

# Regiochemical Flexibility: The Optional Functionalization of 2,3,5-Trihalopyridines at the 4- or 6-Position

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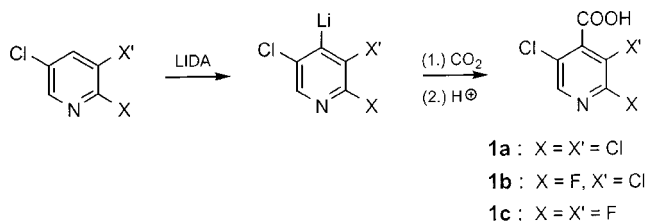
**Keywords:** Regioselectivity / Hydrogen-metal permutation (“metalation”) / Halogen/metal permutation / Iodine migration / Carboxylation

A deprotonation study was performed using 2,3,5-trichloropyridine, 3,5-dichloro-2-fluoropyridine and 5-chloro-2,3-difluoropyridine as the substrates. Upon reaction with lithium diisopropylamide (LDA), deprotonation occurred exclusively at the 4-position. Subsequent carboxylation and iodination led to the acids **1** and 4-iodopyridines **2**. The exposure of the latter compounds to lithium 2,2,6,6-tetramethylpiperide (LITMP) caused deprotonation and immediately ensuing iodine migration. The intermediates were trapped with dry ice to afford the carboxylic acids **3**. Upon neutralization, the

6-iodopyridines **4** were obtained. These compounds readily exchanged the heavy halogen for metal when treated with isopropylmagnesium chloride. In this way, functional groups could be selectively introduced in the 6-position. Employing carbon dioxide routinely as the model electrophile, trihalopyridinecarboxylic acids were formed which, all unknown so far, should provide valuable new building blocks for pharmaceutical research. Moreover, the selective nucleophilic displacement of the halogen at the 2-position could give rise to an immense variety of new structures.

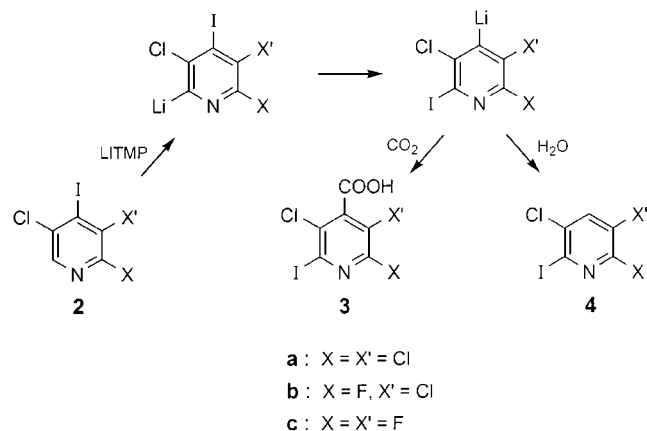
As we have demonstrated in a recent systematic study, a metal can be introduced at virtually any vacant position of the six possible dichloropyridines and subsequently replaced by a functional group.<sup>[1]</sup> The required selectivity was achieved either by exploiting fortunate optional site selectivities or by relying on basicity gradient-driven halogen migration (halogen shuffling) as the key steps. We have extended now these investigations to 2,3,5-trichloropyridine, 3,5-dichloro-2-fluoropyridine and 5-chloro-2,3-difluoropyridine.

At first sight, the project appears to be trivial as there remain only two unoccupied sites which can accommodate a metal. It is nevertheless a challenge to introduce the metal in the only moderately acidic 6-position despite the presence of the highly acidic 4-position flanked by two electro-negative halogen atoms. Actually, consecutive treatment of the three model compounds with lithium diisopropylamide (LIDA), carbon dioxide and acid afforded exclusively the 4-pyridinecarboxylic acids **1a** (75%), **1b** (79%) and **1c** (69%).



