

## Palladium-Catalyzed Decarboxylative Carbonylative Transformation of Benzyl Aryl Carbonates: Direct Synthesis of Aryl 2-Arylacetates

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**Supporting Information** 

**ABSTRACT:** A procedure on palladium-catalyzed decarboxylative alkoxycarbonylation of carbonates for the synthesis of aryl 2arylacetates has been developed. A broad range of aryl 2-arylacetates were obtained in good yields under mild conditions under a carbon monoxide atmosphere. Interestingly, other alcohols can be added as nucleophiles as well, and the corresponding esters were also obtained in good yields.



E sters are widely present in fine chemicals, agrochemicals, and natural products.<sup>1</sup> Among the different types of esters, arylacetates are common skeletons found in pharmaceuticals. In the past decades, numerous synthetic approaches have been developed for their synthesis.<sup>1</sup> Among them, transition-metalcatalyzed carbonylation, which uses CO as an inexpensive and readily available C1 building block, has emerged as one of the most attractive and powerful strategies for the efficient construction of various esters, in terms of atom and step economy.<sup>2</sup> In the developed carbonylative methodologies, the usage of benzylic halides as the substrates is one of the choices. However, the formation of a stoichiometric amount of halogen wastes is unavoidable.<sup>3</sup> Oxidative carbonylation of benzylic  $C(sp^3)$ -H bond is an ideal option, but the reaction efficiency still must be improved.<sup>4</sup> Alternatively, palladium-catalyzed alkoxycarbonylation of benzyl amines or benzyl alcohols also are possible. However, the reaction should be conducted in dimethyl carbonate (DMC), which is also acting as the activator.5

On the other hand, transition-metal-catalyzed decarboxylative couplings have recently emerged as a powerful strategy for C-C and C-heteroatom bond formations.<sup>6</sup> Compared with traditional cross-coupling reactions; decarboxylative coupling reactions are milder and more environmentally friendly. Carboxylic acids or carbonatese, as the applied substrates, are nontoxic, stable, and readily available.<sup>7,8</sup> As expected, palladium-catalyzed decarboxylative carbonylations have also been reported.9 In 2011, Lee and co-workers reported a palladium-catalyzed decarboxylative carbonylation of aryl alkynyl carboxylic acids and aryl iodides for synthesis of  $\alpha,\beta$ alkynyl ketone under CO pressure (10 bar).9a Shortly afterward, they were able to use the same method to synthesize various alkynyl amides.<sup>9c</sup> Our group also developed a palladium-catalyzed decarboxylative carbonylation synthesis of  $\alpha,\beta$ -alkynyl ketone, employing formic acid as the CO source.9d Herein, we developed the first decarboxylative carbonylation procedure for the synthesis of aryl 2-arylacetates from benzyl aryl carbonates under mild conditions. Compared with the reported alkoxycarbonylation procedures, this process avoided the use of halides or stoichiometric amounts of oxidant. Moreover, concerning the nucleophiles or ester products, aliphatic alcohols are more commonly studied to give alkyl benzoates, while phenol, as the reaction partner, is much less studied.<sup>1</sup>

To begin this study, we chose benzyl phenyl carbonate (1a) as the model substrate to establish the reaction conditions. After extensive experimentation, we found that the decarboxylative carbonylation synthesis of phenyl-2-phenylacetate (3a) can be achieved in 85% yield with [(cinnamyl)PdCl]<sub>2</sub> (2.5 mol%)/dppp (5.5 mol%) as the catalytic system in o-xylene under 1 bar of CO gas without any additive (Table 1, entry 1). As we expected, no desired product was determined in the absence of CO (Table 1, entry 2). Both palladium salt and phosphine are required for the reaction to proceed (Table 1, entry 3). Alternative palladium precursors, including PdCl<sub>2</sub>,  $Pd(OAc)_2$ , and  $Pd_2(dba)_3$  were tested as well, and only  $Pd_2(dba)_3$  can deliver 3a in 71% yield (Table 1, entry 6). We also investigated different ligands, and dppp was found to be superior to other ligands (Table 1, entries 7 and 8). In addition, the results show that the bite angle of the ligands has a great influence on the reaction outcome. Other solvents, such as CH<sub>3</sub>CN, toluene, or 1,4-dioxane, was less effective than oxylene (Table 1, entry 11). Moreover, increasing or decreasing the amount of catalyst led to a reduced yield of 3a (Table 1, entries 10 and 11). Here, it is also important to mention that the addition of nitrogen is done to avoid the overflow of reagents from the reaction vial under 120 °C and maintain the reproducibility of our procedure.

