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Application of palladacycle catalyst in the synthesis of mono-arylpyridyl bromides

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The mono-arylpyridyl bromides are very useful key intermediates that can be further functionalized to generate bioactive compounds. It is possible to obtain mono-arylation products of 3,5-dibromopyridine with high preferentiality and high yields by air- and moisture-stable palladacycle (catalyst II) catalyzed Suzuki reaction of 3,5-dibromopyridine with a series of arylboronic acids—ester under the conditions of K_2CO_3–toluene–methanol (4 : 1, v/v), reflux (75 °C), 5.6 equiv. of 3,5-dibromopyridine with the ratio (mono : bis) ranging from of 99 : 1 to 90 : 10. This new method could also be used to easily achieve pyridyl–pyridyl bond formation to afford 3-bromo-5-pyridylpyridine (3j). Copyright © 2007 John Wiley & Sons, Ltd.

KEYWORDS: 3,5-dibromopyridine; preferentiality; monoarylation; palladacycle; Suzuki reaction

INTRODUCTION

In recent years, pyridine derivatives have received research attention due to their wide occurrence in pharmaceuticals, natural products and tobacco alkaloids.[1–4] These compounds are widely used in pharmacy,[5,6] forensic chemistry,[7] medicinal chemistry, materials science and supramolecular chemistry.[8] Since Shigyo[9] reported that some disubstituted phenylpyridine derivatives offer antiarrhythmic activity, the synthesis of aryl-substituted pyridine arouses continuing interest in biology and pharmacy.[1–4,7] However, the classical method for direct arylation of pyridine nucleus has limited scope owing to the restricted applications for active halides and concomitant formation of homo-coupling products (Ullmann reaction),[10] the lack of regioselectivity and low yields (e.g. Gomherg–Bachmann reaction),[1–4] or the tedious procedures and limited scope of the reactants (e.g. Grignard reactions).[11]

Recently, some improved methods for arylation or heteroarylation of the pyridine nucleus have been reported, i.e. regioselective nucleophilic addition via halogen–lithium,[12–22] bromine–magnesium exchange[8,23–25] or transition metal-catalyzed cross-coupling reaction between halopyridines and arylmetallic compounds (Kumade,[26,27] Nigishi,[28–30] Stille,[31] Suzuki[32–35] coupling reactions) although a number of difficulties were encountered. Among the numerous reports of palladium-catalyzed cross-coupling of either heteroarylhalides with arylmetals or arylhalides with heteroaryl metals, Suzuki cross-coupling of arylboronic acids with heteroarylhalides has received widespread attention.

Mono-arylpyridyl bromides are very useful key intermediates for pharmaceutical research, which can be further functionalized to generate bioactive compounds.[30,36–40] As we know, the 2- and 4-substituted pyridyl moiety can be easily prepared through coupling reaction since the 2 and the 4 positions of halo-pyridines should be most susceptible to the oxidative addition of palladium(0) due to the electronegativity of the nitrogen atom.[4] The 3-bromopyridyl moiety is difficult to arylate as anticipated. This is partially due to the π-electron deficient nature of the pyridine ring.

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Several studies regarding palladium-catalyzed Suzuki arylation of dihalopyridines, mainly on 2,6-, 2,3-, 2,5- and 2,4-disubstituted pyridine[41] have been reported using various Pd(0)–(II) ligand systems. However, the use of 3,5-dibromopyridine for mono-arylation remains elusive and only a few reports[8,27,38,42,43] have appeared in the literature.

Herein, we report a simple, efficient method for the synthesis of mono-arylpyridyl bromides *via* Suzuki cross-coupling using palladacycle catalysts with high preference for mono-arylation under mild reaction conditions including formation of pyridyl–pyridyl bonds.

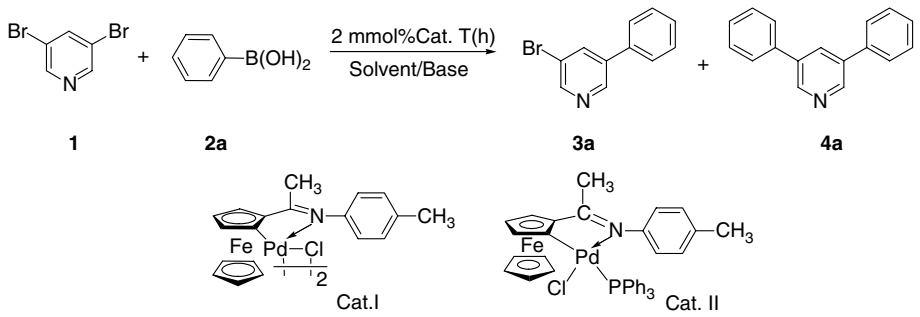
RESULTS AND DISCUSSION

The mono-arylation between 3,5-dibromopyridine **1** and phenylboronic acid **2a** (Scheme 1) were first investigated under various conditions to find the optimal reaction conditions. The data were listed in Table 1.

