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Acid-catalyzed chirality-transferring intramolecular Friedel–Crafts cyclization of α-hydroxy-α-alkenylsilanes†

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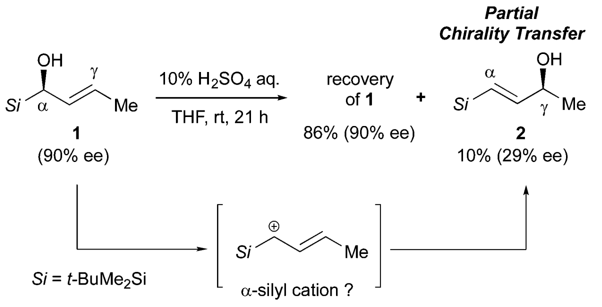
Acid-catalyzed intramolecular Friedel–Crafts cyclization of optically active α-hydroxy-α-alkenylsilanes possessing a benzene ring (>99% ee) with TMSOTf as a Lewis acid gave enantio-enriched tetrahydronaphthalenes (up to 98% ee). The silyl group attached to the chiral carbon played a crucial role in the 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,[1] gold,[2] bismuth[3] and rhenium,[4] have been reported. During the course of our studies regarding the cationic reactions of optically active α-hydroxysilanes,[5] we found that the reaction of the α-hydroxy-α-alkenylsilane **1** with 10% H_2SO_4 gave the allylic rearrangement product, γ-hydroxyvinylsilane **2** (10%), along with a recovery of **1** (86%, Scheme 1).[6] Despite the acidic reaction conditions in which the cationic species (α-silyl cation)[7] 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 α-hydroxy-α-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-transferring Friedel–Crafts cyclization of the α-hydroxy-α-alkenylsilanes.

Enantiopure α-hydroxy-α-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,[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** (Si = $PhMe_2Si$, >99% ee) with TMSOTf (1.0 equiv.) in CH_2Cl_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 *R*,[9] which suggested that the chirality of the starting **3a** was completely transferred to **4a** in an *anti*-S_N2' 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, γ-hydroxyvinylsilane (*S*)-**7a**[10,11] (6%, >99% ee, entry 3). This indicates that the presence of H_2O, which is a by-product in the cyclization reaction, prohibits the acid-catalyzed reaction probably due to the formation of hydronium (H_3O^+) as an inactive acid. The acid-catalyzed chirality-transferring reaction on a 1 mmol scale also proceeded to give **4a** (82%, 98% ee) and



Scheme 1 1,3-Chirality transfer of α-hydroxy-α-alkenylsilane under acidic condition.

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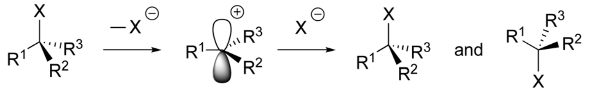
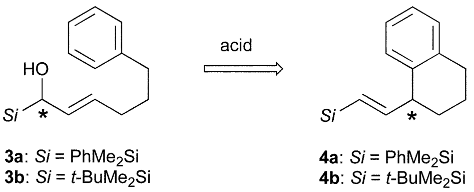
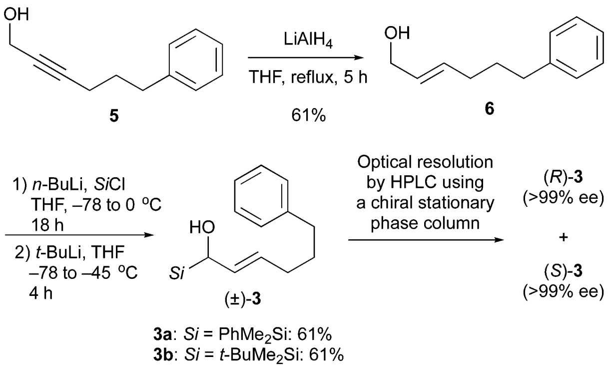


Scheme 2 Loss of original chirality by the formation of carbocation.

