Accepted Manuscript

One-pot synthesis of 2,3-disubstituted benzofurans from 2-chlorophenols using palladium–dihydroxyterphenylphosphine catalyst

Miyuki Yamaguchi, Hayato Ozawa, Haruka Katsumata, Tomoyo Akiyama, Kei Manabe

PII: S0040-4039(18)30879-7
DOI: https://doi.org/10.1016/j.tetlet.2018.07.019
Reference: TETL 50128

To appear in: *Tetrahedron Letters*

Received Date: 4 June 2018
Revised Date: 30 June 2018
Accepted Date: 5 July 2018

Please cite this article as: Yamaguchi, M., Ozawa, H., Katsumata, H., Akiyama, T., Manabe, K., One-pot synthesis of 2,3-disubstituted benzofurans from 2-chlorophenols using palladium–dihydroxyterphenylphosphine catalyst, *Tetrahedron Letters* (2018), doi: https://doi.org/10.1016/j.tetlet.2018.07.019

Tetrahedron Letters
journal homepage: www.elsevier.com

One-pot synthesis of 2,3-disubstituted benzofurans from 2-chlorophenols using palladium–dihydroxyterphenylphosphine catalyst

Miyuki Yamaguchi, Hayato Ozawa, Haruka Katsumata, Tomoyo Akiyama, and Kei Manabe*

School of Pharmaceutical Sciences, University of Shizuoka, 52-1 Yada, Suruga-ku, Shizuoka 422-8526, Japan

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

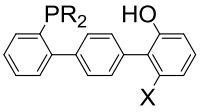
Keywords:
Benzofuran
Palladium
Ligand
Sonogashira coupling
Cyclization

ABSTRACT

2,3-Disubstituted benzofurans possessing 2-hydroxyphenyl moiety at the C-3 position were synthesized from readily available 2-chlorophenols and terminal alkynes by hydroxy-directed *ortho*-Sonogashira coupling and subsequent oxypalladation/reductive elimination, using Pd-dihydroxyterphenylphosphine catalyst. The catalyst accelerates not only the Sonogashira coupling but also the introduction of 2-hydroxyphenyl group at the C-3 position of benzofuran.

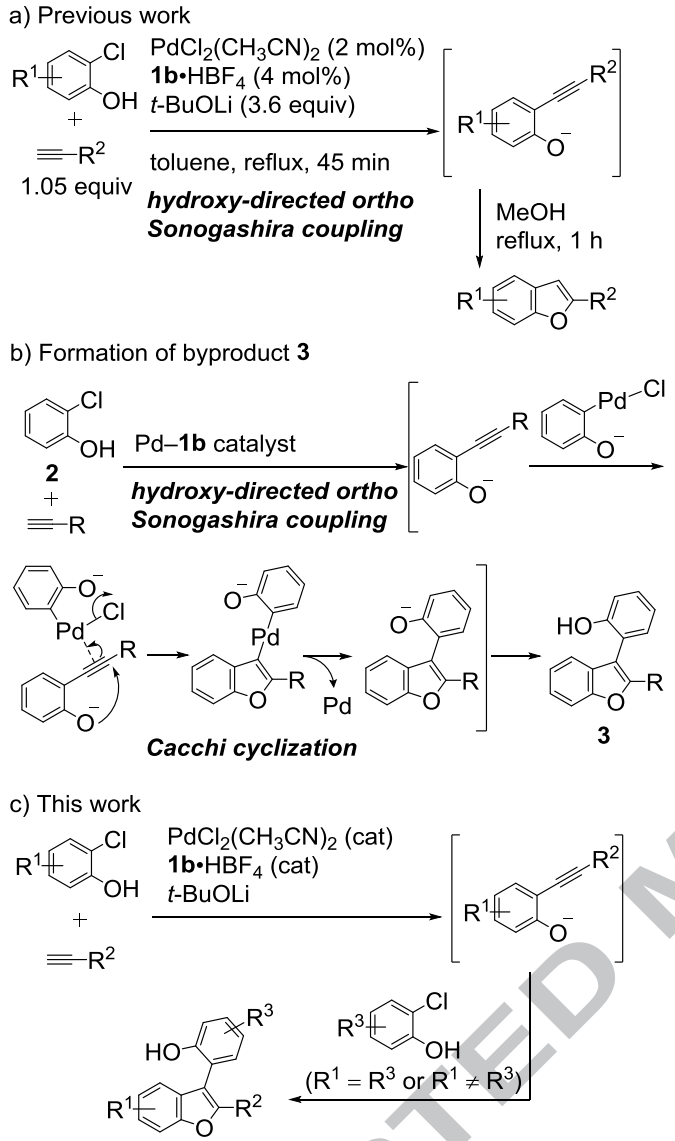
The benzofuran framework is ubiquitously present in many natural products, biologically active compounds, and functionalized materials.[1] Among them, the 2,3-disubstituted benzofuran scaffold, often containing one or more hydroxy groups, has attracted considerable attention. To construct 2,3-disubstituted benzofurans, a number of synthetic methods have been developed.[2] However, direct approaches to obtain 2,3-disubstituted benzofurans possessing hydroxy groups are still limited,[3] and efficient synthetic methods from readily available compounds are highly desired.

