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Copper-Catalyzed, C−C Coupling-Based One-Pot Tandem Reactions for the Synthesis of Benzofurans Using *o*-Iodophenols, Acyl Chlorides, and Phosphorus Ylides

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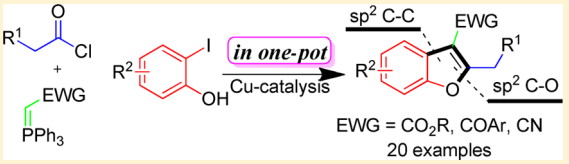
Supporting Information

ABSTRACT: One-pot reactions involving acyl chlorides, phosphorus ylides, and *o*-iodophenols with copper catalysis have been established for the rapid synthesis of functionalized benzofurans. With all of these easily available and stable reactants, the construction of the target products has been accomplished via tandem transformations involving a key C−C coupling, leading to the formation of one C(sp^2)−C bond, one C(sp^2)−O bond, and one C═C bond.



The formation of C−C and C−heteroatom single bonds is the central and basic transformation in a tremendous number of organic syntheses. Thanks to the rapid advances of modern synthetic organic chemistry, there are presently a vast number of methods available for achieving these bond formations. In the synthetic toolbox, C−C and C−heteroatom coupling reactions that enable the transformation of C(sp^2)−X (X = halide) bonds such as Ar−X and vinyl−X bonds into new C−C/C−heteroatom bonds are of particular significance. One typical example of the category is the Ullmann reaction, which involves the copper-catalyzed coupling of aryl/vinyl halides and corresponding C- or heteroatom-based nucleophiles.[1] Among the versatile utilities of Ullmann couplings in organic synthesis, the direct synthesis of various N-, O-, and/or S-containing heterocyclic products constitutes a major frontier.[2,3]

Benzofuran is a motif of prevalent presence in natural products and biologically relevant organic molecules. The investigation of benzofuran-based scaffolds has led to the discovery of many promising lead compounds. For instance, SKF-64346 (**1**) (Figure 1) has been identified as a potent inhibitor of *β*-amyloid aggregation and shown therapeutic potential toward Alzheimer's disease,[4] and amiodarone (**2**) is a widely utilized clinical drug in the treatment of intractable cardiac arrhythmias.[5] Daphnodorin B (**3**) is one of the natural products of the Daphnodorin family and possesses a broad spectrum of biological functions such as antifungal activity,[6] antitumor activity,[7] and cytotoxic activity[8] as well as inhibition activity against *α*-glucosidase,[9] 12-lipoxygenase,[10] and human chymase-dependent angiotensin II.[11] The long-lasting and extensive efforts toward the synthesis of benzofurans have inspired the establishment of numerous elegant synthetic methodologies targeting this heterocyclic scaffold. Some particularly interesting and novel ones are those employing transition-metal-catalyzed versions based on the conversion of stable chemical bonds such as C(sp^2)−H and C(sp^2)−X bonds. For example, Willis and co-workers[12] developed the palladium-catalyzed intramolecular C−H arylation/alkene isomerization reactions of *o*-bromoaryl allyl ethers **4** for the synthesis of benzofurans (eq 1 in Scheme 1). Maiti and co-workers[13] achieved benzofuran synthesis using simple phenols and alkenes via palladium/copper-cocatalyzed intermolecular C−H annulation (eq 2 in Scheme 1). In another work, Yi and co-workers[14] employed a ruthenium-catalyzed tandem intermolecular C−H dehydration/intramolecular dehydration transformation to assemble benzofurans from phenols **5** and 1,2-diols **7** (eq 3 in Scheme 1). Alternatively, by utilization of Ullmann C−C coupling as a key transformation, Ma and co-workers[15] accomplished the construction of benzofurans with copper-catalyzed tandem reactions of 2-bromophenyl iodides **8**

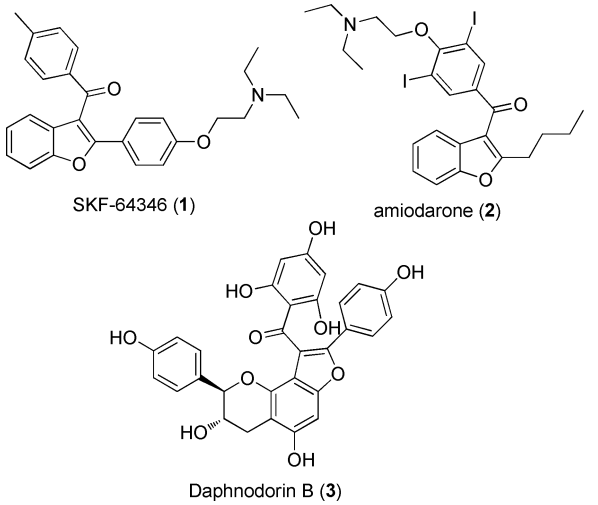


Figure 1. Benzofuran-based lead compounds and natural products.