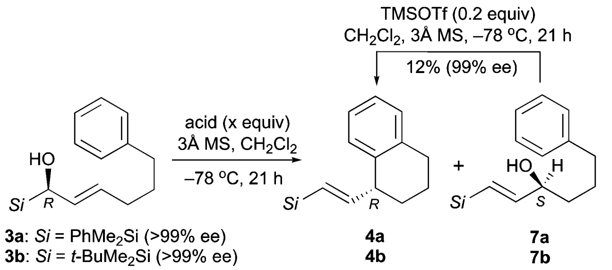


Scheme 3 Intramolecular Friedel–Crafts cyclization of α-hydroxy-α-alkenylsilanes.



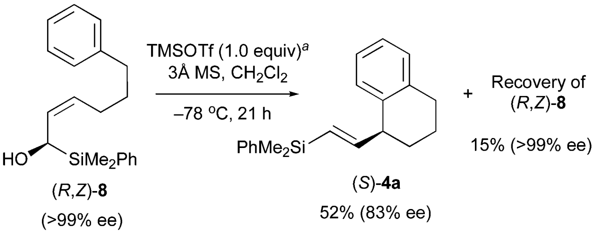
Scheme 4 Preparation of optically active α-hydroxy-α-alkenylsilanes.

Table 1 Reaction of α-hydroxy-α-alkenylsilanes with acid



Entry	Substrate	Acid	*x* (equiv)	**4** (ee)	**7** (ee)	Recovery of **3** (ee)
1[a]	**3a**	TMSOTf	1.0	76% (98%)	0%	0%
2[a]	**3a**	TMSOTf	0.2	Trace	0%	Quant (>99%)
3	**3a**	TMSOTf	0.2	66% (98%)	6% (>99%)	0%
4[b]	**3a**	TMSOTf	0.2	82% (98%)	15% (>99%)	0%
5[c]	**3a**	TMSOTf	0.2	59% (95%)	0%	0%
6[d]	**3a**	TMSOTf	0.2	43%[e]	20%[e]	0%
7	**3a**	TfOH	0.2	67% (98%)	Trace	0%
8	**3a**	Tf_2O	0.2	65% (97%)	0%	0%
9	**3a**	$FeCl_3$	0.2	39% (60%)	8% (66%)	37% (>99%)
10	**3a**	$BF_3{\cdot}OEt_2$	0.2	0%	0%	80% (>99%)
11	**3a**	TsOH[f]	0.2	0%	0%	85% (>99%)
12[g]	**3b**	TMSOTf	0.2	61% (96%)	Trace	0%

[a] Without 3 Å MS. [b] The reaction was performed using (*S*)-**3a** in 1 mmol scale to give (*S*)-**4a** and (*R*)-**7a**. [c] −45 °C, 3 h. [d] CH_3CN was used as a solvent. [e] The ee was not determined. [f] *p*-Toluenesulfonic acid. [g] The reaction was performed in 1 mmol scale.



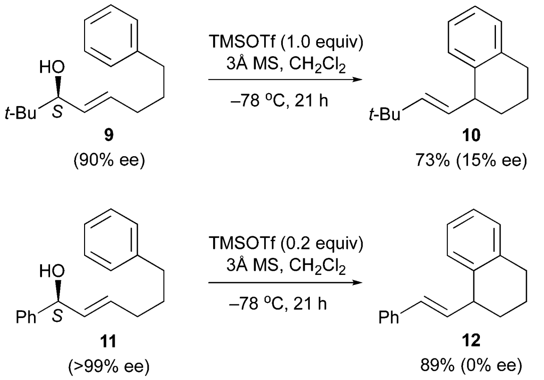
Scheme 5 Acid-catalyzed reaction of (*Z*)-α-hydroxy-α-alkenylsilane. [a] Reaction using TMSOTf (0.2 equiv.) gave (*S*)-**4a** (9%, 79% ee) with a recovery of (*R*,*Z*)-**8** (61%).

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_3CN 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_2O) was also effective for producing **4a** (65%, 97% ee, entry 8), where the *in situ* generated TfOH would act as a catalyst. $FeCl_3$ as a Lewis acid could also promote the reaction, but the ee's of the products were low (entry 9). $BF_3{\cdot}OEt_2$ 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.), 3 Å MS, CH_2Cl_2, −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 α-hydroxy-α-alkenylsilane **3b**[5e] having a *t*-BuMe$_2$Si group instead of a PhMe$_2$Si group is also a useful substrate for the present chirality-transferring reaction (entry 12).

