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A Novel Synthesis of 2-Functionalized Benzofurans by Palladium-Catalyzed Cycloisomerization of 2-(1-Hydroxyprop-2-ynyl)phenols Followed by Acid-Catalyzed Allylic Isomerization or Allylic Nucleophilic Substitution

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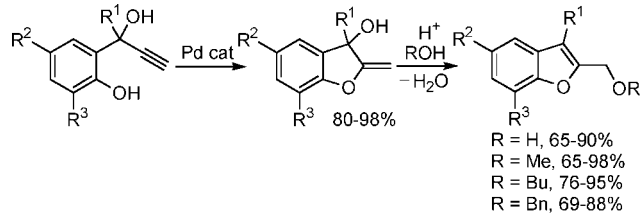

A novel two-step synthesis of 2-hydroxymethylbenzofurans **3** and 2-alkoxymethylbenzofurans **4**−**6**, based on palladium-catalyzed cycloisomerization of 2-(1-hydroxyprop-2-ynyl)phenols **1** under basic conditions to give 2-methylene-2,3-dihydrobenzofuran-3-ols **2**, followed by acid-catalyzed isomerization or allylic nucleophilic substitution with alcohols as nucleophiles, is reported. Cycloisomerization reactions leading to **2** (80−98% yields) were carried out at 40 °C in MeOH as the solvent, in the presence of a base and catalytic amounts of PdX_2 + 2KX (X = Cl, I). Isomerization reactions of **2** readily occurred at 25−60 °C in DME as the solvent, with H_2SO_4 as the proton source, to give 2-hydroxymethylbenzofurans **3** in 65−90% yields. In a similar manner, allylic nucleophilic substitution reactions of **2** with ROH as nucleophiles [carried out at 25−40 °C in ROH (R = Me) or ROH-DME mixtures (R = Bu, Bn) in the presence of H_2SO_4] afforded 2-alkoxymethylbenzofurans **4**, **5**, and **6** (R = Me, Bu, and Bn, respectively), in 65−98% yields.

Introduction

Benzofurans represent a very important class of heterocyclic compounds. The benzofuran core is present in many biologically active products, displaying a wide range of pharmacological activities, including anti-HIV, anticancer, and antimicrobial activity.[1] The importance of benzofurans justifies the continuous efforts directed toward the development of new, selective, and efficient syntheses of these heterocycles. In particular, during the last years, several approaches to benzofurans by heteroannulation of acyclic precursors have appeared in the literature.[2]

In this work, we report a novel method for the synthesis of functionalized benzofurans, 2-hydroxymethylbenzofurans **3** and 2-alkoxymethylbenzofurans **4**−**6** (R = Me, Bu, Bn, respectively) based on palladium-catalyzed cycloisomerization of 2-(1-hydroxyprop-2-ynyl)phenols **1** to give 2-methylene-2,3-dihydrobenzofuran-3-ols **2** followed by acid-catalyzed isomerization or allylic nucleophilic substitution using alcohols as nucleophiles, according to Scheme 1.

SCHEME 1

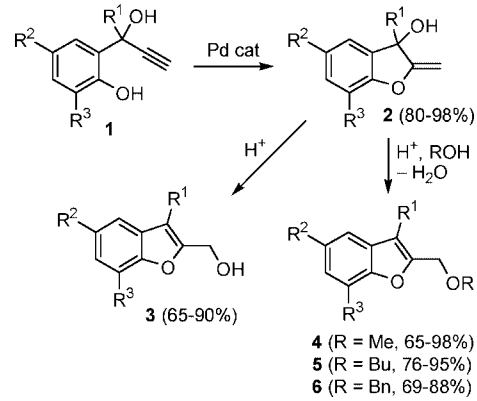

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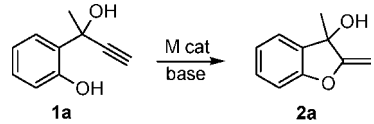
TABLE 1. Cycloisomerization Reactions of 2-(1-Hydroxy-1-methylprop-2-ynyl)phenol 1a under Different Conditions[a]



1a **2a**

entry	metal catalyst	base	**1a**/base/metal molar ratio	solvent	conversion of **1a**[b](%)	yield of **2a**[c](%)
1	PdI_2 + 2KI	none	100/0/1	MeOH	<10	traces[d]
2	PdI_2 + 2KI	morpholine	100/10/1	MeOH	86	70
3	PdI_2 + 2KI	morpholine	100/30/1	MeOH	91	74
4	PdI_2 + 2KI	morpholine	100/100/1	MeOH	100	98
5	$Pd(PPh_3)_4$	none	100/0/1	MeOH	100	49
6	$Pd(dba)_2$	none	100/0/1	MeOH	97	51
7	none	none		MeOH	<10	<5[d]
8	none	morpholine	100/10/0	MeOH	24	<5[d]
9	$PdCl_2$ + 2KCl	morpholine	100/10/1	MeOH	100	86
10	$PdCl_2$ + 2KCl	morpholine	100/100/1	MeOH	100	79
11	$CuCl_2$	morpholine	100/10/1	MeOH	70	47
12	$CuCl_2$	morpholine	100/100/1	MeOH	68	41
13	AuCl	morpholine	100/10/1	MeOH	100	61
14	$PdCl_2$ + 2KCl	Et_2NH	100/10/1	MeOH	100	74
15	$PdCl_2$ + 2KCl	$(i\text{-}Pr)_2NH$	100/10/1	MeOH	100	71
16	$PdCl_2$ + 2KCl	$(i\text{-}Pr)_2NEt$	100/10/1	MeOH	100	86
17	$PdCl_2$ + 2KCl	K_2CO_3	100/10/1	MeOH	100	42
18	$PdCl_2$ + 2KCl	morpholine	100/10/1	DME	100	69
19	$PdCl_2$ + 2KCl	morpholine	100/10/1	dioxane	100	15[d]
20	$PdCl_2$ + 2KCl	morpholine	100/10/1	MeCN	32	10
21	$PdCl_2$ + 2KCl	morpholine	100/10/1	DMA	100	72

[a] Unless otherwise noted, all reactions were carried out with a substrate concentration of 0.22 mmol of **1a**/mL of solvent (3 mmol scale based on **1a**) at 40 °C for 2 h. [b] Based on starting **1a**, by GLC. [c] Based on starting **1a**. [d] Partial decomposition of the substrate with formation of unidentified products was observed under these conditions.

