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Efficient synthesis of 3-acyl-5-hydroxybenzofurans via copper(II) triflate-catalyzed cycloaddition of unactivated 1,4-benzoquinones with 1,3-dicarbonyl compounds

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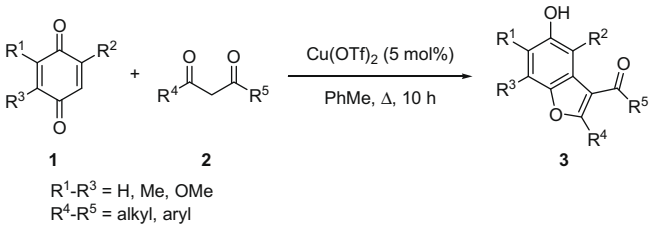
ABSTRACT

A method to prepare a variety of substituted 3-acyl-5-hydroxybenzofurans efficiently that relies on copper(II) triflate-catalyzed cycloaddition of unactivated 1,4-benzoquinones with 1,3-dicarbonyl compounds is reported. The reaction was shown to be operationally straightforward and proceeds expediently under mild conditions to give the corresponding products in good to excellent yields (up to 95%) and with complete regioselectivity.

Benzofurans are found in a wide variety of bioactive natural products and compounds of current therapeutic interest.[1,2] However, while this has led to a myriad of methods for benzofuran synthesis under strongly acidic and basic conditions, examples of the analogous reactions catalyzed by a Lewis acid have received less attention.[1,3] To our knowledge, approaches to benzofurans that explore the use of ecologically benign Lewis acid catalysts in combination with low cost and readily available substrates under mild conditions are limited to only three reported methods.[4,5] The first two reported the 1,4-conjugate addition/cyclization of 1,4-benzoquinones with 1,3-dicarbonyl compounds in the presence of a stoichiometric amount of $ZnCl_2$ as a catalyst that was achieved in low to moderate product yields.[4] More recently, De Kimpe and co-workers showed that $Yb(OTf)_3$ mediated the cycloaddition of activated 1,4-naphthoquinones with 1,3-dicarbonyl compounds and provided the corresponding 3-acyl-5-hydroxynaphtho[1,2-*b*]furans in good to excellent yields and regioselectivity.[5] As part of an ongoing programme on developing new Lewis acid-catalyzed reactions,[6] we report herein the use of $Cu(OTf)_2$ as a catalyst for the cycloaddition of unactivated 1,4-benzoquinones with 1,3-dicarbonyl compounds (Scheme 1). The 3-acyl-5-hydroxybenzofuran products were obtained in yields and regioselectivities comparable to those reported for the closely related Yb(III)-mediated approach to this synthetically useful *O*-heterocyclic building block.

Initially, we found that treating 2,5-dimethylcyclohexa-2,5-diene-1,4-dione **1a** (1 equiv) with dibenzoylmethane **2a** (2 equiv) and 5 mol % of $Cu(OTf)_2$ in toluene at reflux for 10 h gave the best result (Table 1, entry 1).[7] Under these conditions, (5-hydroxy-4,7-dimethyl-2-phenylbenzofuran-3-yl)(phenyl)methanone **3a**



1 **2** **3**

R^1-R^3 = H, Me, OMe
R^4-R^5 = alkyl, aryl

Scheme 1. $Cu(OTf)_2$-catalyzed formation of 3-acyl-5-hydroxybenzofurans from unactivated 1,4-benzoquinones and 1,3-dicarbonyl compounds

was furnished in 95% yield, and was comparable to the analogous $Yb(OTf)_3$-catalyzed cycloaddition of 1,4-naphthoquinones with 1,3-dicarbonyl compounds.[5] The structure of the benzofuran product was confirmed by ^1H NMR analysis and X-ray crystal structure determination of two closely related products (see below). A slightly lower product yield was observed when the reaction was carried out in 1,2-dichloroethane as a solvent (entry 2). In contrast, changing the solvent from toluene to THF, CH_3CN or DMF was found to give no reaction and both starting materials were recovered in near quantitative yields (entries 3–5). Similarly, analogous reactions conducted with $Yb(OTf)_3$, $In(OTf)_3$ or TfOH in the place of $Cu(OTf)_2$ as the catalyst gave the product in lower yields of 45–79% (entries 6, 7 and 10). On the other hand, switching the catalyst to $FeCl_3$, $ZnCl_2$, *p*-$TsOH{\cdot}H_2O$ or TFA was found to result in either a trace amount of product or no reaction based on TLC and ^1H NMR analysis of the crude mixtures (entries 8, 9, 11 and 12).

