



Palladium-catalyzed intermolecular coupling of 2-haloallylic acetates with simple phenols, and sequential formation of benzofuran derivatives through the intramolecular cyclization



Takumi Udagawa, Yukiko Tsuchi, Ikuma Takehara, Masaki Kogawa, Hiroataka Watanabe, Mitsuaki Yamamoto, Hiroaki Tsuji, Motoi Kawatsura*

Department of Chemistry, College of Humanities & Sciences, Nihon University, Sakurajosui, Setagaya-ku, Tokyo 156-8550, Japan

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ABSTRACT

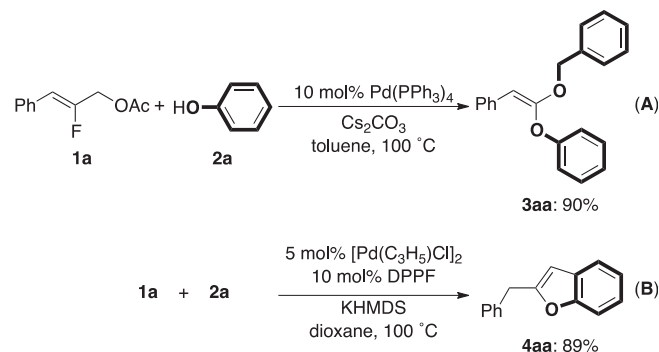
We accomplished the synthesis of 2-substituted benzofuran derivatives by the palladium-catalyzed reaction of 2-haloallylic acetates with simple phenols in the presence of a base. The reaction proceeded through the intermolecular attack of the nucleophile on the central carbon atom of the π -allyl group, carbon-halogen bond cleavage, and sequential intramolecular cyclization.

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1. Introduction

Benzofuran is an important scaffold for several biologically-active organic compounds, and the 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 for the synthesis of benzofuran derivatives involving a transition metal catalyzed reaction,¹ most of them are achieved by the reaction of prefunctionalized substrates,^{2–4} while there are only limited examples of the construction of benzofuran derivatives by intermolecular coupling using simple phenols and a sequential cyclization reaction.⁵ To the best of our knowledge, β -keto esters,^{5a} alkynes,^{5b–e} and alkenes^{5f} were used as the coupling partner for the transition metal catalyzed construction of benzofuran derivatives with simple phenols. However, there was no example of the construction of benzofuran derivatives by the transition metal catalyzed reaction of allylic esters with simple phenols. On the other hand, we have studied the palladium-catalyzed reaction of fluorine-containing allylic esters,^{6–8} which includes the double etherification of 2-fluoroallylic acetates with phenols (Scheme 1, A),^{6b} and during the course of the study, we also examined the

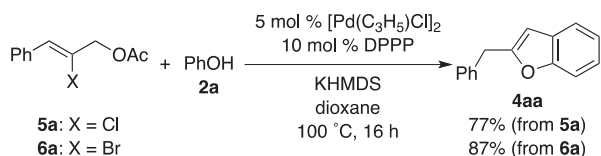
[Pd(C₃H₅)Cl]₂/DPPP catalyzed reaction of 2-fluoroallylic acetates with simple phenols, and succeeded in obtaining 2-benzyl benzofuran derivatives instead of doubly phenoxyated products (Scheme 1, B).^{6d} Based on our previous study of 2-fluoroallylic acetates, as an extension of our reaction system, we investigated the reaction of 2-chloro- or 2-bromoallylic acetate with phenols, and confirmed the formation of the 2-benzyl benzofuran derivatives. Therefore, we now report our results of the palladium-catalyzed reaction of 2-haloallylic acetates with simple phenols, and the synthesis of 2-



Scheme 1. Our previous study of the palladium-catalyzed reactions of 2-fluoroallylic acetate **1a** with phenol (**2a**).

* Corresponding author.

E-mail address: kawatsur@chs.nihon-u.ac.jp (M. Kawatsura).



