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Stereoselective Synthesis of Chiral 2,3-*cis*-2-Ethynylaziridines by Base-Mediated Intramolecular Amination of Bromoallenes

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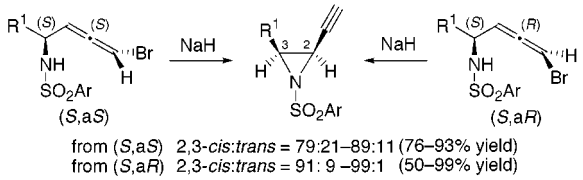
ABSTRACT



Novel stereoselective synthesis of 2,3-*cis*-2-ethynylaziridines from amino allenes is presented. While sodium hydride mediated intramolecular amination of (4*S*,a*S*)-4-alkyl-4-[*N*-(arylsulfonyl)amino]-1-bromobuta-1,2-dienes yields a mixture of 2,3-*cis*- and 2,3-*trans*-2-ethynylaziridines in which the *cis*-isomer predominates (79:21−89:11), the amination of (4*S*,a*R*)-isomers affords 2,3-*cis*-aziridines in excellent selectivities (91:9−100:0). Conversion of 2,3-*trans*-2-ethynylaziridines into the corresponding *cis*-isomers via a sequence of reactions (methanesulfonic acid mediated ring-opening reaction, bromination, and aziridination) is also described.

Chiral *N*-activated aziridines are widely used in organic synthesis.[1] Particularly, aziridines bearing an alkenyl[2] or ethynyl[3,4] group on one of the aziridine-ring carbon atoms have proven to be extremely useful intermediates for preparation of various types of natural and synthetic compounds. Recently, we have shown that 2-ethynylaziridines can function as both chiral carbon electrophiles[3] and nucleophiles,[4] which provide stereoselective synthetic routes to chiral amino allenes and 2-ethynyl-1,3-amino alcohols, respectively. However, a stereoselective preparative route to enantiomerically enriched 2-ethynylaziridines is rare.

Recently, Dai and co-workers have reported the asymmetric synthesis of 2-ethynylaziridines in moderate to good enantioselectivities (14−85% ee) by the reaction of *N*-tosylimines and D-(+)-camphor-derived sulfonium ylide.[5] One of the simplest methods for the synthesis of enantiopure ethynylaziridines involves the Mitsunobu reaction of the propargyl alcohol **1** (Scheme 1),[6] which could be readily

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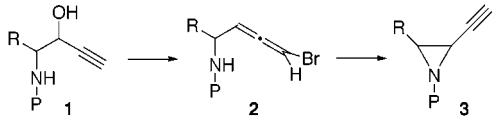
Scheme 1

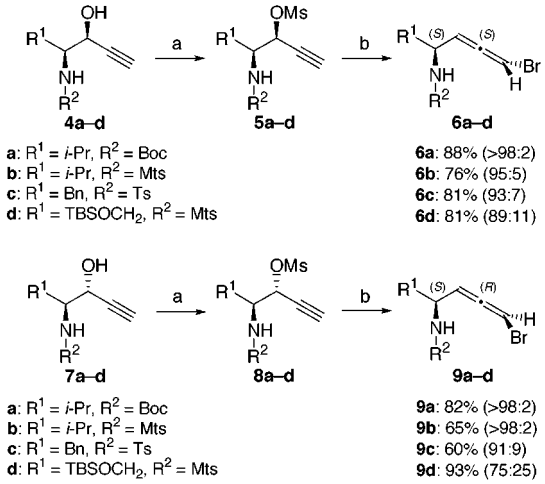


prepared from chiral aldehydes derived from α-amino acids. However, a highly diastereoselective synthesis of either *syn*- or *anti*-**1** by the reaction of amino aldehydes with metal acetylides has proven to be difficult,[6] with the exception of a few examples.[7] Thus, aziridination of the diastereomixture of amino alcohols **1** under Mitsunobu conditions again gives a mixture of 2,3-*cis*- and *trans*-2-ethynylaziridines in moderate selectivities.

