ORGANIC LETTERS

2006
Vol. 8, No. 16
3573−3575

A New Entry to Polycyclic Indole Skeletons via Palladium-Catalyzed Intramolecular Heteroannulation

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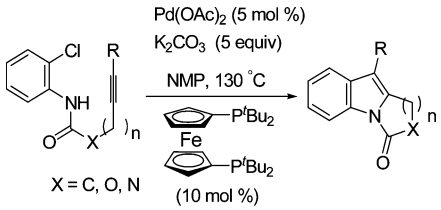
Received June 12, 2006

ABSTRACT

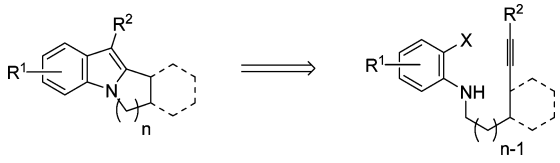


A one-step method was developed for elaboration of a variety of polycyclic indole skeletons via a novel palladium-catalyzed intramolecular indolization of 2-chloroanilines bearing tethered acetylenes. This novel intramolecular indolization method unveils an unusual *syn* amidopalladation pathway of a tethered alkyne.

Alkaloids containing the indole structure motif are found in numerous natural products and synthetic compounds of vital medicinal value.[1] Construction of polycyclic indoles usually requires multistep approaches.[2] The exploration of new methodologies that allow rapid establishment of these indole skeletons in a single operation remains an important challenge facing organic chemists.[3]

Recently we have developed a novel Pd-catalyzed regioselective intermolecular indolization of 2-bromo- or chloroanilines with internal alkynes,[4] based on Larock's protocol.[5] The feasibility of using chloroaniline derivatives as the starting material has significant practical and economical value from a cost and throughput standpoint. We were curious whether the same Pd-catalyzed alkyne insertion protocol could be applied for the preparation of polycyclic indoles via an intramolecular indolization process (Scheme 1). Herein we report our first results on this program.

Scheme 1. Synthesis of Polycyclic Indoles via Pd-Catalyzed Intramolecular Heteroannulation



Mechanistically, to achieve the successful execution of this catalytic process, one prerequisite is to form the desired

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(1) For recent reviews of indole-containing natural products, see: (a) Lounasmaa, M.; Tolvanen, A. *Nat. Prod. Rep.* **2000**, *17*, 175. (b) Faulkner, D. J. *Nat. Prod. Rep.* **1999**, *16*, 155. (c) Michael, J. P. *Nat. Prod. Rep.* **1998**, *15*, 571.

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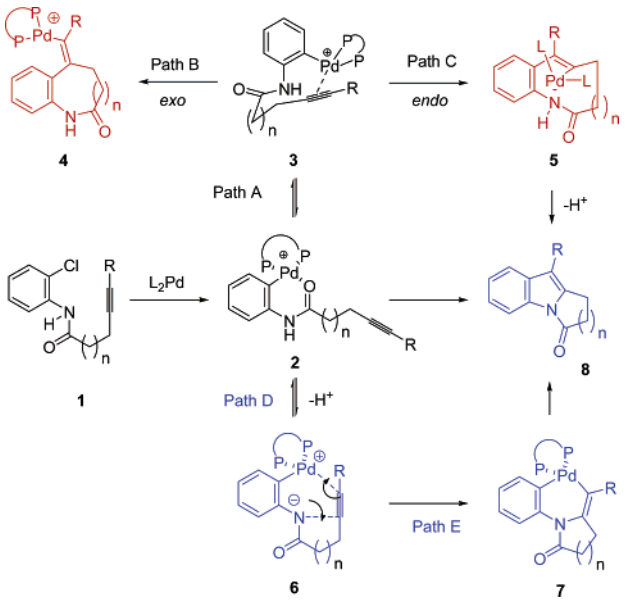
10.1021/ol061440j CCC: $33.50
Published on Web 07/04/2006

amidopalladacycle **5** via the "*endo-dig*" carbopalladation, which would afford the indoles by subsequent C−N reductive elimination (path C).[5] Given the strained geometry of amidopallacycle **5**, as well as the potential competing "*exo-dig*"-carbopalladation of **3** (path B),[6] we expected that the reaction may work only for large rings (i.e., n = a rather large number). Surprisingly, we have observed that the desired product is formed even when n (Schemes 1 and 2)

