JOC The Journal of Organic Chemistry

Article

Palladium-Catalyzed C-4 Selective Coupling of 2,4-Dichloropyridines and Synthesis of Pyridine-based Dyes for Live Cell Imaging

Min Yang, Jing Chen, Chen He, Xin Hu, Yechun Ding, Ying Kuang, Jin-Biao Liu, and Qitong Huang

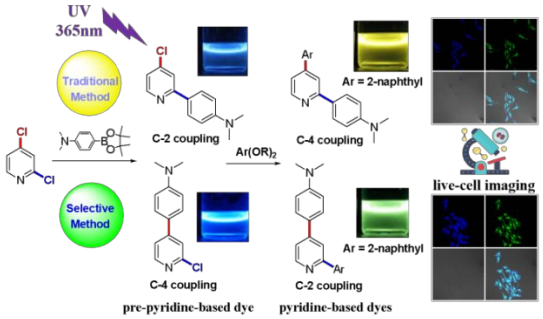
J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.0c00449 • Publication Date (Web): 24 Apr 2020

Palladium-Catalyzed C-4 Selective Coupling of 2,4-Dichloropyridines and Synthesis of Pyridine-based Dyes for Live Cell Imaging

Min Yang,[*,†] Jing Chen,[†] Chen He,[†] Xin Hu,[†] Yechun Ding,[†] Ying Kuang,[†] Jinbiao Liu,[*,‡] Qitong Huang,[*,†]

[†] Department of Forensic Science, Oil-tea in Medical Health Care and Functional Product Development Engineering Research Center in Jiangxi, Gannan Medical University, 1 Yixueyuan Road, Ganzhou, Jiangxi 341000, China.
[‡] Department of Chemistry, Jiangxi University of Science and Technology, 86 Hongqi Road, Ganzhou, 341000, China.

Supporting Information Placeholder



ABSTRACT: An alternative process of Pd-catalyzed C-4 selective coupling of 2,4-dichloropyridines with boronic esters was developed, which afforded 24 examples of C-4 coupled pyridines in moderate to good yields. After further arylation, 21 examples of C-2, C-4 diarylated pyridines with significant photophysical property were obtained, which were applied as pyridine-based dyes into live-cell imaging with good biocompatibility and low toxicity.

■ INTRODUCTION

Pyridines are obviously important members of nitrogen-containing heterocycles, which are widely used in pharmacy and agriculture fields.[1] Due to the high demand in small-molecule fluorescent probes for their small, noninvasive size, high sensitivity, and fast response time, many approaches and major improvements have been explored.[2,3] Although numerous fluorescent probes have been developed over the past decades, there is still a need for simple fluorescent molecules, and challenges still exist. In recent years, pyridines are utilized as fluorescent dyes employed in the biological application,[4,5] such as the thiazolo[4,5-b]pyridine-based fluorescent probe for detection of zinc ions,[5a] terpyridine derivatives for biological imaging.[5b] In 2018, Chenoweth and co-workers synthesized quinoline-based probes by Pd-catalyzed C-2 Suzuki coupling of 2,4-dichloroquinolines to afford quinoline-based fluorophores for live-cell imaging.[6]

Pd-catalyzed Suzuki cross-coupling reaction on pyridine derivatives, which could allow for the chemoselective or regioselective formation of a C-C bond, is still an intriguing challenge for synthetic chemists.[7] Although Pd-catalyzed site-selective C-C coupling on 2,4-dichloropyridine derivatives has been reported, examples about C-4 selective couplings are scarce,[8] presumably due to the intrinsic reactivity of C=N bond and the effect of the pyridine nitrogen coordinating to the palladium catalyst.[9] Pioneering computational chemistry work by Houk and co-workers indicated that bond-dissociation energies (BDEs) could be one determining factor in achieving selective couplings on polyhalogenated heterocycles under palladium catalysis.[10] In this regard, the C-C bond would be easier formed at the C-2 position of 2, 4-dichloropyridine than C-4 position through Pd-catalyzed coupling reaction, due to the lower BDE of C-Cl bond at the C-2 position (Figure 1). Dai and co-workers reported a ligand-dependent site-selective Suzuki coupling, which achieved predominant C-2 coupling and obtained the 2-substituted product in 90% yield (Figure 1a).[8b] In contrast, Rao *et al*. described the palladium-catalyzed C-C coupling of 2-chloro-4-iodopyridine with atom-economic BiPh3 reagent to produce the 4-substituted product in 96% yield (Figure 1b).[8c] Despite abundant examples in this research area, there are still no reports for 2,4-dichloropyridine to access C-4 coupling. In this context, numerous efforts have been focused on the development of Pd-catalyzed C-4 selective coupling processes with $RB(OR)_2$, which performed

24 examples of C-4 coupled pyridine derivatives in 10-77% yields (Figure 1c). Furthermore, the C-2, C-4 diarylated pyridine products could be applied as pyridine-based dyes into live-cell imaging with good biocompatibility and low toxicity.

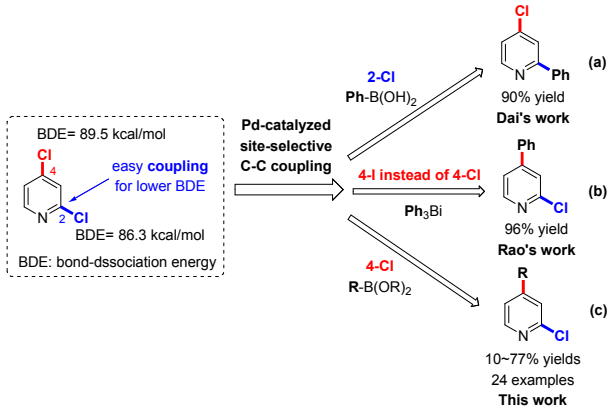
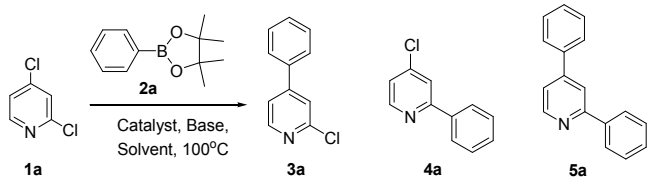


Figure 1. Development of Pd-catalyzed site-selective C-C coupling reaction

■ RESULTS AND DISCUSSION

Due to the lack of literature guidance to this challenge, much efforts were made to develop the C-4 selective coupling protocol of 2,4-dichloropyridines with diverse boronic acids or boronic esters. At the outset of this investigation, the optimization of the reaction parameters was performed using 2,4-dichloropyridine (**1a**) and 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane (**2a**) as the model substrates, and the results are summarized in Table 1. Initial screening of a series of palladium catalysts to evaluate the regio-selectivity was conducted. $Pd(PPh_3)_4$ was examined in the reaction, affording C-2 coupled pyridine as the major product (**4a**) minor over-coupled product (**5a**), and only trace C-4 coupled product (**3a**, detected by GC-MS) (Table 1, Entry 1). Then further attempts by extensive catalyst screening delivered a higher C-4 arylation selectivity (Table 1, Entries 2-6). To our surprise, although giving rise to more than half of **5a** in the presence of PEPPSI-IPr [a Pd(II)-NHC precatalyst], a large proportion of **3a**/**4a** (~4.5/1) was observed (Table 1, Entry 7). Since the over-coupled product could be avoidable according to subsequent attempts, we chose PEPPSI-IPr as the optimal catalyst for the further condition screening. In order to investigate the effect of solution polarity, other mixed solvents were tried (Table 1, Entries 8-9). Notably, PEG400/H_2O, green solvents, led to **3a** in the yield of 45%. Considering the polarity of H_2O might accelerate overreaction, PEG400 was used alone, giving the dominant ratio of **3a**/**4a**, and a significant decline in ratio of **5a** was obtained (Table 1, Entry 10). Next, K_3PO_4 and NaOAc were explored as alterative bases (Table 1, Entries 11-12). Interestingly, it can be found that a great disparity in the proportion of **3a**/**4a** (~10/1) was detected when using NaOAc. However, only 33% yield of **3a** was obtained probably for the reason of low conversion of **1a**. Subsequently, we adjusted the ratio of **1a**/**2a** to 1.5/1.0, and the yield of **3a** was increased to 57% (Table 1, Entry 13). When introducing KI as an additive[11] to the model reaction (Table 1, Entries 14-15), we found that KI could promote the reaction to afford **3a** in 63% or 64% yield, respectively. In order to explore the role of KI in the Pd-catalyzed C-4 selective coupling reaction, we have performed two additional control experiments (Figure S1, see ESI). In the control experiments, a small amount of mono-iodinated pyridine (<5%) was detected by GCMS. From the reported literatures[11] and our finding, KI might promote the selective substitution of the 4-chloro group with an iodide as a prelude to cross-coupling. Furthermore, the desired product **3a** was observed in 55% yield when the reaction temperature was lowed to 60 °C (Table 1, Entry 16). Considering the excellent C-4 selectivity given by NaOAc and good conversion acted by Na_2CO_3, we improved the procedure that the mixed bases of NaOAc/Na_2CO_3 were used as below. In addition, considering the possible toxic effect of pyridine substrate on palladium catalyst, we delivered twice addition of catalyst and base. To our delight, the optimal ratio of **3a**/**4a**/**5a** (99:1:0) and the good yield of **3a** (76%) were obtained (Table 1, Entry 17).

Table 1. Condition optimizations for the Pd-catalyzed C-4 selective coupling reaction of **1a** and **2a** [a]



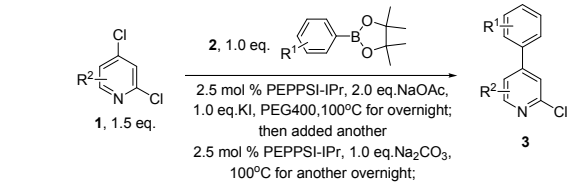
Entry	Catalyst	Base	Solvent	**3a**:**4a**:**5a** [b] (yield of **3a**) [c]
1	$Pd(PPh_3)_4$	Na_2CO_3	dioxane:H_2O=10:1	2:80:18
2	*t*-BuDavePhos -Pd-G3	Na_2CO_3	dioxane:H_2O=10:1	34:52:14
3	RuPhos-Pd-G3	Na_2CO_3	dioxane:H_2O=10:1	15:37:48
4	$Pd(Pt\text{-}Bu_3)_2$	Na_2CO_3	dioxane:H_2O=10:1	56:36:8
5	cataCXium A - Pd-G3	Na_2CO_3	dioxane:H_2O=10:1	49:24:27
6	BrettPhos- Pd-G3	Na_2CO_3	dioxane:H_2O=10:1	57:24:19
7	PEPPSI-IPr [d]	Na_2CO_3	dioxane:H_2O=10:1	37:8:55
8	PEPPSI-IPr	Na_2CO_3	toluene:H_2O =10:1	61:24:15
9	PEPPSI-IPr	Na_2CO_3	PEG400:H_2O =10:1	60:14:26 (45%)
10	PEPPSI-IPr	Na_2CO_3	PEG400	69:16:15 (50%)
11	PEPPSI-IPr	K_3PO_4	PEG400	48:9:43 (40%)
12	PEPPSI-IPr	NaOAc	PEG400	83:8:9 (33%)
13 [e]	PEPPSI-IPr	Na_2CO_3	PEG400	70:11:19 (57%)
14 [e,f]	PEPPSI-IPr	Na_2CO_3	PEG400	80:11:9 (63%)
15 [e,g]	PEPPSI-IPr	Na_2CO_3	PEG400	8212:6

