Asymmetric recognition and sequential ring opening of 2-substituted-*N*-nosylaziridines with $(DHQD)_2AQN$ and TMSNu†

Satoshi Minakata,* Yuta Murakami, Masamitsu Satake, Ikumasa Hidaka, Yuriko Okada and Mitsuo Komatsu

Received 2nd December 2008, Accepted 15th December 2008
First published as an Advance Article on the web 7th January 2009
DOI: 10.1039/b821650a

A new method for asymmetric ring opening of terminal aziridines using a chiral amine, $(DHQD)_2AQN$, is described; the reaction is based on the asymmetric recognition of aziridines using $(DHQD)_2AQN$ and on sequential ring opening using TMSNu.

Aziridines are very useful building blocks for the synthesis of biologically active compounds and functional materials.[1] The ring opening of aziridines, involving induction of chirality, leads directly to the synthesis of valuable intermediates. The asymmetric ring opening of aziridines has been investigated mainly with meso-aziridines.[2] Although the highly enantioselective desymmetrization of aziridines has been elegantly achieved by several groups, the substituents of the resulting amino group are logically restricted.[3] Thus far, there has been only one example of an alternative to the asymmetric ring opening of aziridines, which is based on the palladium-catalyzed kinetic resolution of racemic terminal aziridines.[4] However, this reaction has been limited to the use of a phenyl group-substituted aziridine, and the enantioselectivity is unsatisfactory. This novel method of ring opening of aziridines, developed using TMSNu (Nu: CN, N_3, Br, I) catalyzed by a simple tertiary amine,[5] would serve as the kinetic resolution of racemic terminal aziridines using chiral tertiary amines. In particular, the ring opening products using TMSCN are a precursor to chiral β-amino acids.[6] While the preliminary experiment unexpectedly gave an optically active aziridine, the pathway of the reaction was found to be different from our proposed mechanism[5] based on the activation of TMSNu with a chiral amine (vide infra). From this background, we herein report on the asymmetric recognition and sequential ring opening of terminal *N*-nosylaziridines using TMSNu and a chiral amine.

Since the reaction of 2-benzyl-*N*-tosylaziridine with TMSCN in the presence of $(DHQD)_2PHAL$[7] (20 mol%) did not give good selectivity (ring opening product: 6% ee, aziridine: 2% ee) to increase the reactivity of aziridine, the change to an *o*-nosyl group from *p*-tosyl on the nitrogen of the aziridine improved the enantioselectivity (ring opening product: 25% ee, aziridine: 33% ee). However, the absolute configuration of the major products (the ring opening product and the remaining aziridine) was the same (*R*), indicating that the chiral amine recognized (captured) (*S*)-aziridine, and the remaining aziridine was partially opened with TMSCN in the presence of the amine. In order to confirm the phenomenon, the time course of the reaction of *N*-(*o*-nitrobenzenesulfonyl)-2-benzylaziridine (**1a**) with $(DHQD)_2AQN$[7] was examined and the results are shown in Fig. 1 (left). Interestingly, the consumption of aziridine induced an increase in enantio-purity, indicating that (*S*)-aziridine was selectively captured by $(DHQD)_2AQN$. Fig. 1 (right). This profile represents the time courses of theoretical yields of (*R*)-**1a** and (*S*)-**1a** calculated from the results in Fig. 1 (left). It is easy to see that the chiral amine reacted faster with (*S*)-**1a** than with (*R*)-**1a**.