We have developed hydroxyterphenylphosphines **1** (Figure 1) and applied them to Pd-catalyzed site-selective cross couplings.[4] In the reactions of dihalogenated phenols or anilines, the catalyst derived from Pd and **1** binds with the substrate via metal phenoxides or anilides, and site-selectively accelerates oxidative addition of the 2-halo group to Pd. We have also reported benzofuran synthesis from readily available 2-chlorophenols and terminal alkynes using the Pd–**1b** catalyst via hydroxy-directed *ortho*-Sonogashira coupling and subsequent cyclization (Scheme 1a).[5] This catalytic system enabled the use of 2-chlorophenols, which are less reactive but more readily available than 2-bromo or 2-iodophenols. During this study, we observed the formation of a small amount (~5% yield) of 2,3-disubstituted benzofuran **3** bearing 2-hydroxyphenyl moiety at the C-3 position as a byproduct (Scheme 1b), presumably via Sonogashira coupling followed by an oxypalladation/reductive elimination sequence. This type of sequence, which is known as Cacchi cyclization, is a powerful method to afford 2,3-disubstituted benzofurans; Pd-catalyzed annulations of 2-alkynylphenol with aryl iodides or bromides have been previously reported.[6] One-pot synthesis of 2,3-diarylated benzofurans from 2-iodophenol, terminal alkyne, and aryl iodide has been also conducted.[7] Therefore, we expected that the Pd–**1b** catalyst would enable one-pot synthesis of 2,3-disubstituted benzofurans from readily available 2-chlorophenols and terminal alkynes via hydroxy-directed *ortho*-Sonogashira coupling and oxypalladation/reductive elimination (Scheme 1c). Herein, we report the one-pot synthesis of 2,3-disubstituted benzofurans possessing a hydroxyphenyl group from 2-chlorophenols using the Pd–**1b** catalyst.



1a: X = H, R = Cy
1b: X = OH, R = Cy
1c: X = OH, R = Ph

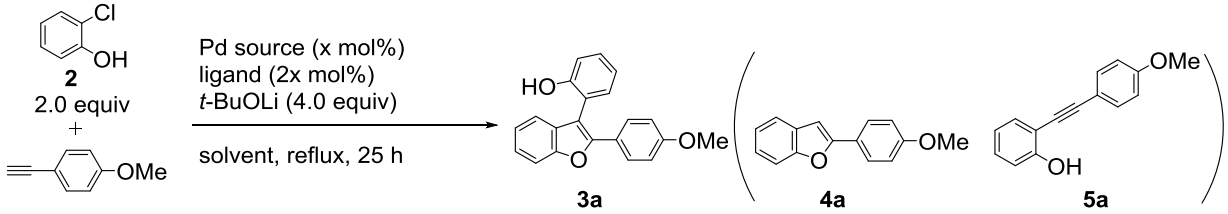
Figure 1. Hydroxyterphenylphosphines **1**.



