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Synthesis of 2-substituted indoles via a palladium-catalyzed domino Heck reaction and dealkylation

Hui Mao, Jie-Ping Wan, Yuanjiang Pan, Cuirong Sun *

Department of Chemistry, Zhejiang University, Hangzhou 310027, PR China

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ABSTRACT

A palladium-catalyzed domino Heck reaction and dealkylation for the preparation of 2-substituted indoles is described. This novel transformation is based on an intramolecular Heck reaction followed by dealkylation.

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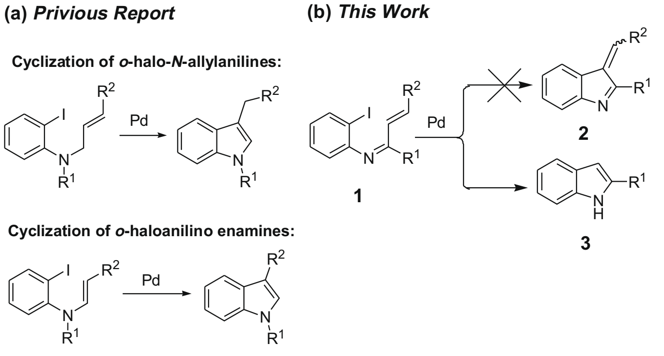
The indole skeleton is prevalent in numerous biologically active natural products and pharmaceuticals.[1] For example, indolodioxane (U86192A) is found to be active in anti-hypertension.[2] The MDL 103371 is a kind of glycine receptor antagonist for the potential treatment of stroke.[3] Tryptophan derivatives are proved to possess inhibitory activity against the IDO enzyme.[4]

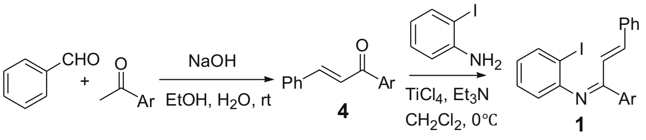
During the past 100 years, considerable attention had been directed toward the synthesis and functionalization of compounds containing the indole unit. Classical methods used for indole synthesis include the Fisher indole synthesis,[5] the Bischler indole synthesis,[6] and the Madelung cyclization of *N*-acyl-*o*-toluidines.[7] Recently, transition metal-catalyzed reactions especially the palladium-catalyzed transformations have been widely applied to the synthesis and functionalization of indoles.[8] In particular, the cyclization of *o*-halo-*N*-allylanilines[9] and *o*-haloanilino enamines[10] based on the intramolecular Heck reaction to form the indole ring has been extensively investigated. Based on these literature results, we envisioned that the compound **1** readily prepared from chalcone may undergo similar transformation to provide novel indole derivatives **2**. Unexpectedly, the further transformed product **3** instead of **2** was formed in our study. To the best of our knowledge, this kind of cascade transformation has not been previously reported. Therefore, systematic study on the new reaction was carried out, and herein we wish to report our results on the unprecedented synthesis of 2-substituted indoles (Scheme 1).

In order to explore the potential reaction, we prepared the *o*-iodo-*N*-allylimines **1** in two steps from benzaldehyde (Scheme 2). Firstly, the cross condensation between benzaldehyde and different aromatic ketones afforded chalcones.[11] Secondly, the condensation of chalcone with 2-iodobenzenamine was carried out by $TiCl_4/Et_3N$ catalyst system as described by Saito et al.[12]

To investigate the proposed reaction for indole synthesis, we firstly selected the *o*-iodo-*N*-allylimine **1c** as model reaction. After 12 h, in the presence of $Pd(OAc)_2$, PPh_3, and KOBu-*t* in DMF at 120 °C, the product was isolated as indole **3c** as mentioned above. The interesting transformation resulted from a Heck/dealkylation domino process triggered us to further explore the potential reaction parameters affecting the result. Briefly, the solvent and temperature, as well as different palladium sources including $Pd(OAc)_2$, $PdCl_2$, and $Pd(PPh_3)_2Cl_2$ were tested in this reaction and $Pd(OAc)_2$ was found to be the most effective palladium catalyst (Table 1, entries 1–3). Compared with DMF and toluene, DMSO was the best solvent as reaction medium (Table 1, entries 1, 4, and 5). Finally, both the reactions carried out at 110 °C and 130 °C gave



Scheme 1. Palladium-catalyzed cyclization for the synthesis of indoles based on the intramolecular Heck reaction.



