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# Acid-Catalyzed Chirality-Transferring Intramolecular Friedel–Crafts Cyclization of $\alpha$ -Hydroxy- $\alpha$ -alkenylsilanes

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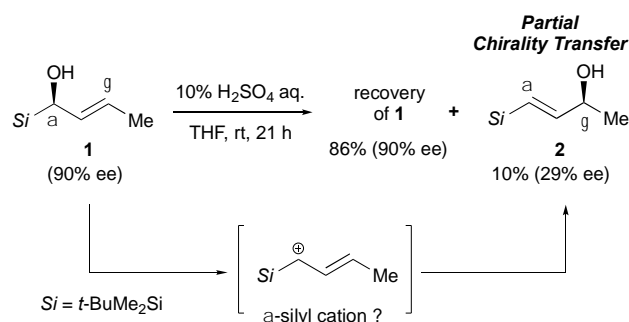
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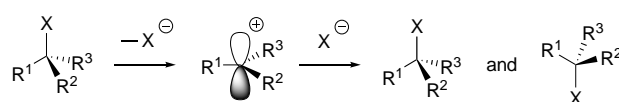
**Acid-catalyzed intramolecular Friedel–Crafts cyclization of optically active  $\alpha$ -hydroxy- $\alpha$ -alkenylsilanes possessing a benzene ring (>99% ee) with TMSOTf as a Lewis acid gave enantio-enriched tetrahydronaphthalenes (up to 98% ee). The silyl group attached to the chiral carbon played a crucial role in the chirality transfer.**

The synthesis of enantiopure organic molecules is an important research issues in organic synthesis. A chiral allyl alcohol having an asymmetric carbon adjacent to a hydroxyl group is useful as a chiral source, and the reaction involving its chirality transfer is one of the useful methods for synthesizing optically active organic molecules. Several  $S_N2'$  reactions of chiral allylic alcohols with 1,3-chirality transfer using transition metal catalysts, e.g., palladium,<sup>1</sup> gold,<sup>2</sup> bismuth<sup>3</sup> and rhenium,<sup>4</sup> have been reported. During the course of our studies regarding the cationic reactions of optically active  $\alpha$ -hydroxysilanes,<sup>5</sup> we found that the reaction of the  $\alpha$ -hydroxy- $\alpha$ -alkenylsilane **1** with 10%  $H_2SO_4$  gave the allylic rearrangement product,  $\gamma$ -hydroxyvinylsilane **2** (10%), along with a recovery of **1** (86%, Scheme 1).<sup>6</sup> Despite the acidic reaction conditions in which the cationic species ( $\alpha$ -silyl cation)<sup>7</sup> may be generated, the chirality of starting **1** (90% ee) was partially transferred to product **2** (29% ee). The carbocation has an achiral  $sp^2$  hybridized structure, which means the generation of a carbocation derived from an  $sp^3$  chiral carbon leads to a complete loss of its original chirality (Scheme 2). The above experimental result prompted us to explore the intramolecular Friedel–Crafts cyclization of optically active  $\alpha$ -hydroxy- $\alpha$ -alkenylsilane **3**, which possesses a benzene ring, to provide vinylsilane-tethered tetrahydronaphthalene **4** with chirality transfer (Scheme 3). The intramolecular Friedel–Crafts reaction of allylic alcohols with chirality transfer has not been reported.<sup>8</sup> In this paper, we wish

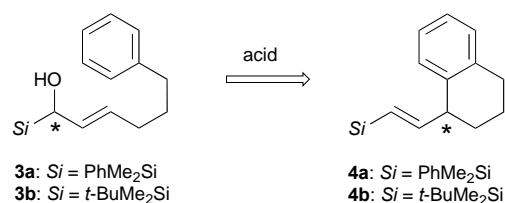
to report the acid-catalyzed chirality-transferring Friedel–Crafts cyclization of the  $\alpha$ -hydroxy- $\alpha$ -alkenylsilanes.



