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A General Approach to (Trifluoromethoxy)pyridines: First X-ray Structure Determinations and Quantum Chemistry Studies

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The previously unknown 2-, 3-, and 4-(trifluoromethoxy)pyridines have now become readily accessible by means of an efficient and straightforward large-scale synthesis. Their regioselective functionalization by organometallic methods has been studied and has afforded new and highly important building blocks for life-sciences-oriented research. In addition, the first X-ray crystallographic structure determinations of (trifluoromethoxy)pyridines have been performed. Lowest-energy conformations of (trifluoromethoxy)pyridines and (trifluoromethoxy)pyridinium cations were determined by in silico studies.

Introduction

Fluorine today plays an increasing role in life-sciences-oriented research[1] because it can confer metabolic stability, lipophilicity, and bioavailability to potential drug candidates and crop protection agents.[2] Of the currently employed fluorinated moieties, the trifluoromethoxy group (OCF_3) is becoming more and more important.[2f–2h,3] At present the trifluoromethoxy-substituted compounds that can be found in the literature are essentially aromatic ones.[3e] The trifluoromethoxy group cannot be formed analogously to the methoxy group, by simple treatment of trifluorohalomethanes with alkoxides, so it has to be introduced or constructed by one of five approaches recently reviewed by us.[2f,2h] In contrast, trifluoromethoxy-substituted heterocycles are rare in the literature.[4]

Because of the importance of heterocyclic structures in pharmaceutical and agrochemical research and the use of fluorine atoms and fluorinated groups in general, there is currently a real need for preparative methods for OCF_3-substituted heterocyclic building blocks with potential for further functionalization.

Here we report on the first general and efficient synthetic approach to OCF_3-pyridines.[5] We describe how simple precursors were functionalized regioselectively at any vacant position of the aromatic ring to provide a library of (trifluoromethoxy)pyridine building blocks.

Results and Discussion

Synthesis

In the course of our studies, we investigated without success the introduction of trifluoromethoxy substituents on various heterocycles by classical approaches. Hiyama's oxidative desulfurization/fluorination,[6] developed in the aromatic and aliphatic series, for example, already required careful optimization of the reaction conditions in the synthesis of the required xanthogenates, due to the low nucleophilicity of the hydroxy group. The dithiocarbamates **1a**–**c** (Scheme 1) were finally obtained, but their conversion into the corresponding (trifluoromethoxy)pyridines failed. After several fruitless attempts we observed a need for chlorine atoms on the pyridine ring if the desired outcome of the oxidative desulfurization/fluorination was to be achieved. Unlike the dithiocarbamates **1a**–**c**, 2-chloro-5-(*S*-methyl)dithiocarbamate pyridine (**2**, Scheme 1), prepared from 2-chloro-5-hydroxypyridine, sodium methanethiolate, and thiophosgene,[7] reacted with excess (80 equiv.) HF/pyridine and 1,3-dibromo-5,5-dimethylhydantoine (DBH, 4.5 equiv.) to afford the desired 2-chloro-5-(trifluoromethoxy)pyridine (**3**) in 56% yield.

Although we had been able to show that the oxidative desulfurization/fluorination of a pyridine xanthogenate was only possible in the presence of ring chlorine atoms, this

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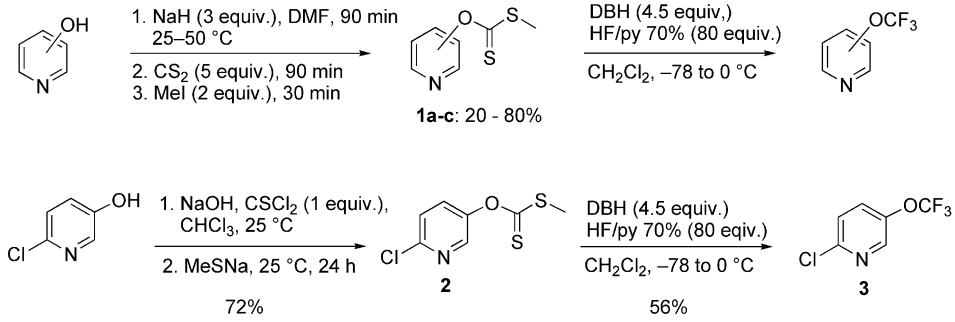


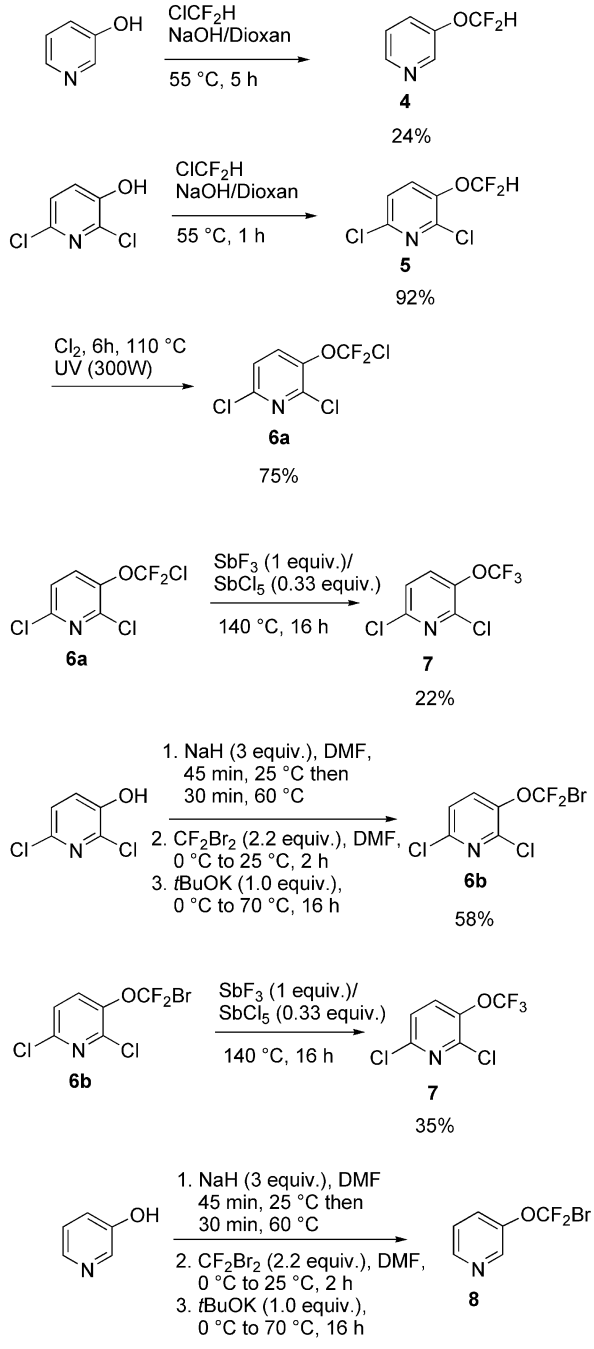
Scheme 1. Preparation of the pyridine xanthogenates **1a**–**c** and route to the 3-(trifluoromethoxy)pyridine **3**.

method was not convenient because it involves large quantities of toxic and corrosive HF/pyridine, which considerably limits scale-up. Another standard route to aromatic trifluoromethyl ethers is based on treatment of phenolates with chlorodifluoromethane (CHF_2Cl)[4b,4i,8] or dibromodifluoromethane (CF_2Br_2)[4i,9] in the presence of a base, with subsequent introduction of the third fluorine atom. We therefore studied this approach for the synthesis of pyridine trifluoromethyl ethers.

In a competition experiment we were once again able to underline the importance of chlorine substituents for the reactivities of hydroxypyridines. When 3-hydroxypyridine and 2,6-dichloro-3-hydroxypyridine were treated with chlorodifluoromethane in a biphasic mixture of aqueous sodium hydroxide and dioxane, the difluoromethoxypyridines **4** and **5** were obtained in 24% and 92% yields (Scheme 2). The photochlorination of **5** gave 2,6-dichloro-3-(chlorodifluoromethoxy)pyridine (**6a**) but required a large amount of elemental chlorine and worked only on small scale. In an analogous manner, treatment of 2,6-dichloro-3-hydroxypyridine with CF_2Br_2 afforded a 58% yield of 2,6-dichloro-3-(bromodifluoromethoxy)pyridine (**6b**). Both 2,6-dichloro-3-(halodifluoromethoxy)pyridines **6** were subjected to fluorination with antimony trifluoride (SbF_3, Swart's reagent) in the presence of catalytic amounts of antimony pentachloride ($SbCl_5$), which afforded 2,6-dichloro-3-(trifluoromethoxy)pyridine (**7**) in 22% and 35% yields, respectively (Scheme 2). In contrast, 3-hydroxypyridine afforded only a 7% yield of 3-(bromodifluoromethoxy)pyridine (**8**).

Although we had shown that OCF_3-substituted pyridines are accessible through the alkylation of hydroxypyridines with CF_2Br_2 and subsequent nucleophilic substitution with antimony trifluoride, two main drawbacks still remained: a) the optimized overall yields of these two-step syntheses were low (about 15%), and b) the alkylating reagents (CF_2Br_2 or CF_2BrCl) are no longer commercially available because they are now classified as ozone-depleting substances (ODSs).

In 1957, Iarovenko and Vasil′eva discovered that the phenyl ester of chlorothiocarbonic acid adds chlorine with formation of phenoxydichloromethylenesulfenyl chloride.[10] Upon further chlorination, the sulfur is completely eliminated as sulfur chloride with the formation of trichloromethyl phenyl ether. However, this approach was not further exploited. We therefore decided to study it in more



Scheme 2. (Trifluoromethoxy)pyridine synthesis through alkylation of hydroxypyridines with difluorocarbene.

detail. The chlorothionoformiates were obtained by treatment of the hydroxypyridines with thiophosgene in aqueous sodium hydroxide at 0 °C and directly subjected to chlorination without isolation. The crude Cl_3CO-pyridines were then used for the fluorination step without further purification (Table 1). The advantage of this approach is that no large amounts of chlorine gas are required, as is often the case for radical chlorination of methoxy groups. We were successfully able to convert the (trichloromethoxy)pyridines into (trifluoromethoxy)pyridines with antimony trifluoride (SbF_3) and catalytic antimony pentachloride ($SbCl_5$). This reaction had not been demonstrated on pyridines previously (Table 1). The chlorine/fluorine exchange proceeds rapidly to the OCF_2Cl intermediate.[11] However, the final Cl/F exchange is the rate-determining step, as had also previously been observed in the aromatic series for the conversion of $-CCl_3$ into $-CF_3$. Under optimized reaction conditions, $SbCl_5$ (0.15 equiv.) and SbF_3 (2 equiv.) for 6 h at 150 °C were required for complete conversion. The (trifluoromethoxy)pyridine **7** was then obtained in 64% yield without any traces of the OCF_2Cl derivative. Similarly, the syntheses of compounds **3** and **14**–**16** were efficiently performed. All OCF_3-pyridines were readily isolated as colorless liquids after distillation under reduced pressure.

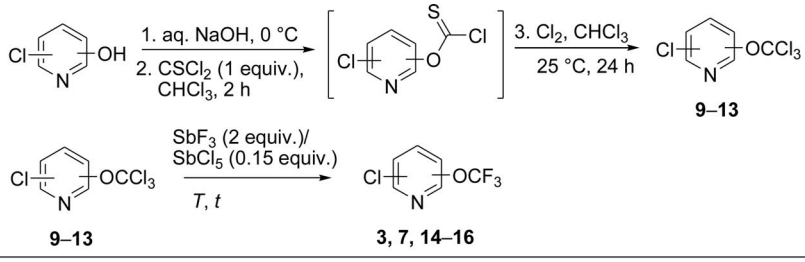
Once again, this reaction proved to be highly sensitive to the presence of chlorine atoms on the pyridine ring and failed when starting from unsubstituted hydroxypyridines. In a comparative study on the natures of the halogen atoms and their relative positions on the pyridine ring (Scheme 3) we observed: 1) no great difference between F-, Cl-, and Br-substituted derivatives in influencing the outcome of the chlorination reaction towards (trichloromethoxy)pyridines, but 2) that the fluorination step proved to be sensitive to the natures of the halogen atoms.

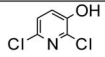
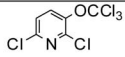
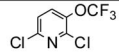
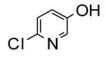
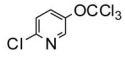
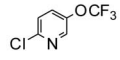
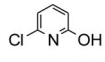
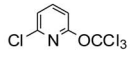
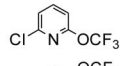
2-Bromo-3-(trichloromethoxy)pyridine (**17**) was converted into a 1:1 mixture of $-OCF_2Cl$ and $-OCF_3$ products after 10 h at 150 °C. Complete conversion into 2-bromo-3-(trifluoromethoxy)pyridine (**19**) was achieved after 3 more days of heating. 2-Fluoro-3-(trichloromethoxy)pyridine (**18**), after heating at 150 °C for 11 h, afforded a mixture containing mainly 2-chloro-3-(trifluoromethoxy)pyridine (**15**). In addition, a nucleophilic F/Cl exchange occurred on the pyridine ring. Heating of this mixture for 6 h more at 180 °C afforded a 55% yield of a mixture of compound **15** and 2-fluoro-3-chlorodifluoromethoxypyridine in an 85:15 ratio.

To investigate the influence of the relative chlorine ring position on the synthesis of (trifluoromethoxy)pyridines, we studied 3-hydroxypyridines bearing Cl atoms at the 2-, 5-, and 6-positions (Scheme 4). 1) No specific influence on the chlorodesulfurization and fluorination step was observed when the Cl atom was present at the 2- and/or 6-positions. 2) However, the chlorodesulfurization of 3-chloro-5-hydroxypyridine, with the Cl atom not at the position α to the pyridine ring nitrogen, occurred only in 55% yield together with a 10% yield of the dimerization byproduct. The fluorination with SbF_3 failed completely and no trace of the OCF_3-product was obtained.

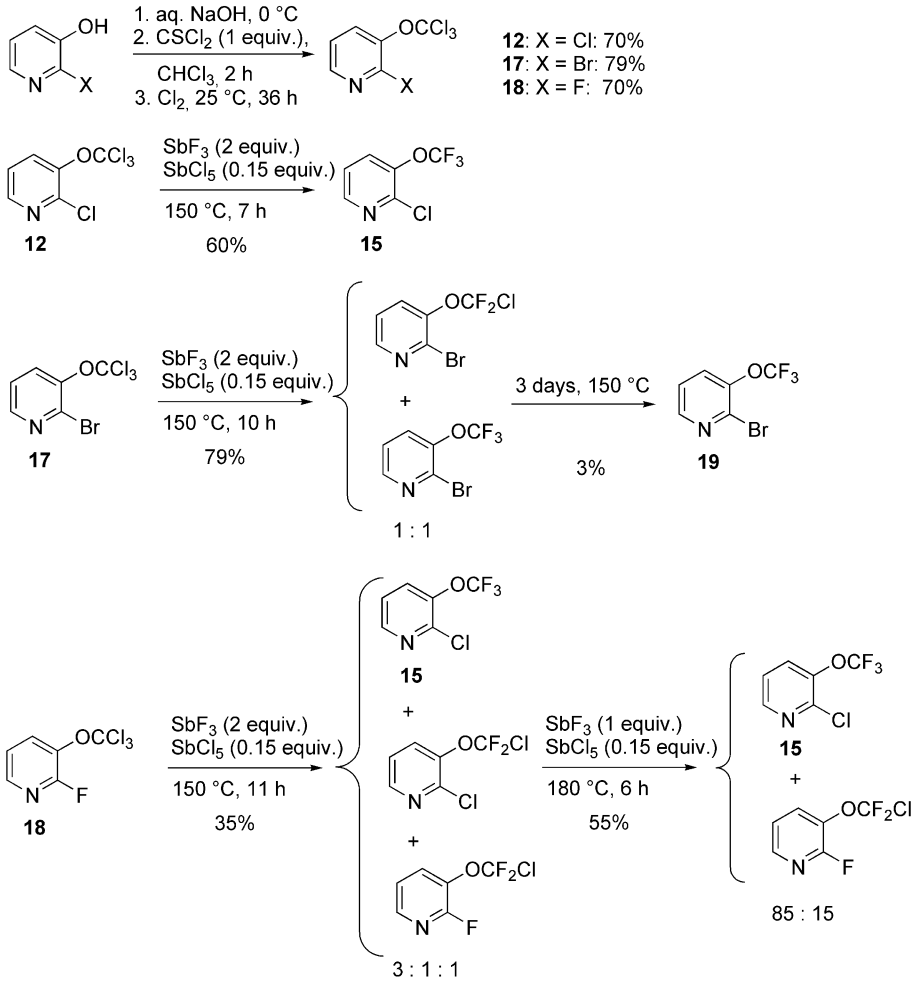
We have thus shown that at least one Cl atom at the position α to the ring nitrogen is essential for success in the synthesis of 3-(trifluoromethoxy)pyridines, as well as for the

Table 1. Synthesis of (trifluoromethoxy)pyridines.

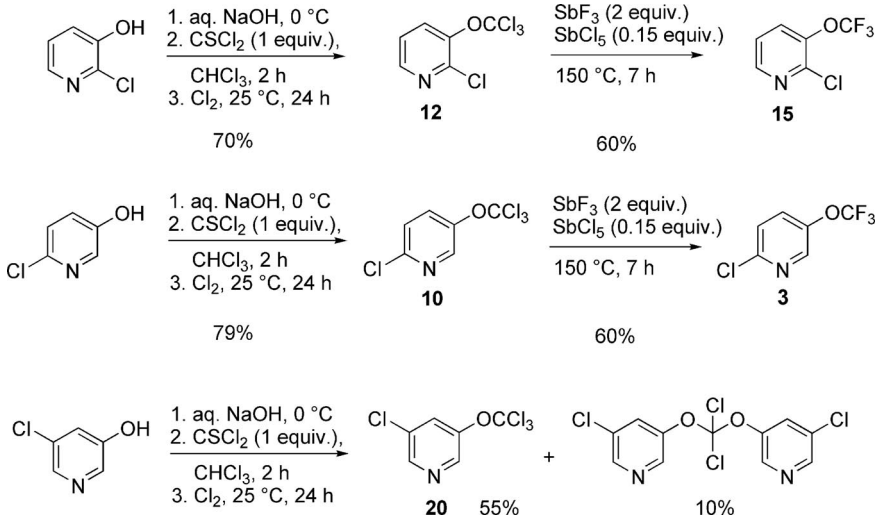


Entry	Substrate	t/h[a]		Product	% Yield[b]	T/°C	t/h		Product	% Yield[c]
1		36	**9**		70	150	6	**7**		64
2		24	**10**		79	150	3	**3**		60
3		24	**11**		60	140	3	**14**		53
4		36	**12**		70	150	7	**15**		60
5		24	**13**[d]		50	140	7	**16**[d]		50

[a] Reaction times with chlorine-saturated solution at 25 °C. [b] Overall yields of isolated compounds. [c] Isolated yields after distillation. [d] 2,4-Dichloropyridine isolated as byproduct.



Scheme 3. Influence of the natures of the halogen atoms on the outcome of the chlorination/fluorination sequence.



Scheme 4. Influence of the relative ring position of the Cl atom on the outcome of the chlorination/fluorination sequence.

synthesis of 2- and 4-OCF_3-pyridines. This fact might explain the absence of efficient preparative methods for OCF_3-pyridines in the literature.

Next, with an efficient route to (trifluoromethoxy)-pyridine precursors to hand, we started to look into methods for accessing libraries of 2-, 3-, and 4-(trifluoro-

methoxy)pyridines functionalized at the vacant positions. As representative but non-exhaustive examples, we chose the preparation of carboxylic acids, amines, and halides.

2-(Trifluoromethoxy)pyridines

Access to 6-functionalized 2-(trifluoromethoxy)pyridines was based on a chlorine/bromine exchange on 2-chloro-6-(trifluoromethoxy)pyridine (**14**, Scheme 5) with hydrobromic acid in acetic acid, affording 2-bromo-6-(trifluoromethoxy)pyridine (**21**) in 48% yield. 6-(Trifluoromethoxy)-picolinic acid (**22a**) was obtained after bromine/lithium exchange with butyllithium and subsequent carboxylation. The palladium-catalyzed amination of 2-bromo-6-(trifluoromethoxy)pyridine afforded 2-amino-6-(trifluoromethoxy)pyridine (**22b**) in 40% yield (Scheme 5).[12] 6-Chloro-2-(trifluoromethoxy)nicotinic acid (**23a**, 63%), 5-amino-2-chloro-6-(trifluoromethoxy)pyridine (**23b**, 71%), and 2-chloro-5-iodo-6-(trifluoromethoxy)pyridine (**23c**, 78%) were prepared by *ortho*-lithiation with LDA followed by trapping with dry ice, benzenesulfonyl azide,[13] and iodine, respectively. After palladium-catalyzed reductive dechlorination of **23a**, 2-(trifluoromethoxy)nicotinic acid (**24a**) was obtained in a yield of 82%. The analogous reaction with the amine **23b** gave 3-amino-2-(trifluoromethoxy)pyridine (**24b**, 80%). Deprotonation with LDA at –78 °C occurred exclusively at the position *ortho* to the OCF_3 group (Scheme 5). In contrast, Schlosser observed concomitant deprotonation at the 3- and 4-positions in 2-chloro-6-trifluoromethyl pyridine.[14]

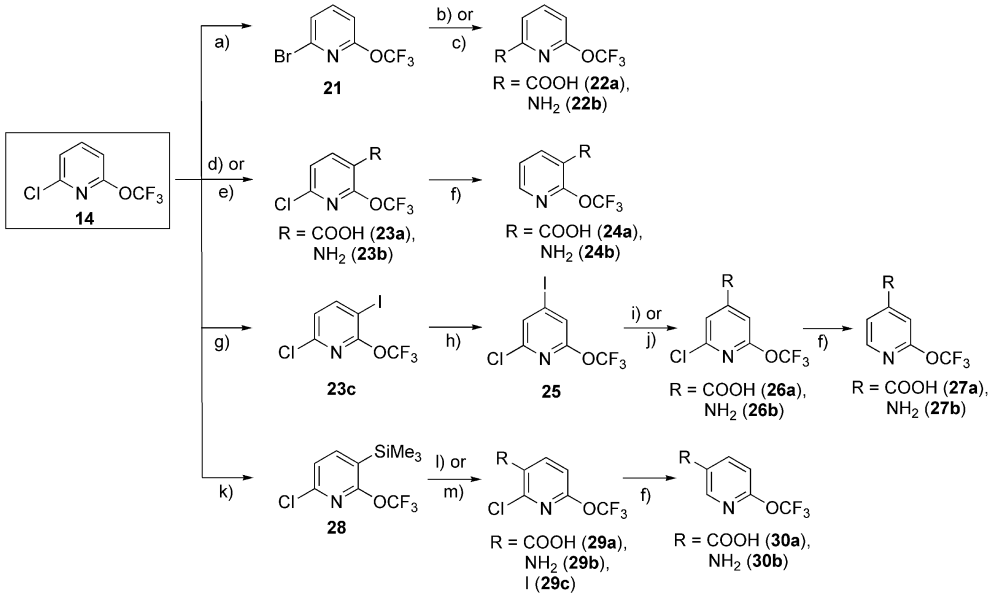
The 4-position in 2-(trifluoromethoxy)pyridine was made accessible through a base-mediated iodine migration in 2-chloro-5-iodo-6-(trifluoromethoxy)pyridine (**23c**). It was cleanly converted into its 4-iodo isomer **25** in 80% yield (Scheme 5). Subsequent iodine/lithium exchange with butyllithium followed by carboxylation provided 2-chloro-6-(trifluoromethoxy)isonicotinic acid (**26a**), which allowed the preparation of 2-(trifluoromethoxy)isonicotinic acid (**27a**) after dechlorination. Similarly, 4-amino-2-chloro-6-(trifluoromethoxy)pyridine (**26b**) was obtained by trapping with benzenesulfonyl azide in 46% yield. Finally, subsequent catalytic hydrogenation afforded the amine **27b** in 79% yield (Scheme 5).

