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Short communication

Synthetic utility of 4-bromo-2,3,5,6-tetrafluoropyridine

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Abstract

The regiochemistry of nucleophilic substitution of 4-bromo-2,3,5,6-tetrafluoropyridine has been investigated. Efficient, regioselective reactions occur with alkylamine, benzylamine and alkoxide nucleophiles, yielding products where substitution occurs *ortho* to the ring nitrogen. The resulting 2-substituted-4-bromo-3,5,6-trifluoropyridines can be functionalised further, either by a second regioselective nucleophilic displacement or palladium catalysed elaboration at the 4-position. Reactions with aromatic *N*-nucleophiles yield mixtures of *ortho*- and *para*-substituted products.

Keywords: Heterocyclic; Scaffold; Perfluoroheterocycle; 4-Bromo-2,3,5,6-tetrafluoropyridine; Suzuki reaction; Nucleophilic aromatic substitution

1. Introduction

The use of perfluorinated heteroaromatic molecules as synthetically versatile building blocks for the creation of new molecular scaffolds for drug discovery is a growing area of research, stimulated by the enhanced reactivity to nucleophiles that results from their electron-deficient nature [1,2]. For example, the use of pentafluoropyridine in the synthesis of pentasubstituted pyridine derivatives [3], tetrahydropyrido[3,4-*b*]pyrazines [4], imidazopyridines and pyrimidinopyridines [5], and in the creation of polyfunctional tetrahydropyrido[2,3-*b*]pyrazines from a range of tetrafluoropyridine derivatives [6,7] has recently been published, demonstrating some of the possibilities that exist for creating multi-functional heterocyclic scaffolds from such a readily available and simple fluorinated heteroaromatic substrate.

Whilst pentafluoropyridine has been used very successfully as a core scaffold for the synthesis of various drug-like systems, its reactivity largely involves nucleophilic aromatic substitution processes. In order to further extend the range of scaffolds for drug discovery that could be accessed from highly fluorinated pyridine derivatives by our general strategy, we became interested in developing the chemistry of 4-bromo-tetrafluoropyridine **1**, a building block which could complement the synthetic versatility of pentafluoropyridine. In principle, the presence of a bromine atom attached to the pyridine ring would allow further synthetic possibilities such as, for example, a variety of palladium catalysed processes, in addition to nucleophilic aromatic substitution reactions of either the fluorine or bromine atoms.

To our surprise, little precedent for reactions involving **1** has been reported, although nucleophilic substitution reactions with diethylamine [7] and methoxide [8] have been published.

In this paper, we describe our initial investigations which demonstrate regiocontrolled nucleophilic substitution of **1** with a wide range of nucleophiles and highlight how the resulting products can be elaborated further *via* a second sequential nucleophilic displacement step or a palladium catalysed Suzuki–Miyuara coupling process.

2. Results and discussion

Our initial investigations centred on the use of alkylamines and benzylamines as nucleophiles. Reactions of several 4-substituted 2,3,5,6-tetrafluoropyridines, including **1**, with diethylamine as a model nucleophile have shown a preference for nucleophilic attack at the position *ortho* to the ring nitrogen

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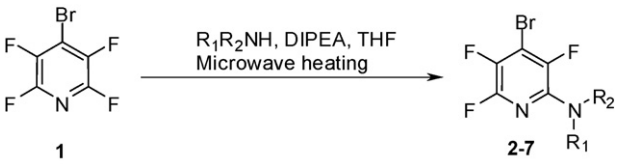
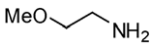
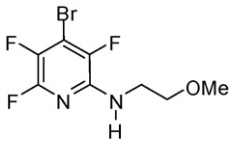
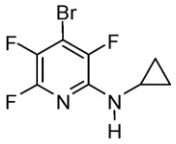
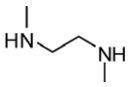
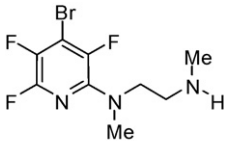
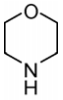
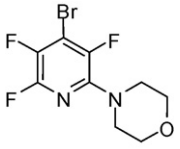
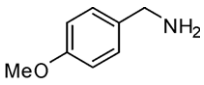
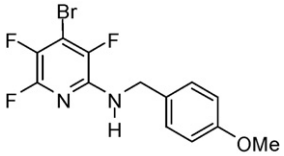
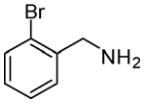
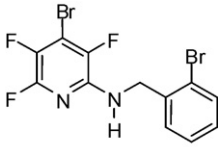
Table 1
Reaction of **1** with amine nucleophiles



Nucleophlie	Conditions	Product (yield %)
	100 °C, 3 h	 **2**, 76%
	100 °C, 3 h	 **3**, 56%
	100 °C, 3 h	 **4**, 47%
	100 °C, 3 h	 **5**, 53%
	100 °C, 1 h	 **6**, 74%
	100 °C, 4 h	 **7**, 61%

[7] and we sought to understand the generality of this regioselectivity with a wider range of nucleophiles. Typically, a slight excess of nucleophile was reacted with **1** in the presence of diisopropylethylamine in THF at elevated temperature in a microwave reactor, Table 1, until analysis of the crude reaction mixtures by ^{19}F NMR indicated substantial conversion to products.

Universally, substitution was observed only at the position *ortho* to the ring nitrogen, as assessed by ^{19}F NMR of the crude

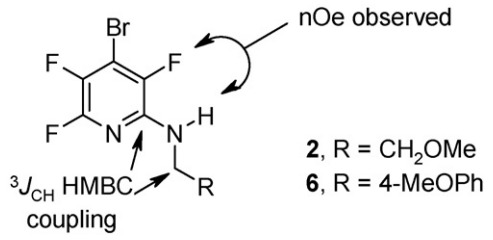
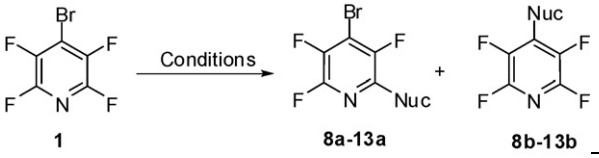
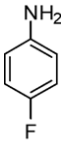
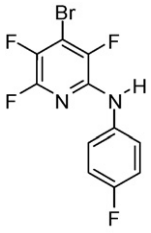
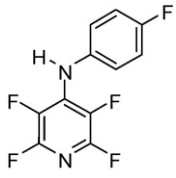
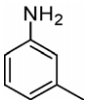
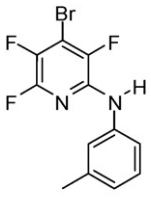
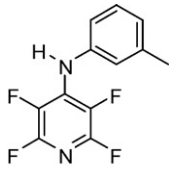
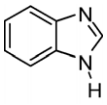
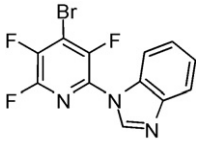
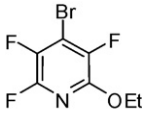
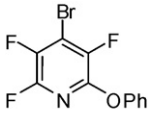
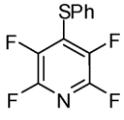


Fig. 1. HMBC and nOe confirmation of regiochemistry of products **2** and **6**.

