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Regioselective Preparation of Benzo[*b*]furans from Phenols and α-Bromoketones

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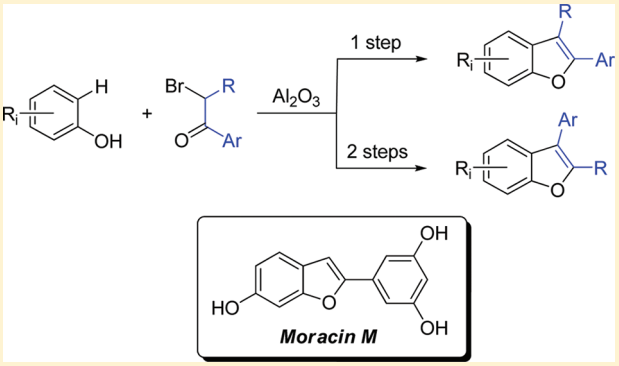
Supporting Information

ABSTRACT: In this paper, a fully regiocontrolled synthesis of either 2- and 3-substituted benzo[*b*]furans is described. Direct reaction between phenols and α-bromoacetophenones in the presence of neutral alumina yields 2-substituted benzo[*b*]furans with complete regiocontrol. When a basic salt such as potassium carbonate is used, the corresponding 2-oxoether is obtained. Cyclization of these latter compounds promoted by neutral alumina yields the corresponding 3-substituted benzo[*b*]furans. Using the former method, Moracin M and other analogues can be obtained from commercial sources in two preparative steps. DFT calculations provide reasonable reaction paths to understand the formation of 2-substituted benzo[*b*]furans.



INTRODUCTION

Benzo[*b*]furans have attracted considerable interest because of the presence of these heterocycles in natural products,[1] biologically active compounds,[2] and other molecules of pharmaceutical interest.[3] In particular, 2-aryl benzo[*b*]furans possessing methoxy and/or hydroxy groups are attractive compounds because of their wide spectrum of biological activity, which includes anticancer,[4] antioxidative,[5] and anti-inflammatory[6] properties.

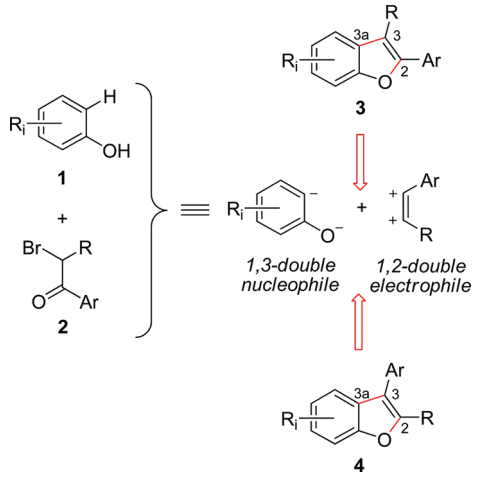
Most of the convergent syntheses of 2-aryl benzo[*b*]furans require carbonyl compounds and ortho-functionalized phenols or phenoxy derivatives. These ortho functionalities include bromo,[7] formyl,[8] and trimethylsilyl groups.[9] In contrast, the reported methods involving ortho-unsubstituted phenols are quite scarce. These methods involve intramolecular cyclizations of previously formed aryl ethers or sigmatropic rearrangements.[10] Recently, Jing et al. have reported a convergent synthesis of 3-substituted benzo[*b*]furans via a one-pot reaction between phenols and α-bromoacetophenones in the presence of Al_2O_3.[10e]

In this paper, we present a convergent and regiocontrolled method for the synthesis of either 2-and 3-substituted benzo[*b*]furans involving ortho-unsubstituted phenols or naphthols and α-bromoacetophenones. This method provides a general entry to these important compounds starting from readily available reactants. In addition, we provide a rationale of the role of alumina in this reaction on the basis of DFT calculations.

RESULTS AND DISCUSSION

The synthesis method described in this work relies on the double nucleophilic/electrophilic character of the reactants and on the double disconnection of the O1–C2 and C3–C3a bonds (Scheme 1). The corresponding synthetic equivalents are an ortho-unsubstituted phenol **1** and a α-bromoacetophenone **2**. In the case of reactants **1**, the position(s) at which electron-releasing group(s) is/are installed on the reacting aromatic system may have an influence on the activation of the corresponding ortho-centers (Scheme 1). The main issue

Scheme 1. Convergent Synthesis of 2- and 3-Substituted Benzo[*b*]furans via Formation of O1–C2 and C3–C3a Bonds



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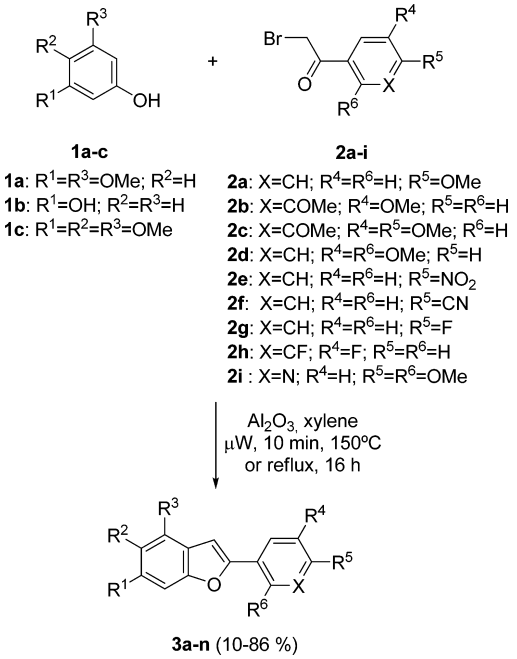
associated with this approach is the control of the regioselectivity of the process in order to obtain either 2- or 3-substituted benzo[*b*]furans using the same reactants as starting materials.

When the reaction is carried out in refluxing xylene in the presence of neutral alumina, we have found that only the corresponding 2-substituted benzo[*b*]furans are formed (Scheme 2, Table 1).

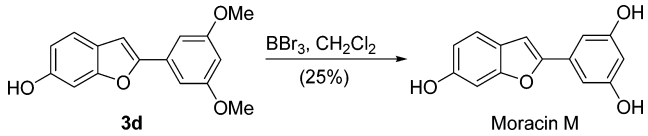
Scheme 2. Preparation of 2-Substituted Benzo[*b*]furans 3a–n from Phenols 1a–c and α-Bromoacetophenones 2a–i in the Presence of Neutral Alumina



The possible 3-substituted regioisomers were not detected in the crude reaction mixtures. The yields were, in general, moderate but acceptable given the availability of the starting materials. These yields did not improve significantly when microwave irradiation was used instead of thermal heating. Phenol itself and phenols incorporating electron-withdrawing groups did not react under these conditions. On the contrary, the best results were obtained when electron-releasing methoxy groups were present in the starting phenol **1**. The aryl group of reactant **2** tolerates electron-releasing and electron-withdrawing groups (Compounds **3g–j**). In addition, a pyridyl group can also be incorporated into the reaction product (Table 1, compound **3k**). In order to verify the regiochemistry of these compounds, the structure of known compound **3a** (see the Experimental Section) was unambiguously determined by X-ray diffraction analysis (see the Supporting Information).

Resorcinol **1b** reacts under these conditions to yield only products resulting from the reaction with 1 equiv of **2a**,**b** (Table 1, entries 4 and 5). Attempts to obtain the products associated with the double condensation reaction met with no success. In addition, analysis of the reaction mixtures did not permit the detection of the regioisomers associated with the formation of the regioisomer in which the furan ring is fused at the ortho position in between the two oxygen atoms of resorcinol. Deprotection of the two methoxy groups of **3d** led to the formation of natural product Moracin M[11] in a two-step synthesis from resorcinol and **2b** (Scheme 3).

Scheme 3. Preparation of Moracin M from 3d



Quite surprisingly, 3,4,5-trimethoxyphenol **1c** in which there is an additional activating methoxy group led to the corresponding 2-substituted benzo[b]furans **3l–n** in low yields (Table 1, entries 12–14).

