Brønsted Acid/Silane Catalytic System for Intramolecular Hydroalkoxylation and Hydroamination of Unactivated Alkynes

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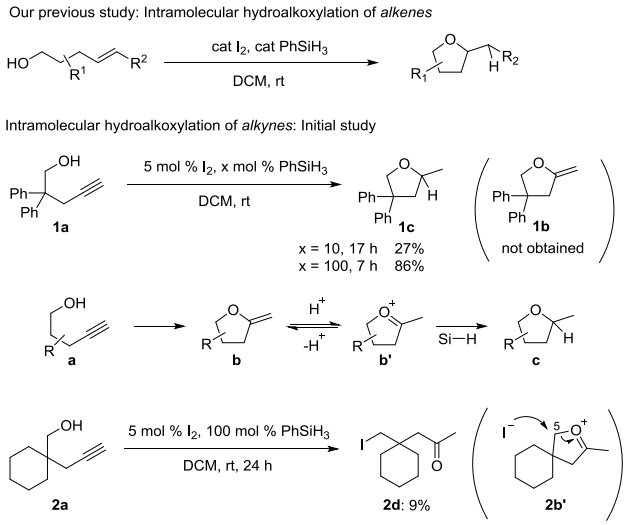
ABSTRACT: The Brønsted acid-catalyzed intramolecular hydroalkoxylation and hydroamination of unactivated alkynes are described. We found that unactivated alkynes are electrophilically activated by a catalytic amount of bis(trifluoromethanesulfonyl)imide to undergo intramolecular hydroalkoxylation and hydroamination. In the presence of silane, the formed reactive *exo*-cyclic enol ether and *exo*-cyclic enamine intermediates are effectively reduced to the corresponding saturated cyclic ethers and *N*-protected cyclic amines. The 2,4-*cis* and 2,5-*cis* pyrrolidine derivatives are produced with high diastereoselectivity. Taking advantage of this selectivity, the 2,5-*cis*-disubstituted prolinol was also synthesized from glutamic acid in the optically active form.

KEYWORDS: Brønsted acid, hydroalkoxylation, hydroamination, alkyne, electrophilic activation

The intramolecular hydroalkoxylation and hydroamination of alkynes are expedient and atom-economical methods for constructing heterocycles similar to those of alkenes.[1] Although toxic Hg(II)-mediated methods were applied in early studies, a variety of catalytic methods using late transition metals have since been developed, beginning with Utimoto's pioneering work using a palladium catalyst.[2-6] Late transition metals efficiently interact with alkynes through not only the in-plane π-orbital, but also through the orthogonal π-orbital, enabling the electrophilic activation of alkynes in the presence of hydroxyl groups or amines/amides.[6] In addition, it has been reported that lanthanide and actinide complexes efficiently catalyze various hydrofunctionalizations of alkynes including hydroalkoxylation and hydroamination.[7] Group-IV metal complexes (i.e., titanium and zirconium) can also catalyze the hydroamination of alkynes.[8] On the other hand, to the best of our knowledge, there are no reports of a Brønsted acid-catalyzed hydrofunctionalization of alkyl-substituted unactivated alkynes, although the intramolecular hydroamination and hydroalkoxylation of unactivated alkenes have been reported by Hartwig and Duñach.[9,10] One hindrance to the development of Brønsted acid-catalyzed methods is the inherent instability of the non-stabilized vinyl cation.[11] Due to the fact that a vinyl cation is much less stable than a secondary carbocation, alkynes are thought to require more effective activation than alkenes.[12] Although it is reported that simple alkynes without any Lewis basic functional groups are electrophilically activated by superacids to cause the reaction via vinyl-type cations,[13] the electrophilic activation of alkynes by a catalytic amount of a Brønsted acid in the presence of Lewis basic hydroxy groups and amides is typically needed to promote the desired reaction. Another challenge is that the *exo*-cyclic enol ethers and enamines are more susceptible to electrophilic activation by Brønsted acids than are the alkyne, which leads to undesired reactions such as oligomerization. We report herein the efficient electrophilic activation of alkynes by Brønsted acid catalysts in the presence of hydroxy groups and sulfonamides to undergo intramolecular hydroalkoxylation and hydroamination reaction.

