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Acid-Catalyzed Cyclization of Vinylsilanes Bearing an Amino Group. Stereoselective Synthesis of Pyrrolidines[1]

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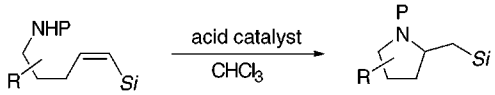
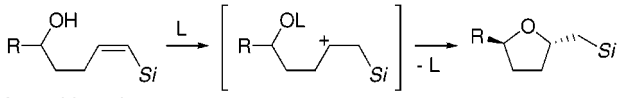
ABSTRACT



In the presence of an acid catalyst, vinylsilanes 1 bearing an amino group protected by an electron-withdrawing group were smoothly cyclized to 2-(silylmethyl)pyrrolidines 2. This cyclization was utilized for the stereoselective synthesis of 2,*n*-disubstituted pyrrolidines (*n* = 3–5). The cyclized products could be converted to the corresponding alcohols by oxidative cleavage of the carbon–silicon bond with TBAF and H_2O_2.

In recent years, the silicon-directed reactions via intramolecular nucleophilic addition to a β-silylcarbenium ion intermediate, particularly [3 +2] cycloadditions of allylsilanes to electron-deficient unsaturated bonds, have been proven to provide an efficient and reliable method for the stereoselective synthesis of carbocycles and heterocycles containing an oxygen or nitrogen atom.[2−5] In this context, we have reported that vinylsilanes bearing a hydroxy group undergo acid-catalyzed cyclization to give tetrahydrofurans with high levels of diastereoselectivity, and the cyclization proceeds through a stepwise mechanism including protonation of the α-carbon and intramolecular addition of the oxygen nucleophile to the formed β-silylcarbenium ion intermediate (Scheme 1).[6,7] Thus, our attention was next focused on the application of this cyclization to the construction of cyclic amines.[1]

Scheme 1



Cyclization of alkenyl amines is one of the most straightforward routes to cyclic amines.[8] Although several methods

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(2) Reviews: (a) Knölker, H.-J. *J. Prakt. Chem.* **1997**, *339*, 304. (b) Masse, C. E.; Panek, J. S. *Chem. Rev.* **1995**, *95*, 1293. (c) Panek, J. S. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 1, p 579.

(3) Recent reports on [3 + 2] cycloadditions of allylsilanes: (a) Roberson, C. W.; Woerpel, K. A. *J. Org. Chem.* **1999**, *64*, 1434. (b) Knölker, H.-J.; Jones, P. G.; Wanzl, G. *Synlett* **1998**, 613. (c) Akiyama, T.; Hoshi, E.; Fujiyoshi, S. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2121. (d) Akiyama, T.; Yamanaka, M. *Tetrahedron Lett.* **1998**, *39*, 7885. (e) Groaning, M. D.; Brengel, G. P.; Meyers, A. I. *J. Org. Chem.* **1998**, *63*, 5517.

(4) Other reactions via β-silylcarbenium ions generated from allylsilanes: (a) Sugimura, H. *Tetrahedron Lett.* **1990**, *31*, 5909. (b) Kiyooka, S.; Shiomi, Y.; Kira, H.; Kaneko, Y.; Tanimori, S. *J. Org. Chem.* **1994**, *59*, 1958. (c) Akiyama, T.; Nakano, M.; Kanatani, J.; Ozaki, S. *Chem. Lett.* **1997**, 385. (d) Brocherieux-Lanoy, S.; Dhimane, H.; Poupon, J.-C.; Vanucci, C.; Lhommet, G.; *J. Chem. Soc., Perkin Trans. 1* **1997**, 2163. (e) Monti, H.; Rizzotto, D.; Léandri, G. *Tetrahedron* **1998**, *54*, 6725. (f) Akiyama, T.; Ishida, Y. *Synlett* **1998**, 1150; **1999**, 160. (g) Akiyama, T.; Ishida, Y.; Kagoshima, H. *Tetrahedron Lett.* **1999**, *40*, 4219.(h) Sugita, Y.; Kimura, Y.; Yokoe, I. *Tetrahedron Lett.* **1999**, *40*, 5877. (i) Angle, S. R.; El-Said, N. A. *J. Am. Chem. Soc.* **1999**, *121*, 10211.

(5) Reactions using vinylsilanes: (a) Brook, M. A.; Sebastian, T.; Jueschke, R.; Dallaire, C. *J. Org. Chem.* **1991**, *56*, 2273. (b) Brook, M. A.; Henry, C.; Jueschke, R.; Modi, P. *Synlett* **1993**, 97. (c) Yamazaki, S.; Tanaka, M.; Yamabe, S. *J. Org. Chem.* **1996**, *61*, 4046.