In order to metalate 2-chloro-6-(trifluoromethoxy)-pyridine **14** exclusively at the 5-position, the 3-position had to be protected with a sterically demanding trimethylsilyl group. When 2-chloro-6-(trifluoromethoxy)pyrid-5-yllithium was trapped with chlorotrimethylsilane, 2-chloro-6-(trifluoromethoxy)-5-(trimethylsilyl)pyridine (**28**, Scheme 5) was isolated in 68% yield. Its consecutive treatment with LTMP, carbon dioxide, and tetrabutylammonium fluoride (TBAF) gave 2-chloro-6-(trifluoromethoxy)nicotinic acid (**29a**, 70%). Finally, the Cl atom was removed through catalytic hydrogenation to afford 6-(trifluoromethoxy)nicotinic acid (**30a**) in 81% yield.

Similarly, trapping with benzenesulfonyl azide and iodine instead of dry ice afforded the 5-amino- and 5-iodo-2-(trifluoromethoxy)pyridines (**29b**, 64%) and (**29c**, 65%), respectively, upon reduction of the azide unit. The aminopyridine **29b** was then dechlorinated to afford compound **30b**.

3-(Trifluoromethoxy)pyridines

The series of 3-trifluoromethoxy-substituted pyridines were accessed from 2-chloro-3-(trifluoromethoxy)pyridine



Scheme 5. Functionalization of 2-(trifluoromethoxy)pyridines. *Reagents and conditions*: a) HBr, AcOH, 100 °C, 3 d. b) BuLi, toluene, –78 °C, 2 h; CO_2; neutralization. c) Ph_2CNH, Pd_2dba_3, DPEPhos, NaO*t*Bu, toluene, 80 °C; citric acid aq., 16 h; aq. NaOH. d) LDA, THF, –78 °C, 2 h; CO_2; neutralization. e) LDA, THF, –78 °C, 2 h; $PhSO_2N_3$; $LiAlH_4$, Et_2O, reflux. f) Pd/C (10%), $HCOONH_4$, MeOH, 16 h, 55 °C. g) LDA, THF, –78 °C, 2 h; I_2/THF. h) LDA, THF, –78 °C, 1 h; aq. HCl. i) BuLi, THF, –78 °C, 5 min; CO_2; neutralization. j) BuLi, THF, –78 °C, 5 min; $PhSO_2N_3$; $LiAlH_4$, Et_2O, reflux. k) LDA, THF, –78 °C, 2 h; TMSCl. l) LTMP, THF, –78 °C, 2 h; CO_2; neutralization; TBAF, THF, 25 °C. m) LTMP, THF, –78 °C, 2 h; $PhSO_2N_3$; $LiAlH_4$, Et_2O, reflux; TBAF, THF, 25 °C.

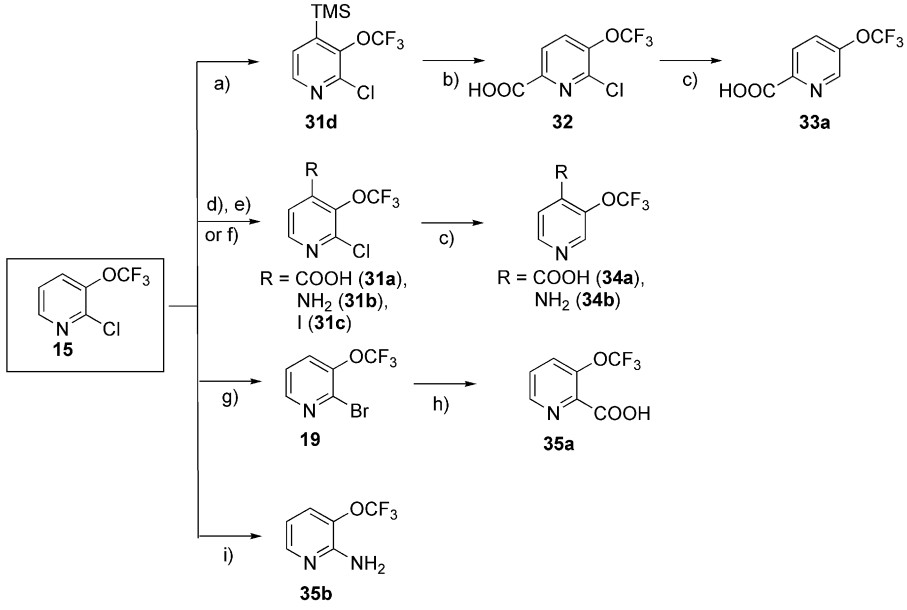
(**15**, Scheme 6) and 6-chloro-3-(trifluoromethoxy)pyridine (**3**, Scheme 7, below). Deprotonation of **15** with LDA at the most acidic 4-position, followed by trapping with chlorotrimethylsilane, afforded 2-chloro-3-(trifluoromethoxy)-4-(trimethylsilyl)pyridine (**31d**, 69%). A second deprotonation, with LTMP, occurred exclusively at the 6-position. Trapping with dry ice, followed by treatment with tetrabutylammonium fluoride (TBAF), afforded 6-chloro-5-(trifluoromethoxy)picolinic acid (**32**, 67%), which readily underwent a palladium-catalyzed reductive dechlorination to provide 5-(trifluoromethoxy)picolinic acid (**33a**).

The 4-position was functionalized by trapping of 2-chloro-3-(trifluoromethoxy)pyrid-4-yllithium with carbon dioxide, instead of TMSCl, which gave 2-chloro-3-(trifluoromethoxy)isonicotinic acid (**31a**) in 70% yield. Similarly, 4-amino-2-chloro-3-(trifluoromethoxy)pyridine (**31b**) and 2-chloro-4-iodo-3-(trifluoromethoxy)pyridine (**31c**) were obtained either after trapping with benzenesulfonyl azide followed by reduction or through trapping with iodine, in 75% and 78% yields, respectively. The palladium-catalyzed reductive dechlorination of the acid **31a** and the amine **31b** afforded 3-(trifluoromethoxy)isonicotinic acid (**34a**) and the aminopyridine **34b** in excellent yields (Scheme 6).

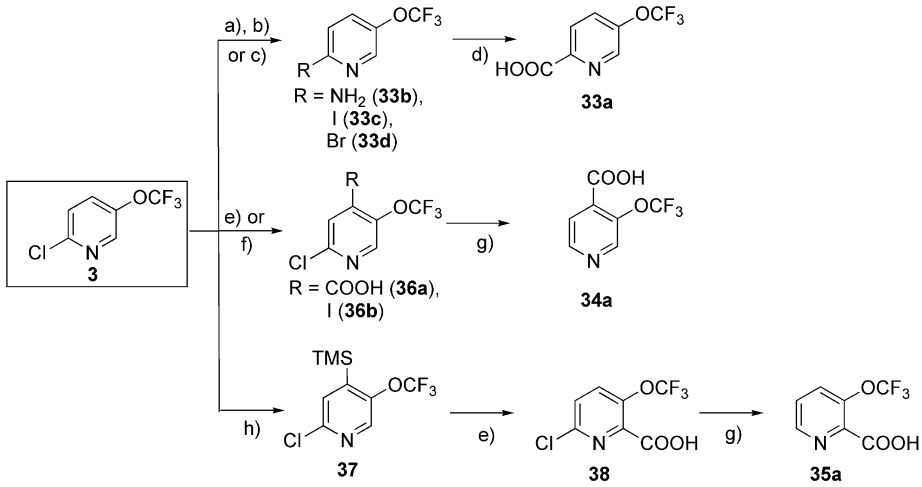
The fact that the 2-position of (trifluoromethoxy)-pyridine **15** was already "functionalized" by a Cl atom allowed us to access the corresponding bromopyridine by a silane-mediated chlorine/bromine exchange.[14–15] 2-Bromo-3-(trifluoromethoxy)pyridine (**19**, 80%) was obtained by heating 2-chloro-3-(trifluoromethoxy)pyridine (**15**) and bromotrimethylsilane at reflux in propionitrile. Consecutive bromine/lithium exchange with butyllithium in toluene at –78 °C and carboxylation provided 3-(trifluoromethoxy)-picolinic acid (**35a**) in 64% yield. When benzenesulfonyl azide was used as the trapping reagent after a bromine/lithium exchange of **19** and reduction of the azide, 2-amino-3-(trifluoromethoxy)pyridine (**35b**) was obtained only in trace amounts. A better way to obtain the desired aminopyridine **35b**, in 44% yield, consisted of a palladium-catalyzed coupling reaction of the starting reagent **15** with benzophenone imine, followed by hydrolysis of the intermediate imino adduct (Scheme 6).

5-(Trifluoromethoxy)picolinic acid (**33a**) could also be prepared from 2-chloro-5-(trifluoromethoxy)pyridine (**3**, Scheme 7). A silane-mediated chlorine/bromine exchange with bromotrimethylsilane allowed the preparation of 2-bromo-5-(trifluoromethoxy)pyridine (**33d**) in an excellent 81% yield. A bromine/lithium exchange followed by carboxylation gave the 3-(trifluoromethoxy)picolinic acid (**33a**) in 60% yield. When the trapping was performed with benzenesulfonyl azide followed by reduction with lithium aluminum hydride, only traces of the expected 2-aminopyridine **33b** were isolated. The palladium-catalyzed coupling reaction with benzophenone imine was therefore applied, which allowed the preparation of 2-amino-5-(trifluoromethoxy)-pyridine (**33b**) in 40% yield. From the starting pyridine **3**, a silane-mediated chlorine/iodine exchange with sodium iodide and TMSCl under reflux in propionitrile[16] gave 2-iodo-5-(trifluoromethoxy)pyridine (**33c**) in 49% yield (Scheme 7).

2-Chloro-5-(trifluoromethoxy)isonicotinic acid (**36a**, 75%, Scheme 7) was prepared from 2-chloro-5-(trifluoromethoxy)pyridine (**3**) by deprotonation with LDA followed by carboxylation. Subsequent reductive removal of the ring



Scheme 6. Functionalization of 3-(trifluoromethoxy)pyridines starting from 2-chloro-3-(trifluoromethoxy)pyridine (**15**). Reagents and conditions: a) LDA, THF, –78 °C, 2 h; TMSCl. b) LTMP, THF, –78 °C, 2 h; CO_2; neutralization; TBAF, THF, 25 °C. c) Pd/C (10%), $HCOONH_4$, MeOH, 16 h, 55 °C. d) LDA, THF, –78 °C, 2 h; CO_2; neutralization. e) LDA, THF, –78 °C, 2 h; $PhSO_2N_3$; $LiALH_4$, Et_2O, reflux. f) LDA, THF, –78 °C, 2 h; I_2/THF. g) TMSBr, propionitrile, 2 d, 100 °C. h) BuLi, toluene, –78 °C, 2 h; CO_2; neutralization. i) Ph_2CNH, Pd_2dba_3, DPEPhos, NaO*t*Bu, toluene, 80 °C; citric acid aq., 16 h; aq. NaOH.



Scheme 7. Functionalization of 3-(trifluoromethoxy)pyridines starting from 2-chloro-5-(trifluoromethoxy)pyridine (**3**). Reagents and conditions: a) Ph_2CNH, Pd_2dba_3, DPEPhos, NaO*t*Bu, toluene, 80 °C; citric acid aq., 16 h; aq. NaOH. b) TMSCl, NaI, propionitrile, 1 d, 100 °C. c) TMSBr, propionitrile, 3 d, 100 °C. d) BuLi, toluene, –78 °C, 2 h; CO_2; neutralization. e) LDA, THF, –78 °C, 2 h; CO_2; neutralization. f) LDA, THF, –78 °C, 2 h; I_2/THF. g) Pd/C (10%), $HCOONH_4$, MeOH, 16 h, 55 °C. h) LDA, THF, –78 °C, 2 h; TMSCl.

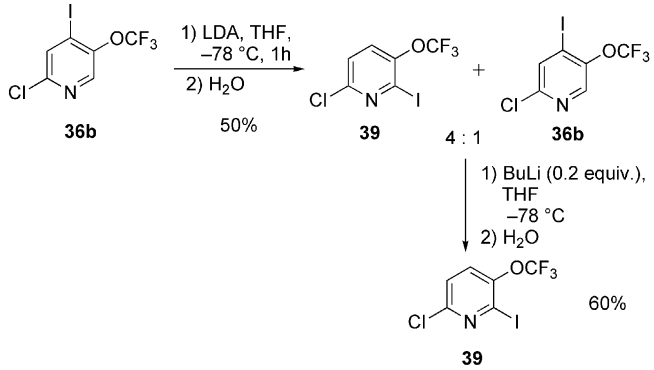
Cl atom with palladium on charcoal and ammonium formate in methanol afforded 3-(trifluoromethoxy)isonicotinic acid (**34a**) in 81% yield. The same acid had previously been obtained from 2-chloro-3-(trifluoromethoxy)pyridine (**15**, Scheme 5). Trapping with iodine led to 2-chloro-4-iodo-5-(trifluoromethoxy)pyridine (**36b**, Scheme 7) in 89% yield.

3-(Trifluoromethoxy)picolinic acid (**35a**, Scheme 7) could also be prepared from 2-chloro-5-(trifluoromethoxy)pyridine (**3**). Metalation at the 4-position and protection as a silane gave compound **37** in 92% yield. Subsequent metalation at the 2-position and carboxylation afforded 6-chloro-3-(trifluoromethoxy)picolinic acid (**38**) in 61% yield, and this was then dechlorinated to provide 3-(trifluoromethoxy)picolinic acid (**35a**) in 80% yield (Scheme 7).

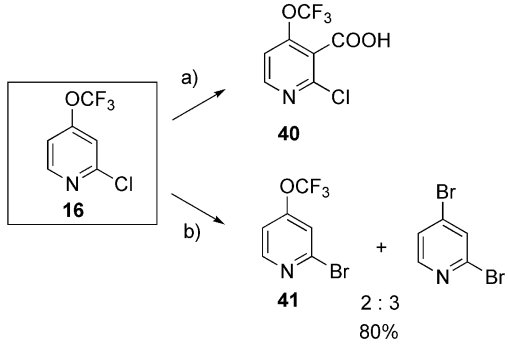
Interestingly, the 5-position appeared to be the most difficult to functionalize. Unlike in the case of the 3-trifluoromethylpyridines described by Schlosser,[14] pure 2-chloro-3-iodo-5-(trifluoromethoxy)pyridine could not be obtained from 2-chloro-4-iodo-5-(trifluoromethoxy)pyridine (**36b**) by base-induced iodine migration. Piperidyllithium, successfully applied previously in the trifluoromethyl derivative, did not afford any migration product. When LDA was used (Scheme 8), migration to the 6-position rather than the desired 3-position yielded an inseparable 4:1 mixture of 2-chloro-6-iodo-5-(trifluoromethoxy)pyridine (**39**) and starting material **36b**. It was found that the remaining starting material could be destroyed by addition of a stoichiometric quantity of butyllithium. By this method, pure 2-chloro-6-iodo-5-(trifluoromethoxy)pyridine (**39**) was obtained through "kinetic cleanup".[17]

4-(Trifluoromethoxy)pyridines

The route to 4-(trifluoromethoxy)-substituted pyridines was based on 2-chloro-4-(trifluoromethoxy)pyridine (**16**, Scheme 9). 4-(Trifluoromethoxy)nicotinic acid (**40**) was prepared in 80% yield by metalation with LDA and subsequent carboxylation. A silane-promoted chlorine/bromine exchange afforded an inseparable mixture of the desired 2-bromo-4-(trifluoromethoxy)pyridine (**41**) and 2,4-dibromopyridine. After quaternization of the pyridine nitrogen by the trimethylsilyl group, the OCF_3 unit is displaced by a bromine atom by a S_NAr mechanism.



Scheme 8. Base-induced iodine migration in 2-chloro-4-iodo-5-(trifluoromethoxy)pyridine (**36b**), followed by "kinetic cleanup".



Scheme 9. Functionalization of 4-(trifluoromethoxy)pyridines. Reagents and conditions: a) LDA, THF, –78 °C, 2 h; CO_2; neutralization. b) TMSBr, propionitrile, 2 d, 100 °C.

X-ray Structure Determinations

We were able to perform the first X-ray structure determinations of trifluoromethoxy-substituted heterocycles, which now allows comparison with aromatic analogues. Unlike in methoxybenzenes without *ortho* substituents, for example, in which planar conformations are favored, trifluoromethoxybenzenes showed a C–C–O–C dihedral angle of approximately 90°.[2b,18] Study of the conformational preferences and the variations on the bond lengths of these new trifluoromethoxy-substituted pyridines was therefore highly intriguing. The X-ray structure obtained for **23a** (Figure 1) is consistent with that of 2-(trifluoromethoxy)-nicotinic acid. The OCF_3 group is in plane with the heteroaromatic ring, showing a C(COOH)-C-O-CF_3 dihedral angle of 175°.

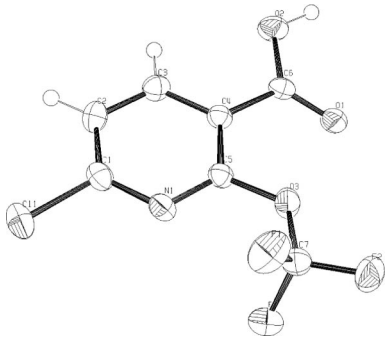


Figure 1. ORTEP plot of the molecular structure of **23a**.

Interestingly, the hydrogen of the COOH group could be observed and was not calculated and reveals an O–H distance of 0.97(10) Å. Moreover, the solid-state structure revealed intermolecular COOH···O=C(OH) hydrogen bonding with an O···H length of 1.664 Å (O···O distance = 2.631 Å) leading to a dimer in which the eight atoms of the two carboxylic groups share the same plane (see the Supporting Information).

The X-ray structure of **29a** (Figure 2) showed a C–C–O–CF_3 dihedral angle of 158°. This is the first example in which the 2-OCF_3 group has no *ortho* substituents. OCF_3 groups in the 2-positions of pyridines avoid unfavorable electronic interactions with the neighboring ring hydrogen atoms by an in-plane orientation towards the nitrogen atom. The OCF_3 group benefits at the same time from a better overlap between the pyridine ring π-system and the lone-pair orbital at oxygen, the latter involving the σ*-C–F orbital.

The solid-state structure of 2-chloro-6-(trifluoromethoxy)nicotinic acid (**29a**) shows intermolecular COOH···O=C(OH) hydrogen bonding (1.961 Å, O···O distance 2.663 Å). All atoms (except the CF_3 groups) are in almost the same plane, which indicates that the chlorine atoms do not disturb the dimeric association (see the Supporting Information).

The same tendency was observed in the solid-state structure of 6-(trifluoromethoxy)picolinic acid (**22a**, Figure 3).

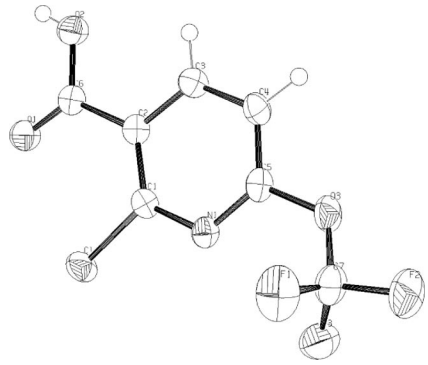


Figure 2. ORTEP plot of the molecular structure of **29a**.

The C–C–O–CF_3 dihedral angle is 170°, which once again revealed an in-plane conformation for the 2-OCF_3-pyridine moiety.

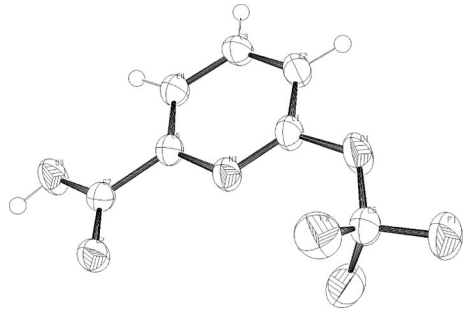


Figure 3. ORTEP plot of the molecular structure of **22a**.