Analogously, the three 4-iodopyridines **2a** (89%), **2b** (73%) and **2c** (75%) have been prepared by interception with iodine. They were expected to play a pivotal role in

our search for an access to 6-functionalized trihalopyridines. When LIDA was used as the base, only poor yields of the isomerized iodo compounds **3** or **4** were found and by-products were formed predominantly. As the 4-iodo intermediates **2** are far less acidic than their trihalopyridine precursors, this deprotonation had to be performed with the stronger base lithium 2,2,6,6-tetramethylpiperide (LITMP). Not surprisingly, the initially generated 6-lithiated species instantaneously metamorphosed by migration of the heavy halogen to the less basic 4-lithiated isomer. The latter was trapped by carboxylation or neutralization giving the carboxylic acids **3a** (52%), **3b** (50%) and **3c** (29%) and the 6-iodopyridines **4a** (59%), **4b** (56%) and **4c** (46%), respectively. These compounds were inevitably accompanied by minor amounts (10–25%) of 5-chloro-2,3-dihalo-pyridines resulting from the reductive deiodination<sup>[2]</sup> of the precursors **2**.

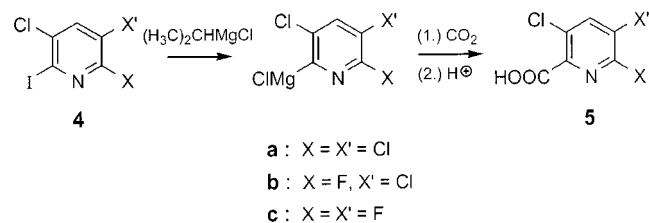


The LITMP-mediated “halogen shuffling” obviously follows previously established mechanistic precedents.<sup>[3–5]</sup>

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Catalytic amounts of accidentally formed halogen-rich species (e.g., 2,3,5-trichloro-4,6-diiodopyridine) act as self-restoring turntables that propagate a perpetually ongoing halogen/metal permutation process.

When the 6-iodopyridines **4** were submitted to a halogen/metal interconversion with butyllithium followed by carbonylation and neutralization, the acids **5** were formed in only moderate yield. Presumably, the organolithium intermediates are labile and are partly consumed in subsequent reactions such as nucleophilic additions to the heterocyclic CN double bond. The acids **5a** (76%), **5b** (51%) and **5c** (74%) were isolated in satisfactory yields when isopropylmagnesium chloride was used for the iodine displacement.



## Experimental Section

### General

Starting materials, if commercial, were purchased from Aldrich-Fluka (CH-9479 Buchs) and the specified purity was checked (melting ranges,  $n_D^{20}$ , gas chromatography). Solutions of butyllithium in hexanes were supplied by Chemetall (60487 Frankfurt). When known compounds had to be prepared according to literature procedures, pertinent references are given.

Air- and moisture-sensitive materials were stored in Schlenk tubes or Schlenk burettes. They were protected by and handled under an atmosphere of 99.995% pure nitrogen, using appropriate glassware (Glasgerätebau Pfeifer, 98711 Frauenwald).

Diethyl ether and tetrahydrofuran were dried by distillation from sodium wire after the characteristic blue color of in situ generated sodium diphenyl ketyl (benzophenone-sodium "radical-anion") had been found to persist.<sup>[6–7]</sup>

Ethereal or other organic extracts were dried by washing with brine and then by storage over sodium sulfate. A spatula tip of hydroquinone or potassium carbonate was added to compounds prone to radical polymerization or sensitive to acids, respectively, prior to distillation. If no reduced pressure is specified, boiling ranges were read under ordinary atmospheric conditions ( $725 \pm 25$  Torr).

Melting ranges (mp) given were found to be reproducible after resolidification, unless stated otherwise ("dec."), and were corrected using a calibration curve established with authentic standards. If melting points are missing, it means all attempts to crystallize the liquid at temperatures down to  $-75^\circ\text{C}$  failed. The temperature of dry ice/methanol baths is consistently indicated as  $-75^\circ\text{C}$  and "room temperature" ( $22\text{--}26^\circ\text{C}$ ) as  $25^\circ\text{C}$ .

