (5.5 g, 20 mmol) were added consecutively to a solution of butyllithium (20 mmol) in tetrahydrofuran (20 mL) and hexanes (12 mL). After 2 h at −75 °C, the mixture was neutralized with methanol (1.0 mL, 0.8 g, 25 mmol), the solvents were evaporated, and the residue was crystallized from hexanes; colorless needles; m.p. 24−26 °C; yield: 3.33 g (61%). ^{1}H NMR: δ = 8.40 (d, *J* = 5.1 Hz, 1 H), 8.06 (s, 1 H), 7.90 (d, *J* = 5.1 Hz, 1 H) ppm. ^{13}C NMR: δ = 150.0, 148.8 (q, *J* = 35 Hz), 135.7, 130.0, 120.6 (q, *J* = 276 Hz), 106.1. $C_6H_3F_3IN$ (272.99): calcd. C 26.40, H 1.11, N 5.13; found C 26.35, H 1.24, N 5.17.

2-Chloro-4-iodo-5-(trifluoromethyl)pyridine: Tetrahydrofuran (0.15 L), diisopropylamine (14 mL, 10 g, 0.10 mol), lithium bromide (0.87 g, 10 mmol), and lithium *N*,*N*-diisopropylcarbamate (15 g, 0.10 mol; freshly prepared from molar equivalents of diisopropylamine and butyllithium and an excess of carbon dioxide gas in tetrahydrofuran, isolated as a white powder after evaporation of the volatiles and drying) were added consecutively, at 0 °C, to butyllithium (0.10 mol) in hexanes (60 mL). The mixture was vigorously stirred until it became homogeneous. It was then placed in a dry ice/methanol bath and, after the addition of neat 2-chloro-5-(trifluoromethyl)pyridine (18 g, 0.10 mol), was kept for 2 h at −75 °C, after which iodine (25 g, 0.10 mol) in tetrahydrofuran (0.15 L) was rapidly added. After the mixture had been kept for 45 min at −75 °C, the solvents were evaporated, and the residue was taken up in diethyl ether (0.10 L), washed with saturated aqueous sodium thiosulfate (50 mL), hydrochloric acid (2.0 M, 2 × 100 mL), saturated aqueous sodium hydrogen carbonate (50 mL), and brine (2

× 50 mL), and dried, and the solvents were again evaporated. Crystallization from ethanol gave colorless platelets; m.p. 126−127 °C; yield: 20.6 g (67%). ^{1}H NMR: δ = 8.55 (s, 1 H), 8.04 (s, 1 H) ppm. ^{13}C NMR: δ = 154.9, 147.1 (q, *J* = 6 Hz), 136.4, 129.1 (q, *J* = 32 Hz), 122.2 (q, *J* = 274 Hz), 104.6. $C_6H_2ClF_3IN$ (307.44): calcd. C 23.44, H 0.66; found 23.46, H 0.81.

2-Chloro-3-iodo-5-(trifluoromethyl)pyridine: Piperidine (4.9 mL, 4.2 g, 50 mmol) and 2-chloro-4-iodo-5-(trifluoromethyl)pyridine (15 g, 50 mmol) were consecutively added to a solution of butyllithium (50 mmol) in tetrahydrofuran (0.20 L) and hexanes (35 mL), cooled in a dry ice/methanol bath. After 20 h at −75 °C, the mixture was neutralized with hydrochloric acid (2.0 M, 50 mL). Steam distillation, followed by distillation under reduced pressure, afforded a colorless, slowly solidifying oil; prisms (from acetone); m.p. 37−39 °C; b.p. 85−86 °C/8 Torr; yield: 7.07 g (46%). ^{1}H NMR: δ = 8.63 (s, 1 H), 8.36 (s, 1 H) ppm. ^{13}C NMR: δ = 158.4, 145.7, 145.7, 126.3 (q, *J* = 34 Hz), 122.0 (q, *J* = 273 Hz), 94.8. $C_6H_2ClF_3IN$ (307.44): calcd. C 23.44, H 0.66; found C 23.38, H 0.65.

3. Chloro(trifluoromethyl)pyridinecarboxylic Acids

2-Chloro-5-trifluoromethyl-4-pyridinecarboxylic Acid: 2-Chloro-4-iodo-5-(trifluoromethyl)pyridine (7.7 g, 25 mmol) was added as a solid, at −75 °C, to butyllithium (50 mmol) in hexanes (30 mL) and tetrahydrofuran (0.10 L). After 15 min at −75 °C, the suspension formed was poured onto an excess of freshly crushed dry ice before being treated, at +25 °C, with ethereal hydrochloric acid (2.0 M, 50 mL). All volatiles were evaporated and the residue was crystallized from a 1:1 mixture of ethyl acetate and hexanes; tiny colorless needles; m.p. 185−186 °C (decomp.); yield: 4.9 g (87%). ^{1}H NMR: δ = 8.76 (s, 1 H), 7.72 (s, 1 H) ppm. ^{13}C NMR: δ = 165.4, 155.7, 148.0 (q, *J* = 6 Hz), 142.7, 124.4, 122.6 (q, *J* = 274 Hz),122.5 (q, *J* = 35 Hz). $C_7H_3ClF_3NO_2$ (225.55): calcd. C 37.27, H 1.34; found C 36.94, H 1.76.

2-Chloro-5-trifluoromethyl-3-pyridinecarboxylic Acid: This compound was prepared analogously, from 2-chloro-3-iodo-5-(trifluoromethyl)pyridine (7.7 g, 25 mmol); tiny colorless needles (from ethyl acetate/hexanes); m.p. 167−168 °C (decomp.); yield: 3.67 g (65%). ^{1}H NMR: δ = 8.75 (dq, *J* = 2.5, 0.8 Hz, 1 H), 8.47 (dq, *J* = 2.5, 0.6 Hz, 1 H) ppm. ^{13}C NMR: δ = 164.9, 153.6, 148.1 (q, *J* = 4 Hz), 137.8 (q, *J* = 3 Hz), 127.9, 125.6 (q, *J* = 34 Hz), 122.7 (q, *J* = 273 Hz). $C_7H_3ClF_3NO_2$ (225.55): calcd. C 37.27, H 1.34; found C 37.31, H 0.95.