Results and Discussion

The first experiments were carried out with 2-(1-hydroxy-1-methylprop-2-ynyl)phenol **1a** (R^1 = Me, R^2 = R^3 = H), easily obtained by ethynylation of 2-hydroxyacetophenone. This substrate was initially allowed to react in MeOH at 40 °C for 2 h in the presence of catalytic amounts of PdI_2 (1 mol %) in conjunction with 2 equiv of KI.[3] No reaction occurred under these conditions, as shown in Table 1, entry 1. However, the same reaction, carried out in the presence of 10 mol % of a base such as morpholine, did afford the desired 5-membered cycloisomerization product, 3-methyl-2-methylene-2,3-dihydrobenzofuran-3-ol **2a**, in 70% yield at 86% substrate conversion (Table 1, entry 2). With 30 mol % of morpholine, the substrate conversion and product yield after 2 h were 91% and 74%, respectively (Table 1, entry 3). With an equimolar amount of morpholine with respect to **1a**, substrate conversion rate and product yield reached 100% and 98%, respectively (entry 4, Table 1). These results suggest that deprotonation of the phenolic hydroxyl group is necessary for the reaction to occur. Either 5-*exo-dig* intramolecular nucleophilic attack to the triple bond coordinated to the metal center or triple bond insertion into the Pd−O bond of a phenoxypalladium intermediate, followed by protonolysis, may occur (Scheme 2; anionic ligands are omitted for clarity). In any case, no formation of the 6-membered

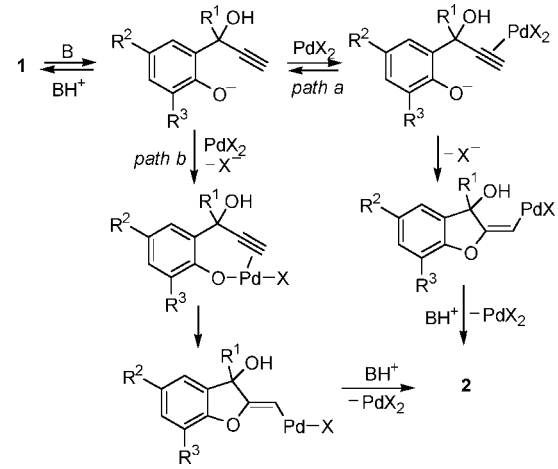
(1) For recent examples, see: (a) Schultz, D. M.; Prescher, J. A.; Kidd, S.; Marona-Lewicka, D.; Nichols, D. E.; Monte, A. *Bioorg. Med. Chem.* **2008**, *16*, 6242–6251. (b) Rizzo, S.; Riviere, C.; Piazzi, L.; Bisi, A.; Gobbi, S.; Bartolini, M.; Andrisano, V.; Morroni, F.; Tarozzi, A.; Monti, J.-P.; Rampa, A. *J. Med. Chem.* **2008**, *51*, 2883–2886. (c) Kirilmis, C.; Ahmedzade, M.; Servi, S.; Koca, M.; Kizirgil, A.; Kazaz, C. *Eur. J. Med. Chem.* **2008**, *43*, 300–308. (d) Ando, K.; Kawamura, Y.; Akai, Y.; Kunitomo, J.; Yokomizo, T.; Yamashita, M.; Ohta, S.; Ohishi, T.; Ohishi, Y. *Org. Biomol. Chem.* **2008**, *6*, 296–307. (e) Ettaoussi, M.; Peres, B.; Klupsch, D.; Delagrange, P.; Boutin, J.-A.; Renard, P.; Caignard, D.-H.; Chavatte, P.; Berthelot, P.; Lesieur, D.; Yous, S. *Bioorg. Med. Chem.* **2008**, *16*, 4954–4962. (f) Lee, Y.-K.; Woo, M.-H.; Kim, C.-H.; Kim, Y.; Lee, S.-H.; Jeong, B.-S.; Chang, H.-W.; Son, J.-K. *Planta Med.* **2007**, *73*, 1287–1291. (g) Oda, K.; Yamaguchi, Y.; Yoshimura, T.; Wada, K.; Nishizono, N. *Chem. Pharm. Bull.* **2007**, *55*, 1419–1421. (h) Filzen, G. F.; Bratton, L.; Cheng, X.-M.; Erasga, N.; Geyer, A.; Lee, C.; Lu, G.; Pulaski, J.; Sorenson, R. J.; Unangst, P. C.; Trivedi, B. K.; Xu, X. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3630–3635. (i) Cowart, M.; Gfesser, G. A.; Browman, K. E.; Faghih, R.; Miller, T. R.; Milicic, I.; Baranowski, J. L.; Krueger, K. M.; Witte, D. G.; Molesky, A. L.; Komater, V. A.; Buckley, M. J.; Diaz, G. J.; Gagne, G. D.; Zhou, D.; Deng, X.; Pan, L.; Roberts, E. M.; Diehl, M. S.; Wetter, J. M.; Marsh, K. C.; Fox, G. B.; Brioni, J. D.; Esbenshade, T. A.; Hancock, A. A. *Biochem. Pharmacol.* **2007**, *73*, 1243–1255. (j) Dixit, M.; Tripathi, B. K.; Tamrakar, A. K.; Srivastava, A. K.; Kumar, B.; Goel, A. *Bioorg. Med. Chem.* **2007**, *15*, 727–734. (k) Ohishi, Y. *Mol. Cancer Ther.* **2007**, *6*, 3605S–3605S. (l) Sakata, Y.; Kuramoto, M.; Ando, K.; Yamaguchi, M.; Kawasaki, I.; Kunitomo, J.; Yokomizo, T.; Ohishi, Y. *Org. Biomol. Chem.* **2007**, *5*, 3083–3086. (m) Mahboobi, S.; Uecker, A.; Cenac, C.; Sellmer, A.; Eichhorn, E.; Elz, S.; Boehmer, F.-D.; Dove, S. *Bioorg. Med. Chem.* **2007**, *15*, 2187–2197. (n) Yang, H.; Pang, J.-Y.; Cai, Y.-C.; Xu, Z.-L.; Xian, L.-J. *J. Pharm. Pharmacol.* **2006**, *58*, 1281–1287. (o) Rida, S. M.; El-Hawash, S. A. M.; Fahmy, H. T. Y.; Hazzaa, A. A.; El-Meligy, M. M. M. *Arch. Pharm. Res.* **2006**, *29*, 826–833. (p) Miklya, I. *Int. J. Neuropsychopharmacol.* **2006**, *9*, S197–S197. (q) Takahata, K.; Tsunekawa, H.; Hirami, C.; Yoshimi, K.; Shimazu, S.; Yoneda, F.; Katsuki, H.; Akaike, A. *Neurosci. Res.* **2006**, *55*, S117-S117. (r) Useglio, M.; Castellano, P. M.; Operto, M. A.; Torres, R.; Kaufman, T. S. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5097–5101. (s) Patel, H. J.; Sarra, J.; Caruso, F.; Rossi, M.; Doshi, U.; Stephani, R. A. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4644–4637. (t) Lazo, J. S.; Nunes, R.; Skoko, J. J.; de Oliveira, P. E. Q.; Vogt, A.; Wipf, P. *Bioorg. Med. Chem.* **2006**, *14*, 5643–5650. (u) Gundogdu-Karaburun, N.; Benkli, K.; Tunali, Y.; Ucucu, U.; Demirayak, S. *Eur. J. Med. Chem.* **2006**, *41*, 651–656. (v) Pautus, S.; Yee, S. W.; Jayne, M.; Coogan, M. P.; Simons, C. *Bioorg. Med. Chem.* **2006**, *14*, 3643–3653. (w) Dawood, K. M.; Abdel-Gawad, H.; Ellithey, M.; Mohamed, H. A.; Hezagi, B. *Arch. Pharm.* **2006**, *339*, 133–140. (x) Ahmad, G.; Mishra, P. K.; Gupta, P.; Yadav, P. P.; Tiwari, P.; Tamrakar, A. K.; Srivastava, A. K.; Maurya, R. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2139–2143. (y) Ujjinamatada, R. K.; Appala, R. S.; Agasimundin, Y. S. *J. Heterocycl. Chem.* **2006**, *43*, 437–441. (z) Saberi, M. R.; Vinh, T. K.; Yee, S. W.; Griffiths, B. J. N.; Evans, P. J.; Simons, C. *J. Med. Chem.* **2006**, *49*, 1016–1022. (aa) Rida, S. M.; El-Hawash, S. A. M.; Fahmy, H. T. Y.; Hazza, A. A.; El-Meligy, M. M. M. *Arch. Pharm. Res.* **2006**, *29*, 16–25. (bb) Gopalsamy, A.; Aplasca, A.; Ciszewski, G.; Park, K.; Ellingobe, J. W.; Orlowski, M.; Feld, B.; Howe, A. Y. M. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 457–460. (cc) Caijo, F.; Mosset, P.; Gree, R.; Chomarat, P.; Audinot-Bouchez, V.; Boutin, J.; Renard, P.; Caignard, D. H.; Dacquet, C. *Lett. Org. Chem.* **2006**, *3*, 103–106. (dd) Khan, M. W.; Alam, M. J.; Rashid, M. A.; Chowdhury, R. *Bioorg. Med. Chem.* **2005**, *13*, 4796–4805.

