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Lewis Acid Mediated [3+2] Coupling of Masked Benzoquinones with Styrenes: Facile Synthesis of 2,3-Dihydrobenzofurans

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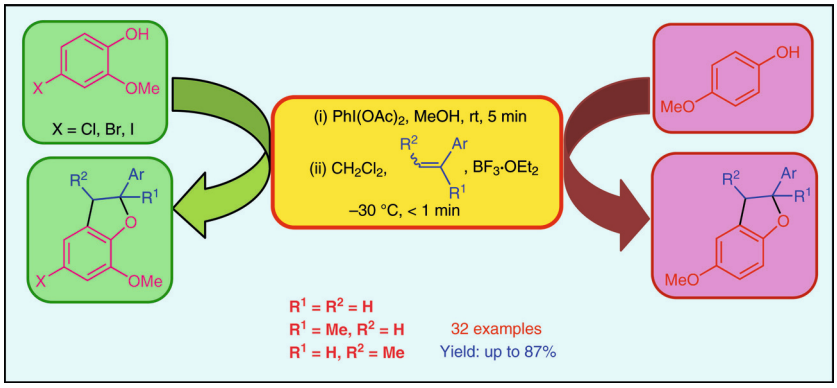

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Abstract We have developed an efficient, simple, mild, and rapid method for the construction of dihydrobenzofuran derivatives by the [3+2] coupling of masked *o*-benzoquinones with styrene derivatives triggered by boron trifluoride diethyl etherate. This new [3+2] coupling protocol proceeds smoothly to afford dihydrobenzofuran derivatives in good to high yields within one minute. The method was extended to cycloaddition of *p*-benzoquinone monoketal with styrenes.

Key words hypervalent iodine reagents, oxidation, dearomatization, benzoquinone monoketals, cycloaddition, benzofurans

The dihydrobenzofurans (DHBs) are a significant family of oxygen heterocycles, and the DHB privileged scaffold appears in many natural products and biologically active molecules (Figure 1).[1–3] DHBs are present as core structures of many molecules that exhibit such properties as anti-multidrug resistance, insecticidal, anticancer, antifungal, antibacterial, antitrypanosomal, and antimalarial activities; furthermore, some members of this class act as potent inducers of quinone reductase, an anticarcinogenic marker enzyme.[2,4] Consequently, the synthesis of DHBs has received much attention, and many efficient protocols have been reported in literature.[5,6] DHBs can also be synthesized by [3+2] coupling of quinones with alkene nucleophiles.[7] In recent years, the enantioselective synthesis of DHBs has also received attention.[8]

Over the past few decades, dearomatization of phenols has received much attention.[9] Phenols are readily available electron-rich compounds that exhibit nucleophilic character. However, in the presence of various oxidizing reagents, these nucleophilic hydroxyarenes and their ether derivatives can be converted into electrophilic intermediates that will then couple with various nucleophiles.

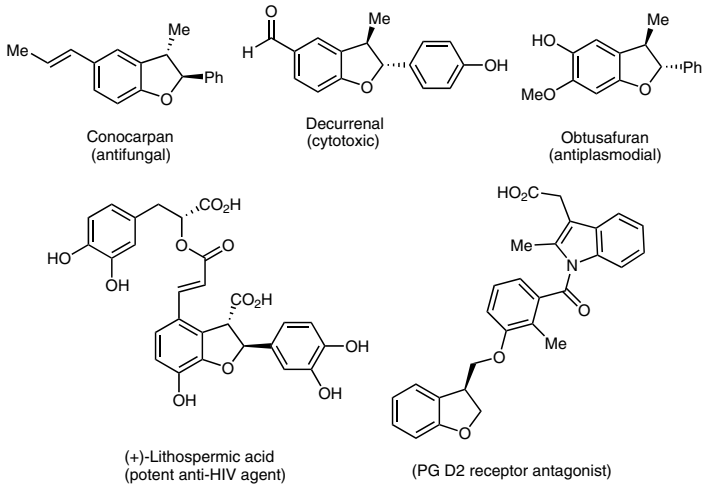
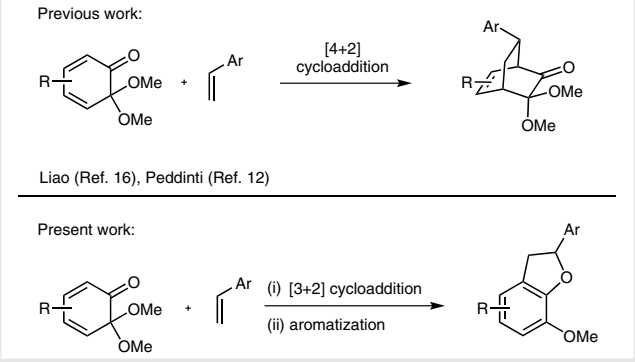


