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Regioselective Nucleophilic Ring Opening of 2,3-Aziridino Alcohols

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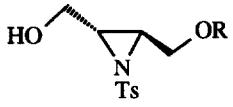
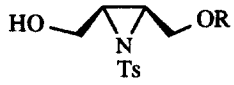
Abstract: *Nucleophilic ring-opening of trans and cis aziridino alcohols* **1** (**1'**) *and* **2** (**2'**) *by hydride- and by methyl-transfer reagents has been studied. In general, good to excellent C-2 selectivity was observed (the regioselectivity being better for the trans isomers) and the results can be interpreted in terms of directive effects exerted by the C-1 hydroxyl group. However, complete C-3 selectivity was observed in the reactions of* **1** *and* **2** *with* $AlMe_3$*, indicating a complexation effect of the C-4 benzyloxy group in those cases.*

We have previously described methods for the preparation of optically pure aziridino alcohols, and have used these compounds as starting materials for the enantioselective synthesis of β-lactam antibiotics[1,2]. Key steps in our routes to (+)-thienamycin and (+)-PS-5 were thus regioselective ring-openings of suitable aziridino alcohols by hydride-[1] and alkyl-transfer[2] reagents, respectively. In this paper, we present the results of a more systematic investigation of the regioselectivity of such ring-opening reactions.

The substrates chosen were the trans and cis aziridino alcohols **1** (**1'**) and **2** (**2'**) which provide variations in both aziridine ring stereochemistry and in the steric/electronic effects of the C-4 substituents. The N-tosyl protective group activates the aziridine ring towards nucleophilic attack, and also offers advantages in subsequent β-lactam ring-closure[2]. The substrates used in the present study were racemic, but materials of high enantiomeric purity are readily available from Sharpless-type epoxides as demonstrated previously[1,2] and in the following paper[3]. As in our preliminary study[1], the hydride-transfer reagents chosen were Red-Al, DIBAL, and $LiAlH_4$, while organocuprates[2] and trimethylaluminium reagents were used to introduce alkyl groups.





1 $R = CH_2C_6H_5$ **2**

1' $R = SiMe_2{}^tBu$ **2'**

The general scheme is shown below, ring-opening occurring with inversion and stereoisomeric aziridines yielding different pairs of diastereomeric products. In this study, only **1** and **2** were reacted with the hydrides, while all four aziridines were exposed to the methyl-transfer reagents; the latter reaction type is of greater interest, since the products still contain two stereogenic centres. The results with hydride reagents are shown in Table 1.

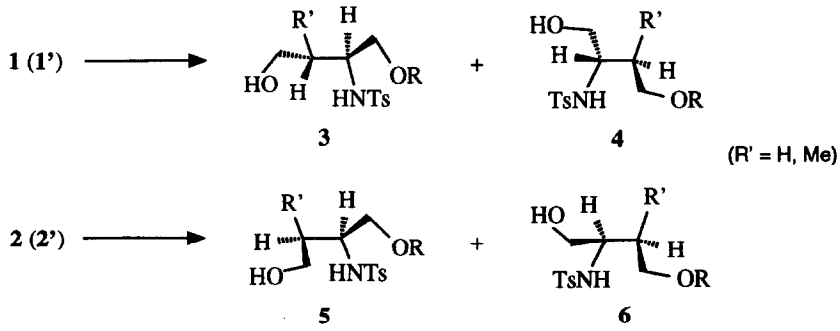


Table 1. Ring-opening of **1** *and* **2** *by hydride reagents.*

Entry	Substrate	Reagent/Conditions	Ratio[a] **3:4** (R' = H)	**5:6**	%Yield[b]
1.	**1**	Red-Al, THF, -78°C	>99 : 1		86
2.	**2**			>99 : 1	81
3.	**1**	$LiAlH_4$, THF, -20°C	>99 : 1		80
4.	**2**			>99 : 1	70
5.	**1**	DIBAL,THF,-78°C to RT	>99 : 1		30[c]
6.	**2**			58 : 42	19[c]
7.	**1**	DIBAL, C_6H_6, 0°C to RT	50 : 50		20[c]
8.	**2**			70 : 30	53[c]

(a) By high-field ^1H NMR spectroscopy. (b) After flash chromatography. (c) Reaction incomplete.