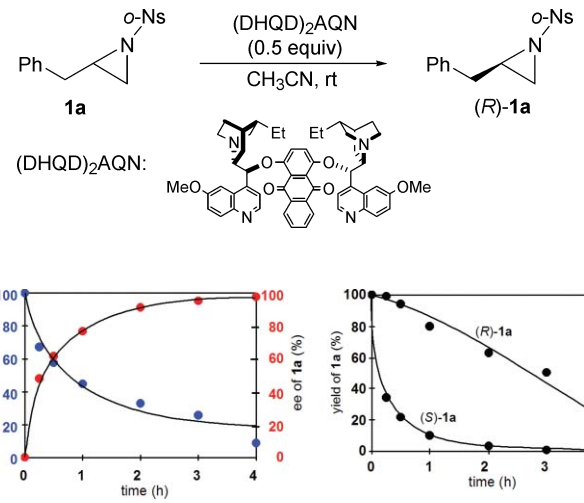
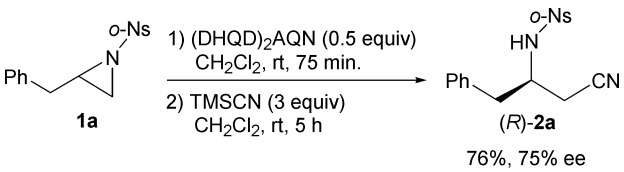


Fig. 1 Time course of the reaction of **1a** with $(DHQD)_2AQN$ (left) and time courses of the theoretical yield of **1a** (right).

This recognition ability of (*S*)-**1a** with $(DHQD)_2AQN$ was applied to the sequential ring opening of the remaining (*R*)-**1a** (Scheme 1). Aziridine **1a** was treated with $(DHQD)_2AQN$ in acetonitrile at room temperature for 75 min., and then three equivalents of TMSCN were added to the mixture, giving the regioselective ring opening product with cyanide in a 76% yield with 75% ee. The chemical yield was based on the consumption of a half-amount of the starting aziridine. The reaction time of the first step should be very important for yield and selectivity, and a time of 75 min. was found to be the best among several investigations.

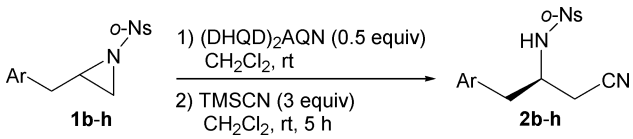


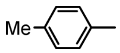
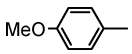
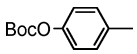
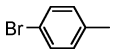
Scheme 1 Asymmetric recognition of **1a** with $(DHQD)_2AQN$ and its ring opening with TMSCN.

Department of Applied Chemistry, Graduate School of Engineering, Osaka University, Yamadaoka 2-1, Suita, Osaka 565-0871, Japan. E-mail: minakta@chem.eng.osaka-u.ac.jp; Fax: +81 6-6879-7402

† Electronic supplementary information (ESI) available: Synthetic procedures and experimental data for the products. See DOI: 10.1039/b821650a

Table 1 Asymmetric ring opening of arylmethylated *N*-nosylaziridines with TMSCN



Entry	Ar		Time (min)		Yield[a] (%)	*ee*[b] (%)
1		**1b**	75	**2b**	70	87
2		**1c**	90	**2c**	68	80
3		**1d**	75	**2d**	62	81
4		**1e**	60	**2e**	72	86
5		**1f**	120	**2f**	68	82
6		**1g**	105	**2g**	78	75
7		**1h**	90	**2h**	72	95

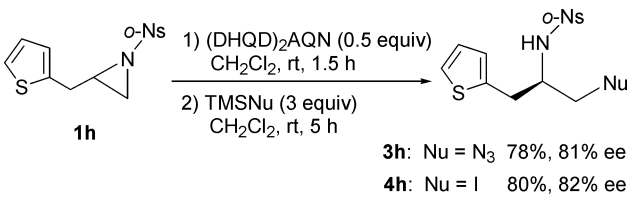
[a] Isolated yield based on consumption of half the amount of aziridine **1**. [b] Determined by chiral HPLC.

