Three Chloro(trifluoromethyl)pyridines as Model Substrates for Regioexhaustive Functionalization

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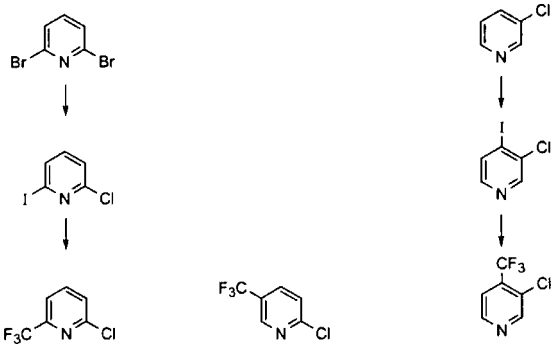
As a further test of the concept of regioexhaustive functionalization, 2-chloro-6-(trifluoromethyl)pyridine, 2-chloro-5-(trifluoromethyl)pyridine and 3-chloro-4-(trifluoromethyl)-pyridine were each converted into the three possible carboxylic acids **2, 4, 6, 8**, **10, 12**, **16, 17** and **20**. This was achieved by employing several, but not all of the organometallic "toolbox methods": transformation of a more basic organometallic species into a less basic isomer by transmetalation-equilibration, site discriminating deprotonation with lithium *N*,*N*-diisopropylamide or lithium 2,2,6,6-tetramethylpiperidide, regio-divergent iodine migration and steric screening of acidic positions by a bulky trialkylsilyl group.

Introduction

The concept of "regioexhaustive substitution" [1] has been devised to optimally exploit the derivatization potential of a given core structure. The practical realization relies on a set of complementary organometallic methods (the "toolbox methods" [1]) which enables the site-specific introduction of an alkali or alkaline earth metal in any vacant position of the substrate. The choice of suitable electrophilic trapping reagents is almost unlimited, and hence, a single organometallic intermediate can be proliferated into hundreds of new compounds.

The concept of regioexhaustive substitution and the toolbox methods have so far been tested with 1,3-difluorobenzene,[2] 1,3-dichlorobenzene,[3] a series of di- and trifluorophenols,[4] 6- and 7-fluoroquinolines,[5] 4-, 5-, 6- and 7-fluoroindoles,[6] and 3-fluoropyridine.[1,7] The reason to extend such kind of investigations to chloro(trifluoromethyl)-pyridines was twofold. In this way, a variety of halogenated pyridinecarboxylic acids and other attractive building blocks, all unknown prior to our preliminary work in this field,[8] would become easily available. On the other hand, success was by no means guaranteed. (Trifluoromethyl)arenes tend to deviate the attack of a strong base from an adjacent to a more remote position.[9,10] Apparently, the bulkiness [11–17] of the substituent offsets its powerful inductive electron-withdrawing effect. As a chlorine atom can also act as a strong *ortho*-activator,[18] we were not sure whether the metalation, whatever the reagent, could be directed at all in the vicinity of the trifluoromethyl group.

The three model substrates selected carry the CF_3 substituent at a different ring position: 2-chloro-6-(trifluoromethyl)pyridine, 2-chloro-5-(trifluoromethyl)pyridine and 3-chloro-4-(trifluoromethyl)pyridine. All three are commercial reagents, but only 2-chloro-5-(trifluoromethyl)pyridine is inexpensive (about 100 EUR/mol). Thus, we prepared the other two by applying the iodine/trifluoromethyl[19] displacement method.



Carboxylic Acids Derived From 2-Chloro-6-(trifluoromethyl)-pyridine

As reported,[20] 2-chloro-6-(trifluoromethyl)pyridine was deprotonated by lithium diisopropylamide (LIDA) concomitantly at the 3- and 4-positions. However, after the reaction mixture had been stored for 4 h at −85 °C, the more basic 4-lithio species was found to have been completely converted into the less basic 3-lithio isomer. Upon trapping with iodine, only 2-chloro-3-iodo-6-(trifluoromethyl)pyridine (**1**; 69%) was obtained.[20]

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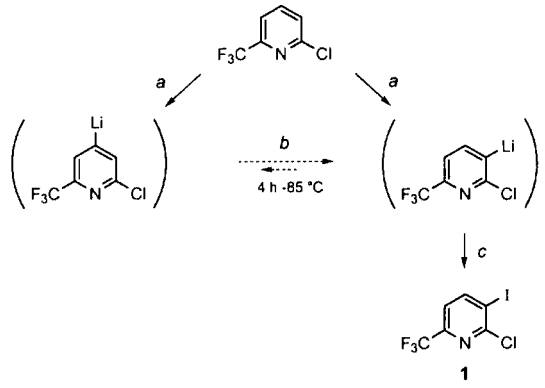
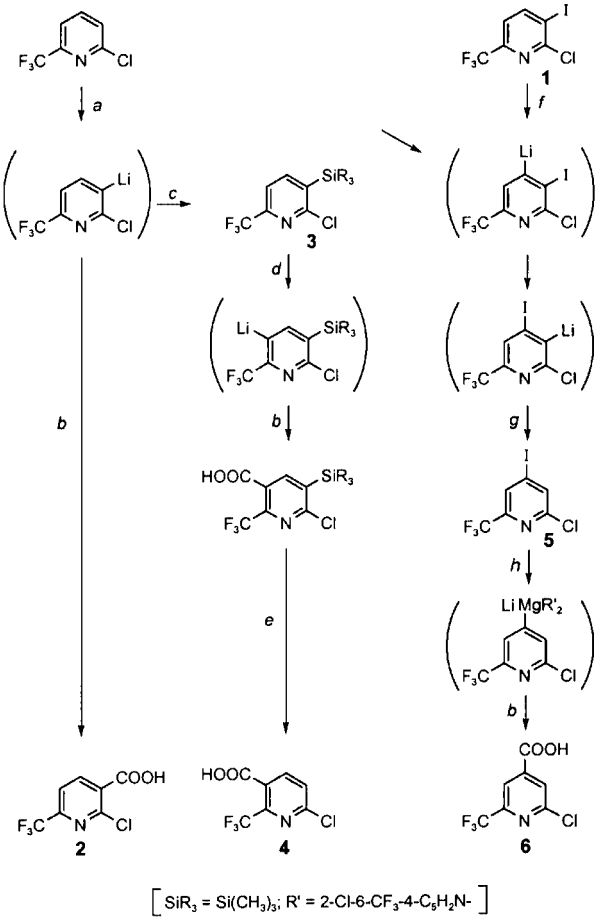


