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Graphical Abstract

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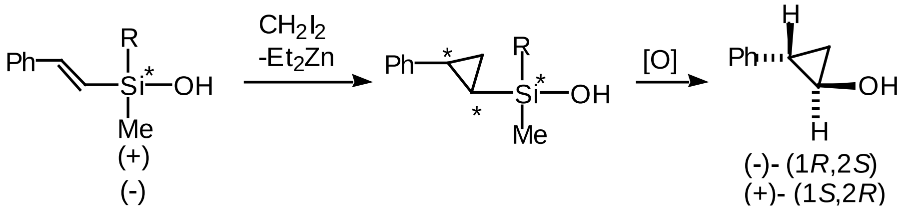

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Chirality transfer from silicon to carbon via diastereoselective Simmons-Smith cyclopropanation of chiral alkenylsilanols

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Abstract—Simmons-Smith cyclopropanation of chiral alkenylsilanol with CH_2I_2-Et_2Zn proceeds diastereoselectively to give cyclopropylsilanol. Chirality of the silicon atom was transferred to carbons on a silicon substituent. Stereochemistry of the obtained cyclopropylsilanol is confirmed by converting to cyclopropanol via Tamao oxidation.

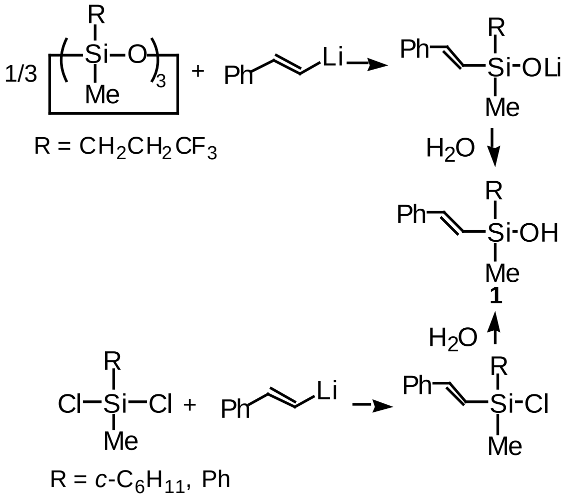
Silicon-centered chirality attracts much attention but has less been studied compared with extensive works on that of analogous carbon.[1] Chirality transfer from silicon to neighboring carbon atoms, accordingly, has little been investigated so far.[2] However, the reaction with high efficiency, if possible, would open a new area of stereochemical studies in organic synthesis

We recently reported synthesis and resolution of silanols with a chirality on their silicon atoms by using HPLC with a chiral column.[3] Hence, our continuous interest on the chemistry of silanol[4] has turned to chirality transfer of thus obtained chiral silanols with a diastereoselective reaction to a functional group on the silicon substituent.

On the other hand, Simmons-Smith cyclopropanation with CH_2I_2-Et_2Zn to non-chiral alkenylsilanols was shown to be accelerated by the hydroxy group to afford cyclopropylsilanols.[5] With such reaction, the chirality of silicon might be efficiently transferred to carbons when the reaction proceeds in a highly diastereoselective manner as observed in that of allylic alcohols.[6] Herein, we report such a diastereoselective Simmons-Smith cyclopropanation of chiral non-racemic alkenylsilanols.

The diastereoselective reaction was first examined with several racemic silanols **1a-c** under the standard conditions for the Simmons-Smith cyclopropanation reported previously.[5] Synthesis of **1** was carried out by the following methods as shown in Scheme 1: (a) The cleavage of cyclic siloxane with alkenyllithium followed by hydrolysis of the formed lithium silanolate to give **1** in 50-70% yield, and (b) alkenylation of a dichlorosilane with the corresponding organolithium reagent followed by a careful hydrolysis of the obtained chlorosilane. (55-58% yield)

