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Palladium-catalyzed Suzuki–Miyaura cross-coupling reaction of potassium 2-pyridyl trifluoroborate with aryl (heteroaryl) halides

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ABSTRACT

Palladium-catalyzed Suzuki–Miyaura cross-coupling reaction of potassium pyridine-2-trifluoroborates and various aryl (heteroaryl) halides can generate the corresponding desired coupling products with moderate to good yields. It can be carried out under the conditions with ethanol as solvent, $Pd(OAc)_2$ and SPhos as catalyst system and Na_2CO_3 as a base.

1. Introduction

Substituted heterobiaryls widely exist in natural products, pharmaceutically active molecules, agrochemicals and functional materials, and are mainly prepared by transition-metal-catalyzed cross-coupling reactions,[1,3] such as Kumada–Corriu cross-coupling,[2] Stille cross-coupling,[3] Negishi cross-coupling[4] or Suzuki–Miyaura cross-coupling.[5] Among the various cross-coupling reactions, Suzuki–Miyaura reaction has become an indispensable instrument for preparing these compounds owing to its tolerance of a wide range of functional groups, high stability, relatively low toxicity and ready availability of organoboron compounds.[6]

Considerable efforts have been made to develop metal–ligand catalyst systems that facilitate the Suzuki–Miyaura cross-coupling reaction and increase its scope.[7] In these known reports, the cross-coupling reaction of 2-pyridyl boron-based nucleophiles under palladium catalysis is inherently difficult due to their propensity to decompose via protodeboronation.[8] Regarding Suzuki–Miyaura reaction of 2-pyridyl nucleophiles with aryl halides, only aryl iodides have been demonstrated as suitable coupling partners in the few published reports.[5,9] Recently, some new catalytic system has been developed. Li and co-workers have reported cross-coupling reaction of 2-pyridylboronic esters with aryl bromides by using palladium phosphine chloride and oxide catalysts under Suzuki–Miyaura conditions.[10] Deng and co-workers have reported cross-coupling reaction of 2-pyridylboronic esters with aryl bromides by using palladium acetate and 1,1′-bis(diphenylphosphino) ferrocene with copper (I) halide as additive under Suzuki–Miyaura conditions.[11] And to address this problem, many important surrogates have been developed, including trialkoxy or trihydroxyborate salts, diethanolamine adducts, sterically bulky boronic esters and boroxines.[8,9,12] These methods can perform well for special substrates, but for heteroaryl halides and less expensive substrates, such as aryl chlorides, there is still a lot of challenge. In 2009, Burke and co-workers successfully applied the coupling of 2-pyridyl MIDA boronate with aryl chlorides to get moderate to good yields by using a slow-release strategy to circumvent the instability problems of 2-pyridylboronic acids.[13]

In recent years, organotrifluoroborates have become an important nucleophilic reagent in Suzuki–Miyaura cross-coupling, and it has been widely used due to its stability to air and moisture. Besides, this kind of potassium trifluoroborates can be easily made from a wide variety of organoboron reagents together with inexpensive potassium hydrogen fluoride (KHF_2). For the most part, these salts can be easily purified by recrystallization, precipitation, or Soxhlet extraction.[14–16] Byproducts of the cross-coupling of organotrifluoroborates with organic halides are inorganic salts, which are readily separable from the desired products. However, regarding the direct coupling of potassium pyridine-2-

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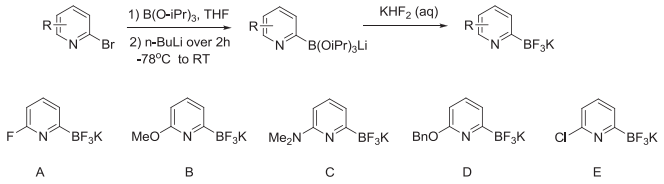
trifluoroborate with aryl halides, there were only two reports previously and the study results were not optimized.[6d,15,16] Therefore, we synthesized a series of potassium pyridine-2-trifluoroborates based on literature methods[16] (Scheme 1). The catalytic system composed of $Pd(OAc)_2$ and SPhos efficiently promotes cross-coupling reactions of various potassium pyridine-2-trifluoroborates with aryl halides and heteroaryl halides, allowing these coupling processes to produce moderate to good yields.

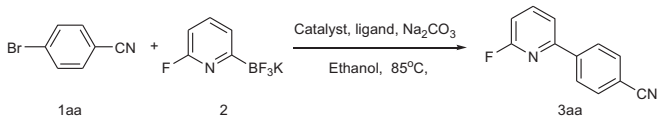


Scheme 1. Synthesis of potassium 2-pyridyltrifluoroborates.

2. Results and discussion

To find optimal cross-coupling conditions for potassium pyridine-2-trifluoroborate with aryl and heteroaryl halides, the coupling between potassium 6-fluoropyridine-2-trifluoroborate and 4-bromobenzonitrile is chosen as a model reaction under the conditions with ethanol as solvent at 85 °C in an oil bath and Na_2CO_3 as a base (as shown in Table 1), with the aim of testing the catalytic activity of different catalysts and ligands (Fig. 1). As seen from Table 1, the combination of $Pd(OAc)_2$ and PPh_3, PCy_3, DavePhos, CyJohnPhos, RuPhos or XPhos generates moderate yields (Table 1, entries 1–6). When SPhos was used as ligand, 83% yield was offered (Table 1, entry 7). When 2 mol % of the catalyst loading was used, the coupling yield was decreased. But the yield was not improved significantly when the catalyst loading was increased to 5 mol %. So 3 mol % loading of catalyst $Pd(OAc)_2$ and 6 mol % SPhos was fixed. Under the same catalytic system, when the equiv of potassium pyridine-2-trifluoroborate was decreased to 1.5 equiv, the yield was comparative lower. Next, the catalyst was changed to a Pd source of $Pd_2(dba)_3\cdot CHCl_3$, resulting in an 83% yield of **3aa** (Table 1, entry 11). $Pd(OAc)_2$ is chosen as Pd source for this reaction because it is cheaper than $Pd_2(dba)_3\cdot CHCl_3$.

Table 1
Screen of catalysts and ligands for the cross-coupling of potassium 6-fluoropyridine-2-trifluoroborate with 4-bromobenzonitrile[a]



Entry	Catalyst	Ligand	Yield[b] (%)
1	$Pd(OAc)_2$	PCy_3	67
2	$Pd(OAc)_2$	PPh_3	72
3	$Pd(OAc)_2$	DavePhos	67
4	$Pd(OAc)_2$	CyJohnPhos	63
5	$Pd(OAc)_2$	XPhos	76
6	$Pd(OAc)_2$	RuPhos	63
7	$Pd(OAc)_2$	SPhos	83
8	$Pd(OAc)_2$	SPhos	61[c]
9	$Pd(OAc)_2$	SPhos	85[d]
10	$Pd(OAc)_2$	SPhos	71[e]
11	$Pd_2(dba)_3\cdot CHCl_3$	SPhos	83

[a] All reactions are based on 4-bromobenzonitrile (0.25 mmol), potassium 6-fluoropyridine-2-trifluoroborate (0.50 mmol), catalyst (3 mol %), ligand (6 mol %), Na_2CO_3 (0.50 mmol), ethanol (2.0 ml), 85 °C, 16 h.
[b] Isolated yield based on **1aa**.
[c] Catalyst (2 mol %), ligand (4 mol %).
[d] Catalyst (5 mol %), ligand (10 mol %).
[e] Potassium 6-fluoropyridine-2-trifluoroborate (0.375 mmol).

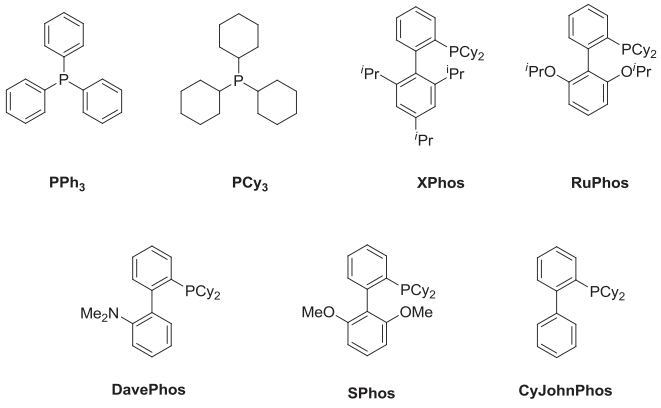
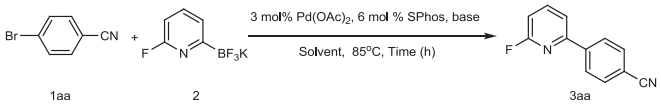


Fig. 1. The structure of phosphine ligands.

