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Copper-Catalyzed Alkynylation/Cyclization/Isomerization Cascade for Synthesis of 1,2-Dihydrobenzofuro[3,2-*b*]pyridines and Benzofuro[3,2-*b*]pyridines

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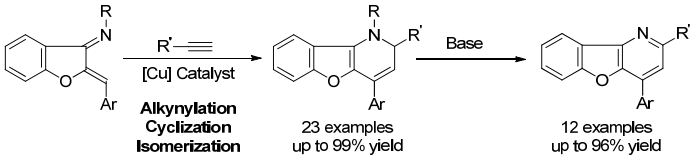
ABSTRACT



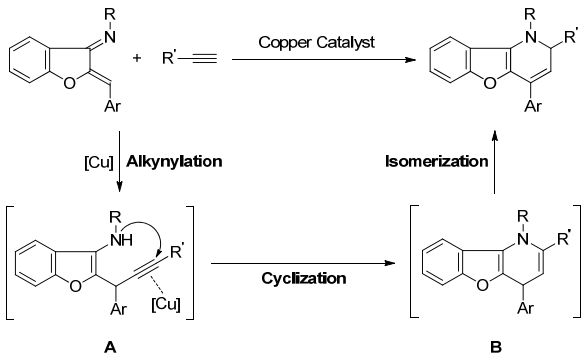
Three bioactive molecules with potent topoisomerase inhibition were synthesized

An efficient copper-catalyzed cascade alkynylation/cyclization/isomerization reactions of aurone-derived azadienes with terminal alkynes has been developed, giving a series of 1,2-dihydrobenzofuro[3,2-*b*]pyridines with excellent yields. The obtained 1,2-dihydrobenzofuro[3,2-*b*]pyridines can be conveniently transformed to the corresponding benzofuro[3,2-*b*]pyridines under basic condition. Additionally, benzofuro[3,2-*b*]pyridines can also be prepared from azadienes and terminal alkynes in one-pot reaction. The synthetic utility was demonstrated by the synthesis of three bioactive molecules with potent topoisomerase inhibition in high yields. This strategy provides a facile approach to 1,2-dihydrobenzofuro[3,2-*b*]pyridines and benzofuro[3,2-*b*]pyridines.

INTRODUCTION

The direct and rapid construction of complicated and diversified molecules from easily available starting materials has great importance in synthetic chemistry and industrial processes.[1] In this regard, cascade reactions enable multiple transformations in a single step and provide diverse scaffolds with undoubted

benefits involving atom economy, efficiency and sustainability of resources.[2] Consequently, the development of cascade reactions has attracted considerable attention and been a powerful strategy for the synthesis of various scaffolds and complex natural products.[2,3] Dihydropyridines (DHPs) are ubiquitous structural fragments in a myriad of biologically active molecules, natural products, and synthetic drugs.[4] In particular, 1,2-dihydropyridines are prominent synthetic intermediates to prepare a wide range of organic molecules, such as piperidines, indolizidines, quinolizidines, and isoquinuclidines.[5] Due to the prevalence and significance of 1,2-dihydropyridines, various strategies for their construction have been developed, including condensation reactions of amines and carbonyl compounds,[6] partial reduction or nucleophilic addition to pyridines and pyridinium salts,[7] and pericyclic reactions.[8] Although considerable progress has been achieved, there are still some disadvantages, such as harsh conditions, noble metal catalysts, etc., inhibiting their wide application. Hence, the development of straightforward and convenient synthesis of 1,2-dihydropyridines is highly desirable.



Scheme 1. Copper-Catalyzed Cascade Reactions for the Synthesis of 1,2-Dihydrobenzofuro[3,2-*b*]pyridines

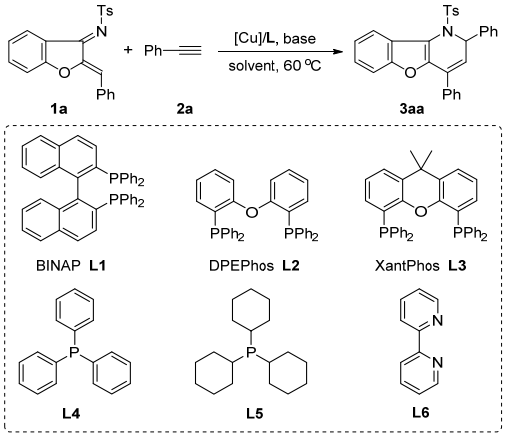
Aurone-derived azadienes have been recognized as a crucial class of highly reactive intermediates in organic synthesis due to the driving force of aromatization.[9] In the past few years, numerous annulations of aurone-derived azadienes to construct benzofuran-fused heterocyclic compounds have been reported.[9a-h,k-o,s-t] As our contiguous interests in the utilization of azadienes, we previously disclosed the systematic work of asymmetric nucleophilic addition and annulation.[9h-j,9r] Considering that copper-catalyzed alkynylation with terminal alkynes is a straightforward and general access to substituted alkynes, we envisioned copper-catalyzed cascade reactions of azadienes and terminal alkynes to give 1,2-dihydrobenzofuro[3,2-*b*]pyridines. The mechanism might be hypothesized as following. Firstly, copper-catalyzed alkynylation of azadiene produced substituted alkyne **A**. Subsequently, intermediate **A** underwent an intramolecular 6-*endo*-*dig* cyclization through the activation of the triple bond with a π-philic metal, delivering 1,4-dihydropyridine **B**. Finally, the isomerization of intermediate **B** afforded 1,2-dihydrobenzofuro[3,2-*b*]pyridines. Herein, we described copper-catalyzed cascade alkynyltion/cyclization/isomerization reactions of azadienes with

terminal alkynes for the synthesis of 1,2-dihydrobenzofuro[3,2-*b*]pyridines (Scheme 1). The obtained 1,2-dihydrobenzofuro[3,2-*b*]pyridines can be conveniently transformed to the corresponding benzofuro[3,2-*b*]pyridines under basic conditions.

RESULTS AND DISCUSSION

To initiate our investigation, azadiene **1a** and phenylacetylene **2a** were chosen as model substrates for condition optimization. Under the catalysis of $Cu(CH_3CN)_4BF_4$/BINAP in tetrahydrofuran at 60 ^oC, the cascade reaction occurred with moderate 48% yield in 48 h (Table 1, entry 1). The structure of the product was determined to be 1,2-dihydropyridine derivative **3aa** by X-ray single crystal diffraction analysis (see SI). Alteration of copper precursors to $Cu(OTf)_2$ and CuI resulted in a significant decrease in reactivity (Table 1, entries 2 and 3). A series of commercially available ligands were evaluated, and it was found that ligand had an obvious influence. Monophosphorus ligands such as triphenylphosphine **L4** and tricyclohexylphosphine **L5** exhibited low reactivity. Bipyridine ligand **L6** shut down the reaction. Diphosphine ligand XantPhos **L3** was the most efficient ligand, providing the product in 86% yield (Table 1, entries 4-9). The effect of base was explored. Good yield was obtained with *N*,*N*-diisopropylethylamine and moderate yield was achieved with potassium carbonate (Table 1, entries 10 and 11). Subsequently, the effect of solvents was evaluated. 1,4-Dioxane proved to be the most favorable solvent in 96% yield (Table 1, entries 12-14). Notably, the reactivity could be maintained when the catalyst loading was reduced to 5 mol% (Table 1, entry 15). Therefore, the optimal condition was established: using $Cu(CH_3CN)_4BF_4$/XantPhos as catalyst, triethylamine as base and 1,4-dioxane as solvent to perform the reaction at 60 ^oC.

Table 1. Optimization of Reaction Conditions[a]



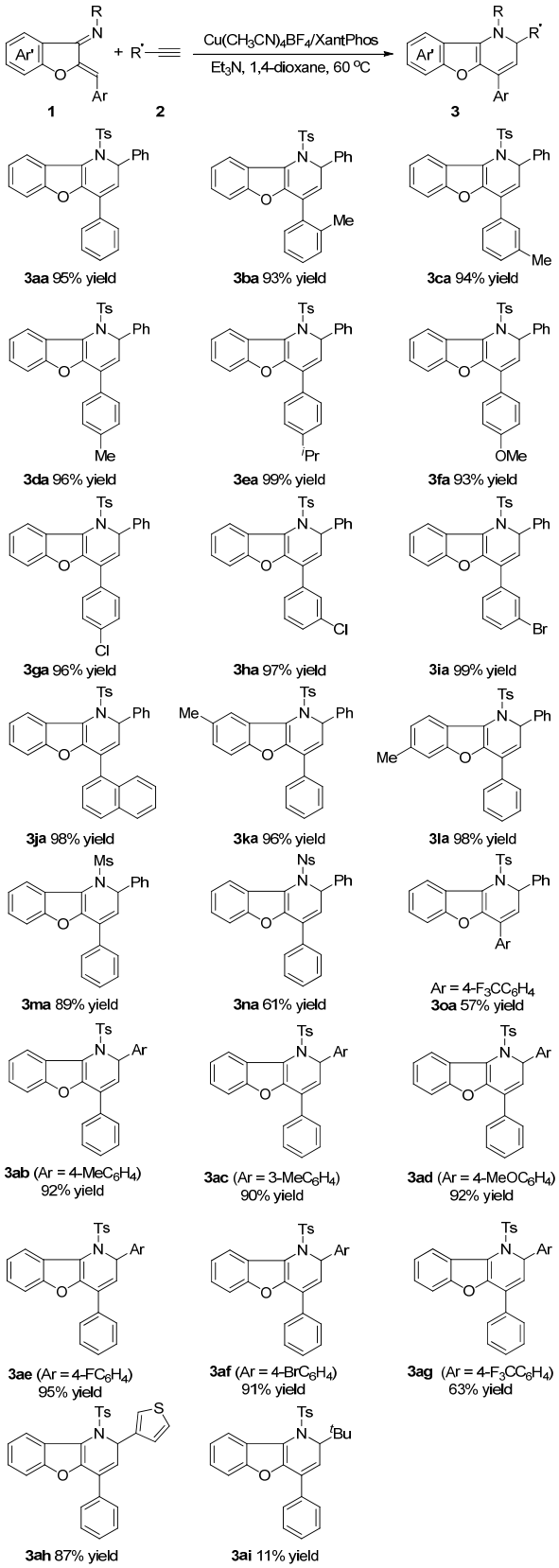
Entry	[Cu]	L	solvent	yield (%)[b]
1	$Cu(CH_3CN)_4BF_4$	**L1**	THF	48
2	$Cu(OTf)_2$	**L1**	THF	12
3	CuI	**L1**	THF	17