Figure 1 Examples of dihydrobenzofuran-containing natural products and pharmaceuticals

The oxidative dearomatization of 2- and 4-alkoxyphenols leads to the formation of cyclohexa-2,4-dien-1-ones (masked *o*-benzoquinones; MOBs) and cyclohexa-2,5-dien-1-ones (masked *p*-benzoquinones; MPBs).[10] These reactive entities can be easily synthesized from the corresponding alkoxyphenols by treatment with hypervalent iodine reagents in alcoholic solvents.

Masked benzoquinones with various functionalities are important intermediates in the synthesis of many natural products.[11] MOBs, which are linearly conjugated cyclohexadienones, undergo various types of reactions, including cycloaddition[12] and conjugate addition,[13] whereas MPBs, which are the cross-conjugated cyclohexadienones, display reactivity towards various nucleophilic species.[14]

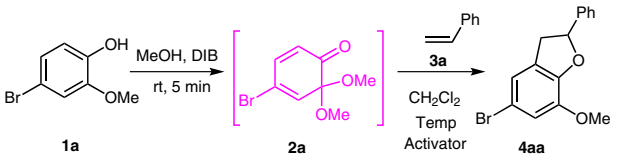
We recently developed an efficient and rapid method for substitution of MOBs with electron-rich arenes for the synthesis of oxygenated biaryls by using a Lewis acid as an activator; this reaction is unprecedented in MOB chemistry.[15] The *o*-benzoquinone monoketals generated in situ undergo [4+2] cycloaddition with styrenes[12,16] (Scheme 1, top). In continuation of our efforts to harness the reactivity of *o*-benzoquinone monoketals, we report here a simple, mild, and rapid protocol for the synthesis of dihydrobenzofurans through [3+2] coupling of MOBs with styrenes in the presence of a Lewis acid (Scheme 1, bottom).



Scheme 1 [4+2] and [3+2] cycloaddition reactions of MOBs.

To optimize the reaction conditions, we started our investigations by selecting 4-bromoguaiacol (**1a**; 4-bromo-2-methoxyphenol) and styrene (**3a**) as model reactants. In our initial experiments, we dearomatized **1a** by treatment with (diacetoxyiodo)benzene (DIB) in methanol to generate the MOB **2a**. The methanol was then removed under vacuum to prevent its nucleophilic attack on the cyclohexadienone. The resulting residue was diluted with CH_2Cl_2, styrene and 3,5-dinitrobenzoic acid (3,5-DNB) were added sequentially at 0 °C, and the mixture was kept at room temperature for one hour; however, no reaction was observed (Table 1, entry 1). Similarly, PTSA did not promote the reaction (entry 2). When TFA was added as an activator, the dihydrobenzofuran derivative **4aa** was obtained in 59% yield in 40 min (entry 3). This product was formed by a formal [3+2] coupling of the MOB with the alkene. To improve the yield of the product, we screened various Lewis acid activators ($ZrCl_4$, $FeCl_3$, and $BF_3{\cdot}OEt_2$), all of which gave the dihydrobenzofuran product **4aa** (Table 1, entries 4–6). Among the activators used, $BF_3{\cdot}OEt_2$ (1.0 equiv) was the most effective, producing the dihydrobenzofuran in the highest yield within one minute at 0 °C. Consequently, we continued further screening of the reaction with $BF_3{\cdot}OEt_2$. However, when the reaction was performed at room temperature, the yield of the product decreased to 42% (entry 7). On increasing the amount of $BF_3{\cdot}OEt_2$ to 2.0 equivalents, dihydrobenzofuran **4aa** was obtained in a higher yield when the reaction was performed at 0 °C or at –30 °C (entry 9). However, we observed a decrease in the yield on changing the solvent from CH_2Cl_2 to MeCN (entry 10).

