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One-Pot Synthesis of Substituted Benzo[*b*]furans from Mono- and Dichlorophenols Using Palladium Catalysts Bearing Dihydroxyterphenylphosphine

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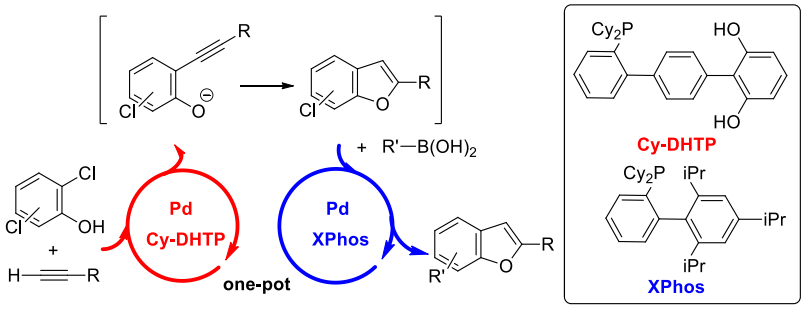


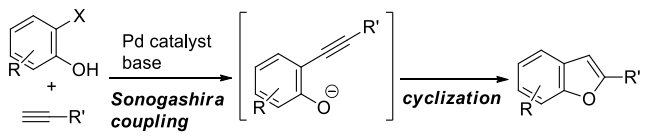
ABSTRACT: Dihydroxyterphenylphosphine bearing cyclohexyl groups on the phosphorous atom (Cy-DHTP) was found to be a powerful ligand for the palladium-catalyzed one-pot synthesis of substituted benzo[*b*]furans from 2-chlorophenols and terminal alkynes. This catalyst system was also applicable to the sequential one-pot synthesis of disubstituted benzo[*b*]furans from dichlorophenols via the Suzuki-Miyaura cross-coupling of chlorobenzo[*b*]furan with boronic acids. The use of two ligands, Cy-DHTP and XPhos, is the key to promote the reactions. Mechanistic studies suggest that the Pd–

Cy-DHTP catalyst is the active species in the Sonogashira cross-coupling step, while the Pd–XPhos catalyst accelerates the Suzuki-Miyaura cross-coupling step.

Introduction

Benzo[*b*]furan is a ubiquitous framework found in many natural products and pharmaceuticals.[1] The biological activity of this class of compounds has received considerable attention and many synthetic methodologies have been developed for obtaining these compounds.[2] Palladium-catalyzed cross-coupling reactions are one of the powerful method for constructing the benzo[*b*]furan backbone.[3] The palladium-catalyzed Sonogashira cross-coupling of 2-halophenols and terminal alkynes followed by cyclization has been widely used for synthesizing 2-substituted benzo[*b*]furans (Scheme 1).[4] These reactions commonly employ 2-iodo- and 2-bromophenols as substrates. On the other hand, there are a few reports[5,6] using 2-chlorophenols, which are less expensive and more readily available than 2-iodo or 2-bromophenols, as the starting material. However, in one such attempt, the desired product was obtained in less than 10% yield.[5]

Scheme 1. One-Pot Benzo[*b*]furan Synthesis from 2-Halophenols and Terminal Alkynes



We have previously reported the one-pot synthesis of benzo[*b*]furan from 2-chlorophenols and terminal alkynes using palladium catalysts bearing hydroxyterphenylposphine (HTP)[7] with cyclohexyl groups on the phosphorous atom (Cy-HTP, Figure 1a).[8] Cy-HTP works as a bifunctional ligand in the presence of palladium and *t*-BuOLi. We hypothesize that the phosphine moiety of Cy-HTP binds to Pd while the hydroxy group is deprotonated by *t*-BuOLi and the resulting lithium phenoxide moiety act as a binding site for the substrate, which also forms the lithium phenoxide. These lithium phenoxides are in equilibrium with the heteroaggregate in which the 2-chloro group is in close proximity to the palladium atom (Figure 1b). Therefore, the oxidative addition of C–Cl at the position *ortho* to the Pd atom is accelerated. However, the above reaction suffers from drawbacks such as long reaction times, narrow substrate scope, and the necessity of having to use a sealed tube for the reaction.

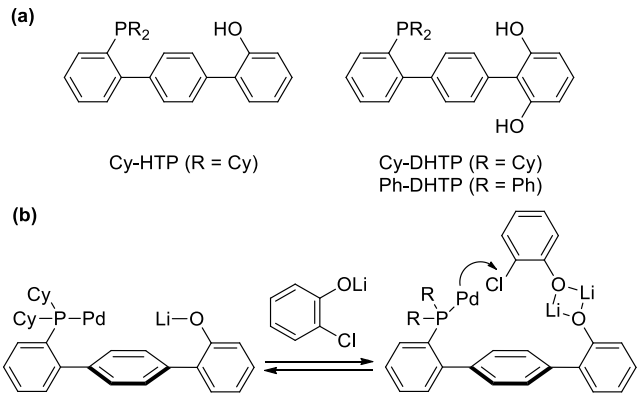


Figure 1. (a) Hydroxyterphenylphosphines. (b) Formation of the proposed intermediate in the Pd-HTP-catalyzed benzo[*b*]furan synthesis.

We have previously shown that dihydroxyterphenylphosphine (DHTP, Figure 1a) ligands are more

effective than HTP for the ortho-selective, palladium-catalyzed cross-coupling of dihaloarenes and Grignard reagents.[9] Introduction of the second hydroxy group in terphenylphosphine dramatically improved its catalytic efficiency and expanded the scope of the reaction. Therefore, we expected that the use of DHTP would improve the catalytic efficiency and broaden the substrate scope of benzo[*b*]furan synthesis. The expected high reactivity of DHTP can be explained by a conformational effect depicted in Figure 2. The assumed catalytic species have flexibility in rotation of the C–C single bonds. In the case of HTP, the conformation in which the lithium phenoxide moiety is close to palladium is in equilibrium with that in which they are on the opposite side of the terphenyl group (Figure 2a). On the other hand, in the case of DHTP, the lithium phenoxide moiety and the Pd atom are always located on the same side of the terphenyl structure (Figure 2b). This results in a more effective cooperation between palladium and the lithium phenoxide moieties affording higher reactivities in the Sonogashira coupling step.

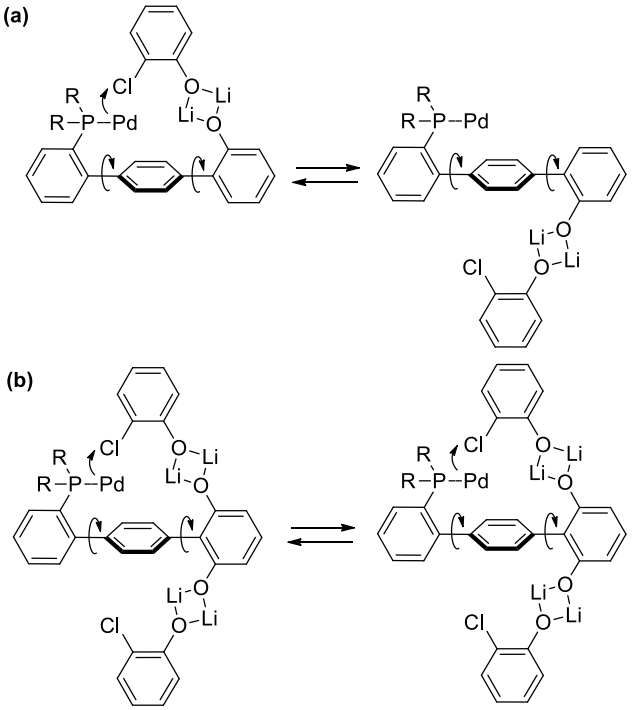
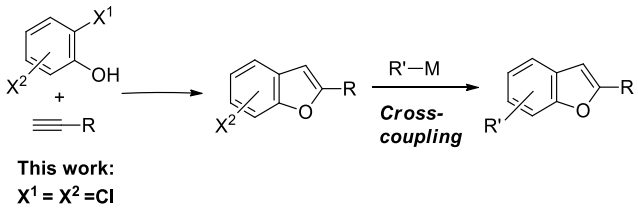


Figure 2. C-C bond rotation for the assumed intermediates from (a) HTP and (b) DHTP.

To afford multisubstituted benzo[*b*]furans, efficient synthetic methods need to be developed.[10] Halogenated benzo[*b*]furans, which can be easily converted to other functional groups by cross-coupling, are one of the versatile intermediates for multisubstituted benzo[*b*]furan syntheses (Scheme 2).[4h, 11] Thus, various methods to obtain halogenated benzo[*b*]furans[12] have been developed. These include the palladium-catalyzed Sonogashira coupling of dihalophenols and terminal alkynes followed by cyclization.[4h,13] However, substrates are limited to dihalophenols bearing different halogen atoms ($X^1 \neq X^2$) to achieve site-selective Sonogashira cross-coupling. In addition, the presence of a bromo or an iodo group at the C2-position is crucial to achieving high reactivities. On the other hand, by using the Pd–Cy-HTP catalyst, we obtained benzo[*b*]furans containing a chloro-group at different positions from various dichlorophenols ($X^1 = X^2 = Cl$), which are inexpensive and easily available.[8]

This preliminary success was realized because Cy-HTP promoted ortho-selective Sonogashira coupling presumably through formation of heteroaggregate (Figure 1b) in which the chloro-group *ortho* to the oxido group is placed close to the Pd. Therefore, we hypothesized that the Pd–DHTP catalyst would further improve the reactivity and selectivity of chlorobenzo[*b*]furan synthesis from dichlorophenols and terminal alkynes. In addition, we expected that various disubstituted benzo[*b*]furans would also be synthesized via chlorobenzo[*b*]furans starting from dichlorophenols instead of using 2-bromo- or 2-iodophenols.

Scheme 2. One-Pot Synthesis of Disubstituted Benzo[*b*]furan from Dihalophenols and Terminal Alkynes



Due to increasing demand for development of rapid and environmentally friendly synthetic methods, one-pot synthesis has been considered to be an attractive choice.[14,15] Palladium-catalyzed reactions have been widely applied to the one-pot synthesis because they generally show high chemo-, regio-, and stereoselectivity along with high functional-group tolerance.[15] Therefore, we hypothesized that the synthesis of disubstituted benzo[*b*]furans from dichlorophenols would be performed sequentially in a one-pot reaction (Scheme 2) by using Pd–DHTP as the catalyst.