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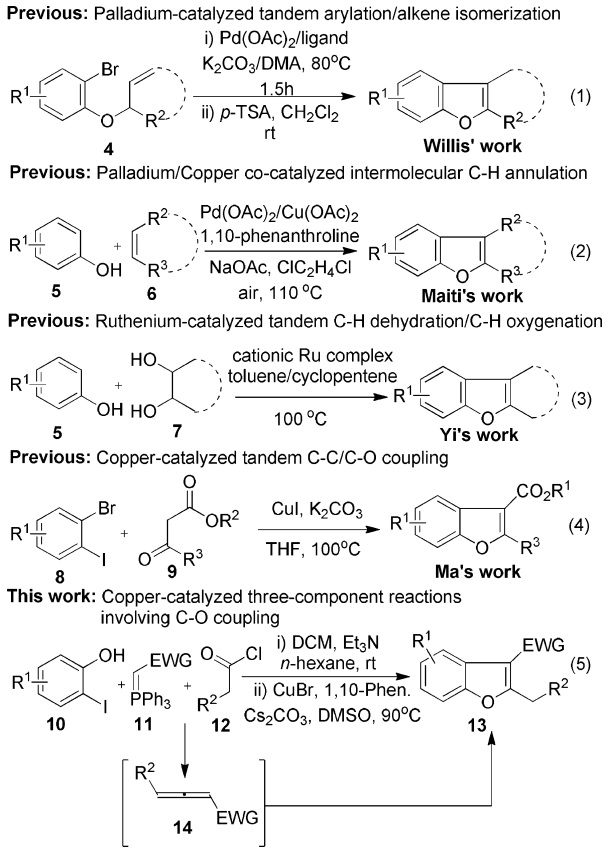
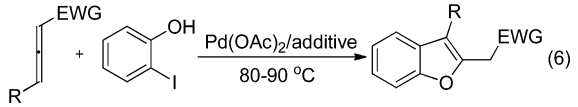
Scheme 1. Different Routes To Access Functionalized Benzofurans



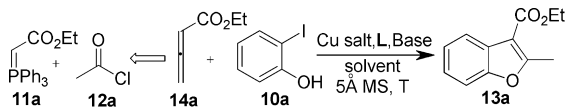
and β-keto esters **9** (eq 4 in Scheme 1). In addition, on the basis of classical routes such as the palladium-catalyzed Larock-type annulation using *o*-halophenols and alkynes,[16] a variety of other practical protocols are also available to enable the synthesis of benzofurans by catalysis with palladium, silver, copper, or a Pd/Cu cocatalyst.[17] While each of these known protocols for benzofuran synthesis has specific features and/or advantages, the design of new tandem reactions using simpler starting materials to expand the structural diversity of the products is still highly desirable. Herein we report a new copper-catalyzed tandem approach for the synthesis of benzofurans involving the assembly of allenes **14** and *o*-iodophenols **10**, wherein **14** are generated in situ by the direct use of the corresponding Wittig reagents **11** and acyl chlorides **12** in one pot (eq 5 in Scheme 1). To the best of our knowledge, no allene-based coupling reactions with copper catalysis have been hitherto known for benzofuran synthesis, and a palladium-catalyzed coupling protocol involving allenylphosphonates and *o*-iodophenol proceeds via a different selectivity to produce benzofurans by incorporating a β,γ-C=C bond (eq 6).[18] Besides involving a novel selective reaction



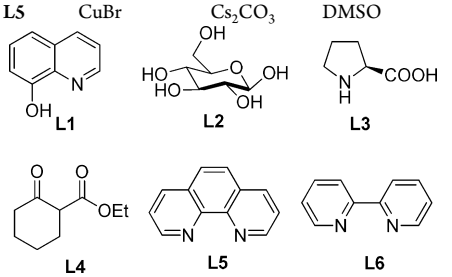
pathway, the present method is also advantageous for avoiding the tedious prior isolation of unstable allenes and allowing the generation of high product diversity by employing simple and readily available reactants such as acyl chlorides and different Wittig reagents.

Originally, the reaction of *o*-iodophenol (**10a**), phosphorus ylide **11a**, and acetyl chloride (**12a**) was employed to probe the expected transformation, wherein **11a** and **12a** were first reacted following a literature procedure to prepare the corresponding allene **14a**.[19] Subsequent employment of **10a**, a copper catalyst, ligand, base, etc., was discovered to be capable of producing **13a**. Therefore, the initial efforts focused on optimizing the conditions for the assembly of allene **14a** and *o*-iodophenol **10a**. As shown in Table 1, comparison of a series of

