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Highly Selective Aziridination of Imines Using Trimethylsilyldiazomethane and Applications of *C*-Silylaziridines in Synthesis

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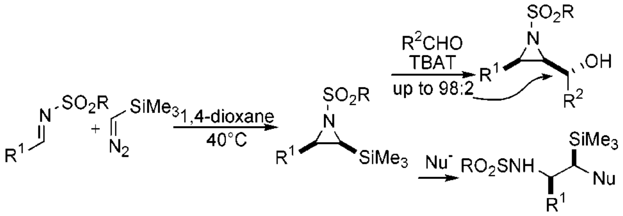
ABSTRACT



Trimethylsilyldiazomethane has been found to add directly to *N*-sulfonyl (Ts and SES) imines to afford aziridines in good yields and high *cis* stereoselectivities. The silyl group can be substituted by treatment with a fluoride source and electrophiles again with high selectivity. Complete regioselectivity is observed in ring opening of these aziridines with nucleophiles.

Like epoxides, aziridines are useful synthetic intermediates which undergo stereospecific nucleophilic ring opening, often with high regioselectivity.[1] In contrast to epoxides, aziridines can be readily metalated and reacted with electrophiles,[2] providing access to an even broader range of functionalized aziridines.

We became interested in the synthesis of *C*-silylated aziridines because we recognized that the silyl group could potentially control ring opening and metalation reactions and could itself be substituted by electrophiles, thereby considerably broadening the usefulness of this class of molecules. In this paper we report the synthesis and synthetic potential of *C*-silylated aziridines.

Although several methods have been developed for the preparation of aziridines (ring closure of amino alcohols,[3] ring opening of epoxides using metal azides,[4] addition of α-haloester enolates to imines,[5] transition metal-catalyzed nitrene transfer to alkenes,[6] and carbene/carbenoid transfer to imines[7]), there are limited examples of the synthesis of *C*-silylaziridines, despite their potential as synthetic intermediates.[7h,8] During the course of this work, Jørgensen reported the aziridination of α-imino esters with trimethyl-

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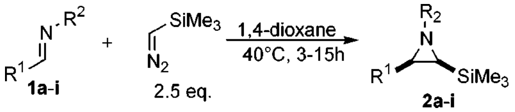
silyldiazomethane (TMSD)[9] in the presence of Lewis acids.[7h] In our independent study we found that the *N*-tosylbenzaldimine (**1a**) reacted with TMSD directly to give the aziridine **2a** in good yield and high *cis* selectivity without the need of Lewis acids to promote the reaction (Table 1, entry 1). 1,4-Dioxane proved to be the solvent of choice, and an excess of TMSD was necessary to ensure the complete consumption of the starting imine in a reasonably short time. High yields and high diastereoselectivity were achieved with both electron-rich and electron-deficient aldimines (Table 1, entries 2−4). The unsaturated aziridine *cis*-**2e** derived from cinnamaldimine **1e** proved to be somewhat unstable to the reaction conditions and chromatography, accounting for the lower yield in this case (Table 1, entry 5). Enolizable imines **1f** and **1g** were also effective substrates (Table 1, entries 6 and 7), although lower yields of the corresponding aziridines were obtained with substantial amounts of the methylketoimine. Evidently in this case, following betaine formation, H-migration competes with direct ring closure (Scheme 1). The imine activating group can be changed from Ts to SES with equally good results (Table 1, entry 9).

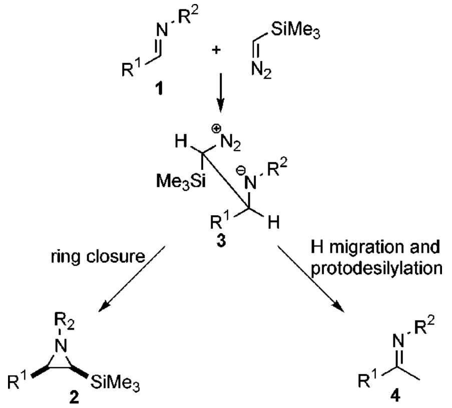
Table 1. Aziridination of Imines Using TMSD



