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# Selective synthesis of functionalized allylic compounds by Pd(0)-catalyzed three-component reaction of methyl propargyl carbonate with phenols and nucleophiles

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#### ABSTRACT

A Pd(0)-catalyzed three-component reaction of methyl propargyl carbonate with phenols and nucleophiles is described. The reaction proceeded smoothly and various allylic compounds were synthesized selectively in good to excellent yields under neutral conditions. The regioselective introduction of functional groups into the allylic compounds could also be achieved. The reaction with nitrogen and carbon nucleophiles afforded mainly 2-aryloxyallylic compounds. On the other hand, aliphatic alcohols gave 2alkoxyallylic compounds.

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Palladium-catalyzed reactions of propargylic compounds are used as a powerful tool for the formation of carbon-carbon and carbon-hetero atom bonds.<sup>1</sup> The key step in these reactions is the formation of  $\eta^3$ -allenyl/propargyl intermediates by facile decarboxylation, which are subjected to two successive nucleophilic attacks to form products.<sup>2</sup> In the reactions, control of regio and stereoselectivities is a challenging topic. Generally, the palladium-catalyzed reaction of a propargylic ester with two nucleophiles affords a mixture of regioisomers. Recently, Sinou<sup>3</sup> and Yoshida<sup>4</sup> reported the selective synthesis of heterocyclic compounds such as 1,4-benzodioxins and substituted 2,3-dihydrofurans by combination of inter and intramolecular nucleophilic reactions (Scheme 1). To our knowledge, however, the palladium(0)-catalyzed intermolecular three-component reaction using propargylic carbonates and two different nucleophiles for the synthesis of multi-functionalized allylic compounds has not been reported so far.<sup>5,6</sup> It would be a very interesting and useful synthetic method if two different nucleophiles can be introduced regioselectively into the resulting allylic products. Organ et al.<sup>7</sup> reported a new synthetic route for substituted allylic compounds by palladium(0)-catalyzed reaction of 1,2-diphenoxy-2-propene with sodium dimethyl methylmalonate. However, a strong base, sodium hydride, is required for the reaction. More recently, Kazmaier et al.<sup>8</sup> reported a combination reaction of allylic aminations and stille

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couplings for the synthesis of functionalized allylic amines, but toxic Bu<sub>3</sub>SnH must be employed for preparation of stannylated allylic carbonates as the starting materials. Furthermore, carbon nucleophiles instead of amines cannot be applied to the Pd(0)-catalyzed reaction of the stannylated allylic carbonates. Herein we report a facile method for the regioselective synthesis of functionalized allylic compounds by Pd(0)-catalyzed three-component reaction between methyl propargyl carbonate (1) and two different nucleophiles via sequential intermolecular reactions.







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## Table 1Palladium(0)-catalyzed reaction of 1 with 2a and 3a



_	-					-
	1	$Pd(PPh_3)_4$	THF	80	0	
	2	$Pd(PPh_3)_4$	Dioxane	80	0	
	3	$Pd(PPh_3)_4$	Dioxane	100	28	
	3	Pd <sub>2</sub> (dba) <sub>3</sub> ·CHCl <sub>3</sub> /DPPE	Dioxane	100	0	
	4	Pd <sub>2</sub> (dba) <sub>3</sub> ·CHCl <sub>3</sub> /DPEphos	Dioxane	100	51	
	5 <sup>c</sup>	Pd <sub>2</sub> (dba) <sub>3</sub> ·CHCl <sub>3</sub> /DPEphos	Dioxane	100	54	
	6 <sup>d</sup>	Pd <sub>2</sub> (dba) <sub>3</sub> ·CHCl <sub>3</sub> /DPEphos	Dioxane	100	26	

<sup>a</sup> Pd/P = 1:4.

 $^{c}$  1/2a/3a = 1:2:1.

