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Highly Efficient Synthesis of 2-Substituted Benzo[*b*]furan Derivatives from the Cross-Coupling Reactions of 2-Halobenzo[*b*]furans with Organoalane Reagents

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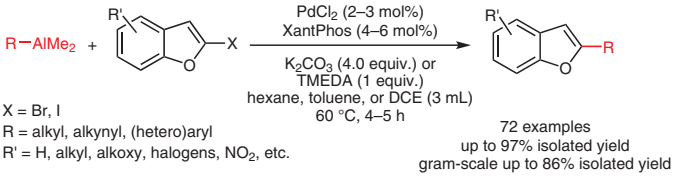

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Abstract A highly efficient and simple route for the synthesis of 2-substituted benzo[*b*]furans has been developed by palladium-catalyzed cross-coupling reaction of 2-halobenzo[*b*]furans with aryl, alkynyl, and alkylaluminum reagents. Various 2-aryl-, 2-alkynyl-, and 2-alkyl-substituted benzo[*b*]furan derivatives can be obtained in 23–97% isolated yields using 2–3 mol% $PdCl_2$/4–6 mol% XantPhos as the catalyst under mild reaction conditions. The aryls bearing electron-donating or electron-withdrawing groups in 2-halobenzo[*b*]furans gave products in 40–97% isolated yields. In addition, aluminum reagents containing thienyl, furanyl, trimethylsilanyl, and benzyl groups worked efficiently with 2-halobenzo[*b*]furans as well, and three bioactive molecules with 2-substituted benzo[*b*]furan skeleton were synthesized. Furthermore, the broad substrates scope and the typical maintenance of vigorous efficiency on gram scale make this protocol a potentially practical method to synthesize 2-substituted benzo[*b*]furan derivatives. On the basis of the experimental results, a possible catalytic cycle has been proposed.

Key words 2-substituted benzo[*b*]furans, palladium, organoalane reagents, 2-halobenzo[*b*]furan, cross-coupling reaction

2-Substituted benzo[*b*]furans are important structural scaffolds found in many natural products and pharmaceutical products.[1,2] Some of these compounds have been known to exhibit anti-inflammatory,[3] antitumor,[4] anticancer,[4,5] lipoxygenase inhibitor,[6] antifungal,[7] antiplasmodial,[8] antioxidant,[9] anti-HIV, and estrogenic activity[10] properties. In addition, they serve as building blocks for many organic transformations.[11] Thus, their synthesis and applications have attracted considerable attention in the chemical and pharmaceutical industries over the past decades.[2b,c] Developing some simple and effective method for the synthesis of 2-substituted benzo[*b*]furans from simple and easily available organic compounds is very important. In addition to the traditional synthetic methods,[12] transition-metal-mediated cross-coupling method provides an effective route for the synthesis of functionalized benzo[*b*]furans.[13] Until now numerous effective synthetic methodologies for the synthesis 2-substituted benzo[*b*]furans have been reported. Typical synthetic protocols for 2-substituted benzo[*b*]furans include transition-metal-catalyzed (such as Pt,[14] Pd,[15] Au/Ag,[16] Au,[17] Rh,[18] Ir,[19] Zn,[20] and Cu[21]) cyclization of *o*-alkynylphenols or *o*-allylphenols, transition-metal-catalyzed (such as Pd,[22] Cu,[23] and Fe[24]) coupling and cyclization of *o*-halophenols with alkynes, transition-metal-catalyzed 2-benzo[*b*]furanylboronic acid or 2-benzo[*b*]furanyl dimethyl silanolate coupling with aryl halides,[25] and 2-halobenzo[*b*]furan coupling with organometallic nucleophiles.[26] Transition-metal-free synthesis of 2-substituted benzo[*b*]furans include use of base[27] and by photochemical[28] or oxidative[7a,29] [3,3] sigmatropic rearrangement of *N*-trifluoroacetylene hydroxylamines,[30] and the intramolecular Wittig reaction.[31]

Despite these efforts the reported alternative methods for the synthesis of 2-substituted benzo[*b*]furans, in most cases, generally suffer from one or more drawbacks such as requirement of restrictive functional group and co-catalyst, limited substrate scope, multistep synthesis, and poor chemoselectivity, etc. Therefore, the development of more efficient and atom economical approaches for the preparation of 2-substituted benzo[*b*]furans remains as a desirable work. Among the reported synthetic methodologies for 2-substituted benzo[*b*]furans, the metal-catalyzed 2-halobenzo[*b*]furan coupling with organometallic nucleophiles is

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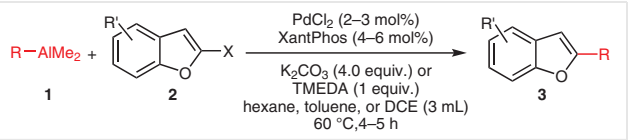
one of the most generally useful. Although organotin and bismuth reagents have been successfully used in the cross-coupling reaction of 2-halobenzo[*b*]furans, the cross-coupling reaction of 2-halobenzo[*b*]furans with organoaluminum reagents has not been reported. Recently, organoaluminum reagents are widely applied in organic synthesis due to their low toxicity, rich variety, easy preparation, and strong nucleophilic character.[32,33]

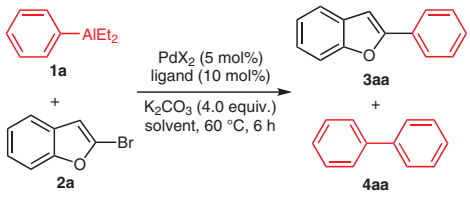
Previous studies show that organoaluminum reagents are highly efficient nucleophiles for cross-coupling reactions with aromatic halides[34] or benzylic halides.[35] In continuation of our effort to develop efficient cross-coupling reactions using reactive organometallic reagents,[33h,36] we herein report a $PdCl_2$ (2–3 mol%)/XantPhos (4–6 mol%) catalyzed cross-coupling reactions of 2-halobenzo[*b*]furans with organoaluminum reagents at 60–80 °C in short reaction time and in good yields for the synthesis of various 2-substituted benzo[*b*]furans. The process was simple and easily performed, and it provides an efficient method for the synthesis of 2-aryl/alkyl/alkynyl/alkenylbenzo[*b*]furans derivatives (Scheme 1).



Scheme 1 Palladium-catalyzed cross-coupling reactions of 2-halobenzo[*b*]furan derivatives with organoaluminum nucleophiles

To optimize the reaction conditions, effects of palladium source, phosphine ligand, solvent, reaction time, base, the amount of organoaluminum reagent, and the molar ratio of metal to ligand were investigated using the cross-coupling reaction of diethylphenylaluminum ($PhAlEt_2$) (**1a**) with 2-bromobenzo[*b*]furan (**2a**) as a model system (Table 1). In a preliminary study, 5 mol% $PdCl_2$ as catalyst and K_2CO_3 as base were used in the cross-coupling reaction of diethylphenylaluminum (**1a**) with 2-bromobenzo[*b*]furan (**2a**) to afford the coupled product 2-phenylbenzo[*b*]furan (**3aa**) in 27% isolated yield and a ratio of 76:24 in favor of the coupled product **3aa** (Table 1, entry 1). In the same conditions, other palladium sources were subsequently surveyed. Although $Pd(PPh_3)_4$, $Pd(AcO)_2$, and $Pd(acac)_2$ can effectively catalyze the cross-coupling reaction, the coupled product selectivities of **3aa** were lower than with $PdCl_2$ (entries 2–4). When 10 mol% of PPh_3 was used as ligand, the $PdCl_2$-catalyzed cross-coupling reaction of diethylphenylaluminum (**1a**) with 2-bromobenzo[*b*] furan (**2a**) produced the coupled product **3aa** in 36% yield (entry 5). The coupled product ratio is about 89:11 in favor of the coupled product **3aa**. The other phosphine ligands, XantPhos, Davephos, and PCy_3 were further examined (entries 6–8). It was found that the XantPhos was the best effective ligand for the reactivity and selectivity (60% yield, **3aa**:**4aa** = 92:8, entry 6). The other phosphine ligands, Davephos and PCy_3 did not provide satisfactory results. Solvents were then screened under the model reaction conditions, and the results are summarized in Table 1 (entries 9–11). The coupled product **3aa** could not be obtained in DMF. Hexane was suitable for this reaction since it gave higher yield. To our delight, when the loading of $PdCl_2$ was decreased from 5 to 3 mol%, the yield of coupled product **3aa** increased from 64 to 66%, and the selectivity of coupled product **3aa** increased from 72:28 to 91:9 (entries 9, 11).

Table 1 Optimizations of Cross-Coulping Reaction of Diethylphenylaluminum (**1a**) with 2-Bromobenzo[*b*]furan (**2a**) Catalyzed by Palladium[a]



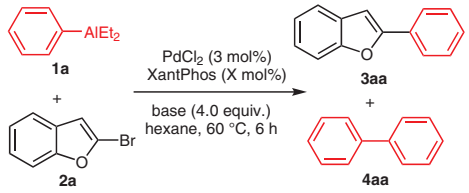
Entry	Pd salt	Ligand	Solvent	**3aa**:**4aa** (%)[b]	**3aa** Yield (%)[c]
1	$PdCl_2$	–	THF	76:24	27
2	$Pd(PPh_3)_4$	–	THF	63:37	37
3	$Pd(AcO)_2$	–	THF	52:48	19
4	$Pd(acac)_2$	–	THF	36:64	10
5	$PdCl_2$	PPh_3	THF	89:11	36
6	$PdCl_2$	XantPhos	THF	92:8	60
7	$PdCl_2$	Davephos	THF	82:18	31
8	$PdCl_2$	PCy_3	THF	79:21	38
9	$PdCl_2$	XantPhos	hexane	72:28	64
10	$PdCl_2$	XantPhos	DMF	-	NR
11[d]	$PdCl_2$	XantPhos	hexane	91:9	66

[a] Reaction conditions: **1a**/**2a**/PdX_2/Ligand = 0.8/0.5/0.025/0.05 mmol, solvent (3 mL), 60 °C, 4 h.
[b] The ratio of **3aa**:**4aa** was determined by isolated yield.
[c] Isolated yield of **3aa**. N.R.: No reaction.
[d] **1a**/**2a**/$PdCl_2$/XantPhos = 0.8/0.5/0.015/0.03 mmol.

