Further Metalations and Functionalizations of Chloro-, Bromo- and Iodo(trifluoromethyl)pyridines

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Abstract: In accordance with the concept of regioexhaustive functionalization, both 3-chloro-2-(trifluoromethyl)pyridine and 2-bromo-6-(trifluoromethyl)pyridine were converted each time into the three possible carboxylic acids (**1**, **4** and **5** and **6**, **9** and **12**, respectively). 2-Bromo-4-(trifluoromethyl)pyridine, 2-bromo-5-(trifluoromethyl)pyridine, 2-iodo-4-(trifluoromethyl)pyridine and 4-iodo-2-(trifluoromethyl)pyridine were selectively deprotonated and subsequently carboxylated at the respective 3-positions thus affording the acids **13**–**16**. Finally, the *N*-pivaloyl-protected 2-amino-3-chloro-5-(trifluoromethyl)pyridine was deprotonated at the 4-position and the intermediate trapped with iodine and benzaldehyde to provide, after amide cleavage, the aminopyridines **17** and **18**.

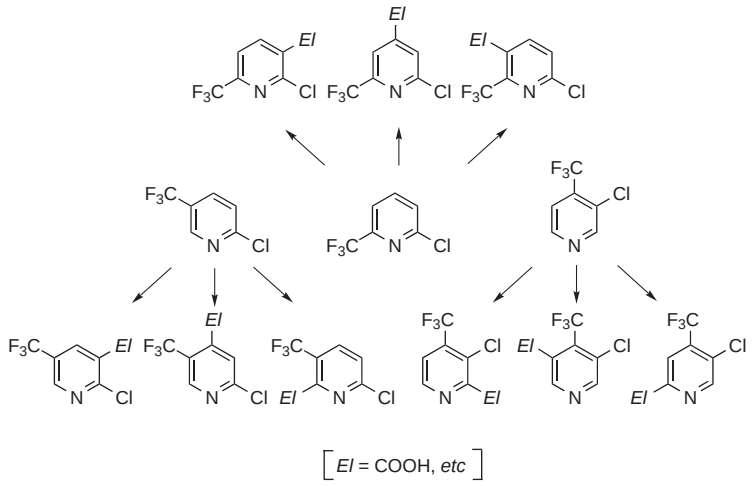
Key words: halogen/metal permutation ('exchange'), halogen migration, metalations, lithium diisopropylamide, pyridines, site selectivity

In a preceding article it was demonstrated how the concept of *regioexhaustive functionalization*[1] can be applied to 2-chloro-5-(trifluoromethyl)pyridine, 2-chloro-6-(trifluoromethyl)pyridine and 3-chloro-4-(trifluoromethyl)pyridine.[2] Taking advantage of the 'toolbox methods',[1] any of the each time three vacant positions was lithiated and the metal was subsequently replaced by an electrophilically delivered substituent (*El*), in general a carboxy group (Scheme 1, *El* = COOH).

The present article describes the extension of this study to another chloro(trifluoromethyl)pyridine and to a bromo(trifluoromethyl)pyridine. In addition, the direct metalation of two further bromo(trifluoromethyl)pyridines, two iodo(trifluoromethyl)pyridines and of one aminochloro(trifluoromethyl)pyridine are reported.

Three Regioisomeric Derivatives of 3-Chloro-2-(trifluoromethyl)pyridine

Readily prepared from 3-chloro-2-iodopyridine[3] and (trifluoromethyl)trimethylsilane in 46% yield,[4] 3-chloro-2-(trifluoromethyl)pyridine underwent selective deprotonation when treated with lithium diisopropylamide (LIDA) in tetrahydrofuran at –75 °C for two hours. Upon trapping of the intermediate with carbon dioxide or molecular iodine, 3-chloro-2-(trifluoromethyl)pyridine-4-carboxylic acid (**1**, 81%) or 3-chloro-4-iodo-2-(trifluoromethyl)pyridine (**2**, 86%) were obtained, respectively. LIDA-triggered heavy halogen migration followed by neutralization



