Stereoselective Cyclization of Highly Enantioenriched Allylsilanes with Aldehydes via Acetal Formation: New Asymmetric Access to Tetrahydropyrans and Piperidines

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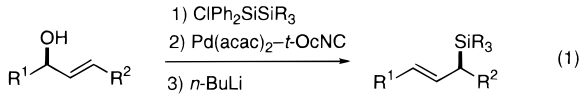
Allylsilanes are the practically applicable building block for selective organic synthesis, being utilized for efficient and selective carbon−carbon bond formation with various cationic electrophiles.[1] Of particular use is that allylsilanes having a chiral center at the allylic carbon atom adjacent to the silicon atom undergo regio- and stereoselective carbon−carbon bond formation with the 1,3-chirality transfer.[2,3] However, the potential usefulness of intramolecular cyclization with optically active allylsilanes has not been exploited because of the synthetic inaccessibility of optically active allylsilanes having functional groups.[3−5]

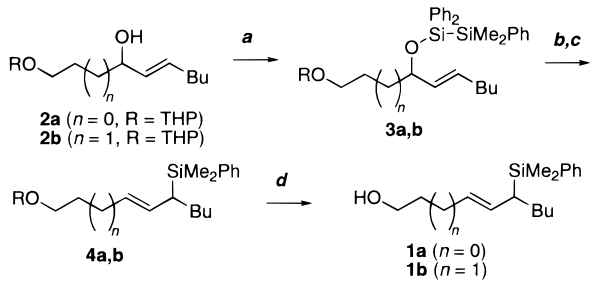
Recently, we have reported a new synthetic method for highly enantioenriched (*E*)-allylsilanes having a stereogenic carbon adjacent to the silicon.[6] The new synthesis of optically active allylsilanes, which involves an intramolecular bis-silylation of optically active allylic alcohols, proceeds with highly stereoselective 1,3-chirality transfer, producing optically active (*E*)-allylsilanes without loss of the enantiomeric excesses of the starting alcohols (eq 1).



(1)

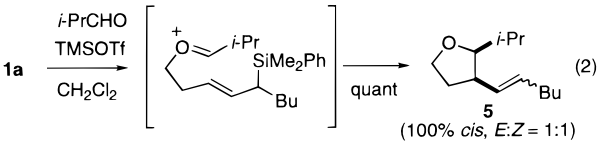
Herein, we describe stereoselective synthesis of enantioenriched (*E*)-allylsilanes bearing hydroxy and amino functionalities, which undergo intramolecular allylation via acetal or aminal formation under acidic conditions, giving highly enantioenriched 2,3-disubstituted cyclic ethers and amines, respectively. Since the related heterocyclic structures are involved in many naturally occurring compounds in enantiomerically pure forms, development of facile access to the heterocycles is highly desirable. For instance, according to the procedure reported by us,[6] racemic disilanyl ethers **3a** and **3b**, which were prepared from the corresponding allylic alcohols with the terminal hydroxy groups protected by THP, were subjected to the intramolecular bis-silylation catalyzed by palladium isonitrile complex at 110 °C,[7] followed by treatment of the resulting reaction mixture with *n*-BuLi at 0 °C to give the expected allylsilanes **4a** and **4b** in good yields (Scheme 1).[8] Subsequent deprotection of the THP was carried out by a catalytic amount of pyridinium *p*-toluenesulfonate in ethanol at 55 °C to afford allylsilanes **1a** and **1b** in high yields.

Scheme 1[a]



[a] Reagents and Conditions: (a) $ClPh_2SiSiMe_2Ph$, Et_3N, THF, rt, 93% (**3a**) and 99% (**3b**); (b) $Pd(acac)_2$ (0.02 equiv), *t*-OcNC (0.15 equiv), toluene, reflux; (c) *n*-BuLi, 0 °C, 73% (**4a**) and 75% (**4b**); (d) PPTS (0.2 equiv), EtOH, 55 °C, 96% (**1a**) and 90% (**1b**).