We also performed the same reaction but using potassium carbonate as additive instead of alumina. Under these moderately basic conditions, the corresponding ethers[12] were obtained in good to excellent yields (Scheme 4, Table 2). In contrast with the preceding reaction, microwave irradiation gave better yields and lower reaction times with respect to thermal heating. Thus, the reaction in acetone in a sealed vessel with an external bath at 130 °C required 3 h to complete, whereas microwave irradiation under the same conditions required only 20 min. In general, the yields of the isolated pure products **5** were good, with the exception of compounds **5i** and **5j** (Table 2, entries 9 and 10, respectively). When the reaction involved α-methyl bromoacetophenone **2k**, the corresponding ether **5h** was obtained in good yield (Table 2, entry 8).

Table 1. Synthesis of of 2-Substituted Benzo[*b*]furans 3a–n from Phenols 1a–c and α-Bromoacetophenones 2a–i

entry	reaction	R^1	R^2	R^3	X	R^4	R^5	R^6	yield[a] (%)
1	**1a** + **2a** → **3a**	OMe	H	OMe	CH	H	OMe	H	50
2	**1a** + **2b** → **3b**	OMe	H	OMe	COMe	OMe	H	H	86
3	**1a** + **2c** → **3c**	OMe	H	OMe	COMe	OMe	OMe	H	75
4	**1b** + **2b** → **3d**	OH	H	H	COMe	OMe	H	H	26
5	**1b** + **2a** → **3e**	OH	H	H	CH	H	OMe	H	32
6	**1a** + **2d** → **3f**	OMe	H	OMe	CH	OMe	H	OMe	25
7	**1a** + **2e** → **3g**	OMe	H	OMe	CH	H	NO_2	H	44
8	**1a** + **2f** → **3h**	OMe	H	OMe	CH	H	CN	H	24
9	**1a** + **2g** → **3i**	OMe	H	OMe	CH	H	F	H	49
10	**1a** + **2h** → **3j**	OMe	H	OMe	CF	F	H	H	46
11	**1a** + **2i** → **3k**	OMe	H	OMe	N	H	OMe	OMe	53
12	**1c** + **2b** → **3l**	OMe	OMe	OMe	COMe	OMe	H	H	9
13	**1c** + **2c** → **3m**	OMe	OMe	OMe	COMe	OMe	OMe	H	11
14	**1c** + **2a** → **3n**	OMe	OMe	OMe	CH	H	OMe	H	10

[a]Yield of isolated pure product after column chromatography.

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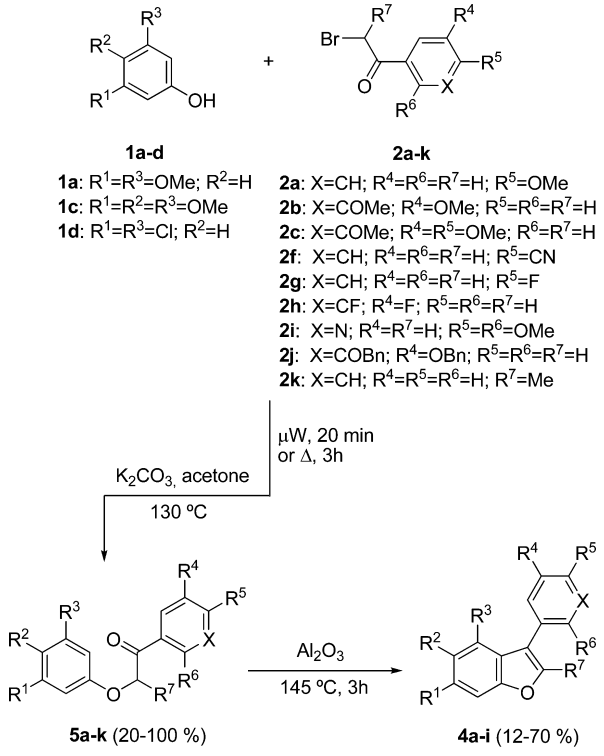
Scheme 4. Preparation of 3-Substituted Benzo[*b*]furans 4a–i from Phenols 1a–d and α-Bromoacetophenones 2a–k via Intermediate Williamson Synthesis of Ethers 5a–k



Thermal heating of a dispersion of α-alkoxy ethers **5** in Al_2O_3 yielded the corresponding 3-aryl benzo[*b*]furans **4a–i** (Scheme 4, Table 3). When this cyclization was carried out under microwave irradiation, lower yields were obtained. Similarly, reaction of ethers **5** in the presence of alumina in refluxing xylene resulted in lower yields of products **4**. Using the best conditions (Scheme 4), the observed yields of pure products **4** were, in general, moderate with the exception of the densely substituted compound **4g** (Table 3, entry 7). In the case of 2,3-disubstituted benzo[*b*]furan **4h** (Table 3, entry 8), the yield was moderate but acceptable given the availability of the starting materials. Also in this case, the structure of known compound **4a** (see the Experimental Section) was secured by X-ray diffraction analysis (see the Supporting Information).

In order to get a better understanding of the distinct behavior of these α-bromoketones in the presence or absence of Al_2O_3, we performed computational studies to assess the electrophilic behavior of α-bromoacetophenone in both cases. DFT[13,14] studies at the B3LYP/6-31+G* level[15] on the reaction paths associated with the interaction between α-bromoacetophenone **2l** and phenoxide anion generated in the presence of a base (Figure 1) showed a low activation barrier for the S_N2 process, whereas the nucleophilic addition reaction resulted to be an uphill process with no detectable transition structure. All our attempts to locate saddle point **TS1′** were unfruitful and spontaneously converged to **TS1**. Although in this latter stationary point the bond distance between the nucleophilic oxygen atom and the carbon atom of the carbonyl group of **2l** was quite short, harmonic analysis revealed that **TS1** corresponds to a true S_N2 transition structure. This saddle point is associated with the reaction between the oxygen atom of the phenoxide anion (which is the harder nucleophilic center) and the electrophilic methylene moiety of **2l**. This result agrees with our experimental findings because they suggest that in the absence of alumina, only the S_N2 process is energetically available, thus resulting in the formation of ethers **5** and finally in their

Table 2. Synthesis of Ethers 5a–k from Phenols 1a–d and α-Bromoacetophenones 2a–k

entry	reaction	R^1	R^2	R^3	X	R^4	R^5	R^6	R^7	yield[a] (%)
1	**1a + 2a → 5a**	OMe	H	OMe	CH	H	OMe	H	H	99
2	**1a + 2b → 5b**	OMe	H	OMe	COMe	OMe	H	H	H	93
3	**1a + 2c → 5c**	OMe	H	OMe	COMe	OMe	OMe	H	H	99
4	**1a + 2g → 5d**	OMe	H	OMe	CH	H	F	H	H	97
5	**1a + 2j → 5e**	OMe	H	OMe	COBn	OBn	H	H	H	99
6	**1a + 2f → 5f**	OMe	H	OMe	CH	H	CN	H	H	99
7	**1a + 2i → 5g**	OMe	H	OMe	N	H	OMe	OMe	H	73
8	**1a + 2k → 5h**	OMe	H	OMe	CH	H	H	H	Me	84
9	**1a + 2h → 5i**	OMe	H	OMe	CF	F	H	H	H	24
10	**1c + 2j → 5j**	OMe	OMe	OMe	COBn	COBn	H	H	H	20
11	**1d + 2a → 5k**	Cl	H	Cl	CH	H	OMe	H	H	99

[a]Yield of isolated pure product after column chromatography.

Table 3. Synthesis of of 3-Substituted Benzo[*b*]furans 4a–i from Ethers 5a–i

entry	reaction	R^1	R^2	R^3	X	R^4	R^5	R^6	R^7	yield[a] (%)
1	**5a → 4a**	OMe	H	OMe	CH	H	OMe	H	H	70
2	**5b → 4b**	OMe	H	OMe	COMe	OMe	H	H	H	54
3	**5c → 4c**	OMe	H	OMe	COMe	OMe	OMe	H	H	50
4	**5d → 4d**	OMe	H	OMe	CH	H	F	H	H	37
5	**5e → 4e**	OMe	H	OMe	COBn	OBn	H	H	H	26
6	**5f → 4f**	OMe	H	OMe	CH	H	CN	H	H	42
7	**5g → 4g**	OMe	H	OMe	N	H	OMe	OMe	H	12
8	**5h → 4h**	OMe	H	OMe	CH	H	H	H	Me	40
9	**5i → 4i**	OMe	H	OMe	CF	F	H	H	H	68

[a]Yield of isolated pure product after column chromatography.