To further study the reactivity and product selectivity, other parameters of the reaction conditions were optimized (Table 2). The effect of the amount of diethylphenylaluminum (**1a**) was also investigated. When the $PhAlEt_2$ (**1a**) loading was increased from 0.8 mmol to 1.0 mmol, the yield and selectivity of coupled product **3aa** increased from 66% to 77% and 91:9 to 92:8, respectively (Table 1, entry 11; Table 2, entry 1). However, when the $PhAlEt_2$ (**1a**) loading was increased from 1.0 mmol to 1.2 mmol, the yield and selectivity of coupled product **3aa** were unchanged (Table 2, entries 1 and 2). While, excellent selectivity (**3aa**:**4aa** = 92:8) and good yield of coupled product **3aa** (84%) were obtained when the reaction time was extended to 5 hours (Table 2, entry 1). When the ratio of $PdCl_2$ and XantPhos was

altered to 1:1 or 1:3, low yield of coupled product **3aa** was obtained (entries 3 and 4). When the reaction temperature was decreased from 60 to 50 °C, the yield and selectivity of coupled product **3aa** decreased from 84% to 38% and 92:8 to 88:12, respectively (entries 1 and 5). While the reaction temperature was increased, the yield and selectivity were unchanged (entries 1, 6). Then, various types of bases were used in the cross-coupling reaction as shown in Table 2 (entries 7 and 8). The low yield of coupled product **3aa** was obtained when CsF was used as the base. However, the coupled product **3aa** could not be obtained when using Cs_2CO_3 as base (entry 8). Therefore, the optimal cross-coupling reaction conditions are: $PdCl_2$ (3 mol%)/XantPhos (6 mol%), K_2CO_3 (2.0 mmol), $PhAlEt_2$ (**1a**; 1.0 mmol), 2-bromobenzo[*b*]furan (**2a**; 0.5 mmol) in hexane (3 mL) at 60 °C for 5 hours (entry 1).

Table 2 Optimizations of Cross-Coulping Reaction of Diethylphenylaluminum (**1a**) with 2-Bromobenzo[*b*]furan (**2a**) Catalyzed by Palladium[a]

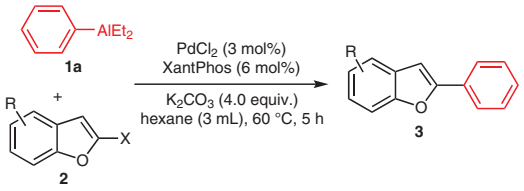


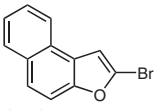
Entry	XantPhos (x mol%)	Base (4.0 equiv)	**3aa**:**4aa** (%)[b]	**3aa** Yield (%)[c]
1	6	K_2CO_3	92:8	77 (84)[d]
2[e]	6	K_2CO_3	91:9	78
3	9	K_2CO_3	89:11	54
4	3	K_2CO_3	92:8	35
5[f]	6	K_2CO_3	88:12	38
6[g]	6	K_2CO_3	91:9	84
7	6	CsF	91:9	42
8	6	Cs_2CO_3	–	NR

[a] Reaction conditions: **1a**/**2a**/$PdCl_2$ = 1.0/0.5/0.015 mmol, solvent (3 mL), 60 °C, 4 h.
[b] The ratio of **3aa**:**4aa** was determined by isolated yield.
[c] Isolated yield of **3aa**. N.R.: No reaction.
[d] Reaction time: 5 h.
[e] **1a**/**2a**/$PdCl_2$ = 1.2/0.5/0.015 mmol.
[f] Reaction temperature: 50 °C.
[g] Reaction temperature: 70 °C.

Under the optimized reaction conditions, the scope of catalytic cross-coupling reactions of diethylphenylaluminum (**1a**) with 2-bromobenzo[*b*]furan derivatives **2** was then explored, and results are presented in Table 3. In all the cases, high yields were obtained for all evaluated substrates (Table 3, entries 1–13). The cross-coupling reactions of 2-bromobenzo[*b*]furan derivatives **2a–l** with $PhAlEt_2$ (**1a**) gave 2-arylbenzo[*b*]furans **3aa–al** in excellent isolated yields (40–93%, entries 1–12). Reactions of 2-bromobenzo[*b*]furans bearing electron-donating or electron-withdrawing substituents on the aromatic ring furnished 2-arylbenzo[*b*]furans **3ab–al** in good to excellent isolated yields (entries 2–12). Importantly, with halogen-containing substituents (entries 7–9, 11, 12), dehalogenation was not observed, so the further functionalization using halogen functionality is feasible. Furthermore, 2-bromonaphtho-[2,3-*b*]furan afforded also the 2-phenylnaphtho[2,1-*b*]furan (**3am**) in isolated yield of 69% (entry 13). Interestingly, 2-iodobenzo[*b*]furan can also couple smoothly with diethylphenylaluminum (**1a**) affording the coupled 2-phenylbenzo[*b*]furan **3aa** in good isolated yield (83%) (entry 1). However, 2-bromofuran and 2-bromothiophene are not suitable for this cross-coupling reaction (entries 14, 15).

Table 3 The Cross-Coupling Reaction of Diethylphenylaluminum (**1a**) with 2-Halobenzo[*b*]furan Derivatives **2** Catalyzed by Palladium[a]



Entry	**2** R	Product **3**	Yield (%)[b]
1	H (**2a**)	**3aa**	84 (83)[c]
2	5-Me (**2b**)	**3ab**	77
3	6-Me (**2c**)	**3ac**	90
4	7-Me (**2d**)	**3ad**	73
5	6-MeO (**2e**)	**3ae**	73
6	7-MeO (**2f**)	**3af**	72
7	5-F (**2g**)	**3ag**	75
8	5-Cl (**2h**)	**3ah**	93
9	5-Br (**2i**)	**3ai**	76
10	5-NO_2 (**2j**)	**3aj**	40
11	5,7-Cl_2 (**2k**)	**3ak**	88
12	5,7-Br_2 (**2l**)	**3al**	60
13	 (**2m**)	**3am**	69
14	 (**2n**)	**3an**	0
15	 (**2o**)	**3ao**	0

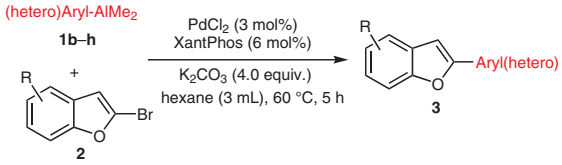
[a] Reaction conditions: **1a**/**2**/$PdCl_2$/XantPhos = 1.0/0.5/0.015/0.03 mmol, hexane (3 mL), 60 °C, 5 h.
[b] Isolated yield of **3**, two runs.
[c] Starting from 2-iodobenzo[*b*]furan.

The cross-coupling reactions of the various organoaluminum reagents **1b–h** with 2-bromobenzo[*b*]furans **2** gave 2-substituted benzo[*b*]furans **3** in moderate to good isolated yields (23–90%, Table 4, entries 1–27). The results indicate that the reactions of arylaluminum reagents with electron-donating or electron-withdrawing groups on the aromatic rings underwent the cross-coupling reactions smoothly to give the 2-arylbenzo[*b*]furans in moderate to good isolated yields (37–90%, entries 1–17). The 2-thienyl- and 3-thienylaluminum were also explored, and after 5 hours, 2-(2-thienyl)benzo[*b*]furans **3fa–fk** and 2-(3-thienyl)benzo[*b*]furans **3ga–gk** were formed with 26–78% and 24–58% isolated yields, respectively (entries 18–21, 22–25). Under the same conditions, 2-furylaluminum (**1h**), also reacted with 2-bromobenzo[*b*]furans **2h** and **2k** to provide the 2-(2-furnyl)benzo[*b*]furans **3hh** and **3hk** in 23–53% isolated yields (entries 26, 27).

Encouraged by the good performance of the current catalyst system shown above, we subsequently investigated cross-coupling reactions of alkynylaluminum reagents with 2-bromobenzo[*b*]furan derivatives. However, the cross-coupling reaction of 2-bromobenzo[*b*]furan (**2a**) with dimethyl(2-phenylethynyl)aluminum (PhC≡CAlMe$_2$, **5a**), employing 3 mol% PdCl$_2$ as the catalyst and 6 mol% of XantPhos, could not produce the 2-(2-phenylethynyl)benzo[*b*]furan **6aa**. Therefore, the reaction conditions were retuned. After extensive experimentation (Table S1), the best performed catalyst was found to be 2 mol% PdCl$_2$/4 mol% XantPhos and 1.0 equivalent TMEDA while the reaction was conducted in toluene at 60 °C for 4 hours, furnishing the coupled product **6aa** in 86% isolated yield.

With the optimized conditions in hand, the reaction scope was further explored on the substrates RC≡CAlMe$_2$ [R = Ph (**5a**), 4-MeC$_6$H$_4$ (**5b**), 4-FC$_6$H$_4$ (**5c**), TMS (**5d**), 2-thienyl (**5e**), PhCH$_2$ (**5f**)] and various 2-halobenzo[*b*]furans derivatives **2** using 2 mol% PdCl$_2$ and 4 mol% XantPhos and 1.0 equivalent TMEDA by conducting the reaction in toluene at 60 °C for 4 hours, and the results are summarized in Table 5. Satisfactory application scope was demonstrated by this section of experiment. The cross-coupling reaction can be applied to C(sp^2)–C(sp) bond formations, affording the coupled products 2-ynylbenzo[*b*]furans in 41–97% isolated yield (Table 5, entries 1–25). Cross-coupling reactions of substituted aromatic alkynylaluminum reagents **5a**, **5b**, and **5c** with various 2-bromobenzo[*b*]furans reagents containing different functional groups such as alkyl and halo could potentially take place, giving the corresponding coupled products 2-ynylbenzo[*b*]furan derivatives in moderate to excellent isolated yields (entries 2–9, 14–16, 19–21). Furthermore, the 2-bromonaphtho[2,3-*b*]furan (**2m**) can be smoothly coupled with various aromatic alkynylaluminum reagents **5a–c** to provide the corresponding coupled products 2-ynylnaphtho[2,3-*b*]furans in 84–97% isolated yields (entries 10, 17, 22). Reactions of dimethyl(trimethylsilanylethynyl)aluminum reagent (TMSC≡CAlMe$_2$) (**5d**) proceed

Table 4 Cross-Coulping Reactions of Arylaluminums **1b–h** with 2-Bromobenzo[*b*]furan Derivatives **2** Catalyzed by Palladium[a]