2-Chloro-4-trifluoromethyl-3-pyridinecarboxylic Acid: Diisopropylamine (7.0 mL, 5.1 g, 50 mmol) and 2-chloro-4-(trifluoromethyl)pyridine[16] (6.4 mL, 9.1 g, 50 mmol) were added consecutively to a solution of butyllithium (50 mmol) in tetrahydrofuran (70 mL) and hexanes (25 mL). After 2 h at −75 °C, the mixture was poured onto an excess of freshly crushed dry ice before being treated, at +25 °C, with hydrochloric acid (2.0 M, 50 mL). All volatiles were evaporated, and the residue was crystallized from ethyl acetate to provide colorless prisms; m.p. 150−151 °C; 9.3 g (82%). ^{1}H NMR: δ = 8.62 (d, *J* = 5.2 Hz, 1 H), 7.54 (d, *J* = 5.2 Hz, 1 H) ppm. ^{13}C NMR: δ = 165.4, 150.5, 148.9, 137.4 (q, *J* = 35 Hz), 124.4, 121.7 (q, *J* = 275 Hz), 118.8 (q, *J* = 4 Hz). $C_6H_3ClF_3NO_2$ (225.55):calcd. C 37.28, H 1.34, N 6.21; found C 37.21, H 1.32, N 6.26.

4. (Trifluoromethyl)pyridinecarboxylic Acids

2-Trifluoromethyl-3-pyridinecarboxylic Acid (1): A solution of 3-bromo-2-(trifluoromethyl)pyridine (see above; 4.5 g, 20 mmol) and isopropylmagnesium chloride (20 mmol) in tetrahydrofuran (0.10 L) was kept for 2 h at 0 °C, before being poured onto an excess of freshly crushed dry ice. The solvent was evaporated and the residue was partitioned between diethyl ether (50 mL) and aqueous sodium hydroxide (2.0 M, 50 mL). The aqueous layer was washed with diethyl ether (2 × 10 mL), acidified to pH 2, and extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried, the solvents were evaporated, and the residue was crystallized from ethyl acetate; colorless needles; m.p. 175−176 °C (ref.[10] m.p. 175−176 °C; mixture m.p. without depression); yield: 3.21 g (84%). ^{1}H NMR*: δ = 8.87 (dd, *J* = 4.7, 0.8 Hz, 1 H), 8.32 (dd, *J* = 7.9, 0.8 Hz, 1 H), 7.86 (dd, *J* = 7.9, 0.8 Hz, 1 H) ppm. ^{13}C NMR*: δ = 166.6, 151.6, 145.1 (q, *J* = 35 Hz), 139.1, 129.5, 127.5, 122.4 (q, *J* = 274 Hz). $C_7H_4F_3NO_2$ (191.11): calcd. C 43.99, H 2.11; found C 44.13, H 2.23.

2-Trifluoromethyl-4-pyridinecarboxylic Acid (2): This compound was prepared analogously, from 4-iodo-2-(trifluoromethyl)pyridine (see Section 2; 2.7 g, 10 mmol) and butyllithium (10 mmol) in tetrahydrofuran (15 mL) and hexanes (5 mL) for 5 min at −75 °C; colorless prisms (from chloroform); m.p. 215−216 °C (reprod.); yield: 1.59 g (83%). ^{1}H NMR: δ = 9.00 (d, *J* = 4.9 Hz, 1 H), 8.26 (s, 1 H), 8.21 (d, *J* = 4.9 Hz, 1 H) ppm. ^{13}C NMR*: δ = 165.3, 152.5, 149.3 (q, *J* = 35 Hz), 141.0, 127.4, 122.5 (q, *J* = 276 Hz), 120.8. $C_7H_4F_3NO_2$ (191.11): calcd. C 43.99, H 2.11; found C 44.01, H 2.24.

6-Trifluoromethyl-3-pyridinecarboxylic Acid (3): This compound was prepared as described above (see the preparation of the acid **1**), from 5-bromo-2-(trifluoromethyl)pyridine (see above; 11 g, 50 mmol) and isopropylmagnesium chloride (50 mmol) in tetrahydrofuran; colorless prisms (from a 1:1 mixture of methanol and chloroform); m.p. 188−189 °C; yield: 8.50 g (89%). ^{1}H NMR: δ = 9.28 (s, 1 H), 8.63 (d, *J* = 8.2 Hz, 1 H), 8.03 (d, *J* = 8.2 Hz, 1 H) ppm. ^{13}C NMR*: δ = 165.3, 151.8, 151.2 (q, *J* = 35 Hz), 140.1, 130.1, 122.4 (q, *J* = 274 Hz), 121.4. $C_7H_4F_3NO_2$ (191.11): calcd. C 43.99, H 2.11; found C 43.94, H 2.23.

6-Trifluoromethyl-2-pyridinecarboxylic Acid (4): This compound was prepared by treatment of 2-bromo-6-(trifluoromethyl)pyridine[16] (4.5 g, 20 mmol) with butyllithium (20 mmol, added dropwise) in diethyl ether (0.10 L) and hexanes (15 mL) for 15 min at −75 °C; colorless prisms (from a 3:1 mixture of ethyl acetate and hexanes); m.p. 156−157 °C (ref.[35] m.p. 156−157 °C; mixture m.p. without depression); yield: 3.33 g (87%). ^{1}H NMR: δ = 8.41−8.32 (m, 2 H), 8.13 (dd, *J* = 7.6, 1.2 Hz, 1 H) ppm. ^{13}C NMR*: δ = 166.0, 150.4, 149.0 (q, *J* = 35 Hz), 141.8, 129.3, 125.8, 122.8 (q, *J* = 275 Hz). $C_7H_4F_3NO_2$ (191.11): calcd. C 43.99, H 2.11; found C 44.07, H 2.23.