Scheme 1

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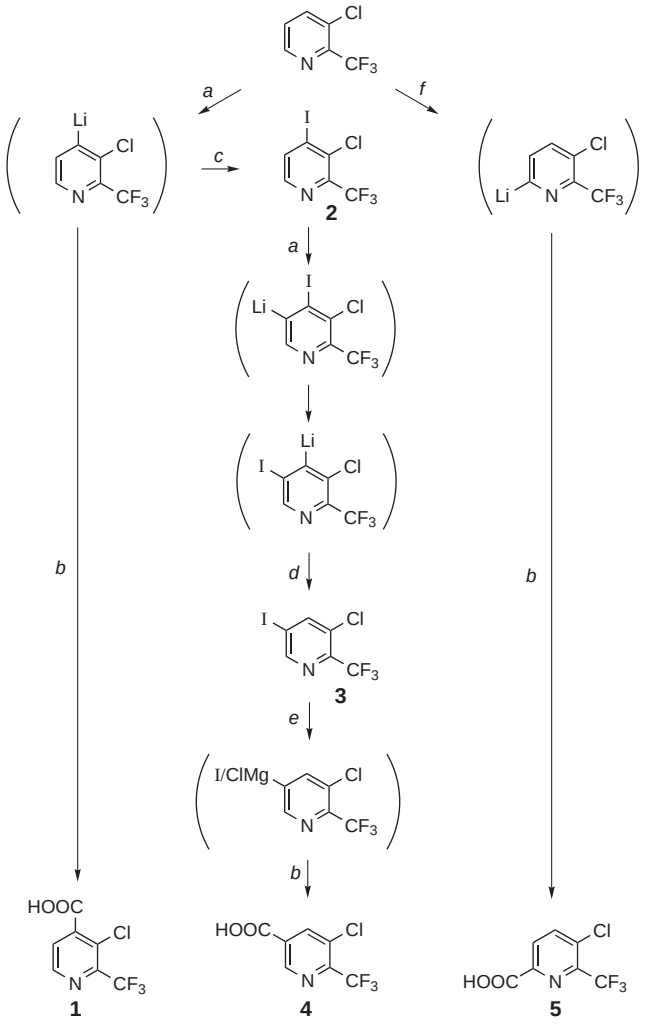
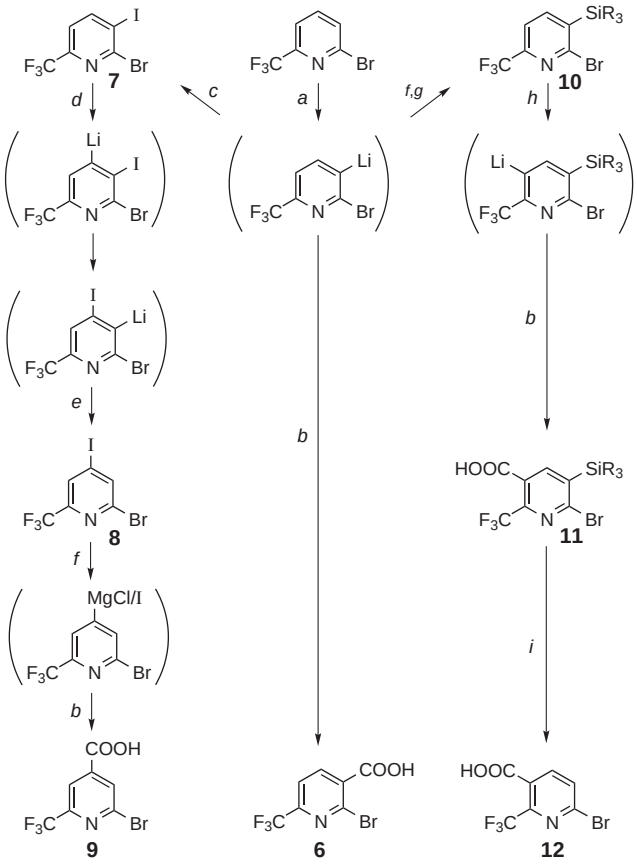
isomerized the latter compound to 3-chloro-5-iodo-2-(trifluoromethyl)pyridine (**3**, 69% after crystallization). Halogen/metal permutation with isopropylmagnesium chloride in tetrahydrofuran at 0 °C, carboxylation and neutralization afforded the 5-chloro-6-(trifluoromethyl)pyridine-3-carboxylic acid (**4**, 77%). 5-Chloro-6-(trifluoromethyl)pyridine-2-carboxylic acid (**5**) was formed after metalation with Caubère's base,[5,6] excess of butyllithium and lithium 2-(dimethylamino)ethoxide (LIDMAE), although only in poor yield (26%) (Scheme 2).



Scheme 2 *a*) Lithium diisopropylamide (LIDA) in THF at –75 °C for 2 h; *b*) (1.) Excess solid carbon dioxide, (2.) Ethereal hydrogen chloride; *c*) Molecular iodine in THF; *d*) Methanol; *e*) Isopropylmagnesium chloride in THF at 0 °C; *f*) Butyllithium and lithium 2-(dimethylamino)ethoxide (LIDMAE) in hexanes at –75 °C for 45 min.

Three Regioisomeric Derivatives of 2-Bromo-6-(trifluoromethyl)pyridine

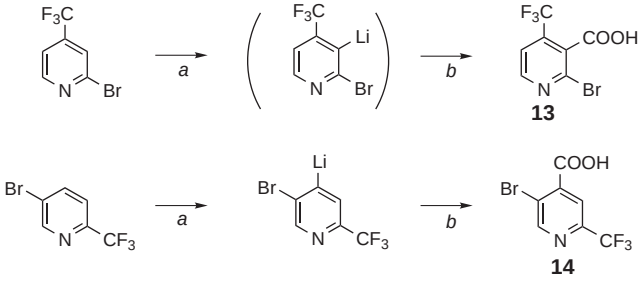
As previously described for 2-chloro-6-(trifluoromethyl)pyridine,[2] the 2-bromo analog was readily converted into the three isomeric carboxylic acids (Scheme 3). The treatment with LIDA followed by carboxylation and neutralization afforded directly the 2-bromo-6-(trifluoromethyl)pyridine-3-carboxylic acid (**6**, 49%). When the organometallic intermediate was trapped with molecular iodine instead, 2-bromo-3-iodo-6-(trifluoromethyl)pyridine (**7**, 78%) was obtained. Its LIDA-promoted isomerization by basicity gradient-driven heavy halogen migration gave 2-bromo-4-iodo-6-(trifluoromethyl)pyridine (**8**, 82%) which, when subjected to a halogen/metal permutation using isopropylmagnesium chloride, afforded the 2-bromo-6-(trifluoromethyl)pyridine-4-carboxylic acid (**9**, 88%). Consecutive exposure of 2-bromo-6-(trifluoromethyl)pyridine to LIDA and chlorotrimethylsilane produced the silane **10** (85%) which upon deprotonation by lithium 2,2,6,6-tetramethylpiperidide (LITMP) followed by carboxylation, neutralization and deprotection of the silylated intermediate **11** provided 6-bromo-2-(trifluoromethyl)pyridine-3-carboxylic acid (**12**) in satisfactory overall yield (49%).



