



# Efficient and selective palladium-catalyzed direct oxidative esterification of benzylic alcohols under aerobic conditions

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## ARTICLE INFO

### Article history:

Received 13 September 2017

Received in revised form

2 November 2017

Accepted 10 November 2017

Available online 13 November 2017

### Keywords:

Esterification

Oxidation

Alcohols

Palladium

## ABSTRACT

A highly efficient palladium-catalyzed approach for the direct oxidative esterification of benzylic alcohols with methanol and long-chain aliphatic alcohols under mild conditions has been achieved. This practical catalyst system exhibits a broad substrate scope and good functional group tolerance. Catalytic amount of Bi(OTf)<sub>3</sub> is used as co-catalyst to improve the activity and selectivity of the reactions. A variety of esters are obtained in yields of 43–96%.

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## 1. Introduction

The ester group is an important functional group in organic chemistry and can be widely found in natural products, fine chemicals, pharmaceuticals and synthetic intermediates.<sup>1</sup> Because of their importance, the synthesis of esters has extensively attracted much attention and numerous transformations have been developed. Traditionally, the classical and common strategies for the preparation of esters involve the nucleophilic substitution of carboxylic acid derivatives (carboxylic halides, anhydrides and active esters) with alcohols (Scheme 1, a).<sup>2</sup> These protocols usually require stoichiometric amounts of reagents such as strong acid or basic and large amounts of unwanted by-products are produced. In recent years, considerable efforts have been devoted to the direct synthesis of esters from the oxidative esterification of aldehydes with alcohols (Scheme 1, b).<sup>3</sup> However, stoichiometric amounts of oxidants such as MnO<sub>2</sub>,<sup>4</sup> oxone,<sup>5</sup> *N*-iodosuccinimide,<sup>6</sup> hydrogen peroxide,<sup>7</sup> *tert*-butyl hydroperoxide,<sup>8</sup> TCCA,<sup>9</sup> (NH<sub>4</sub>)<sub>2</sub>S<sub>2</sub>O<sub>8</sub>,<sup>10</sup> or noble transition-metal catalysts including vanadium,<sup>11</sup> ruthenium,<sup>12</sup> iridium,<sup>13</sup> gold<sup>14</sup> were usually employed in this reaction. Moreover, the required aldehydes are chemical unstable. Thus, these protocols of the direct oxidative esterification of aldehydes are still environmentally unfavorable. As is well known, aldehydes can be

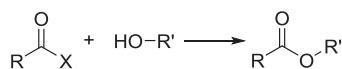
easily prepared by the selective oxidation of alcohols and numerous methods have been developed.<sup>15</sup> Additionally, alcohols are inexpensive, benign and readily available chemical feedstock. Therefore, the development of one-pot process for the direct oxidative esterification of alcohols is highly desirable from both economic and environmental points of view (Scheme 1, c). However, the main challenge of this process is the selectivity between oxidation of alcohols to aldehydes and esterification. To the best of our knowledge, few works have been reported for the aerobic oxidative esterification of alcohols.<sup>16</sup>

Over the past few years, homogeneous and heterogeneous palladium-catalyzed oxidation reactions are of great interest and have been developed rapidly.<sup>17</sup> The majority of this work has focused on conversion of alcohols to aldehydes and ketones, relatively few works were carried out on the oxidative esterification of alcohols. In 2011, the group of Lei<sup>18</sup> and Beller<sup>19</sup> reported palladium-catalyzed oxidative cross-esterification of benzylic and aliphatic alcohols, respectively. In their methods, molecular oxygen was used as the terminal oxidant, and various esters were prepared in good yields. However, both of the two strategies required expensive Ag salt and special ligand, which was a disadvantage for its practical application. Subsequently, Lei also found that PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> could act as the sole catalyst for the oxidative esterification of alcohols.<sup>20</sup> The approach used benzyl chloride as the oxidant and stoichiometric amounts of unwanted toluene were produced as by-product. Very recently, S. Stahl and coworkers described a heterogeneous Pd/charcoal in combination with

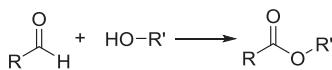
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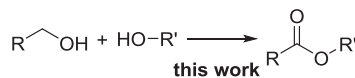
## a) Conventional Methods



## b) Oxidative esterification of aldehydes



## c) Direct oxidative esterification of alcohols



Scheme 1. Methods for the synthesis of esters.

bismuth(III) nitrate and tellurium metal catalyst system for the synthesis of esters.<sup>21</sup> Although, this catalyst system was highly efficient and readily accessible, but prevalently furnished methyl esters. Similarly, Cravotto reported Pd/C-catalyzed aerobic oxidative esterification of alcohols, but the reaction was carried out under MW irradiation and high temperature.<sup>22</sup> Therefore, the development of a selective, efficient and practical protocol for the aerobic oxidative direct esterification of alcohols is still desirable in both academia and industry.

