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Synthesis of 3-Acyl-2-arylindole via Palladium-catalyzed Isocyanide Insertion and Oxypalladation of Alkyne

Takeshi Nanjo, Sho Yamamoto, Chihiro Tsukano, and Yoshiji Takemoto*

Graduate School of Pharmaceutical Sciences, Kyoto University, Yoshida, Sakyo-ku, Kyoto 606-8501, Japan

takemoto@pharm.kyoto-u.ac.jp

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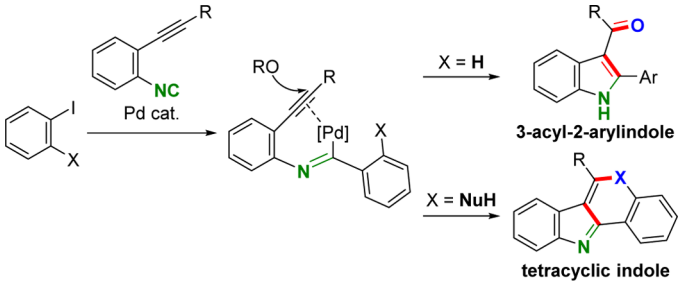
ABSTRACT



The synthesis of 3-acyl-2-arylindole derivatives was performed through palladium-catalyzed isocyanide insertion and oxypalladation of an alkyne. As a result of the introduction of internal nucleophiles, domino cyclization was also achieved for the synthesis of several tetracyclic indole derivatives. Imidoylpalladium generated by isocyanide insertion is a key intermediate in these reactions.

Isocyanides are valuable building blocks in the synthesis of nitrogen-containing compounds and are mainly used for multicomponent reactions such as the Passerini and Ugi reactions.[1] It is known that isocyanides coordinate to transition-metal centers, and the insertion reaction proceeds similarly to that of carbon monoxide.[2,3] However, palladium-catalyzed isocyanide insertion is still a developing area, in contrast to the well-developed chemistry of carbon monoxide, probably because of the difficulty of controlling the isocyanide reactivity.[1a,b] In recent years, there has been a focus on palladium-catalyzed coupling reactions to form C−N and C−O bonds via isocyanide insertion.[4] However, the formation of two C−C bonds via isocyanide insertion has rarely been reported.[5] Furthermore, in most of the previously reported studies, isocyanides were simply used instead of carbon monoxide as a C1 unit. We believe that multi C−C bond formation reactions, in which the C and N atoms of the isocyanide are both

(1) For recent reviews, see: (a) Lang, S. *Chem. Soc. Rev.* **2013**, *42*, 4867. (b) Qiu, G.; Ding, Q.; Wu, J. *Chem. Soc. Rev.* **2013**, *42*, 5257. (c) Tobisu, M.; Chatani, N. *Chem. Lett.* **2011**, *40*, 330. (d) Sadjadi, S.; Heravi, M. M. *Tetrahedron* **2011**, *67*, 2707. (e) Lygin, A. V.; de Meijere, A. *Angew. Chem., Int. Ed.* **2010**, *49*, 9094. (f) Dömling, A. *Chem. Rev.* **2006**, *106*, 17.

(2) (a) *Organotransition Metal Chemistry; from Bonding to Catalysis*; Hartwig, J. F., Ed; University Science Books: Sausalito, 2010. (b) *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed; Wiley-VCH: Weinheim, 2002.

(3) (a) Chicote, M.-T.; Vicente-Harnández, I.; Jones, P. G.; Jicente, J. *Organometallics* **2012**, *31*, 6252. (b) Vincente, J.; Abad, J.-A.; Förtsch, W. *Organometallics* **2001**, *20*, 2704 and references therein.