Scheme 3 *a*) LIDA in THF at –85 °C for 2 h; *b*) (1.) Excess solid carbon dioxide, (2.) HCl; *c*) Molecular iodine in THF; *d*) LIDA in THF at –75 °C for 15 min; *e*) HCl; *f*) Isopropylmagnesium chloride in THF at 0 °C for 5 min; *g*) Chlorotrimethylsilane; *h*) Lithium 2,2,6,6-tetramethylpiperidide (LITMP) in THF at –75 °C for 45 min; *i*) Tetrabutylammonium fluoride trihydrate (TBAF) in refluxing THF for 1 min.

Derivatization of 2-Bromo-4- and 5-Bromo-2-(trifluoromethyl)pyridine

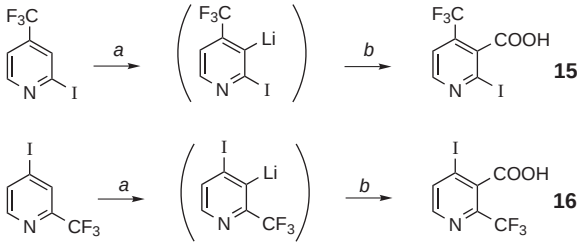
2-Bromo-4-(trifluoromethyl)pyridine[7] and 5-bromo-2-(trifluoromethyl)pyridine[4] were cleanly deprotonated by LIDA at the bromine-adjacent position. After carboxylation and neutralization, 2-bromo-4-(trifluoromethyl)pyridine-3-carboxylic acid (**13**) and 5-bromo-2-(trifluoromethyl)pyridine-4-carboxylic acid (**14**) were isolated in 54% and 67% yield, respectively (Scheme 4).



Scheme 4 *a*) LIDA in THF at –75 °C for 45 min; *b*) (1.) Excess solid carbon dioxide, (2.) Hydrochloric acid.

Derivatization of 2-Iodo-4-(trifluoromethyl)pyridine and 4-Iodo-2-(trifluoromethyl)pyridine

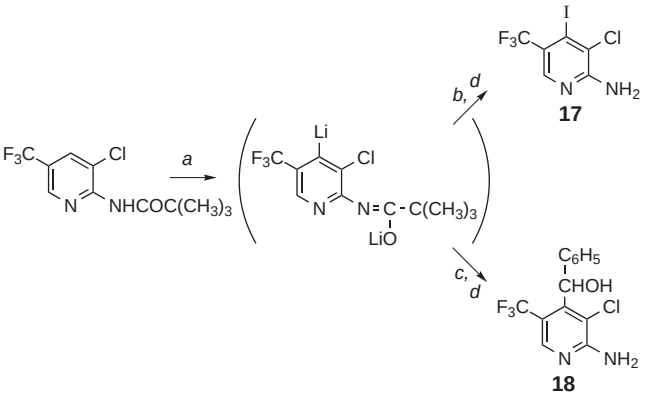
Even 2-iodo-4-(trifluoromethyl)pyridine[8] and 4-iodo-2-(trifluoromethyl)pyridine[7] were cleanly deprotonated by LIDA in tetrahydrofuran at –75 °C. Trapping of the organometallic intermediates with dry ice followed by neutralization gave the 2-iodo-4-(trifluoromethyl)pyridine-3-carboxylic acid (**15**, 51%) and the 4-iodo-2-(trifluoromethyl)pyridine-3-carboxylic acid (**16**, 31%) (Scheme 5).



Scheme 5 *a*) LIDA in THF at –75 °C for 2 h; *b*) (1.) Excess solid carbon dioxide, (2.) Hydrochloric acid.

Derivatization of 2-Amino-3-chloro-5-(trifluoromethyl)pyridine

2-Amino-3-chloro-5-(trifluoromethyl)pyridine is readily accessible from the industrially inexpensive 2,3-dichloro-5-(trifluoromethyl)pyridine by simple nucleophilic substitution with ammonia.[9] The *N*-pivaloyl-protected substrate was treated with two equivalents of LIDA in tetrahydrofuran at –75 °C for two hours before the organometallic intermediate was trapped with iodine and benzaldehyde. The deprotected forms of the iodo compound **17** and of the alcohol **18** were obtained in 39% and 47% overall yield, respectively (Scheme 6).



Scheme 6 *a*) LIDA (2 equiv) in THF at –75 °C for 2 h; *b*) Molecular iodine; *c*) Benzaldehyde; *d*) Kept in refluxing 20% H_2SO_4 for 15 h.

Working practices and abbreviations are specified in previous articles from this laboratory.[10–12] ^{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 $\delta = 0.00$ ppm). The samples were dissolved in $CDCl_3$ or, if marked by an asterisk, in acetone-d_6.

3-Chloro-2-(trifluoromethyl)pyridine

After thorough mixing, spray-dried KF (4.6 g, 80 mmol) and CuI (15 g, 80 mmol) were heated with the flame of a Bunsen burner under gentle shaking and at reduced pressure (1 Torr) for some 10 min until a homogeneous greenish color appeared. Anhydrous *N*-methylpyrrolidinone (75 mL), 3-chloro-2-iodopyridine[3] (18 g, 75 mmol) and trimethyl(trifluoromethyl)silane (11 mL, 11 g, 75 mmol) were added. Being vigorously stirred for 6 h at 50 °C, the slurry gradually changed to a brownish solution which was eventually poured into 12% aq NH_3 (0.20 L). The product was extracted with Et_2O (3 × 0.10 L). The combined organic layers were washed with 12% aq NH_3 (3 × 50 mL), 1.0 M HCl (0.10 L), a sat. solution of $NaHCO_3$ (0.10 L), and brine (0.10 L) and dried. Upon distillation, a colorless oil was collected which solidified.

