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A Highly *cis*-Selective Synthesis of 2-Ethynylaziridines by Intramolecular Amination of Chiral Bromoallenes: Improvement of Stereoselectivity Based on the Computational Investigation

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Abstract: The base-mediated intramolecular amination of bromoallenes having an axial chirality is described. The treatment of (4*S*,a*R*)-4-alkyl-4-[*N*-(arylsulfonyl)amino]-1-bromobuta-1,2-dienes with NaH in DMF affords 2,3-*cis*-2-ethynylaziridines in good to excellent selectivity (2,3-*cis*:*trans* = 92:8−99:1). The reaction of (4*S*,a*S*)-bromoallenes with NaH/DMF also gives 2,3-*cis*-2-ethynylaziridines selectively (79:21−91:9). These experimental results have been rationalized by B3LYP density functional calculations together with the 6-31+G(d) basis set and the Onsager solvation model. The transition structures for *cis*-aziridine formation of both (4*S*,a*R*)- and (4*S*,a*S*)-bromoallenes in DMF are favored over the corresponding *trans* transition structures by 4.35 and 1.41 kcal/mol, respectively. Furthermore, the calculations predicted that a less polar solvent gives higher *cis* selectivity for (4*S*,a*S*)-bromoallenes. In fact, improvement of the *cis* selectivity to 99:1 has been realized by using a less polar solvent such as THF. The cyclization of bromoallenes bearing a β- or γ-amino group also affords four- and five-membered azacycles in a highly *cis*-selective manner.

Introduction

Reactions of bromoallenes have attracted much interest in recent years, because of their cumulated double bonds and high reactivity. These reactions involve organocopper-mediated substitutions,[1] palladium-catalyzed cross-coupling reactions,[2] and the formation of nucleophilic allenylmetal reagents.[3] Among them, the organocopper-mediated substitution of bromoallenes is extremely useful in that the substitution of propargylic oxygen by an alkyl group can be carried out with overall retention of configuration:[1c,d] both the bromination of propargyl esters with CuBr/LiBr[4] and alkylation of the resulting bromoallenes by organocopper reagents proceed with inversion of configuration.[5] In contrast, the reaction of bromoallenes with nitrogen nucleophiles is relatively limited. Although the intermolecular amination of racemic bromoallenes has been already reported,[6] an intramolecular reaction and a stereochemical course of the amination toward chiral bromoallenes are unprecedented as far as we are aware.

In connection with a research program directed toward the reactions of 2-ethynylaziridines both as carbon electrophiles[7] and nucleophiles,[8,9] we required a reliable synthetic method of

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(1) (a) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett*. **1984**, *25*, 3059−3062. (b) Caporusso, A. M.; Polizzi, C.; Lardicci, L. *Tetrahedron Lett*. **1987**, *28*, 6073−6076. (c) D′Aniello, F.; Mann, A.; Taddei, M. *J. Org. Chem*. **1996**, *61*, 4870−4871. (d) D′Aniello, F.; Mann, A.; Schoenfelder, A.; Taddei, M. *Tetrahedron* **1997**, *53*, 1447−1456. (e) Bernard, N.; Chemla, F.; Normant, J. F. *Tetrahedron Lett*. **1999**, *40*, 1649−1652. (f) Chemla, F.; Bernard, N.; Normant, J. *Eur. J. Org. Chem*. **1999**, 2067−2078. (g) Caporusso, A. M.; Filippi, S.; Barontini, F.; Salvadori, P. *Tetrahedron Lett*. **2000**, *41*, 1227−1230. (h) Conde, J. J.; Mendelson, W. *Tetrahedron Lett*. **2000**, *41*, 811−814.

(2) (a) Märkl, G.; Attenberger, P.; Kellner, J. *Tetrahedron Lett*. **1988**, *29*, 3651−3654. (b) Gillmann, T.; Hülsen, T.; Massa, W.; Wocadlo, S. *Synlett* **1995**, 1257−1259. (c) Saalfrank, R. W.; Haubner, M.; Deutscher, C.; Bauer, W.; Clark, T. *J. Org. Chem*. **1999**, *64*, 6166−6168. (d) Saalfrank, R. W.; Haubner, M.; Deutscher, C.; Bauer, W. *Eur. J. Org. Chem*. **1999**, 2367−2372.

(3) (a) Marshall, J. A.; Adams, N. D. *J. Org. Chem*. **1997**, *62*, 8976−8977. For a reaction of iodoallenes, see: (b) Marshall, J. A.; Grant, C. M. *J. Org. Chem*. **1999**, *64*, 8214−8219.

(4) (a) Montury, M.; Goré, J. *Synth. Commun*. **1980**, *10*, 873−879. (b) Elsevier, C. J.; Meijer, J.; Tadema, G.; Stehouwer, P. M.; Bos, H. J. T.; Vermeer, P. *J. Org. Chem*. **1982**, *47*, 2194−2196.

(5) Elsevier, C. J.; Vermeer, P.; Gedanken, A.; Runge, W. *J. Org. Chem*. **1985**, *50*, 364−367.

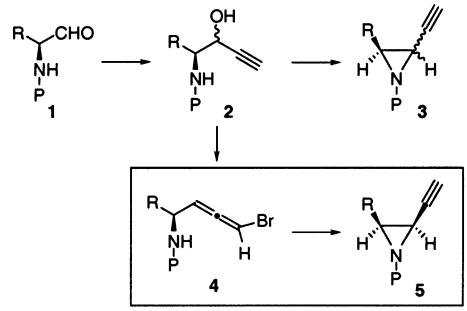
(6) (a) Mavrov, M. V.; Voskanyan, E. S.; Kucherov, V. F. *Tetrahedron* **1969**, *25*, 3277−3285. (b) Mavrov, M. V.; Rodionov, A. P.; Kucherov, V. F. *Tetrahedron Lett*. **1973**, *10*, 759−760. (c) Caporusso, A. M.; Geri, R.; Polizzi, C.; Lardicci, L. *Tetrahedron Lett*. **1991**, *32*, 7471−7472. (d) Joshi, R. V.; Zemlicka, J. *Tetrahedron* **1993**, *49*, 2353−2360.

(7) (a) Ohno, H.; Toda, A.; Miwa, Y.; Taga, T.; Fujii, N.; Ibuka, T. *Tetrahedron Lett*. **1999**, *40*, 349−352. (b) Ohno, H.; Toda, A.; Fujii, N.; Takemoto, Y.; Tanaka, T.; Ibuka, T. *Tetrahedron* **2000**, *56*, 2811−2820. (c) Ohno, H.; Toda, A.; Miwa, Y.; Taga, T.; Osawa, E.; Yamaoka, Y.; Fujii, N.; Ibuka, T. *J. Org. Chem*. **1999**, *64*, 2992−2993. (d) Ohno, H.; Anzai, M.; Toda, A.; Ohishi, S.; Fujii, N.; Tanaka, T.; Takemoto, Y.; Ibuka, T. *J. Org. Chem*. **2001**, *66*, 4904−4914.

(8) (a) Ohno, H.; Hamaguchi, H.; Tanaka, T. *Org. Lett*. **2000**, *2*, 2161−2163. (b) Ohno, H.; Hamaguchi, H.; Tanaka, T. *J. Org. Chem*. **2001**, *66*, 1867−1875.

(9) 2-Ethynylaziridines are also known as a versatile building block for the synthesis of 1*H*-azepine: Mannisse, N.; Chuche, J. *J. Am. Chem. Soc*. **1977**, *99*, 1272−1273.

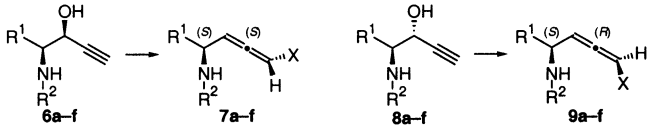
Scheme 1. Aziridination of Bromoallenes



chiral 2-ethynylaziridines in a stereoselective manner. Ethynylaziridines can be synthesized by the reaction of *N*-tosylimines with sulfonium ylide,[10] reaction of lithium acetylides[11] or allenylzincs[12] with imines, or the Mitsunobu reaction of amino alcohols bearing an ethynyl group;[13] however, the stereoselective synthesis of enantiopure 2-ethynylaziridines is still difficult. Apparently, one of the simplest methods for the synthesis of enantiopure ethynylaziridines **3** is the Mitsunobu reaction of the propargyl alcohol **2** (Scheme 1), which in turn could be readily prepared from amino aldehydes **1** derived from α-amino acids. However, a highly diastereoselective synthesis of either *syn*- or *anti*-**2** by the reaction of amino aldehydes with metal acetylides has proven to be difficult,[13] with the exception of some examples.[14] Since aziridination under the Mitsunobu conditions proceeds with inversion of configuration, a mixture of 2,3-*cis*- and 2,3-*trans*-2-ethynylaziridines **3** is always obtained from a diastereomixture of **2**.

To establish a stereoselective synthetic method for chiral 2-ethynylaziridines, we have been involved in the investigation of the intramolecular amination of the bromoallene **4**,[15] which can be prepared from the propargyl alcohol **2** (Scheme 1). In this paper, we present a full account of our study of the base-mediated aziridination of chiral bromoallenes. We found that the 2,3-*cis*-2-ethynylaziridines can be obtained in good to high selectivities by the reaction of both (*S*,a*S*)- and (*S*,a*R*)-bromoallenes bearing an *N*-sulfonylated amino group with NaH/DMF, and the experimental results have been well rationalized by the computational investigation [B3LYP/6-31+G(d)]. Furthermore, as the calculations predicted, the improvement of the 2,3-*cis* selectivities up to 99:1 has been realized by the use of a less polar solvent such as THF. This is a striking example of the calculation finely contributing to the improvement of the experimental results.

Table 1. Synthesis of (*S*,a*S*)- and (*S*,a*R*)-Haloallenes **7** and **9**[a,e]



entry	amino alcohol	R^1	R^2	X	product ratio[b]	yield[c] (%)	$[\alpha]_D$[d]
1	**6a**	*i*-Pr	Boc	Br	**7a**:**9a** = >99:1	88	+118
2	**6b**	*i*-Pr	Mts	Br	**7b**:**9b** = 95:5	76	+153
3	**6b**	*i*-Pr	Mts	I	**7c**:**9c** = >99:1	82	+231
4	**6d**	*i*-Pr	Ts	Br	**7d**:**9d** = 92:8	65	+116
5	**6e**	Bn	Ts	Br	**7e**:**9e** = 93:7	81	+85
6	**6f**	$TBSOCH_2$	Mts	Br	**7f**:**9f** = 89:11	81	+82
7	**8a**	*i*-Pr	Boc	Br	**9a**:**7a** = >99:1	82	−304
8	**8b**	*i*-Pr	Mts	Br	**9b**:**7b** = >99:1	65	−251
9	**8b**	*i*-Pr	Mts	I	**9c**:**7c** = >99:1	63	−344
10	**8d**	*i*-Pr	Ts	Br	**9d**:**7d** = >99:1	82	−282
11	**8e**	Bn	Ts	Br	**9e**:**7e** = 91:9	60	−130
12	**8f**	$TBSOCH_2$	Mts	Br	**9f**:**7f** = 75:25	93	−133

[a] Amino alcohols were converted into bromoallenes by mesylation with MsCl (2 equiv) and Et_3N (5 equiv) in THF, followed by bromination using $CuBr·Me_2S$ (2 equiv) and LiBr (2 equiv) in THF. Similarly, iodoallenes were synthesized using CuI/LiI. [b]Diastereomeric ratios of **7** and **9** were determined by ^1H NMR. [c]Isolated overall yields based on the starting amino alcohols. [d]Optical rotations were measured in $CHCl_3$ after separation of the diastereomers except for entry 5 (96% de) and entry 11 (82% de): separation of **7e** and **9e** was extremely difficult. [e]Abbreviations: Mts = 2,4,6-trimethylphenylsulfonyl, TBS = *tert*-butyldimethylsilyl.

Results and Discussion

Synthesis of Bromoallenes Bearing a Protected Amino Group. To reveal the stereochemical course of the intramolecular amination using diastereomerically pure bromoallenes, mixtures of amino alcohols **6** and **8**[13b,16] were carefully separated by repeated flash column chromatography and converted into the bromoallenes, as shown in Table 1. Thus, the treatment of **6** with MsCl and Et_3N gave the corresponding mesylates, and the crude mesylates were then allowed to react with $CuBr·Me_2S$/LiBr[4] or CuI/LiI[3b] to afford the desired (*S*,a*S*)-haloallenes **7**. Similarly, the *anti*-amino alcohols **8** were converted into (*S*,a*R*)-allenes **9** in good to high yields. Although diastereoselectivities of the bromination reaction were not high in some cases, diastereomerically pure allenes **7** and **9** were obtained by flash column chromatography or recrystallization. However, the separation of the diastereomixtures of **7e** and **9e** (entries 5 and 11) was extremely difficult.