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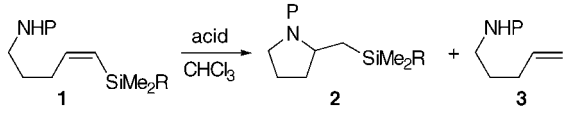
have been developed to realize this strategy, acid-catalyzed systems are rarely utilized for the cyclization.[4g] Herein, we report that the cyclization of vinylsilanes bearing an amino group protected by an electron-withdrawing group is effectively promoted by an acid catalyst, and it serves for the stereoselective synthesis of 2,*n*-disubstituted (n = 3−5) pyrrolidines.[9]

Initially, vinylsilane **1a** (P, R = Bn) bearing a benzylamino group was used as a substrate. The $TiCl_4$-catalyzed reaction, however, gave no cyclized product. This seemed to be due to the low acidity of the proton on the nitrogen, which would prevent protonation of the carbon α to the silyl group (vide infra). Therefore, the amino group was protected by an electron-withdrawing group for promotion of the acid-catalyzed cyclization. As expected, treatment of *N*-acetyl-protected substrate **1b** with a catalytic amount of $TiCl_4$ or TsOH gave the corresponding cyclized product, pyrrolidine **2b**, although the yield was rather low (entries 1 and 2 in Table 1). Sulfonyl groups were effective in accelerating the cyclization, and a tosyl group provided the best result among the examined protective groups (entries 5 and 6). In the presence of the $TiCl_4$ catalyst, *N*-Boc-protected vinylsilane **1g** was also efficiently converted to the corresponding pyrrolidine **2g** (entry 11), which could be easily unprotected by the action of 3 M HCl in MeOH (Scheme 2). Interestingly, the cyclization of **1g** was only slightly induced by TsOH (entry 12). The reactivity of vinylsilanes was affected by the substituent on the silicon as well as nitrogen. The change of the benzyl to a phenyl group diminished the cyclization rate (entries 13 and 14). This observation is consistent with our previous results in the cyclization to tetrahydrofurans.[10]

While the present method was applicable to the synthesis of piperidines **5** (Table 2), the cyclization efficiency decreased because of competitive desilylation to **6**. For inhibition of the desilylation, a more bulky substituent, a 1-phenylethyl group, was introduced on the silicon atom instead of the benzyl group (entries 3 and 4).[11] The change of substituent suppressed the desilylation and somewhat improved the yield of **5** in the $TiCl_4$-catalyzed system.

We next investigated the diastereoselectivity of the present cyclization using racemic vinylsilanes **7a**−**c** with a phenyl group on the methylene tether (Scheme 3). The $TiCl_4$ (5 mol %)-catalyzed reaction of **7a** at room temperature gave 2,5-disubstituted pyrrolidine **8a** in a moderate yield with low *cis*-selectivity. This result stands in sharp contrast to our previous finding that the acid-catalyzed addition of a hydroxy

Table 1. Acid-Catalyzed Cyclization of Vinylsilanes **1**[a]



	vinylsilane					yield (%)	
entry	P	R		condns[a]	time (h)	**2**	**3**
1	Ac	Bn	**1b**	A	24	26[c]	0
2			**1b**	B	24	14[c]	0
3	CF_3CO	Bn	**1c**	A[b]	34	33	55
4			**1c**	B	48	78	<1
5	Ts	Bn	**1d**	A	3.3	93	5
6			**1d**	B	3.3	96	<4
7	Ms	Bn	**1e**	A	1.2	90	
8			**1e**	B	1.2	86	
9	Tf	Bn	**1f**	A	44	64[d]	
10			**1f**	B	11	92	
11	Boc	Bn	**1g**	A	24	89[e]	
12			**1g**	B	25	<1[d]	0
13	Ts	Ph	**1h**	A	11	80	9
14			**1h**	B	6.5	92	5

[a] All reactions were performed with a vinylsilane (0.50 mmol) in $CHCl_3$ (2.5 mL). Condition A: $TiCl_4$ (5 mol %) at room temperature. Condition B: $TsOH{\cdot}H_2O$ (5 mol %) at 60 °C. [b] 10 mol % of $TiCl_4$. [c] Estimated by ^1H NMR analysis of the crude product including **1b** and **2b**. [d] More than 95% of **1g** and 20% of **1f** were recovered. [e] A mixture of **2d** (89%) and **1d** (7%) was obtained after purification by column chromatography.