3-Trifluoromethyl-2-pyridinecarboxylic Acid (5): Butyllithium (50 mmol) in hexanes (30 mL) was added at −100 °C to 2-bromo-3-(trifluoromethyl)pyridine (see Section 2; 11 g, 50 mmol) in azeotropically dried toluene (0.10 L). After 2 h at −75 °C, the mixture was carboxylated and worked up as described above; tiny colorless platelets (from equal volumes of ethyl acetate and hexanes); m.p. 116−117 °C (decomp.); yield: 6.5 g (68%). ^{1}H NMR: δ = 8.91 (s, 1 H), 8.22 (d, *J* = 8.0 Hz, 1 H), 7.42 (dd, *J* = 7.8, 4.9 Hz, 1 H) ppm. ^{13}C NMR: δ = 164.1, 151.0, 147.3, 136.4 (q, *J* = 5 Hz), 126.3 (q, *J* = 35 Hz), 126.2, 122.5 (q, *J* = 274 Hz). $C_7H_4F_3NO_2$ (191.11): calcd. C 43.99, H 2.11, N 7.33; found C 43.91, H 2.17, N 7.21.

3-Trifluoromethyl-4-pyridinecarboxylic Acid (6): Palladium (10% on charcoal, 1.5 g) was added with stirring, at +25 °C, to a solution of 2-chloro-5-trifluoromethyl-4-pyridinecarboxylic acid (see Section 3; 5.6 g, 25 mmol) and ammonium formate (5.0 g, 42 mmol) in methanol (25 mL). The evolution of a gas started almost immediately

and ceased completely some 15 min later. The reaction mixture was filtered under suction and the filter cake was washed with methanol (50 mL). The solution was evaporated and the residue was crystallized from equal volumes of ethyl acetate and hexanes; colorless prisms; m.p. 205−207 °C (decomp.); yield: 3.87 g (81%). ^{1}H NMR: δ = 9.00 (s, 1 H), 8.90 (d, *J* = 5.0 Hz, 1 H), 7.70 (d, *J* = 4.9 Hz, 1 H) ppm. ^{13}C NMR: δ =166.6, 153.4, 147.5 (q, *J* = 6 Hz) 140.0, 123.2 (q, *J* = 32 Hz), 123.0, 122.8 (q, *J* = 274 Hz). $C_7H_4F_3NO_2$ (191.11): calcd. C 43.99, H 2.11, N 7.33; found C 43.90, H 1.99, N 7.33.

5-Trifluoromethyl-3-pyridinecarboxylic Acid (7): This compound was prepared analogously, from 2-chloro-5-trifluoromethyl-3-pyridinecarboxylic acid (see Section 3; 5.6 g, 25 mmol); colorless platelets (from a 1:1 mixture of ethyl acetate and hexanes); m.p. 180−182 °C (decomp.); yield: 4.16 g (87%). ^{1}H NMR: δ = 9.43 (d, *J* = 1.7 Hz, 1 H), 9.06 (d, *J* = 1.4 Hz, 1 H), 8.59 (symm. m, 1 H) ppm. ^{13}C NMR: δ = 165.5, 153.7, 149.3 (q, *J* = 4 Hz), 134.5 (q, *J* = 4 Hz), 127.1, 126.6 (q, *J* = 34 Hz), 122.9 (q, *J* = 272 Hz). $C_7H_4F_3NO_2$ (191.11): calcd. C 43.99, H 2.11, N 7.33; found C 43.92, H 2.02, N 7.24. Acid **7** was also obtained from 3-bromo-5-(trifluoromethyl)pyridine[16] (6.8 g, 30 mmol), although in at most 33% yield. The best reaction conditions identified were treatment with lithium tributylmagnesiate[37−39] [obtained by mixing 20 mmol of butyllithium in 12 mL of hexanes and 10 mmol of butylmagnesium chloride in 6.0 mL of tetrahydrofuran] in toluene (40 mL) for 15 min at −75 °C before carboxylation.

5-Trifluoromethyl-2-pyridinecarboxylic Acid (8): This compound was prepared by consecutive treatment of 2-bromo-5-(trifluoromethyl)pyridine (see Section 2; 22 g, 50 mmol) with butyllithium (50 mmol) in toluene (50 mL) for 2 h at −75 °C and carbon dioxide as described above (see the preparation of the acid **5**); colorless tiny needles (from a 1:1 mixture of ethyl acetate and hexanes); m.p. 134−135 °C; yield: 6.4 g (67%). ^{1}H NMR: δ = 9.17 (s,1 H), 8.45 (d, *J* = 8.1 Hz, 1 H), 8.27 (d, *J* = 8.1 Hz, 1 H) ppm. ^{13}C NMR: δ = 164.1, 150.0, 145.6, 136.0, 130.4 (q, *J* = 34 Hz), 124.8, 122.7 (q, *J* = 273 Hz). $C_7H_4F_3NO_2$ (191.11): calcd. C 43.99, H 2.11, N 7.33; found C 44.13, H 2.21, N 7.29. The yield dropped to 47% when the same product **8** was prepared from 2-iodo-5-(trifluoromethyl)pyridine as the starting material.

4-Trifluoromethyl-2-pyridinecarboxylic Acid (9): This compound was prepared analogously, from 2-bromo-4-(trifluoromethyl)pyridine (see Section 2; 5.6 g, 25 mmol); colorless needles (from equal volumes of ethyl acetate and hexanes); m.p. 156−157 °C (ref.[10] m.p. 156−158 °C; no depression upon mixing); yield: 2.6 g (54%).^{1}H NMR: δ = 9.82 (s, 1 H), 9.05 (d, *J* = 5.0 Hz, 1 H), 8.51 (s, 1 H), 7.89 (d, *J* = 5.0 Hz, 1 H) ppm. ^{13}C NMR: δ = 165.0, 150.4, 149.5, 139.7 (q, *J* = 35 Hz), 122.4 (q, *J* = 3 Hz), 122.2 (q, *J* = 273 Hz), 121.0 (q, *J* = 3 Hz). $C_7H_4F_3NO_2$ (191.11): calcd. C 43.99, H 2.11; found C 43.71, H 1.99.

