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Sequential One-Pot Synthesis of 3-Arylbenzofurans from *N*-Tosylhydrazones and Bromophenol Derivatives

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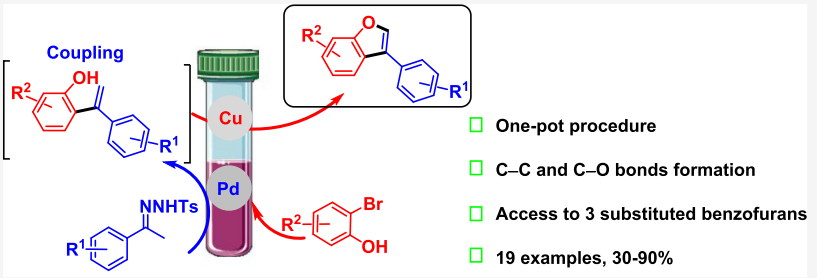

ABSTRACT: A divergent and efficient one-pot sequence allowing direct access to 3-arylbenzofuran derivatives has been developed. The process, involving *N*-tosylhydrazones and bromophenols, proceeds via a palladium-catalyzed Barluenga–Valdés cross-coupling, followed by an aerobic, copper-catalyzed, radical cyclization to form $Csp^2–Csp^2$ and $O–Csp^2$ bonds. 3-Arylated benzofurans bearing various substituents were obtained with good to excellent yields (up to 90%). Mechanistic investigation strongly supports a radical process for the cyclization step.

INTRODUCTION

The benzofuran skeleton constitutes an essential class of compounds and is widely present in many pharmaceuticals,[1] biologically active compounds,[2] and natural products.[3] For instance, the related drugs amiodarone and dronedarone showing antiarrhythmic effects, lifitegrast, a recently FDA-approved drug for the treatment of keratoconjunctivitis sicca[4] (dry eye syndrome), methoxsalen, a naturally occurring furocoumarin compound found in several species of plants including *Psoralea corylifolia*, showing activity in case of psoriasis and vitiligo, vilazodone, a novel active compound combining high-affinity and selectivity for the 5-hydroxytryptamine (5-HT) transporter and 5-HT(1A) receptors[5] and indicated for the treatment of the major depressive disorder, all display a benzofuran core (Figure 1).

Over recent years, many effective strategies, including heteroannulation[6] and transition-metal-catalyzed reactions,[7] have been described for the synthesis of 2-arylbenzofurans or polysubstituted benzofurans. However, and contrary to the 2-arylated benzofuran derivatives, only a few methods for the synthesis of 3-arylbenzofurans **3** (Scheme 1) are known in the literature. Some of these synthetic strategies are shown in Scheme 1.

A typical method involves the Suzuki cross-coupling starting from 3-brominated benzofurans[8] or the Larock coupling between 2-iodophenols and internal alkynes.[9] Zeolite-catalyzed direct cyclization of α-aryloxyketones is also a notable strategy; however, bulky derivatives tend to rearrange into the 2-substituted isomer.[10] Copper(II) acetate and 8-hydroxyquinoline are efficient to promote the formation of 3-phenylbenzofurans from 2-hydroxyacetophenones and dimethylacetamide (DMA).[11] 2-Hydroxy-arylstyrenes were also used to obtain the corresponding benzofurans in moderate to good yields. Maiti et al. developed a Pd-catalyzed intermolecular annulation of cinnamic acids and phenols for the selective synthesis of 3-substituted benzofurans (Scheme 1).[12] Anbarasan et al. reported a cobalt(III)-catalyzed intramolecular cross-dehydrogenative C–H/O–H coupling of *ortho*-alkenylphenols using O_2 as an oxidant.[13] Finally, the C3-selective direct C–H activation of benzofurans has been rarely achieved because, in addition to obtaining mixtures of C2 and C3 isomers, low to modest yields were observed.[14]

Consequently, there is considerable interest from the synthetic organic point of view to obtain the 3-arylbenzofuran motif by efficient methodologies. In the past decade, *N*-tosylhydrazones (NTH) have been well recognized as powerful cross-coupling partners for several transformations,[15] especially

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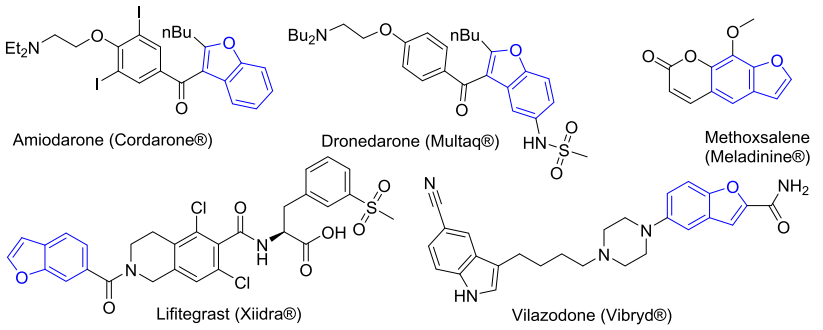


Figure 1. Approved drugs containing the benzofuran moiety.

Scheme 1. Synthesis of 3-Arylbenzofuran Derivatives

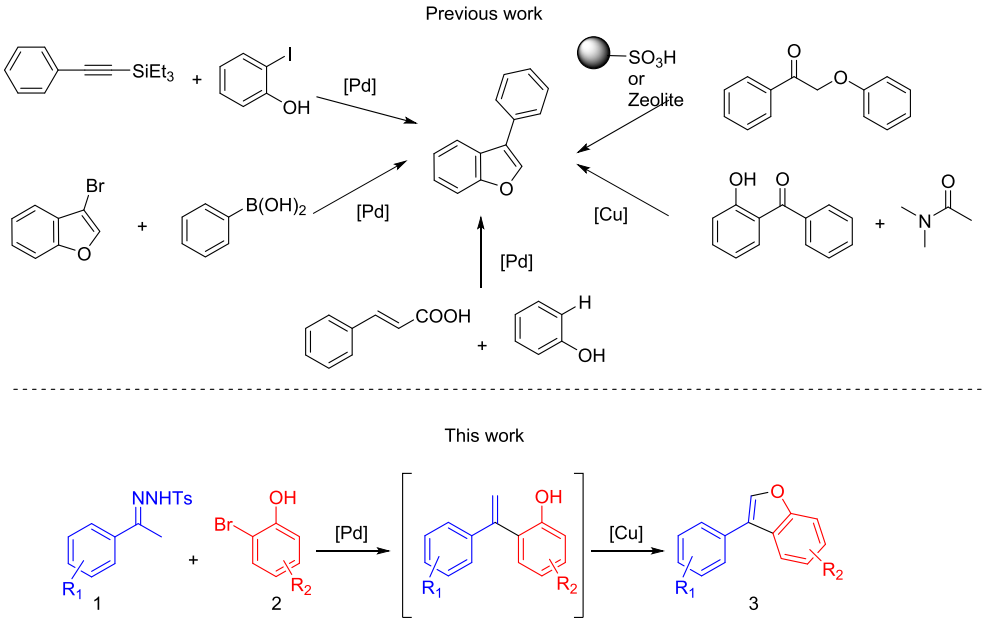
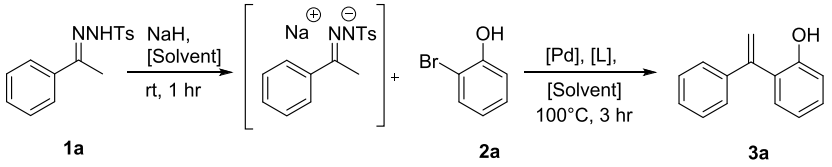