Entry	**1** R	**2** R	Product **3**	Yield (%)[b]
1	4-MeOC$_6$H$_4$AlMe$_2$	H (**2a**)	**3ba**	67
2	4-MeOC$_6$H$_4$AlMe$_2$	6-Me (**2c**)	**3bc**	72
3	4-MeOC$_6$H$_4$AlMe$_2$	5-Cl (**2h**)	**3bh**	58
4	4-MeOC$_6$H$_4$AlMe$_2$	5,7-Cl$_2$ (**2k**)	**3bk**	40
5	3-MeOC$_6$H$_4$AlMe$_2$	H (**2a**)	**3ca**	70
6	3-MeOC$_6$H$_4$AlMe$_2$	6-Me (**2c**)	**3cc**	71
7	3-MeOC$_6$H$_4$AlMe$_2$	5-Cl (**2h**)	**3ch**	90
8	3-MeOC$_6$H$_4$AlMe$_2$	5,7-Cl$_2$ (**2k**)	**3ck**	84
9	2-MeOC$_6$H$_4$AlMe$_2$	H (**2a**)	**3da**	67
10	2-MeOC$_6$H$_4$AlMe$_2$	6-Me (**2c**)	**3dc**	43
11	2-MeOC$_6$H$_4$AlMe$_2$	6-MeO (**2f**)	**3df**	37
12	2-MeOC$_6$H$_4$AlMe$_2$	5-Cl (**2h**)	**3dh**	81
13	2-MeOC$_6$H$_4$AlMe$_2$	5,7-Cl$_2$ (**2k**)	**3dk**	77
14	4-FC$_6$H$_4$AlMe$_2$	H (**2a**)	**3ea**	84
15	4-FC$_6$H$_4$AlMe$_2$	6-Me (**2c**)	**3ec**	61
16	4-FC$_6$H$_4$AlMe$_2$	5-Cl (**2h**)	**3eh**	81
17	4-FC$_6$H$_4$AlMe$_2$	5,7-Cl$_2$ (**2k**)	**3ek**	68
18	2-thienylAlMe$_2$	H (**2a**)	**3fa**	34
19	2-thienylAlMe$_2$	6-Me (**2c**)	**3fc**	26
20	2-thienylAlMe$_2$	5-Cl (**2h**)	**3fh**	78
21	2-thienylAlMe$_2$	5,7-Cl$_2$ (**2k**)	**3fk**	74
22	3-thienylAlMe$_2$	H (**2a**)	**3ga**	24
23	3-thienylAlMe$_2$	5-Cl (**2h**)	**3gh**	58
24	3-thienylAlMe$_2$	5-Br (**2i**)	**3gi**	53
25	3-thienylAlMe$_2$	5,7-Cl$_2$ (**2k**)	**3gk**	52
26	2-furylAlMe$_2$	5-Cl (**2h**)	**3hh**	53
27	2-furylAlMe$_2$	5,7-Cl$_2$ (**2k**)	**3hk**	23

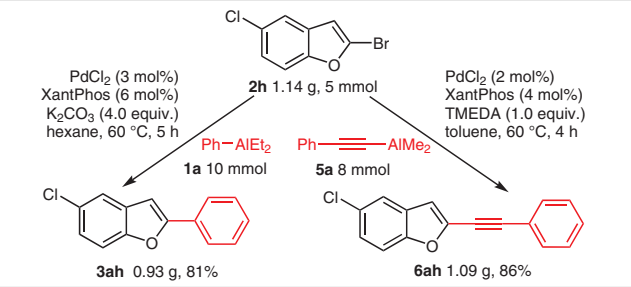
[a] Reaction conditions: **1**/**2**/PdCl$_2$/XantPhos = 1.0/0.5/0.015/0.03 mmol, hexane (3 mL), 60 °C, 5 h.
[b] Isolated yield of **3**, two runs.

with 2-bromobenzo[*b*]furans affording the corresponding coupled product 2-ynylbenzo[*b*]furan **6da** in 41% isolated yield only (entry 23). The cross-coupling reaction of dimethyl(2-thienylethynyl)aluminum (**5e**) with 2-bromobenzo[*b*]furan (**2a**) gave the coupled product 2-(2-thienylethynyl)benzo[*b*]furan (**6ea**) in an 88% isolated yield (entry 24). Furthermore, dimethyl(3-phenylprop-1-ynyl)aluminum (**5f**) is also suitable for this cross-coupling reaction, and afforded the corresponding coupled product 2-(3-

phenylprop-1-ynyl)benzo[*b*]furan (**6fa**) in an 87% isolated yield (entry 25). The coupling reactions with 2,5-dibromobenzo[*b*]furan proceeded regioselectively at 2-position affording the coupled products in good isolated yields (entries 7, 16, 21). The reactivity of 2-bromo-5,7-dichlorobenzo[*b*]furan was also found to be similar and coupling underwent at 2-position furnishing the corresponding 2-ynylbenzo[*b*]furan in an 81% isolated yield (entry 9). Importantly, the dehalogenation was not observed in the cross-coupling with 2-bromobenzo[*b*]furans containing halogen substituents (entries 6, 7, 9, 15, 16, 20, 21). Under the same reaction conditions, high isolated yield of 2-(2-phenylethynyl)benzo[*b*]furan **6aa** can be obtained by coupling 2-iodobenzo[*b*]furan with dimethyl(2-phenylethynyl)aluminum (**5a**) (90%, entry 1). Furthermore, 2-bromothiophene is also suitable for this cross-coupling reaction, and the coupling product 2-(phenylethynyl)thiophene **6an** was obtained in 76% isolated yield (entry 11). In contrast, 2-bromofuran is not suitable for the reaction system (entry 12)

Fortunately, we found that the 2-bromobenzo[*b*]furans can also be smoothly coupled with alkylaluminum reagents using 2 mol% $PdCl_2$/4 mol% XantPhos as catalyst in DCE at 60 °C for 4 hours (Table S2). The results are summarized in Table 6. From Table 6, we can see that the Me_3Al and Et_3Al are suitable for this coupling reaction, and afford the corresponding coupled products 2-alkylbenzo[*b*]furans in 61–88% isolated yields (Table 6, entries 1–5). Furthermore, the cross-coupling reactions of 2-iodobenzo[*b*]furan with Me_3Al afforded the coupled product 2-methylbenzo[*b*]furan in 72% isolated yield (entry 1). Especially, the dehalogenation was not observed in the cross-coupling with 5-chloro-2-bromobenzo[*b*]furan (**2h**) and 5-chloro-2-bromobenzo[*b*]furan (**2k**) (entries 2, 3). However, 2-bromofuran is not suitable for the reaction system (entry 6).

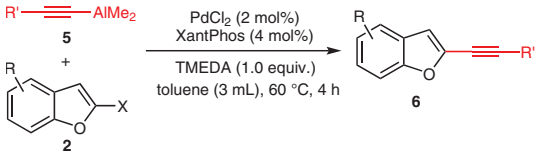
The reaction was found to be effective in gram-scale synthesis, which indicated its potential for practical application (Scheme 2). 2-Subtitutedbenzo[*b*]furans **3ah** and **6ah** were synthesized in 0.93–1.09 grams using this methodology.

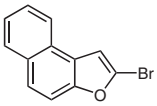
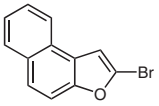
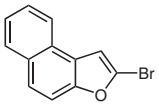


Scheme 2 Preparative-scale synthesis of selected compounds

Furthermore, these transformations can be utilized as precursors for the synthesis of important bioactive compounds. For example, 5-bromo-2-(2-arylethynyl)benzo

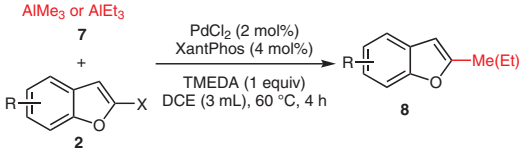
Table 5 Palladium-Catalyzed Cross-Coupling Reactions of 2-Halobenzo[*b*]furan Derivatives **2** with Various RC≡CAlMe_2 **5**[a]



Entry	**5** R′	**2** R	Product **6**	Yield (%)[b]
1	Ph (**5a**)	H (**2a**)	**6aa**	86 (90)[c]
2	Ph (**5a**)	5-Me (**2b**)	**6ab**	84
3	Ph (**5a**)	6-Me (**2c**)	**6ac**	75
4	Ph (**5a**)	6-MeO (**2e**)	**6ae**	93
5	Ph (**5a**)	7-MeO (**2f**)	**6af**	95
6	Ph (**5a**)	5-Cl (**2h**)	**6ah**	87
7	Ph (**5a**)	5-Br (**2i**)	**6ai**	44
8	Ph (**5a**)	5-NO_2 (**2j**)	**6aj**	44
9	Ph (**5a**)	5,7-Cl_2 (**2k**)	**6ak**	81
10	Ph (**5a**)	 (**2m**)	**6am**	96
11	Ph (**5a**)	 (**2n**)	**6an**	76
12	Ph (**5a**)	 (**2o**)	**6ao**	0
13	4-MeC_6H_4 (**5b**)	H (**2a**)	**6ba**	84
14	4-MeC_6H_4 (**5b**)	5-Me (**2b**)	**6bb**	83
15	4-MeC_6H_4 (**5b**)	5-Cl (**2h**)	**6bh**	86
16	4-MeC_6H_4 (**5b**)	5-Br (**2i**)	**6bi**	72
17	4-MeC_6H_4 (**5b**)	 (**2m**)	**6bm**	84
18	4-FC_6H_4 (**5c**)	H (**2a**)	**6ca**	93
19	4-FC_6H_4 (**5c**)	5-Me (**2b**)	**6cb**	95
20	4-FC_6H_4 (**5c**)	5-Cl (**2h**)	**6ch**	91
21	4-FC_6H_4 (**5c**)	5-Br (**2i**)	**6ci**	80
22	4-FC_6H_4 (**5c**)	 (**2m**)	**6cm**	97
23	$SiMe_3$ (**5d**)	H (**2a**)	**6da**	41
24	2-thienyl (**5e**)	H (**2a**)	**6ea**	88
25	$PhCH_2$ (**5f**)	H (**2a**)	**6fa**	87

[a] Reaction conditions: **5**/**2**/$PdCl_2$/XantPhos = 0.8/0.5/0.01/0.02 mmol, toluene (3 mL), 60 °C, 4 h.
[b] Isolated yield of **6**, two runs.
[c] Starting from 2-iodobenzo[*b*]furan.

