



# Intramolecular construction of trifluoromethyl group by the palladium-catalyzed reaction of 2,3,3-trifluoroallylic carbonates with *O*-nucleophiles

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## ABSTRACT

The synthesis of the trifluoromethyl group containing enol ethers by the palladium-catalyzed intermolecular reaction of 2,3,3-trifluoroallylic carbonates with oxygen nucleophiles was accomplished. The reaction proceeds through the intermolecular attack of oxygen nucleophiles on the C-2 carbon atom of the allylic unit, and the intramolecular fluorine atom shift from the C-2 position to the C-3 position. The reactions with several types of alcohols and phenols proceeded smoothly, and afforded the corresponding trifluoromethyl group containing enol ethers in good to high yields.

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## 1. Introduction

Fluorine-containing organic compounds have attracted much interest in the fields of medicinal chemistry and material science,<sup>1</sup> and the development of new transformation methods of fluorine-containing organic compounds is also a challenging subject in organic chemistry. Based on this background, there are several reports of the palladium-catalyzed allylic substitution reactions of fluorine-containing allylic esters.<sup>2,3</sup> Generally, the palladium-catalyzed reaction of allylic esters with nucleophiles provides allylic-substituted products or cyclopropane derivatives,<sup>4,5</sup> and we also demonstrated the transition-metal-catalyzed branch selective allylic substitutions of the 2,3,3-trifluoroallylic acetates with nucleophiles.<sup>6</sup> However, during our study of the palladium-catalyzed reaction of several types of fluorine-containing allylic esters,<sup>7–9</sup> we examined the reaction of 2,3,3-trifluoroallylic carbonates with amines and revealed that the amine nucleophiles were introduced at the C-2 position of the allylic moiety,<sup>7</sup> and the trifluoromethyl group was constructed by an intramolecular fluorine atom shift from the C-2 position to the C-3 position of the allyl group.<sup>7a</sup> As part of this study, we recently examined the alkylation

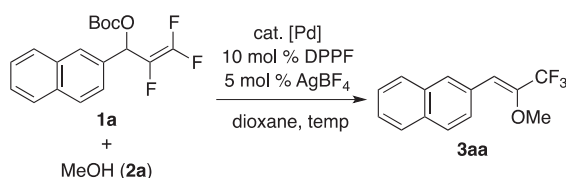
reaction of 2,3,3-trifluoroallylic carbonates with indoles, and succeeded in obtaining the intended trifluoromethyl group containing 3-substituted indole derivatives.<sup>7b</sup> However, there is still no report about the reaction of 2,3,3-trifluoroallylic esters with oxygen nucleophiles, which provides the trifluoromethyl-substituted enol ethers. Therefore, as a further development of this type of reaction, we now report herein the palladium-catalyzed reaction of the 2,3,3-trifluoroallylic carbonates with oxygen nucleophiles to synthesize the trifluoromethyl group-substituted enol ethers.

## 2. Results and discussion

We first examined the reaction of the 2-naphthyl-substituted 2,3,3-trifluoroallylic carbonates **1a** with methanol (**2a**). Based on our previous work, we screened several palladium precatalysts in the presence of DPPF as a ligand. As shown in Table 1, the reaction using Pd(OAc)<sub>2</sub>, which effectively catalyzed the reaction of the 2,3,3-trifluoroallylic carbonates with nitrogen nucleophiles, did not produce the desired product **3aa** (Table 1, entries 1 and 2). Then, the reaction with [Pd(C<sub>3</sub>H<sub>5</sub>)(cod)]BF<sub>4</sub>, which was a suitable palladium precatalyst for the alkylation reaction of 2,3,3-trifluoroallylic carbonates with indoles, provided **3aa**, but the NMR yield was moderate (59%) (entries 3 and 4). Based on this initial observation, we screened other palladium precatalysts (entries 5–7, 9, and 10),

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**Table 1**  
Optimization of Reaction Conditions.<sup>a</sup>

