



16 examples

# Efficient Carbazole Synthesis via Pd/Cu-Cocatalyzed Cross-Coupling/ Isomerization of 2-Allyl-3-iodoindoles and Terminal Alkynes

Can Zhu<sup>†</sup> and Shengming Ma<sup>\*,†,‡</sup>

<sup>†</sup>State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Lu, Shanghai 200032, P. R. China

<sup>‡</sup>Shanghai Key Laboratory of Green Chemistry and Chemical Process, Department of Chemistry, East China Normal University, 3663 North Zhongshan Lu, Shanghai, 200062, P. R. China

Supporting Information

**ABSTRACT:** The Pd/Cu-cocatalyzed one-pot reaction of 2allyl-3-iodo-1-tosyl-1*H*-indoles and terminal alkynes afforded carbazoles highly efficiently via sequential carbon–carbon coupling, isomerization, cyclization, and aromatization forming a benzene ring. Both Pd and Cu are responsible for the coupling step, while  $K_2CO_3$  was observed to be critical for the subsequent cyclization.

arbazoles are important heteroaromatic compounds in many natural products and compounds displaying significant pharmacological and biological activities.<sup>1,2</sup> They are also observed in well-known hole-transporting and electroluminescent materials<sup>3</sup> and, therefore, are considered as potential building blocks for functional materials due to electrical and thermal properties.<sup>4</sup> Based on this, chemists devoted themselves to develop new methods for the synthesis of polysubstituted carbazoles.<sup>5,6</sup> Among them, synthetic pathways to carbazoles from indoles, which involves the formation of a benzene ring, have drawn great attention, considering the fact that indole substances are widely existing compounds.<sup>5,7</sup> However, reported typical methods sometimes suffer from several drawbacks: the severe conditions combined with poor atom economy and multistep synthesis may limit their potential application. Thus, developing novel methodologies involving a simple, mild, efficient, and diversified preparation toward polysubstituted carbazoles from indoles is still highly desirable.

On the other hand, tandem reactions,<sup>8,9</sup> in which multistep reactions are combined into one synthetic operation, have attracted much attention for their efficiency in forming a complex skeleton. For example, the palladium-catalyzed coupling/ cyclization reaction has drawn particular interest because significant molecular complexity can be obtained in one step starting from easily available materials.<sup>10,11</sup> Recently, we reported a one-pot reaction for the synthesis of dihydrocycloocta[b]indoles from 2-allyl-3-iodoindoles and propargylic bromides<sup>12</sup> via palladium(0)-catalyzed carbon–carbon coupling forming the intermediate 3-allenylindoles Int-A, which was followed by cycloisomerization to form the 8-membered ring (Scheme 1). Interestingly, we observed a novel transition-metal-catalyzed coupling/cyclization reaction when terminal alkynes were applied under alkalinic conditions via the intermediacy of 3alkynylindoles Int-B, and base is responsible for the both steps. Herein, we disclose our recent observations.



*cat.* Pd, *cat.* Cu K<sub>2</sub>CO<sub>3</sub>, THF

MeOH, 50 °C



Our initial attempt began with the coupling reaction of iodoindole 1a with phenylacetylene 2a in the presence of [Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>] and [CuI]. Interestingly, when the reaction was carried out in MeOH at 40 °C with 2.0 equiv of K<sub>2</sub>CO<sub>3</sub> as the base, the carbazole derivative 3a was obtained in 16% yield, unexpectedly, while the formation of the coupling product 4a was not detected (Table 1, entry 1). With these inspiring results in hand, we turned to optimizing the reaction conditions for selective formation of 3a. The yield of 3a was improved dramatically to 58% with only 4% of 4a observed when the reaction was conducted at 50 °C, while the same reaction at room temperature led to disappointing results (Table 1, entries 2 and 3). We next turned to examining the solvent effect (Table 1, entries 4-9), and a mixed solvent of THF and MeOH (1:1) was observed to be the best, improving the yield of 3a additionally to 75%, with only 6% yield of 4a (Table 1, entry 9). Further screening was focused on the base effect: other bases such as Et<sub>3</sub>N, Na<sub>2</sub>CO<sub>3</sub>, and Cs<sub>2</sub>CO<sub>3</sub> failed to show better performance than  $K_2CO_3$  (Table 1, entries 10–12). Finally, it was observed that the amount of K<sub>2</sub>CO<sub>3</sub> was also crucial to the reaction, the yield of 3a was improved further to 82% with a trace amount of