Table 1. Different Conditions for the Synthesis of Benzofuran 13a[a]



entry	ligand	cat.	base	solvent	yield (%)[b]
1	**L1**	CuBr	Cs_2CO_3	DMSO	53
2	**L2**	CuBr	Cs_2CO_3	DMSO	32
3	**L3**	CuBr	Cs_2CO_3	DMSO	36
4	**L4**	CuBr	Cs_2CO_3	DMSO	41
5	**L5**	CuBr	Cs_2CO_3	DMSO	72
6	**L6**	CuBr	Cs_2CO_3	DMSO	51
7	**L5**	CuBr	Et_3N	DMSO	trace
8	**L5**	CuBr	NaOAc	DMSO	trace
9	**L5**	CuBr	K_2CO_3	DMSO	29
10	**L5**	CuBr	*t*-BuOK	DMSO	33
11	**L5**	CuI	Cs_2CO_3	DMSO	61
12	**L5**	CuO	Cs_2CO_3	DMSO	47
13	**L5**	$CuBr_2$	Cs_2CO_3	DMSO	26
14[c]	**L5**	$Cu(OAc)_2$	Cs_2CO_3	DMSO	45
15	**L5**	CuBr	Cs_2CO_3	DMF	21
16	**L5**	CuBr	Cs_2CO_3	toluene	trace
17	**L5**	CuBr	Cs_2CO_3	dioxane	trace
18	**L5**	CuBr	Cs_2CO_3	acetonitrile	25
19[d]	**L5**	CuBr	Cs_2CO_3	DMSO	65
20[e]	**L5**	CuBr	Cs_2CO_3	DMSO	56



[a]General conditions: **10a** (0.5 mmol), **11a** (0.75 mmol), **12a** (0.75 mmol), copper catalyst (0.075 mmol), ligand (0.2 mmol), base (2.0 mmol), and 5 Å molecular sieves (150 mg) in solvent (2 mL), stirred at 90 °C for 12 h (TLC). [b]Yield of isolated products. [c]Commercial $Cu(OAc)_2 \cdot H_2O$ was used. [d]The temperature was 110 °C. [e]The temperature was 70 °C.

different typical ligands such as 8-hydroxyquinoline (**L1**), D-glucose (**L2**), L-proline (**L3**), ethyl 2-oxocyclohexanecarboxylate (**L4**), 1,10-phenanthroline (**L5**), and bipyridine (**L6**) revealed that **L5** was the optimal ligand (Table 1, entries 1–6). Subsequent comparison of different organic and inorganic bases, including Et_3N, K_2CO_3, NaOAc, *t*-BuOK, etc., did not provide a better result than the entry with Cs_2CO_3, which had also been previously known as a favorable base additive for

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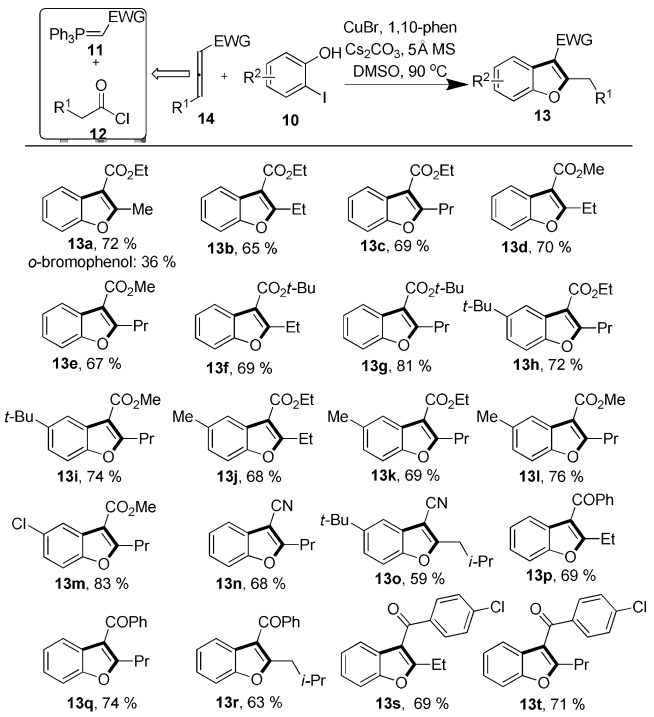
other C−O coupling process (Table 1, entries 7−10).[20] Later on, as the catalysts, various Cu(I) and Cu(II) salts were also employed for the reaction. In these experiments, CuBr turned out to be evidently better than all of the other copper catalysts tested (Table 1, entries 11−14). The subsequent examination of reaction media of different polarity, including toluene, 1,4-dioxane, DMF, and acetonitrile, demonstrated that a polar solvent was better favored by the model reaction, and DMSO was among the best ones (Table 1, entries 15−18). Finally, variation of the reaction temperature proved that 90 °C was the favored temperature (Table 1, entries 19 and 20).

Under the optimized conditions, various phosphorus ylides, acyl chlorides, and *o*-iodophenols were employed for the synthesis of different benzofurans, and the corresponding results are outlined in Scheme 2. According to the obtained

Scheme 2. Synthesis of Different Benzofurans[a]