The stereochemistries of the synthesized haloallenes could be deduced by the well-documented *anti*-S_N2' reaction course.[4,5] Furthermore, the (*S*,a*S*)-haloallenes **7** show positive signs of the optical rotation, as can be seen from Table 1 (entries 1−6), while (*S*,a*R*)-allenes **9** exhibit negative values (entries 7−12). This trend is in good agreement with Lowe's rule[17] and the optical rotations of the related compounds.[7b]

Base-Mediated Aziridination of Bromoallenes. First, the intramolecular amination of the bromoallenes bearing an (*N*-Boc)amino group was investigated (Scheme 2). The (*S*,a*S*)-**7a** was treated with NaH in DMF to give the expected 2,3-*cis*- and 2,3-*trans*-2-ethynylaziridines **10a** and **11a** (**10a**:**11a** = 60:40),[13b] although in low yield (35%). A similar result was obtained using KH as a base. The treatment of **7a** with LDA/

(10) (a) Li, A.-H.; Zhou, Y.-G.; Dai, L.-X.; Hou, X.-L.; Xia, L.-J.; Lin, L. *Angew. Chem., Int. Ed. Engl*. **1997**, *36*, 1317−1319. (b) Li, A.-H.; Zhou, Y.-G.; Dai, L.-X.; Hou, X.-L.; Xia, L.-J.; Lin, L. *J. Org. Chem*. **1998**, *63*, 4338−4348.

(11) Florio, S.; Troisi, L.; Capriati, V.; Suppa, G. *Eur. J. Org. Chem*. **2000**, 3793−3797.

(12) Chemla, F.; Hebbe, V.; Normant, J. F. *Tetrahedron Lett*. **1999**, *40*, 8093−8096.

(13) (a) Ohno, H.; Toda, A.; Fujii, N.; Ibuka, T. *Tetrahedron: Asymmetry* **1998**, *9*, 3929−3933. (b) Ohno, H.; Toda, A.; Takemoto, Y.; Fujii, N.; Ibuka, T. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2949−2962. For another related synthesis, see: (c) Chen, S.-T.; Fang, J.-M. *J. Org. Chem*. **1997**, *62*, 4347−4357.

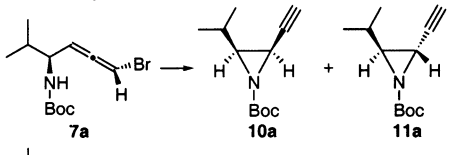
(14) In limited cases, the reaction of metal acetylide with amino aldehydes proceeds in a highly stereoselective manner. For example, see: (a) Garner, P.; Park, J. M. *J. Org. Chem*. **1990**, *55*, 3772−3787. (b) D′Aniello, F.; Schoenfelder, A.; Mann, A.; Taddei, M. *J. Org. Chem*. **1996**, *61*, 9631−9636. For related works, see: (c) Frantz, D. E.; Fässler, R.; Carreira, E. M. *J. Am. Chem. Soc*. **2000**, *122*, 1806−1807. (d) Boyall, D.; López, F.; Sasaki, H.; Frantz, D.; Carreira, E. M. *Org. Lett*. **2000**, *2*, 4233−4236.

(15) A portion of this study was reported in a preliminary communication: Ohno, H.; Hamaguchi, H.; Tanaka, T. *Org. Lett*. **2001**, *3*, 2269−2271.

(16) The amino alcohols **6d**,**e** and **8d**,**e** were also synthesized by an identical procedure described in the literature.[13b] For details, see the Supporting Information.

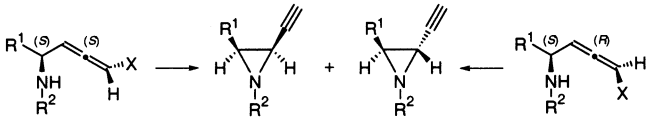
(17) Lowe, G. *J. Chem. Soc., Chem. Commun*. **1965**, 411−413.

Scheme 2. Aziridination of Bromoallenes Bearing an (*N*-Boc)amino Group



allene	conditions	10a:11a	yield
7a	NaH, DMF, rt	60:40	35%
7a	KH, DMF, rt	65:35	42%
7a	LDA, THF, −78 °C	52:48	77%
7a	*t*-BuOK, DMF, −78 °C	22:78	85%
9a	NaH, DMF, rt	53:47	28%
9a	*t*-BuOK, DMF, −78 °C	41:59	83%

Table 2. Aziridination of Bromoallenes Bearing an (*N*-ArSO$_2$)amino Group in DMF[a]



b: R^1 = *i*-Pr, R^2 = Mts, X = Br **e**: R^1 = Bn, R^2 = Ts, X = Br
c: R^1 = *i*-Pr, R^2 = Mts, X = I **f**: R^1 = TBSOCH$_2$, R^2 = Mts, X = Br
d: R^1 = *i*-Pr, R^2 = Ts, X = Br **g**: R^1 = Me, R^2 = Ts, X = Br

entry	allene	base	time (min)	ratio[b] *cis*:*trans*	yield[c] (%)
1	**7b**	*t*-BuOK[d]	10	**10b:11b** = 40:60	88
2	**7b**	NaH	60	**10b:11b** = 82:18	93
3	**7c**	NaH	30	**10b:11b** = 86:14	98
4	**7d**	NaH	60	**10d:11d** = 88:12	99
5	**7e**	NaH	90	**10e:11e** = 89:11	88
6	**7f**	NaH	60	**10f:11f** = 79:21	76
7	**7g**[e]	NaH	180	**10g:11g** = 91:9	85
8	**9b**	*t*-BuOK[d]	10	**10b:11b** = 77:23	73
9	**9b**	NaH	30	**10b:11b** = >99:1	99
10	**9c**	NaH	20	**10b:11b** = >99:1	98
11	**9d**	NaH	30	**10d:11d** = >99:1	84
12	**9e**[e]	NaH	150	**10e:11e** = 97:3	78
13	**9f**	NaH	30[f]	**10f:11f** = 92:8	91
14	**9g**[e]	NaH	240	**10g:11g** = 93:7	76

[a] Reactions were carried out at 25 °C in DMF using diastereomerically pure bromoallenes and a base (1.2 or 1.3 equiv) unless otherwise stated. [b]Ratios were determined by ^{1}H NMR (270 MHz) or isolation of products. [c]Combined isolated yields. [d]The reaction was conducted at −78 °C using 2 equiv of *t*-BuOK. [e]Diastereomixture of the bromoallenes was used (96:4 for **7g**, 91:9 for **9e**, and 97:3 for **9g**). [f]Reaction was conducted at 50 °C.

THF resulted in the expected aziridines in higher yield (77%); however, diastereoselectivity was poor (**10a**:**11a** = 52:48). Although the reaction of **7a** with *t*-BuOK in DMF gave a promising result (85% yield, **10a**:**11a** = 22:78), almost no selectivity was observed starting from (*S*,a*R*)-**9a** (**10a**:**11a** = 41:59) under the identical reaction conditions.

In contrast, the reaction of *N*-arylsulfonylated amino allenes showed good to high 2,3-*cis* selectivity. The results are summarized in Table 2. Although the aziridination reaction of **7b** using *t*-BuOK gave a 40:60 mixture of the corresponding aziridines **10b** and **11b** (entry 1), the NaH-mediated reaction afforded 2,3-*cis*-aziridines **10b** in both good diastereoselectivity (82:18) and high yield (93%, entry 2). As one might expect, iodoallene **7c** was more reactive (entry 3) than the corresponding bromoallene **7b** (entry 2). Similarly, other (*S*,a*S*)-bromoallenes **7d**−**g**[18] yielded mixtures of 2,3-*cis*- and 2,3-*trans*-2-ethynylaziridines in which the *cis*-isomers **10** predominated (79:21−91:9, entries 4−7). Interestingly, we observed the highest 2,3-*cis* selectivity in the reaction of bromoallene **7g** bearing the smallest substituent (R^1 = Me) at C-4 (91:9, entry 7). Furthermore, upon the treatment of (*S*,a*R*)-bromoallenes **9b**−**g** with NaH/DMF (entries 9−14), 2,3-*cis*-aziridines **10b**−**g** were obtained in higher selectivities (>92:8). When the allenes **9b**−**d** bearing an isopropyl group were used (entries 9−11), only the *cis*-isomers **10b** and **d** were obtained. The cyclization of **9f** bearing a siloxy group was relatively slow; however, increased reaction temperature (50 °C) led to completion of the reaction within 30 min, and the desired *cis*-aziridine **10f** was obtained in a high yield (91%, entry 13). From these observations, the aziridination of the (*S*,a*S*)-bromoallenes **7** with NaH/DMF proceeds in a *syn*-S$_N$2′ manner, while an *anti*-S$_N$2′ pathway predominates in the reaction of the (*S*,a*S*)-allenes **9** (Figure 1).

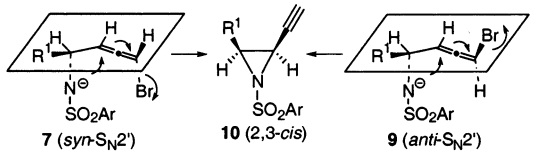
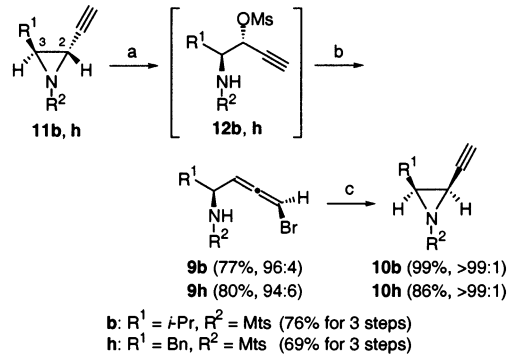


Figure 1. Stereochemical Course of the NaH-Mediated Aziridination of **7** and **9** in DMF.

Scheme 3. Conversion of the *trans*-Aziridines **11** into the *cis*-Isomers **10**[a]



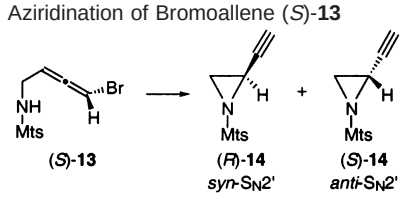
[a] Reagents and conditions: (a) MeSO$_3$H (2 equiv), CH$_2$Cl$_2$, 0 °C, 15 min; (b) CuBr·Me$_2$S (2 equiv), LiBr (2 equiv), THF, 50 °C, 1 h; (c) NaH (1.3 equiv), DMF, 25 °C, 3 h.

This reaction is also useful for the conversion of the 2,3-*trans*-2-ethynylaziridines **11** into the corresponding 2,3-*cis*-isomers **10** (Scheme 3). Typically, a methanesulfonic-acid-mediated ring-opening reaction[19] of **11b** in CH$_2$Cl$_2$ gave a crude mesylate **12b**, which was directly converted into the bromoallene **9b** without purification (77% yield, 2 steps). The intramolecular amination of **9b** with NaH in DMF afforded the expected 2,3-*cis*-2-ethynylaziridine **10b** as a single isomer in 99% yield. The overall yield of the three-step sequence for the inversion of *trans*-**11b** at C-2 was 76%. Similarly, the *trans*-aziridine **11h**[13b] was converted into the *cis*-isomer **10h** in 69% yield in three steps.

(18) For synthesis of bromoallenes **7g** and **9g** bearing a methyl group, see the Supporting Information.

(19) For a methanesulfonic acid mediated ring-opening reaction of vinylaziridines, see: (a) Tamamura, H.; Yamashita, M.; Muramatsu, H.; Ohno, H.; Ibuka, T.; Otaka, A.; Fujii, N. *Chem. Commun.* **1997**, *23*, 2327−2328. (b) Tamamura, H.; Yamashita, M.; Nakajima, Y.; Sakano, K.; Otaka, A.; Ohno, H.; Ibuka, T.; Fujii, N. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2983−2996.

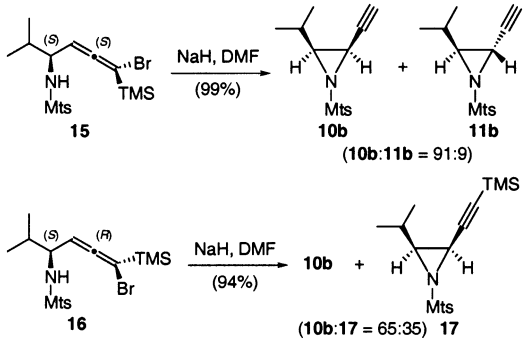
Scheme 4. Aziridination of Bromoallene (*S*)-**13**



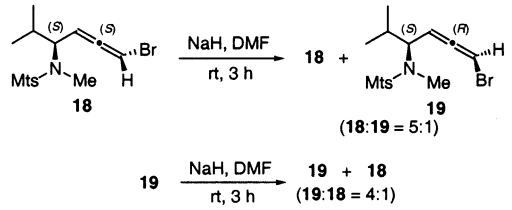
conditions		(*R*)-**14**:(*S*)-**14**[a]	yield
NaH, DMF	rt, 6 h	–	no reaction
t-BuOK, THF	0 °C, 5.3 h	–	no reaction
KHMDS, THF	−78 °C, 1 h	57:43	16%
LDA, THF	−78 °C, 1 h	32:68	28%
LHMDS, THF	−78 °C, 40 min	30:70	45%

[a] Determined by comparison of optical rotations with that of the authetic sample.

