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Synthesis of functionalised fluorinated pyridine derivatives by site-selective Suzuki-Miyaura cross-coupling reactions of halogenated pyridines

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Abstract: The Suzuki-Miyaura reaction of 2,6-dichloro-3-(trifluoromethyl)pyridine with 1 equiv of arylboronic acids resulted in site-selective formation of 2-aryl-6-chloro-3-(trifluoromethyl)pyridine. Due to electronic reasons, the reaction takes place at the sterically more hindered position. The selectivity was rationalised by DFT calculations. The one-pot reaction with two different arylboronic acids afforded 2,6-diaryl-3-(trifluoromethyl)pyridine containing two different aryl substituents. The reactions proceeded smoothly in the absence of phosphine ligands. In addition, Suzuki-Miyaura reactions of 2,6-dichloro-4-(trifluoromethyl)pyridine with one or two equivalents of arylboronic acids were carried out.

Keywords: catalysis; ligand free; organofluorine compounds; regioselectivity; Suzuki-Miyaura reaction.

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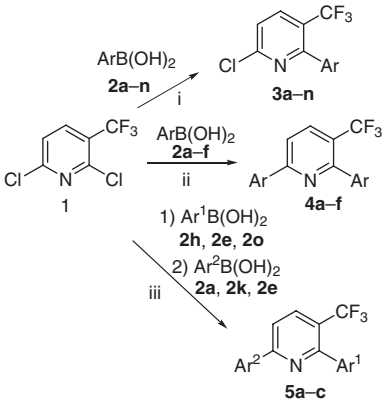
1 Introduction

Functionalised pyridine derivatives are of great importance as drugs and as agricultural products, such as herbicides, insecticides, fungicides, and plant growth regulators [1–6]. The pyridine nucleus is also present in many natural products [7–9]. Many pyridine derivatives are inhibitors of certain enzymes. For example, pyridine derivatives fused to a naphthalene ring are inhibitors of phosphodiesterase and thus used as antiasthmatic agents [10]. Certain pyridine N-oxide rings are CCR5 antagonists and used as anti-HIV-1 agents [11]. Other pyridine derivatives are PI3 kinase and p110α inhibitors [12]. Pyridines have also been reported to act as anti-tumour [13] and antifungal [14] derivatives.

The Hantzsch and the Chichibabin processes are classical pyridine syntheses and functionalisations [15, 16]. The synthesis of trifluoromethyl-substituted pyridines is a challenging task. Such molecules have been prepared by cycloaddition of nitriles with dienes [17], by cyclisation reactions of ethyl 3-amino-3-ethoxypropenoate [18], and by cyclisations of CF_3 substituted electrophiles with cyanoacetic amide [19]. 2,6-Diaryl-3-cyano-4-(trifluoromethyl)pyridines have been prepared by cyclocondensation of 1-aryl-4-trifluoro-1,3-butadienones with β-amino-β-arylacrylonitrile [20]. Recently, we have reported the synthesis of 4-trifluoromethylpyridines by cyclisation of 3-hydroxy-pent-4-yn-1-ones with urea [21]. In recent years, pyridines have been prepared by transition metal catalysed reactions [22–24]. To date, Suzuki-Miyaura reactions of polyhalogenated heterocycles have been studied [25–38]. This includes site-selective palladium catalysed cross-coupling reactions of dihalogenated

pyridine derivatives [39]. Based on our interest in Pd-catalysed coupling reactions [39] we disclosed Suzuki [40] and Sonogashira [41] reactions of pentachloropyridine. Recently, we reported site-selective Suzuki-Miyaura reactions of 2,4-dichloro-1-(trifluoromethyl)benzene and related fluorinated substrates [42–44]. In 2013, we also disclosed a preliminary report on Suzuki-Miyaura reactions of 2,6-dichloro-3-(trifluoromethyl)-pyridine [45]. Herein, we wish to present full details of this latter work, which includes also a rationalisation of the results based on DFT calculations. In addition, we report, for the first time, the synthesis of 2,6-diaryl-4-(trifluoromethyl) pyridines by Suzuki-Miyaura reactions of 2,6-dichloro-4-(trifluoromethyl)pyridine.



Scheme 1: Reagents and conditions: i, synthesis of **3a–n**: **1** (1.0 equiv), **2a–n** (0.9 equiv), K_3PO_4 (1.5 equiv), $Pd(OAc)_2$ (2 mol%), H_2O-DMF (1:1), 20°C, 12 h; ii, synthesis of **4a–f: 1** (1.0 equiv), **2a–f** (2.2 equiv), K_3PO_4 (2.5 equiv), $Pd(OAc)_2$ (2 mol%), H_2O-DMF (1:1), 20°C, 12–16 h. iii, one-pot synthesis of **5a–e**: **1** (1.0 equiv), **2h**, **2e**, **2o**, **2e**, **2b** (1.0 equiv), K_3PO_4 (1.5 equiv), $Pd(OAc)_2$ (2 mol%), H_2O-DMF (1:1), 20°C, 8 h, (2) **2a**, **2k**, **2f** (1.2 equiv), K_3PO_4 (1.5 equiv), $Pd(OAc)_2$ (2 mol%), H_2O-DMF (1:1), 50°C, 8 h.

2 Results and discussion

2.1 Reactions of 2,6-dichloro-3-(trifluoromethyl)pyridine

In our preliminary report [45], we studied Suzuki-Miyaura reactions of 2,6-dichloro-3-(trifluoromethyl)pyridine(**1**). The reaction with phenyl boronic acid (**2a**, 0.9 equiv) was chosen as a model reaction for optimisation of the conditions. The study was carried out by using various Pd catalysts in combination with various ligands. 6-Chloro-2-phenyl-3-(trifluoromethyl)pyridine (**3a**) was isolated in very good yield (87%) using $Pd(OAc)_2$ (2 mol%) in the absence of any ligand. The reaction proceeded with excellent site-selectivity in favour of position 2. The Suzuki-Miyaura reaction of **1** with one equivalent of aryl boronic acids **2a–n** afforded 2-aryl-6-chloro-3-(trifluoromethyl) pyridines **3a–n** in moderate to good yields (Scheme 1, Table 1). All reactions were carried out using $Pd(OAc)_2$ (2 mol%) as the catalyst (in the absence of any ligand), K_3PO_4 (1.5 equiv) as the base, and a mixture of H_2O and DMF (1:1) as the solvent. The reactions proceeded at room temperature.

The Suzuki-Miyaura reaction of **1** with 2.2 instead of 0.9 equiv of arylboronic acids **2a–d**, **2f**, **2i**, carried out under otherwise identical conditions as given for the synthesis of **3a–n**, afforded 2,6-diaryl-3-(trifluoromethyl)pyridines **4a–f** in good yields (Scheme 1, Table 2).

The one-pot reaction of **1** with two different arylboronic acids (sequential addition) afforded the unsymmetrical 2,6-diphenyl-3-trifluoromethyl-pyridines **5a–e** containing two different aryl groups (Scheme 1, Table 3) After addition of 1.0 equiv of the first arylboronic acid, the mixture was stirred for 8–10 h at 20°C. Subsequently,

Table 1: Synthesis of **3a–n.**

2, 3	Ar	% (3)[a]
a	C_6H_5	87
b	4-MeC_6H_4	92
c	4-(Acetyl)C_6H_4	69
d	4-(CF_3O)C_6H_4	65
e	3,5-$(Me)_2C_6H_3$	78
f	4-EtC_6H_4	72
g	4-(EtO)C_6H_4	78
h	4-*t*BuC_6H_4	82
i	4-(MeO)C_6H_4	61
j	4-FC_6H_4	68
k	3-MeC_6H_4	71
l	2-Thienyl	65
m	4-(Ph)C_6H_4	63
n	3,5-$(CF_3)_2C_6H_3$	71

[a]Yields of isolated products.

Table 2: Synthesis of **4a–f.**

2	4	Ar	% (4)[a]
b	**a**	4-MeC_6H_4	70
c	**b**	4-(Acetyl)C_6H_4	68
d	**c**	4-(CF_3O)C_6H_4	58
a	**d**	C_6H_5	68
i	**e**	4-(MeO)C_6H_4	63
f	**f**	4-EtC_6H_4	76

[a]Yields of isolated products.

Table 3: Synthesis of **5a–e.**

2	5	Ar^1	Ar^2	% (5)[a]
h, a	**a**	4-t-BuC_6H_4	C_6H_5	65
e, k	**b**	3,5-$(Me)_2C_6H_3$	3-$MeOC_6H_4$	54
o, a	**c**	4-(vinyl)C_6H_4	C_6H_5	59
e, f	**d**	3,5-$(Me)_2C_6H_3$	4-EtC_6H_4	71
b, f	**e**	4-MeC_6H_4	4-EtC_6H_4	69

[a]Yields of isolated products.

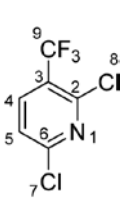
the second arylboronic was added (1.2 equiv). At the same time, a fresh amount of catalyst (2 mol%) was added. The mixture was subsequently stirred at elevated temperature (50°C, 8 h) to complete the reaction.

DFT calculations have been performed to understand the site-selectivity in favour of position 2 (Scheme 2). Position 2 is, although sterically crowded, electronically more deficient and thus favorable for Pd catalysed cross-coupling reactions. Our calculations illustrate that the CF_3 group is very influential at each step of the catalytic cycle (*vide infra*).

2.2 Calculations

2.2.1 Oxidative addition

Coordination of the starting material 1 with the Pd(0) catalyst generates two isomeric complexes **Int1A** and **Int1B** responsible for Suzuki coupling at positions 6 and 2, respectively. In both of these intermediates, the pyridine ring is η^2 coordinated to the metal centre. In **Int1B**, palladium is coordinated to C2–C3 whereas in **Int1A**, palladium is bonded to C5–C6 (Fig. 1). In **Int1A**, Pd–C5 and Pd–C6 bond lengths are 2.17 Å and 2.08Å, respectively, whereas **Int1B** Pd–C3 and Pd–C2 bond lengths are 2.15 Å and 2.076 Å, respectively. **Int1B** is 0.48 kcal mol^{-1} more stable than **Int1A**. A plausible reason for this energy difference is the relatively shorter palladium–carbon bond lengths in **Int1B** as compared to **Int1A** (*vide supra*). **Int1A**



Scheme 2: Numbering scheme for the discussion of the computational results.

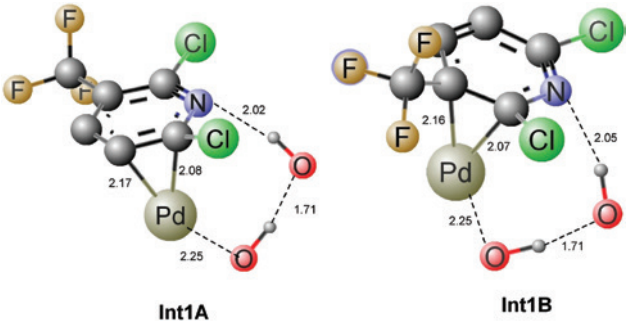


Fig. 1: Optimized geometries of **Int1A** and **Int1B**. All bond distances are in Ångströms. Unnecessary hydrogen atoms are removed for clarity.

and **Int1B** have several other common structural features. For example, only one water molecule is coordinated to palladium, whereas the second water molecule undergoes a hydrogen bonding interaction with the nitrogen of the pyridine ring and the water molecule coordinated to palladium. The Pd–O1 bond length is 2.25 Å. A proton of thecoordinated water molecule is hydrogen bonded to the other water molecule which is in turn hydrogen bonded to the nitrogen of the pyridine ring.

Oxidative addition of palladium in the C–Cl bond of **Int1B** is more favourable than in case of **Int1A**. The transition state TS1B is located at a barrier of 8.60 kcal mol^{-1} from **Int1B**, whereas the analogous transition state TS1A from **Int1A** lies at a barrier of 9.76 kcal mol^{-1}. This finding is consistent with the experimental observation that the Suzuki reaction favourably occurs at position 2. Recently, Huang and co-workers [46] have shown that B3LYP/6-31G* with pseudopotential on Pd (LANL2DZ) can reliably model the Suzuki coupling reaction. The activation barriers for the oxidative addition of our substrates are comparable to those reported by Huang and co-workers [46]. **TS1A** and **TS1B** are structurally very similar. We believe that the low activation barrier for **TS1B** is not due to the highly electron deficient nature of C2, because the Pd–Cl bond of **TS1A** is much shorter and stronger as compared to the analogous bonds in case of **TS1B**. In **TS1B**, Pd–Cl8 and C2–Cl8 bond lengths are 2.60 Å and 2.00 Å, whereas in **TS1A**, Pd–Cl7 and C6–Cl7 bond lengths are 2.58 and 1.95 Å, respectively. The higher stability of **TS1B** over **TS1A** is probably due to the interaction of a fluorine atom of the CF_3 group with the metal centre (Fig. 2). The Pd–F bond is 2.91 Å. The oxidative addition step is exothermic by 17.28 and 16.89 kcal mol^{-1} for **Int1A** (Fig. 4) and **Int1B** (Fig. 3), respectively. Int2B, product of oxidative addition from **Int1B**, is less stable than the analogous species **Int2A**. The reason for this difference may be attributed to the steric effect in the

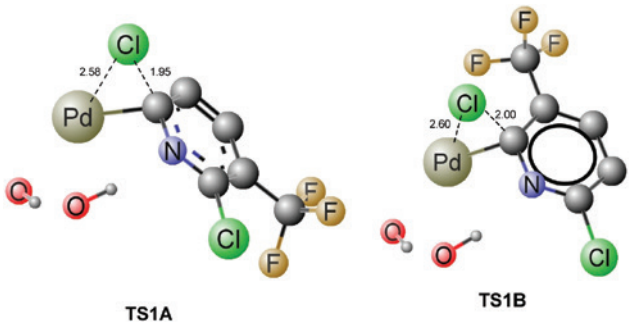


Fig. 2: Optimised geometries of **TS1A** and **TS1B**. All bond distances are in Ångströms. Unnecessary hydrogen atoms are removed for clarity.

former species. A favourable F–Pd interaction available in **TS1B** is diminished in **Int2B** which leaves behind only the steric interactions responsible for the destabilisation of **Int2B** (chlorine orientation).