To define the scope of the present procedure, we next examined the reactions of a variety of unactivated 1,4-benzoquinones and 1,3-dicarbonyl compounds (Table 2). Experiments revealed that with $Cu(OTf)_2$ as the catalyst, 1,4-benzoquinones **1a–c**

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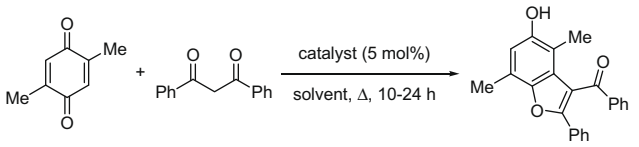
Table 1
Optimization of the reaction conditions[a]



1a **2a** **3a**

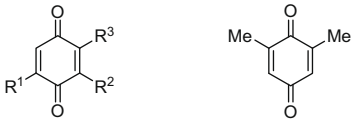
Entry	Catalyst	Solvent	Time (h)	Yield[b] (%)
1	$Cu(OTf)_2$	PhMe	10	95
2	$Cu(OTf)_2$	$(CH_2Cl)_2$	12	85
3	$Cu(OTf)_2$	THF	12	—[c]
4	$Cu(OTf)_2$	CH_3CN	12	—[c]
5	$Cu(OTf)_2$	DMF	12	—[c]
6	$Yb(OTf)_3$	PhMe	10	79
7	$In(OTf)_3$	PhMe	24	76
8	$FeCl_3$	PhMe	24	—[c]
9	$ZnCl_2$	PhMe	24	—[d]
10	TfOH	PhMe	24	45
11	*p*-TsOH·H_2O	PhMe	24	—[c]
12	TFA	PhMe	24	—[d]

[a] All reactions were performed at reflux temperature with a ratio of catalyst/**1a**/**2a** = 1:20:40.
[b] Isolated yield.
[c] No reaction based on TLC and ^{1}H NMR analysis.
[d] Trace amount (<1%) of product was obtained.

and 1,3-dicarbonyl compounds **2a**–**h** underwent the cycloaddition process and gave the corresponding benzofuran products in good to excellent yields (entries 1–17). Notably, this included the cycloaddition of **1a**–**c** with the less acidic β-ketoester **2d** which gave the corresponding adducts **3d**, **3i** and **3o** in good to excellent yields (entries 3, 8 and 14). Moreover, in instances where it was envisaged that reactions with 1,3-dicarbonyl compounds containing two different aryl substituents as in **2g**–**h** would lead to a mixture of isomers, only one regioisomer was obtained (entries 10, 11 and 17). Similarly, the analogous cycloadditions of unactivated 1,4-benzoquinones with 1,3-dicarbonyl compounds bearing both an aryl and alkyl group as in **2c** and **2e** were found to provide the corresponding 3-acyl-5-hydroxybenzofurans as the sole product (entries 2, 7, 13 and 15). This was further confirmed by X-ray structure analysis of **3k** and **3o** as shown in Figure 1.[8] With the cycloaddition process proceeding at either the more electropositive or less sterically hindered carbonyl carbon centre of the 1,3-dicarbonyl compound under our conditions, this suggested that the present procedure was regioselective. Under the standard conditions, reaction of **1d** with **2a** was the only example where no reaction could be detected on the basis of ^{1}H NMR and TLC analysis of the crude reaction mixture (entry 18).

