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Asymmetric Reaction of Chiral Azomethines with Organometallic Reagents

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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 reagents¹⁾ or organolithium reagents²⁾ 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 (¹H-NMR) spectrum. The structure of this compound was confirmed by ¹H-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 ¹H-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 ¹H-NMR spectroscopy.

Chart 2

The reaction of (*E*)-(*S*)-*N*-(2-hydroxy-1-isopropylethyl)benzylideneamine (**6**) with benzylmagnesium chloride¹⁾ or phenyllithium²⁾ 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 ¹H-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 ¹H-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 Δε (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 Δε (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 ¹H-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 (CH₄) 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⁺). ¹H-NMR (CDCl₃) δ: 0.93 (6H, d, *J* = 6.6 Hz, CH(CH₃)₂), 3.32 (3H, s, OCH₃), 3.50 (1H, dd, *J* = 7.1 and 9.5 Hz, OCH₂), 3.62 (1H, dd, *J* = 4.4 and 9.5 Hz, OCH₂), 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 NH₄Cl solution, the organic layer was dried over anhydrous MgSO₄ and the solvent was evaporated off. The residue was column-chromatographed on silica gel with hexane–CH₂Cl₂ (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 ¹H-NMR spectrum. IR (film): 3350 (NH) cm^{−1}. MS *m/e*: 236 (M·H⁺), 119 (PhCH⁺CH₂CH₃). ¹H-NMR (CDCl₃) δ: Major product; 0.71 (3H, d, *J* = 6.8 Hz, CHCH₃), 0.74 (3H, t, *J* = 7.6 Hz, CH₂CH₃), 0.78 (3H, d, *J* = 6.8 Hz, CHCH₃), 3.27 (3H, s, OCH₃), 3.33 (2H, d, *J* = 4.6 Hz, OCH₂), 3.52 (1H, dd, *J* = 6.1 and 7.1 Hz, PhCH).

N*-Methylation of **3*—Methyl iodide (0.5 ml) and K₂CO₃ (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⁺CH₂CH₃). ¹H-NMR (CDCl₃) δ: Major product; 0.64 (3H, t, *J* = 7.3 Hz, CH₂CH₃), 0.77 (3H, d, *J* = 6.8 Hz, CHCH₃), 0.88 (3H, d, *J* = 6.8 Hz, CHCH₃), 2.31 (3H, s, NCH₃), 3.20 (3H, s, OCH₃), 3.31 (2H, d, *J* = 4.2 Hz, OCH₂), 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 MgSO₄ (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⁺). ¹H-NMR (CDCl₃) δ: 0.85 (3H, d, *J* = 6.6 Hz, CHCH₃), 0.89 (3H, d, *J* = 6.6 Hz, CHCH₃), 1.10 (3H, t, *J* = 7.6 Hz, CH₂CH₃), 2.28 (2H, dq, *J* = 4.9 and 7.6 Hz, N=CHCH₂CH₃), 3.32 (1H, s, OCH₃), 7.59 (1H, t, *J* = 4.9 Hz, N=CHCH₂CH₃).

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 MgSO₄ and concentrated. The residue was column-chromatographed on silica gel with hexane–CH₂Cl₂ (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 ¹H-NMR spectroscopy. ¹H-NMR (CDCl₃) δ: Major product; 0.82 (3H, t, *J*=7.6 Hz, CH₂CH₃), 0.85 (3H, d, *J*=6.6 Hz, CHCH₃), 0.92 (3H, d, *J*=6.6 Hz, CHCH₃), 3.17 (3H, s, OCH₃), 3.18 (2H, d, *J*=5.7 Hz, OCH₂), 3.53 (1H, dd, *J*=6.3 and 7.3 Hz, PhCH).

This product was treated with methyl iodide and K₂CO₃ in DMF as described above to give the *N*-methyl derivatives [major, (1*R*, 1'*S*)-4; minor, (1*S*, 1'*S*)-4]. ¹H-NMR (CDCl₃) δ: Major product; 0.68 (3H, t, *J*=7.3 Hz, CH₂CH₃), 0.93 (3H, d, *J*=6.8 Hz, CHCH₃), 1.00 (3H, d, *J*=6.8 Hz, CHCH₃), 2.06 (3H, s, NCH₃), 3.20 (3H, s, OCH₃), 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 ¹H-NMR spectrum. IR (film): 3400 (OH) cm⁻¹. MS *m/e*: 222 (M·H⁺), 119 (PhCH⁺CH₂CH₃). ¹H-NMR (CDCl₃) δ: Major product; 0.80 (3H, t, *J*=7.3 Hz, CH₂CH₃), 0.81 (3H, d, *J*=6.8 Hz, CHCH₃), 0.86 (3H, d, *J*=6.8 Hz, CHCH₃), 3.35 (1H, dd, *J*=4.5 and 10.6 Hz, OCH₂), 3.61 (1H, d, *J*=4.4 and 10.6 Hz, OCH₂).

***N*-Methylation of 7**—Methyl iodide (0.5 ml) and K₂CO₃ (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·H⁺), 119 (PhCH⁺CH₂CH₃). ¹H-NMR (CDCl₃) δ: Major product; 0.66 (3H, t, *J*=7.2 Hz, CH₂CH₃), 0.83 (3H, d, *J*=6.8 Hz, CHCH₃), 0.96 (3H, d, *J*=6.8 Hz, CHCH₃), 2.13 (3H, s, NCH₃), 3.41 (1H, dd, *J*=9.7 and 10.3 Hz, OCH₂), 3.65 (1H, dd, *J*=4.9 and 10.3 Hz, OCH₂). Minor product; 0.64 (3H, t, *J*=7.3 Hz, CH₂CH₃), 0.74 (3H, d, *J*=6.8 Hz, CHCH₃), 0.91 (3H, d, *J*=6.8 Hz, CHCH₃), 2.40 (3H, s, NCH₃), 3.25 (1H, dd, *J*=9.0 and 10.0 Hz, OCH₂), 3.39 (1H, dd, *J*=6.2 and 10.0 Hz, OCH₂).

***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 CH₂Cl₂ to give a colorless oil in quantitative yield. This product was confirmed to be 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 MgSO₄ (2 g) was added to the mixture. After 30 min, the solvent was evaporated off under reduced pressure. The residue⁴⁾ 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 CH₂Cl₂-ether (9:1). Yield, 0.75 g (68%). IR (film): 3400 (OH) cm⁻¹. MS *m/e*: 222 (M·H⁺), 119 (PhCH⁺CH₂CH₃). ¹H-NMR (CDCl₃) δ: 0.82 (3H, t, *J*=7.3 Hz, CH₂CH₃), 0.89 (3H, d, *J*=6.8 Hz, CHCH₃), 0.91 (3H, d, *J*=6.8 Hz, CHCH₃), 3.16 (1H, dd, *J*=7.8 and 10.4 Hz, OCH₂), 3.34 (1H, dd, *J*=4.6 and 10.4 Hz, OCH₂), 3.62 (1H, t, *J*=6.8 Hz, PhCHCH₂).

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 K₂CO₃ (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 CH₂Cl₂ 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 ¹H-NMR spectrum. Treatment of this compound with methyl iodide and K₂CO₃ 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

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- 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 ¹H-NMR signal of CH=N. Accordingly, the structure of this compound was assumed to be 2-ethyl-4-isopropylloxazolidine.
- 5) The (*R*)-1-phenylpropylamine used gave [α]_D²⁰ +14.8° (neat); lit. [α]_D²⁴ +21.2° (neat) [M. E. Warren and A. W. Ingersoll, *J. Am. Chem. Soc.*, **87**, 1757 (1965)].