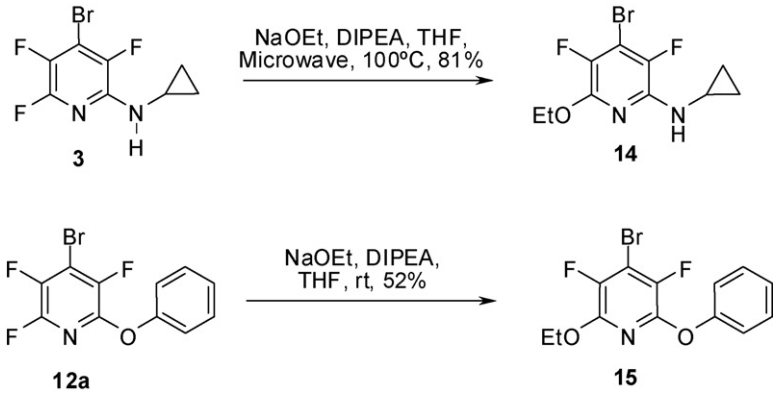
Table 2
Reaction of **1** with nucleophiles



1 **8a-13a** **8b-13b**

Nucleophlie	Conditions	Product (yield %)	
	DIPEA, DMSO, microwave 160 °C, 3 h	 **8a**, 20%	 **8b**, 38%
	DIPEA, DMSO, microwave 160 °C, 1 h	 **9a**, 43%	 **9b**, 50%
	Et_3N, MeCN, rt, 2 days	 **10a**, 25%	
EtONa	DIPEA, THF, rt, 2 h	 **11a**, 59%	
PhONa	DIPEA, THF, 0 °C–rt, 7 h	 **12a**, 60%	
PhSH	K_2CO_3, THF, rt, 12 h	 **13b**, 79%	

reaction mixtures and of isolated compounds **2**–**7** which showed three inequivalent fluorine resonances. The regiochemistry of **2**–**7** was assigned by reference to previous discussions [4,7] and by extensive heteronuclear multiple bond correlation (HMBC) and heteronuclear nOe evaluation of **2** and **6**, Fig. 1. HMBC confirmed a $^3J_{CH}$ correlation between the C-2 pyridine carbon (identified as such by chemical shift and a lack of a characteristically large $^1J_{CF}$ coupling) to protons on the methylene carbon proximal to the nucleophile nitrogen in each case. N15 HMBC on compound **2** showed a $^3J_{NH}$ correlation between the pyridine nitrogen and the nucleophile amine NH (**6** was not evaluated in this fashion). Irradiation of the fluorine resonances at −137.1 and −136.9 ppm of **2** and **6** respectively in heteronuclear nOe experiments yielded an enhancement of the NH proton signal, allowing the fluorines at the 3- and 5-positions of the pyridine ring to be assigned.



Scheme 1. Reaction of **3** and **12a** with sodium ethoxide.

Compounds **3**–**5** and **7** have very similar ^{19}F NMR spectra, and analogous fluorine assignments have been made.

In all cases, the unoptimised yields were good to moderate, Table 1. For convenience, reactions were performed using microwave heating, and the isolated yields compare favourably with that reported for the attack of diethylamine upon **1** under conventional heating conditions [7], indicating that either synthetic mode is applicable.

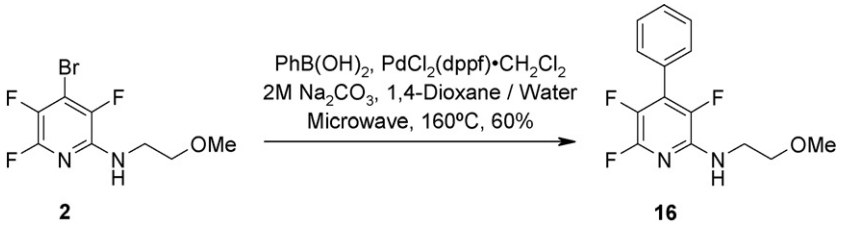
With these successful and clean reactions in hand, we then proceeded to investigate other nucleophiles, Table 2. Here, in some cases, mixtures of products were obtained, resulting from competing substitution at the positions *ortho* and *para* to the ring nitrogen. Aromatic *N*-nucleophiles (entries 1 and 2) required elevated temperatures and extended reaction times or excess nucleophile to proceed to completion, and ^{19}F NMR analysis of the crude reaction mixtures indicated substantially less selective reactions than those in Table 1. In each of these cases mixtures of products were obtained, which could be separated by column chromatography, with substitution at the position *para* to the ring nitrogen appearing to dominate. Benzimidazole, sodium ethoxide and sodium phenoxide gave clean conversions to the *ortho* substituted products exclusively, albeit in poor, unoptimised, yield for benzimidazole. The use of thiophenol resulted in regiospecific displacement at the *para*-position, yielding **13b** [9] in 80% yield.

These results suggest that the regiochemistry of nucleophilic attack for system **1** is, in general, governed by the hard/soft nature of the nucleophile/electrophile [10] whereby hard nucleophiles, such as alkoxides, preferentially attack at the 'hard' activated carbon–fluorine bond *ortho* to ring nitrogen whilst soft nucleophiles, such as thiophenol, prefer to attack at the 'soft' carbon bromine bond at the 4-position. 'Borderline' hard/soft nucleophiles, such as anilines, give mixtures arising from competing substitution of both fluorine and bromine. Consequently, these results provide encouraging guidance regarding the synthetic utility of **1** for new scaffold generation and elaboration.

2-Substituted-4-bromo-3,5,6-trifluoropyridine products **2**–**7** and **8a**–**12a** have the potential to be reacted further *via* the remaining fluoro- or bromo-substituents and initial studies concerning the regioselectivity of a second nucleophilic displacement step were carried out. 4-Bromo-*N*-cyclopropyl-3,5,6-trifluoro-2-pyridinamine **3** was reacted with sodium ethoxide and was cleanly converted to 2,6-disubstituted bromopyridine **14** in 81% isolated yield, Scheme 1. Disappearance of the characteristic ^{19}F resonance at approximately −90 ppm was indicative of displacement of the fluorine *ortho* to the pyridine nitrogen. Similarly, fluorine displacement from 4-bromo-2,3,5-trifluoro-6-(phenyloxy)pyridine **12a** by sodium ethoxide at room temperature produced **15** in 52% isolated yield. The regiochemistry of this second displacement complements the well established order of attack of nucleophiles upon pentafluoropyridine ($4 > 2 > 3$) [1–4] and the hard/soft principles outlined above.