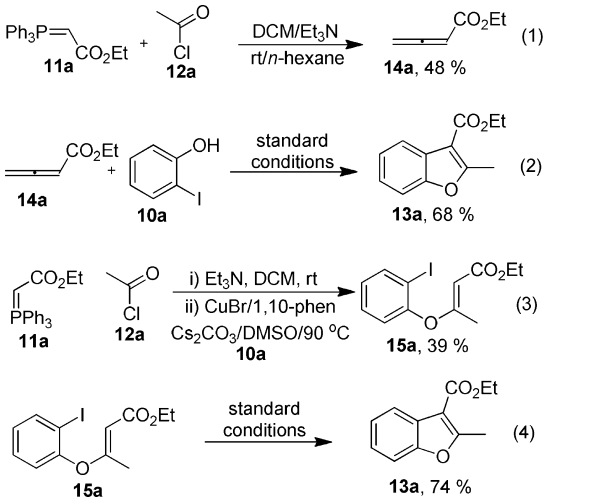


[a]Yields of isolated products based on **10** are shown.

results, the present protocol tolerated different functional groups well. For example, the electron-withdrawing group (EWG) in the ylide component could be an ester, carbonyl (ketone), or cyano group, while different functional groups in the *o*-iodophenol and acyl chloride components were also found to be compatible. Generally, benzofurans could be obtained in moderate to good yields via this tandem reaction, and products provided by ester-based phosphorus ylides displayed excellent tolerance, yielding 3-alkylate-functionalized benzofurans with broad diversity. No systematic impact of the functional groups in any of the components was observed, probably because complex factors such as the efficiency of allene synthesis and the C-arylative coupling between nucleophilic allene intermediates and iodophenols, etc., were involved in the process. While substituents with different properties in the iodophenol component could also be tolerated, the present transformation was found to be sensitive to the structure of the acyl chloride component. Specifically, our studies demonstrated that linear acyl chlorides were generally good reaction partners, while acyl chlorides bearing an aryl fragment, such as 2-phenylacetyl chloride, could not undergo the expect transformation to give the corresponding product. On the other hand, the reactions of ketone- and nitrile-based ylides were also smoothly run to afford the corresponding benzofurans **13n−t**, which assured the broader scope of application of the present protocol toward benzofuran synthesis. In addition, an entry using *o*-bromophenol as an alternative substrate for synthesizing **13a** gave a yield of 36% (Scheme 2).

After the examination of the scope of application, we also compared the efficiency of the model reaction with that of the stepwise operation using isolated allene **14a**. As shown in Scheme 3, the reaction of **11a** and **12a** in identical amounts

Scheme 3. Results for the Synthesis of Benzofuran 13a Using Allene 14a



(0.75 mmol) as shown in the model reaction in Table 1 was conducted following a literature procedure[17] to provide allene **14a** in 48% yield (eq 1 in Scheme 3). The obtained **14a** (40 mg) was then reacted with 0.5 mmol of **1a** under the standard reaction conditions (eq 2 in Scheme 3) and provided benzofuran **13a** in 68% isolated yield (50 mg), which was apparently lower than the total yield of the one-pot version (73 mg). With the further consideration of the consumption of chemicals for the isolation of the allene, the one-pot method is inarguably superior to the equivalent stepwise version in terms of both efficiency and atom economy.

Being aware of the fact that the benzofuran products were assembled from allene and *o*-iodophenol, we then attempted to isolate possible intermediates from the reaction to explore the reaction mechanism. When the model reaction was run under modified conditions, ethyl 3-(2-iodophenoxy)but-2-enoate (**15a**) was observed (eq 3 in Scheme 3), and in addition, subjecting **15a** to the standard copper-catalyzed conditions efficiently yielded benzofuran **13a** (eq 4 in Scheme 3). With these results and related literature reports of indole synthesis involving the allene intermediate,[21] we postulated the reaction mechanism shown in Scheme 4. At first, after the in situ formation, allene **14** undergoes the oxa-Michael addition with *o*-iodophenol **10** to provide intermediate **16**, which quickly isomerizes to give **15**. Subsequently, the insertion of Cu(I) into the Ar−I bond in **15** leads to the formation of intermediate **17**,

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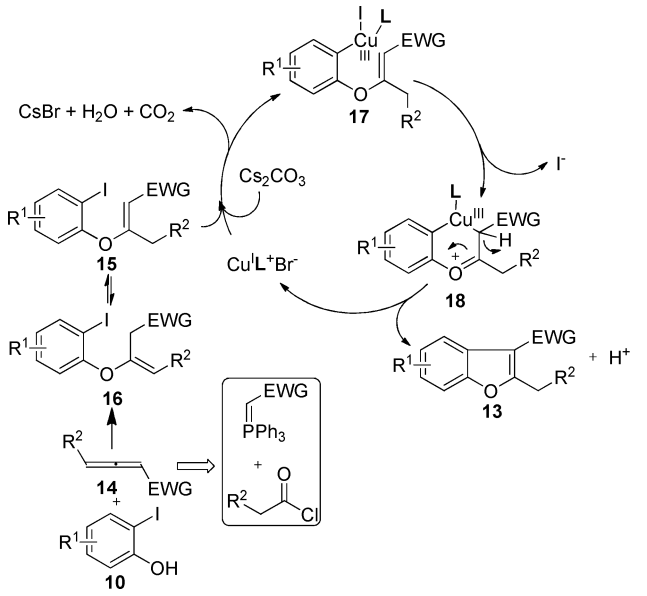
Scheme 4. General Mechanism for the Copper-Catalyzed, One-Pot Cascade Synthesis of Benzofurans



which affords intermediate **18** via an intramolecular annulation. Finally, a typical reductive elimination on **18** leads to the production of benzofuran **13**.

