

0040-4039(95)00286-7

Intramolecular Amidoalkylation of Chiral Imines and Iminium Ions: Stereoselective Synthesis of *anti*-1,2- and -1,3-Aminoalcohols

Hideaki Hioki,* Tatsuo Izawa, Makoto Yoshizuka, Rieko Kunitake, and Shô Itô

Faculty of Pharmaceutical Sciences, Tokushima Bunri University, Yamashiro-cho, Tokushima, 770 Japan

Abstract: When treated with Lewis acids, 2- or 3-vinyl- or -phenylsiloxyaminoacetals generated the corresponding imines or iminium ions which in turn underwent smooth intramolecular amidoalkylation to afford *anti*-1,2- or -1,3-aminoalcohol derivatives in very high chemical yields and excellent diastereomeric ratios. Applying the reaction, Z-*allo*-L-threonine and (\pm) -N-ethoxycarbonyl-*anti*- γ -hydroxynorvaline were successfully synthesized.

1,2- and 1,3-Aminoalcohols are fundamental structural units of many bioactive natural products, and various methods have therefore been developed for their construction.¹ We have recently achieved the highly stereoselective (up to 200 : 1) synthesis of two types of *syn*-1,3-aminoalcohols by a combination of the intramolecular amidoalkylation of chiral iminium ions and the Hosomi-Sakurai reaction (Eq. 1).² In this communication we describe the construction of *anti*-1,2- and -1,3-aminoalcohol units with excellent selectivity by the combination of the same amidoalkylation and the migration of a vinyl or a phenyl group from a siloxy group situated at the 2- or 3-position (Eq. 2).



The vinylsiloxy- or phenylsiloxyaminoacetals 1 or 2^3 were treated under Ar atmosphere with 2.2 equivalents of a Lewis acid at 0°C in CH₂Cl₂ to generate the imines 3 or 4 or the iminium ions 5 or 6, which in turn underwent smooth 1,4- or 1,5-migration of the vinyl or the phenyl group from the silicon atom to the iminocarbon to afford, after desilylation with methanol, 1,2- or 1,3-aminoalcohol derivatives 7 and 9, or 8 and 10, respectively. In cases where

desilylation was not effected by methanol, the reaction mixture was treated with sodium bicarbonate and then with tetrabutylammonium fluoride. The diastereomeric ratio was determined by direct G. C. analysis, while the chemical yield was obtained after purification by SiO_2 column chromatography.⁴ The results of the 1,4-migration of a vinyl or a phenyl group onto the iminocarbons of the C=N or C=N⁺ bond (n = 0 in Eq. 2) are listed in Table 1.

Entry		Co	ompou	nd			Reaction conditions			Product		
	No.	x	R ¹	R ²	R ³	R ⁴	Lewis acid	temp. (°C)	period (h)	yield ^a (%)	syn	ratio ^b : anti
1	1a	н	Vin ^c	Me	Me	Bn	SnCl ₄	0	1	74	1	: 20
2	"	"	"	"	"	"	TiCl ₄	0	1	60	1	: 17
3	"	4	"	4	"	"	BF3• OEt2	0	1	56	1	: 60
4	1b	Н	Vin	Vin	Vin	Bn	SnCl ₄	0	1	74	1	: 19
5	"	"	"	"	"	"	SnCl ₄	-40	48	86	1	: 30
6	1c	н	Vin	Ph	Ph	Et	SnCl ₄	0	1	44, 49 ^d	-	e
7	1 d	Н	Ph	Ph	t-Bu	Et	SnCl ₄	0	1	85	1	: 60
8	"	"	"	"	"	"	TiCl ₄	0	1	85	1	: 30
9	4	"	"	"	"	"	BF3• OEt2	0	1	85	1	: >300 ^f
10	1e	Bn	Vin	Me	Me	Et	SnCl ₄	0	1	37 (54) ⁴	31	: >300 ^f
11	"	"	4	"	"	"	BF3• OEt2	0	1	19 (19)	3 1	:>300 ^f
12	1f	Bn	Vin	Vin	Vin	Et	TiCl ₄	0	12	57 (26)	⁸ 1	:>300 ^f
13	1g	Bn	Ph	Ph	t-Bu	Et	SnCl ₄	0	1	78	1	:>300 ^f
14	"	"	"	"	"	4	TiCl ₄	0	1	95	1	:>300 ^f
15	"	"	"	"	"	"	BF3• OEt2	0	1	98	1	:>300 ^f

Table 1. Vinyl and phenyl migration from silicon in 2-siloxy group to C=N or $C=N^+$ carbon.

a. Isolated yield. b. Determined by G. C. c. Vin refers to vinyl group. d. Yield of vinyl and phenyl migration products, respectively. e. Not determined. f. No trace of *syn* products was detected by G. C. g. Yield of simple desilylation product 11 in parentheses.

