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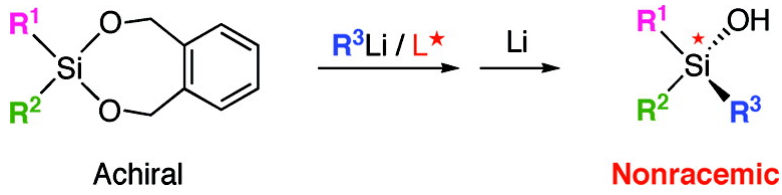

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Enantioselective Synthesis of Silanol

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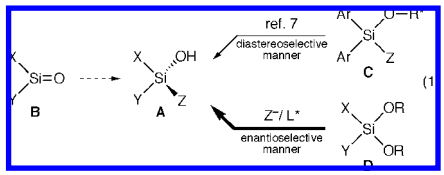
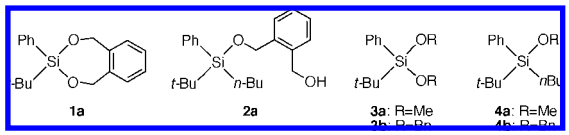
Nonracemic organosilicon compounds that possess the central chirality on silicon are attractive and potentially useful unnatural chiral molecules.[1−5] Among the variety of organosilanes, silanol A is one of the most promising compounds as a sila-chiral building block, similar to carbinol in chiral carbon chemistry, but so far its asymmetric synthesis had been almost unexplored.[6] The lack of their efficient stereoselective synthesis can be attributed to the unavailability of silaketone **B**, which could be envisioned as a prochiral precursor in analogy with the asymmetric synthesis of carbinols using ketones. The development of a useful desymmetrization reaction of the readily available symmetrical tetragonal silicon compounds seems a promising approach to synthesis of the desired silanols. Our recent contribution to this area has been the development of a chiral auxiliary-induced aryl migration reaction of symmetrical diarylsilyl compound **C** wherein one of the two aryl groups can be asymmetrically substituted by suitable alkoxy groups in a highly diastereoselective manner, leading to enantioenriched silanols **A**.[7] To develop a more versatile stereoselective approach, we then focused on the desymmetrization of dialkoxysilane **D**. Herein, we wish to report the asymmetric nucleophilic substitution reaction of symmetrical dialkoxysilane **D** that proceeds with efficient stereocontrol of the chirality center on silicon in the presence of a chiral coordinating agent to give the enantioenriched silyl ether, which could be converted to silanol **A** without loss of enantiopurity.

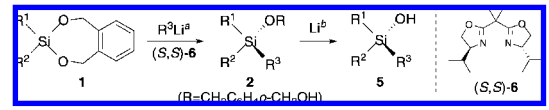


At the outset, we examined the reaction of a variety of dialkoxysilanes with *n*-BuLi under achiral conditions and found that seven-membered cyclic silane **1** is a suitable substrate for this approach. For example, the reaction of *n*-BuLi (3 equiv) with silane **1a**, prepared from Ph*t*-BuSiCl$_2$ and 1,2-di(hydroxymethyl)benzene, in THF at −78 to −40 °C provided the desired silane (±)-**2a** as a sole product in 93% yield. In sharp contrast, acyclic silanes **3a** and **3b** gave poor results under similar conditions (**3a**→**4a**: 19%, **3b**→**4b**: trace).[8]



Based on this result, we examined an enantioselective variant using bisoxazoline (*S*,*S*)-**6**[9] (3 equiv) as a chiral coordinating agent in Et$_2$O and afforded silyl ether **2a** in enantioenriched form [48% ee, (*R*)] in almost quantitative yield (Table 1, entry 1).[10,11] Moreover, (*R*)-**2a** was successfully converted to silanol (*R*)-**5a** via Birch reduction without loss of enantiopurity.[12] This represents the first example of the enantioselective synthesis of a silanol, albeit the enantiopurity is moderate.

