

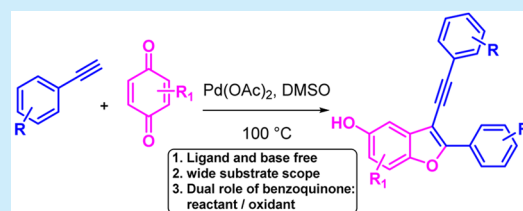
Palladium-Catalyzed Tandem C–H Functionalization/Cyclization Strategy for the Synthesis of 5-Hydroxybenzofuran Derivatives

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Supporting Information

ABSTRACT: A palladium-catalyzed benzoquinone C–H functionalization/cyclization strategy with terminal alkynes was employed for the synthesis of some biologically relevant 2,3-disubstituted 5-hydroxybenzofuran derivatives. The benzoquinone acts as a reactant as well as an oxidant. During the process, an additional alkyne functionality can be introduced at the C3 position of the benzofuran. Base, ligand, and external oxidant are not required in this protocol.



Benzofuran, an important oxygen-containing heterocycle, has been shown to be a potent inhibitor against many diseases, viruses, microbes, fungi, and enzymes.¹ As a result, a wide variety of benzofuran-containing drugs play an important role in the treatment of various types of diseases. 5-Hydroxybenzofuran, a derivative of benzofuran, has attracted considerable interest due to its presence in an enormous number of natural products that have a wide range of biological activities. For example, natural products such as gnetumelin B (anti-inflammatory activity),² corsifuran C (antibacterial activity),³ moracin U (antioxidant activity),⁴ sainfuran (antifungal activity)⁵ and lespedezavirgatal (oxygen radical absorbance capacity)⁶ contain a 5-hydroxybenzofuran core (Figure 1). In addition, 5-hydroxybenzofuran derivatives that contain a 1-oxo/hydroxy-5-methyl-4-hexenyl substituent at the C-2 position function as insect toxins.⁷

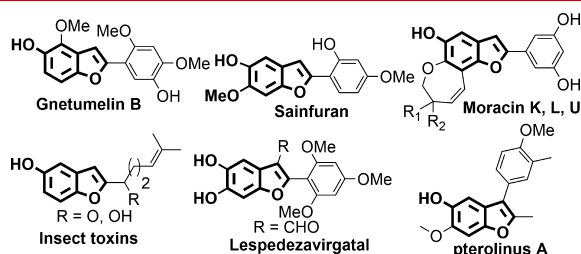


Figure 1. Representative natural products and biologically active compounds that contain a 5-hydroxybenzofuran core.

The development of palladium-catalyzed C–C bond formation reactions has dramatically changed the fate of organic synthesis.⁸ A literature survey indicates that the palladium-catalyzed direct C–H functionalization of quinones with aryl boronic acid⁹ or arenes/aryl chlorides¹⁰ can be used for the synthesis of aryl-substituted quinones. Other metals such as silver and titanium and rhodium-catalyzed C–H functionalization reactions of quinones with aryl boronic acid, arenes, and aryltrifluoroborates, respectively, have also been reported.¹¹ No reports, however, are available regarding the C–H functionaliza-

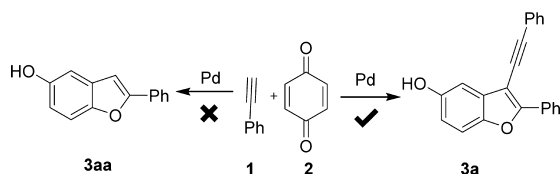
tion of quinones with terminal alkynes. Previous reports suggested that 5-hydroxybenzofuran derivatives can be synthesized by the condensation of 4-methoxyphenol with 2-bromoacetaldehyde diethyl acetal, followed by acid-promoted intramolecular cyclization¹² or by the cyclocondensation of *p*-benzoquinone and enaminones either by heating or by microwave assistance.¹³ These two strategies involve multistep processes accompanied by low yields of the final product. 5-Hydroxybenzofuran derivatives can also be prepared by the condensation of *p*-benzoquinone with acetyl acetone or ethyl acetoacetate in the presence of a Lewis acid catalyst.¹⁴ Very recently, Wu et al. extended the above protocol to ketones for the synthesis of 5-hydroxybenzofuran derivatives in the presence of scandium triflate and triethyl orthoformate.¹⁵ Kim et al. reported on the synthesis of 2-substituted 5-hydroxybenzofuran from alkyne-containing quinols using a Pt-catalyzed domino dienone–phenol rearrangement/intramolecular 5-*endo-dig* cyclization reaction sequence.¹⁶ Although 5-hydroxybenzofuran derivatives are present in a wide variety of natural products and have a wide range of biological activities, efficient synthetic routes for hydroxybenzofuran derivative production are few in number. As a result, an efficient protocol for the synthesis of 5-hydroxybenzofurans derivatives starting from readily available starting materials would be highly desirable.