Entry	Conditions: [Pd] (mol%)	Temp (°C)	Yield <sup>b</sup> (%) of <b>3aa</b>
1	Pd(OAc) <sub>2</sub> (5) without AgBF <sub>4</sub>	60	<2
2	Pd(OAc) <sub>2</sub> (5)	60	<2
3	[Pd(C <sub>3</sub> H <sub>5</sub> )(cod)]BF <sub>4</sub> (5) without AgBF <sub>4</sub>	60	59
4	[Pd(C <sub>3</sub> H <sub>5</sub> )(cod)]BF <sub>4</sub> (5)	60	<2
5	[Pd(C <sub>3</sub> H <sub>5</sub> )Cl] <sub>2</sub> (2.5) without AgBF <sub>4</sub>	60	40
6	[Pd(C <sub>3</sub> H <sub>5</sub> )Cl] <sub>2</sub> (2.5)	60	94
7	[Pd(C <sub>3</sub> H <sub>5</sub> )Cl] <sub>2</sub> (2.5)	80	97 (91) <sup>c</sup>
8 <sup>d</sup>	[Pd(C <sub>3</sub> H <sub>5</sub> )Cl] <sub>2</sub> (2.5)	80	92 (88) <sup>c</sup>
9	Pd <sub>2</sub> (dba) <sub>3</sub> (2.5) without AgBF <sub>4</sub>	60	72
10	Pd <sub>2</sub> (dba) <sub>3</sub> (2.5)	60	75

<sup>a</sup> Reaction conditions: **1a** (0.17 mmol), **2a** (0.24 mmol), [Pd] (0.0043 or 0.0085 mmol), DPPF (0.017 mmol), and AgBF<sub>4</sub> (0 or 0.0085 mmol) in dioxane (1.0 mL) at the indicated temperature for 16 h.

<sup>b</sup> Yields are determined by <sup>19</sup>F NMR of crude materials using an internal standard (trifluoromethylbenzene).

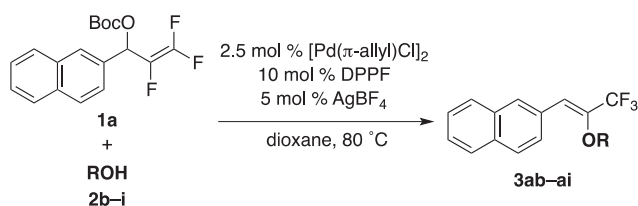
<sup>c</sup> Isolated yield is shown in parentheses.

<sup>d</sup> Reaction of **1a** on a 1 g scale.

and revealed that [Pd(C<sub>3</sub>H<sub>5</sub>)Cl]<sub>2</sub> in the presence of AgBF<sub>4</sub> exhibits the intended catalytic activity. For example, the reaction of **1a** with **2a** in the presence of [Pd(C<sub>3</sub>H<sub>5</sub>)Cl]<sub>2</sub>/DPPF/AgBF<sub>4</sub> catalyst at 60 °C afforded an enol ether possessing a trifluoromethyl group **3aa** in 94% NMR yield, and the best result (97% NMR yield and 91% isolated yield) was obtained when the reaction was conducted at 80 °C (entries 6 and 7).

With the optimal reaction conditions [2.5 mol% [Pd(C<sub>3</sub>H<sub>5</sub>)Cl]<sub>2</sub>, 10 mol% DPPF, and 5 mol% AgBF<sub>4</sub> in dioxane at 80 °C for 16 h (Table 1, entry 7)] in hand, we first examined the reaction of **1a** with several alcohols **2b–i**, and these results are summarized in Table 2. The reactions of **1a** with alcohols **2b** and **2c** afforded the expected products **3ab** and **3ac** in 84% and 70% yields, respectively (Table 2, entries 1 and 2). The reaction with *n*-butyl alcohol (**2d**) required a longer reaction time, but we confirmed formation of the desired product **3ad** in 82% yield (entry 3). We also succeeded in obtaining the desired product **3ae** from the reaction with a benzyl alcohol **2e** (entry 4). Furthermore, although it needed optimization of the reaction conditions, the reactions with secondary alcohols **2f** and **2h** also provided the intended trifluoromethyl group-substituted enol ethers **3af** and **3ah** in good yields, respectively (entries 5 and 7). Unfortunately, even though we observed 100% conversion of **1a**, we confirmed that the reactions with **2g** and **2i**, resulted in low yields probably due to the steric bulkiness of alcohols (entries 6 and 8).