Reactions of the imines 3a-d. Although $SnCl_4$ gave slightly better results than $TiCl_4$ for both the vinyl and phenyl migrations (entries 1 vs 2, and 7 vs 8), and yield and selectivity increased somewhat at lower temperature and longer reaction time (entries 4 vs 5), BF₃ etherate is always by far a better reagent than those two Lewis acids (entries 3 and 9). An interesting competitive migration was observed in 1c; the migratory aptitude of a vinyl group is ca 1.8 times that of a phenyl group (entry 6).⁵

Reactions of the iminium salts 5e-g. Reactions of **5e-g** gave better results than in the above cases: Perfect *anti* selectivity was obtained for both the vinyl and phenyl migrations with all three Lewis acids. While the yield in vinyl migration was rather low because of the sizable desilylation to **11** (entries 10-12), that in phenyl migration was quite satisfactory. BF₃ etherate was again the best reagent (entry 15). TiCl₄ is better than SnCl₄ in this series (entries 13 and 14).⁵

HO X CO₂Et 11: n = 0, X = Bn 12: n = 1, X = H

The yield from the vinyl migration is generally lower than that from phenyl migration, probably owing to the instability of the vinylsiloxy group under the reaction conditions compared to the phenylsiloxy group. In the vinyl migration to $C=N^*$ addition, simple desilylation product 11 was obtained in considerable yields (entries 10-11).

The preferred anti-selectivity observed in these intramolecular reactions⁶ is explicable by comparison of the allylic strain in the transition states resulting from the nucleophilic attack of vinyl or phenyl group to either face of the coordinated C=N bond or C=N⁺ bond. Thus, as exemplified here by the vinyl migration to the latter, the transition state A which lead to the *anti* products has less A-strain (H-Bn) than in B (Me-Bn) leading to the *syn* products. This rationalization is also valid for the phenyl migration and for the migrations to the coordinated C=N bonds. The observation that SnCl₄ and TiCl₄ with chelating capability tend to show smaller ratios in the addition to C=N bond than BF₃ probably originate from the intervention of the chelating transition states C and D of comparable strain energy. The

reaction with singly-coordinating BF₃ and the addition to the noncoordinating $C=N^+$ bond do not involve C and D and result in much better stereocontrol.⁷



Reactions of imines 4d and iminium ions 6g. For the imines and iminium ions with a 3-siloxy group (n = 1, Eq. 2) only phenyl migration proceeded as is listed in Table 2,⁸ but the yield and/or ratio for the addition to C=N bond were unsatisfactory (entries 1-4). By contrast, the migration to the C=N^{*} bond was invariably quite stereoselective to give *anti* products, though the yield is not always excellent (entries 7 and 8); the lower the reaction temperature, the higher the yield and ratio (entries 5 vs 6). The best result in this scries was obtained with SnCl₄ (entry 6).

	Compound						Reaction conditions			Product			
Entry													
	No.	x	R ¹	R ²	R ³	R ⁴	Lewis acid	temp. (°C)	period (h)	yield ^a (%)	r syn	atio ^b : anti	
1	2d	н	Ph	Ph	t-Bu	Et	SnCl ₄	0	1.5	49	1	: 4.5	
2	"	"	4	"	"	"	SnCl ₄	-10	24	74	1	: 5.0	
3	"	"	"	"	"	"	TiCl4	-10	24	82	1	: 5.5	
4	"	4	"	"	"	"	BF3• OEt2	-10	24	16	1	: 41	
5	2g	Bn	"	"	"	"	SnCl ₄	0	2	53	1	: 120	
6	"	"	"	"	"	"	SnCl ₄	-10	24	64	1	: 140	
7	"	"	"	"	"	"	TiCl ₄	-10	24	37	1	: 87	
8	"	"	"	"	"	"	BF3• OEt2	-10	24	5	1	: 100	

Table 2. Phenyl migration from silicon in 3-siloxy group to C=N or $C=N^+$ carbon.

a. Isolated yield. b. Determined by G. C.

