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Palladium-catalyzed intermolecular coupling of 2-haloallylic acetates with simple phenols, and sequential formation of benzofuran derivatives through the intramolecular cyclization

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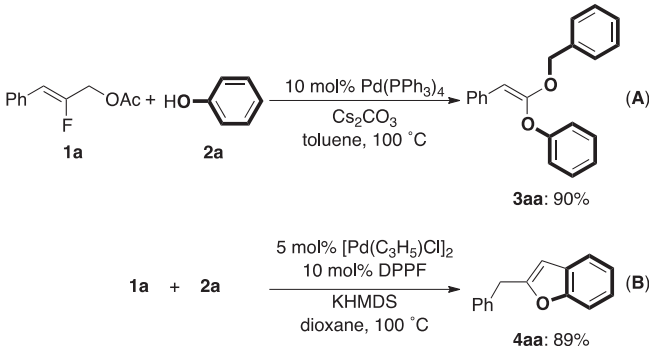
ABSTRACT

We accomplished the synthesis of 2-substituted benzofuran derivatives by the palladium-catalyzed reaction of 2-haloallylic acetates with simple phenols in the presence of a base. The reaction proceeded through the intermolecular attack of the nucleophile on the central carbon atom of the π-allyl group, carbon-halogen bond cleavage, and sequential intramolecular cyclization.

1. Introduction

Benzofuran is an important scaffold for several biologically-active organic compounds, and the development of an efficient method to construct it and its derivatives is one of the major topics in organic synthesis. Although several methods have been reported for the synthesis of benzofuran derivatives involving a transition metal catalyzed reaction,[1] most of them are achieved by the reaction of prefunctionalized substrates,[2–4] while there are only limited examples of the construction of benzofuran derivatives by intermolecular coupling using simple phenols and a sequential cyclization reaction.[5] To the best our knowledge, β-keto esters,[5a] alkynes,[5b-e] and alkenes[5f] were used as the coupling partner for the transition metal catalyzed construction of benzofuran derivatives with simple phenols. However, there was no example of the construction of benzofuran derivatives by the transition metal catalyzed reaction of allylic esters with simple phenols. On the other hand, we have studied the palladium-catalyzed reaction of fluorine-containing allylic esters,[6–8] which includes the double etherification of 2-fluoroallylic acetates with phenols (Scheme 1, A),[6b] and during the course of the study, we also examined the $[Pd(C_3H_5)Cl]_2$/DPPP catalyzed reaction of 2-fluoroallylic acetates with simple phenols, and succeeded in obtaining 2-benzyl benzofuran derivatives instead of doubly phenoxylated products (Scheme 1, B).[6d] Based on our previous study of 2-fluoroallylic acetates, as an extension of our reaction system, we investigated the reaction of 2-chloro- or 2-bromoallylic acetate with phenols, and confirmed the formation of the 2-benzyl benzofuran derivatives. Therefore, we now report our results of the palladium-catalyzed reaction of 2-haloallylic acetates with simple phenols, and the synthesis of 2-



Scheme 1. Our previous study of the palladium-catalyzed reactions of 2-fluoroallylic acetate **1a** with phenol (**2a**).

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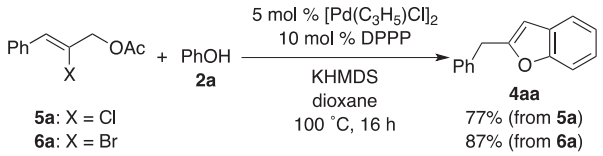
0040-4020/



Scheme 2. Palladium-catalyzed reactions of 2-haloallylic acetates **5a** and **6a** with **2a**.

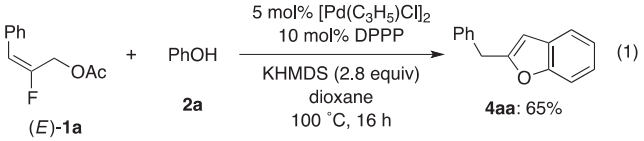
substituted benzofuran derivatives.

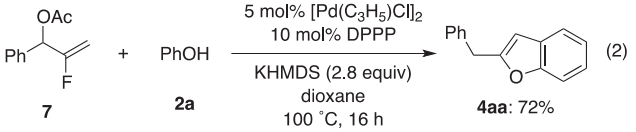
2. Results and discussion

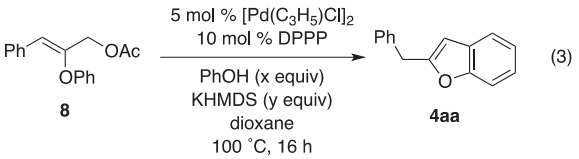
We first tried the reactions of 2-chloro- or 2-bromoallylic acetate **5a** or **6a** with phenol (**2a**) using the $[Pd(C_3H_5)Cl]_2$/DPPP catalyst, which was an effective catalyst for the synthesis of 2-substituted benzofuran derivatives from 2-fluoroallylic acetates **1a** with **2a** (Scheme 1, B),[6d] and confirmed that the reactions afforded the intended benzofuran derivative **4aa** in 77% and 87% yields, respectively (Scheme 2). These initial results indicated that the three types of 2-haloallylic acetates produced the same products, which is a 2-substituted benzofuran derivative, in almost similar yields.