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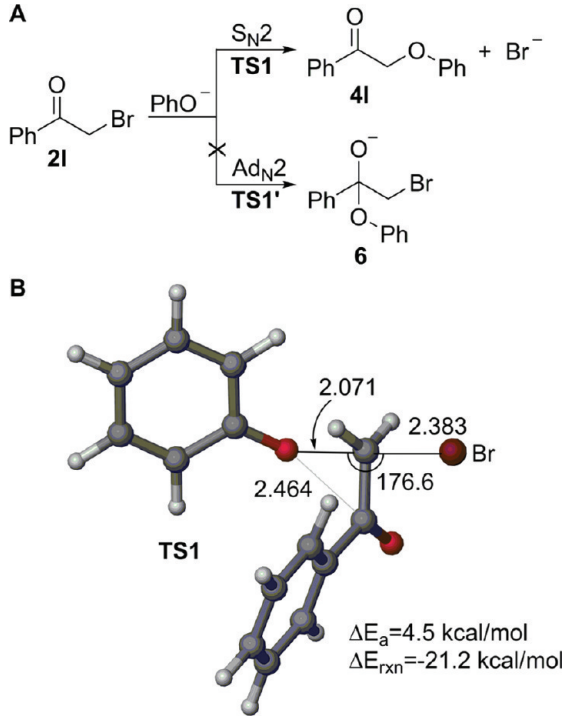

Figure 1. (A) Model S_N2 and Ad_N2 reactions between phenoxide anion and acetophenone **2l**. (B) Fully optimized structure of **TS1**, computed at the B3LYP/6-31+G* level of theory. Bond distances and angle are given in Å and degrees, respectively. Reaction and activation energies are given in kcal/mol and have been computed at the B3LYP/6-31+G*+ΔZPVE level of theory.

transformation into the corresponding 3-substituted benzo[*b*]-furans **4** (Scheme 4). However, the presence of alumina is needed to promote the cyclization step via carbonyl activation of compounds **5**.

Previous computational studies on the reactivity of alumina[16] reveal tetrahedral and cubic reactive sites for aluminum (Figure 2A

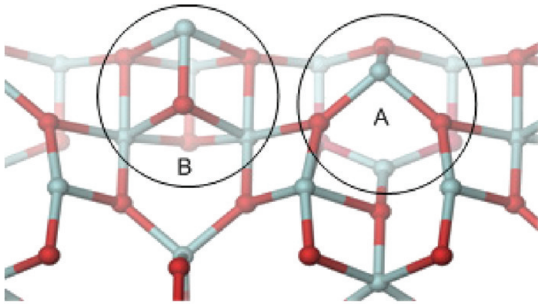

Figure 2. Tetrahedral (A) and cubic (B) environments for aluminum in γ-Al_2O_3 surface. Aluminum and oxygen atoms are represented in light blue and red, respectively. Structural data have been taken form ref 16a.

and B, respectively). First, we considered in our calculations a tetrahedral environment for Al_4O_6, denoted as A in Figure 2.

We analyzed computationally the interaction of **2l** with Al_4O_6 according to pattern A (Figure 2) as a simplified model for the alumina surface. This complex showed an enlargement of both the C−O and C−Br bond distances (Figure 3A), together with a significant CO−Al interaction. As a result, the enhancement of the electrophilicity of the Al_4O_6-**2l** complex is localized at the

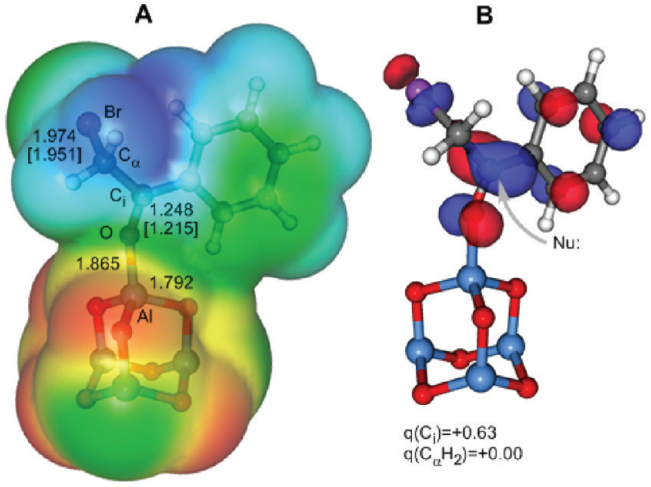

Figure 3. (A) Fully optimized (B3LYP/6-31+G* level) structure of benzophenone **2l** bound to Al_4O_6, showing the electrostatic potential projected onto the electron density. Negative and positive potentials are given in red and blue, respectively. Bond distances are in Å. Values in square brackets correspond to those of isolated **2l**. (B) Kohn−Sham LUMO of the **2l**-Al_4O_6 complex. The preferential site of a nucleophilic attack is shown. The NBO charges of the *ipso*-carbonyl and the α-methylene groups (C_i and $C_\alpha H_2$, respectively, in a.u.) are also given.

carbonyl group because the charge of the corresponding carbon atom is increased with respect to isolated **2l**. In addition, the LUMO of this complex is localized mainly on the carbonyl group, thus suggesting that this will be the preferred electrophilic center for the interaction with the nucleophile (Figure 3B).

A similar analysis of the interaction between phenol and Al_4O_6 led to two possible structures (Figure 4). The neutral

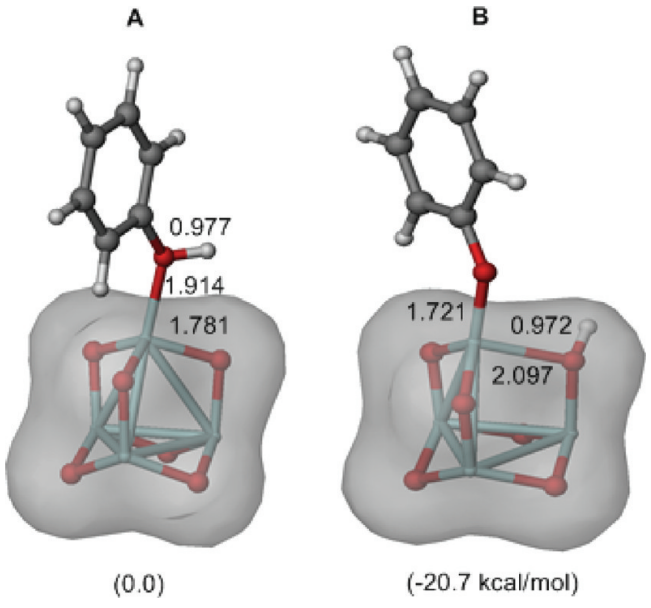

Figure 4. Fully optimized (B3LYP/6-31+G* level of theory) structures for phenol on tetrahedral Al_4O_6. Bond distances are given in Å. Numbers in parentheses are the corresponding relative energies, calculated at the B3LYP/6-31+G*+ΔZPVE level.

hydroxyl structure denoted as A in Figure 4 is computed to be significantly less stable than structure B, associated with a proton transfer from phenol to the alumina surface. Therefore, formation of phenoxide anion in the reaction media can occur

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in a significant extent. In the following part of this study, only phenoxide nucleophile will be considered.

DFT exploration of the reaction paths between phenoxide anion and **2l** on Al_2O_6 led to two possible situations. When pattern A (Figure 2) was considered, only transition structure **TS2** could be located, associated with a S_N2 process (Figure 5).