The 4-bromo substituent can also be utilised as a synthetic handle. For example, **2** was reacted with phenylboronic acid under Suzuki–Miyuara coupling conditions, and produced **16** in acceptable yield, Scheme 2. There was no evidence to suggest that the fluorine atoms present in **2** significantly participated in deleterious nucleophilic substitution side-reactions.

In conclusion, we have shown that 4-bromo-2,3,5,6-tetrafluoropyridine can be successfully reacted with a variety of nucleophiles. With alkylamines, benzylamines, alkoxides and benzimidazole, nucleophilic aromatic substitution occurs



Scheme 2. Suzuki–Miyaura coupling reaction of **2**.

cleanly at the position *ortho* to the ring nitrogen whilst clean substitution occurs at the *para* position with thiophenol. In contrast, aromatic *N*-nucleophiles gave a mixture of *ortho*- and *para*-substituted products. These results have been rationalised by using hard/soft principles. We have established that the functionality remaining in the mono-substituted products can be exploited in a regiocontrolled second nucleophilic displacement or a Suzuki–Miyaura coupling. These initial investigations indicate that 4-bromo-2,3,5,6-tetrafluoropyridine is a reactive, versatile and controllable building block with great potential to be exploited in drug discovery and other arenas.

3. Experimental

3.1. General

4-Bromo-2,3,5,6-tetrafluoropyridine was obtained from Aldrich. All other starting materials were obtained commercially. Microwave reactions were performed in a Biotage Initiator 60 EXP. NMR spectra were obtained in the deuterated solvents indicated, on Bruker DPX400, AV400 or AVII600 spectrometers with referencing to tetramethylsilane and $CFCl_3$ for proton and fluorine spectra, respectively. Elemental analyses were performed by Butterworth Laboratories Limited, Teddington, UK. Mass spectra (LC/MS) were recorded in electrospray positive and negative ion modes on a Waters ZQ Mass Spectrometer coupled to a Waters Acquity HPLC system. Accurate mass measurements were performed on Bruker Daltonics 7T FTICR-MS or Micromass Q-Tof 2 hybrid quadrupole mass spectrometers, operating in electrospray positive ion mode. Melting points were recorded on a Gallenkamp apparatus and are uncorrected.

3.2. General procedure for reaction of alkylamine and benzylamine nucleophiles with 4-bromo-2,3,5,6-tetrafluoropyridine

A mixture of 4-bromo-2,3,5,6-tetrafluoropyridine (2.5–6.9 mmol), nucleophile (1.1–1.2 equiv.) and diisopropylethylamine (3.0 equiv.) in THF (8–10 mL) was heated in a microwave reactor at the temperature and time indicated in Table 1. After concentration *in vacuo*, the material was partitioned between water and CH_2Cl_2, the phases separated, and the aqueous phase extracted with CH_2Cl_2. The combined organic phases were concentrated *in vacuo* and purified by flash column chromatography.

3.2.1. 4-Bromo-3,5,6-trifluoro-N-[2-(methyloxy)ethyl]-2-pyridinamine **2**

mp 92–93 °C; ^{1}H NMR (400 MHz, DMSO-*d*6) δ 3.25 (3H, s, OMe), 3.35–3.47 (4H, m (CH_2)$_2$), 7.22 (1H, br. s, NH); ^{13}C NMR (101 MHz, DMSO-*d*6) δ 40.0 (br. s, $\underline{C}H_2CH_2OMe$), 57.9 (s, $CH_2(O\underline{Me})$), 70.0 (s, $\underline{C}H_2(OMe)$), 109.2 (td, $^2J_{CF}$ 21.0, $^3J_{CF}$ 5.0, C-4), 131.4 (dd, $^1J_{CF}$ 243.0, $^2J_{CF}$ 33.0, C-5), 140.3 (ddd, $^1J_{CF}$ 251.0, $^3J_{CF}$ 5.5, $^4J_{CF}$ 1.5, C-3), 142.1 (t, $^2J_{CF}$ 16.5, $^3J_{CF}$ 16.5, C-2), 144.7 (ddd, $^1J_{CF}$ 229.0, $^2J_{CF}$ 15.0, $^4J_{CF}$ 2.5, C-6); ^{19}F NMR (377 MHz, DMSO-*d*6) δ −92.8 (1F, dd, $^5J_{FF}$ 28.0, $^3J_{FF}$ 25.0, F-6), −137.1 (1F, dd, $^5J_{FF}$ 28.0, $^4J_{FF}$ 9.0, F-3), −155.9 (1F, dd, $^3J_{FF}$ 25.0, $^4J_{FF}$ 9.0, F-5); *m/z* (Electrospray) 285.2/287.1 (1:1 ratio, $[M+H]^+$, 10); M^+ 284.98441. $C_8H_8BrF_3N_2O$ requires 284.98449.

3.2.2. 4-Bromo-N-cyclopropyl-3,5,6-trifluoro-2-pyridinamine **3**

mp 49–50 °C; ^{1}H NMR (400 MHz, DMSO-*d*6) δ 0.50 (2H, m, CH_2), 0.69 (2H, m, CH_2), 2.65 (1H, m, CH), 7.41 (br. s, NH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 7.2 (2C, s, $\underline{C}H_2$), 23.7 (s, $\underline{C}H$), 109.2 (td, $^2J_{CF}$ 21.0, $^3J_{CF}$ 5.0, C-4), 133.7 (ddd, $^1J_{CF}$ 249.6, $^2J_{CF}$ 33.0, $^3J_{CF}$ 1.5, C-5), 140.7 (ddd, $^1J_{CF}$ 249.0, $^3J_{CF}$ 6.0, $^4J_{CF}$ 2.5, C-3), 142.2 (ddd, $^2J_{CF}$ 16.5, $^3J_{CF}$ 14.0, $^4J_{CF}$ 2.5, C-2), 145.7 (ddd, $^1J_{CF}$ 234.0, $^2J_{CF}$ 15.0, $^4J_{CF}$ 3.0, C-6); ^{19}F NMR (377 MHz, MeOD-*d*4) δ −92.5 (1F, dd, $^5J_{FF}$ 28.0, $^3J_{FF}$ 23.0, F-6), −137.3 (1F, dd, $^5J_{FF}$ 28.0, $^4J_{FF}$ 8.0, F-3), −154.3 (1F, dd, $^3J_{FF}$ 23.0, $^4J_{FF}$ 8.0, F-5); *m/z* (Electrospray) 267.0/269.0 (1:1 ratio, $[M+H]^+$, 100); Anal. Calcd for $C_8H_6BrF_3N_2$: C, 36.4; H, 1.8, N, 7.1. Found: C, 36.5; H, 1.7; N, 6.8%.