Whenever possible and appropriate, yields of products were determined, prior to isolation, by gas chromatographic comparison of their peak areas with that of a known amount of a reference substance ("internal standard") and correction of the ratios thus obtained by means of separately measured calibration factors. The

purity of distilled compounds was checked on at least two columns loaded with stationary phases of contrasting polarity. Chromosorb G-AW of 80–100 and 60–80 mesh particle size was used as the support for packed columns for the analytical and preparative scale (2 or 3 m long, 2 mm inner diameter and 3 or 6 m long, 1 cm inner diameter, respectively). Packed columns were made of glass, while quartz was the material chosen for capillary columns ( $\geq 10$  m long). In case of a programmed temperature increase, a constant rate of  $25^\circ\text{C}$  per minute was applied. The stationary phases employed are encoded as DB-23 (of the silicone type) and DB-WAX (belonging to the polyethylene glycol family).

$^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded of samples dissolved in deuteriochloroform at 400 and 101 MHz, respectively (other solvents are specified). Chemical shifts  $\delta$  refer to the signal of tetramethylsilane ( $\delta = 0.00$ ) and coupling constants  $J$  are given in Hz. Coupling patterns are, for example, abbreviated as s (singlet), d (doublet), t (triplet) and m (multiplet).

Elementary analyses were performed by the laboratory of I. Beetz (96301 Kronach, Germany). The expected percentages were calculated using the atomic weight numbers listed in the 1986 IUPAC recommendations.

### Starting Material

2,3,5-Trichloropyridine is commercial and inexpensive (about 150 €/mol). It can be easily converted into 5-chloro-2,3-difluoropyridine.<sup>[8–10]</sup>

**3,5-Dichloro-2-fluoropyridine:** A mixture of 2,3,5-trichloropyridine (46 g, 0.25 mol) and spray-dried potassium fluoride (29 g, 0.50 mol) in anhydrous sulfolane (tetramethylenesulfone; 0.15 L) was heated to  $180^\circ\text{C}$  under stirring for 20 h. The product was purified by steam distillation, extracted with diethyl ether ( $3 \times 50$  mL) and, after evaporation of the solvent, crystallized from methanol; colorless platelets; m.p.  $39\text{--}41^\circ\text{C}$  (ref.<sup>[11]</sup>  $42\text{--}43^\circ\text{C}$ ); yield 36.1 g (86%);  $^1\text{H}$  NMR:  $\delta = 8.08$  (dd,  $J = 2.5, 1.7$  Hz, 1 H), 7.84 (dd,  $J = 7.5, 2.4$  Hz, 1 H);  $^{13}\text{C}$  NMR:  $\delta = 157.4$  (d,  $J = 239$  Hz), 143.7 (d,  $J = 14.0$  Hz), 140.2 (s), 128.9 (d,  $J = 5$  Hz), 117.9 (d,  $J = 36$  Hz);  $\text{C}_5\text{H}_2\text{Cl}_2\text{FN}$  (165.98): calcd. C 36.18, H 1.21; found C 35.98, H 1.21.

### 5-Chloro-2,3-dihalo-4-pyridinecarboxylic Acids 1

**2,3,5-Trichloro-4-pyridinecarboxylic Acid (1a):** Diisopropylamine (3.5 mL, 2.5 g, 25 mmol) and 2,3,5-trichloropyridine (4.6 g, 25 mmol) were consecutively added at  $-75^\circ\text{C}$  to butyllithium (25 mmol) in tetrahydrofuran (35 mL) and hexanes (15 mL). After 2 h at  $-75^\circ\text{C}$ , the mixture was poured onto an excess of freshly crushed dry ice. After evaporation of the solvents, the residue was taken up in water and washed with ether ( $2 \times 25$  mL). The aqueous phase was acidified with concentrated hydrochloric acid to pH 1 and extracted with diethyl ether ( $3 \times 50$  mL). The combined organic layers were washed with brine ( $2 \times 50$  mL), dried and the solvents evaporated. The residue was crystallized from chloroform to give colorless prisms; m.p.  $186\text{--}189^\circ\text{C}$ ; yield 4.2 g (75%);  $^1\text{H}$  NMR ( $\text{D}_3\text{CCOCD}_3$ ):  $\delta = 8.56$  (s);  $^{13}\text{C}$  NMR ( $\text{D}_3\text{CCOCD}_3$ ):  $\delta = 163.2$  (s), 148.5 (s), 148.0 (s), 144.2 (s), 127.6 (s), 127.2 (s);  $\text{C}_6\text{H}_2\text{Cl}_3\text{NO}_2$  (226.45): calcd. C 31.82, H 0.89; found C 31.97, H 0.95.