An intermolecular COOH···O=C(OH) hydrogen bond length of 1.789 Å (O···O distance 2.614 Å) can be observed. If one compares the bond length of a 2-OCH_3-substituted pyridine with that of the corresponding trifluoromethoxy-substituted derivative, a shortening of the anomerically active O–CF_3 bond by about 0.1 Å is observed, which reveals the shortening of the donor bond (O–CH_3: 1.438 Å[19] vs. O–CF_3: 1.337 Å). The C(pyridine)–O bond is elongated by almost 0.03 Å when the methoxy group [C(pyridine)–OCH_3: 1.364 Å][19] is replaced by a trifluoromethoxy substituent [C(pyridine)–OCF_3: 1.397 Å]. This underlines the fact that the lone-pair electrons of a methoxy group are preferentially delocalized into the π-system of the electron-deficient heterocycle, whereas in the case of the trifluoromethoxy group these lone-pair electrons are no longer accessible, due to the interaction with the σ*-C–F orbital resulting in a lengthening of the C(pyridine)–O bond and a shortening of the O–CF_3 bond. Such an interaction has been deduced in the aromatic series by UV spectroscopy,[20] molecular photoelectron spectroscopy,[21] and dipole moment studies.[22] These values are comparable to those reported in the Cambridge Crystallographic Database. In tris-(dimethylamino)sulfonium (TAS) trifluoromethoxide, for example, the C–O bond is contracted by 0.09 Å relative to trifluoromethanol[23] and by 0.21 Å relative to methanol.[24]

We have also performed single-crystal X-ray analyses for 3-trifluoromethoxy-substituted pyridines. 2-Chloro-3-(trifluoromethoxy)isonicotinic acid (**31a**, Figure 4) showed a

solid-state structure in which the molecules are connected in a chain manner through OH···N hydrogen bonds (N···H: 1.795 Å, N···O: 2.699 Å). Once again it can be seen in the crystal that the OCF_3 does not interact through hydrogen bonding with the carboxylic group. A C(COOH)–C–O–CF_3 dihedral angle of 87° was observed, revealing that the OCF_3 group, unlike in 2-OCF_3-substituted pyridines, adopted a perpendicular orientation with respect to the pyridine ring plane (see the Supporting Information).

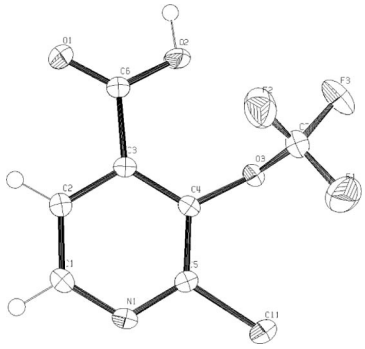


Figure 4. ORTEP plot of the molecular structure of **31a**.

The solid-state structure of 6-chloro-3-(trifluoromethoxy)picolinic acid (**38**, Figure 5) shows a C(COOH)–C–O–CF_3 dihedral angle of 98°. In this structure, a H-bonding system with an H···N length of 1.981 Å and an H···O length of 2.395 Å was observed.

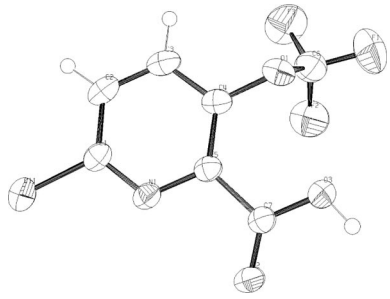


Figure 5. ORTEP plot of the molecular structure of **38**.

The five crystallographic studies[25] revealed various kinds of molecular interactions (for details see the Supporting Information). Dimeric associations in which carboxylic groups are linked to one another through hydrogen bonding interactions were found in compounds **23a**, **29a**, and **22a**. The through-space distances between the H atom of one molecule and the O atom of another molecule are 1.800 Å (**23a**), 1.961 Å (**29a**), and 1.789 Å (**22a**). No such association was found with compounds **31a** and **38**, in which the acidic hydrogen of the carboxylic group is in each case oriented towards the pyridine nitrogen atom of another molecule. Distances of 1.795 Å for **31a** and 1.981 Å for **38** were found. The aromatic rings were often seen to associate in parallel planes, including all atoms except those of the CF_3 group. No hydrogen-bond interaction involving the OCF_3 group was observed.

Quantum Chemical Calculations

Quantum chemistry calculations[26] were performed on trifluoromethoxy heterocycles to compare the rotational barriers of OCF_3 groups in 2- and 3-OCF_3-pyridines relative to those in trifluoromethoxy benzene. Molecular modeling studies dealing with the conformations of aryl trifluoromethyl ethers had been performed previously, but only at the CNDO/2 level, by McBee in the early 1970s.[22a] We performed gas-phase quantum chemistry calculations using the Møller–Plesset MP2 technique (TZVPP basis set),[27] in order to determine the lowest-energy conformations.

2-Trifluoromethoxy compounds showed much lower overall rotational barriers than 2-methoxy compounds, both for the pyridine and for the pyridinium series (Figure 6). The *anti* conformer (with respect to the relative orientations of the hetero ring and O–R in-plane lone pairs) was found to be more stable than the *syn* conformer in each case. The same preferences were observed for 2-methoxypyridine, but with a higher barrier to rotation. It was reported recently that the orientations of the methoxy groups in 2-methoxyheteroarenes could be explained by the electron-pair repulsion of oxygen and nitrogen atoms. By DFT calculations, barriers of rotation of about 8 kcal mol^{-1} for 2-methoxypyridine and of about 3 kcal mol^{-1} for 3-methoxypyridine were calculated, which are in excellent agreement with our MP2 calculations.[28] After protonation of the ring nitrogen atom, the *syn* conformer becomes more stable.

3-(Trifluoromethoxy)pyridine and 3-(trifluoromethoxy)-pyridinium each showed a flatter energy profile than their 3-methoxy counterparts (Figure 7). In contrast to the methoxy group in 3-methoxypyridine, the trifluoromethoxy group is tilted out of the plane by ca. 90°. The interconversion barrier is, however, much lower for the trifluoromethoxy derivative than for the methoxy compound.

Table 2 summarizes the carbon–oxygen and oxygen–CF_3 bond lengths as obtained from X-ray structure determination. For comparison, bond lengths taken from the optimized geometries based on ab initio calculations (MP2/TZVPP gas phase) are depicted in Table 3.[27] In all trifluoromethoxy derivatives the bond linking the oxygen atom to the aromatic carbon is always greater in length than the bond linking the oxygen to the –CF_3 carbon. Differences range from 0.02 to 0.04 Å (Table 2). This is the converse in the methoxy series (Table 3). These observations underline the anomeric effect between the oxygen lone-pair orbitals and the C–F σ* orbital described previously. As a result of this interaction the lone-pair electrons are involved in O–CF_3 bonding and do not interact with the heteroaromatic π-system, as in the methoxy case.

We performed a search in the Cambridge Structure Database for X-ray crystal data for 2-methoxypyridine derivatives. The preferred orientation of the methoxy group, in which the direction of the methyl group is parallel to that of the nitrogen lone pair, is found in the crystal structures of substituted 2-methoxypyridines. An example is given by

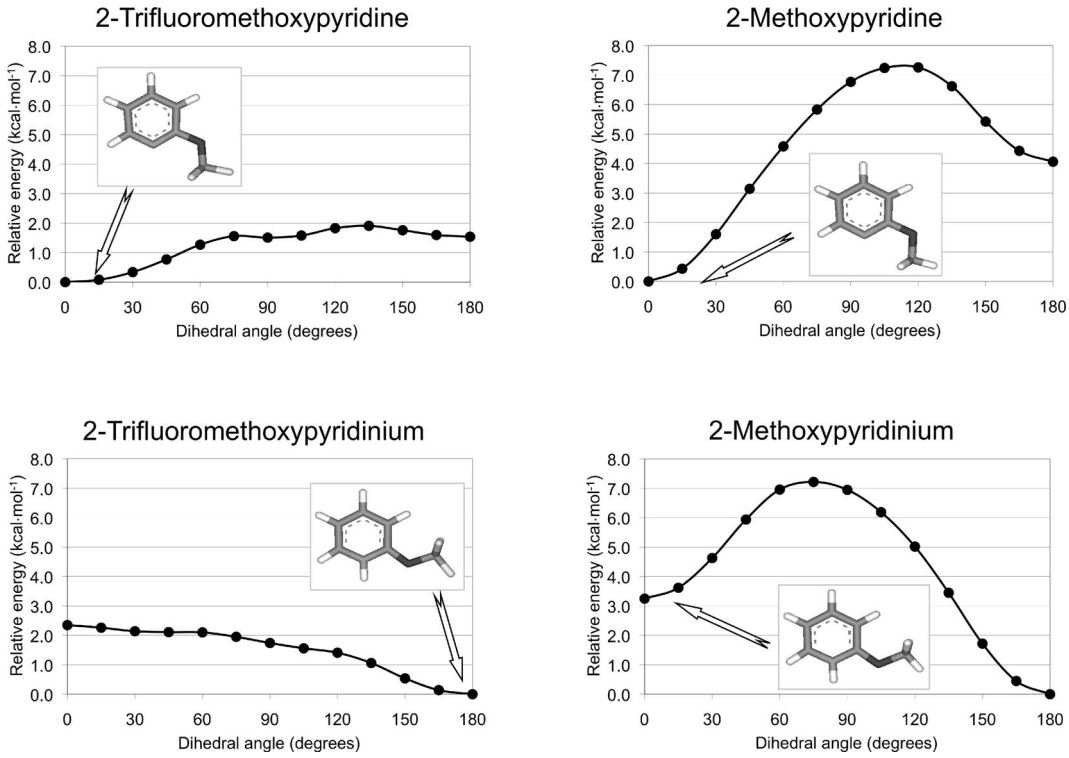


Figure 6. Calculated energy profiles for the rotation of the trifluoromethoxy or methoxy groups in 2-substituted pyridines and pyridinium cations. Energy scales are directly comparable [kcal mol^{-1}] and are offset by the energy value of the global minimum.

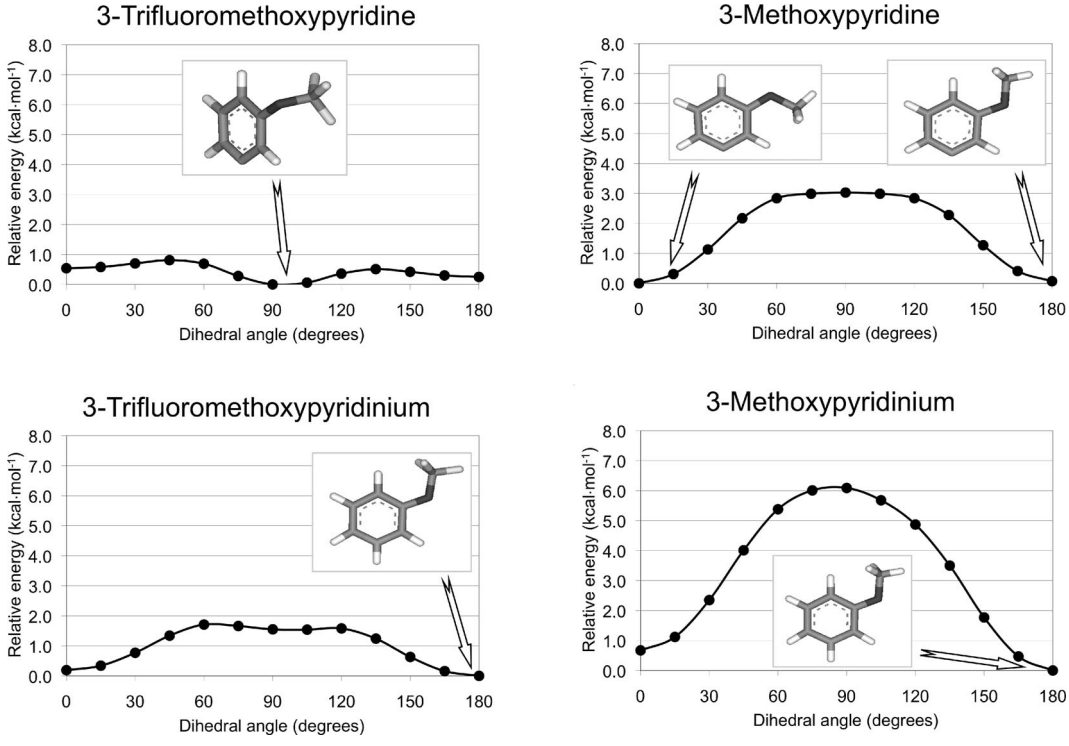


Figure 7. Calculated energy profiles for the rotation of the trifluoromethoxy or methoxy groups in 3-substituted pyridines and pyridinium cations. Energy scales are directly comparable [kcal mol^{-1}] and are offset by the energy value of the global minimum.

2-methoxy-4-methyl-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]-pyridine.[29] In 2-methoxypyridinium, the preferred orientation of the methoxy group is tilted by 180° in relation to that in non-protonated species. This behavior is also found experimentally; a crystal structure of a closely related analogue has been published.[30]

Table 2. Selected bond lengths of (trifluoromethoxy)pyridines.

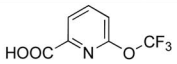
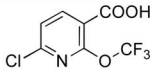
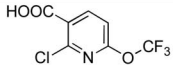
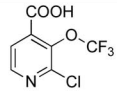
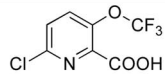
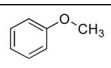
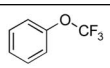
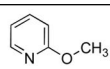
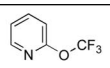
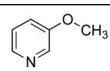
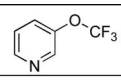
Bond length					
	22a	**23a**	**29a**	**31a**	**38**
C–O	1.397 Å	1.370 Å	1.390 Å	1.385 Å	1.393 Å
O–CF_3	1.337 Å	1.350 Å	1.351 Å	1.362 Å	1.349 Å
Δ	0.06 Å	0.02 Å	0.039 Å	0.023 Å	0.044 Å

Table 3. Bond length from ab initio calculations (MP2/TZVPP gas phase).

Bond length										
Torsion angle / deg	0	0	0	0	0	180	90	0	180	90
C–O / Å	1.363	1.402	1.351	1.383	1.357	1.356	1.372	1.386	1.386	1.395
O–CF_3 / Å	1.417	1.351	1.428	1.364	1.421	1.419	1.427	1.354	1.352	1.356
Δ / Å	–0.054	0.051	–0.077	0.019	–0.064	–0.063	–0.055	0.032	0.034	0.039

These results comfort the energy profile results obtained from the quantum chemistry calculations, both for the free base and for the protonated forms.

Conclusions

Over the past twenty years, the trifluoromethoxy substituent has become increasingly interesting for pharmaceutical, agrochemical, and academic research. Although efficient methods for its introduction into aliphatic and aromatic scaffolds have been developed, the synthesis of heteroaromatic trifluoromethyl ethers has remained elusive. In this paper we have presented an efficient and straightforward large-scale synthesis of previously unknown 2-, 3-, and 4-(trifluoromethoxy)pyridines. The crucial role of chlorine atoms α to the ring nitrogen has been described. In this manner simple OCF_3-pyridine precursors have been prepared and functionalized at all vacant positions of the ring by means of a subtle interplay of organometallic methods. New and highly interesting building blocks have thus been prepared, not only for pharmaceutical and agrochemical research, but also for materials sciences.

The first X-ray crystallographic structure determinations have been performed, revealing an in-plane conformation of the OCF_3 group when at the 2-position of the pyridine ring. At the 3-position the perpendicular conformation was observed. For the first time, conformations of (trifluoromethoxy)pyridines and of pyridinium cations have been calculated. The O–CF_3 group has the ability to rotate much more easily than the methoxy group. 2-(Trifluoromethoxy)pyridine preferably adopts an in-plane conformation in which the OCF_3 group is oriented towards the pyridine nitrogen (*anti* conformer). In contrast, 3-(trifluoromethoxy)pyridine preferably adopts a conformation in which the O–CF_3 bond is orthogonal to the plane of the ring, analogously to trifluoromethoxy benzene. This results in a minimization of electronic repulsions between neighboring hydrogen atoms. In the case of 2-(trifluoromethoxy)pyridinium, the calculated conformation analysis shows that the 2-trifluoromethoxy group is rotated by 180° relative to the free base (*syn* conformer). This was also observed for the 2-methoxy derivatives, although the overall energy barrier of rotation was shown to be markedly decreased in relation to the latter case. Similarly, 3-(trifluoromethoxy)pyridine and 3-(trifluoromethoxy)pyridinium cations showed flatter energy profiles than their 3-methoxy counterparts.

Experimental Section

General Remarks: Starting materials, if commercially available, were purchased and used as such, provided that adequate checks (melting ranges, refractive indices, and gas chromatography) had confirmed the claimed purities. When known compounds had to be prepared by literature procedures, pertinent references are given. Air- and moisture-sensitive materials were stored in Schlenk tubes. They were protected by and handled under argon in appropriate glassware. Diethyl ether and tetrahydrofuran were dried by distillation from sodium after the characteristic blue color of sodium diphenyl ketyl (benzophenone-sodium "radical-anion") had been observed to persist. Ethereal or other organic extracts were dried by washing with brine and then by storage over sodium sulfate. If no reduced pressure is specified, boiling ranges (b.p.s) refer to ordinary atmosphere conditions (725 ± 25 Torr). Melting ranges (m.p.s) given were found to be reproducible after recrystallization, unless stated otherwise ("decomp."), and are uncorrected. Thin-layer chromatography (TLC) were carried out on silica gel (Merck, 0.25 mm, 60-F254). Column chromatography was carried out on columns packed with silica gel (60N spherical neutral size 63–210 μm). ^1H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded at 300 and 75 MHz, respectively. ^{19}F NMR was recorded at 282 MHz. Chemical shifts are reported in δ units, parts per million (ppm), and were measured relative to the signals for residual deuterated solvents. Coupling constants (J) are given in Hz. Coupling patterns are abbreviated as, for example, s (singlet), d (doublet), t (triplet), q (quartet), td (triplet of doublets), m (multiplet), and br s (broad singlet). Gas chromatography monitoring was performed with HP 6890 Series apparatus, capillary column

HP-5 (5% phenylmethylsiloxane), FID detector (250 °C), with the following program: 60 °C for 3 min, 30 °C min^{-1} until 300 °C, 30 °C for 45 min, injector (230 °C). Butyllithium and *tert*-butyllithium were used as solutions in hexanes or pentane and their concentrations were determined by the Wittig–Harborth double titration method [(total base) – (residual base after treatment with 1,2-dibromoethane)]. Organometallic reagents were usually checked by Gilman tests 1 (all organolithiums) and 2 (only for alkyllithiums).

***S*-Methyl Pyridine-3-dithiocarbamate (1a):** 3-Hydroxypyridine (980 mg, 10.0 mmol, 1 equiv.) in *N*,*N*-dimethylacetamide (10 mL) was added at 0 °C to a suspension of sodium hydride (60%, 1.20 g, 30.0 mmol, 3 equiv.) in *N*,*N*-dimethylacetamide (10 mL). The reaction mixture was then vigorously stirred for 1 h at 25 °C and for 30 min at 50 °C. Carbon disulfide (3.8 g, 3.0 mL, 50 mmol, 5 equiv.) was added dropwise at 0 °C, and the reaction mixture was allowed to reach 25 °C for 90 min. Iodomethane (3.0 g, 1.3 mL, 20 mmol, 2 equiv.) was then added dropwise at 0 °C and the reaction mixture was allowed to reach 25 °C for 30 min. The reaction mixture was filtered through a pad of silica gel with dichloromethane and the filtrate was concentrated. The crude product was purified by chromatography on silica gel with ethyl acetate/cyclohexane (1:4) as eluent, which afforded pure **1a** (1.35 g, 7.30 mmol, 73%) as a red oil. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 8.44 (dd, J = 4.7, 1.4 Hz, 1 H, 6-H), 8.33 (d, J = 2.6 Hz, 1 H, 2-H), 7.37 (ddd, J = 8.3, 1.4, 2.6 Hz, 1 H, 4-H), 7.27 (dd, J = 8.3, 4.7 Hz, 1 H, 5-H), 2.59 (s, 3 H, SCH_3) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 215.4 (=CS), 151.2 (C), 147.6 (CH), 144.0 (CH), 130.0 (CH), 123.9 (CH), 20.1 (CH_3) ppm. HRMS for $C_7H_8NOS_2$: calcd. 186.0042 [M + H]; found 186.0035.

***S*-Methyl Pyridine-2-dithiocarbamate (1b):** 2-Hydroxypyridine (4.80 g, 50.0 mmol, 1 equiv.) in *N*,*N*-dimethylformamide (40 mL) was added at 0 °C to a suspension of sodium hydride (60%, 8.0 g, 150 mmol, 3 equiv.) in *N*,*N*-dimethylformamide (40 mL). The reaction mixture was then stirred vigorously for 1 h at 25 °C and for 30 min at 50 °C. Carbon disulfide (18.9 g, 15.0 mL, 250 mmol, 5 equiv.) was added dropwise at 0 °C, and the reaction mixture was allowed to reach 25 °C for 16 h. Iodomethane (13.7 g, 6.0 mL, 100 mmol, 2 equiv.) was then added dropwise at 0 °C, and the reaction mixture was allowed to reach 25 °C for 60 min. After addition of water (100 mL) the organic phase was separated and the aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were dried with sodium sulfate before concentration. The crude product was purified by chromatography on silica gel with ethyl acetate/cyclohexane (1:4) as eluent, which afforded pure **1b** (1.85 g, 10.0 mmol, 20%) as a yellow powder; m.p. 54–56 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 8.08 (ddd, J = 7.3, 1.9, 0.6 Hz, 1 H, 6-H), 7.25 (ddd, J = 9.3, 6.5, 1.9 Hz, 1 H, 4-H), 6.51 (ddd, J = 9.3, 1.0, 0.6 Hz, 1 H, 3-H), 6.16 (ddd, J = 7.3, 6.5, 1.0 Hz, 1 H, 5-H), 2.67 (s, 3 H, SCH_3) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 209.1 (=CS), 161.0 (C), 140.0 (CH), 134.9 (CH), 122.7 (CH), 106.6 (CH), 23.3 (CH_3) ppm. $C_7H_7NOS_2$ (185.27): calcd. C 45.33, H 3.78, N 7.55; found C 45.36, H 3.99, N 7.47.