3.2.3. N′-(4-Bromo-3,5,6-trifluoro-2-pyridinyl)-N,N-dimethyl-1,2-ethanediamine formate **4**

mp 108–110 °C; ^{1}H NMR (400 MHz, DMSO-*d*6) δ 2.33 (6H, s, $CH_2N\underline{Me}_2$), 2.63 (2H, t, *J* 6.5, $C\underline{H}_2NMe_2$), 3.41 (2H, q, *J* 6.5, $NHC\underline{H}_2$), 7.21 (1H, br. s, NH), 8.24 (1H, br. s, $\underline{H}CO_2H$); ^{13}C NMR (101 MHz, DMSO-*d*6) δ 37.6 (s, $NH\underline{C}H_2$), 44.3 (2C, s, NMe_2), 56.9 (s, $\underline{C}H_2NMe_2$), 109.2 (td, $^2J_{CF}$ 20.8, $^3J_{CF}$ 4.8, C-4), 131.4 (dd, $^1J_{CF}$ 243.7, $^2J_{CF}$ 33.6, C-5), 140.3 (ddd, $^1J_{CF}$ 250.9, $^3J_{CF}$ 5.6, $^4J_{CF}$ 2.4, C-3), 142.0 (td, $^2J_{CF}$ 16.4, $^3J_{CF}$ 16.4, $^4J_{CF}$ 2.0, C-2), 144.7 (ddd, $^1J_{CF}$ 229.3, $^2J_{CF}$ 15.2, $^4J_{CF}$ 2.4, C-6), 164.2 (s, $H\underline{C}O_2H$); ^{19}F NMR (377 MHz, DMSO-*d*6) δ −93.3 (1F, dd, $^5J_{FF}$ 28.0, $^3J_{FF}$ 25.0, F-6), −137.6 (1F, dd, $^5J_{FF}$ 28.0, $^4J_{FF}$ 9.0, F-3), −156.3 (1F, dd, $^3J_{FF}$ 25.0, $^4J_{FF}$ 9.0, F-5); *m/z* (Electrospray) 298.2/300.2 (1:1 ratio, $[M+H]^+$, 100); Anal. Calcd for $C_9H_{11}BrF_3N_3{\cdot}CH_2O_2$: C, 34.9; H, 3.8, N, 12.2. Found: C, 35.1; H, 3.6; N, 11.8%.

3.2.4. 4-(4-Bromo-3,5,6-trifluoro-2-pyridinyl)morpholine **5**

mp 69–71 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.45 (4H, t, *J* 4.8, $C\underline{H}_2NC\underline{H}_2$), 3.80 (4H, t, *J* 4.8, $C\underline{H}_2OC\underline{H}_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 48.2 (2C, d, $^4J_{CF}$ 5.6, $\underline{C}H_2N\underline{C}H_2$), 67.0 (2C, s, $\underline{C}H_2O\underline{C}H_2$), 112.3 (td, $^2J_{CF}$ 20.0, $^2J_{CF}$ 20.0, $^3J_{CF}$ 4.8, C-4), 136.3 (dd, $^1J_{CF}$ 254.1, $^2J_{CF}$ 32.8, C-5), 142.7 (ddd, $^{2or3}J_{CF}$ 11.8, $^{2or3}J_{CF}$ 10.2, $^4J_{CF}$ 3.0, C-2), 143.6 (ddd, $^1J_{CF}$ 254.8, $^3J_{CF}$ 6.4, $^4J_{CF}$ 3.2, C-3), 144.9 (ddd, $^1J_{CF}$ 235.7, $^2J_{CF}$ 15.2, $^4J_{CF}$ 2.4, C-6); ^{19}F NMR (377 MHz, $CDCl_3$) δ −90.0 (1F, dd, $^5J_{FF}$ 28.0, $^3J_{FF}$ 25.0, F-6), −125.9 (1F, dd, $^5J_{FF}$ 28.0, $^4J_{FF}$ 6.0, F-3), −145.9 (1F, dd, $^3J_{FF}$ 25.0, $^4J_{FF}$ 6.0, F-5); *m/z* (Electrospray) 297.1/299.2 (1:1 ratio, $[M+H]^+$, 100); $[M+H]^+$ 296.98420. $C_9H_9BrF_3N_2O$ requires 296.98449.

3.2.5. 4-Bromo-3,5,6-trifluoro-N-{[4-(methyloxy)phenyl]methyl}-2-pyridinamine **6**

mp 72–74 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.81 (3H, s, OMe), 4.52 (2H, d, *J* 5.5, $NHC\underline{H}_2$), 4.89 (1H, br. s, NH), 6.89 (2H, d, *J* 8.5, Ar), 7.28 (2H, d, *J* 8.5, Ar); ^{13}C NMR (101 MHz, DMSO-*d*6) δ 44.7 (1C, s, $\underline{C}H_2Ar$), 55.1 (1C, s, $O\underline{Me}$), 109.4

(1C, td, $^2J_{CF}$ 21.0, $^3J_{CF}$ 5.0, C-4), 114.0 (2C, s, Ar), 129.1 (2C, s, Ar), 130.1 (1C, Ar), 133.2 (1C, dd, $^1J_{CF}$ 244.9, $^2J_{CF}$ 33.2, C-5), 140.1 (1C, ddd, $^1J_{CF}$ 250.9, $^3J_{CF}$ 6.0, $^4J_{CF}$ 2.0, C-3), 141.8 (1C, ddd, $^2J_{CF}$ 16.4, $^3J_{CF}$ 16.4, $^4J_{CF}$ 1.6, C-2), 144.6 (1C, ddd, $^1J_{CF}$ 229.1, $^2J_{CF}$ 14.6, $^4J_{CF}$ 2.6, C-6), 158.2 (1C, s, Ar); ^{19}F NMR (377 MHz, DMSO-*d*6) δ −92.7 (1F, dd, $^5J_{FF}$ 28.0, $^3J_{FF}$ 25.0, F-6), −136.9 (1F, dd, $^5J_{FF}$ 28.0, $^4J_{FF}$ 9.0, F-3), −155.6 (1F, dd, $^3J_{FF}$ 25.0, $^4J_{FF}$ 9.0, F-5); *m/z* (Electrospray) 347.1/349.0 (1:1 ratio, $[M+H]^+$, 18); Anal. Calcd for $C_{13}H_{10}BrF_3N_2$: C, 45.0; H, 2.9 N, 8.1. Found: C, 44.6; H, 2.8; N, 7.7%.

