

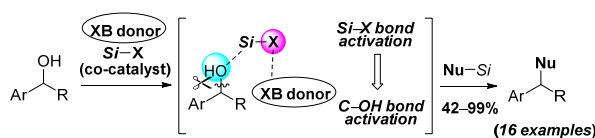
Title	Direct Dehydroxylative Coupling Reaction of Alcohols with Organosilanes through Si–X Bond Activation by Halogen Bonding
Author(s)	Saito, Masato; Tsuji, Nobuya; Kobayashi, Yusuke; Takemoto, Yoshiji
Citation	Organic Letters (2015), 17(12): 3000-3003
Issue Date	2015-6-19
URL	http://hdl.handle.net/2433/242995
Right	<p>This document is the Accepted Manuscript version of a Published Work that appeared in final form in 'Organic Letters', copyright © American Chemical Society after peer review and technical editing by the publisher. To access the final edited and published work see https://doi.org/10.1021/acs.orglett.5b01290; The full-text file will be made open to the public on 28 May 2016 in accordance with publisher's 'Terms and Conditions for Self-Archiving'.; This is not the published version. Please cite only the published version. この論文は出版社版ではありません。引用の際には出版社版をご確認ご利用ください。</p>
Type	Journal Article
Textversion	author

Direct **dehydroxylative** coupling reaction of alcohols with organosilanes through Si–X bond activation by halogen bonding

Masato Saito, Nobuya Tsuji,[†] Yusuke Kobayashi, and Yoshiji Takemoto*

Graduate School of Pharmaceutical Sciences, Kyoto University Institution, Yoshida, Sakyo-ku, Kyoto 606-8501, Japan.

Supporting Information



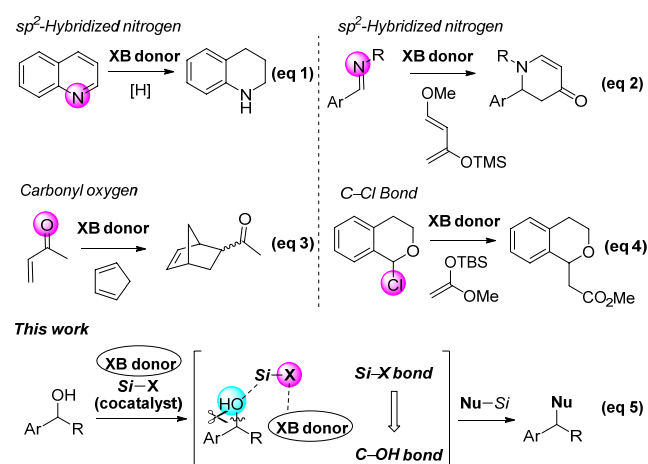
ABSTRACT: A combined use of a halogen bond (XB) donor with trimethylsilyl halide was found to be an efficient co-catalytic system for the direct **dehydroxylative** coupling reaction of alcohol with various nucleophiles, such as allyltrimethylsilane and trimethylcyanide, to give the corresponding adduct in moderate to excellent yields. Detailed control experiments and mechanistic studies revealed that the XB interaction was crucial for the reaction. The application of this coupling reaction is also described.

Lewis acid catalysts are indispensable and used in various fields in organic synthesis.¹ However, many of these catalysts contain metals that are expensive or sometimes difficult to handle. In the past few decades, air- and moisture-stable Lewis acids have been developed,² and investigation of novel Lewis acid catalysis is still a major research area in organic chemistry. Electron-deficient organoiodine(I) compounds are known to form a non-covalent interaction with Lewis bases, called halogen bonding (XB)³ and have been used in the field of crystal engineering.⁴ Although such organoiodine compounds (XB donors) have recently begun to be used in organic synthesis as organo-Lewis acids,^{5–8} the catalytic use of XB donors is still developing and a challenging research area (Scheme 1).⁹ Moreover, variation of the activation mode of substrates is limited: 1) activation of sp^2 hybridized nitrogen atoms (Scheme 1, eq 1 and 2);⁵ 2) activation of carbonyl oxygen (Scheme 1, eq 3);⁶ or 3) activation of C–Cl bonds (Scheme 1, eq 4).⁸ A novel strategy is required to activate the different types of substrates to expand the utilities of the XB donor as catalysts. We envisioned that the activation of the Si–X bond by the XB donor would increase the Lewis acidity of the silicon atom, which in turn activates the OH group of an alcohol,¹⁰ enabling the direct coupling reaction with TMSNu (Scheme 1, eq 5). From the viewpoint of synthetic organic chemistry, the use of alcohols for coupling reactions is more straightforward and divergent, because various alcohols are more readily accessible than the corresponding halides. For the success of such a coupling reaction, however, the design of the XB donor is important,⁸ because a strong XB donor could form an inert complex with the eliminated halide anion, thereby preventing the catalytic use of the XB donor.⁷ Herein, we report a novel XB-donor catalyzed direct coupling reaction of alcohols and the salient features of this method are as follows: 1) the reaction is operationally simple; 2) various nucleophiles can be introduced by the same catalytic system; and 3) the newly developed XB donor is air- and moisture-stable.

