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Graphical Abstract

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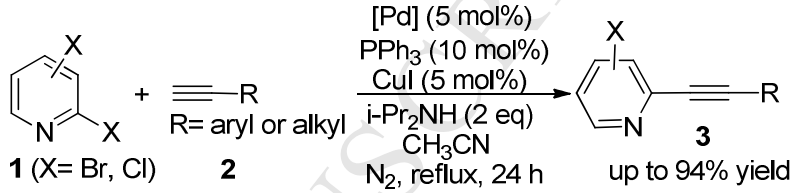

Pergamon

TETRAHEDRON

Palladium-Catalyzed Highly Regioselective 2-alkynylation of 2,x-Dihalopyridines

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Dedicated to Academician Xikui Jiang on the occasion of his 90th birthday and Professor Zhenchu Chen on the occasion of his 80th birthday

Abstract—2,4-Dibromopyridines reacted with arylacetylenes, catalyzed by $Pd(CF_3COO)_2$/CuI/PPh_3 in the presence of i-Pr_2NH in CH_3CN at reflux for 24 hours, to afford 2-alkynylpyridines in good to high yields, while 2,3- and 2,5-Dihalopyridines reacted with arylacetylenes, catalyzed by $Pd(OAc)_2$/CuI/PPh_3 in the presence of i-Pr_2NH in CH_3CN at reflux for 24 hours, to afford 2-alkynylpyridines in good to high yields.

1 Introduction

Pyridines are significant components of many drugs and natural products.[1-3] There are more than 15617 substituted 2-alkynylpyridines in database of SciFinder. Substituted 2-alkynylpyridines are found in a wide range of anti-inflamatory agents and antitumor agents,[4] and AMPA receptors, dopamine receptors, NMDA receptors and metabotropic glutamate receptors.[5] (Figure 1). Substituted 2-alkynylpyridines can be prepared by Sonogashira coupling from 2,x-dihalopyridines and alkynes using palladium catalysis. Nowadays, palladium catalysis catch so much attention in organic synthesis.[6] Previously, we have reported the copper-catalyzed highly regioselective 2-aryloxylation of 2,x-dihalopyridines,[7] and a highly regioselective and efficient palladium-catalyzed arylation of 2,x-dibromopyridines.[8] Herein, we describe a highly regioselective and efficient palladium-catalyzed 2-alkynylation of 2,x-dihalopyridines.

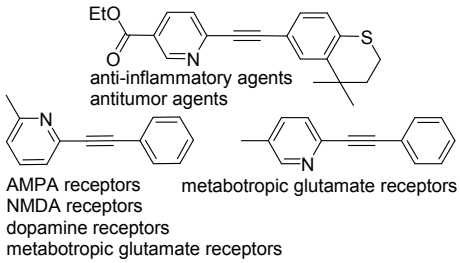


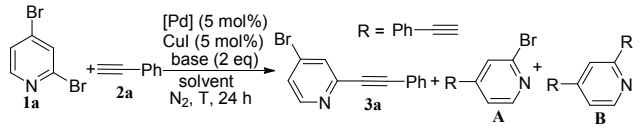
Figure 1. The substituted 2-pyridyl motif is found in many important small molecules.

2 Results and Discussion

First, a set of experiments was performed using 2,4-dibromopyridine and phenylacetylene as the model substrates in the presence of different ligands or bases in different temperatures to explore the optimized reaction conditions (Table 1). In DME with $PdCl_2(PPh_3)_2$ as catalyst and Et_3N as base, the reaction afforded **3a**, **A** and **B** in 50%, 6% and 0% isolated yields, respectively (entry 4), while in MeCN a better selectivity was achieved (entry 8). Encouraged by these results, we investigated different palladium catalysis system and found better selectivity can be achieved under conditions listed in entry 9. In MeCN/EtOH (2:1) at 50 ^oC, the three products were obtained in 80%, 2% and 0% yields, respectively (entry 18).

In the end, we thus established the optimized conditions for this reaction: $Pd(CF_3COO)_2$ /PPh_3 as the catalysis system, i-Pr_2NH as the base, CH_3CN as the solvent and at reflux.

