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Palladium catalyzed amide-oxazoline directed C–H acetoxylation of arenes†

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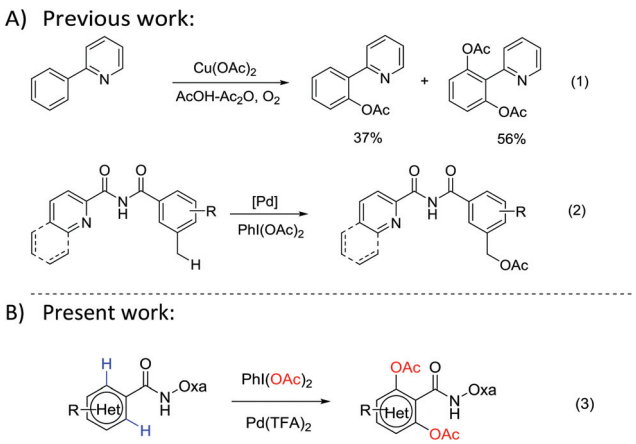
Herein we reported a Pd-catalyzed *ortho*-acetoxylation of arenes through a six-membered system using an amide-oxazoline as the directing group. A wide range of aryls and heteroaryls are tolerated. The approach provides general and straightforward access to phenol esters without the need for extra oxidants.

The direct acetoxylation of a C–H bond into a C–O bond has attracted considerable attention in recent years due to the industrially important roles of phenol or ester compounds.[1] For example, both of them are key structural motifs in numerous drugs, carbohydrates and natural products. Transition-metal-catalyzed C–H bond activation is a new strategy for the step-economical synthesis. It can be used for the direct modification of many biologically important molecules without prefunctionalization.[2] Pd-catalyzed pyridine-directed acetoxylation of the C–H bond was first demonstrated by Sanford and co-workers in 2004.[3] Later, Yu *et al.*[4] reported various Cu-mediated *ortho*-acetoxylations of aryl C–H bonds, which showed high regio-selectivity and efficiency (Scheme 1, eqn (1)). Thereafter, various directing groups (DGs) such as pyridine,[5] amine,[6] oxime[7] and carbonyl[8] have been used in the transition-metal-catalyzed C–H activation. Despite these advances, the directed acetoxylation has been rarely used for aryls. In addition, the directing groups are hard to be removed after the reaction. Recently, Zhang[9] reported a Pd-catalyzed oxidative acetoxylation of the benzylic C(sp^3)–H bond with PhI$(OAc)_2$ as an oxidant (Scheme 1, eqn (2)). Meanwhile, Liang[10] also demonstrated the Pd-catalyzed acetoxylations with amide-pyridine and Daugulis amide-quinoline[11] as DGs. However, longer reaction times and higher reaction temperatures are required in these acetoxylations. Moreover, electron-deficient arenes and heteroarenes have not been demonstrated. Therefore, an efficient synthesis pathway under milder conditions is still a challenge.

Very recently, Yu reported an amide-tethered oxazoline as a directing group (DG).[12] It can form a six-membered bis-dentate complex with Cu(II) or Pd(II),[13] which is different from the amide-quinoline DG. In the present work, we propose a direct *ortho*-acetoxylation of amide-tethered oxazoline through



Scheme 1 Transition-metal-catalyzed acetoxylation of C–H bonds.

the Pd$(TFA)_2$-catalyzed C–H activation in aromatic rings and heteroaryl amides with PhI$(OAc)_2$ as both the oxidant and acetate source (Scheme 1, eqn (3)).

