

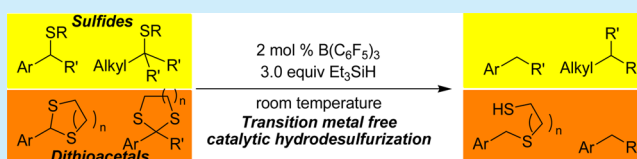
$B(C_6F_5)_3$ -Catalyzed Hydrodesulfurization Using Hydrosilanes – Metal-Free Reduction of Sulfides

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S Supporting Information

ABSTRACT: $B(C_6F_5)_3$ -catalyzed hydrodesulfurization of carbon–sulfur bonds was achieved using triethylsilane as the reducing agent. The corresponding products were obtained in good yields under mild reaction conditions. This protocol could be applied to the reduction of sulfides, including benzyl and alkyl sulfides and dithianes, with high chemoselectivities.



The importance of the carbon–sulfur (C–S) bond is reflected in the extensive use of sulfur-containing building blocks in diverse areas of synthetic organic chemistry. The high demand for organosulfur compounds is mainly attributed to the various functions of the sulfur atom attached to the carbon atom,¹ such as stabilizing the adjacent carbanions,² acting as a leaving group for reductive metalation,³ acting as an electrophile for cross-coupling reaction,⁴ etc.⁵ Cleavage of the C–S bond is important for the removal of the sulfur unit.⁶ However, methods for C–S bond cleavage are highly limited due to the inertness of the bond.

Hydrodesulfurization (HDS), which is the conversion of a C–SR bond to a C–H bond, is the simplest transformation reaction of the C–S bond (Figure 1). Although main-group

Tris(pentafluorophenyl)borane $B(C_6F_5)_3$ is widely used in organic synthesis, and the combination of $B(C_6F_5)_3$ and a Lewis base, in particular, has been recognized as an efficient tool for the activation of inert molecules.⁹ The combined use of $B(C_6F_5)_3$ and hydrosilanes is also one of the representative methods for the generation of a silylium cation.¹⁰ Piers and Gevorgyan et al. independently reported the cleavage reaction of the C–O–H and C–O–C bonds of alcohols and ethers based on the $B(C_6F_5)_3$ – Et_3SiH system.^{10b,c} Subsequent to their reports, several research groups developed the reduction reactions of ketones and imines using this system. However, the application of this method to the cleavage of C–S bonds had not been reported. We wish to report herein a $B(C_6F_5)_3$ -catalyzed HDS of C–S bonds using triethylsilane as the reducing agent. A wide substrate scope was confirmed in the reactions of benzyl (tertiary C–SR) and alkyl (quaternary C–SR) sulfides and dithioacetals and dithioketals with high chemoselectivities.

An initial attempt was carried out with benzyl sulfide **1a** and an excess amount of triethylsilane in the presence of a catalytic amount of $B(C_6F_5)_3$ in $CDCl_3$ (Table 1). When 3.0 equiv of Et_3SiH were used for HDS,¹¹ target product **2a** was obtained in 98% yield by NMR measurement (entry 1). $PhSiH_3$, Ph_3SiH , and $(EtO)_3SiH$ were less effective for this HDS (entries 2–4). To our delight, **2a** was obtained in high yield with a low catalyst loading in CH_2Cl_2 (2 mol %, entry 5). When this reaction was performed in larger scale, **2a** was successfully obtained in 92% isolated yield (entry 6). On the other hand, the use of $BF_3 \cdot OEt_2$, which is one of the representative boron Lewis acids, was not effective, and no **2a** was formed (entries 7 and 8). Finally, the optimum conditions were established as follows: 2 mol % $B(C_6F_5)_3$, Et_3SiH (3 equiv), and sulfide (1.0 equiv) at room temperature.

