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Regiochemically Flexible Substitutions of Di-, Tri-, and Tetrahalopyridines: The Trialkylsilyl Trick

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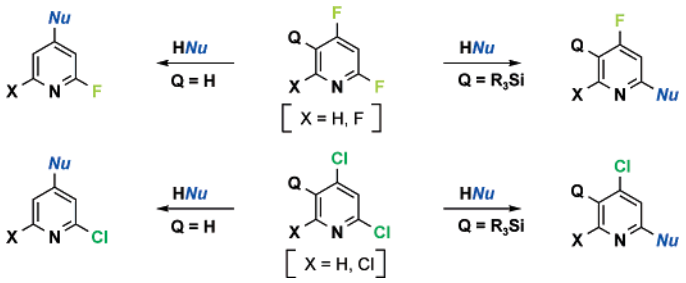

2,4-Difluoropyridine, 2,4-dichloropyridine, 2,4,6-trifluoropyridine, 2,4,6-trichloropyridine and 2,3,4,6-tetrafluoropyridine react with standard nucleophiles exclusively at the 4-position under halogen displacement. However, the regioselectivity can be completely reversed if a trialkylsilyl group is introduced in the 5-position of the 2,4-dihalopyridines or in the 3-position of the 2,4,6-trihalopyridines or 2,3,4,6-tetrahalopyridine. Then only the halogen most remote from the bulky silyl unit (at the 2-position in the case of the 2,4-halopyridines, at the 6-position with the other substrates) gets involved in the exchange process. After removal of the silyl protective group the nucleophile is invariably found to occupy the nitrogen-neighboring position.

Introduction

In recent years we have devoted much effort toward the implementation of regioflexibility in the generation of organometallic intermediates from arenes and heterocycles. As demonstrated in numerous model studies, our *toolbox methods*[1] offer indeed the possibility to selectively introduce a metal into any vacant position of an aromatic or heterocyclic substrate and thus enable its site-specific *electrophilic* derivatization, in particular, functionalization. These achievements drew our attention to the rather gloomy situation encountered with *nucleophilic* (het)-aromatic substitutions as far as the control of their regiochemical outcome is concerned. Of course, no ambiguity exists when the substrate harbors just one halogen atom in an *ortho* or *para* position with respect to an activating nitro substituent or a 2-(6-) or 4-position in a pyridine or pyrimidine. It will be displaced more or less readily by a variety of nucleophiles. Problems arise as soon as two or more potential leaving groups are located at activated positions. Depending on their nature, a mixture of substitution products may be obtained, or if just one isomer is formed, it may be not the required one.

The problem was recognized a long while ago, when 2,4-dihalopyridines and 2,4,6-trihalopyridines were found to undergo nucleophilic substitutions preferentially or exclusively at the 4-position.[2−7] Attempts to alter this order of priority were undertaken but were rewarded with little success.

When pentafluoropyridine, 3-chlorotetrafluoropyridine and 3,5-dichlorotrifluoropyridine were exposed to the action of lithium or sodium oximates rather than of more current nucleophiles, the ratios of 4- vs 2-attack did decrease from >10:1 to 1:1 or even 1:2.[8] However, no selective 2-substitution could ever be accomplished.

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We are now able to show how this goal can be attained. As already disclosed in a preliminary communication,[9] the key to the solution is the steric screening exerted by a trialkylsilyl group on its immediate vicinity. The novel principle of regiocontrol is illustrated below by the transformations of several fluorinated or chlorinated pyridines selected as model compounds.

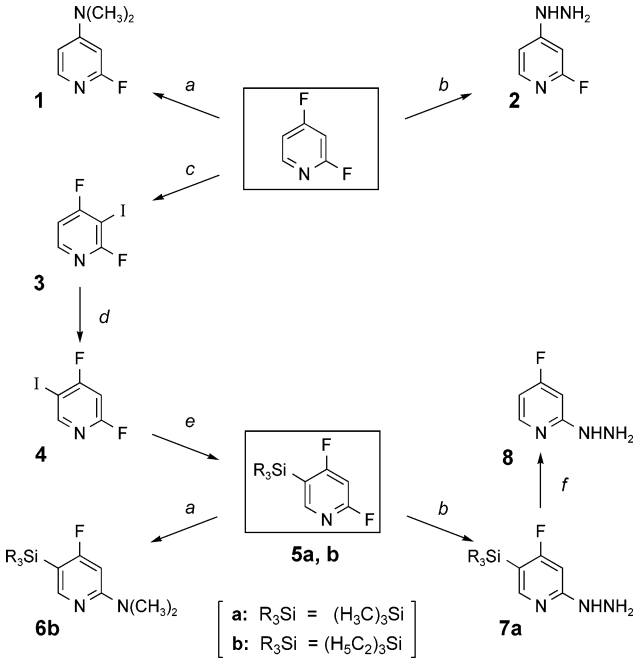
Results and Discussion

As expected, 2,4-difluoropyridine[10,11] underwent substitution with dimethylamine and hydrazine exclusively at the 4-position to afford 4-(dimethylamino)-2-fluoropyridine (**1**; 94%) and 2-fluoro-4-hydrazinopyridine (**2**; 73%), respectively (Scheme 1). In contrast, 2,4-difluoro-5-(trimethylsilyl)pyridine (**5a**) and 2,4-difluoro-5-(triethylsilyl)-pyridine (**5b**) reacted with the same nucleophiles cleanly at the 2-position, thus producing 2-(dimethylamino)-4-fluoro-5-(triethylsilyl)pyridine (**6b**; 78%) and 4-fluoro-2-hydrazino-5-(trimethylsilyl)pyridine (**7a**; 63%). The latter compound was protodesilylated to give 4-fluoro-2-hydrazinopyridine (**8**; 53%). The removal of the trialkylsilyl group was readily accomplished in the given case as in similar situations described below by treatment with tetrabutylammonium fluoride trihydrate. The silanes **5** were readily prepared starting from 2,4-difluoropyridine by lithiation and iodination, isomerization of the resulting 2,4-difluoro-3-iodopyridine (**3**; 82%) by deprotonation-triggered heavy halogen migration[12] to 2,4-difluoro-5-iodopyridine (**4**; 67%) and consecutive treatment of the latter with isopropylmagnesium chloride and chlorotrimethylsilane or chlorotriethylsilane (Scheme 1).

At first sight, the obstruction of the nucleophilic attack at the 4-position can be attributed to trivial steric hindrance caused by the bulky trialkylsilyl substituent. However, the rehybridization of the nucleophile-accommodating center from trigonal (sp^2-like) to tetragonal (sp^3-like) should entail relief of steric repulsion built up between the trialkylsilyl group and the neighboring fluorine or (see below) chlorine atoms. A more subtle explanation may be warranted. There are reasons why the nucleophile may be forced to approach in the ring plane rather than from a perpendicular direction as one may intuitively assume. The silyl substituent would of course heavily interfere with such a trajectory.[9]

The attempted condensation of 2,4-difluoropyridine with sodium ethoxide in ethanol was found to be unselective, leading to a mixture of 2- and 4-ethoxy isomers. In contrast, the reaction of 2,4,6-trifluoropyridine with sodium ethoxide as well as with the *N*-nucleophiles dimethylamine and hydrazine proceeded regioselectively at the 4-position to provide 4-ethoxy-2,6-difluoropyridine (**9**; 81%), 4-(dimethylamino)-2,6-difluoropyridine (**10**; 86%) and 2,6-difluoro-4-hydrazinopyridine (**11**; 85%), respectively (Scheme 2). 2,4,6-Trifluoro-3-(trimethylsilyl)pyridine (**12a**) and 2,4,6-trifluoro-3-(triethylsilyl)pyridine (**12b**), easily accessible by the consecutive metalation and trialkylsilylation of 2,4,6-trifluoropyridine (in 90% and 84% yield), exhibited under the same conditions the opposite site selectivity, furnishing 6-ethoxy-2,4-difluoro-3-(trimethylsilyl)pyridine (**17a**; 92%), 6-(dimethylamino)-2,4-difluoro-3-(trimethylsilyl)pyridine (**13a**; 95%) and 2,4-difluoro-6-hydrazino-3-(triethylsilyl)pyridine (**15b**; 98%), respectively. Protodesilylation converted the silanes **13a** and **15b** into 2-(dimethylamino)-4,6-difluoropyridine (**14**; 91%) and 2,4-difluoro-6-hydrazinopyridine (**16**; 85%).

SCHEME 1. Nucleophilic Aromatic Substitutions Starting from 2,4-Difluoropyridine[a]



[a] Reagents and conditions: (a) Aqueous $HN(CH_3)_2$. (b) $N_2H_4 \cdot H_2O$. (c) (i) $LiN(^iC_3H_7)_2$, (ii) I_2. (d) (i) $LiN(^iC_3H_7)_2$, (ii) H_2O. (e) (i) $ClMgCH(CH_3)_2$, (ii) $ClSi(CH_3)_3$ or $ClSi(C_2H_5)_3$. (f) $(H_9C_4)_4NF \cdot (H_2O)_3$.

Hydrazinopyridines[13] are extremely versatile intermediates. They can be incorporated into pyrazoles[14] by cyclization with 1,3-dicarbonyls or reduced to aminopyridines by *N,N*-cleaving hydrogenolysis.[15] Moreover, one can remove both nitrogen atoms by dediazotation of a transient diazenylpyridine. Such species can be generated by dehydrogenation of the hydrazinopyridine with copper sulfate[16] or manganese dioxide[17] and by base-promoted 1,6-dehydrochlorination of the tautomeric form of a

(8) (a) Banks, R. E.; Jondi, W. J.; Tipping, A. E. *J. Fluorine Chem.* **1996**, *79*, 87. (b) Banks, R. E.; Jondi, W. J.; Tipping, A. E. *J. Fluorine Chem.* **1996**, *80*, 109.