**Scheme 1** 1,3-Chirality transfer of  $\alpha$ -hydroxy- $\alpha$ -alkenylsilane under acidic condition.



**Scheme 2** Loss of original chirality by the formation of carbocation.



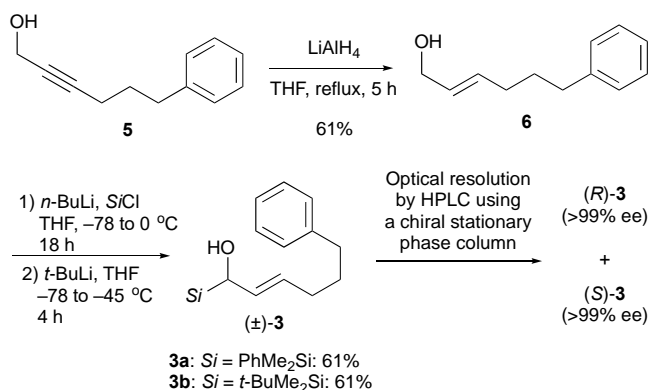
**Scheme 3** Intramolecular Friedel–Crafts cyclization of  $\alpha$ -hydroxy- $\alpha$ -alkenylsilanes.

Enantiopure  $\alpha$ -hydroxy- $\alpha$ -alkenylsilanes **3a** and **3b** (>99% ee) was prepared by the optical resolution of ( $\pm$ )-**3**, synthesized

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from 6-phenyl-2-hexyn-1-ol **5** via retro-Brook rearrangement,<sup>5e</sup> using HPLC with a chiral stationary phase column (Scheme 4).



**Scheme 4** Preparation of optically active  $\alpha$ -hydroxy- $\alpha$ -alkenylsilanes.

We initially examined the reaction using a stoichiometric amount of trimethylsilyl trifluoromethanesulfonate (TMSOTf) as a Lewis acid. The treatment of (*R*)-**3a** (Si = PhMe<sub>2</sub>Si, >99% ee) with TMSOTf (1.0 equiv) in CH<sub>2</sub>Cl<sub>2</sub> at -78 °C for 21 h gave cyclization product **4a** in 76% yield (Table 1, entry 1). The optical purity of **4a** was 98% ee, and its absolute configuration was *R*,<sup>9</sup> which suggested that the chirality of the starting **3a** was completely transferred to **4a** in an *anti*-S<sub>N</sub>2' manner (vide infra). We next investigated the reaction using catalytic amounts of Lewis acid. The reaction of (*R*)-**3a** with TMSOTf (0.2 equiv) did not occur, and **3a** was recovered with retention of its original chirality (entry 2). However, the reaction in the presence of 3 Å molecular sieves (MS) proceeded to give (*R*)-**4a** (66%, 98% ee) accompanied with the allylic rearrangement product,  $\gamma$ -hydroxyvinylsilane (*S*)-**7a**<sup>10,11</sup> (6%, >99% ee, entry 3). This indicates that the presence of H<sub>2</sub>O, which is a by-product in the cyclization reaction, prohibits the acid-catalyzed reaction probably due to the formation of hydronium (H<sub>3</sub>O<sup>+</sup>) as an inactive acid. The acid-catalyzed chirality-transferring reaction on a 1 mmol scale also proceeded to give **4a** (82%, 98% ee) and **7a** (15%, >99% ee) in excellent yields and ee (entry 4). The reaction at a higher temperature (-45 °C) decreased the ee of **4a** (entry 5). The use of CH<sub>3</sub>CN as a solvent reduced the yield of **4a** (entry 6). Trifluoromethanesulfonic acid (TfOH) was also a suitable catalyst for this reaction (entry 7). Trifluoromethanesulfonic anhydride (Tf<sub>2</sub>O) was also effective for producing **4a** (65%, 97% ee, entry 8), where the *in situ* generated TfOH would act as a catalyst. FeCl<sub>3</sub> as a Lewis acid could also promote the reaction, but the ee's of the products were low (entry 9). BF<sub>3</sub>•OEt<sub>2</sub> and TsOH did not promote the reaction (entries 10, 11). When the isolated (*R*)-**7a** (>99% ee) was subjected to the reaction conditions {TMSOTf (0.2 equiv), 3 Å MS, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C, 21 h}, a slight amount of (*S*)-**4a** (12%, 99% ee) was formed with a recovery of (*R*)-**7a**. This result shows that the formation of **4a** not only directly occurs from **3a** but also occurs via **7a**. The enantiopure  $\alpha$ -hydroxy- $\alpha$ -alkenylsilane **3b**<sup>5e</sup> having a *t*-BuMe<sub>2</sub>Si group instead of a PhMe<sub>2</sub>Si group is also a useful substrate for the present chirality-transferring reaction (entry 12).

