[Chem. Pharm. Bull. 31(8)2895—2898(1983)]

Asymmetric Reaction of Chiral Azomethines with Organometallic Reagents

YUJI SUZUKI[b] and HIROSHI TAKAHASHI*,[a]

Faculty of Pharmaceutical Sciences, Hoshi University,[a] Ebara, Shinagawa, Tokyo 142, Japan and Kaken Pharmaceutical Co., Ltd.,[b] Shinomiya-kawaramachi, Yamashina, Kyoto 607, Japan

(Received January 31, 1983)

Reaction of (*E*)-(*S*)-*N*-(1-isopropyl-2-methoxyethyl)benzylideneamine (**2**) with ethylmagnesium bromide gave a mixture of (1*S*, 1′*S*)- and (1*R*, 1′*S*)-*N*-(1′-isopropyl-2′-methoxyethyl)-1-phenylpropylamines (**3**) (91 : 9%). (*E*)-(*S*)-*N*-(1-Isopropyl-2-methoxyethyl)propylideneamine (**5**) was treated with phenyllithium to give (1*R*, 1′*S*)- and (1*S*, 1′*S*)-**3** (95 : 5%). On the other hand, reaction of (*E*)-(*S*)-*N*-(2-hydroxy-1-isopropylethyl)benzylideneamine (**6**) with ethylmagnesium bromide yielded a mixture of (1*S*, 1′*S*)- and (1*R*, 1′*S*)-*N*-(2′-hydroxy-1′-isopropylethyl)-1-phenylpropylamines (**7**) (78 : 22%).

The absolute configurations of these amines were determined by circular dichroism (CD) spectroscopy and comparison with authentic samples synthesized by alternative methods.

Keywords——absolute configuration; asymmetric reaction; chiral amine; chiral azomethine; Grignard reaction; *N*-methylation; (*S*)-*N*-methylvalinol; *O*-methylation; phenyllithium; phenylpropylamine

In the previous papers, the extremely highly stereoselective reactions of chiral azomethines with Grignard reagents[1] or organolithium reagents[2] were reported. In order to elucidate the stereoselectivity of the reaction using alkylmagnesium halide, we investigated the reaction of (*E*)-(*S*)-*N*-(1-isopropyl-2-methoxyethyl)benzylideneamine with ethylmagnesium bromide, and related reactions.

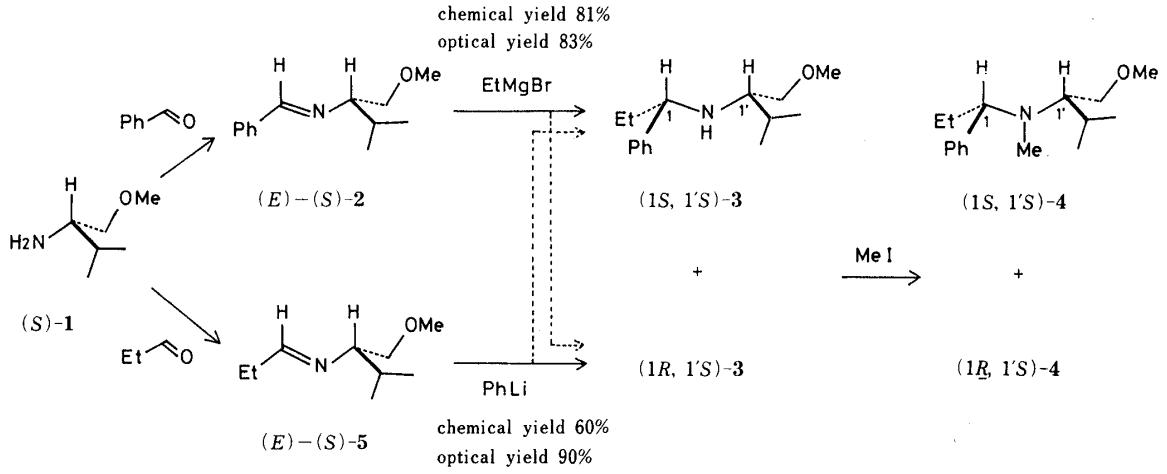

Chart 1

(*E*)-(*S*)-*N*-(1-Isopropyl-2-methoxyethyl)benzylideneamine (**2**) was synthesized by the condensation of (*S*)-1-methoxy-3-methyl-2-butylamine (**1**)[3] with benzaldehyde. This compound was established to consist of one isomer by analysis of its proton nuclear magnetic resonance (^{1}H-NMR) spectrum. The structure of this compound was confirmed by ^{1}H-NMR

and mass spectroscopies.

