Copper- and Ligand-free Heteroannulation of *o*-Halohydroxypyridine with Terminal Alkynes Using Pd/C Catalyst: One-Pot Synthesis of 2-Substituted Furopyridines and their Functionalization

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Three types of isomeric 2-substituted furo[3,2-*b*]pyridine, furo[2,3-*b*]pyridine and furo[3,2-*c*]pyridine were prepared using Pd/C-catalyzed heteroannulation of *o*-halopyridinols and terminal alkynes under copper- and ligand-free conditions. We also demonstrated that double functionalization yielding 2,3-disubstituted furopyridines could be achieved through heteroannulation followed by bromination and Suzuki/Heck reactions. In addition, the use of recoverable Pd/C in the absence of a cocatalyst and ligand can aid in the development of greener chemical processes.

Keywords: Heteroannulation, Furopyridine, Pd/C, Terminal alkyne, Copper- and ligand free

Introduction

Furopyridines represent useful scaffolds in a variety of therapeutic areas, functioning as antivirals against herpes simplex virus type-1,[1] cannabinoid-1 receptor inverse agonists,[2] antibiotics,[3] protein kinase inhibitors,[4] and gastric H^+/K^+-ATPase inhibitors.[5] Furopyridines, consisting of an electron-rich furan ring fused to an electron-deficient pyridine ring, form six possible structural isomers depending on the combination mode of the two heterocycles. Isomers of these fused aromatic heterocycles have attracted much interest as pharmacophore units due to their characteristic chemical properties and their structural similarity to important moieties in many biologically active compounds such as benzofuran, azaindole, benzothiophene, and quinolone.[6] These furopyridine derivatives, rarely found in nature, are prepared using two general strategies. One approach is the formation of the pyridine ring through electrophilic cyclization of the carbon in the preformed furan skeleton catalyzed by a strong acid. The other is the formation of the furan ring from the preformed pyridine derivative,[7] which has been recently utilized for synthetic methods such as aryl(alkynyl)iodonium salts,[8] gold-catalyzed tandem reaction,[9] and palladium-catalyzed reaction to develop a general and versatile furopyridine derivative.[10] In previous studies, the majority of 2-, 3-, and 2,3-substituted furopyridines were prepared through palladium-catalyzed cyclization of iodopyridinyl allyl ethers,[11] iodonium-promoted 5-endo intramolecular cyclization,[12] and intermolecular palladium-catalyzed coupling of aryl halides with terminal alkynes.[13] Although typical examples of Sonogashira couplings have employed homogeneous palladium catalysts together with copper(I) cocatalyst, base, and ligand, many variations in reaction conditions have been documented. In recent years, heterogeneous palladium catalysts with diverse solid supports such as metal oxide, silica, and carbon have been used in organic reactions.[14] Among these, Pd/C is a facile and efficient alternative to conventional homogeneous conditions.[15] However, there are only a few reports on its use as a catalyst for Sonogashira coupling of aryl halides and terminal alkynes without any cocatalyst, such as copper(I) iodide.

As a part of our continuing organometallic studies on diversification of nitrogen-containing, biologically active heterocycles such as indole, azaindole, furopyridine, pyrroloquinoline, carbazole, and thiazole,[16] the present study was performed to develop green and practical methods of furopyridine synthesis. Here, we report a one-pot heteroannulation for 2-substituted furopyridines such as furo[3,2-*b*]-, furo[2,3-*b*]-, and furo[3,2-*c*]pyridine starting from *o*-halohydroxypyridines and terminal alkynes catalyzed by commercial Pd/C under copper- and ligand-free conditions. We also demonstrate that double functionalization can be performed on furopyridine, thereby affording 2,3-disubstituted furopyridines through heteroannulation followed by bromination and Suzuki/Heck reactions.

Results and Discussion

o-Hydroxyalkynyl substituents can cyclize spontaneously to form furan rings.[13h,17] Recently, we exploited this phenomenon to prepare fused heterocycles of 2-substituted benzofurans from *o*-iodophenols and terminal alkynes catalyzed by palladium supported on nanosized carbon balls under copper- and ligand-free conditions.[16f] As an extension of this work, we attempted to prepare furopyridines by reacting

2-bromo-3-hydroxypyridine, 3-bromo-2-hydroxypyridine, and 4-hydroxy-3-iodopyridine, respectively, with terminal alkynes. For this purpose, Pd/C was used to develop a greener and more practical synthesis protocol. First, optimization studies for **2a** by varying the palladium catalysts, solvents, and temperatures were performed (Table 1) with LiCl as an additive for the stabilization of palladium intermediates. Under our reaction conditions in the presence of both LiCl and $CsCO_3$, the yields were highly dependent on the solvents (entries 1 and 3, Table 1), catalysts (entries 1, 7–10, Table 1), and temperatures (entries 1, 4, and 5, Table 1). An interesting observation was that different loading amounts of Pd did not influence yields at 110 °C (entries 5 and 6, Table 1). The best reaction condition was achieved when DMF and commercial 5% Pd/C were used at 150 °C (entry 1, Table 1).

Next, we extended the scope of this protocol to the synthesis of **2a–e** from the reactions of 2-bromo-3-hydroxypyridine and **1a–e** (Table 2).