Based on these initial results, we investigated the reactions of three types of 2-haloallylic acetates, such as the 2-fluoro, 2-chloro, and 2-bromoallylic acetates **1a** (X = F), **5a** (X = Cl), and **6a** (X = Br) with several phenols **2b**–**q**, and the results are summarized in Table 1. For example, the reactions of **1a**, **5a**, and **6a** with 4-methylphenol (**2b**) (5 equic.) with $[Pd(C_3H_5)Cl]_2$/DPPP and KHMDS (2.8 equiv.) in dioxane at 100 °C for 16 h provided **4ab** in 72%, 77%, and 72% yields, respectively. The reactions of the three 2-haloallylic acetates **1a**, **5a**, and **6a** with other phenols **2c**–**e** also produced intended products **4ac**–**ae** in similar yields, respectively. We also confirmed that the cyclization mainly occurred at the sterically-less-hindered site during the reaction of the 3-substituted phenols **2e**. The reactions with 4-methoxyphenol (**2f**) gave the desired product **4af** in the range of 74–88% yields. As we previously reported, the reaction of **1a** with 3-methoxyphenol (**2g**) by the $[Pd(C_3H_5)Cl]_2$/DPPP catalyst resulted in a 58% yield, but the yield increased to 76% when the $[Pd(C_3H_5)Cl]_2$ was changed to $Pd(OAc)_2$.[6d] However, for the reactions of 2-chloro- or 2-bromoallylic acetate **5a** and **6a** with **2g**, we confirmed that the yields did not increase even when the $Pd(OAc)_2$ was used,[9] therefore, we indicated the results from the reactions using $[Pd(C_3H_5)Cl]_2$ in Table 1. The three reactions of **1a**, **5a** and **6a** with **2h** produced the intended benzofuran derivative **4ah** in almost same yields (76–78%), respectively. Again, although changing the palladium catalyst from $[Pd(C_3H_5)Cl]_2$ to $Pd(OAc)_2$ was needed for the reaction of 2-fluoroallylic acetate **1a**, the reactions of 2-haloallylic acetates with phenols **2i**–**n**, which possess electron-withdrawing groups on the benzene ring, produced intended 2-substituted benzofuran derivatives in moderate to good yields. On the other hand, the reaction of **1a** with 4-cyanophenol (**2o**) gave **4ao** in 91% under modified reaction conditions ($Pd(OAc)_2$ and Cs_2CO_3 were used instead of $[Pd(C_3H_5)Cl]_2$ and KHMDS), but the reactions of **5a** and **6a** resulted in low yields due to the decomposition of the 2-haloallylic acetates. We succeeded in obtaining **4ap** by the reaction of 2-fluoroallylic acetate **1a** with 4-nitrophenol (**2p**) (3 equiv.) in 80% using the $Pd(OAc)_2$/DPPP catalyst, but the reactions of **5a** and **6a** did not produce any product. On the other hand, we examined the reaction of three types of 2-haloallylic acetates with 2-naphthol (**2q**), and obtained the desired product **4aq** in 73–90% yields, respectively.

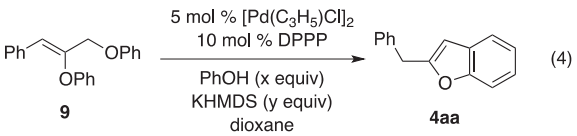
We next demonstrated the reactions of the 3-aryl-2-haloallylic acetates **1b**–**j**, **5b**–**j**, and **6b**–**j** with phenol (**2a**), and the results are summarized in Table 2. The 2-fluoroallylic acetate **1b**, which possesses the 4-methoxyphenyl group at the C-3 position, gave the corresponding benzofuran derivative **4ba** in 76% yield. On the other hand, the reactions of the 2-chloro- or 2-bromoallylic acetates **5b** and **6b** with **2a** produced the same products **4ba**, but the yields were slightly lower. This trend in the yield was also observed in the reaction of **1c**, **5c**, and **6c** with **2a**. For the reactions of the 4-trifluoromethylphenyl group-substituted 2-haloallylic acetates **1d**, **5d**, and **6d** with **2a**, the best yield was obtained by the reaction of the 2-chloroallylic acetate **5d**. The allylic acetates **1e**, **5e**, and **6e** produced the intended product **4ea** in the range of 59–72% yields. We also examined the reactions of the 1-naphthyl or 2-tolyl group substituted allylic acetate, and obtained the desired products **4fa** or **4ga** in acceptable yields, respectively. We next investigated the reaction of the 3-pyridyl group substituted 2-fluoroallylic acetate **1h** and confirmed that the reaction provided the benzofuran derivative **4ha** in 75% yield, but the 2-chloro or 2-bromoallylic acetates **5h** and **6h** did not afford any intended product and we observed the decomposition of the allylic substrates. However, we succeeded in obtaining the desired products **4ia** in the range of 66–76% yields for the reactions of the 2-thienyl group possessing allylic acetates **1i**, **5i**, and **6i** with **2a**. Furthermore, we confirmed that the alkyl group-substituted 2-fluoroallylic acetates **1j** also provide **4ja** in 60% yield, but the reactions of **5j** and **6j** resulted in low yields.







PhOH (x equiv)	KHMDS (y equiv)	yield (%) of **4aa**
0	0	<2
1.0	1.0	66



PhOH (x equiv)	KHMDS (y equiv)	yield (%) of **4aa**
1.0	1.0	56
3	2.8	71

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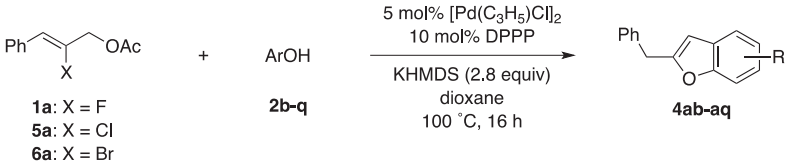
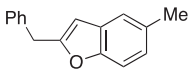
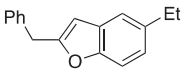
Table 1
Palladium-catalyzed reaction of 2-haloallylic acetates **1a**, **5a**, and **6a** with phenols **2b-q**.[a,b,c]

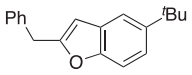




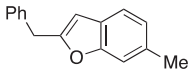
4ab
72% (from **1a**)
77% (from **5a**)
72% (from **6a**)



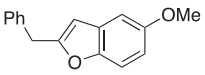
4ac
59% (from **1a**)
68% (from **5a**)
73% (from **6a**)