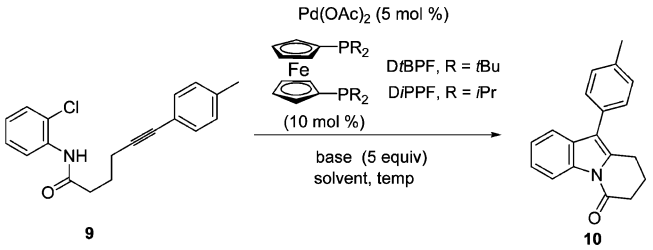
Scheme 2. Mechanism Insight into Pd-Catalyzed Intramolecular Heteroannulation



is very small (n = 1). This observation points, therefore, to a new and unanticipated mechanism being responsible for this novel transformation. In this preliminary Letter, we disclose a novel domino process that involves, most likely, the following steps: (a) formation of the Pd-containing zwitterion **6** (Scheme 2, path D) by standard oxidative addition of Pd(0) to **1**, probably through depot form **2**;[7] (b) formation of the bicyclic palladacycle **7** by *syn* amidopalladation of the acetylene into **6**;[8−10] and (c) reductive elimination of the palladacycle **7** to afford the indole ring. To the best of our knowledge, intramolecular *syn* amidopalladation of this type has never been reported in the literature.

We started the investigation with the 2-chloroaniline derivative **9** by evaluating the influence of several important reaction parameters. On the basis of our previous experience on *intermolecular* indolization, D*t*BPF or Cy_3P is superior to the other conventional electron-rich ligands for the alkyne insertion to the arylpalladium chloride intermediates. However, we envisioned that the choice of the optimum base would be very crucial in order to overcome the "*exo-dig*" carbopalladation pathway (to yield **4**, path B, Scheme 2). Thus, our initial efforts were mainly focused on the investigation of base effects. These results are summarized in Table 1.

Table 1. Conditions Screened for the Intramolecular Heteroannulation of **9**[a]



entry	ligand	base	solvent	temp/time (°C/ min)	solution assay (%)
1	D*t*BPF	DBU	NMP	130/120	trace
2	D*t*BPF	TMG	NMP	130/120	trace
3	D*t*BPF	$KHCO_3$	NMP	130/90	25
4	D*t*BPF	K_2CO_3	NMP	130/40	70
5	D*t*BPF	Na_2CO_3	NMP	130/90	11
6	D*t*BPF	K_3PO_4	NMP	130/60	50
7[b]	D*t*BPF	K_2CO_3	NMP	130/150	49
8	D*t*BPF	K_2CO_3	NMP	110/240	41
9	D*t*BPF	Cs_2CO_3	NMP	130/90	26
10	D*t*BPF	NaH	NMP	130/20	trace
11	CTC-Q-Phos	K_2CO_3	NMP	130 /180	trace
12	tBu_3P	K_2CO_3	NMP	130/40	37
13	D*i*PPF	K_2CO_3	NMP	130/40	35

[a] All reactions were carried out with anilide **9** (1.0 mmol), $Pd(OAc)_2$ (5 mol %), D*t*BPF (10 mol %), and K_2CO_3 (5 equiv) in NMP (10 mL). [b] $Pd_2(dba)_3$ (2.5 mol %) was used.

As anticipated, the optimal results were obtained by using D*t*BPF as ligand. K_2CO_3 was the optimal base and NMP proved to be the superior solvent. The reaction of **9** was complete within 1 h at 130 °C under these conditions, which is much faster than the intermolecular reaction under the same conditions,[4] providing the desired product **10** in 70% isolated yield (entry 4, Table 1).