Subsequent to the oxidative addition, boronic acid coordinates to palladium which is followed by cleavage of the Pd–Cl bond to generate a palladium species **Int4B**, which undergoes transmetalation.

2.2.2 Transmetalation

Coordination of boronic acid with **Int2A** generates **Int3A** and the process is exothermic by 55.13 kcal mol^{-1}, however, the cleavage of the Pd–Cl bond is endothermic by 72.92 kcal mol^{-1}. Intermediate **Int4A**, generated from cleavage of the Pd–Cl bond, is almost comparable in energy to **Int1A**. Similarly, the coordination of the boronic acid with **Int2B** is exothermic by 53.19 kcal mol^{-1} to generate **Int3B**. However, the detachment of chlorine from **Int3B** to generate **Int4B** is less endothermic than the similar process in **Int4A** (compare 61.88 kcal mol^{-1} for **Int3B** with 72.92 kcal mol^{-1} for **Int3A**). Structures of **Int4A** and **Int4B** are very different in terms of coordination around the metal centre. **Int4B** has a fluorine atom from the CF_3 group bonded to the metal which does not leave behind any vacant coordination site for the interaction of boronic acid derived oxygen atoms with the metal centre. Boronic acid in **Int4B** is not bonded to the metal centre rather it is held by hydrogen bonds with the water molecules around palladium. All attempts to locate an intermediate where boronic acid is coordinated to palladium resulted in **Int4B**, probably due to the higher stability

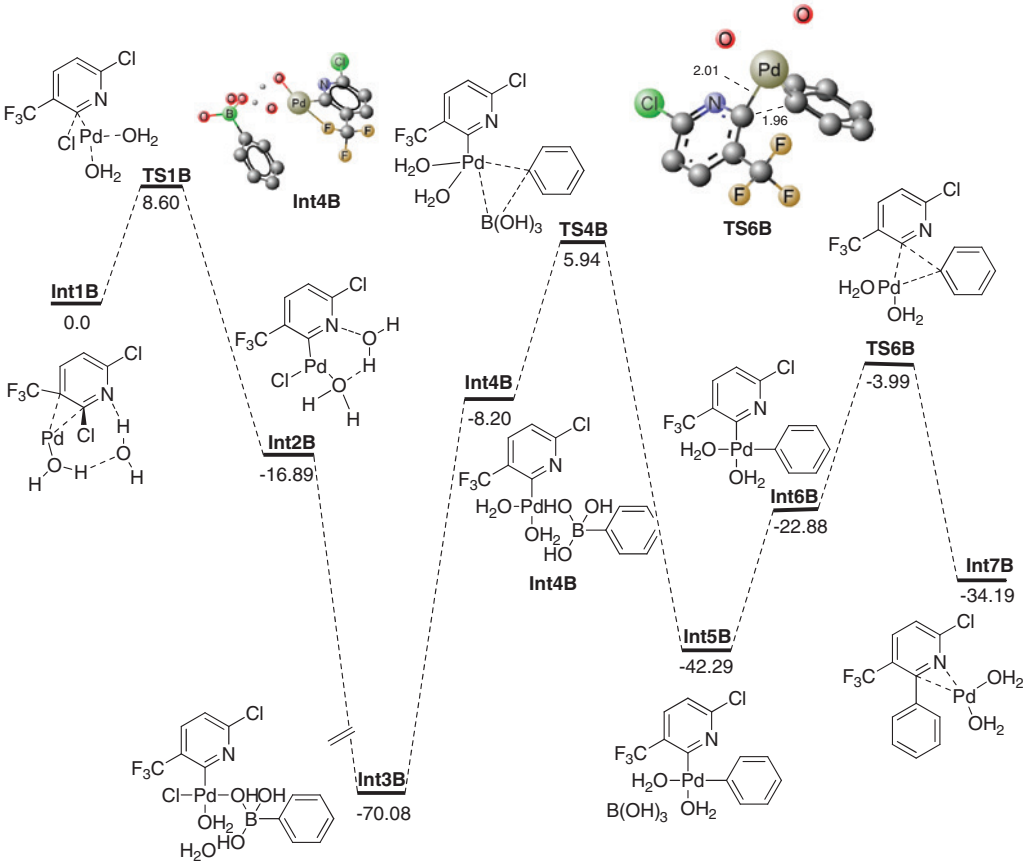


Fig. 3: Energy profile for three major steps of the Suzuki coupling starting from **Int1B**. All values are in kcal mol^{-1} and all bond lengths are in Ångströms. Unnecessary hydrogen atoms are removed for clarity.

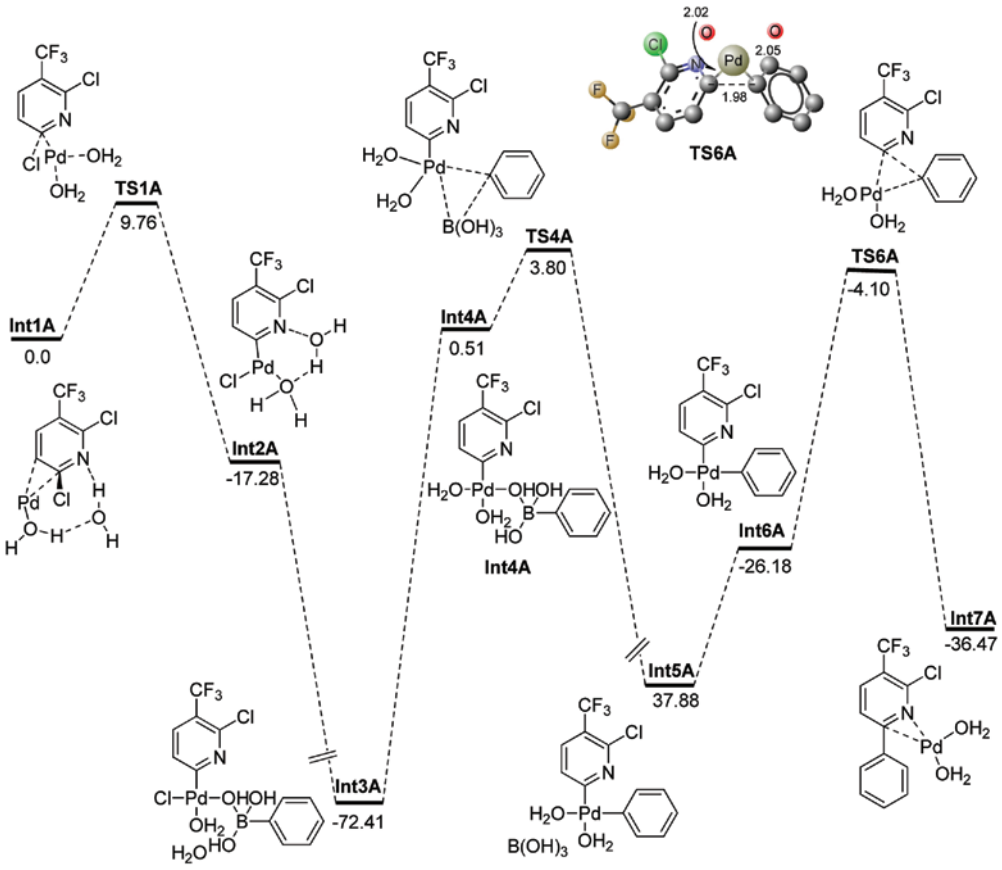


Fig. 4: Energy profile for three major steps of the Suzuki coupling starting from **Int1A**. All values are in kcal mol^{-1} and all bond lengths are in Ångströms. Unnecessary hydrogen atoms are removed for clarity.

of **Int4B**. On the other hand, in **Int4A**, boronic acid is coordinated to palladium through an oxygen atom.

The higher stability of **Int4B** over **Int4A** is translated into a higher activation barrier for the transmetalation of the former as compared to the latter. The transition state for transmetalation **TS4B**, derived from **Int4B**, is located at a barrier of 14.14 kcal mol^{-1} whereas the activation barrier for transmetalation from **Int4A** is only 3.29 kcal mol^{-1}. The transmetalation step is highly exothermic. Formation of **Int5A** from **Int4A** is exothermic by 38.39 kcal mol^{-1}, whereas the analogous reaction in **Int4B** is exothermic by 34.09 kcal mol^{-1}. Loss of $B(OH)_3$ from **Int5A** and **Int5B** generates **Int6A** and **Int6B**, respectively, which undergo reductive elimination to deliver the final products.

2.2.3 Reductive elimination

Very surprisingly, the reductive elimination step turned out to be the one with the highest activation barrier in the catalytic cycle for both products (rate limiting step). A transition state **TS6A** is located at a barrier of 22.08 from **Int6A**. The C–C bond, which is being formed in the transition state, has a length of 1.98 Å, whereas the Pd–C bonds are 2.02 Å and 2.05 Å (shown in Figure). The analogous transition state for the formation of **Int7B** is 18.89 kcal mol^{-1}. The C–C bond is 1.96 Å and the Pd–C bonds are 2.01 and 2.07 Å. Two fluorine atoms of the CF_3 group are involved in hydrogen bonding with the *ortho* hydrogen of the phenyl ring. The high activation barriers for the reductive elimination step may be attributed to the electron rich nature of Pd. The activation barrier for the reduction is high, but still accessible at room temperature. From the computational studies, it is evident that the observed regioselectivity may be attributed to the low activation barrier of the oxidative addition of **Int1B** over **Int1A**, and to the associated low activation barrier of the reductive elimination in **Int6B**.

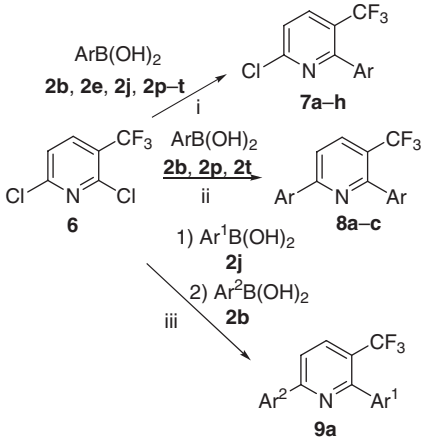
2.3 Reactions of 2,6-dichloro-4-(trifluoromethyl)pyridine

The Suzuki-Miyaura reaction of commercially available (symmetrical) 2,6-dichloro-4-(trifluoromethyl)pyridine **6**

with one equivalent of aryl boronic acids **2b**, **2e**, **2f**, **2j**, **2p–t** afforded 2-aryl-6-chloro-3-(trifluoromethyl)pyridine **7a–h** in moderate to good yields by adopting the same synthetic protocol as for the synthesis of compounds **3a–n** (Scheme 3, Table 4). First, the reaction conditions were optimised in order to achieve the product in high yield. The best yields were obtained using 0.9 equiv of the arylboronic acid, $Pd(OAc)_2$ (2 mol%) as the catalyst, K_3PO_4 (1.5 equiv) as the base and H_2O-DMF (1:1) as the solvent (20°C, 8–12 h). In this case, small amounts (2%–5%) of 2,6-diaryl-4-(trifluoromethyl)pyridine were obtained in some cases as side-product.

The Suzuki-Miyaura reaction of **6** with 2.2 equiv of arylboronic acids **2b**, **2p**, **2t**, carried out under otherwise identical conditions as given for the synthesis of **3a–n**, afforded the 2,6-diaryl-4-trifluoromethyl-pyridines **8a–c** in good yields (Scheme 3, Table 5). In this case predominantly 2,6-diaryl-4-trifluoromethyl pyridines were obtained.

The one-pot reaction of **6** with two different arylboronic acids (4-fluorophenylboronic acid, 4-methylphenylboronic acid) afforded the unsymmetrical 2-(4-fluorophenyl)-6-*p*-tolyl-4-(trifluoromethyl) pyridine **9a** containing two different aryl groups (Scheme 4, adopting the same procedure as for synthesis of **3a–n**. After addition of 1.0 equiv of 4-fluorophenylboronic acid, the mixture was stirred for 8–10 h at 20°C. Subsequently, 4-methylphenylboronic acid was added (1.2 equiv). At the same time, fresh loading of catalyst (2 mol%) was carried out in order to provide the reaction conditions of the second aryl boronic acid addition. The mixture was subsequently stirred at elevated temperature (50°C, 8 h) to complete the reaction.



Scheme 3: Reagents and conditions: i, synthesis of **7a–h**: **6** (1.0 equiv), **2b**, **2e**, **2j**, **2p–t** (0.9 equiv), K_3PO_4 (1.5 equiv), $Pd(OAc)_2$ (2 mol%), H_2O-DMF (1:1), 20°C, 8–12 h: ii, synthesis of **8a–c**: **6** (1.0 equiv), **2b**, **2p**, **2t** (2.2 equiv), K_3PO_4 (2.5 equiv), $Pd(OAc)_2$ (2 mol%), H_2O-DMF (1:1), 20°C, 12–16 h: iii, one-pot synthesis of **9a**: 1), **6** (1.0 equiv), **2j** (0.9 equiv), K_3PO_4 (1.5 equiv), $Pd(OAc)_2$ (2 mol%), H_2O-DMF (1:1), 20°C, 8 h, 2), **2b** (1.2 equiv), K_3PO_4 (1.5 equiv), $Pd(OAc)_2$ (2 mol%), H_2O-DMF (1:1), 50°C, 8 h.