To examine the influence of bases and solvents, the potassium 6-fluoropyridine-2-trifluoroborate with 4-bromobenzonitrile was also chosen as the model reaction by fixing 3 mol % loading of $Pd(OAc)_2$ and 6 mol % SPhos. Various bases, such as $NaHCO_3$, Cs_2CO_3, K_3PO_4, K_2CO_3, Na_2CO_3 were examined in the reaction. When Cs_2CO_3 and Na_2CO_3 were used as base, the excellent yield was obtained (Table 2, entries 4 and 5). It was found that the solvent played a critical role on the reaction efficiency (Table 2) by using dioxane and THF as solvent, only lower yield of **3aa** was obtained (Table 2, entries 6 and 7). DMSO, DMF and isopropanol also offer moderate yields in this reaction (Table 2, entries 8 and 9). The desired product was obtained in 83% when ethanol was used as solvent (Table 2, entry 5), and water does not improve this reaction. Moreover, the yield was not improved evidently by prolonging the reaction time from 16 h to 18 h (Table 2, entry 5 vs 12). So, the combination of 3 mol % $Pd(OAc)_2$ and 6 mol % SPhos in ethanol in the presence of Na_2CO_3 at 85 °C in an oil bath is chosed as optimum conditions.

Table 2
Screen of solvents and bases for the cross-coupling of potassium 6-fluoropyridine-2-trifluoroborate with 4-bromobenzonitrile[a]

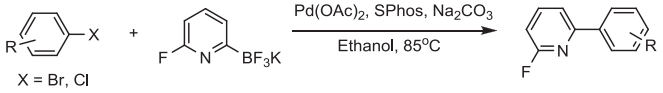


Entry	Base	Solvent	*t*/h	Yield[b] (%)
1	$NaHCO_3$	Ethanol	16	78
2	$K_3PO_4\cdot 7H_2O$	Ethanol	16	80
3	K_2CO_3	Ethanol	16	81
4	Cs_2CO_3	Ethanol	16	83
5	Na_2CO_3	Ethanol	16	83
6	Na_2CO_3	Dioxane	16	14
7	Na_2CO_3	THF	16	30
8	Na_2CO_3	DMF	16	68
9	Na_2CO_3	DMSO	16	77
10	Na_2CO_3	Isopropanol	16	68
11	Na_2CO_3	Ethanol/H_2O (4:1)	16	81
12	Na_2CO_3	Ethanol	18	83

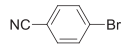
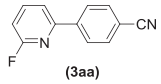
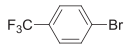
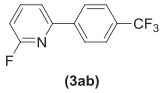
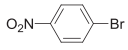
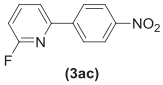
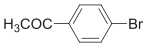
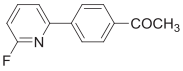
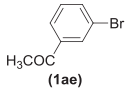
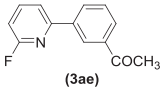
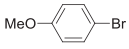
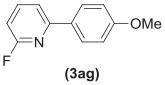
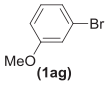
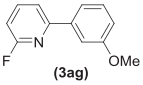
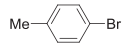
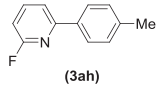
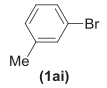
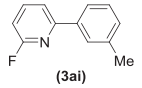
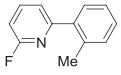
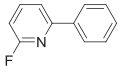
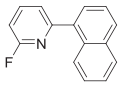
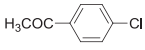
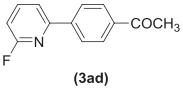
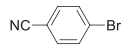
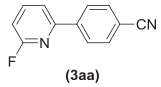
[a] All reactions are based on 4-bromobenzonitrile (0.25 mmol), potassium 6-fluoropyridine-2-trifluoroborate (0.50 mmol), 3 mol % $Pd(OAc)_2$, 6 mol % SPhos, 0.50 mmol base, 2.0 ml solvent, 85 °C (oil bath), 16 h.
[b] Isolated yield based on **1aa**.

Under the optimized reaction conditions, we extended Suzuki–Miyaura cross-coupling reaction of potassium 6-fluoropyridine-2-trifluoroborate and various aryl halides. It can be seen from Table 3 that the optimized reaction conditions tolerate a variety of functional groups, including acetyl, cyano, nitro, keto, trifluoromethyl and methyl (Table 3, entries 1–11). Moreover, a series of aryl bromides, which contain different substitution groups, such as electron-

Table 3
Pd-catalyzed Suzuki–Miyaura cross-coupling reaction of potassium 6-fluoropyridine-2-trifluoroborate with aryl halides[a]



1a 2 3a

Entry	Aryl halide	Product	Yield[b] (%)
1	 (1aa)	 (3aa)	83
2	 (1ab)	 (3ab)	84
3	 (1ac)	 (3ac)	73
4	 (1ad)	 (3ad)	81
5	 (1ae)	 (3ae)	80
6	 (1ag)	 (3ag)	94
7	 (1ag)	 (3ag)	88
8	 (1ah)	 (3ah)	93
9	 (1ai)	 (3ai)	91
10	 (1aj)	 (3aj)	49
11	 (1ak)	 (3ak)	82
12	 (1al)	 (3al)	68
13	 (1am)	 (3ad)	77
14	 (1an)	 (3aa)	79

[a] Reaction conditions: aryl halides (0.25 mmol), potassium 6-fluoropyridine-2-trifluoroborate (0.50 mmol), $Pd(OAc)_2$ (3 mol %), SPhos (6 mol %), Na_2CO_3 (0.50 mmol), ethanol (2.0 mL), 85 °C (oil bath), 16 h.
[b] Isolated yields based on **1a**.

donating and electron-withdrawing can readily be coupled with potassium 6-fluoropyridine-2-trifluoroborate to produce moderate to good yields of 73–94% (Table 3, entries 1–11).

ortho-Substituted aryl bromides can also cross-couple with potassium 6-fluoropyridine-2-trifluoroborate under the optimized reaction conditions with moderate yields (49% and 68%, respectively, for Table 3, entries 10 and 12). Most notably, the coupling reaction can also happen between 4-chloroacetophenone or 4-chlorobenzonitrile and potassium 6-fluoropyridine-2-trifluoroborate to smoothly produce the desired products with yields of 77% and 79% (Table 3, entries 13 and 14). Overall, under these reaction conditions, substrates with electron-donating groups gave little higher yields than those with electron-withdrawing groups, which indicate that the electronic effects likely have an effect on the reaction. Substrates with substituents at *ortho*-position (Table 3, entry 10) gave lower yields than those at *meta*-position (Table 3, entry 9) or *para*-position (Table 3, entry 8), which shows that steric hindrance likely has a negative effect on the reaction.

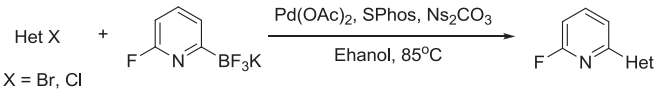
We further investigated the coupling reaction between potassium 6-fluoropyridine-2-trifluoroborate and a range of substituted heteroaryl halides. As shown in Table 4, a variety of heteroaryl halides containing nitrogen- and sulfur-heteroaryl halides can be converted to coupling products with moderate to good yields (Table 4). The reaction of 6-bromo-2-methoxypyridine with potassium 6-fluoropyridine-2-trifluoroborate can proceed well to provide the desired product with 82% yield (Table 4, entry 1). However, when coupling an unsubstituted 2-bromopyridine with potassium 6-fluoropyridine-2-trifluoroborate, it only produced 27% yield (Table 4, entry 2). A cross-coupling product with 78% yield is obtained from coupling 3-bromopyridine and 4-bromopyridine with potassium 6-fluoropyridine-2-trifluoroborate (Table 4, entries 3 and 7). It is interesting to see that a challenging substrate, 5-bromo-2-aminopyridine, was coupled with potassium 6-fluoropyridine-2-trifluoroborate, producing 89% yield (Table 4, entry 4). Similarly, 5-bromo-*N*-methyl-2-pyridinamine can be successfully converted into the corresponding coupling product with 61% yield (Table 4, entry 8). This is in sharp contrast to the fact that 5-bromobenzo[*b*] thiophene can successfully couple with potassium 6-fluoropyridine-2-trifluoroborate to produce the corresponding coupling product in yield of 94% (Table 4, entry 12). The cross-coupling condition can also be applied to heteroaryl chlorides, such as 2-chloro-6-methoxy pyridine and 2-chloro-6-phenylpyrazine and the corresponding coupling products were obtained in yields of 65% and 59% (Table 4, entries 10 and 11).

