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Relay Propagation of Crowding: The Trifluoromethyl Group as Both an Emitter and Transmitter of Steric Pressure

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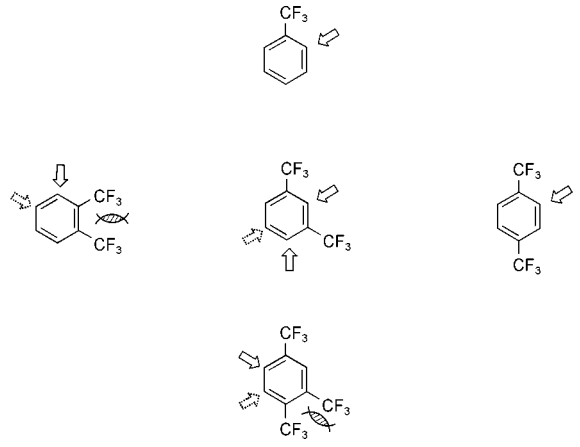
Whereas lithium 2,2,6,6-tetramethylpiperidide (LITMP) abstracts a proton exclusively from the 4-position of 3-bromobenzotrifluoride, the same base attacks selectively the 2-position when employed in the presence of *N*,*N*,*N*′,*N*′′,*N*′′-pentamethyldiethylenetriamine and potassium *tert*-butoxide ("Faigl mix"). 1-Bromo-3,5-bis(trifluoromethyl)benzene also undergoes metalation at the 2-position but [2-bromo-4-(trifluoromethyl)phenyl]silane does not react at all, evidently locked up by a C–SiR_3/C–Br buttressing effect. 2-Bromo-4-(trifluoromethyl)pyridine, aza-analogous to the parent model arene 3-bromobenzotrifluoride, and both the benzo-aza-analogous 2-bromo-4-(trifluoromethyl)quinoline and its regioinverted isomer 4-bromo-2-(trifluoromethyl)quinoline are again readily deprotonated at the Br- and CF_3-flanked positions. However, the buttressing caused by the introduction of a methoxy group at the *peri*-(5-)position impedes the deprotonation of either bromo(trifluoromethyl)quinoline. Compared with methoxy, a *peri*-methyl substituent (to be assimilated to an *ortho*-*tert*-butyl substituent) exerts a smaller buttressing effect. Although 4-bromo-5,7-*dimethoxy*-4-(trifluoromethyl)quinoline proves to be again totally inert towards bases, 4-bromo-5,7-*dimethyl*-4-(trifluoromethyl)quinoline can be lithiated at the 3-position. Obviously, methoxy is more powerful as an emitter of steric pressure than methyl is and bromine is superior to trifluoromethyl as a transmitter of steric pressure.

Introduction

The trifluoromethyl group exerts one of the strongest inductively electron-withdrawing effects so far recognized.[1,2] At the same time, it is a relatively bulky substituent.[3] Early attempts to metalate (trifluoromethyl)benzene with butyllithium in refluxing diethyl ether proved regiochemically unclean, affording, after trapping with dry ice, a 100:40:1 mixture of 2-, 3- and 4-(trifluoromethyl)benzoic acid in moderate yield (33–48%).[4,5] However, (trifluoromethyl)benzene can be effectively and selectively metalated at the *ortho*-position when superbasic mixed-metal reagents such as methyllithium in the presence of potassium *tert*-butoxide are employed.[1] 1,4-Bis(trifluoromethyl)benzene undergoes almost quantitative deprotonation when lithium 2,2,6,6-tetramethylpiperidide (LITMP) serves as the base.[1] However, the isomeric 1,2-bis(trifluoromethyl)benzene causes the first surprise. After consecutive treatment with LITMP and carbon dioxide the 2,3- and 3,4-bis(trifluoromethyl)benzoic acids are isolated in a 2:1 ratio and a total yield of 80%.[1] 1,3-Bis(trifluoromethyl)benzene is an even more capricious substrate. LITMP in tetrahydrofuran abstracts a proton exclusively from the 4-position if used alone and exclusively from the 2-position when in the presence of stoichiometric amounts of potassium *tert*-butoxide. With *tert*-butyllithium in tetrahydro*pyran* metalation occurs concomitantly, in equal proportions, at the 4- and 5-position.[1] Finally, LITMP promotes the deprotonation of 1,2,4-tris(trifluoromethyl)benzene at the 5- and 6-position in the ratios of 25:1 and 8:1 when the reaction is accomplished in diethyl ether (at –25 °C) and tetrahydrofuran (at –75 °C), respectively.[1,6]



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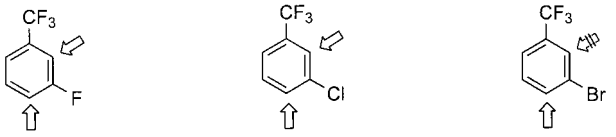
No low molecular weight products are obtained at all, when this substrate is treated with alkyllithium or superbasic mixed-metal reagents as nucleophilic aromatic addition supersedes metalation.