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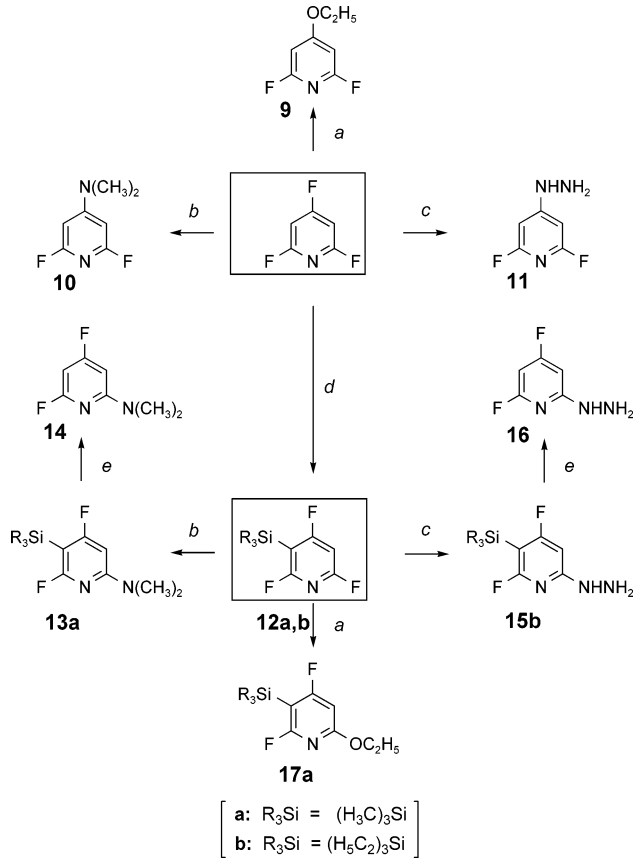
SCHEME 2. Nucleophilic Aromatic Substitutions Starting from 2,4,6-Trifluoropyridine[a]



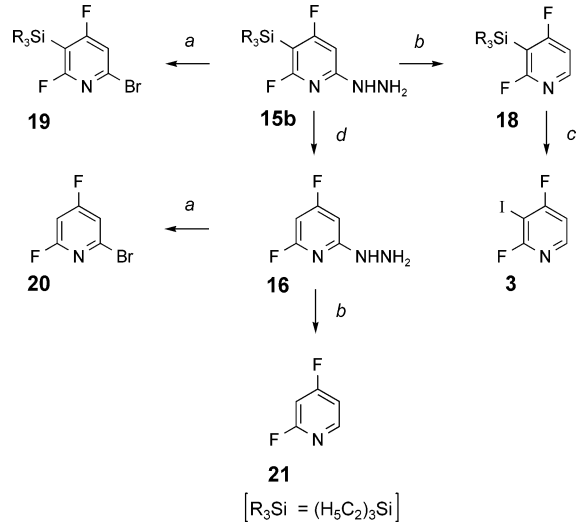
[a] Reagents and conditions: (a) $NaOC_2H_5$. (b) Aqueous $HN(CH_3)_2$. (c) $N_2H_4{\cdot}H_2O$. (d) (i) LiC_4H_9, (ii) $ClSi(CH_3)_3$ or $ClSi(C_2H_5)_3$. (e) $(H_9C_4)_4NF{\cdot}(H_2O)_3$.

chlorohydrazinopyridine.[18] Finally, the hydrazino group may be replaced by a bromine rather than hydrogen atom. To achieve this, one has simply to use elemental bromine for the dehydrogenation of the hydrazinopyridine.[19]

Applying these methods, we have converted 2,4-difluoro-6-hydrazino-3-(triethylsilyl)pyridine (**15b**) into 2,4-difluoro-3-(triethylsilyl)pyridine (**18**; 89%), which gave 2,4-difluoro-3-iodopyridine (**3**; 93%) upon iododesilylation, and 6-bromo-2,4-difluoro-3-(triethylsilyl)pyridine (**19**; 52%). In the same way, the highly volatile 2,4-difluoropyridine (**21**; 51%) and 2-bromo-4,6-difluoropyridine (**20**; 71%) were obtained from 2,4-difluoro-6-hydrazinopyridine (**16**) (Scheme 3).

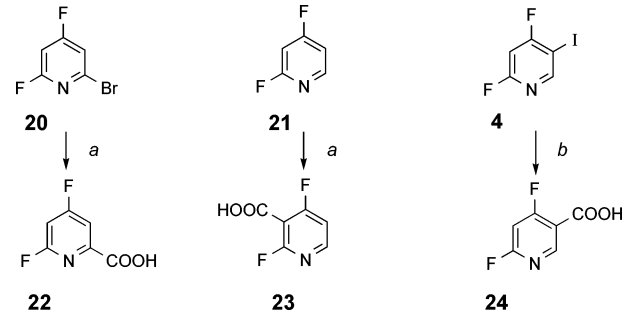
Having both 2-bromo-4,6-difluoropyridine (**20**) and 2,4-difluoro-5-iodopyridine (**4**) at hand we could easily prepare the 4,6-difluoropyridine-2-carboxylic acid (**22**; 39%) and the 4,6-difluoropyridine-3-carboxylic acid (**24**; 56%) by permutational halogen/metal interconversion followed by carboxylation and neutralization (Scheme 4). The 2,4-difluoropyridine-3-carboxylic acid (**23**; 71%) was simply made by metalation and subsequent carboxylation of 2,4-difluoropiridine (**21**).

SCHEME 3. 2,4-Difluoro-6-hydrazinopyridine: Replacement of the Nitrogen Substituent by a Hydrogen or Bromine Atom[a]



[a] Reagents and conditions: (a) Br_2. (b) $CuSO_4{\cdot}(H_2O)_5$. (c) ICl. (d) $(H_9C_4)_4NF{\cdot}(H_2O)_3$.

SCHEME 4. A Convenient Access to All Three 2,4-Difluoropyridinecarboxylic Acids[a]



[a] Reagents and conditions: (a) (i) LiC_4H_9, (ii) CO_2, (iii) aqueous HCl. (b) (i) $ClMgCH(CH_3)_2$, (ii) CO_2, (iii) aqueous HCl.

The reactions of 2,3,4,6-tetrafluoropyridine and its 5-(alkylsilyl) derivatives **28a** and **28b** (formed in 91% and 82% yield, respectively, upon metalation of the tetrafluoropyridine and subsequent condensation with chlorotrimethylsilane or chlorotriethylsilane) obeyed the established regioselectivity pattern (Scheme 5). When treated with hydrazine, the parent compound afforded 2,3,6-trifluoro-4-hydrazinopyridine (**25**; 90%), which was bromodediazotized to the 4-bromo-2,3,6-trifluoropyridine (**26**; 89%) and dehydrogenated-dediazotized to the 2,3,6-trifluoropyridine (**27**; 73%). On the other hand, the silanes **28a** and **28b** were attacked by hydrazine exclusively at the 2-position. The 2,4,5-trifluoro-6-hydrazino-3-(trimethylsilyl)pyridine (**29a**) and 2,4,5-trifluoro-6-hydrazino-3-(triethylsilyl)pyridine (**29b**) were not isolated but directly converted with bromine into 2-bromo-3,4,6-trifluoro-5-(triethylsilyl)pyridine (**30b**; 55%) or, after protodesilylation, with copper(II) sulfate into 2,4,5-trifluoropyridine (**31**; 65% from the trimethyl derivative **29a**).

Nucleophilic (het)aromatic substitutions occur more slowly if chlorine rather than fluorine acts as the nucleofugal leaving group. This is the major difference en-

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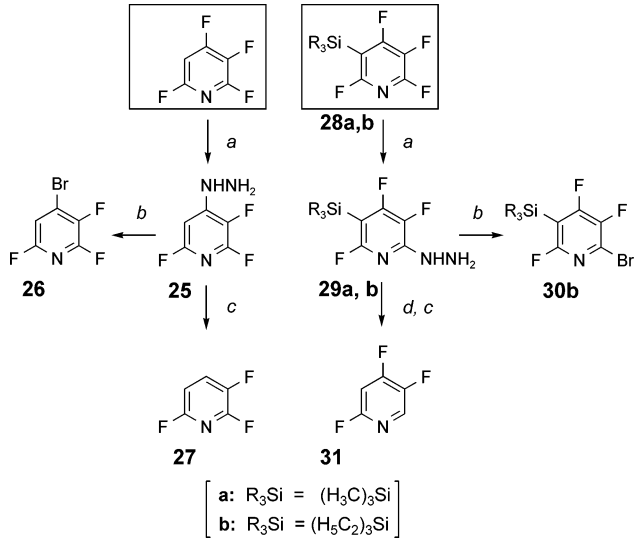
SCHEME 5. Nucleophilic Aromatic Substitutions Starting from 2,3,4,6-Tetrafluoropyridine[a]



[a] Reagents and conditions: (a) $N_2H_4 \cdot H_2O$. (b) Br_2. (c) $CuSO_4 \cdot (H_2O)_5$. (d) $(H_9C_4)_4NF \cdot (H_2O)_3$.

countered when we switched from fluorinated to chlorinated pyridines as substrates. However, the regioselectivities remained the same.