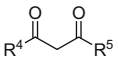
A tentative mechanism for the present reaction is shown in Scheme 2. This could involve initial activation of both **1** and **2**

Table 2
Copper(II) triflate-catalyzed cycloaddition of unactivated 1,4-benzoquinones **1a**–**d** with 1,3-dicarbonyl compounds **2a**–**h**[a]

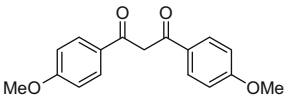


1b, $R^1 = R^2 = R^3 = H$
1c, R^1 = Me, $R^2 = R^3$ = OMe

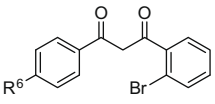
1d



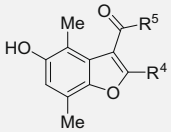
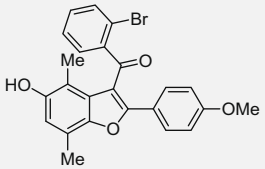
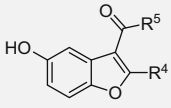
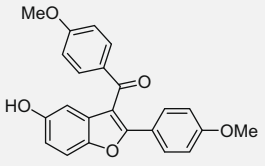
2b, $R^4 = R^5$ = Me
2c, R^4 = Ph, R^5 = Me
2d, R^4 = Ph, R^5 = OEt
2e, R^4 = Ph, $R^5 = (CH_2)_{10}Me$



2f

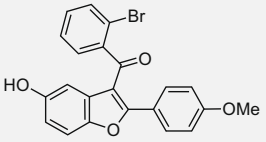
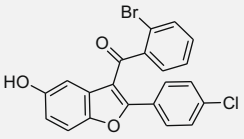
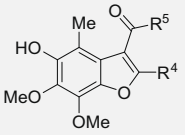
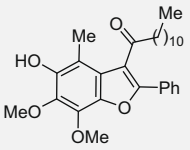
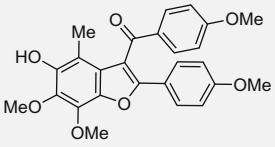
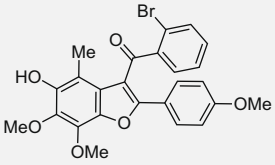
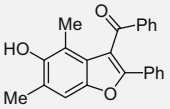


2g, R^6 = OMe
2h, R^6 = Cl

Entry	Substrates	Product		Yield[b] (%)
1	**1a** + **2b**		**3b**, $R^4 = R^5$ = Me	40
2	**1a** + **2c**		**3c**, R^4 = Ph, R^5 = Me	81
3	**1a** + **2d**		**3d**, R^4 = Ph, R^5 = OEt	88
4	**1a** + **2g**		**3e**	78
5	**1b** + **2a**		**3f**, $R^4 = R^5$ = Ph	91
6	**1b** + **2b**		**3g**, $R^4 = R^5$ = Me	45
7	**1b** + **2c**		**3h**, R^4 = Ph, R^5 = Me	83
8	**1b** + **2d**		**3i**, R^4 = Ph, R^5 = OEt	87
9	**1b** + **2f**		**3j**	68

(*continued on next page*)

Table 2 (*continued*)

Entry	Substrates	Product	Yield[b] (%)
10	**1b** + **2g**	 **3k**	79
11	**1b** + **2h**	 **3l**	64
12	**1c** + **2a**	 **3m**, $R^4 = R^5 =$ Ph	71
13	**1c** + **2c**	**3n**, $R^4 =$ Ph, $R^5 =$ Me	67
14	**1c** + **2d**	**3o**, $R^4 =$ Ph, $R^5 =$ OEt	69
15	**1c** + **2e**	 **3p**	62
16	**1c** + **2f**	 **3q**	62
17	**1c** + **2g**	 **3r**	65
18	**1d** + **2a**	 **3s**	—[c]

[a] All reactions were performed at reflux temperature for 10 h in PhMe with a ratio of catalyst/**1**/**2** = 1:20:40.
[b] Isolated yield.
[c] No reaction detected based on TLC and ^{1}H NMR analysis of the crude reaction mixture.

through coordination with the metal catalyst in a manner similar to that proposed by De Kimpe and co-workers for the $Yb(OTf)_3$-catalyzed cycloaddition of activated 1,4-naphthoquinones with 1,3-dicarbonyl compounds. Subsequent 1,4-conjugate addition of the resulting enolate **A** to the copper-activated 1,4-benzoquinone **1** affords the cyclic enolate **B**. Aromatization of this newly formed intermediate gives the hydroquinone **C** which can undergo intramolecular 5-*exo*-*trig* cyclization. Elimination of H_2O from 2,3-dihydrobenzofuran-2-ol adduct **D** then delivers the product **3**.[9]