[a] Lithium diisopropylamide (LIDA) in tetrahydrofuran (THF) at -100 °C for 15 min. [b] At -85 °C for 4 h in the presence of diisopropylamine. [c] Elemental iodine.

Equilibration of the organometallic intermediates at −85 °C followed by carboxylation and neutralization provided the 2-chloro-6-(trifluoromethyl)pyridine-3-carboxylic acid (**2**; 79%). When the 2-chloro-6-(trifluoromethyl)pyrid-3-yllithium was trapped with chlorotrimethylsilane rather than with dry ice, 2-chloro-6-trifluoromethyl-3-(trimethylsilyl)pyridine (**3**) was isolated in 85% yield.[20] Its consecutive treatment with lithium 2,2,6,6-tetramethylpiperidide (LITMP), carbon dioxide and tetrabutylammonium fluoride trihydrate gave the 6-chloro-2-(trifluoromethyl)pyridine-3-carboxylic acid (**4**; 70%). The compound 2-chloro-3-iodo-6-(trifluoromethyl)pyridine (**1**) was cleanly converted by LIDA-promoted heavy halogen migration [11,20−22] into its 4-iodo isomer **5** (83%). Halogen/metal permutation, carboxylation and neutralization provided the 2-chloro-6-(trifluoromethyl)pyridine-4-carboxylic acid (**6**; 74%).

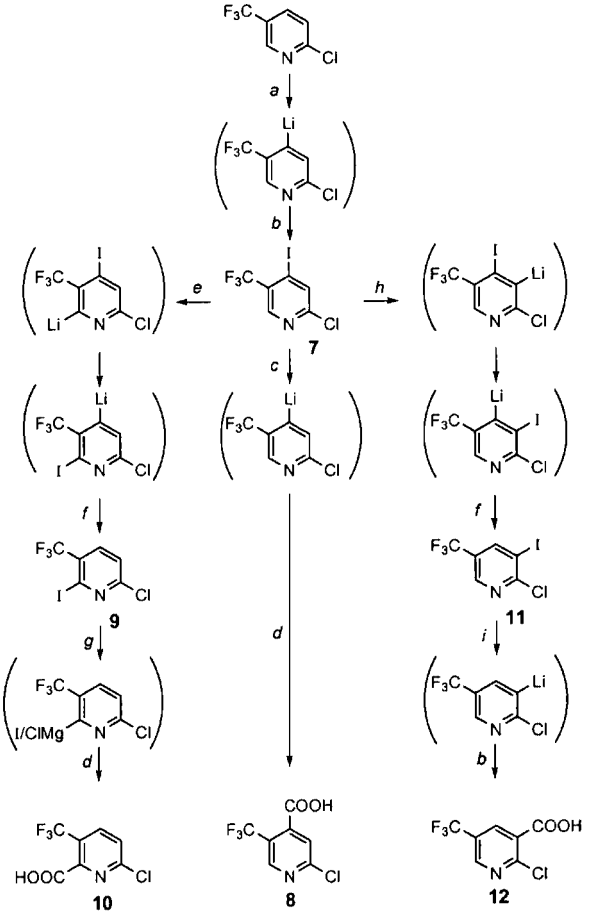


[SiR_3 = $Si(CH_3)_3$; R' = 2-Cl-6-CF_3-4-C_5H_2N-]

[a] LIDA in THF at -85 °C for 4 h. [b] (1.) Excess dry ice; (2.) hydrogen chloride in diethyl ether (DEE). [c] Chlorotrimethylsilane. [d] Lithium 2,2,6,6-tetramethylpiperidide (LITMP) in THF at −75 °C for 45 min. [e] Tetrabutylammonium fluoride trihydrate in THF at 25 °C for 20 h. [f] LIDA in THF at −75 °C for 45 min. [g] Hydrochloric acid. [h] Lithium tributylmagnesate [23,24] in THF at 0 °C for 5 min.