4	$Cu(CH_3CN)_4BF_4$	**L2**	THF	25
5	$Cu(CH_3CN)_4BF_4$	**L3**	THF	86
6	$Cu(CH_3CN)_4BF_4$	**L4**	THF	12
7	$Cu(CH_3CN)_4BF_4$	**L5**	THF	37
8	$Cu(CH_3CN)_4BF_4$	**L6**	THF	--
9	$Cu(CH_3CN)_4BF_4$	--	THF	--
10[c]	$Cu(CH_3CN)_4BF_4$	**L3**	THF	84
11[d]	$Cu(CH_3CN)_4BF_4$	**L3**	THF	32
12	$Cu(CH_3CN)_4BF_4$	**L3**	toluene	94
13	$Cu(CH_3CN)_4BF_4$	**L3**	1,4-dioxane	96
14	$Cu(CH_3CN)_4BF_4$	**L3**	acetonitrile	7
15[e]	$Cu(CH_3CN)_4BF_4$	**L3**	1,4-dioxane	97

[a] Conditions: **1a** (0.10 mmol), **2a** (0.30 mmol), [Cu] (10 mol%), **L** (10 mol%), while **L4** and **L5** were used in 20 mol%, solvent (1.5 mL), Et_3N (0.10 mmol), 60 °C, 48 h. [b] Isolated yields. [c] DIPEA (0.10 mmol) was used. [d] K_2CO_3 (0.10 mmol) was used. [e] Catalyst loading was reduced to 5 mol%.

With the aforementioned optimal reaction conditions, we turned our attention to the scope of this cascade reaction between azadienes **1** and alkynes **2**. The results were summarized in Scheme 2. In general, the transformation proceeded smoothly, delivering the desired benzofuran-fused 1,2-dihydropyridines **3** in excellent yields. Various aurone-derived azadienes were suitable for the cascade reaction. The steric and electronic properties of the substituents on the aromatic ring had only marginal effect on yields. For instance, the reaction afforded the target products **3ba** and **3ga** in 93% and 96% yield, respectively. For azadienes with methyl substituent at the 5- or 6-position of benzofuryl ring, products **3ka** and **3la** in 96% and 98% yield, respectively. Sulfonylimines **1m-1n** were transformed successfully with moderate to good yields. Additionally, azadiene containing trifluoromethyl substituent performed the cascade reaction smoothly, offering the target product **3oa** in 57% yield. Furthermore, a series of terminal alkynes were evaluated. Excellent yields were observed for substituted phenylacetylenes as well as terminal alkyne bearing thienyl functionality. When strong electron-withdrawing group such as trifluoromethyl was introduced to terminal alkyne, only moderate yield was obtained. The yield decreased dramatically for terminal alkynes bearing alkyl substituents. Only 11% yield was achieved with *tert*-butylacetylene and the reaction shut down with cyclohexylacetylene.

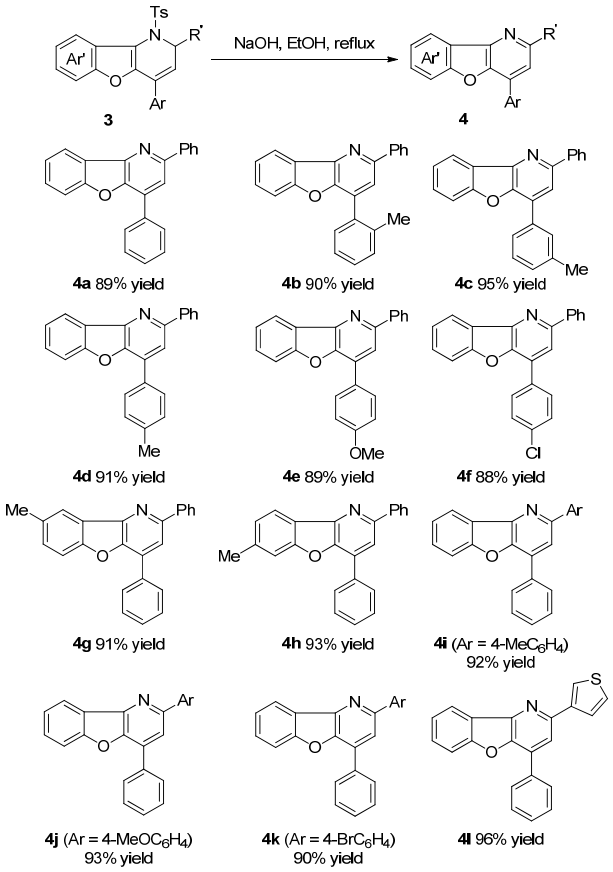
Scheme 2. Substrate Scope[a]



[a] Conditions: **1** (0.20 mmol), **2** (0.60 mmol), $Cu(CH_3CN)_4BF_4$ (5 mol%), XantPhos (5 mol%), Et_3N (0.20 mmol), 1,4-dioxane (3.0 mL), 60 °C, 48 h.

To extend the synthetic utility of this cascade reaction, we made further efforts to the transformation of 1,2-dihydrobenzofuro[3,2-*b*]pyridines. Benzofuro[3,2-*b*]pyridine moieties have been found with various pharmaceutical and biological activities, such as antiallergic, anti-inflammatory, antimicrobial, and analgesic activity, cyclin-dependent kinase inhibitors, and topoisomerase inhibitors.[10] 1,2-Dihydrobenzofuro[3,2-*b*]pyridines were easily deprotected and aromatized to the corresponding benzofuro[3,2-*b*]pyridines under basic conditions through E1cb mechanism (Scheme 3).

Scheme 3. Synthesis of Benzofuro[3,2-*b*]pyridines[a]



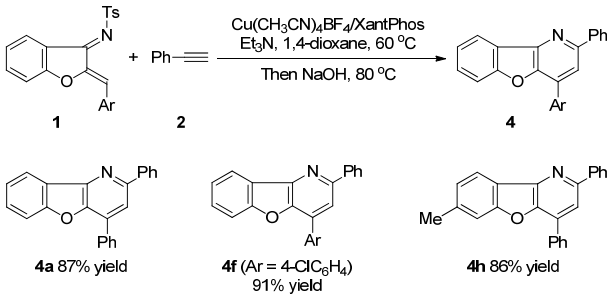
[a] Conditions**: 3** (0.15 mmol), NaOH (0.75 mmol), EtOH (2.0 mL), reflux, 0.5 h.

A series of 1,2-dihydrobenzofuro[3,2-*b*]pyridines bearing both electron-donating and electron-withdrawing groups on the aromatic rings of substrates underwent the deprotection and aromatization successfully, generating the desired benzofuro[3,2-*b*]pyridine products **4a-4k** in excellent yields. It is worthy to note that the benzofuro[3,2-*b*]pyridine bearing thienyl functionality **4l** could also be obtained in 96% yield. This method provides a practical and alternative route to a series of benzofuro[3,2-*b*]pyridines.

Encouraged by the results above, we decided to apply this new methodology to the one-pot synthesis of benzofuro[3,2-*b*]pyridines. As shown in Scheme 4, the corresponding benzofuro[3,2-*b*]pyridines **4** could be

prepared from azadienes **1** and terminal alkynes **2** in 86-91% yields *via* copper-catalyzed cascade reaction followed by basic deprotection and aromatization.