***S*-Methyl Pyridine-4-dithiocarbamate (1c):** 4-Hydroxypyridine (4.80 g, 50.0 mmol, 1 equiv.) in *N*,*N*-dimethylformamide (40 mL) was added at 0 °C to a suspension of sodium hydride (60%, 8.0 g, 0.15 mol, 3 equiv.) in *N*,*N*-dimethylformamide (40 mL). The reaction mixture was then stirred vigorously for 1 h at 25 °C and for 30 min at 50 °C. Carbon disulfide (18.9 g, 15.0 mL, 0.25 mol, 5 equiv.) was added dropwise at 0 °C, and the reaction mixture was allowed to reach 25 °C for 16 h. Iodomethane (13.7 g, 6.0 mL, 0.10 mol, 2 equiv.) was then added dropwise at 0 °C, and the reaction mixture was allowed to reach 25 °C for 60 min. After addition of ice water (100 mL), the product precipitated. The mixture was cooled overnight at 0 °C before being filtered. The crude product was purified by chromatography on silica gel with ethyl acetate/cyclohexane (1:4) as eluent, which afforded **1c** (7.38 g, 39.9 mmol, 80%) as a yellow powder; m.p. 132–134 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 8.53 (d, J = 8.2 Hz, 2 H, 2-H, 6-H), 6.24 (d, J = 8.2 Hz, 2 H, 3-H, 5-H), 2.72 (s, 3 H, SCH_3) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 202.3 (=CS), 180.7 (C), 135.4 (2 × CH), 118.1 (2 × CH), 21.6 (CH_3) ppm.

***S*-Methyl 2-Chloropyridine-5-dithiocarbamate (2):** Thiophosgene (0.9 g, 0.6 mL, 7.7 mmol, 1 equiv.) in chloroform (4 mL) was added dropwise at 0 °C to a solution of 2-chloro-5-hydroxypyridine (1.0 g, 7.7 mmol) in aqueous sodium hydroxide (5%, 7 mL). The reaction mixture was then vigorously stirred for 2 h at 0 °C before being extracted with chloroform (3 × 4 mL). The combined organic layers were washed with dilute hydrochloric acid (1 N, 5 mL) and water (5 mL), and were dried with sodium sulfate before being filtered. Sodium methanethiolate (0.6 g, 8.4 mmol, 1.1 equiv.) was added to the filtrate at 25 °C, and the suspension was vigorously stirred at this temperature for 3 d. The reaction mixture was filtered through a pad of silica gel with dichloromethane and the filtrate was concentrated. The crude product was purified by chromatography on silica gel with ethyl acetate/cyclohexane (1:4) as eluent, which afforded **2** (1.2 g, 5.5 mmol, 72%) as a yellow powder. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 8.13 (d, J = 2.8 Hz, 1 H, 6-H), 7.37 (dd, J = 8.5, 2.8 Hz, 1 H, 4-H), 7.31 (d, J = 8.5 Hz, 1 H, 3-H), 2.61 (s, 3 H, SCH_3) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 215.2 (=CS), 150.1 (C), 148.5 (C), 143.7 (CH), 133.1 (CH), 124.8 (CH), 20.2 (CH_3) ppm.

2-Chloro-5-(trifluoromethoxy)pyridine (3): Hydrogen fluoride in pyridine (70%, 65 mL, 0.5 mol, 80 equiv.) was added dropwise at –78 °C to a suspension of 1,3-dibromo-5,5-dimethylhydantoin (8.20 g, 28.0 mmol, 4.5 equiv.) in dichloromethane (80 mL). The mixture was then vigorously stirred for 30 min at –78 °C, after which **2** (1.4 g, 6.0 mmol) in dichloromethane (20 mL) was added dropwise. The reaction mixture was then vigorously stirred at –5 °C for 2 h before being diluted with diethyl ether (40 mL) at this temperature and neutralized with cold, saturated aqueous solutions of sodium hydrogen carbonate (500 mL) and sodium bisulfate (150 mL) until the red color disappeared. At 0 °C, the pH was adjusted to 10–11 with a sodium hydroxide solution (5.0 N, 100 mL) and the layers were separated. The organic layer was dried with sodium sulfate prior to concentration. The crude product was purified by chromatography on silica gel with ethyl acetate/cyclohexane (1:9) as eluent, which afforded pure 2-chloro-5-(trifluoromethoxy)-pyridine (**3**, 0.66 g, 3.36 mmol, 56%) as a pale yellow oil; b.p. 41–43 °C/20 mbar. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 8.26 (d, J = 2.9 Hz, 1 H, 6-H), 7.45 (dd, J = 8.7, 2.9 Hz, 1 H, 4-H), 7.31 (d, J = 8.7 Hz, 1 H, 3-H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 149.3 (C), 145.1 (C), 142.7 (CH), 131.3 (CH), 125.1 (CH), 120.2 (q, $^2J_{C,F}$ = 260 Hz, OCF_3) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = –58.9 ppm. $C_6H_3ClF_3NO$ (197.54): calcd. C 36.48, H 1.53, N 7.09; found C 36.64, H 1.47, N 7.32.

3-(Difluoromethoxy)pyridine (4): 3-Hydroxypyridine (9.8 g, 0.10 mol) was dissolved at 25 °C in a solution of sodium hydroxide (20.0 g, 0.50 mol, 5 equiv.) in distilled water (50 mL) and dioxane (100 mL). The mixture was warmed up to 55 °C and vigorously stirred, while gaseous chlorodifluoromethane (50.0 g, 0.57 mol, 5.7 equiv.) was passed through the reaction mixture through a gas frit over 5 h. After addition of diethyl ether (200 mL) the organic phase was separated and the aqueous layer was extracted with diethyl ether (2 × 100 mL). The combined organic layers were washed

with brine (100 mL) and dried with sodium sulfate prior to concentration. The crude product was purified by chromatography on silica gel with ethyl acetate/cyclohexane (5:95) as eluent, which afforded 3-(difluoromethoxy)pyridine (**4**, 3.51 g, 24.2 mmol, 24%) as a pale red oil. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 8.37 (m, 2 H, 2-H, 6-H), 7.37 (d, J = 8.3 Hz, 1 H, 4-H), 7.21 (dd, J = 8.3, 4.7 Hz, 1 H, 5-H), 6.45 (t, $^2J_{H,F}$ = 72.7 Hz, 1 H, OCF_2 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 147.4 (C), 146.7 (CH), 142.2 (CH), 127.3 (CH), 124.1 (CH), 115.3 (t, $^2J_{C,F}$ = 263 Hz, OCF_2 H) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = –84.4 ppm.

2,6-Dichloro-3-(difluoromethoxy)pyridine (5): 2,6-Dichloro-3-hydroxypyridine (3.0 g, 18.3 mmol) was dissolved at 25 °C in a solution of sodium hydroxide (3.7 g, 91.5 mmol, 5 equiv.) in distilled water (9 mL) and dioxane (18 mL). The mixture was warmed up to 55 °C and vigorously stirred, while gaseous chlorodifluoromethane (8.0 g, 91.5 mmol, 5 equiv.) was passed through the reaction mixture through a gas frit over 1 h. After addition of diethyl ether (100 mL) the organic phase was separated and the aqueous layer was extracted with diethyl ether (2 × 50 mL). The combined organic layers were washed with brine (50 mL) and dried with sodium sulfate prior to concentration. The crude product was further dried under vacuum to afford 2,6-dichloro-3-difluoromethoxypyridine (**5**, 3.58 g, 16.8 mmol, 92%) as a pale yellow oil. According to ^{1}H and ^{13}C NMR, almost 10% of the regioisomer 2,6-dichloro-4-(difluoromethoxy)pyridine was also obtained as an inseparable byproduct resulting from contamination of the starting material with 2,6-dichloro-4-hydroxypyridine. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 7.48 (d, J = 8.4 Hz, 1 H, 4-H), 7.20 (d, J = 8.4 Hz, 1 H, 5-H), 6.49 (t, $^2J_{H,F}$ = 71.9 Hz, 1 H, OCF_2 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 146.4 (C), 143.4 (C), 142.4 (C), 132.7 (CH), 123.8 (CH), 115.1 (t, $^2J_{C,F}$ = 264 Hz, OCF_2 H) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = –82.7 ppm. $C_6H_3Cl_2F_2NO$ (214.00): calcd. C 33.68, H 1.41, N 6.55; found C 33.06, H 1.81, N 6.74.

2,6-Dichloro-4-(difluoromethoxy)pyridine: ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 6.96 (s, 2 H, 3-H, 5-H), 6.55 (t, $^2J_{H,F}$ = 71.1 Hz, 1 H, OCF_2H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 159.9 (C), 151.8 (2 C), 114.5 (t, $^2J_{C,F}$ = 267 Hz, OCF_2H), 112.7 (2 × CH) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = –84.2 ppm. $C_6H_3Cl_2F_2NO$ (214.00): calcd. C 33.68, H 1.41, N 6.55; found C 33.06, H 1.81, N 6.74.

2,6-Dichloro-3-(chlorodifluoromethoxy)pyridine (6a): Elemental chlorine was passed at 110 °C, through a gas frit, through pure 2,6-dichloro-3-(difluoromethoxy)pyridine (**5**, 0.80 g, 3.7 mmol) under external irradiation (UV lamp, Osram, 300 W) for 6 h. GC monitoring indicated 80% conversion. During the reaction, excess chlorine in the output was neutralized with an aqueous solution of sodium hydrogen carbonate (10%) and sodium hydroxide (10%). At the end of the reaction, it was removed from the reaction mixture with a stream of Ar gas. The crude pale yellow oil was distilled under vacuum to afford 2,6-dichloro-3-(chlorodifluoromethoxy)-pyridine (**6a**, 0.690 g, 2.77 mmol, 75%) as a colorless oil. b.p. 93–96 °C/20 mbar. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 7.58 (d, J = 8.5 Hz, 1 H, 4-H), 7.26 (d, J = 8.5 Hz, 1 H, 5-H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 148.8 (C), 144.5 (C), 141.8 (C), 133.3 (CH), 121.9 (t, $^2J_{C,F}$ = 293 Hz, OCF_2Cl), 124.7 (CH) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = –27.7 ppm. MS (EI): m/z = 248 $[M]^+$, 213 $[M - Cl]^+$.

2,6-Dichloro-3-(bromodifluoromethoxy)pyridine (6b): Sodium hydride (60%, 3.6 g, 0.9 mol, 3 equiv.) was added portionwise at 0 °C to a solution of 2,6-dichloro-3-hydroxypyridine (5.0 g, 30.5 mmol) in DMF (50 mL). The reaction mixture was then vigorously stirred for 1 h at 25 °C and for 30 min at 60 °C. A solution of dibromodifluoromethane (25.7 g, 11.2 mL, 122.0 mmol, 4 equiv.) in DMF (10 mL) was added dropwise at 0 °C, and the reaction mixture was allowed to reach 25 °C for 2 h. Potassium *tert*-butoxide (3.6 g, 30.5 mmol, 1.1 equiv.) was then added portionwise at 0 °C, and the reaction mixture was vigorously stirred for 16 h at 70 °C in a closed reactor. After addition of water (100 mL) the organic layer was separated and the aqueous layer was extracted with diethyl ether (3 × 50 mL). The combined organic layers were dried with sodium sulfate prior to concentration. The crude product was purified by chromatography on silica gel with ethyl acetate/cyclohexane (2:98) as eluent, which afforded 2,6-dichloro-3-(bromodifluoromethoxy)-pyridine (**6b**, 4.10 g, 17.7 mmol, 58%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 7.60 (d, J = 8.5 Hz, 1 H, 4-H), 7.26 (d, J = 8.5 Hz, 1 H, 5-H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 147.8 (C), 144.0 (C), 142.8 (C), 133.0 (CH), 123.9 (CH), 114.0 (t, $^2J_{C,F}$ = 313 Hz, OCF_2Br) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = –17.3 ppm.

2,6-Dichloro-3-(trifluoromethoxy)pyridine (7)

Procedure A: 2,6-Dichloro-3-(chlorodifluoromethoxy)pyridine (**6a**, 600 mg, 2.4 mmol) was added dropwise at 120 °C to a mixture of SbF_3 (440 mg, 2.4 mmol, 1 equiv.) and $SbCl_5$ (108 mg, 50 µL, 0.4 mmol, 0.15 equiv.) and the mixture was stirred for 16 h at 140 °C. The mixture was then cooled to 0 °C and dissolved in dichloromethane (10 mL). The solution was washed with saturated aqueous solutions of sodium hydrogen carbonate (50 mL) and brine (25 mL) and the aqueous layer was extracted with dichloromethane (2 × 10 mL). The combined organic layers were dried with sodium sulfate before being distilled. The crude product was distilled under vacuum to afford pure 2,6-dichloro-3-(trifluoromethoxy)pyridine (**7**, 122 mg, 0.53 mmol, 22%) as a colorless oil; b.p. 65–66 °C/20 mbar.

Procedure B: Procedure B was as described in Procedure A, but this time with 2,6-dichloro-3-(bromodifluoromethoxy)pyridine (**6b**, 4.0 g, 13.7 mmol), SbF_3 (2.5 g, 13.7 mmol, 1 equiv.), and $SbCl_5$ (1.4 g, 0.6 mL, 4.5 mmol, 0.33 equiv.) for 16 h at 140 °C, which afforded 2,6-dichloro-3-(trifluoromethoxy)pyridine (**7**, 1.1 g, 4.80 mmol, 35%) as a colorless oil after distillation under vacuum; b.p. 65–66 °C/20 mbar. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 7.54 (d, J = 8.5 Hz, 1 H, 4-H), 7.25 (d, J = 8.5 Hz, 1 H, 5-H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 147.9 (C), 144.2 (C), 141.5 (C), 132.9 (CH), 124.0 (CH), 120.4 (q, $^2J_{C,F}$ = 261 Hz, OCF_3) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = –58.5 ppm. $C_6H_2Cl_2F_3NO$ (231.99): calcd. C 31.06, H 0.87, N 6.04; found C 31.21, H 0.95, N 6.01.

3-(Bromodifluoromethoxy)pyridine (8): 3-Hydroxypyridine (5.0 g, 52.6 mmol) in DMF (20 mL) was added at 0 °C to a suspension of sodium hydride (60%, 6.3 g, 156 mmol, 3 equiv.) in DMF (20 mL). The reaction mixture was then vigorously stirred for 1 h at 25 °C and for 30 min at 60 °C. A solution of dibromodifluoromethane (25.2 g, 11.0 mL, 115.6 mmol, 2.2 equiv.) in DMF (20 mL) was added dropwise at 0 °C, and the reaction mixture was allowed to reach 25 °C for 2 h. Potassium *tert*-butoxide (6.2 g, 52.6 mmol, 1 equiv.) was then added portionwise at 0 °C, and the reaction mixture was vigorously stirred for 16 h at 70 °C in a closed reactor. After addition of water (100 mL) the organic phase was separated and the aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were dried with sodium sulfate prior to concentration. The crude product was purified by chromatography on silica gel with ethyl acetate/cyclohexane (5:95) as eluent, which afforded 3-(bromodifluoromethoxy)pyridine (**8**, 820 mg,

3.68 mmol, 7%) as a red oil. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 8.50 (dd, J = 4.7, 1.3 Hz, 2 H, 2-H, 6-H), 7.51 (ddd, J = 8.3, 4.7, 1.3 Hz, 1 H, 4-H), 7.30 (dd, J = 8.3, 4.7 Hz, 1 H, 5-H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 148.2 (CH), 147.5 (C), 143.4 (CH), 128.8 (CH), 124.2 (CH), 114.4 (t, $^2J_{C,F}$ = 313 Hz, OCF_2Br) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = –17.6 ppm.

General Route to (Trifluoromethoxy)pyridines

2,6-Dichloro-3-(trichloromethoxy)pyridine (9): Thiophosgene (4.3 g, 2.9 mL, 36.6 mmol, 1 equiv.) in chloroform (22 mL) was added dropwise at 0 °C to a solution of 2,6-dichloro-3-hydroxypyridine (6.0 g, 36.6 mmol) in aqueous sodium hydroxide (5%, 32 mL). The reaction mixture was vigorously stirred for 2 h at 0 °C before being extracted with chloroform (3 × 20 mL). The combined organic layers were washed with dilute hydrochloric acid (1 N, 20 mL) and water (20 mL) and dried with sodium sulfate before being filtered. The filtrate was then saturated with chlorine at 25 °C until the reaction mixture began to warm up. After 2 h at 25 °C, excess chlorine was again added until a yellow solution was obtained. After 24 h at 25 °C, excess chlorine was removed with a stream of Ar gas and the solution was concentrated. The crude pale yellow oil was distilled under vacuum to afford pure 2,6-dichloro-3-(trichloromethoxy)pyridine (**9**, 7.13 g, 25.4 mmol, 70%) as a colorless oil that crystallized on standing; b.p. 78–81 °C/0.5 mbar; m.p. 41–43 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 8.02 (d, J = 8.5 Hz, 1 H, 4-H), 7.37 (d, J = 8.5 Hz, 1 H, 5-H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 147.5 (C), 144.6 (C), 132.9 (CH), 123.6 (CH), 115.0 (C), 112.2 ($OCCl_3$) ppm. HRMS for $C_6H_2Cl_5NO$: calcd. 279.8652 [M + H]; found 279.8628.

2,6-Dichloro-3-(trifluoromethoxy)pyridine (7): 2,6-Dichloro-3-(trichloromethoxy)pyridine (**9**, 4.0 g, 14.3 mmol) was added dropwise at 120 °C to a molten mixture of SbF_3 (5.2 g, 28.7 mmol, 2.0 equiv.) and $SbCl_5$ (0.6 g, 0.3 mL, 2.1 mmol, 0.15 equiv.) and the mixture was stirred for 6 h at 150 °C. GC monitoring indicated 100% conversion and disappearance of the OCF_2Cl byproduct. The mixture was then cooled to 0 °C and dissolved in dichloromethane (100 mL). The solution was quenched with saturated aqueous sodium hydrogen carbonate (300 mL) and potassium fluoride (20%, 50 mL) and the aqueous layer was extracted with dichloromethane (2 × 50 mL). The combined organic layers were dried with sodium sulfate and the solvent was distilled off. The crude product was distilled under vacuum to afford pure 2,6-dichloro-3-(trifluoromethoxy)pyridine (**7**, 2.11 g, 9.15 mmol, 64%) as a colorless oil; b.p. 65–66 °C/20 mbar; n_D^{20} = 1.5912. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 7.54 (d, J = 8.5 Hz, 1 H, 4-H), 7.25 (d, J = 8.5 Hz, 1 H, 5-H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 147.9 (C), 144.2 (C), 141.5 (C), 132.9 (CH), 124.0 (CH), 120.4 (q, $^2J_{C,F}$ = 261 Hz, OCF_3) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = –58.5 ppm. $C_6H_2Cl_2F_3NO$ (231.99): calcd. C 31.06, H 0.87, N 6.04; found C 31.21, H 0.95, N 6.01.

2-Chloro-5-(trichloromethoxy)pyridine (10): Thiophosgene (4.3 g, 2.9 mL, 37.0 mmol, 1 equiv.) in chloroform (22 mL) was added dropwise at 0 °C to a solution of 2-chloro-5-hydroxypyridine (4.8 g, 37.0 mmol) in aqueous sodium hydroxide (5%, 32 mL). The reaction mixture was vigorously stirred for 2 h at 0 °C before being extracted with chloroform (3 × 20 mL). The combined organic layers were washed with dilute hydrochloric acid (1 N, 20 mL) and water (20 mL) and dried with sodium sulfate before being filtered. The filtrate was then saturated with chlorine at 25 °C until the reaction mixture began to warm up. After 2 h at 25 °C, excess chlorine was again added until a yellow solution was obtained. After 24 h at 25 °C, excess chlorine was removed with a stream of Ar gas and the solution was concentrated. The crude pale yellow oil was distilled under vacuum to afford 2-chloro-5-(trichloromethoxy)pyridine (**10**, 7.11 g, 28.9 mmol, 79%) as a colorless oil that crystallized on standing; b.p. 71–73 °C/0.5 mbar; m.p. 38–41 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 8.47 (d, J = 2.8 Hz, 1 H, 6-H), 7.75 (dd, J = 8.7, 2.8 Hz, 1 H, 4-H), 7.42 (d, J = 8.7 Hz, 1 H, 3-H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 149.4 (C), 147.9 (C), 144.2 (CH), 132.9 (CH), 124.8 (CH), 112.2 ($OCCl_3$) ppm. MS (EI): m/z = 246 $[M]^+$, 211 $[M - Cl]^+$.