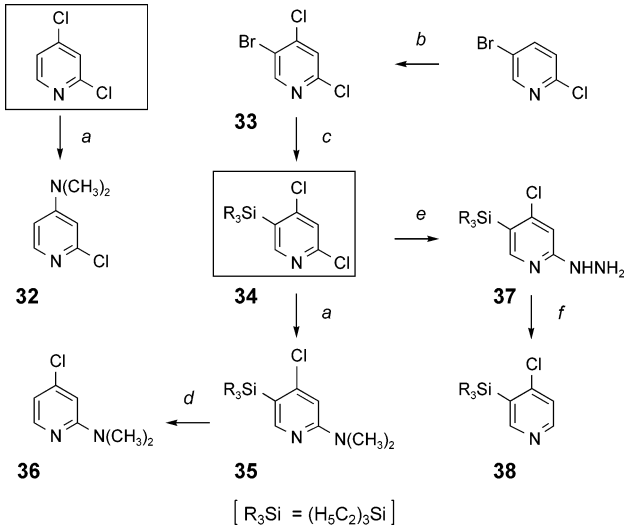
2,4-Dichloropyridine reacted with dimethylamine cleanly at the 4-position, providing pure 2-chloro-4-(dimethylamino)pyridine (**32**; 88%) as the sole product. Conversely, the 2,4-dichloro-5-(triethylsilyl)pyridine (**34**) gave with dimethylamine 4-chloro-2-(dimethylamino)-5-(triethylsilyl)pyridine (**35**; 79%) and, after protodesilylation, 4-chloro-2-(dimethylamino)pyridine (**36**; 86%) or with hydrazine 4-chloro-2-hydrazino-5-(triethylsilyl)pyridine (**37**; not isolated) and, after dehydrogenation-dediazotization, 4-chloro-3-(triethylsilyl)pyridine (**38**; 64%). The silane **34** was prepared in 89% yield starting from 5-bromo-2-chloropyridine through 5-bromo-2,4-dichloropyridine (**33**; 83%), which was subjected to a bromine/lithium permutation followed by condensation with chlorotriethylsilane (Scheme 6).

2,4,6-Trichloropyridine, prepared from 2,6-dichloro-4-iodopyridine, reacted with dimethylamine exclusively at the 4-position to furnish 2,6-dichloro-4-(dimethylamino)-pyridine (**39**; 66%). When treated consecutively with butyllithium and chlorotrimethylsilane or chlorotriethylsilane, 2,4,6-trichloropyridine afforded 2,4,6-trichloro-3-(trimethylsilyl)pyridine (**40a**; 92%) or 2,4,6-trichloro-3-(triethylsilyl)pyridine (**40b**; 81%). Condensation of these silanes with dimethylamine gave 2,4-dichloro-6-(dimethylamino)-3-(triethylsilyl)pyridine (**41**; not isolated) and, after protodesilylation, 2,4-dichloro-6-(dimethylamino)pyridine (**42**; 83%) or with hydrazine 2,4-dichloro-6-hydrazino-(trimethylsilyl)pyridine (**43**; not isolated) and, after protodesilylation, 2,4-dichloro-6-hydrazinopyridine (**44**; 72%), which was converted into 2,4-dichloropyridine (**45**; 67%) by dehydrogenation-dediazotation using copper(II) sulfate (Scheme 7).

Conclusions

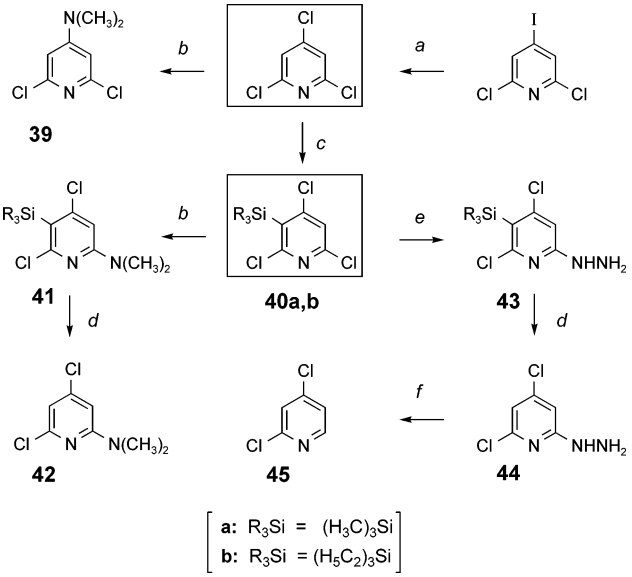
In conclusion, the intrinsic tendency of representative halopyridines such as 2,4-difluoropyridine, 2,4,6-trifluoropyridine, 2,3,4,6-tetrafluoropyridine, 2,4-dichloropyridine and 2,4,6-trichloropyridine to undergo nucleophilic substitution at the 4-position can be circumvented by resorting to the "silyl trick". After introduction of a trialkylsilyl entity at the 3-position, the attack of the nucleophile is completely diverted to the 6-position. Trimethylsilyl and triethylsilyl groups being equivalent in this respect, the choice in a given case depends on the volatility of the products or their tolerance of special reaction conditions.

SCHEME 6. Nucleophilic Aromatic Substitutions Starting from 2,4-Dichloropyriadine[a]



[a] Reagents and conditions: (a) Aqueous $HN(CH_3)_2$. (b) (i) $LiN(^iC_3H_7)_2$, (ii) $Cl_2CFCClF_2$. (c) (i) LiC_4H_9, (ii) $ClSi(C_2H_5)_3$. (d) $(H_9C_4)_4NF \cdot (H_2O)_3$. (e) N_2H_4. (f) $CuSO_4 \cdot (H_2O)_5$.

SCHEME 7. Nucleophilic Aromatic Substitutions Starting from 2,4,6-Trichloropyridine[a]



[a] Reagents and conditions: (a) (i) $ClMgCH(CH_3)_2$, (ii) ClN-$(COCH_2)_2$ [*N*-chlorosuccinimide]. (b) Aqueous $HN(CH_3)_2$. (c) (i) LiC_4H_9, (ii) $ClSi(CH_3)_3$ or $ClSi(C_2H_5)_3$. (d) $(H_9C_4)_4NF \cdot (H_2O)_3$. (e) N_2H_4. (f) $CuSO_4 \cdot (H_2O)_5$.

Experimental Section

General Procedures. Working practices and abbreviations are specified in previous articles from this laboratory.[20−22] ^{1}H and ^{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 deuteriochloroform, if nothing specified, or hexadeuterioacetone, if marked with an asterisk.

The regioisomeric purity of most products was checked by gas chromatographic analysis of the crude reaction mixtures using at least two capillary columns of different phase polarities (detection limit <1%). In cases of insufficient product volatility, one had to rely on NMR spectroscopy (accuracy approximately 5%).

1. Starting Materials. 2,4-Difluoropyridine, 2,4,6-trifluoropyridine and 2,3,4,6-tetrafluoropyridine were prepared according to literature procedures.[11] 2,4-Dichloropyridine was purchased from Apollo Scientific (Stockport, SK6 2QR, UK) and was also obtained by the reaction sequence described in Section 3 (see below). 5-Bromo-2-chloropyridine was purchased from Lancaster Synthesis (Frankfurt am Main, D-65933, Germany).

2,6-Dichloro-4-iodopyridine[23] has been already reported in the literature. However, the access to this compound has been considerably improved as specified below.

2. 2,4-Difluoropyridine Series. 4-Dimethylamino-2-fluoropyridine (1). 2,4-Difluoropyridine (2.9 g, 25 mmol) was added to a 40% aqueous solution (25 mL) of dimethylamine. After 2 h at 25 °C, the reaction mixture was extracted with diethyl ether (3 × 25 mL). The organic phase was dried and evaporated. Crystallization from chloroform afforded 3.30 g (94%) of colorless platelets, mp 53−54 °C. ^{1}H NMR: δ 7.82 (d, J = 6.1 Hz, 1 H), 6.38 (dt, J = 6.1, 2.0 Hz, 1 H), 5.99 (dd, J = 1.9, 1.3 Hz, 1 H), 3.01 (s, 6 H) ppm. ^{13}C NMR: δ 165.2 (d, J = 230 Hz), 157.8 (d, J = 12 Hz), 146.4 (d, J = 19 Hz), 104.8 (d, J = 2 Hz), 89.1 (d, J = 43 Hz), 38.9 (2 C) ppm. $C_7H_9FN_2$ (140.16): calcd C 59.99, H 6.47; found C 59.92, H 6.14.

2-Fluoro-4-hydrazinopyridine (2). A solution of 2,4-difluoropyridine (2.9 g, 25 mmol) and hydrazine monohydrate (2.5 mL, 2.5 g, 50 mmol) in tetrahydrofuran (25 mL) was heated at 50 °C for 4 h. After evaporation of the solvent, the residue was triturated with water (10 mL) and hexanes (5.0 mL); colorless platelets (from tetrahydrofuran and hexanes), mp 97−99 °C, yield 2.32 g (73%). ^{1}H NMR*: δ 9.0 (s, broad, 1 H), 7.79 (d, J = 5.8 Hz, 1 H), 6.85 (dt, J = 5.8, 1.6 Hz, 1 H), 6.57 (d, J = 1.6 Hz, 1 H), 3.0 (s, broad, 2 H) ppm. ^{13}C NMR*: δ 167.0 (d, J = 229 Hz), 158.0 (d, J = 12 Hz), 148.7 (d, J = 19 Hz), 107.9 (d, J = 3 Hz), 91.7 (d, J = 44 Hz) ppm. $C_5H_6FN_3$ (127.12): calcd C 47.24, H 4.76; found C 47.15, H 4.56.

2,4-Difluoro-3-iodopyridine (3). At −100 °C, diisopropylamine (7.1 mL, 5.1 g, 50 mmol) and 2,4-difluoropyridine (5.8 g, 50 mmol) were added consecutively to a solution of butyllithium (50 mmol) in tetrahydrofuran (0.10 L) and hexanes (30 mL), cooled in a liquid nitrogen/methanol bath. After 45 min at −100 °C, the mixture was treated with iodine (13 g, 50 mmol) in tetrahydrofuran (50 mL) and kept 15 min at −75 °C, before being decolorized with a 10% aqueous solution (25 mL) of sodium sulfite. The organic phase was dried and the volatiles evaporated. Crystallization from hexanes afforded colorless needles, mp 76−78 °C, yield 9.88 g (82%). ^{1}H NMR: δ 8.12 (dd, J = 7.7, 5.8 Hz, 1 H), 6.94 (t, J = 5.8 Hz, 1 H) ppm. ^{13}C NMR: δ 170.6 (dd, J = 262, 7 Hz), 163.9 (dd, J = 234, 7 Hz), 148.8 (dd, J = 17, 9 Hz), 110.1 (dd, J = 21, 6 Hz), 65.3 (dd, J = 47, 27 Hz) ppm. $C_5H_2F_2IN$ (240.98): calcd C 24.92, H 0.84; found C 25.07, H 0.96.

