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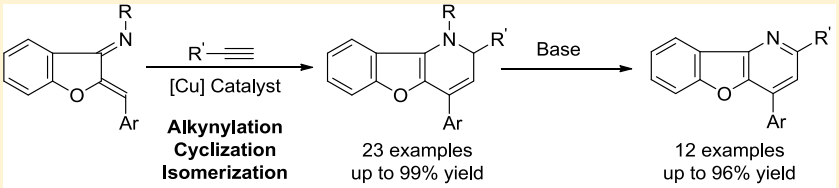
Copper-Catalyzed Alkynylation/Cyclization/Isomerization Cascade for Synthesis of 1,2-Dihydrobenzofuro[3,2-*b*]pyridines and Benzofuro[3,2-*b*]pyridines

Huan-Ping Xie,[†,‡] Lei Sun,[†] Bo Wu,[†] and Yong-Gui Zhou*[,†,§]

[†]State Key Laboratory of Catalysis, Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, P. R. China
[‡]University of Chinese Academy of Sciences, Beijing 100049, P. R. China
[§]State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, P. R. China

Supporting Information



Three bioactive molecules with potent topoisomerase inhibition were synthesized

ABSTRACT: An efficient copper-catalyzed cascade alkynylation/cyclization/isomerization reaction 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 into the corresponding benzofuro[3,2-*b*]pyridines under basic conditions. Additionally, benzofuro[3,2-*b*]pyridines can also be prepared from azadienes and terminal alkynes in a 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 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.

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 interest in the utilization of azadienes, we previously disclosed the systematic work of asymmetric nucleophilic addition and annulation.[9h−j,r] 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 follows. First, 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 alkynylation/

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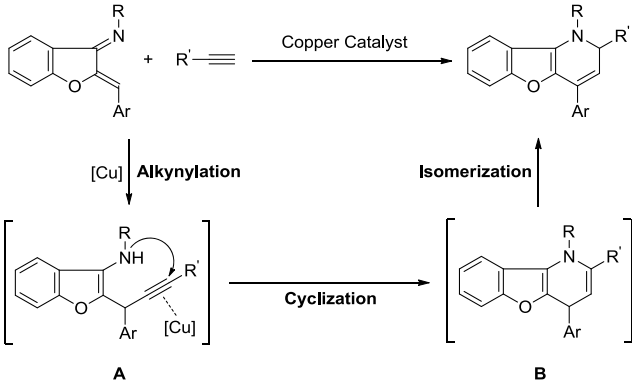
cyclization/isomerization reactions of azadienes with terminal alkynes for the synthesis of 1,2-dihydrobenzofuro[3,2-*b*]-pyridines (Scheme 1). The obtained 1,2-dihydrobenzofuro-[3,2-*b*]pyridines can be conveniently transformed into the corresponding benzofuro[3,2-*b*]pyridines under basic conditions.

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

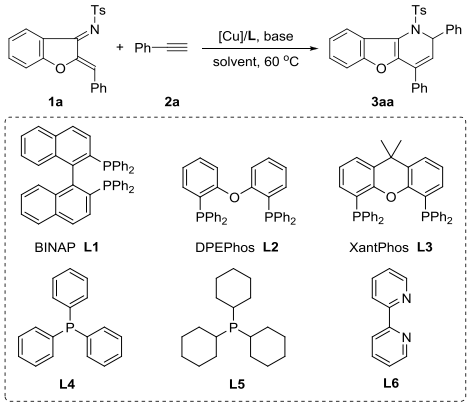


RESULTS AND DISCUSSION

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 °C, the cascade reaction occurred with a 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 Supporting Information (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** stopped 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 the base was explored. Good yield was obtained with *N*,*N*-diisopropylethylamine (DIPEA) 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 the catalyst, triethylamine as the base, and 1,4-dioxane as the solvent to perform the reaction at 60 °C.

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 are 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 a marginal effect on yields. For instance, the reaction afforded the target products **3ba** and **3ga** in 93

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 %.

and 96% yield, respectively. For azadienes with a methyl substituent at the 5- or 6-position of the benzofuryl ring, products **3ka** and **3la** were afforded in 96 and 98% yield, respectively. Sulfonylimines **1m** and **1n** were transformed successfully with moderate to good yields. Additionally, azadiene containing a 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 a strong electron-withdrawing group such as trifluoromethyl was introduced into 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 was stopped with cyclohexylacetylene.