Scheme 2

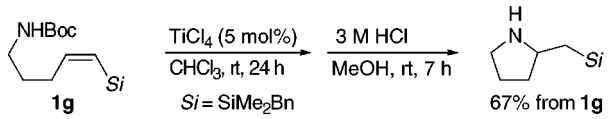
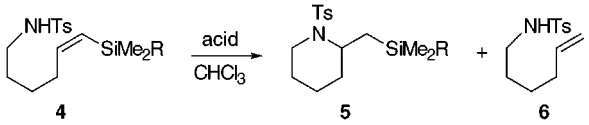


Table 2. Acid-Catalyzed Cyclization of Vinylsilanes **4**[a]



	vinylsilane				yield (%)	
entry	R		condns[a]	time (h)	**5**	**6**
1	Bn	**4a**	A[b]	24	54	45
2		**4a**	B	24	75	25
3	CHMePh	**4b**	A[b]	3.5	78	21
4		**4b**	B	22	76	15

[a,b] See footnotes *a* and *b* in Table 1.

(6) (a) Miura, K.; Okajima, S.; Hondo, T.; Hosomi, A. *Tetrahedron Lett.* **1995**, *36*, 1483. (b) Miura, K.; Hondo, T.; Okajima, S.; Hosomi, A. *Tetrahedron Lett.* **1996**, *37*, 487. (c) Miura, K.; Hondo, T.; Saito, H.; Ito, H.; Hosomi, A. *J. Org. Chem.* **1997**, *62*, 8292.

(7) Related work: Adiwidjaja, G.; Flörke, H.; Kirschning, A.; Schaumann, E. *Liebigs Ann.* **1995**, 501.

(8) Jahn, U.; Aussieker, S. *Org. Lett.* **1999**, *1*, 849 and references therein.

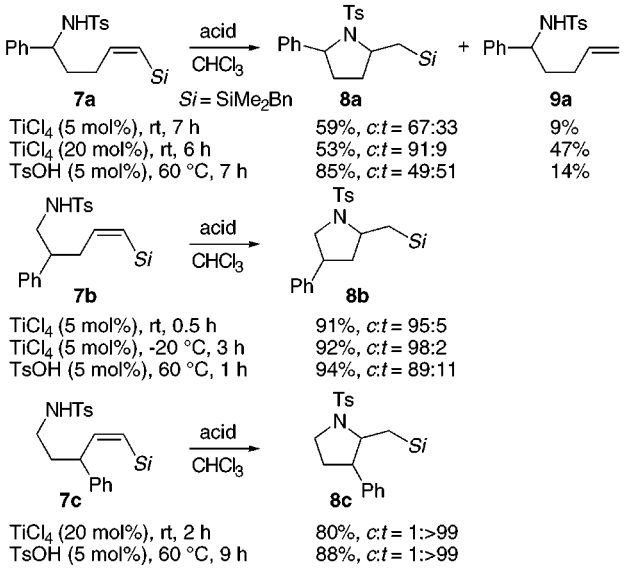
(9) We used only (*Z*)-vinylsilanes as substrates in the present work because (*E*)-isomers exhibit lower reactivity and stereoselectivity than (*Z*)-isomers in the cyclization shown in Scheme 1. See ref 6.

(10) Miura, K.; Hondo, T.; Hosomi, A. Manuscript submitted.

(11) Knölker, H.-J.; Foitzik, N.; Goesmann, H.; Graf, R. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1081.

group to vinylsilanes is valuable for the synthesis of *trans*-2,5-disubstituted tetrahydrofurans (Scheme 1).[6b] In this case, unreacted **7a** was recovered in 29% yield. An increased amount of $TiCl_4$ effected complete conversion of **7a** but did not improve the yield of **8a** because of a considerable formation of **9a**. However, it led to higher *cis*-selectivity of **8a**. TsOH was more effective in the cyclization of **7a**, which exhibited no stereoselectivity. The cyclization of **7b** proceeded much faster than that of **7a**, forming **8b** in a high yield with high *cis*-selectivity. Lowering the reaction temperature further improved the selectivity. The allylic phenyl group of **7c** completely controlled the diastereoselectivity, and only *trans*-**8c** was obtained independently of the reaction conditions.