2,4-Difluoro-5-iodopyridine (4). Under vigorous mechanical stirring, a solution of lithium diisopropylamide (prepared from butyllithium and diisopropylamine, 0.10 mol each) was added in the course of 2 h to a solution of 2,4-difluoro-3-iodopyridine (**3**; 24 g, 0.10 mol) in tetrahydrofuran (0.10 L) cooled in a dry ice/methanol bath. After a further 30 min at −75 °C, the mixture was treated with water (50 mL). The organic layer was washed with 5% hydrochloric acid (4 × 30 mL), dried and evaporated. A colorless liquid was collected upon distillation, mp 20−22 °C, bp 76−77 °C/15 mmHg, n^{20}_D = 1.5641, yield 16.1 g (67%). ^{1}H NMR: δ 8.49 (d, J = 8.8 Hz, 1 H), 6.73 (dd, J = 7.4, 2.5 Hz, 1 H) ppm. ^{13}C NMR: δ 169.8 (dd, J = 262, 13 Hz), 165.0 (dd, J = 240, 12 Hz), 155.7 (dd, J = 17, 4 Hz), 98.7 (dd, J = 42, 24 Hz), 76.5 (dd, J = 23, 6 Hz) ppm. $C_5H_2F_2IN$ (240.98): calcd C 24.92, H 0.84; found C 25.01, H 0.82.

2,4-Difluoro-5-(trimethylsilyl)pyridine (5a). 2,4-Difluoro-5-iodopyridine (**4**; 12 g, 50 mmol) was added to a solution of isopropylmagnesium chloride (50 mmol) in tetrahydrofuran (50 mL) kept in an ice bath, followed, after 45 min, by chlorotrimethylsilane (6.4 mL, 5.4 g. 50 mmol). The mixture was heated at 50 °C for 2 h before it was poured into a satured aqueous solution of ammonium chloride (40 mL) and the phases separated. Distillation of the organic phase afforded 7.68 g (82%) of a colorless liquid, mp 17−19 °C, bp 77−78 °C/20 mmHg, n^{20}_D = 1.4582. ^{1}H NMR: δ 8.16 (d, J = 8.9 Hz, 1 H), 6.61 (dd, J = 8.0, 1.6 Hz, 1 H), 0.37 (d, J = 1.0 Hz, 9 H) ppm. ^{13}C NMR: δ 175.7 (dd, J = 258, 12 Hz), 166.2 (dd, J = 239, 13 Hz), 154.2, (dd, J = 17, 13 Hz), 120.3 (dd, J = 28, 5 Hz), 97.0 (dd, J = 40, 23 Hz), −1.3 (3 C) ppm. $C_8H_{11}F_2NSi$ (187.27): calcd C 51.31, H 5.92; found C 51.04, H 5.71.

2,4-Difluoro-5-(triethylsilyl)pyridine (5b). Prepared analogously as described above but using chlorotriethylsilane (8.4 mL, 7.5 g, 50 mmol) as the reagent and keeping the mixture at 25 °C for 15 h; colorless liquid, bp 104−106 °C/10 mmHg, n^{20}_D = 1.4735, yield 8.84 g (77%). ^{1}H NMR: δ 8.15 (d, J = 9.0 Hz, 1 H), 6.59 (dd, J = 8.0, 1.6 Hz, 1 H), 0.9 (m, 15 H) ppm. ^{13}C NMR: δ 175.9 (dd, J = 258, 12 Hz), 166.3 (dd, J = 239, 13 Hz), 155.1, (dd, J = 17, 14 Hz), 117.5 (d, J = 29 Hz), 97.1 (dd, J = 40, 28 Hz), 7.2 (3 C), 3.3 (3 C) ppm. $C_{11}H_{17}F_2NSi$ (229.35): calcd C 57.61, H 7.47; found C 57.66, H 7.24.

2-Dimethylamino-4-fluoro-5-(triethylsilyl)pyridine (6b). 2,4-Difluoro-5-(triethylsilyl)pyridine (**5b**; 12 g, 50 mmol) was added to a 40% aqueous solution (50 mL) of dimethylamine. After 6 h at 50 °C, the reaction mixture was extracted with diethyl ether (3 × 0.10 L). Distillation afforded a colorless liquid, mp −4 to −2 °C, bp 104−106 °C/0.5 mmHg, n^{20}_D = 1.5237, yield 9.92 g (78%). ^{1}H NMR: δ 8.10 (d, J = 9.9 Hz, 1 H), 6.11 (d, J = 12.2 Hz, 1 H) 3.08 (s, 6 H), 0.95 (t, J = 7.6 Hz, 9 H), 0.79 (q, J = 7.6 Hz, 6 H) ppm. ^{13}C NMR: δ 174.9 (d, J = 251 Hz), 162.2 (d, J = 11 Hz), 155.7 (d, J = 14 Hz), 104.4 (d, J = Hz), 91.3 (d, J = 26 Hz), 37.6 (2 C), 7.1 (3 C), 3.4 (3 C) ppm. $C_{13}H_{23}FN_2Si$ (254.42): calcd C 61.37, H 9.11; found C 61.25, H 9.09.

4-Fluoro-2-hydrazino-5-(trimethylsilyl)pyridine (7a). A solution containing hydrazine monohydrate (40 mmol) and 2,4-difluoro-5-(trimethylsilyl)pyridine (**5a**; 3.7 g, 20 mmol) in tetrahydrofuran (20 mL) was heated under reflux for 24 h. After evaporation of the solvent, the residue was partitioned between water (25 mL) and diethyl ether (25 mL); slightly pink prisms (from toluene), mp 70−72 °C, yield 2.51 g (63%). ^{1}H NMR: δ 8.02 (d, J = 9.4 Hz, 1 H), 6.40 (d, J = 10.6 Hz,1 H), 5.9 (s, broad, 1 H), 0.29 (d, J = 0.7 Hz, 9 H) ppm. ^{13}C NMR: δ 175.0 (d, J = 253 Hz), 165.2 (d, J = 11 Hz), 154.9 (d, J = 13 Hz), 111.2 (d, J = 29 Hz), 92.3 (d, J = 26 Hz), −1.0 (3 C) ppm. $C_8H_{14}FN_3Si$ (199.31): calcd 48.21, H 7.08; found C 48.27, H 6.85.

4-Fluoro-2-hydrazinopyridine (8). A solution of 4-fluoro-2-hydrazino-5-(trimethylsilyl)pyridine (**7a**; 1.0 g, 5.0 mmol) and tetrabutylammonium fluoride trihydrate (1.6 g, 5.0 mmol) in tetrahydrofuran (10 mL) was stored at 25 °C for 20 h. After evaporation of the solvent, the residue was triturated with water (2 × 15 mL) and crystallized from chloroform and hexanes as colorless cottonlike needles, mp 87−88 °C, yield

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0.34 g (53%). ^{1}H NMR: δ 8.05 (dd, J = 8.7, 5.9 Hz, 1 H), 6.49 (dd, J = 11.2, 2.3 Hz, 1 H), 6.43 (ddd, J = 8.3, 5.8, 2.3 Hz, 1H), 6.2 (s, broad, 1 H), 3.6 (s, broad, 2 H) ppm. ^{13}C NMR: δ 170.3 (d, J = 258 Hz), 164.1 (d, J = 10 Hz), 150.2 (d, J = 10 Hz), 103.1 (d, J = 19 Hz), 93.1 (d, J = 21 Hz) ppm. $C_5H_6FN_3$ (127.12): calcd 47.24, H 4.76; found C 47.21, H 4.66.

3. 2,4,6-Trifluoropyridine Series. 2,6-Difluoro-4-ethoxypyridine (9). When sodium (1.2 g, 50 mmol) had completely dissolved in ethanol (50 mL), 2,4,6-trifluoropyridine (6.7 g, 50 mmol) was added at 0 °C. After 2 h, the mixture was evaporated. Crystallization from hexanes afforded colorless needles, mp 57−59 °C, yield 6.41 g (81%). ^{1}H NMR: δ 6.28 (s, 2 H), 4.11 (q, J = 7.0 Hz, 2 H), 1.45 (t, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR: δ 171.8 (t, J = 12 Hz), 162.9 (dd, J = 241, 20 Hz, 2 C), 92.4 (symm. m, 2 C), 65.1, 14.2 ppm. $C_7H_7F_2NO$ (159.13): calcd C 52.83, H 4.43; found C 52.82, H 4.43.

4-Dimethylamino-2,6-difluoropyridine (10). At 0 °C, 2,4,6-trifluoropyridine (6.7 g, 50 mmol) was added to a 40% aqueous solution (50 mL) of dimethylamine. After 45 min, the solid formed was collected by filtration and crystallized from chloroform; colorless needles, mp 120−122 °C, yield 6.80 g (86%). ^{1}H NMR: δ 5.91 (s, 2 H), 3.02 (s, 6 H) ppm. ^{13}C NMR: δ 163.1 (dd, J = 236, 21 Hz, 2 C), 160.7 (t, J = 12 Hz), 87.0 (symm. m, 2 C), 39.4 (2 C) ppm. $C_7H_8F_2N_2$ (158.15): calcd C 53.16, H 5.10; found C 52.86, H 4.97.

