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Highly Efficient Construction of Benzene Ring in Carbazoles by Palladium-Catalyzed *endo*-Mode Oxidative Cyclization of 3-(3′-Alkenyl)indoles

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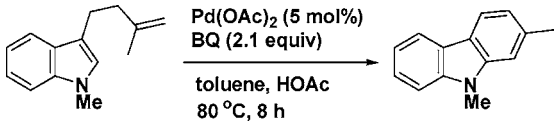
ABSTRACT



A highly efficient construction of the benzene ring in carbazoles by palladium-catalyzed *endo*-mode oxidative cyclization of 3-(3′-alkenyl)-indoles was developed. The reaction utilizes benzoquinone as the stoichiometric oxidant and is conducted under mild conditions.

The transition-metal-catalyzed intramolecular cyclization of indole derivatives represents an attractive route for the synthesis of polycyclic compounds.[1] For example, Stoltz reported the formation of cyclopentane-fused indoles from the 3-nonterminal-alkenyl indoles under the catalysis of Pd(II).[1h] Widenhoefer used the platinum-catalyzed cyclization of 2-alkenylindoles to obtain the cyclohexane-fused indoles.[1i] On the other hand, carbazole alkaloids are a class of natural products that exhibit a variety of biological activities,[2] of which indolocarbazoles represent an important class of antitumor antibiotics, such as the protein kinase C (PKC) inhibitor.[3] Carbazole derivatives are also widely used as organic materials, due to their photorefractive, photoconductive, and light-emitting properties.[4] Thus, the synthesis of substituted carbazoles has attracted considerable attention.[2c,5] Among the many methods available, the synthetic strategies which utilize indole derivatives as the starting materials are often very fruitful.[6] However, the palladium-mediated reactions available often need severe conditions,[7] multiple steps,[8]

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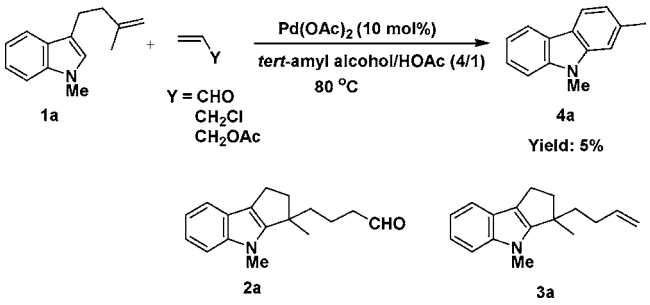
or require stoichiometric amounts of palladium.[9] In this paper, we wish to report our recent observations on the direct construction of the benzene ring in carbazoles by palladium-catalyzed *endo*-mode oxidative cyclization of 3-(3′-alkenyl)-indoles.

During the course of our studies on the palladium(II)-catalyzed reactions of the 3-(3′-alkenyl)indole (**1a**) with acrolein or allyl chloride (or acetate), we failed to get the expected coupling product **2a** or **3a**; instead, to our surprise, we obtained a 5% yield of an unexpected carbazole derivative **4a** in which a benzene ring was annulated onto the indole in a one-step operation (Scheme 1). The production of this

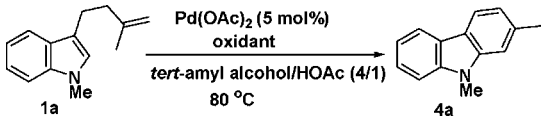
Scheme 1. Pd-Catalyzed Reaction of **1a** with Olefin Derivatives



carbazole, even in small amounts, attracted our interest and led to us studying this fascinating reaction in more detail.

After considering the possible pathway by which the carbazole was formed, we felt that optimization of the efficiency of aromatization and the in situ oxidation of Pd(0) to Pd(II) would be central to the development of a high-yielding catalytic reaction. Thus, different oxidants were tried first with the typical results listed in Table 1. The yield was only 14% using O_2 as the oxidant, while $CuCl_2$ gave 35% yield of the product. However, to our great delight, when 2 equiv of benzoquinone (BQ) was used as oxidant, an 84% yield of carbazole **4a** was obtained. We next surveyed the solvent dependence of the reaction (Table 2). The results showed that HOAc was crucial for success in the reaction. Both nonpolar and polar solvents (e.g., toluene, THF, dioxane, nitromethane, DMF, and *tert*-amyl alcohol) gave only traces of the desired product **4a** in the absence of HOAc with most of the substrate **1a** left unreacted. HOAc alone gave the product **4a** in 52% yield (Table 2, entry 1). The cyclization occurred smoothly in a mixture of common solvents and HOAc (v/v = 4/1), producing carbazole **4a** in moderate to good yields (Table 2, entries 2−8). The highest yield was obtained when the reaction was carried out in a mixture of toluene and HOAc (v/v = 4/1) (Table 2, entry 8).

