

Stereoselective Synthesis of 3-Alkylideneoxindoles by Rhodium-Catalyzed Cyclization Reaction of 2-Alkynylaryl Isocyanates with Aryl- and Alkenylboronic Acids

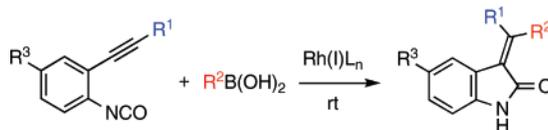
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ABSTRACT



The rhodium-catalyzed cyclization reaction of 2-alkynylaryl isocyanates with aryl- and alkenylboronic acids furnishes 3-alkylideneoxindoles in a stereoselective manner. The reaction allows arrangement of various substituents on the exocyclic double bond and aromatic ring with wide functional tolerance.

The rhodium-catalyzed addition reaction of organoboron reagents to unsaturated organic compounds has gained much attention in organic synthesis.¹ The reaction generally proceeds via rhodium/boron transmetalation generating an intermediate organorhodium(I) species followed by a subsequent carborhodation step. It has been demonstrated by us² and others³ that multiple carborhodation steps can operate sequentially on acceptor compounds possessing two or more unsaturated functionalities to yield a variety of cyclic compounds. Since both alkynes⁴ and isocyanates⁵ are good acceptors of organorhodium(I) species, 2-alkynylaryl isocyanates

are interesting bifunctional substrates with regard to the possibility of a cascade-type cyclization reaction, for which an alkynylpalladium species has presented a leading example.⁶ We report herein the rhodium-catalyzed reaction of 2-alkynylaryl isocyanates with organoboron reagents. This scheme permits the sp² carbon on boron to be transferred regioselectively onto the alkyne moiety producing 3-alkylideneoxindoles,⁷ which are versatile synthetic intermediates⁸ as well as drug candidates.⁹

2-(1-Hexynyl)phenyl isocyanate (**1a**, 1.0 equiv) was treated with phenylboronic acid (**2a**, 1.5 equiv) in the presence of [Rh(OH)(cod)]₂ (5 mol % Rh, cod = cycloocta-1,5-diene) in THF (0.1 M) at room temperature for 12 h. Chromatographic isolation on silica gel afforded 3-alkylideneoxindole **3aa** as a single stereoisomer (*Z/E* = >20:1 by ¹H NMR) in 78% yield (eq 1). The *Z* stereochemistry of the exocyclic

(1) For reviews, see: (a) Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169. (b) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829.

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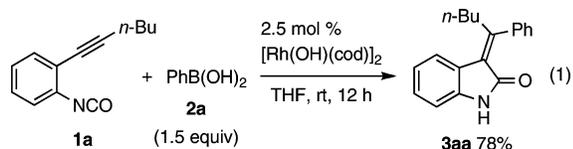
(3) For selected examples, see: (a) Cauble, D. F.; Gipson, J. D.; Krische, M. J. *J. Am. Chem. Soc.* **2003**, *125*, 1110. (b) Shintani, R.; Tsurusaki, A.; Okamoto, K.; Hayashi, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 3909. (c) Tseng, N.-W.; Mancuso, J.; Lautens, M. *J. Am. Chem. Soc.* **2006**, *128*, 5338. (d) Harada, Y.; Nakanishi, J.; Fujihara, H.; Tobisu, M.; Fukumoto, Y.; Chatani, N. *J. Am. Chem. Soc.* **2007**, *129*, 5766 and references therein.

(4) (a) Hayashi, T.; Inoue, K.; Taniguchi, N.; Ogasawara, M. *J. Am. Chem. Soc.* **2001**, *123*, 9918. (b) Murakami, M.; Igawa, H. *Helv. Chim. Acta* **2002**, *85*, 4182. (c) Lautens, M.; Yoshida, M. *Org. Lett.* **2002**, *4*, 123. (d) Genin, E.; Michelet, V.; Genêt, J.-P. *Tetrahedron Lett.* **2004**, *45*, 4157.