Recently, we developed a silane-iodine system for the intramolecular hydroalkoxylation of alkenes.[14] The reaction of unactivated alkenes proceeds efficiently at room temperature in this catalytic system (Scheme 1). Anticipating that the transition-metal-free silane-iodine system could be applicable to the reaction of alkynes, hydroxy alkyne **1a** was subjected to the standard reaction



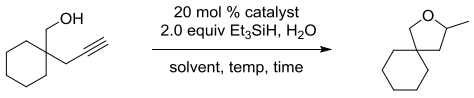
Scheme 1. Reaction of Hydroxy Alkenes and Alkynes in the Silane-Iodine System

conditions. As a result, saturated cyclic ether **1c**, as opposed to *exo*-cyclic enol ether **1b**, was obtained in 27% yield. It is plausible that **1c** was produced by the silane reduction of **1b** after the desired hydroalkoxylation took place, which suggests that

electrophilic activation of the alkyne did occur. Since a stoichiometric amount of the hydride source is required for the quantitative production of **1c**, **1a** was again subjected to the reaction in the presence of 100 mol % $PhSiH_3$. As suspected, a high yield of **1c** was obtained. These results indicated that the transiently-formed more reactive *exo*-cyclic enol ether **1b** immediately generates oxocarbenium ion **1b'**, which is effectively reduced by $PhSiH_3$ to afford saturated cyclic ether **1c** before any undesired side reactions could be induced. However, the reaction of alkyne **2a** resulted in the recovery of most of the starting material together with a small amount of iodoketone **2d**. It is possible that **2d** was produced by the nucleophilic attack of iodide on the 5 position of oxocarbenium ion **2b'**, which could lead to deactivation of the catalyst.

To prevent the iodinative ring-opening reaction, we decided to examine a TfOH-catalyzed reaction because the triflate ion (TfO^-) is less nucleophilic than iodide (I^-) (Table 1). γ-Hydroxy alkyne **2a** was treated with 20 mol % TfOH in the presence of 2.0 equivalents of Et_3SiH at r.t., and the desired product **2c** was obtained in 60% yield along with 18% of recovered **2a** (entry 1). Because the TES ether of **2a** was detected in the reaction mixture, it was assumed that the recovered **2a** was produced from hydrolysis of the TES ether during workup. The TES ether presumably formed due to a shortage of available protons. Therefore, the reaction was repeated in the presence of 1.0 equivalent of H_2O as a proton source[16] and a high yield of **2c** was obtained with no recovered starting material, although an elevated temperature was required (entries 2–4). The use of a stronger Brønsted acid, Tf_2NH, shortened the reaction time (entry 5).[15] An examination of the amount of H_2O revealed that 0.2 equivalent was optimal (entries 5–8). The remainder of the newly introduced protons of the products may originate from adventitious water. The catalyst loading amount could be reduced to 10 mol % of Tf_2NH without diminishing the yield (entry 9).

Table 1. Optimization of Reaction Conditions[a]