Table 1. Optimization of the Reaction Conditions for Pd-Catalyzed Coupling of NTH and Bromophenol[a]



entry	[Pd]	[L]	solvent	yield (%)
1	$Pd(OAc)_2$	Xphos	dioxane	55
2	$Pd(OAc)_2$	Sphos	dioxane	67
3	$Pd(OAc)_2$	Sphos	DMF	40
4	$Pd(OAc)_2$	Sphos	toluene	30
5	$Pd(OAc)_2$	Sphos	DMA	0
6	$Pd_2dba_3{\cdot}CHCl_3$	Sphos	dioxane	95
7	$Pd_2dba_3{\cdot}CHCl_3$	Sphos	toluene	50
8	CuOAc	8-HQ	dioxane	nd[b]

[a]Reaction conditions: NTH **1a** (1.5 mmol), 2-bromophenol **2a** (1 mmol), [Pd] source (5 mol %), ligand (10 mol %), base (1.6 mmol), solvent (5.0 mL), sealed tube, 100 °C, and 3 h. [b]nd: not detected.

their application as metal carbene precursors in the efficient construction of carbon−carbon and carbon−heteroatom bonds.[16] It is still highly desirable to explore NTH as substrates to enable the concise preparation of complex molecules, leading to crucial molecular diversity. Herein, we present a one-pot approach to access a series of 3-arylbenzofurans from NTHs and bromophenol derivatives.

RESULTS AND DISCUSSION

Before optimizing the one-pot sequence of this transformation, initial studies were devoted to finding the best conditions for

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each step: the formation of the C−C and then the C−O bond. Thus, we began our investigations by studying the cross-coupling between NTH derivative **1a** and bromophenol **2a**. The challenge of this coupling was to find optimal conditions that tolerate the presence of free phenol, since NTH could react with alcohols or phenols, leading to the corresponding ethers.[17] As a consequence, to avoid the formation of an ether bond, we first prepared the NTH salt and then realized the coupling with the bromophenol partner (Table 1). Coupling conditions using $Pd(OAc)_2$ as a palladium source and XPhos as a ligand in dioxane led to the desired product **3a** in a moderate 55% yield. The reaction with a catalyst based on the Sphos ligand exhibited better efficiency, the 1,1-diarylethylene product being obtained in a 67% yield (entry 2). Changing dioxane for other solvents such as dimethylformamide (DMF), toluene, or DMA led to a dramatic decrease of the yield (entries 3−5). Next, we turned our attention to the palladium source, and we observed a significant improvement of the yield to 95% using $Pd_2dba_3{\cdot}CHCl_3$ instead of $Pd(OAc)_2$ in dioxane (entry 6). In toluene, the product was isolated in a 50% yield using the same catalytic system (entry 7). Performing the reaction in the presence of a copper catalyst did not afford the desired compound **3a**.

Next, we turned our attention to the cyclization reaction to form the benzofuran derivatives. For this purpose, we have first treated the 2-hydroxyarylstyrene **3a** under the conditions developed by Dominguez et al.:[11] $Cu(OAc)_2$ (50 mol %), O_2, and 8-hydroxyquinoline (8-HQ) at 140 °C for 24 h (Table 2, entry 1).

Under these standard conditions, the desired product **4a** was obtained in a moderate 50% yield, which is incompatible with the development of a one-pot reaction. Performing the reaction in dry DMA reduced the yield to 33% (entry 2). On the other hand, adding a controlled amount of 40 equiv of H_2O to the reaction medium promoted a significant increase of the yield to 77% (entry 3). Screening of different solvents revealed that the best yield was obtained in toluene or dioxane in the presence of 40 equiv of H_2O (entries 4 and 5).

Then, a variety of reaction conditions were screened to show the importance of each parameter of this copper catalyst system (entries 6−10). Surprisingly, the results of the control experiments showed that the formation of the benzofuran ring could occur in the absence of ligand and base (entries 6 and 7). However, no formation of the desired compound **4a** was observed when the reaction was performed without a copper source (entry 8). It is important to note that dioxygen also plays an important role in this process, with a dramatic decrease in the yield when the reaction was carried out under N_2 (entry 9). Finally, we rechecked the role of water in this transformation, and we observed a significant decrease in the yield when the reaction was carried out in dry toluene (entry 10).

Based on these interesting results (Tables 1 and 2), we attempted the one-pot sequential reaction to form the 3-arylbenzofuran **4a** starting from NTH **1a** and bromophenol **2a** (Table 3). Contrary to our expectations, performing the reaction sequence under the best-obtained conditions: dioxane for the first step (solvent 1), then H_2O 40 equiv (solvent 2) for the second step, afforded a low yield unfortunately (entry 1). As the cyclization step worked better in toluene, we tried to add toluene as a cosolvent: dioxane/toluene 1:2 V/V (entry 2), but again a low yield of **4a** was obtained. Inversion of the ratio between dioxane and toluene (dioxane/toluene 2:1) provided a slight increase in the yield (entry 3). This observation led us to conduct the first step of the coupling (C−C bond formation) only in anhydrous dioxane, and we added toluene for the second step with a ratio of dioxane/toluene of 2:1 (entries 4−5).

Without the addition of water for the second step, the reaction was not totally completed (entry 4), whereas the addition of 40 equiv of H_2O resulted in a 90% isolated yield (entry 5).

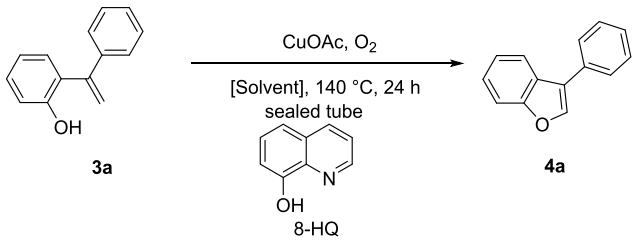
With the optimized conditions in hand, the generality of this sequential one-pot reaction was examined using a series of NTHs **1** and different 2-hydroxy-bromoaryls **2** (Scheme 2).

Gratifyingly, the reaction works efficiently, affording the coupling products in good to high yields (46−90%). The Pd/Cu system catalyzes the coupling of 2-hydroxybromophenol **2a** using neutral (**4a**, **4b**), electron-rich (**4c**−**4e**), and -deficient (**4f**−**4g**) NTHs. In addition, this transformation tolerates the coupling of heterocyclic NTHs, affording the corresponding products in good yields (compounds **4h**−**i**).

Encouraged by these results, we further examined the substrate scope with respect to the bromophenol. Thus, we explored modifications on the electrophilic partner **2**. It should be noted that the reaction proceeded successfully when using bromophenols bearing electron-donating groups (compounds **4j**−**o**). Lastly, we were interested in the application of this method to the synthesis of benzofuran **4a** in a millimole quantity. Performing the reaction in a large sealed tube under the standard conditions afforded compound **4a** in a 62% yield (Scheme 2).