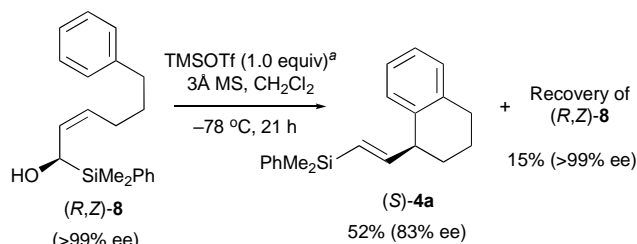
**Table 1** Reaction of  $\alpha$ -hydroxy- $\alpha$ -alkenylsilanes with acid

3a: Si = PhMe<sub>2</sub>Si (>99% ee)  
3b: Si = *t*-BuMe<sub>2</sub>Si (>99% ee)

entry	substrate	acid	x (equiv)	<b>4</b> (ee)	<b>7</b> (ee)	recovery of <b>3</b> (ee)
1 <sup>a</sup>	<b>3a</b>	TMSOTf	1.0	76% (98%)	0%	0%
2 <sup>a</sup>	<b>3a</b>	TMSOTf	0.2	trace	0%	quant (>99%)
3	<b>3a</b>	TMSOTf	0.2	66% (98%)	6% (>99%)	0%
4 <sup>b</sup>	<b>3a</b>	TMSOTf	0.2	82% (98%)	15% (>99%)	0%
5 <sup>c</sup>	<b>3a</b>	TMSOTf	0.2	59% (95%)	0%	0%
6 <sup>d</sup>	<b>3a</b>	TMSOTf	0.2	43% <sup>e</sup>	20% <sup>e</sup>	0%
7	<b>3a</b>	TfOH	0.2	67% (98%)	trace	0%
8	<b>3a</b>	Tf <sub>2</sub> O	0.2	65% (97%)	0%	0%
9	<b>3a</b>	FeCl <sub>3</sub>	0.2	39% (60%)	8% (66%)	37% (>99%)
10	<b>3a</b>	BF <sub>3</sub> •OEt <sub>2</sub>	0.2	0%	0%	80% (>99%)
11	<b>3a</b>	TsOH <sup>f</sup>	0.2	0%	0%	85% (>99%)
12 <sup>g</sup>	<b>3b</b>	TMSOTf	0.2	61% (96%)	trace	0%

<sup>a</sup> without 3 Å MS. <sup>b</sup> The reaction was performed using (*S*)-**3a** in 1 mmol scale to give (*S*)-**4a** and (*R*)-**7a**. <sup>c</sup> -45 °C, 3 h. <sup>d</sup> CH<sub>3</sub>CN was used as a solvent. <sup>e</sup> The ee was not determined. <sup>f</sup> *p*-toluenesulfonic acid. <sup>g</sup> The reaction was performed in 1 mmol scale.

The reaction of the alternative geometric isomer was slow, and the ee of the cyclization product was lowered. The reaction of (*R,Z*)-**8**<sup>5e</sup> (>99% ee) with TMSOTf (1.0 equiv) using 3 Å MS in CH<sub>2</sub>Cl<sub>2</sub> at -78 °C for 21 h gave (*S*)-**4a** (52%, 83% ee) accompanied with a recovery of (*R,Z*)-**8** (15%, >99% ee, Scheme 5).