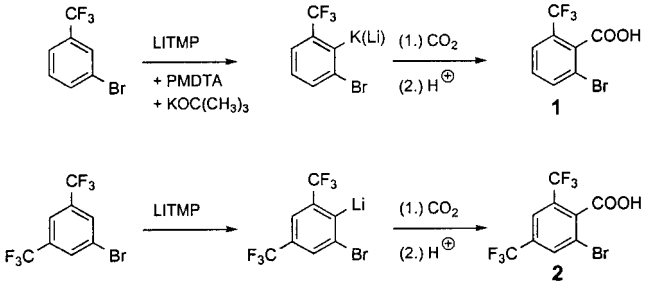
This last example is most instructive as it simultaneously reveals two anomalies. The pronounced regiodiscrimination against an attack at the 6-position must be imputed to a "buttressing effect".[7,8] The same holds for the regiochemically unselective metalation of 1,2-bis(trifluoromethyl)benzene. The vicinal proximity of two trifluoromethyl groups deprives each of them of flexibility. Held tightly at their respective places they cannot get out of the trajectory of the approaching base and thus must interfere with the proton transfer process if taking place at a neighboring position. On the other hand, also non-vicinal trifluoromethyl groups can give rise to steric hindrance as illustrated by the case of 1,3-bis(trifluoromethyl)benzene mentioned above. Bulky reagents like *tert*-butyllithium or LITMP, unless activated by potassium *tert*-butoxide, are unable to enter the congested region flanked by the two trifluoromethyl substituents and to accomplish there a permutational hydrogen/metal interconversion.

The 3-halobenzotrifluoride series offers another impressive illustration of how sensitive bases monitor steric screening. Both 3-fluoro- and 3-chlorobenzotrifluoride react with butyllithium solely at the doubly activated 2-position whereas bulkier reagents such as *sec*-butyllithium, alone or complexed to *N*,*N*,*N*′,*N*′′,*N*′′-pentamethylethylenediamine (PMDTA), metalate preferentially or exclusively the 4-position.[9,10] No such "optional site selectivity"[11–14] was found so far with 3-bromobenzotrifluoride as the substrate, mainly because the choice of bases must be kept restricted to metal dialkylamides as organolithium reagents would give rise to permutational halogen/metal interconversions.

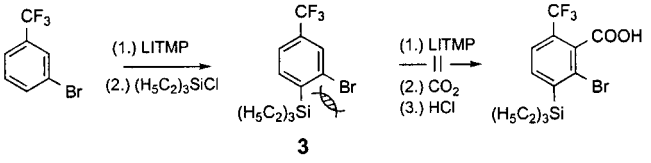


Results and Discussion

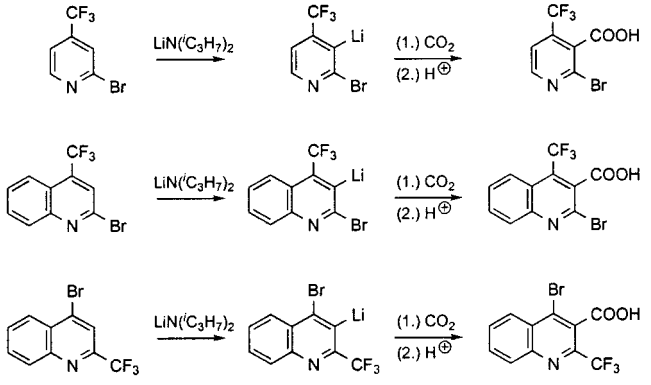
We wanted first to clarify whether it was really impossible to abstract a proton from the doubly activated, though crowded position flanked by the trifluoromethyl group and the bromine atom. In fact, when the three-component base ("Faigl mix"[15]) consisting of LITMP, PMDTA and potassium *tert*-butoxide was used, only the 2-position and no longer the 4-position was attacked. However, the yield of the 2-bromo-6-(trifluoromethyl)benzoic acid (**1**) isolated after carboxylation remained poor (24%). In contrast, 1-bromo-3,5-bis(trifluoromethyl)benzene, a more acidic substrate, reacted even with unactivated LITMP smoothly to afford almost quantitatively the 2-bromo-4,6-bis(trifluoromethyl)benzoic acid (**2**; 83% of purified product) after carboxylation.



A seemingly straightforward way to direct the base to the 2-position of 3-bromobenzotrifluoride should be the blocking of the 4-position by a trialkylsilyl group, one of the favorite "toolbox methods".[16] However, this attempt failed completely, [2-bromo-4-(trifluoromethyl)phenyl]triethylsilane (**3**) proving totally inert toward LITMP or the Faigl mix at –100 °C and –75 °C. Obviously due to the buttressing effect exerted by the bulky silyl substituent and transmitted by the bromine atom, proton abstraction from the 2-position was definitively suppressed.