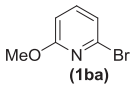
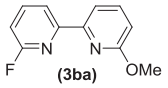
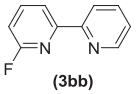
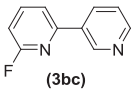
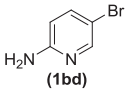
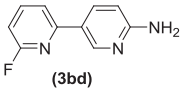
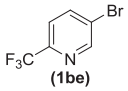
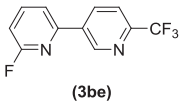
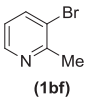
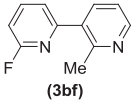
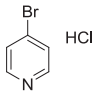
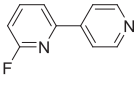
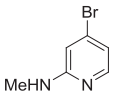
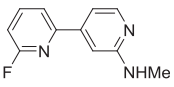
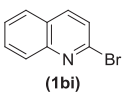
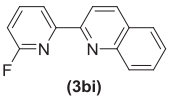
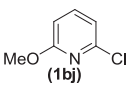
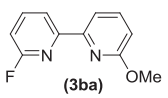
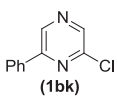
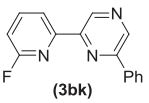
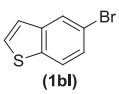
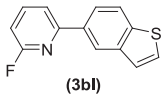
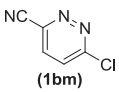
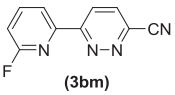
Under these conditions, we expanded the Suzuki–Miyaura cross-coupling reaction to different potassium pyridine-2-trifluoroborates. For example, potassium 6-methoxypyridine-2-trifluoroborate is coupled with 5-bromo-2-trifluoromethylpyridine and 4-chlorobenzonitrile, giving desired coupling products with good yields of 80% and 83%, respectively (Table 5, entries 1 and 2). In addition, the coupling reaction of potassium 6-*N*,*N*-dimethylpyridine-2-trifluoroborate with 4-bromobenzonitrile and 1-bromo-4-(trifluoromethyl) benzene generated the desired products with 77% and 52% yields (Table 5, entries 3 and 4). Similarly, potassium 6-benzyloxypyridine-2-trifluoroborate is coupled with 5-bromo-2-trifluoromethylpyridine and 4-bromotoluene to produce the corresponding coupling products in 34% and 25% yields, respectively (Table 5, entries 5 and 6). Coupling potassium 6-chlorinelypyridine-2-trifluoroborate with 4-bromobenzonitrile provides the desired product with 26% yield (Table 5, entry 7).

3. Conclusions

In summary, Palladium-catalyzed Suzuki–Miyaura cross-coupling reaction of potassium 2-pyridyltrifluoroborates with aryl

Table 4
Pd-catalyzed Suzuki–Miyaura cross-coupling reaction of potassium 6-fluoropyridine-2-trifluoroborate with heteroaryl halides[a]



Entry	Aryl halide	Product	Yield[b] (%)
1	 (1ba)	 (3ba)	82
2	 (1bb)	 (3bb)	27
3	 (1bc)	 (3bc)	78
4	 (1bd)	 (3bd)	89
5	 (1be)	 (3be)	94
6	 (1bf)	 (3bf)	75
7	 (1bg)	 (3bg)	78[c]
8	 (1bh)	 (3bh)	61
9	 (1bi)	 (3bi)	64
10	 (1bj)	 (3ba)	65
11	 (1bk)	 (3bk)	59
12	 (1bl)	 (3bl)	94
13	 (1bm)	 (3bm)	Trace

[a] Reaction conditions: heteroaryl halides (0.25 mmol), potassium 6-fluoropyridine-2-trifluoroborate (0.50 mmol), $Pd(OAc)_2$ (3 mol %), SPhos (6 mol %), Na_2CO_3 (0.50 mmol), ethanol (2.0 mL), 85 °C (oil bath), 16 h.
[b] Isolated yields based on **1b**.
[c] Na_2CO_3 (0.75 mmol).

and heteroaryl halides can produce moderate to good yields by using Na_2CO_3 as a base, ethanol as a solvent and $Pd(OAc)_2$ and SPhos as catalyst system. Moreover, a wide range of substrates with electron-donating, electron-neutral, electron-withdrawing and other functional groups can as well fit with this system.

4. Experimental section

4.1. General methods

^1H and ^{13}C NMR spectroscopic data were recorded with a Bruker DPX 400 instrument by using tetramethylsilane (TMS) as the internal standard. All coupling constants (*J*) are reported in hertz (Hz). Melting points were measured with an XT4A microscopic apparatus. High-resolution mass spectra were recorded with a Waters Q-Tof micro spectrometer by using electrospray ionization (ESI). Preparative TLC was performed on silica gel plates and developed with ethyl acetate/hexane. All solvents were dried according to standard methods. Aryl halides were obtained from commercial sources and were generally used without further purification.

4.2. Preparation of potassium 2-pyridyltrifluoroborates (A–E)

A 100 mL single-neck flask was evacuated under vacuum, flame-dried and then charged with nitrogen gas three times. Anhydrous THF was added to the flask via syringe and a solution of a variety of functional groups 2-bromopyridine (1.0 equiv) in THF was added following by triisopropyl borate (1.1 equiv) via syringe at −78 °C. A solution of 2.5 M *n*-BuLi in hexane (1.1 equiv) was added dropwise via constant pressure funnel over 2.0 h at −78 °C. After the addition of *n*-BuLi was complete, the mixture was kept at −78 °C with stirring for an additional 3.0 h, then allowed to warm up room temperature overnight. The mixture was then cooled to 0 °C and an aqueous solution of KHF_2 (3.0 equiv) was added dropwise with vigorous stirring. After stirring for an additional 4.0 h, the solvents were completely removed under vacuum. The crude product was then taken up in methanol and filtered, elimination of the solvent of methanol gave the white solid, and then the white solid was washed with acetone and filtered, collected, and dried in vacuo to afford the desired pure product as a light white solid (**A**–**E**).

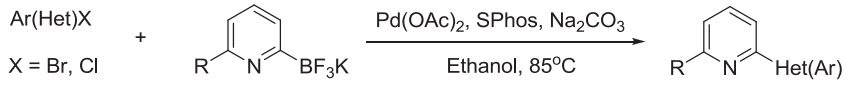
*4.2.1. Characterization data for potassium 6-fluoropyridine-2-trifluoroborate (**A**).* White solid; mp >247 °C; 21% yield. ^1H NMR (400 MHz, DMSO, ppm): δ 6.65 (dd, *J*=8.0, 5.2 Hz, 1H), 7.24 (dd, *J*=7.0, 3.3 Hz, 1H), 7.59 (q, *J*=16.1, 8.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO, ppm): δ 103.7 (d, *J*=38.8 Hz), 122.4, 138.0 (d, *J*=6.9 Hz), 163.2; HRMS (ESI): *m*/*z* calcd for $[C_5H_3BF_4KN-K]^-$: 164.0295, found: 164.0290.