Table 4: Synthesis of **7a–h.**

2	7	Ar	% (7)[a]
b	**a**	4-MeC_6H_4	75
e	**b**	3,5-$(Me)_2C_6H_3$	70
j	**c**	4-FC_6H_4	71
p	**d**	2-$MeOC_6H_4$	69
q	**e**	3-$MeOC_6H_4$	67
r	**f**	4-*i*PrC_6H_4	71
s	**g**	3-FC_6H_4	72
t	**h**	3,5-$(MeO)_2C_6H_3$	70

[a]Yields of isolated products.

3 Experimental section

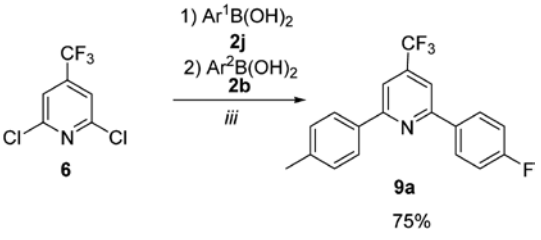
3.1 General

Chemicals were purchased from Alfa Aesar, Sigma Aldrich and were used without further purification. NMR spectra were recorded on Bruker AV 300 and 250 MHz instruments. IR spectra were recorded on a Perkin Elmer FT IR 1600 spectrometer (ATR). Mass spectra were obtained on

Table 5: Synthesis of **8a–c.**

2	8	Ar	% (8)[a]
b	**a**	4-MeC_6H_4	65
p	**b**	2-$MeOC_6H_4$	68
t	**c**	3,5-$(MeO)_2C_6H_3$	58

[a]Yields of isolated products.



Scheme 4: Reagents and conditions: iii, one-pot synthesis of **9a**: 1), **6** (1.0 equiv), **2j** (0.9 equiv), K_3PO_4 (1.5 equiv), $Pd(OAc)_2$ (2 mol%), H_2O-DMF (1:1), 20°C, 8 h, 2), **2b** (1.2 equiv), K_3PO_4 (1.5 equiv), $Pd(OAc)_2$ (2 mol%), H_2O-DMF (1:1), 50°C, 8 h.

a Hewlett-Packard HPGC/MS 5890/5972 instrument (EI, 70 eV) by GC inlet or on an MX-1321 instrument (EI, 70 eV) by direct inlet. Column chromatography was performed on silica gel (63–200 mesh, Merck) and silica gel Merck 60F254 plates were used for TLC. Commercially available solvents were distilled for column chromatography. All other solvents were purified and dried by standard methods.

3.2 General procedure for the synthesis of 6-chloro-2-aryl-3-(trifluoromethyl) pyridine (3a–n)

Mixture of commercially available 2,6-dichloro-3-(trifluoromethyl)pyridine**1** (1 mmol), aryl boronic acids **2a–n** (0.9 mmol), $Pd(OAc)_2$ (2 mol%), K_3PO_4 (1.5 mmol) were added into a solution of H_2O-DMF (1:1, 4 mL) in a oven dried reaction pressure tubes under argon atmosphere. The reaction mixture was stirred at room temperature for 8–12 h. After completion of reaction (TLC controlled), the organic and aqueous layer were separated and the latter was extracted with CH_2Cl_2 (3×25 mL). The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuum. The product was purified by column chromatography (silica gel, EtOAc-heptane). All products were characterised by NMR, GC-MS, HRMS and IR spectroscopic techniques.

3.2.1 6-Chloro-2-phenyl-3-(trifluoromethyl)pyridine (3a)

Starting with **1** (216 mg, 1 mmol), phenyl boronic acid (110 mg, 0.9 mmol), $Pd(OAc)_2$ (2 mol%), K_3PO_4 (207 mg, 1.5 mmol) and mixture of H_2O-DMF (1:1, 2 mL), **3a** was isolated as white solid (233 mg, 87% yield), m.p.: 52–54°C. –^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.90–7.45 (m, 3H, ArH), 7.66 (dd, J = 8.1 Hz, 1H, ArH), 7.91–7.99 (m, 3H, ArH). –^{13}C NMR (300 MHz, $CDCl_3$): δ = 117.9 (CH), 119.1 (d, $^1J_{CF}$ = 272.31 Hz, CF_3), 123.2 (q, $^2J_{CF3}$ = 32.5 Hz, C), 127.3 (2CH), 129.0 (2CH), 130.7 (CH), 136.2 (C), 137.3 (q, $^3J_{CF3}$ = 4.0 Hz CH), 148.7 (C), 160.5 (C). –^{19}F NMR 300 MHz, $CDCl_3$): δ = –63.11 (CF_3). –IR (ATR, cm^{-1}): ν = 2923 (w), 2852 (w), 1590 (w), 1556 (m), 1456 (w), 1312 (w), 1124 (s), 1025 (m), 833 (m), 747 (s), 686 (s). MS (EI, 70 eV): *m/z* (%), 259 (33) $[M+2]^+$, 257 (100) $[M]^+$, 256 (10), 222 (33), 202 (22), 133 (13), 69 (13). –HRMS (EI) calcd. for $C_{12}H_7ClF_3N$ $[M]^+$: 257.04484, found: 257.04504.

3.2.2 6-Chloro-2-p-tolyl-3-(trifluoromethyl)pyridine (3b)

Starting with **1** (216 mg, 1 mmol), (*p*-tolyl)boronic acid (122.4 mg, 0.9 mmol), $Pd(OAc)_2$ (2 mol%), K_3PO_4 (207 mg, 1.5 mmol) and solution of H_2O-DMF (1:1, 2 mL). **3b** was isolated as white solid (249 mg, 92% yield), m.p.: 81–83°C. –^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.33 (s, 3H, CH_3), 7.20 (d, J = 8.4 Hz, 2H, ArH), 7.62 (dd, J = 8.0, J = 0.6 Hz, 1H, ArH), 7.85 (d, J = 8.4 Hz, 2H, ArH), 7.91 (d, J = 8.0 Hz, 1H, ArH). –^{13}C NMR (62.89 MHz, $CDCl_3$): δ = 21.36 (CH_3), 117.5 (CH), 122.5 (d, $^1J_{CF}$ = 272.3 Hz, CF_3), 122.7 (q, $^2J_{CF}$ = 65.8, 32.9 Hz, C), 127.3 (2CH), 129.7 (2CH), 133.5 (C), 137.2 (q, $^3J_{CF}$ = 9.6, 4.2 Hz CH), 141.1 (C), 148.6 (C), 160.5 (C). –^{19}F NMR (282.4 MHz, $CDCl_3$): δ = –63.0 (CF). –IR (ATR, cm^{-1}): ν = 2980 (w), 2962 (w), 2876 (w), 1613 (m), 1583 (m), 1519 (w), 1302 (m), 1140 (s), 1123 (s), 1111 (s), 1019 (s), 841 (s), 820(s). MS (EI, 70 eV): *m/z* (%) 271 (100) $[M]^+$, 273 (34) $[M+2]^+$, 277 (44), 91 (10). –HRMS (ESI) calcd. for $C_{13}H_{10}ClF_3N$ $[M+H]^+$: 272.04484, found 272.04504.

3.2.3 6-Chloro-2-(4-acetylphenyl)-3-(trifluoromethyl) pyridine (3c)

Starting with **1** (216 mg, 1 mmol), 4-acetylphenyl boronic acid (0.9 mmol), $Pd(OAc)_2$ (2 mol%), K_3PO_4 (207 mg, 1.5 mmol) and solution of H_2O-DMF (1:1, 2 mL). **3c** was isolated as white solid (206 mg, 69% yield), m.p.: 115–117°C. –^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.30 (s, 3H, CH_3), 7.76 (dd, J = 8.2, 1H, ArH), 7.98–8.00 (m, 3H, ArH), 8.03–8.08 (m, 2H, ArH). –^{13}C NMR (300 MHz, $CDCl_3$): δ = 25.7 (CH_3), 115.8 (CH), 121.2 (q, $^1J_{CF}$ = 272.4 Hz, CF_3), 122.8 (q, $^2J_{CF3}$ = 32.4, C), 126.5 (2CH), 127.9 (2CH), 136.5 (q, $^3J_{CF3}$ = 9.6, CH), 137.4 (C), 139.2 (C), 147.9 (C), 158.0 (C), 195.4 (C). –^{19}F NMR (300 MHz, $CDCl_3$): δ = –63.2 (CF_3). –IR (ATR, cm^{-1}): ν = 2982 (w), 2964 (w), 1717 (s), 1613 (m), 1591 (m), 1415 (w), 1306 (m), 1144 (s), 1110 (s), 1019 (s), 841 (s), 820(s) MS (EI, 70 eV): *m/z* (%) 299 (22) $[M]^+$, 286 (33), 284 (100), 285 (10), 256 (32). –HRMS (ESI) calcd. for $C_{14}H_{10}ClF_3NO$ $[M+H]^+$: 300.04030, found 300.03248.

3.2.4 6-Chloro-2-(4-(trifluoromethoxy)phenyl)-3-(trifluoromethyl) pyridine (3d)

Starting with **1** (216 mg, 1 mmol), 4-(trifluoromethoxy) phenylboronic acid (184.5 mg, 0.9 mmol), $Pd(OAc)_2$ (2 mol%), K_3PO_4 (1.5 mmol) and solution of H_2O-DMF (1:1, 2 mL). **3d** was isolated as light yellow liquid (221 mg, 65% yield). –^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.23 (dd, J = 9.0, 1.2 Hz, 2H, ArH), 7.63 (dd, J = 8.2 Hz, 1H, ArH), 7.96 (d, J = 8.0 Hz, 2H, ArH), 7.98 (d, J = 8.9 Hz, 1H, ArH). –^{13}C NMR (300 MHz, $CDCl_3$): δ = 116.9 (CH), 120.1 (2CH), 119.4 (q, $^1J_{CF}$ = 259.1 Hz, OCF_3), 121.4 (q, $^1J_{CF}$ = 272.6 Hz, CF_3), 124.5 (C), 127.9 (2CH), 133.7 (C), 137.5 (q, $^3J_{CF3}$ = 9.6 Hz

CH), 147.9 (C), 150.1 (d, J_{CF3} = 1.7 Hz, C), 157.9 (C). –^{19}F NMR (300 MHz, $CDCl_3$): δ = –63.0 (CF_3). –IR (ATR, cm^{-1}): ν = 1589 (m), 1560 (w), 1315 (m), 1251 (s), 1209 (s), 1140 (s), 1171 (s), 1022 (s), 832 (m). MS (EI, 70 eV): *m/z* (%), 343 (33) $[M+2]^+$, 341 (100) $[M]^+$, 306 (15), 244 (19), 69 (21). –HRMS (EI) calcd. for $C_{13}H_6ClF_6NO$ $[M]^+$: 341.00366, found 341.00351.

3.2.5 6-Chloro-2-(3,5-dimethylphenyl)-3-(trifluoromethyl)pyridine (3e)

Starting with **1** (216 mg, 1 mmol), 3,5-dimethylphenylboronic acid (135 mg, 0.9 mmol), $Pd(OAc)_2$ (2 mol%), K_3PO_4 (207 mg, 1.5 mmol) and solution of H_2O-DMF (1:1, 2 mL). **3e** was isolated as colorless liquid (222 mg, 78% yield). –^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.30 (s, 6H, $2CH_3$), 7.02 (s, 1H, ArH), 7.54 (s, 2H, ArH), 7.61 (d, J = 8.1 Hz, 1H, ArH), 7.90 (d, J = 8.3 Hz, 1H, ArH). –^{13}C NMR (300 MHz, $CDCl_3$): δ = 21.36 ($2CH_3$), 118.1 (CH), 122.6 (d, $^1J_{CF}$ = 272.1 Hz, CF_3), 122.9 (q, $^2J_{CF}$ = 66.7 Hz, C), 125.1 (2CH), 132.4 (2CH), 136.2 (C), 137.1 (q, $^3J_{CF}$ = 9.7 Hz, CH), 138.6 (2C), 148.5 (C), 160.9 (C). –^{19}F NMR (300 MHz, $CDCl_3$): δ = –63.0 (CF_3). –IR (ATR, cm^{-1}): ν = 2919 (w), 2962 (w), 2863 (w), 1590 (m), 1556 (m), 1349 (m), 1315 (s), 1138 (s), 1121 (s), 1020 (s), 834 (m). MS (EI, 70 eV): *m/z* (%) 285 (100) $[M]^+$, 287 (33) $[M+2]^+$, 270 (17). –HRMS (EI) calcd. for $C_{14}H_{11}ClF_3N$ $[M]^+$: 285.05266, found 285.05199.

3.2.6 6-Chloro-2-(4-ethylphenyl)-3-(trifluoromethyl) pyridine (3f)

Starting with **1** (216 mg, 1 mmol), 4-ethylphenylboronic acid (135 mg, 0.9 mmol), $Pd(OAc)_2$ (2 mol%), K_3PO_4 (207 mg, 1.5 mmol) and solution of H_2O-DMF (1:1, 2 mL). **3f** was isolated as colorless liquid (205 mg, 72% yield). –^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.18 (t, J = 7.8 Hz, 3H, CH_3), 2.63 (q, J = 15.3, 7.5 Hz, 2H, CH_2), 7.23 (d, J = 8.4 Hz, 2H, ArH), 7.62 (dd, J = 8.1, 0.7 Hz, 1H, ArH), 7.87 (d, J = 8.4 Hz, 2H, ArH), 7.91 (dd, J = 8.1, 0.4 Hz, 1H, ArH). –^{13}C NMR (300 MHz, $CDCl_3$): δ = 15.29 (CH_3), 28.71 (CH_2), 117.5 (CH), 122.5 (d, $^1J_{CF}$ = 272.1 Hz, CF_3), 122.7 (q, $^2J_{CF}$ = 33.3 Hz, C), 127.4 (2CH), 128.6 (2CH), 133.7 (C), 137.2 (q, $^3J_{CF3}$ = 4.3 Hz CH), 147.4 (C), 148.6 (C), 160.6 (C). –^{19}F NMR (300 MHz, $CDCl_3$): δ = –63.0 (CF_3). –IR (ATR, cm^{-1}): ν = 2958 (w), 2963 (w), 2863 (w), 1592 (s), 1560 (m), 1348 (s), 1315 (s), 1137 (s), 1120 (s), 1023 (s), 834 (m), 742 (s). MS (EI, 70 eV): *m/z* (%) 285 (100) $[M]^+$, 287 (33) $[M+2]^+$, 284 (51), 272 (33), 271 (18), 270 (98), 269 (15). –HRMS (EI) calcd. for $C_{14}H_{11}ClF_3N$ $[M]^+$: 285.05266, found 285.05203.

