

Synthesis of Tertiary Alkyl Amines from Terminal Alkenes: Copper-Catalyzed Amination of Alkyl Boranes

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S Supporting Information

ABSTRACT: A method for highly selective anti-Markovnikov hydroamination of terminal alkenes is reported. The one-pot procedure involves hydroboration of the alkene followed by a novel electrophilic amination of the alkyl borane catalyzed by an NHC–Cu complex. Terminal alkenes are successfully transformed into tertiary alkyl amines in the presence of a variety of functional groups in yields ranging from 80 to 97% with excellent regioselectivity. Results of a preliminary study of the reaction mechanism are also described.

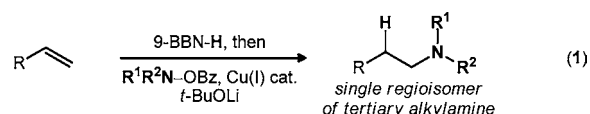
Amines are ubiquitous among biologically active small molecules, and their synthesis is one of the most common and important synthetic tasks.¹ In practice, amino groups are usually introduced into organic molecules by transformations of carbonyl compounds, amides, or alkyl electrophiles (halides or sulfonates).² Considerable effort has been devoted to broadening the scope of alkyl amine precursors by the development of methods for direct amination of other common functional groups. In this context, hydroamination of alkenes, which would allow direct preparation of alkyl amines from alkenes, has received a lot of attention as a highly desirable transformation.³

Despite the great progress made in developing hydroamination reactions,^{4–7} control of the regioselectivity is still a major problem. Particularly challenging has been the development of anti-Markovnikov hydroamination of simple alkenes. In metal-catalyzed hydroamination reactions, anti-Markovnikov selectivity has been observed only with special substrates, such as activated alkenes⁸ and styrenes.⁹ Control of the regioselectivity has also been a major problem in amination methods based on free radical and pericyclic additions, developed by Studer¹⁰ and Beauchemin.¹¹

The best results in anti-Markovnikov hydroamination to date have been achieved using a hydroboration–amination sequence. Primary amines can be prepared using procedures developed by Brown¹² and Kabalka.¹³ Secondary amines can be prepared from boronic esters after conversion to trifluoroborates, followed by a reaction with excess Lewis acid (BF₃ or SnCl₄) and alkyl azide.^{14,15} Unfortunately, while these methods are still the best option for anti-Markovnikov hydroamination of alkenes because of their exquisite regioselectivity, they often provide the amination products in low yield (<50% based on the alkene).^{16,17} Furthermore, strong Lewis acids are usually used for the reaction of organoboron compounds with azides, and this method has rarely been used for the synthesis of

secondary amines from alkenes.¹⁸ Finally, none of the existing procedures for anti-Markovnikov hydroamination allows the preparation of tertiary alkyl amines from alkenes.

In this communication, we report a one-pot procedure for the highly regioselective synthesis of tertiary alkyl amines from terminal alkenes (eq 1). We describe the reaction development



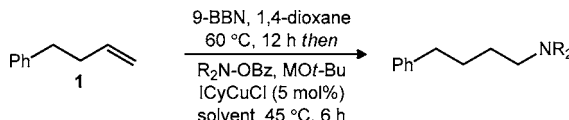
and exploration of the substrate scope together with the results of our preliminary study of the reaction mechanism.

We recently reported a catalytic method for the synthesis of hindered anilines featuring copper-catalyzed electrophilic amination of aryl boronic esters.¹⁹ At the same time, we were exploring the possibility that the analogous copper-catalyzed amination of alkyl boranes could be used to achieve a direct synthesis of tertiary alkyl amines from alkenes. To test this idea, we decided to explore the hydroamination of 4-phenyl-1-butene (**1**) using 9-borabicyclo[3.3.1]nonane (9-BBN) as a hydroboration reagent and *O*-benzoyl-*N,N*-dibenzylhydroxylamine **2** as the electrophilic source of nitrogen.²⁰ On the basis of our experience with copper-catalyzed transformations of organoboron compounds,²¹ we chose ICyCuCl (ICy = 1,3-dicyclohexylimidazol-2-ylidene) as a catalyst and sodium *tert*-butoxide as a base additive. The hydroboration of the alkene was performed in 1,4-dioxane at 60 °C, after which all of the components required for the electrophilic amination were simply added to the reaction flask. Under these reaction conditions, the hydroamination product was obtained in 16% yield (Table 1, entry 1),²² while an imine was identified as the major product. A control experiment confirmed the fast formation of this imine by the reaction of the electrophile **2** with sodium *tert*-butoxide.²³ We found the electrophile decomposition to be significantly slower in the presence of lithium *tert*-butoxide in noncoordinating solvents such as benzene (4% conversion after 2 h at 45 °C).²⁴ Consistent with this finding, the yield of the hydroamination product obtained in the catalytic reaction significantly increased when lithium *tert*-butoxide was used together with pentane as the solvent (Table 1, entry 4).