The allylsilanes **1** having a hydroxy group thus prepared were reacted with isobutyraldehyde (1 molar equiv) in the presence of trimethylsilyl triflate (TMSOTf, 1.1 molar equiv) at −78 °C in CH_2Cl_2 to afford the corresponding cyclic ethers **5** and **6** (eqs 2 and 3).[9] The intramolecular cyclization



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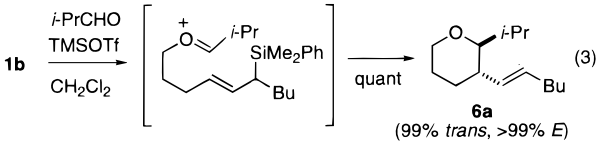

(3)

reactions may involve oxonium ion intermediates generated via the acetal formation from **1** and aldehydes. The stereochemical discrepancy between the cyclic ethers **5** and **6** is worth noting: **1a** afforded exclusively cis-2,3-disubstituted tetrahydrofuran, which is a 1:1 mixture of *E* and *Z* isomers with respect to the olefin geometry, while **1b** gave only trans-2,3-disubstituted tetrahydropyran with an (*E*)-carbon−carbon double bond.[10] The stereochemical outcome suggests that diastereofacial selection at the C=C as well as the C=O^+ is highly controlled for the intramolecular allylation with **1b** rather than **1a**.

Next, enantioenriched allylsilane (*S*)-**1b** of 93.2% ee,[11] prepared from the allylic alcohol (*R*)-**2b** of 93.6% ee, which is synthetically available by the Sharpless procedure (eq 4),[12] was subjected to the intramolecular cyclization under conditions identical to those for racemic **1b** (Table 1). As expected, reaction with isobutyraldehyde furnished the trans-2,3-

(1) Fleming, I.; Dunogues, J.; Smithers, R. *Org. React.* **1989**, *37*, 57−575. Sarkar, T. K. *Synthesis* **1990**, 969−983. Sarkar, T. K. *Synthesis* **1990**, 1101−1111.

(2) Hayashi, T.; Konishi, M.; Kumada, M. *J. Am. Chem. Soc.* **1982**, *104*, 4963. Hayashi, T.; Konishi, M.; Kumada, M. *J. Org. Chem.* **1983**, *48*, 281−282.

(3) Masse, C. E.; Panek, J. S. *Chem. Rev.* **1995**, *95*, 1293−1326.

(4) Mikami, K.; Maeda, T.; Kishi, N.; Nakai, T. *Tetrahedron Lett.* **1984**, *25*, 5151−5154.

(5) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115−136.

(6) (a) Suginome, M.; Matsumoto, A.; Ito, Y. *J. Am. Chem. Soc.* **1996**, *118*, 3061−3062. (b) Suginome, M.; Iwanami, T.; Matsumoto, A.; Ito, Y. *Tetrahedron: Asymmetry* **1997**, *8*, 859−862. (c) Suginome, M.; Matsumoto, A.; Ito, Y. *J. Org. Chem.* **1996**, *61*, 4884−4885.

(7) (a) Suginome, M.; Ito, Y. *J. Chem. Soc., Dalton Trans.* **1998**, 1925−1934. (b) Suginome, M.; Ito, Y. *J. Synth. Org. Chem. Jpn.* **1997**, *55*, 1040−1051. (c) Ito, Y.; Suginome, M.; Murakami, M. *J. Org. Chem.* **1991**, *56*, 1948−1951. (d) Suginome, M.; Takama, A.; Ito, Y. *J. Am. Chem. Soc.* **1998**, *120*, 1930−1931.

(8) Peterson, D. J. *J. Org. Chem.* **1968**, *33*, 780−784.

(9) Markó, I. E.; Mekhalfia, A. *Tetrahedron Lett.* **1992**, *33*, 1799−1802. Markó, I. E.; Bayston, D. J. *Tetrahedron Lett.* **1993**, *34*, 6595−6598. Markó, I. E.; Bayston, D. J. *Tetrahedron* **1994**, *50*, 7141−7156. Markó, I. E.; Bailey, M.; Murphy, F.; Declercq, J. P.; Tinant, B.; Feneau-Dupont, J.; Krief, A.; Dumont, W. *Synlett* **1995**, 123−126. Mohr, P. *Tetrahedron Lett.* **1993**, *34*, 6251−6254. Oriyama, T.; Ishiwata, A.; Sano, T.; Matsuda, T.; Takahashi, M.; Koga, K. *Tetrahedron Lett.* **1995**, *36*, 5581−5584. Sano, T.; Oriyama, T. *Synlett* **1997**, 716−718.

(10) For the stereochemical assignments, see the Supporting Information.