3.2.6. Preparation of 4-bromo-N-[(2-bromophenyl)methyl]-3,5,6-trifluoro-2-pyridinamine **7**

mp 91–93 °C; ^{1}H NMR (400 MHz, MeOD-*d*4) δ 4.60 (2H, s, $\underline{C}H_2$), 7.15 (1H, br. t, *J* 7.5, Ar), 7.28 (1H, t, *J* 7.5, Ar), 7.34 (1H, br. d, *J* 7.5, Ar), 7.56 (1H, d, *J* 7.5, Ar); ^{13}C NMR (101 MHz, DMSO-*d*6) δ 44.6 (1C, s, $\underline{C}H_2$Ar), 109.9 (1C, td, $^2J_{CF}$ 21.0, $^3J_{CF}$ 5.3, C-4), 122.6 (1C, s, Ar), 128.1 (1C, s, Ar), 128.8 (1C, s, Ar), 129.2 (1C, s, Ar), 132.4 (1C, dd, $^1J_{CF}$ 244.1, $^2J_{CF}$ 32.4, C-5), 132.7 (1C, s, Ar), 137.9 (1C, s, Ar), 140.8 (1C, ddd, $^1J_{CF}$ 250.1, $^3J_{CF}$ 5.6, $^4J_{CF}$ 2.4, C-3), 142.1 (1C, br. td, $^2J_{CF}$ 16.0, $^4J_{CF}$ 1.6, C-2), 145.1 (1C, ddd, $^1J_{CF}$ 230.0, $^2J_{CF}$ 15.2, $^4J_{CF}$ 2.4, C-6); ^{19}F NMR (377 MHz, MeOD-*d*4) δ −95.2 (1F, dd, $^5J_{FF}$ 28.0, $^3J_{FF}$ 23.0, F-6), −140.4 (1F, dd, $^5J_{FF}$ 28.0, $^4J_{FF}$ 9.0, F-3), −156.8 (1F, dd, $^3J_{FF}$ 23.0, $^4J_{FF}$ 9.0, F-5); *m/z* (Electrospray) 392.8/394.7/396.6 (approx 1:2:1 ratio, $[M+H]^+$, 100); Anal. Calcd for $C_{12}H_7BrF_3N_2$: C, 36.4; H, 1.8, N, 7.1. Found: C, 36.5; H, 1.7; N, 6.8%.

3.3. Reaction of 4-bromo-2,3,5,6-tetrafluoropyridine with other nucleophiles

3.3.1. Preparation of 4-bromo-3,5,6-trifluoro-N-(4-fluorophenyl)-2-pyridinamine **8a** and 2,3,5,6-tetrafluoro-N-(4-fluorophenyl)-4-pyridinamine **8b**

A mixture of 4-bromo-2,3,5,6-tetrafluoropyridine (1.03 g, 4.49 mmol), 4-fluoroaniline (446 μL, 4.71 mmol) and DIPEA (2.35 mL, 13.5 mmol) in DMSO (15 mL) was heated at 160 °C in a microwave reactor for 3 h, before cooling to room temperature and concentration *in vacuo*. Purification by reverse-phase flash chromatography (gradient elution; 40–95% MeCN (+0.05% HCO_2H) in water (+0.1% HCO_2H)) on a C18 column yielded **8a** (439 mg, 1.69 mmol) as a brown solid; mp 97–99 °C; ^{1}H NMR (400 MHz, MeOD-*d*4) δ 7.03 (2H, t, *J* 8.5, Ar), 7.56–7.60 (2H, m, Ar); ^{13}C NMR (101 MHz, DMSO-*d*6) δ 110.2 (1C, td, $^2J_{CF}$ 21.2, $^3J_{CF}$ 4.8, C-4), 115.2 (2C, d, $^2J_{CF}$ 22.4, Ar), 121.7 (2C, d, $^3J_{CF}$ 7.2, Ar), 133.5 (1C, dd, $^1J_{CF}$ 247.2, $^2J_{CF}$ 33.2, C-5), 135.5 (1C, d, $^4J_{CF}$ 2.4, Ar), 138.3 (1C, td, $^2J_{CF}$ 15.6, $^4J_{CF}$ 2.4, C-2), 140.9 (1C, ddd, $^1J_{CF}$ 253.4, $^3J_{CF}$ 6.2, $^4J_{CF}$ 2.2 C-3), 143.8 (ddd, $^1J_{CF}$ 230.7, $^2J_{CF}$ 15.4, $^4J_{CF}$ 2.6, C-6), 157.9 (1C, d, $^1J_{CF}$ 238.9, Ar); ^{19}F NMR (377 MHz, DMSO-*d*6) δ −92.1 (1F, dd, $^5J_{FF}$ 28.0, $^3J_{FF}$ 25.0, F-6), −133.2 (1F, dd, $^5J_{FF}$ 28.0, $^4J_{FF}$ 7.0, F-3), −120.6 (1F, br. s, ArF), −150.6 (1F, dd, $^3J_{FF}$ 25.0, $^4J_{FF}$ 7.0, F-5); *m/z* (Electrospray) 319.2/321.2 (approx. 1:1 ratio, $[M-H]^-$, 89); Anal. Calcd for $C_{11}H_5BrF_4N_2$: C, 41.2; H, 1.6, N, 8.7. Found: C, 41.3; H, 1.5; N, 8.4%; and **8b** (283 mg, 0.88 mmol) as a brown solid; mp 80–82 °C; ^{1}H NMR (400 MHz, DMSO-*d*6) δ 7.14–7.22 (4H, m, Ar), 9.39 (1H, s, NH); ^{13}C NMR (101 MHz, DMSO-*d*6) δ 115.2 (2C, d, $^2J_{CF}$ 22.4, Ar), 123.6 (2C, d, $^3J_{CF}$ 8.0, Ar), 132.5 (2C, dm, $^1J_{CF}$ 252.2, C-3/C-5), 134.9 (1C, m, C-4), 135.7 (1C, Ar), 143.7 (2C, dm, $^1J_{CF}$ 234.9, C-2/C-6), 159.0 (1C, d, $^1J_{CF}$ 240.5, Ar); ^{19}F NMR (377 MHz, DMSO-*d*6) δ −95.7 (2F, m, F-2/F-6), −119.1 (1F, s, ArF), −155.1 (2F, m, F-3/F-5); *m/z* (Electrospray) 259.3 ($[M-H]^-$, 100); $[M+H]^+$ 261.04447. $C_{11}H_6F_5N_2$ requires 261.04457.