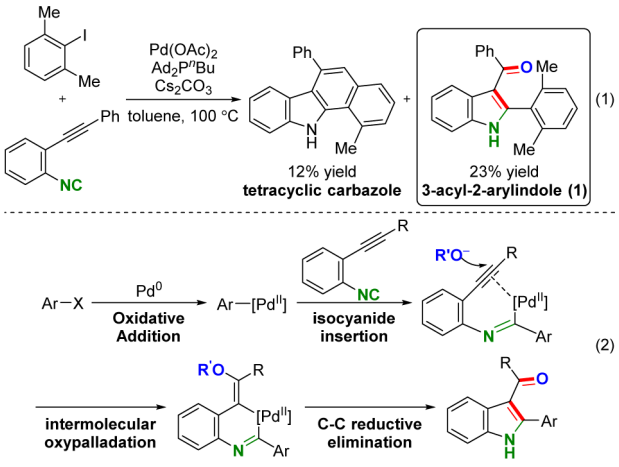
(4) For recent examples of C−N and C−O bond formation via isocyanide insertion, see: (a) Geden, J. V.; Pancholi, A. K.; Shipman, M. *J. Org. Chem.* **2013**, *78*, 4158. (b) Liu, B.; Yin, M.; Wu, W.; Jiang, H. *J. Org. Chem.* **2013**, *78*, 3009. (c) Bochatay, V. N.; Boissarie, P. J.; Murphy, J. A.; Suckling, C. J.; Lang, S. *J. Org. Chem.* **2013**, *78*, 1471. (d) Fei, X.-D.; Ge, Z.-Y.; Tang, T.; Zhu, Y.-M.; Ji, S.-J. *J. Org. Chem.* **2012**, *77*, 10321. (e) Qiu, G.; Liu, G.; Pu, S.; Wu, J. *Chem. Commun.* **2012**, *48*, 2903. (f) Liu, B.; Li, Y.; Jiang, H.; Yin, M.; Huang, H. *Adv. Synth. Catal.* **2012**, *354*, 2288. (g) Wang, Y.; Zhu, Q. *Adv. Synth. Catal.* **2012**, *354*, 1902. (h) Vlaar, T.; Ruijter, E.; Znabet, A.; Janssen, E.; de Kanter, F. J. J.; Maes, B. U. W.; Orru, R. V. A. *Org. Lett.* **2011**, *13*, 6496. (i) Wang, Y.; Wang, H.; Peng, J.; Zhu, Q. *Org. Lett.* **2011**, *13*, 4604. (j) Miura, T.; Nishida, Y.; Morimoto, M.; Yamauchi, M.; Murakami, M. *Org. Lett.* **2011**, *13*, 1429. (k) Jiang, H.; Liu, B.; Li, Y.; Wang, A.; Huawen, H. *Org. Lett.* **2011**, *13*, 4604. (l) Baelen, G. V.; Kuijer, S.; Rýček, L.; Sergeyev, S.; Janssen, E.; de Kanter, F. J. J.; Maes, B. U. W.; Ruijter, E.; Orru, R. V. A. *Chem.—Eur. J.* **2011**, *17*, 15039. (m) Saluste, C. G.; Whitby, R. J.; Furber, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 4156.

(5) (a) Tang, T.; Fei, X.-D.; Ge, Z.-Y.; Chen, Z.; Zhu, Y.-M.; Ji, S.-J. *J. Org. Chem.* **2013**, *78*, 3170. (b) Tobisu, M.; Imoto, S.; Ito, S.; Chatani, N. *J. Org. Chem.* **2010**, *75*, 4835. (c) Curran, D. P.; Du, W. *Org. Lett.* **2002**, *4*, 3215. (d) Onitsuka, K.; Suzuki, S.; Takahashi, S. *Tetrahedron Lett.* **2002**, *43*, 6197. (e) Ishiyama, T.; Oh-e, T.; Miyaura, N.; Suzuki, A. *Tetrahedron Lett.* **1992**, *33*, 4465.