Next, we explored the substrate scope of this HDS reaction (Scheme 1). Both aryl and alkyl sulfides **1a–1c** underwent highly efficient HDS to afford 2-ethylnaphthalene (**2a**) (85–

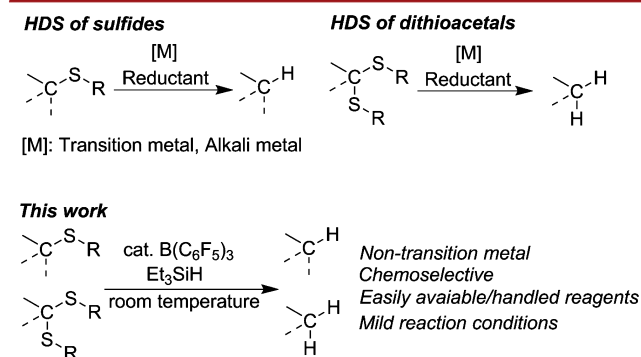
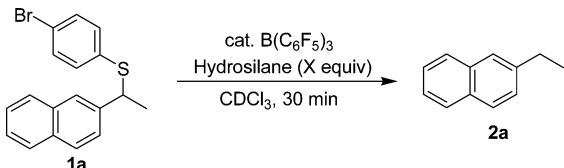


Figure 1. HDS of organosulfur compounds and concepts presented in this work.

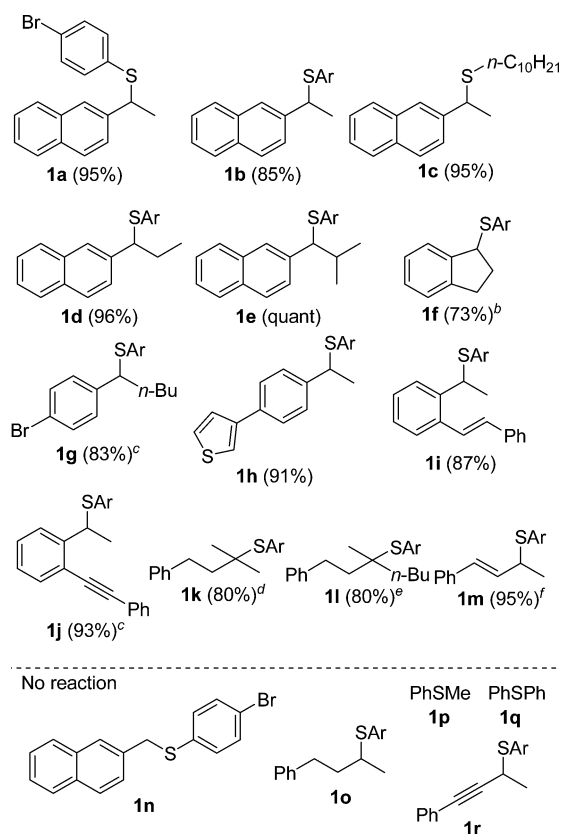
metal reagents⁷ or transition metal catalysts,⁸ including Raney nickel, are typically employed for the cleavage of the C–S bond of sulfides, those reagents are generally flammable and difficult to handle and require use of more than their stoichiometric amounts. In addition, the chemoselective reduction of the C–S bond is rather difficult by previous methods. Therefore, work is ongoing to develop a novel method for the activation and transformation of the C–S bond by means of an easily available and handled nonmetal catalyst.

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Table 1. Examination of Reaction Conditions^a


entry	B(C ₆ F ₅) ₃	hydrosilane	yield (%) ^b
1	20 mol %	Et ₃ SiH	98
2	20 mol %	PhSiH ₃	71
3	20 mol %	Ph ₃ SiH	49
4	20 mol %	(EtO) ₃ SiH	no reaction
5 ^d	2 mol %	Et ₃ SiH	99 (95) ^c
6 ^e	2 mol %	Et ₃ SiH	92 ^c
7	BF ₃ ·OEt ₂ (20 mol %)	Et ₃ SiH	0 ^f
8	BF ₃ ·OEt ₂ (100 mol %)	Et ₃ SiH	0 ^f

^aConditions: Reactions were carried out with **1a** (0.1 mmol), Et₃SiH (0.3 mmol), and B(C₆F₅)₃ in CDCl₃ (0.7 mL) at rt for 30 min. ^bNMR yields. ^cIsolated yields. ^dReaction time was 1 h in CH₂Cl₂. ^e**1a** (5 mmol) was used in CH₂Cl₂. ^fNo reaction.