In summary, an efficient and regioselective copper-catalyzed synthetic route to 3-acyl-5-hydroxybenzofurans based on cycloaddition of unactivated 1,4-benzoquinones with 1,3-dicarbonyl compounds has been reported. These results show that the reaction tolerates a structurally diverse set of substrates and complements earlier work with activated 1,4-naphthoquinones and 1,3-dicarbonyl compounds mediated by $Yb(OTf)_3$.[5] In addition, the present method was shown to be practical and operationally straightforward and gives good product yields. Efforts to apply this method to natural product synthesis are currently underway and will be reported in due course.

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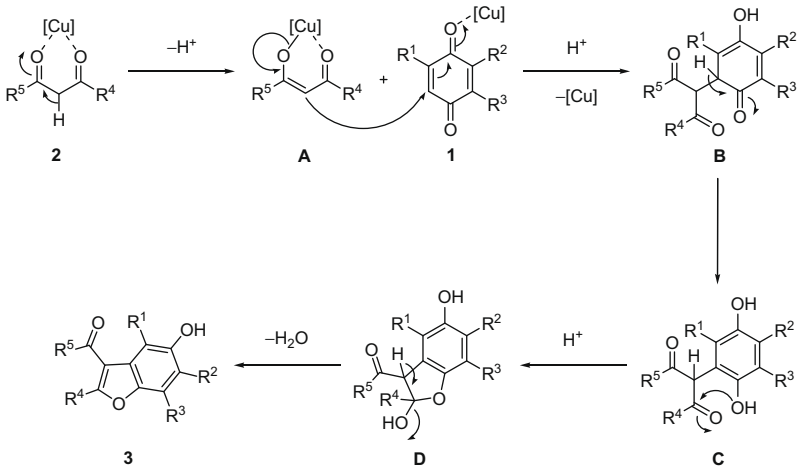

Scheme 2. Tentative mechanism for $Cu(OTf)_2$-catalyzed cycloaddition of **1** with **2**.

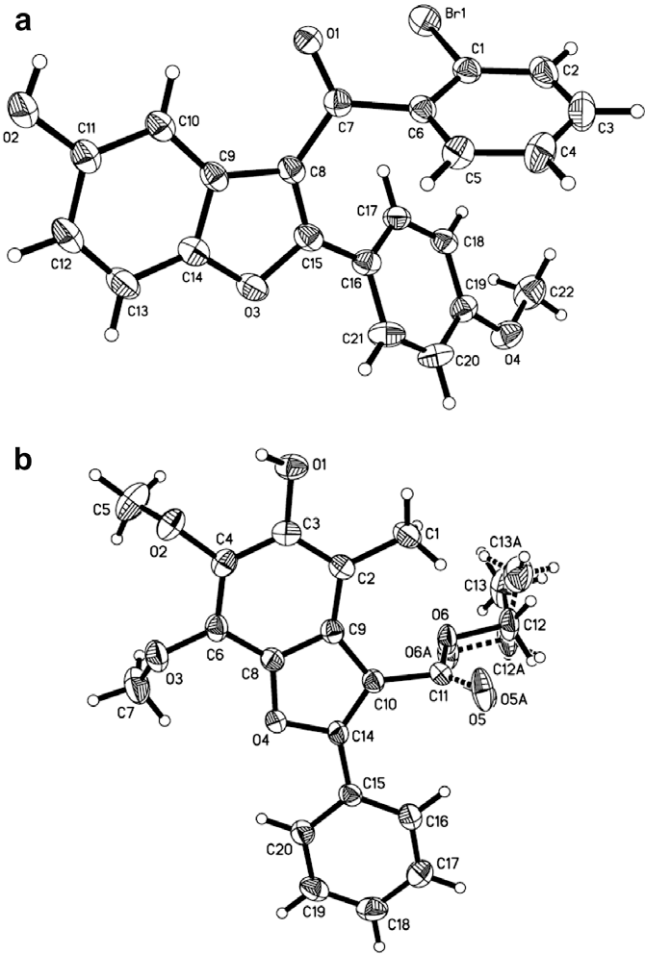

Figure 1. ORTEP drawings of (a) **3k** and (b) **3o** with thermal ellipsoids at 50% probability levels.[8]