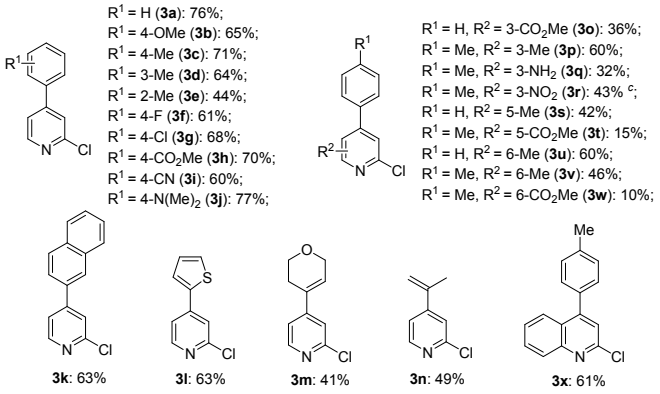
				(64%)
16 [e,f,h]	PEPPSI-IPr	Na_2CO_3	PEG400	78:12:10 (55%)
17 [i]	PEPPSI-IPr	NaOAc + Na_2CO_3	PEG400	99:1:0 (76%)

[a] Reaction conditions: **1a** (0.2 mmol) and **2a** (1.2 equiv) in the presence of catalyst (5.0 mol %), base (2.0 equiv), solvent (1 mL) at 100 °C under N_2; [b] Determined by GC-MS analysis of the crude reaction mixture; [c] isolated yield of **3a** by column purification. [d] [1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium(II) dichloride. [e] adjusted the ratio of **1a**/**2a** to 1.5/1. [f] KI (1.0 equiv) was added as an additive. [g] KI (2.0 equiv) was added as an additive. [h] Reaction temperature was lowed to 60 °C; [i] Reaction condition: **1a** (1.5 equiv), **2a** (1.0 equiv), PEPPSI-IPr (2.5 mol %), NaOAc (2.0 equiv), KI (1.0 equiv) and PEG400 (1 mL) were proceeded at 100 °C under N_2 for overnight, then added another PEPPSI-IPr (2.5 mol %) and Na_2CO_3 (1.0 equiv), and heated to 100 °C under N_2 for another overnight.

The scope and generality of C-4 selective coupling of 2,4-dichloropyridines (**1**) with various aryl boronic esters (**2**) was investigated using the optimized condition (Scheme 1). **2** containing either electron-donating or electron-withdrawing groups were smoothly converted into the desired products (**3a-3j**) in good yields, except 44% yield of **3e** probably for the steric hindrance of *o*-Me from **2e**. Among these reactions above, there were little C-2 coupled byproducts detected by TLC, and the outcome was in the same range for entry 17 in Table 1. Moreover, other boronic esters were explored, which provided the desired products (**3k-3n**) in moderate yields. The reaction of **2a** or **2c** with various 2,4-dichloropyridines was then examined. A variety of electron-donating or electron-withdrawing groups substituted at the C-3 position of **1** were tolerated under the optimized condition, giving the corresponding products (**3o-3r**) in moderate yields. In contrast, when introducing the substitution on C-5 position of **1**, only 15% yield of **3t** was obtained probably for the steric hindrance and its electron-withdrawing effect. Interestingly, different substituents in the C-6 position of **1** gave different yields of **3u-3w** for the electronic difference. Impressively, when 2,4-dichloroquinoline was employed under the identical condition, the C-4 coupled product (**3x**) was obtained in 61% yield. With regard to the good C-4 selectivity by PEPPSI.IPr, we speculated that bearing bulky ligands of [Pd(II)-NHC], coordination between the substrate and the catalyst might be avoid. However, there is still no clear evidence that the regioselective outcome is because of steric effects rather than electronic differences.[12]

Scheme 1. Scope of Pd-catalyzed C-4 selective coupling reaction of **1** and **2** [a,b]

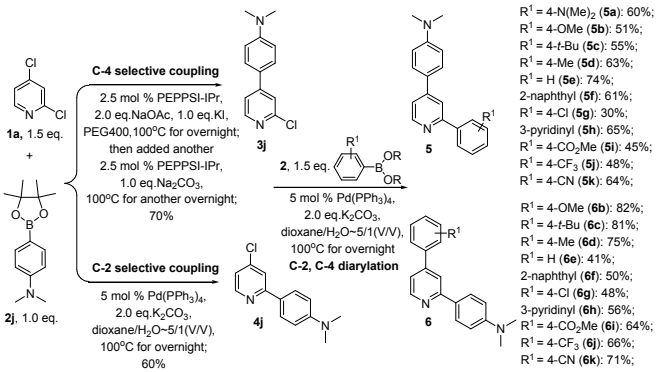




[a] All reactions were carried out on a 0.20 mmol scale: **1** (1.5 equiv) and **2** (1.0 equiv) in the presence of PEPPSI-IPr (2.5 mol %), NaOAc (2.0 equiv), KI (1.0 equiv) and PEG400 (1 mL) at 100 °C under N_2 for overnight; then added another PEPPSI-IPr (2.5 mol %) and Na_2CO_3 (1.0 equiv), 100 °C under N_2 for another overnight. [b] isolated yields based on **2** by column purification. [c] 60 °C instead of 100 °C.

Among these C-4 coupled products, we are surprised to find that 4-(2-chloropyridin-4-yl)-N, N-dimethylbenzenamine (**3j**) shows a significant photophysical property due to the electron-donating dimethylamino group at the C-4 position, which might push electron density into the pyridine. Based on our initial study, we predict the tuning of photophysical properties through the further C-2 arylation of **3j**. As a contrast, the C-4 arylation of **4j** was screened after delivering C-2 selective coupling. Herein, C-2, C-4 diarylation of 2,4-dichloropyridine were synthesized as pyridine-based dyes by Pd-catalyzed C-C coupling reaction without further condition optimization (Scheme 2). Both electron-donating and electron-withdrawing substituents were tolerated to **5a-5k** and **6b-6k** in moderate to good yields. Interestingly, because of the over coupling reaction of **5g** with 4-chlorophenylboronic acid (detected by GC-MS), only 30% yield of **5g** was obtained.

Scheme 2. Synthesis of pyridine-based dyes **5** and **6** [a,b,c]



[a] **3j** and **4j** were prepared in a 4.0 mmol scale of **2j**. [b] synthesis of **5** or **6**: **3j** or **4j** (1.0 equiv) and **2** (1.5 equiv) in the presence of $Pd(PPh_3)_4$ (5 mol %), K_2CO_3 (2.0 equiv) and dioxane/H_2O (5/1~V/V) at 100 °C under N_2 for overnight. [c] isolated yields based on **3j** or **4j** by column purification.

Inspection on photophysical properties of **5** and **6** (see ESI S97-S104), Figure 2 showed that the stronger the electron-absorbing ability of C-2 or C-4 substitution, the greater the red-shifted emission in DMSO in the push-pull system of pyridine-based dyes, indicating the formation of a D-π-A system. According to the Hammett substituent constants[13] of the para-functional groups in the C-2 or C-4 phenyl ring, **5** (**5b**, **5d**, **5e**, **5g**, **5j**) and **6** (**6b**, **6d**, **6e**, **6g**, **6j**) were analyzed, which provided theoretical guidance for the para-substitution reaction of pyridine-based dyes. It fits well that electronegativity is positively correlated with the emission wavelength. The correlation of pyridine-based dyes **5** and **6** in other solvents, which also basically abide by Hammett's law, was shown in ESI S96-S101.

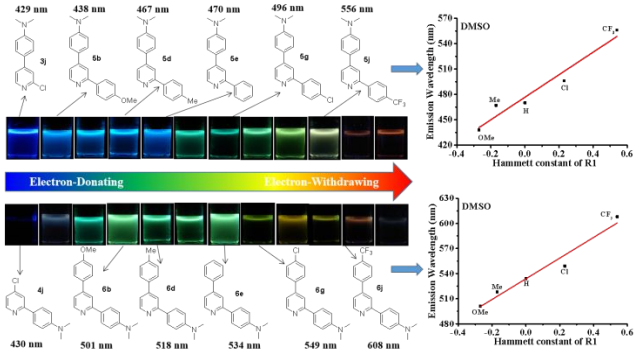


Figure 2. Structure-photophysical property relationship of pyridine-based dyes **5** and **6**. The compound order are **3j**, **5b**, **5d**, **5e**, **5a**, **5g**, **5g**, **5j** from left to right and **4j**, **5a**, **6b**, **6d**, **6e**, **6g**, **6j** from left to right, which stock solutions were made in DMSO (5 mM) and the image was taken using a hand-held UV lamp (365 nm). Correlation between emission wavelength and Hammett constant (σ_p) of R1 substituents in pyridine-based dyes **5** and **6**.

In order to obtain more spectral information about the properties of pyridine-based dyes, we designed a multi-well analysis method to evaluate the spectral characteristics of each compound in the library, such as the fluorescence intensity and emission wavelength. Due to the dimethylamino and pyridine nitrogen in pyridine-based dyes may cause lyochromism sensitivity, five organic solvents with different properties were selected: non-polar solvents (toluene, dioxane, DCM) and polar solvents (DMSO, EtOH). As shown in Figure 3, pyridine-based dyes' emission wavelength is the shortest in the non-polar solvents, while the wavelength of the substance is obviously red-shifted in the polar solvents. And it found that the emission wavelength of **6** had red-shifted about 50 nm in any solvent (such as **5f** and **6f**).

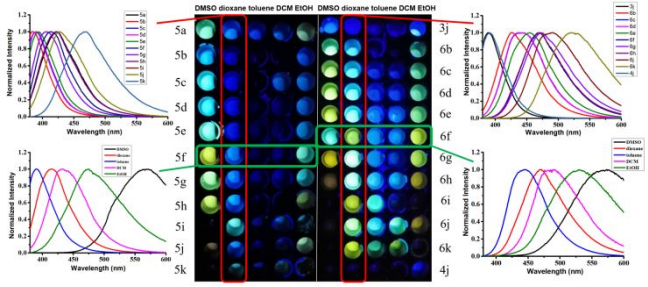


Figure 3. Emission spectra were measured at λ_{ex} of 365 nm regardless of their optimal max absorption and the image was taken under a hand-held UV lamp (365 nm).