Scheme 1



The cyclopropanation was carried out using the obtained alkenylsilanols with diethylzinc and diiodomethane (1:2) that is considered to generate $(ICH_2)_2Zn$.[7] When the reaction of **1a** was performed with 3 mol amounts of diethylzinc and 6 mol amounts of diiodomethane in diethyl ether at room temperature for 3 h, most of **1a** was confirmed to be consumed by ^1H NMR analysis and the

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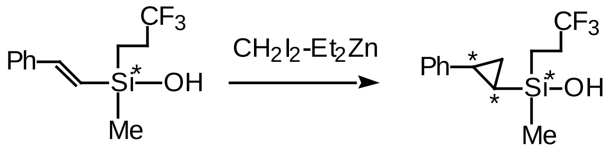
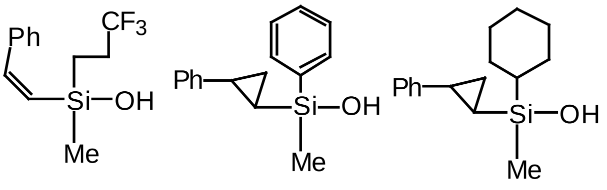
corresponding cyclopropylsilanol **2a** was isolated in 80% yield after the purification by column chromatography on silica gel. The diastereoselectivity was tentatively estimated by ^{1}H NMR analysis of methyl signals on the silicon atom, which appeared at δ = 0.162 (minor) and 0.166 (major) ppm, respectively. As summarized in Table 1, the diastereoselectivity appeared constantly 80-85%, irrespective to the reaction temperature when **1a** was employed. In addition, the combined use of $(ICH_2)_2Zn$ and a Lewis acid, Et_2AlCl or $TiCl_4$, at lower a temperature that was shown to be an efficient system to enhance the reaction rate in the Simmons-Smith reaction of allylic alcohols[8] showed little effect to improve the diastereoselectivity. Although the Simmons-Smith reaction of Z-allylic alcohol was shown relatively higher,[7] the reaction with Z-isomer **3a** exhibited lower diastereoselectivity (68:32).



1a **2a**

equation 1.

We next examined the substituent effect on the silanol. When phenyl group was employed instead of 3,3,3-trifluoropropyl group, the selectivity for the reaction of silanol **1b** was found much inferior although the reaction proceeded smoothly. In contrast, higher selectivity was achieved in the reaction of **1c**, bearing a cyclohexyl substituent; single diastereomer was observed by the measurement of ^{1}H NMR, δ = 0.04 ppm ($CDCl_3$). The results suggest that introduction of the sterically larger substituent on the silicon atom seems necessary to improve the diastereoselectivity.



3a **2b** **2c**

Chart 1

Table 1. Diastereoselective Simmons-Smith cyclopropanation of alkenylsilanols **1a**-**c**.[a]

Entry	substrate	additive	temp, °C	time, h	Yield %	selectivity[b]
1	**1a**	none	rt	3	80	84:16
2		none	-20	3	32	83:17
3		$TiCl_4$	-20	3	7	–
4		$TiCl_4$	-20	25	55	81:19
5		Et_2AlCl	-20	3	58	78:22
6		Et_2AlCl	-40	9	49	81:19
7	**3**	none	rt	3	92	68:32[c]
8	**1b**	none	rt	3	88	60:40
9	**1c**	none	rt	3	>99	>99:1

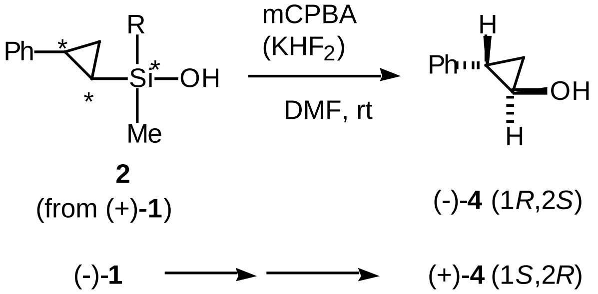
[a] The reaction was carried out in dichloromethane using 3 mol amounts of Et_2Zn and 6 mol amounts of CH_2I_2.