2a **2c**

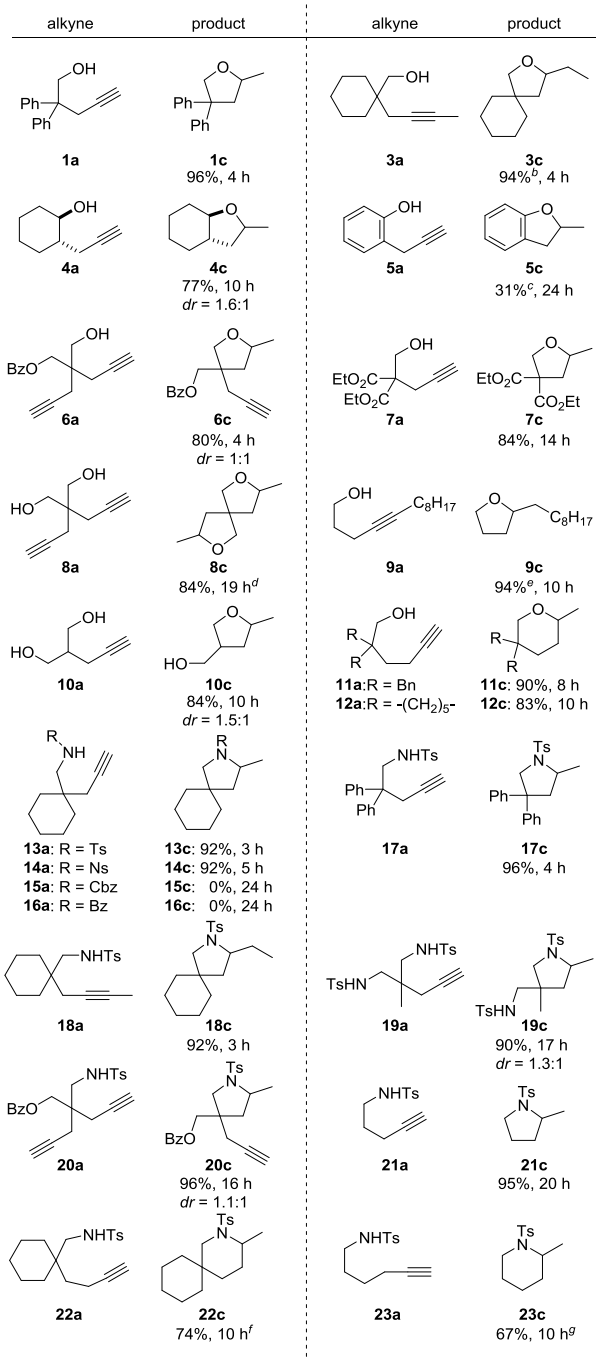
entry	catalyst	H_2O (equiv)	solvent	temp (°C)	time (h)	yield (%)[b]
1	TfOH	0	DCM	r.t.	24	60 (18)[c]
2	TfOH	1.0	DCM	r.t.	24	trace (89)[c]
3	TfOH	1.0	DCM	reflux	24	86
4	TfOH	1.0	DCE	60	11	87
5	Tf_2NH	1.0	DCE	60	4	82
6	Tf_2NH	0.5	DCE	60	2	86
7	Tf_2NH	0.2	DCE	60	1	84
8	Tf_2NH	0.1	DCE	60	3	79
9	Tf_2NH (10 mol %)	0.2	DCE	60	4	82

[a] Reaction conditions: 0.1 M solution of alkyne (0.2-0.3 mmol) in DCM or DCE, catalyst (20 mol %), Et_3SiH (2.0 equiv), H_2O (0-1.0 equiv). [b] Isolated yield. [c] Yield in parenthesis represents recovered starting material as determined by ^1H NMR.

With the optimal reaction conditions in hand, the substrate scope was investigated (Table 2). Internal alkyne **3a** and secondary alcohol **4a** provided the desired products **3c** and **4c** in high yields, although the cyclization of 2-propargyl phenol (**5a**) was slow and afforded only a moderate yield of **5c** after 24 h. Diyne **6a** and diester **7a** provided **6c** and **7c** with the additional alkyne and esters remaining intact. Note that the neither hydration of the alkyne or hydrolysis of the ester occurred under the reaction conditions. Spirocyclic ether **8c** was also afforded in high yield from the double hydroalkoxylation/reduction of **8a**. Alkyne **9a**, with no substituent on the linker between the hydroxy group and the alkyne, underwent efficient hydroalkoxylation/reduction, which suggests that Thorpe-Ingold effect is not essential for this cyclization.[17] While it is reported that dihydroxy alkynes often afford bicyclic acetals via double cyclization under transition metal-catalyzed conditions,[4a,c] dihydroxy alkyne **10a** interestingly furnished monocyclic ether **10c** with a hydroxymethyl moiety. The 6-membered ethers **11c** and **12c** were also efficiently formed from the corresponding δ-hydroxy alkynes, whereas the hydroalkoxylation of the ε-hydroxy alkyne to the 7-membered ether did not take place (Scheme S3). Next, we examined the reaction of *N*-protected amino alkynes. Tosylamide **13a** and nosylamide **14a** efficiently underwent the desired hydroamination/reduction to furnish *N*-Ts pyrrolidine **13c** and *N*-Ns pyrrolidine **14c** in high yields. However, carbamate **15a** and benzamide **16a** resulted in no reaction, which is consistent with the results from the TfOH-catalyzed intramolecular hydroamination of alkenes.[9] Alkynes **17a**–**21a** also provided the desired products **17c**–**21c** in high yields. 5-Hexynylsulfoneamide **22a** and **23a** afforded *N*-Ts piperidine **22c** and **23c** in 74% and 67% yields, respectively, together with the isomeric five-membered products (23% and 20%). While the characteristic feature of the diastereoselectivity for the formation of disubstituted cyclic ethers and amide was uncovered as Table 3 shows, that for **4c**, **6c**, **10c**, **19c**, **20c** was low.