We next examined the reactions of **1a** with several types of phenol analogues **4a–x**, and the results are summarized in Table 3. The reaction of **1a** with phenol (**4a**) gave the desired trifluoromethyl-substituted aryl enol ether **5aa** in 77% yield (Table 3, entry 1). The reactions with other phenols **4b–f**, which have several alkyl groups on the benzene ring, also provided the corresponding products **5ab–af** in the range of 58–85% yields (entries 2–6). We next examined the reaction with phenols bearing a methoxy group **4g–j**, and succeeded in obtaining the intended products **5ag–aj** in moderate to good yields (entries 7–10). We also attempted the reactions with phenol **4k–t**, which have an electron-withdrawing group, such as the trifluoromethyl, fluoro-, chloro-, or

**Table 2**  
Palladium-catalyzed Reaction of **1a** with Alcohols **2b–i**.<sup>a</sup>

Entry	<b>2</b>	Yield <sup>b</sup> (%) of <b>3</b>
1	<b>2b</b>	84 ( <b>3ab</b> )
2	<b>2c</b>	70 ( <b>3ac</b> )
3 <sup>c</sup>	<b>2d</b>	82 ( <b>3ad</b> )
4	<b>2e</b>	77 ( <b>3ae</b> )
5 <sup>c</sup>	<b>2f</b>	70 ( <b>3af</b> )
6	<b>2g</b>	32 ( <b>3ag</b> )
7 <sup>d</sup>	<b>2h</b>	67 ( <b>3ah</b> )
8 <sup>e</sup>	<b>2i</b>	26 ( <b>3ai</b> )

<sup>a</sup> Reaction conditions: **1a** (0.17 mmol), **2b–i** (0.24 mmol), [Pd] (0.0043 mmol), DPPF (0.017 mmol), and AgBF<sub>4</sub> (0.0085 mmol) in dioxane (1.0 mL) at 80 °C for 16 h.

<sup>b</sup> Isolated yields.

<sup>c</sup> 24 h.

<sup>d</sup> Reaction was conducted in toluene at 60 °C.

<sup>e</sup> 100 °C.

bromo-group on the benzene ring, and succeeded in obtaining the desired products **5ak–at** in good to high yields (entries 11–20). We further investigated the reaction of **1a** with 4-cyanophenol (**4u**) or 4-nitrophenol (**4v**), and revealed that the reactions provided the corresponding products **5au** and **5av** in 77% and 75%, respectively (entries 21 and 22). Furthermore, the reaction with naphthols **4w** and **4x** also afforded **5aw** and **5ax** in 76% and 63% yields, respectively (entries 23 and 24).

Furthermore, we investigated the palladium-catalyzed reactions of several allylic carbonates **1b–i**, which possess several substituents at the C-1 position, with methanol (**2a**) or phenol (**4a**), and the results are summarized in Table 4. At first, we examined the reaction of **1b–i** with **2a** using the optimized reaction conditions (Table 4, entries 1–8). For example, the reaction of 2,3,3-trifluoro-1-phenylallylic carbonate **1b** with **2a** gave **3ba** in 68% (entry 1). On the other hand, the reaction of the allylic carbonate **1c**, which possesses the 4-methoxy phenyl group, gave a slightly decreased yield (53%) (entry 2), but we confirmed that the reaction of **1d** afforded the desired product **3da** in good yield (77%) (entry 3). We also demonstrated the reaction of **1e**, which has a trifluoromethyl group at the *para*-position of the benzene ring, with **2a** and succeeded in obtaining **3ea** in a moderate yield (entry 4). Although the reaction of **1f**, which has the *o*-tolyl group, gave **3fa** in 65%, and the higher yield (87%) was observed in the reaction of **1g**, which has the 1-naphthyl group as a substituent of the 2,3,3-

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