Table 1 Optimization of the Reaction Conditions



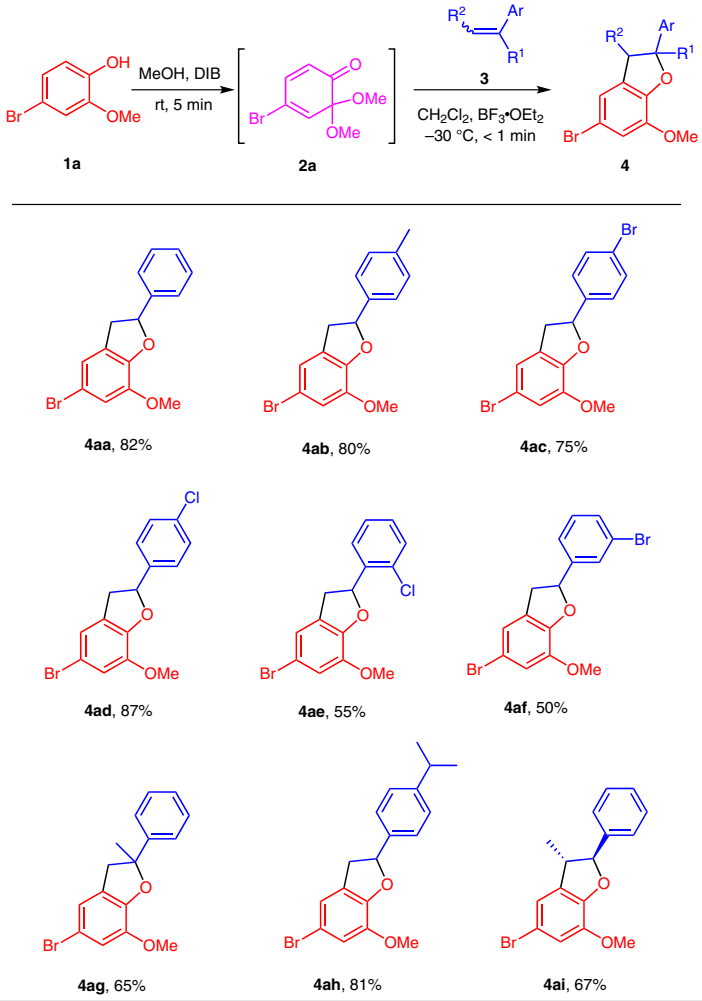
1a **2a** **4aa**

Entry	Activator	Equiv	Temp	Time[a] (min)	Yield[b] (%)
1	3,5-DNB	0.2	0 °C–r.t.	60	–[c]
2	PTSA	0.2	0 °C–r.t.	60	–[c]
3	TFA	2	0 °C	40	59
4	$ZrCl_4$	2	0 °C	10	32
5	$FeCl_3$	2	0 °C	10	32
6	$BF_3{\cdot}OEt_2$	1	0 °C	<1	60
7	$BF_3{\cdot}OEt_2$	1	r.t.	<1	42
8	$BF_3{\cdot}OEt_2$	2	0 °C	<1	80
9	$BF_3{\cdot}OEt_2$	2	–30 °C	<1	82
10[d]	$BF_3{\cdot}OEt_2$	2	0 °C	<1	60

[a] Time after addition of activator.
[b] Isolated yield.
[c] No reaction.
[d] MeCN was used instead of CH_2Cl_2.

