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# Domino [Pd]-Catalysis: One-Pot Synthesis of Isobenzofuran-1(3*H*)-ones

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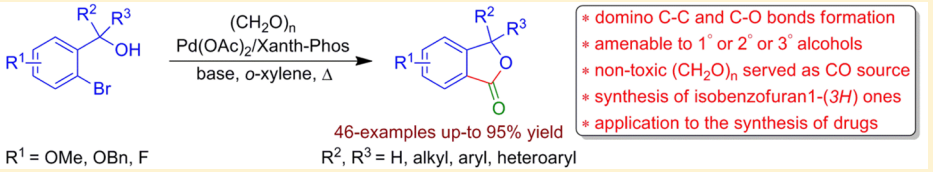
Supporting Information




**ABSTRACT:** An efficient domino [Pd]-catalysis for the synthesis of isobenzofuran-1(3*H*)-ones is presented. The strategy shows broad substrate scope and is amenable to *o*-bromobenzyl tertiary/secondary/primary alcohols. Significantly, the method was applied to the synthesis of antiplatelet drug *n*-butyl phthalide and cytotoxic agonist 3a-[4′-methoxylbenzyl]-5,7-dimethoxyphthalide.

## INTRODUCTION

Isobenzofuranones (phthalides) are an emerging class of compounds in medicinal chemistry. Phthalides are found in many naturally occurring compounds that exhibit interesting biological activities (Figure 1).[1] They are proven to be useful in the treatment of circulatory and heart diseases.[1a] Phthalides also act as key structural units in organic synthesis, particularly in the synthesis of functionalized anthracenes, naphthalenes, and naphthacene-based natural products.[2] As a result, their synthesis has attracted much attention from organic as well as pharmaceutical chemists.[3] In this context, reasonable attempts have been made on the synthesis of isobenzofuran-1(3*H*)-ones.[4] Nevertheless, some of the reported methods still lack simplicity and generality.[5]

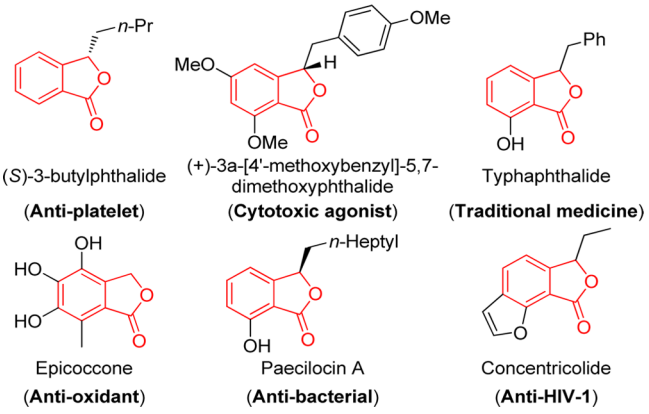
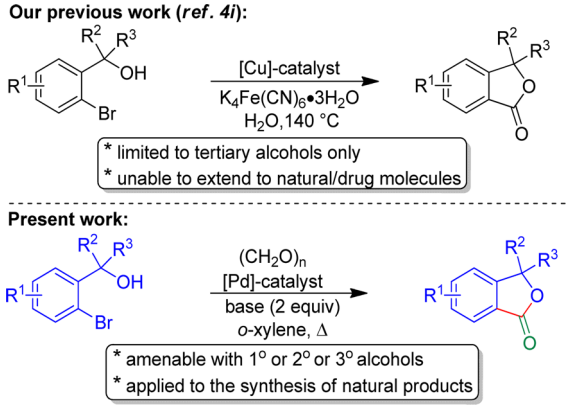



**Figure 1.** Biologically active natural isobenzofuranones.

Domino processes are extremely useful in organic synthesis, as they can be performed under simple one-step conditions, thus eliminating tedious isolation and purification of intermediate products(s). Therefore, such processes are ultimately useful in saving energy and minimizing the waste formation.[6] Transition metal catalysis has been proven to be an efficient tool for the development of new synthetic methods, especially in the creation of new C−C and C−X heteroatom bonds with increasing molecular complexity.[7] In continuation of our ongoing research interests in domino processes using transition metal-catalysis,[8] we have reported an efficient [Cu]-catalyzed domino one-pot method for the synthesis of isobenzofuran-1(3*H*)-ones using nontoxic $K_4[Fe(CN)_6]$ as the source of CO, under environmentally benign conditions (Scheme 1).[4i] However, this process was limited to *o*-bromobenzyl tertiary alcohols. Though carbon monoxide (CO)[9] is an inexpensive and readily available carbonylation

**Scheme 1. Present Study and Our Previous Approach for the Synthesis of Isobenzofuranones**

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source, its toxicity and the requirement of high pressure operations limits its synthetic applications. CO remains significant to the advancement of carbonylation reactions.[10] On these grounds, Skrydstrup et al. reported CO-free carbonylations using in situ-generated carbon monoxide.[11] Also, the research group of Beller et al. developed new methods using CO surrogates, such as aryl formates and $[Mo(CO)_6]$.[12] However, compared to all CO surrogates used in previous reports, paraformaldehyde was found superior, because it is inexpensive, stable, and easily used. As a result, the research group of Beller disclosed an elegant approach demonstrating the palladium-catalyzed reductive carbonylations and alkoxycarbonylations using paraformaldehyde as an external CO source.[13a] Subsequently, Xiao-Feng Wu et al. disclosed paraformaldehyde-mediated carbonylations for the synthesis of benzoxazinones.[13b] Paraformaldehyde had also been used in Rh-catalyzed CO-free carbonylations of alkynes.[14] However, paraformaldehyde has not been properly explored for [Pd]-catalyzed carbonylation.[13,15] In continuation of our research interests on domino transition metal catalysis, herein we report an efficient [Pd]-catalyzed concise approach for the syntheses of phthalides, using paraformaldehyde as the source of CO (Scheme 1). Significantly, the strategy was extended to the synthesis of isobenzofuranone-based natural products, from simple *o*-bromobenzyl alcohols. Remarkably, unlike our previous report,[4i] the present strategy was proved to be very versatile, as it was amenable to primary/secondary/tertiary *o*-bromobenzyl alcohols and was also applied to the synthesis of natural/drug products. To the best of our knowledge, there are no reports on the synthesis of isobenzofuran-1(3*H*)-ones using paraformaldehyde as carbonylating agent.

