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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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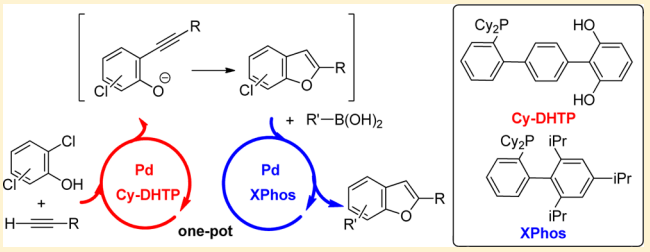
Supporting Information

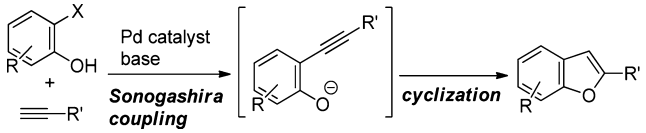
ABSTRACT: A dihydroxyterphenylphosphine bearing cyclohexyl groups on the phosphorus atom (Cy-DHTP) was found to be a powerful ligand for the palladium-catalyzed one-pot synthesis of substituted benzo[*b*]furans from 2-chlorophenols and terminal alkynes. This catalyst system was also applicable to the 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 promoting 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 to obtain these compounds have been developed.[2] Palladium-catalyzed cross-coupling reactions are one of the powerful methods 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 to synthesize 2-substituted benzo[*b*]furans (Scheme 1).[4] These reactions

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



commonly employ 2-iodo- and 2-bromophenols as substrates. On the other hand, there are a few reports[5,6] of the use of 2-chlorophenols, which are less expensive and more readily available than 2-iodo- and 2-bromophenols, as the starting material. However, in one such attempt, the desired product was obtained in less than 10% yield.[5]

We previously reported the one-pot synthesis of benzo[*b*]-furans from 2-chlorophenols and terminal alkynes using palladium catalysts bearing a hydroxyterphenylphosphine (HTP) ligand[7] with cyclohexyl groups on the phosphorus atom (Cy-HTP) (Figure 1a).[8] Cy-HTP works as a bifunctional

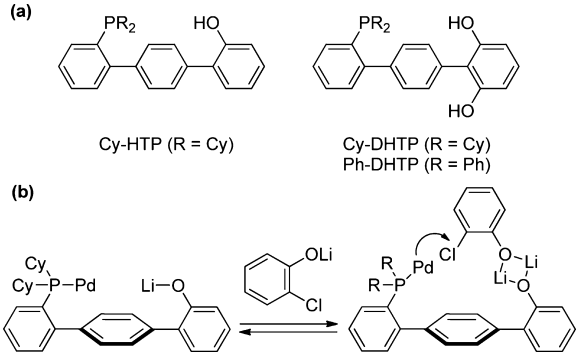


Figure 1. (a) Hydroxyterphenylphosphines. (b) Formation of the proposed intermediate in the Pd–HTP-catalyzed benzo[*b*]furan synthesis.

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 acts 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 need to use a sealed tube for the reaction.

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We previously showed that dihydroxyterphenylphosphine (DHTP) ligands (Figure 1a) are more effective than HTP ligands for the *ortho*-selective palladium-catalyzed cross-coupling of dihaloarenes and Grignard reagents.[9] Introduction of the second hydroxy group into the 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 the benzo[*b*]furan synthesis. The expected high reactivity of DHTP can be explained by the conformational effect depicted in Figure 2. The assumed catalytic species

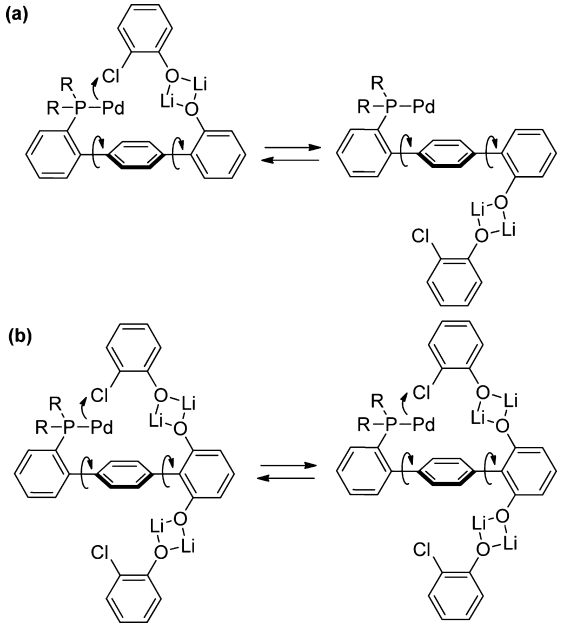
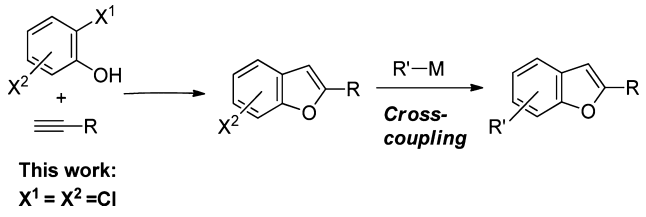