Unfortunately, with a variety of electrophilicities, we observed an alternative decomposition pathway under these reaction

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Table 1. Development of the Hydroamination Procedure^a


Entry	R ₂ N-OBz	M	Co-solvent	Yield ^b
1.		Na	1,4-dioxane	16%
2.		K	1,4-dioxane	11%
3.	Bn ₂ N-OBz 2	Li	1,4-dioxane	56%
4.		Li	pentane	97%

5.		Li	pentane	<5%
6. ^c		Li	pentane	52%
7. ^d		Li	toluene	86%
8. ^{d,e}	3	Li	toluene	99%

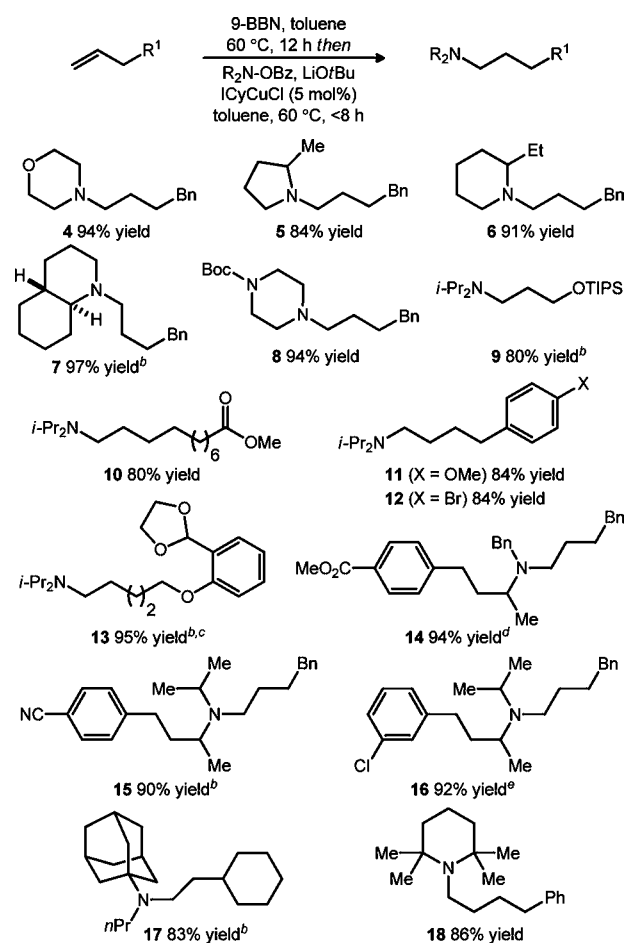
^a1 (1.0 equiv), R₂N-OBz (1.3 equiv, 0.2 M), MOt-Bu (1.3 equiv). ICy = 1,3-dicyclohexylimidazol-2-ylidene; 9-BBN = 9-borabicyclo[3.3.1]nonane. ^bDetermined by GC. ^cR₂N-OBz was added over 6 h. The reaction was conducted at 60 °C. ^dR₂N-OBz was added over 3 h. Toluene was used as the solvent in the hydroboration reaction. The reaction was conducted at 60 °C. ^eR₂N-OBz (1.1 equiv) and LiOt-Bu (1.1 equiv), 0.05 M concentration.

conditions. For example, the reaction with 3 provided no hydroamination product and instead resulted in almost quantitative formation of *tert*-butyl benzoate (Table 1, entry 5). To prevent the decomposition of 3 during the course of the reaction, we added the electrophile over a 6 h period and observed the formation of the hydroamination product in 52% yield (Table 1, entry 6). Using toluene led to a further increase in the yield of the desired product (Table 1, entry 7). However, the formation of a small amount of toluene amination product²⁵ complicated the purification of the desired amine. Finally, a 99% yield of the hydroamination product was obtained when 1.1 equiv of electrophile was added to a relatively dilute reaction mixture (0.05 M in alkyl borane) over 3 h at 60 °C (entry 8). In view of the difficulties often encountered in the purification of tertiary alkyl amines, it is important to note that these reaction conditions allowed pure hydroamination products to be isolated by an acid–base extraction.