4-Trifluoromethyl-3-pyridinecarboxylic Acid (10): This compound was prepared by transfer hydrogenolysis of 2-chloro-4-trifluoromethyl-4-pyridinecarboxylic acid (see Section 3; 11 g, 50 mmol) as described above (see the preparation of the acid **6**); colorless platelets (from equal volumes of ethyl acetate and hexanes); m.p. 146−147 °C (ref.[10] m.p. 146−147 °C; no depression upon mixing); yield: 8.5 g (89%). ^{1}H NMR: δ = 9.17 (s, 1 H), 9.04 (d, *J* = 5.2 Hz, 1 H), 7.88 (d, *J* = 5.2 Hz, 1 H) ppm. ^{13}C NMR*: δ = 165.9, 154.1, 152.0, 136.9 (q, *J* = 35 Hz), 126.8, 128.4 (q, *J* = 275 Hz), 121.3 (q, *J* = 5 Hz). $C_7H_4F_3NO_2$ (191.11): calcd. C 43.99, H 2.11; found C 44.12, H 2.30.

5. Bromoquinolinones and Haloquinolines

8-Bromo-2(1*H*)-quinolinone: A mixture of cinnamoyl chloride (84 g, 0.50 mol), 2-bromoaniline (86 g, 0.50 mol), and potassium carbonate (0.10 kg, 0.75 mol) in water (0.25 L) and acetone (0.20 L) was kept for 2 h at 0 °C before being poured into ice-water (0.50 L). The precipitate formed was collected and crystallized from hexanes to afford **2-bromocinnamanilide**; colorless prisms; m.p. 152−154 °C; yield: 139 g (92%). ^{1}H NMR: δ = 8.51 (d, *J* = 8.2 Hz, 1 H), 7.81 (s, 1 H), 7.77 (d, *J* = 15.9 Hz, 1 H), 7.59−7.38 (m, 6 H), 7.34 (t, *J* = 7.9 Hz, 1 H), 6.99 (t, *J* = 7.9 Hz, 1 H), 6.60 (d, *J* = 15.9 Hz, 1 H) ppm. ^{13}C NMR: δ = 163.9, 143.8, 135.8, 134.3, 132.2, 130.0, 128.8, 128.4, 128.0, 125.2, 122.3, 120.6. $C_{15}H_{12}BrNO$ (302.17): calcd. C 59.62, H 4.00; found C 59.65, H 4.01. A solution of 2-bromocinnamanilide (0.12 kg, 0.40 mol) and aluminium chloride (0.32 kg, 2.4 mol) in chlorobenzene (0.40 L) was heated to 125 °C for 2 h. At 50 °C, it was then poured onto ice, and the resulting precipitate was filtered and crystallized from ethanol; colorless needles; m.p. 196−198 °C; yield: 50.2 g (56%). ^{1}H NMR: δ = 8.11 (s, 1 H), 7.71 (d, *J* = 9.4 Hz, 1 H), 7.53 (dd, *J* = 7.8, 1.1 Hz, 1 H), 7.80 (t, *J* = 7.8 Hz, 1 H), 6.68 (d, *J* = 9.4 Hz, 1 H) ppm. ^{13}C NMR: δ = 161.8, 140.1, 135.3, 133.2, 127.2, 122.9, 122.4, 120.6, 115.8. C_9H_6BrNO (224.06): calcd. C 48.25, H 2.70; found C 48.54, H 2.69.

8-Bromo-2-chloroquinoline: Phosphorus oxychloride (37 mL, 61 g, 0.40 mol) and 8-bromo-2(*1H*)-quinolinone (45 g, 0.20 mol) were heated to 125 °C for 2 h before being poured onto ice. The resulting precipitate was filtered and crystallized from methanol; colorless prisms; m.p. 113−114 °C; yield: 40.3 g (83%). ^{1}H NMR: δ = 8.10 (d, *J* = 8.3 Hz, 1 H), 8.05 (d, *J* = 7.8 Hz, 1 H), 7.78 (d, *J* = 7.8 Hz, 1 H), 7.49−7.39 (m, 2 H) ppm. ^{13}C NMR: δ = 151.8, 145.0, 139.3, 134.1, 131.2, 128.0, 127.4, 123.4, 122.5. C_9H_5BrClN (242.50): calcd. C 44.58, H 2.08; found C 44.78, H 2.09.

8-Bromo-2-chloro-3-iodoquinoline: Diisopropylamine (21 mL, 15 g, 0.15 mol) and 8-bromo-2-chloroquinoline (36 g, 0.15 mol) were added consecutively to butyllithium (0.15 mol) in tetrahydrofuran (0.20 L) and hexanes (90 mL), cooled in a methanol/dry ice bath. After 2 h at −75 °C, iodine (76 g, 0.30 mol) in precooled tetrahydrofuran (75 mL) was added. The mixture was washed with aqueous sodium thiosulfate (1.0 M, 0.20 L). The organic phase was dried over anhydrous sodium sulfate and the solvents were evaporated. Crystallization from methanol gave colorless prisms; m.p. 184−186 °C; yield: 43.7 g (79%). ^{1}H NMR: δ = 8.67 (s, 1 H), 8.06 (dd, *J* = 7.5, 1.3 Hz, 1 H), 7.69 (dd, *J* = 8.3, 1.3 Hz, 1 H), 7.43 (dd, *J* = 8.1, 7.5 Hz, 1 H) ppm. ^{13}C NMR: δ = 153.5, 149.0, 144.2, 135.5, 129.0, 128.0, 126.1, 123.4, 92.5. $C_9H_4BrClIN$ (368.39): calcd. C 29.34, H 1.09; found C 29.43, H 1.09.