Table 1: Palladium-catalyzed 2-alkynylation of 2,4-dibromopyridine with phenylacetylene: parametric study.[a,b]



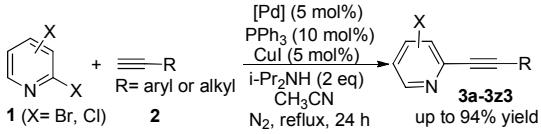
entry	catalyst	base	solvent	T/°C	Yield% (**3a**:**A:B**)
1	$PdCl_2(PPh_3)_2$	Et_3N	toluene	reflux	51:18: 0
2	$PdCl_2(PPh_3)_2$	Et_3N	dioxane	reflux	21: 10: 0
3	$PdCl_2(PPh_3)_2$	Et_3N	DMF	110	20: 21: 0
4	$PdCl_2(PPh_3)_2$	Et_3N	DME	reflux	50: 6: 0
5	$PdCl_2(PPh_3)_2$	Et_3N	$CHCl_3$	reflux	60: 5: 9
6	$PdCl_2(PPh_3)_2$	Et_3N	MeOH	reflux	59:12: 25
7	$PdCl_2(PPh_3)_2$	Et_3N	DMSO	110	46: 3: 12
8	$PdCl_2(PPh_3)_2$	Et_3N	CH_3CN	reflux	65: 7: 0
9	$Pd(OAc)_2/PPh_3$	Et_3N	CH_3CN	reflux	67: 2: 2
10	$PdCl_2/PPh_3$	Et_3N	CH_3CN	reflux	63: 6: 9
11	$Pd(OAc)_2/PPh_3$	i-Pr_2NH	CH_3CN	reflux	73: 4: 5
12	$Pd(OAc)_2/PPh_3$	K_2CO_3	CH_3CN	reflux	63: 6: 8
13	$Pd(OAc)_2/PPh_3$	Cs_2CO_3	CH_3CN	reflux	60: 6: 12
14	$Pd(OAc)_2/PPh_3$	K_3PO_4	CH_3CN	reflux	64: 4: 13
15	$Pd(OAc)_2/PPh_3$	KOAc	CH_3CN	reflux	61: 3: 11
16	$Pd(OAc)_2/PPh_3$	KOH	CH_3CN	reflux	40: 7: 4
17	$Pd(OAc)_2/PPh_3$	CsOAc	CH_3CN	reflux	39: 10: 5
18[c]	$Pd(OAc)_2/PPh_3$	i-Pr_2NH	CH_3CN	reflux	80: 2: 0
19	$Pd(OAc)_2/PPh_3$	i-Pr_2NH	CH_3CN	65	70: 2: 5
20	$Pd(OAc)_2/PPh_3$	i-Pr_2NH	CH_3CN	30	64: 0: 8
21	**$Pd(CF_3COO)_2$ /PPh_3**	**i-Pr_2NH**	**CH_3CN**	**reflux**	**84: 3: 0**

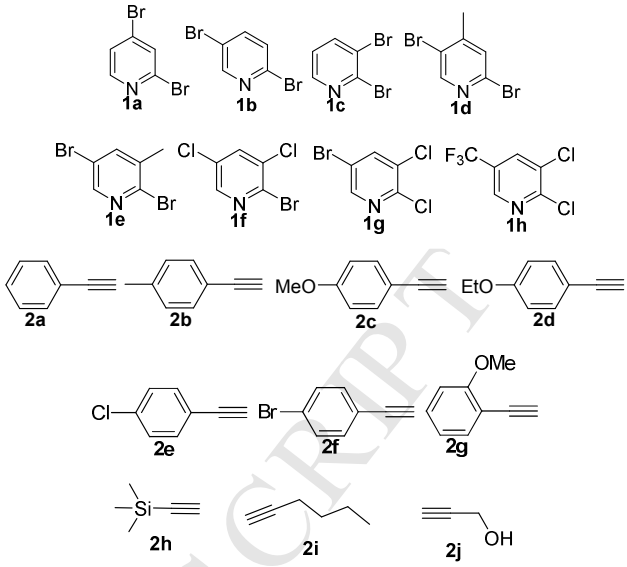
The bold signifies the best reaction condition.

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.6 mmol), [Pd] (5 mol%), ligand (10 mol%), CuI (5 mol%), base (1 mmol), 24h. [b] isolated yield. [c] **1a** (1 mmol), **2a** (0.5 mmol), [Pd] (5 mol%), ligand (10 mol%), CuI (5 mol%), base (1 mmol), 24h.