The reactions of **1** and **2** with Red-Al were highly regioselective, giving, within the limits of NMR spectroscopic detection, exclusively the products of ring-opening at C-2. This behaviour resembles that of the corresponding 2,3-epoxy alcohols[4a], and both Kishi[4b] and Viti[4c] have made the very reasonable suggestion that such reactions proceed *via* initial coordination of the reagent to the C-1

hydroxyl, followed by intramolecular delivery of hydride to the proximal (C-2) carbon. In the epoxy series, the Red-Al reactions were found to be C-2 selective irrespective of ring stereochemistry or the nature of the C-4 substituent; in the aziridine series, *en route* to (+)-thienamycin, we have shown[1] that Red-Al also attacks **1'** exclusively at the C-2 site to give the ring-opened product in 92% yield.

Excellent C-2 selectivity was also observed in the reactions of **1** and **2** with $LiAlH_4$ (Table 1, entries 3 and 4). This is again reminiscent of the results obtained with the corresponding epoxy alcohols[4a] (4:1 C-2 selectivity for trans, 11:1 for cis; THF, 0°C) but the selectivity is much better in the aziridine cases (>99:1 for both stereoisomers). The preference for C-2 attack can be rationalised in the same way as the results obtained with Red-Al, and the higher regioselectivity found for the aziridine series may be simply due to the fact that these reactions can be run at lower temperature (-20°C). Our experience with both epoxy alcohols and their N-tosyl aziridino counterparts indicates that the latter are generally more reactive towards nucleophiles; the aforementioned reactions with Red-Al, for example, were run at 0°C for the epoxy alcohols, while aziridines **1** and **2** react smoothly at -78°C.

The results obtained with DIBAL (Table 1, entries 5-8) are less coherent and more difficult to explain. The analogy with epoxy alcohols now seems less relevant, since such materials have been reported[4b] to undergo selective attack at C-3, the selectivity varying with temperature and solvent. Aziridines **1** and **2**, however, showed no such preference, the trans isomer being attacked exclusively at C-2 if the reaction is run in THF (entry 5). The cis isomer **2** was also opened predominantly at C-2 (in THF solution) but the selectivity was much poorer (entry 6). If DIBAL complexes to the C-1 hydroxyl (with evolution of H_2) subsequent delivery of hydride obviously can not be the type of intramolecular process suggested for the reactions of **1** and **2** with Red-Al and $LiAlH_4$. Switching the solvent to benzene (entries 7 and 8) led to a complete loss of selectivity in the reaction of **1**, but actually resulted in a moderate increase in the C-2 selectivity for the cis isomer **2**. For non-coordinating solvents such as benzene, it could be argued that complexation of the (Lewis acidic) reagent to the C-4 benzyloxy group could become important, thus promoting a competitive intramolecular attack at C-3 (Table 1, entry 7). However, this type of argument is apparently untenable as far as the cis isomer is concerned (entry 8). Although these results are obviously of mechanistic interest, the use of DIBAL was not further explored since these reactions were extremely sluggish and consequently less synthetically useful. A "C-3 selective" hydride reagent thus remains to be found for 2,3-aziridino alcohols.

Table 2. Ring-opening of **1** *and* **1'** *by methyl-transfer reagents.*

Entry	Substrate	Reagent/Conditions	Ratio[a] **3:4** (R' = Me)	%Yield[b]
1.	**1**	$LiMe_2Cu$, Et_2O,-20°C	>99 : 1	80
2.	**1'**		>99 : 1	98
3.	**1**	Li_2Me_2CuCN, THF,-20°C	92 : 8	81
4.	**1'**		>99 : 1	92
5.	**1**	$AlMe_3$, toluene, 75°C	<1 : 99	71
6.	**1'**		15 : 85	82

(a) By high field ^1H NMR spectroscopy. (b) After flash chromatography.

We next turned our attention to ring-opening reactions involving the transfer of alkyl groups. As mentioned above, this is synthetically more interesting since the products contain two contiguous stereocentres. The results with methyl-transfer reagents are shown in Tables 2 and 3.