In summary, by employing copper-catalyzed C-arylation as a key transformation, we have established a new synthetic protocol for benzofurans. The synthesis employs simple phosphorus ylides, acyl chlorides, and *o*-iodophenols as starting materials to assemble target products with high diversity and efficiency. In addition to providing a new practical and useful method for the synthesis of 2,3-disubstituted benzofurans, the present work can also guide the design of new reactions using allene-based C−C coupling.

EXPERIMENTAL SECTION

General Procedure for the One-Pot Synthesis of Benzofurans 13. A 25 mL round-bottom flask was charged with phosphorus ylide **11** (0.75 mmol), CH_2Cl_2 (5 mL), and Et_3N (0.5 mmol). A solution of acyl chloride **12** (0.75 mmol) in CH_2Cl_2 (1 mL) was added dropwise with stirring. After an additional 1.5 h of stirring, the CH_2Cl_2 was completely evaporated under reduced pressure. To the residue was added *n*-hexane (3 mL), and the resulting mixture was stirred at rt for an additional 2 h. Subsequently, *o*-iodophenol **10** (0.5 mmol), CuBr (0.075 mmol), 1,10-phenanthroline (0.2 mmol), Cs_2CO_3 (2.0 mmol), 5 Å MS (150 mg), and DMSO (2 mL) were added. The resulting mixture was heated at 90 °C in the presence of a water condenser (sealed with a 1 atm air balloon) for 12 h (TLC). Upon completion (TLC), the reaction mixture was allowed to cool to rt, and H_2O (5 mL) was added. The resulting suspension was extracted with ethyl acetate (3 × 8 mL). The organic phases were combined and dried over Na_2SO_4. After filtration and removal of the solvent at reduced pressure, the residue was subjected to silica gel column chromatography using 60:1 (v/v) petroleum ether/ethyl acetate as the eluent to give the pure product **13**.

*Ethyl 2-Methylbenzofuran-3-carboxylate (**13a**).*[15] Yield 73 mg, 72%; colorless liquid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.96−7.95 (m, 1H), 7.42−7.39 (m, 1H), 7.27−7.25 (m, 2H), 4.41 (q, 2H, J = 7.2 Hz), 2.76 (s, 3H), 1.44 (t, 3H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.7, 163.6, 153.6, 126.2, 124.3, 123.7, 121.7, 110.7, 109.1, 60.2, 14.4 (2C).

*Ethyl 2-Ethylbenzofuran-3-carboxylate (**13b**).* Yield 71 mg, 65%; colorless liquid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.99−7.96 (m, 1H), 7.46−7.43 (m, 1H), 7.30−7.28 (m, 2H), 4.42 (q, 2H, J = 7.6 Hz), 3.21 (q, 2H, J = 7.6 Hz), 1.46 (t, 3H, J = 7.2 Hz), 1.36 (t, 3H, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.4, 164.5, 153.6, 126.3, 124.2, 123.7, 121.9, 110.8, 108.0, 60.2, 21.7, 14.2, 11.9; IR (KBr, cm^{-1}) 2968, 1721, 1449, 1369, 1290, 1221, 1031, 756; ESI-HRMS calcd for $C_{13}H_{15}O_3$ $[M + H]^+$ 219.1021, found 219.1024.

*Ethyl 2-Propylbenzofuran-3-carboxylate (**13c**).* Yield 80 mg, 69%; colorless liquid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.90−7.88 (m, 1H), 7.35−7.33 (m, 1H), 7.22−7.17 (m, 2H), 4.32 (q, 2H, J = 7.2 Hz), 3.08 (t, 2H, J = 7.6 Hz), 1.76−1.71 (m, 2H), 1.36 (t, 3H, J = 7.2 Hz), 0.93 (t, 3H, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.4, 164.5, 153.6, 126.3, 124.3, 123.7, 121.9, 110.8, 108.7, 60.2, 30.0, 21.4, 14.4, 13.9; IR (KBr, cm^{-1}) 2962, 1716, 1466, 1377, 1284, 1210, 1074, 751; ESI-HRMS calcd for $C_{14}H_{17}O_3$ $[M + H]^+$ 233.1178, found 233.1184.

*Methyl 2-Ethylbenzofuran-3-carboxylate (**13d**).* Yield 71 mg, 70%; colorless liquid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.89−7.87 (m, 1H), 7.37−7.36 (m, 1H), 7.22−7.20 (m, 2H), 3.87 (s, 3H), 3.13 (q, 2H, J = 7.2 Hz), 1.28 (t, 3H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.6, 164.9, 153.7, 126.2, 124.3, 123.7, 121.9, 110.9, 107.9, 51.4, 21.7, 11.9; IR (KBr, cm^{-1}) 2971, 1725, 1452, 1389, 1227, 1109, 813; ESI-HRMS calcd for $C_{12}H_{12}NaO_3$ $[M + Na]^+$ 227.0684, found 227.0686.