Received:January 14, 2014Published:March 12, 2014

**4a** when using 2.5 equiv of  $K_2CO_3$  (Table 1, entries 13–16). Thus,  $Pd(PPh_3)_2Cl_2$  (2 mol %), CuI (2 mol %), and  $K_2CO_3$  (2.5 equiv) in the mixed solvent (THF/MeOH = 1:1) at 50 °C have been defined as the optimized reaction conditions for scope study.

Table 1. Optimization of the Reaction Conditions for the Pd/Cu Co-catalyzed Cross-coupling Reaction and

Cycloisomerization of Iodoindole 1a with Phenylacetylene 2a.<sup>*a*</sup>



<sup>*a*</sup>The reaction was conducted in solvent (2 mL) with **1a** (0.30 mmol), **2a** (0.45 mmol) and base in the presence of Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (2 mol %) and CuI (2 mol %). <sup>*b*</sup>Determined by <sup>1</sup>H NMR analysis with nitromethane as the internal standard. <sup>*c*</sup>The reaction was carried out at 40 °C. <sup>*d*</sup>The reaction was carried out at room temperature. <sup>*e*</sup>THF/ MeOH = 1:1.

With the optimal reaction conditions in hand, we then turned to investigating the substrate scope. First, differently substituted terminal aryl-substituted alkynes together with iodoindole 1a were examined: the analogues substituted with m-Me, m-Cl, p-Me, p-Cl, and p-<sup>n</sup>C<sub>5</sub>H<sub>11</sub> groups all afforded good yields of the products, exhibiting diversity (Table 2, entries 2, 3, and 5-7). It is worth mentioning that free *p*-NH<sub>2</sub> substituent on the benzene ring was observed to be compatible under the standard reaction conditions, affording the corresponding product 3d in 74% (Table 2, entry 4). The reaction worked equally well using heteroaryl-substituted terminal alkynes: 2-thienyl- and 3-thienylsubstituted alkynes produced 3h and 3i in 80% and 71% yields, respectively (Table 2, entries 8 and 9). Furthermore, alkylsubstituted alkyne could also be successfully employed (Table 2, entry 10). Notably, different R<sup>1</sup> groups, such as fluoro and chloro substituents at the 5-position (Table 2, entries 11 and 12) and the chloro substituent at the 6-position (Table 2, entry 13) may be introduced to the indole unit, leading to the corresponding carbazole derivatives in moderate to good yields.

It is easy to conduct the reaction of **1a** and **2d** to afford **3d** in 77% yield on a 1-g scale (Scheme 2). The structures of products



