



## Chelation-assisted palladium-catalyzed acyloxylation of benzyl $sp^3$ C–H bonds using $\text{PhI}(\text{OAc})_2$ as oxidant

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### ABSTRACT

A chelation-assisted palladium-catalyzed acyloxylation of the  $sp^3$  C–H bond of benzyl by carboxylic acid is described, which employs  $\text{PhI}(\text{OAc})_2$  as a stoichiometric oxidant. The procedure tolerates a series of functional groups, such as methoxyl, chloro, bromo, iodo, vinyl, formyl, phenolic hydroxyl, nitro, and cyano groups, providing the acyloxylation products in moderate to good yields.

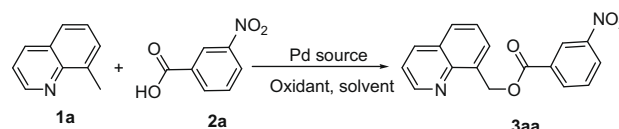
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Transition-metal-catalyzed direct C–H bond functionalization has become a versatile synthetic method for the regional oxidation of organic molecules.<sup>1</sup> Recently, much attention has been paid to the development of regioselective C–O bond formation via C–H cleavage.<sup>2</sup> In 2006, Yu reported  $\text{Cu}(\text{OAc})_2$ -catalyzed oxidative acetoxylation of arene C–H bonds using oxygen as terminal oxidant.<sup>3</sup> Recently, Sanford reported a detailed study of C–O reductive elimination from palladium(IV) complexes via arene C–H bond functionalization.<sup>4</sup> Very recently, we also developed an efficient chelation-assisted rhodium-catalyzed *ortho*-acyloxylation of the  $sp^2$  C–H bond.<sup>5</sup> However, examples of C–O bond-forming reaction through  $sp^3$  C–H bond cleavage were rarely reported before and were almost limited to acetoxylation.<sup>6</sup> Furthermore, from the synthetic point of view, it is more cost-efficient to directly employ the inexpensive carboxylic acid as reaction partner in  $sp^3$  C–H acyloxylation reaction. Herein, we wish to report a chelation-assisted palladium-catalyzed acyloxylation of benzyl  $sp^3$  C–H bond employing  $\text{PhI}(\text{OAc})_2$  as a stoichiometric oxidant.

Initially, we investigated the reaction of 3-nitrobenzoic acid and 8-methyl quinoline using  $\text{Pd}(\text{OAc})_2$  as the catalyst (Table 1). The oxidant had a dramatic effect on the reaction. Among the oxidant tested, Oxone, BQ, and  $\text{O}_2$  were totally ineffective for this transformation (Table 1, entries 1–3), and  $\text{Cu}(\text{OAc})_2$  and  $\text{CuBr}_2$  also showed less reactivity (Table 1, entries 4 and 6). On the contrary, the yield of **3aa** could increase to 50% using  $\text{K}_2\text{S}_2\text{O}_8$  (Table 1, entry 5). To our delight,  $\text{PhI}(\text{OAc})_2$  which was a versatile oxidant in Pd(IV)-mediated C–H functionalization<sup>7,8</sup> turned out to be the best (Table 1, entry 7), and the yield of **3aa** was sharply increased to 90% with the same condition. Moreover, the mono-acyloxylation product was mainly obtained. Replacing toluene with other solvents such as 1,4-dioxane, DMF, NMP, and xylene decreased the yield (Table 1, entries 8–11). Further studies revealed that other Pd(II) and Pd(0)

catalysts were inferior to  $\text{Pd}(\text{OAc})_2$  (Table 1, entries 12–14), and no product was observed in the absence of Pd(II) (Table 1, entry 15). The reaction conducted on a 5 mmol scale could gain the acyloxylation product **3aa** in 82% yield. Moreover, this transformation is very practical, for it does not need the strong bases or expensive ligands and the rigorous exclusion of air and moisture was also not required.