Scheme 2. Preparation of *o*-iodo-*N*-allylimines from benzaldehyde and different aromatic ketones.

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* Corresponding author. Tel.: +86 0571 8795 1264; fax: +86 0571 8795 1629.
E-mail address: suncuirong@zju.edu.cn (C. Sun).

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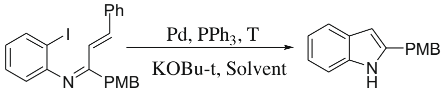
Table 1
Optimization of the reaction conditions[a]



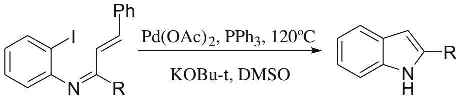
1c **3c**

Entry	Pd salt	Solvent	Temperature (°C)	Yield[b] (%)
1	$Pd(OAc)_2$	DMF	120	46
2	$PdCl_2$	DMF	120	Trace
3	$P(PPh_3)_2Cl_2$	DMF	120	40
4	$Pd(OAc)_2$	DMSO	120	70
5	$Pd(OAc)_2$	Toluene	120	30
6	$Pd(OAc)_2$	DMSO	110	45
7	$Pd(OAc)_2$	DMSO	130	35

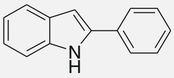
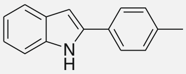
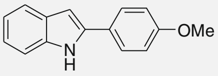
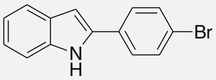
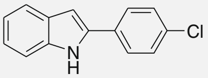
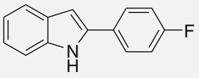
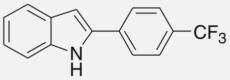
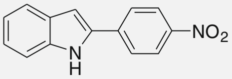
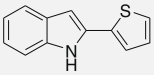
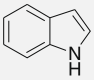
[a] Conditions: **1c** (0.5 mmol), Pd (0.025 mmol), PPh_3 (0.05 mmol), KOBu-*t* (1 mmol), solvent (3 ml), 12 h.

[b] Isolated yield.

Table 2
Synthesis of 2-substituted indoles from *o*-iodo-*N*-allylimines[a]

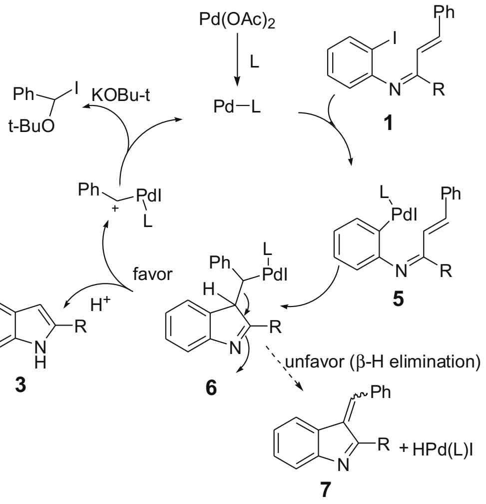


1 **3**

Entry	Product	Yield[b] (%)
1	 **3a**	63
2	 **3b**	67
3	 **3c**	70
4	 **3d**	59
5	 **3e**	57
6	 **3f**	55
7	 **3g**	52
8	 **3h**	51
9	 **3i**	40
10	 **3j**	71

[a] Conditions: **1** (0.5 mmol), $Pd(OAc)_2$ (0.025 mmol), PPh_3 (0.05 mmol), KOBu-*t* (1 mmol), DMSO (3 ml), 12–16 h.