Scheme 3

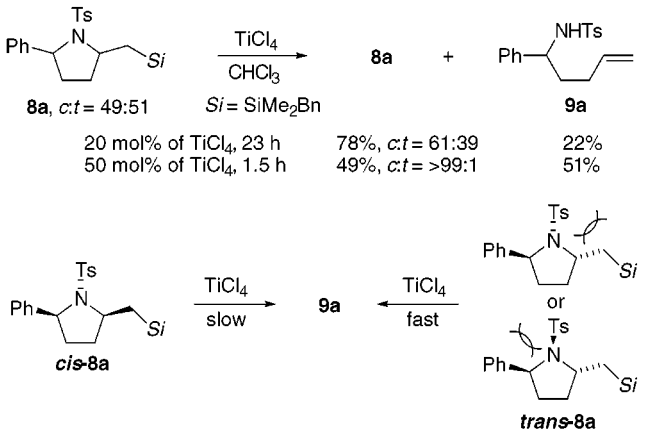


The increased *cis*-selectivity in the cyclization of **7a** using 20 mol % of $TiCl_4$ is attributable to fast desilylation of *trans*-**8a**. Indeed, treatment of a ca. 1:1 diastereomeric mixture of **8a** with 20 mol % of $TiCl_4$ gave a *cis*-rich mixture of **8a** and desilylated product **9a** (Scheme 4). The use of 50 mol % of $TiCl_4$ completely desilylated *trans*-**8a** to **9a**, and only *cis*-**8a** was recovered in 49% yield. The *trans*-selective desilylation resulted probably because the *cis*-isomer is thermodynamically more stable than the *trans*-isomer, which has an unfavorable steric interaction between the tosyl and silylmethyl groups or the phenyl and tosyl groups.

From our previous results,[6b] the present cyclization of **1** is considered to proceed via a mechanism comprising the following steps (Scheme 5): (1) an acid adds to the protected amino group of **1** on the nitrogen atom and/or the oxygen atom of the protective group,[12] (2) intramolecular proton transfer from the nitrogen to the carbon α to the silyl group

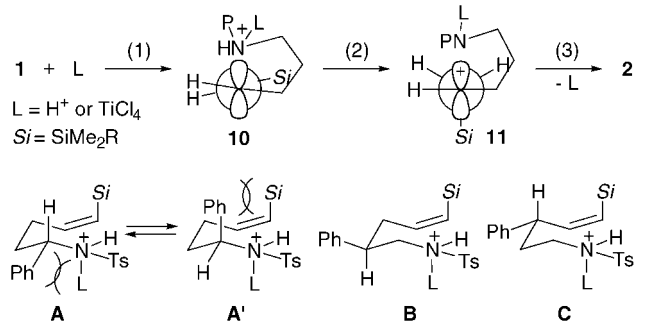
(12) For simplification, attachment of an acid to the oxygen atom or both the nitrogen and oxygen atoms is not depicted in Scheme 5. In these cases also, the reaction mechanism and the stereochemical outcome can be explained as in the text.

Scheme 4



forms a β-silylcarbenium ion intermediate, and (3) nucleophilic attack of the nitrogen to the positively charged carbon from the opposite site to the silyl group gives a cyclic amine and regenerates the acid catalyst. This mechanism indicates that the proton transfer in step 2 and the nucleophilic attack in step 3 take place on the same side of the initial π-face, and the diastereoselectivity in the cyclization of **7** is determined in step 2.[6b] Therefore, the high stereoselectivity with **7b** and **7c** is attributable to diastereoface-selective protonation via chairlike conformations **B** and **C** bearing a phenyl group at the pseudoequatorial position. On the other hand, a similar conformation **A** arising from **7a** would be destabilized by the steric repulsion between the phenyl and protective groups, which reduces the energy difference between **A** and another conformation (**A′**). This consideration provides a reasonable explanation for the low selectivity in the TsOH-catalyzed cyclization of **7a**.

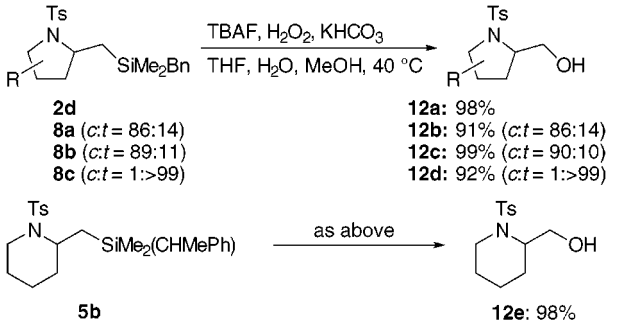
Scheme 5



To enhance the synthetic utility of the present cyclization, we attempted oxidative cleavage of the silicon−carbon bond of the cyclized products. As shown in Scheme 6, benzyldimethylsilyl and dimethyl(1-phenylethyl)silyl groups could beconverted to hydroxy groups in high yield with stereochemical retention by the Tamao method.[13]

In conclusion, we have developed a new method for the stereoselective construction of cyclic amines utilizing the

Scheme 6



reactivity of vinylsilanes. The scope and limitations of the present cyclization are now under investigation, and the results will be presented in due course.

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Supporting Information Available: Experimental procedure, stereochemical assignment, and spectral data for the substrates and the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) (a) Tamao, K.; Ishida, N. *J. Organomet. Chem.* **1984**, *269*, C 37. (b) Murakami, M.; Suginome, M.; Fujimoto, K.; Nakamura, H.; Andersson, P. G.; Ito, Y. *J. Am. Chem. Soc.* **1993**, *115*, 6487.