Aza-Payne Rearrangement of Activated 2-Aziridinemethanols and 2,3-Epoxy Amines under Basic Conditions

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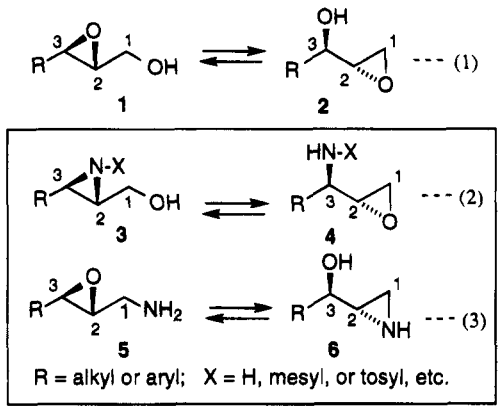
An aza-Payne rearrangement of activated 2-aziridinemethanols with *t*-BuOK, NaH, or KH at near 0 °C in common solvents such as THF, toluene, 1,2-dimethoxyethane, 1,4-dioxane, or a mixed solvent of THF-HMPA followed by quenching at −78 °C gives the corresponding epoxysulfonamides. Exposure of *N*-tosyl-(2*S*)-azetidinemethanol (**36**) and *N*-tosyl-(*S*)-prolinol (**37**) to NaH or KH in dichloromethane yielded only the respective dimeric compounds that resulted by joining 2 equiv of reactant through a methylene group. Reaction of *N*-tosyl-(2*S*,3*S*)-3-methyl-2-aziridinemethanol (**9**) and its (2*R*,3*S*)-isomer **23** with Gilman reagents (R_2CuLi; R = Me and Bu) or "higher order" cuprates [$R_2Cu(CN)Li_2$; R = Me and Bu] yielded the two expected aziridine ring-opening products. In sharp contrast, treatment of **9** and **23** with "lower order" cuprates afforded rearrangement-opened products. Thus, if the nucleophile is highly reactive, then the expected nucleophilic ring opening of the aziridine predominates. However, if the nucleophile is less reactive, then it becomes possible to cleave the resulting rearranged epoxide. Upon exposure of 2,3-epoxy amines to an equimolar mixture of *t*-BuOK–*n*-BuLi in a mixed solvent of THF and *n*-hexane at −78 °C, the equilibrium lies exclusively toward the hydroxy aziridine forming direction.

Since the discovery of the Sharpless asymmetric epoxidation of allylic alcohols,[1] the selective nucleophilic ring opening at the C-1 position of reactive terminal epoxides **2** that resulted from the Payne rearrangement[2] of primary 2,3-epoxy alcohols **1** in basic media has become an important procedure for the synthesis of polyfunctional compounds (Scheme 1, eq 1).[3] One important aspect of the Payne rearrangement is that the reaction

Scheme 1



is usually stereospecific, proceeding with inversion of configuration at the C-2 carbon of the epoxide ring via an S_N2 mechanism.[2,3]

On the other hand, aziridine-ring-bearing compounds are often vital structural units of biologically active molecules.[4] The importance of chiral *N*-tosylaziridines as key intermediates for the synthesis of various types of compounds has focused widespread attention on these

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compounds.[5,6] Recently, as shown in eqs 2 and 3 (Scheme 1), the aza-Payne rearrangement of aziridinemethanols **3** and 2,3-epoxy amines **5** has received much interest in connection with the synthesis of bioactive compounds.[7]

Under basic conditions, the relative portions of the 2-aziridinemethanols **3** and the epoxy amines **4** would be substrate as well as reaction condition dependent (Scheme 1, eq 2, X = Ts). However, conflicting experimental evidence for the direction of the aza-Payne rearrangement has appeared recently. Some reactions of epoxy sulfonamides **4** (X = Ts) have been reported to produce 2-aziridinemethanols **3** under basic conditions.[7b] In contrast, in some *N*-*p*-tosyl-2-aziridinemethanols **3**, the equilibrium lies exclusively toward the opposite direction, yielding epoxy *N*-tosylamides **4** under basic conditions.[8,9] Furthermore, epoxy amines **5** have been reported to yield hydroxy aziridines **6** in the presence of Lewis acids such as BF_3,[7a] Me_3Al,[7c] $Ti(OPr^i)_4$,[7d] and TMSOTf[7e] (Scheme 1, eq 3).

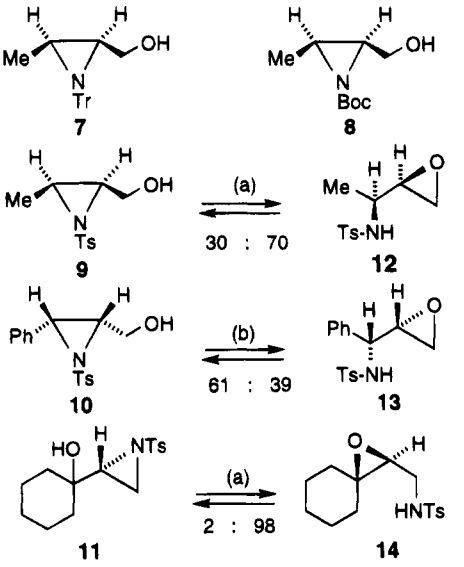
There have been no systematic investigations of this phenomenon, and the problem of delineating the factors which are responsible for controlling the direction of the aza-Payne rearrangement remains a topics that continues to attract much attention. We therefore examined the equilibrium of the aza-Payne rearrangement (**3** ⇌ **4** and **5** ⇌ **6**) by chemical and theoretical studies in simple systems under basic conditions.[10] Herein also presents an unprecedented reaction (an aza-Payne rearrangement-opening reaction) of *N*-tosyl-2-aziridinemethanols with "lower order" cyanocuprates.

(1) The Aza-Payne Rearrangement of 2-Aziridinemethanols. The requisite optically pure α-amino acid- and amino alcohol-derived 2-aziridinemethanols **7**–**10** (Scheme 2), **15** (Scheme 3), **17**, **19**, **21**, **23**, **25**, and **27** (Scheme 4) were readily prepared following literature procedures.[11] Other substrates **11**, **29**, **31**, and **33** (Schemes 2 and 5) used in this section were prepared by *N*-tosylation of hydroxy aziridines noted in section 3 (see supplementary material).

It has been well documented that the Payne rearrangement of 2,3-epoxy alcohols is carried out in aqueous sodium hydroxide and results in an equilibrium mixture of the starting 2,3-epoxy alcohol and the isomeric 3-hydroxy 1,2-epoxide (Scheme 1, eq 1).[2a] We initiated our study on the analogous aza-Payne rearrangement to determine the scope of the reaction with respect to *N*-protecting or activating groups on the nitrogen atom. Not unexpectedly, whereas exposure of *N*-tritylaziridine **7** to an aqueous sodium hydroxide solution in the presence of *tert*-butyl alcohol as cosolvent [2a] at 0 °C for 18 h resulted in recovered unchanged starting material, *N*-Boc-aziridine **8** yielded a complex mixture of products under the same conditions.[9]

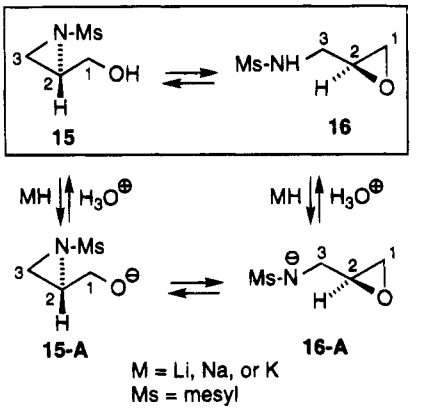
It therefore seemed that activation by the introduction of a strong electron-withdrawing group on the nitrogen atom of the aziridine was desired. The term "activated aziridines" for aziridines that easily undergo nucleophilic ring opening in the absence of a positive charge on the nitrogen atom has been introduced by Ham.[12] The *p*-tosyl or methanesulfonyl (mesyl) group serves as an effective activating group.[13] In fact, as shown in Scheme 2, treatment of *N*-tosyl-2-aziridinemethanol (**9**) under the same conditions as noted above, produced a 3:7 equilibrium mixture of **9** and a rearranged product **12**. Similarly, activated aziridine **10** yields a 61:39 equilibrium

Scheme 2



(a) 0.36 *N*-NaOH in *t*-BuOH-H_2O (2:5), 0 °C, 18 h.
(b) 0.28 *N*-NaOH in *t*-BuOH-H_2O (4:5), 0 °C, 18 h.

Scheme 3



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(8) Kawabata, T.; Kiryu, Y.; Sugiura, Y.; Fuji, K. *Tetrahedron Lett.* **1993**, *34*, 5127.

(9) The Payne rearrangement of a primary 2,3-epoxy alcohol to a secondary 1,2-epoxy alcohol usually requires basic aqueous medium. This requirement places a serious restriction on the types of nucleophilic agents which may be used in the reaction.

(10) Although details are unclear, for a report on intramolecular oxirane ring openings involving alkoxide attack on the unprotonated epoxide, see: Na, J.; Houk, K. N.; Shevlin, C. G.; Janda, K. D.; Lerner, R. A. *J. Am. Chem. Soc.* **1993**, *115*, 8453.

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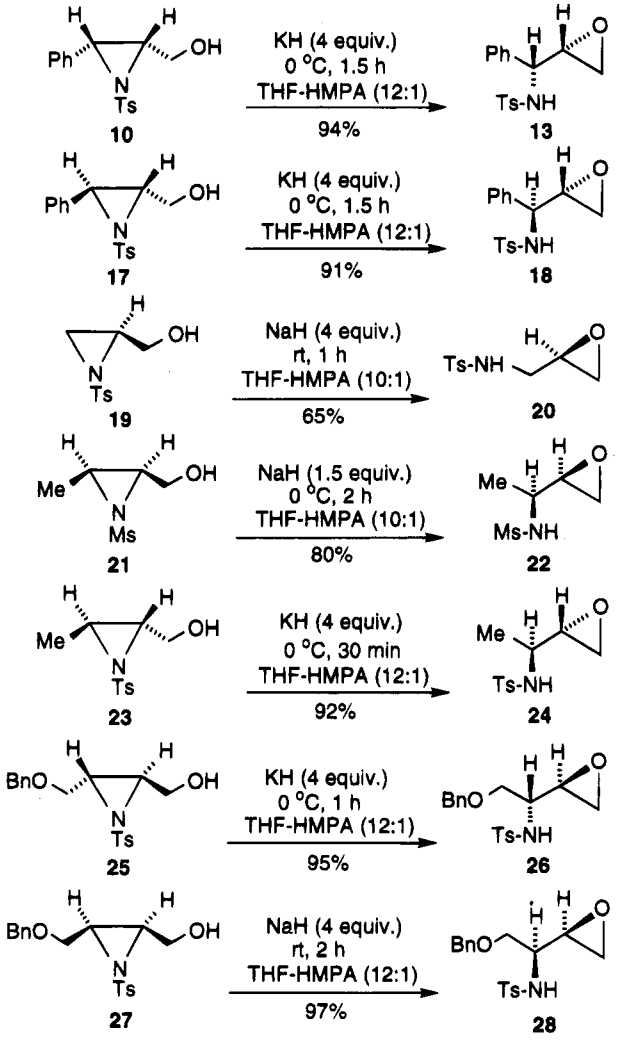
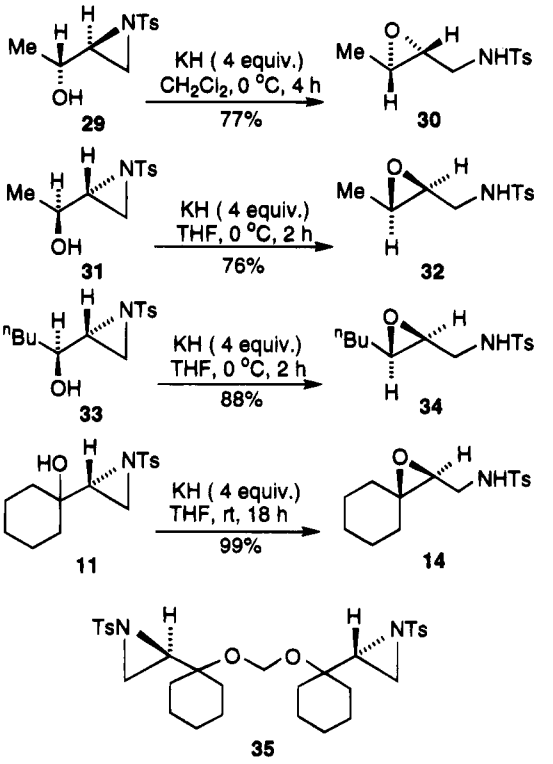
Scheme 4



Abbreviations: Ms = mesyl; Ts = tosyl; Bn = benzyl

Scheme 5



mixture of **10** and epoxy sulfonamide **13**. Much higher selectivity (**11**:**14** = 2:98) is found with activated aziridine **11** in which there is branching at the hydroxy-bearing carbon. From the results in Scheme 2 it is apparent that the relative portions of the 2-aziridinemethanols (**9**–**11**) and epoxy sulfonamides (**12**–**14**) at equilibrium are highly structure dependent. Consequently, the preparative value of the aza-Payne rearrangement under aqueous alkaline conditions is rather limited due to its reversible nature.

The aqueous conditions preclude the use of many synthetically important organometallic nucleophiles such as organocopper reagents. Under basic conditions in *an aprotic solvent*, would the oxa anion **15-A** of *N*-mesyl-2-aziridinemethanol (**15**) or the aza anion **16-A** of epoxy sulfonamide **16** (Scheme 3) be expected to be the more stable anion? In order to gain an understanding of the direction of the aza-Payne rearrangement of activated 2-aziridinemethanols, we have undertaken *ab initio* molecular orbital calculations.[14]

Both theoretical and experimental aspects of this study were carried out with *N*-mesyl-2-aziridinemethanol (**15**, Scheme 3). The geometries of the reactant oxa anion **15-A** of **15**, the transition state **TS**, and the product aza anion **16-A** of **16** were located with *ab initio* calculations involving full optimizations with the RHF/3-21+G* basis set,[14,15] followed by a single-point energy evaluation at the MP2/6-31+G* level. The optimized reactant oxa anion, the transition state, and the product aza anion geometries are shown in Figure 1, and total and relative energies are summarized in Table 1.

The product aza anionic energy minimum **16-A** was predicted to be approximately 18.6 kcal mol^{-1} lower in energy than the reactant oxa anionic energy minimum **15-A** at the RHF/3-21+G* level. A comparable result was obtained at the MP2/6-31+G* level as shown in Table 1. Therefore, formation of the epoxy sulfonamide **16** could be expected to predominate by treatment of **15** with a base, such as NaH or KH followed by quenching of the reaction mixture at low temperature.[16]

In actuality, the *N*-mesyl-2-aziridinemethanol (**15**) did give the rearranged product **16** in 55% isolated yield upon exposure to NaH (1.3 equiv) in a mixed solvent of THF-HMPA (12:1) at 20 °C for 45 min followed by quenching

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(14) All *ab initio* calculations were performed using the program GAUSSIAN 92 on a CRAY Y-MP2E/264 at the Supercomputer Laboratory, Institute for Chemical Research, Kyoto University. GAUSSIAN 92, Revision C: Frisch, M. J.; Trucks, G. W.; Head-Gordon, M.; Gill, P. M. W.; Wong, M. W.; Forseman, J. B.; Johnson, B. G.; Schlegel, H. B.; Robb, M. A.; Replogle, E. S.; Gomperts, R.; Andres, J. L.; Raghavachari, K.; Binkley, J. S.; Gonzalez, C.; Martin, R. L.; Fox, D. J.; Defrees, D. J.; Baker, J.; Stewart, J. J. P.; Pople, J. A. Gaussian Inc., Pittsburgh, PA, 1992.