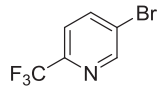
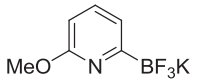
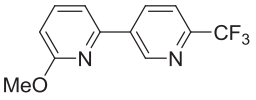
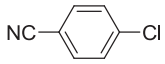
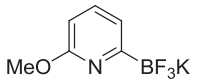
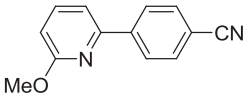
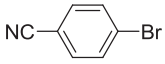
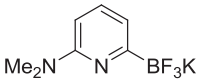
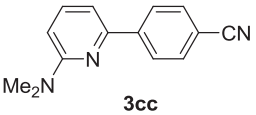
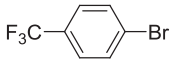
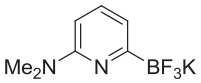
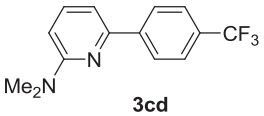
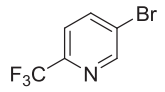
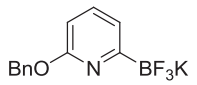
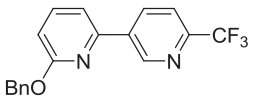
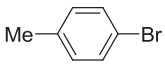
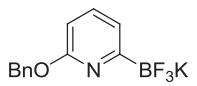
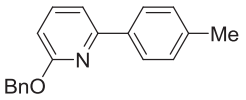
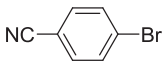
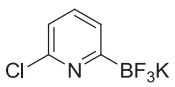
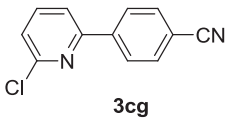
*4.2.2. Characterization data for potassium 6-methoxypyridine-2-trifluoroborate (**B**).* White solid; mp >247 °C; 26% yield. ^1H NMR (400 MHz, DMSO, ppm): δ 3.80 (s, 3H), 6.40 (d, *J*=8.2 Hz, 1H), 6.93 (d, *J*=7.0 Hz, 1H), 7.36 (t, *J*=7.5 Hz, 1H); ^{13}C NMR (100 MHz, DMSO, ppm): δ 52.4, 106.1, 118.7, 136.6, 162.4; HRMS (ESI): *m*/*z* calcd for $[C_6H_6BF_3KNO-K]^-$: 176.0495, found: 176.0492.

*4.2.3. Characterization data for potassium 6-N,N-dimethylpyridine-2-trifluoroborate (**C**).* White solid; mp >247 °C; 32% yield. ^1H NMR (400 MHz, DMSO, ppm): δ 3.29 (s, 6H), 6.35 (d, *J*=8.4 Hz, 1H), 6.65 (d, *J*=7.0 Hz, 1H), 7.28 (t, *J*=7.8 Hz, 1H); ^{13}C NMR (100 MHz, DMSO, ppm): δ 37.6, 107.1, 117.05, 136.1, 158.5; EIMS: *m*/*z* calcd for $[C_7H_9BF_3KN_2-K]^-$: 189.1, found: 189.1.

*4.2.4. Characterization data for potassium 6-benzyloxypyridine-2-trifluoroborate (**D**).* White solid; mp >247 °C; 30% yield. ^1H NMR

Table 5
Pd-catalyzed Suzuki–Miyaura cross-coupling reaction of potassium pyridine-2-trifluoroborate with aryl (heteroaryl) halides[a]



Entry	Aryl halides	Potassium pyridine-2-trifluoroborate	Product	Yield[b] (%)
1	 **1ca**		 **3ca**	80
2	 **1cb**		 **3cb**	83
3	 **1cc**		 **3cc**	77
4	 **1cd**		 **3cd**	52
5	 **1ce**		 **3ce**	34
6	 **1cf**		 **3cf**	25
7	 **1cg**		 **3cg**	26[c]

[a] Reaction conditions: aryl halides (0.25 mmol), potassium 2-pyridyl trifluoroborate (0.50 mmol), Pd $(OAc)_2$ (3 mol %), SPhos (6 mol %), Na_2CO_3 (0.50 mmol), ethanol (2.0 mL), 16 h, 85 °C.
[b] Isolated yields based on **1c**.
[c] 4-Bromobenzonitrile (0.50 mmol), E (1.0 mmol), Pd $(OAc)_2$ (5 mol %), SPhos (10 mol %), Na_2CO_3 (1.0 mmol), ethanol (4.0 mL), 24 h, 85 °C.

(400 MHz, DMSO, ppm): δ 5.33 (s, 2H), 6.46 (d, J=8.0 Hz, 1H), 6.94 (d, J=6.8 Hz, 1H), 7.28–7.40 (m, 4H), 7.46 (d, J=6.8 Hz, 2H); ^{13}C NMR (100 MHz, DMSO, ppm): δ 66.1, 107.0, 119.5, 127.8, 128.2, 128.3, 128.6, 136.7, 138.6, 162.2; HRMS (ESI): m/z calcd for $[C_{12}H_{10}BF_3KNO-K]^-$: 252.0808, found: 252.0803.

*4.2.5. Characterization data for potassium 6-chlorinepyridine-2-trifluoroborate (**E**).* White solid; mp >247 °C; 35% yield. ^{1}H NMR (400 MHz, DMSO, ppm): δ 7.05 (d, J=7.7 Hz, 1H), 7.31 (d, J=7.3 Hz, 1H), 7.48 (t, J=7.5 Hz, 1H); ^{13}C NMR (100 MHz, DMSO, ppm): δ 119.6, 124.2, 136.7, 149.4; HRMS (ESI): m/z calcd for $[C_5H_3BClF_3KN-K]^-$: 179.9999, found: 180.0002.

4.3. General procedure for the Pd-catalyzed Suzuki–Miyaura reaction of potassium 6-fluoropyridine-2-trifluoroborate with aryl halides (Table 3)

A 10-mL Schlenk tube was charged with $Pd(OAc)_2$ (1.7 mg, 0.0075 mmol, 3 mol %), SPhos (6.2 mg, 0.015 mmol, 6 mol %), Na_2CO_3 (53.0 mg, 0.50 mmol, 2 equiv), potassium 6-fluoropyridine-2-trifluoroborate (101.5 mg, 0.50 mmol, 2 equiv) and aryl halides (0.25 mmol, 1.0 equiv), followed by the addition of ethanol (2.0 ml). The reaction was carried out at 85 °C for 16 h under the protection of nitrogen gas. Then, the reaction mixture was allowed to cool down to room temperature and the reaction solution was filtered through a thin pad of silica gel (eluting with ethyl acetate) and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel flash chromatography to produce the desired products (ethyl acetate/hexane=1:2–1:80).

4.4. General procedure for the Pd-catalyzed Suzuki–Miyaura cross-coupling reaction of potassium 6-fluoropyridine-2-trifluoroborate with heteroaryl halides (Table 4)

A 10-mL Schlenk tube was charged with $Pd(OAc)_2$ (1.7 mg, 0.0075 mmol, 3.0 mol %), SPhos (6.2 mg, 0.015 mmol, 6.0 mol %), Na_2CO_3 (53.0 mg, 0.50 mmol, 2.0 equiv), potassium 6-fluoropyridine-2-trifluoroborate (101.5 mg, 0.50 mmol, 2.0 equiv)

and heteroaryl halides (0.25 mmol, 1.0 equiv), followed by the addition of ethanol (2.0 ml). The reaction was carried out at 85 °C for 16 h under the protection of nitrogen gas. Then, the reaction mixture was allowed to cool down to room temperature and the reaction solution was filtered through a thin pad of silica gel (eluting with ethyl acetate) and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel flash chromatography to produce the desired products (ethyl acetate/hexane=1:2–1:80).

4.5. General procedure for the Pd-catalyzed Suzuki–Miyaura cross-coupling reaction of potassium 2-pyridyltrifluoroborates with aryl halides (Table 5)

A 10-mL Schlenk tube was charged with Pd $(OAc)_2$ (1.7 mg, 0.0075 mmol, 3.0 mol %), SPhos (6.2 mg, 0.015 mmol, 6.0 mol %), Na_2CO_3 (53.0 mg, 0.50 mmol, 2.0 equiv), potassium 2-pyridyltrifluoroborates (0.50 mmol, 2.0 equiv) and aryl halides (0.25 mmol, 1.0 equiv), followed by the addition of ethanol (2.0 ml). The reaction was carried out at 85 °C for 16 h under the protection of nitrogen gas. Then, the reaction mixture was allowed to cool down to room temperature and the reaction solution was filtered through a thin pad of silica gel (eluting with ethyl acetate) and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel flash chromatography to produce the desired products (ethyl acetate/hexane=1:15–1:25).