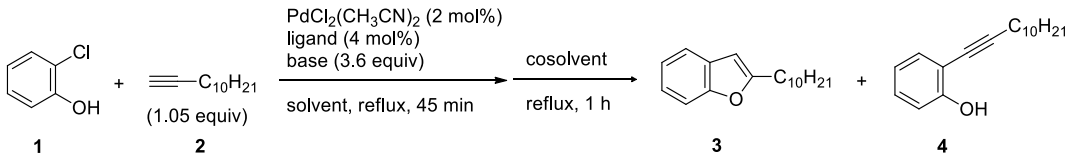
Herein, we present the palladium-catalyzed one-pot synthesis of substituted benzo[*b*]furans from 2-chlorophenols and terminal alkynes, using DHTP as the ligand. We further applied this catalyst system to the sequential one-pot synthesis of disubstituted benzo[*b*]furans from dichlorophenols via the Suzuki-Miyaura cross coupling of chlorobenzo[*b*]furan with boronic acids (Scheme 2, M = $B(OH)_2$).

Results and Discussion

Synthesis of Benzo[*b*]furans from Monochlorophenols. First, we investigated the synthesis of benzo[*b*]furans from monochlorophenols. We determined the best reaction conditions to obtain 2-decylbenzo[*b*]furan (**3**) from 2-chlorophenol (**1**) and 1-dodecyne (**2**) using the catalyst derived from Cy-DHTP·HBF_4 and $PdCl_2(CH_3CN)_2$. The choice of using Cy-DHTP·HBF_4, which has a dicyclohexylphosphine moiety (Figure 1a), over Ph-DHTP was based on our previous study[8] using Cy-HTP·HBF_4 as the ligand. During optimization studies, we found that the addition of a polar cosolvent after the Sonogashira cross-coupling step promoted the subsequent cyclization reaction, which proceeds through base catalysis.[16] Among the solvents and the cosolvents tested, the combination of toluene as the solvent and MeOH as the cosolvent resulted in the highest yields of the desired benzo[*b*]furan **3** (Table 1, entry 1). Compared to our previous attempts with the catalyst derived from Cy-HTP·HBF_4, this reaction proceeded much faster, indicating the high reactivity and effectiveness of Cy-DHTP. In this case, the first Sonogashira cross-coupling step was completed within 45 min and the

second cyclization step reached completion within one hour. In addition, no sealed-tube was necessary in this case. Water was also found to be an effective cosolvent in promoting cyclization, although longer reaction times were required (entry 2). On the other hand, the use of *t*-BuOH and CF_3CH_2OH as cosolvents resulted in lowered yields of **3** and significant amounts of the Sonogashira cross-coupling product **4** (entries 3 and 4). In the absence of a cosolvent, the cyclization of **4** proceeded slowly and did not reach completion (entry 5). The importance of adding the cosolvent after the Sonogashira cross-coupling step was evident when the use of MeOH or a mixture of MeOH/toluene as the solvent did not give the desired product **3** (entries 6 and 7). When *t*-BuOH or DMF was used as the solvent in the absence of a cosolvent, **3** was obtained in lower yields (entries 8 and 9). As for ligands, Ph-DHTP[9] was found to be ineffective for this reaction (entry 10). Cy-HTP·HBF_4 afforded the product in moderate yields under the same conditions (entry 11). These results also show the effectiveness of Cy-DHTP. Other commonly used phosphines for the cross-coupling of chloroarenes such as XPhos,[17] PCy_3, P(*t*-Bu)$_3$·HBF_4,[18] and DPPF did not work well (entries 12–15). Finally, various bases were tested. However, none of them worked as well as *t*-BuOLi (entries 16–19).

Table 1. Optimization of Reaction Conditions for Benzo[*b*]furan Synthesis from 2-Chlorophenol and 1-Dodecyne



1 2 3 4

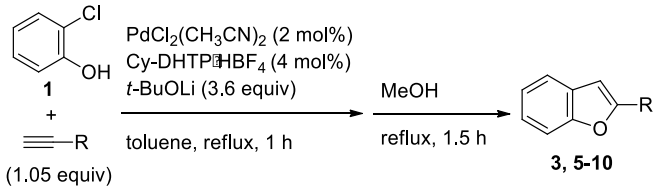
entry	ligand	base	solvent	cosolvent	yield (%)[a]	
					3	**4**
1	Cy-DHTP·HBF_4	*t*-BuOLi	toluene	MeOH	79	0
2[b]	Cy-DHTP·HBF_4	*t*-BuOLi	toluene	H_2O	71	trace
3[c]	Cy-DHTP·HBF_4	*t*-BuOLi	toluene	*t*-BuOH	38	28
4	Cy-DHTP·HBF_4	*t*-BuOLi	toluene	CF_3CH_2OH	34	44
5[d, e]	Cy-DHTP·HBF_4	*t*-BuOLi	toluene	-[f]	59	24
6	Cy-DHTP·HBF_4	*t*-BuOLi	MeOH	-[f]	No reaction	
7	Cy-DHTP·HBF_4	*t*-BuOLi	toluene/MeOH	-[f]	No reaction	
8[d, g]	Cy-DHTP·HBF_4	*t*-BuOLi	*t*-BuOH	-[f]	42	23
9[d, h]	Cy-DHTP·HBF_4	*t*-BuOLi	DMF	-[f]	57	10
10	Ph-DHTP	*t*-BuOLi	toluene	MeOH	trace	trace
11	Cy-HTP·HBF_4	*t*-BuOLi	toluene	MeOH	40	0
12	XPhos	*t*-BuOLi	toluene	MeOH	16	0
13	PCy_3	*t*-BuOLi	toluene	MeOH	No reaction	
14	P(*t*-Bu)$_3$·HBF_4	*t*-BuOLi	toluene	MeOH	No reaction	
15	DPPF	*t*-BuOLi	toluene	MeOH	trace	0
16	Cy-DHTP·HBF_4	Li_3PO_4	toluene	MeOH	No reaction	
17	Cy-DHTP·HBF_4	LiOH	toluene	MeOH	0	0

18	Cy-DHTP·HBF_4	*t*-BuOK	toluene	MeOH	No reaction	
19	Cy-DHTP·HBF_4	K_3PO_4	toluene	MeOH	0	0

[a]Isolated yield. [b]After H_2O addition, reflux for 2 h. [c]After *t*-BuOH addition, reflux for 7 h. [d]Alkyne (1.5 equiv) used. [e]Reflux for 1 h. [f]Without cosolvent, additional reflux was not conducted. [g]110 °C for 23 h. [h]110 °C for 1 h.

Next, various other substrates were tested under these optimized reaction conditions. A variety of terminal alkynes reacted with **1** to afford the corresponding benzo[*b*]furans (Table 2). When aliphatic alkynes were used, products **3**, **5**, and **6** were obtained in moderate to good yields (entries 1–3). Aromatic alkynes also gave the products **7**–**10** in moderate to high yields (entries 4–7). Substituents on the phenyl ring significantly affected the yield; 4-fluoro group slowed down Sonogashira cross-coupling more than electron-donating 4-methoxy group. Notably, the chloro-containing benzo[*b*]furan **8** was obtained in good yields (entry 5), even though the chloro-group of 3-chloroethynylbenzene is generally expected to be more reactive than that of 2-chlorophenol. These results show the high *ortho*-selectivity of the Pd–Cy-DHTP catalyst.

Table 2. Benzo[*b*]furan Synthesis Using 2-Chlorophenol and Various Alkynes



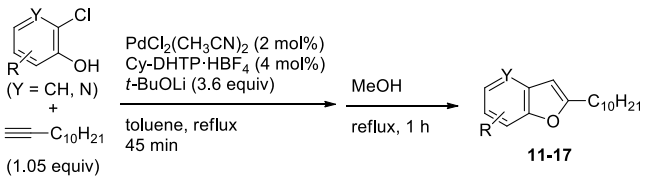
entry	R	yield (%)[a]
1[b]	$C_{10}H_{21}$ (**3**)	79
2	Ph-CH_2CH_2 (**5**)	82
3	Cl-$CH_2CH_2CH_2$ (**6**)	58
4[c, d]	Ph (**7**)	52
5[d, e]	3-Cl-C_6H_4 (**8**)	64
6	4-F-C_6H_4 (**9**)	33
7[c, d]	4-MeO-C_6H_4 (**10**)	97

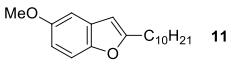
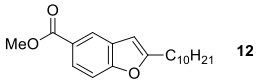
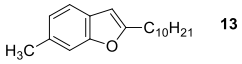
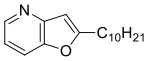
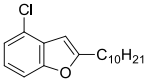
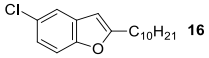
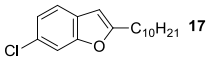
[a]Isolated yield. [b]Toluene reflux: 45 min and MeOH reflux: 1 h. [c]Toluene reflux: 45 min and MeOH reflux: 7 h. [d]Alkyne (1.5 equiv) used. [e]MeOH reflux: 3 h.

We also carried out reactions between various 2-chlorophenols and terminal alkyne **2** (Table 3). Chlorophenols bearing electron-donating methoxy or methyl groups gave the corresponding benzo[*b*]furans **11** and **13** in good yields (entries 1 and 3), while methyl 3-chloro-4-hydroxybenzoate afforded the product **12** in moderate yield (entry 2). 2-Chloro-3-hydroxypyridine also reacted well with the desired terminal alkyne to form product **14** in modest yield (entry 4). This catalyst system was also used to synthesize chlorobenzo[*b*]furans from various 2-dichorophenols (entries 5–7). The use of 2,3-dichlorophenol or 2,4-dichlorophenol resulted in high yields of the corresponding chl*o*robenzo[*b*]furans **15** and **16** (entries 5 and 6). However, when 2,5-dichlorophenol was used, product

17 was obtained only in moderate yields along with the formation of byproducts such as overreacted 6-(1-dodecynyl)-1-decylbenzo[*b*]furan (entry 7).

Table 3. Benzo[*b*]furan Synthesis Using Various 2-Chlorophenols and 1-Dodecyne



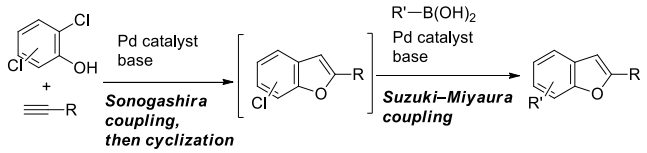
entry	product	yield (%)[a]
1[b]	 **11**	78
2	 **12**	37
3[b, c]	 **13**	82
4	 **14**	53
5	 **15**	77
6	 **16**	80
7	 **17**	37

[a]Isolated yield. [b]Alkyne (1.5 equiv) used. [c]Toluene reflux 90 min and MeOH reflux 2 h.