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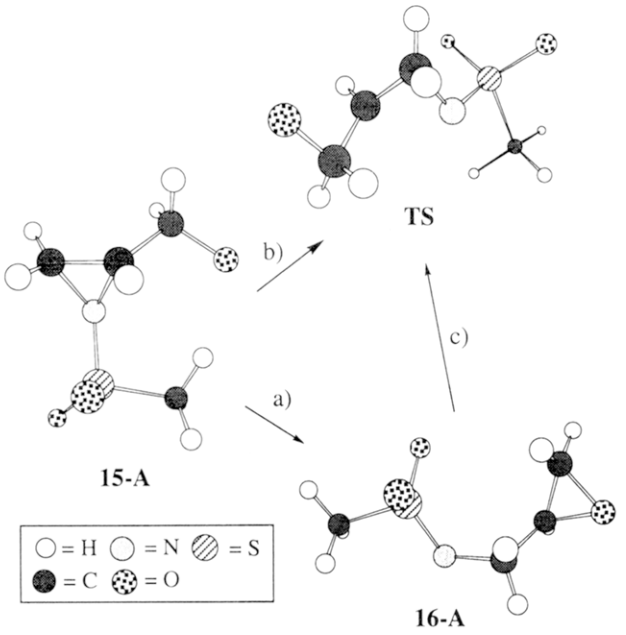


Figure 1. RHF/3-21+G* optimized geometries: **15-A**, the reactant oxa anionic energy minimum originating from **15** through deprotonation; **TS**, the transition structure; **16-A**, the product aza anionic energy minimum originating from **16** through deprotonation. (a) $\Delta E = -18.59$ kcal/mol; (b) $\Delta E = 9.12$ kcal/mol; (c) $\Delta E = 27.71$ kcal/mol. (From relative energies at the MP2/6-31+G* level, see Table 1.)

Table 1. Total and Relative Energies of the Critical Points[a]

	RHF/3-21+ G* (MP2/6-31+G*)[b]	
geometry	E[c]	ΔE[d]
reactant oxa anion **15-A** of **15**	−828.390 536	0.0
	(−833.947 846	0.0)
transition state **TS**	−828.376 001	9.12
	(−833.929 565	11.47)
product aza anion **16-A** of **16**	−828.420 167	−18.59
	(−833.973 692	−16.22)

[a] The character of all energy minima and transition states was confirmed with calculation of force constant analyses at the Hartree−Fock level. [b] Computed at the RHF/3-21+G* optimized geometries. [c] Hartree. [d] kcal mol^{-1}. Energies are relative to the lowest energy reactant anion.

at −78 °C. We were unable to detect unreacted starting **15** by ^{1}H NMR analysis. The epoxy sulfonamide **16** can be purified by flash chromatography, but with an inevitable significant loss of product. Consequently, the low yield could be attributed to both water solubility and instability of product **16**.

In order to gain suitable reaction conditions for the rearrangement, the influences of base, solvent, and reaction temperature were studied in more detail with readily available *N*-tosyl-2-aziridinemethanol (**9**) as the test starting material (Table 2). Although all controlling factors in the rearrangement reaction are not clear, the following conclusions concerning the direction of the rearrangement may be drawn:

(1) Bases such as *t*-BuOK, NaH, or KH gave satisfactory results (entries 4, 8, 9, and 11−16, Table 2). LDA, DBU, and *n*-BuLi are inappropriate for clean and efficient rearrangements (entries 1−3, Table 2).

(2) THF or a mixed solvent of THF and HMPA is the solvent of choice. Although rearrangement of **9** with NaH in THF alone is rather sluggish, acceleration of the rearrangement is accomplished by the addition of HMPA (THF:HMPA = 12:1) (entry 9, Table 2). Toluene, dichloromethane (CH_2Cl_2), dimethoxyethane (DME), and 1,4-dioxane could be used equally well for the reaction of **9** with KH (entries 13−16, Table 2). However, as discussed later, care must be taken to avoid the dimerization in the reactions of the activated aziridine **11** (possessing a tertiary hydroxy group) with NaH or KH in CH_2Cl_2.

(3) The rearrangement temperature should be carefully controlled. For example, while **9** reacted with KH at −20 °C after 2 h to afford only the rearranged product **12** in 96% isolated yield (entry 11), treatment of the same substrate **9** at −78 °C for 5 h led to complete recovery of unchanged starting material (entry 10). Although the rearrangement rates are dependent upon the base used, the reaction normally proceeds completely in the direction of epoxy sulfonamide **12** at 0 °C or rt (ca. 25 °C).

The reaction rate using KH as a base is qualitatively enhanced compared to the rearrangement with NaH. For example, treatment of **9** with NaH at 0 °C for 5 h yields the epoxy sulfonamide **12** in 77% yield, while exposure of **9** to KH at 0 °C for 30 min affords **12** in 96% isolated yield (compare, entries 7 and 12, Table 2).

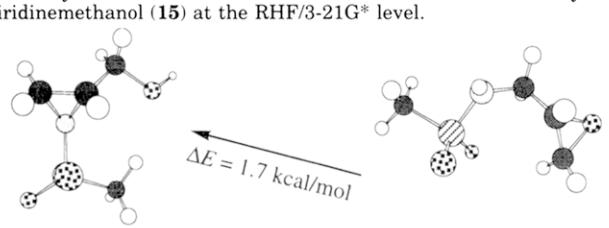
Results obtained for seven different activated aziridines (**10**, **17**, **19**, **21**, **23**, **25**, and **27**) having primary hydroxymethyl groups at the C-2 position of the aziridine ring are summarized in Scheme 4. All aziridines afforded the corresponding rearranged products in high isolated yields by exposure to either NaH or KH followed by quenching. In a similar manner, as shown in Scheme 5,

Table 2. Aza-Payne Rearrangement of (2*S*,3*S*)-3-Methyl-*N*-tosyl-2-aziridinemethanol 9 To Yield Epoxy Sulfonamide 12[a]

entry	base	solvent	T °C (time)	yield of **12**%[b]
1	LDA (4 equiv)	THF	rt (1 h)	0[c]
2	DBU (5 equiv)	THF-HMPA[d]	rt (3 h)	0
3	*n*-BuLi (1.2 equiv)	THF-HMPA[d]	0 (18 h)	17
4	*t*-BuOK (1.2 equiv)	THF-HMPA[d]	0 (2 h)	99
5	NaH (0.3 equiv)	THF	rt (5 h)	35
6	NaH (4 equiv)	THF	−20 (4 h)	<1
7	NaH (4 equiv)	THF	0 (5 h)	77
8	NaH (4 equiv)	THF	rt (2 h)	82
9	NaH (4 equiv)	THF-HMPA[e]	rt (2 h)	92
10	KH (4 equiv)	THF	−78 (5 h)	<1
11	KH (4 equiv)	THF	−20 (2 h)	96
12	KH (4 equiv)	THF	0 (30 min)	96
13	KH (4 equiv)	toluene	0 (1 h)	99
14	KH (4 equiv)	CH_2Cl_2	0 (1 h)	99
15	KH (4 equiv)	DME	0 (2 h)	99
16	KH (4 equiv)	1,4-dioxane	rt (30 min)	99

[a] In entries 4, 8, 9, and 11−16, the starting material **9** could not be detected by HPLC analysis of the reaction mixture. [b] Isolated and unoptimized yields of epoxy sulfonamide **12**. [c] A complex mixture of products was obtained. [d] THF−HMPA = 10:1. [e] THF−HMPA = 12:1.

(16) The energy minimum of epoxy sulfonamide **16** was predicted to be only 1.7 kcal mol^{-1} lower than the minimum of *N*-mesyl-2-aziridinemethanol (**15**) at the RHF/3-21G* level.



3-21G* optimized structure of **15**. E(RHF) = - 828.60697 A.U.

3-21G* optimized structure of **16**. E(RHF) = - 828.60963 A.U.

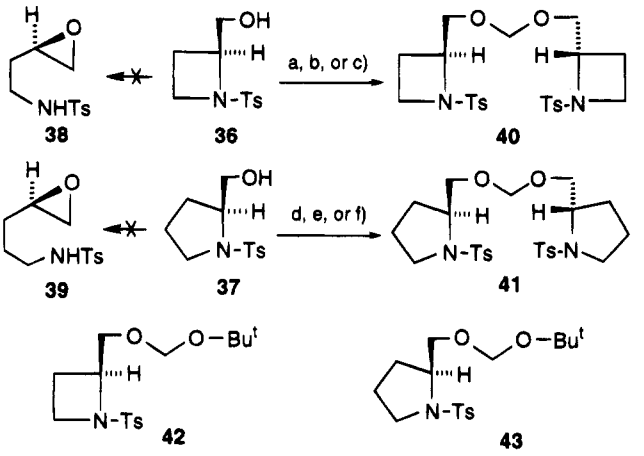
activated aziridines (**29**, **31**, **33**, and **11**) having a secondary or tertiary hydroxymethyl group at the C-2 position react equally well to yield respective epoxy sulfonamides in high isolated yields. Space restrictions prevent detailed descriptions of all results for these rearrangements; however, it is readily apparent that the aziridine alcohols listed in Scheme 5 give very good results. In all the rearrangements listed in Schemes 4 and 5, no evidence for unrearranged starting material was detected by HPLC analysis of the crude reaction product(s). Thus, the reaction appears to be quite general for activated aziridines possessing wide structural variety, giving isolated yields which are good to excellent. In addition, the reversible nature of the reaction in protic solvents as shown in Scheme 2 can be altered to an essentially irreversible process in aprotic solvents.

It should be clearly noted that the less reactive aziridine **11** (Scheme 5), possessing a tertiary hydroxy group, rearranged slowly in THF in the presence of KH to give solely the epoxy sulfonamide **14**. However, similar treatment with KH (4 equiv) in CH_2Cl_2 at room temperature for 18 h unexpectedly provided a mixture of **14** (85% yield) and a dimeric compound **35** (4.4% yield) rather than pure **14**. Consequently, despite the slow rate of rearrangement in THF, this is the solvent of choice for the reaction of **11**. The dimeric structure assigned for **35** rested strongly on MS and NMR (NOESY, $^1H-^1H$ COSY, $^{13}C-^1H$ COSY) spectral analyses. This was the only reaction of aziridinemethanols in which we observed formation of the dimeric compound.

After the useful reaction conditions for the synthesis of epoxy sulfonamides from aziridinemethanols were established, the use of CH_2Cl_2 as a solvent for the reaction of *N*-tosyl-(2*S*)-azetidinemethanol **36** and *N*-tosyl-(2*S*)-prolinol **37** in the presence of NaH or KH was briefly investigated in connection with the above mentioned dimeric compound **35**. The required chiral four- and five-membered heterocycles **36** and **37** were readily prepared in high yields from (2*S*)-azetidinecarboxylic acid and (*S*)-proline via a routine sequence of reactions (see supplementary material). Both **36** and **37** were reacted in the presence of KH or NaH in CH_2Cl_2 to afford solely the corresponding dimeric compounds **40** and **41** in high yields (Scheme 6). Not unexpectedly, we were unable to detect a rearrangement product **38** or **39** by HPLC analysis. On the other hand, if the reaction is performed in the presence of *t*-BuOK, a considerable amount of a cross-coupled product **42** is obtained. Similarly, the treatment of **37** with *t*-BuOK in CH_2Cl_2 yielded a separable 82:17 mixture of **41** and **43**. This demonstrates that a small change in the ring size of azacycloalkanes alters the course of the reaction (compare Schemes 4 and 5 with Scheme 6).

(2) Organocopper-Mediated Reaction of *N*-Tosyl-3-methyl-2-aziridinemethanols (9 and 23). Unprecedented Aza-Payne Rearrangement-Opening Reactions with "Lower Order" Alkylcyanocuprates. Aziridines undergo ring-opening reactions with various kinds of nucleophiles such as organocopper reagents,[17] Grignard reagents,[18] heteroatomic nucleophiles,[19] cyanotrimethylsilane–lanthanide tricyanide,[20] acetone cyanohydrine–lanthanide alkoxide,[21] and trialkylaluminum[6a] to give *N*-substituted primary or secondary amines. We have briefly examined the ring-opening reactions of activated 2-aziridinemethanols possessing stereochemically well-defined structures with organocopper reagents

Scheme 6



Bases and conditions: a) KH, 0 °C, 3 h, **40** (84%); b) NaH, rt, 36 h, **40** (67%); c) *t*-BuOK, rt., 1 h, **40** (75%) and **42** (7.7%); d) KH, 0 °C, 3 h, **41** (95%); e) NaH, rt., 36 h, **41** (82%); f) *t*-BuOK, rt, 1 h, **41** (82%) and **43** (17%).

in connection with our studies of amino alcohols and peptide isosteres.[22,23]

Reaction of *N*-tosyl-(2*S*,3*S*)-2-aziridinemethanol (**9**) with Gilman reagent, $Me_2CuLi{\cdot}2LiBr{\cdot}LiI$, initially at −78 °C then at rt for 18 h in ether, yielded a mixture (51:49) of the two expected ring-opened products **44** and **45** in 94% combined yield (entry 1, Table 3). A comparable result was obtained by treatment of **9** with the "higher order" (HO) cyanocuprate $Me_2Cu(CN)Li_2{\cdot}2LiBr$ (entry 2, Table 3).[24] Although reagents prepared from CuCN and 2 equiv of RLi could be represented as $R_2CuLi{\cdot}LiCN$ by analogy to Gilman reagents $R_2CuLi{\cdot}LiI$ for the cuprates prepared from CuI and 2 equiv of RLi as suggested Dr. Bertz and others,[24g-i] the constitutional formula $R_2Cu(CN)Li_2$[24a-f] has been used throughout this paper as a matter of convenience. The absolute configuration at the chiral carbon center in **44** was substantiated by comparison of **44** with an authentic sample prepared by diisobutylaluminum hydride reduction of methyl L-*N*-*p*-tosylvalinate (**46**). The structure and stereochemistry of **45** was established as follows. Treatment of **45** with diethyl azodicarboxylate–triphenylphosphine in THF gave the

(17) (a) Eis, M. J.; Ganem, B. *Tetrahedron Lett.* **1985**, *26*, 1153. (b) Duréault, A.; Tranchepain, I.; Greck, C.; Depezay, J. C. *Tetrahedron Lett.* **1987**, *28*, 3341. (c) Baldwin, J. E.; Adlington, R. M.; O'Neil, I. A.; Schofield, C.; Spivey, A. C.; Sweeney, J. B. *J. Chem. Soc., Chem. Commun.* **1989**, 1852. (d) Tanner, D.; Birgersson, C.; Dhaliwal, H. K. *Tetrahedron Lett.* **1990**, *31*, 1903. (e) Tanner, D.; He, H. M.; Somfai, P. *Tetrahedron* **1992**, *48*, 6069.

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(19) Stamm, H.; Weiss, R. *Synthesis* **1986**, 392. Dellaria, J. F., Jr.; Sallin, K. J. *Tetrahedron Lett.* **1990**, *31*, 2661. Baldwin, J. E.; Adlington, R. M.; Robinson, N. G. *J. Chem, Soc., Chem. Commun.* **1987**, 153.

(20) Matsubara, S.; Kodama, T.; Utimoto, K. *Tetrahedron Lett.* **1990**, *31*, 6379.

(21) Ohno, H.; Mori, A.; Inoue, S. *Chem. Lett.* **1993**, 975.

(22) (a) Fujii, N.; Habashita, H.; Shigemori, N.; Otaka, A.; Ibuka, T.; Tanaka, M.; Yamamoto, Y. *Tetrahedron Lett.* **1991**, *32*, 4969. (b) Ibuka, T.; Yoshizawa, H.; Habashita, H.; Fujii, N.; Chounan, Y.; Tanaka, M.; Yamamoto, Y. *Tetrahedron Lett.* **1992**, *33*, 3783. (c) Wada, M.; Doi, R.; Hosotani, R.; Ibuka, T.; Habashita, H.; Nakai, K.; Fujii, N.; Imamura, M. *Pancreas*, in press.

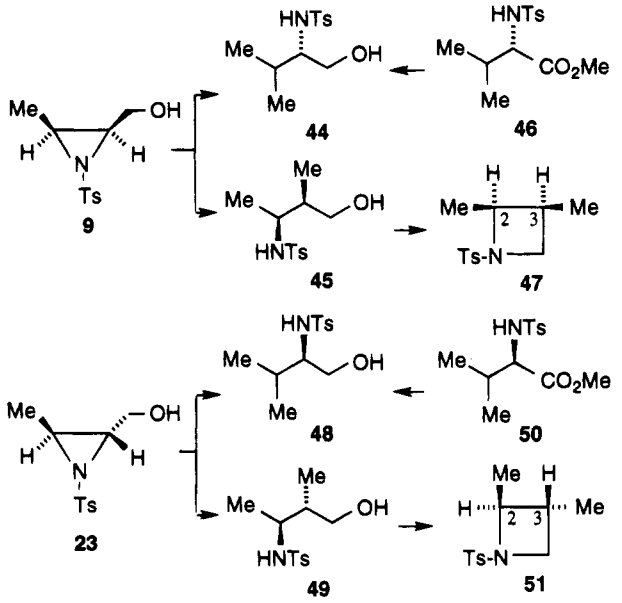
(23) For a preliminary communication of a portion of this organocopper chemistry, see: Ibuka, T.; Nakai, K.; Habashita, H.; Fujii, N.; Garrido, F.; Mann, A.; Chounan, Y.; Yamamoto, Y. *Tetrahedron Lett.* **1993**, *34*, 7421.