The optimized reaction conditions and purification procedure proved to be quite general (Table 2). The highly selective anti-Markovnikov hydroamination of alkenes could be accomplished in the presence of esters, acetals, nitriles, aryl bromides, aryl chlorides, Boc-protected amines, and silyl and alkyl ethers.

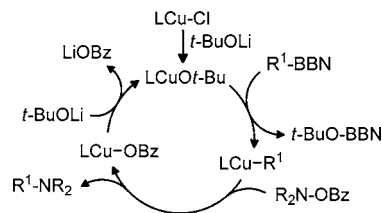
The procedure could be used to prepare morpholine, piperidine, pyrrolidine, piperazine, and decahydroquinoline derivatives (compounds 4–8). Equally good results were obtained in the preparation of acyclic amines, including sterically hindered *N,N*-diisopropyl-*N*-alkyl amines (9–13). Even the highly hindered *N*-alkyl-2,2,6,6-tetramethylpiperidine 18 could be formed in 86% yield. The synthesis of such hindered trialkyl amines is not only impossible to achieve using the existing hydroamination methods but is also difficult to accomplish using the standard reductive amination or alkylation reactions.²⁶ Finally, in all of these examples, only the product of anti-Markovnikov hydroamination was formed.²⁷

We propose that the amination of alkyl boron compounds proceeds according to the mechanism shown in Scheme 1. The reaction involves transmetalation from boron to copper^{21,28} followed by electrophilic amination of the alkylcopper

Table 2. Hydroamination of Terminal Alkenes^a

^aAlkene (0.50 mmol), 9-BBN (0.5 mmol), R₂N-OBz (0.55 mmol), and *t*-BuOLi (0.55 mmol) in 10 mL of toluene. R₂N-OBz was added over 4 h. Yields of isolated products are shown, unless otherwise noted. ^bBenzene was used as the solvent. ^cGC yield. After purification, the corresponding aldehyde was isolated in 92% yield. ^d2.5 mol % catalyst was used. ^eGC yield. The isolated yield was 72%.

Scheme 1. Proposed Mechanism



intermediate.²⁹ Finally, copper *tert*-butoxide is regenerated in a reaction with lithium alkoxide.³⁰ The most intriguing aspect of the proposed mechanism is the presence of a neutral copper(I) alkyl intermediate in a reaction performed at a relatively high temperature. Such complexes are known to decompose quickly above −35 °C,³¹ and to the best of our knowledge, there are no examples of fully characterized neutral copper(I) alkyl complexes containing β-hydrogen substituents. While similar intermediates have previously been proposed in copper-catalyzed reactions of alkyl boranes,^{28a,21a} there is little experimental evidence for their involvement.

In an effort to explore the role of copper(I) alkyl complexes in the amination reaction, we prepared IMesCuEt (19) by

addition of ethyllithium to IMesCuCl at low temperature. To our surprise, we were able not only to isolate the IMesCuEt complex, albeit in low yield (37%), but also to characterize it by X-ray diffraction (Figure 1). We discovered that the complex is

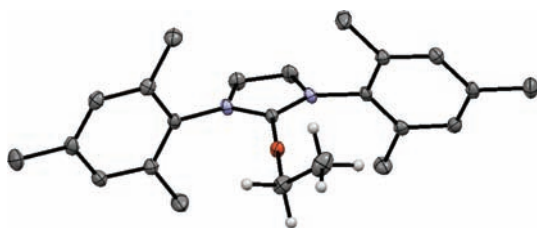
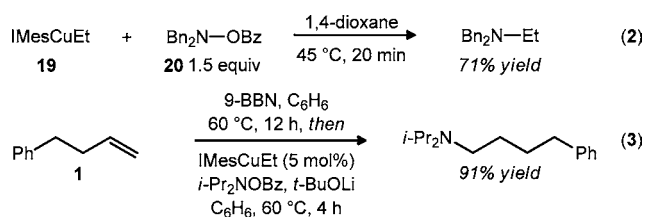


Figure 1. ORTEP of IMesCuEt (**19**) at 50% probability. Selected H atoms have been omitted for clarity.

stable in benzene for at least 4 h at 60 °C if kept in the dark. However, it decomposes quite readily at room temperature upon exposure to light (~50% conversion after 4 h).