With the optimized reaction conditions in hand, we next investigated the scope of this decarboxylative carbonylation procedure (Table 2). A variety of benzyl aryl carbonates containing electron-donating or electron-withdrawing groups are compatible for this transformation. Benzyl group bearing substituents with fluoride-, trifluoromethyl-, and methoxygroups at the ortho- or para-position all give high yields of the corresponding esters (see Table 2, entries 2-5). Benzo[d]-

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

$\bigcirc$	0 [(cinnamyl)PdC dppp (5.5 mol 1 o-xylene (2	H] <sub>2</sub> (2.5 mol %) %), <u>CO (1 bar)</u> mL), 120 °C 3a
	variation from the standard	
entry	conditions	yield <sup>b</sup> (%)
1		85
2	without CO	n.r.
3	without catalyst/ligand	n.r.
4	PdCl <sub>2</sub> instead of [(cinnamyl) PdCl] <sub>2</sub>	n.r.
5	Pd(OAc) <sub>2</sub> instead of [(cinnamyl)PdCl] <sub>2</sub>	9
6	Pd <sub>2</sub> (dba) <sub>3</sub> instead of [(cinnamyl)PdCl] <sub>2</sub>	71
7	PPh <sub>3</sub> , or dppm instead of dppp	n.r.
8	dppe, or dppb instead of dppp	18 (using dppe), 77 (using dppb)
9	CH <sub>3</sub> CN, toluene, or 1,4- dioxane instead of <i>o</i> -xylene	62 (using CH <sub>3</sub> CN), 77 (using toluene), 75 (using 1,4-dioxane)
10	1 mol % [(cinnamyl)PdCl] <sub>2</sub> , 2.2 mol % dppp	68
11	5 mol % [(cinnamyl)PdCl] <sub>2</sub> , 11 mol % dppp	64
an		

<sup>a</sup>Reaction conditions: benzyl phenyl carbonate (0.2 mmol), [(cinnamyl)PdCl]<sub>2</sub> (2.5 mol %), dppp (5.5 mol %), CO (1 bar), N<sub>2</sub> (9 bar), *o*-xylene (2 mL), 120 °C, 12 h. Abbreviations used in this table: n.r. = no reaction, [(cinnamyl)PdCl]<sub>2</sub> = dichlorobis[(1,2,3-)-1phenyl-2-propenyl]dipalladium(II), dppp = 1,3-bis-(diphenylphosphino)propane, dppm = bis(diphenylphosphino)methane, dppe = 1,2-bis(diphenylphosphino)ethane, and dppb = 1,4-bis(diphenylphosphino)butane. <sup>b</sup>As determined by gas chromatography (GC), using hexadecane as the internal standard.