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*]-

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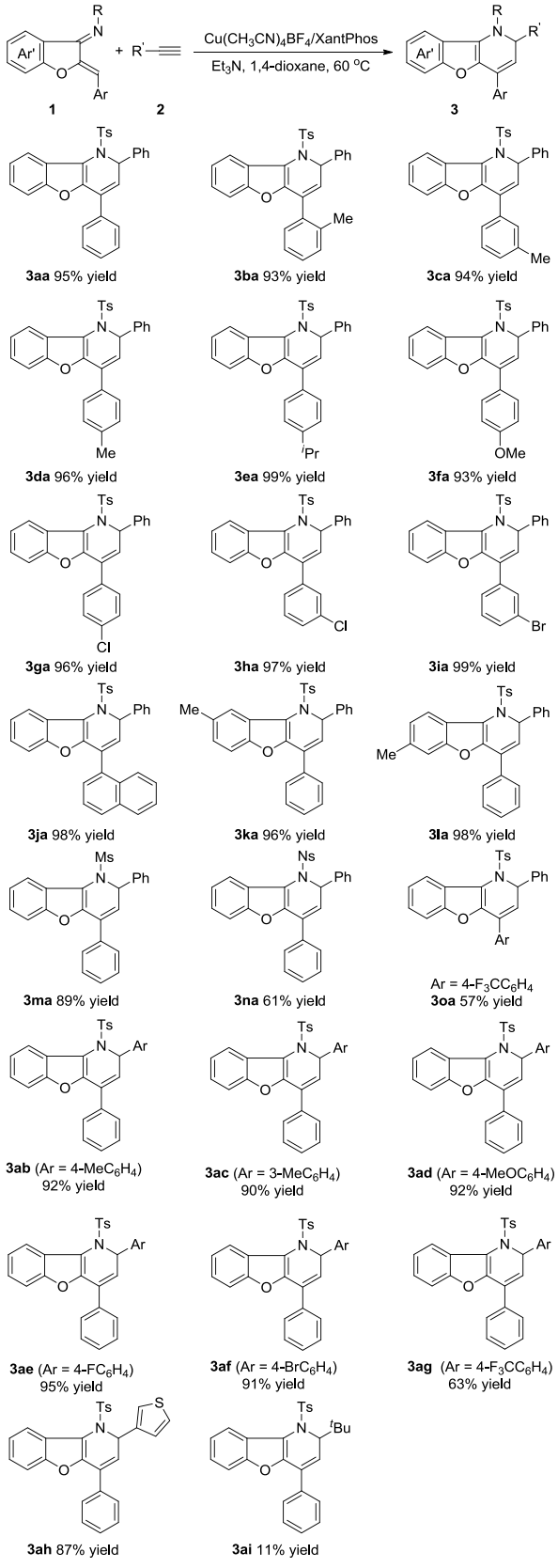
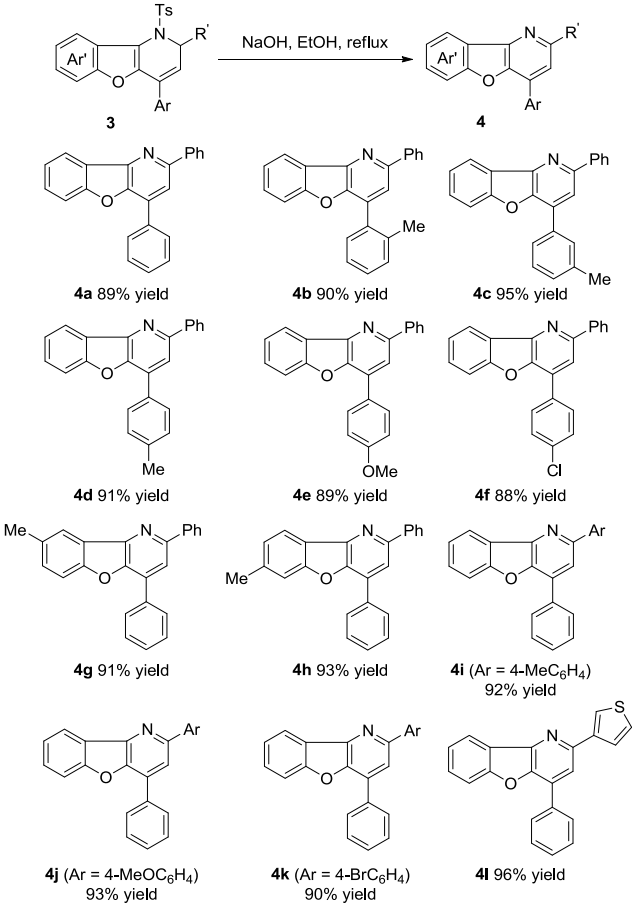
Scheme 2. Substrate Scope[a]