To identify suitable XB donor catalysts, we first focused on the direct coupling reaction of alcohol with allylsilane (Table 1), because this reaction is difficult due to the poor leaving ability of the hydroxyl group and side reactions such as dimerization. In fact, only limited examples have succeeded in the catalytic direct allylation of alcohols.^{11,12}

Scheme 1. Utilization of XB donors as catalysts for organic synthesis

Reported substrates activated by XB-donor catalysts

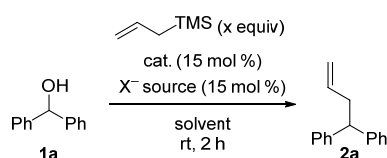


We first screened various XB donors (15 mol %), combined with TMSBr (15 mol %) as the co-catalyst for direct allylation of benzhydrol **1a** (Table 1, entries 1–8). Although a neutral XB donor pentafluoroiodobenzene (**3**)¹³ was found to be ineffective (Table 1, entry 1), iodoimidazolium triflate **4** promoted slightly the reaction to give the desired product (Table 1, entry 2). The iodine atom of the imidazolium salt appeared to be necessary for the reaction (Table 1, entry 2 vs. 3). Unexpectedly, a bidentate iodoimidazolium salt **6** did not dramatically improve the chemical yield (Table 1, entry 4). Then, we inves-

tigate the effect of several counteranions of monodentate iodoimidazolium salts **7–10** (Table 1, entries 5–8). It is worth noting that the XB donor catalyst **10**, bearing hexafluoroantimonate (SbF_6^-) as a counteranion, accelerated the reaction significantly to furnish the coupling adduct **2a** in 64% yield (Table 1, entry 8). Fortunately, it was also found that **10** can be readily prepared as an air- and moisture-stable white solid.¹⁴ The replacement of TMSBr to TMSI improved the reactivity and the chemical yield to 75% (Table 1, entry 10).¹⁵ Practically, TMSI could be successfully replaced with I_2 , which is known to form TMSI when reacted with allylsilane,¹⁶ exhibiting a similar reactivity as TMSI alone (Table 1, entry 11). We then investigated the solvent effect for this reaction (Table 1, entries 12–14) and found that MeNO_2 gave the best results over any other solvent (Table 1, entry 14). Further optimization revealed that 2 equivalents of allylsilane were sufficient to afford **2a** without a significant decrease in the chemical yield (Table 1, entry 15). **As the control experiments, it was confirmed that the strong acids, which might be generated *in situ*, did not afford **2a** at all (Table 1, entries 16 and 17).**^{14,17}

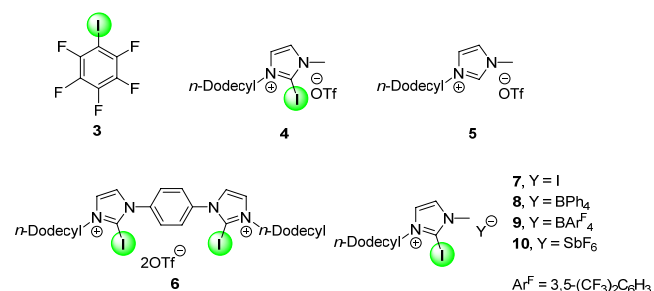
Table 1. Optimization of the reaction conditions for the direct

