[Chem. Pharm. Bull. 34(2) 479—485 (1986)]

Highly Diastereoselective 1,5-Asymmetric Induction to 3-Oxazolidino-1-phenylpropan-1-ones by Using Organotitanium Triisopropoxides

HIROSHI TAKAHASHI,* KOJI TANAHASHI, KIMIO HIGASHIYAMA, and HIRAKU ONISHI

Institute of Medicinal Chemistry, Hoshi University, Ebara, Shinagawa, Tokyo 142, Japan

(Received June 12, 1985)

The reaction of (*S*)-3-4′-isopropyl-1′,3′-oxazolidino-1-phenylpropan-1-ones (**1a**, **1b**) with 4 mol eq of various organotitanium triisopropoxides in ether at room temperature for 18—20 h gave 1-alkyl(or aryl)-3-*N*-alkyl(or arylmethyl)-*N*-1′-isopropyl-2′-hydroxyethylamino-1-phenylpropan-1-ols (**2a**—**h**) in good yields.

This 1,5-asymmetric induction proceeded with extremely high diastereoselectivity. The absolute configurations of **2d** and **3d** were determined by X-ray analysis.

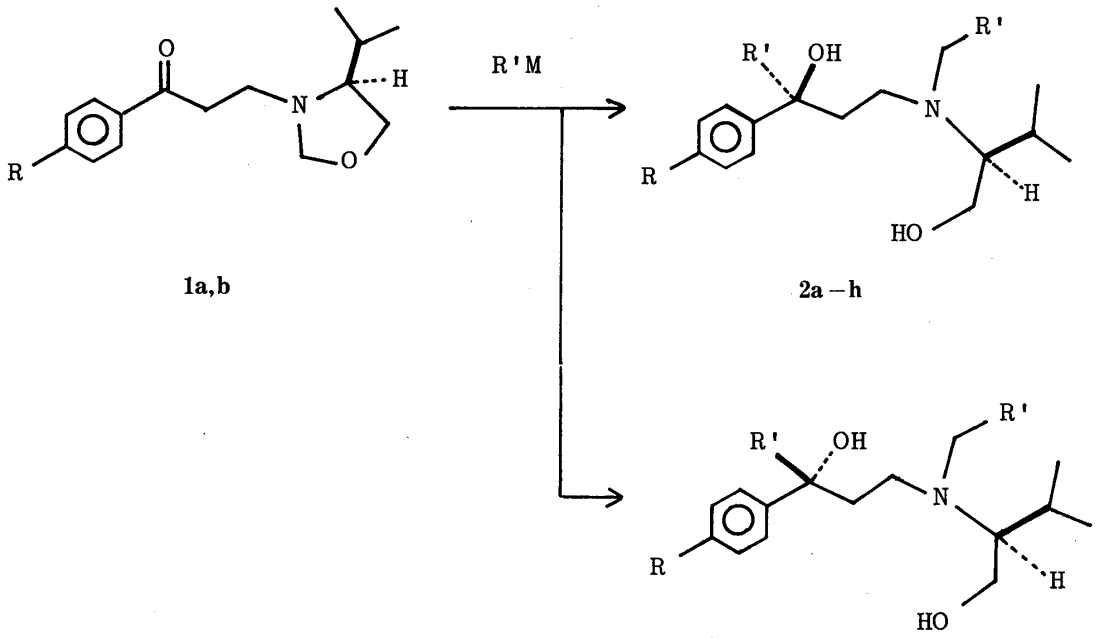
Keywords——absolute configuration; 1,5-asymmetric induction; chiral 1,3-oxazolidine; chiral phenylpropan-1-ol; chiral phenylpropan-1-one; diastereoselective; Grignard reagent; organolithium; organotitanium triisopropoxide; X-ray analysis

Organotitanium reagents of the type $RTiX_3$ (X=Cl, OR′) play an important role in various organic synthetic reactions with high chemo- and stereoselectivities.[1] We wish to describe herein a new highly diastereoselective reaction of chiral 3-oxazolidino-1-phenylpropan-1-ones (**1a**, **1b**) with organotitanium triisopropoxides. It is generally considered that the 1,5-asymmetric induction reaction of carbonyl compounds with Grignard or organolithium reagents proceeds with low diastereoselectivity (ds) because the carbonyl group is situated far from the chiral center. In the preceding paper, we reported that the reactions of **1a** and **1b** with Grignard and organolithium reagents could be carried out with ds 6—23%.[2]

The reaction of (*S*)-3-4′-isopropyl-1′,3′-oxazolidino-1-phenylpropan-1-ones (**1a**, **1b**) with 4 mol eq of various organotitanium triisopropoxides in ether at room temperature under a nitrogen atmosphere for 18—20 h gave 1-alkyl(or aryl)-3-*N*-alkyl(or arylmethyl)-*N*-1′-isopropyl-2′-hydroxyethylamino-1-phenylpropan-1-ols (**2a**—**h**) in good yields. The organotitanium reagents, *i.e.*, methyl, benzyl, phenyl, 4-methoxyphenyl, and 4-chlorophenyltitanium triisopropoxides, were prepared in the usual way.[3,4]

