JOC Article
pubs.acs.org/joc

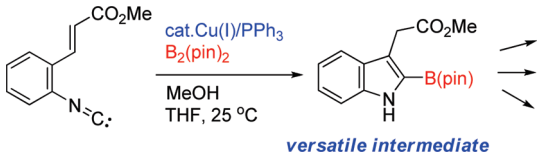
Synthesis of 2-Boryl- and Silylindoles by Copper-Catalyzed Borylative and Silylative Cyclization of 2-Alkenylaryl Isocyanides

Mamoru Tobisu,[‡] Hirokazu Fujihara,[†] Keika Koh,[†] and Naoto Chatani*[,†]

[†]*Department of Applied Chemistry, Faculty of Engineering and* [‡]*Frontier Research Base for Global Young Researchers, Graduate School of Engineering, Osaka University, Suita, Osaka 565-0871, Japan*

chatani@chem.eng.osaka-u.ac.jp

Received May 26, 2010



We have developed a method for the synthesis of 2-borylindoles via the copper(I)-catalyzed borylative cyclization of 2-alkenylphenyl isocyanides using diboronate. The reaction proceeds at room temperature under neutral conditions and exhibits high tolerance to functional groups, such as Br, CO_2R, COR, $CONMe_2$, and CN. The 2-borylindoles synthesized in the present study can be elaborated into an array of indole-based derivatives, for example, through the Suzuki−Miyaura reaction. The utility of this method is demonstrated in the rapid synthesis of a kinase inhibitor, paullone. The reaction can be extended to the synthesis of 2-hydride indole and 2-silylindole by using hydroboronate (or hydrosilane) and silylboronate, respectively. Under these copper-catalyzed conditions, a quinoxaline ring system can also be constructed by using 1,2-isocyanobenzene as a substrate.

Introduction

The indole motif is a ubiquitous feature of alkaloid and peptide natural products and represents a privileged structural element for pharmaceutical agents.[1] Due to the importance of this heterocycle, indole-based scaffolds that can readily be elaborated into a variety of derivatives would find widespread utility in diversity-oriented synthesis.[2] Borylated indoles should serve as a versatile intermediate, in view of the availability of contemporary catalytic transformation methods using organoboron reagents.[3] Borylindoles can be synthesized via either a protocol of lithiation/trap with boron electrophiles[4] or the catalytic direct borylation of indoles.[5] However, the former method cannot be applied to base-sensitive substrates, and the latter suffers from susceptibility to the steric effect. A new method is therefore needed for the synthesis of a series of borylated indoles that cannot be accessed by conventional methods. One such group of compounds is 2-(2-boryl-1*H*-indol-3-yl)acetic acid derivatives **1**, which could be utilized as useful precursors for a variety of tryptophan-derived natural and nonnatural products (Scheme 1).[6] Despite their potential utility, the synthesis of borylindoles **1** has never been reported, to the best of our knowledge.

On the other hand, Fukuyama reported that 2-stannylindoles **3** can be synthesized from 2-alkenylaryl isocyanides **2** via a radical-mediated process (Fukuyama indole synthesis) and can be elaborated into an array of derivatives through Migita−Kosugi−Stille coupling (Scheme 2).[7,8] If this reaction could be extended to the synthesis of the boron analogue **4**, it would lead to a nontoxic and more versatile platform for indole-based compounds, particularly for those derived

(1) Selected recent reviews: (a) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875. (b) Joucla, L.; Djakovitch, L. *Adv. Synth. Catal.* **2009**, *351*, 673.

(2) Selected reviews: (a) Schreiber, S. L. *Science* **2000**, *287*, 1964. (b) Burke, M. D.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 46. (c) Spandl, R. J.; Bender, A.; Spring, D. R. *Org. Biomol. Chem.* **2008**, *6*, 1149.

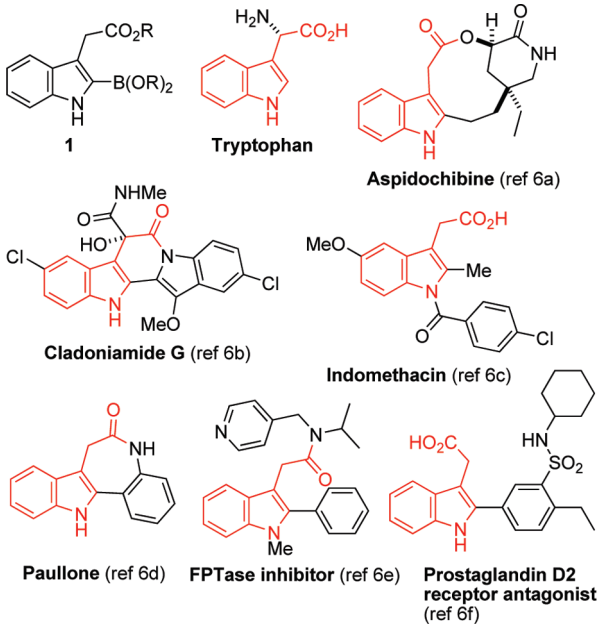
(3) Selected reviews: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829. (c) Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169. (d) Miura, T.; Murakami, M. *Chem. Commun.* **2007**, 217. (e) Miyaura, N. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 1535. (f) Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, *41*, 1461. (g) Tobisu, M.; Chatani, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 3565. (h) Goossen, L. J.; Goossen, K.; Stanciu, C. *Angew. Chem., Int. Ed.* **2009**, *48*, 3569.

(4) Vazquez, E.; Davies, I. W.; Payack, J. F. *J. Org. Chem.* **2002**, *67*, 7551 and references therein.