To establish a stereoselective synthetic method of chiral 2-ethynylaziridines **3**, we planned an aziridination of bromoallenes **2** bearing a protected amino group, which would be readily prepared from the propargyl alcohol **1** (Scheme 1). Although intermolecular amination of racemic bromoallenes has been already reported by Caporusso and coworkers,[8] a stereochemical course of amination toward chiral bromoallenes and intramolecular amination of bromoallenes are unprecedented as far as we are aware. In this communication, we present a highly 2,3-*cis*-selective synthesis of 2-ethynylaziridines by base-mediated intramolecular amination of bromoallenes.[9,10]

The (*S*,a*S*)-bromoallenes **6a**−**d** bearing a protected amino group were synthesized from *syn*-amino alcohols **4a**−**d**[6] in high yields. Thus, mesylation of **4** by the standard method gave **5**, which was then converted into the desired bromoallenes **6** by treatment with CuBr·DMS/LiBr.[11] Similarly, (*S*,a*R*)-**9a**−**d** were synthesized from the *anti*-amino alcohols **7a**−**d**. Although the stereoselectivities for the bromination of **5d** and **8d** bearing a siloxy group were relatively low (89:11 and 75:25, respectively), pure **6d** and **9d** were obtained by flash column chromatography. The stereochemistries of the synthesized bromoallenes could be deduced by the well-documented *anti*-S_N2' reaction course[11b,12] and comparison of their optical rotations with the related compounds.[3]

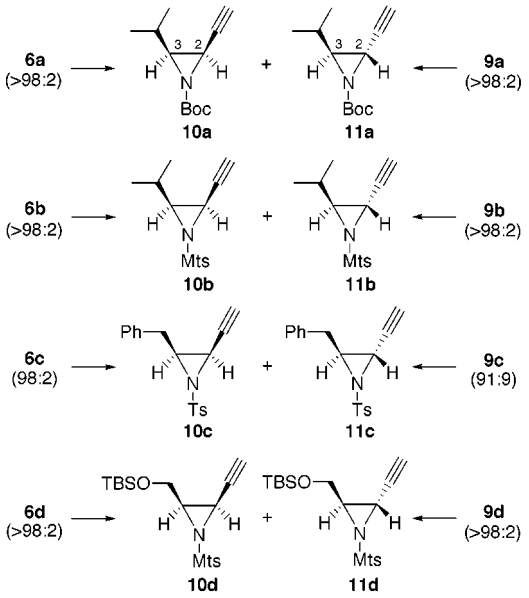
Scheme 2[a]



[a] Reagents and conditions: (a) MsCl, Et_3N, THF, −78 to −40 °C; (b) CuBr·DMS, LiBr, THF, 25 or 50 °C. Abbreviations: Mts = 2,4,6-trimethylphenylsulfonyl, TBS = *tert*-butyldimethylsilyl, DMS = dimethyl sulfide.

With the requisite substrates in hand, we investigated the intramolecular amination of bromoallenes under basic conditions (Scheme 3 and Table 1). The *N*-Boc-(*S*,a*S*)-**6a** was

Scheme 3



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, entry 1), although in low yield (35%). A

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(9) For related works, see: (a) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1984**, *25*, 3059. (b) Caporusso, A. M.; Polizzi C.; Lardicci, L. *Tetrahedron Lett.* **1987**, *28*, 6073. (c) D'Aniello, F.; Mann, A.; Schoenfelder, A.; Taddei, M. *Tetrahedron* **1997**, *53*, 1447. (d) Bernard, N.; Chemla, F.; Normant, J. F. *Tetrahedron Lett.* **1999**, *40*, 1649. (e) Chemla, F.; Bernard N.; Normant, J. *Eur. J. Org. Chem.* **1999**, 2067. (f) Caporusso, A. M.; Filippi, S.; Barontini F.; Salvadori, P. *Tetrahedron Lett.* **2000**, *41*, 1227. (g) Conde, J. J.; Mendelson, W. *Tetrahedron Lett.* **2000**, *41*, 811.

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Table 1. Base-Mediated Aziridination of Bromoallenes[a]

entry	allene	base	temp (°C)	time (min)	product ratio[b]	yield[c] (%)
1	**6a**	NaH	25	20	**10a**:**11a** = 60:40	35
2	**6a**	KH	25	120	**10a**:**11a** = 65:35	42
3[d]	**6a**	LDA	−78	30	**10a**:**11a** = 52:48	77
4	**9a**	NaH	25	60	**10a**:**11a** = 53:47	28
5	**6b**	NaH	25	60	**10b**:**11b** = 82:18	93
6	**6c**	NaH	25	90	**10c**:**11c** = 89:11	88
7	**6d**	NaH	25	60	**10d**:**11d** = 79:21	76
8	**9b**	NaH	25	30	**10b**:**11b** = >99:1	99
9	**9c**	NaH	25	150	**10c**:**11c** = 97:3	78
10	**9d**	NaH	70	10	**10d**:**11d** = 91:9	50