Considering the large Stokes shifts and polarity-sensitive fluorescence properties, the pyridine-based dyes (**5a**-**5k**, **6b**-**6k**) were all subjected to live HeLa cell Imaging (see S104-S114). **5b** and **6b** with high quantum yields (Φ_{5b} = 0.85 and Φ_{6b} = 0.73), were chosen as representatives to illustrate its applicability in live-cell imaging (405 nm and 488 nm lasers) (Figure 4). Blue staining (Figure 4A) obtained by exciting at 405 nm, green staining produced by exciting at 488 (Figure 4B), and merged images showing bright cyan regions (Figure 4D) identified a subset of pyridine-based fluorescent dyes. Other pyridine-based dyes have also been well used for live-cell imaging, indicating a good biocompatibility and low toxicity. Moreover, the HOMO-LUMO of representative pyridine compounds (**3j**, **4j**, **5a**, **5b**, **6b**, **5e**, **6e**, **5j**, **6j**) were calculated, exhibiting the electron density shifts from C-4/C-2 dimethylamino group to C-2/C-4 aryl group upon excitation from S_0 to S_1 (see S115-S118). As showed in Figure 5, the relative ΔLUMO-HOMO of **6b** is smaller than **5b**, conforming to our test results that the emission wavelength of **6b** is longer than **5b** (~50 nm red-shifted).

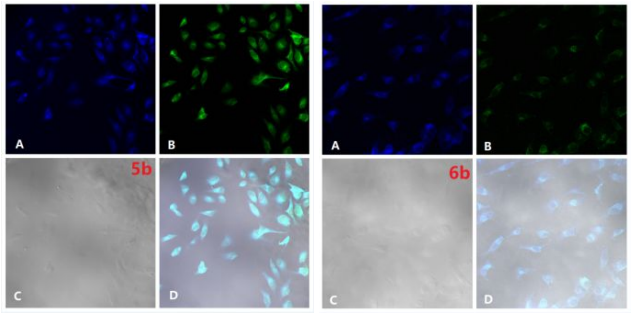


Figure 4. Live HeLa cell imaging after 2 h incubation of **5b** and **6b**. (A) DAPI channel: λ_{ex}= 405 nm; (B) FITC channel: λ_{ex}= 488 nm; (C) Bright field; (D) Merged image.

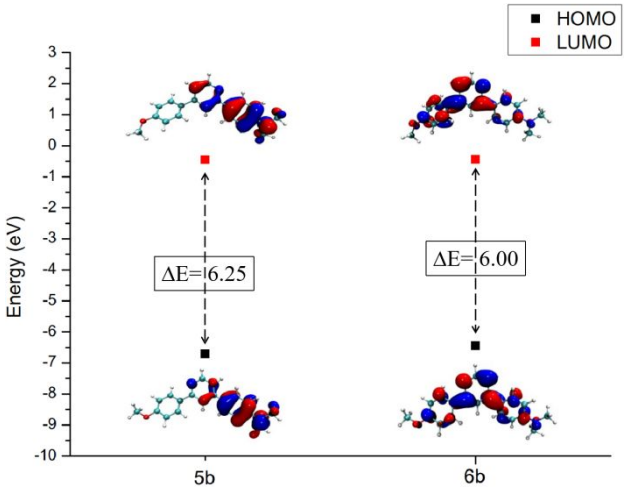


Figure 5. The relative HOMO & LUMO energy gap (eV) of **5b** and **6b**.

■ CONCLUSIONS

In conclusion, we have developed a less expensive and more accessible alternative approach toward C-4 arylated pyridine derivatives via Pd-catalyzed C-C coupling of 2,4-dichloropyridines withboronic esters , which overcame the

intrinsic reactivity and the bond-dissociation energy to achieve 24 examples in moderate to good yields. Based on a significant photophysical property, the further arylation was proceeded. 21 examples of C-2, C-4 diarylated pyridine derivatives were prepared and applied as pyridine-based dyes into the fluorescence spectrum and live-cell imaging with good biocompatibility and low toxicity. In order to explore our site-selective coupling method and develop some multifunctional dyes in biological processes, more investigations will be reported in due course.

■ EXPERIMENTAL SECTION

General experimental methods: Unless otherwise stated, all commercial reagents and solvents were used without additional purification. All solvents were dried and distilled according to standard procedures. Flash column chromatography was performed using silica gel (60-Å poresize, 32-63 μ m, standard grade). Analytical thin-layer chromatography was performed using glass plates pre-coated with 0.25 mm 230-400 mesh silica gel impregnated with a fluorescent indicator (254 nm). Thin layer chromatography plates were visualized by exposure to ultraviolet light. Organic solutions were concentrated on rotary evaporator sat ~20 Torr (house vacuum) at 25-35°C. Commercial reagents and solvents were used as received. The 1H, 13C and 19F NMR spectra were recorded on a BruckerDRX-400 at 400 MHz, 100 MHz and 376 MHz respectively, and NMR spectra were recorded in parts per million from internal tetramethylsilane on the δ scale. The IR spectra were recorded on Nicolet 380. The GC-MS results were recorded on a GCMS-TQ8040 equipment. High resolution mass spectrometry (HRMS) spectra were obtained on Synapt G2-Si HDMS. The fluorescence spectra were recorded on ThermoFisher Varioskan LUX. The live-cell imaging was recorder on ZEISS LSM880.

General procedure for the synthesis of compound 3a. 2,4-dichloropyridine **1a** (0.3 mmol), 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane **2a** (0.2 mmol), PEPPSI-IPr (2.5 mol %), NaOAc (2.0 equiv.), KI (1.0 equiv.) and PEG400 (1 mL) were added to a test tube at 100oC under N2 for overnight. Then added another PEPPSI-IPr (2.5 mol %) and Na_2CO_3 (1.0 equiv.), the reaction was heated to 100°C in an oil bath under N2 for another overnight. After the disappearance of **2a** as indicated by TLC, the mixture was filtrated and the resulting filtrate was extracted by DCM (3*10 mL). The organic layers were combined and dried by Na_2SO_4. Then evaporation of the solvent and purification by flash column chromatograph using PE/EA as eluent to afford the desired product **3a** in 76% yield. Other desired products **3** were obtained in the similar procedure.

Procedure for the synthesis of compound 3j on a 4 mmol scale.
2,4-dichloropyridine **1a** (6 mmol, 888mg), N,N-dimethyl-4-(4,4,5,5-tetramethyl- 1,3,2-dioxaborolan-2-yl)benzenamine **2j** (4 mmol, 988mg), PEPPSI-IPr (2.5 mol %, 68 mg), NaOAc (2.0 equiv, 656 mg), KI (1.0 equiv, 664 mg) and PEG400 (20 mL) were added to a 100mL-round-bottom flask at 100°C under N_2 for overnight. Then added another PEPPSI-IPr (2.5 mol %, 68 mg) and Na_2CO_3 (1.0 equiv, 424 mg), the reaction was heated to 100°C in an oil bath under N_2 for another overnight. After the disappearance of **2j** as indicated by TLC, the mixture was filtrated and the resulting filtrate was extracted by DCM (3*150 mL). The organic layers were combined and dried by Na_2SO_4. Then evaporation of the solvent and purification by flash column chromatograph using PE/EA as eluent to afford the desired product **3j** (650 mg) in 70% yield.

2-chloro-4-phenylpyridine (3a). (29 mg, 76%). R_f = 0.30 (PE/EA, 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, J = 5.2 Hz, 1H), 7.61 (dd, J = 7.8, 1.5 Hz, 2H), 7.56-7.38 (m, 5H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 152.2, 151.6, 150.0, 136.9, 129.7, 129.3, 127.0, 122.1, 120.5. GC-MS: $[M]^+$= 189. Spectral data match those previously reported.[14]

2-chloro-4-(4-methoxyphenyl)pyridine (3b). (28 mg, 65%). R_f = 0.30 (PE/EA, 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, J = 5.2 Hz, 1H), 7.57-7.50 (m, 2H), 7.47 (d, J = 1.1 Hz, 1H), 7.35 (dd, J = 5.3, 1.6 Hz, 1H), 7.01-6.93 (m, 2H), 3.84 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 161.0, 152.2, 151.0, 149.9, 128.9, 128.3, 121.3, 119.8, 114.7, 55.4. GC-MS: $[M]^+$= 219. Spectral data match those previously reported.[14]

2-chloro-4-p-tolylpyridine (3c). (29 mg, 71%). R_f = 0.50 (PE/EA, 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, J = 2.9 Hz, 1H), 7.52 (m, 3H), 7.41 (m, 1H), 7.30 (d, J = 6.6 Hz, 2H), 2.42 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 152.2, 151.4, 149.9, 134.0, 133.8, 130.0, 126.8, 121.7, 120.2, 21.2. GC-MS: $[M]^+$= 203. Spectral data match those previously reported. [14]

2-chloro-4-m-tolylpyridine (3d). (26 mg, 64%). R_f = 0.55 (PE/EA, 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (d, J = 5.0 Hz, 1H), 7.61 (dt, J = 34.3, 25.6 Hz, 6H), 2.67 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 152.2, 151.8, 149.9, 139.0, 136.8, 130.4, 129.2, 127.7, 124.2, 122.0, 120.5, 21.5. GC-MS: $[M]^+$= 203. Spectral data match those previously reported.[16]

2-chloro-4-o-tolylpyridine (3e). (18 mg, 44%). R_f = 0.60 (PE/EA, 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, J = 5.0 Hz, 1H), 7.60-7.28 (m, 6H), 2.41 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 153.0, 151.6, 149.4, 137.8, 134.9, 130.8, 129.1, 128.9, 126.3, 124.6, 123.1, 20.2. GC-MS: $[M]^+$= 203. Spectral data match those previously reported.[17]

2-chloro-4-(4-fluorophenyl)pyridine (3f). (25 mg, 61%). R_f = 0.40 (PE/EA, 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, J = 5.2 Hz, 1H), 7.68-7.56 (m, 2H), 7.52 (d, J = 1.1 Hz, 1H), 7.40 (dd, J = 5.2, 1.5 Hz, 1H), 7.25-7.16 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 165.0, 162.5, 152.3, 150.5, 150.1, 133.0, 128.9, 121.9, 120.3, 116.5, 116.3. ^{19}F NMR (377 MHz, $CDCl_3$) δ -111.3. GC-MS: $[M]^+$= 207. Spectral data match those previously reported. [14]

2-chloro-4-(4-chlorophenyl)pyridine (3g). (30 mg, 68%). R_f = 0.40 (PE/EA, 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, J = 5.2 Hz, 1H), 7.57-7.42 (m, 5H), 7.38 (dd, J = 5.2, 1.6 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 152.4, 150.2, 136.0 , 135.3, 129.5, 128.3, 121.9, 120.3. GC-MS: $[M]^+$= 223. Spectral data match those previously reported.[15]

methyl 4-(2-chloropyridin-4-yl)benzoate (3h). white solid, m. p. = 132-136 °C (35 mg, 70%). R_f = 0.25 (PE/EA, 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (d, J = 5.2 Hz, 1H), 8.15 (d, J = 8.3 Hz, 2H), 7.67 (d, J = 8.4 Hz, 2H), 7.56 (d, J = 0.8 Hz, 1H), 7.44 (dd, J = 5.2, 1.5 Hz, 1H), 3.95 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.4 , 152.4 , 150.4, 150.2, 141.1, 131.2, 130.5, 127.1, 122.2, 120.5, 52.4. IR (neat): 2921.27, 1722.05, 1592.13, 1533.18, 1471.41, 1428.59, 1370.47, 1281.42, 1090.09, 831.47, 799.27, 768.12, 717.43. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{13}H_{11}ClNO_2^+$: 248.0473 ; found 248.0483. GC-MS: $[M]^+$= 247.

