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Novel Palladium-Catalyzed Acyloxylation/Cyclization of 2-(3′-Alkenyl)indoles

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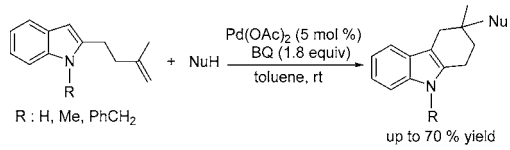
ABSTRACT



A new and mild palladium(II)-catalyzed reaction for the intramolecular acyloxylation/cyclization of 2-(3′-alkenyl)indoles was developed. The newly formed cycles involve oxygen-containing functionalized groups, which might be transferred further to provide other indole derivatives.

Owing to the potent and diverse biological activity exhibited by various indole derivatives, this heterocyclic system has attracted considerable attention in chemistry and medicinal chemistry.[1] There are some reports related to the synthesis of indole derivatives, including fused polycyclic indoles and carbazoles catalyzed by platinum(II)[2] or palladium(II)[3] using the substituted indoles with an unactivated olefin as the substrate. In these reactions,[2,3] one of the possible pathways involves nucleophilic attack of the indole on a metal-coordinated olefin followed by protonolysis, alkoxycarbonylation, or β-hydride elimination (initiated by carbometalation). Another possible pathway is functionization of the C−H bond of indole followed by olefin insertion and β-hydride elimination (initiated by C−H bond functionization). The reason for the success of all these reactions lies in the fact that indole rings are electron-rich, and thus they can easily act as nucleophiles. In most of these reactions catalyzed by Pd(II) species, β-hydride elimination is usually the last step, and no other nucleophiles participate. Herein, we report a mild, novel, Pd(II)-catalyzed cyclization of 2-(3′-alkenyl)indoles, in which some nucleophiles, including organic acids or pentafluorophenol, can be introduced.

We have recently reported the Pd(II)-catalyzed oxidative cyclization of 3-(3′-alkenyl)indoles to form carbazoles (Scheme 1).[3j] The reactions of indoles with substitution at the C-3 position proceeded smoothly and had good results. However, when we conducted the reaction using a C-2 -substituted substrate, 2-(3′-alkenyl)indole (**1a**), under the same conditions, the reaction was more complex to give carbazole **4aa** and another product, **3aa**[4] (Scheme 2).

From the structure of **3aa**, it was not difficult to determine that acetic acid, which served as cosolvent, participated in the reaction and acted as a nucleophile. In previous literature

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(2) (a) Liu, C.; Han, X.; Wang, X.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2004**, *126*, 3700. (b) Han, X.; Widenhoefer, R. A. *Org. Lett.* **2006**, *8*, 3801.

(3) (a) Trost, B. M.; Godleski, S. A.; Genêt, J. P. *J. Am. Chem. Soc.* **1978**, *100*, 3930. (b) Trost, B. M.; Fortunak, J. M. D. *Organometallics* **1982**, *1*, 7. (c) Cushing, T. D.; Sanz-Cervera, J. F.; Williams, R. M. *J. Am. Chem. Soc.* **1993**, *115*, 9323. (d) Baran, P. S.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 7904. (e) Baran, P. S.; Guerrero, C. A.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 5628. (f) Ferreira, E. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2003**, *125*, 9578. (g) Beccalli, E. M.; Broggini, G. *Tetrahedron Lett.* **2003**, *44*, 1919. (h) Liu, C.; Han, X.; Wang, X.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2004**, *126*, 10250. (i) Liu, C.; Widenhoefer, R. A. *Chem. Eur. J.* **2006**, *12*, 2371. (j) Kong, A.; Han, X.; Lu, X. *Org. Lett.* **2006**, *8*, 1339.