[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.

pyridines under basic conditions through the 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 deprotection and aromatization successfully, generating the desired benzofuro-[3,2-*b*]pyridine products **4a**–**k** in excellent yields. It is worth noting 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 the copper-catalyzed cascade reaction followed by basic deprotection and aromatization.

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 the $Cu(CH_3CN)_4BF_4$/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).

To further demonstrate the synthetic utility, three bioactive molecules with potent topoisomerase (topo) inhibition were

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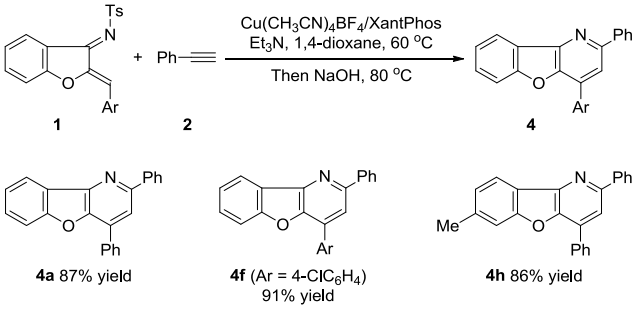
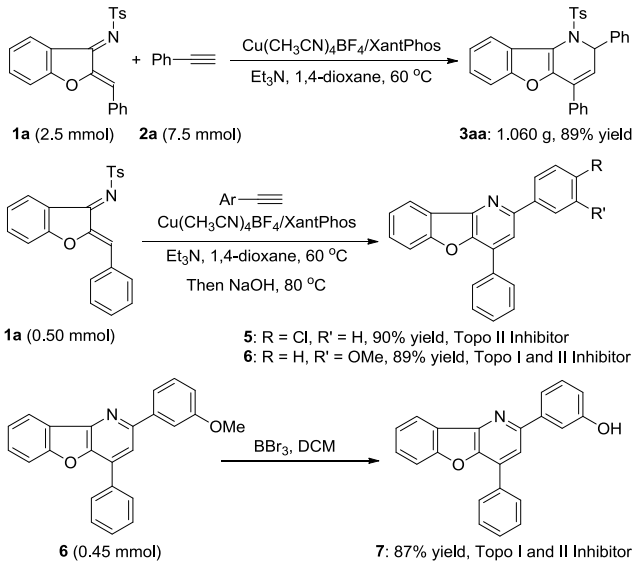
Scheme 4. One-Pot Synthesis of Benzofuro[3,2-*b*]pyridines[a]



[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.

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



synthesized in high yields (Scheme 5). 4-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 activities[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 to be a nonintercalative topo I and II dual catalytic inhibitors,[10d] and could also be 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 into the corresponding aromatic benzofuro[3,2-*b*]pyridines in high yields under the basic conditions. 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 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. ^1H NMR, ^{13}C NMR spectra were recorded at 400 and 100 MHz with a Bruker spectrometer. ^{19}F NMR spectra were recorded at 376 MHz with a Bruker spectrometer. Chemical shifts are reported in ppm using tetramethylsilane as an internal standard when using $CDCl_3$ as a solvent for ^1H NMR spectra. The following abbreviations were used to symbolize the multiplicities: s = singlet, d = doublet, t = triplet, m = multiplet, and brs = broad singlet. Flash column chromatography was performed on silica gel (200−300 mesh). All reactions were monitored by thin-layer chromatography (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 an 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−d**,[9a] **1e**,[9i] **1f−j**,[9a] **1k**,[9r] **1l**,[9j] **1m**,[9c] and **1n**[9i] are the known compound. Starting materials benzofuran-3(2*H*)-ones[12] and intermediate enones[9j,11] are the known compounds.