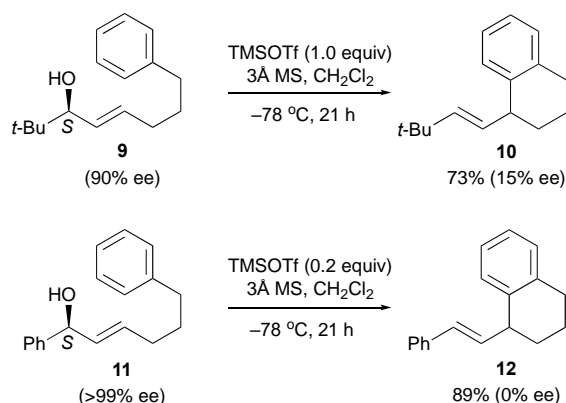


<sup>a</sup> Reaction using TMSOTf (0.2 equiv) gave (*S*)-**4a** (9%, 79% ee) with a recovery of (*R,Z*)-**8** (61%).

**Scheme 5** Acid-catalyzed reaction of (*Z*)- $\alpha$ -hydroxy- $\alpha$ -alkenylsilane.

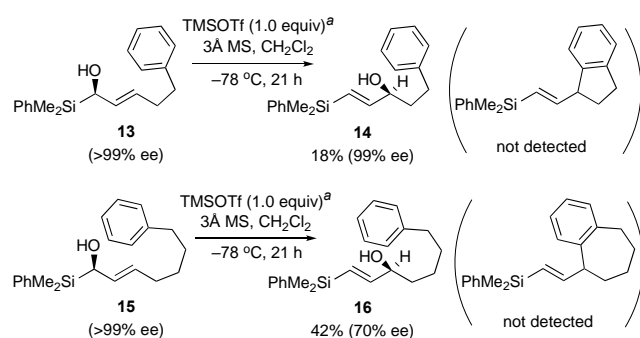
To confirm the contribution of the silyl group attached to a chiral carbon for the chirality transfer, we examined the reaction employing the carbon-substituted analogs (Scheme 6). Although the reaction of the *t*-Bu-substituted (*S*)-**9** (91% ee)<sup>5e</sup> under the reaction conditions {TMSOTf (1.0 equiv), 3 Å MS, CH<sub>2</sub>Cl<sub>2</sub> -78 °C, 21 h} gave the cyclization product **10** in good yield (73%), its ee was very low (15% ee).<sup>12</sup> The reaction of the Ph-substituted **11** (>99% ee)<sup>13</sup> under acid-catalyzed reaction conditions gave the racemic **12** (0% ee) in excellent yield (89%). These experimental results indicate that the silyl group

attached to the chiral carbon plays a crucial role in the efficient chirality transfer.



**Scheme 6** Acid-catalyzed reaction of carbon-substituted analogs.

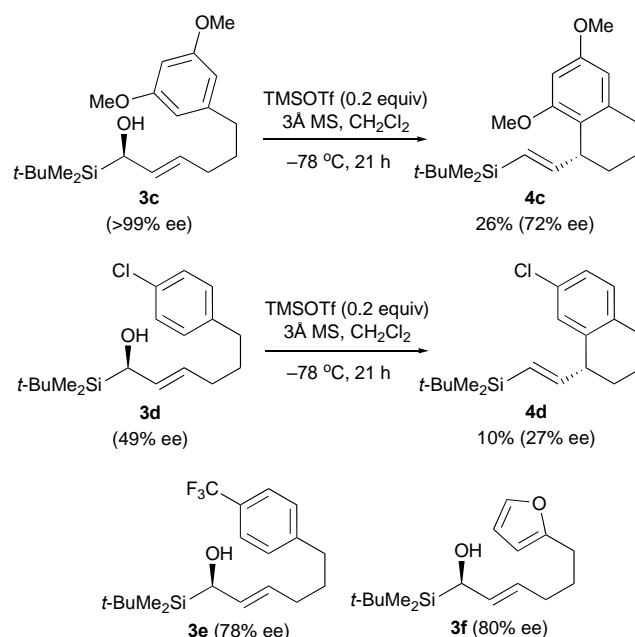
In contrast to the successful cyclization of the six-membered carbocycles, formation of five- and seven-membered carbocycles under the optimized reaction conditions did not occur, and the corresponding allylic rearrangement products were obtained (Scheme 7).<sup>14</sup>