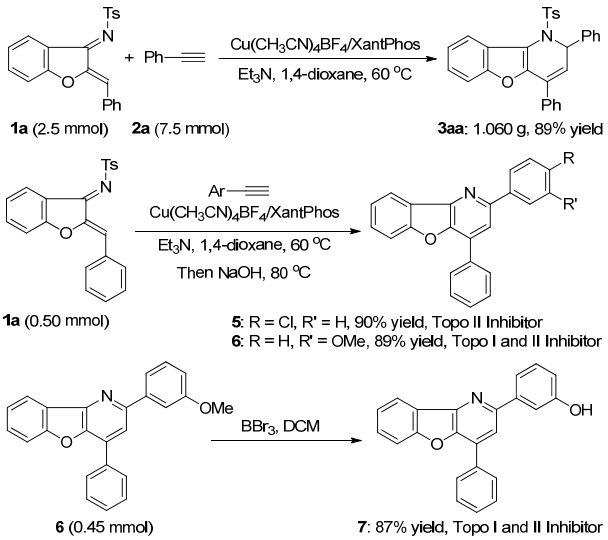
Scheme 4. One-Pot Synthesis of Benzofuro[3,2-*b*]pyridines[a]



[a] Conditions**: 1** (0.20 mmol), **2** (0.60 mmol), $Cu(CH_3CN)_4BF_4$ (5 mol%), XantPhos (5 mol%), Et_3N (0.20 mmol), 1,4-dioxane (3.0 mL), 60 °C, 48 h. Then, NaOH (1.0 mmol), 80 °C, 2 h.

To evaluate the synthetic potential of this cascade reaction, a gram scale experiment of azadiene **1a** and phenylacetylene **2a** was conducted in the presence of $Cu(CH_3CN)_4BF_4$/XantPhos catalyst (5 mol%). Gratifyingly, the transformation proceeded smoothly to afford 1,2-dihydropyridine derivative **3aa** in 89% yield without noticeable loss of yield (Scheme 5).

Scheme 5. Gram Scale Experiment and Synthesis of Three Bioactive Molecules



To further demonstrating the synthetic utility, three bioactive molecules with potent topoisomerase (topo) inhibition were synthesized in high yields (Scheme 5). 2-Chlorophenyl-substituted benzofuro[3,2-*b*]pyridine **5** exhibits potent topo II inhibition and antiproliferative activity,[10e] which could be conveniently obtained in 90% yield using the one-pot synthesis. Additionally, the compound **6** which showed endogenous topo I and II inhibitory activity[10d] could be achieved in 89% yield with the same method. 3-(4-Phenylbenzofuro[3,2-*b*]pyridin-2-yl)phenol **7** has been determined be a noninter-calative topo I and II dual catalytic inhibitor,[10d]

and could be also synthesized with 87% yield through deprotection of methyl with tribromoboron.

CONCLUSIONS

In conclusion, an efficient copper-catalyzed alkynylation/cyclization/isomerization cascade has been developed, giving a variety of 1,2-dihydrobenzofuro[3,2-*b*]pyridines with high yields. The obtained 1,2-dihydrobenzofuro[3,2-*b*]pyridines can be conveniently transformed to the corresponding aromatic benzofuro[3,2-*b*]pyridines in high yields under the basic condition. Additionally, the one-pot synthesis of benzofuro[3,2-*b*]pyridines can also be realized from azadienes and terminal alkynes *via* copper-catalyzed cascade reactions and basic deprotection and aromatization. The synthetic utility of this methodology was demonstrated by the synthesis of three bioactive molecules with potent topoisomerase inhibition in high yields. This protocol not only provides a facile approach to 1,2-dihydrobenzofuro[3,2-*b*]pyridines, but also affords a new access to aromatic benzofuro[3,2-*b*]pyridines.

EXPERIMENTAL SECTION

All reactions were carried out under an atmosphere of nitrogen using the standard Schlenk techniques, unless otherwise noted. Commercially available reagents were used without further purification. Solvents were treated prior to use according to the standard methods. ^{1}H NMR, ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz with the Brucker spectrometer. ^{19}F NMR spectra was recorded at 376 MHz with Brucker spectrometer. Chemical shifts are reported in ppm using tetramethylsilane as internal standard when using $CDCl_3$ as solvent for ^{1}H NMR spectra. The following abbreviations were used to symbolize the multiplicities: s = singlet, d = doublet, t = triplet, m = multiplet, brs = broad singlet. Flash column chromatography was performed on silica gel (200-300 mesh). All reactions were monitored by TLC analysis. High-resolution mass spectrometry (HRMS(ESI-TOF) M/Z) was measured on an electrospray ionization (ESI) apparatus using time-of-flight (TOF) mass spectrometry. The heat source in reaction procedures was oil bath.

Procedures for Synthesis of Azadienes: azadienes **1** could be synthesized from enones and sulfonamides according to the known literature procedures.[9,11,12] Among them, azadienes **1a**-**1d**,[9a] **1e**,[9i] **1f**-**1j**,[9a] **1k**,[9r] **1l**,[9j] **1m**[9c] and **1n**[9i] are the known compound. Starting materials benzofuran-3(2H)-ones[12] and intermediate enones[9j,11] are the known compounds.

Under nitrogen, aluminium oxide (65 g, activated, basic) was added to a solution of ketones (20 mmol) and aldehydes (40 mmol) in dichloromethane (80 mL). The mixture was stirred at room temperature under

nitrogen and exclusion of light. The reaction progress was monitored by TLC. The suspension was filtered off, the residue washed with dichloromethane, and the filtrate was combined with the filtrate. The solvent was evaporated in vacuo. The residue was purified by flash chromatography and recrystallized from ethyl acetate/hexanes to give the intermediate enones for the next step.

To a solution of the above enones (5 mmol) and sulfonamides (5 mmol) in toluene (50 mL), triethylamine (1.39 mL, 10 mmol) and titanium tetrachloride (0.55 mL, 5 mmol) were successively added at 0 ^{o}C in ice bath. The reaction mixture was heated in oil bath for reflux overnight. The solution was cooled, quenched with water and extracted with dichloromethane. The combined organic phase was dried over ahydrous sodium sulfate and concentrated. The residue was purified by silical gel flash chromatography using ethyl acetate/hexanes as eluent, and further recrystallized from ethyl acetate/ hexanes to give the pure azadienes **1**.

4-Methyl-*N*-((*Z*)-2-((*Z*)-4-(trifluoromethyl)benzylidene)benzofuran-3(2*H*)-ylidene)benzenesulfonamide (1o): 0.401 g, 18% yield, yellow solid, m.p. = 145-146 ^{o}C, new compound, R_f = 0.50 (hexanes/ethyl acetate = 40/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 (d, *J* = 7.6 Hz, 1H), 8.19-7.88 (m, 4H), 7.79-7.59 (m, 3H), 7.53-7.28 (m, 4H), 7.04 (s, 1H), 2.48 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 164.9, 164.8, 150.9, 143.8, 138.7, 138.1, 135.7, 131.6, 131.5, 131.1 (q, J_{C-F} = 32.0 Hz), 129.6, 127.2, 125.8 (q, J_{C-F} = 4.0 Hz), 124.2, 123.9 (q, J_{C-F} = 271.0 Hz), 118.0, 112.8, 112.5, 21.7; ^{19}F{1H} NMR (376 MHz, $CDCl_3$) δ -62.8. HRMS (ESI-TOF) *m/z* Calculated for $C_{23}H_{17}F_3NO_3S$ $[M+H]^+$ 444.0876, found 444.0879.

General Procedure for Synthesis of Dihydrobenzofuro[3,2-*b*]pyridines

Under nitrogen, the solution of $Cu(MeCN)_4BF_4$ (3.1 mg, 0.01 mmol) and ligand XantPhos (5.8 mg, 0.01 mmol) in 1,4-dioxane (0.5 mL) was stirred at room temperture for 1.5 h, azadienes **1** (0.20 mmol), 1,4-dioxane (2.5 mL), triethylamine (20.2 mg, 0.2 mmol), terminal alkynes **2** (0.6 mmol) was added in sequence. The reaction was stirred at 60 ^{o}C in oil bath for 2 days, which was monitored by thin-layer chromatography. The solvent was evaporated under the reduced pressure and the crude product was directly purified by silica gel column chromatography (eluent: hexanes/ethyl acetate = 50:1 to 30:1) to give the desired products **3**.

2,4-Diphenyl-1-tosyl-1,2-dihydrobenzofuro[3,2-*b*]pyridine (3aa): 91 mg, 95% yield, pale yellow solid, m.p. = 178-179 ^{o}C, new compound, R_f = 0.30 (hexanes/ethyl acetate = 30:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11-7.89 (m, 1H), 7.54-7.41 (m, 4H), 7.41-7.33 (m, 4H), 7.34-7.27 (m, 3H), 7.26-7.18 (m, 4H), 7.07 (d, *J* = 7.9 Hz, 2H), 6.12 (d, *J* = 5.7 Hz, 1H), 5.88-5.61 (m, 1H), 2.25 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 154.0, 147.4, 144.2, 138.1, 134.6, 134.1, 131.1, 129.3, 128.7, 128.7, 128.5, 128.3, 127.6, 127.6, 127.4, 125.3, 124.6, 123.8, 121.9, 121.7, 117.5, 111.7, 59.4, 21.5. HRMS (ESI-TOF) *m/z* Calculated For $C_{30}H_{24}NO_3S$ $[M+H]^+$ 478.1471, found: 478.1473.