Scheme 1. (a) Pd–**1b**-catalyzed benzofuran synthesis from chlorophenols (previous work). (b) Proposed mechanism of the formation of byproduct **3**. (c) 2,3-Disubstituted benzofuran synthesis from 2-chlorophenols (this work).

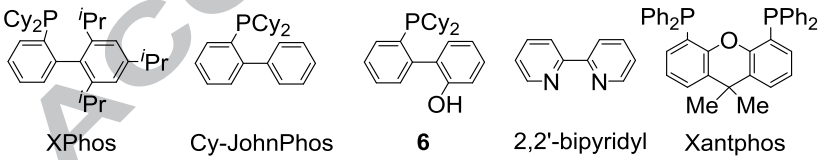
First, the reaction conditions were optimized using 4-ethynylanisole and 2-chlorophenol **2** (2 equiv) and as model substrates, *t*-BuOLi as base, and toluene as solvent (Table 1). When the reaction was conducted with 2 mol% of the catalyst derived from $PdCl_2(CH_3CN)_2$ and **1b**, the desired C-3-arylated benzofuran **3a** was obtained in 23% yield, along with 31% of C-3-protonated benzofuran **4a** and <16% of 2-alkynylphenol **5a** (Entry 1). When 4 mol% of the catalyst was used, the yield of **3a** was increased and that of **5a** was decreased (Entry 2). When 6 mol% of the catalyst was used, 64% yield of **3a** was obtained and formation of **4a** was suppressed (Entry 3). Reaction using 8 mol% of the catalyst gave **3a** in slightly lower yield (Entry 4). Use of other Pd sources resulted in moderate yield of the product (Entries 5 and 6). Thus, 6 mol% was identified as the optimum loading amount for the catalyst. Then, various solvents were screened using 6 mol% of the catalyst. For xylenes and mesitylene, the yield of **3a** was decreased and that of **4a** was increased (Entries 7 and 8). Use of heptane also resulted in similar yields (Entry 9). When THF was used, only a small amount of **3a** was obtained (Entry 10). On the other hand, reaction using 1,4-dioxane proceeded smoothly to give 60% yield of **3a** along with only 5% of **4a** (Entry 11). 1,2-Dimethoxyethane solvent gave **3a** in moderate yield (Entry 12), whereas DMF was not effective for the reaction (Entry 13). While both toluene and 1,4-dioxane gave almost the same yields of **3a**, smaller amounts of byproducts formed in 1,4-dioxane enabled easier purification of **3a**. Therefore, we decided to use 1,4-dioxane as the solvent for screening various ligands. Reaction with dihydroxyterphenylphosphine **1c**, bearing a diphenylphosphino group afforded **3a** in moderate yield (Entry 14). Use of monohydroxyterphenylphosphine **1a** resulted in low yield of **3a** (Entry 15). When XPhos was used,[8] small amounts of **3a** and **4a** were obtained (Entry 16). Other ligands, including the hydroxy-group-containing ligand **6** and bidentate ligands, were found to be ineffective (Entries 17-22). Reaction using 2-bromophenol instead of **2** also proceeded smoothly to afford **3a** in 69% yield with 16% of **4a** (Entry 23).

Table 1. Optimization of reaction conditions.



