ORGANIC LETTERS

2007
Vol. 9, No. 24
5075−5077

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

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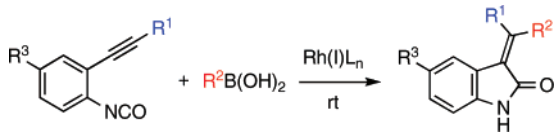
Received October 3, 2007

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 us[2] and others[3] 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 alkynes[4] and isocyanates[5] 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 sp^2 carbon on boron to be transferred regioselectively onto the alkyne moiety producing 3-alkylideneoxindoles,[7] which are versatile synthetic intermediates[8] 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 ^{1}H NMR) in 78% yield (eq 1). The Z stereochemistry of the exocyclic

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(2) Miura, T.; Murakami, M. *Chem. Commun.* **2007**, 217.
(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.
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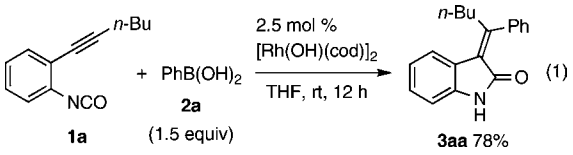
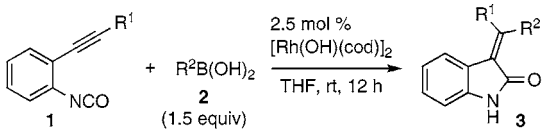
10.1021/ol7024185 CCC: $37.00
Published on Web 10/25/2007

double bond was determined by derivatization of **3aa** to the corresponding *N*-benzylated compound.[7e]



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**



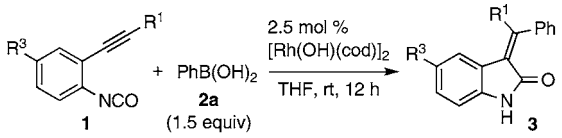
entry	1	R^1	2	R^2	3	yield (%)[a]
1	**1a**	*n*-Bu	**2b**	3-$MeOC_6H_4$	**3ab**	78
2	**1a**	*n*-Bu	**2c**	3-BrC_6H_4	**3ac**	84
3	**1a**	*n*-Bu	**2d**	2-MeC_6H_4	**3ad**	78[b]
4	**1a**	*n*-Bu	**2e**	3-thienyl	**3ae**	82
5	**1a**	*n*-Bu	**2f**	2-thienyl	**3af**	56[c]
6	**1a**	*n*-Bu	**2g**	β-styryl	**3ag**	76[d]
7	**1a**	*n*-Bu	**2h**	(*E*)-pentenyl	**3ah**	64[d]
8	**1b**	Et	**2a**	Ph	**3ba**	76
9	**1c**	*n*-Pr	**2a**	Ph	**3ca**	79
10	**1d**	CH_2OTBS	**2a**	Ph	**3da**	74[d]
11	**1e**	*i*-Pr	**2a**	Ph	**3ea**	85
12	**1f**	*t*-Bu	**2a**	Ph	**3fa**	18
13	**1g**	Ph	**2a**	Ph	**3ga**	26
14	**1h**	H	**2a**	Ph	**3ha**	70[d]
15	**1h**	H	**2h**	(*E*)-pentenyl	**3hh**	74[d]

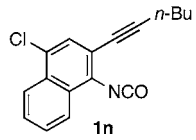
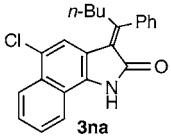
[a] Isolated yield. [b] **2** (2.0 equiv), 40 °C. [c] **2** (3.0 equiv), dioxane, 100 °C. [d] **2** (2.0 equiv).

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), 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^3	3	yield (%)[a]
1	**1i**	*n*-Bu	Cl	**3ia**	76
2	**1j**	*n*-Bu	OMe	**3ja**	75
3	**1k**	*n*-Bu	CN	**3ka**	79
4	**1l**	*n*-Bu	CO_2Et	**3la**	80
5	**1m**	H	CO_2Et	**3ma**	74
6					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

(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. Commum.* **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.

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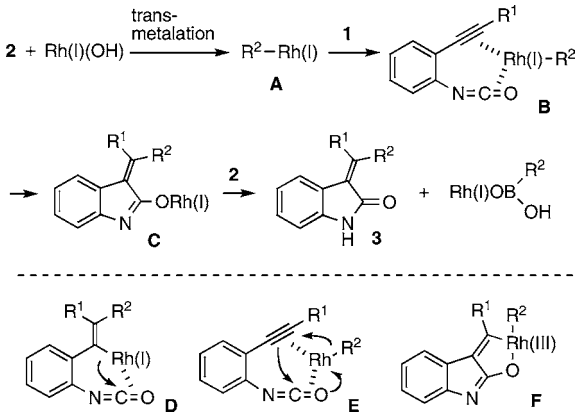
(10) For 1,1-carborhodation of terminal alkynes with organoboron reagents through a rhodium vinylidene intermediate, see: Chen, Y.; Lee, C. *J. Am. Chem. Soc.* **2006**, *128*, 15598.

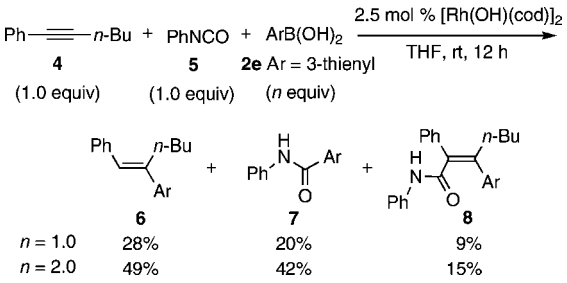
Scheme 1



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 R^2 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.

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.

Acknowledgment. This work was supported by the Takeda Science Foundation and the Ministry of Education, Culture, Sports, Science, and Technology, Japan (Grant-in-Aids for Young Scientists (B) 18750084 and Scientific Research on Priority Areas 18032040).

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.

OL7024185

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(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 regioselectively (ca. 20:1) was observed by ^{1}H NMR.