entry	imine R^1	imine R^2	Im	Az	yield(%)	*c*:*t*
1	Ph	Ts	**1a**	**2a**	72	95:5
2	*p*-OMe-Ph	Ts	**1b**	**2b**	65	100:0
3	*p*-Cl-Ph	Ts	**1c**	**2c**	64	91:9
4	*p*-NO$_2$-Ph	Ts	**1d**	**2d**	83	94:6
5	*E*-PhCH═CH	Ts	**1e**	**2e**	32[a]	100:0
6	*n*-Bu	Ts	**1f**	**2f**	53[b]	85:15
7	Cy	Ts	**1g**	**2g**	40[b]	80:20
8[c]	CO$_2$Et	Ts	**1h**	**2h**	91	11:89
9	Ph	SES[d]	**1i**	**2i**	72	96:4

[a] 43% spectroscopic yield. [b] Obtained together with the corresponding methyl-ketoimine (19% yield in entry 6 and 29% in entry 7). [c] Reaction carried out in THF with slow warming from −78 to 0 °C. [d] SES = trimethylsilylethanesulfonyl.

Scheme 1. Aziridination of Imines Using TMSD



Reaction with *N*-tosyliminoacetate **1h** (Table 1, entry 8) followed a different course, as it was found that rapid reaction occurred even at room temperature. At low temperature an adduct was formed, which upon addition of anhydrous silica gel resulted in gas evolution and formation of *trans*-aziridine **2h** as the major product. It was not possible to determine the structure of the intermediate, but we believe it is the product of a 1,3-dipolar cycloaddition between the imine and the diazo compound.[10]

Reactions of diazo compounds with imines in the presence of metal catalysts usually occur with high *cis* selectivity,[11] but the origin of this selectivity has not been satisfactorily rationalized. We believe that the reaction is controlled by both electronic and steric effects. If the developing charges in the betaine are placed gauche to each other, the least sterically hindered TS has the silyl group opposite the bulky imine nitrogen (structure **3**, Scheme 1). This TS leads to the *cis* aziridine. It is noteworthy that, in contrast to all of the other imines, *N*-tosyliminoacetate **1h** gave the *trans* aziridine with high selectivity. This clearly suggests an alternative mechanism (a 1,3-dipolar cycloaddition followed by fragmentation and ring closure is proposed) although the origin of the *trans* selectivity is unclear at present.

TMSD was unique in its reactivity with imines: neither phenyldiazomethane nor ethyl diazoacetate gave useful products under the same reaction conditions.

Further transformations of the aziridines have been studied. Treatment of *cis*-**2a** with tetrabutylammonium triphenyldifluorosilicate (TBAT)[12] and aldehydes at 40 °C resulted in efficient formation of the expected aziridinemethanols (Table 2, entries 1−3). The silyl group was substituted with retention

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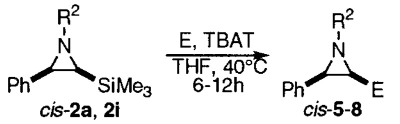
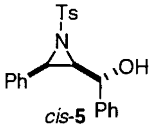
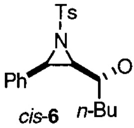
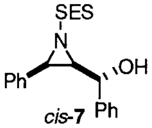
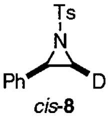
(9) TMSD is a safe and stable commercially available diazo compound. For a review on TMSD, see: Shioiri, T.; Aoyama, T. In *Advances in Using Synthons in Organic Chemistry*; Dondoni, A., Ed; JAI Press: London, 1993; Vol. 1, pp 51−101.

(10) For examples of decomposition of triazoline to the corresponding *C*-silylaziridine with silica gel, see refs 8e and 8f.

(11) See ref 7. For the rare examples where *trans* aziridines are the main isomers, see refs 7o and 7p.