6. Bromo- and Chloro(trifluoromethyl)quinolines

The preparation of 4-bromo-2-(trifluoromethyl)quinoline,[25] 8-bromo-2-(trifluoromethyl)quinoline,[25] 4,8-dibromo-2-(trifluoromethyl)quinoline,[25] 2-bromo-4-(trifluoromethyl)quinoline,[25,40] 8-bromo-4-(trifluoromethyl)quinoline,[25,40] and 2-bromo-8-iodo-4-(trifluoromethyl)quinoline[25,40] is reported in detail in forthcoming publications.

2-Chloro-3-(trifluoromethyl)quinoline: 2-Chloro-3-iodoquinoline[41] (38 g, 0.13 mol) was treated and worked up as described for the preparation of 3-bromo-2-(trifluoromethyl)pyridine (Section 2), except that the reaction time was extended to 20 h and the reaction temperature was increased to 50 °C; colorless needles (from hexanes); m.p. 98−100 °C (ref.[42] m.p. 98−100 °C); yield: 24.1 g (80%).

4-Chloro-3-(trifluoromethyl)quinoline: This compound was prepared analogously, from 4-chloro-3-iodoquinoline[43] (43 g, 0.15

mol); colorless needles (from hexanes); m.p. 79−81 °C; yield: 27.4 g (79%). ^{1}H NMR: δ = 9.01 (s, 1 H), 8.37 (d, *J* = 8.6 Hz, 1 H), 8.12 (d, *J* = 8.6 Hz, 1 H), 7.89 (ddd, *J* = 8.6, 7.0, 1.3 Hz, 1 H), 7.74 (ddd, *J* = 8.6, 7.0, 1.1 Hz, 1 H) ppm. ^{13}C NMR: δ = 150.1, 146.1 (q, *J* = 6 Hz), 142.8, 132.5, 130.0, 128.9, 125.8, 124.9, 122.8 (q, *J* = 274 Hz), 121.4 (q, *J* = 32 Hz). $C_{10}H_5ClF_3N$ (231.60): calcd. C 51.86, H 2.18; found C 51.56, H 2.15.

2-Bromo-3-(trifluoromethyl)quinoline: 2-Chloro-3-(trifluoromethyl)quinoline (6.9 g, 30 mmol) was treated with bromotrimethylsilane (5.9 mL, 6.9 g, 45 mmol) as described for the preparation of 2,3-dibromopyridine (Section 2). The residue was crystallized from hexanes; colorless needles; m.p. 93−95 °C; yield: 6.9 g (83%). ^{1}H NMR: δ = 8.45 (s, 1 H), 8.08 (d, *J* = 8.3 Hz, 1 H), 7.90 (d, *J* = 8.0 Hz, 1 H), 7.87 (ddd, *J* = 8.6, 7.0, 1.3 Hz, 1 H), 7.68 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1 H) ppm. ^{13}C NMR: δ = 149.0, 137.4 (q, *J* = 5 Hz), 136.6, 132.9, 129.7, 128.6, 128.5, 125.2, 124.3 (q, *J* = 33 Hz), 122.4 (q, *J* = 272 Hz). $C_{10}H_5BrF_3N$ (276.06): calcd. C 43.51, H 1.83; found C 43.75, H 1.85.

4-Bromo-3-(trifluoromethyl)quinoline: This compound was prepared analogously, from 4-chloro-3-(trifluoromethyl)quinoline (12 g, 50 mmol), but with extension of the reflux time to 20 h; colorless needles from hexanes; m.p. 79−80 °C; yield: 12.8 g (93%). ^{1}H NMR: δ = 9.04 (s, 1 H), 8.43 (dd, *J* = 8.6, 1.3 Hz, 1 H), 8.18 (d, *J* = 8.3 Hz, 1 H), 7.90 (ddd, *J* = 8.3, 7.0, 1.1 Hz, 1 H), 7.76 (ddd, *J* = 8.6, 7.0, 1.3 Hz, 1 H) ppm. ^{13}C NMR: δ = 149.8, 146.1 (q, *J* = 6 Hz), 134.6, 132.4, 130.1, 129.1, 127.9, 127.4, 124.0 (q, *J* = 31 Hz), 123.0 (q, *J* = 274 Hz). $C_{10}H_5BrF_3N$ (276.06): calcd. C 43.51, H 1.83; found C 43.66, H 1.91.

8-Bromo-2-(trifluoromethyl)quinoline: 4,8-Dibromo-2-(trifluoromethyl)quinoline[24] (7.1 g, 20 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 injected and the product was isolated by crystallization from pentanes; colorless needles; m.p. 62−63 °C (ref.[44,45]: m.p. 63.5−64.0 °C); yield: 4.20 g (76%). ^{1}H NMR: δ = 8.39 (d, *J* = 8.6 Hz, 1 H), 8.16 (dd, *J* = 7.5, 1.1 Hz, 1 H), 7.89 (dd, *J* = 8.3, 1.1 Hz, 1 H), 7.80 (d, *J* = 8.6 Hz, 1 H), 7.54 (dd, *J* = 8.1, 7.8 Hz, 1 H) ppm. ^{13}C NMR: δ = 148.5 (q, *J* = 35 Hz), 144.3, 138.8, 134.5, 130.0, 129.0, 127.5, 125.5, 121.2 (q, *J* = 276 Hz), 117.8.

