Cascade Cyclization

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Benzofurans from Benzophenones and Dimethylacetamide: Copper-Promoted Cascade Formation of Furan O1–C2 and C2–C3 Bonds Under Oxidative Conditions**

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Dedicated to Professor Carmen Nájera on the occasion of her 60th birthday

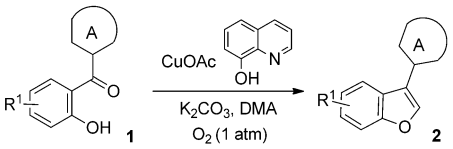
The benzofuran core is a ubiquitous heterocyclic motif that is very common in natural products and biologically active compounds. Among this prolific family of heterocycles, the 3-arylbenzofuran framework can be found in a series of pharmacologically relevant structures.[1]

In the course of our research on copper-catalyzed oxidative processes, we attempted an intramolecular oxidative O-arylation on *ortho*-hydroxybenzophenones. Surprisingly, in one of the assays, 3-phenylbenzofuran **2a** was isolated instead of the expected xanthone derivative. We were initially puzzled by such an unexpected result, as this transformation was utterly unrelated to the methods for 3-arylbenzofuran synthesis described in the literature.[2] Moreover, it had nothing in common with the general entries to the benzofuran core, as an unprecedented simultaneous formation of the furan O1–C2 and C2–C3 bonds was involved.[3]

Herein, we present the synthesis of a series of 3-arylbenzofurans and the progress made to gain a more profound knowledge of the possible pathways that could explain this novel entry to the benzofuran core. As an additional proof to support our proposal, an innovative cyclization of *ortho*-hydroxy-α-arylstyrenes is also presented.

As shown in Table 1, treatment of 2-hydroxybenzophenone **1a** with CuOAc (50 mol%) in the presence of one atmosphere of oxygen, 8-hydroxyquinoline (8-OQ, 40 mol%) and potassium carbonate (1 equiv) in *N,N*-dimethylacetamide (DMA) at 140°C provided 3-phenylbenzofuran **2a** in 80% yield. An array of assays was performed to optimize the reaction conditions;[4a] these assays reveal that other bases, ligands (even closely structurally related ones, such as sulfoxine), and/or solvents provide negligible results, and only $Cu(OAc)_2 \cdot H_2O$ and CuI can be used as alternate copper sources (75% and 53% yields, respectively). The extension of the procedure to a number of commercially available or readily synthesized[4a] diarylketone derivatives **1** afforded the benzofuran derivatives **2** (displayed in Table 1) bearing alkyl, alkoxy, heteroaryl, or halogen functional groups. However, strong electron-withdrawing groups such as nitro or sulfonic acid on the aryl rings were not tolerated by this procedure.

Table 1: One-pot approach to benzofurans from benzophenones, and functional group tolerance studies.[a]



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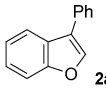
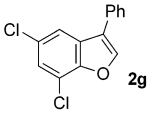
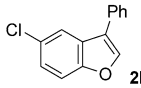
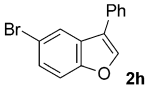
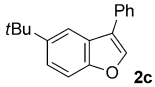
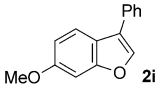
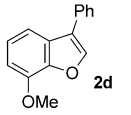
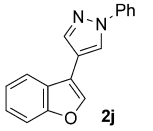
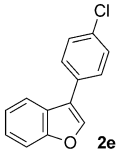
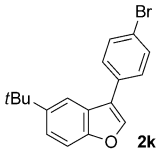
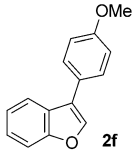
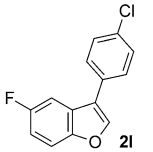
1	 **2a**	80 (75)[c]	7	 **2g**	93
2	 **2b**	69 (60)[c]	8	 **2h**	75 (69)[c]
3	 **2c**	90	9	 **2i**	39
4	 **2d**	53	10	 **2j**	62 (65)[c]
5	 **2e**	69	11	 **2k**	74
6	 **2f**	71	12	 **2l**	80 (50)[c]

[a] Reaction conditions: Ketone **1**, CuOAc (50 mol%), 8-OQ (50 mol%), K_2CO_3 (1 equiv) and anhydrous DMA (10 mL mmol^{-1} of **1**), 140°C, 24 h.; DMA = *N,N*-dimethylacetamide, 8-OQ = 8-hydroxyquinoline. [b] Yield of isolated product. [c] The yields from the reaction using $Cu(OAc)_2 \cdot H_2O$ (50 mol%) as the copper source are shown in parentheses.