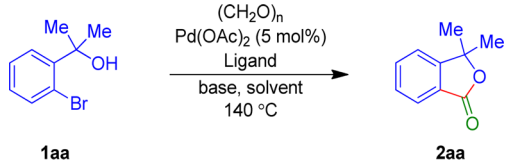
## RESULT AND DISCUSSION

To initiate the synthetic study, we have chosen *o*-bromobenzyl tertiary alcohol **1aa** as a model. Thus, the reaction was carried out with paraformaldehyde as CO source in the presence of $Pd(OAc)_2$ and base KOAc in $H_2O$, and with $PPh_3$ and Xanth-Phos, respectively. The desired product **2aa** was formed, albeit in poor to moderate yields (Table 1, entries 1 and 2). The reaction was then conducted under different solvents using Xanth-Phos as the ligand (Table 1, entries 3 to 10). Gratifyingly, *o*-xylene was found as the best solvent and afforded product **2aa** in excellent yield (Table 1, entry 6). Other conditions used, such as different bases in *o*-xylene, were found inferior to the conditions of entry 6 (Table 1, entries 11−18).

With the optimized conditions in hand (Table 1, entry 6), to check the scope and generality of the method, the reaction was explored with other *o*-bromobenzyl tertiary alcohols **1aa**−**1bd**. To our delight, the reaction showed broad substrate scope and furnished the benzofuranones **2aa**−**2bd**, in very good to excellent yields (Table 2). Interestingly, the reaction was successful with dialkyl substituents (entries **2aa**−**2ar**), cyclic tertiary alcohol **1as** (entry **2as**), alkyl-aryl groups (entries **2at**−**2az**), alkyl-heteroaryl groups (entries **2ba** and **2ab**) as well as diaryl substituents (entries **2bc** and **2bd**). Remarkably, the reaction showed broad functional group tolerance, such as donating groups on the *o*-bromoarene moiety (compare entries **2ae** vs **2ar**).

After successful synthesis of benzofuranones **2aa**−**2bd** (Table 2) with a quaternary carbon atom, to demonstrate the scope and generality of the method, we planned to explore the reaction with *o*-bromobenzyl secondary alcohols. Thus, the

**Table 1. Screening Conditions for the Synthesis of 2aa**




**1aa** **2aa**

| entry[a] | ligand (10 mol %) | solvent | base (2 equiv) | **2aa** (%)[b] |
|---|---|---|---|---|
| 3 | $PPh_3$ | $H_2O$ | KOAc | 36[d] |
| 2 | Xant-Phos | $H_2O$ | KOAc | 51[d] |
| 3 | Xant-Phos | DMA | KOAc | –[c] |
| 4 | Xant-Phos | DMSO | KOAc | 45[d] |
| 5 | Xant-Phos | DMF | KOAc | 41[d] |
| 6 | Xant-Phos | *o*-xylene | KOAc | 93 |
| 7 | Xant-Phos | dioxane | KOAc | 42[d] |
| 8 | Xant-Phos | $CH_3CN$ | KOAc | 60 |
| 9 | Xant-Phos | *p*-xylene | KOAc | 87 |
| 10 | Xant-Phos | DCE | KOAc | –[c] |
| 11 | Xant-Phos | *o*-xylene | $K_3PO_4$ | 71 |
| 12 | Xant-Phos | *o*-xylene | $K_2CO_3$ | 61 |
| 13 | Xant-Phos | *o*-xylene | $Na_2CO_3$ | –[c] |
| 14 | Xant-Phos | *o*-xylene | NaOAc | 66 |
| 15 | Xant-Phos | *o*-xylene | $Cs_2CO_3$ | 48[d] |
| 16 | Xant-Phos | *o*-xylene | $NEt_3$ | 46[d] |
| 17 | Xant-Phos | *o*-xylene | $HNEt_2$ | 48[d] |
| 18 | Xant-Phos | *o*-xylene | DMED | 26[d] |

[a]All reactions were carried out on a 0.5 mol scale of **1aa** and 2.5 mol scale of $(CH_2O)_n$ and with solvent (0.5 mL). [b]Isolated yields of chromatographically pure products. [c]Starting material was recovered. [d]Starting material **1aa** was recovered along with the product **2aa**.

reaction was performed with *o*-bromobenzyl secondary alcohols **1be**−**1bo**, under standard conditions. Gratifyingly, the reaction was quite successful and furnished the desired lactones **2be**−**2bo**, in fair to good yields (Table 3). Notably, the reaction proceeded smoothly with different alkyl substituents on the carbinol center (Table 3, entries **2be**−**2bo**). Significantly, this strategy was successfully applied to the synthesis of an antiplatelet drug *n*-butylphthalide (NBP)[16] **2bm**. Notably, the reaction was also amenable with cyclic alkyl as well as benzyl groups (entries **2bn** and **2bo**). Most significantly, demonstrating the utility of the current method over previous reported methods, primary alcohols **1bp**−**1bs** were successfully cyclized to give the desired lactones **2bp**−**2bs** (Table 3). It is worth noting that the reaction with primary alcohols **1bp**−**1bs** was not successful with the base KOAc. However, to our delight, changing the base from KOAc to $Na_2CO_3$ gave the desired lactones in good yields (Table 3). In contrast to our previous report,[4i] which was limited to *o*-bromobenzyl tertiary alcohols, the present protocol is amenable to *o*-bromobenzyl secondary/primary alcohols.

To demonstrate the utility of the domino [Pd]-catalysis process, we applied the strategy to the synthesis of a cytotoxic antagonist, 3a-[4′-methoxybenzyl]5,7-dimethoxypthalide **2bt**[17] (Scheme 2). Therefore, the required secondary alcohol **1bt** was synthesized using established conditions as depicted in Scheme 2. Thus, NBS-promoted bromination and methylmagnesium iodide addition, followed by oxidation protocol, afforded the acetophenone **4** (Scheme 2). The [Pd]-catalyzed $\alpha$-arylation of acetophenone **4** and reduction of the resultant ketone **3** with $NaBH_4$ furnished the alcohol **1bt** (Scheme 2). Finally, the key [Pd]-catalyzed lactonization of **1bt** was amenable and furnished