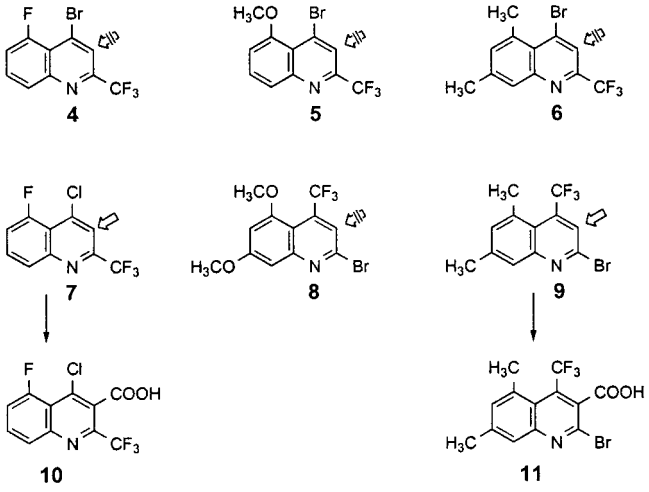


Another simple way to prevent proton abstraction from the 4-position is to replace the CH unit by a nitrogen atom. The latter might at the same time facilitate the deprotonation by virtue of its electron-withdrawing effect. 2-Bromo-4-(trifluoromethyl)pyridine and even 2-iodo-4-(trifluoromethyl)pyridine had been found to react indeed smoothly with amide-type bases such as lithium diisopropylamide to furnish the 2-bromo- and 2-iodo-4-(trifluoromethyl)pyridine-3-carboxylic acids (54 and 51%, respectively) after carboxylation.[17] In the same way, 2-bromo-4-(trifluoromethyl)quinoline[18] and 4-bromo-2-(trifluoromethyl)quinoline[19] have been successfully subjected to the lithiation/carboxylation sequence.



However, 5-fluoro- and 5-methoxy-substituted 4-bromo-2-(trifluoromethyl)quinolines (**4** and **5**) were reported to resist the attack of all amide bases.[19] Meanwhile we have extended the investigation to additional model compounds. 4-Bromo-5,7-dimethyl-2-(trifluoromethyl)quinoline (**6**) and

2-bromo-5,7-dimethoxy-4-(trifluoromethyl)quinoline (**8**) were also found to be totally inert toward lithium diisopropylamide or LITMP. On the other hand, 4-chloro-5-fluoro-2-(trifluoromethyl)quinoline (**7**) and 2-bromo-5,7-dimethyl-4-(trifluoromethyl)quinoline (**9**) did react under such conditions. Upon carboxylation, the 4-chloro-5-fluoro-2-(trifluoromethyl)quinoline-3-carboxylic acid (**10**; 61%) and 2-bromo-5,7-dimethyl-4-(trifluoromethyl)quinoline-3-carboxylic acid (**11**; 26%) were formed.

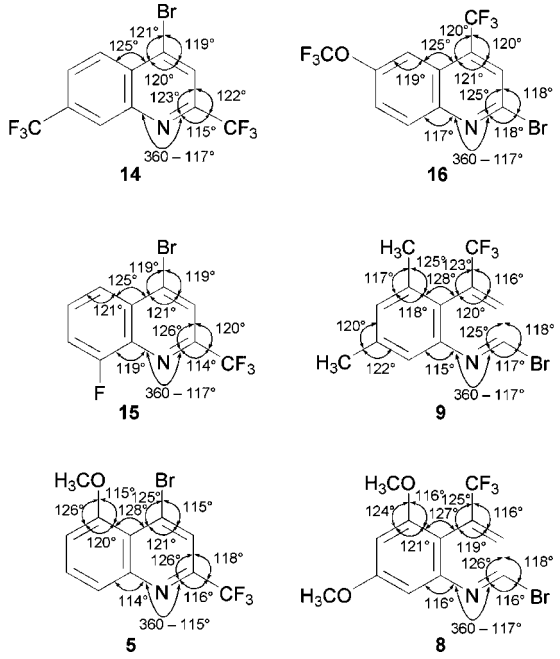


On the basis of such findings we dare to make a counter-intuitive prediction. Although 4-bromo-2-(trifluoromethyl)-pyridine (**12**) is readily deprotonated by LIDA or LITMP at the 3-position, we expect any attempt to metalate 4-bromo-2,5-*bis*(trifluoromethyl)pyridine (**13**) to be doomed to failure despite the increased acidity of the latter substrate.

When evaluating the role of substituents in the given context one has to differentiate between *emitters* and *transmitters* of buttressing effects. For example, the perturbation affecting 4-bromo-5-fluoro-2-(trifluoromethyl)quinoline (**4**) [19] originates from the fluorine atom and is propagated by the bromine atom which, being buttressed, cannot move away when the base tries to approach and abstract a proton from the 3-position. Comparing the various substrates **4**–**11** for their propensity to undergo metalation at the 3-position and combining this with knowledge derived from other sources[8,17,20] one can rank typical substituents according to their emitter and transmitter aptitudes.

Emitter: $R_3Si > F_3C \approx H_3CO > H_3C > H$
Transmitter: $I > Br > F_3C \approx Cl >> F > H$

