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Stereoselective Synthesis of 3-Alkylideneoxindoles by Palladium-Catalyzed Cyclization Reaction of 2-(Alkynyl)aryl Isocyanates with Organoboron Reagents

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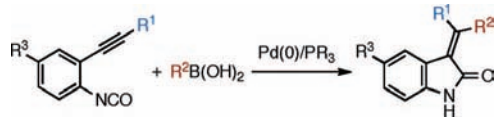
ABSTRACT



A palladium(0)/monophosphine catalyst promotes a cyclization reaction of 2-(alkynyl)aryl isocyanates with organoboron reagents to produce stereodefined 3-alkylideneoxindoles. The alkynyl and isocyanato groups undergo oxidative cyclization with Pd(0) to form an oxapalladacycle intermediate. Subsequent transmetalation and reductive elimination afford the product.

The 3-alkylideneoxindole ring system represents a key substructure found in a number of biologically active compounds.[1] In addition, 3-alkylideneoxindoles are valuable intermediates in the synthesis of naturally occurring alkaloids[2] and drug candidates.[3] Although Knoevenagel condensation between oxindole derivatives and carbonyl compounds is one of the most reliable procedures for their preparation, a mixture of both stereoisomers is often formed with regard to the resulting carbon−carbon double bond.[1a,2a−c] Therefore, the development of a method for the stereoselective synthesis of these important molecules is needed, and several transition-metal-mediated procedures have been developed.[4] We have previously described the rhodium(I)-catalyzed cyclization reaction of 2-(alkynyl)aryl isocyanates with aryl- and alkenylboronic acids.[5] This reaction permits the sp^2 carbon

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(4) For recent examples of the synthesis of 3-alkylideneoxindoles with catalysis of transition metals, see: (a) Kamijo, S.; Sasaki, Y.; Kanazawa, C.; Schüβeler, T.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 7718. (b) Yanada, R.; Obika, S.; Inokuma, T.; Yanada, K.; Yamashita, M.; Ohta, S.; Takemoto, Y. *J. Org. Chem.* **2005**, *70*, 6972. (c) Cheung, W. S.; Patch, R. J.; Player, M. R. *J. Org. Chem.* **2005**, *70*, 3741. (d) Shintani, R.; Yamagami, T.; Hayashi, T. *Org. Lett.* **2006**, *8*, 4799. (e) Pinto, A.; Neuville, L.; Zhu, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 3291. (f) Tang, S.; Yu, Q.-F.; Peng, P.; Li, J.-H.; Zhong, P.; Tang, R.-Y. *Org. Lett.* **2007**, *9*, 3413. (g) Tang, S.; Peng, P.; Pi, S.-F.; Liang, Y.; Wang, N.-X.; Li, J.-H. *Org. Lett.* **2008**, *10*, 1179. (h) Miura, T.; Takahashi, Y.; Murakami, M. *Org. Lett.* **2008**, *10*, 1743. (i) Tang, S.; Peng, P.; Wang, Z.-Q.; Tang, B.-X.; Deng, C.-L.; Li, J.-H.; Zhong, P.; Wang, N.-X. *Org. Lett.* **2008**, *10*, 1875.

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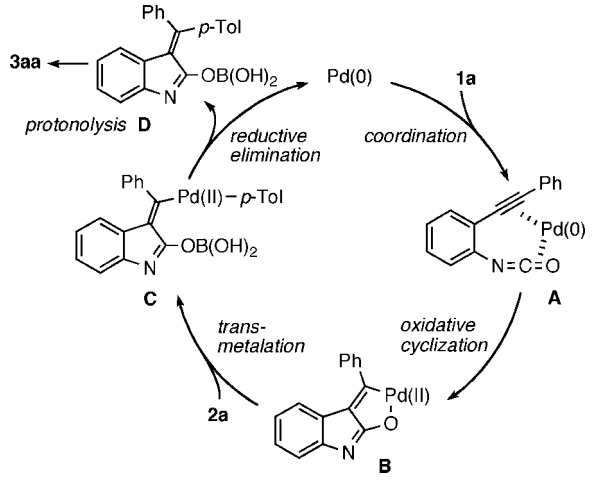
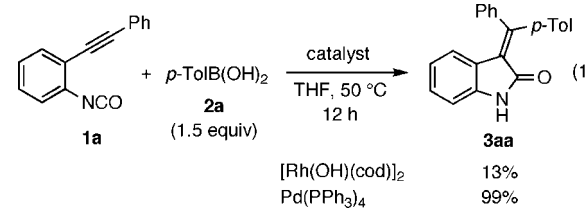
on boron to be transferred regioselectively onto the alkyne moiety to produce arylated and alkenylated 3-alkylideneoxindoles in a stereoselective manner. In this paper, we report that palladium(0) catalysts promote an analogous type of cyclization reaction with greater efficiency. The palladium-catalyzed system not only expands the substrate scope for the substituents at the alkyne termini but also permits the installation of sp^3 and sp carbons on the exocyclic double bond.

