## A Novel One-Pot, Two-Step Synthesis of Polycyclic Indoles *via* Tandem Intramolecular Hydroamidation/Palladium-Catalyzed Annulation

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**Abstract:** A robust one-pot process has been developed for the synthesis of a variety of polycyclic indole skeletons *via* a consecutive sequence of hydroamidation and palladium-catalyzed annulation, from inexpensive 2-chloroanilines bearing tethered acetylenes.

**Keywords:** chloroanilines; hydroamidation; palladium; polycyclic indoles

The indole structural motif is abundantly found in natural products and synthetic compounds of vital medicinal value.<sup>[1]</sup> Construction of polycyclic indoles

usually requires multistep approaches.<sup>[2]</sup> The exploration of new methodologies that allow for the rapid construction of complex indole skeletons in a single operation remains an important challenge facing organic chemists.<sup>[3]</sup>

Recently, we have disclosed a novel regioselective Pd-catalyzed indolization from 2-chloroanilides tethered to internal alkynes,<sup>[4]</sup> based on the previous protocol developed in this group.<sup>[5]</sup> This unusual transformation plausibly involves the formation of the bicyclic palladacycle **4** by *syn* amidopalladation of the acetylene into the Pd-containing zwitterion **3**, $[^{6,7,8]}$  followed by reductive elimination to form the pyrrole ring (Scheme 1). It was observed that in cases where the substrates contained a urea moiety (**1**, X = NH), the transformation was significantly slower. For example,



Scheme 1. Synthesis of polycyclic indoles via Pd-catalyzed intramolecular heteroannulation.

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**Scheme 2.** Synthesis of polycyclic indoles *via* Pd-catalyzed intramolecular heteroannulation.

HPLC monitoring of urea 6 (Scheme 2) showed that the starting material was consumed in about 1 h, forming a small amount of the desired indole product 8 along with a 1:1 ratio of two intermediates identified by NMR as the Z/E isomers of the enamides 7. These intermediates gradually converted to the product upon prolonged heating at 130 °C (Scheme 2).

To further probe the reaction path, we treated urea **6** with  $K_2CO_3$  in NMP in the absence of the catalyst. Indeed, urea **6** was completely converted to **7** at 130 °C in 2 h. The addition of Pd(OAc)<sub>2</sub> and D'BPF to the *Z/E-***7** mixture led to indole **8** in 75% isolated yield. It was then decided to further evaluate the two-step, one-pot protocol, and compare it with our previously reported "batch" approach.<sup>[9]</sup>

Urea **6** was used as substrate for further evaluation of the reaction conditions, mainly focusing on the Pdcatalyzed annulation, aiming at faster turnover rate of the catalyst or milder conditions to minimize product degradation. Thus, **6** was first converted to **7** in NMP at 130 °C, in the presence of 5 equivalents of K<sub>2</sub>CO<sub>3</sub>, and the reaction mixture was used directly to screen conditions for the subsequent Pd-catalyzed annulation. Several conventional electron-rich, bulky ligands suitable for the oxidative addition of aryl chlorides to Pd(0) were examined. As shown in the Table 1, D'BPF is the ligand of choice, giving significantly better results than other ligands.<sup>[10,11]</sup>

To illustrate the scope of the new methodology, a variety of polycyclic indoles containing the imidazolone moiety (8–19) was synthesized using the following conditions: treatment of the substrates with  $K_2CO_3$  in NMP at 130 °C for 2 h to form the enamides, followed by addition of catalytic Pd(OAc)<sub>2</sub> and D'BPF. In all examined cases, the Pd-catalyzed annulation was completed in *ca.* 12 h. The influence of substituents on both the acetylene and the benzene **Table 1.** Conditions screened for the intramolecular Pd-catalyzed heteroannulation of  $\mathbf{7}^{[a]}$ 



 <sup>[</sup>a] All reactions were carried out with anilide 7 (1.0 mmol), Pd(OAc)<sub>2</sub> (5 mol%), ligand (10 mol%), K<sub>2</sub>CO<sub>3</sub> (5 equiv.) in NMP (10 mL).

ring turned out to be fairly marginal. Good to excellent yields were obtained in all cases (Table 2).