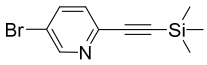
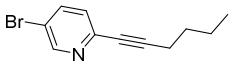
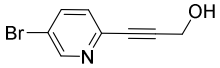
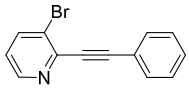
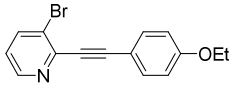
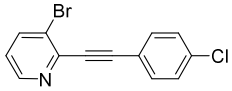
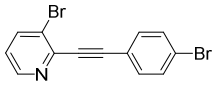
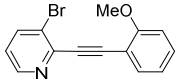
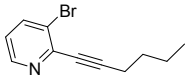
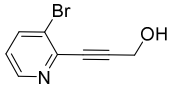
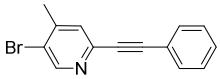
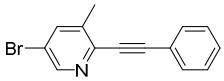
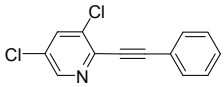
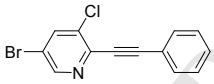
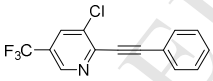
With the optimized reaction condition available, the scope of the reaction was then investigated (Table 2). It can be found that substituted phenylacetylenes generally afforded products (**3a–3g**, **3j-3n**, **3r-3v, 3y-3z3**) in good to high yields (74–94%). In contrast, trimethylsilyl-substituted acetylene, hexyne and propargyl alcohol gave mild yields (43-70%, **3h-3i**, **3o-3q**, **3w-3x**) due to low conversion. Clearly, the new methodology has the advantages of higher regioselectivity, higher yields, more generality, simpler and cheaper catalyst system.[9]

Table 2: Scope of Pd-catalyzed 2-alkynylation of 2,x-dihalopyridines. [a,b]





entry	**1**	**2**	Products	Yield (%)
1	**1a**	**2a**	**3a**	84
2	**1a**	**2b**	**3b**	80
3	**1a**	**2c**	**3c**	82
4	**1a**	**2d**	**3d**	81
5	**1a**	**2e**	**3e**	77
6	**1a**	**2f**	**3f**	74
7	**1a**	**2g**	**3g**	78
8[c]	**1a**	**2h**	**3h**	43
9[c]	**1a**	**2i**	**3i**	55
10[d]	**1b**	**2a**	**3j**	91
11[d]	**1b**	**2b**	**3k**	85
12[d]	**1b**	**2c**	**3l**	83
13[d]	**1b**	**2f**	**3m**	80
14[d]	**1b**	**2g**	**3n**	83

15 [c]	**1b**	**2h**		**3o**	52
16 [c]	**1b**	**2i**		**3p**	58
17 [c]	**1b**	**2j**		**3q**	61
18 [d]	**1c**	**2a**		**3r**	94
19 [d]	**1c**	**2d**		**3s**	85
20 [d]	**1c**	**2e**		**3t**	85
21 [d]	**1c**	**2f**		**3u**	81
22 [d]	**1c**	**2g**		**3v**	81
23 [c]	**1c**	**2i**		**3w**	68
24 [c]	**1c**	**2j**		**3x**	70
25 [d]	**1d**	**2a**		**3y**	90
26 [d]	**1e**	**2a**		**3z**	84
27 [d]	**1f**	**2a**		**3z1**	88
28 [d]	**1g**	**2a**		**3z2**	82
29 [d]	**1h**	**2a**		**3z3**	76

[a] Reaction conditions: dibromopyridine (1 mmol), phenylacetylene (0.5 mmol), $Pd(CF_3COO)_2$ (5 mol%), PPh_3 (10 mol%), CuI (5 mol%), i-Pr_2NH (1 mmol), CH_3CN, 24h. [b] Isolated yield. [c] dibromopyridine (0.5 mmol), phenylacetylene (0.75 mmol), $Pd(OAc)_2$ (5 mol%), PPh_3 (10 mol%), CuI (5 mol%), i-Pr_2NH (1 mmol), CH_3CN, 24h. [d] dibromopyridine (0.5 mmol), phenylacetylene (0.6 mmol), $Pd(OAc)_2$ (5 mol%), PPh_3 (10 mol%), CuI (5 mol%), i-Pr_2NH (1 mmol), CH_3CN, 24h.

Why the regioselectivity is so high for the alkynylation of 2,3-, 2,5- and 2,4-dihalopyridines? We can explain that the 2-halo of 2,x-dihalopyridines is more reactive than the 4-halo, 5-halo and 3-halo of 2,x-dihalopyridines.[7-12]

3 Conclusion

In summary, we have described a highly regioselective approach to halo-2-alkynylpyridines which involves palladium-catalyzed direct 2-alkynylation of 2,4-, 2,5-, and 2,3-dihalopyridines in high yields. Step-by-step coupling reaction of other dihalopyridines is being investigated and the results will be reported in due course.