Amide (**1a**) was prepared from the acylation of benzoyl chloride and 2-(2-oxazolyl)aniline and used as the substrate. In our initial study, iodobenzene diacetate (**2a**) was used as the AcO source (Table 1). However, no desired product **3a** was observed by treating **1a** with **2a** in the presence of Cu$(OAc)_2$ (1 equiv.) in *o*-xylene at 100 °C (Table 1, entry 1). Product **3a** was formed in 20% yield with Pd$(OAc)_2$ as the catalyst under the same conditions (Table 1, entry 2). Its yield was slightly increased when the reaction temperature was increased to 130 °C (Table 1, entry 3). Other metal catalysts including Co$(OAc)_2$, Mn$(OAc)_3{\cdot}2H_2O$, Ni$(OAc)_2$, $Rh_2(OAc)_4$, CuCl, $InCl_3$ and Fe$(acac)_3$ showed no catalytic activity for the reaction, indicating the unique catalytic ability of Pd in this transformation reaction (Table 1, entry 4). Therefore, a series of Pd salts including Pd$(CH_3CN)_2Cl_2$, Pd$(acac)_2$, Pd$(PPh_3)_2Cl_2$ and Pd$(TFA)_2$ were screened (Table 1, entries 5–8). All of them showed catalytic activity for the transformation reaction and Pd$(TFA)_2$

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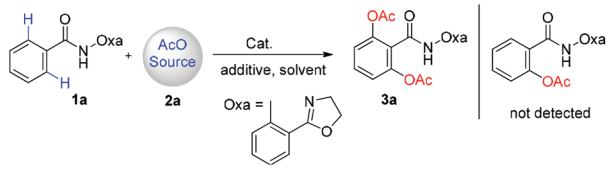
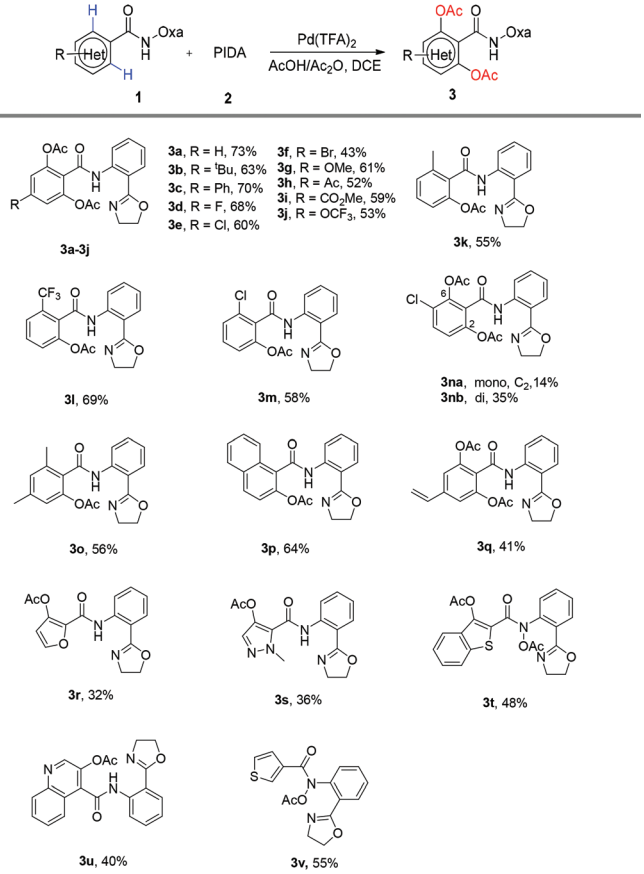
Table 1 Optimization of the reaction conditions[a]



Entry	Cat.	Solvent	AcO source	Yield **3a** (%)
1	$Cu(OAc)_2$	*o*-Xylene	PIDA	N.R.
2[b]	$Pd(OAc)_2$	*o*-Xylene	PIDA	20
3	$Pd(OAc)_2$	*o*-Xylene	PIDA	29
4[c]	Other metals	*o*-Xylene	PIDA	N.R.
5	$Pd(CH_3CN)_2Cl_2$	*o*-Xylene	PIDA	28
6	$Pd(acac)_2$	*o*-Xylene	PIDA	18
7	$Pd(PPh_3)_2Cl_2$	*o*-Xylene	PIDA	25
8	$Pd(TFA)_2$	*o*-Xylene	PIDA	40
9	$Pd(TFA)_2$	DMF	PIDA	N.R.
10	$Pd(TFA)_2$	DMSO	PIDA	N.R.
11	$Pd(TFA)_2$	Chlorobenzene	PIDA	25
12	$Pd(TFA)_2$	DCE	PIDA	62
13[d]	$Pd(TFA)_2$	DCE	$Cu(OAc)_2$	N.R.
14[d]	$Pd(TFA)_2$	DCE	AgOAc	N.R.
15[d]	$Pd(TFA)_2$	DCE	$AcOH/Ac_2O$	Trace
16[e]	$Pd(TFA)_2$	DCE	PIDA + additive	73
17[f]	$Pd(TFA)_2$	DCE	PIDA + additive	55
18	—	DCE	PIDA + additive	N.R.