**3,5-Dichloro-2-fluoro-4-pyridinecarboxylic Acid (1b):** Prepared as described above from 3,5-dichloro-2-fluoropyridine (4.1 g, 25 mmol); colorless cubes; m.p.  $158\text{--}160^\circ\text{C}$  (from ethyl acetate); yield 4.1 g (79%);  $^1\text{H}$  NMR ( $\text{D}_3\text{CCOCD}_3$ ):  $\delta = 8.37$  (s);  $^{13}\text{C}$  NMR ( $\text{D}_3\text{CCOCD}_3$ ):  $\delta = 163.0$  (d,  $J = 3$  Hz), 158.3 (d,  $J = 237$  Hz),

146.0 (s), 145.9 (d,  $J = 15$  Hz), 125.8 (d,  $J = 5$  Hz), 114.8 (d,  $J = 39$  Hz);  $C_6H_2Cl_2FNO_2$  (209.99): calcd. C 34.32, H 0.96; found C 34.40, H 1.02.

**5-Chloro-2,3-difluoro-4-pyridinecarboxylic Acid (1c):** Prepared as described above from 5-chloro-2,3-difluoropyridine (3.7 g, 25 mmol); colorless needles; m.p. 115–117 °C (from chloroform); yield 3.3 g (69%);  $^1H$  NMR ( $D_3CCOCD_3$ ):  $\delta = 8.23$  (d,  $J = 1.8$ , 0.8 Hz);  $^{13}C$  NMR ( $D_3CCOCD_3$ ):  $\delta = 161.4$  (d,  $J = 3$  Hz), 151.6 (dd,  $J = 238$ , 15 Hz), 142.8 (dd,  $J = 267$ , 32 Hz), 142.3 (dd,  $J = 14$ , 7 Hz), 133.9 (d,  $J = 17$  Hz), 126.1 (d,  $J = 5$  Hz);  $C_6H_2ClF_2NO_2$  (193.54): calcd. C 37.24, H 1.04; found C 37.30, H 1.12.

### 5-Chloro-2,3-dihalo-4-iodopyridines 2

**2,3,5-Trichloro-4-iodopyridine (2a):** Diisopropylamine (3.5 mL, 2.5 g, 25 mmol) and 2,3,5-trichloropyridine (4.6 g, 25 mmol) were consecutively added at  $-75$  °C to butyllithium (25 mmol) in tetrahydrofuran (35 mL) and hexanes (15 mL). After 2 h at  $-75$  °C, the reaction mixture was siphoned through a Teflon capillary into a vigorously stirred solution of iodine (7.7 g, 30 mmol) in tetrahydrofuran (15 mL) kept at  $-75$  °C. The mixture was diluted with diethyl ether (100 mL), washed with a saturated aqueous solution ( $3 \times 50$  mL) of sodium thiosulfate, water (25 mL) and brine (25 mL), dried and concentrated. The residue was crystallized from methanol affording colorless needles; m.p. 116–118 °C; yield 6.9 g (89%);  $^1H$  NMR:  $\delta = 8.24$  (s);  $^{13}C$  NMR:  $\delta = 146.0$  (s), 144.3 (s), 137.3 (s), 136.7 (s), 116.8 (s);  $C_5HCl_3IN$  (308.33): calcd. C 19.48, H 0.33; found C 19.69, H 0.48.

**3,5-Dichloro-2-fluoro-4-iodopyridine (2b):** Prepared as described above from 3,5-dichloro-2-fluoropyridine (4.1 g, 25 mmol); colorless needles; m.p. 121–124 °C (from methanol); yield 5.3 g (73%);  $^1H$  NMR:  $\delta = 8.10$  (s);  $^{13}C$  NMR:  $\delta = 156.0$  (d,  $J = 242$  Hz), 142.1 (d,  $J = 14$  Hz), 135.2 (d,  $J = 5$  Hz), 124.3 (d,  $J = 36$  Hz), 118.5 (s);  $C_5HCl_2FIN$  (291.87): calcd. C 20.58, H 0.35; found C 20.66, H 0.31.