(11) The enantiomeric excess of (*S*)-**1b** was determined by the reported procedure involving regio- and stereoselective hydroboration with 9-BBN followed by oxidation. See ref 7b. For the reaction of allylsilanes with 9-BBN, see: Fleming, I.; Lawrence, H. J. *J. Chem. Soc., Perkin Trans. 1* **1992**, 3309−3326.

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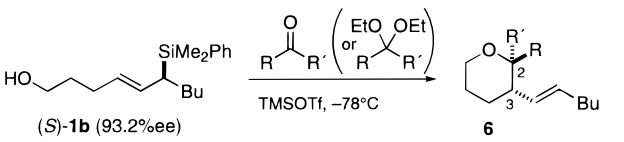
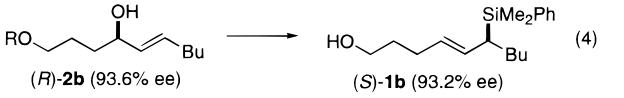
Table 1. Asymmetric Synthesis of Tetrahydropyrans by Stereoselective Cyclization of Enantioenriched Allylsilane (*S*)-1b with Carbonyl Compounds[a]

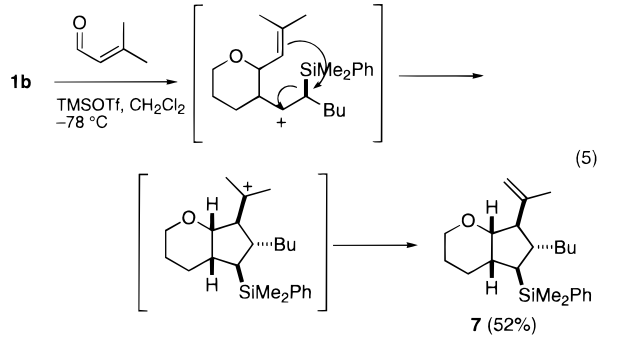


	carbonyl compd					
entry	R	R′	product **6**	yield/%	trans/cis[b]	ee[c]/%
1[d]	Me	H	**b**	89	>10:1	93.4
2	*n*-Hex	H	**c**	92	>10:1	92.1
3	*i*-Pr	H	**a**	98	99:1	92.8
4	*cyclo*-Hex	H	**d**	99	99:1	92.3
5	*t*-Bu	H	**e**	88	9:1	93.6
6	Me	Me	**f**	95		91.5
7[e]	$CH{=}CMe_2$	H	**g**	72	12:1	92.0

[a] (*S*)-**1b** (93.2 ± 0.2% ee), carbonyl compounds (1.1 equiv), and TMSOTf (1.1−2 equiv) were reacted in CH_2Cl_2 at −78 °C unless otherwise noted. [b] Stereochemistry in the six-membered ring. [c] The values (±0.2) were determined by HPLC (entries 2−7) or GC (entry 1). [d] Acetaldehyde diethyl acetal was used. [e] Reaction in CH_3CN at −30 °C to rt in the presence of TMSOTf (0.1 equiv).

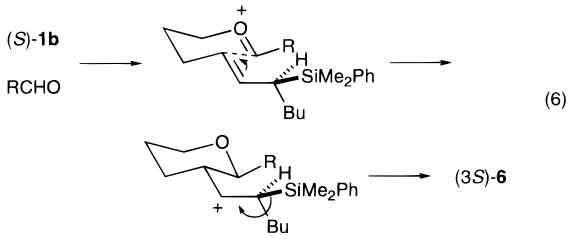


disubstituted THP derivative **6a** of 92.8% ee (entry 3),[13] indicating the intramolecular cyclization proceeded with nearly complete (>99%) chirality transfer. Cyclohexanecarboxaldehyde also provided enantioenriched trans-2,3-disubstituted THP (**6d**) diastereoselectively (entry 4). Acetaldehyde diethyl acetal as well as heptanal and pivalaldehyde afforded enantioenriched trans-2,3-disubstituted THP (**6b**,**c**,**e**) but with the respective cis isomers in ratios of ≥9:1 (entries 1, 2, and 5). Similarly, acetone underwent the cyclization to give product **6f** of 91.5% ee in high yield (entry 6). Unexpectedly, the intramolecular allylation with α,β-unsaturated aldehyde under identical reaction conditions gave bicyclic organosilicon derivative **7** as a single diastereomer in moderate yield (eq 5). The cyclization may