3.2.7 6-Chloro-2-(4-ethoxyphenyl)-3-(trifluoromethyl) pyridine (3g)

Starting with **1** (216 mg, 1 mmol), 4-ethoxyphenylboronic acid (149.4 mg, 0.9 mmol), $Pd(OAc)_2$ (2 mol%), K_3PO_4 (207 mg, 1.5 mmol) and solution of H_2O-DMF (1:1, 2 mL). **3g** was isolated as white solid (235 mg, 78% yield), m.p.: 74–75°C. –^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.36 (t, J = 6.9 Hz, 3H, CH_3), 4.01 (q, J = 13.8, 6.8 Hz, 2H, CH_2), 6.87 (d, J = 8.9 Hz, 2H, ArH), 7.30 (dd, J = 8.3, 0.7 Hz, 1H, ArH), 7.40 (d, J = 8.4 Hz, 2H, ArH), 7.90 (d, J = 8.5 Hz, 1H, ArH). –^{13}C NMR (300 MHz, $CDCl_3$): δ = 13.7 (CH_3), 62.5 (OCH_2), 113.1 (CH), 115.3 (d, $^1J_{CF3}$ = 272.4 Hz, CF_3), 120.9 (CH), 122.0 (q, $^2J_{CF3}$ = 32.0 Hz, C), 124.3(C), 126.6 (C), 127.9 (C), 129.1(C), 129.3 (d, $^4J_{CF3}$ = 1.9 Hz, CH), 136.6 (q, $^3J_{CF}$ = 5.0 Hz, CH), 152.3 (C), 157.9 (d, $^4J_{CF3}$ = 2.8 Hz, C), 159 (C). –^{19}F NMR (300 MHz, $CDCl_3$): δ = –57.0 (CF_3). –IR (ATR, cm^{-1}): ν = 3064 (w), 2980 (m), 2877 (w), 1660 (w), 1544 (w), 1140 (m), 816 (s). MS (EI, 70 eV): *m/z* (%) 301 (57) $[M]^+$, 273 (100), 238 (12). –HRMS (EI) calcd. for $C_{14}H_{11}ClF_3NO$ $[M]^+$: 301.04758, found 301.04758.

3.2.8 6-Chloro-2-(4-tert-butylphenyl)-3-(trifluoromethyl) pyridine (3h)

Starting with **1** (216 mg, 1 mmol), 4-*t*-butylphenylboronic acid (160 mg, 0.9 mmol), $Pd(OAc)_2$ (2 mol%), K_3PO_4 (207 mg, 1.5 mmol) and solution of H_2O-DMF (1:1, 2 mL). **3h** was isolated as colourless liquid (256 mg, 82% yield). –^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.35 (s, 9H, $3CH_3$), 7.51 (d, J = 8.6 Hz, 2H, ArH), 7.71 (dd, J = 8.1, 0.7 Hz, 1H, ArH), 7.96 (d, J = 8.8 Hz, 2H, ArH), 8.01 (d, J = 8.8 Hz, 1H, ArH). –^{13}C NMR (300 MHz, $CDCl_3$): δ = 31.1 ($3CH_3$), 34.8 (C), 117.6 (CH), 122.5 (d, $^1J_{CF}$ = 272.0 Hz, CF_3), 122.8 (q, $^2J_{CF3}$ = 33.4 Hz, C), 126.1 (2CH), 127.2 (2CH), 133.5 (C), 137.2 (q, $^3J_{CF3}$ = 5.0 Hz CH), 148.6 (C), 154.2 (C), 160.5 (C). –^{19}F NMR (300 MHz, $CDCl_3$): δ = –63.0 (CF_3). –IR (ATR, cm^{-1}): ν = 3064 (w), 2980 (m), 2877 (w), 1660 (w), 1544 (w), 1140 (m), 816 (s). MS (EI, 70 eV): *m/z* (%) 313 (17) $[M]^+$, 300 (33), 299 (17), 298 (100), 270 (17). –HRMS (EI) calcd. for $C_{16}H_{15}ClF_3N$ $[M]^+$: 313.08396, found 313.08355.

3.2.9 6-Chloro-2-(4-methoxyphenyl)-3-(trifluoromethyl) pyridine (3i)

Starting with **1** (216 mg, 1 mmol), 4-methoxyphenyl boronic acid (137 mg, 0.9 mmol), $Pd(OAc)_2$ (2 mol%), K_3PO_4 (207 mg, 1.5 mmol) and solution of H_2O-DMF (1:1, 2 mL). **3i** was isolated as colourless liquid (175 mg, 61% yield).

–^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.85 (s, 3H, OCH_3), 6.97 (d, J = 8.9 Hz, 2H, ArH), 7.39 (dd, J = 8.3, 0.7 Hz, 1H, ArH), 7.49 (d, J = 8.4 Hz, 2H, ArH), 8.00 (d, J = 8.3 Hz, 1H, ArH). –^{13}C NMR (300 MHz, $CDCl_3$): δ = 55.3 (OCH_3), 113.6 (2CH), 123.4 (d, $^1J_{CF3}$ = 273.9 Hz, CF_3), 122.1 (CH), 123.4 (q, $^2J_{CF3}$ = 32.6 Hz, C), 128.9 (C), 130.4 (2CH), 137.6 (q, $^3J_{CF3}$ = 4.7 Hz CH), 153.4 (C), 158.9 (C), 160.6 (C). –^{19}F NMR (300 MHz, $CDCl_3$): δ = –57.0 (CF_3). –IR (ATR, cm^{-1}): ν = 3064 (w), 2980 (m), 2877 (w), 1660 (w), 1544 (w), 1140 (m), 816 (s). MS (EI, 70 eV): *m/z* (%): 289 (35) $[M+2]^+$, 287 (100) $[M]^+$, 244 (13), 224 (15). –HRMS (EI) calcd. for $C_{13}H_9ClF_3NO$ $[M]^+$: 287.03193, found 287.03186.

3.2.10 6-Chloro-2-(4-fluorophenyl)-3-(trifluoromethyl) pyridine (3j)

Starting with **1** (216 mg, 1 mmol), 4-fluorophenyl boronic acid (126 mg, 0.9 mmol), $Pd(OAc)_2$ (2 mol%), K_3PO_4 (207 mg, 1.5 mmol) and solution of H_2O-DMF (1:1, 2 mL). **3j** was isolated as colourless liquid (187 mg, 68% yield). –^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.06–7.09 (m, 2H, ArH), 7.62 (d, J = 8.4, Hz, 1H, ArH), 7.95 (d, J = 8.3 Hz, 2H, ArH), 7.97 (d, J = 9.5 Hz, 1H, ArH). –^{13}C NMR (250 MHz, $CDCl_3$): δ = 115.9 (CH), 116.3 (CH), 117.6 (CH), 122.3 (d, $^1J_{CF3}$ = 272.1 Hz, CF_3), 122.8 (q, $^2J_{CF3}$ = 33.8 Hz, C), 129.3 (CH), 129.5 (CH), 137.4 (q, $^3J_{CF}$ = 4.8 Hz CH), 148.7 (C), 159.3 (C), 162.5 (C), 166.5 (C). –^{19}F NMR (300 MHz, $CDCl_3$): δ = –63.1 (CF_3). –IR (ATR, cm^{-1}): ν = 1590 (m), 1582 (w), 1508 (w), 1315 (m), 1304 (m), 1136 (s), 1115 (m), 1020 (m), 826 (s). MS (EI, 70 eV): *m/z* (%): 277 (33) $[M+2]^+$, 275 (100) $[M]^+$, 240 (32), 220 (21), 151 (15). –HRMS (EI) calcd. for $C_{12}H_6ClF_4N$ $[M]^+$: 275.01194, found 275.01108.

3.2.11 6-Chloro-2-m-tolyl-3-(trifluoromethyl)pyridine (3k)

Starting with **1** (216 mg, 1 mmol), 3-methylphenyl boronic acid (122 mg, 0.9 mmol), $Pd(OAc)_2$ (2 mol%), K_3PO_4 (207 mg, 1.5 mmol) and solution of H_2O-DMF (1:1, 2 mL). **3k** was isolated as colourless liquid (192 mg, 71% yield). –^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.32 (s, 3H, CH_3), 7.19–7.25 (m, 4H, ArH), 7.34 (dd, J = 8.3, 0.6 Hz, 1H, ArH), 7.91 (d, J = 8.3 Hz, 1H, ArH). –^{13}C NMR (300 MHz, $CDCl_3$): δ = 21.4 (CH_3), 122.4 (CH), 123.3 (d, $^1J_{CF3}$ = 273.2 Hz, CF_3), 123.7 (q, $^2J_{CF3}$ = 32.3 Hz, C), 125.7 (CH), 127.9 (CH), 129.3 (CH), 130.1 (CH), 137.4 (q, $^3J_{CF3}$ = 4.6 Hz CH), 137.7 (C), 137.8 (C), 153.4 (C), 159.5 (C). –^{19}F NMR (300 MHz, $CDCl_3$): δ = –57.0 (CF_3). –IR (ATR, cm^{-1}): ν = 3064 (w), 2980 (m), 2877 (w), 1660 (w), 1544 (w), 1140 (m), 816 (s). MS (EI, 70 eV): *m/z* (%):273 (33) $[M+2]^+$, 272 (31), 271 (100) $[M]^+$, 270 (56), 202 (11), 166 (15), 139 (11), 91 (18). –HRMS (EI) calcd. for $C_{13}H_9ClF_3N$ $[M]^+$: 271.03701, found 271.03667.

3.2.12 6-Chloro-2-(thiophen-2-yl)-3-(trifluoromethyl) pyridine (3l)

Starting with **1** (216 mg, 1 mmol), 2-thienylboronic acid (115 mg, 0.9 mmol), $Pd(OAc)_2$ (2 mol%), K_3PO_4 (207 mg, 1.5 mmol) and solution of H_2O-DMF (1:1, 2 mL). **3l** was isolated as yellowish greenish liquid (170 mg, 65% yield). –^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.09–7.15 (m, 1H, ArH), 7.44 (dd, J = 5.0, 1.1 Hz, 1H, ArH), 7.54 (dd, J = 8.1, 0.7 Hz, 1H, ArH), 7.65 (dd, J = 3.7, 1.15 Hz, 1H, ArH), 7.89 (dd, J = 8.2 Hz, 1H, ArH). –^{13}C NMR (300 MHz, $CDCl_3$): δ = 116.4 (CH), 122.3 (d, $^1J_{CF3}$ = 271.6 Hz, CF_3), 122.5 (q, $^2J_{CF3}$ = 34.4 Hz, C), 127.5 (CH), 127.8 (C), 128.5 (CH), 130.2 (CH), 137.1 (q, $^3J_{CF3}$ = 5.1 Hz CH), 141.5 (C), 155.5 (C). –^{19}F NMR (300 MHz, $CDCl_3$): δ = –63.0 (CF_3). –IR (ATR, cm^{-1}): ν = 1582 (w), 1556 (w), 1373 (m), 1343 (m), 1309 (m), 1116 (s), 1020 (m), 828 (m). MS (EI, 70 eV): *m/z* (%):265 (33) $[M+2]^+$, 263 (100) $[M]^+$, 228 (17), 69 (10). HRMS (EI) calcd. for $C_{10}H_5ClF_3NS$ $[M]^+$: 263.03710, found 263.03677.

3.2.13 6-Chloro-2-biphenyl-3-(trifluoromethyl)pyridine (3m)

Starting with **1** (216 mg, 1 mmol), 4-(phenyl phenyl) boronic acid (178 mg, 0.9 mmol), $Pd(OAc)_2$ (2 mol%), K_3PO_4 (207 mg, 1.5 mmol) and solution of H_2O-DMF (1:1, 2 mL). **3m** was isolated as white solid (209 mg, 63% yield), m.p.: 197–199°C. –^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.30–7.41 (m, 1H, ArH), 7.60–7.80 (m, 4H, ArH), 7.90–7.98 (m, 2H, ArH), 8.23 (d, J = 8.2 Hz, 2H, ArH), 8.40–8.43 (m, 2H, ArH). –^{13}C NMR (250 MHz, $CDCl_3$): δ = 122.1 (2CH), 123.4 (d, $^1J_{CF3}$ = 273.1 Hz, CF_3), 123.7 (q, $^2J_{CF}$ = 33.3 Hz, C), 123.9 (2CH), 126.7 (2CH), 127.2 (2C), 128.8 (C), 130.2 (2CH), 133.0 (2CH), 140.3 (q, $^3J_{CF3}$ = 4.6 Hz CH), 148.9 (2C). –^{19}F NMR (250 MHz, $CDCl_3$): δ = –57.3 (CF3). –IR (ATR, cm^{-1}): ν = 1682(w), 1557 (w), 1283 (m), 1126 (s), 1030 (m), 828 (m). –HRMS (EI) calcd. for $C_{18}H_{11}ClF_3N$ $[M]^+$: 333.08836, found: 333.08860.