As a part of our interest in developing efficient methodologies for the synthesis of active heterocycles,¹⁷ our recent studies dealing with the chemistry of benzoquinones encouraged us to focus on exploring the multiple roles of benzoquinone¹⁸ in the same reaction. A review of the literature suggested that the C–H functionalization of quinones with alkynes by palladium catalysis is an unexplored area. We anticipated that 2-phenyl-5-hydroxybenzofuran **3aa** derivatives could be prepared from benzoquinone **2** and the terminal alkyne **1** in the presence of a palladium catalyst via C–H functionalization, followed by the nucleophilic addition of the phenolic OH to the alkyne¹⁹ as

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shown in Scheme 1. Benzoquinone would function as an oxidant²⁰ as well as a reactant in such a reaction sequence.

Scheme 1. Palladium-Catalyzed C–H Functionalization of Benzoquinones with Alkynes



In order to validate our hypothesis, we began by examining the reactivity of phenylacetylene toward benzoquinone in the presence of a palladium catalyst in various solvents, ligands, and bases. The reaction was initially carried out at 100 °C in the presence of 10 mol % of Pd(OAc)₂ and 20 mol % of PPh₃ ligand. Surprisingly, the expected 2-phenyl-5-hydroxybenzofuran 3aa was not detected, and instead, the more interesting 3-phenylethynyl-substituted 2-phenyl-5-hydroxybenzofuran 3a was obtained in 50% yield along with 10% of the homocoupling product 4a (Table 1, entry 1). The structure of 3a was further

Table 1. Optimization Studies^{a–d}

entry ^a	catalyst (mol %)	solvent (2 mL)	base/ligand (equiv)	yield ^b (%) (3a/4a)
1	Pd(OAc) ₂ (10)	DMSO	PPh ₃ (0.2)	50/10
2	Pd(OAc) ₂ (10)	DMSO	PCy ₃ (0.2)	25/26
3	Pd(OAc) ₂ (10)	DMSO	1,10-phenanthroline (0.2)	0/47
4	Pd(OAc) ₂ (10)	DMSO	K ₂ CO ₃ (2.0)	0/80
5	Pd(OAc) ₂ (10)	DMSO	Cs ₂ CO ₃ (2.0)	0/75
6	Pd(OAc) ₂ (10)	DMSO		74/5
7 ^c	Pd(OAc) ₂ (10)	DMSO		58/10
8 ^d	Pd(OAc) ₂ (10)	DMSO		42/28
9	Pd(OAc) ₂ (2.5)	DMSO		18/40
10	Pd(OAc) ₂ (5)	DMSO		40/20
11	PdCl ₂ (PPh ₃) ₂ (10)	DMSO		0/0
12	PdCl ₂ (10)	DMSO		0/0
13	Pd(OAc) ₂ (10)	DMF		8/40
14	Pd(OAc) ₂ (10)	acetonitrile		0/0
15	Pd(OAc) ₂ (10)	THF		0/0