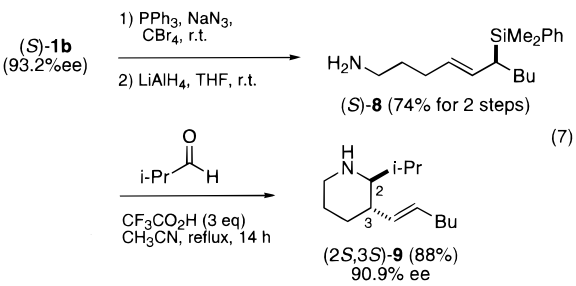


proceed through [1,2]-migration of the silyl group in the β-silyl cationic species initially formed,[14] followed by a second cyclization with the C=C bond. Notable is that use of CH_3CN solvent with the decreased amount of TMSOTf to 0.1 equiv successfully led to the expected formation of **6g** of 92.0% ee in 72% yield along with bicyclic **7** in less than 5% yield (entry 7). No formation of 5-decen-1-ol, which may arise from protodesilylation of the starting allylsilane, was observed in any case.

The 2,3-trans stereochemistry in the six-membered cyclic products **6** indicates that the intramolecular cationic allylation proceeds through a chairlike transition state, in which the R group of the aldehyde and the C=C bond occupy the equatorial positions (eq 6). Furthermore, the absolute (*S*)-configuration at the 3-position in **6b**, which was determined according to the Trost's procedure,[15] reveals that the intramolecular allylation takes place at the C=C π-face anti to the silyl group.



The present methodology involving acetal formation followed by intramolecular allylation was applicable to the asymmetric synthesis of a piperidine derivative.[16] Azidation and subsequent reduction of (*S*)-**1b** afforded optically active allylsilane (*S*)-**8** having an amino functionality in good yield (eq 7). Although the cyclization reaction of (*S*)-**8** with



isobutyraldehyde hardly proceeded in the presence of TMSOTf, the reaction in the presence of CF_3CO_2H in refluxing CH_3CN gave trans-2,3-disubstituted piperidine **9** in high yield (88%). The high ee of **9** reveals that the piperidine ring formation also takes place with highly effective chirality transfer as shown for the formation of THP derivatives.

In summary, the new optically active allylsilanes with an hydroxy as well as an amino group were found to serve as highly useful tools for the synthesis of optically active six-membered ring heterocycles from aldehydes through the effective chirality transfer.

Supporting Information Available: Detailed experimental procedures and characterization of the new compounds, including determination of the enantiomeric excesses of the enantioenriched compounds (10 pages).

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(12) (a) Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237−6240. (b) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765−5780. Enantioenriched (*R*)-**2b** of 93.6% ee was obtained by the kinetic resolution at 0 °C (L-(+)-DIPT, TBHP 0.6 equiv) and used for the synthesis of (*S*)-**1b**. The ee was, however, found to be improved to 98.5% by carrying out the resolution at −20 °C.

(13) The enantiomeric excesses described in this paper were determined by HPLC or GC analyses (±0.2%) with chiral columns. For the determination of those for **6**, the analyses were carried out for *N*-(3,5-dinitrophenyl)-carbamates of the corresponding 2-substituted tetrahydropyran-3-ylmethanol derivatives, which are prepared by oxidative cleavage of the C=C bonds (OsO_4, NMO, then HIO_4) followed by reduction with $NaBH_4$. The chiral columns used are specified in the Supporting Information.

(14) For examples, see: Danheiser, R. L.; Carini, D. J.; Basak, A. *J. Am. Chem. Soc.* **1981**, *103*, 1604−1606. Knölker, H.-J.; Jones, P. G.; Pannek, J.-B. *Synlett* **1990**, 429. Also see refs 3 and 7d.

(15) The mandelate procedure reported by Trost et al. was applied to *trans*-2-hexyltetrahydropyran-3-ol, which was derived from **6b**. For the transformation, see the Supporting Information. Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M. *J. Org. Chem.* **1986**, *51*, 2370−2374.

(16) (a) Grieco, P. A.; Fobare, W. F. *Tetrahedron Lett.* **1986**, *27*, 5067−5070. (b) Hiemstra, H.; Fortgens, H. P.; Speckamp, W. N. *Tetrahedron Lett.* **1985**, *26*, 3155−3158.