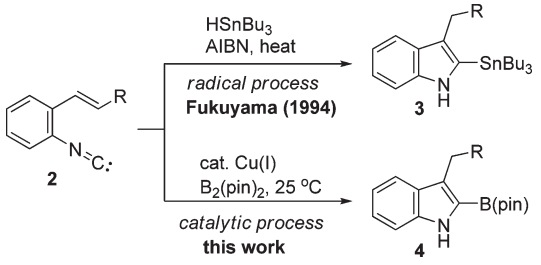
(5) For a review on catalytic borylation of C−H bonds, see: (a) Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2009**, *110*, 890. Catalytic borylation of indoles: (b) Ishiyama, T.; Takagi, J.; Hartwig, J. F.; Miyaura, N. *Angew. Chem., Int. Ed.* **2002**, *41*, 3056. (c) Takagi, J.; Sato, K.; Hartwig, J. F.; Ishiyama, T.; Miyaura, N. *Tetrahedron Lett.* **2002**, *43*, 5649. (d) Ishiyama, T.; Nobuta, Y.; Hartwig, J. F.; Miyaura, N. *Chem. Commun.* **2003**, 2924. (e) Mertins, K.; Zapf, A.; Beller, M. *J. Mol. Catal. A: Chem.* **2004**, *207*, 21. (f) Tagata, T.; Nishida, M. *Adv. Synth. Catal.* **2004**, *346*, 1655. (g) Paul, S.; Chotana, G. A.; Holmes, D.; Reichle, R. C.; Maleczka, R. E.; Smith, M. R. *J. Am. Chem. Soc.* **2006**, *128*, 15552. (h) Kallepalli, V. A.; Shi, F.; Paul, S.; Onyeozili, E. N.; Maleczka, R. E.; Smith, M. R. *J. Org. Chem.* **2009**, *74*, 9199. (i) Robbins, D. W.; Boebel, T. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 4068.

DOI: 10.1021/jo101024f Published on Web 06/17/2010

SCHEME 1. 2-(1*H*-Indol-3-yl)acetic Acid Substructure Found in Natural and Non-natural Products



SCHEME 2. 2-Metalated Indoles from 2-Alkenylaryl Isocyanides



from tryptophan. This paper reports the catalytic synthesis of 2-borylindole **4** through the nucleophilic addition of in situ generated borylcopper(I) species to isocyanide **2**. The reactivity of this new family of organoboron compounds in several catalytic reactions, such as Suzuki−Miyaura coupling, is investigated, and its application to the rapid synthesis of paullone is also demonstrated. In addition, in situ generated aryl-, hydride, and silylcopper(I) species are examined for their ability to promote the cyclization process, which sheds light on the nature of the key addition reaction to isocyanide.

Results and Discussion

On the basis of the potential electrophilic reactivity of isocyanides,[9] we envisioned that the cyclization of **2** to **4** could be initiated by the addition of nucleophilic boron species[10] to the isocyano group in **2**. Guided by several reports on copper-catalyzed nucleophilic borylation of various electrophiles (unsaturated carbonyls,[11] aldehydes and ketones,[12] imines,[13] allylic and propargylic carbonates,[14] and others[15]), we initially examined the reaction of isocyanide **5a**[16] with diboronate **6** in the presence of a copper catalyst (Table 1). We found that the borylated product **7a** was indeed obtained with the CuOAc/PPh_3 catalytic system at ambient temperature (entry 1). Consistent with previous reports,[11] protic additives improved the yield of **7a**, although it was accompanied by the formation of deborylated product **8a** (entries 2−4). Finally, decreasing the amount of MeOH to 1 equiv relative to **5a** completely suppressed the formation of **8a** and afforded **7a** quantitatively (entry 6).

The reaction is presumably initiated by the addition of borylcopper **A**, which can be generated in situ by the transmetalation of CuOAc with **6** to the isocyano moiety in **5a** (Scheme 3). Intramolecular 1,4-addition of the resultant imidoylcopper **B** leads to the formation of copper enolate **C**. Since the transmetalation of **C** with **6** is relatively slow, the addition of MeOH is required to effectively liberate borylated product **E** and to generate Cu-OMe **D**, which serves as a more competent precursor of **A**.[11h]

(6) Selected examples: (a) Aimi, N.; Uchida, N.; Ohya, N.; Hosokawa, H.; H., T.; Sakai, S.-i.; Mendonza, L. A.; Polz, L.; Stöckigt, J. *Tetrahedron Lett*. **1991**, *32*, 4949. (b) Williams, D. E.; Davies, J.; Patrick, B. O.; Bottriell, H.; Tarling, T.; Roberge, M.; Andersen, R. J. *Org. Lett*. **2008**, *10*, 3501. (c) Shen, T. Y.; Winter, C. A. *Adv. Drug Res*. **1977**, *12*, 90. (d) Schultz, C.; Link, A.; Leost, M.; Zaharevitz, D. W.; Gussio, R.; Sausville, E. A.; Meijer, L.; Kunick, C. *J. Med. Chem*. **1999**, *42*, 2909. (e) Trotter, B. W.; Quigley, A. G.; Lumma, W. C.; Sisko, J. T.; Walsh, E. S.; Hamann, C. S.; Robinson, R. G.; Bhimnathwala, H.; Kolodin, D. G.; Zheng, W.; Buser, C. A.; Huber, H. E.; Lobell, R. B.; Kohl, N. E.; Williams, T. M.; Graham, S. L.; Dinsmore, C. J. *Bioorg. Med. Chem. Lett*. **2001**, *11*, 865. (f) Yang, Z.; Reiling, S.; Nieduzak, T. R.; Mathew, R. M.; Jackson, S.; Harris, K. J. PCT Int. Appl. WO 2008014186 *Chem. Abstr*. 2008, *148*, 214951.

(7) A seminal report: (a) Fukuyama, T.; Chen, X.; Peng, G. *J. Am. Chem. Soc*. **1994**, *116*, 3127A review:. (b) Tokuyama, H.; Fukuyama, T. *Chem. Rec*. **2002**, *2*, 37.

(8) A review of indole synthesis from isocyanides: Campo, J.; Garciá-Valverde, M.; Marcaccini, S.; Rojo, M. J.; Torrroba, T. *Org. Biomol. Chem*. **2006**, *4*, 757.

(9) (a) Niznik, G. E.; Morrison, W. H.; Walborsky, H. M. *J. Org. Chem*. **1974**, *39*, 600. (b) Murakami, M.; Ito, H.; Ito, Y. *J. Org. Chem*. **1988**, *53*, 4158. (c) Suginome, M.; Fukuda, T.; Ito, Y. *Org. Lett*. **1999**, *1*, 1977. (d) Tobisu, M.; Yamaguchi, S.; Chatani, N. *Org. Lett*. **2007**, *9*, 3351.

(10) For an excellent introduction to nucleophilic boryl species, see: (a) Segawa, Y.; Suzuki, Y.; Yamashita, M.; Nozaki, K. *J. Am. Chem. Soc*. **2008**, *130*, 16069. (b) Dang, L.; Lin, Z.; Marder, T. B. *Chem. Commun*. **2009**, 3987.