To compare the Rh- and Pd-catalyzed reactions, we examined the arylative cyclization reaction of 2-(2-phenylethynyl)phenyl isocyanate (**1a**). When **1a** was treated with 4-methylphenylboronic acid (**2a**) in the presence of $[Rh(OH)(cod)]_2$ (5 mol % of Rh) at 50 °C for 12 h, 3-alkylideneoxindole **3aa** was obtained in only 13% yield.[5] Remarkably, the use of readily available $Pd(PPh_3)_4$ (5 mol % of Pd) provided **3aa** in 99% yield as a single stereoisomer (Z/E = >20:1,[6] eq 1) at 50 °C. No base is required to promote the catalytic cycle unlike the Suzuki−Miyaura cross-coupling reaction.[7] Palladium(II) catalysts such as $PdCl_2(PPh_3)_2$, $Pd(OAc)_2$, and $Pd(OAc)_2$/dppe failed to promote the present reaction or gave a complex mixture of products.[8,9] We propose that the reaction proceeds through the pathway outlined in Scheme 1. Substrate **1a** binds to a palladium(0) catalyst to generate the chelate complex **A**, which then forms the oxapalladacycle **B** by oxidative cyclization. Subsequent transmetalation of **B** with **2a** produces the alkenylpalladium species **C**.[10] Reductive elimination from **C** then affords arylated intermediate **D** and regenerates the palladium(0) catalyst.[11] Protonolysis of **D** occurs during aqueous workup to give **3aa**.

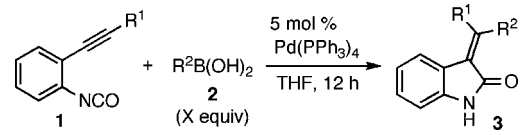
Scheme 1. Proposed Reaction Pathway





The results obtained with various combinations of 2-(alkynyl)aryl isocyanates **1** and organoboronic acids **2** are listed in Table 1. Not only arylboronic acids **2b**−**2d** but also heteroaryl- and alkenylboronic acids **2e**−**2g** reacted with **1a** to give the corresponding 3-alkylideneoxindoles **3ab**−**3ag** stereoselectively in yields ranging from 87% to 99% (entries 1−6). In contrast to the rhodium system with which only an sp^2 carbon on boron could be introduced efficiently, even