product, corresponding to 6-*endo-dig* cyclization, could be detected in the reaction mixture.

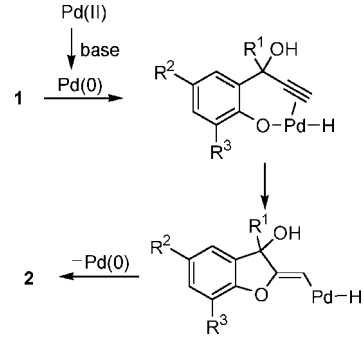
An alternative mechanism would involve the base-promoted reduction of Pd(II) to Pd(0) followed by oxidative addition of the phenolic −OH group to Pd(0), triple bond insertion, and reductive elimination (Scheme 3).

To test the likelihood of this mechanism, **1a** was reacted in MeOH at 40 °C for 2 h but in the absence of PdI_2, KI, and morpholine and in the presence of a Pd(0) catalyst, such as $Pd(PPh_3)_4$ or $Pd(dba)_2$. Under these conditions, the formation of **2a** was observed, even though in significantly lower yields (49−51%, entries 5 and 6) with respect to the yield obtained with the PdI_2/KI/morpholine system (98%, entry 4). These results show that the mechanism starting with Pd(0) (Scheme 3) may also be at work under the reaction conditions of entries 2−4. In any case, in the absence of the metal catalyst, the reaction occurred to a very limited extent, either in the absence (entry 7) or in the presence of the base (entry 8).

SCHEME 2



SCHEME 3



Interestingly, the use of $PdCl_2$ + 2KCl rather than PdI_2 + 2KI led to better results in the presence of a catalytic rather than a stoichiometric amount of morpholine (Table 1, entries 9 and 10). The catalytic activity of $CuCl_2$ and AuCl in this reaction was also tested; however, less satisfying results with respect to PdX_2 + 2KX were obtained, as shown in Table 1, entries 11−13. The influence of the nature of the base and of the solvent on the reaction rate and product yield was also studied. Under the same conditions as those of entry 9 (Table 1), the use of acyclic secondary (entries 14 and 15) or tertiary amines (entry 16) as well as of an inorganic base such as K_2CO_3 (entry 17) led to poorer results with respect to morpholine (entry 9). On the other hand, with morpholine as the base, the use of aprotic solvents such as 1,2-dimethoxyethane (DME), dioxane, acetonitrile, or *N*,*N*-dimethylacetamide (DMA) (entries 18−21) led to less satisfactory results with respect to MeOH (entry 9).

The cycloisomerization reaction was then generalized to other 2-(1-hydroxyprop-2-ynyl)phenols **1b**−**g**, bearing different substituents at the benzylic position and on the aromatic ring. The results obtained are reported in Table 2. As can be seen, high yields in the corresponding 2-methylene-2,3-dihydrobenzofuran-3-ols **2b**−**g** were consistently obtained by employing the conditions previously optimized for **1a** with PdI_2 + 2KI or $PdCl_2$ + 2KCl as catalysts.