Herein, we report a facile and efficient approach for the direct oxidative esterification of alcohols catalyzed by PdCl<sub>2</sub>(CH<sub>3</sub>CN)<sub>2</sub> with dioxygen as the environmentally benign oxidant. This protocol tolerates a variety of primary alcohols, especially long-chain aliphatic alcohols. In the present of catalytic amount of Bi(OTf)<sub>3</sub>, the activity and selectivity of the reactions were significantly improved.

## 2. Results and discussion

Initially, benzyl alcohol (**1a**) and methanol were employed as model substrates to optimize the reaction conditions using molecular oxygen as the oxidant. The optimized results including catalyst, additive, base and reaction time were summarized in Table 1. As shown in Table 1, different palladium catalysts were investigated in the present of K<sub>2</sub>CO<sub>3</sub> with O<sub>2</sub> balloon (Table 1, entries 1–5). To our delight, PdCl<sub>2</sub>(CH<sub>3</sub>CN)<sub>2</sub> showed the best catalytic reactivity and the desired product **2a** was formed in 61% yield with 34% yield of aldehyde **2a'** (Table 1, entry 5). Bismuth salts have been widely used in organic synthesis, especially in oxidative esterification.<sup>21,23</sup> In order to improve the yield of ester **2a**, various bismuth salts such as Bi(NO<sub>3</sub>)<sub>3</sub>, Bi(OAc)<sub>3</sub>, Bi(OTf)<sub>3</sub>, BiCl<sub>3</sub> and Bi<sub>2</sub>O<sub>3</sub> were screened (Table 1, entries 6–10). Notably, Bi(OTf)<sub>3</sub> was found to be the best co-catalyst because it significantly improved the activity and selectivity of the reaction and gave the yield of **2a** up to 93%. It was obvious that PdCl<sub>2</sub>(CH<sub>3</sub>CN)<sub>2</sub> was crucial for the oxidative esterification of alcohols (Table 1, entry 11). Then, we investigated the influence of various bases in detail, the results revealed that K<sub>2</sub>CO<sub>3</sub> was most effective for the reaction and gave good yield of **2a** (Table 1, entries 8 and 12–15). The reaction with organic base NEt<sub>3</sub> gave **2a** in trace yield (Table 1, entry 15). Furthermore, when the reaction was performed without base, the desired product was obtained in 62% yield (Table 1, entry 16). The reaction time could be reduced to 3 h also providing 93% yield of **2a** (Table 1, entries 17 and 18). In addition, the reaction temperature and the amount of catalyst loadings were also tested to further optimize the reaction conditions (Table 1, entries 19–23). In our hands the addition of polymethylhydrosiloxane (PMHS) as additive as reported by Xu et al.<sup>23b</sup> did not influence the yield of the product (Table 1, entry 24). When the reaction was carried out under air, the product was