Heteroannulation of **1a–e** and 2-bromo-3-hydroxypyridine (Table 2) proceeded smoothly to afford **2a–e** in excellent (95%) to average yields (52%). We also observed that aliphatic alkynes gave yields (95–52%) comparable to those of phenylacetylene (82%). Considering that most previous reports have used homogeneous catalysts such as $PdCl_2(PPh_3)_2$ and CuI as a cocatalyst in the Sonogashra coupling reactions, the results (Table 2) obtained under copper- and ligand-free conditions (particularly using reusable heterogeneous Pd/C catalyst) provided another example of a greener approach. We also prepared **3** based on our present protocol. For the heterogeneous Pd/C-based catalysis, we performed annulation of 3-bromo-2-hydroxypyridine with **1** (Table 3).

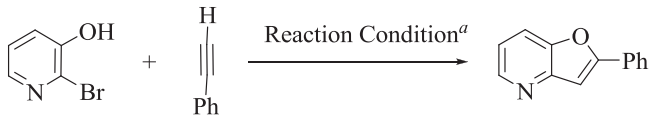
Preparation of **3** resulted in somewhat lower yields (70–48%) (Table 3) compared to those obtained for **2** (Table 2).

Following the same protocol, **4** was prepared in moderate yields from 4-hydroxy-3-iodopyridine and **1** (Table 4). Lactam–lactim tautomerism may be the cause of the relatively low yields obtained for both **3** (Table 3) and **4** (Table 4). That is, 3-bromo-2-hydroxypyridine (Table 3) and 4-hydroxy-3-iodopyridine (Table 4) likely exist as 2- and 4-pyridones, predominantly exerting lower nucleophilicity for cyclization. Recently, the Fort group published successive regioselective metalation with furopyridines for the polyfunctionalization of furopyridines.[18] Based on their results, we performed functionalizations at position 3 in furo[3,2-*b*]pyridines to synthesize 2,3-disubstituted furopyridines, which we could not synthesize using our heteroannulation with internal alkynes. Considering Suzuki and Heck reactions, **5a** and **b** were chosen as substrates, and bromination was performed using 1.5 equiv NBS/CH_2Cl_2 for 12 h at room temperature. Table 5 summarizes the results of Suzuki and Heck reactions of **5a** and **b,** respectively.

Yields of the Suzuki reactions (entries 1–9, Table 5) ranged from good to average and were not sensitive to substituents, while yields of Heck reactions were relatively low (entries 10–11, Table 5). Overall, functionalization reactions of **5** were able to make 2,3-disubstituted furo[3,2-*b*]pyridine **6**.

This study was designed partly to develop a greener approach, *i.e.*, recovery and reuse of the heterogeneous Pd/C catalyst. To accomplish this, the Pd/C catalyst was recovered using a membrane filter, washed with methylene chloride, and reused in the one-pot heteroannulation for **2a** (Table 6).[16f] The results indicate that the catalyst can be reused several times, although the yields gradually decrease.

Table 1. Optimization studies for Pd/C-catalyzed synthesis of 2-phenylfuro[3,2-*b*]pyridines (**2a**).

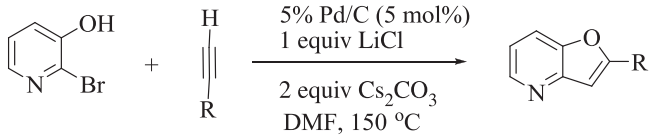


1a **2a**

Entry[a]	Halide source	Base	Solvent	5 mol% Pd source	Temp (°C)	Reaction time (h)	Yields[b] (%)
1	LiCl	Cs_2CO_3	DMF	5% Pd/C	150	16	82
2	LiCl	Cs_2CO_3	DMA	5% Pd/C	150	16	77
3	LiCl	Cs_2CO_3	NMP	5% Pd/C	150	16	52
4	LiCl	Cs_2CO_3	DMF	5% Pd/C	130	16	62
5	LiCl	Cs_2CO_3	DMF	5% Pd/C	110	16	52
6	LiCl	Cs_2CO_3	DMF	10% Pd/C	110	16	53
7	LiCl	Cs_2CO_3	DMF	$Pd(PPh_3)_4$	150	16	62
8	LiCl	Cs_2CO_3	DMF	$Pd(OAc)_2$	150	16	39
9	LiCl	Cs_2CO_3	DMF	$PdCl_2$	150	16	41
10	LiCl	Cs_2CO_3	DMF	$PdCl_2(PPh_3)_2$	150	16	73

[a] All reactions were performed at the 0.5 mmol scale.
[b] Isolated yields.

Table 2. One-pot synthesis of furo[3,2-*b*]pyridines **2a–e**.

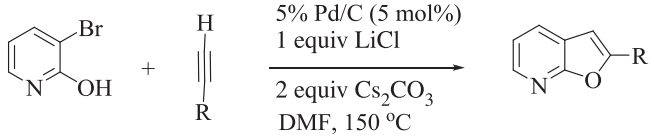


1a–1e **2a–2e**

	Alkyne[b]			Product		
Entry[a]	**1**	R	Reaction time (h)	**2**	R	Yields[c] (%)
1	**a**	C_6H_5	16	**a**	C_6H_5	82
2	**b**	$CH_2CH_2CH_3$	18	**b**	$CH_2CH_2CH_3$	95
3	**c**	$CH_2CH_2CH_2CH_3$	18	**c**	$CH_2CH_2CH_2CH_3$	66
4	**d**	$CH_2CH_2CH_2OH$	20	**d**	$CH_2CH_2CH_2OH$	62
5	**e**	$CH_2CH_2CH_2CH_2OH$	20	**e**	$CH_2CH_2CH_2CH_2OH$	52

[a] All reactions were performed at the 0.5 mmol scale.
[b] 2 equiv.
[c] Isolated yields.