With a simple and convenient method for the preparation of 2-methylene-2,3-dihydrobenzofuran-3-ols **2** in hand, we next tried to synthesize 2-hydroxymethylbenzofurans **3** by acid-catalyzed allylic isomerization of **2**. The key intermediate of the process was clearly expected to be the allyl cation **I** (ensuing

(2) For recent advances in the synthesis of benzofuran derivatives, see: (a) Sakai, N.; Uchida, N.; Konakahara, T. *Tetrahedron Lett.* **2008**, *49*, 3437–3440. (b) Fiandanese, V.; Bottalico, D.; Marchese, G.; Punzi, A. *Tetrahedron* **2008**, *64*, 53–60. (c) Huang, X.-C.; Liu, Y. L.; Liang, Y.; Pi, S.-F.; Wang, F.; Li, J.-H. *Org. Lett.* **2008**, *10*, 1525–1528. (d) Nakamura, I.; Mizushima, Y.; Yamagishi, U.; Yamamoto, Y. *Tetrahedron* **2007**, *63*, 8670–8676. (e) Rasool, N.; Rashid, M. A.; Reinke, H.; Fischer, C.; Langer, P. *Tetrahedron* **2007**, *63*, 11626–11635. (f) Witayakran, S.; Gelbaum, L.; Ragauskas, A. J. *Tetrahedron* **2007**, *63*, 10958–10962. (g) Tadd, A. C.; Fielding, M. R.; Willis, M. C. *Tetrahedron Lett.* **2007**, *48*, 7578–7581. (h) Bekassy, S.; Agai, B.; Farkas, J.; Gabor, E.; Ferenczi, M.; Figueras, F. *Catal. Lett.* **2007**, *118*, 219–223. (i) Fakhari, A. R.; Nematollahi, D.; Shamsipur, M.; Makarem, S.; Davarani, S. S. H.; Alizadeh, A.; Khavasi, H. 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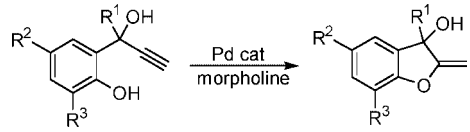
TABLE 2. Synthesis of 2-Methylene-2,3-dihydrobenzofuran-3-ols 2b−g by Pd-Catalyzed Cycloisomerization of 2-(1-Hydroxyprop-2-ynyl)phenols 1b−g[a]



1 **2**

entry	metal catalyst	**1**	R^1	R^2	R^3	**1**/morpholine/metal molar ratio	**2**	yield of **2**[b] (%)
1	PdI_2 + 2KI	**1b**	H	H	H	100/100/1	**2b**	82
2	$PdCl_2$ + 2KCl	**1b**	H	H	H	100/10/1	**2b**	85
3	PdI_2 + 2KI	**1c**	Ph	H	H	100/100/1	**2c**	96
4	$PdCl_2$ + 2KCl	**1c**	Ph	H	H	100/10/1	**2c**	86
5	PdI_2 + 2KI	**1d**	H	Cl	H	100/100/1	**2d**	88
6	$PdCl_2$ + 2KCl	**1d**	H	Cl	H	100/10/1	**2d**	85
7	PdI_2 + 2KI	**1e**	Me	Cl	H	100/100/1	**2e**	86
8	$PdCl_2$ + 2KCl	**1e**	Me	Cl	H	100/10/1	**2e**	84
9	PdI_2 + 2KI	**1f**	H	OMe	H	100/100/1	**2f**	82
10	$PdCl_2$ + 2KCl	**1f**	H	OMe	H	100/10/1	**2f**	80
11	PdI_2 + 2KI	**1g**	H	H	OMe	100/100/1	**2g**	88
12	$PdCl_2$ + 2KCl	**1g**	H	H	OMe	100/10/1	**2g**	82

[a] All reactions were carried out in MeOH (substrate concentration = 0.22 mmol of **1**/mL of solvent, 3 mmol scale based on **1**) at 40 °C for 2 h. Substrate conversion was quantitative in all cases. [b] Based on starting **1**.

SCHEME 4

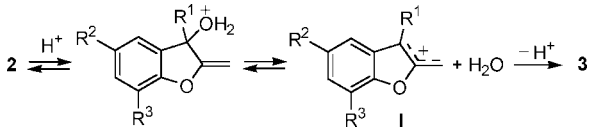
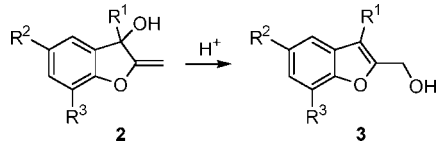


TABLE 3. Synthesis of 2-Hydroxymethylbenzofurans 3a−g by Acid-Catalyzed Allylic Isomerization of 2-Methylene-2,3-dihydrobenzofuran-3-ols 2a−g[a]



2 **3**

entry	**2**	R^1	R^2	R^3	*T* (°C)	**3**	yield of **3**[b] (%)
1	**2a**	Me	H	H	25	**3a**	83
2	**2b**	H	H	H	40	**3b**	85
3	**2c**	Ph	H	H	40	**3c**	89
4	**2d**	H	Cl	H	60	**3d**	65
5	**2e**	Me	Cl	H	40	**3e**	90
6	**2f**	H	OMe	H	40	**3f**	81
7	**2g**	H	H	OMe	40	**3g**	86

[a] All reactions were carried out in a 9:1 mixture of DME−H_2SO_4 (0.2 M in H_2O) (substrate concentration = 0.22 mmol of **2**/mL of solvent, 0.6 mmol scale based on **2**) for 15 h. Substrate conversion was quantitative in all cases. [b] Based on starting **2**.

from protonation of the −OH group followed by elimination of water), which then would convert into **3** by nucleophilic attack by water to the exocyclic carbon with aromatization and loss of proton (Scheme 4).

We indeed found that in DME as the solvent in the presence of dilute H_2SO_4 at 25−60 °C, dihydrobenzofuranols **2a−g** were readily converted into the corresponding 2-hydroxymethylbenzofurans **3a−g** in good to high yields (65−90%, Table 3).