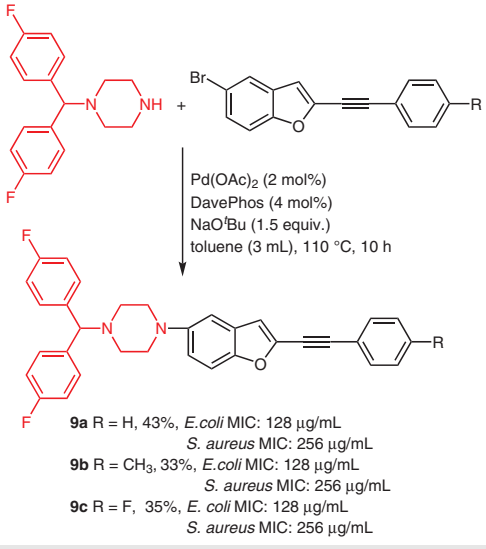
Table 6 Cross-Coupling Reactions of $AlMe_3$ (**7a**) or $AlEt_3$ (**7b**) with Various 2-Halobenzo[*b*]furans **2**[a]



Entry	**2** R	**7**	Product **8**	Yield (%)[b]
1	H (**2a**)	$AlMe_3$ (**7a**)	**8aa**	61 (72)[c]
2	5-Cl (**2h**)	$AlMe_3$ (**7a**)	**8ah**	67
3	5,7-Cl_2 (**2k**)	$AlMe_3$ (**7a**)	**8ak**	88
4	7-MeO (**2f**)	$AlMe_3$ (**7a**)	**8af**	73
5	H (**2a**)	$AlEt_3$ (**7b**)	**8ba**	83
6	 (**2n**)	$AlMe_3$ (**7a**)	**8na**	0

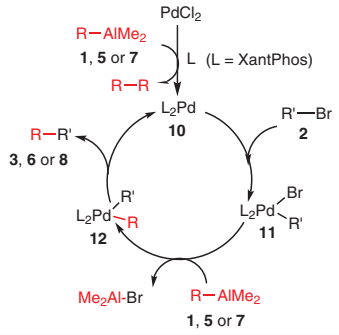
[a] Reaction conditions: **7**/**2**/$PdCl_2$/XantPhos = 0.6/0.5/0.01/0.02 mmol, DCE (3 mL), 60 °C, 4 h.
[b] Isolated yield of **8**, two runs.
[c] Starting from 2-iodobenzo[*b*]furan.

[*b*]furan could be functionalized to a variety of important bioactive compounds. The 1-[bis(4-fluorophenyl)methyl]-4-[2-(2-phenylethynyl)benzo[*b*]furan-5-yl]piperazine (**9a**), 1-[bis(4-fluorophenyl)methyl]-4-[2-(2-*p*-tolyl ethynyl)-benzo[*b*]furan-5-yl]piperazine (**9b**), and 1-[bis(4-fluorophenyl)methyl]-4-{2-[2-(4-fluorophenyl)ethynyl]benzo[*b*]-furan-5-yl}piperazine (**9c**) were obtained in 43%, 33%, and 35% isolated yields, respectively (Scheme 3). The antibacterial activity in vitro showed that the compounds had a certain inhibitory effect on *Escherichia coli* and *Staphylococcus aureus*.



Scheme 3 Functionalization of 5-bromo-2-(2-arylethynyl)benzo[*b*]-furans to different bioactive compounds derivatives

A proposed possible reaction mechanism for the cross-coupling reaction, based on known palladium chemistry and the above results on the coupling reaction of 2-bromobenzo[*b*]furans with organometallic nucleophiles, is shown in Scheme 4. The first step is the oxidative addition of 2-bromobenzo[*b*]furans **2** to Pd(0) phosphine complex **10** (which in turn is from $PdCl_2$ and $RAlMe_2$ **1** reagents) to form the organopalladium(II) bromide intermediate **11**. Transmetalation of $RAlMe_2$ (**1**, **5**, or **7**) with complex **11** gives R′PdR(II) intermediate **12** and Me_2AlBr. Finally, complex **12** undergoes reductive elimination to afford the desired coupling product of 2-substituted benzo[*b*]furans **3**, **6**, or **8** and regenerate the active Pd(0) species for the next catalytic cycle.



Scheme 4 The proposed catalytic cycle for the formation of coupled products **3**, **6**, or **8**

In conclusion, a palladium-catalyzed cross-coupling reaction of 2-halobenzo[*b*]furans with organoaluminum reagents is reported. The cross-coupling reactions of 2-halobenzo[*b*]furans with (hetero)arylaluminum reagents afforded the coupled products 2-(hetero)arylbenzo[*b*]furan derivatives in good to excellent yields (up to 93%). The 2/3-thienylaluminum reagents afforded the coupled products 2-thienylbenzo[*b*]furans in moderate yields (23–78%). Furthermore, coupling reactions of arylaluminum reagents proceeded with electron-neutral, electron-rich, and electron-deficient 2-bromobenzo[*b*]furans affording the coupled products 2-arylbenzo[*b*]furans in 23–97% isolated yields. The cross-coupling reactions of 2-halobenzo[*b*]furans with alkynylaluminum reagents produced the 2-ynylbenzo[*b*]furans in 41–97% isolated yields. Importantly, reactions of dimethyl(trimethylsilanylethynyl)aluminum reagent proceeded with electron-neutral 2-bromobenzo[*b*]furan affording the corresponding coupled product [2-(benzo[*b*]furan-2-yl)ethynyl]trimethylsilane in 41% isolated yield. Dimethyl (2-thienylethynyl)aluminum and dimethyl-(3-phenylprop-1-ynyl)aluminum are also suitable to this cross-coupling reaction, and afforded the corresponding coupled products in 87–88% isolated yields. Furthermore, coupling reactions of 2-bromobenzo[*b*]furans proceeded with electron-neutral, electron-rich, and electron-deficient alkynylaluminum reagents affording the coupled products

2-ynylbenzo[*b*]furans in 44–97% isolated yields. Me_3Al and Et_3Al are also suitable to this coupling reaction, and afford the corresponding coupled products 2-alkylbenzo[*b*]furans in 61–88% isolated yields. More importantly, the reaction was found to be effective in gram-scale synthesis, and can be utilized as precursors for the synthesis of important bioactive compounds. The methodology provides useful procedure for the synthesis of 2-aryl-, alkynyl-, and alkyl-substituted benzo[*b*]furan derivatives. The coupling reactions with 2,5-dibromobenzo[*b*]furan and 2-bromo-5,7-dichlorobenzo[*b*]furan proceeded regioselectively at 2-position furnishing the corresponding 2-substituted benzo[*b*]furans in good yields. Further studies on the application of this catalytic system to the synthesis of bioactive compounds are currently under way.

^{1}H NMR and ^{13}CNMR spectra were recorded on a Varian 400 MHz spectrometer. The chemical shifts are reported relative to TMS. Analytical TLC was performed on silica 60F-254 plates. Flash column chromatography was carried out on silica gel (200–400 mesh). HRMS were recorded on a Bruker Micro TOF spectrometer equipped with an ESI ion source. All reactions were carried out under N_2 atmosphere. Chemical reagents and solvents were purchased from Adamas-beta, Aldrich, and XPKchem, and were used without further purification with the exception of the following reagents: THF, Et_2O, and toluene were distilled from Na under N_2. DCE was distilled from CaH_2 under N_2. Diethylphenylaluminum (**1a**) and dimethylarylaluminums **1b–h** reagents were prepared according to literature procedures[36b,i,37] [see also Supporting Information (SI)]. Compounds of alkynylaluminum reagents **5a–f** were synthesized according to literature procedures[36j,k] (see also SI). The preparation of 2-bromobenzo[*b*]furans **2** is described in SI. Purification of reaction products was carried out by flash chromatography.

Coupling Reaction of 2-Halobenzo[*b*]furans with Arylaluminums; General Procedure

Under a dry N_2 atmosphere, to a mixture of $PdCl_2$ (0.0026 g, 0.015 mmol), XantPhos (0.0174 g, 0.03 mmol), and K_2CO_3 (0.276 g, 2.0 mmol) in a reaction vessel was added an arylaluminum **1** (1.0 mmol) in hexane (3 mL) followed by the addition of the corresponding 2-halobenzo[*b*]furan **2** (0.50 mmol). The resulting solution was stirred at 60 °C for 5 h. After completion of the reaction, the mixture was diluted with sat. aq NH_4Cl (5 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layers were dried (anhyd Na_2SO_4), filtered, and evaporated under vacuum. The residue was subjected to flash column chromatography on silica gel (hexane or EtOAc or hexane) to afford the corresponding coupled product **3**.

2-Phenylbenzofuran (3aa)[26i]

White oil; yield: 82 mg (84%); mp 113–115 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85 (d, *J* = 7.7 Hz, 2 H), 7.56 (d, *J* = 7.5 Hz, 1 H), 7.51 (d, *J* = 8.0 Hz, 1 H), 7.42 (t, *J* = 7.4 Hz, 2 H), 7.33 (t, *J* = 7.3 Hz, 1 H), 7.24 (dt, *J* = 7.6, 22.1 Hz, 2 H), 6.99 (s, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.9, 154.9, 130.5, 129.2, 128.8, 128.6, 124.9, 124.3, 123.0, 121.0, 111.2, 101.3.

5-Methyl-2-phenylbenzofuran (3ab)[26j]

White solid; yield: 80 mg (77%); mp 112–115 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.84 (d, *J* = 7.4 Hz, 2 H), 7.41 (m, 3 H), 7.34 (s, 2 H), 7.08 (d, *J* = 8.1 Hz, 1 H), 6.92 (s, 1 H), 2.43 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 156.0, 153.3, 132.3, 130.6, 129.3, 128.8, 128.4, 125.5, 124.8, 120.7, 110.7, 101.1, 21.4.

6-Methyl-2-phenylbenzofuran (3ac)[22g]

White solid; yield: 94 mg (90%); mp 113–114 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83 (d, *J* = 7.6 Hz, 2 H), 7.44–7.41 (m, 3 H), 7.33 (d, *J* = 5.7 Hz, 2 H), 7.04 (d, *J* = 7.8 Hz, 1 H), 6.96 (s, 1 H), 2.47 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.3, 134.6, 130.7, 128.7, 128.3, 126.7, 124.7, 124.3, 120.4, 111.4, 101.2, 21.8.

7-Methyl-2-phenylbenzofuran (3ad)[23h]

White solid; yield: 81 mg (73%); mp 131–133 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83 (d, *J* = 7.8 Hz, 2 H), 7.44–7.40 (m, 3 H), 7.33 (d, *J* = 6.8 Hz, 2 H), 7.07 (d, *J* = 8.4 Hz, 1 H), 6.92 (s, 1 H), 2.43 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 156.0, 153.3, 132.3, 130.6, 129.3, 128.8, 128.4, 125.5, 124.8, 120.7, 110.7, 101.1, 21.4.

6-Methoxy-2-phenylbenzofuran (3ae)[15e]

White solid; yield: 82 mg (73%); mp 79–80 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.73 (d, *J* = 8.3 Hz, 2 H), 7.35 (d, *J* = 7.5 Hz, 3 H), 7.23 (t, *J* = 7.5 Hz, 1 H), 6.99 (s, 1 H), 6.86 (s, 1 H), 6.79 (d, *J* = 6.6 Hz, 1 H), 3.78 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.1, 155.9, 155.1, 130.7, 128.7, 128.0, 124.4, 122.5, 121.0, 112.0, 101.1, 95.9, 55.7.

7-Methoxy-2-phenylbenzofuran (3af)[26i]

White solid; yield: 81 mg (72%); mp 66–68 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88 (d, *J* = 7.9 Hz, 2 H), 7.42 (t, *J* = 7.3 Hz, 2 H), 7.33 (t, *J* = 7.1 Hz, 1 H), 7.23–7.10 (m, 2 H), 7.00 (s, 1 H), 6.79 (d, *J* = 7.3 Hz, 1 H), 4.03 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 156.0, 145.3, 144.1, 130.9, 130.3, 128.7, 128.6, 125.0, 123.6, 113.3, 106.6, 101.6, 56.1.