Table 3. One-pot synthesis of furo[2,3-*b*]pyridines.



1 **3**

	Alkyne[b]			Product		
Entry[a]	**1**	R	Reaction time (h)	**3**	R	Yields[c] (%)
1	**a**	C_6H_5	16	**a**	C_6H_5	61
2	**c**	$CH_2CH_2CH_2CH_3$	18	**c**	$CH_2CH_2CH_2CH_3$	70
3	**d**	$CH_2CH_2CH_2OH$	22	**d**	$CH_2CH_2CH_2OH$	48
4	**e**	$CH_2CH_2CH_2CH_2OH$	22	**e**	$CH_2CH_2CH_2CH_2OH$	53

[a] All reactions were performed at the 0.5 mmol scale.
[b] 2 equiv.
[c] Isolated yields.

Conclusions

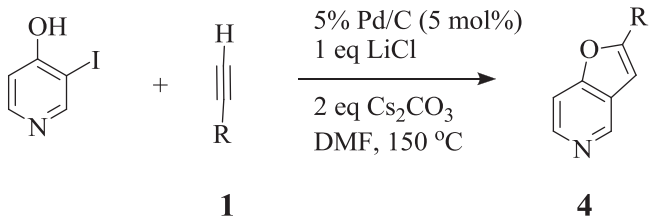
We synthesized diverse 2-substituted isomeric furopyridines such as furo[3,2-*b*]pyridines **2**, furo[2,3-*b*] pyridines **3** and furo[3,2-*c*]pyridines **4** using a one-pot procedure starting from *o*-halopyridinol and various terminal alkynes under much greener reaction conditions, *i.e.*, catalyzed by commercially available Pd/C under copper- and ligand-free conditions. The Pd/C catalyst could be reused more than five times during the same heteroannulation process while still affording acceptable yields. We also demonstrated that diversification could be achieved at the 3-position in furopyridines **5** using Suzuki and Heck coupling reactions, providing 2,3-disubstituted furopyridines **6**. The present protocol provides not only a synthetic methodology for biologically important scaffolds but can also be used for the development of greener chemical processes.

Experimental Section

General. ^1H and ^{13}C NMR spectra were recorded on a JEOL JNM-AL400 spectrometer (400 MHz for ^1H and 100 MHz for ^{13}C) using $CDCl_3$ as the solvent and tetramethylsilane as internal standard. Chemical shifts are quoted in parts per million and *J* values are given in hertz. The GC–MS spectra were obtained using a Shimadzu QP 1000 GC-MS instrument. Elemental analyses were carried out using Thermo Fisher Scientific (EA 1112). Melting points were obtained (uncorrected) on a Thermo Scientific Electrothermal 9100 melting point apparatus and were uncorrected. All chemicals were used as received without any further purification.

Reagents. All reagents such as 3-bromo-2-hydroxypyridine, 2-bromo-3-hydroxypyridine, and alkynes were commercially available and were used without further purifications.

Table 4. One-pot synthesis of furo[3,2-*c*]pyridines **4**.

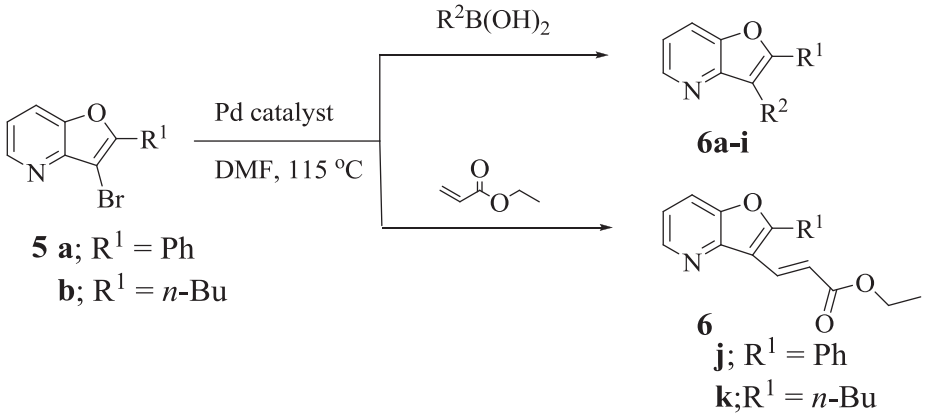


1 **4**

Entry[a]	Alkyne[b] **1**	R	Reaction time (h)	Product **4**	R	Yields[c] (%)
1	**a**	C_6H_5	16	**a**	C_6H_5	68
2	**c**	$CH_2CH_2CH_2CH_3$	18	**c**	$CH_2CH_2CH_2CH_3$	60
3	**d**	$CH_2CH_2CH_2OH$	20	**d**	$CH_2CH_2CH_2OH$	56
4	**e**	$CH_2CH_2CH_2CH_2OH$	20	**e**	$CH_2CH_2CH_2CH_2OH$	62

[a] All reactions were performed at a 0.5 mmol scale.
[b] 2 equiv.
[c] Isolated yields.