4 Experimental Section

Typical procedure for the 2-alkynylation of 2,4-dibromopyridine: 2,4-dibromopyridine (237 mg, 1.0 mmol), phenylacetylene (51 mg, 0.5 mmol), i-Pr_2NH (101 mg, 1.0 mmol), $Pd(CF_3COO)_2$ (16.6 mg, 5 mol%), PPh_3 (26 mg, 10 mol%) and CuI (9.5 mg, 5 mol%) were dissolved in CH_3CN (5 mL). The reaction was stirred at reflux under nitrogen atmosphere for 24 h and then cooled. The solid was filtered off and the filtrate was concentrated. The crude product was then dissolved in CH_2Cl_2 (10 mL) and the solution was washed with brine (10 mL), and dried over sodium sulfate. Upon evaporation, the resulting residue was subjected to column chromatography (petroleum ether/AcOEt, 200:1) to give **3a** (108 mg, 84%) as a colorless liquid.

Typical procedure for the 2-alkynylation of 2,5- and 2,3-dihalopyridines: 2,5-dibromopyridine (119 mg, 0.50 mmol), phenylacetylene (61 mg, 0.6 mmol), i-Pr_2NH (101 mg, 1.0 mmol), $Pd(OAc)_2$ (11 mg, 5 mol%), PPh_3 (26 mg, 10 mol%) and CuI (9.5 mg, 5 mol%) were dissolved in CH_3CN/CH_3OH (2:1, 6 mL). The solution was stirred at reflux under nitrogen atmosphere for 24 h and then cooled and the solid was filtered off. The filtrate was then concentrated and the resulting crude product was dissolved in CH_2Cl_2 (10 mL). The solution was washed with brine (10 mL), and dried over sodium sulfate. Upon removal of the solvent with a rotavapor, the resulting residue was subjected to column chromatography (petroleum ether/AcOEt, 200:1) to give the desired product **3i** (117 mg, 91%) as a white solid.

(1) 4-bromo-2-(phenylethynyl)pyridine (**3a**)
3a: yellow liquid; ^1H NMR ($CDCl_3$, 400 MHz): 8.42 (d, J = 4 Hz, 1H), 7.71 (d, J = 4 Hz, 1H), 7.57-7.60 (m, 2H), 7.32-7.35 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): 150.4, 144.5, 132.7, 132.1, 130.2, 129.4, 128.5, 126.1, 121.8, 90.7, 87.5; HRMS (ESI) $[M+H]^+$ calcd for $C_{13}H_8BrN$: 257.9913, found: 257.9912.

(2) 2-bromo-5-(phenylethynyl)pyridine (**A**)
A: yellow solid, m.p. 49-50 °C; ^1H NMR ($CDCl_3$, 400 MHz): 8.35 (d, J = 4 Hz, 1H), 7.52-7.59 (m, 3H), 7.32-7.40 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): 149.9, 142.2, 134.1, 132.0, 129.7, 129.6, 128.6, 124.5, 121.6, 95.5, 85.3; HRMS (ESI) $[M+H]^+$ calcd for $C_{13}H_8BrN$: 257.9913, found: 257.9912.

(3) 2,4-di(phenylethynyl)pyridine (**B**)
B: yellow solid, m.p. 109-110 °C; ^1H NMR ($CDCl_3$, 400 MHz): 8.60 (d, J = 4 Hz, 1H), 7.53-7.64 (m, 5H), 7.31-7.37 (m, 7H); ^{13}C NMR ($CDCl_3$, 100 MHz): 150.1, 143.6, 132.1, 131.9, 129.4, 129.1, 128.9, 128.5, 128.4, 124.5, 122.1, 121.9, 94.7, 89.9, 88.2, 86.2; HRMS (ESI) $[M+H]^+$ calcd for $C_{21}H_{13}N$: 280.1121, found: 280.1120.

(4) 4-bromo-2-(4-methylphenylethynyl)pyridine (**3b**)
3b: yellow solid, m.p. 104-105 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 8.42 (d, *J* = 4 Hz, 1H), 7.70 (s, 1H), 7.49 (d, *J* = 8 Hz, 2H), 7.40 (dd, J_1 = 4 Hz, J_2 = 8 Hz, 1H) ,7.18 (d, *J* = 8 Hz 2H), 2.28 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 150.5, 144.7, 139.7, 132.6, 132.1, 130.1, 129.2, 125.9, 118.7, 91.0, 87.0, 21.6; HRMS (ESI) $[M+H]^+$ calcd for $C_{14}H_{10}BrN$: 272.0069, found: 272.0072.

(5) 4-bromo-2-(4-methyloxyphenylethynyl)pyridine (**3c**)
3c: yellow solid, m.p. 91-92 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 8.41 (d, *J* = 4 Hz, 1H), 7.68 (s, 1H), 7.54 (d, *J* = 8 Hz, 2H), 7.39 (dd, J_1 = 4 Hz, J_2 = 8 Hz, 1H), 6.89 (d, *J* = 8 Hz, 2H), 3.83 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 160.5, 150.5, 144.9, 133.8, 132.6, 129.9, 125.8, 114.2, 113.8, 91.1, 86.6, 55.3; HRMS (ESI) $[M+H]^+$ calcd for $C_{14}H_{10}BrNO$: 288.0019, found: 288.0028.