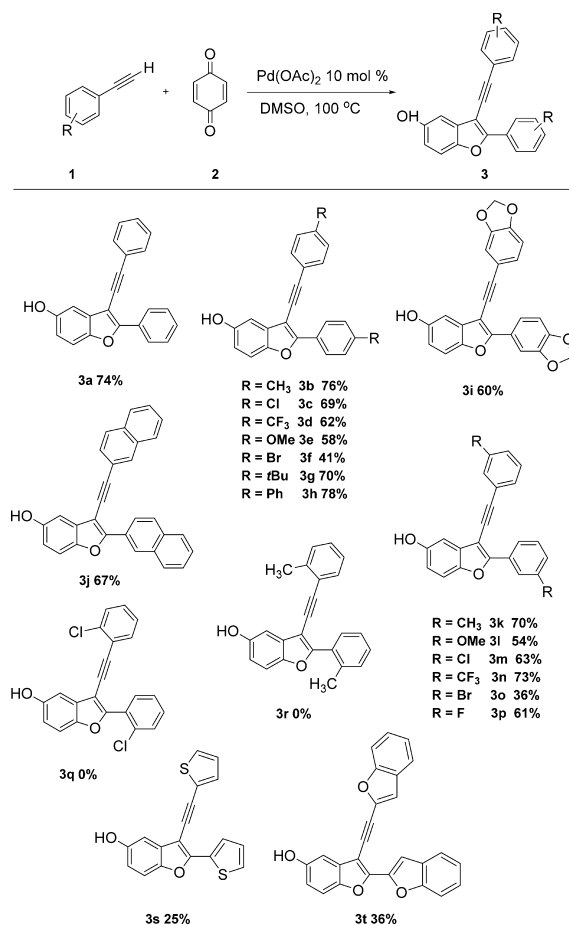
^aAll of the reactions were carried out using 0.5 mmol of 1a and 1.5 mmol of BQ in 2 mL of solvent at 100 °C for 12 h. ^bIsolated yields. ^cReaction carried out at 80 °C. ^dReaction carried out at 120 °C.

confirmed by ¹H, ¹³C NMR spectroscopy and HRMS data. To further increase the yield of 3a, ligands such as PCy₃ and 1,10-phenanthroline were employed, but no significant increase in product yield was observed (Table 1, entries 2 and 3). In the presence of bases such as K₂CO₃ and Cs₂CO₃, the desired product 3a was not observed, and instead, the self-coupled product 4a was obtained (Table 1, entries 4 and 5). It is possible that the presence of base might be impede the anticipated reaction by rapidly converting phenylacetylene to the com-

paratively less reactive homocoupling product. Interestingly, when we repeated the reaction in the absence of a base and a ligand, the product 3a was obtained in 74% yield (Table 1, entry 6). Also, lowering (80 °C) or increasing (120 °C) the reaction temperature was ineffective in producing the product 3a (Table 1, entries 7 and 8). Notably, by decreasing the catalyst loading to 5 mol % and to 2.5 mol %, the yield of 3a gradually decreased (Table 1, entries 9 and 10). Further, other palladium salts including PdCl₂ (PPh₃)₂ and PdCl₂ were also found to be unproductive (Table 1, entries 11 and 12). Finally, the product was formed in trace amounts when DMF was used as the solvent (Table 1, entry 13), but other solvents failed to afford product 3a (Table 1, entries 14 and 15).

Prompted by our initial results and with optimized reaction conditions in hand, we next focused our attention on substrate scope to determine the generality of this reaction. As summarized in Scheme 2, a wide range of electron-donating, electron-

