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Pd-Catalyzed Direct and Selective C–H Functionalization: C3-Acetoxylation of Indoles

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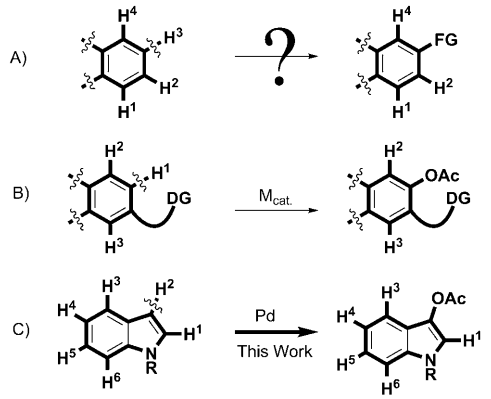
Direct functionalization of C–H bonds has been a hot topic in organic chemistry during recent years.[1–11] Arenes—one of the most abundant chemical motifs—usually have multiple C–H bonds. Although, some examples of direct functionalizations of arenes have been reported recently,[1,3] the selectivity of C–H bond activation remains a challenge (Scheme 1 A).[5] Several strategies have been applied to achieve selective C–H activation; these mainly included *ortho*-directing groups[12–14] or selective deprotonation–metallation.[15–17]



Scheme 1. Selectivities of direct C–H functionalizations of arenes: A) without and B) with a directing group as well as C) the approach used herein. FG = functional group; DG = directing group; the wavy lines highlight the chemical bonds involved in C–H activation process and represent the neglected structures in the molecules.

By employing the directing-group strategy (Scheme 1 B), direct acetoxylation of arene C–H bonds has received considerable attention during the past few years.[5] Pioneered by Sanford et al., Pd-catalyzed acetoxylation of arenes directed by, for example, pyridine, imine, or amides groups were reported recently.[17,22–26] Yu et al. also described a nice Cu-catalyzed acetoxylation of arenes directed by pyridine.[27] Even for traditional C–O cross-coupling reactions that employ ArX as the electrophile, efficient examples are rare.[18–21]

On the other hand, the electrophilic palladation of indole derivatives first takes place in a selective manner (in C3-position) and then the C2-isomer is formed from the 1,2-migration of the C3-isomer.[30] Due to our interest in Pd^{IV} chemistry,[31,32] we envisioned that, in the presence of appropriate oxidant, the C3–Pd^{II} species could be easily oxidized, owing to the existence of a carbon anion as a δ-donor and the proposed direct and selective acetoxylation of indole derivatives could be accomplished (Scheme 1 C).

Indole derivatives are of great scientific interest on account of their biological activities.[33–36] 3-Acetoxyindole is a useful compound for the detection of acetylcholinesterase in tissue slices and this technique can also be applied in serum.[37] Many C–C bond formation reactions involving indole derivatives as nucleophiles have been studied.[30,38] However, to the best of our knowledge, no examples for direct and selective C3-acetoxylation of indole derivatives have been disclosed. In addition, a published method for C3-acetoxylation of indoles suffered from multiple steps, the expensive Ag(OAc) reagent, and low yield (28%).[37] Herein, we report an efficient Pd-catalyzed oxidative acetoxylation of indole derivatives through C–H activation in a highly regioselective fashion without the assistance of a directing group. Only a few examples of selective oxidative acetoxylation of C–H bonds without chelation assistance have been reported so far.[28,29]

The reaction of *N*-benzylindole (**1a**) and (diacetoxyiodo)benzene (**2a**) was chosen for the initial studies (Table 1). After many attempts, we obtained the best conditions for the formation of **3a**, involving $Pd(OAc)_2$ as the catalyst precursor, KOH as the base, and MeCN as the solvent at 70 °C (Table 1, entry 10). Both phosphine ligands and nitrogen ligands inhibited this transformation (Table 1, entries 1–6). The presence of CO did not affect the reaction significantly (Table 1, entry 7). Pd precursors were critical for the reactions. When $[PdCl_2(MeCN)_2]$ and $PdCl_2$ were employed as catalyst precursors, the reactions gave poor yields (Table 1, entries 8 and 9). When dimethylacetamide (DMA), toluene, or dioxane was used as solvents, the yields were also reduced (Table 1, entries 11–13). Without a Pd catalysts, only 7% acetoxylation product was obtained