R <sup>1</sup>		Ph + R <sup>2</sup> -== 2 mol % Pd(F 2 mol % Cul 2.5 equiv K <sub>2</sub> C 1.5 equiv K <sub>2</sub> C THF:MeOH = 50 °C, <i>t</i>	PPh <sub>3</sub> )₂Cl₂ O <sub>3</sub> R <sup>1</sup> ∬ 1:1	R <sup>2</sup> Ph N Ts 3
entry	$\mathbb{R}^{1}\left(1\right)$	$R^{2}(2)$	time (h)	yield of $3^{b}$ (%)
1	H (1a)	Ph (2a)	6	72 ( <b>3a</b> )
2	H (1a)	$3-MeC_{6}H_{4}(2b)$	10	68 ( <b>3b</b> )
3	H (1a)	$3\text{-ClC}_{6}\text{H}_{4}(2c)$	6	70 ( <b>3c</b> )
4	H (1a)	$3-H_{2}NC_{6}H_{4}(2d)$	10	74 ( <b>3d</b> )
5	H (1a)	$4\text{-}MeC_{6}H_{4}\left(\mathbf{2e}\right)$	7	76 ( <b>3e</b> )
6	H (1a)	$4-ClC_{6}H_{4}(2f)$	7	68 (3f)
7	H (1a)	$4-{}^{n}C_{5}H_{11}C_{6}H_{4}\left( 2g\right)$	10.5	71 ( <b>3g</b> )
8	H (1a)	2-thienyl (2h)	6	80 $(3h)^c$
9	H (1a)	3-thienyl (2i)	6	71 $(3i)^c$
$10^d$	H (1a)	${}^{n}C_{5}H_{11}(2k)$	14	42 (3p)
11	5-F (1b)	$4\text{-}MeC_{6}H_{4}\left(\mathbf{2e}\right)$	6	62 ( <b>3</b> j)
12	5-Cl (1c)	$4\text{-}MeC_{6}H_{4}\left(\mathbf{2e}\right)$	5	52 ( <b>3</b> k)
13	6-Cl (1d)	$4\text{-}MeC_{6}H_{4}\left(\mathbf{2e}\right)$	5	53 ( <b>3</b> l)

<sup>*a*</sup>The reaction was conducted at 50 °C in the mixed solvent (THF/ MeOH = 1:1) with 1 (0.30 mmol, c = 0.15 M), 2 (0.45 mmol) and K<sub>2</sub>CO<sub>3</sub> (0.75 mmol) in the presence of Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (2 mol %) and CuI (2 mol %). <sup>*b*</sup>Yield of isolated product. <sup>*c*</sup>Isolated yield after chromatography on silica gel and then recrystallization from dichloromethane and petroleum ether. <sup>*d*</sup>K<sub>2</sub>CO<sub>3</sub> (3.5 equiv) was used.

Scheme 2. Gram-Scale Reaction of 1a with 2d





Figure 1. ORTEP representation of 3a.

3a-1 and 3p were determined by the X-ray single-crystal diffraction study of 3a (Figure 1).<sup>13</sup>

Further studies were focused on the coupling/cyclization reaction using TMS-substituted (TMS = trimethylsilyl) acetylene (2j) with differently substituted 3-iodioindoles 1 in a two-step manner given the fact that TMS-acetylene was unstable under  $K_2CO_3$ /MeOH conditions (Scheme 3). When R<sup>3</sup> was H

or Ph, the corresponding desilylated products **3m** and **3n** were also formed in good yields, 70% and 72%, respectively. Moreover, substrate with a chloro substituent at the 5-position of the indole unit afforded carbazole derivative in a relatively lower yield (50%).

Scheme 3. Reactions of Iodoindoles 1 with TMS-Substituted Acetylene 2j (TMS = Trimethylsilyl)



Finally, the structure of the products 3m-o was determined by the X-ray single-crystal diffraction study of 3m (Figure 2).<sup>14</sup>



Figure 2. ORTEP representation of 3m.

In order to show the synthetic potential of the current method, 4-(3-aminobenzyl)-3-phenyl-9-tosyl-9*H*-carbazole (3d) was treated with KOH/EtOH at 80 °C for 12 h to afford the NH carbazole derivative 5 in 86% yield (Scheme 4).<sup>15</sup>

## Scheme 4. Detosylation of 3d



To investigate the mechanism, the reaction was conducted in THF with  $Et_3N$  as the base, and the coupling product **4e** was obtained in 71% isolated yield. Subsequent treatment of **4e** in MeOH at 50 °C for 5 h afforded a trace amount of the expected carbazole product **3e**, with 99% recovery of **4e** (Scheme 5 (a)). However, when **4e** was treated with  $K_2CO_3$  in methanol- $d_4$  at 50 °C, the corresponding products (**3e**/**3e**-d/**3e**-d' = 7:40:53) were obtained in 73% combined yield, indicating the intermediacy of 3-alkynylindole **4e** and the fact that  $K_2CO_3$  was indispensable for the cyclization step (Scheme 5 (b)).