Under nitrogen, aluminum 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 was 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 °C in an ice bath. The reaction mixture was heated in an oil bath for reflux overnight. The solution was cooled, quenched with water, and extracted with dichloromethane. The combined organic phase was dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel flash chromatography using ethyl acetate/hexanes as the 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(2H)-ylidene)benzenesulfon-amide (**1o**).* 0.401 g, 18% yield, yellow solid, m.p. = 145−146 °C, new compound, R_f = 0.50 (hexanes/ethyl acetate = 40/1). ^1H 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); $^{13}C\{^1H\}$ 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* calcd for $C_{23}H_{17}F_3NO_3S$ $[M + H]^+$ 444.0876, found 444.0879.

General Procedure for the 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 temperature for 1.5 h, and azadienes **1** (0.20 mmol), 1,4-dioxane (2.5 mL), triethylamine (20.2 mg, 0.2 mmol), and terminal alkynes **2** (0.6 mmol) were added in sequence. The reaction mixture was stirred at 60 °C in an oil bath for 2 days, which was monitored by thin-layer chromatography. The

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solvent was evaporated under the reduced pressure and the crude product was directly purified by silica gel column chromatography (eluent: hexanes/ethyl acetate = 50:1−30:1) 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 °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 calcd 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 calcd 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 calcd 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 calcd 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 calcd 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{^{1}H} 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 calcd 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). ^{1}H 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{^{1}H} 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 calcd 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). ^{1}H 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{^{1}H} 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 calcd 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). ^{1}H 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{^{1}H} 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 calcd 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). ^{1}H 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{^{1}H} 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 calcd 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 calcd 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,

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111.9, 59.4, 21.9, 21.5. HRMS (ESI-TOF) m/z calcd 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 calcd 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 calcd 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{^{1}H} 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{^{1}H} NMR (376 MHz, $CDCl_3$) δ −62.6. HRMS (ESI-TOF) m/z calcd 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). ^{1}H 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{^{1}H} 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 calcd 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). ^{1}H 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{^{1}H} 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 calcd 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). ^{1}H 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{^{1}H} 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 calcd 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). ^{1}H 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{^{1}H} 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-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 calcd 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). ^{1}H 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 calcd 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). ^{1}H 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-F} = 32.0 Hz), 129.4, 128.9, 128.6, 127.6, 127.6, 126.0, 125.6 (q, J_{C-F} = 4.0 Hz), 125.6, 124.3, 124.1 (q, J_{C-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 calcd 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). ^{1}H 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 calcd 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). ^{1}H 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 calcd for $C_{28}H_{28}NO_3S$ $[M + H]^+$ 458.1784, found: 458.1789.

General Procedure for the 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 the tosyl group in the 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 an 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 the eluent to give the desirable aromatization products **4**.

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*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 calcd 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 calcd 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 calcd 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 calcd 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 calcd 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 calcd 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 calcd 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 calcd 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 calcd 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 calcd 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 calcd 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 temperature for 1.5 h, and azadienes **1** (0.20 mmol), 1,4-dioxane (2.5 mL), triethylamine (20.2 mg, 0.2 mmol), and terminal alkynes **2** (0.6 mmol) were added in sequence. The reaction mixture was stirred at 60 °C in an 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 an 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 the 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 temperature for 2 h, and azadiene **1a** (0.939 g, 2.5 mmol), 1,4-dioxane (31.5 mL), triethylamine (253 mg, 2.5 mmol), and terminal alkyne **2a** (0.768 g, 7.5 mmol) were added in sequence. The reaction mixture was stirred at 60 °C in an 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 the eluent to give the desired product **3aa**, 1.060 g, 89% yield.

Synthesis of Three Bioactive Molecules. *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

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mg, 0.025 mmol) in 1,4-dioxane (2.0 mL) was stirred at room temperature for 1.5 h, and azadienes **1a** (0.50 mmol), 1,4-dioxane (5.5 mL), triethylamine (50.6 mg, 0.50 mmol), and terminal alkynes (1.50 mmol) were added in sequence. The reaction mixture was stirred at 60 °C in an 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 °C in an 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 the 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). ^{1}H 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{^{1}H} 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). ^{1}H 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{^{1}H} 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.

*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 °C and stirred for 10 min, then the reaction mixture was moved to room temperature and stirred overnight.[15] The reaction was quenched with 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 the 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). ^{1}H 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{^{1}H} 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 the 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 the 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 Center.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.9b02512.

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)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: ygzhou@dicp.ac.cn.

ORCID

Yong-Gui Zhou: 0000-0002-3321-5521

Notes

The authors declare no competing financial interest.

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