After establishing the optimal reaction conditions, we studied the scope of the reaction. First, we explored the reaction of 4-bromoguaiacol (**1a**) with various substituted styrenes **3a–i** with electron-donating or electron-withdrawing groups at various positions (Scheme 2). All the reactions reached completion within a minute of addition of $BF_3{\cdot}OEt_2$, giving the corresponding dihydrobenzofuran derivatives **4aa–ai** in good to high yields of 50–87%.[17]

To demonstrate the generality of the present protocol, we chose 4-haloguaiacols with chloro or iodo substituents as substrates. We dearomatized 4-chloroguaiacol (**1b**) by treatment with DIB in MeOH. After formation of the corresponding MOB **2b**, the solvent was evaporated under reduced pressure and the residue was dissolved in CH_2Cl_2. The

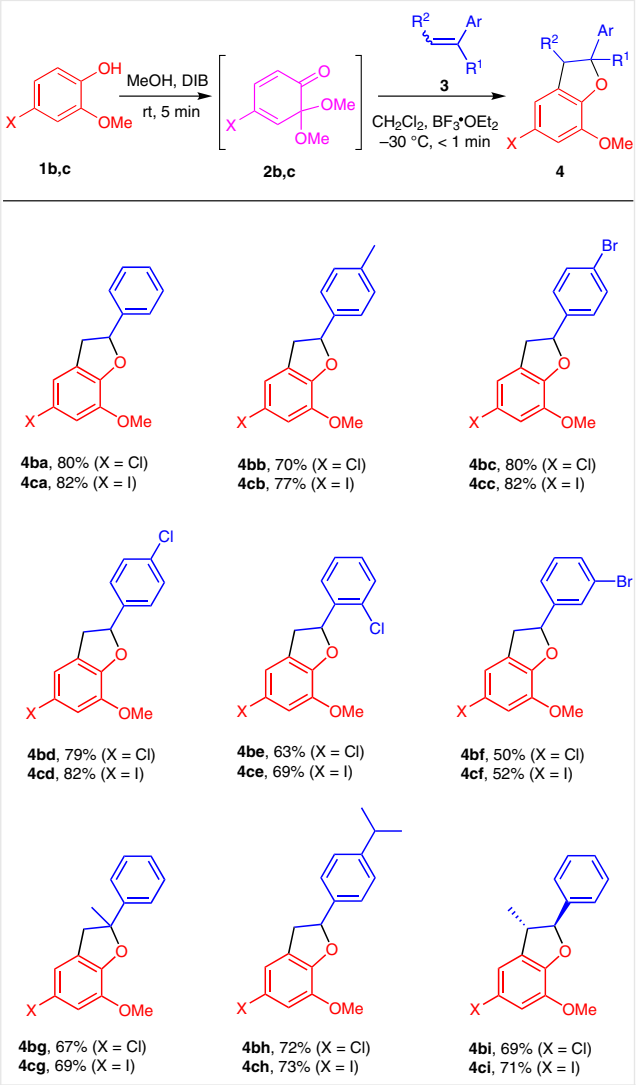


Scheme 2 Scope of styrenes. After oxidation of the guaiacol derivative, MeOH was removed and the residue was diluted with CH_2Cl_2, cooled to –30 °C, and treated sequentially with alkene **3** and $BF_3{\cdot}OEt_2$.