The allyl cation **I**, obtained from **2** under acidic conditions (Scheme 4), could also be easily trapped by other oxygen nucleophiles such as alcohols (Scheme 5). Thus, under conditions similar to those of entry 1 (Table 3), but using MeOH as cosolvent and with a lower concentration of H_2SO_4, 2-methoxymethylbenzofurans **4** were selectively obtained in 70−98%

SCHEME 5

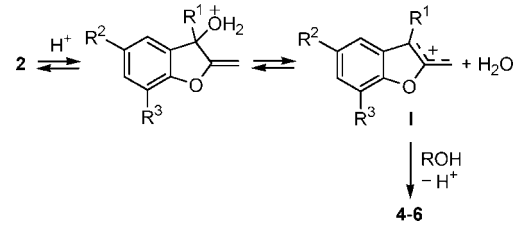
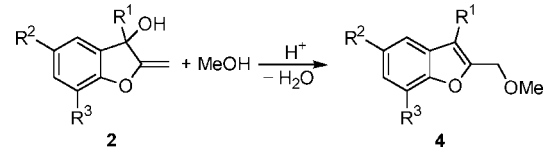


TABLE 4. Synthesis of 2-Methoxymethylbenzofurans 4a−g by Acid-Catalyzed Allylic Nucleophilic Substitution of 2-Methylene-2,3-dihydrobenzofuran-3-ols 2a−g with MeOH[a]



2 **4**

entry	**2**	R^1	R^2	R^3	**4**	yield of **4**[b] (%)
1[c]	**2a**	Me	H	H	**4a**	78
2	**2a**	Me	H	H	**4a**	80
3	**2b**	H	H	H	**4b**	78
4	**2c**	Ph	H	H	**4c**	93
5	**2d**	H	Cl	H	**4d**	15[d]
6[e]	**2d**	H	Cl	H	**4d**	25[f]
7[c,e]	**2d**	H	Cl	H	**4d**	65
8	**2e**	Me	Cl	H	**4e**	98
9	**2f**	H	OMe	H	**4f**	87
10	**2g**	H	H	OMe	**4g**	70

[a] Unless otherwise noted, all reactions were carried out in a 9:1 mixture of MeOH−H_2SO_4 (0.02 M in H_2O) (substrate concentration = 0.22 mmol of **2**/mL of solvent, 0.6 mmol scale based on **2**) at room temperature for 15 h. Unless otherwise noted, substrate conversion was quantitative. [b] Based on starting **2**. [c] The reaction was carried out using a 1:9 mixture of 0.2 M H_2SO_4−MeOH (substrate concentration = 0.22 mmol of **2**/mL of solvent). [d] Substrate conversion was 25%. [e] Reaction temperature was 40 °C. [f] Substrate conversion was 40%.

yields (Table 4, entries 2−4 and 8−10). In the case of **2d**, a higher temperature and a higher concentration of H_2SO_4 were necessary in order to attain an acceptable reaction rate and a good product yield (Table 4, entry 7).

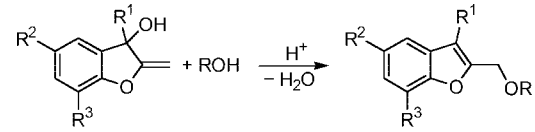
In addition to methanol, other nucleophilic alcohols, such as 1-butanol or benzyl alcohol (Scheme 4, R = Bu or Bn,

respectively) could be used to give the corresponding 2-alkoxymethylbenzofurans **5** and **6** in good to excellent yields (69−95%), as exemplified by the results reported in Table 5.[4] DME was the solvent of choice for these reactions in the presence of a 5-fold excess of ROH with respect to starting 2-methylene-2,3-dihydrobenzofuran-3-ols **2**.

Conclusions

In conclusion, we have shown that a simple catalytic system, consisting of PdX_2 in conjunction with 2 equiv of KX (X = Cl, I) and in the presence of a base such as morpholine, is an excellent catalyst for the conversion of 2-(1-hydroxyprop-2-ynyl)phenols **1** into 2-methylene-2,3-dihydrobenzofuran-3-ols **2** in high to excellent yields (80−98%).[5] With PdI_2 + 2KI as the catalyst, the use of a stoichiometric rather than catalytic amount of base led to better results in terms of reaction rate and product yield. On the other hand, the use of $PdCl_2$ + 2KCl led to better results in the presence of a catalytic rather than a stoichiometric amount of base. The 2-methylene-2,3-dihydrobenzofuran-3-ols **2** thus obtained could be efficiently converted into functionalized benzofurans by acid-promoted allylic isomerization (with formation of 2-hydroxymethylbenzofurans **3** in 65−90% yields) or allylic nucleophilic substitution with primary alcohols as nucleophiles (with formation of 2-alkoxymethylbenzofurans **4**−**6** in 65−98% yields). The methodology here reported allows an easy entry to both 2,3-dihydrobenzofuran and benzofuran derivatives starting from readily available starting materials.

TABLE 5. 5. Synthesis of 2-Alkoxymethylbenzofurans 5a−g and 6a−g by Acid-Catalyzed Allylic Nucleophilic Substitution of 2-Methylene-2,3-dihydrobenzofuran-3-ols 2a−g with Primary Alcohols[a]



2 **5-6**

entry	**2**	R^1	R^2	R^3	R	product	yield of product[b] (%)
1	**2a**	Me	H	H	Bu	**5a**	95
2	**2b**	H	H	H	Bu	**5b**	80
3	**2e**	Me	Cl	H	Bu	**5e**	83
4	**2f**	H	OMe	H	Bu	**5f**	76
5	**2a**	Me	H	H	Bn	**6a**	81
6	**2b**	H	H	H	Bn	**6b**	71
7	**2e**	Me	Cl	H	Bn	**6e**	88
8	**2f**	H	OMe	H	Bn	**6f**	69

[a] All reactions were carried out in the presence of a 5-fold excess of ROH with respect to **2**, in a 9:1 mixture of DME−H_2SO_4 (0.02 M in DME) (substrate concentration = 0.22 mmol of **2**/mL of solvent, 0.6 mmol scale based on **2**) at room temperature for 15 h. Substrate conversion was quantitative in all cases. [b] Based on starting **2**.

Experimental Section

Starting 2-(1-hydroxyprop-2-ynyl)phenols **1** were prepared as we already described.[2ii,3b,6] Typical procedures for the synthesis of 2-methylene-2,3-dihydrobenzofuran-3-ols **2**, 2-hydroxymethylbenzofurans **3**, and 2-alkoxymethylbenzofurans **4**−**6** are given below.

