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cis-Selective Aziridination of *cis*- or *trans*-α,β-Unsaturated Amides Using Diaziridine

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Abstract: Aziridination of α,β-unsaturated amides was effected by treatment with lithiated 3,3-pentamethylenediaziridine in high diastereoselectivity. *cis*-Aziridine was the predominant diastereomer irrespective of the geometry of the substrates. A stepwise mechanism, 1,4-addition of a lithiated diaziridine to α,β-unsaturated amides and subsequent ring closure at the nitrogen atom, was proposed to explain the unusual *cis*-selectivity.

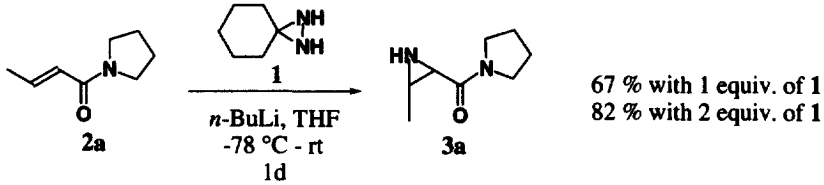
Keywords: Aziridines; Diaziridines; Amides; Diastereoselection.

Three-membered ring compounds with two heteroatoms such as dioxiranes and *N*-sulfonylated oxaziridines have been well recognized as potential one-heteroatom transfer agents to olefins owing to their high ring strain. Their reactions proceed in a concerted manner. However, diaziridine, which is a dinitrogen equivalent of dioxirane and readily available from a carbonyl compound, amine, and hydroxylamine derivative, has not been used so far as a nitrogen donor agent and is mostly employed as a precursor of carbene synthesis.[1] However, since the nitrogen-nitrogen bond is as weak as an oxygen-oxygen or oxygen-nitrogen bond, it was expected that diaziridine would serve as a nitrogen donor agent, in the case that one of the nitrogen atoms functions as a nucleophile.[2] Thus, we examined aziridination of α,β-unsaturated amides. The unusual stereochemistry of this aziridination is reported.

diaziridine

As the diaziridine compound, 3,3-pentamethylenediaziridine (**1**), which was prepared according to the reported method,[3] was employed for this investigation. Recrystallization from toluene gave pure **1** as colorless crystals that could be stored at rt for several months.[3]

The reactivity of **1** as an aziridinating agent of olefins was poor. Treatment of *N*-(*E*)-crotonoylpyrrolidine (**2a**) with **1** did not bring about any reaction at rt. Elevating the reaction temperature resulted in the decomposition of **1**. However, on pretreatment with *n*-butyllithium at –78℃, **1** was found to react with **2a** giving *N*-unsubstituted aziridine amide **3a** in 67% yield as shown in Scheme 1. The yield of **3a** increased to



Scheme 1

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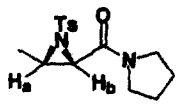
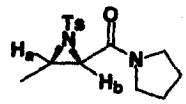
82% by using two equivalents of **1**.[4] Although many hydroxylamine or hydrazine derivatives have been reported to effect 1,4-addition to α,β-unsaturated carbonyl compounds, the 1,4-adducts cannot undergo the ring-closure reaction unless the oxygen or nitrogen group is activated as a leaving group.[5] One advantage of the present reaction is that the desired ring closure proceeds without any activation of the intermediary 1,4-adduct.[5,6]

The stereochemistry of **3a** was confirmed to be 2,3-*cis* by chemical correlation to *N*-(*p*-toluenesulfonyl)aziridine amide **4** which was prepared based on reported methods.[7] The coupling constant between hydrogens on the aziridine ring showed 7.5 Hz for *cis*-aziridine amide **4**, while 4.0 Hz was observed for *trans*-aziridine amide **5**.

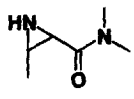


4 J_{ab}=7.5Hz

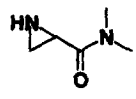


5 J_{ab}=4.0Hz

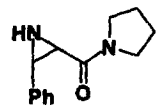
Similar conditions could be applied for the aziridination of other α,β-unsaturated amides such as *N*-(*E*)-crotonoyldimethylamine (**2b**), *N*-acryloyldimethylamine (**2c**), and *N*-(*E*)-cinnamoylpyrrolidine (**2d**). The corresponding *N*-unsubstituted aziridines **3b** (63%), **3c** (39%), **3d** (72%) were isolated.[8] Interestingly, the formation of *trans*-aziridines could not be detected under the conditions. Namely, *cis*-aziridine was obtained exclusively in this aziridination of *trans*-α,β-unsaturated amides **2a,b,d**.[9]