2-Phenyl-4-(*o*-tolyl)-1-tosyl-1,2-dihydrobenzofuro[3,2-*b*]pyridine (3ba): 91 mg, 93% yield, pale yellow solid, m.p. = 174-175 °C, new compound, R_f = 0.30 (hexanes/ethyl acetate = 30:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18-8.01 (m, 1H), 7.62-7.49 (m, 4H), 7.37-7.26 (m, 6H), 7.26-7.23 (m, 1H), 7.22-7.11 (m, 4H), 6.86 (d, *J* = 7.4 Hz, 1H), 6.20 (d, *J* = 5.9 Hz, 1H), 5.72 (d, *J* = 5.9 Hz, 1H), 2.38 (s, 3H), 1.77 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 154.0, 147.4, 144.2, 138.8, 136.6, 135.6, 134.3, 131.6, 130.3, 129.7, 129.6, 128.9, 128.8, 128.4, 127.8, 127.3, 126.0, 125.1, 124.6, 123.7, 123.1, 122.1, 116.1, 111.7, 59.6, 21.6, 19.7. HRMS (ESI-TOF) *m/z* Calculated For $C_{31}H_{26}NO_3S$ $[M+H]^+$ 492.1628, found: 492.1635.

2-Phenyl-4-(*m*-tolyl)-1-tosyl-1,2-dihydrobenzofuro[3,2-*b*]pyridine (3ca): 92 mg, 94% yield, pale yellow solid, m.p. = 163-164 °C, new compound, R_f = 0.30 (hexanes/ethyl acetate = 30:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15-7.86 (m, 1H), 7.50-7.43 (m, 4H), 7.42-7.36 (m, 1H), 7.33-7.26 (m, 4H), 7.26-7.20 (m, 2H), 7.18 (d, *J* = 7.7 Hz, 1H), 7.08 (d, *J* = 8.0 Hz, 2H), 7.04-6.97 (m, 2H), 6.11 (d, *J* = 6.1 Hz, 1H), 5.73 (d, *J* = 6.0 Hz, 1H), 2.38 (s, 3H), 2.27 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 154.0, 147.5, 144.2, 138.2, 134.6, 134.2, 131.3, 129.5, 129.3, 128.7, 128.4, 128.3, 127.7, 127.4, 125.2, 124.8, 124.7, 123.8, 121.9, 121.7, 117.4, 111.7, 59.4, 21.6, 21.5. HRMS (ESI-TOF) *m/z* Calculated For $C_{31}H_{26}NO_3S$ $[M+H]^+$ 492.1628, found: 492.1618.

2-Phenyl-4-(*p*-tolyl)-1-tosyl-1,2-dihydrobenzofuro[3,2-*b*]pyridine (3da): 94 mg, 96% yield, white solid, m.p. = 175-176 °C, new compound, R_f = 0.30 (hexanes/ethyl acetate = 30:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01-7.97 (m, 1H), 7.49-7.42 (m, 4H), 7.40-7.35 (m, 1H), 7.33-7.26 (m, 3H), 7.25-7.20 (m, 2H), 7.19-7.14 (m, 2H), 7.14-7.08 (m, 2H), 7.07 (d, *J* = 8.0 Hz, 2H), 6.10 (d, *J* = 6.1 Hz, 1H), 5.72 (d, *J* = 6.1 Hz, 1H), 2.38 (s, 3H), 2.26 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 153.9, 147.5, 144.2, 138.6, 138.2, 134.6, 131.2, 131.0, 129.2, 129.2, 128.6, 128.3, 127.6, 127.5, 127.4, 125.2, 124.7, 123.8, 121.8, 121.1, 117.3, 111.6, 59.4, 21.5, 21.4. HRMS (ESI-TOF) *m/z* Calculated For $C_{31}H_{26}NO_3S$ $[M+H]^+$ 492.1628, found: 492.1615.

4-(4-Isopropylphenyl)-2-phenyl-1-tosyl-1,2-dihydrobenzofuro[3,2-*b*]pyridine (**3ea**): 103 mg, 99% yield, pale yellow solid, m.p. = 95-96 °C, new compound, R_f = 0.40 (hexanes/ethyl acetate = 30:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05-7.97 (m, 1H), 7.51-7.43 (m, 4H), 7.42-7.38 (m, 1H), 7.33-7.27 (m, 3H), 7.26-7.22 (m, 4H), 7.21-7.16 (m, 2H), 7.08 (d, *J* = 8.0 Hz, 2H), 6.11 (d, *J* = 6.1 Hz, 1H), 5.74 (d, *J* = 6.1 Hz, 1H), 2.95 (hept, *J* = 6.9 Hz, 1H), 2.25 (s, 3H), 1.30 (s, 3H), 1.28 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 154.0, 149.6, 147.6, 144.2, 138.3, 134.6, 131.6, 130.9, 129.3, 128.6, 128.3, 127.6, 127.6, 127.4, 126.6, 125.2, 124.7, 123.8, 121.9, 121.2, 117.4, 111.7, 59.4, 34.1, 24.1, 24.0, 21.5. HRMS (ESI-TOF) *m/z* Calculated For $C_{33}H_{30}NO_3S$ $[M+H]^+$ 520.1941, found: 520.1931.

4-(4-Methoxyphenyl)-2-phenyl-1-tosyl-1,2-dihydrobenzofuro[3,2-*b*]pyridine (3fa): 94 mg, 93% yield, pale yellow solid, m.p. = 169-170 °C, new compound, R_f = 0.50 (hexanes/ethyl acetate = 10:1). ^{1}H NMR

(400 MHz, $CDCl_3$) δ 8.08-7.91 (m, 1H), 7.48-7.42 (m, 4H), 7.41-7.36 (m, 1H), 7.33-7.26 (m, 3H), 7.25-7.16 (m, 4H), 7.07 (d, *J* = 8.0 Hz, 2H), 6.92-6.86 (m, 2H), 6.10 (d, *J* = 6.1 Hz, 1H), 5.69 (d, *J* = 6.1 Hz, 1H), 3.84 (s, 3H), 2.26 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.0, 153.9, 147.6, 144.2, 138.3, 134.6, 130.5, 129.2, 128.9, 128.6, 128.7, 127.6, 127.4, 126.5, 125.2, 124.7, 123.8, 121.8, 120.4, 117.4, 113.9, 111.6, 59.4, 55.5, 21.6. HRMS (ESI-TOF) *m/z* Calculated For $C_{31}H_{26}NO_4S$ $[M+H]^+$ 508.1577, found: 508.1572.

4-(4-Chlorophenyl)-2-phenyl-1-tosyl-1,2-dihydrobenzofuro[3,2-*b*]pyridine (3ga): 98 mg, 96% yield, pale yellow solid, m.p. = 177-178 °C, new compound, R_f = 0.55 (hexanes/ethyl acetate = 10:1). ^1H NMR (400 MHz, $CDCl_3$) δ 8.30-7.70 (m, 1H), 7.46 (d, *J* = 8.2 Hz, 4H), 7.43-7.38 (m, 1H), 7.38-7.29 (m, 5H), 7.28-7.23 (m, 2H), 7.22-7.15 (m, 2H), 7.09 (d, *J* = 8.0 Hz, 2H), 6.14 (d, *J* = 6.1 Hz, 1H), 5.77 (d, *J* = 6.1 Hz, 1H), 2.29 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 154.0, 146.9, 144.3, 137.9, 134.7, 134.6, 132.5, 130.0, 129.3, 128.9, 128.7, 128.7, 128.4, 127.7, 127.3, 125.5, 124.5, 124.0, 122.0, 117.8, 111.7, 59.4, 21.5. HRMS (ESI-TOF) *m/z* Calculated For $C_{30}H_{23}ClNO_3S$ $[M+H]^+$ 512.1082, found: 512.1100.

4-(3-Chlorophenyl)-2-phenyl-1-tosyl-1,2-dihydrobenzofuro[3,2-*b*]pyridine (3ha): 99 mg, 97% yield, pale yellow solid, m.p. = 70-72 °C, new compound, R_f = 0.45 (hexanes/ethyl acetate = 30:1). ^1H NMR (400 MHz, CDCl3) δ 8.08-7.98 (m, 1H), 7.51-7.40 (m, 5H), 7.39-7.30 (m, 5H), 7.29-7.23 (m, 2H), 7.22-7.16 (m, 1H), 7.16-7.07 (m, 3H), 6.14 (d, *J* = 6.1 Hz, 1H), 5.77 (d, *J* = 6.1 Hz, 1H), 2.31 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 154.0, 146.8, 144.5, 137.8, 135.9, 134.5, 134.4, 130.0, 129.8, 129.3, 128.7, 128.4, 127.7, 127.3, 125.8, 125.5, 124.5, 124.0, 122.6, 122 .0, 117.8, 111.8, 59.4, 21.5. HRMS (ESI-TOF) *m/z* Calculated For $C_{30}H_{23}ClNO_3S$ $[M+H]^+$ 512.1082, found: 512. 1075.