In addition, bromophenols with different R^2 electron-withdrawing substituents underwent the reaction to afford the desired compounds (**4p**−**r**) in good yields (52−72%). Our

Table 2. Optimization of the Cyclization Step[a]



entry	ligand	base	solvent	additive	yield (%)[b]
1	8-HQ[c]	K_2CO_3	DMA		50
2	8-HQ	K_2CO_3	anhyd DMA		33
3	8-HQ	K_2CO_3	DMA	H_2O 40 equiv[d]	77
4	8-HQ	K_2CO_3	dioxane	H_2O 40 equiv	70
5	8-HQ	K_2CO_3	toluene	H_2O 40 equiv	88[e]
6		K_2CO_3	toluene	H_2O 40 equiv	82
7			toluene	H_2O 40 equiv	80
8			toluene	H_2O 40 equiv	0[f]
9			toluene	H_2O 40 equiv	12[g]
10			toluene		35

[a]All of the reactions were carried out in a sealed tube using **3a** (1 mmol), CuOAc (50 mol %), 8-HQ (50 mol %), K_2CO_3 (1 mmol), and solvent (5 mL). [b]Isolated yield. [c]8-Hydroxyquinoline. [d]Reaction in the presence of 20 and 60 equiv of H_2O gave 66 and 76% yields, respectively. [e]A low yield (25%) was obtained when the reaction was performed in toluene without the addition of water. [f]The reaction was carried out without CuOAc. [g]The reaction was degassed with N_2 (without O_2).

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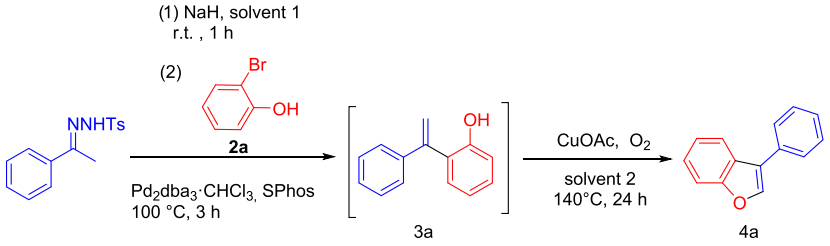
Table 3. Optimization of the Sequential One-Pot Reaction: Formation of Csp^2-Csp^2 and then $O-Csp^2$ Bonds[a]



entry	solvent 1	solvent 2	yield[b]
1	dioxane	H_2O 40 equiv	46%[c]
2	dioxane/toluene (1:2)	H_2O 40 equiv	25%
3	dioxane/toluene (2:1)	H_2O 40 equiv	35%
4	anhyd. dioxane	dioxane/toluene = 2:1	42%
5	anhyd. dioxane	dioxane/toluene = 2:1 + H_2O (40 equiv)	90%

[a]Reaction conditions: In a sealed tube, NTH **1a** (0.6 mmol), NaH (0.64 mmol), and solvent 1 (2.5 mL) were reacted at RT for 1 h; then, 2-bromophenol **2a** (0.4 mmol), $Pd_2dba_3·CHCl_3$ (5 mol %), and Sphos (10 mol%) were added and heated at 100 °C for 3 h. After completion of the first step, solvent 2, CuOAc (50 mol %), was added under O_2 at 140 °C for 24 h. [b]Isolated yield. [c]In the absence of copper, **4a** was not detected.

standard conditions were used to realize the coupling between NTH derived from 2-phenylacetophenone (Scheme 3). The first coupling led to a mixture of the *E*/*Z* isomer with a 60/40 ratio. Only the *E*-isomer undergoes cyclization, and the diphenylbenzofuran derivative **4s** was obtained in a 30% yield (Scheme 3).

Mechanism. While the first step of this one-pot sequence has a well-established mechanism (Scheme 4),[14,15] the nature of the second step was not obvious. As previously demonstrated in Table 1, there is no need for a ligand or a base, but O_2 and H_2O are required to reach a good yield, and of course, CuOAc (50 mol %) is indispensable in all cases.

The formation of a copper vinylidene under such conditions is unlikely. The reaction did not work with a methyl group installed at the oxygen atom or at the terminal alkene carbon of **3a**. Besides, we could not trap the carbene with $TMSN_3$, which is a known vinylidene scavenger (Scheme 4, eq 1).[18] Interestingly, in the presence of $TMSN_3$, the methyl-substituted substrate **3s** transformed into ketone **6s** (eq 2). Such aerobic oxidation of terminal olefins using $TMSN_3$ as a reagent and TEMPO as a catalyst has been reported.[19] In this case, the mechanism involves the formation of free radicals and their reaction with O_2 to give peroxide radical intermediates. This led us to consider that perhaps TEMPO could also catalyze the cyclization of **3a** into **4a**. In the absence of $TMSN_3$, and under similar reaction conditions as those disclosed with copper, **4a** was indeed obtained in a 63% yield (eq 3).

The catalytic cycle postulated for this coupling (Scheme 5, the top part) starts with the oxidative addition of the bromophenol **2a** to the Pd(0) to give the aryl−Pd complex **I**. Then, the reaction of the diazo compound **II** (generated by decomposition of NTH **1a** in the presence of the base) with **I** led to the formation of Pd−carbene complex **III**. The latter complex **III** evolves through the migratory insertion of the carbene and produces the alkyl−Pd complex **IV**. At the end of this first cycle, *β*-hydride elimination provides the olefin **3a**.

The results obtained in Scheme 4 strongly support a radical mechanism, summarized in Scheme 5 (lower part).

In the presence of O_2 and H_2O, the copper(I) salt generates hydroxyl radicals and hydroxides,[20] while being oxidized into Cu(II). Compound **3a** reacts with a hydroxyl radical to give phenoxyl radical **A**, which undergoes 5-*endo*-trig cyclization to give radical **B**.[21] The latter is oxidized by Cu(II) into carbocation **C**, which is deprotonated by a hydroxide to furnish the final product **4a**.

We believe that our method can be used to obtain other functionalized 3-arylbenzofurans and will contribute to the discovery of new biologically active compounds.

In summary, we have developed a sequential palladium/copper synthesis of a library of 3-arylbenzofuran derivatives. This one-pot reaction associates a Barluenga−Valdés cross-coupling, followed by a radical cyclization, leading to the formation of Csp^2-Csp^2 and $O-Csp^2$ bonds. This method, based on simple starting materials, tolerates various functional groups. From the mechanistic point of view, this one-pot sequence associates a transition-metal-catalyzed reaction with an aerobic cyclization that is not disrupted by the presence of the cross-coupling catalytic mixture.

EXPERIMENTAL SECTION

General Methods. Melting points (mp) were uncorrected. Solvent peaks were used as reference values with $CDCl_3$ at 7.26 ppm for ^1H NMR and 77.16 ppm for ^{13}C NMR, with DMSO at 2.50 ppm for ^1H NMR and 39.52 ppm for ^{13}C NMR, with CD_3CN at 1.94 ppm for ^1H NMR, and 1.79, 118.26 ppm for ^{13}C NMR, with $(CD_3)_2CO$ at 2.05 ppm for ^1H NMR, and 29.84 and 206.26 ppm for ^{13}C NMR. Chemical shifts δ are given in ppm, and the following abbreviations are used: singlet (s), doublet (d), doublet of doublet (dd), triplet (t), quadruplet (q), and multiplet (m). High-resolution mass spectra were recorded on a Microtof-Q II. Reaction courses and product mixtures were routinely monitored by TLC on a silica gel, and compounds were visualized under a UVP Mineralight UVGL-58 lamp (254 nm) and with phosphomolybdic acid/Δ, or vanillin/Δ. Flash chromatography was performed using silica gel 60 (40−63 mm, 230−400 mesh) at medium pressure (200 mbar). Dioxane was distilled over CaH_2. Other solvents were used as received. *N*-Tosylhydrazones were prepared according to the literature procedure. $Pd_2(dba)_3·CHCl_3$ was prepared according to the literature procedure.[22] All products reported showed ^1H and ^{13}C NMR spectra in agreement with the assigned structures.