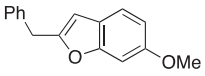
4ad
59% (from **1a**)
62% (from **5a**)
65% (from **6a**)



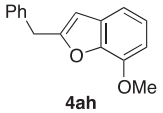
4ae
60% (97 : 3) (from **1a**)
63% (98 : 2) (from **5a**)
61% (97 : 3) (from **6a**)



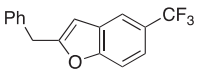
4af
88% (from **1a**)
74% (from **5a**)
79% (from **6a**)



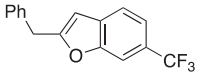
4ag
76% (76 : 24) (from **1a**)[d]
61% (75 : 25) (from **5a**)
54% (76 : 24) (from **6a**)



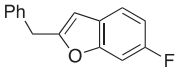
4ah
77% (from **1a**)
78% (from **5a**)
76% (from **6a**)



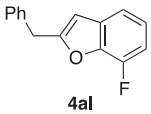
4ai
83% (from **1a**)[d]
59% (from **5a**)
54% (from **6a**)



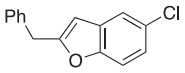
4aj
81% (>98 : 2) (from **1a**)
77% (>98 : 2) (from **5a**)
76% (>98 : 2) (from **6a**)



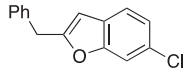
4ak
96% (85 : 15) (from **1a**)
75% (86 : 14) (from **5a**)
77% (84 : 16) (from **6a**)



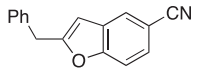
4al
90% (from **1a**)[d]
74% (from **5a**)
70% (from **6a**)



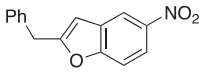
4am
91% (from **1a**)[d]
84% (from **5a**)
81% (from **6a**)



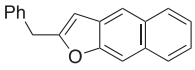
4an
79% (95 : 5) (from **1a**)[d]
63% (96 : 4) (from **5a**)
66% (95 : 5) (from **6a**)



4ao
91% (from **1a**)[d,e]
22% (from **5a**)
23% (from **6a**)



4ap
80% (from **1a**)[d,e,f]
0% (from **5a**)
0% (from **6a**)



4aq
90% (67 : 33) (from **1a**)
79% (54 : 46) (from **5a**)
73% (13 : 87) (from **6a**)

[a]Reaction conditions: 2-haloallylic acetate (0.25 mmol), **2b–q** (1.25 mmol), $[Pd(C_3H_5)]Cl]_2$ (5 mol%), DPPP (10 mol%), and KHMDS (0.7 mmol, 1.4 mL of 0.5 M in toluene) in dioxane (1.3 mL) at 100 °C, for 16 h.

[b]Yields are isolated yields after silica gel column chromatography.

[c]Regioselectivity ratio was determined by ^{1}H NMR of crude materials, and shown in parentheses.

[d]$Pd(OAc)_2$ (10 mol%) was used instead of $[Pd(C_3H_5)Cl]_2$ (5 mol%).

[e]Cs_2CO_3 was used instead of KHMDS.

[f]3 equiv. of **2p** were used.

In support of the possible reaction mechanism, we next attempted the reactions of the (*E*)-2-fluoroallylic acetate ((*E*)-**1a)** and 2-fluoro-1-phenylallylic acetate (**7**) with **2a** under the optimized reaction conditions, and confirmed that both reactions provided the 2-substituted benzofuran **4aa**, which is the same product from the reaction of (*Z*)-**1a**, in 65% and 72% yields, respectively (eqs. 1 and 2). These results suggest that these three reactions of the stereoisomeric allylic acetates, (*Z*)-**1a**, (*E*)-**1a**, and **7**, proceeded through the same reaction pathway, which includes a 2-fluoro-π-allylpalladium intermediate. Furthermore, we examined the reaction of the 2-phenoxyallylic acetate **8**, and confirmed the formation of **4aa** (66%) in the presence of additional phenol (**2a**) and KHMDS (eq. 3). This result indicated that the 2-phenoxy-π-allylpalladium, which was produced by the oxidative addition of **8** to Pd(0), is an intermediate for the formation of the 2-substituted benzofuran **4aa**. On the other hand, as we previously reported, the palladium-catalyzed reaction of the 2-haloallylic acetates with phenols provided doubly-substituted products when the appropriate palladium catalyst ($Pd(PPh_3)_4$) was used.[6b] Therefore, we also investigated the reaction of the doubly-substituted products **9** by the $[Pd(C_3H_5)Cl]_2$/DPPP catalyst, and confirmed that the formation of the 2-substituted benzofuran **4aa** in the presence of KHMDS and additional phenol (**2a**) (eq. 3). This result suggested the possibility that the present reaction initially produced the doubly-substituted product **9**, and the further reaction of **9** provides the 2-substituted benzofuran **4aa**. This proposed reaction pathway supports the reason that the present reaction requires an excess amount of the phenols.

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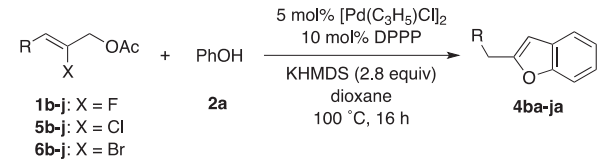
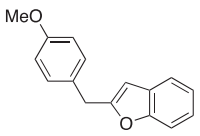
Table 2
Palladium-catalyzed reaction of 2-haloallylic acetates with phenol (**2a**).[a].