On the basis of these results, a mechanism was proposed to explain the coupling/cyclization reaction affording polysubstituted carbazoles (Scheme 6): Oxidative addition of 3iodoindole 1a with Pd(0) followed by a transmetalation step with Scheme 5. Mechanistic Studies



the copper acetylide *Int-2* generated from phenylacetylene 2e and CuI in the presence of base would afford the palladium complex *Int-3*. Reductive elimination of *Int-3* gives rise to the coupling product 4e,<sup>16</sup> which has been identified in the previous mechanistic studies (see Scheme 5). The presence of K<sub>2</sub>CO<sub>3</sub> would lead to deprotonation of 4e resulting in the formation of *Int-4*, which was followed by isomerization and protonation to generate the intermediate *Int-5*.<sup>17</sup> Finally,  $6\pi$ -electrocyclization of *Int-5* afforded the intermediate *Int-6*. Subsequent isomerization involving aromatization afforded carbazole derivative 3e-*d'*. Base was observed to be essential for both of the coupling and cyclization steps.

## Scheme 6. A Possible Mechanism



In conclusion, we have developed a Pd/Cu-cocatalyzed onepot reaction for the synthesis of polysubstituted carbazoles from 2-allyl-3-iodo-1-tosyl-1*H*-indoles and terminal alkynes. The coupling/cyclization approach is highly efficient and proceeds via sequential carbon—carbon coupling, isomerization, and cyclization involving aromatization forming a benzene ring. The role of the base effect has been identified in both steps of the coupling and cyclization. This chemistry will be of great interest to organic and medicinal chemists for further studies in this area. Further studies are currently underway in our laboratory.

## **Organic Letters**

ASSOCIATED CONTENT

#### **Supporting Information**

Detailed experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs. acs.org.

# AUTHOR INFORMATION

## **Corresponding Author**

\*E-mail: masm@sioc.ac.cn.

# Notes

The authors declare no competing financial interest.

### ACKNOWLEDGMENTS

Financial support from National Basic Research Program (2011CB808700) and National Natural Science Foundation of China (21232006). We thank Mr. Y. Qiu of our research group for reproducing the results of **3d** and **3k** of Table 2 and **3n** of Scheme 3.

# REFERENCES

 (1) (a) Kapil, R. S. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1971; Vol. 13, p 273. (b) Husson, H. P. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1985; Vol. 26, p 1.
 (c) Gallagher, P. T. In *Science of Synthesis*; Thomas, E. J., Ed.; Thieme: Stuttgart, 2001; Vol. 10, p 693. (d) Knölker, H.-J. *Curr. Org. Synth.* 2004, 1, 309. (e) Knölker, H.-J. *Chem. Lett.* 2009, 38, 8.

(2) (a) Knölker, H.-J. *Chem. Soc. Rev.* **1999**, 28, 151. (b) Kong, W.; Fu, C.; Ma, S. *Chem.—Eur. J.* **2011**, 17, 13134. (c) Qiu, Y.; Ma, D.; Fu, C.; Ma, S. *Org. Biomol. Chem.* **2013**, *11*, 1666. (d) Bauer, I.; Knölker, H.-J. *Top. Curr. Chem.* **2012**, 309, 203.

(3) (a) Wang, Y. Z.; Epstein, A. J. Acc. Chem. Res. 1999, 32, 217.
(b) O'Brien, D. F.; Burrows, P. E.; Forrest, S. R.; Koene, B. E.; Loy, D. E.; Thompson, M. E. Adv. Mater. 1998, 10, 1108.