Scheme 5. Aziridination of Bromoallenes Bearing a TMS Group



Scheme 6. Isomerization of Bromoallenes under the Aziridination Conditions



To reveal the effect of the 4-substituent on the aziridination reaction, we synthesized bromoallene (*S*)-**13** (Scheme 4) from L-serine, lacking an alkyl substituent at C-4 (see the Supporting Information). Unfortunately, the treatment of **13** with NaH or KH in DMF afforded no aziridine, and the starting material was recovered unchanged. The allene **13** was also inert to the cyclization conditions using *t*-BuOK in THF. In contrast, a reaction with a metal amide base such as KHMDS, LDA, or LHMDS in THF yielded mixtures of (*R*)- and (*S*)-aziridines **14**, although in low yields. From these observations, an alkyl substituent at the 4-position is quite important for the efficient and stereoselective conversion of bromoallenes into ethynylaziridines, and the *syn*- and *anti*-S_N2' processes compete when bromoallenes lacking the 4-alkyl group are used.

Aziridination of terminally silylated bromoallenes **15** and **16** accompanied desilylation (Scheme 5). Interestingly, while (*S*,a*S*)-bromoallene **15** yielded completely desilylated *cis*-aziridine **10b** and *trans*-isomer **11b**, cyclization of **16** afforded *cis*-aziridines **10b** and **17**,[13b] the latter of which still has the TMS group on the acetylene terminus. In both cases, the reaction proceeded in high 2,3-*cis* selectivities and high yields.

Since the 2,3-*cis* selectivities in the reaction of (*S*,a*S*)-allenes **7** were relatively low (entries 2−7, Table 2), we investigated other reaction conditions using **7d**. The addition of HMPA (10 equiv) to the NaH/DMF reaction mixture was less effective

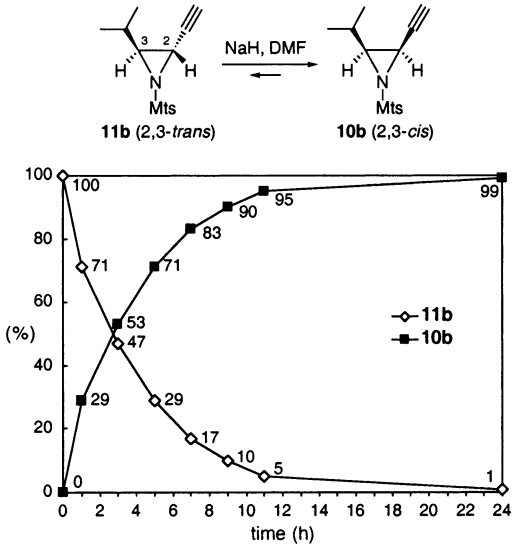


Figure 2. NaH-Mediated Isomerization of 2,3-*trans*-Aziridine **11b**.

(96% yield, **10d**:**11d** = 87:13). The reaction of **7d** with KHMDS in THF gave aziridines **10b** and **11b** in 82% yield (**10b**:**11b** = 69:31), while a slightly improved result was obtained when the same reaction was conducted in the presence of 18-crown-6 (96% yield, **10b**:**11b** = 83:17). From these observations, it has proven to be difficult to improve the 2,3-*cis* selectivities without understanding the origin of the selectivities. Accordingly, we next turned our attention to the elucidation of the selectivities.

Influence of Isomerization of the Bromoallenes and 2-Ethynylaziridines on the Stereoselectivity. It is known that abstraction of a proton on the allenic carbon substituted by a bromine or chlorine atom gives an allenic anion species.[20] Evidence for the generation of allene carbene intermediates by elimination of bromide or chloride from such allenic anion species has been also reported.[20] Accordingly, a base-mediated racemization of the bromoallene moiety, which could be possible via such a process, might exert significant influence on our aziridination reaction. To check the importance of the isomerization of the starting bromoallenes on the observed stereoselectivity, we exposed the related compounds **18** and **19** bearing a tertiary amino group to the aziridination conditions (Scheme 6). These allenes were synthesized by methylation of bromoallenes **7b** and **9b** by the Mitsunobu reaction with MeOH (see the Experimental Section). A slight degree of epimerization of the (*S*,a*S*)-bromoallene **18** was observed (**18**:**19** = 5:1, ^{1}H NMR) by exposure to the cyclization conditions (NaH/DMF) for 3 h. A similar result was obtained starting from (*S*,a*R*)-**19** (**19**:**18** = 4:1). However, these results suggest that the racemization of the bromoallene moiety is not a predominant factor for the *cis*-selective aziridination.

Although deprotonation with NaH is usually accompanied with the evolution of hydrogen gas, the formation of water from NaOH present in NaH was reported.[21] Mediated by the generated water and alkaline in the reaction mixture, equilibration of 2,3-*cis*- and 2,3-*trans*-2-ethynylaziridines might occur during the aziridination. However, such equilibration of 2-ethynylaziridines

(20) (a) Hennion, G. F.; Maloney, D. E. *J. Am. Chem. Soc.* **1951**, *73*, 4735−4737. (b) Shiner, V. J.; Humphrey, J. S., Jr. *J. Am. Chem. Soc.* **1967**, *89*, 622−630. See also ref 6a and b.
(21) Organ, M. G.; Miller, M.; Konstantinou, Z. *J. Am. Chem. Soc.* **1998**, *120*, 9283−9290.

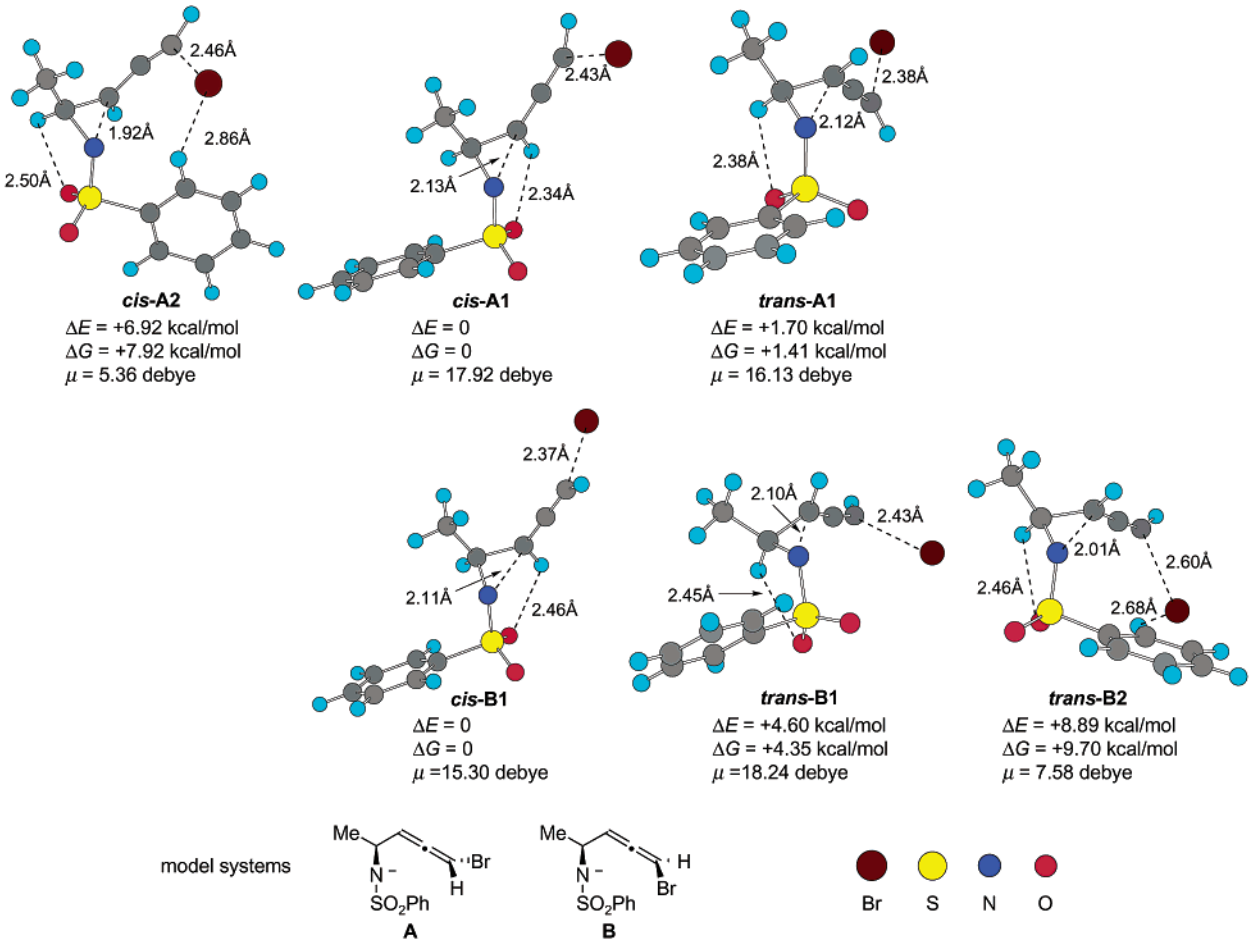


Figure 3. Transition structures for the cyclization reaction of **A** and **B** [B3LYP/6-31+G(d), SCRF (Dipole, solvent = DMF)]. *cis*-**A** and *trans*-**A** are the *cis* and *trans* transition stuctures of **A**, respectively. *cis*-**B** and *trans*-**B** are the *cis* and *trans* transition stuctures of **B**, respectively. ΔE and ΔG are the differences between the transition structures in energy and the Gibbs free energy at 298.15 K, respectively. μ shows the dipole moment.

has proven to be less important from the following observation: by monitoring the change in 2,3-*trans*-2-ethynylaziridine **11b** under the cyclization conditions (NaH, DMF, room temperature), the epimerization of **11b** at C-2 did occur but slowly (Figure 2), and the complete isomerization into the corresponding 2,3-*cis*-aziridine **10b** required over 10 h.[22] This result cannot explain the extremely high 2,3-*cis* selectivity on the aziridination within 0.5−4 h. As expected, no isomerization of *trans*-aziridine **11b** was observed by treatment with NaBr in DMF, which in turn is produced from the reaction of bromoallene with NaH.

From these results, the origin of the *cis* selectivity would be mainly assumed to be preference of the transition state for the 2,3-*cis*-aziridines over the *trans*-isomers, although the equilibration of the products might assist the increase of the selectivity. Furthermore, the 2,3-*cis*-2-ethynylaziridine **10b** was found to be more stable than the corresponding *trans*-isomer **11b**, which is in good agreement with the relative thermodynamic stability of 2-vinylaziridines.[23]

Computational Investigation on the 2,3-*cis* Selective Aziridination Reaction and Improvement of the Stereoselectivity. To understand the stereoselectivity of this *cis*-aziridine formation reaction, we have studied it computationally. The cyclization reactions of the amino anions **A** and **B** (Figure 3) were chosen as model systems for the reactions of **7** and **9** in the presence of NaH/DMF, respectively, which both gave the *cis*-aziridines selectively (Table 2). All calculations were performed using the Gaussian 98 program.[24] Gibbs free energies are the values at 298.15 K and 1.00 atm obtained from frequency calculations. The thermal energy corrections are not scaled.[25] Vibrational frequency calculations gave only one imaginary frequency for

(22) Although the 2,3-*cis* selective synthesis of 2-ethynylaziridines was possible by the treatment of bromoallenes with NaH/DMF for a prolonged reaction time, yields of the one-pot aziridination−equilibration reaction are unsatisfactory.

(23) The thermodynamic preference of the related 2,3-*cis*-aziridines over their *trans*-isomers is well documented in our previous study; see: (a) Ibuka, T.; Mimura, N.; Aoyama, H.; Akaji, M.; Ohno, H.; Miwa, Y.; Taga, T.; Nakai, K.; Tamamura, H.; Fujii, N.; Yamamoto, Y. *J. Org. Chem.* **1997**, *62*, 999−1015. (b) Ibuka, T.; Mimura, N.; Ohno, H.; Nakai, K.; Akaji, M.; Habashita, H.; Tamamura, H.; Miwa, Y.; Taga, T.; Fujii, N.; Yamamoto, Y. *J. Org. Chem.* **1997**, *62*, 2982−2991. (c) Ohno, H.; Ishii, K.; Honda, A.; Tamamura, H.; Fujii, N.; Takemoto, Y.; Ibuka, T. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3703−3716. (d) Ohno, H.; Toda, A.; Fujii, N.; Miwa, Y.; Taga, T.; Yamaoka, Y.; Osawa, E.; Ibuka, T. *Tetrahedron Lett.* **1999**, *40*, 1331−1334.

(24) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, revision A.9; Gaussian, Inc.: Pittsburgh, PA, 1998.

(25) For the scale factors for B3LYP, see: Bauschlicher, C. W., Jr.; Partridge, H. *J. Chem. Phys.* **1995**, *103*, 1788−1791.