To probe such emitter and transmitter effects not only on reactivity but also on structure we have carried out a crystallographic study of three 4-bromo-2-(trifluoromethyl)-quinolines and equally of three 2-bromo-4-(trifluoromethyl)-quinolines, each one harboring a characteristic substituent pattern. 4-Bromo-2,7-bis(trifluoromethyl)quinolines (**14**), 4-bromo-8-fluoro-2-(trifluoromethyl)quinolines (**15**) and 2-bromo-8-fluoro-2-(trifluoromethyl)quinolines (**16**) were selected as sterically unbiased reference compounds. As this is the case with any ordinary quinoline derivative (e.g., quinoline[21] itself) too, all bond angles approximate 120° except those at the junction, where the C(4),C(4a),C(5) angle is widened to 125° and the C(8),C(8a),N angle is shortened to 118°, and except for the C(9),N,C(1) angle which decreases to 117°. The introduction of a substituent into the 5-position inevitably causes severe skeletal distortions in the vicinity. The *peri*-methyl group in 2-bromo-5,7-dimethyl-4-(trifluoromethyl)quinolines (**9**) forces the trifluoromethyl neighbor to make room for it by expanding the C(4a),C(4),C(CF_3) angle from 119° to 123° at the expense of the C(CF_3),C(4),C(3) angle which shrinks from 120° to 116°. The *peri*-methoxy group in 2-bromo-5,7-dimethoxy-4-(trifluoromethyl)quinolines has an even more pronounced effect and, still slightly more, in 4-bromo-5-methoxy-2-(trifluoromethyl)quinoline (**5**), enlarging the C(4a),C(4),C(CF_3) angles to 125° and compressing the C(CF_3),C(4),C(5) angles to 116° and 115°, respectively. In all these compounds the C(5),C(4a),C(4) angle is widened to 127° or 128°. The most striking difference between the 5-methyl and 5-methoxy series is the orientation of the *peri* substituent. Steric repulsion causes the methyl group in quinolines **9** to bend away from its CF_3 neighbor [C(4),C(5),C(CH_3) angle 125°, C(CH_3),C(5),C(6) angle 116°]. In contrast, the methoxy group leans over to get closer to the CF_3 substituent [C(4),C(5),C(CH_3) angles of 116° and 115°, C(OCH_3),C(5),C(6) angles of 124° and 126° in compounds **8** and **5**, respectively].



On the whole, the comparison between the ground-state structures of the quinolines **5**, **8** and **9** and those of the *peri*-unsubstituted model compounds **14**, **15** and **16** does not reveal conspicuous features that would immediately forecast

trouble with the deprotonation of the *peri*-substituted substrates. The CF_3–C(4)/C(2)–Br "yawning angle" averages 116° or 114° depending on whether a *peri* substituent is absent or present. It is true, this difference is more pronounced in the regioisomeric series, the Br–C(4)/C(2)–CF_3 angle decreases from 121° to approximately 112° upon the introduction of a *peri* substituent. However, there are no steric constraints that should definitively prevent a base from frontally approaching the C(3)–H bond. Therefore, we maintain our view[20] that electronic reasons force the substituents surrounding a center undergoing metalation to step away from the trajectory of the reagent. This dodging movement is blocked if there are buttressing substituents.

Conclusions

Success and failure alternate when CF_3-bearing model compounds of the arene and quinoline type are exposed to a variety of metalating agents. Although the introduction of an additional electron-withdrawing substituent (such as F, CF_3 or OCH_3) increases the (thermodynamic) acidity of the substrate, it does not necessarily facilitate its (kinetic) deprotonation and may even prevent it. This counterintuitive conclusion can be rationalized by taking buttressing effects into account.

Buttressing effects have been ignored for too long time. We believe the scope of this newly recognized phenomenon to be far-reaching. It may help to rationalize anomalies which otherwise remain unexplained.

Experimental Section

Generalities: Working practices and abbreviations are specified in previous articles from this laboratory.[22–24] ^{1}H and (^{1}H-decoupled) ^{13}C NMR spectra were recorded at 400 and 101 MHz, respectively, relative to the internal standard tetramethylsilane (chemical shift δ = 0.00 ppm). The samples were dissolved in deuteriochloroform or, if marked by an asterisk, in hexadeuterioacetone. Mass spectra were obtained at 70 eV ionization potential while a source temperature of 200 °C was maintained. Whenever no molecular peak was observed under such conditions, chemical ionization ("c.i.") in an ammonia atmosphere at 100 °C source temperature was applied. To avoid redundancy, in all cases only the [^{35}Cl] and [^{79}Br] fragments and not the [^{37}Cl] and [^{81}Br] isotopomers are listed.

1. Starting Materials

4-Bromo-5-fluoro-2-(trifluoromethyl)quinoline (**4**) and 4-bromo-5-methoxy-2-(trifluoromethyl)quinoline (**5**) have already been reported.[19] The quinolines **6**–**9** were prepared according to well-established procedures as described below.

1-[2-Bromo-4-(trifluoromethyl)phenyl]trimethylsilane (3): At –100 °C 2,2,6,6-tetramethylpiperidine (8.4 mL, 7.1 g, 50 mmol), 1-bromo-3-(trifluoromethyl)benzene (11 g, 50 mmol) and chlorotrimethylsilane (6.3 mL, 5.4 g, 50 mmol) were added consecutively to butyllithium (50 mmol) in tetrahydrofuran (65 mL) and hexanes (35 mL). After 2 h at –100 °C, the solvents were evaporated and the residue distilled; colorless liquid; b.p. 68–69 °C/2 Torr; yield: 11.2 g (75%). ^{1}H NMR: δ = 7.77 (s, 1 H), 7.55 (d, J = 8.0 Hz, 1 H), 7.51 (d, J = 8.0 Hz, 1 H) ppm. ^{13}C NMR: δ = 146.1, 136.4, 132.7 (q, J = 33 Hz), 130.4, 129.3 (q, J = 4 Hz), 123.2 (q, J = 273 Hz), 123.0 (q, J = 4 Hz), –0.9 ppm. MS (c.i.): m/z (%) = 315 (0) [M^+ + NH_4], 297 (3) [M^+], 281 (49), 203 (29), 140 (100). $C_{10}H_{12}BrF_3Si$ (297.19): calcd. C 40.42, H 4.07; found C 40.34, H 4.00.