Scheme 2. Scope with Various Terminal Alkynes^{a–c}



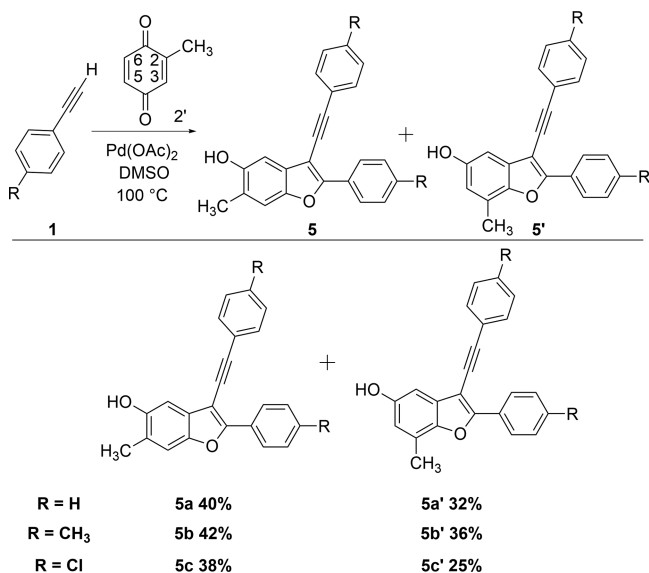
^aAll of the reactions were carried out using 0.5 mmol of 1, 3 equiv 2, and 10 mol % Pd(OAc)₂ in DMSO (2 mL), 100 °C for 12 h. ^bIsolated yields. ^cIn all cases, 5–8% alkyne self-coupled product isolated.

withdrawing, and halogen substituents at the para position of the aromatic ring of terminal alkynes were utilized, and all were converted smoothly into the desired benzofuran derivatives using our protocol, although a bromo substituent gave a slightly lower yield of 3f, but the other products 3a–e and 3g were isolated in good to moderate yields. The structure of 3c was also confirmed by X-ray crystallography.²¹ It is also noteworthy that 4-phenyl-substituted phenylacetylene also gave the desired

product **3h** in good yield. 2-Ethynynaphthalene and 3,4-(methylenedioxy)phenylacetylene were also converted into the expected benzofuran derivatives **3i** and **3j** in good yields. Moreover, the scope of the reaction with respect to meta substituents on the phenylacetylene was also examined; the 3-bromo-substituted phenylacetylene derivative gave lower yields of the expected product **3o**, whereas the expected products **3k–n** and **3p** were formed in good to moderate yields. The reactions of phenylacetylenes bearing ortho substituents such as 2-Me and 2-Cl under optimized conditions failed to afford the desired products **3q** and **3r**, and instead, alkyne homocoupling products were observed. We attribute this to the fact that steric effects likely have a major effect on this reaction. Heterocycle terminal alkynes such as 2-ethynylthiophene and 2-ethynylbenzofuran were also well tolerated and converted to the corresponding benzofuran derivatives **3s** and **3t** in slightly lower yields using current protocol. An inseparable mixture of products was obtained when the reaction was conducted with two different alkynes (**2b** and **2c**) under the optimized reaction conditions.

In an attempt to enhance the scope of the reaction further, we examined the reaction of phenylacetylenes with 2-methylbenzoquinone under optimized reaction conditions (Scheme 3). To

Scheme 3. Scope with Substituted Benzoquinones^{a–c}

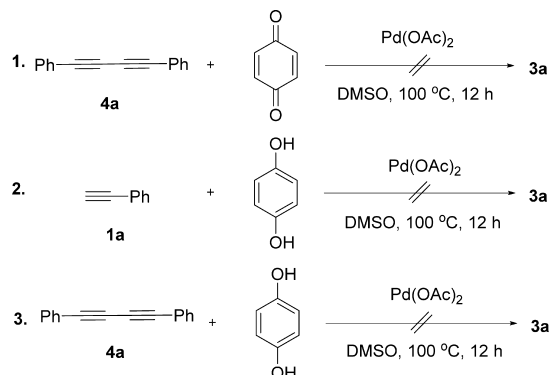


^aAll of the reactions were carried out using 0.5 mmol of **1**, 3 equiv of **2'**, and 10 mol % Pd(OAc)₂ in DMSO (2 mL), at 100 °C for 12 h. ^bIsolated yields. ^cIn all cases 5–8% alkyne self-coupled product isolated.

our delight, the reaction proceeded exclusively at the C5 and C6 positions of benzoquinone, but unfortunately, no product corresponding to the C3 position was observed. Steric hindrance by the C2 methyl group might be prohibit the reaction at the C3 position. Both regioisomeric benzofuran derivatives were separated by column chromatography to afford **5a** in 40% yield and **5a'** in 32% yield, the structures of which were confirmed by ¹H and ¹³C NMR spectroscopy and X-ray crystallography.²¹ Other substituted phenylacetylenes such as 4-Me and 4-Cl were also well tolerated in reactions with 2-methylbenzoquinone, and in both cases, the anticipated isomeric products **5b**, **5b'** and **5c**, **5c'** were obtained in good yields. However, naphthoquinone failed to produce the expected product under optimized reaction conditions.

