



## Palladium/NHC-catalyzed oxidative esterification of aldehydes with phenols

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### ABSTRACT

A palladium-catalyzed oxidative esterification of aldehydes with phenols is described, using air as the clean oxidant. This reaction tolerates many functional groups, providing esters with yields ranging from moderate to excellent.

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Carboxylic acid esters are not only important building blocks in the synthesis of natural and pharmacologically active compounds,<sup>1</sup> but are also used as protecting groups in synthesis.<sup>2</sup> Esters are generally prepared from acyl chlorides and mixed anhydrides, which are commonly derived from free carboxylic acids, or with carbodiimides, 1-hydroxybenzotriazoles and other expensive coupling agents.<sup>3</sup> Oxidative esterification has received increasing attention and has become an economical alternative to traditional ester synthesis.<sup>4</sup> Among these, the use of heterocyclic carbenes as catalysts provided elegant access to esters.<sup>5</sup> In 2008, we described an NHC-palladium-catalyzed aromatic esterification of aldehydes with organoboronic acids and molecular oxygen.<sup>6</sup> Subsequently, Gois disclosed the NHC-iron-catalyzed aerobic oxidative aromatic esterification of aldehydes with boronic acids.<sup>7</sup> The direct transformation of aldehydes with alcohols accessing esters would be attractive from an atom economic point of view. Recently, Rovis and Bode demonstrated the NHC-catalyzed oxidative esterifications of aldehydes with alcohols by the internal redox and in situ activation of  $\alpha$ -functionalized aldehydes, respectively.<sup>8</sup> However, the requirement of an  $\alpha$ -functional group in the aldehydes would greatly diminish the substrate scope. Accordingly, the NHC-catalyzed oxidative esterification of aldehydes with transition-metal based oxidants<sup>9</sup> or organic oxidants<sup>10</sup> has been investigated. Nevertheless, the excess or stoichiometry oxidant was used for the aforementioned transformation. Very recently, Studer reported the NHC-catalyzed oxidation of aldehydes to esters by quinone derivatives. The quinone derivatives could be recovered by air oxidation, rendering the process economically attractive.<sup>11</sup> However, to develop a facile and versatile procedure on such transformation still remains a highly desired goal for organic chemists. Herein, we report our study on the palladium/NHC-catalyzed oxidative esterification of aldehydes with phenols, which used air as the clean oxidant and did not require special functional group and oxidant.<sup>12</sup>

Initially, we studied the reaction of benzaldehyde (**1a**) with 4-nitrophenol (**2a**) as the model reaction for screening the reaction parameters (Table 1). To our delight, the product (**3aa**) was isolated in 48% yield by using the combination of Pd(OAc)<sub>2</sub> (5.0 mol %), **L1** as precursor of N-heterocyclic carbene (NHC) (Fig. 1) (5.0 mol %) and Na<sub>2</sub>CO<sub>3</sub> (3.0 equiv) in dry xylene at 100 °C under air. Ligand played a significant role in the esterification of aldehydes. After screening the imidazolium salts, we found that **L2** was better than other ligands, producing **3aa** in 74% yield (Table 1, entry 2). Increasing the amount of **L2** in the system had little influence on the yield. The yield greatly improved to 87% using 4 equiv of Na<sub>2</sub>CO<sub>3</sub> (Table 1, entry 6). However, the yield decreased to 68% when 5 equiv of Na<sub>2</sub>CO<sub>3</sub> was employed (Table 1, entry 7). Notably, Na<sub>2</sub>CO<sub>3</sub> gave a significantly higher yield than other inorganic bases (Table 1, entries 10–13). In the absence of base, product **3aa** could be gained in only 10% yield (Table 1, entry 8). A compatible yield was obtained under O<sub>2</sub>, however, the yield dramatically decreased to 25% under N<sub>2</sub> (Table 1, entry 6). This result indicated the air may serve as the terminal oxidant in the reaction. Next, the solvent effect was studied, and xylene was the best (Table 1, entries 14–17). Among the palladium species screened, Pd(OAc)<sub>2</sub> was superior to PdCl<sub>2</sub>, Pd<sub>2</sub>(dba)<sub>3</sub> and Pd(dppf)Cl<sub>2</sub> (Table 1, entries 18–20). The product **3aa** was isolated in 40% yield in the absence of Pd (Table 1, entry 21), suggesting that **L2** could catalyze the reaction to some extent. The NHC was essential for the esterification reaction since no product was observed without NHC (Table 1, entry 9). The employment of 1.5 equiv of benzaldehyde was optimal, since more or less amount of benzaldehyde resulted in decreased yields. Notably, the reaction conducted on a 10 mmol scale produced the esterification product **3aa** in 80% yield.