4-(2-chloropyridin-4-yl)benzonitrile (3i). (26 mg, 60%). R_f = 0.15 (PE/EA, 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (dd, J = 5.2, 0.5 Hz, 1H), 7.84-7.76 (m, 2H), 7.75-7.66 (m, 2H), 7.54 (dd, J = 1.5, 0.6 Hz, 1H), 7.42 (dd, J = 5.2, 1.6 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 152.5, 150.4, 149.5, 141.2, 133.0, 127.9, 122.3, 120.5, 118.2, 113.4. GC-MS: $[M]^+$= 214. Spectral data match those previously reported. [18]

4-(2-chloropyridin-4-yl)-N,N-dimethylbenzenamine (3j). white solid, m. p. = 126-130 °C (36 mg, 77%). R_f = 0.30 (PE/EA, 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, J = 5.3 Hz, 1H), 7.57-7.50 (m, 2H), 7.48 (d, J = 1.2 Hz, 1H), 7.36 (dd, J = 5.3, 1.6 Hz, 1H), 6.80-6.71 (m, 2H), 3.02 (s,

6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 152.1, 151.4, 151.3, 149.7, 127.8, 123.4, 120.2, 119.0, 112.3, 40.2. IR (neat): 2920.42, 2360.32, 1609.70, 1580.79, 1521.24, 1446.76, 1362.30, 1277.42, 1231.60, 1209.13, 1123.17, 1087.35, 1042.60, 987.07, 809.56, 744.07, 681.67. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{13}H_{14}ClN_2^+$: 233.0840 ; found 233.0856. GC-MS: $[M]^+$= 232.

2-chloro-4-(naphthalen-2-yl)pyridine (3k). (30 mg, 63%). R_f = 0.40 (PE/EA, 10:1). ^1H NMR (400 MHz, $CDCl_3$) δ 8.47 (dd, *J* = 5.2, 0.5 Hz, 1H), 8.11 (d, *J* = 1.6 Hz, 1H), 7.97 (d, *J* = 8.7 Hz, 1H), 7.92 (ddd, *J* = 15.4, 6.1, 3.3 Hz, 2H), 7.70 (ddd, *J* = 5.0, 2.1, 1.2 Hz, 2H), 7.60-7.52 (m, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 152.3, 151.5, 150.1, 134.0, 133.7, 133.4, 129.2, 128.5, 127.8, 127.2, 126.9, 124.2, 122.2, 120.7. GC-MS: $[M]^+$= 239. Spectral data match those previously reported. [19]

2-chloro-4-(thiophen-2-yl)pyridine (3l). (25 mg, 63%). R_f = 0.45 (PE/EA, 10:1). ^1H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 5.3 Hz, 1H), 7.51 (d, *J* = 2.1 Hz, 2H), 7.45 (dd, *J* = 5.1, 0.9 Hz, 1H), 7.39 (dd, *J* = 5.3, 1.5 Hz, 1H), 7.14 (dd, *J* = 5.0, 3.8 Hz, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 152.4, 150.1, 144.4, 139.7, 128.6, 128.1, 126.2, 120.0, 118.7. GC-MS: $[M]^+$= 197. Spectral data match those previously reported. [15]

2-chloro-4-(3,6-dihydro-2H-pyran-4-yl)pyridine (3m). yellow solid, m. p. = 108-111 °C (16 mg, 41%). R_f = 0.15 (PE/EA, 10:1). ^1H NMR (400 MHz, $CDCl_3$) δ 8.34-8.29 (m, 1H), 7.28 (d, *J* = 1.3 Hz, 1H), 7.19 (dd, *J* = 5.3, 1.6 Hz, 1H), 6.44-6.33 (m, 1H), 4.34 (q, *J* = 2.8 Hz, 2H), 3.92 (t, *J* = 5.4 Hz, 2H), 2.47 (tdd, *J* = 5.4, 2.8, 1.1 Hz, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 152.2, 150.3, 149.7, 131.3, 127.7, 119.7, 118.0, 77.4, 77.1, 76.8, 65.6, 64.0, 26.3. IR (neat): 2919.98, 2849.76, 2360.17, 1588.32, 1458.13, 1385.26, 1359.80, 1258.93, 1012.91, 789.90. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{10}H_{11}ClNO^+$: 196.0524 ; found 196.0536. GC-MS: $[M]^+$= 195.

2-chloro-4-(prop-1-en-2-yl)pyridine (3n). light yellow oil (15 mg, 49%). R_f = 0.60 (PE/EA, 10:1). ^1H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, *J* = 5.4 Hz, 1H), 7.37 (d, *J* = 1.2 Hz, 1H), 7.28 (dd, *J* = 5.2, 1.6 Hz, 1H), 5.60 (s, 1H), 5.35-5.31 (m, 1H), 2.14 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 152.0, 151.6, 149.6, 140.0, 120.7, 119.0, 117.2, 20.8. IR (neat): 2923.97, 2854.10, 2360.04, 2588.78, 1528.35, 1464.77, 1383.63, 1367.82, 1313.41, 1151.10, 1087.43, 989.58, 908.05, 844.20, 811.11, 731.36, 702.15. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_8H_9ClN^+$: 154.0418 ; found 154.0433. GC-MS: $[M]^+$= 153.

methyl 2-chloro-4-phenylnicotinate (3o). colourless oil (18 mg, 36%). R_f = 0.30 (PE/EA, 10:1). ^1H NMR (400 MHz, $CDCl_3$) δ 8.46 (d, *J* = 5.1 Hz, 1H), 7.45-7.38 (m, 5H), 7.28 (d, *J* = 5.1 Hz, 1H), 3.73 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 166.4, 150.5, 149.9, 148.2, 136.7, 129.4, 128.9, 127.8, 123.1, 52.9. IR (neat): 2950.16, 1732.76, 1575.44, 1535.69, 1432.70, 1375.76, 1267.33, 1197.61, 1130.48, 1057.31, 952.05, 821.91, 757.34, 698.22. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{13}H_{11}ClNO_2^+$: 248.0473 ; found 248.0486. GC-MS: $[M]^+$= 247.

2-chloro-3-methyl-4-p-tolylpyridine (3p). brown solid, m. p. = 66-68 °C (26 mg, 60%). R_f = 0.50 (PE/EA, 10:1). ^1H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 4.8 Hz, 1H), 7.29 (d, *J* = 7.9 Hz, 2H), 7.20 (d, *J* = 8.1 Hz, 2H), 7.11 (d, *J* = 4.9 Hz, 1H), 2.44 (s, 3H), 2.34 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 152.7, 152.4, 146.2, 138.3, 135.8, 130.1, 129.2, 128.5, 123.8, 21.2, 17.3. IR (neat): 2918.63, 2851.42, 2359.88, 1581.61, 1529.77, 1513.78, 1458.92, 1445.85, 1359.39, 1260.64, 1189.65, 1093.61, 1060.97, 996.28, 871.22, 812.41, 752.11, 718.53. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{13}H_{13}ClN^+$: 218.0731 ; found 218.0741. GC-MS: $[M]^+$= 217.

2-chloro-4-p-tolylpyridin-3-amine (3q). yellow solid, m. p. = 87-90 °C (14 mg, 32%). R_f = 0.30 (PE/EA, 10:1). ^1H NMR (400 MHz, CDCl3) δ 7.81 (d, *J* = 4.7 Hz, 1H), 7.56-7.08 (m, 4H), 6.97 (d, *J* = 4.7 Hz, 1H), 4.20 (m, 2H), 2.41 (m, 3H), 1.25 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, CDCl3) δ 138.7, 138.0, 137.5, 137.2, 135.3, 133.5, 123.0, 128.2, 124.1, 21.3. IR (neat): 3463.33, 3302.14, 3189.57, 2919.28, 2849.16, 2359.78, 1611.14, 1508.64, 1462.32, 1413.24, 1272.28, 1218.70, 1182.05, 1104.13, 1070.99, 816.04, 756.21. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{12}H_{12}ClN_2^+$: 219.0684 ; found 219.0694. GC-MS: $[M]^+$= 218.

2-chloro-3-nitro-4-p-tolylpyridine (3r). light yellow solid, m. p. = 72-76 °C (21 mg, 43%). R_f = 0.35 (PE/EA, 10:1). ^1H NMR (400 MHz, CDCl3) δ 8.51 (d, *J* = 5.1 Hz, 1H), 7.36 (d, *J* = 5.1 Hz, 1H), 7.27 (d, *J* = 6.9 Hz, 4H), 2.40 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 149.95, 145.13 , 144.62, 142.24, 140.83, 130.04, 127.48, 124.31, 21.31. IR (neat): 2919.63, 2849.52, 2359.66, 1737.90, 1646.10, 1610.87, 1586.13, 1536.33, 1452.23, 1352.13, 1209.45, 1116.78, 1056.38, 850.37, 816.08, 777.05, 728.44. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{12}H_{10}ClN_2O_2^+$: 249.0425 ; found 249.0435. GC-MS: $[M]^+$= 203. GC-MS: $[M]^+$= 248.

2-chloro-5-methyl-4-phenylpyridine (3s). colourless oil (17 mg, 42%). R_f = 0.50 (PE/EA, 10:1). ^1H NMR (400 MHz, $CDCl_3$) δ 8.27 (s, 1H), 7.50-7.39 (m, 3H), 7.33–7.27 (m, 2H), 7.20 (s, 1H), 2.23 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 152.4, 150.8, 149.0, 137.9, 129.8, 128.6, 128.5, 128.4, 124.2, 16.7. IR (neat): 2923.82, 1584.18, 1536.75, 1496.65, 1461.15, 1345.21, 1102.13, 1043.65, 877.14, 846.45, 770.55, 730.60, 699.42. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{12}H_{11}ClN^+$: 204.0575 ; found 204.0586. GC-MS: $[M]^+$= 203.

methyl 6-chloro-4-p-tolylnicotinate (3t). withe solid, m. p. = 64-67 °C (8 mg, 15%). R_f = 0.45 (PE/EA, 10:1). ^1H NMR (400 MHz, $CDCl_3$) δ 8.81 (s, 1H), 7.36 (s, 1H), 7.25 (dd, *J* = 19.7, 8.0 Hz, 4H), 3.76 (s, 3H), 2.43 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 154.1, 153.2, 151.1, 139.2, 129.2, 127.9, 125.3, 52.4, 21.3. IR (neat): 3064.72, 2919.51, 2849.48, 2359.78, 1731.51, 1576.79, 1528.97, 1463.80, 1432.70, 1344.84, 1273.21, 1215.59, 1190.59, 1114.16, 1038.46, 1016.34, 912.04, 892.74, 844.71, 818.14, 790.24, 731.41, 696.54. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{14}H_{13}ClNO_2^+$: 262.0629 ; found 262.0640. GC-MS: $[M]^+$= 261.