General Procedure for the Synthesis of Benzofuran from the One-Pot Reaction (Method A). To a solution in a sealed tube of *N*-tosylhydrazone (0.6 mmol) in distilled dioxane (5.0 mL/mmol) was added NaH (0.96 mmol). This resulting suspension was stirred at rt for one hour; 2-bromophenol (0.4 mmol), $Pd_2dba_3CHCl_3$ (5 mol %), and Sphos (10 mol %) were added. The mixture was then heated at 100 °C for 3 h in an oil bath. The reaction mixture was allowed to

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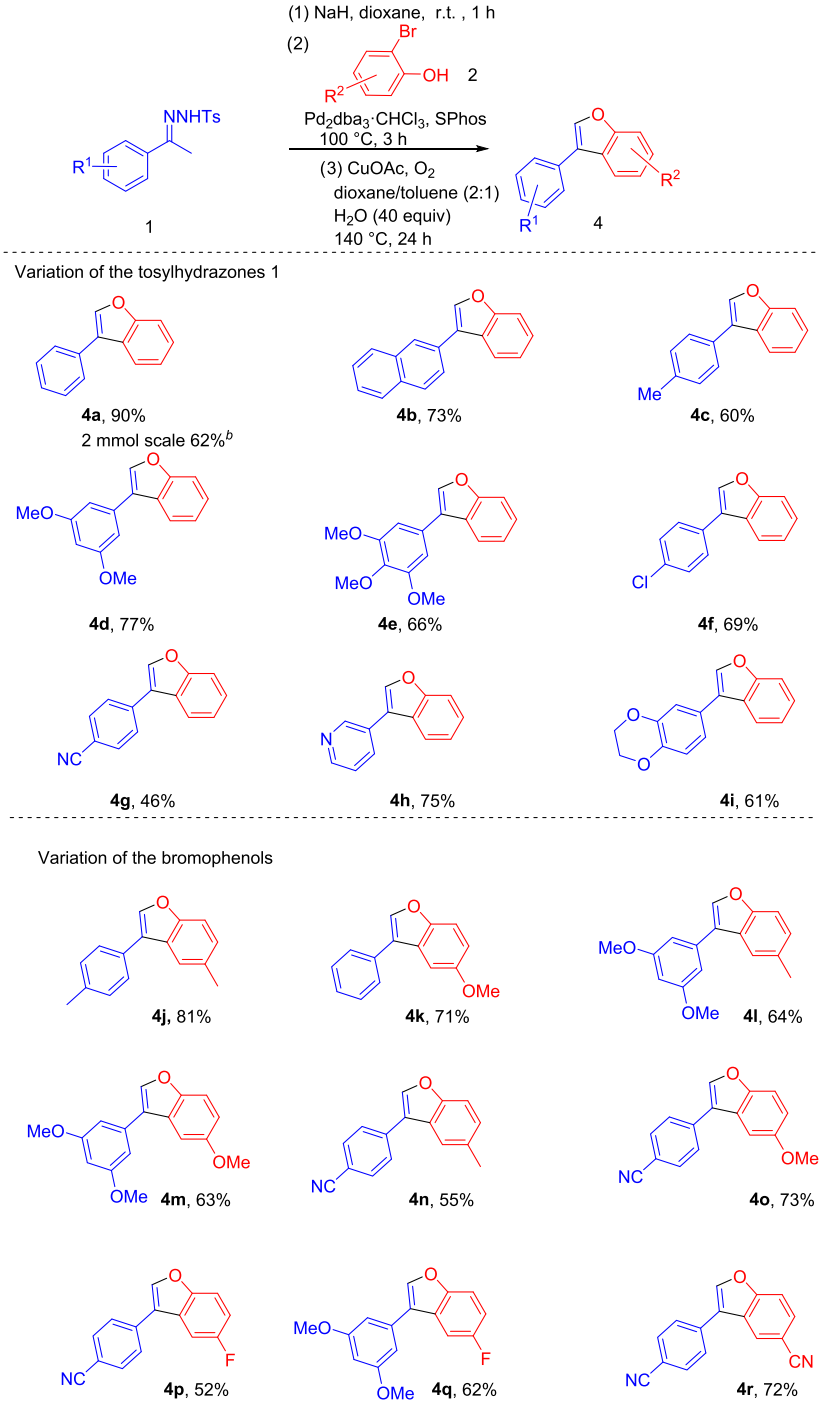
Scheme 2. Sequential One-Pot Reaction of NTH 1 and Bromophenol 2: Substrate Scope[a]



[b]Reaction was performed using 2 mmol of 2-bromophenol and NTH. [a]Conditions: step 1: in a sealed tube, NTH **1** (0.6 mmol), bromophenol **2** (0.4 mmol), $Pd_2dba_3{\cdot}CHCl_3$ (5 mol %), Sphos (10 mol %), and NaH (0.64 mmol) were added in dry dioxane (2.5 mL); step 2: after cooling, CuOAc (50 mol %), toluene 1 mL, and H_2O (40 equiv) were added under O_2 and the mixture was heated at 140 °C for 24 h.

cool to rt. Then, toluene (2.5 mL/mmol), copper(I) acetate (0.2 mmol), and H_2O (40 equiv) were added. Oxygen was then bubbled into the reaction mixture, which was later allowed to stir at 140 °C for 24 h in an oil bath. The reaction mixture was cooled to room temperature and filtered through Celite. The solvent was evaporated under reduced pressure, and the crude product was purified by flash chromatography on a silica gel.

*3-Phenylbenzofuran (**4a**).*[23] **4a** was prepared according to method A; column chromatography on a silica gel afforded 70 mg of the desired compound as a colorless oil, yield 90%; R_f = 0.8 (EtOAc/heptane, 5/95, SiO_2); IR (film, cm^{-1}) 2926, 2854, 1606, 1577, 1491, 1451, 1260, 1218, 1153, 1108, 1092, 962, 743; ^1H NMR (300 MHz, $CDCl_3$) δ 7.86 (d, J = 7.6 Hz, 1H), 7.80 (s, 1H), 7.66 (d, J = 6.6 Hz, 2H), 7.56 (d, J = 7.1 Hz, 1H), 7.49 (t, J = 7.7 Hz, 2H), 7.41−7.30 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.9 (C), 141.4 (CH), 132.2 (C), 129.1 (2CH), 127.7 (2CH), 127.6 (CH), 126.6 (C), 124.7 (CH), 123.1 (CH), 122.4 (C), 120.5 (CH), 111.92 (CH); HRMS (ESI) for $C_{14}H_9O$ $(M - H)^-$ calcd 193.0653, found 193.0656.