10.1021/ol4016699

incorporated as ring components, would be atom-economical for the synthesis of heterocycles. However, to the best of our knowledge, there are only two reports on this type of palladium-catalyzed reaction: the synthesis of tetracyclic quinazolines by Curran[5c] and of indoles by Takahashi.[5d]

Scheme 1. Synthesis of 3-Acyl-2-arylindole via Palladium-catalyzed Isocyanide Insertion and Oxypalladation of Alkyne



Recently, we reported a palladium-catalyzed cascade process consisting of sequential insertions of an isocyanide and an alkyne, and C(sp^3)–H activation to form polycyclic carbazoles.[6] During this reaction, we obtained 3-acyl-2-arylindole **1** as a byproduct (Scheme 1, eq 1). We supposed that addition of the oxygen nucleophile to the alkyne,[7,8] activated by internal imidoylpalladium, followed by C–C reductive elimination, gave 3-acyl-2-arylindole **1** (Scheme 1, eq 2). The indole moiety is present in a wide range of natural products and pharmaceuticals, and 3-acylindoles are particularly useful intermediates for the preparation of important therapeutic agents.[9] Various methods have therefore been used for their preparation. The majority of these methods involve acylation of preformed indole derivatives,[10] and direct construction of the 3-acylindole skeleton from acyclic precursors has received less attention.[11] We envisioned that the reaction shown in eq 2 could be a new approach for the direct construction of 3-acyl-2-arylindoles, using both the C and N atoms of the isocyanide. In this letter, we describe the synthesis of 3-acyl-2-arylindoles using palladium-catalyzed isocyanide insertion and oxypalladation of an alkyne.

Our initial efforts focused on optimization of the reaction conditions, using **2a** and **3a** (Table 1). Treatment of **2a** and **3a** with 10 mol % $Pd(OAc)_2$, 20 mol % di(1-adamantyl)-*n*-butylphosphine (Ad_2P^nBu) and 3 equiv of Cs_2CO_3 in toluene at 100 °C gave the indole **1a** in 43% yield (entry 1). The addition of 10 equiv of H_2O accelerated the reaction and increased the yield of **1a** to 61% (entry 2). Next, several bases were screened; it was found that carbonates were effective, and Cs_2CO_3 gave the best results in this reaction (entries 2–7). When *N*,*N*-dimethylformamide (DMF) was used instead of toluene, the reaction proceeded effectively and the product **1a** was obtained in 80% yield (entry 8). Lowering the amount of the catalyst did not significantly influence the yields, using DMF as a solvent without H_2O (entry 9). Finally, screening of various ligands revealed that Ad_2P^nBu was the best ligand (entries 10–13). The conditions used in entry 9 were therefore the best for this reaction.

We investigated the substrate scope of the reaction under the optimal conditions (Scheme 2). Initially, various aryl iodides were used as the coupling partner. The reactions of aryl iodides bearing electron-donating groups and chlorine at the para position gave the desired products **1b**–**1d** in good yields. Strong electron-withdrawing groups such as ester, nitrile, and trifluoromethyl groups decreased the yields of products **1e**–**1g**. Introducing a methyl group at the meta and ortho positions maintained high yields (**1h** and **1i**). Next, the reaction was performed using several *o*-alkynylphenyl isocyanides. The reactions of substrates bearing chloro and methoxy groups at the para position of the isocyanide gave the corresponding products **1j** and **1k** in 41 and 69% yields, respectively. The electronic state of the alkyne did not significantly influence the reaction (**1l** and **1m**).

3-Acyl-2-arylindole is a useful intermediate for the construction of polycyclic indole derivatives such as carbolines and carbazoles.[12] We therefore used this reaction

(6) Nanjo, T.; Tsukano, C.; Takemoto, Y. *Org. Lett.* **2012**, *14*, 4270.

(7) For examples of oxypalladation with external nucleophiles, see: (a) Zhou, P.; Jiang, H.; Huang, L.; Li, X. *Chem. Commun.* **2011**, *47*, 1003. (b) Zhao, L.; Lu, X.; Xu, W. *J. Org. Chem.* **2005**, *70*, 4059. (c) Okumoto, H.; Nishihara, S.; Nakagawa, H.; Suzuki, A. *Synlett* **2000**, 217. (d) Kataoka, Y.; Matsumoto, O.; Ohashi, M.; Yamagata, T.; Tani, K. *Chem. Lett.* **1994**, 1283. (e) Utimoto, K. *Pure Appl. Chem.* **1983**, *55*, 1845.