The intramolecular hydroalkoxylation and hydroamination of alkenes afford saturated heterocycles similar to these hydroalkoxylation/reduction and hydroamination/reduction products of alkynes. In most of the previously reported reactions of alkenes, the diastereoselectivity for the formation of disubstituted heterocycles was moderate to low.[18,19] Thus, we compared the diastereoselectivity for the formation of disubstituted cyclic ethers and amides with the Brønsted acid-catalyzed cyclization of alkenes. The results are summarized in Table 3. Secondary alcohol **24a** provided 2,5-disubstitued cyclic ether **24c** with low diastereoselectivity, as did the corresponding reaction of alkene **25**. Alkyne **26a**, with a substituent on the β-position of the alkyne, provided **26c** with better diastereoselectivity. To our delight, the characteristic *cis* selectivity was observed in the subsequent examination of the hydroamination/reduction of alkyne **27a** to 2,5-disubstituted pyrrolidine **27c**. While the TfOH-catalyzed hydroamination of alkene **28** provided *trans*-**27c** as a major diastereomer with moderate selectivity,[9] and the several methods using transition-metal catalysts such as Sc(III) complex and $FeCl_3$ provided 2,5-*trans* pyrrolidines with high diastereoselectivity,[19b,20] the hydroamination/reduction of alkynes afforded the 2,5-*cis* pyrrolidines with complementary diastereoselectivity. On subsequent examination of the syntheses of 2,4-disubstituted products, *cis*-2,4-disubstituted pyrrolidines **32c** and **33c** were

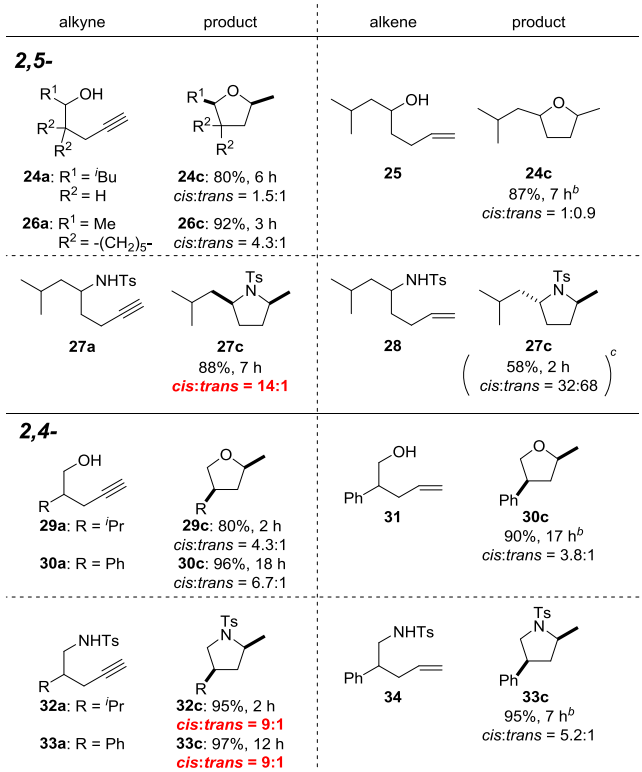
Table 2. Substrate Scope of the Hydroalkoxylation/Reduction and the Hydroamination/Reduction[a]



[a] Reaction conditions: Tf_2NH (10 mol %), Et_3SiH (2.0 equiv), H_2O (0.2 equiv), DCE, 60 ˚C. [b] 3% of the six-membered compound is contained. [c] Determined by ^1H MNR. [d] Tf_2NH (20 mol %), H_2O (0.4 equiv). [e] 17% of the six-membered compound is contained. [f] Inseparable mixture with five-membered isomer **13c** (23%). [g] Inseparable mixture with *N*-Ts 2-ethylpyrrolidine (20%)

obtained with markedly higher diastereoselectivity as compared with reports on hydroamination methods of alkenes.[19] The formation of the 2,3-disubstituted cyclic ether and pyrrolidine proceeded with moderate diastereoselectivity (Table S1), whereas high diastereoselectivity was observed with the formation of 2,5- and 2,4-disubstituted pyrrolidines.