Two diastereomeric forms (**2a**—**h** and **3a**—**h**) could be considered because of the newly created chiral center, but the products were established to consist almost exclusively of one isomer by analysis of the 100 MHz proton nuclear magnetic resonance (^{1}H-NMR) spectra. The ratios of major to minor products were estimated by measurement of the peak heights in the ^{1}H-NMR (400 MHz) spectra; the peaks of the major products (**2a**—**h**) and the minor products (**3a**—**h**) were correlated to those of corresponding compounds synthesized by using Grignard and organolithium reagents. These results are summarized in Table I.

The absolute configuration of the newly created asymmetric carbon atom was elucidated by X-ray analysis. A colorless columnar crystal of the major component (**3d**) prepared by the reaction of **1b** with benzylmagnesium chloride was used. The atomic numbering of **3d** is shown in Fig. 1, and the crystal data are summarized in Table II. Stereoscopic drawings of the



1a: R=H; **1b**: R=MeO; **2a, 3a**: R=H, R′=Me; **2b, 3b**: R=MeO, R′=Me; **2c, 3c**: R=H, R′=$C_6H_5CH_2$; **2d, 3d**: R=MeO, R′=$C_6H_5CH_2$; **2e, 3e**: R=MeO, R′=Ph; **2f, 3f**: R=H, R′=4-$MeOC_6H_4$; **2g, 3g**: R=H, R′=4-ClC_6H_4; **2h, 3h**: R=MeO, R′=4-ClC_6H_4 M=Li, MgX (X=Cl, Br), $Ti(OPr^i)_3$

Chart 1

TABLE I. Reactions of 3—4′-Isopropyl-1′,3′-oxazolidino-1-phenylpropan-1-ones (**1a**, **1b**) with Organometallic Reagents and Ratios of the Major to the Minor Products

Compd. 2 and 3	R	R′	R′Ti(OPr^i) Yield[a] (%)	R′Ti(OPr^i) Ratio of[b] 2:3[c]	R′MgX Yield[a] (%)	R′MgX Ratio of[b] 2:3[c]	R′Li Yield[a] (%)	R′Li Ratio of[b] 2:3[c]
a	H	Me	86	93: 7	93	47:53[d]	95	54:46
b	MeO	Me	84	94: 6	86	46:54[d]	42	48:52
c	H	$C_6H_5CH_2$	63	96: 4	95	39:61[d]		
d	MeO	$C_6H_5CH_2$	65	95: 5	94	41:59[d,e]		
e	MeO	Ph	74	87:13	88	66:34	8	64:36[d]
f	H	4-$MeOC_6H_4$	69	>98[f]	84	65:35	6	63:37[d]
g	H	4-ClC_6H_4	72	>98[f]			66	63:37
h	MeO	4-ClC_6H_4	86	88:12			78	64:36

a) Isolated yield. *b*) Estimated from the peak heights in the ^{1}H-NMR (400 MHz) spectra. *c*) Major products obtained by using organotitanium triisopropoxide are represented by **2**, and minor products are represented by **3**. *d*) Cited from our previous paper (Ref. 2). *e*) The major product was used in X-ray analysis. *f*) No peak of the other isomer was observed.

molecular structure are shown in Fig. 2. The positional and thermal parameters with their standard deviations are listed in Table III. The intramolecular bond distances and bond angles for nonhydrogen atoms are given in Table IV.

The structure of this compound (**3d**) was determined as (1*R*,1′*S*)-1-benzyl-3-*N*-1′-isopropyl-2′-hydroxyethyl-*N*-phenylethylamino-1-(4-methoxyphenyl)propan-1-ol.[5] Consequently, the absolute configuration of the major component (**2d**) obtained from benzyltitanium triisopropoxide was elucidated as (1*S*,1′*S*). The other products are assumed to

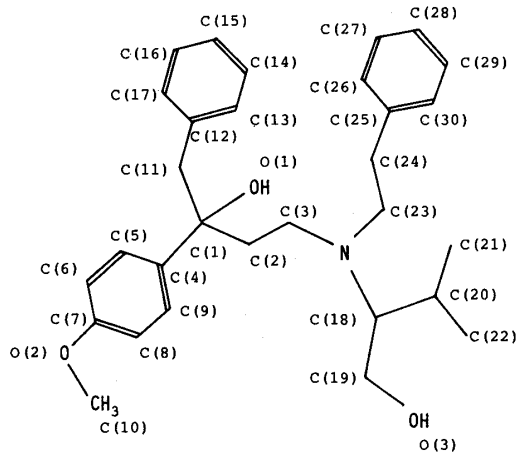


Fig. 1. Atomic Numbering of (1*R*,1′*S*)-**3d**

TABLE II. Crystal Data

Chemical formula	$C_{30}H_{39}NO_3$
Formula weight	461.65
Crystal system	Orthorhombic
Cell dimensions (Å)	$a=10.079$ (2)
	$b=32.337$ (7)
	$c=8.056$ (3)
Cell volume (Å^3)	2625.9 (1)
Space group	$p2_12_12$
Z	4
D_c (g cm^{-3})	1.17
μ (Mo K_α) (cm^{-1})	0.7