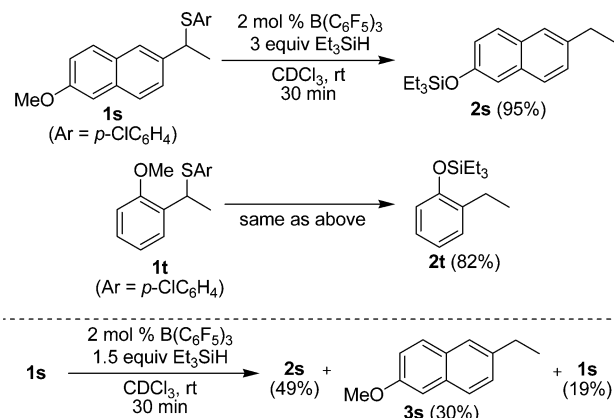
Scheme 1. Substrate Scope for HDS of Sulfides Using B(C₆F₅)₃–Et₃SiH System^{a,b}

^aConditions: Reactions were carried out with starting material **1** (0.1 mmol, Ar = *p*-ClC₆H₄), Et₃SiH (0.3 mmol), and B(C₆F₅)₃ (2 mol %) in CDCl₃ (0.7 mL) at room temperature (details in Supporting Information). Isolated yields. ^bNMR yields. ^cEt₃SiH (0.6 mmol) and B(C₆F₅)₃ (10 mol %) were used. ^dEt₃SiH (0.6 mmol) and B(C₆F₅)₃ (20 mol %) were used. ^eEt₃SiH (0.6 mmol) was used. ^fIsomer ratio is 3.4/1 (details in Supporting Information).

95% yields). Ethyl and isopropyl group substituted benzyl sulfides **1d** and **1e** afforded target products **2d** and **2e** in 96%

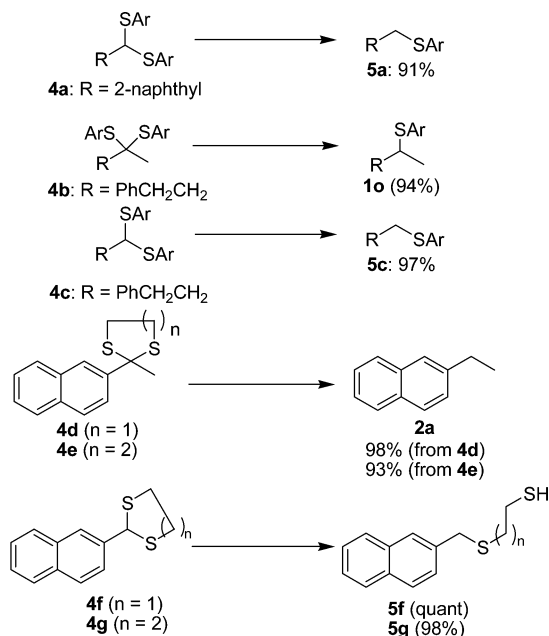
and quantitative yields, respectively. **1f** derived from 1-indanol also participated in HDS to furnish Indane (**2f**) in 73% yield, which is a volatile material, and the formation of **2f** was confirmed by ¹H NMR measurement. Next, we examined the chemoselectivity of the present HDS reaction. Benzyl sulfide **1g** bearing a 4-bromophenyl group gave 4-butylbromobenzene (**2g**) in 83% yield without affecting the C–Br bond. Substrate **1h** bearing a 2-thienyl group, which has potential coordinating ability to a Lewis acid and is easily cleaved by using Raney nickel, also worked well. Alkenyl¹² and alkynyl groups were not affected under the reaction conditions. Alkyl sulfides **1k** and **1l** connected to a quaternary carbon atom were reduced to hydrocarbons in good yields. Allylsulfide **1m** could be employed for this HDS to afford the product in high yield involving the isomerization of a double bond. In contrast, primary benzyl sulfide **1n**, secondary alkyl sulfide **1o**, aryl sulfides **1p** and **1q**, and propargyl sulfide **1r** did not undergo HDS at all.