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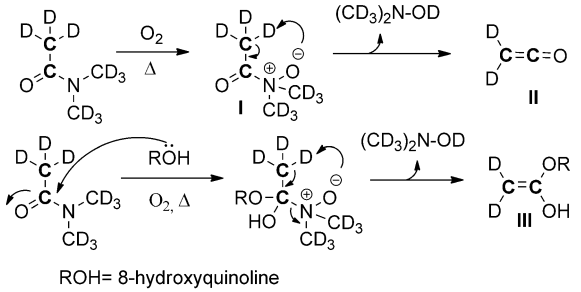
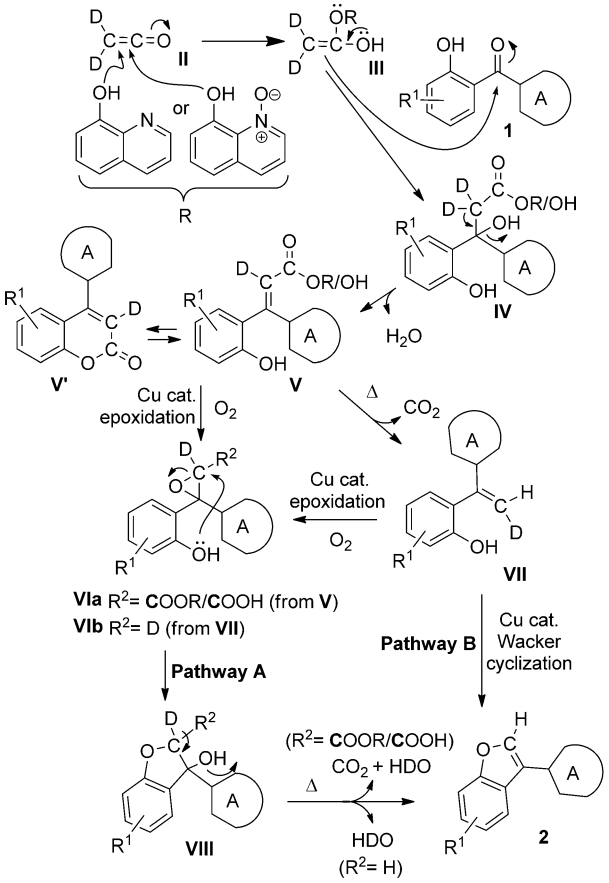
Furthermore, the presence of an aryl or heteroaryl ring attached to the 2-hydroxybenzoyl moiety is a requirement for this reaction, as *o*-hydroxyacetophenones and other alkyl ketones and esters did not react under the above conditions.[4a] Considering the relatively high amount of copper salt employed, we decided to attempt to recycle it, using oxidative cyclization to 3-phenylbenzofuran **2a** as a model reaction. After workup and product separation from the initial reaction, further runs were conducted by just adding the hydroxyketone **1a** and K_2CO_3 to a DMA solution of the active catalyst. The second run provided a 64% yield, whereas a slightly lower 54% was obtained on the third run. Unfortunately, only traces of the target ketone were observed in the following runs. It was also possible to perform the reaction either by using $Cu(OAc)_2{\cdot}H_2O$ as an alternative copper source (for a comparison, see Table 1) or with smaller amounts of CuOAc (40 mol% and 20 mol%), but in these cases the above recycling procedure gave significantly poorer results (69% to 25% to < 5% for 40 mol% CuOAc; 37% to 8% to < 5% for 20 mol% CuOAc; and 75% to 32% to < 5% for 50 mol% $Cu(OAc)_2{\cdot}H_2O$).