4-(3-Bromophenyl)-2-phenyl-1-tosyl-1,2-dihydrobenzofuro[3,2-*b*]pyridine (3ia): 109 mg, 99% yield, pale yellow solid, m.p. = 75-76 °C, new compound, R_f = 0.45 (hexanes/ethyl acetate = 30:1). ^1H NMR (400 MHz, $CDCl_3$) δ 8.13-7.91 (m, 1H), 7.53-7.46 (m, 1H), 7.46-7.38 (m, 5H), 7.34-7.26 (m, 4H), 7.25-7.18 (m, 4H), 7.09 (d, *J* = 8.1 Hz, 2H), 6.11 (d, *J* = 6.1 Hz, 1H), 5.73 (d, *J* = 6.1 Hz, 1H), 2.30 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 154.0, 146.8, 144.5, 137.8, 136.2, 134.5, 131.6, 130.6, 130.1, 129.9, 129.3, 128.7, 128.5, 127.7, 127.3, 126.3, 125.5, 124.5, 124.0, 122.7, 122.5, 122.0, 117.8, 111.8, 59.4, 21.6. HRMS (ESI-TOF) *m/z* Calculated For $C_{30}H_{23}BrNO_3S$ $[M+H]^+$ 556.0577, found: 556.0568.

4-(Naphthalen-1-yl)-2-phenyl-1-tosyl-1,2-dihydrobenzofuro[3,2-*b*]pyridine (3ja): 103 mg, 98% yield, pale yellow solid, m.p. = 185-187 °C, new compound, R_f = 0.35 (hexanes/ethyl acetate = 30:1). ^1H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 7.9 Hz, 1H), 7.81 (t, *J* = 8.1 Hz, 2H), 7.56 (t, *J* = 7.2 Hz, 4H), 7.40 (t, *J* = 7.5 Hz, 2H), 7.33-7.21 (m, 4H), 7.20-7.03 (m, 6H), 6.71 (brs, 1H), 6.25 (d, *J* = 5.8 Hz, 1H), 5.89 (d, *J* = 5.8 Hz, 1H), 2.27 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 154.1, 147.8, 144.3, 138.8, 135.6, 133.6, 132.6, 131.4, 130.7, 129.8, 129.4, 128.8, 128.4, 128.4, 127.9, 127.3, 126.1, 126.1, 125.5, 125.5, 125.2, 124.5, 124.2,

123.7, 122.1, 111.8, 59.6, 21.8. HRMS (ESI-TOF) *m/z* Calculated For $C_{34}H_{26}NO_3S$ $[M+H]^+$ 528.1628, found: 528.1638.

8-Methyl-2,4-diphenyl-1-tosyl-1,2-dihydrobenzofuro[3,2-*b*]pyridine (3ka): 94 mg, 96% yield, pale yellow solid, m.p. = 160-162 °C, new compound, R_f = 0.30 (hexanes/ethyl acetate = 30:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (s, 1H), 7.54-7.43 (m, 4H), 7.42-7.32 (m, 3H), 7.30-7.18 (m, 6H), 7.14-6.97 (m, 3H), 6.11 (d, *J* = 6.1 Hz, 1H), 5.73 (d, *J* = 6.1 Hz, 1H), 2.46 (s, 3H), 2.24 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 152.5, 147.6, 144.2, 138.2, 134.6, 134.2, 133.4, 131.2, 129.2, 128.6, 128.5, 128.3, 127.7, 127.6, 127.4, 126.7, 124.7, 121.5, 121.5, 117.2, 111.2, 59.4, 21.6, 21.5. HRMS (ESI-TOF) *m/z* Calculated For $C_{31}H_{26}NO_3S$ $[M+H]^+$ 492.1628, found: 492.1623.

7-Methyl-2,4-diphenyl-1-tosyl-1,2-dihydrobenzofuro[3,2-*b*]pyridine (3la): 96 mg, 98% yield, pale yellow solid, m.p. = 139-141 °C, new compound, R_f = 0.30 (hexanes/ethyl acetate = 30:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.1 Hz, 1H), 7.54-7.43 (m, 4H), 7.40-7.33 (m, 3H), 7.30-7.20 (m, 6H), 7.16-7.11 (m, 1H), 7.07 (d, *J* = 8.0 Hz, 2H), 6.11 (d, *J* = 6.1 Hz, 1H), 5.72 (d, *J* = 6.1 Hz, 1H), 2.46 (s, 3H), 2.25 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 154.4, 146.8, 144.1, 138.3, 135.8, 134.6, 134.3, 131.1, 129.2, 128.6, 128.5, 128.3, 127.6, 127.6, 127.4, 125.3, 122.2, 121.3, 120.9, 117.5, 111.9, 59.4, 21.9, 21.5. HRMS (ESI-TOF) *m/z* Calculated For $C_{31}H_{26}NO_3S$ $[M+H]^+$ 492.1628, found: 492.1603.

1-(Methylsulfonyl)-2,4-diphenyl-1,2-dihydrobenzofuro[3,2-*b*]pyridine (3ma): 71 mg, 89% yield, pale yellow solid, m.p. = 154-155 °C, new compound, R_f = 0.15 (hexanes/ethyl acetate = 30:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03-7.88 (m, 1H), 7.87-7.74 (m, 2H), 7.60-7.42 (m, 6H), 7.36-7.22 (m, 5H), 6.34 (d, *J* = 6.1 Hz, 1H), 6.12 (d, *J* = 6.1 Hz, 1H), 2.94 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 154.2, 146.4, 138.1, 133.9, 131.8, 129.3, 129.0, 128.7, 128.5, 127.7, 127.2, 125.6, 124.2, 123.9, 121.8, 121.2, 117.9, 111.8, 59.2, 37.1. HRMS (ESI-TOF) *m/z* Calculated For $C_{24}H_{20}NO_3S$ $[M+H]^+$ 402.1158, found: 402.1148.

7-Methyl-1-((4-nitrophenyl)sulfonyl)-2,4-diphenyl-1,2-dihydrobenzofuro[3,2-*b*]pyridine (3na): 62 mg, 61% yield, pale yellow solid, m.p. = 192-193 °C, new compound, R_f = 0.20 (hexanes/ethyl acetate = 30:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.7 Hz, 2H), 8.04-7.89 (m, 1H), 7.77 (d, *J* = 8.7 Hz, 2H), 7.58-7.40 (m, 3H), 7.40-7.27 (m, 7H), 7.25-7.19 (m, 2H), 6.16 (d, *J* = 6.0 Hz, 1H), 5.84 (d, *J* = 6.0 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 154.1, 150.3, 147.5, 143.0, 137.2, 133.3, 131.5, 129.2, 128.9, 128.8, 128.7, 127.3, 127.2, 125.8, 124.2, 124.0, 123.8, 121.6, 121.3, 116.9, 112.0, 59.8. HRMS (ESI-TOF) *m/z* Calculated For $C_{32}H_{17}N_2O_5$ $[M+H]^+$ 509.1132, found: 509.1150.

2-Phenyl-1-tosyl-4-(4-(trifluoromethyl)phenyl)-1,2-dihydrobenzofuro[3,2-*b*]pyridine (3oa): 62 mg, 57% yield, white solid, m.p. = 158-159 °C, new compound, R_f = 0.35 (hexanes/ethyl acetate = 30:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13-7.96 (m, 1H), 7.66 (d, *J* = 8.3 Hz, 2H), 7.49 (d, *J* = 8.2 Hz, 4H), 7.46-7.41

(m, 1H), 7.41-7.29 (m, 6H), 7.29-7.24 (m, 1H), 7.11 (d, J = 8.0 Hz, 2H), 6.19 (d, J = 6.1 Hz, 1H), 5.86 (d, J = 6.1 Hz, 1H), 2.28 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 154.0, 146.6, 144.3, 137.7, 137.6, 134.5, 130.7 (q, J_{C-F} = 32.0 Hz), 129.9, 129.3, 128.8, 128.5, 127.9, 127.7, 127.3, 125.6, 125.5 (q, J_{C-F} = 4.0 Hz), 124.5, 124.1 (q, J_{C-F} = 271.0 Hz), 124.0, 123.1, 122.0, 118.0, 111.7, 59.4, 21.5. $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ -62.6. HRMS (ESI-TOF) *m/z* Calculated For $C_{31}H_{23}F_3NO_3S$ $[M+H]^+$ 546.1345, found: 546.1336.

4-Phenyl-2-(*p*-tolyl)-1-tosyl-1,2-dihydrobenzofuro[3,2-*b*]pyridine (3ab): 90 mg, 92% yield, pale yellow solid, m.p. = 199-201 °C, new compound, R_f = 0.30 (hexanes/ethyl acetate = 30:1). ^1H NMR (400 MHz, $CDCl_3$) δ 8.11-7.95 (m, 1H), 7.50-7.44 (m, 2H), 7.43-7.33 (m, 6H), 7.33-7.27 (m, 2H), 7.26-7.22 (m, 2H), 7.17-6.98 (m, 4H), 6.11 (d, J = 6.0 Hz, 1H), 5.76 (d, J = 6.0 Hz, 1H), 2.28 (s, 3H), 2.26 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 154.0, 147.4, 144.2, 138.2, 135.0, 134.6, 134.2, 131.0, 129.4, 129.3, 128.6, 128.5, 127.7, 127.6, 127.4, 125.2, 124.7, 123.8, 122.0, 121.9, 117.4, 111.7, 59.3, 21.5, 21.2. HRMS (ESI-TOF) *m/z* Calculated For $C_{31}H_{26}NO_3S$ $[M+H]^+$ 492.1628, found: 492.1620.