[1,3]dioxol-5-ylmethyl phenyl carbonate and naphthalen-1ylmethyl phenyl carbonate, including a sterically hindered group, can also give the desired esters in excellent yields (see Table 2, entries 7 and 8). Similar to benzyl group, a phenyl group with electron-withdrawing groups (F, Cl, CN, and COCH<sub>3</sub>), or electron-donating groups all generated the corresponding esters in good to excellent yields (Table 2, entries 9-13). In addition, heteroaromatic carbonates such as furan-2-ylmethyl phenyl carbonate and benzylpyridin-3-yl carbonate, can be applied as well and gave high yields of the desired products (Table 2, entries 6 and 16). Moreover, multifluoro-substituted benzyl (perfluorophenyl) carbonate, and benzyl naphthalen-2-yl carbonate can all be transformed to the desired esters in good yields (Table 2, entries 15 and 17). However, the reaction failed with substrates substituted with bromide (for a list of failed examples, see Table S1 in the Supporting Information (SI)). This phenomenon is mainly due to the low activating energy of the C-Br bond, compared with the carbonate, and palladium catalyst reacted faster with bromide and then decomposed. In addition, under the optimized conditions, cinnamyl phenyl carbonate can be transformed as well; however, a mixture of two products was obtained (see Scheme 1).

Since the importance of alkyl arylacetates such as methylphenidate and Plavix is well-known,<sup>11</sup> we investigated the reaction with aliphatic alcohols as well (see Table 3). As we expected, when the decarboxylative carbonylation was performed in methanol, the benzyl phenyl carbonate could be completely converted to the desired methyl 2-phenylacetate in good yield (see Table 3, entry 1). Inspired by this result, we

# Table 2. Decarboxylative Carbonylation of Different Carbonates<sup>a</sup>



<sup>a</sup>Reaction conditions: benzyl phenyl carbonate (0.2 mmol), [(cinnamyl)PdCl]<sub>2</sub> (2.5 mol %), dppp (5.5 mol %), CO (1 bar), N<sub>2</sub> (9 bar), *o*-xylene (2 mL), 120 °C, 12 h, isolated yield.

also tested other alcohols, such as ethanol, 1-pentanol, cyclohexanol, and benzyl alcohol, and the desired products were all generated in moderate to good yields (see Table 3, entries 2-5).

# Scheme 1. Decarboxylative Carbonylation of Cinnamyl Phenyl Carbonate



## Table 3. Decarboxylative Carbonylation of Carbonates with other Alcohols<sup>a</sup>



<sup>*a*</sup>Reaction conditions: benzyl phenyl carbonate (0.3 mmol), R<sup>3</sup>OH (2 mL), [(cinnamyl)PdCl]<sub>2</sub> (2.5 mol %), dppp (5.5 mol %), CO (1 bar), N<sub>2</sub> (14 bar), 120 °C, 15 h, isolated yield (NMR yield given in parentheses, using dibromomethane as an internal standard). <sup>*b*</sup>I-pentanol (5 equiv), *o*-xylene (2 mL). 'R<sup>3</sup>OH (1 mL).

Based on the experimental data and precedents regarding relevant palladium-catalyzed carbonylation reactions,<sup>2,8</sup> a possible reaction pathway is proposed and shown in Scheme 2. Initially, the reactive  $Pd^0$  species was generated by the ligand exchange, followed by the oxidative addition with **1a** to form **IM1**. After the elimination of one molecule of  $CO_2$ , **IM2** was generated. Both the **IM4** and **IM5** then are possible after the coordination and insertion of CO with **IM2**. Finally, the

### Scheme 2. Proposed Mechanism



terminal product 3a and  $Pd^0$  were obtained by reductive elimination of acyl palladium species IM4 or IM5.

In summary, we have successfully developed a new palladium-catalyzed decarboxylative carbonylation of benzyl aryl carbonates for the synthesis of aryl 2-arylacetates. Without any additive or external phenol addition, the desired aryl arylacetic acid esters were obtained in good to excellent yields. In addition, alkyl arylacetic acid esters can also be prepared by adding the corresponding alcohols.

## ASSOCIATED CONTENT

## **Supporting Information**

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.8b02631.

Experimental details, additional reaction data, and NMR spectra of products. General comments, procedure for substrates and products preparation, analytic data for substrates and products, and NMR spectra for substrates and products (PDF)

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#### Notes

The authors declare no competing financial interest.

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