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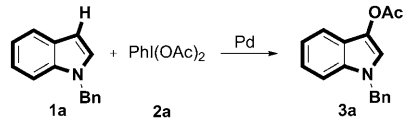
Table 1. Reaction parameters of the oxidative acetoxylation of **1a**.[a]

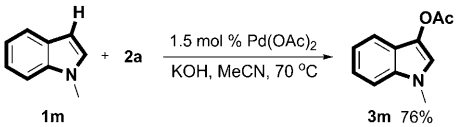


Entry	Catalyst	Ligand[e]	Solvent	Yield [%][b]
1	$Pd(OAc)_2$	dppe	MeCN	16
2	$Pd(OAc)_2$	bipy	MeCN	12
3	$Pd(OAc)_2$	py	MeCN	33
4	$Pd(OAc)_2$	tmeda	MeCN	21
5	$Pd(OAc)_2$	dmeda	MeCN	40
6	$[PdCl_2(PPh_3)_2]$	none	MeCN	12
7	$Pd(OAc)_2$	CO	MeCN	92
8	$[PdCl_2(MeCN)_2]$	none	MeCN	40
9	$PdCl_2$	none	MeCN	64
10	$Pd(OAc)_2$	none	MeCN	95
11	$Pd(OAc)_2$	none	DMA	44
12	$Pd(OAc)_2$	none	dioxane	52
13	$Pd(OAc)_2$	none	toluene	34
14	none	none	MeCN	7
15[c]	$Pd(OAc)_2$	none	MeCN	80
16[d]	$Pd(OAc)_2$	none	MeCN	84

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (1 mmol), KOH (1 mmol), Pd precursor (1.5 mol%, 0.0075 mmol) in solvent (2 mL) at 70°C for 1 h. [b] Yields determined by GC. [c] Reaction was performed at 50°C for 3 h. [d] Reaction was performed at 25°C for 12 h. [e] dppe = 1,2-bis(diphenylphosphino)ethane, bipy = 2,2′-bipyridine, py = pyridine, tmeda = *N,N,N′,N′*-tetramethylethylenedimaine, dmeda = *N,N′*-dimethylethane-1,2-diamine DMA = dimethylacetamide.

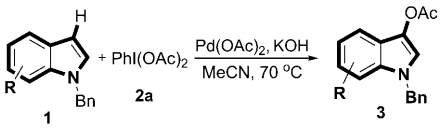
(Table 1, entry 14). When the reaction was carried out at 50°C, it took 3 h for complete conversion, which afforded 80% yield (Table 1, entry 15). The reaction could operate at room temperature to give 84% yield after 12 h (Table 1, entry 16). The amounts of oxidant and base were also optimized. Weak bases were inferior to KOH. More detailed reaction parameters are listed in the Supporting Information (Table S1 and S2).

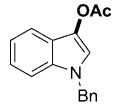
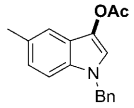
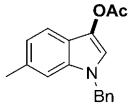
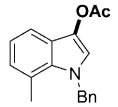
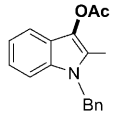
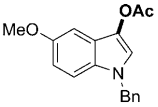
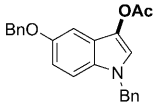
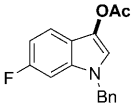
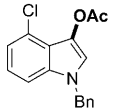
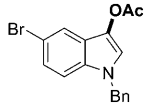
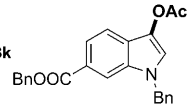
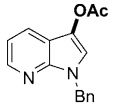
The substrate scope of this reaction was further investigated and the results are compiled in Table 2. *N*-Benzylindoles with a wide range of substitution groups could be oxidatively acetoxylated under the optimized conditions ($Pd(OAc)_2$ as the catalyst precursor, two equivalents $PhI(OAc)_2$ as the oxidant, and one equivalent KOH as the base in MeCN). Reaction yields involving indoles with electron-donating groups were higher than those with electron-withdrawing groups (Table 2, entries 1–7 and 8–12, respectively). In addition, the reaction rates of the indoles with electron-donating groups were faster than those with electron-withdrawing groups. Usually, the former could be accomplished within 1 h, whereas the latter needed more than 12 h. Under the standard conditions, the reaction of *N*-methylindole **1m** underwent smoothly. The direct-regioselective acetoxylation product **3m** was obtained in 76% isolated yield [Eq. (1)].



