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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 *

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

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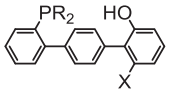
ABSTRACT

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** (Fig. 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

Fig. 1. Hydroxyterphenylphosphines **1**.

* Corresponding author.
E-mail address: manabe@u-shizuoka-ken.ac.jp (K. Manabe).

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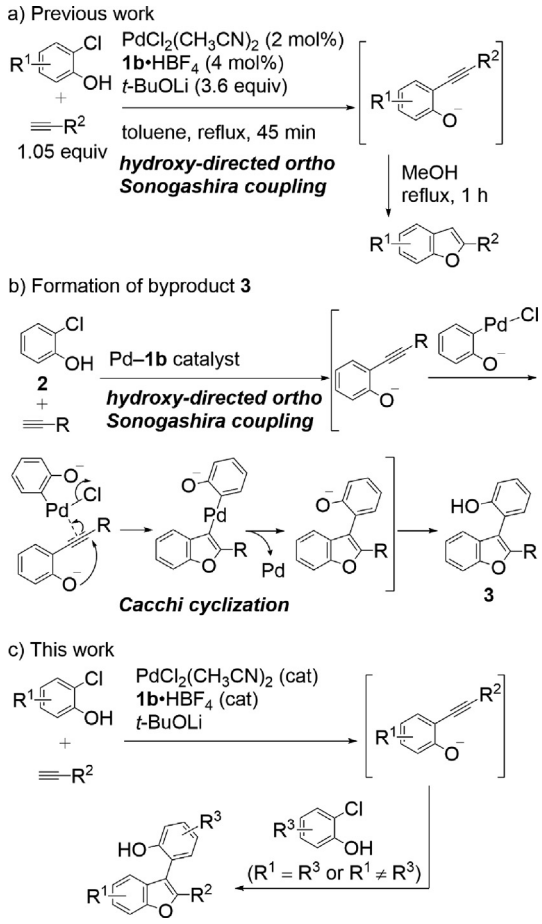
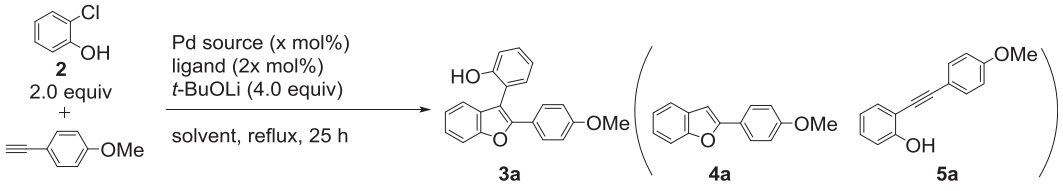


Scheme 1. (a) Pd–**1b**-catalyzed benzofuran synthesis from chlorophenols (previous work). (b) Proposed mechanism of the formation of byproduct **3**. (c) 2,3-Disubstituted benzofuran synthesis from 2-chlorophenols (this work).

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

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