4-Phenyl-2-(*m*-tolyl)-1-tosyl-1,2-dihydrobenzofuro[3,2-*b*]pyridine (3ac): 88 mg, 90% yield, white solid, m.p. = 151-152 °C, new compound, R_f = 0.30 (hexanes/ethyl acetate = 30:1). ^1H NMR (400 MHz, $CDCl_3$) δ 8.15-7.95 (m, 1H), 7.52 (d, J = 8.2 Hz, 2H), 7.48-7.40 (m, 4H), 7.40-7.31 (m, 5H), 7.31-7.27 (m, 1H), 7.20 (t, J = 7.6 Hz, 1H), 7.14-7.06 (m, 3H), 6.17 (d, J = 6.1 Hz, 1H), 5.82 (d, J = 6.1 Hz, 1H), 2.35 (s, 3H), 2.29 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 153.9, 147.4, 144.2, 138.3, 138.0, 134.5, 134.1, 130.9, 129.2, 129.1, 128.6, 128.5, 128.4, 128.1, 127.6, 127.6, 125.2, 124.7, 124.4, 123.7, 121.9, 121.8, 117.4, 111.6, 59.4, 21.5, 21.4. HRMS (ESI-TOF) *m/z* Calculated For $C_{31}H_{26}NO_3S$ $[M+H]^+$ 492.1628, found: 492.1627.

2-(4-Methoxyphenyl)-4-phenyl-1-tosyl-1,2-dihydrobenzofuro[3,2-*b*]pyridine (3ad): 93 mg, 92% yield, white solid, m.p. = 201-202 °C, new compound, R_f = 0.20 (hexanes/ethyl acetate = 30:1). ^1H NMR (400 MHz, $CDCl_3$) δ 8.10-7.84 (m, 1H), 7.45 (d, J = 8.3 Hz, 2H), 7.42-7.33 (m, 6H), 7.33-7.27 (m, 2H), 7.25-7.19 (m, 2H), 7.07 (d, J = 8.0 Hz, 2H), 6.83-6.75 (m, 2H), 6.07 (d, J = 6.0 Hz, 1H), 5.71 (d, J = 6.0 Hz, 1H), 3.73 (s, 3H), 2.24 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 159.7, 154.0, 147.4, 144.1, 134.6, 134.2, 130.9, 129.8, 129.2, 128.8, 128.6, 128.5, 127.6, 125.2, 124.7, 123.8, 122.0, 121.9, 117.3, 114.1, 111.6, 59.1, 55.3, 21.5. HRMS (ESI-TOF) *m/z* Calculated For $C_{31}H_{26}NO_4S$ $[M+H]^+$ 508.1577, found: 508.1575.

2-(4-Fluorophenyl)-4-phenyl-1-tosyl-1,2-dihydrobenzofuro[3,2-*b*]pyridine (3ae): 94 mg, 95% yield, white solid, m.p. = 193-194 °C, new compound, R_f = 0.35 (hexanes/ethyl acetate = 30:1). ^1H NMR (400 MHz, $CDCl_3$) δ 8.04-7.89 (m, 1H), 7.49-7.33 (m, 8H), 7.30 (m, 2H), 7.21 (m, 2H), 7.06 (d, J = 8.0 Hz, 2H), 6.93 (t, J = 8.7 Hz, 2H), 6.06 (d, J = 6.0 Hz, 1H), 5.70 (d, J = 6.0 Hz, 1H), 2.23 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 162.8 (d, J_{C-F} = 247.1 Hz), 154.0, 147.3, 144.3, 134.5, 134.0, 133.8 (d, J_{C-F} = 2.9 Hz), 131.3, 129.3, 129.2 (d, J_{C-F} = 8.4 Hz), 128.8, 128.5, 127.6, 127.6, 125.4, 124.5, 123.9, 121.9, 121.3, 117.4, 115.6 (d,

$J_{C\text{-}F}$ = 21.7 Hz), 111.7, 58.8, 21.5; $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$) δ -113.8. HRMS (ESI-TOF) *m/z* Calculated For $C_{30}H_{23}FNO_3S$ $[M+H]^+$ 496.1377, found: 496.1370.

2-(4-Bromophenyl)-4-phenyl-1-tosyl-1,2-dihydrobenzofuro[3,2-*b*]pyridine (3af): 101 mg, 91% yield, yellow solid, m.p. = 214-216 °C, new compound, R_f = 0.35 (hexanes/ethyl acetate = 30:1). ^1H NMR (400 MHz, $CDCl_3$) δ 8.09-7.89 (m, 1H), 7.47-7.41 (m, 2H), 7.41-7.27 (m, 10H), 7.25-7.18 (m, 2H), 7.07 (d, *J* = 8.0 Hz, 2H), 6.05 (d, *J* = 6.1 Hz, 1H), 5.71 (d, *J* = 6.1 Hz, 1H), 2.24 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 154.0, 147.2, 144.4, 137.3, 134.4, 133.9, 131.8, 131.5, 129.3, 129.1, 128.8, 128.5, 127.6, 127.6, 125.5, 124.4, 124.0, 122.4, 121.8, 120.8, 117.5, 111.8, 58.8, 21.5. HRMS (ESI-TOF) *m/z* Calculated For $C_{30}H_{23}BrNO_3S$ $[M+H]^+$ 556.0577, found: 556.0574.

4-Phenyl-1-tosyl-2-(4-(trifluoromethyl)phenyl)-1,2-dihydrobenzofuro[3,2-*b*]pyridine (3ag): 69 mg, 63% yield, white solid, m.p. = 170-171 °C, R_f = 0.35 (hexanes/ethyl acetate = 30:1). ^1H NMR (400 MHz, $CDCl_3$) δ 8.07-7.92 (m, 1H), 7.71-7.48 (m, 4H), 7.48-7.43 (m, 2H), 7.42-7.35 (m, 4H), 7.35-7.28 (m, 2H), 7.25-7.19 (m, 2H), 7.08 (d, *J* = 8.0 Hz, 2H), 6.15 (d, *J* = 6.1 Hz, 1H), 5.76 (d, *J* = 6.1 Hz, 1H), 2.25 (s, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 154.0, 147.2, 144.5, 142.4, 134.3, 133.8, 131.7, 130.5 (q, $J_{C\text{-}F}$ = 32.0 Hz), 129.4, 128.9, 128.6, 127.6, 127.6, 126.0, 125.6 (q, $J_{C\text{-}F}$ = 4.0 Hz), 125.6, 124.3, 124.1 (q, $J_{C\text{-}F}$ = 271.0 Hz), 124.0, 121.8, 120.5, 117.6, 111.8. 58.8, 21.5. $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$) δ -62.6. HRMS (ESI-TOF) *m/z* Calculated For $C_{31}H_{23}F_3NO_3S$ $[M+H]^+$ 546.1345, found: 546.1345.

4-Phenyl-2-(thiophen-3-yl)-1-tosyl-1,2-dihydrobenzofuro[3,2-*b*]pyridine (3ah): 84 mg, 87% yield, white solid, m.p. = 90-91 °C, new compound, R_f = 0.20 (hexanes/ethyl acetate = 30:1). ^1H NMR (400 MHz, $CDCl_3$) δ 8.07-7.95 (m, 1H), 7.45 (d, *J* = 8.3 Hz, 2H), 7.43-7.34 (m, 4H), 7.34-7.28 (m, 2H), 7.25-7.18 (m, 4H), 7.17-7.12 (m, 1H), 7.07 (d, *J* = 8.1 Hz, 2H), 6.15 (d, *J* = 5.9 Hz, 1H), 5.76 (d, *J* = 5.9 Hz, 1H), 2.25 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 154.0, 147.2, 144.2, 139.2, 134.6, 134.1, 130.7, 129.3, 128.7, 128.5, 127.6, 126.8, 126.4, 125.3, 124.6, 123.9, 123.3, 121.8, 121.8, 117.5, 111.7, 56.4, 21.5. HRMS (ESI-TOF) *m/z* Calculated For $C_{28}H_{22}NO_3S_2$ $[M+H]^+$ 484.1036, found: 484.1041.

2-(*tert*-Butyl)-4-phenyl-1-tosyl-1,2-dihydrobenzofuro[3,2-*b*]pyridine (3ai): 10 mg, 11% yield, yellow oil, R_f = 0.45 (hexanes/ethyl acetate = 30:1). ^1H NMR (400 MHz, $CDCl_3$) δ 8.11-8.02 (m, 1H), 7.43-7.35 (m, 4H), 7.34-7.28 (m, 4H), 7.17-7.09 (m, 2H), 7.02 (d, *J* = 8.1 Hz, 2H), 5.52 (d, *J* = 5.9 Hz, 1H), 4.63 (d, *J* = 5.9 Hz, 1H), 2.22 (s, 3H), 0.93 (s, 9H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 153.9, 147.8, 143.9, 134.5, 134.2, 130.9, 129.0, 128.5, 128.4, 127.7, 127.5, 125.1, 124.7, 123.9, 122.6, 121.7, 119.0, 111.7, 66.2, 37.6, 25.9, 21.5. HRMS (ESI-TOF) *m/z* Calculated For $C_{28}H_{28}NO_3S$ $[M+H]^+$ 458.1784, found: 458.178.