5-Fluoro-2-phenylbenzofuran (3ag)[23h]

White solid; yield: 80 mg (75%); mp 95–97 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83 (d, *J* = 7.6 Hz, 2 H), 7.44–7.41 (m, 3 H), 7.35 (t, *J* = 7.3 Hz, 1 H), 7.21 (dd, *J* = 2.2, 8.6 Hz, 1 H), 6.99 (dd, *J* = 2.4, 9.1 Hz, 1 H), 6.95 (s, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 160.5, 158.1, 157.7, 151.1, 130.1, 129.9, 128.9, 128.8, 125.0, 112.0, 111.8, 111.7, 111.7, 106.4, 106.2, 101.4, 101.4.

5-Chloro-2-phenylbenzofuran (3ah)[26j]

White solid; yield: 106 mg (93%); mp 145–146 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83 (d, *J* = 7.3 Hz, 2 H), 7.52 (s, 1 H), 7.44–7.41 (m, 4 H), 7.22 (d, *J* = 9.0 Hz, 1 H), 6.93 (s, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.3, 153.2, 130.5, 129.9, 129.0, 128.8, 128.4, 125.0, 124.4, 120.4, 112.1, 100.8.

5-Bromo-2-phenylbenzofuran (3ai)[26i]

White solid; yield: 104 mg (76%); mp 138–140 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85 (d, *J* = 7.7 Hz, 2 H), 7.70 (s, 1 H), 7.47–7.44 (m, 2 H), 7.37 (d, *J* = 9.7 Hz, 3 H), 6.96 (s, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.2, 153.6, 131.2, 129.9, 129.0, 128.8, 127.1, 125.0, 123.5, 116.0, 112.6, 100.6.

5-Nitro-2-phenylbenzofuran (3aj)[23h]

Yellow solid; yield: 48 mg (40%); mp 151–152 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.51 (s, 1 H), 8.22 (d, *J* = 9.0 Hz, 1 H), 7.88 (d, *J* = 7.6 Hz, 2 H), 7.60 (d, *J* = 9.1 Hz, 1 H), 7.53–7.40 (m, 3 H), 7.13 (s, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.2, 157.6, 129.7, 129.6, 129.2, 129.0, 128.8, 125.3, 120.1, 117.3, 111.4, 101.6.

5,7-Dichloro-2-phenylbenzofuran (3ak)[26i]

White solid; yield: 116 mg (88%); mp 128–130 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85 (d, *J* = 7.4 Hz, 2 H), 7.42 (dq, *J* = 7.0, 16.0 Hz, 4 H), 7.25 (s, 1 H), 6.94 (s, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.1, 149.2, 131.5, 129.4, 129.3, 128.9, 128.6, 125.2, 124.2, 119.0, 117.1, 101.2.

5,7-Dibromo-2-phenylbenzofuran (3al)[38]

White solid; yield: 106 mg (60%); mp 138–140 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.84 (d, *J* = 7.8 Hz, 2 H), 7.59 (s, 1 H), 7.53 (s, 1 H), 7.45 (t, *J* = 7.5 Hz, 2 H), 7.41–7.34 (m, 1 H), 6.95 (s, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.9, 151.0, 131.7, 129.4, 129.3, 129.2, 128.9, 125.2, 122.6, 116.0, 104.6, 101.1.

2-Phenylnaphtho[2,1-*b*]furan (3am)[23h]

White solid; yield: 0.084 mg (69%); mp 145–147 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13 (d, *J* = 8.1 Hz, 1 H), 7.93–7.89 (m, 3 H), 7.74–7.62 (m, 2 H), 7.57 (t, *J* = 7.5 Hz, 1 H), 7.48–7.42 (m, 4 H), 7.33 (t, *J* = 7.3 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.4, 152.4, 130.6, 130.4, 128.9, 128.8, 128.3, 127.6, 126.3, 125.2, 124.7, 124.6, 124.6, 123.5, 112.3, 100.5.

2-(4-Methoxyphenyl)benzofuran (3ba)[26i]

White solid; yield: 75 mg (67%); mp 145–146 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.84 (d, *J* = 8.4 Hz, 2 H), 7.58 (dd, *J* = 7.6, 17.2 Hz, 2 H), 7.29 (p, *J* = 7.2 Hz, 2 H), 7.01 (d, *J* = 8.4 Hz, 2 H), 6.92 (s, 1 H), 3.88 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 160.0, 156.0, 154.7, 129.5, 126.4, 123.7, 123.3, 122.8, 120.6, 114.2, 111.0, 99.7, 55.3.

2-(4-Methoxyphenyl)-6-methylbenzofuran (3bc)[15d]

White solid; yield: 86 mg (72%); mp 138–140 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76 (d, *J* = 8.2 Hz, 2 H), 7.41 (d, *J* = 7.8 Hz, 1 H), 7.30 (s, 1 H), 7.03 (d, *J* = 7.8 Hz, 1 H), 6.95 (d, *J* = 8.2 Hz, 2 H), 6.82 (s, 1 H), 3.83 (s, 3 H), 2.47 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.8, 155.5, 155.1, 134.0, 126.9, 126.2, 124.2, 123.6, 120.0, 114.2, 111.3, 99.5, 55.3, 21.7.

5-Chloro-2-(4-methoxyphenyl)benzofuran (3bh)[26j]

White solid; yield: 75 mg (58%); mp 162–163 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80 (d, *J* = 8.2 Hz, 2 H), 7.39 (s, 1 H), 7.23 (d, *J* = 1.8 Hz, 1 H), 6.98 (d, *J* = 8.2 Hz, 2 H), 6.87–6.77 (m, 1 H), 3.86 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 160.6, 158.3, 149.0, 131.8, 128.5, 126.8, 123.7, 122.1, 118.7, 116.9, 114.3, 99.5, 55.4.

5,7-Dichloro-2-(4-methoxyphenyl)benzofuran (3bk)[21d]

White solid; yield: 58 mg (40%); mp 166–168 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76 (d, *J* = 8.6 Hz, 2 H), 7.49 (s, 1 H), 7.39 (d, *J* = 8.6 Hz, 1 H), 7.19 (d, *J* = 8.7 Hz, 1 H), 6.96 (d, *J* = 8.4 Hz, 2 H), 6.79 (s, 1 H), 3.85 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 160.3, 157.5, 153.0, 130.9, 128.3, 126.5, 123.8, 122.7, 120.1, 114.3, 111.9, 99.1, 55.4.

2-(3-Methoxyphenyl)benzofuran (3ca)[26i]

White solid; yield: 78 mg (70%); mp 52–55 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57 (d, *J* = 7.5 Hz, 1 H), 7.52 (d, *J* = 8.1 Hz, 1 H), 7.45 (d, *J* = 7.6 Hz, 1 H), 7.41 (s, 1 H), 7.34 (t, *J* = 7.9 Hz, 1 H), 7.31–7.25 (m, 1 H), 7.25–7.19 (m, 1 H), 7.01 (s, 1 H), 6.89 (d, *J* = 8.1 Hz, 1 H), 3.87 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.9, 155.7, 154.9, 131.8, 129.9, 129.2, 124.3, 123.0, 120.9, 117.5, 114.5, 111.2, 110.1, 101.6, 55.4.

2-(3-Methoxyphenyl)-6-methylbenzofuran (3cc)

White solid; yield: 85 mg (71%); mp 63–65 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47–7.29 (m, 5 H), 7.05 (d, *J* = 7.9 Hz, 1 H), 6.96 (s, 1 H), 6.88 (d, *J* = 8.2 Hz, 1 H), 3.87 (s, 3 H), 2.47 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.9, 155.3, 155.2, 134.6, 132.0, 129.8, 126.6, 124.4, 120.4, 117.4, 114.2, 111.4, 110.0, 101.5, 55.3, 21.8.

HRMS (ESI): *m*/*z* calcd for $C_{16}H_{15}O_2^+$ (M + H)$^+$: 239.10666; found: 239.10689.

5-Chloro-2-(3-methoxyphenyl)benzofuran (3ch)[26j]

White solid; yield: 116 mg (90%); mp 69–70 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.52 (d, *J* = 2.2 Hz, 1 H), 7.42 (d, *J* = 8.7 Hz, 2 H), 7.39–7.32 (m, 2 H), 7.22 (dd, *J* = 2.2, 8.7 Hz, 1 H), 6.96–6.88 (m, 2 H), 3.88 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.9, 157.2, 153.2, 131.2, 130.5, 129.9, 128.5, 124.4, 120.4, 117.6, 114.8, 112.1, 110.3, 101.1, 55.4.

5,7-Dichloro-2-(3-methoxyphenyl)benzofuran (3ck)[21d]

White solid; yield: 123 mg (84%);mp 103–105 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44–7.30 (m, 4 H), 7.23 (d, *J* = 1.9 Hz, 1 H), 6.94–6.86 (m, 2 H), 3.86 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.9, 157.9, 149.2, 131.4, 130.5, 130.0, 128.7, 124.3, 119.0, 117.8, 117.1, 115.0, 110.6, 101.5, 55.4.

2-(2-Methoxyphenyl)benzofuran (3da)[23h]

White solid; 75 mg (67%); mp 77–79 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07 (d, *J* = 7.8 Hz, 1 H), 7.59 (d, *J* = 7.5 Hz, 1 H), 7.50 (d, *J* = 7.1 Hz, 1 H), 7.35 (s, 1 H), 7.33–7.18 (m, 3 H), 7.07 (td, *J* = 1.2, 7.6 Hz, 1 H), 6.98 (dd, *J* = 1.2, 8.3 Hz, 1 H), 3.97 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 156.5, 153.9, 152.2, 129.8, 129.3, 127.1, 124.1, 122.6, 121.0, 120.8, 119.4, 111.0, 110.8, 106.3, 55.4.

2-(2-Methoxyphenyl)-6-methylbenzofuran (3dc)

White solid; yield: 51 mg (43%); mp 84–86 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04 (dd, *J* = 1.8, 7.8 Hz, 1 H), 7.45 (d, *J* = 7.8 Hz, 1 H), 7.28 (d, *J* = 18.3 Hz, 3 H), 7.08–7.00 (m, 2 H), 6.96 (d, *J* = 8.2 Hz, 1 H), 3.95 (s, 3 H), 2.46 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 156.4, 154.3, 151.6, 134.4, 129.0, 127.3, 126.9, 124.1, 120.8, 120.5, 119.6, 111.1, 111.0, 106.3, 55.4, 21.8.

HRMS (ESI): *m*/*z* calcd for $C_{16}H_{15}O_2^+$ (M + H)$^+$: 239.10666; found: 239.10634.