2-chloro-6-methyl-4-phenylpyridine (3u). colourless oil (24 mg, 60%). R_f = 0.60 (PE/EA, 10:1). ^1H NMR (400 MHz, $CDCl_3$) δ 7.60-7.56 (m, 2H), 7.50-7.41 (m, 3H), 7.34 (d, *J* = 0.6 Hz, 1H), 7.27 (s, 1H), 2.58 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 159.6, 151.8, 151.2, 137.2, 129.5, 129.2, 127.0, 120.0, 119.1, 24.3. IR (neat): 2922.43, 1594.18, 1537.08, 1496.65, 1445.78, 1390.53, 1305.42, 1146.91, 899.26, 863.05, 815.14, 759.87, 693.82. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{12}H_{11}ClN^+$: 204.0575 ; found 204.0586. GC-MS: $[M]^+$= 203.

2-chloro-6-methyl-4-p-tolylpyridine (3v). light yellow oil (20 mg, 46%). R_f = 0.50 (PE/EA, 10:1). ^1H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.2 Hz, 2H), 7.33 (d, *J* = 0.6 Hz, 1H), 7.31-7.24 (m, 3H), 2.59 (s, 3H), 2.42 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 159.5, 151.6, 151.1, 139.7, 134.1, 129.9, 126.9, 119.7, 118.7, 24.3, 21.3. IR (neat): 2921.29, 1592.79, 1534.35, 1450.59, 1387.55, 1305.23, 1211.16, 1146.34, 1087.83, 1019.54, 995.87, 900.84, 867.32, 830.83, 810.70. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{13}H_{13}ClN^+$: 218.0731 ; found 218.0741. GC-MS: $[M]^+$= 217.

methyl 6-chloro-4-p-tolylpicolinate (3w). light yellow solid, m. p. = 81-86 °C (5 mg, 10%). R_f = 0.25 (PE/EA, 10:1). ^1H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 1.5 Hz, 1H), 7.70 (d, *J* = 1.5 Hz, 1H), 7.57 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 7.9 Hz, 2H), 4.02 (s, 3H), 2.42 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 164.8, 152.2, 148.5, 140.7, 132.9, 130.2, 127.0, 124.9, 121.8, 53.2, 21.3. IR (neat): 3391.78, 2918.61, 2848.09, 1719.69, 1645.45, 1593.22, 1536.74, 1448.80, 1394.04, 1314.92, 1170.14, 1124.61, 1065.74, 988.93, 968.36, 833.66, 809.15, 784.48, 741.50. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{14}H_{13}ClNO_2^+$: 262.0629 ; found 262.0637. GC-MS: $[M]^+$= 261.

2-chloro-4-p-tolylquinoline (3x). (31 mg, 61%). R_f = 0.30 (PE/EA, 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J = 8.4 Hz, 1H), 7.90 (dd, J = 8.4, 0.7 Hz, 1H), 7.73 (ddd, J = 8.4, 6.9, 1.3 Hz, 1H), 7.49 (ddd, J = 8.2, 6.9, 1.2 Hz, 1H), 7.36 (dd, J = 18.9, 8.7 Hz, 5H), 2.47 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 152.1, 151.4, 149.7, 127.8, 123.4, 120.3, 119.0, 112.3, 40.2. GC-MS: $[M]^+$= 253. Spectral data match those previously reported. [20]

General procedure for the synthesis of compound 5. 4-(2-chloropyridin-4-yl)-N,N-dimethylbenzenamine **3j** (0.2 mmol), aryl boronic acids **2** (0.3 mmol), $Pd(PPh_3)_4$ (5 mol %), K_2CO_3 (2.0 equiv.) and dioxane/H_2O (V/V~5/1, 1.2 mL) were added to a test tube at 100ºC in an oil bath under N_2 for overnight. After the disappearance of substrate as indicated by TLC, the mixture was filtrated and the resulting filtrate was extracted by DCM (3*10 mL). The organic layers were combined and dried by Na_2SO_4. Then evaporation of the solvent and purification by flash column chromatograph using PE/EA as eluent to afford the desired product **5**.

4-(4-(4-(dimethylamino)phenyl)pyridin-2-yl)-N,N-dimethylbenzenamine (5a). yellow solid, m. p. = 125-128 °C (38 mg, 60%). R_f = 0.30 (PE/EA, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, J = 5.2 Hz, 1H), 7.95 (d, J = 8.8 Hz, 2H), 7.81 (s, 1H), 7.62 (d, J = 8.8 Hz, 2H), 7.30 (d, J = 5.2 Hz, 1H), 6.80 (dd, J = 8.7, 4.6 Hz, 4H), 3.01 (s, 12H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 157.9, 151.1, 149.4, 148.9, 127.9, 127.7, 127.5, 125.9, 117.8, 116.3, 112.5, 112.3, 40.4, 40.3. IR (neat): 2920.77, 1588.33, 1522.76, 1469.63, 1356.38, 1193.11, 1167.25, 1125.14, 946.32, 810.26, 733.71, 556.20. HRMS (ESI-TOF) m/z: $[M + H]^+$ (ESI) calcd for $C_{21}H_{24}N_3^+$: 318.1965 ; found 318.1972. GC-MS: $[M]^+$= 317.

4-(2-(4-methoxyphenyl)pyridin-4-yl)-N,N-dimethylbenzenamine (5b). yellow solid, m. p. = 156-160 °C (31 mg, 51%). R_f = 0.30 (PE/EA, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, J = 5.2 Hz, 1H), 8.01 (d, J = 8.6 Hz, 2H), 7.85 (s, 1H), 7.63 (d, J = 8.6 Hz, 2H), 7.36 (d, J = 5.0 Hz, 1H), 7.03 (d, J = 8.6 Hz, 2H), 6.80 (d, J = 8.6 Hz, 2H), 3.87 (s, 3H), 3.01 (s, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 160.4, 157.5, 151.1, 149.7, 149.0, 132.5, 128.3, 127.7, 125.5, 118.5, 116.8, 114.1, 112.5, 55.4, 40.3. IR (neat): 3675.22, 2987.64, 2900.74, 1393.76, 1249.85, 1066.00, 891.46. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{20}H_{21}N_2O^+$: 305.1648 ; found 305.1658. GC-MS: $[M]^+$= 304. Spectral data match those previously reported. [21]

4-(2-(4-tert-butylphenyl)pyridin-4-yl)-N,N-dimethylbenzenamine (5c). yellow solid, m. p. = 163-166 °C (36 mg, 55%). R_f = 0.40 (PE/EA, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (d, J = 5.2 Hz, 1H), 8.00 (d, J = 8.4 Hz, 2H), 7.91 (d, J = 0.6 Hz, 1H), 7.64 (d, J = 8.8 Hz, 2H), 7.54 (d, J = 8.4 Hz, 2H), 7.40 (dd, J = 5.2, 1.5 Hz, 1H), 6.82 (d, J = 8.8 Hz, 2H), 3.03 (s, 6H), 1.40 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 157.9, 152.0, 151.1, 149.8, 148.9, 137.1, 127.7, 126.8, 125.7, 125.6, 118.8, 117.3, 112.5, 40.3, 34.7, 31.4. IR (neat): 2958.52, 1728.07, 1588.66, 1526.68, 1468.77, 1445.32, 1360.11, 1202.22, 1117.52, 811.36, 703.31. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{23}H_{27}N_2^+$: 331.2169 ; found 331.2175. GC-MS: $[M]^+$= 330.

N,N-dimethyl-4-(2-p-tolylpyridin-4-yl)benzenamine (5d). yellow solid, m. p. = 136-139 °C (36 mg, 63%). R_f = 0.35 (PE/EA, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (d, J = 5.2 Hz, 1H), 7.97 (d, J = 8.1 Hz, 2H), 7.90 (d, J = 0.8 Hz, 1H), 7.64 (d, J = 8.8 Hz, 2H), 7.39 (dd, J = 5.2, 1.6 Hz, 1H), 7.32 (d, J = 8.0 Hz, 2H), 6.81 (d, J = 8.9 Hz, 2H), 3.02 (s, 6H), 2.43 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 157.9, 151.1, 149.8, 149.0, 138.8, 137.1, 129.5, 127.7, 126.9, 125.6, 118.8, 117.2, 112.5, 40.3, 21.3. IR (neat): 1590.85, 1527.61, 1472.25, 1362.02, 1209.71, 1168.59, 811.66. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{20}H_{21}N_2^+$: 289.1699 ; found 289.1708. GC-MS: $[M]^+$= 288.

N,N-dimethyl-4-(2-phenylpyridin-4-yl)benzenamine (5e). yellow solid, m. p. = 134-138 °C (41 mg, 74%). R_f = 0.35 (PE/EA, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (d, J = 5.2 Hz, 1H), 8.06 (d, J = 7.3 Hz, 2H), 7.91 (s, 1H), 7.64 (d, J = 8.8 Hz, 2H), 7.51 (t, J = 7.4 Hz, 2H), 7.46-7.38 (m, 2H), 6.81 (d, J = 8.8 Hz, 2H), 3.03 (s, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 157.9, 151.2, 149.9, 149.1, 139.9, 128.8, 128.7, 127.8, 127.1, 125.4, 119.1, 117.5, 112.5, 40.3. IR (neat): 2918.68, 1591.11, 1256.95, 1471.27, 1444.16, 1360.36, 1209.58, 1168.12, 814.20, 775.82, 741.18, 700.87. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{19}H_{19}N_2^+$: 275.1543 ; found 275.1549. GC-MS: $[M]^+$= 274.

N,N-dimethyl-4-(2-(naphthalen-2-yl)pyridin-4-yl)benzenamine (5f). yellow solid, m. p. = 99-102 °C (40 mg, 61%). R_f = 0.35 (PE/EA, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (d, J = 5.2 Hz, 1H), 8.55 (s, 1H), 8.21 (dd, J = 8.6, 1.5 Hz, 1H), 8.05 (s, 1H), 7.98 (dd, J = 8.8, 3.6 Hz, 2H), 7.92-7.84 (m, 1H), 7.68 (d, J = 8.8 Hz, 2H), 7.56-7.48 (m, 2H), 7.45 (dd, J = 5.2, 1.5 Hz, 1H), 6.82 (d, J = 8.8 Hz, 2H), 3.03 (s, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 157.7, 151.2, 149.9, 149.3, 137.1, 133.7, 133.6, 128.8, 128.4, 127.8, 127.7, 126.5, 126.4, 126.3, 125.4, 124.8, 119.1, 117.8, 112.5, 40.3. IR (neat): 2918.62, 1590.27, 1526.85, 1482.55, 1372.57, 1207.18, 1168.88, 945.14, 867.96, 806.16, 759.52. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{23}H_{21}N_2^+$: 325.1699 ; found 325.1709. GC-MS: $[M]^+$= 324.