Synthesis of 3-Phenylbenzofuran (4a) on a 2 mmol Scale. To a solution in a sealed tube of *N*-tosylhydrazone (3 mmol, 865 mg)

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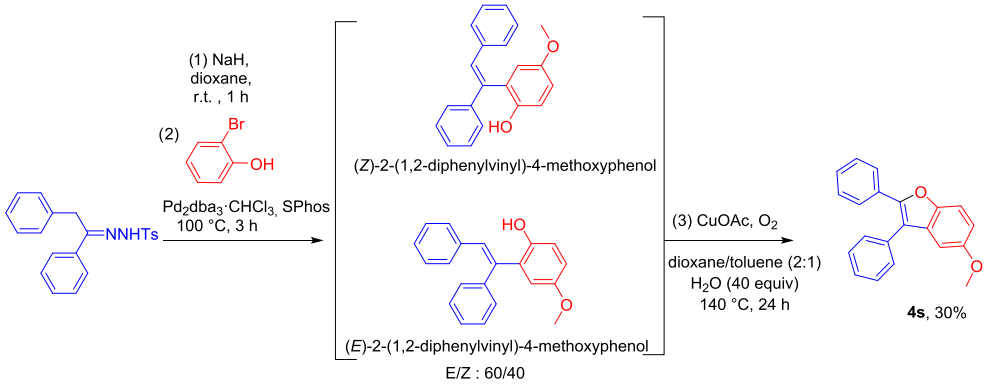
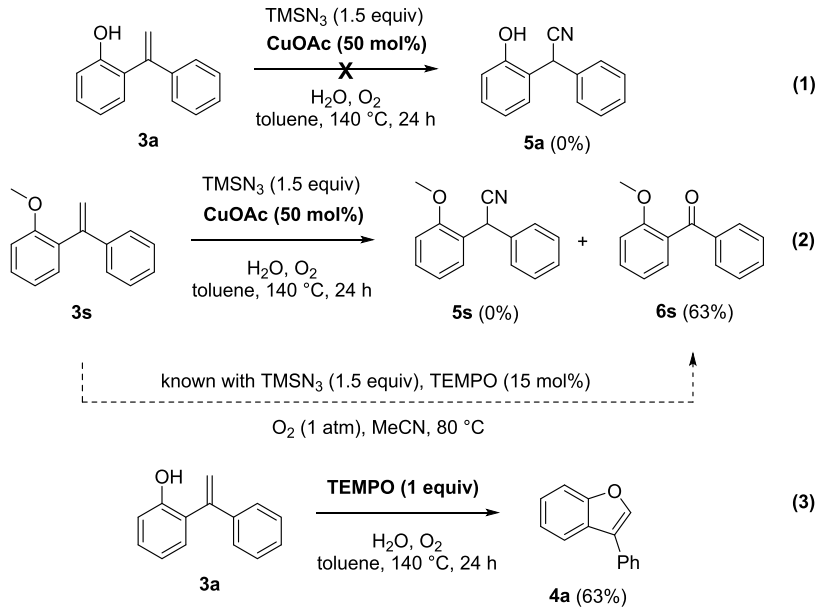
Scheme 3. Coupling of 2-Bromophenol with NTH Derived from 2-Phenylacetophenone: Access to 2,3-Disubstituted Benzofurans



Scheme 4. Mechanistic Investigation



in distilled dioxane (15.0 mL) was added NaH (4.8 mmol). This resulting suspension was stirred at rt for one hour; 2-bromophenol (2 mmol, 342 mg), $Pd_2dba_3CHCl_3$ (5 mol %, 103.5 mg), and Sphos (10 mol %, 82 mg) were added. The mixture was then heated at 100 °C for 3 h in an oil bath. The reaction mixture was allowed to cool to rt. Then, toluene (7.5 mL), copper(I) acetate (1 mmol, 122 mg), and H_2O (40 equiv) were added. Oxygen was then bubbled into the reaction mixture, which was later allowed to stir at 140 °C for 24 h in an oil bath. The reaction mixture was cooled to room temperature and filtered through Celite. The solvent was evaporated under reduced pressure, and the crude product was purified by flash chromatography on a silica gel to afford 240 mg of compound 4a as a colorless oil, yield 62%.

*3-(Naphthalen-2-yl)benzofuran (**4b**).*[24] **4b** was prepared according to method A; column chromatography on a silica gel afforded 71 mg of the desired compound as a colorless oil, yield 73%; R_f = 0.81 (EtOAc/heptane, 5/95, SiO_2); IR (film, cm^{-1}) 2955, 2867, 1603, 1589, 1499, 1443, 1245; ^1H NMR (300 MHz, $CDCl_3$) δ 8.17 (s, 1H), 8.05−7.87 (m, 5H), 7.78 (dd, J = 8.4, 1.7 Hz, 1H), 7.67−7.60 (m, 1H), 7.60−7.50 (m, 2H), 7.46−7.35 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.9 (C), 141.7 (CH), 133.8 (C), 132.7 (C), 129.5 (C), 128.6 (CH), 127.9 (CH), 127.8 (CH), 126.6 (C), 126.4 (CH), 126.0 (CH), 125.9 (CH), 125.8 (CH), 124.7 (CH), 123.1 (CH), 122.3 (C), 120.6 (CH), 111.9 (CH). HRMS (ESI) for $C_{18}H_{11}O$ $(M - H)^-$ calcd 243.0809, found 243.0805.

*3-(p-Tolyl)benzofuran (**4c**).*[24] **4c** was prepared according to method A; column chromatography on a silica gel afforded 50 mg of the desired compound as a yellow oil, yield 60%; R_f = 0.7 (EtOAc/heptane, 5/95, SiO_2); IR (film, cm^{-1}) 2919, 1575, 1541, 1508, 1453, 1340, 1109, 1091, 964, 746; ^1H NMR (400 MHz, $CDCl_3$) δ 7.84 (dd, J =1.2, 7.2 Hz, 1H), 7.77 (s, 1H), 7.55 (d, J = 8.0 Hz, 3H), 7.37−7.28 (m, 4H), 2.42 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 155.9 (C), 141.2 (CH), 137.4 (C), 129.8 (2CH), 129.2 (C), 127.5 (2CH), 126.7 (C), 124.6 (CH), 123.0 (CH), 122.3 (C), 120.6 (CH), 111.9 (CH), 21.4 (CH_3); HRMS (ESI) for $C_{15}H_{13}O$ $(M + H)^+$ calcd 209.0961, found 231.0960.

*3-(3,5-Dimethoxyphenyl)benzofuran (**4d**).* **4d** was prepared according to method A; column chromatography on a silica gel afforded 78 mg of the desired compound as a yellow oil, yield 77%; R_f = 0.4 (EtOAc/heptane, 1/9, SiO_2); IR (film, cm^{-1}) 2838, 1608, 1597, 1453, 1359, 1267, 1205, 1155, 1110, 1096, 746; ^1H NMR (300 MHz, $CDCl_3$) δ 7.86 (d, J = 7.2 Hz, 1H), 7.80 (s, 1H), 7.56 (d, J = 8.3 Hz, 1H), 7.39−−7.29 (m, 2H), 6.81 (d, J = 2.3 Hz, 2H), 6.51 (s, 1H), 3.87 (s, 6H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 161.4 (2C), 155.9 (C), 141.7 (CH), 134.0 (C), 126.6 (C), 124.7 (CH), 123.1 (CH), 122.5 (C), 120.6 (CH), 111.9 (CH), 105.9 (2CH), 99.7 (CH), 55.6 ($2OCH_3$); HRMS (ESI) for $C_{16}H_{15}O_3$ $(M + H)^+$ calcd 255.1021, found 255.1027.

