doi:10.1246/cl.130485
Published on the web June 20, 2013

Formal *anti*-Markovnikov Hydroamination of Terminal Aryl Alkynes with Pinacolborane and Hydroxylamines via Zr/Cu Sequential Catalysis

Ryosuke Sakae, Koji Hirano,* Tetsuya Satoh, and Masahiro Miura*
Department of Applied Chemistry, Faculty of Engineering, Osaka University, Suita, Osaka 565-0871

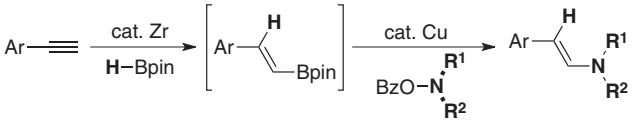
(Received May 24, 2013; CL-130485; E-mail: miura@chem.eng.osaka-u.ac.jp)

We have developed sequential Zr/Cu catalysis involving regioselective hydroboration and electrophilic amination for the formal *anti*-Markovnikov hydroamination of terminal aryl alkynes. The reaction system can provide a facile access to enamines from terminal acetylenes with high regioselectivity under mild conditions.

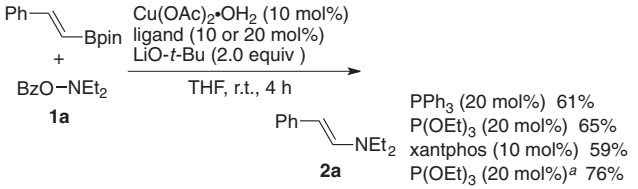
Enamines are important building blocks in organic synthesis because of their versatile reactivity directed toward alkylations, cycloadditions, and some related bond-forming reactions for heterocycle synthesis.[1] In general, enamines are prepared by condensation of the corresponding aldehydes or ketones and amines in the presence of Brønsted acids or Lewis acids.[2] However, due to relatively harsh reaction conditions, the above processes sometimes suffer from low functional compatibility. On the other hand, transition-metal-catalyzed hydroamination of alkynes with amines has recently received significant attention because it can complement the traditional condensation methodology and provide functional-group-tolerant approach to the target enamines. To date, a variety of catalyst systems have been reported.[3] However, in view of regioselectivity and efficiency, there still remains some room for the *anti*-Markovnikov hydroamination of terminal alkynes. Although Rh-,[4] Ru-,[5] and Zr-based[6] catalysts have been successfully employed,[7] most of them require elevated temperature.[8] Thus, further developments appear to be desired.

Meanwhile, our group[9] and others[10] have recently focused on the unique reactivity of chloramines and hydroxylamine derivatives and succeeded in the catalytic C–N bond formation through an electrophilic amination. In this context, we envisioned that a combination of regioselective hydroboration of terminal alkynes and electrophilic amination of preformed alkenylborane intermediates could be a good alternative to the above hydroamination protocols. Here, we report sequential Zr/Cu catalysis for a formal *anti*-Markovnikov hydroamination of terminal aryl alkynes. The process involves Zr-catalyzed hydroboration with pinacolborane and Cu-catalyzed electrophilic amination with *O*-benzoylhydroxylamines, leading to the corresponding enamines regioselectively under very mild conditions (Scheme 1).[11]

To establish the second electrophilic amination step shown in Scheme 1, we first chose (*E*)-4,4,5,5-tetramethyl-2-styryl-1,3,2-dioxaborolane (0.25 mmol) and *O*-benzoyl-*N*,*N*-diethylhydroxylamine (**1a**, 0.30 mmol) as model substrates and extensively screened various reaction parameters such as catalysts, bases, and solvents. It was found that the reaction proceeded in THF smoothly even at room temperature in the presence of a catalytic amount of $Cu(OAc)_2 \cdot OH_2$ together with several phosphorous ligands using LiO–*t*-Bu as the base (Scheme 2). Among the phosphorus ligands we tested, $P(OEt)_3$, PPh_3, and



Scheme 1. A formal *anti*-Markovnikov hydroamination of terminal aryl alkynes via sequential Zr/Cu catalysis. Bpin: 4,4,5,5-tetramethyl-1,3,2-dioxaborolanyl.