(6) 4-bromo-2-(4-ethyloxyphenylethynyl)pyridine (**3d**)
3d: yellow solid, m.p. 93-94 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 8.40 (d, *J* = 4 Hz, 1H), 7.67 (s, 1H), 7.50-7.53 (m, 2H), 7.38 (d, *J* = 4Hz, 1H), 6.86-6.89 (m, 2H), 4.05 (q, *J* = 8 Hz, 2H), 1.42 (t, *J* = 8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 159.9, 150.4, 144.9, 133.7, 132.6, 129.9, 125.7, 114.6, 113.6, 91.2, 86.5, 63.6, 14.7; HRMS (ESI) $[M+H]^+$ calcd for $C_{15}H_{13}BrNO$: 302.0175, found: 302.0170.

(7) 4-bromo-2-(4-chlorophenylethynyl)pyridine (**3e**)
3e: yellow solid, m.p. 105-106 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 8.43 (d, *J* = 4 Hz, 1H), 7.71 (s, 1H), 7.52 (d, *J* = 4 Hz, 2H), 7.43 (d, *J* = 4 Hz, 1H), 7.35 (d, *J* = 4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): 150.6, 144.2, 135.5, 133.3, 132.7, 130.2, 128.9, 126.3, 120.2, 89.4, 88.3; EI $[M]^+$ for $C_{13}H_7ClBrN$: 292.1; Anal. Calcd. for $C_{13}H_7ClBrN$: C 53.37; H 2.41; N 4.79; Found: C 53.55, H 2.48, N 4.77.

(8) 4-bromo-2-(4-bromophenylethynyl)pyridine (**3f**)
3f: yellow solid, m.p. 106-107 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 8.43 (d, *J* = 4 Hz, 1H), 7.71 (s, 1H), 7.51 (d, *J* = 8 Hz, 2H), 7.43-7.46 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 150.6, 144.2, 133.5, 132.7, 131.8, 130.2, 126.4, 123.9 120.7, 89.4, 88.4; HRMS (ESI) $[M+H]^+$ calcd for $C_{13}H_7Br_2N$: 337.9018, found: 337.9021.

(9) 4-bromo-2-(2-methyloxyphenylethynyl)pyridine (**3g**)
3g: yellow solid, m.p. 69-70 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 8.42 (d, *J* = 4 Hz, 1H), 7.73 (s, 1H), 7.55 (d, *J* = 8 Hz, 1H), 7.34-7.40 (m, 2H), 6.90-6.97 (m, 2H), 3.92 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 160.5, 150.5, 144.9, 134.1, 132.5, 130.9, 130.2, 125.9, 120.5, 111.1, 110.7, 91.7, 87.4, 55.8; HRMS (ESI) $[M+H]^+$ calcd for $C_{14}H_{10}BrNO$: 288.0019, found: 288.0017.

(10) 4-bromo-2-trimethylsilylethynyl pyridine (**3h**)
3h: yellow liquid; ^{1}H NMR ($CDCl_3$, 400 MHz): 8.38 (d, *J* = 4 Hz, 1H), 7.64 (s, 1H), 7.41 (d, *J* = 4 Hz, 1H), 0.26 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): 150.8, 144.5, 133.0, 130.8, 126.8, 102.7, 97.1, 0.0; HRMS (ESI) $[M+H]^+$ calcd for $C_{10}H_{12}BrNSi$: 253.9995, found: 253.9994.

(11) 4-bromo-2-(hexynyl)pyridine (**3i**)
3i: yellow liquid; ^{1}H NMR ($CDCl_3$, 400 MHz): 8.35 (d, *J* = 5.2 Hz, 1H), 7.55 (d, *J* = 1.6 Hz, 1H), 7.36 (dd, J_1 = 2.0 Hz, J_2 = 1.6 Hz, 1H), 2.45 (t, *J* = 7.2 Hz, 2H), 1.58-1.63 (m, 2H), 1.45-1.51 (m, 2H), 0.94 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 150.5, 145.3, 132.7, 130.1, 125.9, 93.1, 79.6, 30.5, 22.3, 19.2, 13.8; HRMS (ESI) $[M+H]^+$ calcd for $C_{11}H_{12}BrN$: 238.0231, found: 238.0226.