Typical Procedure for the Synthesis of 2-Methylene-2,3-dihydrobenzofuran-3-ols 2 in the Presence of PdI_2+2KI. We report here as a typical procedure the preparation of 3-methyl-2-methylene-2,3-dihydrobenzofuran-3-ol **2a** (Table 1, entry 4). Details for the preparation of all the other 2-methylene-2,3-dihydrobenzofuran-3-ols **2b**−**g** can be found in the Supporting Information. In a typical experiment, PdI_2 (10.5 mg, 2.92×10^{-2} mmol), KI (9.7 mg, 5.84×10^{-2} mmol), and morpholine (253.0 mg, 2.90 mmol) were added under nitrogen to a solution of **1a** (470.0 mg, 2.90 mmol) in anhydrous MeOH (13.2 mL) in a Schlenk flask. The resulting mixture was stirred under nitrogen at 40 °C for 2 h. Solvent was evaporated and the crude product purified by column chromatography on silica gel using 80:20 hexane−AcOEt as eluent to

(3) We have recently shown that PdI_2 in conjunction with an excess of KI is an excellent catalyst for the heterocyclization of several acetylenic substrates bearing a suitably placed nucleophilic group. See ref 2r, ii, yy and: (a) Gabriele, B.; Mancuso, R.; Salerno, G.; Lupinacci, E.; Ruffolo, G.; Costa, M. *J. Org. Chem.* **2008**, *73*, 4971–4977. (b) Gabriele, B.; Mancuso, R.; Salerno, G.; Plastina, P. *J. Org. Chem.* **2008**, *73*, 756–759. (c) Plastina, P.; Gabriele, B.; Salerno, G. *Synthesis* **2007**, 3083–3087. (d) Gabriele, B.; Mancuso, R.; Salerno, G.; Ruffolo, G.; Plastina, P. *J. Org. Chem.* **2007**, *72*, 6873–6877. (e) Gabriele, B.; Plastina, P.; Salerno, G.; Mancuso, R.; Costa, M. *Org. Lett.* **2007**, *9*, 3319–3322. (f) Gabriele, B.; Salerno, G. PdI_2. In *e-EROS, Electronic Encyclopedia of Reagents for Organic Synthesis*; Crich, D., Ed.; Wiley-Interscience: New York, 2006. (g) Gabriele, B.; Plastina, P.; Salerno, G.; Mancuso, R. *Synthesis* **2006**, 4247–4251. (h) Gabriele, B.; Salerno, G.; Fazio, A.; Veltri, L. *Adv. Synth. Catal.* **2006**, *348*, 2212–2222. (i) Gabriele, B.; Salerno, G.; Veltri, L.; Mancuso, R.; Li, Z.; Crispini, A.; Bellusci, A. *J. Org. Chem.* **2006**, *71*, 7895–7898. (j) Bacchi, A.; Costa, M.; Della Cà, N.; Gabriele, B.; Salerno, G.; Cassoni, S. *J. Org. Chem.* **2005**, *70*, 4971–4979. (k) Gabriele, B.; Plastina, P.; Salerno, G.; Costa, M. *Synlett* **2005**, 935–938. (l) Gabriele, B.; Salerno, G.; Costa, M. *Synlett* **2004**, 2468–2483. (m) Gabriele, B.; Salerno, G.; Costa, M.; Chiusoli, G. P. *Curr. Org. Chem.* **2004**, *8*, 919–946. (n) Gabriele, B.; Salerno, G.; Plastina, P. *Lett. Org. Chem.* **2004**, *1*, 134–136. (o) Costa, M.; Della Cà, N.; Gabriele, B.; Massera, C.; Salerno, G.; Soliani, M. *J. Org. Chem.* **2004**, *69*, 2469–2477. (p) Gabriele, B.; Salerno, G.; Plastina, P.; Costa, M.; Crispini, A. *Adv. Synth. Catal.* **2004**, *346*, 351–358. (q) Bacchi, A.; Costa, M.; Della Cà, N.; Fabbricatore, M.; Fazio, A.; Gabriele, B.; Nasi, C.; Salerno, G. *Eur. J. Org. Chem.* **2004**, *57*, 4–585. (r) Gabriele, B.; Salerno, G.; Costa, M.; Chiusoli, G. P. *J. Organomet. Chem.* **2003**, *687*, 219–228. (s) Gabriele, B.; Salerno, G.; Fazio, A. *J. Org. Chem.* **2003**, *68*, 7853–7861. (t) Chiusoli, G. P.; Costa, M.; Cucchia, L.; Gabriele, B.; Salerno, G.; Veltri, L. *J. Mol. Catal. A: Chem.* **2003**, *204*, 133–142. (u) Gabriele, B.; Salerno, G.; Fazio, A.; Pittelli, R. *Tetrahedron* **2003**, *59*, 6251–6259. (v) Bacchi, A.; Costa, M.; Gabriele, B.; Pelizzi, G.; Salerno, G. *J. Org. Chem.* **2002**, *67*, 4450–4457. (w) Gabriele, B.; Salerno, G.; Fazio, A.; Campana, F. B. *Chem. Commun.* **2002**, 1408–1409. (x) Gabriele, B.; Salerno, G.; Veltri, L.; Costa, M.; Massera, C. *Eur. J. Org. Chem.* **2001**, *460*, 7–4613. (y) Gabriele, B.; Salerno, G.; Fazio, A.; Bossio, M. R. *Tetrahedron Lett.* **2001**, *42*, 1339–1341. (z) Gabriele, B.; Salerno, G.; Fazio, A. *Org. Lett.* **2000**, *2*, 351–352. (aa) Gabriele, B.; Salerno, G.; De Pascali, F.; Costa, M.; Chiusoli, G. P. *J. Organomet. Chem.* **2000**, *593*, 409–415. (bb) Gabriele, B.; Salerno, G.; De Pascali, F.; Costa, M.; Chiusoli, G. P. *J. Org. Chem.* **1999**, *64*, 7693–7699. (cc) Gabriele, B.; Salerno, G.; Lauria, E. *J. Org. Chem.* **1999**, *64*, 7687–7692. (dd) Chiusoli, G. P.; Costa, M.; Gabriele, B.; Salerno, G. *J. Mol. Catal. A: Chem.* **1999**, *143*, 297–310. (ee) Bacchi, A.; Chiusoli, G. P.; Costa, M.; Sani, C.; Gabriele, B.; Salerno, G. *J. Organomet. Chem.* **1998**, *562*, 35–43. (ff) Gabriele, B.; Salerno, G.; De Pascali, F.; Tomasi Sciano, G.; Costa, M.; Chiusoli, G. P. *Tetrahedron Lett.* **1997**, *38*, 6877–6880. (gg) Bacchi, A.; Chiusoli, G. P.; Gabriele, B.; Righi, C.; Salerno, G. *Chem. Commun.* **1997**, 1209–1210. (hh) Gabriele, B.; Salerno, G. *Chem. Commun.* **1997**, 1083–1084. (ii) Gabriele, B.; Salerno, G.; De Pascali, F.; Costa, M.; Chiusoli, G. P. *J. Chem. Soc., Perkin Trans. 1* **1997**, 147–154. (jj) Bonardi, A.; Costa, M.; Gabriele, B.; Salerno, G.; Chiusoli, G. P. *Tetrahedron Lett.* **1995**, *36*, 7495–7498. (kk) Gabriele, B.; Costa, M.; Salerno, G.; Chiusoli, G. P. *J. Chem. Soc., Chem. Commun.* **1994**, 1429–1430.