The results for the trans isomers will be discussed first (Table 2). The reagents used were the Gilman cuprate, the Lipshutz cyanocuprate, and trimethylaluminium. In the course of our aziridine-based[2] synthesis of the β-lactam antibiotic (+)-PS-5 we found that cuprate reagents were highly selective for C-2 attack, and an obvious analogy can once more be drawn with the performance of the corresponding epoxy alcohols[5]: complexation of the reagent to the C-1 hydroxyl could allow for intramolecular methyl transfer, largely irrespective of the nature of the substituent on C-4 (*cf.* Table 2, entries 1-4). However, in the reaction with $LiMe_2Cu$, the N-tosyl aziridine **1** shows better regioselectivity than the epoxy analogue (for which C-2 selectivities of 10:1 and 6:1 have been reported by ourselves[6a] and by Roush[6b], respectively).

In contrast to the organocuprate reagents, trimethylaluminium gave good to excellent C-3 selectivity (Table 2, entries 5 and 6). Comparison of entries 1 and 5 thus shows that for the ring-opening of aziridine **1**, complete *regiocontrol* is easily achieved. We rationalise these results as follows. One equivalent of trimethylaluminium removes the hydroxyl proton to form an aluminium alcoholate, from which methyl-transfer is expected to be slower than from a trialkylaluminium species[7a,b]. A second equivalent of the reagent then forms a Lewis acid-base complex with the C-4 benzyloxy group, thus allowing for intramolecular methyl-transfer to C-3. The lower Lewis basicity[8] (and increased steric bulk) of the ^{t}butyldimethylsilyloxy group in **1'** would thus be expected to result in lower C-3 selectivity for this substrate, and this is what is observed in practice (Table 2, entry 6).

Once more, the N-tosyl aziridine **1** appears to afford superior regioselectivity than the epoxy analogue, for which *ca.* 5:1 C-3 selectivity ($AlMe_3$, CH_2Cl_2, 23°C) has been reported[6b]. In the case of epoxides, complexation of Lewis acidic reagents to the epoxide oxygen presumably plays an important role in determining regioselectivity[7a-d]; such complexation is less likely with the relatively electron-deficient nitrogen of the N-tosyl aziridines[9].

The analogous ring-opening reactions of the cis aziridines **2** and **2'** are shown in Table 3.

Table 3. Ring-opening of **2** *and* **2'** *by methyl-transfer reagents.*

Entry	Substrate	Reagent/Conditions	Ratio[a] **5:6** (R' = Me)	%Yield[b]
1.	**2**	$LiMe_2Cu$, Et_2O,-20°C	no reaction[c]	
2.	**2'**		78 : 22	87
3.	**2**	Li_2Me_2CuCN, THF,-20°C	79 : 21	73
4.	**2'**		88 : 12	68
5.	**2**	$AlMe_3$, toluene, 75°C	<1 : 99	92
6.	**2'**		33 : 66	60

(a) By high field ^{1}H NMR spectroscopy. (b) After flash chromatography. (c) Starting material recovered.

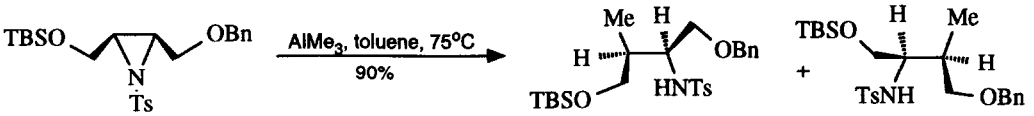
The benzyloxy-substituted cis aziridine **2** surprised us with its lack of reactivity towards lithiumdimethylcuprate - despite several attempts, the starting material was always near-quantitatively

recovered. While we have as yet no convincing explanation for this result, it may be recalled that the corresponding cis epoxy alcohol has also proved recalcitrant, a problem for which Tius[10] has provided a solution in the form of a copper-catalysed Grignard reaction; our own attempts[11] to apply this technique to **2** led only to the products of ring-opening by halide ions, accompanied by extensive decomposition.

The "higher order" cyanocuprates are generally regarded to be more reactive than the classical Gilman cuprates, and this is reflected in entry 3 of Table 3, although the regioselectivity is considerably poorer than that found for the trans isomer (Table 2, entry 3). Indeed, comparison of entries 1-4 of Tables 2 and 3 reveals a general trend of lower regioselectivity for the cis aziridines in their reactions with cuprate reagents. If complexation to the free hydroxyl is indeed important for the regiochemical outcome of the ring-opening reaction, it seems reasonable to assume that this event should be sterically hindered by the C-4 substituent in the cis isomers **2** and **2'**; the non-monomeric nature of the cuprates should also be kept in mind.