(12) 5-bromo-2-(phenylethynyl)pyridine (**3j**)
3j: yellow solid, m.p. 81-82 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 8.67 (d, *J* = 4 Hz, 1H), 7.81 (d, *J* = 8 Hz, 1H), 7.57-7.61 (m, 2H), 7.34-7.42 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): 151.2, 141.8, 138.9, 132.1, 129.2, 128.5, 128.1, 122.0, 120.0, 90.6, 87.7; HRMS (ESI) $[M+H]^+$ calcd for $C_{13}H_8BrN$: 257.9913, found: 257.9912.

(13) 5-bromo-2-(4-methylphenylethynyl)pyridine (**3k**)
3k: yellow solid, m.p. 153-154 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 8.66 (s, 1H), 7.80 (dd, J_1 = 4 Hz, J_2 = 8 Hz, 1H), 7.48 (d, *J* = 8 Hz, 2H), 7.39 (d, *J* = 8 Hz, 1H), 7.17 (d, *J* = 8 Hz, 2H), 2.37 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 151.2, 142.0, 139.6, 138.8, 132.0, 129.2, 128.0, 119.7, 118.9, 90.9, 87.2, 21.6; HRMS (ESI) $[M+H]^+$ calcd for $C_{14}H_{10}BrN$: 272.0069, found: 272.0065.

(14) 5-bromo-2-(4-methyloxyphenylethynyl)pyridine (**3l**)
3l: yellow solid, m.p. 140-141 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 8.51 (s, 1H), 7.70 (s, 1H), 7.78 (dd, J_1 = 4 Hz, J_2 = 8 Hz, 2H), 7.53 (d, *J* = 8 Hz, 1H), 6.89 (d, *J* = 8 Hz, 2H), 3.83 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 160.4, 151.1, 142.2, 138.8, 133.7, 127.8, 119.5, 114.2, 114.0, 90.9, 86.8, 55.3; HRMS (ESI) $[M+H]^+$ calcd for $C_{14}H_{10}BrNO$: 288.0019, found: 288.0018.

(15) 5-bromo-2-(4-bromophenylethynyl)pyridine (**3m**)
3m: yellow solid, m.p. 186-187 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 8.68 (d, *J* = 4Hz,, 1H), 7.82 (dd, J_1 = 4 Hz, J_2 = 8 Hz, 1H), 7.39-7.52 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): 151.3, 141.5, 138.9, 133.4, 131.8, 128.1, 123.7, 120.9, 120.2, 89.3, 88.8; HRMS (ESI) $[M+H]^+$ calcd for $C_{13}H_7Br_2N$: 355.9018, found: 355.9015.

(16) 5-bromo-2-(2-methyloxyphenylethynyl)pyridine (**3n**)
3n: yellow solid, m.p. 62-63 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 8.67 (d, *J* = 4 Hz, 1H), 7.91(d, *J* = 8 Hz, 1H), 7.55 (d, *J* = 8 Hz, 1H), 7.43 (d, *J* = 8 Hz, 1H), 7.33-7.35 (m, 1H), 6.90-6.96 (m, 2H), 3.29 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 160.5, 151.1, 142.1, 138.7, 134.0, 130.8, 128.1, 120.5, 119.7, 111.2, 110.7, 91.7, 87.3, 55.8; HRMS (ESI) $[M+H]^+$ calcd for $C_{14}H_{10}BrNO$: 288.0019, found: 288.0019.

(17) 5-bromo-2-trimethylsilylethynyl pyridine (**3o**)

3o: yellow solid, m.p. 46-47 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 8.55 (s, 1H), 7.70 (d, *J* = 8 Hz, 1H), 7.27 (d, *J*= 8 Hz, 1H), 0.20 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): 151.4, 141.8, 139.1, 128.6, 120.6, 103.0, 96.8, 0.0; HRMS (ESI) $[M+H]^+$ calcd for $C_{10}H_{12}BrNSi$: 253.9995, found: 253.9992.

(18) 5-bromo-2-(hexynyl)pyridine (**3p**)
3p: yellow liquid; ^{1}H NMR ($CDCl_3$, 400 MHz): 8.59 (d, *J* = 2.0 Hz, 1H), 7.74 (dd, J_1 = 2.4 Hz, J_2 = 2.0 Hz, 1H), 7.26 (d, *J* = 8.4 Hz, 1H), 2.43 (t, *J* = 7.2 Hz, 2H), 1.58-1.65 (m, 2H), 1.45-1.51 (m, 2H), 0.94 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 151.1, 142.6, 138.9, 128.0, 119.5, 92.8, 79.7, 30.5, 22.3, 19.3, 13.8; HRMS (ESI) $[M+H]^+$ calcd for $C_{11}H_{12}BrN$: 238.0231, found: 238.0226.