4,4,4-Trifluoro-*N*-(3,5-dimethoxyphenyl)-3-oxobutanamide: Ethyl 2-oxo-1,1,1-trifluorobutanoate (58 mL, 74 g, 0.40 mol) and 3,5-dimethoxyaniline (31 g, 0.20 mol) were heated to 130 °C. A small amount of water (4 mL) was added every 30 min for the duration of 6 h. Upon cooling in an ice bath, the anilide precipitated. It was collected by filtration and washed with hexanes before being recrystallized from ethyl acetate and hexanes; colorless prisms; yield: 46.1 g (79%). ^{1}H NMR*: δ = 6.41 (d, J = 2.2 Hz, 1 H), 6.32 (d, J = 2.3 Hz, 1 H), 6.07 (s, 1 H), 3.99 (s, 3 H), 3.82 (s, 3 H), 2.97 (d, J = 16.8 Hz, 1 H), 2.85 (d, J = 16.8 Hz, 1 H) ppm. ^{13}C NMR*: δ = 165.9, 162.1, 160.1, 140.5, 126.2 (q, J = 289 Hz), 99.5, 94.4, 93.4, 73.6 (q, J = 30 Hz), 56.0, 54.8, 39.0 ppm. MS (c.i.): m/z (%) = 309 (0) [M^+ + NH_4], 292 (22) [M^+ + 1], 291 (11) [M^+], 274 (4), 222 (100). $C_{12}H_{12}F_3NO_4$ (291.23): calcd. C 49.49, H 4.15; found C 49.52, H 4.13.

4,4,4-Trifluoro-*N*-(3,5-dimethylphenyl)-3-oxobutanamide: Prepared analogously from 3,5-dimethylaniline (25 mL, 24 g, 0.20 mol); colorless prisms; yield: 47.3 g (90%). ^{1}H NMR: δ = 7.43 (s, 1 H), 7.10 (s, 2 H), 6.83 (s, 1 H), 2.77 (s, 2 H), 2.28 (s, 6 H) ppm. ^{13}C NMR*: δ = 170.1, 139.2, 138.8, 126.9, 124.0 (q, J = 286 Hz), 118.6, 93.9 (q, J = 32 Hz), 39.2, 21.4 ppm. MS (c.i.): m/z (%) = 277 (25) [M^+ + NH_4], 260 (100) [M^+ + 1], 259 (25) [M^+], 190 (2), 121 (31). $C_{12}H_{12}F_3NO_2$ (259.22): calcd. C 55.60, H 4.67; found C 55.48, H 4.51.

5,7-Dimethoxy-4-(trifluoromethyl)quinolin-2(1*H*)one: 4,4,4-Trifluoro-*N*-(3,5-dimethoxyphenyl)-3-oxobutanamide (29 g, 0.10 mol) was added to 75% aqueous sulfuric acid (0.10 L). The mixture was heated at 90 °C for 45 min and poured onto crushed ice (0.25 L). The precipitate formed was collected by filtration and crystallized from ethanol; colorless needles; m.p. 105–106 °C; yield 23 g (83%). MS (c.i.): m/z (%) = 292 (0) [M^+ + NH_4], 273 (100) [M^+], 244 (11). $C_{12}H_{10}F_3NO_3$ (273.21): calcd. C 52.76, H 3.69; found C 52.75, H 3.66.

5,7-Dimethyl-4-(trifluoromethyl)quinolin-2(1*H*)-one: Prepared analogously starting from 4,4,4-trifluoro-*N*-(3,5-dimethylphenyl)-3-oxobutanamide (26 g, 0.10 mol); colorless needles; m.p. 202–204 °C; yield: 21 g (85%). ^{1}H NMR (D_3CSOCD_3): δ = 7.13 (s, 1 H), 7.01 (s, 1 H), 6.97 (s, 1 H), 2.54 (s, 3 H), 2.33 (s, 3 H) ppm. ^{13}C NMR (D_3CSOCD_3): δ = 159.7, 141.9, 141.5, 136.3 (q, J = 34 Hz), 134.2, 129.5, 123.3 (q, J = 274 Hz), 123.0 (q, J = 8.0 Hz), 115.5, 111.4, 22.5 (q, J = 8 Hz), 21.1 ppm. MS (c.i.): m/z (%) = 259 (0) [M^+ + NH_4], 242 (64) [M^+ + 1], 241 (100) [M^+], 226 (19), 198 (15). $C_{12}H_{10}F_3NO$ (241.21): calcd. C 59.75, H 4.18; found C 59.74, H 3.98.

5,7-Dimethyl-2-(trifluoromethyl)quinolin-4(1*H*)-one: Prepared from 3,5-dimethylaniline (**1**, 31 mL, 30 g, 0.25 mol) and ethyl 4,4,4-trifluoro-3-oxobutanoate (38 mL, 50 g, 0.25 mol) as described in analogous cases;[19] m.p. 251–253 °C (reprod.; colorless needles from ethanol); yield: 31.4 g (52%). ^{1}H NMR (D_3CSOCD_3): δ = 7.51 (s, 1 H), 7.11 (s, 1 H), 6.83 (s, 1 H), 2.81 (s, 3 H), 2.41 (s, 3 H) ppm. ^{13}C NMR (D_3CSOCD_3): δ = 170.0, 147.2, 143.1 (q, J = 34 Hz), 141.0, 136.7, 130.3, 122.9, 121.2 (q, J = 275 Hz), 119.8, 103.1, 23.5, 21.0 ppm. MS (c.i.): m/z (%) = 260 (0) [M^+ +NH_4],

242 (61) [M^+ + 1], 241 (100) [M^+], 193 (9), 91 (3). $C_{12}H_{10}F_3NO$ (241.21): calcd. C 59.75, H 4.18; found C 59.70, H 4.08.