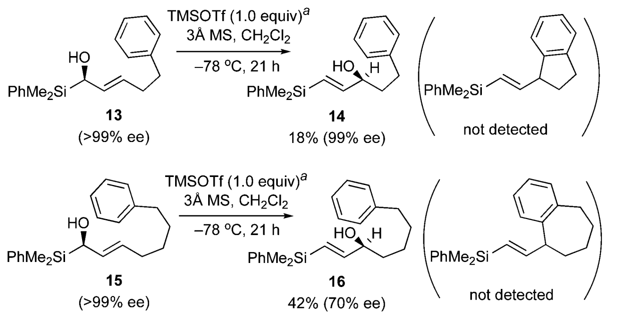
The reaction of the alternative geometric isomer was slow, and the ee of the cyclization product was lowered. The reaction of (*R*,*Z*)-**8**[5e] (>99% ee) with TMSOTf (1.0 equiv.) using 3 Å MS in CH_2Cl_2 at −78 °C for 21 h gave (*S*)-**4a** (52%, 83% ee) accompanied with a recovery of (*R*,*Z*)-**8** (15%, >99% ee, Scheme 5).

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** (90% ee)[5e] under the reaction conditions {TMSOTf (1.0 equiv.), 3 Å MS, CH_2Cl_2 −78 °C, 21 h} gave the cyclization product **10** in good yield (73%), its ee was very low (15% ee).[12] The reaction of the Ph-substituted **11** (>99% ee)[13] 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.

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).[14]



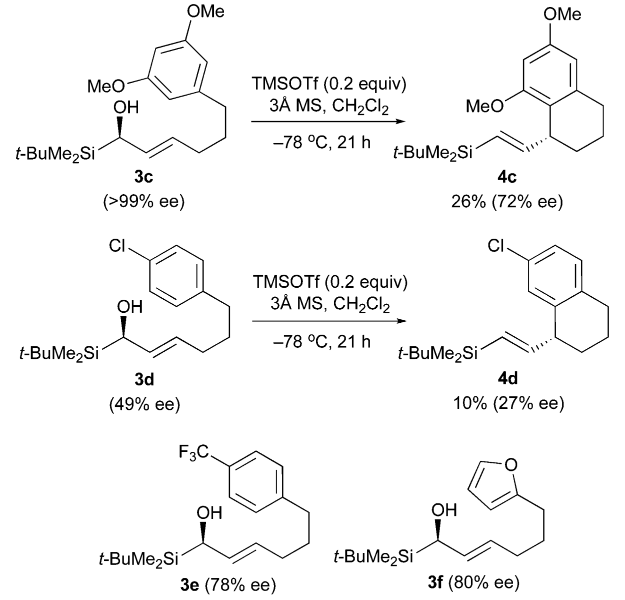
Scheme 6 Acid-catalyzed reaction of carbon-substituted analogs.



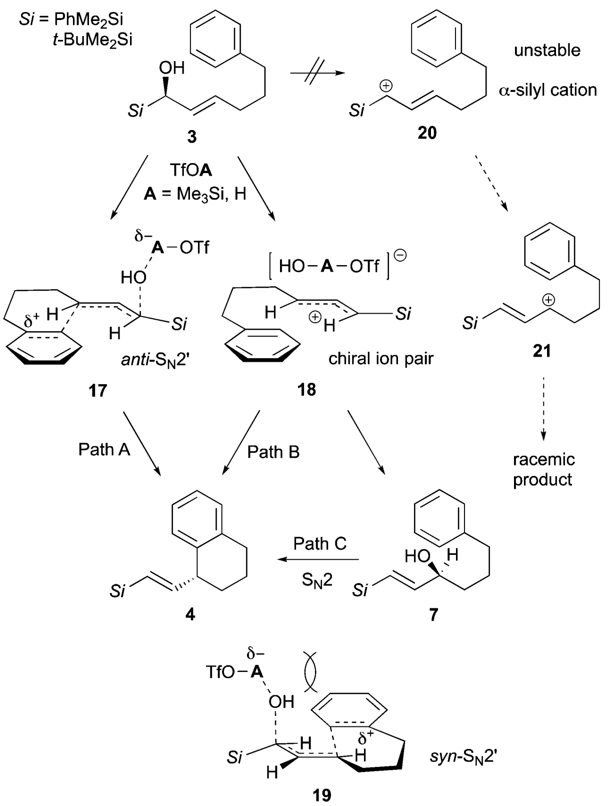
Scheme 7 Acid-catalyzed reaction of α-hydroxy-α-alkenylsilanes having different number of alkyl chains. ^{a} Reaction using TMSOTf (0.2 equiv.) resulted in a recovery of most of the starting material.