Gevorgyan et al. reported the demethylation of anisole derivatives using B(C₆F₅)₃ and Et₃SiH.^{10d} When we subjected benzyl sulfides **1s** and **1t** bearing a methoxy group to the reactions, both methyl ether and aryl sulfide were readily cleaved to afford silyl-protected phenols in 95% and 82% yields, respectively (Scheme 2). Interestingly, the HDS rate was higher than the demethylation rate when a competition experiment using 1.5 equiv of Et₃SiH was performed.

Scheme 2. HDS of Substrates Bearing Methoxy Group^a

^aConditions: Reactions were carried out with starting material (0.1 mmol), Et₃SiH (0.3 mmol), and B(C₆F₅)₃ (2 mol %) in CDCl₃ (0.7 mL) at room temperature (details in Supporting Information). Isolated yields.

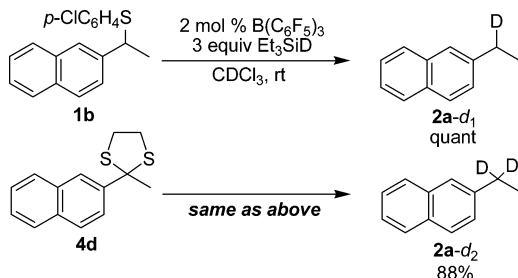
To further test the flexibility of this methodology, attempts were made to perform HDS of dithioacetals (Scheme 3). It is known that dithioacetals are useful umpolungs of carbonyl groups and applicable skeletons for the construction of additional C–C bonds.^{2,13} The Raney nickel catalyzed HDS of dithianes is frequently used for the conversion of a dithioacetal unit into a methylene unit. However, methods for the conversion of a dithioacetal into a methylene unit are limited to transition metal catalyzed reactions or main-group metal-mediated reactions.¹⁴ Dithioacetals **4a**, **4b**, and **4c** underwent selective cleavage of one of the C–S bonds to furnish **5a**, **1o**, and **5c** in high yields. The results indicate that HDS of dithioacetals has similar chemoselectivity to that of the former sulfides. Encouraged by the results, we examined HDS of dithiolane and dithiane. Use of **4d** and **4e**, which were

Scheme 3. HDS of Dithioacetal Derivatives^a

^aConditions: Reactions were carried out with starting material (0.1 mmol), Et₃SiH (0.3–0.6 mmol), and B(C₆F₅)₃ (2 mol %) in CDCl₃ (0.7 mL) at room temperature (details in Supporting Information). Isolated yields.

derived from 2-acetylnaphthalene, furnished **2a** in 98% and 93% yields, respectively. Meanwhile, treatment of dithiane **4f** and **4g**, which are synthesized from 2-naphthalenecarbaldehyde, resulted in the formation of ring-opening thiols **5f** and **5g** in quantitative and 98% yields, respectively. Although the transformations had been reported, all of them required a catalytic amount of transition metal or more than the stoichiometric amount of metal reagents.¹⁴

To prove the utility of this HDS, we examined the deuteration reaction of a C–S bond based on this HDS method (Scheme 4). When substrates **1b** and **4d** were treated

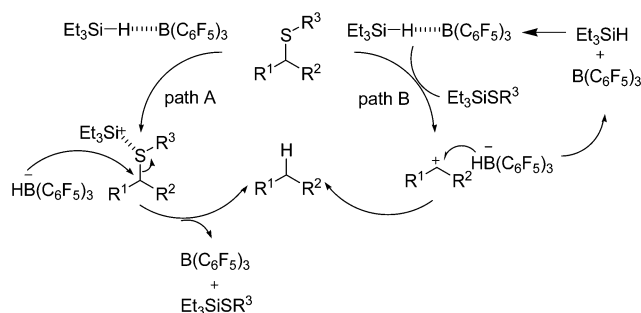
Scheme 4. HDS Using Et₃SiD^a

^aConditions: Reactions were carried out with starting material (0.1 mmol), Et₃SiD (0.3 mmol), and B(C₆F₅)₃ (2 mol %) in CDCl₃ (0.1 M) at room temperature (details in Supporting Information). Isolated yields.

with Et₃SiD in the presence of a catalytic amount of B(C₆F₅)₃ in CDCl₃, corresponding deuterated 2-ethylnaphthalenes **2a-d₁** and **2a-d₂** were obtained in high yields with >97% D.