8-Bromo-2-chloro-3-(trifluoromethyl)quinoline: 8-Bromo-2-chloro-3-iodoquinoline (37 g, 0.10 mol) and (trifluoromethyl)trimethylsilane (22 mL, 21 g, 0.15 mol) in 1-methyl-2-pyrrolidone (0.15 L) were added to a mixture of copper iodide (29 g, 0.15 mol) and potassium fluoride (8.7 g, 0.15 mol), pretreated as described.[16] Having been heated at 50 °C for 20 h, the mixture was poured into aqueous ammonium hydroxide (12%, 0.10 L). The resulting deep blue solution was extracted with diethyl ether (3 × 0.10 L). The combined organic layers were dried and the solvents were evaporated. The residue was crystallized from hexanes; colorless needles; m.p. 107−109 °C; yield: 19.9 g (64%). ^{1}H NMR: δ = 8.53 (s, 1 H), 8.19 (dd, *J* = 7.6, 1.2 Hz, 1 H), 7.90 (dd, *J* = 8.2, 1.2 Hz, 1 H), 7.53 (t, *J* = 7.9 Hz, 1 H) ppm. ^{13}C NMR: δ = 147.0, 145.7, 138.5 (q, *J* = 5 Hz), 136.5, 128.8, 128.2, 126.5, 123.4, 123.2 (q, *J* = 34 Hz), 122.1 (q, *J* = 272 Hz). $C_{10}H_4BrClF_3N$ (310.50): calcd. C 38.68, H 1.30; found C 38.67, H 1.24.

2-Bromo-8-iodo-4-(trifluoromethyl)quinoline: 8-Iodo-4-trifluoromethyl-2(1*H*)-quinolinone[40] (17 g, 50 mmol) was cautiously added at 60 °C to phosphorus oxybromide (29 g, 0.10 mol). After the mixture had been heated at 120 °C for 2 h, it was poured onto crushed ice (0.25 kg). The brown mass that had precipitated was collected and dissolved in methanol (0.25 L). The suspension obtained upon addition of charcoal (3.0 g) was vigorously stirred for 1 h before being filtered through a pad of diatomaceous earth. The solvent was removed by evaporation and the residue was crystallized from methanol; colorless needles; m.p. 102−104 °C (after sublimation); 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. $C_{10}H_4BrF_3IN$ (401.95): calcd. C 29.88, H 1.00; found C 29.90, H 1.11.

7. (Trifluoromethyl)quinolinecarboxylic Acids

Details of the preparation and characterization of 4-bromo-2-trifluoromethyl-3-quinolinecarboxylic acid,[24] 2-bromo-4-trifluoromethyl-3-quinolinecarboxylic acid,[25,40] 2-trifluoromethyl-3-quinolinecarboxylic acid[24] (**11**), 2-trifluoromethyl-4-quinolinecarboxylic acid[24] (**12**), 4-trifluoromethyl-2-quinolinecarboxylic acid[25,40] (**17**), and 4-trifluoromethyl-3-quinolinecarboxylic acid[25,40] (**18**) are presented in forthcoming publications.

2-Trifluoromethyl-3-quinolinecarboxylic Acid (11): Butyllithium (30 mmol) in hexanes (18 mL) was added to a precooled solution of 4-bromo-2-trifluoromethyl-3-quinolinecarboxylic acid[24] (4.8 g, 15 mmol) in diethyl ether and the resulting suspension was stirred at −75 °C for 6 h before being treated with methanol (5.0 mL, 4.0 g, 12 mmol) and water (50 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic layers were dried and the solvents were evaporated. The residue was crystallized from methanol; colorless prisms; m.p. 207−209 °C (reprod.); 3.29 g (91%). ^{1}H NMR*: δ = 9.01 (s, 1 H), 8.1−8.3 (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 (q, *J* = 35 Hz), 142.2, 134.5, 131.5 (2 C), 130.5, 128.5, 126.0, 123.2 (q, *J* = 275 Hz). $C_{11}H_6F_3NO_2$ (241.17): calcd. C 54.78, H 2.51; found C 54.78, H 2.99.

2-Trifluoromethyl-4-quinolinecarboxylic Acid (12): 4-Bromo-2-(trifluoromethyl)quinoline[24] (6.9 g, 25 mmol) was added to a solution of butyllithium (25 mmol) in tetrahydrofuran (15 mL) and hexanes (15 mL), cooled to −75 °C. After 45 min at this temperature, the mixture was poured onto an excess of freshly crushed dry ice. Water (0.10 mL) was added, and the aqueous phase was washed with diethyl ether (3 × 50 mL) before being acidified to pH 1 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; colorless prisms; m.p. 181−182 °C, 4.46 g (74%). ^{1}H NMR*: δ = 8.96 (d, *J* = 8.4 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 (q, *J* = 34 Hz), 139.7, 133.0, 132.0 (2 C), 127.8 (2 C), 123.4 (q, *J* = 274 Hz), 119.7. $C_{11}H_6F_3NO_2$ (241.17): calcd. C 54.78, H 2.26; found C 54.78, H 2.88.

2-Trifluoromethyl-8-quinolinecarboxylic Acid (13): This compound was prepared analogously, from 8-bromo-2-(trifluoromethyl)quinoline (see Section 6; 4.1 g, 15 mmol); colorless needles (from chloroform); m.p. 177−178 °C; yield: 2.64 g (73%). ^{1}H NMR: δ = 8.94 (dd, *J* = 7.3, 1.4 Hz, 1 H), 8.69 (d, *J* = 8.6 Hz, 1 H), 8.25 (dd, *J* = 8.2, 1.4 Hz, 1 H), 7.96 (d, *J* = 8.6 Hz, 1 H), 7.93 (t, *J* = 7.5 Hz, 1 H) ppm. ^{13}C NMR*: δ = 165.8, 147.0 (q, *J* = 36 Hz), 144.1, 141.1, 137.3, 133.1, 129.4 (2 C), 125.5, 119.5 (q, *J* = 276 Hz), 117.8. $C_{11}H_6F_3NO_2$ (241.17): calcd. C 54.78, H 2.51; found C 55.16, H 2.18.