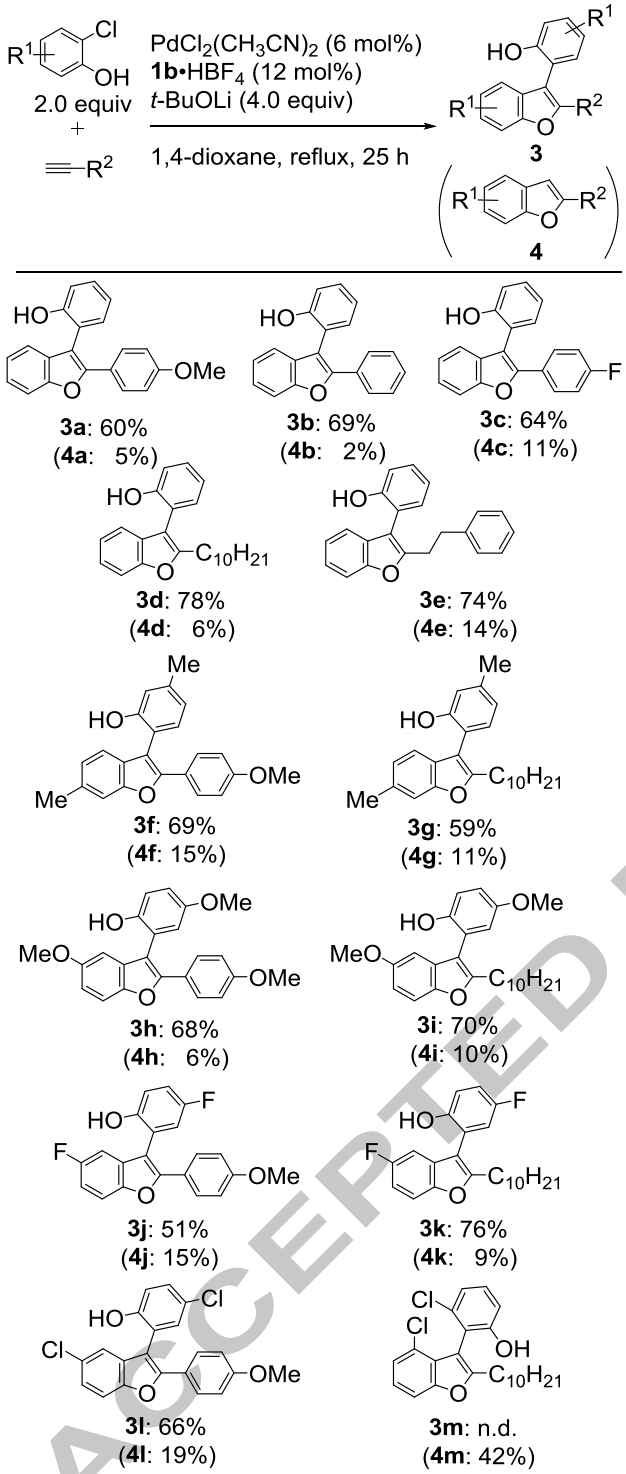
Entry	Pd source (x mol%)	Ligand (2x mol%)	Solvent	Yield (%)[a]		
				3a	**4a**	**5a**
1	$PdCl_2(CH_3CN)_2$ (2)	**1b**·HBF_4 (4)	toluene	23	31	<16
2	$PdCl_2(CH_3CN)_2$ (4)	**1b**·HBF_4 (8)	toluene	41	30	<4
3	$PdCl_2(CH_3CN)_2$ (6)	**1b**·HBF_4 (12)	toluene	64	13	2
4	$PdCl_2(CH_3CN)_2$ (8)	**1b**·HBF_4 (16)	toluene	56	10	2
5	$Pd(OAc)_2$ (6)	**1b**·HBF_4 (12)	toluene	51	22	4
6	$Pd_2(dba)_3$ (3)	**1b**·HBF_4 (12)	toluene	49	25	3
7[b]	$PdCl_2(CH_3CN)_2$ (6)	**1b**·HBF_4 (12)	xylenes	46	22	2
8[b]	$PdCl_2(CH_3CN)_2$ (6)	**1b**·HBF_4 (12)	mesitylene	31	38	n.d.[c]
9	$PdCl_2(CH_3CN)_2$ (6)	**1b**·HBF_4 (12)	heptane	38	37	n.d.[c]
10	$PdCl_2(CH_3CN)_2$ (6)	**1b**·HBF_4 (12)	THF	<12	46	n.d.[c]
11	$PdCl_2(CH_3CN)_2$ (6)	**1b**·HBF_4 (12)	1,4-dioxane	60	5	n.d.[c]
12	$PdCl_2(CH_3CN)_2$ (6)	**1b**·HBF_4 (12)	1,2-dimethoxyethane	44	7	n.d.[c]
13	$PdCl_2(CH_3CN)_2$ (6)	**1b**·HBF_4 (12)	DMF	<4	18	n.d.[c]
14	$PdCl_2(CH_3CN)_2$ (6)	**1c** (12)	1,4-dioxane	37	4	n.d.[c]
15	$PdCl_2(CH_3CN)_2$ (6)	**1a**·HBF_4 (12)	1,4-dioxane	17	3	trace
16	$PdCl_2(CH_3CN)_2$ (6)	XPhos (12)	1,4-dioxane	<6	9	trace
17	$PdCl_2(CH_3CN)_2$ (6)	Cy-JohnPhos (12)	1,4-dioxane	trace	n.d.[c]	trace
18	$PdCl_2(CH_3CN)_2$ (6)	**6** (12)	1,4-dioxane	trace	7	n.d.[c]
19	$PdCl_2(CH_3CN)_2$ (6)	PCy_3 (12)	1,4-dioxane	trace	n.d.[c]	trace
20	$PdCl_2(CH_3CN)_2$ (6)	(*t*-Bu)$_3$P·HBF_4 (12)	1,4-dioxane	trace	10	n.d.[c]
21	$PdCl_2(CH_3CN)_2$ (6)	2,2'-bipyridyl (12)	1,4-dioxane	n.d.[c]	n.d.[c]	n.d.[c]
22	$PdCl_2(CH_3CN)_2$ (6)	Xantphos (12)	1,4-dioxane	n.d.[c]	n.d.[c]	n.d.[c]
23[d]	$PdCl_2(CH_3CN)_2$ (6)	**1b**·HBF_4 (12)	1,4-dioxane	69	16	n.d.[c]