(1)

Table 2. Oxidative acetoxylation of substituted indole **1**.[a]

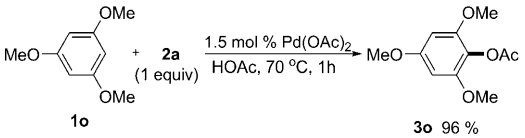


Entry	Products	Yield [%][b]
1	**3a** 	86
2	**3b** 	65 (75)
3	**3c** 	73
4	**3d** 	84
5	**3e** 	64
6	**3f** 	73
7	**3g** 	70
8[c]	**3h** 	20 (53)
9	**3i** 	65
10[c]	**3j** 	50 (63)
11[c]	**3k** 	37 (52)
12[c]	**3l** 	20 (59)

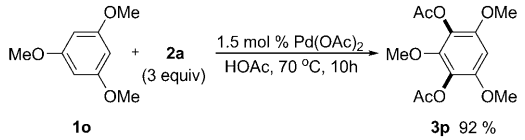
[a] Reaction conditions: **1a** (0.5 mmol), **2a** (1 mmol), KOH (0.5 mmol), $Pd(OAc)_2$ (1.5 mol%, 0.0075 mmol) at 70°C in MeCN (2 mL) for 1 h; Bn = benzyl. [b] Isolated yield. The data in the parenthesis were collected in the presence of 5 mol% $Pd(OAc)_2$. [c] Reaction time 12 h.

To further expand the substrate scope, some simple arenes were tested under the standard conditions. No desired product was obtained when 1,3,5-trimethoxybenzene

(**1o**) was employed as the substrate. To our delight, acetoxylated products of **1o** were obtained under the acidic conditions provided by using acetic acid as the solvent. Monoacetoxyl-1,3,5-trimethoxybenzene (**3o**) was produced in 96% isolated yield in the presence of one equivalent of oxidant **2a**. When the amount of oxidant **2a** was increased to three equivalents, diacetoxyl-1,3,5-trimethoxybenzene (**3p**) was generated in 92% isolated yield [Eqs. (2) and (3)].



(2)



(3)

During the investigation of the reaction parameters shown in Table 1, for most of the reactions 100% conversion was achieved, but low yields of the desired direct-acetoxylation product were identified. To obtain more information, the reaction of **1a** and **2a**, under the standard conditions, was monitored by using in situ IR spectroscopy and the results are shown in Figure 1. We could clearly observe decreasing intensity of the signal at 1245 cm^{-1} and increasing intensity of the signal at 1214 cm^{-1} with time. By comparing to authentic samples (see the Supporting Information), we could assign the signals at 1245 and 1214 cm^{-1} to **2a** and **3a**, respectively.

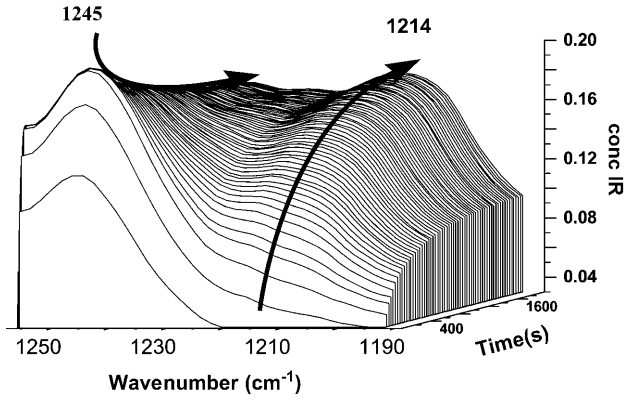


Figure 1. The 3D-IR profiles over time of the reaction of **1a** and **2a** under the standard conditions.

Interestingly, when we monitored the blank reaction of **1a** and **2a** in MeCN without Pd catalyst, the intensity of the signal at 1245 cm^{-1} (assigned to **2a**) decreased with time, but no signal was detected at 1214 cm^{-1} (Figure 2A). As shown in Figure 2B, the reaction in the presence of a Pd catalyst was clearly different. As **2a** was consumed the intensity of the signal at 1214 cm^{-1} (assigned to **3a**) increased, indicating that another reaction happened in the blank vessel. From the blank reaction product **4**—a dimer of **1a**—was isolated in 88% yield [Eq. (4)].