We have previously shown[44] that catalyst **I** was efficient for the catalytic coupling of a range of aryl halides with 3-pyridyl boronic pinacol ester under air. Firstly, we tested the reactivity of catalyst **I** in toluene–Cs_2CO_3 with a co-solvent (ethanol or methanol). It was found that the ratio of mono-arylation increased significantly when methanol was used (Table 1, entries 1 and 2). Then, base screening studies were run (entries 2 and 3) with the system of toluene–methanol (4 : 1)–K_2CO_3 giving higher yields for both **3a** and **4a**.

Our initial goal was to obtain mono-arylation products 3-bromo-5-arylpyridine with high yields and preferences. A significant number of reports for mono-couplings with di- or trihaloaromatics employed a low molar ratio of boronic acids–polyhalobenzenes to increase mono-coupling.[45] Thus, to determine the optimal ratio of 3,5-dibromopyridine *vs* phenylboronic acid, we ran series 4–7. It was found that the best result (entry 5) was obtained when 5.6 equiv. of 3,5-dibromopyridine were added and any further increase in the concentration of 3,5-dibromopyridine has no dramatic effect on the preferentiality (entries 6 and 7).

Since it has been established that the phosphine has an important influence on the stability of the catalysts and the rate of the reaction,[46] we then checked the reactivity of catalyst **II** (entry 8). Surprisingly, it was found that the Suzuki reaction of **1** with **2a** afforded the mono-arylation products **3a** in a yield



Scheme 1. Suzuki reaction between 3,5-dibromopyridine with phenylboronic acid.

Table 1. Optimization of the reaction conditions for the mono-arylation of **1** with **2a**

Entry[a]	Solvent–base	Molar ratio of $PyBr_2$: $PhB(OH)_2$	*T* (h)	Ratio of mono : bis[c]	Yield of **4a**[d] (%)	Yield of **4a**[d] (%)
1	Toluene—ethanol (4 : 1)Cs_2CO_3	1 : 1	10	29 : 71	10	76
2	Toluene—methanol (4 : 1)Cs_2CO_3	1 : 1	10	52 : 48	21	17
3	Toluene—methanol (4 : 1)—K_2CO_3	1 : 1	10	38 : 62	38	60
4	Toluene—methanol (4 : 1)—K_2CO_3	3 : 1	3	53 : 47	48[e]	42
5	Toluene—methanol (4 : 1)—K_2CO_3	5.6 : 1	3	88 : 12	74[e]	25
6	Toluene—methanol (4 : 1)—K_2CO_3	7 : 1	3	67 : 33	67[e]	30
7	Toluene—methanol (4 : 1)—K_2CO_3	10 : 1	3	73 : 27	72[e]	20
8[b]	Toluene—methanol (4 : 1)—K_2CO_3	1 : 1	10	63 : 27	65	30
9[b]	Toluene—methanol (4 : 1)—K_2CO_3	5.6 : 1	2	98 : 2	96[e]	trace

Reaction conditions: [a] 3,5-dibromopyridine (0.5 mmol), $PhB(OH)_2$ (0.5 mmol), base (0.75 mmol), solvent 4 ml, 2 mmol% of **catalyst** I, reflux; [b] 2 mmol% **catalyst** II was employed. [c] Determined by GC. [d] Isolated yields based on 3,5-dibromopyridine. [e] Isolated yields based on phenylboronic acid.