Table 1. Enantioselective Substitution Reaction of Dialkoxysilane **1**[a]



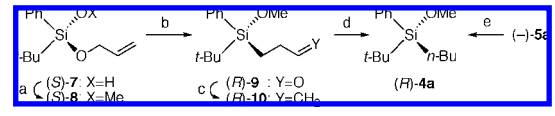
entry	1	R^1	R^2	R^3		2 yield (%)[c]	ee (%)[d,e]		5 yield (%)[c]
1[f]	**1a**	Ph	*t*-Bu	*n*-Bu	**2a**	99	48 (*R*)	(−)-(*R*)-**5a**	93
2	**1a**	Ph	*t*-Bu	*n*-Bu	**2a**	96	55 (*R*)	(−)-(*R*)-**5a**	93
3[g]	**1a**	Ph	*t*-Bu	*n*-Bu	**2a**	86	53 (*R*)	(−)-(*R*)-**5a**	93
4[f]	**1a**	Ph	*t*-Bu	Me	**2b**	99	21 (*R*)	(+)-(*R*)-**5b**	99
6	**1b**	Me	Ph	*t*-Bu	**2b**	86	66 (*R*)	(+)-(*R*)-**5b**	99
7	**1c**	Me	*c*-Hex	*t*-Bu	**2c**	94	76 (*S*)	(+)-(*S*)-**5c**	83
8[h]	**1c**	Me	*c*-Hex	*t*-Bu	**2c**	92	84 (*S*)	(+)-(*S*)-**5c**	83

[a] Unless otherwise specified, the reactions were performed using 3.0 equiv of R^3Li/(*S*,*S*)-**6** in hexane at −78 °C. [b] Reactions were performed in NH$_3$−THF at −78 °C. [c] Isolated yield. [d] Determined via chiral HPLC analysis. [e] Absolute configurations were determined by derivatization to known compounds. [f] Reactions were performed in Et$_2$O at −78 °C. [g] Reaction was performed with 3.0 equiv of *n*-BuLi and 10 mol% of (*S*,*S*)-**6** in hexane at −40 °C. [h] Reaction was performed in hexane at −90 °C.

Because of the limitation of the available atlas of sila-stereochemistry, we developed a unique reaction sequence to determine the absolute configuration of **5**. Silanol (+)-**5a** obtained in the reaction in Table 1 was converted to **4a**, and its sign of optical rotation was identical to that of (*R*)-**4a**; the authentic sample of (*R*)-**4a** was prepared from the previously synthesized silanol (*S*)-**7** via a four-step transformation including (i) methyl etherification, (ii) retro [1,4]-Brook rearrangement,[13] (iii) Wittig olefination, and (iv) hydrogenation, as shown in Scheme 1.[14]

A similar enantioselective substitution reaction performed in hexane gave (*R*)-**2a** with a considerably higher enantiopurity (55% ee) (entry 2). Significantly enough, a reaction in hexane without (*S*,*S*)-**6** gave no silane **2a** at all, and **1a** was recovered quantitatively. These results indicated the feasibility that the enantioselective substitution reaction could proceed even in a catalytic fashion in terms of (*S*,*S*)-**6**. As

Scheme 1. Synthesis of an Authentic Sample of (*R*)-**4a**[a]



[a] Reagents and conditions: (a) MeI, KH, DMF, 0 °C, 94%; (b) *t*-BuLi, HMPA, THF, −78 °C, 40%; (c) CH_3PPh_3Br, *n*-BuLi, THF, 0 °C, 55%; (d) H$_2$, Pd−C, EtOH, rt, 82%; (e) MeI, KH, DMF, 0 °C, 93%.

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anticipated, the reaction of **1a** with 10 mol% of (*S*,*S*)-**6** and 3 equiv of *n*-BuLi provided silanol (*R*)-**2a** with an equal level of enantioselectivity and chemical yield (53% ee, 86%) (entry 3). The developed approach has been applied to a variety of silanols. As shown in Table 1, a similar reaction of dialkoxysilanes **1a**−**c** with various types R^3Li provided corresponding silanols in enantioenriched form.[15,16] Especially, the reaction of **1c** with *t*-BuLi provided **2c** with a relatively high enantioselectivity (84% ee, 92%) (entry 8). In these reactions using (*S*,*S*)-**6**, the bulkier substituents on silane **1** were positioned at R^2 on the major enantiomer of silyl ether **2**.

To clarify the steric course of the present substitution reaction, we conducted the computational analysis of the reaction of simplified silane **1d** (R^1, R^2 = Me) with MeLi by using DFT calculations.[17,18] The result of the DFT calculations revealed that the feasible reaction pathway is a retention process involving apical attack and apical departure (Figure 1). In the first step, a complex **i**, which is composed of MeLi and **1d**, engages in the C−Si bond formation via transition state **ii** (+8.5 kcal mol^{-1}) wherein the methyl anion and O^2 are in the apical positions of the trigonal bipyramidal structure; thus, a five-coordinated silicate **iii** is formed. In the second step, **iii** converts to product **v** over an energy barrier (transition state **iv**: +10.7 kcal mol^{-1}) accompanied by a pseudorotation and elimination of the lithium coordinating oxygen (O^1) from an apical position.

