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Palladium-catalyzed carbonylative synthesis of benzufuran-2(3*H*)-ones from 2-hydroxybenzyl alcohols with formic acid as the CO source

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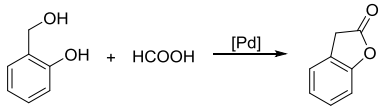
A palladium-catalyzed carbonylative intramolecular synthesis of benzofuran-2(3*H*)-ones from 2-hydroxybenzyl alcohols has been developed. In this procedure, formic acid has been utilized as the CO source, and various desired benzofuran-2(3*H*)-one derivatives were obtained in moderate to good yields.

Palladium-catalyzed carbonylative transformation via the insertion of carbon monoxide (CO) is one of the most important reactions in organic synthesis. It has attracted lots of attentions since the first report by Heck in 1970s,[1] and many impressive progresses have been achieved during the last few decades.[2] Carbonylative reaction provides a powerful strategy to introduce C=O group into the parent molecules to construct a wide range of carbonyl containing compounds. Considering the disadvantages of gaseous CO, many efforts have been put on this topic and a variety of CO sources have been developed.[3] Our group has been interested in this area as well and achieved a series of palladium-catalyzed carbonylative coupling reactions with formic acid as the CO precursor.[4]

Benzofuranones, a class of valuable molecule appeared in a variety of natural products and pharmaceutical compounds,[5] and shown various biological activities.[6] It also serves as an key moiety in many drug scaffolds and biological products.[7] Most recently, our group reported a general procedure for benzofuran-2(3*H*)-ones synthesis through palladium-catalyzed carbonylation using formic acid as the CO surrogate.[8] With phenols and aldehydes as the substrates, the desired products can be produced in moderate to good yields in the presence of trifluoroacetic acid in chlorobenzene. In this procedure, we believe the in situ formed 2-hydroxybenzyl alcohols should be the key intermediate for the transformation. And the 2-hydroxybenzyl alcohols were produced from phenols and aldehydes with CF_3CO_2H as the catalyst. Theoretically, the acid additive can be successfully avoid if we directly using 2-hydroxybenzyl alcohols as the starting materials. With this idea in mind and also as our continuous efforts on CO sources development and heterocycles synthesis, we describe here a palladium-catalyzed intramolecular carbonylative reaction for benzofuranone synthesis with 2-hydroxybenzyl alcohols as the starting materials and formic acid as the CO source. Moderate to good yields of the desired benzofuranones can be obtained.

Table 1. Screening of the reaction conditions.[a]



1a 2a

Entry	Catalyst	Ligand	Temp. (°C)	Yield (%)[b]
1	$Pd(PPh_3)_4$	PPh_3	100	72
2	$Pd(PPh_3)_4$	P(*o*-tolyl)$_3$	100	91
3	$Pd(PPh_3)_4$	-	100	48
4	Pd/C	-	100	0
5	Pd/C	PPh_3	100	0
6	$Pd(PPh_3)_4$	P(*o*-tolyl)$_3$	90	83
7	$Pd(PPh_3)_4$	P(*o*-tolyl)$_3$	130	65

[a] Reaction conditions: 2-(hydroxymethyl)phenol (1.0 mmol), $Pd(PPh_3)_4$ (5 mol%), ligand (20 mol%), HCOOH (3.0 mmol), acetic anhydride (3.0 mmol), toluene (2 mL), 100 °C, 2 h. [b] GC yields with dodecane as the internal standard.

Initially, 2-(hydroxymethyl)phenol was used as the model substrate, with $Pd(PPh_3)_4$ as the catalyst, PPh_3 as the ligand and formic acid as the CO source in toluene at 100 °C for 2 h (Table 1, entry 1). To our delight, 72% yield of the target