(4) (a) Thomas, J. K. R.; Lin, J. T.; Tao, Y.-T.; Ko, C.-W. J. Am. Chem. Soc. 2001, 123, 9404. (b) Huang, J.; Niu, Y.; Yang, W.; Mo, Y.; Yuan, M.; Cao, Y. Macromolecules 2002, 35, 6080. (c) Sanda, F.; Nakai, T.; Kobayashi, N.; Masuda, T. Macromolecules 2004, 37, 2703. (d) Häussler, M.; Liu, J.; Zheng, R.; Lam, J. W. Y.; Qin, A.; Tang, B. Z. Macromolecules 2007, 40, 1914.

(5) For reviews, see: (a) Knölker, H.-J.; Reddy, K. R. *Chem. Rev.* 2002, 102, 4303. (b) Schmidt, A. W.; Reddy, K. R.; Knölker, H.-J. *Chem. Rev.* 2012, 112, 3193.

(6) For selected examples, see: (a) Kong, W.; Fu, C.; Ma, S. Chem. Commun. 2009, 4572. (b) Qiu, Y.; Kong, W.; Fu, C.; Ma, S. Org. Lett. 2012, 14, 6198. (c) Ackermann, L.; Althammer, A. Angew. Chem., Int. Ed. 2007, 46, 1627. (d) Lim, B.-Y.; Choi, M.-K.; Cho, C.-G. Tetrahedron Lett. 2011, 52, 6015. (e) Hernandez-Perez, A. C.; Collins, S. K. Angew. Chem., Int. Ed. 2013, 52, 12696. (f) Tsang, W. C. P.; Zheng, N.; Buchwald, S. L. J. Am. Chem. Soc. 2005, 127, 14560. (g) Forke, R.; Jäger, A.; Knölker, H.-J. Org. Biomol. Chem. 2008, 6, 2481. (h) Gruner, K. K.; Knölker, H.-J. Org. Biomol. Chem. 2008, 6, 3902. (i) Knott, K. E.; Auschill, S.; Jäger, A.; Knölker, H.-J. Chem. Commun. 2009, 1467. (j) Kumar, V. P.; Gruner, K. K.; Kataeva, O.; Knölker, H.-J. Angew. Chem., Int. Ed. 2013, 52, 11073.

(7) (a) Shu, D.; Winston-McPherson, G. N.; Song, W.; Tang, W. Org. Lett. 2013, 15, 4162. (b) Tu, S.; Ding, C.; Hu, W.; Li, F.; Yao, Q.; Zhang, A. Mol. Divers. 2011, 15, 91. (c) Ozaki, K.; Zhang, H.; Ito, H.; Lei, A.; Itami, K. Chem. Sci 2013, 4, 3416.

(8) For reviews, see: (a) Wasilke, J.-C.; Obrey, S. J.; Baker, R. T.; Bazan, G. C. *Chem. Rev.* **2005**, *105*, 1001. (b) Denmark, S. E.; Thorarensen, A. *Chem. Rev.* **1996**, *96*, 137. (c) Guo, H.-C.; Ma, J.-A. *Angew. Chem., Int. Ed.* **2006**, *45*, 354.

(9) For recent examples, see: (a) Loh, C. C. J.; Atodiresei, I.; Enders, D. *Chem.—Eur. J.* **2013**, *19*, 10822. (b) Kanbayashi, N.; Takenaka, K.; Okamura, T.-a.; Onitsuka, K. *Angew. Chem., Int. Ed.* **2013**, *52*, 4897.

(c) Liu, T.-P.; Xing, C.-H.; Hu, Q.-S. Angew. Chem., Int. Ed. 2010, 49, 2909. (d) Jia, Z.-X.; Luo, Y.-C.; Wang, Y.; Chen, L.; Xu, P.-F.; Wang, B. Chem.—Eur. J. 2012, 18, 12958. (e) Cai, Q.; Liang, X.-W.; Wang, S.-G.; Zhang, J.-W.; Zhang, X.; You, S.-L. Org. Lett. 2012, 14, 5022.

(10) For reviews, see: (a) Miyaura, N.; Suzuki, A. Chem. Rev. **1995**, 95, 2457. (b) Alonso, F.; Beletskaya, I. P.; Yus, M. Chem. Rev. **2004**, 104, 3079.