One-Pot Sequential Synthesis of Disubstituted Benzo[*b*]furans from Dichlorophenols. To further apply our catalyst system, we attempted the sequential one-pot synthesis of disubstituted benzo[*b*]furans from dichlorophenols via the Suzuki-Miyaura cross-coupling between chlorobenzo[*b*]furans and

boronic acids (Scheme 3).[11b, 19]

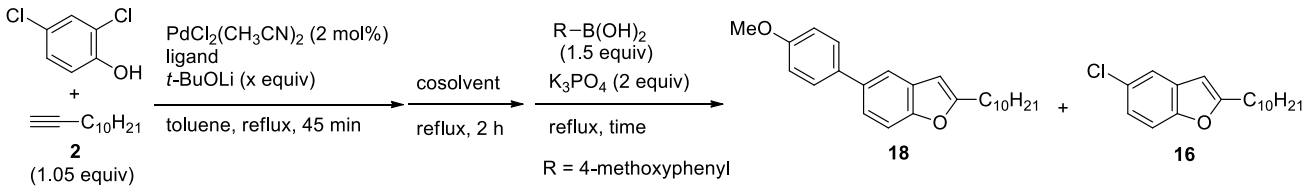
Scheme 3. One-Pot Substituted Benzo[*b*]furan Synthesis from Dichlorophenols, Terminal Alkynes, and Boronic Acids



In the one-pot procedure depicted above, we expected the Pd–Cy-DHTP catalyst to promote both the Sonogashira and Suzuki-Miyaura cross-coupling reactions. The reaction was carried out using 2,4-dichlorophenol, alkyne **2**, and 4-methoxyphenylboronic acid as model substrates. Optimization studies showed that the use of the second ligand and the additional base was necessary to promote the Suzuki-Miyaura cross-coupling reaction. Thus, the use of Cy-DHTP·HBF_4 and XPhos[17] as the ligands, H_2O as the cosolvent, and K_3PO_4 as the additional base resulted in high yields of the desired 2,5-disubstituted benzo[*b*]furan **18** with trace amounts of 5-chlorobenzo[*b*]furan **16** (Table 4, entry 1). We found that the presence of XPhos did not affect the first Sonogashira cross-coupling step, and it could therefore be present in the initial reaction mixture along with Cy-DHTP·HBF_4, thereby simplifying the process. Boronic acid and the additional base could only be added after chlorobenzo[*b*]furan formation. When they were added with cosolvent, the Suzuki-Miyaura cross-coupling reaction did not proceed smoothly, and large amounts of biaryls were obtained as a

byproduct resulting from the homocoupling between arylboronic acids. The use of MeOH as a cosolvent was not suitable for this reaction (entry 2). Increasing the amount of *t*-BuOLi in the reaction significantly affected the efficiency of the Suzuki-Miyaura cross-coupling (entry 3), and 2.4 equivalents of the base was found to be optimum. The Suzuki-Miyaura cross-coupling reaction did not proceed well in the absence of K_3PO_4 (entry 4). The use of two ligands is important in promoting the one-pot sequential reaction. Use of 8 mol% of Cy-DHTP·HBF_4 formed product **18** in low yields (entry 5). Decreasing the amount of Cy-DHTP·HBF_4 to 4 mol% (entry 6), resulted in better yields of **16** and **18** than those of entry 5, indicating the higher amount of Cy-DHTP had adverse effects on the reaction. On the other hand, the conditions in entry 6 slowed down the Suzuki-Miyaura cross-coupling reaction in comparison to the reaction in presence of Cy-DHTP/XPhos, although the Sonogashira cross-coupling step proceeded smoothly. From these results, we conclude that the Pd-Cy-DHTP catalyst is less reactive than the Pd–XPhos catalyst in Suzuki-Miyaura cross-coupling reactions. When only XPhos was used as the ligand, no Sonogashira cross-coupling was observed (entry 7). Decreasing the amount of both ligands to 2 mol% resulted in slightly lower yields of the product **18** (entry 8).

Table 4. Optimization of Reaction Conditions for the One-pot Synthesis of 2,5-Disubstituted Benzo[*b*]furan



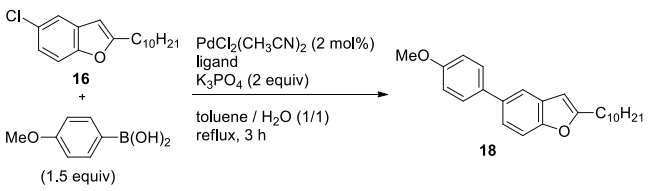
entry	ligand (mol%)	*t*-BuOLi (equiv)	cosolvent	K_3PO_4	time (h)	yield (%)[a]	
						18	**16**
1	Cy-DHTP·HBF_4 (4)/XPhos (4)	2.4	H_2O	+	6	73	trace
2[e]	Cy-DHTP·HBF_4 (4)/XPhos (4)	2.4	MeOH	+	23	23	49
3	Cy-DHTP·HBF_4 (4)/XPhos (4)	3.6	H_2O	+	24	18	43
4	Cy-DHTP·HBF_4 (4)/XPhos (4)	3.6	H_2O	-	26	12	58
5	Cy-DHTP·HBF_4 (8)	2.4	H_2O	+	6	13	trace
6	Cy-DHTP·HBF_4 (4)	2.4	H_2O	+	6	31	41
7	XPhos (4)	2.4	H_2O	+	-	-	n. d.[c]
8	Cy-DHTP·HBF_4 (2)/XPhos (2)	2.4	H_2O	+	15	65	trace

[a]Isolated yield. [b]MeOH reflux for 1 h. [c]Not detected.

To further understand the role of the two ligands in the Suzuki-Miyaura cross-coupling, 5-chlorobenzo[*b*]furan **16** was tested for the reaction with 4-methoxyphenylboronic acid in the presence of $PdCl_2(MeCN)_2$ and using Cy-DHTP·HBF_4 and/or XPhos as ligands (Table 5). As expected, the combination of Cy-DHTP·HBF_4 and XPhos formed the desired product **18** in high yields (entry 1). When only XPhos was used, the reaction also proceeded smoothly (entry 2). On the other hand, use of

only Cy-DHTP·HBF_4 resulted in moderate yields of **18** and large amounts of **16** (entry 3). In this case, even longer reaction times did not improve the yields (data not shown). These results support our finding that the second ligand XPhos is necessary to promote the Suzuki-Miyaura cross-coupling reaction shown in Table 4.

Table 5. Suzuki-Miyaura Cross-coupling of 5-Chlorobenzo[*b*]furan and 4-Methoxyphenylboronic Acid



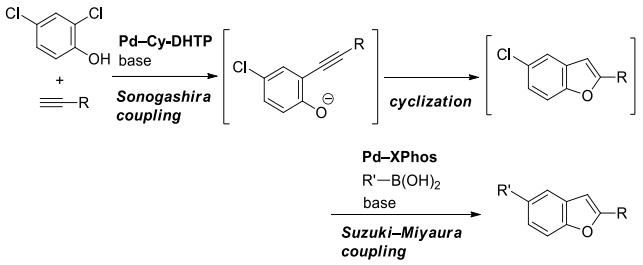
entry	ligand (mol%)	yield (%)[a]
1	Cy-DHTP·HBF_4 (4)/XPhos (4)	85
2	XPhos (4)	91
3	Cy-DHTP·HBF_4 (4)	43

[a]Isolated yield.

Based on these results, we propose the following reaction mechanism for the one-pot sequential synthesis of disubstituted benzo[*b*]furans from dichlorophenols, terminal alkynes, and boronic acids as shown in Scheme 3. During the Sonogashira cross-coupling of dichlorophenols and terminal alkynes, Pd–Cy-DHTP works as the active species. It seems that Pd–XPhos neither catalyzes nor affects the

above reaction. Following cyclization catalyzed by the base, the Suzuki-Miyaura cross-coupling of chlorobenzo[*b*]furans with boronic acid seems to be accelerated mainly by the Pd–XPhos catalyst, although we cannot deny the possibility that Pd–Cy-DHTP also catalyzes the reaction to a lesser extent. In this manner, the use of two ligands in the reaction makes it possible to sequentially carry out benzo[*b*]furan formation and Suzuki-Miyaura cross-coupling in one-pot. Interestingly, both these catalysts show specificity towards one of the two reactions, although both ligands have the same 2-dicyclohexylphosphinobiphenyl substructure.[20]

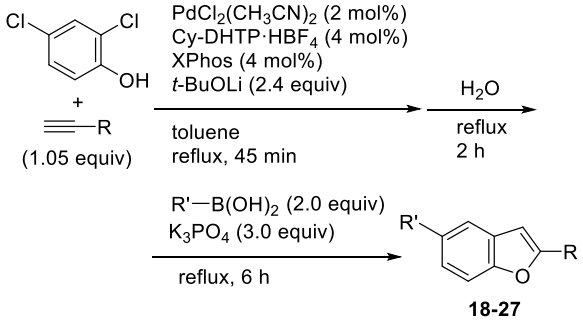
Scheme 4. Proposed Reaction Mechanism



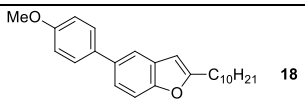
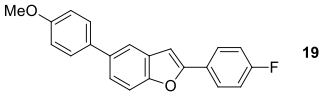
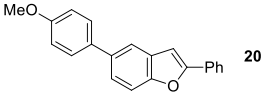
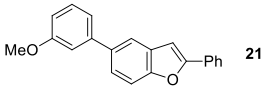
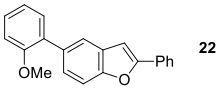
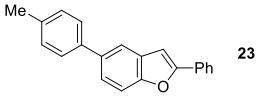
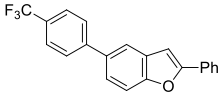
We then applied this catalyst in the synthesis of various 2,5-disubstituted benzo[*b*]furans from 2,4-dichlorophenol (Table 6). Both alkyl and aryl alkynes could be used in this reaction, and the corresponding disubstituted benzo[*b*]furans **18**–**20** were obtained in high yields (entries 1–3). Next, various boronic acids were utilized to introduce substituents at the C(5) position. Arylboronic acids bearing a methoxy group at different positions reacted efficiently to afford products **20**–**22** in high yields (entries 3–5). Reactions using arylboronic acids bearing either an electron-donating methyl group

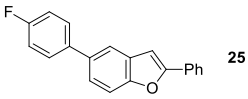
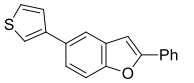
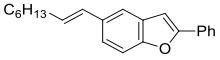
or an electron withdrawing trifluoromethyl or fluoro group also formed the corresponding products **23**–**25** in good yields (entries 6–8). The 3-thienyl group could be successfully introduced at the C(5) position to yield product **26** (entry 9). The use of alkenylboronic acid resulted in moderate yields of product **27** (entry 10).