TABLE III. Positional ($\times 10^4$) and Thermal Parameters of (1*R*,1′*S*)-**3d** for Nonhydrogen Atoms with Their Standard Deviations in Parentheses

Atom	*X*	*Y*	*Z*	B_{eq} (Å^2)[a]
N	3115 (9)	1491 (3)	9498 (10)	3.4
O(1)	3362 (8)	1397 (2)	6159 (9)	3.9
O(2)	9557 (13)	1748 (4)	5177 (17)	10.3
O(3)	2800 (9)	1819 (3)	13157 (10)	5.5
C(1)	4391 (11)	1078 (3)	6351 (16)	3.8
C(2)	4251 (14)	893 (4)	8127 (14)	4.7
C(3)	4324 (11)	1204 (3)	9486 (12)	3.3
C(4)	5695 (13)	1285 (4)	6099 (13)	4.4
C(5)	6871 (14)	1032 (5)	6297 (19)	6.9
C(6)	8131 (16)	1206 (4)	6029 (19)	6.2
C(7)	8218 (13)	1611 (5)	5514 (16)	5.6
C(8)	7155 (15)	1882 (5)	5313 (17)	6.3
C(9)	5854 (14)	1696 (5)	5635 (15)	6.0
C(10)	9654 (25)	2126 (4)	4524 (26)	10.4
C(11)	4149 (14)	742 (4)	4982 (17)	4.9
C(12)	2843 (12)	538 (3)	5059 (15)	4.0
C(13)	1738 (13)	722 (4)	4218 (16)	4.9
C(14)	519 (15)	513 (4)	4269 (16)	5.6
C(15)	330 (15)	118 (5)	5053 (19)	6.2
C(16)	1400 (17)	−36 (4)	5892 (19)	6.4
C(17)	2691 (17)	155 (4)	5846 (17)	5.8
C(18)	3440 (11)	1887 (4)	10244 (15)	3.8
C(19)	3877 (13)	1865 (5)	12119 (15)	5.0
C(20)	2342 (14)	2201 (4)	10006 (17)	5.1
C(21)	2024 (17)	2260 (5)	8084 (17)	6.3
C(22)	2831 (21)	2639 (5)	10643 (23)	8.6
C(23)	1937 (12)	1265 (4)	10246 (14)	4.3
C(24)	818 (13)	1188 (6)	8890 (20)	7.1
C(25)	−316 (13)	980 (4)	9747 (17)	4.8
C(26)	−549 (15)	550 (5)	9569 (20)	6.7
C(27)	−1627 (16)	358 (5)	10335 (23)	7.6
C(28)	−2518 (14)	611 (5)	11378 (21)	6.4
C(29)	−2276 (14)	1012 (5)	11489 (20)	6.2
C(30)	−1180 (14)	1214 (5)	10777 (20)	6.3

a) $B_{eq}=(4/3)\sum_i\sum_j\beta_{ij}\boldsymbol{a}_i\boldsymbol{a}_j$.

TABLE IV. Bond Distances (Å) and Bond Angles (°) of (1*R*,1′*S*)-**3d** for Nonhydrogen Atoms with Their Standard Deviations in Parentheses