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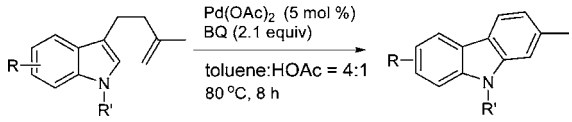
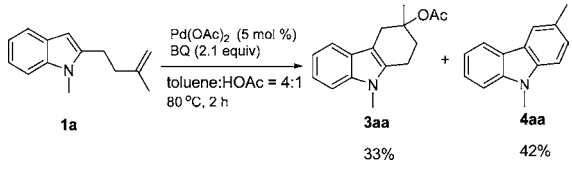
Scheme 1. Pd(II)-Catalyzed Oxidative Cyclization of 3-(3′-Alkenyl)indoles



for the intramolecular cyclization of alkenylindoles, such phenomena have never been reported. This intrigued us to focus our attention on improving the formation of **3aa**.

Scheme 2. Pd(II)-Catalyzed Oxidative Cyclization of 2-(3′-Alkenyl)indoles



To our delight, when the reaction was carried out at room temperature, the yield of **3aa** was raised from 33% to 56%, while the time required was somewhat longer (Table 1, entries 1 and 2). When the reaction was performed at lower temperature (10 °C), only a trace of **3aa** was formed, and most of the starting material remained even after 30 h (Table 1, entry 3). Fortunately, a 73% yield of **3aa** was obtained when the ratio of solvent was changed from toluene:HOAc = 4:1 (the amount of HOAc was 33 equiv with respect to **1a**) to 9:1 (the amount of HOAc was 20 equiv with respect to **1a**) (Table 1, entry 4). Almost the same result was obtained when using 10 equiv of acetic acid instead of using 20 equiv (Table 1, entry 5). Further decreasing the amount of the acid to 2 equiv slowed down the reaction dramatically (Table 1, entry 6). In this reaction, the oxidant used was very important; benzoquinone (BQ) showed a good effect here. When the amount of benzoquinone was decreased to 1.2 equiv, the yield of **3aa** was only 40% (Table 1, entry 8). Thus, the use of 1.8 equiv of BQ was selected in our reactions. No product was detected in the presence of other oxidants such as $CuCl_2$ or $Cu(OAc)_2$. When the benzoquinone/MnO_2 system was used to decrease the amount of benzoquinone,[5] product **3aa** could not be successfully obtained at room temperature, but the reaction did occur when the temperature was raised to 50 °C (Table 1, entries 11−14). In the absence of $Pd(OAc)_2$, no reaction occurred. Most of the polar solvents such as THF, DMF, and CH_3CN were ineffective in the reaction. Reaction in 1,2-dichloroethane gave a yield of **3aa** (68%) similar to that in toluene. Finally, the following reaction conditions were chosen as our optimal conditions: 0.3 mmol of 2-(3′-alkenyl)indole, 10 equiv of nucleophile, 5 mol % of $Pd(OAc)_2$, and 1.8 equiv of BQ in 3 mL of toluene at room temperature for 8 h.

Table 1. Palladium-Catalyzed Reaction of **1a** and Acetic Acid in Toluene with Different Conditions[a]

entry	amt of HOAc (equiv)	oxidant (amt (equiv))	temp (°C)/ time (h)	yield (%)[b] 3aa	4aa
1	33	BQ (2.1)	80/2	33	42
2	33	BQ (1.8)	room temp/8	56	33
3	33	BQ (1.8)	10/30	trace	
4	20	BQ (1.8)	room temp/8	73	trace
5	10	BQ (1.8)	room temp/10	71	trace
6	2	BQ (1.8)	room temp/30	trace	
7[c]	as solvent	BQ (1.8)	room temp/20	complicated	
8	10	BQ (1.2)	room temp/20	40	trace
9	10	$CuCl_2$ (2.2)	room temp/30	NR	
10	10	$Cu(OAc)_2$ (2.2)	room temp/30	NR	
11	10	BQ/MnO_2 (0.2/1.2)	room temp/30	trace	
12	10	BQ/MnO_2 (0.2/1.2)	50/15	60	20
13	10	BQ/MnO_2 (0.1/1.2)	room temp/30	trace	
14	10	BQ/MnO_2 (0.1/1.2)	50/20	68	10

[a] Reaction was performed with **1a** (0.3 mmol) in the presence of $Pd(OAc)_2$ (0.015 mmol) in toluene (3 mL). [b] Isolated yield. [c] HOAc was the only solvent.