Figure 2. C−C bond rotation for the assumed intermediates from (a) HTP and (b) DHTP.

have flexibility in rotation about 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 sides of the terphenyl group (Figure 2a). On the other hand, in the case of DHTP, a lithium phenoxide moiety and the Pd atom are always located on the same side of the terphenyl structure (Figure 2b). This results in more effective cooperation between palladium and the lithium phenoxide moieties, affording higher reactivities in the Sonogashira coupling step.

To afford multisubstituted benzo[*b*]furans, efficient synthetic methods need to be developed.[10] Benzo[*b*]furans with halogen substituents, which can be easily converted to other functional groups by cross-coupling, are versatile intermediates for multisubstituted benzo[*b*]furan syntheses (Scheme 2).[4h,11]

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



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 group or an iodo group at the C2 position is crucial for 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 readily available.[8] This preliminary success was realized because Cy-HTP promotes *ortho*-selective Sonogashira coupling, presumably through formation of a 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 could also be synthesized via chlorobenzo[*b*]furans starting from dichlorophenols instead of using 2-bromo- or 2-iodophenols.

Because of the increasing demand for the development of rapid and environmentally friendly synthetic methods, one-pot syntheses have been considered to be an attractive choice.[14,15] Palladium-catalyzed reactions have been widely applied to one-pot syntheses 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 could 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 Suzuki−Miyaura cross-coupling of the corresponding chlorobenzo[*b*]furans 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 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 with our previous attempts using 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 initial Sonogashira cross-coupling step was completed within 45 min and the subsequent cyclization step reached completion within 1 h. In addition, no sealed tube was necessary in this case. Water was also found

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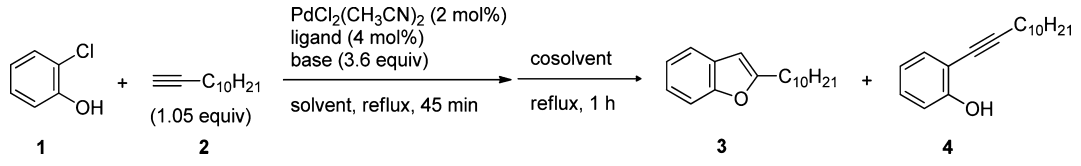
Table 1. Optimization of the Reaction Conditions for Benzo[*b*]furan Synthesis from 2-Chlorophenol and 1-Dodecyne



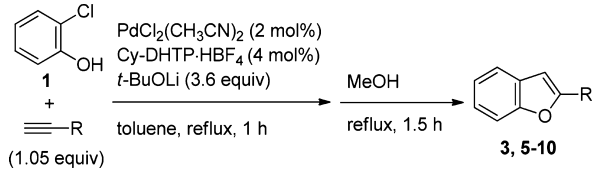
					yield (%)[a]	
entry	ligand	base	solvent	cosolvent	**3**	**4**
1	Cy-DHTP·HBF_4	*t*-BuOLi	toluene	MeOH	79	0
2[b]	Cy-DHTP·HBF_4	*t*-BuOLi	toluene	H_2O	71	trace
3[c]	Cy-DHTP·HBF_4	*t*-BuOLi	toluene	*t*-BuOH	38	28
4	Cy-DHTP·HBF_4	*t*-BuOLi	toluene	CF_3CH_2OH	34	44
5[d,e]	Cy-DHTP·HBF_4	*t*-BuOLi	toluene	–[f]	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 yields. [b]Refluxed for 2 h after H_2O addition. [c]Refluxed for 7 h after *t*-BuOH addition. [d]Alkyne (1.5 equiv) was used. [e]Refluxed for 1 h. [f]Without cosolvent, additional reflux was not conducted. [g]At 110 °C for 23 h. [h]At 110 °C for 1 h.

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 or CF_3CH_2OH as the cosolvent resulted in lower 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 MeOH/toluene mixture 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).