In view of the relatively poor performance of the cuprates, the results with $AlMe_3$ (Table 3, entry 5) were most gratifying - complete C-3 regioselectivity, combined with excellent chemical yield, just as observed for the trans isomer (Table 2, entry 5). An explanation similar to that advanced above for the reaction of **1** with $AlMe_3$ is thus reasonable, and further evidence for the role proposed for the benzyloxy substituent is provided by entry 6 of Table 3.

Finally, the importance of a free hydroxyl group in the reaction of **2** with $AlMe_3$ is demonstrated by the following result:

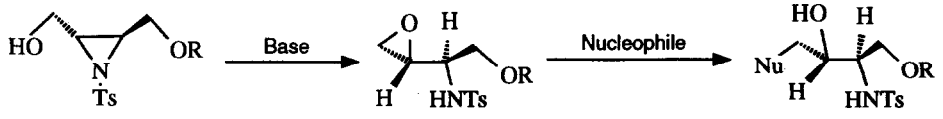


7 TBS = $SiMe_2{}^tBu$
Bn = $CH_2C_6H_5$

24 : 76

We have thus shown that high levels of C-2 or C-3 selectivity can be attained in the nucleophilic ring-opening of 2,3-aziridino alcohols, and it appears that the ability of the reagent to coordinate to the free hydroxyl, or to a relatively unhindered (and Lewis basic) C-4 substituent, is of importance in determining the site of nucleophilic attack. Many of the results can thus be interpreted in terms of initial coordination followed by intramolecular delivery of the nucleophile - a very simple mechanistic rationale which seems plausible, and may even have some predictive value. However, we are fully aware that the actual course of events is probably extremely complex and subject to very subtle steric and electronic effects. Cogent arguments in favour of intermolecular mechanisms can, of course, also be advanced[12].

Complementary methods for the introduction of substituents at C-1 *via* the aziridine version of the Payne rearrangement[13] shown below are currently being studied.



As noted in the introduction, enantiomerically pure aziridino alcohols are readily available[1,2], and the use of such materials in combination with the trialkylaluminium ring-opening methodology forms the basis of the route to 1β-methylcarbapenems described[3] in the following paper.

EXPERIMENTAL

The aziridines were prepared from the corresponding epoxides *via* previously described procedures[1,2]. The epoxides were themselves prepared *via* standard mCPBA epoxidation of the relevant mono-protected trans- or cis-2-butene-1,4-diols[14].

Data for **1**: ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 7.86 and 7.30 (each 2H, AA'BB', J_{AB}= 9 Hz; tosyl) partly overlapping 7.22 (5H, m; phenyl); 4.42 (2H, AB, J=12; benzyl); 4.12 (1H, ddd, J=14, 9, 3; C<u>H</u>OH); 3.96 (1H, ddd, J=14, 8, 5; C<u>H</u>OH); 3.70 (1H, dd, J=11, 4.5; C<u>H</u>OBn); 3.58 (1H, dd, J=11, 6; C<u>H</u>OBn); 3.25 (1H, ddd, J=6, 4.5, 4.5; aziridine); 3.06 (1H, ddd, J=8, 4.5, 3; aziridine); 2.69 (1H, dd, J=9, 5; O<u>H</u>); 2.42 (3H, s; Me). IR: 3500 cm^{-1} (b; OH); 1320 (s; sulfonamide); 1150 (s; sulfonamide). Anal. Calcd. for $C_{18}H_{21}NO_4S$: C, 62.22%; H, 6.09. Found: C, 62.17; H, 6.12.