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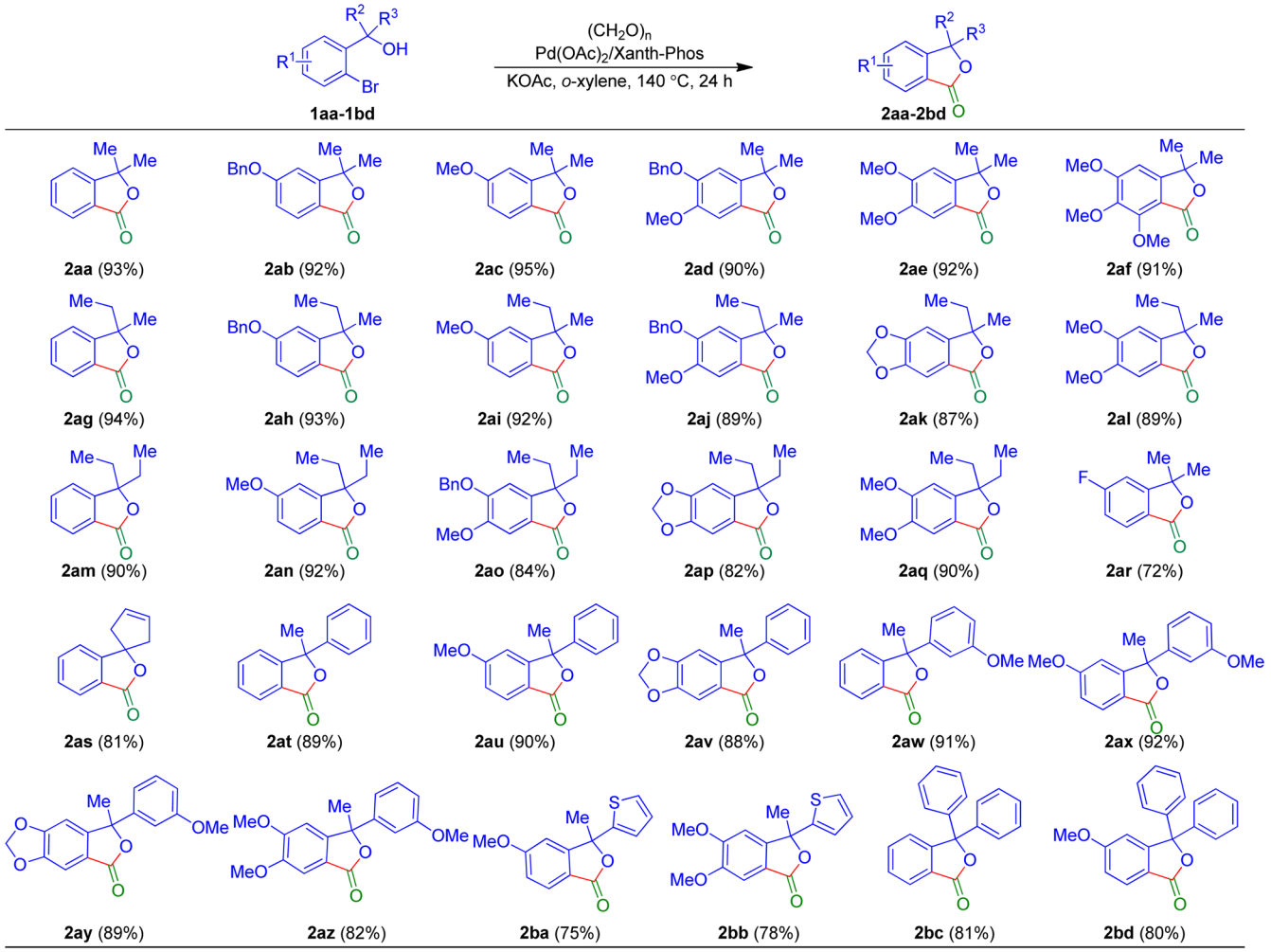
Table 2. Syntheses of Isobenzofuranones 2aa−2bd from *o*-Bromobenzyl Tertiary Alcohols 1aa−1bd[a,b]




[a]Reaction conditions: **1aa−1bd** (0.50 mmol), $(CH_2O)_n$ (2.5 mmol), $Pd(OAc)_2$ (5 mol %), Xanth-Phos (10 mol %), KOAc (2 equiv) in 0.5 mL *o*-xylene, at 140 °C for 24 h. [b]Isolated yields of chromatographically pure products.

the cytotoxic agonist 3a-[4′-methoxybenzyl]-5,7-dimethoxyphthalide **2bt** in its racemic form, in good yield (Scheme 2).

Interestingly, when we attempted the reaction of silyl ether **9**, the benzofuranone **2ai** was obtained in 67% yield (Scheme 3). This is probably due to in situ deprotection of the TMS group, which might be feasible under basic reaction conditions and then the usual [Pd]-catalyzed lactonization process.

Further, the chemical structure of **2** was confirmed by single crystal X-ray diffraction analysis of **2bq** and **2br** as shown in Figure 2 (see; Supporting Information for X-ray data of **2bq** and **2br**).

On the basis of established reports using paraformaldehyde as CO-free carbonylating agent and experimental studies probing the mechanistic path,[13] the plausible reaction mechanism for the formation of isobenzofuranones **2** is shown in Scheme 4. Thus, the initial oxidative insertion of $Pd^0$- catalyst into the C−Br bond of **1** generates the aryl-$Pd^{II}$ species **A**. Then the migratory insertion of CO on **A** furnishes new $Pd^{II}$-species **B**. Subsequent intramolecular nucleophilic chelation of the OH group and concomitant elimination of HBr leads to the six-membered $Pd^{II}$-intermediate **C**. Finally, reductive elimination of **C** through the formation of $Pd^0$-catalyst gives isobenzofuranones **2** and thus completes the catalytic cycle. Presumably, CO might be formed via an independent path by the reaction of paraformdaldehyde with the [Pd]-catalyst.

## CONCLUSIONS

We have described an efficient domino [Pd]-catalysis for the one-pot synthesis of isobenzofuran-1(3*H*)-ones. Unlike our previous report, the present strategy showed broad substrate scope and is amenable to *o*-bromobenzyl tertiary/secondary/primary alcohols. Significantly, the method was also successfully applied to the synthesis of antiplatelet drug *n*-butyl phthalide and cytotoxic agonist 3a-[4′-methoxylbenzyl]-5,7-dimethoxyphthalide.