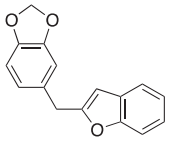
1b-j: X = F
5b-j: X = Cl
6b-j: X = Br

2a

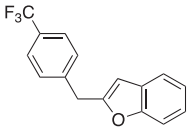
4ba-ja



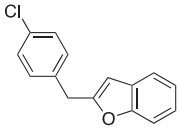
4ba
76% (from **1b**)
68% (from **5b**)
52% (from **6b**)



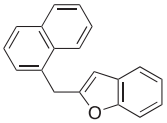
4ca
82% (from **1c**)
61% (from **5c**)
54% (from **6c**)



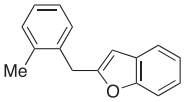
4da
72% (from **1d**)
83% (from **5d**)
74% (from **6d**)



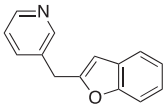
4ea
72% (from **1e**)
65% (from **5e**)
59% (from **6d**)



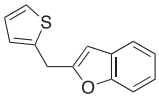
4fa
73% (from **1f**)
74% (from **5f**)
63% (from **6f**)



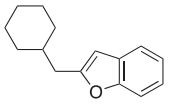
4ga
60% (from **1g**)
67% (from **5g**)
73% (from **6g**)



4ha
75% (from**1h**)
0% (from **5h**)
0% (from **6h**)



4ia
76% (from **1i**)
66% (from **5i**)
67% (from **6i**)



4ja
60% (from **1j**)[b]
21% (from **5j**)
19% (from **6j**)

[a]Yields are isolated yields after silica gel column chromatography.

[b]$Pd(OAc)_2$ (10 mol%) and $(4\text{-}MeOC_6H_4)_2P(CH_2)_3P(4\text{-}MeOC_6H_4)_2$ were used at 80 °C.

Based on these observations, we propose the possible reaction pathway for the formation of 2-substituted benzofurans by the palladium-catalyzed reaction of 2-haloallylic acetates with phenols in Scheme 3. The *syn*-2-halo-π-allylpalladium intermediate (*syn*-**A**) was formed by the oxidative addition of the (*Z*)-**1**, (*Z*)-**5**, and (*Z*)-**6** to Pd(0), and the allylic acetate **7** also provided *syn*-**A** as the major 2-halo-π-allylpalladium intermediate.[10] On the other hand, (*E*)-**1** mainly afforded the *anti*-2-halo-π-allylpalladium intermediate (*anti*-**A**), but the *anti*-**A** isomerizes to the more stable *syn*-**A** through the π-σ-π isomerization of the π-allylpalladium complex. The attack of the phenoxide anion on the central carbon atom (C-2) of the π-allyl group of *syn*-**A** produced the halogenated palladacyclobutane **B** followed by the carbon-halogen bond cleavage, which produces the 2-substituted-π-allylpalladium complex **C**. The second attack of the phenoxide anion on the C-3 carbon atom of the π-allyl group provides doubly-substituted products **9**, but the oxidative addition of **9** to Pd(0) regenerated the complex **C**. Therefore, when the intermolecular cyclization of complex **C** occurred, the desired 2-substituted benzofuran derivative **4** was obtained through the initial formation of the 2,3-dihydrobenzofuran analogue and it isomerized to the thermodynamically-stable benzofuran.

3. Conclusion

In summary, we demonstrated the palladium-catalyzed reactions of the 2-haloallylic acetates with phenols, and succeeded in obtaining the 2-substituted benzofuran derivatives through the intermolecular coupling, carbon-halogen bond cleavage, and sequential intramolecular cyclization. Further studies of the mechanistic details and development of other reactions with different nucleophiles are currently underway in our group.

4. Experimental section

4.1. General

All manipulations were carried out under a nitrogen atmosphere. NMR spectra were recorded on a 270 MHz (for ^1H), 67.5 or 125 MHz (for ^{13}C), and 470 MHz (for ^{19}F). Chemical shifts are reported in δ ppm referenced to an internal $SiMe_4$ standard for ^1H NMR and an internal C_6F_6 standard for ^{19}F NMR. Residual chloroform (δ 77.0 for ^{13}C) was used as internal reference for ^{13}C NMR. All NMR spectra were recorded in $CDCl_3$ at 25 °C. The NMR yields were determined by ^1H NMR using an internal standard (trioxane).

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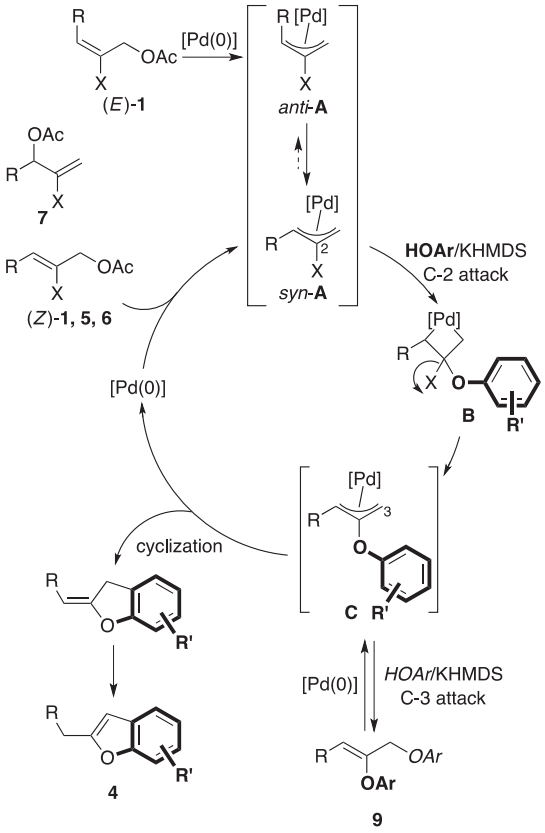

Scheme 3. A possible reaction mechanism.