[a]Isolated yield. [b]120 °C. [c]Not detected. [d]2-Bromophenol was used instead of **2**.



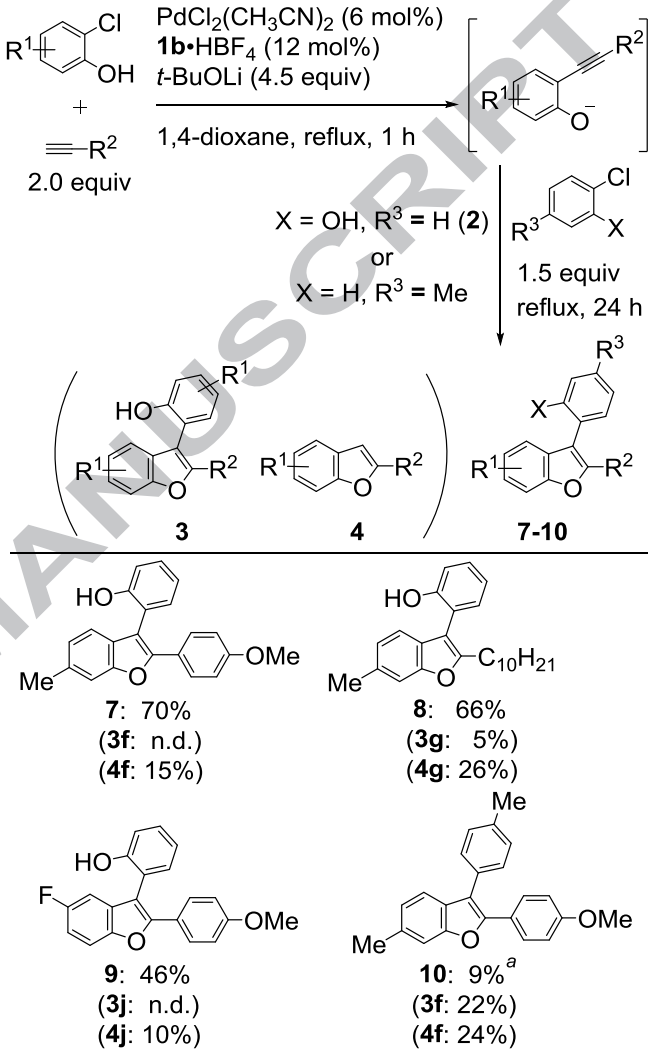
With the optimized conditions in hand, reactions using various 2-chlorophenols and terminal alkynes were studied (Table 2). Both aromatic and aliphatic alkynes gave the corresponding 2,3-disubstituted benzofurans **3a-e** in good yields. When 2-chlorophenol bearing electron donating groups were employed, the reaction proceeded smoothly, and the desired products **3f-i** were obtained in good yield. In addition, 2-chloro-4-fluorophenol afforded **3j** and **3k** in moderate-to-good yield. It is noteworthy that 2,4-dichlorophenol selectively gave **3l** in good yield, indicating that oxidative addition of 2,4-dichlorophenol to Pd(0) occurs selectively at the 2-chloro group. On the other hand, reaction with 2,3-dichlorophenol did not afford the C-3-arylated **3m** at all and only the C-3-protonated benzofuran **4m** was obtained. We assume that oxypalladation did not proceed after Sonogashira coupling due to the steric hindrance of the remaining 3-chloro group of the intermediate alkynylphenol.