Table 6. Synthesis of 2,5-Disubstituted Benzo[*b*]furan Using Various Alkynes and Boronic Acids



18-27

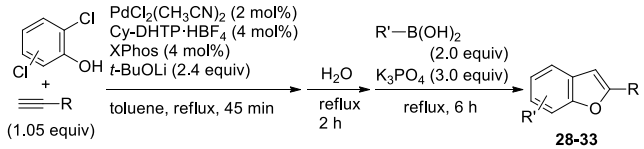
entry	product	yield (%)[a]
1[b]	 **18**	73
2	 **19**	82
3	 **20**	78
4	 **21**	81
5	 **22**	84
6	 **23**	94
7[c]	 **24**	84

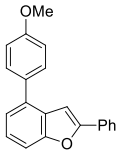
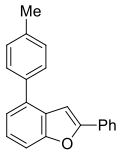
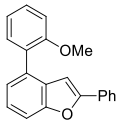
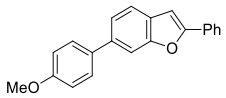
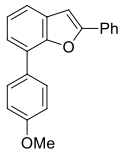
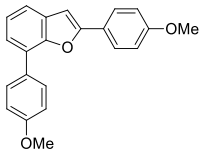
8[d]		**25**	67
9		**26**	76
10		**27**	60

[a]Isolated yield. [b]Boronic acid (1.5 equiv) and K_3PO_4 (2.0 equiv) were used. [c]8 h for Suzuki-Miyaura coupling. [d]10 h for Suzuki-Miyaura coupling.

Then, disubstituted benzo[*b*]furans bearing substituents at different positions were prepared from various dichlorophenols by using this catalyst system (Table 7). When 2,3-dichlorophenol was used, the corresponding 2,4-disubstituted benzo[*b*]furans **28**–**30** were obtained in good yields (entries 1–3). Notably, introduction of the aryl group at the more sterically hindered C(4) position still allowed the reaction to proceed smoothly to completion via the Suzuki-Miyaura cross-coupling step. On the other hand, 2,5-dichlorophenol gave the 2,6-disubstituted benzo[*b*]furan **31** only in moderate yields (entry 4). This could be due to low yields of the 6-chlorobenzo[*b*]furan intermediate, as shown in Table 3. We also applied this catalyst in the synthesis of 2,7-disubstituted benzo[*b*]furans from 2,6-dichlorophenol. The use of ethynylbenzene resulted in low yields of the desired product **32** and the formation of many byproducts (entry 5), while 4-ethynylanisole afforded the corresponding 2,7-disubstituted benzo[*b*]furan **33** in modest yields (entry 6).

Table 7. Synthesis of Disubstituted Benzo[*b*]furan Using Various Dichlorophenols



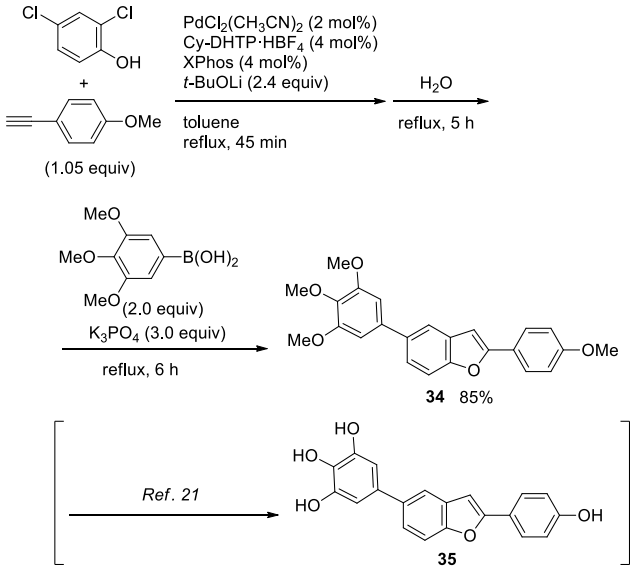
entry	product	yield (%)[a]
1	 **28**	73
2	 **29**	73
3	 **30**	62
4	 **31**	44
5	 **32**	28
6	 **33**	56

[a]Isolated yield.

Finally, we used this sequential one-pot method to synthesize precursor **34** of a biologically active compound (Scheme 5). Tetrahydroxylated 2,5-diarylbenzofuran **35** and related compounds have been recently reported to inhibit amyloid beta (Aβ) aggregation and cause dissociation of Aβ fibrils.[21] We

synthesized its precursor **34** from 2,4-dichlorophenol, 4-ethynylanisole, and 3,4,5-trimethoxyphenylboronic acid using the one-pot procedure. The desired product **34** was successfully obtained in 85% yield. Unlike the previous attempt[21] in which compound **35** was prepared in three steps from 5-bromo-2-hydroxybenzyl alcohol, we could obtain compound **35** from commercially available substrates using a one-pot reaction. This shows the effectiveness and utility of our method in constructing more complex, multi-substituted structures.

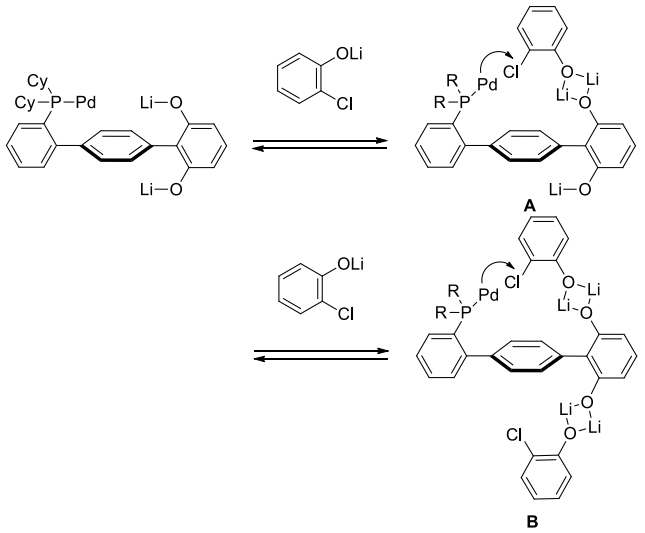
Scheme 5. Synthesis of the Precursor of the Bioactive Compound



Mechanistic Study Using ESI-MS. As discussed above, the mechanism of the acceleration by Cy-DHTP for the Sonogashira coupling step can be explained as follows: (1) both the two hydroxy groups of Cy-DHTP and 2-chlorophenol **1** are deprotonated to generate lithium phenoxides under the reaction conditions, and (2) these lithium phenoxides are in equilibrium with a heteroaggregate **A** and **B**

(Scheme 6) in which the 2-chloro group is easily accessed by the Pd atom located nearby. This heteroaggregate formation between the lithium phenoxides is responsible for the observed acceleration in reaction rates and the ortho-selectivity of Cy-DHTP. To confirm the formation of a heteroaggregate between Cy-DHTP and 2-chlorophenol, we performed electrospray ionization-mass spectrometry (ESI-MS) analyses of these mixtures in the presence of *t*-BuOLi.

Scheme 6. Formation of the Proposed Intermediate



2-Chlorophenol (**1**) and 40 mol % of Cy-DHTP were dissolved in toluene with 1 equivalent of *t*-BuOLi[22] and the resulting solution was stirred at room temperature for 30 min. The resulting solution was injected into the ESI-MS after diluting with acetonitrile. A signal corresponding to the 1:1 complex between lithium phenoxides of Cy-DHTP and 2-chlorophenol (**1)** (Figure 3c) was detected at *m/z* 591 in the negative ion mode (Figure 3a). The observed isotopic distribution of the signal is consistent with the

theoretical isotopic pattern of the complex (Figure 3b). Signals corresponding to the 1:2 and 1:3 complex between lithium phenoxides of Cy-DHTP and 2-chlorophenol (**1**) were also observed at *m/z* 725 and *m/z* 861, respectively (Figure S1). In addition, the signals whose isotopic distribution correspond to the aggregates of lithium 2-chlorophenoxide were also observed at *m/z* 665 and 799 (Figure S2).[23] This suggests that lithium 2-chlorophenoxide can form aggregates in the presence of *t*-BuOLi. On the other hand, no complex formation between XPhos and lithium 2-chlorophenoxide was observed when XPhos was used as the ligand instead of Cy-DHTP (data not shown). However, when a 1:1 mixture of Cy-DHTP (40 mol %) and XPhos (40 mol %) in the presence of lithium 2-chlorophenoxide was used, a spectrum similar to Figure 3a was observed, with the peak corresponding to the 1:1 complex appearing at *m/z* 591 (Figure S3). These results show that Cy-DHTP has the ability to form complexes with 2-chlorophenols in the presence of *t*-BuOLi while XPhos cannot. This supports our hypothesis about the formation of the heteroaggregate A shown in Scheme 6 and the subsequent acceleration of the Sonogashira coupling at the ortho-position. In addition, it also seems that XPhos does not affect the formation of the complex between Cy-DHTP and 2-chlorophenols, which is consistent with the results of the one-pot reaction using these two ligands.

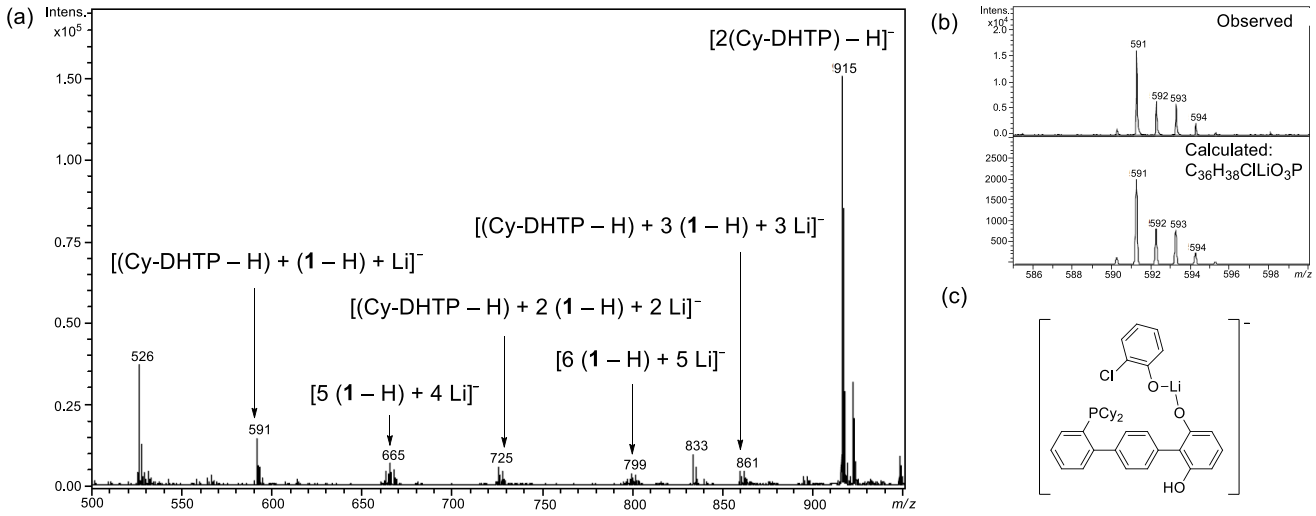


Figure 3. Complex formation between 2-chlorophenol and Cy-DHTP (0.4 equiv) in the presence of *t*-BuOLi (1 equiv) studied by ESI-MS in the negative ion mode. (a) ESI-mass spectrum obtained after stirring for 30 min. (b) A detailed view of the observed isotopic distribution (i) compared to the theoretical isotopic patterns of the complex shown in Figure 3c (ii). (c) Assumed structure of the complex observed at *m/z* 591.