3.2.14 2-(3,5-Bis(trifluoromethyl)phenyl)-6-chloro-3-(trifluoromethyl)pyridine (3n)

Starting with **1** (216 mg, 1 mmol), 3,5-bis(trifluoromethyl) phenylboronic acid (232 mg, 0.9 mmol), $Pd(OAc)_2$ (2 mol%),

K_3PO_4 (207 mg, 1.5 mmol) and solution of H_2O-DMF (1:1, 2 mL). **3n** was isolated as colourless liquid (279 mg, 71% yield). –^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.79$ (dd, $J = 8.0$, 0.6 Hz, 1H, ArH), 7.97 (s, 1H, ArH), 8.08 (dd, $J = 8.0$, 0.4 Hz, 1H, ArH), 8.43 (s, 2H, ArH). –^{13}C NMR (250 MHz, $CDCl_3$): $\delta = 118.4$ (CH), 122.0 (d, $^1J_{CF3} = 272.4$ Hz, CF_3), 123.0 (d, $^1J_{CF3} = 273.8$ Hz, $2CF_3$), 124.1 (C), 125.2 (C), 127.3 (2CH), 137.6 (q, $^2J_{CF3} = 33.4$ Hz, 2C), 125.7 (CH), 137.4 (q, $^3J_{CF3} = 4.6$ Hz CH), 138.1 (C), 149.5 (C), 157.0 (C). –^{19}F NMR (250 MHz, $CDCl_3$): $\delta = -62.9$ (CF3), –63.4 (CF3). –IR (ATR, cm^{-1}): $\nu = 1622$ (w), 1588 (w), 1355 (w), 1309 (w), 1273 (s), 1144 (s), 1106 (s), 1025 (s), 841 (s). MS (EI, 70 eV): *m/z* (%): 395 (33) $[M+2]^+$, 393 (100) $[M]^+$, 376 (10), 374 (32), 373 (10), 358 (31), 338 (47), 324 (21), 304 (12), 69 (29). HRMS (EI) calcd. for $C_{14}H_5ClF_9N$ $[M]^+$: 393.03620, found; 393.03588.

3.3 General procedure for the synthesis of 2,6-di(aryl)-3-(trifluoromethyl)pyridine (4a–f)

Mixture of commercially available 2,6-dichloro-3-(trifluoromethyl)pyridine **1** (1 mmol), aryl boronic acids **2a–d**, **2f**, **2i** (2.2 mmol), $Pd(OAc)_2$ (2mol%), K_3PO_4 (345 mg, 2.5 mmol) were added into a solution of H_2O-DMF (1:1) in a oven dried reaction pressure tubes under argon atmosphere. The reaction mixture was stirred at room temperature for 8–12 h. After completion of reaction (TLC controlled), the organic and aqueous layer were separated and the latter was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuum. The product was purified by column chromatography (silica gel, EtOAc-heptane). All products were characterised by NMR, GC-MS, HRMS and IR spectroscopic techniques.

3.3.1 2,6-Di-p-tolyl-3-(trifluoromethyl)pyridine (4a)

Starting with **1** (216 mg, 1 mmol), 4-methylphenyl boronic acid (299 mg, 2.2 mmol), $Pd(OAc)_2$ (2 mol%), K_3PO_4 (345 mg, 2.5 mmol) and solution of H_2O-DMF (1:1, 2 mL). **4a** was isolated as colourless liquid (228 mg, 70% yield). –^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.30$ (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 7.20 (d, $J = 8.1$ Hz, 4H, ArH), 7.43 (d, $J = 8.1$ Hz, 2H, ArH), 7.69 (dd, $J = 8.4$, 0.9 Hz, 1H, ArH), 7.92 (d, $J = 8.2$ Hz, 2H, ArH), 7.99 (d, $J = 8.4$ Hz, 1H, ArH). –^{13}C NMR (250 MHz, $CDCl_3$): $\delta = 21.3$ ($2CH_3$), 117.3 (CH), 122.5 (q, $^2J_{CF3} = 31.7$ Hz, C), 124.4 (q, $^1J_{CF3} = 272.8$ Hz, CF_3), 127.2 ($2CH_2$), 128.6 ($2CH_2$), 128.8 (CH), 128.9 (CH), 129.5 (2CH), 135.1 (C), 135.6 (q, $^3J_{CF3} = 4.7$ Hz, CH), 136.9 (C), 138.6 (C), 140.1 (C), 158.0 (C), 159.0 (C). –^{19}F NMR (300 MHz, $CDCl_3$): $\delta = -56.8$ (CF). –IR (ATR, cm^{-1}): $\nu = 2930$ (w), 2851 (w), 1665 (s), 1590 (m), 1319 (m), 1130 (s), 1020 (s), 831 (s). MS (EI, 70 eV): *m/z* (%) 327 (100) $[M]^+$, 326 (38). –HRMS (EI) calcd. for $C_{20}H_{16}F_3N$ $[M]^+$: 327.12248, found 327.12294.

3.3.2 2,6-Di(4-acetylphenyl)-3-(trifluoromethyl) pyridine (4b)

Starting with **1** (216 mg, 1 mmol), 4-acetylphenyl boronic acid (361 mg, 2.2 mmol), $Pd(OAc)_2$ (2 mol%), K_3PO_4 (345 mg, 2.5 mmol) and solution of H_2O-DMF (1:1, 2 mL). **4b** was isolated as white solid (260 mg, 68% yield), m.p.: 147–149°C. –^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.57$ (s, 3H, CH_3), 2.60 (s, 3H, CH_3), 7.62 (d, $J = 8.2$ Hz, 2H, ArH), 7.86 (dd, $J = 8.4$, 0.9 Hz, 1H, ArH), 7.98–8.00 (m, 4H, ArH), 8.01–8.13 (m, 3H, ArH). –^{13}C NMR (300 MHz, $CDCl_3$): $\delta = 26.7$ (CH_3), 26.7 (CH_3), 119.0 (2CH), 123.6 (d, $^1J_{CF3} = 273.1$ Hz, CF_3), 123.9 (q, $^2J_{CF3} = 32.5$ Hz, C), 127.5 (2CH), 128.0, 128.9 (2CH), 129.2 (2CH) 136.0 (q, $^3J_{CF3} = 4.9$ Hz, CH), 137.2 (C), 138.1 (C), 141.5 (C), 143.6 (C), 157.2 (C), 158.0 (C), 197.5 (C), 197.6 (C). –^{19}F NMR (300 MHz, $CDCl_3$): $\delta = -56.9$ (CF3). –IR (ATR, cm^{-1}): $\nu = 2930$ (w), 2851 (w), 1673 (s), 1589 (m), 1576 (w), 1320 (m), 1312 (m), 1262 (m), 1126 (s), 1019 (s), 834 (s). MS (EI, 70 eV): *m/z* (%) 383 (27) $[M]^+$, 369 (24), 368 (100), 340 (19), 297 (10), 296 (14), 177 (11). –HRMS (ESI) calcd. for $C_{22}H_{16}F_3NO_2$ $[M+H]^+$: 384.11331, found 384.11040.

3.3.3 2,6-Bis(4-(trifluoromethoxy)phenyl)-3-(trifluoromethyl)-pyridine (4c)

Starting with **1** (216 mg, 1 mmol), 4-trifluoromethoxyphenyl boronic acid (453 mg, 2.2 mmol), $Pd(OAc)_2$ (2 mol%), K_3PO_4 (345 mg, 2.5 mmol) and solution of H_2O-DMF (1:1, 2 mL). **4c** was isolated as colourless liquid (270 mg, 58% yield). –^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.23–7.27$ (m, 4H, ArH), 7.56 (d, $J = 8.5$ Hz, 2H, ArH), 7.75 (dd, $J = 8.5$, 0.92 Hz, 1H, ArH), 8.03–8.09 (m, 3H, ArH). –^{13}C NMR (250 MHz, $CDCl_3$): $\delta = 118.2$ (CH), 120.3 (2CH), 121.1 (2CH), 122.9 (q, $^2J_{CF3} = 33.1$ Hz, C), 123.6 (q, $^1J_{CF3} = 257.2$ Hz, $2OCF_3$), 124.4 (q, $^1J_{CF3} = 273.4$ Hz, CF_3), 128.9 (2CH), 130.5 (CH), 130.6 (CH), 136.1 (q, $^3J_{CF3} = 5.2$ Hz, CH), 137.8 (2C), 149.8 (C), 150.7 (C), 156.8 (C), 157.9 (C). –^{19}F NMR (250 MHz, $CDCl_3$): $\delta = -56.9$, –57.6, –57.7, (CF_3). –IR (ATR, cm^{-1}): $\nu = 1656$ (s), 1489 (m), 1322 (m), 1162 (m), 1126 (s), 1020 (s), 830 (s).MS (EI, 70 eV): *m/z* (%) 467 (100) $[M]^+$, 466 (47), 398 (12), 69 (17).

3.3.4 2,6-Diphenyl-3-(trifluoromethyl)pyridine (4d)

Starting with **1** (216 mg, 1 mmol), phenyl boronic acid (268 mg, 2.2 mmol), $Pd(OAc)_2$ (2 mol%), K_3PO_4 (345 mg, 2.5 mmol) and solution of H_2O-DMF (1:1, 2 mL). **4d** was isolated as colourless liquid (203 mg, 68% yield). –^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.38–7.41$ (m, 6H, ArH), 7.51–7.52 (m, 2H, ArH), 7.74 (dd, $J = 8.4$, 0.8 Hz, 1H, ArH), 8.00–8.04 (m, 2H, ArH), 8.03 (d, $J = 8.4$ Hz, 1H, ArH). –^{13}C NMR (300 MHz, $CDCl_3$): $\delta = 117.9$ (CH), 122.9 (q, $^2J_{CF3} = 33.4$ Hz, C), 123.9 (d, $^1J_{CF3} = 273.5$ Hz, CF_3), 127.4 (2CH), 127.9 (2CH), 128.7 (CH), 128.8 (2CH), 128.9 (2CH), 129.9 (CH), 135.7 (q, $^3J_{CF3} = 5.1$ Hz, CH), 137.8 (C), 139.6 (C), 158.1 (C), 159.2 (C). –^{19}F NMR (300 MHz, $CDCl_3$): $\delta = -56.8$ (CF_3). –IR (ATR, cm^{-1}): $\nu = 1586$ (m), 1573 (m), 1494 (w), 1121 (s), 1101 (s), 1018 (m), 761 (s), 692(s). MS (EI, 70 eV): *m/z* (%) 299 (100) $[M]^+$, 298 (71), 230 (21). –HRMS (ESI) calcd. for $C_{18}H_{13}F_3N$ $[M+H]^+$: 300.09946 found, 300.09960.

3.3.5 2,6-Di(4-methoxyphenyl)-3-(trifluoromethyl) pyridine (4e)

Starting with **1** (216 mg, 1 mmol), 4-methoxyphenylboronic acid (334 mg, 2.2 mmol), $Pd(OAc)_2$ (2 mol%), K_3PO_4 (345 mg, 2.5 mmol) and solution of H_2O-DMF (1:1, 2 mL). **4e** was isolated as white solid (226 mg, 63% yield), m.p.: 104–105°C. –^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.86$ (s, 3H, CH_3), 3.87 (s, 3H, CH_3), 6.90 (dd, $J = 8.8$, 1.5 Hz, 4H, ArH), 7.58 (d, $J = 8.6$, 2H, ArH), 7.71 (dd, $J = 8.4$, 0.7 Hz, 1H, ArH), 8.00–8.05 (m, 3H, ArH). –^{13}C NMR (300 MHz, $CDCl_3$): $\delta = 55.31$ (CH_3), 55.39 (CH_3), 113.4 (2CH), 114.2 (2CH), 116.6 (2CH), 121.7 (C), 124.2 (d, $^1J_{CF3} = 272.0$ Hz, CF_3), 128.8 (2CH), 130.4 (d, $^4J_{CF3} = 1.6$ Hz, CH), 130.5 (C), 132.4 (C), 135.7 (q, $^3J_{CF3} = 4.9$ Hz, CH), 157.5 (C), 158.7 (C), 160.1 (C), 161.3 (C). –^{19}F NMR (300 MHz, $CDCl_3$): $\delta = -57.0$ (CF_3). –IR (ATR, cm^{-1}): $\nu = 3075$ (w), 2969 (w), 2846 (w), 1605 (m), 1581 (m), 1510 (m), 1249(s), 1124 (s), 1019 (s), 828 (s).MS (EI, 70 eV): *m/z* (%) 359 (100) $[M]^+$, 316 (8). –HRMS (EI) calcd. for $C_{20}H_{16}F_3NO_2$ $[M]^+$: 359.11276, found 359.11258.

3.3.6 2,6-Dis(4-ethylphenyl)-3-(trifluoromethyl)pyridine (4f)

Starting with **1** (216 mg, 1 mmol), 4-ethylphenyl boronic acid (330 mg, 2.2 mmol), $Pd(OAc)_2$ (2 mol%), K_3PO_4 (345 mg, 2.5 mmol) and solution of H_2O-DMF (1:1, 2 mL). **4c** was isolated as colourless liquid (270 mg, 76% yield). –^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.16–1.24$ (m, 6H, $2CH_3$), 2.59–2.69 (m, 4H, $2CH_2$), 7.22 (d, $J = 7.9$ Hz, 4H, ArH), 7.46 (d, $J = 8.0$ Hz, 2H, ArH), 7.69 (dd, $J = 8.3$, 0.8 Hz, 1H, ArH), 7.94 (d, $J = 8.4$ Hz, 2H, ArH), 8.00 (d, $J = 8.3$ Hz, 1H, ArH). –^{13}C NMR (250 MHz, $CDCl_3$): $\delta = 15.3$ (CH_3), 15.4 (CH_3), 28.7 ($2CH_3$), 117.4 (CH), 122.5 (q, $^2J_{CF3} = 65.0$, 32.1 Hz, CF_3), 124.4 (q, $^1J_{CF3} = 272.5$ Hz, CF_3), 127.4 (4CH), 128.3 (2CH), 128.9 (2CH), 130.4 (C), 135.6 (q, $^3J_{CF3} = 5.1$ Hz, CH), 137.1 (C), 144.8 (C), 146.5 (C), 158.1 (C), 159.2 (C). –^{19}F NMR (300 MHz, $CDCl_3$): $\delta = -56.7$, (CF_3). –IR (ATR, cm^{-1}): $\nu = 2932$ (w), 2861 (w), 1680 (s), 1570 (w), 1321 (m), 1110 (s), 1019 (s), 834 (s).MS (EI, 70 eV): *m/z* (%) 355 (100) $[M]^+$, 354 (47), 341 (12), 340 (54). –HRMS (EI) calcd. for $C_{20}H_{16}F_3NO_2$ $[M]^+$: 354.15328, found 354.15424.