References and notes

1. (a) Donnelly, D. M. X.; Meegnan, M. J.. In *Furans and Their Benzo Derivatives: (iii) Synthesis and Application In Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: New York, 1984; Vol. 4, p 657; (b) Bird, C. W.; Cheeseman, G. W. H.. In *Synthesis of Five-Membered Rings with One Heteroatom In Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: New York, 1984; Vol. 4, p 89; (c) Cagniant, P.; Cagniant, D. Recent Advances in the Chemistry of Benzo[*b*]furan and Its Derivatives. Part I: Occurrence and Synthesis. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Boulton, A. J., Eds.; Academic Press: New York, 1975; Vol. 18, p 337.
2. Selected recent examples: (a) Pocas, E. S. C.; Lopes, D. V. S.; da Silva, A. J. M.; Pimenta, P. H. C.; Leitao, F. B.; Netto, C. D.; Buarque, C. D.; Brito, F. V.; Costa, P. R. R.; Noel, F. *Bioorg. Med. Chem.* **2006**, *14*, 7962; (b) Schneider, B. *Phytochemistry* **2003**, *64*, 459; (c) Ebiike, H.; Masubuchi, M.; Liu, P. L.; Kawasaki, K.; Morikami, K.; Sogabe, S.; Hayase, M.; Fujii, T.; Sakata, K.; Shindoh, H.; Shiratori, Y.; Aoki, Y.; Ohtsuka, T.; Shimma, N. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 607; (d) Su, B. N.; Cuendet, M.; Hawthorne, M. E.; Kardono, L. B. S.; Riswan, S.; Fong, H. H. S.; Mehta, R. G.; Pezzuto, J. M.; Kinghorn, A. D. *J. Nat. Prod.* **2002**, *65*, 163; (e) Yoo, S.; Kim, S.-H.; Lee, S.-H.; Kim, N.-J.; Lee, D.-W. *Bioorg. Med. Chem.* **2000**, *8*, 2311.
3. Selected recent examples: (a) Bellur, E.; Freifeld, I.; Langer, P. *Tetrahedron Lett.* **2005**, *46*, 2185; (b) Tseng, C.-M.; Wu, Y.-L.; Chuang, C.-P. *Tetrahedron* **2004**, *60*, 12249; (c) Konno, T.; Chae, J.; Ishihara, T.; Yamanaka, H. *Tetrahedron* **2004**, *60*, 11695; (d) del Carman Cruz, M.; Tamariz, J. *Tetrahedron Lett.* **2004**, *45*, 2377; (e) Lee, H.-J.; Park, S.-Y.; Kim, J. S.; Song, H. M.; Suh, M.-E.; Lee, C.-O. *Bioorg. Med. Chem.* **2003**, *11*, 4791; (f) Kraus, G. A.; Kim, I. *Org. Lett.* **2003**, *5*, 1191; (g) Macleod, C.; McKiernan, G. J.; Guthrie, E. J.; Farrugia, L. J.; Hamprecht, D. W.; Macritchie, J.; Hartley, R. C. *J. Org. Chem.* **2003**, *68*, 387; (h) Tseng, C.-C.; Wu, Y.-L.; Chuang, C.-P. *Tetrahedron* **2002**, *58*, 7625; (i) Kao, C.-L.; Chern, J.-W. *J. Org. Chem.* **2002**, *67*, 6772; (j) Inoue, M.; Carson, M. W.; Frontier, A. J.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 1878; (k) Hu, Y.; Yang, Z. *Org. Lett.* **2001**, *3*, 1387.
4. (a) Matiichuk, V. S.; Martyak, R. L.; Obushak, M. D.; Vasilishin, R. Y. *Farmatsevtichnii Zhurnal (Kiev)* **2002**, *6*, 45; (b) McPherson, H. L.; Ponder, B. W. *J. Heterocycl. Chem.* **1976**, *13*, 909.
5. Mudiganti, N. V. S.; Claessens, S.; De Kimpe, N. *Tetrahedron* **2009**, *65*, 1716.