**Table 1**  
Optimization of reaction conditions.<sup>a</sup>

Entry	Pd-catalyst	Additive	Base	Time	Yield (%) <sup>b</sup>	
					2a	2a'
1	PdCl <sub>2</sub>	–	K <sub>2</sub> CO <sub>3</sub>	5	–	–
2	Pd(OAc) <sub>2</sub>	–	K <sub>2</sub> CO <sub>3</sub>	5	43	46
3	5 wt%Pd/C	–	K <sub>2</sub> CO <sub>3</sub>	5	39	25
4	PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>	–	K <sub>2</sub> CO <sub>3</sub>	5	52	41
5	PdCl <sub>2</sub> (CH <sub>3</sub> CN) <sub>2</sub>	–	K <sub>2</sub> CO <sub>3</sub>	5	61	34
6	PdCl <sub>2</sub> (CH <sub>3</sub> CN) <sub>2</sub>	Bi(NO <sub>3</sub> ) <sub>3</sub>	K <sub>2</sub> CO <sub>3</sub>	5	85	11
7	PdCl <sub>2</sub> (CH <sub>3</sub> CN) <sub>2</sub>	Bi(OAc) <sub>3</sub>	K <sub>2</sub> CO <sub>3</sub>	5	78	17
8	PdCl <sub>2</sub> (CH <sub>3</sub> CN) <sub>2</sub>	Bi(OTf) <sub>3</sub>	K <sub>2</sub> CO <sub>3</sub>	5	93	<1
9	PdCl <sub>2</sub> (CH <sub>3</sub> CN) <sub>2</sub>	BiCl <sub>3</sub>	K <sub>2</sub> CO <sub>3</sub>	5	81	12
10	PdCl <sub>2</sub> (CH <sub>3</sub> CN) <sub>2</sub>	Bi <sub>2</sub> O <sub>3</sub>	K <sub>2</sub> CO <sub>3</sub>	5	68	22
11	–	Bi(OTf) <sub>3</sub>	K <sub>2</sub> CO <sub>3</sub>	5	–	–
12	PdCl <sub>2</sub> (CH <sub>3</sub> CN) <sub>2</sub>	Bi(OTf) <sub>3</sub>	<i>t</i> -BuOK	5	89	<5
13	PdCl <sub>2</sub> (CH <sub>3</sub> CN) <sub>2</sub>	Bi(OTf) <sub>3</sub>	K <sub>3</sub> PO <sub>4</sub>	5	67	23
14	PdCl <sub>2</sub> (CH <sub>3</sub> CN) <sub>2</sub>	Bi(OTf) <sub>3</sub>	CS <sub>2</sub> CO <sub>3</sub>	5	76	18
15	PdCl <sub>2</sub> (CH <sub>3</sub> CN) <sub>2</sub>	Bi(OTf) <sub>3</sub>	NEt <sub>3</sub>	5	–	45
16	PdCl <sub>2</sub> (CH <sub>3</sub> CN) <sub>2</sub>	Bi(OTf) <sub>3</sub>	–	5	62	16
<b>17</b>	<b>PdCl<sub>2</sub>(CH<sub>3</sub>CN)<sub>2</sub></b>	<b>Bi(OTf)<sub>3</sub></b>	<b>K<sub>2</sub>CO<sub>3</sub></b>	<b>3</b>	<b>93</b>	<b>&lt;1</b>
18	PdCl <sub>2</sub> (CH <sub>3</sub> CN) <sub>2</sub>	Bi(OTf) <sub>3</sub>	K <sub>2</sub> CO <sub>3</sub>	2	81	<5
19 <sup>c</sup>	PdCl <sub>2</sub> (CH <sub>3</sub> CN) <sub>2</sub>	Bi(OTf) <sub>3</sub>	K <sub>2</sub> CO <sub>3</sub>	3	92	<1
20 <sup>d</sup>	PdCl <sub>2</sub> (CH <sub>3</sub> CN) <sub>2</sub>	Bi(OTf) <sub>3</sub>	K <sub>2</sub> CO <sub>3</sub>	3	85	<5
21 <sup>e</sup>	PdCl <sub>2</sub> (CH <sub>3</sub> CN) <sub>2</sub>	Bi(OTf) <sub>3</sub>	K <sub>2</sub> CO <sub>3</sub>	3	78	16
22 <sup>f</sup>	PdCl <sub>2</sub> (CH <sub>3</sub> CN) <sub>2</sub>	Bi(OTf) <sub>3</sub>	K <sub>2</sub> CO <sub>3</sub>	3	93	<1
23 <sup>e</sup>	PdCl <sub>2</sub> (CH <sub>3</sub> CN) <sub>2</sub>	Bi(OTf) <sub>3</sub>	K <sub>2</sub> CO <sub>3</sub>	5	86	10
24 <sup>g</sup>	PdCl <sub>2</sub> (CH <sub>3</sub> CN) <sub>2</sub>	Bi(OTf) <sub>3</sub>	K <sub>2</sub> CO <sub>3</sub>	3	93	<1
25 <sup>h</sup>	PdCl <sub>2</sub> (CH <sub>3</sub> CN) <sub>2</sub>	Bi(OTf) <sub>3</sub>	K <sub>2</sub> CO <sub>3</sub>	3	87	<5

The significance of bold in the table 1 shows the optimal reaction condition.

<sup>a</sup> Reaction conditions: benzyl alcohol (1 mmol), 5 mol% Pd catalyst, 5 mol% additive, base (1 mmol) and MeOH (2 mL), O<sub>2</sub>-balloon, 60 °C, 3 h.

<sup>b</sup> Determined by GC using internal standard.

<sup>c</sup> Reaction at 65 °C.

<sup>d</sup> Reaction at 55 °C.

<sup>e</sup> 3 mol% PdCl<sub>2</sub>(CH<sub>3</sub>CN)<sub>2</sub>.

<sup>f</sup> 10 mol% PdCl<sub>2</sub>(CH<sub>3</sub>CN)<sub>2</sub>.

<sup>g</sup> 0.2 eq. polymethylhydrosiloxane (PMHS) was added.

<sup>h</sup> Under air.

obtained in 87% yield. It was slightly lower than the reaction under oxygen.

With the optimal reaction condition in hand (Table 1, entry 17), the substrate scope and limitation of this catalytic system were examined. Firstly, we investigated the reaction of a variety of benzylic alcohols with MeOH under standard conditions (Table 2). To our delights, both electron-donating groups and electron-withdrawing groups were well tolerated in the reactions. As is shown in Table 2, primary benzylic alcohols bearing electron-donating groups such as methyl, methoxyl, *tert*-butyl proceeded smoothly to give the desired products in 79–96% yields. (**2b–2f**). However, the electron-withdrawing groups such as -F, -Cl, -NO<sub>2</sub> and -CF<sub>3</sub> substituted benzylic alcohols provided comparably low yields of the corresponding methyl esters (**2g–2l**). Halogenated benzyl alcohols (**1i**) were susceptible to dehydrohalogenation under standard conditions and lower reaction temperature was needed to obtain the product **2i**. Disubstituted benzylic alcohols were still suitable in this transformation with good efficiency (**2m** and **2n**). Of particular note was that benzylic alcohols bearing thioether, ester and amino functional groups were smoothly converted into the desired products in 72%, 69% and 43% yields, respectively (**2o–2q**). 4-Phenylbenzyl alcohol, 1-naphthalenemethanol and 2-naphthalenemethanol furnished the corresponding methyl esters in moderate to good yields (**2r–2t**). In

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