Allylic acetates **1a**–**j**,[6a] **5a**,[11] **5b**,[12] and **9**[6b] were prepared according to the literature. Allylic acetate **7** was prepared by the reaction of corresponding allylic alcohol with acetic anhydride.[13] Allylic acetates (*E*)-**1a** and **8** were prepared by the acetylation of corresponding alcohols, which were obtained by the reduction of esters.[14,15] Other 2-haloallylic acetates were prepared by the acetylation of corresponding alcohols, which were easily prepared by the sequence of (1) reaction of benzaldehyde with α-halophosphonium ylide in DCM, and (2) reduction with DIBAL.[16]

*4.2. General procedure for the palladium-catalyzed reaction of 2-fluoroallylic acetates 1a with phenols (**2a**)*

A typical procedure is given for the reaction of 2-fluorocinnamyl acetate (**1a**) (Scheme 1, A). To a solution of $[Pd(C_3H_5)Cl]_2$ (4.6 mg, 0.0125 mmol), DPPP (10.3 mg, 0.025 mmol), phenol (**2a**) (118 mg 1.25 mmol), and (*Z*)-2-fluoro-3-phenylallyl acetate (**1a**) (49 mg, 0.25 mmol) in dioxane (1.3 mL) was slowly added KHMDS (0.7 mmol, 1.4 mL of 0.5 M in toluene) at room temperature, then stirred at 100 °C for 16 h. The reaction mixture was quenched with 2 N HCl, and extracted with diethyl ether. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane/EtOAc = 99/1) to give 46 mg (89%) of **4aa**.

*4.2.1. 2-Benzylbenzofuran (**4aa**).*[4b]

Colorless oil. ^{1}H NMR (270 MHz, $CDCl_3$): δ 4.11 (s, 2H), 6.37–6.38 (m, 1H), 7.16–7.48 (m, 9H). ^{13}C NMR (67.5 MHz, $CDCl_3$): δ 35.0, 103.3, 110.9, 120.4, 122.5, 123.4, 126.7, 128.6, 128.8, 128.9, 137.2, 154.9, 157.8. IR (neat) 3030, 2906, 1601, 1585, 1495, 1454, 1254, 1164, 954, 794, 750, 704 cm^{-1}.

*4.2.2. 2-Benzyl-5-methylbenzofuran (**4ab**).*[6d]

Colorless oil. ^{1}H NMR (270 MHz, $CDCl_3$): δ 2.40 (s, 3H), 4.09 (s, 2H), 6.30 (s, 1H), 7.00 (dd, *J* = 4.2, 1.6 Hz, 1H), 7.21–7.35 (m, 7H). ^{13}C NMR (67.5 MHz, $CDCl_3$): δ 21.3, 35.0, 103.1, 110.4, 120.3, 124.5, 126.7 (2C), 128.6, 128.9, 131.9, 137.3, 153.3, 157.8. IR (neat) 3029, 2919, 1599, 1496, 1474, 1454, 1264, 1203, 955, 798, 704 cm^{-1}. HRMS (ESI): *m/z*: calcd for [M] $C_{16}H_{14}O$ 222.1045, found 222.1073.

*4.2.3. 2-Benzyl-5-ethylbenzofuran (**4ac**).*[6d]

Colorless oil. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.25 (t, *J* = 7.6 Hz, 3H), 2.70 (q, *J* = 7.6 Hz, 2H), 4.09 (s, 2H), 6.31–6.32 (m, 1H), 7.04 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.21–7.35 (m, 7H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 16.4, 28.8, 35.0, 103.2, 110.5, 119.1, 123.5, 126.7, 128.5, 128.7, 128.8, 137.3, 138.6, 153.5, 157.8. IR (neat) 3029, 2963, 1599, 1496, 1472, 1454, 1264, 1202, 955, 810, 704 cm^{-1}. HRMS (ESI): *m/z*: calcd for [M] $C_{17}H_{16}O$ 236.1201, found 236.1219.

*4.2.4. 2-Benzyl-5-tert-butylbenzofuran (**4ad**).*[2o]

Colorless oil. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.35 (s, 9H), 4.09 (s, 2H), 6.34–6.35 (m, 1H), 7.20–7.34 (m, 7H), 7.47 (d, *J* = 1.6 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 31.9, 34.6, 35.0, 103.5, 110.2, 116.7, 121.2, 126.7, 128.4, 128.5, 128.8, 137.4, 145.5, 153.2, 157.8. IR (neat) 3030, 2962, 1600, 1477, 1200, 1124, 955, 809, 703 cm^{-1}.

*4.2.5. 2-Benzyl-6-methylbenzofuran (**4ae**).*[2o]

Colorless oil. ^{1}H NMR (270 MHz, $CDCl_3$): δ 2.40 (s, 3H), 4.04 (s, 2H), 6.27–6.28 (m, 1H), 6.95–6.99 (m, 1H), 7.19–7.32 (m, 7H). Selected ^{1}H NMR of minor isomer ***4ae'***: δ 2.42 (s, 3H), 4.07 (s, 2H), 6.33–6.34 (m, 1H), aromatic region overlaps with major isomer. ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.6, 34.9, 103.1, 111.2, 119.8, 123.8, 126.2, 126.6, 128.5, 128.8, 133.5, 137.4, 155.4, 157.1. IR (neat) 3030, 2920, 1730, 1600, 1496, 1454, 1265, 1118, 958, 814, 704, 600 cm^{-1}. HRMS (ESI): *m/z*: calcd for [M] $C_{16}H_{14}O$ 222.1045, found 222.1018.

*4.2.6. 2-Benzyl-5-methoxybenzofuran (**4af**).*[2o]

Pale yellow oil. ^{1}H NMR (270 MHz, $CDCl_3$): δ 3.76 (s, 3H), 4.04 (s, 2H), 6.27 (m, 1H), 6.79 (dd, *J* = 8.9, 2.4 Hz, 1H), 6.91 (d, *J* = 2.4 Hz, 1H), 7.16–7.33 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 35.0, 55.8, 103.3, 103.5, 111.2, 111.7, 126.7, 128.5, 128.8, 129.3, 137.2, 149.9, 155.8, 158.6. IR (neat) 3029, 2949, 2832, 1602, 1475, 1205, 1168, 1031, 956, 769, 706 cm^{-1}.