Table 3. Aziridine Ring-Opening Reactions of 9 and 23 with R_2CuLi and $R_2Cu(CN)Li_2$[a]

entry	starting material	reagent	regioselectivity C-3:C-2	combined isolated yield (%)
1	**9**	$Me_2CuLi{\cdot}2LiB{\cdot}LiI$ (4 equiv)	**44:45** = 51:49	94[b]
2	**9**	$Me_2Cu(CN)Li_2{\cdot}2LiBr$ (5 equiv)[c]	**44:45** = 44:56	80[d]
3	**9**	$Bu_2CuLi{\cdot}LiI$ (5 equiv)	**52:53** = 45:55	45[d,f]
4	**9**	$Bu_2Cu(CN)Li_2$ (10 equiv)[c]	**52:53** = 58:42	34[e,f]
5	**23**	$Me_2CuLi{\cdot}2LiBr{\cdot}LiI$ (5 equiv)	**48:49** = 65:35	98[b]
6	**23**	$Bu_2CuLi{\cdot}LiI$ (10 equiv)	**54:55** = 42:58	91[d]
7	**23**	$Bu_2Cu(CN)Li_2$ (10 equiv)[c]	**54:55** = 79:21	86[e]

[a] All reactions were carried out by treatment of the starting material (**9** or **23**) with the indicated reagent initially at −78 °C followed by warming the reaction mixture to 0 °C (butylcopper reagents) or ambient temperature (methylcopper reagents) with stirring for 18 h. The ring-opened products could be separated by flash chromatography or preparative HPLC and characterized independently; however, the product distributions were more conveniently determined by HPLC analysis. [b] Reaction was carried out in Et_2O. [c] Could be represented as $Me_2CuLi{\cdot}LiCN{\cdot}2LiBr$ and $Bu_2CuLi{\cdot}LiCN$.[2g-i] [d] Reaction was performed in Et_2O–THF (1:4). [e] Reaction was carried out in *n*-hexane–THF (ca. 4:3). [f] The reaction was incomplete, but the yield has not been corrected for unreacted starting **9**.

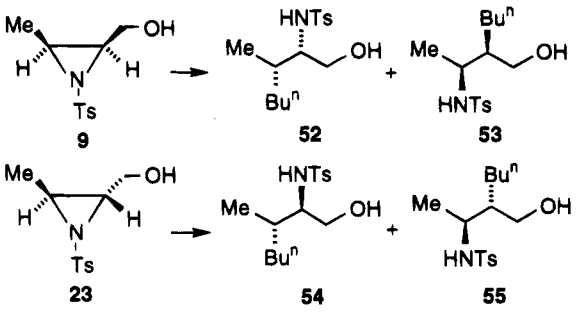
Scheme 7



azacyclobutane derivative **47** in 99% yield. The 2,3-*cis* stereochemistry of vicinal hydrogens in **47**, and hence the 2,3-*syn* stereochemistry of **45**, could easily be determined by the NOE difference spectroscopy of the C-2-hydrogen on irradiation of the C-3-hydrogen (ca. 4% enhancement). In a similar manner, exposure of aziridinemethanol **23** to $Me_2CuLi{\cdot}2LiBr{\cdot}LiI$ yielded a 65:35 mixture of protected amino alcohols **48** and **49** (entry 5, Table 3). The stereochemistry of both products (**48** and **49**) was confirmed by a procedure similar to that for the stereochemical assignments of **44** and **45** (Scheme 7).

A similar trend in low-regioselectivity was observed for $Bu_2CuLi{\cdot}LiI$ or $Bu_2Cu(CN)Li_2$ mediated ring-opening reactions of aziridinemethanols **9** and **23**. Thus, treatment of **9** or **23** with either $Bu_2CuLi{\cdot}LiI$ or the "higher order" reagent $Bu_2Cu(CN)Li_2$ resulted in the formation of ring-opened products (**52** and **53**) and (**54** and **55**), respectively, as shown in Scheme 8 (entries 3, 4, 6, and 7, Table 3). A reactivity difference between the 2,3-*cis*–*trans* pair of *N*-tosylaziridines **9** and **23** was observed. The 2,3-*trans*-**23** provided high yields of the epoxy ring-opened products following treatment with organocopper reagents (entries 6 and 7, Table 3). Under the same conditions, the reaction of 2,3-*cis*-**9** was rather sluggish. A similar difference in reactivity between a *cis*–*trans* pair of aziridines has recently appeared.[25]

Scheme 8



From the above results, it is apparent that the presence of a hydroxymethylene group on the aziridine ring has no significant directive effect on the regiochemical course of the reaction. Similar low regioselectivities in the reaction of chiral 2,3-epoxy alcohols with Gilman-type organocopper reagents have been reported by Katsuki[26a,b] and others.[26c-g]

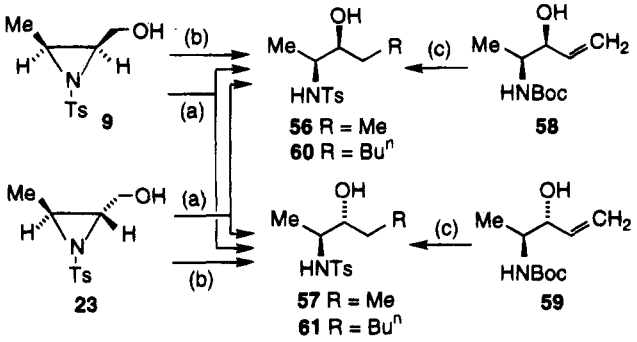
Literature reports clearly demonstrate that reactions of aziridines with organocopper reagents lead to aziridine ring-opened product(s).[17] Consequently, it was assumed that the aziridines **9** and **23** would provide the same aziridine ring-opened products in varying ratios following treatment with "lower order" (LO) cyanocuprates. Surprisingly, this was not observed. As shown in Scheme 9, it was found that the reaction of **9** with MeCu(CN)Li yielded a separable 36:55 mixture of unexpected amino alcohols **56** and **57** along with the "normal" ring-opened product **45** (ca. 7% yield) as a minor product (entry 1, Table 4). The isomeric starting material **23** yielded the same amino alcohols **56** and **57** in a comparable ratio

(24) (a) Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A. *Tetrahedron* **1984**, *40*, 5005. (b) Lipshutz, B. H. *Synthesis* **1987**, 325. (c) Lipshutz, B. H.; Ellsworth, E. L.; Siahaan, T. J. *J. Am. Chem. Soc.* **1988**, *110*, 4834. (d) Lipshutz, B. H. *Synlett.* **1990**, *3*, 119. (e) Lipshutz, B. H.; Sharma, S.; Ellsworth, E. L. *J. Am. Chem. Soc.* **1990**, *112*, 4032. (f) Lipshutz, B. H.; Sengupta, S. In *Organic Reactions*; Paquette, L. A., Ed.; John Wiley & Sons: New York, 1992; p 135. (g) Bertz, S. H. *J. Am. Chem. Soc.* **1990**, *112*, 4031. (h) Bertz, S. H. *J. Am. Chem. Soc.* **1991**, *113*, 5470. (i) Bertz, S. H.; Dabbagh, G.; He, X.; Power, P. P. *J. Am. Chem. Soc.* **1993**, *115*, 11640. (j) Stemmler, T.; Penner-Hahn, J. E.; Knochel, P. *J. Am. Chem. Soc.* **1993**, *115*, 348. (k) Synder, J. P.; Spangler, D. P.; Behling, J. R. *J. Org. Chem.* **1994**, *59*, 2665.

(25) Falkenstein, R.; Mall, T.; Speth, D.; Stamm, H. *J. Org. Chem.* **1993**, *58*, 7377.

(26) (a) Honda, M.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1984**, *25*, 3857. For reports of ring opening reactions of epoxy alcohols and their derivatives with organocopper reagents, see: (b) Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873. (c) Hayami, H.; Sato, M.; Kanemoto, S.; Morizawa, Y.; Oshima, K.; Nozaki, H. *J. Am. Chem. Soc.* **1983**, *105*, 4491. (d) McWhorter, W. W., Jr.; Kang, S. H.; Kishi, Y. *Tetrahedron Lett.* **1983**, *24*, 2243. (e) Tius, M. A.; Fauq, A. H. *J. Org. Chem.* **1983**, *48*, 4131. (f) Fuganti, C.; Grasselli, P.; Servi, S.; Zirotti, C. *Tetrahedron Lett.* **1982**, *23*, 4269. (g) Chong, J. M.; Cyr, D. R.; Mar, E. K. *Tetrahedron Lett.* **1987**, *28*, 5009. For a report of ring opening reactions of epoxy carboxylic acids with dialkyl cuprates, see: Chong, J. M.; Sharpless, K. B. *Tetrahedron Lett.* **1985**, *26*, 4683.

Scheme 9



Reagent: (a) MeCu(CN)Li·LiBr; (b) *n*-BuCu(CN)Li; (c) i. H_2 / PtO_2 in EtOH; ii. TFA - CH_2Cl_2; iii. TsCl-Et_3N

Table 4. Aza-Payne Rearrangement-Opening Reaction of 9 and 23 with the "Lower Order" Alkylcyanocuprates RCu(CN)Li[a]

entry	starting material	reagent	product(s)	combined isolated yield (%)
1	**9**	MeCu(CN)Li·LiBr (4 equiv)[b]	**56**:**57** = 36:55	93[c]
2	**9**	BuCu(CN)Li·2LiCl (10 equiv)[d]	**60**	41[e]
3	**23**	MeCu(CN)Li·LiBr (5 equiv)[b]	**56**:**57** = 39:53	81[f]
4	**23**	BuCu(CN)Li·2LiCl (10 equiv)[d]	**61**	91

[a] All reactions were carried out by treatment of the starting material (**9** or **23**) with the indicated reagent at −78 °C followed by warming to 0 °C (butylcopper reagents) or ambient temperature (methylcopper reagents) with stirring for 18 h. [b] Reaction was carried out in THF−Et_2O (3−4:1). [c] Obtained along with ca. 1% yield of **44** and 7% yield of **45**. [d] Reaction was performed in *n*-hexane−THF (1:2). [e] The reaction was incomplete; however, the yield has not been corrected for unreacted starting material **9**. [f] Obtained along with ca. 6% yield of **48** and 0.6% yield of **49**.

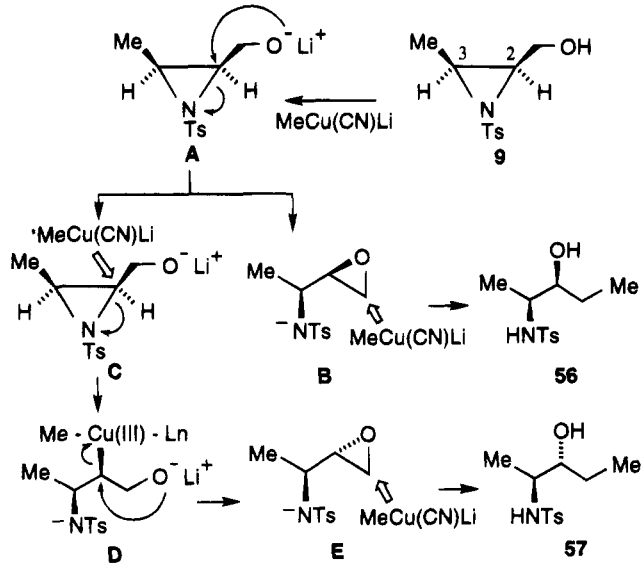
under the same reaction conditions (entry 3, Table 4). Structural and stereochemical assignments for the amino alcohols **56** and **57** were made by comparison of spectral data (^1H NMR, IR, and $[\alpha]_D$) with those of authentic samples prepared from known homochiral amino alcohols **58**[27b] and **59**[27b] through a sequence of reactions (i. H_2/PtO_2; ii. TFA; iii. TsCl−Et_3N). Similarly, the reactions of **9** and **23** with BuCu(CN)Li provided rearrangement-opened products **60** and **61**, respectively (entries 2 and 4, Table 4).

It is noteworthy that the formation of secondary alcohols in the reactions of aziridines **9** and **23** with LO cyanocuprates is a striking difference from that observed by using the Gilman reagents or "higher order" cyanocuprates (compare Schemes 7 and 8 with 9). Because the organocopper-mediated ring opening of aziridines usually proceeds via an S_N2-type mechanism at the C-2 or C-3 carbon center,[12,28] the question remains why 2-aziridinemethanols **9** and **23** are transformed into

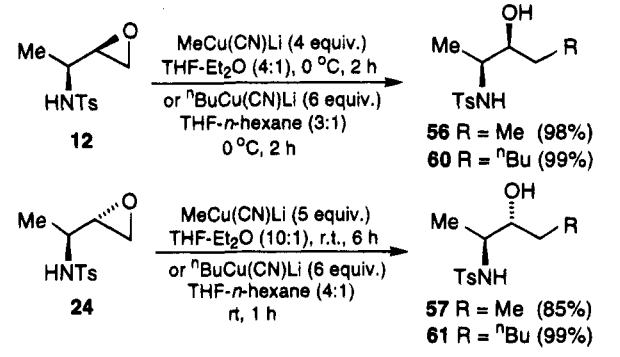
(27) (a) Ibuka, T.; Habashita, H.; Funakoshi, S.; Fujii, N.; Oguchi, Y.; Uyehara, T.; Yamamoto, Y. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 801. (b) Ibuka, T.; Habashita, H.; Otaka, A.; Fujii, N.; Oguchi, Y.; Uyehara, T.; Yamamoto, Y. *J. Org. Chem.* **1991**, *56*, 4370. (c) Ibuka, T.; Taga, T.; Habashita, H.; Nakai, K.; Tamamura, H.; Fujii, N.; Chounan, Y.; Nemoto, H.; Yamamoto, Y. *J. Org. Chem.* **1993**, *58*, 1207. (d) Ibuka, T.; Nakai, K.; Habashita, H.; Hotta, Y.; Fujii, N.; Mimura, N.; Miwa, Y.; Taga, T.; Yamamoto, Y. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 652.

(28) Stamm, H.; Assithianakis, P.; Buchholz, B.; Weiss, R. *Tetrahedron Lett.* **1982**, *23*, 5021.

Scheme 10



Scheme 11



secondary amino alcohols by treatment with LO cyanocuprates. Although all controlling factors in the reaction of **9** and **23** with LO cyanocuprates are not clear, the following reasoning concerning the formation of secondary amino alcohols may be drawn.

One equivalent of MeCu(CN)Li would remove the hydroxyl proton to generate an anionic species **A**, from which formation of oxirane **B** via intramolecular attack of the anion on a proximal electrophilic carbon center could be expected (aza-Payne rearrangement, Scheme 10). Isolation of a protonated form of **B** in very low yield from the reaction of **9** with MeCu(CN)Li at 0 °C for 3 h supports the possible involvement of such an oxirane intermediate **B**. Subsequent nucleophilic attack of MeCu(CN)Li on the less-substituted carbon of the oxirane **B** would provide the amino alcohol **56**. Alternatively, nucleophilic attack of the LO cyanocuprate at the C-2 position, followed by oxirane formation via an intermediate **D**, could lead to an oxirane **E**. Finally, attack of MeCu(CN)Li on the less substituted carbon of oxirane **E** would provide the isomeric amino alcohol **57**.