6-Methoxy-2-(2-methoxyphenyl)benzofuran (3df)[12a]

White solid; yield: 47 mg (37%); mp 85–86 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01 (d, *J* = 7.8 Hz, 1 H), 7.44 (d, *J* = 8.4 Hz, 1 H), 7.31–7.20 (m, 2 H), 7.09–7.02 (m, 2 H), 6.96 (d, *J* = 8.3 Hz, 1 H), 6.85 (d, *J* = 8.5 Hz, 1 H), 3.96 (s, 3 H), 3.84 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.0, 156.1, 154.9, 151.4, 128.7, 126.6, 123.2, 121.1, 120.8, 119.6, 111.6, 111.0, 106.2, 95.6, 55.7, 55.4.

5-Chloro-2-(2-methoxyphenyl)benzofuran (3dh)[21d]

White solid; yield: 105 mg (81%); mp 97–100 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04 (d, *J* = 7.7 Hz, 1 H), 7.54 (d, *J* = 2.1 Hz, 1 H), 7.41 (d, *J* = 8.6 Hz, 1 H), 7.37–7.31 (m, 1 H), 7.29 (s, 1 H), 7.25–7.19 (m, 1 H), 7.12–7.05 (m, 1 H), 7.00 (d, *J* = 8.3 Hz, 1 H), 3.99 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 156.6, 153.7, 152.2, 131.2, 129.7, 128.1, 127.1, 124.2, 120.8, 120.5, 118.8, 111.7, 111.0, 105.8, 55.5.

5,7-Dichloro-2-(2-methoxyphenyl)benzofuran (3dk)[21d]

White solid; yield: 113 mg (77%); mp 128–130 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05 (d, *J* = 7.8 Hz, 1 H), 7.37 (d, *J* = 1.9 Hz, 1 H), 7.34–7.29 (m, 1 H), 7.24–7.18 (m, 2 H), 7.08–7.02 (m, 1 H), 6.94 (d, *J* = 8.3 Hz, 1 H), 3.94 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 156.6, 154.4, 148.2, 132.1, 130.1, 128.3, 127.3, 124.0, 120.8, 119.1, 118.2, 116.8, 111.0, 106.1, 55.4.

2-(4-Fluorophenyl)benzofuran (3ea)[26j]

White solid; yield: 89 mg (84%); mp 118–120 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77–7.70 (m, 2 H), 7.48 (d, *J* = 7.6 Hz, 1 H), 7.42 (d, *J* = 8.0 Hz, 1 H), 7.19–7.12 (m, 2 H), 7.04 (t, *J* = 8.4 Hz, 2 H), 6.85 (s, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.1, 161.6, 155.0, 154.8, 129.2, 126.8, 126.7, 124.3, 123.0, 120.9, 116.0, 115.8, 111.1, 101.0, 101.0.

2-(4-Fluorophenyl)-6-methylbenzofuran (3ec)[15d]

White solid; yield: 69 mg (61%); mp 129–131 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80 (dd, *J* = 5.6, 7.9 Hz, 2 H), 7.44 (d, *J* = 7.9 Hz, 1 H), 7.32 (s, 1 H), 7.12 (t, *J* = 8.5 Hz, 2 H), 7.06 (d, *J* = 7.8 Hz, 1 H), 6.89 (s, 1 H), 2.49 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 163.9, 161.5, 155.3, 154.4, 134.6, 126.6, 126.6, 126.5, 124.4, 120.3, 115.9, 115.7, 111.4, 100.9, 100.9, 21.7.

5-Chloro-2-(4-fluorophenyl)benzofuran (3eh)[26j]

White solid; yield: 99 mg (81%); mp 127–128 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82–7.73 (m, 2 H), 7.50 (s, 1 H), 7.39 (d, *J* = 8.7 Hz, 1 H), 7.22 (t, *J* = 8.4 Hz, 1 H), 7.12 (t, *J* = 8.4 Hz, 2 H), 6.84 (s, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.3, 161.8, 156.4, 153.2, 130.5, 128.5, 126.9, 126.9, 124.4, 120.4, 116.1, 115.9, 112.0, 100.5, 100.4.

5,7-Dichloro-2-(4-fluorophenyl)benzofuran (3ek)[26i]

White solid; yield: 96 mg (68%); mp 142–143 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.87–7.77 (m, 2 H), 7.41 (s, 1 H), 7.25 (s, 1 H), 7.14 (t, *J* = 8.5 Hz, 2 H), 6.87 (s, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.6, 162.1, 157.2, 149.2, 131.4, 128.8, 127.2, 127.1, 125.6, 124.3, 119.0, 117.1, 116.2, 115.9, 100.9, 100.9.

2-(Thiophen-2-yl)benzofuran (3fa)[26j]

White solid; 34 mg (34%); mp 94–95 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53 (d, *J* = 7.3 Hz, 1 H), 7.48 (d, *J* = 7.5 Hz, 2 H), 7.32 (d, *J* = 5.0 Hz, 1 H), 7.25 (d, *J* = 6.6 Hz, 2 H), 7.08 (t, *J* = 4.8 Hz, 1 H), 6.85 (s, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 154.5, 151.3, 133.3, 129.1, 127.9, 125.8, 124.6, 124.3, 123.1, 120.8, 111.1, 101.1.

6-Methyl-2-(thiophen-2-yl)benzofuran (3fc)[26j]

White solid; yield: 28 mg (26%); mp 77–79 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45–7.36 (m, 2 H), 7.28 (s, 2 H), 7.05 (d, *J* = 6.5 Hz, 2 H), 6.79 (s, 1 H), 2.45 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.0, 150.7, 134.6, 133.5, 127.8, 126.6, 125.4, 124.5, 124.2, 120.2, 111.3, 101.0, 21.8.

HRMS (ESI): *m*/*z* calcd for $C_{13}H_{11}OS^+$ (M + H)$^+$: 215.05251; found: 215.05270.

5-Chloro-2-(thiophen-2-yl)benzofuran (3fh)

White solid; yield: 92 mg (78%); mp 150–151 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.49 (s, 2 H), 7.37 (dd, *J* = 6.8, 11.4 Hz, 2 H), 7.21 (d, *J* = 8.5 Hz, 1 H), 7.10 (t, *J* = 4.8 Hz, 1 H), 6.78 (s, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 152.9, 152.7, 132.7, 130.5, 128.6, 128.0, 126.4, 125.1, 124.4, 120.2, 112.0, 100.5.

5,7-Dichloro-2-(thiophen-2-yl)benzofuran (3fk)

White solid; yield: 100 mg (74%); mp 92–94 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.52 (s, 1 H), 7.41–7.32 (m, 2 H), 7.22 (s, 1 H), 7.12–7.06 (m, 1 H), 6.76 (s, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 153.5, 148.9, 131.9, 131.4, 128.8, 128.0, 126.9, 125.9, 124.2, 118.8, 117.0, 100.9.

2-(Thiophen-3-yl)benzofuran (3ga)[26j]

White solid; yield: 22 mg (24%); mp 131–132 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72 (s, 1 H), 7.55 (d, *J* = 7.2 Hz, 1 H), 7.47 (d, *J* = 6.5 Hz, 2 H), 7.38 (s, 1 H), 7.30–7.22 (m, 2 H), 6.82 (s, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 154.5, 152.7, 132.2, 129.1, 126.5, 125.1, 124.1, 122.9, 121.4, 120.8, 111.0, 101.0.

5-Chloro-2-(thiophen-3-yl)benzofuran (3gh)

White solid; yield: 68 mg (58%); mp 130–133 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72 (s, 1 H), 7.51 (s, 1 H), 7.45–7.36 (m, 3 H), 7.21 (d, *J* = 8.7 Hz, 1 H), 6.76 (s, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 154.1, 152.9, 131.7, 130.5, 128.4, 126.7, 125.0, 124.2, 122.1, 120.3, 111.9, 100.5.

5-Bromo-2-(thiophen-3-yl)benzofuran (3gi)

White solid; yield: 74 mg (53%); mp 125–127 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72 (s, 1 H), 7.65 (s, 1 H), 7.44–7.36 (m, 2 H), 7.34 (s, 2 H), 6.74 (s, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 153.9, 153.2, 131.6, 131.1, 126.9, 126.7, 125.0, 123.4, 122.1, 116.0, 112.4, 100.3.

5,7-Dichloro-2-(thiophen-3-yl)benzofuran (3gk)

White solid; yield: 70 mg (52%); mp 109–110 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.81 (s, 1 H), 7.44 (d, *J* = 5.0 Hz, 1 H), 7.40 (s, 2 H), 7.25 (s, 1 H), 6.77 (s, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 154.8, 148.9, 131.4, 131.0, 128.7, 126.9, 125.0, 124.1, 123.0, 118.9, 117.0, 100.9.

5-Chloro-2-(furan-2-yl)benzofuran (3hh)

White solid; yield: 58 mg (53%); mp 74–76 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51 (s, 2 H), 7.39 (d, *J* = 8.7 Hz, 1 H), 7.22 (d, *J* = 8.7 Hz, 1 H), 6.82 (d, *J* = 7.3 Hz, 2 H), 6.52 (s, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 145.7, 143.4, 130.1, 128.7, 124.5, 121.0, 120.5, 112.3, 112.0, 111.8, 108.3, 100.5.

5,7-Dichloro-2-(furan-2-yl)benzofuran (3hk)

White solid; yield: 28 mg (23%); mp 98–101 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.81 (s, 1 H), 7.44 (d, *J* = 5.0 Hz, 1 H), 7.40 (s, 2 H), 7.25 (s, 1 H), 6.77 (s, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 150.1, 145.0, 143.8, 131.1, 128.9, 124.4, 119.1, 117.0, 111.9, 109.2, 107.0, 100.8.

Coupling Reaction of 2-Halobenzo[*b*]furans with Alkynylaluminums; General Procedure

Under a dry N_2 atmosphere, to a mixture of $PdCl_2$ (0.0013 g, 0.01 mmol), XantPhos (0.0116 g, 0.02 mmol), and TMEDA (1 equiv) in a reaction vessel was added an alkynylaluminum **5** (0.80 mmol) in toluene (3 mL) followed by the addition of the corresponding 2-halidebenzo[*b*]furan **2** (0.50 mmol). The resulting solution was stirred at 60 °C for 4 h. After completion of the reaction, the mixture was diluted with sat. aq NH_4Cl (5 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layers were dried (anhyd Na_2SO_4), filtered, and evaporated under vacuum. The residue was subjected to flash column chromatography on silica gel (hexane or EtOAc and hexane) to afford the corresponding coupled product **6**.