As mentioned above, a literature search revealed a complete lack of precedent for the presented formation of the benzofuran core. Nevertheless, we undertook mechanistic studies to elucidate the probable pathways. The reaction could be initiated from a Cope-type ketene formation (structure **II**) from DMA solvent in an oxidizing atmosphere, or alternatively by an initial addition of the ligand to the solvent followed by a Cope elimination that generates ketene hemiketal **III** (Scheme 1). In both cases, DMA participation is



Scheme 1. A tentative proposal for ketene formation from DMA.

clear; other solvents, such as DMF, DMSO, *N,N*-dimethylformamide dimethyl acetal, MeOH, or AcOEt, provided negligible results. Formation of ketene-type *N,N*-dimethylketeniminium ions by thermal elimination of DMA has already been reported, as has the trapping of such reactive ketenimininium species with hydroxy compounds.[4b,c] Ligand addition to **II** would generate **III**, which could attack the ketone carbonyl of starting benzophenone **1**, thus forming unsaturated ester **V** after dehydration (Scheme 2). From this key intermediate, two alternative routes can be proposed. Pathway A is based on the participation of epoxides **VIa** or **VIb**, formed either by an epoxidation[5] of **V** (**VIa**) or by a sequential decarboxylation/epoxidation (**VIb**). Decarboxylation and/or dehydration of intermediate **VIII** would



Scheme 2. Possible pathways for copper-promoted benzofuran formation.

provide target **2**. Pathway B involves a Wacker-type cyclization[6] of 2-hydroxy-α-phenylstyrene **VII** (Scheme 2).

Support for pathway A comes from literature examples of the aerobic epoxidation of olefins.[5] However, most of the related research to date is limited to multi-metal catalysts and/or relatively high oxygen pressures.[7] In our case, only a single copper catalyst would be involved and only under an atmospheric pressure of oxygen. It should also be pointed out that the reaction does not proceed in the absence of oxygen. Pathway B, on the other hand, involves an unprecedented copper-catalyzed Wacker-type cyclization. Whereas palladium-catalyzed Wacker reactions in the presence or absence of copper reoxidants are well-known processes in synthetic chemistry (and many of them are conducted in DMA),[6] a literature search revealed that no examples of copper-catalyzed Wacker oxidations have been described so far. Intrigued by this challenging proposal, ICP-MS analyses of the copper source employed, the carbonate base, and starting material **1a** were performed, showing that the palladium content in the reaction mixture was around 10^{-5} mol%, which is a homeophatic amount for any Wacker cyclization.[8]

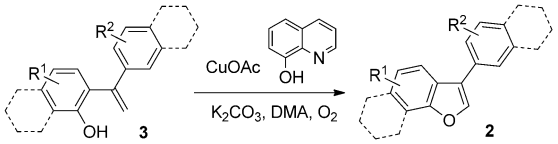
A number of additional experiments were carried out to shed light on this rather obscure mechanistic crossover. The first one involved the use of [D_9]DMA as solvent. No deuterated positions were observed in the resulting product **2**. A closer look at Scheme 2 ([D_9]DMA has been used as

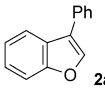
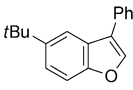
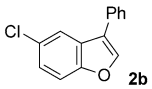
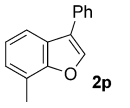
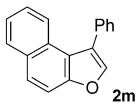
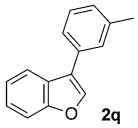
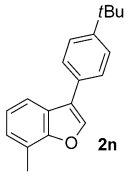
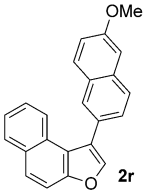
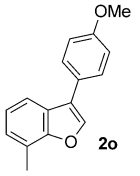
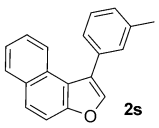
a starting material in both Scheme 1 and Scheme 2 to clarify this point) shows that the dehydration and decarboxylation steps (from **IV** to **V**, from **V** to **VII**, and from **VIII** to **2**) can provide non-deuterated product **2** by pathway A. In pathway B, deuterium could be also lost at the Wacker cyclization step (from **VII** to **2**). ^{13}C-Labeled DMA (with ^{13}C-enriched acetyl carbon atoms; see carbon atoms **C** in Scheme 1 and Scheme 2) was next employed and the corresponding ^{13}C2 labeled product was obtained (Scheme 2) with a similar enrichment percentage. Further to this unquestionable proof of the participation of the DMA solvent in the reaction, a more profitable assay was finally performed, submitting readily synthesized[9] intermediate **VII** to the same reaction conditions.