As described in the introduction, the ring opening products of terminal aziridines with TMSCN are versatile precursors of chiral β-amino acids and β-lactams. Among them, β-homo phenylalanine is currently of great interest for μ-type opioid receptor affinity.[8] The demand for this type of β-amino acid prompted us to investigate the enantioselective ring opening of arylmethylated aziridines, which are readily prepared from the aziridination of allyl arenes using our method.[9] The asymmetric recognition and sequential ring opening of arylmethylated *N*-nosylaziridines with TMSCN was examined in Table 1.

The reaction time for the recognition of electron-sufficient, aromatic-substituted aziridines tended to be rather longer than that of electron-deficient ones. The ring opening reactions proceeded with good to excellent enantioselectivity. In particular, thiophenylmethylaziridine **1h** ring-opened efficiently to afford a precursor of a unique β-amino acid. Consequently, this is the first example of the asymmetric ring opening of terminal aziridines with TMSCN.

In addition to TMSCN, $TMSN_3$ and TMSI were applicable to the ring opening reaction, as reported in our previous work.[5] Thus, these TMSNu were employed in the ring opening of **1h** to give the corresponding products in good enantioselectivity (Scheme 2).

In addition to arylmethyl-substituted terminal aziridines, *n*-hexyl-substituted aziridine was also applicable to the ring opening reaction. Although the selectivity of the reaction was rather low compared with that of arylmethylated aziridines, chiral ring opening products with cyanide, azide and iodide were obtained with moderate enantioselectivity.[10]

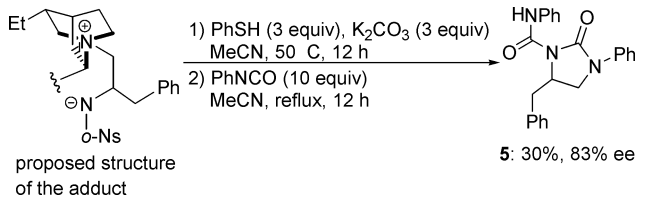


Scheme 2 Asymmetric ring opening of **1h** with TMSNu.

On the other hand, adducts of **1** with $(DHQD)_2AQN$ were separated from the mixtures of the reactions shown in Scheme 1 and Table 1 using flash column chromatography on silica gel (eluent: MeOH/diethylamine = 50/50). The FAB mass spectrum of aziridine **1a** trapped by $(DHQD)_2AQN$ shows peaks at 1175 and 1493, which are attributed to peaks of a mixture of 1:1 and 2:1 adducts of **1a** and $(DHQD)_2AQN$. The analysis of the ^1H NMR spectra of the adducts was very difficult because so many signals were observed, but the signal of the α-hydrogen of the quinoline moiety did not shift compared with that of $(DHQD)_2AQN$. Moreover, the polarity of the adduct was very high. From these results, the structure of the adducts would be salts that are formed by the ring opening of **1a** with a tertiary amine (nitrogen of quinuclidine) of $(DHQD)_2AQN$.[10]

Much effort was devoted to the liberation of the enantio-enriched aziridine unit from the adducts. For example, although the adduct of **1a** with $(DHQD)_2AQN$ was treated with TMSCN (5 equiv) in acetonitrile at refluxing temperature for 24 h, the reaction did not proceed at all. Consequently, the nosyl group was

deprotected using Fukuyama's method[11] followed by a reaction with phenyl isocyanate to give a chiral cyclic urea (Scheme 3). The starting adduct, which was recovered from the reaction shown in Scheme 1, was used for this reaction.



Scheme 3 Transformation of the adduct of **1a** to $(DHQD)_2AQN$.

In summary, this paper describes the asymmetric ring opening of aziridines based on chiral recognition and sequential ring opening. Although good methods have been in use for the asymmetric ring opening of meso-aziridines thus far, this is the first example presenting high selectivity for the ring opening of terminal aziridines, and this method contributes to the supply of a new series of chiral β-amino acids.