*3-(3,4,5-Trimethoxyphenyl)benzofuran (**4e**).* **4e** was prepared according to method A; column chromatography on a silica gel afforded 75 mg of the desired compound as a yellow oil, yield 66%; R_f

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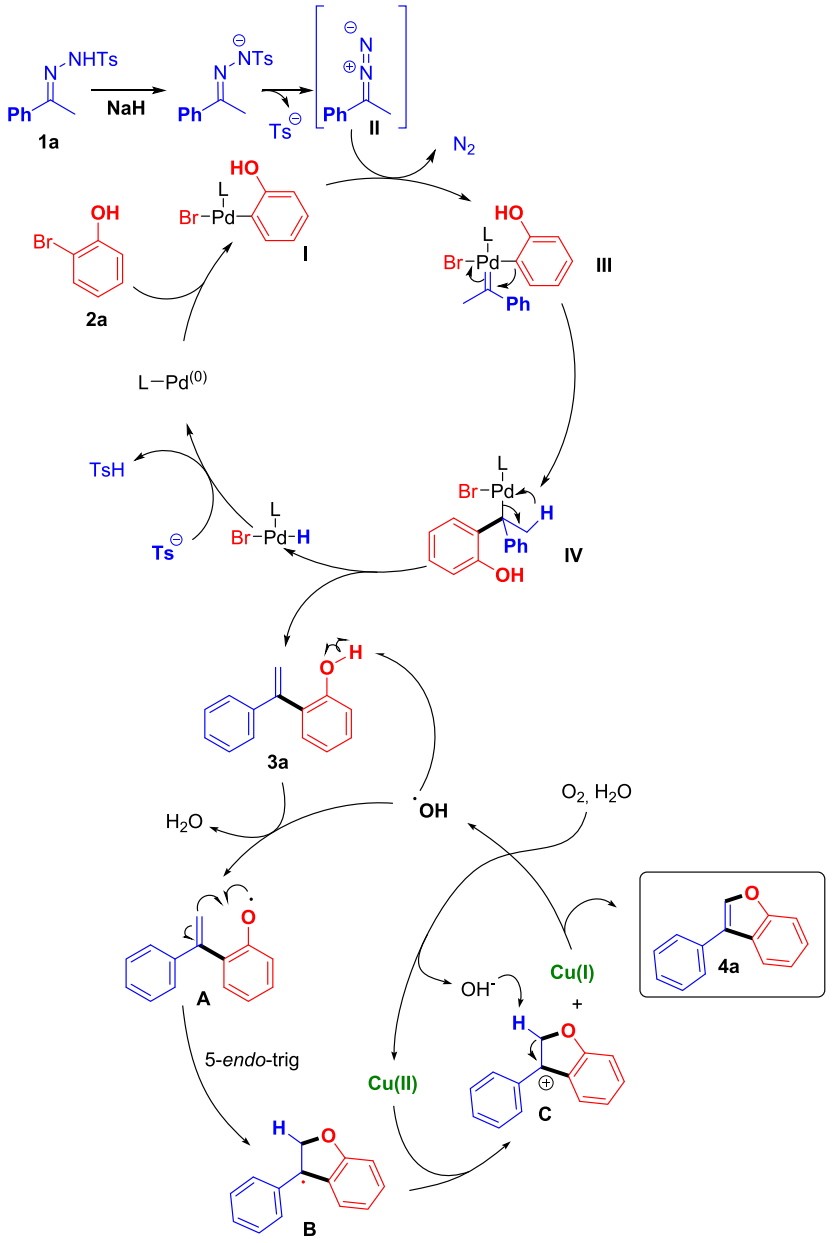
Scheme 5. Mechanism Proposal



= z0.36 (EtOAc/heptane, 2/8, SiO_2); IR (film, cm^{-1}) 2840, 1607, 1592, 1579, 1506, 1453, 1360, 1272, 1239, 1127, 747; ^1H NMR (300 MHz, $CDCl_3$) δ 7.83−7.80 (m, 1H), 7.77 (s, 1H), 7.56 (dd, J = 7.2, 1.3 Hz, 1H), 7.39−7.29 (m, 2H), 6.85 (s, 2H), 3.94 (s, 6H), 3.92 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 155.9 (C), 153.9 (2C), 141.2 (CH), 137.9 (C), 127.72 (C), 126.6 (C), 124.8 (CH), 123.1 (CH), 122.5 (C), 120.3 (CH), 112.0 (CH), 105.1 (2CH), 61.1 (OCH_3), 56.4 ($2OCH_3$); HRMS (ESI) for $C_{17}H_{17}O_4$ $(M + H)^+$ calcd 285.1127, found 285.1131.

*3-(4-Chlorophenyl)benzofuran (**4f**).*[24] **4f** was prepared according to method A; column chromatography on a silica gel afforded 63 mg of the desired compound as a colorless oil, yield 69%; R_f = 0.79 (EtOAc/heptane, 5/95, SiO_2); IR (film, cm^{-1}) 2922, 2866, 1606, 1588, 1495, 1451, 1272, 1220; ^1H NMR (400 MHz, $CDCl_3$) δ 7.81−7.77 (m, 2H), 7.60−7.55 (m, 3H), 7.48−7.43 (m, 2H), 7.40−7.30 (m, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 155.8 (C), 141.4 (CH), 133.3 (C), 130.5 (C), 129.1 (2CH), 128.7 (2CH), 126.2 (C), 124.7 (CH), 123.1 (CH), 121.2 (C), 120.1 (CH), 111.8 (CH); HRMS for $C_{14}H_{10}ClO$ $(M + H)^+$ calcd 229.0426, found 229.0421.

*4-(Benzofuran-3-yl)benzonitrile (**4g**).*[25] **4g** was prepared according to method A; column chromatography on a silica gel afforded 40 mg of the desired compound as a colorless oil, yield 46%; R_f = 0.66 (EtOAc/pentane, 1/9, SiO_2); IR (film, cm^{-1}) 3060, 2226, 1610, 1576, 1501, 1452, 1345, 1277, 1219, 1114, 1093, 964, 745; ^1H NMR (300 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.81 (d, J = 7.7 Hz, 1H), 7.76 (s, 4H), 7.58 (d, J = 7.9 Hz, 1H), 7.38 (m, 2H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 156.1 (C), 142.6 (CH), 137.1 (C), 132.9 (2CH), 127.9 (2CH), 125.6 (C), 125.3 (CH), 123.7 (CH), 121.1 (C), 120.1 (CH), 118.9 (C), 112.2 (CH), 111.1 (C). HRMS for $C_{15}H_{10}NO$ $(M + H)^+$ calcd 220.0762, found 220.0756.

*3-(Benzofuran-3-yl)pyridine (**4h**).* **4h** was prepared according to method A; column chromatography on a silica gel afforded 59 mg of the desired compound as a yellow oil, yield 75%; R_f = 0.33 (EtOAc/cyclohexane, 2/8, SiO_2); IR (film, cm^{-1}) 2967, 2245, 1620, 1567, 1510, 1477, 1399; ^1H NMR (300 MHz, $CDCl_3$) δ 8.97 (s, 1H), 8.67 (s, 1H), 7.94 (d, J = 7.6 Hz, 1H), 7.84 (s, 1H), 7.83−7.76 (m, 1H), 7.61−7.55 (m, 1H), 7.47−7.25 (m, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 155.8 (C), 148.6 (CH), 148.4 (CH), 141.8 (CH), 134.5 (2CH), 125.9 (C), 125.0 (CH), 123.4 (CH), 120.0 (CH), 119.1 (C),

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112.0 (CH). HRMS for $C_{13}H_{10}ON$ $(M + H)^+$ calcd 196.0762, found 196.0759.