3.3.2. Preparation of 4-bromo-3,5,6-trifluoro-N-(3-methylphenyl)-2-pyridinamine **9a** and 2,3,5,6-tetrafluoro-N-(3-methylphenyl)-4-pyridinamine **9b**

A mixture of 4-bromo-2,3,5,6-tetrafluoropyridine (1.13 g, 4.93 mmol), *m*-toluidine (793 μL, 7.40 mmol) and DIPEA (2.58 mL, 14.8 mmol) in DMSO (9 mL) was heated at 160 °C in a microwave reactor for 1 h, before cooling to room temperature and concentration *in vacuo*. Water and CH_2Cl_2 (50 mL each) were added, the phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (2× 25 mL). The combined organic phases were concentrated *in vacuo*, and purification by reverse-phase flash chromatography (gradient elution; 40–95% MeCN (+0.1% CF_3CO_2H) in water (+0.1% CF_3CO_2H)) on a C18 column yielded **9a** (591 mg, 2.31 mmol) as a ginger solid; mp 110–111 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.38 (3H, s, Me), 6.49 (1H, br. s, NH), 6.93 (1H, br. d, *J* 8.0, Ar), 7.24 (1H, d, *J* 8.0, Ar), 7.33 (1H, br. s, Ar), 7.41 (1H, br. d, *J* 8.0, Ar); ^{13}C NMR (101 MHz, DMSO-*d*6) δ 20.6 (1C, s, Me), 109.5 (1C, td, $^2J_{CF}$ 21.2, $^3J_{CF}$ 4.8, C-4), 116.3 (1C, s, Ar), 119.7 (1C, s, Ar), 122.8 (1C, s, Ar), 127.8 (1C, s, Ar), 132.9 (1C, dd, $^1J_{CF}$ 248.1, $^2J_{CF}$ 33.2, C-5), 137.1 (1C, s, Ar), 137.7 (1C, dd, $^2J_{CF}$ 15.6, $^3J_{CF}$ 3.2, C-2), 138.5 (1C, s, Ar), 140.4 (1C, ddd, $^1J_{CF}$ 254.0, $^3J_{CF}$ 6.4, $^4J_{CF}$ 2.4, C-3), 143.3 (1C, ddd, $^1J_{CF}$ 230.3, $^2J_{CF}$ 15.4, $^4J_{CF}$ 2.6, C-6); ^{19}F NMR (377 MHz, DMSO-*d*6) δ −92.0 (1F, dd, $^5J_{FF}$ 28.0, $^3J_{FF}$ 26.0, F-6), −132.6 (1F, dd, $^5J_{FF}$ 28.0, $^4J_{FF}$ 7.0, F-3), −150.6 (1F, dd, $^3J_{FF}$ 26.0, $^4J_{FF}$ 7.0, F-5); *m/z* (Electrospray) 314.8/316.8 (approx. 1:1 ratio, $[M-H]^-$, 100); $[M+H]^+$ 316.98956 $C_{12}H_9BrF_3N_2$ requires 316.98957; and **9b** (551 mg, 1.74 mmol) as a cream solid; mp 97–99 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.38 (3H, s, Me), 6.27 (1H, br. s, NH), 6.92 (1H, d, *J* 8.0, Ar), 6.93 (1H, s, Ar), 7.04 (1H, d, *J* 8.0, Ar), 7.26 (1H, t, *J* 8.0, Ar); ^{13}C NMR (151 MHz, DMSO-*d*6) δ 20.9 (1C, s, Me), 118.3 (1C, s, Ar), 121.6 (1C, s, Ar), 124.7 (1C, s, Ar), 128.4 (1C, s, Ar), 132.9 (2C, dm, $^1J_{CF}$ 249.5, C-3/C-5), 134.6 (1C, m, C-4), 137.9 (1C, s, Ar), 139.3 (1C, s, Ar), 143.7 (2C, br. dt, $^1J_{CF}$ 234.8, $^2J_{CF}$ 16.0, C-2/C-6); ^{19}F NMR (377 MHz, $CDCl_3$) δ −99.9 (2F, m, F-2/F-6), −156.2.1 (2F, m, F-3/F-5); *m/z* (Electrospray) 255.0 ($[M-H]^-$, 100); $[M+H]^+$ 257.06953. $C_{12}H_9F_4N_2$ requires 257.06964.

3.3.3. Preparation of 1-(4-bromo-3,5,6-trifluoro-2-pyridinyl)-1H-benzimidazole **10a**

A mixture of 4-bromo-2,3,5,6-tetrafluoropyridine (1.00 g, 4.35 mmol), benzimidazole (514 mg, 4.35 mmol) and triethylamine (1.82 mL, 13.1 mmol) in acetonitrile (20 mL) was stirred at room temperature for 2 days before concentration *in vacuo*. Water (15 mL) and CH_2Cl_2 (25 mL) were added, the

phases were separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were concentrated *in vacuo*, and purification by flash chromatography on silica (gradient elution; 10–50% EtOAc in cyclohexane) yielded the title compound (352 mg, 1.07 mmol) as a white solid; mp 213–215 °C; ^{1}H NMR (400 MHz, DMSO-*d*6) δ 7.40 (2H, m, Ar), 7.82 (2H, m, Ar), 8.68 (1H, d, *J* 2.8, Ar); ^{13}C NMR (151 MHz, DMSO-*d*6) δ 112.4 (1C, s, Ar), 114.1 (1C, ddd, $^2J_{CF}$ 24.6, $^2J_{CF}$ 20.7, $^3J_{CF}$ 4.4, C-4), 120.0 (1C, s, Ar), 123.6 (1C, s, Ar), 124.3 (1C, s, Ar), 129.4 (1C, td, $^2J_{CF}$ 15.5, $^4J_{CF}$ 4.4, C-2), 132.1 (1C, s, Ar), 141.9 (1C, dd, $^1J_{CF}$ 259.9, $^2J_{CF}$ 32.1, C-5), 142.6 (1C, d, $^{4or5}J_{CF}$ 7.7, Ar), 142.9 (1C, s, Ar), 145.0 (1C, dd, $^1J_{CF}$ 238.8, $^2J_{CF}$ 17.7, C-6), 146.8 (1C, dd, $^1J_{CF}$ 257.6, $^3J_{CF}$ 4.4, C-3); ^{19}F NMR (377 MHz, DMSO-*d*6) δ −88.9 (1F, dd, $^5J_{FF}$ 28.0, $^3J_{FF}$ 24.5, F-6), −123.2 (1F, d, $^5J_{FF}$ 28.0, F-3), −133.3 (1F, d, $^3J_{FF}$ 24.5, F-5); *m/z* (Electrospray) 327.8/329.8 (1:1 ratio, $[M+H]^+$, 100); $[M+H]^+$ 327.96913. $C_{12}H_6BrF_3N_3$ requires 327.96917.