Table 2. Coupling of Si-Aziridines with Electrophiles



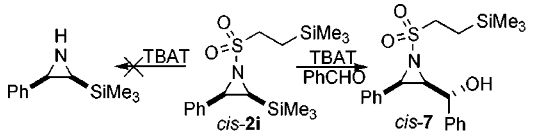
entry	Si-aziridine	E	product	yield % (d.r.)
1	*cis*-**2a**	PhCHO (3eq.)		60 (98:2)
2	*cis*-**2a**	*n*-BuCHO (3eq.)		54 (92:8)
3	*cis*-**2i**	PhCHO (3eq.)		64 (86:15)
4	*cis*-**2a**	$CDCl_3$ (5eq.)		84[a]

[a] 88% D incorporation.

of configuration, and high selectivity was observed in the newly created stereogenic center. The stereochemistry of the major adduct with benzaldehyde was determined by X-ray analysis.[13]

Interestingly, the SES aziridine **2i** could also be treated with TBAT and benzaldehyde to give *cis*-**7** in 64% yield (Table 2, entry 3). This clearly shows that the silyl group attached to the aziridine ring is more prone to attack by fluoride than the silyl group attached to the sulfonyl group (Scheme 2).

Scheme 2. Coupling of *cis*-**2i** with Benzaldehyde

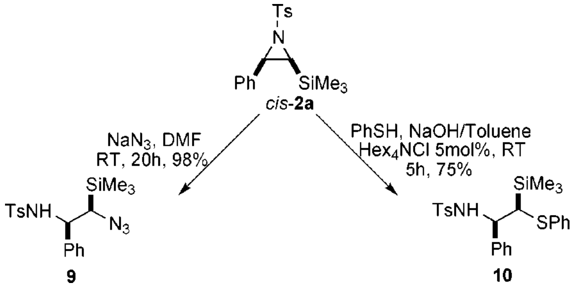


The silyl group could also be substituted for deuterium using $CDCl_3$ (superior to D_2O), again with complete retention of configuration (Table 2, entry 4).

In none of these cases were any *trans* aziridines formed, indicating that the aziridinyl anions were configurationally stable under the reaction conditions.

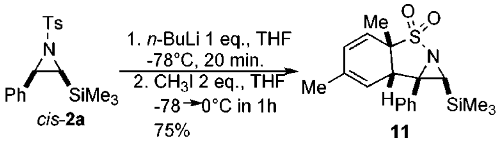
Ring opening of *cis*-**2a** was readily accomplished with a thiol and azide and led to single regioisomeric products in high yield (Scheme 3). In both cases ring opening occurred exclusively at the silicon-bearing carbon and not at the benzylic carbon. The greater activation by silicon over a phenyl group is particularly noteworthy, especially considering the greater steric bulk of the silyl group and the electronic activation by the phenyl group. However there is some precedence for such selectivity: α,*β*-alkylsilylepoxides undergo ring opening at the silicon-bearing carbon with high selectivity.[14]

Scheme 3. Ring Opening of *cis*-**2a** with Nucleophiles



Treatment of *cis*-**2a** with *n*-BuLi followed by quenching with iodomethane gave the tricyclic aziridine **11** in 75% yield as a single diastereoisomer (Scheme 4). Presumably this product arises from deprotonation of the benzylic carbon followed by intramolecular nucleophilic addition of the anion on the tosyl ring and subsequent methylation.[15] The structure of **11** was confirmed by X-ray analysis.[13] No products arising from deprotonation at the ring carbon atom α to the silicon were observed.

Scheme 4. Deprotonation and Cyclization of *cis*-**2a**



In summary, we have reported a simple and general synthesis of silyl-substituted aziridines and described several applications of these compounds in synthesis. In particular, high diastereoselectivity is obtained in the fluoride-promoted

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(12) Recently TBAT has been introduced and, being non-hygroscopic, non-basic, and soluble in a wide range of organic solvents, has proved to be very effective for Si−C bond cleavage. See: Pilcher, A. S.; DeShong, P. *J. Org. Chem.* **1996**, *61*, 6901.

(13) Full details will be reported elsewhere.

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(15) For a related example, see: Breternitz, H.-J.; Schaumann, E.; Adiwidjaja, G. *Tetrahedron Lett.* **1991**, *32*, 1299.

synthesis of aziridinemethanols, and complete regioselectivity is observed in ring opening with nucleophiles. Further studies on metalation of these aziridines are ongoing.

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Supporting Information Available: General experimental procedures for the reactions shown and data for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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