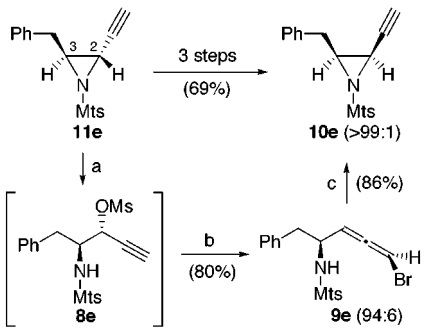
[a] All reactions were carried out in DMF using 1.2 or 1.3 equiv of base unless otherwise stated. [b] Ratios were determined by ^{1}H NMR (270 MHz) or isolation of products. [c] Combined isolated yields. [d] The reaction was conducted in THF using 3 equiv of LDA.

similar result was obtained using potassium hydride as a base (entry 2). Treatment of **6a** with LDA in THF resulted in the expected aziridines in higher yield (77%, entry 3); however, diastereoselectivity was poor (**10a**:**11a** = 52:48). Similarly, almost no selectivity was observed starting from (*S*,a*R*)-**9a** using either NaH (entry 4) or other bases. From the above results, we were initially apprehensive that the stereoselective aziridine-ring-forming reaction from bromoallenes could not be realized.

However, we found that sodium hydride mediated cyclization of (*S*,a*S*)-bromoallenes **6b**−**d** bearing an *N*-sulfonylated amino group yielded 2,3-*cis*-2-ethynylaziridines **10b**−**d** in good to high selectivities (**10**:**11** = 79:21−89:11, entries 5−7), in high yields. When (*S*,a*R*)-bromoallenes **9b**−**d** were treated with sodium hydride in DMF, the desired *cis*-aziridines **10b**−**d** were again obtained in excellent selectivities (entries 8−10). The cyclization of **9d** bearing a siloxy group was relatively slow; however, increased reaction temperature (70 °C) led to a completion of the reaction within 10 min (entry 10). Although the origin of the *cis*-selectivities for the aziridination reaction of the bromoallenes bearing a sulfonamide group is unclear at the present stage,[13] an efficient synthesis of *cis*-2-ethynylaziridines was realized.

Finally, we applied the novel aziridination to convert the 2,3-*trans*-2-ethynylaziridine **11e** into the corresponding 2,3-*cis*-isomer **10e** (Scheme 4). Methanesulfonic acid mediated

Scheme 4[a]



[a] Reagents and conditions: (a) $MeSO_3H$ (2 equiv), CH_2Cl_2, 0 °C, 15 min; (b) CuBr·DMS (2 equiv), LiBr (2 equiv), THF, 50 °C, 1 h; (c) NaH (1.3 equiv), DMF, 25 °C, 3 h.

ring-opening reaction[14] of **11e** gave a crude mesylate **8e**, which was directly converted into the bromoallene **9e** without purification (80% yield, 2 steps). Intramolecular amination of **9e** with sodium hydride in DMF afforded the expected 2,3-*cis*-2-ethynylaziridine **10e** as a single isomer in 86% yield. The overall yield of the three-step sequence for the inversion of *trans*-**11e** at C-2 was 69%.

In conclusion, we have presented the first intramolecular amination of bromoallenes for the 2,3-*cis*-selective synthesis of *N*-sulfonylated 2-ethynylaziridines. The described method would provide a selective synthesis of 2,3-*cis*-2-ethynylaziridine from a mixture of *syn*- and *anti*-amino alcohols **4** and **7**.

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Supporting Information Available: Representative experimental procedures as well as ^{1}H 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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(13) We observed isomerization of the 2,3-*trans*-2-ethynylaziridine **11b** into the corresponding 2,3-*cis*-isomer **10b** under the aziridination conditions (NaH, DMF, room temperature). Although a prolonged reaction time (>10 h) was required for an efficient conversion (*cis*:*trans* = >95:5), equilibration of the products would be one of the important factors for the *cis*-selective aziridination. Thermodynamic preference of the related 2,3-*cis*-aziridines over their *trans*-isomers is well documented by our previous study; see: ref 2g.

(14) 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. (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.