3.3.4. Preparation of 4-bromo-2-(phenyloxy)-3,5,6-trifluoropyridine **11a**

A mixture of 4-bromo-2,3,5,6-tetrafluoropyridine (2.12 g, 9.24 mmol), sodium ethoxide (21 wt.% in EtOH, 3.62 mL, 9.70 mmol) and DIPEA (4.83 mL, 27.7 mmol) in anhydrous THF (9.0 mL) was stirred at rt for 2.5 h, before concentration *in vacuo*. Water and CH_2Cl_2 (50 mL each) were added, the phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (2× 50 mL). The combined organic phases were concentrated *in vacuo*, and the title compound (1.33 g, 5.19 mmol) was isolated by short-path distillation (bp 55–57 °C/3 mbar) as a clear oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (3H, t, *J* 7.0, Me), 4.40 (2H, q, *J* 7.0, CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 14.6 (1C, s, $CH_2\underline{Me}$), 64.4 (1C, s, $\underline{C}H_2Me$), 112.1 (1C, td, $^2J_{CF}$ 20.7, $^3J_{CF}$ 4.3, C-4), 137.0 (1C, dd, $^1J_{CF}$ 253.2, $^2J_{CF}$ 31.2, C-5), 142.4 (1C, ddd, $^1J_{CF}$ 258.0, $^3J_{CF}$ 7.2, $^4J_{CF}$ 2.4, C-3), 144.5 (1C, ddd, $^1J_{CF}$ 239.0, $^2J_{CF}$ 16.2, $^4J_{CF}$ 3.4, C-6), 146.2 (1C, br. td, $^2J_{CF}$ 13.4, $^4J_{CF}$ 2.7, C-2); ^{19}F NMR (377 MHz, $CDCl_3$) δ −92.5 (1F, dd, $^5J_{FF}$ 28.0, $^3J_{FF}$ 21.0, F-6), −135.5 (1F, dd, $^5J_{FF}$ 28.0, $^4J_{FF}$ 6.0, F-3), −145.5 (1F, dd, $^3J_{FF}$ 21.0, $^4J_{FF}$ 6.0, F-5); *m/z* (Electrospray): failed to ionise in positive or negative ion modes; Anal. Calcd for $C_7H_5BrF_3NO$: C, 32.8; H, 2.0, N, 5.5. Found: C, 32.6; H, 1.8; N, 5.3%.

3.3.5. Preparation of 4-bromo-2-(ethyloxy)-3,5,6-trifluoropyridine **12a**

Sodium phenoxide (562 mg, 4.84 mmol) was added to a solution of 4-bromo-2,3,5,6-tetrafluoropyridine (1.06 g, 4.61 mmol) and DIPEA (2.41 mL, 13.8 mmol) in anhydrous THF (20 mL) at 0 °C. The reaction was allowed to warm to room temperature and stirred for 17 h before concentration *in vacuo*. Purification by reverse-phase flash chromatography (gradient elution; 35–85% MeCN (+0.1% HCO_2H) in water (+0.05% HCO_2H)) on a C18 column yielded the title compound (842 mg, 2.77 mmol) as a white solid; mp 53–55 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (2H, br. d, *J* 8.0, Ph), 7.25–7.29 (1H, m, Ph), 7.43 (2H, t, *J* 8.0, Ph); ^{13}C (101 MHz, DMSO-*d*6) δ 113.2 (1C, td, $^2J_{CF}$ 21.6, $^3J_{CF}$ 3.7, C-4), 120.4 (2C, s, Ph), 125.5 (1C, s, Ph), 129.9 (2C, s, Ph), 138.4 (1C, dd, $^1J_{CF}$ 253.3, $^2J_{CF}$ 31.2, C-5), 142.7 (1C, ddd, $^1J_{CF}$ 254.8, $^3J_{CF}$ 6.4, $^4J_{CF}$ 1.6, C-3), 143.2 (1C, ddd, $^1J_{CF}$ 238.1, $^2J_{CF}$ 16.8, $^4J_{CF}$ 3.2, C-6), 143.4 (1C, ddd, $^2J_{CF}$ 15.2, $^3J_{CF}$ 12.4, $^4J_{CF}$ 2.8, C-2), 152.7 (1C, s, Ph); ^{19}F NMR (377 MHz, $CDCl_3$) δ −89.8 (1F, dd, $^5J_{FF}$ 28.0, $^3J_{FF}$ 22.0, F-6), −133.0 (1F, dd, $^5J_{FF}$ 28.0, $^4J_{FF}$ 4.5, F-3), −140.4 (1F, dd, $^3J_{FF}$ 22.0, $^4J_{FF}$ 4.5, F-5); *m/z* (Electrospray) 304.0/306.0 (1:1 ratio, $[M+H]^+$, 59). Anal. Calcd for $C_{11}H_5BrF_3NO$: C, 43.5; H, 1.7, N, 4.6. Found: C, 43.3; H, 1.6; N, 4.5%.

3.3.6. Preparation of 2,3,5,6-tetrafluoro-4-(phenylthio)pyridine **13b**

4-Bromo-2,3,5,6-tetrafluoropyridine (213 mg, 0.93 mmol), thiophenol (90 μL, 0.88 mmol) and potassium carbonate (345 mg, 2.5 mmol) in anhydrous THF (5 mL) were stirred at room temperature for 12 h. 2 M aqueous sodium hydroxide (10 mL) was added to the reaction mixture, the phases were separated, the aqueous phase was extracted with CH_2Cl_2 (3× 5 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by silica column chromatography (CH_2Cl_2/cyclohexane, 1:4) yielded the title compound (181 mg, 0.70 mmol) as a yellow oil. NMR data were in accordance with the literature [9].