2,6-Difluoro-4-hydrazinopyridine (11). 2,4,6-Trifluoropyridine (6.7 g, 50 mmol) and hydrazine monohydrate (4.9 mL, 5.0 g, 0.10 mol) were heated in tetrahydrofuran (50 mL) at 50 °C for 2 h. After the solvent had been evaporated, the residue was triturated with water (25 mL) and hexanes (12 mL). Crystallization from ethyl acetate afforded colorless platelets, mp 200−202 °C, yield 6.17 g (85%). ^{1}H NMR*: δ 9.3 (s, broad, 1 H), 6.48 (s, 2 H), 3.0 (s, broad, 2 H) ppm. ^{13}C NMR*: δ 164.6 (dd, J = 235, 20 Hz, 2 C), 161.0 (t, J = 12 Hz), 89.5 (symm. m, 2 C) ppm. $C_5H_5F_2N_3$ (145.11): calcd C 41.38, H 3.47; found C 41.55, H 3.23.

2,4,6-Trifluoro-3-(trimethylsilyl)pyridine (12a). At −100 °C, 2,4,6-trifluoropyridine (6.7 g, 50 mmol) in tetrahydrofuran (0.10 L) and butyllithium (50 mmol) in hexanes (32 mL) were mixed. After 45 min at −100 °C, chlorotrimethylsilane (6.3 mL, 5.4 g, 50 mmol) and, after 45 min at −75 °C, water (25 mL) were added. The product was collected as a colorless liquid upon distillation, mp −17 to −16 °C, bp 69−71 °C/20 mmHg, n^{20}_D = 1.4456, yield 9.24 g (90%). ^{1}H NMR: δ 6.49 (dd, J = 7.7, 1.9 Hz,1 H), 0.38 (t, J = 1.4 Hz, 9 H) ppm. ^{13}C NMR: δ 177.8 (ddd, J = 258, 16,12 Hz), 166.1 (ddd, J = 241, 22, 18 Hz), 163.9 (ddd, J = 244, 21, 18 Hz), 104.8 (ddd, J = 48, 34, 6 Hz), 94.8 (ddd, J = 38, 29, 7 Hz), −0.37 (t, J = 3 Hz, 3 C) ppm. $C_8H_{10}F_3NSi$ (205.25): calcd C 46.81, H 4.91; found C 46.94, H 4.83.

2,4,6-Trifluoro-3-(triethylsilyl)pyridine (12b). Prepared analogously as described above but working on a 0.10 mol scale and using chlorotriethylsilane (17 mL, 15 g, 0.10 mol) as the reagent; colorless liquid, bp 65−67 °C/1.6 mmHg; n^{20}_D 1.4630, yield 20.8 g (84%). ^{1}H NMR: δ 6.50 (dd, J = 7.6, 1.9 Hz, 1 H), 0.9 (m, 15 H). ^{13}C NMR: δ 178.2 (ddd, J = 259, 16, 12 Hz), 166.5 (ddd, J = 243, 22, 18 Hz), 164.0 (ddd, J = 245, 20, 17 Hz), 102.3 (ddd, J = 50, 35, 6 Hz), 94.8 (ddd, J = 37, 30, 7 Hz), 7.1 (s), 3.8 (t, J = 2.1 Hz). $C_{11}H_{16}F_3NSi$ (247.34): calcd C 53.42, H 6.52; found C 53.46, H 6.48.

2,4-Difluoro-6-(dimethylamino)-3-(trimethylsilyl)pyridine (13a). At 25 °C, 2,4,6-trifluoro-3-(trimethylsilyl)pyridine (**12a**; 5.1 g, 25 mmol) was added to a 40% aqueous solution (25 mL) of dimethylamine. After 45 min, the product was extracted from the reaction mixture with diethyl ether (3 × 25 mL). Evaporation and crystallization from chloroform afforded 5.47 g (95%) of colorless platelets, mp 43−45 °C. ^{1}H NMR: δ 5.92 (dd, J = 11.2, 1.0 Hz, 1 H), 3.04 (s, 6 H), 0.30 (t, J = 1.3 Hz, 9 H) ppm. ^{13}C NMR: δ 176.7 (dd, J = 251, 17 Hz), 167.1 (dd, J = 230, 22 Hz), 159.9 (dd, J = 22, 15 Hz), 91.0 (dd, J = 51, 35 Hz), 88.7 (dd, J = 29, 5 Hz), 37.6 (2 C), 0.1 (t, J = 2 Hz, 3 C) ppm. $C_{10}H_{16}F_2N_2Si$ (230.33): calcd C 52.15, H 7.00; found C 52.07, H 6.73.

2,4-Difluoro-6-(dimethylamino)pyridine (14). 2,4-Difluoro-6-(dimethylamino)-3-(trimethylsilyl)pyridine (**13a**; 12 g, 50 mmol) and tetrabutylammonium fluoride trihydrate (16 g, 50 mmol) were dissolved in tetrahydrofuran (50 mL). After 2 h at 25 °C, the solvent was evaporated and the residue partitioned between water (25 mL) and diethyl ether (50 mL). The organic phase was dried and distilled; colorless liquid, mp 29−31 °C, bp 75−77 °C/16 mmHg, yield 7.21 g (91%). ^{1}H NMR: δ 5.96 (dd, J = 11.2, 1.6 Hz, 1 H), 5.85 (dt, J = 8.3, 1.6 Hz, 1 H), 3.04 (s, 6 H) ppm. ^{13}C NMR: δ 172.2 (dd, J = 254, 14 Hz), 163.5 (dd, J = 233, 17 Hz), 159.0 (dd, J = 21, 14 Hz), 88.6 (dd, J = 23, 6 Hz), 83.5 (dd, J = 43, 25 Hz), 37.6 (2 C) ppm. $C_7H_8F_2N_2$ (158.15): calcd C 53.16, H 5.10; found C 53.22, H 5.35.

2,4-Difluoro-6-hydrazino-3-(triethylsilyl)pyridine (15b). 2,4,6-Trifluoro-3-(triethylsilyl)pyridine (**12b**; 74 g, 0.30 mol) and hydrazine monohydrate (29 mL, 30 g, 0.60 mol) were heated in tetrahydrofuran (0.10 L) for 2 h at 50 °C. After evaporation of the solvent and addition of diethyl ether (75 mL), the organic phase was washed with water (50 mL). Evaporation of the solvent afforded a yellowish oil, n^{20}_D = 1.5226, yield 76.3 g (98%). ^{1}H NMR: δ 6.8 (s, broad, 1 H), 6.33 (d, J = 10.2 Hz, 1 H), 3.8 (s, broad, 2 H), 0.9 (m, 15 H) ppm. ^{13}C NMR: δ 177.4 (dd, J = 253, 17 Hz), 167.6 (dd, J = 233, 22 Hz), 163.1 (dd, J = 20, 15 Hz), 90.8 (dd, J = 51, 36 Hz), 89.3 (dd, J = 29, 5 Hz), 7.1 (3 C), 3.9 (t, J = 2 Hz, 3 C) ppm. $C_{11}H_{19}F_2N_3Si$ (259.37): calcd C 50.94, H 7.38; found C 51.21, H 7.31.

2,4-Difluoro-6-hydrazinopyridine (16). 2,4-Difluoro-6-hydrazino-3-(triethylsilyl)pyridine (**15b**; 13 g, 50 mmol) and tetrabutylammonium fluoride trihydrate (16 g, 50 mmol) were stored in tetrahydrofuran (50 mL) for 2 h at 25 °C. The solvent was evaporated and the residue was triturated with water (25 mL) and hexanes (50 mL); colorless needles (from chloroform and hexanes), mp 101−103 °C. yield 6.21 g (85%). ^{1}H NMR: δ 6.37 (dd, J = 10.0, 1.6 Hz, 1 H), 6.3 (s, broad, 1 H), 5.98 (dt, J = 8.4, 1.7 Hz), 3.8 (s, broad, 2 H) ppm. ^{13}C NMR: δ 172.6 (dd, J = 257, 14 Hz), 163.9 (dd, J = 236, 17 Hz), 162.0 (dd, J = 20, 14 Hz), 89.7 (dd, J = 24, 5 Hz), 86.5 (dd, J = 41, 25 Hz) ppm. $C_5H_5F_2N_3$ (145.11): calcd C 41.39, H 3.47; found C 41.69, H 3.27.

2,4-Difluoro-6-ethoxy-3-(trimethylsilyl)pyridine (17a). Sodium ethoxide (1.7 g, 25 mmol) and 2,4,6-trifluoro-3-(trimethylsilyl)pyridine (**12a**; 5.1 g, 25 mmol) were mixed in diethyl ether (50 mL). After 2 h at 25 °C, distillation afforded a colorless liquid, mp −6 to −4 °C, bp 83−85 °C/11 mmHg, n^{20}_D = 1.4673, yield 5.32 g (92%). ^{1}H NMR: δ 6.22 (d, J = 9.0 Hz, 1 H), 4.32 (q, J = 7.04 Hz, 2 H), 1.37 (t, J = 7.04 Hz, 3 H), 0.33 (t, J = 1.3 Hz, 9 H) ppm. ^{13}C NMR: δ 176.8 (dd, J = 254, 16 Hz), 165.5 (dd, J = 235, 21 Hz), 165.3 (dd, J = 19, 17 Hz), 98.0 (dd, J = 49, 34 Hz), 94.3 (dd, J = 28, 7 Hz), 62.8, 14.4, −0.2 (t, J = 2.0 Hz, 3 C) ppm. $C_{10}H_{15}F_2NOSi$ (231.31): calcd C 51.92, H 6.54; found C 51.88, H 6.50.