N–C(3)	1.533 (14)	C(12)–C(13)	1.434 (18)
N–C(18)	1.451 (14)	C(12)–C(17)	1.399 (16)
N–C(23)	1.517 (15)	C(13)–C(14)	1.404 (20)
O(1)–C(1)	1.471 (13)	C(14)–C(15)	1.436 (20)
O(2)–C(7)	1.447 (18)	C(15)–C(16)	1.367 (22)
O(2)–C(10)	1.334 (21)	C(16)–C(17)	1.441 (23)
O(3)–C(19)	1.378 (16)	C(18)–C(19)	1.575 (17)
C(1)–C(2)	1.556 (17)	C(18)–C(20)	1.515 (18)
C(1)–C(4)	1.491 (17)	C(20)–C(21)	1.593 (19)
C(1)–C(11)	1.566 (17)	C(20)–C(22)	1.585 (20)
C(2)–C(3)	1.487 (16)	C(23)–C(24)	1.591 (19)
C(4)–C(5)	1.451 (20)	C(24)–C(25)	1.495 (20)
C(4)–C(9)	1.388 (21)	C(25)–C(26)	1.418 (20)
C(5)–C(6)	1.405 (22)	C(25)–C(30)	1.420 (20)
C(6)–C(7)	1.377 (21)	C(26)–C(27)	1.395 (23)
C(7)–C(8)	1.393 (21)	C(27)–C(28)	1.477 (23)
C(8)–C(9)	1.466 (21)	C(28)–C(29)	1.322 (22)
C(11)–C(12)	1.474 (18)	C(29)–C(30)	1.405 (21)
C(3)–N–C(18)	110.9 (8)	C(11)–C(12)–C(17)	120.9 (12)
C(3)–N–C(23)	109.5 (8)	C(13)–C(12)–C(17)	119.9 (12)
C(18)–N–C(23)	115.8 (8)	C(12)–C(13)–C(14)	117.7 (12)
C(7)–O(2)–C(10)	115.0 (15)	C(13)–C(14)–C(15)	123.9 (13)
O(1)–C(1)–C(2)	107.6 (9)	C(14)–C(15)–C(16)	116.0 (13)
O(1)–C(1)–C(4)	106.9 (9)	C(15)–C(16)–C(17)	122.8 (13)
O(1)–C(1)–C(11)	107.6 (9)	C(12)–C(17)–C(16)	119.3 (13)
C(2)–C(1)–C(4)	112.2 (10)	N–C(18)–C(19)	114.9 (10)
C(2)–C(1)–C(11)	111.6 (9)	N–C(18)–C(20)	112.0 (10)
C(4)–C(1)–C(11)	110.7 (10)	C(19)–C(18)–C(20)	110.8 (10)
C(1)–C(2)–C(3)	114.4 (10)	O(3)–C(19)–C(18)	111.5 (10)
N–C(3)–C(2)	112.0 (9)	C(18)–C(20)–C(21)	110.5 (11)
C(1)–C(4)–C(5)	116.8 (12)	C(18)–C(20)–C(22)	109.4 (12)
C(1)–C(4)–C(9)	124.7 (11)	C(21)–C(20)–C(22)	105.7 (11)
C(5)–C(4)–C(9)	118.4 (12)	N–C(23)–C(24)	111.0 (9)
C(4)–C(5)–C(6)	119.6 (14)	C(23)–C(24)–C(25)	107.2 (12)
C(5)–C(6)–C(7)	119.0 (14)	C(24)–C(25)–C(26)	121.4 (13)
O(2)–C(7)–C(6)	114.1 (13)	C(24)–C(25)–C(30)	120.0 (12)
O(2)–C(7)–C(8)	120.2 (14)	C(26)–C(25)–C(30)	118.6 (13)
C(6)–C(7)–C(8)	125.7 (13)	C(25)–C(26)–C(27)	121.3 (14)
C(7)–C(8)–C(9)	114.1 (14)	C(26)–C(27)–C(28)	118.6 (14)
C(4)–C(9)–C(8)	123.0 (13)	C(27)–C(28)–C(29)	118.0 (14)
C(1)–C(11)–C(12)	114.8 (11)	C(28)–C(29)–C(30)	124.9 (14)
C(11)–C(12)–C(13)	119.1 (10)	C(25)–C(30)–C(29)	118.3 (13)

have the same chirality, because the reaction mechanism are expected to be similar.

In the reactions of **1a** and **1b** with the benzyltitanium triisopropoxide, the by-products lacking the benzyl group at the 1-position, *i.e.*, 3-*N*-1′-isopropyl-2′-hydroxyethyl-*N*-phenylethylamino-1-phenyl(and 4-methoxyphenyl)propan-1-ols (**4a**, **4b**), were obtained together with **2c**, **3c** and **2d**, **3d** in yields of 9% and 11%, respectively. The products (**4a**, **4b**) were established to consist of two diastereomers by ^{1}H-NMR spectroscopy, and this result suggested that Meerwein–Ponndorf–Verley type reduction occurred with the metal alkoxide reagent.[3)]

The reactions of (*S*)-3-oxazolidino-1-phenylpropan-1-ones (**1a**, **1b**) with Grignard reagents (phenyl- and 4-methoxyphenylmagnesium bromides) and with organolithium reagents