The selectivity is accounted for by comparing the steric energies in the transition states E leading to *anti* products and F to *syn* products. The former is obviously more stable than the latter (*gauche* interaction around $C^2 - C^3$ bond). The reduced selectivity in the addition to C=N is explained by the intervention of the chelating transition states G and H (corresponding to C and D).





Utilizing the present reactions, Z-allo-L-threonine (13) $[\alpha]_D^{22} + 18.4^\circ$ (c 1.1, CHCl₃)⁹ and (±)-N-ethoxycarbonylanti- γ -hydroxynorvaline (14)¹⁰ were successfully synthesized via the standard reaction sequences shown.



References and Notes

- For example, Yamamoto, Y.; Komatsu, T; Maruyama, K. J. Chem. Soc., Chem. Commun. 1985, 814-816.
 Yamamoto, Y.; Schmid, M. *ibid.* 1989, 1310-1312. Evans, D. A.; Weber, A. E.; J. Am. Chem. Soc. 1986, 108, 6757-6761. Evans, D. A.; Sjogren, E. B.; Weber, A. E.; Conn, R. E. Tetrahedron Lett. 1987, 27, 39-42. Harding, K. E.; Marman, T. H.; Nam, D.-H. Tetrahedron 1988, 44, 5605-5614.
- 2. Hioki, H.; Okuda, M.; Miyagi, W.; Itô, S. Tetrahedron Lett. 1993, 34, 6131-6134.
- Starting materials were synthesized from the corresponding hydroxy carboxamides following the general scheme described by Matsuda et al. in their total synthesis of (+)-pederin (Matsuda, F.; Tomiyoshi, N.; Yanagiya, M.; Matsumoto, T. Tetrahedron 1988, 44, 7063-7080). Also see Ref. 2.
- 4. The stereochemistry of the products was established by their interconversions and the NOE or *J*-values of their cyclic derivatives. Some examples are shown below.



- 5. Trimethylsilyl triflate gave a 74% yield and excellent (1:>300) *anti*-selectivity for the phenyl migration to the C=N bond (3d), but gave only complex mixture for the vinyl migration (3a). It afforded the normal product in only 23% yield with a 1:3 *anti*-selectivity for the phenyl migration to the C=N⁺ bond (3g).
- 6. The intramolecular nature of the reaction is supported by the following experimental evidence. The intermolecular vinylation reaction of 3 and 5 each having no migrating group on the silicon (TBDMS) with trimethylvinylsilane under standard conditions only afforded either ethoxycarbonylaminoacetone or ethyl N-benzylcarbamate in good yield.
- The difference in selectivity between the BF₃-mediated addition to C=N bond and the addition to C=N⁺bond is probably due to difference in bond lengths; the C=N→B coordination bond (ca 1.60 Å) is considerably longer than C=N⁺-C single bond (ca 1.52 Å). Sucrow, W.; Zuhlke, L.; Slopianka, M.; Pickardt, J. Chem. Ber. 1977, 110, 2818-2833. Caira, M. R.; Nasisimbeni, L. R.; Stephen, A. M.; Van Schalkwyk, T. G. D. Acta Cryst. 1993, C49, 22-26.
- The attempted vinyl migration with either SnCl₄ or BF₃ etherate resulted in a complex mixture from which a small amount of the desilylation product 12 was isolated.
- 9. Pavia, A. A.; Lacombe, J. M. J. Org. Chem. 1983, 48, 2564-2568.
- The lactone 14 is a new compound: colorless oil: IR (neat): v 1780, 1705 cm⁻¹; ¹H NMR (CDCl₃): δ 1.26 (3 H, t, J = 7.1Hz), 1.46 (3 H, d, J = 6.1Hz), 1.84 (1 H, ddd, J = 10.8, 12.2, 12.2Hz), 2.81 (1 H, ddd, J = 5.1, 8.4, 12.2Hz), 4.15 (2 H, q, J = 7.1Hz), 4.55 (2 H, m), 5.56 (1 H, brs). N-Boc derivative: colorless needles, m.p. 103 104 °C.

(Received in UK 24 October 1994; revised 31 January 1995; accepted 3 February 1995)