**5-Chloro-2,3-difluoro-4-iodopyridine (2c):** Prepared as described above from 5-chloro-2,3-difluoropyridine (3.7 g, 25 mmol); colorless prisms; m.p. 105–107 °C (from methanol); yield 5.2 g (75%);  $^1H$  NMR:  $\delta = 8.0$  (t,  $J = 1.3$  Hz);  $^{13}C$  NMR:  $\delta = 149.2$  (dd,  $J = 226$ , 17 Hz), 146.8 (dd,  $J = 262$ , 30 Hz), 139.2 (dd,  $J = 14$ , 6 Hz), 101.1 (d,  $J = 20$  Hz);  $C_5HClF_2IN$  (275.42): calcd. C 21.80, H 0.37; found C 22.03, H 0.57.

### 5-Chloro-2,3-dihalo-6-iodo-4-pyridinecarboxylic Acids 3

**2,3,5-Trichloro-6-iodo-4-pyridinecarboxylic Acid (3a):** 2,2,6,6-Tetramethylpiperidine (5.0 mL, 4.2 g, 30 mmol) and 2,3,5-trichloro-4-iodopyridine (2a; 4.6 g, 15 mmol) were consecutively added at  $-100$  °C to a vigorously stirred solution of hexane-free butyllithium (30 mmol) in tetrahydrofuran (30 mL). After 2 h at  $-100$  °C, the mixture was poured onto an excess of freshly crushed dry ice. Extraction as described above (see the preparation of acids 1) and trituration with chloroform of the red oil obtained afforded colorless prisms; m.p. 252 °C (from ethyl acetate; dec.); yield 2.7 g (52%);  $^{13}C$  NMR ( $D_3CCOCD_3$ ):  $\delta = 162.7$  (s), 145.6 (s), 143.5 (s), 132.4 (s), 125.1 (s), 120.1 (s);  $C_6HCl_3INO_2$  (352.34): calcd. C 20.45, H 0.29; found C 20.64, H 0.35. Virtually the same result was obtained after pyridine 2a had been treated with lithium diisopropylamide for 45 min at  $-75$  °C.

**3,5-Dichloro-2-fluoro-6-iodo-4-pyridinecarboxylic Acid (3b):** 2,2,6,6-Tetramethylpiperidine (5.0 mL, 4.2 g, 30 mmol) and 3,5-dichloro-2-fluoro-4-iodopyridine (2b; 4.4 g, 15 mmol) were consecutively ad-

ded at  $-100$  °C to a vigorously stirred solution of hexane-free butyllithium (30 mmol) in tetrahydrofuran (30 mL). The temperature was raised during 45 min to  $-75$  °C where it was kept constant for 15 min before the mixture was poured onto an excess of freshly crushed dry ice. Extraction (as described above, see the preparation of acids 1) and trituration with chloroform of the red oil obtained gave colorless prisms; m.p. 179–181 °C (from chloroform); yield 2.5 g (50%);  $^{13}C$  NMR ( $D_3CCOCD_3$ ):  $\delta = 162.6$  (s), 155.8 (d,  $J = 242$  Hz), 145.6 (s), 132.2 (s), 115.6 (d,  $J = 14$  Hz), 114.5 (d,  $J = 38$  Hz);  $C_6HCl_2FINO_2$  (335.89): calcd. C 21.45, H 0.30; found C 21.50, H 0.40.