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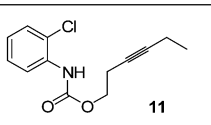
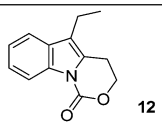
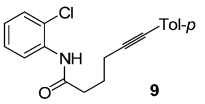
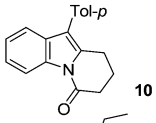
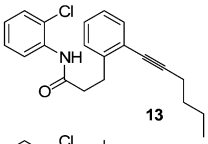
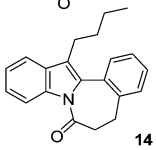
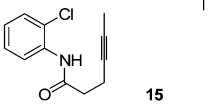
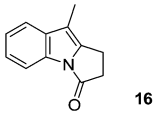
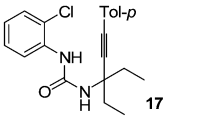
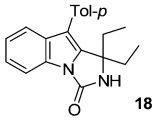
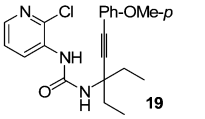
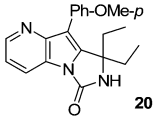
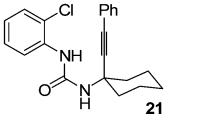
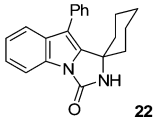
(10) For related chemistry that may have similar mechanism, see: (a) Maassarani, F.; Pfeffer, M.; Spencer, J.; Wehman, E. *J. Organomet. Chem.* **1994**, *466*, 265. (b) Korivi, R. P.; Cheng, C. H. *Org. Lett.* **2005**, *7*, 5179.

Table 2. Synthesis of Polycyclic Indoles via Pd-Catalyzed Intramolecular Heteroannulation of Tethered Alkynes with 2-Chloroanilides[a]

entry	substrate	product	yield(%)[b]
1	 **11**	 **12**	56
2	 **9**	 **10**	70
3	 **13**	 **14**	61
4	 **15**	 **16**	59
5	 **17**	 **18**	78
6	 **19**	 **20**	50
7	 **21**	 **22**	75

[a] All reactions were carried out with 2-chloroanilides (1.0 mmol), $Pd(OAc)_2$ (5 mol %), D^{t}BPF (10 mol %), and K_2CO_3 (2.5 equiv) in NMP (10 mL). [b] Isolated yield of major product.

The dependence on the base used is rather remarkable, as organic bases are totally ineffective (entries 1 and 2) and other inorganic bases are also quite inefficient. To illustrate the scope of this methodology, a variety of polycyclic indoles were synthesized with our standard conditions, even though better yield may be obtainable through re-optimization of each individual entry. These results are summarized in Table 2. (2-Chloroaryl)carbamate **11** and ureas **17**, **19**, and **21** are readily prepared from (2-chlorobenzene)isocyanate with alkynyl alcohols or amines. Reaction of the carbamate **11** is very fast. However, reduced yields were obtained due to the decomposition of the starting material under the reaction conditions, presumably through the corresponding isocyanate (Table 2, entry 1). The influence of substituents on both ends of the acetylene and the ring size are illustrated by the amides **9**, **13**, and **15** (Table 2, entries 2−4). Five-, six-, and seven-membered rings were formed uneventfully. The major side product frequently observed is the dechlorinated starting material, the result of a reductive process. Work toward identifying the source of reducing agent is underway as are further studies on the optimization of these processes.

At this moment, we have no mechanistic understanding of this process, but we believe that the rationale presented in Scheme 2 adequately explains our observations and is sufficiently precedented in the *aminopalladation of alkenes*.

In summary, we have developed a one-step method for elaboration of a variety of polycyclic indole skeletons via a novel palladium-catalyzed intramolecular indolization of 2-chloroanilines bearing tethered acetylenes. This novel intramolecular indolization method unveils an unusual *syn* amidopalladation pathway of a tethered alkyne. Further studies on this protocol and its scope are in progress.

Acknowledgment. We acknowledge Dr. Heewon Lee of Boehringer-Ingelheim Pharmaceuticals for analytical support.

Supporting Information Available: Reaction procedures and characterization of products. This material is available free of charge via the Internet at http://pubs.acs.org.

OL061440J