(4) The methodology could not be applied to alcohols of low nucleophilicity, such as isopropyl alcohol (R = *i*-Pr) or *tert*-butylalcohol (R = *t*-Bu), or to phenols (R = Ar); in these cases, the GLC, GLC−MS, and TLC analyses of the reaction crudes showed that substrates **2** preferentially underwent decomposition, with formation of small amounts of the desired products, which, however, owing to the complexity of the mixture, could not be isolated at the pure state.

(5) To our knowledge, this is the first method reported in the literature of catalytic conversion of 2-(1-hydroxyprop-2-ynyl)phenols into 2-methylene-2,3-dihydrobenzofuran-3-ols. The cyclization of 4-hydroxy-4-(2-hydroxyphenyl)pent-2-ynoic acid ethyl ester (obtained by in situ $HgCl_2$-promoted deprotection of the corresponding methylthiomethyl ether) by classical intramolecular conjugate addition to give a mixture of (3-hydroxy-3-methyl-3*H*-benzofuran-2-ylidene) acetic acid ethyl ester (15%) and hydroxy-(3-methylbenzofuran-2-yl)acetic acid ethyl ester (68%) was reported some years ago. Pflieger, D.; Muckensturm, B. *Tetrahedron* **1989**, *45*, 2031–2040.

(6) We report here the correct GC−MS data for 2-(1-hydroxyprop-2-ynyl)phenol **1b** and 2-(1-hydroxyprop-2-ynyl)-4-methoxyphenol **1f**, which were inadvertently reported incorrect in refs 2ii and 3b: MS (EI, 70 eV) for **1b**, *m*/*z* = 148 (4) [M^+], 130 (25), 121 (3), 103 (11), 102 (100), 91 (8), 77 (19), 76 (26), 75 (12), 74 (10), 65 (14), 63 (14), 53 (11), 51 (16), 50 (11); for **1f**, *m*/*z* = 178 (13) [M^+], 161 (13), 160 (87), 145 (7), 132 (21), 118 (16), 117 (41), 103 (30), 102 (43), 89 (100), 77 (22), 63 (59), 62 (23), 53 (33), 51 (22).

give **2a** as a yellow solid: mp 67−68 °C (462.2 mg, 98%); IR (KBr) ν 3338 (s, br), 1673 (m), 1619 (m), 1595 (m), 1496 (s), 1460 (m), 1439 (m), 1324 (w), 1287 (m), 1175 (m), 1092 (w), 1036 (s), 930 (m), 847 (m), 804 (w), 756 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.33 (ddd, J = 7.5, 1.4, 0.6, 1 H), 7.24 (distorted ddd, J = 8.1, 7.5, 1.4, 1 H), 7.00 (td, J = 7.5, 0.9, 1 H), 6.89 (ddd, J = 8.1, 0.9, 0.6, 1 H), 4.77 (distorted d, J = 2.9, 1 H), 4.62 (distorted d, J = 2.9, 1 H), 2.68 (s, br, 1 H), 1.61 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.3, 156.1, 131.6, 130.1, 123.7, 122.4, 110.1, 86.3, 75.8, 28.4; GC−MS m/z = 162 (40) [M^+], 161 (12), 148 (19), 147 (100), 145 (25), 121 (13), 115 (17), 91 (51), 77 (16), 65 (12). Anal. Calcd for $C_{10}H_{10}O_2$ (162.19): C, 74.06; H, 6.21. Found: C, 74.15; H, 6.19.

Typical Procedure for the Synthesis of 2-Methylene-2,3-dihydrobenzofuran-3-ols 2 in the Presence of $PdCl_2$ + 2KCl. We report here as a typical procedure the preparation of 3-methyl-2-methylene-2,3-dihydrobenzofuran-3-ol **2a** (Table 1, entry 9). Details for the preparation of all the other 2-methylene-2,3-dihydrobenzofuran-3-ols **2b**−**g** can be found in the Supporting Information. In a typical experiment, $PdCl_2$ (5.1 mg, 2.88×10^{-2} mmol), KCl (4.3 mg, 5.77×10^{-2} mmol), and morpholine (25.3 mg, 0.29 mmol) were added under nitrogen to a solution of **1a** (470.0 mg, 2.90 mmol) in anhydrous MeOH (13.2 mL) in a Schlenk flask. The resulting mixture was stirred under nitrogen at 40 °C for 2 h. Solvent was evaporated and the crude product purified by column chromatography on silica gel using 80:20 hexane−AcOEt as the eluent to give **2a** as a yellow solid: mp 67−68 °C (405.1 mg, 86%).

Typical Procedure for the Synthesis of 2-Hydroxymethylbenzofurans 3. We report here as a typical procedure the preparation of (3-methylbenzofuran-2-yl)methanol **3a** (Table 3, entry 1). Details for the preparation of all the other 2-hydroxymethylbenzofurans **3b**−**g** can be found in the Supporting Information. In a typical experiment, a mixture of **2a** (103.5 mg, 0.64 mmol) and H_2SO_4 (0.2 M in H_2O, 290 μL) in DME (2.6 mL) was stirred under nitrogen at room temperature for 15 h. After evaporation of the solvent, the residue was purified by column chromatography on silica gel using 95:5 hexane−acetone as eluent to give pure **3a** as a yellow solid: mp 84−85 °C (lit.[7] mp 83−84 °C) (86.1 mg, 83%); IR (KBr) ν 3231 (s, br), 1451 (s), 1426 (w), 1337 (w), 1271 (m), 1224 (m), 1177 (w), 1104 (w), 1004 (s), 942 (w), 849 (m), 748 (s), 692 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.50−7.45 (m, 1 H), 7.43−7.38 (m, 1 H), 7.31−7.18 (m, 2 H), 4.72 (s, 2 H), 2.22 (s, 3 H), 2.16 (s, br, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.2, 151.2, 129.7, 124.5, 122.3, 119.6, 112.9, 111.1, 55.8, 7.8; GC−MS m/z = 162 (91) [M^+], 161 (55), 147 (45), 146 (12), 145 (100), 131 (11), 119 (11), 115 (39), 105 (23), 103 (15), 91 (28), 77 (17), 63 (11), 51 (17). Anal. Calcd for $C_{10}H_{10}O_2$ (162.19): C, 74.06; H, 6.21. Found: C, 74.15; H, 6.19.