*Methyl 2-Propylbenzofuran-3-carboxylate (**13e**).* Yield 73 mg, 67%; colorless liquid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.97−7.96 (m, 1H), 7.45−7.43 (m, 1H), 7.30−7.28 (m, 2H), 3.95 (s, 3H), 3.17 (t, 2H, J = 7.6 Hz), 1.84−1.79 (m, 2H), 1.01 (t, 3H, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.5, 165.1, 153.6, 126.1, 124.3, 123.7, 121.8, 110.9, 108.5, 51.4, 30.0, 21.3, 13.8; IR (KBr, cm^{-1}) 2973, 1731, 1438, 1381, 1231, 1106, 827; ESI-HRMS calcd for $C_{13}H_{15}O_3$ $[M + H]^+$ 219.1021, found 219.1030.

*tert-Butyl 2-Ethylbenzofuran-3-carboxylate (**13f**).* Yield 85 mg, 69%; colorless liquid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.96−7.94 (m, 1H), 7.43−7.41 (m, 1H), 7.28−7.26 (m, 2H), 3.18 (q, 2H, J = 7.6 Hz), 1.64, (s, 9H), 1.35 (t, 3H, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.9, 163.8, 153.5, 126.5, 124.1, 123.6, 121.8, 110.8, 109.2, 81.0, 28.4, 21.7, 12.2; IR (KBr, cm^{-1}) 2976, 1675, 1439, 1326, 1209, 1108, 786; ESI-HRMS calcd for $C_{15}H_{19}O_3$ $[M + H]^+$ 247.1334, found 247.1331.

*tert-Butyl 2-Propylbenzofuran-3-carboxylate (**13g**).* Yield 105 mg, 81%; colorless liquid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.97−7.95 (m, 1H), 7.43−7.41 (m, 1H), 7.28−7.26 (m, 2H), 3.13 (t, 2H, J = 7.6 Hz), 1.86−1.76 (m, 2H), 1.64 (s, 9H), 1.01 (t, 3H, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.9, 163.8, 153.5, 126.5, 124.1, 123.5, 121.9, 110.8, 109.9, 81.0, 30.0, 28.5, 21.3, 13.7; IR (KBr, cm^{-1}) 2981, 1673, 1424, 1306, 1247, 1121, 785; ESI-HRMS calcd for $C_{16}H_{20}NaO_3$ $[M + Na]^+$ 283.1310, found 283.1304.

*Ethyl 5-tert-Butyl-2-propylbenzofuran-3-carboxylate (**13h**).* Yield 103 mg, 72%; colorless liquid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.02 (s, 1H), 7.35 (s, 2H), 4.41 (q, 2H, J = 7.2 Hz), 3.14 (t, 2H, J = 7.6 Hz), 1.85−1.75 (m, 2H), 1.45 (t, 3H, J = 7.6 Hz), 1.39 (s, 9H), 0.99 (t, 3H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.4, 164.6, 151.9, 146.9, 126.1, 122.1, 118.1, 110.1, 108.7, 60.1, 34.8, 31.8, 30.1, 21.4, 14.1, 13.7; IR (KBr, cm^{-1}) 2923, 1717, 1453, 1362, 1279, 1203, 1069, 768; ESI-HRMS calcd for $C_{18}H_{25}O_3$ $[M + H]^+$ 289.1804, found 289.1807.

*Methyl 5-(tert-Butyl)-2-propylbenzofuran-3-carboxylate (**13i**).* Yield 101 mg, 74%; colorless liquid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.98 (s, 1H), 7.35 (s, 2H), 3.95 (s, 3H), 3.14 (t, 2H, J = 7.2 Hz), 1.82−1.77 (m, 2H), 1.39 (s, 9H), 0.99 (t, 3H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.7, 165.3, 151.9, 146.9, 125.8, 122.2, 118.0, 110.1, 108.6, 51.4, 34.8, 31.8, 30.1, 21.4, 13.8; IR (KBr, cm^{-1}) 2963, 1714, 1447, 1367, 1231, 1113, 813; ESI-HRMS calcd for $C_{17}H_{23}O_3$ $[M + H]^+$ 275.1647, found 275.1652.

*Ethyl 2-Ethyl-5-methylbenzofuran-3-carboxylate (**13j**).* Yield 79 mg, 68%; colorless liquid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.76 (s, 1H), 7.31 (d, 1H, J = 8.4 Hz), 7.08 (d, 1H, J = 8.4 Hz), 4.41 (q, 2H, J = 7.2 Hz), 3.18 (q, 2H, J = 7.2 Hz), 2.46 (s, 3H), 1.44 (t, 3H, J = 7.2 Hz), 1.34 (t, 3H, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.4, 164.6, 152.0, 133.2, 126.4, 125.4, 121.7, 110.3, 107.8, 60.2, 21.8, 21.5, 14.4, 12.1; IR (KBr, cm^{-1}) 2953, 1732, 1445, 1378, 1229, 1106, 787; ESI-HRMS calcd for $C_{14}H_{17}O_3$ $[M + H]^+$ 233.1178, found 233.1180.