The reaction of the chiral azomethine (**2**) with ethylmagnesium bromide gave a mixture of two diastereomers of *N*-(1′-isopropyl-2′-methoxyethyl)-1-phenylpropylamine [major product, (1*S*, 1′*S*)-**3**; minor product, (1*R*, 1′*S*)-**3**] in 81% chemical yield. This product was treated with methyl iodide to give *N*-(1′-isopropyl-2′-methoxyethyl)-*N*-methyl-1-phenylpropylamines [(1*S*, 1′*S*)-**4** and (1*R*, 1′*S*)-**4**] in quantitative yield. The ratio of the two diastereomers was estimated to be 91 : 9% by comparison of the ^{1}H-NMR spectral peak areas.

On the other hand, (*E*)-(*S*)-*N*-(1-isopropyl-2-methoxyethyl)propylideneamine (**5**), synthesized from **1** and propionaldehyde, was treated with phenyllithium to give a mixture of chiral amines [major product, (1*R*, 1′*S*)-**3**; minor product, (1*S*, 1′*S*)-**3**] in 60% chemical yield. This product was converted to *N*-methyl compounds [(1*R*, 1′*S*)-**4** and (1*S*, 1′*S*)-**4**], and the ratio of the two compounds was estimated to be 95 : 5% by ^{1}H-NMR spectroscopy.

