Acid-catalyzed chirality-transferring intramolecular Friedel–Crafts cyclization of \(\alpha\)-hydroxy-\(\alpha\)-alkenylsilanes

Kazuhiko Sakaguchi, Shunnichi Kubota, Wataru Akagi, Naoko Ikeda, Masato Higashino, Shoma Ariyoshi, Tetsuro Shinada, Yasufumi Ohfune, Takahiro Nishimura

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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 tetrahydronaphthalene (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 issue 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 \( \text{Sn}2^\prime \) reactions of chiral allylic alcohols with 1,3-chirality transfer using transition metal catalysts, e.g., palladium,\(^1\) gold,\(^2\) bismuth\(^3\) and rhenium,\(^4\) have been reported. During the course of our studies regarding the cationic reactions of optically active \( \alpha \)-hydroxy-silanes,\(^5\) we found that the reaction of the \( \alpha \)-hydroxy-\( \alpha \)-alkenyli silane 1 with 10% \( \text{H}_2\text{SO}_4 \) gave the allylic rearrangement product, \( \gamma \)-hydroxyvinylsilane 2 (10%), along with a recovery of 1 (86%, Scheme 1).\(^6\) Despite the acidic reaction conditions in which the cationic species \((\alpha\)-silyl cation\)\(^7\) may be generated, the chirality of starting 1 (90% ee) was partially transferred to product 2 (29% ee). The carboxylation 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.\(^8\) In this paper, we wish to report the acid-catalyzed chirality-transfering Friedel–Crafts cyclization of the \( \alpha \)-hydroxy-\( \alpha \)-alkenylsilanes.

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**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 (±)-3, synthesized...
from 6-phenyl-2-hexyn-1-ol 5 via retro-Brook rearrangement,\textsuperscript{5e} using HPLC with a chiral stationary phase column (Scheme 4).

We initially examined the reaction using a stoichiometric amount of trimethylsilyl trifluoromethanesulfonate (TMSOTf) as a Lewis acid. The treatment of (R)-3a (S\textsubscript{i} = PhMe\textsubscript{2}Si, >99% ee) with TMSOTf (1.0 equiv) in CH\textsubscript{2}Cl\textsubscript{2} 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 \textit{R}\textsuperscript{9}, which suggested that the chirality of the starting 3a was completely transferred to 4a in an \textit{anti}-\textit{Su}\textsuperscript{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 3Å molecular sieves (MS) proceeded to give (R)-4a (66%, 98% ee) accompanied with the allylic rearrangement product, \textit{γ}-hydroxyvinylsilane (5)-7a\textsuperscript{10,11} (6%, >99% ee, entry 3). This indicates that the presence of H\textsubscript{2}O, which is a by-product in the cyclization reaction, prohibits the acid-catalyzed reaction probably due to the formation of hydronium (H\textsubscript{2}O\textsuperscript{+}) as an inactive acid. The acid-catalyzed chirality-shuffling 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\textsubscript{3}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\textsubscript{2}O) was also effective for producing 4a (65%, 97% ee, entry 8), where the \textit{in situ} generated TfOH would act as a catalyst. FeCl\textsubscript{3} as a Lewis acid could also promote the reaction, but the ee’s of the products were low (entry 9). BF\textsubscript{3}\textsuperscript{••}OEt\textsubscript{2} 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), 3Å MS, CH\textsubscript{2}Cl\textsubscript{2} at –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 \textit{α}-hydroxy-\textit{α}-alkenylsilane 3b\textsuperscript{5e} having a \textit{t}-BuMe\textsubscript{2}Si group instead of a PhMe\textsubscript{2}Si group is also a useful substrate for the present chirality-shuffling reaction (entry 12).

**Table 1** Reactors of \textit{α}-hydroxy-\textit{α}-alkenylsilanes with acid

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>acid (x equiv)</th>
<th>4a (ee)</th>
<th>7a (ee)</th>
<th>recovery of 3a (ee)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3a TMSOTf</td>
<td>1.0</td>
<td>76% (88%)</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>2*</td>
<td>3a TMSOTf</td>
<td>0.2</td>
<td>trace</td>
<td>0%</td>
<td>quant (99%)</td>
</tr>
<tr>
<td>3</td>
<td>3a TMSOTf</td>
<td>0.2</td>
<td>66% (98%)</td>
<td>6%</td>
<td>(99%)</td>
</tr>
<tr>
<td>4b</td>
<td>3a TMSOTf</td>
<td>0.2</td>
<td>82% (98%)</td>
<td>15%</td>
<td>(99%)</td>
</tr>
<tr>
<td>5*</td>
<td>3a TMSOTf</td>
<td>0.2</td>
<td>59% (95%)</td>
<td>0%</td>
<td>(99%)</td>
</tr>
<tr>
<td>6f</td>
<td>3a TMSOTf</td>
<td>0.2</td>
<td>43%</td>
<td>20%</td>
<td>(99%)</td>
</tr>
<tr>
<td>7</td>
<td>3a TIOH</td>
<td>0.2</td>
<td>67% (98%)</td>
<td>0%</td>
<td>(99%)</td>
</tr>
<tr>
<td>8</td>
<td>3a Tf\textsubscript{2}O</td>
<td>0.2</td>
<td>65% (97%)</td>
<td>0%</td>
<td>(99%)</td>
</tr>
<tr>
<td>9</td>
<td>3a FeCl\textsubscript{3}</td>
<td>0.2</td>
<td>39% (80%)</td>
<td>8%</td>
<td>(66%) (99%)</td>
</tr>
<tr>
<td>10</td>
<td>3a BF\textsubscript{3}\textsuperscript{••}OEt\textsubscript{2}</td>
<td>0.2</td>
<td>0%</td>
<td>0%</td>
<td>(99%)</td>
</tr>
<tr>
<td>11</td>
<td>3a TsOH</td>
<td>0.2</td>
<td>0%</td>
<td>0%</td>
<td>(99%)</td>
</tr>
<tr>
<td>12b</td>
<td>3b TMSOTf</td>
<td>0.2</td>
<td>61% (98%)</td>
<td>0%</td>
<td>(99%)</td>
</tr>
</tbody>
</table>