To investigate the mechanism for the reaction, some control experiments were conducted, as shown in Scheme 4. When the

Scheme 4. Control Experiment



alkyne self-coupled product **4a** was treated with benzoquinone under optimized reaction conditions, the desired product **3a** was not produced. This rules out the possibility that the reaction proceeds via an alkyne self-coupled product. The possibility that the reaction proceeds through a hydroquinone intermediate was also eliminated based on the finding that when **1a** or **4a** were directly exposed to the hydroquinone under optimized reaction conditions no reaction occurred.

On the basis of the results of the above control experiments and substrate scope, especially when ortho-substituted phenylacetylenes and 2-substituted benzoquinones were used, a plausible mechanism is depicted as shown in Figure 2. These

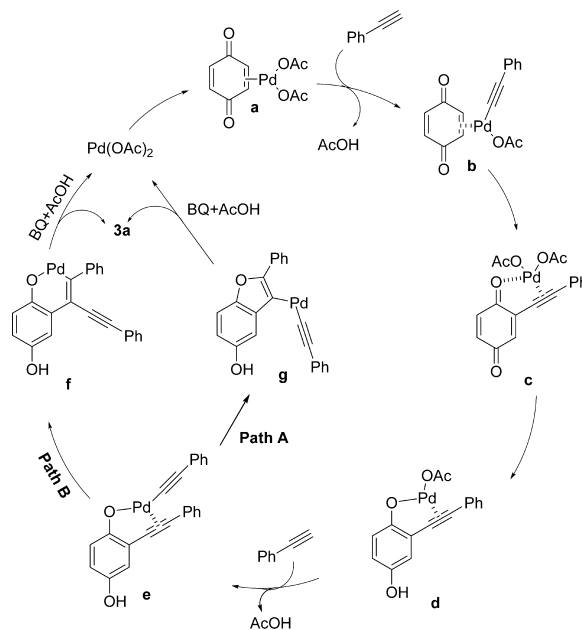


Figure 2. Plausible reaction pathway.

results suggest that Pd(OAc)₂ initially coordinates with benzoquinone to form complex **a**. The triple bond of the alkyne then coordinates to the palladium center of complex **a**, followed by a direct deprotonation with the assistance of an acetate ligand to generate alkynylpalladium complex **b**.²² The resulting alkynylpalladium undergoes oxidative insertion followed by reductive elimination to form a 2-ethynylphenylbenzoquinone

intermediate. This intermediate again coordinates with the Pd complex to generate complex **c** followed by aromatization to form complex **d**. A second molecule of alkyne then coordinates to the palladium center of complex **d** followed by a direct deprotonation with the assistance of an acetate ligand to generate complex **e**. After the formation of complex **e**, the desired product **3a** is then produced, through either path A or path B, along with the regeneration of the catalyst in the presence of benzoquinone.

In conclusion, a palladium-catalyzed benzoquinone C–H functionalization/cyclization strategy using terminal alkynes was employed for the synthesis of 2,3-disubstituted 5-hydroxybenzofuran derivatives by taking advantage of the dual role of benzoquinone. The main challenge associated with the current protocol, i.e., the tendency for the alkyne to undergo self-coupling and the selection of an appropriate ligand, was successfully overcome. Easily available starting materials, ligand free, and a wide substrate scope makes this protocol potentially very useful. Control experiments suggest that the benzofuran core is formed in an unconventional manner.¹⁹

■ ASSOCIATED CONTENT

■ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: [10.1021/acs.orglett.6b03310](https://doi.org/10.1021/acs.orglett.6b03310).

