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Palladium-catalyzed intermolecular coupling of 3-substituted propargylic carbonates with phenols: Synthesis of 2-substituted benzofuran derivatives

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ABSTRACT

We accomplished the synthesis of 2-substituted benzofuran derivatives by the palladium-catalyzed reaction of 3-substituted propargylic carbonates with phenols. The 2-substituted benzofuran derivatives were obtained through the intermolecular coupling of the 3-substituted propargylic carbonates with phenols, and sequential intramolecular cyclization reaction.

Benzofuran is an important scaffold in several biologically-active organic compounds, and development of an efficient method to construct it and its derivatives is one of the major topics in organic synthesis. Although several methods have been reported to construct benzofuran derivatives involving the transition metal catalyzed reaction,[1] most of them are achieved by the annulation reaction of prefunctionalized substrates,[2–4] but there are only limited examples of the construction of benzofuran derivatives by the intermolecular coupling using simple phenols and the sequential cyclization reaction. To the best of our knowledge, alkynes,[5] alkenes,[6] or β-keto esters[7] were used as the coupling partner for the transition metal catalyzed construction of benzofuran derivatives with simple phenols. Furthermore, we have studied the palladium-catalyzed double substitution reactions of 2-haloallylic esters,[8] and during the course of these studies, we also succeeded in constructing the benzofuran derivatives by the palladium-catalyzed intermolecular coupling reaction of 2-fluoroallylic acetates with simple phenols.[9]

On the other hand, there are several reports of palladium-catalyzed coupling reactions of propargylic compounds,[10–18] and the palladium catalyzed reaction of propargylic esters with nucleophiles generally provides doubly substituted products or cyclized products. Furthermore, several groups have developed the palladium-catalyzed reactions of several types of propargylic compounds with phenols.[5c,5f,19–23] For example, Koizumi reported the palladium-catalyzed double substitution of propargylic carbonates with phenols,[19] and Sinou demonstrated the construction of 2,3-dihydro-1,4-benzodioxines by the palladium-catalyzed reaction of propargylic carbonates with catechols.[20] Based on this background and our previous study,[8,9] we expect that the palladium-catalyzed reaction of propargylic compounds with simple phenols provides 2-substituted benzofuran derivatives through the intermolecular attack of the phenoxide anion and sequential intermolecular cyclization.

To realize the construction of benzofuran derivatives by the palladium-catalyzed intermolecular reaction of propargylic compounds with simple phenols, we examined the reaction of methyl (3-phenylprop-2-yn-1-yl) carbonate (**1a**), which is a 3-substituted propargylic carbonate, with phenol (**2a**). As shown in Table 1, the reactions by $Pd(PPh_3)_4$ in the presence of Cs_2CO_3 in toluene, dioxane or DMF produced no or low product yields, and doubly substituted product **4aa**[8,19b] as a major product (Table 1, entries 1–3). However, when DMSO was used as the solvent, we detected the formation of the benzofuran derivative **3aa** in 27% NMR yield without formation of **4aa** (entry 4). To increase the yield of **3aa**, we investigated the reactions by $Pd(OAc)_2$ using several phosphine ligands, such as PPh_3, $P(4\text{-}FC_6H_4)_3$, $P(4\text{-}MeOC_6H_4)_3$, DPPE, and DPPF, and confirmed that $P(4\text{-}MeOC_6H_4)_3$ produced a better result (39% NMR yield) compared to the other phosphine

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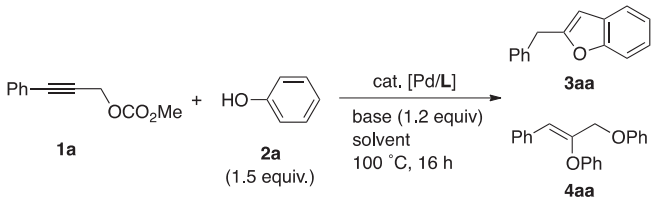
Table 1
Palladium-catalyzed reaction of propargylic ester **1a** with phenol **2a**[a].



Entry	[Pd/**L**] (mol%)	Base	Solvent	Yield[b] (%)	
				3aa	**4aa**
1	$Pd(PPh_3)_4$ (10)	Cs_2CO_3	Toluene	0	71
2	$Pd(PPh_3)_4$ (10)	Cs_2CO_3	Dioxane	6	27
3	$Pd(PPh_3)_4$ (10)	Cs_2CO_3	DMF	6	65
4	$Pd(PPh_3)_4$ (10)	Cs_2CO_3	DMSO	27	0
5	$Pd(OAc)_2$ (10)/$P(PPh_3)_4$ (20)	Cs_2CO_3	DMSO	25	5
6	$Pd(OAc)_2$ (10)/$P(4\text{-}FC_6H_4)_3$ (20)	Cs_2CO_3	DMSO	22	9
7	$Pd(OAc)_2$ (10)/$P(4\text{-}MeOC_6H_4)_3$ (20)	Cs_2CO_3	DMSO	39	0
8	$Pd(OAc)_2$ (10)/DPPE (20)	Cs_2CO_3	DMSO	0	49
9	$Pd(OAc)_2$ (10)/DPPF (20)	Cs_2CO_3	DMSO	26	16
10	$[Pd(C_3H_5)Cl]_2$ (5)/$P(4\text{-}MeOC_6H_4)_3$ (20)	Cs_2CO_3	DMSO	45	22
11[c]	$[Pd\ (C_3H_5)Cl]_2$ (5)/$P(4\text{-}MeOC_6H_4)_3$ (20)	Cs_2CO_3	DMSO	63	0
12[c]	$[Pd(C_3H_5)Cl]_2$ (5)/$P(4\text{-}MeOC_6H_4)_3$ (20)	CsOAc	DMSO	90 (87)[d]	0

