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

Hiroaki Ohno, Hisao Hamaguchi, and Tetsuaki Tanaka*

Graduate School of Pharmaceutical Sciences, Osaka University, 1–6 Yamadaoka, Suita, Osaka 565-0871, Japan

t-tanaka@phs.osaka-u.ac.jp

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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*,*aS*)-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*,*aR*)-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 alkenyl² 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 electrophiles³ 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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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*,*aS*)-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*,*aR*)-**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

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the well-documented *anti*- $S_N 2'$ reaction course^{11b,12} and comparison of their optical rotations with the related compounds.³



^{*a*} Reagents and conditions: (a) MsCl, Et₃N, 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,aS)-**6a** 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, entry 1), although in low yield (35%). A

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⁽⁷⁾ 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. (b) D'Aniello, F.; Schoenfelder, A.; Mann A.; Taddei, M. J. Org. Chem. **1996**, 61, 9631. For related works, see: (c) Frantz, D. E.; Fässler, R.; Carreira, E. M. J. Am. Chem. Soc. **2000**, *122*, 1806. (d) Boyall, D.; López, F.; Sasaki, H.; Frantz, D.; Carreira E. M. Org. Lett. **2000**, *2*, 4233.

Table 1. Base-Mediated Aziridination of Bromoallenes^a

entry	allene	base	temp (°C)	time (min)	product ratio ^b	yield (%)
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 ¹H 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*,*aR*)-**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 *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



^{*a*} Reagents and conditions: (a) MeSO₃H (2 equiv), CH₂Cl₂, 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 reaction¹⁴ 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 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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⁽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.

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