Experiments have been performed which support the above hypotheses, that the postulated epoxy intermediates **B** and **E** might be converted by MeCu(CN)Li into **56** and **57**, respectively. As shown in Scheme 11, the lower order reagents react cleanly with epoxides **12** and **24** solely at the less sterically hindered position. Although the precise reaction mechanisms for the formation of the unexpected amino alcohols **56** and **57** are not known for certainty, the picture shown in Scheme 10 is

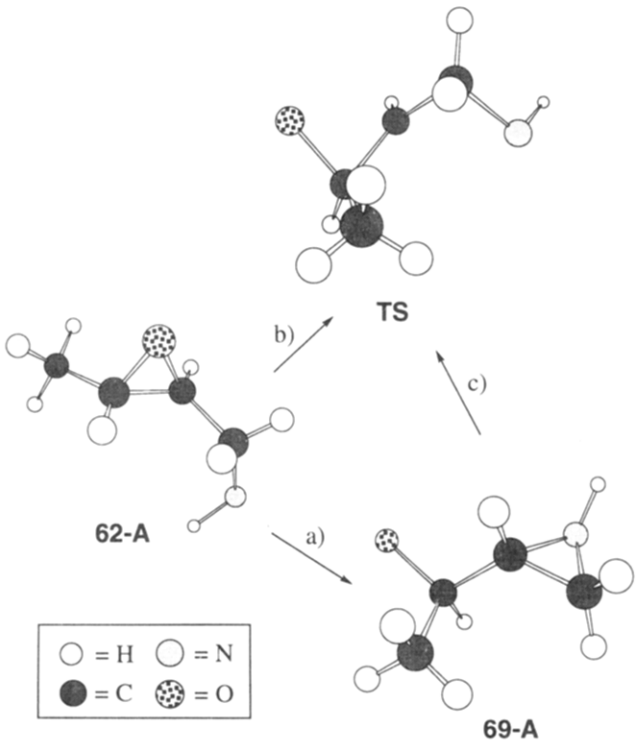


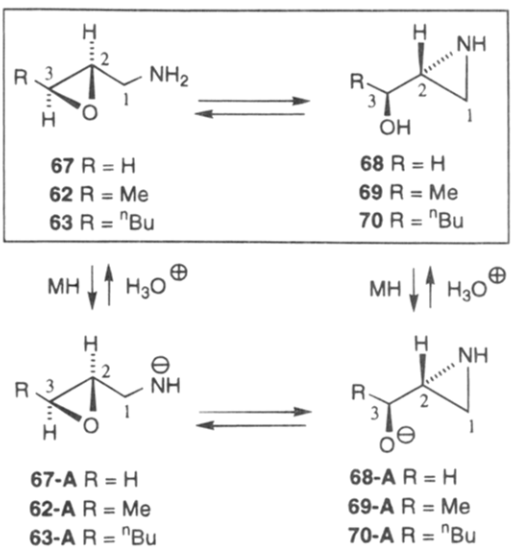
Figure 2. RHF/3-21+G* optimized geometries: **62-A**, the reactant aza anionic minimum originated from **62** through deprotonation; **TS**, the transition structure; **69-A**, the product oxa anionic minimum originated from **69** through deprotonation. (a) $\Delta E = -15.40$ kcal/mol; (b) $\Delta E = 10.34$ kcal/mol; (c) $\Delta E = 25.74$ kcal/mol.

conveniently simple for this stage in the development of our understanding.[29]

We have shown in this section that complementary selectivity can be achieved in ring-opening reactions of 2-aziridinemethanols by using either the more reactive Gilman reagents (or "higher order" reagents) or less reactive LO cyanocuprates. If the reagents are more reactive, e.g., $Me_2CuLi{\cdot}LiI$, then aziridine ring cleavage of the 2-aziridinemethanols predominates. In contrast, if the organocopper reagents are less reactive, e.g., MeCu(CN)Li, then it becomes possible to open the epoxide ring at the less sterically hindered position, yielding unexpected secondary alcohol(s). This behavior is reminiscent of the Payne rearrangement-opening reaction of chiral primary 2,3-epoxy alcohols with organocopper reagents reported by Bulman Page and Sutherland.[2d]

(3) Aza-Payne Rearragements of 2,3-Epoxy Amines. Finally, the direction of the equilibrium of an aza-Payne rearrangement of epoxy amines under aprotic basic conditions was examined by chemical and theoretical studies on simple systems. Although methods for the synthesis of epoxides possessing secondary or tertiary amino groups are available,[30] the required 2,3-epoxy amines **62**–**66** listed in Scheme 13 were synthesized from the corresponding optically active 2,3-epoxy alcohols according to a known three-step sequence of reactions.[7c] This involved (1) tosylation of the primary hydroxy group,[31] (2) substitution of the tosyloxy group by treatment with sodium azide,[32] and (3) reduction of the azide group with triphenylphosphine.[33,34] It should be noted

Scheme 12



that low molecular weight epoxy amines such as **62** and **63** pose serious problems with respect to product isolation. The usual extractive workup leads to considerable loss of the water-soluble epoxy amines. Consequently, after the reduction of azides with triphenylphosphine was complete, the reaction mixture was concentrated prior to distillation using a bulb-to-bulb distillation apparatus under reduced pressure. The distillate was redistilled under reduced pressure to remove a small amount of impurities that had been introduced by bumping. In this way, all 2,3-epoxy amines listed in Scheme 13 were obtained in pure forms.

In view of the synthetic utility of the rearrangement of 2,3-epoxy amines, it was of interest to determine whether this rearrangement is generally characteristic of 2,3-epoxy amines. We initiated our study on the rearrangement of 2,3-epoxy amines to determine the scope of the reaction (Scheme 12).[10] The geometries of the reactant aza anions (**67-A**, **62-A**, and **63-A**) of 2,3-

(29) For an interesting epoxy alcohol rearrangement using $Ti(OPr^i)_4$, see: Morgans, D. J. Jr.; Sharpless, K. B.; Traynor, S. G. *J. Am. Chem. Soc.* **1981**, *103*, 462. See also: Yamazaki, T.; Iwatsubo, H.; Kitazume, T. *Tetrahedron: Asymmetry* **1994**, *5*, 1823.

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(32) For regioselective ring-opening reactions of 2,3-epoxy alcohols and their derivatives with azides, see: (a) Zamboni, R.; Rokach, J. *Tetrahedron Lett.* **1983**, *24*, 331. (b) Behrens, C. H.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 5696. (c) Caron, M.; Carlier, P. R.; Sharpless, K. B. *J. Org. Chem.* **1988**, *53*, 5185.

(33) Staudinger, H.; Meyer, J. *Helv. Chim. Acta* **1919**, *2*, 635. Mungall, W. S.; Greene, G. L.; Heavner, G. A.; Letsinger, R. L. *J. Org. Chem.* **1975**, *40*, 1659. Vaultier, M.; Knouzi, N.; Carrié, R. *Tetrahedron Lett.* **1983**, *24*, 763.

(34) Because space does not permit the inclusion of synthetic details, preparative methods and spectroscopic as well as analytical data for all 2,3-epoxy amines are presented as supplementary material.

Table 5. Total and Relative Energies of the Critical Points[a]

	RHF/3-21+ G* (MP2/6-31+G*)[b]	
geometry	E[c]	ΔE[d]
reactant aza anion **67-A** of **67**[e]	−244.936 537	0.0
	(−247.043 810	0.0)
transition state **TS**	−244.921 328	9.54
	(−247.032 082	7.36)
product oxa anion **68-A** of **68**[e]	−244.960 622	−15.11
	(−247.068 379	−15.42)
reactant aza anion **62-A** of **62**	−283.764 421	0.0
transition state **TS**	−283.747 951	10.34
product oxa anion **69-A** of **69**	−283.788 964	−15.40
reactant aza anion **63-A** of **63**	−400.227 633	0.0
transition state **TS**	−400.211 136	10.35
product oxa anion **70-A** of **70**	−400.253 528	−16.25

[a] The character of all minima and transition states was confirmed with calculation of force constant analyses at the Hartree−Fock level. [b] Computed at the RHF/3-21+G* optimized geometries. [c] Hartree. [d] kcal mol^{-1}. Energies are relative to the lowest energy reactant anion. [e] Compounds **67** and **68** were model compounds for calculations.

epoxy amines (**67**,[35] **62**, and **63**), the transition state structures, and the oxa anions (**68-A**, **69-A**, and **70-A**) of product hydroxy aziridines (**68**,[35] **69**, and **70**) were obtained using *ab initio* calculations involving full optimizations with the RHF/3-21+G* basis set,[14,15] followed by a single-point energy evaluation at the MP2/6-31+G* level. Energy calculations for the aza anion of 2,3-epoxy amine **67**, the transition state structure, and the oxa anion of 3-hydroxyaziridine **68** at the MP2 level were performed on the RHF/3-21+G* geometries. The optimized reactant aza anion **62-A** of **62**, the transition state structure **TS**, and the product oxa anion **69-A** of **69** are shown in Figure 2, with total and relative energies summarized in Table 5.[36]

It is apparent that the aza anions (**67-A**, **62-A**, and **63-A**, Scheme 12) of 2,3-epoxy amines (**67**, **62**, and **63**) were estimated to be 15−16 kcal/mol higher in energy than the oxa anions (**68-A**, **69-A**, and **70-A**) of the 3-hydroxy aziridines (**68**, **69**, and **70**) at the RHF/3-21+G* and the MP2/6-31+G* levels as shown in Figures 2 and 3, and Table 5. Therefore, the nearly exclusive formation of hydroxy aziridines **69** and **70** could be expected by treatment of **62** and **63** with NaH or KH in an aprotic solvent followed by quenching of the reaction mixture at low temperature.[16]

Unexpectedly, the aza-Payne rearrangement of epoxy amines proved considerably more difficult than first envisioned. A number of common bases (NaH, KH, *t*-BuOK, etc.) were attempted unsuccessfully on epoxy amines **62** and **63**. The rearrangement of epoxy amines with alkyllithiums such as MeLi and *n*-BuLi was rather slow and did not go to completion. For example, although the epoxy amine **63** reacted with MeLi (1.1 equiv as complexed with LiBr, −78 °C, 1 h, THF/Et_2O = 6:1) and *n*-BuLi (1.1 equiv, 0 °C, 18 h, THF/*n*-hexane = 2:1) to yield the hydroxy aziridine **70**, the reaction never proceeded beyond 83% and 71% completion, respectively. The prolonged reaction time gave an inseparable mixture of products.

Finally, it was found that treatment of the 2,3-epoxy amines (**62** and **63**) with a mixture of 1.5 equiv of *n*-BuLi and 1.5 equiv of *t*-BuOK ("super base")[37] at −78 °C yielded only the respective rearranged hydroxy aziridines

(35) The epoxy amine **67** and the hydroxy aziridine **68** were model compounds for computations.

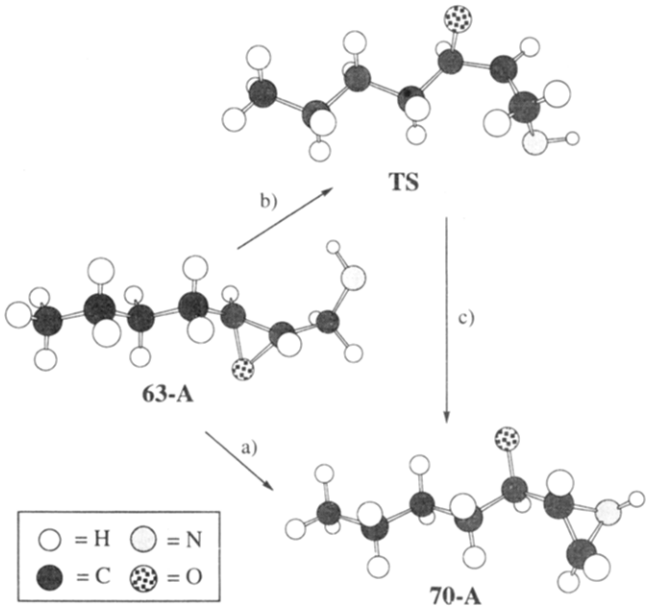
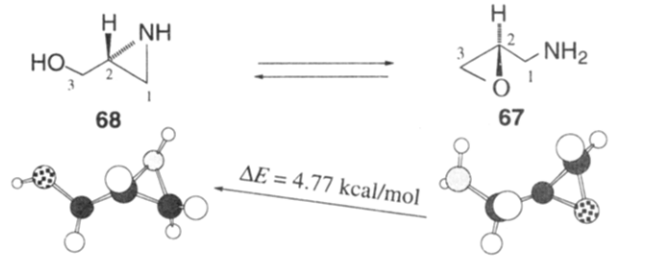


Figure 3. RHF/3-21+G* optimized geometries and their relative energies for the aza-Payne rearrangement: **TS**, the transition structure, **63-A**, the reactant aza anionic energy minimum originated from **63** through deprotonation; **70-A**, the product oxa anionic energy minimum originated from **70** through deprotonation. (a) ΔE = −16.25 kcal/mol; (b) ΔE = 10.35 kcal/mol; (c) ΔE = −26.6 kcal/mol.

(**69** and **70**) in high isolated yields. There were no detectable traces (by ^{1}H NMR and TLC) of the reactants **62** and **63**. It should be noted that the resulting low molecular weight, water-soluble hydroxy aziridines pose a problem with respect to product isolation. Consequently, following the reaction of epoxy amines with the super base, the reaction was quenched at −78 °C with a saturated ammonium chloride solution. The mixture was allowed to warm to 0 °C and then filtered through a short Celite pad. Concentration, followed by recrystallization or distillation using a bulb-to-bulb distillation apparatus under reduced pressure, yielded pure materials.

Disubstitution at the C-3 position of 2,3-epoxy amines does not exert any influence on the rearrangement (see reactions of **64** and **65**, Scheme 13). As anticipated,

(36) The energy minimum of the aziridinemethanol **68** was predicted to be 4.77 kcal mol^{-1} higher than the minimum of epoxy amine **67** at the RHF/3-21G level.

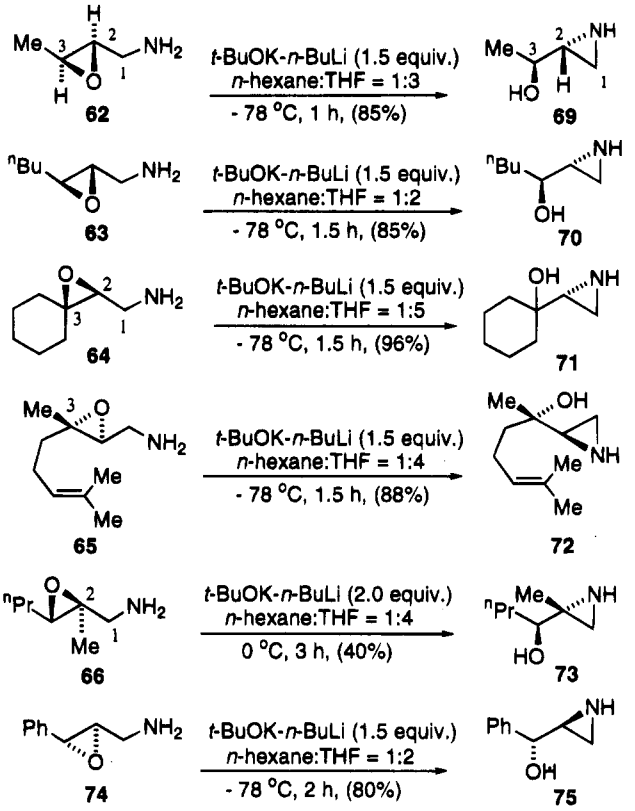


3-21G optimized structure of **68**. E(RHF) = - 245.530624 A.U.

3-21G optimized structure of **67**. E(RHF) = - 245.538228 A.U.

(37) Lochmann, L.; Pospisil, J.; Lim, D. *Tetrahedron Lett.* **1966**, 257. Schlosser, M. *J. Organomet. Chem.* **1967**, *8*, 9. Schlosser, M.; Strunk, S. *Tetrahedron Lett.* **1984**, *25*, 741. Lehmann, R., Schlosser, M. *Tetrahedron Lett.* **1984**, *25*, 745. Lochmann, L.; Trekoval, J. *Collect. Czech. Chem. Commun.* **1988**, *53*, 76. Faigl, F.; Schlosser, M. *Tetrahedron Lett.* **1991**, *32*, 3369. Takagishi, S.; Katsoulos, G.; Schlosser, M. *Synlett.* **1992**, 360 and references cited. Bauer, W.; Lochmann, L. *J. Am. Chem. Soc.* **1992**, *114*, 7482. Weiss, E. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1501. Bailey, W. F.; Punzalan, E. R. *J. Am. Chem. Soc.* **1994**, *116*, 6577.

Scheme 13



increased steric bulk at the C-2 carbon decreases the tendency for the aza-Payne rearrangement to proceed (compare the reaction of **64** and **65** with **66**, Scheme 13).

The present study demonstrates that the aza-Payne rearrangement of 2,3-epoxy amines following treatment with *t*-BuOK–*n*-BuLi proceeds at −78 °C in high isolated yields except for the less reactive substrate **66**.