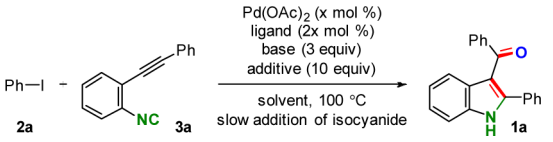
(8) For selected examples of nucleophilic addition to alkyne activated by acyl or aryl Pd(II) species, see: (a) Lu, Z.; Cui, W.; Xia, S.; Bai, Y.; Luo, F.; Zhu, G. *J. Org. Chem.* **2012**, *77*, 9871. (b) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Marinelli, F.; Parisi, L. M. *Tetrahedron* **2003**, *59*, 4661. (c) Hu, Y.; Zhang, Y.; Yang, Z.; Fathi, R. *J. Org. Chem.* **2002**, *67*, 2365. (d) Dai, G.; Larock, R. C. *Org. Lett.* **2002**, *4*, 193. (e) Dai, G.; Larock, R. C. *Org. Lett.* **2001**, *3*, 4035. (f) Arcadi, A.; Cacchi, S.; Carnicelli, V.; Marinelli, F. *Tetrahedron* **1994**, *50*, 437. (g) Arcadi, A.; Cacchi, S.; Marinelli, F. *Tetrahedron Lett.* **1992**, *33*, 3915.

(9) (a) Wu, Y.-S.; Coumar, M. S.; Chang, J.-Y.; Sun, H.-Y.; Kuo, F.-M.; Kuo, C.-C.; Chen, Y.-J.; Chang, C.-Y.; Hsiao, C.-L.; Liou, J.-P.; Chen, C.-P.; Yao, H.-T.; Chiang, Y.-K.; Tan, U.-K.; Chen, C.-T.; Chu, C.-Y.; Wu, S.-Y.; Yeh, T.-K.; Lin, C.-Y.; Hsieh, H.-P. *J. Med. Chem.* **2009**, *52*, 4941. (b) Barreca, M. L.; Ferro, S.; Rao, A.; De Luca, L.; Zappalà, M.; Monforte, A.-M.; Debyser, Z.; Witvrouw, M.; Chimirri, A. *J. Med. Chem.* **2005**, *48*, 7084. (c) Pais, G. C. G.; Zhang, X.; Marchand, C.; Neamati, N.; Cowansage, K.; Svarovskaia, E. S.; Pathak, V. K.; Tang, Y.; Nicklaus, M.; Pommier, Y.; Burke, T. R. *J. Med. Chem.* **2002**, *45*, 3184.

(10) (a) Wu, C.-Y.; Hu, M.; Liu, Y.; Song, R.-J.; Lei, Y.; Tang, B.-X.; Li, R.-J.; Li, J.-H. *Chem. Commun.* **2012**, *48*, 3197. (b) Ali, M. A.; Punniyamurthy, T. *Synlett* **2011**, 623. (c) Bernini, R.; Fabrizi, G.; Sferrazza, A.; Cacchi, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 8078. (d) Yu, W.; Du, Y.; Zhao, K. *Org. Lett.* **2009**, *11*, 2417. (e) Yin, Y.; Ma, W.; Chai, Z.; Zhao, G. *J. Org. Chem.* **2007**, *72*, 5731. (f) Shimada, T.; Nakamura, I.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 10546. (g) Cacchi, S.; Fabrizi, G.; Parisi, L. M. *Synthesis* **2004**, 1889.

(11) (a) Qiu, G.; Chen, C.; Yao, L.; Wu, J. *Adv. Synth. Catal.* **2013**, *355*, 1579. (b) Hu, Z.; Liang, D.; Zhao, J.; Huang, J.; Zhu, Q. *Chem. Commun.* **2012**, *48*, 7371. (c) Kamijo, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 11940. (d) Ottoni, O.; Neder, A. de V. F.; Dias, A. K. B.; Cruz, R. P. A.; Aquino, L. B. *Org. Lett.* **2001**, *3*, 1005. (e) Faul, M. M.; Winneroski, L. L. *Tetrahedron Lett.* **1997**, *38*, 4749. (f) Bergman, J.; Venemalm, L. *Tetrahedron* **1990**, *46*, 6061. (g) Ketcha, D. M.; Gribble, G. W. *J. Org. Chem.* **1985**, *50*, 5451. (h) Eyley, S. C.; Giles, R. G.; Heaney, H. *Tetrahedron Lett.* **1985**, *26*, 4649.