4-Bromo-5,7-dimethyl-2-(trifluoromethyl)quinoline (6): Prepared from 5,7-dimethyl-2-(trifluoromethyl)quinolin-4(1*H*)-one (24 g, 0.10 mol) and phosphoric tribromide (29 g, 0.10 mol) as described in analogous cases;[19] m.p. 172–174 °C (reprod.; colorless needles from methanol); yield: 23.4 g (77%). ^{1}H NMR: δ = 7.94 (s, 1 H), 7.89 (s, 1 H), 7.35 (s, 1 H), 3.06 (s, 3 H), 2.51 (s, 3 H) ppm. ^{13}C NMR: δ = 146.9 (q, J = 35 Hz), 145.3, 141.0, 132.2, 131.6, 127.1, 126.8, 124.2, 119.0 (q, J = 275 Hz), 118.6, 21.2, 18.4 ppm. MS (c.i.): m/z (%) = 321 (0) [M^+ + NH_4], 304 (100) [M^+ + 1], 303 (41) [M^+], 260 (15), 127 (3). $C_{12}H_9BrF_3NO$ (304.11): calcd. C 47.39, H 2.98; found C 47.50, H 2.92.

2-Bromo-5,7-dimethoxy-4-(trifluoromethyl)quinoline (8): Prepared analogously from 5,7-dimethoxy-4-(trifluoromethyl)quinolin-2(1*H*)-one (14 g, 50 mmol); colorless needles from methanol; m.p. 107–109 °C; yield: 8.7 g (52%). ^{1}H NMR: δ = 7.70 (s, 1 H), 7.08 (d, J = 2.2 Hz, 1 H), 6.66 (d, J = 2.2 Hz, 1 H), 3.96 (s, 3 H), 3.94 (s, 3 H) ppm. ^{13}C NMR: δ = 162.3, 155.8, 152.6, 141.8, 135.6 (q, J = 34 Hz), 124.4, 122.4 (q, J = 274 Hz), 121.4 (q, J = 8 Hz), 101.2, 100.9, 56.2, 55.8 ppm. MS (c.i.): m/z (%) = 353 (0) [M^+ + NH_4], 336 (66) [M^+ + 1], 335 (42) [M^+], 226 (37), 185 (46), 86 (100). However, the product proved contaminated from the beginning by some 10% of 2,7-dibromo-5-methoxy-4-(trifluoromethyl)quinoline [^{1}H NMR: δ = 7.89 (s, 1 H), 7.85 (s, 1 H), 7.14 (s, 1 H), 4.00 (s, 3 H) ppm]. After repetitive recrystallization from methanol, a 1:1 complex ("molecular compound") composed of this by-product and quinoline **8** was obtained; yellowish prisms; m.p. 103–107 °C. $C_{23}H_{15}Br_3F_6N_2O_3$ (721.08): calcd. C 38.31, H 2.10; found C 38.69, H 2.48.

2-Bromo-5,7-dimethyl-4-(trifluoromethyl)quinoline (9): Analogously starting from 5,7-dimethyl-4-(trifluoromethyl)quinolin-2(1*H*)-one (12 g, 50 mmol); colorless needles from methanol; m.p. 60–62 °C; yield: 11 g (74%). ^{1}H NMR: δ = 7.82 (s, 1 H), 7.75 (s, 1 H), 7.36 (s, 1 H), 2.74 (s, 3 H), 2.49 (s, 3 H) ppm. ^{13}C NMR: δ = 151.6; 141.1, 140.0, 135.4 (q, J = 33 Hz), 135.2, 133.6, 128.2, 123.7 (q, J = 8 Hz), 122.8 (q, J = 276 Hz), 120.4, 22.8 (q, J = 8 Hz), 21.2 ppm. MS (c.i.): m/z (%) = 312 (0) [M^+ + NH_4], 304 (100) [M^+ + 1], 303 (73) [M^+]. $C_{12}H_9BrF_3N$ (304.11): calcd. C 47.39, H 2.98; found C 46.96, H 2.55.

