Published in final edited form as:

Chem Commun (Camb). 2010 January 7; 46(1): 150–152. doi:10.1039/b919991h.

Pd-catalyzed cascade carbopalladation-annulation reaction of 3-(2-iodobenzyl)-indoles into fused 6/5/7/6- and 6/5/5/6-heterocyclic systems†

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Abstract

Polycyclic indole structures, possessing fused seven-membered rings were efficiently synthesized *via* the Pd-catalyzed intramolecular carbopalladation-annulation of 3-(2-iodobenzyl)-indoles and alkynes. A remarkable base effect on the chemoselectivity of this transformation has been found: switching from Et₃N to CsOAc completely reverses the reaction path to intramolecular cyclization forming fused five-membered rings.

Polycyclic derivatives of indole have received increasing attention due to their high importance in modern science, particularly in bio-related fields.¹ Tricyclic and tetracyclic derivatives of indole, possessing seven-membered rings, are used as direct precursors in synthesis of anti-histaminic and anti-inflammatory compounds.^{1*h–k*} Although numerous methods have been developed for assembly of these polycyclic frameworks, they are generally lengthy or require employment of stoichiometric amounts of organometallic reagents, which largely limits their scope.^{2–4} Accordingly, development of alternative catalytic methods for assembly of these important heterocyclic cores is justified. Herein we wish to report the Pd-catalyzed intermolecular cascade annulations reactions of iodobenzyl derivatives of indole **1** with alkynes leading to the formation of polycyclic fused seven-membered heterocycles **2** and five-membered structures **3**.

We envisioned that the *intermolecular* cascade arylation/cyclization reaction of haloaryl heterocycles **1** with alkynes might be an attractive alternative for construction of fused polycyclic compounds possessing seven-membered rings **2** (Scheme 1). The palladium-catalyzed intermolecular reaction of *o*-halobiaryls with alkynes was developed by Larock.⁵ This approach represents a powerful approach for construction of fused aromatic systems. The reaction is known to proceed efficiently on polysubstituted electron-rich *o*-halobiaryls, however, to the best of our knowledge, this annulations strategy has never been used for construction of fused heterocyclic frameworks. Thus, we explored this concept toward assembly of fused derivatives of indole.

First, 3-benzoyl derivative **4a** was examined in arylation/cyclization reaction with 5-decyne (Scheme 2). However, formation of the targeted seven-membered heterocycle **5** was not observed. Instead, tetracyclic indenone **3a**, a product of *intramolecular* arylation, was obtained in 80% yield. The related reaction on indole derivatives is precedented. Thus, it was reported that isomeric 2-benzoyl indole undergoes intramolecular cyclization under

†This article is part of a ChemComm 'Catalysis in Organic Synthesis' web-theme issue showcasing high quality research in organic chemistry. Please see our website (<http://www.rsc.org/chemcomm/organicwebtheme2009>) to access the other papers in this issue.

palladium catalysis to produce indenoindolone.⁶ We decided to explore the scope of this novel mode of intramolecular arylation reaction (Table 1). Thus, cyclization of **4a** provided slightly better yields of **3a** (entry 1) compared to that in the presence of alkyne (Scheme 2). It was found that unprotected indole **4b**, in the presence of 5 mol% of PdCl₂(Ph₃P)₂ and CsOAc, produces indeno[1,2]indole-10(5H)-one (**3b**) in excellent yield (entry 2). *N*-Phenyl indole derivative **4c** cyclized uneventfully, as well. Analogously, carbonyl derivatives of thiophene (entry 4), and furan (entry 5) produced tetracyclic indenones in very good yields.