[b] Isolated yield.



Scheme 3. A plausible mechanism for this novel domino Heck reaction and dealkylation.

sharply decreased yield (Table 1, entries 4, 6, and 7). According to these results, the optimal reaction conditions for this reaction were determined as $Pd(OAc)_2$ (0.05 equiv)/PPh_3 (0.10 equiv) in the presence of KOBu-*t* (2 equiv) by using DMSO as solvent at 120 °C.[13]

Under the established conditions, we then investigated the application scope of the novel transformation by using different imine substrates **1** derived from the corresponding chalcones. As shown in Table 2, a wide range of functionalized imines **1** had been found to smoothly lead to corresponding indoles, including aromatic, heteroaromatic, and hydrogen substitutions. Notably, the R groups with electron-donating substituent were favored and gave relatively higher yields (Table 2, entries 2 and 3). On the other hand, the indoles obtained from electron-withdrawing groups were in lower yields (Table 2, entries 4–8). In addition, heteroaromatic-substituted entry gave the product in moderate yield (Table 2, entry 9). Finally, the imine directly prepared from cinnamaldehyde afforded unsubstantiated indole in good yield under standard reaction conditions (Table 2, entry 10).

According to the reaction results and related Heck reaction mechanistic study,[14] we proposed the catalytic mechanism for this novel transformation. As shown in Scheme 3, the palladium–ligand complex generated from the reduction of $Pd(OAc)_2$, firstly undergoes oxidative addition to the carbon–iodine bond of *o*-iodo-*N*-allylimine **1** to produce intermediate **5**. Followed by the intramolecular Heck insertion, the secondary alkylpalladium species **6** is formed. Finally, to aromatize this five-membered ring, the dealkylation rather than β-hydrogen elimination of intermediate **6** provides indole derivative **3** after neutralization.

In summary, we have developed a palladium-catalyzed Heck reaction/dealkylation domino process for the synthesis of 2-substituted indoles. Through the reaction of 2-iodobenzenamine and readily available chalcones, the *o*-iodo-*N*-allylimine **1** could be facilely prepared and undergo this novel transformation under palladium catalysis. The results from our study demonstrated an unprecedented reaction pattern compared with classical Heck reaction. This study therefore provided useful considerations for new reaction design of palladium catalysis. Further investigations into the mechanism are undergoing in our laboratory.

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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.2010.01.113.

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13. *Typical procedure*: KOBu-*t* (1 mmol) was added to a solution of *o*-iodo-*N*-allylimine (0.5 mmol), $Pd(OAc)_2$ (0.025 mmol), and PPh_3 (0.05 mmol) in DMSO (3 mL) under nitrogen atmosphere. The mixture was stirred at room temperature for 1 h and then heated at 120 °C for 12 h. Then it was cooled, the reaction was quenched with hydrochloric acid (5%), and the mixture was extracted with ethyl acetate (30 ml). The organic layer was washed with sodium carbonate (5%), brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography to give the product. One example (**3c**): White solid, yield 70%, ^1H NMR (DMSO, 500 MHz): δ 11.39 (1H, s, NH), 7.78–7.79 (2H, d, J = 8.7 Hz), 7.46–7.49 (1H, d, J = 7.75 Hz), 7.36–7.37 (1H, d, J = 6.95 Hz), 7.02–7.07 (3H, m), 6.95–6.98 (1H, m), 6.75 (1H, s), 3.80 (1H, s, COMe). ^{13}C NMR (DMSO, 125 MHz): δ 158.5, 138.9, 138.0, 129.0, 127.0, 125.0, 122.2, 120.8, 120.3, 115.0, 112.2, 98.2, 55.3. Mass (ESI, *m*/*z*): 246.1 $(M+Na)^+$. HRMS (ESI, *m*/*z*): calcd for $C_{15}H_{13}NONa$: 246.0895; found: 246.0892.
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