3.4 General procedure for one pot synthesis of 2, 6-diaryl-3-(trifluoromethyl)pyridine (5a–e)

Mixture of commercially available 2,6-dichloro-3-(trifluoromethyl)pyridine**1** (1 mmol), aryl boronic acids **2h**, **2e**, **2o**, **2e**, **2b** (0.9 mmol), $Pd(OAc)_2$ (2 mol%), K_3PO_4 (1.5 mmol) were added into a solution of H_2O-DMF (1:1, 2 mL) in a oven dried reaction pressure tubes under argon atmosphere. The reaction mixture was stirred at room temperature for 8–12 h. Subsequently, second aryl boronic acids **2a**, **2k**, **2f** (1.2 mmol), $Pd(OAc)_2$ (2 mol%), K_3PO_4 (1.5 mmol), H_2O-DMF (1:1, 2 mL) were then added to the reaction mixture. The reaction mixture was then heated at 50°C. After completion of reaction (TLC – controlled), the organic and aqueous layer were separated and the latter was extracted with CH_2Cl_2 (3×25 mL). The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo. The product was purified by column chromatography (silica gel, EtOAc-heptane). All products were characterised by NMR, GC-MS, HRMS and IR spectroscopic techniques.

3.4.1 2-(4-Tert-butylphenyl)-6-phenyl-3-(trifluoromethyl)pyridine (5a)

Starting with **1** (216 mg, 1 mmol), 4-*t*-butylphenylboronic acid (160 mg, 0.9 mmol), $Pd(OAc)_2$ (2 mol%), K_3PO_4 (207 mg, 1.5 mmol), and solution of H_2O-DMF (1:1, 2 mL), After 8 h phenylboronic acid (146 mg, 1.2 mmol), $Pd(OAc)_2$ (2 mol%), K_3PO_4 (207 mg, 1.5 mmol), and solution of H_2O-DMF (1:1, 2 mL). **5a** was isolated as colourless liquid (248 mg, 70% yield). –^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.30$ (s, 9H, CH_3), 7.38–7.45 (m, 3H, ArH), 7.42 (d, $J = 8.7$, 2H, ArH), 7.51–7.54 (m, 2H, ArH) 7.72 (dd, $J = 8.3$, 0.7 Hz, 1H, ArH), 7.95 (d, $J = 8.7$, 2H, ArH), 8.02 (d, $J = 8.4$, 1H, ArH). –^{13}C NMR

(300 MHz, $CDCl_3$): $\delta = 31.2$ ($3CH_3$), 34.7 (C) 117.7 (2CH), 122.8 (d, $^1J_{CF3} = 259.0$ Hz, CF_3), 125.8 (3CH), 127.1 (2CH), 127.9 (2CH), 128.7 (C), 128.9 (d, $^4J_{CF3} = 1.7$ Hz CH), 135.1(C), 135.6 (q, $^3J_{CF3} = 4.9$ Hz CH), 139.7 (C), 153.4 (C), 158.0 (C), 159.3 (C). –^{19}F NMR (282.4 MHz, $CDCl_3$): $\delta = -56.7$ (CF_3). –IR (ATR, cm^{-1}): $\nu = 3059$ (w), 2962 (w), 2903 (w), 2868 (w), 1610 (w), 1587 (m), 1574 (m), 1455 (w), 1307(s), 1111 (s), 1098 (s), 1026 (s), 1018 (s), 826 (s), 767 (m), 697 (m). (23) $[M]^+$, 340 (100). –HRMS (EI) calcd. for $C_{22}H_{20}F_3N$ $[M]^+$: 355.15424, found 355.15430.

3.4.2 2-(3,5-Dimethylphenyl)-6-(3-methoxyphenyl)-3-(trifluoromethyl)pyridine (5b)

Starting with **1** (216 mg, 1 mmol), 3,5-dimethylphenylboronic acid (135 mg, 0.9 mmol), $Pd(OAc)_2$ (2 mol%), K_3PO_4 (207 mg, 1.5 mmol), and solution of H_2O-DMF (1:1, 2 mL), After 8 h 3-methoxyphenylboronic acid (182 mg, 1.2 mmol), $Pd(OAc)_2$ (2 mol%), K_3PO_4 (207 mg, 1.5 mmol), and solution of H_2O-DMF (1:1) (2 mL). **5b** was isolated as colourless liquid (192 mg, 54% yield). –^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.31$ (s, 6H, CH_3), 3.78 (s, 3H, OCH_3) 6.81–7.13 (m, 5H, ArH), 7.25–7.34 (m, 2H, ArH), 7.61–8.02 (m, 2H, ArH). –^{13}C NMR (300 MHz, $CDCl_3$): $\delta = 31.24$ ($3CH_3$), 34.79 (C) 117.7 (2CH), 122.8 (d, $^1J_{CF3} = 269.0$ Hz, CF_3), 125.8 (3CH), 127.1 (2CH), 127.9 (2CH), 128.7 (C), 128.9 (d, $^4J_{CF3} = 1.7$ Hz CH), 135.1(C), 135.6 (q, $^3J_{CF3} = 4.9$ Hz CH), 139.7 (C), 153.4 (C), 158.0 (C), 159.3 (C). –^{19}F NMR (300 MHz, $CDCl_3$): $\delta = -56.7$ (CF3). –IR (ATR, cm^{-1}): $\nu = 2936$ (w), 2916 (w), 2858 (w), 1579 (m), 1568 (m), 1462 (m), 1303(s), 1119 (s), 1022 (s), 835 (m), 774 (m).MS (EI, 70 eV): *m/z* (%) 357 (65) $[M]^+$, 356 (100), 328 (20), 327 (32), 326 (14).

3.4.3 6-Phenyl-3-(trifluoromethyl)-2-(4-vinylphenyl) pyridine (5c)

Starting with **1** (216 mg, 1 mmol), 4-vinylphenylboronic acid (133.2 mg, 0.9 mmol), $Pd(OAc)_2$ (2 mol%), K_3PO_4 (207 mg, 1.5 mmol), and solution of H_2O-DMF (1:1, 2 mL), After 8 h phenylboronic acid (122 mg, 1.2 mmol), $Pd(OAc)_2$ (2 mol%), K_3PO_4 (207 mg, 1.5 mmol), and solution of H_2O-DMF (1:1, 2 mL). **5c** was isolated as colourless liquid (191 mg, 59% yield). –^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 5.25$ (dd, $J = 10.8$, 09 Hz, 1H, ArH), 5.77 (dd, $J = 17.6$, 09 Hz, 1H, ArH), 6.72 (dd, $J = 17.6$, 10.9 Hz, 1H, ArH), 7.26–7.61 (m, 7H, ArH) 7.75 (dq, $J = 8.3$, 0.9 Hz, 1H, ArH), 7.90–8.15 (m, 2H, ArH). –^{13}C NMR (300 MHz, $CDCl_3$): $\delta = 113.66$, 116.8, 124.78, 126.35, 127.83, 128.16, 128.19, 128.98 134.71, 134.79, 135.41, 136.78, 137.01, 158.20. –^{19}F NMR (282.4 MHz, $CDCl_3$): $\delta = -56.7$ (CF_3). –IR (ATR, cm^{-1}): $\nu = 2937$ (w), 2957 (w), 1679 (m), 1462 (m), 1310 (s), 1121 (s), 1032 (s), 823 (m). MS (EI, 70 eV): *m/z* (%); 325 (100) $[M]^+$, 324 (45). –HRMS (EI) calcd. for $C_{20}H_{14}F_3N$ $[M]^+$: 325.10729, found 325.10684.

3.4.4 2-(3,5-Dimethylphenyl)-6-(4-ethylphenyl)-3-(trifluoromethyl)-pyridine (5d)

Starting with **1** (216 mg, 1 mmol), 3,5-dimethylphenylboronic acid (135 mg, 0.9 mmol), $Pd(OAc)_2$ (2 mol%), K_3PO_4 (207 mg, 1.5 mmol), and solution of H_2O-DMF (1:1, 2 mL), After 8 h 4-ethylphenylboronic acid (180 mg, 1.2 mmol), $Pd(OAc)_2$ (2 mol%), K_3PO_4 (207 mg, 1.5 mmol), and solution of H_2O-DMF (1:1, 2 mL). **5d** was isolated as white solid (252 mg, 71% yield), m.p.: 95–97°C. –^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.22$ (t, 3H, CH_3), 2.31 (s. 6H, $2CH_3$), 2.64–2.66 (m, 2H, CH_2), 7.01 (s, 2H, ArH), 7.23 (d, $J = 8.3$ Hz, 2H, ArH), 7.46 (d, $J = 8.0$ Hz, 2H, ArH), 7.62 (s, 2H, ArH), 7.69 (dd, $J = 8.5$, 0.8 Hz, 2H, ArH), 8.00 (d, $J = 8.5$ Hz, 1H, ArH). –^{13}C NMR (300 MHz, $CDCl_3$): $\delta = 15.37$ (CH_3), 21.4 ($2CH_3$), 28.7 (CH_2), 117.9 (CH), 122.3 (q, $J_{CF3} = 32.8$ Hz, C), 124.0 (d, $^1J_{CF3} = 272.7$ Hz, CF_3), 125.2 (2CH), 127.4 (2CH), 128.9 (2CH), 131.6 (CH), 135.5 (d, $^2J_{CF3} = 9.6$, Hz, CH), 137.1 (C), 137.9 (C), 138.4 (2C), 144.9 (2C), 152.9 (C). –^{19}F NMR (300 MHz, $CDCl_3$): $\delta = -56.8$ (CF_3). –IR (ATR, cm^{-1}): $\nu = 3059$ (w), 2962 (w), 2903 (w), 2868 (w), 1610 (w), 1587 (m), 1574 (m), 1455 (w), 1307(s), 1111 (s), 1098 (s), 1026 (s), 1018 (s), 826 (s), 767 (m), 697 (m). MS (EI, 70 eV): *m/z* (%) 356 (23) $[M+1]^+$, 355 (100) $[M]^+$, 341 (12), 340 (54). –HRMS (EI) calcd. for $C_{22}H_{20}F_3N$ $[M]^+$: 355.15424, found 355.15430.

3.4.5 6-(4-Ethylphenyl)-2-p-tolyl-3-(trifluoromethyl) pyridine (5e)

Starting with **1** (216 mg, 1 mmol), 4-methylphenylboronic acid (122.4 mg, 0.9 mmol), $Pd(OAc)_2$ (2 mol%), K_3PO_4 (207 mg, 1.5 mmol) and solution of H_2O-DMF (1:1, 2 mL), After 8 h 4-ethylphenylboronic acid (180 mg, 1.2 mmol), $Pd(OAc)_2$ (2 mol%), K_3PO_4 (207 mg, 1.5 mmol), and solution of H_2O-DMF (1:1, 2 mL). **5d** was isolated as yellow liquid (235 mg, 69% yield). –^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.20$–1.22 (m, 3H, CH_3), 2.33 (s, 3H, CH_3), 2.64–2.68 (m, 2H, CH_2), 7.19–7.29 (m, 4H, ArH), 7.46 (d, $J = 8.0$ Hz, 2H, ArH), 7.69 (dd, $J = 8.4$, 0.8 Hz, 1H, ArH), 7.92 (d, $J = 8.2$ Hz, 2H, ArH), 8.00 (d, $J = 8.4$ Hz, 1H, ArH). –^{13}C NMR (250 MHz, $CDCl_3$): $\delta = 15.35$ (CH_3), 21.33 (CH_3), 28.68 (CH_2), 117.3 (CH), 122.2 (q, $^2J_{CF3} = 31.5$ Hz, C), 124.2 (d, $J_{CF3} = 273.9$ Hz, CF_3), 127.2 (2CH), 127.4 (2CH), 128.8 (CH), 128.9 (CH), 129.5 (CH), 135.1 (C),

135.6 (q, $^3J_{CF3}$ = 4.8 Hz, CH), 137.1 (C), 140.1 (2C), 144.8 (C), 159.1 (C). –^{19}F NMR (250 MHz, $CDCl_3$): δ = –56.7 (CF3). –IR (ATR, cm^{-1}): ν = 2965 (w), 2929 (w), 2872 (w), 1586 (m), 1563 (w), 1452 (w), 1305 (s), 1113 (s), 1098 (s), 1023 (s), 1014 (m), 817 (m), 791 (m).MS (EI, 70 eV): *m/z* (%) 341 (100) $[M]^+$, 340 (54), 327 (13). 326 (60). –HRMS (EI) calcd. for $C_{21}H_{18}F_3N$ $[M]^+$: 341.13859, found 341.13779.

3.5 General procedure for the synthesis of 6-aryl-2-chloro-4-(trifluoromethyl) pyridine

The same procedure was followed as for given for the synthesis of **3a–n**. Mixture of commercially available 2,6-dichloro-4-(trifluoromethyl)pyridine **6** (1 mmol), aryl boronic acids **2b**, **2e**, **2f**, **2j**, **2p–t** (1.0 mmol), $Pd(OAc)_2$ (2 mol%), K_3PO_4 (207 mg, 1.5 mmol) were added into a solution of H_2O-DMF (1:1, 2 mL) in a oven dried reaction pressure tubes under argon atmosphere. The reaction mixture was stirred at room temperature for 8–12 h. After completion of reaction (TLC controlled), the organic and aqueous layer were separated and the latter was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuum. The product was purified by column chromatography (silica gel, EtOAc-heptane). All products were characterised by NMR, GC-MS, HRMS and IR spectroscopic techniques.