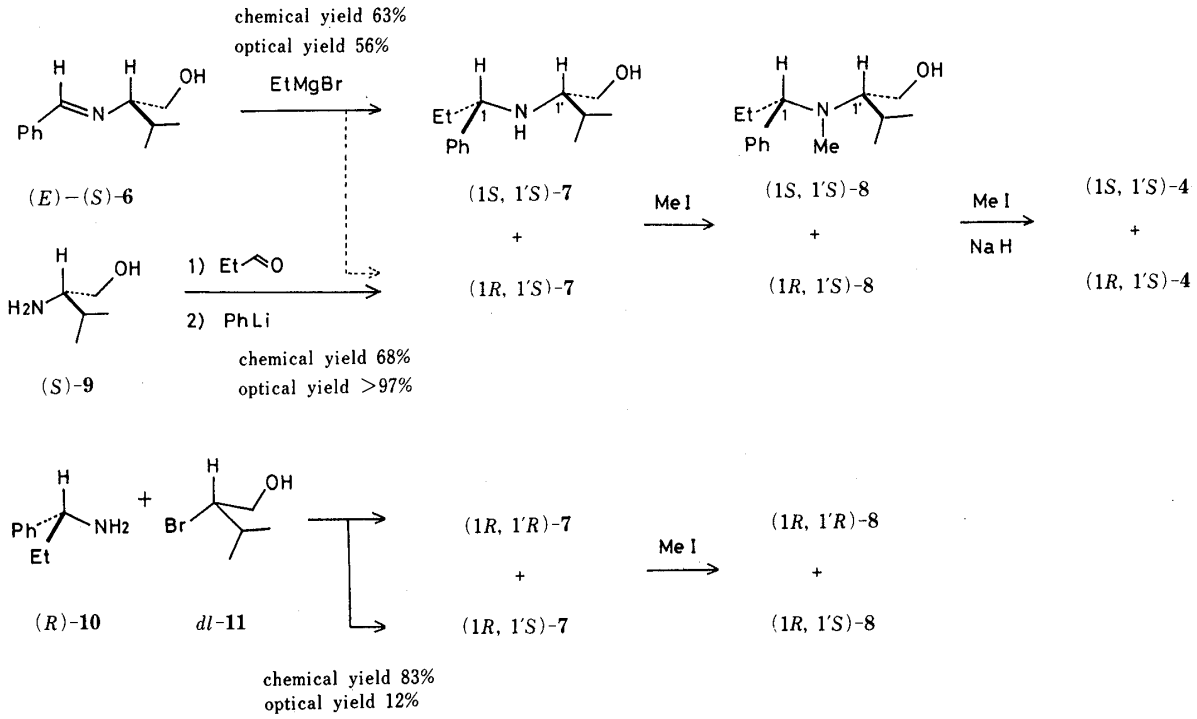

Chart 2

The reaction of (*E*)-(*S*)-*N*-(2-hydroxy-1-isopropylethyl)benzylideneamine (**6**) with benzylmagnesium chloride[1] or phenyllithium[2] occurred in extremely high diastereomer excess. However, the reaction of **6** with ethylmagnesium bromide gave a mixture of *N*-(2′-hydroxy-1′-isopropylethyl)-1-phenylpropylamines [major product, (1*S*, 1′*S*)-**7**; minor product, (1*R*, 1′*S*)-**7**] in 63% chemical yield. This product was converted to *N*-(2′-hydroxy-1′-isopropylethyl)-*N*-methyl-1-phenylpropylamines [(1*S*, 1′*S*)-**8** and (1*R*, 1′*S*)-**8**] by *N*-methylation. The ratio of the two diastereomers was estimated to be 78 : 22% by ^{1}H-NMR spectroscopy. This product was treated with methyl iodide and sodium hydride to give the *O*-methyl compound, which was identical with **4** obtained from **2**.

On the other hand, optically pure (>97%) *N*-(2′-hydroxy-1′-isopropylethyl)-1-phenylpropylamine (**7**) was synthesized by the condensation of (*S*)-valinol (**9**) with propionaldehyde,[4] followed by treatment with phenyllithium. This compound was identical with the minor product obtained from **6** and ethylmagnesium bromide.

We attempted to determine the absolute configuration of the newly created asymmetric carbon atom at the 1-phenylpropylamine moiety in the compounds thus obtained. The chiral amine (**7**) was synthesized *via* an alternative route by the condensation of (*R*)-1-phenyl-

propylamine (**10**) [optical purity: 70%][5] with *dl*-2-bromo-3-methylbutanol (**11**). The *N*-methylation of this product gave **8**. The ratio of the major compound to the minor compound was estimated as 56 : 44% by ^{1}H-NMR spectroscopy.

Cotton effects of **7** were observed in the ^1L_a band (210—240 nm region) and ^1L_b band (240—270 nm region) which are attributable to the phenyl chromophore.[1b] The circular dichroism (CD) spectrum [maximum $\Delta\varepsilon$ (nm)] of the amine prepared from (*R*)-**10** showed +0.74 (221), −0.10 (253), −0.18 (259), −0.17 (266), whereas the CD spectrum [maximum $\Delta\varepsilon$ (nm)] of the amine derived from (*S*)-**9** showed +1.10 (221), −0.13 (253), −0.19 (259), −0.17 (266). Consequently, it was concluded that the asymmetric carbon atom at the phenylpropylamine moiety has *R*-configuration. Then, the absolute configurations of **3**, **4**, **7**, and **8** were elucidated.

The asymmetric reaction of the azomethines (**2**, **5**, and **6**) with organometallic reagents was considered to proceed by a mechanism similar to that previously reported.[1,2] Moreover, it may be concluded that; (1) the stereoselectivity of ethylmagnesium bromide is lower than that of aryllithium or benzylmagnesium chloride; (2) **2** and **5** show better stereoselectivity than **6**.

Experimental

The infrared (IR) spectra were recorded with a Hitachi 260-10 spectrometer and the ^{1}H-NMR spectra were obtained with a JEOL FX100 spectrometer. The mass spectra (MS) were recorded with a JEOL JMS-D300 spectrometer by using the CI (CH_4) method.

The CD spectra were measured at 20—23 °C with a Jasco J-40 spectropolarimeter; the magnitudes of the bands were calibrated with D-10-camphorsulfonic acid (at 289 nm) and D-pantolactone (at 221 nm) as standards.

(*E*)-(*S*)-*N*-(1-Isopropyl-2-methoxyethyl)benzylideneamine (2)——A mixture of (*S*)-1 (3.51 g, 30 mmol) and benzaldehyde (3.18 g, 30 mmol) in benzene (50 ml) was refluxed for 1 h using a Dean-Stark trap. The solvent was evaporated off and the residue was distilled under reduced pressure. Yield, 4.8 g (78%). bp 113 °C/0.3 mmHg. IR (film): 1640 (C=N) cm^{-1}. MS *m/e*: 206 (M·H$^+$). ^{1}H-NMR ($CDCl_3$) δ: 0.93 (6H, d, J=6.6 Hz, $CH(C\underline{H}_3)_2$), 3.32 (3H, s, OCH_3), 3.50 (1H, dd, J=7.1 and 9.5 Hz, OCH_2), 3.62 (1H, dd, J=4.4 and 9.5 Hz, OCH_2), 8.22 (1H, s, N=CH).