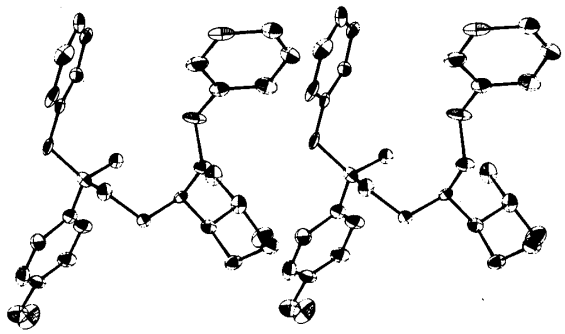


Fig. 2. Stereoscopic Drawings of the Structure of (1*R*,1′*S*)-**3d**

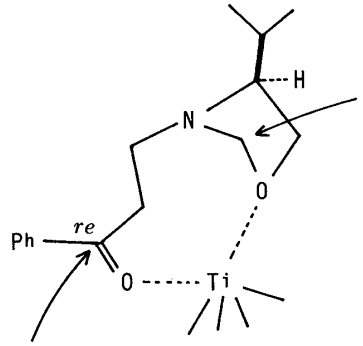
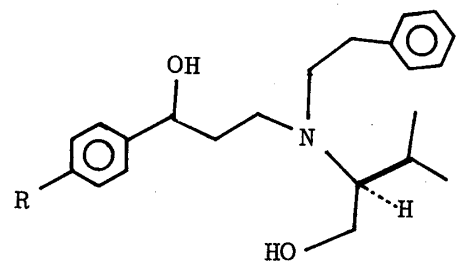


Fig. 3

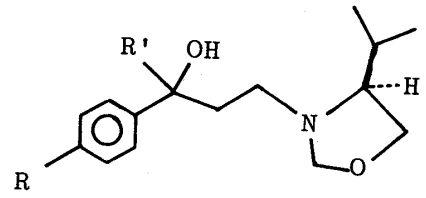
(methyl- and 4-chlorophenyllithiums) were attempted in order to compare the products with those obtained using the organotitanium reagents; the results are shown in Table I. The reactions with methyllithium and methylmagnesium bromide were poorly diastereoselective.

In the case of organolithium reagents, diastereomeric mixtures of 1-alkyl (or aryl)-3-4′-isopropyl-1′,3′-oxazolidino-1-phenylpropan-1-ols (**5a**, **5b**, **5c**) were obtained together with the mixtures of **2** and **3**, as in the previous paper.[2)]



4

a: R=H; **b**: R=MeO



5

a: R=MeO, R′=Me; **b**: R=H, R′=4-ClC$_6$H$_4$; **c**: R=MeO, R′=4-ClC$_6$H$_4$

Chart 2

Reetz *et al.*[6)] have reported that 1,4-asymmetric induction in the reaction of chiral 4-benzyloxy-1-butanal with titanium tetrachloride and dimethylzinc at −95 °C afforded a diastereomeric mixture of 5-benzyloxy-2-pentanols in a ratio of 85:15, *via* a flexible 7-membered ring chelate intermediate. This reaction of 4-benzyloxy-1-butanal with methyltitanium trichloride proceeded without diastereoselectivity, suggesting that the reagent adds rapidly to the aldehyde function before the formation of the chelate intermediate.

Our experimental results indicated that 1,5-asymmetric induction was achieved with extremely high diastereoselectivity by using organotitanium triisopropoxide. Such effective 1,5-asymmetirc induction has not been reported previously.

In further experiments, no reaction of **1a** and **1b** occurred with 2 mol eq of methyltitanium triisopropoxide at room temperature for 18—20 h. It is considered that a complex was formed containing titanium and two oxygens of the 1,3-oxazolidine ring and the carbonyl function, based on the characteristic affinity of titanium for oxygen, as shown in Fig. 3, though organotitanium triisopropoxide is a weak Lewis acid. On the other hand, the yields in the reaction of **1a** and **1b** with 4 mol eq of methyltitanium triisopropoxide at −78 °C for 42—44 h were no more than about 10%; this result suggests that the organotitanium triisopropoxide is a mild nucleophilic reagent as compared with the corresponding Grignard and organolithium reagents.

Moreover, the reactions of **1a** and **1b** with 4 mol eq of dimethyltitanium diisopropoxide gave **2a** and **2b** of the same configuration with the same diastereoselectivity. Thus, it may be assumed that the nucleophilic moiety attacks the carbonyl function from the opposite face to that involved in the initial approach of the reagent during complex formation, as shown in Fig. 3.

Experimental

The ^{1}H-NMR spectra were obtained with JEOL JNM-FX100 and/or JNM-GX400 spectrometers. The mass spectra (MS) were recorded with JEOL JMS-D300 spectrometer by using the electron impact (EI) and/or chemical isonization (CI) (isobutane) methods.

General Procedure for the Reaction of (*S*)-3-4′-Isopropyl-1′,3′-oxazolidino-1-phenylpropan-1-ones (1a, 1b) with Organotitanium Triisopropoxide——A solution of $ClTi(OPr^i)_3$ (4 mmol) in *n*-hexane (5 ml) was slowly added dropwise to a stirred suspension of a Grignard or organolithium reagent (MeMgBr, $C_6H_5CH_2MgCl$, PhLi, 4-$MeOC_6H_4Li$ or 4-ClC_6H_4Li; 4 mmol in 5 ml of ether) at -10——-20 °C under a nitrogen atmosphere for 2 h. An ethereal solution of the resulting mixture (4 mmol, 10 ml) was added, drop by drop, to a stirred solution of **1a** or **1b** (0.25 g or 0.28 g; 1 mmol) in ether (5 ml) at 0——5 °C, and the stirring was continued at room temperature under a nitrogen atmosphere for 18—20 h.