As shown in Table 2, several 2-hydroxy-α-arylstyrenes **3** were treated with our CuOAc/8-hydroxyquinoline/DMA/O_2 system to afford target benzofurans **2** in moderate to good yields. Halogen, alkyl, and alkoxy functional groups were again well tolerated under these oxidative conditions. Because of the difficulty of preparing 2′-substituted 2-hydroxy-α-arylstyrene derivatives,[9] the effect of steric hindrance on this reaction was not evaluated. No examples of copper-catalyzed electrophilic addition processes[10] from 2-hydroxystyrenes have been found, and the need for molecular oxygen to produce the desired reaction outcome in this case was also significant. Recycling of the DMA phase containing the promoter was tested with the parent styrene **3a** in a similar procedure to that performed with **1a**. Using the same loading as in the optimized procedure (CuOAc (50 mol%), 8-OQ (0.4 equiv)), the second run provided a 51% yield of the target heterocycle **2a**, the third a 38% yield and only traces of **2a** were detected in the following runs.

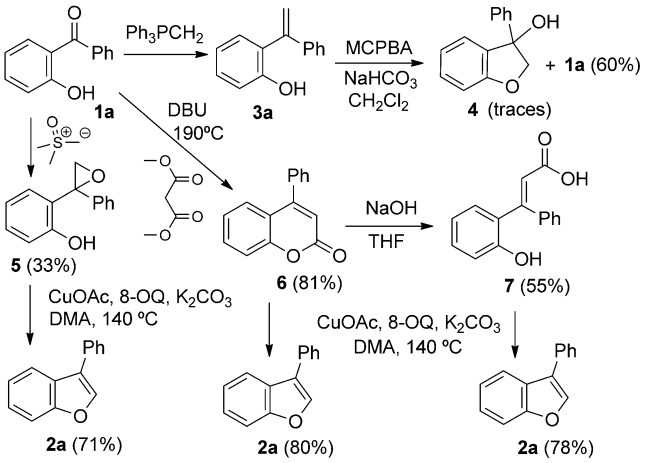
The participation of phenoxy radicals and their addition to the alkene moiety might be suggested as an alternative pathway to a Wacker-type mechanism for the transformation from intermediate **VII** (or styrenes **3**) to benzofurans **2**. Nevertheless, the presence of stoichiometric amounts of TEMPO, a known radical scavenger,[11] did not affect the reaction outcome with either **1a** or **3a**. Dihydrobenzofuran derivative **4** (Scheme 3), with the structure of intermediate

Table 2: Formation of the benzofuran core by copper-catalyzed oxidative cyclization of 2-hydroxy-α-arylstyrene derivatives.[a]



Entry	Product	Yield[b]	Entry	Product	Yield[b]
1	 **2a**	77	6	 **2c**	59
2	 **2b**	72	7	 **2p**	83
3	 **2m**	53	8	 **2q**	54
4	 **2n**	57	9	 **2r**	50
5	 **2o**	57	10	 **2s**	62

[a] Reaction conditions: Alkene **3**, CuOAc (50 mol%), 8-OQ (50 mol%), K_2CO_3 (1 equiv), and anhydrous DMA (10 mL mmol^{-1} of **3**), 140°C, 24 h.; DMA = *N*,*N*-dimethylacetamide, 8-OQ = 8-hydroxyquinoline.
[b] Yield of isolated product.



Scheme 3. Detection of 3-hydroxy-3-phenyldihydrobenzofuran **4** in reaction mixtures from 2-hydroxy-α-arylstyrene derivatives, and synthesis of 3-phenylbenzofuran **2a** from epoxide **5** and unsaturated acid derivatives **6** and **7**.