We first attempted the reaction of propargyl carbonate **1** with 4-hydroxyacetophenone (**2a**) and piperidine (**3a**) in the presence of Pd(PPh<sub>3</sub>)<sub>4</sub> at 80 °C for 3 h as shown in Table 1. However, the expected product **4aa** could not be obtained at all (entries 1 and 2). At elevated temperature (100 °C), the product **4aa** was produced, but the yield was not high (entry 3). Various phosphine ligands other than PPh<sub>3</sub> were tested under the same conditions. DPPE<sup>9</sup> (entry 4) and the analogous ligands such as DPPP<sup>10</sup> and DPPB<sup>11</sup> were not effective. Among the phosphine ligands employed, DPEphos<sup>12</sup> was found to be the most effective ligand for the reaction (51%; entry 5). There was no significant change in yield of **4aa** when the molar ratio of **2a** to **1** was 2:1 (entry 5). The use of a two-fold excess of **3a** decreased the yield of **4aa** (entry 6). In the reaction with **2a** and **3a**, the regioisomer was not formed.

We next examined the reaction of allyl aryl ether **5a** with **3a** in dioxane at 100 °C for 3 h because it is likely that the allylic amine **4aa** was formed by reaction of **5a** with amine **3a** in a manner similar to Pd(0)-catalyzed allylic substitution reactions of allylic compounds (Scheme 2). Allyl aryl ether **5a** was prepared by Pd(0)-catalyzed reaction of **1** with 2 equiv of **2a**. As expected, allylic amine **4aa** was obtained from **5a** and **3a** in a good yield.

The three-component product **4aa** was formed selectively in the reaction of **1** with **2a** and **3a**. A plausible mechanism is shown in Scheme 3. The palladium catalyst initially promotes decarboxylation of the substrate **1** to generate  $\eta^3$ -allenyl/propargyl intermediate **A**. The intermediate undergoes nucleophilic attack only by **2a** to form  $\eta^3$ -allylpalladium intermediate **B**, followed by reaction with **2a** or **3a** to afford allylic compound **5a** or **4aa**. Product **5a** readily reacts again with Pd(0) catalyst under the conditions to regenerate  $\pi$ -allylpalladium intermediates **B**, which was attacked by **3a** at the terminal carbon to afford product **4aa**.



Scheme 2. Palladium(0)-catalyzed reaction between 5a and 3a.



Scheme 3. A plausible mechanism.

We next attempted to conduct the Pd(0)-catalyzed one-pot, two-step reaction of propargyl carbonate **1** with phenols **2** and **3a** because **5a** gave **4aa** in good yield by reaction with **3a**. Allylic compound **5a** was prepared in situ by the Pd(0)-catalyzed reaction of **1** with 2 equiv of **2a** in dioxane at 60 °C for 1 h, and then amine **3a** was added to the reaction mixture and stirred at 100 °C for 2 h. The reaction with **2a** and **3a** proceeded successfully and gave the expected allylic amine **4aa** in 79% yield (entry 1, Table 2). The yield of **4aa** increased significantly compared to the result of entry 5 in Table 1. Various phenols could be used in this reaction. These results were shown in Table 2.

When **1** was treated with substituted phenols having an electron-withdrawing group **2b**–**e**, 2-aryloxyallyl amines **4ba–ea** were produced selectively in good to excellent yields (entries 2–5). On the other hand, the reaction using 4-nitrophenol (**2f**) did not proceed when using  $Pd_2(dba)_3$ ·CHCl<sub>3</sub>/DPEphos system. The corresponding allylic compound **4fa** was obtained in 46% yield by use of Pd(PPh<sub>3</sub>)<sub>4</sub> (entry 6). Phenol **2g** having a methoxy group gave 66% yield of allyl amine **4ga** along with 32% yield of by-product **5g** (entry 7). Halogen-substituted phenols were found to be good oxygen nucleophiles for the synthesis of allylic amines **4**.

#### Table 2

Palladium(0)-catalyzed one-pot, two-step reaction of 1 with various phenols 2 and 3a



<sup>a</sup> Isolated yield.

<sup>b</sup> Pd(PPh<sub>3</sub>)<sub>4</sub> was used as catalyst.

<sup>c</sup> By-product **5g** was obtained in 32% yield.



<sup>&</sup>lt;sup>b</sup> Determined by <sup>1</sup>H NMR.

<sup>&</sup>lt;sup>d</sup> **1/2a/3a** = 1:1:2.