Having identified the optimal reaction conditions, the substituent effects of aldehydes were examined as shown in Figure 2. The aromatic esterification of aldehydes with phenols proceeded smoothly in good to excellent yields. The electronic properties of the substituents on the phenyl ring of aldehydes had some effect on the reaction. Generally, the aldehydes possessing electron-withdrawing groups gave slightly higher yields than those of

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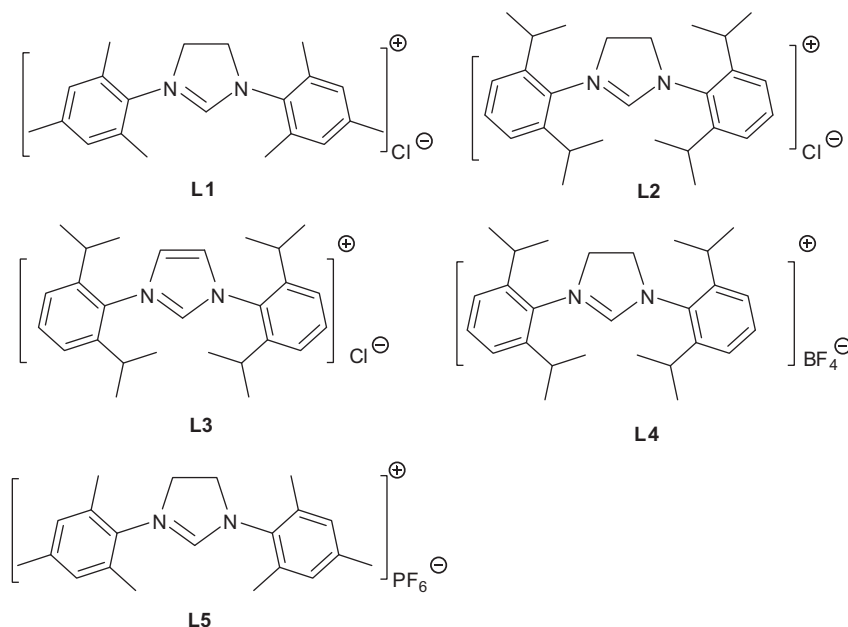


Figure 1. Pre-ligands evaluation using Pd(OAc)<sub>2</sub> as the Pd source.