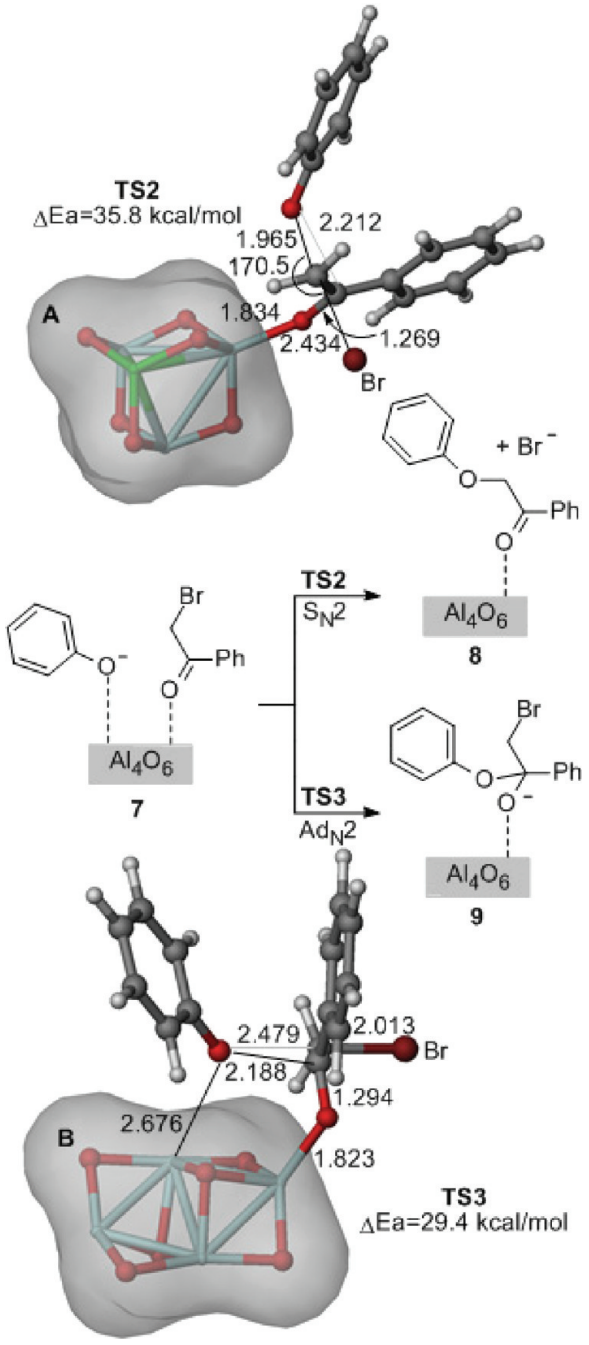

Figure 5. Possible reaction paths for the interaction between phenoxide and α-bromoacetophenone **2l** in Al_4O_6. Fully optimized (B3LYP/6-31+G* level) structures of transition structures leading to intermediates **8** and **9**. Aluminum atoms are represented in light blue. The Al_4O_6 clusters are represented in configurations (A) and (B), together with the solvent accessible surfaces (probe radius: 1.4 Å).

In contrast, when the B environment (Figure 2) for alumina was considered, another saddle point, denoted as **TS3** in Figure 5, was located and characterized. This latter transition structure is associated with an addition reaction on the carbonyl group of benzophenone and has an activation energy 6.4 kcal/mol lower than that associated with **TS2** (Figure 5). Therefore, we conclude that in the presence of alumina, formation of the Ad_N2 product **9a** is strongly favored.

Next, we studied the cyclization step leading to the precursors of benzo[*b*]furans **3**. We found that the S_N2 transition structure **TS4a** leads to intermediate **10a** with a calculated activation energy of 45.6 kcal/mol (Figure 6). This

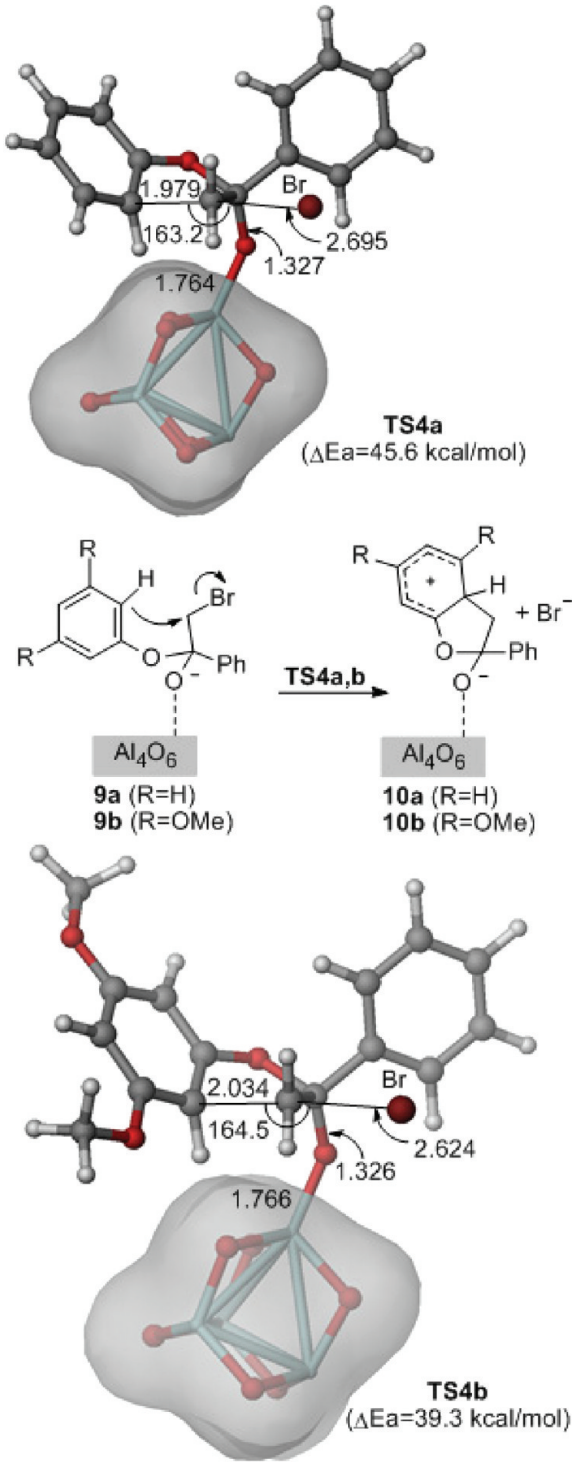

Figure 6. Chief geometric features of transition structures **TS4a,b**, associated with conversion of intermediates **9a,b** into bicyclic structures **10a,b**, respectively.

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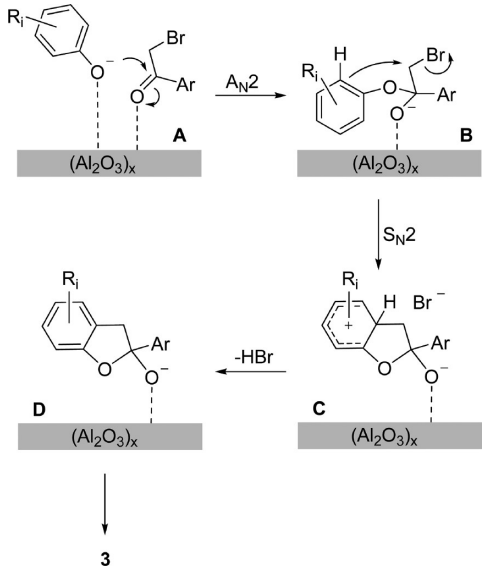
value is quite high and agrees with our experimental finding that reaction between unsubstituted phenol and bromoacetophenone in the presence of alumina does not lead to the formation of 2-phenyl benzo[*b*]furan. However, adequately located methoxy or hydroxy groups in the starting phenol can promote the formation of the corresponding aromatic bicyclic compounds **3**. Our calculations on the S_N2 process associated with the transformation of intermediate **9b**, with two methoxy groups in ortho and para disposition with respect to the reacting carbon atom, led to the formation of bicyclic intermediate **10b** via **TS4b**, with an activation energy 6.3 kcal/mol lower than that associated with the reaction of nonactivated intermediate **9a** (Figure 6).