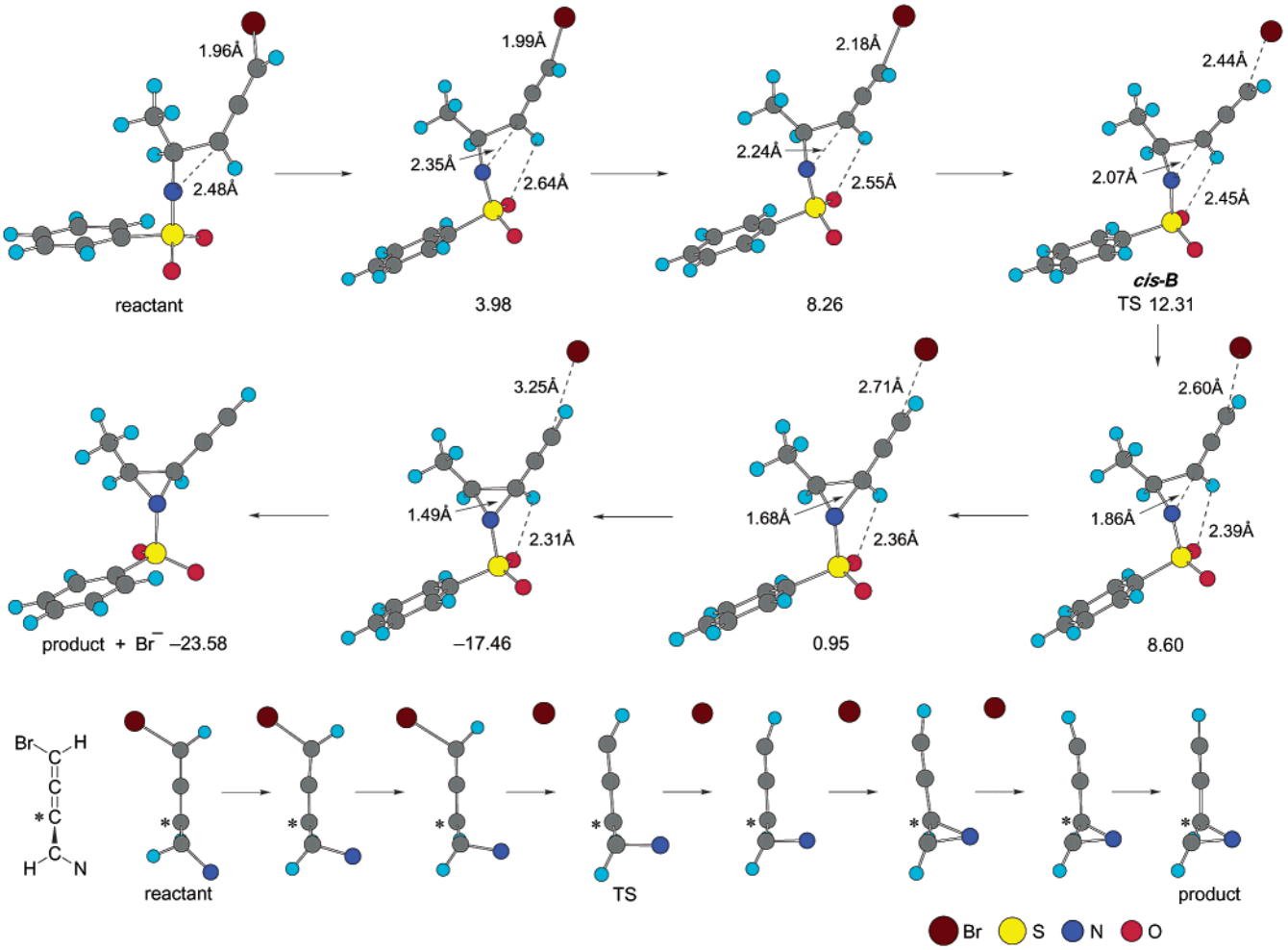


Figure 4. Representative intermediates on the IRC of the *cis* cyclization reaction of **B** [B3LYP/6-31G(d)] together with those energies (kcal/mol). The side-views without the $PhSO_2$ and Me groups are also shown below.

all transition structures and confirmed that those structures are authentic transition structures.

The transition structures for both *cis*- and *trans*-aziridine cyclization of **A** and **B** were located by the B3LYP hybrid functional[26] together with the 6-31+G(d) basis set and the Onsager solvation model ($\epsilon = 37.06$ for DMF).[27] The *cis* transition structure (*cis*-**A1**) is favored over the *trans* transition structure (*trans*-**A1**) by 1.41 kcal/mol. In the same way, the *cis* transition structure (*cis*-**B1**) is favored over the *trans* transition structure (*trans*-**B1**) by 4.35 kcal/mol. These energy differences correspond to the product ratios 91.5:8.5 and 99.94:0.06 at 298.15 K, respectively. These calculations predict the stereochemistry of the products correctly, and the predicted relative selectivity is in good agreement with experimental results (see entries 2−7 and 9−14 in Table 2). The transition structures *cis*-**A2** and *trans*-**B2** have a different conformation of SO_2Ph part with much higher energies. Both *cis*-**A2** and *trans*-**B2** have a small dipole moment (5.36 and 7.58) and an interaction between the Ph−H and the leaving Br. The distances between Ph−H and Br are 2.86 and 2.60 Å, which are less than the sum of their van der Waals radii (3.05 Å).

We further performed an intrinsic reaction coordinate (IRC) analysis[28] of the *cis*-cyclization reaction of **B** for deeper understanding of this cyclization reaction. The IRC analysis was carried out at the B3LYP/6-31G(d) level.[29] Several representative intermediates on the IRC are shown together with those energies in Figure 4. From the starting point of the reactant **B**, the energy increases with the increase in the distance of the C−Br bond. At the transition state (*cis*-**B**), the C−Br bond is almost broken, while the C−N bond just starts to form. After going beyond the transition state (*cis*-**B**), the energy decreases rapidly with the decrease in the distance between the carbon and the nitrogen atoms. The side-views of these structures without the $PhSO_2$ and Me groups clearly show that the allenic carbon indicated by * starts to pyramidalize after the transition state.

In the *cis* transition structures (*cis*-**A1** and *cis*-**B1**) in Figure 3, the sulfonamide oxygen is close enough to the allenic hydrogen to interact with it and stabilize the transition state. On the other hand, the sulfonamide oxygen in the *trans* transition structures cannot interact with the allenic hydrogen; therefore, it moved to the direction of the hydrogen connected to the next

(26) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648−5652. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785−789.
(27) (a) Wong, M. W.; Frisch, M. J.; Wiberg, K. B. *J. Am. Chem. Soc.* **1991**, *113*, 4776−4782. (b) Wong, M. W.; Wiberg, K. B.; Frisch, M. J. *J. Am. Chem. Soc.* **1992**, *114*, 523−529. (c) Wong, M. W.; Wiberg, K. B.; Frisch, M. J. *J. Am. Chem. Soc.* **1992**, *114*, 1645−1652.
(28) (a) Fukui, K. *Acc. Chem. Res.* **1981**, *14*, 363−368. (b) Ishida, K.; Morokuma, K.; Komornicki, A. *J. Chem. Phys.* **1977**, *66*, 2153.
(29) The calculations at B3LYP/6-31G(d) level gave similar energy differences [e.g., ΔG (*trans*-**B**−*cis*-**B**) = 3.92 kcal/mol, vs 4.35 kcal/mol] and similar transition structures with the ones at B3LYP/6-31+G(d). Compare *cis*-**B1** in Figure 3 with *cis*-**B** in Figure 4.

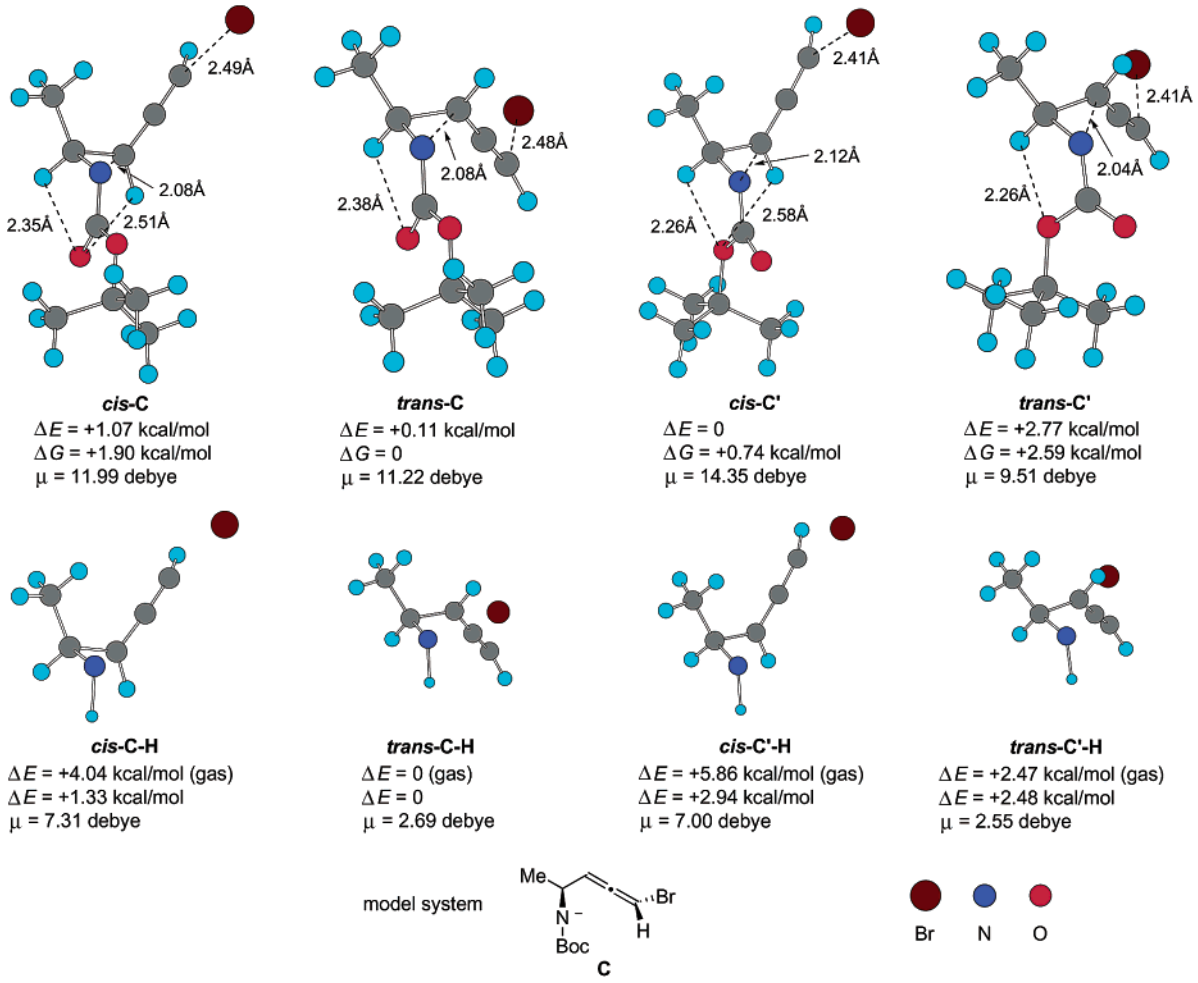


Figure 5. *cis*-**C**, -**C′** and *trans*-**C**, -**C′** are the transition structures for the cylization reaction of **C** [B3LYP/6-31+G(d), SCRF (Dipole, solvent = DMF)]. *cis*-**C**−**H**, *cis*-**C′**−**H**, *trans*-**C**−**H**, and *trans*-**C′**−**H** are the structures in which the ester group of *cis*-**C**, *cis*-**C′**, *trans*-**C**, and *trans*-**C′** is replaced by hydrogen, respectively. Δ*E* (gas) and Δ*E* show the energy difference in a gas phase and in DMF, respectively. μ shows the dipole moment.

carbon with some conformational change. This conformational change may cause the increase of the energy. If the hydrogen bond with the sulfonamide oxygen controls the stereochemistry, then the change in the stereoselectivity depending on the *N*-protecting group is explainable. We investigated the cyclization reaction of the amino anion **C** as a model system for the reaction of *N*-Boc substrate **7a**, which showed poor diastereoselectivity (Scheme 2). Figure 5 shows the transition structures for both *cis*- and *trans*-aziridine cyclization of **C** located by B3LYP/6-31+G(d) with the Onsager solvation model (ϵ = 37.06 for DMF). The transition structure *cis*-**C′** has the lowest energy; on the other hand, *trans*-**C** is the most favorable transition structure on the basis of the Gibbs free energy. The product ratios (*cis*:*trans*) calculated from a Boltzmann distribution including all transition structures (*cis*-**C**, **C′** and *trans*-**C**, **C′**) are 58:42 by the potential energy and 31:69 by the Gibbs free energy. These results show the selectivity of the reaction is poor in accord with the experimental results (Scheme 2). Both *cis*-**C** and *trans*-**C** have a similar dipole moment and a similar ester conformation. The differences of these are only the arrangement of methyl and bromoallenyl groups and the direction of the leaving bromide. The steric repulsion between methyl and bromoallenyl groups is plausible for *cis*-**C**. To investigate the effect of the interactions between the protecting group and the reaction center, we calculated the energies of the structures *cis*-**C**−**H** and *trans*-**C**−**H**, in which the ester group of *cis*-**C** and *trans*-**C** was replaced by hydrogen [B3LYP/6-31+G(d), SP, SCRF (Dipole, DMF)]. The energy of *trans*-**C**−**H** is lower than that of *cis*-**C**−**H** by 1.33 kcal/mol (Δ*E*). This energy difference can be explained by the steric repulsion. Thus, *trans*-**C** is sterically favored over *cis*-**C**. In the same way, the energies of *cis*-**C′**−**H** and *trans*-**C′**−**H** were calculated. Since the dipole moments of *cis*-**C**−**H** and *trans*-**C**−**H** are nearly equal to those of *cis*-**C′**−**H** and *trans*-**C′**−**H**, respectively, those solvation energies ($\Delta E - \Delta E_{gas}$) are about the same (*cis*-**C**−**H** and *cis*-**C′**−**H**, ∼2.8 kcal/mol; *trans*-**C**−**H** and *trans*-**C′**−**H**, ∼0). In other words, transition structures with a larger dipole moment can be better stabilized in a polar solvent such as DMF. From these results, we can conclude that *cis*-**C′** with a larger dipole moment is favored by a polar solvent, while the steric factor favors *trans*-**C**. Thus, the *cis*/*trans* selectivity is low.