We also showed that IMesCuEt reacts at 45 °C with electrophile **20** to produce the expected amination product in 71% yield (eq 2 in Scheme 2). Furthermore, when **19** was used

Scheme 2. Reactivity of IMesCuEt



as the catalyst in the hydroamination of **1**, the desired product was obtained in 91% yield (eq 3 in Scheme 2). The results of these experiments provide support for the proposed participation of neutral copper(I) alkyl complexes in the catalytic amination of alkyl boron compounds.

In conclusion, we have developed a one-pot hydroamination procedure that allows the direct formation of tertiary alkyl amines from terminal alkenes. The method is compatible with a wide variety of functional groups and can be used to prepare a range of both cyclic and acyclic amines. Furthermore, the procedure can be used to prepare highly sterically hindered amines that can be challenging to prepare even by well-established methods such as reductive amination and alkylation. Finally, we have prepared and characterized a stable copper(I) alkyl complex capable of β -hydride elimination and also provided experimental evidence that supports the proposed role of copper(I) alkyl complexes as intermediates in the hydroamination reaction.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

- (1) (a) Henkel, T.; Brunne, R. M.; Müller, H.; Reichel, F. *Angew. Chem., Int. Ed.* **1999**, *38*, 643. (b) Hili, R.; Yudin, A. K. *Nat. Chem. Biol.* **2006**, *2*, 284.
- (2) Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. *Org. Biomol. Chem.* **2006**, *4*, 2337.
- (3) For general reviews, see: (a) Müller, T. E.; Hultsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, *108*, 3795. (b) Hultsch, K. C. *Adv. Synth. Catal.* **2005**, *347*, 367. (c) Beller, M.; Seayad, J.; Tillack, A.; Jiao, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 3368.
- (4) For selected examples of intramolecular hydroamination catalyzed by complexes of group IV metals and lanthanides, see: (a) Manna, K.; Xu, S.; Sadow, A. D. *Angew. Chem., Int. Ed.* **2011**, *50*, 1865. (b) Leitch, D. C.; Payne, P. R.; Dunbar, C. R.; Schafer, L. L. *J. Am. Chem. Soc.* **2009**, *131*, 18246. (c) Wood, M. C.; Leitch, D. C.; Yeung, C. S.; Kozak, J. A.; Schafer, L. L. *Angew. Chem., Int. Ed.* **2007**, *46*, 354. (d) Watson, D. A.; Chiu, M.; Bergman, R. G. *Organometallics* **2006**, *25*, 4731. (e) Gribkov, D. V.; Hultsch, K. C.; Hampel, F. *J. Am. Chem. Soc.* **2006**, *128*, 3748. (f) Kim, J. Y.; Livinghouse, T. *Org. Lett.* **2005**, *7*, 1737. (g) Hong, S.; Marks, T. J. *Acc. Chem. Res.* **2004**, *37*, 673. (h) Hong, S.; Tian, S.; Metz, M. V.; Marks, T. J. *J. Am. Chem. Soc.* **2003**, *125*, 14768.
- (5) For selected examples of intramolecular hydroamination catalyzed by complexes of late transition metals, see: (a) Shen, X.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2010**, *49*, 564. (b) Julian, L. D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 13813. (c) Ohmiya, H.; Moriya, T.; Sawamura, M. *Org. Lett.* **2009**, *11*, 2145. (d) Hesp, K. D.; Tobisch, S.; Stradiotto, M. *J. Am. Chem. Soc.* **2009**, *132*, 413. (e) Liu, Z.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 1570. (f) Cochran, B. M.; Michael, F. E. *J. Am. Chem. Soc.* **2008**, *130*, 2786. (g) Michael, F. E.; Cochran, B. M. *J. Am. Chem. Soc.* **2006**, *128*, 4246. (h) Han, X.; Widenhofer, R. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 1747. (i) Bender, C. F.; Widenhofer, R. A. *J. Am. Chem. Soc.* **2005**, *127*, 1070.
- (6) For selected examples of intermolecular hydroamination, see: (a) Zhou, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 12220. (b) McBee, J. L.; Bell, A. T.; Tilley, T. D. *J. Am. Chem. Soc.* **2008**, *130*, 16562. (c) Brunet, J.-J.; Chu, N.-C.; Rodriguez-Zubiri, M. *Eur. J. Inorg. Chem.* **2007**, 4711. (d) Zhang, J.; Yang, C.-G.; He, C. *J. Am. Chem. Soc.* **2006**, *128*, 1798. (e) Dorta, R.; Egli, P.; Zürcher, F.; Togni, A. *J. Am. Chem. Soc.* **1997**, *119*, 10857. (f) Casalnuovo, A. L.; Calabrese, J. C.; Milstein, D. *J. Am. Chem. Soc.* **1988**, *110*, 6738.
- (7) For recent examples of enantioselective intermolecular hydroamination reactions, see: (a) Zhang, Z.; Lee, S. D.; Widenhofer, R. A. *J. Am. Chem. Soc.* **2009**, *131*, 5372. (b) Reznichenko, A. L.; Nguyen, H. N.; Hultsch, K. C. *Angew. Chem., Int. Ed.* **2010**, *49*, 8984.
- (8) (a) Munro-Leighton, C.; Blue, E. D.; Gunnoe, T. B. *J. Am. Chem. Soc.* **2006**, *128*, 1446. (b) Fadini, L.; Togni, A. *Chem. Commun.* **2003**, 30. (c) Seligson, A. L.; Trogler, W. C. *Organometallics* **1993**, *12*, 744. (d) Castonguay, A.; Spasyuk, D. M.; Madern, N.; Beauchamp, A. L.; Zargarian, D. *Organometallics* **2009**, *28*, 2134. (e) Kawatsura, M.; Hartwig, J. F. *Organometallics* **2001**, *20*, 1960.
- (9) (a) Beller, M.; Trauthwein, H.; Eichberger, M.; Breindl, C.; Herwig, J.; Müller, T. E.; Thiel, O. R. *Chem.—Eur. J.* **1999**, *5*, 1306. (b) Ryu, J.-S.; Li, G. Y.; Marks, T. J. *J. Am. Chem. Soc.* **2003**, *125*, 12584. (c) Utsunomiya, M.; Kuwano, R.; Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 5608. (d) Utsunomiya, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2004**, *126*, 2702. (e) Takaya, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 5756. (f) Munro-Leighton, C.; Delp, S. A.; Alsop, N. M.; Blue, E. D.; Gunnoe, T. B. *Chem. Commun.* **2008**, 111.