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 products **7**–**10** in moderate to high yields (entries 4–7). Substituents on the phenyl ring significantly affected the yield: a 4-fluoro group slowed the Sonogashira cross-coupling more than an electron-donating 4-methoxy group. Notably, chloro-substituted benzo[*b*]furan **8** was obtained in good yield (entry 5), even though the chloro group of 3-chloro-1-ethynylbenzene would generally be 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	$PhCH_2CH_2$ (**5**)	82
3	$ClCH_2CH_2CH_2$ (**6**)	58
4[c,d]	Ph (**7**)	52
5[d,e]	3-ClC_6H_4 (**8**)	64
6	4-FC_6H_4 (**9**)	33
7[c,d]	4-$MeOC_6H_4$ (**10**)	97

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

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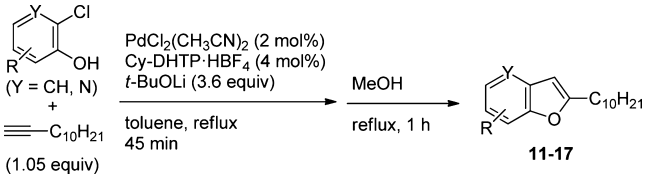
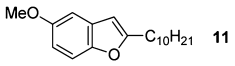
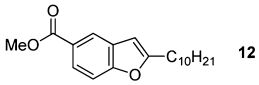
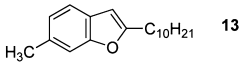
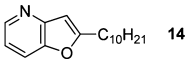
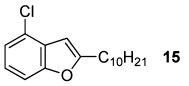
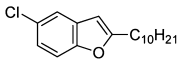
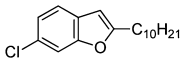
Table 3. Benzo[*b*]furan Synthesis Using Various 2-Chlorophenols and 1-Dodecyne



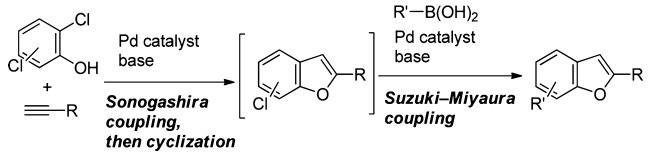
entry	product	yield (%)[a]
1[b]	 **11**	78
2	 **12**	37
3[b,c]	 **13**	82
4	 **14**	53
5	 **15**	77
6	 **16**	80
7	 **17**	37

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

afforded 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,*n*-dichlorophenols (entries 5−7). The use of 2,3- and 2,4-dichlorophenol resulted in high yields of the corresponding chlorobenzo[*b*]furans **15** and **16** (entries 5 and 6). However, when 2,5-dichlorophenol was used, product **17** was obtained in only moderate yield along with byproducts such as overreacted 6-(1-dodecynyl)-2-decylbenzo[*b*]furan (entry 7).

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 Suzuki−Miyaura cross-coupling between chlorobenzo[*b*]-furans and boronic acids (Scheme 3).[11b,19]. In this one-pot procedure, 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 a second ligand and an 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

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



cosolvent, and K_3PO_4 as the additional base resulted in high yields of the desired 2,5-disubstituted benzo[*b*]furan **18** along with trace amounts of 5-chlorobenzo[*b*]furan **16** (Table 4, entry 1). We found that the presence of XPhos did not affect the initial Sonogashira cross-coupling step and therefore could be present in the initial reaction mixture along with Cy-DHTP·HBF_4, thereby simplifying the process. The boronic acid and additional base could be added only after chlorobenzo[*b*]furan formation. When they were added with the cosolvent, the Suzuki−Miyaura cross-coupling reaction did not proceed smoothly, and large amounts of biaryls were obtained as a byproducts resulting from homocoupling of the 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 equiv 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 was important in promoting the one-pot sequential reaction. The use of 8 mol % 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 in entry 5, indicating that the higher amount of Cy-DHTP had an adverse effect on the reaction. On the other hand, the conditions in entry 6 slowed the Suzuki−Miyaura cross-coupling reaction in comparison with 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 product **18** (entry 8).

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 $PdCl_2(MeCN)_2$ 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 yield (entry 1). When only XPhos was used, the reaction also proceeded smoothly (entry 2). On the other hand, the 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 yield (data not shown). These results support our finding that the second ligand XPhos is necessary to promote the Suzuki−Miyaura cross-coupling reaction as shown in Table 4.