dehydroxylative coupling reaction of alcohol



entry	x	cat.	X ⁻ source	solvent	yield ^a (%)
1	10	3	TMSBr	CH_2Cl_2	0
2	10	4	TMSBr	CH_2Cl_2	6
3	10	5	TMSBr	CH_2Cl_2	0
4	10	6	TMSBr	CH_2Cl_2	9
5	10	7	TMSBr	CH_2Cl_2	0
6	10	8	TMSBr	CH_2Cl_2	0
7	10	9	TMSBr	CH_2Cl_2	13
8	10	10	TMSBr	CH_2Cl_2	64
9	10	none	TMSBr	CH_2Cl_2	0
10	10	10	TMSI	CH_2Cl_2	75
11	10	10	I_2	CH_2Cl_2	68
12	10	10	I_2	MeCN	36
13	10	10	I_2	Toluene	22
14	10	10	I_2	MeNO_2	78
15	2	10	I_2	MeNO_2	78
16	2	HI	none	MeNO_2	0
17 ^b	2	TfOH	none	MeNO_2	0

^a Determined by ^1H NMR based on dimethylsulfoxide as an internal standard. ^b Tf = trifluoromethanesulfonyl



With the optimized reaction conditions in hand, we subsequently examined the reaction scope (Figure 1) and found that various substituents on the aromatic ring were tolerated (products **2b–2i**). Allylation of alcohols bearing electron-rich aryl groups gave the corresponding adducts **2b–e** in good to excellent yields. However, when the substrates with electron-withdrawing groups, such as $-\text{F}$ and $-\text{Cl}$, were used, the chemical yields of **2f,g** were slightly lower,¹⁸ implying that the coupling reaction proceeds through a carbocation intermediate (*vide infra*). An unprotected phenolic OH group and secondary amide, as well as a carbamate protecting group (*N*-Boc) were tolerated under the optimized reaction condition to give the allylated products **2h–j** in 44–97% yields. In addition to the above mentioned diarylmethanol derivatives, different types of substrates, such as a tertiary alcohol and a hemiaminal, could also be applied to the coupling reaction, furnishing the desired products **2k–m** in excellent yields. Notably, several different nucleophiles were introduced to this established coupling reaction, and the coupling adducts **2n–p** with alkynyl, cyano and 2-keto groups were obtained, albeit in lower yields.

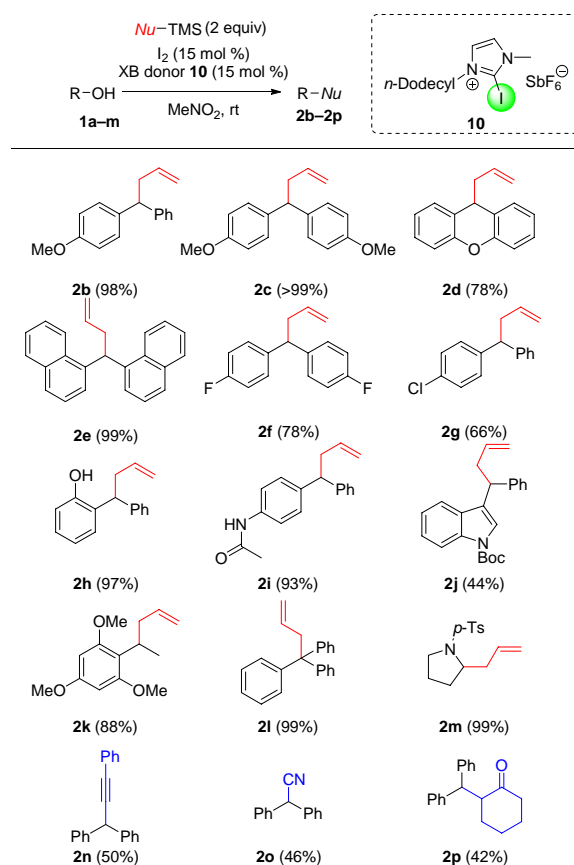


Figure 1. Substrate scope of the coupling reaction of alcohol (isolated yields are indicated).