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double bond was determined by derivatization of **3aa** to the corresponding *N*-benzylated compound.^{7c}



The results obtained with various combinations of 2-alkynylaryl isocyanates **1** and organoboronic acids **2** are listed in Table 1. Not only substituted phenylboronic acids **2b–d**

Table 1. Rh(I)-Catalyzed Cyclization Reaction of **1** with **2**

entry	1	R ¹	2	R ²	3	yield (%) ^a
1	1a	<i>n</i> -Bu	2b	3-MeOC ₆ H ₄	3ab	78
2	1a	<i>n</i> -Bu	2c	3-BrC ₆ H ₄	3ac	84
3	1a	<i>n</i> -Bu	2d	2-MeC ₆ H ₄	3ad	78 ^b
4	1a	<i>n</i> -Bu	2e	3-thienyl	3ae	82
5	1a	<i>n</i> -Bu	2f	2-thienyl	3af	56 ^c
6	1a	<i>n</i> -Bu	2g	β-styryl	3ag	76 ^d
7	1a	<i>n</i> -Bu	2h	(<i>E</i>)-pentenyl	3ah	64 ^d
8	1b	Et	2a	Ph	3ba	76
9	1c	<i>n</i> -Pr	2a	Ph	3ca	79
10	1d	CH ₂ OTBS	2a	Ph	3da	74 ^d
11	1e	<i>i</i> -Pr	2a	Ph	3ea	85
12	1f	<i>t</i> -Bu	2a	Ph	3fa	18
13	1g	Ph	2a	Ph	3ga	26
14	1h	H	2a	Ph	3ha	70 ^d
15	1h	H	2h	(<i>E</i>)-pentenyl	3hh	74 ^d

^a Isolated yield. ^b **2** (2.0 equiv), 40 °C. ^c **2** (3.0 equiv), dioxane, 100 °C. ^d **2** (2.0 equiv).

but also isomeric thienylboronic acids **2e** and **2f** reacted with **1a** to give oxindoles **3ab–3af** stereoselectively in yields ranging from 56% to 84% (entries 1–5). More forcing conditions were applied to the reaction of **2d** and **2f**, which are thought to be less nucleophilic due to steric and electronic reasons, respectively. In addition, even alkenylboronic acids **2g** and **2h** participated in the reaction with **1a** (entries 6 and 7). Whereas primary and secondary alkyl groups were suitable substituents at the alkyne termini of **1** (entries 8–11),

(7) For recent examples of the synthesis of 3-alkylideneoxindoles with catalysis of transition metals, see: (a) Fielding, M. R.; Grigg, R.; Urch, C. *J. Chem. Commun.* **2000**, 2239. (b) Yanada, R.; Obika, S.; Oyama, M.; Takemoto, Y. *Org. Lett.* **2004**, 6, 2825. (c) D'Souza, D. M.; Rominger, F.; Müller, T. J. *J. Angew. Chem., Int. Ed.* **2005**, 44, 153. (d) Cheung, W. S.; Patch, R. J.; Player, M. R. *J. Org. Chem.* **2005**, 70, 3741. (e) Yanada, R.; Obika, S.; Inokuma, T.; Yanada, K.; Yamashita, M.; Ohta, S.; Takemoto, Y. *J. Org. Chem.* **2005**, 70, 6972. (f) Kobayashi, Y.; Kamisaki, H.; Yanada, K.; Yanada, R.; Takemoto, Y. *Tetrahedron Lett.* **2005**, 46, 7549. (g) Shintani, R.; Yamagami, T.; Hayashi, T. *Org. Lett.* **2006**, 8, 4799. (h) Pinto, A.; Neuville, L.; Zhu, J. *Angew. Chem., Int. Ed.* **2007**, 46, 3291.