3-Trifluoromethyl-2-quinolinecarboxylic Acid (14): 2-Bromo-3-(trifluoromethyl)quinoline (see Section 5; 6.9 g, 25 mmol) in toluene (50 mL) was added dropwise, over 15 min, to a solution of butyllithium (25 mmol) in toluene (50 mL) and hexanes (15 mL), cooled in a dry ice/methanol bath. After 45 min at −75 °C, the mixture was poured onto an excess of freshly crushed solid carbon dioxide covered with tetrahydrofuran (0.10 L). At +25 °C, it was treated with ethereal hydrogen chloride (2.0 M, 15 mL), after which all volatiles were evaporated. The residue was extracted with a hot 1:3 (v/v) mixture of ethyl acetate and hexanes and, after concentration, crystallized from this medium; colorless platelets; m.p. 125−126 °C (ref.[10] m.p. 125−127 °C; no depression upon mixing); yield: 4.94 g (82%). ^{1}H NMR: δ = 8.77 (s, 1 H), 8.26 (d, *J* = 8.6 Hz, 1 H), 8.07 (d, *J* = 8.3 Hz, 1 H), 8.01 (ddd, *J* = 8.4, 7.0, 1.4 Hz, 1 H), 7.86 (ddd, *J* = 8.1, 7.0, 1.1 Hz) ppm. ^{13}C NMR: δ = 161.8, 146.1, 143.6, 138.5 (q, *J* = 6 Hz), 133.5, 130.6, 129.3, 128.5, 128.0, 122.8 (q, *J* = 35 Hz), 122.6 (q, *J* = 272 Hz). $C_{11}H_6F_3NO_2$ (241.17): calcd. C 54.78, H 2.51, N 5.81; found C 54.63, H 2.41, N 5.77.

3-Trifluoromethyl-4-quinolinecarboxylic Acid (15): 4-Bromo-3-(trifluoromethyl)quinoline (see Section 5; 2.8 g, 10 mmol) in tetrahydrofuran (20 mL) was added dropwise at −100 °C, over 15 min, to butyllithium (10 mmol) in tetrahydrofuran (20 mL) and hexanes. Immediately afterwards the mixture was poured onto an excess of freshly crushed dry ice. The product was isolated as described in the preceding paragraph; colorless tiny needles (from ethyl acetate); m.p. 259−260 °C (decomp.; ref.[10] m.p. 259−262 °C; m.p. of mixture without depression); yield: 1.95 g (81%). ^{1}H NMR*: δ = 9.24 (s, 1 H), 8.24 (d, *J* = 8.5 Hz, 1 H), 8.10 (d, *J* = 8.4 Hz, 1 H), 8.04 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1 H), 7.88 (ddd, *J* = 8.3, 7.0, 1.3 Hz, 1 H) ppm. ^{13}C NMR*: δ = 168.0, 151.0, 147.5, 142.3, 134.0, 131.5, 127.6, 125.4 (q, *J* = 273 Hz), 123.8, 119.1 (q, *J* = 32 Hz). $C_{11}H_6F_3NO_2$ (241.17): calcd. C 54.78, H 2.51, N 5.81; found C 54.73, H 2.48, N 5.92.

3-Trifluoromethyl-8-quinolinecarboxylic Acid (16): Palladium (10% on charcoal, 2.0 g) was added to a solution of 2-chloro-3-trifluoromethyl-8-quinolinecarboxylic acid (see following paragraph; 4.1 g, 15 mmol) and ammonium formate (1.9 g, 30 mmol) in methanol (30 mL). The suspension was stirred for 45 min at +25 °C before being filtered. The volatiles were evaporated and the residue was crystallized from ethanol; colorless prisms; m.p. 182−185 °C (decomp.); yield: 1.95 g (54%). ^{1}H NMR: δ = 9.45 (d, *J* = 2.0 Hz, 1 H), 9.22 (q, *J* = 1.0 Hz, 1 H), 8.88 (dd, *J* = 7.2, 1.6 Hz, 1 H), 8.59 (dd, *J* = 8.2, 1.6 Hz, 1 H), 8.06 (dd, *J* = 8.2, 7.2 Hz, 1 H) ppm. ^{13}C NMR: δ = 167.0, 157.9, 147.0, 139.2, 138.7, 136.2, 130.3, 128.6, 127.4, 125.5 (q, *J* = 32 Hz), 125.3 (q, *J* = 272 Hz). $C_{11}H_6F_3NO_2$ (241.17): calcd. C 54.78, H 2.51; found C 54.43, H 2.50.

2-Chloro-3-trifluoromethyl-8-quinolinecarboxylic Acid: Precooled solutions of 8-bromo-2-chloro-3-(trifluoromethyl)quinoline (see above; 7.8 g, 25 mmol) in toluene (30 mL) and butyllithium (25 mmol) in hexanes (15 mL) were mixed and kept for 15 min at −75 °C before being poured onto an excess of freshly crushed dry ice. At +25 °C, water was added (50 mL). The aqueous layer was washed with diethyl ether (3 × 25 mL), acidified to pH 1 with hydrochloric acid, and extracted with ethyl acetate (3 × 25 mL). The combined organic layers were dried and the solvents were evaporated; colorless prisms (from ethanol); m.p. 212−215 °C (decomp.); yield: 4.68 g (68%). ^{1}H NMR: δ = 9.30 (s, 1 H), 8.85 (dd, *J* = 7.6, 1.3 Hz, 1 H), 8.61 (dd, *J* = 8.2, 1.3 Hz, 1 H), 8.06 (dd, *J* = 8.2, 7.6 Hz, 1 H) ppm. ^{13}C NMR: δ = 168.4, 145.8, 145.6, 141.9 (m), 134.8, 133.5, 132.1, 129.5, 126.5, 123.4 (q, *J* = 272 Hz), 122.3 (q, *J* = 33 Hz). $C_{11}H_5ClF_3NO_2$ (275.61): calcd. C 47.94, H 1.83; found C 48.26, H 1.68.