(11) (a) Ito, H.; Yamanaka, H.; Tateiwa, J.-i.; Hosomi, A. *Tetrahedron Lett*. **2000**, *41*, 6821. (b) Takahashi, K.; Ishiyama, T.; Miyaura, N. *Chem. Lett*. **2000**, *29*, 982. (c) Takahashi, K.; Ishiyama, T.; Miyaura, N. *J. Organomet. Chem*. **2001**, *625*, 47. (d) Mun, S.; Lee, J.-E.; Yun, J. *Org. Lett*. **2006**, *8*, 4887. (e) Lee, J.-E.; Yun, J. *Angew. Chem., Int. Ed*. **2008**, *47*, 145. (f) Lee, J.-E.; Kwon, J.; Yun, J. *Chem. Commun*. **2008**, 733. (g) Lillo, V.; Prieto, A.; Bonet, A.; Díaz-Requejo, M. M.; Ramírez, J.; Párez, P. J.; Fernández, E. *Organometallics* **2008**, *28*, 659. (h) Dang, L.; Lin, Z.; Marder, T. B. *Organometallics* **2008**, *27*, 4443. (i) Sim, H.-S.; Feng, X.; Yun, J. *Chem.—Eur. J*. **2009**, *15*, 1939. (j) Feng, X.; Yun, J. *Chem. Commun*. **2009**, 6577. (k) Lillo, V.; Bonet, A.; Fernández *Dalton Trans*. **2009**, 2899. (l) Chea, H.; Sim, H.-S.; Yun, J. *Adv. Synth. Catal*. **2009**, *351*, 855. (m) Fleming, W. J.; Müller-Bunz, H.; Lillo, V.; Fernández, E.; Guiry, P. J. *Org. Biomol. Chem*. **2009**, *7*, 2520. (n) Chen, I. H.; Yin, L.; Itano, W.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc*. **2009**, *131*, 11664. (o) Schiffner, J. A.; Müther, K.; Oestreich, M. *Angew. Chem., Int. Ed*. **2010**, *49*, 1194.

(12) (a) Laitar, D. S.; Tsui, E. Y.; Sadighi, J. P. *J. Am. Chem. Soc*. **2006**, *128*, 11036. (b) McIntosh, M. L.; Moore, C. M.; Clark, T. B. *Org. Lett*. **2010**, *12*, 1996.

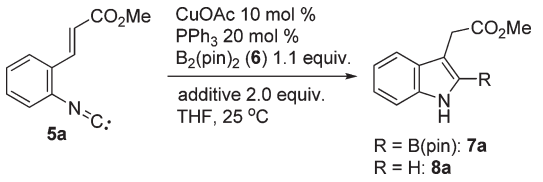
(13) Beenen, M. A.; An, C.; Ellman, J. A. *J. Am. Chem. Soc*. **2008**, *130*, 6910.

(14) (a) Ramachandran, P. V.; Pratihar, D.; Biswas, D.; Srivastava, A.; Ram Reddy, M. V. *Org. Lett*. **2004**, *6*, 481. (b) Ito, H.; Kawakami, C.; Sawamura, M. *J. Am. Chem. Soc*. **2005**, *127*, 16034. (c) Ito, H.; Ito, S.; Sasaki, Y.; Matsuura, K.; Sawamura, M. *J. Am. Chem. Soc*. **2007**, *129*, 14856. (d) Ito, H.; Sasaki, Y.; Sawamura, M. *J. Am. Chem. Soc*. **2008**, *130*, 15774. (e) Ito, H.; Kosaka, Y.; Nonoyama, K.; Sasaki, Y.; Sawamura, M. *Angew. Chem., Int. Ed*. **2008**, *47*, 7424. (f) Ito, H.; Okura, T.; Matsuura, K.; Sawamura, M. *Angew. Chem., Int. Ed*. **2010**, *49*, 560. (g) Ito, H.; Toyoda, T.; Sawamura, M. *J. Am. Chem. Soc*. **2010**, *132*, 5990.

(15) Styrenes: (a) Laitar, D. S.; Tsui, E. Y.; Sadighi, J. P. *Organometallics* **2006**, *25*, 2405. (b) Dang, L.; Zhao, H.; Lin, Z.; Marder, T. B. *Organometallics* **2007**, *26*, 2824. (c) Lee, Y.; Hoveyda, A. H. *J. Am. Chem. Soc*. **2009**, *131*, 3160. 1,3-Dienes: (d) Sasaki, Y.; Zhong, C.; Sawamura, M.; Ito, H. *J. Am. Chem. Soc*. **2010**, *132*, 1226. CO_2: (e) Laitar, D. S.; Muller, P.; Sadighi, J. P. *J. Am. Chem. Soc*. **2005**, *127*, 17196. (f) Zhao, H.; Lin, Z.; Marder, T. B. *J. Am. Chem. Soc*. **2006**, *128*, 15637. Alkynes: (g) Lee, Y.; Jang, H.; Hoveyda, A. H. *J. Am. Chem. Soc*. **2009**, *131*, 18234. (h) Kim, H. R.; Jung, I. G.; Yoo, K.; Jang, K.; Lee, E. S.; Yun, J.; Son, S. U. *Chem. Commun*. **2010**, 758.

(16) The starting isocyanides used in this study can readily be prepared from the corresponding 2-iodoanilines. See the Supporting Information for details.

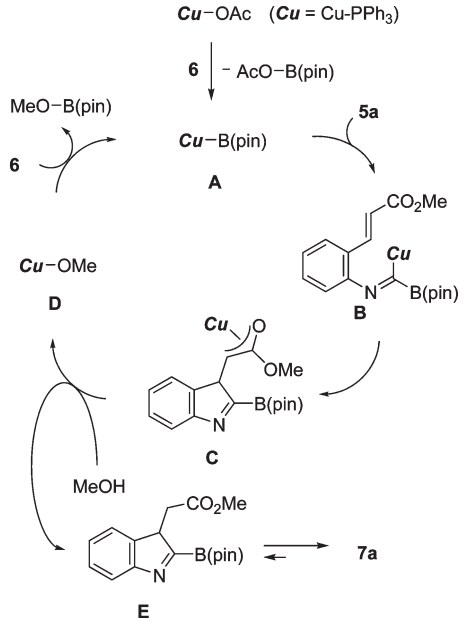
TABLE 1. Optimization of Reaction Conditions[a]



			yield[b] (%)	
entry	additive	time (h)	**7a**	**8a**
1	none	24	59	0
2	H_2O	5	67	13
3	MeOH	5	86	11
4	*t*-BuOH	5	66	6
5	PhOH	5	trace	0
6	MeOH[c]	5	98	trace

[a]Reaction conditions: **5a** (0.5 mmol), **6** (0.55 mmol), CuOAc (0.05 mmol), PPh_3 (0.10 mmol), additive (1.0 mmol), THF (4 mL) in a two-necked flask under N_2. [b]NMR yields based on **5a**. [c]MeOH (0.5 mmol) was added.