Colorless prisms (from hexanes); mp 40–42 °C; bp 172–174 °C; yield: 6.4 g (46%).

^{1}H NMR: $\delta = 8.55$ (dd, 1 H, $J = 4.7, 1.1$ Hz), 7.87 (d, 1 H, $J = 8.1$ Hz), 7.46 (dd, 1 H, $J = 8.0, 4.7$ Hz).

^{13}C NMR: $\delta = 146.7, 144.7$ (q, $J = 34$ Hz), 139.6, 130.5, 127.3, 121.0 (q, $J = 274$ Hz).

Anal. Calcd for $C_6H_3ClF_3N$ (181.54): C, 39.70; H, 1.67. Found: C, 39.71; H, 1.69.

N-[3-Chloro-5-(trifluoromethyl)pyridin-2-yl]-2,2-dimethylpropanamide

The solution of 2-amino-3-chloro-5-(trifluoromethyl)pyridine (4.9 g, 25 mmol), pivaloyl chloride (3.4 mL, 3.4 g, 28 mmol) and pyridine (2.2 mL, 2.2 g, 28 mmol) in CH_2Cl_2 (50 mL) was heated under reflux for 5 d. The organic phase was washed with a 2.0 M aq solution Na_2CO_3 (50 mL), dried and evaporated. Crystallization from hexanes gave colorless needles.

Mp 106–109 °C; yield: 3.0 g (43%).

^{1}H NMR: $\delta = 8.78$ (q, 1 H, $J = 1.1$ Hz), 8.41 (s, 1 H), 8.07 (d, 1 H, $J = 4.0$ Hz), 1.40 (s, 9 H).

^{13}C NMR: δ = 175.6, 150.6, 144.0 (q, *J* = 4.0 Hz), 134.9 (q, *J* = 3.2), 123.6 (q, *J* = 22.3 Hz), 122.7 (q, *J* = 271.5), 121.4, 40.5, 27.4 (3 C).

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

3-Chloro-2-(trifluoromethyl)pyridine-4-carboxylic Acid (1)
Diisopropylamine (2.8 mL, 2.0 g, 20 mmol) and 3-chloro-2-(trifluoromethyl)pyridine (3.6 g, 20 mmol) were consecutively added to a solution of BuLi (20 mmol) in THF (30 mL) and hexanes (10 mL) and cooled in a dry ice/MeOH 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 crystallized from a 9:1 (v/v) mixture of 2.0 M HCl–EtOH as colorless needles.

Mp 184–186 °C; yield: 3.66 g (81%).

^{1}H NMR*: δ = 8.82 (d, 1 H, *J* = 4.7 Hz), 8.05 (d, 1 H, *J* = 4.8 Hz).

^{13}C NMR*: δ = 164.4, 148.0, 145.6 (q, *J* = 34 Hz), 142.7, 127.6, 127.6, 121.6 (q, *J* = 275 Hz).

Anal. Calcd for $C_7H_3ClF_3NO_2$ (225.55): C, 37.28; H, 1.34. Found: C, 37.46; H, 1.41.

3-Chloro-4-iodo-2-(trifluoromethyl)pyridine (2)
Iodine (5.1 g, 20 mmol) in THF (20 mL) was poured all at once into an analogously prepared reaction mixture. After evaporation of the solvents, the residue was dissolved in Et_2O (40 mL) and washed with a 2.0 M aq solution of $Na_2S_2O_3$ (20 mL), 2.0 M HCl (20 mL), and a sat. aq solution of $NaHCO_3$ (20 mL), dried and evaporated. The residue crystallized from hexanes as yellowish needles.

Mp 81–82 °C; yield: 5.27 g (86%).

^{1}H NMR: δ = 8.17 (d, 1 H, *J* = 4.8 Hz), 8.04 (d, 1 H, *J* = 4.8 Hz).

^{13}C NMR: δ = 146.1, 144.9 (q, *J* = 34 Hz), 138.1, 135.1, 120.4 (q, *J* = 273 Hz).

Anal. Calcd for $C_6H_2ClF_3IN$ (307.44): C, 23.44; H, 0.65. Found: C, 23.40; H, 0.71.

5-Iodo-3-chloro-2-(trifluoromethyl)pyridine (3)
BuLi (15 mmol) in hexanes (9.1 mL) and 3-chloro-4-iodo-2-(trifluoromethyl)pyridine (4.6 g, 15 mmol) were consecutively added to diisopropylamine (2.1 mL, 1.5 g, 15 mmol) in THF (60 mL) and kept in a dry ice/MeOH bath. After 2 h at –75 °C, the mixture was treated with MeOH (2.0 mL) and the solvents were evaporated. The residue was taken up in Et_2O (30 mL) and washed with 2.0 M HCl (20 mL) and a sat. aq solution of $NaHCO_3$ (20 mL). The organic phase was dried and evaporated to yield 4.38 g of an orange oil containing 5-iodo-3-chloro-2-(trifluoromethyl)pyridine (78%), 3-chloro-4-iodo-2-(trifluoromethyl)pyridine (9%) and 3-chloro-2-(trifluoromethyl)pyridine (9%) as determined by gas chromatography (DB-WAX, 30 m, 150 °C; DB-1, 30 m, 150 °C; tridecane as an internal standard). The products were eluted from silica gel (0.10 L) with a 9:1 (v/v) mixture of hexanes and EtOAc. After evaporation of the solvents, 5-iodo-3-chloro-2-(trifluoromethyl)pyridine crystallized slowly as colorless needles.