## EXPERIMENTAL SECTION

**General Considerations.** IR spectra were recorded on a FTIR spectrophotometer. $^1H$ NMR spectra were recorded on 400 MHz spectrometer at 295 K in $CDCl_3$; chemical shifts ($\delta$ ppm) and coupling constants (Hz) are reported in standard fashion with reference to either internal standard tetramethylsilane (TMS) ($\delta_H$ = 0.00 ppm) or $CHCl_3$ ($\delta_H$ = 7.25 ppm). $^{13}C$ NMR spectra were recorded on 100 MHz spectrometer at RT in $CDCl_3$; chemical shifts ($\delta$ ppm) are reported relative to $CHCl_3$ [$\delta_C$ = 77.00 ppm (central line of triplet)]. In the $^{13}C$ NMR spectra, the nature of carbons (C, CH, $CH_2$, and $CH_3$) was determined by recording the DEPT-135 spectra and is given in parentheses and noted as s = singlet (for C), d =



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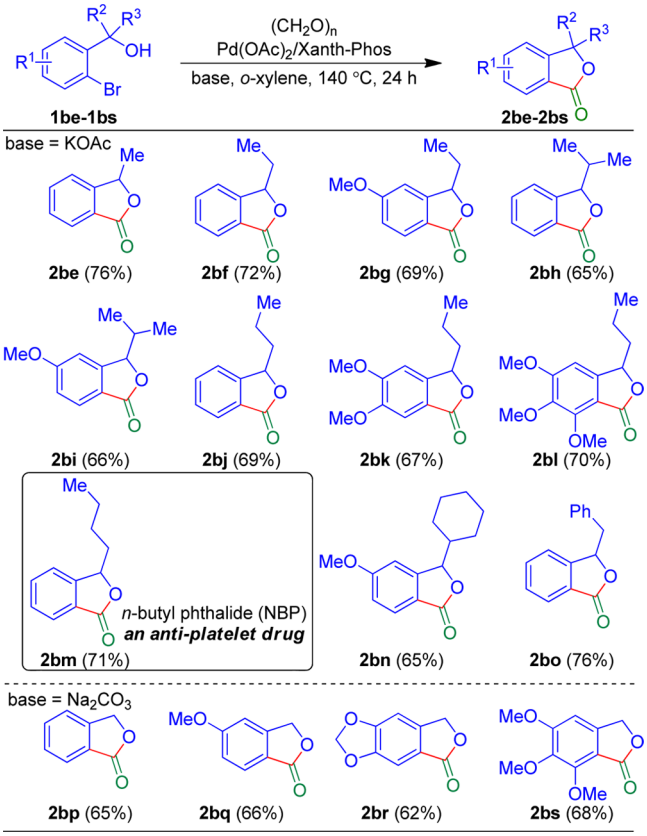
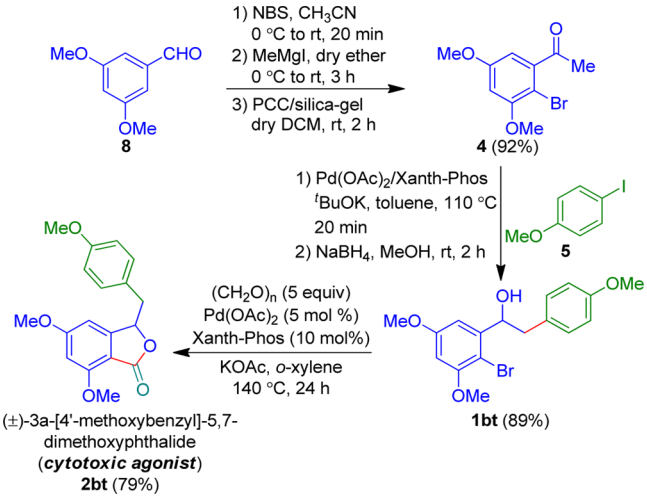
**Table 3. Syntheses of Isobenzofuranones 2be−2bs from 1be−1bs[a−d]**




[a]Reaction conditions: **1be−1bo/1bp−1bs** (0.50 mmol), $(CH_2O)_n$ (2.5 mmol), $Pd(OAc)_2$ (5 mol %), Xanth-Phos (10 mol %), base (2 equiv) in 0.5 mL *o*-xylene, at 140 °C for 24 h. [b]For **1be−1bo**, KOAc was used as the base. [c]In the case of **1bp−1bs**, $Na_2CO_3$ was used as the base. [d]Isolated yields of chromatographically pure products.

**Scheme 2. Synthesis of Cytotoxic Agonist 3a-[4′-Methoxybenzyl]-5,7-dimethoxyphthalide 2bt**




doublet (for CH), t = triplet (for $CH_2$), and q = quartet (for $CH_3$). In the $^1H$ NMR spectra, the following abbreviations were used throughout: s = singlet, d = doublet, t = triplet, q = quartet, qui = quintet, m = multiplet, and br s = broad singlet. The assignment of signals was confirmed by $^1H$, $^{13}C$ CPD (carbon proton decoupled), and DEPT spectra. High-resolution mass spectra (HR-MS) were

**Scheme 3. Formation of Isobenzofuranone 2ai from TMS Ether 9**

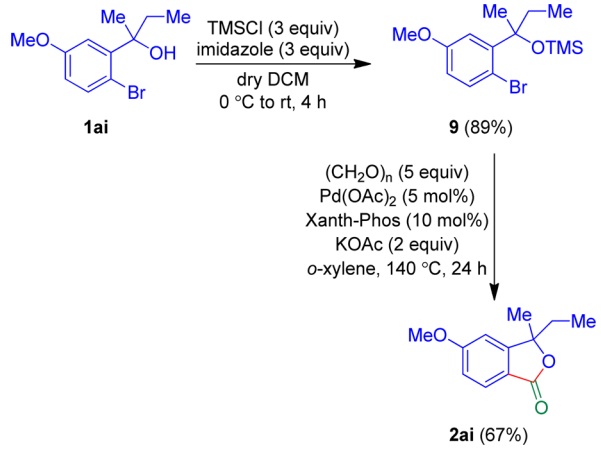
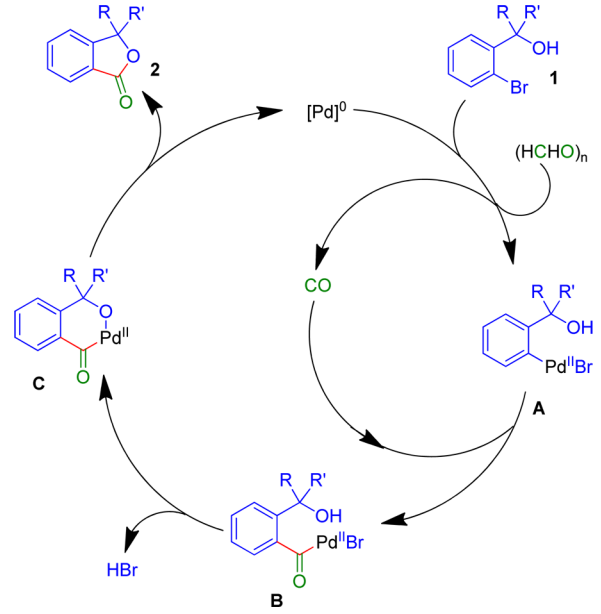




**Figure 2.** X-ray crystal structures for products **2bq** and **2br**.

**Scheme 4. Plausible Reaction Path for the Formation of 2**




recorded using Q-TOF multimode source. Melting points were determined on an electrothermal melting point apparatus and are uncorrected. Benzaldehydes, immidazole, aryl halides, methyl iodide, bromoethane, Mg metal, and $Na_2SO_4$ were commercially available (local made) used without further purification, $Pd(OAc)_2$, $PPh_3$, Xanth-Phos, $(HCHO)_n$, $Cs_2CO_3$, KOAc, $K_3PO_4$, $K_2CO_3$, $Na_2CO_3$, NaOAc, $NEt_3$, $NHEt_2$, and DMED (dimethylethelenediamine) purchased from a commercial source. Dry solvents were used: diethyl ether, toluene, dioxane, and THF were dried over sodium metal, and DCM, DMA, $CH_3CN$, DCE, and DMF were dried over calcium hydride.