Table 1. Pd(0)-Catalyzed Cyclization Reaction of **1** with **2**



entry	1	R^1	2	R^2	X	t (°C)	3	yield (%)[a]
1	**1a**	Ph	**2b**	4-$CF_3C_6H_4$	1.5	80	**3ab**	89[b]
2	**1a**	Ph	**2c**	4-$MeOC_6H_4$	1.5	50	**3ac**	99
3	**1a**	Ph	**2d**	2-MeC_6H_4	1.5	50	**3ad**	87
4	**1a**	Ph	**2e**	3-thienyl	1.5	rt	**3ae**	91
5	**1a**	Ph	**2f**	β-styryl	1.5	50	**3af**	97
6	**1a**	Ph	**2g**	(*E*)-pentenyl	2.0	rt	**3ag**	99
7	**1a**	Ph	**2h**	cyclopropyl	2.0	80	**3ah**	76[b,c]
8	**1a**	Ph	**2i**	Me	2.0	80	**3ai**	95[b,c]
9	**1a**	Ph	**2j**	*n*-Bu	3.0	100	**3aj**	49[b,d]
10	**1b**	4-MeC_6H_4	**2k**	Ph	1.5	50	**3bk**	98
11	**1c**	4-$CF_3C_6H_4$	**2k**	Ph	1.5	rt	**3ck**	99
12	**1d**	4-$MeOC_6H_4$	**2k**	Ph	1.5	50	**3dk**	99
13	**1e**	2-MeC_6H_4	**2k**	Ph	1.5	50	**3ek**	97
14	**1f**	3-thienyl	**2k**	Ph	2.0	rt	**3fk**	99
15	**1g**	*n*-Bu	**2k**	Ph	1.5	50	**3gk**	98 (78)
16	**1g**	*n*-Bu	**2i**	Me	2.0	80	**3gi**	68[b,c] (13)
17	**1h**	*n*-Pr	**2k**	Ph	1.5	rt	**3hk**	88 (79)
18	**1i**	*i*-Pr	**2k**	Ph	1.5	rt	**3ik**	92 (85)
19	**1j**	cyclopropyl	**2k**	Ph	1.5	80	**3jk**	99[b,e] (76)
20	**1k**	H	**2k**	Ph	2.0	100	**3kk**	55[b,f] (70)

[a] Isolated yield (stereoisomer ratio = >20:1) unless otherwise noted. The yield using the Rh(I) catalyst was in parenthesis; see Supporting Information for details. [b] 1,4-Dioxane was used. [c] 3 h. [d] $Pd_2(dba)_3$•$CHCl_3$ (5 mol % of Pd) and P(2-furyl)$_3$ (10 mol %) were used. [e] 2 h. [f] E/Z = 15:1∼20:1.

(6) The ratio of stereoisomers was determined by ^1H NMR. The *Z* configuration of the exocyclic double bond of **3aa** was assigned by an NOE study.

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(8) For a Pd(II)-catalyzed addition reaction of arylboronic acids, see: (a) Nishikata, T.; Yamamoto, Y.; Miyaura, N. *Angew. Chem., Int. Ed.* **2003**, *42*, 2768. (b) Lautens, M.; Dockendorff, C. *Org. Lett.* **2003**, *5*, 3695.

(9) For a Pd(II)-catalyzed cyclization reaction of alkynones with arylboronic acids, see: (a) Song, J.; Shen, Q.; Xu, F.; Lu, X. *Org. Lett.* **2007**, *9*, 2947. (b) Tsukamoto, H.; Kondo, Y. *Org. Lett.* **2007**, *9*, 4227. (c) Yang, M.; Zhang, X.; Lu, X. *Org. Lett.* **2007**, *9*, 5131.

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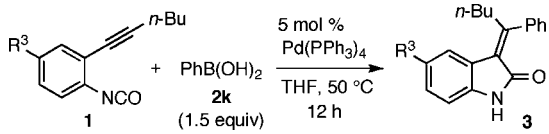
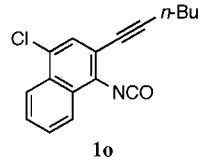
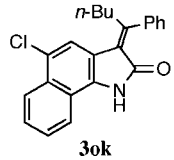
alkylboronic acids **2h**−**2j** participated in the reaction with **1a** (entries 7−9). A wide range of aryl groups **1b**−**1e** and a heteroaryl group **1f** proved to be suitable as the substituents at the alkyne termini of **1** (entries 10−14). With primary and secondary alkyl-substituted substrates **1g**−**1j**, the palladium(0)-catalyzed reaction gave higher yields than the rhodium(I)-catalyzed reaction (entries 15−19). However, terminal alkyne **1k**, which was an appropriate substrate for the rhodium system, required heating at 100 °C using the current conditions and was accompanied by isomerization of product **3kk** to the thermally stable (*E*)-isomer (entry 20).[12]

The results in Table 2 show that a variety of functional groups including chloride, ether, and ester are tolerated on the aryl group of **1**. The palladium system gave consistently better yields (over 90% yield) than the rhodium system.