A plausible reaction mechanism¹⁷ is shown in Figure 2. First, allylsilane (TMSNu) and molecular iodine react to form TMSI,¹⁶ which is then activated by the XB donor, enhancing the Lewis acidity of the silicon atom. Then, the oxophilic Lewis acid activates the OH group of substrate **1** through an intermediate **A**, generating the carbocation intermediates **B**. The subsequent addition of TMSNu furnishes the coupling product **2** and regenerates TMSI as well as the XB donor cata-

lyst. However, an alternative mechanism through the intermediate **A** cannot be ruled out at this stage, where a silylation (or $\text{Me}_3\text{SiSbF}_6$) is generated via complete anion exchange between the XB donor and TMSI, and functions as the active species for the activation of the alcohol.

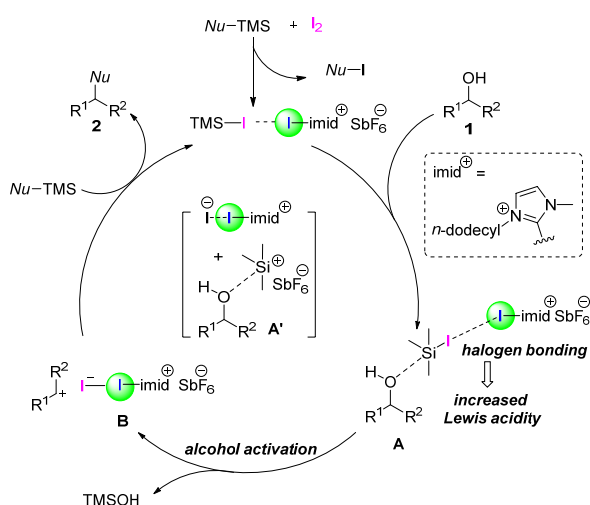
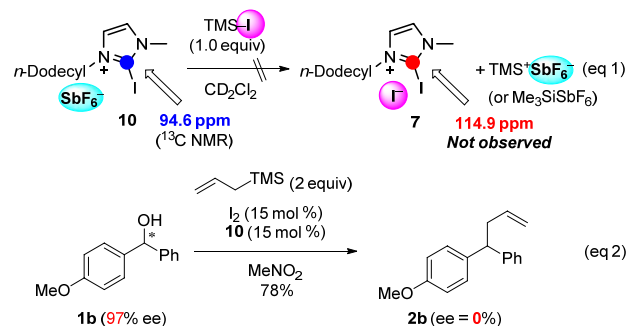


Figure 2. A plausible reaction mechanism.

To gain insight into the active species, ^{13}C NMR studies were performed (Scheme 2, eq 1). Upon mixing an equimolar amount of TMSI with the donor **10**, the chemical shift of the signal representing C2 (94.6 ppm) did not shift downfield in the ^{13}C NMR spectrum.¹⁴ This result strongly indicated that anion exchange between TMSI and the XB donor did not occur, because the chemical shift of the iodoimidazolium C2 position bearing a halide counter anion, such as **7**, is observed at much further downfield (114.9 ppm).^{4a} Therefore, the active species for the promotion of the reaction is TMSI activated by the XB donor (Figure 2). We also performed a mechanistic study using a chiral substrate (Scheme 2, eq 2). When the chiral alcohol **1b**¹⁴ was reacted under the optimized reaction condition, the racemic product **2b** was obtained in 78% yield, strongly suggesting that the reaction proceeds via an $\text{S}_{\text{N}}1$ pathway, which also supports the proposed mechanism shown in Figure 2.

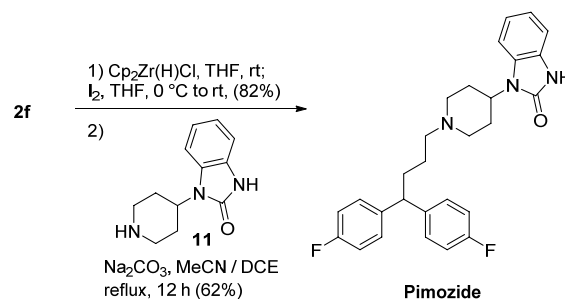
Scheme 2. Mechanistic studies



Finally, this catalytic direct coupling reaction of alcohol with allylsilane was applied to the synthesis of pimozone, which is known to be an antipsychotic drug¹⁹ (Scheme 3). The coupling

adduct **2f** was treated with Schwartz's reagent,²⁰ followed by molecular iodine to give the corresponding primary iodide in 82% yield,¹⁴ which was then coupled with the secondary amine **11** to give pimozone in 62% yield.

