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Chiral Syntheses of 2,3,5-Trisubstituted Pyrrolidines by Silicon-Directed Cyclization of Allylsilanes Bearing a Sulfonamide Moiety

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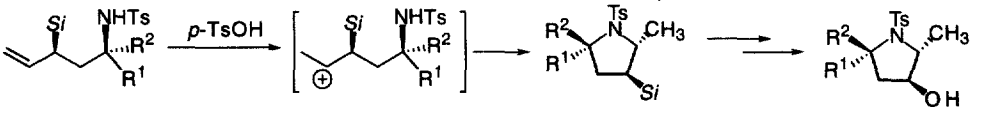
Abstract: Brønsted acid-catalyzed cyclization of chiral N-tosyl-3-silyl-4-pentenamine proceeded smoothly by way of a β-silyl carbocation intermediate to furnish 2,3,5-trisubstituted pyrrolidines in enantiomerically pure form.

Keywords: Asymmetric Synthesis; Pyrrolidines; Aziridines; Silicon and compounds

Allylsilane has been extensively used as an allyl anion equivalent in the Lewis acid-catalyzed addition reaction with α,β-unsaturated carbonyl compounds or aldehydes since the pioneering work of Sakurai and Hosomi.[1] It is well known that these reactions proceed by way of a β-silyl carbocation intermediate, which is stabilized by σ-π conjugation,[2] and desilylation from the β-silyl carbocation intermediate results in the desired allylation product. On the other hand, nucleophilic attack onto the carbon center of the β-silyl carbocation intermediate has recently attracted attention as a novel method for the formation of a carbon-carbon bond[3,4,5] as well as a carbon-hetero atom bond.[6,7]

Highly stereoselective formation of tetrahydrofurans by Brønsted acid-catalyzed cyclization of 3-silyl-4-pentenol via a β-silyl carbocation intermediate has been reported.[8,9] We wish to report herein that a pyrrolidine derivative, which is an important framework of alkaloid,[10] could be synthesized highly stereoselectively by *p*-TsOH catalyzed-cyclization of *N*-tosyl-3-silyl-4-pentenamine, readily available by ring opening of *N*-tosylaziridines by silyl-substituted allyl anions.[11,12] Employing chiral aziridine resulted in the formation of the pyrrolidines in enantiomerically pure form. Recent development of the asymmetric synthesis of aziridines[13] renders the present method a more valuable way for the preparation of optically active pyrrolidines. Although Hg(II)-mediated cyclization of *N*-tosyl-4-pentenamine derivatives is already known,[14] Brønsted acid-catalyzed cyclization has not been reported, to our knowledge.



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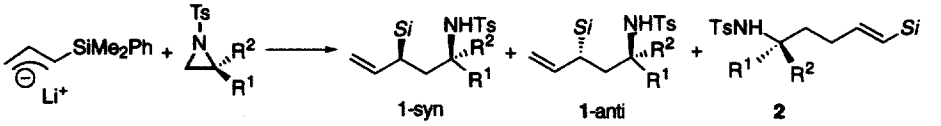


Table 1. Reaction of the allylsilane with aziridines *Si* =$SiMe_2Ph$

Entry	R^1	R^2	Product	Yield of 1/%	Syn : Anti	Yield of 2/%
1	H	H	**1a**	74	–	16
2	CH_3	CH_3	**1b**	57	–	38
3	CH_3	H	**1c**	66	67:33	22
4	*i*-Pr	H	**1d**	71	78:22	21
5	*i*-Bu	H	**1e**	61	79:21	25
7	$PhCH_2$	H	**1f**	74	73:27	16

On treatment of the allylsilyllithium, generated from allyldimethylphenylsilane and *n*-BuLi (2.0 equiv) in the presence of TMEDA (1.3 equiv) at 0 °C for 1 h, with *N*-tosyl aziridine at –78 °C for 1 h afforded the requisite allylsilanes bearing a sulfonamide moiety (**1**) and the results are shown in Table 1.[12] α-Adducts (**1**) were obtained preferentially and in favor of the syn isomer (**1**-syn).[15] Use of chiral aziridines,[16] which are readily available from the corresponding L-amino acids, afforded allylsilanes (**1**-syn) in optically pure form (Entries 3-7). The relative stereochemistry of **1** was determined after cyclization.