All the solvents (diethyl ether, THF, DCM, DMF, *p*-xylene, DMSO, and *o*-xylene) are commercially available (LR grade). All small-scale



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dry reactions were carried out using the standard syringe-septum technique. Reactions were monitored by TLC on silica gel using a combination of petroleum ether and ethyl acetate as eluents. Solvents were distilled prior to use; petroleum ether with a boiling range of 40 to 60 °C was used. Acme silica gel (60−120 mesh) was used for column chromatography (approximately 20 g per 1 g of crude material).

*General Procedure (for the synthesis of lactones) (**2aa**−**2bt**).* To an oven-dried Schlenk tube were added 2-bromobenzyl alcohols **1** (0.50 mmol), paraformaldehyde (2.50 mmol), $Pd(OAc)_2$ (0.02 mmol), Xanth-Phos (0.05 mmol), base [(1.00 mmol) for primary alcohols $Na_2CO_3$ for tertiary and secondary alcohols KOAc], and solvent (*o*-xylene) (0.5 mL). The resulting reaction mixture was stirred at 140 °C for 24 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was allowed to cool to room temperature and then diluted with (10 mL) ethyl acetate, and saturated $NH_4Cl$ was added followed by extraction with ethyl acetate. The organic layers were dried ($Na_2SO_4$) and concentrated in vacuo. Purification of the residue by silica gel column chromatography using petroleum ether/ethyl acetate as the eluent furnished the lactone **2**.

*1-(2-Bromo-3,5-dimethoxyphenyl)ethanol (**1bu**).* To a cold (0 °C), magnetically stirred solution of a bromobenzaldehyde **7f** (1.29 mmol) in dry dry ether (2 mL) was added methylmagnesium iodide (2.59 mmol) [prepared from magnesium (2.59 mmol) and methyl iodide (2.59 mmol) in 10 mL of dry ether]. The reaction mixture was stirred at 0 °C to room temperature for 3 h. It was then poured into saturated aqueous $NH_4Cl$ solution and extracted with ethyl acetate (3 × 15 mL). The combined organic layers were dried ($Na_2SO_4$) and concentrated in vacuo. The crude secondary alcohol **1bu** was purified by column chromatography on silica using petroleum ether/ethyl acetate (85:15) as eluent and isolated as a white colored solid 89% yield (339 mg): mp 76−78 °C; [TLC (petroleum ether/ethyl acetate 8:2, $R_f$(**7f**) = 0.40, $R_f$(**1bu**) = 0.30, UV detection]. $^1$H NMR ($CDCl_3$ 400 MHz): $\delta$ = 6.79 (d, $J$ = 2.9 Hz, 1H), 6.40 (d, $J$ = 2.4 Hz, 1H), 5.27 (q, $J$ = 6.3 Hz, 1H), 3.86 (s, 3H), 3.82 (s, 3H), 2.00 (br s, 1H), 1.45 (d, $J$ = 6.3 Hz, 3H) ppm. $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ = 160.1 ($C_q$), 156.4 ($C_q$), 146.8 ($C_q$), 102.4 (CH), 101.8 ($C_q$), 98.8 ($C_q$), 69.4 (CH), 56.3 ($CH_3$), 55.6 ($CH_3$), 23.4 ($CH_3$) ppm. IR (MIR-ATR, 4000−600 cm$^{-1}$): $\nu_{max}$ = 3320, 2932, 1490, 1345, 1286, 1181, 1050, 962, 758, 689 cm$^{-1}$. HR-MS (ESI+) $m/z$ calculated for $[C_{10}H_{14}BrO_3]^+$ = $[M + H]^+$: 261.0121; found: 261.0125.

*1-(2-Bromophenyl)butan-1-ol (**1bj**).* To a cold (0 °C), magnetically stirred solution of a bromobenzaldehyde **7a** (2.70 mmol) in dry THF (2 mL) were added propylmagnesium bromide (5.40 mmol) [prepared from magnesium (5.40 mmol), 1-bromopropane (5.40 mmol), and a catalytic amount of iodine in 10 mL of dry THF]. The reaction mixture was stirred at 0 °C to room temperature for 3 h. It was then poured into saturated aqueous $NH_4Cl$ solution and extracted with ethyl acetate (3 × 15 mL). The combined organic layers were dried ($Na_2SO_4$) and concentrated in vacuo. The crude secondary alcohol **1bj** was purified by column chromatography on silica using petroleum ether/ethyl acetate (92:08) as eluent and isolated as a colorless liquid 78% yield (486 mg); [TLC (petroleum ether/ethyl acetate 9:1, $R_f$(**7a**) = 0.50, $R_f$(**1bj**) = 0.40, UV detection]. $^1$H NMR ($CDCl_3$ 400 MHz): $\delta$ = 7.58−7.40 (m, 2H), 7.31 (dd, $J$ = 7.3 and 7.3 Hz, 1H), 7.10 (dd, $J$ = 7.8 and 7.3 Hz, 1H), 5.10−5.00 (m, 1H), 2.23 (br s, 1H), 1.80−1.60 (m, 2H), 1.58−1.35 (m, 2H), 0.95 (t, $J$ = 7.3 Hz, 3H) ppm. $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ = 143.9 ($C_q$), 132.5 (CH), 128.6 (CH), 127.6 (CH), 127.3 (CH), 121.9 ($C_q$), 72.6 (CH), 39.8 ($CH_2$), 18.9 ($CH_2$), 13.8 ($CH_3$) ppm. IR (MIR-ATR, 4000−600 cm$^{-1}$): $\nu_{max}$ = 3320, 2930, 1496, 1341, 1286, 1181, 1050, 962, 750, 687 cm$^{-1}$. HR-MS (ESI+) $m/z$ calculated for $[C_{10}H_{13}OBrNa]^+$ = $[M + Na]^+$: 251.0042; found: 251.0046.