General experimental procedures and spectroscopic data of all the compounds; ¹H and ¹³C NMR spectral data for representative compounds; X-ray crystallographic data for **3c**, **5a** and **5a'** (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

- (1) (a) Dawood, K. M. *Expert Opin. Ther. Pat.* **2013**, *23*, 1133. (b) Khanam, H.; Shamsuzzaman, E. *Eur. J. Med. Chem.* **2015**, *97*, 483. (c) Hiremathad, A.; Patil, M. R.; Chethana, K. R.; Chand, K.; Santos, M. A.; Keri, R. S. *RSC Adv.* **2015**, *5*, 96809.
- (2) Wang, L.-Q.; Zhao, Y.-X.; Hu, J. M.; Jia, A.-Q.; Zhou, J. *Helv. Chim. Acta* **2008**, *91*, 159.
- (3) (a) Xiao, K.; Zhang, H. J.; Xuan, L. J.; Zhang, J.; Xu, Y. M.; Bai, D. L. Stilbenoids: chemistry and bioactivities. In *Studies in Natural Products Chemistry*; Rahman, A. U., Ed.; Elsevier, 2008; Vol.34, pp 453–478. (b) Liu, W.; Jiang, X.; Zhang, W.; Jiang, F.; Fu, L. *Organic Chem. Curr. Res.* **2016**, *5*, 1000164.
- (4) (a) Kapche, G. D. W. F.; et al. *Phytochemistry* **2009**, *70*, 216. (b) *Dictionary of Flavonoids*; Buckingham, J.; Ranjit, V.; Munasinghe, N., Eds.; Taylor and Francis Group: Boca Raton, 2015.
- (5) Geiger, H.; Quinn, C. Biflavonoids. In *The Flavonoids: Advances in Research since 1980*; Harborne, J. B., Ed.; Chapman and Hall: London, 1988; pp 99–124.
- (6) Chen, Y.; Wei, X.; Xie, H.; Deng, H. *J. Nat. Prod.* **2008**, *71*, 929.
- (7) Findlay, J. A.; Buthelezi, S.; Li, G.; Seveck, M.; Miller, J. D. *J. Nat. Prod.* **1997**, *60*, 1214.
- (8) (a) *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley and Sons: New York, 2002; 2 vols. (b) *Palladium Reagents and Catalysts Innovations in Organic Synthesis*; Tsuji, J., Ed.; Wiley and Sons: New York, 1995. (c) *Palladium Reagents and Catalysts: New Perspectives for the 21st Century*; Tsuji, J., Ed.; Wiley and Sons: Chichester, U.K., 2004.
- (9) (a) Walker, S. E.; Jordan-Hore, J. A.; Johnson, D. G.; Macgregor, S. A.; Lee, A.-L. *Angew. Chem., Int. Ed.* **2014**, *53*, 13876. (b) Molina, M. T.; Navarro, C.; Moreno, A.; Csáky, A. G. *Org. Lett.* **2009**, *11*, 4938. (c) Gan, X.; Jiang, W.; Wang, W.; Hu, L. *Org. Lett.* **2009**, *11*, 589.
- (10) (a) Itahara, T. *J. Org. Chem.* **1985**, *50*, 5546. (b) Singh, P. K.; Rohtagi, B. K.; Khanna, R. N. *Synth. Commun.* **1992**, *22*, 987. (c) Rao, M. L. N.; Giri, S. *RSC Adv.* **2012**, *2*, 12739.
- (11) (a) Fujiwara, Y.; Domingo, V.; Seiple, I. B.; Gianatassio, R.; Del Bel, M.; Baran, P. S. *J. Am. Chem. Soc.* **2011**, *133*, 3292. (b) Engler, T. A.; Reddy, J. P. *J. Org. Chem.* **1991**, *56*, 6491. (c) Demchuk, O. G.; Pietrusiewicz, K. *Synlett* **2009**, 2009, 1149. (d) Lockner, J. W.; Dixon, D. D.; Risgaard, R.; Baran, P. S. *Org. Lett.* **2011**, *13*, 5628. (e) Shintani, R.; Duan, W.-L.; Hayashi, T. *J. Am. Chem. Soc.* **2006**, *128*, 5628. (f) Duan, W.-L.; Imazaki, Y.; Shintani, R.; Hayashi, T. *Tetrahedron* **2007**, *63*, 8529.