Scheme 3. Synthesis of pimozone via direct allylation of an alcohol



In conclusion, we have developed an XB donor–TMSX cocatalytic system to activate alcohol, enabling a direct **dehydroxylative** coupling reaction with various nucleophiles bearing TMS groups. We believe that the combination of an XB donor with different catalysts will broaden the utilities and application of XB donors as organo-Lewis acids, which is now undergoing in our laboratory and will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

The experimental details, compound characterization data, and the complete copies of NMR charts. This material is available free of charge via the Internet at <http://pubs.acs.org>.

AUTHOR INFORMATION

Corresponding Author

*takemoto@pharm.kyoto-u.ac.jp

Present Addresses

†Max-Planck-Institut für Kohlenforschung

ACKNOWLEDGMENT

We gratefully acknowledge a Grant-in-Aid for Scientific Research (YT) on Innovative Areas “Advanced Molecular Transformations by Organocatalysis” and a Grant-in-Aid for Challenging Exploratory Research (YK) from MEXT, Japan. We thank Prof. V. H. Rawal (Univ. of Chicago) for fruitful discussion.

REFERENCES

- (1) For reviews, see: (a) *Comprehensive Organic Synthesis*, ed. Trost, B. M.; Fleming, I. Pergamon Press, Oxford, 1991; (b) *Lewis Acids in Organic Synthesis*, Ed. Yamamoto, H. Wiley-VCH, Weinheim, 2000, vol. 1–2.
- (2) For reviews, see: (a) Li, C. J. *Chem. Rev.* **2005**, *105*, 3095. (b) Okumura, T. *Chem. Rev.* **2002**, *102*, 3641. (c) Corna, A.; Garcia, H. *Chem. Rev.* **2003**, *103*, 4307. (d) Kobayashi, S.; Sugiura, M.; Kitagawa, H.; Lam, W. W. M. *Chem. Rev.* **2002**, *102*, 2227.
- (3) For selected recent reports, see: (a) Clark, T.; Hennemann, M.; Murray, J. S.; Politzer, P. *J. Mol. Model.* **2007**, *13*, 291. (b) Politzer, P.; Murray, J. S.; Clark, T. *Phys. Chem. Chem. Phys.* **2010**, *12*, 7748.
- (4) For selected recent reviews, see: (a) Metrangolo, P.; Nuwkirch, H.; Pilati, T.; Resnati, G. *Acc. Chem. Res.* **2005**, *38*, 386. (b) Rissanen, K. *CrystEngComm.* **2008**, *10*, 1107. (c) Beale, T. M.; Chudzinski, M. G.; Sarwar, M. G.; Taylor, M. S. *Chem. Soc. Rev.* **2013**, *42*, 1667. (d) Meyer, F.; Dubois, P. *CrystEngComm.* **2013**, *15*, 3058. (e) Troff, R.

W.; Mäkelä, T.; Topić, F.; Valkonen, A.; Raatikainen, K.; Rissanen, K. *Eur. J. Org. Chem.* **2013**, 1617.

(5) For catalytic activation of sp^2 -hybridized nitrogen atoms, see: (a) Bruckman, A.; Pene, M. A.; Bolm, C. *Synlett* **2008**, 900. (b) He, W.; Ge, Y.-C.; Tan, C.-H. *Org. Lett.* **2014**, *16*, 3244. (c) Takeda, Y.; Hisakuni, D.; Lin, C.-H.; Minakata, S. *Org. Lett.* **2015**, *17*, 318.

(6) For catalytic activation of carbonyl oxygen, see: (a) Coulembier, O.; Meyer, F.; Dubois, P. *Polym. Chem.* **2010**, *1*, 434. (b) Jungbauer, S. H.; Walter, S. H.; Schindler, S.; Rout, L.; Kniep, F.; Huber, S. M. *Chem. Commun.* **2014**, *50*, 6281.