4-Chloro-5-fluoro-2-(trifluoromethyl)quinoline (7) and 4-Chloro-7-fluoro-2-(trifluoromethyl)quinoline: At 125 °C, a mixture of 5-fluoro- and 7-fluoroquinolin-4(1*H*)-ones[19] (23 g, 0.10 mol) was slowly added to phosphoric trichloride (18 mL, 31 g, 0.20 mol). After 2 h at this temperature, the mixture was poured into ice/water (0.40 L). The insoluble material was collected. A 28:72 mixture of 4-chloro-5-fluoro- and 4-chloro-7-fluoro-2-(trifluoromethyl)quinoline was obtained according to gas chromatography (30 m, DB 1701, 110 °C; 30 m, DB 210, 100 °C) and separated by elution from silica gel (0.60 L) with hexanes. **4-Chloro-5-fluoro-2-(trifluoromethyl)quinoline (7):** M.p. 31–33 °C; yield: 6.08 g (24%). ^{1}H NMR ($CDCl_3$): δ = 8.08 (d, J = 8.6 Hz, 1 H), 7.81 (m, 2 H), 7.42 (dd, J = 11.8, 8.0 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 157.3 (d, J = 262 Hz), 149.5, 148.3 (q, J = 35 Hz), 141.8 (d, J = 2 Hz), 131.0 (d, J = 10 Hz), 127.0 (d, J = 5 Hz), 120.7 (q, J = 276 Hz), 119.3 (quint, J = 2 Hz), 118.0 (d, J = 9 Hz), 114.6 (d, J = 22 Hz) ppm. MS (c.i.): m/z (%) = 267 (0) [M^+ + NH_4], 250 (100) [M^+ + 1], 249 (80) [M^+], 180 (8), 99 (4). $C_{10}H_4ClF_4N$ (249.59): calcd. C 48.12, H 1.62; found C 47.83, H 1.44. **4-Chloro-7-fluoro-2-(trifluoromethyl)quinoline**: M.p. 37–38 °C; yield: 15.5 g (62%). ^{1}H NMR ($CDCl_3$): δ = 8.34 (dd, J = 9.3, 5.8 Hz, 1 H), 7.89 (dd, J = 9.6, 2.6 Hz, 1 H), 7.80 (s, 1 H), 7.68 (ddd, J = 10.6, 8.0, 2.6 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 164.1 (d, J = 255 Hz), 149.0 (d, J = 13 Hz), 148.9 (q, J = 35 Hz), 144.5, 126.4 (d, J = 10 Hz), 124.0, 120.6 (q, J = 276 Hz), 120.1 (d, J = 26 Hz), 116.5 (quint, J = 2 Hz), 114.0 (d, J = 21 Hz) ppm. MS (c.i.): m/z (%) = 267 (0) [M^+ + NH_4], 250 (100) [M^+ + 1], 249 (86) [M^+], 180 (45), 145 (18). $C_{10}H_4ClF_4N$ (249.59): calcd. C 48.12, H 1.62; found C 48.39, H 1.39.

2. Metalation and Subsequent Carboxylation of Trifluoromethyl-Substituted Benzenes and Quinolines

2-Bromo-6-(trifluoromethyl)benzoic Acid (1): Potassium *tert*-butoxide (2.8 g, 25 mmol) and *N*,*N*,*N*′,*N*′,*N*′′-pentamethyldiethylenetriamine (3.7 mL, 2.9 g, 25 mmol) were added consecutively to the solution prepared from 2,2,6,6-tetramethylpiperidine (4.2 mL, 3.5 g, 25 mmol) and butyllithium (25 mmol) in tetrahydrofuran (50 mL) and hexanes (16 mL), cooled in a dry ice/methanol bath. After the dissolution of the potassium *tert*-butoxide, the mixture was diluted with diethyl ether (15 mL) and pentanes (15 mL). At –115 °C, 3-bromo(trifluoromethyl)benzene (5.6 g, 25 mmol) was added. After 45 min at –115 °C, the reaction mixture was poured onto an excess of freshly crushed dry ice covered with tetrahydrofuran (25 mL). It was later extracted with 1.0 M aqueous sodium hydroxide (3 × 50 mL). The combined aqueous layers were washed with diethyl ether (2 × 50 mL) and acidified to pH = 1 with concentrated hydrochloric acid. Upon extraction with diethyl ether (2 × 50 mL), drying and concentration, a viscous brown residue was left behind. It was extracted with boiling hexanes (3 × 75 mL). Upon concentration and cooling, slightly greenish needles formed; m.p. 129–130 °C (ref.[9] m.p. 131–133 °C); 1.62 g (24%).

2-Bromo-4,6-bis(trifluoromethyl)benzoic Acid (2): 3,5-Bis(trifluoromethyl)bromobenzene (4.3 mL, 7.3 g, 25 mmol) was added to the solution prepared from 2,2,6,6-tetramethylpiperidine (4.2 mL, 3.5 g, 25 mmol) and butyllithium (25 mmol) in tetrahydrofuran (50 mL) and hexanes (15 mL), kept in a dry ice/methanol bath. After 45 min at –75 °C, the reaction mixture was poured onto an excess of freshly crushed dry ice covered with tetrahydrofuran (25 mL). The volatiles were evaporated and the residue partitioned between diethyl ether (100 mL) and 6.0 M hydrochloric acid (50 mL). Upon drying and evaporation, a slightly yellow solid was obtained (7.81 g, m.p. 161–165 °C). Direct sublimation afforded colorless needles; 7.00 g (83%); m.p. 174–175 °C. ^{1}H NMR: δ = 8.12 (s, 1 H), 7.94 (s, 1 H) ppm. ^{13}C NMR: δ = 169.5, 136.1, 133.7 (q, J = 34 Hz), 133.5 (q, J = 3 Hz), 130.2 (q, J = 34 Hz), 122.5 (hept, J = 4 Hz), 122.0 (q, J = 274 Hz), 121.9 (q, J = 275 Hz), 121.4 ppm. $C_9H_3BrF_6O_2$ (337.01): calcd. C 32.08, H 0.90, found C 31.98, H 0.89.