On the basis of these results, we propose the reaction mechanism shown in Scheme 4 for the one-pot sequential synthesis of disubstituted benzo[*b*]furans from dichlorophenols, terminal alkynes, and boronic acids. During the Sonogashira cross-coupling of the dichlorophenol and the terminal alkyne, Pd−Cy-DHTP works as the active species. It

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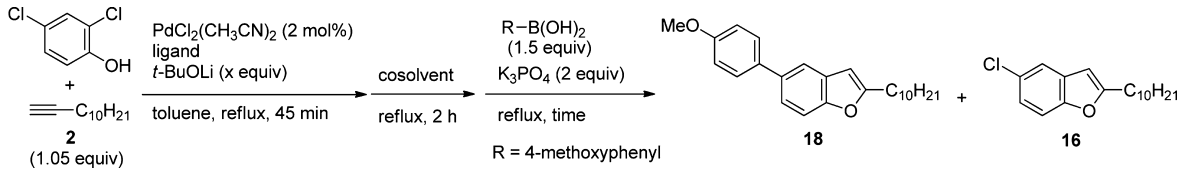
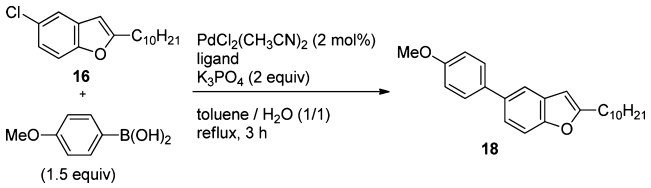
Table 4. Optimization of the Reaction Conditions for the One-Pot Synthesis of 2,5-Disubstituted Benzo[*b*]furans



						yield (%)[a]	
entry	ligand (mol %)	*t*-BuOLi (equiv)	cosolvent	K_3PO_4	time (h)	**18**	**16**
1	Cy-DHTP·HBF_4 (4)/XPhos (4)	2.4	H_2O	+	6	73	trace
2[b]	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 yields. [b]MeOH reflux for 1 h. [c]Not detected.

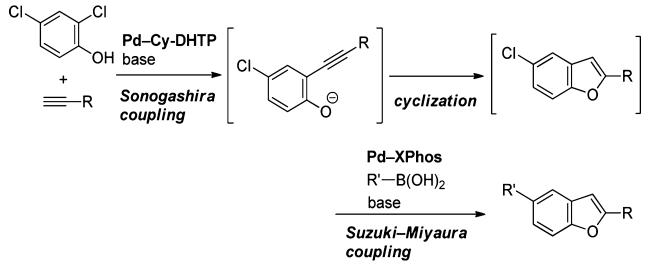
Table 5. Suzuki−Miyaura Cross-Coupling of 5-Chlorobenzo[*b*]furan and 4-Methoxyphenylboronic Acid



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 yields.

Scheme 4. Proposed Reaction Mechanism



seems that Pd−XPhos neither catalyzes nor affects this reaction. Following cyclization catalyzed by the base, the Suzuki−Miyaura cross-coupling of the chlorobenzo[*b*]furan with the boronic acid seems to be accelerated mainly by the Pd−XPhos catalyst, although we cannot rule out 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 carry out benzo[*b*]furan formation and Suzuki−Miyaura cross-coupling sequentially in one pot. Interestingly, each catalyst shows specificity toward one of the two reactions even though the two ligands have the same 2-dicyclohexylphosphinobiphenyl substructure.[20]

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 C5 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 C5 position to yield product **26** (entry 9). The use of an alkenylboronic acid resulted in moderate yields of product **27** (entry 10).

Next, disubstituted benzo[*b*]furans bearing substituents at different positions were prepared from various dichlorophenols 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 C4 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 2,6-disubstituted benzo[*b*]furan **31** in only a moderate yield (entry 4). This could be due to the low yield 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 a low yield 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).

Finally, we used this sequential one-pot method to synthesize **34**, which is a precursor of a biologically active compound (Scheme 5). Tetrahydroxylated 2,5-diarylbenzo[*b*]furan **35** and related compounds have been recently reported to inhibit amyloid β (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 were able to obtain compound **35** from commercially available substrates using a one-pot reaction. This shows the effectiveness and