We then examined the enamide substrates: the results varied significantly, depending on the terminal substituents of the acetylene and the ring size of the formed enamide intermediates (Table 3). In general, the hydroamidation to form five-membered ring enamides proceeded smoothly at 130°C, furnishing enamides 21, 27, 30 in less than 2 h (Table 3, entries 1, 3, 4). On the contrary, formation of six-membered ring enamides 24, 33 and 39 required prolonged reaction time or elevated reaction temperature (Table 3, entries 2, 5, 8). The fact that anilide 32 underwent no reaction until the temperature was increased to 170°C, as well as the different reactivities between 26 and 29, points to a counterproductive electron-donating effect of the *para*-methyl substituent on the benzene ring. Additives such as CuI, ZnBr<sub>2</sub>, Pd(OAc)<sub>2</sub> and (n-Bu)<sub>4</sub>NBr, have no effect on the hydroamidation.<sup>[12]</sup> However, use of Cs<sub>2</sub>CO<sub>3</sub> as the base facilitated the hydroamidation remarkably, allowing the cyclization of 32 to be completed in 2 h at 130°C (entry 6, Table 3). But the efficiency was compromised due to hydrolysis of the enamide intermediate and formation of by-products during the subsequent palladium-catalyzed annulation. Nevertheless, the indole product was obtained in 72% isolated yield. No hydroamidation occurred for substrates 35 and 41, even at 180°C (entries 7 and 9, Table 3), suggesting that the reaction cannot be extended to substrates that involve formation of seven-membered ring enamides or that contain alkyl substituents at the acetylene terminus.

**Table 2.** Synthesis of polycyclic indoles *via* consecutive hydroamidation and Pd-catalyzed heteroannulation of tethered alkynes with 2-chloro-anilides.<sup>[a]</sup>



 [a] All reactions were carried out with anilide 7 (1.0 mmol), Pd(OAc)<sub>2</sub> (5 mol%), ligand (10 mol%), K<sub>2</sub>CO<sub>3</sub> (5 equiv.) in NMP (10 mL).<sup>[a]</sup> All reactions were carried out with anilide 7 (1.0 mmol), Pd(OAc)<sub>2</sub> (5 mol%), ligand (10 mol%), K<sub>2</sub>CO<sub>3</sub> (5 equiv.) in NMP (10 mL).

<sup>[b]</sup> Isolated yield of major product.

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A similar trend was observed in the Pd-catalyzed annulation of enamides **21**, **27**, and **30** containing a five-membered ring, which underwent facile cyclization at 130 °C (Table 3, entries 1, 3, 4), whereas the one bearing a six-membered ring enamide required prolonged reaction times or higher temperature (Table 3, entries 2, 5, 8).

It is noteworthy that remarkable differences exist in both reaction profile and scope between the current sequential procedure and the previously reported "batch" protocol, in which the catalyst was added together with base at the beginning of the reaction. For instance, with the sequential procedure, the substrates containing a terminal acetylene such as 20 and 23, smoothly underwent hydroamidation and indolization, producing the desired products in good yield (entries 1, 2, Table 3), while the "batch" protocol afforded complex reactions, suggesting the shuttling of these substrates toward other Pd-catalyzed processes. On the other hand, for substrates 32 and 41, which were very sluggish or totally unreactive toward hydroamidation, the "batch" protocol exhibited advantages, rapidly producing the desired products in good yield.<sup>[4]</sup> These results unambiguously illustrate the distinct mechanisms and the complementary scope of the two procedures. Further work is ongoing to extend this stepwise protocol to substrates containing alkyl substituents at the alkyne terminus.

In summary, we have developed a practical one-pot process for synthesis of a variety of polycyclic indoles from readily available, inexpensive 2-chloroanilines bearing tethered alkynes. Distinct in mechanism from the previous "batch" method, this alternative protocol involves consecutive intramolecular hydroamidation and palladium-catalyzed annulation. In many cases, the "two-step" approach is more robust and affords higher yields than the "batch" process, although these two protocols are complementary with respect to scope. Further exploration of the reaction conditions to expand the reaction scope is underway.

#### **Experimental Section**

# General Procedure for Polycyclic Indole Synthesis *via* Consecutive Hydroamidation and Palladium-Catalyzed Intramolecular Heteroannulation

To a dry round-bottom flask containing a magnetic stir bar was charged the alkynyl-2-chloroanilide (1.0 mmol), potassium carbonate (690 mg, 5.0 mmol, 5.0 equiv.) and NMP (10 mL) under nitrogen. The mixture was heated at 130 °C, or the specified temperature until the starting material was consumed completely.  $Pd(OAc)_2$  (5 mol%) and D'BPF (10 mol%) were added at room temperature. The mixture was degassed and then heated at 130 °C or the specified temperature until the reaction was completed. After being cooled to room temperature, the mixture was diluted with



**Table 3.** Synthesis of polycyclic indoles *via* consecutive hydroamidation and Pd-catalyzed heteroannulation of tethered alkynes with 2-chloroanilides.<sup>[a]</sup>

[a] All reactions were carried out with anilide 7 (1.0 mmol), Pd(OAc)<sub>2</sub> (5 mol%), ligand (10 mol%), K<sub>2</sub>CO<sub>3</sub> (5 equiv.) in NMP (10 mL).

<sup>[b]</sup> Isolated yield.

<sup>[c]</sup> The reaction was carried out under the same conditions except for the use of Cs<sub>2</sub>CO<sub>3</sub> as base.

EtOAc and washed with water. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with water, brine, and dried over anhydrous  $Na_2SO_4$  and concentrated. Purification of the crude product by column chromatography on silica gel gave analytically pure product.

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