Mp 42–44 °C; yield: 3.20 g (69%).

^{1}H NMR: δ = 8.78 (d, 1 H, *J* = 1.6 Hz), 8.24 (dq, 1 H, *J* = 1.6, 0.6 Hz).

^{13}C NMR: δ = 152.9, 147.2, 143.8 (q, *J* = 35 Hz), 131.0, 121.0 (q, *J* = 275 Hz), 96.6.

Anal. Calcd for $C_6H_2ClF_3IN$ (307.44): C, 23.44; H, 0.65. Found: C, 23.57; H, 0.65.

5-Chloro-6-(trifluoromethyl)pyridine-3-carboxylic Acid (4)
Isopropylmagnesium chloride (3.0 mmol) in THF (1.4 mL) was added to 3-chloro-5-iodo-2-(trifluoromethyl)pyridine (0.92 g, 3.0 mmol) in THF (6 mL) at 0 °C. After 2 h, CO_2 was bubbled into the solution for 20 min. The mixture was partitioned between Et_2O (20 mL) and 6.0 M HCl (10 mL). After another extraction of the aqueous layer with Et_2O (10 mL), the combined organic layers were dried and evaporated to yield 0.63 g (94%) of a yellowish solid which crystallized from a 6:1 (v/v) mixture of hexanes and EtOAc as colorless needles.

Mp 112–114 °C; yield: 0.52 g (77%).

^{1}H NMR: δ = 9.23 (d, 1 H, *J* = 1.6 Hz), 8.54 (d, 1 H, *J* = 1.6 Hz).

^{13}C NMR: δ = 168.0, 148.4 (q, *J* = 35 Hz), 147.9, 141.3, 131.3, 128.9, 120.5 (q, *J* = 276 Hz).

Anal. Calcd for $C_7H_3ClF_3NO_2$ (225.55): C, 37.27; H, 1.34. Found: C, 37.04; H, 1.24.

5-Chloro-6-(trifluoromethyl)pyridine-2-carboxylic Acid (5)
N,*N*-Dimethylaminoethanol (0.60 mL, 0.53 g, 6.0 mmol) in hexanes (8 mL) was added dropwise over 15 min to BuLi (12 mmol) in hexanes (7.5 mL) and kept at 0 °C. At –75 °C, 3-chloro-2-(trifluoromethyl)pyridine (0.36 g, 2.0 mmol) in hexanes (3.0 mL) was added and the temperature was maintained for 45 min before the reaction mixture was poured onto an excess of freshly crushed dry ice covered with Et_2O (50 mL). At 25 °C, the reaction mixture was extracted with a 2.0 M aq solution of NaOH (3 × 25 mL). The combined aqueous layers were washed with Et_2O (2 × 25 mL), acidified to pH 1 with 20% HCl, extracted with Et_2O (3 × 25 mL), dried and evaporated. Most of the valeric acid was eliminated by co-evaporating the oily residue 4 times with toluene (40 mL). Crystallization from cyclohexane gave 0.17 g of yellowish needles. After sublimation, a colorless solid was obtained.

Mp 106–108 °C; yield: 0.12 g (26%).

^{1}H NMR: δ = 8.38 (d, 1 H, *J* = 8.3 Hz), 8.16 (d, 1 H, *J* = 8.3 Hz).

^{13}C NMR: δ = 163.1, 144.1 (q, *J* = 36 Hz), 143.7, 142.1, 135.4, 127.8, 120.1 (q, *J* = 276 Hz).

Anal. Calcd for $C_7H_3ClF_3NO_2$ (225.55): C, 37.27; H, 1.34. Found: C, 37.63; H, 1.50.

Derivatives of 2-Bromo-6-(trifluoromethyl)pyridine

2-Bromo-6-(trifluoromethyl)pyridine-3-carboxylic Acid (6)
2-Bromo-6-(trifluoromethyl)pyridine[4] (2.3 g, 10 mmol) in THF (25 mL) was added over 10 min to a solution prepared from BuLi (10 mmol) and diisopropylamine (1.4 mL, 1.0 g, 10 mmol) in THF (15 mL) and hexanes (6.5 mL) at –85 °C. After 2 h at –85 °C, the reaction mixture was poured onto an excess of freshly crushed dry ice covered with THF (25 mL). The solvents were evaporated and the residue partitioned between Et_2O (20 mL) and 6.0 M HCl (15 mL). The aqueous phase was extracted with Et_2O (20 mL). The combined organic phases were dried and evaporated and the residue crystallized from a 5:1 (v/v) mixture of heptane and EtOAc to give the product as colorless needles.

Mp 116–119 °C; yield: 1.32 g (49%).

^{1}H NMR: δ = 8.46 (d, 1 H, *J* = 8.0 Hz), 7.81 (d, 1 H, *J* = 8.0 Hz).

^{13}C NMR: δ = 168.9, 150.8 (q, *J* = 35 Hz), 142.0, 141.7, 130.8, 120.0 (q, *J* = 275 Hz), 119.2 (q, *J* = 3 Hz).

Anal. Calcd for $C_7H_3BrF_3NO_2$ (270.00): C, 31.14; H, 1.12. Found: C, 31.08; H, 1.21.

