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Hydroxyterphenylphoshine−Palladium Catalyst for Benzo[*b*]furan Synthesis from 2-Chlorophenols. Bifunctional Ligand Strategy for Cross-Coupling of Chloroarenes

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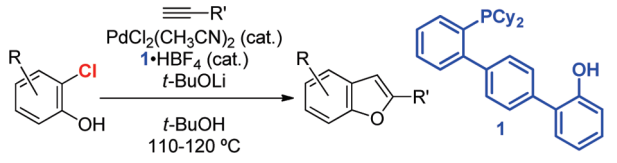
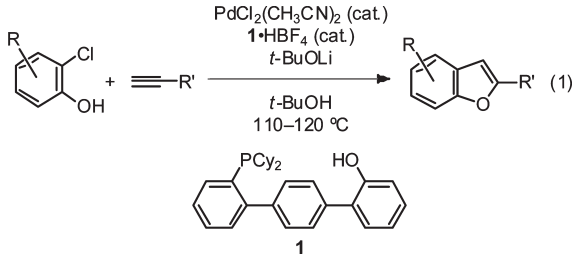


A catalyst composed of Pd and hydroxyterphenylphosphine was found to be effective for one-pot benzo[*b*]-furan synthesis from 2-chlorophenols and alkynes.

The benzo[*b*]furan framework is ubiquitous in natural products and pharmaceuticals.[1] Various methods have been developed for the synthesis of benzo[*b*]furans, and among those methods, Pd-catalyzed one-pot synthesis from 2-halophenols and terminal alkynes by a Sonogashira coupling−cyclization sequence is a useful and reliable way to construct 2-substituted benzo[*b*]furans.[2] 2-Iodo- and 2-bromophenols have been widely used as the 2-halophenols.[3] However, there are no examples of 2-chlorophenols except one example in which a benzofuran was obtained in a low yield (<10%).[3h] Although recent progress in the field of Pd catalysis realizes various types of cross-coupling of chloroarenes,[4] which are cheaper and more widely available than iodo- and bromoarenes, chloroarenes with an electron-donating substituent are still challenging substrates because of their low reactivity. The lack of examples of benzo[*b*]furan synthesis from 2-chlorophenol probably results from slow oxidative addition of the C−Cl bond, which is deactivated by the *o*-hydroxy group, to Pd.

Recently, we found that bifunctional hydroxyterphenylphosphines such as **1**[5] dramatically accelerated cross-coupling of 2-chlorophenols with Grignard reagents in the presence of a Pd source.[6] This catalytic system offers a new strategy to activate chloroarenes. This acceleration is assumed to be the result of transition state stabilization by the Mg-phenoxide moiety of the bifunctional ligand in the rate-determining oxidative-addition step of the catalytic cycle.[6a] We envisioned that this accelerating effect would also be applicable to one-pot synthesis of benzo[*b*]furans from 2-chlorophenols. Here we report the first Pd-catalyzed one-pot synthesis of benzo[*b*]furans from 2-chlorophenols and terminal alkynes (eq 1).



First, we searched reaction conditions to obtain benzo[*b*]-furan **2** from 2-chlorophenol and 1-dodecyne, and found that the catalyst derived from **1**·HBF_4 and $PdCl_2(CH_3CN)_2$[4d] gave the desired product in good yield (Table 1, entry 1). The use of *t*-BuOLi as a base is the key for this reaction, and other bases as shown in entries 2−6 resulted in much lower yields. Phosphines such as *t*-Bu_3P·HBF_4,[7] **3**,[8] and **4**,[9] which have often been used for cross-coupling of chloroarenes, did not work well (entries 7−9). Bidentate ligand **5**[10,11] also failed to

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(11) Ligand **5** was very effective for the reaction of 2-bromophenol (see the Supporting Information).