Reaction of 2 with Ethylmagnesium Bromide——An ethereal solution of ethylmagnesium bromide (20 mmol in 7 ml of ether) was added to a stirred solution of **2** (0.98 g, 5 mmol) in ether (10 ml) at 0—5 °C under a nitrogen atmosphere. After being stirred for 8 h, the mixture was poured into NH_4Cl solution, the organic layer was dried over anhydrous $MgSO_4$ and the solvent was evaporated off. The residue was column-chromatographed on silica gel with hexane–CH_2Cl_2 (2 : 3) to yield a colorless oil (0.95 g, 81%). This product was confirmed to consist of a mixture of two diastereomers [major, (1*S*, 1′*S*)-**3**; minor, (1*R*, 1′*S*)-**3**] by analysis of the ^{1}H-NMR spectrum. IR (film): 3350 (NH) cm^{-1}. MS *m/e*: 236 (M·H$^+$), 119 ($PhCH^+CH_2CH_3$). ^{1}H-NMR ($CDCl_3$) δ: Major product; 0.71 (3H, d, J=6.8 Hz, $CHC\underline{H}_3$), 0.74 (3H, t, J=7.6 Hz, $CH_2C\underline{H}_3$), 0.78 (3H, d, J=6.8 Hz, $CHC\underline{H}_3$), 3.27 (3H, s, OCH_3), 3.33 (2H, d, J=4.6 Hz, OCH_2), 3.52 (1H, dd, J=6.1 and 7.1 Hz, PhCH).

***N*-Methylation of 3**——Methyl iodide (0.5 ml) and K_2CO_3 (0.1 g) were added to a solution of the above mixture [(1*S*, 1′*S*)-**3** and (1*R*, 1′*S*)-**3**] (0.12 g, 0.5 mmol) in *N*,*N*-dimethylformamide (DMF, 2 ml). After being stirred at room temperature for 20 h, the mixture was poured into water and extracted with ether. Removal of the solvent gave an oily product which was confirmed to be a mixture of two diastereomers [major, (1*S*, 1′*S*)-**4**; minor, (1*R*, 1′*S*)-**4**]. MS *m/e*: 250 (M·H$^+$), 119 ($PhCH^+CH_2CH_3$). ^{1}H-NMR ($CDCl_3$) δ: Major product; 0.64 (3H, t, J=7.3 Hz, $CH_2C\underline{H}_3$), 0.77 (3H, d, J=6.8 Hz, $CHC\underline{H}_3$), 0.88 (3H, d, J=6.8 Hz, $CHC\underline{H}_3$), 2.31 (3H, s, NCH_3), 3.20 (3H, s, OCH_3), 3.31 (2H, d, J=4.2 Hz, OCH_2), 3.54 (1H, dd, J=4.4 and 9.3 Hz, PhCH).

(*E*)-(*S*)-*N*-(1-Isopropyl-2-methoxyethyl)propylideneamine (5)——A solution of (*S*)-**1** (1.17 g, 10 mmol) and propionaldehyde (0.70 g, 12 mmol) in ether (20 ml) was stirred in the presence of $MgSO_4$ (2 g) at room temperature for 2 h. After removal of the solid, the mixture was concentrated to give a colorless oil in quantitative yield. This material was unstable. IR (film): 1670 (C=N) cm^{-1}. MS *m/e*: 158 (M·H$^+$). ^{1}H-NMR ($CDCl_3$) δ: 0.85 (3H, d, J=6.6 Hz, $CHC\underline{H}_3$), 0.89 (3H, d, J=6.6 Hz, $CHC\underline{H}_3$), 1.10 (3H, t, J=7.6 Hz, $CH_2C\underline{H}_3$), 2.28 (2H, dq, J=4.9 and 7.6 Hz, $N=CHC\underline{H}_2CH_3$), 3.32 (1H, s, OCH_3), 7.59 (1H, t, J=4.9 Hz, $N=C\underline{H}CH_2$).