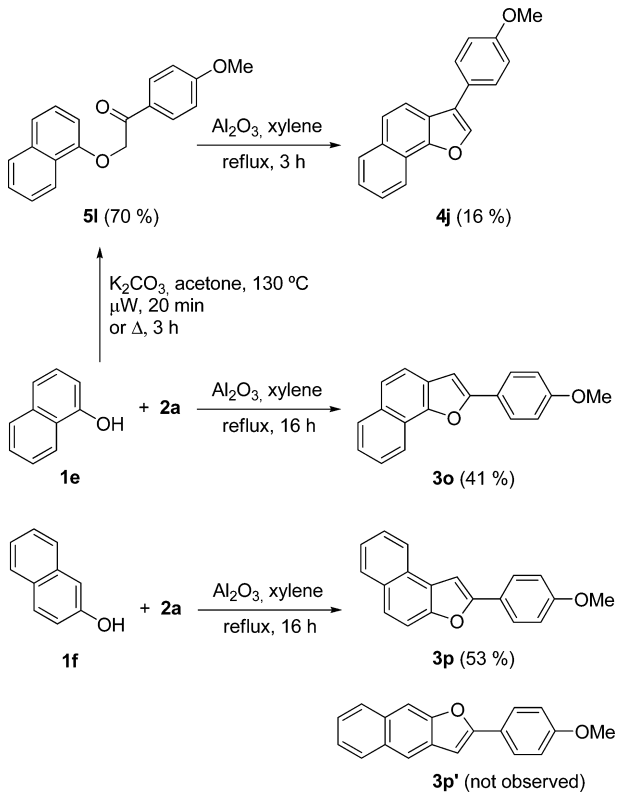
Therefore, on the basis of our DFT calculations, we propose the mechanism outlined in Scheme 5 to explain the exclusive formation of 2-aryl benzo[*b*]furans **3**: the reaction consists of a stepwise process, in which the first step is a nucleophilic addition of the phenol on the carbonyl group of *α*-bromoacetophenone **2**. The second step consists of an intramolecular S_N2 process, where elimination of HBr and dehydration leads to the formation of the corresponding product **3**.

Scheme 5. Proposed Mechanism for the Formation of 2-Substituted Benzo[*b*]furans 3

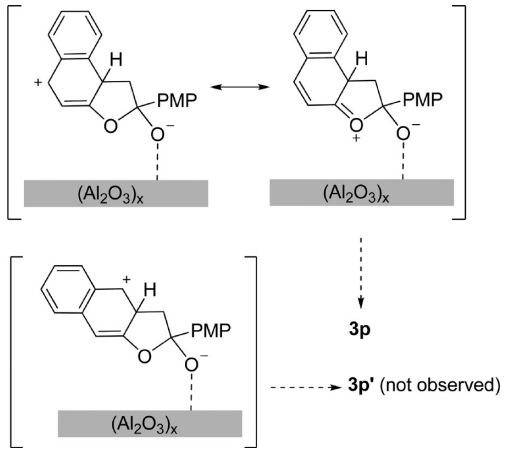


In the case of naphthols **1e,f** (Scheme 6), no additional activation of the aryl moiety is required. Thus, reaction between *α*-naphthol **1e** and **2a** in the presence of alumina yields **3o**, whereas microwave irradiation in the presence of K_2CO_3 leads to the formation of ether **5l**. Cyclization of this latter compound yields **4j**, the 3-substituted analogue of **3o**. In this case, only one possibility exists to form the naphtho[1,2-*b*]furan scaffold, and both 2- and 3-(4-methoxyphenyl) derivatives can be prepared from **1e** and **2a**. However, in the case of *β*-naphthol **1f**, two possible adducts can be envisaged in its reaction with **2a** in the presence of alumina. Under these conditions, however, only compound **3p** was obtained in moderate yield, whereas the corresponding naphtho[2,3-*b*]furan analogue **3p′** was not observed. This result is compatible with the model proposed in Scheme 5 because in the cyclization step the intermediate leading to **3p** preserves the aromaticity of one phenyl group in the naphthol moiety (Scheme 7).

Scheme 6. Reaction between Naphthols 1e,f and *α*-Bromoacetophenone 2a



Scheme 7. Proposed Cyclic Intermediates for the Reaction between Naphthol 1f and 2a[a]



[a]Only the resonance forms in which the aromaticity of one benzene ring is preserved are shown.

CONCLUSIONS

In this paper, we describe a method for the preparation of benzo[*b*]furans from *α*-bromoacetophenones and activated phenols. When the reaction is carried out in the presence of alumina, only the 2-substituted compounds are formed. The corresponding 3-substituted derivatives can be obtained via a two-step Williamson-cyclization sequence. Therefore, both regioisomers can be obtained with complete control and from the same readily available reactants. The reaction permits the two-step preparation of natural product Moracin M. Both

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α- and β-naphthols permit the preparation of naphthofurans under these conditions and also with complete regiocontrol. Finally, a model based on DFT calculations has been proposed to understand the experimentally observed results.

EXPERIMENTAL SECTION

General Experimental Procedures. Microwave irradiations were conducted in a focused microwave reactor Biotage Initiator or CEM Discover at the temperature, at the power, and for the time indicated. All melting points are uncorrected. Column cromatographies were carried out with silica gel 60 (0.040−0.063 mm). The aluminum oxide used was activated, neutral, Brockmann I, STD grade, approx. 150 mesh, 58 Å. Reagents were purchased from commercial suppliers or prepared following procedures described in the literature. Some of the α-bromoketones **2** were prepared according to the method reported by Chen et al.[17]

General Procedure for the Synthesis of 2-Aryl Benzo[*b*]-furans 3a−n and Naphthofurans 3o−p. A mixture of the phenol **1** (3.0 mmol), the α-haloketone **2** (4.2 mmol), and neutral aluminum oxide (21 mmol, 2.14 g) was refluxed in xylene (12 mL) for 16 h. The resulting mixture was filtered through a Celite pad and evaporated. The residue was purified by column chromatography on silica gel using ethyl acetate/hexane as eluent to yield the corresponding product **3**.

4,6-Dimethoxy-2-(4-methoxyphenyl)benzofuran,[18] ***3a.*** Yield = 50%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.8, 2H), 6.95 (d, *J* = 8.8, 2H), 6.89 (s, 1H), 6.69 (s, 1H), 6.32 (d, *J* = 1.6, 1H), 3.91 (s, 3H), 3.86 (s, 3H), 3.85 (s, 3H).

2-(3,5-Dimethoxyphenyl)-4,6-dimethoxybenzofuran,[19] ***3b.*** Yield = 86%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.02 (s, 1H), 6.95 (s, 2H), 6.70 (s, 1H), 6.43 (s, 1H), 6.33 (s, 1H), 3.92 (s, 3H), 3.86 (s, 3H), 3.85 (s, 6H).

4,6-Dimethoxy-2-(3,4,5-trimethoxyphenyl)benzofuran, ***3c.*** Yield = 75%. White solid: mp 131−132 °C; IR 2960, 1619, 1497, 1227, 1203, 1134, 1110 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.04 (s, 2H), 7.00 (s, 1H), 6.74 (s, 1H), 6.36 (d, *J* = 1.8, 1H), 3.97 (s, 6H), 3.95 (s, 3H), 3.91 (s, 3H), 3.89 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.4, 156.7, 153.8, 153.8, 153.7, 138.4, 126.6, 113.5, 101.9, 98.7, 94.6, 88.5, 61.2, 56.4, 56.0, 55.8. Anal. Calcd. for $C_{19}H_{20}O_6$: C, 66.3; H, 5.8. Found: C, 66.0; H, 6.0.

2-(3,5-Dimethoxyphenyl)benzofuran-6-ol,[11a] ***3d.*** Yield = 26%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.0, 1H), 7.01 (s, 1H), 6.97 (s, 2H), 6.92 (s, 1H), 6.77 (d, *J* = 7.9, 1H), 6.45 (s, 1H), 5.02 (s, 1H), 3.86 (s, 6H).

2-(4-Methoxyphenyl)benzofuran-6-ol,[19] ***3e.*** Yield = 32%. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.49 (s, 1H), 7.76 (d, *J* = 8.7, 2H), 7.37 (d, *J* = 8.3, 1H), 7.09 (s, 1H), 7.03 (d, *J* = 8.8, 2H), 6.93 (s, 1H), 6.73 (dd, *J* = 8.3, 1.9, 1H), 3.81 (s, 3H).

2-(2,5-Dimethoxyphenyl)-4,6-dimethoxybenzofuran, ***3f.*** Yield = 25%. Pale pink solid: mp 82−83 °C; IR 2896, 1604, 1503, 1212, 1130 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, *J* = 3.0, 1H), 7.37 (s, 1H), 6.89 (d, *J* = 8.9, 1H), 6.80 (dd, *J* = 8.9, 3.0, 1H), 6.69 (s, 1H), 6.31 (d, *J* = 1.6, 1H), 3.92 (s, 3H), 3.91 (s, 3H), 3.85 (s, 3H), 3.84 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.5, 155.9, 153.9, 150.7, 150.0, 120.5, 114.1, 114.0, 112.5, 111.7, 104.2, 94.4, 88.3, 56.1, 56.1, 56.0, 55.8. Calcd. for $C_{18}H_{18}O_5$: C, 68.8; H, 5.8. Found: C, 68.9; H, 5.7.