Table 5. Functionalization of **5** using Suzuki[a] and Heck[b] reactions.



5 **a**; R^1 = Ph
b; R^1 = *n*-Bu

Entry	Reagent R^2	Substrate **5**	Product R^1	R^2	**6**	Yields (%)
1	Ph	**a**	Ph	Ph	**a**	69
2	2-MeOPh	**a**	Ph	2-MeOPh	**b**	52
3	4-$MeSO_2$Ph	**a**	Ph	4-$MeSO_2$Ph	**c**	56
4	4-F_3CPh	**a**	Ph	4-CF_3CPh	**d**	60
5	2-MeOPy-3-yl	**a**	Ph	2-MeOPy-3-yl	**e**	62
6	3-NCPh	**a**	Ph	3-NCPh	**f**	70
7	Ph	**b**	*n*-Bu	Ph	**g**	65
8	4-F_3CPh	**b**	*n*-Bu	4-F_3CPh	**h**	71
9	3-NCPh	**b**	*n*-Bu	3-NCPh	**i**	73
10	Ethylacrylate	**a**	Ph	—	**j**	68
11	Ethylacrylate	**b**	*n*-Bu	—	**k**	58

[a] For the Suzuki reaction, 3 mol% $Pd(PPh_3)_4$, EtOH, and Na_2CO_3 were mixed for 24 h.
[b] For Heck reactions, 5 mol% $Pd(OAc)_2$, 2 equiv Cs_2CO_3, and 1 equiv LiCl were mixed for 30 h.

Table 6. Synthesis of **2a** using recovered Pd/C.

Entry	Recycling	Reaction time (h)	Isolated yield (%)
1	Fresh	16	82
2	First	16	76
3	Second	20	72
4	Third	20	65
5	Fourth	24	57

Palladium (5 wt%) on carbon (5% Pd/C) was available from Aldrich (205680). Column and thin-layer chromatography were performed on Merck silica gel 230–400 mesh and 60 PF_{254} respectively.

General Procedure for the Preparation of Furopyridines. In a pressure tube, a suspension of 5% Pd/C (5 mol%), 2-bromo-3-hydroxypyridine (0.5 mmol), LiCl (0.5 mmol), cesium carbonate (1 mmol), and terminal alkyne (1.0 mmol) in DMF (3 mL) was stirred for designated period at 150 °C. The reaction mixture was filtered, and neutralized with saturated NH_4Cl solution, followed by extraction with ethyl acetate. The crude product was purified by column chromatography with the use of hexane and ethyl acetate as eluents.

The following compounds were prepared with above described general procedure.

2-Phenylfuro[3,2-*b*]pyridine (2a):[19a,c] The product was obtained as a pale yellow powder (82%) from 2-bromo-3-hydroxypyridine and phenylacetylene after 16 h of reaction; m.p. 90–91 °C (lit. m.p. 87–90 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (dd, *J* = 4.8, 3.4 Hz, 1H), 7.36–7.44 (m, 4H), 7.76 (d, *J* = 8.4 Hz, 1H), 7.84 (d, *J* = 7.0 Hz, 2H), 8.46 (d, *J* = 4.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 111.6, 118.2, 122.1, 127.5, 128.8, 129.3, 130.8, 137.0, 145.7, 148.1, 154.0; MS (EI) *m/z* 195 ([M]$^+$, 100), 117 (34); calcd for $C_{13}H_9NO$: C, 80.00; H, 4.61; N, 7.18; found: C, 80.15; H, 4.59; N, 7.13.

2-Propylfuro[3,2-*b*]pyridine (2b):[19b] The product was obtained as a pale yellow oil (95%) yield from 2-bromo-3-hydroxypyridine and 1-pentyne after 18 h of reaction; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (t, *J* = 7.4 Hz, 3H), 1.71 (m, 2H), 2.7 (t, *J* = 6.8 Hz, 2H), 6.55 (s, 1H), 7.04 (dd, *J* = 8.2, 4.8 Hz, 1H), 7.57 (d, *J* = 8.2 Hz, 1H), 8.37 (dd, *J* = 8.2, 4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.3, 22.4, 36.8, 94.8, 118.4, 122.0, 142.7, 144.3, 148.1, 155.5; MS (EI) *m/z* 161 ([M]$^+$, 100), 115 (31); calcd for $C_{10}H_{11}NO$: C, 74.53; H, 6.83; N, 8.70; found: C, 74.60; H, 6.79; N, 8.65.

2-Butylfuro[3,2-*b*]pyridine (2c):[19b] The product was obtained as a pale yellow oil (66%) from 2-bromo-3-hydroxypyridine and 1-hexyne after 18 h of reaction; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, *J* = 7.4 Hz, 3H), 1.35 (m, 2H), 1.69 (m, 2H), 2.76 (t, *J* = 7.8 Hz, 2H), 6.62 (s, 1H), 7.12 (dd, *J* = 8.2, 5.0 Hz, 1H), 7.65 (d, *J* = 8.2 Hz, 1H), 8.39 (d, *J* = 4.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.2, 20.1, 31.7, 34.8, 97.1, 118.4, 122.0, 142.7, 144.6, 147.1, 155.7; MS (EI) *m/z* 175 ([M]$^+$, 100), 117 (45); calcd for $C_{11}H_{13}NO$: C, 75.43; H, 7.43; N, 8.00; found: C, 75.61; H, 7.53; N, 7.95.