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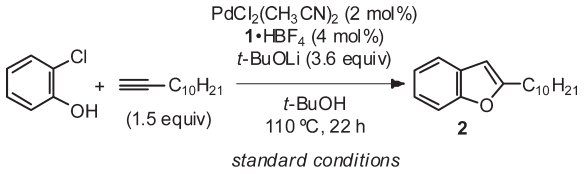
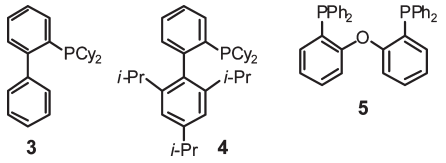
TABLE 1. Optimized Reaction Conditions and Effects of Reaction Parameters



entry	variation of the standard conditions	yield (%)
1	none	82
2	*t*-BuOK instead of *t*-BuOLi	6
3	K_3PO_4 instead of *t*-BuOLi	5
4	Cs_2CO_3 instead of *t*-BuOLi	7
5	EtMgBr (2.6 equiv) instead of *t*-BuOLi	0
6	*i*-Pr_2NEt instead of *t*-BuOLi	trace
7	*t*-$Bu_3P \cdot HBF_4$ instead of $\mathbf{1} \cdot HBF_4$	3
8	**3** instead of $\mathbf{1} \cdot HBF_4$	8
9	**4** instead of $\mathbf{1} \cdot HBF_4$	17
10	**5** (2.4 mol %) instead of $\mathbf{1} \cdot HBF_4$	0
11	DMF instead of *t*-BuOH	28
12	toluene instead of *t*-BuOH	72

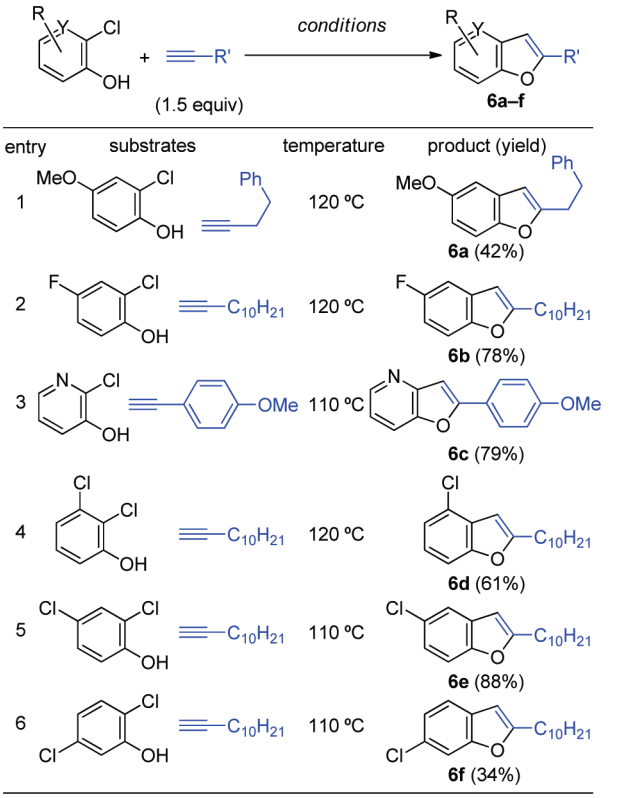
give the product (entry 10). In the reactions in entries 2−10, large amounts of 2-chlorophenol remained after 22 h, indicating that the first Sonogashira coupling step did not proceed well. Among the solvents tested, *t*-BuOH was found to be the best (entries 11 and 12).



The optimized reaction conditions were applied to other substrates as shown in Table 2. A chlorophenol with an electron-donating methoxy group slowly reacted to give the desired product **6a** in a modest yield (entry 1), while a chlorophenol with a fluoro group reacted faster to give **6b** in a higher yield (entry 2). 2-Chloro-3-hydroxypyridine also reacted under these conditions, producing furo[3,2-*b*]pyridine **6c** in good yield (entry 3).