4-Trifluoromethyl-2-quinolinecarboxylic Acid (17): 2-Bromo-4-(trifluoromethyl)quinoline[25] (4.1 g, 15 mmol) was added to a solution of butyllithium (15 mmol) in tetrahydrofuran (20 mL) and hexanes (10 mL), cooled in dry ice/methanol bath. After 45 min at −75 °C, the mixture was poured onto an excess of freshly crushed solid carbon dioxide covered with tetrahydrofuran (0.10 L). At +25 °C, it was treated with ethereal hydrogen chloride (2.0 M, 15 mL), after which all volatiles were evaporated. The residue was extracted with ethyl acetate (3 × 15 mL) and, after concentration, crystallized from a 1:3 (v/v) mixture of chloroform and pentanes; colorless prisms; m.p. 142−143 °C; yield: 4.3 g (72%). ^{1}H NMR*: δ = 8.47 (s, 1 H), 8.37 (dd, *J* = 8.4, 1.4 Hz, 1 H), 8.27 (d, *J* = 8.5 Hz, 1 H), 8.06 (td, *J* = 6.9, 1.4 Hz, 1 H), 7.99 (td, *J* = 7.0, 1.5 Hz, 1 H) ppm. ^{13}C NMR*: δ = 165.0, 158.5 (2 C), 139.0, 136.0 (q, *J* = 35 Hz), 132.5, 131.8 (2 C), 124.7, 124.4 (q, *J* = 274 Hz), 118.3. $C_{11}H_6F_3NO_2$ (241.17): calcd. C 54.78, H 2.51; found C 54.52, H 2.48.

4-Trifluoromethyl-3-quinolinecarboxylic Acid (18): 2-Bromo-4-trifluoromethyl-3-quinolinecarboxylic acid[25] (1.5 g, 5.0 mmol) in diethyl ether (15 mL) was added dropwise, over the course of 15 min, to a vigorously stirred solution of butyllithium in diethyl ether (15 mL) and hexanes (6.0 mL), cooled to −100 °C. After 2 h at this temperature, the mixture was treated with methanol (1.0 mL, 0.80 g, 25 mmol). After evaporation of the volatiles, the residue was crystallized from acetic acid; colorless prisms; m.p. 182−184 °C (decomp.); yield: 0.76 g (64%). ^{1}H NMR*: δ = 9.14 (s, 1 H), 8.27 (d, *J* = 8.1 Hz, 1 H), 8.26 (d, *J* = 8.7 Hz, 1 H), 8.00 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1 H), 7.90 (ddd, *J* = 8.9, 7.0, 1.6 Hz, 1 H) ppm. ^{13}C NMR*: δ = 167.9, 150.0, 148.8, 132.3, 131.3, 130.4, 127.3, 125.4 (q, *J* = 3 Hz), 124.6 (q, *J* = 276 Hz), 122.7. $C_{11}H_6F_3NO_2$ (241.17): calcd. C 54.78, H 2.51, N 5.80; found C 54.81, H 2.45, N 5.76.

2-Bromo-4-trifluoromethyl-8-quinolinecarboxylic Acid: 2-Bromo-8-iodo-4-(trifluoromethyl)quinoline (see Section 6; 8.0 g, 20 mmol) was added to butyllithium (20 mmol) in toluene (90 mL) and hexanes (10 mL), kept in a methanol/dry ice bath. After 15 min at −75 °C, the mixture was poured onto an excess of freshly crushed solid carbon dioxide. After treatment with ethereal hydrogen chloride (2.0 M, 15 mL), the volatiles were evaporated and the residue crystallized from ethyl acetate; colorless needles; m.p. 169−171 °C; yield: 5.19 g (81%). ^{1}H NMR: δ = 8.81 (dd, *J* = 9.0, 1.4 Hz, 1 H), 8.50 (dm, *J* = 8.8 Hz, 1 H), 8.35 (s, 1 H), 8.12 (dd, *J* = 8.8, 7.2 Hz, 1 H) ppm. ^{13}C NMR*: δ = 165.4, 147.4, 141.9, 138.2 (q, *J* = 33 Hz), 137.0, 130.4, 129.8, 126.9, 125.4 (q, *J* = 6 Hz), 123.4 (q, *J* = 276 Hz), 123.1. $C_{11}H_5BrF_3NO_2$ (320.07): calcd. C 41.28, H 1.57; found C 41.75, H 1.58.

4-Trifluoromethyl-8-quinolinecarboxylic Acid (19): 2-Bromo-4-trifluoromethyl-8-quinolinecarboxylic acid (see the preceding paragraph; 1.6 g, 10 mmol) and zinc (1.3 g, 20 mmol) were added to aqueous sodium hydroxide (15%, 10 mL, 42 mmol),[46] and the slurry was vigorously stirred at 25 °C. After 2 h, the mixture was filtered, acidified to pH 2 with hydrochloric acid, and extracted with ethyl acetate (3 × 15 mL). The combined organic layers were evaporated and the residue was crystallized from a 1:3 mixture of ethyl acetate and hexanes; colorless prisms; m.p. 186−189 °C; yield: 1.91 g (79%). ^{1}H NMR: δ = 9.39 (d, *J* = 4.6 Hz, 1 H), 8.86 (dd, *J* = 7.4, 1.4 Hz, 1 H), 8.51 (dm, *J* = 8.7 Hz, 1 H), 8.26 (d, *J* = 4.7 Hz, 1 H), 8.10 (dd, *J* = 8.6, 7.4 Hz, 1 H) ppm. ^{13}C NMR*: δ = 166.2, 150.3, 146.7, 136.8 (q, *J* = 33 Hz), 136.5, 130.2, 129.8, 127.8, 124.1 (q, *J* = 276 Hz), 123.9, 120.6 (q, *J* = 6 Hz). $C_{11}H_6F_3NO_2$ (241.17): calcd. C 54.78, H 2.51; found C 54.70, H 2.30.

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