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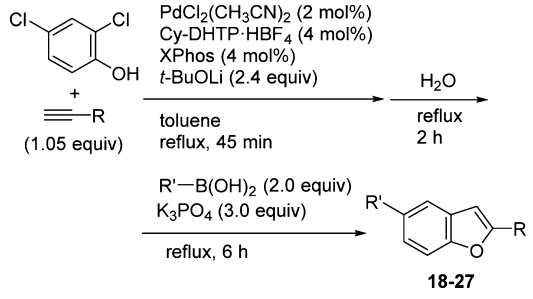
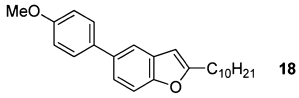
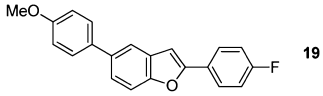
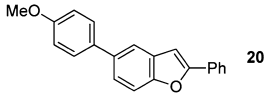
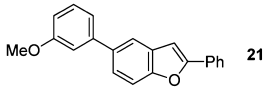
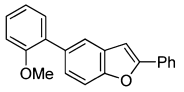
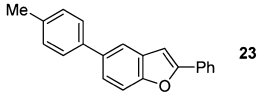
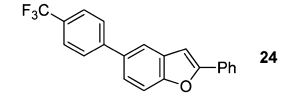
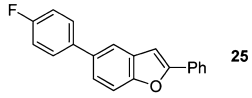
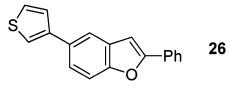
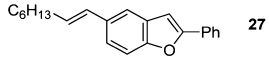
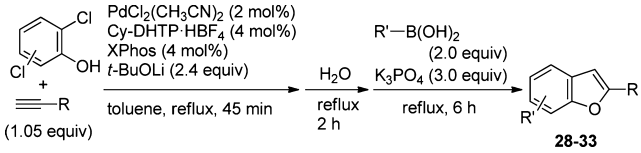
Table 6. Synthesis of 2,5-Disubstituted Benzo[*b*]furans Using Various Alkynes and Boronic Acids

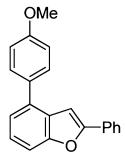
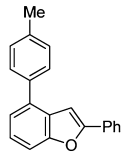
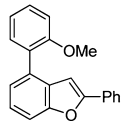
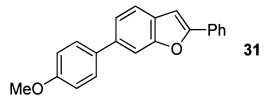
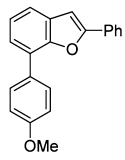
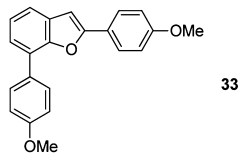


entry	product	yield (%)[a]
1[b]	 **18**	73
2	 **19**	82
3	 **20**	78
4	 **21**	81
5	 **22**	84
6	 **23**	94
7[c]	 **24**	84
8[d]	 **25**	67
9	 **26**	76
10	 **27**	60

[a]Isolated yields. [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.

Table 7. Synthesis of Disubstituted Benzo[*b*]furans 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 yields.

utility of our method in constructing more complex, multi-substituted structures.

Mechanistic Study Using ESI-MS. As discussed above, the mechanism of the acceleration of the Sonogashira coupling step by Cy-DHTP can be explained as follows: (1) the two hydroxy groups of Cy-DHTP and the 2-chlorophenol hydroxy group are deprotonated to generate lithium phenoxides under the reaction conditions, and (2) these lithium phenoxides are in equilibrium with heteroaggregates **A** and **B** (Scheme 6) in which the 2-chloro group is easily accessed by the Pd atom located nearby. This heteroaggregate formation by the lithium phenoxides is responsible for the observed reaction rate acceleration and *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.

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

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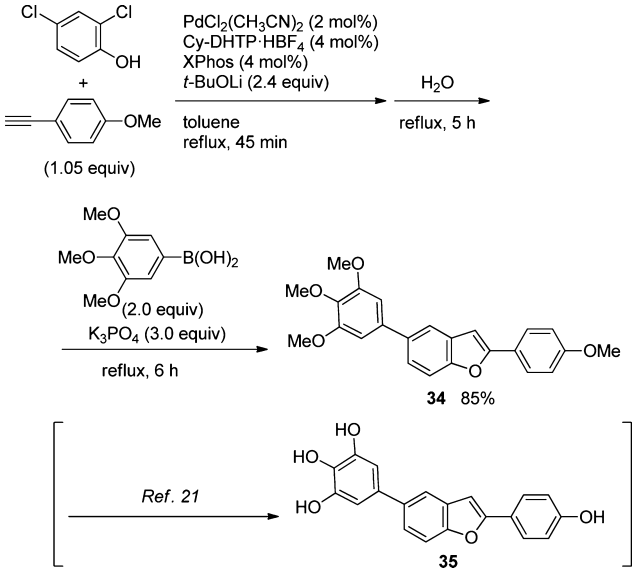
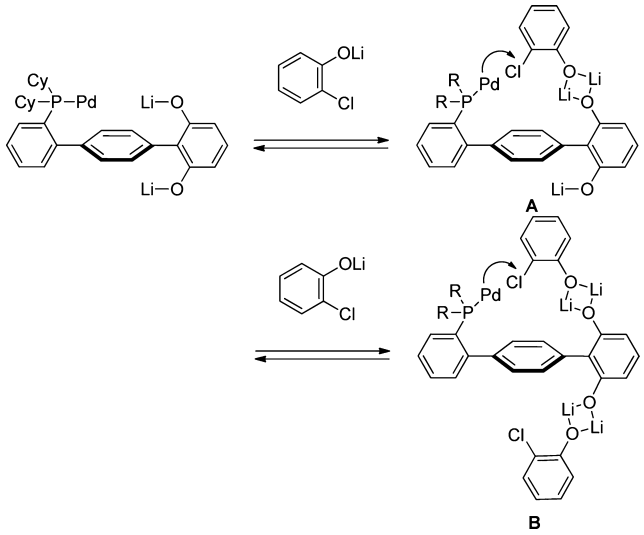
Scheme 5. Synthesis of the Precursor of a Bioactive Compound