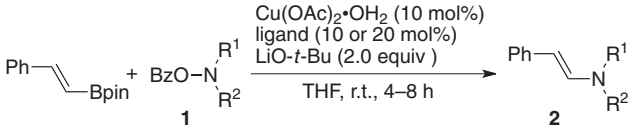
Scheme 2. Copper-catalyzed electrophilic amination of (*E*)-4,4,5,5-tetramethyl-2-styryl-1,3,2-dioxaborolane (0.25 mmol) with *O*-benzoyl-*N*,*N*-diethylhydroxylamine (**1a**, 0.30 mmol). [a]With 0.30 mmol of the styrylboronate and 0.25 mmol of hydroxylamine **1a**.

4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (xantphos) showed better activity, and the corresponding enamine **2a** was obtained in 59–65% yields, as judged by ^{1}H NMR. In the case of $P(OEt)_3$, when **1a** was used as the limiting agent (0.25 mmol), the yield was further improved to 76%.[12]

With the conditions in Scheme 2, we investigated the scope of *O*-benzoylhydroxylamines **1** (Table 1). The optimal ligand was highly dependent on the electronic and steric nature of hydroxylamines. In addition to **2a** (Entry 1), acyclic amines that bear *N*,*N*-diallyl, *N*,*N*-dibenzyl, and *N*-benzyl-*N*-methyl substituents underwent the reaction with the styrylboronate to form the corresponding enamines in moderate to good yields (Entries 2–4). The resultant allyl and benzyl moieties can be useful synthetic handles after appropriate deprotection.[13] The 4-pentenylamine also reacted, and the usual aminated product **2e** was obtained exclusively (Entry 5). Thus, an aminyl radical pathway is less likely.[14] The cyclic pyrrolidine and azepane also could be employed (Entries 6 and 7). In several cases, products were isolated in a saturated alkylamine form after the reduction with $NaB(OAc)_3H$ and AcOH. In most cases, the corresponding homocoupling products, 1,4-diaryl-1,3-butadienes, arising from alkenylboronates, were observed as a by-product (ca. 10%). Regio- and stereoisomers of enamines were not detected.

On the basis of the above success, we attempted the hydroboration/electrophilic amination sequence for the formal *anti*-Markovnikov hydroamination of terminal alkynes. Initially, we focused on the catalyst-free mild hydroboration of alkynes with two equivalents of pinacolborane, reported by Knochel.[15]

Table 1. Copper-catalyzed electrophilic amination of (*E*)-4,4,5,5-tetramethyl-2-styryl-1,3,2-dioxaborolane with *O*-benzoyl-*N*,*N*-diethylhydroxylamine (**1a**)[a]



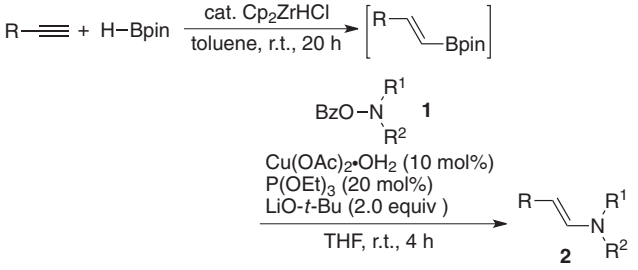
Entry	R^1, R^2 **1**	Ligand	**2**, Yield[b]/%
1	$R^1 = R^2 =$ Et (**1a**)	$P(OEt)_3$	**2a**, 76 (65)
2	$R^1 = R^2 =$ allyl (**1b**)	Xantphos	**2b**, 65 (48)
3	$R^1 = R^2 =$ benzyl (**1c**)	PPh_3	**2c**, (53)[c]
4	$R^1 =$ benzyl, $R^2 =$ Me (**1d**)	Xantphos	**2d**, 71 (65)[c]
5	$R^1 =$ Bu, $R^2 = (CH_2)_3(CH{=}CH_2)$ (**1e**)	$P(OEt)_3$	**2e**, 80 (66)[c]
6	$R^1 = R^2 = (CH_2)_5$ (**1f**)	Xantphos	**2f**, 45
7	$R^1 = R^2 = (CH_2)_6$ (**1g**)	Xantphos	**2g**, 72 (57)