4.6. Characterization of products

*4.6.1. 4-(6-Fluoro-2-pyridinyl)benzonitrile (Table 3, entries 1 and 14) (**3aa**).* White solid; mp 134–135 °C; 83% and 79% yield. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 6.97 (dd, J=5.0, 8.0 Hz, 1H), 7.67 (dd, J=5.1, 7.6 Hz, 1H), 7.76 (d, J=8.4 Hz, 2H), 7.91 (q, J=7.8, 15.9 Hz, 1H), 8.12 (d, J=8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 109.3 (d, J=37.2 Hz), 113.0, 117.9 (d, J=4.0 Hz), 118.5, 127.4, 132.6, 141.5, 142.0 (d, J=7.7 Hz), 153.9 (d, J=13.4 Hz), 163.4 (d, J=238.9 Hz); HRMS (ESI): m/z calcd for $[C_{12}H_7FN_2+H]^+$: 199.0672, found: 199.0674.

*4.6.2. 2-Fluoro-6-[4-(trifluoromethyl)phenyl]pyridine (Table 3, entry 2) (**3ab**).* White solid; mp 43–46 °C; 84% yield. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 6.95 (dd, J=5.2, 8.2 Hz, 1H), 7.68 (dd, J=5.1, 7.5 Hz, 1H), 7.73 (d, J=8.3 Hz, 2H), 7.90 (q, J=7.9, 15.9 Hz, 1H), 8.12 (d, J=8.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 108.9 (d, J=37.3 Hz), 117.8 (d, J=4.1 Hz), 125.8 (q, J=3.7 Hz), 127.2, 128.1 (q, J=270.8 Hz), 131.8 (q, J=32.2 Hz), 140.8, 142.0, 154.6 (d, J=13.3 Hz), 163.4 (d, J=238.1 Hz); HRMS (ESI): m/z calcd for $[C_{12}H_7F_4N+H]^+$: 242.0593, found: 242.0583.

*4.6.3. 2-Fluoro-6-(4-nitrophenyl)pyridine (Table 3, entry 3) (**3ac**).* Yellow solid; mp 128–129 °C; 73% yield. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.00 (dd, J=5.1, 8.3 Hz, 1H), 7.72 (dd, J=5.3, 7.8 Hz, 1H), 7.94 (q, J=7.7, 15.7 Hz, 1H), 8.17–8.20 (m, 2H), 8.31–8.35 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 109.6 (d, J=37.1 Hz), 118.2 (d, J=3.8 Hz), 124.0, 127.7, 142.1 (d, J=7.6 Hz), 143.2, 148.4, 153.5 (d, J=13.3 Hz), 163.4 (d, J=238.9 Hz); HRMS (ESI): m/z calcd for $[C_{11}H_7FN_2O_2+H]^+$: 219.0570, found: 219.0578.

*4.6.4. 1-[4-(6-Fluoro-2-pyridinyl)phenyl]ethanone (Table 3, entries 4 and 13) (**3ad**).* White solid; mp 126–128 °C; 81% and 77% yield. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 2.64 (s, 3H), 6.93 (dd, J=5.1, 8.0 Hz, 1H), 7.68 (dd, J=5.0, 7.4 Hz, 1H), 7.88 (q, J=7.8, 15.8 Hz, 1H), 8.03–8.05 (m, 2H), 8.08–8.10 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 26.7, 108.7 (d, J=37.4 Hz), 117.9 (d, J=4.0 Hz), 127.0, 128.9 (d, J=18.8 Hz), 137.5, 141.6, 141.9 (d, J=7.7 Hz), 154.8 (d, J=13.3 Hz), 163.4 (d, J=237.9 Hz), 197.7; HRMS (ESI): m/z calcd for $[C_{13}H_{10}FNO+H]^+$: 216.0825, found: 216.0827.

*4.6.5. 1-[3-(6-Fluoro-2-pyridinyl)phenyl]ethanone (Table 3, entry 5) (**3ae**).* Yellow oil; 80% yield. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 2.69 (s, 3H), 6.93 (dd, J=5.2, 8.1 Hz, 1H), 7.59 (t, J=7.8 Hz, 1H), 7.71 (dd, J=5.0, 7.5 Hz, 1H), 7.89 (q, J=7.9, 15.8 Hz, 1H), 8.03 (d, J=7.7 Hz, 1H), 8.23 (d, J=7.8 Hz, 1H), 8.58 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 26.7, 108.3 (d, J=37.2 Hz), 117.5 (d, J=4.0 Hz), 126.6, 129.1, 129.2, 131.4, 137.6, 138.0, 141.9 (d, J=7.7 Hz), 155.1 (d, J=13.2 Hz), 163.4 (d, J=237.7 Hz), 197.9; HRMS (ESI): m/z calcd for $[C_{13}H_{10}FNO+H]^+$: 216.0825, found: 216.0823.

*4.6.6. 2-Fluoro-6-(4-methoxyphenyl)pyridine (Table 3, entry 6) (**3af**).* White solid; mp 69–71 °C; 94% yield. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 3.87 (s, 3H), 6.80 (dd, J=4.9, 7.9 Hz, 1H), 6.99 (d, J=6.8 Hz, 2H), 7.55 (dd, J=5.0, 7.4 Hz, 1H), 7.79 (q, J=7.9, 15.8 Hz, 1H), 7.97 (d, J=6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 55.3, 106.6 (d, J=37.6 Hz), 114.1, 116.3 (d, J=4.0 Hz), 128.2, 130.1, 141.5 (d, J=7.7 Hz), 155.9 (d, J=13.4 Hz), 160.8, 163.3 (d, J=236.1 Hz); HRMS (ESI): m/z calcd for $[C_{12}H_{10}FNO+H]^+$: 204.0825, found: 204.0821.

*4.6.7. 2-Fluoro-6-(3-methoxyphenyl)pyridine (Table 3, entry 7) (**3ag**).* Yellow oil; 88% yield. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 3.89 (s, 3H), 6.87 (dd, J=5.0, 8.3 Hz, 1H), 6.97–7.00 (m, 1H), 7.38 (t, J=8.0 Hz, 1H), 7.55–7.59 (m, 2H), 7.62 (dd, J=4.9, 7.7 Hz, 1H), 7.83 (q, J=8.0, 15.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 55.3, 107.8 (d, J=37.5 Hz), 112.0, 115.6, 117.4 (d, J=3.6 Hz), 119.2, 129.7, 138.9, 141.6 (d, J=7.6 Hz), 156.0 (d, J=13.2 Hz), 160.0, 163.3 (d, J=236.6 Hz); HRMS (ESI): m/z calcd for $[C_{12}H_{10}FNO+H]^+$: 204.0825, found: 204.0821.

*4.6.8. 2-Fluoro-6-p-tolylpyridine (Table 3, entry 8) (**3ah**).* Yellow oil; 93% yield. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 2.39 (s, 3H), 6.81 (dd, J=5.1, 8.0 Hz, 1H), 7.26 (d, J=8.0 Hz, 2H), 7.57 (dd, J=5.1, 7.5 Hz, 1H), 7.79 (q, J=7.9, 15.9 Hz, 1H), 7.89 (d, J=8.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 21.3, 107.2 (d, J=37.5 Hz), 116.9 (d, J=4.0 Hz), 126.8, 129.5 (d, J=3.4 Hz), 134.7, 139.7, 141.6 (d, J=7.6 Hz), 156.3 (d, J=13.3 Hz), 163.4 (d, J=236.3 Hz); HRMS (ESI): m/z calcd for $[C_{12}H_{10}FN+H]^+$: 188.0876, found: 188.0870.