After addition of ether and 3% NH_3 aqueous solution to the reaction mixture, the resulting white precipitate was filtered off, and the filtrate was extracted with ether. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was dissolved in a 5% HCl aqueous solution and neutral by-products were removed by extraction with ether. The residual aqueous solution was made alkaline with Na_2CO_3 solution, and extracted with CH_2Cl_2. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting oily product was fractionated by chromatography on silica gel with *n*-hexane–ether (1 : 1) to give a colorless oil.

These products were identical with authentic samples prepared with corresponding Grignard and organolithium reagents on the basis of ^{1}H-NMR spectral comparisons. The structures of new compounds were confirmed by MS and ^{1}H-NMR analyses. The reaction mixture of **1a** with $C_6H_5CH_2Ti(OPr^i)_3$ was chromatographed on silica gel with *n*-hexane–ether (1 : 1) to give **2c** and **3c** as the first fraction and a diastereomeric mixture of **4a** as the second fraction. The ratio of the diastereomers of **4a** was estimated to be 55 : 45 by ^{1}H-NMR spectroscopy.

Mixture of 3-*N*-1′-isopropyl-2′-hydroxyethyl-*N*-phenylethylamino-1-phenylpropan-1-ols (**4a**): MS *m/z*: 342 ($M \cdot H^+$). ^{1}H-NMR ($CDCl_3$) δ: Major product; 0.86 (3H, d, J=6.6 Hz, $CHC\underline{H}_3$), 1.00 (3H, d, J=6.6 Hz, $CHC\underline{H}_3$), 4.76 (1H, t, J=7.2 Hz, $CH_2C\underline{H}O$). Minor product; 0.88 (3H, d, J=6.6 Hz, $CHC\underline{H}_3$), 1.02 (3H, d, J=6.6 Hz, $CHC\underline{H}_3$), 4.76 (1H, t, J=7.2 Hz, $CH_2C\underline{H}O$).

The reaction mixture of **1b** with $C_6H_5CH_2Ti(OPr^i)_3$ was worked up as described above for the reaction of **1a** to give **4b**. The product ratio was estimated to be 57 : 43 by ^{1}H-NMR spectroscopy.

Mixture of 3-*N*-1′-isopropyl-2′-hydroxyethyl-*N*-phenylethylamino-1-(4-methoxyphenyl)propan-1-ols (**4b**): MS *m/z*: 372 ($M \cdot H^+$). ^{1}H-NMR ($CDCl_3$) δ: Major product; 0.86 (3H, d, J=6.6 Hz, $CHC\underline{H}_3$), 1.01 (3H, d, J=6.6 Hz, $CHC\underline{H}_3$), 3.80 (3H, s, CH_3O), 4.68 (1H, t, J=7.1 Hz, $CH_2C\underline{H}O$). Minor product; 0.85 (3H, d, J=6.6 Hz, $CHC\underline{H}_3$), 0.99 (3H, d, J=6.6 Hz, $CHC\underline{H}_3$), 3.80 (3H, s, CH_3O), 4.68 (1H, t, J=7.1 Hz, $CH_2C\underline{H}O$).

3-*N*-(4-Chlorobenzyl)-*N*-1′-isopropyl-2′-hydroxyethylamino-1-(4-chlorophenyl)-1-phenylpropan-1-ol (**2g**): MS *m/z*: 472 ($M \cdot H^+$). ^{1}H-NMR ($CDCl_3$) δ: 0.83 (3H, d, J=6.8 Hz, $CHC\underline{H}_3$), 0.96 (3H, d, J=6.8 Hz, $CHC\underline{H}_3$), 1.84 (1H, septet, J=6.8 Hz, $(CH_3)_2C\underline{H}$), 3.65 (1H, d, J=13.0 Hz, CH_2O), 3.76 (1H, d, J=13.0 Hz, CH_2O).

3-*N*-(4-Chlorobenzyl)-*N*-1′-isopropyl-2′-hydroxyethylamino-1-(4-chlorophenyl)-1-(4-methoxyphenyl)propan-1-ol (**2h**): MS *m/z*: 502 ($M \cdot H^+$). ^{1}H-NMR ($CDCl_3$) δ: 0.84 (3H, d, J=6.6 Hz, $CHC\underline{H}_3$), 0.97 (3H, d, J=6.6 Hz, $CHC\underline{H}_3$), 1.84 (1H, septet, J=6.6 Hz, $(CH_3)_2C\underline{H}$), 3.78 (3H, s, CH_3O).