*4.2.7. 2-Benzyl-6-methoxybenzofuran (**4ag**).*[4b]

Pale yellow oil. ^{1}H NMR (270 MHz, $CDCl_3$): δ 3.74 (s, 3H), 4.02 (s, 2H), 6.25–6.26 (m, 1H), 6.79 (dd, 8.6, 2.4 Hz, 1H), 6.93 (d, *J* = 2.4 Hz, 1H), 7.18–7.32 (m, 6H). Selected ^{1}H NMR of minor isomer ***4ag'***: δ 3.83 (s, 3H), 4.03 (s, 2H), 6.44–6.45 (m, 1H), 6.57 (dd, *J* = 7.6, 1.1 Hz), 7.01–7.04 (m, 1H), 7.10 (dd, *J* = 8.6, 7.6 Hz, 1H), aromatic region overlaps with major isomer. ^{13}C NMR (125 MHz, $CDCl_3$): δ 34.8, 55.5, 95.8, 103.0, 111.2, 120.3, 122.0, 126.6, 128.5, 128.8, 137.4, 155.8, 156.7, 157.3. IR (neat) 3029, 2941, 2834, 1627, 1492, 1438, 1278, 1149, 1107, 704 cm^{-1}.

*4.2.8. 2-Benzyl-7-methoxybenzofuran (**4ah**).*[4b]

Pale yellow oil. ^{1}H NMR (270 MHz, $CDCl_3$): δ 3.98 (s, 3H), 4.13 (s, 2H), 6.31 (s, 1H), 6.72 (dd, *J* = 6.9, 2.2 Hz, 1H), 7.04–7.13 (m, 2H), 7.21–7.35 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 34.8, 55.8, 103.6, 105.7, 112.8, 123.1, 126.6, 128.5, 128.7, 130.4, 137.1, 143.9, 144.9, 158.0. IR (neat) 3029, 2940, 2838, 1601, 1493, 1437, 1272, 1209, 1094, 953, 731, 700 cm^{-1}.

*4.2.9. 2-Benzyl-5-(trifluoromethyl)benzofuran (**4ai**).*[6d]

Colorless oil. ^{1}H NMR (270 MHz, $CDCl_3$): δ 4.13 (s, 2H), 6.45 (s, 1H), 7.25–7.38 (m, 5H), 7.48 (s, 2H), 7.76 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 34.9, 103.5, 111.2, 118.0 (q, J_{CF} = 4.4 Hz), 120.6 (q,

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J_{CF} = 3.6 Hz), 124.8 (q, 270.3 Hz), 125.2 (q, J_{CF} = 32.4 Hz), 127.0, 128.7, 128.9 (2C), 136.6, 156.3, 159.9. ^{19}F NMR (470 MHz, $CDCl_3$): δ 101.0 (s, 3F). IR (neat) 3032, 1704, 1597, 1496, 1448, 1331, 1120, 891, 818, 706, 661 cm^{-1}. HRMS (ESI): *m/z*: calcd for $[M+H]^+$ $C_{16}H_{12}F_3O$ 277.0840, found 277.0859.

4.2.10. 2-Benzyl-6-(trifluoromethyl)benzofuran (**4aj**).[6d]

Colorless oil. ^{1}H NMR (270 MHz, $CDCl_3$): δ 4.13 (s, 2H), 6.42 (s, 1H), 7.24–7.37 (m, 5H), 7.44 (d, 8.6 Hz, 1H), 7.54 (d, 8.6 Hz, 1H), 7.67 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 35.0, 103.3, 108.4 (q, J_{CF} = 4.0 Hz), 119.5 (q, J_{CF} = 3.6 Hz), 120.7, 124.7 (q, J_{CF} = 270.3 Hz), 125.7 (q, J_{CF} = 32.3 Hz), 127.0, 128.7, 128.9, 131.9, 136.6, 154.0, 160.9. ^{19}F NMR (470 MHz, $CDCl_3$): δ 101.1 (s, 3F). IR (neat) 3066, 3032, 1599, 1496, 1435, 1328, 1121, 1049, 956, 831, 707 cm^{-1}. HRMS (ESI): *m/z*: calcd for [M] $C_{16}H_{11}F_3O$ 276.0762, found 276.0771.

4.2.11. 2-Benzyl-6-fluorobenzofuran (**4ak**).[6d]

Colorless oil. ^{1}H NMR (270 MHz, $CDCl_3$): δ 4.11 (s, 2H), 6.47 (s, 1H), 6.84–6.90 (m, 1H), 7.10–7.37 (m, 7H). Selected ^{1}H NMR of minor isomer **4ak'**: δ 4.03 (s, 2H), 6.27–6.28 (m, 1H), aromatic region overlaps with major isomer. ^{13}C NMR (125 MHz, $CDCl_3$): δ 34.9, 99.5, 107.1 (d, J_{CF} = 4.8 Hz), 108.0, 108.2, 117.7 (d, J_{CF} = 22.8 Hz), 123.8 (d, J_{CF} = 8.3 Hz), 126.9, 128.8 (d, J_{CF} = 26.1 Hz), 136.8, 155.5 (d, J_{CF} = 246.9 Hz), 156.8 (d, J_{CF} = 13.8 Hz), 157.8. ^{19}F NMR (470 MHz, $CDCl_3$): δ 41.1 (m, 1F). IR (neat) 3031, 1590, 1494, 1437, 1267, 1241, 1026, 772, 732, 700 cm^{-1}. HRMS (ESI): *m/z*: calcd for [M] $C_{15}H_{11}FO$ 226.0794, found 226.0823.