VIII (R^2 = H; Scheme 2), was detected in the reaction between styrene derivative **3a** and *m*-chloroperbenzoic acid (MCPBA), in an assay intended to obtain the corresponding epoxide **VIb**. Unfortunately, **3a** provided benzophenone **1a** and a small amount of the aforementioned species **4**. Even treatment of [2-(1-phenylvinyl)phenoxy]*tert*-butyldimethylsilane, which is readily prepared by silylation of **3a**, with MCPBA afforded **4** along with only traces of the expected epoxide. A Johnson–Corey–Chaykovsky reaction[12] performed on **1a** afforded epoxide **5**, which, under oxidative cyclization conditions (O_2, CuOAc, 8-OQ, K_2CO_3, DMA, 140°C), provided benzofuran **2a** (Scheme 3). From all of these assays it was clear that, although unstable, epoxide-type intermediates such as **VI** were closely related to dihydrofuran intermediates **VIII** and benzofurans **2** (Scheme 2). Finally, the participation of unsaturated acid and lactone derivatives as

intermediates (**V** and **V′**, Scheme 2) in the mechanism was also examined and confirmed. 4-Phenylcoumarin **6** was easily prepared (81%) by reaction of *ortho*-hydroxybenzophenone **1a** with dimethylmalonate,[13] and then hydrolyzed[14] to give 3-(2-hydroxyphenyl)-3-phenylacrylic acid **7**. Both lactone **6** and carboxylic acid **7** were then submitted to our oxidative conditions, providing the corresponding benzofuran **2a** with good yields (80% and 78%, respectively; Scheme 3).

In summary, two synthetically useful entries to the benzofuran core have been presented, starting from commercially available or readily synthesized 2-hydroxybenzophenones and 2-hydroxy-α-arylstyrene derivatives. Both approaches are based on the same oxidative reaction conditions, which involve the use of molecular oxygen at atmospheric pressure and CuOAc/8-hydroxyquinoline/K_2CO_3 in DMA. Insights into the mechanistic pathways that may take place in such unprecedented transformations is provided, suggesting DMA activation to generate ketene derivatives and either epoxidation under oxygen atmosphere or Wacker cyclization as copper-catalyzed key steps. According to the proposed mechanism, DMA is the source of the carbon unit required for this new approach to benzofurans from 2-hydroxybenzophenones by the cascade formation of O1–C2 and C2–C3 bonds. The participation of 2-hydroxy-α-arylstyrene intermediates is demonstrated by the fact that the latter can be effectively used as substrates, thus leading to benzofurans under similar oxidative conditions. The occurrence of other proposed intermediates, such as unsaturated acids, lactones, epoxides, and dihydrofuran derivatives is also discussed and demonstrated.

Experimental Section

General procedure for the synthesis of benzofurans **2** from 2-hydroxybenzophenones **1** or 2-hydroxy-α-arylstyrenes **3**: A mixture of the 2-hydroxybenzophenone **1** or 2-hydroxy-α-arylstyrene **3** (0.252 mmol), copper(I) acetate (15 mg, 0.123 mmol), 8-hydroxyquinoline (15 mg, 0.103 mmol), and K_2CO_3 (35 mg, 0.252 mmol) in anhydrous DMA (2.5 mL) was stirred in a round-bottom flask for 24 h at 140 °C under an oxygen atmosphere. The reaction mixture was cooled to room temperature, then H_2O (5.0 mL) was added and the resulting aqueous suspension was extracted with ethyl acetate (3 × 5 mL). The organic layer was washed with H_2O (15 mL) and brine (15 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by flash chromatography using ethyl acetate/n-hexane 1:9 as eluent, to provide pure benzofuran **2**.