(19) 5-bromo-2-(hydroxypropynyl)pyridine (**3q**)
3q: yellow solid, m.p. 112-113 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 8.62 (d, *J* = 2.0 Hz, 1H), 7.80 (dd, J_1 = 2.4 Hz, J_2 = 2.4 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 4.52 (s, 2H), 3.74 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): 151.3, 141.3, 139.4, 128.3, 120.6, 89.8, 83.7, 51.3; HRMS (ESI) $[M+H]^+$ calcd for C_8H_6BrNO: 211.9711, found: 211.9706.

(20) 3-bromo-2-(phenylethynyl)pyridine (**3r**)
3r: yellow solid, m.p. 44-45 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 8.55 (d, *J* = 4Hz,, 1H), 7.92 (d, *J* = 8Hz, 1H), 7.62-7.67 (m, 2H), 7.35-7.39 (m, 3H), 7.12 (dd, J_1 = 4 Hz, J_2 = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): 148.3, 143.8, 139.8, 132.2, 129.4, 128.4, 123.9, 123.5, 122.0, 94.1, 87.5; HRMS (ESI) $[M+H]^+$ calcd for $C_{13}H_8BrN$: 257.9913, found: 257.9917.

(21) 3-bromo-2-(4-ethyloxyphenylethynyl)pyridine (**3s**)
3s: yellow solid, m.p. 92-93 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 8.53 (d, *J* = 4 Hz, 1H), 7.90 (d, *J* = 8 Hz, 1H), 7.57 (d, *J* = 8 Hz, 2H), 7.09 (dd, J_1 = 4 Hz, J_2 = 8 Hz, 1H), 6.88 (d, *J* = 8 Hz, 2H)，4.06 (q, *J* = 8 Hz, 2H), 1.42 (t, *J* = 8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 160.0, 148.2, 144.1, 139.7, 133.8, 123.5, 123.1, 114.6, 113.8, 94.7, 86.6, 63.6, 14.7; HRMS (ESI) $[M+H]^+$ calcd for $C_{15}H_{12}BrNO$: 302.0175, found: 302.0175.

(22) 3-bromo-2-(4-chlorophenylethynyl)pyridine (**3t**)
3t: yellow solid, m.p. 84-85 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 8.55 (d, *J* = 4 Hz, 1H), 7.93 (d, *J* = 4 Hz, 1H), 7.57 (d, *J* = 8Hz, 2H), 7.36 (d, *J* = 8 Hz, 2H), 7.35 (dd, J_1 = 4 Hz, J_2 = 4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): 148.3, 143.5, 139.9, 135.6, 133.4, 128.9, 123.9, 123.7, 120.5, 92.7, 88.3; EI $[M]^+$ for $C_{13}H_7ClBrN$: 291; Anal. calcd for $C_{13}H_7ClBrN$: C 53.37; H 2.41; N 4.79; Found: C, 53.34; H, 2.42; N, 4.74.

(23) 3-bromo-2-(4-bromophenylethynyl)pyridine (**3u**)
3u: yellow solid, m.p. 75-76 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 8.55 (d, *J* = 4 Hz, 1H), 7.93 (d, *J* = 8 Hz, 1H), 7.49-7.53 (m, 4H), 7.14 (dd, J_1 = 4 Hz, J_2 = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): 148.4, 143.5, 139.9, 133.5, 131.8, 123.9, 123.7, 120.9, 92.8, 88.4; HRMS (ESI) $[M+H]^+$ calcd for $C_{13}H_7Br_2N$: 355.9018, found: 355.9017.

(24) 3-bromo-2-(2-methyloxyphenylethynyl)pyridine (**3v**)
3v: yellow solid, m.p. 101-102 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 8.55 (d, *J* = 4 Hz, 1H), 7.91 (d, *J* = 4 Hz, 1H), 7.61 (d, *J* = 4 Hz, 1H), 7.36 (t, *J* = 4 Hz, 1H), 7.10 (dd, J_1 = 4 Hz, J_2 = 8 Hz, 1H), 6.91-6.97 (m, 2H), 3.92 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 160.8, 148.2, 144.1, 139.8, 134.1, 130.9, 123.6, 123.3, 120.5, 111.3, 110.9, 91.4, 90.9, 55.9; HRMS (ESI) $[M+H]^+$ calcd for $C_{14}H_{11}BrNO$: 288.0019, found: 288.0020.

