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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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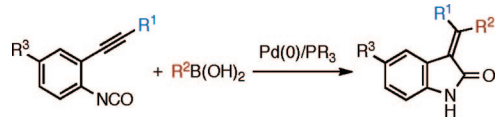
## ABSTRACT




**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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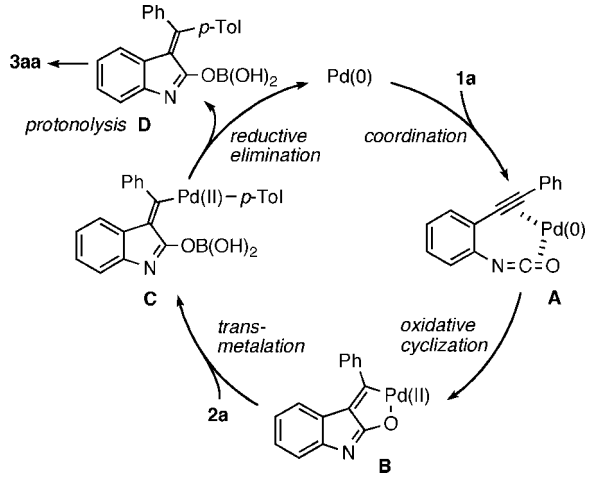
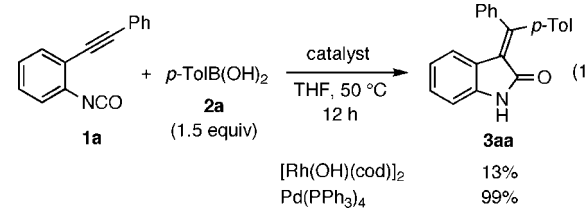
on boron to be transferred regioselectively onto the alkyne moiety to produce arylated and alkenylated 3-alkylideneoxindoles in a stereoselective manner. In this paper, we report that palladium(0) catalysts promote an analogous type of cyclization reaction with greater efficiency. The palladium-catalyzed 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**.

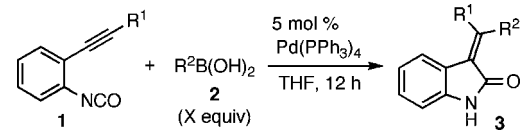
**Scheme 1.** Proposed Reaction Pathway




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 $^1$H 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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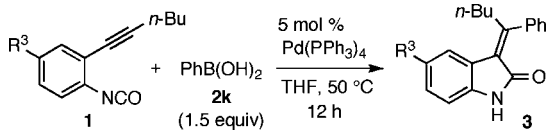
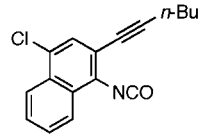
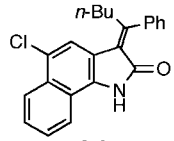
alkylboronic acids **2h**−**2j** participated in the reaction with **1a** (entries 7−9). A wide range of aryl groups **1b**−**1e** and a heteroaryl group **1f** proved to be suitable as the substituents at the alkyne termini of **1** (entries 10−14). With primary and secondary alkyl-substituted substrates **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**

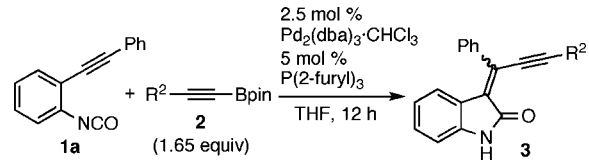



| entry | **1** | $R^3$ | **3** | yield (%)[a] |
|---|---|---|---|---|
| 1 | **1l** | Cl | **3lk** | 92 (76) |
| 2 | **1m** | OMe | **3mk** | 97 (75) |
| 3 | **1n** | $CO_2Et$ | **3nk** | 98 (80) |
| 4 |  **1o** | |  **3ok** | 99 (89) |

[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.