(8) For the intermediates in total synthesis, see: (a) Carroll, W. A.; Grieco, P. A. *J. Am. Chem. Soc.* **1993**, 115, 1164. (b) Rasmussen, H. B.; MacLeod, J. K. *J. Nat. Prod.* **1997**, 60, 1152. (c) Lin, S.; Yang, Z.-Q.; Kwok, B. H. B.; Koldoskiy, M.; Crews, C. M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2004**, 126, 6347. (d) Trost, B. M.; Cramer, N.; Bernsmann, H. *J. Am. Chem. Soc.* **2007**, 129, 3086.

the reaction of *tert*-butyl-substituted alkyne **1f** failed to reach completion and the product **3fa** was obtained in only 18% yield (entry 12). Interestingly, terminal alkynes successfully participated in this process. Thus, oxindoles **3ha** and **3hh** possessing *Z* stereochemistries for the exocyclic trisubstituted double bonds were obtained in 70% and 74% yields, respectively (entries 14 and 15). These results stand in contrast to other rhodium-catalyzed reactions in which a complex mixture often arises from a terminal alkyne via pathways other than simple 1,2-addition, probably involving a rhodium vinylidene intermediate.¹⁰

The results of the reaction of functionalized aryl isocyanates **1** with **2a** shown in Table 2 demonstrated that a wide

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

entry	1	R ¹	R ²	3	yield (%) ^a
1	1i	<i>n</i> -Bu	Cl	3ia	76
2	1j	<i>n</i> -Bu	OMe	3ja	75
3	1k	<i>n</i> -Bu	CN	3ka	79
4	1l	<i>n</i> -Bu	CO ₂ Et	3la	80
5	1m	H	CO ₂ Et	3ma	74
6	1n	<i>n</i> -Bu	Cl	3na	89

^a Isolated yield.

range of functional groups including chloro, methoxy ether, cyano, and ester groups were tolerated on the aryl group of **1**.

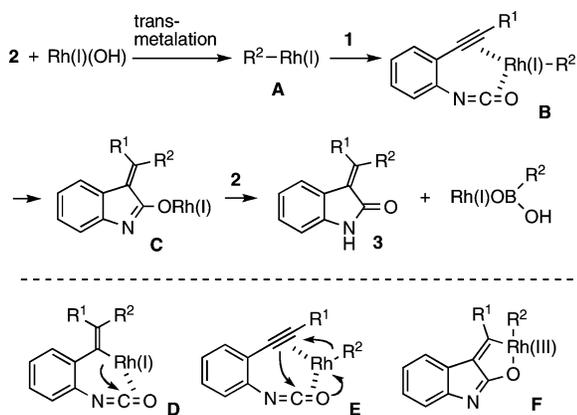
We propose the reaction pathway depicted in Scheme 1 for the stereoselective production of oxindoles **3**. Initially, intermediate organorhodium(I) species **A** is generated by transmetalation of rhodium with **2**. Both alkynyl and isocyanato groups of **1** coordinate to the rhodium center to form the chelate complex **B**, which then leads to the cyclized rhodium(I) alkoxide **C**. Protonolysis of **C** with **2** releases the product **3** along with a rhodium(I) boronate, which regenerates **A** to promote the next catalytic cycle.¹¹

Three mechanistic possibilities are conceivable for the cyclization of **B** forming **C**. The first one consists of two

(9) (a) Sun, L.; Tran, N.; Tang, F.; App, H.; Hirth, P.; McMahon, G.; Tang, C. *J. Med. Chem.* **1998**, 41, 2588. (b) Vieth, M.; Cummins, D. J. *J. Med. Chem.* **2000**, 43, 3020. (c) Woodard, C. L.; Li, Z.; Kathcart, A. K.; Terrell, J.; Gerena, L.; Lopez-Sanchez, M.; Kyle, D. E.; Bhattacharjee, A. K.; Nichols, D. A.; Ellis, W.; Prigge, S. T.; Geyer, J. A.; Waters, N. C. *J. Med. Chem.* **2003**, 46, 3877. (d) Pandit, B.; Sun, Y.; Chen, P.; Sackett, D. L.; Hu, Z.; Rich, W.; Li, C.; Lewis, A.; Schaefer, K.; Li, P.-K. *Bioorg. Med. Chem.* **2006**, 14, 6492. (e) Andreani, A.; Burnelli, S.; Granaola, M.; Leoni, A.; Locatelli, A.; Morigi, R.; Rambaldi, M.; Varoli, L.; Kunkel, M. *W. J. Med. Chem.* **2006**, 49, 6922.