Table 1  
Selected results of screening the optimal conditions

Entry	Pd sources	Ligand	Base (equiv)	Solvent	Yield <sup>a</sup> (%)
1	Pd(OAc) <sub>2</sub>	<b>L1</b>	Na <sub>2</sub> CO <sub>3</sub> (3.0)	Xylene	48
2	Pd(OAc) <sub>2</sub>	<b>L2</b>	Na <sub>2</sub> CO <sub>3</sub> (3.0)	Xylene	74
3	Pd(OAc) <sub>2</sub>	<b>L3</b>	Na <sub>2</sub> CO <sub>3</sub> (3.0)	Xylene	28
4	Pd(OAc) <sub>2</sub>	<b>L4</b>	Na <sub>2</sub> CO <sub>3</sub> (3.0)	Xylene	46
5	Pd(OAc) <sub>2</sub>	<b>L5</b>	Na <sub>2</sub> CO <sub>3</sub> (3.0)	Xylene	21
6	Pd(OAc) <sub>2</sub>	<b>L2</b>	Na <sub>2</sub> CO <sub>3</sub> (4.0)	Xylene	87(88) <sup>b</sup>
7	Pd(OAc) <sub>2</sub>	<b>L2</b>	Na <sub>2</sub> CO <sub>3</sub> (5.0)	Xylene	68
8	Pd(OAc) <sub>2</sub>	<b>L2</b>	–	Xylene	10(8) <sup>c</sup>
9	Pd(OAc) <sub>2</sub>	–	Na <sub>2</sub> CO <sub>3</sub> (4.0)	Xylene	<5
10	Pd(OAc) <sub>2</sub>	<b>L2</b>	Cs <sub>2</sub> CO <sub>3</sub> (3.0)	Xylene	40
11	Pd(OAc) <sub>2</sub>	<b>L2</b>	K <sub>2</sub> CO <sub>3</sub> (3.0)	Xylene	<5
12	Pd(OAc) <sub>2</sub>	<b>L2</b>	NaHCO <sub>3</sub> (3.0)	Xylene	71
13	Pd(OAc) <sub>2</sub>	<b>L2</b>	<i>t</i> -BuOK(4.0)	Xylene	36
14	Pd(OAc) <sub>2</sub>	<b>L2</b>	Na <sub>2</sub> CO <sub>3</sub> (4.0)	DMF	<5
15	Pd(OAc) <sub>2</sub>	<b>L2</b>	Na <sub>2</sub> CO <sub>3</sub> (4.0)	Toluene	65
16	Pd(OAc) <sub>2</sub>	<b>L2</b>	Na <sub>2</sub> CO <sub>3</sub> (4.0)	DCE	36
17	Pd(OAc) <sub>2</sub>	<b>L2</b>	Na <sub>2</sub> CO <sub>3</sub> (4.0)	CH <sub>2</sub> Cl <sub>2</sub>	30
18	PdCl <sub>2</sub>	<b>L2</b>	Na <sub>2</sub> CO <sub>3</sub> (4.0)	Xylene	68
19	Pd <sub>2</sub> (dba) <sub>3</sub>	<b>L2</b>	Na <sub>2</sub> CO <sub>3</sub> (4.0)	Xylene	45
20	Pd(dppf)Cl <sub>2</sub>	<b>L2</b>	Na <sub>2</sub> CO <sub>3</sub> (4.0)	Xylene	72
21	–	<b>L2</b>	Na <sub>2</sub> CO <sub>3</sub> (4.0)	Xylene	40

<sup>a</sup> All reactions were run with 4-nitrophenol (0.2 mmol), benzaldehyde (0.3 mmol, 1.5 equiv), base (3.0–5.0 equiv), Pd source (5 mol %) and ligand (5 mol %) in 2 mL of dry solvent under air at 100 °C in a sealed reaction tube for 24 h. Isolated yield.

<sup>b</sup> Under O<sub>2</sub>.