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), [Pd] (5 or 10 mol%), **L** (20 mol%), and base (0.24 mmol) in solvent (2.8 mL) at 100 °C for 16 h.
[b] Yields are determined by ^1H NMR of crude materials using internal standard (trioxane).
[c] LiCl (10 mol%) was added.
[d] Isolated yield is shown in parentheses.

ligands (entries 5–9). These results indicate that, in the reactions by $Pd(OAc)_2$ with monophosphine ligands, $P(4\text{-}MeOC_6H_4)_3$ accelerated the oxidative addition of **1** to Pd(0). Changing the $Pd(OAc)_2$ to $[Pd(C_3H_5)Cl]_2$ was also effective in increasing the yield (entry 10), and the addition of LiCl (10 mol%) realized the higher yield (63% NMR yield) (entry 11). To our delight, the highest yield (90% NMR yield, 87% isolated yield) was obtained when the base was changed from Cs_2CO_3 to CsOAc (entry 12).

Based on this initial result, we examined the reaction of **1a** with several phenols **2b–y**, and the results are summarized in Table 2. The reactions with phenols **2b** and **2c**, which possess an alkyl group at the *para*-position, smoothly proceeded, and the intended 2-substituted benzofuran derivatives **3ab** and **3ac** were produced in 79% and 82%, respectively (Table 2, entries 1 and 2). The reaction with *m*-cresole (**2d**) afforded a product in 77% yield as a mixture of two regioisomers, and we confirmed that the major product was 2-benzyl-6-methylbenzofuran (**3ad**) (entry 3). This result indicated that the cyclization occurred at the sterically less hindered site of **2d**. Furthermore, the reaction of the *ortho*-substituted phenols **2e** and **2f** provided the desired products **3ae** and **3af** in 81% yields, respectively (entries 4 and 5). The reactions with the dimethyl phenols **2g–i** also gave the corresponding benzofuran derivatives **3ag–ai** in the range of 72–82% yields (entries 6–8), respectively. We next demonstrated the reactions of **1a** with methoxyphenols **2j–m**, and succeeded in obtaining the desired products **3aj–am** in good yields (entries 9–12). The reactions with fluoro- or chlorophenols, such as **2n–r**, also afforded the 2-benzylbenzofuran derivatives in moderate to good yields (entries 13–17), but the reaction with *p*-bromophenol (**2s**) resulted in a low yield (38%) (entry 18). We further investigated the reactions of the trifluoromethylphenols **2t** and **2u**, and obtained the intended benzofuran derivatives **3at** and **3au** in 66% and 70% yields, respectively (entries 19 and 20). For the reaction of **2u**, we also confirmed that **3au** was obtained as a single regioisomer (entry 20). The reactions of **1a** with naphthols **2v** and **2w** also occurred in good yields (entries 21 and 22), but the regioselectivity for the reaction of **2v** was low (entry 21). Furthermore, we conducted the reactions with *p*-cyanophenol (**2x**) or *p*-nitrophenol (**2y**) and confirmed that these reactions provide **3ax** and **3ay** in 83% and 54% yields, respectively (entries 23 and 24).

We next investigated the reactions of several aryl group substituted carbonates **1b–k** with phenol (**2a**). As shown in Table 3, most of the reactions smoothly proceeded and provided the intended 2-substituted benzofuran derivatives in moderate to good yields. For example, the reactions of the carbonates **1b–h** with **2a** gave the desired products **3ba–ha** in the range of 71–94% yields, respectively (Table 3, entries 1–7). We confirmed that the reaction of **1i**, which has a 1-naphthyl group at the C-3 position, also afforded the corresponding product **3ia** in 74% yield (entry 8). Furthermore, we succeeded in proceeding the reaction of the thienyl group substituted carbonate **1j**, and obtained **3ja** in 61% yield (entry 9). Unfortunately, we also examined the reaction of **1k**, which possessed an alkyl group instead of an aryl group, but the reaction did not afford any intended benzofuran derivative (entry 10).

Although the mechanistic details of the present reaction are unclear, according to the reported reaction mechanism of palladium-catalyzed reaction of propargylic compounds,[10] we outlined a possible reaction pathway in Scheme 1. The reaction of **1** with Pd (0) initially generates an allenylpalladium intermediate **A**. Attack of the phenoxide anion on the central carbon of **A** provides the π-allylpalladium complex **C** through the σ-allylpalladium complex **B**. Although the details are unclear, the regioselective cyclization of **C** proceeded at the sterically less hindered site and the thermodynamically stable 2-substituted benzofuran **3** was formed.

In conclusion, we demonstrated the palladium-catalyzed reaction of 3-substituted propargylic carbonates with simple phenols, and succeeded in obtaining the 2-substituted benzofuran derivatives through the intermolecular coupling of the 3-substituted propargylic carbonates with phenols, and sequential intramolecular cyclization reaction.