2-Bromo-3-iodo-6-(trifluoromethyl)pyridine (7)
Analogously, 2-bromo-6-(trifluoromethyl)pyridine (9.0 g, 40 mmol) was treated with a solution of lithium diisopropylamide (40 mmol) in THF (60 mL) and hexanes (25 mL) for 2 h at –85 °C before iodine (11 g, 40 mmol) in THF (50 mL) was added. The sol-

vents were evaporated. The residue was taken up in Et_2O (0.10 L) and washed with a 2.0 M aq solution of $Na_2S_2O_3$ (20 mL), 2.0 M HCl (2 × 50 mL), a sat. solution of $NaHCO_3$ (50 mL) and brine (50 mL), dried and evaporated. The residue was distilled to afford slightly yellowish needles.

Mp 28–31 °C; bp 93–95 °C/5 Torr; yield: 11.0 g (78%).

^{1}H NMR: δ = 8.31 (d, 1 H, *J* = 8.0 Hz), 7.37 (d, 1 H, *J* = 8.0 Hz).

^{13}C NMR: δ = 150.1, 149.1, 148.0 (q, *J* = 36 Hz), 121.0 (q, *J* = 274 Hz), 120.3 (q, *J* = 3 Hz), 104.3.

Anal. Calcd for $C_6H_2BrF_3IN$ (351.89): C, 20.48; H, 0.57. Found: C, 20.48; H, 0.63.

2-Bromo-4-iodo-6-(trifluoromethyl)pyridine (8)

Diisopropylamine (3.5 mL, 2.5 g, 25 mmol) and 2-bromo-3-iodo-6-(trifluoromethyl)pyridine (8.8 g, 25 mmol) in THF (10 mL) were consecutively added in 10 min interval to a solution of BuLi (25 mmol) in hexanes (16 mL) and THF (30 mL) and kept in a dry ice/MeOH bath. After 15 min at –75 °C, the reaction mixture was partitioned between 2.0 M HCl (30 mL) and Et_2O (50 mL). The organic phase was filtered through a pad of basic alumina (100 mL) and eluted with Et_2O (150 mL). After evaporation of the volatiles, the residue crystallized from hexanes as colorless needles.

Mp 115–116 °C (after sublimation); yield: 7.20 g (82%).

^{1}H NMR: δ = 8.10 (s, 1 H), 7.98 (s, 1 H).

^{13}C NMR: δ = 148.8 (q, *J* = 36 Hz), 142.5, 139.6, 128.8 (q, *J* = 3 Hz), 119.7 (q, *J* = 275 Hz), 107.2.

Anal. Calcd for $C_6H_2BrF_3IN$ (351.89): C, 20.48; H, 0.57. Found: C, 20.28; H, 0.80.

2-Bromo-6-(trifluoromethyl)pyridine-4-carboxylic Acid (9)

Isopropylmagnesium chloride (10 mmol) in THF (4.9 mL) was added to 2-bromo-4-iodo-6-(trifluoromethyl)pyridine (3.5 g, 10 mmol) in THF (15 mL) at 0 °C. After 5 min, CO_2 was bubbled into the reaction mixture for 20 min. The solvents were evaporated and the residue was partitioned between Et_2O (20 mL) and 6.0 M HCl (20 mL). The aqueous phase was extracted again with Et_2O (20 mL). The combined organic layers were dried and evaporated. The residue was crystallized from heptane to give the product as colorless needles.

Mp 125–127 °C; yield: 2.37 g (88%).

^{1}H NMR: δ = 8.33 (s, 1 H), 8.26 (s, 1 H).

^{13}C NMR: δ = 168.1, 149.9 (q, *J* = 36 Hz), 143.5, 140.1, 131.5, 120.2 (q, *J* = 275 Hz), 119.2 (q, *J* = 3 Hz).

Anal. Calcd for $C_7H_3BrF_3NO_2$ (270.00): C, 31.14; H, 1.12. Found: C, 31.23; H, 0.84.

2-Bromo-6-trifluoromethyl-3-(trimethylsilyl)pyridine (10)

At –85 °C, 2-bromo-6-(trifluoromethyl)pyridine (9.0 g, 40 mmol) in THF (0.12 L) was added in the course of 20 min to the solution prepared from BuLi (40 mmol) and diisopropylamine (5.6 mL, 4.0 g, 40 mmol) in THF (50 mL) and hexanes (25 mL). After 45 min at –85 °C, the mixture was treated with chlorotrimethylsilane (5.1 mL, 4.4 g, 40 mmol), filtered through a pad of basic alumina (50 mL) and eluted with Et_2O (50 mL). Upon distillation, a colorless oil was collected.

Bp 108–110 °C/11 Torr; yield: 10.1 g (85%).

^{1}H NMR: δ = 7.90 (d, 1 H, *J* = 7.7 Hz), 7.61 (d, 1 H, *J* = 7.7 Hz), 0.46 (s, 9 H).

^{13}C NMR: δ = 149.0 (q, *J* = 36 Hz), 148.9, 146.3, 143.6, 120.9 (q, *J* = 274 Hz), 118.9 (q, *J* = 3 Hz).

Anal. Calcd for $C_9H_{11}BrF_3NSi$ (298.18): C, 36.25; H, 3.72. Found: C, 36.64; H, 3.53.