Carboxylic Acids Derived From 2-Chloro-5-(trifluoromethyl)pyridine

Carefully controlled conditions were required to prepare 2-chloro-4-iodo-5-(trifluoromethyl)pyridine (**7**; 67%) from

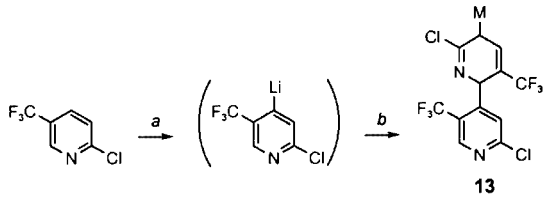


[a] LIDA (1.0 eq.) + LIDCB (1.0 eq.) + LiBr (0.1 eq.) in THF at 0 °C for 15 min with vigorous stirring, then addition of solid 2-chloro-5-(triflluoromethyl)pyridine at −75 °C. [b] Molecular iodine (1.0 eq.). [c] Butyllithium in THF at −75 °C for 15 min. [d] (1.) Excess of dry ice; (2.) ethereal hydrogen chloride. [e] LIDA in THF at −75 °C for 2 h. [f] Hydrochloric acid. [g] Isopropylmagnesium chloride in THF at −75 °C for 15 min. [h] Lithium piperidide (LIPIP) in THF at −75 °C for 20 h. [i] Butyllithium in THF at −75 °C for 10 min.

2-chloro-5-(trifluoromethyl)pyridine by treatment with LIDA in the presence of lithium *N*,*N*-diisopropylcarbamate (LIDCB) and catalytic amounts of lithium bromide, and subsequent addition of molecular iodine. The iodo compound **7** became the turntable leading to the three carboxylic acids **8**, **10** and **12**. Immediate halogen/metal permutation followed by carboxylation and neutralization produced the 2-chloro-5-(trifluoromethyl)pyridine-4-carboxylic acid (**8**; 87%). Treatment with LIDA and subsequent neutralization gave 6-chloro-2-iodo-3-(trifluoromethyl)pyridine (**9**; 77%), the conversion of which into 6-chloro-3-(trifluoromethyl)pyridine-2-carboxylic acid (**10**; 87%) proved to be straightforward. Finally, when lithium piperidide (LIPIP) was used to promote the isomerization of the 4-iodo compound **7**, 2-chloro-3-iodo-6-(trifluoromethyl)pyridine (**11**; 46%) was obtained as a pure isomer. With this intermediate at hand, 2-chloro-5-(trifluoromethyl)pyridine-3-carboxylic acid (**12**; 65%) was prepared without problems.

The dichotomy in the outcome of the iodopyridine **7** isomerization, depending on whether mediated by LIDA or LIPIP, can be rationalized on the basis of the different steric hindrance experienced by these reagents and the differences in their basicities, and hence, proton abstraction capacities.[25] Lithium *N*,*N*-diisopropylcarbamate appears to combine with LIDA, and the resulting adduct discriminates 4:1 in favor of deprotonation of the 4- rather than of the 3-position, whereas in its absence both sites are randomly attacked. In contrast, the role of lithium bromide still remains quite mysterious. The action of lithium bromide must be catalytic as less than stoichiometric amounts of it are used. For example, it may assist in the reorganization of the involved aggregates or mixed aggregates.

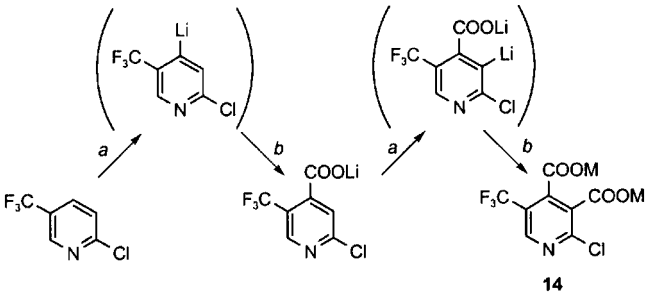
As this example illustrates, clean metalation reactions of pyridines bearing trifluoromethyl groups at the 3- (or 5-) position can be brought about with difficulty, if at all. The major obstacle is presumably their extraordinary tendency towards nucleophilic addition of organometallic reagents and intermediates.[26] Indeed, a considerable quantity (32%) of the dimer **13** (M = H, after neutralization) was formed when only half of the standard amount of base was used under otherwise optimized conditions.



13

[a] LIDA (0.5 eq.) + lithium *N*,*N*-diisopropylcarbamate (LIDCB, 0.5 eq.) + LiBr (0.05 eq.). [b] Hydrochloric acid.

Another complication encountered with 2-chloro-5-(trifluoromethyl)pyridine was the in situ transformation of a primary reaction product. When carbon dioxide was added *slowly* to a solution containing the substrate together with three equivalents of LIDA and some sodium bromide, the diacid **14** (M = H after neutralization) was produced in a 60−70% yield. Obviously, the initially generated lithium 2-chloro-5-(trifluoromethyl)pyridine-4-carboxylate rapidly underwent a new *ortho*-lithiation,[27,28] thus paving the way to the *vic*-diacid.

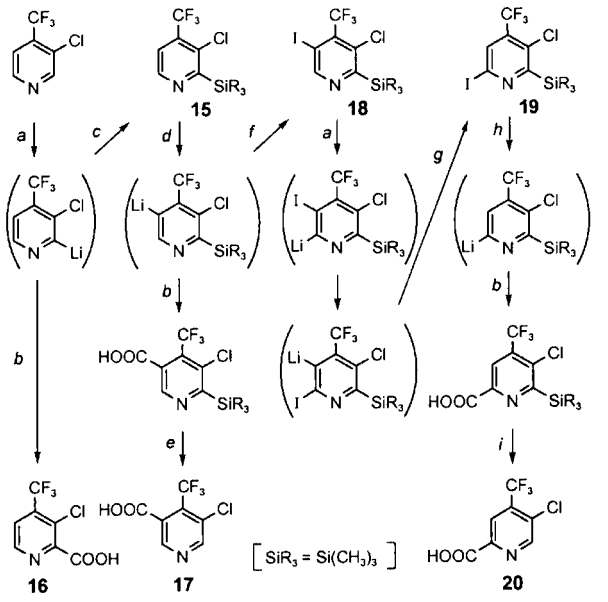


14

[a] LIDA (3.0 eq.) + NaBr (3.0 eq.). [b] Carbon dioxide added as a solid in the reaction mixture.