To gain insight into the origins of high propensity of carbonyl derivatives toward intramolecular arylation, we evaluated arylation of differently-tethered indole derivatives **4a**, **6**, and **1b** (Scheme 3). It was found that the carbonyl derivative **4a** (X = CO) underwent the fastest intramolecular arylation reaction producing indeno[1,2]indole-10(5H)-one **3a** in 100% GC yield. Hydroxymethyl derivative **6** gave 50% yield of **7**, whereas no product formation was observed in the case of benzyl derivative **1b** (X = CH₂) (Scheme 3). These observations imply that the electronic effect of a carbonyl group at the C-3 position accounts for the efficiency of carbonyl derivatives in intramolecular cyclization over the intermolecular arylation/cyclization reaction.⁷ Based on these results, we reasoned that 3-benzyl indole derivative **1b**, unreactive in intramolecular arylation, might be a suitable substrate for intermolecular carbopalladation/annulations cascade toward polycyclic frameworks possessing seven-membered rings.

Next, the influence of different bases on the chemoselectivity of this reaction was examined. When 3-benzyl derivative **1a** was subjected to the reaction with methyl but-2-ynoate, in the presence of a catalytic amount of PdCl₂(Ph₃P)₂ and 2 equivalents of CsOAc, the desired tetracycle **2a** was not formed at all (Table 2). Employment of KOAc resulted in formation of equal amounts of **2a** and **3f** (entry 2). *Finally, use of triethylamine led to exclusive formation of the desired heterocycle 2a possessing a seven-membered ring* (entry 3).

Analogous annulations of NMe indole derivative **1b** in the presence of several bases have been examined, as well. Employment of CsOAc led to formation of seven-membered tetracycle **2b** accompanied by a comparable amount of its chemoisomer **3f**. Surprisingly, switching to KOAc resulted in excellent chemoselectivity of arylation/cyclization of **1b** with methylbut-2-ynoate (entry 5).

With the optimized conditions in hand, we examined the scope of the cascade transformation of indoles **1a** and **1b**. To our delight, a variety of alkynes, possessing electron-rich and electron-deficient triple bonds, worked well in this annulations reaction, leading to the formation of fused seven-membered heterocycles in good yields (Table 3). Thus, reaction of **1a** with 5-decyne led to the formation of **2c** in 98% yield (entry 1). Annulation with diphenylacetylene produced polyaromatic tetracycle **2d** in 78% yield (entry 2). Protected indole derivatives **1b** showed somewhat lower reactivity. Thus, reaction of **1b** with 5-decyne gave **2e** in 70% isolated yield (Table 3, entry 3). Reaction with MOM protected but-2-yne-1,4-diol led to the formation of **2f** in 76% yield (entry 4). Ethyl 3-(trimethylsilyl)-prop-2-ynoate and trimethylsilylprop-2-yne smoothly reacted with *N*-methyl indole derivative **1b** leading to the formation of tetracycles **2g** and **2h**, bearing a trimethylsilyl group at the seven-membered ring (entries 5 and 6). On the other hand, reaction of **1b** with bistrimethylsilylacetylene produced monodesilylated **2i** (entry 7). Analogously, reaction of **1b** with aryltrimethylsilyl alkynes resulted in formation of monodesilylated seven-membered tetracycles **2j** and **2k** (entries 8 and 9).⁹ In all cases, formation of a single regioisomer was observed.

It is believed that the mechanism of the presented herein intermolecular cascade arylation/cyclization reaction of the indole derivatives follows the path proposed by Larock for the

cascade cyclization of *o*-haloaryls.⁵ It starts with the oxidative addition of the Pd(0) to iodobenzylindole **1a** generating the arylpalladium complex **8** (Scheme 4). Carbopalladation of the alkyne triple bond produces vinylpalladium intermediate **9**, which undergoes intermolecular electrophilic carbopalladation at the C-2 position of the indole to form palladacycle **10**. The subsequent reductive elimination, produces product **2** and regenerates the Pd(0) catalyst. On the other hand, complex **8**, in the presence of CsOAc, may undergo a direct *intramolecular* cyclization at the C-2 position *via* a palladacycle **11**¹⁰ to give **3b**.