Table 3. Diastereoselectivity for Disubstituted 5-Membered Products[a]



[a] Reaction conditions: Tf_2NH (10 mol %), Et_3SiH (2.0 equiv), H_2O (0.2 equiv), DCE, 60 ˚C. [b] Our result under the following conditions: Tf_2NH (10 mol %) in DCE at 60 ˚C. [c] The reported result in ref 9.

This observed 2,4-*cis* selectivity is rationalized by Woerpel's "inside attack" model (Figure 1a).[21] The diastereoselectivity for the hydroalkoxylation/reduction is consistent with that of the reduction of lactols with silane.[22] On the other hand, the 2,5-*cis* selectivity for hydroamination/reduction is exceptional. It is plausible that because of the steric repulsion between the tosyl group and the isobutyl substituent on the 5 position, **27b'$_{ax}$** is more stable than **27b'$_{eq}$**, which is supported by the results of our computational study (Figures 1b and 1c).[23] Thus, the hydride must approach the iminium carbon from the inside face of **27b'$_{ax}$** to afford the 2,5-*cis* isomer.

Finally, optically active tosylamide **35a** prepared from L-glutamic acid was subjected to hydroamination/reduction. As a result, optically active 2,5-*cis* prolinol **35c** was obtained with high diastereoselectivity (*cis*:*trans* = >30:1) (Scheme 2a). This representative result shows the synthetic utility of this method. Enyne **36a** was also subjected to the reaction to explore the reaction preference between alkenes and alkynes (Scheme 2b). Interestingly, allyl substituted tetrahydrofuran **36c** was produced as the major product, which suggests that the intramolecular hydroalkoxylation of alkynes is more favorable compared to that of alkenes. It can be rationalized that the less stable cationic intermediate generated from the alkyne would undergo cyclization more rapidly.

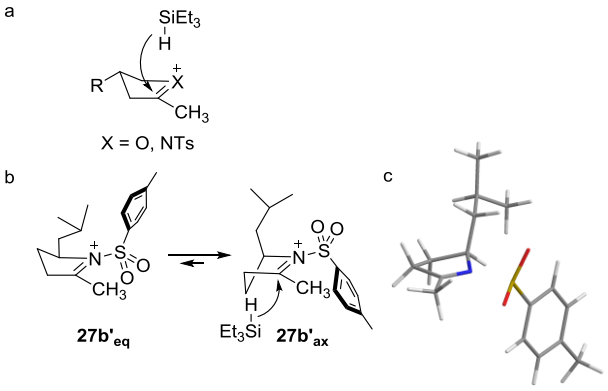
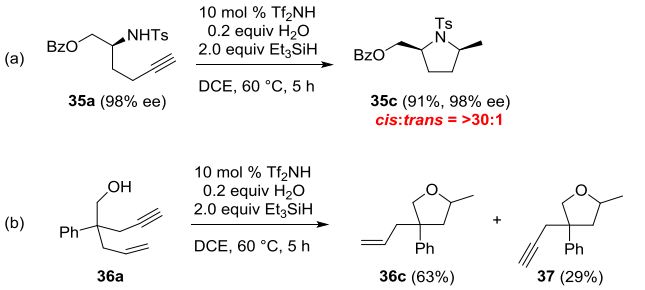


Figure 1. a) Inside attack model. b) Equilibrium of **27b'$_{eq}$** and **25b'$_{ax}$**. c) Energy-minimized structure of **27b'**.