Scheme 6. Formation of the Proposed Intermediate



(Figure 3b). Signals corresponding to the 1:2 and 1:3 complexes between lithium phenoxides of Cy-DHTP and **1** were also observed at *m*/*z* 725 and 861, respectively (Figure S1 in the Supporting Information). In addition, signals whose isotopic distributions correspond to the aggregates of lithium 2-chlorophenoxide were also observed at *m*/*z* 665 and 799 (Figure S2 in the Supporting Information).[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 in the Supporting Information). 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.

■ CONCLUSION

In summary, a dihydroxyterphenylphosphine bearing cyclohexyl groups on the phosphorus 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, the use of XPhos as a second ligand along with an 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*]furans from dichlorophenols and terminal alkynes and the subsequent Suzuki–Miyaura cross-coupling with boronic acids. The two catalysts were found to work independently, with Pd–Cy-DHTP catalyzing the Sonogashira cross-coupling and Pd–XPhos accelerating the Suzuki–Miyaura cross-coupling. 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 multisubstituted 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

General. All of the reactions were performed under an argon atmosphere. For ^{1}H NMR spectroscopy, tetramethylsilane (TMS) (δ = 0 ppm) in $CDCl_3$ served as an internal standard. For ^{13}C NMR spectroscopy, $CDCl_3$ (δ = 77.0 ppm) served as an internal standard. Melting points were uncorrected. All of 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 and then cooled. 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-decylbenzo[*b*]-furan (**3**) (102 mg, 79%) as a yellow oil.

*2-Decylbenzo[b]furan (**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

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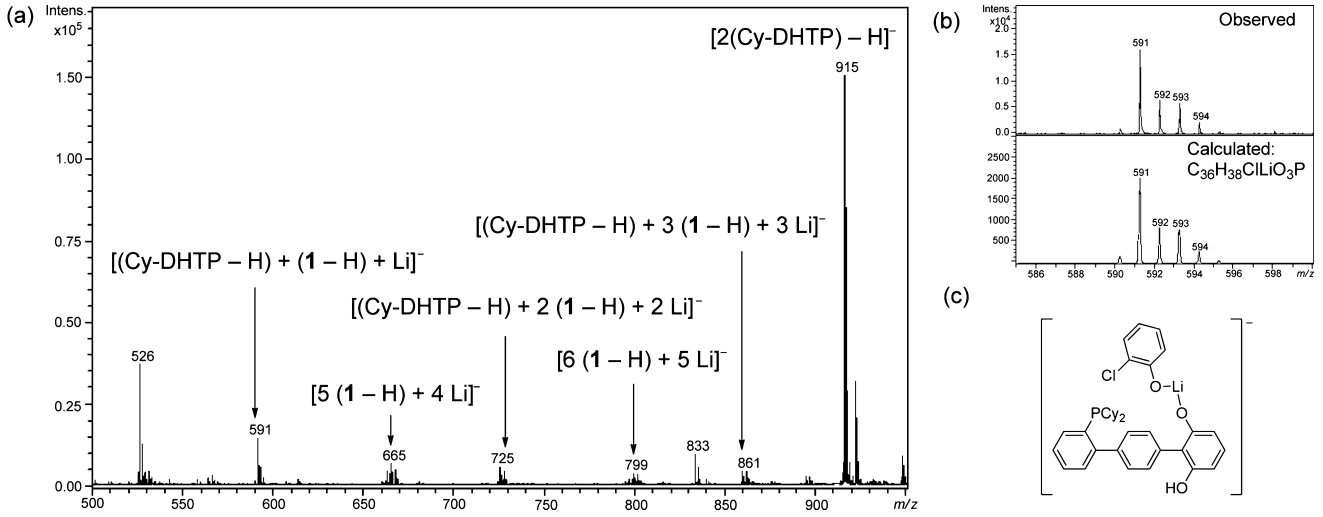