For **1'**: ^{1}H NMR: 7.86 and 7.33 (each 2H, AA'BB', J_{AB}= 9; tosyl); 4.16 (1H, ddd, J=13.5, 9, 3; C<u>H</u>OH); 3.99 (1H, ddd, J=13.5, 8, 5; C<u>H</u>OH); 3.88 (1H, dd, J=11.5, 4; C<u>H</u>OSi); 3.62 (1H, dd, J=11.5, 6; C<u>H</u>OSi); 3.18 (1H, ddd, J=6, 4.5, 4; aziridine); 3.06 (1H, ddd, J=8, 4.5, 3; aziridine); 2.80 (1H, dd, J=9, 5; O<u>H</u>); 2.44 (3H, s; Me); 0.81 (9H, s; ^{t}Bu); -0.05 (3H, s; Si<u>CH</u>$_3$); -0.08 (3H, s; Si<u>CH</u>$_3$). IR: 3500 (b; OH); 1320 (s; sulfonamide); 1155 (s; sulfonamide); 1090 (s; OSi). Anal. Calcd. for $C_{17}H_{29}NO_4SSi$: C, 54.95%; H, 7.87. Found: C, 54.88; H, 7.82.

For **2**: ^{1}H NMR: 7.82 and 7.31 (each 2H, AA'BB', J_{AB}= 8; tosyl) partly overlapping 7.24 (5H, m; phenyl); 4.46 (2H, AB, J=12.5; benzyl); 3.73-3.58 (3H, unresolved m; C<u>H</u>$_2$OH and C<u>H</u>OBn); 3.52 (1H, dd, J=11, 6; C<u>H</u>OBn); 3.12 (2H, m, J_{cis}= 6.5; aziridine); 2.42 (3H, s; Me); 1.97 (1H, bt, J=7; O<u>H</u>). IR: 3500 (b; OH); 1330 (s; sulfonamide); 1160 (s; sulfonamide). Anal. Calcd. for $C_{18}H_{21}NO_4S$: C, 62.22%; H, 6.09. Found: C, 62.20; H, 6.11.

For **2'**: ^{1}H NMR (without TMS): 7.81 and 7.34 (each 2H, AA'BB', J_{AB}= 8; tosyl); 3.89 (1H, dd, J=11.5,4.8; C<u>H</u>OSi); 3.85-3.64 (2H, unresolved m; C<u>H</u>$_2$OH); 3.61 (1H, dd, J=11.5,6.4; C<u>H</u>OSi); 3.08 (2H, m, J_{cis}= 6.5; aziridine); 2.41 (3H, s; Me); 1.68 (1H, bm; O<u>H</u>); 0.82 (9H, s; ^{t}Bu); 0.00 (6H, s; $SiMe_2$). IR: 3500 (b; OH); 1320 (s; sulfonamide); 1150 (s; sulfonamide). Anal. Calcd. for $C_{17}H_{29}NO_4SSi$: C, 54.95%; H, 7.87. Found: C, 54.83; H, 7.91.

General procedures for ring-opening with hydride reagents. In all cases, the crude products were examined by ^{1}H NMR spectroscopy prior to chromatographic purification. NMR spectroscopic analysis of the purified materials indicated that the chromatographic step did not affect the product ratio. Product ratios and yields are shown in Table 1. *(a) With Red-Al.* A 0.1M solution of the aziridine (**1** or **2**) in dry THF was cooled, with stirring under N_2, to -78°C. A solution of Red-Al (from Aldrich, 3.5M in toluene, 2 equiv.) was then added dropwise *via* syringe. The reaction mixture was stirred at -78°C until TLC analysis indicated complete consumption of the substrate (usually *ca.* 30 min.). Water was then added to destroy excess reagent, the reaction mixture was allowed to reach room temperature, and ether was added to precipitate aluminates. The mixture was then filtered through Celite, and the filter-cake washed thoroughly with fresh ether. Removal of the volatiles from the combined filtrate and washings left a residue which was flash chromatographed on silica gel, using ether as eluent. Only one diastereomer could be detected by ^{1}H NMR spectroscopy.

Stereochemistry of the products. Note that for hydride ring-opening of **1** and **2**, the products **3** and **5** are identical; **4** and **6** are enantiomers (*i.e.* have identical NMR spectra under normal conditions).