Scheme 2. Synthesis of Optically Active Prolinol 35c and the Reaction of Enyne 36a

In conclusion, we found that Brønsted acids can electrophilically activate alkynes in the presence of Lewis basic hydroxy groups and sulfonamides to cause intramolecular hydroalkoxylations and hydroaminations, although the possibility that a silylium species works as a catalyst in this system is not excluded. The resulting *exo*-cyclic enol ethers and enamines are immediately reduced in the presence of Et_3SiH and the products are isolated as saturated cyclic ethers and *N*-protected cyclic amines. Although the intramolecular hydrofunctionalization/reduction of alkynes affords saturated heterocycles similar to the hydrofunctionalization of alkenes, fundamental differences in the diastereoselectivity were observed. Further investigation of the transition-metal-free hydrofunctionalization of unactivated alkynes is currently underway.

ASSOCIATED CONTENT

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Notes

The authors declare no competing financial interest.

SUPPORTING INFORMATION.

The Supporting Information is available free of charge via the Internet at http://pubs.acs.org.
Detailed experimental procedures, characterization of new compounds, and NMR spectra (PDF).

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REFERENCES

(1) (a) Zeng, X. M. *Chem. Rev.* **2013**, *113*, 6864-6900. (b) Goodwin, J. A.; Aponick, A. *Chem. Commun.* **2015**, *51*, 8730-8741.
(2) (a) Harding, K. E.; Burks, S. R. *J. Org. Chem.* **1981**, *46*, 3920-3922. (b) Riediker, M.; Schwartz, J. *J. Am. Chem. Soc.* **1982**, *104*, 5842-5844.
(3) (a) Utimoto, K. *Pure. Appl. Chem.* **1983**, *55*, 1845-1852. (b) Fukuda, Y.; Utimoto, K. *Synthesis* **1991**, 975-978.
(4) (a) Elgafi, S.; Field, L. D.; Messerle, B. A. *J. Organomet. Chem.* **2000**, *607*, 97-104. (b) Antoniotti, S.; Genin, E.; V, M.; Genet, J. P. *J. Am. Chem. Soc.* **2005**, *127*, 9976-9977. (c) Barluenga, J.; Dieguez, A.; Fernandez, A.; Rodriguez, F.; Fananas, F. J. *Angew. Chem. Int. Ed.* **2006**, *45*, 2091-2093. (d) Oh, C. H.; Yi, H. J.; Lee, J. H. *New J. Chem.* **2007**, *31*, 835-837. (e) Pouy, M. J.; Delp, S. A.; Uddin, J.; Ramdeen, V. M.; Cochrane, N. A.; Fortman, G. C.; Gunnoe, T. B.; Cundari, T. R.; Sabat, M.; Myers, W. H. *ACS Catal.* **2012**, *2*, 2182-2193.
(5) (a) Burling, S.; Field, L. D.; Messerle, B. A. *Organometallics* **2000**, *19*, 87-90. (b) Kim, H.; Livinghouse, T.; Shim, J. H.; Lee, S. G.; Lee, P. H. *Adv. Synth. Catal.* **2006**, *348*, 701-704. (c) Han, J. B.; Xu, B.; Hammond, G. B. *J. Am. Chem. Soc.* **2010**, *132*, 916-917. (d) Mahdi, T.; Stephan, D. W. *Chem. - Eur. J.* **2015**, *21*, 11134-11142.
(6) (a) Widenhoefer, R. A.; Han, X. Q. *Eur. J. Org. Chem.* **2006**, 4555-4563. (b) Fürstner, A.; Davies, P. W. *Angew. Chem. Int. Ed.* **2007**, *46*, 3410-3449. (c) Huang, L. B.; Arndt, M.; Goossen, K.; Heydt, H.; Goossen, L. J. *Chem. Rev.* **2015**, *115*, 2596-2697.
(7) Seo, S. Y.; Yu, X. H.; Marks, T. J. *J. Am. Chem. Soc.* **2009**, *131*, 263-276.
(8) Bytschkov, I.; Doye, S. *Eur. J. Org. Chem.* **2003**, 935-946.