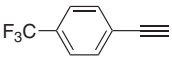
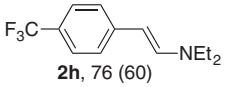
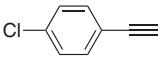
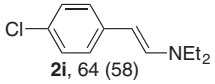
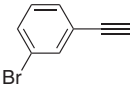
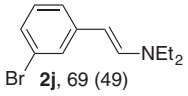
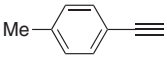
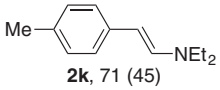
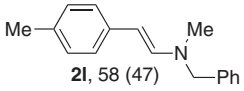
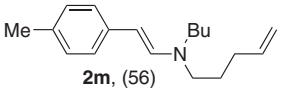
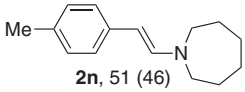
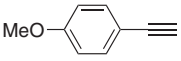
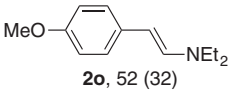
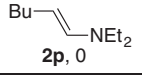
[a]Conditions: $Cu(OAc)_2 \cdot OH_2$ (0.25 mmol), ligand (0.050 mmol for $P(OEt)_3$ and PPh_3, 0.025 mmol for xantphos), styrylboronate (0.30 mmol), **1** (0.25 mmol), LiO–*t*-Bu (0.50 mmol), THF (1.5 mL), r.t., 4–8 h. [b]^{1}H NMR yield. Isolated yield is in parentheses. [c]Isolated yield as the corresponding alkylamine **2′**. See the Supporting Information for detailed procedures.

However, impurities associated with residual excess of pinacolborane were detrimental to subsequent copper catalysis. After evaluation of some reported catalytic hydroborations with nearly one equivalent of pinacolborane to alkynes, we were pleased to identify the Cp_2ZrHCl catalysis, which was originally developed by Srebnik,[16] to be optimal for merging with the above electrophilic amination process (Table 2). Namely, treatment of 4-(trifluoromethyl)phenylacetylene (0.30 mmol) with pinacolborane (0.38 mmol) and Cp_2ZrHCl (0.030 mmol) in toluene at room temperature for 20 h afforded the corresponding alkenylboronate with high regio- and stereoselectivities in a nearly quantitative yield (judged by GC and GCMS analysis). Removal of a small amount of the residual hydroborane and zirconium salt through a pad of Celite and evaporation of volatile materials were followed by the copper-catalyzed electrophilic amination with *O*-benzoyl-*N*,*N*-diethylhydroxylamine (**1a**, 0.25 mmol) to furnish the enamine **2h** in 76% yield (based on **1a**, Entry 1).[17] The sequential catalysis was compatible with aryl chloride and bromide functionalities (Entries 2 and 3). While the electron-neutral 4-methylphenylacetylene was converted into the enamines **2k**, **2l**, **2m**, and **2n** under the standard conditions (Entries 4–7), the electron-rich 4-methoxyphenylacetylene required a higher catalyst loading for the satisfactory conversion (Entry 8). Unfortunately, the reaction with aliphatic terminal alkynes such as 1-hexyne was unsuccessful, despite the smooth hydroboration confirmed by GC analysis (Entry 9). Thus, the present copper catalysis apparently required aryl groups at the position β to the pinacolboryl unit.

In conclusion, we have developed sequential Zr/Cu catalysis for the formal *anti*-Markovnikov hydroamination of terminal aryl alkynes. The catalytic system comprises Zr-catalyzed regioselective hydroboration with pinacolborane and Cu-catalyzed electrophilic amination with *O*-benzoylhydroxylamines, and allows for the selective preparation of enamines from terminal aryl alkynes under very mild conditions.[18] Further development of related electrophilic aminations is now in progress in our laboratory.

Table 2. Sequential Zr/Cu catalysis for formal *anti*-Markovnikov hydroamination of terminal alkynes[a]



Entry	Alkyne	**1**	**2**, Yield[b]/%
1		**1a**	 **2h**, 76 (60)
2		**1a**	 **2i**, 64 (58)
3[c]		**1a**	 **2j**, 69 (49)
4		**1a**	 **2k**, 71 (45)
5[d]		**1d**	 **2l**, 58 (47)
6		**1e**	 **2m**, (56)
7[d]		**1g**	 **2n**, 51 (46)
8[e]		**1a**	 **2o**, 52 (32)
9		**1a**	 **2p**, 0