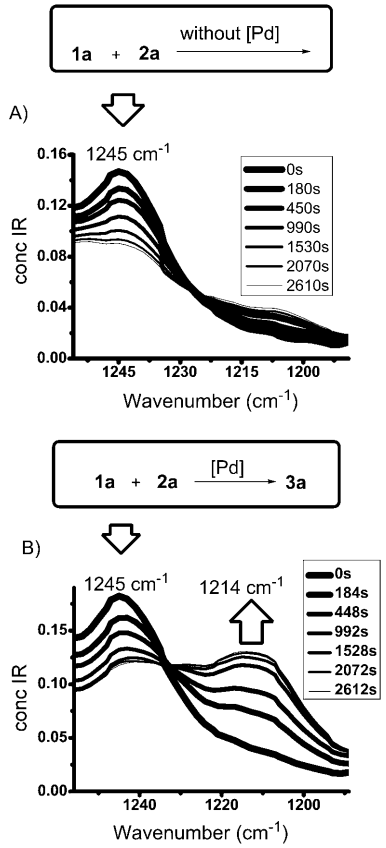
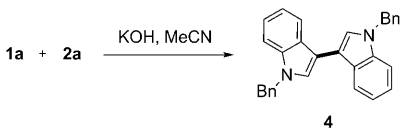


Figure 2. Selected region of the IR spectra of the reaction between **1a** and **2a**; A) blank reaction (without Pd catalyst); B) reaction run in the presence of Pd catalyst under the standard conditions.



(4)

To further investigate the high selectivity (direct acetoxylation of the C–H bond versus dimerization of the indole), kinetic studies of the reactions of **1a** and **2a** with or without the presence of a Pd catalyst were carried out. The results, plotted in Figure 3, clearly indicate that the reaction with a Pd catalyst was much faster than the one without a Pd catalyst and revealed high selectivity in this Pd-catalyzed acetoxylation reaction.

In addition, the reductive elimination of the C_{sp^2}-Pd^{II}-OR moiety is difficult to achieve and usually requires sterically

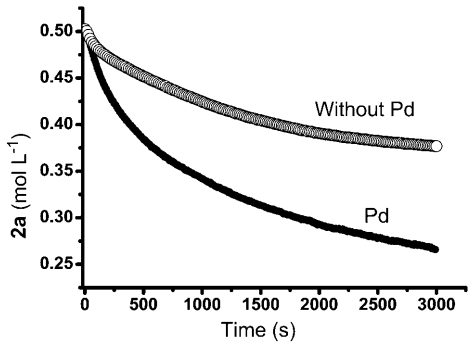
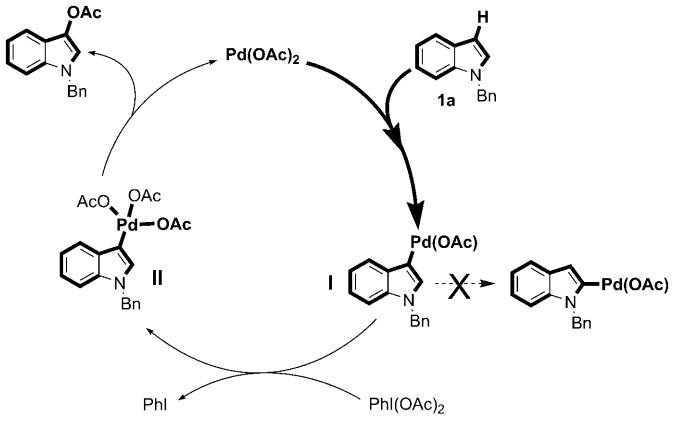


Figure 3. Kinetic profiles (decreased concentration of **2a**) of reactions between **1a** and **2a** with or without the presence of the Pd catalyst.

hindered ligands.[18,39,40] However, this direct acetoxylation of indole derivatives could take place without phosphine ligands and under mild conditions (room temperature); this implies that the C_{sp^2}–O bond formation was not a consequence of the reductive elimination of C_{sp^2}-Pd^{II}-OAc species. In fact, when stoichiometric amounts of $Pd(OAc)_2$ reacted with indole **1a** in MeCN in the presence of KOH at 70 °C (without oxidant **2a**), no acetoxylation product was identified (for details see the Supporting Information). This experiment provided further hints that the C–O bond formation investigated herein was not a result of the reductive elimination of a Pd^{II} species.