*4.6.9. 2-Fluoro-6-m-tolylpyridine (Table 3, entry 9) (**3ai**).* Yellow oil; 91% yield. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 2.45 (s, 3H), 6.86 (dd, J=5.1, 8.1 Hz, 1H), 7.27 (d, J=7.7 Hz, 1H), 7.38 (t, J=7.6 Hz, 1H), 7.61 (dd, J=5.1, 7.5 Hz, 1H), 7.78–7.81 (m, 2H), 7.85 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 21.4, 107.4 (d, J=37.4 Hz), 117.3 (d, J=4.0 Hz), 123.9, 127.5, 128.6, 130.3, 137.4, 138.4, 141.5 (d, J=7.6 Hz), 156.3 (d, J=13.2 Hz), 163.3 (d, J=236.6 Hz); HRMS (ESI): m/z calcd for $[C_{12}H_{10}FN+H]^+$: 188.0876, found: 188.0871.

*4.6.10. 2-Fluoro-6-o-tolylpyridine (Table 3, entry 10) (**3aj**).* Yellow oil; 49% yield. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 2.42 (s, 3H), 6.90 (dd, J=5.0, 8.1 Hz, 1H), 7.27–7.35 (m, 4H), 7.43 (d, J=6.6 Hz, 1H), 7.86 (q, J=15.9, 7.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 21.8, 108.7 (d, J=37.0 Hz), 122.7 (d, J=4.2 Hz), 127.4, 130.2, 131.1, 132.3, 137.4, 140.1, 142.5 (d, J=7.7 Hz), 160.2 (d, J=13.5 Hz), 164.3 (d, J=237.2 Hz); HRMS (ESI): m/z calcd for $[C_{12}H_{10}FN+H]^+$: 188.0876, found: 188.0871.

*4.6.11. 2-Fluoro-6-phenylpyridine (Table 3, entry 11) (**3ak**).* Yellow oil; 82% yield. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 6.85 (dd, J=4.9, 7.9 Hz, 1H), 7.40–7.48 (m, 3H), 7.61 (dd, J=5.0, 7.6 Hz, 1H), 7.82 (q, J=7.9, 15.9 Hz, 1H), 7.98–8.00 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 107.6 (d, J=37.4 Hz), 117.3, 126.9, 128.8 (d, J=3.4 Hz), 129.6, 137.5, 141.6 (d, J=7.6 Hz), 156.2 (d, J=13.3 Hz), 163.4 (d, J=236.7 Hz);

HRMS (ESI): *m*/*z* calcd for $[C_{11}H_8FN+H]^+$: 174.0719, found: 174.0716.

*4.6.12. 2-Fluoro-6-(1-naphthalenyl)pyridine (Table 3, entry 12) (**3al**).* Yellow oil; 68% yield. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 6.98 (dd, *J*=5.1, 7.9 Hz, 1H), 7.47–7.57 (m, 4H), 7.63 (dd, *J*=5.9, 7.1 Hz, 1H), 7.87–7.94 (m, 3H), 8.15 (q, *J*=5.5, 11.0 Hz, 1H,); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 107.7 (d, *J*=36.8 Hz), 122.2 (d, *J*=4.1 Hz), 125.2 (d, *J*=4.4 Hz), 126.0, 126.7, 127.7, 128.4, 129.4, 130.8, 133.8, 136.6, 141.3 (d, *J*=7.7 Hz), 157.8 (d, *J*=13.5 Hz), 163.1 (d, *J*=237.9 Hz); HRMS (ESI): *m*/*z* calcd for $[C_{15}H_{10}FN+H]^+$: 224.0876, found: 224.0874.

*4.6.13. 6-Fluoro-6′-methoxy-2,2′-bipyridine (Table 4, entries 1 and 10) (**3ba**).* White solid; mp 78–79 °C; 82% and 65% yield. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 4.03 (s, 3H), 6.79 (d, *J*=8.2 Hz, 1H), 6.92 (dd, *J*=5.2, 8.1 Hz, 1H), 7.69 (t, *J*=7.9 Hz, 1H), 7.89 (q, *J*=7.9, 15.9 Hz, 1H), 7.96 (d, *J*=7.4 Hz, 1H), 8.30 (dd, *J*=5.3, 7.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 53.2, 109.1 (d, *J*=37.3 Hz), 111.7, 114.0, 117.9, 139.4, 141.6 (d, *J*=7.6 Hz), 151.7, 154.8 (d, *J*=13.0 Hz), 162.9 (d, *J*=236.6 Hz), 163.4; HRMS (ESI): *m*/*z* calcd for $[C_{11}H_9FN_2O+H]^+$: 205.0777, found: 205.0773.

*4.6.14. 6-Fluoro-2,2′-bipyridine (Table 4, entry 2) (**3bb**).* Yellow solid; mp 70–72 °C; 27% yield. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 6.95 (dd, *J*=5.3, 8.0 Hz, 1H), 7.33 (dd, *J*=1.8, 6.9 Hz, 1H), 7.81 (q, 7.0, 14.5 Hz, 1H), 7.90–7.92 (m, 1H), 8.31 (dd, *J*=5.6, 7.6 Hz, 1H), 8.35 (d, *J*=8.0 Hz, 1H), 8.67 (d, *J*=4.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 109.4 (d, *J*=37.1 Hz), 118.1 (d, *J*=3.9 Hz), 121.3, 124.2, 137.0, 141.8 (d, *J*=7.5 Hz), 149.2, 154.5, 154.9 (d, *J*=12.9 Hz), 163.1 (d, *J*=237.1 Hz); HRMS (ESI): *m*/*z* calcd for $[C_{10}H_7FN_2+H]^+$: 175.0672, found: 175.0663.

*4.6.15. 6-Fluoro-2,3′-bipyridine (Table 4, entry 3) (**3bc**).* Yellow solid; mp 36–38 °C; 78% yield. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 6.94 (dd, *J*=5.2, 8.2 Hz, 1H), 7.42 (q, *J*=3.3, 7.9 Hz, 1H), 7.67 (dd, *J*=5.1, 7.6 Hz, 1H), 7.90 (q, *J*=7.7, 15.8 Hz, 1H), 8.3 (d, *J*=4.0 Hz, 1H), 8.67 (d, *J*=3.9 Hz, 1H), 9.20 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 108.6 (d, *J*=37.1 Hz), 117.4 (d, *J*=3.9 Hz), 123.6, 133.1, 134.3, 141.9 (d, *J*=7.7 Hz), 148.1, 150.4, 153.5 (d, *J*=13.4 Hz), 163.5 (d, *J*=238.4 Hz); HRMS (ESI): *m*/*z* calcd for $[C_{10}H_7FN_2+H]^+$: 175.0672, found: 175.0665.

*4.6.16. 6-Fluoro-2,3′-bipyridin-6′-amine (Table 4, entry 4) (**3bd**).* White solid; mp 139–141 °C; 89% yield. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 4.66 (s, 2H), 6.59 (d, *J*=8.2 Hz, 1H), 6.80 (dd, *J*=4.9, 7.9 Hz, 1H), 7.51 (dd, *J*=5.2, 7.8 Hz, 1H), 7.80 (q, *J*=7.7, 15.8 Hz, 1H), 8.12 (dd, *J*=6.1, 8.5 Hz, 1H), 8.70 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 106.8 (d, *J*=37.4 Hz), 108.4, 115.8 (d, *J*=4.0 Hz), 124.0, 136.5, 141.6 (d, *J*=7.8 Hz), 147.1, 154.4 (d, *J*=13.7 Hz), 159.1, 163.5 (d, *J*=236.8 Hz); HRMS (ESI): *m*/*z* calcd for $[C_{10}H_8FN_3+H]^+$: 190.0781, found: 190.0775.

*4.6.17. 6-Fluoro-6′-(trifluoromethyl)-2,3′-bipyridine (Table 4, entry 5) (**3be**).* Yellow solid; mp 102–104 °C; 94% yield. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 6.92 (dd, *J*=8.1, 5.2 Hz, 1H), 7.63 (dd, *J*=7.5, 5.1 Hz, 1H), 7.70 (d, *J*=8.2 Hz, 1H), 7.86 (q, *J*=15.8, 7.8 Hz, 1H), 8.42 (dd, *J*=8.2, 6.5 Hz, 1H), 9.19 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 109.6 (d, *J*=6.6 Hz), 110.0, 118.0, 120.5, 125.6 (q, *J*=272.6 Hz), 135.8, 142.3 (d, *J*=7.8 Hz), 148.2, 149.1 (q, *J*=34.7 Hz), 151.9 (d, *J*=13.5 Hz), 163.6 (d, *J*=239.7 Hz); HRMS (ESI): *m*/*z* calcd for $[C_{11}H_6F_4N_2+H]^+$: 243.0545, found: 243.0546.