4.2.12. 2-Benzyl-7-fluorobenzofuran (**4al**).[6d]

Colorless oil. ^{1}H NMR (270 MHz, $CDCl_3$): δ 4.02 (s, 2H), 6.27–6.29 (m, 1H), 6.84–6.91 (m, 1H), 6.96–7.05 (m, 1H), 7.12–7.29 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 34.7, 103.7 (d, J_{CF} = 2.4 Hz), 109.7 (d, J_{CF} = 15.5 Hz), 116.0 (d, J_{CF} = 4.8 Hz), 123.0 (d, J_{CF} = 6.0 Hz), 126.8, 128.6, 128.8, 132.3 (d, J_{CF} = 3.5 Hz), 136.7, 141.7 (d, J_{CF} = 10.8 Hz), 147.7 (d, J_{CF} = 246.8 Hz), 159.0. ^{19}F NMR (470 MHz, $CDCl_3$): δ 24.1 (m, 1F). IR (neat) 3030, 1633, 1600, 1490, 1442, 1255, 1206, 1041, 949, 729, 699 cm^{-1}. HRMS (ESI): *m/z*: calcd for [M] $C_{15}H_{11}FO$ 226.0794, found 226.0815.

4.2.13. 2-Benzyl-5-chlorobenzofuran (**4am**).[2o]

Colorless oil. ^{1}H NMR (270 MHz, $CDCl_3$): δ 4.10 (s, 2H), 6.320–6.323 (m, 1H), 7.14–7.18 (m, 1H), 7.24–7.37 (m, 6H), 7.42–7.43 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 34.9, 103.0, 111.8, 120.0, 123.5, 126.9, 128.0, 128.7, 128.9, 130.1, 136.7, 153.3, 159.4. IR (neat) 3064, 3030, 1731, 1598, 1467, 1423, 1280, 934, 817, 705, 598 cm^{-1}.

4.2.14. 2-Benzyl-6-chlorobenzofuran (**4an**).[6d]

Colorless oil. ^{1}H NMR (270 MHz, $CDCl_3$): δ 4.03 (s, 2H), 6.28 (s, 1H), 7.10–7.15 (m, 1H), 7.20–7.31 (m, 6H), 7.37 (s, 1H). Selected ^{1}H NMR of minor isomer **4an'**: δ 4.05 (s, 2H), 6.44 (s, 1H), aromatic region overlaps with major isomer. ^{13}C NMR (125 MHz, $CDCl_3$): δ 34.9, 103.0, 111.8, 120.0, 123.5, 126.9, 128.0, 128.6, 128.8, 130.1, 136.7, 153.3, 159.4. IR (neat) 3062, 3030, 2905, 1732, 1597, 1454, 1259, 1190, 1060, 954, 802, 704 cm^{-1}. HRMS (ESI): *m/z*: calcd for $[M+Na]^+$ $C_{15}H_{12}ClNaO$ 265.0396, found 265.0422.

4.2.15. 2-Benzyl-5-cyanobenzofuran (**4ao**).[6d]

White solid. mp. 90–91 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ 4.13 (s, 2H), 6.43 (s, 1H), 7.25–7.39 (m, 5H), 7.41–7.51 (m, 2H), 7.79 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 34.8, 103.0, 106.2, 111.9, 119.5, 125.2, 127.0, 127.1, 128.7, 128.8, 129.3, 136.1, 156.5, 160.4. IR (KBr) 3110, 3061, 3030, 2224, 1880, 1754, 1596, 1496, 1463, 1269, 947, 878, 816, 705, 619 cm^{-1}. HRMS (ESI): *m/z*: calcd for [M] $C_{16}H_{11}NO$ 233.0841, found 233.0843.

4.2.16. 2-Benzyl-5-nitrobenzofuran (**4ap**).[4b]

White solid. mp. 102–104 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ 4.15 (s, 2H), 6.50–6.51 (m, 1H), 7.26–7.40 (m, 5H), 7.47 (d, *J* = 8.9 Hz, 1H), 8.15 (dd, *J* = 8.9, 2.2 Hz, 1H), 8.40 (d, *J* = 2.2 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 34.9, 104.0, 111.1, 116.8, 119.4, 127.1, 128.8, 128.9, 129.1, 136.1, 143.9, 157.7, 161.5. IR (KBr) 3088, 3027, 2925, 1891, 1802, 1597, 1517, 1453, 1335, 1070, 945, 825, 731, 683, 536 cm^{-1}.

4.2.17. 2-Benzyl-naphtho[2,3-b]furan (**4aq**).[6d]

White solid. mp. 119–121 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ 4.13 (s, 2H), 6.43 (s, 1H), 7.21–7.43 (m, 7H), 7.78 (s, 1H), 7.85–7.89 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 35.2, 102.9, 106.3, 117.9, 123.8, 124.5, 126.9, 127.8, 127.9, 128.7, 129.0, 130.0, 130.4, 131.0, 136.8, 154.1, 160.5. IR (KBr) 3029, 1597, 1495, 1454, 1405, 1250, 1143, 1092, 942, 867, 744, 706, 477 cm^{-1}. HRMS (ESI): *m/z*: calcd for [M] $C_{19}H_{14}O$ 258.1045, found 258.1048.

4.2.18. 2-(4-Methoxylbenzyl)benzofuran (**4ba**).[4b]

Colorless oil. ^{1}H NMR (270 MHz, $CDCl_3$): δ 3.80 (s, 3H), 4.05 (s, 2H), 6.34–6.35 (m, 1H), 6.84–6.90 (m, 2H), 7.13–7.26 (m, 4H), 7.39–7.48 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 34.1, 55.2, 103.1, 110.9, 114.0, 120.3, 122.4, 123.3, 128.8, 129.2, 129.9, 154.9, 158.2, 158.4. IR (neat) 3034, 2931, 2835, 1612, 1585, 1513, 1455, 1301, 1249, 1176, 1036, 952, 809, 750, 508, 424 cm^{-1}.

4.2.19. 5-(Benzofuran-2-ylmethyl)benzo[d][1,3]dioxole (**4ca**).[6d]

Colorless oil. ^{1}H NMR (270 MHz, $CDCl_3$): δ 4.02 (s, 2H), 5.94 (s, 2H), 6.38–6.39 (m, 1H), 6.77–6.79 (m, 3H), 7.14–7.26 (m, 2H), 7.39–7.49 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 34.6, 100.9, 103.2, 108.2, 109.3, 110.9, 120.4, 121.8, 122.5, 123.4, 128.7, 130.9, 146.4, 147.7, 154.9, 157.8. IR (neat) 2895, 2777, 1856, 1747, 1601, 1489, 1247, 1039, 929, 806, 751, 611 cm^{-1}. HRMS (ESI): *m/z*: calcd for [M] $C_{16}H_{12}O_3$ 252.0786, found 252.0793.