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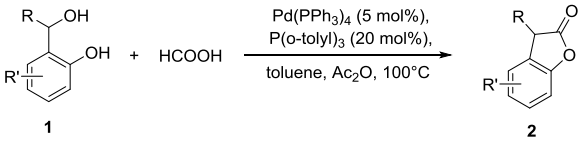
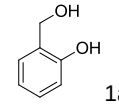
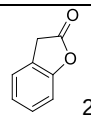
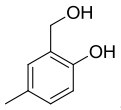
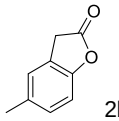
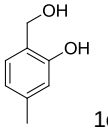
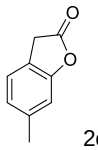
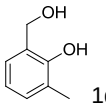
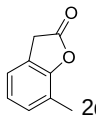
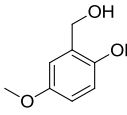
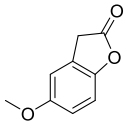
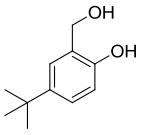
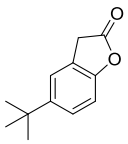
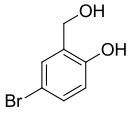
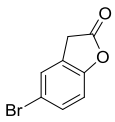
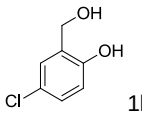
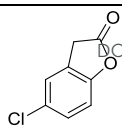
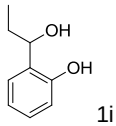
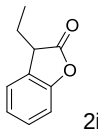
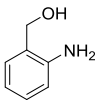
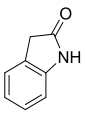
product can be obtained. The yield can be further improved to 91% with P(*o*-tolyl)$_3$ as the ligand (Table 1, entry 2), while lower yield was obtained without any additional ligands (Table 1, entry 3). Pd/C catalyst provided no product with PPh_3 or without ligands (Table 1, entries 4-5). Additionally, 83% of the desired benzofuranone can still be obtained at 90 °C (Table 1, entry 6). Interestingly, the yield dropped to 65% by increase the reaction temperature to 130 °C (Table 1, entry 7).

Table 2. Carbonylative reaction of *o*-hydroxy benzylacohol. [a]

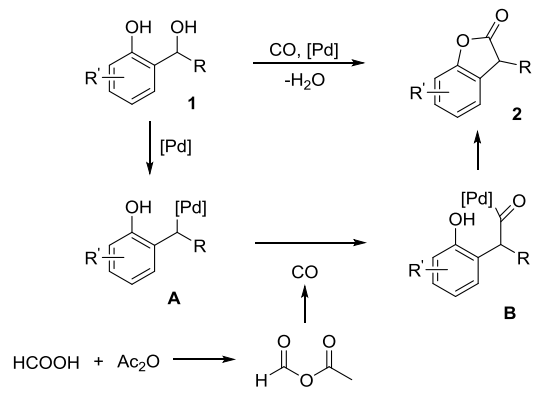


1 2

Entry	2-Hydroxybenzyl alcohols	Product	Yield (%)[b]
1	 1a	 2a	84
2	 1b	 2b	71
3	 1c	 2c	60
4	 1d	 2d	69
5	 1e	 2e	85
6	 1f	 2f	60
7	 1g	 2g	32
8	 1h	 2h	65
9	 1i	 2i	47
10	 1j	 2j	0

[a] Reaction conditions: 2-hydroxybenzyl alcohols (1.0 mmol), $Pd(PPh_3)_4$ (5 mol%), P(*o*-tolyl)$_3$ (20 mol%), HCOOH (3.0 mmol), acetic anhydride (3.0 mmol), toluene (2 mL), 2-3 h. [b] Isolated yields.

With the optimal reaction conditions in hand, we next explored the substrates scope and the results were shown in Table 2. Various substitutions on the phenyl ring were tolerated well to give the desired benzofuranone products in moderate to good yields. Substrates with methyl group on the *para* position to hydroxyl moiety provide the product in 71% yield (Table 2, entry 2). *ortho*-Methyl substitution resulted a comparable yield as *para*-methyl group, while *meta*- methyl substituted substrate furnished a lower yield (Table 2, entries 3-4). The benzofuranone was obtained in high yield with methoxy group (Table 2, entry 5). *tert*-Butyl substrate gave 60% yield (Table 2, entry 6). Furthermore, *para*-halo substitutions such as bromo and chloro were studied as well; bromo-substitution provided a relatively low yield, while chloro group resulted in 65% yield (Table 2, entries 7-8). Additionally, a substrate with an ethyl group substituted at benzyl position was also investigated, and furnished the corresponding product in 47% yield (Table 2, entry 9). However, no desired product can be detected in the case of using (2-aminophenyl)methanol as the substrate (Table 2, entry 10).



Scheme 1. Proposed reaction mechanism.

Based on those results and literature,[9] a possible reaction mechanism is proposed and shown in Scheme 1. Benzylic alcohol **1** was first activated by the palladium catalyst. Then the coordination and insertion of CO (generated from formic acid and acetic anhydride) occurred and finally provide the target benzufuran-2(3*H*)-one **2** products through reductive elimination.

Conclusions

In summary, a palladium-catalyzed carbonylative methodology for the synthesis of benzofuran-2(3*H*)-ones has been developed. Moderate to good yields of the desired benzofuran-2(3*H*)-ones can be obtained from the corresponding 2-hydroxybenzyl alcohols. In this catalytic system, to avoid the use of toxic CO gas, formic acid was used as the CO precursor with acetic anhydride as the activator.

Notes and references

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