Carboxylic Acids Derived From 3-Chloro-4-(trifluoromethyl)pyridine

The reactions involving the third substrate 3-chloro-4-(trifluoro-methyl)pyridine proceeded as expected. Both LIDA or LITMP abstracted a proton rapidly and exclusively from the 2-position. In this way, it was possible to access the silane **15** (74%) and 3-chloro-4-(trifluoromethyl)pyridine-2-carboxylic acid (**16**; 57%) directly. LITMP-promoted metalation of the silane **15** and the subsequent carboxylation occurred at the 5-position, providing the 5-chloro-4-(trifluoromethyl)pyridine-3-carboxylic acid (**17**; 83%) after deprotection of its silylated precursor. Trapping of the lithiated silane **15** with molecular iodine gave 3-chloro-5-iodo-4-



15 **16** **17** **18** **19** **20**

[a] LITMP in DEE (or THF) at –100 °C for 45 min. [b] (1.) Excess dry ice; (2.) hydrochloric acid. [c] Chlorotrimethylsilane. [d] LITMP in THF at –75 °C for 2 h. [e] (1.) Aqueous sodium hydroxide at 100 °C for 1 min. [f] Molecular iodine. [g] Hydrochloric acid. [h] Butyllithium in toluene at –75 °C for 15 min. [i] TBAF in refluxing THF for 1 min.

trifluoromethyl-5-(trimethylsilyl)pyridine (**18**; 85%), which was isomerized to the 6-iodo isomer **19** (62%) by treatment with LITMP and subsequent neutralization. Compound **19** was converted into the 5-chloro-4-(trifluoromethyl)pyridine-2-carboxylic acid (**20**, 75%) by consecutive halogen/metal permutation (using butyllithium), carboxylation and protodesilylation.

Experimental Section

General Remarks: Working practices and abbreviations are specified in previous articles from this laboratory.[29−31] ^{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.

1. Starting Materials

The preparation of 2-chloro-6-(trifluoromethyl)pyridine has been described recently.[19] 2-Chloro-5-(trifluoromethyl)pyridine was purchased from Apollo (Whitefield Rd, Bredbury, Stockport, Cheshire, SK6 2QR). 2-Chloro-3-iodopyridine (**1**),[20] 2-chloro-3-(trimethylsilyl)pyridine (**3**),[20] 2-chloro-4-iodo-6-(trifluoromethyl)-pyridine (**5**)[20] and 3-chloro-4-iodopyridine[32] were prepared following literature procedures.

3-Chloro-4-(trifluoromethyl)pyridine: After thorough mixing, spray dried potassium fluoride (6.4 g, 0.11 mol) and cuprous iodide (21 g, 0.11 mol) were heated with the flame of a Bunsen burner under vacuum (1 Torr) with gentle shaking for about 10 min until a homogeneous greenish color was obtained. *N*-Methylpyrrolidinone (0.10 L) and trimethyl(trifluoromethyl)silane (16 mL, 15.6 g, 0.11 mol) were added, and the slurry was slowly heated to 50 °C under vigorous stirring. After 30 min, when evolution of gas had ceased, 3-chloro-4-iodopyridine[32] (25 g, 0.11 mol) was added, and the mixture was kept for 20 h at 50 °C, before being cooled to 25 °C, poured into a 12% aqueous ammonia solution (0.20 L) and extracted with diethyl ether (3 × 0.15 L). The combined organic phases were consecutively washed with 12% aqueous ammonia solution (3 × 0.10 L), 2.0 M hydrochloric acid (0.10 L), a saturated aqueous solution of sodium hydrogencarbonate (0.10 L) and brine (0.10 L) and dried. Upon distillation, a colorless oil was collected. B.p. 142−144 °C; m.p. −23 to −20 °C; yield: 13.8 g (69%). n_D^{20} 1.4559; d_4^{20} 1.407. ^{1}H NMR: δ = 8.78 (s, 1 H), 8.67 (d, *J* = 4.8 Hz, 1 H), 7.58 (d, *J* = 4.8 Hz, 1 H) ppm. ^{13}C NMR: δ = 151.6, 148.5, 135.8 (q, *J* = 33 Hz), 129.2 (q, *J* = 2 Hz), 121.7 (q, *J* = 274 Hz), 120.9 (q, *J* = 5 Hz) ppm. $C_6H_3ClF_3N$ (181.54): calcd. C 39.78, H 1.74; found C 39.70, H 1.67.