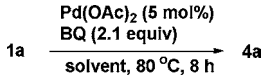
Table 1. The Effect of Oxidant in the Reaction of **1a** to **4a**[a]



entry	oxidant	yield, %[b]
1	O_2 (1 atm)	14
2	$CuCl_2$ (2.1 equiv)	35
3	BQ (1.0 equiv)	50
4	BQ (2.1 equiv)	84

[a] Reaction conditions: **1a** (0.5 mmol, 0.1 M in *tert*-amyl alcohol/HOAc (4/1)), $Pd(OAc)_2$ (0.025 mmol), 80 °C, 8 h. [b] Isolated yield.

Table 2. Solvent Effect in the Reaction of **1a** to **4a**[a]



entry	solvent (v/v)	yield, %[b]
1	HOAc	52
2	acetonitrile/HOAc (4/1)	52
3	benzene/HOAc (4/1)	72
4	dioxane/HOAc (4/1)	72
5	nitromethane/HOAc (4/1)	61
6	DMF/HOAc (4/1)	63
7	*tert*-amyl alcohol/HOAc (4/1)	84
8	toluene/HOAc (4/1)	88
9	toluene/HOAc (2/1)	78
10	toluene/HOAc (10/1)	76
11	toluene/HOAc (20/1)	36

[a] Reaction conditions: **1a** (0.5 mmol, 0.1 M in solvent), $Pd(OAc)_2$ (0.025 mmol), BQ (1.05 mmol), 80 °C, 8 h. [b] Isolated yield.

With the optimal conditions identified,[10] the scope of this reaction was studied, and some of the most typical results we obtained are summarized in Table 3.[11] First, the influence of the substituent R on the nitrogen atom of indole was studied (Table 3, entries 1−4). The unsubstituted indole **1c** gave the corresponding carbazole **4c** in 40% yield (Table 3, entry 3). Substrates with electron-donating groups on nitrogen gave better yields (Table 3, entries 1 and 2). However, the electron-withdrawing benzoyl group on nitrogen hindered the cyclization reaction (Table 3, entry 4). Similar results were obtained in the reactions of 4-, 5-, or 7-substituted indoles (Table 3, entries 5−8, 13, and 14). Indoles with electron-donating groups (**1e**−**1g**, **1m**, and **1n**) gave higher yields of carbazoles than those with electron-withdrawing group (e.g., **1h**). Subsequently, we focused our attention on the alkenyl group connected to the indoles (Table 3, entries 9−14). The rate of the cyclization reaction was slowed by

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(10) See Supporting Information.

(11) Typical procedure: A Schlenk tube was charged with indole **1a** (99.6 mg, 0.50 mmol), palladium acetate (5.6 mg, 0.025 mmol), BQ (113.5 mg, 1.05 mmol), toluene (4 mL), and acetic acid (1 mL) under a nitrogen atmosphere. The flask was heated to 80 °C for 8 h. The solvent was removed under reduced pressure. Then the residue was purified by chromatography on silica gel (eluent: ethyl acetate and petroleum ether = 1:50) to give carbazole **4a** as a white solid (86 mg, yield: 88%).