3b

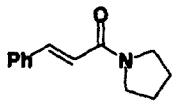


3c



3d

Aziridinations of *trans*- and *cis*-*N*-cinnamoylpyrrolidines (**2d** and **2e**) are good probes for the mechanistic study of the present reaction. If the reaction proceeds in a concerted manner, the stereochemistry of the aziridine reflects the geometry of the starting materials. On the other hand, if the reaction proceeds in a stepwise manner via a common enolate intermediate, the geometry of the starting materials will not be retained after the reaction. Thus, the reaction of **1** and **2e** was examined and found to give only *cis*-aziridine **3d**, demonstrating that the reaction proceeded nonstereospecifically. Namely, the lithiated **1** attacked the β-carbon atom of **2** nucleophilically to produce an enolate intermediate. Subsequent intramolecular amination gave aziridine **3**.

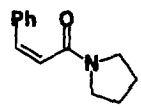


2d

a) 72%

3d

a) 39%



2e

a) **1**, *n*-BuLi, THF, -30°C, 24h

Scheme 2

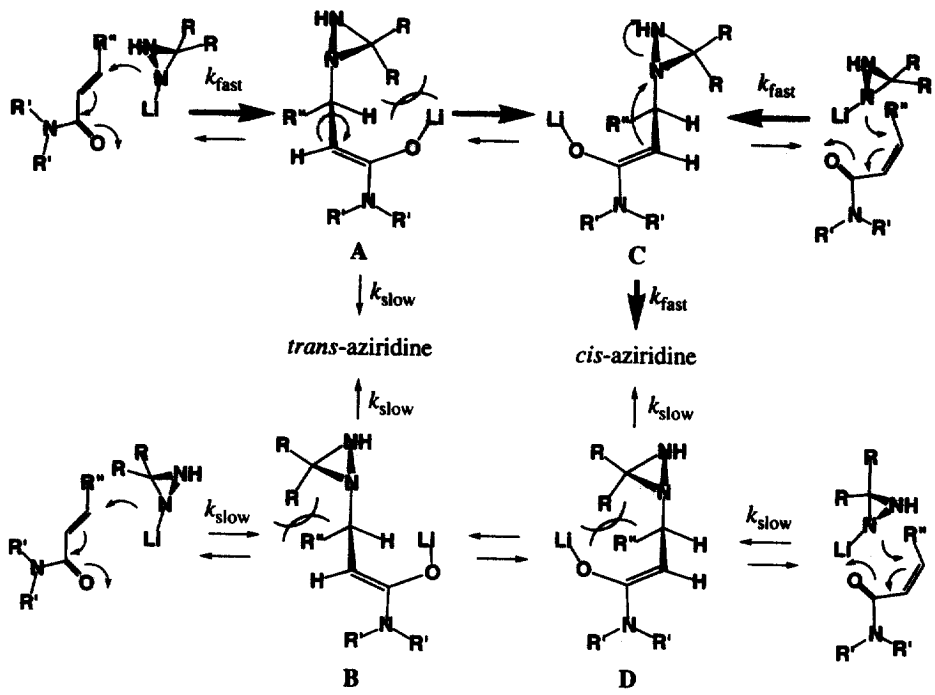


Figure 1. The stepwise reaction mechanism proposed for the *cis*-selective aziridination of α,β-unsaturated amides.

The high *cis*-diastereoselectivity could be explained as shown in Figure 1. The 1,4-addition of lithiated **1** to *trans*-α,β-unsaturated amide affords two diasteromeric enolate intermediates **A** and **B**. On the other hand, **C** and **D** represent addition products to the *cis*-α,β-unsaturated amide. **A** and **C**, or **B** and **D** are interconvertible conformational isomers. The formation of **B** and **D** is disfavored due to the steric repulsion between the β-substituent (R") and the cyclohexane moiety of the diaziridine. The subsequent ring closure requires the appropriate arrangement of enolate and aziridinyl moieties for stereoelectronic reasons. Namely, the π-orbital of the enolate must overlap on the antibonding orbital of the nitrogen-nitrogen bond. Of the two possible conformers (**A** and **C**), conformer **A** suffers the unfavored steric repulsion by this stereoelectronic requirement and should be converted into conformer **C** prior to cyclization. Accordingly, the aziridinations proceed through intermediate **C** to show high *cis*-selectivity.

As shown here, we were able to reveal the high potentiality of diaziridine as a nitrogen donor agent. The ready availability of diaziridine and simple one-pot operation makes the reaction useful as an efficient synthetic method of *N*-unsubstituted *cis*-aziridine amides. Further investigations on the diaziridine chemistry are under way in our laboratory.