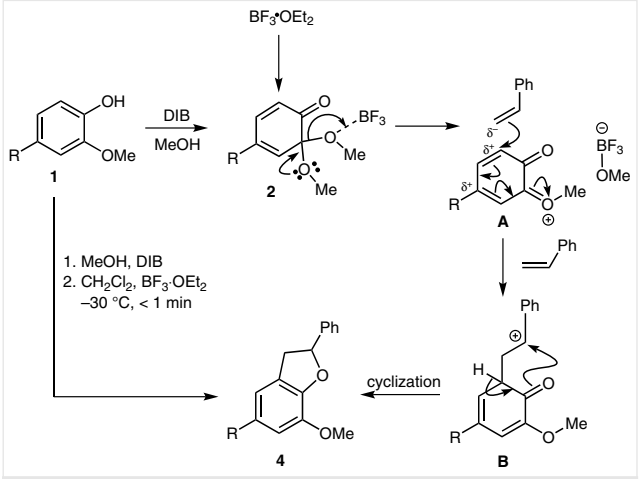
in situ generated MOB **2b** then reacted with various alkene derivatives under the optimized reaction conditions to give the corresponding dihydrobenzofuran derivatives **4ba–bi** rapidly and in moderate to high yields.[17] Similarly, we examined the reactions of 4-iodoguaiacol (**1c**) with various alkenes. Oxidative dearomatization of 4-iodoguaiacol (**1c**) gave intermediate **2c**, which was trapped with various alkene derivatives in the presence of $BF_3{\cdot}OEt_2$ at –30 °C. In all cases, the reactions proceeded cleanly and reached completion within a minute of addition of $BF_3{\cdot}OEt_2$ to provide the corresponding dihydrobenzofuran derivatives **4ca–4ci** in 52–82% yield (Scheme 3).[17] Note that the reactions of **1a**, **1b**, and **1c** with **3i** (*cis* and *trans*) gave the corresponding *trans*-dihydrobenzofurans **4ai**, **4bi**, and **4ci** stereoselectively.[6b,18]

Scheme 4 shows a plausible mechanistic model for the [3+2] coupling reaction of *o*-benzoquinone monoketals **2** with styrene. Initially, one of the methoxy groups of the MOB **2**, derived by oxidative dearomatization of the guaiacol derivative **1**, coordinates with the Lewis acid $BF_3{\cdot}OEt_2$; this is followed by loss of a methoxy group to generate intermediate **A**, bearing a positive charge on the oxygen of the remaining methoxy group. The π-nucleophile then adds to the α-carbon of intermediate **A**. This pseudo-S_N2' attack by styrene gives intermediate **B**, which undergoes further cyclization onto the carbonyl functionality of the MOB, leading to the formation of the dihydrobenzofuran derivative **4**.

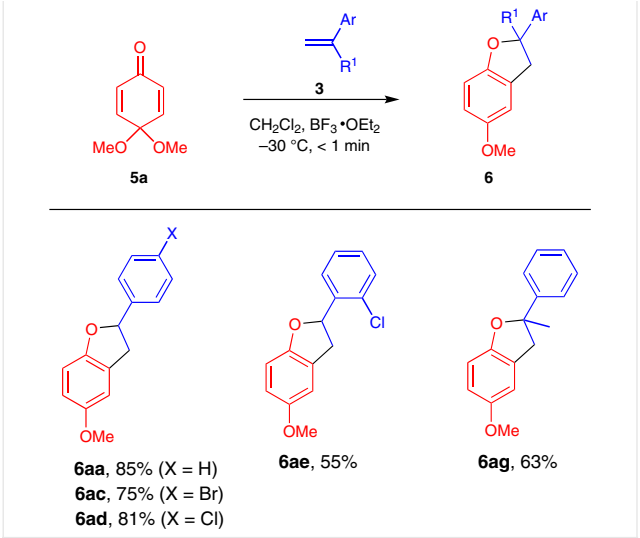
To find out whether our method would tolerate cross-conjugated cyclohexadienones, we applied our protocol to the [3+2] coupling of the *p*-benzoquinone monoketal **5a** with alkenes (Scheme 5). For this, we synthesized **5a** by oxidative dearomatization of 4-methoxyphenol, and we examined its reaction with various styrene derivatives under



Scheme 3 Substrate scope. After oxidation of the guaiacol derivative, MeOH was removed and the residue was diluted with CH_2Cl_2, cooled to –30 °C, and treated sequentially with alkene **3** and $BF_3{\cdot}OEt_2$.



