

## Palladium-catalyzed functionalization of indoles with 2-acetoxymethyl substituted electron-deficient alkenes

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**Abstract**—A new functionalization of indoles via palladium-catalyzed reaction of indoles and 2-acetoxymethyl substituted electron-deficient alkenes is reported. The reaction was carried out under neutral condition and no isomerization of the carbon–carbon double bond was observed.

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Indoles are a class of intensively studied heterocycles, which are important subunits in many naturally occurring biologically active compounds.<sup>1,2</sup> For example, NVP-LAQ824,<sup>2a</sup> currently undergoing human clinical trials, is a potent HDAI and antitumor agent against both solid tumors and leukemia while the Teleocidin family<sup>2b</sup> is a class of tumor promoters. Thus, functionalization at the 3-position of indole skeleton is of great importance for the synthesis of indole derivatives with potential biological activities Figure 1.<sup>3,4</sup>

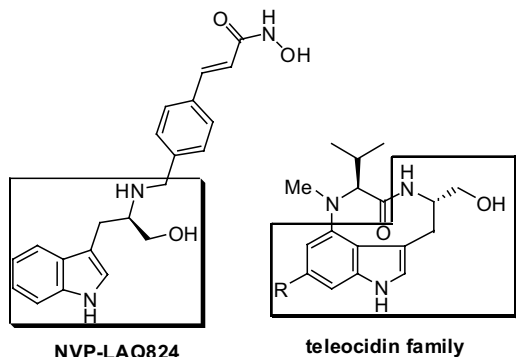


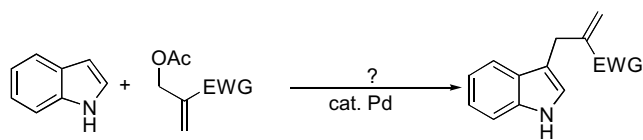
Figure 1.

**Keywords:** Palladium; C–H activation; Indoles; 2-Acetoxymethyl substituted electron-deficient alkene.

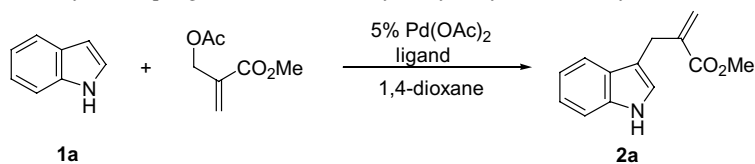
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The Lewis acid-catalyzed alkylation between indoles and an electrophile is a well-established method for the functionalization at the 3-position of the indole nucleus,<sup>3</sup> however, the necessity to utilize a stoichiometric amount of Lewis acid does not meet the contemporary requirement for green chemistry. On the other hand, palladium-catalyzed Heck reactions of 3-halo-substituted indoles<sup>5</sup> and palladium-catalyzed nonselective Friedel–Crafts allylation of indoles with allyl acetate, allylic alcohols, 1,3-dienes,<sup>6</sup> affording a mixture, have also been reported. Herein, we wish to present the first report on the coupling of 2-acetoxymethyl-substituted electron-deficient alkenes with indoles affording 3-functionalized indole derivatives bearing a conjugated carbon–carbon double bond in a highly regioselectivity (Scheme 1). In addition, this new approach makes it possible to install an electron-deficient carbon–carbon double bond ready for further elaboration at an almost unprecedented position.

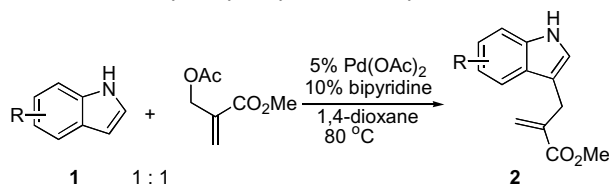
In an initial attempt, we examined the reaction of **1a** with 2-acetoxymethyl acrylic acid methyl ester in 1,4-dioxane under several combinations of Pd(OAc)<sub>2</sub> with monodentate or bidentate nitrogen ligands. With the



Scheme 1.