Conclusion

In summary, dihydroxyterphenylphosphine bearing cyclohexyl groups on the phosphorous atom (Cy-DHTP) has been shown to be a powerful ligand for the palladium-catalyzed one-pot synthesis of 2-substituted benzo[*b*]furans from 2-chlorophenols and terminal alkynes. The Pd–Cy-DHTP catalyst can also be used in the sequential one-pot synthesis of disubstituted benzo[*b*]furans from dichlorophenols, terminal alkynes, and boronic acids. In this strategy, use of XPhos as the second ligand and the additional base is instrumental in promoting the Suzuki-Miyaura cross-coupling reaction. The

use of this catalyst enabled the one-pot formation of chlorobenzo[*b*]furan from dichlorophenols and terminal alkynes and the subsequent Suzuki-Miyaura cross-coupling with boronic acids. Both catalysts were found to work independently, with Pd–Cy-DHTP catalyzing the Sonogashira cross coupling and the Pd–XPhos catalyst accelerating the Suzuki-Miyaura cross-coupling reaction. The results of the ESI-MS study provided strong evidence for the formation of heteroaggregates between lithium phenoxides of 2-chlorophenol and Cy-DHTP in which the 2-chloro group is easily accessible to the Pd atom located nearby. We hope that this catalyst system will not only provide various multi-substituted benzo[*b*]furan derivatives but also lead to the development of new synthetic methods using chloroarenes in the field of cross-coupling chemistry.

Experimental Section

All reactions were performed under argon atmosphere. For ^{1}H NMR, tetramethylsilane (TMS) (δ= 0) in $CDCl_3$ served as an internal standard. For ^{13}C NMR, $CDCl_3$ (δ= 77.0) served as an internal standard. Melting points were uncorrected. All the reagents and anhydrous solvents (except for *t*-BuOH) were purchased from commercial suppliers and used without further purification. *t*-BuOH was distilled from Mg metal under argon. Cy-DHTP·HBF_4 and Ph-DHTP were prepared according to the reported procedure.[7e]

Typical experimental procedure for the synthesis of 2-substituted benzo[*b*]furans (Table 1, Entry 1). Toluene (1.0 mL) was added to $PdCl_2(CH_3CN)_2$ (2.6 mg, 0.01 mmol), Cy-DHTP·HBF_4 (10.6 mg,

0.02 mmol), *t*-BuOLi (144 mg, 1.8 mmol), and 2-chlorophenol (64.3 mg, 0.50 mmol) in a two-neck flask under argon. The reaction mixture was stirred at rt for 30 min, and then 1-dodecyne (112 μL, 0.53 mmol) was added. The reaction mixture was stirred at reflux for 45 min. After cooling down, methanol (1 mL) was added, and the reaction mixture was stirred at reflux for 1 h. The resulting suspension was quenched with aq. NH_4Cl (5 mL) at rt and extracted with ethyl acetate (20 mL × 2). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated, and then the residue was purified by preparative TLC (hexanes) to give 2-decylbenzofuran **3** (102 mg, 79%) as a yellow oil.

2-Decylbenzofuran (3)[24]**:** Prepared from 2-chlorophenol and 1-dodecyne. Purification by preparative TLC (hexanes) afforded **3** (102 mg, 79%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (1H, dd, *J* = 7.2, 2.8 Hz), 7.40 (1H, d, *J* = 8.0 Hz), 7.21-7.15 (2H, m), 6.36 (1H, s), 2.75 (2H, t, *J* = 7.6 Hz), 1.77-1.70 (2H, m), 1.37-1.26 (14H, m), 0.88 (3H, t, *J* = 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.74, 159.67, 154.6, 129.0, 123.0, 122.3, 120.1, 110.7, 101.7, 31.9, 29.6, 29.5, 29.4, 29.3, 29.2, 28.4, 27.7, 22.7, 14.1; HRMS (DART) *m/z* calcd for $C_{18}H_{27}O$ ($[M+H]^+$) 259.2056, found 259.2062**;** IR (ATR) 2922, 2853, 1454, 1252, 748, 739.

2-(1-Dodecyn-1-yl)phenol (4): A yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.26 (1H, m), 7.21-7.17 (1H, m), 6.92 (1H, d, *J* = 7.3 Hz), 5.81 (1H, s), 2.47 (2H, t, *J* = 7.1 Hz), 167-1.58 (2H, m), 1.46-1.27 (14H, m), 0.88 (3H, t, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.5, 131.4, 129.5, 120.1, 114.3, 110.3, 98.1, 31.9, 29.6, 29.5, 29.3, 29.1, 29.0, 28.7, 22.7, 19.6, 14.1; HRMS (DART) *m/z* calcd for $C_{18}H_{27}O$ ($[M+H]^+$) 259.2056, found 259.2058**;** IR (ATR) 2922, 2853, 1576, 1485, 1462, 1286, 1234,

1177, 750.

2-(2-Phenylethyl)-1-benzofuran (5)[25]: Prepared from 2-chlorophenol and 4-phenyl-1-butyne. Purification by preparative TLC (hexanes) afforded **5** (91.1 mg, 82%) as a yellow solid: Mp. 46.7-48.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (2H, dd, *J* = 15.2 Hz, 6.4 Hz), 7.31-7.16 (7H, m), 6.36 (1H, s), 3.08 (4H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.4, 154.6, 140.9, 128.9, 128.4, 128.3, 126.2, 123.2, 122.4, 120.3, 110.7, 102.3, 33.9, 30.3; HRMS (DART) *m/z* calcd for $C_{16}H_{15}O$ ($[M+H]^+$) 223.1117, found 223.1117; IR (ATR) 3109, 3061, 2934, 2857, 1601, 1495, 1452, 1427, 1254, 1167, 1101, 1001, 951, 808, 739, 700.

2-(3-Chloropropyl)-1-benzofuran (6)[26]**:** Prepared from 2-chlorophenol and 5-chloro-1-pentyne. Purification by preparative TLC (hexanes) afforded **6** (56.2 mg, 58%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (1H, d, *J* = 6.8 Hz), 7.40 (1H, d, *J* = 8.0 Hz), 7.23-7.18 (2H, m), 6.43 (1H, s), 3.59 (2H, t, *J* = 7.7 Hz), 2.95 (2H, t, *J* = 7.2 Hz), 2.24-2.19 (2H, quint, *J* = 10.1 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.4, 154.7, 128.7, 123.4, 122.5, 120.33, 120.32, 110.76, 110.75, 102.8, 44.0, 30.5, 25.6; HRMS (DART) *m/z* calcd for $C_{11}H_{12}ClO$ ($[M+H]^+$) 195.0571, found 195.0587; IR (ATR) 2846, 2326, 1585, 1454, 1250, 748.

2-Phenylbenzofuran (7)[27]**:** Prepared from 2-chlorophenol and ethylnylbenzene. Purification by preparative TLC (hexanes/ethyl acetate, 10% ethyl acetate) afforded **7** (50.7 mg, 52%) as a white solid: Mp. 117.1-118.1 °C; ^{1}H NMR(400 MHz, $CDCl_3$) δ 7.87 (2H, d, *J* = 8.4 Hz), 7.58 (1H, d, *J* = 6.8 Hz), 7.52 (1H, d, *J* = 8.4 Hz), 7.45 (2H, t, *J* = 7.6 Hz), 7.35 (1H, t, *J* = 7.4 Hz), 7.30-7.21 (2H, m), 7.03 (1H,

s);[13]C NMR (100 MHz, $CDCl_3$) δ 155.9, 154.9, 130.5, 129.2, 128.8, 128.5, 124.9, 124.2, 122.9, 120.8, 111.2, 101.3**;** HRMS (DART) *m/z* calcd for $C_{14}H_{11}O$ ($[M+H]^+$) 195.0804, found 195.0831**;** IR (ATR) 3105, 3051, 3034, 2955, 2930, 2855, 2648, 2610, 2494, 1441, 1258, 1020, 918, 806, 739, 689.

2-(3-Chlorophenyl)-1-benzofuran (8)[28]: Prepared from 2-chlorophenol and 3-chloro-1-ethynylbenzene. Purification by preparative TLC (hexanes) afforded **8** (73.1 mg , 64% yield) as a yellow solid: Mp. 87.3-88.2 °C; [1]H NMR (400 MHz, $CDCl_3$) δ 7.85 (1H, t, *J* = 1.6 Hz), 7.73 (1H, d, *J* = 7.6 Hz), 7.59 (1H, d, *J* = 8.4 Hz), 7.52 (1H, d, *J* = 8.4 Hz), 7.39-7.22 (4H, m), 7.04 (1H, s); [13]C NMR (100 MHz, $CDCl_3$) δ 154.9, 154.2, 134.8, 132.1, 130.0, 128.9, 128.3, 124.8, 124.7, 123.1, 122.9, 121.1, 111.2, 102.3; HRMS (DART) *m/z* calcd for $C_{14}H_{10}ClO$ ($[M+H]^+$) 229.0415, found 229.0414; IR (ATR) 3109, 3067, 3040, 2957, 2930, 2870, 1603, 1558, 1452, 1408, 1258, 1038, 739, 662.