Table 2. Reaction of Functionalized Aryl Isocyanates **1** with **2k**

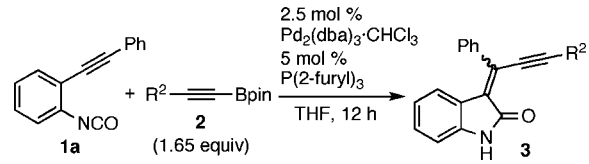


entry	**1**	R^3	**3**	yield (%)[a]
1	**1l**	Cl	**3lk**	92 (76)
2	**1m**	OMe	**3mk**	97 (75)
3	**1n**	CO_2Et	**3nk**	98 (80)
4	 **1o**		 **3ok**	99 (89)

[a] Isolated yield (stereoisomer ratio = >20:1) unless otherwise noted. The yield using the Rh(I) catalyst was in parenthesis; see Supporting Information for details.

We next examined the alkynylative cyclization reaction using alkynylboronates[13] and P(2-furyl)$_3$ as the phosphine ligand,[14,15] with the results being listed in Table 3. Treatment of phenyl-substituted alkyne **1a** with alkynylboronate **2l** in the presence of $Pd_2(dba)_3$•$CHCl_3$ and P(2-furyl)$_3$ afforded the desired oxindole **3al** in 76% yield as a mixture of stereoisomers[16] (*Z*/*E* = 92:8, entry 1). Alkynylboronates **2m**[17] and **2n** bearing trimethylsilyl and *n*-propyl groups also reacted with **1a** to produce the *Z*-isomers preferentially (entries 2 and 3). Yamamoto and co-workers reported a palladium-catalyzed cyclization reaction of 2-(alkynyl)aryl isocyanates with terminal alkynes, which afforded the corresponding alkynylated 3-alkylideneoxindoles.[4a] However, phenyl-substituted alkyne **1a** was an inappropriate substrate, giving a complex mixture of unidentified products. Therefore, the present reaction provides a complementary alkynylative approach to the 3-alkylideneoxindoles.

Table 3. Cyclization Reaction of **1a** with Alkynylboronates **2**



entry	**2**	R^2	*t* (°C)	**3**	yield (%)[a]	(*Z*/*E*)[b]
1	**2l**	Ph	50	**3al**	76	(92:8)
2	**2m**	TMS	50	**3am**	61	(89:11)
3	**2n**	*n*-Pr	rt	**3an**	48	(91:9)

[a] Isolated yield. [b] The ratio of stereoisomers was determined by ^{1}H NMR. pin = pinacolato.

In summary, an efficient cyclization reaction of 2-(alkynyl)aryl isocyanates with organoboron reagents has been developed using a palladium(0) catalyst. The palladium system shows a remarkably broad substrate scope and also achieves the stereoselective incorporation of various substituents on the exocyclic double bond of 3-alkylideneoxindoles.

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Supporting Information Available: Experimental details and spectral data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) At this time, it is not possible to rule out a mechanism involving sequential carbopalladation steps, initially operating on the alkyne moiety and next on the isocyanate moiety in a stepwise manner. For oxidative addition of arylboronic acids to Pd(0), see: (a) Cho, C. S.; Uemura, S. *J. Organomet. Chem.* **1994**, *465*, 85. (b) Moreno-Mañas, M.; Pérez, M.; Pleixats, R. *J. Org. Chem.* **1996**, *61*, 2346.

(12) Villemin, D.; Martin, B. *Synth. Commun.* **1998**, *28*, 3201.

(13) For a Pd(0)-catalyzed alkynylation reaction of aryl halides with alkynylboronates or alkynylborates, see: (a) Castanet, A.-S.; Colobert, F.; Schlama, T. *Org. Lett.* **2000**, *2*, 3559. (b) Torres, G. H.; Choppin, S.; Colobert, F. *Eur. J. Org. Chem.* **2006**, 1450.

(14) (a) Kagawa, N.; Malerich, J. P.; Rawal, V. H. *Org. Lett.* **2008**, *10*, 2381. For a review of P(2-furyl)$_3$ as ligand, see: (b) Andersen, N. G.; Keay, B. A. *Chem. Rev.* **2001**, *101*, 997.

(15) $Pd(PPh_3)_4$ was less effective, and its use under the same reaction conditions gave **3al** in 42% yield (*Z*/*E* = 56/44).

(16) As reported in ref 4a, the *E*/*Z* isomerization of alkynylated 3-alkylideneoxindoles was caused by the phosphine ligand.

(17) Alkynylboronate **2m** was so labile that it was handled in a glovebox.