**Table 1**  
Selected results of screening the optimal conditions



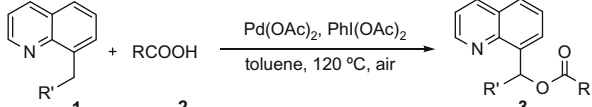
Entry	Pd source	Oxidant	Solvent	Yield <sup>a</sup> (%)
1	$\text{Pd}(\text{OAc})_2$	Oxone	Toluene	<5
2	$\text{Pd}(\text{OAc})_2$	BQ	Toluene	<5
3	$\text{Pd}(\text{OAc})_2$	$\text{O}_2$	Toluene	<5
4	$\text{Pd}(\text{OAc})_2$	$\text{Cu}(\text{OAc})_2$	Toluene	15
5	$\text{Pd}(\text{OAc})_2$	$\text{K}_2\text{S}_2\text{O}_8$	Toluene	50
6	$\text{Pd}(\text{OAc})_2$	$\text{CuBr}_2$	Toluene	15
7	$\text{Pd}(\text{OAc})_2$	$\text{PhI}(\text{OAc})_2$	Toluene	90
8	$\text{Pd}(\text{OAc})_2$	$\text{PhI}(\text{OAc})_2$	Dioxane	40
9	$\text{Pd}(\text{OAc})_2$	$\text{PhI}(\text{OAc})_2$	DMF	40
10	$\text{Pd}(\text{OAc})_2$	$\text{PhI}(\text{OAc})_2$	NMP	55
11	$\text{Pd}(\text{OAc})_2$	$\text{PhI}(\text{OAc})_2$	Xylene	45
12	$\text{PdCl}_2$	$\text{PhI}(\text{OAc})_2$	Toluene	78
13	$\text{Pd}_2(\text{dba})_3$	$\text{PhI}(\text{OAc})_2$	Toluene	77
14	$\text{Pd}(\text{OCOCF}_3)_2$	$\text{PhI}(\text{OAc})_2$	Toluene	70
15		$\text{PhI}(\text{OAc})_2$	Toluene	<5

<sup>a</sup> All reactions were run with 8-methylquinoline (0.2 mmol), 3-nitrobenzoic acid (0.4 mmol), Pd source (10 mol %), oxidant (0.2 mmol), dry solvent (2 mL), air, 120 °C, 24 h. Isolated yield.

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**Table 2**  
Acyloxylation of 8-methyl quinoline with carboxylic acids



Entry	R	R'	Product	Yield <sup>a</sup> (%)
1		H (1a)	<b>3aa</b>	90
2		1a	<b>3ab</b>	76
3		1a	<b>3ac</b>	61
4		1a	<b>3ad</b>	67
5		1a	<b>3ae</b>	81
6		1a	<b>3af</b>	70
7		1a	<b>3ag</b>	77
8		1a	<b>3ah</b>	69
9		1a	<b>3ai</b>	70
10		1a	<b>3aj</b>	58
11		1a	<b>3ak</b>	83
12		1a	<b>3al</b>	73
13		1a	<b>3am</b>	59
14		1a	<b>3an</b>	93
15		1a	<b>3ao</b>	81
16	EtCOOH	1a	<b>3ap</b>	65
17		Ph (1b)	<b>3ba</b>	62

<sup>a</sup> Reaction conditions: **1** (0.2 mmol), **2** (0.4 mmol), Pd(OAc)<sub>2</sub> (10 mol %), PhI(OAc)<sub>2</sub> (0.2 mmol), dry toluene (2 mL), air, 120 °C, 24 h. Isolated yield.

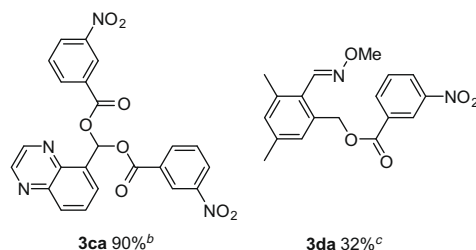
Finally, we found the optimized conditions for this chelation-assisted sp<sup>3</sup> C–H acyloxylation as following: 10 mol % of Pd(OAc)<sub>2</sub> as the catalyst, and a 1:2 mol ratio of 8-methyl quinoline and carboxylic acid substrates in dry toluene in the presence of one equivalent of PhI(OAc)<sub>2</sub> at 120 °C for 24 h.

With the optimized conditions in hand, we explored the scope of the reaction of carboxylic acids with 8-methyl quinoline (Table 2). As expected, all carboxylic acids worked well under the reaction condition. Generally, the arene carboxylic acids possessing electron-withdrawing functional groups were found to give higher yields than those of electron-donating groups (Table 2, entries 1, 11, 12, 14 vs 2, 3, 4, 5). A wide range of functional groups, including methoxy, chloro, bromo, iodo, vinyl, cyano, formyl, nitro, and phenolic hydroxyl groups, were well tolerated in the reaction. Steric hindrance of the carboxylic acids had slight effect on the efficiency. For example, **3ad** and **3ae** were isolated in 67% and 81%, respectively (Table 2, entries 4 and 5). Importantly, the halo groups on the phenyl ring of arene carboxylic acids survived in the procedure (Table 2, entries 6–9). It is remarkable that the aryl halogen (Cl, Br, and I) was a compatible substrate in this transformation, as C–Cl/Br/I of the product could be further functionalized. Moreover, the C–halogen bond is quite sensitive under a Pd<sup>0/II</sup> catalytic cycle. It is also worth noting that hetero-arene, alkenyl, and alkyl carboxylic acids also worked well under the standard reaction condition (Table 2, entries 10, 15, and 16). Particularly, the formyl group was compatible in the presence of PhI(OAc)<sub>2</sub>, and **3al** was isolated in 73% yield. 8-Benzyl quinoline **1b** was subjected to the procedure, delivering **3ba** in 62% yield (Table 2, entry 17).