Furthermore, the energies of the structures *cis*-**A1**−**H** and *trans*-**A1**−**H**, in which the arylsulfonyl group of *cis*-**A1** and *trans*-**A1** was replaced by hydrogen, were calculated [B3LYP/6-31+G(d), SP, SCRF (Dipole, DMF)] (Figure 6). The energy of *trans*-**A1**−**H** is lower than that of *cis*-**A1**−**H** by 3.07 kcal/mol in a gas phase and 0.84 kcal/mol in DMF (Δ*E*). These results show that *trans*-**A1** is sterically favored over *cis*-**A1**. As we discussed before, the sulfonamide oxygen of *cis*-**A1** interacts

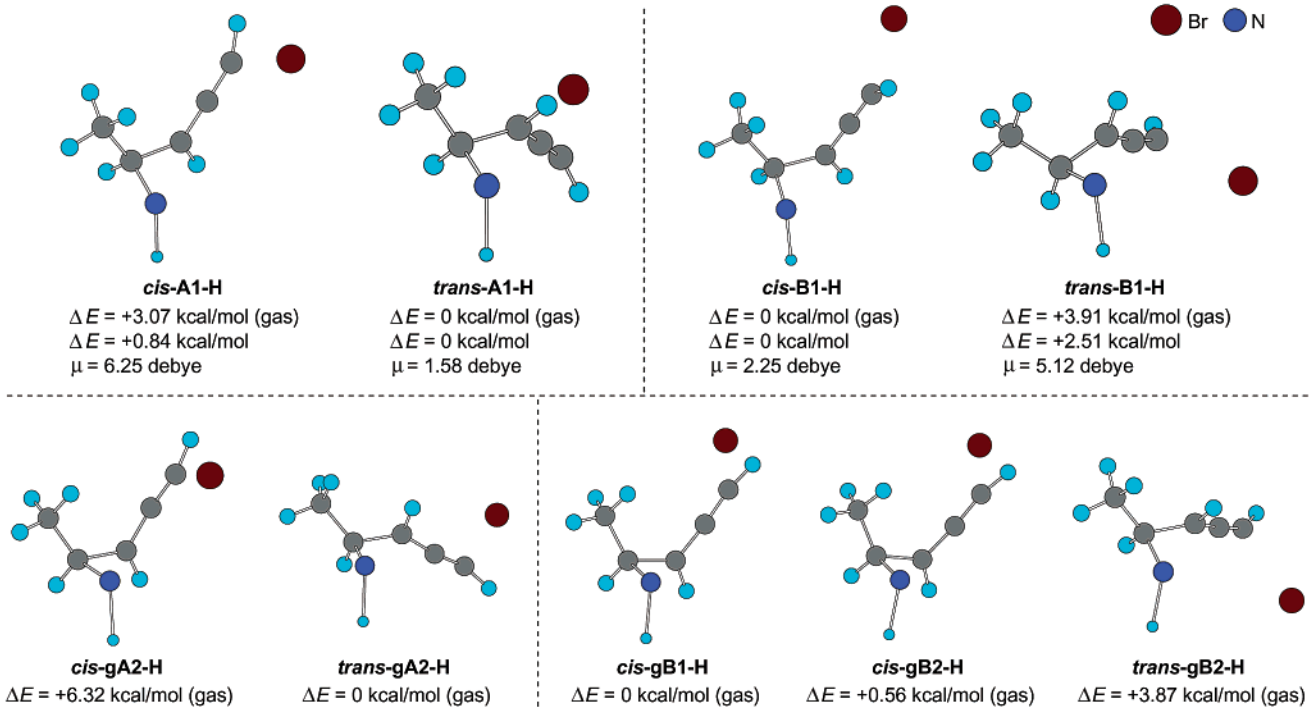


Figure 6. *cis*- and *trans*-**A1-H**, *cis*- and *trans*-**B1**−**H**, *cis*- and *trans*-**gA2**−**H**, *cis*-**gB1**−**H**, *cis*-**gB2**−**H**, and *trans*-**gB2**−**H** are the structures in which the SO_2Ph group of *cis*- and *trans*-**A1**, *cis*- and *trans*-**B1**, *cis*- and *trans*-**gA2**, *cis*-**gB1**, *cis*-**gB2**, and *trans*-**gB2** is replaced by hydrogen, respectively. ΔE (gas) and ΔE show the energy difference in a gas phase and in DMF, respectively [B3LYP/6-31+G(d), SCRF (Dipole, DMF)]. μ shows the dipole moment.

with the allenic hydrogen, while the sulfonamide oxygen of *trans*-**A1** interacts with the hydrogen connected to the next carbon with some conformational change. This conformational change or a weaker hydrogen bond disfavors *trans*-**A1**. Also, *cis*-**A1** with a larger dipole moment is favored over *trans*-**A1**. After all, *cis*-**A1** is favored over *trans*-**A1** by 1.70 kcal/mol (ΔE). In the same way, the energies of *cis*-**B1**−**H** and *trans*-**B1**−**H** were calculated. The energy of *cis*-**B1**−**H** is lower than that of *trans*-**B1**−**H** by 3.91 kcal/mol in a gas phase and 2.51 kcal/mol in DMF (ΔE). Although the steric factor favors *trans*-**B1**−**H**, the electrostatic repulsion between the attacking N^- and the leaving Br^- is a great disadvantage for *trans*-**B1**−**H**. This electrostatic repulsion and the hydrogen bond favor *cis*-**B1** over *trans*-**B1** by 4.60 kcal/mol (ΔE).

In addition, we studied the reaction of **A** and **B** in a gas phase in order to see the solvent effect. The results are shown in Figure 7 [B3LYP/6-31+G(d)]. For the reaction of **A**, the *cis* transition structure, *cis*-**gA2**, is favored over the *trans* transition structures, *trans*-**gA1** and *trans*-**gA2**, by 4.07 and 3.19 kcal/mol, respectively. The structure corresponding to highly polar *cis*-**A1** disappears in a gas phase, whereas the less polar structure like *trans*-**gA2** does not exist in solution. The energy difference corresponds to the product ratio 99.4:0.6. From these data, we can expect that the *cis* selectivity of the reaction of **A** will increase in a solvent less polar than DMF. As will be described in detail, this prediction is in excellent agreement with the experimental results: the reaction of **7** in THF gave the *cis* product in higher selectivity (>99:1, Table 3) than that in DMF (79:21−91:9, Table 2). The reaction of **B** in a gas phase has four kinds of transition structures. The energies of both *cis*-**gB1** and **gB2** are similar to that of *trans*-**gB2**, while *trans*-**gB1** has a much higher energy. From these data, the selectivity is expected to drop in a solvent less polar than DMF. The energies of the structures *cis*-**gA2**−**H** and *trans*-**gA2**−**H**, in which the arylsulfonyl group of *cis*-**gA2** and *trans*-**gA2** was replaced by hydrogen, were calculated [B3LYP/6-31+G(d), SP] (Figure 6). The energy of *trans*-**gA2**−**H** is lower than that of *cis*-**gA2**−**H** by 6.32 kcal/mol (ΔE). Both the steric and electrostatic repulsion disfavor *cis*-**gA2**−**H**. While, both the hydrogen bond and the interaction between the Ph−H and the leaving Br favor *cis*-**gA2**. These factors overwhelm the steric and electrostatic repulsion. In the same way, the energies of *cis*-**gB1**−**H**, *cis*-**gB2**−**H**, and *trans*-**gB2**−**H** were calculated. The energy of *cis*-**gB1**−**H** is lower than that of *cis*-**gB2**−**H** by 0.56 kcal/mol (ΔE). Since the energy of *cis*-**gB2** is lower than that of *cis*-**gB1**, the stronger hydrogen bond in *cis*-**gB2** is conceivable. Although *trans*-**gB2**−**H** has a higher energy due to the electrostatic repulsion, the energy of *trans*-**gB2** is nearly equal to those of *cis*-**gB1** and *cis*-**gB2** because of the interaction between the Ph−H and the leaving Br. Thus, the combination of the hydrogen bonds, the dipole moment of the transition structures, and the steric and electrostatic repulsion controls the stereochemistry.

We next investigated the reaction of **7** with NaH in a less polar solvent, since computational calculations suggested that use of a less polar solvent would give an improved selectivity. The results are summarized in Table 3. As we expected, NaH-mediated cyclization of **7b** in toluene gave a slightly improved selectivity (89:11, entry 1) compared with that in DMF (82:11, Table 2). Furthermore, the reaction in THF afforded only 2,3-*cis*-aziridine **10b** as a single isomer (entry 2). Similarly, other (*S*,a*S*)-bromoallenes **7d-g** gave satisfactory results (entries 3−6). A relatively low yield of the *cis*-aziridine **10f** (48%, entry 5) in the reaction of the bromoallene **7f** bearing a siloxymethyl group is due to the desilylation of **7f** under the basic reaction conditions (30% of the desilylated bromoallene was isolated). In sharp

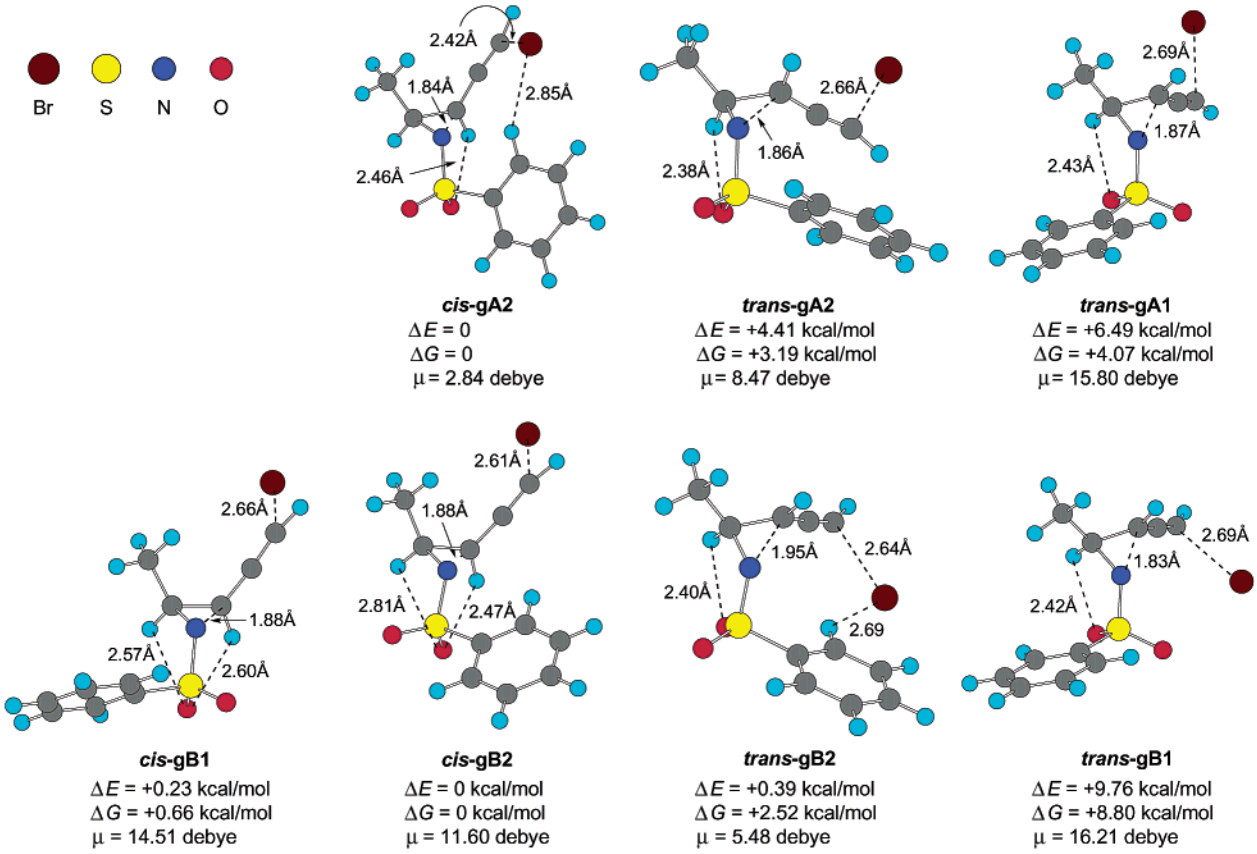
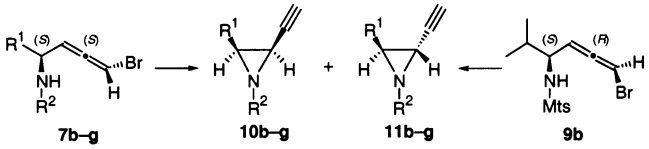


Figure 7. Transition structures for the cyclization reaction of **A** and **B** in a gas phase [B3LYP/6-31+G(d)]. *cis*-**gA** and *trans*-**gA** are the *cis* and *trans* transition stuctures of **A**, respectively. *cis*-**gB** and *trans*-**gB** are the *cis* and *trans* transition stuctures of **B**, respectively. ΔE and ΔG are the differences between transition structures in energy and the Gibbs free energy at 298.15 K, respectively. μ shows the dipole moment.