Table 1. Investigation of Reaction Conditions[a]



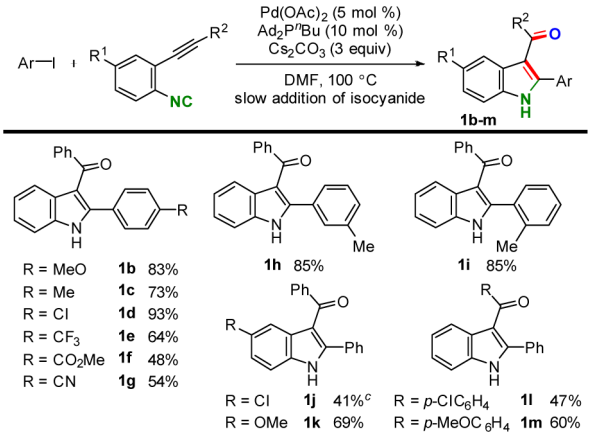
entry	x	ligand	base	additive	solvent	yield[b] (%)
1	10	Ad_2P^nBu	Cs_2CO_3	none	toluene	43
2	10	Ad_2P^nBu	Cs_2CO_3	H_2O	toluene	61
3	10	Ad_2P^nBu	K_2CO_3	H_2O	toluene	30
4	10	Ad_2P^nBu	CsF	H_2O	toluene	7
5	10	Ad_2P^nBu	Et_3N	H_2O	toluene	8
6	10	Ad_2P^nBu	CsOAc	H_2O	toluene	24
7	10	Ad_2P^nBu	$CsOH•H_2O$	H_2O	toluene	45
8	10	Ad_2P^nBu	Cs_2CO_3	H_2O	DMF	80
9	**5**	**Ad_2P^nBu**	**Cs_2CO_3**	**none**	**DMF**	**78**
10	5	PPh_3	Cs_2CO_3	none	DMF	69
11	5	DPPE[c]	Cs_2CO_3	none	DMF	39
12	5	BINAP[c]	Cs_2CO_3	none	DMF	24
13	5	$biphPCy_2$	Cs_2CO_3	none	DMF	29

[a] Isocyanide **2a** was added dropwise to the solution of PhI, $Pd(OAc)_2$, ligand, base and additive for 3 h by using a syringe pump. [b] Isolated yield. [c] 5 mol % of ligand was used. Ad = 1-adamantyl, biph = 2-biphenyl.

to achieve domino cyclization using internal nucleophiles (Scheme 3). *o*-Iodoaniline (**4**) and isocyanide **3a** coupled in the presence of a palladium catalyst to give the tetracyclic γ-carboline **5** in 56% yield. This strategy was applied to the reaction of *o*-iodophenol (**6**), and the corresponding product **7** was obtained in 73% yield. This is the first example of the construction of a chromeno[4,3-*b*]indole skeleton bearing a characteristic conjugated system. The reaction of *o*-iodobenzyl cyanide (**8**) also gave the desired tetracyclic carbazole **9** in 68% yield.[13] Interestingly, when DMF, which is an effective solvent for the formation of **1a**, was used instead of toluene, the reactions using *o*-iodoaniline (**4**) and *o*-iodophenol (**6**) did not give **5** and **7**, respectively. The reaction of *o*-iodobenzyl cyanide with toluene did not give product **9**, similar to the synthesis of **1a**.