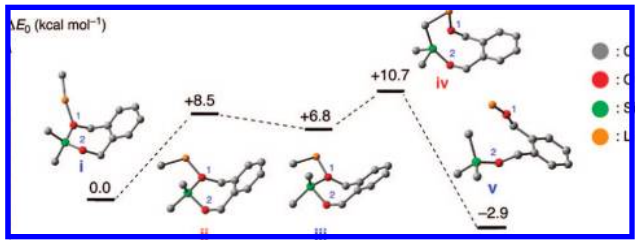
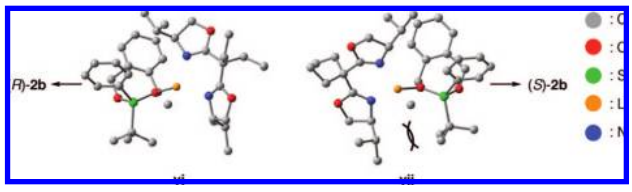


Figure 1. Potential energy surface for nucleophilic substitution reaction of cyclic silane **1d** (R^1, R^2 = Me) and MeLi. Relative zero-point energies (ΔE_0) were calculated at the B3LYP/6-311+G(d) level of theory.

To gain the insight into the enantioselectivity, we calculated the transition structures of the first nucleophilic attack step in the reaction of dialkoxysilane **1a** with the MeLi-(*S*,*S*)-**6** complex and obtained the lowest energy geometries **vi** and **vii** for (*R*)-**2b** and (*S*)-**2b**, respectively.[18,19] The calculated energy of **vi** is lower than that of **vii** (ΔE = 2.5 kcal/mol), which is in good agreement with the experimentally observed enantioselectivity. The disadvantage of transition structure **vii** is due to the severe steric repulsion between the *i*-Pr group of (*S*,*S*)-**6** and *t*-Bu group of **1a**.



We have described the first example of an enantioselective synthesis of silanol. The produced enantioenriched silanols can be used as a sila-chiral building block for various chiral organosilicon compounds. Thus, this work opens a new chapter for chiral organosilicon chemistry. Further work and study for the utilization of enantioenriched silanols is underway.

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Supporting Information Available: Experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Silyl ether **2a** was obtained in racemic form when reaction was performed in THF.
(11) Similar reactions using (−)-sparteine or other chiral bisoxazolines, which have Me, *i*-Bu, or *t*-Bu substituents at *N*-α-positions on oxazoline rings, gave **2a** in 2%−39% ee.
(12) Silanol **5** is stereochemically stable under standard operation. In sharp contrast, Tacke and colleagues have reported a rapid racemization of enantioenriched silanol having β-amino functionality. The stereochemical instability of Tacke's silanol can be attributed to an intramolecular coordination of the amino group to the silicon; see ref 6b.
(13) Nakazaki, A.; Nakai, T.; Tomooka, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 2235.
(14) Absolute stereochemistries of **7** and **9** were determined by X-ray analysis; see refs 7 and 13.
(15) Absolute stereochemistry of (+)-**5b** was determined as the *R* form by derivatization of **2b** to reported hydrosilane: Jankowski, P.; Schaumann, E.; Wicha, J.; Zarecki, A.; Adiwidjaja, G. *Tetrahedron: Asymmetry* **1999**, *10*, 519; see Supporting Information.
(16) Absolute stereochemistry of (+)-**5c** was determined as the *S* form via preparation of authentic sample of (*S*)-**5c** from (*R*)-**5b**; see Supporting Information.
(17) Fundamental theoretical study of nucleophilic substitution at silicon was reported by Holmes et al. : (a) Deiters, J. A.; Holmes, R. R. *J. Am. Chem. Soc.* **1987**, *109*, 1686. (b) Deiters, J. A.; Holmes, R. R. *J. Am. Chem. Soc.* **1987**, *109*, 1692.
(18) All calculations were performed with Gaussian 03 on a TSUBAME system at Tokyo Institute of Technology; see Supporting Information for details.
(19) The calculations were performed at the B3LYP/6-311+G(d)//HF/3-21G level of theory.

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