<sup>a</sup> Reaction using TMSOTf (0.2 equiv) resulted in a recovery of most of the starting material.

**Scheme 7** Acid-catalyzed reaction of  $\alpha$ -hydroxy- $\alpha$ -alkenylsilanes having different number of alkyl chains.

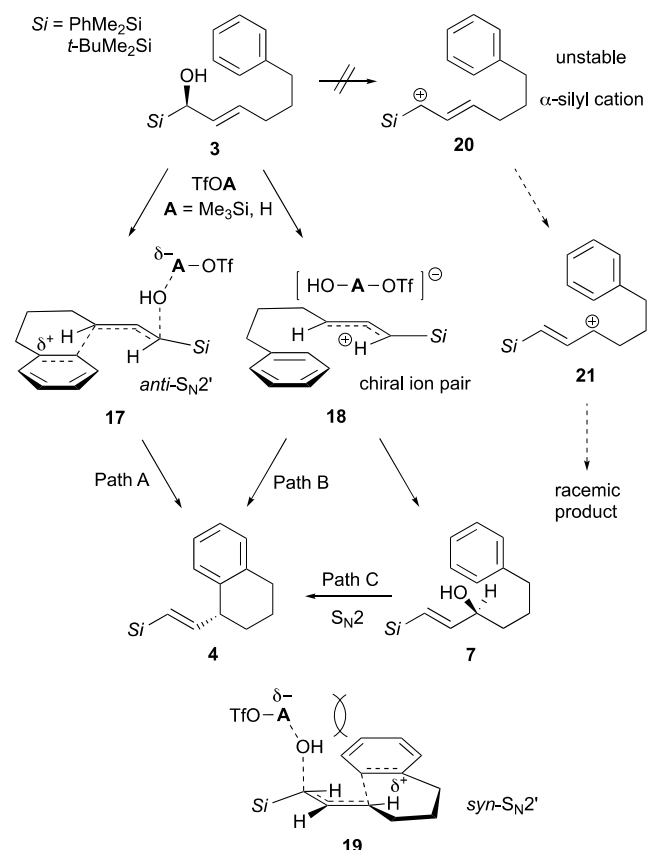
The results of the acid-catalyzed reaction employing several enantio-enriched  $\alpha$ -hydroxy- $\alpha$ -alkenylsilanes **3c–f**<sup>15</sup> are shown in Scheme 8. The reaction of **3c** with an electron rich benzene ring gave cyclized **4c** in low yields and the efficiency of the chirality transfer was reduced.<sup>16</sup> The reaction of **3d** having a benzene ring substituted with a chlorine atom also resulted in low yield of cyclization reaction and reduced the efficiency of chirality transfer. The reaction of **3e** having an electron poor benzene ring gave a small amount of the allylic rearrangement product, and in the case of **3f** having a furan ring, decomposition of the substrate occurred. The present chirality-transferring reaction has not obtained good results other than the substrates **3a** and **3b**.