2-(Phenylethynyl)benzofuran (6aa)[21c]

White solid; yield: 95 mg (86%); mp 72–74 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60–7.45 (m, 4 H), 7.34 (d, *J* = 14.0 Hz, 4 H), 7.24 (t, *J* = 7.6 Hz, 1 H), 7.00 (s, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 154.9, 138.8, 131.7, 129.2, 128.5, 127.7, 125.6, 123.3, 121.8, 121.2, 111.6, 111.3, 95.1.

5-Methyl-2-(phenylethynyl)benzofuran (6ab)[21c]

White solid; yield: 98 mg (84%); mp 76–78 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55 (dd, *J* = 3.1, 6.6 Hz, 2 H), 7.38–7.30 (m, 5 H), 7.12 (d, *J* = 8.4 Hz, 1 H), 6.91 (s, 1 H), 2.41 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 153.4, 138.8, 132.8, 131.7, 129.1, 128.5, 127.9, 127.0, 122.0, 120.9, 111.4, 110.7, 94.9, 21.3.

6-Methyl-2-(phenylethynyl)benzofuran (6ac)

White solid; yield: 87 mg (75%); mp 70–71 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.56 (dd, *J* = 3.0, 6.7 Hz, 2 H), 7.43–7.23 (m, 5 H), 7.05 (d, *J* = 9.4 Hz, 1 H), 6.94 (s, 1 H), 2.45 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.4, 138.2, 136.1, 131.6, 129.0, 128.5, 125.2, 124.9, 122.0, 120.7, 111.6, 111.4, 94.9, 21.8.

HRMS (ESI): *m*/*z* calcd for $C_{17}H_{13}O^+$ (M + H)$^+$: 233.09609; found: 233.09613.

6-Methoxy-2-(phenylethynyl)benzofuran (6ae)[21c]

White solid; yield: 115 mg (93%); mp 116–118 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59–7.52 (m, 2 H), 7.41–7.31 (m, 4 H), 6.98 (d, *J* = 1.4 Hz, 1 H), 6.92 (s, 1 H), 6.88 (dd, *J* = 2.2, 8.6 Hz, 1 H), 3.82 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.2, 156.1, 137.9, 131.5, 128.9, 128.5, 122.1, 121.3, 121.0, 112.7, 111.6, 95.6, 94.9, 55.7.

7-Methoxy-2-(phenylethynyl)benzofuran (6af)

White solid; yield: 118 mg (95%); mp 120–122 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58–7.52 (m, 2 H), 7.38–7.32 (m, 3 H), 7.17–7.12 (m, 2 H), 6.97 (s, 1 H), 6.82 (dd, *J* = 3.5, 5.5 Hz, 1 H), 3.99 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 145.2, 144.3, 139.0, 131.6, 129.3, 129.1, 128.5, 124.0, 121.9, 113.4, 111.7, 107.5, 94.9, 79.6, 56.1.

HRMS (ESI): *m*/*z* calcd for $C_{17}H_{13}O_2^+$ (M + H)$^+$: 249.09101; found: 249.09077.

5-Chloro-2-(phenylethynyl)benzofuran (6ah)[21c]

White solid; yield: 110 mg (87%); mp 66–68 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57–7.53 (m, 2 H), 7.49 (d, *J* = 2.2 Hz, 1 H), 7.40–7.29 (m, 5 H), 7.25 (dd, *J* = 2.1, 8.7 Hz, 1 H), 6.90 (s, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 153.2, 140.2, 129.4, 129.1, 128.9, 125.8, 121.5, 120.6, 112.2, 110.9, 95.7.

5-Bromo-2-(phenylethynyl)benzofuran (6ai)[21c]

White solid; yield: 65 mg (44%); mp 78–80 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.61 (d, *J* = 2.0 Hz, 1 H), 7.55–7.51 (m, 2 H), 7.38–7.28 (m, 5 H), 6.87 (s, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 153.6, 140.0, 131.8, 129.7, 129.4, 128.6, 128.4, 123.7, 121.5, 116.5, 112.7, 110.8, 95.8.

5-Nitro-2-(phenylethynyl)benzofuran (6aj)[21c]

Yellow solid; yield: 58 mg (44%); mp 129–132 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.49 (d, *J* = 2.4 Hz, 1 H), 8.27–8.23 (m, 1 H), 7.60–7.51 (m, 3 H), 7.43–7.38 (m, 3 H), 7.09 (s, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.4, 144.5, 142.0, 131.8, 129.7, 128.6, 128.2, 121.2, 121.1, 117.6, 111.6, 111.5, 96.8.

5,7-Dichloro-2-(phenylethynyl)benzofuran (6ak)

White solid; yield: 116 mg (81%); mp 103–105 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55 (dd, *J* = 2.1, 7.5 Hz, 2 H), 7.41–7.34 (m, 4 H), 7.29 (d, *J* = 2.0 Hz, 1 H), 6.90 (s, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 149.2, 141.1, 131.8, 130.0, 129.6, 129.1, 128.5, 125.5, 121.3, 119.2, 117.2, 111.2, 96.5.

HRMS (ESI): *m*/*z* calcd for $C_{18}H_{15}O^+$ (M + H)$^+$: 287.0025; found: 287.1162.

2-(Phenylethynyl)naphtho[2,1-*b*]furan (6am)[21c]

White solid; yield: 129 mg (96%); mp 93–95 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08 (d, *J* = 8.2 Hz, 1 H), 7.91 (d, *J* = 7.6 Hz, 1 H), 7.74 (d, *J* = 9.0 Hz, 1 H), 7.62–7.54 (m, 4 H), 7.51–7.45 (m, 2 H), 7.39–7.33 (m, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 152.7, 138.2, 131.6, 130.5, 129.1, 128.8, 128.5, 127.4, 126.8, 126.7, 124.9, 123.4, 123.2, 122.0, 112.2, 110.7, 95.2.

2-(Phenylethynyl)thiophene (6an)[36i]

Yellow solid; yield: 70 mg (76%); mp 49–52 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.52–7.50 (m, 2 H), 7.35–7.33 (m, 3 H), 7.28 (d, *J* = 4.0 Hz, 2 H), 7.00 (t, *J* = 4.8, 4.4 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 132.02, 131.54, 128.55, 128.50, 127.38, 127.23, 123.44, 123.04, 93.16, 82.74.

2-(*p*-Tolylethynyl)benzofuran (6ba)[21c]

White solid; yield: 98 mg (84%); mp 110–111 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55 (d, *J* = 7.7 Hz, 1 H), 7.46 (d, *J* = 8.2 Hz, 3 H), 7.32 (t, *J* = 8.4 Hz, 1 H), 7.26–7.20 (m, 1 H), 7.16 (d, *J* = 7.2 Hz, 2 H), 6.97 (s, 1 H), 2.36 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 154.9, 139.5, 139.0, 131.6, 129.3, 127.8, 125.5, 123.2, 121.1, 118.8, 111.2, 111.2, 95.3, 21.6.

5-Methyl-2-(*p*-tolylethynyl)benzofuran (6bb)

White solid; yield: 102 mg (83%); mp 127–130 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47 (d, *J* = 8.1 Hz, 2 H), 7.35 (d, *J* = 8.8 Hz, 2 H), 7.16 (d, *J* = 8.5 Hz, 3 H), 6.91 (s, 1 H), 2.44 (s, 3 H), 2.38 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 153.3, 139.4, 139.0, 132.7, 131.6, 129.2, 127.9, 126.8, 120.8, 118.8, 111.1, 110.7, 95.1, 21.6, 21.3.

HRMS (ESI): *m*/*z* calcd for $C_{18}H_{15}O^+$ (M + H)$^+$: 247.11174; found: 247.11148.

5-Chloro-2-(*p*-tolylethynyl)benzofuran (6bh)[21c]

White solid; yield: 115 mg (86%); mp 125–127 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51 (d, *J* = 2.1 Hz, 1 H), 7.47 (d, *J* = 8.1 Hz, 2 H), 7.37 (d, *J* = 8.7 Hz, 1 H), 7.27 (d, *J* = 8.8 Hz, 1 H), 7.18 (d, *J* = 7.9 Hz, 2 H), 6.90 (s, 1 H), 2.38 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 153.1, 140.4, 139.8, 132.4, 131.6, 129.3, 129.2, 125.6, 120.6, 118.4, 112.1, 110.6, 96.0, 21.6.

5-Bromo-2-(*p*-tolylethynyl)benzofuran (6bi)

White solid; yield: 112 mg (72%); mp 135–138 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68 (d, *J* = 2.0 Hz, 1 H), 7.48–7.39 (m, 3 H), 7.32 (d, *J* = 8.7 Hz, 1 H), 7.18 (d, *J* = 7.9 Hz, 2 H), 6.90 (s, 1 H), 2.38 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 153.5, 140.2, 139.8, 132.4, 131.6, 129.3, 128.3, 123.6, 118.4, 116.3, 112.6, 110.4, 96.0, 21.6.

HRMS (ESI): *m*/*z* calcd for $C_{18}H_{15}O^+$ (M + H)$^+$: 311.0064; found: 311.0066.

2-(*p*-Tolylethynyl)naphtho[2,1-*b*]furan (6bm)[21c]

White solid; yield: 119 mg (84%); mp 161–162 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08 (d, *J* = 8.1 Hz, 1 H), 7.90 (d, *J* = 6.8 Hz, 1 H), 7.73 (d, *J* = 8.9 Hz, 1 H), 7.62–7.42 (m, 6 H), 7.16 (d, *J* = 7.9 Hz, 2 H), 2.36 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 152.6, 139.4, 138.4, 131.5, 130.5, 129.3, 128.8, 127.4, 126.6, 126.6, 124.9, 123.4, 123.2, 118.9, 112.1, 110.3, 95.4, 21.6.

2-[(4-Fluorophenyl)ethynyl]benzofuran (6ca)[21c]

White solid; yield: 110 mg (93%); mp 90–91 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58–7.54 (m, 3 H), 7.47 (d, *J* = 9.1 Hz, 1 H), 7.36–7.32 (m, 1 H), 7.26–7.22 (m, 1 H), 7.07 (t, *J* = 8.8 Hz, 2 H), 7.00 (s, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.2, 161.7, 154.9, 138.6, 133.7, 133.6, 127.7, 125.6, 123.3, 121.2, 116.0, 115.8, 111.6, 111.2, 93.9, 79.4.

2-[(4-Fluorophenyl)ethynyl]-5-methylbenzofuran (6cb)[21c]

White solid; yield: 119 mg (95%); mp 118–120 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57 (d, *J* = 8.9 Hz, 2 H), 7.41–7.34 (m, 2 H), 7.17 (d, *J* = 9.1 Hz, 1 H), 7.08 (t, *J* = 8.7 Hz, 2 H), 6.95 (s, 1 H), 2.46 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.2, 161.7, 153.4, 138.6, 133.7, 133.6, 132.8, 127.8, 127.0, 120.9, 118.1, 118.0, 116.0, 115.8, 111.5, 110.7, 93.8, 21.3.