*6-(Benzofuran-3-yl)-2,3-dihydrobenzo[b][1,4]dioxine (**4i**).* **4i** was prepared according to method A; column chromatography on a silica gel afforded 61 mg of the desired compound as a colorless oil, yield 61%; R_f = 0.7 (EtOAc/pentane, 1/9, SiO_2); IR (film, cm^{-1}) 2842, 1608, 1598, 1452, 1377; ^1H NMR (300 MHz, $CDCl_3$) δ 7.86−7.79 (m, 1H), 7.73 (s, 1H), 7.57−7.51 (m, 1H), 7.39−7.27 (m, 2H), 7.21−7.10 (m, 2H), 6.98 (d, J = 8.3 Hz, 1H), 4.32 (s, 4H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 155.7 (C), 143.9 (C), 143.1 (C), 140.9 (CH), 126.5 (C), 125.4 (C), 124.5 (CH), 122.9 (CH), 121.7 (C), 120.7 (CH), 120.4 (CH), 117.8 (CH), 116.3 (CH), 111.7 (CH), 64.5 ($2CH_2$). HRMS for $C_{16}H_{13}O_3$ $(M + H)^+$ calcd 253.0865, found 253.0861.

*5-Methyl-3-(p-tolyl)benzofuran (**4j**).* **4j** was prepared according to method A; column chromatography on a silica gel afforded 67 mg of the desired compound as a colorless oil, yield 81%; R_f = 0.78 (EtOAc/pentane, 5/95, SiO_2); IR (film, cm^{-1}) 3022, 2895, 1610, 1588, 1502, 1463; ^1H NMR (300 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.66 (s, 1H), 7.58 (d, J = 8.1 Hz, 2H), 7.47 (d, J = 8.4 Hz, 1H), 7.33 (d, J = 7.8 Hz, 2H), 7.20 (d, J = 6.8 Hz, 1H), 2.52 (s, 3H), 2.46 (s, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 154.2 (C), 141.2 (CH), 137.2 (C), 132.4 (C), 129.7 (2CH), 129.3 (C), 127.4 (2CH), 126.7 (C), 125.7 (CH), 121.9 (C), 120.2 (CH), 111.2 (CH), 21.50 (CH_3), 21.29 (CH_3). HRMS for $C_{16}H_{15}O$ $(M + H)^+$ calcd 223.1123, found 223.1119.

*5-Methoxy-3-phenylbenzofuran (**4k**).*[26] **4k** was prepared according to method A; column chromatography on a silica gel afforded 64 mg of the desired compound as a yellow oil, yield 71%; R_f = 0.67 (EtOAc/pentane, 5/95, SiO_2); IR (film, cm^{-1}) 3075, 2967, 2854, 1604, 1584, 1499, 1452; ^1H NMR (300 MHz, acetone-d_6) δ 7.37 (s, 1H), 7.34 (s, 1H), 7.14−7.05 (m, 1H), 6.97 (dd, J = 7.5, 1.8 Hz, 1H), 6.91−6.83 (m, 3H), 6.72−6.59 (m, 2H), 3.37 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, acetone-d_6) δ 159.6 (C), 149.2 (CH), 148.8 (C), 141.5 (2C), 136.8 (CH), 125.8 (C), 122.0 (CH), 120.4 (CH), 115.9 (2CH), 114.9 (2CH), 55.8 (OCH_3). HRMS (ESI) for $C_{15}H_{12}O_2Na$ $(M + Na)^+$: calcd 247.0730, found: 247.0732.

*3-(3,5-Dimethoxyphenyl)-5-methylbenzofuran (**4l**).* **4l** was prepared according to method A; column chromatography on a silica gel afforded 69 mg of the desired compound as a colorless oil, yield 64%; R_f = 0.62 (EtOAc/pentane, 1/9, SiO_2); IR (film) 3082, 2936, 1604, 1588, 150, 1452, 1345, 1277, 1219, 1114, 1093, 964, 745 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.64 (s, 1H), 7.44 (d, J = 8.4 Hz, 1H), 7.18 (d, J = 8.4 Hz, 1H), 6.80 (d, J = 2.3 Hz, 2H), 6.51 (t, J = 2.3 Hz, 1H), 3.88 (s, 6H), 2.49 (s, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 160.1 (2C), 153.1 (C), 140.6 (CH), 133.0 (C), 131.5 (C), 125.4 (C), 124.8 (CH), 121.0 (C), 119.1 (CH), 110.2 (CH), 104.7 (2CH), 98.2 (CH), 54.4 ($2OCH_3$), 20.4 (CH_3). HRMS for $C_{17}H_{17}O_3$ $(M + H)^+$ calcd 269.1178, found 269.1176.

*3-(3,5-Dimethoxyphenyl)-5-methoxybenzofuran (**4m**).* **4m** was prepared according to method A; column chromatography on a silica gel afforded 64 mg of the desired compound as a white solid, yield 63%; R_f = 0.56 (EtOAc/pentane, 5/95, SiO_2); IR (film, cm^{-1}) 3088, 2954, 2886, 1611, 1576, 1520, 1491, 1432; ^1H NMR (300 MHz, $CDCl_3$) δ 7.68 (s, 1H), 7.36 (d, J = 8.9 Hz, 1H), 7.19 (d, J = 3.7 Hz, 1H), 6.88 (dd, J = 8.9, 2.6 Hz, 1H), 6.69 (d, J = 2.3 Hz, 2H), 6.42 (t, J = 2.3 Hz, 1H), 3.79 (s, 9H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 161.2 (2C), 156.2 (C), 150.7 (C), 142.4 (CH), 134.0 (C), 129.8 (C), 126.9 (C), 113.3 (CH), 112.2 (CH), 105.7 (2CH), 102.9 (CH), 99.4 (CH), 56.0 (OCH_3), 55.4 ($2OCH_3$). HRMS (ESI) for $C_{17}H_{16}O_4Na$ $(M + Na)^+$: calcd 307.0946, found: 307.0948.

*4-(5-Methylbenzofuran-3-yl)benzonitrile (**4n**).* **4n** was prepared according to method A; column chromatography on a silica gel afforded 51 mg of the desired compound as a colorless oil, yield 55%; R_f = 0.66 (EtOAc/pentane, 1/9, SiO_2); IR (film, cm^{-1}) 3042, 2933, 2228, 1624, 1577, 1512, 1487, 1452, 1277; ^1H NMR (300 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.73 (s, 4H), 7.59 (s, 1H), 7.45 (d, J = 8.4 Hz, 1H), 7.21 (d, J = 8.4 Hz, 1H), 2.50 (s, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 154.4 (C), 142.7 (CH), 137.2 (C), 133.1 (C), 132.7 (2CH), 127.7 (2CH), 126.4 (CH), 125.5 (C), 120.6 (C), 119.8 (CH), 118.9 (C), 111.6 (CH), 110.8 (C), 21.5 (CH_3). HRMS for $C_{16}H_{12}ON$ $(M + H)^+$ calcd 234.0919, found 234.0924.