Table 3. NaH-Mediated Aziridination of Bromoallenes in Less Polar Solvents[a]



b: R^1 = *i*-Pr, R^2 = Mts **f**: R^1 = $TBSOCH_2$, R^2 = Mts
d: R^1 = *i*-Pr, R^2 = Ts **g**: R^1 = Me, R^2 = Ts
e: R^1 = Bn, R^2 = Ts

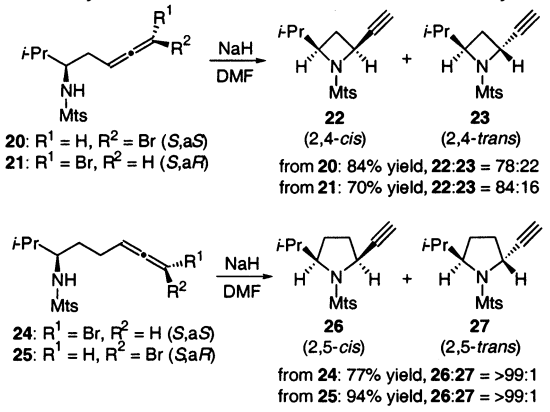
entry	allene	solvent	time (h)	ratio[b] (*cis*:*trans*)	yield[c] (%)
1	**7b**	toluene	13	**10b:11b** = 89:11	87
2	**7b**	THF	4	**10b:11b** = >99:1	84
3	**7d**	THF	17	**10d:11d** = >99:1	99
4	**7e**	THF	22	**10e:11e** = >99:1	71
5	**7f**	THF	5[d]	**10f:11f** = >99:1	48[e]
6	**7g**	THF	48	**10g:11g** = >99:1	77
7	**9b**	toluene	24	**10b:11b** = 25:75	20[f]
8	**9b**	THF	24	**10b:11b** = 29:71	23[g]
9	**9b**	THF	1[d]	**10b:11b** = 26:74	92

[a] Reactions were carried out at 25 °C using NaH (1.2 or 1.3 equiv) unless otherwise stated. [b]Ratios were determined by ^{1}H NMR (270 MHz) or isolation of products. [c]Combined isolated yields. [d]The reaction was conducted at 50 °C. [e]Desilylated bromoallene (30%) was isolated. [f]76% of **9b** was recovered. [g]72% of **9b** was recovered.

contrast, treatment of (*S*,a*R*)-**9b** yielded the *trans*-aziridine **11b** in moderate selectivity (entries 7−9).

Synthesis of Four- and Five-Membered Azacycles. This cyclization is also applicable to the synthesis of 2-ethynylazetidines and 2-ethynylpyrrolidines, although the stereoselectivities

Scheme 7. Synthesis of Four- and Five-Membered Azacycles



are dependent on the structure of the starting materials (Scheme 7). Bromoallenes bearing a protected β-amino group (**20** and **21**) and γ-amino group (**24** and **25**) were prepared from L-valine (see the Supporting Information). The exposure of **20** and **21** to the NaH-mediated cyclization conditions in DMF at room temperature afforded 2,4-*cis*-4-alkyl-2-ethynylazetidine **22**[7b] predominantly over the 2,4-*trans*-isomer **23**[7b] (**22**:**23** = 78:22 and 84:16, respectively), in good yields (70% and 84%). In contrast, the cyclization of **24** and **25** with NaH/DMF at room-temperature proceeded in excellent stereoselectivities (**26**:**27** = >99:1) and in good yields (77% and 94%, respectively). In these cases, only a trace amount of *trans*-isomer **27** was detected by ^{1}H NMR.

Conclusion

We have developed a highly selective synthetic method of 2,3-*cis*-2-ethynylaziridines via the intramolecular amination of bromoallenes. While the treatment of (*S*,a*S*)-bromoallenes **7** with NaH/DMF gives 2,3-*cis*-aziridines **10** in good stereoselectivity (2,3-*cis*:*trans* = 79:21−91:9), the reaction of (*S*,a*R*)-bromoallenes **9** with NaH/DMF shows high 2,3-*cis* selectivity (91:9−99:1). These results are well supported by computational investigations using the B3LYP density functional calculations together with the 6-31+G(d) basis set and the Onsager solvation model: the transition structures for the *cis*-aziridines are more stable than those for *trans*-aziridines, both in the aziridination of **7** and **9** in DMF. These energy differences are ascribed to the combination of the hydrogen bonds with the sulfonamide oxygen and the leaving Br, the dipole moment of the transition structures, and the steric and electrostatic factors. Furthermore, the calculation predicted that use of a less polar solvent could improve the *cis* selectivity in the reaction of (*S*,a*S*)-allene **7**. In fact, excellent selectivities (>99:1) were observed when the reaction was carried out in THF. This study clearly demonstrates that the computational investigation can contribute to the improvement of the experimental results.

Experimental Section

General Methods. Melting points are uncorrected. Chemical shifts are reported in parts per million downfield from internal Me_4Si. Optical rotations were measured in $CHCl_3$. For flash chromatography, silica gel 60 H (silica gel for thin-layer chromatography, Merck) or silica gel 60 (finer than 230 mesh, Merck) was employed.

The known compounds **6a**, **6b**, **8a**, **8b**, and **11h** were synthesized according to the literature.[13b] For synthesis of **7b**, **7d**, **7e**, **9b**, and **25**, see the Supporting Information.

General Procedure for the Synthesis of Bromoallenes from Propargyl Alcohols: Synthesis of (4*S*,a*S*)-1-Bromo-4-[(*tert*-butoxycarbonyl)amino]-5-methylhexa-1,2-diene (7a) (Table 1, Entry 1). To a stirred mixture of the alcohol **6a** (680 mg, 3.0 mmol) and Et_3N (2.08 mL, 15.0 mmol) in THF (5 mL) was added MsCl (0.465 mL, 6.0 mmol) at −78 °C. The stirring was continued for 0.5 h with warming to −40 °C. The mixture was made acidic with 1 N HCl, and the whole was extracted with Et_2O. The extract was washed with water, saturated $NaHCO_3$, and brine and dried over $MgSO_4$. Filtration and solvent evaporation followed by a rapid filtration through a short pad of SiO_2 with Et_2O gave a crude mesylate, which was used without further purification. A mixture of CuBr·Me_2S (1.24 g, 6.0 mmol) and LiBr (521 mg, 6.0 mmol) was dissolved in THF (7 mL) at room temperature under nitrogen. After this solution was stirred for 2 min, a solution of the crude mesylate in THF (3 mL) was added to this reagent at room temperature. The mixture was stirred for 10 h at this temperature and quenched with saturated NH_4Cl (2 mL) and 28% NH_4OH (2 mL). The whole was extracted with Et_2O, and the extract was washed with water and dried over $MgSO_4$. Filtration and solvent evaporation followed by flash chromatography over silica gel with *n*-hexane−EtOAc (1:8) gave **7a** (762 mg, 88% yield) as a colorless oil: $[\alpha]^{24}_D$ +118 (*c* 1.25, $CHCl_3$); IR (KBr) cm^{-1} 3342 ($NHCO_2$), 1959 (C═C═C), 1701 ($NHCO_2$), 1502 ($NHCO_2$); ^1H NMR (270 MHz, $CDCl_3$) δ 0.94 (d, J = 7.0 Hz, 3H, CMe), 0.95 (d, J = 6.8 Hz, 3H, CMe), 1.46 (s, 9H, CMe_3), 1.82−1.94 (m, 1H, 5-H), 4.18 (br s, 1H, 4-H), 4.55−4.65 (m, 1H, NH), 5.37 (dd, J = 5.9, 5.4 Hz, 1H, 3-H), 6.09 (dd, J = 5.9, 2.2 Hz, 1H, 1-H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 18.1, 18.7, 28.5 (3C), 32.4, 54.2, 74.6, 79.6, 101.4, 155.2, 201.0; MS (FAB) *m*/*z* 292 (MH^+, ^{81}Br, 12), 290 (MH^+, ^{79}Br, 15), 236 (92), 234 (100). HRMS (FAB) calcd for $C_{12}H_{21}BrNO_2$ (MH^+, ^{79}Br), 290.0756; found, 290.0745.

(4*S*,a*S*)-1-Iodo-5-methyl-4-[*N*-(2,4,6-trimethylphenylsulfonyl)amino]hexa-1,2-diene (7c) (Table 1, Entry 3). By a procedure identical to that described for the mesylation of the alcohol **6a**, **6b** (201 mg, 0.65 mmol) was converted into the corresponding crude mesylate. According to the literature,[3b] a mixture of CuI (149 mg, 0.78 mmol) and LiI (105 mg, 0.78 mmol) was dissolved in THF (3 mL) at room temperature under nitrogen. After this solution was stirred for 1 h, a solution of the crude mesylate in THF (1 mL) was added to this reagent at room temperature. The mixture was stirred for 24 h at this temperature, followed by quenching with saturated NH_4Cl (1 mL) and 28% NH_4OH (1 mL). The whole was extracted with Et_2O, and the extract was washed with water and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to give an oily residue, which was purified by column chromatography over silica gel with *n*-hexane−EtOAc (8:1) to give **7c** (223 mg, 82% yield, >99% de) as colorless crystals: mp 79 °C (*n*-hexane−Et_2O); $[\alpha]^{24}_D$ +231 (*c* 1.00, $CHCl_3$); IR (KBr) cm^{-1} 3296 ($NHSO_2$), 1950 (C═C═C), 1323 ($NHSO_2$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.85 (d, J = 6.5 Hz, 3H, CMe), 0.92 (d, J = 7.5 Hz, 3H, CMe), 1.83−1.92 (m, 1H, 5-H), 2.29 (s, 3H, Ph*Me*), 2.64 (s, 6H, 2 × Ph*Me*), 3.62−3.67 (m, 1H, 4-H), 4.80 (dd, J = 7.5, 5.5 Hz, 1H, 3-H), 4.83 (d, J = 8.5 Hz, 1H, NH), 5.62 (dd, J = 5.5, 1.5 Hz, 1H, 1-H), 6.94 (s, 2H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.0, 18.3, 20.9, 23.1 (2C), 33.2, 37.2, 57.3, 94.9, 132.0 (2C), 134.4, 138.9 (2C), 142.2, 204.0; MS (EI) *m*/*z* (%) 420 (M + 1, 0.05), 119 (100). Anal. Calcd for $C_{16}H_{22}INO_2S$: C, 45.83; H, 5.29; N, 3.34. Found: C, 45.72; H, 5.14; N, 3.32.

(4*S*,a*R*)-1-Bromo-4-[(*tert*-butoxycarbonyl)amino]-5-methylhexa-1,2-diene (9a) (Table 1, Entry 7). By a procedure identical to that described for the preparation of the bromoallene **7a** from **6a**, the alcohol **8a** (455 mg, 2.0 mmol) was converted into **9a** (477 mg, 82% yield, 99% de) as colorless needles: mp 50 °C (*n*-hexane); $[\alpha]^{27}_D$ −304 (*c* 0.61, $CHCl_3$); IR (KBr) cm^{-1} 3334 ($NHCO_2$), 1959 (C═C═C), 1716 ($NHCO_2$), 1502 ($NHCO_2$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.94 (d, J = 6.6 Hz, 3H, CMe), 0.96 (d, J = 6.6 Hz, 3H, CMe), 1.45 (s, 9H, CMe_3), 1.85−1.93 (m, 1H, 5-H), 4.22 (br s, 1H, 4-H), 4.60 (d, J = 7.8 Hz, 1H, NH), 5.44 (dd, J = 5.7, 4.8 Hz, 1H, 3-H), 6.10 (dd, J = 5.7, 2.7 Hz, 1H, 1-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.9, 18.6, 28.3 (3C), 32.4, 53.8, 75.0, 79.6, 101.6, 155.4, 201.1; MS (FAB) *m*/*z* 314 (MNa^+, ^{81}Br, 18), 312 (MNa^+, ^{79}Br, 18), 176 (100), 136 (48). HRMS (FAB) calcd for $C_{12}H_{20}BrNNaO_2$ (MNa^+, ^{79}Br), 312.0575; found, 312.0567.