- (12) Bonini, C.; Cristiani, G.; Funicello, M.; Viggiani, L. *Synth. Commun.* **2006**, *36*, 1983.
- (13) (a) Cheng, X.-M.; Liu, X.-W. *J. Comb. Chem.* **2007**, *9*, 906. (b) Mukhanova, T. I.; Alekseeva, L. M.; Granik, V. G. *Khim. Geterotsikl. Soedin.* **1990**, 888.
- (14) (a) Bernatek, E. *Acta Chem. Scand.* **1952**, *6*, 160. (b) Bernatek, E.; Ledaal, T. *Acta Chem. Scand.* **1958**, *12*, 2053.
- (15) Wu, F.; Bai, R.; Gu, Y. *Adv. Synth. Catal.* **2016**, *358*, 2307.
- (16) Kim, I.; Kim, K.; Choi, J. *J. Org. Chem.* **2009**, *74*, 8492.
- (17) Some selected publications: (a) Kotipalli, T.; Kavala, V.; Konala, A.; Janreddy, D.; Kuo, C.-W.; Yao, C.-F. *Adv. Synth. Catal.* **2016**, *358*, 2652. (b) Zanzwar, M. R.; Kavala, V.; Gawande, S. D.; Kuo, C.-W.; Huang, W.-C.; Kuo, T.-S.; Huang, H.-N.; He, C.-H.; Yao, C.-F. *J. Org. Chem.* **2014**, *79*, 1842. (c) Raihan, M. J.; Rajawinslin, R. R.; Kavala, V.; Kuo, C.-W.; Kuo, T.-S.; He, C.-H.; Huang, H.-N.; Yao, C.-F. *J. Org. Chem.* **2013**, *78*, 8872. (d) Gawande, S. D.; Kavala, V.; Zanzwar, M. R.; Kuo, C.-W.; Huang, W.-C.; Kuo, T.-S.; Huang, H.-N.; He, C.-H.; Yao, C.-F. *Adv. Synth. Catal.* **2014**, *356*, 2599.
- (18) Kuo, C.-W.; Konala, A.; Lin, L.; Chiang, T.-T.; Huang, C.-Y.; Yang, T.-H.; Kavala, V.; Yao, C.-F. *Chem. Commun.* **2016**, *52*, 7870.
- (19) Selected examples for synthesis of benzofuran. From halo-substituted phenols and internal alkynes: (a) Larock, R. C.; Yum, E. K.; Doty, M. J.; Sham, K. K. *J. Org. Chem.* **1995**, *60*, 3270. (b) Gill, G. S.; Grobelny, D. W.; Chaplin, J. H.; Flynn, B. L. *J. Org. Chem.* **2008**, *73*, 1131. (c) Wang, R.; Mo, S.; Lu, Y.; Shen, Z. *Adv. Synth. Catal.* **2011**, *353*, 713. From phenols and internal alkynes: (d) Kuram, M. R.; Bhanuchandra, M.; Sahoo, A. K. *Angew. Chem., Int. Ed.* **2013**, *52*, 4607. (e) Zeng, W.; Wu, W.; Jiang, H.; Huang, L.; Sun, Y.; Chen, Z.; Li, X. *Chem. Commun.* **2013**, *49*, 6611. (f) Zhu, R.; Wei, J.; Shi, Z. *Chem. Sci.* **2013**, *4*, 3706.
- (20) Popp, B. V.; Stahl, S. S. *Top Organomet. Chem.* **2007**, *22*, 149.
- (21) CCDC 1509374 (**3c**), CCDC 1511959 (**5a**), and CCDC 1509527 (**5a'**). See the Supporting Information for further crystallographic data details.
- (22) (a) Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 9651. (b) Lee, J. T. D.; Zhao, Y. *Angew. Chem., Int. Ed.* **2016**, *55*, 13872. (c) Trost, B. M.; Sorum, M. T.; Chan, C.; Harms, A. E.; Rühler, G. *J. Am. Chem. Soc.* **1997**, *119*, 698.