**Scheme 8** Acid-catalyzed reaction of several  $\alpha$ -hydroxy- $\alpha$ -alkenylsilanes.

Based on the above results, we propose a plausible reaction pathway for the highly stereoselective chirality-transferring conversion of **3** into **4** (Scheme 9). The cyclization of **3** proceeds via **17** in an *anti*- $S_N2'$  manner, wherein the hydroxy group is effectively activated by TMSOTf and/or TfOH, to produce **4** (path A). The alternative *syn*- $S_N2'$  pathway via **19** is unfavorable because of the severe steric repulsion between the leaving group and the aromatic moiety. On the other hand, the formation of **4** competes with that of **7**. The formation of the highly optically active **7** (the *syn*- $S_N2'$  product from **3**) suggests the generation of chiral ion pair intermediate **18**, which was proposed by Woerpel et al.<sup>17</sup> The cyclization, therefore, may also occur via **18** (path B). The conversion from **7** to **4** also slowly occurs in an  $S_N2$  manner (path C). The silyl group, which destabilizes the adjacent carbocation more than an alkyl or aryl group, likely inhibits the formation of the  $\alpha$ -silyl cation **20**,<sup>6,7</sup> which causes racemization of the product via the cation **21**.

In summary, we succeeded in the novel acid-catalyzed chirality-transferring intramolecular cyclization reaction of an optically active  $\alpha$ -hydroxy- $\alpha$ -alkenylsilanes. The reaction was effectively promoted by the catalytic use of TMSOTf and provide the vinylsilane-tethered tetrahydronaphthalenes having a high optical purity (up to 98% ee). To the best of our knowledge, the intramolecular Friedel–Crafts cyclization reaction of allylic alcohols under acid-catalyzed conditions with extremely high chirality transfer has not been reported.<sup>18</sup> During the reaction conditions, the 1,3-rearrangement of the  $\alpha$ -hydroxy- $\alpha$ -alkenylsilanes also occurred to give the highly optically active  $\gamma$ -hydroxyvinylsilanes (>99% ee).<sup>11,17</sup> The silyl group attached to a chiral carbon in the starting materials plays a crucial role in the efficient chirality transfer due to the destabilization of the adjacent carbocation ( $\alpha$ -silyl cation) more than an alkyl or aryl group.<sup>7</sup> Further studies with regard to the synthetic applications toward biologically important compounds via the use of this silicon-assisted chirality-transferring reaction are in progress in our laboratories.



Scheme 9 Plausible reaction pathways.

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## Conflicts of interest

There are no conflicts to declare.

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- The ee of **4a** was determined by the chiral HPLC analysis (DAICEL, CHIRALCEL OD-H, 0.46 cm x 25 cm, *n*-Hexane = 100, 0.5 mL/min, 0 °C, 254 nm). The absolute configuration of **4a** was determined by converting it into the known compound, see Electronic Supplementary Information (ESI).
- The ee of **7a** was determined by the chiral HPLC analysis (DAICEL, CHIRALPAK AD-H, 0.46 cm x 25 cm, *n*-Hexane/EtOH = 50/1, 0.5 mL/min, 25 °C, 254 nm). The absolute configuration of **7a** was determined by the modified Mosher method: I. Ohtani, T. Kusumi, H. Kashman and H. Kakisawa, *J. Am. Chem. Soc.*, 1991, **113**, 4092.
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- The ee of **10** was determined by the chiral HPLC analysis (DAICEL, CHIRALCEL OD-H, 0.46 cm x 25 cm, *n*-Hexane = 100, 0.1 mL/min, 0 °C, 265 nm). The absolute configuration of the resulting **10** was not determined.
- The Ph-substituted **11** (>99% ee) was prepared by the optical resolution of ( $\pm$ )-**11** by HPLC using a chiral stationary phase column (see ESI).
- Treatment of the isolated **14** and **16** under the reaction conditions {TMSOTf (1.0 equiv), 3Å MS, CH<sub>2</sub>Cl<sub>2</sub> -78 °C, 21 h} resulted in the recovery of the starting materials.
- Enantio-enriched  $\alpha$ -hydroxy- $\alpha$ -alkenylsilanes **3d-f** were prepared via enantioselective hydrogenation of corresponding silyl ketones, see ESI.
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