General Procedure for Synthesis of Benzofuro[3,2-*b*]pyridines. The aromatization of 1,2-dihydrobenzofuro[3,2-*b*]pyridines **3** were conveniently conducted in ethanol through deprotection of tosyl group in presence of sodium hydroxide according to the known literature procedure.[13]

To the solution of the cyclization products **3** (0.15 mmol) in anhydrous ethanol (2.0 mL), powder sodium hydroxide (30 mg, 0.75 mmol) was added, the reaction mixture was refluxed in oil bath for 30 min. The solvent was evaporated under the reduced pressure, the crude product was purified by silica gel column chromatography using hexanes/ethyl acetate as eluent to give the desirable aromatization products **4**.

2,4-Diphenylbenzofuro[3,2-*b*]pyridine (4a): 43 mg, 89% yield, white solid, the known compound,[14] R_f = 0.85 (hexanes/ethyl acetate = 30:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, *J* = 7.7 Hz, 1H), 8.17 (d, *J* = 8.1 Hz, 2H), 8.11-8.03 (m, 2H), 7.96 (s, 1H), 7.67-7.50 (m, 7H), 7.50-7.43 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.0, 154.5, 146.6, 145.1, 139.9, 134.3, 132.7, 129.5, 129.2, 129.1, 128.9, 128.9, 128.7, 127.4, 123.8, 123.7, 121.7, 117.8, 112.4.

2-Phenyl-4-(*o*-tolyl)benzofuro[3,2-*b*]pyridine (4b): 45 mg, 90% yield, white solid, m.p. = 54-56 °C, new compound, R_f = 0.85 (hexanes/ethyl acetate = 30:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, *J* = 7.7 Hz, 1H), 8.15 (d, *J* = 7.4 Hz, 2H), 7.75 (s, 1H), 7.63-7.50 (m, 4H), 7.51-7.32 (m, 6H), 2.34 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.0, 154.0, 147.0, 144.4, 139.8, 136.7, 134.5, 133.9, 130.7, 130.0, 129.3, 129.2, 129.0, 128.8, 127.4, 126.2, 124.0, 123.7, 121.7, 120.2, 112.4, 20.4. HRMS (ESI-TOF) *m/z* Calculated For $C_{24}H_{18}NO$ $[M+H]^+$ 336.1383, found: 336.1386.

2-Phenyl-4-(*m*-tolyl)benzofuro[3,2-*b*]pyridine (4c): 48 mg, 95% yield, white solid, m.p. = 139-140 °C, new compound, R_f = 0.85 (hexanes/ethyl acetate = 30:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42-8.33 (m, 1H), 8.24-7.10 (m, 2H), 7.95 (s, 1H), 7.90-7.78 (m, 2H), 7.66 (d, *J* = 8.3 Hz, 1H), 7.62-7.52 (m, 3H), 7.53-7.44 (m, 3H), 7.35 (d, *J* = 7.6 Hz, 1H), 2.53 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.0, 154.4, 146.7, 145.0, 140.0, 138.8, 134.2, 132.9, 130.3, 129.4, 129.2, 129.0, 128.9, 128.7, 127.4, 126.1, 123.8, 123.6, 121.7, 117.9, 112.4, 21.8. HRMS (ESI-TOF) *m/z* Calculated For $C_{24}H_{18}NO$ $[M+H]^+$ 336.1383, found: 336.1382.

2-Phenyl-4-(*p*-tolyl)benzofuro[3,2-*b*]pyridine (4d): 46 mg, 91% yield, white solid, m.p. = 120-122 °C, new compound, R_f = 0.85 (hexanes/ethyl acetate = 30:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 7.6 Hz, 1H), 8.19-8.09 (m, 2H), 8.04-7.87 (m 3H), 7.65 (d, *J* = 8.3 Hz, 1H), 7.61-7.51 (m, 3H), 7.51-7.36 (m, 4H), 2.48 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 157.9, 154.4, 146.6, 144.9, 140.0, 139.6, 132.6, 131.3, 129.8, 129.1, 128.9, 128.7, 128.7, 127.4, 123.8, 123.6, 121.6, 117.5, 112.3, 21.5. HRMS (ESI-TOF) *m/z* Calculated For $C_{24}H_{18}NO$ $[M+H]^+$ 336.1383, found: 336.1383.

4-(4-Methoxyphenyl)-2-phenylbenzofuro[3,2-*b*]pyridine (4e): 47 mg, 89% yield, white solid, m.p. = 141-142 °C, new compound, R_f = 0.70 (hexanes/ethyl acetate = 30:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45-

8.28 (m, 1H), 8.21-8.11 (m, 2H), 8.04 (d, *J* = 8.7 Hz, 2H), 7.92 (s, 1H), 7.67-7.51 (m, 4H), 7.45 (t, *J* = 7.3 Hz, 2H), 7.11 (d, *J* = 8.7 Hz, 2H), 3.91 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 160.7, 157.9, 154.4, 146.5, 144.9, 140.1, 132.3, 130.2, 129.1, 128.9, 128.7, 127.4, 126.5, 123.9, 123.6, 121.7, 117.2, 114.6, 112.3, 55.5. HRMS (ESI-TOF) *m/z* Calculated For $C_{24}H_{18}NO_2$ $[M+H]^+$ 352.1332, found: 352.1330.

4-(4-Chlorophenyl)-2-phenylbenzofuro[3,2-b]pyridine (4f): 47 mg, 93% yield, white solid, m.p. = 164-166 °C, new compound, R_f = 0.80 (hexanes/ethyl acetate = 30:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46-8.25 (m, 1H), 8.19-8.09 (m, 2H), 8.03-7.95 (m, 2H), 7.89 (s, 1H), 7.66-7.51 (m, 6H), 7.50-7.43 (m, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 157.9, 154.5, 146.3, 145.2, 139.8, 135.6, 132.7, 131.3, 130.2, 129.4, 129.0, 128.8, 127.4, 123.8, 123.7, 121.8, 117.3, 112.3. HRMS (ESI-TOF) *m/z* Calculated For $C_{23}H_{15}ClNO$ $[M+H]^+$ 356.0837, found: 356.0837.

8-Methyl-2,4-diphenylbenzofuro[3,2-*b*]pyridine (4g): 46 mg, 91% yield, white solid, m.p. = 153-154 °C, new compound, R_f = 0.85 (hexanes/ethyl acetate = 30:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24-8.12 (m, 3H), 8.10-8.01 (m, 2H), 7.94 (s, 1H), 7.63-7.49 (m, 6H), 7.49-7.43 (m, 1H), 7.40-7.34 (m, 1H), 2.56 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 156.4, 154.2, 146.9, 145.1, 140.0, 134.4, 133.3, 132.5, 130.4, 129.4, 129.1, 128.9, 128.7, 127.4, 123.7, 121.5, 117.5, 111.8, 21.5. HRMS (ESI-TOF) *m/z* Calculated For $C_{24}H_{18}NO$ $[M+H]^+$ 336.1383, found: 336.1371.

7-Methyl-2,4-diphenylbenzofuro[3,2-*b*]pyridine (4h): 47 mg, 93% yield, white solid, m.p. = 150-151 °C, new compound, R_f = 0.85 (hexanes/ethyl acetate = 30:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 7.9 Hz, 1H), 8.19-8.12 (m, 2H), 8.10-8.02 (m, 2H), 7.92 (s, 1H), 7.64-7.49 (m, 5H), 7.48-7.40 (m, 2H), 7.32-7.27 (m, 1H), 2.57 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 158.5, 154.3, 146.5, 145.3, 140.2, 140.1, 134.4, 132.4, 129.4, 129.1, 128.9, 128.7, 127.4, 125.1, 121.2, 121.2, 117.3, 112.6, 22.3. HRMS (ESI-TOF) *m/z* Calculated For $C_{24}H_{18}NO$ $[M+H]^+$ 336.1383, found: 336.1376.

4-Phenyl-2-(*p*-tolyl)benzofuro[3,2-*b*]pyridine (4i): 46 mg, 92% yield, white solid, m.p. = 186-187 °C, new compound, R_f = 0.85 (hexanes/ethyl acetate = 30:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45-8.29 (m, 1H), 8.15-8.01 (m, 4H), 7.94 (d, *J* = 4.4 Hz, 1H), 7.73-7.57 (m, 4H), 7.57-7.43 (m, 2H), 7.35 (d, *J* = 7.9 Hz, 2H), 2.46 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 157.9, 154.5, 146.5, 144.9, 138.6, 137.1, 134.4, 132.6, 129.6, 129.4, 129.1, 129.1, 128.9, 127.2, 123.9, 123.6, 121.7, 117.4, 112.3, 21.4; HRMS (ESI-TOF) *m/z* Calculated For $C_{24}H_{18}NO$ $[M+H]^+$ 336.1383, found: 336.1378.

2-(4-Methoxyphenyl)-4-phenylbenzofuro[3,2-*b*]pyridine (4j): 49 mg, 93% yield, white solid, m.p. = 162-164 °C, new compound, R_f = 0.70 (hexanes/ethyl acetate = 30:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, *J* = 7.6 Hz, 1H), 8.17-8.09 (m, 2H), 8.09-8.00 (m, 2H), 7.90 (s, 1H), 7.70-7.49 (m, 5H), 7.49-7.42 (m, 1H), 7.06 (d, *J* = 8.8 Hz, 2H), 3.90 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 160.4, 157.9, 154.2, 146.3, 144.9,

134.4, 132.7, 132.6, 129.4, 129.1, 128.9, 128.6, 123.9, 123.6, 121.7, 117.1, 114.3, 112.4, 55.5. HRMS (ESI-TOF) *m/z* Calculated For $C_{24}H_{18}NO_2$ $[M+H]^+$ 352.1332, found: 352.1325.