Table 3. Pd-Catalyzed Oxidative Cyclization of 3-(3′-Alkenyl)indoles[a]

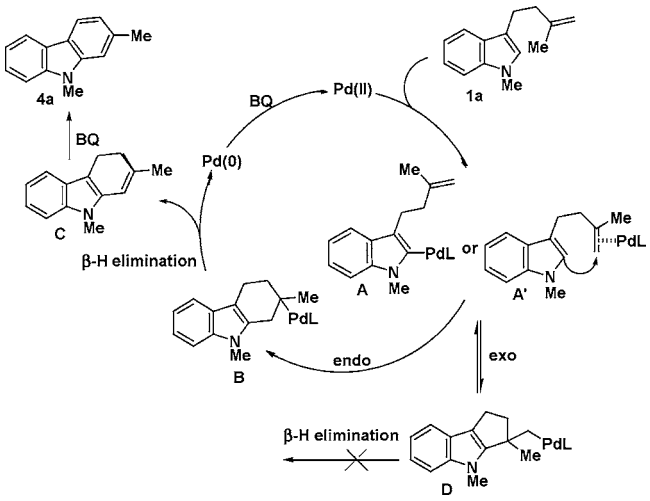
entry	substrate	product	yield, %[b]
1	1a: R = Me	4a	88
2	1b: R = CH_2Ph	4b	65
3	1c: R = H	4c	40
4	1d: R = COPh	4d	0
5	1e	4e	85
6	1f	4f	80
7	1g	4g	83
8	1h	4h	33
9	1i	4i	65[c]
10	1j	4j	86[c]
11	1k	4k	22[d]
12	1l	4l	82
13	1m	4m	76
14	1n	4n	82

[a] Reaction conditions: substrates (0.5 mmol, 0.1 M in toluene/HOAc (4/1)), $Pd(OAc)_2$ (0.025 mmol), BQ (1.05 mmol), 80 °C, 8 h. [b] Isolated yield. [c] The reaction was run at reflux temperature. [d] The reaction was run at reflux temperature for 48 h.

introducing a substituent on the alkenyl group, and a reflux temperature was required for the reaction to occur (Table 3, entries 9 and 10). While an indole with a phenyl group on the olefin (**1k**) gave **4k** in only 22% yield at the reflux temperature after 2 days (Table 3, entry 11), a butyl group at the same site was compatible (Table 3, entries 12−14). These results indicate that the bulkiness of the group also influences the reaction outcome.

A plausible mechanism for the palladium-catalyzed oxidative formation of carbazole is shown in Scheme 2. It is

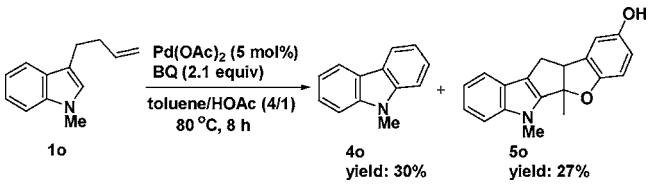
Scheme 2. Plausible Mechanism for the Oxidative Cyclization of 3-(3′-Alkenyl)indoles



suggested that intermediate **A** is generated from **1a**; this then undergoes *endo*-mode olefin insertion to give alkyl palladium species **B**. Following β-H elimination, intermediate **B** gives **C**, which is further aromatized under the reaction conditions to form the corresponding carbazole **4a**. The resulting Pd(0) is oxidized by benzoquinone to a Pd(II) species to complete the catalytic cycle. However, an alternative mechanism for this reaction involving nucleophilic attack of the electron-rich indole ring on the palladium-coordinated olefin through intermediate **A′** to form **C** cannot be excluded.[1a,j]

The presence of a methyl group in the substrate may be crucial for high selectivity in the *endo*-cyclization mode of the reaction since it would make the β-H elimination of the *exo*-mode cyclization intermediate **D**[1a,j] impossible (Scheme 2). To confirm the importance of the olefinic methyl group to the high selectivity observed in the carbazole formation, substrate **1o** was exposed to our standard oxidative cyclization conditions. The reaction gave a phenolic compound **5o** in 27% yield in addition to the target product **4o** only in 30% yield (Scheme 3). The structure of **5o** was confirmed