Table 2. Substrate scope study.



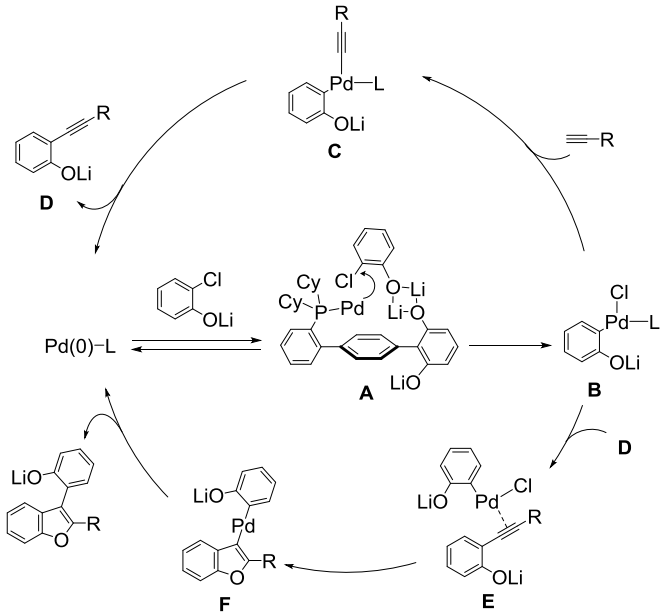
To further broaden the substrate scope of the protocol, we examined the use of two different chloroarenes for introducing 3-substituents different from those on the benzene ring of the benzofuran core (Table 3). After the Sonogashira coupling of 2-chloro-5-methylphenol and 2 equiv of 4-ethynylanisole for 1 h, 1.5 equiv of **2** was added via syringe, and the mixture was refluxed for 24 h. The desired reaction proceeded smoothly, and **7** was obtained in good yield along with 15% of C-3-protonated **4f**. In this case, formation of the byproduct **3f** was not observed. When dodec-1-yne was employed instead of 4-ethynylanisole, the desired product **8** was also obtained in good yield. Use of 2-chloro-4-fluorophenol instead of 2-chloro-5-methylphenol afforded **9** in moderate yield. On the other hand, use of 4-chlorotoluene instead of **2** to introduce 4-tolyl group at the C-3 position of benzofuran was not successful, and only 9% of the desired product **10** was obtained, suggesting that the 2-hydroxy group of **2** is essential for affording 2,3-disubstituted benzofurans in good yield.

Table 3. Use of two different chloroarenes.



[a]1.0 equiv of 4-ethynylanisole was used.

We assume that the reaction proceeds as shown in Scheme 2, and that high reactivity and *ortho*-selectivity induced by the Pd–**1b** catalyst can be explained by complex formation between the catalyst and the substrate.[5] Hydroxy groups of **1b** and 2-chlorophenol are deprotonated by *t*-BuOLi to generate lithium phenoxides, which form heteroaggregates **A** in which the 2-chloro group is located close to Pd. Therefore, oxidative addition of 2-chlorophenol to Pd(0) is accelerated to give intermediate **B**. The reaction with an alkyne affords intermediate **C** and then alkynylphenol **D**, which coordinates to **B** in the second catalytic cycle. Resulting intermediate **E** undergoes oxypalladation to give 3-benzofuranylpalladium intermediate **F**. Subsequently, the desired 2,3-disubstituted benzofuran is formed by reductive elimination.



Scheme 2. Proposed reaction pathways.