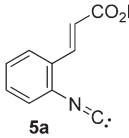
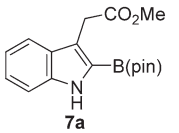
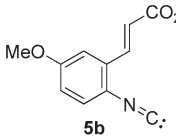
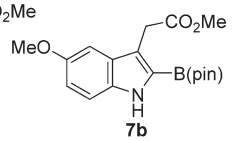
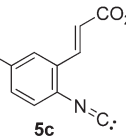
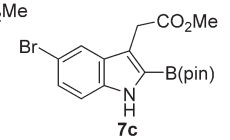
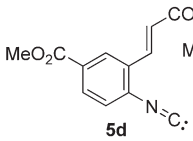
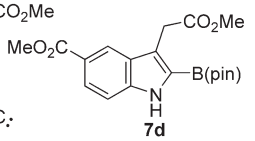
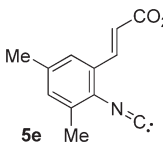
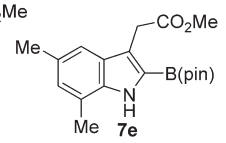
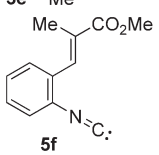
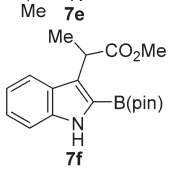
SCHEME 3. Plausible Mechanism for the Copper-Catalyzed Borylative Cyclization of 5a



The catalytic conditions optimized for **5a** proved to be effective for the borylative cyclization of other isocyanides (Table 2). Ethers (entry 2), bromides (entry 3), and esters (entry 4) on the benzene ring of isocyanide were tolerated under these catalytic conditions. Notably, sterically congested ortho-disubstituted isocyanide **5e** was also applicable (entry 5). In agreement with the mechanistic proposal (Scheme 3), several pendant Michael acceptors, including metacrylate **5f** and unsaturated ketone **5g**, amide **5h**, and nitrile **5i**, could undergo borylative cyclization to furnish the corresponding 2-borylindoles (entries 6−9).

With a new class of 2-borylindoles in hand, we next set out to explore the application to Suzuki−Miyaura cross-coupling. Since 2-borylindoles synthesized in the present study are relatively prone to protodeboronation on chromatographic

TABLE 2. Copper-Catalyzed Borylation of Various Aryl Isocyanides[a]

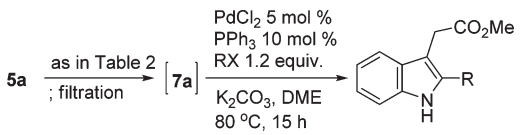
entry	isocyanide	product	yield (%)[b]
1	 **5a**	 **7a**	98
2	 **5b**	 **7b**	84
3	 **5c**	 **7c**	74
4	 **5d**	 **7d**	58
5	 **5e**	 **7e**	62
6	 **5f**	 **7f**	95
7	R = COMe (**5g**)	**7g**	57
8	R = $CONMe_2$ (**5h**)	**7h**	94
9	R = CN (**5i**)	**7i**	63

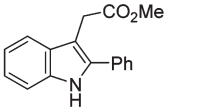
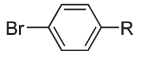
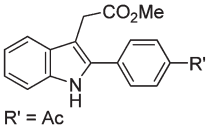
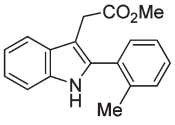
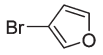
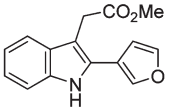
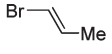
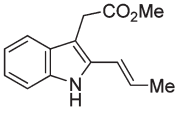
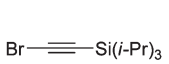
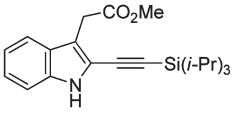
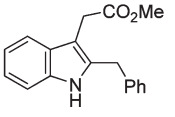
[a]Reaction conditions: **5** (0.5 mmol), **6** (0.55 mmol), CuOAc (0.05 mmol), PPh_3 (0.10 mmol), MeOH (0.5 mmol), THF (4 mL) in a two-necked flask under N_2. [b]NMR yields based on **5**.

separation,[17] we sought to identify a one-pot protocol for their transformation. The cross-coupling product was obtained in a yield of only 32% when the crude 2-borylindole **7a** was subjected to Suzuki−Miyaura conditions (cat. $PdCl_2/PPh_3$, K_2CO_3, DME, reflux) using iodobenzene. However, the yield was dramatically improved to 84% simply by conducting the Suzuki−Miyaura reaction after filtration through a pad of Florisil (entry 1, Table 3). This protocol probably removes the residual copper salt, which would accelerate protodeboronation at elevated temperature. Iodides, bromides, and triflates all afforded 2-arylated products in moderate to good yields without optimization of the catalytic conditions (entries 1−3), while iodides were the most effective partner. This reactivity difference can be utilized for the selective cross-coupling of iodide over bromide (entry 7). Functionalized halides, such as those containing acetyl (entry 4), cyano (entry 5), and methoxy (entry 6) groups, as well as sterically demanding (entry 8) and heteroaryl (entry 9) halides are applicable to this borylative cyclization/Suzuki−Miyaura coupling tandem. Notably,

(17) For the instability of 2-heteroarylboronic acids, see: (a) Billingsley, K.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 3358. (b) Knapp, D. M.; Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* **2009**, *131*, 6961.