5-Chloro-2-[(4-fluorophenyl)ethynyl]benzofuran (6ch)[21c]

White solid; yield: 123 mg (91%); mp 133–134 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.56–7.51 (m, 3 H), 7.37 (d, *J* = 8.7 Hz, 1 H), 7.27 (d, *J* = 8.7 Hz, 1 H), 7.06 (t, *J* = 8.7 Hz, 2 H), 6.91 (s, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.4, 161.9, 153.2, 140.0, 133.8, 133.7, 129.0, 129.0, 125.8, 120.6, 117.7, 117.6, 116.0, 115.8, 112.2, 110.9, 94.5, 78.9.

5-Bromo-2-[(4-fluorophenyl)ethynyl]benzofuran (6ci)[21c]

White solid; yield: 126 mg (80%); mp 125–128 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68 (d, *J* = 2.0 Hz, 1 H), 7.55 (d, *J* = 8.9 Hz, 2 H), 7.42 (d, *J* = 8.7 Hz, 1 H), 7.33 (d, *J* = 8.7 Hz, 1 H), 7.07 (t, *J* = 8.6 Hz, 2 H), 6.91 (s, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.4, 161.9, 153.5, 139.8, 133.8, 133.7, 129.6, 128.5, 123.7, 116.4, 116.1, 115.8, 112.6, 110.8, 94.6, 78.9.

HRMS (ESI): *m*/*z* calcd for $C_{18}H_{15}O^+$ (M + H)$^+$: 314.9815; found: 315.0810.

2-[(4-Fluorophenyl)ethynyl]naphtho[2,1-*b*]furan (6cm)[21c]

White solid; yield: 139 mg (97%); mp 93–95 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03 (d, *J* = 7.0 Hz, 1 H), 7.87 (d, *J* = 9.0 Hz, 1 H), 7.70 (d, *J* = 9.0 Hz, 1 H), 7.60–7.39 (m, 6 H), 7.02 (t, *J* = 8.7 Hz, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.2, 161.7, 152.7, 138.0, 133.6, 133.6, 130.5, 128.8, 127.4, 126.8, 126.7, 124.9, 123.4, 123.2, 118.2, 118.1, 116.0, 115.8, 112.1, 110.7, 94.1, 79.7.

(Benzofuran-2-ylethynyl)trimethylsilane (6da)[37]

White solid; yield: 44 mg (41%); mp 99–100 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.54 (d, *J* = 7.7 Hz, 1 H), 7.43 (d, *J* = 8.3 Hz, 1 H), 7.35–7.29 (m, 1 H), 7.24 (d, *J* = 7.5 Hz, 1 H), 6.94 (s, 1 H), 0.29 (s, 9 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 154.7, 138.4, 127.4, 125.7, 123.3, 121.3, 112.0, 111.3, 101.9, 94.3.

2-(Thiophen-2-ylethynyl)benzofuran (6ea)[22b]

Yellow solid; yield: 99 mg (88%); mp 50–51 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55 (d, *J* = 7.7 Hz, 1 H), 7.46 (d, *J* = 8.2 Hz, 1 H), 7.38–7.30 (m, 3 H), 7.27–7.20 (m, 1 H), 7.04–6.98 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.0, 138.5, 133.3, 128.7, 127.7, 127.3, 125.8, 123.4, 121.7, 121.3, 111.9, 111.3, 88.5, 83.3.

2-(3-Phenylprop-1-yn-1-yl)benzofuran (6fa)

Colorless liquid; yield: 101 mg (87%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50 (d, *J* = 7.7 Hz, 1 H), 7.45–7.14 (m, 8 H), 6.85 (s, 1 H), 3.86 (s, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 154.7, 139.0, 135.6, 128.8, 128.1, 127.8, 127.0, 125.4, 123.2, 121.1, 111.2, 110.8, 94.2, 73.3, 26.0.

HRMS (ESI): *m*/*z* calcd for $C_{17}H_{13}O^+$ (M + H)$^+$: 233.09609; found: 233.09644.

Coupling Reaction of 2-Halobenzo[*b*]furans with Alkylaluminums; General Procedure

Under a dry N_2 atmosphere, to a mixture of $PdCl_2$ (0.0013 g, 0.01 mmol) and XantPhos (0.0116 g, 0.02 mmol) in a reaction vessel was added an alkenylaluminum **7** (0.60 mmol) in DCE (3 mL) followed by the addition of the corresponding 2-halidebenzo[*b*]furan **2** (0.50 mmol). The resulting solution was stirred at 60 °C for 4 h. After completion of the reaction, the mixture was diluted with sat. aq NH_4Cl (5 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layers were dried (anhyd Na_2SO_4), filtered, and evaporated under vacuum. The residue was subjected to flash column chromatography on silica gel (hexane or EtOAc and hexane) to afford the corresponding coupled product **8**.

2-Methylbenzofuran (8aa)[23g]

Colorless liquid; yield: 40 mg (61%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46–7.36 (m, 2 H), 7.21–7.12 (m, 2 H), 6.32 (s, 1 H), 2.41 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.5, 154.8, 129.3, 123.1, 122.5, 120.1, 110.7, 102.6, 14.1.

7-Methoxy-2-methylbenzofuran (8af)[23g]

Colorless liquid; yield: 59 mg (73%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.11–7.04 (m, 2 H), 6.72 (d, *J* = 7.2 Hz, 1 H), 6.35 (d, *J* = 1.1 Hz, 1 H), 3.99 (s, 3 H), 2.46 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.5, 144.9, 143.8, 130.8, 123.1, 112.6, 105.3, 102.9, 55.9, 14.0.

5-Chloro-2-methylbenzofuran (8ah)[23g]

White solid; yield: 56 mg (67%); mp 56–58 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28 (s, 1 H), 7.17 (s, 1 H), 6.31 (s, 1 H), 2.46 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.1, 153.1, 130.6, 127.9, 123.1, 119.7, 111.5, 102.3, 14.1.

5,7-Dichloro-2-methylbenzofuran (8ak)[21]

White solid; yield: 88 mg (88%); mp 102–104 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28 (s, 1 H), 7.17 (s, 1 H), 6.31 (s, 1 H), 2.46 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.0, 149.1, 146.9, 131.4, 128.2, 123.2, 118.4, 103.1, 14.0.

2-Ethylbenzofuran (8ba)[13h]

Colorless liquid; yield: 61 mg (83%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37 (d, *J* = 7.3 Hz, 2 H), 7.16–7.08 (m, 2 H), 6.33–6.27 (m, 1 H), 2.72 (q, *J* = 7.0, 7.6 Hz, 2 H), 1.26 (t, *J* = 7.5 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 161.0, 154.6, 129.0, 123.0, 122.3, 120.2, 110.7, 101.0, 21.8, 11.9.

1-[Bis(4-fluorophenyl)methyl]-4-[2-(2-arylethynyl)benzo[*b*]furan-5-yl]piperazine Derivatives 9; General Procedure

Under a dry N_2 atmosphere, to a mixture of $Pd(OAc)_2$ (0.0022 g, 0.01 mmol), DavePhos (0.0098 g, 0.02 mmol), and NaO^{t}Bu (0.072 g, 0.75 mmol) were added 4,4′-difluorobenzhydrylpiperazine (0.130 g, 0.50 mmol), 5-bromo-2-ynylbenzo[*b*]furan (0.144 g, 0.50 mmol), and toluene (3 mL) in a 25 mL reaction vessel. The resulting solution was stirred at 110 °C for 4 h. After completion of the reaction, the mixture was diluted with sat. aq NH_4Cl (5 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layers were dried (anhyd Na_2SO_4), filtered, and evaporated under vacuum. The residue was subjected to flash column chromatography on silica gel (hexane or EtOAc and hexane) to afford the corresponding coupled product **9**.

1-[Bis(4-fluorophenyl)methyl]-4-[2-(phenylethynyl)benzo[*b*]furan-5-yl]piperazine (9a)

White solid; yield: 108 mg (43%); mp 151–152 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.56 (d, *J* = 9.7 Hz, 2 H), 7.41–7.32 (m, 8 H), 7.03–6.95 (m, 6 H), 6.92 (s, 1 H), 4.27 (s, 1 H), 3.20–3.12 (m, 4 H), 2.59–2.52 (m, 4 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 163.1, 160.6, 150.1, 148.4, 139.1, 138.2, 131.6, 129.3, 129.2, 129.1, 128.5, 128.3, 121.9, 117.4, 115.6, 115.4, 111.7, 111.4, 107.3, 94.9, 74.5, 51.9, 51.0.

HRMS (ESI): *m*/*z* calcd for $C_{33}H_{27}F_2N_2O^+$ (M + H)$^+$: 505.20860; found: 505.20868.

1-[Bis(4-fluorophenyl)methyl]-4-[2-(*p*-tolylethynyl)benzo[*b*]furan-5-yl]piperazine (9b)

White solid; yield: 86 mg (33%); mp 193–194 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47–7.31 (m, 7 H), 7.16 (d, *J* = 8.0 Hz, 2 H), 7.03–6.95 (m, 6 H), 6.89 (s, 1 H), 4.27 (s, 1 H), 3.20–3.11 (m, 4 H), 2.61–2.51 (m, 4 H), 2.36 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 163.1, 160.6, 150.1, 148.3, 139.4, 139.3, 138.1, 131.5, 129.3, 129.2, 129.2, 128.3, 118.8, 117.2, 115.6, 115.4, 111.4, 111.3, 107.3, 95.2, 74.5, 51.9, 51.0, 21.6.

HRMS (ESI): *m*/*z* calcd for $C_{34}H_{29}F_2N_2O^+$ (M + H)$^+$: 519.22425, found 519.22437.

1-[Bis(4-fluorophenyl)methyl]-4-{2-[(4-fluorophenyl)ethynyl]-benzo[*b*]furan-5-yl}piperazine (9c)

White solid; yield: 91 mg (35%); mp 166–167 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53 (dd, *J* = 5.4, 8.8 Hz, 2 H), 7.41–7.31 (m, 5 H), 7.08–6.95 (m, 8 H), 6.91 (s, 1 H), 4.27 (s, 1 H), 3.22–3.11 (m, 4 H), 2.64–2.49 (m, 4 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.2, 163.1, 161.7, 160.6, 150.1, 148.4, 138.9, 138.2, 138.1, 133.7, 133.6, 129.3, 129.2, 128.2, 118.0, 118.0, 117.4, 116.0, 115.8, 115.6, 115.4, 111.8, 111.4, 107.3, 93.8, 79.6, 74.5, 51.9, 51.0.

HRMS (ESI): *m*/*z* calcd for $C_{33}H_{26}F_3N_2O^+$ (M + H)$^+$: 523.19917; found: 523.19904.

Conflict of Interest

The authors declare no conflict of interest.

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