(9) Schlummer, B.; Hartwig, J. F. *Org. Lett.* **2002**, *4*, 1471-1474.
(10) Coulombel, L.; Duñach, E. *Green Chem.* **2004**, *6*, 499-501.
(11) Lucchini, V.; Modena, G. *J. Am. Chem. Soc.* **1990**, *112*, 6291-6296.
(12) Bruce, P. L. *Organic Chemistry*, 6th ed Pearson Education Inc: Illinois, 2011; pp. 256-258.
(13) Vasilyev, A. V. *Russ. Chem. Rev.* **2013**, *82*, 187-204.
(14) (a) Fujita, S.; Abe, M.; Shibuya, M.; Yamamoto, Y. *Org. Lett.* **2015**, *17*, 3822-3825. (b) Shibuya, M.; Abe, M.; Fujita, S.; Yamamoto, Y. *Org. Biomol. Chem.* **2016**, *14*, 5322-5328.
(15) Kutt, A.; Rodima, T.; Saame, J.; Raamat, E.; Maemets, V.; Kaljurand, I.; Koppel, I. A.; Garlyauskayte, R. Y.; Yagupolskii, Y. L.; Yagupolskii, L. M.; Bernhardt, E.; Willner, H.; Leito, I. *J. Org. Chem.* **2011**, *76*, 391-395.
(16) In terms of the mechanism, after the hydration of an alkyne takes place, acetal(aminal) formation/reduction of the resulting ketone gives the same products (Scheme S1). However, the experimental results that the hydration of 4-phenyl-1-butyne as well as **6c** and **20c** did not occur under the reaction conditions, strongly supports the mechanism of hydroalkoxylation(hydroamination)/reduction.
(17) Kaneti, J.; Kirby, A. J.; Koedjikov, A. H.; Pojarlieff, I. G. *Org. Biomol. Chem.* **2004**, *2*, 1098-1103.
(18) (a) Qian, H.; Han, X. Q.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2004**, *126*, 9536-9537. (b) Yang, C. G.; Reich, N. W.; Shi, Z. J.; He, C. *Org. Lett.* **2005**, *7*, 4553-4556. (c) Bender, C. F.; Widenhoefer, R. A. *Org. Lett.* **2006**, *8*, 5303-5305. (d) Komeyama, K.; Morimoto, T.; Nakayama, Y.; Takaki, K. *Tetrahedron Lett.* **2007**, *48*, 3259-3261. (e) Adrio, L. A.; Quek, L. S.; Taylor, J. G.; Hii, K. K. *Tetrahedron* **2009**, *65*, 10334-10338. (f) Schuch, D.; Fries, P.; Donges, M.; Perez, B. M.; Hartung, J. *J. Am. Chem. Soc.* **2009**, *131*, 12918-12920.
(19) (a) Bender, C. F.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2005**, *127*, 1070-1071. (b) Kim, J. Y.; Livinghouse, T. *Org. Lett.* **2005**, *7*, 4391-4393. (c) Bender, C. F.; Widenhoefer, R. A. *Chem. Commun.* **2006**, 4143-4144. (d) Quinet, C.; Jourdain, P.; Hermans, C.; Atest, A.; Lucas, I.; Markó, I. E. *Tetrahedron* **2008**, *64*, 1077-1087. (e) Crimmin, M. R.; Arrowsmith, M.; Barrett, A. G. M.; Casely, I. J.; Hill, M. S.; Procopiou, P. A. *J. Am. Chem. Soc.* **2009**, *131*, 9670-9685. (f) Sipos,

G.; Ou, A.; Skelton, B. W.; Falivene, L.; Cavallo, L.; Dorta, R. *Chem. - Eur. J.* **2016**, *22*, 6939-6946.

(20) Perez, S. J.; Purino, M. A.; Cruz, D. A.; Lopez-Soria, J. M.; Carballo, R. M.; Ramirez, M. A.; Fernandez, I.; Martin, V. S.; Padron, J. I. *Chem. - Eur. J.* **2016**, *22*, 15529-15535.

(21) (a) Larsen, C. H.; Ridgway, B. H.; Shaw, J. T.; Woerpel, K. A. *J. Am. Chem. Soc.* **1999**, *121*, 12208-12209. (b) Smith, D. M.; Woerpel, K. A. *Org. Lett.* **2004**, *6*, 2063-2066.

(22) Yoda, H.; Mizutani, M.; Takabe, K. *Heterocycles* **1998**, *48*, 679-686.

(23) The details are provided in the Supporting Information.

Transition-Metal-Free Brønsted Acid/Silane Catalytic System