2-(4-Fluorophenyl)-1-benzofuran (9)[13d]: Prepared from 2-chlorophenol and 1-ethynyl-4-fluorobenzene. Purification by preparative TLC (hexanes/ethyl acetate, 10% ethyl acetate) afforded **9** (34.8 mg, 33%) as a yellow solid: Mp. 120.2-122.5 °C; [1]H NMR (400 MHz, $CDCl_3$) δ 7.84-7.80 (2H, m), 7.56 (1H, d, *J* = 7.6 Hz), 7.50 (1H, d, *J* = 8.4 Hz), 7.29-7.20 (2H, m), 7.12 (2H, t, *J* = 8.8 Hz), 6.93 (1H, s); [13]C NMR (100 MHz, $CDCl_3$) δ 164.1, 161.7, 155.0, 154.9, 129.2, 126.8, 126.7, 124.3, 123.0, 120.9, 116.0, 115.8, 111.1, 101.01, 101.0**;** HRMS (DART) *m/z* calcd for $C_{14}H_{10}FO$ ($[M+H]^+$) 213.0710, found 213.0705**;** IR (ATR) 3046, 1599, 1499, 1450, 1223, 1206, 1157, 1098, 839, 800.

2-(4-Methoxyphenyl)-1-benzofuran (10)[29]**:** Prepared from 2-chlorophenol and 4-ethynylanisole. Purification by preparative TLC (hexanes/ethyl acetate, 10% ethyl acetate) afforded **10** (109 mg, 97%)

as a brown solid: Mp. 142.6-144.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (2H, d, *J* = 8.0 Hz), 7.55 (1H, d, *J* = 7.2 Hz), 7.49 (1H, d, *J* = 7.6 Hz), 7.24-7.20 (2H, m), 6.96 (2H, d, *J* = 8.8 Hz), 6.87 (1H, s), 3.84 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 156.0, 154.7, 129.5, 126.4, 123.7, 123.3, 122.8, 120.5, 114.2, 110.9, 99.6, 55.2**;** HRMS (DART) *m/z* calcd for $C_{15}H_{13}O_2$ ($[M+H]^+$) 225.0910, found 225.0911**;** IR (ATR) 3121, 3007, 2961, 2837, 1503, 1244, 1169, 741.

2-Decyl-5-methoxybenzofuran (11): Prepared from 2-chloro-4-methoxyphenol and 1-dodecyne. Purification by preparative TLC (hexanes) afforded **11** (111.8 mg, 78%) as a yellow solid: Mp. 41.2-42.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (1H, d, *J* = 8.8 Hz), 6.94 (1H, d, *J* = 2.4 Hz), 6.78 (1H, dd, *J* = 8.4, 2.4 Hz), 6.29 (1H, s), 3.81 (3H, s), 2.7 (2H, t, *J* = 7.6 Hz), 1.73-1.67 (2H, quint, *J* = 5.5 Hz), 1.26 (14H, br s), 0.87 (3H, t, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.6, 155.7, 149.6, 129.5, 111.2, 110.9, 103.0, 101.9, 55.7, 31.9, 29.6, 29.5, 29.34, 29.31, 28.5, 27.6, 22.7, 14.1**;** HRMS (DART) *m/z* calcd for $C_{19}H_{29}O_2$ ($[M+H]^+$) 289.2162, found 289.2151**;** IR (ATR) 2914, 2847, 1614, 1464, 1452, 1207, 1180, 1153, 1136, 1030, 949, 939, 845, 806, 766, 721.

2-Decylbenzofuran-5-carboxylate (12):

Prepared from methyl-3-chloro-4-hydroxybenzoate and 1-dodecyne. Purification by preparative TLC (hexanes/ethyl acetate, 10% ethyl acetate) afforded **12** (58.3 mg, 37%) as a yellow solid: Mp. 39.0-39.2 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (1H, d, *J* = 1.7 Hz), 7.94 (1H, dd, *J* = 1.7, 8.5 Hz), 7.42 (1H, d, *J* = 8.5 Hz), 6.43 (1H, s), 3.93 (3H, s), 2.77 (2H, t, *J* = 7.4 Hz), 1.77-1.70 (2H, quint, *J* = 7.5 Hz), 1.36-1.26 (14H, m), 0.88 (3H, t, *J* = 6.6 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.5, 161.4,

157.3, 129.0, 125.0, 124.7, 122.6, 110.5, 102.2, 52.0, 31.9, 29.6, 29.5, 29.3, 29.2, 28.4, 27.5, 22.7, 14.1; IR (ATR) 2951, 2916, 2900, 2849, 1722, 1472, 1437, 1304, 1269, 1240, 1157, 1144, 1115, 1240, 1090, 802, 766; HRMS (DART) *m/z* calcd for $C_{20}H_{29}O_3$ ($[M+H]^+$) 317.2111, found 317.2102.

2-Decyl-6-methylbenzofuran (13): Prepared from 2-chloro-5-methylphenol and 1-dodecyne. Purification by preparative TLC (hexanes) afforded **13** (85.6 mg, 62% yield) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (1H, d, *J* = 8.0 Hz), 7.21 (1H, s), 6.98 (1H, d, *J* = 7.6 Hz), 6.29 (1H, s), 2.72 (2H, t, *J* = 7.6 Hz), 2.44 (3H, s), 1.73-1.68 (2H, quint, *J* = 5.5 Hz), 1.26 (14H, brs), 0.88 (3H, t, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 155.0, 133.0, 126.4, 123.6, 119.5, 111.0, 101.4, 31.9, 29.6, 29.5, 29.35, 29.30, 29.2, 28.4, 27.7, 22.7, 21.5, 14.1**;** HRMS (DART) *m/z* calcd for $C_{19}H_{29}O$ ($[M+H]^+$) 273.2213, found 273.2195**;** IR (ATR) 2922, 2852, 1728, 1456, 1119, 812**.**

2-Decylfuro[3,2-*b*]pyridine (14): Prepared from 2-chloro-3-hydroxypyridine and 1-dodecyne. Purification by preparative TLC (hexanes/ethyl acetate, 20% ethyl acetate) afforded **14** (69.0 mg, 53%) as a brown oil: ^{1}H NMR(400 MHz, $CDCl_3$) δ 8.45 (1H, dd, *J* = 4.8, 0.8 Hz), 7.63 (1H, dd, *J* = 8.0, 0.8 Hz), 7.11 (1H, t, *J* = 6.8 Hz), 6.59 (1H, s), 2.80 (2H, t, *J* = 7.4 Hz), 1.79-1.72 (2H, quint, *J* = 7.4 Hz), 1.40-1.26 (14H, m), 0.87 (3H, t, *J* = 6.8 Hz); ^{13}C NMR(100 MHz, $CDCl_3$) δ 164.3, 149.1, 147.5, 145.1, 117.7, 117.2, 103.4, 31.8, 29.52, 29.45, 29.3, 29.1, 28.8, 27.4, 22.6, 14.1**;** HRMS (DART) *m/z* calcd for $C_{17}H_{26}NO$ ($[M+H]^+$) 260.2009, found 260.2026**;** IR (ATR) 2922, 2853, 1734, 1595, 1456, 1412, 1261, 935, 785.

2-Decyl-4-chlorobenzofuran (15)[8]**:** Prepared from 2,3-dichlorophenol and 1-dodecyne. Purification by

preparative TLC (hexanes) afforded **15** (112 mg, 77%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (1H, d, *J* = 8.0 Hz), 7.08-7.00 (2H, m), 6.38 (1H, s), 2.66 (2H, t, *J* = 6.0 Hz), 1.64 (2H, quint, *J* = 6.0 Hz), 1.38-1.03 (14H, m), 0.80 (3H, t, *J* = 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.6, 154.8, 128.4, 125.0, 123.6, 122.3, 109.2, 100.4, 31.9, 29.6, 29.5, 29.32, 29.30, 29.2, 28.4, 27.5, 22.7, 14.1**;** HRMS (DART) *m/z* calcd for $C_{18}H_{26}ClO$ ($[M+H]^+$) 293.1667, found 293.1664**;** IR (ATR) 2922, 2853, 1584, 1466, 1425, 1258, 1136, 934, 768.

2-Decyl-5-chlorobenzofuran (16)[8]**:** Prepared from 2,4-dichlorophenol and 1-dodecyne. Purification by preparative TLC (hexanes) afforded **16** (117 mg, 80%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (1H, d, *J* = 2.0 Hz), 7.29 (1H, d, *J* = 8.8 Hz), 7.13 (1H, dd, *J* = 8.0 Hz), 6.29 (1H, d, *J* = 1.0 Hz), 2.73 (2H, t, *J* = 8.0 Hz), 1.72 (2H, quint, *J* = 7.4 Hz), 1.26 (14H, brs), 0.88 (3H, t, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.5, 153.0, 130.4, 127.9, 123.1, 119.8, 111.6, 101.5, 31.9, 29.6, 29.5, 29.3, 29.2, 28.5, 27.5, 22.7, 14.1; HRMS (DART) *m/z* calcd for $C_{18}H_{26}ClO$ ($[M+H]^+$) 293.1667, found 293.1682**;** IR (ATR) 2922, 2853, 1597, 1447, 1258, 1061, 793.

2-Decyl-6-chlorobenzofuran (17)[8]**:** Prepared from 2,5-dichlorophenol and 1-dodecyne. Purification by preparative TLC (hexanes) afforded **17** (57.6 mg, 39%) as a white solid: Mp. 35.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (1H, s), 7.34 (1H, d, *J* = 8.0 Hz), 7.14 (1H, dd, *J* = 8.0 Hz), 6.32 (1H, s), 2.73 (2H, t, *J* = 8.0 Hz), 1.70 (2H, quint, *J* = 6.7 Hz), 1.43-1.16 (14H, m), 0.88 (3H, t, *J* = 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.7, 154.7, 128.7, 127.7, 123.0, 120.6, 111.3, 101.6, 31.9, 29.6, 29.5, 29.3, 29.3, 29.2, 28.4, 27.6, 22.7, 14.1; HRMS (DART) m/z calcd for $C_{18}H_{26}ClO$ ($[M+H]^+$) 293.1667, found 293.1657;

IR (ATR) 2916, 2851, 1597, 1578, 1466, 1275, 1057, 947, 912, 849, 820, 721.

Typical experimental procedure for the synthesis of disubstituted benzo[*b*]furans (Table 4, Entry 1): Toluene (1.0 mL) was added to $PdCl_2(CH_3CN)_2$ (2.6 mg, 0.01 mmol), Cy-DHTP·HBF_4 (10.6 mg, 0.02 mmol), XPhos (9.7 mg, 0.02 mmol), *t*-BuOLi (144 mg, 1.20 mmol), and 2,4-dichlorophenol (64.3 mg, 0.50 mmol) in a two-neck flask under argon. The reaction mixture was stirred at rt for 15 min, and then 1-dodecyne (112 μL, 0.53 mmol) was added. The reaction mixture was stirred at reflux for 45 min. After cooling down, water (1 mL) was added, and the reaction mixture was stirred at reflux for 2 h. After cooling down, 4-methoxyphenylboronic acid (114 mg, 0.75 mmol) and K_3PO_4 (213 mg, 1.0 mmol) were added, then the reaction mixture was stirred at reflux for 6 h. The resulting suspension was quenched with 1M aq. HCl (7 mL) at rt and extracted with ethyl acetate (20 mL × 2). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated, and then the residue was purified by preparative TLC (SiO_2, hexane/AcOEt = 95/5) to give 2-decyl-5-(4-methoxyphenyl)-1-benzofuran (114 mg, 73%) as a white solid.