4,6-Dimethoxy-2-(4-nitrophenyl)benzofuran, ***3g.*** Yield = 44%. Orange solid: mp 192−193 °C; IR 2943, 2914, 1594, 1504, 1319, 1145, 1104 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (d, *J* = 8.8, 2H), 7.88 (d, *J* = 8.8, 2H), 7.24 (s, 1H), 6.69 (s, 1H), 6.34 (s, 1H), 3.93 (s, 3H), 3.88 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 160.3, 156.7, 153.6, 150.6, 146.1, 135.9, 124.5, 124.4, 112.4, 104.0, 95.0, 88.5, 55.8, 55.7. Calcd. for $C_{16}H_{13}NO_5$: C, 64.2; H, 4.4; N, 4.7. Found: C, 64.2; H, 4.3; N, 4.6.

4-(4,6-Dimethoxybenzofuran-2-yl)benzonitrile, ***3h.*** Yield = 24%. Yellow solid: mp 220−221 °C; IR 3042, 2955, 2223, 1600, 1507, 1217, 1145, 1104 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.2, 2H), 7.67 (d, *J* = 8.3, 2H), 7.18 (s, 1H), 6.68 (s, 1H), 6.34 (s, 1H), 3.92 (s, 3H), 3.87 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.5, 157.4, 154.2, 151.6, 135.0, 132.8, 124.5, 119.1, 113.4, 110.8, 102.4, 95.0, 88.4, 56.1, 55.9. Calcd. for $C_{17}H_{13}NO_3$: C, 73.1; H, 4.7; N, 5.0. Found: C, 73.3; H, 5.0; N, 5.1.

2-(4-Fluorophenyl)-4,6-dimethoxybenzofuran, ***3i.*** Yield = 49%. White solid: mp 142−143 °C; IR 2914, 1614, 1496, 1220, 1145, 1116, 1043 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.74 (dd, *J* = 8.8, 5.4, 2H), 7.10 (t, *J* = 8.7, 2H), 6.96 (s, 1H), 6.68 (s, 1H), 6.33 (d, *J* = 1.7, 1H), 3.92 (s, 3H), 3.86 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.6 (d, *J* = 247.7), 159.5, 156.8, 153.7, 153.0, 127.4 (d, *J* = 3.0), 126.2 (d, *J* = 8.0), 116.0 (d, *J* = 22.0), 113.5, 98.7, 94.6, 88.5, 56.0, 55.8. Calcd. for $C_{16}H_{13}FO_3$: C, 70.6; H, 4.8. Found: C, 70.3; H, 4.9.

2-(3,5-Difluorophenyl)-4,6-dimethoxybenzofuran, ***3j.*** Yield = 46%. Pale pink solid: mp 124−125 °C; IR 3084, 2884, 1598, 1466, 1338, 1224, 1145 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.6, 2H), 7.06 (s, 1H), 6.71 (t, *J* = 8.8, 1H), 6.67 (s, 1H), 6.33 (s, 1H), 3.92 (s, 3H), 3.86 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.6 (dd, *J* = 247.6, 13.1), 160.2, 157.0, 154.0, 151.5, 133.9 (t, *J* = 10.5), 113.2, 107.1 (dd, *J* = 20.7, 6.7), 103.0 (t, *J* = 25.6), 101.2, 94.9, 88.3, 56.0, 55.8. Calcd. for $C_{16}H_{12}F_2O_3$: C, 66.2; H, 4.2. Found: C, 66.2; H, 4.1.

3-(4,6-Dimethoxybenzofuran-2-yl)-2,6-dimethoxypyridine, ***3k.*** Yield = 53%. Pale pink solid: mp 155−156 °C; IR 2937, 2961, 1605, 1504, 1475, 1460, 1272, 1107, 1011 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.2, 1H), 7.18 (s, 1H), 6.66 (s, 1H), 6.41 (d, *J* = 8.2, 1H), 6.32 (s, 1H), 4.10 (s, 3H), 3.96 (s, 3H), 3.93 (s, 3H), 3.85 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.0, 159.1, 158.7, 156.0, 153.7, 149.5, 137.4, 113.9, 106.7, 101.7, 101.5, 94.4, 88.4, 56.0, 55.8, 53.8, 53.7. Calcd. for $C_{17}H_{17}NO_5$: C, 64.8; H, 5.4; N, 4.4. Found: C, 64.9; H, 5.2; N, 4.3.

2-(3,5-Dimethoxyphenyl)- 4,5,6-trimethoxybenzofuran, ***3l.*** Yield = 9%. Brown solid: mp 82−84 °C; IR 2938, 2836, 1594, 1414, 1125 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.05 (s, 1H), 6.94 (s, 2H), 6.83 (s, 1H), 6.43 (s, 1H), 4.12 (s, 3H), 3.91 (s, 3H), 3.86 (s, 3H), 3.85 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.3, 154.2, 152.7, 152.0, 146.1, 137.5, 132.4, 115.0, 102.7, 100.8, 100.1, 90.8, 61.6, 60.8, 56.6, 55.6. Calcd. for $C_{19}H_{20}O_6$: C, 66.3; H, 5.8. Found: C, 66.4; H, 5.8.

4,5,6-Trimethoxy-2-(3,4,5-trimethoxyphenyl)benzofuran, ***3m.*** Yield = 11%. White solid: mp 172−173 °C; IR 2940, 2836, 1415, 1203, 1121 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.01 (s, 2H), 6.99 (s, 1H), 6.85 (s, 1H), 4.13 (s, 3H), 3.95 (s, 6H), 3.92 (s, 3H), 3.89 (s, 3H), 3.88 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.3, 153.9, 152.6, 152.0, 146.1, 138.7, 137.7, 126.3, 115.3, 102.1, 99.3, 90.8, 61.6, 61.2, 60.9, 56.6, 56.5. Calcd. for $C_{20}H_{22}O_7$: C, 64.1; H, 5.9. Found: C, 64.0; H, 5.8.

4,5,6-Trimethoxy-2-(4-methoxyphenyl)benzofuran, ***3n.*** Yield = 10%. White solid: mp 120−121 °C; IR 2937, 2836, 1587, 1467, 1247, 1127 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.7, 2H), 6.96 (d, *J* = 8.7, 2H), 6.92 (s, 1H), 6.83 (s, 1H), 4.12 (s, 3H), 3.91 (s, 3H), 3.87 (s, 3H), 3.85 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.9, 154.6, 152.1, 151.9, 145.9, 137.5, 126.1, 123.7, 115.4, 114.5, 97.9, 90.9, 61.6, 60.8, 56.6, 55. 6. Calcd. for $C_{18}H_{18}O_5$: C, 68.8; H, 5.8. Found: C, 68.5; H, 5.8.

2-(4-Methoxyphenyl)naphtho[1,2-b]furan,[20] ***3o.*** Yield = 41%. Light brown solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37 (d, *J* = 8.2, 1H), 7.92 (d, *J* = 8.2, 1H), 7.88 (d, *J* = 8.8, 2H), 7.64 (s, 2H), 7.59 (t, *J* = 7.6, 1H), 7.47 (t, *J* = 7.5, 1H), 7.02 (d, *J* = 8.8, 2H), 7.00 (s, 1H), 3.88 (s, 3H).

2-(4-Methoxyphenyl)naphtho[2,1-b]furan,[21] ***3p.*** Yield = 53%. White solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (d, *J* = 8.2, 1H), 7.93 (d, *J* = 8.1, 1H), 7.84 (d, *J* = 8.9, 2H), 7.67 (d, *J* = 2.6, 2H), 7.57 (t, *J* = 7.0, 1H), 7.47 (t, *J* = 7.0, 1H), 7.37 (s, 1H), 6.99 (d, *J* = 8.8, 2H), 3.86 (s, 3H).