Data for the major isomer **3/5** (R=$CH_2C_6H_5$; R'=H): ^{1}H NMR: 7.69 and 7.22 (each 2H, AA'BB', J_{AB}= 9; tosyl); 7.33 (2H, m; phenyl); 7.21 (3H, m; phenyl); 5.05 (1H, d, J=8.5; NH); 4.36 (2H, AB, J=13; benzyl); 3.84 (1H, bm; CHOH); 3.65 (1H, bm; CHOH); 3.57 (1H, m; methine); 3.31 (1H, dd, J=10, 3; CHOBn); 3.16 (1H, dd, J=10, 4.5; CHOBn); 2.41 (3H, s; Me); 2.27 (1H, bm, exchanges with D_2O; OH); 1.75 (2H, m; CH_2CH_2OH). The assignments were made on the basis of decoupling experiments, *e.g.* decoupling of the OH signal at δ 2.27 sharpened the multiplets at 3.84 and 3.65, while decoupling of the methylene multiplet at 1.75 changed the signals at 3.84 and 3.65 to a broadened AB system (J=12). IR: 3400 (s; OH); 3260 (s; NH); 1315 (s; sulfonamide); 1150 (s; sulfonamide). Anal. Calcd. for $C_{18}H_{23}NO_4S$: C, 61.87%; H, 6.63. Found: C, 61.76; H, 6.50.

(b) With $LiAlH_4$. The reaction was carried as described above, except that 2 equiv. of a 1M solution of $LiAlH_4$/THF (Aldrich) were used, and a reaction temperature of -20°C was maintained (reaction time 2-3 hours). Work-up and chromatography were performed as described above, and the same diastereomer of the product was isolated.

(c) With DIBAL (THF). The reaction was carried out as described under *(a)* except that 2 equiv. of a 1M solution of DIBAL/hexanes (Aldrich) were used, and the reaction temperature was allowed to slowly reach 0°C before addition of a further two equivalents of DIBAL. The reaction mixture was then allowed to reach room temperature and stirring was continued for 2 hours before methanol was added to quench excess reagent. The mixture was partitioned between ether and an aqueous solution of Rochelle salt. The ethereal layer was separated and the aqueous layer was back-extracted thrice with ether. The combined ethereal fractions were dried over Na_2SO_4, the solvents were removed, and the residue was examined by ^{1}H NMR spectroscopy. From the reaction of **1**, only one diastereomer of the product could be detected (see above for data) while **2** gave a chromatographically inseparable mixture of two diastereomers.

Selected ^{1}H NMR spectroscopic data for the minor isomer **4/6** (R=$CH_2C_6H_5$; R'=H): 7.74 (2H; lower-field half of AA'BB', J=9; tosyl); 5.46 (1H, d, J=7.2; NH); 4.45 (2H, AB, J=11; benzyl); 3.11 (2H, m; CH_2OBn); 2.43 (3H, s; Me); 1.78 (2H, m; CH_2CH_2OBn). Other signals overlapped strongly with those of the major isomer. The product ratio was most easily determined by integration of the well-separated NH doublets at δ 5.05 and 5.46.

(d) With DIBAL (benzene). The reaction was carried out as described above, except that the initial reaction temperature was 0°C, and a further two equivalents of DIBAL were added after the reaction mixture had reached 0°C. Excess of reagent was destroyed by addition of methanol, and further work-up was carried out as described under *(a)*.

Ring-opening with organocuprates. Solutions of $LiMe_2Cu$ in ether[15a] and Li_2Me_2CuCN in THF[15b] were prepared according to the literature. A solution of the relevant cuprate (3 equiv.) was stirred under nitrogen at -20°C and a solution of the substrate (1 equiv.) in ether or THF was added dropwise. The reaction mixture was then stirred at -20°C until TLC analysis indicated complete consumption of the starting material (usually a few hours; for substrates requiring longer reaction times, the flask was sealed

and stored in the freezer overnight). The reaction was quenched by addition of NH_4Cl.aq., the mixture was diluted with ether, and air was bubbled through the mixture until the solids had been digested. The organic layer was separated, dried over Na_2SO_4, and stripped down to give the crude product which was analysed by ^1H NMR spectroscopy. The crude material was purified by flash chromatography (silica gel, 70-75% ether/pentane) and re-analysed by ^1H NMR. This showed that chromatographic purification did not change the product ratios, except in the case of the reactions with **2'** (see below). Isolated yields and product ratios are shown in Tables 2 and 3.