TABLE 3. Tandem Borylative Cyclization/Suzuki−Miyaura Coupling of 7a[a]



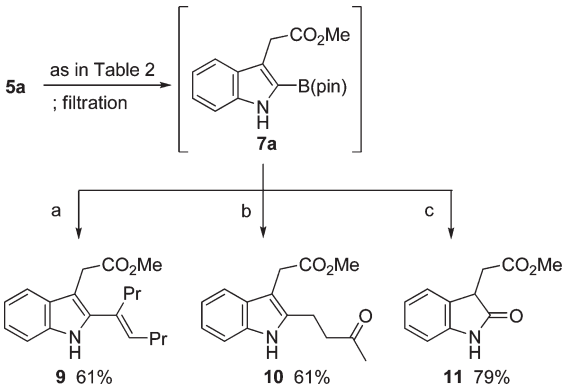
entry	RX	product	overall yield (%)[b]
1	Ph−I		84
2	Ph−Br		76
3	Ph−OTf		53
			
4	R = Ac	R' = Ac	77
5	R = CN	R' = CN	71
6	R = OMe	R' = OMe	61
7	R = I	R' = Br	72
8			70
9			56
10			57
11			64
12			69

[a]Reaction conditions: **5a** (0.5 mmol), **6** (0.55 mmol), CuOAc (0.05 mmol), PPh_3 (0.10 mmol), MeOH (0.5 mmol), THF (4.0 mL) in a two-necked flask under N_2 at 25 °C for 5 h; filtration and evaporation; crude **7a**, RX (0.6 mmol), $PdCl_2$ (0.025 mmol), PPh_3 (0.05 mmol), K_2CO_3 (2.0 mmol), DME (3.0 mL) at 80 °C for 15 h. [b]Overall isolated yield for two steps based on **5a**.

vinylic sp^2 (entry 10), sp (entry 11), and sp^3 (entry 12) carbons can be successfully introduced into the 2-position of indoles under identical conditions, highlighting the utility of 2-borylindoles in diversity-oriented synthesis.

The versatility of 2-borylindoles synthesized by our method is further demonstrated by their application to other transformations (Scheme 4). Rhodium-catalyzed addition of **7a** to alkynes[18] and enones[19] proceeded successfully to furnish 2,3-disubstituted indoles **9** and **10**, respectively. Moreover, the

SCHEME 4. Transformations of 7a[a]



[a]Key: (a) 3-octyne, $[Rh(OH)(cod)]_2$ (cat.), dioxane/H_2O, 80 °C, 15 h; (b) 3-butene-2-one, $[Rh(OH)(cod)]_2$ (cat.), dioxane/H_2O, 80 °C, 15 h; (c) Oxone, acetone/H_2O, 25 °C, 10 min.

oxidation of **7a** led to oxindole **11**, which constitutes an important subclass of indole-based compounds.[20]

Finally, the present reaction was applied to the synthesis of paullone, which is known as a potent inhibitor of cyclin-dependent kinases (Scheme 5).[21] By adapting the borylation/Suzuki−Miyaura coupling sequence, paullone could be rapidly synthesized from **5a** for an overall yield of 74%.[22] This modular catalytic assembly allows straightforward access to a range of paullone derivatives.

The present copper-catalyzed borylative cyclization is initiated by a nucleophilic addition of borylcopper(I) species to isocyanide. Such electrophilic reactivity of isocyanides is relatively unexplored,[9] whereas their nucleophilic character has been utilized in a wide range of reactions.[23] Thus, a better understanding of this key nucleophilic addition to isocyanides is needed to further exploit the electrophilic reactivity of isocyanides for organic synthesis. To obtain qualitative insight into this process, various reagents other than diboronate **6** were examined for their ability to promote the cyclization of **5a** (Table 4). Copper(I) hydride generated in situ by the reaction with HB(pin) (**12a**)[24] or

(18) A seminal report: Hayashi, T.; Inoue, K.; Taniguchi, N.; Ogasawara, M. *J. Am. Chem. Soc.* **2001**, *123*, 9918. See also ref 3b−3e.

(19) Seminal reports: (a) Sakai, M.; Hayashi, H.; Miyaura, N. *Organometallics* **1997**, *16*, 4229. (b) Takaya, Y.; Ogasawara, M.; Hayashi, T.; Sakai, M.; Miyaura, N. *J. Am. Chem. Soc.* **1998**, *120*, 5579. See also ref 3b−3e.

(20) For example, see: Galliford, C. V.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 8748.

(21) For recent studies of biological activities of paullone families, see: (a) Reichwald, C.; Shimony, O.; Dunkel, U.; Sacerdoti-Sierra, N.; Jaffe, C. L.; Kunick, C. *J. Med. Chem.* **2008**, *51*, 659. (b) Stukenbrock, H.; Mussmann, R.; Geese, M.; Ferandin, Y.; Lozach, O.; Lemcke, T.; Kegel, S.; Lomow, A.; Burk, U.; Dohrmann, C.; Meijer, L.; Austen, M.; Kunick, C. *J. Med. Chem.* **2008**, *51*, 2196. (c) Becker, A.; Kohfeld, S.; Lader, A.; Preu, L.; Pies, T.; Wieking, K.; Ferandin, Y.; Knockaert, M.; Meijer, L.; Kunick, C. *Eur. J. Med. Chem.* **2010**, *45*, 335. (d) Egert-Schmidt, A.-M.; Dreher, J.; Dunkel, U.; Kohfeld, S.; Preu, L.; Weber, H.; Ehlert, J. E.; Mutschler, B.; Totzke, F.; Schächtele, C.; Kubbutat, M. H. G.; Baumann, K.; Kunick, C. *J. Med. Chem.* **2010**, *53*, 2433.

(22) Notes: (a) It has been reported that tin-mediated paullone synthesis from **5a** requires the use of *N*-protected iodoaniline and the overall yield is less efficient (43% from **5a**). See: Henry, N.; Blu, J.; Bénéteau, V.; Mérour, J.-Y. *Synthesis* **2006**, *22*, 3895. (b) Synthesis of paullone via the Suzuki−Miyaura coupling of in situ prepared 2-(2-boryl-1*H*-indol-3-yl)-acetonitrile has been reported, but the yield was low (25%). See: Baudoin, O.; Cesario, M.; Guenard, D.; Gueritte, F. *J. Org. Chem.* **2002**, *67*, 1199.

(23) Suginome, M.; Ito, Y. In *Science of Synthesis*; Murahashi, S.-I., Ed.; Thieme: Stuttgart, 2004; Vol. 19; pp 445−530.

(24) For representative recent reports on the catalytic reaction involving CuH species generated from HB(pin), see: (a) Lipshutz, B. H.; Boskovic, Z. V.; Aue, D. H. *Angew. Chem., Int. Ed.* **2008**, *47*, 10183. (b) Du, Y.; Xu, L.-W.; Shimizu, Y.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2008**, *130*, 16146. (c) Noh, D.; Chea, H.; Ju, J.; Yun, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 6062.