(10) (a) Guin, J.; Fröhlich, R.; Studer, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 779. (b) Guin, J.; Mück-Lichtenfeld, C.; Grimme, S.; Studer, A. *J. Am. Chem. Soc.* **2007**, *129*, 4498.

(11) (a) Moran, J.; Gorelsky, S. I.; Dimitrijevic, E.; Lebrun, M.-E.; Bédard, A.-C.; Séguin, C.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2008**, *130*, 17893. (b) Loiseau, F.; Clavette, C.; Raymond, M.; Roveda, J.-G.; Burrell, A.; Beauchemin, A. M. *Chem. Commun.* **2011**, *47*, S62.

(12) (a) Brown, H. C.; Heydkamp, W. R.; Breuer, E.; Murphy, W. S. *J. Am. Chem. Soc.* **1964**, *86*, 3565. (b) Brown, H. C.; Kim, K.-W.; Srebnik, M.; Bakthan, S. *Tetrahedron* **1987**, *43*, 4071.

(13) Kabalka, G. W.; Sastry, K. A. R.; McCollum, G. W.; Yoshioka, H. *J. Org. Chem.* **1981**, *46*, 4296.

(14) (a) Matteson, D. S.; Kim, G. Y. *Org. Lett.* **2002**, *4*, 2153. (b) Hupe, E.; Marek, I.; Knochel, P. *Org. Lett.* **2002**, *4*, 2861.

(15) For a related reaction of alkyl boranes with azides, see: (a) Brown, H. C.; Midland, M. M.; Levy, A. B.; Brown, H. C.; Wetherill, R. B.; Suzuki, A.; Sono, S.; Itoh, M. *Tetrahedron* **1987**, *43*, 4079. (b) Kabalka, G. W.; Wang, Z.; Goudgaon, N. M. *Synth. Commun.* **1989**, *19*, 2409.

(16) The major problem in amination of trialkyl boranes is that at most two alkyl groups are aminated. Furthermore, secondary alkyl groups are aminated faster than the primary ones. Therefore, in reactions of 9-alkyl-9-BBN compounds, selective amination of the BBN backbone is observed (see refs 12b, 13, and 15).

(17) Efficient hydroamination of alkenes has been accomplished using dimethyl borane as a hydroborating reagent (see ref 12b). However, this procedure requires the preparation of dimethyl borane, which is fully described in the following two publications: (a) Brown, H. C.; Cole, T. E.; Srebnik, M.; Kim, K. W. *J. Org. Chem.* **1986**, *51*, 4925. (b) Brown, H. C.; Srebnik, M.; Cole, T. E. *Organometallics* **1986**, *5*, 2300.