6-Bromo-2-(trifluoromethyl)pyridine-3-carboxylic Acid (12)

2-Bromo-6-trifluoromethyl-3-(trimethylsilyl)pyridine (5.3 mL, 7.5 g, 25 mmol) was added to the solution prepared from BuLi (25 mmol) and 2,2,6,6-tetramethylpiperidine (4.2 mL, 3.5 g, 25 mmol) in THF (50 mL) and hexanes (16 mL) and kept in a dry ice/MeOH bath. After 45 min at –75 °C, the reaction mixture was poured onto an excess of freshly crushed dry ice covered with THF (25 mL). The solvents were evaporated and the residue partitioned between Et_2O (0.10 L) and 6.0 M HCl (50 mL). The organic phase was then evaporated and the residue dissolved in THF (50 mL) containing tetrabutylammonium fluoride trihydrate (5.6 g, 18 mmol). The mixture was refluxed for 5 min, before being evaporated. The residue was partitioned between Et_2O (100 mL) and 6.0 M HCl (25 mL). The organic phase was evaporated and the residue crystallized from a 2:1 (v/v) mixture of heptane and EtOAc.

Mp 175–177 °C; yield: 3.34 g (49%).

^{1}H NMR*: δ = 8.28 (d, 1 H, *J* = 8.0 Hz), 8.08 (d, 1 H, *J* = 8.0 Hz).

^{13}C NMR*: δ = 165.8, 145.9 (q, *J* = 36 Hz), 143.4, 142.2, 132.8, 128.8 (q, *J* = 1 Hz), 121.5 (q, *J* = 275 Hz).

Anal. Calcd for $C_7H_3BrF_3NO_2$ (270.01): C, 31.14; H, 1.12. Found: C, 31.45; H, 0.89.

2-Bromo-4-(trifluoromethyl)pyridine-3-carboxylic Acid (13)

Diisopropylamine (1.4 mL, 1.0 g, 10 mmol) and 2-bromo-4-(trifluoromethyl)pyridine[7] (2.3 g, 10 mmol) were consecutively added to a solution of BuLi (10 mmol) in THF (20 mL) and hexanes (6.3 mL) and kept in a dry ice/MeOH bath. After 45 min at –75 °C, the reaction mixture was poured onto an excess of freshly crushed dry ice covered with THF (25 mL). The residue obtained after evaporation of the volatiles crystallized from a 2:1 (v/v) mixture of 2.0 M HCl and EtOH as colorless prisms.

Mp 159–161 °C; yield: 1.46 g (54%).

^{1}H NMR: δ = 8.61 (d, 1 H, *J* = 5.1 Hz), 7.57 (d, 1 H, *J* = 5.1 Hz).

^{13}C NMR: δ = 166.0, 150.7, 139.8, 136.8 (q, *J* = 34 Hz), 131.1, 121.4 (q, *J* = 275 Hz), 119.0 (q, *J* = 4 Hz).

Anal. Calcd for $C_7H_3BrF_3NO_2$ (270.01): C, 31.14; H, 1.12. Found: C, 31.09; H, 1.12.

5-Bromo-2-(trifluoromethyl)pyridine-4-carboxylic Acid (14)

An analogous reaction performed with 5-bromo-2-(trifluoromethyl)pyridine (2.3 g, 10 mmol) afforded colorless pallets.

Mp 215–218 °C; yield: 1.81 g (67%).

^{1}H NMR*: δ = 9.07 (s, 1 H), 8.19 (s, 1 H).

^{13}C NMR*: δ = 164.8, 155.1, 147.6 (q, *J* = 35 Hz), 142.8, 122.9, 122.3 (q, *J* = 3 Hz), 122.3 (q, *J* = 273 Hz).

Anal. Calcd for $C_7H_3BrF_3NO_2$ (270.00): C, 31.14; H, 1.12. Found: C, 31.07; H, 1.14.

2-Iodo-4-(trifluoromethyl)pyridine-3-carboxylic Acid (15)

2-Iodo-4-(trifluoromethyl)pyridine (2.7 g, 10 mmol) in THF (5.0 mL) was added to a solution prepared from BuLi (10 mmol) and diisopropylamine (1.4 mL, 1.0 g, 10 mmol) in hexanes (5.6 mL) and THF (10 mL), kept in a dry ice/MeOH bath. After 2 h at –75 °C, the reaction mixture was poured onto an excess of freshly crushed dry ice covered with THF (25 mL). At 25 °C, H_2O (50 mL) was added. The aqueous layer was washed with Et_2O (3 × 50 mL), acidified to pH 1 with 4.0 M HCl and extracted with Et_2O (3 × 50 mL). The combined organic phases were dried and evaporated. Crystallization of the residue from a 1:1 mixture of $CHCl_3$ and MeOH afforded colorless prisms.

Mp 182–184 °C (dec.); yield: 1.62 g (51%).

^{1}H NMR*: δ = 8.70 (d, 1 H, *J* = 5.2 Hz), 7.85 (d, 1 H, *J* = 5.2 Hz).

^{13}C NMR*: δ = 162.6, 153.0, 152.5, 135.3 (q, *J* = 34 Hz), 122.5 (q, *J* = 275 Hz), 120.3 (q, *J* = 4 Hz), 117.3.

Anal. Calcd for $C_7H_3F_3INO_2$ (317.00): C, 26.52; H, 0.95. Found: C, 26.29; H, 1.04.

4-Iodo-2-(trifluoromethyl)pyridine-3-carboxylic Acid (16)
The same protocol was applied to 4-iodo-2-(trifluoromethyl)pyridine (2.7 g, 10 mmol) and the product was obtained as colorless prisms from a 1:1 (v/v) mixture of $CHCl_3$and MeOH.