The proposed reaction mechanism is shown in Scheme 5. A silylium cation, which was generated by the reaction of Et₃SiH with B(C₆F₅)₃, activates the sulfur atom to give a carbocation

Scheme 5. Proposed Reaction Mechanism



intermediate in path A. The intermediate is rapidly reduced by the hydride on the borate to give the product involving the regeneration of B(C₆F₅)₃. As another plausible reaction pathway, a substitution reaction by hydroborate via the sulfide intermediate activated by the silylium cation in an S_N2 manner could also occur (path B).¹⁵

In summary, we have applied the B(C₆F₅)₃–Et₃SiH system to HDS of various sulfides via the silylium cation catalyzed activation of the sulfur atom. Benzyl sulfides as well as secondary and tertiary sulfides were selectively reduced to hydrocarbons. On the other hand, among the alkyl sulfides, tertiary ones were removed by employing the same conditions. The highly chemoselective HDS could be applied to the deprotection reaction of dithioacetals. Dithioketals were converted into the corresponding hydrocarbons, and a ring-opening thiol-bridged sulfide bond was obtained by the reaction of dithioacetals. Further investigation of the mechanism of and application to the synthesis of more complex molecules is underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, analytical data for all new compounds, NMR spectra for the products. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01651.

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Notes

The authors declare no competing financial interest.

■ REFERENCES

- (1) For selected reviews on the activation of the carbon–sulfur bonds, see: (a) Wang, L.; He, W.; Yu, Z. *Chem. Soc. Rev.* **2013**, *42*, 599. (b) Pan, F.; Shi, Z.-J. *ACS Catal.* **2014**, *4*, 280.
- (2) For a review of sulfur stabilized carbanions, see: Gröbel, B.-T.; Seebach, D. *Synthesis* **1977**, 357.
- (3) For a review, see: (a) Cohen, T.; Bhupathy, M. *Acc. Chem. Res.* **1989**, *22*, 152.
- (4) For reviews, see: (a) Dubbaka, S. R.; Vogel, P. *Angew. Chem., Int. Ed.* **2005**, *44*, 7674. (b) Modha, S. G.; Mehta, V. P.; Van der Eycken, E. V. *Chem. Soc. Rev.* **2013**, *42*, 5042. (c) Luh, T.-Y. *Acc. Chem. Res.* **1991**, *24*, 257.
- (5) For oxidation of sulfides, see: (a) Madesclaire, M. *Tetrahedron* **1986**, *42*, 5459. Chiral sulfur compounds, see: (b) Posner, G. N. In *The Chemistry of Sulfones and Sulfoxides*; Patai, S., Rappoport, Z., Stirling, C. J. M., Eds.; John Wiley & Sons, Ltd.: 1988; Chapter 16, pp 823–849. Sulfur-containing ylide, see: (c) Gololobov, Y. G.;

Nesmeyanov, A. N.; Iysenko, V. P.; Boldeskul, I. E. *Tetrahedron* **1987**, 43, 2609. (d) Li, A.-H.; Dai, L.-X.; Aggarwal, V. K. *Chem. Rev.* **1997**, 97, 2341. (e) Aggarwal, V. K. *Synlett* **1998**, 329. (f) Masdeu-Bultó, A. M.; Diéguez, M.; Martín, E.; Gómez, M. *Coord. Chem. Rev.* **2003**, 242, 159.

(6) For reviews on reductive desulfurization, see: (a) Rentner, J.; Kljajic, M.; Offner, L.; Breinbauer, R. *Tetrahedron* **2014**, 70, 8983. (b) Luh, T.-Y.; Ni, Z.-J. *Synthesis* **1990**, 89.