SCHEME 5. Rapid Synthesis of Paullone, a Kinase Inhibitor

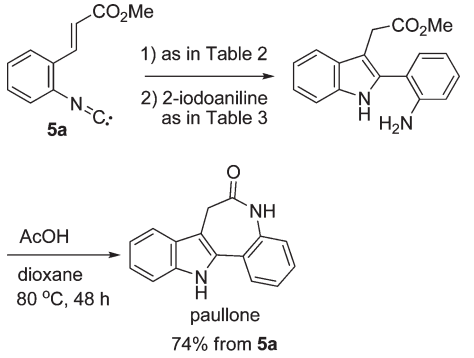
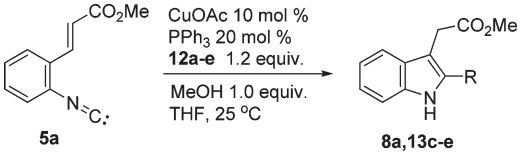


TABLE 4. Copper-Catalyzed Cyclization of 5a Using Various Reagents[a]

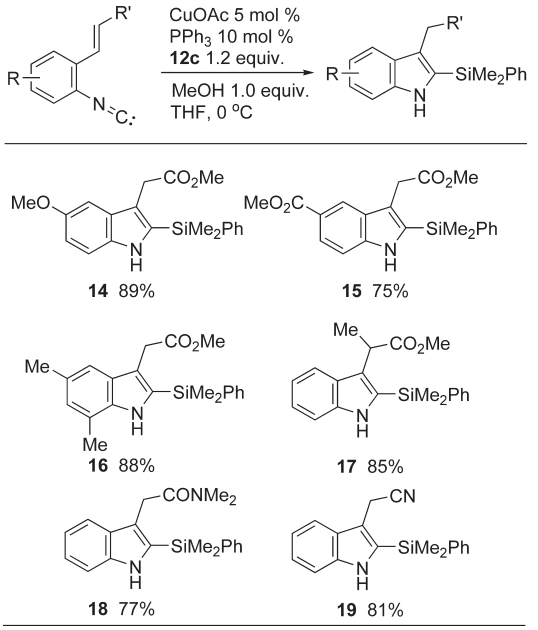


entry	reagents	time (h)	R	yield[b] (%)
1	HB(pin)[c] (**12a**)	1	H (**8a**)	78
2	$HSiPhMe_2$ (**12b**)	5	H (**8a**)	81
3[d]	(pin)B-$SiMe_2Ph$ (**12c**)	3	$SiMe_2Ph$ (**13c**)	87
4[d]	(pin)B-$SiMePh_2$ (**12d**)	3	$SiMePh_2$ (**13d**)	77
5	$PhB(OH)_2$ (**12e**)	24	Ph (**13e**)	0

[a]Reaction conditions: **5a** (0.5 mmol), **12** (0.6 mmol), CuOAc (0.05 mmol), PPh_3 (0.10 mmol), MeOH (0.5 mmol), THF (4.0 mL) in a two-necked flask under N_2 at 25 °C. [b]Isolated yield based on **5a** unless otherwise noted. [c]**12a** (1.0 mmol) was used. [d]Run with CuOAc (0.025 mmol) and PPh_3 (0.05 mmol) at 0 °C.

$HSiMe_2Ph$ (**12b**)[25] was also capable of initiating the cyclization to afford indole **8a** (entries 1 and 2). We next turned our attention to the reactivity of the corresponding silylcopper(I) species. In view of reports on the copper-catalyzed nucleophilic silylation of α,β-unsaturated carbonyl compounds using disilane,[26] we initially examined $(PhMe_2Si)_2$ as a silicon source. However, the desired 2-silylindole was not formed under these catalytic conditions. We then envisioned that silylboronate ($R_3SiB(OR')_2$) would be another candidate for a silyl-transferring reagent in copper catalysis, by analogy with the generation of silylrhodium(I) species from this reagent.[27] As expected, the reaction of isocyanide **5a** with silylboronate **12c** under copper-catalyzed conditions successfully furnished the corresponding 2-silylindole **13c** (entry 3).[28,29] A bulky Ph_2MeSi group could also be incorporated into the indole ring (entry 4). This copper-catalyzed silylative cyclization proved to be applicable to a wide range of isocyanides (Scheme 6). It should also be noted that, in contrast to 2-borylindoles **7**, 2-silylindoles synthesized in this study were all sufficiently stable to be isolated by chromatography. On the other hand, the phenylcopper(I) species generated by transmetalation from phenylboronic acids[30] failed to form indole products (entry 5).

SCHEME 6. 2-Silylindoles Synthesized by the Copper-Catalyzed Cyclization of 5



Lin and Marder investigated the magnitude of the trans influence of a series of ligands in *trans*-[PtL(Cl)$(PMe_3)_2$], based on the calculated bond lengths, and determined the following order: $SiMe_3$ > B(pin) > H > Ph.[31] This order reflects the strong σ-donating ability of the silyl[32] and boryl[10b,33] ligands. Although the corresponding data for copper(I) complexes are unavailable, the order reported above is in good agreement with the reactivity trend observed in Table 4. Thus, the present cyclization reaction requires the use of copper(I) species with highly nucleophilic ligands, including boryl, silyl, and hydride, which allow for nucleophilic attack toward isocyanides.

(25) For representative recent reports on the catalytic reaction involving CuH species generated from $HSiR_3$, see: (a) Welle, A.; Díez-González, S.; Tinant, B.; Nolan, S. P.; Riant, O. *Org. Lett.* **2006**, *8*, 6059. (b) Deutsch, C.; Lipshutz, B. H.; Krause, N. *Angew. Chem., Int. Ed.* **2007**, *46*, 1650. (c) Yoo, K.; Kim, H.; Yun, J. *Chem.—Eur. J.* **2009**, *15*, 11134. (d) Zhong, C.; Sasaki, Y.; Ito, H.; Sawamura, M. *Chem. Commun.* **2009**, 5850. (e) Rupnicki, L.; Saxena, A.; Lam, H. W. *J. Am. Chem. Soc.* **2009**, *131*, 10386.