[a]Conditions; hydroboration: Cp_2ZrHCl (0.030 mmol), alkyne (0.30 mmol), HBpin (0.38 mmol), toluene (0.15 mL), r.t., 20 h; amination: $Cu(OAc)_2 \cdot OH_2$ (0.25 mmol), $P(OEt)_3$ (0.050 mmol), **1** (0.25 mmol), LiO–*t*-Bu (0.50 mmol), THF (1.5 mL), r.t., 4 h. [b]^{1}H NMR yield. Isolated yield as the corresponding alkylamine **2′** is in parentheses. [c]At 60 °C in the hydroboration step. [d]With 0.025 mmol of xantphos instead of $P(OEt)_3$. [e]With 0.050 mmol of $Cu(OAc)_2 \cdot OH_2$ and 0.10 mmol of $P(OEt)_3$.

This work was partly supported by Grants-in-Aid from the Ministry of Education, Culture, Sports, Science and Technology, Japan. K.H. acknowledges The Uehara Memorial Foundation for financial support.

References and Notes

1 a) *Enamines: Synthesis, Structure, and Reactions*, 2nd ed., ed. by A. G. Cook, Dekker, New York, **1987**. b) J. K. Whitesell, in *Heteroatom Manipulation* in *Comprehensive Organic Synthesis*, ed. by B. M. Trost, I. Fleming,

Pergamon, Oxford, UK, **1991**, Vol. 6, pp. 703–732. doi:10.1016/B978-0-08-052349-1.00169-4. c) U. Kuckländer, *The Chemistry of Enamines, Part 1*, ed. by Z. Rappoport, Wiley, New York, **1994**, p. 523. doi:10.1002/0470024763.ch10. d) S. Kobayashi, H. Ishitani, *Chem. Rev.* **1999**, *99*, 1069. e) S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev.* **2007**, *107*, 5471.

2 a) P. W. Hickmott, *Tetrahedron* **1982**, *38*, 1975. b) W. A. White, H. Weingarten, *J. Org. Chem.* **1967**, *32*, 213.

3 Recent reviews: a) R. Severin, S. Doye, *Chem. Soc. Rev.* **2007**, *36*, 1407. b) I. Aillaud, J. Collin, J. Hannedouche, E. Schulz, *Dalton Trans.* **2007**, 5105. c) T. E. Müller, K. C. Hultzsch, M. Yus, F. Foubelo, M. Tada, *Chem. Rev.* **2008**, *108*, 3795. d) Y. Fukumoto, *J. Synth. Org. Chem., Jpn.* **2009**, *67*, 735.

4 a) C. G. Hartung, A. Tillack, H. Trauthwein, M. Beller, *J. Org. Chem.* **2001**, *66*, 6339. b) Y. Fukumoto, H. Asai, M. Shimizu, N. Chatani, *J. Am. Chem. Soc.* **2007**, *129*, 13792.

5 H. W. Cheung, C. M. So, K. H. Pun, Z. Zhou, C. P. Lau, *Adv. Synth. Catal.* **2011**, *353*, 411.

6 a) D. C. Leitch, P. R. Payne, C. R. Dunbar, L. L. Schafer, *J. Am. Chem. Soc.* **2009**, *131*, 18246. b) D. C. Leitch, C. S. Turner, L. L. Schafer, *Angew. Chem., Int. Ed.* **2010**, *49*, 6382.

7 A cesium hydroxide-catalyzed hydroamination was also reported: D. Tzalis, C. Koradin, P. Knochel, *Tetrahedron Lett.* **1999**, *40*, 6193.

8 Recently, Kakiuchi reported the room temperature *anti*-Markovnikov hydroamination of terminal alkynes catalyzed by an 8-quinolinolate rhodium complex: K. Sakai, T. Kochi, F. Kakiuchi, *Org. Lett.* **2011**, *13*, 3928.

9 a) T. Kawano, K. Hirano, T. Satoh, M. Miura, *J. Am. Chem. Soc.* **2010**, *132*, 6900. b) K. Hirano, T. Satoh, M. Miura, *Org. Lett.* **2011**, *13*, 2395. c) N. Matsuda, K. Hirano, T. Satoh, M. Miura, *Org. Lett.* **2011**, *13*, 2860. d) N. Matsuda, K. Hirano, T. Satoh, M. Miura, *J. Org. Chem.* **2012**, *77*, 617. e) N. Matsuda, K. Hirano, T. Satoh, M. Miura, *Angew. Chem., Int. Ed.* **2012**, *51*, 3642. f) N. Matsuda, K. Hirano, T. Satoh, M. Miura, *Synthesis* **2012**, 1792. g) N. Matsuda, K. Hirano, T. Satoh, M. Miura, *Angew. Chem., Int. Ed.* **2012**, *51*, 11827. h) Y. Miki, K. Hirano, T. Satoh, M. Miura, *Org. Lett.* **2013**, *15*, 172. i) N. Matsuda, K. Hirano, T. Satoh, M. Miura, *J. Am. Chem. Soc.* **2013**, *135*, 4934.