4-Chloro-5-fluoro-2-(trifluoromethyl)quinoline-3-carboxylic Acid (10): Diisopropylamine (3.5 mL, 2.5 g, 25 mmol) and 4-chloro-5-fluoro-2-(trifluoromethyl)quinoline (**7**; 6.2 g, 25 mmol) were added consecutively to a solution of butyllithium (25 mmol) in tetrahydrofuran (30 mL) and hexanes (15 mL), kept in a dry ice/methanol bath. After 2 h at –75 °C, the mixture was poured onto an excess of freshly crushed dry ice. A 1.8 M ethereal solution (15 mL) of hydrochloric acid was added. The solvents were evaporated and the residue was crystallized from a 4:1 (v/v) mixture of hexanes and ethyl acetate; colorless prisms; m.p. 225–227 °C (decomp.); yield: 4.48 g (61%). ^{1}H NMR*: δ = 8.14 (d, J = 8.0 Hz, 1 H), 8.07 (ddd, J = 8.3, 7.7, 4.8 Hz, 1 H), 7.72 (ddd, J = 12.5, 7.7, 1.3 Hz, 1 H) ppm. ^{13}C NMR*: δ = 164.9, 158.5 (d, J = 261 Hz), 148.8, 144.6 (qd, J = 35, 2 Hz), 139.0 (d, J = 3 Hz), 133.4 (d, J = 10 Hz), 127.8, 128.0 (d, J = 5 Hz), 120.8 (q, J = 276 Hz), 118.0 (d, J = 8 Hz), 117.0 (d, J = 22 Hz) ppm. MS (c.i.): m/z (%) = 311 (0) [M^+ + NH_4], 294 (100) [M^+ + 1], 293 (87) [M^+], 276 (50), 194 (29).

$C_{11}H_4ClF_4NO_2$ (293.60): calcd. C 45.00, H 1.37; found C 44.79, H 1.12.

2-Bromo-5,7-dimethyl-4-(trifluoromethyl)quinoline-3-carboxylic Acid (11): Prepared analogously from 2-bromo-5,7-dimethyl-4-(trifluoromethyl)quinoline (**9**; 4.6 g, 15 mmol). The product was partitioned between water (50 mL) and diethyl ether (3 × 50 mL). The combined organic layers were concentrated and the residue was crystallized from ethanol; colorless prisms; m.p. 164–165 °C (decomp.); yield: 1.36 g (26%). ^{1}H NMR*: δ = 7.79 (s, 1 H), 7.64 (s, 1 H), 2.78 (q, J = 2.9 Hz, 3 H), 2.57 (s, 3 H) ppm. ^{13}C NMR*: δ = 166.6, 151.0, 143.1, 139.0, 137.2, 134.9, 131.9 (q, J = 32 Hz), 130.9, 128.2, 123.7 (q, J = 276 Hz), 120.7, 23.2 (q, J = 9 Hz), 21.1 ppm. MS (c.i.): m/z (%) = 363 (0) [M^+ + NH_4], 348 (100) [M^+ + 1], 347 (74) [M^+], 303 (14). $C_{13}H_9BrF_3NO_2$ (348.12): calcd. C 44.85, H 2.61; found C 44.79, H 1.12.

No trace of an acid was obtained when 4-bromo-5-fluoro-2-(trifluoromethyl)quinoline (**4**), 4-bromo-5-methoxy-2-(trifluoromethyl)quinoline (**5**), 4-bromo-5,7-dimethyl-2-(trifluoromethyl)-quinoline (**6**) and 2-bromo-5,7-dimethoxy-4-(trifluoromethyl)quinoline (**8**) were subjected to the same and similar reaction conditions.

3. Crystallography

4-Bromo-5-methoxy-2-(trifluoromethyl)quinoline (**5**),[19] 4-bromo-2,7-bis(trifluoromethyl)quinoline (**14**),[25] 4-bromo-8-fluoro-2-(trifluoromethyl)quinoline (**15**)[19] and 2-bromo-6-trifluoromethoxy-4-(trifluoromethyl)quinoline (**16**),[26] were available from previous work. The preparation of compounds **8** and **9** is described above. As explained in Subsection 2, quinoline **8** crystallized as a 1:1 molecular complex together with 2,7-dibromo-5-methoxy-4-(trifluoromethyl)quinoline, accidentally formed as a by-product. Although this contamination certainly constitutes a flaw, it did not compromise the ultimate goal. As the nature of the substituent at the 7-position does not affect the structure of the heterocyclic ring nor of the *peri*-(5-)position, the pertinent data could be acquired without complication. X-ray diffraction data were collected using the Mo-K_α (0.71073 Å) radiation and a low-temperature device [T = 140(2) K] on a four-circle kappa goniometer, equipped with an Oxford Diffraction KM4 Sapphire CCD in the case of compounds **8**, **9**, **14**, and **16**, whereas for compounds **5** and **15** a marresearch mar345 IPDS was used. All data reductions were performed with the CrysAlis RED 1.7.0 software (Oxford Diffraction, Abingdon, UK, 2003). Absorption correction has been applied to all data sets except of compound **14**. The structures were refined using the full-matrix least squares on F^2 with all non-hydrogen atoms anisotropically defined. The hydrogen atoms were placed in calculated positions using the "riding model". Structure refinements and geometrical calculations were carried out with the SHELXTL software (University of Göttingen, 1997; Bruker AXS, Madison, 1997). All crystallographic data the present manuscript refers to are contained in the CCDC-275711 to -275716 files. They can be downloaded free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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