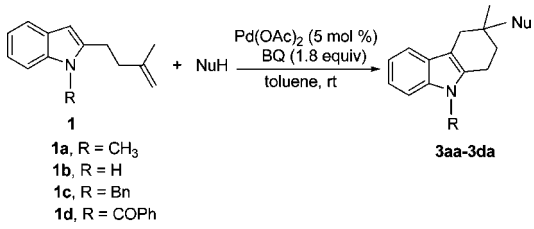
Next, other nucleophiles were examined in this reaction. There was a large variation in yields with respect to the different nucleophiles. While acetic acid, pentafluorophenol, and *o*-nitrobenzoic acid afforded the corresponding products in good yields (Table 2, entries 1, 7, and 8), halo-substituted acetic acid, *n*-butyric acid, acrylic acid, and benzoic acid gave moderate yields (Table 2, entries 2−6). Phenol and benzyl alcohol were unsuccessful as nucleophiles under the reaction conditions. From these results, it was obvious that the pK_a value of the nucleophiles seems to be an important factor, and acids with pK_a values close to that of acetic acid were the best. In addition, some N-containing compounds such as *p*-toluenesulfonamide, phthalimide, and diphenylamine were also investigated, but they were all unreactive. Then the influence of the substituents R on the nitrogen atom of indole was studied. Indoles with electron-donating groups on nitrogen such as benzyl and methyl groups gave similar results (Table 2, entries 1 and 12), but the electron-withdrawing benzoyl group on nitrogen hindered the cyclization reaction (Table 2, entry 13), showing the influence on the electronic density of carbon atoms of indoles through the electron transfer from the nitrogen atom. Indole with unprotected N−H (**1b**) did not inhibit the reaction and gave the desired compound in good yield as well (Table 2, entry 11). In all of the experiments shown in Table 2, byproducts such as **4aa** (less than 10%) were also produced, which cannot be inhibited completely at the present time.

Indoles **1e** and **1f** were also tried. Compound **1e** can react with acetic acid smoothly at 40 °C, just like the substrate **1b**, but its methylated derivative **1f** does not react even when the temperature was raised to 100 °C (Scheme 3). The presence of the olefinic methyl group in substrates **1** is

(4) The structure of **3aa** was confirmed by X-ray crystallography.

(5) (a) Bäckvall, J. E.; Hopkins, R. B.; Grennberg, H.; Mader, M. M.; Awasthi, A. K. *J. Am. Chem. Soc.* **1990**, *112*, 5160. (b) Heumann, A.; Akermark, B.; Hansson, S.; Rein, T. *Org. Synth.* **1990**, *68*, 109.

Table 2. Palladium-Catalyzed Reactions of **1** with Different Nucleophiles[a]