Scheme 4 Plausible mechanism



Scheme 5 The [3+2] coupling of *p*-quinone monoketal **5a** with styrenes. Yields refer to the isolated products.

the optimized conditions. In all cases, the reactions proceeded smoothly to provide the corresponding DHB **6** in good to high yields of 55–85% (Scheme 5). It is worth mentioning that Kita and co-workers have reported a [3+2] cycloaddition of *p*-quinone monoketals with vinyl arenes in fluorinated solvents.[7a]

In conclusion, we have explored the reactivity of masked *o*-benzoquinones toward oxidative [3+2] coupling with alkenes in the presence of a Lewis acid. This method provides dihydrobenzofuran derivatives in short reaction times and in good to high yields. The present simple, mild, and rapid protocol for the synthesis of the target scaffolds is also compatible with *p*-quinone monoketal scaffolds.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588622.

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(17) **2,3-Dihydrobenzofuran Derivatives 4**; **General Procedure**

$PhI(OAc)_2$ (0.177 g, 0.55 mmol, 1.1 equiv) was added to a solution of the appropriate guaiacol derivative **1** (0.5 mmol) in MeOH (5 mL), and the mixture was stirred for 5 min at r.t. After generation of the *o*-benzoquinone monoketal **2**, as indicated by a yellow color of the solution, the MeOH was removed under reduced pressure and the residue was dissolved in CH_2Cl_2. The solution was cooled to –30 °C and the appropriate alkene (1 mmol) and $BF_3{\cdot}OEt_2$ (1 mmol) were added sequentially. When the reaction was complete (TLC), it was quenched with sat. aq $NaHCO_3$ and the mixture was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic phases were dried (Na_2SO_4), filtered, and evaporated to dryness. The crude product was purified by column chromatography (silica gel, 1–2% EtOAc–hexanes).

5-Bromo-7-methoxy-2-phenyl-2,3-dihydrobenzofuran (4aa)

Viscous yellow liquid; yield: 0.124 g (82%). IR (KBr): 2928, 2851, 1615, 1484, 1293, 1270, 1197, 1094, 763, 699 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.41–7.29 (m, 5 H), 6.95–6.94 (m, 1 H), 6.91–6.90 (m, 1 H), 5.80 (t, *J* = 9.0 Hz, 1 H), 3.87 (s, 3 H), 3.61 (dd, *J* = 9.5, 15.5 Hz, 1 H), 3.23 (dd, *J* = 8.5, 16.0 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.1 (C), 144.7 (C), 140.9 (C), 129.1 (C), 128.5 (CH), 128.1 (CH), 125.8 (CH), 119.8 (CH), 114.6 (CH), 112.3 (C), 85.1 (CH), 56.1 (OCH_3), 38.5 (CH_2).

5-Bromo-2-(4-isopropylphenyl)-7-methoxy-2,3-dihydrobenzofuran (4ah)

Viscous colorless liquid; yield: 0.140 g (81%). IR (KBr): 2959, 2931, 1615, 1483, 1293, 1195, 1095, 946, 831, 776 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.30 (d, *J* = 8.0 Hz, 2 H), 7.20 (d, *J* = 7.5 Hz, 2 H), 6.92 (s, 1 H), 6.88 (s, 1 H), 5.75 (t, *J* = 8.5 Hz, 1 H), 3.83 (s, 3 H), 3.56 (dd, *J* = 9.0, 15.5 Hz, 1 H), 3.23 (dd, *J* = 8.5, 16.0 Hz, 1 H), 2.89 (quint, *J* = 6.5 Hz, 1 H), 1.23 (s, 3 H), 1.22 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.0 (C), 147.2 (C), 144.8 (C), 138.3 (C), 129.3 (C), 126.6 (CH), 126.1 (CH), 119.9 (CH), 114.8 (CH), 112.2 (C), 85.2 (CH), 56.2 (OCH_3), 38.3 (CH_2), 33.8 (CH_3), 23.9 (CH_3).