(7) For XB-donor-mediated C–X bond activation, see: (a) Walter, S. M.; Kniep, F.; Herdtweck, E.; Huber, S. M. *Angew. Chem. Int. Ed.* **2011**, *50*, 7187. (b) Kniep, F.; Walter, S. M.; Herdtweck, E.; Huber, S. M., *Chem. Eur. – J.* **2012**, *18*, 1306. (c) Kniep, F.; Rout, L.; Walter, S. M.; Bensch, H. K. V.; Jungbauer, S. H.; Hertweck, E.; Huber, S. M. *Chem. Commun.* **2012**, *48*, 9299. (d) Castelli, R.; Schindler, S.; Walter, S. M.; Kniep, F.; Overkleeft, H. S.; van der Marel, G. A.; Huber, S. M.; Codee, J. D. C. *Chem. Asian J.* **2014**, *9*, 2095. (e) Tsuji, N.; Kobayashi, Y.; Takemoto, Y. *Chem. Commun.* **2014**, *50*, 13691.

(8) For the reactions based on XB-donor-catalyzed C–X bond activation, see: Kniep, F.; Jungbauer, S. H.; Zhang, Q.; Walter, S. M.; Schinsler, S. M.; Codee, J. D. C. *Angew. Chem. Int. Ed.* **2013**, *52*, 7028.

(9) For the related important examples including XB in the catalytic system, see: (a) Lindsay, V. N. G.; Lin, W.; Charette, A. B. *J. Am. Chem. Soc.* **2009**, *131*, 16383. (b) Dordonne, S.; Crousse, B.; Bonnet-Delpon, D.; Legros, J. *Chem. Commun.* **2011**, *47*, 5855. (c) Nakatsuji, H.; Sawamura, Y.; Sakakura, A.; Ishihara, K. *Angew. Chem., Int. Ed.* **2014**, *53*, 6974. (d) Zong, L.; Ban, Xu.; Kee, C. W.; Tan, C.-H. *Angew. Chem. Int. Ed.* **2014**, *53*, 11849.

(10) For the reactions co-catalyzed by the TMSCl–InCl₃ system, see: (a) Mukaiyama, T.; Ohno, T.; Nishimura, T.; Han, J. S.; Kobayashi, S. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 2524. (b) Mukaiyama, T.; Ohno, T.; Han, J. S.; Kobayashi, S. *Chem. Lett.* **1991**, 945. (c) Onishi, Y.; Ito, T.; Yasuda, M.; Baba, A. *Eur. J. Org. Chem.* **2002**, 1578. (d) Onishi, Y.; Ito, T.; Yasuda, M.; Baba, A. *Tetrahedron* **2002**, *58*, 8227. (e) Saito, T.; Yasuda, M.; Baba, A. *Synlett*, **2005**, 1737. (f) Saito, T.; Nishimoto, Y.; Yasuda, M.; Baba, A. *J. Org. Chem.* **2006**, *71*, 8516.

(11) For direct allylation of benzylic alcohols, see: (a) BF₃; Cella, J. A. *J. Org. Chem.* **1982**, *47*, 2125. (b) HN(SO₂F)₂; Kaur, G.; Kaushik, M.; Trehan, S. *Tetrahedron Lett.* **1997**, *38*, 2521. (c) BF₃·Et₂O; Schmitt, A.; Reißig, H.-U. *Eur. J. Org. Chem.* **2000**, 3893. (d) B(C₆F₅)₃; Rubin, M.; Gevorgyan, V. *Org. Lett.* **2001**, *3*, 2705. (e) InCl₃; Yasuda, M.; Saito, T.; Ueba, M.; Baba, A. *Angew. Chem. Int. Ed.* **2004**, *43*, 1414. (f) Ti(IV); Braun, M.; Kotter, W. *Angew. Chem. Int. Ed.* **2004**, *43*, 514. (g) ZrCl₄; Sharma, G. V. M.; Reddy, K. L.; Lakshmi, P. S.; Ravi, R.; Kunwar, A. C. *J. Org. Chem.* **2006**, *71*, 3967. (h) BiCl₃; De, S. K.; Gibbs, R. A. *Tetrahedron Lett.* **2005**, *46*, 834. For reactions by heterogeneous catalysts, see: (i) Wang, J.; Masui, Y.; Onaka, M. *Tetrahedron Lett.* **2010**, *51*, 3300. (j) Kadam, S. T.; Lee, H.; Kim, S. S. *Appl. Organometal. Chem.* **2010**, *24*, 67.