(7) For main-group metal mediated hydrodesulfurization, see: (a) Screttas, G.; Micha-Screttas, M. *J. Org. Chem.* **1979**, 44, 713. (b) Yoshioka, H.; Matsuya, Y.; Choshi, T.; Sugino, E.; Hibino, S. *Chem. Pharm. Bull.* **1996**, 44, 709. (c) Choshi, T.; Tonari, A.; Yoshioka, H.; Harada, K.; Sugino, E.; Hibino, S. *J. Org. Chem.* **1993**, 58, 7952. (d) Caputo, R.; Longobardo, L.; Palumbo, G.; Pedatella, S. *Tetrahedron* **1996**, 52, 11857. (e) Nicolaou, K. C.; Hummel, C. W.; Bockovich, N. J.; Wong, C.-H. *J. Chem. Soc., Chem. Commun.* **1991**, 870. (f) Harring, S. R.; Livinghouse, T. *Tetrahedron Lett.* **1989**, 30, 1499. (g) Rao, H. S. P.; Geetha, K.; Kamairaj, M. *RSC Adv.* **2011**, 1, 1050. (h) Natsugari, H.; Matsushita, Y.; Tamura, N.; Yoshioka, K.; Ochiai, M. *J. Chem. Soc., Perkin Trans. 1* **1983**, 403. (i) Li, Y.; Yue, X.; Xing, Y. *Tetrahedron Lett.* **1993**, 34, 2799.

(8) For transition-metal mediated hydrodesulfurization, see: Nickel and cobalt boride: (a) Back, T. G.; Baron, D. L.; Yang, K. *J. Org. Chem.* **1993**, 58, 2407. $\text{Mo}(\text{CO})_6$ and $\text{W}(\text{CO})_6$: (b) Luh, T.-Y.; Wong, C.-S. *J. Org. Chem.* **1985**, 50, 5413. (c) Ng, C. T.; Wang, X.; Luh, T.-Y. *J. Org. Chem.* **1988**, 53, 2536. Ni-complexes: (d) Becker, S.; Fort, Y.; Vandresse, R.; Caubère, P. *J. Org. Chem.* **1989**, 54, 4848. Zn/HCl: (e) Baldwin, J. J.; Engelhardt, E. L.; Hirschmann, R.; Ponticello, G. S.; Atkinson, J. G.; Wasson, B. K.; Sweet, C. S.; Scriabine, A. *J. Med. Chem.* **1980**, 23, 65. Zn/AcOH: (f) Yamazaki, C.; Arima, H.; Udagawa, S. *J. Heterocycl. Chem.* **1996**, 33, 41. Pd/C-hydrazine: (g) Niwas, S.; Chand, P.; Pathak, V. P.; Montgomery, J. A. *J. Med. Chem.* **1994**, 37, 2477.

(9) For selected reviews of the activation of inert molecules by $\text{B}(\text{C}_6\text{F}_5)_3$ and its derivatives, see: (a) Stephan, D. W.; Erker, G. *Angew. Chem., Int. Ed.* **2010**, 49, 46. (b) Erker, G. *Dalton Trans.* **2005**, 1883. (c) Stephan, D. W. *Org. Biomol. Chem.* **2008**, 6, 1535. (d) Stephan, D. W.; Erker, G. *Chem. Sci.* **2014**, 5, 2625.