In conclusion, the aza-Payne rearrangement of activated 2-aziridinemethanols with *t*-BuOK, NaH, or KH near 0 °C in solvents such as THF, toluene, 1,2-dimethoxyethane, 1,4-dioxane, or a mixed solvent of THF–HMPA, followed by quenching at −78 °C gives the corresponding epoxysulfonamides. Exposure of *N*-tosyl-(2*S*)-azetidinemethanol (**36**) and *N*-tosyl-(*S*)-prolinol (**37**) to NaH or KH in dichloromethane yields only the respective dimeric compounds that result by joining 2 equiv of starting material through a methylene group.

Reaction of *N*-tosyl-(2*S*,3*S*)-3-methyl-2-aziridinemethanol (**9**) and its (2*R*,3*S*)-isomer **23** with Gilman reagents (R_2CuLi; R = Me and Bu) or "higher order" cuprates ($R_2Cu(CN)Li_2$; R = Me and Bu) yielded respectively the two expected ring-opened products. In sharp contrast, treatment of **9** and **23** with "lower order" cuprates afforded rearrangement-opened products. Thus, if the nucleophile is highly reactive, then the expected nucleophilic ring-opening of the aziridine predominates. However, if the nucleophile is less reactive, then it becomes possible to cleave the rearranged epoxide.

Upon exposure of 2,3-epoxy amines to an equimolar mixture of *t*-BuOK–*n*-BuLi in a mixed solvent of THF and *n*-hexane at −78 °C, the equilibrium lies exclusively toward the hydroxy aziridine forming direction.

The chemistry of the aza-Payne rearrangement reported herein increases our understanding of this relatively unexplored class of reactions.

Experimental Section

General Methods. All reactions were carried out under a positive pressure of argon. All glassware and syringes were dried in an electric oven at 100 °C prior to use. Ethereal MeLi (as complex with LiBr) and *n*-BuLi were purchased from Aldrich and Nacalai Tesque, respectively. CuCN was obtained from Mitsuwa Chemicals and dried in an Abderhalden under vacuum at rt. All melting points are uncorrected. Nominal (LR-MS) and exact mass (HR-MS) spectra were recorded on a JEOL JMS-01SG-2 or JMS-HX/HX 110A mass spectrometer. All NMR spectra were recorded in $CDCl_3$ unless otherwise specified. Chemical shifts are reported in parts per million downfield from internal Me_4Si (s = singlet, d = doublet, dd = double doublet, ddd = doublet of double doublet, t = triplet, m = multiplet). Optical rotations were measured in $CHCl_3$ with a JASCO DIP-360 digital polarimeter. For flash chromatographies, silica gel 60 H (silica gel for thin-layer chromatography, Merck) or silica gel 60 (finer than 230 mesh, Merck) was employed. For HPLC, Cosmosil-5SL (10 × 250 mm, Nacalai Tesque) was employed. The enantiomeric excess (ee) was determined using chiral HPLC columns (Chiralcel OD, Daicel, or ChiraSpher, Merck) and found to be > 90%.

Aza-Payne Rearrangement of (2*S*,3*S*)-3-Methyl-*N*-[(4-methylphenyl)sulfonyl]-2-aziridinemethanol (9) in an Aqueous Sodium Hydroxide Solution. To a stirred solution of 3.5 mL of 0.36 *N*-NaOH in *t*-BuOH–H_2O (2:5) under argon was added 60.3 mg (0.25 mmol) of aziridine **9** at 0 °C and the stirring was continued for 18 h at 0 °C. The reaction was quenched with 5 mL of a saturated citric acid solution at 0 °C with vigorous stirring. The mixture was extracted with CH_2Cl_2, and the extract was washed with water and dried over $MgSO_4$. The usual workup gave a 30:70 mixture of **9** and **12** [the ratios of the aziridine **9** and epoxide **12** were determined by HPLC]. The mixture was flash chromatographed on a silica gel column. Elution with *n*-hexane–EtOAc (2:1) gave 42 mg (70% yield) of epoxide **12** and further elution gave 18 mg (30% yield) of aziridine **9**. **9**: colorless crystals from *n*-hexane–CH_2Cl_2–Et_2O (6:1:3); mp 67–69 °C; $[\alpha]^{26}_D$ +5.0° (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 3500 cm^{-1} (OH); ^1H NMR (200 MHz, $CDCl_3$) δ 1.25 (d, J = 5.6 Hz, 3 H), 1.74 (m, 2 H), 2.45 (s, 3 H), 2.97 (m, 2 H), 3.61 (dd, J = 11.5, 6.4 Hz, 1 H), 3.76 (dd, J = 11.5, 4.6 Hz, 1 H), 7.27–7.37 (m, 2 H), 7.81–7.85 (m, 2 H). Anal. Calcd for $C_{11}H_{15}NO_3S$: C, 54.75; H, 6.27; N, 5.80. Found: C, 54.65; H, 6.37; N, 5.68. **12**: Colorless crystals from Et_2O; mp 102–103 °C; $[\alpha]^{20}_D$ +10.0° (*c* 0.90, $CHCl_3$); IR ($CHCl_3$) 3385, 1602, 1335, 1152, 1092 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.14 (d, J = 6.9 Hz, 3 H), 2.43 (s, 3 H), 2.69 (m, 2 H), 2.92 (m, 1 H), 3.60 (dddd, J = 15.5, 13.8, 6.9, 2.9 Hz, 1 H), 4.55 (d, J = 8.5 Hz, 1 H), 7.29–7.32 (m, 2 H), 7.73–7.82 (m, 2 H). Anal. Calcd for $C_{11}H_{15}NO_3S$: C, 54.75; H, 6.27; N, 5.80. Found: C, 54.55; H, 6.34; N, 5.69.

Aza-Payne Rearrangement of (2*R*,3*R*)-*N*-[(4-Methylphenyl)sulfonyl]-3-phenyl-2-aziridinemethanol (10) in an Aqueous Sodium Hydroxide Solution. By use of a procedure similar to that described for the rearrangement of **9**, 60.7 mg (0.2 mmol) of aziridine **10** was treated with 3.6 mL of 0.28 *N*-NaOH in *t*-BuOH–H_2O (4:5) at 0 °C for 18 h followed by flash chromatography over silica gel with *n*-hexane–EtOAc (3:1) to yield, in order of elution, 23.7 mg (39% yield) of **13** and 37 mg (61% yield) of aziridine **10**. **10**: Colorless crystals from *n*-hexane–Et_2O (1:5); mp 88 °C; $[\alpha]^{20}_D$ −127° (*c* = 1.30, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.49 (m, 1 H), 2.44 (s, 3 H), 3.30 (m, 1 H), 3.38 (dd, J = 6.9, 5.0 Hz, 1 H), 3.48 (m, 1 H), 4.04 (d, J = 6.9 Hz, 1 H), 7.20–7.31 (m, 5 H), 7.34–7.37 (m, 2 H), 7.88–7.92 (m, 2 H). Anal. Calcd for $C_{16}H_{17}NO_3S$: C, 63.35; H, 5.65; N, 4.62. Found: C, 63.21; H, 5.61; N, 4.46. **13**: Colorless crystals from Et_2O; mp 151 °C; $[\alpha]^{20}_D$ −99° (*c* 1.20, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 2.36 (s, 3 H), 2.75 (dd, J = 4.5, 3.9 Hz, 1 H), 2.81 (dd, J = 4.5, 2.6 Hz, 1 H), 3.19 (ddd, J = 3.9, 2.6, 2.6 Hz, 1 H), 4.54 (dd, J = 8.1, 2.6 Hz, 1 H), 5.00 (d, J = 8.1 Hz, 1 H), 7.11–7.17 (m, 5 H), 7.18–7.23 (m, 2 H), 7.53–7.56 (m, 2 H). Anal. Calcd for $C_{16}H_{17}NO_3S$: C, 63.35; H, 5.65; N, 4.62. Found: C, 63.12; H, 5.59; N, 4.35.

Aza-Payne Rearrangement of (2R)-2-(1-Hydroxycyclohexyl)-1-[(4-methylphenyl)sulfonyl]aziridine (11) in an

Aqueous Sodium Hydroxide Solution. By use of a procedure similar to that described for the rearrangement of **9**, 59 mg (0.2 mmol) of aziridine **11** was treated with 2.8 mL of 0.36 *N*-NaOH in *t*-BuOH–H_2O (2:5) at 0 °C for 18 h followed by preparative HPLC (Cosmosil packed column 5SL, 10 × 250 mm, Nacalai Tesque) with *n*-hexane–THF (9:1) to yield, in order of elution, 1.2 mg (ca. 2% yield) of **11** and 57 mg (98% yield) of aziridine **14**. **11**: Colorless crystals from a mixed solvent of *n*-hexane–Et_2O (1:1); mp 88 °C; $[\alpha]^{20}_D$ +43.0° (*c* 0.92, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 1.21–1.38 (m, 5 H), 1.42–1.67 (m, 6 H), 2.42 (d, J = 4.6 Hz, 1 H), 2.46 (s, 3 H), 2.55 (d, J = 7.3 Hz, 1 H), 2.84 (dd, J = 7.3, 4.6 Hz, 1 H), 7.34–7.37 (m, 2H), 7.81–7.84 (m, 2 H). Anal. Calcd for $C_{15}H_{21}NO_3S$: C, 60.99; H, 7.17; N, 4.74. Found: C, 60.89; H, 7.17; N, 4.71. **14**: Colorless crystals from Et_2O–*n*-hexane (1:1); mp 80 °C; $[\alpha]^{20}_D$ −50.0° (*c* 0.50, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 1.38–1.59 (m, 8 H), 1.61–1.76 (m, 2 H), 2.43 (s, 3 H), 2.83 (dd, J = 6.8, 4.6 Hz, 1 H), 2.97 (ddd, J = 13.5, 7.3, 4.6 Hz, 1 H), 3.30 (ddd, J = 13.5, 7.8, 4.6 Hz, 1 H), 4.73 (m, 1 H), 7.30–7.33 (m, 2 H), 7.74–7.78 (m, 2 H). Anal. Calcd for $C_{15}H_{21}NO_3S$: C, 60.99; H, 7.17; N, 4.74. Found: C, 60.73; H, 7.07; N, 4.62.

(2*R*,3*S*)-3-Amino-1,2-epoxy-*N*-[(4-methylphenyl)sulfonyl]butane (12) from 9 (entry 9, Table 2). To a stirred suspension of 24 mg (1 mmol) of NaH in a mixture of 2 mL of THF and 0.33 mL of HMPA at −40 °C under argon was added 60.3 mg (0.25 mmol) of alcohol **9** in 2 mL of THF, and then the mixture was allowed to warm to rt and the stirring was continued for 2 h. The reaction was quenched with 2 mL of 5% citric acid at −78 °C with stirring. The mixture was extracted with EtOAc and the extract was washed successively with saturated citric acid, brine, 5% $NaHCO_3$, and brine, and dried over $MgSO_4$. The usual workup followed by flash chromatography over silica gel with *n*-hexane–EtOAc (3:1) gave 56 mg (92% yield) of the title compound **12** as a crystalline mass. Recrystallization from Et_2O gave colorless crystals: mp 102–103 °C; $[\alpha]^{20}_D$ +9.9° (*c* 0.88, $CHCl_3$); IR ($CHCl_3$) 3385, 1602, 1335, 1152, 1092 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.14 (d, J = 6.9 Hz, 3 H), 2.43 (s, 3 H), 2.69 (m, 2 H), 2.92 (m, 1 H), 3.60 (dddd, J = 15.5, 13.8, 6.9, 2.9 Hz, 1 H), 4.55 (d, J = 8.5 Hz, 1 H), 7.29–7.32 (m, 2 H), 7.73–7.82 (m, 2 H). Anal. Calcd for $C_{11}H_{15}NO_3S$: C, 54.75; H, 6.27; N, 5.80. Found: C, 54.93; H, 6.32; N, 5.83.

(2*S*,3*R*)-3-Amino-1,2-epoxy-*N*-[(4-methylphenyl)sulfonyl]-3-phenylpropane (13) from 10. By use of a procedure similar to that described for the rearrangement of **9** with NaH, 455 mg (1.5 mmol) of aziridine **10** was treated with 241 mg (6 mmol) of KH in a mixed solvent of 12 mL of THF and 1 mL of HMPA at 0 °C for 1.5 h. The usual workup followed by flash chromatography over silica gel with *n*-hexane–EtOAc (3:1) to yield 429 mg (94% yield) of the title compound **13** as a crystalline mass. Recrystallization from Et_2O gave colorless crystals: mp 151 °C; $[\alpha]^{20}_D$ −97.6° (*c* 1.17, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 2.36 (s, 3 H), 2.75 (dd, J = 4.5, 3.9 Hz, 1 H), 2.81 (dd, J = 4.5, 2.6 Hz, 1 H), 3.19 (ddd, J = 3.9, 2.6, 2.6 Hz, 1 H), 4.54 (dd, J = 8.1, 2.6 Hz, 1 H), 5.00 (d, J = 8.1 Hz, 1 H), 7.11–7.17 (m, 5 H), 7.18–7.23 (m, 2 H), 7.53–7.56 (m, 2 H). Anal. Calcd for $C_{16}H_{17}NO_3S$: C, 63.35; H, 5.65; N, 4.62. Found: C, 63.11; H, 5.59; N, 4.57.

(2*S*)-2-(Aminomethyl)-*N*-[(4-methylphenyl)sulfonyl]-1-oxaspiro[3.6]octane (14). By a procedure identical with that described for the preparation of **32** from alcohol **31**, 59 mg (0.2 mmol) of aziridine alcohol **11** was converted into 58.4 mg (99% yield) of epoxide **14** by treatment with 32.1 mg (0.8 mmol) of KH in THF at rt for 18 h. **14**: Colorless crystals from *n*-hexane–Et_2O (1:1); mp 80 °C; $[\alpha]^{20}_D$ −49.7° (*c* 0.41, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 1.38–1.59 (m, 8 H), 1.61–1.76 (m, 2 H), 2.43 (s, 3 H), 2.83 (dd, J = 6.8, 4.6 Hz, 1 H), 2.97 (ddd, J = 13.5, 7.3, 4.6 Hz, 1 H), 3.30 (ddd, J = 13.5, 7.8, 4.6 Hz, 1 H), 4.73 (m, 1 H), 7.30–7.33 (m, 2 H), 7.74–7.78 (m, 2 H); LRMS (FAB) m/z 296 (MH^+), 278 (base peak), 184, 155, 139, 91. HRMS (FAB) m/z calcd for $C_{15}H_{22}NO_3S$ (MH^+) 296.1320; found 296.1328. Anal. Calcd for $C_{15}H_{21}NO_3S$: C, 60.99; H, 7.17; N, 4.74. Found: C, 60.35; H, 7.18; N, 4.63.

(2*S*)-2,3-Epoxy-*N*-(methylsulfonyl)-1-propylamine (16). To a stirred suspension of 31 mg (1.3 mmol) of NaH in a mixture of 3 mL of THF and 0.4 mL of HMPA at −78 °C under argon was added 151 mg (1 mmol) of alcohol **15** in 2 mL of THF, and the mixture was allowed to warm to 20 °C and to stir at this temperature for an additional 45 min. The reaction was quenched with 2 mL of 5% HCl at −78 °C with stirring. The mixture was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (1:9) to yield 83 mg (55% yield) of the title compound **16** as a colorless oil: $[\alpha]^{29}_D$ −28.4° (*c* 1.07, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 2.72 (m, 1 H), 2.84 (m, 1 H), 3.02 (s, 3 H), 3.09–3.27 (m, 2 H), 3.50–3.65 (m, 1 H), 4.88 (broad s, 1 H); LRMS (EI) m/z 151 (M^+), 108, 79, 72; HRMS (EI) m/z calcd for $C_4H_9NO_3S$ (MH^+) 151.0303; found 151.0306.