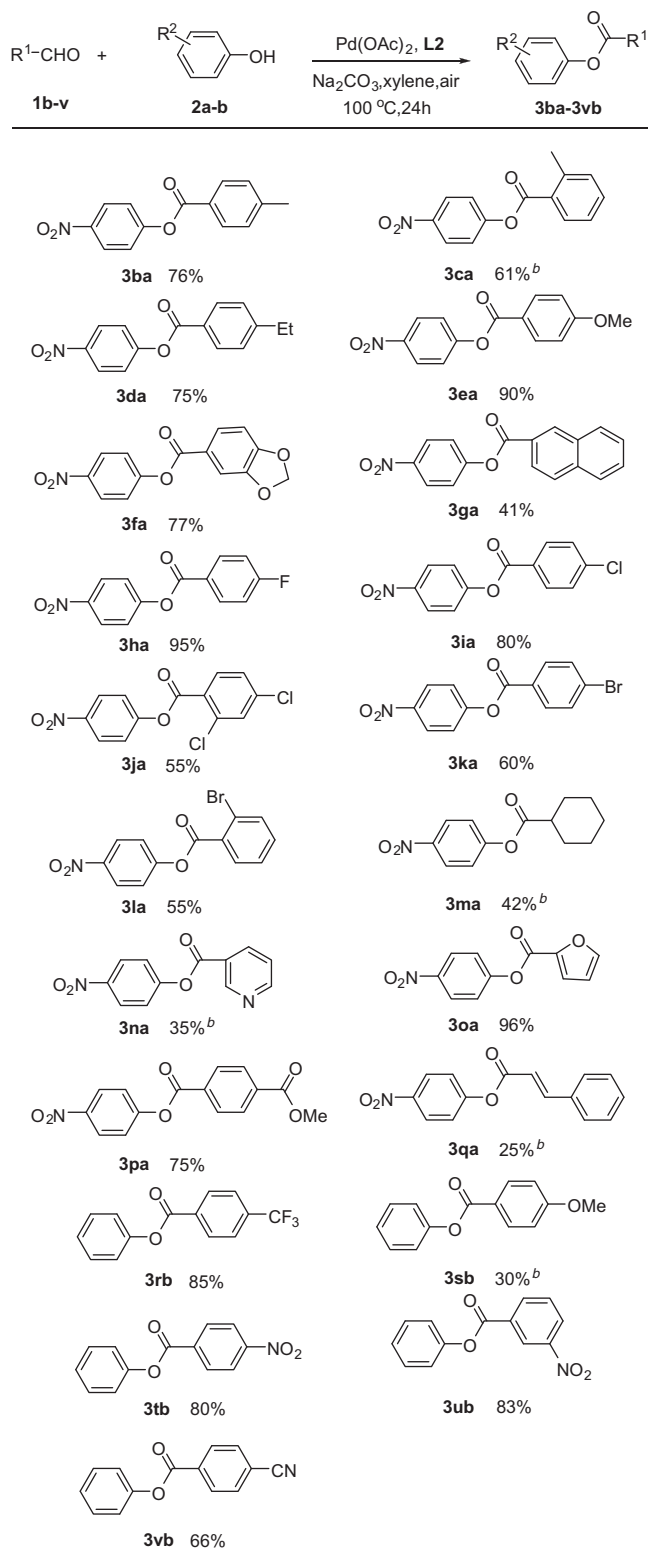
<sup>c</sup> Under N<sub>2</sub>.

electron-donating groups (**3rb**, **3tb**, **3ub** and **3vb** vs **3ba**, **3ca**, **3da**, **3ga** and **3sb**, Fig. 2). Especially, piperonal and anisaldehyde reacted with 4-nitrophenol to produce esters in 90% and 77% yields, respectively (**3fa** and **3ea**, Fig. 2). Notably, halogens were tolerated well under the reaction conditions. For example, **3h**, **3i** and **3k**

delivered the esterification products in moderate to excellent yields (**3ha**, **3ia** and **3ka**, Fig. 2). Importantly, the hindrance of the phenyl ring of aldehydes had a slight effect on the efficiency (**3ba**, **3ia** and **3ka** vs **3ca**, **3ja** and **3la**, Fig. 2). As expected, trifluoromethyl and methoxycarbonyl groups on the phenyl ring were compatible under the reaction conditions (**3pa** and **3rb**, Fig. 2). Several aliphatic aldehydes, such as *n*-butyraldehyde, cyclohexyl aldehyde, acetaldehyde, acrylaldehyde were subjected to the standard procedure; however, only cyclohexyl aldehyde underwent the direct esterification with **1a**, forming **3ma** in 42% yield. Furthermore, furan formaldehyde worked extremely well to give **3oa** in 96% yield. Pyridine aldehyde and cinnamic aldehyde could also afford the products **3na** and **3qa**, albeit in low yields. As such, this method appeared to be versatile and might provide potential opportunities in complex esterifications possessing interesting biological and pharmacological properties.

Next, this protocol was extended to different phenols as shown in Table 2. Once again, the reaction proceeded smoothly and tolerated various functional groups such as nitro, cyano, acetamido, trifluoromethyl, iodo, bromo, chloro, fluoro and methoxy groups on the phenyl ring of phenols and afforded the products in moderate to good yields. Generally, the phenols possessing electron-withdrawing functional groups were found to give better yields than those with electron-donating groups (Table 2, entries 1 and 15 vs 2, 3 and 5). The *ortho*-substitution in the phenols resulted in lower yields, indicating steric hindrance on the phenol affected the efficiency (Table 2, entries 4, 6, 18 and 12 vs 3, 5 and 11). Importantly, halo groups on the phenyl ring of phenols survived under the standard procedure (Table 2, entries 10–14). It is notable that on one hand aryl halogen (Cl, Br, I) substrates are often highly reactive in Pd catalytic cycles and on the other hand the bromide and iodide products could be easily further elaborated. It is noteworthy that an alkenyl and acetamido also underwent the direct esterification with **1a**, forming **3ah** and **3ap** in 43% and 60% yields, respectively (Table 2, entries 8 and 16). Disappointingly, the highly crowded **2q** failed to deliver the esterification product (Table 2, entry 18).