2-(3-Hydroxypropyl)furo[3,2-*b*]pyridine (2d): The product was obtained as a colorless oil (62%) from 2-bromo-3-hydroxypyridine and 4-pentyn-1-ol after 20 h of reaction; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.26 (m, 2H), 2.73 (t, *J* = 7.4 Hz, 2H), 3.56 (t, *J* = 7.4 Hz, 2H), 6.75 (s, 1H), 7.26 (dd, *J* = 5.2, 2.0 Hz, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 8.43 (d, *J* = 4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.1, 31.7, 60.3, 97.1, 118.0, 122.1, 142.6, 144.5, 147.3, 155.0; MS (EI) *m/z* 177 ([M]$^+$, 100), 118 (22); calcd for $C_{10}H_{11}NO_2$: C, 67.80; H, 6.21; N, 7.91; found: C, 67.87; H, 6.23; N, 7.85.

2-(4-Hydroxybuty)furo[3,2-*b*]pyridine (2e): The product was obtained as a colorless oil (52%) from 2-bromo-3-hydroxypyridine and 5-hexyn-1-ol after 20 h of reaction; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.62 (m, 2H), 1.83 (m, 2H), 2.85 (t, *J* = 7.4 Hz, 2H), 3.64 (t, *J* = 6.4 Hz, 2H), 6.79 (s, 1H), 7.24 (dd, *J* = 5.2, 2.0 Hz, 1H), 7.79 (d, *J* = 8.2 Hz, 1H), 8.42 (d, *J* = 5.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.5, 29.5, 34.2, 62.1, 97.1, 118.8, 122.0, 142.7, 144.0, 146.6, 155.2; MS (EI) *m/z* 191 ([M]$^+$, 100), 131 (22); calcd for $C_{11}H_{13}NO_2$: C, 69.11; H, 6.81; N, 7.33; found: C, 69.01; H, 6.83; N, 7.25.

2-Phenylfuro[2,3-*b*]pyridine (3a):[19b,c] The product was obtained as a white powder (61%) from 3-bromo-2-hydroxypyridine and phenylacetylene after 16 h of reaction; m.p. 88–89 °C (lit. m.p. 90–91 °C); ^{1}H NMR (400 MHz, $CDCl_3$,) δ 7.01 (s, 1H), 7.21 (dd, *J* = 7.6, 4.8 Hz, 1H), 7.40 (d, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.2 Hz, 2H), 7.88–7.92 (m, 3H), 8.29 (dd, *J* = 4.8, 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 100.0, 119.5, 121.5, 125.2, 128.9, 129.3, 129.5, 129.6, 143.9, 155.7, 161.9; MS (EI) *m/z* 196 (M$^+$, 100), 197 (M + 1, 12); calcd for $C_{13}H_9NO$: C, 80.00; H, 4.61; N, 7.18; found: C, 80.18; H, 4.58; N, 7.12.

2-Butylfuro[2,3-*b*]pyridine (3b): The product was obtained as a colorless oil (70%) from 3-bromo-2-hydroxypyridine and 1-hexyne after 18 h of reaction; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (t, *J* = 7.4 Hz, 3H), 1.41 (m, 2H), 1.75 (m, 2H), 2.79 (t, *J* = 7.4 Hz, 2H), 6.37 (s, 1H), 7.14 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.78 (dd, *J* = 7.6, 1.8 Hz, 1H), 8.21 (dd, *J* = 5.0, 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 22.2, 28.3, 29.4, 100.9, 118.9, 121.1, 128.7, 142.7, 159.8, 161.9; MS (EI) *m/z* 175 (M$^+$, 100), 190 (40), 124 (10); calcd for $C_{11}H_{13}NO$: C, 75.43; H, 7.43; N, 8.00; found: C, 75.52; H, 7.38; N, 7.93.

2-(3-Hydroxypropyl)furo[2,3-*b*]pyridine (3c): The product was obtained as a pale yellow oil (53%) from 3-bromo-2-hydroxypyridine and 4-pentyn-1-ol after 22 h of reaction; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.99–2.08 (m, 2H), 2.93 (t, *J* = 7.4 Hz, 2H), 3.76 (t, *J* = 6.2 Hz, 2H), 5.4 (s, 1H), 6.43 (s, 1H), 7.80 (d, *J* = 7.6 Hz, 1H), 8.22 (d, *J* = 3.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.0, 30.3, 61.8, 101.4, 119.1, 121.0, 128.9, 142.9, 158.9; MS (EI) *m/z* 177 (M$^+$, 50), 159 (85), 132 (100), 83 (45); calcd for $C_{10}H_{11}NO_2$: C, 67.80; H, 6.21; N, 7.91; found: C, 67.75; H, 6.18; N, 7.93.