*4.6.18. 6-Fluoro-2′-methyl-2,3′-bipyridine (Table 4, entry 6) (**3bf**).* White solid; mp 96–97 °C; 75% yield. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 2.64 (s, 3H), 6.95 (dd, *J*=8.2, 5.4 Hz, 1H,), 7.23 (q, *J*=7.8, 2.9 Hz, 1H), 7.33 (dd, *J*=7.7, 5.4 Hz, 1H), 7.74 (dd, *J*=7.8, 6.0 Hz, 1H), 7.89 (q, *J*=15.8, 7.7 Hz, 1H), 8.56 (dd, *J*=4.8, 3.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 23.5, 108.1 (d, *J*=36.8 Hz), 121.1, 121.3 (d, *J*=4.2 Hz), 134.0, 137.3, 141.4 (d, *J*=7.8 Hz), 149.1, 156.1, 156.7 (d, *J*=13.6 Hz), 163.0 (d, *J*=238.6 Hz); HRMS (ESI): *m*/*z* calcd for $[C_{11}H_9FN_2+H]^+$: 189.0828, found: 189.0816.

*4.6.19. 6-Fluoro-2,4′-bipyridine (Table 4, entry 7) (**3bg**).* White solid; mp 81–83 °C; 78% yield. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 6.99 (dd, *J*=5.6, 8.4 Hz, 1H), 7.71 (dd, *J*=5.6, 7.9 Hz, 1H), 7.87–7.95 (m, 3H), 8.74 (d, *J*=4.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 108.9 (d, *J*=37.2 Hz), 116.9 (d, *J*=3.9 Hz), 119.9, 141.1 (d, *J*=7.7 Hz), 143.5, 149.6, 152.4 (d, *J*=13.2 Hz), 162.5 (d, *J*=238.9 Hz); HRMS (ESI): *m*/*z* calcd for $[C_{10}H_7FN_2+H]^+$: 175.0672, found: 175.0660.

*4.6.20. 6-Fluoro-N-methyl-2,3′-bipyridin-5′-amine (Table 4, entry 8) (**3bh**).* White solid; mp 104–106 °C; 61% yield. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 2.98 (d, *J*=5.1 Hz, 3H), 4.77 (s, 1H), 6.92 (dd, *J*=5.1, 8.1 Hz, 1H), 7.02 (s, 1H), 7.06 (d, *J*=5.3 Hz, 1H), 7.61 (dd, *J*=5.1, 7.5 Hz, 1H), 7.85 (q, *J*=7.9, 15.8 Hz, 1H), 8.17 (d, *J*=5.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 29.2, 103.7, 109.4 (d, *J*=37.6 Hz), 110.2, 117.9 (d, *J*=3.9 Hz), 141.8 (d, *J*=7.7 Hz), 146.0, 148.8, 154.3 (d, *J*=13.1 Hz), 160.3, 163.3 (d, *J*=237.9 Hz); HRMS (ESI): *m*/*z* calcd for $[C_{11}H_{10}FN_3+H]^+$: 204.0937, found: 204.0938.

*4.6.21. 2-(6-Fluoro-2-pyridinyl)quinoline (Table 4, entry 9) (**3bi**).* - White solid; mp 110–112 °C; 64% yield. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.01 (dd, *J*=5.5, 8.3 Hz, 1H), 7.55–7.59 (m, 1H), 7.73–7.77 (m, 1H), 7.86 (d, *J*=7.3 Hz, 1H), 7.97 (q, *J*=7.8, 15.9 Hz, 1H), 8.17 (d, *J*=8.5 Hz, 1H), 8.29 (d, *J*=8.6 Hz, 1H), 8.51 (d, *J*=8.6 Hz, 1H), 8.58 (dd, *J*=5.0, 7.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 109.8 (d, *J*=37.1 Hz), 118.9 (d, *J*=3.1 Hz), 127.1, 127.7, 128.4, 129.8 (d, *J*=8.7 Hz), 137.0, 141.9 (d, *J*=7.4 Hz), 147.9, 154.6, 155.1 (d, *J*=12.6 Hz), 163.2 (d, *J*=237.3 Hz); HRMS (ESI): *m*/*z* calcd for $[C_{14}H_9FN_2+H]^+$: 225.0828, found: 225.0825.

*4.6.22. 2-(6-Fluoropyridin-2-yl)-6-phenylpyrazine (Table 4, entry 11) (**3bk**).* White solid; mp 58–60 °C; 59% yield. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.04 (dd, *J*=5.4, 8.3 Hz, 1H), 7.52–7.58 (m, 3H), 7.98 (q, *J*=7.7, 15.4 Hz, 1H), 8.15 (d, *J*=8.3 Hz, 2H), 8.48 (dd, *J*=5.6, 8.1 Hz, 1H), 9.08 (s, 1H), 9.51 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 110.4 (d, *J*=36.9 Hz), 118.7 (d, *J*=3.9 Hz), 127.0, 129.0, 130.1, 136.1, 141.1, 142.0 (d, *J*=6.4 Hz), 148.5, 151.1, 153.2 (d, *J*=13.4 Hz), 163.1 (d, *J*=238.3 Hz); HRMS (ESI): *m*/*z* calcd for $[C_{15}H_{10}FN_3+H]^+$: 252.0937, found: 252.0930.

*4.6.23. 2-Benzo[b]thiophen-5-yl-6-fluoropyridine (Table 4, entry 12) (**3bl**).* White solid; mp 111–113 °C; 94% yield. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 6.87 (dd, *J*=4.9, 8.0 Hz, 1H), 7.42 (d, *J*=5.4 Hz, 1H), 7.49 (d, *J*=5.4 Hz, 1H), 7.70 (dd, *J*=5.0, 7.7 Hz, 1H), 7.86 (q, *J*=7.7, 15.9 Hz, 1H), 7.94–7.98 (m, 2H), 8.49 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 107.5 (d, *J*=37.4 Hz), 117.3 (d, *J*=3.6 Hz), 122.2, 122.8, 122.9, 124.4, 127.3, 134.0, 140.1, 141.0, 141.7 (d, *J*=7.6 Hz), 156.4 (d, *J*=13.5 Hz), 163.4 (d, *J*=236.6 Hz); HRMS (ESI): *m*/*z* calcd for $[C_{13}H_8FNS+H]^+$: 230.0440, found: 230.0441.

*4.6.24. 6-Methoxy-6′-(trifluoromethyl)-2,3′-bipyridine (Table 5, entry 1) (**3ca**).* Yellow solid; mp 59–61 °C; 80% yield. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 4.04 (s, 3H), 6.79 (d, *J*=8.2 Hz, 1H), 7.39 (d, *J*=7.3 Hz, 1H), 7.66–7.76 (m, 2H), 8.48 (d, *J*=8.2 Hz, 1H), 9.33 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 53.3, 111.4, 113.4, 120.2, 125.7 (q, *J*=272.2 Hz), 135.1, 137.1, 139.4, 147.5, 148.3, 150.3, 164.1; HRMS (ESI): *m*/*z* calcd for $[C_{12}H_9F_3N_2O+H]^+$: 255.0745, found: 255.0744.

*4.6.25. 4-(6-Methoxypyridin-2-yl)benzonitrile (Table 5, entry 2) (**3cb**).* White solid; mp 78–80 °C; 83% yield. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 3.97 (s, 3H), 6.71 (d, *J*=8.2 Hz, 1H), 7.32 (d, *J*=7.4 Hz,

1H), 7.61 (t, *J*=7.9 Hz, 1H), 7.67 (d, *J*=8.4 Hz, 2H), 8.1 (d, *J*=8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 53.4, 111.0, 112.1, 113.5, 119.0, 127.2, 132.4, 139.4, 143.2, 152.3, 163.9; HRMS (ESI): *m*/*z* calcd for $[C_{13}H_{10}N_2O+H]^+$: 211.0871, found: 211.0865.