3.5.1 2-Chloro-6-p-tolyl-4-(trifluoromethyl)pyridine (7a)

Starting with **6** (216 mg, 1 mmol), 4-methylphenylboronic acid (136 mg, 1.0 mmol), $Pd(OAc)_2$ (2 mol%), K_3PO_4 (207 mg, 1.5 mmol) and solution of H_2O-DMF (1:1, 2 mL), **7a** was isolated as colourless liquid (203 mg, 75% yield). –^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.33 (s, 3H, CH_3), 7.21 (d, *J* = 7.8 Hz, 2H, ArH), 7.35 (s, 1H, ArH), 7.72 (s, 1H, ArH), 7.84 (d, *J* = 8.2 Hz, 2H, ArH). –^{13}C NMR (300 MHz, $CDCl_3$): δ = 21.3 (CH_3), 114.0 (q, $^3J_{CF3}$ = 3.3 Hz, CH), 117.9 (q, $^3J_{CF3}$ = 3.7 Hz, CH), 122.7 (q, $^1J_{CF3}$ = 273.7 Hz, CF_3), 127.0 (2CH), 129.7 (2CH), 133.6 (C), 140.9 (C), 141.6 (q, $^2J_{CF3}$ = 34.5 Hz C), 152.1 (C), 159.5 (C). –^{19}F NMR (300 MHz, $CDCl_3$): δ = –64.7 (CF_3). –IR (ATR, cm^{-1}): ν = 2953 (w), 2923 (w), 2866 (w), 1605 (w), 1557 (m), 1407 (m), 1392 (m), 1329 (s), 1171 (s), 1135 (s), 1097 (m), 833 (m), 817(s). MS (EI, 70 eV): *m/z* (%) 273 (33) $[M+2]^+$, 272 (33), 271 (100) $[M]^+$, 270 (51), 91 (17), 69 (10). –HRMS (EI) calcd. for $C_{13}H_9ClF_3N$ $[M]^+$: 271.03701, found 271.03642.

3.5.2 2-Chloro-6-(3,5-dimethylphenyl)-4-(trifluoromethyl)pyridine (7b)

Starting with **6** (216 mg, 1 mmol), 3,5-dimethylphenylboronic acid (150 mg, 1.0 mmol), $Pd(OAc)_2$ (2 mol%), K_3PO_4 (207 mg, 1.5 mmol) and solution of H_2O-DMF (1:1, 2 mL), **7b** was isolated as white solid (198 mg, 70% yield), m.p.: 95–96°C. –^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.43 (s, 6H, $2CH_3$), 7.15 (s, 1H, ArH), 7.48 (s, 1H, ArH), 7.66 (s, 2H, ArH), 7.84 (s, 1H, ArH). –^{13}C NMR (300 MHz, $CDCl_3$): δ = 21.3 ($2CH_3$), 114.5 (q, $^3J_{CF3}$ = 3.4 Hz, CH), 118.1 (q, $^3J_{CF3}$ = 3.6 Hz, CH), 122.2 (q, $^1J_{CF3}$ = 274.0 Hz, CF_3), 124.9 (2CH), 132.2 (CH), 136.4 (C), 138.7 (C), 141.6 (q, $^2J_{CF3}$ = 33.9 Hz C), 152.1 (C), 159.9 (C). –^{19}F NMR (300 MHz, $CDCl_3$): δ = –64.6 (CF_3). –IR (ATR, cm^{-1}): ν = 2958 (w), 2924 (w), 2857 (w), 1598 (w), 1559 (m), 1390 (m), 1375 (m), 1330 (m), 1288 (m), 1162 (m), 1133 (s), 1107 (m), 868 (m), 852 (m), 832 (m). MS (EI, 70 eV): *m/z* (%) 287 (33) $[M+2]^+$, 286 (33), 285 (100) $[M]^+$, 270 (19), 269 (14). –HRMS (ESI) calcd for $C_{14}H_{12}ClF_3N$ $[M+H]^+$: 286.06, found 286.06.

3.5.3 2-Chloro-6-(4-fluorophenyl)-4-(trifluoromethyl) pyridine (7c)

Starting with **6** (216 mg, 1 mmol), 4-fluorophenylboronic acid (140 mg, 1.0 mmol), $Pd(OAc)_2$ (2 mol%), K_3PO_4 (207 mg, 1.5 mmol), and solution of H_2O-DMF (1:1, 2 mL), **7c** was isolated as white solid (195 mg, 71% yield), m.p.: 65–67°C. –^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.32–6.38 (m, 2H, ArH), 6.63 (s, 1H, ArH), 6.95 (s, 1H, ArH), 7.20 (dd, *J* = 9.0, 5.2 Hz, 2H, ArH). –^{13}C NMR (250 MHz, $CDCl_3$): δ = 114.0 (q, $^3J_{CF3}$ = 3.4 Hz, CH), 115.9 (CH), 116.2 (CH), 118.3 (q, $^3J_{CF3}$ = 3.2 Hz, CH), 122.1 (d, $^1J_{CF3}$ = 273.7 Hz, CF_3), 129.1 (CH), 129.2 (CH), 132.6 (d, $^4J_{CF3}$ = 3.1 Hz, C), 141.7 (q, $^2J_{CF3}$ = 34.5 Hz, C), 152.3 (C), 158.3 (C), 164.3 (d, $^1J_{CF3}$ = 251.3 Hz, C). –^{19}F NMR (300 MHz, $CDCl_3$): δ = –110.6 (CF_3), –63.11 (CF_3). –IR (ATR, cm^{-1}): ν = 1600 (m), 1563 (m), 1510 (w), 1329 (m), 1096 (s), 875 (m), 833 (s). MS (EI, 70 eV): *m/z* (%) 277 (33) $[M+2]^+$, 276 (16), 275 (100) $[M^+]$, 240 (23), 220 (32), 206 (12), 171 (10), 170 (11), 144 (10), 75 (12), 69 (15). –HRMS (EI) calcd. for $C_{12}H_6ClF_4N$ $[M]^+$: 275.01194, found 275.01162.

3.5.4 2-Chloro-6-(2-methoxyphenyl)-4-(trifluoromethyl) pyridine (7d)

Starting with **6** (216 mg, 1 mmol), 2-methoxyphenylboronic acid (152 mg, 1.0 mmol), $Pd(OAc)_2$ (2 mol%), K_3PO_4 (207 mg, 1.5 mmol), and solution of H_2O-DMF (1:1, 2 mL), **7d** was isolated as white solid (198 mg, 69% yield), m.p.: 53–55°C. –^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.80 (s, 3H, OCH_3),

6.91 (dd, J = 8.4, 0.7 Hz, 1H, ArH), 6.99 (dt, J = 7.5, 0.9 Hz, 1H, ArH), 7.30–7.34 (m, 1H, ArH), 7.80–7.82 (m, 1H, ArH), 7.84 (d, J = 7.7 Hz, 1H, ArH), 8.03 (d, J = 0.6 Hz, 1H, ArH). –^{13}C NMR (250 MHz, $CDCl_3$): δ = 55.6 (OCH_3), 111.4 (CH), 117.8 (q, $^3J_{CF3}$ = 7.5, 3.9 Hz, CH), 119.4 (q, $^3J_{CF3}$ = 3.5 Hz, CH), 121.2 (CH), 122.4 (q, $^1J_{CF3}$ = 274.3 Hz, CF_3), 125.9 (C), 131.3 (CH), 131.5 (CH), 140.6 (q, $^2J_{CF3}$ = 34.0 Hz, C), 151.4 (C), 157.2 (C), 157.7 (C). –^{19}F NMR (300 MHz, $CDCl_3$): δ = –64.6 (CF_3). –IR (ATR, cm^{-1}): ν = 2964 (w), 2946 (w), 2839 (w), 1600 (m), 1562 (m), 1491 (w), 1327 (m), 1168 (m), 1125 (s), 1096 (s), 860 (m), 830 (s). MS (EI, 70 eV): m/z (%); 289 (30) $[M+2]^+$, 287 (100) $[M]^+$, 286 (82), 268 (11), 260 (13), 259 (16), 258 (47), 257 (38), 252 (24), 222 (36), 202 (25), 188 (16), 184 (23), 183 (23), 182 (74), 140 (11).

3.5.5 2-Chloro-6-(3-methoxyphenyl)-4-(trifluoromethyl) pyridine (7e)

Starting with **6** (216 mg, 1 mmol), 3-methoxyphenylboronic acid (152 mg, 1.0 mmol), $Pd(OAc)_2$ (2 mol%), K_3PO_4 (207 mg, 1.5 mmol), and solution of H_2O-DMF (1:1, 2 mL), **7e** was isolated as a white solid (192 mg, 67% yield), m.p.: 55–57°C. –^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.82 (s, 3H, OCH_3), 6.95 (dd, J = 8.3, 2.3 Hz, 1H, ArH), 7.32–7.36 (m, 1H, ArH), 7.39 (s, 1H, ArH), 7.47–7.52 (m, 2H, ArH), 7.74 (s, 1H, ArH). –^{13}C NMR (250 MHz, $CDCl_3$): δ = 54.5 (OCH_3), 111.4 (CH), 113.6 (q, $^3J_{CF3}$ = 3.8 Hz, CH), 115.4 (CH), 117.5 (q, $^3J_{CF3}$ = 3.8 Hz, CH), 118.4 (CH), 121.1 (q, $^1J_{CF3}$ = 273.7 Hz, CF_3), 129.0 (CH), 136.8 (C), 140.6 (q, $^2J_{CF3}$ = 34.3 Hz, C), 151.2 (C), 158.2 (C), 159.2 (C). –^{19}F NMR (250 MHz, $CDCl_3$): δ = –64.6 (CF_3). –IR (ATR, cm^{-1}): ν = 2965 (w), 2940 (w), 2856 (w), 1630 (m), 1565 (m), 1499 (w), 1328 (m), 1125 (s), 1096 (s), 859 (m), 833 (s). MS (EI, 70 eV): m/z (%): 289 (33) $[M+2]^+$, 288 (43), 287 (100) $[M]^+$, 286 (91), 268 (11), 259 (18), 258 (36), 257 (41), 256 (21), 244 (13), 222 (27), 209 (18), 202 (15), 188 (12), 175 (11), 140 (13), 63 (13). –HRMS (ESI) calcd. for $C_{13}H_{10}ClF_3NO$ $[M+H]^+$: 288.0398, found 288.0398.

3.5.6 2-Chloro-6-(4-isopropylphenyl)-4-(trifluoromethyl) pyridine (7f)

Starting with **6** (216 mg, 1 mmol), 4-isopropylphenylboronic acid (164 mg, 1.0 mmol), $Pd(OAc)_2$ (2 mol%), K_3PO_4 (207 mg, 1.5 mmol), and solution of H_2O-DMF (1:1) (2 mL), **7f** was isolated as a colourless liquid (212 mg, 71% yield). –^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.20 (s, 3H, CH_3), 1.22 (s, 3H, CH_3), 2.90 (sept., 1H, CH), 7.27 (d, J = 8.1 Hz, 2H, ArH), 7.36 (s, 1H, ArH), 7.73 (s, 1H, ArH), 7.87 (d, J = 8.4 Hz, 2H, ArH). –^{13}C NMR (250 MHz, $CDCl_3$): δ = 23.7 ($2CH_3$), 34.02 (CH), 114.1 (q, $^3J_{CF3}$ = 7.4, 3.9 Hz, CH), 117.9 (q, $^3J_{CF3}$ = 3.7 Hz, CH), 122.2 (q, $^1J_{CF3}$ = 273.7 Hz, CF_3), 127.1 (2CH), 127.2 (2CH), 134.0 (C), 141.5 (q, $^2J_{CF3}$ = 30.6 Hz, C), 151.7 (C), 152.2 (C), 159.6 (C). –^{19}F NMR (300 MHz, $CDCl_3$): δ = –64.7 (CF_3). –IR (ATR, cm^{-1}): ν = 2962 (w), 2930 (w), 2893 (w), 1607 (w), 1556 (m), 1409 (m), 1393 (m), 1329 (s), 1291 (m), 1173 (m), 1136 (s), 1093 (m), 827 (s), 690 (s). MS (EI, 70 eV): m/z (%) 301 (13) $[M+2]^+$, 299 (40), $[M]^+$, 286 (32), 285 (15), 284 (100), 271 (13), 269 (38). –HRMS (ESI) calcd. for $C_{15}H_{14}ClF_3N$ $[M+H]^+$: 300.0761 found 300.0759.