(4*S*,a*R*)-1-Iodo-5-methyl-4-[*N*-(2,4,6-trimethylphenylsulfonyl)amino]hexa-1,2-diene (9c) (Table 1, Entry 9). By a procedure identical to that described for the preparation of the iodoallene **7c** from **6b**, the alcohol **8b** (201 mg, 0.65 mmol) was converted into **9c** (173 mg, 63% yield, 99% de) as colorless crystals: mp 63 °C (*n*-hexane−Et_2O); $[\alpha]^{24}_D$ −344 (*c* 1.00, $CHCl_3$); IR (KBr) cm^{-1} 3286 ($NHSO_2$), 1950 (C═C═C), 1325 ($NHSO_2$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (d, J = 6.6 Hz, 3H, CMe), 0.89 (d, J = 6.9 Hz, 3H, CMe), 1.81−1.96 (m, 1H, 5-H), 2.30 (s, 3H, Ph*Me*), 2.65 (s, 6H, 2 × Ph*Me*), 3.79−3.87 (m, 1H, 4-H), 4.62 (d, J = 9.0 Hz, 1H, NH), 4.95 (dd, J = 5.7, 5.4 Hz, 1H, 3-H), 5.58 (dd, J = 5.7, 2.7 Hz, 1H, 1-H), 6.95 (s, 2H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.8, 18.3, 20.9, 23.3 (2C), 33.5, 38.7, 56.0, 95.9, 132.0 (2C), 134.8, 138.8 (2C), 142.1, 203.7; MS (EI) *m*/*z* (%) 420 (MH^+, 17), 136 (100). Anal. Calcd for $C_{16}H_{22}INO_2S$: C, 45.83; H, 5.29; N, 3.34. Found: C, 45.86; H, 5.19; N, 3.32.

General Procedure for the Synthesis of 2-Ethynylaziridines from Bromoallenes. Synthesis of (2*R*,3*S*)-2-Ethynyl-3-isopropyl-*N*-(2,4,6-trimethylphenylsulfonyl)aziridine (10b) and Its (2*S*,3*S*)-Isomer (11b) from the Bromoallene (7b) (Table 2, Entry 2). To a stirred suspension of NaH (9.6 mg, 0.24 mmol) in DMF (1 mL) under nitrogen was added a solution of the bromoallene **7b** (74.3 mg, 0.2 mmol) in DMF (1 mL) at 0 °C. After the mixture was stirred at room temperature for 1 h, the mixture was poured into ice−water (2 mL) saturated with NH_4Cl. The whole was extracted with Et_2O, and the extract was washed with water and dried over $MgSO_4$. Filtration and solvent evaporation followed by

flash chromatography over silica gel with *n*-hexane−EtOAc (10:1) gave, in order of elution, 2,3-*cis*-aziridine **10b** (44.4 mg, 76% yield) and its 2,3-*trans*-isomer **11b** (9.5 mg, 16% yield). When the reaction was conducted in THF (room temperature, 4 h), the *cis*-aziridine **10b** was obtained as the single isomer in 84% yield (Table 3, entry 2). All the spectroscopic data for **10b** and **11b** and the other known aziridines **10f**, **10g**, **11f**, and **11g** listed in Tables 2 and 3 were in good agreement with the literature.[13b,8]

(2*R*,3*S*)-2-Ethynyl-3-isopropyl-*N*-(4-methylphenylsulfonyl)aziridine (10d) and Its (2*S*,3*S*)-Isomer (11d) (Table 2, Entry 4). By a procedure identical to that described for the preparation of the aziridines **10b** and **11b** from **7b**, the bromoallene **7d** (68.9 mg, 0.20 mmol) was converted into the *cis*-aziridine **10d** (46.0 mg, 87% yield) and the *trans*-isomer **11d** (6.5 mg, 12% yield). When the reaction was conducted in THF (room temperature, 17 h), the *cis*-aziridine **10d** was obtained as the single isomer in 99% yield (Table 3, entry 3). Compound **10d**: colorless crystals; mp 111 °C (from *n*-hexane−Et_2O); $[\alpha]^{25}_D$ −64.1 (*c* 1.05, $CHCl_3$); IR (KBr) cm^{-1} 3273 (NSO_2), 2129 (C≡C), 1329 (NSO_2); ^1H NMR (270 MHz, $CDCl_3$) δ 0.84 (d, J = 6.8 Hz, 3H, CMe), 1.00 (d, J = 6.8 Hz, 3H, CMe), 1.55−1.69 (m, 1H, Me_2CH), 2.19 (d, J = 1.9 Hz, 1H, C≡CH), 2.45 (s, 3H, Ph*Me*), 2.55 (dd, J = 9.7, 7.0 Hz, 1H, 3-H), 3.35 (dd, J = 7.0, 1.9 Hz, 1H, 2-H), 7.34 (d, J = 8.1 Hz, 2H, Ph), 7.84 (d, J = 8.1 Hz, 2H, Ph); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 18.7, 20.2, 21.8, 28.4, 33.2, 50.7, 72.4, 76.6, 128.0 (2C), 129.6 (2C), 134.4, 144.7. Anal. Calcd for $C_{14}H_{17}NO_2S$: C, 63.85; H, 6.51; N, 5.32. Found: C, 63.59; H, 6.48; N, 5.26. Compound **11d**: colorless oil; $[\alpha]^{23}_D$ +29.1 (*c* 1.14, $CHCl_3$); IR (KBr) cm^{-1} 3267 (NSO_2), 2125 (C≡C), 1329 (NSO_2); ^1H NMR (300 MHz, $CDCl_3$) δ 0.79 (d, J = 6.6 Hz, 3H, CMe), 0.94 (d, J = 6.6 Hz, 3H, CMe), 1.41−1.53 (m, 1H, Me_2CH), 2.45 (s, 3H, Ph*Me*), 2.51 (d, J = 1.8 Hz, 1H, C≡CH), 2.92 (dd, J = 7.8, 4.5 Hz, 1H, 3-H), 2.99 (dd, J = 4.5, 1.8 Hz, 1H, 2-H), 7.33 (d, J = 8.1 Hz, 2H, Ph), 7.88 (d, J = 8.1 Hz, 2H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.0, 19.3, 21.6, 30.0, 33.8, 53.7, 74.9, 76.6, 128.1 (2C), 129.4 (2C), 136.1, 144.4; MS (FAB) *m*/*z* (%) 264 (MH^+, 100). HRMS (FAB) calcd for $C_{14}H_{18}NO_2S$ (MH^+), 264.1058; found, 264.1059.

(2*R*,3*S*)-3-Benzyl-2-ethynyl-*N*-(4-methylphenylsulfonyl)aziridine (10e) and Its (2*S*,3*S*)-Isomer (11e) (Table 2, Entry 5). By a procedure identical to that described for the preparation of the aziridines **10b** and **11b** from **7b**, the bromoallene **7e** (27.5 mg, 0.07 mmol) was converted into the *cis*-aziridine **10e** (17.1 mg, 78% yield) and the *trans*-isomer **11e** (2.1 mg, 10% yield). When the reaction was conducted in THF (room temperature, 22 h), the *cis*-aziridine **10e** was obtained as the single isomer in 71% yield (Table 3, entry 4). Compound **10e**: colorless needles; mp 115−116 °C (*n*-hexane−Et_2O); $[\alpha]^{24}_D$ −48.1 (*c* 0.50, $CHCl_3$); IR (KBr) cm^{-1} 3288 (NSO_2), 2127 (C≡C), 1327 (NSO_2); ^1H NMR (500 MHz, $CDCl_3$) δ 2.31 (d, J = 1.5 Hz, 1H, C≡CH), 2.43 (s, 3H, Ph*Me*), 2.85 (dd, J = 14.5, 7.0 Hz, 1H, PhC*H*H), 2.95 (dd, J = 14.5, 6.0 Hz, 1H, PhCH*H*), 3.07 (ddd, J = 7.0, 6.5, 6.0 Hz, 1H, 3-H), 3.43 (dd, J = 6.5, 1.5 Hz, 1H, 2-H), 7.10−7.18 (m, 5H, Ph), 7.22−7.23 (m, 2H, Ph), 7.68−7.70 (m, 2H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.6, 32.7, 34.5, 45.6, 73.3, 76.7, 126.6, 127.9 (2C), 128.5 (2C), 128.8 (2C), 129.7 (2C), 134.3, 136.7, 144.7; MS (FAB) *m*/*z* (%) 312 (MH^+, 68), 136 (100). HRMS (FAB) calcd for $C_{18}H_{18}NO_2S$ (MH^+), 312.1058; found, 312.1060. Compound **11e**: colorless oil; $[\alpha]^{25}_D$ +34.6 (*c* 0.585, $CHCl_3$); IR (KBr) cm^{-1} 3267 ($NHSO_2$), 2127 (C≡C), 1331 ($NHSO_2$); ^1H NMR (300 MHz, $CDCl_3$) δ 2.43 (s, 3H, Ph*Me*), 2.47 (d, J = 1.8 Hz, 1H, C≡CH), 2.74 (dd, J = 14.7, 6.9 Hz, 1H, PhC*H*H), 2.98 (dd, J = 14.7, 5.7 Hz, 1H, PhCH*H*), 3.08 (dd, J = 4.2, 1.8 Hz, 1H, 2-H), 3.33 (ddd, J = 6.9, 5.7, 4.2 Hz, 1H, 3-H), 6.99−7.03 (m, 2H, Ph), 7.13−7.23 (m, 5H, Ph), 7.68−7.71 (m, 2H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.6, 34.2, 36.6, 48.9, 75.0, 76.5, 126.7, 127.8 (2C), 128.5 (2C), 128.7 (2C), 129.5 (2C), 136.2 (2C), 144.2; MS (FAB) *m*/*z* (%) 312 (MH^+, 91), 91 (100). HRMS (FAB) calcd for $C_{18}H_{18}NO_2S$ (MH^+), 312.1058; found, 312.1060.

General Procedure for the Ring-Opening Reaction of Ethynylaziridines. Synthesis of (4*S*,a*R*)-1-Bromo-4-[*N*-(2,4,6-trimethylphenylsulfonyl)amino]-5-phenylpenta-1,2-diene (9h). To a solution of the aziridine **11h** (51.0 mg, 0.15 mmol) in CH_2Cl_2 (1 mL) was added dropwise methanesulfonic acid (20 μL, 0.30 mmol) at 0 °C with stirring, and the mixture was stirred for 15 min. The mixture was made alkaline with saturated $NaHCO_3$ at 0 °C and extracted with Et_2O. The extract was washed with water and dried over $MgSO_4$. Concentration under reduced pressure gave a crude mesylate **12h**. A mixture of CuBr·Me_2S (61.6 mg, 0.30 mmol) and LiBr (26.1 mg, 0.30 mmol) was dissolved in THF (1 mL) at room temperature under nitrogen. After this solution was stirred for 2 min, a solution of the crude mesylate **12h** in THF (1 mL) was added to this reagent at room temperature. The mixture was stirred for 1 h with warming to 50 °C and quenched with saturated NH_4Cl (0.5 mL) and 28% NH_4OH (0.5 mL). The whole was extracted with Et_2O. The extract was washed with water and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to give an oily residue, which was purified by column chromatography over silica gel with *n*-hexane−EtOAc (5:1) to give **9h** (50.7 mg, 80% yield, 88% de). Recrystallization from *n*-hexane−Et_2O gave **9h** (94% de) as colorless crystals: mp 73−75 °C; $[\alpha]^{25}_D$ −182 (*c* 0.92, $CHCl_3$, 94% de); IR (KBr) cm^{-1} 3356 ($NHSO_2$), 1957 (C═C═C), 1329 ($NHSO_2$); ^1H NMR (500 MHz, $CDCl_3$) δ 2.28 (s, 3H, Ph*Me*), 2.51 (s, 6H, 2 × Ph*Me*), 2.85 (dd, J = 13.5, 7.0 Hz, 1H, PhC*H*H), 2.89 (dd, J = 13.5, 7.0 Hz, 1H, PhCH*H*), 4.09−4.15 (m, 1H, 4-H), 4.66 (d, J = 7.0 Hz, 1H, NH), 5.38 (dd, J = 5.5, 5.5 Hz, 1H, 3-H), 5.88 (dd, J = 5.5, 2.5 Hz, 1H, 1-H), 6.88 (s, 2H, Ph), 7.04−7.06 (m, 2H, Ph), 7.13−7.23 (m, 3H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.9, 23.0 (2C), 41.7, 52.4, 75.4, 101.7, 127.0, 128.7 (2C), 129.3 (2C), 131.9 (2C), 133.8, 135.8, 139.0 (2C), 142.2, 200.9; MS (FAB) *m*/*z* (%) 422 (MH^+, ^{81}Br, 8), 420 (MH^+, ^{79}Br, 9), 136 (100); HRMS (FAB) calcd for $C_{20}H_{23}BrNO_2S$ (MH^+, ^{79}Br), 420.0633; found, 420.0623.

(4*S*,a*S*)-1-Bromo-5-methyl-4-[*N*-(2,4,6-trimethylphenylsulfonyl)amino]-1-trimethylsilylhexa-1,2-diene (15). By a procedure identical to that described for the synthesis of **7a** from **6a**, (3*S*,4*S*)-5-methyl-4-[*N*-(2,4,6-trimethylphenylsulfonyl)amino]-1-trimethylsilylhex-1-yn-3-ol[13b] (300 mg, 0.786 mmol) was converted into **15** (70 mg, 20% yield, >99% de) as colorless crystals: mp 74−75 °C (*n*-hexane−Et_2O); $[\alpha]^{27}_D$ +5.6 (*c* 0.51, $CHCl_3$); IR (KBr) cm^{-1} 3296 ($NHSO_2$), 1940 (C═C═C), 1323 ($NHSO_2$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.18 (s, 9H, $SiMe_3$), 0.83 (d, J = 6.9 Hz, 3H, CMe), 0.88 (d, J = 6.9 Hz, 3H, CMe), 1.88−1.98 (m, 1H, 5-H), 2.30 (s, 3H, Ph*Me*), 2.65 (s, 6H, 2 × Ph*Me*), 3.70 (ddd, J = 8.4, 5.7, 4.8 Hz, 1H, 4-H), 4.55 (d, J = 8.4 Hz, 1H, NH), 5.01 (d, J = 5.7 Hz, 1H, 3-H), 6.95 (s, 2H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ −1.8 (3C), 17.9, 18.2, 20.9, 23.2 (2C), 32.9, 56.7, 90.6, 94.9, 132.1 (2C), 134.3, 138.8 (2C), 142.1, 202.6; MS (FAB) *m*/*z* (%) 446 (MH^+, 17, ^{81}Br), 444 (MH^+, 18, ^{79}Br), 119 (100). HRMS (FAB) calcd for $C_{19}H_{31}BrNO_2SSi$ (MH^+, ^{79}Br), 444.1028; found, 444.1028.