(10) For review on the combined use of $\text{B}(\text{C}_6\text{F}_5)_3$ with hydrosilanes, see: (a) Oestreich, M.; Hermeke, J.; Mohr, J. *Chem. Soc. Rev.* **2015**, 44, 2202. Examples of the combined use of $\text{B}(\text{C}_6\text{F}_5)_3$ with hydrosilanes, see: (b) Blackwell, J. M.; Foster, K. L.; Beck, V. H.; Piers, W. E. *J. Org. Chem.* **1999**, 64, 4887. (c) Gevorgyan, V.; Liu, J.-X.; Rubin, M.; Benson, S.; Yamamoto, Y. *Tetrahedron Lett.* **1999**, 40, 8919. (d) Gevorgyan, V.; Rubin, M.; Benson, S.; Liu, J.-X.; Yamamoto, Y. *J. Org. Chem.* **2000**, 65, 6179. (e) Rubin, M.; Schwier, T.; Gevorgyan, V. *J. Org. Chem.* **2002**, 67, 1936. (f) Piers, W. E.; Marwitz, A. J. V.; Mercier, L. G. *Inorg. Chem.* **2011**, 50, 12252. (g) Sakata, K.; Fujimoto, H. *J. Org. Chem.* **2013**, 78, 12505. (h) Blackwell, J. M.; Sonmor, E. R.; Scoccitti, T.; Piers, W. E. *Org. Lett.* **2000**, 2, 3921. (i) Chandrasekhar, S.; Reddy, C. R.; Babu, B. N. *J. Org. Chem.* **2002**, 67, 9080. Rosenberg et al. had reported reactions of sulfur compounds using $\text{B}(\text{C}_6\text{F}_5)_3$ with hydrosilanes; see: (j) Harrison, D. J.; Edwards, D. R.; McDonald, R.; Rosenberg, L. *Dalton Trans.* **2008**, 3401. (k) Harison, D. J.; McDonald, R.; Rosenberg, L. *Organometallics* **2005**, 24, 1398. (l) Lee, P. T. K.; Skjel, M. K.; Rosenberg, L. *Organometallics* **2013**, 32, 1575.

(11) For metal-catalyzed reductive cleavage of a carbon–sulfur bond using organosilane, see: (a) Graham, T. H.; Liu, W.; Shen, D.-M. *Org. Lett.* **2011**, 13, 6232. (b) Barbero, N.; Martin, R. *Org. Lett.* **2012**, 14, 796. (c) Matsumura, T.; Niwa, T.; Nakada, M. *Tetrahedron Lett.* **2012**, 53, 4313. (d) Matsumura, T.; Nakada, M. *Tetrahedron Lett.* **2014**, 55, 1412.

(12) Although Gevorgyan et al. reported hydrosilylation of olefins, including styrene and alkyl-substituted olefins, using similar reaction conditions, we did not observe the hydrosilylated product in the reaction of the substrate **1i** bearing a *trans*-stilbene moiety. Rubin, M.; Schweir, T.; Gevorgyan, V. *J. Org. Chem.* **2002**, 67, 1936.

(13) Yus, M.; Nájera, C.; Foubelo, F. *Tetrahedron* **2003**, 59, 6147.

(14) For cleavage of a dithioacetal to methylene unit, see: (a) Kuwahara, S.; Shibata, Y.; Hiramatsu, A. *Liebigs Ann. Chem.* **1992**, 993. (b) Peters, J. A. M.; Posthumus, T. A. P.; Vliet, N. P.; Zeelen, F. J.; Johnson, W. S. *J. Org. Chem.* **1980**, 45, 2208. Cleavage of dithioacetal to sulfide, see: (c) Schmidt, K.; O'Neal, S.; Chan, T. C.; Alexis, C. P.; Uribe, J. M.; Lossener, K.; Gutierrez, C. G. *Tetrahedron Lett.* **1989**, 30, 7301. (d) Stahl, I.; Kühn, I. *Chem. Ber.* **1983**, 116, 1739. (e) Leggetter, B. E.; Brown, R. K. *Can. J. Chem.* **1963**, 41, 2671. (f) Gutierrez, C. G.; Stringham, R. A.; Nitasaka, T.; Glasscock, K. G. *J. Org. Chem.* **1980**, 45, 3393.

(15) Although the reaction mechanism for the reduction of alcohols and ethers catalyzed by $\text{B}(\text{C}_6\text{F}_5)_3\text{--Et}_3\text{SiH}$ was extensively examined in ref 10d, they concluded that reaction of substrates possessing strong cation-stabilizing groups proceeds via an $\text{S}_{\text{N}}1$ pathway. In our case, the HDSs of benzyl and tertiary sulfides proceed well. On the other hand, a primary sulfide was not applicable.