Figure 3. Complex formation between 2-chlorophenol and Cy-DHTP (0.4 equiv) in the presence of *t*-BuOLi (1 equiv) as studied by ESI-MS in the negative-ion mode. (a) ESI-mass spectrum obtained after stirring for 30 min. (b) Detailed view of (i) the observed isotopic distribution compared to (ii) the theoretical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

$C_{18}H_{27}O$ ([M + H]$^+$), 259.2056; found, 259.2062. IR (ATR) cm^{-1}: 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), 1.67−1.58 (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) cm^{-1}: 2922, 2853, 1576, 1485, 1462, 1286, 1234, 1177, 750.

*2-(2-Phenylethyl)benzo[b]furan (**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) cm^{-1}: 3109, 3061, 2934, 2857, 1601, 1495, 1452, 1427, 1254, 1167, 1101, 1001, 951, 808, 739, 700.

*2-(3-Chloropropyl)benzo[b]furan (**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) cm^{-1}: 2846, 2326, 1585, 1454, 1250, 748.

*2-Phenylbenzo[b]furan (**7**).*[27] Prepared from 2-chlorophenol and ethynylbenzene. 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) cm^{-1}: 3105, 3051, 3034, 2955, 2930, 2855, 2648, 2610, 2494, 1441, 1258, 1020, 918, 806, 739, 689.

*2-(3-Chlorophenyl)benzo[b]furan (**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) cm^{-1}: 3109, 3067, 3040, 2957, 2930, 2870, 1603, 1558, 1452, 1408, 1258, 1038, 739, 662.

*2-(4-Fluorophenyl)benzo[b]furan (**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) cm^{-1}: 3046, 1599, 1499, 1450, 1223, 1206, 1157, 1098, 839, 800.

*2-(4-Methoxyphenyl)benzo[b]furan (**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) cm^{-1}: 3121, 3007, 2961, 2837, 1503, 1244, 1169, 741.

*2-Decyl-5-methoxybenzo[b]furan (**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, m), 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) cm^{-1}: 2914, 2847, 1614, 1464, 1452, 1207, 1180, 1153, 1136, 1030, 949, 939, 845, 806, 766, 721.

*Methyl 2-Decylbenzo[b]furan-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,

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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) cm^{-1}: 2951, 2916, 2900, 2849, 1722, 1472, 1437, 1304, 1269, 1240, 1157, 1144, 1115, 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-methylbenzo[b]furan (**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, m), 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) cm^{-1}: 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) cm^{-1}: 2922, 2853, 1734, 1595, 1456, 1412, 1261, 935, 785.

*4-Chloro-2-decylbenzo[b]furan (**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) cm^{-1}: 2922, 2853, 1584, 1466, 1425, 1258, 1136, 934, 768.

*5-Chloro-2-decyl[b]furan (**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, m), 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) cm^{-1}: 2922, 2853, 1597, 1447, 1258, 1061, 793.

*6-Chloro-2-decylbenzo[b]furan (**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) cm^{-1}: 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 and then cooled. Water (1 mL) was added, and the reaction mixture was stirred at reflux for 2 h. After the solution was cooled, 4-methoxyphenylboronic acid (114 mg, 0.75 mmol) and K_3PO_4 (213 mg, 1.0 mmol) were added, and the reaction mixture was stirred at reflux for 6 h. The resulting suspension was quenched with 1 M 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, 95:5 hexanes/ethyl acetate) to give 2-decyl-5-(4-methoxyphenyl)-1-benzo[b]furan (**18**) (114 mg, 73%) as a white solid.

*2-Decyl-5-(4-methoxyphenyl)benzo[b]furan (**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, m), 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) cm^{-1}: 2955, 2914, 2827, 1609, 1520, 1464, 1273, 1236, 1182, 1157, 1038, 947, 806.

*2-(4-Fluorophenyl)-5-(4-methoxyphenyl)benzo[b]furan (**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, $CDCl_3$): δ 7.87−7.874 (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 °C): 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) cm^{-1}: 3576, 3014, 2956, 2839, 1502, 1463, 1236, 1012, 800.