3.5.7 2-Chloro-6-(3-fluorophenyl)-4-(trifluoromethyl) pyridine (7g)

Starting with **6** (216 mg, 1 mmol), 3-fluorophenylboronic acid (140 mg, 1.0 mmol), $Pd(OAc)_2$ (2 mol%), K_3PO_4 (207 mg, 1.5 mmol), and solution of H_2O-DMF (1:1, 2 mL), **7g** was isolated as colourless liquid (195 mg, 71% yield). –^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.09 (dd, J = 8.2, 2.5 Hz, 1H, ArH), 7.37 (m, 1H, ArH), 7.42 (s, 1H, ArH), 7.66–7.73 (m, 3H, ArH). –^{13}C NMR (300 MHz, $CDCl_3$): δ = 114.2 (d, $^2J_{CF3}$ = 23.7 Hz, CH), 114.5 (q, $^3J_{CF3}$ = 3.4 Hz, CH), 117.5 (d, $^2J_{CF3}$ = 21.2 Hz, CH), 119.1 (q, $^3J_{CF3}$ = 3.71 Hz, CH), 122.1 (q, $^1J_{CF3}$ = 273.9 Hz, CF_3), 130.6 (d, $^4J_{CF3}$ = 8.0 Hz, CH), 138.6 (d, $^4J_{CF3}$ = 7.7 Hz, CH), 141.9 (q, $^2J_{CF3}$ = 34.6 Hz, C), 152.4 (C), 158.0(d, $^4J_{CF3}$ = 2.5 Hz, C), 163.4 (d, $^1J_{CF3}$ = 247.4 Hz C). –^{19}F NMR (300 MHz, $CDCl_3$): δ = –111.9 (CF_3), –64.7 (CF_3). –IR (ATR, cm^{-1}): ν = 1591 (w), 1560 (m), 1456 (m), 1329 (s), 1175 (m), 1136 (s), 1099 (m), 869 (m), 834 (s), 776 (m), 693 (s). MS (EI, 70 eV): m/z (%) 277 (33) $[M+2]^+$, 276 (16), 275 (100) $[M]^+$, 256 (10), 240 (22), 220 (29), 206 (11), 170 (11), 75 (14), 69 (15). –HRMS (EI) calcd. for $C_{12}H_6ClF_4N$ $[M]^+$: 275.01194, found 275.01161.

3.5.8 2-Chloro-6-(3,5-dimethoxyphenyl)-4-(trifluoromethyl)pyridine (7h)

Starting with **6** (216 mg, 1 mmol), 3,5-dimethoxyphenylboronic acid (182 mg, 1.0 mmol), $Pd(OAc)_2$ (2 mol%), K_3PO_4 (207 mg, 1.5 mmol), and solution of H_2O-DMF (1:1, 2 mL), **7h** was isolated as colourless liquid (222 mg, 71% yield). –^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.74 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 6.84–6.90 (m, 2H, ArH), 7.34 (s, 1H, ArH), 7.43 (dd, J = 2.7, 0.8 Hz, 1H, ArH), 8.06 (s, 1H, ArH). –^{13}C NMR (250 MHz, $CDCl_3$): δ = 54.8 (OCH_3), 55.2 (OCH_3), 112.0 (CH), 114.8 (CH), 116.2 (CH), 117.0 (q, $^3J_{CF3}$ = 3.7 Hz, CH), 118.4 (q, $^3J_{CF3}$ = 3.4 Hz, CH), 121.3 (q, $^1J_{CF3}$ = 273.5 Hz, CF_3), 125.4 (C), 139.7 (q, $^2J_{CF3}$ = 34.7 Hz, C), 150.4 (C), 150.6 (C), 152.9 (C). –^{19}F NMR (300 MHz, $CDCl_3$): δ = –64.6 (CF_3). –IR (ATR, cm^{-1}): ν = 2946 (w), 2911 (w), 2836 (w), 1560 (m), 1499 (m),

1330 (s), 1211 (m), 1170 (m), 1131 (s), 1042 (m), 833 (m), 696 (s). MS (EI, 70 eV): *m/z* (%); 319 (33) $[M+2]^+$, 318 (31), 317 (100) $[M]^+$, 316 (51), 302 (30), 298 (11), 290 (23), 289 (15), 288 (72), 287 (17), 286 (16), 282 (24), 275 (16), 273 (11), 267 (22), 252 (11), 246 (14), 231 (11), 196 (17), 182 (28), 176 (13), 170 (11), 135 (14). –HRMS (ESI) calcd. for $C_{14}H_{12}F_3NO_2$ $[M]^+$: 318.05032, found 318.05055.

3.6 General procedure for the synthesis of 2,6-diaryl-4-(trifluoromethyl)pyridine (8a–c)

Mixture of 2,6-dichloro-4-(trifluoromethyl)pyridine **6** (1 mmol), aryl boronic acids **2b**, **2p**, **2t** (2.2 mmol), $Pd(OAc)_2$ (2 mol%), K_3PO_4 (345 mg, 2.5 mmol) were added into a solution of H_2O-DMF (1:1, 2 mL). The reaction mixture was stirred at room temperature for 8–12 h. After completion of reaction (TLC controlled), the organic and aqueous layer were separated and the latter was extracted with CH_2Cl_2 (3×25 mL). The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuum. The product was purified by column chromatography (silica gel, EtOAc-heptane). All products were characterised by NMR, GC-MS, HRMS and IR spectroscopic techniques.

3.6.1 2,6-Di-*p*-tolyl-4-(trifluoromethyl)pyridine (8a)

Starting with **6** (216 mg, 1 mmol), 4-methylphenylboronic acid (299 mg, 2.2 mmol), $Pd(OAc)_2$ (2 mol%), K_3PO_4 (345 mg, 2.5 mmol) and solution of H_2O-DMF (1:1, 2 mL). **8a** was isolated as white solid (212 mg, 65% yield), m.p.: 166–167°C. $-^1$H NMR (300 MHz, $CDCl_3$): $\delta = 2.36$ (s, 6H, $2CH_3$), 7.25 (d, $J = 7.9$ Hz, 4H, ArH), 7.74 (s, 2H, ArH), 7.99 (d, $J = 8.2$ Hz, 4H, ArH). $-^{13}$C NMR (300 MHz, $CDCl_3$): $\delta = 21.35$ ($2CH_3$), 113.4 (q, $^3J_{CF3} = 3.9$ Hz, 2CH), 123.2 (d, $^1J_{CF3} = 273.4$ Hz, CF_3), 127.0 ($4CH_2$); 129.6 ($4CH_2$), 135.6 (2C), 139.8 (q, $^2J_{CF3} = 32.7$ Hz, C), 139.9 (2C), 158.1 (2C). $-^{19}$F NMR (300 MHz, $CDCl_3$): $\delta = -64.7$ (CF_3). –IR (ATR, cm^{-1}): $\nu = 2924$ (w), 2863 (w), 1611 (w), 1563 (w), 1511 (w), 1422 (w), 1339 (m), 1262 (m), 1162 (s), 1126 (m), 815 (s). MS (EI, 70 eV): *m/z* (%) 327 (100) $[M]^+$, 326 (28). –HRMS (EI) calcd. for $C_{20}H_{16}F_3N$ $[M]^+$: 327.12294, found 327.12248.

3.6.2 2,6-Bis(2-methoxyphenyl)-4-(trifluoromethyl) pyridine (8b)

Starting with **6** (216 mg, 1 mmol), 2-methoxyphenylboronic acid (334 mg, 2.2 mmol), $Pd(OAc)_2$ (2 mol%), K_3PO_4 (345 mg, 2.5 mmol) and solution of H_2O-DMF (1:1, 2 mL). **8b** was isolated as colourless liquid (244 mg, 68% yield). $-^1$H NMR (300 MHz, $CDCl_3$): $\delta = 3.69$ (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 6.89–7.05 (m, 4H, ArH), 7.15–7.40 (m, 2H, ArH), 7.89–7.97 (m, 4H, ArH). $-^{13}$C NMR (250 MHz, $CDCl_3$): $\delta = 55.6$ (CH_3), 55.7 (CH_3), 111.1 (CH), 111.4 (CH), 118.6 (q, $^3J_{CF3} = 4.0$ Hz, 2CH), 120.3 (CH), 121.1 (CH), 124.7 (q, $^1J_{CF3} = 272.4$ Hz, CF_3), 128.6 (CH), 130.5 (2C), 131.4 (2CH), 137.6 (q, $^2J_{CF3} = 32.7$ Hz, C), 156.3 (C), 157.0 (C), 157.2 (C). $-^{19}$F NMR (300 MHz, $CDCl_3$): $\delta = -64.4$ (CF_3). –IR (ATR, cm^{-1}): $\nu = 2937$ (w), 2829 (w), 1603 (w), 1567 (w), 1496 (m), 1208 (m), 1176 (m), 1037 (m), 806 (s). MS (EI, 70 eV): *m/z* (%) 359 (100) $[M]^+$, 358 (78), 340 (10), 330 (12), 328 (15), 315 (16), 300 (14), 299 (14), 298 (27), 224 (20). –HRMS (EI) calcd. for $C_{20}H_{16}F_3NO_2$ $[M]^+$: 359.12284, found 359.12238.

3.6.3 2,6-bis(3,5-dimethoxyphenyl)-4-(trifluoromethyl) pyridine (8c)

Starting with **6** (216 mg, 1 mmol), 3,5-dimethoxyphenylboronic acid (400.2 mg, 2.2 mmol), $Pd(OAc)_2$ (2 mol%), K_3PO_4 (345 mg, 2.5 mmol), and solution of H_2O-DMF (1:1) (2 mL), **8c** was isolated as white solid (298 mg, 71% yield), m.p.: 82–83°C. $-^1$H NMR (300 MHz, $CDCl_3$): $\delta = 3.62$ (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 6.77–6.85 (m, 3H, ArH), 6.95–7.10 (m, 3H, ArH), 7.50–7.55 (m, 1H, ArH), 8.01 (s, 1H, ArH). $-^{13}$C NMR (250 MHz, $CDCl_3$): $\delta = 55.7$ (OCH_3), 55.8 (OCH_3), 56.3 (OCH_3), 56.5 (OCH_3), 112.5 (CH), 113.0 (CH), 113.4 (CH), 116.0 (CH), 116.3 (CH), 117.2 (CH), 118.8 (q, $^3J_{CF3} = 7.5$, 3.9 Hz, CH), 123.3 (q, $^1J_{CF3} = 272.2$ Hz, CF_3), 128.6 (C), 137.8 (q, $^2J_{CF3} = 33.3$ Hz, C), 151.3 (C), 151.6 (C), 153.9 (C), 155.9 (C). $-^{19}$F NMR (300MHz, $CDCl_3$): $\delta = -64.4$ (CF_3). –IR (ATR, cm^{-1}): $\nu = 2937$ (w), 2904 (w), 2829 (w), 1603 (w), 1496 (m), 1469 (m), 1382 (w), 1208 (s), 1176 (m), 1126 (m), 1037 (m), 806 (m). MS (EI, 70 eV): *m/z* (%); 419 (100) $[M]^+$, 418 (55), 404 (23), 400 (10), 388 (15), 374 (11), 372 (10), 360 (29), 285 (15), 284 (82), 269 (10), 254 (15), 209 (12), 194 (17). –HRMS (ESI) calcd. for $C_{22}H_{21}F_3NO_4$ $[M]^+$: 420.14172, found 420.14177.

3.6.4 2-(4-Fluorophenyl)-6-(4-methoxyphenyl)-4-(trifluoromethyl)pyridine (9a)

Starting with **6** (216 mg, 1 mmol), 4-fluorophenylboronic acid (140 mg, 1.0 mmol), $Pd(OAc)_2$ (2 mol%), K_3PO_4 (207 mg, 1.5 mmol), and solution of H_2O-DMF (1:1, 2 mL), After 12 h, 4-methoxyphenylboronic acid (163 mg, 1.2 mmol), $Pd(OAc)_2$ (2 mol%), K_3PO_4 (1.5 mmol), and solution of H_2O-DMF (1:1, 2 mL). **9a** was isolated as colourless liquid

(198 mg, 57% yield). –^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.81$ (s, 3H, OCH_3), 6.76–6.80 (m, 3H, ArH), 6.85–6.89 (m, 3H, ArH), 7.53–7.54 (m, 1H, ArH), 8.01 (s, 1H, ArH). –^{13}C NMR (300 MHz, $CDCl_3$): $\delta = 55.4$ (OCH_3), 112.9 (q, $^3J_{CF} = 6.8$, 3.3 Hz, CH), 113.2 (q, $^3J_{CF} = 6.5$, 3.3 Hz, CH), 114.3 ($2CH_3$), 115.7 (CH), 116.0 (CH), 123.2 (q, $^1J_{CF} = 272.6$ Hz, CF_3), 128.5 (2CH), 128.9 (CH), 129.0 (CH), 130.7 (C), 134.5 (d, $J = 3.0$ Hz, C), 140.0 (q, $^2J_{CF} = 66.9$, 33.6 Hz, C), 156.9 (C), 157.9 (C), 161.2 (C), 163.8 (d, $J = 248.0$ Hz, CF). –^{19}F NMR (300 MHz, $CDCl_3$): $\delta = -64.7$, –111.7 Hz (CF_3). IR (ATR, cm^{-1}): $\nu = 2920$ (w), 2847 (w), 16073 (w), 1564 (m), 1427 (m), 1368 (m), 1117 (m), 1105 (m), 1031 (m), 827 (s). MS (EI, 70 eV): *m/z* (%) 347 (100) $[M]^+$, 304 (25). –HRMS (EI) calcd. for $C_{19}H_{13}F_4NO$ $[M+H]^+$: 347.09278 found: 347.09215.

3.7 Computational methods

All calculations were performed using Gaussian 09 [47]. Geometries of the structures were optimised without any symmetry constraints at hybrid B3LYP method. The B3LYP method, which consists of parameter hybrid functional of Becke [48] three in conjunction with the correlation functional of Lee et al. [49], provides a nice balance between cost and accuracy. For geometries optimisation, 6-31G* [50–52] basis set was used for C, H, N, O, F, B and Cl atoms and LANL2DZ pseudopotential for Pd. Recently Huang and co-workers [46] have shown that B3LYP/6-31G* with pseudopotential on Pd (LANL2DZ) can reliably model the Suzuki coupling reaction. Each optimised structure was confirmed by frequency analysis at the same level as a true minimum (no imaginary frequency) or as a transition state (with one imaginary frequency). Imaginary frequencies of transition states were also evaluated to confirm that their associated eigenvector correspond to the motion along the reaction coordinates. The reported energies for all structures are in kcal mol^{-1} and do not include zero point correction. Zero point corrected and Gibbs free energies are available in the supporting information.

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