2-Chloro-5-(trifluoromethoxy)pyridine (3): 2-Chloro-5-(trichloromethoxy)pyridine (**11**, 7.4 g, 30.0 mmol) was added dropwise at 120 °C to a mixture of SbF_3 (10.7 g, 60.0 mmol, 2.0 equiv.) and $SbCl_5$ (1.4 g, 0.6 mL, 4.6 mmol, 0.15 equiv.) and the mixture was stirred for 3 h at 150 °C. GC monitoring indicated 100% conversion and disappearance of the OCF_2Cl byproduct. The mixture was then cooled to 0 °C and dissolved in dichloromethane (100 mL). The solution was neutralized with saturated aqueous sodium hydrogen carbonate (300 mL) and potassium fluoride (20%, 50 mL) and the aqueous layer was extracted with dichloromethane (2 × 50 mL). The combined organic layers were dried with sodium sulfate and the solvent was distilled off. The crude product was distilled under vacuum to afford pure 2-chloro-5-(trifluoromethoxy)pyridine (**3**, 3.55 g, 18.0 mmol, 60%) as a colorless oil; b.p. 41–43 °C/20 mbar. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 8.26 (d, J = 2.9 Hz, 1 H, 6-H), 7.45 (dd, J = 8.7, 2.9 Hz, 1 H, 4-H), 7.31 (d, J = 8.7 Hz, 1 H, 3-H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 149.3 (C), 145.1 (C), 142.7 (CH), 131.3 (CH), 125.1 (CH), 120.2 (q, $^2J_{C,F}$ = 260 Hz, OCF_3) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = –58.9 ppm. $C_6H_3ClF_3NO$ (197.54): calcd. C 36.48, H 1.53, N 7.09; found C 36.64, H 1.47, N 7.32.

2-Chloro-6-(trichloromethoxy)pyridine (11): Thiophosgene (4.5 g, 3.0 mL, 39 mmol, 1 equiv.) in chloroform (24 mL) was added dropwise at 0 °C to a solution of 2-chloro-6-hydroxypyridine (5.0 g, 39 mmol) in aqueous sodium hydroxide (5%, 34 mL). The reaction mixture was vigorously stirred for 2 h at 0 °C before being extracted with chloroform (3 × 20 mL). The combined organic layers were washed with dilute hydrochloric acid (1 N, 20 mL) and water (20 mL) and dried with sodium sulfate before being filtered. The filtrate was then saturated with chlorine at 25 °C until the reaction mixture began to warm up. After 2 h at 25 °C, excess chlorine was again added until a yellow solution was obtained. After 24 h at 25 °C, excess chlorine was removed with a stream of Ar gas and the solution was concentrated. The crude pale yellow oil was distilled under vacuum to afford pure 2-chloro-6-(trichloromethoxy)pyridine (**11**, 5.66 g, 23.0 mmol, 60%) as a colorless oil that crystallized on standing; b.p. 80–82 °C/1 mbar; m.p. 37–39 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 7.70 (t, J = 7.9 Hz, 1 H, 4-H), 7.19 (d, J = 7.7 Hz, 1 H, 5-H), 7.02 (d, J = 8.1 Hz, 1 H, 3-H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 151.8 (C), 149.0 (C), 141.7 (CH), 122.2 (CH), 112.7 (CH), 109.1 ($OCCl_3$) ppm. MS (EI): m/z = 246 $[M]^+$, 211 $[M - Cl]^+$.

2-Chloro-3-(trichloromethoxy)pyridine (12): Thiophosgene (22.2 g, 14.8 mL, 0.19 mol, 1 equiv.) in chloroform (115 mL) was added dropwise at 0 °C to a solution of 2-chloro-3-hydroxypyridine (25.0 g, 0.19 mol) in aqueous sodium hydroxide (5%, 160 mL). The reaction mixture was vigorously stirred for 2 h at 0 °C before being extracted with chloroform (3 × 100 mL). The combined organic layers were washed with dilute hydrochloric acid (1 N, 100 mL) and water (100 mL) and dried with sodium sulfate before being filtered. The filtrate was then saturated with chlorine at 25 °C until the reaction mixture began to warm up. After 2 h at 25 °C, excess chlorine was again added until a yellow solution was obtained. After

24 h at 25 °C, excess chlorine was removed with a stream of Ar gas and the solution was concentrated. The crude pale yellow oil was distilled under vacuum to afford 2-chloro-3-(trichloromethoxy)pyridine (**12**, 32.0 g, 130 mmol, 70%) as a colorless oil; b.p. 78–80 °C/4 mbar. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 8.36 (dd, J = 4.7, 1.6 Hz, 1 H, 6-H), 8.05 (dd, J = 8.2, 1.6 Hz, 1 H, 4-H), 7.35 (dd, J = 8.2, 4.7 Hz, 1 H, 5-H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 147.1 (CH), 146.7 (C), 145.6 (C), 130.6 (CH), 123.0 (CH), 112.1 ($OCCl_3$) ppm. MS (EI): m/z = 246 $[M]^+$, 211 $[M - Cl]^+$.

2-Chloro-4-(trichloromethoxy)pyridine (13): Thiophosgene (2.5 g, 1.7 mL, 21.5 mmol, 1 equiv.) in chloroform (15 mL) was added dropwise at 0 °C to a solution of 2-chloro-4-hydroxypyridine (2.8 g, 21.5 mmol) in aqueous sodium hydroxide (5%, 20 mL). The reaction mixture was vigorously stirred for 2 h at 0 °C before being extracted with chloroform (3 × 10 mL). The combined organic layers were washed with dilute hydrochloric acid (1 N, 20 mL) and water (20 mL) and dried with sodium sulfate before being filtered. The filtrate was then saturated with chlorine at 25 °C until the reaction mixture began to warm up. After 2 h at 25 °C, excess chlorine was again added until a yellow solution was obtained. After 24 h at 25 °C, excess chlorine was removed with a stream of Ar gas and the solution was concentrated. The crude pale yellow oil was distilled under vacuum to afford 2-chloro-4-(trichloromethoxy)pyridine (**13**, 2.63 g, 10.7 mmol, 50%) as a colorless oil; b.p. 79–81 °C/1 mbar. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 8.36 (d, J = 5.7 Hz, 1 H, 6-H), 7.28 (d, J = 2.1 Hz, 1 H, 3-H), 7.21 (dd, J = 5.7, 2.1 Hz, 1 H, 5-H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 159.6 (C), 152.7 (C), 150.9 (CH), 116.3 (CH), 114.7 (CH), 110.0 ($OCCl_3$) ppm. MS (EI): m/z = 246 $[M]^+$, 211 $[M - Cl]^+$.

2-Chloro-6-(trifluoromethoxy)pyridine (14): 2-Chloro-6-(trichloromethoxy)pyridine (**11**, 5.9 g, 23.8 mmol) was added dropwise at 120 °C to a mixture of SbF_3 (8.7 g, 47.7 mmol, 2.0 equiv.) and $SbCl_5$ (1.0 g, 0.45 mL, 3.6 mmol, 0.15 equiv.) and the mixture was stirred for 3 h at 140 °C. GC monitoring indicated 100% conversion and disappearance of the OCF_2Cl byproduct. The mixture was then cooled to 0 °C and dissolved in dichloromethane (100 mL). The solution was neutralized with saturated aqueous sodium hydrogen carbonate (100 mL) and potassium fluoride (20%, 50 mL) and the aqueous layer was extracted with dichloromethane (2 × 50 mL). The combined organic layers were dried with sodium sulfate and the solvent was distilled off. The crude product was distilled under vacuum to afford pure 2-chloro-6-(trifluoromethoxy)pyridine (**14**, 2.49 g, 12.6 mmol, 53%) as a colorless oil; b.p. 42–44 °C/20 mbar. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 7.67 (t, J = 7.9 Hz, 1 H, 4-H), 7.18 (d, J = 7.7 Hz, 1 H, 5-H), 6.87 (d, J = 8.0 Hz, 1 H, 3-H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 155.6 (C), 149.3 (C), 142.0 (CH), 122.2 (CH), 119.8 (q, $^2J_{C,F}$ = 262 Hz, OCF_3), 111.1 (CH) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = –57.0 ppm. HRMS for $C_6H_4ClF_3NO$: calcd. 197.9928 [M + H]; found 198.0041.

2-Chloro-3-(trifluoromethoxy)pyridine (15): 2-Chloro-3-(trichloromethoxy)pyridine (**12**, 32.9 g, 0.13 mol) was added dropwise at 120 °C to a mixture of SbF_3 (46.5 g, 0.26 mol, 2.0 equiv.) and $SbCl_5$ (5.8 g, 2.5 mL, 19.5 mmol, 0.15 equiv.) and the mixture was stirred for 7 h at 150 °C. GC monitoring indicated 100% conversion and disappearance of the OCF_2Cl byproduct. The mixture was then cooled to 0 °C and dissolved in dichloromethane (300 mL). The solution was neutralized with saturated aqueous sodium hydrogen carbonate (300 mL) and potassium fluoride (20%, 150 mL) and the aqueous layer was extracted with dichloromethane (2 × 150 mL). The combined organic layers were dried with sodium sulfate and the solvent was distilled off. The crude product was distilled under vacuum to afford pure 2-chloro-3-(trifluoromethoxy)pyridine (**15**, 15.4 g, 78.0 mmol, 60%) as a colorless oil; b.p. 57–59 °C/19 mbar. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 8.37 (dd, J = 4.7, 1.5 Hz, 1 H, 6-H), 7.68 (dt, J = 8.1, 1.5 Hz, 1 H, 4-H), 7.34 (dd, J = 8.1, 4.7 Hz, 1 H, 5-H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 147.4 (CH), 144.9 (C), 142.3 (C), 130.5 (CH), 123.2 (CH), 120.2 (q, $^2J_{C,F}$ = 261 Hz, OCF_3) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = –58.7 ppm. $C_6H_3ClF_3NO$ (197.54): calcd. C 36.48, H 1.53, N 7.09; found C 36.08, H 1.68, N 7.28.

2-Chloro-4-(trifluoromethoxy)pyridine (16): 2-Chloro-4-(trichloromethoxy)pyridine (**13**, 3.5 g, 14.2 mmol) was added dropwise at 120 °C to a mixture of SbF_3 (5.0 g, 28.4 mmol, 2.0 equiv.) and $SbCl_5$ (635 mg, 0.27 mL, 2.1 mmol, 0.15 equiv.) and the mixture was stirred for 7 h at 140 °C. GC monitoring indicated 100% conversion and disappearance of the OCF_2Cl byproduct. The mixture was then cooled to 0 °C and dissolved in dichloromethane (100 mL). The solution was neutralized with saturated aqueous sodium hydrogen carbonate (100 mL) and potassium fluoride (20%, 75 mL), and the aqueous layer was extracted with dichloromethane (2 × 50 mL). The combined organic layers were dried with sodium sulfate and the solvent was distilled off. The crude product was distilled under vacuum to afford 2-chloro-4-(trifluoromethoxy)pyridine (**16**, 1.40 g, 7.10 mmol, 50%) as a colorless oil in a mixture with 2,4-dichloropyridine (almost 10%) as an inseparable byproduct; b.p. 39–41 °C/20 mbar. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 8.43 (d, J = 5.4 Hz, 1 H, 6-H), 7.18 (d, J = 1.6 Hz, 1 H, 3-H), 7.08 (dd, J = 5.4, 1.6 Hz, 1 H, 5-H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 157.2 (C), 153.1 (C), 151.3 (CH), 119.9 (q, $^2J_{C,F}$ = 260 Hz, OCF_3), 114.8 (CH), 113.1 (CH) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = –57.9 ppm. MS (EI): m/z = 197 $[M]^+$, 162 $[M - Cl]^+$.

2-Bromo-3-(trichloromethoxy)pyridine (17): Thiophosgene (3.3 g, 2.2 mL, 28.7 mmol, 1 equiv.) in chloroform (18 mL) was added dropwise at 0 °C to a solution of 2-bromo-3-hydroxypyridine (5.0 g, 28.7 mmol) in aqueous sodium hydroxide (5%, 25 mL). The reaction mixture was vigorously stirred for 2 h at 0 °C before being extracted with chloroform (3 × 15 mL). The combined organic layers were washed with dilute hydrochloric acid (1 N, 20 mL) and water (20 mL) and dried with sodium sulfate before being filtered. The filtrate was then saturated with chlorine at 25 °C until the reaction mixture began to warm up. After 2 h at 25 °C, excess chlorine was again added until a yellow solution was obtained. After 24 h at 25 °C, excess chlorine was removed with a stream of Ar gas and the solution was concentrated to afford 2-bromo-3-(trichloromethoxy)pyridine (**17**, 6.60 g, 22.7 mmol, 79%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 8.35 (dd, J = 4.7, 1.6 Hz, 1 H, 6-H), 8.04 (dd, J = 8.2, 1.6 Hz, 1 H, 4-H), 7.37 (dd, J = 8.2, 4.7 Hz, 1 H, 5-H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 147.5 (CH), 145.6 (C), 137.2 (C), 129.7 (CH), 123.2 (CH), 111.9 ($OCCl_3$) ppm. MS (EI): m/z = 290 $[M]^+$, 255 $[M - Cl]^+$.

2-Fluoro-3-(trichloromethoxy)pyridine (18): Thiophosgene (10.2 g, 7.0 mL, 88.5 mmol, 1 equiv.) in chloroform (58 mL) was added dropwise at 0 °C to a solution of 2-fluoro-3-hydroxypyridine (10.0 g, 88.5 mmol) in aqueous sodium hydroxide (5%, 78 mL). The reaction mixture was vigorously stirred for 2 h at 0 °C before being extracted with chloroform (3 × 100 mL). The combined organic layers were washed with dilute hydrochloric acid (1 N, 40 mL) and water (40 mL) and dried with sodium sulfate before being filtered. The filtrate was then saturated with chlorine at 25 °C until the reaction mixture began to warm up. After 2 h at 25 °C, excess chlorine was again added until a yellow solution was obtained. Af-

ter 24 h at 25 °C, excess chlorine was removed with a stream of Ar gas and the solution was concentrated to afford 2-fluoro-3-(trichloromethoxy)pyridine (**18**, 14.2 g, 62.0 mmol, 70%) as a pale yellow oil; b.p. 110–113 °C/16 mbar. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 8.10 (m, 1 H, 6-H), 7.94 (m, 1 H, 4-H), 7.20 (m, 1 H, 5-H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 155.9 (d, $^2J_{C,F}$ = 243 Hz, CF), 145.4 (d, $^4J_{C,F}$ = 14 Hz, CH), 134.8 (d, $^3J_{C,F}$ = 27 Hz, 1 C), 134.3 (d, J = 2 Hz, CH), 121.9 (d, J = 5 Hz, CH), 112.7 ($OCCl_3$) ppm. MS (EI): m/z = 230 $[M]^+$, 195 $[M - Cl]^+$.

2-Bromo-3-(trifluoromethoxy)pyridine (19): 2-Bromo-3-(trichloromethoxy)pyridine (**17**, 7.8 g, 28.0 mmol) was added dropwise at 120 °C to a mixture of SbF_3 (10.2 g, 56.0 mmol, 2.0 equiv.) and $SbCl_5$ (1.7 g, 0.7 mL, 5.6 mmol, 0.2 equiv.) and the mixture was stirred for 10 h at 150 °C. GC monitoring indicated 50% conversion. The mixture was further stirred for 3 d at 150 °C until disappearance of the OCF_2Cl byproduct. The mixture was then cooled to 0 °C and dissolved in dichloromethane (50 mL). The solution was neutralized with saturated aqueous sodium hydrogen carbonate (200 mL) and the aqueous layer was extracted with dichloromethane (2 × 50 mL). The combined organic layers were dried with sodium sulfate and the solvent was distilled off. The crude product was distilled under vacuum to afford pure 2-bromo-3-(trifluoromethoxy)pyridine (**19**, 200 mg, 0.84 mmol, 3%) as a colorless oil; b.p. 63–67 °C/13 mbar. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 8.26 (dd, J = 4.6, 1.2 Hz, 1 H, 6-H), 7.54 (d, J = 8.1, 1.2 Hz, 1 H, 4-H), 7.27 (dd, J = 8.1, 4.6 Hz, 1 H, 5-H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 147.7 (CH), 144.0 (C), 136.1 (C), 129.9 (CH), 123.7 (CH), 120.3 (q, $^2J_{C,F}$ = 260 Hz, OCF_3) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = –58.0 ppm. $C_6H_3BrF_3NO$ (241.99): calcd. C 29.78, H 1.25, N 5.79; found C 29.96, H 1.41, N 5.64.

3-Chloro-5-(trichloromethoxy)pyridine (20): Thiophosgene (5.5 g, 3.8 mL, 47.9 mmol, 1 equiv.) in chloroform (30 mL) was added dropwise at 0 °C to a solution of 3-chloro-5-hydroxypyridine (6.2 g, 47.9 mmol) in aqueous sodium hydroxide (5%, 41 mL). The reaction mixture was vigorously stirred for 2 h at 0 °C before being extracted with chloroform (3 × 50 mL). The combined organic layers were washed with dilute hydrochloric acid (1 N, 20 mL) and water (20 mL) and dried with sodium sulfate before being filtered. The filtrate was then saturated with chlorine at 25 °C until the reaction mixture began to warm up. After 2 h at 25 °C, excess chlorine was again added until a yellow solution was obtained. After 24 h at 25 °C, excess chlorine was removed with a stream of Ar gas and the solution was concentrated. The crude oil was distilled under vacuum to afford 3-chloro-5-(trichloromethoxy)pyridine (**20**, 7.10 g, 28.7 mmol, 55%) as a colorless oil; b.p. 71–75 °C/4 mbar. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 8.67 (m, 2 H, 2-H, 6-H), 8.05 (t, J = 2.1 Hz, 1 H, 4-H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 157.9 (C), 149.3 (C), 143.2 (CH), 138.2 (CH), 134.1 (CH), 111.8 ($OCCl_3$) ppm. MS (EI): m/z = 247 $[M]^+$, 212 $[M - Cl]^+$.

Trifluoromethoxy-Substituted Pyridine Carboxylic Acids, Amines, and Halides

2-Bromo-6-(trifluoromethoxy)pyridine (21): A solution of 2-chloro-6-(trifluoromethoxy)pyridine (**14**, 7.0 g, 35.4 mmol) in hydrobromic acid (33% in acetic acid, 100 mL) was heated for 3 d at 100 °C. The reaction mixture was cooled to 0 °C before being slowly neutralized by addition of saturated aqueous sodium hydrogen carbonate (500 mL). After extraction with ethyl acetate (4 × 100 mL), the combined organic layers were dried with sodium sulfate prior to concentration. The crude oil was distilled under vacuum (67–69 °C/15 mbar) to afford pure 2-bromo-6-(trifluoromethoxy)pyridine (**21**, 4.17 g, 17.3 mmol, 48%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 7.58 (t, J = 7.9 Hz, 1 H, 4-H), 7.37 (d, J = 7.7 Hz, 1 H, 5-H), 6.92 (d, J = 8.0 Hz, 1 H, 3-H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 154.7 (C), 148.4 (C), 141.1 (CH), 121.3 (CH), 120.5 (q, $^2J_{C,F}$ = 260 Hz, OCF_3), 110.2 (CH) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = –56.5 ppm.

6-(Trifluoromethoxy)picolinic Acid (22a): Butyllithium (1.56 M in hexanes, 0.8 mL, 1.2 mmol, 1 equiv.) was added dropwise at –78 °C to a solution of 2-bromo-6-(trifluoromethoxy)pyridine (**21**, 0.3 g, 1.2 mmol) in dry toluene (4 mL). After 40 min at –78 °C, the mixture was poured onto an excess of freshly crushed dry ice before being treated with an aqueous solution of sodium hydroxide (5%, 4 mL). The resulting aqueous layer was collected, washed with diethyl ether (4 mL) and acidified to pH 3 by dropwise addition of hydrochloric acid (6 N, 1 mL) before being extracted with ethyl acetate (3 × 4 mL). The combined organic layers were dried with sodium sulfate and concentrated to afford 6-(trifluoromethoxy)-picolinic acid (**22a**, 150 mg, 0.72 mmol, 60%) as a brown powder. Crystallization from dichloromethane afforded the pure product as colorless needles; m.p. 126–128 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 8.11 (d, J = 7.4 Hz, 1 H, 3-H), 8.02 (t, J = 7.9 Hz, 1 H, 4-H), 7.25 (d, J = 8.1 Hz, 1 H, 5-H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 162.9 (COOH), 155.4 (C), 144.6 (C), 142.7 (CH), 122.1 (CH), 119.8 (q, $^2J_{C,F}$ = 260 Hz, OCF_3), 117.6 (CH) ppm. ^{19}F NMR [$(CD_3)_2CO$, 282 MHz, 25 °C]: δ = –57.6 ppm. $C_7H_4F_3NO_3$ (207.11): calcd. C 40.59, H 1.95, N 10.67; found C 40.15, H 2.17, N 6.45.

2-Amino-6-(trifluoromethoxy)pyridine (22b): 2-Bromo-6-(trifluoromethoxy)pyridine (**21**, 500 mg, 2.1 mmol), benzophenone imine (455 mg, 2.5 mmol, 1.2 equiv.), *t*BuOK (360 mg, 3.1 mmol, 1.5 equiv.), DPEphos (25 mg, 0.04 mmol, 0.02 equiv.), and Pd_2dba_3 (60 mg, 0.08 mmol, 0.04 equiv.) were introduced into dry toluene (6 mL) and the reaction mixture was heated at 70 °C and vigorously stirred for 2 h. GC monitoring indicated 100% conversion. The mixture was allowed to reach 25 °C before being filtered through Celite and washed with ethyl acetate. The filtrate was poured onto an aqueous solution of citric acid (10%, 10 mL) and the reaction mixture was then vigorously stirred for 16 h at room temperature. GC monitoring of the organic layer indicated disappearance of starting reagent and formation of diphenyl ketone. The aqueous layer was adjusted to pH 9–10 with sodium hydroxide (5%, 7 mL) and extracted with ethyl acetate (5 × 5 mL). The combined organic layers were dried with sodium sulfate prior to concentration. The crude oil was purified by chromatography on silica gel with ethyl acetate/cyclohexane (5:95) as eluent, which afforded pure 2-amino-6-(trifluoromethoxy)pyridine (**22b**, 150 mg, 0.8 mmol, 40%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 7.40 (t, J = 7.9 Hz, 1 H, 4-H), 6.28 (d, J = 7.8 Hz, 1 H, 5-H), 6.27 (d, J = 7.3 Hz, 1 H, 3-H), 4.19 (br. s, 2 H, NH_2) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 157.6 (C), 155.6 (C), 141.2 (CH), 120.2 (q, $^2J_{C,F}$ = 260 Hz, OCF_3), 105.8 (CH), 101.2 (CH) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = –56.8 ppm. $C_6H_5F_3N_2O$ (178.11): calcd. C 40.46, H 2.73, N 15.73; found C 40.74, H 3.12, N 16.10.