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[1] For iantheran A, see: a) Y. Okamoto, M. Ojika, S. Suzuki, M. Murakami, Y. Sakagami, *Bioorg. Med. Chem.* **2001**, *9*, 179; b) H. Greve, S. Meis, M. U. Kassack, S. Kehraus, A. Krick, A. D. Wright, G. M. König, *J. Med. Chem.* **2007**, *50*, 5600; for PBFuranAA, see: c) C. Santini, G. D. Berger, W. Han, R. Mosley, K. MacNaul, J. Berger, T. Doebber, M. Wu, D. E. Moller, R. L. Tolman, S. P. Sahoo, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1277; see also: d) J. G. Menke, K. L. MacNaul, N. S. Hayes, J. Baffic, Y. S. Chao, A. Elbrecht, L. J. Kelly, M. H. Lam, A. Schmidt, S. Sahoo, J. Wang, S. D. Wright, P. Xin, G. Zhou, D. E. Moller, C. P. Sparrow, *Endocrinology* **2002**, *143*, 2548; e) M. Saitoh, J. Kunitomo, E. Kimura, H. Iwashita, Y. Uno, T. Onishi, N. Uchiyama, T. Kawamoto, T. Tanaka, C. D. Mol, D. R. Dougan, G. P. Textor, G. P. Snell, M. Takizawa, F. Itoh, M. Kori, *J. Med. Chem.* **2009**, *52*, 6270; f) V. Srivastava, A. S. Negi, J. K. Kumar, U. Faridi, B. S. Sisodia, M. P. Darokar, S. Luqman, S. P. S. Khanuja, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 911.

[2] Previously, 3-arylbenzofurans were synthesized either by dehydration of *o*-hydroxybenzyl ketones under acidic conditions: a) R. Adams, L. Whitaker, *J. Am. Chem. Soc.* **1956**, *78*, 8; b) K. Kalyanasundaram, S. Rajagopalan, S. Swaminathan, *Tetrahedron Lett.* **1980**, *21*, 4391; or by dehydrative cyclization of α-(phenoxy)alkyl ketones: c) J. B. Wright, *J. Org. Chem.* **1960**, *25*, 1867; d) R. Royer, E. Bisagni, C. Hudry, A. Cheutin, M.-L. Desvoye, *Bull. Soc. Chim. Fr.* **1963**, 1003; e) C. Pene, P. Demerseman, A. Cheutin, R. Royer, *Bull. Soc. Chim. Jpn.* **1971**, *44*, 749; f) T. Horaguchi, H. Iwanami, T. Tanaka, E. Hasegawa, T. Shimizu, *J. Chem. Soc. Chem. Commun.* **1991**, 44; however, more recently, the palladium-catalyzed cyclization of aryl acetylenes has been employed: g) T. Ishikawa, T. Miyahara, M. Asakura, S. Higuchi, Y. Miyauchi, S. Saito, *Org. Lett.* **2005**, *7*, 1211; h) A. R. Katritzky, Y. Ji, Y. Fang, I. Prakash, *J. Org. Chem.* **2001**, *66*, 5613; i) P. J. Seo, H. D. Choi, B. W. Son, *J. Korean Chem. Soc.* **2002**, *46*, 384; j) M. C. Willis, D. Taylor, A. T. Gillmore, *Org. Lett.* **2004**, *6*, 4755; k) M. A. Honey, A. J. Blake, I. B. Campbell, B. D. Judkins, C. J. Moody, *Tetrahedron* **2009**, *65*, 8995; l) A. I. Roshchin, S. M. Kel′chevski, N. A. Bumagin, *J. Organomet. Chem.* **1998**, *560*, 163; m) S. N. Aslam, P. C. Stevenson, S. J. Phythian, N. C. Veitch, D. R. Hall, *Tetrahedron* **2006**, *62*, 4214; n) S. S. Hosseiny Davarani, N. M. Najafi, S. Ramyar, L. Masoumi, M. Shamsipur, *Chem. Pharm. Bull.* **2006**, *54*, 959; for other approaches to 3-arylbenzofurans, see: o) I. Kim, S. H. Lee, S. Lee, *Tetrahedron Lett.* **2008**, *49*, 6579; p) J. M. Patel, S. S. Soman, *J. Heterocycl. Chem.* **2007**, *44*, 945; q) K. C. Nicolaou, S. A. Snyder, A. Bigot, J. A. Pfefferkorn, *Angew. Chem.* **2000**, *112*, 1135; *Angew. Chem. Int. Ed.* **2000**, *39*, 1093; r) A. V. Gutnov, A. V. Butin, V. T. Abaev, G. D. Krapivin, V. E. Zavodnik, *Molecules* **1999**, *4*, 204; s) T. Suzuki, T. Horagugchi, T. Shimizu, T. Abe, *Bull. Chem. Soc. Jpn.* **1983**, *56*, 2762; t) R. Romagnoli, P. G. Baraldi, M. D. Carrion, C. L. Cara, O. Cruz-Lopez, M. Tolomeo, S. Grimaudo, A. Di Cristina, M. R. Pipitone, J. Balzarini, N. Zonta, A. Brancale, E, Hamel, *Bioorg. Med. Chem.* **2009**, *17*, 6862.