*1-(2-Bromo-3,4,5-trimethoxyphenyl)butan-1-ol (**1bl**).* To a cold (0 °C), magnetically stirred solution of a bromobenzaldehyde **7d** (2.0 mmol) in dry THF (2 mL) were added propylmagnesium bromide (4.0 mmol) [prepared from magnesium (4.0 mmol), 1-bromopropane (4.0 mmol), and a catalytic amount of iodine in 10 mL of dry THF]. The reaction mixture was stirred at 0 °C to room temperature for 3 h. It was then poured into saturated aqueous $NH_4Cl$ solution and extracted with ethyl acetate (3 × 15 mL). The combined organic layers were dried ($Na_2SO_4$) and concentrated in vacuo. The crude secondary alcohol **1bl** was purified by column chromatography on silica using petroleum ether/ethyl acetate (75:25) as eluent and isolated as a brown colored viscous liquid 85% yield (549 mg); [TLC (petroleum ether/ethyl acetate 7:3, $R_f$(**7d**) = 0.60, $R_f$(**1bl**) = 0.50, UV detection]. $^1$H NMR ($CDCl_3$ 400 MHz): $\delta$ = 6.91 (s, 1H), 5.08−5.00 (m, 1H), 3.84 (s, 3H), 3.83 (s, 2 × 3H), 2.28 (br s, 1H), 1.80−1.30 (m, 4H), 0.93 (t, $J$ = 7.3 Hz, 3H) ppm. $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ = 152.9 ($C_q$), 150.2 ($C_q$), 141.9 ($C_q$), 139.8 ($C_q$), 107.9 ($C_q$), 105.7 (CH), 72.5 (CH), 61.0 ($CH_3$), 60.9 ($CH_3$), 56.0 ($CH_3$), 39.8 ($CH_2$), 19.0 ($CH_2$), 13.8 ($CH_3$) ppm. IR (MIR-ATR, 4000−600 cm$^{-1}$): $\nu_{max}$ = 3349, 2930, 1493, 1355, 1276, 1181, 1052, 962, 759, 679 cm$^{-1}$. HR-MS (ESI+) $m/z$ calculated for $[C_{13}H_{19}O_4BrNa]^+$ = $[M + Na]^+$: 341.0359; found: 341.0350.

*1-(2-Bromo-3,5-dimethoxyphenyl)ethanone (**4**).* To a magnetically stirred solution of the secondary alcohol **1bu** (1.21 mmol) in dry $CH_2Cl_2$ (10 mL) was added a homogeneous mixture (1:1) of PCC (3.64 mmol) and silica gel. The resulting reaction mixture was stirred at room temperature for 2 h. Filtration of the reaction mixture through a short silica column with excess $CH_2Cl_2$ furnished the pure ketone **4** that was isolated as a pale yellow colored oil 94% yield (281 mg); [TLC (petroleum ether/ethyl acetate 8:2, $R_f$(**1bu**) = 0.40, $R_f$(**4**) = 0.50, UV detection]. $^1$H NMR ($CDCl_3$ 400 MHz): $\delta$ = 6.51 (d, $J$ = 2.9 Hz, 1H), 6.46 (d, $J$ = 2.4 Hz, 1H), 3.87 (s, 3H), 3.79 (s, 3H), 2.59 (s, 3H) ppm. $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ = 202.4 ($C_q$), 160.0 ($C_q$), 156.9 ($C_q$), 144.3 ($C_q$), 103.8 (CH), 101.1 (CH), 98.9 ($C_q$), 56.5 ($CH_3$), 55.7 ($CH_3$), 30.6 ($CH_3$) ppm. IR (MIR-ATR, 4000−600 cm$^{-1}$): $\nu_{max}$ = 2939, 1689, 1546, 1460, 1355, 1280, 1171, 1055, 962, 758, 680 cm$^{-1}$. HR-MS (ESI+) $m/z$ calculated for $[C_{10}H_{11}BrO_3Na]^+$ = $[M + Na]^+$: 280.9784; found: 280.9789.

*1-(2-Bromo-3,5-dimethoxyphenyl)-2-(4-methoxyphenyl)-ethanone (**3**).* In an oven-dried Schlenk tube under nitrogen atmosphere were added *p*-iodoanisole **5** (1.34 mmol), *o*-bromoacetophenone **4** (1.22 mmol), $Pd(OAc)_2$ (2 mol %), xantphos (4 mol %), and $^t$BuOK (2.44 mmol) followed by addition of dry toluene (4 mL). The resulting reaction mixture was stirred at 80 °C for 20 min. Progress of the reaction was monitored by TLC until the reaction was completed. The reaction mixture was then quenched with saturated aqueous $NH_4Cl$, and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried ($Na_2SO_4$) and concentrated in vacuo. The crude ketone **3** was purified by column chromatography on silica using petroleum ether/ethyl acetate (85:15) as eluent and isolated as a pale yellow colored liquid 66% yield (296 mg); [TLC (petroleum ether/ethyl acetate 8:2, $R_f$(**4**) = 0.60, $R_f$(**3**) = 0.50, UV detection]. $^1$H NMR ($CDCl_3$ 400 MHz): $\delta$ = 7.15 (d, $J$ = 8.8 Hz, 2H), 6.84 (d, $J$ = 8.8 Hz, 2H), 6.49 (d, $J$ = 2.9 Hz, 1H), 6.27 (d, $J$ = 2.9 Hz, 1H), 4.13 (s, 2H), 3.87 (s, 3H), 3.78 (s, 3H), 3.73 (s, 3H) ppm. $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ = 202.7 ($C_q$), 159.9 ($C_q$), 158.7 ($C_q$), 156.7 ($C_q$), 144.0 ($C_q$), 130.8 (CH), 125.4 ($C_q$), 114.0 (CH), 103.9 (CH), 100.8 (CH), 98.6 ($C_q$), 56.4 ($CH_3$), 55.7 ($CH_3$), 55.2 ($CH_3$), 48.8 ($CH_2$) ppm. IR (MIR-ATR, 4000−600 cm$^{-1}$): $\nu_{max}$ = 2938, 1679, 1550, 1453, 1340, 1280, 1176, 1050, 962, 756, 680 cm$^{-1}$. HR-MS (ESI+) $m/z$ calculated for $[C_{17}H_{18}BrO_4]^+$ = $[M + H]^+$: 365.0383; found: 365.0378.