#### Table 3

Palladium(0)-catalyzed one-pot, two-step reaction of  ${\bf 1}$  with  ${\bf 2a}$  and various nucle-ophiles



<sup>a</sup> Isolated yield. <sup>b</sup> By-product **6** was obtain

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Other nucleophiles capable of the Pd(0)-catalyzed reaction of **1** with **2a** were explored for the synthesis of multi-functional allylic compounds. Various 2-aryloxyallyl compounds could be prepared as shown in Table 3. The reaction with morpholine (**3b**) afforded the corresponding allylic amine **4ab** in 85% yield (entry 1). Benzylic amine **3c** and phthalimide (**3d**) also gave the expected allylic compounds **4ac** and **4ad**, respectively (entries 2 and 3). In the case of entry 3, 8% yield of disubstituted by-product **6** was obtained.

Not only nitrogen nucleophiles but also carbon nucleophiles could be used for the reaction of **1** with **2a**. For example, 2-methylcyclopentane-1,3-dione (**3e**) gave the desired 2-aryloxyallylic compound **4ae** in 84% yield (entry 4). Although 3-ethylpentane-2,4-dione (**3f**) also gave the expected allylic compound **4af**, the yield was lower than that of **4ae** (entry 5). The reaction with dimethyl-2-ethylmalonate (**3g**) did not give the corresponding allylic compound **4ag** at all (entry 6). Thus, the synthesis of various 2-aryloxyallylic compounds was achieved by the Pd(0)-catalyzed

#### Table 4

Palladium(0)-catalyzed reaction between propargylic carbonate,  ${\bf 2a}$  and aliphatic alcohols



<sup>a</sup> Isolated yield.

<sup>b</sup> 2 equiv.

<sup>c</sup> 3 equiv.

one-pot, two-step reaction of propargyl carbonate **1** with two different nucleophiles.

Next, we turned our attention to the utilization of aliphatic alcohols as nucleophiles. The reaction with aliphatic alcohols was carried out under the conditions of entry 5 in Table 1. The unexpected products were formed in all cases. When **1** was subjected to the reaction with **2a** and MeOH, 2-methoxyallyl aryl ether **7i** was obtained in 63% (entry 1, Table 4). The predicted product, 2-aryloxyallylic methyl ester, was not formed at all. Ethanol (**3j**) and benzyl alcohol (**3k**) also afforded 2-ethoxyallyl product **7j** (64%) and 2-benzyloxyallyl product **7k** (75%), respectively (entries 2 and 3). In these two cases, we used propargylic carbonate **8** having *t*-butoxy moiety instead of **1** to prevent the formation of **7i**. We attempted the one-pot, two-step reaction of **8** with **2a** and **3k**, but the yield of **7k** was low (33%).

Finally, we attempted to synthesize 2-benzyloxyallylic amine **9** via **7k** because **9** could not be obtained by the Pd(0)-catalyzed reaction with carbonate **8**, alcohol **3k** and amine **3b**. Allylic ether **7k** was prepared in situ, and then amine **3b** was introduced to the reaction mixture as shown in Scheme 4(1). The desired allylic compound **9** 



Scheme 4. Synthesis of 2-benzyloxyallylic amine 9.

was obtained in 61% yield as expected. On the other hand, allylic amine **4ab** prepared in situ did not afford **9**. Allylic amine **4ab** was only isolated (81%) as shown in Scheme 4(2). Thus, we found that the intermediate product **7k** could react with **3b**, whereas the reaction of allylic amine **4ab** with BnOH did not proceed.

In conclusion, we have developed the Pd(0)-catalyzed reaction of propargyl carbonate **1** with phenols and nucleophiles for the synthesis of multi-functional allylic compounds. The reactions proceeded in regio and chemoselective manners, and various substituted allylic compounds could be synthesized. A variety of nucleophiles such as secondary amines, phthalimide and carbon nucleophiles gave 2-aryloxyallylic compounds in good to excellent yields. On the other hand, the reaction with aliphatic alcohols exhibited different chemoselectivity and afforded 2-alkoxyallyl aryl ethers.

#### Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.05.030.

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