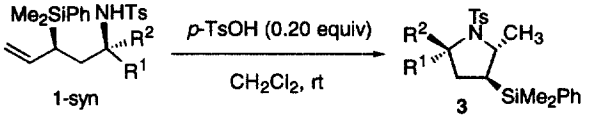
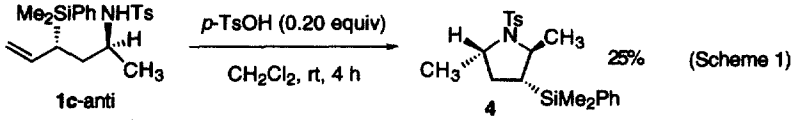


Table 2. Formation of pyrrolidines

Entry	Starting material	R^1	R^2	Product	Time / h	Yield /%
1	**1a**	H	H	**3a**	2	80
2	**1b**	CH_3	CH_3	**3b**	0.3	77
3	**1c**	CH_3	H	**3c**	1	86
4	**1d**	*i*-Pr	H	**3d**	1	84
5	**1e**	*i*-Bu	H	**3e**	1	74
6	**1f**	$PhCH_2$	H	**3f**	1	92

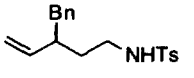
On treatment of **1**-syn with *p*-TsOH (20 mol%) at room temperature, cyclization took place smoothly to afford silyl-substituted pyrrolidines (**3**) highly stereoselectively and the results are shown in Table 2.

The pyrrolidines (**3**) were stereochemically pure by 400 MHz ^{1}H NMR. The relative stereochemistry of **3c** was determined by X-ray analysis. Those of **3a**, **3d**, and **3f** were determined by ^{1}H NMR multiple NOE experiments. Those of **3b** and **3e** were determined by analogy. The corresponding 2,5-*trans* isomer was not detected by 400 MHz ^{1}H NMR analysis.

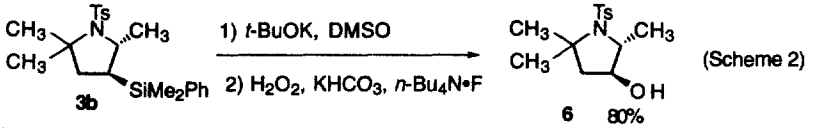


Interestingly, cyclization of **1**-anti was sluggish and the corresponding pyrrolidine (**4**) was obtained in a low yield as shown in Scheme 1. The stereochemical outcome of the present cyclization can be rationalized by considering the stabilization of the β-silyl carbocation intermediate by σ–π conjugation as discussed in a previous paper.[9]

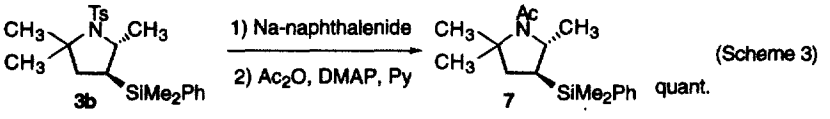
To confirm that the present cyclization is directed by the silyl group, the cyclization reaction of **5** with *p*-TsOH was attempted under the same conditions. No cyclization product was obtained under the identical reaction conditions and the starting material was recovered quantitatively.



Next, oxidative cleavage of the carbon-silicon bond was investigated (Scheme 2).[17] Treatment of **3b** with *t*-BuOK in DMSO[6e,18] at room temperature for 30 min followed by H_2O_2 in the presence of *n*-Bu_4NF[19] at room temperature for 30 min furnished the corresponding alcohol (**6**) in a high yield with the retention of the stereochemistry.



Removal of the tosyl group of **3b** was accomplished by treatment with Na-naphthalenide to furnish **7** in a high yield after *N*-acetylation (Scheme 3).



In summary, we have developed a novel method for the preparation of 2,3,5-trisubstituted pyrrolidines in optically pure form. The silyl group incorporated in the organic structure turned out to play a key role in the stereochemical control in the present cyclization reaction.

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