(26) (a) Ito, H.; Ishizuka, T.; Tateiwa, J.-i.; Sonoda, M.; Hosomi, A. *J. Am. Chem. Soc.* **1998**, *120*, 11196. (b) Clark, C. T.; Lake, J. F.; Scheidt, K. A. *J. Am. Chem. Soc.* **2003**, *126*, 84.

(27) (a) Walter, C.; Auer, G.; Oestreich, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 5675. (b) Walter, C.; Oestreich, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 3818. (c) Walter, C.; Fröhlich, R.; Oestreich, M. *Tetrahedron* **2009**, *65*, 5513. (d) Ohmiya, H.; Ito, H.; Sawamura, M. *Org. Lett.* **2009**, *11*, 5618.

(28) Silylindoles via catalytic C−H bond silylation: (a) Ishiyama, T.; Sato, K.; Nishio, Y.; Saiki, T.; Miyaura, N. *Chem. Commun.* **2005**, 5065. (b) Lu, B.; Falck, J. R. *Angew. Chem., Int. Ed.* **2008**, *47*, 7508. Preparation and cross-coupling of 2-indolylsilanols: (c) Denmark, S. E.; Baird, J. D. *Org. Lett.* **2004**, *6*, 3649. (d) Denmark, S. E.; Baird, J. D. *Org. Lett.* **2006**, *8*, 793. (e) Denmark, S. E.; Baird, J. D.; Regens, C. S. *J. Org. Chem.* **2008**, *73*, 1440. (f) Denmark, S. E.; Baird, J. D. *Tetrahedron* **2009**, *65*, 3120.

(29) During the preparation of this manuscript, a report on copper-catalyzed 1,4-addition of a silyl group in silylboronates to unsaturated carbonyls was published: Lee, K.-s.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 2898.

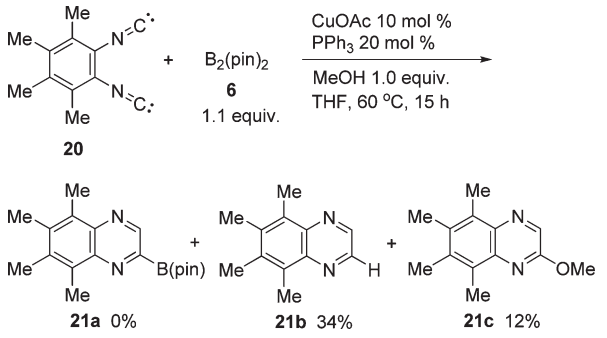
(30) For representative recent reports on the catalytic reaction involving ArCu species generated from $ArB(OH)_2$, see: (a) Uemura, T.; Chatani, N. *J. Org. Chem.* **2005**, *70*, 8631. (b) Villalobos, J. M.; Srogl, J.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2007**, *129*, 15734. (c) Zheng, H.; Zhang, Q.; Chen, J.; Liu, M.; Cheng, S.; Ding, J.; Wu, H.; Su, W. *J. Org. Chem.* **2008**, *74*, 943. (d) Rao, H.; Fu, H.; Jiang, Y.; Zhao, Y. *Angew. Chem., Int. Ed.* **2009**, *48*, 1114.

(31) Zhu, J.; Lin, Z.; Marder, T. B. *Inorg. Chem.* **2005**, *44*, 9384.

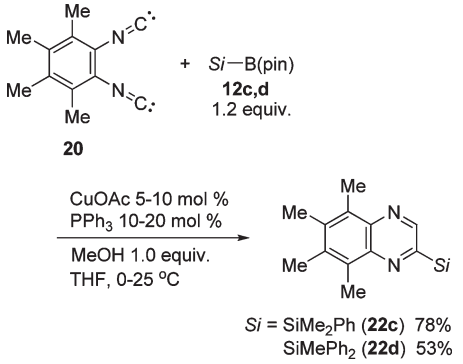
(32) (a) Dioumaev, V. K.; Procopio, L. J.; Carroll, P. J.; Berry, D. H. *J. Am. Chem. Soc.* **2003**, *125*, 8043 and references therein. (b) Takaya, J.; Iwasawa, N. *J. Am. Chem. Soc.* **2008**, *130*, 15254.

(33) Segawa, Y.; Yamashita, M.; Nozaki, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 6710 and references therein.

SCHEME 7



SCHEME 8



As described in Scheme 3, the present reaction is initiated by the nucleophilic borylation (or silylation) of isocyanide to form imidoylcopper, as in **B**, which is subsequently intercepted by α,β-unsaturated carbonyls through intramolecular 1,4-addition, leading to the construction of an indole skeleton. If the intermediate imidoylcopper species could react with other tethered electrophiles, the reaction would be extended to access different ring systems.[34] We found that an isocyanide moiety could be employed for such a purpose. The reaction of 1,2-diisocyanobenzene **20**[35] with diboronate **6** in the presence of a copper(I) catalyst afforded the cyclized products (Scheme 7). However, the expected 2-borylquinoxaline **21a** was not observed, but hydride **21b** was obtained instead, along with 2-methoxyquinoxaline **21c**.[36] Compound **21b** is presumably formed through the protodeboronation of **21a**. The yield of **21b** was only moderate, even when the reaction was conducted at 60 °C.

On the other hand, when silylboronates **12c** and **12d** were used instead of diboronate **6**, the expected 2-silylquinoxalines **22c** and **22d** were obtained (Scheme 8). In addition to the tolerance of 2-silyquinoxaline **22c**,**d** toward protodesilylation, the greater σ-donating nature of a silyl ligand, as compared with boryl, might be an important factor for the achievement of efficient cyclization.

Conclusions

In summary, we have developed the copper-catalyzed borylative cyclization of 2-alkenylphenyl isocyanides, leading to the formation of otherwise inaccessible 2-borylated indoles under very mild conditions (room temperature and neutral pH). The 2-borylated indoles thus obtained serve as versatile platforms for a diverse range of indole derivatives via a boron-based transformation such as the Suzuki–Miyaura reaction. The utility of the method was further demonstrated in the rapid synthesis of paullone. The cyclization process was initiated by the nucleophilic attack of the borylcopper(I) species toward an isocyanide moiety. The cyclization reactions also proceeded when silylboronate and hydroboronate (or hydrosilane) were used to generate silylcopper(I) and hydride copper(I) species, respectively. The strong σ-donating ability of boryl, silyl, and hydride ligands was key to this successful development. Further development of catalytic transformation of isocyanides is ongoing in our laboratory.[37]

Experimental Section

Typical Procedure for a Cu-Catalyzed Borylative Cyclization/Suzuki–Miyaura Coupling Tandem. An oven-dried, N_2-purged, 10 mL, two-necked flask was charged with **6** (139.7 mg, 0.55 mmol), **5a** (93.6 mg, 0.5 mmol), PPh_3 (26.2 mg, 0.1 mmol), Cu(OAc) (6.1 mg, 0.05 mmol), THF (4 mL), and methanol (20 μL, 0.5 mmol). The system was immersed in an oil bath at 25 °C. After 5 h, it was removed from the oil bath. The contents were passed through a short Florisil pad. Evaporation of the solvent afforded crude **7a** as a colorless oil.