**Table 1.** Ligand effects on the Pd-catalyzed coupling of **1a** with 2-acetoxymethyl acrylic acid methyl ester<sup>7</sup>

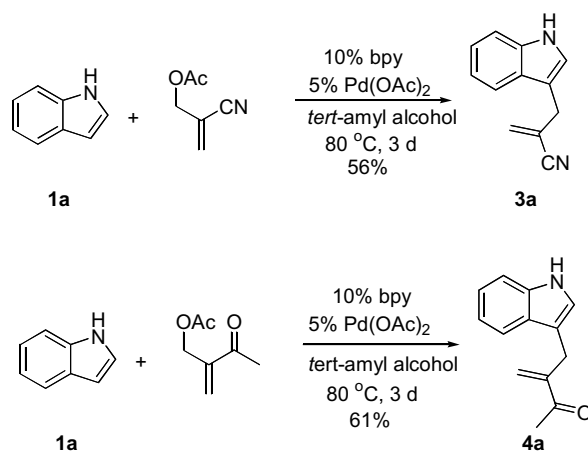
Entry	Ligand	Temp. (°C)	Time (d)	Yield of <b>2a</b> (%)
1		80	3	0
2		80	3	0
3		80	3	10
4		80	4	9
5		80	3	57
6 <sup>a</sup>		100	2	0
7	Pd(PPh <sub>3</sub> ) <sub>4</sub> <sup>b</sup>	80	1	0

<sup>a</sup> No Pd(OAc)<sub>2</sub> was added.<sup>b</sup> Pd(PPh<sub>3</sub>)<sub>4</sub> was used as the catalyst.**Table 2.** Pd-catalyzed coupling of indoles **1** with 2-acetoxymethyl acrylic acid methyl ester<sup>8</sup>

Entry	Indole	Product	Time (d)	Yield of <b>2</b> (%)
1			3	45
2			2	66 <sup>a</sup>
3			2	33 (52) <sup>a</sup>
4			2	50
5			3	53
6			3	37 (48) <sup>a</sup>

<sup>a</sup> 10 mol% of Pd(OAc)<sub>2</sub> was used as catalyst.

addition of 20 mol% of pyridine (Table 1, entry 1) or ethyl nicotinate (Table 1, entry 2), no cross coupled product **2a** was observed. However, when bidentate nitrogen ligands 4-amino-1,8-naphthyridine (Table 1, entry 3) and 1,10-phenanthroline (Table 1, entry 4) were used, we obtained **2a** in 10% and 9% yields, respectively. In an effort to improve the yield of the reaction, we next examined bipyridine derivatives as ligands. To our delight, the catalytically active complex arising from 5% Pd(OAc)<sub>2</sub> and 10% bipyridine in 1,4-dioxane gave the desired cross coupled product in 57% isolated yield (Table 1, entry 5). We also screened some substituted bipyridines, but the results are not impressive (See Supporting Information). It is important to note that the reaction in the absence of bipyridine and Pd(OAc)<sub>2</sub> did not result in the formation of product **2a** (Table 1, entry 6).



Scheme 2.

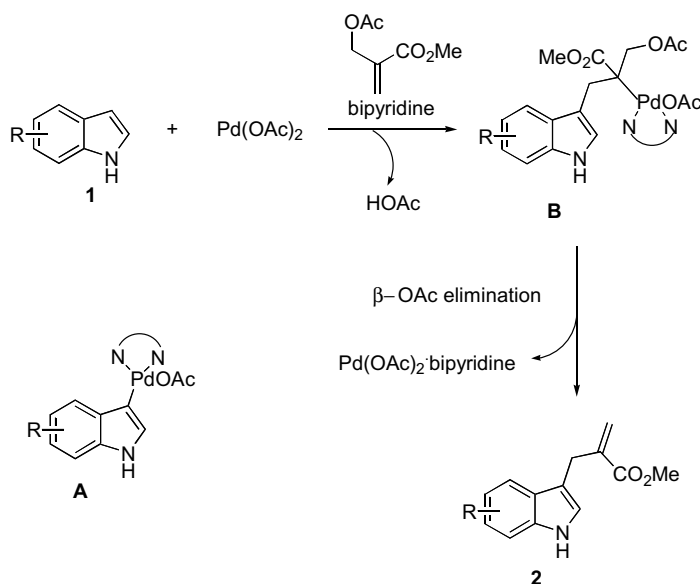
A variety of indoles were next examined to generate the desired coupling products under the standard conditions (Table 2, entry 5). The results are summarized in Table 2. The yield of this reaction is generally modest. It is interesting to see that a bromo substituent is compatible under the cross coupling conditions (Table 2, entries 3 and 6).