4.2.20. 2-(4-Trifluoromethylbenzyl)benzofuran (**4da**).[4b]

Colorless oil. ^{1}H NMR (270 MHz, $CDCl_3$): δ 4.15 (s, 2H), 6.40–6.41 (m, 1H), 7.15–7.26 (m, 2H), 7.39–7.42 (m, 3H), 7.47–7.52 (m, 1H), 7.56–7.59 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 34.7, 103.9, 111.0, 120.6, 122.8, 123.8, 124.3 (q, J_{CF} = 270.3 Hz), 125.6 (q, J_{CF} = 3.6 Hz), 128.7, 129.2 (q, J_{CF} = 32.2 Hz), 129.2, 141.4, 155.1, 156.4. ^{19}F NMR (470 MHz, $CDCl_3$): δ 99.5 (s, 3F). IR (neat) 3057, 2923, 1734, 1619, 1455, 1419, 1326, 1253, 1124, 1066, 1019, 814, 751, 598 cm^{-1}.

4.2.21. 2-(4-Chlorobenzyl)benzofuran (**4ea**).[17]

Colorless oil. ^{1}H NMR (270 MHz, $CDCl_3$): δ 4.07 (s, 2H), 6.380–6.384 (m, 1H), 7.15–7.31 (m, 6H), 7.39–7.49 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 34.3, 103.5, 110.9, 120.5, 122.6, 123.6, 128.6, 128.7, 130.2, 132.6, 135.7, 155.0, 157.0. IR (neat) 3034, 1601, 1491, 1455, 1426, 1253, 1092, 1015, 955, 795, 751, 483 cm^{-1}.

4.2.22. 2-(Naphthalene-1-ylmethyl)benzofuran (**4fa**).[6d]

Pale yellow oil. ^{1}H NMR (270 MHz, $CDCl_3$): δ 4.55 (s, 2H), 6.22–6.23 (m, 1H), 7.11–7.24 (m, 2H), 7.38–7.51 (m, 6H), 7.79–7.90 (m, 2H), 8.03–8.08 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 32.5, 103.7, 110.9, 120.4, 122.5, 123.4, 123.9, 125.6, 125.7, 126.2, 127.3, 127.8, 128.7, 128.8, 131.9, 133.1, 133.9, 154.8, 157.5. IR (neat) 3048, 1598, 1510, 1454, 1397, 1254, 1167, 1010, 951, 778, 750 cm^{-1}. HRMS (ESI): *m/z*: calcd for $[M+H]^+$ $C_{19}H_{15}O$ 259.1123, found 259.1139.

4.2.23. 2-(2-Methylbenzyl)benzofuran (**4ga**).[17]

Colorless oil. ^{1}H NMR (270 MHz, $CDCl_3$): δ 2.34 (s, 3H), 4.09 (s, 2H), 6.23 (s, 1H), 7.13–7.23 (m, 6H), 7.39–7.45 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 19.4, 32.7, 103.2, 110.9, 120.3, 122.5, 123.3, 126.2, 127.1, 128.8, 129.8, 130.4, 135.4, 136.6, 154.9, 157.5. IR (neat) 3064, 1732, 1600, 1455, 1254, 1161, 955, 801, 742 cm^{-1}.

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*4.2.24. 3-(Benzofuran-2-ylmethyl)pyridine (**4ha**).*[6d]

Pale yellow oil. ^{1}H NMR (270 MHz, $CDCl_3$): δ 4.10 (s, 2H), 6.40 (s, 1H), 7.15–7.27 (m, 3H), 7.39–7.50 (m, 2H), 7.61 (dt, J = 7.6, 1.9 Hz, 1H), 8.52 (dd, J = 4.6, 1.9 Hz, 1H), 8.60 (d, 1.9 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 32.2, 103.7, 110.9, 120.5, 122.7, 123.5, 123.7, 128.5, 132.8, 136.3, 148.3, 150.1, 154.9, 156.2. IR (neat) 3032, 1586, 1478, 1454, 1425, 1254, 1028, 949, 793, 752, 722 cm^{-1}. HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{14}H_{12}NO$ 210.0190, found 210.0177.

*4.2.25. 2-(Thiophen-2-ylmethyl)benzofuran (**4ia**).*[2o]

Colorless oil. ^{1}H NMR (270 MHz, $CDCl_3$): δ 4.32 (s, 2H), 6.47–6.48 (m, 1H), 6.96–6.99 (m, 2H), 7.15–7.26 (m, 3H), 7.41–7.51 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 29.2, 103.3, 111.0, 120.6, 122.6, 123.6, 124.4, 126.0, 126.9, 128.6, 139.2, 154.9, 156.6. IR (neat) 3068, 1601, 1454, 1254, 1167, 953, 749, 698, 429 cm^{-1}.

*4.2.26. 2-(Cyclohexylmethyl)benzofuran (**4ja**).*[2o]

Colorless oil. ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.90–1.07 (m, 2H), 1.11–1.31 (m, 3H), 1.63–1.80 (m, 6H), 2.62 (d, J = 7.0 Hz, 2H), 6.33–6.34 (m, 1H), 7.12–7.21 (m, 2H), 7.38–7.47 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 26.1, 26.3, 33.1, 36.3, 37.0, 102.8, 110.7, 120.1, 122.3, 122.9, 129.0, 154.6, 158.5. IR (neat) 3064, 2924, 2851, 1602, 1454, 1254, 1179, 948, 798, 749 cm^{-1}.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.tet.2017.10.001.

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