6-Chloro-2-(trifluoromethoxy)nicotinic Acid (23a): Butyllithium (1.56 M in hexanes, 8.3 mL, 12.6 mmol, 1 equiv.) was added dropwise at 0 °C to a solution of diisopropylamine (1.3 g, 1.8 mL, 12.6 mmol, 1 equiv.) in THF (25 mL). A solution of 2-chloro-6-(trifluoromethoxy)pyridine (**14**, 2.5 g, 12.6 mmol, 1 equiv.) in THF (5 mL) was added dropwise at –100 °C, and the reaction mixture was stirred for 2 h at –78 °C. The mixture was then poured onto an excess of freshly crushed dry ice before being treated with an aqueous solution of sodium hydroxide (5%, 25 mL). The resulting

aqueous layer was collected, washed with diethyl ether (15 mL), and acidified to pH 4 by dropwise addition of hydrochloric acid (6 N, 8 mL). After extraction with ethyl acetate (3 × 20 mL), the combined organic layers were dried with sodium sulfate prior to concentration to afford pure 6-chloro-2-(trifluoromethoxy)nicotinic acid (**23a**, 1.9 g, 7.9 mmol, 63%) as a white powder. Crystallization from chloroform afforded the pure product as colorless needles; m.p. 139–142 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 8.32 (d, J = 8.2 Hz, 1 H, 4-H), 7.29 (d, J = 8.2 Hz, 1 H, 5-H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 167.5 (COOH), 154.3 (C), 154.2 (C), 144.9 (CH), 122.1 (CH), 119.3 (q, $^2J_{C,F}$ = 260 Hz, OCF_3), 113.5 (CH) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = –56.5 ppm. $C_7H_3ClF_3NO_3$ (241.55): calcd. C 34.81, H 1.25, N 5.80; found C 34.88, H 1.32, N 5.78.

5-Amino-2-chloro-6-(trifluoromethoxy)pyridine (23b): Butyllithium (1.56 M in hexanes, 10.7 mL, 16.7 mmol, 1.1 equiv.) was added dropwise at 0 °C to a solution of diisopropylamine (1.7 g, 2.4 mL, 16.7 mmol, 1.1 equiv.) in THF (25 mL). A solution of 2-chloro-6-(trifluoromethoxy)pyridine (**14**, 3.0 g, 15.2 mmol, 1 equiv.) in THF (7 mL) was added dropwise at –78 °C, followed after 2 h by benzenesulfonyl azide (3.3 g, 18.2 mmol, 1.2 equiv.). The reaction mixture was allowed to reach 25 °C before being treated with a saturated aqueous ammonium chloride (30 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic layers were dried with sodium sulfate and concentrated to afford the intermediate 5-azido-2-chloro-6-(trifluoromethoxy)pyridine as crude red oil. It was then dissolved in anhydrous diethyl ether (100 mL) and added dropwise to a suspension of lithium aluminum hydride (690 mg, 18.2 mmol, 1.2 equiv.) in diethyl ether (100 mL). The reaction mixture was heated under reflux for 5 h before being treated with water (100 mL) and extracted with diethyl ether (3 × 80 mL). The combined organic layers were dried with sodium sulfate prior to concentration. The crude product was purified by chromatography on silica gel with ethyl acetate/cyclohexane (3:7) as eluent, which afforded pure 5-amino-2-chloro-6-(trifluoromethoxy)pyridine (**23b**, 2.30 g, 10.8 mmol, 71%) as yellow crystals. Crystallization from cyclohexane afforded the pure product as colorless needles; m.p. 42–45 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 7.07 (AB syst., J = 8.2 Hz, 2 H, 4-H, 5-H), 3.83 (br. s, 2 H, NH_2) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 142.5 (C), 135.3 (C), 131.1 (C), 126.3 (CH), 122.7 (CH), 120.1 (q, $^2J_{C,F}$ = 262 Hz, OCF_3) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = –56.5 ppm. $C_6H_4ClF_3N_2O$ (212.56): calcd. C 33.90, H 1.90, N 13.18; found C 33.54, H 2.06, N 13.00.

2-Chloro-5-iodo-6-(trifluoromethoxy)pyridine (23c): Butyllithium (1.56 M in hexanes, 14.2 mL, 22.2 mmol, 1.1 equiv.) was added dropwise at 0 °C to a solution of diisopropylamine (2.2 g, 3.1 mL, 22.2 mmol, 1.1 equiv.) in THF (35 mL). A solution of 2-chloro-6-(trifluoromethoxy)pyridine (**14**, 4.0 g, 20.2 mmol, 1 equiv.) in THF (10 mL) was added dropwise at –78 °C, followed after 2 h by a solution of iodine (5.7 g, 22.2 mmol, 1.1 equiv.) in THF (10 mL). The reaction mixture was allowed to reach 25 °C before being treated with a saturated aqueous sodium sulfite (30 mL) and extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried with sodium sulfate prior to concentration. The crude dark oil was distilled under vacuum (b.p. 103–106 °C/16 mbar) to afford pure 2-chloro-5-iodo-6-(trifluoromethoxy)pyridine (**23c**, 5.05 g, 15.7 mmol, 78%), which crystallized on standing as colorless needles; m.p. 33–35 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 8.11 (d, J = 8.1 Hz, 1 H, 5-H), 7.03 (d, J = 8.1 Hz, 1 H, 4-H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 154.9 (C), 151.3 (CH), 148.9 (C), 142.0 (C), 123.3 (CH), 120.4 (q, $^2J_{C,F}$ = 264 Hz, OCF_3) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = –57.1 ppm.

2-(Trifluoromethoxy)nicotinic Acid (24a): Palladium (10% on charcoal, 450 mg) was added at 25 °C with stirring to a solution of 6-chloro-2-(trifluoromethoxy)nicotinic acid (**23a**, 1.5 g, 6.2 mmol) and ammonium formate (790 mg, 12.4 mmol, 2 equiv.) in methanol (10 mL). The reaction mixture was stirred for 16 h at 55 °C before being filtered under suction and the filtrate was concentrated. The residue was partitioned between ethyl acetate (2 × 20 mL) and hydrochloric acid (2 N, 30 mL). The combined organic layers were dried with sodium sulfate prior to concentration to afford pure 2-(trifluoromethoxy)nicotinic acid (**24a**, 1.05 g, 5.02 mmol, 82%) as a colorless powder. Crystallization from cyclohexane afforded the pure product as colorless needles; m.p. 82–85 °C. ^{1}H NMR (CD_3OD, 300 MHz, 25 °C): δ = 8.15 (dd, J = 4.6, 1.9 Hz, 1 H, 6-H), 7.92 (dd, J = 7.6, 1.9 Hz, 1 H, 4-H), 7.24 (dd, J = 7.6, 4.6 Hz, 1 H, 5-H) ppm. ^{13}C NMR (CD_3OD, 75 MHz, 25 °C): δ = 164.8 (COOH), 154.2 (C), 150.3 (CH), 142.2 (CH), 121.9 (CH), 120.4 (q, $^2J_{C,F}$ = 260 Hz, OCF_3), 117.6 (C) ppm. ^{19}F NMR [$(CD_3)_2CO$, 282 MHz, 25 °C]: δ = –56.7 ppm. $C_7H_4F_3NO_3$ (207.11): calcd. C 40.59, H 1.95, N 6.76; found C 40.35, H 2.03, N 6.65.

3-Amino-2-(trifluoromethoxy)pyridine (24b): Palladium (10% on charcoal, 730 mg) was added at 25 °C with stirring to a solution of 5-amino-2-chloro-6-(trifluoromethoxy)pyridine (**23b**, 1.6 g, 7.4 mmol) and ammonium formate (940 mg, 14.8 mmol, 2 equiv.) in methanol (12 mL). The reaction mixture was stirred for 16 h at 55 °C before being filtered under suction and the solvent was evaporated. The residue was partitioned between ethyl acetate (2 × 20 mL) and water (30 mL). The combined organic layers were dried with sodium sulfate prior to concentration to afford pure 3-amino-2-(trifluoromethoxy)pyridine (**23b**, 1.05 g, 5.92 mmol, 80%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 7.68 (dd, J = 4.6, 1.7 Hz, 1 H, 6-H), 7.09 (dd, J = 7.8, 1.7 Hz 1 H, 4-H), 7.02 (dd, J = 7.8, 4.6 Hz, 1 H, 5-H), 3.90 (br. s, 2 H, NH_2) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 144.6 (C), 135.7 (CH), 132.3 (C), 123.7 (CH), 122.6 (CH), 120.4 (q, $^2J_{C,F}$ = 260 Hz, OCF_3) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = –56.2 ppm. $C_6H_5F_3N_2O$ (178.11): calcd. C 40.46, H 2.83, N 15.73; found C 41.28, H 2.90, N 16.02.

2-Chloro-4-iodo-6-(trifluoromethoxy)pyridine (25): Butyllithium (1.56 M in hexanes, 9.0 mL, 13.6 mmol, 1.1 equiv.) was added dropwise at 0 °C to a solution of diisopropylamine (1.4 g, 1.9 mL, 13.6 mmol, 1.1 equiv.) in THF (20 mL). A solution of 2-chloro-5-iodo-6-(trifluoromethoxy)pyridine (**23c**, 4.0 g, 12.4 mmol, 1 equiv.) in THF (10 mL) was added dropwise at –78 °C, and the reaction mixture was stirred for 1 h at this temperature. It was then neutralized with a solution of hydrochloric acid (2 N, 10 mL), treated with a saturated aqueous sodium hydrogen carbonate solution (30 mL), and extracted with diethyl ether (3 × 20 mL). The combined organic layers were dried with sodium sulfate prior to concentration. The crude dark oil was distilled under vacuum (b.p. 104–107 °C/16 mbar) to afford pure 2-chloro-4-iodo-6-(trifluoromethoxy)pyridine (**25**, 3.20 g, 9.92 mmol, 80%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 7.66 (d, J = 1.0 Hz, 1 H, 5-H), 7.34 (d, J = 1.0 Hz, 1 H, 3-H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 155.1 (C), 149.4 (C), 130.7 (CH), 120.3 (CH), 119.1 (q, $^2J_{C,F}$ = 262 Hz, OCF_3), 108.3 (C) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = –57.0 ppm.

2-Chloro-6-(trifluoromethoxy)isonicotinic Acid (26a): Butyllithium (1.56 M in hexane, 6.0 mL, 9.3 mmol, 1 equiv.) was added dropwise at –78 °C to a solution of 2-chloro-4-iodo-6-(trifluoromethoxy)pyridine (**25**, 3.0 g, 9.3 mmol, 1 equiv.) in THF (15 mL). After 5 min at this temperature, the reaction mixture was poured onto an excess of freshly crushed dry ice before being treated with an aqueous

solution of sodium hydroxide (5%, 15 mL). The resulting aqueous layer was collected, washed with diethyl ether (10 mL) and acidified to pH 4 by dropwise addition of hydrochloric acid (6 N, 5 mL). After extraction with ethyl acetate (3 × 10 mL), the combined organic layers were dried with sodium sulfate prior to concentration to afford 2-chloro-6-(trifluoromethoxy)isonicotinic acid (**26a**, 1.60 g, 6.60 mmol, 71%) as a colorless powder. Crystallization from chloroform afforded the pure product as colorless needles; m.p. 65–68 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 10.12 (br. s, 1 H, COOH), 7.88 (d, J = 0.9 Hz, 1 H, 5-H), 7.57 (d, J = 0.9 Hz, 1 H, 3-H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 167.6 (COOH), 156.3 (C), 150.4 (C), 143.0 (C), 122.5 (CH), 120.2 (q, $^2J_{C,F}$ = 260 Hz, OCF_3), 111.5 (CH) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = –57.3 ppm. $C_7H_3ClF_3NO_3$ (241.55): calcd. C 34.81, H 1.25, N 5.80; found C 34.64, H 1.55, N 5.76.

4-Amino-2-chloro-6-(trifluoromethoxy)pyridine (26b): Butyllithium (1.56 M in hexane, 2.2 mL, 3.4 mmol, 1.1 equiv.) was added dropwise at –78 °C to a solution of 2-chloro-4-iodo-6-(trifluoromethoxy)pyridine (**25**, 1.0 g, 3.1 mmol) in THF (8 mL), followed after 10 min by a solution of benzenesulfonyl azide (0.6 g, 3.4 mmol, 1.1 equiv.) in THF (5 mL). The reaction mixture was allowed to reach 25 °C before being treated with saturated aqueous ammonium chloride (10 mL) and extracted with diethyl ether (3 × 8 mL). The combined organic layers were dried with sodium sulfate and concentrated to afford crude 4-azido-2-chloro-6-(trifluoromethoxy)pyridine as a red oil. It was then dissolved in anhydrous diethyl ether (25 mL) and added dropwise to a suspension of lithium aluminum hydride (130 mg, 3.4 mmol, 1.1 equiv.) in diethyl ether (25 mL). The reaction mixture was heated under reflux for 5 h before being treated with water (10 mL) and extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried with sodium sulfate prior to concentration. The crude product was purified by chromatography on silica gel with ethyl acetate/cyclohexane (1:9) as eluent, which afforded pure 4-amino-2-chloro-6-(trifluoromethoxy)pyridine (**26b**, 0.30 g, 1.43 mmol, 46%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 6.41 (d, J = 1.6 Hz, 1 H, 5-H), 6.07 (d, J = 1.6 Hz, 1 H, 3-H), 4.30 (br. s, 2 H, NH_2) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 156.4 (C), 155.7 (C), 148.8 (C), 118.9 (q, $^2J_{C,F}$ = 260 Hz, OCF_3), 106.5 (CH), 95.0 (CH) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = –56.8 ppm. $C_6H_4ClF_3N_2O$ (212.56): calcd. C 33.90, H 1.90, N 13.18; found C 33.56, H 2.01, N 12.87.

2-Trifluoromethoxyisonicotinicacid (27a): Palladium (10% on charcoal, 330 mg) was added at 25 °C with stirring to a solution of 2-chloro-6-(trifluoromethoxy)isonicotinic acid (**26a**, 1.1 g, 4.6 mmol) and ammonium formate (574 mg, 9.1 mmol, 2 equiv.) in methanol (8 mL). The reaction mixture was stirred for 16 h at 55 °C before being filtered under suction and the filtrate was concentrated. The residue was partitioned between ethyl acetate (2 × 15 mL) and hydrochloric acid (2 N, 20 mL). The combined organic layers were dried with sodium sulfate prior to concentration to afford pure 2-(trifluoromethoxy)isonicotinic acid (**27a**, 760 mg, 3.73 mmol, 81%) as a white powder. Crystallization from chloroform afforded the pure product as colorless needles; m.p. 149–152 °C. ^{1}H NMR (CD_3OD, 300 MHz, 25 °C): δ = 8.39 (d, J = 5.1 Hz, 1 H, 6-H), 7.77 (dd, J = 5.1, 1.0 Hz, 1 H, 5-H), 7.51 (d, J = 1.0 Hz, 1 H, 3-H) ppm. ^{13}C NMR (CD_3OD, 75 MHz, 25 °C): δ = 164.9 (COOH), 157.2 (C), 148.5 (CH), 143.3 (C), 121.8 (CH), 120.3 (q, $^2J_{C,F}$ = 260 Hz, OCF_3), 112.5 (CH) ppm. ^{19}F NMR [$(CD_3)_2CO$, 282 MHz, 25 °C]: δ = –57.6 ppm. $C_7H_4F_3NO_3$ (207.11): calcd. C 40.59, H 1.95, N 6.76; found C 40.28, H 2.21, N 6.67.

4-Amino-2-(trifluoromethoxy)pyridine (27b): Palladium (10% on charcoal, 220 mg) was added at 25 °C with stirring to a solution of 4-amino-2-chloro-6-(trifluoromethoxy)pyridine (**26b**, 600 mg, 2.8 mmol, 1 equiv.) and ammonium formate (350 mg, 5.6 mmol, 2 equiv.) in methanol (10 mL). The reaction mixture was stirred for 16 h at 55 °C before being filtered under suction, and the filtrate was concentrated. The residue was partitioned between ethyl acetate (2 × 10 mL) and an aqueous solution of sodium hydroxide (4%, 15 mL). The combined organic layers were dried with sodium sulfate prior to concentration. The crude oil was purified by chromatography on silica gel with ethyl acetate/cyclohexane (2:8) as eluent to afford pure 4-amino-2-(trifluoromethoxy)pyridine (**27b**, 390 mg, 2.21 mmol, 79%) as a colorless oil that crystallized on standing. Crystallization from cyclohexane afforded the pure product as colorless needles; m.p. 67–69 °C. ^{1}H NMR (CD_3OD, 300 MHz, 25 °C): δ = 7.74 (d, J = 5.9 Hz, 1 H, 6-H), 6.54 (dd, J = 5.9, 1.9 Hz, 1 H, 5-H), 6.30 (d, J = 1.9 Hz, 1 H, 3-H) ppm. ^{13}C NMR (CD_3OD, 75 MHz, 25 °C): δ = 160.3 (C), 158.9 (C), 148.2 (CH), 121.5 (q, $^2J_{C,F}$ = 260 Hz, OCF_3), 109.7 (CH), 97.7 (CH) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = –56.6 ppm. HRMS (ESI$^+$) for $C_6H_5F_3N_2O$: calcd. 179.042 [M + H]; found 179.043.

2-Chloro-6-(trifluoromethoxy)-5-(trimethylsilyl)pyridine (28): Butyllithium (1.56 M in hexanes, 5.7 mL, 8.9 mmol, 1.1 equiv.) was added dropwise at 0 °C to a solution of diisopropylamine (0.9 g, 1.2 mL, 8.9 mmol, 1.1 equiv.) in THF (15 mL). A solution of 2-chloro-6-(trifluoromethoxy)pyridine (**14**, 1.6 g, 8.1 mmol, 1 equiv.) in THF (5 mL) was added dropwise at –78 °C, and the reaction mixture was stirred for 2 h at this temperature. Chlorotrimethylsilane (1.0 g, 1.2 mL, 8.9 mmol, 1.1 equiv.) was then added dropwise and the mixture was allowed to reach 25 °C before being neutralized with water (20 mL) and extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried with sodium sulfate prior to concentration. The crude product was distilled under vacuum to afford pure 2-chloro-6-(trifluoromethoxy)-5-(trimethylsilyl)pyridine (**28**, 1.50 g, 5.51 mmol, 68%) as a colorless oil; b.p. 89–93 °C/14 mbar. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 7.78 (d, J = 7.6 Hz, 1 H, 3-H), 7.22 (d, J = 7.6 Hz, 1 H, 4-H), 0.34 (s, 9 H, $SiMe_3$) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 159.5 (C), 149.8 (C), 147.7 (CH), 147.3 (C), 121.6 (CH), 120.4 (q, $^2J_{C,F}$ = 260 Hz, OCF_3), –1.7 (3 × CH_3) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = –56.5 ppm.

2-Chloro-6-(trifluoromethoxy)nicotinic Acid (29a): Butyllithium (1.56 M in hexanes, 3.65 mL, 5.7 mmol, 1.1 equiv.) was added dropwise at 0 °C to a solution of 2,2,6,6-tetramethylpiperidine (0.84 g, 1.0 mL, 5.7 mmol, 1.1 equiv.) in THF (10 mL). A solution of 2-chloro-6-(trifluoromethoxy)-5-(trimethylsilyl)pyridine (**28**, 1.4 g, 5.2 mmol, 1 equiv.) in THF (5 mL) was added dropwise at –78 °C, and the reaction mixture was stirred for 2 h at this temperature. The mixture was then poured onto an excess of freshly crushed dry ice before being treated with an aqueous solution of sodium hydroxide (5%, 10 mL). The resulting aqueous layer was collected, washed with diethyl ether (10 mL), and acidified to pH 4 by dropwise addition of hydrochloric acid (6 N, 4 mL). After extraction with ethyl acetate (3 × 10 mL), the combined organic layers were dried with sodium sulfate prior to concentration. The crude oil was treated with tetrabutylammonium fluoride (1 M in THF, 5.7 mL, 5.7 mmol, 1.1 equiv.) for 20 h at 25 °C. The mixture was then neutralized by addition of hydrochloric acid (2 N, 10 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried with sodium sulfate prior to concentration to afford pure 2-chloro-6-(trifluoromethoxy)nicotinic acid (**29a**, 880 mg, 3.65 mmol, 70%) as a colorless powder. Crystallization from dichloromethane afforded the pure product as colorless needles; m.p. 135–138 °C. ^{1}H NMR (CD_3OD, 300 MHz, 25 °C): δ = 8.44 (d, J = 8.3 Hz, 1

H, 4-H), 7.21 (d, J = 8.3 Hz, 1 H, 5-H) ppm. ^{13}C NMR (CD_3OD, 75 MHz, 25 °C): δ = 164.9 (COOH), 156.1 (C), 147.9 (C), 144.7 (CH), 125.5 (C), 120.1 (q, $^2J_{C,F}$ = 260 Hz, OCF_3), 110.8 (CH) ppm. ^{19}F NMR [$(CD_3)_2CO$, 282 MHz, 25 °C]: δ = –57.9 ppm. $C_7H_3ClF_3NO_3$ (241.55): calcd. C 34.81, H 1.25, N 5.80; found C 34.70, H 1.47, N 5.53.