*5-(4-Methoxyphenyl)-2-phenylbenzo[b]furan (**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) cm^{-1}: 3062, 2960, 1517, 1463, 1232, 1035, 802, 759.

*5-(3-Methoxyphenyl)-2-phenylbenzo[b]furan (**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) cm^{-1}: 3055, 2997, 2913, 2833, 1597, 1464, 1319, 1252, 1215, 1045, 912, 793, 762, 689, 662.

*5-(2-Methoxyphenyl)-2-phenylbenzo[b]furan (**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

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$C_{21}H_{17}O_2$ ([M + H]$^+$), 301.1223; found, 301.1254. IR (ATR) cm^{-1}: 2957, 1599, 1520, 1506, 1464, 1439, 1277, 1236, 1184, 1155, 1034, 1013, 837, 800.

*5-(4-Methylphenyl)-2-phenylbenzo[b]furan (**23**).* Prepared from 2,4-dichlorophenol, ethynylbenzene, and 4-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) cm^{-1}: 2912, 1463, 800, 758.

*2-Phenyl-5-(4-trifluoromethylphenyl)benzo[b]furan (**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) cm^{-1}: 3088, 1614, 1468, 1333, 1279, 1105, 1070, 804, 764, 689, 590.

*5-(4-Fluorophenyl)-2-phenylbenzo[b]furan (**25**).* Prepared from 2,4-dichlorophenol, ethynylbenzene, and 4-fluorophenylboronic acid. Purification 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) cm^{-1}: 3115, 1516, 1464, 1445, 1227, 1211, 802, 760, 745, 687.

*2-Phenyl-5-(thiophen-3-yl)benzo[b]furan (**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. ^{1}H 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) cm^{-1}: 3099, 1463, 1444, 775, 758, 682.

*(E)-5-(Oct-1-en-1-yl)-2-phenylbenzo[b]furan (**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. ^{1}H 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 Hz). ^{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) cm^{-1}: 3034, 2955, 2920, 2851, 1464, 1447, 1267, 1020, 962, 916, 804, 758, 689.

*4-(4-Methoxyphenyl)-2-phenylbenzo[b]furan (**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) cm^{-1}: 3055, 3030, 3003, 2953, 2934, 2905, 2833, 1609, 1518, 1476, 1294, 1246, 1179, 1026, 839, 779, 756, 685.

*4-(4-Methylphenyl)-2-phenylbenzo[b]furan (**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) cm^{-1}: 3028, 2913, 1609, 1476, 1425, 1252, 1163, 1042, 1022, 922, 826, 775, 754, 685, 544.

*4-(2-Methoxyphenyl)-2-phenylbenzo[b]furan (**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) cm^{-1}: 3059, 2931, 2832, 1597, 1474, 1414, 1238, 1020, 906, 756, 729, 691.

*6-(4-Methoxyphenyl)-2-phenylbenzo[b]furan (**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) cm^{-1}: 3040, 3017, 2955, 2922, 2839, 1605, 1522, 1470, 1252, 1186, 1167, 1033, 824, 814, 758, 691.

*7-(4-Methoxyphenyl)-2-phenylbenzo[b]furan (**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, $CDCl_3$): 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) cm^{-1}: 3061, 3009, 2955, 2835, 1614, 1516, 1476, 1429, 1400, 1279, 1254, 1217, 1182, 1020, 783, 745, 691.

*2-(4-Methoxyphenyl)-7-(4-methoxyphenyl)benzo[b]furan (**33**).* Prepared from 2,6-dichlorophenol, 4-ethynylanisole, and 4-methoxyphenylboronic acid. Purification 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) cm^{-1}: 3057, 2955, 2907, 2835, 1612, 1504, 1462, 1246, 1175, 1111, 1026, 907, 831, 802, 731, 592.

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*2-(4-Methoxyphenyl)-5-(3,4,5-trimethoxyphenyl)benzo[b]furan (**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) cm^{-1}: 2932, 2832, 1582, 1508, 1462, 1412, 1246, 1173, 1123, 1022, 999, 810.

Typical Experimental Procedure for the Detection of Heteroaggregate Formation by Lithium Phenoxides of Cy-DHTP and 1 by ESI-MS. **1** (0.03 mmol, 3.8 mg) and 40 mol % 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. Next, a 10 μL aliquot was taken, diluted with acetonitrile (1 mL), and filtered, and the resulting solution was injected into the ESI-MS instrument.

■ ASSOCIATED CONTENT

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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Notes

The authors declare no competing financial interest.

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