[b] The selectivity was estimated by ^{1}H NMR spectrum of the methyl signal on the silanol.

[c] Deduced from the results on the reaction of **1a**.

The stereochemistry of cyclopropylsilanol **2** was determined by converting into cyclopropanol **4** via Tamao oxidation.[9] The cyclopropanation of (-)-**1a** (the latter eluate enriched; 92% ee), which was obtained by the separation with HPLC using chiral stationary phase column as reported previously,[3] was carried out to afford cyclopropylsilanol **2a**, whose diastereoselectivity was confirmed to be 84:16 by ^{1}H NMR analysis. Tamao oxidation with 3-chloroperbenzoic acid (mCPBA) in DMF at room temperature for 3 h furnished the cyclopropanol (+)-**4** in 31% yield. The absolute configuration of **4** was confirmed to be 1*S*, 2*R* by comparison with the literature.[10] HPLC analysis of the cyclopropanol after transformation to its benzoate revealed to show 58 % ee suggesting that the stereochemistry was retained throughout the oxidation. Alkenylsilanol (+)-**1a** (80% ee), the antipode of (-)-**1a** was also conducted to the similar protocol to give (1*R*, 2*S*)-2-phenyl-1-cyclopropanol of 55% ee..

Separation of (±)-**1c** was also successful by HPLC with a chiral column (Daicel OD-H or AD) to afford 98% ee of (+)-**1c** and (-)-**1c**, respectively and the cyclopropanation of each enantiomer was subjected in a similar manner to afford the corresponding cyclopropylsilanol with a single diastereomer predominantly. The Tamao oxidation of **2** with mCPBA in the presence of KHF_2 at room temperature in DMF gave (+)- and (-)- **4** with 97% ee, respectively, which were also confirmed by HPLC analyses of the benzoates.



equation 2

In conclusion, absolute configuration of cyclopropylsilanol **2** was confirmed to be 1*S*, 2*R*, when (-)-**1** was employed and 1*R*, 2*S* isomer was furnished from (+)-**1** although the absolute configuration of the silicon atom has been unrevealed yet. Chirality of the silicon center was successfully transferred onto carbon atoms via Simmons-Smith cyclopropanation. When a practical and preparative method to give chiral non-racemic **1** is in hand, the present chirality transfer would be a powerful tool for the synthesis of a variety of chiral organic molecules.

Typical experimental procedure: To a solution of (-)-**1c** (170 mg, 0.69 mmol) in 2.1 mL of diethyl ether were added diethylzinc (2.07 mmol, 2.07 mL of 1 M hexane solution) and diiodomethane (0.34 mL, 4.14 mmol) at 0 °C. The mixture was stirred at room temperature for 3 h and poured into 20 mL of sat. NH_4Cl and 10 mL of diethyl ether. Aqueous was extracted with diethyl ether (20 mL x 2) and the combined organic layer was dried over anhydrous sodium sulfate. Removal of the solvent under reduced pressure left a crude oil, which was separated by column chromatography on silica-gel (hexane-ethyl acetate = 85:15) to yield 152 mg of **2c** (84%). ^1H NMR (300 MHz, $CDCl_3$) δ 0.05 (s, 3 H), 0.09 (m, 1 H), 0.78 (brs 1 H), 0.98-1.06 (m, 2 H), 1.12-1.33 (m, 5 H), 1.61-1.56 (m, 5 H), 1.86 (m, 1 H), 7.07-7.16 (m, 3 H), 7.23-7.28 (m, 2 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 5.3, 8.5 12.3 19.1 26.8 26.9 27.8 125.4 125.5 128.3; IR (neat) 3300 br, 2921, 2847, 1605, 1499, 1447, 1252, 1102, 911, 849 cm^{-1}; HRMS: found 260.1594, calcd for $C_{16}H_{24}OSi$: 260.1595.

Acknowledgments

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