Diastereofacial Selectivity in the Intramolecular Conjugate Addition of a Nitrogen Nucleophile; Stereocontrolled Piperidine Synthesis

Masahiro Hirama,* Toshihiro Iwakuma, and Shô Itô

Department of Chemistry, Tohoku University, Sendai 980, Japan

Complementary and high diastereoselection is readily achieved by changing the geometry of the double bond in the base-induced cyclization of acyclic unsaturated amine derivatives (**2**), leading to the stereodivergent synthesis of 2,3-disubstituted piperidines.

Previously we have shown that allylic oxygen functions play a major role in the stereocontrol of the conjugate addition of acyclic homoallylic carbamates (**1**).[1,2] 1,2-*anti*-Asymmetric induction was always observed irrespective of the double-bond geometry of the α,β-unsaturated esters. In connection with studies of the synthesis of piperidine and indolizidine alkaloids,[3] we have recently investigated the related reactions of amine derivatives (**2**),[4] and have found a remarkable dependence of their diastereofacial selection both on the geometry of the double bond, in contrast to the carbamates (**1**),[1,2] and on the nature of the nucleophile.

When methyl 4-t-butyldimethylsilyloxy-7-acylaminohept-2-enoates (**2**)† were treated with Bu^{t}OK (0.8 equiv.) in THF, the cyclizations proceeded smoothly at below 25 °C to give mixtures of diastereoisomeric piperidine derivatives (**3**) and (**4**) in moderate to good yields. The results with five amides are presented in Table 1. The (*Z*)-alkene (*Z*)-(**2a**) gave cyclization products in 81% yield at −50 °C after 5 min (entry 1). The major product (**3a**) (ratio 23 : 1) has a *trans*- (1,2-*anti*-) configuration as in the case of the carbamates (**1**). The (*E*)-alkene (*E*)-(**2a**) also cyclized smoothly under similar conditions (entry 2). However, the product obtained almost exclusively (>50 : 1) was the *cis*- (1,2-*syn*) isomer (**4a**), as a result of the opposite diastereofacial selection. This remarkable stereochemical reversal was also observed in the reaction of the acetamide derivatives (**2b**) (entries 4 and 5). The (*Z*)-isomer exhibited a very high *anti*-selectivity [(**3b**) : (**4b**) 50 : 1], while (*E*)-(**2b**) showed a *syn*-preference (1 : 7.4). The degree of stereoselection depends on the reaction temperature (entries 1 and 3). For example, with (*E*)-(**2a**) the ratio was only 1 : 7 at room temperature. The trifluoroacetamide derivatives (*E*)-(**2c**), however, did not cyclize under similar aprotic conditions with Bu^{t}OK or KH, probably owing to the low nucleophilicity of the stable conjugate base (entry 6). Although cyclization of (*E*)-(**2c**) occurred under hydrolytic conditions (saturated K_2CO_3 in MeOH), the diastereoselectivity was very low and the trifluoroacetamide group was eliminated during the reaction. Therefore, it is likely that conjugate addition occurred through the free amine (**2d**).[4a]

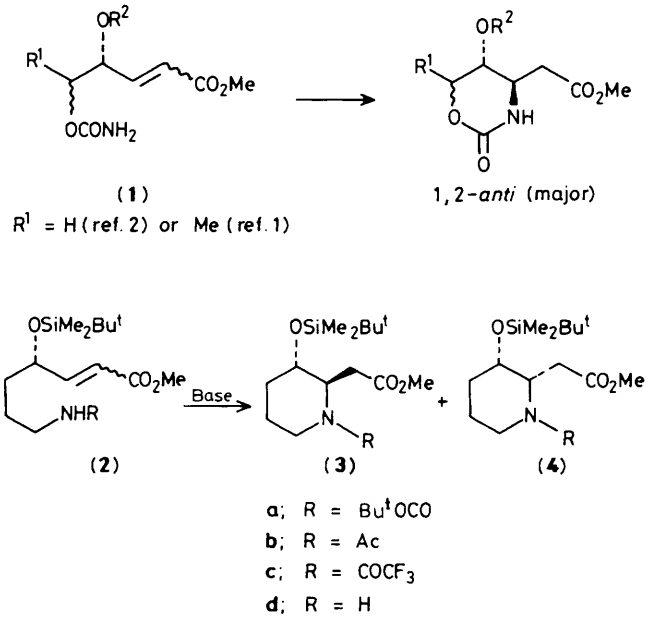
The stereochemical outcome of these cyclizations can be rationalized by considering three controlling factors: the antiperiplanar effect[1,5] and two kinds of steric interaction in the transition state. The antiperiplanar effect, a principal factor, would require the allylic conformation in which the double bond is oriented perpendicularly to the allylic C–O