Reaction of 1a and 1b with Phenyl- and 4-Methoxyphenylmagnesium Bromide——An ethereal suspension of PhMgBr or 4-$MeOC_6H_4MgBr$ (4.4 mmol in 10 ml of ether) was added, drop by drop, to a stirred solution of **1a** or **1b** (1 mmol) in ether (5 ml) under a nitrogen atmosphere, and the stirring was continued at room temperature for 6 h. The reaction mixture was poured into ice-cold water and was made alkaline with NH_3 solution. The whole was extracted with CH_2Cl_2 and the organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed on silica gel with *n*-hexane–ether (1 : 1) to give an oily product (**2e**, **3e**; **2f**, **3f**). These products were identical with authentic samples on the basis of ^{1}H-NMR spectral comparisons.

Reaction of 1a with Methyllithium——An ethereal solution of MeLi (10 mmol in 10 ml of ether) was added dropwise to a solution of **1a** (1 mmol) in ether (5 ml) under a nitrogen atmosphere, and stirring was continued at room temperature for 18—20 h. The reaction mixture was poured into ice-cold water and made alkaline with NH_3 solution. The whole was extracted with ether and the ethereal solution was dried over anhydrous Na_2SO_4 then concentrated under reduced pressure to give a colorless oil (mixture of **2a** and **3a**; identical with authentic samples).

Reaction of 1b with Methyllithium——The reaction of **1b** (1 mmol) with MeLi (5 mmol) was carried out at

−20 °C for 4 h. The reaction mixture was worked up as described above for the reaction of **1a**. The oily residue was fractionated by chromatography on silica gel using *n*-hexane–ether (1 : 1). The first fraction gave a diastereomeric mixture of **5b** (0.16 g, 55%); and the second fraction gave a mixture of **2b** and **3b**, which were identical with authentic samples.

3-4′-Isopropyl-1′,3′-oxazolidino-1-methyl-1-(4-methoxyphenyl)propan-1-ol (**5a**): Ratio of major to minor products = 52 : 48. MS *m/z*: 294 ($M \cdot H^+$). ^{1}H-NMR ($CDCl_3$) δ: Major product; 0.81 (3H, d, J = 6.6 Hz, $CHC\underline{H}_3$), 0.87 (3H, d, J = 6.6 Hz, $CHC\underline{H}_3$), 1.44 (3H, s, CCH_3), 3.81 (3H, s, OCH_3), 6.86 (2H, d, J = 8.6 Hz, aromatic H), 7.39 (2H, d, J = 8.6 Hz, aromatic H). Minor product; 0.91 (3H, d, J = 6.6 Hz, $CHC\underline{H}_3$), 1.01 (3H, d, J = 6.6 Hz, $CHC\underline{H}_3$), 1.54 (3H, s, CCH_3), 3.80 (3H, s, OCH_3), 6.86 (2H, d, J = 8.6 Hz, aromatic H), 7.37 (2H, d, J = 8.6 Hz, aromatic H).

Reaction of 1a and 1b with 4-Chlorophenyllithium——An ethereal solution of 4-ClC_6H_4Li (4.2 or 5.5 mmol in 10 ml of ether) was added, drop by drop, to a solution of **1a** or **1b** (1 mmol) in ether (5 ml) under a nitrogen atmosphere, and the mixture was stirred at −20 °C for 4 h. The reaction mixture was worked up as described above for the reaction of MeLi. The oily residue was fractionated by chromatography on silica gel using *n*-hexane–ether (1 : 1).

The first fraction gave a diastereomeric mixture of **5g** (0.11 g, 31%) or **5h** (0.07 g, 18%); and the second fraction gave a mixture of **2g**; **3g** or **2h**; **3h**, respectively. Compounds **2g** and **2h** were identical with authentic samples.

1-(4-Chlorophenyl)-3-4′-isopropyl-1′,3′-oxazolidino-1-phenylpropan-1-ol (**5b**): Ratio of major to minor products = 60 : 40. MS *m/z*: 360 ($M \cdot H^+$). ^{1}H-NMR ($CDCl_3$) δ: Major product; 0.78 (3H, d, J = 4.9 Hz, $CHC\underline{H}_3$), 0.85 (3H, d, J = 4.9 Hz, $CHC\underline{H}_3$), 3.45 (1H, dd, J = 6.0, 8.3 Hz, $OC\underline{H}_2CH$), 3.86 (1H, t, J = 8.3 Hz, $OC\underline{H}_2CH$), 4.32 (2H, s, OCH_2N). Minor product; 0.80 (3H, d, J = 4.9 Hz, $CHC\underline{H}_3$), 0.87 (3H, d, J = 4.9 Hz, $CHC\underline{H}_3$), 3.45 (1H, dd, J = 6.0, 8.3 Hz, $OC\underline{H}_2CH$), 3.86 (1H, t, J = 8.3 Hz, $OC\underline{H}_2CH$), 4.32 (2H, s, OCH_2N).