(11) For selected examples, see: (a) Roesch, K. R.; Larock, R. C. Org. Lett. 1999, 1, 553. (b) Yue, D.; Larock, R. C. J. Org. Chem. 2002, 67, 1905. (c) Roesch, K. R.; Larock, R. C. J. Org. Chem. 2002, 67, 86. (d) Zhu, C.; Ma, S. Org. Lett. 2013, 15, 2782. (e) Kim, H.; Lee, K.; Kim, S.; Lee, P. H. Chem. Commun. 2010, 46, 6341.

(12) Zhu, C.; Zhang, X.; Lian, X.; Ma, S. Angew. Chem., Int. Ed. 2012, 51, 7817.

(13) Crystal data for **3a**: C<sub>32</sub>H<sub>25</sub>NO<sub>2</sub>S, MW = 487.59, monoclinic, space group *P*2(1)/*c*, final *R* indices [ $I > 2\sigma(I)$ ],  $R_1 = 0.0572$ ,  $wR_2 = 0.1336$ , *R* indices (all data),  $R_1 = 0.0643$ ,  $wR_2 = 0.1379$ , a = 10.2775(6) Å, b = 11.5290(7) Å, c = 21.0711(12) Å,  $\alpha = 90.00^{\circ}$ ,  $\beta = 101.4250(10)^{\circ}$ ,  $\gamma = 90.00^{\circ}$ , V = 2447.2(2) Å<sup>3</sup>, T = 293(2) K, Z = 4, reflections collected/ unique: 13011/4813 (*R*(int) = 0.0240), no. of observations [> $2\sigma(I)$ ] 4318; parameter: 326. Supplementary crystallographic data have been deposited with the Cambridge Crystallographic Data Centre. CCDC 979538 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data\_request/ cif.

(14) Crystal data for **3m**: C<sub>20</sub>H<sub>17</sub>NO<sub>2</sub>S, MW = 335.41, monoclinic, space group P2(1)/*c*, final R indices  $[I > 2\sigma(I)]$ ,  $R_1 = 0.0448$ , w $R_2 = 0.1114$ , R indices (all data),  $R_1 = 0.0564$ , w $R_2 = 0.1185$ , a = 12.928(2) Å, b = 11.9718(19) Å, c = 11.6528(18) Å,  $\alpha = 90.00^\circ$ ,  $\beta = 114.040(2)^\circ$ ,  $\gamma = 90.00^\circ$ , V = 1647.1(4) Å<sup>3</sup>, T = 293(2) K, Z = 4, reflections collected/ unique: 8407/3231 (R(int) = 0.0208), no. of observations  $[>2\sigma(I)]$  2629; parameter: 219. Supplementary crystallographic data have been deposited at the Cambridge Crystallographic Data Centre. CCDC 979539 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data\_request/ cif.

(15) MacKay, J. A.; Bishop, R. L.; Rawal, V. H. Org. Lett. 2005, 7, 3421.
(16) For reviews, see: (a) Chinchilla, R.; Nájera, C. Chem. Rev. 2007, 107, 874. (b) Köllhofer, A.; Plenio, H. Chem.—Eur. J. 2003, 9, 1416.
(c) Doucet, H.; Hierso, J.-C. Angew. Chem., Int. Ed. 2007, 46, 834.
(d) Lamblin, M.; Nassar-Hardy, L.; Hierso, J.-C.; Fouquet, E.; Felpin, F.-X. Adv. Synth. Catal. 2010, 352, 33. (e) Chinchilla, R.; Nájera, C. Chem. Soc. Rev. 2011, 40, 5084. (f) Torborg, C.; Huang, J.; Schulz, T.; Schäffner, B.; Zapf, A.; Spannenberg, A.; Börner, A.; Beller, M. Chem.— Eur. J. 2009, 15, 1329.

(17) Zhao, G.; Zhang, Q.; Zhou, H. Adv. Synth. Catal. 2013, 355, 3492.