**5-Chloro-2,3-difluoro-6-iodo-4-pyridinecarboxylic Acid (3c):** Prior to carboxylation, 5-chloro-2,3-difluoro-4-iodopyridine (2c; 4.1 g, 15 mmol) was treated with lithium 2,2,6,6-tetramethylpiperidide essentially as described in the two preceding paragraphs, but for only 45 min at  $-100$  °C. Trituration with chloroform of the red oil obtained after extraction afforded colorless prisms; m.p. 166–168 °C (from chloroform; dec.); yield 1.4 g (29%);  $^{13}C$  NMR ( $D_3CCOCD_3$ ):  $\delta = 161.0$  (s), 149.2 (dd,  $J = 244$ , 15 Hz), 142.5 (dd,  $J = 267$ , 31 Hz), 134.2 (d,  $J = 16$  Hz), 132.2 (d,  $J = 5$  Hz), 110.1 (dd,  $J = 12$ , 5 Hz);  $C_6HClF_2INO_2$  (319.43): calcd. C 22.56, H 0.31; found C 22.77, H 0.53.

### 5-Chloro-2,3-dihalo-6-iodopyridines 4

**2,3,5-Trichloro-6-iodopyridine (4a):** 2,2,6,6-Tetramethylpiperidine (8.4 mL, 7.1 g, 50 mmol) and 2,3,5-trichloro-6-iodopyridine (2a; 7.7 g, 25 mmol) were consecutively added at  $-100$  °C to a vigorously stirred solution of butyllithium (50 mmol) in tetrahydrofuran (60 mL) and hexanes (30 mL). After 2 h at  $-100$  °C, the mixture was treated with methanol (5.0 mL) before being poured into water (0.10 L) and extracted with diethyl ether ( $3 \times 50$  mL). The combined organic layers were washed with brine ( $2 \times 25$  mL), dried and the solvents evaporated. Upon distillation of the residue, a colorless liquid was collected which crystallized in the form of needles; m.p. 60–62 °C (from ethanol); b.p. 125–127 °C/4 Torr; yield 4.5 g (59%);  $^1H$  NMR:  $\delta = 7.76$  (s);  $^{13}C$  NMR:  $\delta = 146.0$  (s), 137.6 (s), 137.6 (s), 130.6 (s), 115.8 (s);  $C_5HCl_3IN$  (308.33): calcd. C 19.48, H 0.33; found C 19.52, H 0.44.

**3,5-Dichloro-2-fluoro-6-iodopyridine (4b):** 2,2,6,6-Tetramethylpiperidine (5.0 mL, 4.2 g, 30 mmol) and 3,5-dichloro-2-fluoro-4-iodopyridine (2b; 7.3 g, 25 mmol) were consecutively added at  $-100$  °C to a vigorously stirred solution of hexane-free butyllithium (30 mmol) in tetrahydrofuran (30 mL). The temperature was slowly raised to  $-75$  °C where it was kept constant for 15 min. The mixture was treated with methanol (5.0 mL) before being poured into water (0.10 L) and extracted with diethyl ether ( $3 \times 50$  mL). The combined organic layers were washed with brine ( $2 \times 25$  mL), dried and the solvents evaporated. Upon distillation of the residue, a colorless liquid was collected which solidified to give needles; m.p. 34–35 °C (from methanol); b.p. 102–105 °C/4 Torr; yield 4.1 g (56%);  $^1H$  NMR:  $\delta = 7.78$  (d,  $J = 7.5$  Hz);  $^{13}C$  NMR:  $\delta = 155.0$  (d,  $J = 245$  Hz), 139.6, 135.9 (d,  $J = 6$  Hz), 117.4 (d,  $J = 35$  Hz), 113.1 (d,  $J = 13$  Hz);  $C_5HCl_2FIN$  (291.87): calcd. C 20.57, H 0.34; found C 20.70, H 0.54.

**5-Chloro-2,3-difluoro-6-iodopyridine (4c):** Prepared as described above for 2b, but starting from 5-chloro-2,3-difluoro-4-iodopyridine (2c; 6.9 g, 25 mmol) and with a reaction time of 45 min; colorless liquid; b.p. 85–87 °C/4 Torr;  $n_D^{20}$  1.5824; yield 3.2 g (46%);  $^1H$  NMR:  $\delta = 7.63$  (t,  $J = 8.0$ );  $^{13}C$  NMR:  $\delta = 148.3$  (dd,  $J = 246$ , 15 Hz), 144.7 (dd,  $J = 268$ , 29 Hz), 135.5 (d,  $J = 5$  Hz), 127.0 (dd,

$J = 18, 3 \text{ Hz}$ ), 107.7 (dd,  $J = 12, 4 \text{ Hz}$ );  $\text{C}_5\text{HClF}_2\text{IN}$  (275.42): calcd. C 21.80, H 0.37; found C 22.14, H 0.57.