The kinetic isotope effect studies employing **1b** and **1b-d** revealed the value of $k_H/k_D = 1.1$, thus supporting the suggested above electrophilic nature of the cyclization step (Scheme 5).⁷

In conclusion, we have developed an efficient methodology for construction of fused polycyclic indole heterocycles from easily available starting materials *via* the palladium-catalyzed cascade annulations/cyclization reaction with both electron rich and electron deficient alkynes. Remarkably, it was found that the base has a dramatic effect on *inter*- and *intramolecular* cyclizations leading to seven- or five-membered fused ring systems. In contrast, acyl-tethered substrates, regardless of the base used, undergo intramolecular cyclization to produce five-membered fused structures exclusively.

Acknowledgments

We are grateful to the National Institutes of Health for funding (Grant GM-64444).

Notes and references

1. For reviews on biologically important indole derivatives, see: Lewis SE. Tetrahedron. 2006; 62:8655. Higuchi T, Kawasaki T. Nat. Prod. Rep. 2007; 24:843. [PubMed: 17653362]
2. Kashulin IA, Nifant'ev IE. J. Org. Chem. 2004; 69:5476. [PubMed: 15287801]
3. For radical cyclization reactions in synthesis of polycyclic indole derivatives, see, for example: Flanagan SR, Harrowven DC, Bradley M. Tetrahedron Lett. 2003; 44:1795. Bennasar ML, Roca T, Griera R, Bosch J. J. Org. Chem. 2001; 66:7547. [PubMed: 11681979]
4. For Pd-catalyzed synthesis of fused nitrogen containing heterocycles, see: Zeni G, Larock RC. Chem. Rev. 2004; 104:2285. [PubMed: 15137792] Xie C, Zhang Y, Huang Z, Xu P. J. Org. Chem. 2007; 72:543. Harayama T, Akiyama T, Akamutsu H, Kawano K, Abe H, Takeuchi Y. Synthesis. 2001:444. Campeau L-C, Parisien M, Jean A, Fagnou K. J. Am. Chem. Soc. 2006; 128:581. [PubMed: 16402846] Zhang H, Larock RC. J. Org. Chem. 2003; 68:5132. [PubMed: 12816467] Campo MA, Larock RC. J. Org. Chem. 2002; 67:5616. [PubMed: 12153259] Bressy C, Alberico D, Lautens MJ. J. Am. Chem. Soc. 2005; 127:13148. See also ref. 9. [PubMed: 16173734]
5. Larock RC, Dolty MJ, Tian Q, Zenner M J. J. Org. Chem. 1997; 62:7536.
6. Kozikowski AP, Ma D. Tetrahedron Lett. 1991; 32:3317.
7. For reviews discussing different mechanisms of Pd-catalyzed arylation of heteroaromatic compounds, see: Seregin IV, Gevorgyan V. Chem. Soc. Rev. 2007; 36:1173. [PubMed: 17576484] Alberico D, Scott ME, Lautens M. Chem. Rev. 2007; 107:174. [PubMed: 17212475] Zeni G, Larock RC. Chem. Rev. 2006; 106:4644. [PubMed: 17091931] See also: Chuprakov S, Chernyak N, Dudnik AS, Gevorgyan V. Org. Lett. 2007; 9:2333. [PubMed: 17489598] Chiong HA, Daugulis O. Org. Lett. 2007; 9:1449. [PubMed: 17358073] Deprez NR, Kalyani D, Krause A, Sanford MS. J. Am. Chem. Soc. 2006; 128:4972. [PubMed: 16608329] Stuart DR, Villemure E, Fagnou K. J. Am. Chem. Soc. 2007; 129:12072. [PubMed: 17880083] Gorelsky SI, Lapointe D, Fagnou K. J. Am. Chem. Soc. 2008; 130:10848. [PubMed: 18661978] Garcia-Cuadrado D, de Mendoza P, Braga AAC, Maseras F, Echavarren AM. J. Am. Chem. Soc. 2007; 129:6880. [PubMed: 17461585] Zhao Z, Jaworski A, Piel I, Snieckus V. Org. Lett. 2008; 10:2617. [PubMed: 18543941] Lebrasseur N, Larrosa I. J. Am. Chem. Soc. 2008; 130:2926. [PubMed: 18278918] Wang X, Gribkov DV, Sames D. J. Org. Chem. 2007; 72:1476. [PubMed: 17288392]