4-(2-(4-chlorophenyl)pyridin-4-yl)-N,N-dimethylbenzenamine (5g). yellow solid, m. p. = 121-125 °C (18 mg, 30%). R_f = 0.35 (PE/EA, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (d, J = 5.2 Hz, 1H), 7.99 (d, J = 8.4 Hz, 2H), 7.85 (s, 1H), 7.61 (d, J = 8.2 Hz, 2H), 7.46 (d, J = 8.4 Hz, 2H), 7.40 (d, J = 5.2 Hz, 1H), 6.79 (d, J = 8.4 Hz, 2H), 3.02 (s, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 156.6, 151.2, 149.9, 149.2, 138.3, 134.9, 128.9, 128.3, 127.7, 125.1, 119.3, 117.2, 112.5, 40.3. IR (neat): 2987.99, 1393.90, 1241.49, 1066.00, 890.89, 810.91. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{19}H_{18}ClN_2^+$: 309.1153 ; found 309.1163. GC-MS: $[M]^+$= 308.

N,N-dimethyl-4-(2-(pyridin-3-yl)pyridin-4-yl)benzenamine (5h). yellow solid, m. p. = 161-166 °C (36 mg, 65%). R_f = 0.25 (PE/EA, 2:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.23 (s, 1H), 8.65 (d, J = 4.9 Hz, 2H), 8.35 (d, J = 7.9 Hz, 1H), 7.89 (s, 1H), 7.62 (d, J = 8.6 Hz, 2H), 7.49-7.35 (m, 2H), 6.79 (d, J = 8.5 Hz, 2H), 3.02 (s, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 155.1, 151.3, 150.2, 149.7, 149.4, 148.3, 135.4, 134.5, 127.7, 124.9, 123.6, 119.6, 117.5, 112.5, 40.3. IR (neat): 2987.78, 2900.76, 1590.70, 1393.76, 1250.14, 1065.99, 879.41, 809.36, 706.33. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{18}N_3^+$: 276.1495 ; found 276.1507. GC-MS: $[M]^+$= 275.

methyl 4-(4-(4-(dimethylamino)phenyl)pyridin-2-yl)benzoate (5i). yellow solid, m. p. = 217-230 °C (30 mg, 45%). R_f = 0.30 (PE/EA, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72-8.65 (m, 1H), 8.22-8.09 (m, 4H), 7.96 (d, J = 1.1 Hz, 1H), 7.70-7.62 (m, 2H), 7.49 (dd, J = 5.2, 1.7 Hz, 1H), 6.86-6.80 (m, 2H), 3.97 (s, 3H), 3.06 (s, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 167.0, 156.6, 151.2, 150.0, 149.4, 144.0, 130.2, 130.0, 127.8, 127.0, 125.0, 119.7, 118.0, 112.5, 52.2, 40.3. IR (neat): 2917.88, 1713.07, 1587.07, 1527.30, 1437.35, 1361.37, 1267.05, 1113.94, 1015.72, 969.43, 864.8, 813.75, 775.56, 697.29. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{21}H_{21}N_2O_2^+$: 333.1598 ; found 333.1605. GC-MS: $[M]^+$= 332.

N,N-dimethyl-4-(2-(4-(trifluoromethyl)phenyl)pyridin-4-yl)benzenamine (5j). yellow solid, m. p. = 205-211 °C (33 mg, 48%). R_f = 0.35 (PE/EA, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (d, J = 5.2 Hz, 1H), 8.16 (d, J = 8.1 Hz, 2H), 7.92 (d, J = 1.0 Hz, 1H), 7.75 (d, J = 8.2 Hz, 2H), 7.68-7.60 (m, 2H), 7.47 (dd, J = 5.2, 1.7 Hz, 1H), 6.86-6.78 (m, 2H), 3.04 (s, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 156.2, 151.3, 150.0,

149.4, 143.1, 130.8, 130.5, 127.8, 127.3, 125.7, 125.7, 125.6, 125.6, 125.0, 122.9, 119.8, 117.8, 112.5, 40.3. ^{19}F NMR (377 MHz, $CDCl_3$) δ -62.5. IR (neat): 2987.98, 2900.68, 1393.79, 1249.92, 1066.04, 891.76. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{20}H_{18}F_3N_2^+$: 343.1417 ; found 343.1427. GC-MS: [M]$^+$= 342.

4-(4-(4-(dimethylamino)phenyl)pyridin-2-yl)benzonitrile (5k). yellow solid, m. p. = 199-204 °C (38 mg, 64%). R_f = 0.25 (PE/EA, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (dd, J = 4.8, 2.8 Hz, 1H), 8.13 (dd, J = 8.3, 2.4 Hz, 2H), 7.89 (s, 1H), 7.75 (dd, J = 8.2, 2.4 Hz, 2H), 7.61 (dd, J = 8.9, 2.6 Hz, 2H), 7.46 (dd, J = 5.0, 1.7 Hz, 1H), 6.79 (dd, J = 8.9, 2.6 Hz, 2H), 3.03 (d, J = 2.8 Hz, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 155.5, 151.3, 150.1, 149.5, 144.0, 132.5, 127.7, 127.6, 124.6, 120.1, 118.9, 117.8, 112.5, 112.3, 40.3. IR (neat): 2988.04, 1393.77, 1249.90, 1066.07, 829.63. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{20}H_{18}N_3^+$: 300.1495 ; found 300.1504. GC-MS: [M]$^+$= 299.

General procedure for the synthesis of compound 6. 4-(4-chloropyridin-2-yl)-N,N-dimethylbenzenamine **4j** (0.2 mmol), aryl boronic acids **2** (0.3 mmol), $Pd(PPh_3)_4$ (5 mol %), K_2CO_3 (2.0 equiv.) and dioxane/H_2O (V/V~5/1, 1.2 mL) were added to a test tube at 100°C in an oil bath under N_2 for overnight. After the disappearance of substrate as indicated by TLC, the mixture was filtrated and the resulting filtrate was extracted by DCM (3*10 mL). The organic layers were combined and dried by Na_2SO_4. Then evaporation of the solvent and purification by flash column chromatograph using PE/EA as eluent to afford the desired product **6**.

Procedure for the synthesis of compound 4j on a 4 mmol scale.

2,4-dichloropyridine **1a** (6 mmol, 888mg), N,N-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2- dioxaborolan-2-yl)benzenamine **2j** (4 mmol, 988mg), $Pd(PPh_3)_4$ (5 mol %, 231 mg), K_2CO_3 (2.0 equiv, 1104 mg) and 1, 4-dioxane/H_2O (v/v~5/1, 24 mL) were added to a 100mL-round-bottom flask at 100°C in an oil bath under N_2 for overnight. After the disappearance of **2j** as indicated by TLC, the mixture was filtrated and the resulting filtrate was extracted by DCM (3*150 mL). The organic layers were combined and dried by Na_2SO_4. Then evaporation of the solvent and purification by flash column chromatograph using PE/EA as eluent to afford the desired product **4j** (557 mg) in 60% yield.

4-(4-chloropyridin-2-yl)-N,N-dimethylbenzenamine (4j). white solid, m. p. = 101-104 °C (556 mg, 60%). R_f = 0.30 (PE/EA, 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52-8.46 (m, 1H), 7.92-7.85 (m, 2H), 7.63 (dd, J = 1.9, 0.4 Hz, 1H), 7.09 (dd, J = 5.3, 1.9 Hz, 1H), 6.80-6.72 (m, 2H), 3.02 (s, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 159.2, 151.4, 150.2, 144.4, 127.9, 125.7, 120.7, 119.2, 112.1, 40.3. IR (neat): 2921.80, 1606.89, 1570.79, 1524.03, 1428.86, 1380.56, 1362.51, 1261.72, 1227.58, 1193.62, 1105.93, 1051.38, 948.53, 862.44, 805.03, 736.36, 693.42. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{13}H_{14}ClN_2^+$: 233.0840 ; found 233.0849. GC-MS: [M]$^+$= 232.

4-(4-(4-methoxyphenyl)pyridin-2-yl)-N,N-dimethylbenzenamine (6b). yellow solid, m. p. = 138-140 °C (50 mg, 82%). R_f = 0.25 (PE/EA, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (d, J = 5.2 Hz, 1H), 8.02-7.95 (m, 2H), 7.84 (d, J = 1.0 Hz, 1H), 7.70-7.64 (m, 2H), 7.32 (dd, J = 5.2, 1.7 Hz, 1H), 7.08-7.00 (m, 2H), 6.87-6.79 (m, 2H), 3.89 (s, 3H), 3.05 (s, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 160.4, 158.0, 151.1, 149.6, 148.6, 131.1, 128.2, 127.9, 127.2, 118.4, 116.9, 114.5, 112.3, 55.4, 40.4. IR (neat): 3676.65, 2988.00, 2901.08, 2333.02, 1383.45, 1240.82, 1066.29, 895.9, 804.72. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{20}H_{21}N_2O^+$: 305.1648 ; found 305.1657. GC-MS: [M]$^+$= 304.

4-(4-(4-tert-butylphenyl)pyridin-2-yl)-N,N-dimethylbenzenamine (6c). yellow solid, m. p. = 122-127 °C (53 mg, 81%). R_f = 0.35 (PE/EA, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (d, J = 5.1 Hz, 1H), 8.01 (d, J = 8.8 Hz, 2H), 7.88 (s, 1H), 7.65 (d, J = 8.3 Hz, 2H), 7.54 (d, J = 8.3 Hz, 2H), 7.34 (dd, J = 5.1, 1.3 Hz, 1H), 6.84 (d, J = 8.8 Hz, 2H), 3.03 (s, 6H), 1.40 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 158.0, 152.2, 151.2, 149.6, 149.0, 136.0, 127.9, 127.2, 126.8, 126.1, 118.8, 117.2, 112.3, 40.4, 34.7, 31.4. IR (neat): 3675.08, 2987.92, 2900.70, 1393.76, 1249.88, 1066.01, 891.89, 816.92. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{23}H_{27}N_2^+$: 331.2169 ; found 331.2167. GC-MS: [M]$^+$= 330.

N,N-dimethyl-4-(4-p-tolylpyridin-2-yl)benzenamine (6d). yellow solid, m. p. = 152-157 °C (43 mg, 75%). R_f = 0.30 (PE/EA, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (d, J = 5.2 Hz, 1H), 8.00 (d, J = 8.9 Hz, 2H), 7.85 (s, 1H), 7.60 (d, J = 8.1 Hz, 2H), 7.32 (dd, J = 7.1, 4.7 Hz, 3H), 6.82 (d, J = 8.9 Hz, 2H), 3.03 (s, 6H), 2.43 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 158.0, 151.2, 149.6, 149.0, 139.0, 136.0, 129.8, 127.9, 127.2, 126.9, 118.7, 117.1, 112.3, 40.4, 21.3. IR (neat): 2987.91, 2900.69, 1406.69, 1251.11, 1228.39, 1064.80, 892.25, 809.48. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{20}H_{21}N_2^+$: 289.1699 ; found 289.1713. GC-MS: [M]$^+$= 288.