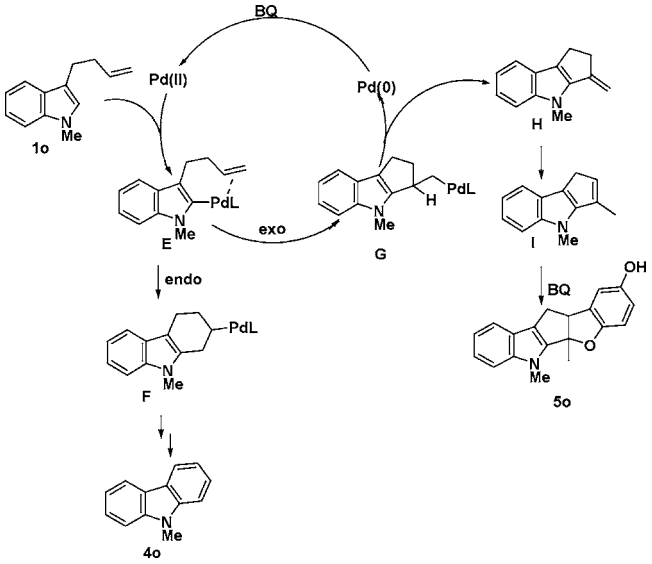
Scheme 3. Pd-Catalyzed Oxidative Cyclization Reaction of **1o**



by X-ray analysis of its benzoyl derivative **6o**.[12]

A rationale for the palladium-catalyzed formation of **5o** is shown in Scheme 4. Similar to the mechanism mentioned

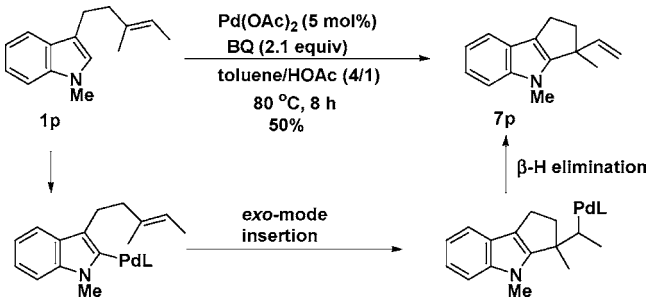
Scheme 4. The Rationale for the Oxidative Cyclization of **1o**



above, 3-(3′-alkenyl)indole **1o** and the Pd(II) species would first form the intermediate **E** which would undergo *endo*-mode and *exo*-mode cyclization by olefin insertion to give alkyl palladium species **F** and **G**, respectively. The intermediate **F** will give **4o** in a similar way as in Scheme 2. As for intermediate **G**, it undergoes β-H elimination to give the olefin **H**, which can isomerize to the thermodynamically more stable intermediate **I**. A formal hetero-[3+2]-cycloaddition reaction between **I** and benzoquinone would give the phenolic compound **5o**.[13] The low yield of **4o** and the formation of **5o** from **1o** further illustrate the importance of the methyl or the alkyl (for compounds **1l**, **1m**, and **1n**) substituent.

To confirm the role of the terminal olefin in these reactions, compound **1p** was used as the substrate for this oxidative cyclization. The reaction gave the *exo*-mode cyclization product **7p**[1h] in 50% yield. This implies that the presence of the terminal methyl group on the olefin makes the β-H elimination possible for the Pd species resulting from the *exo*-cyclization mode with **7p** finally formed as the product (Scheme 5).

Scheme 5. The *exo*-Mode Cyclization of **1p**



In conclusion, we have developed a direct synthesis of carbazoles by palladium-catalyzed intramolecular oxidative cyclization of 3-(3′-alkenyl)indoles under mild conditions. In this reaction, the benzene ring is constructed by an *endo*-cyclization and a subsequent oxidation reaction of the so-formed cyclohexadiene moiety with benzoquinone, which is also responsible for regenerating the catalytically active Pd(II) species. Further investigation of the scope and mechanism of this reaction is underway.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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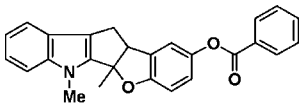
(12) The structure of **5o** was confirmed by X-ray analysis of its benzoyl derivative **6o**.



6o

(13) For similar formal [3+2]-cycloaddition reactions, see: (a) Engler, T. A.; Combrink, K. D.; Ray, J. E. *J. Am. Chem. Soc.* **1988**, *110*, 7931. (b) Engler, T. A.; Reddy, J. P.; Combrink, K. D.; Velde, D. V. *J. Org. Chem.* **1990**, *55*, 1248. (c) Engler, T. A.; Gfesser, G. A.; Draney, B. W. *J. Org. Chem.* **1995**, *60*, 3700. (d) Subburaj, K.; Murugesh, M. G.; Trivedi, G. K. *Synth. Commun.* **1996**, *26*, 2881.