Typical Procedure for the Synthesis of 2-Methoxymethylbenzofurans 4. We report here as a typical procedure the preparation of 2-methoxymethyl-3-methylbenzofuran **4a** (Table 4, entry 2). Details for the preparation of all the other 2-hydroxymethylbenzofurans **4b**−**g** can be found in the Supporting Information. In a typical experiment, a mixture of **2a** (103.5 mg, 0.64 mmol) and H_2SO_4 (0.02 M in H_2O, 290 μL) in MeOH (2.6 mL) was stirred under nitrogen at room temperature for 15 h. After evaporation of the solvent, the residue was purified by column chromatography on silica gel using 95:5 hexane−acetone as eluent to give pure **4a** as a yellow oil (90.4 mg, 80%): IR (film) ν 2923 (w), 1454 (s), 1246 (w), 1188 (w), 1085 (s), 961 (w), 852 (w), 748 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.52−7.48 (m, 1 H), 7.47−7.42 (m, 1 H), 7.33−7.20 (m, 2 H), 4.56 (s, 2 H), 3.42 (s, 3 H), 2.28 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.4, 149.2, 129.6, 124.6, 122.3, 119.5, 114.4, 111.2, 64.7, 58.1, 8.0; GC−MS m/z = 176 (68) [M^+], 175 (16), 161 (13), 146 (24), 145 (100), 144 (12), 115 (41), 91 (11), 77 (11). Anal. Calcd for $C_{11}H_{12}O_2$ (176.21): C, 74.98; H, 6.86. Found: C, 75.12; H, 6.85.

Typical Procedure for the Synthesis of 2-Butoxymethylbenzofurans 5. We report here as a typical procedure the preparation of 2-butoxymethyl-3-methylbenzofuran **5a** (Table 5, entry 1). Details for the preparation of all the other 2-butoxymethylbenzofurans **5b**, **5e**, and **5f** can be found in the Supporting Information. In a typical experiment, a mixture of **2a** (103.5 mg, 0.64 mmol), H_2SO_4 (0.02 M in DME, 290 μL), and BuOH (237.0 mg, 3.20 mmol) in DME (2.6 mL) was stirred under nitrogen at room temperature for 15 h. After evaporation of the solvent, the residue was purified by column chromatography on silica gel using 95:5 hexane−acetone as eluent to give pure **5a** as a yellow oil (133.0 mg, 95%): IR (film) ν 2962 (s), 2923 (m), 2864 (m), 1459 (m), 1239 (w), 1092 (s), 853 (w), 751 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.48−7.45 (m, 1 H), 7.44−7.41 (m, 1 H), 7.27−7.24 (m, 1 H), 7.22−7.18 (m, 1 H), 4.57 (s, 2 H), 3.50 (t, J = 6.6, 2 H), 2.24 (s, 3 H), 1.62−1.55 (m, 2 H), 1.41−1.33 (m, 2 H), 0.90 (t, J = 7.4, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.3, 149.8, 129.7, 124.4, 122.2, 119.4, 114.0, 111.2, 70.3, 63.2, 31.7, 19.3, 13.9, 7.9; GC−MS m/z = 218 (37) [M^+], 161 (15), 147 (13), 146 (29), 145 (100), 131 (29), 115 (24), 91 (11), 77 (7). Anal. Calcd for $C_{14}H_{18}O_2$ (218.29): C, 77.07; H, 8.31. Found: C, 77.18; H, 8.29.

Typical Procedure for the Synthesis of 2-Benzyloxymethylbenzofurans 6. We report here as a typical procedure the preparation of 2-benzyloxymethyl-3-methylbenzofuran **6a** (Table 5, entry 5). Details for the preparation of all the other 2-benzyloxymethylbenzofurans **6b**, **6e**, and **6f** can be found in the Supporting Information. In a typical experiment, a mixture of **2a** (103.5 mg, 0.64 mmol), H_2SO_4 (0.02 M in DME, 290 μL), and BnOH (346.0 mg, 3.20 mmol) in DME (2.6 mL) was stirred under nitrogen at room temperature for 15 h. After evaporation of the solvent, the residue was purified by column chromatography on silica gel using 95:5 hexane−acetone as eluent to give pure **6a** as a yellow oil (130.2 mg, 81%): IR (film) ν 1447 (m), 1238 (w), 1071 (s), 853 (w), 743 (s), 698 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.49−7.46 (m, 1 H), 7.45−7.43 (m, 1 H), 7.38−7.31 (m, 4 H), 7.29−7.24 (m, 2 H), 7.23−7.19 (m, 1 H), 4.61 (s, 2 H), 4.57 (s, 2 H), 2.20 (s, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.4, 149.4, 137.9, 129.7, 128.4, 127.9, 127.7, 124.5, 122.3, 119.5, 114.5, 111.2, 72.0, 62.2, 7.9; GC−MS m/z 252 (41) [M^+], 161 (57), 146 (81), 145 (100), 144 (28), 133 (24), 132 (31), 131 (94), 115 (67), 105 (49), 92 (51), 91 (68), 77 (48), 65 (42), 63 (22), 51 (42), 50 (20). Anal. Calcd for $C_{17}H_{16}O_2$ (252.12): C, 80.93; H, 6.39. Found: C, 81.03; H, 6.37.

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Supporting Information Available: General experimental methods, general procedure for the synthesis of 2-methylene-2,3-dihydrobenzofuran-3-ols **2** in the presence of PdI_2 + 2KI, general procedure for the synthesis of 2-methylene-2,3-dihydrobenzofuran-3-ols **2** in the presence of $PdCl_2$ + 2KCl, general procedure for the synthesis of 2-hydroxymethylbenzofurans **3**, general procedure for the synthesis of 2-methoxymethylbenzofurans **4**, general procedure for the synthesis of 2-butoxymethylbenzofurans **5**, general procedure for the synthesis of 2-benzyloxymethylbenzofurans **6**, characterization data and copies of ^1H and ^{13}C NMR spectra for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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