*1-(2-Bromo-3,5-dimethoxyphenyl)-2-(4-methoxyphenyl)ethanol (**1bt**).* To a magnetically stirred solution of the aryl ketone **3** (0.54 mmol) in dry MeOH (10 mL) was added $NaBH_4$ (1.08 mmol). The resulting reaction mixture was stirred at room temperature for 2 h. It was then poured into saturated aqueous $NH_4Cl$ solution and extracted with ethyl acetate (3 × 15 mL). The combined organic layers were dried ($Na_2SO_4$) and concentrated in vacuo. The crude secondary alcohol **1** was purified by column chromatography on silica using petroleum ether/ethyl acetate (85:15) as eluent and isolated as a colorless oil 92% yield (186 mg); [TLC (petroleum ether/ethyl acetate 8:2, $R_f$(**3**) = 0.50, $R_f$(**1bt**) = 0.30, UV detection]. $^1$H NMR ($CDCl_3$ 400 MHz): $\delta$ = 7.24 (d, $J$ = 8.8 Hz, 2H), 6.87 (d, $J$ = 8.8 Hz, 2H), 6.79 (d, $J$ = 2.9 Hz, 1H), 6.43 (d, $J$ = 2.9 Hz, 1H), 5.28−5.20 (m, 1H), 3.88 (s, 3H), 3.81 (s, 3H), 3.80 (s, 3H), 3.20−3.10 (m, 1H),



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J. Org. Chem. 2016, 81, 7685−7691

2.65−2.55 (m, 1H), 2.11 (br s, 1H) ppm. $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ = 160.0 ($C_q$), 158.4 ($C_q$), 158.3 ($C_q$), 145.0 ($C_q$), 130.4 (CH), 130.3 ($C_q$), 113.9 (CH), 102.8 (CH), 101.9 ($C_q$) 98.9 ($C_q$), 74.3 (CH), 56.3 ($CH_3$), 55.5 ($CH_3$), 55.2 ($CH_3$), 43.1 ($CH_2$) ppm. IR (MIR-ATR, 4000−600 cm$^{-1}$): $\nu_{max}$ = 3329, 2930, 1530, 1443, 1350, 1240, 1178, 1050, 945, 750, 676 cm$^{-1}$. HR-MS (ESI+) $m/z$ calculated for $[C_{17}H_{19}BrO_4Na]^+$ = $[M + Na]^+$: 389.0359; found: 389.0364.

*[(2-(2-Bromo-5-methoxyphenyl)butan-2-yl)oxy]trimethylsilane (**9**).* To a magnetically stirred solution of the tertiary alcohol **1ai** (0.39 mmol) and imidazole (3 mmol) in dry $CH_2Cl_2$ (6 mL) was added trimethylsilyl chloride (3 mmol) at 0 °C. The resulting reaction mixture was stirred at room temperature for 4 h. The reaction mixture was quenched and extracted with $CH_2Cl_2$ (3 × 15 mL). The collected organic layers were dried ($Na_2SO_4$) and concentrated under reduced pressure. Purification of the residue on a silica gel column chromatography (petroleum ether/ethyl acetate 97:03) as eluent furnished trimethylsilyl ether **9** in 89% yield (114 mg) as colorless viscous liquid: [TLC (petroleum ether/ethyl acetate 9:1, $R_f$(**1ai**) = 0.40, $R_f$(**9**) = 0.60, UV detection]. $^1$H NMR ($CDCl_3$ 400 MHz) $\delta$ = 7.42 (d, 1H, $J$ = 8.3 Hz), 7.33 (d, 1H, $J$ = 3.4 Hz), 6.61 (dd, 1H, $J$ = 8.3 and 3.4 Hz), 3.78 (s, 3H), 2.55−2.40 (m, 1H), 1.85−1.71 (m, 1H), 1.76 (s, 3H), 0.64 (t, 3H, $J$ = 7.3 Hz), 0.18 (s, 9H) ppm; $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ = 158.5 ($C_q$), 147.1 ($C_q$), 135.5 (CH), 115.5 (CH), 113.1 (CH), 110.1 ($C_q$), 79.4 ($C_q$), 55.2 ($CH_3$), 33.5 ($CH_2$), 28.0 ($CH_3$), 8.5 ($CH_3$), 2.4 (3 × $CH_3$) ppm; IR (MIR-ATR, 4000−600 cm$^{-1}$) $\nu_{max}$ = 2958, 1568, 1460, 1372, 1249, 1170, 1056, 835, 752, 673 cm$^{-1}$; HR-MS (ESI+) $m/z$ calculated for $[C_{14}H_{23}{}^{81}BrNaSiO_2]^+$ = $[M + Na]^+$ 353.0543, found 353.0540.

*3-Ethyl-5-methoxyisobenzofuran-1(3H)-one (**2bg**).* This compound was prepared according to the GP using petroleum ether/ethyl acetate (85:15) as eluent and isolated as a brown colored viscous liquid 72% yield (75 mg): [TLC (petroleum ether/ethyl acetate 8:2, $R_f$(**1bg**) = 0.50, $R_f$(**2bg**) = 0.40, UV detection]. $^1$H NMR ($CDCl_3$ 400 MHz): $\delta$ = 7.76 (d, $J$ = 8.3 Hz, 1H), 6.99 (dd, $J$ = 1.9 and 8.3 Hz, 1H), 6.93 (d, $J$ = 1.9 Hz, 1H), 5.33 (dd, $J$ = 4.4 and 7.3 Hz, 1H), 3.87 (s, 3H), 2.00−2.15 (m, 1H), 1.85−1.70 (m, 1H), 0.96 (t, $J$ = 7.3 Hz, 3H) ppm. $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ = 170.4 ($C_q$), 164.6 ($C_q$), 152.4 ($C_q$), 127.1 (CH), 118.5 ($C_q$), 116.2 (CH), 105.8 (CH), 81.5 ($C_q$), 55.8 ($CH_3$), 27.6 ($CH_2$), 8.7 ($CH_3$) ppm. IR (MIR-ATR, 4000−600 cm$^{-1}$): $\nu_{max}$ = 2947, 1750, 1598, 1465, 1338, 1282, 1190, 1054, 965, 741, 692 cm$^{-1}$. HR-MS (ESI+) $m/z$ calculated for $[C_{11}H_{13}O_3]^+$ = $[M + H]^+$: 193.0859; found: 193.0853.