Mp 217–219 °C (dec.); yield: 0.98 g (31%).

^{1}H NMR*: δ = 8.45 (d, 1 H, *J* = 5.2 Hz), 8.32 (d, 1 H, *J* = 5.2 Hz).

^{13}C NMR*: δ = 167.9, 151.5, 144.8 (q, *J* = 35 Hz), 139.8, 137.5, 122.6 (q, *J* = 276 Hz), 107.5.

Anal. Calcd for $C_7H_3F_3INO_2$ (317.00): C, 26.52; H, 0.95. Found: C, 26.57; H, 1.08.

***N*-[3-Chloro-4-iodo-5-(trifluoromethyl)pyridin-2-yl]-2,2-dimethylpropanamide**
Diisopropylamine (3.5 mL, 2.5 g, 25 mmol) and *N*-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]-2,2-dimethylpropanamide (7.0 g, 25 mmol) were added consecutively to BuLi (50 mmol) in THF (65 mL) and hexanes (35 mL), cooled in a dry ice/MeOH bath. After having been kept for 2 h at –75 °C, the mixture was treated with iodine (6.3 g, 25 mmol), absorbed on silica gel (20 mL) and eluted from a column filled with more silica (0.10 L) using solvent mixtures which were gradually changed from neat Et_2O to neat CH_2Cl_2. The product was collected as colorless needles.

Mp 152–154 °C; yield: 8.74 g (86%).

^{1}H NMR: δ = 8.51 (s, 1 H), 8.33 (s, 1 H), 1.37 (s, 9 H).

^{13}C NMR: δ = 175.7, 149.9, 144.2 (q, *J* = 7.2 Hz), 128.1, 127.7 (q, *J* = 31.3), 121.9 (q, *J* = 273.8 Hz), 109.4, 40.7, 27.4 (3 C).

Anal. Calcd for $C_{11}H_{11}ClF_3IN_2O$ (406.57): C, 32.50; H, 2.73. Found: C, 32.53; H, 2.90.

***N*-[3-Chloro-4-(α-hydroxybenzyl)-5-(trifluoromethyl)pyridin-2-yl]-2,2-dimethylpropanamide**
Prepared analogously by replacing iodine with benzaldehyde (2.5 mL, 2.7 g, 25 mmol). The reaction mixture was treated with 2.0 M ethereal hydrogen chloride (30 mL, 60 mmol). The product was isolated by column chromatography (as specified in the preceding paragraph) as colorless needles.

Mp 168–170 °C; yield: 5.61 g (58%).

^{1}H NMR: δ = 8.90 (s, 1 H), 8.49 (s, 1 H), 7.4 (m, 5 H), 6.51 (d, 1 H, *J* = 8.3 Hz), 3.43 (d, 1 H, *J* = 8.5 Hz), 1.33 (s, 9 H).

^{13}C NMR: δ = 175.7, 152.0, 149.0, 144.4 (q, *J* = 7.2 Hz), 139.7, 128.4, 127.6, 125.6, 125.4, 123.2 (q, *J* = 273.9 Hz), 1221.9 (q, *J* = 29.7 Hz), 121.3, 70.5, 40.6, 27.3 (3 C).

Anal. Calcd for $C_{18}H_{18}ClF_3N_2O_2$ (386.80): C, 55.89; H, 4.69. Found: C, 55.73; H, 4.82.

3-Chloro-4-iodo-5-(trifluoromethyl)pyridin-2-amine (17)
N-[3-Chloro-4-iodo-5-(trifluoromethyl)pyridin-2-yl]-2,2-dimethylpropanamide (6.1 g, 15 mmol) was added to an 20% aq solution of H_2SO_4 (0.15 L). The solution was heated for 15 h under reflux before it was poured into a mixture of ice (0.15 kg) and concentrated NH_3 (0.10 L). The product was extracted with EtOAc (3 × 25 mL), purified by column chromatography (see above) and obtained as colorless needles.

Mp 125–127 °C; yield: 2.66 g (55%).

^{1}H NMR: δ = 8.08 (s, 1 H), 5.68 (s, 2 H).

^{13}C NMR: δ = 156.2, 144.3 (q, *J* = 7.2 Hz), 122.6 (q, *J* = 273.1 Hz), 121.8, 121.5, 108.2.

Anal. Calcd for $C_6H_3ClF_3IN_2$ (322.45): C, 22.35; H, 0.94. Found: C, 22.21; H, 0.91.

[2-Amino-3-chloro-5-(trifluoromethyl)pyridin-4-yl](phenyl)methanol (18)
N-[3-Chloro-4-(α-hydroxybenzyl)-5-(trifluoromethyl)pyridin-2-yl]-2,2-dimethylpropanamide (5.8 g, 15 mmol) was hydrolyzed and isolated as described in the preceding paragraph to afford the product as colorless needles.

Mp 126–129 °C; yield: 3.09 g (68%).

^{1}H NMR: δ = 8.35 (s, 1 H), 7.3 (m, 5 H), 6.30 (s, 1 H), 5.40 (s, 2 H), 3.36 (s, 1 H).

^{13}C NMR: δ = 158.3, 147.6, 144.6 (q, *J* = 6.4 Hz), 140.2, 128.4, 127.5, 125.4, 123.9 (q, *J* = 273.0 Hz), 116.4 (q, *J* = 30.6), 114.6, 70.8.

Anal. Calcd for $C_{13}H_{10}ClF_3N_2O$ (302.68): C, 51.59; H, 3.33. Found: C, 51.27; H, 3.25.

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