(18) For an excellent example of the use of this procedure in other transformations, see: Scott, H. K.; Aggarwal, V. K. *Chem.—Eur. J.* **2011**, *17*, 13124.

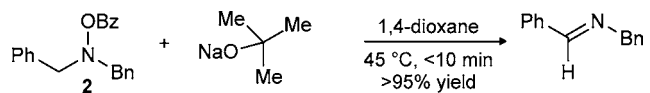
(19) Rucker, R. P.; Whittaker, A. M.; Dang, H.; Lalic, G. *Angew. Chem., Int. Ed.* **2012**, DOI: 10.1002/ange.201200480.

(20) For selected examples of electrophilic amination reactions, see: (a) Casarini, A.; Dembech, P.; Lazzari, D.; Marini, E.; Reginato, G.; Ricci, A.; Seconi, G. *J. Org. Chem.* **1993**, *58*, 5620. (b) Zheng, B.; Srebnik, M. *J. Org. Chem.* **1995**, *60*, 1912. (c) Berman, A. M.; Johnson, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 5680. (d) Berman, A. M.; Johnson, J. S. *J. Org. Chem.* **2006**, *71*, 219. (e) Zhang, Z.; Yu, Y.; Liebeskind, L. S. *Org. Lett.* **2008**, *10*, 3005. (f) Barker, T. J.; Jarvo, E. R. *J. Am. Chem. Soc.* **2009**, *131*, 15598. (g) Hatakeyama, T.; Yoshimoto, Y.; Ghorai, S. K.; Nakamura, M. *Org. Lett.* **2010**, *12*, 1516. (h) He, C.; Chen, C.; Cheng, J.; Liu, C.; Liu, W.; Li, Q.; Lei, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 6414.

(21) (a) Uehling, M. R.; Marionni, S. T.; Lalic, G. *Org. Lett.* **2012**, *14*, 362. (b) Whittaker, A. M.; Rucker, R. P.; Lalic, G. *Org. Lett.* **2010**, *12*, 3216.

(22) In the absence of a copper catalyst or the alkoxide additive, the hydroamination product was obtained in less than 5% yield.

(23) Reaction of sodium *tert*-butoxide with **2** to form the imine byproduct:



(24) Reaction mixtures formed by adding lithium *tert*-butoxide to a 0.2 M solution of the electrophile in 1,4-dioxane or benzene at 45 °C are homogeneous, suggesting that the difference in reactivity is not simply a result of the difference in solubility of the alkoxide. See the Supporting Information for details.

(25) Ni, Z.; Zhang, Q.; Xiong, T.; Zheng, Y.; Li, Y.; Zhang, H.; Zhang, J.; Liu, Q. *Angew. Chem., Int. Ed.* **2012**, *51*, 1244.

(26) (a) Abdel-Magid, A. F.; Mehrman, S. *J. Org. Process Res. Dev.* **2006**, *10*, 971. (b) Baxter, E. W.; Reitz, A. B. *Org. React.* **2002**, *59*, 1.

(27) According to the GC/MS analysis of crude reaction mixtures.

(28) (a) Ohmiya, H.; Yokobori, U.; Makida, Y.; Sawamura, M. *J. Am. Chem. Soc.* **2010**, *132*, 2895. (b) Ohmiya, H.; Yoshida, M.; Sawamura, M. *Org. Lett.* **2011**, *13*, 482. (c) Ohmiya, H.; Tanabe, M.; Sawamura, M. *Org. Lett.* **2011**, *13*, 1086. (d) Ohishi, T.; Nishiura, M.; Hou, Z. *Angew. Chem., Int. Ed.* **2008**, *47*, 5792. (e) Dang, L.; Lin, Z.; Marder, T. B. *Organometallics* **2010**, *29*, 917.

(29) Campbell, M. J.; Johnson, J. S. *Org. Lett.* **2007**, *9*, 1521.

(30) Mankad, N. P.; Laitar, D. S.; Sadighi, J. P. *Organometallics* **2004**, *23*, 3369.

(31) (a) Whitesides, G. M.; Stedronsky, E. R.; Casey, C. P.; San Filippo, J. *J. Am. Chem. Soc.* **1970**, *92*, 1426. (b) Goj, L. A.; Blue, E. D.; Delp, S. A.; Gunnoe, T. B.; Cundari, T. R.; Pierpont, A. W.; Petersen, J. L.; Boyle, P. D. *Inorg. Chem.* **2006**, *45*, 9032.