2. Derivatives of 2-Chloro-6-(trifluoromethyl)pyridine

The preparation of 2-chloro-3-iodo-6-trifluoromethylpyridine (**1**) and 2-chloro-6-trifluoromethyl-3-(trimethylsilyl)pyridine (**3**) has already been described in a previous publication.[20]

2-Chloro-6-(trifluoromethyl)pyridine-3-carboxylic Acid (2): At −85 °C, diisopropylamine (2.8 mL, 2.0 g, 20 mmol) and 2-chloro-6-(trifluoromethyl)pyridine[19] (3.6 g, 20 mmol) were added consecutively to a solution of butyllithium (10 mmol) in tetrahydrofuran (50 mL) and hexanes (6 mL). After 4 h at −85 °C, the reaction mixture was poured onto an excess of freshly crushed dry ice before being treated at +25 °C with 2.0 M hydrochloric acid (50 mL). The volatiles were evaporated and the residue crystallized from a 6:1 (v/v) mixture of hexanes and ethyl acetate as colorless needles. M.p. 106−108 °C; yield: 3.56 g (79%). ^{1}H NMR*: δ = 8.59 (dq, *J* = 7.7, 0.7 Hz, 1 H), 8.03 (d, *J* = 8.0 Hz, 1 H) ppm. ^{13}C NMR*: δ = 164.9, 150.3, 149.6 (q, *J* = 35 Hz), 143.4, 131.9, 121.5 (q, *J* = 274 Hz), 120.8 (q, *J* = 3 Hz) ppm. $C_7H_3ClF_3NO_2$ (225.55): calcd. C 37.28, H 1.34; found C 37.15, H 1.54.

6-Chloro-2-(trifluoromethyl)pyridine-3-carboxylic Acid (4): 2-Chloro-6-trifluoromethyl-3-(trimethylsilyl)pyridine[20] (5.4 g, 25 mmol) was added to a solution prepared from butyllithium (25 mmol) and 2,2,6,6-tetramethylpiperidine (4.2 mL, 3.5 g, 25 mmol) in tetrahydrofuran (50 mL) and hexane (16 mL) cooled 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 solvents were evaporated and the residue partitioned between diethyl ether (75 mL) and 6.0 M hydrochloric acid (20 mL). The organic layer was dried and the solvents evaporated. The residue was treated with tetrabutylammonium fluoride trihydrate (7.9 g, 25 mmol) in tetrahydrofuran (50 mL) for 20 h at 25 °C. The solvents were evaporated, and the residue taken back into diethyl ether (100 mL) and washed with 2.0 M hydrochloric acid (2 × 50 mL). The organic phase was dried, evaporated and the residue crystallized from chloroform as colorless needles. M.p. 160−162 °C; 3.8 g (70%). ^{1}H NMR*: δ = 8.40 (d, *J* = 8.0 Hz, 1 H), 7.93 (d, *J* = 8.0 Hz, 1 H) ppm. ^{13}C NMR*: δ = 165.7, 153.0, 145.7 (q, *J* = 36 Hz), 142.9, 128.9, 128.5, 121.6 (q, *J* = 275 Hz) ppm. $C_7H_3ClF_3NO_2$ (225.55): calcd. C 37.28, H 1.34; found C 37.09, H 1.08.

2-Chloro-4-iodo-6-(trifluoromethyl)pyridine (5): 2-Chloro-3-iodo-6-(trifluoromethyl)pyridine[20] (**1**; 6.1 g, 20 mmol) was added to a solution prepared from butyllithium (20 mmol) and diisopropylamine (2.8 mL, 2.0 g, 20 mmol) in tetrahydrofuran (40 mL) and hexanes (13 mL) cooled in a dry ice/methanol bath. After 45 min at −75 °C, the reaction mixture was partitioned between 2.0 M hydrochloric acid (20 mL) and diethyl ether (40 mL). The organic layers were washed with a saturated aqueous solution (20 mL) of sodium hydrogencarbonate and brine (20 mL), dried and the solvents evaporated. Crystallization of the residue from ethanol afforded colorless prisms. M.p. 94−95 °C (ref. 20: m.p. 93−95 °C); yield: 5.10 g (83%).

2-Chloro-6-(trifluoromethyl)pyridine-4-carboxylic Acid (6): Butylmagnesium chloride (3.3 mmol), tetrahydrofuran (15 mL) and 2-chloro-4-iodo-6-(trifluoromethyl)pyridine[20] (**5**; 3.1 g, 10 mmol) were added at 10 min intervals to a solution of butyllithium (6.7 mmol) in hexanes (4 mL) at 0 °C. After 5 min, the reaction mixture was poured onto an excess of freshly crushed dry ice, evaporated and partitioned between diethyl ether (50 mL) and 2.0 M hydrochloric acid (50 mL). The organic layer was dried and the solvents were evaporated. The residue crystallized from hexanes as pale yellow needles. M.p. 116−118 °C; yield: 1.68 g (74%). ^{1}H NMR: δ = 8.23 (s, 1 H), 8.18 (s, 1 H) ppm. ^{13}C NMR: δ = 167.3, 153.3, 149.6 (q, *J* = 37 Hz), 141.0, 127.8, 120.3 (q, *J* = 275 Hz), 118.9 (q, *J* = 3 Hz) ppm. $C_7H_3ClF_3NO_2$ (225.55): calcd. C 37.28, H 1.34; found C 37.15, H 1.39.