2,4-Difluoro-3-(triethylsilyl)pyridine (18). 2,4-Difluoro-6-hydrazino-3-(triethylsilyl)pyridine (**15b**; 39 g, 0.15 mol) and copper(II) sulfate pentahydrate (75 g, 0.30 mol) were heated in water (0.30 L) under reflux for 2 h. The product was isolated as a colorless liquid by steam distillation followed by in vacuo distillation, bp 85−86 °C/3 mmHg, yield 30.6 g (89%); n^{20}_D 1.4781. ^{1}H NMR: δ 8.18 (dd, J = 8.9, 5.5 Hz, 1 H), 6.87 (ddd, J = 7.4, 5.6, 0.7 Hz, 1 H), 0.9 (m, 15 H). ^{13}C NMR: δ 176.0 (dd, J = 259, 16 Hz), 168.4 (dd, J = 235, 18 Hz), 150.2 (dd, J = 19, 12 Hz), 109.8 (dd, J = 24, 5 Hz), 105.4 (dd, J = 51, 33 Hz), 7.2 (s), 3.8 (t, J = 2.5 Hz). $C_{11}H_{17}F_2NSi$ (229.35): calcd C 57.61, 7.47; found C 57.43, H 7.38.

6-Bromo-2,4-difluoro-3-(triethylsilyl)pyridine (19). Bromine (2.6 mL, 8.0 g, 50 mmol) was added to a solution of 2,4-difluoro-6-hydrazino-3-(triethylsilyl)pyridine (**15b**; 6.5 g, 25 mmol) in chloroform (50 mL). The mixture was heated under reflux for 4 h before being washed with a saturated aqueous

solution (25 mL) of sodium sulfite, dried and evaporated. Upon distillation a colorless liquid was collected, bp 78−80 °C/1 mmHg, n^{20}_D = 1.5068, yield 4.01 g (52%). ^{1}H NMR: δ 7.12 (d, J = 6.7 Hz, 1H), 0.9 (m, 15 H) ppm. ^{13}C NMR: δ 175.9 (dd, J = 262, 15 Hz), 166.7 (dd, J = 241, 19 Hz), 140.7 (dd, J = 19, 12 Hz), 113.9 (dd, J = 28, 6 Hz), 104.5 (dd, J = 49, 35 Hz), 7.1 (3 C), 3.6 (t, J = 2 Hz, 3 C) ppm. $C_{11}H_{16}BrF_2NSi$ (308.24): calcd C 42.86, H 5.23; found C 42.79, H 5.18.

2-Bromo-4,6-difluoropyridine (20). Bromine (3.1 mL, 9.6 g, 60 mmol) was slowly added to a suspension of 2,4-difluoro-6-hydrazinopyridine (**16**; 4.4 g, 30 mmol) in chloroform (60 mL) kept at 40 °C. The mixture was then heated under reflux for 3 h before being poured into a satured aqueous solution (50 mL) of sodium hydrogenocarbonate. After extraction with diethyl ether (2 × 20 mL), the combined organic layers were dried with sodium sulfate and distilled under reduced pressure; slightly yellowish liquid, mp −21 to −24 °C, bp 69−71 °C/30 mmHg; n^{20}_D = 1.5051, yield 4.11 g (71%). ^{1}H NMR: δ 7.20 (dd, J = 7.1, 2.0 Hz, 1 H), 6.66 (dt, J = 7.9, 1.9 Hz, 1 H) ppm. ^{13}C NMR: δ 171.1 (dd, J = 268, 12 Hz), 163.2 (dd, J = 246, 14 Hz), 139.7 (dd, J = 18, 12 Hz), 114.5 (d, J = 21, 6 Hz), 97.3 (dd, J = 40, 22 Hz) ppm. $C_5H_2BrF_2N$ (193.98): calcd C 30.96, H 1.04; found C 31.18, H 1.18.

2,4-Difluoropyridine (21). 2,4-Difluoro-6-hydrazinopyridine (**16**; 15 g, 0.10 mol) and copper(II) sulfate pentahydrate (50 g, 0.20 mol) in water (0.45 L) were heated under reflux for 25 min. A steam distillation followed by a distillation under atmospheric pressure afforded a colorless liquid, bp 104−106 °C (lit.[24] 107 °C), n^{20}_D = 1.4385, yield 5.87 g (51%). ^{1}H NMR: δ 8.22 (dd, J = 8.3, 5.8 Hz, 1 H), 6.97 (ddd, J = 7.7, 5.8, 1.9 Hz, 1 H), 6.68 (dt, J = 8.6, 1.9 Hz, 1 H) ppm. According to gas chromatography (30 m DB-1, 50 °C; 30 m DB-WAX, 50 °C), the crude product contained 1.4% of 2,6-difluoropyridine, arising from an incomplete regioselectivity in the preparation of compound **16**.

4,6-Difluoro-2-pyridinecarboxylic acid (22). At −75 °C, 2-bromo-4,6-difluoropyridine (**20**; 1.9 g, 10 mmol) was added to a solution of butyllithium (10 mmol) in toluene (14 mL) and hexanes (6 mL). After 15 min, the mixture was poured onto freshly crushed carbon dioxide. After addition of 5.0 M hydrochloric acid (20 mL) the product was extracted with diethyl ether (3 × 20 mL) and the solvent was evaporated; yellowish powder (from chloroform), mp 139−141 °C, yield 0.62 g (39%). ^{1}H NMR*: δ 7.87 (dd, J = 8.4, 2.0 Hz, 1 H), 7.33 (dt, J = 8.4, 1.8 Hz, 1 H) ppm. ^{13}C NMR*: δ 173.6 (dd, J = 263, 12 Hz), 165.7 (239, 13 Hz), 164.8 (d, J = 4 Hz), 150.5 (dd, J = 16, 9 Hz), 113.4 (dd, J = 21, 5 Hz), 103.3 (dd, J = 43, 23 Hz) ppm. $C_6H_3F_2NO_2$ (159.09): calcd C 45.30, H 1.90; found C 45.06, H 1.78.

2,4-Difluoro-3-pyridinecarboxylic acid (23). At −100 °C, butyllithium (5.0 mmol) in hexanes (3.0 mL) was added to a solution of 2,4-difluoropyridine (0.58 g, 5.0 mmol) in tetrahydrofuran (7.0 mL). After 2 h at −100 °C, the mixture was poured onto freshly crushed carbon dioxide and, at 25 °C, treated with 4.5 M ethereal hydrogen chloride (3.0 mL). After evaporation of the solvent, ethyl acetate (20 mL) was added and the solid formed was removed by filtration. The product was crystallized from the filtrate by adding hexanes; colorless prisms, mp 152−153 °C (decomp), yield 0. 57 g (71%). ^{1}H NMR*: δ 8.43 (dd, J = 8.1, 5.8 Hz, 1 H), 7.38 (dd, J = 8.7, 5.7 Hz, 1 H) ppm. ^{13}C NMR*: δ 169.6 (dd, J = 269, 8 Hz), 162.3 (dd, J = 241, 8 Hz), 161.3 (d, J = 5 Hz), 152.3 (dd, J = 19, 11 Hz), 112.0 (dd, J = 19, 5 Hz), 106.6 (d, J = 35, 16 Hz) ppm. $C_6H_3F_2NO_2$ (159.09): calcd C 45.30, H 1.90; found C 45.37, H 1.83.

4,6-Difluoro-3-pyridinecarboxylic acid (24). A mixture of 2,4-difluoro-5-iodopyridine (**4**; 1.2 g, 5.0 mmol) and isopropylmagnesium chloride (5.0 mmol) in tetrahydrofuran (10 mL) was kept for 1 h at 0 °C, before being poured onto freshly crushed carbon dioxide. After addition of 5.0 M hydrochloric acid (10 mL), the product was extracted with diethyl ether (3 × 20 mL). Crystallization from toluene afforded 0.54 g (68%) of colorless prisms, mp 99−101 °C (decomp). ^{1}H NMR*: δ 8.82 (d, J = 10.2 Hz, 1 H), 7.17 (dd, J = 10.3, 1.8 Hz, 1 H) ppm. ^{13}C NMR*: δ 171.5 (dd, J = 274, 14 Hz), 167.7 (dd, J = 242, 14 Hz), 163.0 (d, J = 3 Hz), 153.8 (dd, J = 20, 2 Hz), 115.8 (dd, J = 8, 6 Hz), 99.6 (d, J = 42, 24 Hz) ppm. $C_6H_3F_2NO_2$ (159.09): calcd C 45.30, H 1.90; found C 45.24, H 1.81.

4. 2,3,4,6-Tetrafluoropyridine Series. 2,3,6-Trifluoro-4-hydrazinopyridine (25). 2,3,4,6-Tetrafluoropyridine (15 g, 0.10 mol) and hydrazine monohydrate (9.8 mL, 10 g, 0.20 mol) were heated in tetrahydrofuran (0.10 L) under reflux for 2 h. After evaporation of the solvent, the residue was triturated with water (50 mL) and hexanes (25 mL). Crystallization from ethyl acetate afforded colorless platelets, mp 149−151 °C, yield 14.7 g (90%). ^{1}H NMR*: δ 8.9 (s, broad, 1 H), 6.89 (d, J = 4.2 Hz, 1 H), 2.9 (s, broad, 2 H) ppm. ^{13}C NMR*: δ 158.1 (ddd, J = 234, 17, 2 Hz), 150.5 (ddd, J = 233, 20, 13 Hz), 148.6 (ddd, J = 13, 8, 6 Hz), 131.2 (ddd, J = 244, 29, 6 Hz), 91.9 (dd, J = 46, 5 Hz) ppm. $C_5H_4F_3N_3$ (163.10): calcd C 36.82, H 2.47; found C 37.14, H 2.33.