10 Reviews: a) E. Erdik, M. Ay, *Chem. Rev.* **1989**, *89*, 1947. b) K. Narasaka, M. Kitamura, *Eur. J. Org. Chem.* **2005**, 4505. c) E. Ciganek, in *Organic Reactions*, John Wiley & Sons, Inc., **2009**, p. 1. doi:10.1002/0471264180.or072.01. d) T. J. Barker, E. R. Jarvo, *Synthesis* **2011**, 3954. Recent examples: e) A. M. Berman, J. S. Johnson, *J. Am. Chem. Soc.* **2004**, *126*, 5680. f) S. Liu, L. S. Liebeskind, *J. Am. Chem. Soc.* **2008**, *130*, 6918. g) C. He, C. Chen, J. Cheng, C. Liu, W. Liu, Q. Li, A. Lei, *Angew. Chem., Int. Ed.* **2008**, *47*, 6414. h) T. J. Barker, E. R. Jarvo, *J. Am. Chem. Soc.* **2009**, *131*, 15598. i) T. Hatakeyama, Y. Yoshimoto, S. K. Ghorai, M. Nakamura, *Org. Lett.* **2010**, *12*, 1516. j) R. P. Rucker, A. M. Whittaker, H. Dang, G. Lalic, *J. Am. Chem. Soc.* **2012**, *134*, 6571. k) C. Grohmann, H. Wang, F. Glorius, *Org. Lett.* **2012**, *14*, 656. l) Q. Xiao, L. Tian, R. Tan, Y. Xia, D. Qiu, Y. Zhang, J. Wang, *Org. Lett.* **2012**, *14*, 4230. m) S. N. Mlynarski, A. S. Karns, J. P. Morken, *J. Am. Chem. Soc.* **2012**, *134*, 16449. n) C. Zhu, G. Li, D. H. Ess, J. R. Falck, L. Kürti, *J. Am. Chem. Soc.* **2012**, *134*, 18253. o) T. Miura, M. Morimoto, M. Murakami, *Org. Lett.* **2012**, *14*, 5214. p) X. Qian, Z. Yu, A. Auffrant, C. Gosmini, *Chem.—Eur. J.* **2013**, *19*, 6225.

11 In the course of this study, Chen and Xi reported a relevant Cu-catalyzed electrophilic amination of alkenylzirconiums with *O*-benzoylhydroxylamines: X. Yan, C. Chen, Y. Zhou, C. Xi, *Org. Lett.* **2012**, *14*, 4750.

12 See Supporting Information for detailed optimization studies.

13 a) S. Jaime-Figueroa, Y. Liu, J. M. Muchowski, D. G. Putman, *Tetrahedron Lett.* **1998**, *39*, 1313. b) V. Cadierno, S. E. García-Garrido, J. Gimeno, N. Nebra, *Chem. Commun.* **2005**, 4086. c) J.-Y. Wang, D.-X. Wang, Q.-Y. Zheng, Z.-T. Huang, M.-X. Wang, *J. Org. Chem.* **2007**, *72*, 2040.

14 a) M. Noack, R. Göttlich, *Chem. Commun.* **2002**, 536. Also see: b) T. Tsuritani, H. Shinokubo, K. Oshima, *Org. Lett.* **2001**, *3*, 2709. c) T. Tsuritani, H. Shinokubo, K. Oshima, *J. Org. Chem.* **2003**, *68*, 3246.

15 C. E. Tucker, J. Davidson, P. Knochel, *J. Org. Chem.* **1992**, *57*, 3482.

16 S. Pereira, M. Srebnik, *Organometallics* **1995**, *14*, 3127.

17 Although we have tested one-pot or one-flask reactions, no enamine was detected. This is probably because the residual zirconium salts interfered with the copper catalysis.

18 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