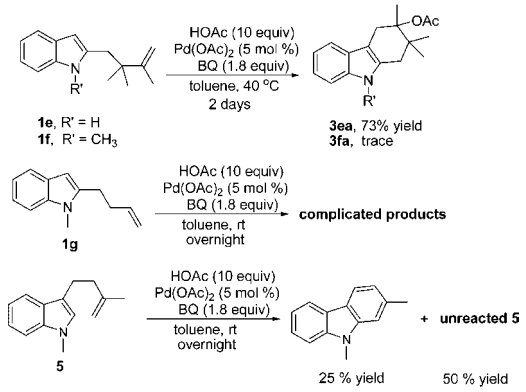


entry	indole	nucleophile (NuH)	yield, %[b]
1	**1a**	CH_3COOH (**2a**)	71 (**3aa**)
2[c]	**1a**	$BrCH_2COOH$ (**2b**)	52 (**3ab**)
3[c]	**1a**	$ClCH_2COOH$ (**2c**)	55 (**3ac**)
4	**1a**	CH_2=$CHCOOH$ (**2d**)	32 (**3ad**)
5[d]	**1a**	n-C_3H_7COOH (**2e**)	42 (**3ae**)
6	**1a**	C_6H_5COOH (**2f**)	38 (**3af**)
7	**1a**	o-NO_2-C_6H_4COOH (**2g**)	64 (**3ag**)
8[e]	**1a**	C_6F_5OH (**2h**)	74 (**3ah**)
9	**1a**	C_6H_5OH (**2i**)	0 (**3ai**)
10	**1a**	$C_6H_5CH_2OH$ (**2j**)	0 (**3aj**)
11[f]	**1b**	CH_3COOH (**2a**)	70 (**3ba**)
12	**1c**	CH_3COOH (**2a**)	64 (**3ca**)
13	**1d**	CH_3COOH (**2a**)	trace (**3da**)

[a] A solution of **1** (0.3 mmol, 1.0 equiv), $Pd(OAc)_2$ (0.015 mmol, 0.05 equiv), BQ (0.54 mmol, 1.8 equiv) and nucleophile (10 equiv) in toluene (3 mL) was stirred for 8 h at room temperature. [b] Isolated yield. [c] The amount of NuH was 1.2 equiv with respect to **1a**. [d] The reaction time was 72 h. [e] The amount of **2h** was 2 equiv with respect to **1a**. [f] The reaction temperature was 40 °C.

important in yielding products **3** with high selectivity, similar to their influence in yielding carbazoles from 3-(3′-alkenyl)indoles.[3j] When the reaction of substrate **1g** was

Scheme 3

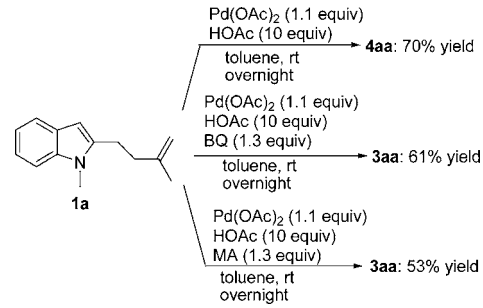


carried out under the same conditions, no acyloxypalladation product was detected but a mixture of complicated products was obtained, indicating that an olefinic methyl group is crucial for the success of our reactions (Scheme 3).

The question arose that **3aa** might be the intermediate of the formation of **4aa**. When the isolated **3aa** was further reacted in the presence of 2.1 equiv of BQ and 5 mol % of $Pd(OAc)_2$ in the solvent (toluene:HOAc = 4:1) at 80 °C overnight, **4aa** was obtained in 40% yield. No reaction occurred in the case without $Pd(OAc)_2$ and BQ. On the other hand, when the 3-substituted indole **5** was used to conduct the reaction at room temperature, the same carbazole product, which is identical with that produced at 80 °C,[3j] was obtained in low yield without the formation of acetoxypalladation product (Scheme 3). These results showed that the reaction behaviors of 2- and 3-substituted[3j] indoles are different, which may be due to the different reactivities of the C-2 and C-3 of indoles.