(4*S*,a*R*)-1-Bromo-5-methyl-4-[*N*-(2,4,6-trimethylphenylsulfonyl)amino]-1-trimethylsilylhexa-1,2-diene (16). By a procedure identical to that described for the synthesis of **7a** from **6a**, (3*R*,4*S*)-5-methyl-4-[*N*-(2,4,6-trimethylphenylsulfonyl)amino]-1-trimethylsilylhex-1-yn-3-ol[13b] (840 mg, 2.2 mmol) was converted into **16** (296 mg, 30% yield, >99% de) as colorless crystals: mp 97−99 °C (*n*-hexane−Et_2O); $[\alpha]^{24}_D$ −147 (*c* 1.00, $CHCl_3$); IR (KBr) cm^{-1} 3284 ($NHSO_2$), 1940 (C═C═C), 1327 ($NHSO_2$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.21 (s, 9H, $SiMe_3$), 0.75 (d, J = 6.6 Hz, 3H, CMe), 0.84 (d, J = 6.9 Hz, 3H, CMe), 1.73−1.84 (m, 1H, 5-H), 2.23 (s, 3H, Ph*Me*), 2.65 (s, 6H, 2 × Ph*Me*), 3.75 (ddd, J = 9.0, 5.4, 4.5 Hz, 1H, 4-H), 4.53 (d, J = 9.0 Hz, 1H, NH), 5.05 (d, J = 5.4 Hz, 1H, 3-H), 6.94 (s, 2H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ −1.9 (3C), 17.7, 18.2, 20.9, 23.1 (2C), 33.0, 56.6, 91.0, 95.4, 132.0 (2C), 134.6, 138.8 (2C), 142.1, 202.8; MS (FAB) *m*/*z* (%) 446 (MH^+, 12, ^{81}Br), 444 (MH^+, 13, ^{79}Br), 119 (100). HRMS (FAB) calcd for $C_{19}H_{31}BrNO_2SSi$ (MH^+, ^{79}Br), 444.1028; found,

444.1026. Anal. Calcd for $C_{19}H_{30}BrNO_2SSi$: C, 51.34; H, 6.80; N, 3.15. Found: C, 51.45; H, 6.72; N, 3.00.

(4*S*,a*S*)-1-Bromo-5-methyl-4-[*N*-methyl-*N*-(2,4,6-trimethylphenylsulfonyl)amino]hexa-1,2-diene (18). To a stirred solution of PPh_3 (337 mg, 1.29 mmol) and **7b** (68.4 mg, 0.184 mmol) in THF (2 mL) under nitrogen were added MeOH (0.052 mL, 1.29 mmol) and DEAD (0.20 mL, 1.29 mmol) at 0 °C. The solution was stirred for 1.5 h at room temperature, and the mixture was concentrated under reduced pressure. The residue was purified by column chromatography over silica gel with *n*-hexane−EtOAc (14:1) to give **18** (66.7 mg, 94% yield) as a colorless oil: $[\alpha]^{27}_D$ +45.5 (*c* 1.10, $CHCl_3$); IR (KBr) cm^{-1} 3056 ($NHSO_2$), 1957 (C═C═C), 1322 ($NHSO_2$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.84 (d, J = 6.0 Hz, 3H, CMe), 0.93 (d, J = 6.3 Hz, 3H, CMe), 1.81−1.95 (m, 1H, 5-H), 2.30 (s, 3H, Ph*Me*), 2.61 (s, 6H, 2 × Ph*Me*), 2.72 (s, 3H, NMe), 3.78−3.84 (m, 1H, 4-H), 5.40 (dd, J = 7.5, 5.7 Hz, 1H, 3-H), 6.01 (dd, J = 6.0, 1.5 Hz, 1H, 1-H), 6.94 (s, 2H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.5, 20.4, 20.9, 23.2 (2C), 28.1, 29.5, 61.1, 73.9, 97.0, 131.9 (2C), 132.7, 140.1 (2C), 142.4, 202.7; MS (FAB) *m*/*z* (%) 388 (MH^+, ^{81}Br, 35), 386 (MH^+, ^{79}Br, 35), 119 (100). HRMS (FAB) calcd for $C_{17}H_{25}BrNO_2S$ (MH^+, ^{79}Br), 386.0789; found, 386.0784.

(4*S*,a*R*)-1-Bromo-5-methyl-4-[*N*-methyl-*N*-(2,4,6-trimethylphenylsulfonyl)amino]hexa-1,2-diene (19). By a procedure identical to that described for the preparation of **18** from **7b**, **9b** (51.2 mg, 0.138 mmol) was converted into **19** (52.6 mg, 99% yield): colorless oil; $[\alpha]^{25}_D$ −279 (*c* 0.955, $CHCl_3$); IR (KBr) cm^{-1} 3058 ($NHSO_2$), 1957 (C═C═C), 1323 ($NHSO_2$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.82 (d, J = 6.6 Hz, 3H, CMe), 0.97 (d, J = 6.6 Hz, 3H, CMe), 1.81−1.98 (m, 1H, 5-H), 2.30 (s, 3H, Ph*Me*), 2.61 (s, 6H, 2 × Ph*Me*), 2.67 (s, 3H, NMe), 3.87 (ddd, J = 10.2, 6.3, 1.5 Hz, 1H, 4-H), 5.48 (dd, J = 6.3, 5.7 Hz, 1H, 3-H), 5.97 (dd, J = 5.7, 1.5 Hz, 1H, 1-H), 6.94 (s, 2H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.6, 20.5, 20.9, 23.3 (2C), 28.2, 29.5, 60.8, 74.1, 97.8, 132.0 (2C), 132.9, 140.0 (2C), 142.4, 203.0; MS (FAB) *m*/*z* (%) 388 (MH^+, ^{81}Br, 37), 386 (MH^+, ^{79}Br, 38), 268 (72), 119 (100). HRMS (FAB) calcd for $C_{17}H_{25}BrNO_2S$ (MH^+, ^{79}Br), 386.0789; found, 386.0769.

(5*R*,a*S*)-1-Bromo-6-methyl-5-[*N*-(2,4,6-trimethylphenylsulfonyl)amino]hepta-1,2-diene (20). By a procedure identical to that described for the synthesis of **7a** from **6a**, (3*R*,5*R*)-6-methyl-5-[*N*-(2,4,6-trimethylphenylsulfonyl)amino]hept-1-yn-3-ol[30] (113 mg, 0.35 mmol) was converted into **20** (107 mg, 79% yield, >98% de). Recrystallization from *n*-hexane−Et_2O gave pure **20** as colorless crystals: mp 99 °C; $[\alpha]^{23}_D$ +81.0 (*c* 0.915, $CHCl_3$); IR (KBr) cm^{-1} 3288 ($NHSO_2$), 1956 (C═C═C), 1323 ($NHSO_2$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.79 (d, J = 6.6 Hz, 3H, CMe), 0.83 (d, J = 6.9 Hz, 3H, CMe), 1.73−1.88 (m, 1H, 6-H), 2.23−2.28 (m, 2H, 4-CH_2), 2.30 (s, 3H, Ph*Me*), 2.65 (s, 6H, 2 × Ph*Me*), 3.09−3.18 (m, 1H, 5-H), 4.50 (d, J = 8.7 Hz, 1H, NH), 5.15 (ddd, J = 7.2, 7.2, 5.7 Hz, 1H, 3-H), 5.89 (ddd, J = 5.7, 2.1, 2.1 Hz, 1H, 1-H), 6.95 (s, 2H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.6, 18.7, 20.9, 23.2 (2C), 30.7, 31.3, 58.4, 72.5, 96.3, 132.0 (2C), 134.6, 138.7 (2C), 142.1, 202.9; MS (FAB) *m*/*z* (%) 388 (MH^+, ^{81}Br, 31), 386 (MH^+, ^{79}Br, 30), 254 (100). HRMS (FAB) calcd for $C_{17}H_{25}BrNO_2S$ (MH^+, ^{79}Br), 386.0789; found, 386.0797. Anal. Calcd for $C_{17}H_{24}BrNO_2S$: C, 52.85; H, 6.26; N, 3.63. Found: C, 52.68; H, 6.15; N, 3.63.

(5*R*,a*R*)-1-Bromo-6-methyl-5-[*N*-(2,4,6-trimethylphenylsulfonyl)amino]hepta-1,2-diene (21). By a procedure identical to that described for the synthesis of **7a** from **6a**, (3*S*,5*R*)-6-methyl-5-[*N*-(2,4,6-trimethylphenylsulfonyl)amino]hept-1-yn-3-ol[30] (113 mg, 0.35 mmol) was converted into **21** (93 mg, 69% yield, >98% de). Recrystallization from *n*-hexane−Et_2O gave pure **21** as colorless crystals: mp 57 °C; $[\alpha]^{25}_D$ −179 (*c* 0.87, $CHCl_3$); IR (KBr) cm^{-1} 3284 ($NHSO_2$), 1956 (C═C═C), 1323 ($NHSO_2$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.77 (d, J = 6.9 Hz, 3H, CMe), 0.83 (d, J = 6.9 Hz, 3H, CMe), 1.73−1.86 (m, 1H, 6-H), 2.23−2.29 (m, 2H, 4-CH_2), 2.30 (s, 3H, Ph*Me*), 2.64 (s, 6H, 2 × Ph*Me*), 3.09−3.18 (m, 1H, 5-H), 4.46 (d, J = 9.0 Hz, 1H, NH), 5.11 (ddd, J = 7.5, 7.5, 5.7 Hz, 1H, 3-H), 5.91 (ddd, J = 5.7, 2.1, 2.1 Hz, 1H, 1-H), 6.95 (s, 2H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.4, 18.8, 20.9, 23.2 (2C), 30.9, 31.8, 58.6, 72.4, 96.4, 132.0 (2C), 134.7, 138.7 (2C), 142.1, 203.2; MS (FAB) *m*/*z* (%) 388 (MH^+, ^{81}Br, 29), 386 (MH^+, ^{79}Br, 32), 254 (100). HRMS (FAB) calcd for $C_{17}H_{25}BrNO_2S$ (MH^+, ^{79}Br), 386.0789; found, 386.0783.

(2*S*,5*R*)-2-Ethynyl-5-isopropyl-*N*-(2,4,6-trimethylphenylsulfonyl)pyrrolidine (26). By a procedure identical to that described for the preparation of the aziridines **10b** and **11b** from **7b**, the bromoallene **25** (40 mg, 0.10 mmol) was converted into 2,5-*cis*-pyrrolidine **26** (30.0 mg, 94% yield, >99:1). Recrystallization from *n*-hexane−Et_2O gave pure **26**. The stereochemistry of **26** was determined by NOE analysis. Colorless needles: mp 104 °C (*n*-hexane); $[\alpha]^{23}_D$ −35.8 (*c* 0.90, $CHCl_3$); IR (KBr) cm^{-1} 3261 (NSO_2), 2114 (C≡C), 1308 (NSO_2); ^1H NMR (500 MHz, $CDCl_3$) δ 0.72 (d, J = 7.0 Hz, 3H, CMe), 0.83 (d, J = 6.5 Hz, 3H, CMe), 1.72−1.81 (m, 1H, Me_2CH), 1.91−2.00 (m, 3H, 3-C*H*H and 4-CH_2), 2.10−2.17 (m, 1H, 3-CH*H*), 2.19 (d, J = 2.5 Hz, 1H, C≡CH), 2.30 (s, 3H, Ph*Me*), 2.69 (s, 6H, 2 × Ph*Me*), 3.80 (ddd, J = 6.0, 6.0, 6.0 Hz, 1H, 5-H), 4.64−4.66 (m, 1H, 2-H), 6.94 (s, 2H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.8, 19.9, 21.0, 22.9 (2C), 25.8, 30.3, 33.3, 50.3, 66.1, 71.4, 83.4, 131.8 (2C), 132.4, 140.6 (2C), 142.9; MS (FAB) *m*/*z* (%) 320 (MH^+, 100). HRMS (FAB) calcd for $C_{18}H_{26}NO_2S$ (MH^+), 320.1684; found, 320.1674.

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Supporting Information Available: Synthetic procedures and characterization for **6d**, **6e**, **7b**, **7d**−**g**, **8d**, **8e**, **9b**, **9d**−**g**, **13**, **14**, **24**, and **25**; ^1H NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(30) For synthesis of the starting amino alcohols, see the Supporting Information of ref 7d.