6. (a) Zhang, X.; Teo, W. T.; Chan, P. W. H. *Org. Lett.* **2009**, *11*, 4990; (b) Kothandaraman, P.; Foo, S. J.; Chan, P. W. H. *J. Org. Chem.* **2009**, *74*, 5947; (c) Zhang, X.; Rao, W.; Sally; Chan, P. W. H. *Org. Biomol. Chem.* **2009**, *7*, 4186; (d) Kothandaraman, P.; Rao, W.; Zhang, X.; Chan, P. W. H. *Tetrahedron* **2009**, *65*, 1833; (e) Rao, W.; Zhang, X.; Sze, E. M. L.; Chan, P. W. H. *J. Org. Chem.* **2009**, *74*, 1740; (f) Rao, W.; Chan, P. W. H. *Chem. Eur. J.* **2008**, *14*, 10486; (g) Wu, W.; Rao, W.; Er, Y. Q.; Loh, J. K.; Poh, C. Y.; Chan, P. W. H. *Tetrahedron Lett.* **2008**, *49*, 2620. *Tetrahedron Lett.* **2008**, *49*, 4981; (h) Rao, W.; Chan, P. W. H. *Org. Biomol. Chem.* **2008**, *6*, 2426; (i) Rao, W.; Tay, A. H. L.; Goh, P. J.; Choy, J. M. L.; Ke, J. K.; Chan, P. W. H. *Tetrahedron Lett.* **2008**, *49*, 122. *Tetrahedron Lett.* **2008**, *49*, 5115.
7. *Typical experimental procedure*: To a suspension of **2** (0.72 mmol) and $Cu(OTf)_2$ (5 mol %) in toluene (2 mL) under a nitrogen atmosphere was added drop wise a solution of **1** (0.36 mmol) dissolved in toluene (1 mL). The reaction mixture was stirred at reflux for 10 h and monitored by TLC analysis using a 4:1 *n*-hexane/EtOAc solvent system. Upon completion, the reaction mixture was quenched with 10 mL of saturated NH_4Cl solution and extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous $MgSO_4$, concentrated under reduced pressure and purified by flash silica gel column chromatography (*n*-hexane/EtOAc as eluent) to give the title compound **3**. Compound **3a**: Pale yellow solid; mp 114–116 °C; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.95 (d, 2H, J = 7.5 Hz), 7.67 (d, 2H, J = 6.7), 7.54 (t, 1H, J = 7.2 Hz), 7.41–7.25 (m, 5H), 6.68 (s, 1H), 4.55 (s, 1H), 2.53 (s, 3H), 1.98 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 195.3, 153.4, 149.5, 147.8, 137.8, 133.9, 129.9, 129.8, 129.0, 128.8, 128.6, 128.0, 126.9, 119.3, 116.9, 115.2, 112.7, 14.8, 12.0; IR (neat, cm^{-1}): 3018, 1215, 767; HRMS (ESI): calcd for $C_{23}H_{19}O_3$ $[M+H]^+$ 343.1334, found 343.1328. Compound **3d**: Pale yellow solid; mp 133–135 °C; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.81 (d, 2H, J = 7.5 Hz), 7.47–7.40 (m, 3H), 6.65 (s, 1H), 4.76 (s, 1H), 4.40 (q, 2H, J = 7.1 Hz), 2.45 (s, 3H), 2.37 (s, 3H), 1.32 (t, 3H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 166.4, 155.8, 149.6, 147.9, 130.0, 129.4, 128.4, 127.6,

126.2, 119.3, 114.9, 112.6, 111.1, 61.5, 14.7, 13.9, 11.6; IR (neat, cm^{-1}): 3018, 1215, 756; HRMS (ESI): calcd for $C_{19}H_{19}O_4$ $[M+H]^+$ 311.1283, found 311.1286.

8. CCDC 754898 (**3o**) and 754899 (**3k**) contains the supplementary crystallographic data for this Letter. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
9. It is possible that the copper(II) catalyst could also act as a simple electron-oxidizing agent and that more complex radical processes are involved, this cannot be ruled out at this time.