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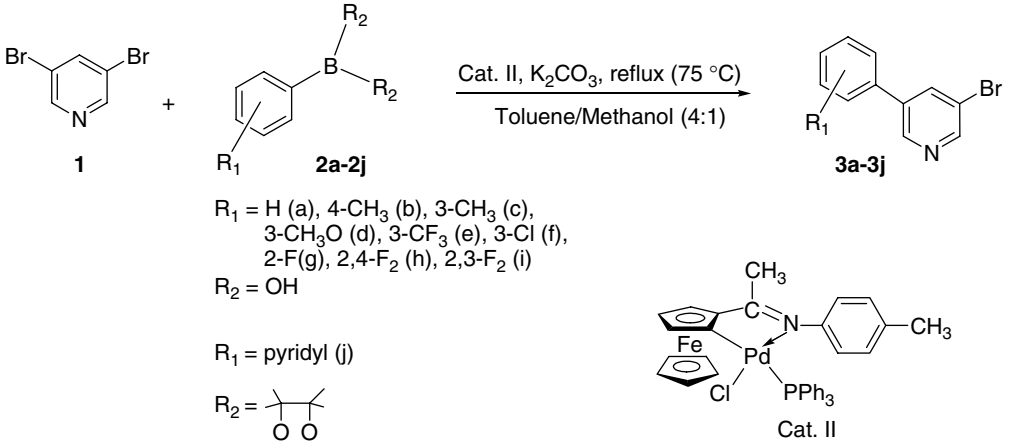
of 65% with a ratio of 63 : 27 (ratio of mono : bis). The yield and preferentiality for mono-arylation was higher than those obtained with catalyst **I** (entry 8 and 3).

Therefore, when catalyst **II** was employed with 5.6-fold 3,5-dibromopyridine under the same conditions of toluene–methanol (4 : 1, v/v)–K_2CO_3, the Suzuki reaction gave a yield of 96% of mono-arylation products with a ratio of 98 : 2 (mono : bis ratio) within 2 h (entry 9).

We then tested the Suzuki reaction of 3,5-dibromopyridine with a series of arylboronic acids–ester bearing electron-donor, electro-neutral and electron-withdrawing substituents under the above optimal conditions. As shown in Table 2, mono-arylation was obtained preferentiality at 90 : 10 to 99 : 1 ratios with yields from 58 to 99% (entries 1–10).

Electron-rich arylboronic acids (entries 1–4) afforded the corresponding mono-arylated pyridine products **3a–3d** in

Table 2. Mono-arylation of **2a–2j** with 1 catalyzed by catalyst **II**



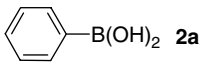
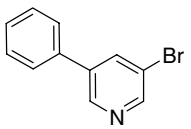
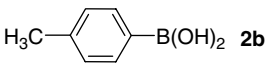
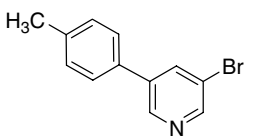
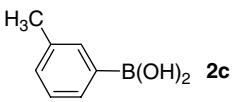
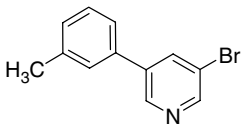
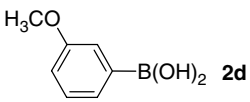
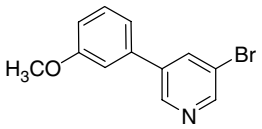
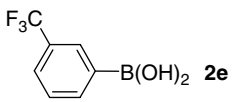
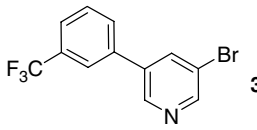
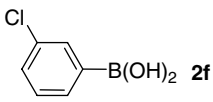
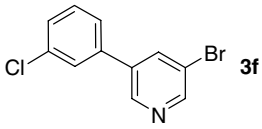
Entry[a]	Arylboronic acid–ester	*T* (h)	Product	Yields[b]	Product ratio, mono : bis[c]
1	 **2a**	2	 **3a**	96	98 : 2
2	 **2b**	2	 **3b**	94	99 : 1
3	 **2c**	2	 **3c**	99	95 : 5
4	 **2d**	2	 **3d**	97	98 : 2
5	 **2e**	6	 **3e**	70	95 : 5
6	 **2f**	2	 **3f**	91	99 : 1

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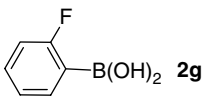
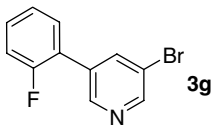
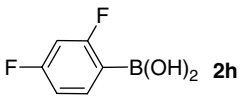
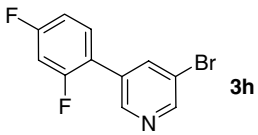
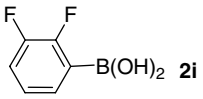
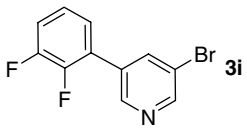
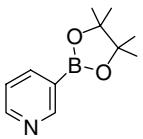
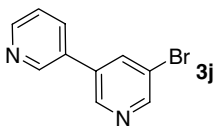
Table 2. (*Continued*).