3-Amino-2-chloro-6-(trifluoromethoxy)pyridine (29b): Butyllithium (1.56 M in hexanes, 23.5 mL, 36.7 mmol, 1.1 equiv.) was added dropwise at 0 °C to a solution of diisopropylamine (3.7 g, 5.2 mL, 36.7 mmol, 1.1 equiv.) in THF (60 mL). A solution of 2-chloro-6-(trifluoromethoxy)-5-(trimethylsilyl)pyridine (**28**, 9.0 g, 33.4 mmol) in THF (20 mL) was added dropwise at –78 °C, followed after 3 h by a solution of benzenesulfonyl azide (6.7 g, 36.7 mmol, 1.1 equiv.) in THF (10 mL). The reaction mixture was allowed to reach 25 °C before being treated with a saturated aqueous ammonium chloride (50 mL) and extracted with diethyl ether (3 × 40 mL). The combined organic layers were dried with sodium sulfate and concentrated to afford crude 3-azido-2-chloro-6-(trifluoromethoxy)pyridine as a red oil. It was then dissolved in anhydrous diethyl ether (250 mL) and added dropwise to a suspension of lithium aluminum hydride (1.4 g, 37.0 mmol, 1.5 equiv.) in diethyl ether (250 mL). The reaction mixture was heated under reflux for 5 h before being treated with water (100 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic layers were dried with sodium sulfate prior to concentration. The crude oil was treated with tetrabutylammonium fluoride (1 M in THF, 34 mL, 33.4 mmol, 1 equiv.) for 20 h at 25 °C. The mixture was neutralized by addition of sodium hydroxide (4%, 100 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were dried with sodium sulfate prior to concentration. The crude product was purified by chromatography on silica gel with ethyl acetate/cyclohexane (5:95) as eluent, which afforded pure 3-amino-2-chloro-6-(trifluoromethoxy)pyridine (**29b**, 4.53 g, 21.4 mmol, 64%) as yellow crystals; m.p. 58–61 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 7.05 (d, J = 8.4 Hz, 1 H, 5-H), 6.78 (d, J = 8.4 Hz, 1 H, 4-H), 4.03 (br. s, 2 H, NH_2) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 146.0 (C), 138.8 (C), 132.8 (C), 125.9 (CH), 120.2 (q, $^2J_{C,F}$ = 257 Hz, OCF_3), 113.7 (CH) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = –57.2 ppm. $C_6H_4ClF_3N_2O$ (212.56): calcd. C 33.90, H 1.90, N 13.18; found C 33.32, H 2.21, N 13.27.

2-Chloro-3-iodo-6-(trifluoromethoxy)pyridine (29c): Butyllithium (1.56 M in hexanes, 1.8 mL, 2.8 mmol, 1.1 equiv.) was added dropwise at 0 °C to a solution of diisopropylamine (0.3 g, 0.4 mL, 2.8 mmol, 1.1 equiv.) in THF (6 mL). A solution of 2-chloro-6-(trifluoromethoxy)-5-(trimethylsilyl)pyridine (**28**, 0.7 g, 2.6 mmol) in THF (3 mL) was added dropwise at –78 °C, followed after 3 h by a solution of iodine (0.7 g, 2.8 mmol, 1.1 equiv.) in THF (5 mL). The mixture was then treated with saturated aqueous sodium sulfite (5 mL) and extracted with dichloromethane (3 × 5 mL). The combined organic layers were dried with sodium sulfate prior to concentration. The crude oil was treated with tetrabutylammonium fluoride (1 M in THF, 2.6 mL, 2.6 mmol, 1 equiv.) for 20 h at 25 °C. The mixture was neutralized by addition of hydrochloric acid (2 N, 5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried with sodium sulfate prior to concentration. The crude oil was purified by distillation under vacuum (50–51 °C/1 mbar) to afford 2-chloro-3-iodo-6-(trifluoromethoxy)pyridine (**29c**, 550 mg, 1.69 mmol, 65%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 8.11 (d, J = 8.3 Hz, 1 H, 4-H), 6.65 (d, J = 8.3 Hz, 1 H, 5-H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 154.3 (C), 150.9 (CH), 129.7 (C), 122.3 (C), 118.8 (q, $^2J_{C,F}$ = 260 Hz, OCF_3), 111.5 (CH) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = –57.4 ppm.

6-(Trifluoromethoxy)nicotinic Acid (30a): Palladium (10% on charcoal, 334 mg) was added at 25 °C with stirring to a solution of 2-chloro-6-(trifluoromethoxy)nicotinic acid (**29a**, 835 mg, 3.45 mmol, 1 equiv.) and ammonium formate (435 mg, 6.9 mmol, 2 equiv.) in methanol (6 mL). The reaction mixture was stirred for 16 h at 55 °C before being filtered under suction, and the filtrate was concentrated. The residue was partitioned between ethyl acetate (2 × 10 mL) and hydrochloric acid (2 N, 15 mL). The combined organic layers were dried with sodium sulfate prior to concentration to afford 6-(trifluoromethoxy)nicotinic acid (**30a**, 580 mg, 2.80 mmol, 81%) as a colorless powder. Crystallization from dichloromethane afforded the pure product as colorless needles; m.p. 118–121 °C. ^{1}H NMR (CD_3OD, 300 MHz, 25 °C): δ = 8.91 (d, J = 2.3 Hz, 1 H, 2-H), 8.48 (dd, J = 8.4, 2.3 Hz, 1 H, 4-H), 7.24 (d, J = 8.4 Hz, 1 H, 5-H) ppm. ^{13}C NMR (CD_3OD, 75 MHz, 25 °C): δ = 165.5 (COOH), 159.0 (C), 150.3 (C), 149.5 (CH), 141.8 (CH), 123.7 (q, $^2J_{C,F}$ = 260 Hz, OCF_3), 112.1 (CH) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = –57.0 ppm. $C_7H_4F_3NO_3$ (207.11): calcd. C 40.59, H 1.95, N 6.76; found C 40.40, H 2.20, N 6.88.

3-Amino-6-(trifluoromethoxy)pyridine (30b): Palladium (10% on charcoal, 700 mg) was added at 25 °C with stirring to a solution of 3-amino-2-chloro-6-(trifluoromethoxy)pyridine (**29b**, 1.3 g, 6.1 mmol, 1 equiv.) and ammonium formate (770 mg, 12.1 mmol, 2 equiv.) in methanol (20 mL). The reaction mixture was stirred for 16 h at 55 °C before being filtered under suction, and the filtrate was concentrated. The residue was partitioned between ethyl acetate (2 × 30 mL) and an aqueous solution of sodium hydroxide (4%, 30 mL). The combined organic layers were dried with sodium sulfate prior to concentration to afford pure 3-amino-6-(trifluoromethoxy)pyridine (**30b**, 920 mg, 5.18 mmol, 85%) as yellow crystals. Crystallization from cyclohexane afforded the pure product as colorless needles; m.p. 31–33 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 7.69 (d, J = 2.9 Hz, 1 H, 2-H), 7.01 (dd, J = 8.6, 2.9 Hz, 1 H, 4-H), 6.79 (d, J = 8.6 Hz, 1 H, 5-H), 3.55 (br. s, 2 H, NH_2) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 148.8 (C), 141.6 (C), 133.9 (CH), 125.8 (CH), 120.3 (q, $^2J_{C,F}$ = 257 Hz, OCF_3), 114.3 (CH) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = –57.7 ppm. $C_6H_5F_3N_2O$ (178.11): calcd. C 40.46, H 2.83, N 15.73; found C 40.00, H 2.92, N 15.37.

2-Chloro-3-(trifluoromethoxy)-4-(trimethylsilyl)pyridine (31d): Butyllithium (1.14 M in hexanes, 4.9 mL, 5.6 mmol, 1.1 equiv.) was added dropwise at 0 °C to a solution of diisopropylamine (0.6 g, 0.8 mL, 5.6 mmol, 1.1 equiv.) in THF (10 mL). A solution of 2-chloro-3-(trifluoromethoxy)pyridine (**15**, 1.0 g, 5.1 mmol, 1 equiv.) in THF (4 mL) was added dropwise at –78 °C, and the reaction mixture was stirred for 2 h at this temperature. Chlorotrimethylsilane (0.6 g, 0.7 mL, 5.6 mmol, 1.1 equiv.) was then added dropwise and the mixture was allowed to reach 25 °C before being neutralized with water (15 mL) and extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried with sodium sulfate prior to concentration. The crude product was distilled under vacuum to afford 2-chloro-3-(trifluoromethoxy)-4-(trimethylsilyl)pyridine (**31d**, 950 mg, 3.52 mmol, 69%) as a colorless oil; b.p. 93–96 °C/16 mbar. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 8.32 (d, J = 4.7 Hz, 1 H, 6-H), 7.36 (d, J = 4.7 Hz, 1 H, 5-H), 0.39 (s, 9 H, $SiMe_3$) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 146.8 (CH), 145.9 (C), 144.4 (C), 128.8 (CH), 127.2 (C), 120.5 (q, $^2J_{C,F}$ = 260 Hz, OCF_3), –0.8 (3 × CH_3) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = –57.6 ppm.

6-Chloro-5-(trifluoromethoxy)picolinic Acid (32): Butyllithium (1.54 M in hexanes, 1.3 mL, 2.0 mmol, 1.1 equiv.) was added dropwise at 0 °C to a solution of 2,2,6,6-tetramethylpiperidine (0.3 g,

0.35 mL, 2.0 mmol, 1.1 equiv.) in THF (3 mL). A solution of 2-chloro-3-(trifluoromethoxy)-4-(trimethylsilyl)pyridine (**31d**, 500 mg, 1.9 mmol, 1 equiv.) in THF (1 mL) was added dropwise at –78 °C, and the reaction mixture was stirred for 2 h at this temperature. The mixture was then poured onto an excess of freshly crushed dry ice before being treated with an aqueous solution of sodium hydroxide (5%, 4 mL). The resulting aqueous layer was collected, washed with diethyl ether (3 mL), and acidified to pH 4 by dropwise addition of hydrochloric acid (6 N, 2 mL). After extraction with ethyl acetate (3 × 3 mL), the combined organic layers were dried with sodium sulfate prior to concentration. The crude oil was treated with tetrabutylammonium fluoride (1 M in THF, 2.0 mL, 2.0 mmol, 1.1 equiv.) for 20 h at 25 °C. The mixture was neutralized by addition of hydrochloric acid (2 N, 4 mL) and extracted with ethyl acetate (3 × 3 mL). The combined organic layers were dried with sodium sulfate prior to concentration to afford pure 6-chloro-5-(trifluoromethoxy)picolinic acid (**32**, 310 mg, 1.27 mmol, 67%) as a colorless powder. Crystallization from heptanes afforded the pure product as colorless needles; m.p. 99–102 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 8.44 (br. s, 1 H, COOH), 8.16 (d, J = 8.3 Hz, 1 H, 3-H), 7.79 (dq, J = 8.3, 1.4 Hz, 1 H, 4-H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 163.4 (COOH), 145.5 (C), 144.0 (C), 143.9 (C), 130.8 (CH), 124.7 (CH), 120.2 (q, $^2J_{C,F}$ = 263 Hz, OCF_3) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = –58.7 ppm. $C_7H_3ClF_3NO_3$ (241.55): calcd. C 34.81, H 1.25, N 5.80; found C 34.56, H 1.49, N 5.47.

5-(Trifluoromethoxy)picolinic Acid (33a)

Procedure A: Palladium (10% on charcoal, 140 mg) was added at 25 °C with stirring to a solution of 6-chloro-5-(trifluoromethoxy)-picolinic acid (**32**, 300 mg, 1.25 mmol, 1 equiv.) and ammonium formate (160 mg, 2.5 mmol, 2 equiv.) in methanol (4 mL). The reaction mixture was stirred for 16 h at 55 °C before being filtered under suction, and the filtrate was concentrated. The residue was partitioned between ethyl acetate (2 × 5 mL) and hydrochloric acid (2 N, 8 mL). The combined organic layers were dried with sodium sulfate prior to concentration to afford pure 5-(trifluoromethoxy)-picolinic acid (**33a**, 207 mg, 1.00 mmol, 80%) as a white powder.

Procedure B: Butyllithium (1.56 M in hexanes, 5.5 mL, 8.3 mmol, 1 equiv.) was added dropwise at –100 °C to a solution of 2-bromo-5-(trifluoromethoxy)pyridine (**33d**, 2.0 g, 8.3 mmol) in dry toluene (15 mL). After 2 h at –78 °C, the mixture was poured onto an excess of freshly crushed dry ice before being treated with an aqueous solution of sodium hydroxide (5%, 15 mL). The resulting aqueous layer was collected, washed with diethyl ether (10 mL), and acidified to pH 4 by dropwise addition of hydrochloric acid (6 N, 4 mL) before being extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried with sodium sulfate and concentrated to afford pure 5-(trifluoromethoxy)picolinic acid (**33a**, 1.0 g, 4.98 mmol, 60%) as a colorless powder. Crystallization from a mixture of ethyl acetate and cyclohexane (1:1) afforded the pure product as colorless needles; m.p. 123–125 °C. ^{1}H NMR (CD_3OD, 300 MHz, 25 °C): δ = 8.56 (d, J = 1.2 Hz, 1 H, 6-H), 8.19 (d, J = 8.6 Hz, 1 H, 3-H), 7.87 (dd, J = 8.6, 1.2 Hz, 1 H, 4-H) ppm. ^{13}C NMR (CD_3OD, 75 MHz, 25 °C): δ = 165.0 (COOH), 148.3 (C), 146.5 (C), 141.8 (CH), 129.2 (CH), 126.3 (CH), 120.3 (q, $^2J_{C,F}$ = 259 Hz, OCF_3) ppm. ^{19}F NMR [$(CD_3)_2CO$, 282 MHz, 25 °C]: δ = –59.3 ppm. $C_7H_4F_3NO_3$ (207.11): calcd. C 40.59, H 1.95, N 6.76; found C 40.34, H 2.21, N 6.71.

2-Amino-5-(trifluoromethoxy)pyridine (33b): 2-Chloro-5-(trifluoromethoxy)pyridine (**3**, 1.0 g, 5.0 mmol), benzophenone imine (1.09 g, 6.0 mmol, 1.2 equiv.), *t*BuONa (0.72 g, 7.5 mmol, 1.5 equiv.), DPEphos (0.03 g, 0.05 mmol, 0.01 equiv.), and Pd_2dba_3 (0.07 g, 0.1 mmol, 0.02 equiv.) were introduced into dry toluene (15 mL) and the reaction mixture was heated at 80 °C and vigorously stirred for 2 h. GC monitoring indicated 100% conversion. The mixture was allowed to cool to ambient temperature before being filtered through Celite and washed with ethyl acetate. The filtrate was poured onto an aqueous solution of citric acid (10%, 30 mL) and the reaction mixture was then vigorously stirred for 16 h at room temperature. GC monitoring of the organic layer indicated disappearance of starting reagent and formation of diphenyl ketone. The aqueous layer was adjusted to pH 9–10 with sodium hydroxide (5%, 40 mL) and extracted with ethyl acetate (5 × 20 mL). The combined organic layers were dried with sodium sulfate prior to concentration to afford a crude yellow powder. Crystallization from hexane provided pure 2-amino-5-(trifluoromethoxy)pyridine (**33b**, 0.36 g, 2.0 mmol, 40%) as colorless needles; m.p. 71–73 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 8.01 (d, J = 2.6 Hz, 1 H, 6-H), 7.34 (dd, J = 2.6, 8.9 Hz, 1 H, 4-H), 6.50 (d, J = 8.9 Hz, 1 H, 3-H), 4.59 (br. s, 2 H, NH_2) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 157.1 (C), 141.4 (CH), 138.7 (C), 131.6 (CH), 120.6 (q, $^2J_{C,F}$ = 256 Hz, OCF_3), 108.7 (CH) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = –58.9 ppm. $C_6H_5F_3N_2O$ (178.11): calcd. C 40.46, H 2.83, N 15.73; found C 40.46, H 2.90, N 16.02.

2-Iodo-5-(trifluoromethoxy)pyridine (33c): A suspension of 2-chloro-5-(trifluoromethoxy)pyridine (**3**, 9.3 g, 47.0 mmol), chlorotrimethylsilane (5.1 g, 6.1 mL, 47.0 mmol, 1 equiv.), and sodium iodide (21.3 g, 142.0 mmol, 3 equiv.) in propionitrile (35 mL) was heated under reflux for 24 h. GC monitoring indicated 100% conversion. The reaction mixture was neutralized by addition of distilled water (100 mL) before being extracted with diethyl ether (3 × 40 mL). The combined organic layers were washed with saturated aqueous sodium sulfite (30 mL) and dried with sodium sulfate prior to concentration. The crude dark oil was distilled under vacuum (90–93 °C/26 mbar) to afford pure 2-iodo-4-(trifluoromethoxy)pyridine (**33c**, 6.68 g, 23.2 mmol, 49%) as a colorless oil that crystallized on standing. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 8.26 (d, J = 2.6 Hz, 1 H, 6-H), 7.69 (d, J = 8.6 Hz, 1 H, 3-H), 7.16 (dd, J = 8.6, 2.6 Hz, 1 H, 4-H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 146.4 (C), 143.9 (CH), 135.7 (CH), 130.3 (CH), 120.2 (q, $^2J_{C,F}$ = 259 Hz, OCF_3), 114.2 (C) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = –58.9 ppm.

2-Bromo-5-(trifluoromethoxy)pyridine (33d): A solution of 2-chloro-5-(trifluoromethoxy)pyridine (**3**, 7.0 g, 35.4 mmol) and bromotrimethylsilane (10.8 g, 9.3 mL, 70.8 mmol, 2 equiv.) in propionitrile (35 mL) was heated under reflux for 24 h. GC monitoring indicated almost 90% conversion. The mixture was distilled in vacuo to afford pure 2-bromo-4-(trifluoromethoxy)pyridine (**33d**, 7.0 g, 28.7 mmol, 81%) as a colorless oil; b.p. 63–66 °C/14 mbar. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 8.27 (d, J = 2.8 Hz, 1 H, 6-H), 7.49 (d, J = 8.7 Hz, 1 H, 3-H), 7.37 (dd, J = 8.7, 2.8 Hz, 1 H, 4-H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 143.8 (C), 141.4 (CH), 137.5 (C), 129.3 (CH), 127.1 (CH), 119.4 (q, $^2J_{C,F}$ = 260 Hz, OCF_3) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = –58.8 ppm. $C_6H_3BrF_3NO$ (241.99): calcd. C 29.78, H 1.25, N 5.79; found C 29.96, H 1.41, N 5.64.

2-Chloro-3-(trifluoromethoxy)isonicotinic Acid (31a): Butyllithium (1.56 M in hexanes, 7.1 mL, 11.1 mmol, 1.1 equiv.) was added dropwise at 0 °C to a solution of diisopropylamine (1.2 g, 1.6 mL, 11.1 mmol, 1.1 equiv.) in THF (15 mL). A solution of 2-chloro-3-(trifluoromethoxy)pyridine (**15**, 2.0 g, 10.1 mmol, 1 equiv.) in THF (5 mL) was added dropwise at –78 °C, and the reaction mixture was stirred for 2 h at this temperature. The mixture was then

poured onto an excess of freshly crushed dry ice before being treated with an aqueous solution of sodium hydroxide (5%, 20 mL). The resulting aqueous layer was collected, washed with diethyl ether (10 mL), and acidified to pH 4 by dropwise addition of hydrochloric acid (6 N, 4 mL). After extraction with ethyl acetate (3 × 15 mL), the combined organic layers were dried with sodium sulfate prior to concentration to afford pure 2-chloro-3-(trifluoromethoxy)isonicotinic acid (**31a**, 1.70 g, 7.07 mmol, 70%) as a white powder. Crystallization from chloroform afforded the pure product as colorless needles; m.p. 157–159 °C. ^{1}H NMR (CD_3OD, 300 MHz, 25 °C): δ = 8.41 (d, J = 4.9 Hz, 1 H, 6-H), 7.70 (d, J = 4.9 Hz, 1 H, 5-H) ppm. ^{13}C NMR (CD_3OD, 75 MHz, 25 °C): δ = 163.8 (COOH), 148.4 (CH), 146.7 (C), 138.9 (C), 137.8 (C), 123.9 (CH), 120.3 (q, $^2J_{C,F}$ = 260 Hz, OCF_3) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = –57.3 ppm. HRMS (APCI+) for $C_6H_3ClF_3NO$: calcd. 197.9928 [M – CO_2]; found 197.9956. $C_7H_3ClF_3NO_3$ (241.55): calcd. C 34.81, H 1.25, N 5.80; found C 34.38, H 1.46, N 5.83.

4-Amino-2-chloro-3-(trifluoromethoxy)pyridine (31b): Butyllithium (1.56 M in hexanes, 7.1 mL, 11.1 mmol, 1.1 equiv.) was added dropwise at 0 °C to a solution of diisopropylamine (1.2 g, 1.6 mL, 11.1 mmol, 1.1 equiv.) in THF (15 mL). A solution of 2-chloro-3-(trifluoromethoxy)pyridine (**15**, 2.0 g, 10.1 mmol, 1 equiv.) in THF (5 mL) was added dropwise at –78 °C, followed after 2 h by a solution of benzenesulfonyl azide (2.8 g, 15.2 mmol, 1.5 equiv.) in THF (5 mL). The reaction mixture was allowed to reach 25 °C before being treated with saturated aqueous ammonium chloride (20 mL) and extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried with sodium sulfate and concentrated to afford crude 4-azido-2-chloro-3-(trifluoromethoxy)pyridine as a red oil. It was then dissolved in anhydrous diethyl ether (90 mL) and added dropwise to a suspension of lithium aluminum hydride (430 mg, 11.2 mmol, 1.1 equiv.) in diethyl ether (90 mL). The reaction mixture was heated under reflux for 5 h before being treated with water (100 mL) and extracted with diethyl ether (3 × 30 mL). The combined organic layers were dried with sodium sulfate prior to concentration. The crude product was purified by chromatography on silica gel with ethyl acetate/cyclohexane (1:4) as eluent, which afforded pure 4-amino-2-chloro-3-(trifluoromethoxy)pyridine (**31b**, 1.60 g, 7.57 mmol, 75%) as yellow crystals. Crystallization from a mixture of 1% ethyl acetate in cyclohexane afforded the pure product as colorless needles; m.p. 54–56 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 7.91 (d, J = 5.5 Hz, 1 H, 6-H), 6.60 (d, J = 5.5 Hz, 1 H, 5-H), 4.57 (br. s, 2 H, NH_2) ppm. ^{13}C NMR (CD_3OD, 75 MHz, 25 °C): δ = 152.3 (C), 147.5 (CH), 146.7 (C), 129.0 (C), 122.8 (q, $^2J_{C,F}$ = 260 Hz, OCF_3), 112.0 (CH) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = –57.0 ppm. HRMS (ESI+) for $C_6H_5ClF_3N_2O$: calcd. 213.0037 [M + H]; found 213.0051. $C_6H_4ClF_3N_2O$ (212.56): calcd. C 33.90, H 1.90, N 13.18; found C 33.45, H 2.10, N 13.40.