2-(4-Bromophenyl)-5-chloro-7-methoxy-2,3-dihydrobenzofuran (4bc)

Viscous colorless liquid; yield: 0.135 g (80%). IR (KBr): 2931, 2840, 1617, 1485, 1297, 1196, 1097, 1072, 946, 826, 790 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.38 (d, *J* = 8.0 Hz, 2 H), 7.17 (d, *J* = 7.5 Hz, 2 H), 6.69 (s, 1 H), 6.67 (s, 1 H), 5.66 (t, *J* = 8.5 Hz, 1 H), 3.77 (s, 3 H), 3.50 (dd, *J* = 10.0, 16.0 Hz, 1 H), 3.06 (dd, *J* = 8.5, 15.5 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.4 (C), 144.4 (C), 140.1 (C), 131.7 (CH), 128.1 (C), 127.5 (CH), 125.6 (C), 122.0 (C), 116.9 (CH), 111.9 (CH), 84.3 (CH), 56.1 (OCH_3), 38.5 (CH_2).

5-Chloro-7-methoxy-2-methyl-2-phenyl-2,3-dihydrobenzofuran (4bg)

Viscous colorless liquid; yield: 0.092 g (67%). IR (KBr): 2981, 2925, 1616, 1487, 1444, 1301, 1233, 1099, 838, 764 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.46 (d, *J* = 8.0 Hz, 2 H), 7.34 (t, *J* = 7.5 Hz, 2 H), 7.24–7.28 (m, 1 H), 6.76 (s, 1 H), 6.74 (s, 1 H), 3.91 (s, 3 H), 3.40 (q, *J* = 15.5 Hz, 2 H), 1.81 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.0 (C), 145.9 (C), 144.6 (C), 128.4 (CH), 127.2 (CH), 125.2 (C), 124.4 (CH), 117.1 (CH), 111.9 (CH), 90.5 (C), 56.2 (OCH_3), 45.0 (CH_2), 29.2 (CH_3).

5-Iodo-7-methoxy-2-methyl-2-phenyl-2,3-dihydrobenzofuran (4cg)

Viscous colorless liquid; yield: 0.126 g (69%). IR (KBr): 2966, 1609, 1482, 1294, 1141, 1093, 832, 761 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.47 (d, *J* = 7.5 Hz, 2 H), 7.36 (t, *J* = 7.5 Hz, 2 H), 7.29–7.26 (m, 1 H), 7.09 (s, 1 H), 7.07 (s, 1 H), 3.92 (s, 3 H), 3.42 (q, *J* = 15.5 Hz, 2 H), 1.83 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.2 (C), 145.9 (C), 145.3 (C), 129.7 (C), 128.3 (CH), 127.2 (CH), 126.1 (CH), 124.4 (CH), 120.2 (CH), 90.5 (C), 81.4 (C), 56.2 (OCH_3), 44.7 (CH_2), 29.1 (CH_3).

***trans*-5-Iodo-7-methoxy-3-methyl-2-phenyl-2,3-dihydrobenzofuran (4ci)**

Viscous colorless liquid; yield: 0.130 g (71%). IR (KBr): 2960, 1610, 1479, 1279, 1195, 1078, 965, 833 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.42–7.32 (m, 5 H), 7.08 (s, 2 H), 5.22 (d, *J* = 9.0 Hz, 1 H), 3.51 (s, 3 H), 3.48 (quint, *J* = 7.0 Hz, 1 H), 1.41 (d, *J* = 6.5 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.5 (C), 145.1 (C), 139.9 (C), 135.2 (C), 128.6 (CH), 128.4 (CH), 126.2 (CH), 125.0 (CH), 120.5 (CH), 93.3 (CH), 81.9 (C), 56.2 (OCH_3), 45.7 (CH), 18.0 (CH_3).

(18) For the stereochemistry of similar compounds, see ref. 6b and: Juhász, L.; Szilágyi, L.; Antus, S.; Visy, J.; Zsila, F.; Simonyi, M. *Tetrahedron* **2002**, *58*, 4261.