(2*R*,3*R*)-2,3-Epoxy-*N*-[(4-methylphenyl)sulfonyl]-1-butylamine (30) from Aziridine 29. To a stirred suspension of 40.1 mg (1 mmol) of KH in 2 mL of CH_2Cl_2 at −78 °C under argon was added a solution of 60.3 mg (0.25 mmol) of alcohol **29** in 2 mL of CH_2Cl_2. The mixture was allowed to warm to 0 °C and the stirring was continued for 4 h. The reaction was quenched with 2 mL of 5% NH_4Cl at −78 °C with stirring. The mixture was extracted with CH_2Cl_2, and the extract was washed with water and dried over $MgSO_4$. The usual workup followed by flash chromatography over silica gel with *n*-hexane–EtOAc (2:1) gave 46.1 mg (77% yield) of the title compound **30** as a crystalline mass. Recrystallization from Et_2O gave colorless crystals: mp 86 °C; $[\alpha]^{20}_D$ +36.3° (*c* 0.622, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 1.27 (d, J = 5.1 Hz, 3 H), 2.43 (s, 3 H), 2.80 (ddd, J = 5.1, 3.5, 2.2 Hz, 1 H), 2.90 (ddd, J = 10.5, 5.4, 2.2 Hz, 1 H), 3.03 (ddd, J = 13.8, 6.3, 5.4 Hz, 1 H), 3.27 (ddd, J = 13.8, 6.3, 3.5 Hz, 1 H), 4.76 (m, 1 H), 7.30–7.33 (m, 2 H), 7.69–7.75 (m, 2 H). Anal. Calcd for $C_{11}H_{15}NO_3S$: C, 54.75; H, 6.27; N, 5.80. Found: C, 54.67; H, 6.38; N, 5.70.

(2*S*,3*S*)-2,3-Epoxy-*N*-[(4-methylphenyl)sulfonyl]-1-butylamine (32). To a stirred suspension of 40.1 mg (1 mmol) of KH in 2 mL of THF at −78 °C under argon was added a solution of 60.3 mg (0.25 mmol) of alcohol **31** in 2 mL of THF. The mixture was allowed to warm to 0 °C and the stirring was continued for 2 h. The reaction was quenched with 2 mL of 5% NH_4Cl at −78 °C with stirring. The mixture was extracted with CH_2Cl_2, and the extract was washed with water and dried over $MgSO_4$. The usual workup followed by flash chromatography over silica gel with *n*-hexane–EtOAc (2:1) gave 45.5 mg (76% yield) of the title compound **32** as a crystalline mass. Recrystallization from Et_2O gave colorless crystals: mp 86 °C; $[\alpha]^{20}_D$ −36.4° (*c* 0.556, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 1.27 (d, J = 5.1 Hz, 3 H), 2.43 (s, 3 H), 2.80 (ddd, J = 5.1, 3.5, 2.2 Hz, 1 H), 2.90 (ddd, J = 10.5, 5.4, 2.2 Hz, 1 H), 3.03 (ddd, J = 13.8, 6.3, 5.4 Hz, 1 H), 3.27 (ddd, J = 13.8, 6.3, 3.5 Hz, 1 H), 4.80 (m, 1 H), 7.30–7.33 (m, 2 H), 7.69–7.75 (m, 2 H). Anal. Calcd for $C_{11}H_{15}NO_3S$: C, 54.75; H, 6.27; N, 5.80. Found: C, 54.95; H, 6.32; N, 5.81.

(2*S*,3*S*)-2,3-Epoxy-*N*-[(4-methylphenyl)sulfonyl]-1-heptylamine (34). By a procedure identical with that described for the preparation of **32** from aziridine **31**, 42.5 mg (0.15 mmol) of aziridine alcohol **33** was converted into 37.2 mg (88% yield) of epoxide **34** by treatment with 24 mg (0.6 mmol) of KH in THF at 0 °C for 2 h. **34**: Colorless crystals from *n*-hexane–Et_2O (1:1); mp 45 °C; $[\alpha]^{20}_D$ −40.0° (*c* 0.585, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 0.89 (tripletoid m, 3 H), 1.24–1.41 (m, 4 H), 1.43–1.68 (m, 2 H), 2.43 (s, 3 H), 2.81 (m, 2 H), 3.03 (ddd, J = 13.9, 6.3, 4.9 Hz, 1 H), 3.27 (ddd, J = 13.9, 6.3, 3.2 Hz, 1 H), 4.85 (m, 1 H), 7.30–7.33 (m, 2 H), 7.72–7.76 (m, 2 H). Anal. Calcd for $C_{14}H_{21}NO_3S$: C, 59.34; H, 7.47; N, 4.94. Found: C, 59.05; H, 7.38; N, 4.85.

Reaction of Activated Aziridne 11 with KH in CH_2Cl_2. Synthesis of 14 and 35. To a stirred suspension of 64.2 mg (1.6 mmol) of KH in 2 mL of CH_2Cl_2 at 0 °C under argon was added a solution of 118 mg (0.4 mmol) of alcohol **11** in 2 mL of CH_2Cl_2. The mixture was allowed to warm to rt and the stirring was continued for 18 h. The reaction was quenched with 2 mL of 5% NH_4Cl at −78 °C with stirring. The mixture was extracted with EtOAc and the extract was washed with water and dried over $MgSO_4$. The usual workup followed by flash chromatography over silica gel with *n*-hexane–EtOAc (4:1) gave 5.3 mg (4.4% yield) of **35**, and further elution gave

100 mg (84.7% yield) of **14**. The structure of **14** was identified by comparing its ^{1}H NMR spectrum (270 MHz, $CDCl_3$) with that of an authentic sample of **14**. **35**: A colorless oil; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.22–1.76 (m, 20 H), 2.42 (s, 6 H), 2.85 (dd, J = 7.0, 3.2 Hz, 2 H), 3.46 (dd, J = 15.8, 7.0 Hz, 2 H), 3.71 (dd, J = 15.8, 3.2 Hz, 2 H), 4.93 (s, 2 H), 7.27–7.32 (m, 4 H), 7.69–7.74 (m, 4 H); LRMS (FAB) m/z 603 (MH^+), 585, 584, 308 (base peak), 278, 184, 155, 152, 91, 81, 42, 41; HRMS (FAB) m/z calcd for $C_{31}H_{43}N_2O_6S_2$ (MH^+) 603.2562; Found: 603.2556.

Reaction of (2*S*)-*N*-[(4-Methylphenyl)sulfonyl]-2-azetidinemethanol (36) with KH in CH_2Cl_2. By a procedure identical with that described for the preparation of **35** from alcohol **11**, 60.3 mg (0.25 mmol) of alcohol **36** was converted into 52 mg (84% yield) of dimer **40** by treatment with 40.1 mg (1 mmol) of KH in CH_2Cl_2 at 0 °C for 3 h. **40**: Colorless crystals from Et_2O–CH_2Cl_2 (5:1); mp 100–101 °C; $[\alpha]^{20}_D$ −122° (c 0.583, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.96 (m, 2 H), 2.22 (ddd, J = 16.7, 11.0, 8.6 Hz, 2 H), 2.45 (s, 6 H), 3.58 (m, 2 H), 3.68–3.80 (m, 6 H), 4.07 (m, 2 H), 4.74 (s, 2 H), 7.35–7.39 (m, 4 H), 7.72–7.76 (m, 4 H); LRMS (FAB) m/z 495 (MH^+), 254 (base peak), 155, 91; HRMS (FAB) m/z calcd for $C_{23}H_{31}N_2O_6S_2$ (MH^+) 495.1623; found 495.1629. Anal. Calcd for $C_{23}H_{30}N_2O_6S_2$: C, 55.85; H, 6.11; N, 5.66. Found: C, 55.87; H, 6.13; N, 5.63.

Reaction of (2*S*)-*N*-[(4-Methylphenyl)sulfonyl]-2-azetidinemethanol (36) with *tert*-BuOK in CH_2Cl_2. To a stirred suspension of 112 mg (1 mmol) of *t*-BuOK in 2 mL of CH_2Cl_2 at 0 °C under argon was added a solution of 60.3 mg (0.25 mmol) of alcohol **36** in 2 mL of CH_2Cl_2. The mixture was allowed to stir at rt for 1 h. The reaction was quenched with 2 mL of 5% NH_4Cl at 0 °C with vigorous stirring. The mixture was extracted with EtOAc and the extract was washed with water and dried over $MgSO_4$. The usual workup followed by flash chromatography over silica gel with *n*-hexane–EtOAc (2:1) gave 6.3 mg (7.7% yield) of **42**, and further elution gave 49 mg (75% yield) of **40.** The structure of **40** was identified by comparing its ^{1}H NMR spectrum (270 MHz, $CDCl_3$) with that of an authentic sample of **40**. **42**: A colorless oil; $[\alpha]^{32}_D$ −80.4° (c 0.16, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.24 (s, 9 H), 1.95 (m, 1 H), 2.20 (ddd, J = 17.0, 10.8, 8.3 Hz, 1 H), 2.46 (s, 3 H), 3.59 (dd, J = 17.0, 8.3 Hz, 1 H), 3.67–3.75 (m, 3 H), 4.07 (ddd, J = 12.7, 8.3, 4.7 Hz, 1 H), 4.76 (d, J = 7.4 Hz, 1 H), 4.82 (d, J = 7.4 Hz, 1 H), 7.34–7.37 (m, 2 H), 7.72–7.75 (m, 2 H); LRMS (FAB) m/z 328 (MH^+), 270, 242 (base peak), 210, 155, 91, 57; HRMS (FAB) m/z calcd for $C_{16}H_{26}NO_4S$ (MH^+) 328.1582; found: 328.1585.

Reaction of (2*S*)-*N*-[(4-Methylphenyl)sulfonyl]prolinol (37) with KH in CH_2Cl_2. By a procedure identical with that described for the preparation of **40** from alcohol **36**, 63.8 mg (0.25 mmol) of alcohol **37** was converted into 62 mg (95% yield) of dimer **41** by treatment with 40.1 mg (1 mmol) of KH in CH_2Cl_2 at 0 °C for 3 h. **41**: A colorless oil; $[\alpha]^{20}_D$ −108° (c 1.36, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.50–1.66 (m, 4 H), 1.78–1.95 (m, 4 H), 2.42 (s, 6 H), 3.10 (m, 2 H), 3.44 (m, 2 H), 3.54 (m, 2 H), 3.77 (m, 4 H), 4.69 (s, 2 H), 7.30–7.33 (m, 4 H), 7.72–7.76 (m, 4 H); LRMS (FAB) m/z 523 (MH^+), 521, 268 (base peak), 224, 155, 112, 91; HRMS (FAB) m/z calcd for $C_{25}H_{35}N_2O_6S_2$ (MH^+) 523.1936; found 523.1927. Anal. Calcd for $C_{25}H_{34}N_2O_6S_2$: C, 57.45; H, 6.56; N, 5.36. Found: C, 57.23; H, 6.57; N, 5.09.

Reaction of (2*S*)-*N*-[(4-Methylphenyl)sulfonyl]prolinol (37) with *t*-BuOK in CH_2Cl_2. By a procedure identical with that described for the preparation of **40** and **42** from alcohol **36**, 63.8 mg (0.25 mmol) of alcohol **37** was converted into dimeric compounds **41** (53.2 mg, 82% yield) and **43** (14.1 mg, 17% yield) by treatment with 112 mg (1 mmol) of *t*-BuOK in CH_2Cl_2. The structure of **41** was confirmed by comparing its ^{1}H NMR spectrum (270 MHz, $CDCl_3$) with that of an authentic sample of **41**. **43**: A colorless oil; $[\alpha]^{32}_D$ −81.7° (c 0.35, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.25 (s, 9 H), 1.53–1.64 (m, 2 H), 1.80–1.86 (m, 2 H), 2.43 (s, 3 H), 3.11 (m, 1 H), 3.42 (m, 1 H), 3.51 (dd, J = 10.5, 9.2 Hz, 1 H), 3.77 (m, 2 H), 4.75 (d, J = 7.3 Hz, 1 H), 4.79 (d, J = 7.3 Hz, 1 H), 7.29–7.32 (m, 2 H), 7.71–7.75 (m, 2 H); LRMS (FAB) m/z 342 (MH^+), 340, 268, 256 (base peak), 238, 224, 188, 186, 155, 91, 70, 57. HRMS (FAB) m/z calcd for $C_{17}H_{28}NO_4S$ (MH^+) 342.1739; found: 342.1731.

(*S*)-*N*-[(4-Methylphenyl)sulfonyl]valinol (44) and (2*R*,3*S*)-3-Amino-2-methyl-*N*-[(4-methylphenyl)sulfonyl]-1-butanol (45) from 9. To a stirred slurry of CuI (8.27 g, 43.4 mmol) in 50 mL of Et_2O at −78 °C under argon was added by syringe 58 mL (87 mmol) of 1.5 M MeLi–LiBr in Et_2O, and the mixture was allowed to warm to rt. The mixture was recooled to −78 °C, where a solution of aziridine **9** (2.62 g, 10.9 mmol) in 50 mL of Et_2O was added dropwise with stirring and the mixture was stirred for 18 h with warming rt. The mixture was recooled to −78 °C, and the reaction was quenched with 20 mL of a saturated NH_4Cl–28% NH_4OH (1:1) solution with vigorous stirring. The mixture was extracted with Et_2O–CH_2Cl_2 (4:1), and the usual workup followed by flash chromatography over silica gel with *n*-hexane–EtOAc (1:1) gave 1.35 g (48% yield) of **44**, and further elution gave 1.30 g (46% yield) of **45**. **44**: Colorless crystals from *n*-hexane–Et_2O (1:2); mp 88–89 °C; $[\alpha]^{27}_D$ −26° (c 0.90, $CHCl_3$); IR ($CHCl_3$) 3540, 3400 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.786 (d, J = 6.8 Hz, 3 H), 0.791 (d, J = 6.8 Hz, 3 H), 1.82 (m, 1 H), 1.99 (broad s, 1 H), 2.43 (s, 3 H), 3.07 (m, 1 H), 3.50–3.65 (m, 2 H), 4.95 (m, 1 H), 7.26–7.33 (m, 2 H), 7.75–7.80 (m, 2 H). Anal. Calcd for $C_{12}H_{19}NO_3S$: C, 56.01; H, 7.45; N, 5.45. Found: C, 55.86; H, 7.40; N, 5.41. **45**: Colorless crystals from *n*-hexane–Et_2O (1:3); mp 99 °C; $[\alpha]^{26}_D$ −5.1° (c 0.923, $CHCl_3$); IR ($CHCl_3$) 3570, 3400, 3280 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.73 (d, J = 7.1 Hz, 3 H), 0.89 (d, J = 6.8 Hz, 3 H), 1.74 (m, 2 H), 2.44 (s, 3 H), 2.61 (broad s, 1 H), 3.48 (dd, J = 11.2, 4.6 Hz, 1 H), 3.50–3.71 (m, 2 H), 4.75 (d, J = 9.3 Hz, 1 H), 7.30–7.34 (m, 2 H), 7.74–7.80 (m, 2 H). Anal. Calcd for $C_{12}H_{19}NO_3S$: C, 56.01; H, 7.45; N, 5.45. Found: C, 55.83; H, 7.59; N, 5.34.

(*S*)-*N*-[(4-Methylphenyl)sulfonyl]valinol (44) from 46. To a stirred solution of 285 mg (1 mmol) of methyl (*S*)-*N*-[(4-methylphenyl)sulfonyl]valinate (**46**) in 2 mL of CH_2Cl_2 at −78 °C under argon was added dropwise 4.3 mL (4 mmol) of a 0.93 M solution of DIBAL in *n*-hexane. The mixture was allowed to warm to rt and the stirring was continued for 18 h. The mixture was recooled to −78 °C, where a saturated NH_4Cl solution (5 mL) was added dropwise with vigorous stirring. The mixture was made acidic with 1 N HCl at −20 °C and extractred with EtOAc. The usual workup followed by flash chromatography over silica gel with *n*-hexane–EtOAc (2:1) gave a crystalline mass. Recrystallization from *n*-hexane–Et_2O (1:2) gave 215 mg (84% yield) of the title compound **44** as colorless crystals: mp 88–89 °C; $[\alpha]^{20}_D$ −29.4° (c 0.837, $CHCl_3$); IR ($CHCl_3$) 3540, 3400 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.786 (d, J = 6.8 Hz, 3 H), 0.791 (d, J = 6.8 Hz, 3 H), 1.82 (m, 1 H), 1.99 (broad s, 1 H), 2.43 (s, 3 H), 3.07 (m, 1 H), 3.50–3.65 (m, 2 H), 4.95 (m, 1 H), 7.26–7.33 (m, 2 H), 7.75–7.80 (m, 2 H). Anal. Calcd for $C_{12}H_{19}NO_3S$: C, 56.01; H, 7.45; N, 5.45. Found: C, 55.84; H, 7.51; N, 5.39.