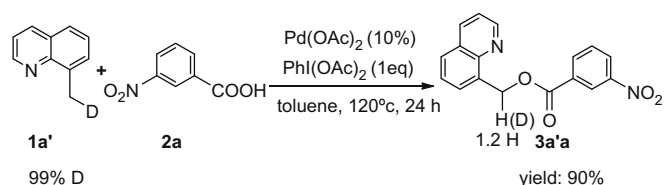
Next, the acyloxylation of other substrates with carboxylic acids was investigated (Fig. 1). To our delight, the di-acyloxylation product **3ca** was formed with excellent yield. Particularly, the product of **3da** could be gained in moderate yield. As such, it represents a general and versatile chelation-assisted acyloxylation of benzyl sp<sup>3</sup> C–H bond.

The intramolecular isotope kinetic effect of benzyl was studied (Scheme 1). The *k<sub>H</sub>/k<sub>D</sub>* was found to be 2.0, indicating slow C–H bond activation.

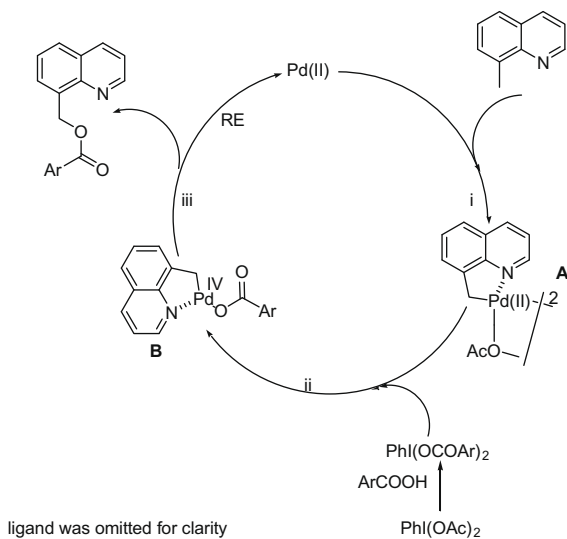
Based on the experimental and the well-established Pd(IV)-mediated C–H functionalization using PhI(OAc)<sub>2</sub> as an oxidant,<sup>7,8</sup>



**Figure 1.** Acyloxylation of other substrates. <sup>a</sup> Reaction conditions: **1** (0.2 mmol), **2** (0.4 mmol), Pd(OAc)<sub>2</sub> (10 mol %), PhI(OAc)<sub>2</sub> (0.2 mmol), dry toluene (2 mL), air, 120 °C, 24 h. Isolated yield. <sup>b</sup> **2** (0.8 mmol), PhI(OAc)<sub>2</sub> (0.4 mmol). <sup>c</sup> O<sub>2</sub>, 130 °C, 36 h.



**Scheme 1.** Kinetic isotope effect study.



Scheme 2. Plausible mechanism.

a plausible mechanism was outlined in Scheme 2. To start with, step (i) involves the chelation-assisted  $sp^3$  C–H activation of benzyl to form a cyclopalladated intermediate A. Secondly, the Pd(II) intermediate A is oxidized by  $\text{PhI}(\text{OCOAr})_2$ , which derives from the reaction of  $\text{PhI}(\text{OAc})_2$  and  $\text{ArCOOH}$ ,<sup>9</sup> to form a Pd(IV) intermediate B. Finally, in step (iii), the reductive elimination of the Pd(IV) intermediate B takes place to deliver the acyloxylation product and regenerates Pd(II) species. It should be noted that a mechanism of Pd(0)/Pd(II) cycle could not be completely excluded.<sup>10</sup>

In summary, we have developed a general and efficient chelation-assisted palladium-catalyzed acyloxylation reaction of the benzyl  $sp^3$  C–H bond, providing the mono or di-acyloxylation products in moderate to good yields. Works focusing on exploring further insights into the mechanism of the reaction and expanding the reaction scope to unactivated  $sp^3$  C–H in more substrates are ongoing in our laboratory.<sup>11</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.2010.04.075.

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- General procedure*: Under air atmosphere, a reaction tube was charged with substrates (0.2 mmol), carboxylic acid (0.4 mmol),  $\text{Pd}(\text{OAc})_2$  (4.5 mg, 10 mol %),  $\text{PhI}(\text{OAc})_2$  (64.4 mg, 1 equiv), and dry toluene (2 mL). The mixture was stirred at 120 °C for 24 h. After 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 to give the desired product.