General Procedure for the Synthesis of α-Phenoxyketones 5a−j and α-Naphthoxyketone 5l.[12] A mixture of the phenol or naphthol **1** (2 mmol), the α-haloketone **2** (2 mmol) and potassium carbonate (4 mmol, 0.55 g) in acetone (2 mL) was irradiated with microwaves at 130 °C and 100−400 W for 10 min (pressure 5−10 bar) in a focused Biotage Initiator microwave reactor. The resulting mixture was filtered through a Celite pad and evaporated. The residue was purified by precipitation in diethylether or by column chromatography

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on silica gel using ethyl acetate/hexane as eluent to yield the corresponding product **5**.

2-(3,5-Dimethoxyphenoxy)-1-(4-methoxyphenyl)ethanone,[22] ***5a.*** Yield = 99%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, J = 8.9, 2H), 6.96 (d, J = 8.9, 2H), 6.13 (d, J = 2.1, 2H), 6.11 (t, J = 2.0, 1H), 5.15 (s, 2H), 3.88 (s, 3H), 3.75 (s, 6H).

2-(3,5-Dimethoxyphenoxy)-1-(3,5-dimethoxyphenyl)ethanone, ***5b.*** Yield = 93%. Yellow solid: mp 104−105 °C; IR 2931, 1709, 1209, 1160,1023 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.11 (d, J = 2.2, 2H), 6.69 (t, J = 2.2, 1H), 6.13 (d, J = 1.9, 2H), 6.12 (d, J = 1.9, 1H), 5.18 (s, 2H), 3.84 (s, 6H), 3.76 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.0, 161.8, 161.3, 160.1, 136.6, 106.3, 106.1, 94.1, 71.0, 55.8, 55.6. Calcd. for $C_{18}H_{20}O_6$: C, 65.0; H, 6.1. Found: C, 65.0; H, 6.1.

2-(3,5-Dimethoxyphenoxy)-1-(3,4,5-trimethoxyphenyl)ethanone, ***5c.*** Yield = 99%. White solid: mp 86−87 °C; IR 2937, 1703, 1203, 1148, 1130, 1075 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (s, 2H), 6.13 (d, J = 1.9, 2H), 6.12 (d, J = 1.9, 1H), 5.16 (s, 2H), 3.93 (s, 3H), 3.91 (s, 6H), 3.76 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.4, 161.8, 160.1, 153.5, 143.6, 129.9, 106.1, 94.1, 94.0, 71.1, 61.1, 56.6, 55.6. Calcd. for $C_{19}H_{22}O_7$: C, 63.0; H, 6.1. Found: C, 62.8; H, 6.2.

2-(3,5-Dimethoxyphenoxy)-1-(4-fluorophenyl)ethanone,[10c] ***5d.*** Yield = 97%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (dd, J = 8.1, 5.6, 2H), 7.19 (t, J = 8.4, 2H), 6.15 (s, 3H), 5.18 (s, 2H), 3.78 (s, 6H).

1-(3,5-bis(Benzyloxy)phenyl)-2-(3,5-dimethoxyphenoxy)-ethanone, ***5e.*** Yield = 99%. White solid: mp 125 °C; IR 2914, 1703, 1201, 1166, 1070 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (ddd, J = 26.6, 13.5, 7.0, 10H), 7.20 (d, J = 2.2, 2H), 6.84 (t, J = 2.2, 1H), 6.12 (s, 3H), 5.15 (s, 2H), 5.08 (s, 4H), 3.75 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.8, 161.8, 160.4, 160.1, 136.6, 136.5, 128.9, 128.4, 127.8, 107.9, 107.3, 94.1, 94.0, 70.9, 70.7, 55.6. Calcd. for $C_{30}H_{28}O_6$: C, 74.4; H, 5.8. Found: C, 74.3; H, 5.8.

4-(2-(3,5-Dimethoxyphenoxy)acetyl)benzonitrile, ***5f.*** Yield = 99%. Yellow solid: mp 116−117 °C; IR 2885, 2229, 1706, 1215, 1157 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, J = 8.3, 2H), 7.79 (d, J = 8.3, 2H), 6.12 (d, J = 1.8, 1H), 6.09 (d, J = 1.8, 2H), 5.16 (s, 2H), 3.75 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.0, 162.0, 159.7, 137.8, 132.8, 129.0, 117.9, 117.3, 94.2, 94.0, 71.3, 55.6. Calcd. for $C_{17}H_{15}NO_4$: C, 68.7; H, 5.1; N, 4.7. Found: C, 68.7; H, 5.0; N, 4.8.

2-(3,5-Dimethoxyphenoxy)-1-(2,6-dimethoxypyridin-3-yl)-ethanone, ***5g.*** Yield = 73%. White solid: mp 108−109 °C; IR 2919, 1683, 1590, 1336, 1167, 1155, 1088 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (d, J = 8.4, 1H), 6.42 (d, J = 8.4, 1H), 6.12 (d, J = 1.9, 2H), 6.10 (d, J = 1.9, 1H), 5.17 (s, 2H), 4.10 (s, 3H), 4.00 (s, 3H), 3.76 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 192.0, 166.4, 162.8, 161.7, 160.5, 143.4, 111.0, 103.7, 94.1, 93.6, 73.9, 55.5, 54.3, 54.2. Calcd. for $C_{17}H_{19}NO_6$: C, 61.2; H, 5.8; N, 4.2. Found: C, 61.3; H, 5.7; N, 4.2.

2-(3,5-Dimethoxyphenoxy)-1-phenylpropan-1-one,[23] ***5h.*** Yield = 84%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (d, J = 8.3, 2H), 7.61−7.53 (m, 1H), 7.46 (t, J = 7.3, 2H), 6.06 (d, J = 0.6, 3H), 5.45 (q, J = 6.7, 1H), 3.71 (s, 3H), 3.70 (s, 3H), 1.68 (dd, J = 6.8, 1.0, 3H).

1-(3,5-Difluorophenyl)-2-(3,5-dimethoxyphenoxy)ethanone, ***5i.*** Yield = 24%. Yellow solid: mp 92−93 °C; IR 2847, 1713, 1309, 1203, 1150, 1056 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (d, J = 5.6, 2H), 7.06 (t, J = 8.2, 1H), 6.13 (s, 1H), 6.11 (s, 2H), 5.12 (s, 2H), 3.76 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 192.6, 163.3 (dd, J = 251.5, 11.7), 161.9, 159.7, 137.5 (t, J = 7.7), 111.5 (dd, J = 20.1, 6.6), 109.4 (t, J = 25.3), 94.3, 94.0, 71.2, 55.6. Calcd. for $C_{16}H_{14}F_2O_4$: C, 62.3; H, 4.6. Found: C, 62.3; H, 4.5.

1-(3,5-bis(Benzyloxy)phenyl)-2-(3,4,5-trimethoxyphenoxy)-ethanone, ***5j.*** Yield = 20%. White solid: mp 111 °C; IR 2942, 1704, 1289, 1152, 1020 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50−7.29 (m, 10H), 7.22 (s, 2H), 6.86 (s, 1H), 6.19 (s, 2H), 5.16 (s, 2H), 5.08 (s, 4H), 3.82 (s, 6H), 3.78 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.1, 160.4, 154.8, 154.0, 136.5, 136.4, 133.3, 128.9, 128.5, 127.8, 107.7, 107.3, 93.1, 71.4, 70.6, 61.2, 56.4. Calcd. for $C_{31}H_{30}O_7$: C, 72.4; H, 5.9. Found: C, 72.1; H, 5.6.

2-(3,5-Dichlorophenoxy)-1-(4-methoxyphenyl)ethanone, ***5k.*** Yield = 99%. Pale pink solid: mp 95−96 °C; IR 2838, 1691, 1241, 1085 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, J = 8.9, 2H), 6.96 (s, 1H), 6.96 (d, J = 8.8, 2H), 6.82 (s, 2H), 5.20 (s, 2H), 3.88 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 191.8, 164.5, 159.4, 135.7, 130.6, 127.5, 122.1, 114.4, 114.2, 70.9, 55.7. Calcd. for $C_{15}H_{12}Cl_2O_3$: C, 57.9; H, 3.9. Found: C, 58.1; H, 4.0.

1-(4-Methoxyphenyl)-2-(naphthalen-1-yloxy)ethanone,[20] ***5l.*** Yield = 70%. White solid: ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.44−8.27 (m, 1H), 7.85 (d, J = 7.7, 2H), 7.76−7.64 (m, 1H), 7.47−7.30 (m, 3H), 7.21 (t, J = 7.9, 1H), 6.74 (d, J = 7.7, 2H), 6.62 (d, J = 7.5, 1H), 5.16 (s, 2H), 3.62 (s, 3H).