4-Bromo-2,3,6-trifluoropyridine (26). A mixture of 2,3,6-trifluoro-4-hydrazinopyridine (**25**; 8.2 g, 50 mmol) and bromine (5.2 mL, 16 g, 0.10 mol) in chloroform (0.10 L) was heated under reflux for 6 h before being washed with a saturated aqueous solution (50 mL) of sodium sulfite, dried and distilled, mp 6−8 °C, bp 59−61 °C/28 mmHg, n^{20}_D = 1.4836, yield 9.43 g (89%). ^{1}H NMR: δ 7.1 (m, 1 H) ppm. ^{13}C NMR: δ 155.03 (ddd, J = 248, 13, 4 Hz), 149.0 (dt, J = 248, 17 Hz), 141.4 (ddd, J = 255, 27, 7 Hz), 125.2 (ddd, J = 19, 11, 3 Hz), 110.9 (ddd, J = 41, 7, 3 Hz) ppm. C_5HBrF_3N (211.97): calcd C 28.33, H 0.48; found C 28.63, H 0.52.

2,3,6-Trifluoropyridine (27). 2,3,6-Trifluoro-4-hydrazinopyridine (**25**; 8.2 g, 50 mmol) and copper(II) sulfate pentahydrate (25 g, 0.10 mol) were heated in water (0.10 L) under reflux for 45 min. After steam distillation, a colorless liquid was collected upon another distillation at atmospheric pressure, bp 115−117 °C (lit.[25] 115−116 °C), yield 4.86 g (73%). ^{1}H NMR: δ 7.71 (tdd, J = 9.0, 8.0, 6.1 Hz, 1 H), 6.84 (ddd, J = 8.6, 3.2, 2.2 Hz, 1 H) ppm.

2,3,4,6-Tetrafluoro-5-(trimethylsilyl)pyridine (28a). Diisopropylamine (28 mL, 20 g, 0.20 mol), 2,3,4,6-tetrafluoropyridine (30 g, 0.20 mol) and chlorotrimethylsilane (25 mL, 22 g, 0.20 mol) were added consecutively to a solution of butyllithium (0.20 mol) in tetrahydrofuran (0.25 L) and hexanes (0.13 L), cooled in a methanol/dry ice bath. After 45 min at −75 °C, the mixture was treated with water (0.10 L). The organic phase was dried and distilled; colorless liquid, bp 67−69 °C/20 Torr (lit.[26] 71−73 °C/20 Torr), yield 40.6 g (91%). ^{1}H NMR: δ 0.41 (s, 9 H) ppm.

2,3,4,6-Tetrafluoro-5-(triethylsilyl)pyridine (28b). Prepared analogously as described in the preceding paragraph but working on a 50 mmol scale and using chlorotriethylsilane (8.4 mL, 7.5 g, 50 mmol) as the reagent; colorless liquid, bp 99−101 °C/7 mmHg, n^{20}_D = 1.4555, yield 10.9 g (82%). ^{1}H NMR: δ 0.9 (m, 15 H) ppm. ^{13}C NMR: δ 164.2 (dddd, J = 259, 17, 9, 5 Hz), 158.4 (dddd, J = 240, 21, 15, 5 Hz), 151.0 (dddd, J = 244, 20,13, 7 Hz), 132.8 (dddd, J = 259, 27, 19, 9 Hz), 104.7 (dddd, J = 52, 32, 7, 4 Hz), 7.0 (3 C), 3.5 (t, J = 2 Hz, 3 C) ppm. $C_{11}H_{15}F_4NSi$ (265.32): calcd C 49.80, H 5.70; found C 50.13, H 5.95.

2-Bromo-3,4,6-trifluoro-5-(triethylsilyl)pyridine (30b). A solution of 2,3,4,6-tetrafluoro-5-(triethylsilyl)pyridine (**28b**; 6.6 g, 25 mmol) and hydrazine (50 mmol) in tetrahydrofuran (50 mL) was kept for 2 h at 25 °C. The precipitate formed was removed by filtration and the solvent evaporated. Bromine (8.0 g, 2.6 mL, 50 mmol) in chloroform (25 mL) was added and the

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mixture heated under reflux for 6 h before being washed with a saturated aqueous solution (25 mL) of sodium sulfite. The product was isolated by distillation under reduced pressure as a colorless liquid, bp 105−107 °C/3 mmHg, n^{20}_D = 1.5008, yield 4.49 g (55%). ^{1}H NMR: δ 0.9 (m, 15 H) ppm. ^{13}C NMR: δ 162.4 (ddd, J = 262, 16, 12 Hz), 160.4 (ddd, J = 239, 19, 4 Hz), 144.3 (ddd, J = 257, 16, 7 Hz), 127.5 (ddd, J = 23, 20, 3 Hz), 107.6 (ddd, J = 53, 31, 3 Hz), 7.0 (s, 3 C), 3.4 (t, J = 2 Hz, 3 C) ppm. $C_{11}H_{15}BrF_3NSi$ (326.23): calcd C 40.50, H 4.63; found C 40.75, H 4.34.

2,4,5-Trifluoropyridine (31). A solution of 2,3,4,6-tetrafluoro-5-(trimethylsilyl)pyridine (**28a**; 22 g, 0.10 mol) and hydrazine (0.20 mol) in tetrahydrofuran (0.20 L) was kept at 0 °C for 2 h. After the precipitate formed had been removed by filtration, tetrabutylammonium fluoride trihydrate (32 g, 0.10 mol) was added. After 2 h at 25 °C, the solvent was evaporated and the residue triturated with water (0.10 L), before being heated in the presence of copper(II) sulfate pentahydrate (50 g, 0.20 mol) and water (0.20 L) under reflux for 45 min. Steam distillation followed by distillation under atmospheric pressure afforded a colorless liquid, bp 99−101 °C, n^{20}_D = 1.4201, yield 8.65 g (65%). ^{1}H NMR: δ 8.15 (dt, J = 9.6, 1.3 Hz, 1 H), 6.83 (ddd, J = 8.0, 4.8, 2.9 Hz, 1 H) ppm. ^{13}C NMR: δ 159.2 (ddd, J = 237, 11, 2 Hz), 158.2 (dt, J = 267, 13 Hz), 146.7 (ddd, J = 254, 11, 6 Hz), 135.9 (ddd, J = 21, 19, 2 Hz), 99.3 (dd, J = 46, 19 Hz) ppm. $C_5H_2F_3N$ (133.07): calcd C 45.13, H 1.51; found C 45.27, H 1.61.

5. 2,4-Dichloropyridine Series. 2-Chloro-4-(dimethylamino)pyridine (32). 2,4-Dichloropyridine (7.4 g, 50 mmol) and a 40% aqueous solution (50 mL) of dimethylamine were heated at 50 °C for 20 h. The product was extracted with diethyl ether (3 × 50 mL) and crystallized from chloroform; colorless needles, mp 68−70 °C (lit.[27] 80−82 °C), yield 6.92 g (88%). ^{1}H NMR: δ 7.97 (d, J = 6.1 Hz, 1 H), 6.47 (d, J = 2.2 Hz, 1 H), 6.41 (dd, J = 6.1, 2.2 Hz, 1 H), 3.00 (s, 6 H) ppm. ^{13}C NMR: δ 155.8, 151.9, 148.7, 105.6, 105.1, 39.0 (2 C) ppm.

2,4-Dichloro-5-bromopyridine[28] (33). At −100 °C, diisopropylamine (14 mL, 10 g, 0.10 mol) and 5-bromo-2-chloropyridine (19 g, 0.10 mol) were added consecutively to a solution of butyllithium (0.10 mol) in tetrahydrofuran (0.23 L) and hexanes (60 mL). After 45 min at −100 °C, the mixture was treated with 1,1,2-trichloro-1,2,2-trifluoroethane (12 mL, 19 g, 0.10 mol) and, after 45 min at −75 °C, with water (50 mL). Upon distillation, the product was collected as a colorless liquid, bp 60−62 °C/0.9 mmHg, yield 18.7 g (83%). ^{1}H NMR: δ 8.53 (s, 1 H), 7.47 (s, 1 H) ppm.

2,4-Dichloro-5-(triethylsilyl)pyridine (34). At −75 °C, 2,4-dichloro-5-bromopyridine (**33**; 23 g, 0.10 mol) was added to butyllithium (0.10 mol) in diethyl ether (0.20 L) and hexanes (60 mL). After 45 min at −75 °C, the mixture was treated with chlorotriethylsilane (17 mL, 15 g, 0.10 mol) and distilled; colorless liquid, bp 98−100 °C/2 mmHg, n^{20}_D = 1.5345, yield 23.3 g (89%). ^{1}H NMR: δ 8.30 (s, 1 H), 7.35 (s, 1 H), 0.9 (m, 15 H) ppm. ^{13}C NMR: δ 155.8, 152.9, 152.2, 129.9, 124.4, 7.1 (3 C), 2.9 (3 C) ppm. $C_{11}H_{17}Cl_2NSi$ (262.25): calcd C 50.38, H 6.53; found C 50.68, H 6.37.

4-Chloro-2-(dimethylamino)-5-(triethylsilyl)pyridine (35). 2,4-Dichloro-5-(triethylsilyl)pyridine (**34**; 13 g, 50 mmol) and a 40% aqueous solution (50 mL) of dimethylamine were heated at 50 °C for 60 h. The reaction mixture was extracted with diethyl ether (3 × 50 mL). According to gas chromatography (30 m DB-1, 150 °C; 30 m DB-WAX, 150 °C; internal standard: tridecane), it contained 4-chloro-2-(dimethylamino)-5-(triethylsilyl)pyridine (**35**) and 2,4-dichloro-5-(triethylsilyl)-pyridine (**34**) in a 5:1 ratio. The organic phase was evaporated and distilled to give a yellowish oil which was used for the next step without further purification, bp 111−113 °C/2.2 mmHg, n^{20}_D = 1.5420, yield 10.7 g (79%). ^{1}H NMR: δ 8.08 (s, 1 H), 6.51 (s, 1 H), 3.08 (s, 6 H), 0.9 (m, 15 H) ppm. ^{13}C NMR: δ 160.2, 155.0, 151.3, 115.0, 105.8, 37.5 (2 C), 7.3 (3 C), 3.4 (3 C) ppm.