2-Chloro-4-iodo-3-(trifluoromethoxy)pyridine (31c): Butyllithium (1.56 M in hexanes, 3.5 mL, 5.5 mmol, 1.1 equiv.) was added dropwise at 0 °C to a solution of diisopropylamine (0.6 g, 0.8 mL, 5.5 mmol, 1.1 equiv.) in THF (8 mL). A solution of 2-chloro-3-(trifluoromethoxy)pyridine (**15**, 1.0 g, 5.0 mmol, 1 equiv.) in THF (3 mL) was added dropwise at –78 °C, followed after 2 h by a solution of iodine (1.3 g, 7.5 mmol, 1.5 equiv.) in THF (5 mL). The reaction mixture was allowed to reach 25 °C before being treated with a saturated aqueous sodium sulfite (10 mL) and extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried with sodium sulfate prior to concentration. The crude dark oil was distilled under vacuum (b.p. 78–81 °C/16 mbar) to afford pure 2-chloro-4-iodo-3-(trifluoromethoxy)pyridine (**31c**, 1.25 g, 3.90 mmol, 78%), which crystallized as colorless needles on standing; m.p. 40–43 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 7.88 (d, J = 5.0 Hz, 1 H, 6-H), 7.69 (d, J = 5.0 Hz, 1 H, 5-H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 153.4 (C), 147.7 (CH), 145.8 (C), 144.1 (C), 134.4 (CH), 120.7 (q, $^2J_{C,F}$ = 260 Hz, OCF_3) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = –58.4 ppm.

3-(Trifluoromethoxy)isonicotinic Acid (34a): Palladium (10% on charcoal, 200 mg) was added at 25 °C with stirring to a solution of 2-chloro-3-(trifluoromethoxy)isonicotinic acid (**31b**, 660 mg, 2.7 mmol) and ammonium formate (290 mg, 4.6 mmol, 1.7 equiv.) in methanol (5 mL). The reaction mixture was stirred for 16 h at 55 °C before being filtered under suction, and the filtrate was concentrated. The residue was partitioned between ethyl acetate (2 × 10 mL) and hydrochloric acid (2.0 M, 15 mL). The combined organic layers were dried with sodium sulfate prior to concentration to afford 3-(trifluoromethoxy)isonicotinic acid (**34a**, 450 mg, 2.18 mmol, 81%) as a white powder. Crystallization from diisopropyl ether afforded the pure product as colorless needles; m.p. 181–183 °C. ^{1}H NMR (CD_3OD, 300 MHz, 25 °C): δ = 8.62 (d, J = 4.9 Hz, 1 H, 6-H), 8.61 (s, 1 H, 2-H), 7.80 (d, J = 4.9 Hz, 1 H, 5-H) ppm. ^{13}C NMR (CD_3OD, 75 MHz, 25 °C): δ = 165.5 (COOH), 150.3 (CH), 145.8 (CH), 144.5 (C), 135.5 (C), 126.1 (CH), 121.7 (q, $^2J_{C,F}$ = 258 Hz, OCF_3) ppm. ^{19}F NMR [$(CD_3)_2CO$, 282 MHz, 25 °C]: δ = –59.1 ppm. HRMS (ESI negative) for $C_7H_3F_3NO_3$: calcd. 206.0060 [M – H]; found 206.0033.

4-Amino-3-(trifluoromethoxy)pyridine (34b): Palladium (10% on charcoal, 470 mg) was added at 25 °C with stirring to a solution of 4-amino-2-chloro-3-(trifluoromethoxy)pyridine (**31c**, 1.5 g, 7.0 mmol) and ammonium formate (880 mg, 14.0 mmol, 2 equiv.) in methanol (12 mL). The reaction mixture was stirred for 16 h at 55 °C before being filtered under suction and the solvent was evaporated. The residue was partitioned between ethyl acetate (2 × 20 mL) and water (30 mL). The combined organic layers were dried with sodium sulfate prior to concentration. The crude yellow oil was distilled under vacuum to afford pure 4-amino-3-(trifluoromethoxy)pyridine (**34b**, 997 mg, 5.60 mmol, 80%) as a colorless oil; b.p 110–114 °C/14 mbar. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 8.19 (s, 1 H, 2-H), 8.05 (d, J = 5.5 Hz, 1 H, 6-H), 6.59 (d, J = 5.5 Hz, 1 H, 5-H), 4.41 (br. s, 2 H, NH_2) ppm. ^{13}C NMR (CD_3OD, 75 MHz, 25 °C): δ = 148.5 (C), 147.1 (CH), 141.7 (CH), 132.9 (C), 120.8 (q, $^2J_{C,F}$ = 259 Hz, OCF_3), 110.4 (CH) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = –58.7 ppm. $C_6H_5F_3N_2O$ (178.11): calcd. C 40.46, H 2.83, N 15.73; found C 40.28, H 2.74, N 15.94.

2-Bromo-3-(trifluoromethoxy)pyridine (19): A solution of 2-chloro-3-(trifluoromethoxy)pyridine (**15**, 4.0 g, 20.2 mmol) and bromotrimethylsilane (6.3 g, 5.4 mL, 40.4 mmol, 2 equiv.) in propionitrile (20 mL) was heated under reflux for 24 h. GC monitoring indicated almost 90% conversion. The mixture was distilled in vacuo to afford pure 2-bromo-3-(trifluoromethoxy)pyridine (**19**, 3.90 g, 16.1 mmol, 80%) as a colorless oil; b.p. 63–67 °C/13 mbar. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 8.26 (dd, J = 4.6, 1.2 Hz, 1 H, 6-H), 7.54 (d, J = 8.1, 1.2 Hz, 1 H, 4-H), 7.27 (dd, J = 8.1, 4.6 Hz, 1 H, 5-H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 147.7 (CH), 144.0 (C), 136.1 (C), 129.9 (CH), 123.7 (CH), 120.3 (q, $^2J_{C,F}$ = 260 Hz, OCF_3) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = –58.0 ppm. $C_6H_3BrF_3NO$ (241.99): calcd. C 29.78, H 1.25, N 5.79; found C 29.96, H 1.41, N 5.64.

3-(Trifluoromethoxy)picolinic Acid (35a)

Procedure A: Butyllithium (1.56 M in hexanes, 5.5 mL, 8.3 mmol, 1 equiv.) was added dropwise at –100 °C to a solution of 2-bromo-3-(trifluoromethoxy)pyridine (**19**, 2.0 g, 8.3 mmol) in dry toluene (15 mL). After 2 h at –78 °C, the mixture was poured onto an ex-

cess of freshly crushed dry ice before being treated with an aqueous solution of sodium hydroxide (5%, 15 mL). The resulting aqueous layer was collected, washed with diethyl ether (10 mL), and acidified to pH 4 by dropwise addition of hydrochloric acid (6 N, 4 mL) before being extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried with sodium sulfate and concentrated to afford pure 3-(trifluoromethoxy)picolinic acid (**35a**, 1.10 g, 5.31 mmol, 64%) as a colorless powder. Crystallization from diisopropyl ether afforded the pure product as colorless needles; m.p. 84–87 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 8.63 (d, J = 4.5 Hz, 1 H, 6-H), 7.85 (d, J = 8.3 Hz, 1 H, 4-H), 7.71 (dd, J = 8.3, 4.5 Hz, 1 H, 5-H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 160.4 (COOH), 146.4 (C), 146.2 (CH), 139.1 (C), 132.3 (CH), 129.3 (CH), 120.3 (q, $^2J_{C,F}$ = 260 Hz, OCF_3) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = –58.6 ppm. $C_7H_4F_3NO_3$ (207.11): calcd. C 40.59, H 1.95, N 6.76; found C 40.21, H 2.17, N 6.97.

Procedure B: Palladium (10% on charcoal, 280 mg) was added at 25 °C with stirring to a solution of 6-chloro-3-(trifluoromethoxy)-picolinic acid (**38**, 1.0 g, 4.1 mmol) and ammonium formate (520 mg, 8.2 mmol, 2 equiv.) in methanol (8 mL). The reaction mixture was stirred for 16 h at 55 °C before being filtered under suction, and the filtrate was concentrated. The residue was partitioned between ethyl acetate (2 × 12 mL) and hydrochloric acid (2.0 M, 20 mL). The combined organic layers were dried with sodium sulfate prior to concentration to afford 3-(trifluoromethoxy)picolinic acid (**35a**, 690 mg, 3.3 mmol, 80%) as a white powder.

2-Amino-3-(trifluoromethoxy)pyridine (35b): 2-Chloro-3-(trifluoromethoxy)pyridine (**15**, 1.0 g, 5.0 mmol), benzophenone imine (1.1 g, 6.0 mmol, 1.2 equiv.), *t*BuOK (0.85 g, 7.5 mmol, 1.5 equiv.), DPEphos (0.03 g, 0.05 mmol, 0.01 equiv.), and Pd_2dba_3 (0.07 g, 0.1 mmol, 0.02 equiv.) were introduced into dry toluene (15 mL) and the reaction mixture was heated at 70 °C and vigorously stirred for 2 h. GC monitoring indicated 100% conversion. The mixture was allowed to cool to ambient temperature before being filtered through Celite and washed with ethyl acetate. The filtrate was poured onto an aqueous solution of citric acid (10%, 20 mL) and the reaction mixture was then vigorously stirred for 16 h at room temperature. GC monitoring of the organic phase indicated disappearance of starting reagent and formation of diphenyl ketone. The aqueous layer was adjusted to pH 9–10 with sodium hydroxide (5%, 30 mL) and extracted with ethyl acetate (5 × 20 mL). The combined organic layers were dried with sodium sulfate prior to concentration to afford a crude brown powder. Crystallization from cyclohexane provided pure 2-amino-3-(trifluoromethoxy)pyridine (**35b**, 0.40 g, 2.20 mmol, 44%) as colorless needles; m.p. 69–71 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 8.00 (dd, J = 4.9, 1.4 Hz, 1 H, 6-H), 7.38 (dd, J = 8.0, 1.4 Hz, 1 H, 4-H), 6.68 (dd, J = 8.0, 4.9 Hz, 1 H, 5-H), 4.76 (br. s, 2 H, NH_2) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 151.8 (C), 146.2 (CH), 133.0 (C), 128.4 (CH), 120.9 (q, $^2J_{C,F}$ = 259 Hz, OCF_3), 113.9 (CH) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = –58.6 ppm. HRMS (ESI+) for $C_6H_5F_3N_2O$: calcd. 179.041 [M + H]; found 179.043.

2-Chloro-5-(trifluoromethoxy)isonicotinic Acid (36a): Butyllithium (1.56 M in hexanes, 1.8 mL, 2.8 mmol, 1 equiv.) was added dropwise at 0 °C to a solution of diisopropylamine (0.28 g, 0.38 mL, 2.8 mmol, 1.1 equiv.) in THF (4 mL). A solution of 2-chloro-5-(trifluoromethoxy)pyridine (**3**, 0.50 g, 2.5 mmol, 1 equiv.) in THF (2 mL) was added dropwise at –78 °C, and the reaction mixture was stirred for 2 h at this temperature. The mixture was then poured onto an excess of freshly crushed dry ice and allowed to reach 25 °C before being treated with an aqueous solution of sodium hydroxide (5%, 5 mL). The resulting aqueous layer was collected, washed with diethyl ether (2 mL), and acidified to pH 4 by dropwise addition of hydrochloric acid (6 N, 1 mL) before being extracted with ethyl acetate (3 × 3 mL). The combined organic layers were dried with sodium sulfate and the solvents were evaporated to afford pure 2-chloro-5-(trifluoromethoxy)isonicotinic acid (**36a**, 0.46 g, 1.87 mmol, 75%) as a colorless powder. Crystallization from chloroform afforded the pure product as colorless needles; m.p. 150–152 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 8.45 (s, 1 H, 6-H), 7.84 (s, 1 H, 3-H), 3.85 (br. s, 1 H, COOH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 164.7 (COOH), 150.3 (CH), 144.8 (CH), 142.5 (C), 134.9 (C), 126.0 (C), 120.2 (q, $^2J_{C,F}$ = 260 Hz, OCF_3) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = –57.9 ppm. MS (APCI+): m/z = 241 $[M]^+$, 197 $[M - CO_2]^+$. $C_7H_3ClF_3NO_3$ (241.55): calcd. C 34.81, H 1.25, N 5.80; found C 34.75, H 1.53, N 5.77.

2-Chloro-4-iodo-5-(trifluoromethoxy)pyridine (36b): Butyllithium (1.56 M in hexanes, 14.2 mL, 22.2 mmol, 1.1 equiv.) was added dropwise at 0 °C to a solution of diisopropylamine (2.2 g, 3.1 mL, 22.2 mmol, 1.1 equiv.) in THF (35 mL). A solution of 2-chloro-5-(trifluoromethoxy)pyridine (**3**, 4.0 g, 20.2 mmol, 1 equiv.) in THF (10 mL) was added dropwise at –78 °C, followed after 2 h by a solution of iodine (5.7 g, 22.2 mmol, 1.1 equiv.) in THF (10 mL). The reaction mixture was allowed to reach 25 °C before being treated with a saturated aqueous sodium sulfite (30 mL) and extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried with sodium sulfate prior to concentration. The crude dark oil was distilled under vacuum (b.p. 95–97 °C/16 mbar) to afford pure 2-chloro-4-iodo-5-(trifluoromethoxy)pyridine (**36b**, 5.80 g, 18.0 mmol, 89%), which on standing crystallized as colorless needles; m.p. 85–87 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 8.17 (s, 1 H, 6-H), 7.80 (s, 1 H, 3-H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 149.4 (C), 146.6 (C), 141.3 (CH), 134.9 (CH), 120.3 (q, $^2J_{C,F}$ = 260 Hz, OCF_3), 103.5 (C) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = –58.0 ppm.

2-Chloro-5-(trifluoromethoxy)-4-(trimethylsilyl)pyridine (37): Butyllithium (1.56 M in hexanes, 17.8 mL, 27.8 mmol, 1.1 equiv.) was added dropwise at 0 °C to a solution of diisopropylamine (2.8 g, 3.9 mL, 27.8 mmol, 1.1 equiv.) in THF (40 mL). A solution of 2-chloro-5-(trifluoromethoxy)pyridine (**3**, 5.0 g, 25.3 mmol, 1 equiv.) in THF (10 mL) was added dropwise at –78 °C, and the reaction mixture was stirred for 2 h at this temperature. Chlorotrimethylsilane (3.0 g, 3.5 mL, 27.8 mmol, 1.1 equiv.) was then added dropwise and the mixture was allowed to reach 25 °C before being neutralized with water (40 mL) and extracted with diethyl ether (3 × 15 mL). The combined organic layers were dried with sodium sulfate prior to concentration. The crude product was distilled under vacuum to afford pure 2-chloro-5-(trifluoromethoxy)-4-(trimethylsilyl)pyridine (**37**, 6.25 g, 23.2 mmol, 92%) as a colorless oil; b.p. 96–98 °C/14 mbar. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 8.20 (s, 1 H, 6-H), 7.28 (s, 1 H, 5-H), 0.26 (s, 9 H, $SiMe_3$) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 150.6 (C), 137.8 (CH), 133.4 (C), 132.0 (CH), 124.0 (C), 120.1 (q, $^2J_{C,F}$ = 260 Hz, OCF_3), –1.6 (3 × CH_3) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = –57.9 ppm.

6-Chloro-3-(trifluoromethoxy)picolinic Acid (38): Butyllithium (1.56 M in hexanes, 13.2 mL, 20.5 mmol, 1.1 equiv.) was added dropwise at 0 °C to a solution of diisopropylamine (2.1 g, 2.9 mL, 20.5 mmol, 1.1 equiv.) in THF (30 mL). A solution of 2-chloro-5-(trifluoromethoxy)-4-trimethylsilylpyridine (**37**, 5.0 g, 18.6 mmol) in THF (10 mL) was added dropwise at –78 °C, and the reaction mixture was stirred for 3 h at this temperature. The mixture was then poured onto an excess of freshly crushed dry ice and allowed

to reach 25 °C before being treated with an aqueous solution of sodium hydroxide (5%, 30 mL). The resulting aqueous layer was collected, washed with diethyl ether (10 mL), and acidified to pH 4 by dropwise addition of hydrochloric acid (6 N, 10 mL) before being extracted with ethyl acetate (3 × 15 mL). The combined organic layers were dried with sodium sulfate and the solvents were evaporated. Crystallization of the residue from chloroform afforded colorless needles of pure 6-chloro-3-(trifluoromethoxy)picolinic acid (**38**, 2.72 g, 11.3 mmol, 61%); m.p. 93–96 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 7.72 (dq, J = 8.7, 1.3 Hz, 1 H, 4-H), 7.58 (d, J = 8.7 Hz, 1 H, 5-H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 161.4 (COOH), 148.1 (C), 145.1 (C), 139.7 (C), 134.7 (CH), 130.0 (CH), 120.1 (q, $^2J_{C,F}$ = 261 Hz, OCF_3) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = –58.1 ppm. HRMS (ESI negative) for $C_7H_3ClF_3NO_3$: calcd. 239.966 [M – H]; found 239.967.

2-Chloro-6-iodo-5-(trifluoromethoxy)pyridine (39): A solution of LDA [diisopropylamine (0.6 g, 0.9 mL, 6.2 mmol, 2 equiv.) and butyllithium (1.56 M in hexanes, 4.0 mL, 6.2 mmol, 1.1 equiv.) in THF (6 mL)] was added dropwise at –78 °C to a solution of 2-chloro-4-iodo-5-(trifluoromethoxy)pyridine (**36b**, 1.0 g, 3.1 mmol) in THF (6 mL) over a period of 20 min and the reaction mixture was further stirred for 1 h at this temperature. It was then hydrolyzed with an aqueous solution of hydrochloric acid (5%, 5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried with sodium sulfate and the solvents were evaporated. The crude oil was purified by distillation under vacuum (b.p. 96–100 °C/16 mbar) to afford a 1:4 mixture (0.50 g, 1.55 mmol, 50%) of 2-chloro-4-iodo-5-(trifluoromethoxy)pyridine (**36b**) and 2-chloro-6-iodo-5-(trifluoromethoxy)pyridine (**39**). The mixture was dissolved in THF (4 mL), and BuLi (1.56 M in hexanes, 0.2 mL, 0.31 mmol, 0.2 equiv.) was added dropwise at –78 °C. After 10 min at this temperature, the mixture was neutralized with an aqueous solution of hydrochloric acid (5%, 5 mL) before being extracted with diethyl ether (3 × 5 mL). The combined organic layers were dried with sodium sulfate and the solvents were evaporated. The crude oil was purified by distillation under vacuum (b.p. 98–102 °C/16 mbar) to afford pure 2-chloro-6-iodo-5-(trifluoromethoxy)pyridine (**39**, 0.30 g, 0.93 mmol, 60% in relation to the previous mixture, 30% overall yield) as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 7.47 (d, J = 8.4 Hz, 1 H, 4-H), 7.33 (d, J = 8.4 Hz, 1 H, 3-H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 147.2 (C), 145.7 (C), 128.9 (CH), 123.2 (CH), 119.8 (q, $^2J_{C,F}$ = 260 Hz, OCF_3), 111.4 (C) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = –57.8 ppm.

2-Chloro-4-(trifluoromethoxy)nicotinic Acid (40): Butyllithium (1.42 M in hexanes, 6.8 mL, 9.7 mmol, 1.1 equiv.) was added dropwise at 0 °C to a solution of diisopropylamine (1.0 g, 1.4 mL, 9.7 mmol, 1.1 equiv.) in THF (25 mL). A solution of 2-chloro-4-(trifluoromethoxy)pyridine (**16**, 1.7 g, 8.8 mmol, 1 equiv.) in THF (5 mL) was added dropwise at –78 °C, and the reaction mixture was stirred for 2 h at this temperature. The mixture was then poured onto an excess of freshly crushed dry ice before being treated with an aqueous solution of sodium hydroxide (5%, 25 mL). The resulting aqueous layer was collected, washed with diethyl ether (15 mL), and acidified to pH 4 by dropwise addition of hydrochloric acid (6 N, 8 mL). After extraction with ethyl acetate (3 × 20 mL), the combined organic layers were dried with sodium sulfate and the solvents were evaporated. Crystallization from a mixture of hexanes and ethyl acetate (3:1) afforded pure 2-chloro-4-(trifluoromethoxy)nicotinic acid (**40**, 1.70 g, 7.04 mmol, 80%) as colorless needles; m.p. 111–114 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 8.51 (d, J = 5.9 Hz, 1 H, 6-H), 8.34 (br. s, 1 H, COOH), 7.21 (dq, J = 5.9, 2.0 Hz, 1 H, 5-H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 165.1 (COOH), 154.4 (C), 151.5 (CH), 149.6 (C), 122.1 (C), 119.9 (q, $^2J_{C,F}$ = 261 Hz, OCF_3), 112.2 (CH) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = –57.7 ppm. $C_7H_3ClF_3NO_3$ (241.55): calcd. C 34.81, H 1.25, N 5.80; found C 34.68, H 1.56, N 5.90.

Supporting Information (see footnote on the first page of this article): Details concerning the X-ray structures.

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