In summary, 2,3-disubstituted benzofurans, bearing hydroxy group on the phenyl substituent at the C-3-position, were successfully prepared from readily available 2-chlorophenols and terminal alkynes using the catalyst derived from Pd and **1b**. Complex formation between the catalyst and 2-chlorophenols is the key to the success of both Sonogashira coupling and the subsequent Cacchi cyclization.

Acknowledgments

This work was partially supported by JSPS KAKENHI (Grant Numbers 15H04634, 15K18833, and 17K08214), the Society of Synthetic Organic Chemistry (Japan), the Uehara Memorial Foundation, and Basis for Supporting Innovative Drug Discovering and Life Science Research (BINDS) from AMED.

References and notes

1. (a) Keay, B. A.; Hopkins, J. M.; Dibble, P. W. In *Comprehensive Heterocyclic Chemistry III* Katritzky, A. R.; Ramsden, C. A.; Scriven, E. F. V.; Taylor, R. J. K., Eds. Elsevier: Oxford, UK, **2008**; Vol. 3, pp 571–623.
(b) Hiremathad, A.; Patil, M. R.; Chethana, K. R.; Chand, K.; Santos, M. A.; Keri, R. S. *RSC Adv.* **2015**, *5*, 96809–96828.
(c) Radadiya, A.; Shah, A. *Eur. J. Med. Chem.* 2015, 97, 356–376.
(d) Chand, K.; Rajeshwari; Hiremathad, A.; Singh, M.; Santos, M. A.; Keri, R. S. *Pharmacol. Rep*. **2017**, *69*, 281–295.
2. Selected resent reviews: (a) El Kazzouli, S.; Koubachi, J.; El Brahmi, N.; Guillaumet, G. *RSC Adv.* 2015, 5, 15292–15327.
(b) Blanc, A.; Beneteau, V.; Weibel, J.-M.; Pale, P. *Org. Biomol. Chem.* **2016**, *14*, 9184–9205.
(c) Agasti, S.; Dey, A.; Maiti, D. *Chem. Commun.* **2017**, *53*, 6544–6556.
Selected recent examples: (d) Kraus, G. A.; Chaudhary, D. *Tetrahedron Lett.* **2012**, *53*, 7072–7074.
(e) Yeh, C.-H.; Chen, W.-C.; Gandeepan, P.; Hong, Y.-C.; Shih, C.-H.; Cheng, C.-H. *Org. Biomol. Chem.* **2014**, *12*, 9105–9108.
(f) Lee, J. H.; Kim, M.; Kim, I. *J. Org. Chem.* **2014**, *79*, 6153–6163.
(g) Hussain, M.; Hung, N. T.; Abbas, N.; Khera, R. A.; Malik, I.; Patonay, T.; Kelzhanova, N.; Abilov, Z. A.; Villinger, A.; Langer, P. *J. Heterocyclic Chem.* **2015**, *52*, 497–505.
(h) Khoobi, M.; Molaverdi, F.; Jafarpour, F.; Abbasnia, M.; Kubicki, M.; Shafiee, A. *Chem. Commun*. **2015**, *51*, 11713–11716.
(i) Jia, Y.; Li, T.; Yu, C.; Jiang, B.; Yao, C. *Org. Biomol. Chem.* **2016**, *14*, 1982–1987.
(j) Liu, W.; Chen, N.; Yang, X.; Li, L.; Li, C.-J. *Chem. Commun.* **2016**, *52*, 13120–13123.
(k) Sreenivasulu, C.; Gopi Krishna Reddy, A.; Satyanarayana, G. *Org. Chem. Front.* **2017**, *4*, 972–977.
(l) Ao, J.; Liu, Y.; Jia, S.; Xue, L.; Li, D.; Tan, Y.; Qin, W.; Yan, H. *Tetrahedron* **2018**, *74*, 433–440.
3. (a) Talınlı, N.; Karlıga, B. *J. Heterocyclic Chem.* **2004**, *41*, 205–209.
(b) Kundu, A.; Pramanik, A. *Mol. Divers.* **2016**, *20*, 619–626.
(c) He, G.-X.; Yuan, J.-M.; Zhu, H.-M.; Wei, K.; Wang, L.-Y.; Kong, S.-L.; Mo, D.-L.; Pan, C.-X.; Su, G.-F. *Bioorg. Med. Chem. Lett.* **2017**, *27*, 1660–1664.
4. (a) Ishikawa, S.; Manabe, K. *Chem. Lett.* **2007**, *36*, 1302–1303.
(b) Ishikawa, S.; Manabe, K. *Chem. Lett.* **2007**, *36*, 1304–1305.
(c) Wang, J.-R.; Manabe, K. *J. Org. Chem.* **2010**, *75*, 5340–5342.
(d) Ishikawa, S.; Manabe, K. *Angew. Chem. Int. Ed.* **2010**, *49*, 772–775.
(e) Yamaguchi, M.; Manabe, K. *Org. Lett.* **2014**, *16*, 2386–2389.
(f) Yamaguchi, M.; Suzuki, K.; Manabe, K. *Tetrahedron* **2015**, *71*, 2743–2747.
(g) Yamaguchi, M.; Manabe, K. *Org. Biomol. Chem.* **2017**, *15*, 6645–6655.
(h) Yamaguchi, M.; Suzuki, K.; Sato, Y.; Manabe, K. *Org. Lett.* **2017**, *19*, 5388–5391.
5. (a) Yamaguchi, M.; Katsumata, H.; Manabe, K. *J. Org. Chem.* **2013**, *78*, 9270–9281.
(b) Yamaguchi, M.; Akiyama, T.; Sasou, H.; Katsumata, H.; Manabe, K. *J. Org. Chem.* **2016**, *81*, 5450–5463.
6. (a) Arcadi, A.; Cacchi, S.; Rosario, M. D.; Fabrizi, G.; Marinelli, F. *J. Org. Chem.* **1996**, *61*, 9280–9288.
(b) Hu, Y.; Nawoschik, K. J.; Liao, Y.; Ma, J.; Fathi, R.; Yang, Z. *J. Org. Chem.* **2004**, *69*, 2235–2239.
(c) Bernini, R.; Cacchi, S.; Salve, I. D.; Fabrizi, G. *Synthesis* **2007**, *6*, 873–882.
7. (a) Chaplin, J. H.; Flynn, B. L. *Chem. Commun.* **2001**, 1594–1595.
(b) Markina, N. A.; Chen, Y.; Larock, R. C. *Tetrahedron* **2013**, *69*, 2701–2713.
(c) Saleeb, M.; Mojica, S.; Eriksson, A. U.; Andersson, C. D.; Gylfe, A.; Elofsson, M. *Eur. J. Med. Chem.* **2018**, *143*, 1077–1089.
8. Huang, X.; Anderson, K. W.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 6653–6655.