Reaction of 5 with Phenyllithium——An ethereal solution of phenyllithium (25 mmol in 20 ml of ether) was added to a stirred solution of **5** (0.79 g, 5 mmol) in ether (10 ml) at 0—5 °C under a nitrogen atmosphere. After being stirred at room temperature for 16 h, the mixture was poured into ice-water and the organic layer was dried over anhydrous $MgSO_4$ and concentrated. The residue was column-chromatographed on silica gel with hexane–CH_2Cl_2 (3 : 2) to give

a colorless oil (0.7 g, 60%). It was confirmed that the product consists of two diastereomers [major, (1*R*, 1′*S*)-**3**; minor, (1*S*, 1′*S*)-**3**] by means of ^{1}H-NMR spectroscopy. ^{1}H-NMR ($CDCl_3$) δ: Major product; 0.82 (3H, t, J=7.6 Hz, $CH_2C\underline{H}_3$), 0.85 (3H, d, J=6.6 Hz, $CHC\underline{H}_3$), 0.92 (3H, d, J=6.6 Hz, $CHC\underline{H}_3$), 3.17 (3H, s, OCH_3), 3.18 (2H, d, J=5.7 Hz, OCH_2), 3.53 (1H, dd, J=6.3 and 7.3 Hz, PhCH).

This product was treated with methyl iodide and K_2CO_3 in DMF as described above to give the *N*-methyl derivatives [major, (1*R*, 1′*S*)-**4**; minor, (1*S*, 1′*S*)-**4**]. ^{1}H-NMR ($CDCl_3$) δ: Major product; 0.68 (3H, t, J=7.3 Hz, $CH_2C\underline{H}_3$), 0.93 (3H, d, J=6.8 Hz, $CHC\underline{H}_3$), 1.00 (3H, d, J=6.8 Hz, $CHC\underline{H}_3$), 2.06 (3H, s, NCH_3), 3.20 (3H, s, OCH_3), 3.52 (1H, dd, J=5.4 and 8.5 Hz, PhCH).

Reaction of 6 with Ethylmagnesium Bromide——An ethereal solution of ethylmagnesium bromide (20 mmol in 7 ml of ether) was added to a stirred solution of **6** (0.98 g, 5 mmol) in ether (10 ml) at room temperature under a nitrogen atmosphere. After being stirred at room temperature for 48 h, the mixture was worked up as described above to give a colorless oil (0.7 g, 63%), which was confirmed to consist of two diastereomers [major, (1*S*, 1′*S*)-**7**; minor, (1*R*, 1′*S*)-**7**] by analysis of the ^{1}H-NMR spectrum. IR (film): 3400 (OH) cm^{-1}. MS *m/e*: 222 ($M \cdot H^+$), 119 ($PhCH^+CH_2CH_3$). ^{1}H-NMR ($CDCl_3$) δ: Major product; 0.80 (3H, t, J=7.3 Hz, $CH_2C\underline{H}_3$), 0.81 (3H, d, J=6.8 Hz, $CHC\underline{H}_3$), 0.86 (3H, d, J=6.8 Hz, $CHC\underline{H}_3$), 3.35 (1H, dd, J=4.5 and 10.6 Hz, OCH_2), 3.61 (1H, d, J=4.4 and 10.6 Hz, OCH_2).

***N*-Methylation of 7**——Methyl iodide (0.5 ml) and K_2CO_3 (0.1 g) were added to a solution of the above mixture [(1*S*, 1′*S*)-**7** and (1*R*, 1′*S*)-**7**] (0.11 g, 0.5 mmol) in DMF (2 ml). After being stirred at room temperature for 20 h, the mixture was worked-up as described above. A mixture of (1*S*, 1′*S*)-**8** and (1*R*, 1′*S*)-**8** was obtained as a colorless oil in quantitative yield. IR (film): 3450 (OH) cm^{-1}. MS *m/e*: 236 ($M \cdot H^+$), 119 ($PhCH^+CH_2CH_3$). ^{1}H-NMR ($CDCl_3$) δ: Major product; 0.66 (3H, t, J=7.2 Hz, $CH_2C\underline{H}_3$), 0.83 (3H, d, J=6.8 Hz, $CHC\underline{H}_3$), 0.96 (3H, d, J=6.8 Hz, $CHC\underline{H}_3$), 2.13 (3H, s, NCH_3), 3.41 (1H, dd, J=9.7 and 10.3 Hz, OCH_2), 3.65 (1H, dd, J=4.9 and 10.3 Hz, OCH_2). Minor product; 0.64 (3H, t, J=7.3 Hz, $CH_2C\underline{H}_3$), 0.74 (3H, d, J=6.8 Hz, $CHC\underline{H}_3$), 0.91 (3H, d, J=6.8 Hz, $CHC\underline{H}_3$), 2.40 (3H, s, NCH_3), 3.25 (1H, dd, J=9.0 and 10.0 Hz, OCH_2), 3.39 (1H, dd, J=6.2 and 10.0 Hz, OCH_2).