Moreover, the mechanism of the Pd-catalyzed direct acetoxylation of the C–H bond, with $PhI(OAc)_2$ as the oxidant and the assistance of directing groups, was proposed to occur through a high valent Pd species.[41–44]

Based on all aforementioned mechanistic information, we propose the catalytic cycle for the direct acetoxylation of indole derivatives shown in Scheme 2. The electrophilic palladation of indole **1a** generated Pd^{II}-intermediate **I**, which could be oxidized to Pd^{IV}-intermediate **II** due to the existence of a carbon anion as a strong δ-donor ligand. The subsequent reductive elimination afforded the desired acetoxylation product. The reductive elimination of Pd^{IV} species has



Scheme 2. Proposed reaction mechanism of the Pd-catalyzed acetoxylation of indoles.

been speculated to be a facile process.[32] If the oxidation of intermediate **I** by **2a** is facile, the 1,2-migration could also be inhibited. This could rationalize the selectivity of this reaction and why it could take place at room temperature.

To obtain a further understanding of the direct acetoxylation of indoles, kinetic studies were undertaken of the reaction of **1a** and **2a** in the presence of $Pd(OAc)_2$ as catalyst in MeCN. By varying the concentration of **2a**, we noted that the reaction rate was independent of this substrate. The initial reaction rates were identical and are plotted in Figure 4.

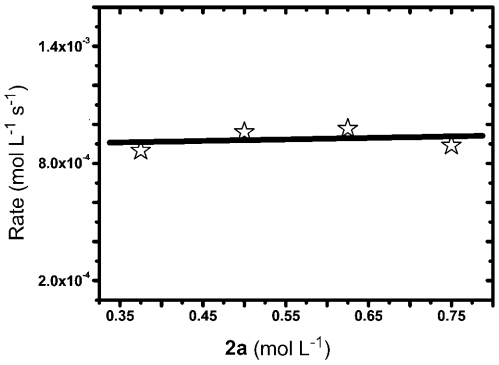


Figure 4. Zero-order kinetic dependence on **2a**.

Thus, zero-order kinetic dependence in respect to **2a** was established. The kinetic results of a fixed concentration of **2a** and varied concentrations of **1a** are illustrated in Figure 5. It is clear that the reaction is first-order with respect to **1a**.

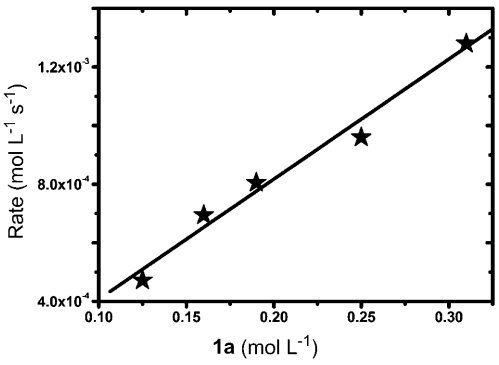


Figure 5. First-order kinetic dependence on **1a**.

The kinetic experiment indicated that the rate-limiting step was the electrophilic palladation of indoles. This is consistent with our initial hypotheses that the C3-acetoxylation could be accomplished by employing appropriate oxidant to inhibit the 1,2-migration. In addition, the kinetics also rationalized the other experimental fact that the reactions of indoles with electron-withdrawing groups were slower than those with electron-donating groups.

In conclusion, transition-metal-catalyzed C–O bond formation through C–H activation has been evidenced. We

have explored a novel Pd-catalyzed direct and selective C3-acetoxylation of indole derivatives. This selective C–H activation reaction was implemented without the assistance of directing groups. The kinetic study uncovered that the reaction was zero-order with respect to the oxidant and first-order with respect to the indole derivatives. More detailed mechanistic research and exploration of further applications are under investigation in our laboratory and will be reported in due course.

Experimental Section

General procedure: A 10 mL Schlenk tube equipped with a stirring bar was charged with $Pd(OAc)_2$ (0.0075 mmol), substrate (0.5 mmol), (diacetoxyiodo)benzene (1 mmol), and KOH (0.5 mmol). The reaction tube was purged with nitrogen. MeCN (2 mL) was then added to the reaction tube with a syringe. The Schlenk tube was placed in an oil bath and heated to 70 °C for 1 or 12 h and then cooled to room temperature. The mixture was then quenched by a sodium bisulfite solution (10 mL) and extracted by ethyl acetate (2×20 mL). The combined organic phases were dried over anhydrous Na_2SO_4, and concentrated under vacuum. The residue was then purified by flash chromatography on silica gel with a mixture eluent of petroleum ether (with 0.5 % triethylamine), ethyl acetate, and dichloromethane. After concentrating the fractions containing the product, the residue was dried under reduced pressure.

Acknowledgements

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Keywords: acetoxylation · C–H bond activation · indoles · kinetics · regioselectivity

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