3.4. Reactions of 2-substituted 4-bromo-tetrafluoropyridines

3.4.1. Preparation of 4-bromo-N-cyclopropyl-6-(ethyloxy)-3,5-difluoro-2-pyridinamine **14**

4-Bromo-2-cyclopropyl-3,5,6-trifluoropyridine (100 mg, 0.37 mmol), sodium ethoxide (21 wt.% in EtOH, 225 μL, 0.51 mmol) and DIPEA (190 μL, 1.11 mmol) in anhydrous THF (1 mL) were stirred at room temperature for 30 min before heating in a microwave reactor at 100 °C for 15 min. After cooling to room temperature water (1 mL) was added, the phases were separated, the aqueous layer was extracted with CH_2Cl_2 (3× 2 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by silica column chromatography (Et_2O/cyclohexane, 1:19) yielded the title compound (88.7 mg, 0.30 mmol) as a colourless oil; ^{1}H NMR (400 MHz, MeOD) δ 0.49 (2H, td, *J* 7.0, 5.0, CH_2), 0.70 (2H, td, *J* 7.0, 5.0, CH_2), 1.37 (3H, t, *J* 7.0, Me), 2.65 (1H, m, CH), 4.40 (2H, q, *J* 7.0, OCH_2); ^{13}C NMR (101 MHz, MeOD) δ 7.2 (2C, s, CyPr), 15.1 (1C, s, $OCH_2\underline{Me}$), 24.5 (1C, s, CyPr), 63.3 (1C, s, $O\underline{C}H_2Me$), 108.3 (1C, t, $^2J_{CF}$ 20.4, C-4), 136.3 (1C, dd, $^1J_{CF}$ 246.1, $^3J_{CF}$ 2.4, C-3), 138.5 (1C, dd, $^1J_{CF}$ 245.7, $^3J_{CF}$ 2.8, C-5), 143.6 (1C, dd, $^2J_{CF}$ 13.6, $^4J_{CF}$ 3.2, C-2), 147.6 (1C, dd, $^2J_{CF}$ 11.6, $^4J_{CF}$ 2.8, C-6); ^{19}F NMR (376 MHz, MeOD) δ −155.4 (1F, apparent d, $^4J_{FF}$ 11.5, F-3 or F-5), −149.6 (1F, apparent d, $^4J_{FF}$ 11.5, F-3 or F-5); *m/z* (Electrospray) 292.9/294.9 (1:1 ratio, $[M+H]^+$, 100); $[M+H]^+$ 293.00930. $C_{10}H_{11}BrF_2N_2O$ requires 293.00956.

3.4.2. Preparation of 4-bromo-2-(ethyloxy)-3,5-difluoro-6-(phenyloxy)pyridine **15**

4-Bromo-2-(phenyloxy)-3,5,6-trifluoropyridine (96.0 mg, 0.32 mmol), sodium ethoxide (21 wt.% in EtOH, 124 μL, 0.33 mmol) and DIPEA (165 μL, 0.95 mL) in anhydrous THF

(1.0 mL) were stirred at room temperature for 17 h. After concentration *in vacuo* water and CH_2Cl_2 (10 mL each) were added, the phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (2× 5 mL). The combined organic phases were concentrated *in vacuo* and purified by mass-directed preparative HPLC (50–98% aqueous MeCN gradient), yielding the title compound (54.6 mg, 0.17 mmol) as an off-white solid; mp 61–62 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (3H, t, *J* 7.0, Me), 4.15 (2H, q, *J* 7.0, CH_2), 7.12 (2H, br. d, *J* 8.0, Ph), 7.20 (1H, t, *J* 8.0, Ph), 7.38 (2H, t, *J* 8.0, Ph); ^{13}C NMR (101 MHz, DMSO-*d*6) δ 14.4 (1C, s, $CH_2\underline{Me}$), 63.5 (1C, s, $\underline{C}H_2Me$), 111.3 (1C, t, $^2J_{CF}$ 21.2, C-4), 120.2 (2C, s, Ph), 125.1 (1C, s, Ph), 130.0 (2C, s, Ph), 139.6 (1C, dd, $^1J_{CF}$ 250.1, $^3J_{CF}$ 1.6, C-3 or C-5), 140.4 (1C, dd, $^1J_{CF}$ 252.8, $^3J_{CF}$ 2.0, C-3 or C-5), 143.1 (1C, dd, $^2J_{CF}$ 14.0, $^4J_{CF}$ 3.6, C-6), 145.8 (1C, dd, $^2J_{CF}$ 13.6, $^4J_{CF}$ 2.4, C-2), 154.0 (1C, s, Ph); ^{19}F NMR (377 MHz, $CDCl_3$) δ −139.5 (1F, br. d, $^4J_{FF}$ 6.0, F-3 or F-5), −142.2 (1F, d, $^4J_{FF}$ 6.0, F-3 or F-5); *m/z* (Electrospray) 330.1 / 332.1 (1:1 ratio, $[M+H]^+$, 44); $[M+H]^+$ 329.99359. $C_{13}H_{11}BrF_2NO_2$ requires 329.99357.

3.4.3. Preparation of 3,5,6-trifluoro-N-[2-(methyloxy)ethyl]-4-phenyl-2-pyridinamine ***16***

A mixture of 4-bromo-3,5,6-trifluoro-*N*-[2-(methyloxy)ethyl]-2-pyridinamine (99.5 mg, 0.35 mmol), phenyl boronic acid (298 mg, 2.44 mmol), dichloro(1,1′-bis(diphenylphosphino)ferrocene)palladium(II)-dichloromethane adduct (28.5 mg, 0.03 mmol) and aqueous sodium carbonate (524 μL of a 2 M solution, 1.05 mmol) in 1,4-dioxane (2.0 mL) was heated in a microwave reactor at 160 °C for 40 min. After filtration and concentration *in vacuo*, water and CH_2Cl_2 (20 mL each) were added and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (2× 15 mL) and the combined organic phases were concentrated *in vacuo* and purified by preparative HPLC (35–85% aqueous MeCN gradient), yielding the title compound (59.4 mg, 0.21 mmol) as an off-white solid; mp 65–67 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.41 (3H, s, OMe), 3.59–3.66 (4H, m, $C\underline{H}_2C\underline{H}_2OMe$), 4.98 (1H, br. s, NH), 7.47–7.52 (5H, m, Ph); ^{13}C NMR (101 MHz, DMSO-*d*6) δ 39.7 (1C, s, $NH\underline{C}H_2$), 57.9 (1C, s, OMe), 70.2 (1C, s, $\underline{C}H_2OMe$), 127.1 (1C, br. t, $^3J_{CF}$ 2.4, Ph), 128.1 (1C, td, $^2J_{CF}$ 15.6, $^3J_{CF}$ 3.5, C-4), 128.7 (2C, s, Ph), 129.6 (1C, s, Ph), 129.6 (2C, s, Ph), 130.5 (1C, dd, $^1J_{CF}$ 243.3, $^2J_{CF}$ 30.8, C-5), 138.7 (1C, dd, $^1J_{CF}$ 250.1, $^3J_{CF}$ 4.8, C-3), 142.4 (1C, dd, $^2J_{CF}$ 17.2, $^3J_{CF}$ 15.6, C-2), 145.2 (1C, ddd, $^1J_{CF}$ 227.5, $^2J_{CF}$ 15.4, $^4J_{CF}$ 2.6, C-6); ^{19}F NMR (377 MHz, $CDCl_3$) δ −95.2 (1F, dd, $^5J_{FF}$ 29.5, $^3J_{FF}$ 24.0, F6), −148.7 (1F, br. d, $^5J_{FF}$ 29.5, F-3), −162.4 (1F, dd, $^3J_{FF}$ 24.0, $^4J_{FF}$ 4.0, F-5); *m/z* (Electrospray) 283.2 ($[M+H]^+$, 100); $[M+H]^+$ 283.10499. $C_{14}H_{14}F_3N_2O$ requires 283.10527.

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