3. Derivatives of 2-Chloro-5-(trifluoromethyl)pyridine

The preparation of 2-chloro-4-iodo-5-(trifluoromethyl)pyridine (**7**), 2-chloro-5-(trifluoromethyl)pyridine-4-carboxylic acid (**8**), 2-chloro-3-iodo-5-(trifluoromethyl)pyridine (**11**) and 2-chloro-5-(tri-

fluoromethyl)-pyridine-3-carboxylic acid (**12**) have been described in a previous publication.[8]

6-Chloro-2-iodo-3-(trifluoromethyl)pyridine (9): In a dry ice/methanol bath, 2-chloro-4-iodo-5-(trifluoromethyl)pyridine (31 g, 0.10 mol) was added to a solution prepared from diisopropylamine (14 mL, 10 g, 0.10 mmol) and butyllithium (0.10 mol) in tetrahydrofuran (0.15 L) and hexane (60 mL) containing also a spatula tip of iodine. After 2 h at −75 °C, 2.0 M hydrochloric acid (0.10 L) was added. The organic layer was decanted and the aqueous phase extracted with diethyl ether (0.10 L). The combined organic phases were evaporated and the residue subjected to steam distillation. The slightly yellow oil obtained was distilled. M.p. −5 to −4 °C; b.p. 65−66 °C/1.5 Torr; yield: 23.8 g (77%). n_D^{20} 1.557. ^{1}H NMR: δ = 7.78 (d, J = 8.2 Hz, 1 H), 7.42 (d, J = 8.2 Hz, 1 H) ppm. ^{13}C NMR: δ = 153.0, 137.0 (q, J = 5 Hz), 130.9 (q, J = 33 Hz), 122.9, 122.2 (q, J = 273 Hz), 113.0 ppm. $C_6H_2ClF_3IN$ (307.44): calcd. C 23.44, H 0.66; found C 23.38, H 0.77.

6-Chloro-3-(trifluoromethyl)pyridine-2-carboxylic Acid (10): Isopropylmagnesium chloride (25 mmol) was added to a solution of 6-chloro-2-iodo-3-(trifluoromethyl)pyridine (7.7 g, 25 mmol) in tetrahydrofuran (50 mL) cooled in a dry ice/methanol bath. After 15 min at −75 °C, the suspension was poured onto an excess of freshly crushed dry ice. It was treated with 2.0 M ethereal hydrochloric acid (50 mL) and the solvents were evaporated. The residue was crystallized from a 1:1 (v/v) mixture of ethyl acetate and hexanes as tiny colorless needles. M.p. 109−110 °C (reprod.); yield: 4.56 g (81%). ^{1}H NMR: δ = 8.05 (d, J = 8.4 Hz, 1 H), 7.60 (d, J = 8.4 Hz, 1 H) ppm. ^{13}C NMR: δ = 165.6, 154.0, 150.5, 137.7 (q, J = 4 Hz), 125.7, 123.2 (q, J = 34 Hz), 122.5 (q, J = 273 Hz) ppm. $C_7H_3ClF_3NO_2$ (225.55): calcd. C 37.27, H 1.34; found C 37.47, H 1.72.

2,6′-Dichloro-3,5′-bis(trifluoromethyl)-2,5-dihydro-2,4′-bipyridine (13): Lithium *N*,*N*-diisopropylcarbamate (3.8 g, 25 mmol) was freshly prepared from molar equivalents of diisopropylamine and butyllithium and an excess of carbon dioxide gas in tetrahydrofuran. It was isolated after evaporation of the volatiles and dried as a white powder. It was added at 0 °C to the solution prepared from diisopropylamine (3.5 mL, 2.5 g, 25 mmol), lithium bromide (0.17 g, 2.0 mmol) and butyllithium (25 mmol) in tetrahydrofuran (35 mL) and hexanes (15 mL). The mixture was vigorously stirred until it became homogeneous. It was placed in a dry ice/methanol bath and, after solid 2-chloro-5-(trifluoromethyl)pyridine (9.1 g, 50 mmol) was dissolved in it, kept for 2 h at −75 °C before it was treated with 2.0 M hydrochloric acid (10 mL). The solvents were evaporated, the residue taken up in diethyl ether (0.10 L), washed with 2.0 M hydrochloric acid (2 × 50 mL), a saturated aqueous solution (50 mL) of sodium hydrogencarbonate and brine (2 × 50 mL), dried. The solvents were evaporated. Crystallization from chloroform gave colorless needles. M.p. 208−210 °C (reprod.); yield: 2.92 g (32%). ^{1}H NMR: δ = 8.70 (s, 1 H), 7.53 (s, 1 H), 7.17 (dq, J = 5.4, 1.6 Hz, 1 H), 4.32 (d, J = 9.0 Hz, 1 H), 3.16 (dd, J = 17.2, 9.1 Hz, 1 H), 2.66 (d, J = 17.1 Hz, 1 H) ppm. ^{13}C NMR: δ = 167.3, 156.9, 163.9, 149.1 (q, J = 6 Hz), 134.5 (q, J = 6 Hz), 125.4 (q, J = 269 Hz), 124.6 (q, J = 273.4 Hz), 123.9, 123.3 (q, J = 31 Hz), 104.8 (q, J = 32 Hz), 37.5, 33.0 ppm. $C_{12}H_6Cl_2F_6N_2$ (363.08): calcd. C 39.69, H 1.66; found C 36.63, H 2.04.