1-(4-Chlorophenyl)-3-4′-isopropyl-1′,3′-oxazolidino-1-(4-methoxyphenyl)propan-1-ol (**5c**): Ratio of major to minor products = 66 : 34. MS *m/z*: 390 ($M \cdot H^+$). ^{1}H-NMR ($CDCl_3$) δ: Major product; 0.80 (3H, d, J = 4.9 Hz, $CHC\underline{H}_3$), 0.87 (3H, d, J = 4.9 Hz, $CHC\underline{H}_3$), 3.79 (3H, s, OCH_3), 4.34 (2H, s, OCH_2N). Minor product; 0.81 (3H, d, J = 4.9 Hz, $CHC\underline{H}_3$), 0.88 (3H, d, J = 4.9 Hz, $CHC\underline{H}_3$), 3.76 (3H, s, OCH_3), 4.34 (2H, s, OCH_2N).

3-*N*-(4-Chlorobenzyl)-*N*-1′-isopropyl-2′-hydroxyethylamino-1-(4-chlorophenyl)-1-phenylpropan-1-ol (**3g**): MS *m/z*: 472 ($M \cdot H^+$). ^{1}H-NMR ($CDCl_3$) δ: 0.83 (3H, d, J = 6.8 Hz, $CHC\underline{H}_3$), 0.94 (3H, d, J = 6.8 Hz, $CHC\underline{H}_3$), 1.83 (1H, septet, J = 6.8 Hz, $(CH_3)_2C\underline{H}$), 3.74 (1H, d, J = 13.2 Hz, CH_2O).

3-*N*-(4-Chlorobenzyl)-*N*-1′-isopropyl-2′-hydroxyethylamino-1-(4-chlorophenyl)-1-(4-methoxyphenyl)propan-1-ol (**3h**): MS *m/z*: 502 ($M \cdot H^+$). ^{1}H-NMR ($CDCl_3$) δ: 0.87 (3H, d, J = 6.8 Hz, $CHC\underline{H}_3$), 0.96 (3H, d, J = 6.8 Hz, $CHC\underline{H}_3$), 3.77 (3H, s, CH_3O).

Crystallographic Measurements——A single crystal of (1*R*,1′*S*)-**3d**[2] was grown in *n*-hexane–ethanol solution as a colorless column with dimensions of 0.5 × 0.5 × 0.3 mm. All the measurements were performed on a Rigaku AFC-5 diffractometer using graphite-monochromated Mo K_α radiation. The unit cell dimensions were determined by least-squares calculation with 24 high-angle reflections.

Intensity data were collected by using the $2\theta/\omega$ scan technique for $2\theta < 52.0°$ with an average scan rate of 4 °/min. In total, 3004 independent reflectioned with $0 < 2\theta < 52.0°$ were collected, of which 1748 that satisfied the condition $F_0 \geqq 3\sigma(F)$ were used for calculations.

Structure Analysis and Refinement——The structure was solved by the direct method using MULTAN[7] and the Rigaku crystallographic package RASA-II. The structure was refined by the block-diagonal least-squares technique with anisotropic thermal factors for all non-hydrogen atoms. The *R* factor was finally reduced to 0.1206.

Acknowledgement We are grateful to Mrs. M. Yuyama and Miss T. Tanaka of Hoshi University for ^{1}H-NMR spectra and mass spectra.

References and Notes

1) B. Weidmann and D. Seebach, *Angew. Chem. Int. Ed. Engl.*, **22**, 31 (1983); M. T. Reetz, *ibid.*, **23**, 556 (1984).
2) H. Takahashi, K. Tanahashi, and K. Higashiyama, *Chem. Pharm. Bull.*, **32**, 4323 (1984).
3) D. Seebach, B. Weidmann, and L. Widler, "Modern Synthetic Methods," Vol. 3, ed. by R. Scheffold, Otto Salle Verlag, 1983, pp. 217—353.
4) A. Segnitz, "Methoden der Organischen Chemie," Vol. 13/7, ed. by E. Müller, Georg Thieme Verlag Stuttgart, 1975, pp. 265—334.
5) The (1*S*, 1′*S*)-configuration, assumed in our previous paper (H. Takahashi, K. Tanahashi, and K. Higashiyama, *Chem. Pharm. Bull.*, **32**, 4323 (1984)) on the basis of ^{1}H-NMR spectral analysis, should be corrected.
6) M. T. Reetz, K. Kesseler, S. Schmidtbergen, B. Wenderoth, and R. Steinbach, *Angew. Chem. Int. Ed. Engl.*, **22**, 989 (1983); *idem, Angew. Chem. Suppl.*, **1983**, 1511.
7) P. Main, M. M. Woolfson, and G. Germin, *Acta Crystallogr., Sect. A*, **27**, 368 (1971).