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References and Notes

1 Vasella, A.; Witzig, C.; Husi, R. *Helv. Chim. Acta* **1991**, *74*, 1362.

2 In heteroatom transfer reaction, the heteroatom works both as a nucleophile and an electrophile.

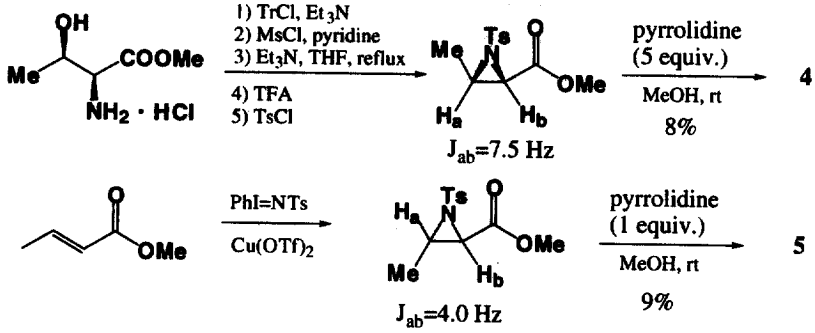
3 Schmitz, E.; Ohme, R. *Org. Syn.* **1973**, *Coll. Vol. V*, 897.

4 Typical experiment is as follows. A solution of *n*-butyllithium in hexane (1.6 mol/l, 0.254 ml, 0.40 mmol) was added to a solution of 1 (44.8 mg, 0.40 mmol) in THF (4 ml) at -78 ℃. A THF solution of **2a** (27.8 mg, 0.20 mmol) was added to the mixture at the same temperature and the mixture was allowed to warm to rt. After stirring for 1 d at rt, the mixture was diluted with water. Extraction and column chromatography on basic silica gel (Fuji Silysia Chemical Ltd., NH-DM1020, hexane-AcOEt 4:1-7:3) afforded **3a** as a colorless oil (25.2 mg, 82 %).

5 Various types of *O*-substituted hydroxylamine have been reported to react with electron-deficient olefins to produce 1,4-adducts that can be transformed to *trans*-aziridines. Blatt, A. H. *J. Am. Chem. Soc.* **1939**, *61*, 3494. Cromwell, N. H.; Barker, N. G.; Wankel, R. A.; Vanderhorst, P. J.; Olson, F. W.; Anglin, J. H. Jr. *J. Am. Chem. Soc.* **1951**, *73*, 1044. Nagel, D. L.; Woller, P. B.; Cromwell, N. H. *J. Org. Chem.* **1971**, *36*, 3911. Asymmetric aziridination using benzyloxyamine was reported. Cardillo, G.; Bongini, A.; Cardillo, G.; Gentilucci, L.; Tomasini, C. *J. Org. Chem.* **1997**, *62*, 9148. Stereospecific aziridinations using $HN(OCH_3)_2$ were also reported. Vedejs E.; Sano, H. *Tetrahedron Lett.* **1992**, *33*, 3261 and references cited therein.

6 *N*-Acyloxyamines have been reported to be efficient reagents for the one-pot aziridination reaction under basic conditions. This reaction has been proposed to proceed in a concerted manner through a 2-oxide-oxaziridine intermediate. Pereira, M. M.; Santos, P. P. O.; Reis, L. V.; Lobo, A. M.; Prabhakar, S. *J. Chem. Soc., Chem. Commun.* **1993**, 38. Chaves, H. T.; Lobo, A. M.; Prabhakar, S.; Rzepa, H. S. *AIP Conf. Proc.* **1995**, *330* (E.C.C.C. 1 Computational Chemistry), 140. $ArSO_3NHCO_2R$; Fioravanti, S.; Pellacani, L.; Stabile, S.; Tardella, P. A.; Ballini, R. *Tetrahedron Lett.* **1997**, *38*, 3309. See also Tamura, Y.; Minamikawa, J.; Ikeda, M. *Synthesis* **1977**, 1.

7 The reaction of **3a** with *p*-toluenesulfonyl chloride gave **4** in 90% yield. Authentic samples of **4** and **5** were prepared by amidolysis of the corresponding methyl esters as shown in the following scheme. *cis*-Aziridine methyl ester was prepared from threonine. Funaki, I.; Bell, R. P. L.; Thijs, L.; Zwanenburg, B. *Tetrahedron* **1996**, *52*, 12253. *trans*-Aziridine methyl ester was prepared from methyl crotonate. Evans, D. A.; Faul, M. M.; Bilodeau, M. T. *J. Org. Chem.* **1991**, *56*, 6744.



8 These reactions were conducted at a temperature below -25 ℃ for one day. Satisfactory H NMR spectra were observed for every aziridine product.

9 The present reaction is in a striking contrast to the *trans*-selective aziridination using methoxyamine (reference 6). Relative stability of *trans*- and *cis*-3-methyl-2-vinylaziridines has been reported. 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.