Supplementary Material

Supplementary data associated with this article can be found, in the online version, at htpps://doi.org/10.1016/j.tetlett.

Click here to remove instruction text...

Highlights

- One-pot synthesis of 2,3-disubstituted benzofurans has been achieved.
- Readily available chlorophenols can be used as substrates.
- Only the Pd–DHTP catalyst can catalyze the desired reaction.
- 2-Hydroxyphenyl group can be introduced at C3 of benzofurans.
- Two different chlorophenols can be used.

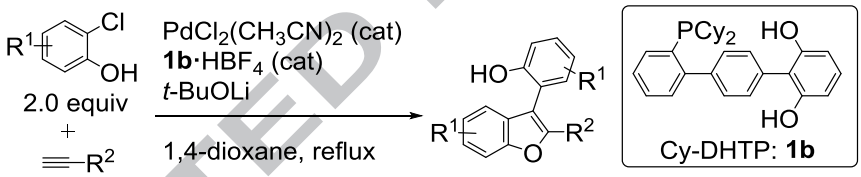
Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed

One-pot synthesis of 2,3-disubstituted benzofurans from 2-chlorophenols using palladium–dihydroxyterphenylphosphine catalyst

Leave this area blank for abstract info.

*Miyuki Yamaguchi, Hayato Ozawa, Haruka Katsumata, Tomoyo Akiyama, and Kei Manabe**



or altere