4-(Hydroxybutyl)furo[2,3-*b*]pyridine (3d): The product was obtained as a pale yellow oil (48%) from 3-bromo-2-hydroxypyridine and 5-hexyn-1-ol after 22 h of reaction; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.69 (m, 2H), 1.90 (m, 2H), 2.85 (t, *J* = 7.2 Hz, 2H), 3.71 (t, *J* = 6.4 Hz, 2H), 6.41 (s, 1H), 7.17 (dd, *J* = 7.6, 4.8 Hz, 1H), 7.81 (d, *J* = 7.6 Hz, 1H), 8.22 (d, *J* = 4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.6, 28.3, 32.0, 62.4, 101.2, 119.0, 121.0, 128.8, 142.7, 159.2, 161.8; MS (EI) *m/z* 192 (M^+, 100), 131(5); calcd for $C_{11}H_{13}NO_2$: C, 69.11; H, 6.81; N, 7.33; found: C, 69.25; H, 6.83; N, 7.25.

2-Phenylfuro[3,2-c]pyridine (4a):[19c] The product was obtained as a yellow powder (61%) from 4-hydroxy-3-iodopyridine and phenylacetylene after 16 h of reaction; m. p. 117–119 °C (lit. m.p. 120–121 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (s, 1H), 7.51 (t, *J* = 7.2 Hz, 2H), 7.68 (dd, *J* = 5.4, 2.0 Hz, 2H), 7.94 (d, *J* = 8.0 Hz, 2H), 8.65 (s, 1H), 8.86 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ, 107.4, 115.9, 127.5, 128.8, 129.1, 130.2, 142.2, 148.8, 154.0; MS (EI) *m/z* 195 (M^+, 100), 116 (32); calcd for $C_{13}H_9NO$: C, 80.00; H, 4.61; N, 7.18; found: C, 80.13; H, 4.58; N, 7.23.

2-Butylfuro[3,2-c]pyridine (4b):[19b] The product was obtained as a colorless oil (60%) from 4-hydroxy-3-iodopyridine and 1-hexyne after 18 h of reaction; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (t, *J* = 4.0 Hz, 3H), 1.51–1.58 (m, 2H), 1.72–1.77 (m, 2H), 2.82 (t, *J* = 7.6 Hz, 2H), 6.43 (s, 1H), 7.86 (d, *J* = 7.6 Hz, 1H), 8.44 (d, *J* = 7.6 Hz, 1H), 8.67 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 19.8, 22.3, 30.6, 97.8, 100.0, 125.6, 141.5, 146.6, 158.9, 161.3; MS (EI) *m/z* 175 (M^+, 100), 118 (40); calcd for $C_{11}H_{13}NO$: C, 75.43; H, 7.43; N, 8.00; found: C, 75.54; H, 7.40; N, 7.95.

2-(3-Hydroxypropyl)furo[3,2-*c*]pyridine (4c): The product was obtained as a pale yellow oil (56%) from 4-hydroxy-3-iodopyridine and 4-penyn-1-ol after 20 h of reaction; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.08–2.14 (m, 2H), 2.83 (t, *J* = 7.6 Hz, 2H), 4.39 (t, *J* = 6.8 Hz, 2H), 5.64 (s, 1H), 6.42 (s, 1H), 7.89 (d, *J* = 7.4 Hz, 1H), 8.74 (d, *J* = 7.8 Hz, 1H), 9.01 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.7, 31.3, 61.7, 100.6, 106.6, 125.1, 143.1, 143.7, 155.4, 160.7; MS (EI) *m/z* 177 (M^+, 100); calcd for $C_{10}H_{11}NO_2$: C, 67.80; H, 6.21; N, 7.91; found: C, 67.75; H, 6.18; N, 7.89.

2-(4-Hydroxybutyl)furo[3,2-*c*]pyridine (4d): The product was obtained as a colorless oil (62%) from 4-hydroxy-3-iodopyridine and 5-hexyn-1-ol after 20 h of reaction; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.69 (m, 2H), 2.01 (m, 2H), 2.84 (t, *J* = 7.2 Hz, 2H), 3.98 (t, *J* = 5.0 Hz, 2H), 4.58 (t, *J* = 3.6 Hz, 1H), 6.43 (s, 1H), 7.86 (d, *J* = 7.6 Hz, 1H), 8.29 (d, *J* = 6.8 Hz, 1H), 8.65 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.2, 28.1, 31.9, 62.4, 97.7, 100.3, 125.7, 141.0, 143.9, 151.4, 160.2; MS (EI) *m/z* 191 (M^+, 100), 118 (35); calcd for $C_{11}H_{13}NO_2$: C, 69.11; H, 6.81; N 7.33; found: C, 68.91; H, 6.78; N, 7.35.

Functionalization of 5 by Suzuki/Heck Reaction for Synthesis of 2,3-Disubstituted Furo[3,2-*b*]pyridines 6

General Procedure for Suzuki Reactions. To a pressure tube was added **5** (0.5 mmol), boronic acid (0.75 mmol), $Pd(PPh_3)_4$ (3 mol%), EtOH (0.1 mL), 20% Na_2CO_3 (0.2 mL), and DMF (3 mL). After 24 h of reaction at 115 °C, the reaction mixture was poured into saturated NH_4Cl (10 mL) solution and extracted by ethyl acetate. The crude product obtained after usual work-up was purified by column chromatography on silica gel eluting with hexane and ethyl acetate.