4-Chloro-2-(dimethylamino)pyridine (36). 4-Chloro-2-(dimethylamino)-5-(triethylsilyl)pyridine (**35**; 6.8 g, 25 mmol) and tetrabutylammonium fluoride trihydrate (7.9 g, 25 mmol) were dissolved in tetrahydrofuran (25 mL). After 2 h at 25 °C, the solvent was stripped off before adding water (15 mL) and diethyl ether (30 mL). The organic phase was evaporated and the residue was treated with 2.0 M ethereal hydrogen chloride (75 mmol) and water (75 mL). The aqueous phase was separated and basified with a 2.0 M aqueous solution of sodium hydroxide. After extraction with diethyl ether (3 × 25 mL), the organic phase was dried and evaporated. Crystallization from hexanes afforded 3.37 g (86%) of colorless needles, mp 32−34 °C. ^{1}H NMR: δ 8.04 (d, J = 5.1 Hz, 1 H), 6.53 (dd, J = 5.1, 1.3 Hz, 1 H), 6.48 (d, J = 1.3 Hz, 1 H), 3.08 (s, 6 H) ppm. ^{13}C NMR: δ 160.0, 148.7, 144.4, 111.7, 105.3, 37.9 (2 C) ppm. $C_7H_9ClN_2$ (156.61): calcd C 53.68, H 5.79; found C 53.74, H 5.68.

4-Chloro-3-(triethylsilyl)pyridine (38). A solution of 2,4-dichloro-5-(triethylsilyl)pyridine (**34**; 6.6 g, 25 mmol) and hydrazine (0.10 mol) in tetrahydrofuran (0.10 mL) was heated for 5 days (120 h) under reflux before the solvent was evaporated. After addition of copper(II) sulfate pentahydrate (12.5 g, 50 mmol) and water (50 mL), the mixture was heated for 45 min under reflux. A steam distillation followed by a distillation under reduced pressure afforded a colorless liquid, bp 60−62 °C/0.5 mmHg, n^{20}_D = 1.5197, yield 3.68 g (64%). ^{1}H NMR: δ 8.53 (s, 1 H), 8.47 (d, J = 5.1 Hz, 1 H), 7.28 (d, J = 5.1 Hz, 1 H) ppm. ^{13}C NMR: δ 156.3, 150.9 (2 C), 131.1, 124.4, 7.1 (3 C), 3.0 (3 C). ppm. $C_{11}H_{18}ClNSi$ (227.81): calcd C 58.00, H 7.96; found C 58.04, H 7.99.

6. 2,4,6-Trichloropyridine Series. 2,6-Dichloro-4-iodopyridine. 2,6-Dichloropyridine (44 g, 0.30 mol) was added to a solution of butyllithium in tetrahydrofuran (0.50 L) and hexanes (0.20 L) cooled in a dry ice/methanol bath. After 45 min at −75 °C, the mixture was treated with iodine (76 g, 0.30 mol) in tetrahydrofuran (0.20 L) and, 15 min later, with a 10% aqueous solution (0.25 L) of sodium sulfite. According to gas chromatography (30 m DB-1, 150 °C; 30 m DB−WAX, 150 °C), the crude product contained 2,6-dichloro-4-iodopyridine and 2,6-dichloro-3-iodopyridine in a 5:2 ratio. Evaporation and crystallization from ethyl acetate afforded colorless platelets, mp 162−164 °C (lit.[29] 160 °C), yield 52.6 g (64%). ^{1}H NMR: δ 7.66 (s, 2 H) ppm.

2,4,6-Trichloropyridine. 2,6-Dichloro-4-iodopyridine (13.7 g, 50 mmol) was added to an ice-cold solution of isobutylmagnesium chloride (50 mmol) in tetrahydrofuran (75 mL). After 45 min at 0 °C, the mixture was treated with *N*-chlorosuccinimide (6.7 g, 50 mmol) and, 45 min later, with a saturated aqueous solution (50 mL) of ammonium chloride. The organic phase was decanted, dried and distilled; colorless liquid, bp 88−90 °C/10 mmHg (lit.[30] 217.5−218.5 °C/760 mmHg), yield 8.57 g (94%). ^{1}H NMR: δ 7.31 (s, 2 H) ppm.

2,6-Dichloro-4-(dimethylamino)pyridine (39). 2,4,6-Dichloropyridine (9.2 g, 50 mmol) and a 40% aqueous solution (50 mL) of dimethylamine were stirred at 25 °C for 6 h. The reaction mixture was extracted with diethyl ether (3 × 50 mL). According to gas chromatography (30 m DB-1, 150 °C; 30 m DB-WAX, 150 °C), it contained 2,6-dichloro-4-(dimethylamino)-pyridine (**39**) and 2,4-dichloro-6-(dimethylamino)pyridine in a 3:1 ratio. Evaporation and crystallization from chloroform afforded colorless needles, mp 136−138 °C, yield 6.3 g (66%). ^{1}H NMR: δ 6.41 (s, 2 H), 3.01 (s, 6 H) ppm. ^{13}C NMR: δ 156.9, 150.1 (2 C), 104.3 (2 C), 39.2 (2 C) ppm. $C_7H_8Cl_2N_2$ (191.06): calcd C 44.01, H 4.22; found C 44.12, H 4.21.

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2,4,6-Trichloro-3-(trimethylsilyl)pyridine (40a). 2,4,6-Trichloropyridine (9.2 g, 50 mmol) in tetrahydrofuran (0.10 L) was added to a solution of butyllithium (50 mmol) in hexanes (32 mL) cooled in a dry/ice methanol bath. After 45 min at −75 °C, the mixture was treated with chlorotrimethylsilane (6.3 mL, 5.4 g, 50 mmol). Distillation afforded a colorless liquid, mp 26−28 °C, bp 90−92 °C/2.5 mmHg, yield 11.7 g (92%). ^{1}H NMR: δ 7.27 (s, 1 H), 0.52 (s, 9 H) ppm. ^{13}C NMR: δ 156.4, 153.6, 150.7, 131.8, 123.9, 2.0 (3 C) ppm. $C_8H_{10}Cl_3NSi$ (254.62): calcd C 37.74, H 3.96; found C 37.78, H 4.06.

2,4,6-Trichloro-3-(triethylsilyl)pyridine (40b). Prepared analogously as described in the preceding paragraph but working on a 0.16 mol scale and using chlorotriethylsilane (27 mL, 24 g, 0.16 mol) as the reagent; colorless liquid, bp 128−130 °C/3 mmHg, $n^{20}_D = 1.5525$, yield 38.5 g (81%). ^{1}H NMR: δ 7.28 (s, 1 H), 1.0 (m, 15 H) ppm. ^{13}C NMR: δ 157.1, 154.3, 150.7, 130.2, 123.9, 7.5 (3 C), 5.3 (3 C) ppm. $C_{11}H_{16}Cl_3NSi$ (296.70): calcd C 44.53, H 5.44; found C 44.53, H 5.47.

2,4-Dichloro-6-(dimethylamino)pyridine (42). 2,4,6-Trichloro-3-(triethylsilyl)pyridine (**40b**; 15 g, 50 mmol) and a 40% aqueous solution (50 mL) of dimethylamine was stirred for 20 h at 50 °C. The reaction mixture was extracted with diethyl ether (3 × 50 mL) and the solvent evaporated. The residue and tetrabutylammonium fluoride trihydrate (16 g, 50 mmol) were dissolved in tetrahydrofuran (50 mL). After 2 h at 25 °C, the solvent was evaporated before adding water (25 mL) and diethyl ether (50 mL). The organic phase was dried, evaporated and the product was crystallized from hexanes; colorless platelets, mp 45−46 °C, yield 7.93 g (83%). ^{1}H NMR: δ 6.54 (d, J = 1.3 Hz, 1 H), 6.33 (d, J = 1.3 Hz, 1 H), 3.06 (s, 6 H) ppm. ^{13}C NMR: δ 159.0, 149.8, 145.5, 110.3, 103.2, 37.8 (2 C) ppm. $C_7H_8Cl_2N_2$ (191.06): calcd C 44.01, H 4.22; found C 43.88, H 4.09.

2,4-Dichloro-6-hydrazinopyridine (44). At 25 °C, 2,4,6-trichloro-3-(trimethylsilyl)pyridine (**40a**; 13 g, 50 mmol) was added to a solution of hydrazine (0.10 mol) in tetrahydrofuran (0.10 L). After 20 h and at 50 °C, tetrabutylammonium fluoride trihydrate (16 g, 50 mmol) was added. After 2 h at 25 °C, the solvent was evaporated. The residue was triturated with water (50 mL) and crystallized from ethyl acetate; colorless needles, mp 170−172 °C, yield 6.41 g (72%). ^{1}H NMR*: δ 8.9 (s, broad, 1 H), 7.08 (d, J = 1.6 Hz, 1 H), 6.77 (d, J = 1.6 Hz, 1 H), 3.0 (s, broad, 2 H) ppm. ^{13}C NMR*: δ 160.2 (s), 151.2 (s), 147.6 (s), 114.6 (s), 106.1 (s) ppm. $C_5H_5Cl_2N_3$ (178.02): calcd C 33.73, H 2.83; found C 33.77, H 2.94.

2,4-Dichloropyridine (45). 2,4-Dichloro-6-hydrazinopyridine (**44**; 4.5 g, 25 mmol) and copper (II) sulfate pentahydrate (13 g, 50 mmol) were heated in water (50 mL) for 45 min under reflux. A steam distillation followed by a distillation under reduced pressure afforded a colorless liquid, bp 67−69 °C/15 Torr (lit.[31] 73−75 °C/15 mmHg), yield 2.47 g (67%). ^{1}H NMR: δ 8.31 (d, J = 5.4 Hz, 1 H), 7.37 (d, J = 1.9 Hz, 1 H), 7.25 (dd, J = 5.4, 1.9 Hz, 1 H) ppm.

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