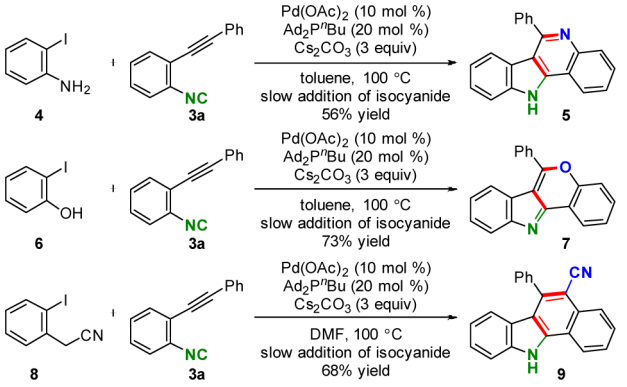
In order to gain insight into the reaction, the following experiments were performed (Scheme 4). When bromobenzene was used as the substrate instead of iodobenzene, the yield was low (Scheme 4, eq 1). Also, the addition of a silver salt significantly inhibited the reactions of both iodo- and bromo-benzene (not shown). These results suggest that halides play an important role in the reaction. Based on this hypothesis, we examined the addition of some iodide sources, and found that tetrabutylammonium iodide (TBAI, 1 equiv) increased the yield of **1a** to 41%.

Scheme 2. Substrate Scope[a,b]



[a] Isocyanides were added dropwise to the solution of ArI, $Pd(OAc)_2$, Ad_2P^nBu and Cs_2CO_3 for 3 h by using syringe pump. [b] Isolated yield. [c] Ten mol % of $Pd(OAc)_2$ and 20 mol % of Ad_2P^nBu were used.

Scheme 3. Synthesis of Tetracyclic Indole Derivatives by Domino Cyclization of Internal Nucleophiles



We also performed labeling experiments to identify the oxygen source in product **1a** (Scheme 4, eq 2). The ^{18}O-incorporated product **1a-^{18}O** was formed in the presence of $H_2{}^{18}O$ as the additive, and the ratio of **1a-^{18}O**:**1a** was 69:31.[14] These results and examination of the reaction conditions (Table 1) suggested that H_2O is one of the oxygen sources, and other species such as acetate and carbonate can also supply an oxygen atom.

A plausible mechanism is shown in Figure 1. First, oxidative addition of Pd(0) to aryl iodide, followed by isocyanide insertion, generates imidoylpalladium **A**.[15] Imidoylpalladium effectively activates the internal alkyne, and oxypalladation[6,16] with acetate, carbonate, or hydroxide

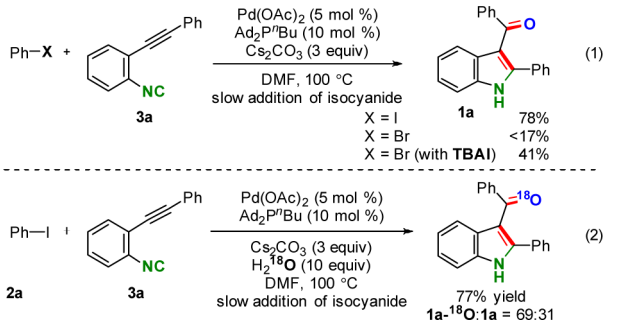
(12) (a) Wahlström, N.; Slätt, J.; Stensland, B.; Ertan, A.; Bergman, J.; Janosik, T. *J. Org. Chem.* **2007**, *72*, 5886. (b) Pathak, R.; Nhlapo, J. M.; Govender, S.; Michael, J. P.; van Otterlo, W. A. L.; de Koning, C. B. *Tetrahedron* **2006**, *62*, 2820. (c) de Koning, C. B.; Michael, J. P.; Nhlapo, J. M.; Pathak, R.; van Otterlo, W. A. L. *Synlett* **2003**, 705. (d) Cacchi, S.; Fabrizi, G.; Pace, P.; Marinelli, F. *Synlett* **1999**, 620.

(13) The structure of **9** was determined by X-ray crystallography. See Supporting Information.

(14) The treatment of **1a** with $H_2{}^{18}O$, $Pd(OAc)_2$, Ad_2P^nBu, Cs_2CO_3 in DMF at 100 °C did not give **1a-^{18}O**. This result denies the possiblity of the exchange of the oxygen atom of **1a**.