Entry[a]	Arylboronic acid–ester	*T* (h)	Product	Yields[b]	Product ratio, mono : bis[c]
7	 **2g**	2	 **3g**	88	94 : 6
8	 **2h**	2	 **3h**	91	97 : 3
9	 **2i**	6	 **3i**	69	99 : 1
10	 **2j**	8	 **3j**	58	90 : 10

Reaction conditions: [a] 3,5-dibromopyridine (1.4 mmol), $ArB(OH)_2$ (0.25 mmol), K_2CO_3 (0.375 mmol), toluene 4 ml, methanol 1 ml, 2 mmol% catalyst **II**, reflux (75 °C). [b] Isolated yields based on arylboronic acid of two runs. [c] Determined by GC.

relatively better yields at similar ratios. The use of 2-fluoro,2,4-difluorophenyl did not have much effect on the mono-arylation yields, indicating limited steric effects (entries 7 and 8). A combination of 3,5-dibromopyridine with 2,3-difluorophenylboronic acid gave lower yields (69%), although the ratio of mono-arylation was not affected (Table 2, entries 7 and 9).

Pyridyl–pyridyl bond formation has received attention because of its synthetic usefulness in pharmaceuticals.[1–4] However, heteroaryl–heteroaryl formation is very difficult because of the difference in electron-donating abilities of hetero-atoms in heterocycles such as π-electron excessive heterocycles (bromothiophene) and π-electron deficient heterocycles (bromopyridine). The commonly used lithiation[12–22] or halogen-magnesium exchange[8,23–25] often requires low temperatures or restricted application to active halides (yielding bis-arylation products in most cases) to azaxanthone series.[47] We find that, under our optimized preferential mono-arylation conditions, 3-bromo-5-pyridylpyridine **3j** could be obtained easily using 3-pyridylboronic pinacol ester as the coupling partner, in moderate yields with preferential 90 : 10 mono-arylation (entry 10). Other derivatives can be synthesized by using **3j** as a substrate.

The results in Table 2 demonstrate that these optimal reaction conditions [catalyst **II**, 5.6 equiv. of 3,5-dibromopyridine, K_2CO_3 and toluene–methanol (4 : 1, v/v), reflux (75 °C)] for mono-arylation are applicable for a wide range of arylboronic acids–ester.

CONCLUSIONS

In conclusion, 3-bromo-5-arylsubstituted pyridines could be prepared from the corresponding 3,5-dibromopyridine by preferential mono-arylation of palladacycle-catalyzed Suzuki reaction. The main advantage of this methodology is the relative mild reaction conditions in air and easy prevention of the formation of bis-arylation products by simply increasing the concentration of 3,5-dibromopyridine. This method can be used to synthesize a series of potentially biologically active 3-bromo-5-arylsubstituted pyridines and more diversely substituted pyridines by subsequent coupling reactions.

EXPERIMENTAL

Materials

Toluene was purchased from Acros and distilled from Na–benzophenone prior to use. Methanol was purchased from Acros and distilled from Mg prior to use. Catalyst **I** was prepared in high yield from the cyclopalladation of the corresponding ferrocenylimine with Li_2PdCl_4 in MeOH in the presence of NaOAc at room temperature.[48] Catalyst **II** was synthesized from catalyst **I** with PPh_3 in CH_2Cl_2 at room temperature stirring for 30 min.[48] The arylboronic acids except phenylboronic acid[49] and 3-pyridyl boronic pinacol ester[50] were purchased from Acros and were generally used without further purification.

Analyses

Melting points were measured on a XT-5 microscopic apparatus and uncorrected. All ^1H and ^{13}C-NMR were

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performed in $CDCl_3$ and recorded on a Bruker DPX 400 spectrometer. ^{1}H-NMR spectra were collected at 400.0 MHz using a 8000 Hz spectral width, a relaxation delay of 2.0 s, 32K data points, a pause width of 30° and $CHCl_3$ (7.27 ppm) as the internal standard. ^{13}C-NMR spectra were collected at 100.0 MHz using a 2500 Hz spectral width, a relaxation delay of 2.0 s, 32K data points, a pause width of 30° and $CHCl_3$ (7.27 ppm) as the internal standard.

High-resolution mass spectra were performed in MeOH and measured on a Waters Q-Tof of Micro™ spectrometer. Preparative TLC was performed on dry silica gel plates developed with acetic ether–petroleum ether (1 : 1 to 1 : 10).