General Procedure for Heck Reactions. To a pressure tube was added **5** (0.5 mmol), ethyl acrylate (1.0 mmol), $Pd(OAc)_2$ (5 mol%), LiCl (0.5 mmol), Ce_2CO_3 (1 mmol), and DMF (3 mL). After 30 h of reaction at 115 °C, the product was obtained following same work-up procedure described in Suzuki reactions.

2,3-Diphenylfuro[3,2-*b*]pyridine (6a): The product was obtained as a colorless oil (69%) from **5a** and phenylboronic acid after 24 h of reaction; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27–7.52 (m, 8H), 7.64–7.88 (m, 4H), 8.61 (d, *J* = 4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 117.8, 119.1, 127.3, 127.9, 128.5, 128.9, 129.2, 129.9, 130.1, 130.9, 146.1, 147.3, 148.5, 154.4; MS (EI) *m/z* 271 ($[M]^+$, 100), 270 (10), 124 (25).

3-(2-Methoxyphenyl)-2-phenylfuro[3,2-*b*]pyridine (6b): The product was obtained as a pale yellow oil (52%) from **5a** and (2-methoxyphenyl)boronic acid after 24 h of reaction; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.58 (s, 3H), 7.02 (d, *J* = 7.4 Hz, 1H), 7.11 (t, *J* = 7.8 Hz, 1H), 7.29 (d, *J* = 3.9 Hz, 1H), 7.30–7.32 (m, 3H), 7.42 (t, *J* = 7.5 Hz, 1H), 7.49 (dd, *J* = 7.4, 1.6 Hz, 1H), 7.65–7.68 (m, 2H), 7.78 (dd, *J* = 8.2, 1.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.4, 111.6, 114.3, 117.6, 118.9, 120.0, 121.2, 126.4, 128.3, 128.8, 129.7, 130.9, 132.0, 146.1, 147.2, 149.2, 154.7, 157.4; MS (EI) *m/z* 301 ($[M]^+$, 100), 270 (55), 196 (35).

3-(4-(Methylsulfonyl)phenyl)-2-phenylfuro[3,2-*b*]pyridine (6c): The product was obtained as a colorless oil (56%) from **5a** and (4-methylsulfonylphenyl)boronic acid after 24 h of reaction; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.10 (s, 3H), 7.32 (q, *J* = 4.8 Hz, 1H), 7.41–7.42 (m, 3H), 7.66–7.69 (m, 2H), 7.86 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.87 (s, 1H), 7.9 (s, 1H), 8.04 (d, *J* = 7.8 Hz, 2H), 8.60 (dd, *J* = 4.8, 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 44.5, 115.8, 118.2, 119.7, 127.6, 128.0, 128.9, 129.4, 130.0, 137.2, 139.5, 146.5, 147.5, 147.6, 155.63; MS (EI) *m/z* 348 ($[M]^+$, 100), 269 (60).

2-Phenyl-3-[4-(trifluoromethyl)phenyl]furo[3,2-*b*]pyridine (6d): The product was obtained as a colorless oil (60%) from **5a** and (4-trifluoromethylphenyl)boronic acid after 24 h of reaction; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (dd, *J* = 11.2, 4.8 Hz, 1H), 7.38 (s, 3H), 7.40 (d, *J* = 2.2 Hz, 1H), 7.68–7.84 (m, 7H), 8.58 (d, *J* = 4.2 Hz, 1H,); ^{13}C NMR (100 MHz, $CDCl_3$) δ 115.8, 118.2, 119.7, 124.1, 125.2, 125.6, 127.6, 128.0, 128.9, 129.4, 131.1, 132.1, 139.7, 145.5, 147.5, 155.6. MS (EI) *m/z* 338 ($[M]^+$, 65), 269 (10).

3-(2-Methoxypyridin-3-yl)-2-phenylfuro[3,2-*b*]pyridine (6e): The product was obtained as a colorless oil (62%) from **5a** and (2-methoxypyridin-3-yl)boronic acid after 24 h of reaction; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.10 (s, 3H), 6.88 (d, *J* = 8.6 Hz, 1H), 7.39 (d, *J* = 4.8 Hz, 2H), 7.42 (d, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.4 Hz, 1H), 7.73 (d, *J* = 3.6 Hz, 1H), 7.77

(d, J = 8.2 Hz, 1H), 7.81 (d, J = 8.2 Hz, 1H), 7.88 (dd, J = 8.6, 2.2 Hz, 1H), 8.45 (d, J = 2.2 Hz, 1H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.4, 111.6, 114.3, 118.2, 118.9, 125.2, 126.7, 126.9, 129.2, 131.0, 132.0, 134.6, 145.1, 146.1, 146.2, 153.8, 158.4.

3-(3-Cyanophenyl)-2-phenylfuro[3,2-*b*]pyridine (6f): The product was obtained as a yellow oil (70%) from **5a** and (3-cyanophenyl)boronic acid after 24 h of reaction; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (q, J = 4.8 Hz, 1H), 7.38–4.2 (m, 3H), 7.56 (t, J = 8.4 Hz, 1H), 7.64–7.68 (m, 3H), 7.83 (d, J = 8.2 Hz, 1H), 7.91 (d, J = 7.8 Hz, 1H), 7.99 (s, 1H), 8.58 (d, J = 4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 111.6, 113.1, 118.2, 118.6, 119.9, 125.2, 126.7, 128.9, 129.4, 130.5, 131.1, 131.8, 132.1, 137.1, 139.7, 145.5, 146.3, 153.6.; MS (EI) *m/z* 296 ([M]$^+$, 65), 295 (100), 266 (20).