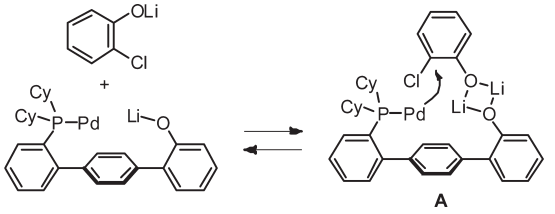
This catalytic system could also be used for synthesis of chloro-substituted benzo[*b*]furans **6d**−**f** from dichlorophenols through site-selective Sonogashira coupling. As shown in Table 2, entries 4−6, dichlorophenols gave the desired benzo[*b*]furans in modest to high yields. Although small amounts of 4-(1-dodecynyl)-2-decylbenzo[*b*]furan (3%) and 6-(1-dodecynyl)-2-decylbenzo[*b*]furan (10%) were produced in the reactions of 2,3-dichlorophenol (entry 4) and 2,5-dichlorophenol (entry 6), respectively, such a byproduct was not obtained at all in the reaction of 2,4-dichlorophenol (entry 5). The success in the synthesis of chlorobenzo[*b*]furans indicates that the first Sonogashira coupling step site-selectively occurred at the 2-position, the more sterically hindered position especially in the case of 2,3-dichlorophenol, emphasizing the effect of the present catalytic system to accelerate cross-coupling at the 2-chloro group.[12] In previous examples of Pd-catalyzed synthesis of chlorobenzo[*b*]furans, chloro-substituted 2-iodo- and 2-bromophenols were used as the starting compounds.[3e,f]

TABLE 2. Benzo[*b*]furan Synthesis from Various 2-Chlorophenols and Alkynes[a]



[a]Conditions: $PdCl_2(CH_3CN)_2$ (2 mol %), $\mathbf{1} \cdot HBF_4$ (4 mol %), *t*-BuOLi (3.6 equiv), *t*-BuOH, 22 h.

SCHEME 1. Formation of Proposed Intermediate A



Now, our method enables the use of dichlorophenols, which are much cheaper than chloroiodo- or bromochlorophenols. These results exemplify the importance of the present catalytic system.

The benzo[*b*]furan formation consists of two steps: the Sonogashira coupling of 2-chlorophenols with alkynes and the subsequent cyclization of the corresponding 2-alkynylphenols presumably catalyzed by Pd(II). The present catalytic system improves the first Sonogashira coupling step probably due to acceleration of oxidative addition of the starting 2-chlorophenols. Although we do not have clear evidence for the mechanism of the acceleration, the following scheme is proposed: (1) both the hydroxy groups of **1** and chlorophenol are deprotonated to generate Li phenoxides under the reaction conditions, and (2) these Li phenoxides are in equilibrium with a heteroaggregate[13] such as **A** (Scheme 1) in which the 2-chloro group is easily accessed by the Pd atom located nearby.

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In summary, we developed a method of one-pot benzo[*b*]furan synthesis from 2-chlorophenols catalyzed by Pd bearing bifunctional ligand **1**. Thanks to progress in transition metal catalysis, chloroarenes are becoming widely used coupling partners. The acceleration induced by the bifunctional catalyst shown here provides another strategy to improve the usability of chloroarenes in cross-coupling chemistry.

Experimental Section

Typical Experimental Procedure of Benzofuran Synthesis (Table 1, Entry 1). *t*-BuOH (1.0 mL) was added to $PdCl_2(CH_3CN)_2$ (2.6 mg, 0.01 mmol), **1**·HBF_4 (10.6 mg, 0.02 mmol), *t*-BuOLi (144 mg, 1.8 mmol), and 2-chlorophenol (64.3 mg, 0.5 mmol) in a sealable tube under argon. The reaction mixture was stirred at rt for 45 min, and then 1-dodecyne (125 mg, 0.75 mmol) was added. The tube was sealed, and the reaction mixture was stirred at 110 °C for 22 h. The resulting suspension was quenched with aq NH_4Cl at rt and extracted with ethyl acetate (2 × 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated, and then the residue was purified by preparative thin-layer chromatography (SiO_2, hexane) to give 2-decylbenzofuran[14] (106 mg, 82% yield) as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.45 (d, 1H, J = 7.5 Hz), 7.40 (d, 1H, J = 8.0 Hz), 7.18−7.14 (m, 2H), 6.34 (d, 1H, J = 1.0 Hz), 2.73 (t, 2H, J = 7.5 Hz), 1.72 (quint, 2H, J = 7.5 Hz), 1.31−1.26 (m, 14H), 0.88 (t, 3H, J = 7.0 Hz) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.8, 154.7, 129.1, 123.0, 122.4, 120.2, 110.7, 101.8, 32.0, 29.7, 29.6, 29.5, 29.4, 29.3, 28.5, 27.8, 22.8, 14.2 ppm;

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Supporting Information Available: Experimental procedures, characterization data, and a result of benzofuran synthesis from 2-bromophenol with **5**. This material is available free of charge via the Internet at http://pubs.acs.org.