Notes and references

1 (*a*) J. B. Sweeny, *Chem. Soc. Rev.*, 2002, **31**, 247; (*b*) D. Tanner, *Angew. Chem.*, 1994, **106**, 625; D. Tanner, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 599; (*c*) A. Padwa, W. H. Pearson, B. N. Lian, S. C. Bergmeier, in *Comprehensive Heterocyclic Chemistry II*, Vol. 1A (Eds.: A. R. Katritzky, C. W. Rees and E. F. Scriven), Pergamon, Oxford, 1996, pp. 1-60; (*d*) A. Padwa, A. D. Woolhouse, In *Comprehensive Heterocyclic Chemistry Vol. 7* (Ed.: W. Lwowski), Pergamon, Oxford, 1984.

2 (*a*) Z. D. Zhang and R. Scheffold, *Helv. Chim. Acta*, 1993, **76**, 2602; (*b*) M. Hayashi, K. Ono, H. Hoshimi and N. Oguni, *J. Chem. Soc., Chem. Commun.*, 1994, 2699; (*c*) P. Muller and P. Nury, *Org. Lett.*, 1999, **1**, 1611.

3 (*a*) Z. Li, M. Fernández and E. N. Jacobsen, *Org. Lett.*, 1999, **1**, 439; (*b*) T. Mita, I. Fujimori, R. Wada, J. Wen, M. Kanai and M. Shibasaki, *J. Am. Chem. Soc.*, 2005, **127**, 11252; (*c*) I. Fujimori, T. Mita, K. Maki, M. Shiro, A. Sato, S. Furusho, M. Kanai and M. Shibasaki, *J. Am. Chem. Soc.*, 2006, **128**, 16438; (*d*) K. Arai, S. Lucarini, M. M. Salter, K. Ohta, Y. Yamashita and S. Kobayashi, *J. Am. Chem. Soc.*, 2007, **129**, 8103; (*e*) E. B. Rowland, G. B. Rowland, E. Rivera-Otero and J. C. Antilla, *J. Am. Chem. Soc.*, 2007, **129**, 12084.

4 W.-H. Leung, W.-L. Mak, E. Y. Y. Chan, T. C. H. Lam, W.-S. Lee, H.-L. Kwong and L.-L. Yeung, *Synlett*, 2002, 1688.

5 S. Minakata, Y. Okada, Y. Oderaotoshi and M. Komatsu, *Org. Lett.*, 2005, **7**, 3509.

6 (*a*) S. Abele and D. Seebach, *Eur. J. Org. Chem.*, 2000, 1; (*b*) F. Fülöp, *Chem. Rev.*, 2001, **101**, 2181; (*c*) M. Liu and M. P. Sibi, *Tetrahedron*, 2002, **58**, 7991.

7 S. G. Hentges and K. B. Sharpless, *J. Am. Chem. Soc.*, 1980, **102**, 4263 $(DHQD)_2PHAL$ is a good chiral source for asymmetric silylcyanation of ketones. See: S.-K. Tian, R. Hong and L. Deng, *J. Am. Chem. Soc.*, 2003, **125**, 9900. However, $(DHQD)_2AQN$ was better than $(DHQD)_2PHAL$ for the present asymmetric induction.

8 L. Longobardo, D. Melck, R. Siciliano, A. Santini, V. D. Marzo and G. Cammarota, *Bioorg. Med. Chem. Lett.*, 2000, **10**, 1185.

9 (*a*) T. Ando, D. Kano, S. Minakata, I. Ryu and M. Komatsu, *Tetrahedron*, 1998, **54**, 13485; (*b*) S. Minakata, D. Kano, Y. Oderaotoshi and M. Komatsu, *Angew. Chem.*, 2004, **116**, 81; S. Minakata, D. Kano, Y. Oderaotoshi and M. Komatsu, *Angew. Chem., Int. Ed.*, 2004, **43**, 79.

10 See Supporting Information for details†.

11 W. Kurosawa, T. Kan and T. Fukuyama, *Org. Synth.*, 2004, **10**, 482. The deprotected product was not isolated and the resulting mixture was treated with the isocyanate.