2-(4-Bromophenyl)-4-phenylbenzofuro[3,2-*b*]pyridine (4k): 54 mg, 90% yield, white solid, m.p. = 213-215 °C, new compound, R_f = 0.85 (hexanes/ethyl acetate = 30:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, *J* = 7.7 Hz, 1H), 8.04 (d, *J* = 8.5 Hz, 4H), 7.91 (s, 1H), 7.69-7.63 (m, 3H), 7.63-7.56 (m, 3H), 7.56-7.51 (m, 1H), 7.50-7.42 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.1, 153.1, 146.7, 145.2, 138.8, 134.1, 132.8, 132.0, 129.6, 129.4, 129.2, 128.9, 123.8, 123.7, 123.2, 121.7, 117.4, 112.4. HRMS (ESI-TOF) *m/z* Calculated For $C_{23}H_{15}BrNO$ $[M+H]^+$ 400.0332, found: 400.0328.

4-Phenyl-2-(thiophen-3-yl)benzofuro[3,2-*b*]pyridine (4l): 47 mg, 96% yield, white solid, m.p. = 148-149 °C, new compound, R_f = 0.65 (hexanes/ethyl acetate = 30:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, *J* = 7.6 Hz, 1H), 8.12-7.98 (m, 3H), 7.87 (s, 1H), 7.83 (m, 1H), 7.68-7.51 (m, 5H), 7.50-7.42 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 157.9, 150.5, 146.3, 144.9, 142.5, 134.2, 132.7, 129.5, 129.2, 129.1, 128.9, 126.8, 126.4, 123.7, 123.6, 123.2, 121.7, 117.4, 112.3. HRMS (ESI-TOF) *m/z* Calculated For $C_{21}H_{14}NOS$ $[M+H]^+$ 328.0791, found: 328.0791.

One Pot Synthesis of Benzofuro[3,2-*b*]pyridines. Under nitrogen, the solution of $Cu(MeCN)_4BF_4$ (3.1 mg, 0.01 mmol) and ligand XantPhos (5.8 mg, 0.01 mmol) in 1,4-dioxane (0.5 mL) was stirred at room temperture for 1.5 h, azadienes **1** (0.20 mmol), 1,4-dioxane (2.5 mL), triethylamine (20.2 mg, 0.2 mmol), terminal alkynes **2** (0.6 mmol) was added in sequence. The reaction was stirred at 60 °C in oil bath for 2 days, which was monitored by thin-layer chromatography, then powder sodium hydroxide (40 mg, 1.0 mmol) was added, the reaction was stirred at 80 °C in oil bath for 2 h. The volatiles were evaporated under the reduced pressure, the residue was purified by silica gel column chromatography using hexanes/ethyl acetate as eluent to give the desired products **4**.

2,4-Diphenylbenzofuro[3,2-*b*]pyridine (**4a**): 56 mg, 87% yield; **4-(4-Chlorophenyl)-2-phenyl-benzofuro[3,2-b]pyridine** (**4f**): 65 mg, 91% yield; **7-Methyl-2,4-diphenylbenzofuro[3,2-*b*]pyridine** (**4h**): 61 mg, 86% yield.

Experiment at Gram Scale. Under nitrogen, the solution of $Cu(MeCN)_4BF_4$ (39.3 mg, 0.125 mmol) and ligand XantPhos (72.3 mg, 0.125 mmol) in 1,4-dioxane (6.0 mL) was stirred at room temperture for 2 h, azadiene **1a** (0.939 g, 2.5 mmol), 1,4-dioxane (31.5 mL), triethylamine (253 mg, 2.5 mmol), terminal alkyne **2a** (0.768 g, 7.5 mmol) was added in sequence. The reaction was stirred at 60 °C in oil bath for 55 h, which was monitored by thin-layer chromatography. The volatiles were evaporated under the reduced pressure, the residue was purified by silica gel column chromatography using hexanes/ethyl acetate as eluent to give the desired product **3aa**, 1.060 g, 89% yield.

Synthesis of Three Bioactive Molecules.

The Synthesis of Bioactive Molecules 5 and 6

Under nitrogen, the solution of $Cu(MeCN)_4BF_4$ (7.8 mg, 0.025 mmol) and ligand XantPhos (14.5 mg, 0.025 mmol) in 1,4-dioxane (2.0 mL) was stirred at room temperture for 1.5 h, azadienes **1a** (0.50 mmol), 1,4-dioxane (5.5 mL), triethylamine (50.6 mg, 0.50 mmol), terminal alkynes (1.50 mmol) was added in sequence. The reaction was stirred at 60 ^oC in oil bath for 2 days, which was monitored by thin-layer chromatography, then powder sodium hydroxide (100 mg, 2.5 mmol) was added, the reaction was stirred at 80 ^oC in oil bath for 2 h. The volatiles were evaporated under the reduced pressure, the residue was purified by silica gel column chromatography using hexanes/ethyl acetate = 80:1 as eluent to give the bioactive compounds **5** and **6**.

2-(4-Chlorophenyl)-4-phenylbenzofuro[3,2-*b*]pyridine (5): 160 mg, 90% yield, white solid, the known compound,[10e] R_f = 0.65 (hexanes/ethyl acetate = 30:1). ^1H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 7.7 Hz, 1H), 8.12 (d, *J* = 8.5 Hz, 2H), 8.06 (d, *J* = 7.4 Hz, 2H), 7.93 (s, 1H), 7.71-7.59 (m, 4H), 7.59-7.45 (m, 4H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 158.0, 153.1, 146.7, 145.2, 138.3, 134.9, 134.1, 132.8, 129.6, 129.4, 129.2, 129.1, 128.9, 128.6, 123.8, 123.6, 121.7, 117.4, 112.4.

2-(3-Methoxyphenyl)-4-phenylbenzofuro[3,2-*b*]pyridine (6): 157 mg, 89% yield, colorless oil, the known compound,[10d] R_f = 0.60 (hexanes/ethyl acetate = 30:1). ^1H NMR (400 MHz, $CDCl_3$) δ 8.43-8.32 (m, 1H), 8.12-8.01 (m, 2H), 7.96 (s, 1H), 7.79-7.73 (m, 1H), 7.74-7.40 (m, 8H), 7.11-6.88 (m, 1H), 3.95 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.3, 158.0, 154.3, 146.7, 145.0, 141.4, 134.3, 132.7, 129.9, 129.5, 129.3, 129.2, 128.9, 123.8, 123.7, 121.8, 119.9, 118.0, 114.6, 112.9, 112.4, 55.6

The Synthesis of Bioactive Molecule 7

Under nitrogen, to the solution of **6** (0.157 g, 0.45 mmol) in dichloromethane (2.0 mL) was added BBr_3 (0.338 g, 1.35 mmol) in dichloromethane (3.0 mL) at -78 ^oC and stirred for 10 min, then the reaction was moved to room temperature and stirred for overnight.[15] The reaction was quenched by 20 mL water and extracted with dichloromethane, dried over anhydrous sodium sulfate and concentrated. The crude products were purified by silica gel column chromatography using hexanes/ethyl acetate = 10:1 as eluent to give the bioactive compounds **7**.

3-(4-Phenylbenzofuro[3,2-*b*]pyridin-2-yl)phenol (7): 132 mg, 87% yield, shallow yellow solid, the known compound,[10d] R_f = 0.40 (hexanes/ethyl acetate = 5:1). ^1H NMR (400 MHz, $CDCl_3$) δ 8.46-8.25 (m, 1H), 8.14-7.97 (m, 2H), 7.92 (s, 1H), 7.89-7.82 (m, 1H), 7.66-7.49 (m, 6H), 7.43-7.32 (m, 2H), 7.05-6.80 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 158.0, 157.0, 154.6, 146.8, 144.8, 141.1, 134.0, 133.3, 130.2, 129.7, 129.5, 129.2, 129.0, 123.9, 123.2, 122.0, 119.5, 118.5, 116.4, 115.1, 112.4.

Determination of the Structure of Compound 3aa

To determine the structure of cascade product, the compound **3aa** was obtained as a colorless crystal after the recrystallization from dichloromethane/hexanes. Based on single crystal X-ray diffraction analysis, the structure of compound **3aa** was determined as 2,4-diphenyl-1-tosyl-1,2-dihydronzofuro[3,2-b]pyridine (see Supporting Information). The CCDC number is 1911582. These details can be obtained free of charge via www.ccdc.com.ac.uk /data_request/cif from the Cambridge Crystallographic Data Centre.

ASSOCIATED CONTENT

Supporting information

NMR spectra of products, This material is available free of charge via the internet at http://pubs.acs.org.

Copies of ^{1}H, $^{13}C\{^{1}H\}$and $^{19}F\{^{1}H\}$ spectra of all new compounds (PDF)

X-ray crystallography data **3aa** (CCDC 1911582) (CIF)

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Notes

The authors declare no competing financial interest.

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