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.5 mmol), catalyst (0.02 mmol), additive (0.2 mmol) in solvent (3 mL) was stirred at 130 °C for 10 h in a sealed tube. [b] The temperature used was 100 °C. [c] Other metals: $Co(OAc)_2$, $Mn(OAc)_3{\cdot}2H_2O$, $Ni(OAc)_2$, $Rh_2(OAc)_4$, CuCl, $InCl_3$, $Fe(acac)_3$ respectively. [d] Different AcO sources (2.5 eq.) were added. [e] $AcOH/Ac_2O$ = 1 : 2 (1 eq.) or PhCOOH (1 eq.) was added as the additive. [f] 5% of the catalyst was employed.

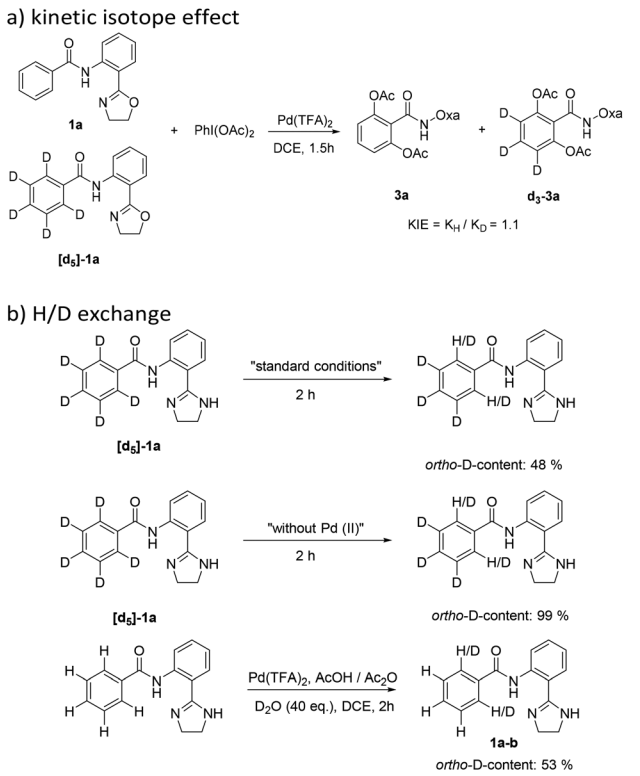
Table 2 Transformations of benzamide substrates[a,b]



[a] Reaction conditions: a mixture of **1a** (0.2 mmol), **2a** (0.5 mmol), $Pd(TFA)_2$ (0.02 mmol), $AcOH/Ac_2O$ (1 : 2) (0.2 mmol) in DCE (3 mL) was stirred at 130 °C for 10 h in a sealed tube. [b] Isolated yield.