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*Ethyl 5-Methyl-2-propylbenzofuran-3-carboxylate (**13k**).* Yield 85 mg, 69%; colorless liquid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.76 (s, 1H), 7.31 (d, 1H, J = 8.4 Hz), 7.08 (dd, 1H, J = 1.2 Hz, J = 8.4 Hz), 4.41 (q, 2H, J = 7.2 Hz), 3.14 (t, 2H, J = 7.6 Hz), 2.46 (s, 3H), 1.85−1.76 (m, 2H), 1.45 (t, 3H, J = 7.2 Hz), 1.0 (t, 3H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.5, 164.7, 152.1, 133.2, 126.3, 125.4, 121.7, 110.4, 108.4, 60.0, 30.1, 21.5, 21.4, 14.4, 13.8; IR (KBr, cm^{-1}) 2963, 1714, 1463, 1378, 1279, 1075, 763; ESI-HRMS calcd for $C_{15}H_{19}O_3$ $[M + H]^+$ 247.1334, found 247.1338.

*Methyl 5-Methyl-2-propylbenzofuran-3-carboxylate (**13l**).* Yield 88 mg, 76%; colorless liquid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.74 (s, 1H), 7.30 (d, 1H, J = 8.4 Hz), 7.07 (d, 1H, J = 8.0 Hz), 3.94 (s, 3H), 3.14 (t, 2H, J = 7.6 Hz), 2.45 (s, 3H), 1.83−1.77 (m, 2H), 1.00 (t, 3H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.8, 165.3, 152.3, 133.5, 126.4, 125.7, 121.9, 110.6, 108.5, 51.5, 30.3, 21.6, 21.5, 14.0; IR (KBr, cm^{-1}) 2962, 1716, 1443, 1374, 1243, 1115, 812; ESI-HRMS calcd for $C_{14}H_{17}O_3$ $[M + H]^+$ 233.1178, found 233.1179.

*Methyl 5-Chloro-2-propylbenzofuran-3-carboxylate (**13m**).* Yield 104 mg, 83%; colorless liquid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.83−7.82 (m, 1H), 7.25 (d, 1H, J = 8.4 Hz), 7.16−7.15 (m, 1H), 3.86 (s, 3H), 3.06 (t, 2H, J = 7.6 Hz), 1.75−1.69 (m, 2H), 0.92 (t, 3H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.8, 164.3, 152.0, 129.5, 127.5, 124.5, 121.6, 111.8, 108.4, 51.5, 30.0, 21.2, 13.8; IR (KBr, cm^{-1}) 2963, 1719, 1448, 1374, 1241, 1110, 804, 712; ESI-HRMS calcd for $C_{13}H_{14}ClO_3$ $[M + H]^+$ 253.0631, found 253.0640.

*2-Propylbenzofuran-3-carbonitrile (**13n**).* Yield 63 mg, 68%; colorless liquid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.63−7.61 (m, 1H), 7.48 (d, 1H, J = 7.6 Hz), 7.36−7.34 (m, 2H), 2.96 (t, 2H, J = 7.6 Hz), 1.90−1.83 (m, 2H), 1.04 (t, 3H, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.4, 153.7, 126.0, 125.5, 124.3, 120.0, 113.3, 111.5, 91.0, 30.0, 20.9, 13.5; IR (KBr, cm^{-1}) 2977, 2227, 1736, 1433, 1367, 1279, 1201, 753; EI-HRMS calcd for $C_{12}H_{11}NO$ $[M]^+$ 185.0841, found 185.0838.

*5-tert-Butyl-2-isobutylbenzofuran-3-carbonitrile (**13o**).* Yield 75 mg, 59%; colorless liquid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.61 (s, 1H), 7.40 (s, 2H), 2.83 (d, 2H, J = 6.8 Hz), 2.25−2.18 (m, 1H), 1.38 (s, 9H), 1.02 (d, 6H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.0, 152.0, 147.8, 125.6, 123.4, 115.9, 113.8, 110.9, 91.5, 37.0, 34.9, 31.7, 28.2, 22.2; IR (KBr, cm^{-1}) IR (KBr, cm^{-1}) 3423, 2926, 2227, 1637, 1429, 1207, 1109, 779; ESI-HRMS calcd for $C_{17}H_{22}NO$ $[M + H]^+$ 256.1701, found 256.1705.

*(2-Ethylbenzofuran-3-yl)(phenyl)methanone (**13p**).* Yield 86 mg, 69%; colorless liquid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.85 (d, 2H, J = 7.6 Hz), 7.63 (t, 1H, J = 7.2 Hz), 7.53−7.50 (m, 3H), 7.40 (d, 1H, J = 7.6 Hz), 7.33−7.28 (m, 1H), 7.21 (t, 1H, J = 7.6 Hz), 2.92 (q, 2H, J = 7.6 Hz), 1.34 (t, 3H, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 192.1, 166.5, 153.6, 139.4, 132.7, 129.2, 128.4, 127.0, 124.2, 123.7, 121.4, 116.1, 110.8, 21.9, 12.4; IR (KBr, cm^{-1}) 3423, 2926, 1644, 1439, 1271, 1063, 781; ESI-HRMS calcd for $C_{17}H_{15}O_2$ $[M + H]^+$ 251.1072, found 251.1077.

