Highly Diastereoselective Aziridination of α,β-Unsaturated Amides Using Diaziridine

Hiroyuki Ishihara, Yoshio N. Ito,* and Tsutomu Katsuki*
Department of Chemistry, Faculty of Sciences, Kyushu University, Hakozaki, Higashi-ku, Fukuoka 812-8581

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Racemic 3-cyclohexyl-1-methyldiaziridine was found to react with α,β-unsaturated amides in basic conditions, giving *N*-unprotected *trans*-aziridines, while 3,3-pentamethylenediaziridine had been reported to afford *cis*-aziridines in high diastereoselectivity. The *trans*-selectivity was partially dependent on the stereochemistry of the substrate. The stereochemistries of these reactions were reasonably explained by the conformational analysis of the intermediary enolates.

Three-membered ring compounds undergo various ring-opening reactions due to their high strain energies. We recently reported a non-stereospecific *cis*-aziridination of α,β-unsaturated amides by treatment with a lithiated diaziridine derivative which was produced in situ from 3,3-pentamethylenediaziridine (**1**) and butyllithium at low temperature (Figure 1, upper scheme).[1] The reaction was considered to proceed in a stepwise manner, (i) 1,4-addition of *N*-lithiodiaziridine and (ii) the ring closure of the resulting enolate, as similar to the epoxidation of enones by hydrogen peroxide in basic conditions. Although N–N bond is less reactive than O–O bond, the strain energy of diaziridine enables the N–N bond fission by nucleophilic attack of the enolate to give aziridine.

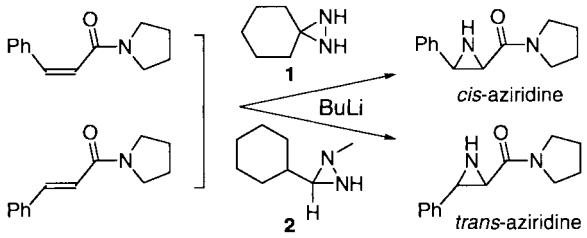


Figure 1. Highly *cis*- and *trans*-selective aziridinations of α,β-unsaturated amides.

The high *cis*-selectivity was explained by conformational consideration of the enolate intermediates. Reversible 1,4-addition of *N*-lithiodiaziridine gives two diastereomeric enolates (Figure 2, **A** and **B**).[1] For the subsequent ring-closure, antiperiplanar N–N–C–C conformation is required. Thus, the enolate moiety can adopt two conformational orientations, giving four conformers (**A1**, **A2**, **B1**, **B2**). Among the conformers, **A2** is considered to be the most preferred when $R^4 \neq H$.[2]

The above mechanistic consideration for the *cis*-selectivity further suggested that *trans*-selectivity would be realized by an appropriate modification of the diaziridine. It may be the case that 3-mono-substituted diaziridine **2** is used in place of 3,3-di-substituted one. Because, the *cis*-*trans* selectivity is largely dependent on the steric repulsion of R^4 or R^5 group with the β-substituent (R^1) and enolate moiety in transition state for the

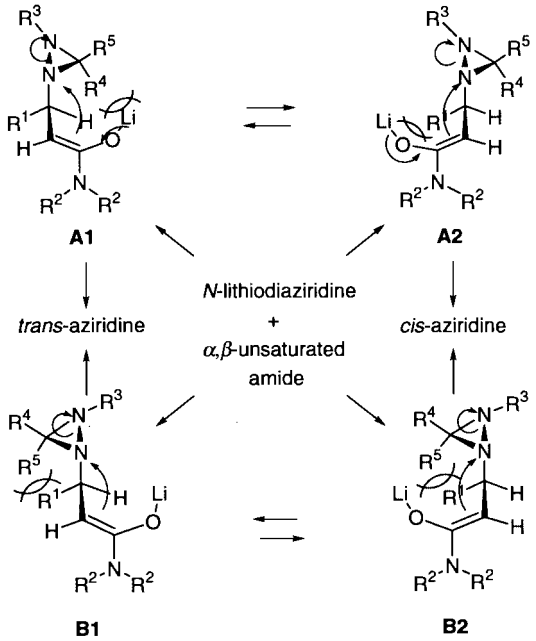
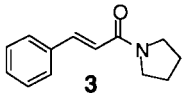
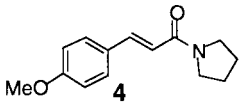
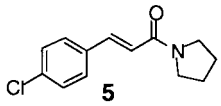
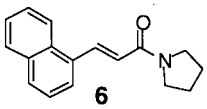
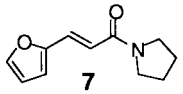
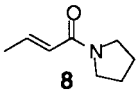
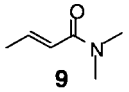
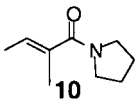
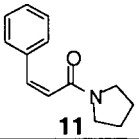


Figure 2. Proposed mechanism for the aziridination using diaziridine.