General procedure for monoarylation reactions on a 0.25 mmol scale (product 3a–3j)

A 10 ml round-bottom flask was charged with 3,5-dibromopyridine (1.4 mmol, 333 mg), phenylboronic acid (0.25 mmol, 31 mg), potassium carbonate (1.5 mmol, 52 mg) and 2 mmol% catalyst **II** (5×10^{-3} mmol, 3.6 mg) in toluene–methanol (4.0 : 1.0 ml) at room temperature. The reaction mixture was stirred at reflux temperature (75 °C) in air and the reaction progress was monitored by GC. After disappearance of the arylboronic acids–ester, the mixture was quenched with 5 ml water and then extracted with EtOAc (3×10 ml). The combined organic layer was dried over anhydrous Na_2SO_4. After removal of the solvent *in vacuo*, the product was obtained by preparative TLC, eluting with acetic ether–petroleum ether (1 : 1 to 1: 10) and the yield was calculated based on $PhB(OH)_2$. Final products were characterized by ^{1}HNMR and ^{13}CNMR. New compounds were confirmed by high-resolution mass spectra.

General procedure for monoarylation reactions on a 2.5 mmol scale (product 3a)

A 100 ml round-bottom flask was charged with 3,5-dibromopyridine (14 mmol, 3.33 g), phenylboronic acid (2.5 mmol, 310 mg), potassium carbonate (15 mmol, 520 mg) and 0.8% mmol catalyst **II** (2×10^{-2} mmol, 14.4 mg) in toluene–methanol (40 : 10 ml) at room temperature. The reaction mixture was stirred at reflux temperature (75 °C) in air and the reaction progress was monitored by GC. After disappearance of phenylboronic acid, the mixture was quenched using 10 ml water and then extracted with EtOAc (3×50 ml). The combined organic layer was dried over anhydrous Na_2SO_4. After removal of the solvent *in vacuo*, the product was obtained by preparative TLC, eluting with acetic ether–petroleum ether (1 : 10) and the isolated yield (98%) was calculated based on $PhB(OH)_2$. The excess 3,5-dibromopyridine was recovered.

3-Bromo-5-phenylpyridine[51] (3a)

White solid, m.p. 50.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.74$ (s, 1H), 8.64 (s, 1H), 8.00 (t, $J = 1.6$ Hz, 1H), 7.54–7.39 (m, $J = 7.6$ Hz, 4.8 Hz, 1.2 Hz, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 120.86$, 127.09, 128.63, 129.13, 136.17, 136.78, 138.17, 146.24, 149.21.

3-Bromo-5-(p-tolyl)pyridine[43] (3b)

White solid m.p. 96.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.74$ (s, 1H), 8.63 (s, 1H), 8.00 (s, 1H), 7.46, 7.44 (d, $J = 8.0$ Hz, 2H), 7.28, 7.26 (d, $J = 8.1$ Hz, 2H), 2.41 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.19$, 120.94, 127.01, 129.95, 133.37, 136.68, 136.27, 138.80, 146.14, 148.93.

3-Bromo-5-(m-tolyl)pyridine (3c)

White solid, m.p. 55.7–56.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.73$ (d, $J = 0.4$ Hz, 1H), 8.63 (d, $J = 1.6$ Hz, 1H), 7.99 (m, $J = 1.6$ Hz, 1H), 7.38–7.22 (m, $J = 7.6$ Hz, 7.2 Hz, 4H), 2.42 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.49$, 120.88, 124.28, 127.89, 129.11, 129.46, 136.22, 136.85, 138.39, 138.94, 146.36, 149.19. HRMS (positive ESI): m/z $[M + H]^+$ calcd for $C_{12}H_{10}BrN$: 248.0075; found: 248.0064.

3-Bromo-5-(3-methoxyphenyl)pyridine[52] (3d)

Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.73$ (s, 1H), 8.64 (s, 1H), 7.99 (s, 1H), 7.40–7.36 (m, $J = 8.0$ Hz, 1H), 7.12–6.94 (m, $J = 7.6$ Hz, 2.0 Hz, 3H), 3.86 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 55.40$, 112.95, 114.02, 119.56, 120.89, 130.28, 136.91, 137.66, 138.14, 146.36, 149.41, 160.18.