Ring-opening with $AlMe_3$. A 0.1M solution of the aziridine in dry toluene was stirred under nitrogen at room temperature during the dropwise addition of a 2M solution of $AlMe_3$ in hexanes (from Aldrich, 6 equiv.). The resultant mixture was then heated to 75°C until reaction was complete according to TLC analysis (usually overnight). The reaction mixture was cooled to 0°C and diluted with ether before addition of NH_4Cl.aq. The resultant mixture was filtered through Celite, the organics were dried over Na_2SO_4, and the solvents were removed to give the crude product which was examined by ^1H NMR spectroscopy prior to flash chromatographic purification. Yields and product ratios are shown in Tables 2 and 3.

Stereochemistry of the products. (a) With the methyl-transfer reagents, the trans aziridine **1** (**1'**) gives rise to (2*S**,3*S**)-**3** and/or (2*S**,3*S**)-**4**, the former being the major product from the cuprate reactions (see Table 2, entries 1-4) while the latter is the major product from the reactions with $AlMe_3$ (Table 2, entries 5 and 6).

Data for (2*S**,3*S**)-**3** (R=$CH_2C_6H_5$, R'=Me): ^1H NMR: 7.64 and 7.22 (each 2H, AA'BB', J_{AB}= 8; tosyl); 7.32 (2H, m; phenyl); 7.20 (3H, m; phenyl); 5.16 (1H, d, J=8.5; NH); 4.33 (2H, AB, J=12.5; benzyl); 3.93 (1H, m; CHOH); 3.47 (1H, m; CHOH); 3.37 (1H, dd, J=11, 4; CHOBn); 3.24 (1H, m; CHN); 2.98 (1H, dd, J=11, 6; CHOBn); 2.49 (1H, m; OH); 2.41 (3H, s; tosyl Me); 1.88 (1H, m; $CHCH_3$); 0.90 (3H, d, J=7; Me). Assignments were made on the basis of decoupling experiments. IR: 3500 (b; OH); 3250 (b, NH); 1325 (s; sulfonamide); 1160 (s; sulfonamide). Anal. Calcd. for $C_{19}H_{25}NO_4S$: C, 62.78%; H, 6.93. Found: C, 62.71; H, 6.81.

For (2*S**,3*S**)-**3** (R=$SiMe_2{}^tBu$, R'=Me): ^1H NMR: 7.75 and 7.31 (each 2H, AA'BB', J_{AB}= 8.3; tosyl); 5.22 (1H, d, J=8.9; NH); 3.93 (1H, bdd, J=11, 3; CHOH); 3.53 (1H, dd, J=9, 1.5; CHOSi); 3.50 (1H, bdd, J=11, 4; CHOH); 3.19 (1H, m; CHN); 3.15 (1H, dd, J=9, 4.5; CHOSi); 2.62 (1H, b; OH); 2.44 (3H, s; tosyl Me); 1.83 (1H, m; $CHCH_3$); 0.89 (3H, d, J=7; Me); 0.83 (9H, s; ^{t}Bu); -0.03 (3H, s; SiMe); -0.04 (3H, s; SiMe). IR: 3500 (b; OH) overlapping 3300 (b; NH); 1310 (s; sulfonamide); 1160 (s; sulfonamide); 1085 (s; OSi). MS: m/z 330 (M-^{t}Bu, 15%); 91(90%); 75(100%).

For (2*S**,3*S**)-**4** (R=$CH_2C_6H_5$, R'=Me): ^1H NMR: 7.74 and 7.28 (each 2H, AA'BB', J_{AB}= 7.5; tosyl) partly overlapping 7.35 (5H, m; phenyl); 5.60(1H, d, J=7.5; NH); 4.44 (2H, s, benzyl); 3.49 (1H, m, CHOH); 3.38 (1H, dd, J=10, 3.5; CHOBn); 3.34-3.25 (2H, m; CHOH, CHOBn); 3.19 (1H, m; CHN); 3.06 (1H, dd, J=9, 4.5; OH); 2.41 (3H, s; tosyl Me); 1.95(1H, m; $CHCH_3$); 0.84 (3H, d, J=7; Me).