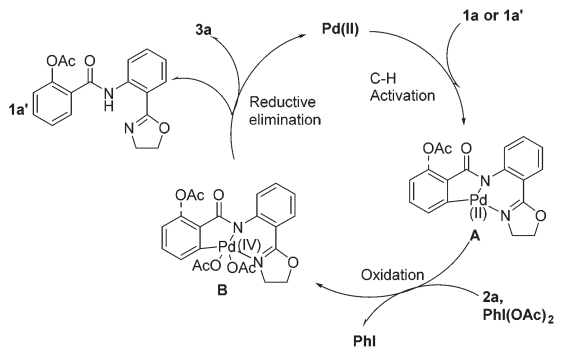
gave the highest yield of 40% (Table 1, entry 8). With $Pd(TFA)_2$ as the catalyst, various solvents were tested (Table 1, entries 9–12). The results indicate that no desired product can be formed in aprotic polar solvents, such as DMF and DMSO (Table 1, entries 9–10). A small amount of the product was observed with chlorobenzene as the reaction solvent (Table 1, entry 11). DCE is the best solvent for the reaction in which **3a** was formed in 62% yield (Table 1, entry 12). Next, different AcO sources including $Cu(OAc)_2$, AgOAc and $AcOH/Ac_2O$ were investigated (Table 1, entries 13–15). It is noteworthy that only a trace amount of product **3a** was observed with $AcOH/Ac_2O$ (1 : 2) as the AcO source (Table 1, entry 15). Meanwhile, the yield of **3a** was significantly increased to 73% with both PIDA and additive added (Table 1, entry 16). The yield of **3a** decreased to 55% when the catalyst loading was decreased to 5 mol% (Table 1, entry 17). No desired product was obtained in the absence of the Pd catalyst (Table 1, entry 18).

Next, various benzamide substrates were tested under the optimized reaction conditions (Table 1, entry 16). As shown in Table 2, the transformations of most functionalized benzamides were able to produce the desired products **3** under the optimized reaction conditions. Both electron-donating and electron-withdrawing groups on the phenyl ring are compatible with the transformation reaction. The transformation reaction can be applied to compound **1** with a variety of substituents including alkyl, aryl, halo (F, Cl, Br), methoxy, acetyl, ester and trifluoromethoxy to afford the desired products (**3a–3j**) in moderate to good yields (43%–73%). Remarkably, the reaction with *ortho*-substituted **1** as a substrate afforded mono-products **3k–3m** and **3o–3p** in similar yields. For the *meta*-substituted substrate **1n**, the double *ortho*-acetoxylation product (**3nb**) was major and only a small amount of the mono *ortho*-acetoxylation product (**3na**) was separated. The vinylated arene can still be transformed into **3q** in 41% yield. It is worth noting that heterocyclic substrates, including furan, pyrazole, benzothiophene and quinoline, were also transformed into **3r–3u** in 32%–55% yields, respectively. To the best of our knowledge the *ortho*-acetoxylation of these heterocycles with other directing groups has not yet been reported. Interestingly, substrate **1t** with benzothiophene produced not only the expected acetoxylation, but also *N*-acetoxylation, affording the product **3t** in a moderate yield, and the substrate **1v** with thiophene gave only the *N*-acetoxylation product **3v**. Further work is needed to understand these two transformations.



Scheme 2 Determination of the kinetic isotope effect and H/D exchange.

To further understand the catalytic cycle of the reaction, a 1 : 1 mixture of **1a** and **[d$_5$]-1a** was used as a substrate and transformed under the optimized reaction conditions (Scheme 2(a)). No kinetic isotopic effects (KIEs $\approx$ 1.0) were observed, suggesting that C–H activation of arenes might not be a rate-limiting step. Furthermore, control experiments were designed (Scheme 2(b)), in which H/D exchange was clearly observed in the reaction of **[d$_5$]-1a**. Meanwhile, with the excess introduction of D_2O, the deuterated product **1a–b** was obtained (52% D incorporation). These observations suggest that the C–H activation step is reversible.



Scheme 3 Proposed mechanism.

Although details about the mechanism remain to be ascertained, based on the previous reports[13,14] and above results, a plausible mechanism for the Pd-catalyzed transformation is proposed (Scheme 3). The catalytic cycle starts with an initial C–H bond activation of **1a** (**1a′**), followed by the oxidation of palladium (II–IV) complex **A–B**, which undergoes reductive elimination to afford product **1a′** followed by another catalytic cycle to produce **3a**.

Conclusions

In summary, we have developed a Pd(II) catalyzed *ortho*-acetoxylation of arenes including heterocycles, with $PhI(OAc)_2$ as both the AcO source and oxidant. This synthesis pathway provides a new strategy for the *ortho*-acetoxylation of aryl compounds with high regio-selectivity. Further investigations and applications of this reaction are currently underway in our laboratory.

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