3-Bromo-5-(3-trifluoromethylphenyl)pyridine[52] (3e)

Light yellow solid, m.p. 49.0–50.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.77$ (d, $J = 1.2$ Hz, 1H), 8.72 (d, $J = 1.2$ Hz, 1H), 8.04 (t, $J = 1.8$ Hz, 1H), 7.80–7.61 (m, $J = 8.0$ Hz, 7.6 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 121.12$, 124.1 ($J = 3.7$ Hz), 125.5 ($J = 3.7$ Hz), 119.78, 122.49, 125.20, 127.91 ($J = 271$ Hz), 130.53, 129.84, 123.28, 131.96, 131.64, 131.31 ($J = 32.4$ Hz), 136.92, 137.10, 137.18, 146.27, 150.14.

3-Bromo-5-(3-chlorophenyl)pyridine[52] (3f)

White solid, m.p. 85.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.73$ (s, 1H), 8.68 (s, 1H), 8.00 (s, 1H), 7.54 (s, 1H), 7.44–7.41 (t, $J = 6.0$ Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 121.45$, 125.79, 127.76, 129.24, 130.92, 135.66, 137.38, 138.50, 146.62, 150.34.

3-Bromo-5-(2-fluorophenyl)pyridine (3g)

White solid, m.p. 46.7–47.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.71$ (s, 1H), 8.67 (s, 1H), 8.03 (s, 1H), 7.44–7.17 (m, $J =$ 8.0 Hz, 7.6 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 116.75$, 116.97 ($J = 22$ Hz), 120.97, 124.48, 124.61 ($J = 13$ Hz), 125.24, 125.28 ($J = 4.0$ Hz), 130.79, 130.82, 131.01, 131.09 ($J = 8.0$ Hz, 3.0 Hz), 133.57, 139.18, 139.14 ($J = 4.0$ Hz), 148.08, 150.10, 158.92, 161.40. HRMS (positive ESI): m/z $[M + H]^+$ calcd for $C_{11}H_7BrFN$: 251.9824; found: 251.9810.

3-Bromo-5-(2,4-difluorophenyl)pyridine (3h)

White needles, m.p. 83.3–84.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.68$ (s, 1H), 8.67 (s, 1H), 7.99 (d, $J = 1.3$ Hz, 1H), 7.44–7.38 (dt, $J = 8.2$ Hz, 6.4 Hz, 1H), 7.04–6.94 (m, $J = 8.8$ Hz, 8.0 Hz, 2.5 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 104.64$, 104.90,

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105.15 ($J = 25$ Hz), 112.40, 112.36, 112.19, 112,15 ($J = 3.6$ Hz, 21 Hz), 120.41, 120.55 ($J = 14$ Hz),120.62 (C), 131.21, 131.25, 131.30, 131.35 ($J = 9.5$ Hz, 4.3 Hz), 132.34, 138.68, 138.65, 147.53, 149.83, 158.62, 158.74, 161.13, 161.25 ($J = 63$ Hz), 161.93, 162.05, 164.43, 164.55 ($J = 120$ Hz). HRMS (positive ESI): m/z $[M + H]^+$ calcd for $C_{11}H_6BrF_2N$: 269.9730; found: 269.9724.

3-Bromo-5-(2,3-difluorophenyl)pyridine (3i)

White needles, m.p. 84.9–86.5 °C. ^{1}HNMR (400 MHz, $CDCl_3$): $\delta = 8.71$ (s, 2H), 8.02 (s, 1H), 7.27–7.18 (m, $J = 8.0$ Hz, 7.8 Hz, 3.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 118.09$, 118.26 ($J = 17$ Hz), 121.07, 125.11, 125.16, 125.18, 125.23 ($J = 5.0$ Hz, 2.0 Hz), 125.41, 125.42, 125.44, 125.46 ($J = 3.0$ Hz, 2.0 Hz), 126.77, 126.87 ($J = 10$ Hz), 132.48, 139.05, 139.08 ($J = 3.0$ Hz), 147.98, 147.17, 147.31, 149.67, 149.80 ($J = 130$ Hz), 150.70, 150.20, 150.33, 152.68, 152.81 ($J = 130$ Hz). HRMS (positive ESI): m/z $[M + H]^+$ calcd for $C_{11}H_6BrF_2N$: 269.9730; found: 269.9724.

3-(5-Bromopyridin-3-yl)pyridine[53] (3j)

Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.85$ (s, 1H), 8.77 (s, 1H), 8.73 (s, 1H), 8.70 (s, 1H), 8.04 (s, 1H), 7.88 (d, $J = 8.0$ Hz, 1H), 7.44 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 121.15$, 123.88, 132.12, 134.50, 135.12, 136.95, 146.23, 147.79, 148.12, 149.86, 150.30.

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