N,N-dimethyl-4-(4-phenylpyridin-2-yl)benzenamine (6e). yellow solid, m. p. = 90-93 °C (22 mg, 41%). R_f = 0.30 (PE/EA, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (d, J = 5.0 Hz, 1H), 8.03-7.92 (m, 2H), 7.85 (s, 1H), 7.69 (d, J = 7.5 Hz, 2H), 7.54-7.41 (m, 3H), 7.35-7.28 (m, 1H), 6.85-6.75 (m, 2H), 3.03 (d, J = 2.2 Hz, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 158.1, 151.2, 149.6, 149.2, 139.0, 129.1, 128.9, 127.9, 127.1, 118.9, 117.4, 112.3, 40.4. IR (neat): 2919.00, 1610.56, 1587.09, 1540.04, 1456.77, 1444.60, 1383.66, 1368.90, 1236.23, 1196.59, 1067.70, 881.45, 808.83, 763.71. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{19}H_{19}N_2^+$: 275.1543 ; found 275.1555. GC-MS: [M]$^+$= 274.

N,N-dimethyl-4-(4-(naphthalen-2-yl)pyridin-2-yl)benzenamine (6f). yellow solid, m. p. = 135-137 °C (32 mg, 50%). R_f = 0.30 (PE/EA, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (d, J = 5.0 Hz, 1H), 8.16 (s, 1H), 8.07-8.00 (m, 2H), 7.99-7.92 (m, 3H), 7.90 (d, J = 7.5 Hz, 1H), 7.80 (d, J = 8.4 Hz, 1H), 7.60-7.49 (m, 2H), 7.48-7.39 (m, 1H), 6.89-6.75 (m, 2H), 3.04 (d, J = 2.2 Hz, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 158.2, 151.2, 149.9, 148.9, 136.3, 133.5, 133.4, 128.9, 128.5, 127.9, 127.8, 127.2, 126.7, 126.6, 126.4, 124.8, 119.1, 117.5, 112.3, 40.4. IR (neat): 2919.70, 1592.64, 1526.36, 1460.33, 1392.80, 1356.49, 1263.86, 1193.22, 947.00, 813.40, 731.35. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{23}H_{21}N_2^+$: 325.1699 ; found 325.1708. GC-MS: [M]$^+$= 324.

4-(4-(4-chlorophenyl)pyridin-2-yl)-N,N-dimethylbenzenamine (6g). yellow solid, m. p. = 134-139 °C (30 mg, 48%). R_f = 0.30 (PE/EA, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (dd, J = 5.1, 0.6 Hz, 1H), 8.03-7.97 (m, 2H), 7.81 (dd, J = 1.6, 0.7 Hz, 1H), 7.65-7.59 (m, 2H), 7.51-7.45 (m, 2H), 7.28 (dd, J = 5.1, 1.7 Hz, 1H), 6.86-6.80 (m, 2H), 3.05 (d, J = 2.4 Hz, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 158.3, 151.2, 150.0, 147.7, 137.4, 135.0, 129.3, 128.4, 127.9, 127.0, 118.6, 117.0, 112.2, 40.4. IR (neat): 2849.32, 1595.49, 1521.43, 1493.37, 1379.52, 1348.07, 1224.63, 1196.46, 1166.21, 1122.96, 1087.02, 1009.21, 944.50, 812.29, 706.91. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{19}H_{18}ClN_2^+$: 309.1153 ; found 309.1162. GC-MS: [M]$^+$= 308.

N,N-dimethyl-4-(4-(pyridin-3-yl)pyridin-2-yl)benzenamine (6h). brown oil (31 mg, 56%). R_f = 0.20 (PE/EA, 2:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (s, 1H), 8.68 (t, J = 5.1 Hz, 2H), 7.96 (t, J = 8.3 Hz, 3H), 7.82 (s, 1H), 7.42 (dd, J = 7.8, 4.9 Hz, 1H), 7.29 (d, J = 5.1 Hz, 1H), 6.80 (d, J = 8.7 Hz, 2H), 3.02 (s, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 158.5, 151.3, 150.0, 148.2, 145.8, 134.6, 134.4, 127.9, 126.7, 123.8, 118.6, 117.1, 112.2, 40.3. IR (neat): 2919.34, 2849.24, 1926.40, 1674.01, 1599.56, 1526.17, 1465.45, 1429.62, 1382.12, 1358.25, 1263.48, 1194.50,

1125.06, 1018.21, 946.03, 800.54, 705.63. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{18}H_{18}N_3^+$: 276.1495 ; found 276.1502. GC-MS: [M]$^+$= 275.

methyl 4-(2-(4-(dimethylamino)phenyl)pyridin-4-yl)benzoate (6i). yellow solid, m. p. = 172-177 °C (42 mg, 64%). R_f = 0.25 (PE/EA, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (d, J = 5.1 Hz, 1H), 8.14 (d, J = 8.1 Hz, 2H), 7.98 (d, J = 8.7 Hz, 2H), 7.83 (s, 1H), 7.72 (d, J = 8.2 Hz, 2H), 7.30 (dd, J = 5.1, 0.8 Hz, 1H), 6.79 (d, J = 8.8 Hz, 2H), 3.94 (s, 3H), 3.01 (s, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.7 158.3, 151.2, 149.9, 147.8, 143.3, 130.4, 130.3, 127.9, 127.1, 118.7, 117.2, 112.2, 52.3, 40.3. IR (neat): 2987.93, 2900.69, 1716.08, 1594.46, 1539.69, 1393.65, 1250.53, 1066.10, 892.21, 816.17, 766.48. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{21}H_{21}N_2O_2^+$: 333.1598 ; found 333.1604. GC-MS: [M]$^+$= 332.

N,N-dimethyl-4-(4-(4-(trifluoromethyl)phenyl)pyridin-2-yl)benzenamine (6j). yellow solid, m. p. = 169-174 °C (45 mg, 66%). R_f = 0.30 (PE/EA, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (d, J = 5.1 Hz, 1H), 7.99 (dd, J = 9.4, 2.4 Hz, 2H), 7.82 (d, J = 0.7 Hz, 1H), 7.79-7.70 (m, 4H), 7.28 (dd, J = 5.1, 1.6 Hz, 1H), 6.81 (d, J = 8.9 Hz, 2H), 3.03 (s, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 158.4, 151.3, 150.0, 147.6, 142.6, 131.0, 130.6, 127.9, 127.5, 126.7, 126.0, 126.0, 126.0, 125.9, 125.5, 122.8, 118.8, 117.2, 112.2, 40.3. ^{19}F NMR (377 MHz, $CDCl_3$) δ -62.5. IR (neat): 2987.91, 2900.70, 1393.76, 1249.91, 1066.03, 891.86, 817.94. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{20}H_{18}F_3N_2^+$: 343.1417 ; found 343.1429. GC-MS: [M]$^+$= 342.

4-(2-(4-(dimethylamino)phenyl)pyridin-4-yl)benzonitrile (6k). yellow solid, m. p. = 168-172 °C (42 mg, 71%). R_f = 0.20 (PE/EA, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (dd, J = 5.1, 0.6 Hz, 1H), 8.02-7.94 (m, 2H), 7.84-7.73 (m, 5H), 7.30-7.26 (m, 1H), 6.87-6.78 (m, 2H), 3.05 (s, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 158.6, 151.3, 150.2, 146.9, 143.5, 132.8, 127.9, 127.8, 126.6, 118.6, 117.1, 112.5, 112.2, 40.3. IR (neat): 2920.68, 2225.32, 1709.10, 1598.34, 1491.56, 1362.12, 1264.27, 1188.79, 1081.14, 966.37, 848.75, 813.41, 734.63. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{20}H_{18}N_3^+$: 300.1495 ; found 300.1507. GC-MS: [M]$^+$= 299.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at .

- Control Experiments for the role of KI;
- ^{1}H, ^{13}C, ^{19}F NMR, IR spectra and and GC-MS of compound **3, 4, 5, 6**;
- Fluorescence spectra analysis of pyridine compounds (**3j, 4j, 5a-5k, 6b-6k**);
- Live HeLa cell Imaging of diarylated pyridines (**5a-5k, 6b-6k**);
- Schematic representation of HOMO & LUMO of representative pyridine compounds (**3j, 4j, 5a, 5b, 6b, 5e, 6e, 5j, 6j**);

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: min_yang100@163.com (Min Yang);
*E-mail: liujinbiao@jxust.edu.cn (Jinbiao Liu);
*E-mail: hqtblue@163.com (Qitong Huang);

ORCID

Min Yang: 0000-0001-8338-9725;
Jinbiao Liu: 0000-0002-5038-6541;
Qitong Huang: 0000-0002-3343-3393;

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to the National Science Foundation of China (21762018 and 21961014), the Science and Technology Innovation Outstanding Young Talents Program of Jiangxi Province (20192BCBL23009), the Talents' Start-up Fund of Gannan Medical University (QD201831), the Education Bureau of Jiangxi Province (GJJ190799) and the Research Fund of Gannan Medical University (ZD201905).

■ REFERENCES

(1) (a) Glasby, J. S. Encyclopedia *of the Alkaloids*; Plenum Press: New York, **1975**. (b) Yates, F. S. *In Comprehensive Heterocyclic Chemistry*; Boulton, A. J.; McKillop, A. Ed.; Pergamon Press: Oxford, **1984**, 511. (c) Ladouceur, G. H.; Cook, J. H.; Doherty, E. M.; Schoen, W. R.; MacDougall, M. L.; Livingston, J. N. Discovery of 5-hydroxyalkyl-4-phenylpyridines as a new class of glucagon receptor antagonists. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 461. (d) Wang, Y. -C.; Liu, J. -B.; Zhou, H.; Xie, W.; Rojsitthisak, P.; Qiu, G. Ortho-Hydroxylative ipso-Cyclization of N-arylpropiolamide. *J. Org. Chem.* **2020**, 85, *1906*. (e) Thapa, P.; Karki, R.; Thapa, U.; Jahng, Y.; Jung, M. J.; Nam, J. M.; Na, Y.; Kwon, Y.; Lee E. S. 2-Thienyl-4-furyl-6-aryl pyridine derivatives: Synthesis, topoisomerase I and II inhibitory activity, cytotoxicity, and structure-activity relationship study. *Bioorg. Med. Chem.* **2010**, *18*, 377.

(2) For selected reviews, see: (a) Finney, N. S. Combinatorial discovery of fluorophores and fluorescent probes. *Curr. Opin. Chem. Biol.* **2006**, *10*, 238. (b) Terai, T.; Nagano, T. Fluorescent probes for bioimaging applications. *Curr. Opin. Chem. Biol.* **2008**, *12*, 515. (c) Vendrell, M.; Zhai, D.; Er, J. C.; Chang, Y.-T. Combinatorial strategies in fluorescent probe development. *Chem. Rev.* **2012**, *112*, 4391. (d) Guo, Z.; Park, S.; Yoon, J.; Shin, I. Recent progress in the development of near-infrared fluorescent probes for bioimaging applications. *Chem. Soc. Rev.* **2014**, *43*, 16. (e) Cao, D.; Liu, Z.; Verwilst, P.; Koo, S.; Jangjili, P.; Kim, J. S.; Lin, W. Coumarin-based small-molecule fluorescent chemosensors. *Chem. Rev.* **2019**, *119*, 10403.