(2*S*,3*S*)-2,3-Dimethyl-*N*-[(4-methylphenyl)sulfonyl]-1-azacyclobutane (47) from 45. To a stirred solution of 50 mg (0.194 mmol) of amino alcohol **45** in 2 mL of THF were added 61.2 mg (0.233 mmol) of triphenylphosphine and 40.6 mg (0.233 mmol) of diethyl azodicarboxylate at 0 °C, and the mixture was allowed to warm to rt and to stir at this temperature for 18 h. The mixture was concentrated under reduced pressure to afford an oil, which was flash chromatographed on a silica gel column. Elution with *n*-hexane–EtOAc (3:1) gave a crystalline residue. Recrystallization from *n*-hexane–Et_2O (1:1) gave 46 mg (99% yield) of the title compound **47** as colorless crystals: mp 74 °C; $[\alpha]^{20}_D$ +86.1° (c 0.78, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.15 (d, J = 7.2 Hz, 3 H), 1.28 (d, J = 6.6 Hz, 3 H), 2.24 (ddd, J = 15.4, 7.9, 3.4 Hz, 1 H), 2.46 (s, 3 H), 3.27 (dd, J = 7.9, 3.4 Hz, 1 H), 3.61 (t, J = 7.9 Hz, 1 H), 3.96 (ddd, J = 13.2, 8.2, 6.6 Hz, 1 H), 7.34–7.38 (m, 2 H), 7.68–7.74 (m, 2 H). Anal. Calcd for $C_{12}H_{17}NO_2S$: C, 60.22; H, 7.16; N, 5.85. Found: C, 59.85; H, 7.26; N, 5.88.

(*R*)-*N*-[(4-Methylphenyl)sulfonyl]valinol (48) and (2*S*,3*S*)-3-Amino-2-methyl-*N*-[(4-methylphenyl)sulfonyl]-1-butanol (49) from 23. By a procedure identical with that described for the synthesis of **44** and **45** from **9**, 241 mg (1 mmol) of **23** was converted into 164 mg (64% yield) of **48** and

87 mg (34% yield) of **49** by treatment with $Me_2CuLi{\cdot}LiI{\cdot}2LiBr$ in Et_2O. **48**: Colorless crystals from Et_2O; mp 88–89 °C; $[\alpha]^{20}_D$ +27.3° (*c* 0.70, $CHCl_3$); IR ($CHCl_3$) 3540, 3400 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.795 (d, J = 6.8 Hz, 3 H), 0.788 (d, J = 6.8 Hz, 3 H), 1.78 (m, 1 H), 2.06 (broad s, 1 H), 2.43 (s, 3 H), 3.05 (m, 1 H), 3.52–3.62 (m, 2 H), 4.88 (d, J = 8.4 Hz, 1 H), 7.28–7.32 (m, 2 H), 7.76–7.80 (m, 2 H). Anal. Calcd for $C_{12}H_{19}NO_3S$: C, 56.01; H, 7.45; N, 5.45. Found: C, 55.72; H, 7.49; N, 5.48. **49**: Colorless crystals from Et_2O; mp 79 °C; $[\alpha]^{20}_D$ −17.4° (*c* 0.505, $CHCl_3$); IR ($CHCl_3$) 3550, 3380, 3270 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.90 (d, J = 7.0 Hz, 3 H), 0.98 (d, J = 6.7 Hz, 3 H), 1.57 (m, 1 H), 2.05 (broad s, 1 H), 2.43 (s, 3 H), 3.29 (m, 1 H), 3.43 (dd, J = 11.2, 4.7 Hz, 1 H), 3.87 (dd, J = 11.2, 3.7 Hz, 1 H), 4.94 (d, J = 8.4 Hz, 1 H), 7.26–7.32 (m, 2 H), 7.75–7.79 (m, 2 H). Anal. Calcd for $C_{12}H_{19}NO_3S$: C, 56.01; H, 7.45; N, 5.45. Found: C, 55.91; H, 7.51; N, 5.28.

***(R)*-*N*-[(4-Methylphenyl)sulfonyl]valinol (48) from 50.** By a procedure identical with that described for the synthesis of **44** from **46**, 287 mg (1 mmol) of **50** was reduced to afford 193 mg (75% yield) of the title compound **48** as colorless crystals: mp 88–89 °C (recrystallized from Et_2O); $[\alpha]^{20}_D$ +29.9° (*c* 0.803, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 0.787 (d, J = 6.8 Hz, 3 H), 0.79 (d, J = 6.8 Hz, 3 H), 1.77 (m, 1 H), 2.21 (m, 1 H), 2.43 (s, 3 H), 3.07 (m, 1 H), 3.50–3.65 (m, 2 H), 4.95 (m, 1 H), 7.26–7.33 (m, 2 H), 7.77–7.80 (m, 2 H). Anal. Calcd for $C_{12}H_{19}NO_3S$: C, 56.01; H, 7.45; N, 5.45. Found: C, 55.97; H, 7.64; N, 5.37.

(2*S*,3*R*)-2,3-Dimethyl-*N*-[(4-methylphenyl)sulfonyl]-1-azacyclobutane (51) from 49. By a procedure identical with that described for the synthesis of **47** from **45**, 40 mg (0.155 mmol) of **49** was converted into 25.6 mg (69% yield) of the title compound **51**: Colorless crystals from *n*-hexane–Et_2O (1:1); mp 97 °C; $[\alpha]^{20}_D$ +60° (*c* 0.61, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.83 (d, J = 6.8 Hz, 3 H), 1.36 (d, J = 6.2 Hz, 3 H), 2.19 (m, 1 H), 2.46 (s, 3 H), 3.08 (t, J = 7.7 Hz, 1 H), 3.47 (m, 1 H), 3.80 (m, 1 H), 7.34–7.37 (m, 2 H), 7.69–7.73 (m, 2 H). Anal. Calcd for $C_{12}H_{17}NO_2S$: C, 60.22; H, 7.16; N, 5.85. Found: C, 60.30; H, 7.29; N, 5.83.

(2*S*,3*S*)-2-Amino-*N*-[(4-methylphenyl)sulfonyl]-3-methyl-1-heptanol (52) and (2*S*,3*R*)-2-Amino-3-(hydroxymethyl)-*N*-[(4-methylphenyl)sulfonyl]heptane (53) from 9. To a stirred suspension of CuI (476 mg, 2.5 mmol) in 3 mL of Et_2O at −78 °C under argon was added by syringe 3.03 mL (5 mmol) of 1.65 M *n*-BuLi in *n*-hexane, and the mixture was allowed to warm to 0 °C. The mixture was recooled to −78 °C, where a solution of 121 mg (0.5 mmol) of **9** in 2 mL of Et_2O was added dropwise with stirring and the mixture was stirred for 18 h with warming to rt. The mixture was cooled to −78 °C, and then the reaction was quenched with 4 mL of a saturated NH_4Cl–28% NH_4OH (1:1) solution with stirring. The mixture was extracted with EtOAc and the usual workup followed by flash chromatography over silica gel with *n*-hexane–EtOAc (3:1) gave a 45:55 mixture of **52** and **53** in a combined yield of 45%. (The ratios of the amino alcohols **52** and **53** were determined by HPLC). The mixture was separated by HPLC (Cosmosil packed column 5SL, THF–*n*-hexane = 1:4), yielding, in order of elution, **52** and **53**. **52**: Colorless crysatals from *n*-hexane–Et_2O (1:1); mp 64 °C; $[\alpha]^{20}_D$ −24.8° (*c* 0.156, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.77 (d, J = 6.9 Hz, 3 H), 0.81 (m, 3 H), 0.86–1.32 (m, 6 H), 1.55 (m, 1 H), 2.01 (dd, J = 5.7, 5.7 Hz, 1 H), 2.43 (s, 3 H), 3.11 (m, 1 H), 3.57 (d, J = 5.7 Hz, 1 H), 3.59 (d, J = 5.1 Hz, 1 H), 4.84 (d, J = 8.2 Hz, 1 H), 7.29–7.33 (m, 2 H), 7.76–7.80 (m, 2 H); LRMS (FAB) m/z 300 (MH^+, base peak), 268, 172, 155, 91, 69; HRMS (FAB) m/z calcd for $C_{15}H_{26}NO_3S$ (MH^+) 300.1633; found 300.1628. **53**: A colorless oil; $[\alpha]^{20}_D$ +12.3° (*c* 0.32, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.85 (m, 3 H), 0.95 (d, J = 6.9 Hz, 3 H), 1.05–1.26 (m, 6 H), 1.56 (m, 1 H), 2.30 (dd, J = 5.4, 5.4 Hz, 1 H), 2.43 (s, 3 H), 3.53–3.64 (m, 3 H), 5.15 (d, J = 9.2 Hz, 1 H), 7.29–7.32 (m, 2 H), 7.76–7.78 (m, 2 H); LRMS (FAB) m/z 300 (MH^+, base peak), 198, 172, 155, 146, 139, 91, 69; HRMS (FAB) m/z calcd for $C_{15}H_{26}NO_3S$ (MH^+) 300.1633; found: 300.1640.

(2*R*,3*S*)-2-Amino-3-methyl-*N*-[(4-methylphenyl)sulfonyl]-1-heptanol (54) and (2*S*,3*S*)-2-Amino-3-(hydroxymethyl)-*N*-[(4-methylphenyl)sulfonyl]heptane (55) from 23. To a stirred slurry of CuCN (358.2 mg, 4 mmol) in 5 mL of THF at −78 °C under argon was added by syringe 4.82 mL (8 mmol) of 1.66 M *n*-BuLi in *n*-hexane, and the mixture was allowed to warm to 0 °C. The mixture was recooled to −78 °C, where a solution of **23** (121 mg, 0.5 mmol) in 2 mL of THF was added dropwise with stirring, and the mixture was stirred for 18 h with warming to 0 °C. The mixture was recooled to −78 °C, and then the reaction was quenched with 4 mL of a saturated NH_4Cl–28% NH_4OH (1:1) solution with vigorous stirring. The mixture was extracted with EtOAc and the usual workup gave a 79:21 mixture of **54** and **55** in a combined yield of 86%. (The ratios of the amino alcohols **54** and **55** were determined by HPLC.) The mixture was separated by HPLC (Cosmosil packed column 5SL, THF–*n*-hexane = 1:4), yielding, in order of elution, **54** and **55**. **54**: Colorless crystals from *n*-hexane–Et_2O (1:3); mp 84 °C; $[\alpha]^{20}_D$ +17.0° (*c* 0.283, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.78 (d, J = 6.9 Hz, 3 H), 0.78 (m, 3 H), 0.91–0.98 (m, 2 H), 1.00–1.11 (m, 4 H), 1.61 (m, 1 H), 2.03 (dd, J = 7.1, 4.6 Hz, 1 H), 2.43 (s, 3 H), 3.19 (dddd, J = 12.8, 6.2, 4.6, 4.6 Hz, 1 H), 3.54 (ddd, J = 11.3, 7.1, 4.6 Hz, 1 H), 3.62 (ddd, J = 11.3, 6.2, 4.6 Hz, 1 H), 4.62 (d, J = 8.2 Hz, 1 H), 7.30–7.32 (m, 2 H), 7.76–7.79 (m, 2 H); LRMS (FAB) m/z 300 (MH^+, base peak), 268, 172, 155, 139, 91, 69; HRMS (FAB) m/z calcd for $C_{15}H_{26}NO_3S$ (MH^+) 300.1633; found 300.1641. **55**: A colorless oil; $[\alpha]^{20}_D$ −19.0° (*c* 0.569, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 0.83 (m, 3 H), 1.05 (d, J = 6.9 Hz, 3 H), 1.09–1.38 (m, 7 H), 1.99 (m, 1 H), 2.43 (s, 3 H), 3.39 (m, 1 H), 3.56 (ddd, J = 10.8, 5.5, 3.9 Hz, 1 H), 3.94 (ddd, J = 10.8, 4.6, 2.3 Hz, 1 H), 5.28 (d, J = 8.1 Hz, 1 H), 7.27–7.31 (m, 2 H), 7.75–7.79 (m, 2 H); LRMS (FAB) m/z 300 (MH^+, base peak), 198, 172, 155, 146, 139, 91, 69; HRMS (FAB) m/z calcd for $C_{15}H_{26}NO_3S$ (MH^+) 300.1633; found 300.1631.

(1*S*,2*S*)-2-Amino-1-ethyl-*N*-[(4-methylphenyl)sulfonyl]-1-propanol (56), (1*R*,2*S*)-2-Amino-1-ethyl-*N*-[(4-methylphenyl)sulfonyl]-1-propanol (57), (*S*)-*N*-[(4-Methylphenyl)sulfonyl]valinol (44), and (2*R*,3*S*)-3-Amino-2-methyl-*N*-[(4-methylphenyl)sulfonyl]-1-butanol (45). To a stirred suspension of CuCN (717 mg, 8 mmol) in 15 mL of THF at −78 °C was added by syringe 5.7 mL (8 mmol) of 1.4 M MeLi–LiBr in Et_2O, and the mixture was stirred at −78 °C for 15 min. Aziridinemethanol **9** (483 mg, 2 mmol) in 8 mL of THF was added dropwise with stirring to the reagent at −78 °C and the mixture was stirred for 18 h at rt. The mixture was recooled to −78 °C, and then the reaction was quenched with 16 mL of a saturated NH_4Cl–28% NH_4OH (1:1) solution with vigorous stirring. The mixture was extracted with Et_2O–CH_2Cl_2 (4:1) and the usual workup gave a 1:8:36:55 mixture of **44**, **45**, **56**, and **57** in a combined yield of 93%. (The ratios of the amino alcohols **44**, **45**, **56**, and **57** were determined by HPLC.) The mixture was separated by HPLC (Cosmosil 5C18 packed column; MeCN–H_2O = 22:78), yielding, in order of elution, **45**, **44**, **57**, and **56**. The amino alcohols **44** and **45** thus obtained were identical to the authentic samples of **44** and **45** obtained by reaction of **9** with $Me_2CuLi{\cdot}2LiBr{\cdot}LiI$. **56**: Colorless crystals from *n*-hexane–Et_2O (1:3); mp 91 °C; $[\alpha]^{25}_D$ −7.3° (*c* 0.77, $CHCl_3$); IR ($CHCl_3$) 3550, 3400, 1598 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.88 (t, J = 7.3 Hz, 3 H), 1.02 (d, J = 6.6 Hz, 3 H), 1.44 (m, 2 H), 1.70 (broad s, 1 H), 1.93 (broad s, 1 H), 2.43 (s, 3 H), 3.21–3.37 (m, 2 H), 4.83 (d, J = 8.3 Hz, 1 H), 7.26–7.32 (m, 2 H), 7.74–7.80 (m, 2 H); HRMS (EI) m/z calcd for $C_{12}H_{20}NO_3S$ (MH^+) 258.1164; found 258.1172. **57**: Colorless needles from Et_2O; mp 108 °C; $[\alpha]^{20}_D$ −31.7° (*c* 0.74, $CHCl_3$); IR ($CHCl_3$) 3550, 3400, 3290, 1600 cm^{-1}; ^1H NMR (200 MHHz, $CDCl_3$) δ 0.91 (t, J = 7.3 Hz, 3 H), 0.95 (d, J = 6.8 Hz, 3 H), 1.31–1.45 (m, 2 H), 2.43 (s, 3 H), 3.34 (m, 1 H), 3.48 (ddd, J = 13.2, 6.6, 3.2 Hz, 1 H), 5.04 (m, 1 H), 7.27–7.33 (m, 2 H), 7.75–7.79 (m, 2 H). Anal. Calcd for $C_{12}H_{19}NO_3S$: C, 56.01; H, 7.44; N, 5.44. Found: C, 55.83; H, 7.28; N, 5.52.

By a procedure similar to that described for the reaction of **9** with MeCu(CN)Li·LiBr, 121 mg (0.5 mmol) of aziridinemethanol **23** was reacted with MeCu(CN)Li·LiBr (5 equiv) to yield 104 mg of a 7:0.8:39:53 mixture of amino alcohols **48**, **49**, **56**, and **57** in a combined yield of 81%. (The ratios of the protected amino alcohols **48**, **49**, **56**, and **57** were determined by HPLC.)