(15) For selected examples of isocyanide insertion into the Pd–C bond, see: (a) Yamamoto, Y.; Yamazaki, H. *Inorg. Chim. Acta* **1980**, *41*, 229. (b) Albert, J.; D'Andrea, L.; Granell, J.; Zafrilla, J.; Font-Bradia, M.; Solans, X. *J. Organomet. Chem.* **2007**, *692*, 4895. (c) Vincent, J.; Saura-Llamas, I.; García-López, J.-A.; Bautista, D. *Organometallics* **2009**, *28*, 448.

Scheme 4. Mechanistic Studies



proceeds, to give the six-membered palladacycle **B**. C−C reductive elimination regenerates the Pd(0) species, and subsequent hydrolysis or isomerization of **C** produces the desired product **D**. In the oxypalladation step, the halide leaves the palladium center, along with Pd−C bond formation, so the higher leaving ability of I^- probably gives a better result than Br^-.[17] Tetracyclic indole derivatives **E** could be generated by cyclization of internal nucleophiles of **D**. However, when iodoaniline (**4**) or iodophenol (**6**) was used, the domino cyclization in DMF did not give good results,[18] in contrast to the synthesis of 3-acylindole **1**. We therefore suggest that these reactions in toluene proceeded via another pathway involving carbopalladation of **A** and intramolecular C−X reductive elimination of vinylpalladium intermediate **F**. The related complex of intermediate **F** was isolated by Takahashi and co-workers,[19] and a similar reaction pathway was proposed for the synthesis of heterocycles.[20] However, the best reaction solvent for

(16) We also tried the introduction of other nulceophiles such as amine or alcohols, but the reaction did not give the corresponding products. The reason would be that *o*-alkynylphenylisocyanide **3a** reacted with nucleophiles to give an undesired product without involvement of palladium catalyst under these conditions. Please see: Suginome, M.; Fukuda, T.; Ito, Y. *Org. Lett.* **1999**, *1*, 1977.

(17) Gabriele, B.; Salerno, G.; Lauria, E. *J. Org. Chem.* **1999**, *64*, 7687.

(18) Because isocyanide **3a** would react with phenol and aniline in DMF under these conditions.

(19) Onitsuka, K.; Segawa, M.; Takahashi, S. *Organometallics* **1998**, *17*, 4335.

(20) (a) Larock, R. C.; Yum, E.-K.; Refvik, M. D. *J. Org. Chem.* **1998**, *63*, 7652. (b) Larock, R. C.; Yum, E.-K. *J. Am. Chem. Soc.* **1991**, *113*, 6689.

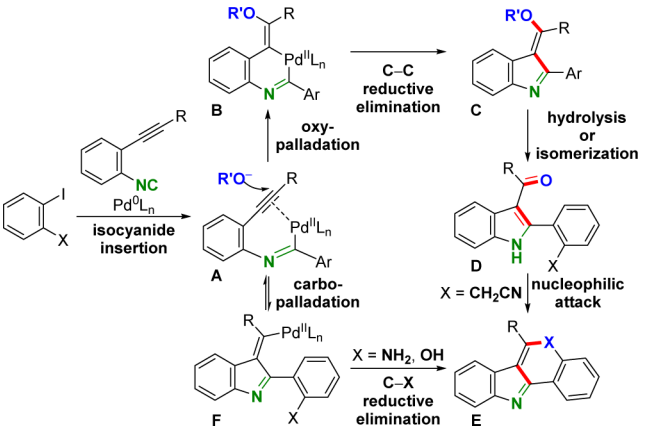


Figure 1. Plausible mechanism.

iodobenzyl cyanide (**8**) is the same as that for the synthesis of 3-acylindole **1**, so carbazole **9** was probably formed via 3-acylindole **D**.

In summary, we have developed palladium-catalyzed isocyanide insertion and alkyne functionalization for the synthesis of 2-arylindole derivatives, including tetracyclic carbazoles. In this process, the formation of two C−C bonds via isocyanide insertion was achieved, and isocyanide was effectively used by incorporating both the C and N atoms as components of the indole skeleton. We are currently extending this strategy to convergent synthesis of nitrogen-containing polycycles and examining further details of the reaction mechanisms.

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

The authors declare no competing financial interest.