A N_2-purged, 10 mL, two-necked flask was charged with K_2CO_3 (276.4 mg, 2.0 mmol), PPh_3 (13.1 mg, 0.05 mmol), palladium(II) chloride (4.4 mg, 0.025 mmol), iodobenzene (122.4 mg, 0.6 mmol), and a solution of 2-borylindole **7a** obtained as above in DME (3 mL). The system was immersed in an oil bath at 80 °C. After 15 h, it was removed from the oil bath and cooled to room temperature. The contents were transferred to a round-bottom flask, and volatiles were removed in vacuo. The residue was subjected to column chromatography on silica gel (eluent; hexane/EtOAc = 5/1) to give (2-phenyl-1*H*-indol-3-yl)acetic acid methyl ester (111.4 mg, 84% yield) as a white solid.

Methyl 2-(2-(4-acetylphenyl)-1*H*-indol-3-yl)acetate (entry 4 in Table 3): R_f 0.23 (hexane/EtOAc = 2/1); yellow solid; mp = 159 °C; ^{1}H NMR ($CDCl_3$, 270.05 MHz) δ 2.65 (s, 3H), 3.74 (s, 3H), 3.88 (s, 2H), 7.16–7.26 (m, 3H), 7.40 (d, J = 7.8 Hz, 1H), 7.69 (d, J = 7.6 Hz, 1H), 7.76 (d, J = 8.4 Hz, 2H), 8.07 (d, J = 8.1 Hz, 1H), 8.29 (s, 1H); ^{13}C NMR ($CDCl_3$, 67.80 MHz) δ 26.6, 30.9, 52.2, 106.9, 111.1, 119.3, 120.3, 123.2, 127.9, 128.8, 128.9,

(34) Synthesis of pyridine derivatives via cyclization of isocyanides: (a) Curran, D. P.; Liu, H. *J. Am. Chem. Soc.* **1991**, *113*, 2127. (b) Curran, D. P.; Liu, H.; Josien, H.; Ko, S. B. *Tetrahedron* **1996**, *52*, 11385. (c) Josien, H.; Ko, S. B.; Bom, D.; Curran, D. P. *Chem.—Eur. J.* **1998**, *4*, 67. (d) Rainier, J. D.; Kennedy, A. R. *J. Org. Chem.* **2000**, *65*, 6213. (e) Curran, D. P.; Du, W. *Org. Lett.* **2002**, *4*, 3215. (f) Lu, X.; Petersen, J. L.; Wang, K. K. *Org. Lett.* **2003**, *5*, 3277. (g) Mitamura, T.; Tsuboi, Y.; Iwata, K.; Tsuchii, K.; Nomoto, A.; Sonoda, M.; Ogawa, A. *Tetrahedron Lett.* **2007**, *48*, 5953. (h) Liu, L.; Wang, Y.; Wang, H.; Peng, C.; Zhao, J.; Zhu, Q. *Tetrahedron Lett.* **2009**, *50*, 6715. (i) Mitamura, T.; Iwata, K.; Ogawa, A. *Org. Lett.* **2009**, *11*, 3422. See also refs 9c and 35.

(35) Suginome and Ito reported that a thermal reaction of 1,2-diisocyanobenzene with $(^iPr_2N)_2BSiMe_2Ph$ affords 2-boryl-3-silylquinoxaline. See: (a) Suginome, M.; Fukuda, T.; Ito, Y. *J. Organomet. Chem.* **2002**, *643–644*, 508. For related polymerization, see: (b) Ito, Y.; Miyake, T.; Hatano, S.; Shima, R.; Ohara, T.; Suginome, M. *J. Am. Chem. Soc.* **1998**, *120*, 11880.

(36) The mechanism for the formation of **21c** is currently unclear. Since **21c** was not observed when the reaction was conducted in the absence of Cu(OAc), **21c** is formed through copper catalysis.

(37) For our work on catalytic reactions using isocyanides, see: (a) Chatani, N.; Oshita, M.; Tobisu, M.; Ishii, Y.; Murai, S. *J. Am. Chem. Soc.* **2003**, *125*, 7812. (b) Oshita, M.; Yamashita, K.; Tobisu, M.; Chatani, N. *J. Am. Chem. Soc.* **2005**, *127*, 761. (c) Yoshioka, S.; Oshita, M.; Tobisu, M.; Chatani, N. *Org. Lett.* **2005**, *7*, 3697. (d) Tobisu, M.; Kitajima, A.; Yoshioka, S.; Hyodo, I.; Oshita, M.; Chatani, N. *J. Am. Chem. Soc.* **2007**, *129*, 11431. (e) Tobisu, M.; Ito, S.; Kitajima, A.; Chatani, N. *Org. Lett.* **2008**, *10*, 5223. See also ref 9d.

134.7, 135.9, 136.1, 136.8, 172.5, 197.8; IR (KBr) 3359 m, 2949 w, 1726 s, 1674 s, 1601 s, 1547 w, 1506 w, 1450 m, 1435 m, 1404 w, 1360 m, 1342 m, 1327 m, 1282 s, 1261 s, 1236 m, 1196 m, 960 m, 835 m, 739 s, 642 w, 621 w, 596 m, 567 w, 536 w, 492 w, 436 w; MS *m*/*z* (relative intensity) 307 (M^+, 56), 248 (63), 206 (62), 205 (38), 204 (41), 43 (100); HRMS calcd for $C_{19}H_{17}NO_3$ 307.1208, found 307.1209.

Acknowledgment. This work was carried out, in part, by the Program of Promotion of Environmental Improvement to Enhance Young Researchers' Independence, the Special Coordination Funds for Promoting Science and Technology, Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japan. We also thank the Instrumental Analysis Center, Faculty of Engineering, Osaka University, for assistance with the MS, HRMS, and elemental analyses.

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