2-Butyl-3-phenylfuro[3,2-*b*]pyridine (6g): The product was obtained as a colorless oil (65%) from **5b** and phenylboronic acid after 24 h of reaction; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (t, J = 7.4 Hz, 3H), 1.39–1.46 (m, 2H), 1.74–1.84 (m, 2H), 2.96 (t, J = 7.4 Hz, 2H), 7.19 (dd, J = 8.2, 4.8 Hz, 1H), 7.37 (t, J = 7.4 Hz, 2H), 7.50 (t, J = 7.4 Hz, 2H), 7.67 (d, J = 7.2 Hz, 2H), 7.70 (d, J = 8.4 Hz, 1H), 8.54 (d, J = 4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 22.2, 28.3, 29.4, 108.9, 118.2, 119.9, 124.2, 126.7, 127.5, 128.5, 129.2, 136.4, 146.5, 153.1. MS (EI) *m/z* 251 ([M]$^+$, 78), 236 (20), 222 (100), 208 (80).

2-Butyl-3-(4-(trifluoromethyl)phenyl)furo[3,2-*b*]pyridine (6h): The product was obtained as a yellow oil (71%) from **5b** and (4-trifluoromethylphenyl)boronic acid after 24 h of reaction; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (t, J = 7.4 Hz, 3H), 1.40–1.47 (m, 2H), 1.8–1.86 (m, 2H), 2.98 (t, J = 7.4 Hz, 2H), 7.24 (dd, J = 8.4, 4.8 Hz, 1H), 8.55 (d, J = 4.8 Hz, 1H), 7.73 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.5, 20.2, 26.3, 31.7, 107.9, 111.6, 119.9, 120.9, 123.3, 124.7, 125.6, 126.4, 127.5, 128.5, 129.2, 154.0, 155.1; MS (EI) *m/z* 319 ([M]$^+$, 50), 290 (100), 276 (60).

2-Butyl-3-(3-cyanophenyl)furo[3,2-*b*]pyridine (6i): The product was obtained as a colorless oil (73%) from **5b** and (3-cyanophenyl)boronic acid after 24 h of reaction; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (t, J = 7.40 Hz, 3H), 1.34–1.42 (m, 2H), 1.69–1.80 (m, 2H), 1.77 (t, J = 7.4 Hz, 2H), 7.02–7.10 (m, 2H), 7.16 (dd, J = 8.2, 4.8 Hz, 1H), 7.39 (t, J = 6.4 Hz, 1H), 7.47 (dd, J = 7.4, 1.6 Hz, 1H,), 7.70 (d, J = 8.2 Hz, 1H), 8.5 (d, J = 4.8 Hz, 1H,); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 20.4, 27.6, 29.6, 30.9, 55.46, 111.2, 113.7, 117.1, 117.8, 119.6, 120.8, 129.1, 130.3, 145.3, 147.1, 148.64, 157.2, 160.6; MS (EI) *m/z* 281 ([M]$^+$, 75), 252 (100), 224 (95), 115 (10).

3-(2-Ethoxycarbonylvinyl)-2-phenylfuro[3,2-*b*]pyridine (6j): The product was obtained as a colorless oil (68%) from **5a** and ethyl acrylate after 30 h of reaction; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H; 1.36 (t, J = 7.2 Hz, 3H), 4.3 (q, 2H), 7.31 (dd, J = 4.8, 8.2 Hz, 1H), 7.53–7.59 (m, 3H), 7.73 (d, J = 15.6 Hz, 1H), 7.80–7.86 (m, 3H), 8.03 (d, J = 15.6 Hz, 1H), 8.65 (d, J = 4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 61.4, 102.8, 118.3, 122.0, 126.2, 127.5, 128.8, 129.3, 130.4, 145.2, 145.9, 148.1, 149.8, 165.5; MS (EI) *m/z* 293 ([M]$^+$, 100), 220 (65), 224 (95), 194 (30).

2-Butyl-3-(2-ethoxycarbonylvinyl)furo[3,2-*b*]pyridine (6k): The product was obtained as a colorless oil (58%) from **5b** and ethyl acrylate after 30 h of reaction; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.96 (t, J = 7.4 Hz, 3H), 1.3 (t, J = 7.2 Hz, 3H), 1.33 (m, 2H), 1.62–1.7 (m, 2H), 2.4 (t, J = 7.4 Hz, 2H), 4.19 (q, 2H), 6.39 (d, J = 15.6 Hz, 1H), 7.38 (d, J = 4.8 Hz, 1H), 7.64 (d, J = 15.6 Hz, 1H,), 7.75 (d, J = 8.2 Hz, 1H), 8.59 (d, J = 4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.5, 14.2, 20, 28.2, 32.1, 61.4, 107.8, 118, 119.5, 122, 122.3, 145.2, 148.0, 155.2, 166.0; MS (EI) *m/z* 273 ([M]$^+$, 100), 228 (52).

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