(3) (a) Lu, L.; Wang, M.; Liu, L. J.; Leung, C. H.; Ma, D. L. Label-Free luminescent switch-on probe for ochratoxin a detection using a G-quadruplex-selective iridium (III) complex. *ACS Appl. Mater. Interfaces*, **2015**, *7*, 8313. (b) Lu, L.; Wang, M.; Liu, L. J.; Wong, C. Y.; Leung, C. H.; Ma, D. L. A luminescence switch-on probe for terminal deoxynucleotidyl transferase (TdT) activity detection by using an iridium (III)-based i-motif probe. *Chem. Commun.* **2015**, *51*, 9953. (c) Passos, S. T.; Correa, J. R.; Soares, S. L.; da Silva, W. A.; Neto, B. A. Fluorescent peptoids as selective live cell imaging probes. *J. Org. Chem.* **2016**, *81*, 2646. (d) Lu, L.; Wang, W.; Yang, C.; Kang, T. S.; Leung, C. H.; Ma, D. L. Iridium (III) complexes with 1, 10-phenanthroline-based N^N ligands as highly selective luminescent G-quadruplex probes and application for switch-on ribonuclease H detection. *J. Mater. Chem. B.* **2016**, *4*, 6791. (e) Gandioso, A.; Bresolí-Obach, R.; Nin-Hill, A.; Bosch, M.; Palau, M.; Galindo, A.; Contreras, S.; Rovira, A.; Rovira, C.; Nonell, S.; Marchán, V. Redesigning the coumarin scaffold into small bright fluorophores with far-red to near-infrared emission and large Stokes shifts useful for cell imaging. *J. Org. Chem.* **2018**, *83*, 1185. (f) Wu, G.; Gao, Q.; Li, M.; Tang, X.; Lai, K. W. C.; Tong, Q. A ratiometric probe based on coumarin-quinoline for highly selective and sensitive detection of Zn^{2+} ions in living cells. *J. Photoch. Photobio. A.* **2018**, *355*, 487. (g) Wang, L.; Frei, M. S.; Salim, A.; Johnsson, K. Small-molecule fluorescent probes for live-cell

super-resolution microscopy. *J. Am. Chem. Soc.* **2019**, *141*, 2770. (h) Zhu, J.; Gao, Q.; Tong, Q.; Wu, G. Fluorescent probes based on benzothiazole-spiropyran derivatives for pH monitoring in vitro and in vivo. *Spectrochim. Acta. A.* **2020,** *225*, 117506.

(4) (a) Chen, J.; Liu, W.; Ma, J.; Xu, H.; Wu, J.; Tang, X.; Wang, P. Synthesis and properties of fluorescence dyes: tetracyclic pyrazolo [3, 4-b] pyridine-based coumarin chromophores with intramolecular charge transfer character. *J. Org. Chem.* **2012**, *77*, 3475. (b) Bonnet, C. S.; Caillé, F.; Pallier, A.; Morfin, J. F.; Petoud, S.; Suzenet, F.; Tóth, É. Mechanistic Studies of Gd^{3+}-Based MRI Contrast Agents for Zn^{2+} Detection: Towards Rational Design. *Chem. Eur. J.* **2014**, *20*, 10959. (c) Seferoğlu, Z.; Ihmels, H.; Şahin, E. Synthesis and photophysical properties of fluorescent arylstyrylimidazo [1, 2-a] pyridine-based donor-acceptor chromophores. *Dyes and Pigments*, **2015**, *113*, 465. (d) Wang, R. X.; Lai, X. J.; Qiu, G.; Liu, J. B. Research progress of reactive fluorescent probe based on ESIPT principle. *Chin. J. Org. Chem.* **2019**, *39*, 952. (e) Golden, J. H.; Facendola, J. W.; D. Sylvinson MR, Baez, C. Q.; Djurovich, P. I.; Thompson, M. E. Boron Dipyridylmethene (DIPYR) Dyes: Shedding Light on Pyridine-Based Chromophores. *J. Org. Chem.* **2017**, *82*, 7215.

(5) (a) Gong, J.; Li, Y. H.; Zhang, C. J.; Huang, J.; Sun, Q. A thiazolo [4, 5-b] pyridine-based fluorescent probe for detection of zinc ions and application for in vitro and in vivo bioimaging. *Talanta*, **2018**, *185*, 396. (b) Zhang, J.; Wang, H. Photophysical investigaions and the bioimaings of α-, β-, γ-pyridine-based terpyridine derivatives. *J. Mol. Struct.* **2018**, *1157*, 457.

(6) Jun, J. V.; Petersson, E. J.; Chenoweth, D. M. Rational design and facile synthesis of a highly tunable quinoline-based fluorescent small-molecule scaffold for live cell imaging. *J. Am. Chem. Soc.* **2018**, *140*, 9486.

(7) (a) Goetz, A. E.; Garg, N. K. Regioselective reactions of 3, 4-pyridynes enabled by the aryne distortion model. *Nat. Chem.* **2013**, *5*, 54. (b) Rivera, R. P.; Ehlers, P.; Ohlendorf, L.; Rodriguez, E. T.; Villinger, A.; Langer, P. Chemoselective Synthesis of Arylpyridines through Suzuki-Miyaura Cross-Coupling Reactions. *Eur. J. Org. Chem.* **2018**, *2018*, 990;

(8) (a) Young, I. S.; Glass, A. L.; Cravillion, T.; Han, C.; Zhang, H.; Gosselin, F. Palladium-catalyzed site-selective amidation of dichloroazines. *Org. Lett.* **2018**, *20*, 3902. (b) Dai, X.; Chen, Y.; Garrell, S.; Liu, H.; Zhang, L. K.; Palani, A.; Nargund, R. Ligand-dependent site-selective Suzuki cross-coupling of 3, 5-dichloropyridazines. *J. Org. Chem.* **2013**, *78*, 7758. (c) Rao, M. L.; Dhanorkar, R. J. Cross-coupling study of iodo/chloropyridines and 2-chloroquinoline with atom-economic triarylbismuth reagents under Pd-catalysis. *Tetrahedron*, **2015**, *71*, 338.

(9) (a) Dai, X.; Chen, Y.; Garrell, S.; Liu, H.; Zhang, L.-K.; Palani, A.; Hughes, G.; Nargund, R. Ligand-dependent site-selective Suzuki cross-coupling of 3, 5-dichloropyridazines. *J. Org. Chem.* **2013**, *78*, 7758. (b) Schroter, S.; Stock, C.; Bach, T. Regioselective cross-coupling reactions of polyhalogenated heterocycles. *Tetrahedron* **2005**, *61*, 2245. (c) Reddy, E. A.; Islam, A.; Mukkanti, K.; Bandameedi, V.; Bhowmik, D. R.; Pal, M. Regioselective alkynylation followed by Suzuki coupling of 2, 4-dichloroquinoline: Synthesis of 2-alkynyl-4-arylquinolines. *Beilstein J. Org. Chem.* **2009**, *5*, 32.

(10) (a) Legault, C. Y.; Garcia, Y.; Merlic, C. A.; Houk, K. N. Origin of regioselectivity in palladium-catalyzed cross-coupling reactions of polyhalogenated heterocycles. *J. Am. Chem. Soc.* **2007**, *129*, 12664. (b) Garcia, Y.; Schoenebeck, F.; Legault, C. Y.; Merlic, C. A.; Houk, K. N. Theoretical bond dissociation energies of halo-heterocycles: Trends and relationships to regioselectivity in palladium-catalyzed cross-coupling reactions. *J. Am. Chem. Soc.* **2009**, *131*, 6632.

(11) Tang, Q.; Zhao, Y.; Du, X.; Gong, P.; Guo, C. *Eur. J. Med. Chem.* **2013**, *69*, 77.

(12) O'Brien, C. J.; Kantchev, E. A. B.; Valente, C.; Hadei, N.; Chass, G. A.; Lough, A.; Hopkinson, A. C.; Organ, M. G. Easily Prepared Air-and Moisture-Stable Pd–NHC (NHC= N-Heterocyclic Carbene) Complexes: A Reliable, User-Friendly, Highly Active Palladium Precatalyst for the Suzuki–Miyaura Reaction. *Chem. Eur. J.* **2006**, *12*, 4743.

(13) Hansch, C.; Leo, A.; Taft, R. W. A survey of Hammett substituent constants and resonance and field parameters. *Chem. Rev.* **1991**, *91*, 165.

(14) Gurung, S. K.; Thapa, S.; Kafle, A.; Dickie, D. A.; Giri, R. Copper-Catalyzed Suzuki-Miyaura Coupling of Arylboronate Esters: Transmetalation with (PN) CuF and Identification of Intermediates. *Org. Lett.* **2014**, *16*, 1264.

(15) Gurung, S. K.; Thapa, S.; Vangala, A. S.; Giri, R. Copper-catalyzed Hiyama coupling of (hetero) aryltriethoxysilanes with (hetero) aryl iodides. *Org. Lett.* **2013**, *15*, 5378.

(16) Rao, M. L.; Dhanorkar, R. J. Cross-coupling study of iodo/chloropyridines and 2-chloroquinoline with atom-economic triarylbismuth reagents under Pd-catalysis. *Tetrahedron*, **2015***, 71*, 338.

(17) Thapa, S.; Basnet, P.; Gurung, S. K.; Giri, R. Copper-catalysed cross-coupling of arylzirconium reagents with aryl and heteroaryl iodides. *Chem. Commun.* **2015**, *51*, 4009.

(18) Ho, K. K.; Parnell, K. M.; Yuan, Y.; Xu, Y.; Kultgen, S. G.; Hamblin, S.; Kanner, S. B. Discovery of 4-phenyl-2-phenylaminopyridine based TNIK inhibitors. *Bioorg. Med. Chem. Lett.* 2013, 23, 569.

(19) Murata, K.; Araki, M.; Inagaki, A.; Akita, M. Syntheses, photophysical properties, and reactivities of novel bichromophoric Pd complexes composed of Ru (II)-polypyridyl and naphthyl moieties. *Dalton Transactions*, **2013**, *42*, 6989.

(20) Hino, K.; Kawashima, K.; Oka, M.; Nagal, Y.; Uno, H.; Matsumoto, J. I. A novel class of antiulcer agents. 4-Phenyl-2-(1-piperazinyl) quinolines. *Chem. Pharm. Bull.* **1989**, *37*, 110.

(21) Wei, Y.; Yoshikai, N. Modular pyridine synthesis from oximes and enals through synergistic copper/iminium catalysis. *J. Am. Chem. Soc.* **2013**, *135*, 3756.