Most of the signals for (2*S**,3*S**)-**4** (R=$SiMe_2{}^tBu$, R'=Me) overlapped or coincided with those of the regioisomer, **3**. The product ratio in Table 2, entry 6 was determined by integration of the well-separated NH doublets at δ 5.81 (from **4**) and 5.22 (from **3**).

Stereochemistry (b). With the methyl-transfer reagents, the cis aziridine **2** (**2'**) gives rise to (2*R**,3*S**)-**5** and/or (2*R**,3*S**)-**6**, the former being the major product from the successful cuprate reactions (see Table 3, entries 2-4) while the latter is the major product from the reactions with $AlMe_3$ (Table 3, entries 5 and 6).

Data for (2*R**,3*S**)-**5** (R=$CH_2C_6H_5$, R'=Me): ^{1}H NMR: 7.70 (2H, AA' portion of AA'BB', J_{AB}= 8; tosyl); 7.30-7.12 (7H, m; tosyl, phenyl); 5.08 (1H, d, J=8; NH); 4.27 (2H, AB, J=13; benzyl); 3.63-3.45 (3H, m; CH_2OH, CHN); 3.30 (1H, dd, J=11, 3.5; CHOBn); 3.12 (1H, dd, J=11, 6; CHOBn); 2.72 (1H, b; OH); 2.40 (3H, s; tosyl Me); 1.90 (1H, m; $CHCH_3$); 0.80 (3H, d, J=7; Me). This material could not be separated from its regioisomer **6** (see below). The product ratio shown in entry 3 of Table 3 was determined by integration of the NH doublets, the benzylic AB multiplets, and the methyl doublets.

(2*R**,3*S**)-**5** (R=$SiMe_2{}^t$Bu, R'=Me) could be partially separated from its regioisomer by careful flash chromatography. Data for the pure isomer **5**: ^{1}H NMR: 7.76 and 7.30 (each 2H; AA'BB', J_{AB}= 8; tosyl); 4.95 (1H, d, J=9; NH); 3.56 (1H, m; CHOH); 3.53-3.43 (2H, m; CHOH, CHN) partly overlapping 3.42 (1H, dd, J=11, 3; CHOBn); 3.23 (1H, dd, J=11, 6; CHOBn); 2.71 (1H, b; OH); 2.42 (3H, s; tosyl Me); 1.87 (1H, m; $CHCH_3$); 0.81 (9H, s; ^{t}Bu); 0.79 (3H, d, J=7; Me); -0.04 (3H, s; SiMe); -0.09 (3H, s; SiMe). Assignments made on the basis of decoupling experiments.

For (2*R**,3*S**)-**6** (R=$CH_2C_6H_5$, R'=Me): ^{1}H NMR: 7.73 (2H, AA' portion of AA'BB', J_{AB}= 8; tosyl); 7.40-7.25 (7H, m; tosyl, phenyl); 5.49 (1H, d, J=8; NH); 4.44 (2H, AB, J=14; benzyl); 3.58 (1H, m; CHOH); 3.49 (1H, dd, J=10, 3.5; CHOBn); 3.28 (1H, dd, J=10, 7; CHOBn) partly overlapping 3.24 (1H, m; CHOH); 3.18 (1H, m; CHN); 2.98 (1H, dd,J=9.5, 4; OH); 2.40 (3H, s; tosyl Me); 1.95 (1H, m; $CHCH_3$); 0.90 (3H, d, J=7; Me).

For (2*R**,3*S**)-**6** (R=$SiMe_2{}^t$Bu, R'=Me): selected ^{1}H NMR data: 5.67 (1H, d, J=7.5; NH); 3.66 (1H, dd, J=10.5, 2.9; CHO); 3.18 (1H, m; CHN); 0.89 (9H, s; ^{t}Bu); 0.06 (6H, s; $SiMe_2$). The other signals overlapped or coincided with those of the regioisomer **5**. The product ratios shown in entries 2,4, and 6 of Table 3 were determined by integration of the NH doublets and the $SiMe_2$ singlets.

Compound **7** was prepared from **2** according to a standard procedure[16a]. The reaction of **7** with $AlMe_3$ was carried out according to the general procedure described above and gave a 90% yield of a crude product which was desilylated[16b] to give a 24:76 mixture (^{1}H NMR analysis) of **5** and **6** (R=$CH_2C_6H_5$, R'=Me).

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