The results of the acid-catalyzed reaction employing several enantio-enriched α-hydroxy-α-alkenylsilanes **3c–f**[15] 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.[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 *anti*-S$_N$2′ manner, wherein the hydroxy group is effectively activated by TMSOTf and/or TfOH, to produce **4** (path A). The alternative *syn*-S$_N$2′ pathway *via* **19** is unfavorable because of the severe steric repulsion between the leaving group and the aromatic moiety. On the other hand, the formation of **4** competes with that of **7**. The formation of the highly optically active **7** (the *syn*-S$_N$2′ product from **3**) suggests the generation of chiral ion pair intermediate **18**, which was proposed by Woerpel *et al.*[17] The cyclization, therefore, may also occur *via* **18** (path B). The conversion from **7** to **4** also slowly occurs in an S$_N$2 manner (path C).



Scheme 8 Acid-catalyzed reaction of several α-hydroxy-α-alkenylsilanes.



Scheme 9 Plausible reaction pathways.

The silyl group, which destabilizes the adjacent carbocation more than an alkyl or aryl group, likely inhibits the formation of the α-silyl cation **20**,[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 α-hydroxy-α-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.[18] During the reaction conditions, the 1,3-rearrangement of the α-hydroxy-α-alkenylsilanes also occurred to give the highly optically active γ-hydroxyvinylsilanes (>99% ee).[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 carbocation (α-silyl cation) more than an alkyl or aryl group.[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.

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Conflicts of interest

There are no conflicts to declare.