2-Decyl-5-(4-methoxyphenyl)-1-benzofuran (18): Prepared from 2,4-dichlorophenol, 1-dodecyne, and 4-methoxyphenylboronic acid. Purification by preparative TLC (hexanes/ethyl acetate, 5% ethyl acetate) afforded **18** (114 mg, 73%) as a white solid: Mp. 69.1-69.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (1H, s), 7.52 (2H, d, *J* = 8.8 Hz), 7.44-7.36 (2H, m), 6.97 (2H, d, *J* = 8.8 Hz), 6.39 (1H, s), 3.85 (3H, s), 2.76 (2H, t, *J* = 7.6 Hz), 1.76-1.70 (2H, quint, *J* = 5.5 Hz), 1.26 (14H, brs), 0.88 (3H, t, *J* = 6.8 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.4, 158.7, 153.9, 135.7, 134.5, 129.5, 128.3, 122.4, 118.2, 114.1,

110.7, 101.9, 55.3, 31.9, 29.6, 29.5, 29.4, 29.3, 27.7, 14.1; HRMS (DART) *m/z* calcd for $C_{25}H_{33}O_2$ ($[M+H]^+$) 365.2475, found 365.2462; IR (ATR) 2955, 2914, 2827, 1609, 1520, 1464, 1273, 1236, 1182, 1157, 1038, 947, 806.

2-(4-Fluorophenyl)-5-(4-methoxyohenyl)-1-benzofuran (19): Prepared from 2,4-dichlorophenol, 1-ethynyl-4-fluorobenzene, and 4-methoxyphenylboronic acid. Purification by column chromatography (hexanes/ dichloromethane, 10% dichloromethane) afforded **19** (128 mg, 80%) as a white solid: Mp. 125.5-126 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ7.87-7.874 (2H, m), 7.71 (1H, d, *J* = 1.2 Hz), 7.57-7.53 (3H, m), 7.48-7.45 (1H, m), 7.15 (2H, t, *J* = 8.4 Hz), 7.00 (3H, d, *J* = 8.8 Hz), 3.87 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$ 50℃) δ 159.1, 155.7, 154.4, 136.6, 134.4, 129.8, 128.45, 128.41, 126.92, 126.85, 123.8, 118.94, 118.92, 116.05, 115.98, 115.9, 115.8, 114.4, 114.3, 111.2, 101.25, 101.20, 55.46, 55.37; HRMS (DART) *m/z* calcd for $C_{21}H_{16}FO_2$ ($[M+H]^+$) 319.1129, found 319.1108**;** IR (ATR) 3576, 3014, 2956, 2839, 1502, 1463, 1236, 1012, 800.

2-Phenyl-5-(4-methoxyphenyl)-1-benzofuran (20): Prepared from 2,4-dichlorophenol, ethynylbenzene, and 4-methoxyphenylboronic acid. Purification by column chromatography (hexanes/ dichloromethane, 10% dichloromethane) afforded **20** (117 mg, 78%) as a white solid: Mp. 182.6-183.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (2H, d, *J* = 8.8 Hz), 7.71 (1H, s), 7.57-7.54 (3H, m), 7.48-7.44 (3H, m), 7.36 (1H, d, *J* = 7.6 Hz), 7.06 (1H, s), 7.00-6.99 (2H, d, *J* = 8.8 Hz), 3.87 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.2, 161.7, 158.9, 155.6, 154.2, 136.4, 134.2, 129.7, 128.4, 126.8, 126.7, 123.7, 118.9, 116.0, 115.8, 114.2, 111.1, 101.1, 55.4; HRMS (DART) *m/z* calcd for $C_{21}H_{17}O_2$ ($[M+H]^+$)

301.1223, found 301.1212**;** IR (ATR) 3062, 2960, 1517, 1463, 1232, 1035, 802, 759.

2-Phenyl-5-(3-methoxyphenyl)-1-benzofuran (21): Prepared from 2,4-dichlorophenol, ethynylbenzene, and 3-methoxyphenylboronic acid. Purification by column chromatography (hexanes/ dichloromethane, 10% dichloromethane) afforded **21** (121 mg, 81%) as a white solid: Mp. 99.1-99.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (2H, d, *J* = 7.2 Hz), 7.74 (1H, d, *J* = 1.2 Hz), 7.55-7.7.47, (2H, m), 7.43 (2H, t, *J* = 7.6 Hz), 7.37-7.33 (2H, m), 7.21-7.16 (2H, m), 7.02 (1H, s), 6.88 (1H, d, *J* = 7.6 Hz), 3.85 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.0, 156.7, 154.7, 143.3, 136.6, 130.5, 129.8, 128.9, 128.8, 125.1, 124.1, 120.1, 119.5, 113.3, 112.4, 111.4, 101.6, 55.4; HRMS (DART) *m/z* calcd for $C_{21}H_{17}O_2$ ($[M+H]^+$) 301.1223, found 301.1209; IR (ATR) 3055, 2997, 2913, 2833, 1597, 1464, 1319, 1252, 1215, 1045, 912, 793, 762, 689, 662.

2-Phenyl-5-(2-methoxyphenyl)-1-benzofuran (22): Prepared from 2,4-dichlorophenol, ethynylbenzene, and 2-methoxyphenylboronic acid. Purification by column chromatography (hexanes/ dichloromethane, 10% dichloromethane) afforded **22** (130 mg, 84%) as a white solid: Mp. 120.5-122.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (2H, d, *J* = 6.4 Hz), 7.71 (1H, d, *J* = 2.0 Hz), 7.54 (1H, d, *J* = 8.8 Hz), 7.48-7.43 (3H, m), 7.38-7.32 (3H, m), 7.07-7.00 (2H, m), 3.83 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.5, 156.2, 154.1, 133.5, 131.2, 131.0, 129.1, 128.7, 128.5, 128.4, 126.3, 124.9, 121.8, 120.8, 111.3, 110.5, 101.5, 55.6; HRMS (DART) *m/z* calcd for $C_{21}H_{17}O_2$ ($[M+H]^+$) 301.1223, found 301.1254**;** IR (ATR) 2957, 1599, 1520, 1506, 1464, 1439, 1277, 1236, 1184, 1155, 1034, 1013, 837, 800**.**

2-Phenyl-5-(4-methylphenyl)-1-benzofuran (23): Prepared from 2,4-dichlorophenol, ethynylbenzene, and 2-methylphenylboronic acid. Purification by column chromatography (hexanes/ dichloromethane, 25% dichloromethane) afforded **23** (134 mg, 94%) as a white solid: Mp. 172.3-172.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (2H, d, *J* = 7.2 Hz), 7.73 (1H, s, *J* =1.6 Hz), 7.56-7.43 (6H, m), 7.37-7.35 (1H, m), 7.25 (2H, d, *J* = 7.6 Hz), 7.03 (1H, s), 2.40 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.4 154.3, 136.5, 130.4, 129.6, 129.6, 129.3, 128.9, 128.7, 128.6, 127.3, 127.1, 124.9, 124.8, 123.9, 123.7, 123.7, 111.2, 111.1, 101.6, 101.2; HRMS (DART) *m/z* calcd for $C_{21}H_{17}O$ ($[M+H]^+$) 285.3585, found 285.1232; IR (ATR) 2912, 1463, 800, 758.

2-Phenyl-5-(4-trifluoromethylphenyl)-1-benzofuran (24): Prepared from 2,4-dichlorophenol, ethynylbenzene, and 4-(trifluoromethyl)phenylboronic acid. Purification by column chromatography (hexanes/ dichloromethane, 10% dichloromethane) afforded **24** (142 mg, 84%) as a white solid: Mp. 194.5-195.1 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (2H, d, *J* = 7.4 Hz), 7.78-7.69 (5H, m) 7.60 (1H, d, *J* = 8.5 Hz), 7.51-7.45 (3H, m) 7.38 (1H, t, *J* = 7.5 Hz), 7.07 (1H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.0, 154.9, 145.2, 135.1, 130.2, 130.0, 128.9, 127.6, 125.69, 125.66, 125.0, 124.0, 119.6, 111.5, 101.3; HRMS (DART) *m/z* calcd for $C_{21}H_{14}F_3O$ ($[M+H]^+$) 339.0991, found 339.1001; IR (ATR) 3088, 1614, 1468, 1333, 1279, 1105, 1070, 804, 764, 689, 590.

2-Phenyl-5-(4-fluorophenyl)-1-benzofuran (25): Prepared from 2,4-dichlorophenol, ethynylbenzene, and 4-fluorophenylboronic acid. Purified by column chromatography (hexanes/ dichloromethane, 10% dichloromethane) afforded **25** (96.6 mg, 67%) as a white solid: Mp. 187.9-188.2 °C; ^{1}H NMR (400

MHz, $CDCl_3$) δ 7.87-7.89 (2H, m), 7.70 (1H, d, *J* = 1.6 Hz), 7.55-7.58 (3H, m), 7.42-7.48 (3H, m), 7.35-7.38 (1H, m), 7.13 (2H, t, *J* = 8.8 Hz), 7.04 (1H, d, *J* = 0.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5, 161.0, 156.7, 154.6, 137.8, 137.8, 135.7, 130.3, 129.8, 128.9, 128.9, 128.8, 128.7, 125.0, 123.8, 119.3, 115.7, 115.4, 111.3, 101.4; HRMS (DART) *m/z* calcd for $C_{20}H_{14}FO$ ($[M+H]^+$) 289.1023, found 289.1012; IR (ATR) 3115, 1516, 1464, 1445, 1227, 1211, 802, 760, 745, 687.

2-Phenyl-5-(3-thiophene)-1-benzofuran (26): Prepared from 2,4-dichlorophenol, ethynylbenzene, and 3-thiopheneboronic acid. Purification by column chromatography (hexanes/ dichloromethane, 10% dichloromethane)afforded **26** (105 mg, 76%) as a white solid: Mp. 208.6-209.6 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.87 (2H, d, *J* = 8.4 Hz), 7.77 (1H, s), 7.52 (2H, s), 7.47-7.36 (6H, m), 7.03 (1H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.6, 154.3, 142.7, 131.3, 130.3, 129.7, 128.8, 128.6, 126.7, 126.1, 124.9, 123.4, 119.7, 118.6, 111.3, 101.4, 56.2**;** HRMS (DART) *m/z* calcd for $C_{18}H_{13}OS$ ($[M+H]^+$) 277.0682, found 277.0675**;** IR (ATR) 3099, 1463, 1444, 775, 758, 682.