*3-Isopropyl-5-methoxyisobenzofuran-1(3H)-one (**2bi**).* This compound was prepared according to the GP using petroleum ether/ethyl acetate (85:15) as eluent and isolated as a colorless oil 66% yield (68 mg): [TLC (petroleum ether/ethyl acetate 8:2, $R_f$(**1bi**) = 0.50, $R_f$(**2bi**) = 0.40, UV detection]. $^1$H NMR ($CDCl_3$ 400 MHz): $\delta$ = 7.88 (d, $J$ = 7.8 Hz, 1H), 7.65 (dd, $J$ = 1.5 and 7.8 Hz, 1H), 7.51 (dd, $J$ = 7.3 and 7.3 Hz, 1H), 7.43 (d, $J$ = 7.8 Hz, 1H), 5.36 (d, $J$ = 3.9 Hz, 1H), 2.35−2.20 (m, 1H), 1.11 (d, $J$ = 7.3 Hz, 3H), 0.79 (d, $J$ = 6.8 Hz, 3H) ppm. $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ = 170.8 ($C_q$), 148.8 ($C_q$), 133.8 (CH), 129.0 (CH), 126.7 ($C_q$), 125.6 (CH), 122.1 (CH), 85.6 ($C_q$), 32.3 (2C, 2 × CH), 18.6 ($CH_3$), 15.6 ($CH_3$) ppm. IR (MIR-ATR, 4000−600 cm$^{-1}$): $\nu_{max}$ = 2941, 1752, 1588, 1460, 1348, 1280, 1191, 1052, 966, 740, 690 cm$^{-1}$. HR-MS (ESI+) $m/z$ calculated for $[C_{12}H_{14}O_3Na]^+$ = $[M + Na]^+$: 229.0835; found: 229.0830.

*5,6-Dimethoxy-3-propylisobenzofuran-1(3H)-one (**2bk**).* This compound was prepared according to the GP using petroleum ether/ethyl acetate (80:20) as eluent and isolated as a white colored solid 69% yield (82 mg): mp 82−84 °C; [TLC (petroleum ether/ethyl acetate 7:3, $R_f$(**1bk**) = 0.40, $R_f$(**2bk**) = 0.30, UV detection]. $^1$H NMR ($CDCl_3$ 400 MHz): $\delta$ = 7.26 (s, 1H), 6.80 (s, 1H), 5.30−5.43 (m, 1H), 3.96 (s, 3H), 3.91 (s, 3H), 1.90−2.07 (m, 1H), 1.60−1.76 (m, 1H), 1.40−1.58 (m, 2H), 0.96 (t, $J$ = 7.3 Hz, 3H) ppm. $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ = 171.0 ($C_q$), 154.7 ($C_q$), 150.3 ($C_q$), 144.7 ($C_q$), 118.0 ($C_q$), 106.1 (CH), 103.0 (CH), 80.6 ($C_q$), 56.4 ($CH_3$), 56.3 ($CH_3$), 36.9 ($CH_2$), 18.2 ($CH_2$), 13.8 ($CH_3$) ppm. IR (MIR-ATR, 4000−600 cm$^{-1}$): $\nu_{max}$ = 2939, 1749, 1582, 1463, 1345, 1286, 1181, 1050, 962, 758, 689 cm$^{-1}$. HR-MS (ESI+) $m/z$ calculated for $[C_{13}H_{17}O_4]^+$ = $[M + H]^+$: 237.1121; found: 237.1115.

*5,6,7-Trimethoxy-3-propylisobenzofuran-1(3H)-one (**2bl**).* This compound was prepared according to the GP using petroleum ether/ethyl acetate (75:25) as eluent and isolated as a colorless oil 67% yield (89 mg): [TLC (petroleum ether/ethyl acetate 6:4, $R_f$(**1bl**) = 0.50, $R_f$(**2bl**) = 0.40, UV detection]. $^1$H NMR ($CDCl_3$ 400 MHz): $\delta$ = 6.56 (s, 1H), 5.20−5.30 (m, 1H), 4.11 (s, 3H), 3.93 (s, 3H), 3.84 (s, 3H), 1.88−2.00 (m 1H), 1.60−1.75 (m 1H), 1.40−1.55 (m 2H), 0.95 (t, $J$ = 7.3 Hz, 3H) ppm. $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ = 168.2 ($C_q$), 159.5 ($C_q$), 152.3 ($C_q$), 148.0 ($C_q$), 141.6 ($C_q$), 110.6 ($C_q$), 99.1 (CH), 79.8 (CH), 62.3 ($CH_3$), 61.4 ($CH_3$), 56.4 ($CH_3$), 37.0 ($CH_2$), 18.2 ($CH_2$), 13.8 ($CH_3$) ppm. IR (MIR-ATR, 4000−600 cm$^{-1}$): $\nu_{max}$ = 2943, 1742, 1578, 1462, 1341, 1282, 1187, 1054, 960, 757, 687 cm$^{-1}$. HR-MS (ESI+) $m/z$ calculated for $[C_{14}H_{18}O_5Na]^+$ = $[M + Na]^+$: 289.1046; found: 289.1038.

*3-Cyclohexyl-5-methoxyisobenzofuran-1(3H)-one (**2bn**).* This compound was prepared according to the GP using petroleum ether/ethyl acetate (85:15) as eluent and isolated as a white colored solid 66% yield (81 mg): mp 200−202 °C; [TLC (petroleum ether/ethyl acetate 8:2, $R_f$(**1bn**) = 0.50, $R_f$(**2bn**) = 0.40, UV detection]. $^1$H NMR ($CDCl_3$ 400 MHz): $\delta$ = 7.76 (d, $J$ = 8.3 Hz, 1H), 6.99 (dd, $J$ = 2.0 and 8.3 Hz, 1H), 6.84 (d, $J$ = 2.0 Hz, 1H), 5.24 (d, $J$ = 3.4 Hz, 1H), 3.89 (s, 3H), 1.55−1.95 (m, 5H), 1.00−1.40 (m, 6H) ppm. $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ = 170.6 ($C_q$), 164.5 ($C_q$), 151.5 ($C_q$), 127.1 (CH), 119.0 ($C_q$), 115.9 (CH), 106.4 (CH), 84.6 (CH), 55.8 ($CH_3$), 42.0 (CH), 29.3 ($CH_2$), 26.2 ($CH_2$), 26.0 ($CH_2$), 25.8 ($CH_2$), 25.6 ($CH_2$) ppm. IR (MIR-ATR, 4000−600 cm$^{-1}$): $\nu_{max}$ = 2940, 1739, 1568, 1469, 1340, 1282, 1187, 1054, 964, 752, 686 cm$^{-1}$. HR-MS (ESI+) $m/z$ calculated for $[C_{15}H_{18}O_3K]^+$ = $[M + K]^+$: 285.0888; found: 285.0882.

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01396.

Copies of NMR spectra (PDF)
CIF data for **2bq** (CIF)
CIF data for **2br** (CIF)

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### Notes

The authors declare no competing financial interest.

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