*4-(5-Methoxybenzofuran-3-yl)benzonitrile (**4o**).* **4o** was prepared according to method A; column chromatography on a silica gel afforded 73 mg of the desired compound as a colorless oil, yield 73%; R_f = 0.66 (EtOAc/pentane, 1/9, SiO_2); IR (film, cm^{-1}) 3121, 2950, 2340, 1620, 1587, 1505, 1467, 1399; ^1H NMR (300 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.77 (d, J = 8.4 Hz, 2H), 7.73 (d, J = 8.4 Hz, 2H), 7.47 (d, J = 9.0 Hz, 1H), 7.22 (d, J = 2.6 Hz, 1H), 7.00 (dd, J = 9.0, 2.6 Hz, 1H), 3.88 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.8 (C), 153.4 (C), 143.4 (CH), 140.5 (CH), 133.0 (2CH), 128.6 (C), 127.9 (2CH), 124.8 (C), 121.2 (C), 113.9 (CH), 112.7 (CH), 103.3 (CH), 102.8 (C), 56.2 (OCH_3). HRMS (ESI) for $C_{16}H_{12}O_2N$ $(M + H)^+$: calcd 250.0868, found: 250.0873.

*4-(5-Fluorobenzofuran-3-yl)benzonitrile (**4p**).* **4p** was prepared according to method A; column chromatography on a silica gel afforded 44 mg of the desired compound as a yellow oil, yield 52%; R_f = 0.8 (EtOAc/pentane, 1/9, SiO_2); IR (film, cm^{-1}) 2954, 2888, 1602, 1566, 1521, 1445, 1398; ^1H NMR (300 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.77 (d, J = 8.6 Hz, 2H), 7.70 (d, J = 8.6 Hz, 2H), 7.51 (dd, J = 9.0, 3.9 Hz, 1H), 7.45 (dd, J = 8.7, 2.6 Hz, 1H), 7.11 (m, 1H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 161.3 (C-F, $^1J_{C\text{-}F}$ = 239.6 Hz), 158.1 (C-F, $^1J_{C\text{-}F}$ = 239.6 Hz), 152.1 (C), 144.1 (CH), 136.4 (C), 132.9 (2CH), 127.6 (2CH), 118.7 (2C), 113.2 (C-F, $^2J_{C\text{-}F}$ = 26.5 Hz), 112.9 (C-F, $^2J_{C\text{-}F}$ = 26.5 Hz), 112.9 (C-F, $^3J_{C\text{-}F}$ = 9.8 Hz), 112.8 (C-F, $^3J_{C\text{-}F}$ = 9.8 Hz) 111.2 (C), 106.0 (C-F, $^2J_{C\text{-}F}$ = 25.8 Hz), 105.6 (C-F, $^2J_{C\text{-}F}$ = 25.8 Hz). ^{19}F NMR (188 MHz, $CDCl_3$) δ −121.3 HRMS (ESI) for $C_{15}H_9ONF$ $(M + H)^+$: calcd 238.0668, found: 238.0672.

*3-(3,5-Dimethoxyphenyl)-5-fluorobenzofuran (**4q**).* **4q** was prepared according to method A; column chromatography on a silica gel afforded 67 mg of the desired compound as a colorless oil, yield 62%; R_f = 0.69 (EtOAc/pentane, 1/9, SiO_2); IR (film, cm^{-1}) 3101, 2930, 2226, 1620, 1589, 1520, 1466, 1345; ^1H NMR (400 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.47 (td, J = 8.8, 3.4 Hz, 2H), 7.07 (td, J = 9.0, 2.6 Hz, 1H), 6.74 (d, J = 2.3 Hz, 2H), 6.50 (t, J = 2.3 Hz, 1H), 3.86 (s, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 161.4 (2C), 160.8 (C-F, $^1J_{C\text{-}F}$ = 238.5 Hz), 158.4 (C-F, $^1J_{C\text{-}F}$ = 238.5 Hz), 152.1 (C), 143.3 (CH), 133.4 (C), 127.4 (C-F, $^3J_{C\text{-}F}$ = 10.3 Hz), 127.3 (C-F, $^3J_{C\text{-}F}$ = 10.3 Hz), 122.7 (C-F, 4JC-F = 3.9 Hz), 122.7 (C-F, 4JC-F = 3.9 Hz), 112.6 (C-F, $^3J_{C\text{-}F}$ = 6.9 Hz), 112.6 (C-F, $^3J_{C\text{-}F}$ = 6.9 Hz), 112.5 (C-F, $^3J_{C\text{-}F}$ = 9.8 Hz), 112.4 (C-F, $^3J_{C\text{-}F}$ = 9.8 Hz), 106.3 (C-F, $^3J_{C\text{-}F}$ = 25.4 Hz), 106.1 (C-F, $^3J_{C\text{-}F}$ = 25.4 Hz), 105.7 (2CH), 99.7 (CH), 55.6 (2OCH3). ^{19}F NMR (188 MHz, $CDCl_3$) δ −120.4. HRMS (ESI) for $C_{16}H_{14}O_3F$ $(M + H)^+$: calcd 273.0927, found: 273.0926.

*3-(4-Cyanophenyl)benzofuran-5-carbonitrile (**4r**).* **4r** was prepared according to method A; column chromatography on a silica gel afforded 70 mg of the desired compound as a colorless oil, yield 72%; R_f = 0.24 (EtOAc/cyclohexane, 3/7, SiO_2); IR (film, cm^{-1}) 2993, 2901, 2225, 1625, 1588, 1510, 1487, 1452; ^1H NMR (300 MHz, DMSO-d_6) δ 8.78 (s, 1H), 8.55 (s, 1H), 8.02 (d, J = 8.3 Hz, 2H), 7.95 (d, J = 8.5 Hz, 2H), 7.93−7.83 (m, 2H). $^{13}C\{^1H\}$ NMR (75 MHz, DMSO) δ 156.9 (C), 146.6 (CH), 135.0 (C), 132.9 (2CH), 128.8 (CH), 127.7 (2CH), 125.9 (CH), 125.4 (C), 119.8 (C), 119.0 (C), 118.6 (C), 113.4 (CH), 110.2 (C), 106.7 (C). HRMS (ESI) for $C_{16}H_9ON_2$ $(M + H)^+$: calcd 245.0715, found: 245.0712.

*5-Methoxy-2,3-diphenylbenzofuran (**4s**).*[27] **4s** was prepared according to method A; column chromatography on a silica gel afforded 36 mg of the desired compound as a colorless oil, yield 30%, R_f = 0.76 (EtOAc/cyclohexane, 1/9, SiO_2); ^1H NMR (300 MHz, $CDCl_3$) δ 7.69−7.62 (m, 2H), 7.55−7.43 (m, 6H), 7.35−7.29 (m, 3H), 6.97-6.94 (m, 2H), 3.82 (s, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 156.3 (C), 151.4 (C), 149.0 (C), 133.0 (C), 130.8 (2C), 129.8 (2CH), 129.0 (2C), 128.4 (2C), 128.3 (CH), 127.6 (CH), 126.9 (2CH), 117.7 (C), 113.6 (CH), 111.6 (CH), 102.3 (CH), 56.0 (OCH_3). HRMS (ESI) for $C_{21}H_{17}O_2$ $(M + H)^+$: calcd 301.1229, found: 301.1224

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c01835.

Experimental procedures; compound characterizations; and ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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