***(E)*-5-(Octo-1-en-1-yl)-2-phenylbenzofuran (27):** Prepared from 2,4-dichlorophenol, ethynylbenzene, and trans-1-octen-1-ylboronic acid. Purification by column chromatography (hexanes/ dichloromethane, 10% dichloromethane) afforded **27** (91.9 mg, 60%) as a yellow solid: Mp. 94.4-96.9 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.84 (2H, d, *J* = 7.2 Hz), 7.51 (1H, s), 7.45-7.42 (3H, d, *J* = 8.8 Hz),, 7.36-7.29 (2H, m), 6.97 (1H, s), 6.46 (1H, d, *J* = 15.6 Hz), 6.24-6.17 (1H, m), 2.25-2.20 (2H, m), 1.52-1.46 (2H, m), 1.32 (6H, br s), 0.90 (3H, t, *J* = 6.4); ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.3, 133.3, 130.5, 130.1, 129.7, 129.5, 128.6, 128.5, 124.9, 122.6, 118.0, 111.0, 101.3, 33.1, 31.8, 29.5, 28.9, 22.7, 14.1; HRMS (DART) *m/z*

calcd for $C_{22}H_{25}O$ ($[M+H]^+$) 305.1900, found 305.1926; IR (ATR) 3034, 2955, 2920, 2851, 1464, 1447, 1267, 1020, 962, 916, 804, 758, 689.

2-Phenyl-4-(4-methoxyphenyl)-1-benzofuran (28):

Prepared from 2,3-dichlorophenol, ethynylbenzene, and 4-methoxyphenylboronic acid. Purification by column chromatography (hexanes/ dichloromethane, 20% dichloromethane) afforded **28** (110 mg, 73%) as a yellow solid: Mp. 73.4-75.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (2H, d, J = 7.2 Hz), 7.59 (2H, d, J = 8.8 Hz) 7.48-7.41 (3H, m), 7.35-7.30 (2H, m) 7.19 (1H, d, J = 1.2 Hz), 7.04 (2H, d, J = 8.8 Hz), 3.87 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.1, 156.1, 155.2, 134.7, 132.6, 130.4, 129.5, 128.8, 128.5, 127.5, 124.9, 124.5, 122.2, 114.2, 109.6, 100.9, 55.4; HRMS (DART) *m/z* calcd for $C_{21}H_{17}O_2$ ($[M+H]^+$) 301.1223, found 301.1215; IR (ATR) 3055, 3030, 3003, 2953, 2934, 2905, 2833, 1609, 1518, 1476, 1294, 1246, 1179, 1026, 839, 779, 756, 685.

2-Phenyl-4-(4-methylphenyl)-1-benzofuran (29): Prepared from 2,3-dichlorophenol, ethynylbenzene, and 4-methylphenylboronic acid. Purification by column chromatography (hexanes/ dichloromethane, 14% dichloromethane) afforded **29** (104 mg, 73%) as a yellow solid: Mp. 71.1-72.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (2H, d, J = 7.2 Hz), 7.55 (2H, d, J = 8.4 Hz) 7.47 (1H, d, J = 8.0 Hz), 7.42 (2H, t, J = 7.2 Hz), 7.34-7.27 (5H, m), 7.19 (1H, s), 2.43 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.1, 155.3, 137.3, 137.1, 135.0, 130.4, 129.4, 128.8, 128.5, 128.3, 127.6, 124.9, 124.5, 122.4, 109.9, 100.9, 21.2; HRMS (DART) *m/z* calcd for $C_{21}H_{17}O$ ($[M+H]^+$) 285.1274, found 285.1314; IR (ATR) 3028, 2913, 1609, 1476, 1425, 1252, 1163, 1042, 1022, 922, 826, 775, 754, 685, 544.

2-Phenyl-4-(2-methoxyphenyl)-1-benzofuran (30): Prepared from 2,3-dichlorophenol, ethynylbenzene, and 2-methoxyphenylboronic acid. Purification by column chromatography (hexanes/ dichloromethane, 5% dichloromethane) afforded **30** (92.5 mg, 62%) as yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (2H, d, *J* = 7.2 Hz), 7.49 (1H, d, *J* = 8.4 Hz) 7.43-7.37 (4H, m), 7.35-7.27 (3H, m) 7.10-7.05 (2H, m), 6.90 (1H, s), 3.80 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.6, 155.5, 154.7, 131.7, 131.3, 130.6, 128.9, 128.82, 128.78, 128.7, 128.4, 124.8, 124.0, 120.7, 111.2, 110.0, 101.83, 101.79, 55.5, 55.4; HRMS (DART) *m/z* calcd for $C_{21}H_{17}O_2$ ($[M+H]^+$) 301.1223, found 301.1225; IR (ATR) 3059, 2931, 2832, 1597, 1474, 1414, 1238, 1020, 906, 756, 729, 691.

2-Phenyl-6-(4-methoxyphenyl)-1-benzofuran (31): Prepared from 2,5-dichlorophenol, ethynylbenzene, and 4-methoxyphenylboronic acid. Purification by column chromatography (hexanes/ dichloromethane, 20% dichloromethane) afforded **31** (66.1 mg, 44%) as a yellow solid: Mp. 171.0-173.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (2H, d, *J* = 7.6 Hz), 7.70 (1H, s) 7.60-7.58 (3H, m), 7.46 (3H, t, *J* = 7.6 Hz), 7.36 (1H, d, *J* = 7.6 Hz), 7.03-6.99 (3H, m), 3.86 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.0, 156.2, 155.6, 137.6, 133.89, 133.88, 130.5, 128.8, 128.5, 128.3, 127.9, 124.8, 122.2, 120.9, 114.3, 109.1, 101.2, 55.4; HRMS (DART) *m/z* calcd for $C_{21}H_{17}O_2$ ($[M+H]^+$) : 301.1223, found : 301.1267**;** IR (ATR) 3040, 3017, 2955, 2922, 2839, 1605, 1522, 1470, 1252, 1186, 1167, 1033, 824, 814, 758, 691.

2-Phenyl-7-(4-methoxyphenyl)-1-benzofuran (32): Prepared from 2,6-dichlorophenol, ethynylbenzene, and 4-methoxyphenylboronic acid. Purification by preparative TLC (hexanes/ ethyl

acetate, 20% ethyl acetate) afforded **32** (41.4 mg, 28%) as a yellow solid: Mp. 98.9-99.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91-7.85 (4H, m), 7.51 (1H, d, *J* = 7.6 Hz), 7.43 (3H, dd, J = 7.6, 15.2 Hz) 7.35 (1H, d, *J* = 7.2 Hz), 7.29 (1H, t, *J* = 8.0 Hz), 7.09-7.07 (3H, m), 3.90 (3H, s); ^{13}C NMR (126 MHz, CDCl3) δ 159.2, 155.9, 151.9, 130.4, 129.9, 129.7, 129.0, 128.8, 128.5, 125.0, 123.5, 123.3, 119.5, 114.1, 101.5, 55.3; HRMS (DART) *m/z* calcd for $C_{21}H_{17}O_2$ ($[M+H]^+$) 301.1223, found 301.1255; IR (ATR) 3061, 3009, 2955, 2835, 1614, 1516, 1476, 1429, 1400, 1279, 1254, 1217, 1182, 1020, 783, 745, 691.

2-(4-Methoxyphenyl)-7-(4-methoxyphenyl)-1-benzofuran (33): Prepared from 2,6-dichlorophenol, 4-ethynylanisole, and 4-methoxyphenylboronic acid. Purified by preparative TLC (hexanes/dichloromethane, 40% dichloromethane) afforded **33** (92.6 mg, 56%) as colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (2H, d, *J* = 8.8 Hz), 7.77 (2H, d, *J* = 8.8 Hz), 7.46 (1H, d, *J* = 7.6 Hz), 7.36 (1H, d, *J* = 6.4 Hz), 7.22-7.28 (1H, m), 7.06 (2H, d, *J* = 8.8 Hz), 6.95 (2H, d, *J* = 8.8 Hz), 6.91 (1H, s), 3.87 (3H, s), 3.82 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.9, 159.1, 156.0, 151.7, 130.2, 129.7, 129.1, 126.6, 126.4, 124.7, 123.4, 123.2, 122.8, 119.1, 114.2, 114.0, 99.8, 55.3; HRMS (DART) *m/z* calcd for $C_{22}H_{19}O_3$ ($[M+H]^+$) 331.1329, found 331.1336; IR (ATR) 3057, 2955, 2907, 2835, 1612, 1504, 1462, 1246, 1175, 1111, 1026, 907, 831, 802, 731, 592.

2-(4-Methoxyphenyl)-5-(3,4,5-trimethoxyphenyl)-1-benzofuran (34)[21]: Prepared from 2,4-dichlorophenol, 4-ethynylanisole, and 3,4,5-trimethoxyphenylboronic acid. Purification by column chromatography (hexanes/ dichloromethane, 20% dichloromethane) afforded **34** (165 mg, 85%) as a

white solid: Mp. 179.0-180.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (2H, d, *J* = 8.8 Hz), 7.70 (1H, s), 7.53 (1H, d, *J* = 8.8 Hz), 7.43 (1H, d, *J* = 8.4 Hz), 6.99 (2H, d, *J* = 8.8 Hz), 6.92 (1H, s), 6.82 (2H, s), 3.91 (3H, s), 3.95 (6H, s), 3.87 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.0, 156.8, 154.2, 153.3, 137.7, 137.2, 136.6, 129.9, 126.4, 123.3, 123.1, 118.9, 114.2, 110.9, 99.6, 60.9, 56.1, 55.3; HRMS (DART) *m/z* calcd for $C_{24}H_{23}O_5$ ($[M+H]^+$) 391.1540, found 391.1550; IR (ATR) 2932, 2832, 1582, 1508, 1462, 1412, 1246, 1173, 1123, 1022, 999, 810.

Typical Experimental Procedure for Detection of heteroaggregate formation of lithium phenoxides of Cy-DHTP and 1 by ESI-MS: 1 (0.03 mmol, 3.8 mg) and 40 mol% of Cy-DHTP (6.7 mg) were dissolved in toluene (1 mL) with 1 equiv of *t*-BuOLi (2.4 mg), and the resulting solution was stirred at room temperature for 30 min. After stirring, an aliquot (10 μL) was taken, diluted by acetonitrile (1 mL), filtered, and the resulting solution was injected to ESI-MS.

Supporting Information. Additional ESI mass spectra and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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