***O*-Methylation of 8**——The above mixture [(1*S*, 1′*S*)-**8** and (1*R*, 1′*S*)-**8**] (0.12 g, 0.5 mmol) in dry THF (2 ml) was added to a suspension of 50% NaH (30 mg, *ca.* 0.6 mmol) in THF (2 ml) under a nitrogen atmosphere. The whole was stirred for 3 h, then methyl iodide (0.14 g, 1 mmol) was added and stirring was continued for 20 h. The mixture was poured into water and extracted with ether. The solvent was evaporated off and the residue was column-chromatographed on silica gel using CH_2Cl_2 to give a colorless oil in quantitative yield. This product was confirmed to identical with **4**.

(1*R*, 1′*S*)-*N*-(2′-Hydroxy-1′-isopropylethyl)-1-phenylpropylamine (7)——A solution of propionaldehyde (0.58 g, 10 mmol) in ether (5 ml) was added to a stirred solution of (*S*)-**9** (1.03 g, 10 mmol) in ether (5 ml), then anhydrous $MgSO_4$ (2 g) was added to the mixture. After 30 min, the solvent was evaporated off under reduced pressure. The residue[4] was dissolved in dry ether (10 ml). An ethereal solution of phenyllithium (35 mmol in 25 ml of ether) was slowly added, drop by drop, to the stirred solution of the product at room temperature. Stirring was continued for 20 h, the mixture was poured into ice-water. The ethereal layer was separated and concentrated. The residue was chromatographed over silica gel using CH_2Cl_2–ether (9 : 1). Yield, 0.75 g (68%). IR (film): 3400 (OH) cm^{-1}. MS *m/e*: 222 ($M \cdot H^+$), 119 ($PhCH^+CH_2CH_3$). ^{1}H-NMR ($CDCl_3$) δ: 0.82 (3H, t, J=7.3 Hz, $CH_2C\underline{H}_3$), 0.89 (3H, d, J=6.8 Hz, $CHC\underline{H}_3$), 0.91 (3H, d, J=6.8 Hz, $CHC\underline{H}_3$), 3.16 (1H, dd, J=7.8 and 10.4 Hz, OCH_2), 3.34 (1H, dd, J=4.6 and 10.4 Hz, OCH_2), 3.62 (1H, t, J=6.8 Hz, $PhC\underline{H}CH_2$).

Condensation of (*R*)-10 with *dl*-11——A solution of (*R*)-**10** (optical purity: 70%, 0.5 g, 3.7 mmol) and *dl*-**11** (2.5 g, 15 mmol) in ethanol (20 ml) was refluxed with stirring in the presence of K_2CO_3 (2.5 g) for 20 h under a nitrogen atmosphere. After removal of the solid, the solvent was evaporated off. The residue was column-chromatographed on silica gel using CH_2Cl_2 to give a colorless oil (0.68 g, 83%), which was confirmed to consist of two diastereomers [major, (1*R*, 1′*R*)-**7**; minor, (1*R*, 1′*S*)-**7**] by analysis of the ^{1}H-NMR spectrum. Treatment of this compound with methyl iodide and K_2CO_3 in DMF gave the *N*-methyl compounds [major, (1*R*, 1′*R*)-**8**; minor, (1*R*, 1′*S*)-**8**] in quantitative yield.

References and Notes

1) *a*) H. Takahashi, Y. Suzuki, and H. Inagaki, *Chem. Pharm. Bull.*, **30**, 3160 (1982); *b*) Y. Suzuki and H. Takahashi, *ibid.*, **31**, 31 (1983).
2) H. Takahashi, Y. Suzuki, and T. Hori, *Chem. Pharm. Bull.*, **31**, 2183 (1983).
3) A. I. Meyers, G. S. Poindexter, and Z. Brich, *J. Org. Chem.*, **43**, 892 (1978).
4) This compound gave a molecular ion peak at *m/e* 144 (M. H^+), but it showed loss of the IR absorption of the C=N bond and of the ^{1}H-NMR signal of CH=N. Accordingly, the structure of this compound was assumed to 2-ethyl-4-isopropyloxazolidine.
5) The (*R*)-l-phenylpropylamine used gave $[\alpha]_D^{20}$ +14.8° (neat); lit. $[\alpha]_D^{24}$ +21.2° (neat) [M. E. Warren and A. W. Ingersoll, *J. Am. Chem. Soc.*, **87**, 1757 (1965)].