[3] For the simultaneous formation of more than one bond in benzofuran synthesis, see: O1–C2 and C3–C3a: a) X. Guo, R. Yu, H. Li, Z. Li, *J. Am. Chem. Soc.* **2009**, *131*, 17387; b) L. Cires, H. Ofenberg, C. Craita, *Org. Prep. Proced. Int.* **2001**, *33*, 361; c) Y. T. Reddy, P. N. Reddy, M. K. Rao, B. Rajitha, S. M. Reddy, M. Sridevi, *Indian J. Chem. Sect. B* **2001**, *40B*, 479; d) B. J. Morrison, O. C. Musgrave, *Tetrahedron* **2002**, *58*, 4255; e) G. C. Kulkarni, S. N. Karmarkar, S. L. Keldar, M. S. Wadia, *Tetrahedron* **1988**, *44*, 5189; f) H. D. Choi, P. J. Seo, B. W. Son, *J. Korean Chem. Soc.* **2001**, *45*, 500; g) S. Spyroudis, *J. Org. Chem.* **1986**, *51*, 3453; h) R. Huisgen, G. Binsch, H. König, *Chem. Ber.* **1964**, *97*, 2884; C7a–O1 and C3–C3a: i) Y. Inukai, T. Sonoda, H. Kobayashi, *Bull. Chem. Soc. Jpn.* **1979**, *52*, 2657; j) M. V. Gorelik, E. V. Mishina, *Zh. Org. Khim.* **1983**, *19*, 2185; k) Y. Terao, T. Satoh, M. Miura, M. Nomura, *Bull. Chem. Soc. Jpn.* **1999**, *72*, 2145; l) B. L. Flynn, E. Hamel, M. K. Jung, *J. Med. Chem.* **2002**, *45*, 2670.

[4] a) For full details on the synthesis of precursors, optimization assays, and other substrates assayed, as well as a discussion of alternative copper sources and the role of water, see the Supporting Information; b) A. Potthast, T. Rosenau, H. Sixta, P. Kosma, *Tetrahedron Lett.* **2002**, *43*, 7757; see also: c) R.

Martinez, M. C. Huff, M. A. Barteau, *Appl. Catal. A* **2000**, *200*, 79.

[5] Some interesting references on the copper-catalyzed epoxidation of olefins can be found in: a) S. Minakata, K. Inaki, M. Komatsu, *J. Oleo Sci.* **2002**, *51*, 549; b) J. Chisem, I. C. Chisem, J. S. Rafelt, D. J. Macquarrie, J. H. Clark, *Chem. Commun.* **1997**, 2203; c) N. Komiya, T. Naota, Y. Oda, S.-I. Murahashi, *J. Mol. Catal. A* **1997**, *117*, 121; d) J. Liang, Q. Tang, G. Meng, H. Wu, Q. Zhang, Y. Wang, *Chem. Lett.* **2004**, *33*, 1140; e) R. M. Lambert, F. J. Williams, R. L. Cropley, A. Palermo, *J. Mol. Catal. A* **2005**, *228*, 27.