*Phenyl(2-propylbenzofuran-3-yl)methanone (**13q**).* Yield 98 mg, 74%; colorless liquid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.82 (d, 2H, J = 7.2 Hz), 7.61 (t, 1H, J = 7.2 Hz), 7.48 (t, 3H, J = 6.8 Hz), 7.34 (d, 1H, J = 8.0 Hz), 7.26 (d, 1H, J = 8.0 Hz), 7.17 (t, 1H, J = 7.6 Hz), 2.87 (t, 2H, J = 7.6 Hz), 1.83−1.75 (m, 2H), 0.94 (t, 3H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 191.9, 165.5, 153.6, 139.6, 132.6, 129.6, 128.5, 126.9, 124.3, 123.4, 121.3, 116.8, 110.9, 30.0, 21.5, 13.8; IR (KBr, cm^{-1}) 3426, 2924, 1659, 1453, 1276, 1079, 763; ESI-HRMS calcd for $C_{18}H_{17}O_2$ $[M + H]^+$ 265.1229, found 265.1233.

*(2-Isobutylbenzofuran-3-yl)(phenyl)methanone (**13r**).* Yield 87 mg, 63%; colorless liquid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.84 (d, 2H, J = 6.8 Hz), 7.62 (t, 1H, J = 7.2 Hz), 7.50 (t, 3H, J = 7.2 Hz), 7.30 (t, 2H, J = 6.8 Hz), 7.19 (t, 1H, J = 8.0 Hz), 2.85 (d, 2H, J = 7.2 Hz), 2.29−2.18 (m, 1H), 0.96 (d, 6H, J = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 192.1, 164.9, 153.6, 139.4, 132.6, 129.2, 128.5, 126.8, 124.3, 123.4, 121.3, 117.4, 111.0, 36.7, 28.4, 22.4; IR (KBr, cm^{-1}) 3429, 2923, 1639, 1476, 1231, 1096, 796; ESI-HRMS calcd for $C_{19}H_{19}O_2$ $[M + H]^+$ 279.1385, found 279.1381.

*(4-Chlorophenyl)(2-ethylbenzofuran-3-yl)methanone (**13s**).* Yield 98 mg, 69%; colorless liquid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.78 (d, 2H, J = 8.4 Hz), 7.47 (t, 3H, J = 8.8 Hz), 7.34−7.25 (m, 2H), 7.18 (t, 1H, J = 7.6 Hz), 2.92 (q, 2H, J = 7.6 Hz), 1.34 (t, 3H, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 190.5, 166.6, 153.7, 139.0, 137.8, 130.5, 128.8, 126.7, 124.4, 123.5, 121.2, 115.7, 111.0, 21.7, 12.1; IR (KBr, cm^{-1}) 3423, 2926, 1644, 1439, 1271, 1063, 781; ESI-HRMS calcd for $C_{17}H_{14}ClO_2$ $[M + H]^+$ 285.0682, found 285.0673.

*(4-Chlorophenyl)(2-propylbenzofuran-3-yl)methanone (**13t**).* Yield 106 mg, 71%; colorless liquid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.70 (d, 2H, J = 8.4 Hz), 7.40 (t, 3H, J = 8.8 Hz), 7.22 (t, 2H, J = 7.6 Hz), 7.12 (t, 1H, J = 7.2 Hz), 2.82 (t, 2H, J = 7.6 Hz), 1.73 (m, 2H), 0.87 (t, 3H, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 190.7, 165.6, 153.7, 139.1, 137.6, 130.6, 128.8, 126.7, 124.4, 123.6, 121.1, 116.5, 111.1, 30.1, 21.2, 13.5; IR (KBr, cm^{-1}) 3428, 2931, 1662, 1424, 1217, 1103, 789, 717; ESI-HRMS calcd for $C_{18}H_{16}ClO_2$ $[M + H]^+$ 299.0839, found 299.0836.

*Ethyl 3-(2-Iodophenoxy)but-2-enoate (**15a**).* Yield 65 mg, 39%; pale-yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, 1H, J = 8.0 Hz), 7.34 (t, 1H, J = 8.0 Hz), 7.04 (d, 1H, J = 8.0 Hz), 6.94 (t, 1H, J = 8.0 Hz), 4.74 (s, 1H), 4.09 (q, 2H, J = 6.8 Hz), 2.54 (s, 3H), 1.19 (t, 3H, J = 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.1, 167.2, 153.2, 140.0, 129.9, 127.4, 122.7, 96.4, 90.4, 59.6, 18.3, 14.3; ESI-HRMS calcd for $C_{12}H_{14}IO_3$ $[M + H]^+$ 332.9988, found 332.9980.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

General experimental information and ^{1}H and ^{13}C NMR spectra of all products. 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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