*4.6.26. 4-(6-(Dimethylamino)pyridin-2-yl)benzonitrile (Table 5, entry 3) (**3cc**).* Green solid; mp 80–82 °C; 77% yield. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 3.18 (s, 6H), 6.56 (d, *J*=8.5 Hz, 1H), 7.07 (d, *J*=7.4 Hz, 1H), 7.56 (t, *J*=8.0 Hz, 1H), 7.72 (d, *J*=8.4 Hz, 2H), 8.15 (d, *J*=8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 37.9, 105.7, 108.4, 111.6, 119.1, 127.1, 132.2, 137.9, 144.3, 152.6, 159.0; HRMS (ESI): *m*/*z* calcd for $[C_{14}H_{13}N_3+H]^+$: 224.1188, found: 224.1183.

*4.6.27. N,N-Dimethyl-6-(4-(trifluoromethyl)phenyl)pyridin-2-amine (Table 5, entry 4) (**3cd**).* White solid; mp 54–56 °C; 52% yield. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 3.17 (s, 6H), 6.54 (d, *J*=8.5 Hz, 1H), 7.06 (d, *J*=7.4 Hz, 1H), 7.55 (t, *J*=7.6 Hz, 1H), 7.68 (d, *J*=8.2 Hz, 2H), 8.14 (d, *J*=8.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 37.9, 105.2, 108.2, 125.4 (q, *J*=3.7 Hz), 126.9, 128.4 (q, *J*=270.2 Hz), 130.6 (q, *J*=32.1 Hz), 137.9, 143.5, 153.4, 159.1; HRMS (ESI): *m*/*z* calcd for $[C_{14}H_{13}F_3N_2+H]^+$: 267.1109, found: 267.1105.

*4.6.28. 2-(Benzyloxy)-6-(4-(trifluoromethyl)phenyl)pyridine (Table 5, entry 5) (**3ce**).* Yellow solid; mp 117–119 °C; 34% yield. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 5.50 (s, 2H), 6.87 (d, *J*=8.3 Hz, 1H), 7.32–7.42 (m, 4H), 7.49 (d, *J*=7.5 Hz, 2H), 7.70–7.77 (m, 2H), 8.44 (d, *J*=8.2 Hz, 1H), 9.3 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 67.7, 111.8, 113.8, 120.3, 123.0 (q, *J*=272.2 Hz), 127.9, 128.5, 135.2, 137.1, 137.2, 139.7, 147.6, 147.9, 148.4, 150.4, 163.6; HRMS (ESI): *m*/*z* calcd for $[C_{19}H_{14}F_3NO+Na]^+$: 352.0925, found: 352.0875.

*4.6.29. 2-(Benzyloxy)-6-p-tolylpyridine (Table 5, entry 6) (**3cf**).* Yellow solid; mp 79–81 °C; 25% yield. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 2.43 (s, 3H), 5.54 (s, 2H), 6.75 (d, *J*=8.2 Hz, 1H), 7.28–7.42 (m, 6H), 7.53 (d, *J*=7.4 Hz, 2H), 7.65 (t, *J*=7.9 Hz, 1H), 7.95 (d, *J*=8.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 21.3, 67.4, 109.3, 112.7, 126.6, 127.8, 128.1, 128.4, 129.3, 136.3, 137.8, 138.8, 139.3, 154.7, 163.2; HRMS (ESI): *m*/*z* calcd for $[C_{19}H_{17}NO+H]^+$: 276.1388, found: 276.1384.

*4.6.30. 4-(6-Chloropyridin-2-yl)benzonitrile (Table 5, entry 7) (**3cg**).* White solid; mp 139–142 °C; 26% yield. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.35 (d, *J*=8.0 Hz, 1H), 7.70 (d, *J*=7.6 Hz, 1H), 7.76–7.79 (m, 3H), 8.12 (d, *J*=8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 112.1, 117.6, 118.2, 123.0, 126.5, 131.6, 138.6, 140.7, 150.8, 154.7; HRMS (ESI): *m*/*z* calcd for $[C_{12}H_7ClN_2+H]^+$: 215.0376, found: 215.0372.

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References and notes

1. (a) Ackermann, L.; Potukuchi, H. K. *Synlett* **2009**, 2852; (b) Meyers, K. M.; Kim, N.; Mendez-Andino, J. L.; Hu, X. E.; Mumin, R. N.; Klopfenstein, S. R.; Wos, J. A.; Mitchell, M. C.; Paris, J. L.; Ackley, D. C.; Holbert, J. K.; Mittelstadt, S. W.; Reizes, O. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 814.
2. Ackermann, L.; Potukuchi, H. K.; Kapdi, A. R.; Schulzke, C. *Chem.—Eur. J.* **2010**, *16*, 3300.
3. Napier, S.; Marcuccio, S. M.; Tye, H.; Whittaker, M. *Tetrahedron Lett.* **2008**, *49*, 6314.
4. Coleridge, B. M.; Bello, C. S.; Ellenberger, D. H.; Leitner, A. *Tetrahedron Lett.* **2010**, *51*, 357.
5. Deshayes, K.; Broene, R. D.; Chao, I.; Knobler, C. B.; Diederich, F. *J. Org. Chem.* **1991**, *56*, 6787.
6. (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457; (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147; (c) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633; (d) Darses, S.; Genet, J. P. *Chem. Rev.* **2008**, *108*, 288; (e) Lindup, R. J.; Marder, T. B.; Perutz, R. N.; Whitwood, A. C. *Chem. Commun.* **2007**, 3664.
7. (a) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722; (b) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550; (c) Bedford, R. B.; Cazin, C. S. J. *Chem. Commun.* **2001**, 1540; (d) Kirchoff, J. H.; Dai, C.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 1945; (e) Grasa, G. A.; Viciu, M. S.; Huang, J.; Zhang, C.; Trudell, M. L.; Nolan, S. P. *Organometallics* **2002**, *21*, 2866; (f) Feuerstein, M.; Berthiol, F.; Doucet, H.; Santinelli, M. *Synlett* **2002**, 1807; (g) Molander, G. A.; Fumagalli, T. *J. Org. Chem.* **2006**, *71*, 5743.
8. Billingsley, K. L.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 4695.
9. For examples, of Suzuki–Miyaura reactions of 2-pyridylboronic acids, see: (a) Mandolesi, S. D.; Vaillard, S. E.; Podesta, J. C.; Rossi, R. A. *Organometallics* **2002**, *21*, 4886; (b) Bouillon, A.; Lancelot, J. C.; Santos, J. S. de O.; Collot, V.; Bovy, P. R.; Rault, S. *Tetrahedron* **2003**, *59*, 10043; (c) Shinozuka, T.; Shimada, K.; Matsui, S.; Yamane, T.; Ama, M.; Fukuda, T.; Taki, M.; Takeda, Y.; Otsuka, E.; Yamato, M.; Naito, S. *Bioorg. Med. Chem.* **2006**, *14*, 6807.
10. Deng, J. Z.; Paone, D. V.; Ginnetti, A. T.; Kurihara, H.; Dreher, S. D.; Weissman, S. A.; Stauffer, S. R.; Burgey, C. S. *Org. Lett.* **2009**, *11*, 345.
11. Yang, D. X.; Colletti, S. L.; Wu, K.; Song, M. Y.; Li, G. Y.; Shen, H. C. *Org. Lett.* **2009**, *11*, 381.
12. (a) Hodgson, P. B.; Salingue, F. H. *Tetrahedron Lett.* **2004**, *45*, 685; (b) Gros, P.; Doudouh, A.; Fort, Y. *Tetrahedron Lett.* **2004**, *45*, 6239; (c) Yamamoto, Y.; Takizawa, M.; Yu, X. Q.; Miyaura, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 928.
13. Knapp, O. M.; Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* **2009**, *131*, 6961.
14. Molander, G. A.; Canturk, B.; Kennedy, L. E. *J. Org. Chem.* **2009**, *74*, 973.
15. (a) Darses, S.; Genet, J. P. *Eur. J. Org. Chem.* **2003**, *22*, 4313; (b) Molander, G. A.; Ellis, N. *Acc. Chem. Res.* **2007**, *40*, 275; (c) Stefani, H. A.; Cella, R.; Vieira, S. A. *Tetrahedron* **2007**, *63*, 3623.
16. Molander, G. A.; Biolatto, B. *J. Org. Chem.* **2003**, *68*, 4302.