General Procedure for the Synthesis of 3-Aryl Benzo[*b*]-furans 4a−i and Naphthofuran 4j. The α-phenoxyketone or α-naphthoxyketone **5** (2.0 mmol) was dispersed in neutral alumina (34 mmol, 3.47 g) and heated in an oil bath at 150 °C (internal temperature monitored by a fiber optic probe) for 3 h. The resulting mixture was filtered through a Celite pad and evaporated. The residue was purified by column chromatography on silica gel using ethyl acetate/hexane as eluent to yield the corresponding product **4**.

4,6-Dimethoxy-3-(4-methoxyphenyl)benzofuran,[22] ***4a.*** Yield = 78%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, J = 8.7, 2H), 7.43 (s, 1H), 6.93 (d, J = 8.7, 2H), 6.67 (d, J = 1.8, 1H), 6.35 (d, J = 1.7, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.80 (s, 3H).

3-(3,5-Dimethoxyphenyl)-4,6-dimethoxybenzofuran, ***4b.*** Yield = 54%. White solid: mp 92−93 °C; IR 2834, 1590, 1415, 1201, 1141, 1082 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (s, 1H), 6.82 (s, 2H), 6.68 (s, 1H), 6.46 (s, 1H), 6.37 (s, 1H), 3.86 (s, 3H), 3.83 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.6, 159.4, 158.1, 154.8, 140.3, 134.4, 123.0, 109.9, 107.6, 99.9, 94.9, 88.7, 55.9, 55.6, 55.6. Calcd. for $C_{18}H_{18}O_5$: C, 68.8; H, 5.8. Found: C, 68.7; H, 5.8.

4,6-Dimethoxy-3-(3,4,5-trimethoxyphenyl)benzofuran, ***4c.*** Yield = 50%. Yellow oil: IR 2934, 1580, 1414, 1215, 1150, 1120 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (s, 1H), 6.89 (s, 2H), 6.68 (d, J = 1.9, 1H), 6.38 (d, J = 1.9, 1H), 3.90 (s, 9H), 3.87 (s, 3H), 3.84 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.4, 158.2, 154.7, 153.0, 140.0, 128.0, 123.1, 109.8, 106.8, 94.9, 88.7, 61.2, 56.3, 56.0, 55.6.

3-(4-Fluorophenyl)-4,6-dimethoxybenzofuran,[10c] ***4d.*** Yield = 37%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (dd, J = 8.2, 5.7, 2H), 7.44 (s, 1H), 7.07 (t, J = 8.6, 2H), 6.67 (s, 1H), 6.35 (s, 1H), 3.85 (s, 3H), 3.79 (s, 3H).

3-(3,5-bis(Benzyloxy)phenyl)-4,6-dimethoxybenzofuran, ***4e.*** Yield = 26%. Yellow oil: IR 2935, 1585, 1453, 1213, 1144, 1050 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (s, 1H), 7.46−7.26 (m, 10H), 6.92 (d, J = 2.2, 2H), 6.66 (d, J = 1.9, 1H), 6.62 (t, J = 2.2, 1H), 6.35 (d, J = 1.8, 1H), 5.07 (s, 4H), 3.84 (s, 3H), 3.76 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.8, 159.4, 158.1, 154.8, 140.4, 137.3, 134.5, 128.8, 128.2, 127.7, 123.0, 109.9, 108.8, 101.6, 94.9, 88.7, 70.4, 56.0, 55.6.

4-(4,6-Dimethoxybenzofuran-3-yl)benzonitrile, ***4f.*** Yield = 42%. Yellow solid: mp 151−152 °C; IR 2938, 2220, 1598, 1503, 1215, 1044, 1085 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, J = 8.0, 2H), 7.66 (d, J = 8.2, 2H), 7.54 (s, 1H), 6.69 (s, 1H), 6.38 (s, 1H), 3.87 (s, 3H), 3.82 (s, 3H); ^{13}C NMR (126 MHz, CDCl3) δ 159.8, 158.3, 154.6, 140.9, 137.6, 131.9, 129.9, 121.9, 119.3, 110.7, 109.2, 95.2, 88.7, 56.0, 55.6. Calcd. for $C_{17}H_{13}NO_3$: C, 73.1; H, 4.7; N, 5.0. Found: C, 73.1; H, 4.6; N, 5.1.

3-(4,6-Dimethoxybenzofuran-3-yl)-2,6-dimethoxyppyridine, ***4g.*** Yield = 12%. Light yellow solid: mp 131 °C; 2943, 1586, 1481, 1315, 1080, 1023 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, J = 8.0, 1H), 7.58 (s, 1H), 6.67 (s, 1H), 6.36 (d, J = 8.0, 1H), 6.32 (s, 1H), 3.97 (s, 3H), 3.95 (s, 3H), 3.85 (s, 3H), 3.76 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.3, 160.3, 159.2, 157.5, 154.8, 143.1, 141.4, 116.0, 110.9, 106.8, 100.1, 94.8, 88.6, 56.0, 55.6, 53.8, 53.6. Calcd. for $C_{17}H_{17}NO_5$: C, 64.8; H, 5.4; N, 4.4. Found: C, 64.6; H, 5.5; 4.5.

4,6-Dimethoxy-2-methyl-3-phenylbenzofuran,[10c,24] ***4h.*** Yield = 40%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47−7.27 (m, 5H), 6.63 (s, 1H), 6.30 (s, 1H), 3.84 (s, 3H), 3.70 (s, 3H), 2.39 (s, 3H).

3-(3,5-Difluorophenyl)-4,6-dimethoxybenzofuran, ***4i.*** Yield = 68%. Light yellow solid: mp 102−103 °C; IR 2937, 1591, 1501, 1444, 1354, 1217, 1113 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) 7.49 (s, 1H), 7.20−7.11 (m, 2H), 6.75 (tt, J = 9.0, 2.3, 1H), 6.66 (d, J = 1.9, 1H), 6.36 (d, J = 1.9, 1H), 3.84 (s, 3H), 3.82 (s, 3H); ^{13}C NMR

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(75 MHz, $CDCl_3$) 162.82 (dd, J = 246.5, 13.3), 159.7, 158.2, 154.6, 140.7, 135.8 (t, J = 10.6), 121.5, 112.2 (dd, J = 8.1, 17.4), 109.2, 102.4 (t, J = 25.5), 95.1, 88.6, 55.9, 55.5. Calcd. for $C_{16}H_{12}F_2O_3$: C, 66.2; H, 4.2. Found: C, 66.2; H, 4.3.

3-(4-Methoxyphenyl)naphtho[1,2-b]furan,[20,22] **4j**. Yield = 16%. Yellow solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 (d, J = 8.2, 1H), 7.95 (d, J = 8.1, 1H), 7.87 (s, 1H), 7.85 (d, J = 8.7, 1H), 7.71 (d, J = 8.6, 1H), 7.61 (t, J = 9.0, 3H), 7.65−7.58 (m, 1H), 7.04 (d, J = 8.5, 2H), 3.88 (s, 3H).

Moracin M.[11] Boron tribromide (1 M in dichloromethane, 1.2 mL, 1.2 mmol, 2 equiv per methoxy group to be deprotected) was added dropwise to a solution of benzofuran **3d** (0.3 mmol) in anhydrous dichloromethane (10 mL) at 0 °C under argon atmosphere. The mixture was stirred for 16 h at room temperature, and then methanol (1.2 mL) was added dropwise at 0 °C.[25] The resulting mixture was purified by column chromatography on silica gel using ethyl acetate/hexane 1:1 as eluent to yield the product. Yield = 25%. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.52 (s, 1H), 9.37 (s, 2H), 7.38 (d, J = 8.4, 1H), 7.06 (s, 1H), 6.92 (s, 1H), 6.74 (d, J = 8.3, 1H), 6.68 (s, 2H), 6.21 (s, 1H).

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra of new compounds, crystallographic data of compounds **3a** and **4a**, and computational data of stationary points **2l** + phenoxide, **TS1**, **6**, **7**, **TS2**, **TS3**, **9a**, **9b**, **TS4a**, and **TS4b**. This material is available free of charge via the Internet at http://pubs.acs.org

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