Notes and references

1 (*a*) N. Kawai, J.-M. Lagrange, M. Ohmi and J. Uenishi, *J. Org. Chem.*, 2006, **71**, 4530; (*b*) Y. S. Vikhe, S. M. Hande, N. Kawai and J. Uenishi, *J. Org. Chem.*, 2009, **74**, 5174.
2 A. Aponick and B. Biannic, *Org. Lett.*, 2011, **13**, 1330.
3 (*a*) N. Kawai, R. Abe and J. Uenishi, *Tetrahedron Lett.*, 2009, **50**, 6580; (*b*) N. Kawai, R. Abe, M. Matsuda and J. Uenishi, *J. Org. Chem.*, 2011, **76**, 2102.
4 C. Morrill and R. H. Grubbs, *J. Am. Chem. Soc.*, 2005, **127**, 2842.
5 (*a*) K. Sakaguchi, M. Fujita and Y. Ohfune, *Tetrahedron Lett.*, 1998, **39**, 4313; (*b*) K. Sakaguchi, T. Yamada and Y. Ohfune, *Tetrahedron Lett.*, 2005, **46**, 5009; (*c*) K. Sakaguchi, T. Okada, T. Yamada and Y. Ohfune, *Tetrahedron Lett.*, 2007, **48**, 3925; (*d*) K. Sakaguchi, T. Okada, T. Shinada and Y. Ohfune, *Tetrahedron Lett.*, 2008, **49**, 25; (*e*) M. Higashino, N. Ikeda, T. Shinada, K. Sakaguchi and Y. Ohfune, *Tetrahedron Lett.*, 2011, **52**, 422.
6 K. Sakaguchi, M. Higashino and Y. Ohfune, *Tetrahedron*, 2003, **59**, 6647.
7 According to the MP2/6-31G*//3-21G calculations, the carbocation α to the SiH_3 group (α-silyl cation) is 18.3 kcal mol^{-1} less stable than the corresponding carbocation α to a methyl group: (*a*) P. J. Stang, M. Ladika, Y. Apeloig, A. Stanger, M. D. Schiavelli and M. R. Hughey, *J. Am. Chem. Soc.*, 1982, **104**, 6852; (*b*) Y. Apeloig and A. Stanger, *J. Am. Chem. Soc.*, 1985, **107**, 2806; (*c*) Y. Apeloig, R. Biton and A. Abu-Freih, *J. Am. Chem. Soc.*, 1993, **115**, 2522; (*d*) M. A. Brook, *Silicon in Organic, Organometallic and Polymer Chemistry*, Wiley, New York, 1st edn, 2000, p. 480, and references cited therein.
8 For the intramolecular Friedel–Crafts cyclization reactions of allyl alcohols and their derivatives, see the following reports and references cited therein: (*a*) S. Ma and J. Shang, *Tetrahedron Lett.*, 2002, **43**, 3435; (*b*) S. Ma and J. Shang, *Tetrahedron*, 2003, **59**, 6273; (*c*) M. Bandini, A. Melloni, F. Piccinelli, R. Sinisi, S. Tommasi and A. Umani-Ronchi, *J. Am. Chem. Soc.*, 2006, **128**, 1424; (*d*) K. Namba, H. Yamamoto, I. Sasaki, K. Mori, H. Imagawa and M. Nishizawa, *Org. Lett.*, 2009, **10**, 1767; (*e*) M. Bandini and A. Eichholzer, *Angew. Chem., Int. Ed.*, 2009, **48**, 9533; (*f*) J. A. McCubbin, H. Hosseini and O. V. Krokhin, *J. Org. Chem.*, 2010, **75**, 959; (*g*) Q.-F. Wu, H. He, W.-B. Liu and S.-L. You, *J. Am. Chem. Soc.*, 2010, **132**, 11418; (*h*) H. Zheng, S. Ghanbari, S. Nakamura and D. G. Hall, *Angew. Chem., Int. Ed.*, 2012, **51**, 6187; (*i*) F.-Z. Zhang, Y. Tian, G.-X. Li and J. Qu, *J. Org. Chem.*, 2015, **80**, 1107; (*j*) J. Li, X. Tan, X. Mu, J. Gong and Z. Yang, *Chin. J. Chem.*, 2017, **35**, 562; For general reviews on asymmetric catalytic Friedel–Crafts alkylation reactions, see the following reports and the references cited therein: (*k*) T. B. Poulsen and K. A. Jorgensen, *Chem. Rev.*, 2008, **108**, 2903; (*l*) *Catalytic Asymmetric Friedel–Crafts Alkylations*, ed. M. Bandini and A. Umani-Ronchi, Wiley-VCH, Weinheim, 2009.
9 The ee of **4a** was determined by the chiral HPLC analysis (DAICEL, CHIRALCEL OD-H, 0.46 cm × 25 cm, *n*-hexane = 100, 0.5 mL min^{-1}, 0 °C, 254 nm). The absolute configuration of **4a** was determined by converting it into the known compound, see ESI†.
10 The ee of **7a** was determined by the chiral HPLC analysis (DAICEL, CHIRALPAK AD-H, 0.46 cm × 25 cm, *n*-hexane/EtOH = 50/1, 0.5 mL min^{-1}, 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.
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 × 25 cm, *n*-hexane = 100, 0.1 mL min^{-1}, 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 (±)-**11** by HPLC using a chital stationary phase column (see ESI†).
14 Treatment of the isolated **14** and **16** under the reaction conditions {TMSOTf (1.0 equiv.), 3 Å MS, CH_2Cl_2 −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).
17 A. I. Kim, K. L. Kimmel, A. Romero, J. H. Smitrovich and K. A. Woerpel, *J. Org. Chem.*, 2007, **72**, 6595.
18 The copper(I)-mediated *anti*-S_N2' allylic substitution of α-acyloxy-α-alkenylsilane with high transfer of chirality was reported. S. Perrone and P. Knochel, *Org. Lett.*, 2007, **9**, 1041.