In the reported palladium-catalyzed reactions in the presence of BQ, there are two roles played by BQ:[6] (1) it serves as the oxidant, resulting in the formation of Pd(II) species and hydroquinone; (2) it can also act as a ligand to stabilize the Pd species present in the catalytic cycle. To examine the role of BQ in our reaction, we conducted two experiments in the presence of a stoichiometric amount of $Pd(OAc)_2$ with or without BQ, and it was surprising that a totally different result was obtained. In the presence of a stoichiometric amount of BQ, the acyloxypalladation product **3aa** was obtained just as previously mentioned, but only carbopalladation product **4aa** was produced in the absence of BQ (Scheme 4). These results suggest that BQ may have

Scheme 4. Stoichiometric Reaction of $Pd(OAc)_2$ and **1a** in the Presence or Absence of Benzoquinone



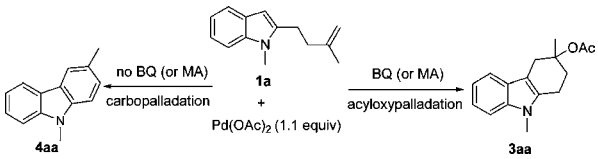
a special function as a π-acid ligand here. It might act to transfer the pathway of this reaction from carbopalladation to acyloxypalladation. Then another π-acid ligand, maleic anhydride (MA),[7] was used to perform the above stoichiometric reaction again, and the acyloxypalladation product **3aa** was also obtained similarly (Scheme 4).

From Scheme 4, it is obvious that BQ or MA is the key in our cyclization reactions, as illustrated in Scheme 5.

(6) (a) Roffia, P.; Conti, F.; Gregorio, G.; Pregaglia, G. F.; Ugo, R. *J. Organomet. Chem.* **1973**, *56*, 391. (b) Bäckvall, J. E.; Andersson, P. J. *J. Am. Chem. Soc.* **1992**, *114*, 6374. (c) Grennberg, H.; Gogoll, A.; Bäckvall, J. E. *Organometallics* **1993**, *12*, 1790. (d) Jia, C.; Kitamura, T.; Fujiwara, Y. *Org. Lett.* **1999**, *1*, 2097. (e) Boele, M. D. K.; van Strijdonck, G. P. F.; de Vries, A. H. M.; Kamer, P. C. J.; de Vries, J. G.; van Leeuwen, P. W. N. M. *J. Am. Chem. Soc.* **2002**, *124*, 1586.

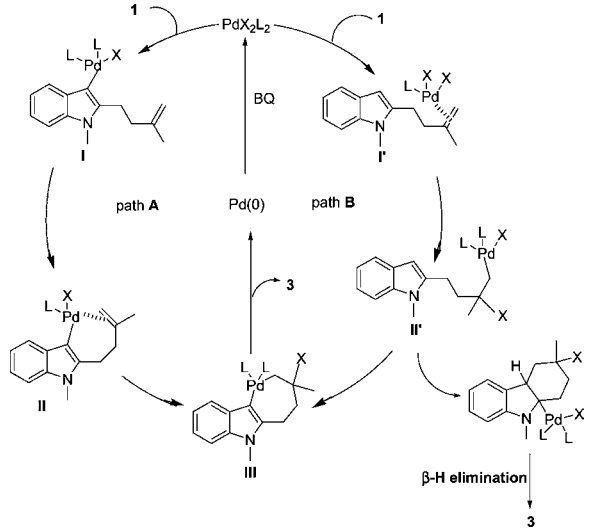
(7) For examples, see: (a) Doyle, M. J.; McMeeking, J.; Binger, P. *J. Chem. Soc., Chem. Commun.* **1976**, 376. (b) Kohara, T.; Komiya, S.; Yamamoto, T.; Yamamoto, A. *Chem. Lett.* **1979**, 1513. (c) Goliaszewski, A.; Schwartz, J. *J. Am. Chem. Soc.* **1984**, *106*, 5028. (d) Goliaszewski, A.; Schwartz, J. *Organometallics* **1985**, *4*, 417.