Scheme 2. Palladium-catalyzed reactions of 2-haloallylic acetates **5a** and **6a** with **2a**, substituted benzofuran derivatives.

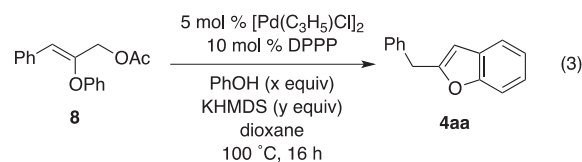
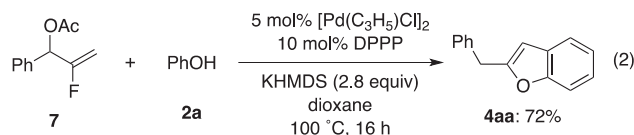
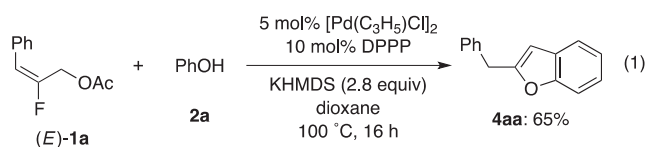
2. Results and discussion

We first tried the reactions of 2-chloro- or 2-bromoallylic acetate **5a** or **6a** with phenol (**2a**) using the $[\text{Pd}(\text{C}_3\text{H}_5)\text{Cl}]_2/\text{DPPP}$ catalyst, which was an effective catalyst for the synthesis of 2-substituted benzofuran derivatives from 2-fluoroallylic acetates **1a** with **2a** (Scheme 1, B),^{6d} and confirmed that the reactions afforded the intended benzofuran derivative **4aa** in 77% and 87% yields, respectively (Scheme 2). These initial results indicated that the three types of 2-haloallylic acetates produced the same products, which is a 2-substituted benzofuran derivative, in almost similar yields.

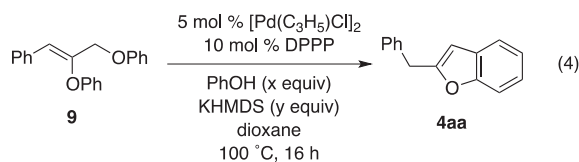
Based on these initial results, we investigated the reactions of three types of 2-haloallylic acetates, such as the 2-fluoro, 2-chloro, and 2-bromoallylic acetates **1a** (X = F), **5a** (X = Cl), and **6a** (X = Br) with several phenols **2b–q**, and the results are summarized in Table 1. For example, the reactions of **1a**, **5a**, and **6a** with 4-methylphenol (**2b**) (5 equiv.) with $[\text{Pd}(\text{C}_3\text{H}_5)\text{Cl}]_2/\text{DPPP}$ and KHMDS (2.8 equiv.) in dioxane at 100 °C for 16 h provided **4ab** in 72%, 77%, and 72% yields, respectively. The reactions of the three 2-haloallylic acetates **1a**, **5a**, and **6a** with other phenols **2c–e** also produced intended products **4ac–ae** in similar yields, respectively. We also confirmed that the cyclization mainly occurred at the sterically-less-hindered site during the reaction of the 3-substituted phenols **2e**. The reactions with 4-methoxyphenol (**2f**) gave the desired product **4af** in the range of 74–88% yields. As we previously reported, the reaction of **1a** with 3-methoxyphenol (**2g**) by the $[\text{Pd}(\text{C}_3\text{H}_5)\text{Cl}]_2/\text{DPPP}$ catalyst resulted in a 58% yield, but the yield increased to 76% when the $[\text{Pd}(\text{C}_3\text{H}_5)\text{Cl}]_2$ was changed to $\text{Pd}(\text{OAc})_2$.^{6d} However, for the reactions of 2-chloro- or 2-bromoallylic acetate **5a** and **6a** with **2g**, we confirmed that the yields did not increase even when the $\text{Pd}(\text{OAc})_2$ was used,⁹ therefore, we indicated the results from the reactions using $[\text{Pd}(\text{C}_3\text{H}_5)\text{Cl}]_2$ in Table 1. The three reactions of **1a**, **5a** and **6a** with **2h** produced the intended benzofuran derivative **4ah** in almost same yields (76–78%), respectively. Again, although changing the palladium catalyst from $[\text{Pd}(\text{C}_3\text{H}_5)\text{Cl}]_2$ to $\text{Pd}(\text{OAc})_2$ was needed for the reaction of 2-fluoroallylic acetate **1a**, the reactions of 2-haloallylic acetates with phenols **2i–n**, which possess electron-withdrawing groups on the benzene ring, produced intended 2-substituted benzofuran derivatives in moderate to good yields. On the other hand, the reaction of **1a** with 4-cyanophenol (**2o**) gave **4ao** in 91% under modified reaction conditions ($\text{Pd}(\text{OAc})_2$ and Cs_2CO_3 were used instead of $[\text{Pd}(\text{C}_3\text{H}_5)\text{Cl}]_2$ and KHMDS), but the reactions of **5a** and **6a** resulted in low yields due to the decomposition of the 2-haloallylic acetates. We succeeded in obtaining **4ap** by the reaction of 2-fluoroallylic acetate **1a** with 4-nitrophenol (**2p**) (3 equiv.) in 80% using the $\text{Pd}(\text{OAc})_2/\text{DPPP}$ catalyst, but the reactions of **5a** and **6a** did not produce any product. On the other hand, we examined the reaction of three types of 2-haloallylic acetates with 2-naphthol (**2q**), and obtained the desired product **4aq** in 73–90% yields, respectively.