More experiments were carried out to gain preliminary insight into the reaction mechanism. No conversion of benzaldehyde to



**Figure 2.** Palladium-catalyzed esterification of aldehydes with 4-nitrophenol or phenol (a) All reactions were run with phenols (0.2 mmol), aldehydes (0.3 mmol, 1.5 equiv),  $\text{Na}_2\text{CO}_3$  (4.0 equiv),  $\text{Pd(OAc)}_2$  (5 mol %) and **L2** (5 mol %) in 2 mL of dry xylene under air at 100 °C in a sealed reaction tube for 24 h. Isolated yield; (b) 48 h.

benzoic acid was observed under the standard procedure. Furthermore, when benzoic acid instead of benzaldehyde was subjected to the standard procedure, no ester product was formed. These results ruled out the possibility of a cascade oxida-

**Table 2**  
Reaction of benzaldehyde with phenols

$$\text{C}_6\text{H}_5\text{-CHO} + \text{R}^2\text{-C}_6\text{H}_4\text{-OH} \xrightarrow[\text{Na}_2\text{CO}_3, \text{xylene, air, 100 }^\circ\text{C, 24 h}]{\text{Pd(OAc)}_2, \text{L2}} \text{C}_6\text{H}_5\text{-O-CO-C}_6\text{H}_4\text{-R}^2$$

**1a** + **2a-q** → **3aa-3aq**

Entry	Phenol 2	Product 3	Yield <sup>a</sup> (%)
1		<b>3aa</b>	87
2		<b>3ab</b>	75
3		<b>3ac</b>	79
4		<b>3ad</b>	50
5		<b>3ae</b>	90
6		<b>3af</b>	50
7		<b>3ag</b>	93
8		<b>3ah</b>	43
9		<b>3ai</b>	94
10		<b>3aj</b>	82
11		<b>3ak</b>	94
12		<b>3al</b>	87
13		<b>3am</b>	97
14		<b>3an</b>	98
15		<b>3ao</b>	99
16		<b>3ap</b>	60
17		<b>3aq</b>	<5

<sup>a</sup> All reactions were run with phenols (0.2 mmol), benzaldehyde (0.3 mmol),  $\text{Na}_2\text{CO}_3$  (4.0 equiv),  $\text{Pd(OAc)}_2$  (5 mol %) and **L2** (5 mol %) in 2 mL of dry xylene under air at 100 °C in a sealed reaction tube for 24 h. Isolated yield.

tion of aldehyde to carboxylic acid followed by an esterification pathway.

In conclusion, we have developed an efficient palladium-NHC catalyzed aromatic esterification reaction between aldehydes and phenols under air. It represents a simple method for the synthesis of functionalized esters from the numerous commercially available aldehydes and phenols. Indeed, this method might have potential application in the synthesis of complex natural compounds. Works focusing on exploring further insights into the mechanism of the reaction and expanding the reaction scope are ongoing in our laboratory.<sup>13</sup>

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.tetlet.2011.03.017](https://doi.org/10.1016/j.tetlet.2011.03.017).

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- Gois reported that the combination of NHC and iron(II) could catalyze the reaction of aldehyde and phenol. Phenyl benzoate was isolated in 88% yield, see Ref 7.
- General Procedure:** Under air atmosphere, a sealed reaction tube was charged with 4-nitrophenol (0.2 mmol), benzaldehyde (0.3 mmol), Pd(OAc)<sub>2</sub> (2.3 mg, 5 mol %), **L2** (4.3 mg, 5 mol %), Na<sub>2</sub>CO<sub>3</sub> (84.8 mg, 4.0 equiv), and dry xylene (2 mL). The mixture was stirred at 100 °C for 24 h. After the completion of the reaction, as monitored by TLC, the solvent was concentrated in vacuo and the residue was purified by flash column chromatography on silica gel (300–400 mesh) with petroleum ether–EtOAc as eluent to give the product.