Scheme 5. Benzoquinone or Maleic Anhydride as the Key Additive between Oxypalladation and Carbopalladation



Two possible pathways for the formation of product **3** are shown in Scheme 6. In path A, the C−H bond of indole is functionalized by $Pd(OAc)_2$ to form intermediate **I**, followed by the attack of nucleophiles on the palladium(II)-coordinated olefin (oxypalladation[8,9]) via intermediate **II** to generate the intermediate **III**; then reductive elimination of **III** provides **3** and Pd(0), which can be reoxidized to Pd(II) by BQ. In path B, nucleophiles attack the palladium(II)-coordinated olefin of the substituted indole **I′** to form intermediate **II′** (oxypalladation[8,9]), which undergoes intramolecular C−H bond functionalization to form the same intermediate **III**, just as in path A. An alternative mechanism involving insertion of the indole double bond into the C−Pd bond in intermediate **II′** followed by β-hydride elimination cannot be excluded. From the literature, it is known that the reaction of AcOH with a C=C bond activated by the coordination of Pd(II) could lead to both vinylic acetate and allylic acetate, depending on the substrates and reaction conditions.[10] Thus, 1,2-acyloxypalladation of olefin is suggested in this reaction. The mechanism for the formation of **4aa** in this catalytic reaction is similar to the mechanism reported,[3j] and it also can be produced by the elimination of acetic acid from **3aa**.[10c]

Scheme 6. Possible Mechanism for the Intramolecular Acyloxylation/Cyclization of 2-(3′-Alkenyl)indoles



In summary, a new and mild palladium(II)-catalyzed reaction for the intramolecular acyloxylation/cyclization of 2-(3′-alkenyl)indoles was developed. The newly formed cycles involve oxygen-containing functionalized groups, which might be transferred further to provide other indole derivatives. Moreover, BQ was found to be crucial for the success of this reaction; it can transfer the pathway of this reaction from carbopalladation to acyloxypalladation.[8,9] Further studies in this area are in progress.

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Supporting Information Available: Text and figures giving experimental procedures, characterization data, and copies of NMR spectra of new compounds and a CIF file giving crystallographic data for compound **3aa**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) For intermolecular acyloxypalladation−dehydropalladation reactions see: (a) Tanaka, M.; Urata, H.; Fuchikami, T. *Tetrahedron Lett.* **1986**, *27*, 3165. (b) Yokota, T.; Fujibayashi, S.; Nishiyama, Y.; Sakaguchi, S.; Ishii, Y. *J. Mol. Catal. A* **1996**, *114*, 113. (c) Jia, C.; Müller, P.; Mimoun, H. *J. Mol. Catal. A* **1995**, *101*, 127. (d) Ferret, N.; Mussate-Mathieu, L.; Zahra, J.-P.; Waegell, B. *J. Chem. Soc., Chem. Commun.* **1994**, 2589.

(9) For intermolecular acyloxypalladation without the dehydropalladation see: (a) Hosokawa, T.; Shinohara, T.; Ooka, Y.; Murahashi, S.-I. *Chem. Lett.* **1989**, 2001. (b) Heumann, A.; Reglier, M.; Waegell, B. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 866. (c) Heumann, A.; Kaldy, S.; Tenaglia, T. *Tetrahedron* **1994**, *50*, 539. (d) Trost, B. M.; Burgess, K. *J. Chem. Soc., Chem. Commun.* **1985**, 1084. (e) Tamaru, M.; Yasui, T. *Chem. Commun. (London)* **1968**, 1209. (f) Kuznetsova, N. I.; Likholobov, V. A.; Fodotov, M. A.; Yermakov, Y. I. *J. Chem. Soc., Chem. Commun.* **1982**, 973.

(10) (a) Negishi, E., Ed. *Handbook of Organopalladium Chemistry for Organic Synthesis*; Wiley-Interscience: New York, 2002. (b) Hansson, S.; Heumann, A.; Rein, T.; Åkermark, B. *J. Org. Chem.* **1990**, *55*, 975. (c) Xu, Y.-H.; Lu, J.; Loh, T.-P. *J. Am. Chem. Soc.* **2009**, *131*, 1372.