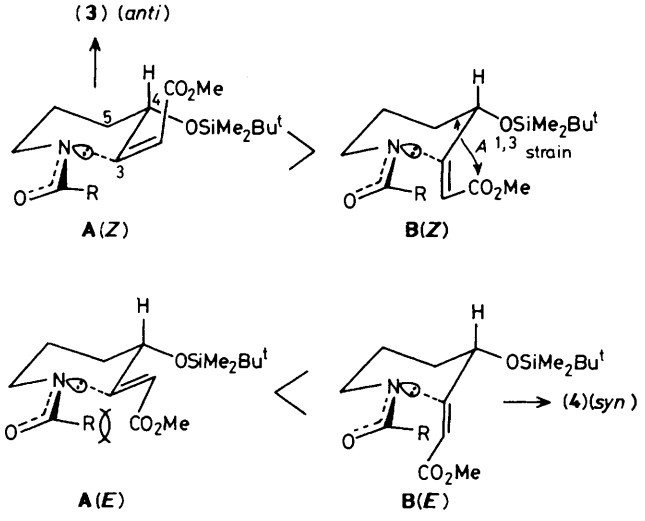
† The esters (**2**) were prepared from L-glutamic acid. The details will be published elsewhere.

Table 1. Results of cyclisations.

Entry	Substrate	Conditions[a]	Ratio[b] (3):(4)	Yield (%) [(3) + (4)]
1	(*Z*)-(**2a**)	−50 °C, 5 min	23:1	81
2	(*E*)-(**2a**)	−42 °C, 5 min	1:>60	81
3	(*E*)-(**2a**)	room temp., 12 min	1:7	61
4	(*Z*)-(**2b**)	−36 °C, 15 min	50:1	56
5	(*E*)-(**2b**)	−48 °C, 15 min	1:7.4	68
6	(*E*)-(**2c**)	0 °C, 1.5 h		0[c]
7	(*E*)-(**2c**)	K_2CO_3, MeOH, room temp., 20 h	1.4:1	89 (R = H)

[a] Carried out in anhydrous THF with Bu^{t}OK (0.8 equiv.) unless otherwise indicated. [b] Determined by h.p.l.c. analysis of the product mixture and/or by 400 MHz ^{1}H n.m.r. spectroscopy‡ of the corresponding acetamides (**3b**) and (**4b**); the t-butoxycarbonyl groups of (**3a**) and (**4a**) were deprotected with CF_3CO_2H/CH_2Cl_2 (1:2) at 0 °C to give (**3d**) and (**4d**), and then acetylated (Ac_2O, pyridine) to give (**3b**) and (**4b**), respectively, in about 70% overall yield. [c] The starting material was recovered.





bond, and attack of the nitrogen anion on the double bond from the direction antiperiplanar to the allylic C–O. Thus **A** and **B** appear to be the most plausible transition states leading to *anti*- (**3**) and *syn*-products (**4**), respectively. As in the cyclizations of carbamates,[1] the transition state **B(Z)** involves severe non-bonded interaction between the ester and the methylene group at C-5 ($A^{1,3}$ strain[6]), as the torsion angle C(2)–C(3)–C(4)–C(5) is small (*ca.* 30°); hence **A(Z)** should be favoured. In **B(E)**, however, this strain may be negligible, but another unfavourable interaction between the ester and the protecting group on the nitrogen occurs in **A(E)**.

Applications of the present methodology to the stereocontrolled synthesis of piperidine and indolizidine alkaloids[3] are in progress.

‡ Two sets of signals appeared in the spectrum of each diastereoisomer, owing to restricted rotation of the N–C bond of the acetamide group[7] [acetyl signals of (**3b**) 2.16 and 2.08 (4.2:1); (**4b**) 2.19 and 2.06 (2.1:1) in $CDCl_3$ at 22 °C]. The characteristic coupling constants [(**3b**) $J_{2,3}$ 2.4, $J_{3,4}$ 2.5 and 2.6 Hz; (**4b**) $J_{2,3}$ 4.5, $J_{3,4}$ 12 and 4.8 Hz] for H-2 [(**3b**) 4.26, (**4b**) 4.42] and H-3 [(**3b**) 3.78,(**4b**) 3.71] of each major rotamer clearly indicate that (**3b**) is a 2,3-*trans*-diastereoisomer with two axial substituents and that (**4b**) is a 2,3-*cis*-isomer with a C-3 equatorial and a C-2 axial substituents, in accord with the well known preference for axial orientation of the C-2 substituent in piperidine acetamides.[7]

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