(12) For direct allylation of propargylic alcohols, see: (a) Luzung, M. R.; Toste, F. D. *J. Am. Chem. Soc.* **2003**, *125*, 15760. (b) Georgy, M.; Boucard, V.; Campagne, J.-M. *J. Am. Chem. Soc.* **2005**, *127*, 14180. (c) Nishibayashi, Y.; Shinoda, A.; Miyake, Y.; Matsuzawa, H.; Sato, M. *Angew. Chem. Int. Ed.* **2006**, *45*, 4835. (d) Cui, Y.-Y.; Yang, R.-F.; Yang, W.-Z.; Li, J.-P. *J. Org. Chem.* **2006**, *71*, 8298. (e) Kuninobu, Y.; Ishii, E.; Takai, K. *Angew. Chem. Int. Ed.* **2007**, *46*, 3296. (f) Meyer, V. J.; Niggemann, M. *Eur. J. Org. Chem.* **2011**, 3671.

(13) For selected theoretical and experimental studies using perfluoro-iodoarene and iodoalkane as XB donors, see: (a) Cabot, R.; Hunter, C. A. *Chem. Commun.* **2009**, *45*, 2005. (b) Huber, S. M.; Jimenez-Izal, E.; Ugalde, J. M.; Infante, I. *Chem. Commun.* **2012**, *48*, 7708. (c) Chudzinski, M. G.; Taylor, M. S. *J. Org. Chem.* **2012**, *77*, 3483. (d) Tsuzuki, S.; Wakisaka, A.; Ono, T.; Sonoda, T. *Chem. – Eur. J.* **2012**, *18*, 951. (e) Aakerçy, C. B.; Baldrighi, M.; Desper, J.; Metrangolo, P.; Resnati, G. *Chem. – Eur. J.* **2013**, *19*, 16240. (f) Han, N.; Zeng, Y.; Sun, C.; Li, X.; Sun, Z.; Meng, L. *J. Phys. Chem. A* **2014**, *118*, 7058.

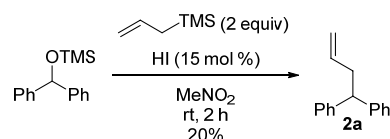
(14) See the Supporting Information for the preparation, and the maximum electrostatic potential (ESP) energy surface of XB donors bearing different counteranions. The complete copies of NMR charts

and the experimental details are also included in the Supporting Information.

(15) Although the XB-accepting abilities of TMSBr and TMSI for the XB donor are not clear, there seemed to be no significant difference between Br[−] and I[−] for their affinities toward the 2-iodoimidazolium cation, see: (a) Cametti, M.; Raatikainen, K.; Metrangolo, P.; Pilati, T.; Terraneo, G.; Resnati, G. *Org. Biomol. Chem.* **2012**, *10*, 1329. For discussion on the affinities of XB donors toward halide anions, also see: (b) Langton, M. J.; Robinson, S. W.; Marques, I.; Félix, V.; Beer, P. D. *Nat. Chem.* **2014**, *6*, 1039. (c) Tepper, R.; Schulze, B.; Jäger, M.; Friebe, C.; Scharf, D. H.; Görls, H.; Schubert, U. S. *J. Org. Chem.* **2015**, *80*, 3139.

(16) (a) Jung, M. E.; Blumenkopf, T. A. *Tetrahedron Lett.* **1978**, *19*, 3657. (b) Saito, T.; Nishimoto, Y.; Yasuda, M.; Baba, A. *J. Org. Chem.* **2007**, *72*, 8588.

(17) When a silylether, which might also be generated *in situ*, was used as a substrate instead of alcohol **1a**, only 20% was **2a** was obtained. Therefore, we proposed a more plausible mechanism as shown in Figure 2.



(18) In these cases, dimerization of the alcohol was observed, therefore lowering the chemical yields of **2**.

(19) Rogers, H. L.; Bhattaram, A.; Zineh, I.; Gobburu, J.; Mathis, M.; Laughren, T. P.; Pacanowski, M. *J. Clin. Psychiatry* **2012**, *73*, 1187, and references cited therein.

(20) Hart, D. W.; Schwartz, J. *J. Am. Chem. Soc.* **1974**, *96*, 8115.