* Without 3Å MS. * The reaction was performed using (S)-3a in 1 mmol scale to give (S)-4a and (R)-7a \textit{in situ} at –45 °C for 3 h. 2 CH\textsubscript{3}CN was used as a solvent. 3 The ee was not determined. 4 Toluenesulfonic acid. 5 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\textsuperscript{a} (>99% ee) with TMSOTf (1.0 equiv) using 3Å MS in CH\textsubscript{2}Cl\textsubscript{2} at –78 °C for 21 h gave (S)-4a (52%, 83% ee) accompanying with a recovery of (R,Z)-8 (15%, >99% ee, Scheme 5).

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 \textit{t}-Bu-substituted (S)-9 (91% ee)\textsuperscript{5e} under the reaction conditions (TMSOTf (1.0 equiv), 3Å MS, CH\textsubscript{2}Cl\textsubscript{2} at –78 °C, 21 h) gave the cyclization product 10 in good yield (73%), its ee was very low (15% ee).\textsuperscript{12} The reaction of the Ph-substituted 11 (>99% ee)\textsuperscript{13} under acid-catalyzed reaction conditions gave the racemic 12 (0% ee) in excellent yield (89%). These experimental results indicate that the silyl group

**Scheme 4** Preparation of optically active \textit{α}-hydroxy-\textit{α}-alkenylsilanes.
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).\textsuperscript{14}

\begin{center}
\begin{tabular}{|c|c|}
\hline
名称 & 反应式 \\
\hline
3a & (78% ee) \\
3b & (72% ee) \\
3c & (99% ee) \\
3d & (99% ee) \\
3e & (78% ee) \\
3f & (80% ee) \\
\hline
\end{tabular}
\end{center}

\textsuperscript{a} Reaction using TMSOTf (0.2 equiv) resulted in a recovery of most of the starting material.

Scheme 7 Acid-catalyzed reaction of -hydroxy- -alkenylsilanes having different number of alkyl chains.

The results of the acid-catalyzed reaction employing several enantio-enriched \(\alpha\)-hydroxy-\(\alpha\)-alkenylsilanes 3c–f\textsuperscript{15} are shown in Scheme 7. 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.\textsuperscript{16} 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.

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 \textit{anti}-\text{Sn}2\textsuperscript{2} manner, wherein the hydroxy group is effectively activated by TMSOTf and/or TFOH, to produce 4 (path A). The alternative \textit{syn}-\text{Sn}2\textsuperscript{2} 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 \textit{syn}-\text{Sn}2\textsuperscript{2} product from 3) suggests the generation of chiral ion pair intermediate 18, which was proposed by Woerpel et al.\textsuperscript{17} The cyclization, therefore, may also occur via 18 (path B). The conversion from 7 to 4 also slowly occurs in an \text{Sn}2 manner (path C). The silyl group, which destabilizes the adjacent carbonation more than an alkyl or aryl group, likely inhibits the formation of the \(\alpha\)-silyl cation 20,\textsuperscript{6,7} 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 vinilsilane-tethered tetrahydroaraphalenes 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.\textsuperscript{18} 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).\textsuperscript{11,17} 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 carboxation (\(\alpha\)-silyl cation) more than an alkyl or aryl group.\textsuperscript{7} 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.
We are grateful to the Japan Society of the Promotion of Science (JSPS KAKENHI Grant Numbers 16201045 and 17K05935) for supporting this work.

Conflicts of interest
There are no conflicts to declare.

Notes and references


9. 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).

10. The ee of 7a was determined by the chiral HPLC analysis (DAICEL, CHIRALPAK AD-H, 0.46 cm x 25 cm, n-Hexane/EOH = 50/1, 0.5 mL/min, 25 °C, 254 nm). The absolute configuration of 7a was determined by the modified Mosher method: I. Ohntani, T. Kusumi, H. Kashiw and H. Kakisawa, J. Am. Chem. Soc., 1991, 113, 4092.

11. The acid-catalyzed 1,3-rearrangement of allylic alcohols with high transfer of chirality (>99%) is unknown.

12. The ee of 10 was determined by the chiral HPLC analysis (DAICEL, CHIRALCEL OD-H, 0.46 cm x 25 cm, n-Hexane = 100, 0.5 mL/min, 0 °C, 265 nm). The absolute configuration of the resulting 10 was not determined.

13. The Ph-substituted 11 (>99% ee) was prepared by the optical resolution of (1S)-11 by HPLC using a chiral stationary phase column (see ESI).

14. Treatment of the isolated 14 and 16 under the reaction conditions (TMSOTf (1.0 equiv), 3Å MS, CH2Cl2–78 °C, 21 h) resulted in the recovery of the starting materials.

15. Enantio-enriched α-hydroxy-α-alkenylsilanes 3d-f were prepared via enantioselective hydrogenation of corresponding silyl ketones, see ESI.

16. The reaction of 3c (68% ee) using TMSOTf (1.0 equiv) gave 4c (53%, 27% ee).


18. The copper(I)-mediated anti-SiOH allylic substitution of α-acloxy-α-alkenylsilane with high transfer of chirality was reported. S. Perrone and P. Knochel, Org. Lett., 2007, 9, 1041.