[6] For some examples of the Wacker reaction leading to furan and benzofuran frameworks, see: a) M. Soledade, C. Pedras, M. Hossain, *Bioorg. Med. Chem.* **2007**, *15*, 5981; b) F. Alonso, D. Sánchez, T. Soler, M. Yus, *Adv. Synth. Catal.* **2008**, *350*, 2118; c) K. Takenaka, S. C. Mohanta, M. L. Patil, C. V. Laxman Rao, S. Takizawa, T. Suzuki, H. Sasai, *Org. Lett.* **2010**, *12*, 3480; d) K. Takenaka, Y. Tanigaki, M. L. Patil, C. V. Laxman Rao, S. Takizawa, T. Suzuki, H. Sasai, *Tetrahedron: Asymmetry* **2010**, *21*, 767; e) A. Wang, H. Jiang, *J. Org. Chem.* **2010**, *75*, 2321; f) T. Mitsudome, T. Umetani, N. Nosaka, K. Mori, T. Mizugaki, K. Ebitani, K. Kaneda, *Angew. Chem.* **2006**, *118*, 495; *Angew. Chem. Int. Ed.* **2006**, *45*, 481; g) T. Mitsudome, K. Mizumoto, T. Mizugaki, K. Jitsukawa, K. Kaneda, *Angew. Chem.* **2010**, *122*, 1260; *Angew. Chem. Int. Ed.* **2010**, *49*, 1238; for a synthesis of 3-phenylbenzofuran from 2-hydroxy-α-phenylstyrene using $PdCl_2/Cu(OAc)_2$, see Ref. [6a]. For the same reaction performed in the absence of copper, see: h) G. Casiraghi, G. Casnati, G. Puglia, G. Sartori, G. Terenghi, *Synthesis* **1977**, 122.

[7] a) X. Zhang, Z.-H. Li, J. Wang, M.-Y. Huang, Y.-Y. Jiang, *Polym. Adv. Technol.* **1999**, *10*, 483; b) A. Seubsai, M. Kahn, S. Senkan, *ChemCatChem* **2011**, *3*, 174; c) L. Hu, L. Shi, H. Hong, M. Li, Q. Bao, J. Tang, J. Ge, J. Lu, X. Cao, H. Gu, *Chem. Commun.* **2010**, *46*, 8591; d) L. Yang, J. He, Q. Zhang, Y. Wang, *J. Catal.* **2010**, *276*, 76.

[8] To the best of our knowledge, palladium catalyst loadings higher than 2×10^{-1} mol% are required for Wacker cyclization; see ref. [6] for more details. See also: a) B. W. Michel, A. M. Camelio, C. N. Cornell, M. S. Sigman, *J. Am. Chem. Soc.* **2009**, *131*, 6076; b) B. Weiner, A. Baeza, T. Jerphagnon, B. L. Feringa, *J. Am. Chem. Soc.* **2009**, *131*, 9473.

[9] a) M. Yamaguchi, M. Arisawa, K. Omata, K. Kabuto, M. Hirama, T. Uchimaru, *J. Org. Chem.* **1998**, *63*, 7298; b) M. Yamaguchi, A. Hayashi, M. Hirama, *J. Am. Chem. Soc.* **1995**, *117*, 1151.

[10] For some metal-catalyzed electrophilic additions to alkenes, and related reactions leading to benzofuran derivatives, see: a) V. Spéziale, D. H. Giao, A. Lattes, *J. Heterocycl. Chem.* **1978**, *15*, 225; b) K. Orito, T. Hatakeyama, M. Takeo, H. Suginome, M. Tokuda, *Synthesis* **1997**, 23.

[11] For example, see: P. J. Wright, A. M. English, *J. Am. Chem. Soc.* **2003**, *125*, 8655.

[12] J. A. Ciaccio, A. L. Drahus, R. M. Meis, C. T. Tingle, M. Smrtka, R. Geneste, *Synth. Commun.* **2003**, *33*, 2135.

[13] For the preparation of 4-phenylcoumarin from the same reagents using microwave irradiation, see: J. Crecente-Campo, M. P. Vazquez-Tato, J. A. Seijas, *Eur. J. Org. Chem.* **2010**, 4130.

[14] For the hydrolysis of a structurally related lactone, see: E. L. Grimm, C. Brideau, N. Chauret, C.-C. Chan, D. Delorme, Y. Ducharme, D. Ethier, J.-P. Falgueyret, R. W. Friesen, J. Guay, P. Hamel, D. Riendeau, C. Soucy-Breau, P. Tagari, Y. Girard, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2528.