In addition, the reaction is not limited to 2-acetoxymethyl acrylic acid methyl ester. 2-Acetoxymethyl acrylonitrile and 3-acetoxymethylbut-3-en-2-one are also effective affording **3a** and **4a** in *tert*-amyl alcohol in 56% and 61% yields, respectively (Scheme 2). It should be noted that the results in 1,4-dioxane are not good.

The presence of an electron-withdrawing group is necessary since no reaction was observed with simple allyl acetate. Although the mechanism may not be very clear,<sup>9</sup> the facts that no reaction was observed with Pd(PPh<sub>3</sub>)<sub>4</sub> (Table 1, entry 7), the reaction can be carried

out in an atmosphere of air, and a bromo substituent can be tolerated implied a Pd(II)-catalyzed mechanism. Although intermediate A<sup>10,11</sup> followed by an intermolecular carbopalladation with the allylic acetate would provide intermediate B, Pd(OAc)<sub>2</sub>-mediated direct formation of intermediate B may also be possible.<sup>3,12</sup> β-OAc elimination of intermediate B would lead to the product and regenerate Pd(OAc)<sub>2</sub> (Scheme 3).<sup>13</sup>

In conclusion, we have developed a Pd-catalyzed cross coupling of indole with 2-acetoxymethyl-substituted electron-deficient alkenes under mild conditions via regioselective functionalization of indoles. This reaction was carried out under neutral conditions and does not require the use of any additive. Compared with the Lewis acid-catalyzed conjugate addition, this protocol is efficient and may open up a new area for the functionalization of indoles. Further studies including the mechanistic study in this area are being carried out in our laboratory.



Scheme 3.

### Acknowledgements

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- In the reactions affording the product in low yields, the formation of a Pd mirror was usually observed.
- Typical procedure: a reaction tube equipped with a magnetic stirring bar was charged with indole **1a** (117 mg, 1 mmol), 2-acetoxymethyl acrylic acid methyl ester (158 mg, 1 mmol), Pd(OAc)<sub>2</sub> (5 mol%, 12 mg), bipyridine (10 mol%, 18 mg), and 1,4-dioxane (2 mL). Then the tube was heated to 80 °C and allowed to stir for 3 days (the reaction was monitored by TLC). Filtration of the reaction mixture through a small pad of silica gel (Et<sub>2</sub>O), concentration and purification of the dark oil by flash chromatography on silica gel (ether/petroleum ether = 1:10 eluent) afforded **2a** as a yellow solid (123 mg, 57%). Mp 69–71 °C (hexane); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ 8.04 (br s, 1H), 7.53 (d, *J* = 8.1 Hz, 1H), 7.36 (d, *J* = 8.1 Hz, 1H), 7.19 (t, *J* = 8.1 Hz, 1H), 7.10 (t, *J* = 8.1 Hz, 1H), 7.03 (d, *J* = 2.4 Hz, 1H), 6.20 (s, 1H), 5.49 (s, 1H), 3.78 (s, 2H), 3.75 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75.4 MHz): δ 167.8, 139.3, 136.2, 127.2, 125.6, 122.8, 121.9, 119.2, 119.0, 112.6, 111.1, 51.9, 27.5 ppm; MS (70 eV): *m/z* (%) 215 (M<sup>+</sup>, 100); IR (neat): ν 3378, 1697, 1628, 1433, 1424, 1310, 1287, 1141, 745 cm<sup>-1</sup>.
- We have conducted the reaction of indole with 2-methoxycarbonyl-2-butenyl acetate or 3-methoxycarbonyl-3-buten-2-yl acetate. However, control experiment showed that there is an isomerization between these two isomeric allylic acetates under the current reaction conditions.
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