### 5-Chloro-2,3-dihalo-6-pyridinecarboxylic Acids 5

**2,3,5-Trichloro-6-pyridinecarboxylic Acid (5a):** 2,3,5-Trichloro-6-iodopyridine (**4a**; 4.6 g, 15 mmol) was added to a 2.0 M solution (7.5 mL) of isopropylmagnesium chloride (15 mmol) in tetrahydrofuran cooled to  $-75^\circ\text{C}$ . After 45 min at this temperature, the mixture was poured onto an excess of freshly crushed dry ice and the product isolated as described above (see the preparation of acids **2**). Crystallization of the residue from hexanes afforded colorless cubes; m.p. 153–155  $^\circ\text{C}$ ; yield 2.6 g (76%);  $^1\text{H}$  NMR ( $\text{D}_3\text{CCOCD}_3$ ):  $\delta = 8.36$  (s);  $^{13}\text{C}$  NMR ( $\text{D}_3\text{CCOCD}_3$ ):  $\delta = 162.8$  (s), 145.9 (s), 145.5 (s), 141.2 (s), 132.6 (s), 129.5 (s);  $\text{C}_6\text{H}_2\text{Cl}_3\text{NO}_2$  (226.45): calcd. C 31.82, H 0.89; found C 31.96, H 0.84.

**3,5-Dichloro-2-fluoro-6-pyridinecarboxylic Acid (5b):** Prepared as described above from 3,5-dichloro-2-fluoro-6-iodopyridine (**4b**; 4.4 g, 15 mmol); colorless prisms; m.p. 107–109  $^\circ\text{C}$  (from ethyl acetate); yield 1.6 g (51%);  $^1\text{H}$  NMR ( $\text{D}_3\text{CCOCD}_3$ ):  $\delta = 8.72$  (d,  $J = 7.8 \text{ Hz}$ );  $^{13}\text{C}$  NMR ( $\text{D}_3\text{CCOCD}_3$ ):  $\delta = 163.9$  (s), 156.3 (d,  $J = 269 \text{ Hz}$ ), 143.9 (d,  $J = 5 \text{ Hz}$ ), 131.4 (d,  $J = 4 \text{ Hz}$ ), 127.0 (d,  $J = 24 \text{ Hz}$ ), 126.5 (d,  $J = 22 \text{ Hz}$ );  $\text{C}_6\text{H}_2\text{Cl}_2\text{FNO}_2$  (209.99): calcd. C 34.32, H 0.96; found C 34.23, H 1.02.

**5-Chloro-2,3-difluoro-6-pyridinecarboxylic Acid (5c):** Prepared as described above from 5-chloro-2,3-difluoro-6-iodopyridine (**4c**; 4.1 g, 15 mmol); colorless cubes; m.p. 98–101  $^\circ\text{C}$  (from ethyl acetate); yield 2.1 g (74%);  $^1\text{H}$  NMR ( $\text{D}_3\text{CCOCD}_3$ ):  $\delta = 8.25$  (t,  $J = 7.8 \text{ Hz}$ );  $^{13}\text{C}$  NMR ( $\text{D}_3\text{CCOCD}_3$ ):  $\delta = 163.5$  (s), 150.0 (dd,  $J = 240, 15 \text{ Hz}$ ), 147.1 (dd,  $J = 269, 30 \text{ Hz}$ ), 140.4 (d,  $J = 12, 5 \text{ Hz}$ ), 131.1 (d,  $J = 4 \text{ Hz}$ ), 126.1 (s);  $\text{C}_6\text{H}_2\text{ClF}_2\text{NO}_2$  (193.54): calcd. C 37.24, H 1.04; found C 37.44, H 1.17.

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