2-Chloro-5-(trifluoromethyl)pyridine-3,4-dicarboxylic Acid (14): 2-Chloro-5-(trifluoromethyl)pyridine (1.8 g, 10 mmol) was added as a solid to a solution prepared from butyllithium (30 mmol) and diisopropylamine (4.2 mL, 3.0 g, 30 mmol) in tetrahydrofuran (30 mL) and hexanes (16 mL) containing finely powdered sodium bromide (3.1 g, 30 mmol) and kept in a dry ice/methanol bath. After 2 h at −75 °C, an excess of solid carbon dioxide was added to the reaction mixture. Diethyl ether (40 mL) was added, and the product was extracted with 1.0 M sodium hydroxide aqueous solution (3 × 20 mL). The combined aqueous layers were washed with diethyl ether (2 × 20 mL), acidified to pH 1 and extracted with diethyl ether (3 × 30 mL). The combined organic layers were dried and the solvents evaporated. According to gas chromatographic analysis of a sample after treatment with diazomethane (30 m, DB-1, 175 °C; DB-WAX, 30 m, 175 °C, methyl benzoate as internal standard), an aliquot of the reaction product was obtained after esterification with diazomethane methyl 2-chloro-5-(trifluoromethyl)pyridine-4-carboxylate (15%), methyl 2-chloro-5-(trifluoromethyl)pyridine-3-carboxylate (16%) and methyl 2-chloro-5-(trifluoromethyl)pyridine-3,4-dicarboxylate (64%). Crystallization of the mixture of acids from a 1:1 (v/v) mixture of toluene and ethanol afforded colorless needles. M.p. 180−182 °C; yield: 1.36 g (37%). ^{1}H NMR: δ = 8.74 (s) ppm. ^{13}C NMR: δ = 165.3, 165.1, 152.1, 147.7 (q, J = 6 Hz), 142.1, 129.0, 122.4 (q, J = 274 Hz), 121.9 (q, J = 33 Hz) ppm. $C_8H_3ClF_3NO_4$ (363.08): calcd. C 35.65, H 1.12; found C 35.95, H 0.87.

4. Derivatives of 3-Chloro-4-(trifluoromethyl)pyridine

3-Chloro-4-trifluoromethyl-2-(trimethylsilyl)pyridine (15): Lithium diisopropylamide prepared from diisopropylamine (4.2 mL, 3.0 g, 30 mmol) and butyllithium (30 mmol) in tetrahydrofuran (30 mL) and hexanes (18 mL) was added dropwise, over 1 h, to a solution of 3-chloro-4-(trifluoromethyl)pyridine (3.9 mL, 5.4 g, 30 mmol) and chlorotrimethylsilane (3.8 mL, 3.3 g, 30 mmol) in tetrahydrofuran (30 mL) cooled in a dry ice/methanol bath. After 1 h at −75 °C, the mixture was filtered through basic alumina (50 mL), eluted with diethyl ether (2 × 50 mL), dried and distilled to obtain a colorless oil. B.p. 75−76 °C/12 Torr; m.p. 4−6 °C; yield: 5.61 g (74%). n_D^{20} 1.4675; d_4^{20} 1.210. ^{1}H NMR: δ = 8.81 (d, J = 4.8 Hz, 1 H), 7.49 (d, J = 4.8 Hz, 1 H), 0.46 (s, 9 H) ppm. ^{13}C NMR: δ = 169.5, 148.1, 135.5 (q, J = 2 Hz), 134.3 (q, J = 32 Hz), 122.1 (q, J = 274 Hz), 120.0 (q, J = 5 Hz), −1.0 ppm. $C_9H_{11}ClF_3NSi$ (253.72): calcd. C 42.60, H 4.37; found C 42.49, H 4.16.

3-Chloro-4-(trifluoromethyl)pyridine-2-carboxylic Acid (16): At −100 °C, 3-chloro-4-(trifluoromethyl)pyridine (1.3 mL, 1.8 g, 10 mmol) was added to a solution prepared from butyllithium (20 mmol) and 2,2,6,6-tetramethylpiperidine (3.4 mL, 2.8 g, 20 mmol) in diethyl ether (50 mL) and hexanes (12 mL). After 2 h at −75 °C, the mixture was poured onto an excess of freshly crushed dry ice covered with diethyl ether (25 mL). At 25 °C, the mixture was extracted with 2.0 M aqueous sodium hydroxide solution (3 × 25 mL). The combined aqueous phases were washed with diethyl ether (2 × 20 mL), acidified to pH 1 and extracted with diethyl ether (3 × 20 mL). The organic solvent was evaporated and the residue crystallized from a 2:1 (v/v) mixture of heptane and ethyl acetate as colorless needles. M.p. 106−108 °C (decomp.); yield: 1.29 g (57%). ^{1}H NMR*: δ = 8.85 (d, J = 4.8 Hz, 1 H), 8.00 (d, J = 4.8 Hz, 1 H) ppm. ^{13}C NMR*: δ = 165.2, 152.8, 149.6 (q, J = 1 Hz), 149.6, 137.6 (q, J = 33 Hz), 124.0 (q, J = 5 Hz), 122.7 (q, J = 274 Hz) ppm. $C_7H_3ClF_3NO_2$ (225.55): calcd. C 37.28, H 1.34; found C 37.30, H 1.27.