(10) For 1,1-carborhodation of terminal alkynes with organoboron reagents through a rhodium vinylidene intermediate, see: Chen, Y.; Lee, C. *J. Am. Chem. Soc.* **2006**, 128, 15598.

Scheme 1



sequential carborhodation steps, initially operating on the alkyne moiety and next on the isocyanato moiety (**D**) in a stepwise manner, as in the palladium-catalyzed case.⁶ Another mechanistic possibility is a more concerted one as schematized in **E**.¹² Formation of two carbon–carbon bonds and a rhodium–oxygen bond occurs simultaneously. The last possibility involves an oxidative cyclization step to form a carbon–carbon bond furnishing rhodacycle **F**¹³ and subsequent reductive elimination to install the R² group.

The following control experiments were carried out to gain some mechanistic insight (Scheme 2). A mixture of 1-hexynylbenzene (**4**, 1.0 equiv) and phenyl isocyanate (**5**, 1.0 equiv) was reacted with 3-thienylboronic acid (**2e**, 1.0 equiv). Both substrates **4** and **5** competed for reaction with **2e** to give the corresponding adducts **6**¹⁴ and **7** in 28% and 20% yield, respectively. In addition, α,β -unsaturated amide **8** was obtained in 9% yield, suggesting that some part of intermediate alkenylrhodium(I) species immediately underwent intermolecular addition to **5**. When 2 equiv of **2e** was employed, the yields of the products **6–8** nearly doubled.

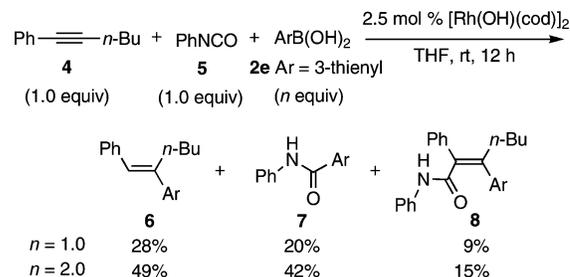
(11) Zhao, P.; Incarvito, C. D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 1876.

(12) Kurahashi, T.; Shinokuba, H.; Osuka, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 6336.

(13) For intermolecular oxidative cyclization with the C≡C triple bond of an alkyne and the N=C double bond of an isocyanate, see: Yu, R. T.; Rovis, T. *J. Am. Chem. Soc.* **2006**, *128*, 12370.

(14) A high regioselectivity (ca. 20:1) was observed by ¹H NMR.

Scheme 2



If the stepwise mechanism operates in a way that the initial carborhodation occurs on one functionality without coordinative participation of the other functionality, the selective production of **3** contradicts the lack of chemoselectivity observed in the intermolecular competitive reaction. However, the stepwise pathway via **D** cannot be ruled out if it is taken into consideration that the reactivity order of two functionalities toward carborhodation can change when chelating coordination is possible. A detailed computational study would help differentiating between the possibilities mentioned above.

To conclude, the rhodium-catalyzed reaction of 2-alkynylaryl isocyanates **1** with organoboronic acids **2** permits the stereoselective placement of various kinds of substituents on the exocyclic double bonds of the resulting 3-alkylideneoxindoles with wide functional group tolerance. Aryl, heteroaryl, and alkenyl groups are delivered cis to the carbonyl group from the boron compounds **2**, and hydrogen, primary alkyl, and secondary alkyl groups are placed trans to the carbonyl group.

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

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