(1*S*,2*S*)-2-Amino-1-ethyl-*N*-[(4-methylphenyl)sulfonyl]-1-propanol (56) from Epoxide 12. To a stirred solution of CuCN (358 mg, 4 mmol) and LiCl (339 mg, 8 mmol) in 5 mL of THF at −78 °C under argon was added by syringe 2.67 mL (4 mmol) of 1.5 M MeLi−LiBr in Et_2O, and the mixture was allowed to warm to 0 °C. The mixture was recooled to −78 °C, where a solution of epoxide **12** (241 mg, 1 mmol) in 2 mL of THF was added dropwise with stirring and the mixture was stirred for 2 h at 0 °C. The mixture was recooled to −78 °C, and then the reaction was quenched with 4 mL of a saturated NH_4Cl−28% NH_4OH (1:1) solution with vigorous stirring. The mixture was extracted with EtOAc and the usual workup followed by flash chromatography over silica gel with *n*-hexane−EtOAc (3:1) gave 252 mg (98% yield) of a crystalline mass. Recrystallization from a mixed solvent of *n*-hexane−Et_2O (1:3) gave the title compound **56** as colorless crystals: mp 91 °C; $[\alpha]^{27}_D$ −7.3° (*c* 0.74, $CHCl_3$); IR ($CHCl_3$) 3550, 3400, 1598 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, J = 7.4 Hz, 3 H), 1.02 (d, J = 6.6 Hz, 3 H), 1.44 (m, 2 H), 1.80 (broad s, 1 H), 2.43 (s, 3 H), 3.21−3.37 (m, 2 H), 4.78 (m, 1 H), 7.29−7.31 (m, 2 H), 7.75−7.79 (m, 2 H). Anal. Calcd for $C_{12}H_{19}NO_3S$: C, 56.01; H, 7.44; N, 5.44. Found: C, 55.50; H, 7.49; N, 5.41.

(1*S*,2*S*)-2-Amino-1-ethyl-*N*-[(4-methylphenyl)sulfonyl]-1-propanol (56) from 58. A suspension of PtO_2 (40 mg) and **58** (201 mg, 1 mmol) in ethanol (15 mL) was subjected to catalytic hydrogenation for 1 h. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure to leave an oily residue, which was purified by flash chromatography over silica gel with *n*-hexane−EtOAc (3:1) to yield 176 mg (87% yield) of (1*S*,2*S*)-2-amino-1-ethyl-*N*-(*tert*-butoxycarbonyl)-1-propanol as a colorless oil: Kugelrohr distillation, 100 °C/1 Torr; $[\alpha]^{20}_D$ −8.19° (*c* 0.464, $CHCl_3$); IR ($CHCl_3$) 3470, 1693, 1493, 1362, 1155 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.97 (t, J = 7.6 Hz, 3 H), 1.18 (d, J = 6.8 Hz, 3 H), 1.44 (s, 9 H), 2.16 (m, 1 H), 3.39 (m, 1 H), 3.69 (m, 1 H), 4.70 (m, 1 H); HRMS (EI) m/z calcd for $C_{10}H_{21}NO_3$ 203.1521; found 203.1525. To a stirred solution of (1*S*,2*S*)-2-amino-1-ethyl-*N*-(*tert*-butoxycarbonyl)-1-propanol (110 mg, 0.54 mmol) in CH_2Cl_2 (8 mL) at 0 °C was added dropwise 2 mL of TFA, and the mixture was allowed to warm to rt and the stirring was continued for 1 h. The mixture was concentrated under reduced pressure to afford an oil. To the oil was added 30 mL of 4 N HCl in dioxane, and the mixture was concentrated under reduced pressure. The residual oil was dissolved in 7 mL of $CHCl_3$. To the stirred chloroform solution were added successively 0.2 mL of Et_3N and 103 mg (0.54 mmol) of tosyl chloride at 0 °C. The mixture was allowed to warm to rt, and the stirring was continued for 20 h. The reaction was quenched with 5 mL of a saturated $NaHCO_3$ solution with vigorous stirring. The mixture was extracted with EtOAc, and the extract was washed successively with 1 N HCl, water, 5% $NaHCO_3$, and water, and dried over $MgSO_4$. The usual workup followed by flash chromatography over silica gel with *n*-hexane−EtOAc (2:1) gave a crystalline residue. Recrystallization from a mixed solvent of *n*-hexane−Et_2O (1:2) gave 107 mg (77% yield) of the title compound **56** as colorless crystals: mp 91 °C; $[\alpha]^{20}_D$ −7.3° (*c* 1.30, $CHCl_3$); IR ($CHCl_3$) 3550, 3400 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.88 (t, J = 7.3 Hz, 3 H), 1.02 (d, J = 6.6 Hz, 3 H), 1.44 (m, 2 H), 1.70 (broad s, 1 H), 1.93 (broad s, 1 H), 2.43 (s, 3 H), 3.21−3.37 (m, 2 H), 4.83 (d, J = 8.3 Hz, 1 H), 7.26−7.32 (m, 2 H), 7.74−7.80 (m, 2 H). Anal. Calcd for $C_{12}H_{19}NO_3S$: C, 56.01; H, 7.44; N, 5.44. Found: C, 55.96; H, 7.52; N, 5.40.

(1*R*,2*S*)-2-Amino-1-ethyl-*N*-[(4-methylphenyl)sulfonyl]-1-propanol (57) from Epoxide 24. By a procedure identical with that described for the preparation of alcohol **56** from epoxide **12**, 30 mg (0.124 mmol) of epoxide **24** was converted into 27.1 mg (85% yield) of alcohol **57** by treatment with MeCu(CN)Li·LiBr for 6 h at rt followed by flash chromatography over silica gel with *n*-hexane−EtOAc (3:1). **57**: Colorless needles from Et_2O; mp 108 °C; $[\alpha]^{27}_D$ −29.0° (*c* 0.29, $CHCl_3$); IR ($CHCl_3$) 3550, 3400, 3290, 1600 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.91 (t, J = 7.3 Hz, 3 H), 0.95 (d, J = 6.8 Hz, 3 H), 1.31−1.45 (m, 2 H), 2.43 (s, 3 H), 3.34 (m, 1 H), 3.48 (m, 1 H), 4.73 (d, J = 8.2 Hz, 1 H), 7.29−7.32 (m, 2 H), 7.75−7.78 (m, 2 H). Anal. Calcd for $C_{12}H_{19}NO_3S$: C, 56.01; H, 7.44; N, 5.44. Found: C, 55.75; H, 7.55; N, 5.24.

(1*R*,2*S*)-2-Amino-1-ethyl-*N*-[(4-methylphenyl)sulfonyl]-1-propanol (57) from 59. By a procedure identical with that described for the preparation of **56** from **58**, 150 mg (0.75 mmol) of **59** was converted into 98 mg (64% yield) of (1*R*,2*S*)-2-amino-1-ethyl-*N*-(*tert*-butoxycarbonyl)-1-propanol by catalytic hydrogenation over PtO_2 for 1 h followed by recrystallization from *n*-hexane to yield colorless silky needles: mp 107 °C; $[\alpha]^{20}_D$ −13.42° (*c* 0.790, $CHCl_3$); IR ($CHCl_3$) 3500, 1700 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.99 (t, J = 7.3 Hz, 3 H), 1.08 (d, J = 6.8 Hz, 3 H), 1.45 (s, 9 H), 2.27 (m, 1 H), 3.56 (m, 1 H), 3.71 (m, 1 H), 4.80 (m, 1 H). Anal. Calcd for $C_{10}H_{21}NO_3$: C, 59.08; H, 10.41; N, 6.89. Found: C, 58.80; H, 10.57; N, 6.90. This compound (88 mg, 0.43 mmol) was converted into 36 mg (33% yield) of the title compound **57** by a procedure identical with that described for the preparation of **56** from **58**. **57**: Colorless silky needles from Et_2O; mp 108 °C; $[\alpha]^{20}_D$ −28.4° (*c* 0.514, $CHCl_3$); IR ($CHCl_3$) 3550, 3400, 3290, 1600 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.91 (t, J = 7.3 Hz, 3 H), 0.95 (d, J = 6.8 Hz, 3 H), 1.31−1.45 (m, 2 H), 2.43 (s, 3 H), 3.34 (m, 1 H), 3.48 (ddd, J = 13.2, 6.6, 3.2 Hz, 1 H), 5.04 (m, 1 H), 7.27−7.33 (m, 2 H), 7.75−7.79 (m, 2 H). Anal. Calcd for $C_{12}H_{19}NO_3S$: C, 56.01; H, 7.44; N, 5.44. Found: C, 55.75; H, 7.55; N, 5.35.

(2*S*,3*S*)-2-Amino-3-hydroxy-*N*-[(4-methylphenyl)sulfonyl]octane (60) from 9. To a stirred solution of CuCN (896 mg, 10 mmol) and LiCl (848 mg, 20 mmol) in 8 mL of THF at −78 °C under argon was added by syringe 6.02 mL (10 mmol) of 1.66 M *n*-BuLi in *n*-hexane, and the mixture was allowed to warm to 0 °C. The mixture was recooled to −78 °C, where a solution of **9** (241 mg, 1 mmol) in 3 mL of THF was added dropwise with stirring and the mixture was stirred for 18 h with warming to rt. The mixture was recooled to −78 °C, and then the reaction was quenched with 4 mL of a saturated NH_4Cl−28% NH_4OH (1:1) solution with vigorous stirring. The mixture was extracted with EtOAc and the usual workup followed by flash chromatography over silica gel with *n*-hexane−EtOAc (3:1) gave 122 mg (41% yield) of the title compound **60**, and further elution gave 38.4 mg (16% recovery) of the unreacted substrate **9**. **60**: Colorless crystals from Et_2O; mp 80 °C; $[\alpha]^{20}_D$ −7.7° (*c* 0.52, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 0.86 (m, 3 H), 1.05 (d, J = 6.5 Hz, 3 H), 1.10−1.40 (m, 8 H), 1.76 (d, J = 4.6 Hz, 1 H), 2.43 (s, 3 H), 3.24 (dddd, J = 17.2, 10.6, 6.8, 3.8 Hz, 1 H), 3.39 (m, 1 H), 4.70 (d, J = 8.4 Hz, 1 H), 7.29−7.32 (m, 2 H), 7.75−7.78 (m, 2 H); LRMS (FAB) m/z 300 (MH^+, base peak), 268, 172, 155, 139, 91, 69; HRMS (FAB) m/z calcd for $C_{15}H_{26}NO_3S$ (MH^+) 300.1633; found: 300.1628.

(2*S*,3*S*)-2-Amino-3-hydroxy-*N*-[(4-methylphenyl)sulfonyl]octane (60) from Epoxide 12. To a stirred slurry of CuCN (268.7 mg, 3 mmol) in 3 mL of THF at −78 °C under argon was added by syringe 1.78 mL (3 mmol) of 1.69 M *n*-BuLi in *n*-hexane, and the mixture was allowed to warm to 0 °C. The mixture was recooled to −78 °C, where a solution of epoxide **12** (120.7 mg, 0.5 mmol) in 2 mL of THF was added dropwise with stirring, and the mixture was stirred for 2 h at 0 °C. The mixture was cooled to −78 °C, and then the reaction was quenched with 4 mL of a saturated NH_4Cl−28% NH_4OH (1:1) solution with stirring. The mixture was extracted with Et_2O−CH_2Cl_2 (4:1), and the usual workup followed by flash chromatography over silica gel with *n*-hexane−EtOAc (2:1) gave 148.2 mg (99% yield) of the title compound **60** as a crystalline mass. Recrystallization from Et_2O gave **60** as colorless crystals: mp 80 °C; $[\alpha]^{20}_D$ −8.1° (*c* 0.38, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 0.86 (m, 3 H), 1.05 (d, J = 6.5 Hz, 3 H),1.10−1.40 (m, 8 H), 1.83 (d, J = 4.6 Hz, 1 H), 2.43 (s, 3 H), 3.24 (dddd, J = 17.2, 10.6, 6.8, 3.8 Hz, 1 H), 3.39 (m, 1 H), 4.77 (d, J = 8.1 Hz, 1 H), 7.29−7.32 (m, 2 H), 7.75−7.78 (m, 2 H); LRMS (FAB) m/z 300 (MH^+, base peak), 282, 198, 155, 137, 136, 91; HRMS (FAB) m/z calcd for $C_{15}H_{26}NO_3S$ (MH^+) 300.1633; found: 300.1650.

(2*S*,3*R*)-2-Amino-3-hydroxy-*N*-[(4-methylphenyl)sulfonyl]octane (61) from 23. By a procedure identical with that described for the synthesis of **60** from **9**, 121 mg (0.5 mmol) of **23** was converted into 121.8 mg (81.4% yield) of the title compound **61** by treatment with BuCu(CN)Li. **61**: Colorless

crystals from Et_2O; mp 120 °C; $[\alpha]^{20}_D$ −21.5° (*c* 0.80, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (m, 3 H), 0.96 (d, *J* = 6.8 Hz, 3 H), 1.21−1.45 (m, 8 H), 1.89 (m, 1 H), 2.43 (s, 3 H), 3.33 (dddd, *J* = 16.7, 9.9, 6.8, 3.0 Hz, 1 H), 3.54 (m, 1 H), 4.90 (d, *J* = 7.9 Hz, 1 H), 7.28−7.33 (m, 2 H), 7.75−7.79 (m, 2 H). Anal. Calcd for $C_{15}H_{25}NO_3S$: C, 60.17; H, 8.42; N, 4.68. Found: C, 59.87; H, 8.62; N, 4.68.

(2*S*,3*R*)-2-Amino-3-hydroxy-*N*-[(4-methylphenyl)sulfonyl]octane (61) from Epoxide 24. By a procedure identical with that described for the preparation of **60** from **12**, 60.3 mg (0.25 mmol) of **24** was converted into 74.1 mg (99% yield) of alcohol **61** by treatment with BuCu(CN)Li followed by flash chromatography over silica gel with *n*-hexane−EtOAc (2:1). **61**: Colorless crystals from Et_2O; mp 120 °C; $[\alpha]^{20}_D$ −19.5° (*c* 0.708, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 0.87 (m, 3 H), 0.96 (d, *J* = 6.8 Hz, 3 H), 1.21−1.45 (m, 8 H), 1.89 (d, *J* = 5.9 Hz, 1 H), 2.43 (s, 3 H), 3.33 (dddd, *J* = 16.7, 9.9, 6.8, 3.0 Hz, 1 H), 3.54 (m, 1 H), 4.90 (d, *J* = 7.9 Hz), 7.28−7.33 (m, 2 H), 7.75−7.79 (m, 2 H); LRMS (FAB) *m*/*z* 300 (MH^+, base peak), 282, 198, 172, 155, 91; HRMS (FAB) *m*/*z* calcd for $C_{15}H_{26}NO_3S$ (MH^+) 300.1633; found 300.1627.

Representative Procedures. The following procedure is representative for reactions of 2,3-epoxy amines with *tert*-BuOK-*n*-BuLi. <sen>**Synthesis of (2*R*,3*S*)-1,2-Imino-3-heptanol (70) from 2,3-Epoxy amine (63).** To a stirred suspension of 505 mg (4.5 mmol) of *t*-BuOK in 5 mL of THF at −78 °C under argon was added dropwise *n*-BuLi (2.76 mL, 4.5 mmol, 1.63 M in *n*-hexane) and the mixture was stirred for 10 min. To the above mixture was added a solution of 388 mg of epoxy amine **63** in 3 mL of THF with stirring and the stirring was continued for 1.5 h. The reaction was quenched with 4 mL of a saturated NH_4Cl solution at −78 °C with vigorous stirring. The inorganic salts were removed by filtration through Celite and the Celite was washed with Et_2O (40 mL × 2). The combined organic solutions were dried over $MgSO_4$ and concentrated under reduced pressure to leave 328 mg (85% yield) of the title compound **70** as a colorless solid. Recrystallization from a mixed solvent of *n*-hexane−Et_2O (5:1) gave colorless crystals: mp 65 °C; $[\alpha]^{25}_D$ 39.9° (*c* 1.69, $CHCl_3$); IR ($CHCl_3$) 3450, 3330 cm^{-1} (OH and NH); ^1H NMR (270 MHz, $CDCl_3$) δ 0.92 (m, 3 H), 1.28−1.43 (m, 4 H), 1.45−1.57 (m, 3 H), 1.61 (d, *J* = 3.6 Hz, 1 H), 1.72 (d, *J* = 5.9 Hz, 1 H), 2.14 (ddd, *J* = 5.9, 3.6, 3.6 Hz, 1 H), 3.63 (m, 1 H); LRMS (FAB) *m*/*z* 130 (MH^+); HRMS (FAB) *m*/*z* calcd for $C_7H_{15}NO$ (MH^+) 130.1232; found 130.1237.

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Supplementary Material Available: Optimized geometries of (**67-A**, **TS**, and **68-A**), experimental procedures and spectral data for compounds **11**, **14**, **18**, **20**, **22**, **24**, **26**, **28**, **29**, **31−34**, **36**, **37**, **52−55**, **62−66**, **69**, and **71−75**, and copies of NMR spectra for compounds that have no combustion analysis (38 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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