We next demonstrated the reactions of the 3-aryl-2-haloallylic acetates **1b–j**, **5b–j**, and **6b–j** with phenol (**2a**), and the results are summarized in Table 2. The 2-fluoroallylic acetate **1b**, which possesses the 4-methoxyphenyl group at the C-3 position, gave the corresponding benzofuran derivative **4ba** in 76% yield. On the other hand, the reactions of the 2-chloro- or 2-bromoallylic acetates **5b**

and **6b** with **2a** produced the same products **4ba**, but the yields were slightly lower. This trend in the yield was also observed in the reaction of **1c**, **5c**, and **6c** with **2a**. For the reactions of the 4-trifluoromethylphenyl group-substituted 2-haloallylic acetates **1d**, **5d**, and **6d** with **2a**, the best yield was obtained by the reaction of the 2-chloroallylic acetate **5d**. The allylic acetates **1e**, **5e**, and **6e** produced the intended product **4ea** in the range of 59–72% yields. We also examined the reactions of the 1-naphthyl or 2-tolyl group substituted allylic acetate, and obtained the desired products **4fa** or **4ga** in acceptable yields, respectively. We next investigated the reaction of the 3-pyridyl group substituted 2-fluoroallylic acetate **1h** and confirmed that the reaction provided the benzofuran derivative **4ha** in 75% yield, but the 2-chloro or 2-bromoallylic acetates **5h** and **6h** did not afford any intended product and we observed the decomposition of the allylic substrates. However, we succeeded in obtaining the desired products **4ia** in the range of 66–76% yields for the reactions of the 2-thienyl group possessing allylic acetates **1i**, **5i**, and **6i** with **2a**. Furthermore, we confirmed that the alkyl group-substituted 2-fluoroallylic acetates **1j** also provide **4ja** in 60% yield, but the reactions of **5j** and **6j** resulted in low yields.



PhOH (x equiv)	KHMDS (y equiv)	yield (%) of 4aa
0	0	<2
1.0	1.0	66



PhOH (x equiv)	KHMDS (y equiv)	yield (%) of 4aa
1.0	1.0	56
3	2.8	71

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