5-Chloro-4-(trifluoromethyl)pyridine-3-carboxylic Acid (17): 3-Chloro-4-trifluoromethyl-2-(trimethylsilyl)pyridine (2.1 mL, 2.5 g, 10 mmol) was added to a solution prepared from 2,2,6,6-tetramethylpiperidine (1.7 mL, 1.4 g, 10 mmol) and butyllithium (10 mmol) in tetrahydrofuran (50 mL) and hexanes (6 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 covered with tetrahydrofuran (25 mL). The solvents were then evaporated, and the residue refluxed for 1 min in 5% aqueous sodium hydroxide solution (50 mL). After cooling, the mixture was washed with diethyl ether (2 × 20 mL), acidified to pH 1 and extracted with diethyl ether (3 × 20 mL). The organic solvent was evaporated, and the residue crystallized from a 3:1 (v/v) mixture of heptanes and ethyl acetate as colorless platelets. M.p. 157−159 °C; yield: 1.87 g (83%). ^{1}H NMR*: δ = 8.98 (s, 1 H), 8.86 (s, 1 H) ppm. ^{13}C NMR*: δ = 166.4, 153.8, 148.4, 132.4 (q, J = 33 Hz), 130.3 (q, J = 2 Hz), 130.0 (q, J = 2 Hz), 122.6 (q, J = 275 Hz) ppm. $C_7H_3ClF_3NO_2$ (225.55): calcd. C 37.28, H 1.34; found C 37.49, H 1.29.

3-Chloro-5-iodo-4-trifluoromethyl-2-(trimethylsilyl)pyridine (18): Compound **18** was made analogously from 3-chloro-4-trifluoromethyl-2-(trimethylsilyl)pyridine (13 mL, 15 g, 60 mmol), but the organometallic intermediate was trapped with iodine (15 g, 60 mmol) in tetrahydrofuran (60 mL). After 15 min at −75 °C, a 2.0 M solution (50 mL) of sodium thiosulfate was added, and the mixture was then allowed to reach 25 °C. The phases were separated, and the aqueous phase extracted with diethyl ether (50 mL). The combined organic phases were washed with brine (0.10 L), dried, evaporated and distilled to obtained a yellowish oil. B.p. 82−83 °C/4 Torr; yield: 19.4 g (85%). n_D^{20} 1.5405; d_4^{20} 1.648. ^{1}H NMR: δ = 9.18 (s, 1 H), 0.42 (s, 9 H) ppm. ^{13}C NMR: δ = 168.6, 156.6, 137.0 (q, J = 1 Hz), 135.8 (q, J = 31 Hz), 120.8 (q, J = 278 Hz), 89.3 (q, J = 2 Hz), −1.1 ppm. $C_9H_{11}ClF_3INSi$ (379.62): calcd. C 28.47, H 2.66; found C 28.66, H 2.66.

3-Chloro-6-iodo-4-trifluoromethyl-2-(trimethylsilyl)pyridine (19): 3-Chloro-5-iodo-4-trifluoromethyl-2-(trimethylsilyl)pyridine (5.7 mL, 9.5 g, 25 mmol) was added to a solution prepared from 2,2,6,6-tetramethylpiperidine (8.4 mL, 7.1 g, 50 mmol) and butyllithium (50 mmol) in diethyl ether (0.13 L) and hexanes (30 mL) cooled in a dry ice/methanol bath. After 1 h at −75 °C, 1.0 M hydrochloric acid (50 mL) was added. The ethereal layer was collected and dried and the solvents were evaporated. Distillation afforded a colorless oil. B.p. 76−78 °C/2 Torr; m.p. 9−11 °C; yield: 5.90 g (62%). n_D^{20} 1.5244; d_4^{20} 1.569. ^{1}H NMR: δ = 7.84 (s, 1 H), 0.42 (s, 9 H) ppm. ^{13}C NMR: δ = 172.5, 135.7 (q, J = 2 Hz), 135.4 (q, J = 32 Hz), 130.9 (q, J = 5 Hz), 120.8 (q, J = 275 Hz), 115.6, −1.3 ppm. $C_9H_{11}ClF_3INSi$ (379.62): calcd. C 28.47, H 2.66; found C 28.75, H 2.53.

5-Chloro-4-(trifluoromethyl)pyridine-2-carboxylic Acid (20): 3-Chloro-6-iodo-4-trifluoromethyl-2-(trimethylsilyl)pyridine (2.4 mL, 3.8 g, 10 mmol) was added to a solution of butyllithium (10 mmol) in toluene (40 mL) and hexanes (6.1 mL) cooled in a dry ice/methanol bath. After 15 min at −75 °C, the mixture was poured onto an excess of freshly crushed dry ice covered with tetrahydrofuran (25 mL). At 25 °C, the mixture was washed with 6.0 M hydrochloric acid (20 mL) and the solvents were evaporated. The residue was dissolved in tetrahydrofuran (25 mL) containing tetrabutylammonium fluoride trihydrate (3.5 g, 10 mmol) and heated under reflux for 1 min. After evaporation of the solvents, the residue was partitioned between diethyl ether (75 mL) and 2.0 M hydrochloric acid (50 mL). The solvent was evaporated, and the residue crystallized from a 4:1 (v/v) mixture of heptanes and ethyl acetate; colorless needles. M.p. 146−144 °C; yield: 1.68 g (75%). ^{1}H NMR*: δ = 9.00 (s, 1 H), 8.39 (s, 1 H) ppm. ^{13}C NMR*: δ = 164.6, 152.2, 148.6, 136.9 (q, J = 33 Hz), 132.9 (q, J = 2 Hz), 123.0 (q, J = 5 Hz), 122.6 (q, J = 274 Hz) ppm. $C_7H_3ClF_3NO_2$ (225.55): calcd. C 37.28, H 1.34; found C 37.15, H 1.20.

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