(25) 3-bromo-2-(hexynyl)pyridine (**3w**)
3w: yellow liquid; ^{1}H NMR ($CDCl_3$, 400 MHz): 8.47 (dd, J_1 = 1.6 Hz, J_2 = 1.2 Hz, 1H), 7.87 (dd, J_1 = 1.6 Hz, J_2 = 1.2 Hz, 1H), 7.07 (q, *J* = 4.8 Hz, 1H), 2.52 (t, *J* = 6.8 Hz, 2H), 1.62-1.69 (m, 2H), 1.50-1.58 (m, 2H), 0.95 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 148.3, 144.3, 139.9, 123.6, 123.3, 96.7, 79.5, 30.4, 22.2, 19.4, 13.8; HRMS (ESI) $[M+H]^+$ calcd for $C_{11}H_{12}BrN$: 238.0232, found: 238.0226.

(26) 3-bromo-2-(hydroxypropynyl)pyridine (**3x**)
3x: yellow solid, m.p. 106-107 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 8.51 (dd, J_1 = 1.2 Hz, J_2 = 1.6 Hz, 1H), 7.91 (dd, J_1 = 1.2 Hz, J_2 = 1.2 Hz, 1H), 7.14 (dd, J_1 = 4.4 Hz, J_2 = 4.8 Hz, 1H), 4.60 (s, 2H), 3.83 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): 148.3, 143.3, 140.4, 124.2, 123.8, 93.3, 83.3, 51.4; HRMS (ESI) $[M+H]^+$ calcd for C_8H_6BrNO: 211.9711, found: 211.9706.

(27) 5-bromo-4-methyl-2-(phenylethynyl)pyridine (**3y**)
3y: yellow solid, m.p. 59-60 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 8.63 (s, 1H), 7.57-7.60 (m, 2H), 7.34-7.41 (m, 4H), 2.40 (s, 3H), ^{13}C NMR ($CDCl_3$, 100 MHz): 151.6 147.2, 141.9, 132.0, 129.1, 129.0, 128.4, 122.8, 122.1, 90.0, 87.9, 22.1; HRMS (ESI) $[M+H]^+$ calcd for $C_{14}H_{10}BrN$: 272.0069, found: 272.0069.

(28) 5-bromo-3-methyl-2-(phenylethynyl)pyridine (**3z**)
3z: yellow solid, m.p. 89-90 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): ^{1}H NMR ($CDCl_3$, 400 MHz): 8.65 (s, 1H), 7.70 (s, 1H), 7.58-7.61 (m, 2H), 7.34-7.38 (m, 3H), 2.50 (s, 3H), ^{13}C NMR ($CDCl_3$, 100 MHz): 148.4, 141.6, 139.4,137.5, 132.0, 129.2, 128.5, 122.2, 119.6, 94.3, 86.7, 19.3; HRMS (ESI) $[M+H]^+$ calcd for $C_{14}H_{10}BrN$: 272.0069, found: 272.0070.

(29) 3,5-dichloro-2-(phenylethynyl)pyridine (**3z1**)
3z1: yellow solid, m.p. 82-83 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 8.43 (d, *J* = 4Hz,, 1H), 7.87 (s, 1H), 7.55-7.57 (m, 2H), 7.28-7.36 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 146.3, 140.8, 138.2, 131.2, 129.8, 128.6, 127.5, 122.5, 120.7, 94.1, 85.6; HRMS (ESI) $[M+H]^+$ calcd for $C_{13}H_8Cl_2N$: 248.0028, found: 248.0030.

(30) 3-chloro-5-bromo-2-(phenylethynyl) pyridine (**3z2**)

3z2: yellow solid, m.p. 93-94 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 8.47 (d, J = 4 Hz, 1H), 7.78 (d, J = 4 Hz, 1H), 7.63 (dd, J_1 = 4 Hz, J_2 = 8 Hz, 2H), 7.35-7.43 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 146.9, 140.2, 136.2, 134.2, 132.2, 130.9, 129.6, 128.5, 121.7, 95.8, 85.1; HRMS (ESI) $[M+H]^+$ calcd for $C_{13}H_8BrClN$: 291.9523, found: 291.9523.

(31) 3-chloro-5-trifluoromethyl-2-(phenylethynyl)pyridine (**3z3**)

3z3: yellow solid, m.p. 76-77 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 8.76 (d, J = 4 Hz, 1H), 7.99 (s, 1H), 7.65-7.68 (m ,2H), 7.38-7.46 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 145.5, 144.5, 134.1, 133.8, 132.5, 130.0, 128.6, 126.0 (q, J = 30 Hz), 122.6 (q, J = 270 Hz), 121.2, 97.6, 85.3; HRMS (ESI) $[M+H]^+$ calcd for $C_{14}H_8ClF_3N$: 282.0292, found: 282.0292.

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