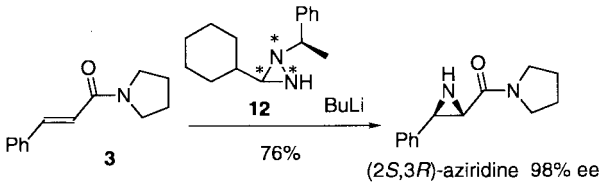
cyclization to aziridine (see Figure 2). Conformer **B1** leading to *trans*-aziridine, has no severe strain when R^5=H and becomes the most preferred. Accordingly, diaziridine **2** was prepared from cyclohexanecarbaldehyde and employed for the aziridination of cinnamide **3** (Table 1, entries 1–4).[3] The reaction afforded *trans*-isomer as the major diastereomer in a ratio of 2.5:1 as expected (entry 1). Lowering the reaction temperature enhanced the selectivity to 5.6:1 (entry 2). Employment of less polar solvent further increased the selectivity and *trans*-isomer was exclusively obtained when toluene was used as the solvent (entry 4).[4] On the other hand, opposite tendency was observed for the aziridination of *cis*-cinnamide **11** (entries 14–16). The ratio of *trans*- and *cis*-aziridines varied from 3:1 to 1:3 merely by switching the solvent from THF to toluene. The use of toluene may increase the diastereoselectivity in the first 1,4-addition and/or stabilize the chelating structure in conformers **A2** and **B1** where the electrophilicity of the coordinating nitrogen is expected to increase. Accordingly, the stereochemistry of the substrate was better retained during the reaction in less-polar solvent. Thus, the aziridination of other *trans*-α,β-unsaturated amides (**4–10**) in toluene was examined. As expected, high *trans*-selectivity was observed for all the reactions, irrespective of the nature of the β-substituents, though the reactions of **8**, **9** and **10** bearing a β-alkyl substituent was slow (entries 9–13).[5]

Table 1. Aziridination of α,β-unsaturated amides using **2**

Entry	Substrate	Solvent	Temp /°C	Time /h	Yield/%[a] *trans*	*cis*
1	 **3**	THF	−30	24	52	21
2		THF	−78	4	78	14
3		ether	−78	4	86	5
4		toluene	−78	4	74	<1
5	 **4**	toluene	−78	4	58	<1
6	 **5**	toluene	−78	4	76	3
7	 **6**	toluene	−78	4	65	<1
8	 **7**	toluene	−78	4	61	<1
9	 **8**	ether	−78	2	61	<1
10		toluene	−78	4	45	<1
11	 **9**	toluene	−78	4	32	<1
12	 **10**	ether	−30[b]	24	16	<1
13		toluene	−30[b]	17	6	<1
14	 **11**	THF	−78	4	48	16
15		ether	−78	12	39	20
16		toluene	−78	4	11	31

[a]Isolated yields after separation of isomers by basic silica gel column chromatography (see Reference 4 for furtber details). All tbe products gave satisfactory ^{1}H NMR and elementary analyses or MS. [b]The reaction was conducted at higher temperature because no aziridine product was detected by TLC for the reaction at −78 °C.

With the generality of the *trans*-selective aziridination, its asymmetric version was next examined by employing optically active diaziridine **12**.[6] As shown in Scheme 1, the reaction proceeded smoothly to give highly optically active aziridine amide in high yield.[7] This result showed good agreement with the above mentioned reaction mechanism. Namely, the first 1,4-addition of diaziridine to α,β-unsaturated amides takes place in a high diastereoselective manner and subsequent cyclization complies with stereoelectronic requirement.



Scheme 1.

As shown here, not only *cis*-selective but also *trans*-selective aziridination of α,β-unsaturated amides was achieved by using reasonably designed diaziridine derivatives. The stereochemistry of the reaction was well predicted by conformation analysis of the transition state model. Further extension to asymmetric aziridination is in investigation in our laboratory.

Dedicated to Prof. Hideki Sakurai on the occasion of his 70th birthday.

References and Notes

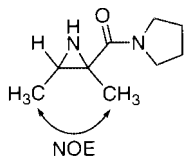
1 K. Hori, H. Sugihara, Y. N. Ito, and T. Katsuki, *Tetrahedron Lett.*, **40**, 5207 (1999).

2 After we published the original paper (Reference 1) on *cis*-selective aziridination, we found that chemical yields of *cis*-aziridines were remarkably improved by optimizing reaction temperature. The results should be published elsewhere.

3 Diaziridine **2** was prepared from cyclohexanecarbaldehyde, methylamine, and chloramine according to the reported method. E. Schmitz, *Chem. Ber.*, **95**, 688 (1962).

4 Typical experiment is as follows (Table 1, entry 4). A solution of butyllithium in hexane (1.56 mol dm^{-3}, 0.256 mL, 0.40 mmol) was added to a solution of **2** (56.1 mg, 0.40 mmol) in toluene (4 mL) at −78 °C and the mixture was stirred for 30 min. A toluene solution of **3** (40.3 mg, 0.20 mmol) was added to the mixture at the same temperature. After stirring for 4 h at −78 °C, the mixture was diluted with water and CH_2Cl_2. Extraction and column chromatography on basic silica gel (Fuji Silysia Chemical Ltd., NH-DM1020, hexane–AcOEt 4:1–3:7) afforded the corresponding *trans*-aziridine as colorless crystals (32.0 mg, 74%).

5 The stereochemistry of the aziridine obtained from **10** was confirmed to be 2,3-*trans* by measuring NOESY. The *tarns*-isomer showed NOE between 2- and 3-methyl groups.



The other 2,3-disubstituted aziridine products were assigned to be *trans* based on the coupling constants of hydrogens at C2 and C3 of the aziridines.

6 Diaziridine **12** was prepared by the method employed for the preparation of **2** (Reference 3). The relative stereochemistry of **12** was not asgined though **12** was single diastereomer.

7 The stereochemistry of the product was determined by the following chemical correlation. Tosylation with tosyl chloride and triethylamine and the subsequent hydrogenolysis with hydrogen and palladium on carbon afforded *N*-(*N*-tosylphenylalanyl)pyrrolidine, which showed identical NMR spectra and retention time in HPLC analysis using chiral stationary phase column with the compound prepared from (*S*)-phenylalanine.