8. General procedure for the palladium-catalyzed annulation-cyclization reaction of 3(2-iodobenzyl)indole derivatives with alkynes: to a solution of 10 mmol 3(2-iodobenzyl)indole derivative in 1 mL of DMA was added $\text{PdCl}_2(\text{Ph}_3\text{P})_2$ (5 mol%), 20 mmol of the corresponding base (see Table 3 for details) and 20 mmol of alkyne under inert atmosphere. The reaction was stirred at 110 °C until full consumption of starting indole derivative (8–10 h). When it was completed the resulting solution was diluted with water (10 mL) and extracted with EtOAc (3×10 mL). The combined organic extracts were dried over the sodium sulfate and concentrated under reduced pressure. Resulting crude product was purified *via* column chromatography on silica gel (Hexanes/EtOAc).
9. For examples on desilylation in palladium catalyzed processes, see: Larock RC, Yum EK, Refvic MD. *J. Org. Chem.* 1998; 63:7652. Crawley ML, Goljer I, Jenkin DJ, Mehlmann JF, Nogle L, Dooley R, Mahaney PE. *Org. Lett.* 2006; 8:5837. [PubMed: 17134285]
10. It has been proposed that employment of OAc-containing bases facilitates inter- or intramolecular deprotonation leading to palladacycle intermediates. See ref. 4*c* and 7*i*.

Scheme 1.
Intramolecular cascade annulation reaction of indole derivatives.

Scheme 2.
Reaction of 2-benzoyl indole **4a** with 5-decyne.

		GC yields, %
X = C=O, 4a	X = C=O, 3a	100
X = CHOH, 6	X = CHOH, 7	50
X = CH ₂ , 1b	X = CH ₂ , 3f	0

Scheme 3.

Relative reactivities of indole derivatives in intramolecular arylation reaction.

Scheme 4.
Proposed mechanism.

Scheme 5.
The kinetic isotope effect studies.

Table 1

Synthesis of heterocycles *via* intramolecular cyclization reaction of *o*-iodobenzoyl heterocycles^a

#	Substrate	Product	Yield, % ^b
1			61
2			90 ^c
3			78
4			81
5			71

^a Conditions: 5 mol% Pd(OAc)₂, 10 mol% Ph₃P, 2 equiv. CsOAc, 1 M DMA, 110 °C, 12 h.

^b Isolated yields.

^c 2 h at 130 °C.

Table 2

Base optimization for cascade carbopalladation-annulation of indole derivatives

Entry	Substrate	Base	Ratios ^a 2 ^a : 3f/2b : 3g
1	1a	CsOAc	0 : 100
2	1a	KOAc	50 : 50
3	1a	TEA	100 : 0
4	1b	CsOAc	60 : 40
5	1b	KOAc	100 : 0

^aThe ratios were determined by GC-MS analysis of the crude reaction mixtures.^bCompounds 2a and 2b are mixtures of regioisomers.

Table 3

Synthesis of tetracycles *via* Pd-catalyzed cascade carbopalladation/annulation reaction of indole derivatives with alkynes⁸

#	Alkyne	Base	Product
1		Et ₃ N	2c 90
2		Et ₃ N	2d 78
3		KOAc	2e 70
4		KOAc	2f 76
5		KOAc	2g 75
6		KOAc	2h 75

#	Alkyne	Base	Product	Yield, % ^a
7	$TMS-C\equiv C-TMS$	KOAc		75
8	$TMS-C\equiv C-Ph$	KOAc		71
9	$TMS-C\equiv C-C_6H_4-OMe-p$	KOAc		75

^a Isolated yields.